UNIVERSITY OF SOUTHAMPTON

FACULTY OF NATURAL AND ENVIRONMENTAL SCIENCES

School of Chemistry

DISUBSTITUTED *BIS*-THF MOIETIES AS NEW P2 LIGANDS IN NONPEPTIDAL HIV-1 PROTEASE INHIBITORS

by

Konrad Hohlfeld

Thesis for the degree of Doctor of Philosophy

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ABSTRACT

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HIV-1 protease inhibitors (PIs) remain a powerful tool in the battle against HIV. The recently approved nonpeptidal HIV-protease inhibitor darunavir has been reported to be highly active against the wild-type virus as well as against a series of mutant strains. A rigid *bis*-tetrahydrofuran (*bis*-THF) moiety, with its two well-positioned hydrogen bond acceptors, has proven to play a crucial role in the interaction of darunavir with the enzyme.

Based on the darunavir structure, a series of novel disubstituted *bis*-THF containing HIV-1 protease inhibitors have been developed, which show very good activities against wild-type HIV-1 protease as well as a panel of multi-PI resistant mutant strains. In particular, PIs have been synthesised that show equivalent and greater activity for mutant strains compared to wild-type HIV-1 protease. The new ligands are derived from a selectively protected *bis*-THF diol scaffold, the synthesis of which has been developed in our group. Alongside the synthesis, a design rational, as well as results from biological testing and molecular modelling will be described.

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I DECLARATION OF AUTHORSHIP

I, KONRAD HOHLFELD, declare that the thesis entitled "DISUBSTITUTED *BIS*-THF MOIETIES AS NEW P2 LIGANDS IN NONPEPTIDAL HIV-1 PROTEASE INHIBITORS" and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

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III ABBREVIATIONS

AIBN	azobisisobutyronitrile
AIDS	acquired immunodeficiency syndrome
aq.	aqueous
CAN	ceric ammonium nitrate
cART	combined antiretroviral therapy
CI	chemical ionisation
CSA	camphorsulfonic acid
DAST	diethylaminosulfur trifluoride
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	*N*,*N'*-dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DIBAL	diisobutylaluminium hydride
DIC	*N*,*N'*-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DMF	*N*,*N*-dimethylformamide
DMBQ	2,6-dimethyl-1,4-benzoquinone
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DRV	darunavir
DSC	*N*,*N'*-disuccinimidyl carbonate
EC_{50}	half maximal effective concentration
EDCI	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride
EI/ESI	electron ionisation / electrospray ionisation
equiv	equivalents (abbreviated as eq in reaction schemes)
FDA	United States Food and Drug Administration
FC	fold change
HB(D)	hydrogen bond (donor)
HIV	human immunodeficiency virus
HOBt	1-Hydroxybenzotriazol
HPLC	high performance liquid chromatography
HWE	Horner-Wadsworth-Emmons reaction
Hz	Hertz

IC_{50}	half maximal inhibitory concentration
IR	infra red
KHMDS	potassium hexamethyldisilazide
LDA	lithium diisopropylamide
mCPBA	3-chloro-perbenzoic acid
MS	mass spectrometry or molecular sieves
NBS	*N*-bromosuccinimide
NFSI	*N*-fluorodibenzensulfonimide
NMO	*N*-methylmorpholine-*N*-oxide
NMR	nuclear magnetic resonance
(N)NRTI	(non)nucleoside reverse transcriptase inhibitor
NOE	nuclear Overhauser effect
PCC	pyridinium chlorochromate
Ph-pybox	2,6-Bis[(4*R*)-4-phenyl-2-oxazolinyl]pyridine
PI	protease inhibitor
PMB	*para*-methoxybenzyl
PNBA	*para*-nitrobenzoic acid
PNP	*para*-nitrophenyl
ppm	parts per million
PR	protease
PTSA	*para*-toluenesulfonic acid
RT	reverse transcriptase
sat.	saturated
SIV	simian immunodeficiency virus
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDPS	*tert*-butyldiphenylsilyl
TEPA	triethyl phosphonoacetate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl
TPSA	total polar surface area
TSA	transition state analogue

Chapter 1 INTRODUCTION

Acquired immunodeficiency syndrome (AIDS) is a degenerative disease of the immune system which is caused by the human immunodeficiency viruses (HIV). Although there has been a significant decrease in HIV incidence, worldwide an estimate of 33.3 million people are living with AIDS/HIV, of which the majority (22.5 million) are located in sub-Saharan Africa.[1] HIV primarily infects and kills $CD4^+$ T lymphocytes, which leads to a decreased immune response and leaves infected individuals susceptible to opportunistic infections and tumors.[2] The two known species of the human immunodeficiency virus (HIV-1 and HIV-2) belong to the genus lentivirus, which is a member of the retrovirus family. HIV-1 is more virulent, more infective than HIV-2 and causes the majority of HIV infections globally.[1] First described in 1983, HIV-1 is believed to originate from simian immunodeficiency virus found in chimpanzees (SIV_{cpz}), while the less common HIV-2 is related to a virus found in sooty mangabeys (SIV_{sm}).[3,4] HIV-1 is subdivided into several groups and subtypes, with group M representing the vast majority of HIV-1 strains.[5] There are distinctive differences in the global distribution of the various subtypes, e.g. subtype C, which accounts for approx. 50 % of all HIV-1 infections, is prevalent in sub-Saharan Africa and India, while subtype B is more predominant in Western Europe and North America.[6]

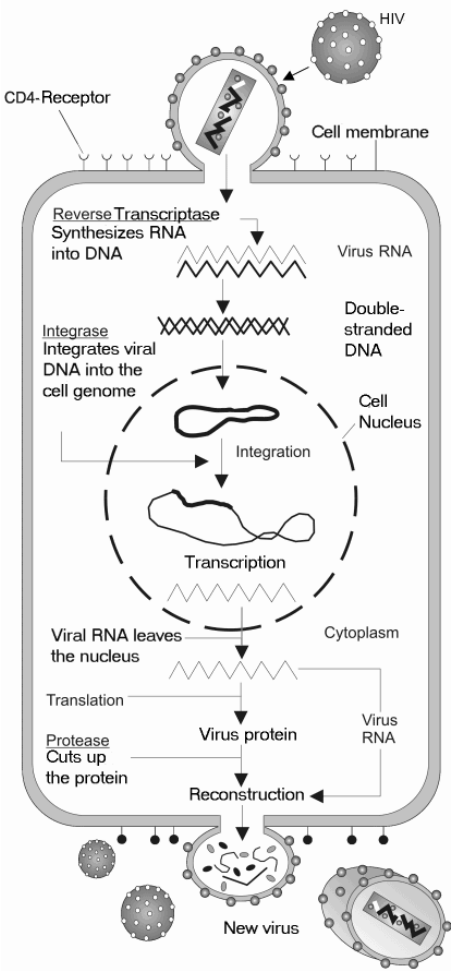


Figure 1-1. HIV life cycle.

Over 25 years of antiviral research yielded about 20 different compounds for the treatment of HIV-1 infection. These drugs affect various targets within the HIV replication cycle (Figure 1-1). Primary targets were the reverse transcription of the viral RNA into proviral DNA catalysed by reverse transcriptase (RT) and the proteolytic cleavage of the precursor polyproteins by a viral protease (PR).[7] In fact, there are two classes of reverse transcriptase inhibitors: nucleoside and non-nucleoside RT inhibitors (NRTI and NNRTI), which either interact with the catalytic site of

reverse transcriptase or an allosteric site in close proximity to the catalytic site. More recent target mechanisms include the integration of proviral DNA into the host cell genome (integrase inhibitors) and the virus-cell fusion (entry inhibitors).[8] These inhibitors interact either with proteins on the HIV surface (gp41 and gp120) or bind to receptor proteins on the $CD4^+$ cell (CCR5 or CXCR4). Anti-HIV drugs are administered in combination therapy, an approach also known as combined antiretroviral therapy (cART). Typical cART regimen comprise two NRTI and one NNRTI or one boosted protease inhibitor (PI).[9]

1.1 HIV-1 PROTEASE AND INHIBITION

HIV-1 contains, like other members of the lentivirus subfamily of retroviruses, three major genes (*gag*, *pol* and *env*).[10] During the viral replication, *gag* and *gag-pol* gene products are translated into precursor polyproteins. Further processing by a virally encoded protease (HIV-1 PR) will then provide structural proteins as well as important viral enzymes, including RT, protease and integrase.[11] HIV-1 PR recognizes the asymmetric shape of the substrate, rather than a defined amino acid sequence.[12] Indeed, all nine recognition sequences within the *gag-pol* polyproteins are different, but share a superimposable secondary structure (substrate "envelope"), which fits within the protease substrate-binding region.[13] However, some amino acid side chains protrude out of this "envelope", resulting in small differences that enable the protease to distinguish the different substrates. Presumably these small differences also contribute to the highly ordered cleavage process of the precursor polyproteins.[14,15]

HIV-1 protease (Figure 1-2, A) is a symmetric homodimer consisting of two 99 amino acid proteins and belongs to the family of aspartic acid proteases.[16] The active site is formed along the dimer interface and each monomer contributes one of the two catalytic aspartate residues (Asp25). The active site is covered by two flexible β-sheets (Lys43 to Arg57). Upon substrate binding, these flaps change their conformation to generate a hydrophobic environment.[17] The catalytic mechanism of HIV-1 PR is proposed to consist of two steps and proceeds via a tetrahedral intermediate, as shown in Figure 1-2.[18] Initial water attack on the peptide carbonyl leads to a metastable *gem-diol* tetrahedral intermediate, which is stabilized by a close hydrogen bonding network as observed in X-ray crystal structure studies.[19,20] Subsequent protonation of the amine group will result in the rapid break down to the C-terminal acid and the N-terminal amine.

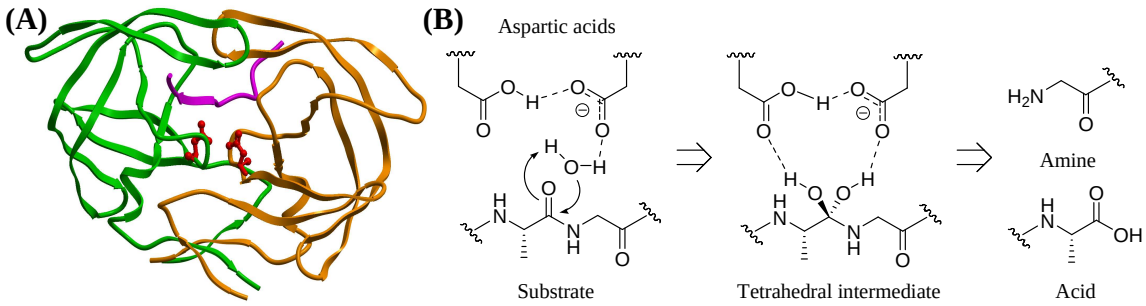
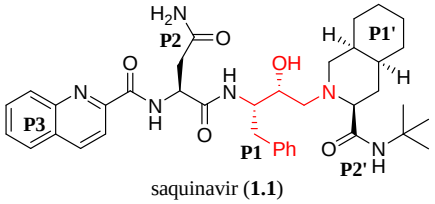


Figure 1-2. 3D structure of HIV-1 PR (**A**) and proposed mode of action (**B**).

Inhibition of HIV-1 protease will lead to the production of immature, non-infectious virus particles.[21] Competitive inhibition of aspartic acid proteases is usually achieved by the introduction of non-hydrolysable transition state analogues (TSA) into the substrates, a concept which was first applied to the design of HIV-1 PIs by Dreyer *et al.*[22] Common transition state mimics include hydroxyethylene, hydroxyethylamine and statine-like isosteres as well as phosphinates and α-fluoroketones. Based on the actual *pol* cleavage site, a five amino acid sequence within the *gag-pol* polyprotein, and the hydroxyethylamine TSA, researchers at Hoffman-LaRoche developed the first approved PI saquinavir (**1.1**, Figure 1-4), by sequentially optimising the ligands for different subsites (residues to the left of the cleavage site are referred to as P1, P2, P3 etc., whilst ligands to the right are designated as P1´, P2´, P3´, etc).[23] A phenylalanyl mimic as P1 and a large amine like decahydroisoquinoline as P1´ were the preferred ligands in the first two hydrophobic subsites. Although being also primarily hydrophobic, the S2 and S2´ subsites can accommodate hydrophilic ligands. An asparagine residue and a *tert*-butyl-carboxamide were found to be optimum for these two positions. The distal subsites are less well defined, a 2-quinoline carboxylic acid was used as P3 ligand in saquinavir.[23]



saquinavir (**1.1**)

Figure 1-3. Structure of the first approved PI.

Nine other PIs (**1.2** to **1.10**, Figure 1-3) have also been approved by the FDA for the treatment of AIDS in combination with RTIs.[24] However, only four out of the ten are currently recommended for initial treatment, these include atazanavir (**1.5**), lopinavir (**1.6**), fosamprenavir (**1.9**) and darunavir (**1.10**).[9] All of these PIs are co-administered or

co-formulated with ritonavir (**1.2**), which is a strong inhibitor of cytochrome P450 mediated metabolism and therefore serves as a pharmacokinetic booster for the other PIs.[25]

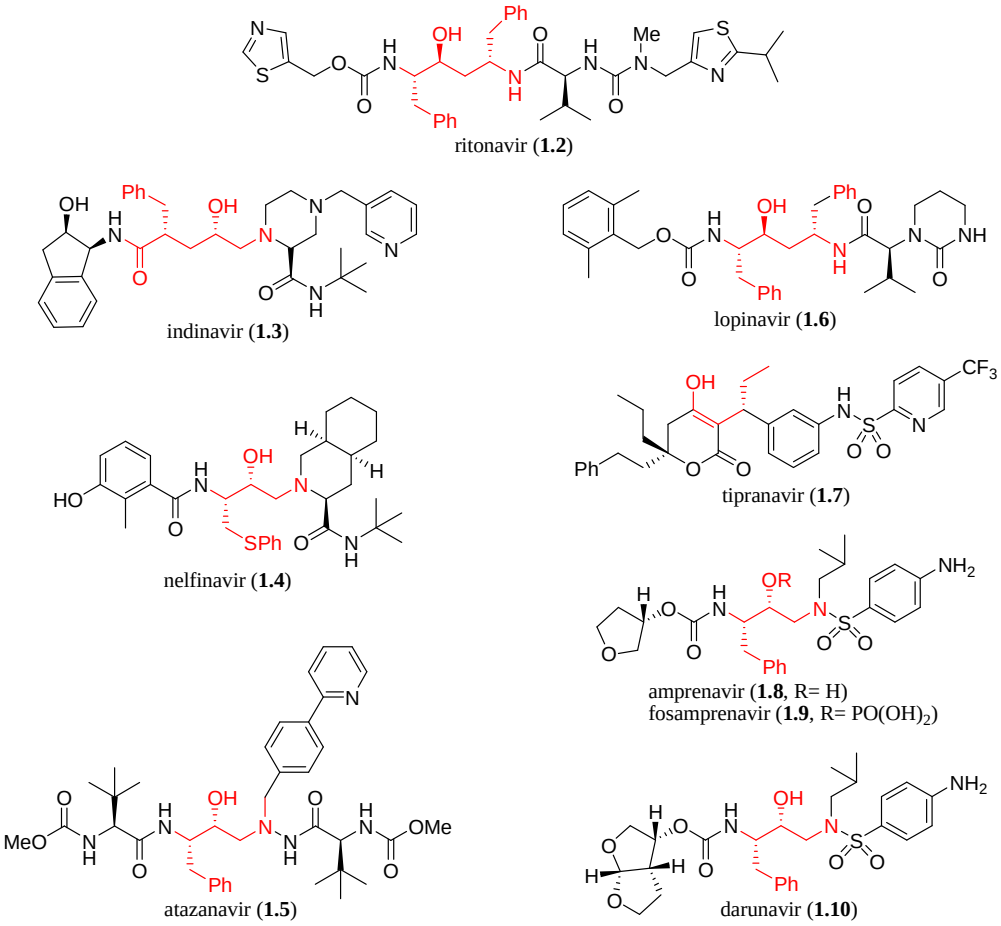


Figure 1-4. FDA-approved HIV protease inhibitors (TSA are highlighted in red).

Although cART treatment significantly reduced HIV-1 mortality and morbidity in industrialized countries, several drawbacks still complicate the PI therapies. High replication rates, the lack of proofreading capacity of the HIV-1 RT and therapeutic pressure produce mutant strains that are resistant to one or more PIs.[26,27] Other limitations arise from the "peptide-like" character of many early PIs, which results in higher therapeutic doses due to poor oral bioavailability, and considerable side effects, including peripheral lipodystrophy, dyslipidemia or insulin resistance as well as drug-induced hepatitis.[9] Subsequent research has focussed on a structure-based design of non-peptidal PIs that are potent against resistant strains. A major breakthrough was the development of a stereochemically defined fused *bis*-tetrahydrofuran (*bis*-THF) moiety as a high-affinity P2-ligand by the group of Arun K. Ghosh.[28] Further development and structural refinement led to the selection of darunavir, which will be discussed in detail in the next section.

1.2 DARUNAVIR, A CONCEPTUALLY NEW HIV-1 PROTEASE INHIBITOR

1.2.1 Development and Properties of Darunavir

Structural analysis has shown that the conformation of the protein backbone in the active site of mutant proteases basically remains unaltered. Based on the presumption that inhibitors with extensive hydrogen-bonding interactions to the protein backbone in wild-type protease will retain its activity in mutants, Ghosh and co-workers developed a series of non-peptidal high-affinity P2 ligands.[29] A key element was the replacement of peptide bonds with conformationally constrained cyclic or heterocyclic moieties to mimic the biological mode of action by retaining important interactions in the active site. In particular, they replaced the asparagine side chain and the P_3 ligand in saquinavir with various bicyclic ethers.[30] Protease inhibitor **1.11**, containing a stereochemically defined (3*R*,3a*S*,6a*R*)-*bis*-THF moiety (Figure 1-5), was identified as the most potent analogue (IC_{50} = 1.8 nM). As shown by X-ray crystal structure analysis, both ring oxygens are involved in effective hydrogen-bonding interactions with the backbone NH of Asp 29 and Asp 30 present in the S2 subsite. Thereby they provide additional binding energy to offset the loss of P_3-hydrophobic binding of the quinoline ring.[30] Based on the promising clinical trials on amprenavir (**1.8**), subsequent incorporation of the novel *bis*-THF moiety into a (*R*)-(hydroxyethyl)-sulfonamide based isostere led to the development of TMC-114 (**1.10**) and TMC-126 (**1.12**).[31]

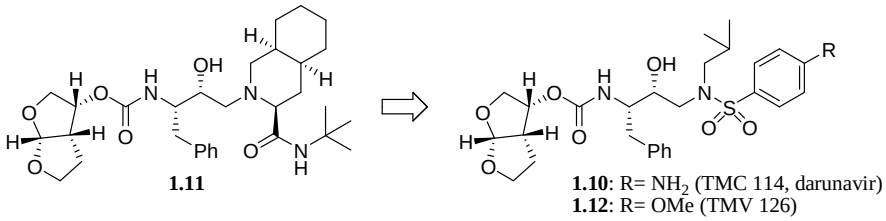


Figure 1-5. Development of PIs **1.10** to **1.12**.

PI **1.10** was found to be slightly less potent than PI **1.12** (EC_{50} = 4.5 nM and 1.4 nM), but the P2´-amine group provided more favourable pharmacokinetic properties in comparison to the *para*-methoxy substitution. Subsequently, TMC-114 was selected for clinical development at TIBOTEC and renamed darunavir, in honour of Arun K. Ghosh.[32] In June 2006, the FDA granted approval to DRV, which still remains the most recent HIV-1 PI to date. Darunavir has proven to be highly effective against a broad spectrum of multi-PI resistant HIV mutant strains.[33] In a panel of 1,501 PI-resistant clinical isolates, 75 % could be inhibited by DRV at low nanomolar concentrations (EC_{50} <10 nM).[34] Darunavir also

successfully inhibits protease dimerisation at higher concentrations (~ 0.1 µM), but fails to dissociate dimerised PR. This suggests that **1.10** can bind to the monomeric precursor and consequently causes the disruption of HIV-1 PR dimerisation.[35] Several X-ray crystal structure studies of DRV-bound HIV-1 protease have revealed an extensive network of ligand-protein hydrogen bonding interactions involving the enzyme backbone.[36,37] The inhibitor binds to the active site cavity of HIV-1 PR in two distinct conformations, which are related by a 180° rotation around the central C−O bond and have a relative occupancy of 60/40. The major conform-ation is shown in Figure 1-5. A second binding site was identified on the flap surface.[37]

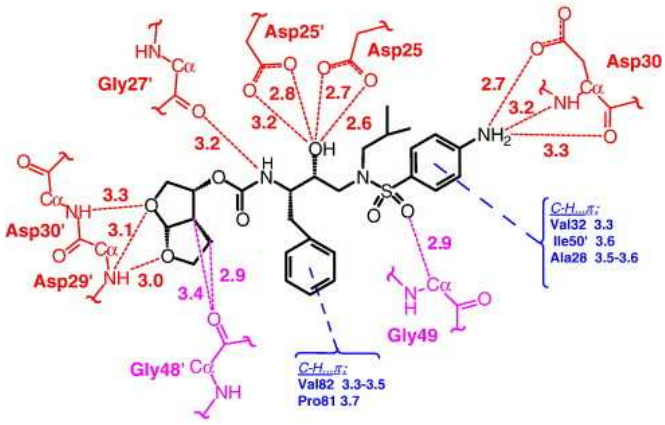
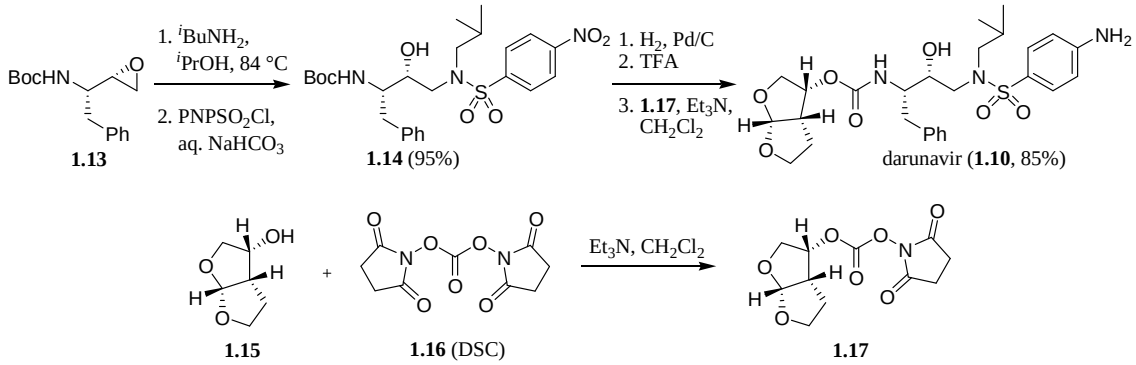


Figure 1-6. Hydrogen bond, C-H···O and C-H·π interactions of **1.10** in the active site of wild-type HIV-1 protease (picture taken from Ref.37).

Darunavir forms various interactions to the active site of the enzyme, including strong hydrogen bonds (HB, shown in red), weaker C-H···O and C-H··π contacts (magenta and blue), as well as weak van der Waals interactions (not shown). The central hydroxy group forms strong HB to the side-chains of the catalytic aspartate residues (Asp 25 and Asp25'). As already identified in the X-ray crystal structure of PI **1.11**, the two ring-oxygens interact with the backbone NH of residues Arg29' and Arg30'. In the S2' subsite the aniline substituent forms similar hydrogen bonds to the backbone and the side chain of Arg30. Further HB contacts were identified between the carbamate moiety and the backbone carbonyl of Gly27'. Weaker C-H···O interactions are formed between the *bis*-THF ligand and Gly48' as well as the C_α of Gly49 and the sulfonamide oxygen.

1.2.2 The Synthesis of Darunavir

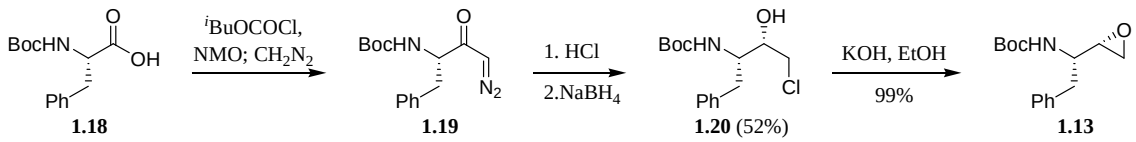
Several convergent synthesis of darunavir have been described.[38] Key-intermediates for the final synthesis of darunavir (**1.10**) are the protected chiral epoxide **1.13** and *bis*-THF alcohol **1.15** (Scheme 1-1).[39]



Scheme 1-1. Synthesis of darunavir (**1.10**).

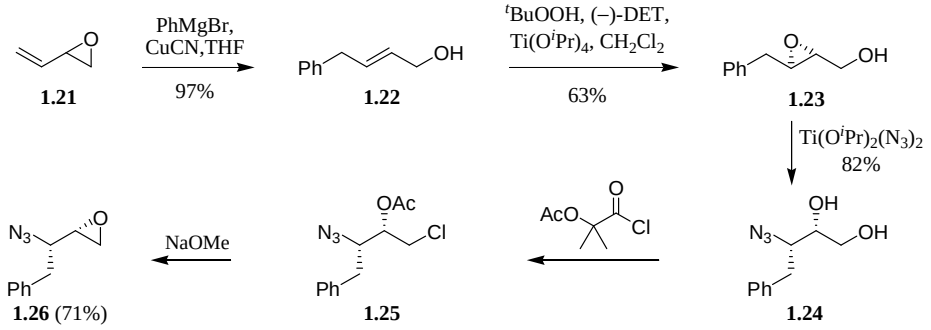
The hydroxyethylsulfonamide isostere was generated from epoxide **1.13**. Initial treatment with isobutyl amine in refluxing isopropanol and subsequent reaction with *para*-nitrophenylsulfonyl chloride (PNPSO$_2$Cl) afforded the intermediate **1.14** in 95 % yield. Sulfonamide **1.14** is converted to darunavir (**1.10**) in a final three-step sequence: (1) Pd-catalysed reduction of the aromatic nitro group; (2) trifluoroacetic acid (TFA) mediated removal of the Boc group and (3) coupling of the intermediate primary amine to the activated mixed carbonate **1.17**, which was derived from *bis*-THF alcohol **1.15** and *N,N'*-disuccinimidyl carbonate (DSC, **1.16**).[39,40]

Epoxide **1.13** is now commercially available, but can also be conveniently synthesised in four steps from Boc-protected phenylalanine (**1.18**, Scheme 1-2).[41] Activation of amino acid **1.18** with isobutyl chloroformate was followed by addition of diazomethane to generate diazoketone **1.19**. Reaction with HCl to form the chloroketone and reduction with NaBH$_4$ provided alcohol **1.20** in 52% yield from **1.18**. Treatment of **1.20** with alcoholic KOH yielded the desired epoxide **1.13**.



Scheme 1-2. Synthesis of epoxide **1.13** from **1.18**.

Alternatively, an asymmetric synthesis from butadiene monoxide (**1.21**) has been reported (Scheme 1-3).[42] Copper(I)-mediated 1,4-addition of PhMgBr to epoxide **1.21** afforded allylic alcohol **1.22**. Subsequent Sharpless epoxidation with (−)-diethyl D-tartrate (DET) gave epoxide **1.23**, which was converted to azidodiol **1.24** via regioselective ring opening with diisopropoxytitanium diazide. Chloro-acetylation of diol **1.24** to azidoester **1.25** was followed by exposure to sodium methoxide to yield epoxide **1.26**.



Scheme 1-3. Synthesis of epoxide **1.26**.

The synthesis of the bis-THF alcohol **1.15** will be discussed in detail in section 1.3.

1.2.3 Further Developments from Darunavir

Since the structure of the *bis*-THF ligand is very significant for the superior resistance profile of darunavir, further research on DRV analogues mainly focussed on alterations around the P1'/P2' sulfonamide[43-46] as well as the P1 phenyl group.[47-49] Two interesting clinical analogues are shown in Figure 1-7.

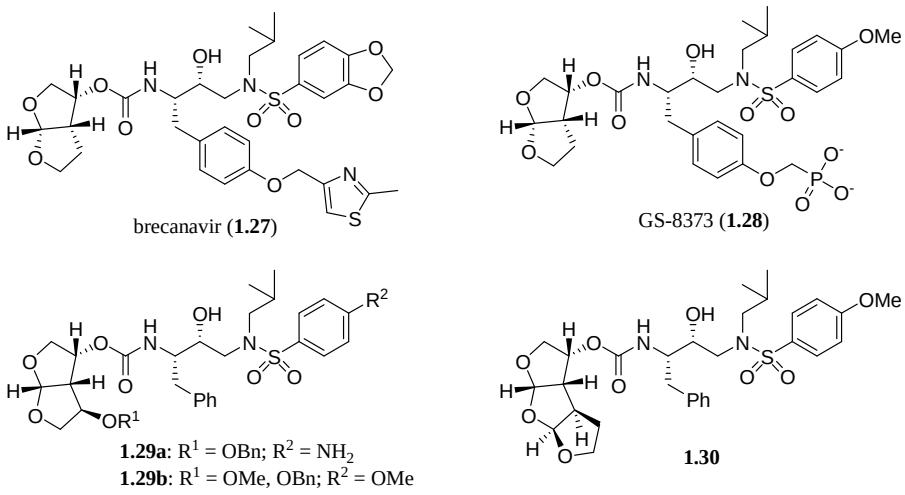


Figure 1-7. Structure of four experimental PIs (**1.27** to **1.30**).

Brecanavir (**1.27**) was developed by GLAXOSMITHKLINE and VERTEX and showed very good activity against wild-type HIV-1 as well as various mutant strains.[48] It incorporates a 1,3-benzodioxole P2' group, which can form additional water-mediated interactions with the flap residue Gly48 of the second monomer,[50] and a thiazoylmethyl ether as additional substitution on the P1 phenyl group. Although **1.27** entered phase II trials, the development was discontinued due to insurmountable formulation issues.

Based on the assumption that metabolically labile PI prodrug, which is converted inside the cell to a charged metabolite with reduced membrane permeability, would exhibit a prolonged antiviral effect, Lee *et al.* developed a series of phosphonate substituted PIs including GS-8373 (**1.28**).[49] These analogues showed good activity against the wild-type virus and virtually unchanged or even improved potency against various multi-PI resistant isolates. The phosphonic acid residue in GS-8373 is positioned at the open end of an hydrophobic channel and is exposed to the solvent with no observable effects on the active site. This "solvent-anchoring" apparently allows a better adaptation of the PI to the larger volume of the mutant binding cavity, resulting in an enhanced resistance profile.[49]

In 2006, our group published the synthesis of the C4-benzyloxlated DRV-analogue **1.29a** based on a disubstituted bis-THF scaffold.[51,52] Ghosh *et al.* also reported the incorporation of various bicyclic ring systems into the darunavir scaffold.[53,54] However, further substitutions on the *bis*-THF moiety have only been reported very recently. In particular, the synthesis of the C4-alkoxylated analogues **1.29b**[55] and the highly active *tris*-THF containing PI **1.30** (EC_{50} = 1.8 nM)[56] have been disclosed.

1.3 BIS-TETRAHYDROFURAN, A PRIVILEGED LIGAND FOR NEW PIS

The *cis*-fused *bis*-THF or 2,8-dioxabicyclo[3.3.0]octane ring system (also called hexahydrofuro-[2,3*b*]furan) can be found in a limited number of biologically active natural products including communiol D (**1.31**)[57], dihydroclerodin (**1.32**),[58] rhyacophiline (**1.33**)[59] or the ATPase inhibitor asteltoxin (**1.34**, Figure 1-8).[60]

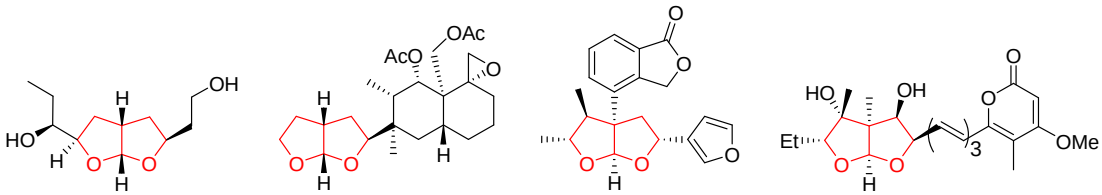
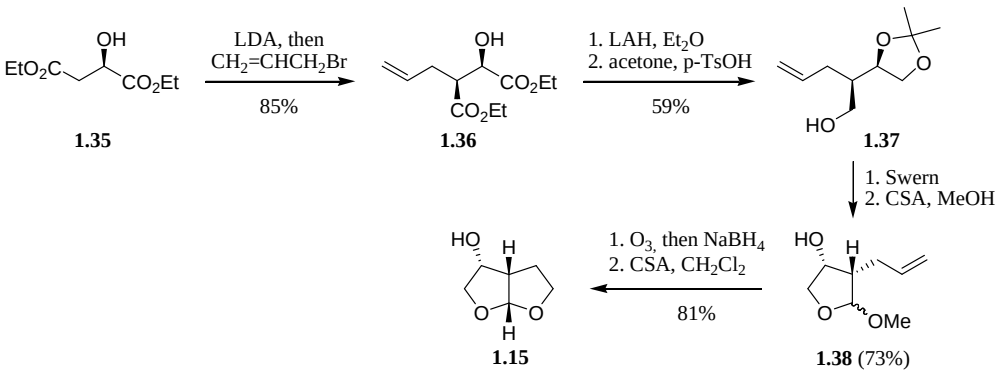


Figure 1-8. *Bis*-THF containing natural products (*cis* fused *bis*-THF moiety is highlighted in red).

Since the first reported synthesis of bis-THF alcohol **1.15** by *Ghosh et al.*[28] in 1994, several other routes to **1.15** have been completed following one of three major strategies: (1) substrate-controlled syntheses from chiral pool materials like (3*R*)-malate[28] or glyceraldehyde derivatives;[39,55,61] (2) racemic formation of the bis-THF alcohol, followed by enzymatic resolution;[62,63] (3) diastereoselective syntheses utilizing chiral auxiliaries.[64-66]

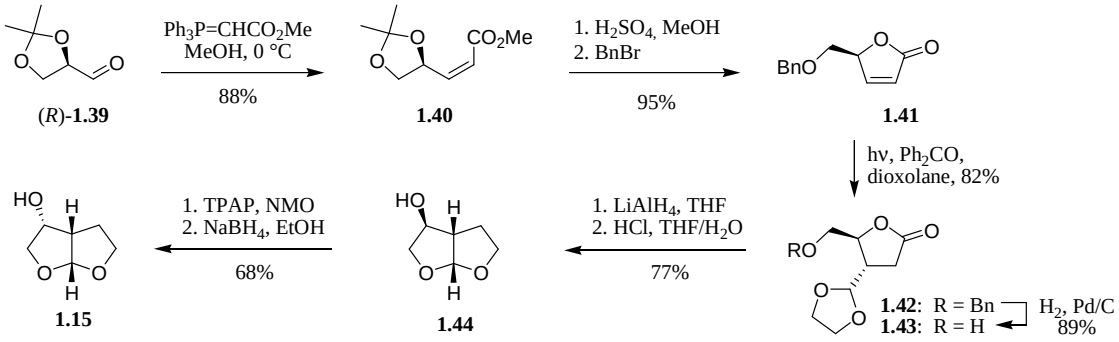
1.3.1 Syntheses of *bis*-THF alcohol 1.15 from chiral pool materials

The first enantioselective procedure afforded *bis*-THF alcohol **1.15** in 30 % overall yield (Scheme 1-4). Diastereoselective α-alkylation of (2*R*)-diethyl malate (**1.35**) with allyl bromide yielded ester **1.36**, which was reduced and protected to give primary alcohol **1.37**. Subsequent oxidation and camphorsulfonic acid (CSA) mediated cyclisation afforded methyl acetal **1.38** that was converted to *bis*-THF **1.15** in two final steps.



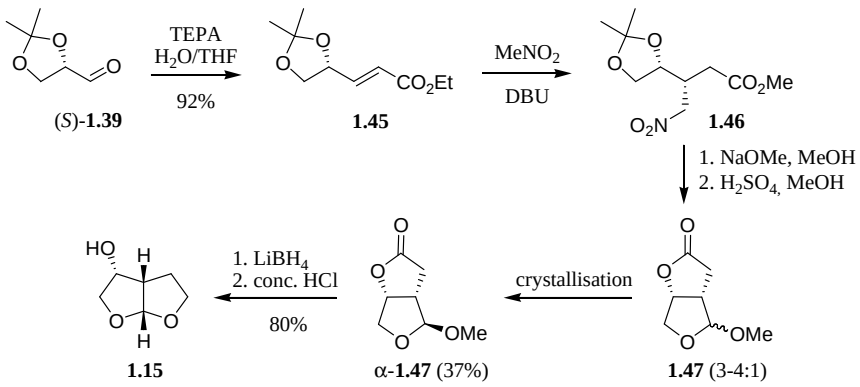
Scheme 1-4. Enantioselective synthesis of *bis*-THF alcohol **1.15** from (2*R*)-diethyl malate.

An enantioselective synthesis utilizing protected D-glyceraldehyde (*R*)-**1.39** was also published by Ghosh and co-workers in 2004 (Scheme 1-5).[39] Wittig reaction of (*R*)-**1.39** afforded a separable mixture of olefins with the desired *Z*-alkene **1.40** as major product. Treatment of **1.40** with catalytic amounts of conc. H_2SO_4 and protection of the primary alcohol furnished intermediate **1.41**. The key step was a stereoselective photochemical addition of 1,3-dioxolane, yielding acetal **1.42** in 82% (dr 96:4), and subsequent dibenzylation gave alcohol **1.43**, which was reduced to the corresponding lactol. Acid-catalysed cyclisation afforded the epimeric alcohol **1.44**, which was inverted to *bis*-THF **1.15**.



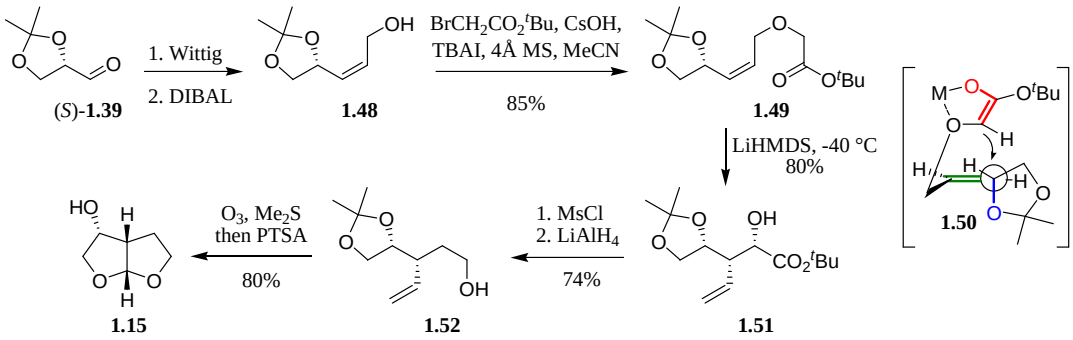
Scheme 1-5. Synthesis of **1.15** via photochemical dioxolane addition.

Quaedflieg *et al.* reported a different approach from the corresponding protected L-glyceraldehyde, which was found to be reliable on a multi-100 kg scale for the synthesis of darunavir (Scheme 1-6).[61] Aldehyde (*S*)-**1.39** was readily converted to enoate **1.45** by a Horner-Wadsworth-Emmons (HWE) reaction using triethyl phosphonoacetate (TEPA). A subsequent Michael addition with nitromethane to **1.46** was followed by a Nef-reaction[67] to an intermediate aldehyde, which cyclised to lactone acetal **1.47** as a mixture of two diastereoisomers. Purification by crystallisation afforded the desired lactone α-**1.47**, which was reduced with $LiBH_4$ and treated with conc. HCl to give **1.15** in 34% overall yield.



Scheme 1-6. Synthesis of bis-THF alcohol 1.15 from protected L-glyceraldehyde.

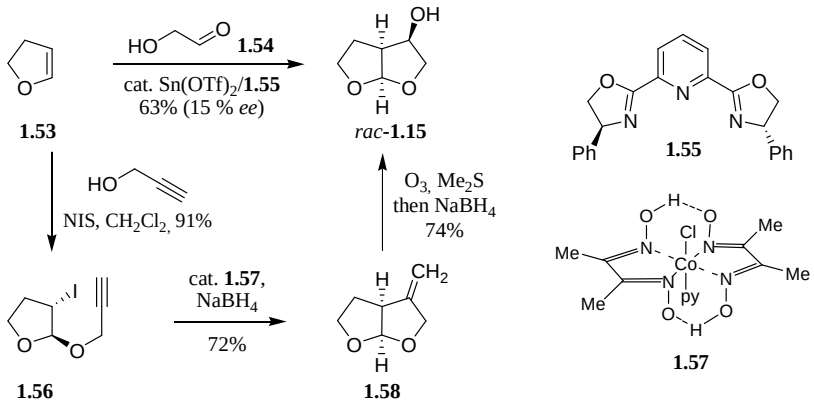
A second approach from aldehyde (*S*)-**1.39** was recently disclosed by Ghosh *et al.* (Scheme 1-7).[55] Wittig reaction of (*S*)-**1.39** and subsequent DIBAL reduction afforded allylic alcohol **1.48**, which was alkylated with *tert*-butyl bromoacetate in the presence of CsOH and tetrabutylammonium iodide (TBAI). A [2,3]-sigmatropic rearrangement of ether **1.49** at −40 °C provided the desired alcohol **1.51** as single isomer in 80% yield. The stereochemical outcome can be explained by the reactive conformation **1.50**, in which the allylic C−O bond (blue) is orthogonal to the allylic C=C (green) and antiperiplanar to the attacking enolate (red). Mesylation and reduction of **1.51** led to alcohol **1.52** that was readily converted to **1.15** via ozonolysis and acid-catalysed cyclisation.



Scheme 1-7. [2,3]-sigmatropic rearrangement pathway to **1.15**.

1.3.2 Racemic approaches to *bis*-THF alcohol 1.15

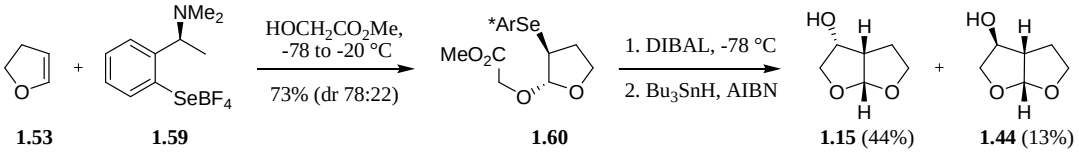
Both racemic syntheses start from 2,3-dihydrofuran (**1.53**, Scheme 1-8). Xie *et al.* reported a one-pot synthesis from **1.53** and glycolaldehyde (**1.54**) inducing diastereoselectivity with the chiral catalyst [Sn((*S*,*S*)-Ph-pybox)]OTf to furnish *rac*-**1.15** in 63% yield (dr 93:7, 15 % *ee* for major product).[62] The catalyst was formed *in situ* from $Sn(OTf)_2$ and bisoxazoline **1.55**. In the earlier approach, ether **1.56** underwent a cobaloxime (**1.57**) mediated radical cyclisation to alkene **1.58**, which was then converted to *rac*-**1.15** via ozonolysis and subsequent reduction.[63] Optical resolution of the racemic alcohol was achieved in both cases by enzymatic acylation or deacylation.



Scheme 1-8. Two racemic approaches to **1.15**.

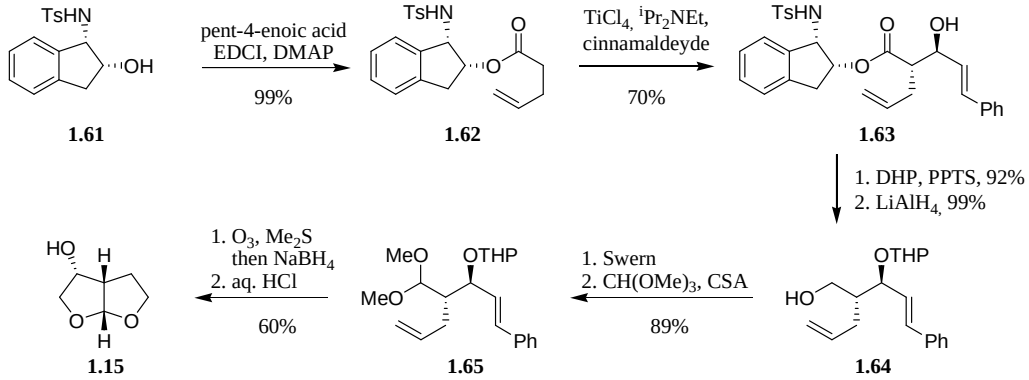
1.3.3 Syntheses of 1.15 utilizing chiral auxiliaries

Uchiyama *et al.* achieved the synthesis of **1.15** via oxyselenylation of 2,3-dihydrofuran (Scheme 1-9).[64] The *in situ* generated chiral selenium salt **1.59** was reacted with methyl glycolate and dihydrofuran **1.53** to form the *anti*-adduct **1.60** in 73 % yield (dr 78:22). Reduction of the ester to the corresponding aldehyde was followed by radical cyclisation with Bu_3SnH and AIBN to afford a mixture of the enantioenriched alcohols **1.15** and **1.44**. Epimer **1.44** was readily converted to **1.15** in two steps (see Scheme 1-5). Optical resolution with (*R*)-1-(1-naphthyl)-ethyl isocyanate afforded the separable diastereomeric carbamates, which were treated with $LiAlH_4$ to provide the enantiopure *bis*-THF alcohols.



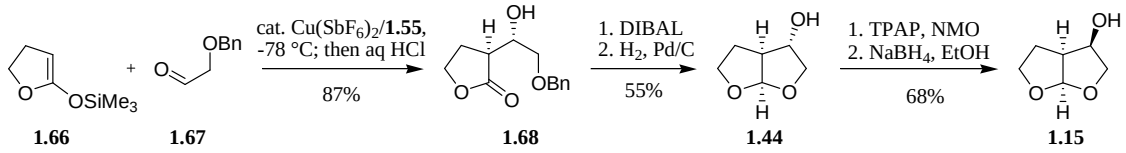
Scheme 1-9. Synthesis of **1.15** via oxyselenylation of **1.53**.

Ghosh *et al.* also reported a highly diastereoselective *anti*-aldol reaction utilising tosylamidoindanol as a chiral auxiliary (Scheme 1-10).[65] Acylation of indanol **1.61** with pent-4-enoic acid yielded ester **1.62,** which was treated with $TiCl_4$ and *N*,*N*-diisopropylethylamine to form the corresponding enolate. Addition to cinnamaldehyde furnished *anti*-aldol product **1.63**. Protection of the secondary alcohol as THP-ether, and removal of the chiral auxiliary via reduction with $LiAlH_4$ afforded alcohol **1.64**, which was subsequently transformed to acetal **1.65**. Ozonolysis of the double bonds, reduction of the aldehydes to the corresponding primary alcohols and acid-catalysed cyclisation finally furnished the desired *bis*-THF ligand **1.15** in 34% yield.



Scheme 1-10. *Anti*-aldol approach to **1.15**.

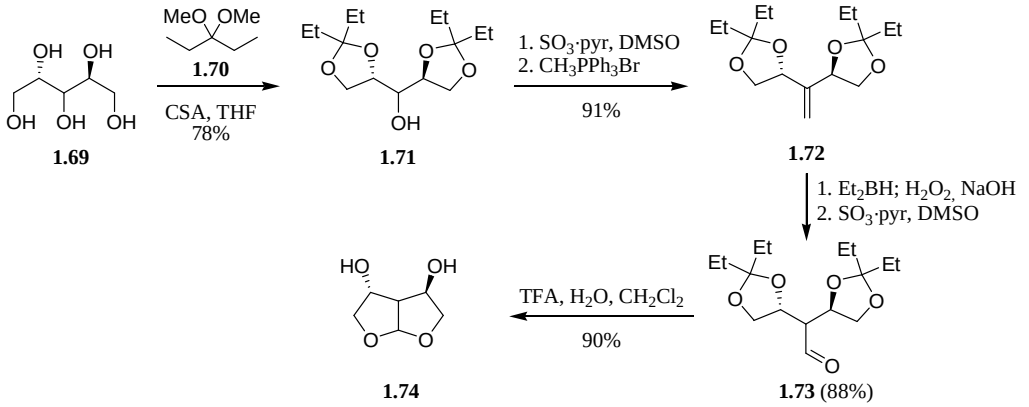
Xie *et al.* published a highly diastereo- and enantioselective Mukaiyama aldol reaction of silyl enol ether **1.66** and (benzyloxy)acetaldehyde **1.67** (Scheme 1-11).[66] Catalysis with 5 mol% of the chiral catalyst [Cu((*S*,*S*)-Ph-pybox)]$(SbF_6)_2$, preformed from $Cu(SbF_6)_2$ and bisoxazolidine **1.55**, and hydrolysis of the trimethylsilyl ether intermediate afforded alcohol **1.68** in 87 % yield (dr 98:2, 94 % *ee* for major product). Reduction to the lactol and debenzylation afforded epimeric alcohol **1.44**, which again was converted to *bis*-THF alcohol **1.15** as described earlier.



Scheme 1-11. Formation of **1.15** via Mukaiyama aldol reaction.

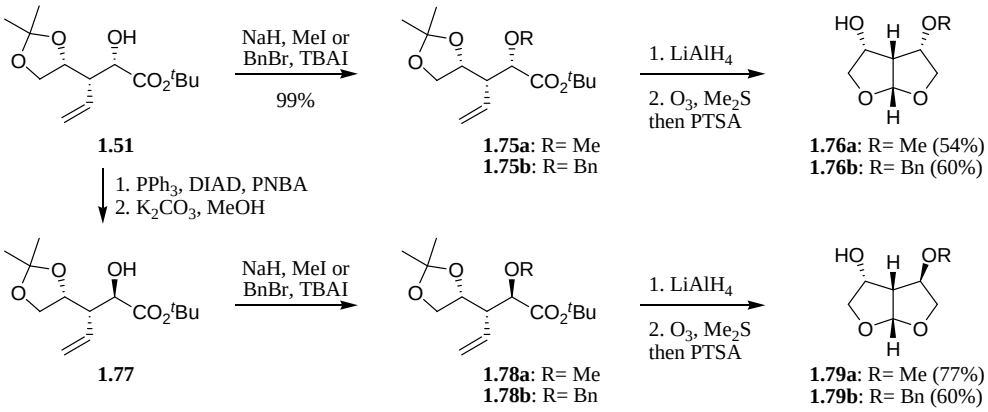
1.3.4 Synthesis of disubstituted bis-THF analogues

All the syntheses described above yield a mono-functionalised *bis*-THF. However, additional functionalities with hydrogen bonding ability could enhance the potency of the ligand by forming additional interactions with the active site. Linclau *et al.* developed a synthesis of chiral disubstituted *bis*-THF *bis*-diol **1.74** from natural sugar alcohol L-arabitol (**1.69**, Scheme 1-12).[68] Selective protection of **1.69** under kinetic conditions to diacetal **1.71** was achieved with 3,3-dimethoxypentane **1.70** in the presence of CSA. Parikh-Döring oxidation[69] of alcohol **1.71** to the corresponding ketone and subsequent Wittig reaction afforded alkene **1.72** in excellent yield.[70,71] Hydroboration of **1.72** with Et_2BH, formed *in situ* from metathesis reaction with Et_3B and BH_3,[72] was followed by a second Parikh-Döring oxidation to yield aldehyde **1.73**. Finally, a TFA-catalysed cyclisation furnished diol **1.74**.



Scheme 1-12. Synthesis of *bis*-THF diol **1.74** from L-arabitol (**1.69**).

Ghosh also reported the synthesis of 4,6-disubstituted *bis*-THF analogues.[55] Direct functionalisation of alcohol **1.51** to ethers **1.75** was followed by subsequent ester reduction, ozonolysis and acid-catalysed cyclisation to afford the disubstituted *bis*-THF **1.76** (Scheme 1-13). On the other hand, Mitsunobu inversion[73] of **1.51**, followed by hydrolysis of the intermediate ester led to diastereomeric alcohol **1.77**, which was functionalised to **1.78** and converted to the corresponding diastereomeric *bis*-THF ethers **1.79** as described above.

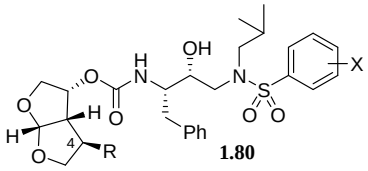


Scheme 1-13. Synthesis of functionalised diols **1.76** and **1.79** from **1.51**.

Although alcohols **1.51** and **1.77** allow access to disubstituted bis-THF analogues, the possible substitutions are limited due to the subsequent chemistry. Hence, diol **1.74** remains as the more versatile scaffold for the synthesis of further disubstituted analogues. In theory, alcohol **1.77** could also be converted to diol **1.74**, whilst **1.51** would lead to a *meso*-diol with two indistinguishable hydroxy groups.

1.4 PROJECT AIM

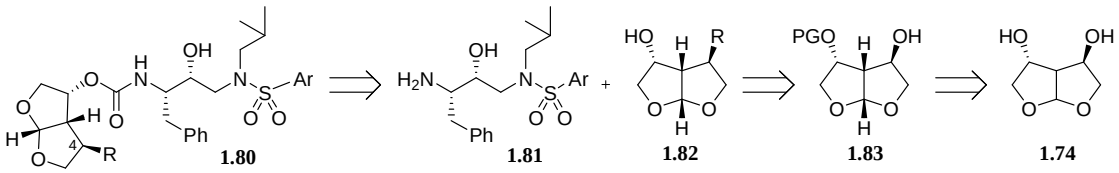
Our studies of the X-ray crystal structure of HIV-1 protease in complex with DRV and several recognition sequences suggested that additional substituents on the C4-position of the *bis*-THF moiety could lead to additional interactions of the PI with the enzyme backbone. In collaboration with TIBOTEC a series of hydroxy and benzyloxy substituted DRV-analogues based on diol **1.74** had been generated (Figure 1-9).[51,52] The activity of the hydroxy PIs (**1.80a-d**) against wild-type HIV-1 was strongly dependent on the P2' sulfonamide substituent, while benzylated analogue **1.80e** showed a low nanomolar activity. The X-ray crystal structure of **1.80a** revealed a water mediated hydrogen bonding interaction to the backbone NH of Gly48.



a: R = OH, X = 4-NH_2 (EC_{50} = 772.9 nM)
b: R = OH, X = 4-OMe (EC_{50} = 6.5 nM)
c: R = OH, X = 4-Br (EC_{50} = 4.8 nM)
d: R = OH, X = 3,4-OCH_2O (EC_{50} = 24.8 nM)
e: R = OBn, X = 4-NH_2 (EC_{50} = 1.5 nM)

Figure 1-9. Structure and activity of PIs synthesised in collaboration with TIBOTEC.

The synthesis of these disubstituted analogues was achieved by DSC-mediated coupling of amine **1.81** and derivatised *bis*-THF alcohol **1.82** (Scheme 1-14). The disubstituted *bis*-THF **1.82** was synthesised from diol **1.74** via the *endo*-protected species **1.83**.



Scheme 1-14. Retrosynthetic approach to C4-substitued bis-THF ligands.

The aim of this project was the synthesis of a variety of *bis*-THF derivatives starting from the *endo*-protected species **1.83**. These new ligands were coupled to various amines scaffolds. The final PIs **1.80** were tested for their antiviral activity on wild-type HIV-1 and several mutant strains. Following the previous results, *bis*-THF analogues with additional hydrogen bonding capacity were of particular interest. Initial focus was placed on the synthesis of 4-*exo*-amino analogues and further 4-*exo*-oxy derivatives (Figure 1-10).

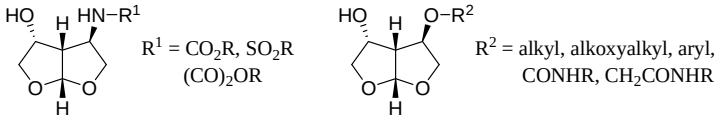


Figure 1-10. Targeted exo-amino and exo-oxy analogues.

Chapter 2 CRYSTAL STRUCTURE ANALYSIS

HIV-1 protease is one of the best studied enzymes with over 220 X-ray crystal structures available in the protein data bank (PDB). Among these, 25 crystal structures show the HIV-1 protease in complex with darunavir. Our analysis and modelling was based on an ultra-high resolution crystal structure with a resolution of 0.84 Å, published by Weber *et al.* in 2006 (PDB: 2HS1).[37] Figure 2-1 shows the interactions of the bis-THF ligand of DRV (**A**) and its hydroxy analogue (**B**) with the HIV-1 PR binding pocket.

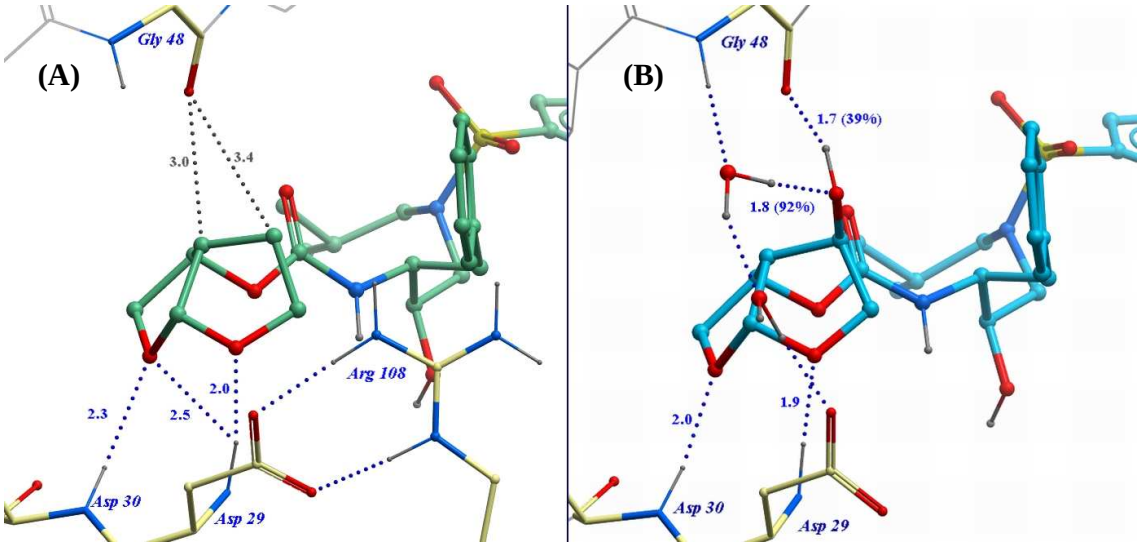


Figure 2-1. 3D depictions of the binding mode of the *bis*-THF moiety in DRV (**A**) and its C4-hydroxy analogue (**B**)

As already described above (1.2.1), the two *bis*-THF ring-oxygens in DRV form strong hydrogen bonding interactions with the backbone NH of residues Asp29 and Asp30. In addition, two weaker C-H···O contacts between the second THF ring and the backbone carbonyl of Gly48 have been identified. Figure 2-1B shows the modelled interactions of the hydroxy PI **1.81a** based on the 2HS1 coordinates. Again, two N-H···O hydrogen bonds between Asp29/30 and the *bis*-THF ligand are present. The C-H···O interactions to Gly48 have now been replaced by a HB from the hydroxy group. Interestingly, the OH also forms a HB to a water network that connects the side chain of Asp29 with the backbone NH of Gly48. In addition to the bonding distances a percentage score is given indicating the likeliness of a hydrogen bond based on statistical analysis as described by Clark and Labute.[74] Although being slightly longer, the water-mediated interaction to the Gly48 (NH) has a better orientation, resulting in an 92% optimal hydrogen bond, while the direct contact

to Gly48 (CO) is only 39% optimal according to Clarke/Labute.[74] As the Gly48 residue is positioned above the *bis*-THF moiety, it is obvious that only an *exo*-substitution at the C4-position is sensible. An *endo*-substituent would point towards the carbamate of the PI and probably not undergo any interactions with the enzyme.

Interactions with Gly48 and/or Gly48' are also known from the natural recognition sequences of HIV-1 protease. A general overview over the hydrogen bonding interactions in the cleavage site is given in Figure 2-2.

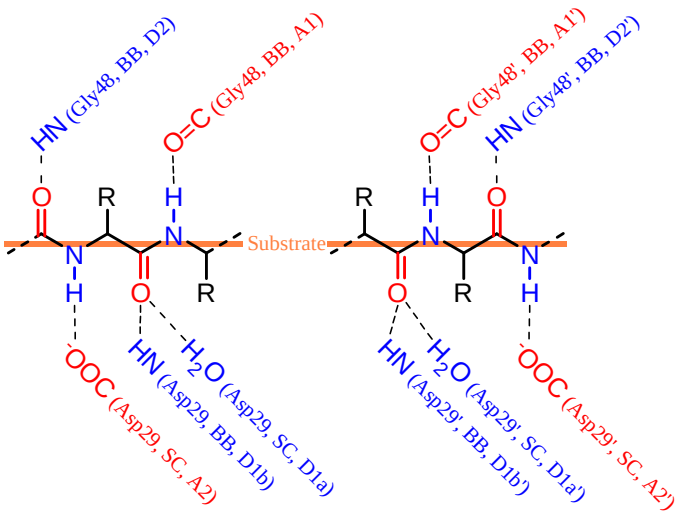


Figure 2-2. Hydrogen bonding substrate/enzyme interactions in cleavage site.

Hydrogen bonding between substrate and enzyme in the active site can be observed to Gly48 and Asp29 of each subunit. Gly48 can serve as HB acceptor (A1) and HB donor (D2) via its backbone (BB) carbonyl and NH group. On the other site, Asp29 can form two HB donor contacts, either directly from the backbone NH (D1b) or water-mediated via the side chain residue (SC, D1a). The aspartate side chain also serves as a direct HB acceptor (A2). But there are no interactions between the substrate and the backbone carbonyl of Asp29, as this points away from the active site. In Table 2-1, seven of the ten natural recognition sequences of HIV-1 protease and their HB interactions in the active site of the enzyme are shown. The actual cleavage site is highlighted in blue, while residues highlighted in red interact with the Gly48 or Gyl48' backbone. All of these hydrogen bonds are backbone-backbone interactions, due to the β strand conformation of the natural substrates.[13]

Table 2-1. Natural recognition sequences in *gag/pol* polyprotein and their HB interactions with the active site of HIV-1 protease.[a]

cleavage site[b]	P4	P3	P2	P1	P1'	P2'	P3'	P4'
MA-CA[c]	**Ser (D2)**	Gln (A2, D1)	**Asn (A1)**	**Tyr**	**Pro**	Ile (D1')	**Val (A1', D2')**	Gln
CA-p2[c]	**Ala (D2)**	Arg (A2, D1)	**Val (A1)**	**Leu**	**Ala**	Glu (D1')	**Ala (A1', D2')**	Met
p2-NC[c]	Ala	Thr (A2, D1)	**Ile (A1)**	**Met**	**Met**	Gln (D1')	**Arg (A1', D2')**	Gly
NC-p1[d]	**Arg (D2)**	Gln	Ala	**Asn**	**Phe**	Leu (D1', A2')	**Gly (A1', D2')**	Lys
p1-p6[c]	Pro	Gly (A1, D1)	**Asn (A1)**	**Phe**	**Leu**	Gln (D1')	**Ser (A1', D2')**	Arg (D1')
RT-RH[c]	**Ala (D2)**	Glu (A2, D1)	**Thr (A1)**	**Phe**	**Tyr**	Val (D1')	**Asp (A1', D2')**	Gly
RH-IN[c]	Arg	Lys (D1)	**Ile (A1)**	**Leu**	**Phe**	Leu (D1')	**Asp (A1', D2')**	Gly (D1')

[a] residues in blue indicate the actual cleavage site, while residues in red interact with Gly48 or Gly48'. [b] The cleavage sites are identified by the proteins released once the site is cleaved: matrix (MA), capsid (CA), mucleocapsid (NC), protease (PR), reverse transcriptase (RT), RNAase H (RH) and integrase (IN). [c] from Ref. 13. [d] from Ref. [75].

Out of the four possible hydrogen bonds to Gly48/Gly48', two (A1' and D2') are conserved throughout all seven recognition sequences, while HBs A1 and D2 can be found in at least four different substrates. The contacts A1' and D2' are formed at the interface between Gly48' and residue P3', each contributing one HB acceptor and one HB donor. Interaction A1 is usually formed between Gly48 (CO, BB) and residue P2 (NH, BB), while hydrogen bond D2 occurs between Gly48 (NH, BB) and residue P4 (CO, BB).

Since interactions of the substrates with Gly48 are prevalent and similar contacts have also been observed with DRV-based PIs, this project focussed on the development of new PIs with disubstituted *bis*-THF ligands, which could mimic these binding modes. In particular, it was envisaged to generate PIs with HB donor ability towards Gly48 (CO) or HB acceptor ability towards Gly48 (NH) or both. Also, a hydrophobic pocket below the flaps could serve as additional target for more lipophilic derivatives. Figure 2-3 shows DRV within the binding pocket of HIV-1 protease. Areas with HB donor/acceptor ability are coloured in blue and red, respectively, while hydrophobic regions are highlighted in green.

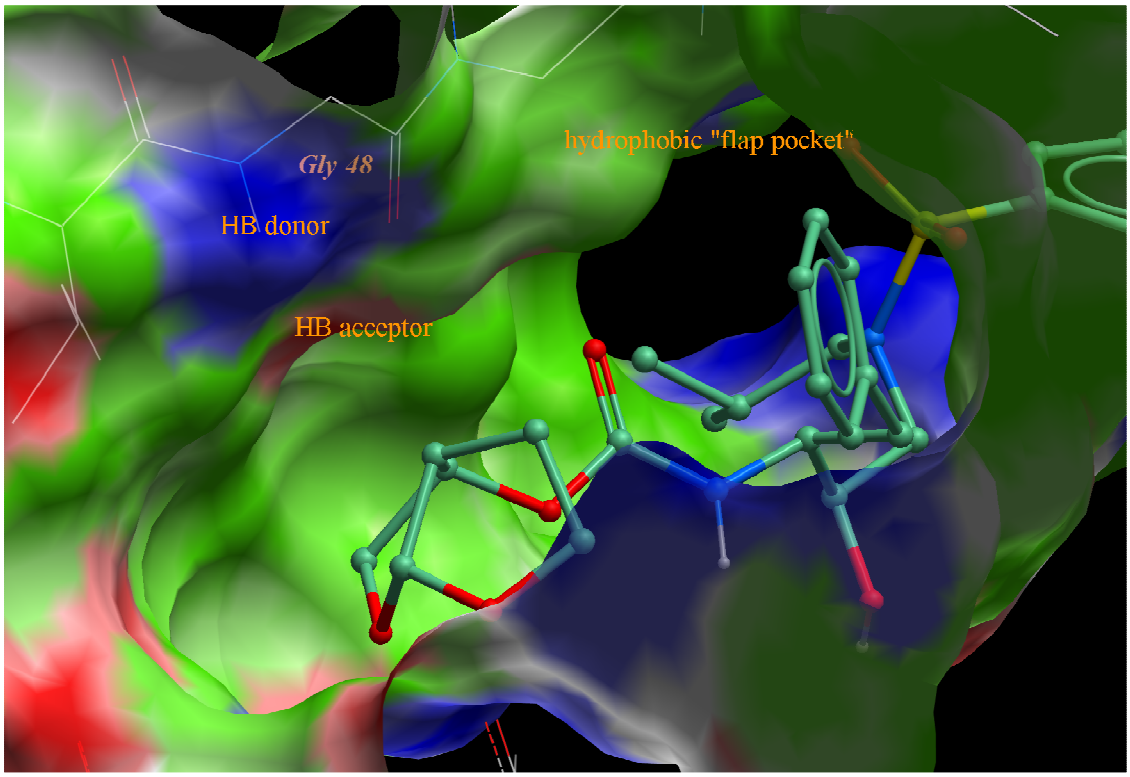


Figure 2-3. DRV within the binding pocket of HIV-1 protease.[37] Targeted binding areas for new analogues are marked.

The modelling , which was performed by Dr. Jörg Wegner at Tibotec, was based on the 2HS1 coordinates[37] and used a stochastic sampling of R-groups using Molsoft's ICM Pro software. This allowed screening for pre-defined R-group sets within ICM and manually drawn groups in the 3D protein-ligand complex. All structures were energy minimized using the standard force-field in ICM and followed-up by a visual inspection and ranking by a structural biology expert. The proposed structures are shown below (Figure 2-4).

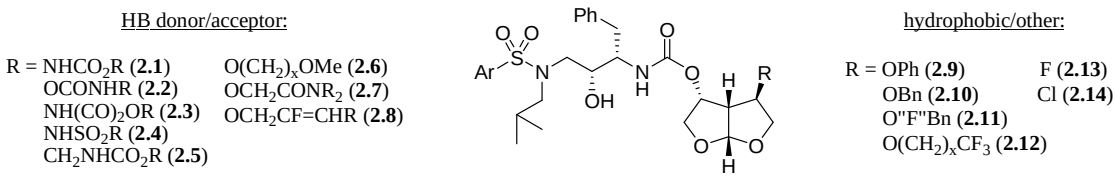


Figure 2-4. Proposed substituents for new PIs.

Carbamate **2.1**, as well as oxalate **2.3** and sulfonamide **2.4**, would be derived from an *exo*-amino group. A substituted NH moiety could retain the ability to form a HB to the carbonyl group of Gly48, while the substituents could serve as HB acceptors for Gly48 (NH). The inverted carbamate **2.2** and the CH_2-extended carbamate **2.5** could be used to establish the optimal position of the HB donor. Analogues **2.6** to **2.8** would again be able to

interact with the backbone NH of Gly48, although the optimal chain-length for the alkoxyalkyl substituent **2.6** has to be identified. Should the increased polarity of the acetamide derivatives **2.7** impair the cell permeability, fluoroalkenes **2.8** could prove as a useful alternative.[76] In these isosteres the double bond mimics the C−N bond and the fluorine replaces the carbonyl oxygen. Although the C−F bond is not as effective as hydrogen bond acceptor as the native C=O bond, the all over representation of the electrostatic potential of the original amide is more accurate than in a simple alkene isostere.[77]

So far, all proposed structures possess some HB donor or acceptor ability, and therefore could extent the "backbone binding concept" introduced by Ghosh.[29] On the other hand it was anticipated to enhance activity by introducing phenyl and benzyl groups (**2.9** and **2.10**), which were predicted to be able to fill the hydrophobic "flap-pocket" in the proximity of the *bis*-THF moiety. Fluorobenzyl ethers **2.11** and trifluoroalkyl derivatives **2.12** would be synthesised to explore possible fluorophilic environments within the binding pocket. Fluorine substituents preferably orientate towards electropositive regions of the receptor, to undergo multipolar C−F···H−N, C−F···C=O and C−F···HC_α interactions.[78,79] Furthermore, C−F bonds like to avoid direct contacts with carbonyl oxygens and prefer an orthogonal C−F···C=O orientation over antiparallel dipolar alignments.[80] Diederich *et al.* have shown, that these interactions generally adopt F−C=O angles between $70° \leq \alpha_1 \leq 110°$ towards the plane of the amide system, while the C−F···C angle α_2 is nearly linear (Figure 2-5, purple residues).[78,80] Similarly, there are no linear C−F···H−N interactions, due to the poor HB acceptor ability of F (Figure 2-5, green residues).[77,78]

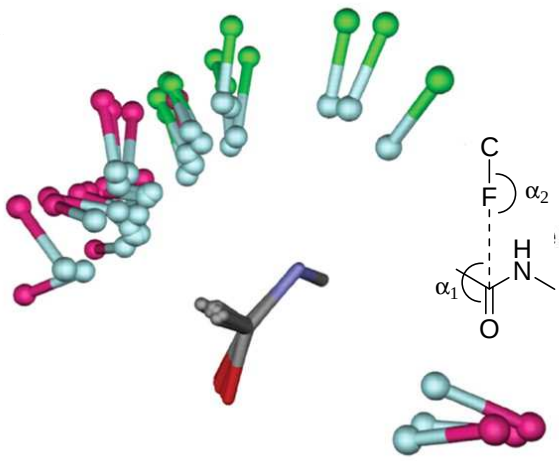


Figure 2-5. Interactions of fluorine ligands (C−F) with backbone N−H (ligand Cs in green) and C=O (ligand Cs in purple) moieties (Picture adapted from Ref. [78])

Deuterated analogues of DRV have been reported to show different pharmacological properties.[81] We are therefore interested in the effects of halogen substituents on the *bis*-THF moiety. Fluorinated and chlorinated *bis*-THF analogues **2.13** and **2.14** are also expected to undergo favourable interactions in the enzyme binding pocket. Although an *exo*-fluorine substituent on the *bis*-THF ring will not be able to form any C-F···C=O contact and might suffer repulsive effects from Gly48 (CO), it could possibly form dipolar interactions to Gly48 (C_α) or the water network, similar to the OH analogue. Of particular interest will be the comparison to the chlorine substituent, which is likely to undergo "halogen bonding" to the backbone carbonyl of Gly48. "Halogen bonding" is defined as a dipolar interaction of the general structure C−X···A between halogenated compounds (with X= Cl, Br, I) and nucleophiles (e.g. C=O).[82] These interactions are possible, as there is no equal distribution of electrostatic potential around the heavier halogen atoms. The atoms are polarised along the C−X axis, resulting in the appearance of an electropositive crown (blue, Figure 2-6) and an electronegative belt (red), separated by an electroneutral ring (green).[82] Due to this polarisation, the dipolar interactions are quite sensitive to the C−X···O angle, which should be close to 180°.[83] However, strong nucleophiles can induce further polarisation of the halogen atom, allowing a bigger deviation from this angle (down to 130°).[82]

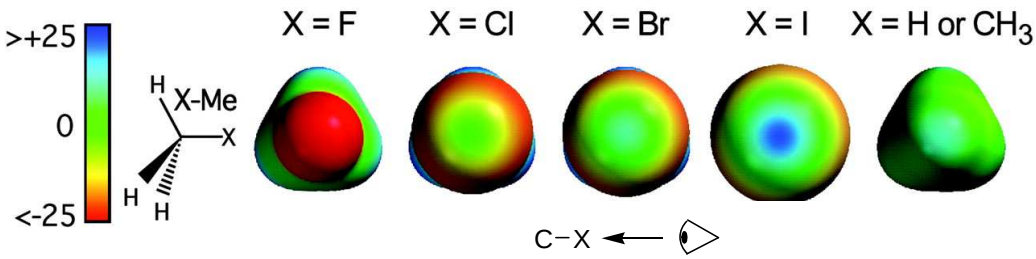


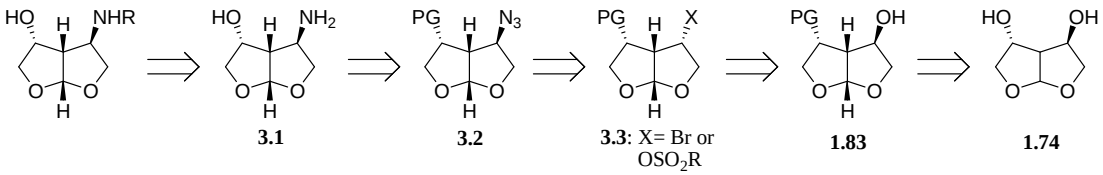
Figure 2-6. Polarisation of C−X bond (Picture taken from Ref. [82]).

In the next chapter the synthesis of the various disubstituted *bis*-THF analogues will be discussed in detail.

Chapter 3 SYNTHESIS OF DISUBSTITUTED *BIS*-THF LIGANDS

3.1 SYNTHESIS OF THE *EXO*-AMINO ANALOGUES

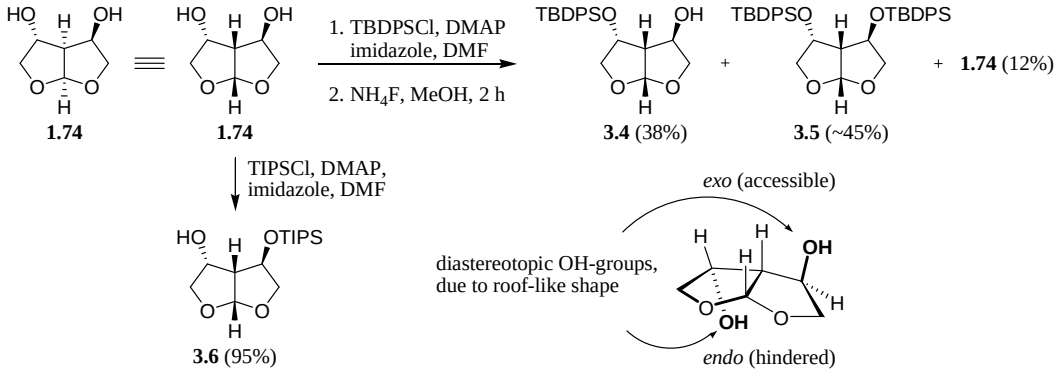
Following the analysis in Chapter 2, initial investigations were focussed on the synthesis of functionalised amines, which would provide HB donor and acceptor abilities. To obtain these analogues, it was necessary to derive the corresponding amino alcohol **3.1** from diol **1.74**, as outlined in the retrosynthetic analysis below (Scheme 3-1). Amine **3.1** can be synthesised by reduction of the corresponding azide **3.2**, which in turn will be readily available from the *endo*-activated species **3.3**. Intermediate **3.3** could be derived from the *endo*-protected diol **1.83** by direct halogenation or activation of the corresponding inverted alcohol. The synthesis of an *endo*-protected alcohol from diol **1.74** has been described by our group.[68]



Scheme 3-1. Retrosynthetic approach to amino alcohol **3.1**.

3.1.1 Stereoselective Protection of Diol 1.74

Diol **1.74** is "*pseudo*"-C_2-symmetric, as it contains a chirotopic, non-stereogenic fused C−C bond. Hence, structure **1.74a** (Scheme 3-2) is related to **1.74b** by a 180° rotation around the central C−C bond and the two hydroxy groups are diastereotopic. The roof-like shape of the molecule, which results from the *cis*-fusion of the THF rings, allows a facile differentiation of the 1,3-diol system, which is a key requirement for the synthesis of the envisaged analogues. In order to enable specific transformations on the accessible *exo*-hydroxy group of **1.74**, it was necessary to selectively protect *endo*-alcohol, to which the rest of the PI scaffold will be attached. Nevertheless, a selective one-step protection of the sterically more hindered *endo*-alcohol was deemed difficult. Therefore a two step protocol was developed, that allowed a selective desilylation of the *bis*-protected diol **3.5** (Scheme 3-2).[68]



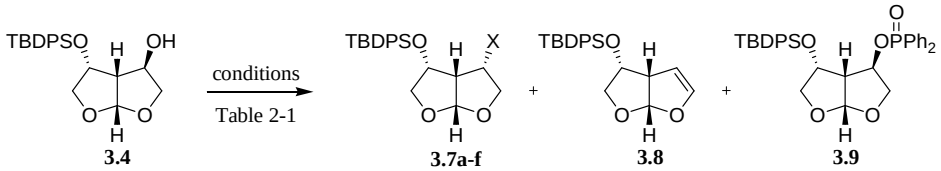
Scheme 3-2. Stereoselective protection of diol **1.74**.

Diol **1.74** was prepared from L-arabitol on 20 g scale as described above (1.3.4). Global protection of **1.74** with excess *tert*-butyldiphenylsilyl chloride (TBDPSCl) gave silylether **3.5**. Subsequent treatment with ammonium fluoride in refluxing MeOH[84] led to the selective removal of the *exo*-protection yielding the desired *endo*-silylated alcohol **3.4**. The reaction requires monitoring by TLC, since complete deprotection to diol **1.74** occurs after prolonged time. After column chromatography unreacted **3.5** is also obtained in mixture with excess silylating agent and can be used in further deprotections. On the other hand, selective *exo*-protection can be achieved with 1.1 equiv of silylating agent. With the bulkier triisopropylsilyl chloride (TIPSCl), which proved to be superior to TBDPSCl, alcohol **3.6** was obtained in 95% yield.

3.1.2 Direct Inversion Attempts on *endo*-protected alcohol 3.4

Following the strategy outlined above, it was attempted to invert the *exo*-hydroxy group in **3.4**. Alongside halogenation, the Mitsunobu inversion[85] and the oxidative-reductive condensation reaction by Mukaiyama[86] were tested on substrate **3.4** (Table 3-1).

Table 3-1. Inversion attempts on alcohol **3.4**.



3.4 **3.7a-f** **3.8** **3.9**

Entry	R =	reagents and conditions[a]	yield (%)[b]			
			3.7a-f	**3.8**	**3.9**	**3.4**
Halogenation:						
1 (**a**)	Br	Br_2 / PPh_3 / imidazole (1.0 equiv), CH_3CN, reflux, 2 h	–	–	–	–
2 (**b**)	I	I_2 / PPh_3 / imidazole (1.1 equiv), toluene, 60 °C, 3 h	traces	–	–	–
Mitsunobu inversion:						
3 (**c**)	OPNBz	PPh_3 / DIAD / PNBA (1.5 equiv), THF, 4 h	–	31	–	–
4 (**d**)	$OCOCH_2Cl$	PPh_3 / DIAD / $ClCH_2CO_2H$ (1.5 equiv), toluene, 18 h	–	–	–	55
5 (**e**)	OCOH	PPh_3 / DIAD / HCO_2H (1.5 equiv), THF, 18 h	2	–	–	74
Mukaiyama-type inversion:						
6 (**f**)	OAc	BuLi / Ph_2PCl (1.0 equiv), THF, 0 °C, 2 h; AcOH / DMBQ (1.0 equiv), CH_2Cl_2, 18 h	–	–	49	–
7 (**d**)	$OCOCH_2Cl$	DMAP (0.3 eq), Et_3N (1.2 equiv), THF, 18 h; $ClCH_2CO_2H$ / DMBQ (1.0 equiv), CH_2Cl_2, 18 h	–	–	95	–

[a] unless otherwise stated, reactions were performed at rt; [b] isolated yield; [c] of **3.8**; [d] of **3.9**.

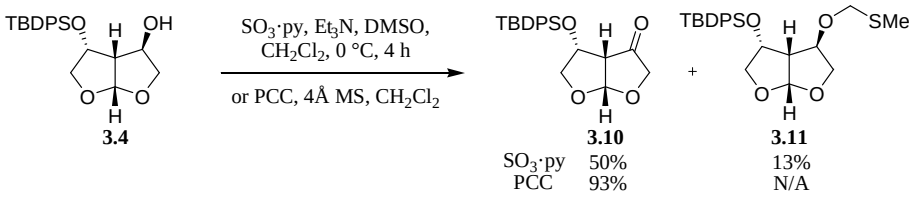
Initial attempts to form halides **3.7a** and **3.7b** from alcohol **3.4** proved to be unsuccessful (entries 1,2). A potential limitation for the halogenation might be the presence of two aromatic rings in the protecting group, possibly leading to electrophilic aromatic substitution under these conditions. Further investigations were made utilizing the Mitsunobu inversion (entries 3−5). Among the various aromatic nucleophiles, *para*-nitrobenzoic acid (PNBA) and chloroacetic acid have been reported to significantly improve the yields with relatively hindered substrates.[73,87] However, when alcohol **3.4** was reacted with PNBA in the presence of triphenylphosphine and diisopropyl azodicarboxylate

(DIAD), *β*-elimination was observed yielding alkene **3.8** instead of the desired inverted ester **3.7c** (entry 3). The observed olefinic proton coupling constant (J = 2.6 Hz) was in good agreement with similar compounds reported in the literature.[88] In order to reduce the influence of steric hindrance, PNBA was then replaced with the smaller chloroacetic acid, but no improvement was observed (entry 4). Only with formic acid[89] as nucleophile were traces of the inverted ester **3.7e** obtained.

Since the Mitsunobu reaction did not give the expected results, a third inversion approach was tested. In 2003, Mukaiyama *et al.* first published a new-type of oxidation-reduction condensation using alkoxydiphenylphosphines, a mild quinone-type oxidant like 2,6-dimethyl-1,4-benzoquinone (DMBQ) and carboxylic acids.[86] This method was reported to be very convenient with bulky secondary or tertiary alcohols to form corresponding carboxylic acid esters with inversion of configuration. However, when alcohol **3.4** was subjected to Mukaiyama's conditions[90,91] using acetic acid or chloroacetic acid, only phosphinate **3.9** was obtained (entries 6,7). Although alkoxydiphenylphosphines are reasonably air-stable,[90] oxidation has occurred during the first workup, resulting in the non-reactive phosphinate **3.9**, which was identified by ^{31}P NMR (δ 32.4 ppm; lit.[92] $Ph_2PO(OMe)$: δ 34.5 ppm).

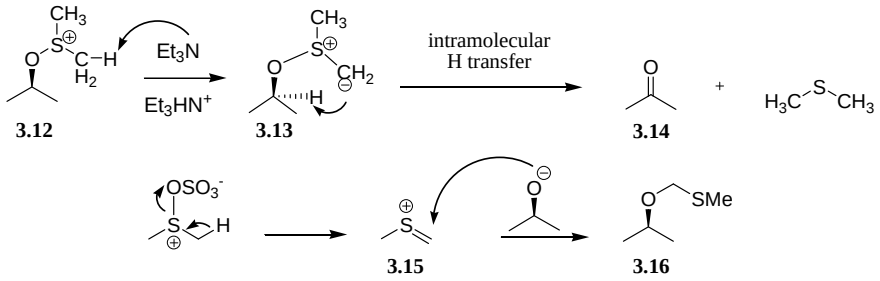
3.1.3 Inversion of 3.4 via an oxidation-reduction sequence

As all direct inversion attempts proved unsuccessful, an oxidation-reduction sequence was envisaged to form the inverted *endo*-alcohol of **3.4**. Parikh-Döring oxidation of **3.4** gave a mixture of the desired ketone **3.10** and mixed acetal **3.11** in moderate yield (Scheme 3-3). The latter product is formed in a Pummerer-like-rearrangement that usually occurs as a side reaction in DMSO-mediated oxidations at higher temperature.[93] Alternatively, oxidation with pyridinium chlorochromate (PCC) afforded ketone **3.10** in 93% yield.



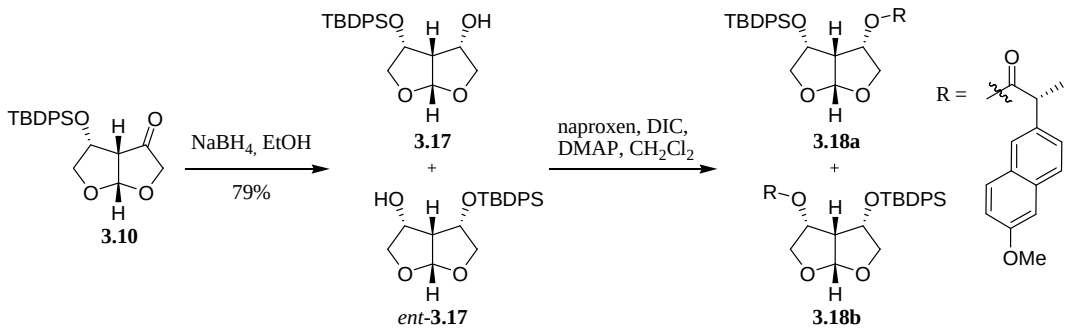
Scheme 3-3. Oxidation of alcohol 3.4 to ketone **3.10**.

The formation of the mixed acetal is a commonly observed side reaction in oxidations with activated DMSO.[93] In the last step of the Parikh-Döring oxidation, deprotonation of the dimethylalkoxysulfonium salt **3.12** with triethylamine leads to ylide **3.13**, which then undergoes an intramolecular hydrogen transfer to give desired carbonyl compound **3.14** and dimethylsulfide (Scheme 3-4). However, at higher temperatures elimination of the activated DMSO to methylenmethylsulfonium species **3.15** is possible. Subsequent reaction with an alkoxide results in the formation of methylthiomethyl ether **3.16**.



Scheme 3-4.

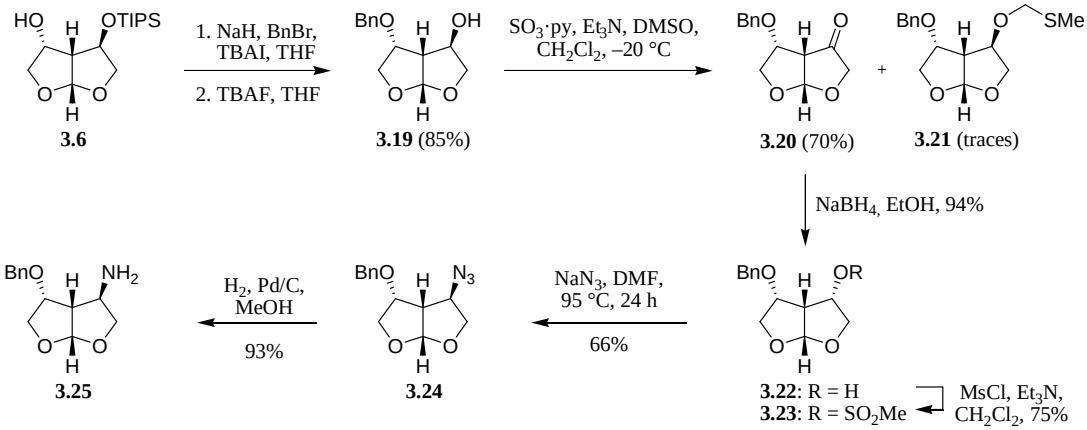
Ketone **3.10** was subsequently reduced with sodium borohydride to form the corresponding *endo*-alcohol **3.17** in 79% yield (Scheme 3-5). Comparison of **3.17** with **3.4** confirmed that hydride attack had occurred from the less hindered *exo*-face to selectively generate the corresponding *endo*-alcohol. Although TBDPS ethers are usually not prone to undergo silyl migration, the proximity of the resulting oxyanion after reduction could effect the silyl ether group. Silyl migration would result in the formation of the enantiomers **3.17** and *ent*-**3.17**. In order to verify that this had not happened, the obtained product was reacted with the homochiral carboxylic acid naproxen, to see whether two corresponding diastereomeric esters would be formed. Although being inseparable by HPLC, the two isomers **3.18a** and **3.18b** (~1:1) could be identified by ^{1}H NMR, indicating that silyl migration had indeed occurred.



Scheme 3-5. Reduction of **3.10** and verification of silyl migration.

3.1.4 The benzyl ether approach to amine 3.1

Following the results above (3.1.2 and 3.1.3), the TBDPS protecting group was found to be too bulky to allow direct inversion of alcohol **3.4**. The initial results of an oxidation-reduction approach were very promising, but silyl migration was observed in the reduction step. It was anticipated that this problem could be overcome by a new protecting group strategy. The benefit of any ester protection is limited, because an alkoxide is formed in the reduction workup and esters are susceptible for migration too. Hence, a benzyl ether was considered to be the best solution, as, in addition, it could be removed in one step together with azide reduction, which would give the desired *exo*-amine group. The results of this approach are outlined in Scheme 3-6.



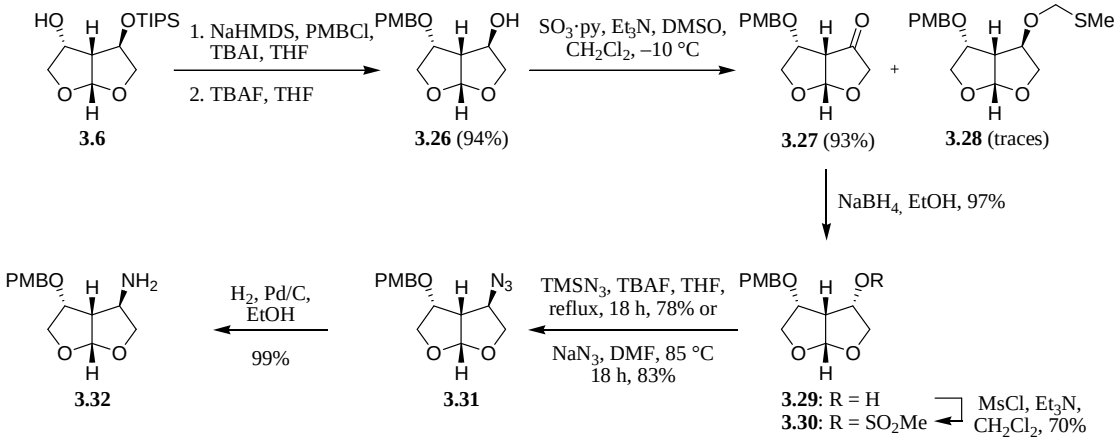
Scheme 3-6. The benzyl ether approach.

Benzylation of alcohol **3.6** was followed by tetrabutylammonium fluoride (TBAF) mediated desilylation to furnish *endo*-protected diol **3.19** in 85% yield over two steps. Parikh-Döring oxidation to ketone **3.20** proceeded in good yield at –20 °C, with only traces of the mixed acetal **3.21** being observed. Subsequent reduction with $NaBH_4$ and activation led to the formation of mesylate **3.23** in 70 % overall yield. The formation of azide **3.24** was achieved in moderate yield using sodium azide in dimethylformamide (DMF) at elevated temperature. Unfortunately, Pd-catalysed reduction only led to azide reduction, to yield amine **3.25**, instead of the desired amino alcohol **3.1**. Similar results were obtained, when Pd/C was replaced by the more reactive $Pd(OH)_2/C$. Bartsch *et al.* have reported that *O*-debenzylation of alkyl benzyl ethers is inhibited in the presence of free amines.[94] In this case, the sterically less hindered azide is reduced first and then inhibits the reduction of the more encumbered benzyl functionality. Further attempts to hydrogenate the benzyl group by trapping the amine with 1 equiv HCl [95] proved unsuccessful too.

The remaining benzyl group decreases the polarity of the molecule and therefore improves the handling of the compound. However, as the functionalisation of the *exo*-amino group includes additional benzyl groups, a late stage selective debenzylation appeared not possible. This therefore limits the usefulness of the remaining *O*-benzyl group and a different protection is necessary that allows the release of the *endo*-hydroxy group in the presence of other benzyl groups .

3.1.5 The PMB-ether approach

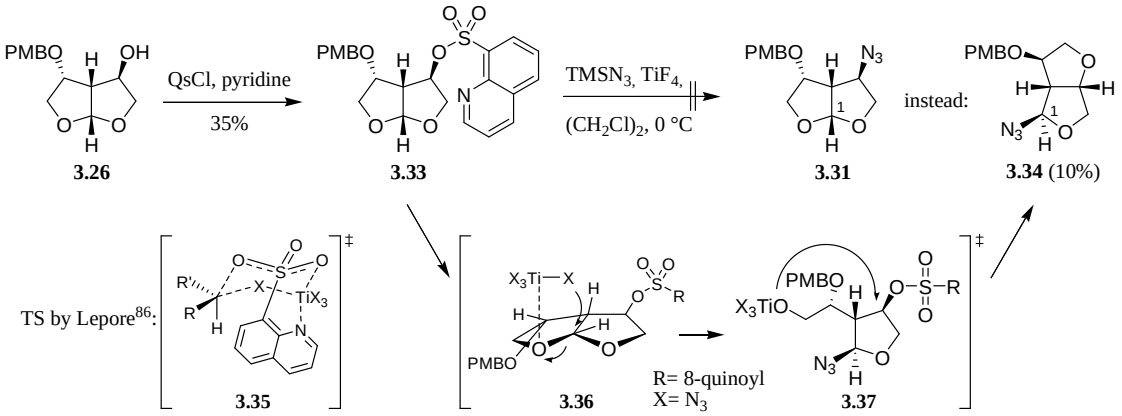
The benzyl group was eventually replaced by a *para*-methoxybenzyl group (PMB), which offered additional possibilities for the final reduction/deprotection step. PMB-ether **3.26** was obtained from alcohol **3.6** in excellent yield and subsequent oxidation to ketone **3.27** was achieved in up to 93% yield (Scheme 3-7). The activation of alcohol **3.29** to mesylate **3.30** proceeded much slower than in the benzyl-route. However, the corresponding triflate was found to be air-sensitive and underwent spontaneous carbonisation. Azide **3.31** was obtained in good yields using either NaN_3/DMF or $TMSN_3$/TBAF/THF.[96,97] The latter method is more favourable as it uses less hazardous reagents and offers an easier work-up. Finally, azide reduction afforded the PMB-protected amine **3.32** in 49% overall yield from alcohol **3.6**, which is an significant improvement over the benzyl-route (26% of **3.25** from **3.6**). The remaining *endo*-PMB protection can easily be removed via DDQ oxidation[98] after functionalisation of the *exo*-amine and, at this stage, improves the handling of the compound, due to the decreased polarity.



