UNIVERSITY OF SOUTHAMPTON

Department of Chemistry

Synthesis and development of novel silicon linkers for solid phase synthesis

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A thesis submitted for the degree of Doctor in Philosophy

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ABSTRACT

FACULTY OF SCIENCE

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SYNTHESIS AND DEVELOPMENT OF NOVEL SILICON LINKERS FOR SOLID PHASE SYNTHESIS

By Marco Massimiliano Meloni

A number of novel silicon linkers were synthesized starting from commercially available Merrifield resin. After validation of the chemistry with a successful solution phase model, the optimized protocol was transferred to the solid phase, affording a range of silyloxy chloride linkers in good and consistent values of loading. These linkers displayed excellent reactivity with primary, secondary and even tertiary alcohols and selective silylations of primary alcohols were also achieved. As part of the study a useful colorimetric test for the detection of polymer supported tertiary alcohols was developed and the utility of the linkers as supported protecting groups for alcohols was demonstrated under a range of experimental conditions, including strong bases, Grignard reagents, Suzuki, Heck, Sonogashira, RCM reactions and SPPS. The synthesis of the cyclopeptide Stylopeptide 1 was attempted, employing the silyl linker as a supported side chain protecting group.

To my parents

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Acknowledgements

The author would like to thank Joan Street and Neil Wells for the NMR spectroscopy, the University of Durham for the gel phase ^{29}Si NMR on resins, John Langley and Julie Herniman for the Mass Spectrometry.

List of abbreviations used

9-BBN = 9-Bora(bicyclo)nonane

AA = Aminoacid

Ac = Acetyl

AIBN = 2,2'-Azobisisobutyronitrile

Ala = Alanine

Ar = Aryl

Bn = Benzyl

Boc = *tert*-Butoxycarbonyl

BP = Boiling point

Bpoc = Biphenylylisopropyloxycarbonyl

br = Broad

^{n}Bu = *n*-Butyl

Bz = Benzoyl

cat = Catalytic

CDI = Carbonyl diimidazole

Cbz = Benzyloxycarbonyl

^{c}Hex = Cyclohexyl

CIMS = Chemical ionization mass spectrometry

Cp = Cyclopentadienyl

CSA = Canphorsulphonic acid

d = Doublet

dba = Dibenzylideneacetone

DBU = Diazabicycloundecene

DCE = Dichloroethane

DCM = Dichloromethane

DDQ = 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone

DEAD = Diethylazodicarboxylate

DIBAL-H = Diisobutyl aluminium hydride

DCC = Dicyclohexylcarbodiimide

DIC = Diisopropylcarbodiimide

DHP = Dihydropyranyl

DIPEA = Diisopropylethylamine

DMA = *N*,*N*-Dimethylacetamide

DMAP = *N*,*N*-Dimethylaminopyridine

DMDO = Dimethyldioxirane

DMF = *N*,*N*-Dimethylformamide

DMP = Dess martin periodinane

DMSO = Dimethylsulphoxide

dppf = 1,1'-bis(diphenylphosphino)ferrocene

dquin = Double quintet

dt = Double triplet

DVB = Divinylbenzene

EDC = *N*-(3-Dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride

EI MS = Electron impact mass spectrometry

eq = Equivalent(s)

ES MS = Electron spray mass spectrometry

Fmoc = 9-Fluorenylmethoxycarbonyl

FT IR = Fourier transform infrared spectroscopy

GC = Gas chromatography

h = Hour(s)

HATU = *O*-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate

HBTU = *O*-(7-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate

HFIP = Hexafluoroisopropanol

HMPA = Hexamethyl phosphoramide

HOBt = 1-Hydroxy 1H-benzotriazole

HPLC = High performance liquid chromatography

HR CIMS = High resolution chemical ionization mass spectrometry

HR EIMS = High resolution electron impact mass spectrometry

HR ESMS = High resolution electron spray mass spectrometry

IIDQ = 1-Isobutyloxycarbonyl-2-isobutyloxy-1,2-dihydroquinoline

IR = Infrared spectroscopy

LDA = Lithium diisopropylamide

m = meta

m = Multiplet

min = Minute(s)

MOM = Methoxymethyl

MP = Melting point

Mol. Wt. = Molecular weight

nm = Nanometers

NMM = *N*-Methylmorpholine

NMP = *N*-Methyl-2-pyrrolidinone

NMR = Nuclear magnetic resonance

o.n. = Overnight

p = para

Ph = Phenyl

PMB = Paramethoxybenzyl

PPTS = Pyridinium *p*-toluene sulphonate

PSDES = Polystyrene diethylsilane

PTC = Phase transfer catalyst

PTSA = *p*-Toluene sulphonic acid

Pyr = Pyridine

PyBop = [(Benzotriazol-1-yl)oxy]-tris(pyrrolidino)phosphonium hexafluorophosphate

PyBroP = Bromo-tris(pyrrolidino)phosphonium hexafluorophosphate

q = Quartet

quin = Quintet

R = Alkyl, unless stated otherwise

RCM = Ring closing metathesis

rt = Room temperature

s = Singlet

sd = Septet of doublets

Ser = Serine

sp = Septet

SPOS = Solid phase organic synthesis

SPPS = Solid phase peptide synthesis

sx = Sextet

t = Triplet

TBAF = *N*-Tetrabutylammonium fluoride

TBDMS = *tert*-Butyldimethylsilyl

TBDPS = *tert*-Butyldiphenylsilyl

^{t}Bu = *tert*-Butyl

TES = Triethylsilyl

Tf = Trifluoromethanesulphonyl

TFA = Trifluoroacetic acid

TFAA = Trifluoroacetic anhydride

THF = Tetrahydrofuran

THP = Tetrahydropyranyl

TIPS = Triisopropylsilyl

TIS = Triisopropylsilane

TLC = Thin layer chromatography

TMEDA = *N*,*N*,*N*',*N*'-Tetramethylethylenediamine

TMG = *N*,*N*,*N*',*N*'-Tetramethylguanidine

TMS = Trimethylsilyl

TMT = Trimethoxytrityl

Ts = Tosyl

Tsoc = Triisopropylsilyloxycarbonyl

UV = Ultraviolet

Val = Valine

X = Any halide, unless stated otherwise

CHAPTER 1. INTRODUCTION AND BACKGROUND

1.1 Solid phase synthesis

Since Bruce Merrifield's pioneering work in 1963, [1] solid phase synthesis has become a very popular technique in organic chemistry. The reason of this success is simple; after its immobilization on a polymeric support, the substrate is subjected to a variety of chemical reactions with the advantage that at the end of each step, the product is still linked to the polymer, and removal of impurities and/or byproducts can be accomplished simply by washing the support. Consequently, the time needed for intermediate purifications is dramatically reduced. Furthermore, the reactions can be driven to completion using an excess of reagents, which can be simply washed away at the end of each step.

This brilliant strategy was first adopted for the synthesis of the peptides, such as Bradykinin, [2] a nonapeptide hormone, which was obtained in a 51% overall yield and in short reaction times.

Over the last few decades there has been a rapidly growing interest to extend solid phase synthesis technique to the synthesis of other biological active compounds, like oligosaccarides, [3] heterocycles and peptidomimetics. [4a]

Despite successes encountered, one drawback of solid phase synthesis has been the lack of methods for the reaction monitoring. Some standard analytical techniques used in solution, like TLC or GC analysis, cannot be used, as the product is linked to the polymer. A solution has been to cleave the product from the support and perform subsequent analysis in solution. However, this method is tiresome, and sometimes required large amounts of material. In addition, the samples of resin analysed cannot be employed anymore for the next transformations.

For these reasons there has been huge interest to develop novel methods to monitor the reaction progress, and nowadays techniques like gel phase NMR, [5-9] FTIR, [10] mass spectrometry and the colorimetric assays are quite common. [11-14] The first two of these are advantageous, as the resin can be recovered after the analysis and used for further transformations. In addition, NMR is useful to check the extent of reaction. [6-9] However, both NMR and IR are time-consuming, as they require the resin to be dried for almost

24 hours prior the analysis. This problem may be overcome by using mass spectrometry, which is still is a quantitative method, and recently it has been applied to the single resin beads. [15]

Finally, colorimetric assays have the advantage of speed of analysis, despite providing qualitative data.

1.2 Linkers and general considerations

To avoid confusions, a clear distinction between resins and linkers has to be done: they can be defined as follows:

1. The resin can be considered as an inert matrix, insoluble in all the solvents and passive to chemistry.
2. The linker can be simply considered as a polymer supported protecting group.

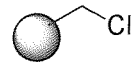
As a general rule, the attachment point of the linker to the polymer has to be chemically stable during all the synthesis and cleavage. In addition, yields for the loading of the linker to the solid support should be as quantitative as possible. A huge number of different linkers have been synthesized over the last 20 years [4b] to allow solid phase multistep syntheses to be performed, allowing cleavage of the final compound in a very selective manner.

As a consequence, several different linkers are currently available for solid phase synthesis; they allow attachment of a broad variety of compounds, such as amines, alcohols, aldehydes, ketones and carboxylic acids. The choice of the best linker depends on the type of the substrate to attach and on its compatibility under the conditions required for the solid phase transformations. Furthermore, the substrate has to be stable under the conditions required for its final cleavage.

1.3 Linkers for immobilization of alcohols

Nowadays alcohol immobilization can be accomplished using a wide variety of linkers; the choice of the best one depends on the alcohol reactivity and on the compatibility of other functional groups eventually present in the molecule, as they have to be compatible under the conditions required for the attachment. In this section, some of the commonly used linkers for the alcohol attachment will be briefly described, along with their advantages and drawbacks.

1.3.1 Merrifield resin



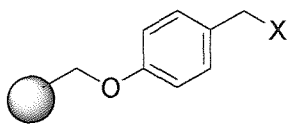
1.1

Figure 1.1 Merrifield resin

Merrifield resin **(1.1)**, which has been used for over 30 years, is the simplest polystyrene resin to which an alcohol can be linked. Couplings are usually performed via the corresponding alkoxides, previously formed by reaction of the alcohol with a metal, [16] or strong bases, like hydride or *tert*-butoxide salts. [17-20] Phenols can be attached as well, in presence of sodium or cesium carbonates. Studies [17, 18] have shown that the reaction rate can be increased either by phase transfer catalysis with crown ethers, or by halogen exchange of the chloromethyl groups with KI. Once formed, the resulting benzyl ether linkage is very stable under the conditions required to carry out a variety of chemical transformations. [17-20] A further advantage of Merrifield resin is the low price.

However, alcohol attachment is sometimes low yielding, as the reactions are often slow and fail to reach completion; moreover the strong basic conditions required for the immobilization make the resin not suitable for molecules bearing base sensitive groups, like Fmoc protected amines. In addition, quantitative cleavage of the compound from the support requires harsh conditions, such as TFA or gaseous HF in high concentrations.

1.3.2 Wang and related resins



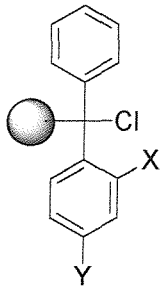
1.2 X = OH
1.3 X = Br
1.4 X = -C(=NH)CCl_3

Figure 1.2 Wang, brominated and trichloroacetimidate Wang resins.

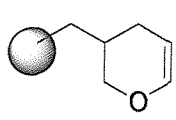
Phenols can be coupled to Wang resin via a Mitsunobu reaction in good yields. [21-23] In addition some variants of this resin have been synthesized, like brominated and trichloroacetimidate Wang resin (**1.3** and **1.4** respectively) [24] which allow attachment of aliphatic alcohols.

Trichloroacetimidate Wang resin **1.4** offers the added advantage of high reactivity: in contrast to Merrifield resin and brominated Wang resin, alcohol and phenol linkage occurs under acidic conditions, employing a catalytic amount of $BF_3 \cdot Et_2O$. [24] The mild Lewis-acidic conditions make this resin extremely useful, especially when base sensitive substrates have to be immobilized. Differently from Merrifield resin, linkage of alcohols to the polymeric matrix occurs via formation of a paramethoxybenzyl ether linker, which displays good stability with organometallic reagents [25]. Alcohols release is usually carried out using a similar approach previously described for the Merrifield resin. However, less harsh conditions are required for the cleavage; the reason of this higher acid sensitivity relies on the electron donating effect of the oxygen in the para position of the aromatic ring.

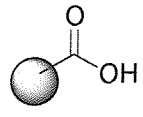
1.3.3 Trityl, DHP, and carboxyl resin



1.5 X=Y=H
1.6 X=Cl Y=H
1.7 X=H Y=Cl



1.8



1.9

Figure 1.3 Structures of trityl, DHP and carboxyl resins.

Since their introduction, the application of trityl chloride resins (**1.5**, **1.6** and **1.7**) has become widespread in SPOS, [26-32] and they represent a valuable alternative to the previously cited resins. Alcohol attachment is usually performed with weak bases, like Et_3N, DMAP, pyridine or DIPEA, and occurs via formation of a trityl ether linker. Differently from Merrifield and Wang resins, alcohols cleavage occurs rapidly upon exposure to 1-5% of TFA in CH_2Cl_2, [32] with PTSA, [30] or HFIP. [33] The high acid sensitivity of the trityl ether linkage is mainly due to the formation of a highly stabilised trityl cation, which occurs upon alcohol release. The mild cleavage conditions reported above are tolerated by many functional groups, and this feature has added to the attraction of these linkers for SPOS applications. However, one drawback is their high moisture sensitivity, which makes them unsuitable for long-term storage.

Ellmann's DHP linker **1.8** has been employed quite successfully for alcohol attachment. [34] The utility of the linker has been demonstrated by the solid phase synthesis of 2-pyrrolidine methanol ligands, [35] protease inhibitors, [36] tropane derivatives, [37] pyrrolidines, [38] and ketones. [39] Immobilization of alcohols occurs via an acetal functional group, and is performed under reflux in presence of PPTS. [34] The resulting THP ether is stable to strong bases such as organolithiums and Grignard reagents. [38, 39] The cleavage of the product can be usually achieved upon treatment with 95% of TFA in CH_2Cl_2. [36]

Carboxyl resin **1.9** has also been employed. Prior to alcohol attachment the resin is usually converted in the corresponding acid chloride, employing oxalyl or thionyl chloride. [40] In contrast to the resins discussed above, linkage of the alcohol occurs via formation of an ester bond. Subsequent release can be accomplished by saponification, transesterification, or reduction. [41, 42]

1.4 Silicon linkers in solid phase organic synthesis

The advent of silicon linkers in the SPOS overcame many of the problems previously encountered. In this case alcohol attachment occurs easily with the corresponding silyl chlorides [55, 105] or triflates, [67] and is usually fast and high yielding at room temperature in presence of weak bases, such as DIPEA or Et_3N. For less reactive alcohols, imidazole [55] or DMAP [58] can be employed to enhance the reaction rate. Once formed, the resulting silyl ethers are stable to strong organic and inorganic bases, [62] Grignard reagents and mildly acidic conditions, [62] depending on the choice of the silyl linker. Cleavage of the

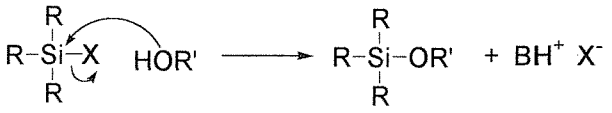
products from the support can be normally accomplished with TBAF, HF pyridine complex or with acids, such as AcOH or TFA.

All of these reasons make the silicon linkers a valuable alternative to the other commercially available linkers, leading to a significant number of applications in SPOS. After a brief introduction about to the silylation of alcohols in solution, the principal aim of the next sections is to demonstrate, with selected examples, the importance of silyl linkers in SPOS.

1.4.1 Silyl ether formation

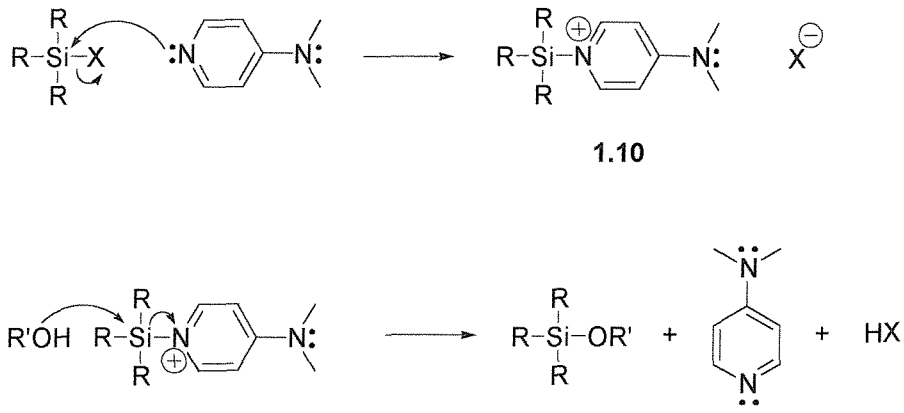
1.4.1.1 Silylation of alcohols, a brief overview

Silylation of alcohols, in order to decrease their reactivity, is a common process in organic chemistry. The reaction usually occur between the alcohol and the silyl chloride, in presence of a weak base (Et_3N or DIPEA) (Scheme 1.1). Solvents typically employed are CH_2Cl_2 or DMF. [43a-c]



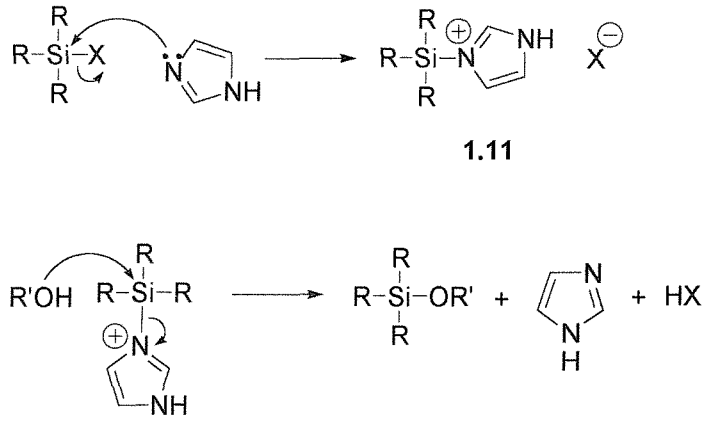
Scheme 1.1 Mechanism of the silylation of alcohols

Nowadays, many silylating reagents are employed, like TMS, TES, TIPS, [45] TBDMS [46] and the TBDPS chloride. [47] The choice relies upon the reactivity of the alcohol (steric hindrance and electronic effects) and on the degree of protection desired. As a general rule, the bulkier the substituents on the silicon, the less reactive the corresponding silyl chloride. TIPS, TBDMS and the TBDPS chlorides react relatively slowly with primary and secondary alcohols. However, catalysts like imidazole or DMAP, can be used to enhance the reaction rate. In this case silylation occurs via the highly reactive intermediates **1.10** and **1.11** (Schemes **1.2** and **1.3**).



1.10

Scheme 1.2 Mechanism of the DMAP catalyzed silylation of alcohols



1.11

Scheme 1.3 Mechanism of the imidazole catalyzed silylation of alcohols

When even greater reactivity is required, silyl triflates [48, 49] can be used in place of silyl chlorides. Under these conditions both primary and secondary alcohols react, but the tertiary ones are still relatively inert. The influence of the solvent on the rate of silylation process has also been demonstrated: the use of polar aprotic solvents like DMF enhance the silylation rate, compared to CH_2Cl_2. [50]

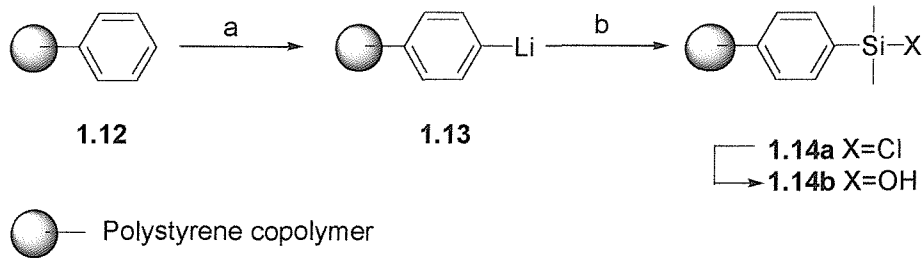
In compounds bearing different hydroxyl functions, the high steric hindrance of TIPS, TBDMS and TBDPS chloride have been used to allow selective silylations of primary alcohols over secondary ones. [47] Once formed, the resulting silyl ethers offer a broad range of stability under different conditions, including organometallic, reducing and oxidizing reagents, depending on the bulkiness of the substituents on the silicon.