Scheme 3-7. The PMB-ether approach to amine **3.32**.

3.1.6 Stereoretentive Azidation utilizing $Ti(N_3)_4$

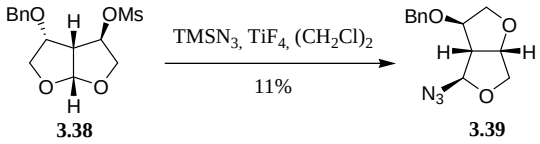
Although a route to the desired *exo*-amine **3.32** has been established (3.1.5), a shorter and more convenient strategy was still sought. Based on a recent publication by Lepore *et al.*,[99] the stereoretentive azidation of quinoline sulfonate **3.33** (also called quisylate) with titanium(IV) azide was investigated (Scheme 3-8).



Scheme 3-8. Azidation attempt from quisylate **3.33**.

Quisylate **3.33** was obtained in moderate yield from the reaction of alcohol **3.26** with quinoline-8-sulfonyl chloride. Subsequent treatment of **3.33** with $Ti(N_3)_4$, generated *in-situ* from $TMSN_3$ and TiF_4, afforded low yields of the rearranged product **3.34** instead of the desired azide **3.31**. Lepore and co-workers proposed a transition state (**3.35**) in which the titanium(IV) species coordinates to a sulfonate oxygen and the quisylate nitrogen allowing a displacement of the sulfonate with retention of configuration. However, the obtained product **3.34** leads to the assumption that in our case the $Ti(N_3)_4$ coordinated to the less hindered ring-oxygen of the *bis*-THF. As shown in transition state **3.36**, this arrangement would facilitate the opening of the acetal by S_N2 attack of the azide to generate intermediate **3.37**. Alternatively, an oxonium ion formation followed by nucleophilic attack of the azide from the least hindered site would also lead to **3.37**. In this case a diaxial arrangement of the N_3-group and the oxygen lonepair would be favoured. From **3.37**, an intramolecular displacement of the quisylate would give azide **3.34**. The structure of **3.34** was confirmed by mass spectrometry (*m*/*z* 314.1 for $(M+Na)^+$), the absorption of the azide group at ~2100 cm^{-1} in the IR spectrum and the presence of a doublet at 5.36 ppm (J = 1.4 Hz) instead of the characteristic doublet of H-1 at 5.80 ppm (J = 5.1 Hz) in the ^1H NMR. The smaller coupling constant also confirms the inversion of C-1, which is now *trans* to the vicinal proton as opposed to *cis* as in the parent sulfonate.

In order to confirm the suggested mechanism and to exclude any interference of the sulfonyl substituent, mesylate **3.38** was reacted under similar conditions to furnish the rearranged azide **3.39** in low yield (Scheme 3-9). Nevertheless, under these conditions a direct azidation of the *exo*-sulfonates to the desired *exo*-azides appears not possible.



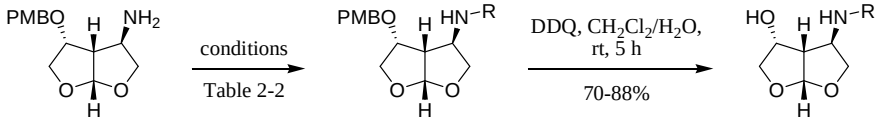
3.38 **3.39**

Scheme 3-9. Formation of azide **3.39** from mesylate **3.38**.

3.1.7 Functionalisation and deprotection of amine 3.32

Amine **3.32** was converted to the benzylated carbamate, oxalate and sulfonamide **3.40a-c** (Table 3-2). Subsequent removal of the PMB protection was achieved with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ)[98] in aqueous dichloromethane to furnish the corresponding alcohols **3.41a-c**.

Table 3-2. Synthesis of alcohols **3.41a-c**.



3.32 **3.40a-c** **3.41a-c**

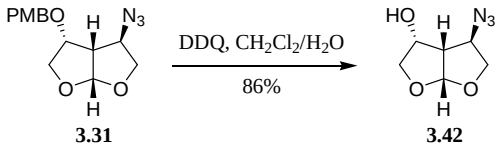
Entry	R =	reagents and conditions	yield (%)[a] 3.40	3.41
1 (**a**)	CO_2Bn	$ClCO_2Bn$ (1.5 equiv), DMAP (0.25 equiv), pyridine (3 equiv), CH_2Cl_2, 0 °C to rt, 2 h	90	88
2 (**b**)	$(CO)_2OBn$	$(COCl)_2$ (1.5 equiv), BnOH (1.5 equiv), 0 °C, 30 min; then **3.32**, DMAP (0.3 equiv), Et_3N (3 equiv), CH_2Cl_2, 0 °C to rt, 1 h	84	86
3 (**c**)	SO_2Bn	$BnSO_2Cl$ (3 equiv), DMAP (0.5 equiv), pyridine, rt, 30 min	86	70

[a] isolated yield

The formation of carbamate **3.40a** from amine **3.32** was achieved with a combined yield of 79% over two steps (entry 1). Benzyl oxalyl chloride was generated prior to use from oxalyl chloride and benzyl alcohol.[100] Subsequent treatment with alcohol **3.32** and DDQ

oxidation of the intermediate **3.40b** gave alcohol **3.41b** in 72% yield over two steps (entry 2). Sulfonamide **3.41c** was obtained in 60% yield from amine **3.32** (entry 3), here the removal of the PMB group proved slightly less effective.

In addition to the synthesis of the substituted amines **3.41**, azidoalcohol **3.42** was formed in good yield by deprotection of azide **3.31** with DDQ (Scheme 3-10).

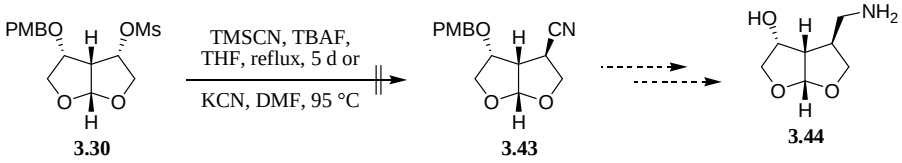


3.31 **3.42**

Scheme 3-10. Synthesis of azidoalcohol **3.42**.

3.1.8 Attempted synthesis of a CH_2-extended amine

Similarly to the substituted exo-amino analogues **3.41**, ligands with a CH_2-extended NH_2 group would have HB donor abilities towards the carbonyl group of Gly48 (compare Chapter 2). It was therefore envisaged to synthesise methylamino derivative **3.44** via the corresponding cyanide **3.43** from mesylate **3.30** (Scheme 3-11). However, neither the reaction with KCN in DMF nor the utilization of the TMSCN/TBAF system yielded any of the desired cyanide **3.43**.



3.30 **3.43** **3.44**

Scheme 3-11. Attempted formation of amino alcohol **3.44**.

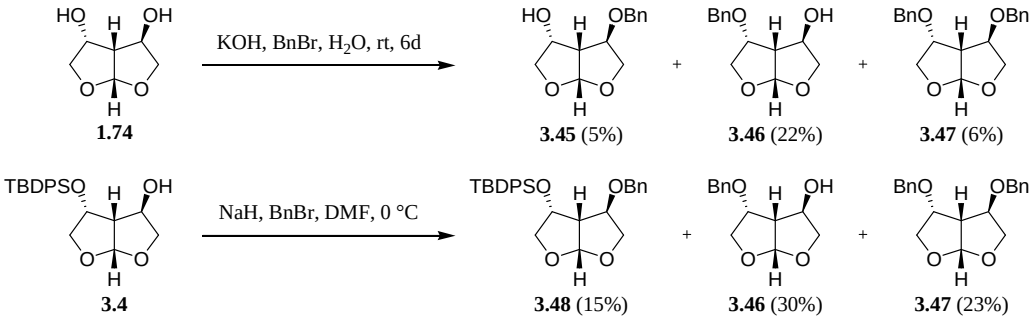
3.2 SYNTHESIS OF *EXO*-OXY ANALOGUES

As already outlined in Chapter 2, for the synthesis of further *O*-substituted analogues two different strategies were pursued. On the one hand it was anticipated to enhance antiviral activity by introducing aryl and benzyl groups, which were predicted to be able to fill a hydrophobic pocket in the proximity of the *bis*-THF moiety. On the other hand it was envisaged to extent the "backbone binding concept"[29] by introducing polar groups, like alkoxyalkyl or acetamide substituents, that could form additional hydrogen bonding interactions with the backbone NH of Gly48.

3.2.1 Synthesis of Hydrophobic Analogues

3.2.1.1 Benzylated *bis*-THF ligands

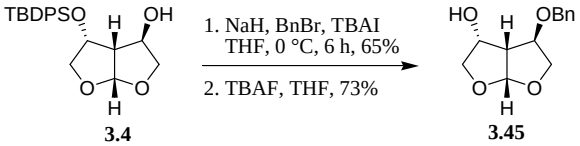
Previous studies by Cyrille Tomassi in our group have shown, that an *exo*-selective benzylation of diol **1.74**, similar to the selective silylation (3.1.1), is not possible.[101] Reaction of **1.74** with 1 equiv benzyl bromide in the presence of potassium hydroxide afforded a mixture of *exo*/*endo*-benzylated product **3.45/3.46** as well as the dibenzylated derivative **3.47** (Scheme 3-12). Surprisingly, the *endo*-benzylated species **3.46** formed the majority of the mono-benzylated product. Variation of base and solvent did not lead to any improvement in yield or selectivity.



Scheme 3-12. Attempted *exo*-benzylations of **1.74** and **3.4**.

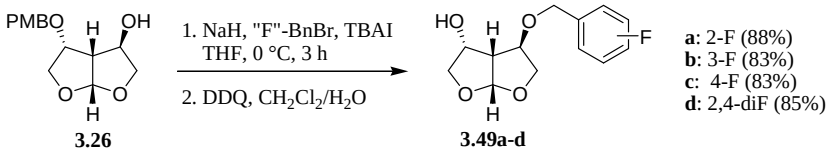
Similarly, the reaction of *endo*-silylated alcohol **3.4** with BnBr in DMF afforded only low yields of the desired product **3.48**. The TBDPS protection proved to be unstable under these conditions and again the *endo*-benzylated species **3.46** was formed as the major product. In addition, a significant amount of the dibenzyl analogue **3.47** could be isolated.[101] These results suggest that the *exo*-alkoxideo is stabilised by solvation effects, which have a greater impact on the outcome of the reaction than the accessibility of the two faces. The *endo*-alkoxide will be less stablised by solvation and is also positioned in a more electron-rich

environment leading to a increased reactivity. However, by changing the solvent to the less polar THF, ether **3.48** could be obtained in up to 65% yield (Scheme 3-13). Subsequent TBAF mediated desilylation afforded alcohol **3.45** in 73% yield.[101]



Scheme 3-13. Synthesis of benzyl ether **3.45**.

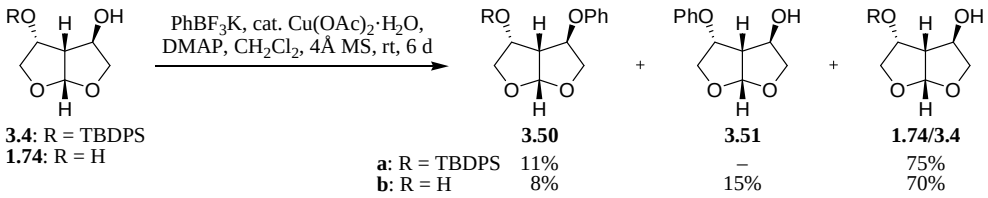
To exploit possible dipolar C-F···C=O interactions (compare Chapter 2), a series of fluoro-benzyl ethers **3.49a-d** was generated (Scheme 3-14). Starting from the *endo*-PMB protected alcohol **3.26**, benzylation and deprotection with DDQ afforded the fluoro-benzylated alcohols **3.49** in combined yields of over 83%, which is a significant improvement over the silylether approach.



Scheme 3-14. Formation of fluorobenzyl ethers **3.49** from alcohol **3.26**.

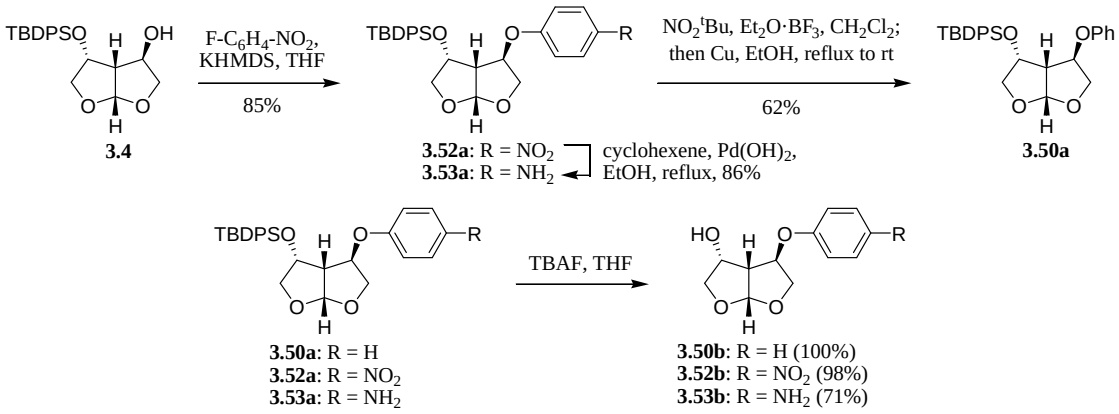
3.2.1.2 Arylated *bis*-THF analogues

In addition to the benzyl analogue **3.45**, three different *exo*-arylated *bis*-THF alcohols have been previously synthesised in our group.[101] Among these, the phenoxy derivative **3.50b** was of particular interest (Scheme 3-15). Direct arylation of alcohol **3.4** or diol **1.74** was attempted using potassium phenyltrifluoroborate in the presence of catalytic amounts of $Cu(OAc)_2 \cdot H_2O$.[102] However, only low yields of the desired aryl ethers **3.50a/b** could be obtained. Interestingly, *endo*-arylated species **3.51** formed again the majority of product when starting from diol **1.74**. In both cases over 70% of starting material were recovered.[101]



Scheme 3-15. Attempted arylation of **1.74**/**2.4** using aryltrifluoroborate salts.

Alternatively, ether **3.50b** was synthesised in four steps from alcohol **3.4** via the corresponding *para*-nitrophenyloxy derivative **3.52a** (Scheme 3-16). Reaction of alcohol **3.4** with 4-fluoronitrobenzene afforded ether **3.52a**, which was reduced to amine **3.53a**. Deamination of **3.53a** was achieved via intermediate diazonium salt formation and subsequent copper catalysed reduction to give **3.48a** in good yield.[103] TBAF-mediated desilylation of **3.50a** and **3.52/53a** afforded phenoxy alcohol **3.50b** as well as the *para*-nitro/*para*-amino analogues **3.52/53b**.[101]

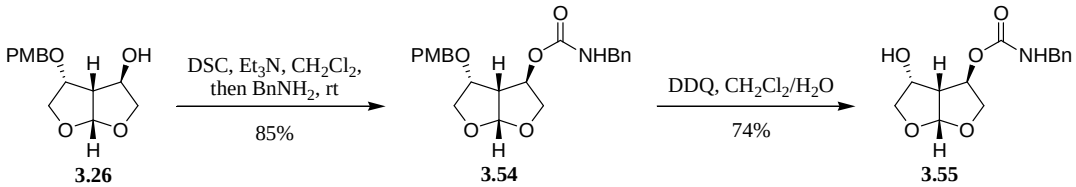


Scheme 3-16. Synthesis of arylated bis-THF analogues.

3.2.2 Synthesis of Polar Analogues

3.2.2.1 Inverted *bis*-THF carbamate

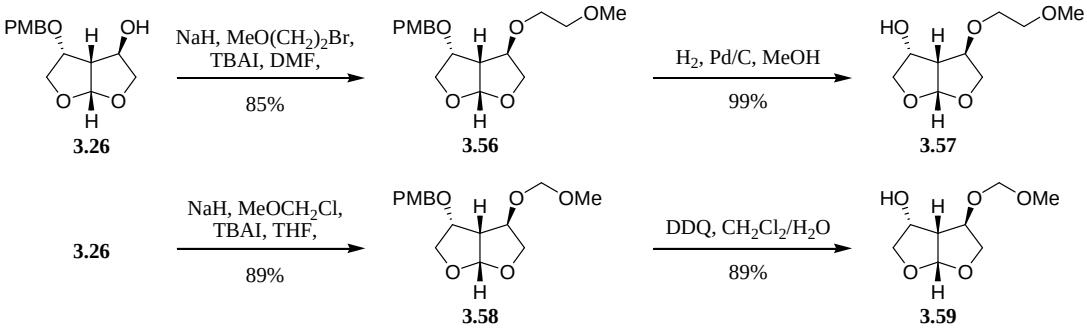
In addition to the *O*-benzylated carbamate **3.41a** (see 3.1.7), the corresponding *N*-benzylated analogue **3.55** has been synthesised from alcohol **3.26** (Scheme 3-17). Activation of the *exo*-hydroxy group of **3.26** with DSC was followed by the addition of benzylamine to furnish carbamate **3.54**. Subsequent DDQ oxidation afforded alcohol **3.55** in 74% yield.



Scheme 3-17. Formation of carbamate **3.55** from alcohol **2.26**.

3.2.2.2 Alkoxyalkyl analogues

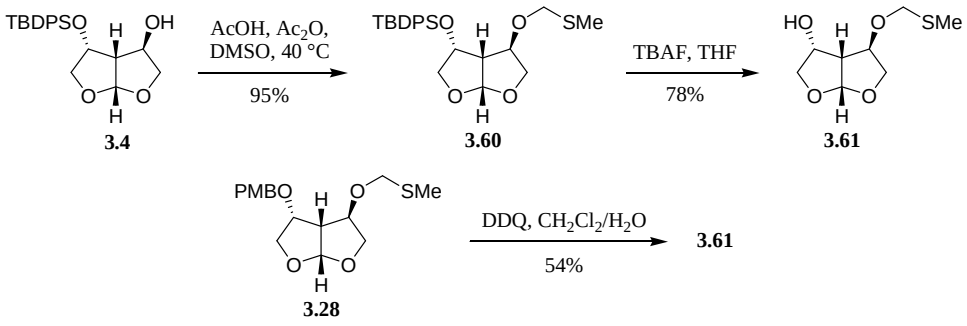
Preliminary modelling studies indicated that alkoxyalkyl substituents would be able to form favourable hydrogen bonding interactions with the enzyme backbone (see Chapter 2). In order to exploit the influence of the chain length, the corresponding methoxyethyloxy ether **3.57** and the methoxymethyloxy ether **3.59** have been synthesised (Scheme 3-18).



Scheme 3-18. Synthesis of alkoxyalkyl ethers **3.57** and **3.59**.

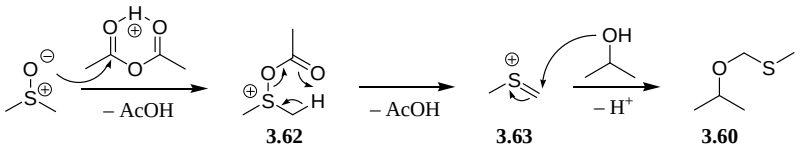
Reaction of alcohol **3.26** with the corresponding alkoxyalkyl halide in the presence of catalytic amounts of TBAI afforded the disubstituted *bis*-THF analogues **3.56** and **3.58**. The PMB protection was then removed by either Pd-catalysed hydrogenolysis or DDQ oxidation to furnish alcohols **3.57**/**3.59**. Interestingly, hydrogenolysis could only be achieved on PMB ether **3.56**, while no reaction was observed with ether **3.58** under similar conditions.

In addition to the two alkoxyalkyl analogues, methylthiomethyl (MTM) ether **3.60** was synthesised from alcohol **3.4** (Scheme 3-19). Treatment of **3.4** with a DMSO/acetic anhydride/acetic acid mixture[104] afforded ether **3.60**,[101] which was subsequently desilylated with TBAF to give alcohol **3.61** in good yield. Alternatively, **3.61** was obtained from mixed acetal **3.28**, which had been isolated as a side product of the Parikh-Döring oxidation, as explained above (3.1.5). Again DDQ oxidation of the PMB ether proved superior to Pd-catalysed hydrogenolysis.



Scheme 3-19. Formation of methylthiomethyl ether **3.61**.

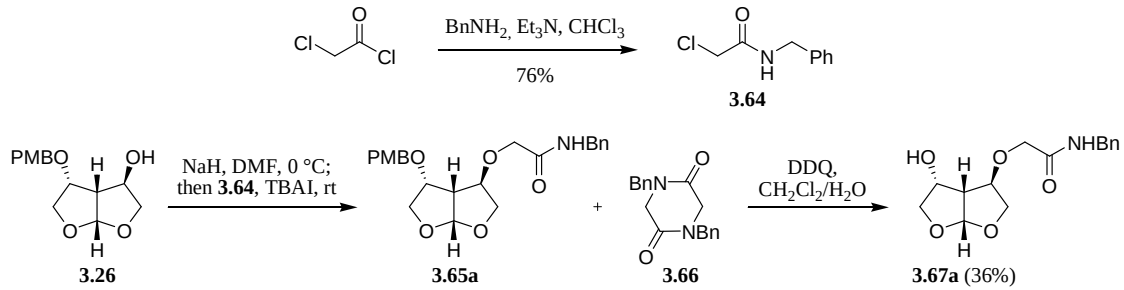
The mechanism for the formation of methylthiomethyl ether is shown in Scheme 3-20. The whole process can be seen as a variation of the Pummerer-rearrangement, only with the exception that in the last step the attacking nucleophile is an alcohol rather than a carboxylate. Initial attack of DMSO onto the activated acetic anhydride would form sulfonium species **3.62**. An intramolecular elimination generates methylenmethylsulfonium ion **3.63**, which is then attacked by the alcohol **3.4** to form MTM ether **3.60**. As the reaction is carried out under acidic conditions, only a very small amount of acetate will be present at any time in the mixture. In addition, there will be always an excess of alcohol, hence, competitive attack of the acetate is limited.



Scheme 3-20. Mechanism of MTM ether formation.

3.2.2.3 Acetamides

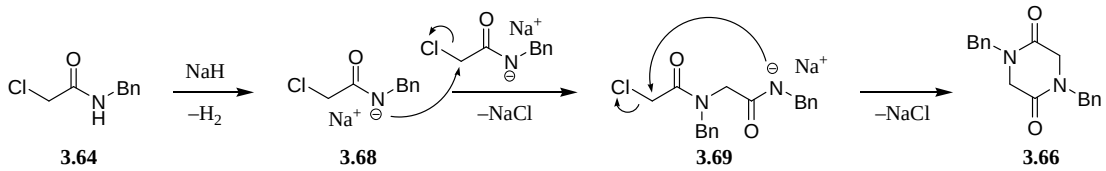
Similar to the alkoxyalkyl substituents, *N*-alkyl acetamides were predicted to have beneficial binding properties towards the protease backbone. Initial focus was placed on the direct coupling of alcohol **2.26** with chloroacetamide **3.64**, which was derived from chloroacetyl chloride and benzylamine (Scheme 3-21).[105] Although the reaction yielded some of the desired protected acetamide **3.65a**, the product was always obtained as an inseparable mixture with diketopiperazine **3.66**. Treatment of this mixture with DDQ afforded acetamide **3.67a** in 36% yield from **3.26**.



Scheme 3-21. Conversion of alcohol **3.26** to benzyl acetamide **3.65a**.

Side product **3.66** arises from the homodimerisation of **3.64** (Scheme 3-22).[106,107] Excess NaH will deprotonate acetamide **3.64** to form **3.68**. Nucleophilic attack on the α-carbon of a

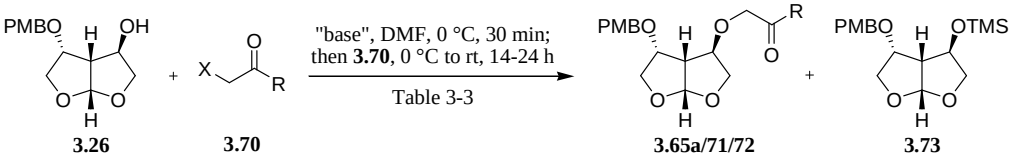
second molecule **3.64/68** will lead via chlorine displacement to **3.69**. An intramolecular attack will then furnish dioxopiperazine **3.66**.



Scheme 3-22. Formation of piperazine **3.66**.

Further investigations towards the synthesis of **3.65a** as well as ester **3.71** and acid **3.72** are summarised in Table 3-1. It was attempted to improve the yield of acetamide **3.65a** by minimizing the side product formation. However, neither the reduction of base equivalents nor variation of the base led to any improvement (entries 1-4). When sodium bis(trimethylsilyl)amide (NaHMDS) was used to deprotonate alcohol **3.26**, the corresponding TMS-ether **3.73** was isolated in good yield (entry 2). A plausible mechanism for this reaction is given below (Scheme 3-23).

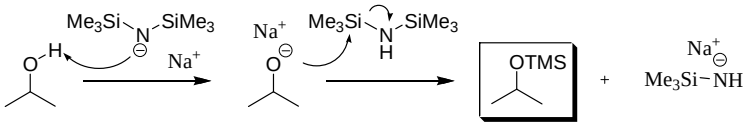
Table 3-3. Formation of β-carbonyl compounds **3.65a/3.71/3.72**.



Entry	R =	X =	3.70 (equiv)	Base (equiv)	TBAI (equiv)	yield (%)[a] 3.65a	3.71	3.72	3.26
1	NHBn (**3.65a**)	Cl	3.0	NaH (1.5)	0.3	–	–	–	91
2			3.0	NaHMDS (1.1)	0.3	(75)[b]	–	–	–
3			3.0	LDA (1.05)	0.3	–	–	–	99
4			3.0	KOtBu (1.2)	0.3	–	–	–	34
5	OMe (**3.71**)	Cl	3.0	NaH (2.0)	0.3	–	11	–	59
6[c]		Cl	3.0	NaH (1.5)	0.5	–	9	–	40
7		Br	3.0	NaH (2.0)	–	–	24	–	61
8[d]	OH (**3.72**)	Br	1.2	NaH (3.0)	–	–	–	–	65
9[c,d,e]			2.0	NaH (1.4 + 2.1)	–	–	–	93	–

[a] isolated yield, [b] of **3.73**, [c] reaction was heated to 80 °C for 16 h, [d] reaction performed in THF and NaH was washed with hexane prior use, [e] reagent was deprotonated prior toaddition

The formation of the TMS-ether **3.25** (Scheme 3-23), could be explained as follows: Initial deprotonation of the alcohol with NaHMDS leads to the formation of an alkoxide and HMDS. Nucleophilic attack of the alkoxide onto one of the TMS-groups will then give the observed TMS-ether. The silazide would subsequently deprotonate the benzylamide to form trimethylsilylamine and the corresponding sodium salt of the amide.

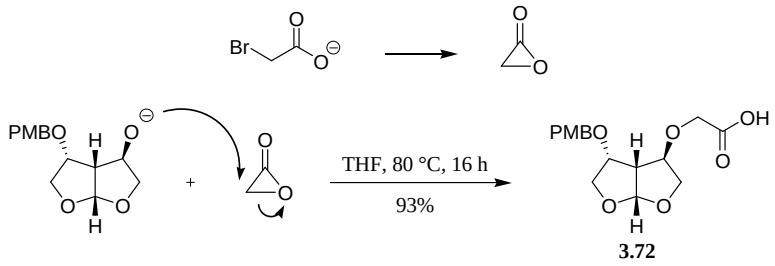


Scheme 3-23.

It remains uncertain, why the nucleophilic attack at the benzylamide is hindered. Here the formation of an Si–O bond appears to energetically favoured and is therefore the driving force of this reaction. Bruynes and Jurriens reported, that silylations with HMDS are catalysed by compounds with the general formula X–NH–Y, in which at least one substituent is electron-withdrawing.[108] In this case the benzylamide could act as a catalyst, although an alkoxide rather than an alcohol is present.

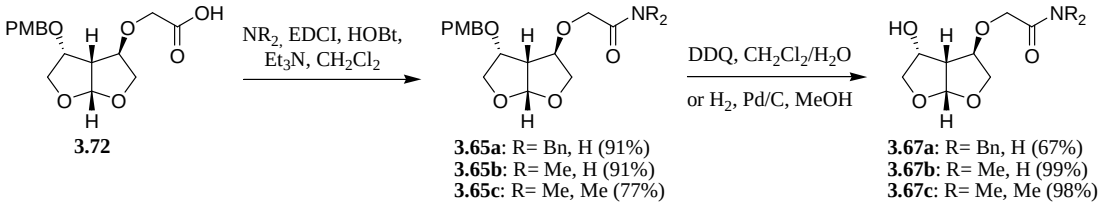
It was then envisaged to first form an ester precursor, which would subsequently be transformed to the corresponding amide. The reaction with chloroacetic acid methyl ester (entries 5,6) afforded, even under more forcing conditions, only low yields of the desired ester **3.71**. With the corresponding bromoester (entry 7) the yield was slightly increased, but still insufficient. In all three cases the majority of starting alcohol **3.26** could be recovered.

A third option was the formation of the free acid **3.72** (entries 8,9). Following a procedure by Crimmins *et al.*,[109] a first attempt with bromoacetic acid only yielded recovered starting material **3.26** (entry 8). In a second reaction, it was then decided to alter these conditions slightly. When both substrates were separately deprotonated with purified NaH and subsequently reacted in THF at elevated temperature, the desired acid **3.72** was obtained in excellent yield (entry 9, Scheme 3-24). Under these conditions, it can be anticipated that the bromoacetate reacts to an intermediate α-lacton, as decribed by Casadei *et al.*[110] The lacton would then be reopened upon addition to the alkoxide leading to the formation of the desired acid **3.72**. This procedure proved to be reliable even on gram-scale.



Scheme 3-24. Formation of acetic acid analogue **3.72**.

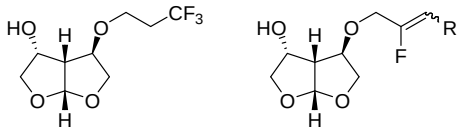
Acetic acid derivative **3.72** was coupled with primary and secondary amines to afford acetamides **3.65a-c** in good yields (Scheme 3-25). The parent acid was activated with the water soluble *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI), which proved to be superior to *N,N'*-diisopropylcarbodiimide (DIC). Subsequent deprotection of the PMB ether was achieved with DDQ for benzyl analogues **3.65a** and via Pd-catalysed hydrogenolysis for the methyl and dimethyl compounds **3.65b/c** to obtain the corresponding alcohols **3.67a-c** in good to excellent yield.



Scheme 3-25. Synthesis of acetamides **3.27a-c**.

3.2.3 Synthesis of fluorinated *O*-alkyl and *O*-alkenyl analogues

In addition to the already described alkoxyalkyl and acetamide analogues, it was envisaged to synthesise their fluorinated isosteres (Figure 3-1). The fluorinated alkyl substituents **3.74** could potentially form dipolar C-F···C=O or C-F···H-N contacts (see Chapter 2), while fluoroalkenes **3.75** would serve as amide mimics.

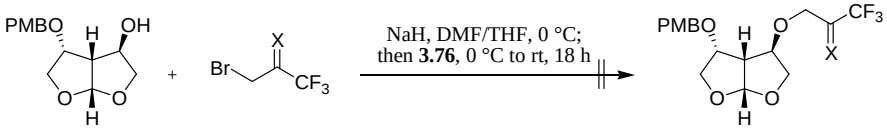


3.74 **3.75**

Figure 3-1. Fluorinated *O*-alkyl analogues.

3.2.3.1 Fluoroalkylation of *bis*-THF alcohol 3.26

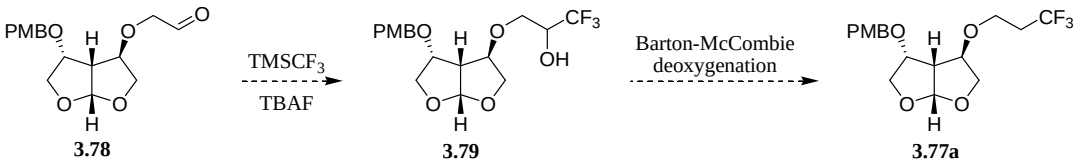
The synthesis of trifluoropropyl ether **3.74** was initially attempted via direct alkylation of alcohol **3.26** with the corresponding alkyl bromide **3.76** (Scheme 3-26), similar to the alkoxyalkyl ether formation described above. However, neither the reaction with 3-bromo-1,1,1-trifluoropropane (**3.76a**) nor treatment with 3-bromo-1,1,1-trifluoroacetone (**3.76b**) yielded any of the desired ethers **3.77**.



3.26 **3.76a**: X = H, H **3.76b**: X = O **3.77a**: X = H, H **3.77b**: X = O

Scheme 3-26. Attempted direct fluoroalkylation of **3.26**.

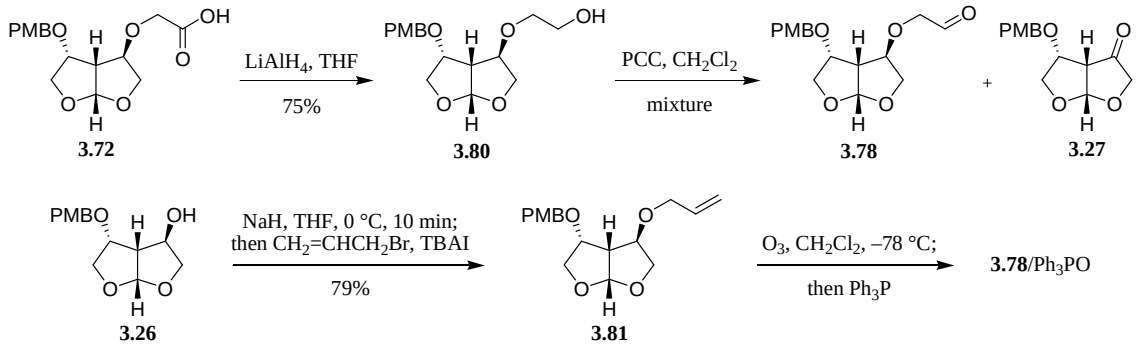
It was then envisaged to derive ether **3.77a** from acetaldehyde **3.78** via addition of $TMSCF_3$ (Ruppert's reagent)[111] and subsequent Barton-McCombie deoxygenation[112] of the intermediate secondary alcohol **3.79**.



3.78 **3.79** **3.77a**

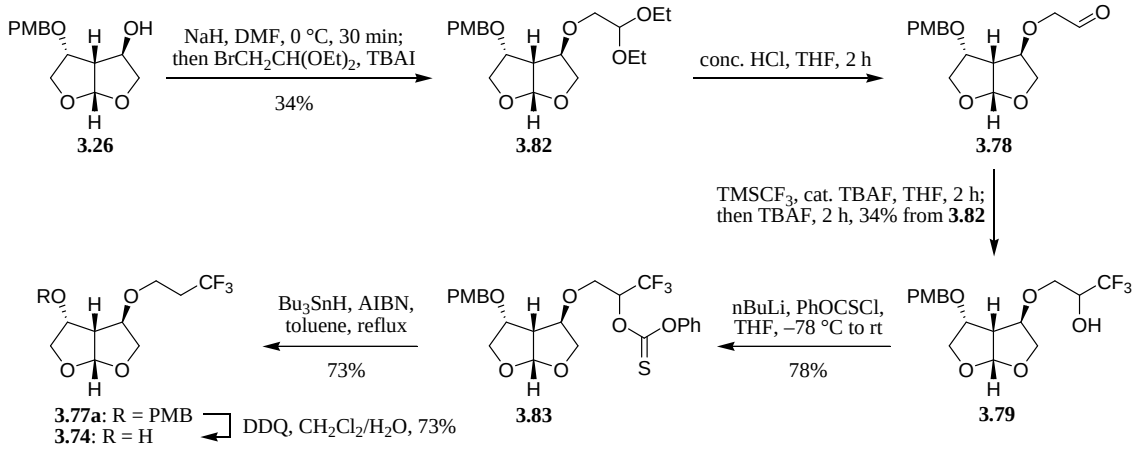
Scheme 3-27. Alternative approach to ether **3.77a**.

Initial attempts of the synthesis of aldehyde **3.78** are outlined below (Scheme 3-28). Reduction of acid **3.72** with $LiAlH_4$ afforded alcohol **3.80**, which was then treated with PCC to afford a complex mixture of the desired aldehyde **3.78**, ketone **3.27** and several other unidentified products. Parikh-Döring oxidation also only gave traces of the aldehyde. It was then attempted to derive **3.78** from allylether **3.81**, which was obtained in good yield from alcohol **2.26** and allyl bromide. However, ozonolysis with subsequent Ph_3P work-up only yielded after column chromatography an inseparable mixture of aldehyde **3.78** and triphenylphosphine oxide. Efforts to remove Ph_3PO with Merrifield peptide resin were not successful.[113]



Scheme 3-28. Attempted formation of acetaldehyde **3.78**.

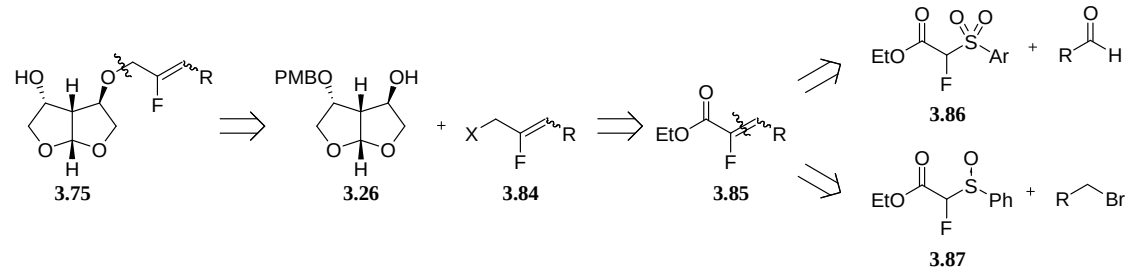
Eventually, acetaldehyde **3.78** could be synthesised from diethylacetal **3.82** via acid-catalysed hydrolysis (Scheme 3-29).[114] The crude aldehyde **3.78** was directly treated with $TMSCF_3$ to afford secondary alcohol **3.79** after silyl removal.[111] Barton-McCombie deoxygenation to ether **3.77a** was achieved in two steps: (1) formation of thionocarbonate **3.83** with PhOCSCl and (2) radical deoxygenation using tributyltin hydride and azobisisobutyronitrile (AIBN) as radical initiator in refluxing toluene.[115] DDQ oxidation subsequently furnished the alcohol **3.74**. Alcohol **3.79** and thionocarbonate **3.83** are a 1:1 mixture of two diastereoisomers as observed by ^{19}F NMR (**3.79**: δ −77.77 (d, J = 6.4 Hz), −77.84 (d, J = 6.4 Hz) ppm; **3.82**: δ −74.64 (d, J = 6.2 Hz), −74.62 (d, J = 6.2 Hz) ppm).



Scheme 3-29. Synthesis of fluoroalkyl ether **3.74**.

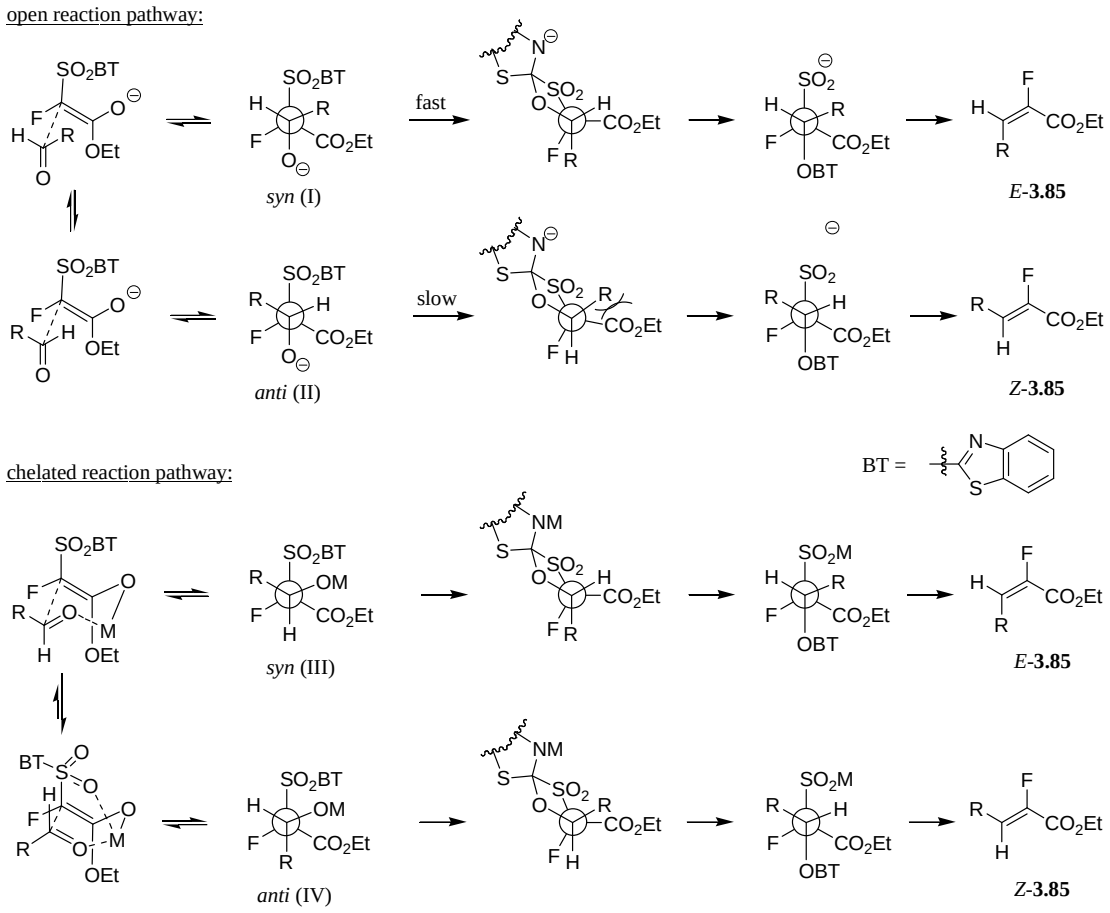
3.2.3.2 Synthesis of fluoroalkenes as amide isosteres

The retrosynthesis of fluoroalkene **3.75** is shown in Scheme 3-30. Cleavage of the C−O bond will give alcohol **3.26** and halide **3.84**, which in turn is derived from α-fluoro acrylate **3.85**. Disconnection of the double bond leads to sulfonylester **3.86** and the corresponding aldehyde. Alternatively **3.85** can be obtained from sulfinylester **3.87** and a halide.



Scheme 3-30. Retrosynthesis of fluoroalkene **3.75**.

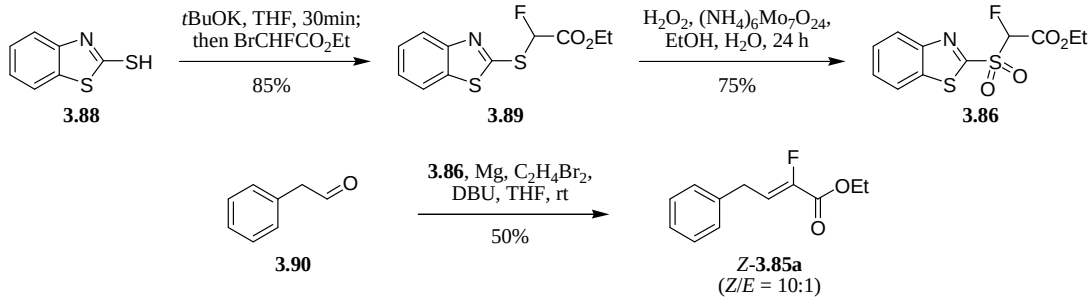
Zajc *et al.* developed a mild, high-yielding access to α-fluoroacrylates utilizing alkyl α-(1,3-benzothiazol-2-yl-sulfonyl)-α-fluoroacetates in a modified Julia olefination.[116] Further modifications by Lequeux *et al.* allowed a better stereocontrol of the reaction.[117] Here the use of *in situ* generated $MgBr_2$ yields the *Z*-fluoroalkene as the major isomer. A plausible mechanism for this selectivity is given below (Scheme 3-31).



Scheme 3-31. Mechanism of Julia olefination to fluoroacrylate **3.85** for the open reaction pathway and proposed mechanism for chelated pathway .

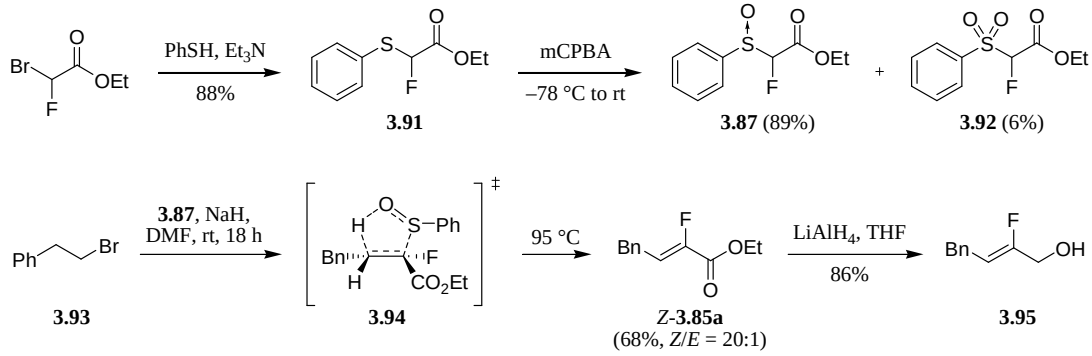
In the nonchelated pathway, initial attack of the enolate to the aldehyde can occur from both faces and is reversible. After a Smiles rearrangement, transfer of the benzothiazole from the sulfonate to the alkoxylate, and subsequent antiperiplanar elimination, this affords the *cis* and *trans* alkenes, respectively.[116] The energy barrier of the rearrangement is higher for *anti*-adduct (II), due to steric hindrance of the ester and the R-group, leading predominantly to the formation of *E*-**3.85** from the *syn*-adduct (I).[118] The modified reaction with $MgBr_2$ presumably proceeds via a closed transition state and results in the predominant formation of the *Z*-alkene.[117] A chair conformation, as shown for the formation of *E*-**3.85** via syn-adduct (III), is most likely. Alternatively a boat conformation could be predicted, allowing additional chelation from the sulfone as shown for the formation of *anti*-adduct (IV), which again undergoes a Smiles rearrangement and antiperiplanar elimination to form *Z*-**3.85**. Another explanation would be an altered reactivity of the intermediates during the irreversible Smiles rearrangement. However, the exact pathway remains hard to predict and many plausible mechanisms have been suggested.[119]

Sulfonylester **3.86** was synthesised in two steps from 2-mercaptobenzothiazole (**3.88**) and ethyl 2-bromo-2-fluoroacetate (Scheme 3-32).[117] Oxidation of the intermediate sulfide **3.89** to sulfone **3.86** was achieved with hydrogen peroxide and catalytic ammonium molybdate. Reaction of aldehyde **3.90** with sulfone **3.86** in the presence $MgBr_2$/DBU afforded acrylate *Z*-**3.85a** in moderate yield and acceptable stereoselectivity (*Z*/*E* = 10:1).[117]



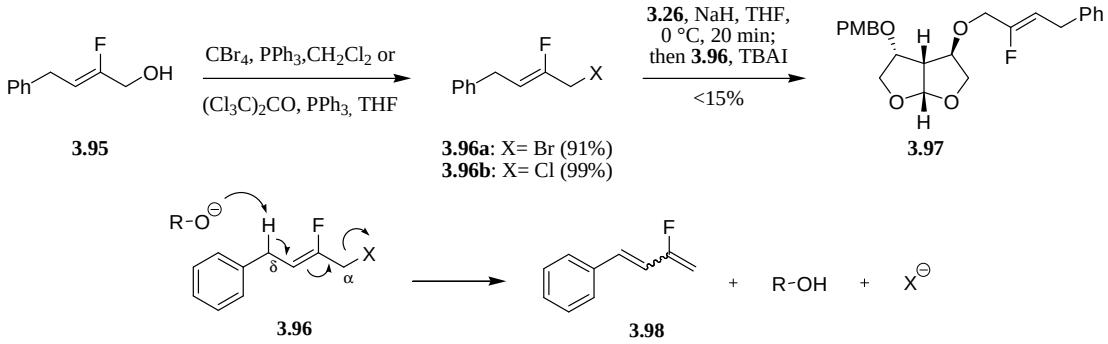
Scheme 3-32. Synthesis of sulfone **3.86** and Julia olefination to ***Z*-3.85a**.

Although the stereoisomers *Z*/*E*-**3.85a** could be separated by HPLC, a higher yielding procedure was sought. Allmendinger previously reported ethyl phenylsulfinyl fluoroacetate **3.87** as a versatile reagent for the synthesis of α-fluoro-α,β-unsaturated carboxylates.[120] Alkylation of thiophenol with ethyl 2-bromo-2-fluoroacetate afforded sulfide **3.91**, which was oxidised with 3-chloro-perbenzoic acid (mCBPA) to sulfinylester **3.87**. Only traces of sulfone **3.92** were observed. Sulfoxide **3.87** was then reacted with 2-phenylethyl bromide **3.93** to furnish alkene *Z*-**3.85a** in good yield and excellent diastereoselectivity (*Z*/*E* = 20:1).[121] The reaction proceeds via transition state **3.94**, in which the benzyl group and CO_2Et are in a *trans* configuration.[120] Subsequent reduction of *Z*-**3.85a** with $LiAlH_4$ afforded alcohol **3.95** in 86% yield.



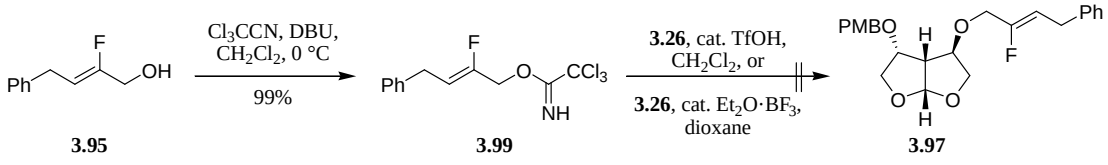
Scheme 3-33. Formation of alkene ***Z*-3.85a** from sulfoxide **3.87**.

Halogenation of fluoroalcohol **3.95** with carbon tetrabromide or hexachloroacetone in the presence of triphenylphosphine gave the corresponding bromide **3.96a** and chloride **3.96b** in excellent yield (Scheme 3-34). However, all attempts to directly couple halides **3.96** to alcohol **3.26** only afforded complex mixtures with the desired ether **3.97** as a minor product. This could be due to the labile nature of halides **3.96**, which were found to decompose easily in the presence of traces of acid or water. Alternatively, deprotonation at the acidic δ-CH_2 of **3.96** might be favoured over S_N2 attack on the α-carbon. The formation of elimination product **3.98** is possibly the major reaction pathway, as no halide **3.96** could be recovered.



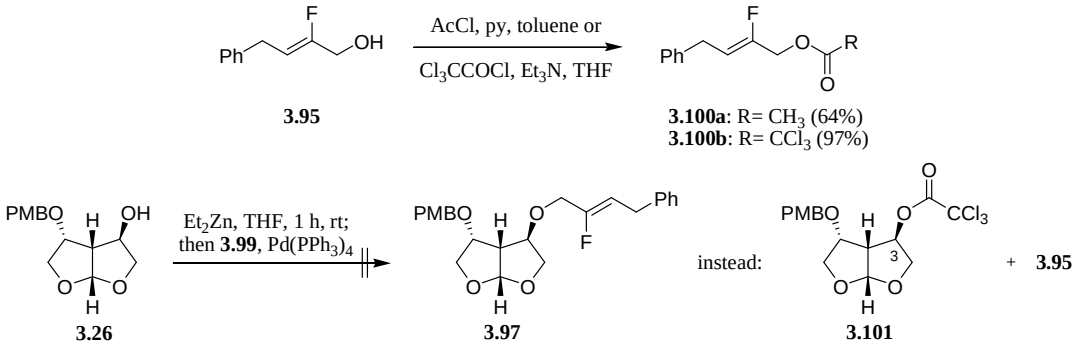
Scheme 3-34. Attempted formation of ether **3.97** from halide **3.96** and possible side reaction.

Further investigations into the formation of ether **3.97** were focussed on the use of trichloroacetamides and palladium-catalysed etherification. Trichloroacetamides, which are readily available from the reaction of alcohols with trichloroacetonitrile,[122] have been established as useful intermediate for allylation,[123] benzylation[124] and glycoside conjugation reactions.[125] Trichloroacetimidate **3.99** was obtained in excellent yield from alcohol **3.95** (Scheme 3-35). Unfortunately, the subsequent coupling reaction with *bis*-THF alcohol **3.26** and catalytic amounts of trifluoromethanesulfonic acid (TfOH)[126,127] or boron trifluoride etherate ($Et_2O{\cdot}BF_3$)[127] did not produce any of the desired product **3.97**, and only starting materials were recovered. Additional trial reactions with **3.99** and a simple secondary alcohol under different solvent conditions did not give any product either, indicating that the reactivity of the acetamide is again reduced by the fluorine substituent.



Scheme 3-35. Attempted synthesis of **3.96** from acetamide **3.98**.

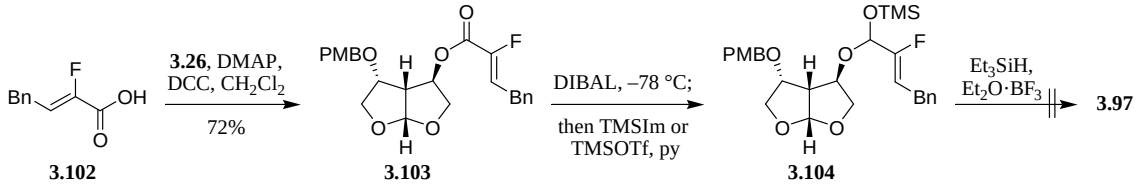
It was now attempted to form ether **3.97** via a palladium-catalysed allylic etherification using zinc(II) alkoxides.[128,129] Alcohol **3.95** was first transformed into the corresponding acetate **3.100a** (Scheme 3-36). Subsequent treatment of the preformed zinc(II) alkoxide of alcohol **3.26** with ester **3.100a** and catalytic amounts of $Pd(PPh_3)_4$ should give ether **3.97**.



Scheme 3-36. Attempted formation of **3.97** via Pd-catalysed allylic etherification.

When $Pd(PPh_3)_4$ was generated *in-situ*[129] from triphenylphosphine and palladium(II) acetate, only a mixture of the starting materials was obtained. Slight modifications of the conditions reported by Kim and Lee,[128] afforded traces of a new compound according to ^{19}F NMR analysis (δ −121.1 ppm). In particular, commercial $Pd(PPh_3)_4$ was used under argon atmosphere and the exclusion of light. When trichloroacetate **3.100b** was used under the same conditions, a 1:1 mixture of ester **3.101** and starting alcohol **3.95** was obtained in 43 % yield, which co-eluted from the column. Ester **3.101** was identified by a significant downfield shift of proton H-3 in the ^1H NMR (δ = 5.71 ppm compared to 4.67 ppm in **3.26**). The new compound from the reaction of **3.26** with ester **3.100a** was also identified as fluoroalkene **3.95** (^{19}F MNR: δ −121.1 ppm). The observed transesterification of the trichloroacetate underlines the low reactivity of these fluoroalkenes towards S_N2 reactions.

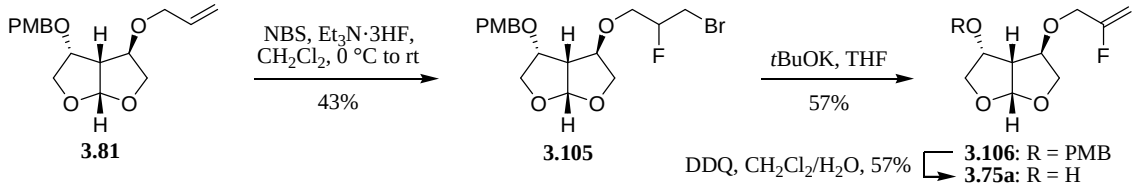
As all direct coupling approaches proved ineffective, it was then envisaged to derive ether **3.97** from the corresponding ester **3.103**, which was obtained in good yield from DCC mediated coupling of acid **3.102** and alcohol **3.26** (Scheme 3-37).



Scheme 3-37. Synthesis of ester **3.102** and attempted reduction to **3.96.**

Treatment of ester **3.103** with DIBAL at −78 °C and trapping of the intermediate hemiacetal with TMS-imidazole[130] or trimethylsilyl triflate (TMSOTf)[131] yielded the TMS-acetal **3.104** according to ^{19}F NMR analysis. Further reduction with $Et_3SiH/BF_3{\cdot}OEt_2$[132] only afforded a complex mixture with alcohol **3.26** as a major product. However, the presence of **3.26** indicates that the initial DIBAL reduction was successful. The work-up of the second step involves the treatment of the reaction mixture with TBAF to remove any silyl side products. It would also remove the TMS group from **3.104** to afford the free hemiacetal, which would then be cleaved to alcohol **3.26** and the corresponding aldehyde of **3.102**.

Eventually, the synthesis of the unsubstituted fluoroalkene **3.106** was achieved via diastereoselective bromofluorination of ally ether **3.81** with *N*-bromosuccinimide (NBS) in the presence of triethylamine tris(hydrofluoride), to give ether **3.105** (Scheme 3-38).[133] Subsequent dehydrobromination with potassium *tert*-butoxide furnished fluoroalkene **3.106**, which was debenzylated with DDQ to yield alcohol **3.75a**.



Scheme 3-38. Synthesis of fluoroalkene **3.75a**.

3.3 HALOGENATED *BIS*-THF LIGANDS

In Chapter 2, the possible effects of halogen substituents on the activity of DRV were described. In addition to the already mentioned 5-*exo*-chlorinated and 5-*exo*-fluorinated *bis*-THF analogues **3.107**/**3.108**, the synthesis of the 5-difluoro derivative **3.109** was also envisaged (Figure 3-2).

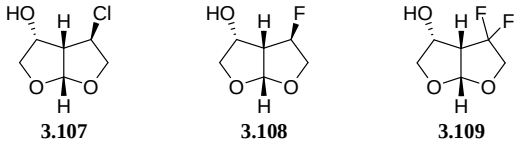
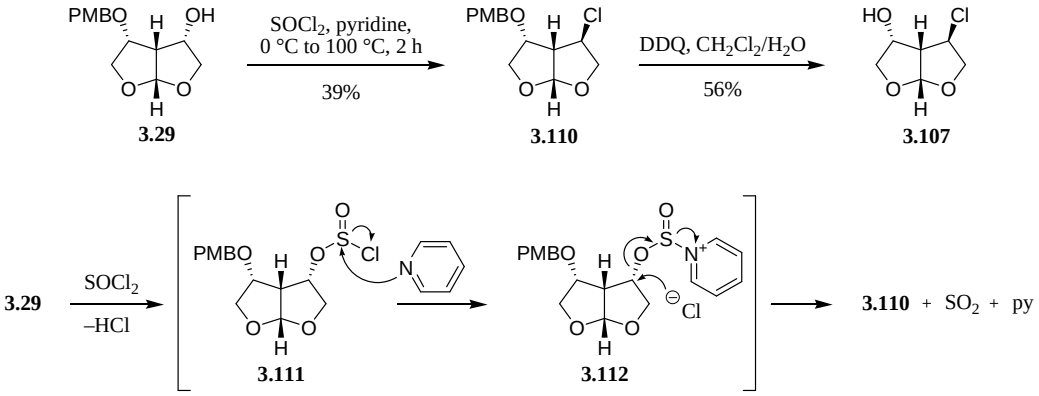


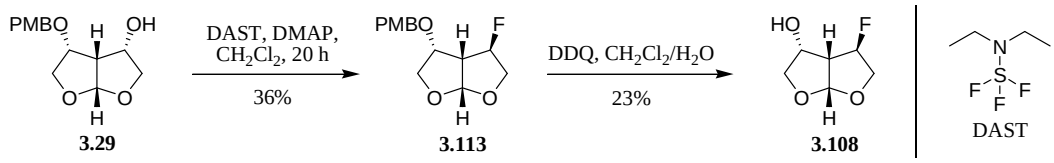
Figure 3-2. Halogenated bis-THF analogues **3.107−109**.

Chloride **3.107** was obtained in two steps from *endo*-alcohol **3.29** via chlorination with thionyl chloride in pyridine[134,135] to **3.110**, followed by DDQ oxidation to alcohol **3.107** (Scheme 3-39). The chlorination step proceeds with inversion of configuration, since pyridine displaces the second chloride in chloro sulfite **3.111** to form intermediate **3.112**. A subsequent S_N2 attack by the chloride ion will then lead to **3.110**.[136] Chlorination of *exo*-alcohol **3.26** with $SOCl_2$ under retention conditions has not been investigated.



Scheme 3-39. Synthesis of chloride **3.107**.

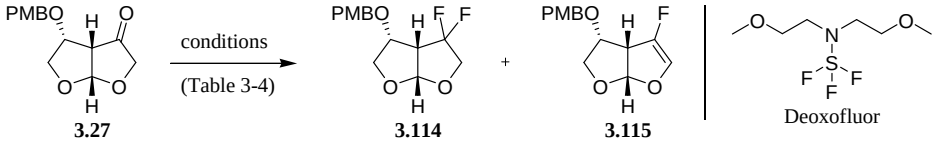
Similarly, the reaction of alcohol **3.29** with diethylaminosulfur trifluoride (DAST) in the presence of catalytic amounts DMAP afforded *exo*-fluoride **3.113** (Scheme 3-40). The removal of the PMB-protection proved to be rather challenging. Initially, hydrogenation appeared to be the best approach, but neither the treatment of PMB-ether **3.113** with Pd/C nor Pd-black gave the desired product. On the other hand debenzylation with DDQ afforded alcohol **3.108** in 23% yield.



Scheme 3-40. Formation of fluoride.

The synthesis of difluoride **3.114** from ketone **3.27** was performed with DAST or Deoxofluor™ at various temperatures and in different solvents (Table 3-4).

Table 3-4. Formation of difluoride **3.114**.

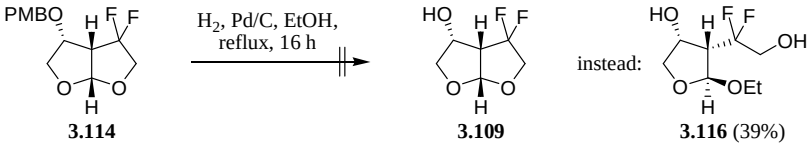


Entry	Reagent (equiv)	Solvent	T in °C	t (h)	yield (%)[a]	
					3.114	**3.27**
1	DAST (4.0)	CH_2Cl_2	−15 °C → rt	20	24	50
2	DAST (10.0)		−45 °C → rt	45	39	31
3	DAST (6.0)		0 °C → 45 °C → rt	68	35	53
4	DAST (5.0)		0 °C → rt	16 d	**66**	19
5	Deoxofluor (2.5)	$CHCl_3$	0 °C → 75 °C	72	32	59

[a] isolated yield.

Initial reactions with DAST (entries 1,2) only afforded moderate yields of the desired difluoride **3.114**. Whilst heating of the reaction to reflux temperature did not favour the reaction (entry 3), the yield was considerably improved by extending the reaction time to 16 days (entry 4). Alternatively, Deoxofluor™ was used to form difluoride **3.114**, but again only moderate yields were obtained. In all cases only traces of the expected side product, fluoroalkene **3.115**, were observed (less than 5% by ^{19}F NMR).

Due to the low yields of the DDQ-oxidation of **3.113**, further investigations into the hydrogenation were made. The treatment of ether **3.114** with Pd-black at rt only showed little conversion to the corresponding alcohol **3.109**. However, hydrogenation of **3.114** with Pd/C in refluxing ethanol afforded one major product, which was found to be the debenzylated, ring-opened acetal **3.116** (Scheme 3-41).



Scheme 3-41. Attempted debenzylation of PMB-ether **3.114**.

Acetal **3.116** crystallised from the NMR-solvent ($CDCl_3$). This allowed us to obtain a crystal structure, which is shown below (Figure 3-3).

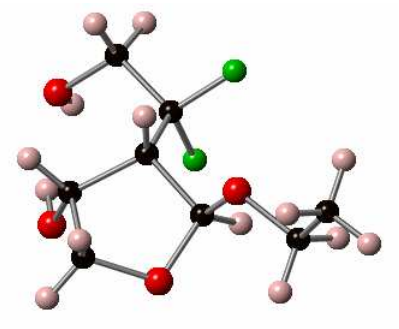
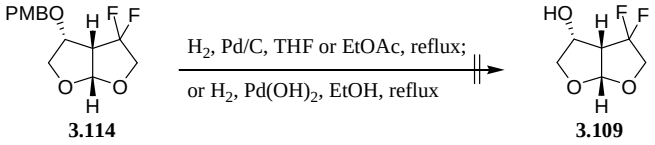


Figure 3-3. X-ray structure of acetal **3.116**.

In order to prevent the formation of this side product, the reaction conditions were slightly adapted (Scheme 3-42). The more basic catalyst $Pd(OH)_2$ was used instead of Pd/C and, in two other reactions, EtOH was replaced by the aprotic THF and EtOAc, respectively.



Scheme 3-42.

However, none of the reactions yielded the desired alcohol **3.109** or the previously isolated diol **3.116**. Only starting material was recovered in both reactions. These results now actually suggest, that the acidic nature of the catalyst (Pd/C) firstly enabled the nucleophilic attack of ethanol on the acetal and then, subsequent debenzylation led to the obtained product **3.117**, rather than vice versa. An attempt to remove the PMB group by oxidation with ceric ammonium nitrate (CAN)[137] only afforded a complex product mixture. Similarly, treatment of diol **3.116** with $TFA/CH_2Cl_2/H_2O$[68] did not yield the re-cyclised *bis*-THF **3.109**.

3.4 SUMMARY

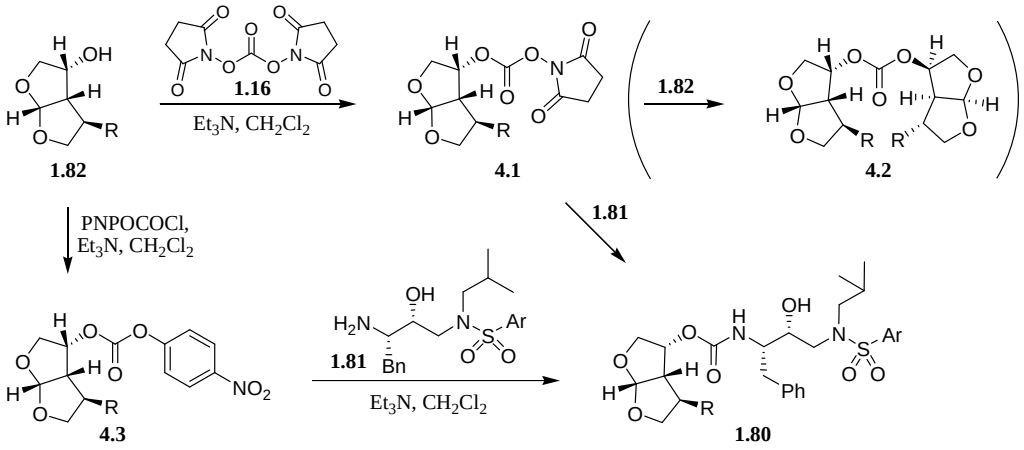
A high yielding route to *exo*-amine **3.32** has been established. The route includes an oxidation-reduction sequence to inverte the *exo*-hydroxy group, as a direct inversion via halogenation or Mitsunobu reaction could not be achieved. Amine **3.32** contains a stable PMB protection on the *endo*-alcohol group, which can be easily removed with DDQ after functionalisation of the amino group. Four new C4-substituted *bis*-THF ligands were synthesised including three substituted amines and one azide. The obtained amino ligands **3.41a-c** represent the three proposed structures with combined HB donor/acceptor ability, as discussed in Chapter 2.

Starting from *endo*-protected *bis*-THF *bis*-diol **3.26**, seventeen new *O*-substituted *bis*-THF analogues have been synthesised. These include eight arylated or benzylated moieties, three alkoxyalkyl ether, a series of acetamide analogues as well as two fluorinated ether. The acetic acid derivative **3.72** might prove a valuable intermediate for further substitutions, like oxazoles or other heterocycles. In addition, two halogenated *bis*-THF analogues could be derived from *endo*-alcohol **3.29**.

In the next chapter, the activation of the synthesised ligands and the formation of the desired protease inhibitors is discussed in detail.

Chapter 4 ACTIVATION AND PI FORMATION

The desired protease inhibitors **1.80** are obtained by coupling the activated *bis*-THF ligand to amines **1.81**, which were provided by Tibotec. Activation of the *bis*-THF alcohol **1.82** was usually achieved with *N*,*N*'-disuccinimidyl carbonate (DSC, **1.16**)[40] to give the mixed carbonate **4.1** (Scheme 4-1). Occasionally further reaction of **4.1** with a second equivalent of **1.82** to the symmetric carbonate **4.2** was observed. Carbonate **4.2** lacks a good leaving group and thus does not react with amines **1.81**. However, treatment of **4.2** with methanolic KOH will recover the starting alcohol **1.82**. If DSC activation failed, alcohol **1.82** was activated with *para*-nitrophenyl chloroformate (PNPOCOCl) to carbonate **4.3**.



Scheme 4-1. Activation of *bis*-THF ligands and PI formation.

Initially we focussed on the synthesis of PIs containing the amine scaffolds **1.81a** and **1.81b** (Figure 4-1). The *para*-aniline substituted sulfonamide **1.81a**[32] is incorporated in the original darunavir structure and provides two hydrogen bond donors to the S2' pocket (compare 1.2.1). Benzoxazole derivative **1.81b** was reported to give an enhanced binding to the S2' pocket by additional HB contacts between the oxazole nitrogen and the backbone NH of Asp30'.[44] At a later stage the *para*-methoxy substituted sulfonamide **1.81c** and benzopyrazine **1.81d** were also included.

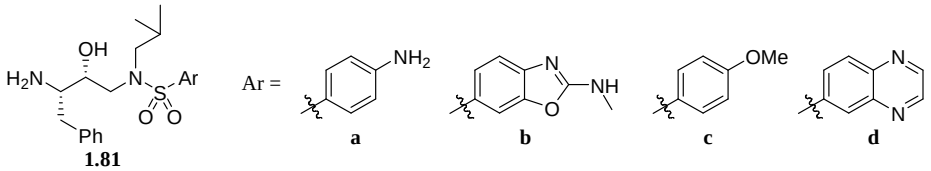
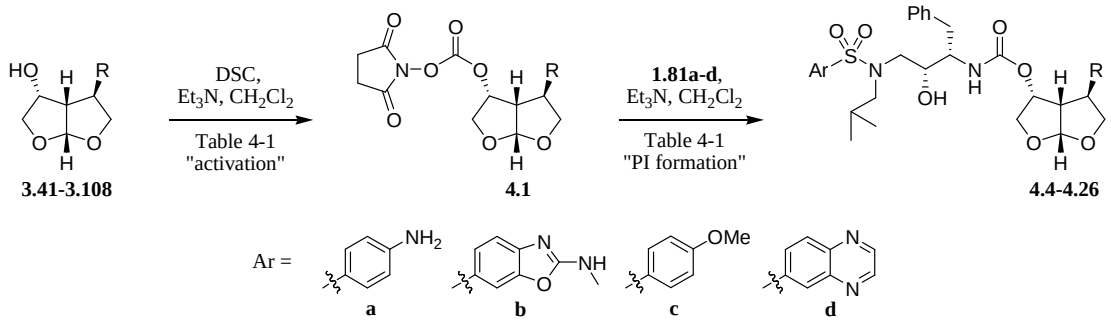


Figure 4-1. Incorporated amine scaffolds **1.81a-d**.

The activation of *bis*-THF ligands **3.41−3.108** and PI formation are shown in Table 4-1.

Table 4-1. Formation of PIs **4.4−4.26**.



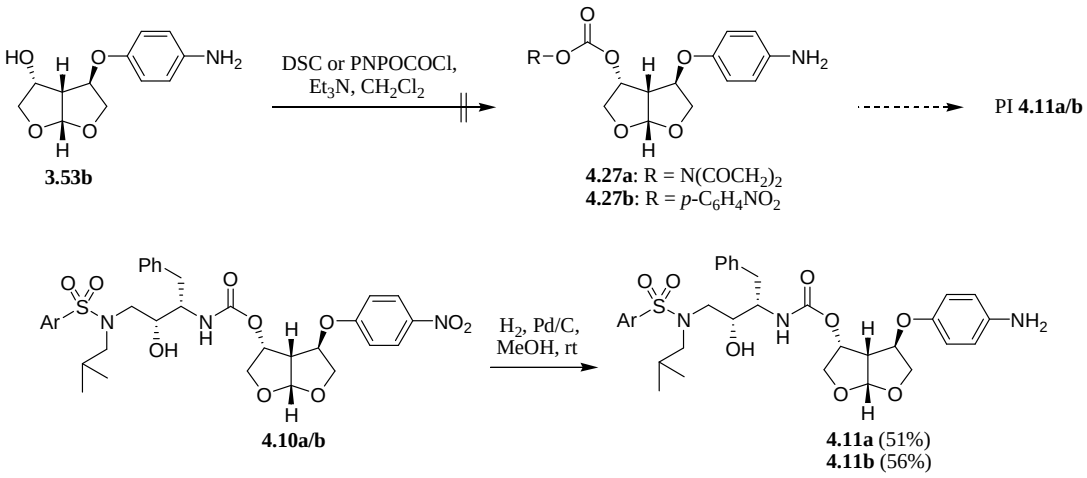
Entry	PI	R =	Activation		PI formation (yield (%))[b]			
			alcohol	yield (%)[a]	a	b	c	d
1	**4.4**	OBn	**3.45**	86	40	64	−	−
2	**4.5**	O(2-F-Bn)	**3.49a**	95	−	67	−	−
3	**4.6**	O(3-F-Bn)	**3.49b**	91	−	65	−	−
4	**4.7**	O(4-F-Bn)	**3.49c**	90	−	65	−	−
5	**4.8**	O(2,4-diF-Bn)	**3.49d**	74	−	67	−	−
6	**4.9**	OPh	**3.50b**	55	70	−	−	−
7	**4.10**	O-(4-NO_2-C_6H_4)	**3.52b**	66[c]	60	49	−	−
8	**4.11**	O-(4-NH_2-C_6H_4)	**3.53b**	−	(51)[d]	(32)[d]	−	−
9	**4.12**	OCONHBn	**3.55**	86	60	63	−	−
10	**4.13**	$NHCO_2Bn$	**3.41a**	78	90	61	−	−
11	**4.14**	$NH(CO)_2OBn$	**3.41b**	–[e]	–	–	–	–
12	**4.15**	$NHSO_2Bn$	**3.41c**	–[e]	–	–	–	–
13	**4.16**	$O(CH_2)_2OMe$	**3.57**	83	64	69	−	59
14	**4.17**	OCH_2OMe	**3.59**	90	−	65	−	−
15	**4.18**	OCH_2SMe	**3.61**	62	−	74	−	−
16	**4.19**	$O(CH_2)_2CF_3$	**3.74**	93	−	70	−	−
17	**4.20**	$OCH_2CONHBn$	**3.67a**	86	68	70	88	−
18	**4.21**	$OCH_2CONHMe$	**3.67b**	64	−	84	82	−
19	**4.22**	OCH_2CONMe_2	**3.67c**	69	−	61	83	−
20	**4.23**	$OCH_2CF{=}CH_2$	**3.75a**	70	−	77	−	−
21	**4.24**	N_3	**3.42**	55[c]	70	−	−	−
22	**4.25**	Cl	**3.107**	72	64	73	−	−
23	**4.26**	F	**3.108**	−	−	12[f]	−	−

[a] isolated yield, [b] isolated yield after HPLC, [c] PNPOCOCl was used instead of DSC, [d] derived from PIs **4.10**, [e] stability issues(see below), [f] yield from **3.108**.

Activation of the substituted *bis*-THF alcohols to the corresponding mixed carbonates **4.1** was achieved with DSC in good to excellent yields. Only analogues **3.52b** and **3.42** (entries 7,21) were activated with *para*-nitrophenyl chloroformate, as the reaction with DSC afforded the desired carbonate **4.1** in a mixture with the corresponding symmetric carbonate **4.2** in variable ratios and only low yields. Normally, the mixed carbonates **4.1** were coupled to benzoxazole containing amine **1.81b** and/or aniline substituted amine **1.81a**. *Bis*-THF ligands that showed interesting results in first activity tests were subsequently derivatised with other amines. In particular, the benzopyrazine containing PI **4.16d** of methoxyethoxy ligand **3.57** (entry 13) and the *para*-methoxyphenyl sulfomanide PIs **4.20-4.22c** of acetamides **3.41** (entries 17−19) have been synthesised.

For PI **4.26** (entry 23) only a small amount of starting alcohol **3.108** was available, it was therefore attempted to perform activation and coupling step in one pot by successively adding the reagents. However, only 12% of the desired PI **4.26** could be obtained after HPLC.

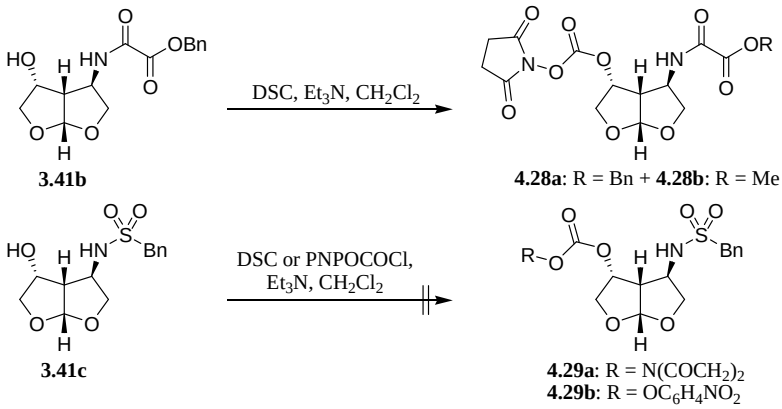
The direct activation of alcohol **3.53b** with DSC or PNPOCOCl failed, as the aromatic amine and the hydroxy group show similar reactivity towards the carbonates (Scheme 4-2). It was therefore decided to derive the desired PIs **4.11a/b** from the corresponding *para*-nitro substituted PIs **4.10a/b**. Selective reduction of the aromatic nitro group to an aromatic amine was achieved via Pd-catalysed hydrogenation.



Scheme 4-2. Synthesis of PIs **4.11a/b**.

Out of the three substituted amino alcohols **3.41a-c** only carbamate **3.41a** could be successfully activated with DSC and subsequently reacted with amines **1.81a/b** to provide PIs **4.13a/b** in good to excellent yield (entry 10). For oxalate **3.41b** and sulfonamide **3.41c** the activation proved less straight forward. Although DSC activation of oxalate **3.41b**

proceeded smoothly according to TLC analysis, a mixture of at least 4 compounds was obtained after column chromatography (Scheme 4-3). Similarly, the reaction of sulfonamide **3.41c** with DSC or PNPOCOCl only afforded complex mixtures with the desired carbonates **4.29a** and **4.29b** as minor products.



3.41b

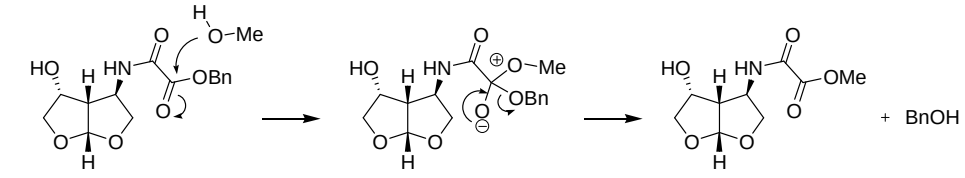
4.28a: R = Bn + **4.28b**: R = Me

3.41c

4.29a: R = $N(COCH_2)_2$
4.29b: R = $OC_6H_4NO_2$

Scheme 4-3. Attempted activation of alcohols **3.41b/c**.

Further analysis of the activation product of **3.41b** revealed that product and starting material are prone to nucleophilic attack. During the purification process the product **4.28a** reacted with methanol, which was used as a co-eluent, to form the corresponding methyl ester **4.28b**. A similar reaction was observed during the mass spectrometric analysis of **3.41b**, which showed an intensive signal at *m/z* = 254.1 (for **4.30**) instead of the expected signal at *m/z* = 330 $(M+Na)^+$ (Scheme 4-4). Akin to the reaction with methanol, water or amine **1.81** might be able to attack the carbonyl group in the oxalate leading to undesired product mixtures. The usefulness of oxalate **3.41b** as a P2 ligand is therefore debatable.



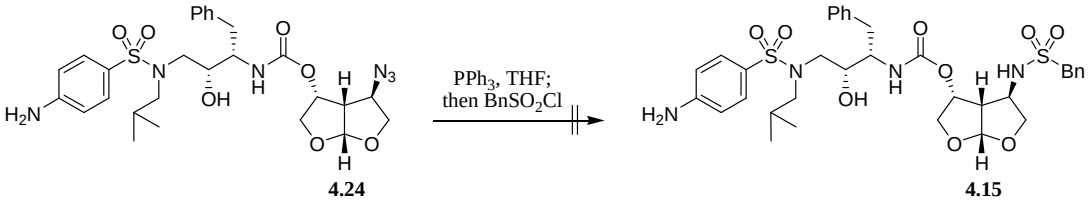
3.41b
m/z = 330 $(M+Na)^+$

4.30
m/z = 254 $(M+Na)^+$

Scheme 4-4. Possible nucleophilic attack of MeOH on **3.41b**.

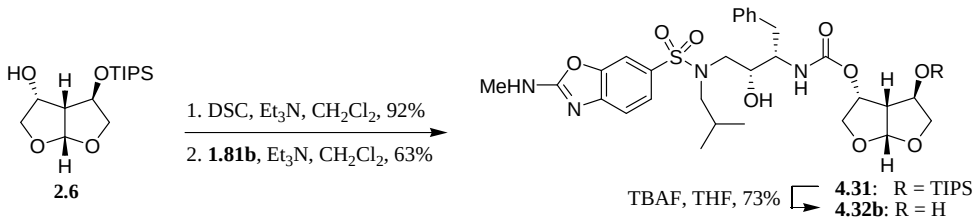
Since the activation of alcohol **3.41c** proved troublesome, it was attempted to derive the sulfonamide PI **4.15** from the azide containing PI **4.24** (Scheme 4-5). The azide group in **4.24** was reduced with triphenylphosphine and the crude product was then treated with phenylmethanesulfonyl chloride to form PI **4.15**. However, no product could be obtained

from the reaction. Due to the encountered problems, no further investigations into the sulfonamide substituted PIs were made.



Scheme 4-5. Attempted synthesis of PI **4.15** from **4.24.**

In addition to the already described hydroxy PIs **1.80a-d** (see 1.4), the corresponding benzoxazole containing PIs **4.32b** was synthesised from silyl ether **2.6** in three steps (Scheme 4-6). Activation with DSC was followed by coupling to amine **1.81b** to yield the protected PI **4.31**. TBAF-mediated desilylation led subsequently to the desired hydroxy analogue **4.32b**.



Scheme 4-6. Formation of hydroxy PI **4.31b** from silyl ether **2.6**.

A total of 34 new protease inhibitors have been synthesised, they include 21 different disubstituted bis-THF scaffolds and 4 different aromatic sulfonamide substituents. Following the different target groups outlined in Chapter 2, the structures of these PIs are shown below (Figure 4.2 to 4.4).

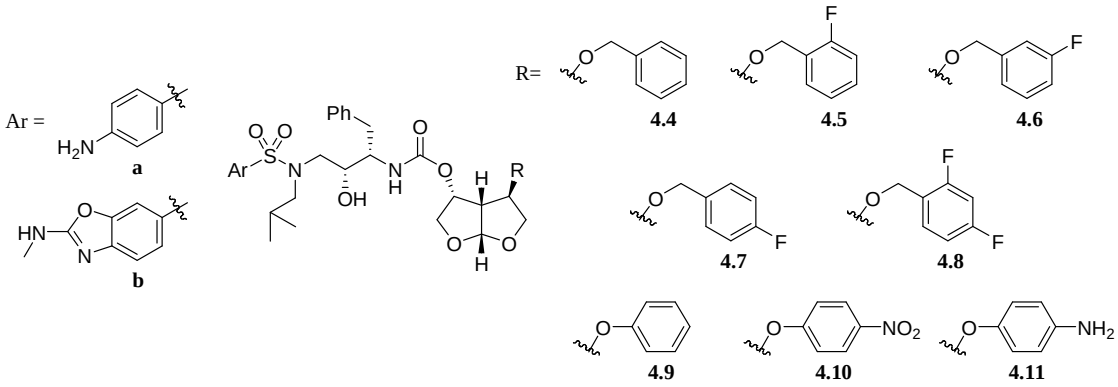


Figure 4-2. Hydrophobic PIs.

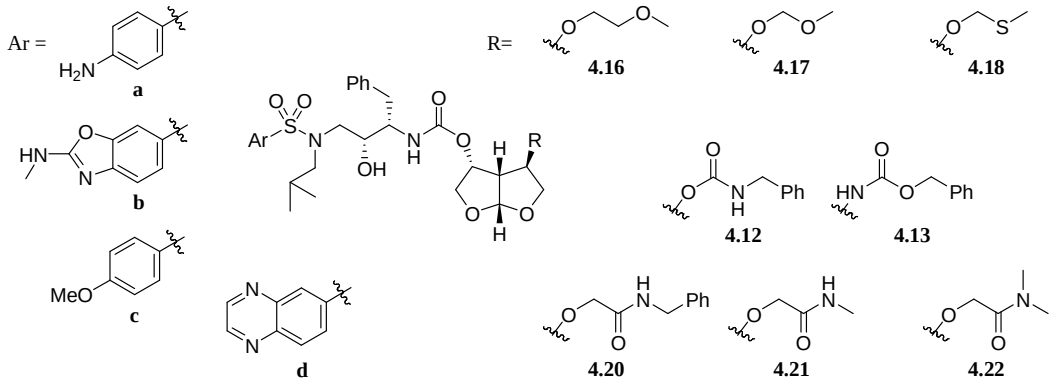


Figure 4-3. PIs with hydrogen bond donor and/or acceptor ability.

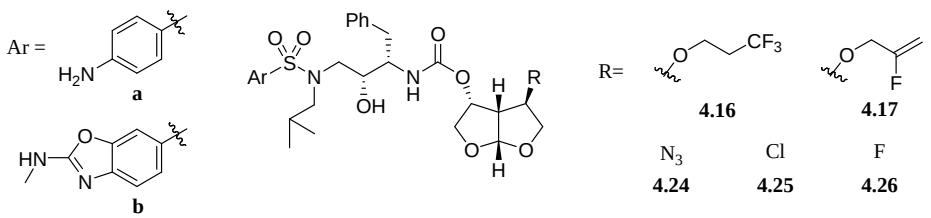


Figure 4-4. Halogenated and azide-containing PIs.

Chapter 5 ANTIVIRAL ACTIVITY AND MOLECULAR MODELLING

5.1 RESISTANCE TO PROTEASE INHIBITORS

Drug resistance to PIs emerges when mutations in the HIV-1 protease gene allow the enzyme to retain its catalytic activity in the presence of the drug. In particular, the enzyme is still able to cleave the *gag-pol* polyprotein in at least nine different recognition sites to produce mature virus particles. Mutations occur due to the high replication rate of the virus, the lack of proofreading capacity of the RT and most importantly the selective pressure of PI therapy on the evolution of the virus.[26,138] Most mutants show a reduced efficiency in comparison to the wild-type virus and are rapidly outgrown by fitter viruses in untreated patients. However, in the presence of drug-induced pressure, replication of the wild-type virus will be impaired and mutant strains with reduced susceptibility can outgrow efficiently.[139] Since the advent of protease inhibitors in 1996, resistance to all marketed PIs has been reported and mutations in 38 out of the 99 amino acid positions were identified.[27] An overview of mutations associated with decreased susceptibility to these inhibitors is shown in Table 5-1.

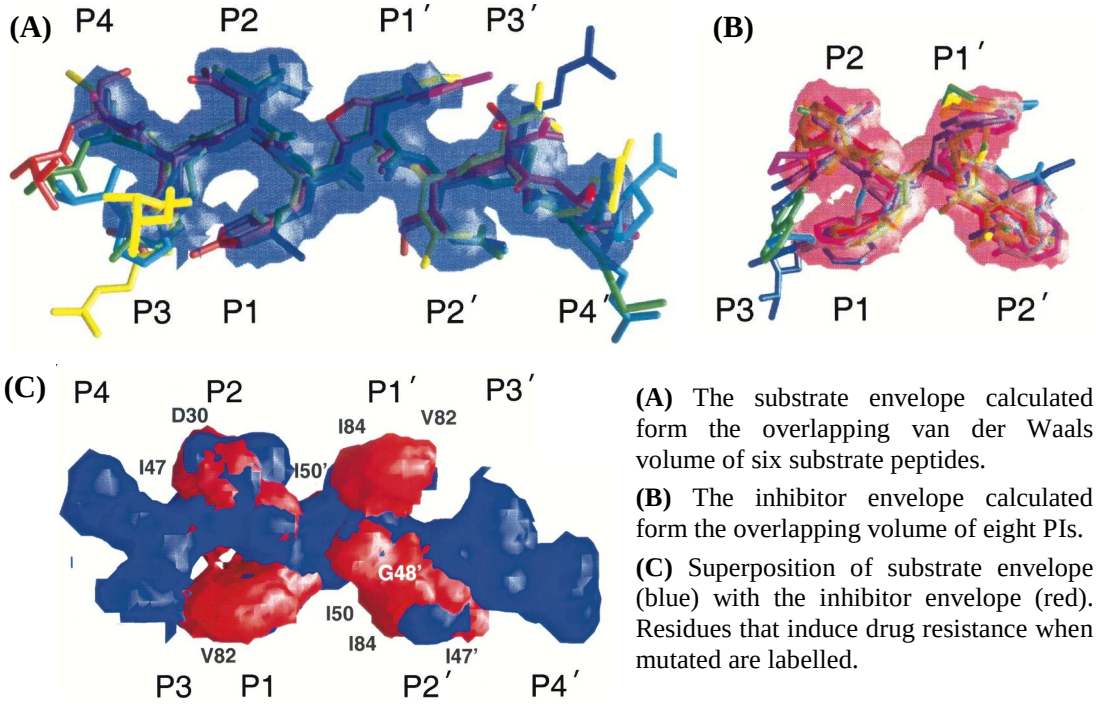
Table 5-1. Mutations in the protease gene associated with resistance to PIs[a]

PI[b]	Primary mutations	Secondary mutations positions
atazanavir	I50L, I84V, N88S	L10, G16, K20, L24, V32, L33, E34, M46, G48, F53, I54, D60, I62, I64, A71, G73, V82, I85, L90, I93
darunavir	I47V, I50V, I54M/L, L76V, I84V	V11, V32, L33, T74, L89
fosamprenavir	I50V, I84V	L10, V32, M46, I47, I54, G73, L76, V82, L90
indinavir	M46I/L, V82A/F/T, I84V	L10, K20, L24, V32, M36, I54, A71, G73, L76, V77, L90
lopinavir	V32I, I47V/A, L76V, V82A/F/T/S	L10, K20, L24, L33, M46, I50, F53, I54, L63, A71, G73, I84, L90
nelfinavir	D30N, L90M	L10, M36, M46, A71, V77, V82, I84, N88
saquinavir	G48V, L90M	L10, L24, I54, I62, A71, G73, V77, V82, I84
tipranavir	I47V, Q58E, T74P, V82L/T, I84V	L10, I13, K20, L33, E35, M36, K43, M46, I54, H69, N83, L90

[a] Data adapted from Ref. (27), [b] all boosted with ritonavir except nelfinavir

PI resistance mutations have been defined as "primary/major" or "secondary/minor" depending on their impact on inhibitor activity.[27] Primary mutations usually have a significant effect on inhibitor activity and they happen to be situated within the active site. Secondary mutations show only a small impact on the susceptibility to PIs, but can enhance resistance in combination with primary mutations or compensate for the reduced efficiency of the mutant virus.[139] In contrast to RTIs where single mutations can lead to >1000-fold decreased activity, high level resistance to PIs usually requires more than one primary mutation.[139]

While some primary mutations only affect one PI: e.g. Asp30→Asn (D30N) for nelfinavir, G48V for saquinavir or Q58E for tipranavir; other mutations are multi-drug-resistant as they were identified with more than one PI (I47V/A, I50V/L, V82A/F/L/S/T and I84V).[27] Based on their "substrate envelope" hypothesis, Schiffer *et al.* could show that the majority of the currently available PIs share a common "inhibitor envelope" resulting in contacts to the same residues of the protease (Figure 5-1, A and B).[138] Although being significantly smaller, the inhibitor envelope protrudes beyond the substrate envelope in several locations (Figure 5-1, C). These locations correspond to the residues of HIV-1 protease where most multi-drug-resistant mutations occur.[138]



(A) The substrate envelope calculated form the overlapping van der Waals volume of six substrate peptides.

(B) The inhibitor envelope calculated form the overlapping volume of eight PIs.

(C) Superposition of substrate envelope (blue) with the inhibitor envelope (red). Residues that induce drug resistance when mutated are labelled.

Figure 5-1. Substrate envelope vs. inhibitor envelope (pictures taken from Ref. ([138])).

Up to date, ten mutations associated to resistance to darunavir have been identified, including five primary mutations (I47V, I50V, I54M/L, L76V and I84V) and five secondary mutations (V11I, V32A, L33F, T74P, L89V).[27,140,141] In addition, one mutation (V82A) was detected that showed a positive impact on the virological response to ritonavir-boosted darunavir (DRV/r).[140,141] However, high level resistance to DRV/r (over 10-fold loss of activity) was only observed with three or more resistance associated mutations.[140] The described primary mutations mainly result in the loss of favourable hydrophobic interactions due to the shorter side chain residues.[36,142,143] Only in the case of I54M where the mutation induces a shift of the main chain atoms, the replacement of a direct HB between the aniline NH_2 of DRV and the side chain of Asp30 with a water-mediated contact was observed.[143] On the other hand, the V82A mutation results in a main chain shift towards the inhibitor and closer van der Waals interactions.[36]

5.2 ANTIVIRAL ACTIVITY

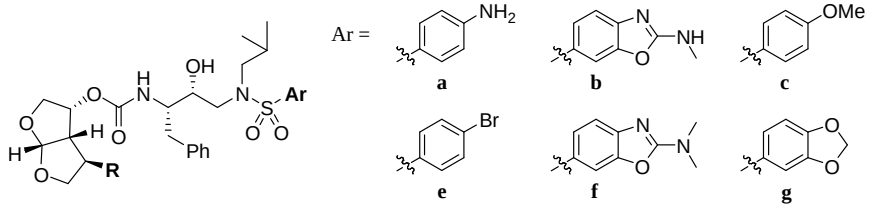
All synthesised PIs (**4.4−4.31**) were tested by Tibotec for their cellular antiviral activity (EC_{50}) against the wild-type virus (HIV-1_{IIIB}) and a panel of recombinant clinical isolates (M1−3), which were selected because of their high level of cross-resistance against several approved PIs (as exemplified by the activity of lopinavir and atazanavir). Every isolate has 6−8 amino acid substitutions in the protease gene that are associated with resistance to protease inhibitors, including the primary mutations M46I, G48V, I50V, L76V, V82A, I84V and L90M (see footnote of Table 5-2 for details).[27] Isolates M1 and M2 are of particular interest, as they were identified with primary mutations (I50V, I84V and L76V) that are associated with resistance to darunavir. The activity on HIV-1_{IIIB} was also measured in the presence of 50% human serum (HIV-1_{IIIB} + 50% HS) as an indication for the tendency of the compounds to bind to plasma proteins. A less than 10-fold change in activity is usually considered as an acceptable level of plasma protein binding.