Silyl ether cleavage can be accomplished in acidic media, with aqueous acetic acid, TFA, or alternatively with a source of fluoride anion, like HF pyridine complex, HF in acetonitrile, TBAF in THF, KF and 18-crown-6, or employing NH_4F in refluxing methanol. [43a-c] The fluoride-mediated cleavage relies upon its high affinity for the silicon (ΔH_f=594 KJmol^{-1} for Si-F bond strenght).

The choice of the cleavage reagent depends on the compatibility of the substrate in the deprotection conditions; as an example, the use of TBAF is not suitable in presence of other base sensitive protecting groups, like the Fmoc. [44] Furthermore, selective deprotection of different silyl ethers in the same molecule can be achieved, depending on the type and concentration of the reagents employed.

1.4.1.2 Alcohol immobilization via silyl ether linker

Fréchet *et al* reported the first synthesis of a silyl chloride resin to 1976. [51] According to their approach, bromination of unfunctionalized polystyrene **1.12** followed by reaction with ^{n}BuLi in THF afforded intermediate resin **1.13**, which was quenched with dimethyldichlorosilane to afford **1.14a** (Scheme 1.4).

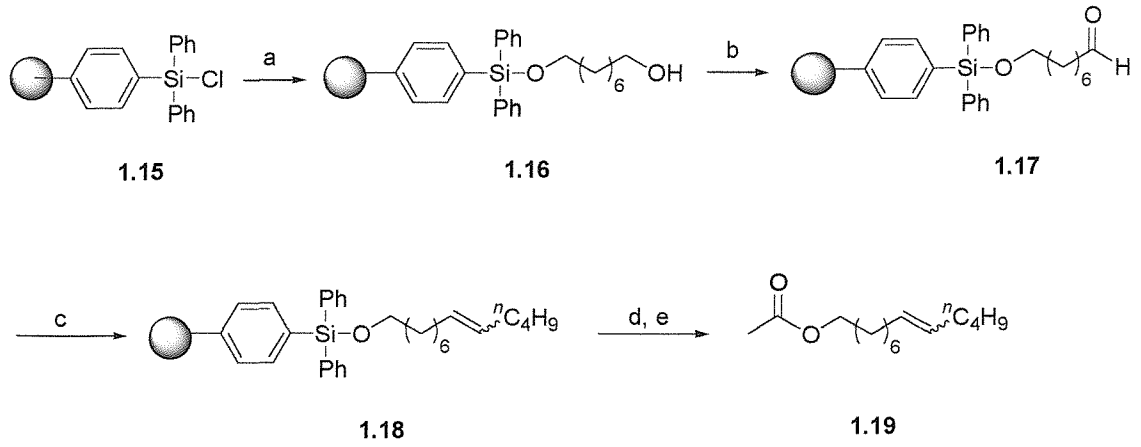


Scheme 1.4 (a) i. Br_2, $FeCl_3$, CCl_4, rt ii. ^{n}BuLi, TMEDA, Δ. **(b)** Me_2SiCl_2, C_6H_6

To check its formation, resin **1.14a** was hydrolyzed to the more stable silanol **1.14b**, which was analysed by IR, showing good results; the presence of the silicon was also confirmed by elemental analysis of **1.14b**. However, the authors limited their investigation only on the synthesis of the linker, and they did not pursue its employment in the SPOS.

The first relevant application was clearly demonstrated by Chan *et al* in 1985. [52] In a similar approach, the authors firstly synthesized silyl resins **1.14a** and **1.15**, and demonstrated the utility of **1.15** as a supported protecting group for alcohols in the synthesis of a pheromone **1.19**. According to Scheme 1.5, attachment of 1,9-nonane diol

to **1.15** followed by its oxidation gave polymer bound aldeyde **1.17**. Wittig reaction afforded alkene **1.18**, which was then cleaved from the support with TBAF and reacted with Ac_2O to afford the final compound **1.19** in a 12:88 *E-Z* ratio and in 43% overall yield from the loading of resin **1.15**.



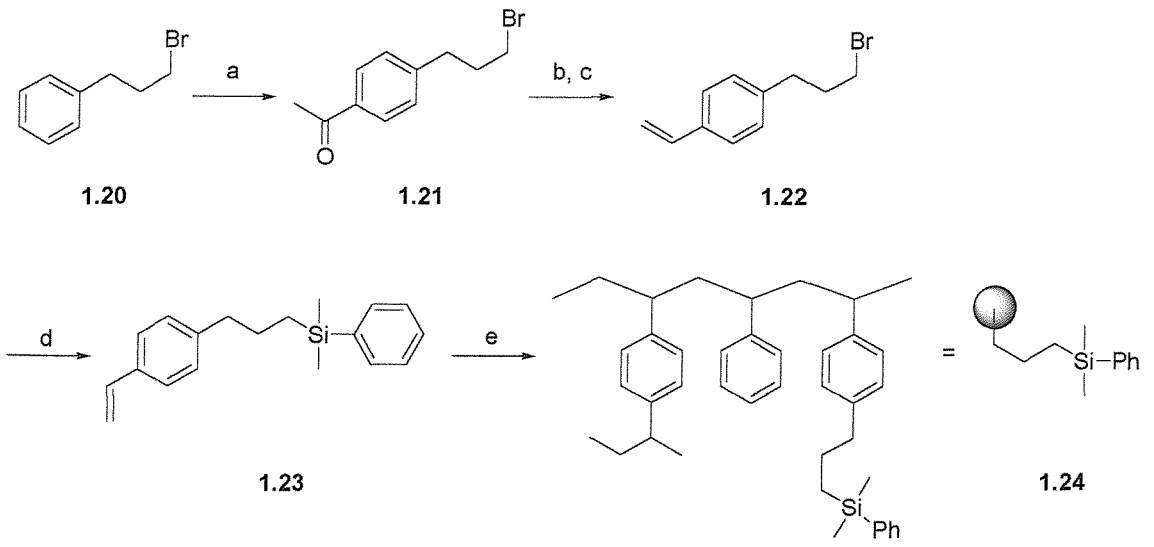
1.15 **1.16** **1.17**

1.18 **1.19**

Scheme 1.5 (a) 1,9-nonane diol, pyridine, rt **(b)** Oxalyl chloride, Et_3N, DMSO **(c)** $Ph_3P^+(CH_2)_4MeBr^-$ ^{n}BuLi, THF **(d)** TBAF, CH_2Cl_2 **(e)** Ac_2O

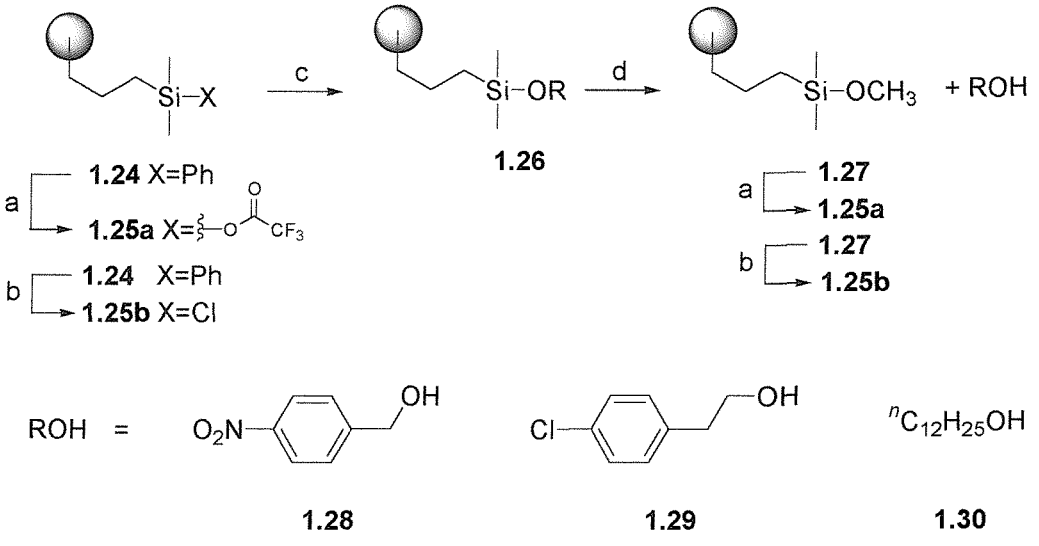
They also demonstrated that silyl chloride resin **1.15** is stable to long term storage and preferentially silylates primary alcohols. As a proof, reaction of **1.15** with a 1:1 mixture of octan-1-ol and octan-2-ol in pyridine, followed by TBAF exposure afforded the 90% and 10% of the primary and the secondary alcohol, respectively.

In 1991 Fréchet *et al* [53] introduced a different route for the synthesis of silicon resins. In the work the author described the preparation of a silicon containing monomer **1.23**, which was subjected to radical copolymerization with styrene and divinylbenzene, in the presence of AIBN, to afford resin **1.24** (Scheme 1.6).



Scheme 1.6 (a) AcCl, $AlCl_3$ **(b)** $NaBH_4$ **(c)** $KHSO_4$ **(d)** i. Mg ii. $PhMe_2SiCl$ **(e)** Styrene, DVB, AIBN

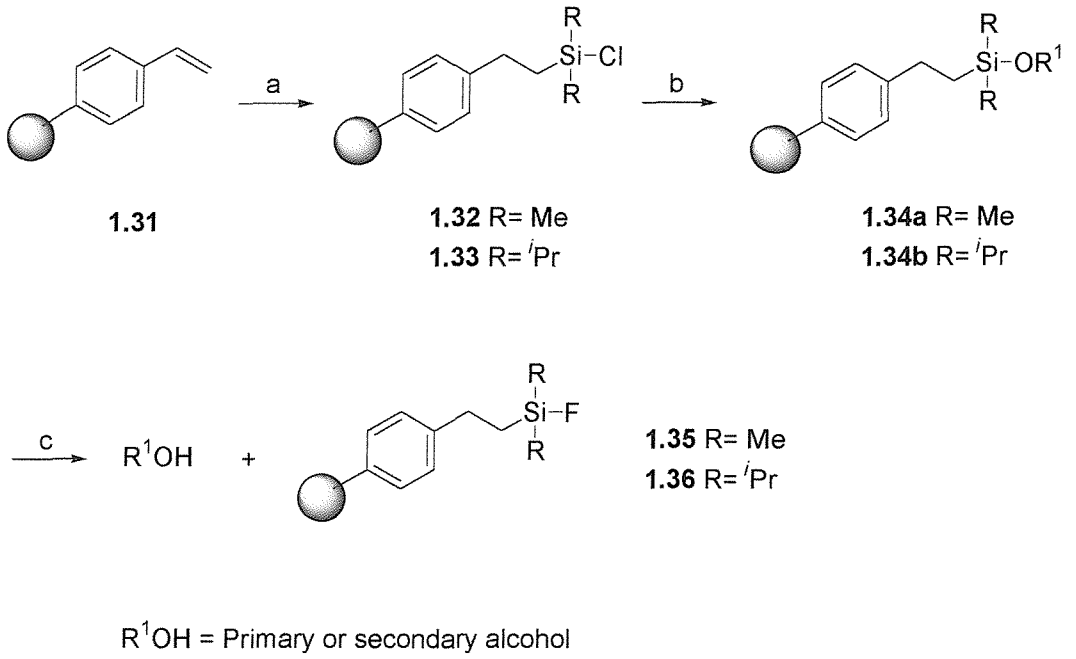
Action of TFA on resin **1.24** gave the corresponding silyl trifluoroacetate **1.25a**. Subsequent coupling of primary alcohols **1.28**, **1.29** and **1.30** afforded the corresponding silyl ethers in yields typically between 52% and 84%. Release of alcohols from the support occurred with acetic acid in methanol. Polymer **1.27** can also be conveniently regenerated, and minimal loss of activity was observed, even after four cycles. Alternatively, silyl resin **1.24** can be converted into the chloride **1.25b** by action of $SOCl_2$.



Scheme 1.7 (a) TFA and TFAA **(b)** $SOCl_2$ **(c)** ROH, Et_3N, DMAP **(d)** AcOH, MeOH

A silyl anchoring group for alcohols was synthesized by Darling *et al* in 1997. [54] Following their approach, vinylpolystyrene resin **1.31** underwent regioselective β-

hydrosilylation with a variety of dialkylmonochlorosilanes in presence of dicobaltoctacarbonyl as catalyst, to afford silyl chloride resins **1.32** and **1.33** (Scheme 1.8).



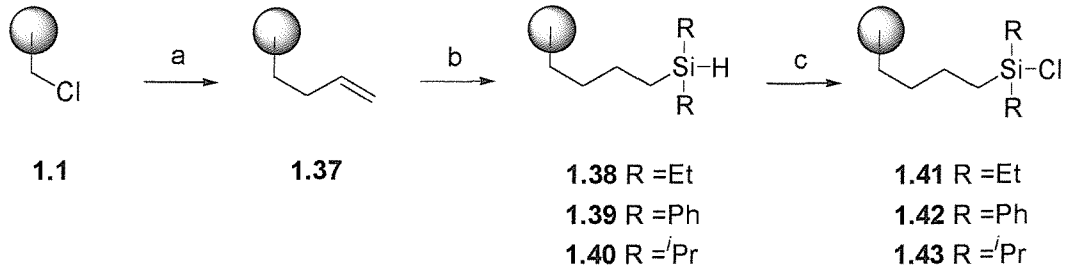
Scheme 1.8 (a) $HSiR_2Cl$, $Co_2(CO)_8$ cat., toluene, 60 °C, 5 days **(b)** R'OH, pyridine, CH_2Cl_2 **(c)** TBAF, THF or HF, CH_3CN

Resin **1.33** successfully reacted with both primary and secondary alcohols; in addition it silylates preferentially primary alcohols over secondary ones. As proof, exposure of **1.33** to a mixture of 1:1:1 EtOH, ^{i}PrOH and ^{t}BuOH, resulted only in the protection of EtOH.

The authors investigated also the stability of silyl ethers **1.34a** and **1.34b** under acidic and basic media, finding that in both cases desilylation of menthol occurs in less than 1 hour in presence of 1N HCl and 0.22 M HF. Between them, however, a better stability was encountered for **1.34b**. Silyl chloride resins **1.32** and **1.33** were also quantitatively regenerated from **1.35** and **1.36** with BCl_3. The authors hypothesized that this transformation is facilitated from the formation of gaseous BF_3 as byproduct.

Hu *et al* also employed the hydrosilylation approach in 1998. [55] Action of an excess of allyl magnesium bromide on Merrifield resin afforded 1-butenyl polystyrene **1.37**, which then underwent regioselective β-hydrosilylation with a variety of dialkylsilanes to afford resins **1.38**, **1.39** and **1.40**. Generation of the corresponding chlorides **1.41**,

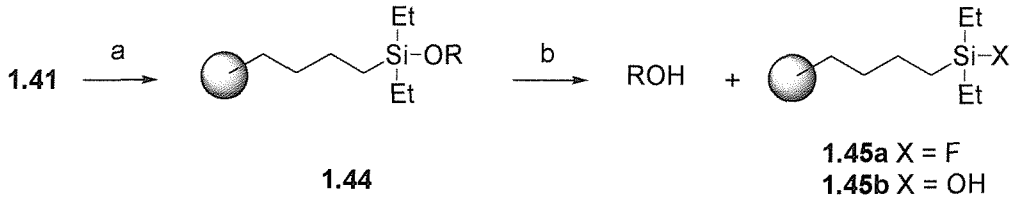
1.42 and **1.43** was accomplished with 1,3-dichloro-5,5-dimethylhydantoin, as confirmed by IR analysis (Scheme 1.9).



1.1 **1.37** **1.38** R =Et, **1.39** R =Ph, **1.40** R =^{i}Pr **1.41** R =Et, **1.42** R =Ph, **1.43** R =^{i}Pr

Scheme 1.9 (a) Allylmagnesium chloride, toluene, 60 °C **(b)** R_2SiH_2, toluene, $RhCl(PPh_3)_3$ cat. **(c)** 1,3-dichloro-5,5-dimethylhydantoin, CH_2Cl_2, rt

Linker **1.41** silylated primary and hindered secondary alcohols, such as steroids, and the resulting cleavage occurred in acidic media, employing HF or aqueous AcOH, or alternatively in basic conditions, employing TBAF.



1.44 **1.45a** X = F, **1.45b** X = OH

ROH = Primary or secondary alcohol

Scheme 1.10 ROH, imidazole, CH_2Cl_2, rt **(b)** TBAF/THF or AcOH/THF/H_2O 6:6:1, 80 °C

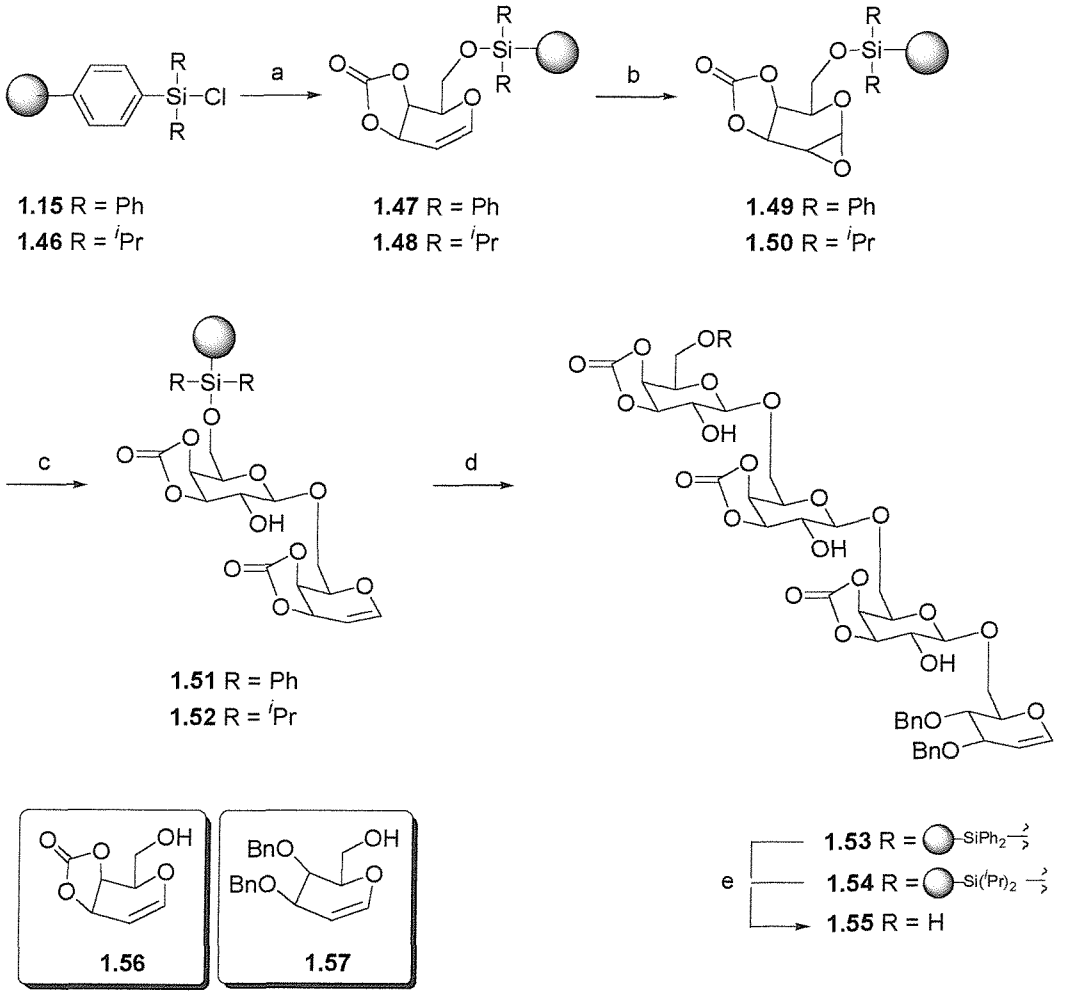
Resin **1.41** was also successfully employed for attachment of carbon nucleophiles and the authors found that alcohols can be directly loaded to silane resin **1.38** in presence of $Rh_2(Pfb)_4$ in high yield.