The test results are divided into several groups according to the different types of targeted interactions that were proposed in Chapter 2.

5.2.1 The hydroxy analogues

In order to give an overview over the influence of the various aromatic sulfonamide substituents, the activities of the previously synthesised hydroxy analogues **4.32a-g** are summarized in Table 5-2. Atazanavir (entry 1), lopinavir (entry 2), darunavir (entry 3) and its previously described benzoxazole analogue **5.1b**[44] (entry 4) serve as reference compounds.

Table 5-2. Antiviral activity (EC_{50}) of OH-analogues **4.31** on HIV-1_{IIIB} and mutant viruses.[a]



Entry	PI	R	EC_{50} [nM][b] *(fold change relative to HIV-1_{IIIB})*				
			HIV-1_{IIIB} (WT)	HIV-1_{IIIB} + 50% HS	M1	M2	M3
1		atazanavir	7.2	13.3	58.0 *(8.4)*	3.2 *(0.5)*	60.5 *(8.8)*
2		lopinavir	13.2	63.2	114.6 *(8.7)*	307.3 *(23)*	32.1 *(2.4)*
3	**1.10**	H (darunavir)	6.6	17.2	11.3 *(1.7)*	51.0 *(7.8)*	2.3 *(0.4)*
4	**5.1b**	H	2.3	8.3	2.7 *(1.2)*	3.2 *(1.4)*	0.9 *(0.4)*
5	**4.32a**	OH	772.9	814.7	112.3 *(0.2)*	204.5 *(0.3)*	40.4 *(0.05)*
6	**4.32b**	OH	137.7	446.3	125.4 *(0.9)*	108.0 *(0.8)*	103.9 *(0.8)*
7	**4.32c**	OH	6.5	12.4	6.9 *(1.1)*	6.7 *(1.0)*	1.6 *(0.2)*
8	**4.32e**	OH	4.8	19.6	4.1 *(0.9)*	8.2 *(1.7)*	2.2 *(0.5)*
9	**4.32f**	OH	39.7	80.9	14.9 *(0.4)*	15.3 *(0.4)*	6.5 *(0.2)*
10	**4.32g**	OH	24.8	45.3	9.1 *(0.4)*	11.1 *(0.4)*	4.5 *(0.2)*

[a] The following PI resistance-associated mutations were identified in the isolates: ***M1:*** L10I, **M46I**, I64V, **I84V**, **L90M**, I93L; ***M2:*** L10I, I13V, **M46I**, **I50V**, L63P, **L76V**; ***M3:*** L10I, K20R, M36I, **G48V**, I62V, A71V, **V82A**, I93L; bold figures represent primary resistance mutations and underlined figures are associated with resistance to DRV according to the IAS (Ref. 27). [b] The EC_{50} values were determined using MT4 cells and all assays were conducted in quadruplicate. The numbers in parentheses represent the fold change in EC_{50} value for each isolate relative to the activity on wild-type HIV-1_{IIIB}.

All three approved PIs (entries 1−3) inhibit HIV-1_{IIIB} at low nanomolar concentrations (EC_{50} = 6.6−13.9 nM) but exhibit a great variation in their resistance profile. Atazanavir and lopinavir, which are, alongside darunavir, recommended for treatment of antiretroviral therapy-naïve patients, showed a decreased activity against the majority of mutants.

Interestingly, with atazanavir an increased inhibition of mutant M2 was observed. Darunavir (**1.10**, entry 3) is equally potent against isolate M1, but a loss in activity was noted with isolate M2, which bears two primary mutations known to be associated with decreased susceptibility to DRV (I50V and L76V). Mutant M3, which includes the favourable V82A mutation,[140] was found to be hypersusceptible to darunavir. Hypersusceptibility is defined as a lower fold-change on a mutant virus when being compared to the wild-type virus (FC<1) and has only been reported for a few cases.[49,140] The benzoxazole analogue **5.1b** (entry 4) is slightly more potent against HIV-1_{IIIB} and shows a better resistance profile against the mutant panel (EC_{50} = 0.9−3.2 nM) when compared to DRV.

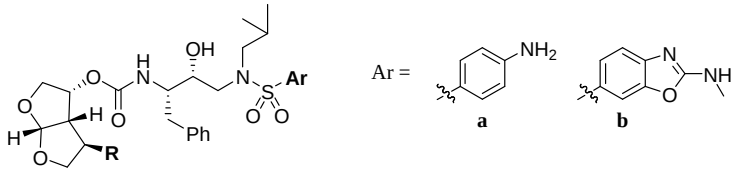
The majority of the hydroxy PIs **4.32a-g** (entries 5−10) are less potent on wild-type HIV-1 and their activity is strongly dependent on the sulfonamide substituent. However, in comparison to darunavir and PI **5.1b** they have a better resistance profile, with all three mutant strains showing hypersusceptibility to the majority of the hydroxy PIs. This might be due to additional interactions of the free hydroxy group with the enzyme (compare Chapter 2) as well as the different P2' ligands. Two general trends can be identified from the sulfonamide substitutions: Firstly, the uptake into the cell appears to be rather dependent on the number of hydrogen bond donors (HBD) than the total polar surface area (TPSA) of the molecule (e.g. compare **4.32a** (entry 5, HBD = 5, TPSA = 160.6 Å^2), **4.32b** (entry 6, HBD = 4, TPSA = 172.7 Å^2) and **4.32f** (entry 9, HBD = 3, TPSA = 163.9 Å^2). And secondly, bicyclic P2' ligands (Ar = **b**, **f**, **g**) seemingly have a greater influence on the hypersusceptibility characteristic of the PIs.

These preliminary results did not favour anilino substituent **a** and *N*-methylamino benzoxazole **b**. Nevertheless, they formed the basis for the new PIs due to their pronounced hydrogen bonding abilities in the S2' pocket.

5.2.2 The hydrophobic analogues

The antiviral activities of the benzyl PIs **4.4−4.8** and the aryl PIs **4.9−4.11** are summarized in Table 5-3. Darunavir (**1.10**), its benzoxazole analogue **5.1b** and the hydroxy PIs **4.32a/b** now serve as references (entries 1−4).

Table 5-3. Antiviral activity (EC_{50}) of PIs **4.4−4.11** on HIV-1_{IIIB} and mutant viruses.[a]



Entry	PI	R	EC_{50} [nM][b] *(fold change relative to HIV-1_{IIIB})*				
			HIV-1_{IIIB}	HIV-1_{IIIB} + 50% HS	M1	M2	M3
1	**1.10**	H (darunavir)	6.6	17.2	11.3 *(1.7)*	51.0 *(7.8)*	2.3 *(0.4)*
2	**5.1b**	H	2.3	8.3	2.7 *(1.2)*	3.2 *(1.4)*	0.9 *(0.4)*
3	**4.32a**	OH	772.9	814.7	112.3 *(0.2)*	204.5 *(0.3)*	40.4 *(0.05)*
4	**4.32b**	OH	137.7	446.3	125.4 *(0.9)*	108.0 *(0.8)*	103.9 *(0.8)*
5	**4.4a**	OBn	1.5	12.1	4.7 *(3.2)*	18.0 *(12)*	1.7 *(1.2)*
6	**4.4b**	OBn	0.8	3.7	1.7 *(2.2)*	3.4 *(4.5)*	1.0 *(1.3)*
7	**4.5b**	O(2-F-Bn)	0.7	4.0	1.3 *(2.0)*	2.1 *(3.1)*	0.9 *(1.3)*
8	**4.6b**	O(3-F-Bn)	0.6	3.7	0.8 *(1.2)*	1.7 *(2.7)*	0.8 *(1.3)*
9	**4.7b**	O(4-F-Bn)	0.6	4.0	1.1 *(1.8)*	2.3 *(3.8)*	1.0 *(1.6)*
10	**4.8b**	O(2,4-diF-Bn)	0.6	5.4	1.1 *(2.0)*	2.3 *(4.1)*	0.7 *(1.3)*
11	**4.9a**	OPh	8.9	47.2	32.5 *(3.6)*	249.1 *(28)*	6.5 *(0.7)*
12	**4.10a**	O-(4-NO_2-C_6H_4)	10.7	128.6	60.0 *(5.6)*	389.7 *(36)*	11.9 *(1.1)*
13	**4.10b**	O-(4-NO_2-C_6H_4)	2.5	15.3	5.0 *(2.0)*	19.9 *(8.0)*	2.2 *(0.9)*
14	**4.11a**	O-(4-NH_2-C_6H_4)	11.1	67.7	13.2 *(1.2)*	75.9 *(6.8)*	9.5 *(0.9)*
15	**4.11b**	O-(4-NH_2-C_6H_4)	8.3	68.8	6.5 *(0.8)*	12.3 *(1.5)*	2.7 *(0.3)*

[a] The following PI resistance-associated mutations were identified in the isolates: ***M1:*** L10I, **M46I**, I64V, **I84V**, **L90M**, I93L; ***M2:*** L10I, I13V, **M46I**, **I50V**, L63P, **L76V**; ***M3:*** L10I, K20R, M36I, **G48V**, I62V, A71V, **V82A**, I93L. [b] The numbers in parentheses represent the fold change in EC_{50} value for each isolate relative to the activity on wild-type HIV-1_{IIIB}.

With activities ranging from 0.6−11.1 nM, all hydrophobic PIs showed a significantly improved potency on the wild-type virus when compared to the hydroxy PIs **4.32a/b**. The benzyl and fluorobenzyl analogues **4.4−4.8** (entries 5−10) were even 4−10 fold more active on HIV-1_{IIIB} than DRV and its benzoxazole analogue **5.1b**. However, all benzylated

analogues exhibit a up to 12-fold reduced activity on the mutant strains and the hypersusceptibility characteristic is lost. This can be explained by the increased lipophilicity of these analogues. On the one hand it facilitates the uptake into the cell and leads to increased binding to HIV-1_{IIIB} via additional van der Waals contacts. On the other hand the mutations lead to an altered enzyme conformation, including significant shifts in the side chain residues, which might then result in the loss of these favourable but weak van der Waals interactions. There is no apparent benefit from the introduction of fluorine atoms on the aromatic ring, only with the 3-fluorobenzyl analogue (entry 8) a slightly improved activity on mutant M1 was observed.

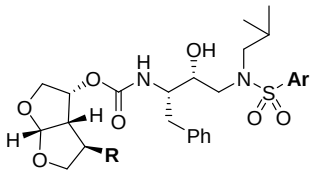
The aryl substituted PIs **4.9−4.11** (entries 11−15) showed similar or slightly decreased potency when compared to DRV and PI **5.1a**. In addition, a considerable loss in activity against clinical isolates M1 and M2 was observed, while mutant strain M3 remained hypersusceptible to the majority of the arylated PIs. The lower activity on the mutants could be explained by the reduced flexibility of the aryl group in comparison to benzyl substituents and, therefore, a decreased ability to adapt to conformational changes induced by the mutations. Interestingly, the 4-amino-phenoxy substituted PI **4.11b** retained its hypersusceptibility characteristic for two of the three mutants, indication additional dipolar or even hydrogen bonding interactions with the enzyme. Further analysis on the possible binding mode of this analogue will be made in the molecular modelling section (see 5.3).

In summary, the hydrophobic PIs showed good activity on HIV-1_{IIIB}, but failed to achieve similar results on the mutant strains. Analogues containing the benzoxazole sulfonamide usually showed a superior resistance profile. The benzylated and arylated PIs also exhibited a significantly higher tendency to bind to plasma proteins when compared to the hydroxy PIs (average FC = 7.2 vs. 2.5). It could be argued that their increased binding is based on a higher gain in entropy rather than an improved enthalpy, i.e. upon binding of the inhibitor more lipophilic surface area is buried resulting within the hydrophobic cleft of the enzyme. This leads to an increased desolvation of the inhibitor and therefore a higher entropy.

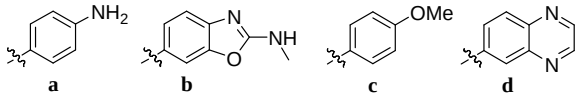
5.2.3 Analogues with hydrogen bond donor/acceptor ability

Table 5-4 shows the activity results for the analogues with modelled hydrogen bond donor and/or acceptor ability. Again PIs **1.10**, **5.1b** and **4.32a** are included as references.

Table 5-4. Antiviral activity (EC_{50}) of PIs **4.12−4.23** on HIV-1_{IIIB} and mutant viruses.[a]



Ar =



a **b** **c** **d**

Entry	PI	R	EC_{50} [nM][b] *(fold change relative to HIV-1_{IIIB})*				
			HIV-1_{IIIB}	HIV-1_{IIIB} + 50% HS	M1	M2	M3
1	**1.10**	H (darunavir)	6.6	17.2	11.3 *(1.7)*	51.0 *(7.8)*	2.3 *(0.4)*
2	**5.1b**	H	2.3	8.3	2.7 *(1.2)*	3.2 *(1.4)*	0.9 *(0.4)*
3	**4.32a**	OH	772.9	814.7	112.3 *(0.2)*	204.5 *(0.3)*	40.4 *(0.05)*
4	**4.12a**	OCONHBn	5.8	30.4	15.5 *(3.2)*	124.5 *(22)*	5.2 *(0.9)*
5	**4.12b**	OCONHBn	5.8	26.7	7.2 *(1.2)*	13.9 *(2.4)*	4.0 *(0.7)*
6	**4.13a**	$NHCO_2Bn$	5.0	35.2	5.7 *(1.1)*	82.5 *(16)*	1.8 *(0.4)*
7	**4.13b**	$NHCO_2Bn$	3.8	16.6	2.4 *(0.6)*	7.5 *(2.0)*	1.0 *(0.3)*
8	**4.16a**	$O(CH_2)_2OMe$	15.5	37.0	11.9 *(0.8)*	71.4 *(4.6)*	6.8 *(0.4)*
9	**4.16b**	$O(CH_2)_2OMe$	8.6	24.0	6.9 *(0.8)*	10.8 *(1.3)*	4.3 *(0.5)*
10	**4.16d**	$O(CH_2)_2OMe$	3.7	4.4	7.4 *(2.0)*	17.5 *(4.7)*	3.4 *(0.9)*
11	**4.17b**	OCH_2OMe	3.4	7.0	5.0 *(1.5)*	11.2 *(3.2)*	1.9 *(0.6)*
12	**4.18b**	OCH_2SMe	1.3	6.7	4.0 *(3.0)*	9.3 *(7.1)*	2.2 *(1.7)*
13	**4.19b**	$O(CH2)_2CF_3$	0.5	8.2	0.9 *(1.9)*	2.8 *(5.9)*	0.8 *(1.6)*
14	**4.20a**	$OCH_2CONHBn$	16.0	93.5	10.8 *(0.7)*	35.2 *(2.2)*	9.3 *(0.6)*
15	**4.20b**	$OCH_2CONHBn$	25.0	102.3	13.4 *(0.5)*	15.1 *(0.6)*	6.4 *(0.3)*
16	**4.20c**	$OCH_2CONHBn$	0.6	4.6	3.3 *(5.6)*	4.4 *(7.5)*	1.0 *(1.7)*
17	**4.21b**	$OCH_2CONHMe$	460.5	376.5	150.7 *(0.3)*	203.6 *(0.4)*	68.5 *(0.1)*
18	**4.21c**	$OCH_2CONHMe$	6.9	16.1	14.3 *(2.1)*	15.7 *(2.3)*	8.3 *(1.2)*
19	**4.22b**	OCH_2CONMe_2	249.1	243.4	101.8 *(0.4)*	83.8 *(0.3)*	50.4 *(0.2)*
20	**4.22c**	OCH_2CONMe_2	3.8	7.0	7.0 *(1.8)*	11.5 *(3.0)*	2.9 *(0.8)*
21	**4.23b**	$OCH_2CF{=}CH_2$	0.4	2.2	0.8 *(1.2)*	2.3 *(6.1)*	0.5 *(1.4)*

[a] The following PI resistance-associated mutations were identified in the isolates: ***M1:*** L10I, **M46I**, I64V, **I84V**, **L90M**, I93L; ***M2:*** L10I, I13V, **M46I**, **I50V**, L63P, **L76V**; ***M3:*** L10I, K20R, M36I, **G48V**, I62V, A71V, **V82A**, I93L. [b] The numbers in parentheses represent the fold change in EC_{50} value for each isolate relative to the activity on wild-type HIV-1_{IIIB}.

The benzyl carbamate containing PIs **4.12/4.13** showed good potency on wild-type HIV and mutant strains M1/3 (entries 4−7). In contrast to their corresponding anilino analogues, the benzoxazole substituted PIs **4.12b** and **4.13b** also retained their potency against clinical isolate M2, which contains two primary mutations associated with resistance to darunavir. Carbamate **4.13**, which is attached to the *bis*-THF moiety via the nitrogen, appears to be slightly more potent than the *O*-bound carbamate **4.12**. This might be due to possible hydrogen bonding interactions between the carbamate NH and the backbone carbonyl of Gly48, as indicated in Chapter 2.

The alkoxyalkyl PIs **4.16−4.18** inhibit HIV-1_{IIIB} at low nanomolar concentrations (EC_{50} = 1.3−15.5 nM, 8−12), which are comparable to darunavir. Although they are not as potent as the corresponding benzylated analogues, the methoxyethoxy-substituted PIs **4.16a/b** show a more balanced resistance profile on the mutant strains (entries 8,9). The clinical isolates M1 and M3 were found to be hypersusceptible to inhibitors **4.16a/b** and only a 1-5 fold increase in EC_{50} was noted against isolate M2. The benzopyrazine **4.16d** proved to be very potent on the wild-type virus, but lost activity against two of the mutant strains (entry 10). A further analysis of the relationship between chain length and antiviral activity showed that a methyl linker (PIs **4.17b** and **4.18b**, entries 16/17) is slightly favoured over the ethyl linker (compound **4.16b**) on HIV-1_{IIIB}. However, the methyl linker exhibits more variation in activity on the mutants and the hypersusceptibility characteristic is lost completely against isolate M1 and partially against M3.

The acetamides (entries 14−20) show a similar activity profile as the hydroxy analogues. Although the *para*-methoxy phenyl substitution (Ar = **b**) significantly improves the absolute potency of these ligands, it also results in the complete loss of the hypersusceptibility, which was very pronounced in the corresponding benzoxazole analogues (e.g. compare entries 17 and 18). The increased polarity, in particular of the methyl acetamides **4.21**, appears to impair the permeability of these compounds.

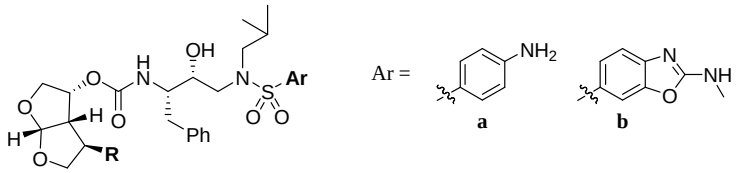
The fluorinated isosteres **4.19b**/**4.23b** exhibit a significantly improved activity on HIV-1_{IIIB} when compared to **4.16b** and **4.21b**, respectively. Although they fail to retain their activity on the mutant strains and no hypersusceptibility was observed, the absolute potency of these PI is notable.

In summary, the antiviral activity of the analogues with HB acceptor/donor ability is strongly dependent on the sulfonamide substituent and the all over polarity of the molecule. As expected they showed a lower tendency to bind to plasma proteins than the hydrophobic PIs (average FC = 3.6). In addition, a hypersusceptibility characteristic was observed for the majority of the more polar PIs.

5.2.4 Halogenated and Azide PIs

The antiviral activity of azide PI **4.24a** is shown in Table 5-5. The corresponding results for the chlorinated PIs **4.25** and fluorinated PI **4.26b** have not been obtained yet.

Table 5-5. Antiviral activity (EC_{50}) of PIs **4.24−4.26** on HIV-1_{IIIB} and mutant viruses.[a]



Entry	PI	R	EC_{50} [nM][b] *(fold change relative to HIV-1_{IIIB})*				
			HIV-1_{IIIB}	HIV-1_{IIIB} + 50% HS	M1	M2	M3
1	**1.10**	H (darunavir)	6.6	17.2	11.3 *(1.7)*	51.0 *(7.8)*	2.3 *(0.4)*
2	**5.1b**	H	2.3	8.3	2.7 *(1.2)*	3.2 *(1.4)*	0.9 *(0.4)*
3	**4.31a**	OH	772.9	814.7	112.3 *(0.2)*	204.5 *(0.3)*	40.4 *(0.05)*
4	**4.24a**	N_3	3.7	18.8	5.6 *(1.5)*	55.6 *(15)*	2.3 *(0.6)*
5	**4.25a**	Cl	0.4	4.6	2.8 *(7.5)*	31.6 *(85)*	1.5 *(4.0)*
6	**4.25b**	Cl	0.5	4.2	0.7 *(1.6)*	2.1 *(4.6)*	0.7 *(1.6)*
7	**4.26b**	F	0.7	8.4	0.8 *(1.2)*	2.8 *(4.1)*	0.7 *(0.9)*

[a] The following PI resistance-associated mutations were identified in the isolates: ***M1:*** L10I, **M46I**, I64V, **I84V**, **L90M**, I93L; ***M2:*** L10I, I13V, **M46I**, **I50V**, L63P, **L76V**; ***M3:*** L10I, K20R, M36I, **G48V**, I62V, A71V, **V82A**, I93L. [b] The numbers in parentheses represent the fold change in EC_{50} value for each isolate relative to the activity on wild-type HIV-1_{IIIB}.

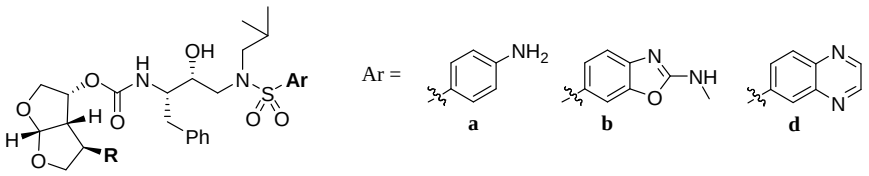
Azide containing PI **4.24a** (entry 4) inhibits HIV-1_{IIIB} and mutant strains M1/3 at low nanomolar concentrations. Only against clinical isolate M2 a reduced activity was noted, which is very similar to the results obtained with darunavir (entry 1). This leads to the conclusion that there is only a very limited influence of the azide group on the binding mode. The chloride and fluoride substituted PIs **4.25**/**4.26** (entries 5−7) exhibit an excellent activity on the wild-type virus. Although these analogues inhibit the mutant strains at low nanomolar concentrations, the hypersusceptibility characteristics of mutants M1/M3 is lost. This is in accordance with the results obtained for the benzylated analogues.

At this stage it remains unclear whether the halide substituents, as well as the fluorinated isosteres **4.19b** and **4.23b**, are able to undergo specific dipolar interactions or if the gain in potency is merely based on entropic effects. This can only be determined by X-ray crystal structure studies of the corresponding enzyme-PI complex.

5.2.5 Enzymatic activity

Several anilino and benzoxazole substituted PIs showed only medium or low potency against the wild-type virus in the cellular essay, but at least two of the mutant strains were found to be hypersusceptible to these analogues. It was therefore decided to determine their activity on the purified enzyme (IC_{50}), in order to be able to rationalize these results. The obtained activities are shown below (Table 5-6). Atazanavir, darunavir and PI **5.1b** are given as reference compounds (entries 1−3).

Table 5-6. Enzymatic activity (IC_{50}) versus cellular activity (EC_{50}).



Entry	PI	R	EC_{50} [nM] HIV-1_{IIIB}	IC_{50} [nM][a] HIV-1 protease
1		atazanavir	7.2	4.1
2	**1.10**	H (darunavir)	6.6	3.8
3	**5.1b**	H	2.3	2.1
4	**4.31a**	OH	**772.8**	**2.9**
5	**4.4a**	OBn	1.5	3.5
6	**4.11a**	O(4-NH_2-C_6H_4)	11.1	11.2
7	**4.11b**	O(4-NH_2-C_6H_4)	8.3	9.9
8	**4.12b**	OCONHBn	5.8	<1.5
9	**4.13b**	$NHCO_2Bn$	3.7	3.3
10	**4.16a**	$O(CH_2)_2OMe$	15.5	2.5
11	**4.16b**	$O(CH_2)_2OMe$	8.6	<1.5
12	**4.16d**	$O(CH_2)_2OMe$	3.7	<1.5
13	**4.17b**	OCH_2OMe	3.4	1.9
14	**4.20a**	$OCH_2CONHBn$	16.0	3.1
15	**4.20b**	$OCH_2CONHBn$	25.0	2.7
16	**4.21b**	$OCH_2CONHMe$	**460.5**	**<1.5**
17	**4.22b**	$OCH_2CONHMe_2$	**249.1**	**4.1**

[a] The substrate for the enzymatic assay reflects only the MA-CA cleavage site.

All PIs are highly active on the purified enzyme and inhibit HIV-1 protease at low nanomolar concentrations (IC_{50} = 1.5−11.2 nM). For several analogues a significant improvement in potency was noted, e.g. the enzymatic activity of hydroxy PI **4.31a** is over 250-fold higher than in the cellular assay. Similar results were obtained for the acetamide analogues **4.21b** and **4.22b** (FC >300 and >60, respectively). This leads to the conclusion that additional ligand−protein interactions, as identified in the X−ray crystal structure of PI **4.31a** (compare Chapter 2), are also present within the amide series. However, the higher polarity and the increased number of hydrogen bond donors seem to limit the uptake into cell, which explains the weak potency of PIs **4.31a** and **4.21/22b** against HIV-1_{IIIB} in the cellular essay.

The benzylated PI and the aminophenoxy analogues (entries 5−7) appear to lose activity on the HIV-1 protease. Although these changes are within the error margins of assay, there are two possible explanations: (1) In the cellular assay, the higher lipophilicity of the compounds could favour the uptake into cell, which would result in different concentrations within and outside the cell. This effect would not apply in the enzymatic assay. (2) The substrate in the enzymatic assay only represents one cleavage site (MA-CA) within the *gag-pol* polyprotein, while in the cellular assay at least nine different recognition sequences are processed by the HIV-1 protease. As these sites are cleaved at different rates, the enzyme might show a higher affinity to this particular cleavage site.[144]

For the carbamate series (entries 8,9) no significant change in activity was observed. Although the *O*-bound carbamate **4.12b** appears to be slightly more potent in the enzymatic assay. The alkoxyalkyl substituted PIs **4.16/17** (entries 10−13) show a particularly good inhibition of the purified enzyme (IC_{50} = 1.5−2.5 nM), which also suggests additional interactions between the enzyme and the inhibitor.

The enzymatic activities proved the general potency of the synthesised protease inhibitors. However, for a better understanding of the new binding interactions it was necessary to perform additional molecular modelling studies, which will be discussed in the next section.

5.3 MOLECULAR MODELLING STUDIES

Based on their good activity against HIV-1_{IIIB} or their pronounced hypersusceptibility characteristics, four analogues were further investigated using molecular modelling studies. In particular, these are the two hydrophobic inhibitors **4.6b** and **4.11b**, as well as the methoxyethoxy analogue **4.16b** and acetamide **4.21b**. All calculations were performed by Dr. Jörg Wegner at Tibotec using the 2HS1-coordinates published by Weber *et al.* in 2006.[37]

5.3.1 Hydrophobic analogues 4.6b and 4.11b

The 3-fluorobenzyl analogue **4.6b** showed the best inhibition of the wild-type virus, while the 4-aminophenoxy substituted PI **4.11b** exhibited a good activity against all three mutant strains. The modelling results are shown in Figure 5-2.

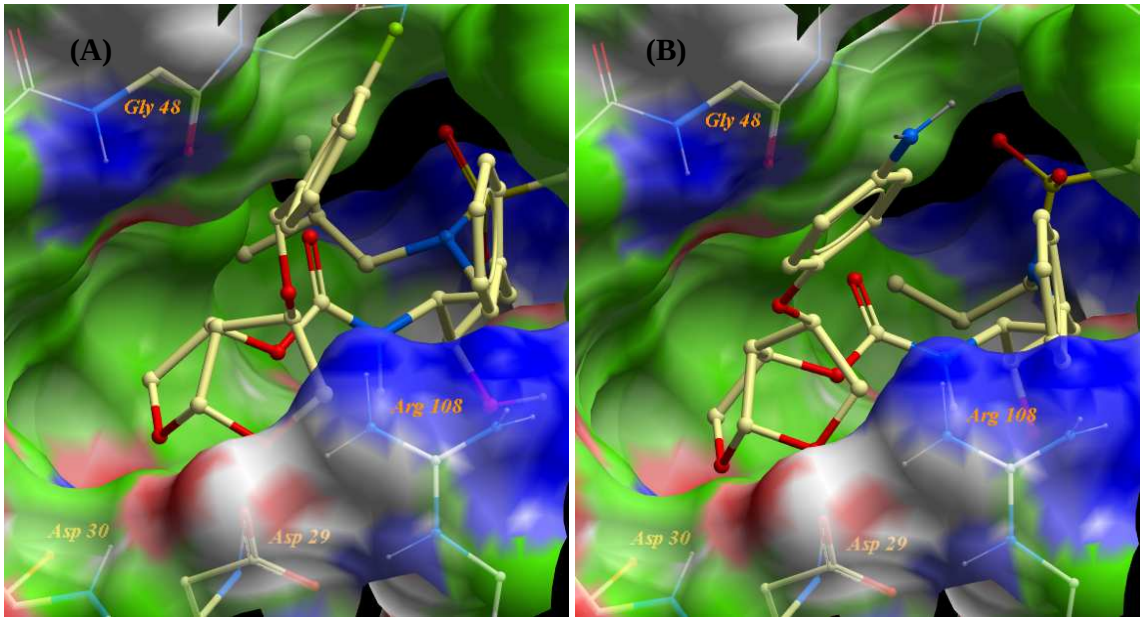


Figure 5-2. 3D depiction of the possible binding mode of the *bis*-THF moiety in PIs **4.6b** and **4.11b**.

In the X-ray crystal structure based modelling of the 3-fluorobenzyl substituted PI **4.6b** (Figure 5-2, A), the benzyl ligand is occupying the hydrophobic space below the flaps. There appears to be a weak C-H··π interaction between Gly48 and the aromatic system. However, the direct or water-mediated hydrogen bonding interactions that were identified with the hydroxy PIs **4.31a** are not present. The anticipated orthogonal C−F··C=O interactions can not be calculated with this approach and would require further analysis on a

crystal structure. Essentially, the increased activity of the benzyl analogues on HIV-1_{IIIB} can be based on a higher logP of these molecules, which in turn stimulates the cell permeability.

For the arylated PI **4.11b** (Figure 5-2, B) a possible cation-π-stacking between the positively charged guanidine side-chain of Arg108 and the aromatic ring has been predicted. However, stacking is hard to calculate and additional thermodynamic measurements would be required to fully understand these interactions. The observed hypersusceptibility characteristic is probably more dependent on the P2' sulfonamide than on the aromatic *bis*-THF substituent, although the *para*-aminophenoxy group shows a better resistance profile when compared to the *para*-nitro analogue.

5.3.2 Methoxyethoxy ether 4.16b and *N*-methyl acetamide 4.21b

Methoxyethoxy substituted PI **4.16b** and *N*-methyl acetamide containing PI **4.21b** showed a very pronounced hypersusceptibility characteristic against several mutant strains. It was therefore anticipated, that they would show additional hydrogen bonding interactions with the enzyme, similar to the hydroxy analogues. The results of the molecular modelling studies are shown below (Figure 5-3).

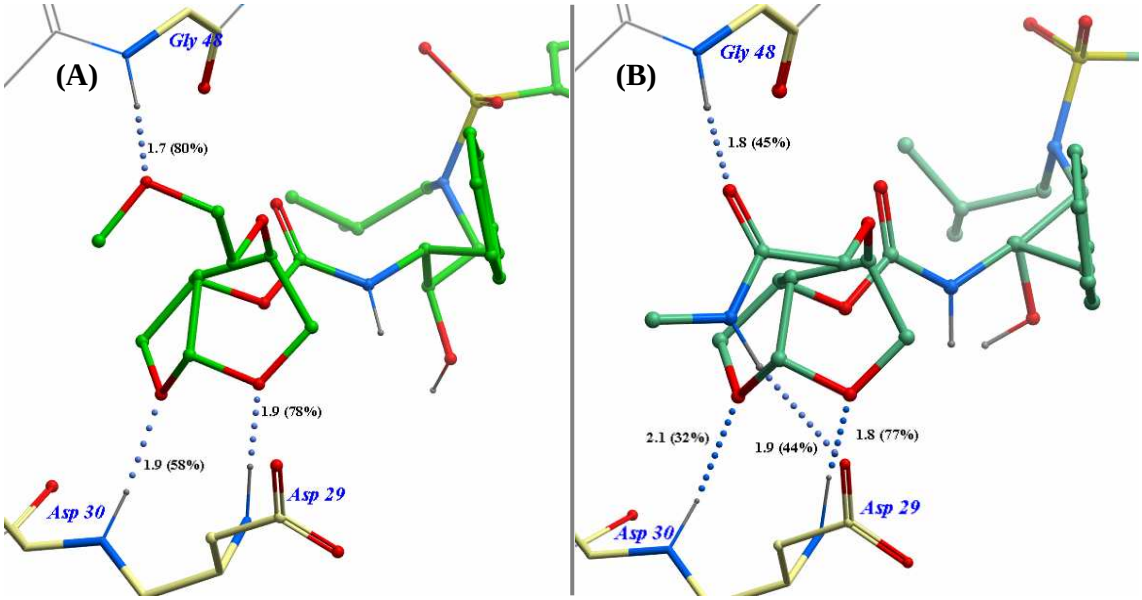


Figure 5-3. Possible binding modes of the *bis*-THF moieties in PIs **4.16b** and **4.21b**.

For PI **4.16b** (Figure 5-3, A) the methoxyethoxy moiety possibly displaces the water molecule which formed the water-mediated contact in the hydroxy PIs, and the second oxygen could now form a direct hydrogen bond to the backbone NH of Gly48. This interaction has been described for some natural substrates of HIV-1 protease (see Chapter2)

and might explain the hypersusceptibility characteristic of PIs **4.16**, as these direct backbone interactions are less influenced by residue mutations. The hydrogen bonding distance is 1.7 Å and would result in an 80% optimal hydrogen bond as calculated by Clark/Labute.[74] In principle, a similar contact could be expected for the methoxymethyl ether in PI **4.17b**. However, the interaction appears to be lost with the mutants, as no hypersusceptibility was observed for PI **4.17b**. The additional CH_2-group in PIs **4.16** allows enough flexibility to retain these contacts within the mutant-inhibitor complexes.

The acetamide moiety in PI **4.21b** (Figure 5-3, B) possibly displaces two water molecules to form a hydrogen bonding network from Gly48 to Asp29. The carbonyl oxygen of the acetamide would interact with the backbone NH of Gly48 (d = 1.8 Å, 45% optimal), while the NH can form a hydrogen bond to the side chain of Asp29 (d = 1.9 Å, 44% optimal). The two important HB contacts between the *bis*-THF ring oxygens and the backbone amide groups of Asp29 and Asp30 would be retained in any case.

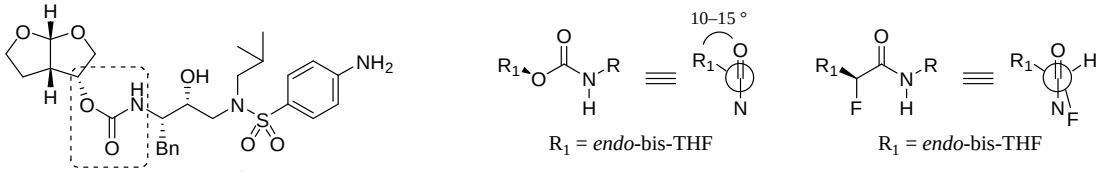
5.4 SUMMARY

Nearly all synthesised PIs showed a good activity against wild-type HIV-1_{IIIB} and a panel of multi-PI resistant HIV-1 mutant strains. With the benzylated and fluorobenzylated analogues inhibition at subnanomolar concentrations was observed. Several more polar PIs suffered from a reduced cell permeability, but their potency could be confirmed on the purified enzyme. Interestingly, all mutant strains were found to be hypersusceptible to analogues that were designed to allow additional HB contacts. This has only been reported in a few cases.[49] Especially the methoxyethoxy derivatives **4.16** and the acetamide series **4.20−22** showed this hypersusceptibility characteristic. Additional molecular modelling studies could confirm particularly favourable interactions with the backbone NH of Gly48. Still, a direct interpretation of the hypersusceptibility remains challenging, since the observed effect might have multiple reasons. The most likely structural reason might be a changed protease or folding dynamics of the protease and substrates due to interference of the inhibitors with the flap region (containing Gly48 and Gly48').

Chapter 6 α-FLUOROAMIDES AS CARBAMATE ALTERNATIVE

6.1 BACKGROUND

Detailed ADME studies have shown that carbamate hydrolysis is a major metabolic pathway for darunavir.[145] When DRV was administered without ritonavir boosting, approximately 13% of the observed metabolites resulted from carbamate cleavage. However, the group has proven to be crucial, as the carbonyl oxygen forms a water-mediated HB interaction with the backbone NH of Ile50. Replacement of the carbamate by an amide group resulted in a decreased activity of the inhibitor, probably due to conformational changes. The crystal structure of DRV-bound HIV-1 protease revealed that the *bis*-THF substituent is located above the plane of the carbamate heteroatoms, with a torsion angle of 10−15 ° (**I**, Figure 6-1). It was envisaged to increase metabolic stability and to retain activity at the same time, by replacing the carbamate oxygen with a CHF moiety. The torsion angle, or at least its direction, would be preserved utilizing the "α-fluoroamide effect",[146] by which the C−F and C−N bonds will be *syn*-coplanar, resulting in the positioning of the *bis*-THF moiety above the amide plane (**II**). It was recognised that the magnitude of the torsion angle may be different to the original carbamate.

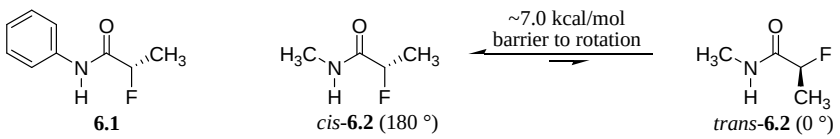


1.10 **I** **II**

Figure 6-1.

6.1.1 The α-Fluoroamide Effect

The X-ray crystal structure of α-fluoroamide **6.1** showed the C−F bond oriented nearly *cis* to the N−H bond and trans to the C=O bond (Figure 6-2).[146] Additional *ab initio* calculations of the preferred conformation of α-fluoroamide **6.2** indicated an energy difference of ~7.0 kcal/mol between the *cis* and *trans* conformers.



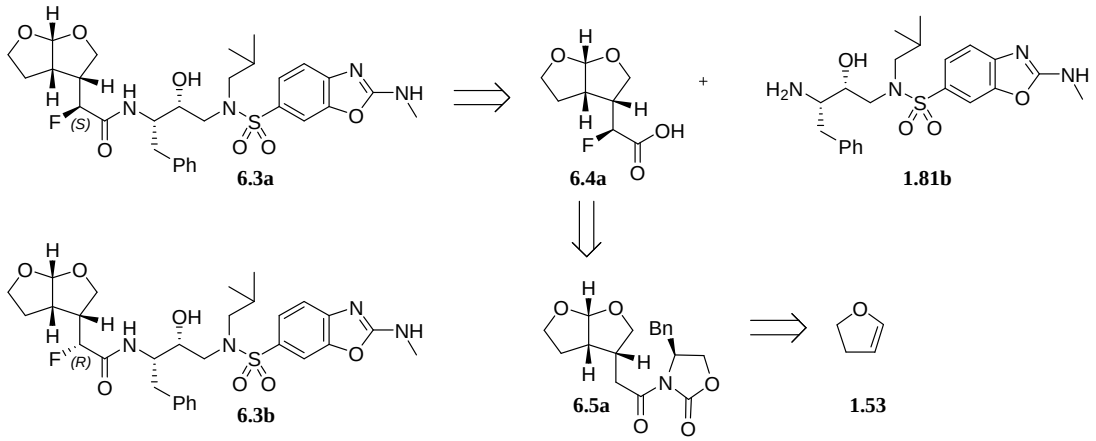
6.1 *cis*-**6.2** (180 °) *trans*-**6.2** (0 °)

Figure 6-2. Preferred conformation of α-fluoroamides.

The *trans* conformer is mainly stabilised by the opposing dipoles of the amide and the C-F group, resulting in a smaller dipole moment.[147] In addition, the formation of an intramolecular hydrogen bond N−H···F can be anticipeted.[146] Based on these observations, an α-CHF moiety could be used for the conformational control of amides.

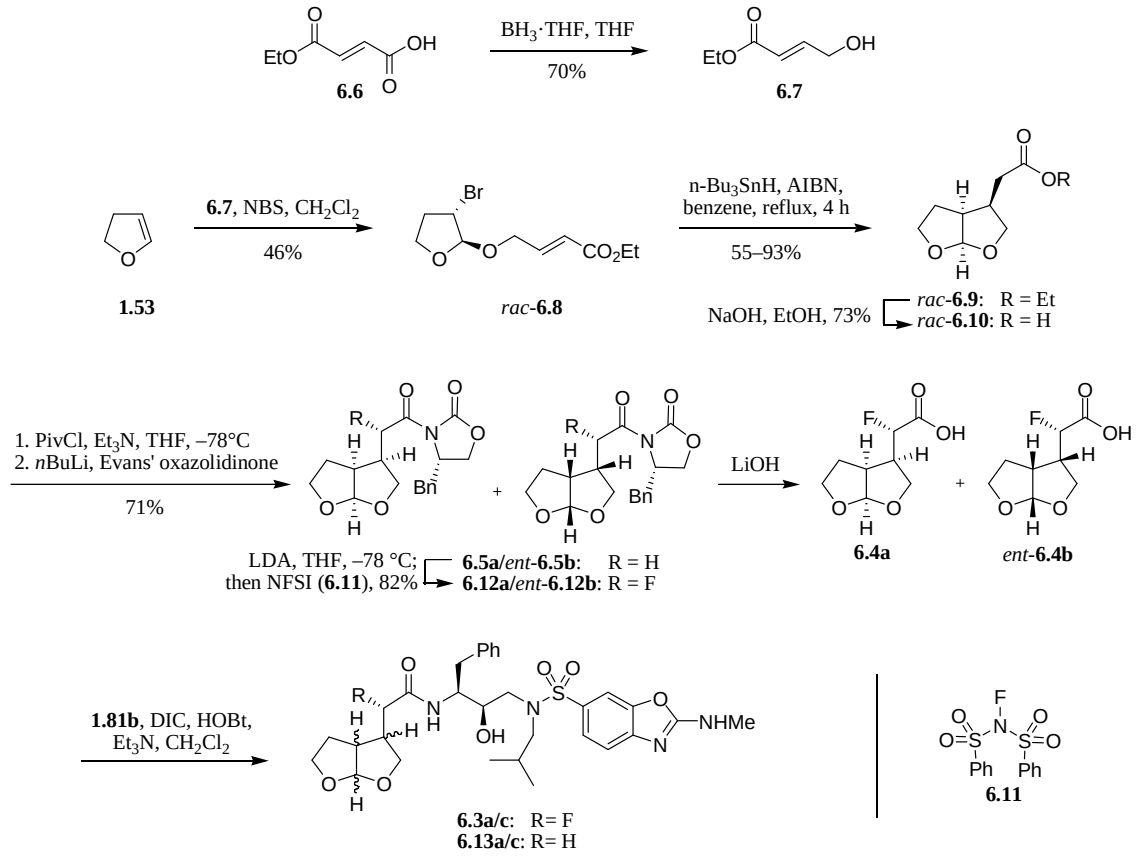
6.2 THE RACEMIC APPROACH

To exploit the α-fluoroamide effect in fluorinated darunavir analogues, it was now envisaged to synthesise the PI **6.3a** (Scheme 6-1). According to the X-ray crystal structure analysis, the (*S*)-configuration is required at the CHF position. In addition, the corresponding (*R*)-diastereoisomer **6.3b** will be targeted as a control. Retrosynthetic analysis leads to the required *bis*-THF moiety **6.4a** and the known amine scaffold **1.81b**. Acetic acid derivative **6.4a** can be obtained from the known oxazolidinone **6.5a**, which in turn is derived in 5 steps from 2,3-dihydrofuran **1.53**.[148]



Scheme 6-1. Retrosynthesis of fluorinated **PI 6.3a**.

Following a publication by Kiso *et al.*, the synthesis of the two inseparable diastereomeric oxazolidinones **6.5a**/**6.5b** was completed in four steps (Scheme 6-2).[148] Allylic alcohol **6.7** was obtained by selective reduction of monoethyl fumarate (**6.6**) with BH_3·THF.[149] The yield of the radical cyclisation step (**6.8** to **6.9**) varied from 55% to 93%, depending on the scale of the reaction. Kiso *et al.* have shown that stereoselective azidation of **6.5a** can be achieved by treatment of the corresponding enolate with 2,4,6-triisopropylbenzene-sulfonyl azide.[148] Hence, it was intended to utilize the same auxiliary-controlled process to selectively fluorinate oxazolidinone **6.5a**.

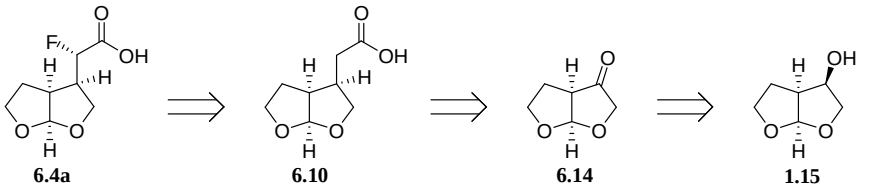


Scheme 6-2. Racemic approach to α-fluoroamide containing PI **6.3**.

Diastereoisomers **6.5a**/**b** were then deprotonated with LDA[150] and subsequently treated with *N*-fluorodibenzenesulfonimide (NFSI, **6.11**)[151] to afford the fluorinated intermediates **6.12a/b**, which were still not separable by column chromatography. Nevertheless, diastereoselective fluorination could be confirmed by ^{19}F NMR, with only two major peaks at δ −191.85 and −197.36 ppm. Subsequent hydrolysis of **6.12a**/**b** with LiOH/H_2O_2[152] surprisingly led to a complex mixture of at least six different compounds (from ^{19}F NMR), indicating that epimerisation had occurred. Alternative hydrolysis with only LiOH[153] afforded only the two expected diastereoisomers **6.4a**/**b**, which were then coupled to amine **1.81b**. TLC analysis showed two major spots, which could be separated by column chromatography and were expected to be the two PIs **6.3a** and **6.3c**. However, ^{19}F NMR analysis revealed two ^{19}F signals (at −188.83 and −191.92 ppm) in the first spot and the absence of fluorine in the second spot. This leads to the conclusion, that the substrate was partially defluorinated during the coupling reaction, although the mechanism remains unclear. Further mass spectrometric analysis confirmed the first spot to be PIs **6.3a**/**c** (*m*/*z* 641.2 $(M+Na)^+$) and the second spot being PIs **6.13a**/**c** (*m*/*z* 623.2 $(M+Na)^+$).

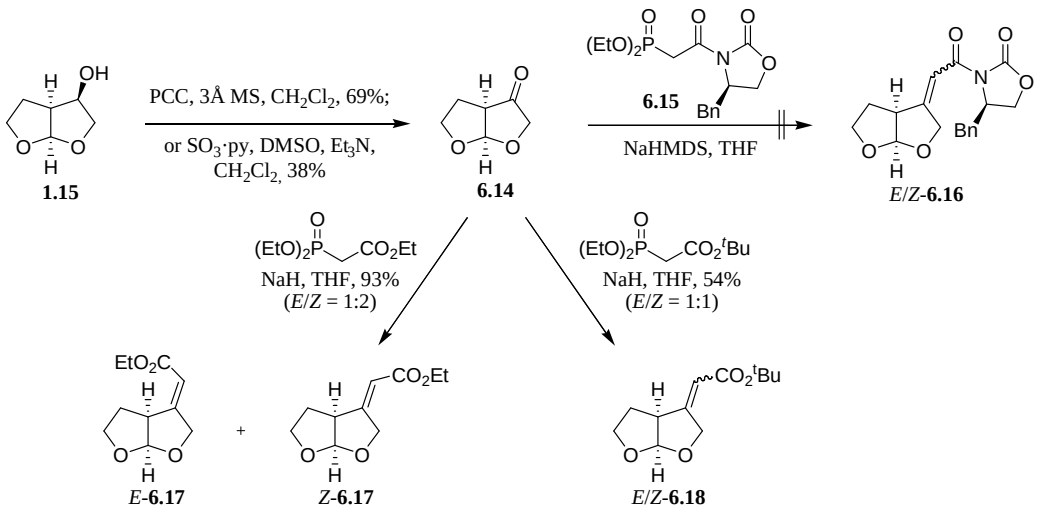
6.3 THE ENANTIOPURE APPROACH

Although the formal synthesis of PI **6.3a** was completed in the racemic approach, it was not possible to separate the diastereoisomers at any stage. Hence, a method for the enantiopure formation of α-fluoroamide **6.4a** was sought. In order to circumvent any separation problems, it was now envisaged to derive acid **6.10** from *bis*-THF alcohol **1.15** via ketone **6.14** and subsequent HWE-reaction (Scheme 6-3).



Scheme 6-3. Retrosynthetic approach to enantiopure acid **6.5** from alcohol **1.15**.

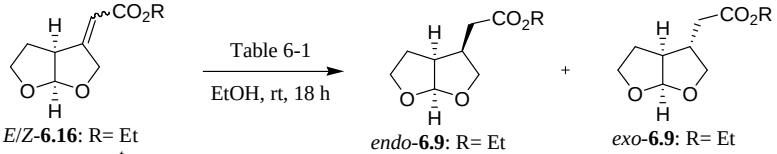
The *bis*-THF alcohol **1.15**, provided by TIBOTEC, was readily oxidised to ketone **6.14** using PCC or Parikh-Döring conditions,[69] although the latter failed to give satisfactory yields (Scheme 6-4). An attempt to directly introduce the oxazolidinone with the corresponding phosphonate **6.15** did not give the desired alkene **6.16**. However, the HWE reaction with triethylphosphono acetate[154,155] afforded a separable mixture of the corresponding alkenes **6.17** (*E*/*Z* = 1:2) in excellent yield. The bulkier *tert*-butyldiethyl-phosphono acetate[156] only furnished a 1:1 mixture of alkenes **6.18**.



Scheme 6-4. Formation of alkenes **6.17** and **6.18**.

The double bond in **6.17** and **6.18** was then reduced by catalytic hydrogenation to give the corresponding ester. The results are summarised in Table 6-1.

Table 6-1. Optimisation of double bond reduction in *E*/*Z*-**6.17**.



E/*Z*-**6.16**: R= Et
E/*Z*-**6.17**: R= ^{t}Bu

endo-**6.9**: R= Et
endo-**6.19**: R= ^{t}Bu

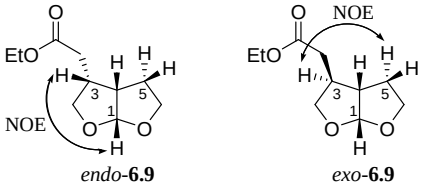
exo-**6.9**: R= Et
exo-**6.19**: R= ^{t}Bu

Entry	Ester	Reagents	Ratio			Yield (%)[a]
			endo		*exo*	
1	*E*/*Z*-**6.17**	H_2, $Pd(OH)_2/C$ [155]	3	:	1	91
2		H_2, Pd/C[157]	10	:	3	100
3		H_2, Rh/Al_2O_3 [158]	5	:	1	100
4		$NaBH_4$ (1.5 equiv)[159, b]	*endo* only			-[c]
5	*Z*-**6.17**	H_2, Rh/Al_2O_3	6	:	1	99
6	*E*-**6.17**		3	:	1	100
7	*E*/*Z*-**6.18**		3	:	1	99

[a] isolated yield, [b] reaction was then heated to reflux for 5 h, [c] reaction was incomplete.

Following a procedure by Florent'ev *et al.*,[155] the mixture of *E*/*Z*-**6.17** was hydrogenated under atmospheric pressure using $Pd(OH)_2/C$ to give a 3:1 mixture of the desired ester *endo*-**6.9** and *exo*-**6.9** in very good yield (entry 1). The formation of the undesired *exo*-ester was expected to be hindered by the roof-like shape of the substrate, since the hydrogenation should happen on the catalyst surface. However, a certain solubility of the catalyst in the solvent might reduce the selectivity of the attack. The hydrogenation with catalytic amounts Pd/C (entry 2)[157] and Rh/Al_2O_3 (entry 3)[158] led to better selectivity towards the desired *endo*-ester. In order to eliminate the formation of *exo*-**6.9**, a 1,4-addition to *E*/*Z*-**6.17** with $NaBH_4$ in EtOH[159] was attempted (entry 4), but even under reflux conditions the reaction did not go to completion. However, the crude ^{1}H NMR only showed the formation of the desired *endo*-product. With Rh/Al_2O_3 (entry 3) giving the best ratio of *endo*-**6.9** to *exo*-**6.9**, the effect of the conformation of the double bond on the hydrogenation was investigated (entry 5 and 6). In both cases a mixture was obtained, albeit the reduction of *Z*-**6.17** afforded a significant higher amount of *endo*-**6.9** in comparison to *E*-**6.17**. Nevertheless, a separation of the *E*/*Z*-**6.17** is not necessary, since the ratios are similar (compare entries 3 and 5) and the two reduction isomers can also be separated by HPLC. The hydrogenation of the *tert*-butyl ester *E*/*Z*-**6.18** only afforded a 3:1 mixture of the corresponding esters *endo*-**6.19** and *exo*-**6.19** (entry 7).

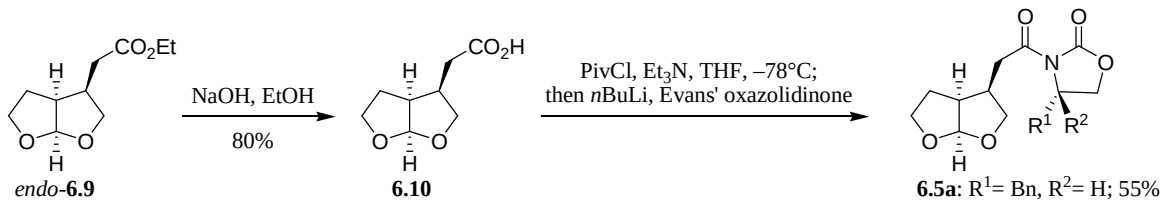
The structures of *endo*-**6.9** and *exo*-**6.9** were confirmed by 1D NOE experiments (GOESY, Figure 6-3). In *endo*-**6.9** a NOE coupling between H-1 and H-3 was observed, while no interaction between H-3 and H-5a/b was found. In comparison, *exo*-**6.9** shows no NOE coupling between H-1 and H-3, but an interaction between H-3 and one proton on C-5 was observed.



endo-**6.9** *exo*-**6.9**

Figure 6-3. Important NOE coupling in *endo*-**6.9** and *exo*-**6.9**.

Hydrolysis of the ester gave free acid **6.10** in good yield, which was then reacted with (*S*)-4-benzyl-2-oxazolidinone and (*R*)-4-benzyl-2-oxazolidinone to give **6.5a** and *ent*-**6.5b**, respectively (Scheme 6-5).[160]

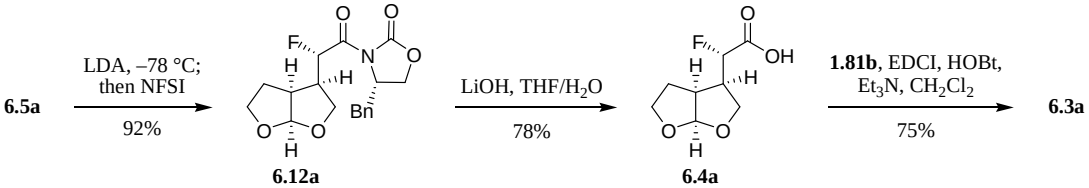


endo-**6.9** **6.10**

6.5a: R^1= Bn, R^2= H; 55%
ent-**6.5b**: R^1= H, R^2= Bn; 65%

Scheme 6-5. Formation of oxazolidinones **6.5a** and *ent*-**6.5b**.

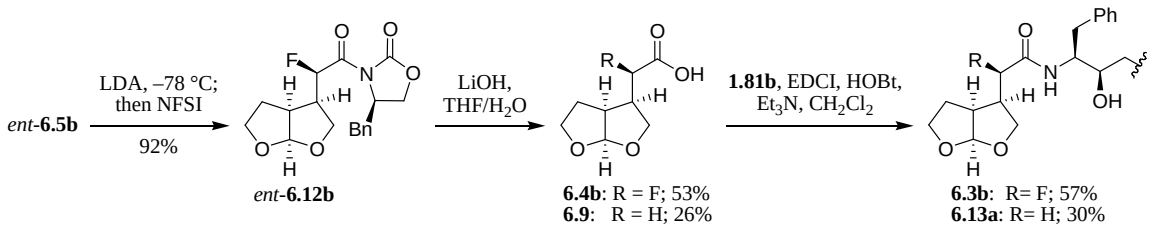
Deprotonation of oxazolidinone **6.5a** with LDA[150] and subsequent treatment with *N*-fluorodibenzensulfonimide (NFSI, **6.11**)[151] afforded the fluorinated intermediate **6.12a** (Scheme 6-6). Diastereoselective fluorination to was confirmed by ^{19}F NMR, with only one major peak at δ –197.36 ppm. Hydrolysis with LiOH[153] afforded the α-fluoroacid **6.4a**, which was then coupled to amine **1.81b** to give PI **6.3a** in good yield. The purity of **6.3a** could be confirmed by ^{19}F NMR (δ –188.8 ppm).



6.12a **6.4a**

Scheme 6-6. Synthesis of PI **6.3a**.

Following the same protocol, oxazolidinone *ent*-**6.5b** was transformed into PI **6.3b** (Scheme 6-7). As observed before in the racemic pathway, hydrolysis of *ent*-**6.12b** with LiOH led to partial defluorination resulting in a mixture of α-fluoroacid **6.4b** and acid **6.9**. This mixture was then coupled to amine **1.81b** to yield a separable mixture of PIs **6.3b** and **6.13a**.

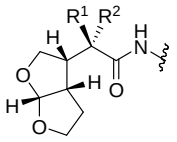


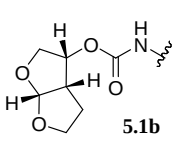
Scheme 6-7. Synthesis of PIs **6.3b** and **6.13a**.

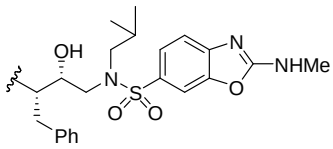
6.4 ANTIVIRAL ACTIVITY OF α-FLUOROAMIDE PIS

Similar to all other synthesised protease inhibitors, the α-fluoroamide containing PIs **6.3a/b** and amide **6.13a** were tested against wild-type HIV-1 and three mutant strains. The obtained activities are shown below, the previously described benzoxazole PI **5.1**[44] serves again as reference compound (Table 6-2).

Table 6-2. Antiviral activity of PIs **6.3a/b** and **6.13a** against HIV-1_{IIIB} and mutant viruses.[a]







Entry	PI	**EC_{50} [nM]** *(fold change relative to HIV-1_{IIIB})*			
		HIV-1_{IIIB}	M1	M2	M3
1	**5.1b**	2.3	2.7 (*1.2*)	3.2 (*1.4*)	0.9 (*0.4*)
2	**6.3a**	1012	*(8.5)*	*(>9.7)*	*(1.5)*
3	**6.3b**	368	*(10.8)*	*(>26.7)*	*(2.2)*
4	**6.13a**	287	*(18.1)*	*(>34.3)*	*(2.2)*

[a] The following PI resistance-associated mutations were identified in the isolates: ***M1:*** L10I, **M46I**, I64V, **I84V**, **L90M**, I93L; ***M2:*** L10I, I13V, **M46I**, **I50V**, L63P, **L76V**; ***M3:*** L10I, K20R, M36I, **G48V**, I62V, A71V, **V82A**, I93L; bold figures represent primary resistance mutations and underlined figures are associated with resistance to DRV according to the IAS.[27]

The fluorinated PIs **6.3a** and **6.3b** only show micromolar activity against wild-type HIV-1 and an even more significant loss of activity against the mutants was observed (entries 2,3). Interestingly, the non-fluorinated amide PI **6.13a** exhibits the best activity among the three synthesised non-carbamate PIs (entry 4). This leads to the conclusion that the presence of a fluorine next to the amide has an influence on the binding mode, although this interaction appears to counteract to the optimal binding of the inhibitor to the enzyme.

There are two possible explanations for these results: (1) the electronegative fluorine reduces the HB acceptor capability of the vicinal carbonyl group, which could result in the loss of a water-mediated interaction to Ile50, and (2) the presence of the "α-fluoroamide effect" forces the *bis*-THF moiety in an unfavourable conformation. This would also explain the better activity of PI **6.3b**, in which the *bis*-THF moiety would be turned away from Asp29/30, while in PI **6.3a** the forced *syn*-coplanar alignment of N−H and C−F bond would result in a steric clash between the *bis*-THF ligand and the enzyme.

6.5 SUMMARY

To increase metabolic stability, the replacement of the carbamate group in darunavir with an α-fluoroamide moiety had been proposed. The required orientation of the *bis*-THF moiety above the plane of the carbamate heteroatoms would have been preserved utilizing the "α-fluoroamide effect"[146] The synthesis of fluorinated bis-THF derivative **6.4** was achieved from alcohol **1.15** via diastereoselective fluorination of an oxazolidinone-intermediate. However, the final PIs **6.3a/b** only showed a weak antiviral activity, indicating that the predicted effect of the CHF-substitution counteracts to the required binding mode of the inhibitor.

Chapter 7 CONCLUSION AND FUTURE WORK

7.1 CONCLUSIONS

A series of 34 disubstituted bis-THF containing HIV-1 protease inhibitors has been synthesised and tested for their in vitro antiviral activity against wild-type virus as well as a panel of multi-PI resistant mutant strains. The majority of analogues showed low nanomolar activity, and in many cases, at least one of the mutant strains was found to be hypersuceptible to these PIs.

Following preliminary modelling studies and X-ray crystal structure analysis, two different strategies were pursued for the synthesis of successful candidates. On the one hand, it was envisaged to extent the "backbone binding" concept[29] by aiming for additional interactions with the peptide backbone of the enzyme. In particular, the proximal Gly48 residue was targeted. On the other hand, the introduction of hydrophobic substituents was investigated to increase the cell permeability of a previously studied hydroxy analogue.

The synthesis of the *bis*-THF scaffolds were based on a *bis*-THF diol, previously described by our group,[68] and involved the selective protection of the *endo*-hydroxy group to allow functionalisation of the *exo*-alcohol. Based on our initial approach to replace the *exo*-hydroxy group with a substituted amine, a high yielding route to an *exo*-amino analogue has been established. In addition, seventeen new *O*-substituted *bis*-THF analogues have been synthesised, including arylated and benzylated moieties, alkoxyalkyl and fluoroalkyl ether as well as a series of acetamide analogues. The latter are derived from a *bis*-THF substituted acetic acid, which could prove a valuable intermediate for further analogues. The formation of the desired PIs was achieved via DSC-mediated coupling of the *bis*-THF moieties to the various amine scaffolds provided by Tibotec.

Additional molecular modelling studies could show that an extended binding to the backbone NH of Gly48 was successfully achieved with the promising methoxyethoxy and acetamide substituted protease inhibitors **4.16b** and **4.21b**, respectively (Figure 7-1.).

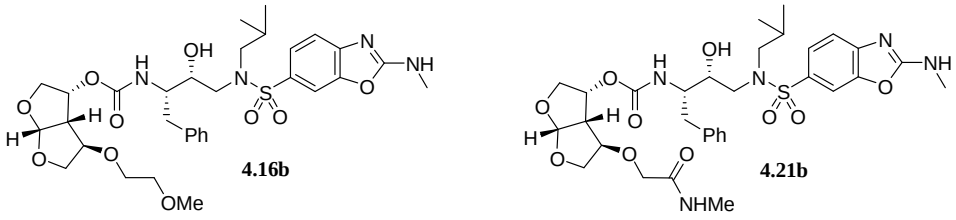


Figure 7-1.

7.2 FUTURE WORK

For a better understanding of the hypersusceptibility characteristic of some analogues, it would be necessary to perform thermodynamic binding studies or to obtain a crystal structure of the inhibitor-enzyme complex. From a medicinal chemistry point, the synthesis of acetamide isosteres would be interesting to improve cell permeability. These analogues could include oxazoles **7.1** and thiazoles **7.2** (Figure 7-2).

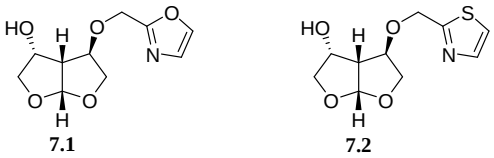
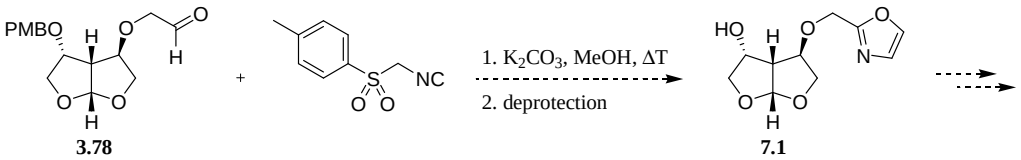


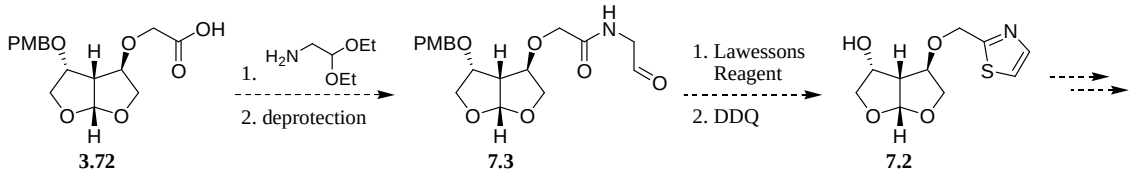
Figure 7-2. Structures of potential acetamide isosteres.

Oxazole **7.1** could be synthesised from aldehyde **3.78** and tosylmethyl isocyanide via the Van Leusen Oxazole Synthesis (Scheme 7-1).[161]



Scheme 7-1. Possible synthesis of oxazole **7.1**.

A possible approach to the desired thiazole **7.2**, is outlined in Scheme 7-2. The synthesis would be based on the cyclisation of a ketoamide **7.3** to a thiazole by treatment with Lawesson's reagent, as previously reported by Sato *et al.*[162] Ketoamide 7.3 could be derived from acid **3.72** after reaction with aminoacetaldehyde diethyl acetal and subsequent acetal cleavage.



Scheme 7-2.

Chapter 8 EXPERIMENTAL SECTION

8.1 GENERAL METHODS

Arabitol was obtained from CMS CHEMICALS. All other chemical reagents were obtained from ACROS, ALFA AESAR, MERCK or SIGMA-ALDRICH, respectively. THF was distilled from Na/benzophenone immediately prior use. CH_2Cl_2 and Et_3N were dried over CaH_2. Extra dry DMF and DMSO (H_2O < 50 ppm) were purchased from commercial sources. All glassware was flame-dried under vacuum and cooled under N_2 prior to use. Water or air sensitive reactions were performed under inert atmosphere, using dry solvents.

Reactions were monitored by TLC (MERCK Kieselgel 60 F_{254}, aluminium sheet). Detection was carried out by UV or by using one of the following dying reagents: *Anisaldehyde-reagent*…A solution of 5.1 mL *p*-anisaldehyde, 2.1 mL AcOH and 6.9 mL H_2SO_4 in 186 mL EtOH gives a reagent that will show coloured spots on the TLC after treatment with the heat gun. *$KMnO_4$-reagent*… A solution of 3 g $KMnO_4$, 20 g K_2CO_3 and 5 mL NaOH (aq., 5 w%) in 300 mL H_2O gives a reagent that will show yellow spots on the TLC after development with the heat gun.

Flash column chromatography was performed on silica gel (60 Å, particle size 35–70 µm). Preparative HPLC was carried out using a BIORAD BioSil D 90−10 column (250×22 mm) eluting at 12.5−15 mL/min or using a MACHERY-NAGEL Nucleodor 100−5 column (250×10 mm) eluting at 5 mL/min. Both columns were connected to a Kontron 475 refractive index detector. All reported solvent mixtures are volume measures.

NMR spectra were recorded on a BRUKER *AV300* [300.13 MHz (^{1}H NMR) and 75.47 MHz (^{13}C NMR)] or a BRUKER *DPX400* [400.13 MHz (^{1}H NMR) and 100.61 MHz (^{13}C NMR)], respectively. The chemical shift (δ) is given in ppm using the residual solvent peak as an internal standard. The coupling constants (*J*) are given in Hertz (Hz) and are reported as measured with ACD Labs 12.0. The splitting of the proton signals were designated as follows: s… singlet, d… doublet, dd… doublet of doublets, t… triplet, dt… doublet of triplets, td… triplet of doublets, q… quartet, m… multiplet and br… broad.

IR spectra were recorded on a Nicolet 380 FT-IR as a film. Absorption peaks are given in cm^{-1} and the intensities were designated as follows: w… weak, m… medium, s… strong, vs… very strong and br… broad.

Optical rotation was measured on an OPTICAL ACTIVITY POLAAR 2001 at 589 nm. Melting points were measured on a GALLENKAMP melting point apparatus and are uncorrected. Low and high resolution electrospray mass spectra were recorded on a WATERS ZMD single quadrupole system and on a BRUKER APEX III FT-ICR MS system.

8.2 PROCEDURES AND CHARACTERISATION

8.2.1 General Procedures

General Procedure A: Parikh-Döring oxidation[69]

To a solution of Et_3N (3.7 equiv) in CH_2Cl_2/DMSO (5 mL/mmol, v/v 1:1) at 0 °C is added SO_3·pyridine (3 equiv) and the resulting mixture is stirred at 0 °C for 15 min. This mixture is then added dropwise over a period of 2−10 min via cannula to a solution of the corresponding alcohol (1 equiv) in CH_2Cl_2/DMSO (10 mL/mmol, v/v 2:1) at −10 °C. The reaction is stirred at −20 to 0 °C for 4 to 6 h and monitored by TLC. After completion, the mixture is poured into sat. aq. NH_4Cl/H_2O/petroleum ether (10 mL/mmol, v/v 1:1:2). The layers are separated and the aqueous phase is extracted with petroleum ether (3 × 5 mL/mmol). The combined organic layers are dried over anhydrous Na_2SO_4, filtered and the solvent is removed in vacuo to afford the desired ketone/aldehyde after purification by column chromatography.

General Procedure B: Benzylation

To a solution of the alcohol in THF (10 mL/mmol) at 0 °C is added NaH (1.25 eq, 60% in mineral oil) and the resulting mixture is stirred for 20 min. TBAI (0.3 equiv) and the corresponding benzyl bromide (3.0 equiv) are added and the reaction is stirred at 0−20 °C for further 1 to 3 h. After completion the mixture is quenched with sat. aq. NH_4Cl (5 mL/mmol) and diluted with petroleum ether (20 mL/mmol). The phases are separated and the aqueous layer is extracted with petroleum ether (3 × 15 mL/mmol). The combined organic phases are dried over anhydrous Na_2SO_4, filtered and the solvent is removed in vacuo. The crude product is then purified by column chromatography.

General Procedure C: DDQ Oxidation[98]

To a solution of the PMB-ether in CH_2Cl_2/H_2O (10 mL/mmol, 18:1, v/v) is added 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ, 1.10 equiv) and the resulting mixture is stirred at rt for 4-6 h. After completion CH_2Cl_2 (10 mL/mmol) and sat. aq. $NaHCO_3$ (5 mL/mmol) are added. The phases are separated and the aqueous layer is extracted with CH_2Cl_2 (3 × 10 mL/mmol). The combined organic phases are washed again with sat. aq. $NaHCO_3$ (5 mL/mmol) and brine (5 mL/mmol), dried over anhydrous Na_2SO_4, filtered and the solvent is removed in vacuo. The crude product is then purified by column chromatography.

General procedure D: Acetamide formation

To a solution of the desired amine or amine hydrochloride (3.0 equiv), *N*-(3-dimethylaminopropyl)-*N′*-ethylcarbodiimide hydrochloride (EDCI, 1.5 equiv) and Et_3N (3 equiv) in CH_2Cl_2 (15 mL/mmol) at 0 °C is added hydroxybenzotriazole (HOBt, 1.4 equiv) and a solution of the corresponding acid in CH_2Cl_2 (5 mL/mmol). The cooling is removed and the resulting mixture is stirred at rt for 15 h. After completion, the reaction mixture is poured into aq. sat. $NaHCO_3$ (10 mL/mmol), the phases are separated and the aqueous phase is extracted with CH_2Cl_2 (2 × 10 mL/mmol). The combined organic phases are washed with aq. HCl (10 mL/mmol, 1 M), dried over anhydrous Na_2SO_4, filtered and the solvent is removed in vacuo. The crude product is purified by column chromatography.

General Procedure E: Activation with DSC[40,163] or $ClCO_2PNP$

To a solution of the alcohol and Et_3N (2.0 equiv) in CH_2Cl_2 (15 mL/mmol) is added *N,N'*-disuccinimidyl carbonate (DSC, 1.5 equiv) or *para*-nitrophenyl chloroformate (PNPOCOCl, 1.5 equiv) and the resulting mixture is stirred at rt for 18−24 h. After completion the reaction is diluted with CH_2Cl_2 (15 mL/mmol) and sat. aq. $NaHCO_3$ (7 mL/mmol). The phases are separated and the aqueous phase is extracted with CH_2Cl_2 (3 × 10 mL/mmol). The combined organic phases are dried over anhydrous Na_2SO_4, filtered and the solvent is removed in vacuo. The crude product is then purified by column chromatography.

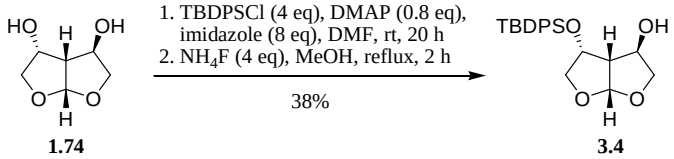
General Procedure F: PI formation

To a solution of the mixed carbonate (1.15 equiv) and Et_3N (2.0 equiv) in CH_2Cl_2 (10 mL/mmol) is added amine **1.81a-d** (1 equiv) and the resulting mixture is stirred at rt for 1–3 d. After completion CH_2Cl_2 (10 mL/mmol) and sat. aq. $NaHCO_3$ (5 mL/mmol) are added. The phases are separated and the aqueous layer is extracted with CH_2Cl_2 (3 × 10 mL/mmol). The combined organic phases are dried over anhydrous Na_2SO_4, filtered and the solvent is removed in vacuo. The crude product is purified by column chromatography and HPLC.

8.2.2 Synthesis of *bis*-THF ligands

8.2.2.1 Synthesis of *exo*-amino analogues

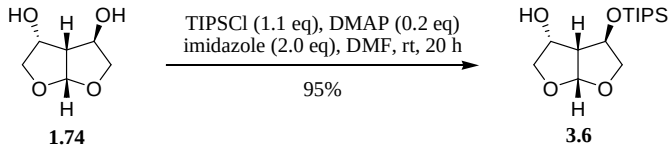
(1*R*,4*R*,5*S*,6*R*)-6-*tert*-Butyldiphenylsilanoxy-4-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.4)



1.74 **3.4**

To a solution of diol **1.74** (5.85 g, 40.1 mmol), imidazole (21.84 g, 320.8 mmol), DMAP (3.92 g, 32.08 mmol) in dry DMF (150 mL) was added *tert*-butyldiphenylsilylchloride (41.7 mL, 160.4 mmol) and the reaction mixture was stirred at rt for 20 h. After completion, Et_2O (150 mL) and H_2O (300 mL) were added and the layers were separated. The organic layer was washed with H_2O and brine (200 mL each), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to give the crude product **3.5** as a colourless oil. To a solution of crude silyl ether **3.5** in MeOH (250 mL) was added NH_4F (5.94 g, 160.4 mmol) and the reaction mixture was heated to reflux for 2 h. Subsequently the solvent was removed under reduced pressure, the precipitate was filtered off and the filter cake was washed with petroleum ether/EtOAc (90:10, 300 mL). The filtrate was again concentrated in vacuo. Further purification by column chromatography (petroleum ether/EtOAc 90:10 to 75:25) afforded the *bis*-silylated compound **3.5** (not isolated pure) and the *title compound* **3.4** as a colourless oil (5.79 g, 38%). Further treatment of the precipitate with acetone afforded the diol **1.74** as an off-white solid (695 mg, 12%). **Formula** $C_{22}H_{28}O_4Si$; **Mw** 384.54; $\mathbf{R_f}$ 0.29 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +17.5 (*c* 0.89, $CHCl_3$, 26 °C), lit.[68] +18.0 (*c* 0.25, $CHCl_3$, 27 °C). The ^1H and ^{13}C NMR spectra corresponded to the reported data.[68]

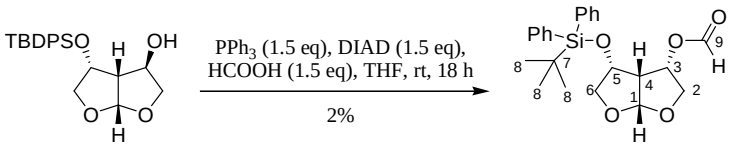
(1*S*,4*R*,5*R*,6*R*)-4-Triisopropylsilanoxy-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.6)



1.74 **3.6**

To a solution of the diol **1.74** (3.00 g, 20.5 mmol), imidazole (2.80 g, 41.0 mmol) and DMAP (500 mg, 4.1 mmol) in DMF (30 mL) was added triisopropylsilyl chloride (4.80 mL, 22.6 mmol) and the resulting mixture was stirred at rt for 20 h. The mixture was then diluted with H_2O (300 mL) and Et_2O (200 mL), and the phases were separated. The aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15) afforded the *title compound* **3.6** as a colourless oil (5.90 g, 95%). **Formula** $C_{22}H_{28}O_4Si$; **Mw** 384.54; $\mathbf{R}_f$ 0.29 (petroleum ether/acetone 85:15); $\mathbf{[\alpha]_D}$ +45.0 (*c* 0.91, $CHCl_3$, 25 °C), lit.[68] +44.7 (*c* 0.99, $CHCl_3$, 23 °C) The ^{1}H and ^{13}C NMR spectra corresponded to the reported data.[68]

Formic acid (1*R*,4*R*,5*S*,6*R*)-6-*tert*-butyldiphenylsilanoxy-2,8-dioxa-bicyclo[3.3.0]-octane-4 yl ester (3.7e)

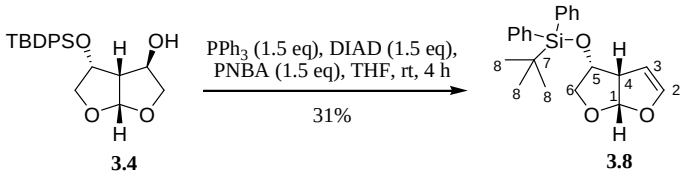


3.4 **3.7e**

To a solution of PPh_3 (331 mg, 1.26 mmol) in THF (3 mL) at 0 °C was added DIAD (250 µL, 1.26 mmol). After 1 h of stirring at 0 °C, formic acid (50 µL, 1.26 mmol) was added and the mixture was stirred for further 30 min at 0 °C. Then a solution of alcohol **3.4** (323 mg, 0.84 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred at rt for 18 h. The solvent was removed in vacuo and the crude mixture was purified by column chromatography (petroleum ether/EtOAc 80:20 to 60:40). Further purification by HPLC (hexane/EtOAc 88:12) afforded the *title compound* **3.7e** as a colourless oil (8.5 mg, 2%) and recovered alcohol **3.4** (238 mg, 74%). **Formula** $C_{23}H_{28}O_5Si$; **Mw** 412.55; $\mathbf{R}_f$ 0.53 (petroleum ether/EtOAc 80:20); **IR** (film) 2931 (br, m), 2858 (m), 1721 (s), 1111 (s), 1016 (s), 701 (s), 506 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.90 (1 H, s, H-9), 7.71–

7.62 (4 H, m, Ar-H), 7.49–7.37 (6 H, m, Ar-H), 6.01 (1 H, d, *J* = 5.1 Hz, H-1), 4.86 (1 H, m, H-3), 4.34 (1 H, dt, *J* = 4.1, 2.1 Hz, H-5), 3.87–3.81 (3 H, m, H-2, H-2' and H-6), 3.76 (1 H, dd, *J* = 10.0, 4.1 Hz, H-6'), 2.83 (1 H, m, H-4), 1.08 (9 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.9 (CH, C-9), 135.74 (2 × CH_{ar}), 135.62 (2 × CH_{ar}), 133.05 (C_{ar}), 133.03 (C_{ar}), 130.07 (CH_{ar}), 130.05 (CH_{ar}), 127.94 (2 × CH_{ar}), 127.90 (2 × CH_{ar}), 108.6 (CH, C-1), 76.2 (CH, C-3), 76.0 (CH, C-5), 75.3 (CH, C-6), 72.4 (CH_2, C-2), 59.1 (CH, C-4), 26.8 (3 × CH_3, C-8), 19.0 (C, C-7) ppm; **LRMS** (ESI$^+$) *m*/*z* 435.4 $(M + Na)^+$; **HRMS** (ESI+) for $C_{23}H_{28}O_5NaSi$ $(M + Na)^+$ calcd 435.1598, found 435.1599.

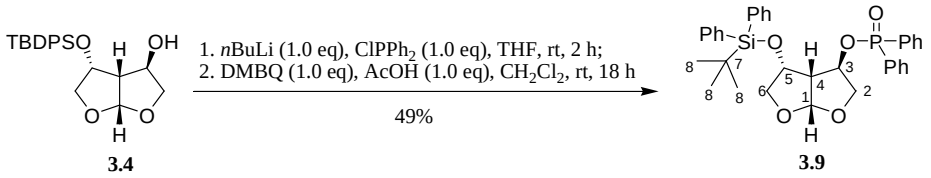
(1*S*,5*S*,6*R*)-6-*tert*-Butyldiphenylsilanoxy-2,8-dioxa-bicyclo[3.3.0]-oct-3-ene (3.8)



3.4 **3.8**

To a solution of PPh_3 (403 mg, 1.54 mmol) in THF (10 mL) at 0 °C was added DIAD (300 µL, 1.54 mmol). After 1 h of stirring at 0 °C, a solution of 4-nitrobenzoic acid (257 mg, 1.54 mmol) and alcohol **3.4** (394 mg, 1.03 mmol) in THF (5 mL) was added via syringe, the reaction mixture was stirred at rt and monitored by TLC. After 4 h, the solvent was removed in vacuo and the crude mixture was purified by column chromatography (petroleum ether/EtOAc 80:20 to 60:40). Further purification by HPLC (hexane/EtOAc 97:3) afforded the *title compound* **3.8** as a white solid (115 mg, 31%). **Formula** $C_{22}H_{26}O_3Si$; **Mw** 366.53; **R_f** 0.38 (hexane/EtOAc 95:5); **Mp** 78–80 °C; **$[\alpha]_D$** –52.3 (*c* 0.93, $CHCl_3$, 25 °C); **IR** (film) 2931 (br. w), 2890 (w), 2858 (w), 1135 (m), 1111 (s), 1013 (m), 701 (s), 505 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71–7.63 (4 H, m, Ar-H); 7.48–7.39 (6 H, m, Ar-H), 6.56 (1 H, t, *J* = 2.5 Hz, H-2), 5.84 (1 H, d, *J* = 6.0 Hz, H-1), 5.07 (1 H, t, *J* = 2.5 Hz, H-3), 4.48 (1 H, ddd, *J* = Hz, H-5), 3.68 (1 H, t, *J* = 6.8 Hz, H-6), 3.53 (1 H, t, *J* = 8.3 Hz, H-6'), 3.35 (1 H, m, H-4), 1.10 (12 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 147.0 (CH, C-2), 135.53 (2 × CH_{ar}), 135.51 (2 × CH_{ar}), 133.34 (C_{ar}), 133.31 (C_{ar}), 130.0 (2 × CH_{ar}), 127.83 (2 × CH_{ar}), 127.78 (2 × CH_{ar}), 108.4 (CH, C-1), 98.0 (CH, C-3), 73.9 (CH, C-5), 69.3 (CH_2, C-6), 50.1 (CH, C-4), 26.8 (3 × CH_3, C-8), 19.2 (C, C-7) ppm. **LRMS** (ESI$^+$) *m*/*z* 389.3 $(M + Na)^+$; **HRMS** (ESI$^+$) for $C_{22}H_{26}O_3SiNa$ $(M + Na)^+$ calcd. 389.1543, found 389.1545.

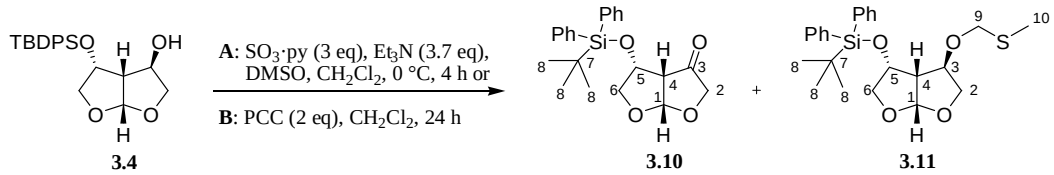
Diphenylphosphinic acid (1*S*,4*R*,5*R*,6*R*)-6-*tert*-butyldiphenylsilanoxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl ester (3.9)



3.4 **3.9**

To a solution of the alcohol **3.4** (466 mg, 1.21 mmol) in THF (5 mL) at 0 °C was added *n*BuLi (490 µL, 1.21 mmol, 2.5 M in hexane) and the resulting mixture was stirred at rt for 1 h. Then chlorodiphenylphosphine (220 µL, 1.21 mmol) was added at 0 °C, the reaction mixture was stirred at rt for further 60 min and subsequently concentrated in vacuo. A solution of acetic acid (70 µL, 1.21 mmol) in CH_2Cl_2 (5 mL) and 2,6-dimethylbenzoquinone (165 mg, 1.21 mmol) were added to the crude product and the resulting mixture was stirred at rt for 18 h. The reaction was quenched with H_2O (2 mL) and diluted with CH_2Cl_2 (10 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether/EtOAc 80:20 to 70:30). Further purification by HPLC (hexane/EtOAc 70:30) afforded the *title compound* **3.9** as a white solid (350 mg, 49%) and recovered starting material **3.4** (76 mg, 16%). **Formula** $C_{34}H_{37}O_5PSi$; **Mw** 584.71; $\mathbf{R_f}$ 0.13 (petroleum ether/EtOAc 80:20); **Mp** 50–53 °C; $\mathbf{[\alpha]_D}$ –26.5 (*c* 0.86, $CHCl_3$, 25 °C); **IR** (film) 3053 (w), 2960 (w), 2931 (w), 2858 (w), 1230 (m), 1112 (s), 983 (s), 699 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.89–7.78 (4 H, m, Ar-H), 7.62–7.32 (16 H, m, Ar-H), 5.84 (1 H, d, *J* = 5.0 Hz, H-1), 5.48 (1 H, dd, *J* = 8.0, 3.0 Hz, H-3), 4.41 (1 H, dt, *J* = 9.4, 7.5 Hz, H-5), 4.31 (1 H, dd, *J* = 10.5, 1.1 Hz, H-2), 4.12 (1 H, ddd, *J* = 10.5, 3.0, 1.0 Hz, H-2'), 3.40 (1 H, dd, *J* = 9.4, 6.7 Hz, H-6), 3.33 (1 H, dd, *J* = 9.4, 7.5 Hz, H-6'), 3.19 (1-H, ddd, *J* = 9.5, 5.0, 1.1 Hz, H-4), 0.92 (9 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 135.7 (2 × CH_{ar}), 135.6 (2 × CH_{ar}), 133.1 (C_{ar}), 132.3 (2 × CH_{ar}, d, *J* = 2.7 Hz), 132.4 (d, *J* = 135.0 Hz, C_{ar}), 132.1 (C_{ar}), 131.7 (2 × CH_{ar}, d, *J* = 10.0 Hz), 131.6 (2 × CH_{ar}, d, *J* = 10.2 Hz), 130.2 (CH_{ar}), 130.0 (CH_{ar}), 128.7 (2 × CH_{ar}, d, *J* = 13.1 Hz), 128.6 (2 × CH_{ar}, d, *J* = 13.1 Hz), 128.0 (2 × CH_{ar}), 127.9 (2 × CH_{ar}), 108.8 (CH, C-1), 77.2 (CH, d, *J* = 4.9 Hz, C-3), 76.6 (CH_2, d, *J* = 4.9 Hz, C-2), 72.6 (CH_2, C-6), 70.8 (CH, C-5), 54.2 (CH, d, *J* = 3.9 Hz, C-4), 26.8 (CH_3, C-8), 19.0 (C, C-7) ppm; **^{31}P NMR** (121 MHz, $CDCl_3$) δ 32.44 (P(O)Ph_2) ppm. **LRMS** (ESI^+) *m*/*z* 607.5 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{34}H_{37}O_5NaPSi$ $(M + Na)^+$ calcd 607.2040, found 607.2038.

(1*S*,5*S*,6*R*)-6-*tert*-Butyldiphenylsilanoxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-one (3.10)



3.4 **3.10** **3.11**

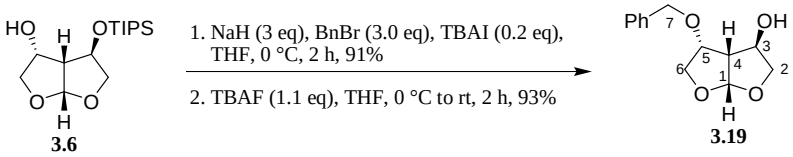
Method A: Following General Procedure A (8.2.1), oxidation of alcohol **3.4** (1.94 g, 5.0 mmol) with SO_3·pyridine (2.44 g, 15.0 mmol) afforded after purification by column chromatography (petroleum ether/EtOAc 80:20) and by HPLC (toluene/diethylether 93:7) the *title compound* **3.10** as a colourless oil (956 mg, 50%), mixed acetal **3.11** as a pale yellow oil (294 mg, 13%) and recovered alcohol **3.4** (163 mg, 8%).

Method B: To a solution of **3.4** (321 mg, 0.84 mmol) in CH_2Cl_2 (10 mL) was added pyridinium chlorochromate (360 mg, 1.67 mmol) and the resulting mixture was stirred at rt for 24 h. After completion, the solvent was removed in vacuo and the crude mixture was directly applied to column chromatography (petroleum ether/EtOAc 90:10, dry loading) to afford the *title compound* **3.10** as a colourless oil (297 mg, 93%). **Formula** $C_{22}H_{26}O_4Si$; **Mw** 382.52; $\mathbf{R_f}$ 0.35 (toluene/diethylether 95:5); $\mathbf{[\alpha]_D}$ –22.9 (*c* 0.61, $CHCl_3$, 25 °C); **IR** (film) 2955 (m), 2932 (m), 2858 (m), 1764 (s), 1111 (s), 1030 (m), 703 (s), 505 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.76–7.64 (4 H, m, Ar-H), 7.51–7.38 (6 H, m, Ar-H), 5.88 (1 H, d, *J* = 5.0 Hz, H-1), 4.58 (1 H, dt, *J* = 9.5, 6.5 Hz, H-5), 4.34 (1 H, dd, *J* = 16.5, 0.7 Hz, H-2), 4.12 (1 H, dd, *J* = 16.5, 0.9 Hz, H-2'), 3.70 (2 H, d, *J* = 6.5 Hz, H-6 and H-6'), 2.92 (1 H, ddt, *J* = 9.5, 5.0, 0.8 Hz, H-4), 1.06 (9 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 209.0 (C, C-3), 135.85 (2 × CH_{ar}), 135.62 (2 × CH_{ar}), 133.07 (C_{ar}), 132.18 (C_{ar}), 130.15 (CH_{ar}), 130.10 (CH_{ar}), 127.90 (2 × CH_{ar}), 127.84 (2 × CH_{ar}), 107.8 (CH, C-1), 73.70 (CH_2, C-2), 73.67 (CH, C-5), 73.2 (CH_2, C-6), 53.1 (CH, C-4), 26.7 (3 × CH_3, C-8), 19.0 (C, C-7) ppm; **LRMS** (ESI^+) *m*/*z* 405.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{22}H_{26}O_4NaSi$ $(M + Na)^+$ calcd 405.1493, found 405.1495.

Byproduct of Method A: (1*R*,4*R*,5*S*,6*R*)-6-*tert*-Butyldiphenylsilanoxy-2,8-dioxa-4-methyl-sulfanylmethoxy-bicyclo[3.3.0]-octane (**3.11**): **Formula**: $C_{24}H_{32}O_4SSi$; **Mw** 444.66; $\mathbf{R_f}$ 0.20 (toluene/diethylether 95:5); $\mathbf{[\alpha]_D}$ –39.2 (*c* 0.63, $CHCl_3$, 25 °C); **IR** (film) 2959 (m), 2930 (m), 2858 (m), 1113 (s), 1020 (s), 702 (s), 504 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72–7.60 (4 H, m, Ar-H), 7.51–7.37 (6 H, m, Ar-H), 5.71 (1 H, d, *J* = 5.1 Hz, H-1), 4.91 (1 H, m, H-3), 4.57 (1 H, d, *J* = 11.7 Hz, H-9), 4.49 (1 H, d, *J* = 11.7 Hz, H-9'), 4.46 (1 H, ddd, *J* = 9.0, 8.3, 6.8 Hz, H-5), 4.12 (1 H, m, H-2), 4.08 (1 H, dd, *J* = 10.3, 3.4 Hz, H-2'),

3.61 (1 H, dd, *J* = 9.0, 6.9 Hz, H-6), 3.45 (1 H, t, *J* = 8.5 Hz, H-6'), 2.80 (1 H, m, H-4), 2.15 (3 H, s, H-10), 1.12 (9 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 135.63 (2 × CH_{ar}), 135.61 (2 × CH_{ar}), 133.1 (C_{ar}), 132.8 (C_{ar}), 130.2 (CH_{ar}), 130.1 (CH_{ar}), 128.0 (2 × CH_{ar}), 127.9 (2 × CH_{ar}), 108.7 (CH, C-1), 77.1 (CH, C-3), 74.5 (CH_2, C-2), 73.2 (CH_2, C-9), 72.6 (CH_2, C-6), 71.1 (CH, C-5), 53.1 (CH, C-4), 27.0 (3 × CH_3, C-8), 19.1 (C, C-7), 13.9 (CH_3, C-10) ppm. **LRMS** (ESI^+) *m/z* 467.4 $(M + Na)^+$, 911.9 $(2M + Na)^+$; **HRMS** (ESI^+) for $C_{24}H_{32}O_4NaSSi$ $(M + Na)^+$ calcd 467.1683, found 467.1685

(1*R*,4*R*,5*S*,6*R*)-6-Benzyloxy-4-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.19)

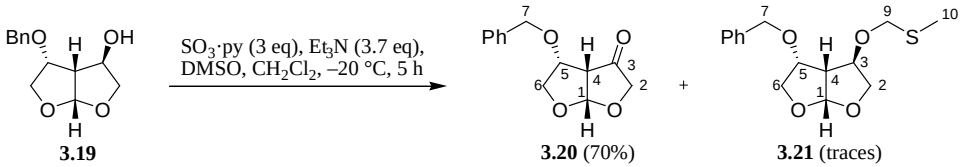


Following General Procedure **B** (8.2.1), the reaction of alcohol **3.6** (500 mg, 1.65 mmol) with benzyl bromide (540 µL, 4.5 mmol) afforded after purification by column chromatography (petroleum ether/acetone 95:5) the *bis*-protected intermediate as a colourless oil (578 mg, 1.47 mmol, 89%; $\mathbf{R_f}$ 0.45 (hexane/acetone 90:10); $\mathbf{[\alpha]_D}$ +32.2 (*c* 1.30, $CHCl_3$, 26 °C); **IR** (film) 2942 (s), 2865 (s), 1463 (m), 1123 (vs), 1022 (vs), 883 (m), 697 (m), 682 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.28 (5 H, m), 5.85 (1 H, d, *J* = 5.1 Hz), 4.81 (1 H, br. d, *J* = 3.4 Hz), 4.55 (2 H, m), 4.20 (1 H, ddd, *J* = 9.2, 7.2, 6.8 Hz), 4.05 (1 H, dd, *J* = 9.5, 3.4 Hz), 3.98–3.92 (2 H, m), 3.65 (1 H, dd, *J* = 9.2, 7.3 Hz), 2.88 (1 H, dd, *J* = 9.2, 5.1 Hz), 1.09–1.03 (21 H, m); **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 137.6 (C_{ar}), 128.4 (2 × CH_{ar}), 127.9 (CH_{ar}), 127.5 (2 × CH_{ar}), 109.1 (CH), 78.3 (CH_2), 76.6 (CH), 73.2 (CH), 72.5 (CH_2), 71.0 (CH_2), 55.5 (CH), 18.0 (6 × CH_3), 12.1 (3 × CH); **LRMS** (ESI^+) *m/z* 415.2 $(M + Na)^+$).