1.4.1.3 Synthesis of biologically active compounds

Oligosaccarides and related compounds represent an important class of biologically active molecules, as they are involved in many processes, like methastasis, and they play an important role at level of cell-cell interactions. [56] As a consequence, a lot of attention has been exerted to search for different synthetic methods for their synthesis.[57]

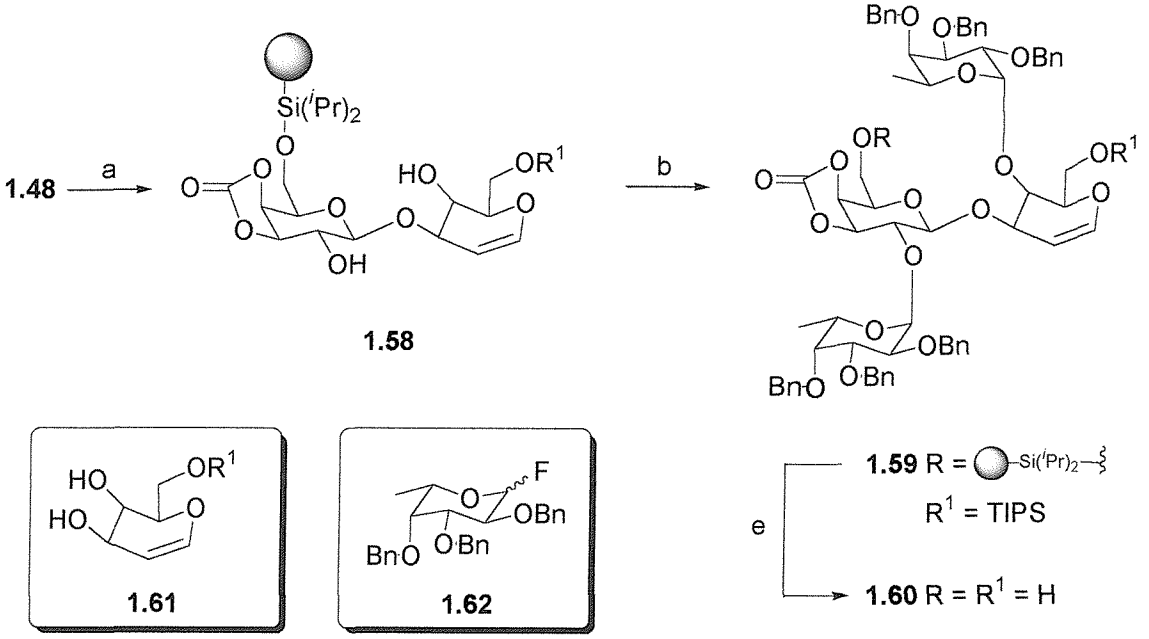
Unfortunately many of the synthetic approaches to complex carbohydrates are quite long, especially if performed in solution. Furthermore the purification of the key intermediates may sometimes be problematic, due to the high polarity of such molecules.

In 1995 Danishefsky *et al* [58] showed that many of these drawbacks can be elegantly overcome by solid phase synthesis. In their work they described the synthesis of oligosaccarides employing silyl linkers **1.15** and **1.46** as a supported side chain protecting group. The glycal unit **1.56** was immobilized on linkers **1.15** and **1.46**. Treatment of **1.47** and **1.48** with DMDO afforded epoxide resins **1.49** and **1.50**, which reacted with another molecule **1.56** in a regioselective ring opening, to afford polymer bound disaccharides **1.51** and **1.52**. Reiteration of the last two steps afforded resins **1.53** or **1.54**, which released the final tetrasaccharide **1.55** upon treatment with a mixture of TBAF and acetic acid (Scheme 1.11).



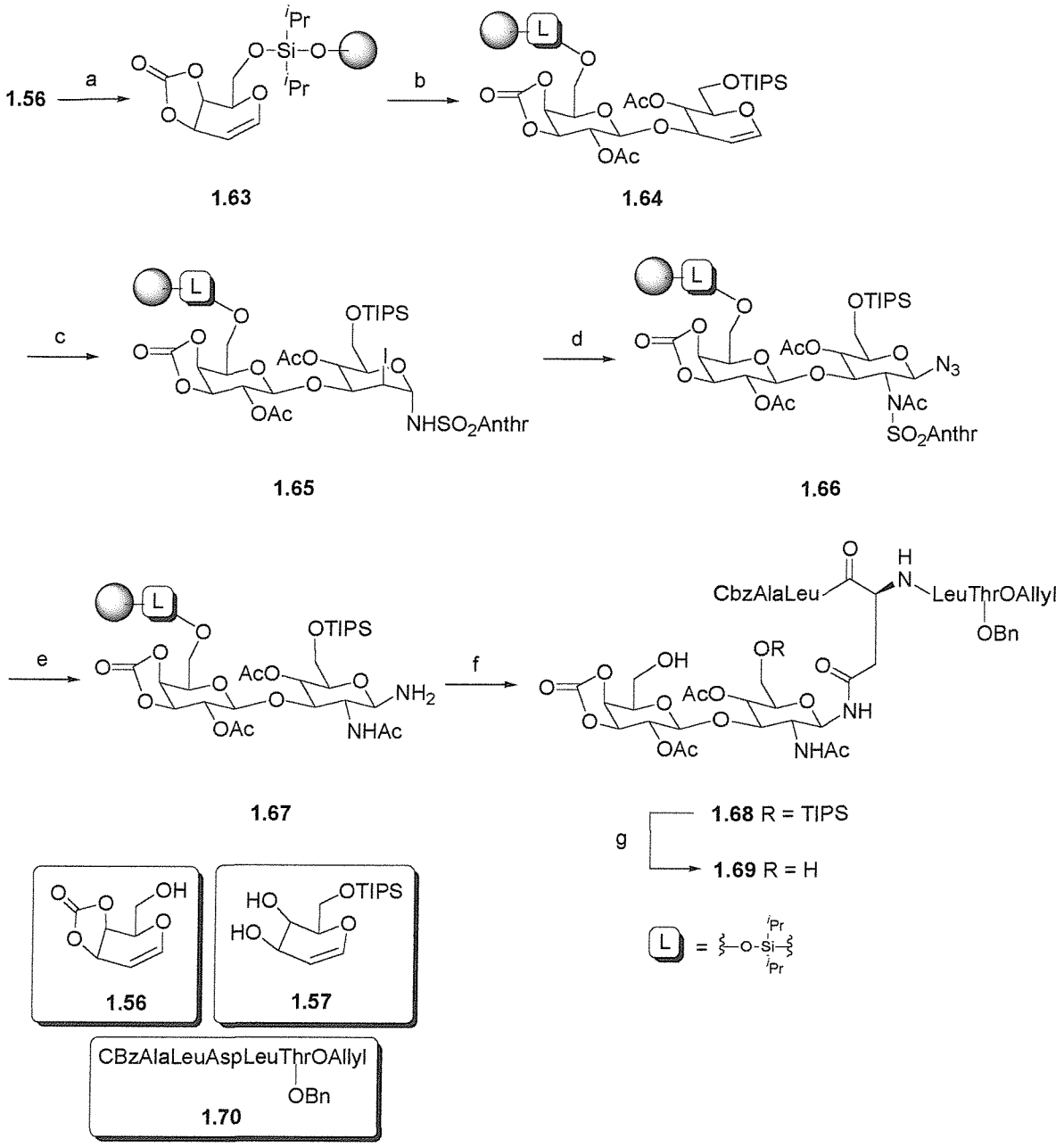
Scheme 1.11 (a) 56, DIPEA, CH_2Cl_2, DMAP **(b)** DMDO, CH_2Cl_2 **(c) 1.56**, $ZnCl_2$, THF **(d)** Repeat steps b and c **(e)** TBAF, AcOH, THF

To demonstrate further the potential of the method, linker **1.46** was employed for the synthesis of the Lewis b blood group determinant **1.60**. Resin **1.48** (prepared as shown in Scheme 1.11) underwent ring opening upon reaction with **1.61**. The resulting immobilized disaccharide **1.58** was then reacted with **1.62** to afford, after cleavage, final compound **1.60** in 40% overall yield (Scheme 1.12). [58]



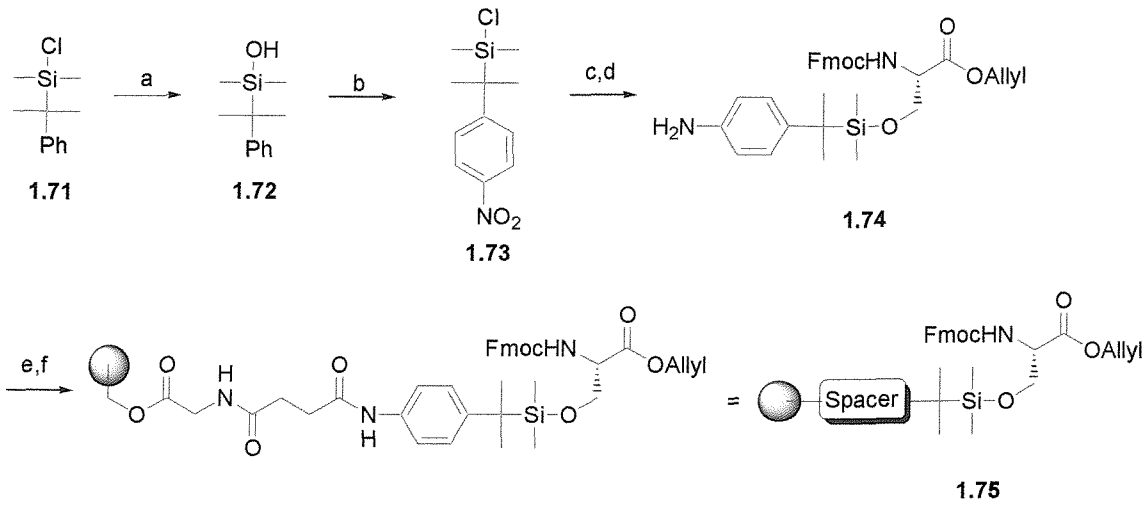
Scheme 1.12 (a) i. DMDO, CH_2Cl_2 ii. **1.61**, $ZnCl_2$ **(b) 1.62**, $Sn(OTf)_2$, THF, 2-6-di-^{t}Bu-pyridine **(e)** TBAF, AcOH, THF

Further investigations in the field were reported by Danishefsky's team in 1999. [59] The authors described the synthesis of a glycopeptide employing a diisopropylsiloxane linker. After a preliminary reaction of the glycal unit **1.56** with diisopropyldichlorosilane in solution, subsequent coupling with Wang resin afforded the immobilized siloxane **1.63**. The oligosaccaride synthesis was then performed as shown in Scheme 1.13 and **1.68** was finally cleaved from the support with either HF in pyridine or TBAF. Desilylation occurred rapidly, due to the high sensitivity of the siloxane linker towards fluoride; subsequent removal of the TIPS group from **1.68** afforded **1.69**.