To a solution of the intermediate silylether (550 mg, 1.40 mmol) in THF (10 mL) was added dropwise TBAF (1.54 mL, 1.54 mmol, 1 M in THF) at 0 °C. After 5 min the cooling was removed and the resulting mixture was stirred at rt for further 2 h. After completion the reaction was diluted with Et_2O (20 mL) and subsequently washed with H_2O (10 mL) and brine (10 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 75:25 to 60:40) afforded the *title compound* **3.19** as a colourless oil (307 mg, 93%). **Formula** $C_{13}H_{16}O_4$; **Mw** 236.26; $\mathbf{R_f}$ 0.35 (petroleum ether/acetone 75:25); $\mathbf{[\alpha]_D}$ –4.3 (*c* 1.18, $CHCl_3$, 26 °C); **IR** (film) 3418 (br, m), 2972 (w), 2878 (w), 1121

(s), 1082 (m), 1023 (s), 971 (m), 741 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.29 (5 H, m, Ar-H), 5.83 (1 H, d, *J* = 5.3 Hz, H-1), 4.69 (1 H, dt, *J* = 3.8, 1.1 Hz, H-3), 4.61 (1 H, d, *J* = 12.2 Hz, part of AB system, H-7), 4.58 (1 H, d, *J* = 12.2 Hz, part of AB system, H-7'), 4.26 (1 H, ddd, *J* = 8.8, 7.8, 6.7 Hz, H-5), 4.07 (1 H, dd, *J* = 10.2, 3.8 Hz, H-2), 3.98 (1 H, dd, *J* = 9.3, 6.7 Hz, H-6), 3.92 (1 H, dt, *J* = 10.2, 1.2 Hz, H-2), 3.64 (1 H, dd, *J* = 9.3, 7.8 Hz, H-6), 2.87 (1 H, ddt, *J* = 8.8, 5.3, 1.2 Hz, H-4), 1.78 (1 H, br, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 137.5 (C_{ar}), 129.6 (2 × CH_{ar}), 128.1 (CH_{ar}), 127.7 (2 × CH_{ar}), 108.8 (CH, C-1), 77.1 (CH_2, C-2), 77.0 (CH, C-5), 72.7 (CH_2, C-7), 72.3 (CH, C-3), 70.9 (CH_2, C-6), 54.6 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 259.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{13}H_{16}O_4Na$ $(M + Na)^+$ calcd 259.0941, found 259.0943

(1*S*,5*S*,6*R*)-6-Benzyloxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-one (3.20)

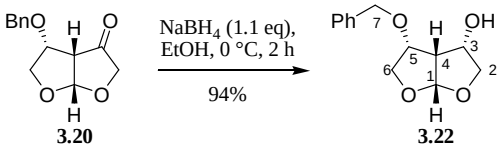


3.19 **3.20** (70%) **3.21** (traces)

Following General Procedure **A** (8.2.1), oxidation of alcohol **3.19** (1.01 g, 4.3 mmol) with SO_3·pyridine (2.06 g, 12.8 mmol) afforded after purification by column chromatography (petroleum ether/acetone 90:10 to 70:30) the *title compound* **3.20** as a colourless oil (738 mg, 70%) and recovered alcohol **3.19** (130 mg, 13%). Traces of the pure mixed acetal **3.21** were isolated as a pale yellow oil after reduction of **3.20** to **3.22**. **Formula** $C_{13}H_{14}O_4$; **Mw** 234.24; **R_f** 0.26 (petroleum ether/EtOAc 80:20); **$[\alpha]_D$** –52.3 (*c* 1.01, $CHCl_3$, 24 °C); **IR** (film) 2876 (w), 1760 (vs), 1115 (s), 1044 (m), 1029 (m), 954 (m), 741 (m), 700 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.28 (5 H, m, Ar-H), 6.00 (1 H, d, *J* = 5.0 Hz, H-1), 4.78 (1 H, d, *J* = 11.4 Hz, H-7), 4.51 (1 H, d, *J* = 11.4 Hz, H-7'), 4.44 (1 H, ddd, *J* = 9.3, 7.1, 6.4 Hz, H-5), 4.30 (1 H, dd, *J* = 16.7, 0.8 Hz, H-2), 4.13 (1 H, dd, *J* = 9.6, 6.4 Hz, H-6), 4.10 (1 H, dd, *J* = 16.7, 1.0 Hz, H-2), 3.95 (1 H, dd, *J* = 9.6, 7.1 Hz, H-6), 3.19 (1 H, m, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 209.7 (C, C-3), 137.0 (C_{ar}), 128.5 (2 × CH_{ar}), 128.0 (CH_{ar}), 127.9 (2 × CH_{ar}), 108.1 (CH, C-1), 79.2 (CH, C-5), 73.5 (CH_2, C-2), 72.9 (CH_2, C-7), 71.2 (CH_2, C-6), 52.3 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 257.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{13}H_{14}O_4Na$ $(M + Na)^+$ calcd 257.0784, found 257.0783.

Byproduct: (1*S*,4*R*,5*R*,6*R*)-6-Benzyloxy-2,8-dioxa-4-methyl-sulfanylmethoxy-bicyclo-[3.3.0]-octane (**3.21**): **Formula** $C_{15}H_{20}O_4S$ **Mw** 296.38 $\mathbf{R_f}$ 0.25 (hexane/acetone 80:20); $\mathbf{[\alpha]_D}$ +26.0 (*c* 1.29, $CHCl_3$, 25 °C); **IR** (film) 2921 (w), 2873 (w), 1116 (m), 1080 (m), 1024 (s), 740 (w), 699 (w) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.30 (5 H, m, Ar-H), 5.82 (1 H, d, *J*= 5.1 Hz, H-1), 4.77 (1 H, m, H-3), 4.66 (1 H, d, *J*=11.8 Hz, H-7), 4.65 (1 H, d, *J*=11.7 Hz, H-8), 4.61 (1 H, d, *J*=11.7 Hz, H-8'), 4.55 (1 H, d, *J*=11.8 Hz, H-7'), 4.27 (1 H, ddd, *J*=8.8, 8.0, 6.7 Hz, H-5), 4.06 (1 H, m, H-2), 4.03 (1 H, d, *J*=10.5 Hz, H-2'), 4.00 (1 H, dd, *J*=9.0, 6.7 Hz, H-6), 3.64 (1 H, dd, *J*=9.0, 8.0 Hz, H-6), 2.97 (1 H, m, H-4), 2.16 (3 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 137.5 (C_{ar}), 128.5 (2 × CH_{ar}), 128.0 (CH_{ar}), 127.6 (2 × CH_{ar}), 108.9 (CH, C-1), 76.9 (CH, C-5), 76.6 (CH, C-3), 74.3 (CH_2, C-2), 73.5 (CH_2, C-8), 72.6 (CH_2, C-7), 70.9 (CH_2, C-6), 51.9 (CH, C-4), 13.9 (CH_3, C-9) ppm. **LRMS** (ESI^+) *m/z* 319.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{15}H_{20}O_4NaS$ $(M + Na)^+$ calcd 319.0975, found 319.0980.

(1*R*,4*S*,5*S*,6*R*)-6-Benzyloxy-4-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.22)

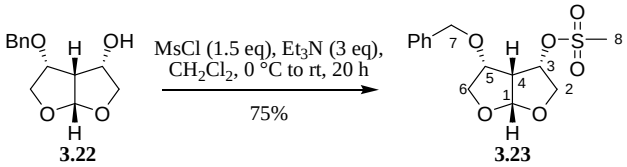


3.20 **3.22**

To a solution of ketone **3.20** (100 mg, 0.43 mmol) in EtOH (5 mL) at 0 °C was added sodium borohydride (18 mg, 0.47 mmol). The resulting mixture was stirred at 0 °C for 2 h. After completion, the reaction was quenched with citric acid (10 w% in water, 1 mL) and concentrated under reduced pressure. The residue was then partitioned between Et_2O and brine (10 mL each), and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15) afforded the *title compound* **3.22** as a colourless oil (96 mg, 94%). **Formula** $C_{13}H_{16}O_4$; **Mw** 236.26; $\mathbf{R_f}$ 0.35 (petroleum ether/acetone 85:15); $\mathbf{[\alpha]_D}$ +22.9 (*c* 0.78, $CHCl_3$, 26 °C); **IR** (film) 3450 (br, w), 2923 (w), 2877 (w), 1101 (s), 1043 (s), 1005 (s), 970 (m), 730 (m), 699 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$, D_2O-shake) δ 7.43–7.31 (5 H, m, Ar-H), 5.61 (1 H, d, *J* = 5.5 Hz, H-1), 4.67 (1 H, d, *J* = 11.5 Hz, H-7), 4.57 (1 H, d, *J* = 11.5 Hz, H-7), 4.49 (1 H, dt, *J* = 7.4, 6.0 Hz, H-3), 4.46 (1 H, ddd, *J* = 8.3, 6.7, 6.1 Hz, H-5), 4.12 (1 H, dd, *J* = 9.2, 6.8 Hz, H-6), 3.98 (1 H, dd, *J* = 8.9, 6.3 Hz, H-2), 3.96 (1 H, dd, *J* = 9.2, 6.0 Hz, H-6'), 3.94 (1 H, dd, *J* = 8.9, 5.9 Hz, H-2'), 2.87 (1 H, td, *J* = 7.8,

5.5 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 136.4 (C_{ar}), 128.8 (2 × CH_{ar}), 128.5 (CH_{ar}), 128.0 (2 × CH_{ar}), 108.8 (CH, C-1), 80.9 (CH, C-5), 74.5 (CH_2, C-2), 73.8 (CH, C-3), 73.3 (CH_2, C-7), 71.3 (CH_2, C-6), 46.7 (CH, C-4) ppm. **LRMS** (ESI^+) *m*/*z* 259.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{13}H_{16}O_4Na$ $(M + Na)^+$ calcd. 259.0941, found 259.0939.

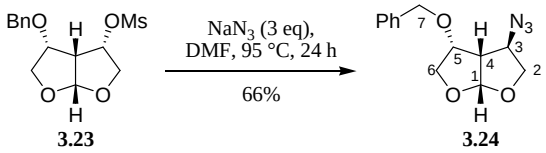
Methanesulfonic acid (1*S*,4*S*,5*R*,6*R*)-6-Benzyloxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl ester (3.23)



3.22 **3.23**

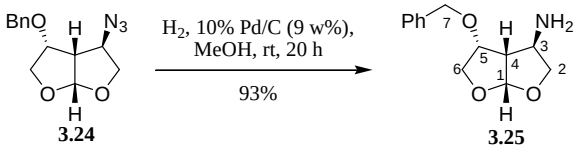
To a solution of alcohol **3.22** (2.48 g, 10.5 mmol) and Et_3N (4.30 mL, 31.0 mmol) in CH_2Cl_2 (35 mL) at 0 °C was added dropwise methanesulfonyl chloride (1.22 mL, 15.7 mmol) and the resulting mixture was stirred at rt for 20 h. After completion, the reaction was diluted with CH_2Cl_2 (100 mL) and consecutively washed with water, sat. aq. $NaHCO_3$ and brine (50 mL each). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15 to 80:20) afforded the *title compound* **3.23** as a colourless oil (2.47 g, 75%). **Formula** $C_{14}H_{18}O_6S$; **Mw** 314.35; $\mathbf{R_f}$ 0.15 (petroleum ether/acetone 80:20); $\mathbf{[\alpha]_D}$ –26.9 (*c* 1.43, $CHCl_3$, 26 °C); **IR** (film) 3030 (w), 2936 (w), 2903 (w), 2875 (w), 1351 (s), 1173 (s), 1028 (m), 967 (s), 912 (s), 751 (m), 701 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.28 (5 H, m, Ar-H), 5.65 (1 H, d, *J* = 5.4 Hz, H-1), 5.26 (1 H, dt, *J* = 7.1, 4.6 Hz, H-3), 4.63 (1 H, d, *J* = 11.5 Hz, H-7), 4.58 (1 H, d, *J* = 11.5 Hz, H-7'), 4.39–4.32 (2 H, m, H-2 and H-5), 4.08 (1 H, dd, *J* = 8.5, 7.5 Hz, H-6), 4.01 (1 H, dd, *J* = 9.5, 4.8 Hz, H-2'), 3.96 (1 H, dd, *J* = 8.5, 6.3 Hz, H-6'), 3.01 (1 H, td, *J* = 7.3, 5.4 Hz, H-4), 2.88 (3 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 137.4 (C_{ar}), 128.5 (2 × CH_{ar}), 128.1 (CH_{ar}), 128.0 (2 × CH_{ar}), 108.0 (CH, C-1), 78.6 (CH, C-5), 77.7 (CH, C-3), 73.29 (CH_2, C-2), 73.27 (CH_2, C-7), 71.8 (CH_2, C-6), 47.7 (CH, C-4), 38.1 (CH_3, C-8) ppm; **LRMS** (ESI^+) *m*/*z* 337.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{14}H_{18}O_6SNa$ $(M + Na)^+$ calcd 337.0716, found 337.0713.

(1*R*,4*R*,5*S*,6*R*)-4-Azido-6-benzyloxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.24)



To a solution of mesylate **3.23** (30 mg, 0.095 mmol) in DMF (3 mL) was added sodium azide (19 mg, 0.29 mmol) and the resulting mixture was stirred at 95 °C for 24 h. After completion, the reaction was diluted with H_2O (10 mL) and extracted with Et_2O (3 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed. Purification of the crude product by column chromatography (petroleum ether/ acetone 90:10 to 80:20) afforded the *title compound* **3.24** as a colourless oil (16.5 mg, 66%). **Formula** $C_{13}H_{15}O_3N_3$; **Mw** 261.28; $\mathbf{R_f}$ 0.29 (petroleum ether/acetone 90:10); $\mathbf{[\alpha]_D}$ +53.2 (*c* 0.71, $CHCl_3$, 25 °C); **IR** (film) 2947 (w), 2881 (w), 2094 (vs), 1253 (m), 1118 (s), 1026 (vs),740 (m), 699 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43–7.30 (5 H, m, Ar-H), 5.80 (1 H, d, *J* = 5.1 Hz, H-1), 4.60 (1 H, d, *J* = 11.7 Hz, H-7), 4.56 (1 H, d, *J* = 11.7 Hz, H-7'), 4.39 (1 H, dt, *J* = 4.5, 1.8 Hz, H-3), 4.27 (1 H, ddd, *J* = 8.5, 7.7, 6.5 Hz, H-5), 4.11 (1 H, dd, *J* = 10.2, 6.5 Hz, H-2), 4.01 (1 H, m, H-2'), 4.00 (1 H, dd, *J* = 9.3, 6.5 Hz, H-6), 3.66 (1 H, dd, *J* = 9.3, 7.7 Hz, H-6'), 2.96 (1 H, ddt, *J* = 8.8, 5.1, 1.3 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 137.1 (C_{ar}), 128.6 (2 × CH_{ar}), 128.2 (CH_{ar}), 127.7 (2 × CH_{ar}), 108.6 (CH, C-1), 76.7 (CH, C-5), 74.0 (CH_2, C-2), 72.7 (CH_2, C-7), 70.9 (CH_2, C-6), 61.3 (CH, C-3), 51.9 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 284.0 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{13}H_{15}O_3N_3Na$ $(M + Na)^+$ calcd 284.1006, found 284.1008.

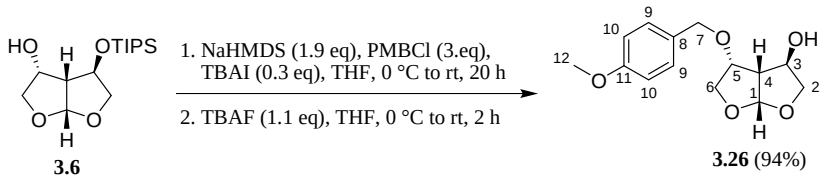
(1*R*,4*R*,5*S*,6*R*)-4-Amino-6-benzyloxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.25)



To a solution of azide **3.24** (220 mg, 0.84 mmol) in dry MeOH (15 mL) under N_2 was added Pd/C (20 mg, 9 w%, 10% Pd). The flask was then put under H_2-atmosphere and the reaction was stirred at rt for 20 h. After completion the reaction mixture was filtered over celite and the filter cake was washed with MeOH. The filtrate was concentrated in vacuo an then redissolved in CH_2Cl_2 (10 mL). This organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford the *title compound* **3.25** as a

colourless oil (186 mg, 93%). **Formula** $C_{13}H_{17}NO_3$; **Mw** 235.28; $\mathbf{R_f}$ 0.20 (CH_2Cl_2/MeOH 90:10); $\mathbf{[\alpha]_D}$ +5.3 (*c* 1.32, $CHCl_3$, 26 °C); **IR** (film) 3356 (w), 2948 (m), 2878 (m), 1604 (w), 1121 (s), 1021 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.41–7.29 (5 H, m, Ar-H), 5.81 (1 H, d, *J* = 5.3 Hz, H-1), 4.62 (1 H, d, *J* = 11.8 Hz, H-7), 4.57 (1 H, d, *J* = 11.8 Hz, H-7'), 4.24 (1 H, td, *J* = 8.0, 7.0 Hz, H-5), 4.09 (1 H, dd, *J* = 9.3, 4.5 Hz, H-2), 3.98 (1 H, dd, *J* = 9.0, 6.8 Hz, H-6), 3.90 (1 H, m, H-3), 3.74 (1 H, dd, *J* = 9.3, 1.0 Hz, H-2'), 3.65 (1 H, app. t, *J* = 8.5, H-6'), 2.69 (1 H, m, H-4), 1.91 (2 H, br. s, NH_2) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 137.6 (C_{ar}), 128.6 (2 × CH_{ar}), 128.0 (CH_{ar}), 127.7 (2 × CH_{ar}), 108.9 (CH, C-1), 77.44 (CH_2, C-2), 77.42 (CH, C-5), 72.7 (CH_2, C-7), 70.8 (CH_2, C-6), 55.0 (CH, C-4), 52.1 (CH, C-3) ppm; **LRMS** (ESI^+) *m*/*z* 236.3 $(M + H)^+$, 258.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{13}H_{17}NO_3H$ $(M + H)^+$ calcd 236.1281, found 236.1282.

(1*R*,4*R*,5*S*,6*R*)-4-Hydroxy-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo-[3.3.0]-octane (3.26)



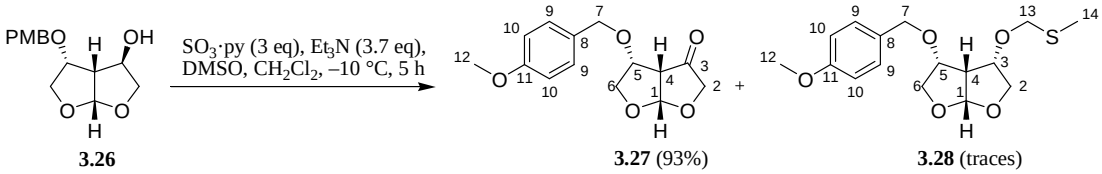
3.6 **3.26** (94%)

To a solution of alcohol **3.6** (5.49 g, 18.1 mmol) in THF (40 mL) at 0 °C was added NaHMDS (14.5 mL, 29.0 mmol, 2 M in THF) and the resulting mixture was stirred for 10 min. Then 4-methoxybenzyl chloride (4.9 mL, 36.2 mmol) and TBAI (2.00 g, 5.4 mmol) were added and the resulting mixture was stirred at rt for 20 h. After completion the reaction was quenched with a mixture of sat. aq. NH_4Cl/petroleum ether (1:1, 200 mL). The phases were separated and the aqueous layer was extracted with petroleum ether (2 × 100 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered over a silica plug and the solvent was removed in vacuo to afford the intermediate *bis*-protected compound in sufficient purity (8.26 g). An analytically pure sample was obtained by column chromatography (petroleum ether/EtOAc 95:5 to 90:10). **Formula** $C_{23}H_{38}O_5Si$; **Mw** 422.63; $\mathbf{R_f}$ 0.38 (hexane/acetone 90:10); $\mathbf{[\alpha]_D}$ +30.9 (*c* 0.8, $CHCl_3$, 25 °C); **IR** (film) 2942 (m), 2865 (m), 1513 (s), 1463 (m), 1247 (s), 1121 (vs), 1016 (vs), 882 (m), 821 (m), 681 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.23 (2 H, d, *J* =8.5 Hz), 6.89 (2 H, d, *J* = 8.5 Hz), 5.84 (1 H, d, *J* = 5.3 Hz), 4.79 (1 H, br. d, *J* = 3.4 Hz), 4.50 (1 H, d, *J* = 11.7 Hz), 4.47 (1 H, d, *J* = 11.7 Hz), 4.17 (1 H, dt, *J* = 9.2, 6.8 Hz), 4.03 (1 H, dd, *J* = 9.4, 3.4 Hz), 3.95–3.90 (2 H, m), 3.83 (3 H, s), 3.61 (1 H, dd, *J* = 9.3, 7.3 Hz), 2.85 (1 H, dd, *J* = 9.2, 5.2 Hz), 1.09–1.04 (21 H, m) ppm. **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.4 (C_{ar}),

129.7 (C_{ar}), 129.1 (2 × CH_{ar}), 113.9 (2 × CH_{ar}), 109.1 (CH), 78.3 (CH_2), 76.2 (CH), 73.2 (CH), 72.2 (CH_2), 71.0 (CH_2), 55.5 (CH), 55.3 (CH_3), 18.0 (6 × CH_3), 12.1 (3 × CH) ppm; **LRMS** (ESI+) *m*/*z* 445.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{23}H_{38}O_5NaSi$ $(M + Na)^+$ calcd 445.2381, found 445.2386.

To a solution of intermediate silylether (8.26 g, 18.1 mmol) in THF (30 mL) at 0 °C was added dropwise TBAF (20.0 mL, 20.0 mmol, 1 M in THF). After 5 min the cooling was removed and the resulting mixture was stirred at rt for further 2 h. After completion, the reaction was diluted with Et_2O (200 mL) and subsequently washed with H_2O and brine (100 mL each). The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 75:25 to 60:40) afforded the *title compound* **3.26** as a colourless oil (4.55 g, 97%). **Formula** $C_{14}H_{18}O_5$; **Mw** 266.29; $\mathbf{R_f}$ 0.25 (petroleum ether/acetone 75:25); $\mathbf{[\alpha]_D}$ –3.2 (*c* 1.2, $CHCl_3$, 26 °C); **IR** (film) 3421 (br, m), 2956 (w), 2877 (w), 1612 (m), 1513 (s), 1464 (w), 1246 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2 H, d, *J* =8.6 Hz, H-9), 6.89 (2 H, d, *J* = 8.6 Hz, H-10), 5.82 (1 H, d, *J* = 5.1 Hz, H-1), 4.67 (1 H, br. d, *J* = 3.5 Hz, H-3), 4.53 (1 H, d, *J* = 11.7 Hz, H-7), 4.50 (1 H, d, *J* = 11.7 Hz, H-7'), 4.23 (1 H, td, *J* = 8.4, 6.7 Hz, H-5), 4.05 (1 H, dd, *J* = 10.0, 3.5 Hz, H-2), 3.96 (1 H, dd, *J* = 9.1, 6.7 Hz, H-6), 3.91 (1 H, dt, *J* = 10.0, 1.4 Hz, H-2'), 3.82 (3 H, s, H-14), 3.60 (1 H, dd, *J* = 9.1, 8.2 Hz, H-6'), 2.85 (1 H, m, H-4), 1.83 (1 H, br. s, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 129.6 (C_{ar}, C-8), 129.4 (2 × CH_{ar}, C-9), 114.0 (2 × CH_{ar}, C-10), 108.8 (CH, C-1), 77.1 (CH_2, C-2), 76.7 (CH, C-5), 72.4 (CH_2, C-7), 72.3 (CH, C-3), 71.0 (CH_2, C-6), 55.3 (CH_3, C-12), 54.6 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 289.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{14}H_{18}O_5Na$ $(M + Na)^+$ calcd 289.1046, found 289.1050.

(1*S*,5*S*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octan-4-one (3.27)



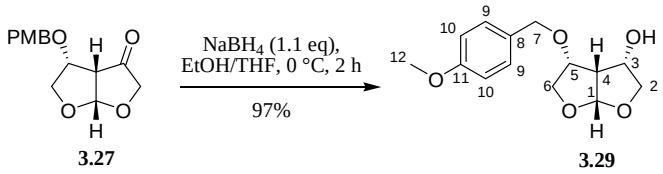
3.26 **3.27** (93%) **3.28** (traces)

Following General Procedure **A** (8.2.1), oxidation of alcohol **3.26** (1.42 g, 5.3 mmol) with SO_3·pyridine (2.58 g, 15.9 mmol) afforded after purification by column chromatography (petroleum ether/EtOAc 80:20 to 70:30) the *title compound* **3.27** as a colourless oil (1.30 g, 93%). Traces of mixed acetal **3.28** could be isolated pure after reduction of **3.27**.

Formula $C_{14}H_{16}O_5$; **Mw** 264.27; $\mathbf{R_f}$ 0.23 (petroleum ether/acetone 80:20); $\mathbf{[\alpha]_D}$ –55.0 (*c* 0.75, $CHCl_3$, 25 °C); **IR** (film) 2937 (w), 2838 (w), 1760 (s), 1612 (m), 1514 (s), 1248 (s), 1179 (m), 1110 (m), 1031 (s), 954 (m), 824 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2 H, d, *J* =8.7 Hz, H-9), 6.89 (2 H, d, *J* = 8.7 Hz, H-10), 5.99 (1 H, d, *J* = 5.1 Hz, H-1), 4.72 (1 H, d, *J* = 11.2 Hz, H-7), 4.44 (1 H, d, *J* = 11.2 Hz, H-7'), 4.42 (1 H, dt, *J* = 9.3, 6.8 Hz, H-5), 4.29 (1 H, d, *J* = 16.7 Hz, H-2), 4.11 (1 H, dd, *J* = 9.5, 6.4 Hz, H-6), 4.09 (1 H, d, *J* = 16.7 Hz, H-2'), 3.91 (1 H, dd, *J* = 9.5, 7.3 Hz, H-6'), 3.91 (3 H, s, H-12), 3.19 (1 H, dd, *J* = 9.3, 5.1 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 209.8 (C, C-3), 159.5 (C_{ar}, C-11), 129.7 (2 × CH_{ar}, C-9), 129.1 (C_{ar}, C-8), 113.9 (2 × CH_{ar}, C-10), 108.1 (CH, C-1), 78.9 (CH, C-5), 73.5 (CH_2, C-2), 72.6 (CH_2, C-7), 71.2 (CH_2, C-6), 55.3 (CH_3, C-12), 52.3 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 287.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{14}H_{16}O_5Na$ $(M + Na)^+$ calcd 287.0890, found 287.0893.

Byproduct: (1*S*,4*R*,5*R*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-4-methylsulfanylmethoxy-bicyclo-[3.3.0]-octane (**3.28**): **Formula** $C_{16}H_{22}O_5S$; **Mw** 326.41; $\mathbf{R_f}$ 0.46 (petroleum ether/ acetone 80:20); $\mathbf{[\alpha]_D}$ +21.6 (*c* 0.73, $CHCl_3$, 24 °C); **IR** (film) 2921 (m, br), 1760 (s), 1612 (w), 1513 (m), 1246 (s), 1020 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (2 H, d, *J* = 8.7 Hz, H-9), 6.91 (2 H, d, *J* = 8.7 Hz, H-10), 5.81 (1 H, d, *J* = 5.1 Hz, H-1), 4.75 (1 H, m, H-3), 4.65 (1 H, d, *J* = 11.7 Hz, H-13), 4.61 (1 H, d, *J* = 11.7 Hz, H-13'), 4.59 (1 H, d, *J* = 11.2 Hz, H-7), 4.48 (1 H, d, *J* = 11.2 Hz, H-7'), 4.24 (1 H, td, *J* = 8.5, 6.8 Hz, H-5), 4.05 (1 H, m, H-2), 4.01 (1 H, dd, *J* = 10.3, 3.5 Hz, H-2'), 3.98 (1 H, dd, *J* = 9.2, 6.7 Hz, H-6), 3.82 (3 H, s, H-12), 3.81 (1 H, app. t, *J* = 8.5 Hz, H-6'), 2.96 (1 H, m, H-4), 2.17 (3 H, s, H-14) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 129.5 (C_{ar}, C-8), 129.3 (2 × CH_{ar}, C-9), 113.9 (2 × CH_{ar}, C-10), 108.9 (CH, C-1), 76.7 (CH, C-5), 76.6 (CH, C-3), 74.3 (CH_2, C-2), 73.4 (CH_2, C-13), 72.4 (CH_2, C-7), 70.9 (CH_2, C-6), 55.3 (CH_3, C-12), 51.8 (CH, C-4), 14.0 (CH_3, C-14) ppm; **LRMS** (ESI^+) *m*/*z* 349.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{16}H_{22}O_5NaS$ $(M + Na)^+$ calcd 349.1080, found 349.1078.

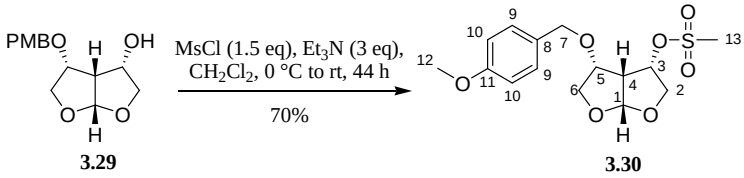
(1*S*,4*S*,5*S*,6*R*)-6-(4-Methoxybenzyloxy)-4-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.29)



3.27 **3.29**

To a solution of ketone **3.27** (1.01 g, 4.1 mmol) in EtOH/THF (15 mL, v/v 2:1) at 0 °C was added sodium borohydride (170 mg, 4.5 mmol). The resulting mixture was stirred at 0 °C for 2 h. After completion, the reaction was quenched with citric acid (10 w% in water, 10 mL) and concentrated under reduced pressure. The residue was then partitioned between Et_2O and brine (20 mL each), and the aqueous phase was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:20) afforded the *title compound* **3.29** as a colourless oil (1.07 g, 97%). **Formula** $C_{14}H_{18}O_5$; **Mw** 266.29; $\mathbf{R_f}$ 0.25 (petroleum ether/acetone 75:25); $\mathbf{[\alpha]_D}$ +19.1 (*c* 0.72, $CHCl_3$, 24 °C); **IR** (film) 3478 (br, w), 2955 (br, w), 2860 (w), 1612 (m), 1514 (s), 1250 (s) cm^{-1}; **^{1}H NMR** (300 MHz, acetone-d_6) δ 7.34 (2 H, d, *J* =8.8 Hz, H-9), 6.94 (2 H, d, *J* = 8.8 Hz, H-10), 5.49 (1 H, d, *J* = 5.6 Hz, H-1), 4.64 (1 H, d, *J* = 11.2 Hz, H-7), 4.58 (1 H, d, *J* = 11.2 Hz, H-7'), 4.49 (1 H, ddd, *J* = 8.2, 6.9, 6.0 Hz, H-5), 4.38 (1 H, m, H-3, simplifies to dt, *J* = 7.3, 5.7 Hz after D_2O-exchange), 4.16 (1 H, d, *J* = 6.0 Hz, OH, disappears after D_2O-exchange), 3.99 (1 H, dd, *J* = 8.8, 6.9 Hz, H-6), 3.88 (1 H, dd, *J* = 8.8, 6.0 Hz, H-6'), 3.80 (1 H, dd, *J* = 8.7, 5.7 Hz, part of ABX system, H-2), 3.80 (3 H, s, H-12), 3.77 (1 H, dd, *J* = 8.7, 5.7 Hz, H-2'), 2.92 (1 H, ddd, *J* = 8.2, 7.3, 5.6 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.8 (C_{ar}, C-11), 129.7 (2 × CH_{ar}, C-9), 128.5 (C_{ar}, C-8), 114.2 (2 × CH_{ar}, C-10), 108.8 (CH, C-1), 80.6 (CH, C-5), 74.5 (CH_2, C-2), 73.8 (CH, C-3), 72.9 (CH_2, C-7), 71.3 (CH_2, C-6), 55.3 (CH_3, C-12), 46.6 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 289.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{14}H_{18}O_5Na$ $(M + Na)^+$ calcd. 289.1046, found 289.1044.

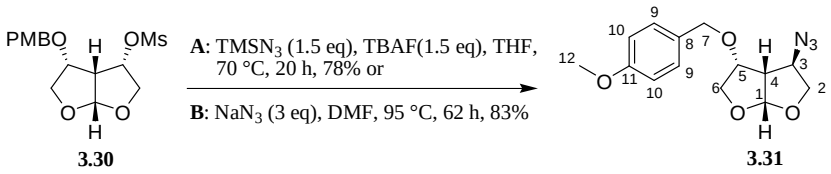
Methanesulfonic acid (1*S*,4S,5*R*,6*R*)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl ester (3.30)



3.29 **3.30**

To a solution of alcohol **3.29** (1.62 g, 6.1 mmol) and Et_3N (2.50 mL, 18.2 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added dropwise methanesulfonyl chloride (720 µL, 9.1 mmol) and the resulting mixture was stirred at rt for 44 h. After completion, the reaction was diluted with CH_2Cl_2 (25 mL) and consecutively washed with water, sat. aq. $NaHCO_3$ and brine (15 mL each). The organic phase was dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:10 to 70:30) afforded the *title compound* **3.30** as a white solid (1.47 g, 70%). **Formula** $C_{15}H_{20}O_7S$; **Mw** 344.38; $\mathbf{R_f}$ 0.20 (petroleum ether/acetone 70:30); **Mp** 85 °C; $\mathbf{[\alpha]_D}$ –31.4 (*c* 1.31, $CHCl_3$, 26 °C); **IR** (film) 2937 (w), 2904 (w), 1612 (m), 1514 (m), 1351 (s), 1247 (s), 1173 (vs), 1030 (s), 968 (s), 912 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.30 (2 H, d, *J* = 8.8 Hz, H-9), 6.89 (2 H, d, *J* = 8.7 Hz, H-10), 5.65 (1 H, d, *J* = 5.4 Hz, H-1), 5.25 (1 H, ddd, *J* = 7.1, 4.8, 4.0 Hz, H-3), 4.56 (1 H, d, *J* = 11.2 Hz, H-7), 4.51 (1 H, d, *J* = 11.2 Hz, H-7'), 4.35 (1 H, dd, *J* = 9.9, 4.0 Hz, H-2), 4.34 (1 H, td, *J* = 7.6, 6.3 Hz, H-5), 4.05 (1 H, dd, *J* = 8.4, 7.7 Hz, H-6), 4.00 (1 H, dd, *J* = 9.9, 4.8 Hz, H-2'), 3.95 (1 H, dd, *J* = 8.5, 6.4 Hz, H-6'), 3.82 (3 H, s, H-12), 2.98 (1 H, td, *J* = 7.3, 5.4 Hz, H-4), 2.90 (3 H, s, H-13) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 129.7 (2 × CH_{ar}, C-9), 129.4 (C_{ar}, C-8), 113.9 (2 × CH_{ar}, C-10), 108.0 (CH, C-1), 78.3 (CH, C-5), 77.9 (CH, C-3), 73.5 (CH_2, C-2), 73.0 (CH_2, C-7), 71.7 (CH_2, C-6), 55.3 (CH_3, C-12), 47.7 (CH, C-4), 38.2 (CH_3, C-13) ppm; **LRMS** (ESI^+) *m*/*z* 367.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{15}H_{20}O_7SNa$ $(M + Na)^+$ calcd 367.0822, found 367.0823.

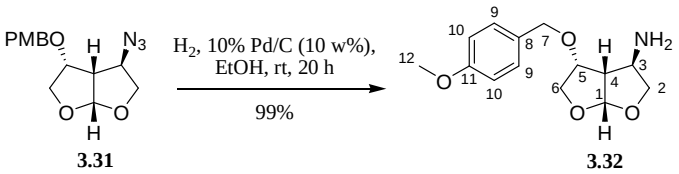
(1*R*,4*R*,5*S*,6*R*)-4-Azido-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.31)



Method A: To a solution of mesylate **3.30** (605 mg, 1.75 mmol) in THF (7 mL) was added trimethylsilyl azide (347 µL, 2.6 mmol) and TBAF (2.6 mL, 2.6 mmol, 1 M in THF).[97] The resulting mixture was heated to 70 °C and stirred for 20 h. After completion the solvent was removed under reduced pressure and the crude product was directly applied to column chromatography (petroleum ether/EtOAc 80:20 to 60:40) afforded the *title compound* **3.31** as a colourless oil (398 mg, 78%).

Method B: To a solution of mesylate **3.30** (1.51 g, 4.4 mmol) in DMF (35 mL) was added sodium azide (860 mg, 13.2 mmol). The resulting mixture was heated to 85 °C and stirred for 62 h. After completion the majority of DMF was removed under reduced pressure and the remaining crude was partitioned between Et_2O and H_2O (25 mL each). The aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15 to 65:35) afforded the *title compound* **3.31** as a colourless oil (1.06 mg, 83%). **Formula** $C_{14}H_{17}O_4N_3$; **Mw** 291.30; $\mathbf{R_f}$ 0.28 (petroleum ether/acetone 85:15); $\mathbf{[\alpha]_D}$ +46.5 (*c* 1.44, $CHCl_3$, 24 °C); **IR** (film) 2954 (w), 2881 (w), 2094 (s), 1612 (m), 1513 (s), 1246 (vs), 1107 (s), 1025 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2 H, d, *J* = 8.7 Hz, H-9), 6.91 (2 H, d, *J* = 8.7 Hz, H-10), 5.79 (1 H, d, *J* = 5.1 Hz, H-1), 4.53 (1 H, d, *J* = 11.3 Hz, H-7), 4.49 (1 H, d, *J* = 11.3 Hz, H-7'), 4.36 (1 H, dt, *J* = 4.4, 1.6 Hz, H-3), 4.25 (1 H, ddd, *J* = 8.8, 7.9, 6.7 Hz, H-5), 4.09 (1 H, dd, *J* = 10.2, 4.5 Hz, H-2), 4.00 (1 H, m, H-2'), 3.97 (1 H, dd, *J* = 9.3, 6.7 Hz, H-6), 3.83 (3 H, s, H-12), 3.62 (1 H, dd, *J* = 9.3, 7.8 Hz, H-6'), 2.93 (1 H, ddt, *J* = 8.8, 5.1, 1.3 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.6 (C_{ar}, C-11), 129.4 (CH_{ar}, C-9), 129.2 (C_{ar}, C-8), 114.0 (CH_{ar}, C-10), 108.6 (CH, C-1), 76.4 (CH, C-5), 74.0 (CH_2, C-2), 72.5 (CH_2, C-7), 70.9 (CH_2, C-6), 61.3 (CH, C-3), 55.3 (CH_3, C-12), 51.9 (CH, C-4) ppm; **LRMS** (ESI^+) *m/z* 314.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{14}H_{17}O_4N_3Na$ $(M + Na)^+$ calcd 314.1111, found 314.1108.

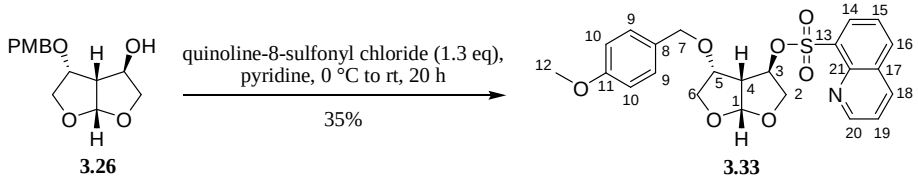
(1*R*,4*R*,5*S*,6*R*)-4-Amino-6-(4-methoxybenzyloxy-2,8-dioxabicyclo[3.3.0]-octane (3.32)



3.31 **3.32**

To a solution of azide **3.31** (393 mg, 1.35 mmol) in dry EtOH (7 mL) under N_2 was added Pd/C (40 mg, 10 w%, 10% Pd). The flask was then put under H_2-atmosphere and the reaction was stirred at rt for 20 h. After completion the reaction mixture was filtered over celite and the filtercake was washed with EtOH. The solvent was removed in vacuo to afford the *title compound* **3.32** as a colourless oil (355 mg, 99%). **Formula** $C_{14}H_{19}NO_4$; **Mw** 265.31; $\mathbf{R_f}$ 0.15 (CH_2Cl_2/MeOH 90:10); $\mathbf{[\alpha]_D}$ +3.6 (c 0.79, CH_2Cl_2, 23 °C); **IR** (film) 3330 (br. w), 2954 (br. m), 2877 (m), 1612 (m), 1514 (vs), 1247 (vs), 1111 (s), 1030 (vs) 820 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2 H, d, *J* = 8.7 Hz, H-9), 6.90 (2 H, d, *J* = 8.7 Hz, H-10), 5.78 (1 H, d, *J* = 5.1 Hz, H-1), 4.54 (1 H, d, *J* = 11.4 Hz, H-7), 4.50 (1 H, d, *J* = 11.4 Hz, H-7'), 4.21 (1 H, td, *J* = 8.4, 6.9 Hz, H-5), 4.07 (1 H, dd, *J* = 9.2, 4.7 Hz, H-2), 3.96 (1 H, dd, *J* = 9.0, 6.8 Hz, H-6), 3.86 (1 H, dt, *J* = 4.4, 1.9 Hz, H-3), 3.82 (3 H, s, H-12), 3.69 (1 H, dd, *J* = 9.1, 2.1 Hz, H-2'), 3.61 (1 H, dd, *J* = 9.0, 8.7 Hz, H-6'), 2.63 (1 H, ddt, *J* = 8.4, 5.1, 1.5 Hz, H-4), 1.41 (2 H, br. s, NH_2) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 129.8 (C_{ar}, C-8), 129.3 (2 × CH_{ar}, C-9), 114.0 (2 × CH_{ar}, C-10), 108.9 (CH, C-1), 77.8 (CH_2, C-2), 77.2 (CH, C-5), 72.4 (CH_2, C-7), 70.8 (CH_2, C-6), 55.3 (CH_3, C-12), 55.2 (CH, C-4), 52.1 (CH, C-3) ppm; **LRMS** (ESI^+) *m*/*z* 266.2 $(M + H)^+$, 288.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{14}H_{20}NO_4$ $(M + H)^+$ calcd 266.1387, found 266.1387.

Quinoline-8-sulfonic acid (1*S*,4*R*,5*R*,6*R*)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo-[3.3.0]-octane-4-yl ester (3.33)

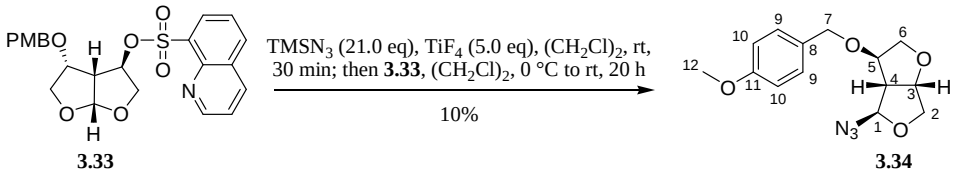


3.26 **3.33**

To a solution of alcohol **3.26** (515 mg, 1.93 mmol) in dry pyridine (10 mL) at 0 °C was slowly added quinoline-8-sulfonyl chloride (572 mg, 2.51 mmol). The resulting mixture was allowed to warm to rt and stirred at this temperature for 20 h. The reaction was quenched by the addition of aq HCl (15 mL, 0.5 M) and the mixture was extracted with

EtOAc (3 × 20 mL). The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (CH_2Cl_2/MeOH 99:1 to 97:3) and HPLC (hexane/acetone 72:28) afforded the *title compound* **3.33** as a colourless oil (310 mg, 35%). **Formula** $C_{23}H_{23}NO_7S$; **Mw** 457.50; $\mathbf{R_f}$ 0.20 (hexane/acetone 70:30); $\mathbf{[\alpha]_D}$ +14.9 (*c* 1.89, $CHCl_3$, 23 °C); **IR** (film) 2945 (w), 2879 (w), 1612 (m), 1514 (m), 1354 (m), 1248 (m), 1173 (s), 1109 (m), 1029 (s), 909 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 9.04 (1 H, dd, *J* = 4.3, 1.9 Hz, H-20), 8.52 (1 H, dd, *J* = 7.4, 1.4 Hz, H-14), 8.27 (1 H, dd, *J* = 8.3, 1.8 Hz, H-18), 8.12 (1 H, dd, *J* = 8.2, 1.5 Hz, H-16), 7.64 (1 H, dd, *J* = 8.3, 7.4 Hz, H-15), 7.56 (1 H, dd, *J* = 8.3, 4.3 Hz, H-19), 7.25 (2 H, d, *J* = 8.8 Hz, H-9), 6.88 (2 H, d, *J* = 8.8 Hz, H-10), 5.97 (1 H, d, *J* = 3.3 Hz, H-3), 5.85 (1 H, d, *J* = 5.1 Hz, H-1), 4.60 (1 H, d, *J* = 11.2 Hz, H-7)´, 4.39 (1 H, d, *J* = 11.2 Hz, H-7'), 4.23 (1 H, ddd, *J* = 9.2, 7.8, 6.8 Hz, H-5), 4.11 (1 H, dd, *J* = 10.9, 1.1 Hz, H-2), 4.04 (1 H, dd, *J* = 11.2, 3.4 Hz, H-2'), 3.95 (1 H, dd, *J* = 9.5, 6.7 Hz, H-6), 3.82 (3 H, s, H-12), 3.59 (1 H, dd, *J* = 9.5, 7.7 Hz, H-6'), 3.34 (1 H, ddd, *J* = 9.2, 5.2, 1.3 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 151.8 (CH_{ar}, C-20), 143.8 (C_{ar}, C-21), 136.5 (CH_{ar}, C-18), 134.8 (CH_{ar}, C-16), 134.2 (C_{ar}, C-13), 133.1 (CH_{ar}, C-14), 129.5 (2 × CH_{ar}, C-9), 129.3 (C_{ar}, C-8 or C-17), 129.0 (C_{ar}, C-17 or C-8), 113.9 (2 × CH_{ar}, C-10), 109.0 (CH, C-1), 83.4 (CH, C-3), 76.1 (CH, C-5), 75.1 (CH_2, C-2), 72.2 (CH_2, C-7), 71.0 (CH_2, C-6), 55.3 (CH_3, C-12), 52.2 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 480.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{23}H_{23}NO_7SNa$ $(M + Na)^+$ calcd. 480.1087, found 480.1088.

(3*R*,3a*R*,4*R*,6a*S*)- 4-Azido-3-(4-methoxybenzyloxy)-hexahydrofuro[3,4-b]furan (3.34)

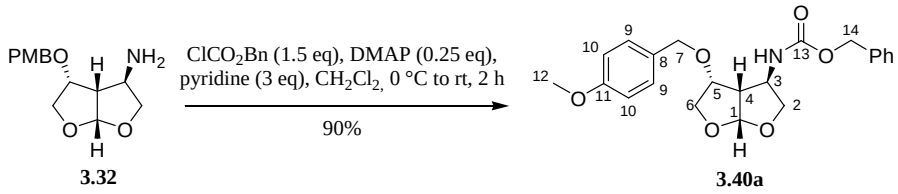


3.33 **3.34**

To a solution of TiF_4 (272 mg, 2.20 mmol) in dichloroethane (10 mL) at rt was added $TMSN_3$ (1.29 mL, 9.18 mmol) and stirred for 30 min. Then the mixture was cooled to 0 °C and a solution of quisylate **2.33** (200 mg, 0.44 mmol) in dichloroethane (2 mL) was added dropwise. The reaction was allowed to warm to rt and stirred for further 20 h. It was then quenched by the addition of H_2O (15 mL) and the mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column

chromatography (petroleum ether/acetone 90:10 to 60:40) afforded the *title compound* **2.34** as a colourless oil (13 mg, 10%) and unreacted starting material **2.33** (113 mg, 56%). **Formula** $C_{14}H_{17}N_3O_4$; **Mw** 291.30; $\mathbf{R_f}$ 0.23 (hexane/acetone 92:8); $\mathbf{[\alpha]_D}$ −113.5 (*c* 0.54, $CHCl_3$, 23 °C); **IR** (film) 2930 (w), 2875 (w), 2103 (vs), 1613 (w), 1514 (m), 1248 (s), 1080 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ .26 (2 H, d, *J* = 8.7 Hz, H-9), 6.91 (2 H, d, *J* = 8.8 Hz, H-10), 5.36 (1 H, d, *J* = 1.4 Hz, H-1), 4.82 (1 H, dd, *J* = 6.7, 3.8 Hz, H-3), 4.48 (2 H, s, AB-system, H-7 and H-7'), 4.09 (1 H, d, *J* = 10.5 Hz, H-2), 4.01 (1 H, td, *J* = 4.1, 2.5 Hz, H-5), 3.99 (1 H, dd, *J* = 10.5, 3.6 Hz, H-2'), 3.86 (1 H, dd, *J* = 9.7, 4.4 Hz, H-6), 3.82 (3 H, s, H-12), 3.81 (1 H, dd, *J* = 9.7, 3.8 Hz, H-6'), 2.75 (1 H, dtd, *J* = 6.6, 1.5, 0.6 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 129.4 (2 × CH_{ar}, C-9), 129.3 (C_{ar}, C-8), 114.0 (2 × CH_{ar}, C-10), 95.9 (CH, C-1), 82.3 (2 × CH, C-3 and C-5), 74.2 (CH_2, C-2), 72.4 (CH_2, C-6), 71.3 (CH_2, C-7), 56.9 (CH, C-4), 55.3 (CH_3, C-12) ppm; **LRMS** (ESI^+) *m*/*z* 314.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{14}H_{17}N_3O_4Na$ $(M + Na)^+$ calcd. 314.1111, found 314.1115.

N-(1*R*,4*R*,5*S*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl carbamic acid benzylester (3.40a)

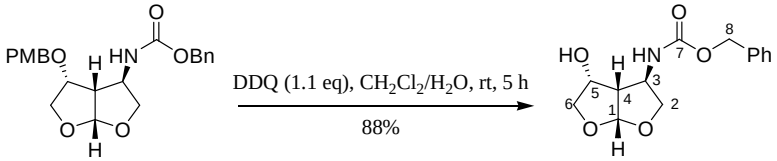


3.32 **3.40a**

To a solution of amine **3.32** (172 mg, 0.65 mmol), DMAP (20 mg, 0.16 mmol) and pyridine (158 µL, 1.95 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise benzyl chloroformate (138 µL, 0.98 mmol) and the resulting mixture was stirred at rt for 2 h. After completion, the reaction mixture was diluted with CH_2Cl_2 and sat. aq. $NaHCO_3$ (10 mL each). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with 2M HCl and brine (5 mL each), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 75:25) afforded the *title compound* **3.40a** as a colourless oil (232 mg, 90%). **Formula** $C_{22}H_{25}NO_6$; **Mw** 399.44; $\mathbf{R_f}$ 0.25 (petroleum ether/acetone 80:20); $\mathbf{[\alpha]_D}$ +30.5 (*c* 0.51, $CHCl_3$, 22 °C); **IR** (film) 3323 (br. w), 2953 (w), 2886 (w), 1715 (s), 1612 (m), 1514 (s), 1246 (vs), 1084 (m), 1027 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.29 (7 H, m, Ar-H

and H-9), 6.90 (2 H, d, *J* = 8.3 Hz, H-10), 5.76 (1 H, d, *J* = 5.1 Hz, H-1), 5.22–5.04 (3 H, m, H-14 and NH), 4.72 (1 H, d, *J* = 11.0 Hz, H-7), 4.63 (1 H, m, *J* = 7.5, 4.5 Hz can be observed, H-3), 4.49 (1 H, d, *J* = 11.2 Hz, H-7'), 4.24 (1 H, dt, *J* = 8.0, 7.8 Hz, H-5), 4.06 (1 H, dd, *J* = 9.8, 4.4 Hz, H-2), 3.97 (1 H, dd, *J* = 9.3, 6.9 Hz, H-6), 3.86 (1 H, m, *J* = 10.5 Hz can be observed, H-2'), 3.81 (3 H, s, H-12), 3.58 (1 H, t, *J* = 8.7 Hz, H-6'), 2.83 (1 H, m, *J* = 8.1, 5.6 Hz can be observed, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 155.6 (C, C-13), 136.2 (C_{ar}), 129.6 (2 ×CH_{ar}), 129.5 (C_{ar}), 128.6 (2 × CH_{ar}), 128.3 (CH_{ar}), 128.1 (2 ×CH_{ar}), 114.0 (2 × CH_{ar}, C-10), 108.7 (CH, C-1), 76.6 (CH, C-5), 75.1 (CH_2, C-2), 72.3 (CH_2, C-7), 71.4 (CH_2, C-6), 66.9 (CH_2, C-14), 55.3 (CH_3, C-12), 52.90 (CH, C-4), 52.88 (CH, C-3) ppm; **LRMS** (ESI^+) *m*/*z* 422.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{22}H_{25}NO_6Na$ $(M + Na)^+$ calcd 422.1571, found 422.1570.

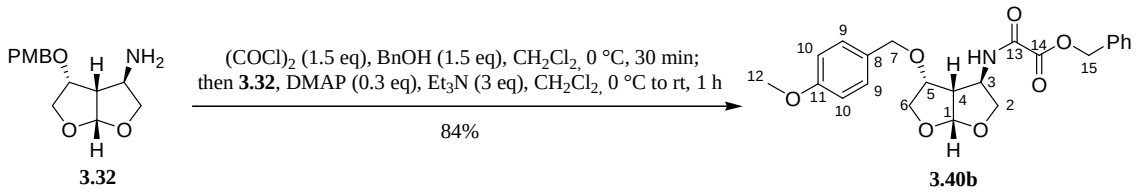
N-(1*R*,4*R*,5*S*,6*R*)-6-Hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl carbamic acid benzylester (3.41a)



3.40a **3.41a**

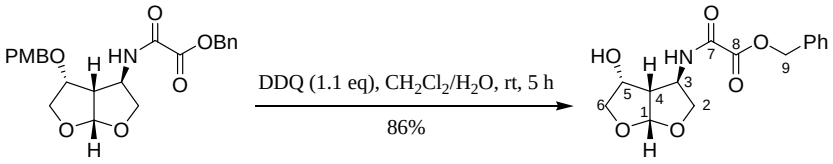
Following General Procedure **C** (8.2.1), deprotection of ether **3.40a** (195 mg, 0.49 mmol) with DDQ (140 mg, 0.61 mmol) afforded after purification of by column chromatography (petroleum ether/acetone 75:25 to 65:35) the *title compound* **3.41a** as a colourless oil (123 mg, 88%). **Formula** $C_{14}H_{17}NO_5$; **Mw** 279.29; $\mathbf{R_f}$ 0.25 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +16.7 (*c* 0.62, $CHCl_3$, 22 °C); **IR** (film) 3960 (br. m) 3312 (br. m), 1690 (vs), 1534 (s), 1256 (s), 1104 (br. s), 1008 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42–7.30 (5 H, m, Ar-H), 5.75 (1 H, d, *J* = 5.3 Hz, H-1), 5.16 (1 H, d, *J* = 6.5 Hz, NH), 5.13 (1 H, d, *J* = 12.3 Hz, H-8), 5.09 (1 H, d, *J* = 12.3 Hz, H-8'), 4.60–4.51 (2 H, m, H-3 and H-5), 4.18 (1 H, dd, *J* = 9.8, 5.7 Hz, H-2), 4.05 (1 H, dd, *J* = 9.2, 6.8 Hz, H-6), 3.77 (1 H, dd, *J* = 9.9, 2.8 Hz, H-2'), 3.66–3.60 (2 H, m, H-6' and OH), 2.83 (1H, ddd, *J* = 7.8, 5.5, 1.9 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 156.3 (C, C-7), 136.0 (C_{ar}), 128.6 (2 × CH_{ar}), 128.4 (CH_{ar}), 128.1 (2 ×CH_{ar}), 109.1 (CH, C-1), 73.6 (CH_2, C-2), 72.9 (CH_2, C-6), 70.0 (CH, C-5), 67.2 (CH_2, C-8), 55.3 (CH, C-4), 51.5 (CH, C-3) ppm; **LRMS** (ESI^+) *m*/*z* 302.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{14}H_{17}NO_5Na$ $(M + Na)^+$ calcd 302.0999, found 302.1002.

_N_-(1_R_,4_R_,5_S_,6_R_)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl oxalamic acid benzylester (3.40b)



To a solution of oxalylchloride (170 µL, 1.98 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise benzyl alcohol (206 µL, 1.98 mmol) and the resulting mixture was stirred at this temperature for 30 min. After completion all volatiles were removed in vacuo and the crude product was redissolved in CH_2Cl_2 (4 mL). This solution was then added dropwise to a solution of amine **3.32** (350 mg, 1.32 mmol), DMAP (49 mg, 0.40 mmol) and Et_3N (550 µL, 3.96 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 5 min the cooling was removed and the resulting mixture was stirred at rt for 1 h. After completion, the reaction was diluted with CH_2Cl_2 (15 mL) and sat. aq. $NaHCO_3$ (5 mL). The phases were separated and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:20 to 70:30) afforded the *title compound* **3.40b** as a colourless oil (473.3 mg, 84%). **Formula** $C_{23}H_{25}NO_7$; **Mw** 427.45; $\mathbf{R_f}$ 0.20 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +29.5 (*c* 0.83, $CHCl_3$, 27 °C); **IR** (film) 3297 (br. w) 2950 (w), 2886 (w), 1735 (m), 1693 (s), 1612 (m), 1514 (s), 1351 (s), 1250 (s), 1197 (s), 1031 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47–7.35 (6 H, m, Ar-H and NH), 7.33 (2 H, d, *J* = 8.7 Hz, H-9), 6.88 (2 H, d, *J* = 8.7 Hz, H-10), 5.80 (1 H, d, *J* = 5.1 Hz, H-1), 5.35 (1 H, d, *J* = 12.5 Hz, H-15, part of AB-system), 5.31 (1 H, d, *J* = 12.5 Hz, H-15', part of AB-system), 4.83 (1 H, m, *J* = 8.3, 4.1 Hz can be observed, H-3), 4.74 (1 H, d, *J* = 11.0 Hz, H-7), 4.51 (1 H, d, *J* = 11.0 Hz, H-7'), 4.26 (1 H, td, *J* = 8.5, 7.1 Hz, H-5), 4.08 (1 H, dd, *J* = 10.2, 4.3 Hz, H-2), 4.00 (1 H, dd, *J* = 9.4, 7.0 Hz, H-6), 3.91 (1 H, m, *J* = 10.3 Hz can be observed, H-2'), 3.80 (3 H, s, H-12), 3.65 (1 H, dd, *J* = 9.3, 8.1 Hz, H-6'), 2.86 (1 H, m, *J* = 8.8, 5.3 Hz can be observed, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 160.2 (C, C-14), 159.5 (C_{ar}, C-11), 155.9 (C, C-13), 134.2 (C_{ar}), 129.8 (2 × CH_{ar}, C-9), 129.4 (C_{ar}, C-8), 129.0 (3 × CH_{ar}), 128.7 (2 × CH_{ar}), 113.9 (2 × CH_{ar}, C-10), 108.7 (CH, C-1), 76.5 (CH, C-5), 74.3 (CH_2, C-2), 72.5 (CH_2, C-7), 71.5 (CH_2, C-6), 68.9 (CH_2, C-15), 55.3 (CH_3, C-12), 52.4 (CH, C-4), 51.9 (CH, C-3) ppm; **LRMS** (ESI^+) *m*/*z* 450.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{15}H_{17}NO_6Na$ $(M + Na)^+$ calcd 450.1523, found 450.1519.

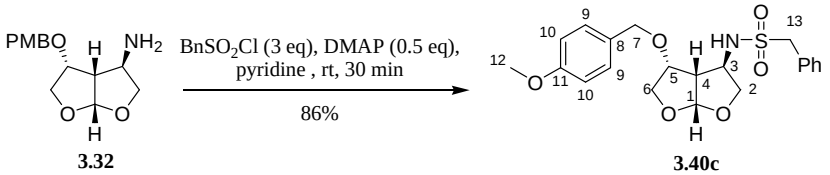
_N_-(1_R_,4_R_,5_S_,6_R_)-6-Hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl oxalamic acid benzylester (3.41b)



3.40b **3.41b**

Following General Procedure **C** (8.2.1), deprotection of ether **3.40b** (714 mg, 1.67 mmol) with DDQ (417 mg, 1.84 mmol) afforded after purification of by column chromatography (petroleum ether/acetone 80:20 to 60:40) the *title compound* **3.41b** as a colourless oil (446 mg, 86%). **Formula** $C_{15}H_{17}NO_6$; **Mw** 307.30; $\mathbf{R_f}$ 0.18 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +15.4 (*c* 0.95, $CHCl_3$, 24 °C); **IR** (film) 3351 (br. m) 2924 (br. m), 2359 (m), 2341 (m), 1737 (m), 1682 (vs), 1533 (m), 1266 (m), 1199 (s), 1007 (m), 948 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47–7.35 (6 H, m, Ar-H and NH, reduces to 5 H after D_2O-shake), 5.78 (1 H, d, *J* = 5.1 Hz, H-1), 5.33 (1 H, d, *J* = 12.0 Hz, H-9, part of AB-system), 5.30 (1 H, d, *J* = 12.0 Hz, H-9', part of AB-system), 4.78 (1 H, ddt, *J* = 7.4, 5.1, 2.4 Hz, H-3, simplifies to dt after D_2O-shake, *J* = 5.3, 2.2 Hz), 4.58 (1 H, qd, *J* = 7.6, 3.3 Hz, H-5, simplifies to dt after D_2O-shake, *J* = 8.0, 7.5 Hz), 4.23 (1 H, dd, *J* = 10.2, 5.6 Hz, H-2), 4.06 (1 H, dd, *J* = 9.3, 6.7 Hz, H-6), 3.89 (1 H,dd, *J* = 10.0, 2.6 Hz, H-2'), 3.65 (1 H, dd, *J* = 9.1, 7.8 Hz, H-6'), 3.19 (1 H, d, *J* = 3.4 Hz, OH, disappears after D_2O shake), 2.86 (1 H, ddd, *J* = 7.9, 5.1, 2.2 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.9 (C, C-8) 156.5 (C, C-7), 134.0 (C_{ar}), 129.04 (CH_{ar}), 128.95 (2 × CH_{ar}), 128.8 (2 × CH_{ar}), 109.0 (CH, C-1), 70.0 (CH, C-5), 73.06 (CH_2, C-2 or C-6), 73.04 (CH_2, C-6 or C-2), 69.0 (CH_2, C-9), 54.9 (CH, C-4), 50.8 (CH, C-3) ppm; **LRMS** (ESI^+) *m/z* 254.1 $(M + Na\text{-}OBn\text{+}OMe)^+$, 286.1 $(M + Na\text{-}CO_2)^+$, 330.1 $(M + Na)^+$.

_N_-(1_R_,4_R_,5_S_,6_R_)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl benzylsulfonamide (3.40c)

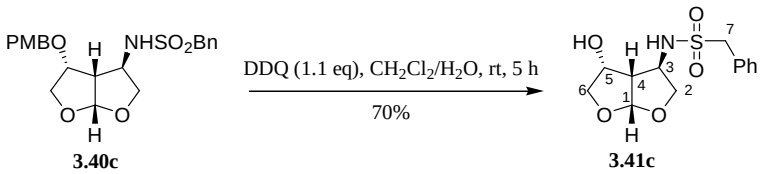


3.32 **3.40c**

A solution of amine **3.32** (112 mg, 0.42 mmol) and DMAP (26 mg, 0.21 mmol) in pyridine (3 ml) was added phenylmethanesulfonyl chloride (240 mg, 1.26 mmol) and the

resulting mixture was stirred at rt for 30 min. After completion the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/ acetone 80:20 to 70:30) afforded the *title compound* **3.40c** as a colourless oil (152 mg, 86%). **Formula** $C_{21}H_{25}NO_6S$; **Mw** 419.49; $\mathbf{R_f}$ 0.38 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +3.4 (*c* 0.67, $CHCl_3$, 26 °C); **IR** (film) 3265 (br. w), 2935 (br. w), 1612 (m), 1514 (s), 1320 (m), 1249 (s), 1154 (m), 1126 (vs), 1029 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.33 (5 H, m, Ar-H), 7.26 (2 H, d, *J* = 8.8 Hz, H-9), 6.90 (2 H, d, *J* = 8.8 Hz, H-10), 5.69 (1 H, d, *J* = 5.3 Hz, H-1), 4.55 (1 H, d, *J* = 8.8 Hz, NH), 4.54 (1 H, d, *J* = 11.3 Hz, H-7), 4.43 (1 H, d, *J* = 11.3 Hz, H-7'), 4.27 (1 H, d, *J* = 14.3 Hz, H-13, part of AB system), 4.25 (1 H, d, *J* = 14.3 Hz, H-13', part of AB system), 4.16 (1 H, ddd, *J* = 8.9, 7.7, 6.7 Hz, H-5), 4.12 (1 H, ddt, *J* = 8.8, 4.5, 1.4 Hz, H-3), 3.92 (1 H, dd, *J* = 9.3, 6.8 Hz, H-6), 3.91 (1 H, dd, *J* = 10.0, 4.3 Hz, H-2), 3.82 (3 H, s, H-12), 3.74 (1 H, dt, *J* = 9.9, 1.2 Hz, H-2'), 3.58 (1 H, dd, *J* = 9.4, 7.7 Hz, H-6'), 2.83 (1 H, ddt, *J* = 8.9, 5.1, 1.3 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 130.7 (2 × CH_{ar}), 129.5 (2 × CH_{ar}, C-9), 129.4 (C_{ar}), 129.1 (C_{ar}), 128.9 (CH_{ar}), 128.8 (2 × CH_{ar}), 114.0 (2 × CH_{ar}, C-10), 108.3 (CH, C-1), 76.3 (CH, C-5), 75.2 (CH_2, C-2), 72.3 (CH_2, C-7), 71.3 (CH_2, C-6), 59.8 (CH_2, C-13), 55.5 (CH, C-3), 55.3 (CH_3, C-12), 53.9 (CH, C-4) ppm. **LRMS** (ESI^+) *m*/*z* 442.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{21}H_{25}NO_6SNa$ $(M + Na)^+$ calcd. 442.1295, found 442.1295.

***N*-(1*R*,4*R*,5*S*,6*R*)-6-Hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl benzylsulfonamide (3.41c)**

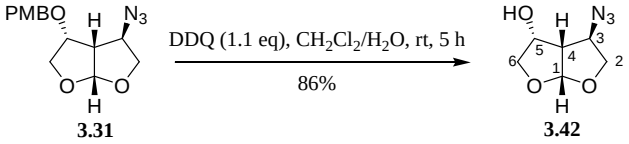


3.40c **3.41c**

Following General Procedure **C** (8.2.1), deprotection of ether **3.40c** (55 mg, 0.13 mmol) with DDQ (33 mg, 0.14 mmol) afforded after purification of by column chromatography (petroleum ether/acetone 80:20 to 60:40) the *title compound* **3.41c** as a yellow solid (27 mg, 70%) and recovered starting material (11 mg, 20%). **Formula** $C_{13}H_{17}NO_5S$; **Mw** 299.34; $\mathbf{R_f}$ 0.19 (petroleum ether/acetone 70:30); **Mp** 153−155 °C; $\mathbf{[\alpha]_D}$ +50.2 (*c* 1.32, MeOH, 27 °C); **IR** (film) 3482 (br. m), 3251 (br. m), 2926 (br. m), 1316 (m), 1153 (m), 1123 (s), 1001 (s), 940 (m) cm^{-1}; **^{1}H NMR** (400 MHz, MeOD-d_4) δ 7.51–7.37 (5 H, m, Ar-H), 5.70 (1 H, d, *J* = 5.3 Hz, H-1), 4.46 (1 H, dt, *J* = 8.7, 6.7 Hz, H-5), 4.42 (1 H, d, *J* = 13.7 Hz, H-7), 4.38 (1 H, d, *J* = 13.8 Hz, H-7'), 4.27 (1 H, dt, *J* = 4.8, 1.8 Hz, H-3), 3.99 (1 H, dd, *J* = 9.5, 4.9 Hz, H-2), 3.94 (1 H, dd, *J* = 9.2, 6.3 Hz, H-6), 3.81 (1 H, ddd, *J* = 9.4, 1.7, 1.0 Hz, H-2'),

3.55 (1 H, dd, *J* = 9.2, 6.9 Hz, H-6'), 2.77 (1 H, ddt, *J* = 8.8, 5.3, 1.6 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, MeOD-d_4) δ 132.2 (2 × CH_{ar}), 131.5 (C_{ar}), 129.7 (2 × CH_{ar}), 129.6 (CH_{ar}), 110.4 (CH, C-1), 77.1 (CH_2, C-2), 74.3 (CH_2, C-6), 70.4 (CH, C-5), 59.8 (CH_2, C-13), 55.63 (CH, C-4), 55.58 (CH, C-3) ppm; **LRMS** (ESI^+) *m*/*z* 322.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{13}H_{17}NO_5SNa$ $(M + Na)^+$ calcd. 322.0720, found 322.0715.

(1*R*,4*R*,5*S*,6*R*)-4-Azido-2,8-dioxa-bicyclo[3.3.0]-octan-6-ol (3.42)

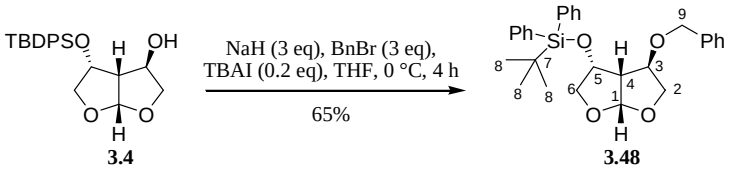


3.31 **3.42**

Following General Procedure **C** (8.2.1), deprotection of ether **3.31** (395 mg, 1.36 mmol) with DDQ (355 mg, 1.56 mmol) afforded after purification of by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **3.42** as a colourless oil (197 mg, 86%). **Formula** $C_6H_9N_3O_3$; **Mw** 171.15; $\mathbf{R}_f$ 0.24 (petroleum ether/acetone 75:25); $\mathbf{[\alpha]_D}$ +106.7 (*c* 0.77, $CHCl_3$, 29 °C); **IR** (film) 3425 (br. m), 2955 (w), 2886 (w), 2095 (vs), 1252 (m), 1112 (s), 1017 (s), 926 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81 (1 H, d, *J* = 5.3 Hz, H-1), 4.65–4.55 (1 H, m, simplifies after D_2O-shake to dt, *J* = 8.7, 6.5 Hz, H-5), 4.43 (1 H, dt, *J* = 4.4, 1.6 Hz, H-3), 4.12 (1 H, dd, *J* = 10.0, 4.4 Hz, H-2), 4.03 (1 H, dd, *J* = 9.4, 6.3 Hz, H-6), 4.02 (1 H, ddd, *J* = 10.0, 1.9, 1.1 Hz, H-2'), 3.65 (1 H, dd, *J* = 9.5, 6.8 Hz, H-6'), 2.90 (1 H, ddt, *J* = 8.7, 5.3, 1.3 Hz, H-4), 2.08 (1 H, d, *J* = 3.0 Hz, OH, exchanges in D_2O-shake) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 108.9 (CH, C-1), 74.1 (CH_2, C-2), 73.2 (CH_2, C-6), 69.8 (CH, C-5), 61.0 (CH, C-3), 53.3 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 171.1 $(M + H)^+$, 194.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_6H_9N_3O_3Na$ $(M + Na)^+$ calcd 194.0536, found 194.0537.

8.2.2.2 Synthesis of *exo*-oxy analogues

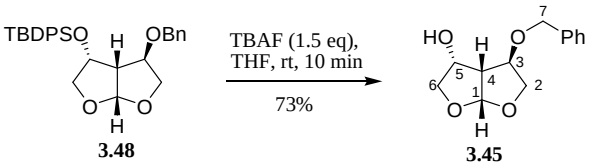
(1*R*,4*R*,5*S*,6*R*)-4-Benzyloxy-6-(*tert*-butyldiphenylsilanoxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.48)



3.4 **3.48**

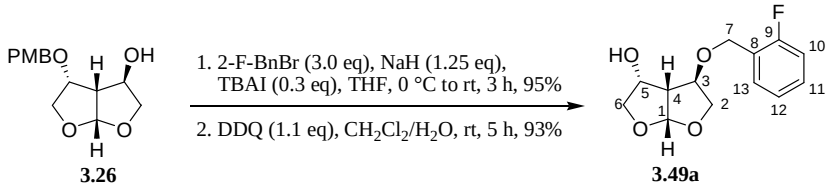
To a stirred suspension of NaH (268 mg, 7.0 mmol, 60% in mineral oil) in THF (3 mL) at 0 °C was added a solution of alcohol **3.4** (900 mg. 2.34 mmol) in THF (9 mL). After 10 min benzyl bromide (0.84 mL, 7.0 mmol) and TBAI (177 mg, 0.47 mmol) were added and the reaction was stirred at 0 °C for 4 h. After completion, the reaction was quenched by dropwise addition of H_2O (2 mL) and the solvent was removed in vacuo. Purification of the crude product by column chromatography (hexane/EtOAc 95:5) afforded the *title compound* **3.48** as colourless oil (725 mg, 65%). **Formula** $C_{29}H_{34}O_4Si$; **Mw** 474.66; $\mathbf{R_f}$ 0.62 (hexane/EtOAc 70:30); $\mathbf{[\alpha]_D}$ −10.6 (*c* 0.7, $CHCl_3$, 25 °C); **IR** (film) 2930 (m), 2857 (m), 1471 (m), 1427 (m), 1362 (w), 1342 (w), 1261 (w), 1231 (w), 1111 (s), 1021 (s), 699 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67−7.58 (5 H, m, Ar-H), 7.51−7.28 (10 H, m, Ar-H), 5.73 (1 H, d, *J* = 5.1 Hz, H-1), 4.64 (1 H, d, *J* = 3.8 Hz, H-3), 4.49 (1 H, d, *J* = 11.8 Hz, H-9), 4.47 (1 H, ddd, *J* = 9.3, 8.3, 6.9 Hz, H-5), 4.42 (1 H, d, *J* = 11.8 Hz, H-9'), 4.20 (1 H, dt, *J* = 10.2, 1.1 Hz, H-2), 4.07 (1 H, dd, *J* = 10.1, 3.8 Hz, H-2'), 3.64 (1 H, dd, *J* = 8.9, 6.9 Hz, H-6), 3.46 (1 H, t, *J* = 8.7 Hz, H-6'), 2.86 (1 H, ddt, *J* = 9.2, 5.1, 1.1 Hz, H-4), 1.06 (9 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 137.9 (C_{ar}), 135.60 (2 × CH_{ar}), 135.57 (2 × CH_{ar}), 133.1 (C_{ar}), 132.8 (C_{ar}), 130.15 (CH_{ar}), 130.09 (CH_{ar}), 138.4 (2 × CH_{ar}), 127.92 (2 × CH_{ar}), 127.86 (2 × CH_{ar}), 127.72 (CH_{ar}), 127.67 (2 × CH_{ar}), 108.8 (CH, C-1), 79.4 (CH, C-3), 74.3 (CH_2, C-2), 72.5 (CH_2, C-6), 71.2 (CH, C-5), 71.1 (CH_2, C-9), 53.2 (CH, C-5), 26.9 (3 CH_3, C-8), 19.1 (C, C-7) ppm; **LRMS** (ESI^+) *m*/*z* 497.3 $(M + Na)^+$.

(1*S*,4*R*,5*R*,6*R*)-4-Benzyloxy-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]octane (3.45)



To a stirred solution of silyl ether **3.48** (532 mg, 1.12 mmol) in THF (20 mL) at rt was added TBAF (1.68 mL, 1.68 mmol, 1 M in THF). After 10 min the solvent was removed in vacuo and the purification of the crude product by column chromatography (hexane/acetone 80:20) afforded the *title compound* **3.45** as a white solid (194 mg, 73%). **Formula** $C_{13}H_{16}O_4$; **Mw** 236.26; **Mp** 51−52 °C, $\mathbf{R_f}$ 0.58 (hexane/acetone 50:50); $\mathbf{[\alpha]_D}$ +74.0 (*c* 0.15, $CHCl_3$, 27 °C); **IR** (film) 3387 (br m), 2940 (m), 2867 (m), 1483 (m), 1456 (m), 1341 (w), 1301 (w), 1261 (w), 1100 (s), 1012 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ .34−7.28 (5 H, m, Ar-H), 5.83 (1 H, d, *J* = 5.1 Hz, H-1), 4.58−4.50 (3 H, m, H-5, H-7 and H-7'), 4.48 (1 H, d, *J* = 3.6 Hz, H-3), 4.13 (1 H, d, *J* = 10.2 Hz, H-2), 4.03 (1 H, dd, *J* = 10.1, 4.0 Hz, H-2'), 4.00 (1 H, d, *J* = 9.3, 6.1 Hz, H-6), 3.62 (1 H, dd, *J* = 9.2, 6.7 Hz, H-6'), 2.93 (1 H, dd, *J* = 8.4, 5.3 Hz, H-4), 1.79 (1 H, br. s, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 137.9 (C_{ar}), 128.5 (2 × CH_{ar}), 127.8 (CH_{ar}), 127.7 (2 × CH_{ar}), 109.2 (CH, C-1), 78.7 (CH, C-3), 74.3 (CH_2, C-2), 73.4 (CH_2, C-7), 71.2 (CH_2, C-6), 70.1 (CH, C-5), 53.6 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 254.1 $(M + NH_4)^+$, 259.1 $(M + Na)^+$, **HRMS** (ESI^+) for $C_{13}H_{16}O_4Na$ $(M + Na)^+$ calcd 259.0941, found 259.0943.

(1*S*,4*R*,5*R*,6*R*)-4-(2-Fluorobenzyloxy)-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.49a)

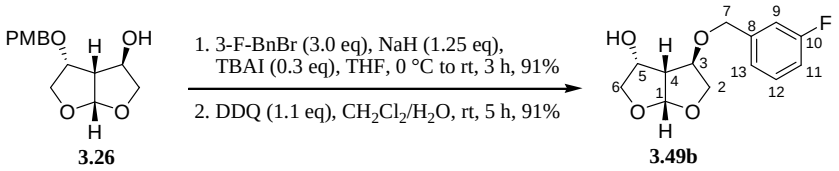


Following general procedure **B** (8.2.1), the reaction of alcohol **3.26** (398 mg, 1.49 mmol) and 2-fluorobenzyl bromide (540 µL, 4.47 mmol) afforded after purification by column chromatography (petroleum ether/acetone 90:10 to 80:20) the intermediate dibenzyl ether as a colourless oil (530 mg, 95%; $\mathbf{R_f}$ 0.53 (petroleum ether/acetone 75:25); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.42 (1 H, td, *J* = 7.5, 1.9 Hz), 7.29 (1 H, tdd, *J* = 7.9, 5.3, 1.9 Hz), 7.20 (2 H, d, *J* = 8.7 Hz), 7.14 (1 H, td, *J* = 7.5, 1.2 Hz), 7.05 (1 H, ddd, *J* = 9.9, 8.4,

1.3 Hz), 6.88 (2 H, d, *J* = 8.8 Hz), 5.83 (1 H, d, *J* = 5.3 Hz), 4.60 (1 H, d, *J* = 11.9 Hz), 4.57 (1 H, d, *J* = 11.9 Hz), 4.49 (1 H, d, *J* = 11.4 Hz), 4.48 (1 H, d, *J* = 3.0 Hz), 4.44 (1 H, d, *J* = 11.3 Hz), 4.24 (1 H, ddd, *J* = 8.9, 8.2, 6.7 Hz), 4.14 (1 H, dt, *J* = 10.3, 1.2 Hz), 4.01 (1 H, dd, *J* = 9.9, 3.6 Hz), 3.97 (1 H, dd, *J* = 9.1, 6.7 Hz), 3.82 (3 H, s), 3.59 (1 H, dd, *J* = 9.0, 8.3 Hz), 3.01 (1 H, ddt, *J* = 8.9, 5.2, 1.2 Hz) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ –119.2 (dt, *J* = 8.6, 6.4 Hz) ppm).

Subsequent treatment of this dibenzyl ether (525 mg, 1.40 mmol) with DDQ (350 mg, 1.54 mmol) according to general procedure **C** (8.2.1) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **3.49a** as a white solid (333 mg, 93%). **Formula** $C_{13}H_{15}FO_4$; **Mw** 254.25; **Mp** 55–56 °C; **R_f** 0.40 (petroleum ether/acetone 70:30); **$[\alpha]_D$** +49.9 (c 0.9, $CHCl_3$, 26 °C); **IR** (film) 3442 (br. m), 2941 (w), 2879 (w), 1619 (w), 1587 (w), 1492 (m), 1456 (m), 1230 (m), 1112 (vs), 1015 (vs), 932 (m), 759 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (1 H, td, *J* = 7.5, 1.9 Hz, H-13), 7.29 (1 H, dddd, *J* = 8.3, 7.5, 5.4, 1.9 Hz, H-11), 7.15 (1 H, td, *J* = 7.5, 1.2 Hz, H-12), 7.05 (1 H, ddd, *J* = 10.0, 8.4, 1.2 Hz, H-10), 5.83 (1 H, d, *J* = 5.3 Hz, H-1), 4.63–4.56 (2 H, m, H-7 and H-7'), 4.56 (1 H, dtd, *J* = 8.6, 6.5, 5.1 Hz, H-5), 4.50 (1 H, dt, *J* = 4.0, 1.2 Hz, H-3), 4.13 (1 H, dt, *J* = 10.2, 1.3 Hz, H-2), 4.04 (1 H, dd, *J* = 10.2, 4.0 Hz, H-2'), 4.01 (1 H, dd, *J* = 9.3, 6.1 Hz, H-6), 3.63 (1 H, dd, *J* = 9.4, 6.7 Hz, H-6') 2.94 (1 H, ddt, *J* = 8.6, 5.2, 1.1 Hz, H-4), 1.94 (1 H, d, *J* = 5.1 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 160.7 (CF_{ar}, d, *J* = 245.2 Hz, C-9), 130.1 (CH_{ar}, d, *J* = 4.1 Hz, C-13), 129.6 (CH_{ar}, d, *J* = 8.0 Hz, C-11), 124.9 (C_{ar}, d, *J* = 14.6 Hz, C-8), 124.2 (CH_{ar}, d, *J* = 3.4 Hz, C-12), 115.2 (CH_{ar}, d, *J* = 21.4 Hz, C-10), 109.2 (CH, C-1), 78.9 (CH, C-3), 74.3 (CH_2, C-2), 73.3 (CH_2, C-6), 70.1 (CH, C-5), 64.5 (CH_2, d, *J* = 3.6 Hz, C-7), 53.4 (CH, C-4) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ −119.3 (dt, *J* = 10.0, 6.4 Hz) ppm; **LRMS** (ESI^+) *m*/*z* 318.2 $(M + Na+MeCN)^+$; **HRMS** (ESI^+) for $C_{13}H_{15}FO_4Na$ $(M + Na)^+$ calcd 277.0847, found 277.0850.

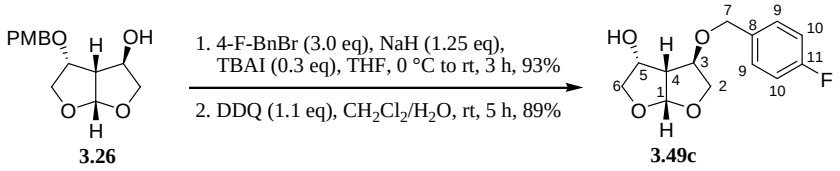
(1*S*,4*R*,5*R*,6*R*)-4-(3-Fluorobenzyloxy)-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.49b)



Following general procedure **B** (8.2.1), the reaction of alcohol **3.26** (352 mg, 1.32 mmol) and 3-fluorobenzyl bromide (488 µL, 4.00 mmol) afforded after purification by column chromatography (petroleum ether/acetone 90:10 to 70:30) the corresponding dibenzyl ether as a colourless oil (448 mg, 91%; $\mathbf{R_f}$ 0.51 (petroleum ether/acetone 75:25); **^{1}H NMR** (300 MHz, $CDCl_3$) δ = 7.30 (1 H, m), 7.18 (2 H, d, *J* = 8.8 Hz), 7.12−6.94 (3 H, m), 6.88 (2 H, d, *J* = 8.7 Hz), 5.84 (1 H, d, *J* = 5.2 Hz), 4.56−4.41 (5 H, m), 4.24 (1 H, td, *J* = 6.9, 8.5 Hz), 4.12 (1 H, d, *J* = 10.3 Hz), 4.02−3.94 (1 H, m), 3.82 (3 H, s), 3.58 (1 H, t, *J* = 8.6 Hz), 3.00 (1 H, dd, *J* = 4.9, 9.0 Hz) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −113.3 (td, *J* = 9.7, 5.4 Hz) ppm).

Subsequent treatment of this dibenzyl ether (445 mg, 1.19 mmol) with DDQ (300 mg, 1.31 mmol) according to general procedure **C** (8.2.1) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **3.49b** as a white solid (276 mg, 91%). **Formula** $C_{13}H_{15}FO_4$; **Mw** 254.25, **Mp** 51–53 °C; $\mathbf{R_f}$ 0.40 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +56.0 (c 0.9, $CHCl_3$, 26 °C); **IR** (film) 3437 (br. m), 2982 (w), 2940 (w), 2878 (w), 1591 (m), 1488 (m), 1450 (m), 1253 (s), 1117 (s), 1016 (s), 929 (s), 785 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (1 H, td, *J* = 7.9, 5.9 Hz, H-12), 7.12–7.05 (2 H, m, H-9 and H-13), 6.99 (1 H, tdd, *J* = 8.5, 2.6, 0.8 Hz, H-11), 5.83 (1 H, d, *J* = 5.1 Hz, H-1), 4.56 (1 H, dddd, *J* = 8.7, 6.7, 6.3 5.1 Hz, H-5), 4.55 (1 H, d, *J* = 12.4 Hz, H-7), 4.51 (1 H, d, *J* = 12.2 Hz, H-7'), 4.48 (1 H, dt, *J* = 4.0, 1.2 Hz, H-3), 4.13 (1 H, dt, *J* = 10.2, 1.3 Hz, H-2), 4.03 (1 H, dd, *J* = 10.3, 4.0 Hz, H-2'), 4.00 (1 H, dd, *J* = 9.4, 6.2 Hz, H-6), 3.62 (1 H, dd, *J* = 9.4, 6.7 Hz, H-6'), 2.93 (1 H, ddt, *J* = 8.5, 5.3, 1.1 Hz, H-4), 1.97 (1 H, d, *J* = 5.1 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 162.9 (CF_{ar}, d, *J* = 245.2 Hz, C-10), 140.5 (C_{ar}, d, *J* = 7.3 Hz, C-8), 129.9 (CH_{ar}, d, *J* = 8.3 Hz, C-12), 122.9 (CH_{ar}, d, *J* = 2.9 Hz, C-13), 114.6 (CH_{ar}, d, *J* = 21.4 Hz, C-9), 114.3 (CH_{ar}, d, *J* = 21.9 Hz, C-11), 109.2 (CH, C-1), 78.9 (CH, C-3), 74.2 (CH_2, C-2), 73.4 (CH_2, C-6), 70.3 (CH_2, C-7), 70.0 (CH, C-5), 53.5 (CH, C-4) ppm; **LRMS** (ESI$^+$) *m/z* 318.2 (M + Na+MeCN)$^+$; **HRMS** (ESI$^+$) for $C_{13}H_{15}FO_4Na$ (M + Na)$^+$ calcd 277.0847, found 277.0844.

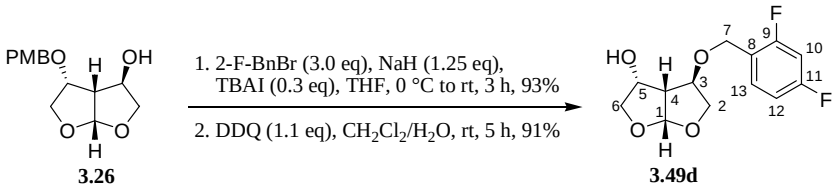
(1*S*,4*R*,5*R*,6*R*)-4-(4-Fluorobenzyloxy)-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.49c)



Following general procedure **B** (8.2.1), the reaction of alcohol **3.26** (338 mg, 1.27 mmol) and 4-fluorobenzyl bromide (470 µL, 3.80 mmol) afforded after purification by column chromatography (petroleum ether/acetone 90:10 to 80:20) the corresponding dibenzyl ether as a colourless oil (443 mg, 93%; $\mathbf{R}_f$ 0.33 (petroleum ether/acetone 80:20); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.30 (2 H, dd, *J* = 5.4, 8.7 Hz), 7.17 (2 H, d, *J* = 8.8 Hz), 7.02 (2 H, t, *J* = 8.7 Hz), 6.88 (2 H, d, *J* = 8.8 Hz), 5.83 (1 H, d, *J* = 5.2 Hz), 4.52−4.40 (5 H, m), 4.24 (1 H, ddd, *J* = 6.7, 8.1, 8.7 Hz), 4.11 (1 H, dt, *J* = 1.1, 10.2 Hz), 3.98 (1 H, dd, *J* = 4.0, 10.2 Hz), 3.98 (1 H, dd, *J* = 6.8, 9.1 Hz), 3.82 (3 H, s), 3.58 (1 H, dd, *J* = 8.3, 9.1 Hz), 2.99 (1 H, ddt, *J* = 1.1, 5.1, 8.9 Hz) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −114.8 (tt, *J* = 8.6, 5.4 Hz) ppm).

Subsequent treatment of this dibenzyl ether (440 mg, 1.18 mmol) with DDQ (295 mg, 1.30 mmol) according to general procedure **C** (8.2.1) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **3.49c** as a white solid (269 mg, 89%). **Formula** $C_{13}H_{15}FO_4$; **Mw** 254.25; **Mp** 50−52 °C; $\mathbf{R}_f$ 0.34 (petroleum ether/acetone 70:30); **$[\alpha]_D$** +56.5 (c 0.9, $CHCl_3$, 26 °C); **IR** (film) 3431 (br. m), 2971 (w), 2941 (w), 2877 (w), 1509 (s), 1220 (s), 1085 (s), 1011 (vs), 929 (s), 821 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.31 (2 H, dd, *J* = 8.8, 5.4 Hz, H-9), 7.04 (2 H, t, *J* = 8.7 Hz, H-10), 5.82 (1 H, d, *J* = 5.3 Hz, H-1), 4.54 (1 H, dtd, *J* = 8.5, 6.4, 5.0 Hz, H-5), 4.50 (1 H, d, *J* = 11.8 Hz, H-7), 4.47 (1 H, dt, *J* = 4.0, 1.2 Hz, H-3), 4.47 (1 H, d, *J* = 11.7 Hz, H-7'), 4.11 (1 H, dt, *J* = 10.2, 1.3 Hz, H-2), 4.02 (1 H, dd, *J* = 10.2, 4.0 Hz, H-2'), 3.99 (1 H, dd, *J* = 9.4, 6.2 Hz, H-6), 3.61 (1 H, dd, *J* = 9.4, 6.8 Hz, H-6'), 2.91 (1 H, ddt, *J* = 8.7, 5.3, 1.1 Hz, H-4), 2.12 (1 H, d, *J* = 5.0 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 162.4 (CF_{ar}, d, *J* = 245.9 Hz, C-11), 133.6 (C_{ar}, d, *J* = 2.9 Hz, C-8), 129.4 (2 × CH_{ar}, d, *J* = 8.3 Hz, C-9), 115.3 (2 × CH_{ar}, d, *J* = 21.4 Hz, C-10), 109.2 (CH, C-1), 78.7 (CH, C-3), 74.2 (CH_2, C-2), 73.3 (CH_2, C-6), 70.4 (CH_2, C-7), 70.0 (CH, C-5), 53.5 (CH, C-4) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −114.8 (tt, *J* = 8.6, 5.4 Hz) ppm; **LRMS** (ESI^+) *m*/*z* 318.2 $(M + Na+MeCN)^+$; **HRMS** (ESI^+) for $C_{13}H_{15}FO_4Na$ $(M + Na)^+$ calcd 277.0847, found 277.0846.

(1*S*,4*R*,5*R*,6*R*)-4-(2,4-Difluorobenzyloxy)-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.49d)



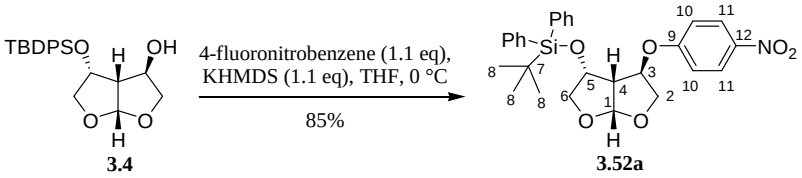
3.26 **3.49d**

Following general procedure **B** (8.2.1), the reaction of alcohol **3.26** (408 mg, 1.53 mmol) and 2,4-difluorobenzyl bromide (580 µL, 4.59 mmol) afforded after purification by column chromatography (petroleum ether/ acetone 90:10 to 80:20) the corresponding dibenzyl ether as a colourless oil (557 mg, 93%; $\mathbf{R}_f$ 0.65 (petroleum ether/acetone 70:30); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37 (1 H, td, *J* = 6.5, 8.4 Hz), 7.20 (2 H, d, *J* = 8.8 Hz), 6.89 (2 H, d, *J* = 8.7 Hz), 6.86 (1 H, tdd, *J* = 1.0, 2.5, 8.3 Hz), 6.80 (1 H, ddd, *J* = 2.5, 8.8, 10.2 Hz), 5.82 (1 H, d, *J* = 5.3 Hz), 4.54−4.48 (3 H, m), 4.46 (1 H, d, *J* = 3.9 Hz), 4.45 (1 H, d, *J* = 11.3 Hz), 4.25 (1 H, ddd, *J* = 6.8, 8.2, 8.8 Hz), 4.12 (1 H, dt, *J* = 1.1, 10.3 Hz), 4.00 (1 H, dd, *J* = 3.9, 10.3 Hz), 3.98 (1 H, dd, *J* = 6.8, 9.2 Hz), 3.82 (3 H, s), 3.59 (1 H, dd, *J* = 8.3, 9.0 Hz), 2.99 (1 H, ddt, *J* = 1.1, 5.2, 8.9 Hz) ppm; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ −110.7 (1 F, d, *J* = 7.5 Hz), −114.9 (1 F, d, *J* = 7.5 Hz) ppm).