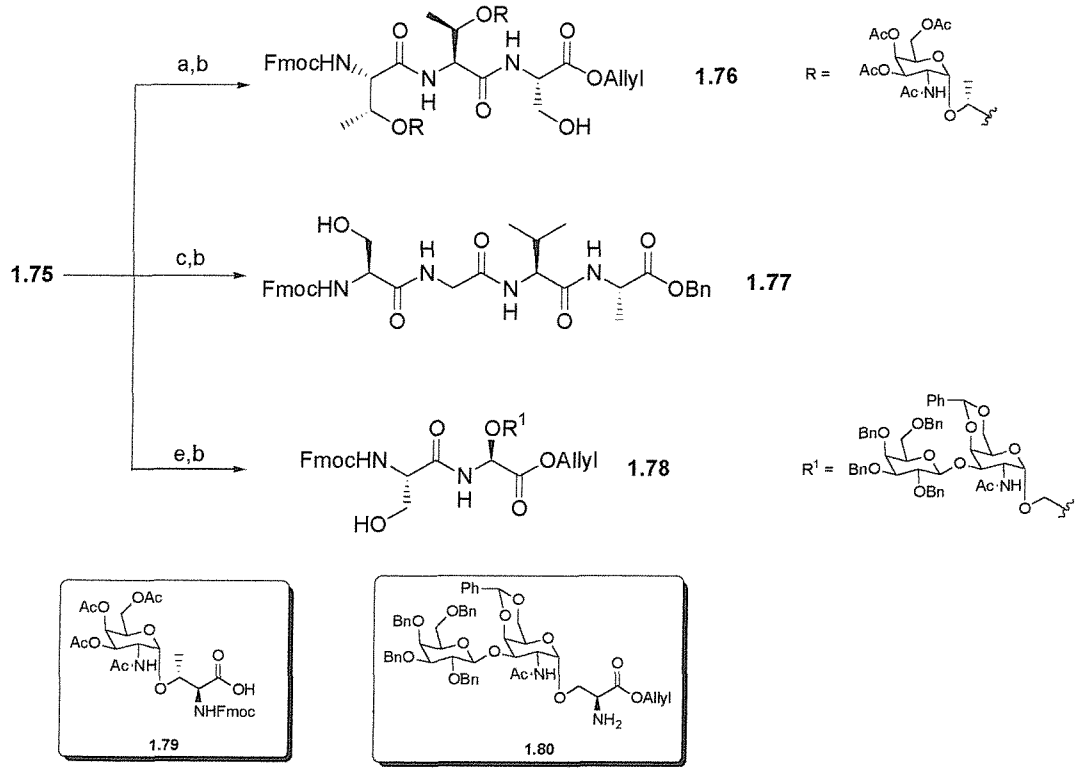
Scheme 1.13 (a) $^{i}Pr_2SiCl_2$, imidazole, then Wang resin, imidazole **(b)** i. DMDO, CH_2Cl_2, 0 °C ii. **1.57**, $ZnCl_2$, followed by Ac_2O, pyridine, DMAP **(c)** Anthracene sulphonamide, I (Coll)$_2ClO_4$ **(d)** $^{n}Bu_4NN_3$, Ac_2O **(e)** 1,3-propanedithiol, DIPEA, THF **(f) 1.70**, IIDQ, CH_2Cl_2, DMF, then HF·Pyr, anisole, THF. **(g)** HF· Pyr 24h

In a series of papers Nakamura *et al* [60, 61] synthesized a linker based on TBDMS chloride for the synthesis of glycopeptides. Hydrolysis of silyl chloride **1.71** afforded silanol **1.72**, which was converted in the *p*-nitroderivative **1.73** by nitration. Conversion to the silyl chloride followed by silylation of Fmoc L-SerOAllyl and action of Zn in acetic acid gave amine **1.74**. Subsequent reaction with succinic anhydride and final attachment to H-Gly-HMP resin afforded linker **1.75** (Scheme 1.14).



Scheme 1.14 (a) KOH, Et_2O/MeOH/H_2O **(b)** i. NH_4NO_3, TFAA, CH_3CN ii. $COCl_2$, CH_2Cl_2, DMF cat. **(c)** Fmoc SerOAllyl, NaI, NMM, DMF, rt **(d)** Zn, AcOH **(e)** Succinic anhydride, NMM, CH_2Cl_2 **(f)** Wang Gly-NH_2 resin, HBTU, HOBT, DIPEA, NMP, rt

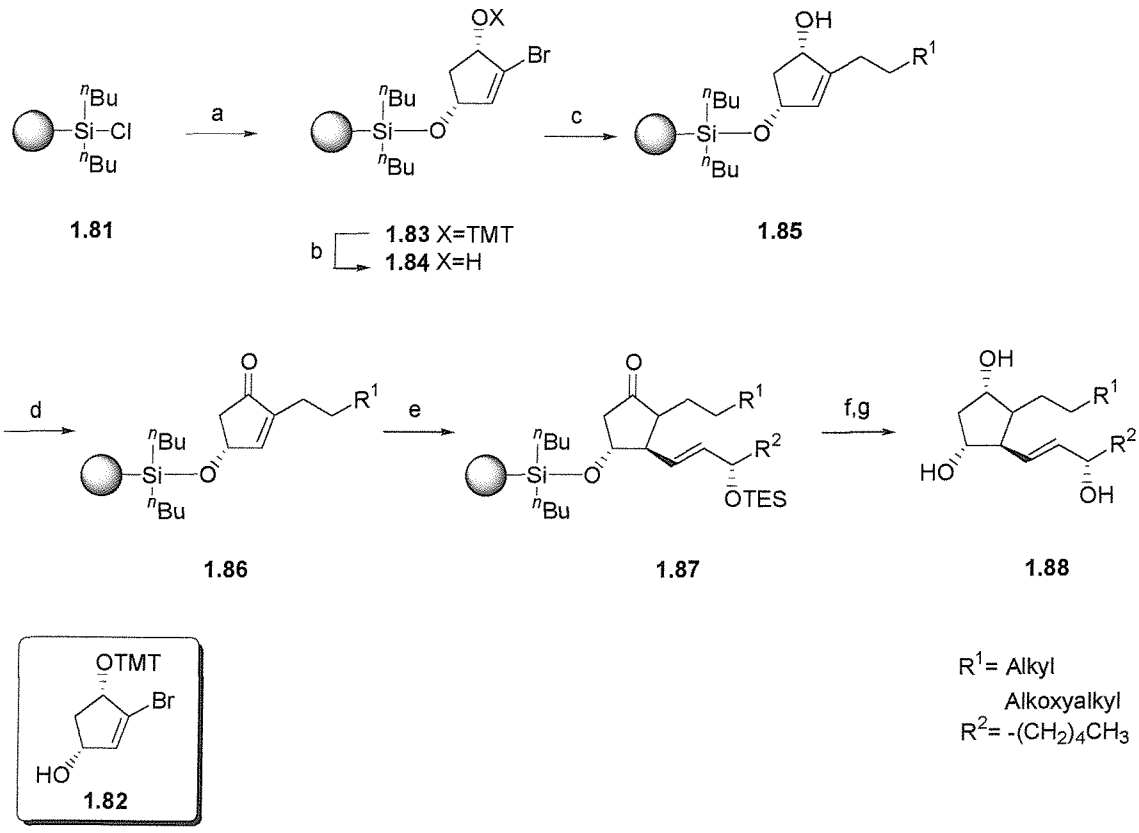
Linker **1.75** was used for the synthesis of glycopeptides, employing the Fmoc chemistry, and using **1.79** as a building block. Final cleavage with CsF and AcOH in THF afforded **1.76** in 73% overall yield. Alternatively, in a reversed approach, deblocking of the ester group in **1.75** followed by coupling with **1.80** and final cleavage afforded glycopeptide **1.78** in 76% yield (Scheme 1.15).



Scheme 1.15 (a) i. 50% piperidine in DMF ii. **1.79**, HBTU, HOBT, DIPEA, 2 cycles **(b)** CsF, 18-Crown-6, AcOH **(c)** i. $Pd(PPh_3)_4$, dimedone ii. H-Gly-Val-Ala-OBn, HBTU, HOBT, DIPEA **(e)** i. $Pd(PPh_3)_4$, dimedone ii. **1.80**, HBTU, HOBT, DIPEA

Importantly, NMR analysis of the purified cleaved products showed that no racemization had occurred during the coupling processes.

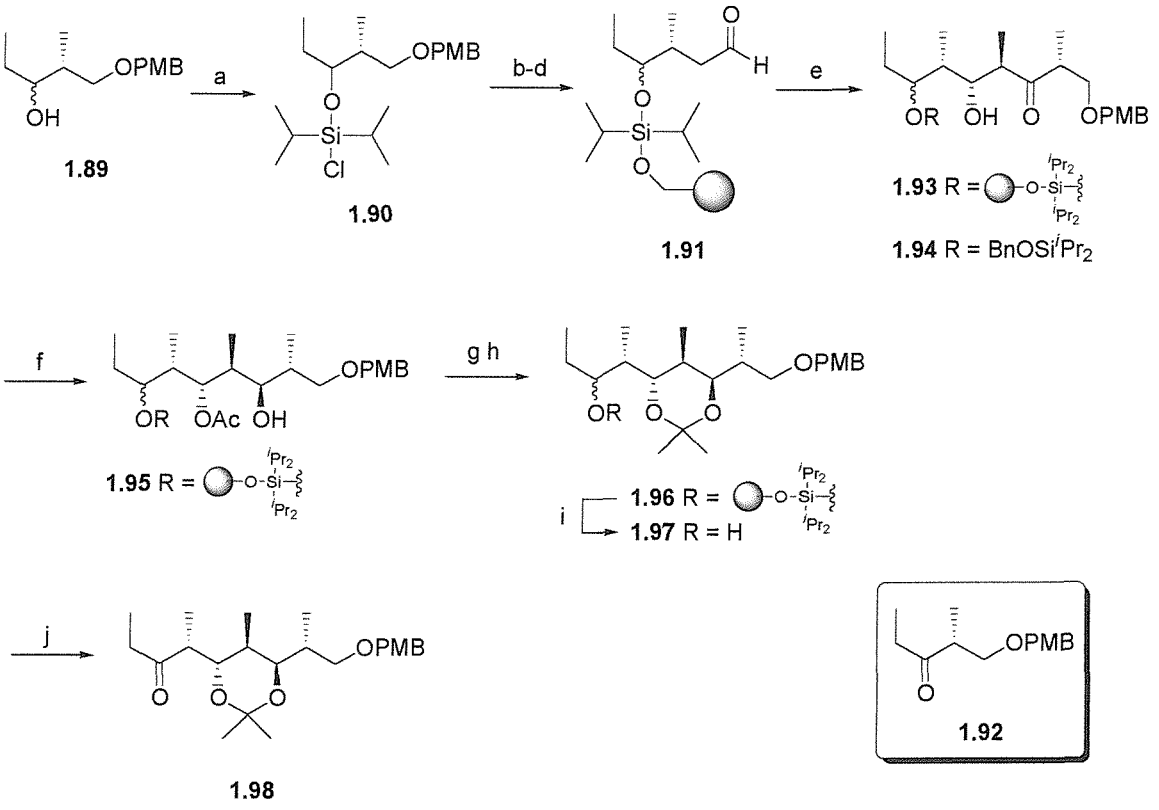
Ellmann *et al.* elegantly employed the silicon linkers for the solid phase synthesis of a library of prostaglandins. [62] They used dibutylsilyl chloride resin **1.81**, prepared by the procedure of Farrall and Fréchet. [51] After immobilization of the cyclic bromoalcohol **1.82** with imidazole in CH_2Cl_2, the remaining hydroxyl was unblocked with formic acid. The first diversity element was then introduced via Suzuki coupling with a variety of 9-BBN derivatives to give intermediate resin **1.85**; subsequent oxidation of the secondary alcohol was accomplished with DMP. In this context the authors reported that the use of other oxidants resulted either in an incomplete reaction or in a partial cleavage of the product from resin. The second diversity element was introduced using vinyl cuprates, employing the chemistry previously optimized by Babiak *et al.* [63] Diastereoselective reduction of ketone **1.87** and final cleavage of **1.88** from the support was performed with 17% HF in pyridine and THF (Scheme 1.16).



Scheme 1.16 (a) 1.82, imidazole, CH_2Cl_2 **(b)** 1M HCOOH, CH_2Cl_2 **(c)** alkyl-9BBN derivative, Pd $(PPh_3)_4$, 2M Na_2CO_3,THF, 65 °C **(d)** DMP, CH_2Cl_2, 45 °C **(e)** alkyne, CpZrHCl, CuCN, MeLi, THF, -78 to 20 °C **(f)** L-Selectride, THF, -78 °C **(g)** 17.5% HF· Pyr, THF, rt

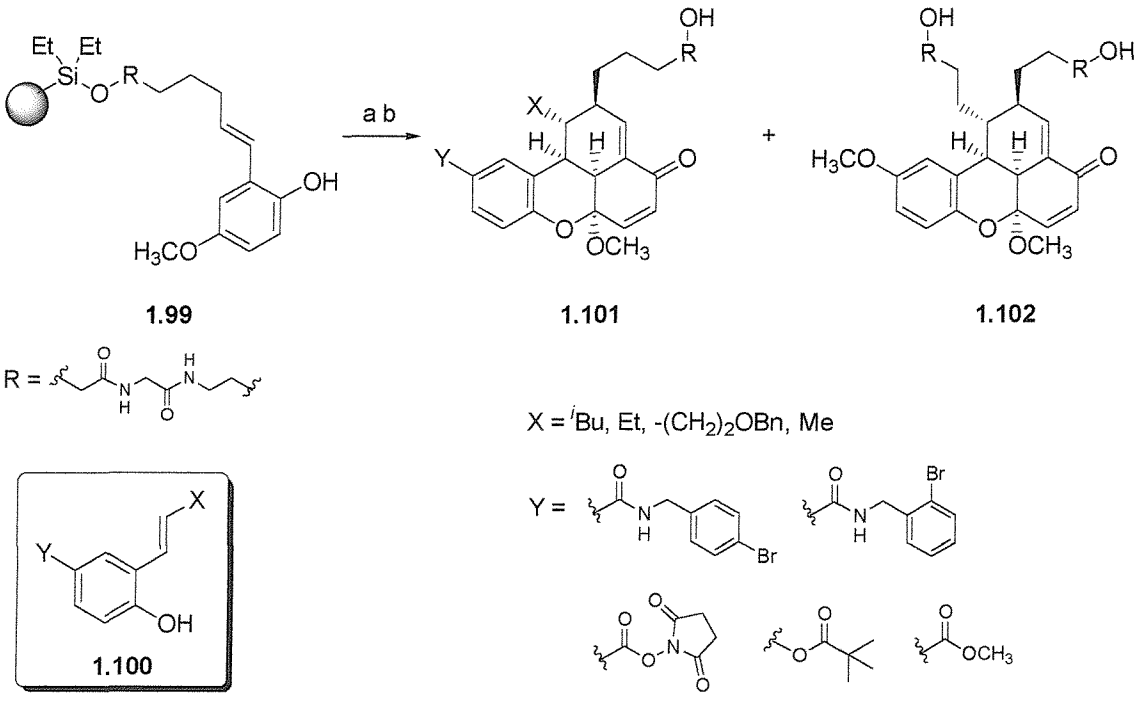
Notably, the authors observed minimal (less than 5%) cleavage of the substrate **1.84** from the support during the deprotection of the TMT ether.

In 2002 Paterson *et al* [64] showed that silicon linkers can be employed for the combinatorial synthesis of poyketide libraries. These compounds are very important as they are the constituents of biologically relevant molecules, like discodermolide and 6-deoxyerhyhronolide B. Reaction between alcohol **1.89** and diisopropyldichlorosilane afforded silyl chloride **1.90**, which was reacted with Wang resin to afford siloxane linker **1.91**. After deprotection of the PMB ether and oxidation with DMP, the aldol condensation with ketone **1.92** in presence of Lewis acid afforded the immobilized adduct **1.93** in an *anti-anti* diastereoselective fashion. Comparison of the gel phase ^{13}C NMR of resin **1.93** with the solution phase model analogue **1.94** indicated essentially complete conversion and high level of diastereoselectivity. Reduction of the hydroxyketone **1.93** in a modified Evans-Tishchenko protocol afforded resin **1.95**; subsequent *O*-deacetylation, ketalization, HF exposure and oxidation with DMP afforded final compound **1.98** (Scheme 1.17).



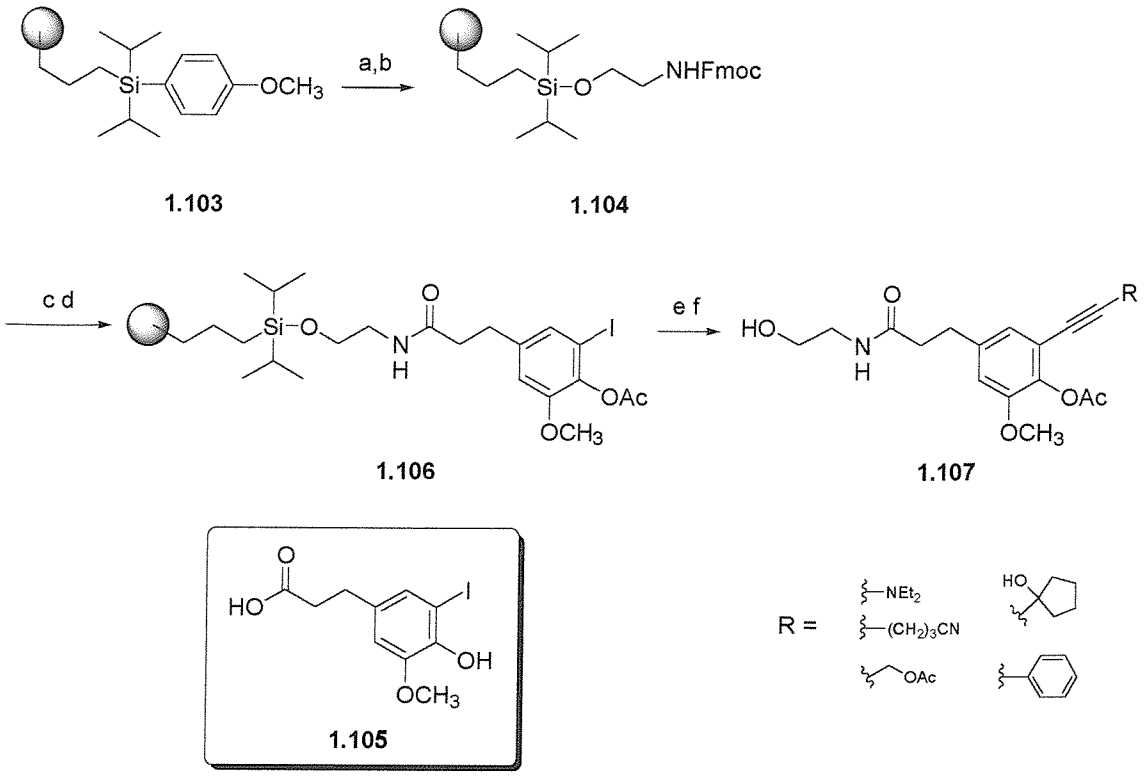
Scheme 1.17 (a) $^{i}Pr_2SiCl_2$, DMF, imidazole **(b)** Wang resin **(c)** DDQ, CH_2Cl_2 **(d)** DMP, CH_2Cl_2, pyridine **(e) 1.92**, $^{c}Hex_2BCl$, Et_3N, Et_2O **(f)** SmI_2, MeCHO, THF **(g)** $LiBH_4$, THF **(h)** $(MeO)_2CMe_2$, CSA, CH_2Cl_2 **(i)** HF·Pyr **(j)** DMP, CH_2Cl_2, pyr

Silicon linkers were also employed by Shair *et al* [65] in the elegant solid phase biomimetic synthesis of Carpanone-like molecules. Here, the key step is the highly diastereoselective Diels-Alder reaction between substrate **1.100** and the electron rich phenol **1.99**, previously immobilized on the solid support via silyl ether linkage (Scheme 1.18). HF·Pyr exposure and purification afforded final compound **1.101** in good yield, along with small amounts of **1.102** coming from dimerization of **1.99**.