Subsequent treatment of this dibenzyl ether (553 mg, 1.41 mmol) with DDQ (352 mg, 1.55 mmol) according to general procedure **C** (8.2.1) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **3.49d** as a white solid (351 mg, 91%). **Formula** $C_{13}H_{14}F_2O_4$; **Mw** 272.24; **Mp** 51 °C; $\mathbf{R}_f$ 0.40 (petroleum ether/acetone 70:30) $\mathbf{[\alpha]_D}$ +47.8 (c 1.0, $CHCl_3$, 26 °C); **IR** (film) 3442 (br. m), 2941 (w), 2880 (w), 1620 (m), 1605 (m), 1505 (s), 1277 (m), 1100 (vs), 1015 (s), 960 (s), 851 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 (1 H, td, *J* = 8.4, 6.5 Hz, H-13), 6.88 (1 H, tdd, *J* = 8.4, 2.6, 1.1 Hz, H-12), 6.81 (1 H, ddd, *J* = 10.2, 8.9, 2.5 Hz, H-10), 5.82 (1 H, d, *J* = 5.1 Hz, H-1), 4.56 (1 H, dtd, *J* = 8.5, 6.4 Hz, 5.0 Hz, H-5), 4.57−4.50 (2 H, m, H-7 and H-7'), 4.49 (1 H, dt, *J* = 4.0, 1.2 Hz, H-3), 4.12 (1 H, dt, *J* = 10.2, 1.3 Hz, H-2), 4.04 (1 H, dd, *J* = 10.3, 4.0 Hz, H-2'), 4.01 (1 H, dd, *J* = 9.4, 6.3 Hz, H-6), 3.62 (1 H, dd, *J* = 9.5, 6.7 Hz, H-6'), 2.92 (1 H, ddt, *J* = 8.6, 5.2, 1.1 Hz, H-4), 2.00 (1 H, d, *J* = 5.0 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 162.7 (CF_{ar}, dd, *J* = 248.7, 11.9 Hz, C-11), 160.7 (CF_{ar}, dd, *J* = 249.4, 11.9 Hz, C-9), 131.0 (CH_{ar}, dd, *J* = 9.7, 5.8 Hz, C-13), 120.9 (C_{ar}, dd, *J* = 14.8, 3.6 Hz, C-8), 111.3 (CH_{ar}, dd, *J* = 21.1, 3.6 Hz, C-12), 109.2 (CH, C-1), 103.7 (CH_{ar}, t, *J* = 25.3 Hz, C-10), 79.0 (CH, C-3), 74.3 (CH_2, C-2), 73.4 (CH_2, C-6), 70.0 (CH, C-5), 64.1 (CH_2, d, *J* = 3.2 Hz, C-7), 53.4 (CH, C-4) ppm;

^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$) δ −110.7 (1 F, d, *J* = 7.5 Hz), −115.0 (1 F, d, *J* = 7.5 Hz) ppm; **LRMS** (ESI^+) *m*/*z* 336.2 $(M + Na+MeCN)^+$; **HRMS** (ESI^+) for $C_{13}H_{14}F_2O_4Na$ $(M + Na)^+$ calcd 295.0752, found 295.0750.

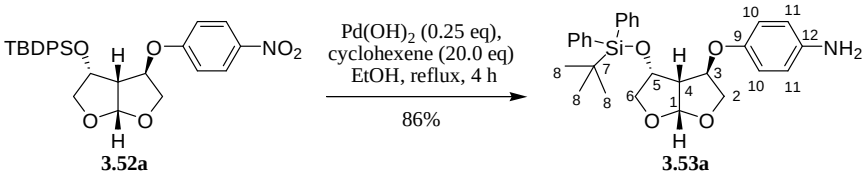
(1*R*,4*R*,5*S*,6*R*)-6-(*tert*-Butyldiphenylsilanoxy)-4-(4-nitrophenoxy)-2,8-dioxa-bicyclo-[3.3.0]octane (3.52a)



3.4 **3.52a**

To a solution of compound **3.4** (3.829 g, 9.96 mmol) in THF (75 mL) at 0 °C was added a solution of 4-fluoronitrobenzene (1.545 g, 10.95 mmol) in THF (2.5 mL). Then KHMDS (21.9 mL, 10.95 mmol, 0.5 M in THF) was added dropwise over a period of 15 min, whereupon the reaction mixture changed its colour from purple to brown. After further 5 min of stirring at 0 °C, the reaction was quenched with H_2O (100 mL) and neutralized with aq. HCl (2 M), at which the colour changes from dark yellow to light yellow when neutralized. Then the reaction mixture was extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (hexane/EtOAc 85:15) afforded the *title compound* **3.52a** as a white solid (4.304 g, 85%). **Formula** $C_{28}H_{31}NO_6Si$; **Mw** 505.63; **Mp** 130−131°C; $\mathbf{R_f}$ 0.38 (hexane/EtOAc 70:30); $\mathbf{[\alpha]_D}$ −57.5 (*c* 0.5, $CHCl_3$, 26 °C); **IR** (film) 2930 (w), 2878 (w), 2858 (w), 2360 (m), 2341 (m), 1506 (m), 1331 (s), 1109 (s), 1032 (w), 1011 (w), 843 (m), 702 (s), 606 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.14 (2 H, d, *J* = 9.2 Hz, H-11), 7.68−7.60 (4 H, m, Ar-H), 7.52−7.47 (2 H, m, Ar-H), 7.43−7.38 (4 H, m, Ar-H), 6.91 (2 H, d, *J* = 9.3 Hz, H-10), 5.78 (1 H, d, *J* = 5.0 Hz, H-1), 5.42 (1 H, d, *J* = 3.5 Hz, H-3), 4.60 (1 H, ddd, *J* = 9.0, 8.2, 6.8 Hz, H-5), 4.29 (1 H, dd, *J* = 10.5, 3.5 Hz, H-2), 4.23 (1 H, dt, *J* = 10.5, 1.0 Hz, H-2'), 3.70 (1 H, dd, *J* = 9.2, 6.8 Hz, H-6), 3.55 (1 H, app t, *J* = 8.5 Hz, H-6'), 2.91 (1 H, dd, *J* = 9.0, 5.1 Hz, H-4), 1.13 (9 H, s, H-8) ppm. **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 162.1 (C_{ar}, C-9), 141.8 (C_{ar}, C-12), 135.6 (2 × CH_{ar}), 135.5 (2 × CH_{ar}), 132.6 (C_{ar}), 132.5 (C_{ar}), 130.43 (CH_{ar}), 130.39 (CH_{ar}), 128.1 (2 × CH_{ar}), 128.0 (2 × CH_{ar}), 126.0 (2 × CH_{ar}, C-11), 115.2 (2 × CH_{ar}, C-10), 108.6 (CH, C-1), 78.7 (CH, C-3), 74.4 (CH_2, C-2), 72.8 (CH_2, C-6), 71.2 (CH, C-5), 52.9 (CH, C-4), 27.0 (3 × CH_3, H-8), 19.2 (C, C-7) ppm. **LRMS** (ESI^+) *m*/*z* 528.3 $(M + Na)^+$.

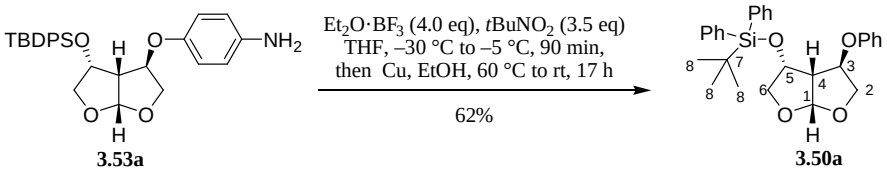
(1*R*,4*R*,5*S*,6*R*)-4-(4-Aminophenoxy)-6-(*tert*-butyldiphenylsilanoxy)-2,8-dioxa-bicyclo-[3.3.0]-octane (3.53a)



3.52a **3.53a**

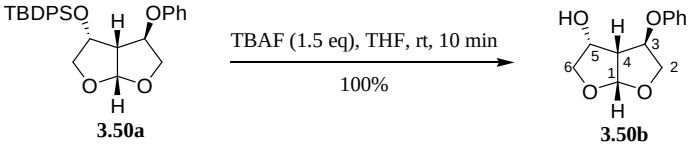
To a suspension of ether **3.52a** (1.00 g, 1.97 mmol) in EtOH (40 mL) was added cyclohexene (4.0 mL, 39.4 mmol) and $Pd(OH)_2$ (346 mg, 0.49 mmol). The reaction was stirred under inert atmosphere at reflux temperature for 4 h. After cooling to rt, the mixture was filtered through celite and the solvent was removed in vacuo. Purification of the crude product by column chromatography (hexane/EtOAc 60:40) afforded the *title compound* **3.53a** as brown oil (809 mg, 86%). **Formula** $C_{28}H_{33}NO_4Si$; **Mw** 475.65; $\mathbf{R_f}$ 0.81 (CH_2Cl_2/MeOH 90:10); $\mathbf{[\alpha]_D}$ −53.6 (*c* 0.14, CH_3OH, 21 °C); **IR** (film) 3426 (m), 3361 (w), 2930 (m), 2858 (m), 1625 (w), 1508 (s), 1427 (m), 1362 (w), 1227 (bs), 1110 (bs), 1008 (m), 907 (m), 821 (m), 739 (m), 700 (s), 608 (m) cm^{-1}; ^{1}**H NMR** (300 MHz, $CDCl_3$) δ 7.66−7.61 (4 H, m, Ar-H), 7.50−7.35 (6 H, m, Ar-H), 6.75 (2 H, d, *J* = 8.9 Hz, H-10 or H-11), 6.64 (2 H, d, *J* = 8.9 Hz, H-11 or H-10), 5.76 (1 H, d, *J* = 5.1 Hz, H-1), 5.27 (1 H, d, *J* = 3.3 Hz, H-3), 4.50 (1 H, ddd, *J* = 9.1, 8.1, 6.7 Hz, H-5), 4.23 (1 H, dt, *J* = 10.5, 1.0 Hz, H-2), 4.17 (1 H, dd, *J* = 10.5, 3.4 Hz, H-2'), 3.59 (1 H, dd, *J* = 9.0, 6.7 Hz, H-6), 3.47 (1 H, app t, *J* = 8.5 Hz, H-6'), 2.96 (1 H, ddt, *J* = 9.0, 5.1, 1.0 Hz, H-4), 1.10 (9 H, s, H-8) ppm; ^{13}**C NMR + DEPT** (75 MHz, $CDCl_3$) δ 150.2 (C_{ar}, C-9), 140.1 (C_{ar}, C-12), 135.63 (2 × CH_{ar}), 135.56 (2 × CH_{ar}), 133.0 (C_{ar}), 132.6 (C_{ar}), 130.2 (CH_{ar}), 130.1 (CH_{ar}), 127.93 (2 × CH_{ar}), 127.92 (2 × CH_{ar}), 117.4 (2 × CH_{ar}, C-10 or C-11), 116.7 (2 × CH_{ar}, C-11 or C-10), 108.8 (CH, C-1), 78.8 (CH, C-3), 74.8 (CH_2, C-2), 72.6 (CH_2, C-6), 71.3 (CH, C-5), 52.8 (CH, C-4), 27.0 (3 × CH_3, H-8), 19.1 (C, C-7) ppm; **LRMS** (ESI^+) *m/z* 476.3 $(M + H)^+$, 498.3 $(M + Na)^+$.

(1*R*,4*R*,5*S*,6*R*)-6-(*tert*-butyldiphenylsilanoxy)-4-phenoxy-2,8-dioxa-bicyclo-[3.3.0]-octane (3.50a)



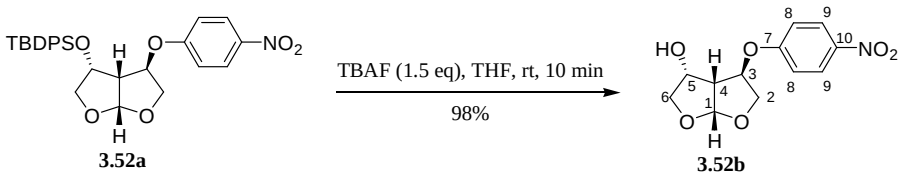
Deamination was achieved via diazonium salt formation.[103] A solution of amine **3.53a** (662 mg, 1.45 mol) in THF (10 mL) was added dropwise *via* cannula to $BF_3 \cdot OEt_2$ (2.84 mL, 5.8 mmol) at −30 °C under inert atmosphere was added. After 20 min, a solution of *tert*-butylnitrite (2.30 mL, 5.07 mmol) in THF (5 mL) was added *via* cannula and the reaction mixture was stirred at −5°C. After further 90 min, copper powder (100 mg) and EtOH (25 mL) were added and the reaction was stirred at 60 °C for 2 h and at rt for further 15 h. After completion, the mixture was filtered through celite, quenched with sat. aq. $NaHCO_3$ (100mL) and extract with EtOAc (3 × 70 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (hexane/EtOAc 90:10) and by HPLC (hexane/EtOAc 90:10) afforded the *title compound* **3.50a** as colourless oil (414 mg, 62%). **Formula** $C_{28}H_{32}O_4Si$; **Mw** 460.64; $\mathbf{R_f}$ 0.54 (hexane/EtOAc 70:30); $\mathbf{[\alpha]_D}$ −38.8 (*c* 0.8, $CHCl_3$, 26 °C); **IR** (film) 3071 (w), 2931 (m), 2858 (m), 1598 (m), 1587 (m), 1489 (m), 1427 (m), 1237 (s), 1110 (s),1025 (m), 973 (m), 911 (m), 821 (m), 740 (m), 700 (s), 691 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68−7.61 (4 H, m, Ar-H), 7.50−7.44 (2 H, m, Ar-H), 7.42−7.36 (4 H, m, Ar-H), 7.27 (2 H, dd, *J* = 8.9, 7.4 Hz, H-11), 6.98 (1 H, tt, *J* = 7.4, 1.1 Hz, H-12), 6.91 (2 H, d, *J* = 8.9, 1.1 Hz, H-10), 5.78 (1 H, d, *J* = 5.1 Hz, H-1), 5.40 (1 H, t, *J* = 2.3 Hz, H-3), 4.54 (1 H, ddd, *J* = 9.2, 8.3, 6.8 Hz, H-5), 4.25 (2 H, d, *J* = 2.4 Hz, H-2 and H-2'), 3.61 (1 H, dd, *J* = 9.0, 6.5 Hz, H-6), 3.47 (1 H, app t, *J* = 8.6 Hz, H-6'), 2.97 (1 H, dd, *J* = 9.0, 5.1 Hz, H-4), 1.12 (9 H, s, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 157.1 (C_{ar}), 135.7 (2 × CH_{ar}), 135.6 (2 × CH_{ar}), 132.9 (C_{ar}), 132.5 (C_{ar}), 130.3 (CH_{ar}), 130.1 (CH_{ar}), 129.6 (2 × CH_{ar}), 127.97 (2 × CH_{ar}), 127.94 (2 × CH_{ar}), 121.2 (CH_{ar}), 115.7 (2 × CH_{ar}), 108.7 (CH, C-1), 77.8 (CH, C-3), 74.8 (CH_2, C-2), 72.7 (CH_2, C-6), 71.3 (CH, C-5), 52.8 (CH, C-4), 27.0 (3 × CH_3, H-8), 19.2 (C, C-7) ppm; **LRMS** (ESI^+) *m/z* 483.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{28}H_{32}O_4SiNa$ $(M + Na)^+$ calcd. 483.1962; found 483.1960.

(1*S*,4*R*,5*R*,6*R*)- 6-Hydroxy-4-phenoxy-2,8-dioxa-bicyclo-[3.3.0]-octane (3.50b)



To a stirred solution of silyl ether **3.50a** (358 mg, 0.78 mmol) in THF (10 mL) at rt was added TBAF (1.16 mL, 1.16 mmol, 1 M in THF). After 10 min the solvent was removed in vacuo and purification of the crude product by column chromatography (CH_2Cl_2/MeOH 95:5) afforded the *title compound* **3.50b** as a white solid (174 mg, 100%). **Formula** $C_{12}H_{14}O_4$; **Mw** 222.24; **Mp** 95−96 °C; $\mathbf{R_f}$ 0.62 (CH_2Cl_2/MeOH 90:10); $\mathbf{[\alpha]_D}$ +60.5 (*c* 0.1, CH_3OH, 26 °C); **IR** (film) 3415 (br. m), 2990 (w), 2963 (w), 2929 (w), 2881 (w), 2863 (m), 1596 (m), 1584 (m), 1482 (s), 1378 (m) 1301 (m), 1238 (s) 1107 (s), 887 (m), 828 (m), 811 (m), 757 (s), 691 (s), 623 (m) cm^{-1}. **^{1}H NMR** (400 MHz, MeOH-d_4) δ 7.30−7.24 (2 H, m, Ar-H), 6.96−6.91 (3 H, m, Ar-H), 5.77 (1 H, d, *J* = 5.3 Hz, H-1), 5.22 (1 H, t, *J* = 2.0 Hz, H-3), 4.53 (1 H, dt, *J* = 8.9 6.7 Hz, H-5), 4.16−4.09 (2 H, m, H-2 and H-2'), 3.96 (1 H, dd, *J* = 9.1, 6.5 Hz, H-6), 3.58 (1 H, dd, *J* = 9.2, 7.0 Hz, H-6'), 2.99 (1 H, dd, *J* = 8.8, 5.3 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, MeOH-d_4) δ 158.7 (C_{ar}, C-7), 130.8 (2 × CH_{ar}, C-9), 122.2 (CH_{ar}, C-10), 116.6 (2 × CH_{ar}, C-8), 110.9 (CH, C-1), 78.8 (CH, C-3), 75.8 (CH_2, C-2), 74.6 (CH_2, C-6), 70.5 (CH, C-5), 54.4 (CH, C-4) ppm; **LRMS** (ESI^+) *m/z* 245.2 $(M + H)^+$; **HRMS** (ESI^+) for $C_{12}H_{14}O_4Na$ $(M + Na)^+$ calcd. 245.0784; found 245.0782.

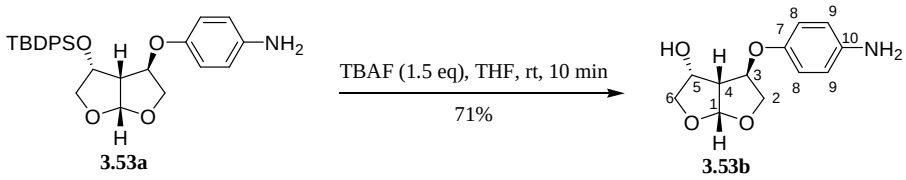
(1*S*,4*R*,5*R*,6*R*)- 6-Hydroxy-4-(4-nitro-phenoxy)-2,8-dioxa-bicyclo-[3.3.0]-octane (3.52b)



To a stirred solution of silyl ether **3.52a** (500 mg, 1.00 mmol) in THF (18 mL) at rt was added TBAF (1.48 mL, 1.48 mmol, 1 M in THF). After 5 min the solvent was removed in vacuo and purification of the crude product by column chromatography (hexane/acetone 60:40) afforded the *title compound* **3.52b** as a white solid (261 mg, 98%). **Formula** $C_{12}H_{13}NO_6$; **Mw** 267.23; **Mp** 123−124 °C; $\mathbf{R_f}$ 0.57 (CH_2Cl_2/MeOH 90:10); $\mathbf{[\alpha]_D}$ +76.8 (*c* 0.11, CH_3OH, 21 °C); **IR** (film) 3426 (m), 3075 (m), 2955 (m), 2896 (m), 2360 (m), 1607 (m), 1590 (s), 1512 (s), 1496 (m), 1345 (s), 1238 (s), 1175 (m), 1112 (s), 1014 (m),

899 (m), 898 (m), 854 (m), 754 (s), 694 (m), 654 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.21 (2 H, d, *J* = 9.3 Hz, H-9), 7.03 (2 H, d, *J* = 9.3 Hz, H-8), 5.88 (1 H, d, *J* = 5.1 Hz, H-1), 5.36 (1 H, dd, *J* = 2.5, 1.6 Hz, H-3), 4.69 (1 H, m, H-5), 4.29−4.21 (2 H, m, H-2 and H-2'), 4.08 (1 H, dd, *J* = 9.4, 6.3 Hz, H-6), 3.70 (1 H, dd, *J* = 9.5, 6.8 Hz, H-6'), 3.03 (1 H, dd, *J* = 8.8, 5.3 Hz, H-4), 2.43 (1 H, d, *J* = 3.9 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 162.2 (C_{ar}, C-7), 141.8 (C_{ar}, C-10), 126.0 (2 × CH_{ar}, C-9), 115.2 (2 × CH_{ar}, C-8), 109.2 (CH, C-1), 78.0 (CH, C-3), 74.5 (CH_2, C-2), 73.7 (CH_2, C-6), 69.8 (CH, C-5), 53.0 (CH, C-4) ppm; **LRMS** (ESI^+) *m/z* 331.2 $(M + Na + MeCN)^+$; **HRMS** (ESI^+) for $C_{12}H_{13}NO_6Na$ $(M + Na)^+$ calcd. 290.0635; found 290.0634.

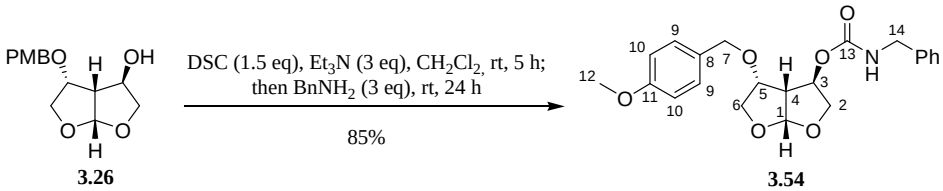
(1*S*,4*R*,5*R*,6*R*)-4-(4-Amino-phenoxy)-6-Hydroxy-2,8-dioxa-bicyclo-[3.3.0]-octane (3.53b)



3.53a **3.53b**

To a stirred solution of silyl ether **3.53a** (272 mg, 0.57 mmol) in THF (10 mL) at rt was added TBAF (0.85 mL, 0.85 mmol, 1 M in THF). After 10 min the solvent was removed in vacuo and purification of the crude product by column chromatography (CH_2Cl_2/MeOH 95:5) afforded the *title compound* **3.53b** as a yellow solid (96 mg, 71%). **Formula** $C_{12}H_{15}NO_4$; **Mw** 237.25; **Mp** 166−167 °C; **R_f** 0.49 (CH_2Cl_2/MeOH 90:10); **$[\alpha]_D$** +57.1 (*c* 0.07, CH_3OH, 21 °C); **IR** (film) 3365 (w), 3302 (w), 3172 (w), 2954 (w), 2878 (w), 1509 (s), 1455 (w), 1362 (m), 1235 (s), 1113 (s), 1054 (s), 996 (m), 945 (m), 898 (m), 833 (m), 810 (m), 745 (m), 695 (w), 911 (m), 591 (m) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 6.65 (2 H, d, *J* = 8.9 Hz, H-9), 6.51 (2 H, d, *J* = 8.9 Hz, H-8), 5.68 (1 H, d, *J* = 5.3 Hz, H-1), 5.51 (1 H, d, *J* = 4.8 Hz, OH), 4.94 (1 H, t, *J* = 2.0 Hz, H-3), 4.61 (2 H, br. s, NH_2), 4.38 (1 H, dddd, *J* = 8.9, 7.5, 6.7, 4.8 Hz, H-5), 3.97−3.91 (2 H, m, H-2 and H-2'), 3.84 (1 H, dd, *J* = 8.9, 6.7 Hz, H-6), 3.38 (1 H, dd, *J* = 8.8, 7.6 Hz, H-6'), 2.82 (1 H, dd, *J* = 9.0, 5.2 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, DMSO-d_6) δ 147.9 (C_{ar}, C-7), 142.7 (C_{ar}, C-10), 116.3 (2 × CH_{ar}, C-9), 115.0 (2 × CH_{ar}, C-8), 108.6 (CH, C-1), 77.7 (CH, C-3), 73.9 (CH_2, C-2), 72.5 (CH_2, C-6), 68.5 (CH, C-5), 52.2 (CH, C-4) ppm; **LRMS** (ESI^+) *m/z* 238.1 $(M + H)^+$; **HRMS** (ESI^+) for $C_{12}H_{16}NO_4$ $(M + H)^+$ calcd. 238.1074; found 238.1082.

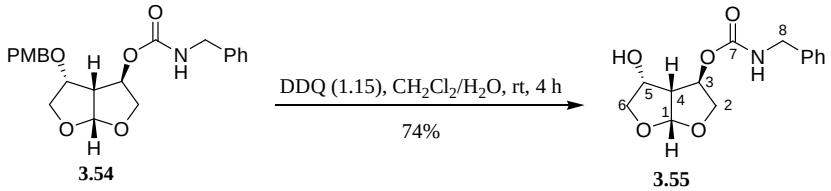
Benzyl carbamic acid (1*S*,4*R*,5*R*,6*R*)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl ester (3.54)



3.26 **3.54**

To a solution of alcohol **3.26** (475 mg, 1.78 mmol) and Et_3N (745 µL, 5.36 mmol) in CH_2Cl_2 (10 mL) was then added *N*,*N*'-disuccinimidyl carbonate (685 mg, 2.68 mmol) and the resulting mixture was stirred at rt for 5 h. When the TLC revealed the absence of starting material, benzylamine (585 µL, 5.36 mmol) was added dropwise and the resulting mixture was stirred at rt for further 24 h. After completion CH_2Cl_2 (20 mL) and sat. aq. $NaHCO_3$ (5 mL) were added, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were washed with sat. aq. NH_4Cl (5 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:20 to 75:25) afforded the *title compound* **3.54** as a yellow oil (605 mg, 85%). **Formula** $C_{22}H_{25}NO_6$; **Mw** 399.44; $\mathbf{R_f}$ 0.38 (petroleum ether/acetone 75:25); $\mathbf{[\alpha]_D}$ +26.4 (*c* 0.63, $CHCl_3$, 27 °C); **IR** (film) 3333 (br. w), 2953 (w), 2880 (w), 1717 (s), 1612 (m), 1514 (s), 1247 (vs), 1128 (m), 1107 (m), 1028 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39–7.28 (7 H, m, Ar-H and H-9), 6.89 (2 H, d, *J* = 8.7 Hz, H-10), 5.81 (1 H, d, *J* = 5.3 Hz, H-1), 5.54 (1 H, d, *J* = 2.6 Hz, H-3), 5.05 (1 H, m, NH), 4.71 (1 H, d, *J* = 11.2 Hz, H-7), 4.51 (1 H, d, *J* = 11.2 Hz, H-7'), 4.41 (1 H, part of AB-system, H-14), 4.39 (1 H, part of AB-system, H-14'), 4.26 (1 H, dt, *J* = 8.3, 7.6 Hz, H-5), 4.12-4.06 (2 H, m, H-2 and H-2'), 3.97 (1 H, dd, *J* = 9.3, 6.7 Hz, H-6), 3.81 (3 H, s, H-12), 3.64 (1 H, dd, *J* = 9.3, 7.9 Hz, H-6'), 2.99 (1 H, m, *J* = 8.8, 5.5 Hz can be observed, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.4 (C_{ar}, C-11), 155.7 (C, C-13), 138.1 (C_{ar}), 129.6 (2 × CH_{ar}, C_{ar}), 128.7 (2 × CH_{ar}), 127.6 (2 × CH_{ar}), 127.5 (CH_{ar}), 113.9 (2 × CH_{ar}, C-10), 108.9 (CH, C-1), 76.3 (CH, C-5), 76.1 (CH, C-3), 75.1 (CH_2, C-2), 72.4 (CH_2, C-7), 71.1 (CH_2, C-6), 55.3 (CH_3, C-12), 51.7 (CH, C-4), 45.1 (CH_2, C-14) ppm; **LRMS** (ESI^+) *m/z* 422.1 $(M + Na)^+$.

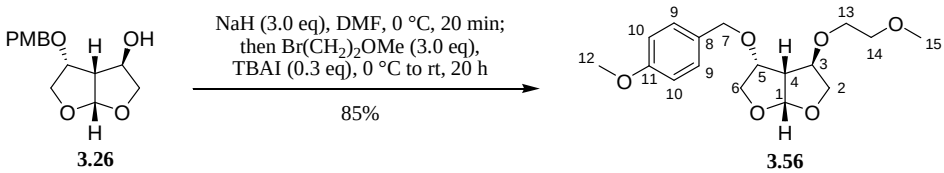
Benzyl carbamic acid (1*S*,4*R*,5*R*,6*R*)-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl ester (3.55)



3.54 **3.55**

Following general procedure **C** (8.2.1), the reaction of ether **3.54** (523 mg, 1.37 mmol) with DDQ (358 mg, 1.58 mmol) afforded after purification by column chromatography (petroleum ether/acetone 70:30 to 60:40) the *title compound* **3.55** as an off-white solid (366 mg, 74%). **Formula** $C_{14}H_{17}NO_5$; **Mw** 279.29; $\mathbf{R_f}$ 0.34 (hexane/acetone 60:40); $\mathbf{[\alpha]_D}$ +61.9 (*c* 0.51, acetone, 23 °C); **IR** (film) 3398 (m), 3330 (br. m), 2979 (w), 2937 (w), 2882 (w), 1695 (vs), 1533 (m), 1249 (s), 1114 (s), 1104 (m), 970 (m), 700 (m) cm^{-1}; **^{1}H NMR** (400 MHz, acetone-d_6) δ 7.34–7.21 (5 H, m, Ar-H), 6.82 (1 H, br. s, N*H*), 5.67 (1 H, d, *J* = 5.3 Hz, H-1), 5.47 (1 H, d, *J* = 3.7 Hz, H-3), 4.58 (1 H, d, *J* = 4.3 Hz, O*H*), 4.52 (1 H, dtd, *J* = 8.8, 6.6, 4.3 Hz, H-5), 4.33 (2 H, d, *J* = 6.2 Hz, H-8), 4.01 (1 H, dd, *J* = 10.5, 3.8 Hz, H-2), 3.90 (1 H, dt, *J* = 10.4, 1.0 Hz, H-2'), 3.89 (1 H, dd, *J* = 9.1, 6.4 Hz, H-6), 3.48 (1 H, dd, *J* = 9.1, 7.1 Hz, H-6'), 2.85 (1 H, dd, *J* = 8.7, 5. 2 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, acetone-d_6) δ 157.2 (C, C-7), 140.8 (C_{ar}), 129.3 ($2 \times CH_{ar}$), 128.2 ($2 \times CH_{ar}$), 127.9 (CH_{ar}), 110.1 (CH, C-1), 76.3 (CH, C-3), 75.6 (CH_2, C-2), 73.9 (CH_2, C-6), 70.1 (CH, C-5), 54.1 (CH, C-4), 45.2 (CH_2, C-8) ppm; **LRMS** (ESI^+) *m/z* 343.2 $(M + Na + MeCN)^+$; **HRMS** (ESI^+) for $C_{14}H_{17}NO_5Na$ $(M + Na)^+$ calcd. 302.0999; found 302.0999.

(1*S*,4*R*,5*R*,6*R*)-4-(2-Methoxyethoxy)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.56)

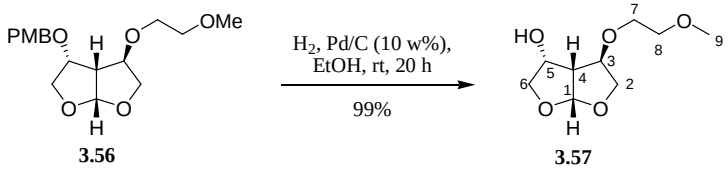


3.26 **3.56**

To a solution of alcohol **3.26** (500 mg, 1.88 mmol) in DMF (10 mL) at 0 °C was added NaH (225 mg, 5.64 mmol, 60% in mineral oil) and the resulting mixture was stirred at this temperature for 20 min. Then TBAI (207 mg, 0.56 mmol) and 2-bromoethyl methyl ether (532 µL, 5.64 mmol) were added. After 10 min the cooling was removed and the reaction was stirred at rt for further 20 h. After completion, the mixture was diluted with H_2O

(100 mL) and Et_2O (100 mL), the phases were separated and the aqueous phase was extracted with Et_2O (2 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 75:25 to 65:35) afforded the *title compound* **3.59** as colourless oil (518 mg, 85%). **Formula** $C_{17}H_{24}O_6$; **Mw** 324.37; $\mathbf{R_f}$ 0.60 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +15.5 (c 0.55, $CHCl_3$, 27 °C); **IR** (film) 2929 (w), 2875 (w), 1612 (w), 1514 (m), 1463 (w), 1247 (s), 1114 (vs), 1028 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2 H, d, *J* = 8.7 Hz, H-9), 6.90 (2 H, d, *J* = 8.7 Hz, H-10), 5.80 (1 H, d, *J* = 5.3 Hz, H-1), 4.55 (1 H, d, *J* = 11.3 Hz, H-7), 4.47 (1 H, d, *J* = 11.3 Hz, H-7'), 4.40 (1 H, dt, *J* = 3.9, 1.1 Hz, H-3), 4.23 (1 H, td, *J* = 8.5, 6.7 Hz, H-5), 4.08 (1 H, dt, *J* = 10.2, 1.1 Hz, H-2), 3.98 (1 H, dd, *J* = 10.2, 3.9 Hz, H-2'), 3.95 (1 H, dd, *J* = 9.0, 6.7 Hz, H-6), 3.82 (3 H, s, H-12), 3.61–3.52 (5 H, m, 2 × H-13, 2 × H-14 and H-6'), 3.38 (3 H, s, H-15), 2.98 (1 H, ddt, *J* = 8.8, 5.2, 1.1 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.4 (C, C-11), 129.6 (C, C-8), 129.3 (2 × CH_{ar}, C-9), 113.9 (2 × CH_{ar}, C-10), 108.9 (CH, C-1), 78.9 (CH, C-3), 76.6 (CH, C-5), 74.1 (CH_2, C-2), 72.2 (CH_2, C-7), 71.9 (CH_2, C-13 or C-14), 70.8 (CH_2, C-6), 68.5 (CH_2, C-14 or C-13), 59.1 (CH_3, C-15), 55.3 (CH_3, C-12), 51.9 (CH, C-4) ppm; **LRMS** (ESI^+) *m/z* 347.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{17}H_{24}O_6Na$ $(M + Na)^+$ calcd 347.1465, found 347.1464.

(1*S*,4*R*,5*R*,6*R*)-6-Hydroxy-4-(2-methoxyethoxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.57)

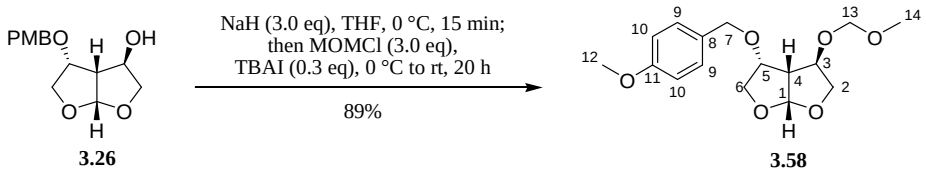


3.56 **3.57**

To a solution of ether **3.56** (518 mg, 1.60 mmol) in dry EtOH (8 mL) under N_2 was added Pd/C (50 mg, 10 w%, 10% Pd). The flask was then put under H_2-atmosphere and the reaction was stirred at rt for 18 h. After completion, the reaction mixture was filtered over celite and the filter cake was washed with EtOH. The solvent was removed in vacuo to afford the crude alcohol **3.57** as colourless oil (325 mg, 97%) in sufficient purity. **Formula** $C_9H_{16}O_5$; **Mw** 204.22; $\mathbf{R_f}$ 0.24 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +45.3 (c 0.98, $CHCl_3$, 23 °C); **IR** (film) 3425 (m), 2929 (m), 2877 (m), 1459 (w), 1244 (w), 1107 (s), 1088 (s), 1002 (s), 975 (s), 933 (s), 847 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.79 (1 H, d, *J* = 5.3 Hz, H-1), 4.54 (1 H, m, H-5), 4.44 (1 H, dt, *J* = 3.1, 1.5 Hz, H-3), 4.04 (2 H, app. d, *J* = 3.2 Hz, H-2 and H-2'), 4.00 (1 H, dd, *J* = 9.2, 6.3 Hz, H-6), 3.69−3.51 (5 H, m, H-6', H-7,

H-7', H-8 and H-8'), 3.40 (3 H, s, H-9), 2.91 (1 H, ddd, *J* = 8.6, 5.3, 1.5 Hz, H-4), 2.39 (1 H, d, *J* = 4.2 Hz) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 109.2 (CH, C-1), 79.5 (CH, C-3), 74.1 (CH_2, C-2), 73.1 (CH_2, C-6), 72.3 (CH_2, C-7 or C-8), 70.0 (CH, C-5), 68.7 (CH_2, C-8 or C-7), 59.1 (CH_3, C-9), 53.5 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 227.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_9H_{16}O_5Na$ $(M + Na)^+$ calcd 227.0890, found 227.0898.

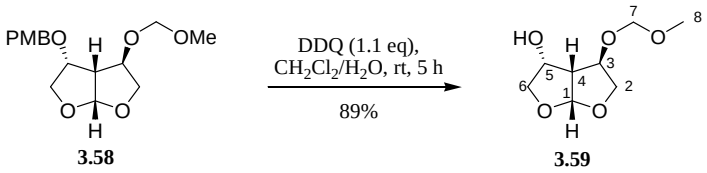
(1*S*,4*R*,5*R*,6*R*)-4-(2-Methoxymethoxy)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo-[3.3.0]-octane (3.58)



3.26 **3.58**

To a solution of alcohol **3.26** (362 mg, 1.35 mmol) in THF (20 mL) at 0 °C was added NaH (162 mg, 4.05 mmol, 60% in mineral oil) and the resulting mixture was stirred at this temperature for 15 min. Then TBAI (151 mg, 0.41 mmol) and chloromethyl methyl ether (MOMCl, 308 µL, 4.05 mmol) were added. After 10 min the cooling was removed and the reaction was stirred at rt for further 20 h. After completion the mixture was quenched with H_2O (10 mL) and extracted with Et_2O (3 × 50 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15 to 70:30) afforded the *title compound* **3.58** as pale yellow oil (371 mg, 89%). **Formula** $C_{16}H_{22}O_6$; **Mw** 310.34; **R_f** 0.48 (petroleum ether/acetone 70:30); **$[\alpha]_D$** −2.4 (c 1.01, $CHCl_3$, 26 °C); **IR** (film) 2940 (w), 2882 (w), 1612 (w), 1513 (m), 1247 (s), 1109 (s), 1018 (vs), 916 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2 H, d, *J* = 8.5 Hz, H-9), 6.90 (2 H, d, *J* = 8.7 Hz, H-10), 5.83 (1 H, d, *J* = 5.1 Hz, H-1), 4.69 (1 H, d, *J* = 7.3 Hz, H-13), 4.67 (1 H, d, *J* = 7.3 Hz, H-13'), 4.61 (1 H, dt, *J* = 3.2, 1.4 Hz, H-3), 4.57 (1 H, d, *J* = 11.3 Hz, H-7), 4.47 (1 H, d, *J* = 11.3 Hz, H-7'), 4.24 (1 H, td, *J* = 8.5, 6.8 Hz, H-5), 4.07–4.00 (2 H, m, H-2 and H-2'), 3.97 (1 H, dd, *J* = 9.2, 6.8 Hz, H-6), 3.82 (3 H, s, H-12), 3.59 (1 H, t, *J* = 8.5 Hz, H-6'), 3.40 (3 H, s, H-14), 2.99 (1 H, m, *J* = 8.9, 5.3 Hz can be observed, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C, C-11), 129.6 (C, C-8), 129.3 (2 × CH_{ar}, C-9), 113.9 (2 × CH_{ar}, C-10), 108.9 (CH, C-1), 95.6 (CH_2, C-13), 77.2 (CH, C-3), 76.5 (CH, C-5), 75.1 (CH_2, C-2), 72.2 (CH_2, C-7), 70.8 (CH_2, C-6), 55.5 (CH_3, C-14), 55.3 (CH_3, C-12), 55.1 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 333.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{16}H_{22}O_6Na$ $(M + Na)^+$ calcd 333.1309, found 333.1303.

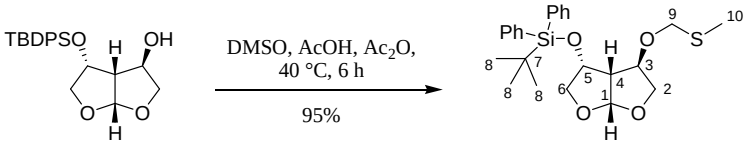
(1*S*,4*R*,5*R*,6*R*)-6-Hydroxy-4-(2-methoxyethoxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.59)



3.58 **3.59**

Following general procedure **C** (8.2.1), the deprotection of ether **3.58** (319 mg, 1.05 mmol) with DDQ (263 mg, 1.16 mmol) afforded after purification by column chromatography (petroleum ether/acetone 70:30 to 60:40) the *title compound* **3.59** as a colourless oil (177 mg, 0.93 mmol, 89%). **Formula** $C_8H_{14}O_5$; **Mw** 190.19; $\mathbf{R_f}$ 0.26 (CH_2Cl_2/MeOH 97:3); $\mathbf{[\alpha]_D}$ +47.8 (c 1.08, $CHCl_3$, 26 °C); **IR** (film) 3434 (br. w), 2948 (w), 2886 (w), 1277 (m), 1150 (m), 1102 (s), 1035 (s), 1008 (vs), 918 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (1 H, d, *J* = 5.3 Hz, H-1), 4.73 (1 H, d, *J* = 6.9 Hz, H-7), 4.69 (1 H, d, *J* = 6.9 Hz, H-7'), 4.59 (1 H, ddd, *J* = 4.9, 2.9, 2.4 Hz, H-3), 4.44 (1 H, dddd, *J* = 8.6, 7.3, 6.4, 4.2 Hz, H-5), 4.14 (1 H, dd, *J* = 10.0, 4.9 Hz, H-2), 4.02 (1 H, dd, *J* = 9.2, 6.4 Hz, H-6), 3.96 (1 H, ddd, *J* = 10.0, 2.9, 0.9 Hz, H-6'), 3.62 (1 H, dd, *J* = 9.3, 7.4 Hz, H-6'), 3.42 (3 H, s, H-8), 2.87 (1 H, dddd, *J* = 8.8, 5.3, 2,4 1.0 Hz, H-4), 2.46 (1 H, d, *J* = 4.0 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 109.2 (CH, C-1), 96.2 (CH_2, C-7), 76.8 (CH, C-3), 74.3 (CH_2, C-2), 72.7 (CH_2, C-6), 70.1 (CH, C-5), 55.7 (CH_3, C-9), 53.7 (CH, C-4) ppm. It was not possible to obtain LRMS/HRMS (ESI, EI or CI) data for this compound.

(1*R*,4*R*,5*S*,6*R*)-6-(*tert*-Butyldiphenylsilanoxy)-4-(2-methylsulfanylmethoxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.60)

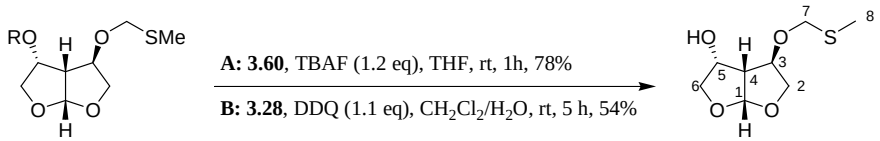


3.4 **3.60**

To a stirred solution of alcohol **3.4** (2.880 g, 5.69 mmol) in DMSO (23 mL) was added a mixture of AcOH and Ac_2O (19 mL, 1:5.6). The reaction mixture was stirred at 40 °C for 6 h. After completion, the reaction mixture was cooled to rt and poured in aq. sat. $NaHCO_3$ (300 mL) at 0 °C. The aqueous phase was extract with Et_2O (3 × 150 mL). The combined organic phases were washed with aq. sat. $NaHCO_3$ and brine (200 mL each), dried over anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. Purification

of the crude product by column chromatography (hexane/EtOAc 90:10) afforded the *title compound* **3.60** as colourless oil (2.396 g, 95 %). **Formula** $C_{24}H_{32}O_4SSi$; **Mw** 444.66; $\mathbf{R_f}$ 0.58 (hexane/EtOAc 70:30); $\mathbf{[\alpha]_D}$ −41.8 (*c* 0.36, $CHCl_3$, 26 °C); **IR** (film) 2930 (m), 2858 (m), 1745 (m), 1589 (w), 1471 (w), 1427 (m), 1214 (m), 1111 (s), 1018 (s), 900 (m), 741 (m), 700 (s), 607 (m), 502 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) .71−7.61 (4 H, m, Ar-H), 7.50−7.37 (6 H, m, Ar-H), 5.71 (1 H, d, *J* = 5.0 Hz, H-1), 4.91 (1 H, d, *J* = 3.0 Hz, H-3), 4.57 (1 H, d, *J* = 11.5 Hz, H-7), 4.50 (1 H, d, *J* = 11.5 Hz, H-7'), 4.47 (1 H, ddd, *J* = 9.2, 8.2, 6.9 Hz, H-5), 4.12 (1 H, dt, *J* = 10.2, 1.3 Hz, H-2), 4.08 (1 H, dd, *J* = 10.3, 3.4 Hz, H-2'), 3.61 (1 H, dd, *J* = 9.0, 6.8 Hz, H-6), 3.45 (1 H, app. t, *J* = 8.3 Hz, H-6'), 2.80 (1 H, dd, *J* = 9.2, 5.1 Hz, H-4), 2.15 (3 H, s, H-8), 1.11 (9 H, s, H-10) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 135.63 (2 × CH_{ar}), 135.61 (2 × CH_{ar}), 133.1 (C_{ar}), 132.8 (C_{ar}), 130.2 (CH_{ar}), 130.1 (CH_{ar}), 127.94 (2 × CH_{ar}), 127.87 (2 × CH_{ar}), 108.7 (CH, C-1), 77.1 (CH, C-3), 74.5 (CH_2, C-2), 73.3 (CH_2, C-7), 72.6 (CH_2, C-6), 71.1 (CH, C-2), 53.1 (CH, C-4), 27.0 (3 × CH_3, H-10), 19.1 (C, C-9), 13.9 (CH_3, C-8) ppm. **LRMS** (ESI^+) *m*/*z* 445.2 $(M + H)^+$, 462.3$(M + NH_4)^+$, 467.2 $(M + Na)^+$.

(1*S*,4*R*,5*R*,6*R*)-6-Hydroxy-4-(2-methylsulfanylmethoxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.61)



3.60: R = TBDPS
3.28: R = PMB

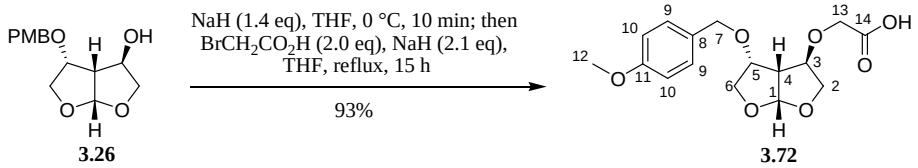
3.61

***Method A*:** To a stirred solution of silyl ether **3.60** (112 mg, 0.25 mmol) in THF (3 mL) at rt was added TBAF (0.30 mL, 0.30 mmol, 1 M in THF). After 1 h the solvent was removed in vacuo and the crude residue was partitioned between CH_2Cl_2 and aq. sat. $NaHCO_3$ (15 mL each). The aqueous phase was extract with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. Purification of the crude product by column chromatography (petroleum ether/acetone 70:30) afforded the *title compound* **3.61** as colourless oil (40 mg, 78%).

***Method B*:** Following general procedure **C** (8.2.1), the deprotection of PMB-ether **3.28** (510 mg, 1.56 mmol) with DDQ (390 mg, 1.72 mmol) afforded after purification by column chromatography (petroleum ether/acetone 75:25 to 70:30) the *title compound* **3.61** as a

colourless oil (172 mg, 54%). **Formula** $C_8H_{14}O_4S$; **Mw** 206.26; $\mathbf{R_f}$ 0.30 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ +60.9 (*c* 0.76, $CHCl_3$, 26 °C); **IR** (film) 3447 (br. w), 2923 (w), 2882 (w), 2359 (w), 1789 (m), 1736 (s), 1210 (s), 1076 (s), 1045 (s), 1000 (vs), 731 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.81 (1 H, d, *J* = 5.3 Hz, H-1), 4.73 (1 H, dt, *J* = 4.0, 1.5 Hz, H-3), 4.68 (1 H, d, *J* = 11.5 Hz, H-7), 4.64 (1 H, d, *J* = 11.5 Hz, H-7'), 4.58 (1 H, dtd, *J* = 8.5, 6.6, 4.9 Hz, H-5), 4.08 (1 H, dd, *J* = 10.3, 4.1 Hz, H-2), 4.05–4.00 (2 H, m, H-2' and H-6), 3.63 (1 H, dd, *J* = 9.3, 6.9 Hz, H-6'), 2.89 (1 H, ddt, *J* = 8.7, 5.3, 1.1 Hz, H-4), 2.18 (3 H, s, H-8), 2.05 (1 H, d, *J* = 4.9 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 109.2 (CH, C-1), 76.4 (CH, C-3), 74.3 (CH_2, C-2), 73.7 (CH_2, C-7), 73.2 (CH_2, C-6), 70.1 (CH, C-5), 53.4 (CH, C-4), 13.9 (CH_3, C-8) ppm; **LRMS** (ESI^+) *m*/*z* 229.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_8H_{14}O_4S$ Na $(M + Na)^+$ calcd 229.0505, found 229.0504.

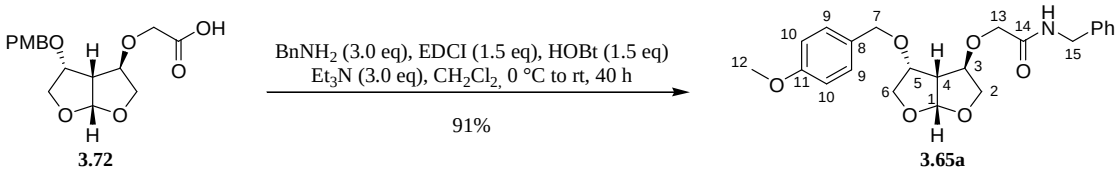
2-((1*S*,4*R*,5*R*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yloxy) acetic acid (3.72)



A flask was charged with NaH (81 mg, 2.02 mmol, 60% in mineral oil). The solid was rinsed with hexane three times, dried under vacuum, diluted with THF (3 mL) and cooled to 0 °C. A solution of bromoacetic acid (267 mg, 1.92 mmol) in THF (5 mL) was added dropwise and the mixture was stirred for 10 min. A second flask was charged with NaH (54 mg, 1.34 mmol, 60% in mineral oil) and the solid was treated as described above. A solution of alcohol **3.26** (255 mg, 0.96 mmol) in THF (5 mL) was added and the mixture was stirred for 10 min. The content of the first flask was then transferred to the second flask via cannula, the cooling was remove, and the resulting mixture was heated to reflux for 15 h. After completion, the reaction mixture was cooled to rt, diluted with THF (10 mL) and H_2O (10 mL), acidified with 2 M HCl (5 mL), and extracted with EtOAc (3 × 25 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to give the desired product in sufficient purity. For characterisation, the crude product was further purified by column chromatography (CH_2Cl_2/MeOH 97:3 to 90:10) to afford the *title compound* **3.72** as a pale yellow oil (292 mg, 93%). **Formula** $C_{16}H_{20}O_7$; **Mw** 324.33; $\mathbf{R_f}$ 0.20 (CH_2Cl_2/MeOH 90:10); $\mathbf{[\alpha]_D}$ +17.9 (c 0.99, $CHCl_3$, 25 °C); **IR** (film) 2937 (br. w), 1733 (m), 1612 (w), 1514 (s), 1247 (s), 1123 (vs), 1026 (vs), 820

(m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2 H, d, *J* = 8.7 Hz, H-9), 6.90 (2 H, d, *J* = 8.8 Hz, H-10), 5.81 (1 H, d, *J* = 5.3 Hz, H-1), 4.53 (1 H, d, *J* = 11.4 Hz, H-7), 4.49 (1 H, d, *J* = 11.4 Hz, H-7'), 4.48 (1 H, d, *J* = 3.8 Hz, H-3), 4.24 (1 H, ddd, *J* = 8.8, 8.0, 6.7 Hz, H-5), 4.13 (1 H, d, *J* = 16.8 Hz, H-13), 4.08 (1 H, dt, *J* = 10.3, 1.3 Hz, H-2), 4.07 (1 H, d, *J* = 16.8 Hz, H-13'), 4.00 (1 H, dd, *J* = 10.3, 3.9 Hz, H-2'), 3.96 (1 H, dd, *J* = 9.2, 6.6 Hz, H-6), 3.81 (3 H, s, H-12), 3.58 (1 H, dd, *J* = 9.2, 8.0 Hz, H-6'), 3.00 (1 H, dd, *J* = 9.0, 5.2 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 173.8 (C, C-14), 159.5 (C, C-11), 129.4 (C, C-8), 129.3 (2 × CH_{ar}, C-9), 114.0 (2 × CH_{ar}, C-10), 108.7 (CH, C-1), 80.5 (CH, C-3), 76.3 (CH, C-5), 73.6 (CH_2, C-2), 72.4 (CH_2, C-7), 70.8 (CH_2, C-6), 65.9 (CH_2, C-13), 55.3 (CH_3, C-12), 51.9 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 347.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{16}H_{20}O_7Na$ $(M + Na)^+$ calcd 347.1101, found 347.1096.

2-((1*S*,4*R*,5*R*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yloxy) *N*-benzyl acetamide (3.65a)

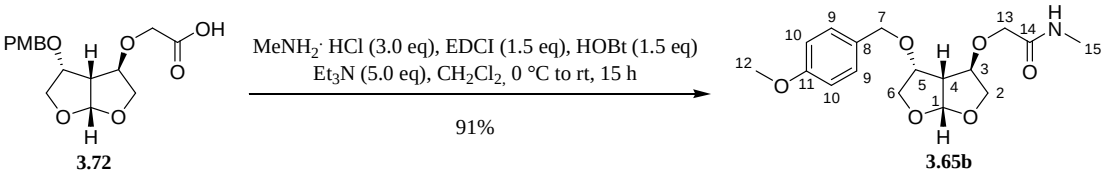


3.72 **3.65a**

Following general procedure **D** (8.2.1), the reaction of acid **3.72** (517 mg, 1.40 mmol) and benzyl amine (460 µL, 4.20 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 96:4) the *title compound* **3.65a** as a colourless oil (527 mg; 91%). **Formula** $C_{23}H_{27}NO_6$; **Mw** 413.46; **R_f** 0.23 (hexane/acetone 65:35); **[α]$_D$** +25.2 (c 1.01, $CHCl_3$, 25 °C); **IR** (film) 3349 (w), 2934 (w), 1666 (s), 1513 (vs), 1247 (s), 1118 (s), 1028 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.27 (5 H, m, Ar-H), 7.23 (2 H, d, *J* = 8.7 Hz, H-9), 6.90 (2 H, d, *J* = 8.7 Hz, H-10), 6.82 (1 H, br. s, N*H*Bn), 5.75 (1 H, d, *J* = 5.1 Hz, H-1), 4.54–4.43 (4 H, m, H-7, H-7', H-15 and H-15'), 4.41 (1 H, d, *J* = 3.5 Hz, H-3), 4.22 (1 H, ddd, *J* = 9.0, 7.9, 6.7 Hz, H-5), 4.03 (1 H, m, *J* = 10.5 Hz can be observed, H-2), 4.02 (1 H, d, *J* = 15.2 Hz, H-13), 3.97 (1 H, d, *J* = 15.2 Hz, H-13'), 3.97 (1 H, dd, *J* = 10.5, 3.5 Hz, H-2'), 3.94 (1 H, dd, *J* = 9.2, 6.5 Hz, H-6), 3.82 (3 H, s, H-12), 3.57 (1 H, dd, *J* = 9.2, 7.9 Hz, H-6'), 2.89 (1 H, m, *J* = 8.9, 5.1 Hz can be observed, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 170.0 (C, C-14), 170.0 (C_{ar}, C-11), 137.9 (C_{ar}), 129.4 (2 × CH_{ar}, C-9), 129.3 (C_{ar}), 128.7 (2 × CH_{ar}), 127.8 (2 × CH_{ar}), 127.6 (CH_{ar}), 114.0 (2 × CH_{ar}, C-10), 108.6 (CH, C-1), 80.7 (CH, C-3), 76.3 (CH, C-5), 73.8 (CH_2, C-2), 72.5 (CH_2, C-7), 71.0 (CH_2, C-6), 68.4 (CH_2, C-13), 55.3 (CH_3, C-12), 51.7 (CH, C-4), 42.9

(CH_2, C-15) ppm; **LRMS** (ESI^+) *m*/*z* 436.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{23}H_{27}NO_6Na$ $(M + Na)^+$ calcd 436.1731, found 436.1734.

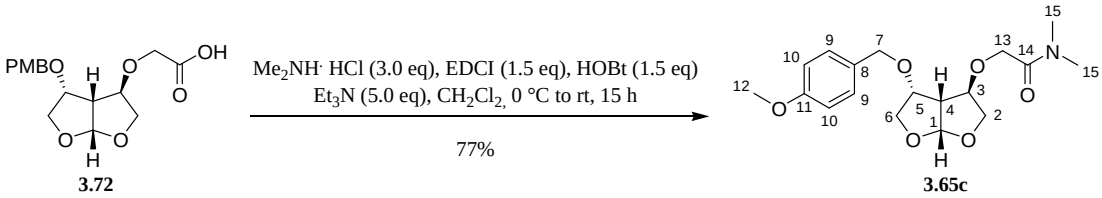
2-((1*S*,4*R*,5*R*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yloxy) *N*-methyl acetamide (3.65b)



3.72 **3.65b**

Following general procedure **D** (8.2.1), the reaction of acid **3.72** (505 mg, 1.36 mmol) and methylamine hydrochloride (275 mg, 4.20 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) the *title compound* **3.65b** as a colourless oil (417 mg, 91%). **Formula** $C_{17}H_{23}NO_6$; **Mw** 337.37; $\mathbf{R}_f$ 0.34 (CH_2Cl_2/MeOH 95:5); **IR** (film) 3369 (br. w), 2940 (w), 2880 (w), 1663 (s), 1612 (m), 1542 (m), 1514 (s), 1247 (s), 1119 (s), 1027 (vs), 821 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.24 (2 H, d, *J* = 8.8 Hz, H-9), 6.90 (2 H, d, *J* = 8.7 Hz, H-10), 6.49 (1 H, br. s, N*H*Me), 5.80 (1 H, d, *J* = 5.2 Hz, H-1), 4.51 (1 H, d, *J* = 11.7 Hz, H-7), 4.48 (1 H, d, *J* = 11.7 Hz, H-7'), 4.40 (1 H, dt, *J* = 3.6, 1.1 Hz, H-3), 4.24 (1 H, ddd, *J* = 9.0, 7.9, 6.6 Hz, H-5), 4.04 (1 H, dt, *J* = 10.5, 1.1 Hz, H-2), 3.98 (1 H, dd, *J* = 10.5, 3.6 Hz, H-2'), 3.97 (1 H, d, *J* = 14.9 Hz, H-13), 3.96 (1 H, dd, *J* = 9.2, 6.6 Hz, H-6), 3.91 (1 H, d, *J* = 14.9 Hz, H-13'), 3.82 (3 H, s, H-12), 3.58 (1 H, dd, *J* = 9.2, 7.9 Hz, H-6'), 2.91 (1 H, ddt, *J* = 8.9, 5.1, 1.0 Hz, H-4), 2.84 (3 H, d, *J* = 5.1 Hz, H-15) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 169.6 (C, C-14), 159.6 (C_{ar}, C-11), 129.4 ($2 \times CH_{ar}$, C-9), 129.3 (C_{ar}, C-8), 114.0 ($2 \times CH_{ar}$, C-10), 108.7 (CH, C-1), 80.6 (CH, C-3), 76.4 (CH, C-5), 73.9 (CH_2, C-2), 72.6 (CH_2, C-7), 71.0 (CH_2, C-6), 68.4 (CH_2, C-13), 55.3 (CH_3, C-12), 51.8 (CH, C-4), 25.5 (CH_3, C-15) ppm; **LRMS** (ESI^+) *m*/*z* 360.2 $(M + Na)^+$.

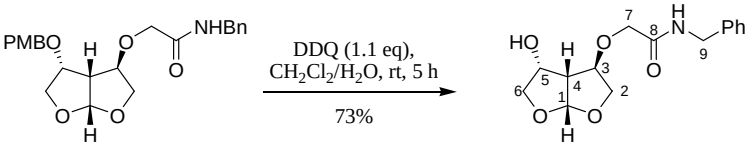
2-((1*S*,4*R*,5*R*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yloxy) *N*,*N*-dimethyl acetamide (3.65c)



3.72 **3.65c**

Following general procedure **D** (8.2.1), the reaction of acid **3.72** (540 mg, 1.66 mmol) and dimethylamine hydrochloride (407 mg, 5.00 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) the *title compound* **3.65c** as a colourless oil (449 mg, 77%). **Formula** $C_{18}H_{25}NO_6$; **Mw** 351.39; $\mathbf{R_f}$ 0.44 (CH_2Cl_2/MeOH 95:5); **IR** (film) 2936 (w), 2875 (w), 1650 (s), 1612 (m), 1513 (s), 1248 (s), 1113 (vs), 1026 (vs), 822 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.27 (2 H, d, *J* = 8.7 Hz, H-9), 6.89 (2 H, d, *J* = 8.7 Hz, H-10), 5.80 (1 H, d, *J* = 5.3 Hz, H-1), 4.58 (1 H, d, *J* = 11.2 Hz, H-7), 4.47 (1 H, d, *J* = 11.2 Hz, H-7'), 4.45 (1 H, dt, *J* = 3.9, 1.3 Hz, H-3), 4.24 (1 H, ddd, *J* = 9.0, 8.1, 6.7 Hz, H-5), 4.18 (1 H, d, *J* = 13.6 Hz, H-13), 4.10 (1 H, d, *J* = 13.6 Hz, H-13'), 4.09 (1 H, dt, *J* = 10.4, 1.3 Hz, H-2), 3.99 (1 H, dd, *J* = 10.5, 3.9 Hz, H-2'), 3.96 (1 H, dd, *J* = 9.1, 6.7 Hz, H-6), 3.82 (3 H, s, H-12), 3.58 (1 H, dd, *J* = 9.2, 8.0 Hz, H-6'), 3.04 (1 H, ddt, *J* = 9.0, 5.2, 1.1 Hz, H-4), 2.97 (3 H, s, H-15), 2.94 (3 H, s, H-15) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.7 (C, C-14), 159.4 (C_{ar}, C-11), 129.6 (C_{ar}, C-8), 129.3 ($2 \times CH_{ar}$, C-9), 113.9 ($2 \times CH_{ar}$, C-10), 108.8 (CH, C-1), 80.2 (CH, C-3), 76.6 (CH, C-5), 73.9 (CH_2, C-2), 72.2 (CH_2, C-7), 70.8 (CH_2, C-6), 68.3 (CH_2, C-13), 55.3 (CH_3, C-12), 51.9 (CH, C-4), 36.4 (CH_3, C-15), 35.5 (CH_3, C-15) ppm; **LRMS** (ESI^+) *m*/*z* 374.2 $(M + Na)^+$.

2-((1*S*,4*R*,5*R*,6*R*)-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yloxy) *N*-benzyl acetamide (3.67a)

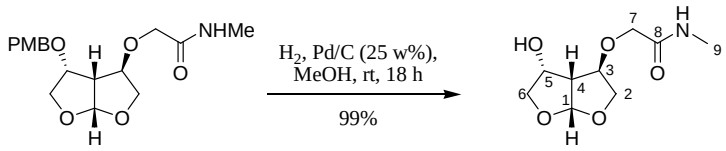


3.65a **3.67a**

Following general procedure **C** (8.2.1), the deprotection of PMB-ether **3.65a** (345 mg, 0.83 mmol) with DDQ (210 mg, 0.92 mmol) afforded after purification by column chromatography (petroleum ether/acetone 75:25 to 50:50) the *title compound* **3.67a** as a

white solid (179 mg, 73%). **Formula** $C_{15}H_{19}NO_5$; **Mw** 292.32; $\mathbf{R_f}$ 0.38 (petroleum ether/ acetone 50:50); **Mp** 132–134 °C; $\mathbf{[\alpha]_D}$ +34.0 (c 0.79, $CHCl_3$, 29 °C); **IR** (film) 3427 (m), 3336 (m), 2882 (w), 2360 (w), 1651 (vs), 1538 (s), 1116 (vs), 1056 (m), 1018 (vs), 1003 (s), 953 (m), 934 (m), 892 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40–7.28 (5 H, m, Ar-H), 6.88 (1 H, br. s, NH, exchanges in D_2O), 5.76 (1 H, d, *J* = 5.1 Hz, H-1), 4.59–4.42 (4 H, m, H-3, H-5, H-9 and H-9'), 4.10–4.02 (4 H, m, H-2, H-2', H-7 and H -7'), 3.99 (1 H, dd, *J* = 9.3, 6.5 Hz, H-6), 3.57 (1 H, dd, *J* = 9.3, 7.4 Hz, H-6'), 2.83 (1 H, dd, *J* = 8.6, 5.2 Hz, H-4), 2.79 (1 H, d, *J* = 4.6 Hz, OH, exchanges in D_2O) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 169.4 (C, C-8), 137.7 (C_{ar}), 128.8 ($2 \times CH_{ar}$), 127.8 ($2 \times CH_{ar}$), 128.7 (CH_{ar}), 109.0 (CH, C-1), 80.3 (CH, C-3), 74.0 (CH_2, C-2), 73.1 (CH_2, C-6), 69.6 (CH, C-5), 68.4 (CH_2, C-7), 53.1 (CH, C-4), 42.9 (CH_2, C-9) ppm.; **LRMS** (ESI+) *m*/*z* 316.2 $(M + Na)^+$; **HRMS** (ESI+) for $C_{15}H_{19}NO_5Na$ $(M + Na)^+$ calcd 316.1155, found 316.1154.

2-((1*S*,4*R*,5*R*,6*R*)-6-Hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yloxy) *N*-methyl acetamide (3.67b)

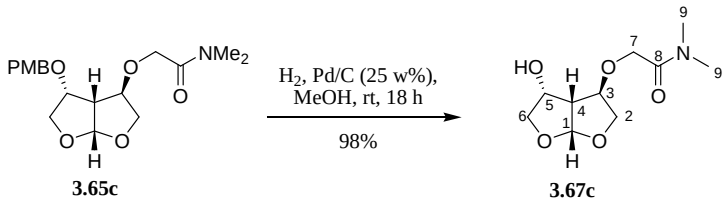


3.65b **3.67b**

To a solution of ether **3.65b** (580 mg, 1.72 mmol) in MeOH (20 mL) under N_2 was added Pd/C (145 mg, 25 w%, 10% Pd). The flask was then put under H_2-atmosphere and the reaction was stirred at rt for 18 h. After completion the reaction mixture was filtered over celite and the filter cake was washed with MeOH. The solvent was removed in vacuo to afford the *title compound* **3.67b** as a white solid (421 mg, 99%) in sufficient purity. **Formula** $C_9H_{15}NO_5$; **Mw** 217.22; $\mathbf{R_f}$ 0.30 (CH_2Cl_2/MeOH 93:7); **Mp** 128 °C; $\mathbf{[\alpha]_D}$ +31.8 (c 0.48, $CHCl_3$, 26 °C); **IR** (film) 3401 (m), 3343 (m), 2965 (w), 2882 (w), 1652 (vs), 1549 (m), 1332 (m), 1118 (vs), 1020 (s), 1003 (s), 953 (s), 638 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.56 (1 H, br. s, N*H*Me, disappears after D_2O-shake), 5.82 (1 H, d, *J* = 5.1 Hz, H-1), 4.59 (1 H, dtd, *J* = 8.7, 6.8, 4.7 Hz, simplifies to dt, *J* = 8.7, 6.7 Hz, after D_2O-shake, H-5), 4.48 (1 H, m, H-3), 4.06–4.00 (4 H, m, H-2, H-2', H-6 and H-7), 3.96 (1 H, d, *J* = 15.1 Hz, H-7'), 3.60 (1 H, dd, *J* = 9.4, 7.2 Hz, H-6'), 2.86 (3 H, d, *J* = 5.0 Hz, simplifies to s after D_2O-shake, H-9), 2.87 (1 H, m, H-4), 2.73 (1 H, d, *J* = 4.8 Hz, OH, disappears after D_2O-shake) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 170.0 (C, C-8), 109.1 (CH,

C-1), 80.2 (CH, C-3), 74.1 (CH_2, C-2), 73.2 (CH_2, C-6), 69.7 (CH, C-5), 68.3 (CH_2, C-7), 53.1 (CH, C-4), 25.6 (CH_3, C-9) ppm; **LRMS** (ESI^+) *m/z* 240.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_9H_{15}NO_5Na$ $(M + Na)^+$ calcd 240.0842, found 240.0845.

2-((1*S*,4*R*,5*R*,6*R*)-6-Hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane-4-yloxy) *N,N*-dimethyl acetamide (3.67c)

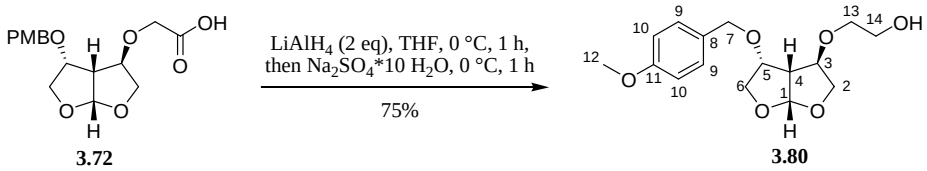


3.65c **3.67c**

To a solution of ether **3.65c** (665 mg, 1.89 mmol) in MeOH (15 mL) under N_2 was added Pd/C (165 mg, 25 w%, 10% Pd). The flask was then put under H_2-atmosphere and the reaction was stirred at rt for 18 h. After completion the reaction mixture was filtered over celite and the filter cake was washed with MeOH. The solvent was removed in vacuo to afford the *title compound* **3.67c** as a colourless oil (477 mg, 98%) in sufficient purity. **Formula** $C_{10}H_{17}NO_5$; **Mw** 231.25; $\mathbf{R_f}$ 0.23 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$ +63.1 (c 1.13, $CHCl_3$, 26 °C); **IR** (film) 3384 (br. w), 2938 (w), 2878 (w), 1635 (s), 1111 (s), 1019 (s), 1003 (s), 930 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.77 (1 H, d, *J* = 5.3 Hz, H-1), 4.55 (1 H, td, *J* = 8.4, 6.8 Hz, H-5), 4.50 (1 H, dt, *J* = 4.8, 2.4 Hz, H-3), 4.28 (1 H, d, *J* = 14.2 Hz, H-7), 4.10 (1 H, d, *J* = 14.3 Hz, H-7'), 4.09 (1 H, dd, *J* = 10.2, 4.9 Hz, H-2), 4.01 (1 H, dd, *J* = 9.0, 6.7 Hz, H-6), 3.96 (1 H, ddd, *J* = 10.0, 2.5, 0.9 Hz, H-2'), 3.53 (1 H, t, *J* = 8.7 Hz, H-6'), 3.01 (3 H, s, H-9), 2.97 (3 H, s, H-9), 2.93 (1 H, dd, *J* = 8.4, 5.5, 2.4 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 169.8 (C, C-8), 109.1 (CH, C-1), 79.5 (CH, C-3), 73.7 (CH_2, C-2), 72.5 (CH_2, C-6), 69.8 (CH, C-5), 68.3 (CH_2, C-7), 53.6 (CH, C-4), 36.4 (CH_3, C-9), 35.6 (CH_3, C-9) ppm; **LRMS** (ESI+) *m/z* 254.1 $(M + Na)^+$; **HRMS** (ESI+) for $C_{10}H_{17}NO_5Na$ $(M + Na)^+$ calcd 254.0999, found 254.1001.

8.2.2.3 Synthesis fluorinated *O*-alk(en)yl analogues

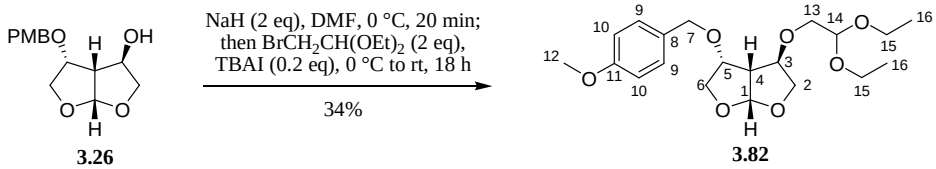
2-((1*S*,4*R*,5*R*,6*R*)-6-(4-Methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yloxy) ethanol (3.80)



3.72 **3.80**

To a stirred solution of acid **3.72** (2.05 g, 6.3 mmol) in THF (15 mL) at 0 °C was added $LiAlH_4$ (12.6 mL, 12.6 mmol, 1 M in THF). After 1 h, $Na_2SO_4 \cdot 10\ H_2O$ (2.0 g) were added slowly and the mixture was stirred for further 60 min at 0 °C until the gas evolution has stopped. The crude mixture was filtered over celite and the filter cake was washed with CH_2Cl_2 (2 × 15 mL). The solvent was removed in vacuo to afford the *title compound* **3.80** as a colourless oil (1.47 g, 75%) in sufficient purity. **Formula** $C_{16}H_{22}O_6$; **Mw** 310.34; $\mathbf{R_f}$ 0.21 (petroleum ether/acetone 70:30); **IR** (film) 3443 (br. w), 2936 (w), 2875 (w), 1612 (m), 1514 (s), 1247 (s), 1109 (s), 1027 (vs), 821 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2 H, d, *J* = 8.7 Hz, H-9), 6.90 (2 H, d, *J* = 8.7 Hz, H-10), 5.80 (1 H, d, *J* = 5.2 Hz, H-1), 4.53 (1 H, d, *J* = 11.3 Hz, H-7), 4.49 (1 H, d, *J* = 11.3 Hz, H-7'), 4.39 (1 H, dt, *J* = 3.9, 1.3 Hz, H-3), 4.24 (1 H, ddd, *J* = 8.9, 8.1, 6.6 Hz, H-5), 4.07 (1 H, dt, *J* = 10.2, 1.2 Hz, H-2), 3.99 (1 H, dd, *J* = 10.2, 3.9 Hz, H-2'), 3.96 (1 H, dd, *J* = 9.2, 6.6 Hz, H-6), 3.82 (3 H, s, H-12), 3.73 (2 H, dt, *J* = 6.2, 4.5 Hz, H-14), 3.59 (1 H, dd, *J* = 9.2, 8.2 Hz, H-6'), 3.54 (2 H, t, *J* = 4.5 Hz, H-13), 2.95 (1 H, ddt, *J* = 9.0, 5.2, 1.1 Hz, H-4), 1.99 (1 H, t, *J* = 6.2 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 129.5 (C_{ar}, C-8), 129.3 (2 × CH_{ar}, C-9), 114.0 (2 × CH_{ar}, C-10), 108.8 (CH, C-1), 79.9 (CH, C-3), 76.6 (CH, C-5), 74.1 (CH_2, C-2), 72.4 (CH_2, C-7), 70.9 (CH_2, C-6), 70.2 (CH_2, C-13), 61.8 (CH_2, C-14), 55.3 (CH_3, C-12), 51.9 (CH, C-4) ppm; LRMS (ESI^+) *m*/*z* 333.2 $(M + Na)^+$.

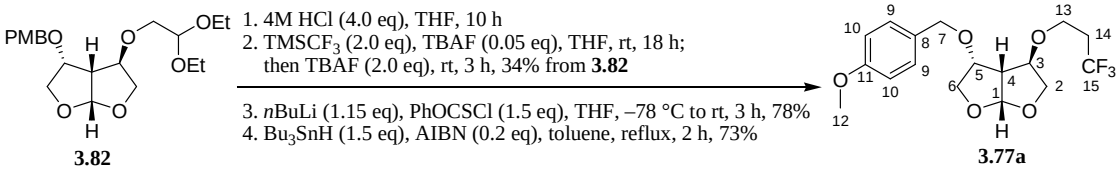
(1*S*,4*R*,5*R*,6*R*)-4-(2,2-Diethoxy-ethoxy)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.82)



3.26 **3.82**

To a stirred solution of alcohol **3.26** (817 mg, 3.07 mmol) in dry DMF (15 mL) at 0 °C was added NaH (245 mg, 6.14 mmol, 60% in mineral oil). After 20 min, bromoacetaldehyde diethyl acetal (940 µL, 6.14 mmol) and TBAI (225 mg, 0.61 mmol) were added and the resulting mixture was stirred at 0 °C for 20 min and at rt for further 18 h. The reaction was quenched carefully with citric acid (5 mL, 10 %), diluted with H_2O (20 mL) and the mixture was extracted with Et_2O (3 × 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 90:10 to 75:25) successively afforded the *title compound* **3.82** as a colourless oil (402 mg, 34%) and starting alcohol **3.26** (271 mg, 33%). **Formula** $C_{20}H_{30}O_7$; **Mw** 382.45; $\mathbf{R_f}$ 0.80 (petroleum ether/acetone 70:30); **IR** (film) 2974 (w), 2931 (w), 2874 (w), 1612 (w), 1514 (m), 1248 (m), 1119 (vs), 1124 (s), 1028 (vs), 821 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2 H, d, *J* = 8.5 Hz, H-9), 6.90 (1 H, d, *J* = 8.7 Hz, H-10), 5.79 (1 H, d, *J* = 5.3 Hz, H-1), 4.59 (1 H, t, *J* = 5.1 Hz, H-14), 4.55 (1 H, d, *J* = 11.2 Hz, H-7), 4.47 (1 H, d, *J* = 11.2 Hz, H-7'), 4.42 (1 H, dt, *J* = 3.9, 1.2 Hz, H-3), 4.22 (1 H, ddd, *J* = 8.8, 8.0, 6.6 Hz, H-5), 4.07 (1 H, dt, *J* = 10.2, 1.3 Hz, H-2), 3.98 (1 H, dd, *J* = 10.1, 3.8 Hz, H-2'), 3.95 (1 H, dd, *J* = 9.0, 6.5 Hz, H-6), 3.82 (3 H, s, H-12), 3.76−3.66 (2 H, m, H-15), 3.61−3.52 (3 H, m, H-6' and H-15), 3.51 (1 H, dd, *J* = 10.5, 5.2 Hz, H-13), 3.48 (1 H, dd, *J* = 10.5, 5.4 Hz, H-13'), 2.98 (1 H, ddt, *J* = 8.9, 5.2, 1.2 Hz, H-4), 1.22 (6 H, t, *J* = 7.1 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 129.6 (C_{ar}, C-8), 129.3 (2 × CH_{ar}, C-9), 114.0 (2 × CH_{ar}, C-10), 109.0 (CH, C-1), 101.2 (CH, C-14), 80.2 (CH, C-3), 76.5 (CH, C-5), 74.3 (CH_2, C-2), 72.2 (CH_2, C-7), 70.9 (CH_2, C-6), 70.1 (CH_2, C-13), 62.6 (CH_2, C-15), 62.5 (CH_2, C-15), 55.3 (CH_3, C-12), 51.8 (CH, C-4), 15.4 (CH_3, C-15), 15.3 (CH_3, C-15) ppm; **LRMS** (ESI+) *m*/*z* 405.3 $(M + Na)^+$.

(1*R*,4*R*,5*S*,6*R*)-6-(4-Methoxybenzyloxy)-4-(3,3,3-trifluoropropoxy)-2,8-dioxa-bicyclo-[3.3.0]-octane (3.77a)



3.82 **3.77a**

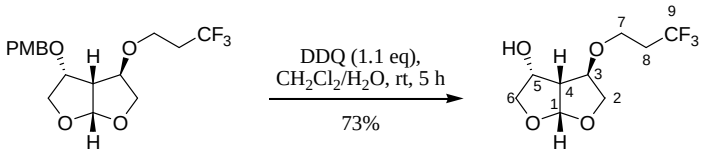
To a solution of acetal **3.82** (400 mg, 1.05 mmol) in THF (15 mL) was added aq. HCl (1 mL, 4.00 mmol, 4 M) and the resulting mixture was stirred at rt and monitored by TLC. When the majority of starting material was consumed, the reaction was neutralised with aq. sat. $NaHCO_3$ (10 mL) and the mixture was extracted with EtOAc (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford the crude aldehyde **3.78** (359 mg) as a pale yellow oil.

Following literature procedures,[111] a solution of crude aldehyde **3.78** (359 mg, 1.0 mmol) in dry THF (15 mL) was treated with $TMSCF_3$ (1.0 mL, 2.00 mmol, 2 M in THF) and cat. TBAF (50 µL, 0.05 mmol, 1 M in THF) and the resulting mixture was stirred at rt. After 18 h, TBAF (2.0 mL, 2.00 mmol, 1 M in THF) was added and the reaction was stirred for further 3 h. The reaction was quenched with H_2O (15 mL) and extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 80:20 to 60:40) afforded the two diastereoisomers of trifluoromethyl alcohol **3.79** as a pale yellow oil (130 mg, 34 %; $\mathbf{R}_f$ 0.40 (petroleum ether/acetone 70:30), ^{19}F NMR δ −77.77 (d, J = 6.4 Hz), −77.84 (d, J = 6.4 Hz) ppm).

Transformation to trifluoropropyl ether **3.77a** was achieved in two steps via Barton-McCombie deoxygenation.[115] To a solution of diastereomeric alcohol **3.79** (253 mg, 0.64 mmol) in dry THF (10 mL) at −78 °C was added *n*BuLi (300 µL, 0.74 mmol, 2.5 M in hexanes) and *O*-phenyl chlorothiono formate (1.35 µL, 1.00 mmol) and the reaction was stirred for 1 h at −78 °C and for further 2 h at rt. After completion, the reaction was quenched with aq. sat. $NaHCO_3$ (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/EtOAc 80:20 to 70:30) afforded the thionocarbonate **3.83** as a colourless oil (257 mg, 73 %; $\mathbf{R}_f$ 0.19 (petroleum ether/EtOAc 80:20), ^{19}F NMR δ −74.64 (d, J = 6.2 Hz), −74.62 (d, J = 6.2 Hz) ppm).

To a solution of thionocarbonate **3.83** (2.55 mg, 0.50 mmol) in toluene (5 mL) was added tributyltin hydride (202 µL, 0.75 mmol) and AIBN (17 mg, 0.1 mmol) and the reaction was heated to reflux for 2 h. After completion, all volatiles were removed on vacuo and the crude product was purified by column chromatography (petroleum ether/EtOAc 80:20 to 70:30) to afford the *title compound* **3.77a** as a colourless oil (132 mg, 73%). **Formula** $C_{17}H_{21}F_3O_5$; **Mw** 362.34; $\mathbf{R_f}$ 0.16 (petroleum ether/EtOAc 80:20); $\mathbf{[\alpha]_D}$ +11.9 (c 0.45, $CHCl_3$, 23 °C); **IR** (film) 2956 (w), 2879 (w), 1612 (m), 1514 (m), 1249 (vs), 1145 (s), 1124 (s), 1026 (vs), 822 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2 H, d, *J* = 8.7 Hz, H-9), 6.91 (1 H, d, *J* = 8.7 Hz, H-10), 5.78 (1 H, d, *J* = 5.2 Hz, H-1), 4.53 (1 H, d, *J* = 11.4 Hz, H-7), 4.49 (1 H, d, *J* = 11.4 Hz, H-7'), 4.35 (1 H, dt, *J* = 3.9, 1.2 Hz, H-3), 4.24 (1 H, ddd, *J* = 8.7, 8.2, 6.7 Hz, H-5), 4.03 (1 H, dt, *J* = 10.2, 1.1 Hz, H-2), 3.97 (1 H, dd, *J* = 10.4, 3.9 Hz, H-2'), 3.97 (1 H, dd, *J* = 9.0, 6.8 Hz, H-6), 3.82 (3 H, s, H-12), 3.62 (2 H, ddt, *J* = 15.7, 9.7, 6.6 Hz, H-13), 3.58 (1 H, dd, *J* = 9.0, 8.3 Hz, H-6'), 2.91 (1 H, ddt, *J* = 9.0, 5.2, 1.2 Hz, H-4), 2.39 (2 H, qtd, *J* = 10.6, 6.7, 0.6 Hz, H-14) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 129.5 (C_{ar}, C-8), 129.3 (2 × CH_{ar}, C-9), 126.0 (CF_3, q, *J* = 277.0 Hz, C-15), 114.0 (2 × CH_{ar}, C-10), 108.8 (CH, C-1), 79.9 (CH, C-3), 76.5 (CH, C-5), 73.8 (CH_2, C-2), 72.4 (CH_2, C-7), 70.9 (CH_2, C-6), 61.9 (CH_2, d, *J* = 3.7 Hz, C-13), 55.3 (CH_3, C-12), 51.9 (CH, C-4), 34.5 (CH_2, q, *J* = 28.8 Hz, C-14) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$): δ −65.0 (t, *J* = 10.5 Hz, F-15); **LRMS** (ESI+) *m*/*z* 385.2 $(M + Na)^+$, 426.2 $(M + Na + MeCN)^+$.

(1*S*,4*R*,5*R*,6*R*)-6-Hydroxy-4-(3,3,3-trifluoropropoxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.74)

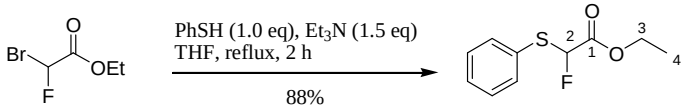


3.77a **3.74**

Following general procedure **C** (8.2.1), the deprotection of PMB-ether **3.77a** (125 mg, 0.34 mmol) with DDQ (90 mg, 0.37 mmol) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **3.74** as a colourless oil (60 mg, 73%). **Formula** $C_9H_{13}F_3O_4$; **Mw** 242.19; $\mathbf{R_f}$ 0.34 (petroleum ether/ acetone 70:30); $\mathbf{[\alpha]_D}$ +30.8 (c 0.41, $CHCl_3$, 23 °C); **IR** (film) 3439 (br. w), 2953 (w), 2885 (w), 1383 (w), 1254 (s), 1146 (s), 1120 (s), 1006 (s), 962 (m), 933 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.80 (1 H, d, *J* = 5.3 Hz, H-1), 4.57 (1 H, m, H-5), 4.38 (1 H, dt, *J* =

3.8, 1.2 Hz, H-3), 4.06 (1 H, dt, *J* = 10.1, 1.2 Hz, H-2), 4.01 (1 H, dd, *J* = 10.1, 3.8 Hz, H-2'), 4.01 (1 H, dd, *J* = 9.5, 6.5 Hz, H-6), 3.66 (2 H, td, *J* = 6.7, 1.7 Hz, H-7), 3.62 (1 H, dd, *J* = 9.5, 6.7 Hz, H-6'), 2.86 (1 H, ddt, *J* = 8.6, 5.2, 1.1 Hz, H-4), 2.41 (2 H, qt, *J* = 10.7, 6.7 Hz, H-8), 1.91 (1 H, d, *J* = 5.1 Hz, O*H*) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 126.0 (CF_3, q, *J* = 275.2 Hz, C-9), 109.1 (CH, C-1), 79.5 (CH, C-3), 74.0 (CH_2, C-2), 73.4 (CH_2, C-6), 70.0 (CH, C-5), 61.9 (CH_2, d, *J* = 3.7 Hz, C-7), 53.2 (CH, C-4), 34.4 (CH_2, q, *J* = 28.9 Hz, C-8) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$): δ −65.0 (t, *J* = 10.5 Hz, F-9); **LRMS** (ESI+) *m*/*z* 306.1 $(M + Na+MeCN)^+$; **HRMS** (ESI+) for $C_9H_{13}F_3O_4Na$ $(M + Na)^+$ calcd 265.0658, found 265.0665.

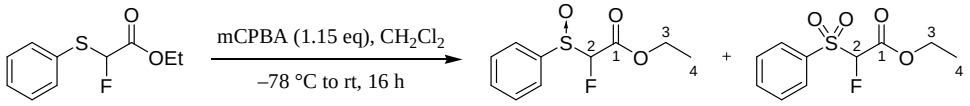
Ethyl 2-Fluoro-2-phenylsulfanyl-acetate (3.91)



3.91

Sulfide **3.91** was synthesised according to literature procedure.[164] To a stirred solution of ethyl bromofluoroacetate (10.0 mL, 84.6 mmol) in dry THF (120 ml) were added successively Et_3N (17.6 ml, 126.9 mmol) and thiophenol (8.6 ml, 84.6 mmol) and the mixture was heated to reflux for 2 h. The precipitate was removed by filtration and the filtrate was concentrated under reduced pressure (T < 35 °C). The residue was purified by distillation to afford the *title compound* **3.91** as a colourless oil (16.0 g, 88%). **Formula** $C_{10}H_{11}FO_2S$; **Mw** 214.26; **Bp** 148−150 °C / 20 mbar (lit.[164] 125 °C / 18 mbar); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.60−7.54 (2 H, m, Ar-H), 7.41−7.33 (3 H, m, Ar-H), 6.08 (1 H, d, *J* = 52.1 Hz, H-2), 4.15 (2 H, q, *J* = 7.2 Hz, H-3), 1.20 (3 H, t, *J* = 7.2 Hz, H-4) ppm; **^{13}C NMR + DEPT** (75 MHz, $CDCl_3$) δ 163.7 (CO, d, *J* = 27.3 Hz, C-1), 134.1 (2 × CH_{ar}), 129.4 (CH_{ar}), 129.2 (2 × CH_{ar}), 94.3 (CH, d, *J* = 233 Hz, C-2), 62.3 (CH_2, C-3), 13.9 (CH_3, C-4) ppm. **^{19}F NMR** (282 MHz, $CDCl_3$) δ −158.4 (d, *J* = 52.1 Hz) ppm. The ^{1}H, ^{13}C and ^{19}F NMR spectra correspond to the reported data.[164]

Ethyl 2-Fluoro-2-phenylsulfinyl-acetate (3.87)

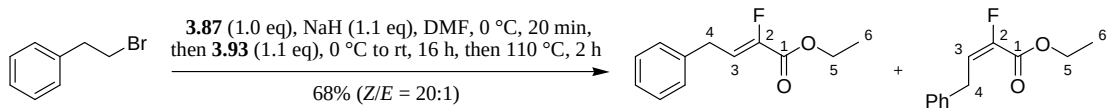


3.91 **3.87** (89%) **3.92** (6%)

Sulfoxide **3.87** was synthesised according to literature procedure.[120] To a solution of sulfide **3.91** (16.0 g, 74.5 mmol) in CH_2Cl_2 (150 mL) at −78 °C was added 3-chloro-perbenzoic acid (19.71 g, 85.7 mmol, 75%). The reaction was stirred overnight and allowed to slowly warm to rt. After completion, the mixture was filtered and the filtrate washed with aq. sat. $NaHCO_3$ and aq. sat. NH_4Cl, dried over anhydrous Na_2SO_4u, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/EtOAc = 90:10 to 60:40) afforded the *title compound* **3.87** as a colourless oil (15.37 g, 89%) and sulfone **3.92** as a white solid (1.12 g, 6%) Sulfoxide **3.87** is a mixture of diastereomers due to asymmetric centres on sulfur and carbon. **Formula** $C_{10}H_{11}FO_3S$; **Mw** 230.26; $\mathbf{R_f}$ 0.20 (petroleum ether/EtOAc 80:20); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.74−7.67 (2 H, m, Ar-H), 7.62−7.53 (3 H, m, Ar-H), 5.70 (0.7 H, d, *J* = 50.0 Hz, major H-2), 5.70 (0.3 H, d, *J* = 48.2 Hz, minor H-2), 4.23 (2 H, q, *J* = 7.2 Hz, H-3), 1.25 (0.9 H, t, *J* = 7.2 Hz, minor H-4), 1.24 (2.1 H, t, *J* = 7.2 Hz, major H-4) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −191.9 (d, *J* = 47.8 Hz, minor), −192.7 (d, *J* = 50.0 Hz, major) ppm. The ^{1}H and ^{19}F NMR spectra correspond to the reported data.[120]

Byproduct: Ethyl 2-Fluoro-2-phenylsulfonyl-acetate (**3.92**): **Formula** $C_{10}H_{11}FO_4S$; **Mw** 246.26; $\mathbf{R_f}$ 0.30 (petroleum ether/EtOAc 80:20); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.02−7.91 (2 H, m, Ar-H), 7.80−7.56 (3 H, m, Ar-H), 5.58 (1 H, d, *J* = 47.9 Hz, H-2), 4.30 (2 H, q, *J* = 7.2 Hz, H-3), 1.29 (3 H, t, *J* = 7.2 Hz, H-4) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −180.6 (d, J = 47.8 Hz) ppm. The ^{1}H and ^{19}F NMR spectra correspond to the reported data.[165]

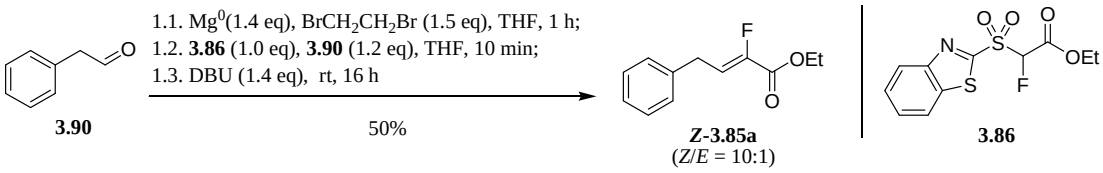
(*Z*)-2-Fluoro-4-phenyl-but-2-enoic acid ethyl ester (*Z*-3.85a)



3.93 *Z*-**3.85a** *E*-**3.85a**

***Method A*:**[121] Ethyl fluorophenylsulfinylacetate (**3.87**, 2.30 g, 10.0 mmol) was added to a suspension of sodium hydride (440 mg, 11.0 mmol, 60% in mineral oil) in DMF (14 mL) at

0 °C and stirred for 20 min. Then (2-Bromoethyl)benzene (**3.93**, 1.50 mL, 11 mmol) was added and the reaction mixture was first stirred for 16 h at rt. After heating to at 110 °C for 2 h, the mixture was poured on ice/aq. sat. NH_4Cl (100 mL) and the solution was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried over $NaSO_4$, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/EtOAc 98:2) afforded the desired alkene *Z*-**3.85a** (1.42 g, 68%, *Z*/*E* = 20:1) as a colourless oil.

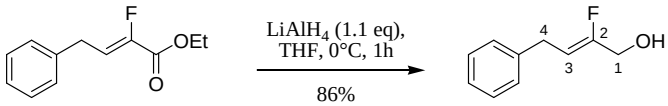


***Method B*:**[117] Dibromoethane (0.128 mL, 1.48 mmol, 1.5 equiv) was added dropwise to a suspension of Mg^0 (35 mg, 1.40 mmol) in THF (5 mL) at 20 °C under N_2. After disappearance of all magnesium (ca. 1 h of stirring), a solution containing 2-phenyl-acetaldehyde (**3.90**, 145 mg, 1.20 mmol) and sulfone **3.86** (303 mg, 1.00 mmol) in THF (2 mL) was added dropwise. After further 10 min, DBU (210 µL, 1.40 mmol) was added dropwise, and the solution was stirred for 16 h at rt. The reaction was quenched with a sat. aq. NH_4Cl (1 mL) and brine (2 mL), then extracted with Et_2O (20 mL). The organic layer was washed with brine, dried over $NaSO_4$, filtered, solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/EtOAc 98:2) afforded the corresponding alkene mixture **3.85a** (104 mg, 50%, *Z*/*E* = 10:1). Further separation by HPLC (hexane/EtOAc 97:3) afforded the pure isomers *Z*-**3.85a** (84 mg, 0.40 mmol) and *E*-**3.85b** (7 mg, 0.03 mmol) both as colourless oils. **Formula** $C_{12}H_{13}FO_2$; **Mw** 208.23; $\mathbf{R_f}$ 0.28 (hexane/EtOAc 97:3); **IR** (film) 3065 (w), 3030 (w), 2983 (w), 2939 (w), 1732 (vs), 1677 (m), 1371 (m), 1302 (s), 1256 (s), 1188 (m), 1104 (s), 747 (m), 698 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36–7.30 (2 H, m, Ar-H), 7.28–7.20 (3 H, m, Ar-H), 6.30 (1 H, dt, *J* = 32.2, 8.0 Hz, H-3), 4.29 (2 H, q, *J* = 7.2 Hz, H-5), 3.60 (2 H, dd, *J* = 8.0, 2.3 Hz, H-4), 1.34 (3 H, t, *J* = 7.1 Hz, H-6) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 160.7 (CO, d, *J* = 35.5 Hz, C-1), 147.9 (CF, d, *J* = 256.8 Hz, C-2), 137.9 (C_{ar}, d, *J* = 1.9 Hz), 128.7 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.7 (CH_{ar}), 118.9 (CH, d, *J* = 11.4 Hz, C-3), 61.7 (CH_2, C-5), 30.5 (CH_2, d, *J* = 3.2 Hz, C-4), 14.1 (CH_3, C-6) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −130.7 (d, *J* = 32.2 Hz) ppm; **LRMS** (EI^+) *m*/*z* (%) 91 ($[C_6H_5]^+$, 20), 115 ($[C_9H_7]^+$, 87), 131 (60), 133 ($[C_9H_6F]^+$, 85), 135 ($[C_9H_8F]^+$, 100), 158.9 (36), 179.9 ([M-

$C_2H_5]^+$, 20), 207.9 ([$M^{+\bullet}$], 27); **HRMS** (EI^+) for $C_{12}H_{13}FO_2$ ($M^{+\bullet}$) calcd 208.0900, found 208.0899.

Byproduct: (*E*)-2-Fluoro-4-phenyl-but-2-enoic acid ethyl ester (*E*-**12**): **Formula** $C_{12}H_{13}FO_2$; **Mw** 208.23; $\mathbf{R}_f$ 0.35 (hexane/EtOAc 97:3); **IR** (film) 3063 (w), 3029 (w), 2984 (w), 2939 (w), 1727 (vs), 1375 (s), 1348 (m), 1300 (m), 1234 (vs), 1129 (m), 699 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.35–7.29 (2 H, m, Ar-H), 7.27–7.21 (3 H, m, Ar-H), 6.09 (1 H, dt, *J* = 20.9, 8.3 Hz, H-3), 4.36 (2 H, q, *J* = 7.1 Hz, H-5), 3.91 (2 H, dd, *J* = 8.3, 1.5 Hz, H-4), 1.38 (3 H, t, *J* = 7.2 Hz, H-6) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 161.0 (CO, d, *J* = 35.2 Hz, C-1), 147.1 (CF, d, *J* = 253.4 Hz, C-2), 138.8 (C_{ar}, d, *J* = 1.9 Hz), 128.7 (2 × CH_{ar}), 128.4 (2 × CH_{ar}), 126.6 (CH_{ar}), 121.9 (CH, d, *J* = 19.4 Hz, C-3), 61.5 (CH_2, C-5), 31.6 (CH_2, d, *J* = 5.8 Hz, C-4), 14.1 (CH_3, C-6) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −122.0 (d, *J* = 21.0 Hz) ppm; **LRMS** (EI^+) *m*/*z*(%) 77 ([$C_6H_5]^+$, 14), 91 ([$C_7H_7]^+$, 10), 115 ([$C_9H_7]^+$, 59), 131 (95), 133 ([$C_9H_6F]^+$, 100), 135 ([$C_9H_8F]^+$, 43), 158.9 (50), 179.9 ([M−$C_2H_5]^+$, 26), 207.9 ([$M^{+\bullet}$], 30); **HRMS** (EI^+) for $C_{12}H_{13}FO_2$ ($M^{+\bullet}$) calcd 208.0900, found 277.0898.

(*Z*)-2-Fluoro-4-phenyl-but-2-en-1-ol (3.95)

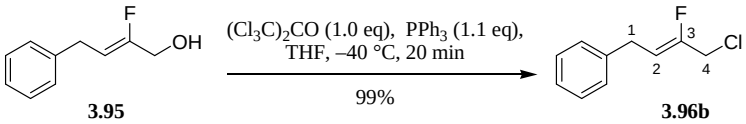


Z-**3.85a** **3.95**

To a solution of ester *Z*-**3.85a** (75 mg, 0.36 mmol) in THF (5 mL) at 0 °C was added $LiAlH_4$ (0.43 mL, 0.43 mmol, 1M in THF) and the resulting mixture was stirred at 0 °C. After 1 h $Na_2SO_4 \cdot 10\ H_2O$ (0.3 g, 0.91 mmol) was added and the reaction was stirred for further 30 min. After completion the mixture was diluted with CH_2Cl_2 (15 mL) and filtered over celite. The filter cake was washed with CH_2Cl_2 (2 × 10 mL) and the combined filtrates were concentrated in vacuo. Purification of the crude product by column chromatography (petroleum ether/EtOAc 85:15) afforded the *title compound* **3.95** as a pale yellow oil (51.6 mg, 86%). **Formula** $C_{10}H_{11}FO$; **Mw** 166.19; $\mathbf{R}_f$ 0.23 (hexane/EtOAc 85:15); **IR** (film) 3335 (br. m), 3063 (w), 3028 (w), 2925 (w), 2685 (w), 1709 (m), 1495 (m), 1454 (m), 1071 (m), 1012 (s), 745 (m), 698 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.28 (2 H, m, Ar-H), 7.25–7.19 (3 H, m, Ar-H), 5.08 (1 H, dt, *J* = 35.8, 7.7 Hz, H-3), 4.17 (2 H, dd, *J* = 15.3, 6.3 Hz, H-1), 3.48 (2 H, d, *J* = 7.7 Hz, H-4), 1.72 (3 H, td, *J* = 6.4, 1.8 Hz, OH) ppm;

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 157.8 (CF, d, *J* = 256.1 Hz, C-2), 139.8 (C_{ar}, d, *J* = 1.7 Hz), 128.5 (2 × CH_{ar}), 128.3 (2 × CH_{ar}), 126.2 (CH_{ar}), 106.9 (CH, d, *J* = 13.6 Hz, C-3), 61.3 (CH_2, d, *J* = 32.3 Hz, C-1), 29.7 (CH_2, d, *J* = 4.9 Hz, C-4) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −121.1 (dt, *J* = 35.7, 15.4 Hz) ppm; **LRMS** (EI^+) *m*/*z* (%) 91 ($[C_7H_7]^+$, 16), 115 ($[C_9H_7]^+$, 66), 134.9 ($[C_9H_8F]^+$, 100), 146.9 ($[C_{10}H_{11}O]^+$, 41), 165.9 ($[M^{+\bullet}]$, 18); **HRMS** (EI^+) for $C_{12}H_{13}FO$ ($M^{+\bullet}$) calcd 166.0794, found 166.0797.

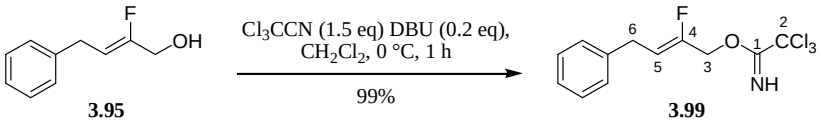
1-((*Z*)-4-Chloro-3-fluorobut-2-enyl)-benzene (3.96b)



3.95 **3.96b**

To a solution of alcohol **3.95** (930 mg, 5.60 mmol) in THF (20 mL) at −40 °C was added PPh_3 (1.61 g, 6.16 mmol) and hexachloroacetone (850 µL, 5.6 mmol). The resulting mixture was stirred at −40 °C for 20 min. After completion, the solvent was removed in vacuo and purification of the crude product by column chromatography (petroleum ether/EtOAc 97:3 to 95:5) afforded the *title compound* **3.96b** as a colourless oil (1.02 g, 99%). **Formula** $C_{10}H_{10}ClF$; **Mw** 184.64; **R_f** 0.55 (petroleum ether/EtOAc 95:5); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.19 (5 H, m, Ar-H), 5.17 (1 H, dt, *J* = 33.6, 7.7 Hz, H-2), 4.10 (2 H, d, *J* = 18.1 Hz, H-4), 3.52 (2 H, dd, *J* = 7.7, 1.5 Hz, H-1) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 154.3 (CF, d, *J* = 253.9 Hz, C-3), 139.2 (C_{ar}, d, *J* = 1.7 Hz), 128.6 (2 × CH_{ar}), 128.3 (2 × CH_{ar}), 126.4 (CH_{ar}), 106.9 (CH, d, *J* = 14.3 Hz, C-2), 41.9 (CH_2, d, *J* = 32.2 Hz, C-4), 30.1 (CH_2, d, *J* = 4.4 Hz, C-1) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −117.1 (dt, *J* = 33.8, 18.0 Hz) ppm.

2,2,2-Trichloro-acetimidic acid (*Z*)-2-fluoro-4-phenyl-but-2-enyl ester (3.99)

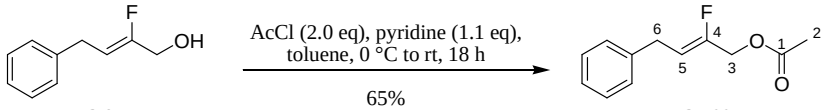


3.95 **3.99**

To a solution of alcohol **3.95** (1.48 g, 8.9 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added DBU (265 µL, 1.8 mmol) and trichloroacetonitrile (1.34 mL, 13.4 mmol). The resulting mixture was stirred at 0 °C for 1 h and monitored by TLC. After completion, the solvent was removed in vacuo and the crude product was purified by filtration over a prewashed silica plug (petroleum ether/EtOAc 95: 5) to afford the *title compound* **3.99** as a pale yellow

oil (2.75 g, 99%). **Formula** $C_{12}H_{11}Cl_3FNO$; **Mw** 310.58; $\mathbf{R_f}$ 0.75 (petroleum ether/EtOAc 90:10); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.45 (1 H, br. s, NH), 7.35–7.17 (5 H, m, Ar-H), 5.27 (1 H, dt, *J* = 34.6, 7.7 Hz, H-5), 4.86 (2 H, d, *J* = 16.4 Hz, H-3), 3.52 (2 H, d, *J* = 7.8 Hz, H-6) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −119.0 (dt, *J* = 34.9, 16.4 Hz) ppm.

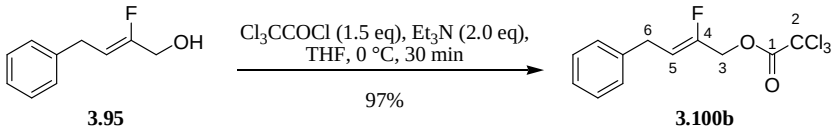
Acetic acid (*Z*)-2-fluoro-4-phenyl-but-2-enyl ester (3.100a)



3.95 **3.100a**

Acetyl chloride (504 µL, 7.10 mmol) was added slowly to a stirred solution of alcohol **3.95** (590 mg, 3.55 mmol) and pyridine (324 µL, 4.00 mmol) in toluene (15 mL) at 0 °C and stirring was continued for 18 h while the mixture warmed to rt. After completion, the reaction was cooled to −78 °C and H_2O (2 mL) was added slowly. The warmed mixture was washed with sat. aq. $NaHCO_3$ (5 mL), the phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/EtOAc 95:5 to 85:15) afforded the *title compound* **3.100a** as a colourless oil (477 mg, 65%). **Formula** $C_{12}H_{13}FO_2$; **Mw** 208.23; $\mathbf{R_f}$ 0.59 (petroleum ether/EtOAc 85:15); **IR** (film) 3063 (w), 3029 (w), 2941 (w), 1740 (vs), 1453 (m), 1364 (m), 1217 (vs), 1160 (m), 1028 (s), 934 (m), 746 (s), 698 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.34–7.29 (2 H, m, Ar-H), 7.25–7.19 (3 H, m, Ar-H), 5.16 (1 H, dt, *J* = 34.6, 7.7 Hz, H-5), 4.62 (2 H, d, *J* = 17.3 Hz, H-3), 3.49 (2 H, dd, *J* = 7.7, 1.5 Hz, H-6), 2.12 (3 H, s, H-2) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 170.4 (CO, C-1), 153.9 (CF, d, *J* = 255.0 Hz, C-4), 139.4 (C_{ar}), 128.6 (2 × CH_{ar}), 128.3 (2 × CH_{ar}), 126.3 (CH_{ar}), 110.3 (CH, d, *J* = 13.2 Hz, C-5), 62.1 (CH_2, d, *J* = 31.1 Hz, C-3), 29.8 (CH_2, d, *J* = 4.4 Hz, C-6), 20.8 (CH_3 C-2) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −118.8 (dt, *J* = 34.7, 17.4 Hz, F-4) ppm.

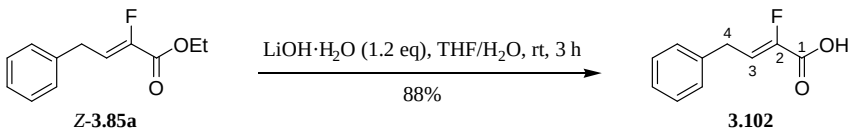
Trichloroacetic acid (*Z*)-2-fluoro-4-phenyl-but-2-enyl ester (3.100b)



3.95 **3.100b**

Trichloroacetyl chloride (640 µL, 5.70 mmol) was added slowly to a stirred solution of alcohol **3.95** (625 mg, 3.80 mmol) and Et_3N (1.05 mL, 7.60 mmol) in THF (10 mL) at 0 °C and stirring was continued at this temperature for 30 min. After completion, the reaction was quenched by the careful addition of sat. aq. $NaHCO_3$ (10 mL) and Et_2O (10 mL). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 15 mL). The combined organic phases were washed with sat. aq. NH_4Cl and H_2O (10 mL each), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/EtOAc 95:5 to 90:10) afforded the *title compound* **3.100b** as a colourless oil (1.15 g, 97%). **Formula** $C_{12}H_{10}Cl_3FO_2$; **Mw** 311.56; $\mathbf{R_f}$ 0.75 (petroleum ether/EtOAc 85:15); **IR** (film) 3064 (w), 3029 (w), 2957 (w), 1766 (vs), 1496 (m), 1454 (m), 1216 (vs), 973 (m), 826 (s), 747 (m), 698 (s), 682 (s) cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.36–7.28 (2 H, m, Ar-H), 7.27–7.18 (3 H, m, Ar-H), 5.32 (1 H, dt, *J* = 33.9, 7.7 Hz, H-5), 4.89 (2 H, d, *J* = 17.2 Hz, H-3), 3.52 (2 H, dd, *J* = 7.8, 1.8 Hz, H-6) ppm; **^{13}C NMR + DEPT** (75 MHz, $CDCl_3$) δ 163.8 (CO, C-1), 152.0 (CF, d, *J* = 255.4 Hz, C-4), 138.8 (C_{ar}), 128.6 (2 × CH_{ar}), 128.3 (2 × CH_{ar}), 126.5 (CH_{ar}), 112.7 (CH, d, *J* = 13.0 Hz, C-5), 77.2 (CCl_3, C-2), 66.3 (CH_2, d, *J* = 31.8 Hz, C-3), 29.9 (CH_2, d, *J* = 4.1 Hz, C-6) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −119.4 (dt, *J* = 35.0, 17.1 Hz, F-4) ppm.

(*Z*)-2-Fluoro-4-phenyl-but-2-enoic acid (3.102)

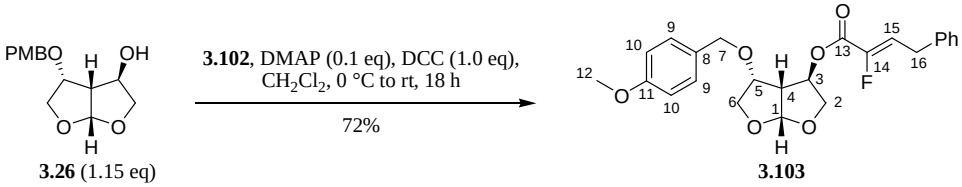


Z-**3.85a** **3.102**

To a solution of $LiOH·H_2O$ (313 mg, 7.4 mmol) in THF/H_2O (4 mL, 1:1) was added a solution of ester *Z*-**3.85a** (1.294 g, 6.2 mmol) in THF (6 mL) and the resulting mixture was stirred at rt for 3 h. After completion, the solvent was removed in vacuo and the crude product was redissolved in Et_2O/H_2O (10 mL each). The phases were separated and the aqueous phase was extracted with Et_2O (2 × 10 mL). The combined organic phases were

washed with aq. HCl (5 mL, 1M), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford the *title compound* **3.102** as a white solid (981 mg, 88%). **Formula** $C_{10}H_9FO_2$; **Mw** 180.19; **Mp** 98−100 °C; **IR** (neat) 3063 (br. m), 3028 (m), 2865 (br. m), 2550 (w), 1688 (vs), 1666 (s), 1449 (s), 1291 (m), 1262 (s), 1114 (s), 940 (s), 738 (m), 695 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.52 (1 H, br. s, OH), 7.38–7.18 (5 H, m, Ar-H), 6.47 (1 H, dt, *J* = 31.6, 8.0 Hz, H-3), 3.60 (2 H, dd, *J* = 8.0, 2.1 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 165.6 (CO, d, *J* = 35.9 Hz, C-1), 147.0 (CF, d, *J* = 253.9 Hz, C-2), 137.4 (C_{ar}), 128.8 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.9 (CH_{ar}), 122.0 (CH, d, *J* = 11.0 Hz, C-3), 30.7 (CH_2, d, *J* = 2.6 Hz, C-4) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −131.7 (d, *J* = 31.6 Hz, F-2) ppm.

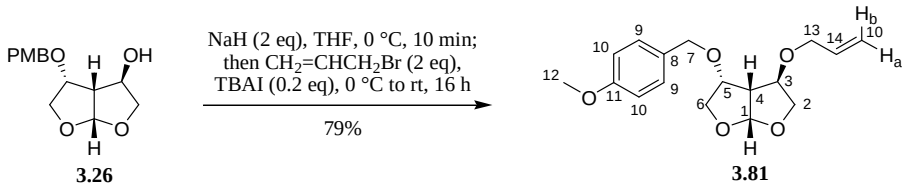
(*Z*)-2-Fluoro-4-phenyl-but-2-enoic acid (1*S*,4*R*,5*R*,6*R*)-6-(4-methoxybenzyloxy)-2,8-dioxabicyclo[3.3.0]-octane-4-yl ester (3.103)



To a solution of acid **3.102** (570 mg, 3.15 mmol), alcohol **3.26** (882 mg, 3.31 mmol) and DMAP (39 mg, 0.32 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added a solution of DCC (603 mg, 3.15 mmol) in CH_2Cl_2 (3 mL) and the resulting mixture was stirred at this temperature for 10 min. The cooling was removed and the reaction was stirred at rt for further 18 h. After completion, the urea precipitate was filtered off and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15 to 50:50) afforded successively the *title compound* **3.103** as a pale yellow oil (1.02 g, 72%) and alcohol **3.26** (133 mg, 15%). **Formula** $C_{24}H_{25}FO_6$; **Mw** 428.45; **R_f** 0.40 (petroleum ether/acetone 75:25); **$[\alpha]_D$** +38.6 (*c* 0.75, $CHCl_3$, 27 °C); **IR** (film) 2933 (w), 2880 (w), 1731 (s), 1514 (m), 1302 (m), 1249 (s), 1110 (s), 1029 (vs), 949 (m), 761 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.37−7.20 (7 H, m, Ar-H); 6.89 (2 H, d, *J* = 8.7 Hz, H-10), 6.32 (1 H, dt, *J* = 32.0, 8.0 Hz, H-15), 5.84 (1 H, d, *J* = 5.2 Hz, H-1), 5.66 (1 H, d, *J* = 3.0 Hz, H-3), 4.66 (1 H, d, *J* = 11.2 Hz, H-7), 4.53 (1 H, d, *J* = 11.2 Hz, H-7'), 4.26 (1 H, ddd, *J* = 9.1, 7.9, 6.7 Hz, H-5), 4.13 (1 H, dd, *J* = 11.0, 3.3 Hz, H-2), 4.08 (1 H, dd, *J* = 11.0, 1.0 Hz, H-2'), 3.98 (1 H, dd, *J* = 9.3, 6.7 Hz, H-6), 3.81 (3 H, s, H-12), 3.63 (1 H, dd, *J* = 9.5, 8.0 Hz, H-6'), 3.60 (2 H, dd, *J* = 8.0, 2.3 Hz, H-16), 3.00 (1 H, ddt, *J* =

9.1, 5.2, 1.0 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 160.2 (C, d, *J* = 36.2 Hz, C-13), 159.5 (C_{ar}, C-11), 147.4 (CF, d, *J* = 256.1 Hz, C-14), 137.6 (C_{ar}, d, *J* = 1.8 Hz), 129.6 (2 × CH_{ar}, C-9), 129.3 (C_{ar}, C-8), 128.8 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.8 (CH_{ar},), 120.0 (CH, d, *J* = 11.3 Hz, C-15), 114.0 (2 × CH_{ar}, C-10), 108.9 (CH, C-1), 79.9 (CH, C-3), 76.3 (CH, C-5), 74.6 (CH_2, C-2), 72.6 (CH_2, C-7), 71.0 (CH_2, C-6), 55.3 (CH_3, C-12), 51.4 (CH, C-4), 30.5 (CH_2, d, *J* = 3.3 Hz, C-16) ppm; **^{19}F NMR** (282 MHz, CDCl3) δ −130.6 (d, *J* = 32.0 Hz, F-14) ppm; **LRMS** (ESI^+) *m/z* 451.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{24}H_{25}FO_6Na$ $(M + Na)^+$ calcd. 451.1527; found 451.1534.

(1*R*,4*R*,5*S*,6*R*)-4-Allyloxy-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.81)

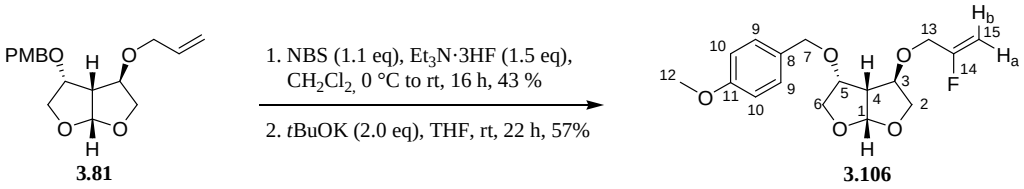


3.26 **3.81**

To a stirred solution of alcohol **3.26** (1.05 g, 3.93 mmol) in THF (15 mL) at 0 °C was added NaH (314 mg, 7.86 mmol, 60% in mineral oil). After 10 min, allyl bromide (680 µL, 7.86 mmol) and TBAI (291 mg, 0.79 mmol) were added and the resulting mixture was stirred at 0 °C for 20 min and at rt for further 16 h. The reaction was quenched carefully with H_2O (20 mL) and Et_2O (20 mL). The phases were separated and the aqueous layer was extracted with Et_2O (2 × 20 mL). The combined organic layers were washed with aq. sat. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 95:5 to 85:15) afforded the *title compound* **3.81** as a colourless oil (950 mg, 79%). **Formula** $C_{17}H_{22}O_5$; **Mw** 306.35; **R_f** 0.25 (petroleum ether/acetone 85:15); **$[\alpha]_D$** +15.4 (*c* 1.0, $CHCl_3$, 27 °C); **IR** (film) 2937 (m), 2874 (m), 1612 (m), 1514 (s), 1249 (s), 1120 (s), 1027 (vs), 821 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2 H, d, *J* = 8.7 Hz, H-9), 6.90 (2 H, d, *J* = 8.7 Hz, H-10), 5.92 (1 H, ddt, *J* = 17.2, 10.4, 5.6 Hz, H-14), 5.81 (1 H, d, *J* = 5.2 Hz, H-1), 5.30 (1 H, dq, *J* = 17.3, 1.6 Hz, H-15b), 5.20 (1 H, d, *J* = 10.4, 1.4 Hz, H-15a), 4.55 (1 H, d, *J* = 11.4 Hz, H-7), 4.48 (1 H, d, *J* = 11.4 Hz, H-7'), 4.40 (1 H, dt, *J* = 3.9, 1.2 Hz, H-3), 4.24 (1 H, ddd, *J* = 8.9, 8.3, 6.7 Hz, H-5), 4.07 (1 H, dt, *J* = 10.1, 1.3 Hz, H-2), 4.03−3.93 (4 H, m, H-2', H-6, H-13 and H-13'), 3.82 (3 H, s, H-12), 3.59 (1 H, dd, *J* = 9.0, 8.3 Hz, H-6'), 2.96 (1 H, ddt, *J* = 9.0, 5.2, 1.1 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.5 (C_{ar}, C-11), 134.5 (CH, C-14), 129.6 (C_{ar}, C-8), 129.3 (2 × CH_{ar}, C-9), 117.3 (CH_2,

C-15), 113.9 (2 × CH_{ar}, C-10), 108.9 (CH, C-1), 78.9 (CH, C-3), 76.6 (CH, C-5), 74.2 (CH_2, C-2), 72.3 (CH_2, C-7), 70.8 (CH_2, C-6), 70.1 (CH_2, C-13), 55.3 (CH_3, C-12), 52.0 (CH, C-4) ppm; **LRMS** (ESI^+) *m*/*z* 329.2 $(M + Na)^+$.

(1*S*,4*R*,5*R*,6*R*)-4-(2-Fluoroallyloxy)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.106)

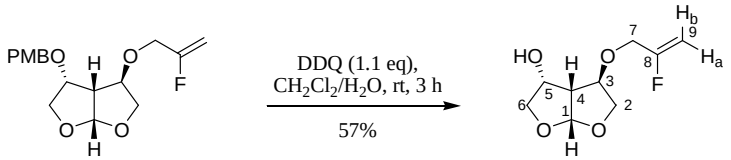


Fluoroalkene **3.106** was prepared in two steps, according to a literature procedure.[166] To a solution of allyl ether **3.81** (937 mg, 3.05 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added *N*-bromosuccinimide (600 mg, 3.36 mmol) and triethylamine tris(hydrofluoride) and stirred at this temperature for 15 min. The cooling was removed and the reaction was stirred at rt for further 16 h. The reaction was poured into ice water (50 mL), basified with aq. NH_3 (~ 1 mL, 35 w%) and the resulting mixture was extracted with CH_2Cl_2 (4 × 30 mL). The combined organic phases were washed with aq. HCl (10 mL, 0.1 N) and aq. $NaHCO_3$ (10 mL, 5 w%), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude by column chromatography (petroleum ether/acetone 90:10 to 80:20) successively afforded allyl ether **3.81** (433 mg, 46%) and bromofluoro ether **3.105** as a colourless oil (532 mg, 43%, 1:1 mixture of two diastereoisomers, $\mathbf{R}_f$ 0.29 (petroleum ether/acetone 80:20); **^{19}F NMR** δ −183.62 (dtdd, *J* = 46.5, 20.4, 19.9, 15.8 Hz), −183.62 (ddt, *J* = 46.4, 38.0, 19.0 Hz) ppm).

To a solution of bromofluoro ether **3.105** (800 mg, 1.97 mmol) in dry THF (15 mL) was added potassium *tert*-butoxide (443 mg, 3.94 mmol) and the reaction was stirred at rt for 22 h. The reaction was diluted with H_2O (15 mL) and the resulting mixture was extracted with Et_2O (3 × 20 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 90:10 to 75:25) afforded the *title compound* **3.106** as a colourless oil (363 mg, 57%). **Formula** $C_{17}H_{21}FO_5$; **Mw** 324.34; $\mathbf{R}_f$ 0.35 (petroleum ether/acetone 80:20); $\mathbf{[\alpha]_D}$ +15.1 (*c* 1.0, $CHCl_3$, 23 °C); **IR** (film) 2937 (w), 2875 (w), 1681 (m), 1514 (s), 1249 (s), 1119 (s), 1028 (vs), 931 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.25 (2 H, d, *J* = 8.7 Hz, H-9), 6.90 (1 H, d, *J* = 8.7 Hz, H-10), 5.81 (1 H, d, *J* = 5.3 Hz, H-1), 4.76 (1 H, dd, *J* = 16.5, 3.0 Hz, H-15a), 4.56 (1 H, ddt, *J* = 48.5,

3.0, 0.8 Hz, H-15b), 4.54 (1 H, d, *J* = 11.4 Hz, H-7), 4.48 (1 H, d, *J* = 11.4 Hz, H-7'), 4.46 (1 H, dt, *J* = 3.9, 1.2 Hz, H-3), 4.24 (1 H, ddd, *J* = 9.0, 8.2, 6.7 Hz, H-5), 4.06 (1 H, dt, *J* = 10.4, 1.3 Hz, H-2), 4.01−3.95 (4 H, m, H-2', H-6, H-13 and H-13'), 3.82 (3 H, s, H-12), 3.58 (1 H, dd, *J* = 9.1, 8.1 Hz, H-6'), 2.96 (1 H, ddt, *J* = 8.9, 5.2, 1.1 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 161.9 (CF, d, *J* = 237.1 Hz, C-14), 159.5 (C_{ar}, C-11), 129.5 (C_{ar}, C-8), 129.3 (2 × CH_{ar}, C-9), 114.0 (2 × CH_{ar}, C-10), 108.8 (CH, C-1), 93.1 (CH_2, d, *J* = 17.2 Hz, C-15), 79.5 (CH, C-3), 76.5 (CH, C-5), 73.9 (CH_2, C-2), 72.4 (CH_2, C-7), 70.8 (CH_2, C-6), 66.5 (CH_2, d, *J* = 33.3 Hz, C-13), 55.3 (CH_3, C-12), 52.1 (CH, C-4) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −105.6 (ddt, *J* = 48.5, 16.5, 13.2 Hz, F-14); **LRMS** (ESI^+) *m*/*z* 388.2 $(M + Na+MeCN)^+$.

(1*S*,4*R*,5*R*,6*R*)-4-(2-Fluoroallyloxy)-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.75a)

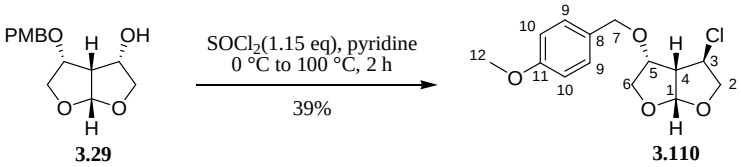


3.106 **3.75a**

Following general procedure **C** (8.2.1), the deprotection of PMB-ether **3.106** (340 mg, 1.05 mmol) with DDQ (262 mg, 1.15 mmol) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 70:30) the *title compound* **3.75a** as a colourless oil (123 mg, 57%). **Formula** $C_9H_{13}FO_4$; **Mw** 204.20; **R_f** 0.29 (petroleum ether/ acetone 70:30); **$[\alpha]_D$** +50.6 (*c* 1.0, $CHCl_3$, 25 °C); **IR** (film) 3434 (br. m), 2942 (w), 2879 (w), 1680 (m), 1219 (m), 1107 (s), 999 (vs), 928 (s), 849 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.82 (1 H, d, *J* = 5.3 Hz, H-1), 4.77 (1 H, dd, *J* = 16.5, 3.0 Hz, H-9a), 4.59 (1 H, ddt, *J* = 48.5, 3.0, 0.8 Hz, H-9b), 4.57 (1 H, dtd, *J* = 8.6, 6.5, 5.1 Hz, H-5), 4.49 (1 H, dt, *J* = 4.0, 1.2 Hz, H-3), 4.08 (1 H, dt, *J* = 10.2, 1.3 Hz, H-2), 4.05−3.99 (4 H, m, H-2', H-6, H-7 and H-7'), 3.62 (1 H, dd, *J* = 9.5, 6.7 Hz, H-6'), 2.90 (1 H, ddt, *J* = 8.6, 5.3, 1.2 Hz, H-4), 1.90 (1 H, d, *J* = 5.2 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 162.1 (CF, d, *J* = 259.1 Hz, C-8), 109.1 (CH, C-1), 162.1 (CH_2, d, *J* = 16.8 Hz, C-9), 79.2 (CH, C-3), 74.1 (CH_2, C-2), 73.3 (CH_2, C-6), 70.0 (CH, C-5), 66.5 (CH_2, d, *J* = 33.3 Hz, C-7), 53.5 (CH, C-4) ppm.; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −105.5 (ddt, *J* = 48.5, 16.5, 13.2 Hz, F-8) ppm; **LRMS** (ESI^+) *m*/*z* 268.2 $(M + Na+MeCN)^+$; **HRMS** (ESI^+) for $C_9H_{13}FO_4Na$ $(M + Na)^+$ calcd 227.0690, found 227.0689.

8.2.2.4 Synthesis of halogenated bis-THF analogues

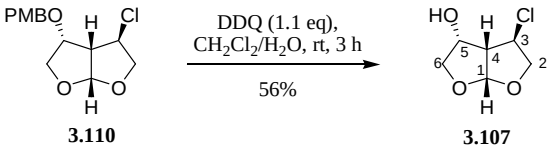
(1*S*,4*R*,5*S*,6*R*)-4-Chloro-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane (3.110)



3.29 **3.110**

To a solution of *endo*-alcohol **3.29** (1.00 g, 3.76 mmol) in pyridine (7 mL) at 0 °C was added thionyl chloride (330 µL, 4.50 mmol) and the resulting mixture was heated to 100 °C for 2 h. After cooling to rt, the reaction was poured into ice water (20 mL) and extracted with Et_2O (2 × 20 mL). The combined organic phases were washed with water and brine (5 mL each), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 90:10 to 80:20) afforded the *title compound* **3.110** as a white solid (422 mg, 39%). **Formula** $C_{14}H_{17}ClO_4$; **Mw** 284.74; $\mathbf{R_f}$ 0.40 (petroleum ether/acetone 80:20); **Mp** 74−76 °C; **IR** (film) 2936 (w), 2875 (w), 2837 (w), 1612 (m), 1514 (s), 1248 (s), 1110 (s), 1027 (vs), 921 (m), 821 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.26 (2 H, d, *J* = 8.7 Hz, H-9), 6.91 (2 H, d, *J* = 8.7 Hz, H-10), 5.90 (1 H, d, *J* = 5.1 Hz, H-1), 4.76 (1 H, dt, *J* = 4.2, 1.4 Hz, H-3), 4.55 (1 H, d, *J* = 11.2 Hz, H-7), 4.49 (1 H, d, *J* = 11.2 Hz, H-7'), 4.26 (1 H, dd, *J* = 10.6, 4.2 Hz, H-2), 4.21 (1 H, ddd, *J* = 8.8, 7.8, 6.7 Hz, H-5), 4.09 (1 H, dt, *J* = 10.6, 1.4 Hz, H-2'), 3.98 (1 H, dd, *J* = 9.3, 6.6 Hz, H-6), 3.83 (3 H, s, H-12), 3.62 (1 H, dd, *J* = 9.3, 7.8 Hz, H-6'), 3.18 (1 H, ddt, *J* = 9.0, 5.1, 1.4 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 159.6 (C_{ar}, C-11), 129.4 (2 × CH_{ar}, C-9), 129.2 (C_{ar}, C-8), 114.0 (2 × CH_{ar}, C-10), 108.8 (CH, C-1), 77.6 (CH_2, C-2), 76.6 (CH, C-5), 72.4 (CH_2, C-7), 70.9 (CH_2, C-6), 57.3 (CH, C-3), 55.8 (CH, C-4), 55.3 (CH_3, C-12) ppm; **LRMS** (ESI^+) *m*/*z* 348.1 $(M + Na+MeCN)^+$, 350.1 $(M + Na+MeCN)^+$.

(1*S*,4*R*,5*S*,6*R*)-4-Chloro-6-hydroxy-2,8-dioxa-bicyclo[3.3.0]-octane (3.107)

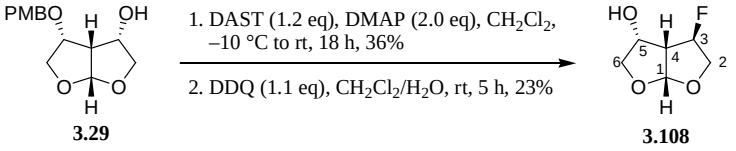


3.110 **3.107**

Following general procedure **C** (8.2.1), the deprotection of PMB-ether **3.110** (539 mg, 1.90 mmol) with DDQ (473 mg, 2.10 mmol) afforded after purification by column

chromatography (petroleum ether/acetone 90:10 to 70:30) the *title compound* **3.107** as a pale yellow oil (174 mg, 56%). **Formula** $C_6H_9ClO_3$; **Mw** 164.59; $\mathbf{R_f}$ 0.26 (petroleum ether/ acetone 70:30); $\mathbf{[\alpha]_D}$ +85.1 (*c* 0.68, $CHCl_3$, 26 °C); **IR** (film) 3430 (br. m), 2982 (w), 2941 (w), 2881 (w), 1309 (w), 1230 (m), 1107 (s), 1077 (m), 1016 (s), 946 (m), 919 (s), 886 (m), 578 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.91 (1 H, d, *J* = 5.2 Hz, H-1), 4.80 (1 H, dt, *J* = 4.1, 1.3 Hz, H-3), 4.56 (1 H, dtd, *J* = 8.8, 6.4, 4.5 Hz, H-5), 4.28 (1 H, dd, *J* = 10.5, 4.0 Hz, H-2), 4.12 (1 H, dt, *J* = 10.5, 1.2 Hz, H-2'), 4.04 (1 H, dd, *J* = 9.7, 6.3 Hz, H-6), 3.64 (1 H, dd, *J* = 9.6, 6.6 Hz, H-6'), 3.12 (1 H, ddt, *J* = 8.8, 5.2, 1.1 Hz, H-4), 2.13 (1 H, d, *J* = 4.7 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 109.0 (CH, C-1), 77.8 (CH_2, C-2), 73.3 (CH, C-5), 70.0 (CH_2, C-6), 57.2 (CH, C-3), 57.1 (CH, C-4) ppm; **LRMS** (CI^+) *m*/*z* (%) 128.0 (61), 129.0 (29), 146.0 (93), 148 (64), 182 (100, $(M+NH_4)^+$), 184 (33, $(M+NH_4)^+$); **HRMS** (ESI^+) for $C_6H_9ClO_3Na$ $(M+Na)^+$ calcd 187.0132, found 187.0132.

(1*S*,4*R*,5*S*,6*R*)-4-Fluoro-6-hydroxy-2,8-dioxa-bicylco-[3.3.0]-octane (3.108)

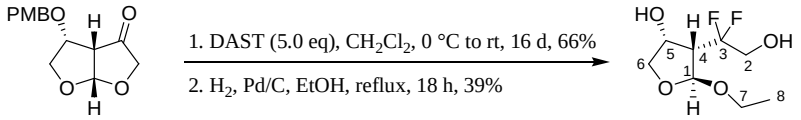


3.29 **3.108**

Diethylaminosulfur trifluoride (170 µL, 1.30 mmol) was added dropwise to a solution of alcohol **3.29** (285 mg, 1.07 mmol) and DMAP (260 mg, 2.14 mmol) in CH_2Cl_2 (2.5 mL) at −10 °C. The reaction was allowed to warm to rt and was stirred for further 18 h. After completion, the reaction mixture was cooled to −20 °C, quenched with MeOH (2 mL) and partitioned between CH_2Cl_2 and sat. aq. $NaHCO_3$ (8 mL each). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15 to 65:35) afforded fluoride **3.113** as a colourless oil (104 mg, 36%; $\mathbf{R_f}$ 0.38 (petroleum ether/acetone 80:20); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.25 (d, *J* = 8.6 Hz, 2 H), 6.91 (d, *J* = 8.8 Hz, 2 H), 5.87 (d, *J* = 5.2 Hz, 1 H), 5.44 (dd, *J* = 53.2, 3.1 Hz, 1 H), 4.54 (d, *J* = 11.3 Hz, 1 H), 4.49 (d, *J* = 11.3 Hz, 1 H), 4.27 (ddd, *J* = 9.1, 7.6, 6.6 Hz, 1 H), 4.21 (ddd, *J* = 23.0, 11.4, 1.6 Hz, 1 H), 4.05 (ddd, *J* = 39.6, 11.3, 3.0 Hz, 1 H), 3.96 (ddd, *J* = 9.4, 6.4, 1.2 Hz, 1 H), 3.83 (s, 3 H), 3.61 (dd, *J* = 9.4, 7.5 Hz, 1 H), 3.13 (dddd, J = 26.0, 9.1, 5.1, 1.5 Hz, 1 H) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −179.7 ppm).

Treatment of the PMB-ether **3.113** (285 mg, 1.07 mmol) with DDQ (270 mg, 1.20 mmol) according to general procedure **C** (8.2.1) afforded after purification by column chromatography (petroleum ether/acetone 80:20 to 60:40) the *title compound* **3.108** as a colourless oil (37.2 mg, 23%). **Formula** $C_6H_9FO_3$; **Mw** 148.13; $\mathbf{R_f}$ 0.25 (hexane/acetone 70:30); $\mathbf{[\alpha]_D}$ +21.2 (c 1.06, $CHCl_3$, 25 °C); **IR** (film) 3417 (br. m), 2982 (w), 2941 (w), 2883 (w), 1228 (m), 1110 (s), 1001 (s), 959 (vs), 926 (s), 856 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.87 (1 H, d, *J* = 5.1 Hz, H-1), 5.47 (1 H, dd, *J* = 53.0, 3.0 Hz, H-3), 4.61 (1 H, dtd, *J* = 8.8, 6.1, 4.8 Hz, H-5), 4.24 (1 H, ddd, *J* = 23.1, 11.3, 1.6 Hz, H-2), 4.08 (1 H, ddd, *J* = 39.7, 11.5, 2.9 Hz, H-2'), 4.01 (1 H, ddd, *J* = 9.8, 6.0, 1.1 Hz, H-6), 3.63 (1 H, dd, *J* = 9.7, 6.1 Hz, H-6'), 3.08 (1 H, dddd, *J* = 25.6, 8.8, 5.3, 1.8 Hz, H-4), 2.18 (1 H, d, *J* = 4.9 Hz, OH) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 109.1 (CH, C-1), 93.7 (CHF, d, *J* = 176.9 Hz, C-3), 75.4 (CH_2, d, *J* = 22.8 Hz, C-2), 73.6 (CH_2, C-6), 69.5 (CH, d, *J* = 9.7 Hz, C-5), 53.6 (CH, d, *J* = 22.1 Hz, C-4) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −180.4 (dddd, *J* = 53.0, 39.7, 25.6, 23.1 Hz) ppm; **LRMS** (CI^+) *m*/*z* (%) 44.1 (12), 68.0 (100), 69.0 (18), 110.9 (10), 128.9 (10), 148.9 ($[M+H]^+$, 5), 165.9 ($[M+NH_4]^+$, 14).

(3*R*,4*S*,5*S*)-4-(1,1-Difluoro-2-hydroxy-ethyl)-5-ethoxy-tetrahydro-furan-3-ol (3.116)



3.27 **3.116**

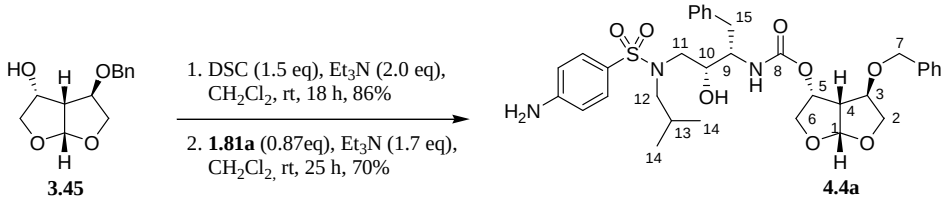
Diethylaminosulfur trifluoride (1.32 mL, 10.0 mmol) was added dropwise to a solution of ketone **3.27** (524 mg, 2.00 mmol) in CH_2Cl_2 (10 mL) at 0 °C. The reaction was allowed to warm to rt and was stirred in a sealed tube for further 16 d. After completion, the reaction mixture was cooled to −20 °C, quenched with sat. aq. $NaHCO_3$ (10 mL), diluted with CH_2Cl_2 (20 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. Purification of the crude product by column chromatography (petroleum ether/acetone 85:15 to 75:25) afforded difluoro ether **3.114** as a colourless oil (377 mg, 66%; $\mathbf{R_f}$ 0.55 (petroleum ether/acetone 80:20); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2 H), 6.89 (d, *J* = 8.8 Hz, 2 H), 5.78 (d, *J* = 5.2 Hz, 1 H), 4.61 (d, *J* = 11.3 Hz, 1 H), 4.49 (d, *J* = 11.4 Hz, 1 H), 4.39 (ddd, *J* = 14.0, 6.1, 0.7 Hz, 1 H), 4.23 (ddd, *J* = 26.3, 9.9, 5.2 Hz, 1 H), 4.09-3.95 (m, 3 H), 3.82 (s, 3 H), 3.03 (ddddd, *J* = 18.2,

8.0, 5.2, 2.1, 1.1 Hz, 1 H) ppm; **^{19}F NMR** (282 MHz, CDCl3) δ −90.6 (d, *J* = 245.0 Hz), −121.3 (d, *J* = 245.0 Hz) ppm).

To a solution of PMB-ether **3.114** (200 mg, 0.72 mmol) in absolute EtOH (7 mL) under N_2-atmosphere was added Pd/C (20 mg, 10w%, 10% Pd). The flask was then put under hydrogen and heated to reflux for 18 h. After completion the reaction mixture was filtered over celite, the filtercake was washed with EtOH and the solvent was removed in vacuo. Recrystallisation from $CDCl_3$ afforded the *title compound* **3.116** as colourless crystals (60.1 mg, 39%). **Formula** $C_8H_{14}F_2O_4$; **Mw** 212.19; **R_f** 0.28 (hexane/acetone 70:30); **$[\alpha]_D$** +138.1 (c 0.71, MeOH, 25 °C); **IR** (film) 3388 (br. m), 2962 (w), 2934 (w), 2887 (w), 1258 (w), 1099 (m), 1036 (vs), 794 (m), cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.42 (1 H, d, *J* = 4.6 Hz, H-1), 4.61 (1 H, ddd, *J* = 7.3, 4.9, 3.0 Hz, H-5), 4.05 (1 H, dd, *J* = 9.9, 3.0 Hz, H-6), 3.94 (1 H, d, *J* = 9.9 Hz, H-6'), 3.99−3.85 (2 H, m, H-2 and H-2'), 3.82 (1 H, dq, *J* = 9.7, 7.1 Hz, H-7), 3.58 (1 H, dq, *J* = 9.7, 7.1 Hz, H-7'), 2.77 (1 H, tt, *J* = 16.6, 4.9 Hz, H-4), 2.57 (1 H, t, *J* = 7.1 Hz, $CH_2O\mathit{H}$), 2.33 (1 H, d, *J* = 7.3 Hz, OH), 1.23 (1 H, t, *J* = 7.1 Hz, H-8) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 122.2 (CF_2, dd, *J* = 246.1, 244.2 Hz, C-3), 102.7 (CH, dd, *J* = 7.3, 3.6 Hz, C-1), 74.1 (CH_2, C-6), 72.1 (CH, d, *J* = 3.6 Hz, C-5), 64.4 (CH_2, t, *J* = 31.6 Hz, C-2), 64.3 (CH_2, C-7), 54.8 (CH, t, *J* = 21.7 Hz, C-4), 15.1 (CH_3, C-8) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −104.2 (dtd, *J* = 261.1, 15.3, 11.3 Hz), −107.5 (dtd, *J* = 261.1, 16.1, 10.7 Hz) ppm. It was not possible to obtain LRMS/HRMS (ESI, EI or CI) data for this compound.

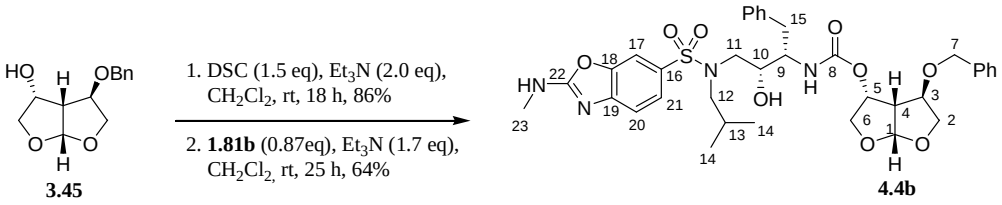
8.2.3 Synthesis of Protease Inhibitors 4.4−4.31

Protease Inhibitor 4.4a



Following general procedure **E** (8.2.1), the reaction of alcohol **3.45** (270 mg, 1.14 mmol) with DSC (440 mg, 1.71 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99:1 to 98:2) the corresponding mixed carbonate as a pale yellow oil (370 mg, 0.98 mmol, 86%). Following general procedure **F** (8.2.1), this mixed carbonate (185 mg, 0.49 mmol) was then reacted with amine **1.81a** (176 mg, 0.45 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 96:4) PI **4.4a** as a white solid (207 mg, 70%). **Formula** $C_{34}H_{43}N_3O_8S$; **Mw** 653.79; $\mathbf{R_f}$ 0.40 (CH_2Cl_2/MeOH 95:5); **Mp** 90−92 °C; $\mathbf{[\alpha]_D}$ +29.6 (c 1.28, $CHCl_3$, 26 °C); **IR** (film) 3469 (w), 3370 (w), 2961 (w), 2872 (w), 1712 (s), 1629 (m), 1596 (s), 1314 (s), 1147 (vs), 1090 (s), 1021 (m), 735 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (2 H, d, *J* = 8.8 Hz, Ar-H), 7.38–7.16 (10 H, m, Ar-H), 6.69 (2 H, d, *J* = 8.7 Hz, Ar-H), 5.80 (1 H, d, *J* = 5.2 Hz, H-1), 5.13 (1 H, dt, *J* = 8.7, 5.6 Hz, H-5), 4.93 (1 H, d, *J* = 8.3 Hz, NH), 4.38 (1 H, d, *J* = 11.8 Hz, H-7), 4.29 (1 H, d, *J* = 11.8 Hz, H-7'), 4.16 (2 H, br. s, NH_2), 4.03 (1 H, d, *J* = 10.1 Hz, H-2), 4.00 (1 H, dd, *J* = 10.0, 6.1 Hz, H-6), 3.90–3.82 (3 H, m, H-2', H-9 and H-10), 3.75 (1 H, d, *J* = 3.5 Hz, H-3), 3.72–3.66 (2 H, m, H-6' and OH), 3.14 (1 H, dd, *J* = 14.8, 8.4 Hz, H-11), 3.02 (1 H, dd, *J* = 14.5, 3.9 Hz, H-15), 3.02 (1 H, dd, *J* = 8.8, 5.2 Hz, H-4), 2.98–2.91 (2 H, m, H-11' and H-12), 2.82 (1 H, dd, *J* = 14.5, 8.6 Hz, H-15'), 2.78 (1 H, dd, *J* = 13.5, 6.7 Hz, H-12'), 1.82 (1 H, m, H-13), 0.93 (3 H, d, *J* = 6.6 Hz, H-14), 0.89 (3 H, d, *J* = 6.6 Hz, H-14) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 155.2 (C, C-8), 150.7 (C_{ar}), 137.8 (C_{ar}), 137.6 (C_{ar}), 129.5 ($2 \times CH_{ar}$), 129.4 ($2 \times CH_{ar}$), 128.6 ($2 \times CH_{ar}$), 128.4 ($2 \times CH_{ar}$), 127.7 (CH_{ar}), 127.5 ($2 \times CH_{ar}$), 126.7 (CH_{ar}), 126.1 (C_{ar}), 114.1 ($2 \times CH_{ar}$), 109.0 (CH, C-1), 79.3 (CH, C-3), 74.4 (CH_2, C-2), 72.8 (CH, C-10), 72.4 (CH, C-5), 71.1 (CH_2, C-6), 70.9 (CH_2, C-7), 58.9 (CH_2, C-12), 55.3 (CH, C-9), 53.8 (CH_2, C-11), 51.7 (CH, C-4), 35.5 (CH_2, C-15), 27.3 (CH, C-13), 20.2 (CH_3, C-14), 19.9 (CH_3, C-14) ppm; **LRMS** (ESI^+) *m/z* 676.5 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{34}H_{43}N_3O_8SNa$ $(M + Na)^+$ calcd. 676.2663; found 676.2649.

Protease Inhibitor 4.4b

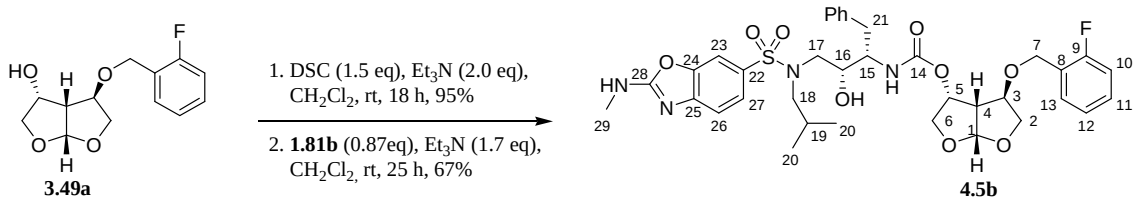


3.45 **4.4b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.45** (270 mg, 1.14 mmol) with DSC (440 mg, 1.71 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99:1 to 98:2) the corresponding mixed carbonate as a pale yellow oil (370 mg, 0.98 mmol, 86%). Following general procedure **F** (8.2.1), this mixed carbonate (185 mg, 0.49 mmol) was then reacted with amine **1.81b** (200 mg, 0.45 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.4b** as a white solid (205 mg, 64%). **Formula** $C_{36}H_{44}N_4O_9S$; **Mw** 708.82; **Mp** 110−112 °C; $\mathbf{R_f}$ 0.38 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$ +33.7 (c 0.95, $CHCl_3$, 26 °C); **IR** (film) 3340 (w), 2960 (w), 2869 (w), 1711 (m), 1657 (vs), 1580 (m), 1326 (m), 1271 (m), 1239 (m), 1144 (s), 1121 (s), 1021 (m), 730 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (1 H, d, *J* = 1.6 Hz, H-17), 7.61 (1 H, dd, *J* = 8.2, 1.6 Hz, H-21), 7.55 (1 H, d, *J* = 8.3 Hz, H-20), 7.37–7.16 (10 H, m, Ar-H), 5.80 (1 H, d, *J* = 5.2 Hz, H-1), 5.54 (1 H, q, *J* = 4.5 Hz, N*H*Me), 5.12 (1 H, dt, *J* = 8.8, 5.9 Hz, H-5), 5.05 (1 H, d, *J* = 8.8 Hz, NH), 4.39 (1 H, d, *J* = 12.0 Hz, H-7), 4.29 (1 H, d, *J* = 12.0 Hz, H-7'), 4.02 (1 H, d, *J* = 10.0 Hz, H-2), 3.99 (1 H, dd, *J* = 10.1, 6.2 Hz, H-6), 3.94–3.86 (2 H, m, H-9 and H-10), 3.86 (1 H, dd, *J* = 10.0, 3.9 Hz, H-2'), 3.76 (1 H, d, *J* = 3.5 Hz, H-3), 3.68 (1 H, dd, *J* = 9.9, 5.6 Hz, H-6'), 3.65 (1 H, br. s, OH), 3.16 (3 H, d, *J* = 4.9 Hz, H-23), 3.13 (1 H, dd, *J* = 15.0, 8.7 Hz, H-11), 3.08–2.98 (3 H, m, H-4, H-11' and H-15), 2.94 (1 H, dd, *J* = 13.5, 8.1 Hz, H-12), 2.84 (1 H, dd, *J* = 13.5, 7.1 Hz, H-12'), 2.81 (1 H, dd, *J* = 14.0, 8.8 Hz, H-15), 1.82 (1 H, m, H-13), 0.92 (3 H, d, *J* = 6.6 Hz, H-14), 0.90 (3 H, d, *J* = 6.6 Hz, H-14) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-22), 155.2 (C, C-8), 148.1 (C_{ar}, C-18 or C-19), 147.8 (C_{ar}, C-19 or C-18), 137.7 (C_{ar}), 137.5 (C_{ar}), 129.6 (C_{ar}, C-17), 129.3 ($2 \times CH_{ar}$), 128.5 ($2 \times CH_{ar}$), 128.4 ($2 \times CH_{ar}$), 127.7 (CH_{ar}), 127.5 ($2 \times CH_{ar}$), 126.7 (CH_{ar}), 124.2 (CH_{ar}, C-21), 116.1 (CH_{ar}, C-20), 109.0 (CH, C-1), 108.4 (CH_{ar}, C-17), 79.2 (CH, C-3), 74.4 (CH_2, C-2), 72.7 (CH, C-10), 72.4 (CH, C-5), 71.2 (CH_2, C-6), 70.9 (CH_2, C-7), 58.9 (CH_2, C-12), 55.3 (CH, C-9), 53.8 (CH_2, C-11), 51.6 (CH, C-4), 35.6 (CH_2, C-15), 29.5 (CH_3, C-23), 27.3 (CH, C-13), 20.1 (CH_3, C-14), 19.9 (CH_3, C-14); **LRMS** (ESI^+) *m/z*

731.5 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{34}H_{43}N_3O_8SNa$ $(M + Na)^+$ calcd. 676.2663; found 676.2649.

Protease Inhibitor 4.5b

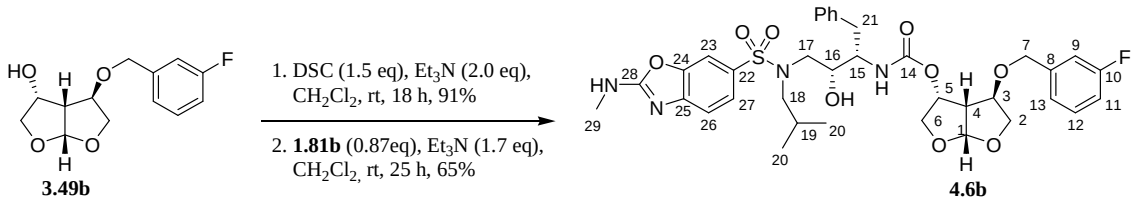


3.49a **4.5b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.49a** (310 mg, 1.22 mmol) with DSC (470 mg, 1.83 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 97:3) the corresponding mixed carbonate as a pale yellow oil (459 mg, 1.16 mmol, 95%). Following general procedure **F** (8.2.1), subsequent reaction with amine **1.81b** (446 mg, 1.00 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 95:5) the PI **4.5b** as a white solid (487 mg, 67%). **Formula** $C_{36}H_{43}FN_4O_9S$; **Mw** 726.81; **Mp** 95–96 °C; $\mathbf{R_f}$ 0.30 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$ +28.9 (c 1.17, $CHCl_3$, 26 °C); **IR** (film) 3342 (br. w), 2960 (w), 2873 (w), 1712 (m), 1656 (s), 1580 (s), 1461 (m), 1325 (m), 1238 (m), 1143 (m), 1121 (m), 727 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (1 H, d, *J* = 1.6 Hz, H-23), 7.61 (1 H, dd, *J* = 8.3, 1.8 Hz, H-27), 7.41 (1 H, d, *J* = 8.3 Hz, H-26), 7.37 (1 H, td, *J* = 7.5, 1.2 Hz, H-13), 7.31–7.15 (6 H, m, H-11 and Ar-H), 7.13 (1 H, td, *J* = 7.5, 1.0 Hz, H-12), 7.03 (1 H, ddd, *J* = 9.7, 8.7, 1.0 Hz, H-10), 5.80 (1 H, d, *J* = 5.1 Hz, H-1), 5.60 (1 H, br. s, NHMe), 5.16–5.07 (2 H, m, H-5 and NH), 4.43 (1 H, d, *J* = 12.2 Hz, H-7), 4.33 (1 H, d, *J* = 12.2 Hz, H-7'), 4.03–3.97 (2 H, m, H-2 and H-6), 3.96–3.88 (2 H, m, H-15 and H-16), 3.86 (1 H, dd, *J* = 10.2, 3.7 Hz, H-2'), 3.76 (1 H, d, *J* = 3.3 Hz, H-3), 3.71–3.65 (2 H, m, H-6' and OH), 3.17–3.04 (3 H, m, H-17, H-21 and H-21'), 3.16 (3 H, d, *J* = 5.0 Hz, H-29), 3.01 (1 H, dd, *J* = 8.7, 5.3 Hz, H-4), 2.94 (1 H, dd, *J* = 13.4, 7.9 Hz, H-18), 2.85 (1 H, dd, *J* = 13.4, 7.0 Hz, H-18'), 2.81 (1 H, dd, *J* = 14.3, 9.3 Hz, H-17'), 1.86 (1 H, m, H-19), 0.92 (3 H, d, *J* = 6.7 Hz, H-20), 0.90 (3 H, d, *J* = 6.7 Hz, H-20) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-28), 160.5 (CF_{ar}, d, *J* = 246.4 Hz, C-9), 155.2 (C, C-14), 148.1 (C_{ar}, C-24 or C-25), 147.8 (C_{ar}, C-25 or C-24), 137.6 (C_{ar}), 129.8 (CH_{ar}, d, *J* = 3.9 Hz, C-13), 129.6 (C_{ar}, C-22), 129.5 (CH_{ar}, d, *J* = 8.0 Hz, C-11), 129.3 ($2 \times CH_{ar}$), 128.5 ($2 \times CH_{ar}$), 126.7 (CH_{ar}), 124.8 (C_{ar}, d, *J* = 14.6 Hz, C-8), 124.2 (C_{ar}, C-27), 124.1 (CH_{ar}, d, *J* = 3.6 Hz, C-12), 116.1 (C_{ar}, C-26), 115.2 (CH_{ar}, d, *J* = 21.4 Hz, C-10), 109.0 (CH, C-1), 108.4 (CH_{ar}, C-23), 79.6 (CH, C-3), 74.3 (CH_2, C-2), 72.8 (CH, C-16), 72.4 (CH, C-5), 71.2

(CH_2, C-6), 64.5 (CH_2, d, *J* = 3.6 Hz, C-7), 58.9 (CH_2, C-18), 55.3 (CH, C-15), 53.8 (CH_2, C-17), 51.6 (CH, C-4), 35.6 (CH_2, C-21), 29.5 (CH_3, C-29), 27.2 (CH, C-19), 20.1 (CH_3, C-20), 19.9 (CH_3, C-20) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −119.1 (1 F, dt, *J* = 9.7, 6.4 Hz, F-9) ppm; **LRMS** (ESI^+) *m/z* 749.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{36}H_{43}FN_4O_9SNa$ $(M + Na)^+$ calcd. 749.2627, found 749.2624.

Protease Inhibitor 4.6b

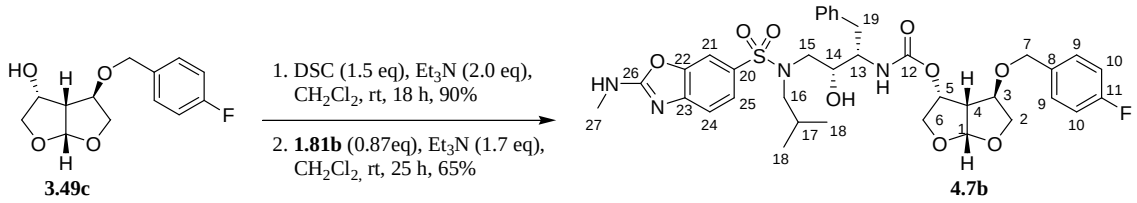


3.49b **4.6b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.49b** (245 mg, 0.96 mmol) with DSC (370 mg, 1.44 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 97:3) the corresponding mixed carbonate as a pale yellow oil (352 mg, 0.89 mmol, 91%). Following general procedure **F** (8.2.1), subsequent reaction with amine **1.81b** (344 mg, 0.77 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.6b** as a white solid (364 mg, 65%). **Formula** $C_{36}H_{43}FN_4O_9S$; **Mw** 726.81; **Mp** 92–94 °C; **R_f** 0.33 (CH_2Cl_2/MeOH 95:5); **$[\alpha]_D$** +30.8 (*c* 1.04, $CHCl_3$, 26 °C); **IR** (film) 3342 (br. w), 2960 (w), 2873 (w), 1716 (m), 1659 (vs), 1580 (m), 1510 (m), 1463 (m), 1326 (m), 1224 (m), 1145 (m), 1053 (m), 733 (s), 600 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (1 H, d, *J* = 1.6 Hz, H-23), 7.62 (1 H, dd, *J* = 8.3, 1.8 Hz, H-27), 7.42 (1 H, d, *J* = 8.3 Hz, H-26), 7.30 (1 H, td, *J* = 8.0, 5.9 Hz, H-12), 7.27–7.14 (5 H, m, Ar-H), 7.08–7.00 (2 H, m, H-9 and H-12), 6.97 (1 H, td, *J* = 8.4, 2.3 Hz, H-10), 5.81 (1 H, d, *J* = 5.1 Hz, H-1), 5.38 (1 H, br. s, N*H*Me), 5.12 (1 H, dt, *J* = 8.9, 6.0 Hz, H-5), 5.02 (1 H, d, *J* = 6.4 Hz, NH), 4.36 (1 H, d, *J* = 12.1 Hz, H-7), 4.24 (1 H, d, *J* = 11.9 Hz, H-7'), 4.05–3.98 (2 H, m, H-2 and H-6), 3.95–3.85 (2 H, m, H-15 and H-16), 3.85 (1 H, dd, *J* = 10.2, 3.6 Hz, H-2'), 3.73–3.67 (2 H, m, H-3 and H-6'), 3.61 (2 H, br. s, OH), 3.17 (3 H, d, *J* = 5.0 Hz, H-29), 3.14 (1 H, dd, *J* = 15.3, 8.4 Hz, H-21), 3.09–2.98 (3 H, m, H-4, H-17 and H-21'), 2.96 (1 H, dd, *J* = 13.4, 8.2 Hz, H-18), 2.84 (1 H, dd, *J* = 13.4, 6.9 Hz, H-18'), 2.80 (1 H, dd, *J* = 14.1, 9.3 Hz, H-17'), 1.86 (1 H, m, H-19), 0.93 (3 H, d, *J* = 6.7 Hz, H-20), 0.90 (3 H, d, *J* = 6.7 Hz, H-20) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-28), 162.9 (CF_{ar}, d, *J* = 246.4 Hz, C-10), 155.2 (C, C-14), 148.2 (C_{ar}, C-24 or C-25), 147.9 (C_{ar}, C-25 or C-24),

140.4 (C_{ar}, d, J = 7.3 Hz, C-8), 137.6 (C_{ar}), 129.9 (CH_{ar}, d, J = 8.0 Hz, C-12), 129.7 (C_{ar}, C-22), 129.3 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.7 (CH_{ar}), 124.2 (C_{ar}, C-27), 122.7 (CH_{ar}, d, J = 1.9 Hz, C-13), 116.2 (C_{ar}, C-26), 114.5 (CH_{ar}, d, J = 21.1 Hz, C-9), 114.1 (CH_{ar}, d, J = 21.9 Hz, C-11), 109.0 (CH, C-1), 108.4 (CH_{ar}, C-23), 79.5 (CH, C-3), 74.3 (CH_2, C-2), 72.8 (CH, C-16), 72.5 (CH, C-5), 71.1 (CH_2, C-6), 70.0 (CH_2, d, J = 1.9 Hz, C-7), 59.0 (CH_2, C-18), 55.4 (CH, C-15), 53.8 (CH_2, C-17), 51.6 (CH, C-4), 35.6 (CH_2, C-21), 29.6 (CH_3, C-29), 27.3 (CH, C-19), 20.1 (CH_3, C-20), 19.9 (CH_3, C-20) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −113.2 (1 F, td, J = 9.1, 5.6 Hz, F-10) ppm; **LRMS** (ESI^+) *m/z* 749.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{36}H_{43}FN_4O_9SNa$ $(M + Na)^+$ calcd. 749.2627, found 749.2619.

Protease Inhibitor 4.7b

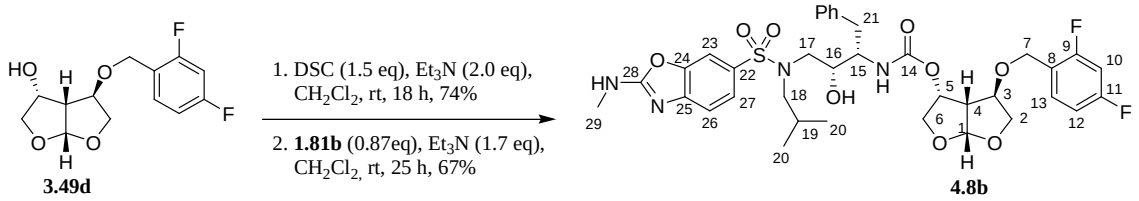


3.49c **4.7b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.49c** (231 mg, 0.91 mmol) with DSC (349 mg, 1.36 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99:1 to 97:3) the corresponding mixed carbonate as a pale yellow oil (323 mg, 0.82 mmol, 90%). Following general procedure **F** (8.2.1), subsequent reaction with amine **1.81b** (330 mg, 0.74 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.7b** as a white solid (352 mg, 65%). **Formula** $C_{36}H_{43}FN_4O_9S$; **Mw** 726.81; **Mp** 97–99 °C; **R_f** 0.24 (CH_2Cl_2/MeOH 95:5); **[α]$_D$** +27.8 (*c* 0.92, $CHCl_3$, 26 °C); **IR** (film) 3339 (br. w), 2961 (w), 2873 (w), 1712 (m), 1658 (vs), 1581 (s), 1463 (m), 1327 (m), 1271 (m), 1142 (s), 1122 (m), 732 (s) cm^{-1}. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (1 H, d, J = 1.6 Hz, H-21), 7.62 (1 H, dd, J = 8.3, 1.8 Hz, H-25), 7.42 (1 H, d, J = 8.3 Hz, H-24), 7.28–7.15 (7 H, m, H-9 and Ar-H), 7.02 (2 H, t, J = 8.7 Hz, H-10), 5.80 (1 H, d, J = 5.1 Hz, H-1), 5.39 (1 H, br. s, NHMe), 5.13 (1 H, dt, J = 8.8, 5.9 Hz, H-5), 5.03 (1 H, br. s, NH), 4.32 (1 H, d, J = 11.8 Hz, H-7), 4.21 (1 H, d, J = 11.4 Hz, H-7'), 4.04–3.97 (2 H, m, H-2 and H-6), 3.97–3.88 (2 H, m, H-13 and H-14), 3.85 (1 H, dd, J = 10.1, 3.8 Hz, H-2'), 3.74–3.67 (2 H, m, H-3 and H-6'), 3.62 (1 H, br. s, OH), 3.17 (3 H, d, J = 5.0 Hz, H-27), 3.14 (1 H, dd, J = 15.1, 8.5 Hz, H-19), 3.09–2.99 (2 H, m, H-15 and H-19'), 2.99 (1 H, dd, J = 8.7, 5.2 Hz, H-4), 2.95 (1 H, dd, J = 13.3, 6.9 Hz, H-16), 2.84 (1 H, dd, J = 13.3, 6.9 Hz, H-16'), 2.81

(1 H, dd, *J* = 13.9, 9.3 Hz, H-15'), 1.86 (1 H, m, H-17), 0.93 (3 H, d, *J* = 6.7 Hz, H-18), 0.90 (3 H, d, *J* = 6.5 Hz, H-18) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-26), 162.3 (CF_{ar}, d, *J* = 245.8 Hz, C-11), 155.3 (C, C-12), 148.2 (C_{ar}, C-22 or C-23), 147.9 (C_{ar}, C-23 or C-22), 137.6 (C_{ar}), 133.5 (C_{ar}, d, *J* = 3.2 Hz, C-8), 129.7 (C_{ar}, C-20), 129.3 (2 × CH_{ar}), 129.2 (2 × CH_{ar}, d, *J* = 8.1 Hz, C-9), 128.6 (2 × CH_{ar}), 126.7 (CH_{ar}), 124.2 (C_{ar}, C-25), 116.1 (C_{ar}, C-24), 115.3 (2 × CH_{ar}, d, *J* = 21.1 Hz, C-10), 109.0 (CH, C-1), 108.4 (CH_{ar}, C-21), 79.4 (CH, C-3), 74.3 (CH_2, C-2), 72.8 (CH, C-14), 72.5 (CH, C-5), 71.1 (CH_2, C-6), 70.2 (CH_2, C-7), 58.9 (CH_2, C-16), 55.3 (CH, C-13), 53.8 (CH_2, C-15), 51.6 (CH, C-4), 35.6 (CH_2, C-19), 29.5 (CH_3, C-27), 27.3 (CH, C-17), 20.1 (CH_3, C-18), 19.9 (CH_3, C-18) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −114.8 (1 F, tt, *J* = 8.6, 5.4 Hz) ppm; **LRMS** (ESI^+) *m/z* 749.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{36}H_{43}FN_4O_9SNa$ $(M + Na)^+$ calcd. 749.2627, found 749.2627.

Protease Inhibitor 4.8b

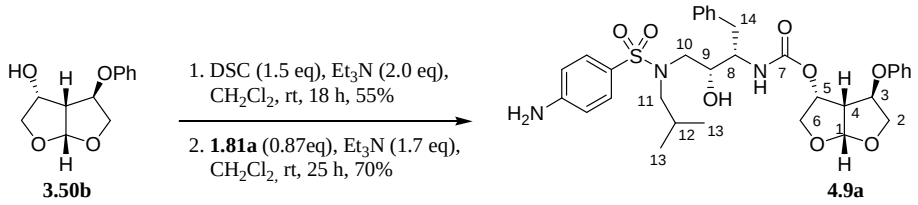


3.49d **4.8b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.49d** (326 mg, 1.20 mmol) with DSC (461 mg, 1.80 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 97:3) the corresponding mixed carbonate as a pale yellow oil (365 mg, 0.88 mmol, 74%). Following general procedure **F** (8.2.1), subsequent reaction with amine **1.81b** (339 mg, 0.76 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 95:5) the PI **4.8b** as a white solid (382 mg, 67%). **Formula** $C_{36}H_{42}F_2N_4O_9S$; **Mw** 744.80; **Mp** 104–106 °C; $\mathbf{R_f}$ 0.30 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$ +22.1 (*c* 0.96, $CHCl_3$, 26 °C); **IR** (film) 3343 (br. w), 2960 (w), 2873 (w), 1716 (m), 1659 (vs), 1580 (m), 1506 (m), 1463 (m), 1326 (m), 1272 (s), 1141 (m), 1052 (m), 735 (m) 600 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (1 H, d, *J* = 1.8 Hz, H-23), 7.62 (1 H, dd, *J* = 8.3, 1.8 Hz, H-27), 7.41 (1 H, d, *J* = 8.3 Hz, H-26), 7.33 (1 H, td, *J* = 8.5, 6.4 Hz, H-13), 7.28–7.15 (5 H, m, Ar-H), 6.86 (1 H, td, *J* = 8.3, 2.5 Hz, H-12), 6.79 (1 H, td, *J* = 9.5, 2.5 Hz, H-10), 5.79 (1 H, d, *J* = 5.3 Hz, H-1), 5.57 (1 H, br. s, NHMe), 5.16–5.10 (2 H, m, H-5 and NH), 4.36 (1 H, d, *J* = 11.8 Hz, H-7), 4.24 (1 H, d, *J* = 11.8 Hz, H-7'), 4.03–3.96 (2 H, m, H-2 and H-6), 3.96–3.87 (2 H,

m, H-15 and H-16), 3.85 (1 H, dd, *J* = 10.2, 3.8 Hz, H-2'), 3.73–3.65 (3 H, m, H-3, H-6' and OH), 3.18–3.03 (3 H, m, H-17, H-21 and H-21'), 3.16 (3 H, d, *J* = 5.0 Hz, H-29), 2.99 (1 H, dd, *J* = 8.8, 5.1 Hz, H-4), 2.95 (1 H, dd, *J* = 13.4, 8.3 Hz, H-18), 2.85 (1 H, dd, *J* = 13.4, 6.9 Hz, H-18'), 2.80 (1 H, dd, *J* = 14.1, 9.2 Hz, H-17'), 1.81 (1 H, m, H-19), 0.93 (3 H, d, *J* = 6.7 Hz, H-20), 0.90 (3 H, d, *J* = 6.7 Hz, H-20) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-28), 162.6 (CF_{ar}, dd, *J* = 248.8, 11.9 Hz, C-11), 160.5 (CF_{ar}, dd, *J* = 249.5, 11.9 Hz, C-9), 155.2 (C, C-14), 148.1 (C_{ar}, C-24 or C-25), 147.9 (C_{ar}, C-25 or C-24), 137.6 (C_{ar}), 130.8 (CH_{ar}, dd, *J* = 9.7, 5.3 Hz, C-13), 129.6 (C_{ar}, C-22), 129.3 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.7 (CH_{ar}), 124.2 (C_{ar}, C-27), 120.9 (C_{ar}, dd, *J* = 14.6, 3.6 Hz, C-8), 116.1 (C_{ar}, C-26), 111.2 (CH_{ar}, dd, *J* = 21.1, 3.6 Hz, C-12), 109.0 (CH, C-1), 108.4 (C_{ar}, C-23), 103.7 (CH_{ar}, t, *J* = 25.5 Hz, C-10), 79.7 (CH, C-3), 74.3 (CH_2, C-2), 72.8 (CH, C-16), 72.4 (CH, C-5), 71.2 (CH_2, C-6), 64.1 (CH_2, d, *J* = 3.2 Hz, C-7), 58.9 (CH_2, C-18), 55.4 (CH, C-15), 53.8 (CH_2, C-17), 51.6 (CH, C-4), 35.6 (CH_2, C-21), 29.5 (CH_3, C-29), 27.2 (CH, C-19), 20.1 (CH_3, C-20), 19.9 (CH_3, C-20) ppm; **^{19}F{^{1}H} NMR** (282 MHz, $CDCl_3$) δ –110.7 (1 F, d, *J* = 7.5 Hz), –114.8 (1 F, d, *J* = 7.5 Hz) ppm; **LRMS** (ESI+) *m*/*z* 767.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{36}H_{42}F_2N_4O_9SNa$ $(M + Na)^+$ calcd. 767.2533, found 767.2532.

Protease Inhibitor 4.9a

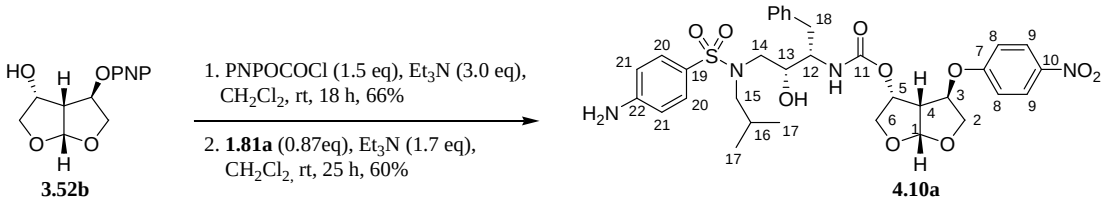


3.50b **4.9a**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.50b** (32.4 mg, 0.15 mmol) with DSC (56 mg, 0.22 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 97:3) the corresponding mixed carbonate as a pale yellow oil (30 mg, 0.08 mmol, 55%). Following general procedure **F** (8.2.1), subsequent reaction with amine **1.81a** (32 mg, 0.08 mmol) afforded after purification by column chromatography (petroleum ether/acetone 70:30 to 50:50) PI **4.9a** as a white solid (36 mg, 70%). **Formula** $C_{33}H_{41}N_3O_8S$; **Mw** 639.76; **Mp** 234 °C; **R_f** 0.50 (CH_2Cl_2/MeOH 95:5); **$[\alpha]_D$** +21.5 (*c* 0.54, CH_2Cl_2, 23 °C); **IR** (film) 3468 (br. w), 3368 (br. m), 2960 (w), 2872 (w), 1713 (m), 1596 (s), 1497 (m), 1314 (m), 1236 (s), 1147 (vs), 1090 (s), 734 (s), 553 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.57 (2 H, d, *J* = 8.7 Hz, H-16), 7.32−6.95 (8 H, m,

Ar-H), 6.81 (2 H, d, *J* = 8.1 Hz, Ar-H), 6.70 (2 H, d, *J* = 8.7 Hz, H-17), 5.80 (1 H, d, *J* = 5.3 Hz, H-1), 5.23 (1 H, ddd, *J* = 8.4, 4.9, 4.4 Hz, H-5), 5.07 (1 H, d, *J* = 9.2 Hz, NH), 4.17 (2 H, br. s, NH_2), 4.15 (1 H, d, *J* = 3.7 Hz, H-3), 4.08 (1 H, d, *J* = 10.5 Hz, H-2), 4.01−3.88 (4 H, m, H-2', H-6, H-8 and H-9), 3.83 (1 H, dd, *J* = 10.1, 4.3 Hz, H-6'), 3.69 (1 H, d, *J* = 2.4 Hz, O*H*), 3.19 (1 H, dd, *J* = 15.2, 8.8 Hz, H-10), 3.08 (1 H, dd, *J* = 14.0, 4.2 Hz, H-14), 3.03−2.94 (3 H, m, H-4, H-10' and H-11), 2.81 (1 H, dd, *J* = 13.5, 6.8 Hz, H-11'), 2.78 (1 H, dd, *J* = 13.8, 10.0 Hz, H-14'), 1.85 (1 H, m, H-12), 0.95 (3 H, d, *J* = 6.7 Hz, H-13), 0.91 (3 H, d, *J* = 6.7 Hz, H-13) ppm. **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 156.5 (C_{ar}), 155.4 (C, C-7), 150.8 (C_{ar}, C-18), 137.5 (C_{ar}), 129.54 (2 × CH_{ar}, C-16), 129.50 (2 × CH_{ar}), 129.1 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.6 (CH_{ar}), 125.9 (C_{ar}, C-15), 121.1 (CH_{ar}), 115.3 (2 × CH_{ar}), 114.1 (2 × CH_{ar}, C-17), 109.1 (CH, C-1), 77.1 (CH, C-3), 74.6 (CH_2, C-2), 72.9 (CH, C-9), 72.4 (CH, C-5), 71.7 (CH_2, C-6), 58.9 (CH_2, C-11), 55.3 (CH, C-8), 53.7 (CH_2, C-10), 51.5 (CH, C-4), 35.6 (CH_2, C-14), 27.3 (CH, C-12), 20.2 (CH_3, C-13), 19.9 (CH_3, C-13) ppm; **LRMS** (ESI+) *m*/*z* 662.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{33}H_{41}N_3O_8SNa$ $(M + Na)^+$ calcd. 662.2507, found 662.2531.

Protease Inhibitor 4.10a



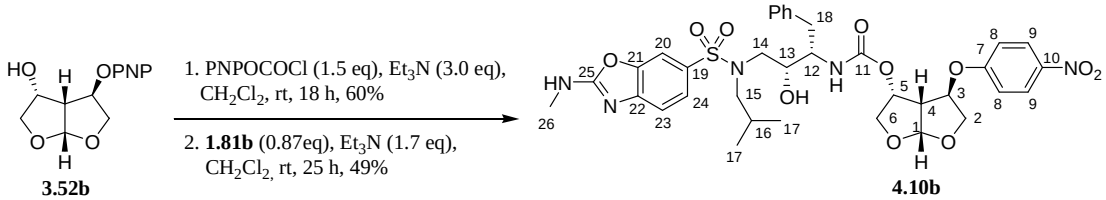
3.52b **4.10a**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.52b** (309 mg, 1.15 mmol) with PNPOCOCl (350 mg, 1.73 mmol) afforded after purification by column chromatography (petroleum ether/acetone 85:15 to 65:35) the corresponding mixed carbonate as a colourless oil (329 mg, 0.76 mmol, 66%; $\mathbf{R_f}$ 0.55 (hexane/EtOAc 60:40); $\mathbf{[\alpha]_D}$ +23.0 (c 1.23, $CHCl_3$, 27 °C); **IR** (film) 3116 (w), 3084 (w), 2980 (w), 2883 (w), 2360 (w), 1766 (m), 1591 (m), 1513 (m), 1493 (m), 1342 (s), 1248 (s), 1211 (vs), 1111 (m), 1097 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.33 (2 H, d, *J* = 9.3 Hz), 8.25 (2 H, d, *J* = 9.3 Hz), 7.42 (2 H, d, *J* = 9.3 Hz), 7.00 (2 H, d, *J* = 9.3 Hz), 5.99 (1 H, d, *J* = 5.1 Hz), 5.45 (1 H, dt, *J* = 8.8, 5.4 Hz), 5.18 (1 H, d, *J* = 2.6 Hz), 4.35 (1 H, dd, *J* = 10.8, 2.6 Hz), 4.31 (1 H, dt, *J* = 10.8, 1.1 Hz), 4.24 (1 H, dd, *J* = 10.7, 5.6 Hz), 4.05 (1 H, dd, *J* = 10.5, 5.0 Hz), 3.30 (1 H, dd, *J* = 8.8, 5.1 Hz) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 161.3 (C_{ar}), 154.9 (C_{ar}), 151.9 (C), 142.2 (C_{ar}), 126.1 (2 × CH_{ar}), 125.5 (2 × CH_{ar}), 121.6 (2 × CH_{ar}), 115.2

(2 × CH_{ar}), 108.9 (CH), 78.1 (CH), 76.3 (CH), 74.0 (CH_2), 71.2 (CH_2), 51.6 (CH) ppm; **LRMS** (ESI^+) *m/z* 455.2 $(M + Na)^+$.

Following general procedure **F** (8.2.1), this mixed carbonate was reacted with amine **1.81a** (287 mg, 0.73 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 97:3) PI **4.10a** as a white solid (300 mg, 60%). **Formula** $C_{33}H_{40}N_4O_{10}S$; **Mw** 684.76 **Mp** 103−105 °C; $\mathbf{R_f}$ 0.39 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$ +5.2 (*c* 0.30, $CHCl_3$, 27 °C); **IR** (film) 3451 (w), 3356 (w), 2953 (w), 2883 (w), 1716 (s), 1591 (m), 1519 (m), 1496 (m), 1315 (s), 1252 (s), 1144 (s), 1082 (s), 993 (m), 757 (s), 748 (s), 547 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6) δ 8.14 (2 H, d, *J* = 9.3 Hz, H-9), 7.52 (1 H, d, *J* = 9.2 Hz, OH), 7.41 (2 H, d, *J* = 8.7 Hz, H-20), 7.18 (2 H, d, *J* = 7.5 Hz, Ar-H), 6.94 (2 H, d, *J* = 9.3 Hz, H-8), 6.90 (2 H, t, *J* = 7.6 Hz, Ar-H), 6.75 (1 H, t, *J* = 7.3 Hz, Ar-H), 6.61 (2 H, d, *J* = 8.7 Hz, H-21), 5.98 (2 H, br. s, NH_2), 5.67 (1 H, d, *J* = 5.3 Hz, H-1), 5.12 (1 H, ddd, *J* = 8.4, 5.0, 3.8 Hz, H-5), 5.05 (1 H, d, *J* = 6.3 Hz, NH), 4.03 (1 H, m, H-2), 3.96−3.91 (2 H, m, H-2' and H-3), 3.88 (1 H, dd, *J* = 10.1, 5.3 Hz, H-6), 4.08 (1 H, dd, *J* = 10.1, 3.7 Hz, H-6'), 3.71−3.65 (2 H, m, H-12 and H-13), 3.35 (1 H, dd, *J* = 14.9, 3.2 Hz, H-14), 3.04 (1 H, dd, *J* = 13.7, 2.2 Hz, H-18), 2.98 (1 H, dd, *J* = 13.4, 8.6 Hz, H-15), 2.91 (1 H, ddd, *J* = 8.5, 5.1, 1.0 Hz, H-4), 2.68 (1 H, dd, *J* = 14.9, 7.8 Hz, H-14'), 2.64 (1 H, dd, *J* = 13.4, 6.3 Hz, H-15'), 2.44 (1 H, dd, *J* = 13.2, 11.1 Hz, H-18'), 1.98 (1 H, m, H-16), 0.89 (3 H, d, *J* = 6.6 Hz, H-17), 0.82 (3 H, d, *J* = 6.7 Hz, H-17) ppm. **^{13}C NMR + DEPT** (100 MHz, DMSO-d_6) δ 161.8 (C_{ar}, C-7), 155.4 (C, C-11), 152.7 (C_{ar}, C-22), 141.0 (C_{ar}, C-10), 139.4 (C_{ar}), 129.1 (2 × CH_{ar}, C-20), 129.0 (2 × CH_{ar}), 127.6 (2 × CH_{ar}), 125.6 (2 × CH_{ar}, C-9), 125.4 (CH_{ar}), 123.4 (C_{ar}, C-19), 115.5 (2 × CH_{ar}, C-8), 112.6 (2 × CH_{ar}, C-21), 108.5 (CH, C-1), 78.5 (CH, C-3), 73.6 (CH_2, C-2), 72.8 (CH, C-13), 71.4 (CH, C-5), 70.9 (CH_2, C-6), 57.5 (CH_2, C-15), 56.1 (CH, C-12), 52.8 (CH_2, C-14), 51.4 (CH, C-4), 35.1 (CH_2, C-18), 26.4 (CH, C-16), 20.1 (2 × CH_3, C-17) ppm; **LRMS** (ESI+) *m/z* 707.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{33}H_{40}N_4O_{10}SNa$ $(M + Na)^+$ calcd. 707.2357, found 707.2370.

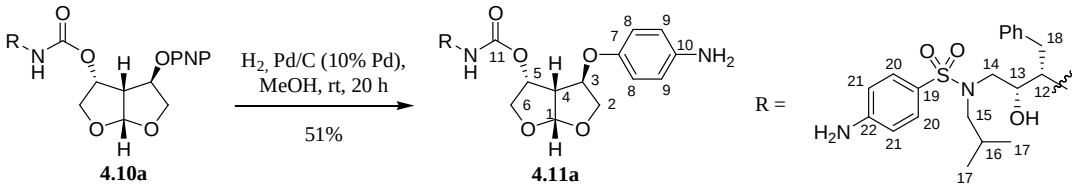
Protease Inhibitor 4.10b



4.10b

Following general procedure **E** (8.2.1), the reaction of alcohol **3.52b** (350 mg, 1.30 mmol) with PNPOCOCl (412 mg, 1.96 mmol) afforded after purification by column chromatography (petroleum ether/acetone 85:15 to 65:35) the corresponding mixed carbonate as a pale yellow oil (334 mg, 0.77 mmol, 60%). Following general procedure **F** (8.2.1), subsequent reaction with amine **1.81b** (313 mg, 0.70 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.10b** as a white solid (252 mg, 49%). **Formula** $C_{35}H_{41}N_5O_{11}S$; **Mw** 739.79 **Mp** 119−121 °C; $\mathbf{R_f}$ 0.38 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$ +3.2 (*c* 1.11, $CHCl_3$, 27 °C); **IR** (film) 3344 (br. w), 2962 (w), 2875 (w), 1715 (m), 1656 (s), 1581 (m), 1513 (m), 1463 (m), 1341 (s), 1252 (s), 1111 (m), 907 (s), 726 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.18 (2 H, d, *J* = 9.0 Hz, H-9), 7.69 (1 H, d, *J* = 1.0 Hz, H-20), 7.64 (1 H, d, *J* = 8.3, 1.8 Hz, H-24), 7.41 (1 H, d, *J* = 8.3 Hz, H-23), 7.16 (2 H, d, *J* = 7.3 Hz, Ar-H), 6.99 (2 H, t, *J* = 7.7 Hz, Ar-H), 6.91 (1 H, t, *J* = 7.5 Hz, Ar-H) , 6.87 (2 H, d, *J* = 9.2 Hz, H-8), 5.77 (1 H, d, *J* = 5.1 Hz, H-1), 5.76 (1 H, br. s, N*H*Me), 5.49 (1 H, d, *J* = 5.0 Hz, NH), 5.21 (1 H, dt, *J* = 8.3, 4.5 Hz, H-5), 4.08–3.97 (3 H, m, H-2, H-12 and H-13), 3.94 (1 H, dd, *J* = 10.4, 5.6 Hz, H-6), 3.90–3.83 (3 H, m, H-2', H-3 and H-6'), 3.73 (1 H, br. s, OH), 3.22 (1 H, dd, *J* = 15.2, 8.7 Hz, H-14), 3.16 (3 H, d, *J* = 4.8 Hz, H-26), 3.14–3.07 (2 H, m, H-14' and H-18), 3.00 (1 H, dd, *J* = 13.3, 8.2 Hz, H-15), 2.93–2.85 (2 H, m, H-4 and H-15'), 2.70 (1 H, dd, *J* = 13.8, 10.8 Hz, H-18'), 1.96–1.84 (1 H, m, H-16), 0.94 (3 H, d, *J* = 6.7 Hz, H-17), 0.92 (3 H, d, *J* = 6.7 Hz, H-17) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.8 (C_{ar}, C-25), 161.7 (C_{ar}, C-7), 155.5 (C, C-11), 148.1 (C_{ar}, C-21 or C-22), 147.9 (C_{ar}, C-22 or C-21), 141.7 (C_{ar}, C-10), 137.7 (C_{ar}), 129.5 (C_{ar}, C-19), 129.2 (2 × CH_{ar}), 128.3 (2 × CH_{ar}), 126.5 (CH_{ar}), 125.9 (2 × CH_{ar}, C-9), 124.2 (C_{ar}, C-24), 116.1 (C_{ar}, C-23), 115.3 (2 × CH_{ar}, C-8), 109.0 (CH, C-1), 108.4 (C_{ar}, C-20), 78.3 (CH, C-3), 74.3 (CH_2, C-2), 73.0 (CH, C-13), 72.4 (CH, C-5), 71.4 (CH_2, C-6), 58.9 (CH_2, C-15), 55.5 (CH, C-12), 53.7 (CH_2, C-14), 51.5 (CH, C-4), 35.7 (CH_2, C-18), 29.5 (CH_3, C-26), 27.2 (CH, C-16), 20.1 (CH_3, C-17), 19.9 (CH_3, C-17) ppm; **LRMS** (ESI+) *m*/*z* 762.5 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{35}H_{41}N_5O_{11}SNa$ $(M + Na)^+$ calcd. 762.2415, found 762.2422.

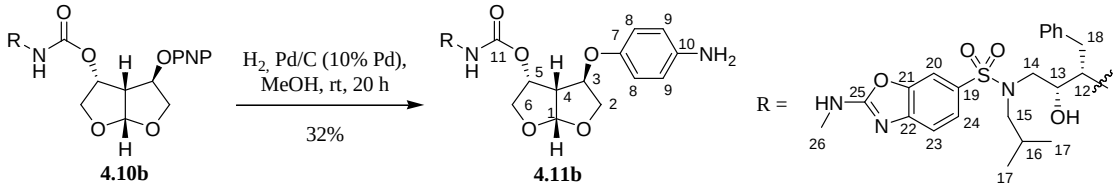
Protease Inhibitor 4.11a



4.10a **4.11a**

To a solution of PI **4.10b** (195 mg, 0.285 mmol) in MeOH (7 mL) under N_2 was added Pd/C (50 mg, 25 w%, 10% Pd). The flask was then put under H_2-atmosphere and the reaction was stirred at rt for 20 h. After completion the mixture was filtered over celite and the filtercake was washed with MeOH (2 × 10 mL). The solvent was removed and the crude product was purified by column chromatography (CH_2Cl_2/MeOH 98:2 to 90:10) and HPLC (CH_2Cl_2/MeOH 96:4) to afford PI **4.11b** as a white solid (95 mg, 51%). **Formula** $C_{33}H_{42}N_4O_8S$; **Mw** 654.77 **Mp** 102−104 °C; $\mathbf{R_f}$ 0.18 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$ +22.5 (*c* 0.35, $CHCl_3$, 27 °C); **IR** (film) 3364 (br. m), 2961 (w), 2873 (w), 1710 (m), 1627 (m), 1595 (m), 1509 (s), 1313 (m), 1227 (s), 1146 (s), 1089 (s), 909 (m), 730 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (2 H, d, *J* = 8.7 Hz, H-20), 7.20–7.05 (5 H, m, Ar-H), 6.68 (2 H, d, *J* = 8.7 Hz, H-21), 6.64 (4 H, br. s, H-8 and H-9), 5.78 (1 H, d, *J* = 5.3 Hz, H-1), 5.18 (1 H, dt, *J* = 9.3, 4.9 Hz, H-5), 5.14 (1 H, d, *J* = 8.7 Hz, NH), 4.11 (1 H, d, *J* = 3.0 Hz, H-3), 4.04 (1 H, d, *J* = 10.0 Hz, H-2), 4.97–3.88 (3 H, m, H-6, H-12 and H-13), 3.87 (1 H, dd, *J* = 10.2, 3.5 Hz, H-2'), 3.79 (1 H, dd, *J* = 10.2, 4.2 Hz, H-6'), 3.16 (1 H, dd, *J* = 15.1, 8.5 Hz, H-14), 3.07 (1 H, dd, *J* = 14.2, 4.1 Hz, H-18), 3.04–2.91 (3 H, m, H-4, H-14' and H-15), 2.81 (1 H, dd, *J* = 13.4, 7.0 Hz, H-15'), 2.77 (1 H, dd, *J* = 14.1, 9.8 Hz, H-18'), 1.85 (1 H, m, H-16), 0.93 (3 H, d, *J* = 6.7 Hz, H-17), 0.90 (3 H, d, *J* = 6.5 Hz, H-17) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 155.3 (C, C-11), 150.8 (C_{ar}, C-22), 149.5 (C_{ar}, C-7), 140.4 (C_{ar}, C-10), 137.6 (C_{ar}), 129.5 (2 × CH_{ar}, C-20), 129.2 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.7 (CH_{ar}), 125.9 (C_{ar}, C-19), 116.7 (2 × CH_{ar}, C-8 or C-9), 116.4 (2 × CH_{ar}, C-9 or C-8), 114.1 (2 × CH_{ar}, C-21), 109.0 (CH, C-1), 77.7 (CH, C-3), 74.5 (CH_2, C-2), 72.8 (CH, C-13), 72.4 (CH, C-5), 71.7 (CH_2, C-6), 58.9 (CH_2, C-15), 55.3 (CH, C-12), 53.8 (CH_2, C-14), 51.4 (CH, C-4), 35.6 (CH_2, C-18), 27.3 (CH, C-16), 20.2 (CH_3, C-17), 19.9 (CH_3, C-17) ppm; **LRMS** (ESI^+) *m/z* 655.5 $(M + H)^+$, 677.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{33}H_{42}N_4O_8SNa$ $(M + Na)^+$ calcd. 655.2796, found 655.2786.

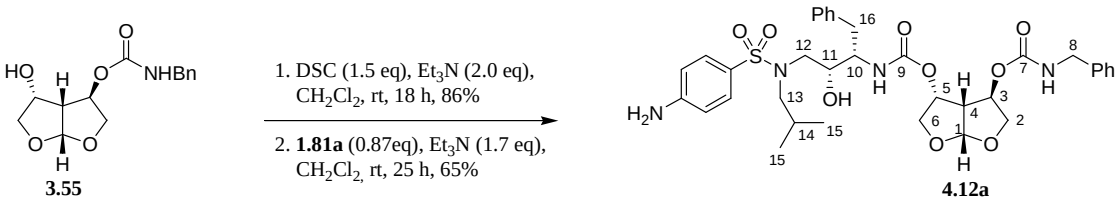
Protease Inhibitor 4.11b



4.10b **4.11b**

To a solution of PI **4.10b** (345 mg, 0.466 mmol) in MeOH (15 mL) under N_2 was added Pd/C (85 mg, 25 w%, 10% Pd). The flask was then put under H_2-atmosphere and the reaction was stirred at rt for 20 h. After completion the mixture was filtered over celite and the filtercake was washed with MeOH (2 × 10 mL). The solvent was removed and the crude product was purified by column chromatography (CH_2Cl_2/MeOH 98:2 to 90:10) and HPLC (CH_2Cl_2/MeOH 96:4) to afford PI **4.11b** as a off-white solid (106 mg, 32%). **Formula** $C_{35}H_{43}N_5O_9S$; **Mw** 709.81 **Mp** 112−114 °C; $\mathbf{R_f}$ 0.25 (CH_2Cl_2/MeOH 96:4); $\mathbf{[\alpha]_D}$ +13.4 (*c* 0.28, $CHCl_3$, 27 °C); **IR** (film) 3337 (br. w), 2960 (w), 2875 (w), 1713 (m), 1658 (vs), 1580 (m), 1509 (vs), 1463 (m), 1323 (m), 1233 (s), 1144 (m), 909 (m), 730 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (1 H, d, *J* = 1.6 Hz, H-20), 7.62 (1 H, dd, *J* = 8.3, 1.8 Hz, H-24), 7.41 (1 H, d, *J* = 8.3 Hz, H-23), 7.20–7.05 (5 H, m, Ar-H), 5.78 (1 H, d, *J* = 5.3 Hz, H-1), 5.72 (1 H, br. s, NHMe), 5.26 (1 H, d, *J* = 9.0 Hz, NH), 5.17 (1 H, dt, *J* = 8.4, 5.0 Hz, H-5), 4.13 (1 H, d, *J* = 3.3 Hz, H-3), 4.03 (1 H, d, *J* = 10.0 Hz, H-2), 3.98–3.91 (3 H, m, H-6, H-12 and H-13), 3.88 (1 H, dd, *J* = 10.2, 3.5 Hz, H-2'), 3.78 (1 H, dd, *J* = 10.2, 4.4 Hz, H-6'), 3.18–3.03 (6 H, m, H-14, H-14', H-18 and H-26), 2.98 (1 H, dd, *J* = 8.3, 5.2 Hz, H-4), 2.94 (1 H, dd, *J* = 13.4, 7.8 Hz, H-15), 2.87 (1 H, dd, *J* = 13.3, 7.3 Hz, H-15'), 2.76 (1 H, dd, *J* = 13.9, 9.5 Hz, H-18'), 1.93–1.81 (1 H, m, H-16), 0.92 (3 H, d, *J* = 6.7 Hz, H-17), 0.91 (3 H, d, *J* = 6.7 Hz, H-17) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-25), 155.4 (C, C-11), 149.5 (C_{ar}, C-7), 148.1 (C_{ar}, C-21 or C-22), 147.9 (C_{ar}, C-22 or C-21), 140.4 (C_{ar}, C-10), 137.5 (C_{ar}), 129.6 (C_{ar}, C-19), 129.1 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.7 (CH_{ar}), 124.2 (C_{ar}, C-24), 116.7 (2 × CH_{ar}, C-8 or C-9), 116.5 (2 × CH_{ar}, C-9 or C-8), 116.1 (C_{ar}, C-23), 109.1 (CH, C-1), 108.4 (C_{ar}, C-20), 77.7 (CH, C-3), 74.5 (CH_2, C-2), 72.8 (CH, C-13), 72.4 (CH, C-5), 71.7 (CH_2, C-6), 58.9 (CH_2, C-15), 55.3 (CH, C-12), 53.8 (CH_2, C-14), 51.4 (CH, C-4), 35.7 (CH_2, C-18), 29.5 (CH_3, C-26), 27.2 (CH, C-16), 20.1 (CH_3, C-17), 19.9 (CH_3, C-17) ppm; **LRMS** (ESI^+) *m*/*z* 710.5 $(M + H)^+$, 732.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{35}H_{41}N_5O_{11}SNa$ $(M + Na)^+$ calcd. 732.2674, found 732.2680.

Protease Inhibitor 4.12a



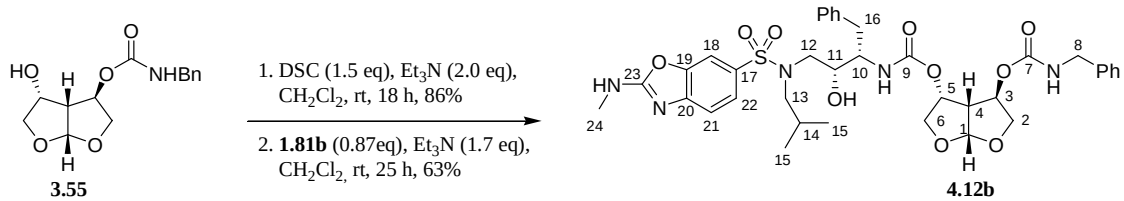
3.55 **4.12a**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.55** (350 mg, 1.25 mmol) with DSC (480 mg, 1.88 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 96:4) the corresponding mixed carbonate as a white solid (451 mg, 1.07 mmol, 82%; $\mathbf{R}_f$ 0.28 (CH_2Cl_2/MeOH 96:4); **Mp** 82 °C; $\mathbf{[\alpha]_D}$ +39.0 (*c* 0.73, $CHCl_3$, 26 °C); **IR** (film) 3348 (br. w), 2930 (w), 2885 (w), 1813 (m), 1789 (m), 1740 (vs), 1525 (m), 1247 (s), 1232 (s), 1080 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.27 (7 H, m, Ar-H), 5.85 (1 H, d, *J* = 5.0 Hz), 5.39 (1 H, br. s), 5.37 (1 H, dt, *J* = 8.5, 5.2 Hz), 5.12 (1 H, m), 4.39 (1 H, part of AB-system), 4.37 (1 H, part of AB-system), 4.21 (1 H, dd, *J* = 10.7, 3.8 Hz), 4.18–4.07 (2 H, m), 3.97 (1 H, dd, *J* = 10.5, 5.1 Hz), 3.17 (1 H, dd, *J* = 8.5, 5.2 Hz), 2.84 (4 H, br. s) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.2 (2 × C), 155.3 (C), 150.9 (C), 138.1 (C_{ar}), 128.7 (2 × CH_{ar}), 127.61 (2 × CH_{ar}), 127.55 (CH_{ar}), 108.5 (CH), 78.1 (CH), 74.9 (CH), 74.7 (CH_2), 70.6 (CH_2), 51.6 (CH), 45.1 (CH_2), 25.4 (2 × CH_2) ppm; **LRMS** (ESI^+) *m*/*z* 443.1 $(M + Na)^+$; **HRMS** (ESI+) for $C_{19}H_{20}N_2O_9Na$ $(M + Na)^+$ calcd. 443.1061, found 443.1066).

Following general procedure **F** (8.2.1), the reaction of this carbonate (210 mg, 0.50 mmol) and amine **1.81a** (168 mg, 0.43 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) and HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.12a** as a white solid (180 mg, 60%). **Formula** $C_{35}H_{44}N_4O_9S$; **Mw** 696.81; $\mathbf{R}_f$ 0.33 (CH_2Cl_2/MeOH 96:4); **Mp** 99−102 °C; $\mathbf{[\alpha]_D}$ +50.7 (c 0.69, $CHCl_3$, 26 °C); **IR** (film) 3364 (br. w), 2961 (w), 2875 (w), 1704 (s), 1628 (w), 1596 (m), 1520 (m), 1312 (m), 1225 (s), 1144 (s), 1089 (s), 1017 (m), 730 (vs), 700 (s) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6, T = 373 K) δ 7.43 (1 H, d, *J* = 8.7 Hz, Ar-H), 7.39−7.08 (11 H, m, Ar-H and NH), 6.82 (1 H, br. s, N*H*), 6.66 (2 H, d, *J* = 8.7 Hz, Ar-H), 5.68 (1 H, d, *J* = 5.2 Hz, H-1), 5.62 (2 H, s, NH_2), 5.10 (1 H, d, *J* = 3.4 Hz, H-3), 5.04 (1 H, dt, *J* = 8.3, 5.6 Hz, H-5), 4.53 (1 H, d, *J* = 5.3 Hz, O*H*), 4.22 (2 H, d, *J* = 6.2 Hz, H-8), 4.07−3.82 (4 H, m, H-2, H-2', H-6 and H-6'), 3.78−3.62 (2 H, m, H-10 and H-11), 3.33 (1 H, dd, *J* = 14.8, 3.3 Hz, H-12), 3.03−2.93 (3 H, m, H-4, H-13 and H-16), 2.89 (1 H, dd, *J* = 14.8, 8.1 Hz, H-12'), 2.80 (1 H, dd, *J* = 13.7, 6.9 Hz, H-13'), 2.64 (1 H, dd, *J* = 14.1, 10.0 Hz, H-16'), 1.97 (1 H, m, H-14), 0.85 (3 H, d, *J* = 6.6 Hz, H-15), 0.82 (3 H, d, *J* = 6.7 Hz, H-15) ppm; **^{13}C NMR + DEPT** (100 MHz,

$CDCl_3$) δ 155.4 (C, C-7 or C-9), 155.1 (C, C-9 or C-7), 150.7 (C_{ar}), 138.1 (C_{ar}), 137.5 (C_{ar}), 129.5 (4 × CH_{ar} and C_{ar}), 128.7 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 127.6 (2 × CH_{ar}), 127.5 (CH_{ar}), 126.6 (CH_{ar}), 114.1 (2 × CH_{ar}), 108.7 (CH, C-1), 75.4 (CH, C-3), 74.9 (CH_2, C-2), 72.3 (CH, C-11), 71.8 (CH, C-5), 71.6 (CH_2, C-6), 58.8 (CH_2, C-13), 55.2 (CH, C-10), 53.7 (CH_2, C-12), 51.6 (CH, C-4), 45.1 (CH_2, C-8), 35.3 (CH_2, C-16), 27.3 (CH, C-14), 20.2 (CH_3, C-15), 19.9 (CH_3, C-15) ppm; **LRMS** (ESI+) *m*/*z* 719.4 $(M + Na)^+$; **HRMS** (ESI+) for $C_{35}H_{44}N_4O_9SNa$ $(M + Na)^+$ calcd. 719.2721, found 719.2714.

Protease Inhibitor 4.12b

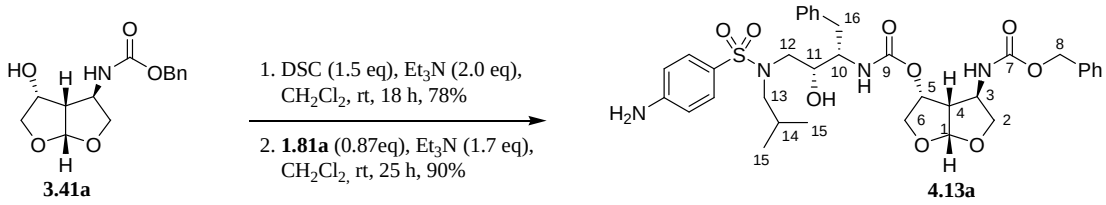


3.55 **4.12b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.55** (350 mg, 1.25 mmol) with DSC (480 mg, 1.88 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 96:4) the corresponding mixed carbonate as a white solid (451 mg, 1.07 mmol, 82%). Following general procedure **F** (8.2.1), the reaction of this carbonate (210 mg, 0.50 mmol) and amine **1.81b** (192 mg, 0.43 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) and HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.12b** as a white solid (207 mg, 63%). **Formula** $C_{37}H_{45}N_5O_{10}S$; **Mw** 751.85; $\mathbf{R_f}$ 0.30 (CH_2Cl_2/MeOH 96:4); **Mp** 109–111 °C; $\mathbf{[\alpha]_D}$ +53.8 (*c* 0.59, $CHCl_3$, 26 °C); **IR** (film) 3342 (br. w), 2961 (w), 2876 (w), 1714 (s), 1660 (vs), 1581 (m), 1530 (m), 1462 (m), 1330 (m), 1237 (s), 1181 (m), 1141 (s), 1031 (m), 908 (m), 730 (vs), 701 (s) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6, T = 353 K) δ 7.95 (1 H, q, *J* = 4.5 Hz, N*H*Me), 7.68 (1 H, d, *J* = 1.8 Hz, H-18), 7.57 (1 H, dd, *J* = 8.3, 1.8 Hz, H-22), 7.43 (1 H, br. s, N*H*Bn), 7.33 (1 H, d, *J* = 8.2 Hz, H-21), 7.33−7.08 (10 H, m, Ar-H), 6.92 (1 H, br. s, N*H*), 5.67 (1 H, d, *J* = 5.1 Hz, H-1), 5.07 (1 H, d, *J* = 3.4 Hz, H-3), 5.02 (1 H, br. s, H-5), 4.66 (1 H, d, *J* = 6.2 Hz, O*H*), 4.20 (2 H, d, *J* = 6.2 Hz, H-8), 4.02−3.83 (3 H, m, H-2, H-2' and H-6), 3.72−3.57 (3 H, m, H-6', H-10 and H-11), 3.37 (1 H, dd, *J* = 14.6, 3.1 Hz, H-12), 3.04 (1 H, dd, *J* = 13.9, 8.0 Hz, H-13), 2.97 (3 H, d, *J* = 4.8 Hz, H-24), 3.01−2.92 (3 H, m, H-4, H-12' and H-16), 2.87 (1 H, dd, *J* = 13.8, 6.9 Hz, H-13'), 2.61 (1 H, dd, *J* = 13.8, 10.2 Hz, H-16'), 1.98 (1 H, m, H-14), 0.85 (3 H, d, *J* = 6.7 Hz, H-15), 0.81 (3 H, d, *J* = 6.6 Hz, H-15) ppm;

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-23), 155.4 (C, C-7 or C-9), 155.2 (C, C-9 or C-7), 148.1 (C_{ar}, C-19 or C-20), 147.7 (C_{ar}, C-20 or C-19), 138.1 (C_{ar}), 137.5 (C_{ar}), 129.7 (C_{ar}, C-17), 129.4 (2 × CH_{ar}), 128.7 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 127.6 (2 × CH_{ar}), 127.5 (CH_{ar}), 126.6 (CH_{ar}), 124.2 (CH_{ar}, C-22), 116.1 (CH_{ar}, C-21), 108.7 (CH, C-1), 108.4 (CH_{ar}, C-18), 75.4 (CH, C-3), 74.8 (CH_2, C-2), 72.3 (CH, C-11), 71.8 (CH, C-5), 71.6 (CH_2, C-6), 58.7 (CH_2, C-13), 55.3 (CH, C-10), 53.7 (CH_2, C-12), 51.6 (CH, C-4), 45.1 (CH_2, C-8), 35.4 (CH_2, C-16), 29.5 (CH_3, C-24), 27.2 (CH, C-14), 20.1 (CH_3, C-15), 19.9 (CH_3, C-15) ppm; **LRMS** (ESI^+) *m*/*z* 774.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{37}H_{45}N_5O_{10}SNa$ $(M + Na)^+$ calcd. 774.2779, found 774.2771.

Protease Inhibitor 4.13a

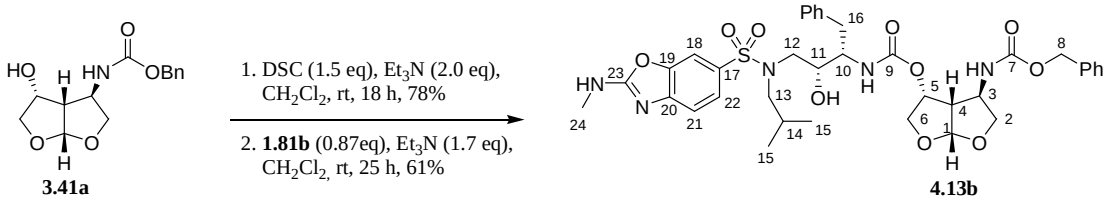


Following general procedure **E** (8.2.1), the reaction of alcohol **3.41a** (118 mg, 0.42 mmol) with DSC (161 mg, 0.63 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2) the corresponding mixed carbonate as a white solid (140 mg, 0.33 mmol, 78%; $\mathbf{R}_f$ 0.28 (CH_2Cl_2/MeOH 98:2); **IR** (film) 3330 (br. w), 2947 (br. w), 1737 (s), 1716 (s), 1525 (m), 1224 (s), 1200 (s), 1078 (m), 907 (s), 724 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.38–7.28 (5 H, m, Ar-H), 5.78 (1 H, d, *J* = 5.1 Hz), 5.35–5.26 (2 H, m), 5.11 (3 H, d, *J* = 11.8 Hz), 5.08 (3 H, d, *J* = 11.8 Hz), 4.42 (1 H, m), 4.13 (1 H, dd, *J* = 9.8, 4.4 Hz), 4.14 (1 H, dd, *J* = 10.7, 5.7 Hz), 3.97 (1 H, dd, *J* = 10.7, 5.0 Hz), 3.90 (1 H, m), 3.08 (1H, m), 2.80 (4 H, br. s) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.3 (2 × C), 155.4 (C), 150.9 (C), 136.2 (C_{ar}), 128.5 (2 × CH_{ar}), 128.2 (CH_{ar}), 128.1 (2 × CH_{ar}), 108.3 (CH), 78.6 (CH), 74.2 (CH_2), 70.6 (CH_2), 66.9 (CH_2), 52.5 (CH), 52.2 (CH), 25.4 (2 × CH_2) ppm; **LRMS** (ESI+) *m*/*z* 443.1 $(M + Na)^+$).

Following general procedure **F** (8.2.1), the reaction of this carbonate (74 mg, 0.18 mmol) and amine **1.81a** (60 mg, 0.15 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) and HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.13a** as a white solid (96 mg, 90%). **Formula** $C_{35}H_{44}N_4O_9S$; **Mw** 696.81; $\mathbf{R}_f$ 0.28 (CH_2Cl_2/MeOH 96:4), **Mp** 118−120 °C, **[α]$_D$** +42.9 (*c* 0.73, $CHCl_3$, 26 °C); **IR** (film) 3363 (br. m), 2960 (br. w), 1701

(vs), 1628 (w), 1598 (s), 1529 (m), 1313 (s), 1251 (s), 1147 (vs), 1090 (vs), 732 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6, T = 373 K) δ 7.42 (2 H, d, *J* = 8.7 Hz, Ar-H), 7.38−7.08 (11 H, m, Ar-H and N*H*), 6.78 (1 H, br. s, N*H*), 6.65 (2 H, d, *J* = 8.7 Hz, Ar-H), 5.65 (1 H, d, *J* = 5.1 Hz, H-1), 5.64 (2 H, s, NH_2), 5.07 (1 H, d, *J* = 12.6 Hz, H-8), 5.04 (1 H, d, *J* = 12.6 Hz, H-8'), 4.98 (1 H, m, H-5), 4.53 (1 H, d, *J* = 5.8 Hz, O*H*), 4.07 (1 H, dd, *J* = 6.1, 4.6 Hz, H-3), 3.96−3.81 (2 H, m, H-2 and H-6), 3.79−3.61 (4 H, m, H-2', H-6', H-10 and H-11), 3.32 (1 H, dd, *J* = 14.9, 3.4 Hz, H-12), 2.99 (1 H, dd, *J* = 14.0, 4.0 Hz, H-16), 2.95 (1 H, dd, *J* = 13.8, 7.8 Hz, H-13), 2.92−2.84 (2 H, m, H-4 and H-12'), 2.79 (1 H, dd, *J* = 13.8, 6.9 Hz, H-13'), 2.63 (1 H, dd, *J* = 14.0, 9.5 Hz, H-16'), 1.96 (1 H, m, H-14), 0.85 (3 H, d, *J* = 6.6 Hz, H-15), 0.82 (3 H, d, *J* = 6.7 Hz, H-15) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 155.4 (C, C-9 or C-7), 155.2 (C, C-7 or C-9), 150.7 (C_{ar}), 137.5 (C_{ar}), 136.2 (C_{ar}), 129.5 (4 × CH_{ar} and C_{ar}), 128.6 (4 × CH_{ar}), 128.3 (CH_{ar}), 128.1 (CH_{ar}), 126.6 (CH_{ar}), 114.1 (2 × CH_{ar}), 108.3 (CH, C-1), 74.6 (CH_2, C-2), 72.3 (CH, H-11), 72.2 (CH, C-5), 71.4 (CH_2, C-6), 66.9 (CH_2, C-8), 58.8 (CH_2, C-13), 55.2 (CH, C-10), 53.7 (CH_2, C-12), 52.7 (CH, C-4 or C-3), 52.5 (CH, C-3 or C-4), 35.4 (CH_2, C-16), 27.3 (CH, C-14), 20.2 (CH_3, C-16), 19.9 (CH_3, C-16) ppm, one quaternary carbon was not observed; **LRMS** (ESI^+) *m/z* 719.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{35}H_{44}N_4O_9SNa$ $(M + Na)^+$ calcd. 719.2721, found 719.2733.

Protease Inhibitor 4.13b

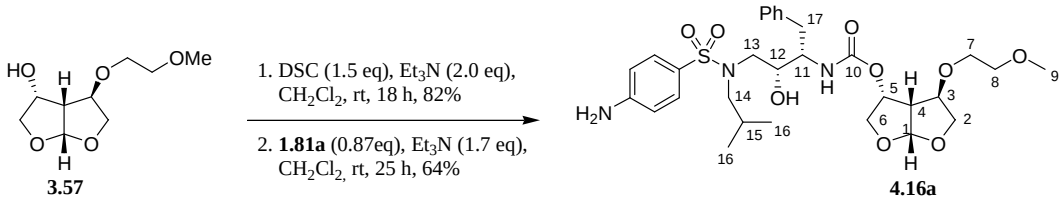


3.41a **4.13b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.41a** (118 mg, 0.42 mmol) with DSC (161 mg, 0.63 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2) the corresponding mixed carbonate as a white solid (140 mg, 0.33 mmol, 78%). Following general procedure **F** (8.2.1), the reaction of this carbonate (115 mg, 0.27 mmol) and amine **1.81b** (111 mg, 0.25 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) and HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.13a** as a white solid (115 mg, 61%). **Formula** $C_{37}H_{45}N_5O_{10}S$; **Mw** 751.85; **R_f** 0.25 (CH_2Cl_2/MeOH 95:5); **Mp** 106–108 °C; **[α]$_D$** +39.1 (c 1.03, $CHCl_3$, 27 °C); **IR** (film) 3326 (br. w), 2960 (w), 1702 (s), 1656 (vs), 1580 (m), 1533 (m), 1463 (m), 1325

(m), 1240 (s), 1144 (s), 910 (m), 730 (vs), 700 (s) cm^{-1}; **^{1}H NMR** (400 MHz, DMSO-d_6, T = 363 K) δ 7.95 (1 H, q, *J* = 4.5 Hz, N*H*Me), 7.68 (1 H, d, *J* = 1.8 Hz, H-18), 7.57 (1 H, dd, *J* = 8.2, 1.8 Hz, H-22), 7.36−7.09 (12 H, m, Ar-H, H-21 and N*H*), 6.88 (1 H, br. s, N*H*), 5.64 (1 H, d, *J* = 5.1 Hz, H-1), 5.06 (1 H, d, *J* = 12.9 Hz, H-8), 5.03 (1 H, d, *J* = 12.9 Hz, H-8'), 4.98 (1 H, br. s, H-5), 4.66 (1 H, d, *J* = 6.1 Hz, O*H*), 4.05 (1 H, dd, *J* = 5.9, 4.9 Hz, H-3), 3.95−3.82 (2 H, m, H-2 and H-6), 3.77−3.58 (4 H, m, H-2', H-6', H-10 and H-11), 3.37 (1 H, dd, *J* = 14.9, 2.5 Hz, H-12), 3.04 (1 H, dd, *J* = 13.9, 8.0 Hz, H-13), 2.97 (3 H, d, *J* = 4.7 Hz, H-24), 3.00−2.84 (4 H, m, H-4, H-12', H-13' and H-16), 2.61 (1 H, dd, *J* = 13.3, 10.0 Hz, H-16'), 1.99 (1 H, m, H-14), 0.85 (3 H, d, *J* = 6.6 Hz, H-15), 0.81 (3 H, d, *J* = 6.7 Hz, H-15) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-23), 155.4 (C, C-7 or C-9), 155.2 (C, C-9 or C-7), 148.1 (C_{ar}, C-19 or C-20), 147.7 (C_{ar}, C-20 or C-19), 137.5 (C_{ar}), 136.1 (C_{ar}), 129.7 (C_{ar}, C-17), 129.4 (2 × CH_{ar}), 128.5 (4 × CH_{ar}), 128.3 (2 × CH_{ar}), 128.1 (CH_{ar}), 126.6 (CH_{ar}), 124.2 (CH_{ar}, C-22), 116.0 (CH_{ar}, C-21), 108.4 (CH, C-1 and CH_{ar}, C-18), 74.5 (CH_2, C-2), 72.3 (CH, C-11), 72.2 (CH, C-5), 71.4 (CH_2, C-6), 66.9 (CH_2, C-8), 58.8 (CH_2, C-13), 55.2 (CH, C-10), 53.7 (CH_2, C-12), 52.6 (CH, C-3 or C-4), 52.5 (CH, C-4 or C-3), 35.4 (CH_2, C-16), 29.5 (CH_3, C-24), 27.2 (CH, C-14), 20.1 (CH_3, C-15), 19.9 (CH_3, C-15) ppm; **LRMS** (ESI^+) *m*/*z* 752.4 $(M + H)^+$, 774.9 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{37}H_{46}N_5O_{10}S$ $(M + H)^+$ calcd. 752.2960, found 752.2958.

Protease Inhibitor 4.16a



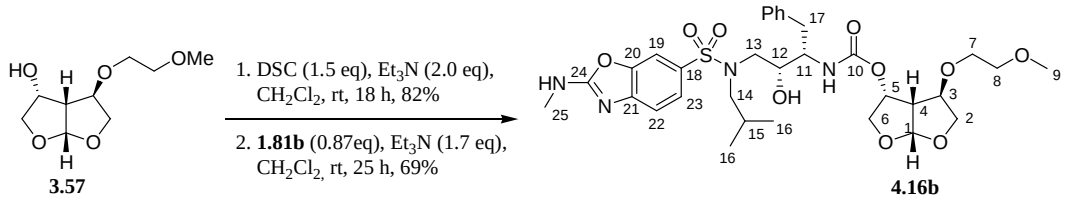
3.57 **4.16a**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.57** (293 mg, 1.43 mmol) with DSC (550 mg, 2.15 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 96:4) the corresponding mixed carbonate as a colourless oil (405 mg, 1.17 mmol, 82%; $\mathbf{R}_f$ 0.40 (CH_2Cl_2/MeOH 97:3); **IR** (film) 2938 (w), 2883 (w), 1811 (m), 1787 (m), 1735 (vs), 1368 (w), 1257 (m), 1231 (s), 1199 (s), 1071 (s), 1047 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.85 (1 H, d, *J* = 5.1 Hz), 5.34 (1 H, dt, *J* = 8.8, 5.9 Hz), 4.21 (1 H, br. d, *J* = 3.9 Hz), 4.13 (1 H, dt, *J* = 10.3, 1.1 Hz), 4.11 (1 H, dd, *J* = 10.4, 6.0 Hz), 4.04 (1 H, dd, *J* = 10.3, 3.9 Hz), 3.91 (1 H, dd, *J* = 10.4, 5.8 Hz), 3.62–3.58 (2 H, m), 3.55–3.52 (2 H, m), 3.37 (3 H, s), 3.15 (1 H, dd, *J* = 8.8, 5.3 Hz), 2.85 (4 H, m) ppm;

^{13}C NMR + DEPT (100 MHz, $CDCl_3$) δ 168.2 (2 × C), 151.1 (C), 108.9 (CH), 79.6 (CH), 78.5 (CH), 74.2 (CH_2), 71.6 (CH_2), 70.1 (CH_2), 68.7 (CH_2), 59.0 (CH_3), 51.6 (CH), 25.4 (2 × CH_3) ppm; **LRMS** (ESI+) *m*/*z* 368.1 $(M + Na)^+$).

Following general procedure **F** (8.2.1), the reaction of this carbonate (200 mg, 0.57 mmol) with amine **1.81a** (196 mg, 0.50 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 96:4) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.16a** as a white solid (200 mg, 64%). **Formula** $C_{30}H_{43}N_3O_9S$; **Mw** 621.74; **R_f** 0.23 (CH_2Cl_2/MeOH 97:3); **Mp** 88 °C; **$[\alpha]_D$** +11.2 (c 0.71, $CHCl_3$, 26 °C); **IR** (film) 3459 (w), 3363 (m), 2959 (w), 2873 (w), 1712 (s), 1631 (w), 1596 (s), 1534 (w), 1314 (s), 1255 (m), 1147 (vs), 1090 (vs), 1018 (m), 734 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (2 H, d, *J* = 8.7 Hz, Ar-H), 7.33–7.18 (5 H, m, Ar-H), 6.69 (2 H, d, *J* = 8.7 Hz, Ar-H), 5.77 (1 H, d, *J* = 5.1 Hz, H-1), 5.12 (1 H, dt, *J* = 8.8, 5.8 Hz, H-5), 5.00 (1 H, d, *J* = 8.4 Hz, NH), 4.18 (2 H, br. s, NH_2), 4.01–3.94 (2 H, m, H-2 and H-6), 3.91–3.84 (2 H, m, H-11 and H-12), 3.82 (1 H, dd, *J* = 10.1, 3.7 Hz, H-2'), 3.72–3.65 (3 H, m, H-3, H-6' and OH), 3.51–3.41 (3 H, m, H-7, H-8 and H-8'), 3.37 (3 H, s, H-9), 3.37–3.32 (1 H, m, H-7'), 3.14 (1 H, dd, *J* = 15.1, 8.3 Hz, H-13), 3.06 (1 H, dd, *J* = 14.4, 4.0 Hz, H-17), 2.99–2.90 (3 H, m, H-4, H-13' and H-14), 2.87–2.75 (2 H, m, H-14' and H-17'), 1.83 (1 H, m, H-15), 0.93 (3 H, d, *J* = 6.7 Hz, H-16), 0.89 (3 H, d, *J* = 6.7 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 155.2 (C, C-10), 150.8 (C_{ar}), 137.7 (C_{ar}), 129.5 (2 × CH_{ar}), 129.3 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.7 (CH_{ar}), 126.0 (C_{ar}), 114.1 (2 × CH_{ar}), 109.0 (CH, C-1), 80.0 (CH, C-3), 74.3 (CH_2, C-2), 72.8 (CH, C-12), 72.4 (CH, C-5), 71.8 (CH_2, C-8), 71.2 (CH_2, C-6), 68.3 (CH_2, C-7), 59.1 (CH_3, C-9), 58.9 (CH_2, C-14), 55.3 (CH, C-11), 53.8 (CH_2, C-13), 51.6 (CH, C-4), 35.5 (CH_2, C-17), 27.3 (CH, C-15), 20.2 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI^+) *m*/*z* 644.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{30}H_{43}N_3O_9SNa$ $(M + Na)^+$ calcd. 644.2612, found 644.2606.

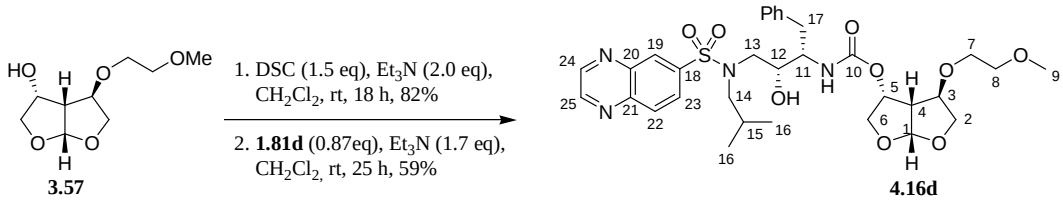
Protease Inhibitor 4.16b



3.57 **4.16b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.57** (293 mg, 1.43 mmol) with DSC (550 mg, 2.15 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 96:4) the corresponding mixed carbonate as a colourless oil (405 mg, 1.17 mmol, 82%). Following general procedure **F** (8.2.1), the reaction of this carbonate (200 mg, 0.57 mmol) with amine **1.81b** (223 mg, 0.50 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 96:4) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.16b** as a white solid (232 mg, 69%). **Formula** $C_{32}H_{44}N_4O_{10}S$; **Mw** 676.78; $\mathbf{R_f}$ 0.25 (CH_2Cl_2/MeOH 96:4); **Mp** 94 °C; **[α]$_D$** +24.1 (c 0.73, $CHCl_3$, 26 °C); **IR** (film) 3337 (br. w), 2959 (w), 2874 (w), 1710 (m), 1658 (s), 1580 (m), 1463 (m), 1327 (m), 1271 (m), 1240 (m), 1143 (s), 1121 (s), 1018 (m), 732 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (1 H, d, *J* = 1.6 Hz, H-19), 7.61 (1 H, dd, *J* = 8.3, 1.8 Hz, H-23), 7.42 (1 H, d, *J* = 8.3 Hz, H-22), 7.33–7.20 (5 H, m, Ar-H), 5.78 (1 H, d, *J* = 5.1 Hz, H-1), 5.45 (1 H, q, *J* = 5.0 Hz, N*H*Me), 5.11 (1 H, dt, *J* = 8.6, 6.0 Hz, H-5), 5.05 (1 H, d, *J* = 8.9 Hz, N*H*), 3.99 (1 H, dd, *J* = 9.8, 5.1 Hz, H-6), 3.98 (1 H, d, *J* = 10.0 Hz, H-2), 3.94–3.86 (2 H, m, H-11 and H-12), 3.84 (1 H, dd, *J* = 10.0, 3.8 Hz, H-2'), 3.70 (1 H, d, *J* = 3.8 Hz, H-3), 3.68 (1 H, dd, *J* = 9.8, 6.0 Hz, H-6'), 3.60 (1 H, d, *J* = 2.5 Hz, O*H*), 3.51–3.39 (3 H, m, H-7, H-8 and H-8'), 3.37 (3 H, s, H-9), 3.39–3.33 (1 H, m, H-7'), 3.13 (1 H, dd, *J* = 15.2, 8.5 Hz, H-13), 3.08 (1 H, dd, *J* = 14.4, 3.9 Hz, H-17), 3.01 (1 H, dd, *J* = 15.1, 2.4 Hz, H-13'), 2.98–2.90 (2 H, m, H-4 and H-14), 2.89–2.78 (2 H, m, H-14' and H-17'), 1.85 (1 H, m, H-15), 0.93 (3 H, d, *J* = 6.7 Hz, H-16), 0.90 (3 H, d, *J* = 6.7 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-24), 155.3 (C, C-10), 148.2 (C_{ar}, C-20 or C-21), 147.9 (C_{ar}, C-21 or C-20), 137.6 (C_{ar}), 129.6 (C_{ar}), 129.3 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 126.7 (CH_{ar}), 124.2 (CH_{ar}, C-23), 116.2 (CH_{ar}, C-22), 109.0 (CH, C-1), 108.4 (CH_{ar}, C-19), 80.0 (CH, C-3), 74.2 (CH_2, C-2), 72.8 (CH, C-12), 72.4 (CH, C-5), 71.8 (CH_2, C-8), 71.2 (CH_2, C-6), 68.3 (CH_2, C-7), 59.1 (CH_3, C-9), 58.9 (CH_2, C-14), 55.3 (CH, C-11), 53.8 (CH_2, C-13), 51.5 (CH, C-4), 35.6 (CH_2, C-17), 29.6 (CH_3, C-25), 27.3 (CH, C-15), 20.1 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI$^+$) *m*/*z* 699.4 $(M + Na)^+$; **HRMS** (ESI$^+$) for $C_{32}H_{44}N_4O_{10}SNa$ $(M + Na)^+$ calcd. 699.2670, found 699.2657.

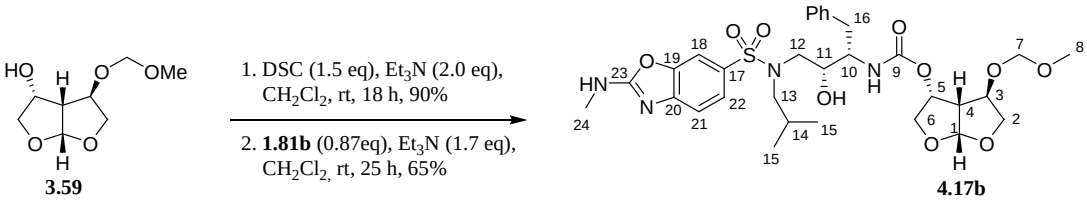
Protease Inhibitor 4.16d



3.57 **4.16d**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.57** (293 mg, 1.43 mmol) with DSC (550 mg, 2.15 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 96:4) the corresponding mixed carbonate as a colourless oil (405 mg, 1.17 mmol, 82%). Following general procedure **F** (8.2.1), the reaction of this carbonate (350 mg, 1.00 mmol) with amine **1.81d** (370 mg, 0.87 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 96:4) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.16b** as a white solid (337 mg, 59%). **Formula** $C_{32}H_{42}N_4O_9S$; **Mw** 658.76; $\mathbf{R_f}$ 0.23 (CH_2Cl_2/MeOH 97:3); **Mp** 68−70 °C; $\mathbf{[\alpha]_D}$ +21.1 (c 1.50, $CHCl_3$, 25 °C); **IR** (film) 3341 (br. w), 2958 (w), 2874 (w), 1716 (m), 1531 (w), 1336 (m), 1255 (m), 1148 (s), 1112 (s), 1067 (s), 1019 (s), 736 (m), 657 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.99 (2 H, s, H-24 and H-25), 8.61 (1 H, d, *J* = 2.0 Hz, H-19), 8.26 (1 H, d, *J* = 8.8 Hz, H-22), 8.07 (1 H, d, *J* = 8.8, 2.1 Hz, H-23), 7.31–7.18 (5 H, m, Ar-H), 5.76 (1 H, d, *J* = 5.3 Hz, H-1), 5.17 (1 H, d, *J* = 7.5 Hz, NH), 5.12 (1 H, dt, *J* = 8.6, 5.9 Hz, H-5), 4.00–3.92 (3 H, m, H-2, H-6 and H-12), 3.88 (1 H, tt, *J* = 9.2, 4.8 Hz, H-11), 3.80 (1 H, dd, *J* = 10.1, 3.8 Hz, H-2'), 3.70 (1 H, dd, *J* = 10.0, 5.5 Hz, H-6'), 3.63–3.59 (2 H, m, H-3 and OH), 3.48–3.37 (3 H, m, H-7, H-8 and H-8'), 3.36 (3 H, s, H-9), 3.34–3.28 (1 H, m, H-7'), 3.25 (1 H, dd, *J* = 15.2, 8.7 Hz, H-13), 3.17 (1 H, dd, *J* = 14.9, 2.5 Hz, H-14), 3.12–3.04 (2 H, m, H-13' and H-14')´, 3.01 (1 H, dd, *J* = 13.7, 7.3 Hz, H-17), 2.94 (1 H, dd, *J* = 8.7, 5.2 Hz, H-4), 2.81 (1 H, dd, *J* = 13.9, 9.7 Hz, H-17'), 1.96–1.84 (1 H, m, H-15), 0.91 (3 H, d, *J* = 6.7 Hz, H-16), 0.89 (3 H, d, *J* = 6.7 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 155.4 (C, C-10), 147.3 (CH_{ar}, C-24 or C-25), 146.7 (CH_{ar}, C-25 or C-24), 144.4 (C_{ar}, C-21), 142.1 (C_{ar}, C-20), 139.7 (C_{ar}, C-18), 137.4 (C_{ar}), 131.3 (CH_{ar}, C-22), 130.0 (CH_{ar}, C-19), 129.3 ($2 \times CH_{ar}$), 128.7 ($2 \times CH_{ar}$), 126.9 (CH_{ar}), 126.8 (CH_{ar}, C-23), 109.0 (CH, C-1), 80.0 (CH, C-3), 74.2 (CH_2, C-2), 72.8 (CH, C-12), 72.5 (CH, C-5), 71.8 (CH_2, C-8), 71.1 (CH_2, C-6), 68.4 (CH_2, C-7), 59.1 (CH_3, C-9), 58.7 (CH_2, C-14), 55.5 (CH, C-11), 53.6 (CH_2, C-13), 51.6 (CH, C-4), 35.5 (CH_2, C-17), 27.3 (CH, C-15), 20.1 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI+) *m*/*z* 681.1 $(M + Na)^+$; **HRMS** (ESI+) for $C_{32}H_{42}N_4O_9S$ $(M + Na)^+$ calcd. 681.2565, found 681.2580.

Protease Inhibitor 4.17b



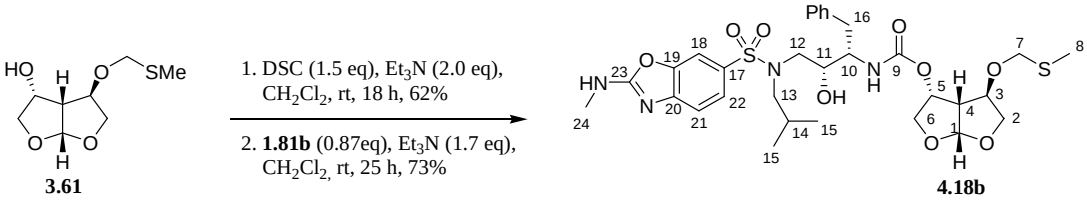
3.59 **4.17b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.59** (177 mg, 0.93 mmol) with DSC (360 mg, 1.40 mmol) afforded after purification by column chromatography (petroleum ether/acetone 70:30 to 60:40) the corresponding mixed carbonate as a pale yellow oil (277 mg, 0.84 mmol, 90%; $\mathbf{R}_f$ 0.23 (petroleum ether/acetone 70:30); $\mathbf{[\alpha]_D}$ −7.4 (*c* 1.93, $CHCl_3$, 25 °C); **IR** (film) 2948 (w), 2885 (w), 1787 (m), 1734 (vs), 1219 (s), 1198 (s), 1076 (s), 1028 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.84 (1 H, d, *J* = 5.3 Hz), 5.32 (1 H, dt, *J* = 8.8, 6.0 Hz), 4.67 (1 H, d, *J* = 6.9 Hz), 4.65 (1 H, d, *J* = 6.9 Hz), 4.61 (1 H, td, *J* = 2.5, 1.1 Hz), 4.10 (1 H, dd, *J* = 10.4, 6.1 Hz), 4.06 (2 H, d, *J* = 2.5 Hz), 3.89 (1 H, dd, *J* = 10.4, 5.8 Hz), 3.35 (3 H, s), 3.15 (1 H, ddd, *J* = 8.8, 5.2, 0.8 Hz), 2.83 (4 H, m) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.3 (C), 151.0 (C), 108.7 (CH), 95.8 (CH_2), 78.3 (CH), 76.9 (CH), 74.7 (CH_2), 70.0 (CH_2), 55.6 (CH_3), 52.0 (CH), 25.4 ($2 \times CH_2$) ppm; **LRMS** (ESI^+) *m*/*z* 386.1 $(M+MeOH+Na)^+$; **HRMS** (ESI^+) for $C_{13}H_{17}NO_9Na$ $(M + Na)^+$ calcd 354.0796, found 354.0796).

Following general procedure **F** (8.2.1), subsequent reaction of the mixed carbonate (235 mg, 0.71 mmol) with amine **1.81b** (288 mg, 0.65 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.17b** as a white solid (281 mg, 65%). **Formula** $C_{31}H_{42}N_4O_{10}S$; **Mw** 662.75; **Mp** 93–95 °C; $\mathbf{R}_f$ 0.23 (CH_2Cl_2/MeOH 97:3); $\mathbf{[\alpha]_D}$ +20.2 (c 0.71, $CHCl_3$, 25 °C); **IR** (film) 3338 (br. w), 2958 (w), 1709 (m), 1659 (vs), 1581 (m), 1463 (m), 1326 (m), 1272 (m), 1240 (m), 1148 (s), 1018 (s), 753 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (1 H, s, H-18), 7.60 (1 H, d, *J* = 8.4 Hz, H-22), 7.42 (1 H, d, *J* = 8.3 Hz, H-21), 7.34–7.20 (5 H, m, Ar-H), 5.81 (1 H, d, *J* = 5.1 Hz, H-1), 5.43 (1 H, d, *J* = 5.0 Hz, N*H*Me), 5.12 (1 H, dt, *J* = 8.9, 6.2 Hz, H-5), 5.05 (1 H, d, *J* = 8.7 Hz, NH), 4.58 (1 H, d, *J* = 7.0 Hz, H-7), 4.54 (1 H, d, *J* = 7.0 Hz, H-7'), 4.13 (1 H, d, *J* = 2.1 Hz, H-3), 4.03 (1 H, dd, *J* = 10.0, 6.3 Hz, H-6), 3.98 (1 H, d, *J* = 9.9 Hz, H-2), 3.95–3.84 (3 H, m, H-2', H-10 and H-11), 3.67 (1 H, dd, *J* = 10.0, 6.1 Hz, H-6'), 3.62 (1 H, br. s, OH), 3.34 (3 H, s, H-8), 3.17 (3 H, d, *J* = 5.0 Hz, H-24), 3.10 (1 H, dd, *J* = 15.2, 9.1 Hz, H-12), 3.06 (1 H, dd, *J* = 14.1, 4.9 Hz, H-13), 3.03–2.94 (2 H, m, H-4 and H-12'), 2.94–2.87 (2 H, m, H-13' and H-16), 2.83 (1 H, dd, *J* = 13.6, 7.2 Hz, H-16'),

1.84 (1 H, m, H-14), 0.92 (3 H, d, *J* = 6.7 Hz, H-15), 0.90 (3 H, d, *J* = 6.7 Hz, H-15) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-23), 155.2 (C, C-9), 148.1 (C_{ar}, C-19 or C-20), 147.8 (C_{ar}, C-20 or C-19), 137.5 (C_{ar}), 129.7 (C_{ar}), 129.4 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 126.7 (CH_{ar}), 124.2 (CH_{ar}, C-22), 116.2 (CH_{ar}, C-21), 108.9 (CH, C-1), 108.4 (CH_{ar}, C-18), 95.4 (CH_2, C-7), 76.8 (CH, C-3), 74.7 (CH_2, C-2), 72.6 (CH, C-12), 72.3 (CH, C-5), 71.1 (CH_2, C-6), 58.9 (CH_2, C-13), 55.5 (CH, C-10), 55.2 (CH_3, C-8), 53.9 (CH_2, C-11), 52.2 (CH, C-4), 35.5 (CH_2, C-16), 29.6 (CH_3, C-24), 27.3 (CH, C-14), 20.1 (CH_3, C-15), 19.9 (CH_3, C-15) ppm; **LRMS** (ESI^+) *m*/*z* 685.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{31}H_{42}N_4O_{10}S$ Na $(M + Na)^+$ calcd. 685.2514, found 685.2521.

Protease Inhibitor 4.18b

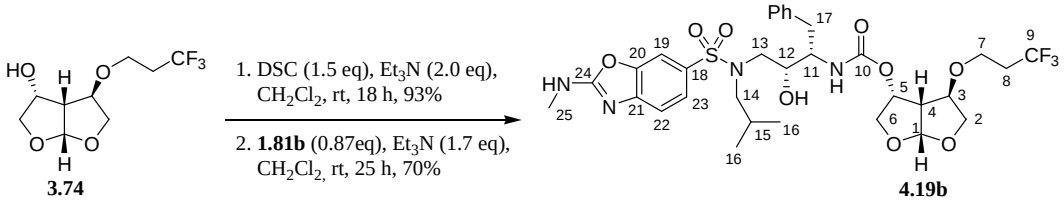


3.61 **4.18b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.61** (160 mg, 0.78 mmol) with DSC (300 mg, 1.16 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99:1 to 97:3) the corresponding mixed carbonate as a pale yellow oil (168 mg, 0.48 mmol, 62%). Following general procedure **F** (8.2.1), subsequent reaction with amine **1.81b** (178 mg, 0.40 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3) and by HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.18b** as a white solid (200 mg, 74%). **Formula** $C_{31}H_{42}N_4O_9S_2$; **Mw** 678.82; **Mp** 101–103 °C; $\mathbf{R_f}$ 0.24 (CH_2Cl_2/MeOH 96:4); $\mathbf{[\alpha]_D}$ +10.5 (c 1.03, $CHCl_3$, 25 °C); **IR** (film) 3341 (br. w), 2961 (w), 2873 (w), 1711 (m), 1656 (vs), 1580 (m), 1325 (m), 1271 (m), 1239 (m), 1143 (s), 1051 (s), 909 (s), 728 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (1 H, d, *J* = 1.3 Hz, H-18), 7.59 (1 H, dd, *J* = 8.2, 1.4 Hz, H-22), 7.40 (1 H, d, *J* = 8.3 Hz, H-21), 7.33–7.19 (5 H, m, Ar-H), 5.80 (1 H, d, *J* = 5.1 Hz, H-1), 5.73 (1 H, *J* = 4.4 Hz, N*H*Me), 5.17 (1 H, d, *J* = 8.5 Hz, N*H*CO_2), 5.11 (1 H, dt, *J* = 8.7, 6.4 Hz, H-5), 4.53 (1 H, d, *J* = 11.5 Hz, H-7), 4.48 (1 H, d, *J* = 11.5 Hz, H-7'), 4.26 (1 H, d, *J* = 3.3 Hz, H-3), 4.01 (1 H, dd, *J* = 9.7, 6.3 Hz, H-6), 3.98–3.84 (4 H, m, H-2, H-2', H-10 and H-11), 3.72 (1 H, d, *J* = 1.4 Hz, OH), 3.67 (1 H, dd, *J* = 9.9, 6.2 Hz, H-6'), 3.16 (3 H, d, *J* = 5.0 Hz, H-24), 3.12–2.96 (4 H, m, H-12, H-13, H-13' and H-16), 2.96–2.80 (3 H, m, H-4 , H-12' and H-16'), 2.74 (1 H, dd, *J* = 13.7, 10.4 Hz, H-17'), 2.11 (3 H, s, H-8), 1.86 (1 H, m, H-14), 0.90 (3 H, d, *J* = 6.7 Hz,

H-15), 0.88 (3 H, d, *J* = 6.7 Hz, H-15) ppm; **^{13}C NMR + DEPT** (100 MHz, CDCl3) δ 164.7 (C_{ar}, C-23), 155.2 (C, C-9), 148.1 (C_{ar}, C-19 or C-20), 147.8 (C_{ar}, C-20 or C-19), 137.5 (C_{ar}), 129.6 (C_{ar}), 129.4 ($2 \times CH_{ar}$), 128.6 ($2 \times CH_{ar}$), 126.7 (CH_{ar}), 124.2 (CH_{ar}, C-22), 116.0 (CH_{ar}, C-21), 108.9 (CH, C-1), 108.4 (CH_{ar}, C-18), 76.3 (CH, C-3), 74.2 (CH_2, C-2), 73.2 (CH_2, C-7), 72.5 (CH, C-11), 72.3 (CH, C-5), 71.0 (CH_2, C-6), 58.8 (CH_2, C-13), 55.2 (CH, C-10), 53.7 (CH_2, C-12), 51.6 (CH, C-4), 35.4 (CH_2, C-16), 29.5 (CH_3, C-24), 27.2 (CH, C-14), 20.1 (CH_3, C-15), 19.9 (CH_3, C-15), 13.8 (CH_3, C-8) ppm; **LRMS** (ESI+) *m*/*z* 701.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{31}H_{42}N_4O_9S_2Na$ $(M + Na)^+$ calcd. 701.2285, found 788.2275.

Protease Inhibitor 4.19b

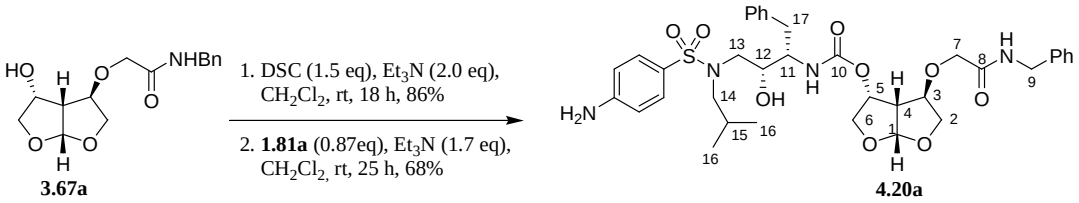


3.74 **4.19b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.74** (55 mg, 0.23 mmol) with DSC (88 mg, 0.35 mmol) afforded the corresponding mixed carbonate as a pale yellow oil (85 mg, 0.22 mmol, 93%). Following general procedure **F** (8.2.1), subsequent reaction with amine **1.81b** (100 mg, 0.22 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 96:4 to 95:5) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.19b** as a white solid (110 mg, 70%). **Formula** $C_{32}H_{41}F_3N_4O_9S$; **Mw** 714.75; **Mp** 110–112 °C; $\mathbf{R_f}$ 0.30 (CH_2Cl_2/MeOH 96:4); $\mathbf{[\alpha]_D}$ +14.2 (c 0.61, $CHCl_3$, 23 °C); **IR** (film) 3339 (m), 2960 (w), 2874 (w), 1716 (m), 1660 (vs), 1581 (m), 1463 (m), 1327 (m), 1255 (s), 1146 (vs), 1021 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1 H, d, *J* = 1.6 Hz, H-19), 7.63 (1 H, dd, *J* = 8.3, 1.8 Hz, H-23), 7.43 (1 H, d, *J* = 8.2 Hz, H-22), 7.33–7.19 (5 H, m, Ar-H), 5.76 (1 H, d, *J* = 5.3 Hz, H-1), 5.29 (1 H, q, *J* = 4.9 Hz, N*H*Me), 5.10 (1 H, dt, *J* = 9.0, 5.8 Hz, H-5), 5.02 (1 H, d, *J* = 9.1 Hz, N*H*), 3.99 (1 H, dd, *J* = 10.0, 5.9 Hz, H-6), 3.96−3.84 (3 H, m, H-2, H-11 and H-12), 3.79 (1 H, dd, *J* = 10.2, 3.7 Hz, H-2'), 3.70 (1 H, dd, *J* = 10.0, 5.7 Hz, H-6'), 3.59 (1 H, d, *J* = 2.5 Hz, O*H*), 3.51−3.42 (2 H, m, H-3 and H-7), 3.34 (1 H, m, H-7'), 3.18 (3 H, d, *J* = 5.2 Hz, H-25), 3.16 (1 H, dd, *J* = 15.2, 8.8 Hz, H-13), 3.09 (1 H, dd, *J* = 14.1, 4.0 Hz, H-17), 3.01 (1 H, dd, *J* = 15.2, 2.7 Hz, H-13'), 2.98 (1 H, dd, *J* = 13.4, 8.0 Hz, H-14), 2.90 (1 H, dd, *J* = 9.0, 5.2 Hz, H-4), 2.85 (1 H, dd, *J* = 13.3, 6.9 Hz, H-14'), 2.79 (1 H, dd, *J* = 14.1, 9.6 Hz, H-17'), 2.33 (2 H, qt, *J* = 10.7, 6.7 Hz,

H-8), 1.86 (1 H, m, H-15), 0.94 (3 H, d, *J* = 6.6 Hz, H-16), 0.91 (3 H, d, *J* = 6.6 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, CDCl3) δ 164.7 (C_{ar}, C-24), 155.2 (C, C-10), 148.2 (C_{ar}, C-20 or C-21), 147.9 (C_{ar}, C-21 or C-20), 137.7 (C_{ar}), 129.7 (C_{ar}, C-18), 129.3 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.7 (CH_{ar}), 124.2 (CH_{ar}, C-20), 116.3 (CH_{ar}, C-19), 109.0 (CH, C-1), 108.4 (CH_{ar}, C-16), 80.0 (CH, C-3), 74.2 (CH_2, C-2), 72.9 (CH, C-12), 72.4 (CH, C-5), 71.1 (CH_2, C-6), 61.7 (CH_2, d, *J* = 3.3 Hz, C-7), 59.0 (CH_2, C-14), 55.5 (CH, C-11), 53.8 (CH_2, C-10), 51.4 (CH, C-4), 35.6 (CH_2, C-17), 34.4 (CH_2, q, *J* = 28.5 Hz, C-8), 29.6 (CH_3, C-25), 27.3 (CH, C-15), 20.1 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −64.88 (CF_3, t, *J* = 10.6 Hz, F-9), **LRMS** (ESI+) *m*/*z* 737.4 $(M + Na)^+$, 753.4 $(M+K)^+$; **HRMS** (ESI^+) for $C_{32}H_{41}F_3N_4O_9SK$ $(M+K)^+$ calcd. 753.2178, found 753.2172.

Protease Inhibitor 4.20a

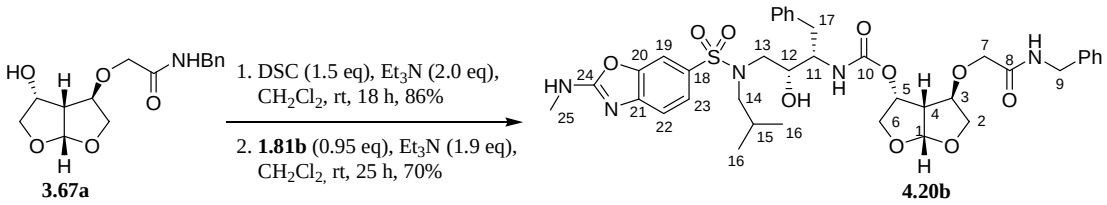


3.67a **4.20a**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.67a** (185 mg, 0.63 mmol) with DSC (242 mg, 0.95 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) the corresponding mixed carbonate as a pale yellow oil (234 mg, 0.54 mmol, 86%). Following general procedure **F** (8.2.1), the reaction of this carbonate (220 mg, 0.51 mmol) with amine **1.81a** (189 mg, 0.48 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 96:4) and by HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.20a** as a white solid (234 mg, 68%). **Formula** $C_{36}H_{46}N_4O_9S$; **Mw** 710.84; **R_f** 0.31 (CH_2Cl_2/MeOH 96:4); **Mp** 95−97 °C; **[α]$_D$** +21.6 (c 0.87, $CHCl_3$, 27 °C); **IR** (film) 3363 (m), 2960 (w), 1712 (m), 1661 (m), 1596 (s), 1534 (m), 1313 (m), 1146 (s), 1090 (s), 909 (m), 729 (vs), 701 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.55 (2 H, d, *J* = 8.7 Hz, Ar-H), 7.39–7.12 (10 H, m, Ar-H), 6.75 (1 H, t, *J* = 5.7 Hz, N*H*Bn), 6.69 (2 H, d, *J* = 8.7 Hz, Ar-H), 5.71 (1 H, d, *J* = 5.3 Hz, H-1), 5.18 (1 H, d, *J* = 5.3 Hz, N*H*), 5.06 (1 H, dt, *J* = 8.5, 5.9 Hz, H-5), 4.51 (1 H, dd, *J* = 14.8, 5.9 Hz, H-9), 4.47 (1 H, dd, *J* = 14.8, 5.9 Hz, H-9'), 4.20 (2 H, br. s, NH_2), 3.96 (1 H, dd, *J* = 10.2, 6.1 Hz, H-6), 3.93–3.86 (4 H, m, H-2, H-7, H-11 and H-12), 3.75 (1 H, dd, *J* = 10.5, 3.6 Hz, H-2'), 3.72–3.64 (3 H, m, H-6', H-7' and O*H*), 3.47 (1 H, d, *J* = 3.0 Hz, H-3), 3.15 (1 H, dd, *J* =

15.2, 8.5 Hz, H-13), 3.05 (1 H, dd, *J* = 14.0, 4.2 Hz, H-17), 3.01–2.92 (2 H, m, H-13' and H-14), 2.88 (1 H, dd, *J* = 8.3, 5.4 Hz, H-4), 2.80 (1 H, dd, *J* = 13.6, 6.8 Hz, H-14'), 2.76 (1 H, dd, *J* = 14.3, 10.2 Hz, H-17'), 1.83 (1 H, m, H-15), 0.94 (3 H, d, *J* = 6.5 Hz, H-16), 0.90 (3 H, d, *J* = 6.5 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.9 (C, C-8), 155.1 (C, C-10), 150.8 (C_{ar}), 137.9 (C_{ar}), 137.8 (C_{ar}), 129.5 (2 × CH_{ar}), 129.4 (2 × CH_{ar}), 128.8 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 127.8 (2 × CH_{ar}), 127.6 (CH_{ar}), 126.6 (CH_{ar}), 126.0 (C_{ar}), 114.1 (2 × CH_{ar}), 108.8 (CH, C-1), 80.6 (CH, C-3), 73.8 (CH_2, C-2), 72.9 (CH, C-12), 72.1 (CH, C-5), 71.0 (CH_2, C-6), 68.2 (CH_2, C-7), 58.9 (CH_2, C-14), 55.5 (CH, C-11), 53.7 (CH_2, C-13), 51.3 (CH, C-4), 42.9 (CH_2, C-9), 35.4 (CH_2, C-17), 27.3 (CH, C-15), 20.2 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI^+) *m/z* 733.5 $(M + Na)^+$; **HRMS** (ESI+) for $C_{36}H_{46}N_4O_9S$ $(M + Na)^+$ calcd. 733.2878, found 733.2873.

Protease Inhibitor 4.20b

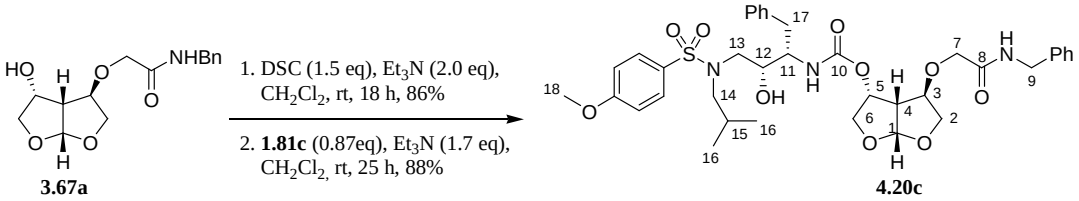


3.67a **4.20b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.67a** (185 mg, 0.63 mmol) with DSC (242 mg, 0.95 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) the corresponding mixed carbonate as a pale yellow oil (234 mg, 0.54 mmol, 86%). Following general procedure **F** (8.2.1), the reaction of this carbonate (212 mg, 0.49 mmol) with amine **1.81b** (208 mg, 0.46 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 96:4 to 94:6) and by HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.20b** as a white solid (248 mg, 70%). **Formula** $C_{38}H_{47}N_5O_{10}S$; **Mw** 795.87; **R_f** 0.29 (CH_2Cl_2/MeOH 95:5); **Mp** 101−103 °C; **[α]$_D$** +26.1 (*c* 0.52, $CHCl_3$, 26 °C); **IR** (film) 3338 (br. w), 2960 (w), 1712 (m), 1655 (vs), 1580 (m), 1534 (m), 1326 (m), 1271 (m), 1239 (m), 1121 (s), 909 (s), 728 (vs), 700 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1 H, d, *J* = 1.6 Hz, H-19), 7.61 (1 H, dd, *J* = 8.3, 1.8 Hz, H-23), 7.40 (1 H, d, *J* = 8.3 Hz, H-22), 7.37–7.11 (10 H, m, Ar-H), 6.80 (1 H, t, *J* = 5.6 Hz, N*H*Bn), 5.93 (1 H, br. s, N*H*Me), 5.70 (1 H, d, *J* = 5.1 Hz, H-1), 5.44 (1 H, d, *J* = 5.0 Hz, N*H*), 5.04 (1 H, dt, *J* = 8.7, 5.9 Hz, H-5), 4.51 (1 H, dd, *J* = 16.9, 5.8 Hz, H-9), 4.47 (1 H, dd, *J* = 16.9, 5.8 Hz, H-9'), 4.00–3.84 (5 H, m, H-2, H-6, H-7, H-11 and H-12), 3.80–3.73 (2 H, m, H-2' and O*H*), 3.69 (1 H, d, *J* = 15.3 Hz, H-7'), 3.66 (1 H, dd, *J* = 10.0, 5.5 Hz,

H-6'), 3.50 (1 H, d, *J* = 2.5 Hz, H-3), 3.14 (3 H, d, *J* = 4.8 Hz, H-25), 3.11 (2 H, dd, *J* = 13.1, 4.1 Hz, H-13 and H-13'), 3.07 (1 H, dd, *J* = 13.7, 4.1 Hz, H-17), 2.98–2.83 (3 H, m, H-4 , H-14 and H-14'), 2.74 (1 H, dd, *J* = 13.7, 10.4 Hz, H-17'), 1.86 (1 H, m, H-15), 0.91 (3 H, d, *J* = 6.4 Hz, H-16), 0.89 (3 H, d, *J* = 6.4 Hz, H-16) ppm. **^{13}C NMR + DEPT** (100 MHz, CDCl3) δ 169.1 (C, C-8), 164.8 (C_{ar}, C-24), 55.2 (C, C-10), 148.1 (C_{ar}, C-20 or C-21), 147.9 (C_{ar}, C-21 or C-20), 137.9 (C_{ar}), 137.5 (C_{ar}), 129.5 (C_{ar}), 129.3 ($2 \times CH_{ar}$), 128.7 ($2 \times CH_{ar}$), 128.4 ($2 \times CH_{ar}$), 127.7 ($2 \times CH_{ar}$), 127.6 (CH_{ar}), 126.5 (CH_{ar}), 124.2 (CH_{ar}, C-23), 116.0 (CH_{ar}, C-22), 108.8 (CH, C-1), 108.4 (CH_{ar}, C-19), 80.5 (CH, C-3), 73.8 (CH_2, C-2), 72.9 (CH, C-12), 72.1 (CH, C-5), 71.0 (CH_2, C-6), 68.1 (CH_2, C-7), 58.8 (CH_2, C-14), 55.6 (CH, C-11), 53.6 (CH_2, C-13), 51.3 (CH, C-4), 42.8 (CH_3, C-9), 35.5 (CH_2, C-17), 29.4 (CH_3, C-25), 27.1 (CH, C-15), 20.1 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI+) *m*/*z* 788.1 $(M + Na)^+$; **HRMS** (ESI+) for $C_{38}H_{47}N_5O_{10}SNa$ $(M + Na)^+$ calcd. 788.2936, found 788.2925.

Protease Inhibitor 4.20c

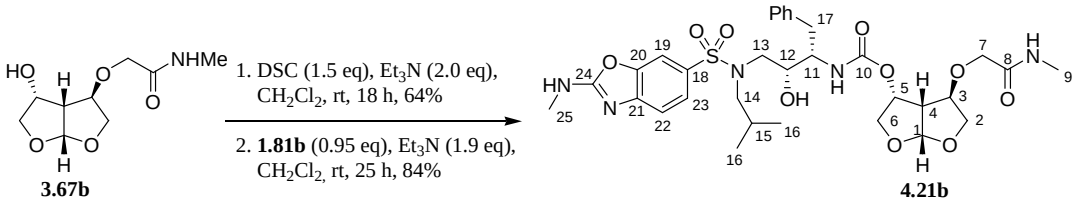


3.67a **4.20c**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.67a** (185 mg, 0.63 mmol) with DSC (242 mg, 0.95 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) the corresponding mixed carbonate as a pale yellow oil (234 mg, 0.54 mmol, 86%). Following general procedure **F** (8.2.1), this carbonate was then reacted with amine **1.81c** (200 mg, 0.49 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 96:4) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.20c** as a white solid (313 mg, 88%). **Formula** $C_{37}H_{47}N_3O_{10}S$; **Mw** 725.85; **R_f** 0.39 (CH_2Cl_2/MeOH 95:5); **Mp** 88−90 °C; **$[\alpha]_D$** +18.6 (c 0.93, $CHCl_3$, 25 °C); **IR** (film) 3360 (w), 2961 (w), 2931 (w), 1715 (m), 1662 (m), 1532 (m), 1332 (m), 1258 (s), 1150 (s), 1091 (s), 1022 (m), 908 (m), 727 (vs), 700 (s), 558 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (2 H, d, *J* = 9.0 Hz, Ar-H), 7.37–7.12 (10 H, m, Ar-H), 6.99 (2 H, d, *J* = 9.0 Hz, Ar-H), 6.79 (1 H, t, *J* = 5.7 Hz, N*H*Bn), 5.70 (1 H, d, *J* = 5.2 Hz, H-1), 5.41 (1 H, d, *J* = 8.8 Hz, N*H*CHBn), 5.05 (1 H, dt, *J* = 8.6, 5.8 Hz, H-5), 4.50 (1 H, dd, *J* = 14.8, 5.9 Hz, H-9), 4.45 (1 H, dd, *J* = 14.8, 5.9 Hz, H-9'), 3.93 (1 H, dd, *J* = 10.0, 6.1 Hz, H-6),

3.92–3.82 (4 H, m, H-2, H-7, H-11 and H-12), 3.87 (3 H, s, H-18), 3.78–3.72 (2 H, m, H-2' and OH), 3.67 (1 H, dd, *J* = 10.0, 5.7 Hz, H-6'), 3.65 (1 H, d, *J* = 14.8 Hz, H-7'), 3.45 (1 H, d, *J* = 3.2 Hz, H-3), 3.14 (1 H, dd, *J* = 15.3, 8.3 Hz, H-13), 3.10–3.01 (2 H, m, H-13' and H-17), 2.95 (1 H, dd, *J* = 13.5, 8.1 Hz, H-14), 2.88 (1 H, dd, *J* = 8.8, 5.2 Hz, H-4), 2.84 (1 H, dd, *J* = 13.5, 6.9 Hz, H-14'), 2.76 (1 H, dd, *J* = 14.0, 10.2 Hz, H-17'), 1.87 (1 H, m, H-15), 0.91 (3 H, d, *J* = 6.6 Hz, H-16), 0.88 (3 H, d, *J* = 6.6 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.9 (C, C-8), 163.0 (C_{ar}), 155.1 (C, C-10), 137.9 (C_{ar}), 137.8 (C_{ar}), 129.6 (C_{ar}), 129.4 (2 × CH_{ar}), 129.3 (2 × CH_{ar}), 128.7 (2 × CH_{ar}), 128.4 (2 × CH_{ar}), 127.7 (2 × CH_{ar}), 127.5 (CH_{ar}), 126.5 (CH_{ar}), 114.3 (2 × CH_{ar}), 108.7 (CH, C-1), 80.5 (CH, C-3), 73.8 (CH_2, C-2), 72.9 (CH, C-12), 72.1 (CH, C-5), 71.0 (CH_2, C-6), 68.1 (CH_2, C-7), 58.7 (CH_2, C-14), 55.6 (CH_3, C-18), 55.5 (CH, C-11), 53.5 (CH_2, C-13), 51.3 (CH, C-4), 42.8 (CH_2, C-9), 35.4 (CH_2, C-17), 27.1 (CH, C-15), 20.1 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI^+) *m*/*z* 748.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{37}H_{47}N_3O_{10}SNa$ $(M + Na)^+$ calcd 748.2874, found 748.2894.

Protease Inhibitor 4.21b

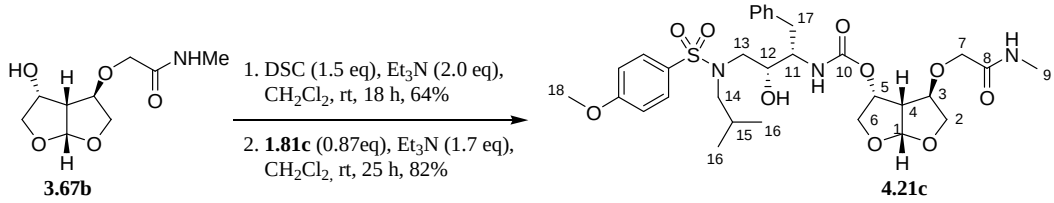


3.67b **4.21b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.67b** (174 mg, 0.80 mmol) with DSC (307 mg, 1.20 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) the corresponding mixed carbonate as a pale yellow oil (183 mg, 0.51 mmol, 64%). Following general procedure **F** (8.2.1), reaction of this carbonate (149 mg, 0.42 mmol) with amine **1.81b** (178 mg, 0.40 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 96:4 to 93:7) and by HPLC (CH_2Cl_2/MeOH 95:5) the PI **4.21b** as a white solid (232 mg, 84%). **Formula** $C_{32}H_{43}N_5O_{10}S$; **Mw** 689.78; **R_f** 0.20 (CH_2Cl_2/MeOH 95:5); **Mp** 91−93 °C; **[α]$_D$** +22.1 (*c* 0.84, $CHCl_3$, 26 °C); **IR** (film) 3348 (br. w), 2959 (w), 1716 (m), 1659 (vs), 1581 (m), 1327 (m), 1272 (m), 1240 (m), 1146 (m), 1123 (m), 733 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1 H, d, *J* = 1.4 Hz, H-19), 7.62 (1 H, dd, *J* = 8.2, 1.7 Hz, H-23), 7.42 (1 H, d, *J* = 8.3 Hz, H-22), 7.31–7.17 (5 H, m, Ar-H), 6.46 (1 H, br. s, CON*H*Me), 5.77 (1 H, d, *J* = 5.1 Hz, H-1), 5.74 (1 H, br. s, N*H*Me), 5.30 (1 H, d, *J* = 8.9 Hz, N*H*), 5.07 (1 H, dt, *J* =

8.7, 5.8 Hz, H-5), 3.99 (1 H, dd, *J* = 9.7, 6.3 Hz, H-6), 3.98–3.81 (4 H, m, H-2, H-7, H-11 and H-12), 3.80 (1 H, dd, *J* = 10.5, 3.6 Hz, H-2'), 3.71–3.63 (3 H, m, H-6', H-7' and O*H*), 3.54 (1 H, d, *J* = 3.0 Hz, H-3), 3.16 (3 H, d, *J* = 4.9 Hz, H-25), 3.13–3.01 (3 H, m, H-13 , H-13' and H-17), 2.99–2.83 (3 H, m, H-4 , H-14 and H-14'), 2.86 (3 H, d, *J* = 5.0 Hz, H-9), 2.77 (1 H, dd, *J* = 13.9, 10.4 Hz, H-17'), 1.86 (1 H, m, H-15), 0.92 (3 H, d, *J* = 6.7 Hz, H-16), 0.90 (3 H, d, *J* = 6.7 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, CDCl3) δ 169.7 (C, C-8), 164.8 (C_{ar}, C-24), 155.1 (C, C-10), 148.2 (C_{ar}, C-20 or C-21), 147.9 (C_{ar}, C-21 or C-20), 137.8 (C_{ar}), 129.6 (C_{ar}), 129.3 ($2 \times CH_{ar}$), 128.5 ($2 \times CH_{ar}$), 126.6 (CH_{ar}), 124.2 (CH_{ar}, C-23), 116.1 (CH_{ar}, C-22), 108.8 (CH, C-1), 108.4 (CH_{ar}, C-19), 80.4 (CH, C-3), 73.8 (CH_2, C-2), 72.8 (CH, C-12), 72.2 (CH, C-5), 71.0 (CH_2, C-6), 68.2 (CH_2, C-7), 58.9 (CH_2, C-14), 55.5 (CH, C-11), 53.6 (CH_2, C-13), 51.4 (CH, C-4), 35.5 (CH_2, C-17), 29.5 (CH_3, C-25), 27.2 (CH, C-15), 25.6 (CH_3, C-9), 20.1 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI^+) *m*/*z* 712.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{32}H_{43}N_5O_{10}SNa$ $(M + Na)^+$ calcd. 712.2623, found 712.2626.

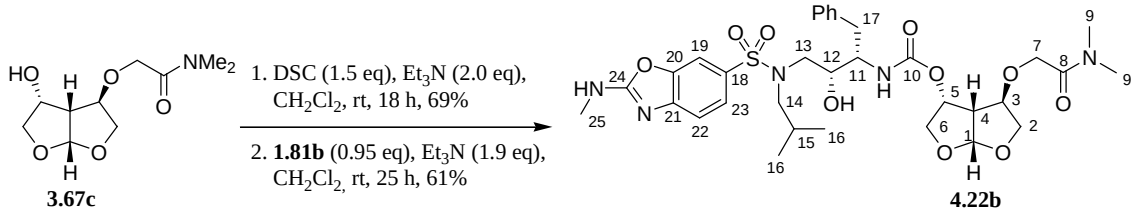
Protease Inhibitor 4.21c



Following general procedure **E** (8.2.1), the reaction of alcohol **3.67b** (174 mg, 0.80 mmol) with DSC (307 mg, 1.20 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 94:6) the corresponding mixed carbonate as a pale yellow oil (183 mg, 0.51 mmol, 64%). Following general procedure **F** (8.2.1), this carbonate was then reacted with amine **1.81c** (200 mg, 0.49 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.21c** as a white solid (260 mg, 82%). **Formula** $C_{31}H_{43}N_3O_{10}S$; **Mw** 649.75; **R_f** 0.36 (CH_2Cl_2/MeOH 95:5); **Mp** 92−94 °C; **$[\alpha]_D$** +15.9 (c 1.38, $CHCl_3$, 24 °C); **IR** (film) 3361 (w), 2960 (w), 2873 (w), 1716 (m), 1662 (m), 1541 (m), 1332 (m), 1258 (s), 1150 (vs), 1091 (s), 1023 (s), 730 (vs), 560 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.72 (2 H, d, *J* = 9.0 Hz, Ar-H), 7.32–7.18 (5 H, m, Ar-H), 7.00 (2 H, d, *J* = 9.0 Hz, Ar-H), 6.42 (1 H, br. s, N*H*Me), 5.77 (1 H, d, *J* = 5.3 Hz, H-1), 5.14 (1 H, d, *J* = 8.8 Hz, N*H*CHBn), 5.08 (1 H, dt, *J* = 8.8, 6.0 Hz, H-5), 3.99 (1 H, dd, *J* = 10.0, 6.3 Hz, H-6),

3.96–3.85 (3 H, m, H-2, H-11 and H-12), 3.89 (3 H, s, H-18), 3.83–3.75 (2 H, m, H-2' and H-7), 3.69 (1 H, dd, *J* = 10.0, 5.9 Hz, H-6'), 3.67–3.62 (2 H, m, H-7' and OH), 3.49 (1 H, d, *J* = 3.2 Hz, H-3), 3.18 (1 H, dd, *J* = 15.2, 8.7 Hz, H-13), 3.06 (1 H, dd, *J* = 13.7, 4.0 Hz, H-17), 3.03–2.95 (2 H, m, H-13' and H-14), 2.91 (1 H, dd, *J* = 8.5, 5.2 Hz, H-4), 2.86 (3 H, s, H-9), 2.85–2.74 (2 H, m, H-14' and H-17'), 1.85 (1 H, m, H-15), 0.94 (3 H, d, *J* = 6.6 Hz, H-16), 0.90 (3 H, d, *J* = 6.7 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 169.5 (C, C-8), 163.1 (C_{ar}), 155.1 (C, C-10), 137.7 (C_{ar}), 129.7 (C_{ar}), 129.5 ($2 \times CH_{ar}$), 129.3 ($2 \times CH_{ar}$), 128.5 ($2 \times CH_{ar}$), 126.6 (CH_{ar}), 114.4 ($2 \times CH_{ar}$), 108.8 (CH, C-1), 80.4 (CH, C-3), 73.8 (CH_2, C-2), 72.9 (CH, C-12), 72.2 (CH, C-5), 71.0 (CH_2, C-6), 68.2 (CH_2, C-7), 58.9 (CH_2, C-14), 55.7 (CH_3, C-18), 55.5 (CH, C-11), 53.7 (CH_2, C-13), 51.4 (CH, C-4), 35.4 (CH_2, C-17), 27.3 (CH, C-15), 25.6 (CH_3, C-9), 20.2 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI^+) *m*/*z* 672.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{31}H_{43}N_3O_{10}SNa$ $(M + Na)^+$ calcd 672.2561, found 672.2536.

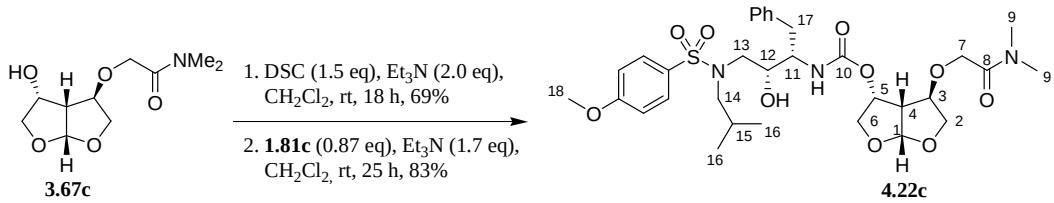
Protease Inhibitor 4.22b



Following general procedure **E** (8.2.1), the reaction of alcohol **3.67c** (200 mg, 0.80 mmol) with DSC (307 mg, 1.20 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) the corresponding mixed carbonate as a pale yellow oil (206 mg, 0.55 mmol, 69%). Following general procedure **F** (8.2.1), the reaction of this carbonate (112 mg, 0.30 mmol) with amine **1.81b** (130 mg, 0.29 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 95:5) the PI **4.22b** as a white solid (124 mg, 61%). **Formula** $C_{33}H_{45}N_5O_9S$; **Mw** 703.80; **R_f** 0.25 (CH_2Cl_2/MeOH 95:5); **Mp** 85−87 °C; **$[\alpha]_D$** +21.9 (c 1.13, $CHCl_3$, 26 °C); **IR** (film) 3307 (br. w), 2959 (w), 1716 (m), 1654 (vs), 1580 (m), 1463 (m), 1327 (m), 1271 (m), 1239 (m), 1121 (s), 730 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (1 H, s, H-19), 7.59 (1 H, d, *J* = 8.3 Hz, H-23), 7.37 (1 H, d, *J* = 8.3 Hz, H-22), 7.29–7.14 (5 H, m, Ar-H), 5.78 (1 H, d, *J* = 5.3 Hz, H-1), 5.67 (1 H, d, *J* = 8.5 Hz, N*H*CO_2), 5.57 (1 H, br. s, N*H*Me), 5.03 (1 H, dt, *J* = 8.4, 6.1 Hz, H-5), 4.16–3.80 (8 H, m, H-2, H-2', H-3, H-6, H-7, H-7', H-11 and H-12), 3.73 (1 H, br. s, OH), 3.61 (1 H, dd, *J* = 9.5, 6.4 Hz, H-6'), 3.13

(3 H, d, *J* = 4.8 Hz, H-25), 3.11–2.93 (4 H, m, H-4, H-13, H-13' and H-17), 2.96 (3 H, s, H-9), 2.93 (3 H, s, H-9), 2.92–2.84 (2 H, m, H-14 and H-14'), 2.80 (1 H, dd, *J* = 13.9, 9.5 Hz, H-17'), 1.86 (1 H, m, H-15), 0.88 (6 H, d, *J* = 6.5 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.8 (C, C-8), 164.8 (C_{ar}, C-24), 155.4 (C, C-10), 148.0 (C_{ar}, C-20 or C-21), 147.8 (C_{ar}, C-21 or C-20), 137.9 (C_{ar}), 129.6 (C_{ar}), 129.4 (2 × CH_{ar}), 128.4 (2 × CH_{ar}), 126.5 (CH_{ar}), 124.1 (CH_{ar}, C-23), 115.9 (CH_{ar}, C-22), 108.7 (CH, C-1), 108.3 (CH_{ar}, C-19), 79.6 (CH, C-3), 73.7 (CH_2, C-2), 72.6 (CH, C-12), 72.1 (CH, C-5), 70.9 (CH_2, C-6), 68.0 (CH_2, C-7), 58.6 (CH_2, C-14), 55.5 (CH, C-11), 53.5 (CH_2, C-13), 51.7 (CH, C-4), 36.5 (CH_3, C-9), 35.7 (CH_2, C-17), 35.5 (CH_3, C-9), 29.4 (CH_3, C-25), 27.1 (CH, C-15), 20.1 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI^+) *m*/*z* 726.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{33}H_{45}N_5O_{10}SNa$ $(M + Na)^+$ calcd. 726.2779, found 726.2778

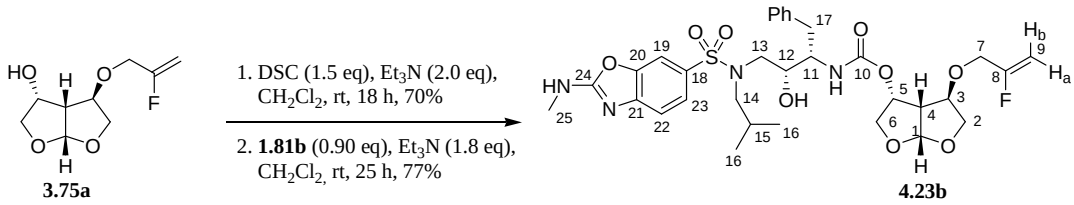
Protease Inhibitor 4.22c



Following general procedure **E** (8.2.1), the reaction of alcohol **3.67c** (200 mg, 0.80 mmol) with DSC (307 mg, 1.20 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) the corresponding mixed carbonate as a pale yellow oil (206 mg, 0.55 mmol, 69%). Following general procedure **F** (8.2.1), this carbonate was then reacted with amine **1.81c** (203 mg, 0.50 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.22c** as a white solid (273 mg, 83%). **Formula** $C_{32}H_{45}N_3O_{10}S$; **Mw** 663.78; **R_f** 0.35 (CH_2Cl_2/MeOH 95:5); **Mp** 89−90 °C; **$[\alpha]_D$** +19.3 (c 1.09, $CHCl_3$, 24 °C); **IR** (film) 3341 (w), 2959 (w), 2872 (w), 1716 (m), 1647 (m), 1497 (m), 1333 (m), 1258 (s), 1151 (vs), 1092 (s), 1023 (s), 730 (vs), 560 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.71 (2 H, d, *J* = 8.6 Hz, Ar-H), 7.32–7.20 (5 H, m, Ar-H), 6.99 (2 H, d, *J* = 9.0 Hz, Ar-H), 5.77 (1 H, d, *J* = 5.2 Hz, H-1), 5.53 (1 H, d, *J* = 8.3 Hz, NH), 5.07 (1 H, dt, *J* = 8.3, 6.6 Hz, H-5), 4.17–3.82 (8 H, m, H-2, H-2', H-3, H-6, H-7, H-7', H-11 and H-12), 3.88 (3 H, s, H-18), 3.67 (1 H, d, *J* = 1.9 Hz, OH), 3.63 (1 H, dd, *J* = 10.0, 6.3 Hz, H-6'), 3.18–2.76 (7 H, m, H-4, H-13, H-13', H-14, H-14', H-17 and H-17'), 2.98 (3 H, s, H-9), 2.94 (3 H, s, H-9), 1.84 (1 H, m, H-15), 0.92 (3 H, d, *J* = 6.6 Hz, H-16), 0.88 (3 H, d, *J* =

6.4 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.8 (C, C-8), 163.0 (C_{ar}), 155.4 (C, C-10), 137.8 (C_{ar}), 129.8 (C_{ar}), 129.5 ($2 \times CH_{ar}$), 129.4 ($2 \times CH_{ar}$), 128.5 ($2 \times CH_{ar}$), 126.6 (CH_{ar}), 114.3 ($2 \times CH_{ar}$), 108.7 (CH, C-1), 79.6 (CH, C-3), 73.8 (CH_2, C-2), 72.7 (CH, C-12), 72.1 (CH, C-5), 70.8 (CH_2, C-6), 68.1 (CH_2, C-7), 58.7 (CH_2, C-14), 55.6 (CH_3, C-18), 55.4 (CH, C-11), 53.6 (CH_2, C-13), 51.8 (CH, C-4), 36.5 (CH_3, C-9), 35.6 (CH_3, C-9), 35.5 (CH_2, C-17), 27.2 (CH, C-15), 20.1 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **LRMS** (ESI^+) *m*/*z* 686.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{32}H_{45}N_3O_{10}SNa$ $(M + Na)^+$ calcd 686.2718, found 686.2744.

Protease Inhibitor 4.23b

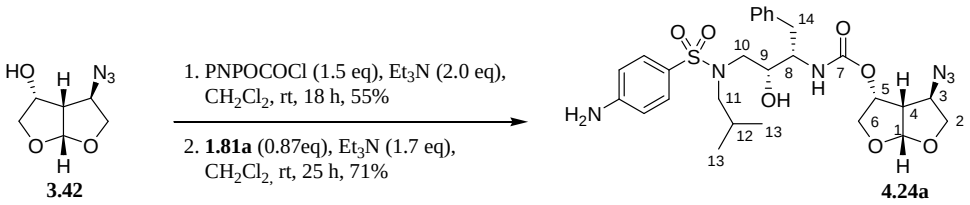


3.75a **4.23b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.75a** (115 mg, 0.56 mmol) with DSC (215 mg, 0.84 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99:1 to 97:3) the corresponding mixed carbonate as a pale yellow oil (136 mg, 0.39 mmol, 70%). Following general procedure **F** (8.2.1), this carbonate was then reacted with amine **1.81b** (156 mg, 0.35 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 95:5 to 90:10) and by HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.23b** as a white solid (182 mg, 77%). **Formula** $C_{32}H_{41}FN_4O_9S$; **Mw** 676.75; **R_f** 0.30 (CH_2Cl_2/MeOH 95:5); **Mp** 116−118 °C; **$[\alpha]_D$** +18.0 (*c* 1.03, $CHCl_3$, 26 °C); **IR** (film) 3339 (m), 2960 (w), 2874 (w), 1716 (m), 1660 (vs), 1581 (m), 1463 (m), 1327 (m), 1255 (s), 1146 (vs), 1021 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.66 (1 H, d, *J* = 1.4 Hz, H-19), 7.62 (1 H, dd, *J* = 8.3, 1.7 Hz, H-23), 7.43 (1 H, d, *J* = 8.2 Hz, H-22), 7.33–7.21 (5 H, m, Ar-H), 5.79 (1 H, d, *J* = 5.1 Hz, H-1), 5.29 (1 H, q, *J* = 5.1 Hz, N*H*Me), 5.11 (1 H, dt, *J* = 8.7, 5.9 Hz, H-5), 5.00 (1 H, q, *J* = 8.8 Hz, NH), 4.73 (1 H, dd, *J* = 16.7, 3.0 Hz, H-9a), 4.53 (1 H, dd, *J* = 48.4, 2.8 Hz, H-9b), 4.04−3.82 (5 H, m, H-2, H-2', H-6, H-11 and H-12), 3.81−3.65 (4 H, m, H-3, H-6', H-7 and H-7'), 3.59 (1 H, br. s, O*H*), 3.18 (3 H, d, *J* = 5.1 Hz, H-22), 3.16–3.05 (2 H, m, H-13 and H-17), 3.04–2.92 (3 H, m, H-4, H-13' and H-14), 2.88−2.79 (2 H, m, H-14' and H-17'), 1.92 (1 H, m, H-15), 0.94 (3 H, d, *J* = 6.6 Hz, H-16), 0.91 (3 H, d, *J* = 6.6 Hz, H-16) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-21), 162.6 (CF, d, *J* = 236.0 Hz, C-8), 155.2 (C, C-10),

148.2 (C_{ar}, C-20 or C-21), 147.9 (C_{ar}, C-21 or C-20), 137.5 (C_{ar}), 129.7 (C_{ar}, C-18), 129.4 ($2 \times CH_{ar}$), 128.6 ($2 \times CH_{ar}$), 126.8 (CH_{ar}), 124.2 (CH_{ar}, C-23), 116.3 (CH_{ar}, C-22), 109.0 (CH, C-1), 108.4 (CH_{ar}, C-19), 92.8 (CH_2, d, J = 16.8 Hz, C-9), 79.7 (CH, C-3), 74.3 (CH_2, C-2), 72.8 (CH, C-12), 72.4 (CH, C-5), 71.0 (CH_2, C-6), 66.3 (CH_2, d, J = 34.0 Hz, C-7), 59.0 (CH_2, C-14), 55.3 (CH, C-11), 53.9 (CH_2, C-13), 51.5 (CH, C-4), 35.6 (CH_2, C-17), 29.6 (CH_3, C-25), 27.3 (CH, C-15), 20.2 (CH_3, C-16), 19.9 (CH_3, C-16) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −105.6 (ddt, J = 48.5, 16.5, 13.2 Hz, F-8); **LRMS** (ESI^+) m/z 699.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{32}H_{41}FN_4O_9SK$ $(M+K)^+$ calcd 715.2210, found 715.2207.

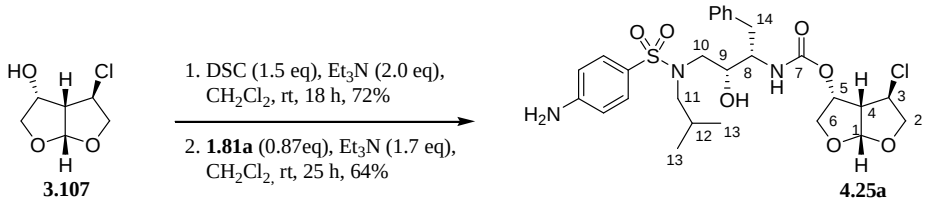
Protease Inhibitor 4.24a



Following general procedure **E** (8.2.1), the reaction of alcohol **3.42** (850 mg, 5.00 mmol) with PNPOCOCl (1.51 g, 7.5 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99.5:0.5 to 99:1) the corresponding mixed carbonate as a pale yellow oil (932 mg, 2.77 mmol, 55%; **Formula** $C_{13}H_{12}N_4O_7$; **Mw** 336.26; $\mathbf{R_f}$ 0.28 (hexane/acetone 75:25); **$[\alpha]_D$** +47.9 (*c* 1.38, CHCl3, 30 °C); **IR** (film) 3115 (w), 3085 (w), 2945 (w), 2887 (w), 2099 (m), 1765 (m), 1523 (m), 1348 (m), 1249 (s), 1212 (vs), 1093 (m), 859 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.32 (2 H, d, J = 9.2 Hz, H-10), 7.41 (2 H, d, J = 9.3 Hz, H-9), 5.89 (1 H, d, J = 5.1 Hz, H-1), 5.37 (1 H, dt, J = 8.7, 5.8 Hz, H-5), 4.32 (1 H, dt, J = 4.4, 1.8 Hz, H-3), 4.22 (1 H, dd, J = 10.0, 4.4 Hz, H-2), 4.19 (1 H, dd, J = 10.4, 6.0 Hz, H-6), 4.08 (1 H, ddd, J = 10.0, 1.9, 1.1 Hz, H-6), 3.97 (1 H, dd, J = 10.3, 5.8 Hz, H-6'), 3.16 (1 H, ddt, J = 8.7, 5.1, 1.3 Hz, H-4) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 155.0 (C_{ar}, C-8), 151.7 (C, C-7), 145.7 (C_{ar}, C-11), 125.5 ($2 \times CH_{ar}$, C-10), 121.6 ($2 \times CH_{ar}$, C-9), 108.6 (CH, C-1), 76.1 (CH, C-5), 73.6 (CH_2, C-2), 70.6 (CH_2, C-6), 61.2 (CH, C-3), 51.7 (CH, C-4) ppm; **LRMS** (ESI^+) m/z 337.1 $(M + H)^+$). Following general procedure **F** (8.2.1), this carbonate was then reacted with amine **1.81a** (980 mg, 2.50 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 97:3) the PI **4.24a** as a white solid (1.04 g, 71%). **Formula** C27H36N6O7S; **Mw** 588.68; $\mathbf{R_f}$ 0.25 (hexane/acetone 60:40); **Mp** 82−84 °C; **$[\alpha]_D$** +30.1 (*c* 0.60, $CHCl_3$, 26 °C); **IR** (film) 3470 (w), 3368 (w), 2962 (w), 2097 (m), 1712 (s), 1629

(m), 1596 (s), 1530 (m), 1313 (s), 1251 (s), 1146 (vs), 1090 (s), 733 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (2 H, d, *J* = 8.7 Hz, H-16), 7.35–7.21 (5 H, m, Ar-H), 6.70 (2 H, d, *J* = 8.7 Hz, H-17); 5.76 (1 H, d, *J* = 5.1 Hz, H-1), 5.09 (1 H, dt, *J* = 8.6, 6.0 Hz, H-5), 4.99 (1 H, d, *J* = 5.3 Hz, NH), 4.16 (2 H, br. s, NH_2), 3.99 (1 H, dd, *J* = 10.0, 6.1 Hz, H-6), 3.95–3.88 (2 H, m, H-8 and H-9), 3.84 (1 H, dt, *J* = 10.2, 1.3 Hz, H-2), 3.81 (1 H, dd, *J* = 10.2, 3.8 Hz, H-2'), 3.71 (1 H, dd, *J* = 10.0, 5.9 Hz, H-6'), 3.69 (1 H, d, *J* = 2.8 Hz, OH), 3.40 (1 H, d, *J* = 3.1 Hz, H-3), 3.19 (1 H, dd, *J* = 15.0, 8.3 Hz, H-10), 3.07 (1 H, dd, *J* = 14.2, 4.2 Hz, H-14), 3.02–2.89 (3 H, m, H-4, H-10' and H-11), 2.83–2.75 (2 H, m, H-11' and H-14'), 1.89–1.78 (1 H, m, H-12), 0.95 (3 H, d, *J* = 6.7 Hz, H-13), 0.90 (3 H, d, *J* = 6.7 Hz, H-13) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 154.9 (C, C-7), 150.7 (C_{ar}), 137.6 (C_{ar}), 129.5 ($2 \times CH_{ar}$ and C_{ar}), 129.3 ($2 \times CH_{ar}$), 128.6 ($2 \times CH_{ar}$), 126.8 (CH_{ar}), 114.1 ($2 \times CH_{ar}$), 108.6 (CH, C-1), 73.6 (CH_2, C-2), 72.8 (CH, C-9), 72.2 (CH, C-5), 71.0 (CH_2, C-6), 61.4 (CH, C-3), 59.0 (CH_2, C-11), 55.2 (CH, C-8), 53.7 (CH_2, C-10), 52.0 (CH, C-4), 35.5 (CH_2, C-14), 27.4 (CH, C-12), 20.2 (CH_3, C-13), 19.9 (CH_3, C-13) ppm; **LRMS** (ESI^+) *m/z* 611.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{27}H_{36}N_6O_7SNa$ $(M + Na)^+$ calcd 611.2258, found 611.2254.

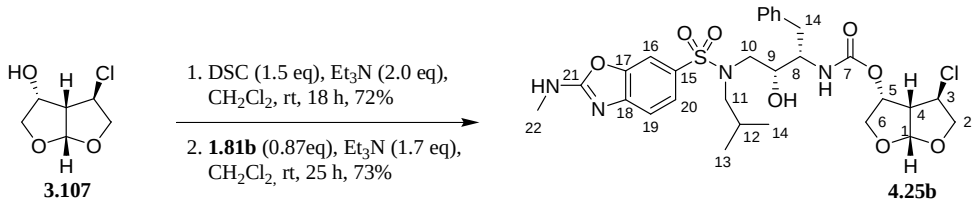
Protease Inhibitor 4.25a



Following general procedure **E** (8.2.1), the reaction of alcohol **3.107** (165 mg, 1.00 mmol) with DSC (384 mg, 1.50 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99:1 to 95:5) the corresponding mixed carbonate as a pale yellow oil (221 mg, 0.72 mmol, 72%). Following general procedure **F** (8.2.1), this carbonate (110 mg, 0.36 mmol) was then reacted with amine **1.81a** (125 mg, 0.32 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 96:4) and by HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.25a** as a white solid (119 mg, 64%). **Formula** $C_{27}H_{36}ClN_3O_7S$; **Mw** 582.11; **R_f** 0.26 (CH_2Cl_2/MeOH 97:3); **Mp** 101−103 °C; **$[\alpha]_D$** +30.0 (*c* 0.82, $CHCl_3$, 26 °C); **IR** (film) 3472 (br. w), 3369 (br, w), 2961 (w), 2873 (w), 1712 (m), 1595 (m), 1311 (m), 1145 (s), 1090 (s), 1020 (m), 910 (m), 729 (vs), 551 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (2 H, d, *J* = 8.6 Hz, H-16), 7.36–7.20 (5 H, m, Ar-H), 6.70 (2 H,

d, *J* = 8.8 Hz, H-17), 5.87 (1 H, d, *J* = 5.1 Hz, H-1), 5.09 (1 H, dt, *J* = 8.6, 5.9 Hz, H-5), 5.01 (1 H, d, *J* = 8.6 Hz, NH), 4.17 (2 H, s, NH_2), 4.02−3.88 (5 H, m, H-2, H-2', H-6, H-8 and H-9), 3.83 (1 H, d, *J* = 2.9 Hz, H-3), 3.73−3.67 (2 H, m, H-6' and OH), 3.18 (1 H, dd, *J* = 15.2, 8.8 Hz, H-10), 3.12 (1 H, dd, *J* = 8.8, 5.1 Hz, H-4), 3.08 (1 H, dd, *J* = 14.1, 4.0 Hz, H-14), 3.01−2.93 (2 H, m, H-10'and H-11), 2.84−2.76 (2 H, m, H-11' and H-14'), 1.84 (1 H, m, H-12), 0.95 (3 H, d, *J* = 6.7 Hz, H-13), 0.90 (3 H, d, *J* = 6.6 Hz, H-13) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 154.8 (C, C-7), 150.8 (C_{ar}, C-18), 137.5 (C_{ar}), 129.5 (2 × CH_{ar}, C-16), 129.3 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 126.8 (CH_{ar}), 126.0 (C_{ar}, C-15), 114.1 (2 × CH_{ar}, C-17), 108.9 (CH, C-1), 77.3 (CH_2, C-2), 72.8 (CH, C-9), 72.1 (CH, C-5), 71.0 (CH_2, C-6), 59.0 (CH_2, C-11), 57.4 (CH, C-3), 55.7 (CH, C-4), 55.2 (CH, C-8), 53.7 (CH_2, C-10), 35.5(CH_2, C-14), 27.4 (CH, C-12), 20.2 (CH_3, C-13), 19.9 (CH_3, C-13) ppm; **LRMS** (ESI^+) *m*/*z* 604.3 $(M + Na)^+$, 606.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{27}H_{36}ClN_3O_7SNa$ $(M + Na)^+$ calcd 604.1855, found 604.1869.

Protease Inhibitor 4.25b

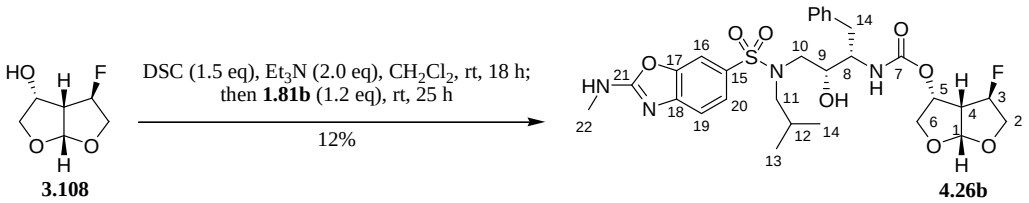


3.107 **4.25b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.107** (165 mg, 1.00 mmol) with DSC (384 mg, 1.50 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99:1 to 95:5) the corresponding mixed carbonate as a pale yellow oil (221 mg, 0.72 mmol, 72%). Following general procedure **F** (8.2.1), this carbonate (110 mg, 0.36 mmol) was then reacted with amine **1.81b** (142 mg, 0.32 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 96:4) and by HPLC (CH_2Cl_2/MeOH 96:4) the PI **4.25b** as a white solid (148 mg, 73%). **Formula** $C_{29}H_{37}ClN_4O_8S$; **Mw** 637.14; **R_f** 0.20 (CH_2Cl_2/MeOH 96:4); **Mp** 138−140 °C; **$[\alpha]_D$** +30.3 (*c* 0.58, $CHCl_3$, 26 °C); **IR** (film) 3337 (m), 2961 (w), 2873 (w), 1710 (m), 1656 (s), 1580 (m), 1324 (m), 1271 (m), 1238 (m), 1143 (m), 909 (m), 727 (vs), 599 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1 H, d, *J* = 1.6 Hz, H-16), 7.63 (1 H, dd, *J* = 8.2, 1.6 Hz, H-20), 7.43 (1 H, d, *J* = 8.3 Hz, H-19), 7.36–7.20 (5 H, m, Ar-H), 5.87 (1 H, d, *J* = 5.1 Hz, H-1), 5.39 (1 H, q, *J* = 4.7 Hz, N*H*Me), 5.11−5.04 (2 H, m, H-5 and NH), 4.03−3.91 (5 H, m, H-2, H-2', H-6, H-8 and H-9), 3.86 (1 H, d, *J* = 3.0 Hz, H-3), 3.69 (1 H, dd, *J* = 10.0, 5.6 Hz,

H-6'), 3.62 (1 H, br. s, OH), 3.18 (3 H, d, *J* = 5.1 Hz, H-22), 3.21–3.07 (3 H, m, H-4, H-10 and H-14), 3.04–2.95 (2 H, m, H-10' and H-11), 2.87−2.77 (2 H, m, H-11' and H-14'), 1.86 (1 H, m, H-12), 0.94 (3 H, d, *J* = 6.6 Hz, H-13), 0.91 (3 H, d, *J* = 6.6 Hz, H-13) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-21), 154.9 (C, C-7), 148.2 (C_{ar}, C-17 or C-18), 147.9 (C_{ar}, C-18 or C-17), 137.4 (C_{ar}), 129.7 (C_{ar}, C-15), 129.3 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 126.9 (CH_{ar}), 124.2 (CH_{ar}, C-20), 116.3 (CH_{ar}, C-19), 108.7 (CH, C-1), 108.4 (CH_{ar}, C-16), 77.3 (CH_2, C-2), 72.8 (CH, C-9), 72.2 (CH, C-5), 71.1 (CH_2, C-6), 59.0 (CH_2, C-11), 57.3 (CH, C-3), 55.7 (CH, C-4), 55.2 (CH, C-8), 53.8 (CH_2, C-10), 35.5 (CH_2, C-14), 29.6 (CH_3, C-22), 27.3 (CH, C-12), 20.1 (CH_3, C-13), 19.9 (CH_3, C-13) ppm; **LRMS** (ESI^+) *m*/*z* 659.3 $(M + Na)^+$, 661.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{29}H_{37}ClN_4O_8SNa$ $(M + Na)^+$ calcd 659.1927, found 659.1937.

Protease Inhibitor 4.26b

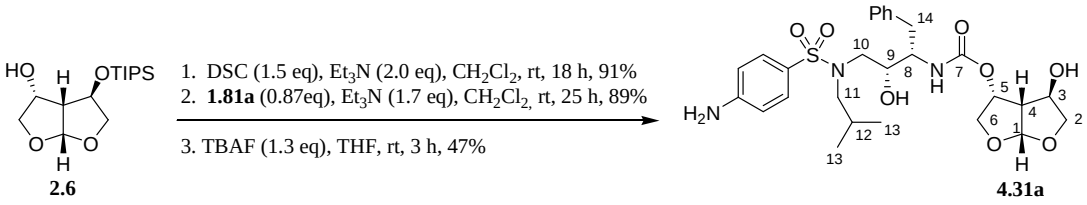


3.108 **4.26b**

Following general procedure **E** (8.2.1), the reaction of alcohol **3.107** (25 mg, 0.17 mmol) with DSC (65 mg, 0.25 mmol) afforded the crude mixed carbonate as a pale yellow oil, which was subsequently reacted with amine **1.81b** (90 mg, 0.20 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 98:2 to 96:4) and by HPLC (CH_2Cl_2/MeOH 97:3) alcohol **3.108** (10.2 mg, 41%) and PI **4.26b** as a white solid (13.1 mg, 12%). **Formula** $C_{29}H_{37}FN_4O_8S$; **Mw** 620.69; **R_f** 0.23 (CH_2Cl_2/MeOH 96:4); **Mp** 122−124 °C; **[α]$_D$** +11.3 (*c* 0.87, $CHCl_3$, 26 °C); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1 H, d, *J* = 1.6 Hz, H-16), 7.62 (1 H, dd, *J* = 8.2, 1.8 Hz, H-20), 7.42 (1 H, d, *J* = 8.3 Hz, H-19), 7.35–7.20 (5 H, m, Ar-H), 5.83 (1 H, d, *J* = 5.2 Hz, H-1), 5.43 (1 H, q, *J* = 4.9 Hz, N*H*Me), 5.15 (1 H, dt, *J* = 8.9, 5.7 Hz, H-5), 5.05 (1 H, d, *J* = 9.0 Hz, N*H*), 4.55 (1 H, dd, *J* = 51.4, 2.3 Hz, H-3), 4.07 (1 H, ddd, *J* = 22.4, 11.1, 1.0 Hz, H-2), 3.97 (1 H, dd, *J* = 10.0, 5.7 Hz, H-6), 3.95−3.89 (2 H, m, H-8 and H-9), 3.82 (1 H, ddd, *J* = 39.8, 11.2, 2.8 Hz, H-2'), 3.67 (1 H, dd, *J* = 10.0, 5.2 Hz, H-6'), 3.62 (1 H, d, *J* = 2.1 Hz, O*H*), 3.17 (3 H, d, *J* = 5.1 Hz, H-22), 3.17 (1 H, dd, *J* = 15.2, 8.7 Hz, H-10), 3.13–3.02 (3 H, m, H-4, H-10' and H-14), 2.98 (1 H, dd, *J* = 13.4, 8.2 Hz, H-11), 4.55 (1 H, dd, *J* = 13.5, 6.9 Hz, H-11'), 2.80 (1 H, dd, *J* = 13.9, 9.3 Hz, H-14'), 1.86 (1 H, m, H-12), 0.94 (3 H, d, *J* = 6.6 Hz, H-13), 0.90

(3 H, d, *J* = 6.6 Hz, H-13) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.7 (C_{ar}, C-21), 154.9 (C, C-7), 148.2 (C_{ar}, C-17 or C-18), 147.9 (C_{ar}, C-18 or C-17), 137.4 (C_{ar}), 129.6 (C_{ar}, C-15), 129.3 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 126.8 (CH_{ar}), 124.2 (CH_{ar}, C-20), 116.3 (CH_{ar}, C-19), 108.8 (CH, C-1), 108.4 (CH_{ar}, C-16), 93.2 (CH, d, *J* = 179.3 Hz, C-3), 74.9 (CH_2, d, *J* = 22.7 Hz, C-2), 72.8 (CH, C-9), 71.7 (CH, d, *J* = 9.5 Hz, C-5), 71.2 (CH_2, C-6), 59.0 (CH_2, C-11), 55.2 (CH, C-8), 53.8 (CH_2, C-10), 52.2 (CH, d, *J* = 23.4 Hz, C-4), 35.6 (CH_2, C-14), 29.6 (CH_3, C-22), 27.3 (CH, C-12), 20.1 (CH_3, C-13), 19.9 (CH_3, C-13) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −179.1 (ddt, *J* = 51.4, 39.8, 23.0 Hz, F-3) ppm; **LRMS** (ESI^+) *m*/*z* 643.4 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{29}H_{37}FN_4O_8SNa$ $(M+Na)^+$ calcd 643.2208, found 643.2222.

Protease Inhibitor 4.31a

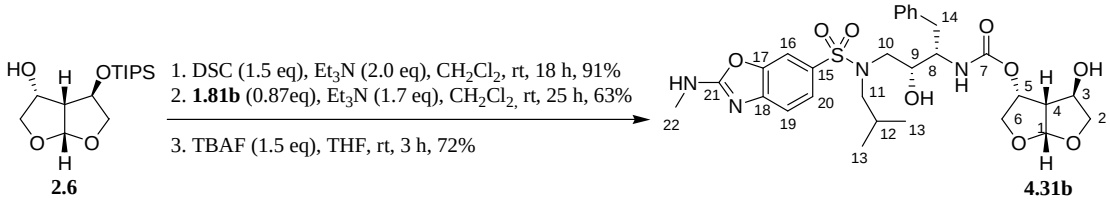


Following general procedure **E** (8.2.1), the reaction of alcohol **2.6** (468 mg, 1.55 mmol) with DSC (590 mg, 2.30 mmol) afforded after purification by column chromatography (CH_2Cl_2/MeOH 99:1 to 97:3) the corresponding mixed carbonate as a pale yellow oil (630 mg, 1.42 mmol, 92%). Following general procedure **F** (8.2.1), this mixed carbonate (210 mg, 0.47 mmol) was then reacted with amine **1.81a** (133 mg, 0.34 mmol) to afford after purification by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) the protected PI as white solid (254 mg, 0.30 mmol, 89%). To a stirred solution this PI (254 mg, 0.30 mmol) in THF (3 mL) at rt was added TBAF (0.40 mL, 0.40 mmol, 1 M in THF). After 3 h the solvent was removed in vacuo and the crude residue was partitioned between CH_2Cl_2 and aq. sat. $NaHCO_3$ (15 mL each). The aqueous phase was extract with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried over anhydrous Na_2SO_4, filtered and solvent was removed under reduced pressure. Purification by column chromatography (CH_2Cl_2/MeOH 95:5 to 90:10) and by HPLC (CH_2Cl_2/MeOH 94:6) afforded the PI **4.31a** as a white solid (80 mg, 47%). **Formula** $C_{27}H_{37}N_3O_8S$; **Mw** 563.66; $\mathbf{R_f}$ 0.28 (CH_2Cl_2/MeOH 93:7); **Mp** 114−115 °C; $\mathbf{[\alpha]_D}$ +8.8 (c 1.03, $CHCl_3$, 23 °C); **IR** (film) 3366 (br. w), 2961 (w), 2873 (w), 1704 (m), 1596 (m), 1311 (m), 1264 (m), 1145 (s), 1089 (s), 733 (s), 551 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.56 (2 H, d, *J* = 8.7 Hz, H-16), 7.34–7.21 (5 H, m, Ar-H), 6.69 (2 H,

d, *J* = 8.6 Hz, H-17), 5.79 (1 H, d, *J* = 5.2 Hz, H-1), 5.12−5.05 (2 H, m, H-5 and NH), 4.19 (1 H, br. s, NH_2), 3.96 (1 H, dd, *J* = 9.7, 6.1 Hz, H-6), 3.93−3.87 (2 H, m, H-8 and H-9), 3.84 (1 H, dd, *J* = 10.3, 3.3 Hz, H-2), 3.79 (1 H, d, *J* = 10.5 Hz, H-2'), 3.77 (1 H, br. s, H-3)

3.71−3.65 (2 H, m, H-6' and OH), 3.16 (1 H, dd, *J* = 15.1, 8.3 Hz, H-10), 3.08 (1 H, dd, *J* = 14.3, 3.5 Hz, H-14), 3.03–2.91 (2 H, m, H-10' and H-11), 2.85 (1 H, dd, *J* = 8.8, 5.3 Hz, H-4), 2.84−2.74 (2 H, m, H-11' and H-14'), 1.90−1.78 (1 H, m, H-12 and OH), 0.93 (3 H, d, *J* = 6.6 Hz, H-13), 0.90 (3 H, d, *J* = 6.6 Hz, H-13) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 155.3 (C, C-7), 150.8 (C_{ar}), 137.8 (C_{ar}), 129.5 (2 × CH_{ar}), 129.4 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.5 (CH_{ar}), 126.0 (C_{ar}), 114.1 (2 × CH_{ar}), 108.9 (CH, C-1), 76.7 (CH_2, C-2), 72.8 (CH, C-9), 72.4 (CH, C-5), 72.0 (CH, C-3), 70.9 (CH_2, C-6), 58.9 (CH_2, C-11), 55.2 (CH, C-8), 54.6 (CH, C-4), 53.7 (CH_2, C-10), 35.6 (CH_2, C-14), 27.3 (CH, C-12), 20.2 (CH_3, C-13), 19.9 (CH_3, C-13) ppm; **LRMS** (ESI^+) *m/z* 586.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{27}H_{37}N_3O_8SNa$ $(M + Na)^+$ calcd. 586.2194; found 586.2213.

Protease Inhibitor 4.31b

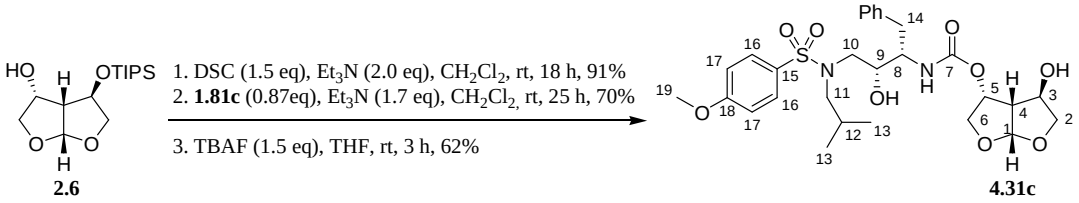


2.6 **4.31b**

According to the synthesis of **4.31a**, the reaction of the activated carbonate of alcohol **2.6** (210 mg, 0.47 mmol) with amine **1.81b** (149 mg, 0.33 mmol) and subsequent treatment of the protected PI (162 mg, 0.21 mmol) with TBAF (310 µL, 0.31 mmol, 1 M in THF) afforded the protease inhibitor **4.31b** as a white solid (98 mg, 72%). **Formula** $C_{29}H_{38}N_4O_9S$; **Mw** 618.70; **R_f** 0.35 (CH_2Cl_2/MeOH 93:7); **Mp** 127−129 °C; **[α]$_D$** +12.8 (c 1.09, $CHCl_3$, 26 °C); **IR** (film) 3338 (m), 2962 (w), 2873 (w), 1704 (m), 1660 (vs), 1582 (m), 1324 (m), 1272 (s), 1240 (m), 1145 (s), 734 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.67 (1 H, d, *J* = 1.6 Hz, H-16), 7.63 (1 H, dd, *J* = 8.2, 1.6 Hz, H-20), 7.42 (1 H, d, *J* = 8.3 Hz, H-19), 7.34–7.20 (5 H, m, Ar-H), 5.80 (1 H, d, *J* = 5.2 Hz, H-1), 5.51 (1 H, br. s, N*H*Me), 5.19−5.05 (2 H, m, H-5 and NH), 4.02−3.88 (3 H, m, H-6, H-8 and H-9), 3.87–3.77 (3 H, m, H-2, H-2' and H-3), 3.67 (1 H, dd, *J* = 10.2, 6.0 Hz, H-6'), 3.64 (1 H, br. s, OH), 3.17 (3 H, d, *J* = 4.9 Hz, H-22), 3.20–3.01 (3 H, m, H-10, H-10' and H-14), 2.97 (1 H, dd, *J* = 13.0, 8.0 Hz, H-11), 2.90−2.75 (3 H, m, H-4, H-11' and H-14'), 1.99 (1 H, br. s, OH), 1.86 (1 H, m, H-12), 0.93 (3 H, d, *J* = 6.7 Hz, H-13), 0.91 (3 H, d, *J* = 6.7 Hz, H-13)

ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 164.8 (C_{ar}, C-21), 155.4 (C, C-7), 148.1 (C_{ar}, C-17 or C-18), 147.8 (C_{ar}, C-18 or C-17), 137.8 (C_{ar}), 129.6 (C_{ar}, C-15), 129.4 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.5 (CH_{ar}), 124.2 (CH_{ar}, C-20), 116.0 (CH_{ar}, C-19), 108.9 (CH, C-1), 108.4 (CH_{ar}, C-16), 76.7 (CH_2, C-2), 72.8 (CH, C-9), 72.4 (CH, C-5), 71.8 (CH, C-3), 71.0 (CH_2, C-6), 58.8 (CH_2, C-11), 55.3 (CH, C-8), 54.6 (CH, C-4), 53.6 (CH_2, C-10), 35.7 (CH_2, C-14), 29.5 (CH_3, C-22), 27.2 (CH, C-12), 20.1 (CH_3, C-13), 19.9 (CH_3, C-13) ppm; **LRMS** (ESI^+) *m/z* 641.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{29}H_{38}N_4O_9SNa$ $(M + Na)^+$ calcd. 641.2252; found 641.2259.

Protease Inhibitor 4.31c

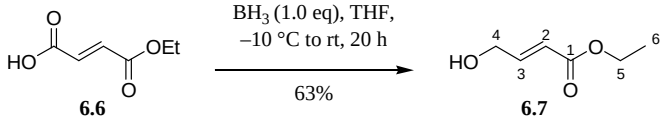


According to the synthesis of **4.31a**, the reaction of the activated carbonate of compound **6.9** (210 mg, 0.47 mmol) with amine **1.81c** (129 mg, 0.32 mmol) and subsequent treatment of the protected PI (165 mg, 0.22 mmol) with TBAF (330 µL, 0.33 mmol, 1 M in THF) afforded the protease inhibitor **4.31c** as a white solid (80 mg, 62%). **Formula** $C_{28}H_{38}N_2O_9S$; **Mw** 578.67; **R_f** 0.29 (CH_2Cl_2/MeOH 95:5); **Mp** 91−93 °C; **$[\alpha]_D$** +5.2 (c 1.04, $CHCl_3$, 23 °C); **IR** (film) 3434 (br. w), 3358 (br, w), 2961 (w), 2873 (w), 1703 (m), 1596 (m), 1330 (m), 1258 (s), 1149 (s), 1091 (s), 1014 (s), 730 (vs), 559 (vs) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.73 (2 H, d, *J* = 9.0 Hz, H-16), 7.35–7.22 (5 H, m, Ar-H), 7.00 (2 H, d, *J* = 8.8 Hz, H-17), 5.79 (1 H, d, *J* = 5.3 Hz, H-1), 5.12−5.01 (2 H, m, H-5 and NH), 4.00−3.90 (3 H, m, H-6, H-8 and H-9), 3.89 (3 H, s, H-19), 3.86−3.74 (3 H, m, H-2, H-2' and H-3), 3.71−3.63 (2 H, m, H-6' and OH), 3.19 (1 H, dd, *J* = 14.6, 8.7 Hz, H-10), 3.12–2.95 (3 H, m, H-10', H-11 and H-14), 2.85 (1 H, dd, *J* = 8.8, 5.2 Hz, H-4), 2.85−2.76 (2 H, m, H-11' and H-14'), 1.85 (1 H, m, H-12), 1.69 (1 H, d, *J* = 5.2 Hz, OH), 0.94 (3 H, d, *J* = 6.6 Hz, H-13), 0.90 (3 H, d, *J* = 6.7 Hz, H-13) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 163.2 (C_{ar}, C-18), 155.3 (C, C-7), 137.7 (C_{ar}), 129.7 (C_{ar}, C-15), 129.5 (2 × CH_{ar}, C-16), 129.4 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 126.5 (CH_{ar}), 114.1 (2 × CH_{ar}, C-17), 108.9 (CH, C-1), 76.7 (CH_2, C-2), 72.8 (CH, C-9), 72.4 (CH, C-5), 72.0 (CH, C-3), 70.8 (CH_2, C-6), 58.9 (CH_2, C-11), 55.7 (CH_3, C-19), 55.2 (CH, C-8), 54.7 (CH, C-4), 53.7 (CH_2, C-10), 35.6 (CH_2, C-14), 27.3 (CH, C-12), 20.1 (CH_3, C-13), 19.9 (CH_3, C-13) ppm; **LRMS** (ESI^+) *m/z*

601.3 $(M + Na)^+$; **LRMS** (ESI^+) *m/z* 641.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{29}H_{38}N_2O_9SNa$ $(M + Na)^+$ calcd. 601.2190; found 601.2205.

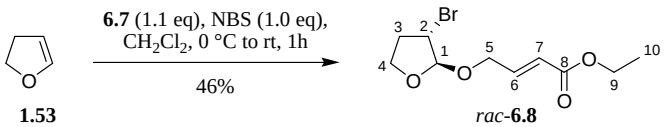
8.2.4 α-Fluoroamide synthesis

(*E*)-4-Hydroxybut-2-enoic acid ethyl ester (6.7)



Allylic alcohol **6.7** was prepared according to literature procedures.[8] To a solution of monoethyl fumarate (**6.6**, 10.0 g, 69.4 mmol) in THF (30 mL) at −10 °C was added under vigorous stirring BH_3 ·THF complex (70.0 mL, 70.0 mmol, 1 M in THF). The cooling was removed and the reaction was stirred at rt for 20 h. After completion the mixture was quenched carefully with AcOH/H_2O (2 mL, 1:1, v/v), concentrated under vacuo and the remaining slurry was poured slowly into ice-cold sat. aq. $NaHCO_3$. The mixture was extracted with EtOAc (3 × 100 mL). The combined organic phases were washed with sat. aq. $NaHCO_3$, dried over anhydrous Na_2SO_4, filtered and the solvent was removed under reduced pressure to afford essentially pure *title compound* **6.7** as a colourless oil (5.71 g, 63%). **Formula** $C_6H_{10}O_3$; **Mw** 130.14; **^{1}H NMR** (300 MHz, CDCl3) δ 7.04 (1 H, dt, *J* = 15.7, 4.0 Hz, H-3), 6.11 (1 H, dt, *J* = 15.7, 2.2 Hz, H-2), 4.36 (2 H, dd, *J* = 4.0, 2.1 Hz, H-4), 4.22 (2 H, q, *J* = 7.1 Hz, H-5), 1.30 (3 H, t, *J* = 7.1 Hz, H-6) ppm; **^{13}C NMR + DEPT** (75 MHz, CDCl3) δ 166.4 (C, C-1), 146.7 (CH, C-3), 120.2 (CH, C-6), 61.9 (CH_2, C-4 or C-5), 60.4 (CH_2, C-5 or C-4), 14.2 (CH_3, C-6) ppm. The ^{1}H and ^{13}C NMR correspond to the reported data.[8]

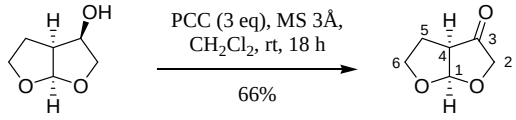
(*E*)-Ethyl 4-((2*R*/*S*,3*S*/*R*)-3-bromo-tetrahydrofuran-2-yloxy)but-2-enoate (*rac*-6.8)



To a solution of 2,3-dihydrofuran (**1.53**, 3.02 mL, 40 mmol) and alcohol **6.7** (5.71 g, 43.9 mmol) in CH_2Cl_2 (40 mL) at 0 °C was added slowly a solution of *N*-bromosuccinimide (7.12 g, 40 mmol) in CH_2Cl_2 (20 mL). The cooling was removed and the reaction was stirred at rt for 1 h. After completion the solvent was removed in vacuo and the crude product was directly applied to column chromatography (hexane/EtOAc 90:10 to 75:25) to afford the *title compound rac*-**6.8** as a colourless oil (5.17 g, 46%). **Formula** $C_{10}H_{15}BrO_4$; **Mw** 279.13; **R_f** 0.40 (hexane/EtOAc 85:15); **IR** (film) 2981 (w), 2900 (w), 1716 (s), 1663

(w), 1445 (w), 1300 (m), 1266 (m), 1176 (s), 1025 (vs), 920 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.93 (1 H, dt, *J* = 15.8, 4.4 Hz, H-6), 6.02 (1 H, dt, *J* = 15.7, 2.1 Hz, H-7), 5.26 (1 H, s, H-2), 4.34 (1 H, ddd, *J* = 15.8, 4.2, 2.1 Hz, H-5), 4.27 (1 H, dd, *J* = 6.0, 1.7 Hz, H-2), 4.21 (2 H, q, *J* = 7.2 Hz, H-9), 4.18 (2 H, dd, *J* = 8.9, 7.2 Hz, H-4), 4.14 (1 H, ddd, *J* = 15.9, 4.6, 2.0 Hz, H-5'), 4.07 (1 H, td, *J* = 8.5, 3.4 Hz, H-4'), 2.67 (1 H, dtd, *J* = 14.2, 8.5, 6.0 Hz, H-3), 2.24 (1 H, dddd, *J* = 14.1, 7.0, 3.4, 1.6 Hz, H-3'), 1.30 (3 H, t, *J* = 7.2 Hz, H-10) ppm; **^{13}C NMR + DEPT** (75 MHz, CDCl3) δ 166.1 (C, C-8), 143.4 (CH, C-6), 121.4 (CH, C-7), 108.2 (CH, C-1), 67.0 (CH_2, C-5), 65.5 (CH_2, C-4), 60.5 (CH_2, C-9), 49.6 (CH, C-2), 33.8 (CH_2, C-3), 14.2 (CH_3, C-10) ppm; **LRMS** (ESI+) *m*/*z* 301.0 $(M + Na)^+$, 303.0 $(M + Na)^+$.

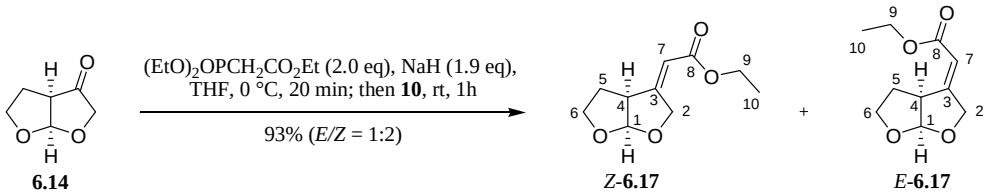
(3a*R*,6a*R*)-Tetrahydrofuro[2,3-*b*]furan-3-one (6.14)



1.15 **6.14**

To a solution of alcohol **1.15** (500 mg, 3.85 mmol) in CH_2Cl_2 (20 mL) was added PCC (2.49 g, 11.55 mmol) and molecular sieves (500 mg, 3 Å). The resulting mixture was stirred at rt for 18 h. After completion the mixture was filtered over celite and the filtrate was concentrated in vacuo. The crude product was purified by column chromatography (petroleum ether/acetone 90:10 to 80:20) to afford the *title compound* **6.14** as an amorphous white solid (324 mg, 66%). **Formula** $C_6H_8O_3$; **Mw** 128.13; **R_f** 0.35 (petroleum ether/acetone 80:20); **$[\alpha]_D$** −127.5 (*c* 1.0, $CHCl_3$, 27 °C), lit.[39] −126.6 (*c* 0.8, $CHCl_3$, 25 °C); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.07 (1 H, d, *J* = 5.1 Hz, H-1), 4.16 (2 H, s, H-2 and H-2'), 4.05 (1 H, m, H-6), 3.80 (1 H, m, H-6'), 3.00 (1 H, m, H-4), 2.28–2.19 (2 H, m, H-5 and H-5') ppm; **^{13}C NMR + DEPT** (75 MHz, $CDCl_3$) δ 215.4 (C=O, C-3), 107.9 (CH, C-1), 71.7 (CH_2, C-2), 67.7 (CH_2, C-6), 49.6 (CH, C-4), 30.4 (CH_2, C-5) ppm. The ^{1}H and ^{13}C NMR spectra corresponded to the reported data.[39]

(3a*R*,6a*R*)-[Tetrahydro-furo[2,3-*b*]furan-(3*E*/*Z*)-ylidene]-acetic acid ethyl ester (*E*/*Z*-6.17)



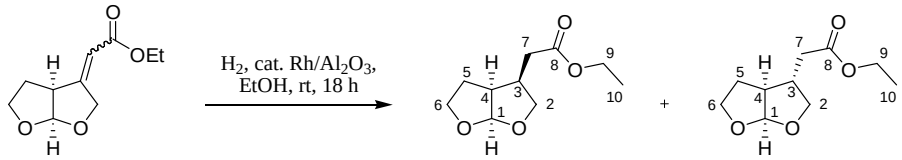
6.14 *Z*-**6.17** *E*-**6.17**

Triethylphosphono acetate (620 µL, 3.12 mmol) was added dropwise to a suspension of NaH (120 mg, 3.00 mmol, 60% in mineral oil) in THF (10 mL) at 0 °C and the resulting mixture was stirred for 20 min at this temperature. Then a solution of ketone **6.14** (200 mg, 1.56 mmol) in THF (5 mL) was added dropwise, the cooling was removed and the reaction was stirred at rt for 1 h. After completion the mixture was quenched with H_2O and EtOAc (10 mL each), the phases were separated and the aqueous phase was extracted with EtOAc (3×15 mL). The combined organic layers were dried over Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether/acetone 90:10 to 80:20) to afford a 2:1 mixture of the *title compounds E*/*Z*-**6.17** as a colourless oil (289 mg, 93%). For characterisation the mixture was further purified by HPLC (hexane/acetone 85:15). *Major product* (presumably *Z*-**6.17**): **Formula** $C_{10}H_{14}O_4$; **Mw** 198.22; $\mathbf{R_f}$ 0.35 (hexane/acetone 80:20); $\mathbf{[\alpha]_D}$ −179.6 (c 1.39, $CHCl_3$, 27 °C); **IR** (film) 2979 (w), 2871 (w), 1707 (s) 1664 (m), 1219 (s), 1132 (s), 1030 (s), 1013 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.89 (1 H, q, *J* = 2.4 Hz, H-7), 5.84 (1 H, d, *J* = 4.9 Hz, H-1), 5.00 (1 H, ddd, *J* = 17.7, 2.6, 0.7 Hz, H-2), 4.91 (1 H, dt, *J* = 17.7, 2.6 Hz, H-2'), 4.19 (2 H, q, *J* = 7.2 Hz, H-9), 3.97 (1 H, td, *J* = 8.3, 1.6 Hz, H-6), 3.78 (1 H, ddd, *J* = 11.3, 8.7, 5.3 Hz, H-6'), 3.46 (1 H, ddd, *J* = 8.8, 4.6, 2.1 Hz, H-4), 2.30 (1 H, dddd, *J* = 12.4, 11.3, 8.8, 4.6 Hz, H-5), 1.98 (1 H, ddtd, *J* = 12.5, 5.3, 1.6, 0.6 Hz, H-5'), 1.30 (3 H, t, *J* = 7.1 Hz, H-10) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 165.8 (C, C-8), 164.2 (C, C-3), 113.2 (CH, C-7), 108.2 , CH, C-1), 72.4 (CH_2, C-2), 67.3 (CH_2, C-6), 60.3 (CH_2, C-9), 48.9 (CH, C-4), 34.7 (CH_2, C-5), 14.3 (CH_3, C-10) ppm; **LRMS** (ESI^+) *m*/*z* 221.1 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{10}H_{14}O_4Na$ $(M + Na)^+$ calcd 221.0784, found 221.0787.

Minor product (presumably *E*-**6.17**): **Formula** $C_{10}H_{14}O_4$; **Mw** 198.22; $\mathbf{R_f}$ 0.40 (hexane/acetone 80:20); $\mathbf{[\alpha]_D}$ −243.2 (c 0.86, $CHCl_3$, 27 °C); **IR** (film) 2981 (w), 2875 (w), 1712 (s) 1673 (m), 1218 (vs), 1173 (m), 1028 (vs), 947 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86 (1 H, d, *J* = 4.9 Hz, H-1), 5.79 (1 H, q, *J* = 2.0 Hz, H-7), 4.65 (1 H, dt, *J* = 15.1, 2.3 Hz, H-2), 4.50 (1 H, dd, *J* = 15.1, 1.8 Hz, H-2'), 4.21 (2 H, qd, *J* = 7.1, 2.3 Hz, H-9), 4.03–3.96

(2 H, m, H-4 and H-6), 3.82 (1 H, ddd, *J* = 10.7, 8.8, 6.0 Hz, H-6'), 2.44 (1 H, dtd, *J* = 13.0, 10.4, 6.1 Hz, H-5), 2.00 (1 H, ddt, *J* = 13.1, 6.1, 2.4 Hz, H-5'), 1.31 (3 H, t, *J* = 7.1 Hz, H-10) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 165.5 (C, C-8), 163.0 (C, C-3), 111.5 (CH, C-7), 109.9 (CH, C-1), 72.6 (CH_2, C-2), 68.0 (CH_2, C-6), 60.2 (CH_2, C-9), 47.0 (CH, C-4), 33.9 (CH_2, C-5), 14.3 (CH_3, C-10) ppm; **LRMS** (ESI+) *m*/*z* 253.1 $(M+MeOH+Na)^+$; **HRMS** (ESI+) for $C_{10}H_{14}O_4Na$ $(M + Na)^+$ calcd 221.0784, found 221.0787.

((3*R*,3a*S*,6a*R*)-Hexahydrofuro[2,3-b]furan-3-yl)-acetic acid ethyl ester (*endo*-6.9)

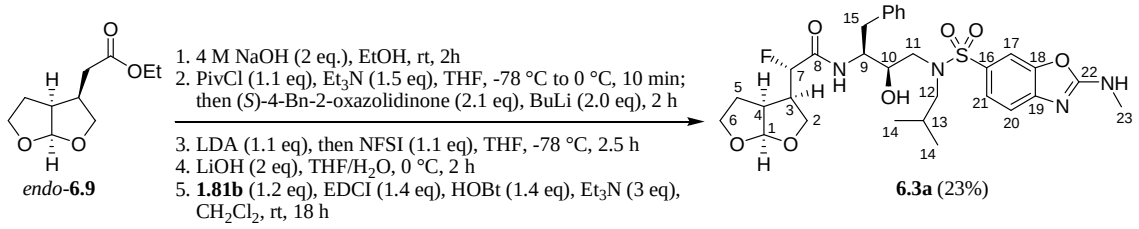


E/*Z*-**6.17** → *endo*-**6.9** (87%) + *exo*-**6.9** (13%)

To a solution of alkene mixture *E*/*Z*-**6.17** (67.3 mg, 0.34 mmol) in EtOH (7.5 mL) was added Rh/Al_2O_3 (5.5 mg, 8 w%, 5% Rh), the flask was put under H_2-atmosphere and the reaction was stirred at rt for 18 h. After completion the mixture was diluted with EtOH (5 mL), filtered over a celite/silica pad and the filter cake was washed with EtOH (3 × 5 mL). The combined filtrates were concentrated in vacuo, to yield a 5:1-mixture of *endo*-**6.9**/*exo*-**6.9** as a colourless oil (68.3 mg, 100%). Further purification by HPLC (hexane/acetone 80:20) afforded the pure *title compound endo*-**6.9** as well as the diastereoisomer *exo*-**6.9**, both as colourless oils. **Formula** $C_{10}H_{16}O_4$; **Mw** 200.23; $\mathbf{R_f}$ 0.24 (hexane/acetone 80:20); $\mathbf{[\alpha]_D}$ −24.9 (c 1.18, $CHCl_3$, 27 °C); **IR** (film) 2978 (w), 2872 (w), 1728 (vs), 1176 (s), 1016 (s), 1001 (s), 924 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.75 (1 H, d, *J* = 5.0 Hz, H-1), 4.16 (2 H, q, *J* = 7.2 Hz, H-9), 4.03 (1 H, dd, *J* = 8.5, 7.3 Hz, H-2), 3.94–3.83 (2 H, m, H-6 and H-6'), 3.47 (1 H, dd, *J* = 11.2, 8.5 Hz, H-2'), 2.94 (1 H, ddt, *J* = 9.3, 8.0, 5.3 Hz, H-4), 2.74 (1 H, dquin, *J* = 11.3, 7.7 Hz, H-3), 2.46 (1 H, dd, *J* = 15.9, 7.8 Hz, H-7), 2.39 (1 H, dd, *J* = 15.9, 7.7 Hz, H-7'), 1.89 (1 H, ddt, *J* = 13.1, 9.4, 7.5 Hz, H-5), 1.82 (1 H, ddt, *J* = 13.0, 6.8, 5.6 Hz, H-5'), 1.27 (3 H, t, *J* = 7.2 Hz, H-10) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 171.8 (C, C-8), 109.6 (CH, C-1), 71.8 (CH_2, C-2), 69.0 (CH_2, C-6), 60.7 (CH_2, C-9), 45.3 (CH, C-4), 38.1 (CH, C-3), 32.7 (CH_2, C-7), 25.4 (CH_2, C-5), 14.2 (CH_3, C-10) ppm; **LRMS** (ESI^+) *m*/*z* 223.2 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{10}H_{16}O_4Na$ $(M + Na)^+$ calcd 223.0941, found 223.0943.

byproduct: (3*S*,3a*S*,6a*R*)-(Hexahydrofuro[2,3-*b*]furan-3-yl)-acetic acid ethyl ester (*exo*-**6.9**): **Formula** $C_{10}H_{16}O_4$; **Mw** 200.23; $\mathbf{R_f}$ 0.24 (hexane/acetone 80:20); $\mathbf{[\alpha]_D}$ −44.9 (c 1.13, $CHCl_3$, 27 °C); **IR** (film) 2951 (w), 2875 (w), 1728 (vs), 1172 (s), 1092 (m), 1021 (s), 921 (m) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.73 (1 H, d, *J* = 5.1 Hz, H-1), 4.16 (2 H, q, *J* = 7.2 Hz, H-9), 4.09 (1 H, m, H-2), 3.91 (1 H, dd, *J* = 8.7, 1.3 Hz, H-6), 3.90 (1 H, d, *J* = 8.7 Hz, H-6'), 3.61 (1 H, m, H-2'), 2.55 (1 H, ddt, *J* = 9.0, 5.1, 2.8 Hz, H-4), 2.47–2.41 (3 H, m, H-3, H-7 and H-7'), 2.13 (1 H, dtd, *J* = 12.6, 9.2, 8.3 Hz, H-5), 1.82 (1 H, dddd, *J* = 12.6, 5.4, 4.3, 2.9 Hz, H-5'), 1.28 (3 H, t, *J* = 7.2 Hz, H-10) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 172.1 (C, C-8), 109.0 (CH, C-1), 72.4 (CH_2, C-2), 67.9 (CH_2, C-6), 60.6 (CH_2, C-9), 48.7 (CH, C-4), 42.0 (CH, C-3), 38.2 (CH_2, C-7), 31.9 (CH_2, C-5), 14.2 (CH_3, C-10) ppm; **LRMS** (ESI+) *m*/*z* 223.2 $(M + Na)^+$; **HRMS** (ESI+) for $C_{10}H_{16}O_4Na$ $(M + Na)^+$ calcd 223.0941, found 223.0937.

Protease inhibitor 6.3a



endo-**6.9**

6.3a (23%)

To a solution of ester *endo*-**6.9** (427 mg, 2.13 mg) in EtOH (20 mL) was added aq. 4 M NaOH (1.05 mL, 4.26 mmol) and the resulting mixture was stirred at rt for 2 h. After completion the reaction mixture was acidified with aq. 2 N HCl (3 mL) and concentrated under reduced pressure. The residue was dissolved in H_2O/EtOAc (10 mL each) and the aqueous phase was extracted with EtOAc (2 × 15 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to afford the crude free acid **6.10** as a white solid (292 mg, 80%).

Following procedures from the literature[160], acid **6.10** was then coupled to the Evan's auxiliary as follows: To a solution of the crude acid **6.10** (195 mg, 1.13 mmol) and Et_3N (235 µL, 1.70 mmol) in THF (15 mL) at −78 °C was added pivaloyl chloride (154 µL, 1.25 mmol) and the mixture was allowed to warm to 0 °C. A second flask was charged with (*S*)-4-benzyl-2-oxazolidinone (420 mg, 2.38 mmol) in THF (10 mL) and n-BuLi (0.9 mL, 2.26 mmol, 2.5 M in THF) was added slowly at −78 °C. After 10 min, the first solution was added via cannula and the resulting mixture was stirred for further 2 h, while slowly warming to rt. After completion, the reaction was quenched with aq. 1 N $NaHSO_4$ (5 mL)

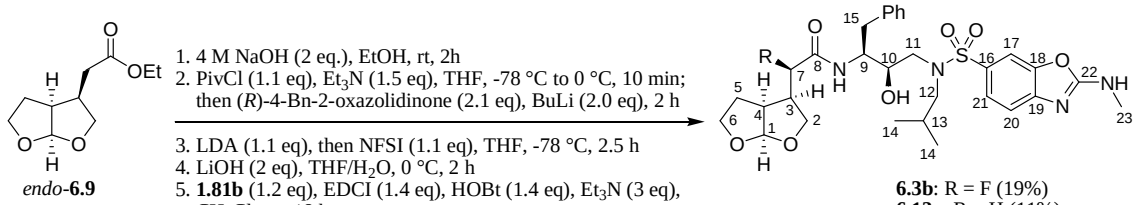
and concentrated under reduced pressure. The remaining aqueous residue was extracted with CH_2Cl_2 (3×25 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ and brine (10 mL each), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether/ acetone 75:25 to 60:40) and by HPLC (hexane/acetone 70:30, R_f 0.3) to afford oxazolidinone **6.5a** as a colourless oil (191 mg, 55%).

Oxazolidinone **6.5a** was then selectively fluorinated using LDA[150] and NFSI[151]. To a solution of **6.5a** (184 mg, 0.55 mmol) in THF (20 mL) at −78 °C was added dropwise LDA (0.3 mL, 0.61 mmol, 2 M in THF) and stirred for 20 min. Then a solution of *N*-fluoro-benzenesulfonimide (192 mg, 0.61 mmol) in THF (5 mL) was added and the resulting mixture was stirred at −78 °C for 2.5 h. The reaction was then allowed to warm to 0 °C over 20 min, quenched with sat. aq. NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (petroleum ether/acetone 75:25 to 70:30) to afford the fluorinated intermediate **6.12a** (176 mg, 92%). The ^{19}F NMR only showed one major peak at −197.3 ppm.

The chiral auxiliary was then removed using $LiOH \cdot H_2O$ in aqeous THF.[153] To a solution of **6.12a** (159 mg, 0.46 mmol) in THF/H_2O (10 mL, 3:1, v/v) at 0 °C was added LiOH (38.2 mg, 0.91 mmol) and the reaction mixture was stirred at this temperature for 75 min. After completion the solution was buffered to pH 9−10 with sat. aq. $NaHCO_3$ and the THF was removed in vacuo. The aqueous residue was first extracted with CH_2Cl_2 (2×10 mL), then acidified with aq. 2 M HCl and again extracted with EtOAc (3×10 mL). The combined CH_2Cl_2-phases were dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo to obtain the crude auxiliary (72 mg, 83%). The combined EtOAc-phases were also dried over anhydrous Na_2SO_4, filtered and the solvent is removed in vacuo to afford the α-fluoroacid **6.4a** (68 mg, 78%, ^{19}F NMR: δ −191.6 ppm). The crude acid was then coupled to amine **1.81b** as follows: To a solution of amine **1.81b** (187 mg, 0.42 mmol), EDCI (94 mg, 0.49 mmol) and Et_3N (145 µL, 1.05 mmol) in CH_2Cl_2 (7 mL) at 0 °C was added HOBt (66 mg, 0.49 mmol) and a solution of **6.4a** (68 mg, 0.35 mmol) in CH_2Cl_2 (3 mL). The cooling was removed and the resulting mixture is stirred at rt for 18 h. After completion, the reaction mixture was diluted with CH_2Cl_2 (10 mL), and subsequently washed with aq. 1 M HCl and H_2O (10 mL each), dried over anhydrous Na_2SO_4, filtered and the solvent was removed in vacuo. The crude product was purified by column chromatography (CH_2Cl_2/MeOH 97:3 to 95:5) and by HPLC (CH_2Cl_2/MeOH 95:5) to

afford the PI **6.3a** as a white solid (163 mg, 75%). **Formula** $C_{30}H_{39}FN_4O_7S$; **Mw** 618.72; $\mathbf{R_f}$ 0.28 (CH_2Cl_2/MeOH 95:5); **Mp** 173–175 °C; $\mathbf{[\alpha]_D}$ +2.4 (c 0.41, MeOH, 27 °C); **IR** (film) 3328 (br. w), 2962 (w), 2870 (w), 1691 (s), 1660 (vs), 1539 (m), 1331 (m), 1274 (m), 1141 (s), 1025 (s), 767 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.68 (1 H, d, *J* = 1.6 Hz, H-17), 7.63 (1 H, dd, *J* = 8.3, 1.8 Hz, H-21), 7.44 (1 H, d, *J* = 8.3 Hz, H-20), 7.34–7.20 (5 H, m, Ar-H), 6.54 (1 H, dd, *J* = 9.3, 4.2 Hz, N*H*CO), 5.64 (1 H, d, *J* = 4.9 Hz, H-1), 5.19 (1 H, m, N*H*Me), 4.74 (1 H, dd, *J* = 49.2, 9.3 Hz, H-7), 4.27 (1 H, tt, *J* = 9.7, 4.8 Hz, H-9), 3.95 (1 H, m, H-10), 3.89 (1 H, dt, *J* = 8.7, 7.1 Hz, H-6), 3.80 (1 H, ddd, *J* = 8.8, 7.4, 5.8 Hz, H-6'), 3.75 (1 H, m, OH), 3.64 (1 H, dd, *J* = 11.2, 9.2 Hz, H-2), 3.56 (1 H, dd, *J* = 9.2, 7.5 Hz, H-2'), 3.19 (3 H, d, *J* = 5.0 Hz, H-23), 3.21 (1 H, dd, *J* = 15.1, 8.9 Hz, H-11), 3.11 (1 H, dd, *J* = 14.2, 5.0 Hz, H-15), 3.02 (1 H, dd, *J* = 13.3, 8.4 Hz, H-12), 2.98 (1 H, dd, *J* = 15.2, 3.0 Hz, H-11'), 2.87 (1 H, dd, *J* = 14.1, 10.5 Hz, H-15'), 2.84 (1 H, dd, *J* = 13.4, 6.7 Hz, H-12'), 2.74 (1 H, ddt, *J* = 9.5, 7.7, 5.5 Hz, H-4), 2.23 (1 H, m, H-3), 1.89–1.68 (3 H, m, H-5, H-5' and H-13), 0.95 (3 H, d, *J* = 6.5 Hz, H-14), 0.90 (3 H, d, *J* = 6.7 Hz, H-14) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.7 (C, d, *J* = 19.9 Hz, C-8), 164.6 (C_{ar}, C-22), 148.2 (C_{ar}, C-18 or C-19) 147.9 (C_{ar}, C-19 or C-18), 137.3 (C_{ar}), 129.8 (C_{ar}, C-16), 129.2 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 126.8 (CH_{ar}), 124.2 (CH_{ar}, C-21), 116.3 (CH_{ar}, C-20), 109.2 (CH, C-1), 108.4 (CH_{ar}, C-17); 89.7 (CHF, d, *J* = 189.0 Hz, C-7), 72.6 (CH, C-10), 69.0 (CH_2, C-6), 67.7 (CH_2, d, *J* = 8.7 Hz, C-2), 59.0 (CH_2, C-12), 53.8 (CH_2, C-11), 52.8 (CH, C-9), 44.5 (CH, d, *J* = 19.4 Hz, C-3), 44.1 (CH, C-4), 35.0 (CH_2, C-15), 29.6 (CH_3, C-23), 27.4 (CH, C-13), 25.2 (CH_2, C-5), 20.2 (CH_3, C-14), 19.9 (CH_3, C-14) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −188.3 (dd, *J* = 48.2, 12.9 Hz) ppm; **LRMS** (ESI^+) *m*/*z* 641.3 $(M + Na)^+$; **HRMS** (ESI^+) for $C_{30}H_{40}FN_4O_7S$ $(M + H)^+$ calcd 619.2596, found 619.2587.

Protease inhibitor 6.3b



endo-**6.9**

6.3b: R = F (19%)
6.13a: R = H (11%)

Following the conditions described for PI **6.3a**, the reaction of acid **6.10** (195 mg, 1.13 mmol) and (*R*)-4-benzyl-2-oxazolidinone (420 mg, 2.38 mmol) afforded after purification by column chromatography (petroleum ether/acetone = 75:25 to 60:40) and by HPLC (hexane/acetone 70:30, R_f 0.31) oxazolidinone **6.5b** as a colourless oil (243 mg,

65%). Diastereoselective fluorination of **6.5b** (234 mg, 0.71 mmol) with *N*-fluorobenzenesulfonimide (245 mg, 0.78 mmol) led after purification by column chromatography (petroleum ether/acetone 75:25 to 70:30) to the fluorinated intermediate **6.12b** (201 mg, 81%, ^{19}F NMR: δ −191.9 ppm). Treatment of **6.12b** (192 mg, 0.55 mmol) with LiOH·H_2O (46.1 mg, 1.10 mmol) afforded a 2:1 mixture of **6.4b**/**6.9** (78 mg, 79%), which was then coupled to amine **1.81b** (205 mg, 0.46 mmol), as described above (8.2.1), to give after purification by column chromatography (CH_2Cl_2/MeOH 95:5) and by HPLC (CH_2Cl_2/MeOH 95:5) the PI **6.3b** as a white solid (134 mg, 57%) and non-fluorinated PI **6.13a** as a pale yellow oil (70 mg, 30%). **Formula** $C_{30}H_{39}FN_4O_7S$; **Mw** 618.72; $\mathbf{R_f}$ 0.28 (CH_2Cl_2/MeOH 95:5); **Mp** 95–97 °C; $\mathbf{[\alpha]_D}$ +13.4 (c 1.31, $CHCl_3$, 27 °C); **IR** (film) 3337 (br. w), 2960 (w), 2873 (w), 1655 (s), 1580 (m), 1463 (m), 1325 (m), 1272 (m), 1143 (m), 1005 (m), 911 (m), 729 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.64 (1 H, d, *J* = 1.8 Hz, H-17), 7.60 (1 H, dd, *J* = 8.3, 1.8 Hz, H-21), 7.41 (1 H, d, *J* = 8.3 Hz, H-20), 7.32–7.20 (5 H, m, Ar-H), 6.54 (1 H, dd, *J* = 9.0, 4.2 Hz, N*H*CO), 5.69 (1 H, d, *J* = 4.9 Hz, H-1), 5.66 (1 H, dd, *J* = 8.0, 4.9 Hz, N*H*Me), 4.83 (1 H, dd, *J* = 49.3, 7.0 Hz, H-7), 4.20 (1 H, ttd, *J* = 9.7, 4.8, 1.1 Hz, H-9), 3.97–3.89 (2 H, m, H-6 and H-10), 3.89–3.80 (3 H, m, H-2, H-6' and OH), 3.76 (1 H, dd, *J* = 11.0, 8.7 Hz, H-2'), 3.16 (3 H, d, *J* = 4.9 Hz, H-23)´, 3.12–3.01 (3 H, m, H-11, H-11' and H-15), 2.99–2.85 (4 H, m, H-4, H-12, H-12' and H-15'), 2.73 (1 H, ddq, *J* = 18.8, 11.2, 7.5 Hz, H-3), 2.00–1.93 (2 H, m, H-5 and H-5'), 1.85 (1 H, m, H-13), 0.90 (6 H, d, *J* = 6.5 Hz, H-14) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 168.7 (C, d, *J* = 19.4 Hz, C-8), 164.8 (C_{ar}, C-22), 148.1 (C_{ar}, C-18 or C-19), 147.9 (C_{ar}, C-19 or C-18), 137.1 (C_{ar}), 129.5 (C_{ar}, C-16), 129.3 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 126.8 (CH_{ar}), 124.2 (CH_{ar}, C-21), 116.2 (CH_{ar}, C-20), 109.6 (CH, C-1), 108.3 (CH_{ar}, C-17), 90.4 (CHF, d, *J* = 186.8 Hz, C-7), 72.3 (CH, C-10), 69.1 (CH_2, C-6), 67.8 (CH_2, d, *J* = 5.6 Hz, C-2), 59.0 (CH_2, C-12), 53.7 (CH_2, C-11), 53.4 (CH, C-9), 44.7 (CH, d, *J* = 4.4 Hz, C-4), 44.3 (CH, d, *J* = 19.2 Hz, C-3), 35.2 (CH_2, C-15), 29.5 (CH_3, C-23), 27.2 (CH, C-13), 26.5 (CH_2, C-5), 20.1 (CH_3, C-14), 19.9 (CH_3, C-14) ppm; **^{19}F NMR** (282 MHz, $CDCl_3$) δ −192.8 (dd, *J* = 47.2, 17.2 Hz) ppm; **LRMS** (ESI+) *m*/*z* 641.3 $(M + Na)^+$; **HRMS** (ESI+) for $C_{30}H_{39}FN_4O_7SNa$ $(M + Na)^+$ calcd 641.2416, found 641.2429.

byproduct: **PI 6.13a**: **Formula**: $C_{30}H_{40}N_4O_7S$; **Mw** 600.73; $\mathbf{R_f}$ 0.21 (CH_2Cl_2/MeOH 95:5); $\mathbf{[\alpha]_D}$ −13.0 (c 0.64, $CHCl_3$, 27 °C); **IR** (film) 3306 (br. w), 2959 (w), 2872 (w), 1657 (s), 1580 (m), 1463 (m), 1324 (m), 1273 (m), 1144 (m), 999 (m), 731 (s) cm^{-1}; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.65 (1 H, d, *J* = 1.6 Hz, H-17), 7.61 (1 H, dd, *J* = 8.3, 1.8 Hz, H-21), 7.42 (1 H, d, *J* = 8.3 Hz, H-20), 7.33–7.18 (5 H, m, Ar-H), 5.85 (1 H, d, *J* = 8.5 Hz,

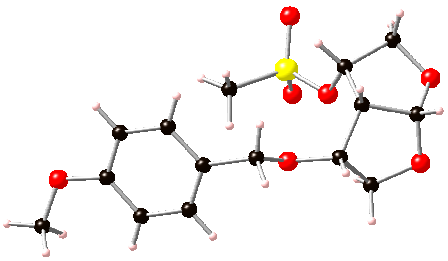
N*H*CO), 5.65 (1 H, d, *J* = 4.9 Hz, H-1), 5.47 (1 H, q, *J* = 4.9 Hz, N*H*Me), 4.25 (1 H, tt, *J* = 9.1, 4.8 Hz, H-9), 3.99 (1 H, br. s, OH), 3.94 (1 H, m, H-10), 3.85 (1 H, dd, *J* = 8.5, 7.4 Hz, H-2), 3.82 (1 H, dt, *J* = 8.8, 7.1 Hz, H-6), 3.75 (1 H, dt, *J* = 8.7, 6.5 Hz, H-6'), 3.38 (1 H, dd, *J* = 11.2, 8.5 Hz, H-2'), 3.17 (3 H, d, *J* = 5.0 Hz, H-23), 3.12–3.02 (3 H, m, H-11, H-11' and H-15), 2.97–2.84 (3 H, m, H-12, H-12' and H-15'), 2.69 (1 H, qd, *J* = 7.5, 4.9 Hz, H-4), 2.57 (1 H, dquin, *J* = 11.2, 7.5 Hz, H-3), 2.19 (1 H, dd, *J* = 14.8, 7.2 Hz, H-7), 2.13 (1 H, dd, *J* = 14.7, 8.2 Hz, H-7'), 1.88 (1 H, m, H-13), 1.56 (2 H, app. q, *J* = 6.9 Hz, H-5 and H-5'), 0.91 (3 H, d, *J* = 6.5 Hz, H-14), 0.90 (3 H, d, *J* = 6.7 Hz, H-14) ppm; **^{13}C NMR + DEPT** (100 MHz, $CDCl_3$) δ 171.3 (C, C-8), 164.7 (C_{ar}, C-22), 148.2 (C_{ar}, C-18 or C-19), 147.9 (C_{ar}, C-19 or C-18), 137.7 (C_{ar}), 129.8 (C_{ar}, C-16), 129.2 (2 × CH_{ar}), 128.6 (2 × CH_{ar}), 126.7 (CH_{ar}), 124.2 (CH_{ar}, C-21), 116.2 (CH_{ar}, C-20), 109.5 (CH, C-1), 108.3 (CH_{ar}, C-17), 72.8 (CH, C-10), 71.5 (CH_2, C-2), 68.9 (CH_2, C-6), 58.9 (CH_2, C-12), 53.7 (CH, C-9), 53.6 (CH_2, C-11), 45.2 (CH, C-4), 38.4 (CH, C-3), 34.9 (CH_2, C-7 or C-15), 34.4 (CH_2, C-15 or C-7), 29.6 (CH_3, C-23), 27.2 (CH, C-13), 25.1 (CH_2, C-5), 20.1 (CH_3, C-14), 20.0 (CH_3, C-14) ppm; **LRMS** (ESI+) *m*/*z* 623.3 $(M + Na)^+$; **HRMS** (ESI+) for $C_{30}H_{40}N_4O_7SNa$ $(M + Na)^+$ calcd 623.2510, found 623.2520.

Chapter 9 APPENDIX

9.1 SINGLE CRYSTAL X-RAY ANALYSIS DATA

Methanesulfonic acid (1*S*,4S,5*R*,6*R*)-6-(4-methoxybenzyloxy)-2,8-dioxa-bicyclo[3.3.0]-octane-4-yl ester (3.30)

Table 1. Crystal data and structure refinement details.



Identification code	**2009sot0875**
Empirical formula	$C_{15}H_{20}O_7S$
Formula weight	344.37
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 7.48670(10) Å
	b = 11.1908(2) Å $\quad\beta$ = 111.1240(10)°
	c = 10.3316(2) Å
Volume	807.44(2) Å^3
Z	2
Density (calculated)	1.416 Mg / m^3
Absorption coefficient	0.234 mm^{-1}
$F(000)$	364
Crystal Fragment	Colourless
Crystal size	0.60 × 0.30 × 0.10 mm^3
θ range for data collection	2.92 – 27.46°
Index ranges	$-9 \le h \le 9$, $-14 \le k \le 14$, $-13 \le l \le 13$
Reflections collected	10379
Independent reflections	3584 [R_{int} = 0.0354]
Completeness to θ = 27.46°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9770 and 0.8724
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3584 / 1 / 210
Goodness-of-fit on F^2	1.042
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0328, $wR2$ = 0.0850
R indices (all data)	$R1$ = 0.0362, $wR2$ = 0.0876
Absolute structure parameter	0.02(6)
Largest diff. peak and hole	0.172 and –0.271 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.
Chirality: C9=R, C11=S, C13=S, C14=R

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S1	−324(1)	−59(1)	−605(1)	19(1)	1
O1	9(2)	3299(1)	5245(1)	30(1)	1
O2	3929(2)	−433(1)	2715(1)	23(1)	1
O3	4775(2)	−3069(1)	1051(2)	29(1)	1
O4	3954(2)	−2283(1)	−1173(1)	29(1)	1
O5	1520(2)	−867(1)	−105(1)	19(1)	1
O6	−1847(2)	−858(1)	−687(1)	28(1)	1
O7	−396(2)	595(1)	−1816(1)	27(1)	1
C1	−757(3)	2825(2)	6226(2)	34(1)	1
C2	1239(3)	2576(2)	4885(2)	22(1)	1
C3	1674(3)	1405(2)	5329(2)	24(1)	1
C4	2965(3)	772(2)	4902(2)	24(1)	1
C5	3804(3)	1273(2)	4027(2)	21(1)	1
C6	3332(3)	2451(2)	3591(2)	22(1)	1
C7	2067(3)	3100(2)	4013(2)	23(1)	1
C8	5071(3)	535(2)	3497(2)	24(1)	1
C9	4981(3)	−1240(2)	2208(2)	20(1)	1
C10	4069(3)	−2479(2)	2017(2)	23(1)	1
C11	5256(3)	−2215(2)	223(2)	22(1)	1
C12	3287(3)	−1095(2)	−1638(2)	25(1)	1
C13	3242(2)	−464(2)	−361(2)	18(1)	1
C14	5029(2)	−965(2)	771(2)	19(1)	1
C15	18(3)	944(2)	772(2)	27(1)	1

Table 3. Bond lengths [Å] and angles [°].

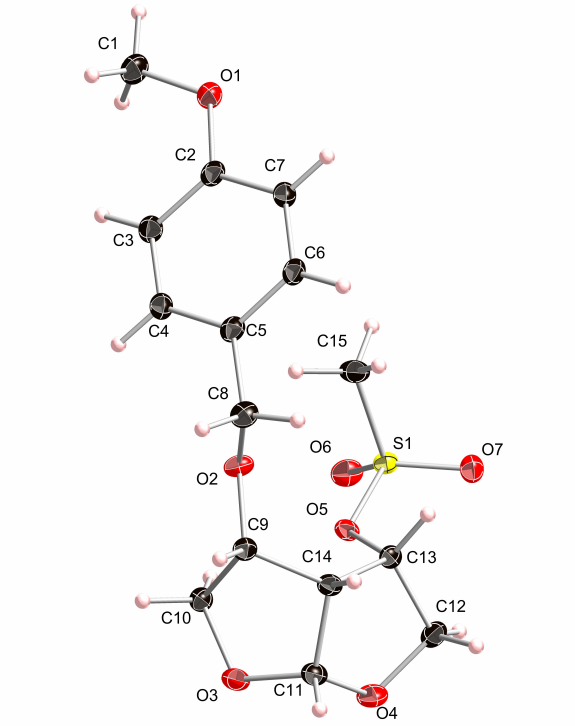
S1–O6	1.4272(13)	C2–C3	1.388(3)
S1–O7	1.4339(13)	C2–C7	1.394(2)
S1–O5	1.5740(12)	C3–C4	1.393(3)
S1–C15	1.756(2)	C4–C5	1.391(2)
O1–C2	1.374(2)	C5–C6	1.397(3)
O1–C1	1.434(2)	C5–C8	1.502(3)
O2–C9	1.416(2)	C6–C7	1.382(3)
O2–C8	1.436(2)	C9–C10	1.526(2)
O3–C11	1.413(2)	C9–C14	1.529(2)
O3–C10	1.447(2)	C11–C14	1.541(3)
O4–C11	1.422(2)	C12–C13	1.508(2)
O4–C12	1.440(2)	C13–C14	1.532(2)
O5–C13	1.4764(19)		
O6–S1–O7	119.32(8)	C6–C5–C8	121.37(17)
O6–S1–O5	104.30(8)	C7–C6–C5	121.06(17)
O7–S1–O5	109.39(7)	C6–C7–C2	119.89(17)
O6–S1–C15	109.16(9)	O2–C8–C5	107.10(14)
O7–S1–C15	109.27(10)	O2–C9–C10	110.15(13)
O5–S1–C15	104.31(8)	O2–C9–C14	116.21(14)
C2–O1–C1	116.81(15)	C10–C9–C14	102.88(14)
C9–O2–C8	113.07(13)	O3–C10–C9	104.27(13)
C11–O3–C10	110.17(13)	O3–C11–O4	110.32(15)
C11–O4–C12	108.52(13)	O3–C11–C14	107.79(13)
C13–O5–S1	118.99(11)	O4–C11–C14	107.16(14)
O1–C2–C3	124.53(17)	O4–C12–C13	104.77(14)
O1–C2–C7	115.19(16)	O5–C13–C12	108.03(14)
C3–C2–C7	120.29(17)	O5–C13–C14	109.27(14)
C2–C3–C4	118.90(18)	C12–C13–C14	101.99(14)
C5–C4–C3	121.85(18)	C9–C14–C13	119.68(14)
C4–C5–C6	118.00(17)	C9–C14–C11	102.63(14)
C4–C5–C8	120.50(16)	C13–C14–C11	103.50(14)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
S1	17(1)	20(1)	21(1)	−1(1)	8(1)	1(1)
O1	36(1)	30(1)	29(1)	7(1)	19(1)	9(1)
O2	21(1)	24(1)	24(1)	−8(1)	9(1)	−1(1)
O3	39(1)	17(1)	38(1)	1(1)	25(1)	3(1)
O4	35(1)	25(1)	28(1)	−8(1)	11(1)	3(1)
O5	17(1)	18(1)	27(1)	2(1)	13(1)	1(1)
O6	18(1)	31(1)	37(1)	−5(1)	14(1)	−4(1)
O7	29(1)	29(1)	24(1)	7(1)	11(1)	6(1)
C1	38(1)	37(1)	37(1)	7(1)	25(1)	7(1)
C2	24(1)	25(1)	15(1)	−1(1)	6(1)	1(1)
C3	26(1)	24(1)	23(1)	1(1)	10(1)	−2(1)
C4	29(1)	22(1)	19(1)	1(1)	7(1)	0(1)
C5	23(1)	23(1)	16(1)	−3(1)	5(1)	−2(1)
C6	28(1)	22(1)	16(1)	−1(1)	8(1)	−4(1)
C7	30(1)	20(1)	19(1)	1(1)	8(1)	1(1)
C8	24(1)	24(1)	24(1)	−5(1)	8(1)	−5(1)
C9	20(1)	21(1)	20(1)	1(1)	8(1)	3(1)
C10	27(1)	21(1)	25(1)	4(1)	16(1)	3(1)
C11	22(1)	21(1)	27(1)	−1(1)	12(1)	2(1)
C12	24(1)	31(1)	21(1)	0(1)	11(1)	3(1)
C13	17(1)	18(1)	21(1)	2(1)	11(1)	0(1)
C14	18(1)	16(1)	24(1)	−1(1)	11(1)	0(1)
C15	27(1)	26(1)	26(1)	−6(1)	7(1)	6(1)

Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

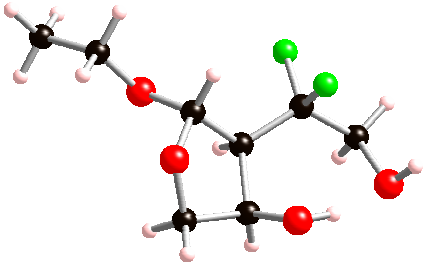
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H1A	–1526	2114	5834	52	1
H1B	–1565	3429	6432	52	1
H1C	296	2608	7082	52	1
H3	1100	1042	5915	29	1
H4	3282	–26	5218	28	1
H6	3890	2813	2995	27	1
H7	1763	3901	3709	28	1
H8A	5561	1026	2900	29	1
H8B	6176	223	4282	29	1
H9	6323	–1292	2891	24	1
H10A	4465	–2914	2910	28	1
H10B	2654	–2421	1632	28	1
H11	6600	–2338	268	27	1
H12A	1994	–1119	–2368	29	1
H12B	4171	–687	–2012	29	1
H13	3291	425	–441	21	1
H14	6168	–459	859	23	1
H15A	–1137	1430	584	41	1
H15B	1109	1466	865	41	1
H15C	273	495	1635	41	1



Thermal ellipsoids drawn at the 35% probability level.

(3*R*,4*S*,5*S*)-4-(1,1-Difluoro-2-hydroxy-ethyl)-5-ethoxy-tetrahydro-furan-3-ol (3.116)

Table 1. Crystal data and structure refinement details.



Identification code	**2010sot0425**
Empirical formula	$C_8H_{14}F_2O_4$
Formula weight	212.19
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 5.29810(10) Å
	b = 6.45980(10) Å β = 95.7630(10)°
	c = 14.2857(3) Å
Volume	486.452(16) Å^3
Z	2
Density (calculated)	1.449 Mg / m^3
Absorption coefficient	0.137 mm^{-1}
F(000)	224
Crystal Fragment:	Colourless
Crystal size	0.32 × 0.20 × 0.10 mm^3
θ range for data collection	3.99 – 27.47°
Index ranges	$-6 \le h \le 6$, $-7 \le k \le 8$, $-18 \le l \le 17$
Reflections collected	5861
Independent reflections	1201 [R_{int} = 0.0345]
Completeness to θ = 27.47°	99.0 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9864 and 0.9574
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	1201 / 1 / 130
Goodness-of-fit on F^2	0.958
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0275, $wR2$ = 0.0688
R indices (all data)	$R1$ = 0.0290, $wR2$ = 0.0705
Absolute structure parameter	10(10)
Largest diff. peak and hole	0.178 and –0.198 e Å^{-3}

Diffractometer: *Nonius KappaCCD* area detector (ϕ scans and ω scans to fill *asymmetric unit*). **Cell determination:** DirAx (Duisenberg, A.J.M.(1992). J. Appl. Cryst. 25, 92-96.) **Data collection:** Collect (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). **Data reduction and cell refinement**: *Denzo* (Z. Otwinowski & W. Minor, *Methods in Enzymology* (1997) Vol. **276**: *Macromolecular Crystallography*, part A, pp. 307–326; C. W. Carter, Jr. & R. M. Sweet, Eds., Academic Press). **Absorption correction**: Sheldrick, G. M. SADABS - Bruker Nonius area detector scaling and absorption correction - V2.10 S**tructure solution**: *SHELXS97* (G. M. Sheldrick, Acta Cryst. (1990) A**46** 467–473). S**tructure refinement**: *SHELXL97* (G. M. Sheldrick (1997), University of Göttingen, Germany). **Graphics:** Cameron - A Molecular Graphics Package. (D. M. Watkin, L. Pearce and C. K. Prout, Chemical Crystallography Laboratory, University of Oxford, 1993).

Special details: All hydrogen atoms were placed in idealised positions and refined using a riding model.

Table 2. Atomic coordinates [$\times 10^4$], equivalent isotropic displacement parameters [$Å^2 \times 10^3$] and site occupancy factors. U_{eq} is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
F1	4798(2)	5579(2)	8668(1)	17(1)	1
F2	7552(2)	5981(2)	7638(1)	21(1)	1
O1	3975(2)	3058(2)	6135(1)	18(1)	1
O2	1588(2)	1519(2)	7237(1)	18(1)	1
O3	4064(2)	1197(2)	9139(1)	18(1)	1
O4	8149(2)	3326(2)	9857(1)	18(1)	1
C1	2778(4)	3465(4)	4492(1)	32(1)	1
C2	1938(4)	3738(3)	5464(1)	25(1)	1
C3	3324(3)	3120(3)	7062(1)	14(1)	1
C4	3054(3)	−214(3)	7608(1)	18(1)	1
C5	5135(3)	750(3)	8279(1)	14(1)	1
C6	5755(3)	2693(3)	7723(1)	12(1)	1
C7	6740(3)	4570(3)	8276(1)	14(1)	1
C8	8933(3)	4300(3)	9038(1)	16(1)	1

Table 3. Bond lengths [Å] and angles [°].

F1–C7	1.3834(18)	O4–C8	1.426(2)
F2–C7	1.3867(18)	C1–C2	1.510(3)
O1–C3	1.4030(18)	C3–C6	1.544(2)
O1–C2	1.438(2)	C4–C5	1.520(2)
O2–C3	1.423(2)	C5–C6	1.539(2)
O2–C4	1.434(2)	C6–C7	1.511(2)
O3–C5	1.4329(18)	C7–C8	1.520(2)
C3–O1–C2	112.43(13)	C7–C6–C5	117.76(12)
C3–O2–C4	107.25(12)	C7–C6–C3	113.55(14)
O1–C2–C1	107.82(16)	C5–C6–C3	104.67(13)
O1–C3–O2	111.68(13)	F1–C7–F2	104.38(13)
O1–C3–C6	107.70(12)	F1–C7–C6	110.96(12)
O2–C3–C6	106.10(13)	F2–C7–C6	107.34(12)
O2–C4–C5	104.18(14)	F1–C7–C8	108.07(12)
O3–C5–C4	107.37(12)	F2–C7–C8	106.31(13)
O3–C5–C6	113.66(13)	C6–C7–C8	118.75(15)
C4–C5–C6	100.81(12)	O4–C8–C7	111.92(12)

Table 4. Anisotropic displacement parameters [$Å^2 \times 10^3$]. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + \cdots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$.

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
F1	17(1)	15(1)	18(1)	−3(1)	3(1)	5(1)
F2	27(1)	17(1)	18(1)	5(1)	4(1)	−5(1)
O1	20(1)	23(1)	10(1)	2(1)	0(1)	2(1)
O2	13(1)	21(1)	19(1)	2(1)	0(1)	−2(1)
O3	22(1)	19(1)	12(1)	0(1)	3(1)	−3(1)
O4	22(1)	18(1)	13(1)	0(1)	1(1)	5(1)
C1	43(1)	37(1)	14(1)	5(1)	−4(1)	−7(1)
C2	28(1)	28(1)	16(1)	4(1)	−6(1)	4(1)
C3	15(1)	15(1)	12(1)	−2(1)	1(1)	1(1)
C4	21(1)	15(1)	18(1)	−1(1)	2(1)	−1(1)
C5	16(1)	13(1)	14(1)	1(1)	3(1)	1(1)
C6	13(1)	12(1)	11(1)	0(1)	3(1)	3(1)
C7	15(1)	12(1)	14(1)	2(1)	5(1)	0(1)
C8	15(1)	20(1)	14(1)	−1(1)	1(1)	0(1)

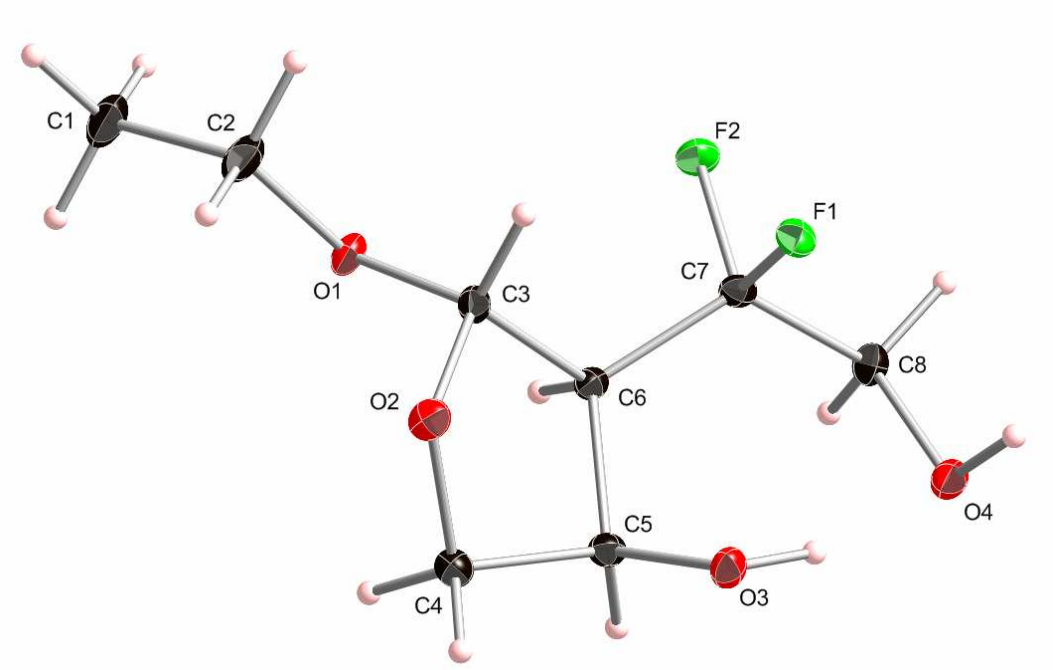
Table 5. Hydrogen coordinates [$\times 10^4$] and isotropic displacement parameters [$Å^2 \times 10^3$].

Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
H903	5146	1807	9511	26	1
H4	7515	4216	10193	27	1
H1A	4304	4295	4436	47	1
H1B	1421	3922	4020	47	1
H1C	3153	2002	4389	47	1
H2A	1543	5211	5574	30	1
H2B	394	2907	5528	30	1
H3	2605	4504	7202	17	1
H4A	3782	−983	7099	22	1
H4B	2001	−1172	7945	22	1
H5	6638	−187	8388	17	1
H6	7097	2285	7314	14	1
H8A	10272	3452	8789	20	1
H8B	9668	5673	9211	20	1

Table 6. Hydrogen bonds [Å and °].

D–H··*A*	*d*(*D*–H)	*d*(H··*A*)	*d*(*D*··*A*)	∠(*DHA*)
O3–H903···O4	0.84	1.89	2.6801(18)	155.7
O4–H4···O3^{i}	0.84	1.85	2.6850(17)	175.9

Symmetry transformations used to generate equivalent atoms: (i) –x+1,y+1/2,–z+2



Thermal ellipsoids drawn at the 35% probability level

9.2 ANTIVIRAL ACTIVITY TEST AND CALCULATED PROPERTIES OF NEW PIS

The antiviral activity has been determined with a cell-based replication assay.[167] This assay directly measures the ongoing replication of virus in MT4 cells via the specific interaction of HIV-tat with LTR sequences coupled to GFP. In the toxicity assay, a reduced expression of the GFP reporter protein serves as a marker for cellular toxicity of a compound. Briefly, various concentrations of the test compounds are brought into a 384-well microtiter plate. Subsequently, MT4 cells and HIV-1/LAI (wild type) are added to the plate at a concentration of 150 000 cells/mL and 200 cell culture infectious doses 50% ($CCID_{50}$). To determine the toxicity of the test compound, mock-infected cell cultures containing an identical compound concentration range are incubated for 3 days (37 °C, 5% CO_2) in parallel with the HIV-infected cell cultures. On the basis of the calculated percent inhibition for each compound concentration, dose response curves are plotted and EC50, pEC50, CC50, and pCC50 values are calculated.

The logP values[168] and the total polar surface areas (TPSA in $Å^2$)[169] were calculated using Cresset FieldView 2.0.1.

PI	R	Ar	EC_{50} [nM]					FC relative to HIV-1 (wt)			IC50 [nM]	CC50 [µM]	MW	wclogP	TPSA
			HIV-1 (wt)	+50% HS	M1	M2	M3	M1	M2	M3					
1.10a	H (DRV)	NH_2	6,6	17,2	11,3	51,0	2,3	1,7	7,8	0,4	3,8	>1.97	547,66	2,76	140,4
1.10b	H	BO-NHMe	2,3	8,3	2,7	3,2	0,9	1,2	1,4	0,4	2,1	n/a	602,70	2,78	152,5
4.31a	OH	NH_2	772,9	814,7	112,3	204,5	40,4	0,1	0,3	0,1	2,9	>31.48	563,66	2,11	160,6
4.31b	OH	BO-NHMe	137,7	446,3	125,4	108,0	103,9	0,9	0,8	0,8	n/a	>31.48	618,70	2,13	172,7
4.31c	OH	OMe	6,5	12,4	6,9	6,7	1,6	1,1	1,0	0,2	n/a	>31.48	578,67	2,53	143,9
4.31e	OH	Br	4,8	19,6	4,1	8,2	2,2	0,9	1,7	0,5	n/a	>31.48	627,54	3,36	134,6
4.31f	OH	BO-NMe_2	39,7	80,9	14,9	15,3	6,5	0,4	0,4	0,2	n/a	>31.48	632,73	2,16	163,9
4.31g	OH	BD	24,8	45,3	9,1	11,1	4,5	0,4	0,4	0,2	n/a	>31.48	624,74	3,53	153,1
4.4a	OBn	NH_2	1,5	12,1	4,7	18,0	1,7	3,2	12,3	1,2	3,5	>31.48	653,79	3,95	149,6
4.4b	OBn	BO-NHMe	0,8	3,7	1,7	3,4	1,0	2,2	4,5	1,3	n/a	>31.48	708,82	3,98	161,7
4.5b	O(2-F)Bn	BO-NHMe	0,7	4,0	1,3	2,1	0,9	2,0	3,1	1,3	n/a	>31.48	726,81	4,39	161,7
4.6b	O(3-F)Bn	BO-NHMe	0,6	3,7	0,8	1,7	0,8	1,2	2,7	1,3	n/a	>31.48	726,81	4,39	161,7
4.7b	O(4-F)Bn	BO-NHMe	0,6	4,0	1,1	2,3	1,0	1,8	3,8	1,6	n/a	>31.48	726,81	4,39	161,7
4.8b	O(2,4-diF)Bn	BO-NHMe	0,6	5,4	1,1	2,3	0,7	2,0	4,1	1,3	n/a	>31.48	744,80	4,80	161,7
4.9a	OPh	NH2	8,9	47,2	32,5	249,1	6,5	3,6	27,9	0,7	n/a	>31.48	639,76	3,81	149,6
4.10a	PNP	NH2	10,7	128,6	60,0	389,7	11,9	5,6	36,3	1,1	14,2	>31.48	684,76	3,61	195,5
4.10b	PNP	BO-NHMe	2,5	15,3	5,0	19,9	2,2	2,0	8,0	0,9	9,5	>32.27	739,79	3,64	207,5
4.11a	PAP	NH2	11,1	67,7	13,2	75,9	9,5	1,2	6,8	0,9	11,2	>32.27	654,78	3,40	175,7
4.11b	PAP	BO-NHMe	8,3	68,8	6,5	12,3	2,7	0,8	1,5	0,3	9,9	>32.27	709,81	3,42	187,7
4.12a	OCONHBn	NH2	5,8	30,4	15,5	124,5	5,2	2,7	21,5	0,9	15,3	>30.61	696,81	3,66	178,8
4.12b	OCONHBn	BO-NHMe	5,8	26,7	7,2	13,9	4,0	1,2	2,4	0,7	<1,5	28,05	751,85	3,69	190,8
4.13a	NHCO2Bn	NH2	5,0	35,2	5,7	82,5	1,8	1,1	16,4	0,4	11,3	29,91	696,81	3,66	178,8
4.13b	NHCO2Bn	BO-NHMe	3,8	16,6	2,4	7,5	1,0	0,6	2,0	0,3	3,3	28,68	751,85	3,69	190,8

PI	R	Ar	EC_{50} [nM]					FC relative to HIV-1 (wt)			IC50 [nM]	CC50 [µM]	MW	wclogP	TPSA
			HIV-1 (wt)	+50% HS	M1	M2	M3	M1	M2	M3					
4.16a	$O(CH_2)_2OMe$	NH_2	15,5	37,0	11,9	71,4	6,8	0,8	4,6	0,4	2,5	>31.48	621,74	2,40	158,9
4.16b	$O(CH_2)_2OMe$	BO-NHMe	8,6	24,0	6,9	10,8	4,3	0,8	1,3	0,5	<1,5	>31.48	676,78	2,42	170,9
4.16d	$O(CH_2)_2OMe$	BP	3,7	4,4	7,4	17,5	3,4	2,0	4,7	0,9	<1,5	>9.84	658,76	2,76	158,6
4.17b	MOM	BO-NHMe	3,4	7,0	5,0	11,2	1,9	1,5	3,2	0,6	1,9	>9.84	662,75	2,38	170,9
4.18b	MTM	BO-NHMe	1,3	6,7	4,0	9,3	2,2	3,0	7,1	1,7	n/a	>31.48	678,81	3,10	161,7
4.19b	$O(CH_2)_2CF_3$	BO-NHMe	0,5	8,2	0,9	2,8	0,8	1,9	5,9	1,6	n/a	>24.59	714,75	3,73	161,7
4.20a	$OCH_2CONHBn$	NH_2	16,0	93,5	10,8	35,2	9,3	0,7	2,2	0,6	3,1	>32.27	710,84	3,07	178,8
4.20b	$OCH_2CONHBn$	BO-NHMe	25,0	102,3	13,4	15,1	6,4	0,5	0,6	0,3	2,7	>9.84	765,88	3,09	190,8
4.20c	$OCH_2CONHBn$	OMe	0,6	4,6	3,3	4,4	1,0	5,6	7,5	1,7	n/a	>31.48	725,85	3,49	162,0
4.21b	$OCH_2CONHMe$	BO-NHMe	460,5	376,5	150,7	203,6	68,5	0,3	0,4	0,1	<1,5	>9.84	689,78	1,52	190,8
4.21c	$OCH_2CONHMe$	OMe	6,9	16,1	14,3	15,7	8,3	2,1	2,3	1,2	n/a	>31.48	649,75	1,92	162,0
4.22b	OCH_2CONMe_2	BO-NHMe	249,1	243,4	101,8	83,8	50,4	0,4	0,3	0,2	4,1	>9.84	703,80	1,86	182,0
4.22c	OCH_2CONMe_2	OMe	3,8	7,0	7,0	11,5	2,9	1,8	3,0	0,8	n/a	>31.48	663,78	2,27	153,2
4.23b	$OCH_2CF=CH_2$	BO-NHMe	0,4	2,2	0,8	2,3	0,5	2,2	6,1	1,4	n/a	>24.59	676,75	3,19	161,7
4.24a	N_3	NH_2	3,7	18,8	5,6	55,6	2,3	1,5	15,0	0,6	4,2	>9.84	589,68	3,16	177,8
4.25a	Cl	NH_2	0,4	4,6	2,8	31,6	1,5	7,5	84,2	4,0	n/a	>24.59	583,12	3,09	140,4
4.25b	Cl	BO-NHMe	0,5	4,2	0,7	2,1	0,7	1,6	4,6	1,6	n/a	>24.59	638,15	3,11	152,5
4.26b	F	BO-NHMe	0,7	8,4	0,8	2,8	0,7	1,2	4,1	0,9	n/a	>24.59	621,70	2,84	152,5

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