Scheme 1.18 (a) 1.100, $PhI(OAc)_2$, CH_2Cl_2/THF, 25 °C, 2h **(b)** HF·Pyr, THF, TMSOMe, rt

Further investigations on silicon linkers were carried out by Liao *et al.* [66] Starting from resin **1.103**, conversion in the silyl triflate and attachment of *N*-Fmoc glycinol afforded resin **1.104**. *N*-deprotection followed by coupling with **1.105** and acetylation afforded iodide resin **1.106**, which underwent to Sonogashira reaction with a variety of terminal acetylenes. After cleavage with HF in pyridine, the internal alkynes **1.107** were obtained in a conversion and purity greater than 95% for all the cases examined, as illustrated in Scheme 1.19

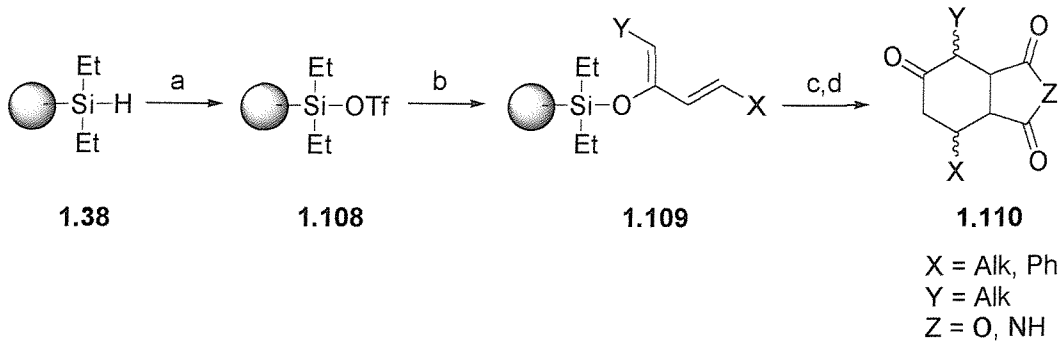


Scheme 1.19 (a) TfOH, CH_2Cl_2 **(b)** *N*-Fmoc Glycinol, 2,6-lutidine, CH_2Cl_2, rt **(c)** i. Piperidine, DMF ii. **1.105**, PyBop, NMM, DMF/THF, rt. **(d)** Ac_2O, pyridine, LiCl, CH_2Cl_2, rt **(e)** H-C≡C-R, CuI, *trans*-$Pd^{II}(PPh_3)_2Cl_2$, DIPEA, CH_3CN **(f)** HF·Pyr, THF, TMSOMe, rt

1.4.2 Silyl enol ethers

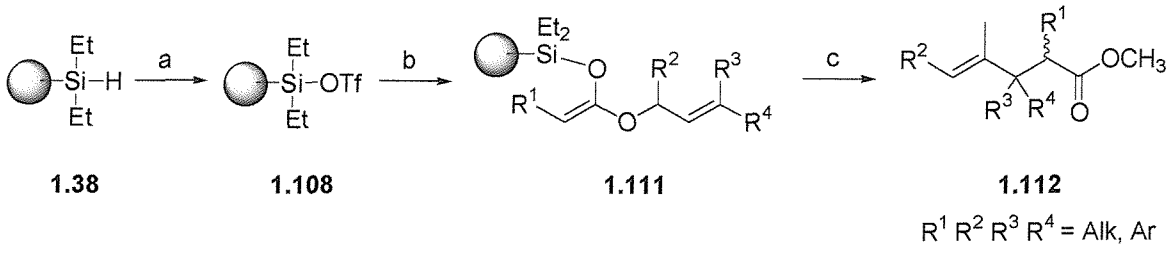
1.4.2.1 Enolate immobilization

In 1999 Smith [67] showed that enolates can be linked to silyl resins. Activation of **1.38** with triflic acid afforded silyl triflate resin **1.108** (Scheme 1.20). Subsequent reaction with a variety of enolizable ketones and aldehydes gave the supported dienes **1.109**, as shown by ^{13}C spectroscopy. Diels-Alder type cycloaddition with a range of dienophiles and TFA acidolysis afforded compounds **1.110** in good overall yield, demonstrating the potential of the method.



Scheme 1.20 (a) TfOH, CH_2Cl_2 **(b)** Aldehyde or ketone, DIPEA, CH_2Cl_2 **(c)** Dienophile, rt, 14h. **(d)** TFA, CH_2Cl_2

In the same period, Porco *et al* [68] demonstrated that enolate of esters, once loaded on a silyl resin, can undergo to Ireland Claisen rearrangment, using a catch and release strategy. Starting from silyl resin **1.108** (prepared in the same way as Scheme 1.20), attachment of esters in Et_3N afforded immobilized enolates **1.111**. Thermal rearrangement and H_2SO_4 acidolysis gave the esters **1.112** in good overall yields.

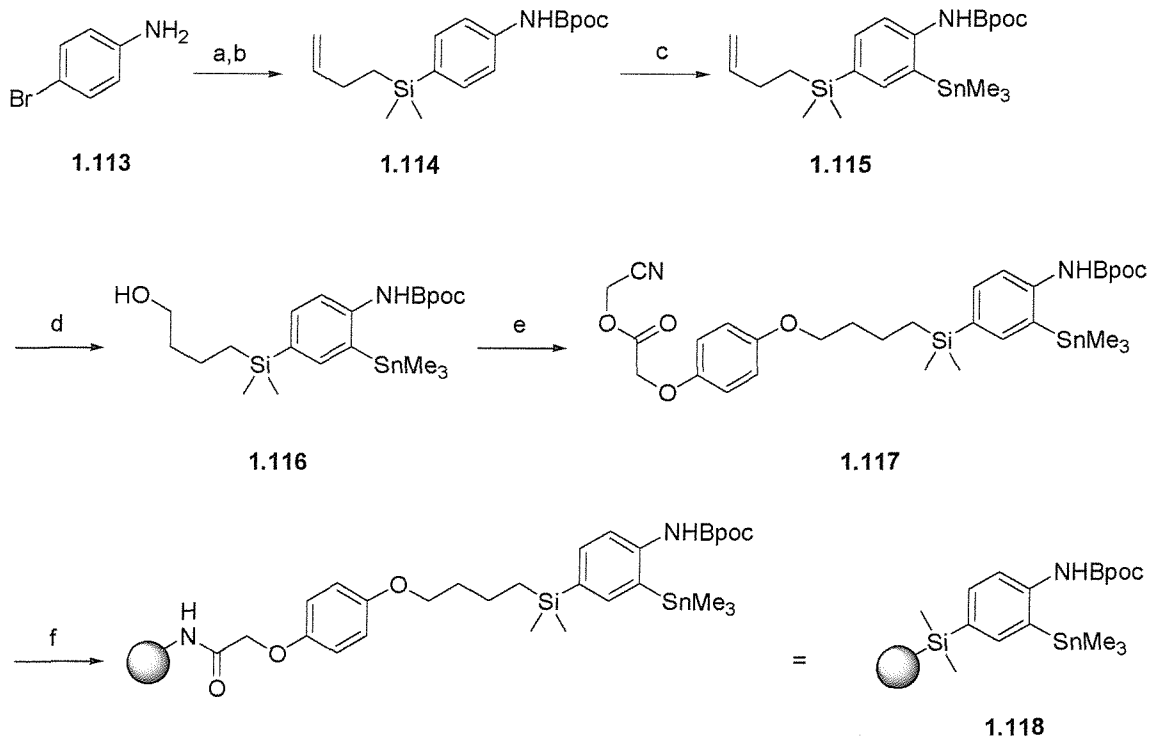


Scheme 1.21 (a) TfOH, CH_2Cl_2 **(b)** Ester, Et_3N, CH_2Cl_2, rt, 2h **(c)** i. THF, 50 °C ii. 5%H_2SO_4, MeOH DCE, 55 °C, 2h

1.4.3 Arylsilane linkers

Silicon linkers have also been used for the traceless release of unsaturated compounds in solid phase organic synthesis. Following this strategy, the linkage of the substrate occurs through a functionality that can be cleaved at the end of the process, leaving behind no trace or "memory of the solid phase".

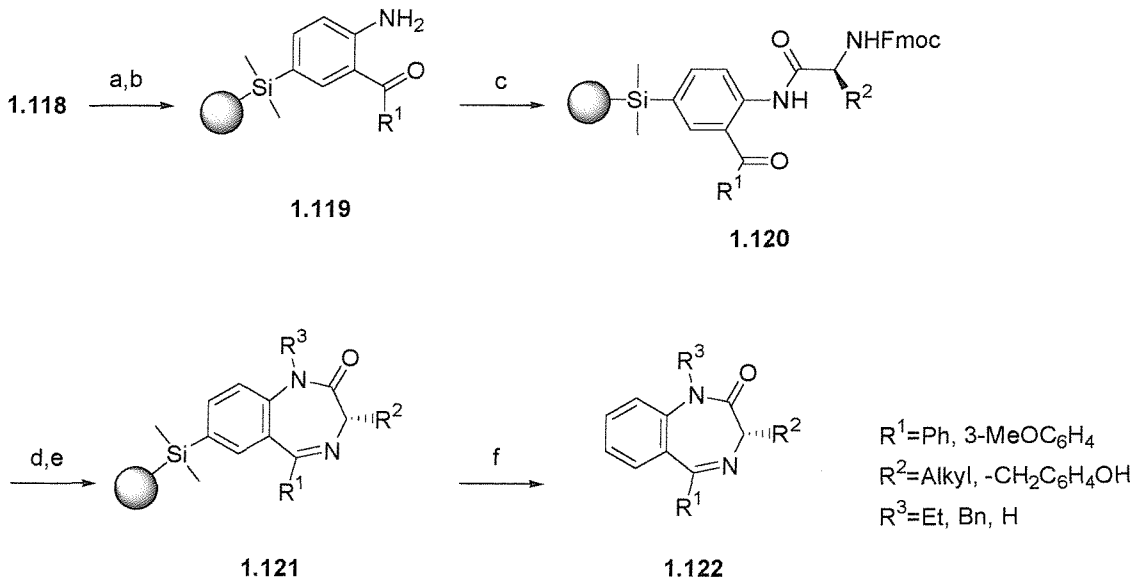
Ellman *et al* reported a silyl linker for the traceless release of aryl containing compounds. [69, 70] In their approach, 4-bromoaniline **1.113** was converted in the silyl derivative **1.114**, subsequent ortho-lithiation followed by quenching with trimethyltin chloride to give arylstannane **1.115**. Hydroboration with 9-BBN and Mitsunobu condensation with cyanomethyl-4-hydroxyphenoxyacetate gave the final linker **1.117**, which was then loaded on aminomethyl polystyrene to afford resin **1.118** (Scheme 1.22).



Scheme 1.22 (a) BpocOPh, KH **(b)** i. KH ii. ^{t}BuLi iii. 3-Butenyl-Me_2SiCl **(c)** i. ^{n}BuLi ii. ^{t}BuLi iii. Me_3SnCl **(d)** 9-BBN, H_2O_2 **(e)** Cyanomethyl 4-hydroxyphenoxyacetate, PPh_3, DEAD **(f)** Aminomethyl polystyrene, DMAP, DIPEA.

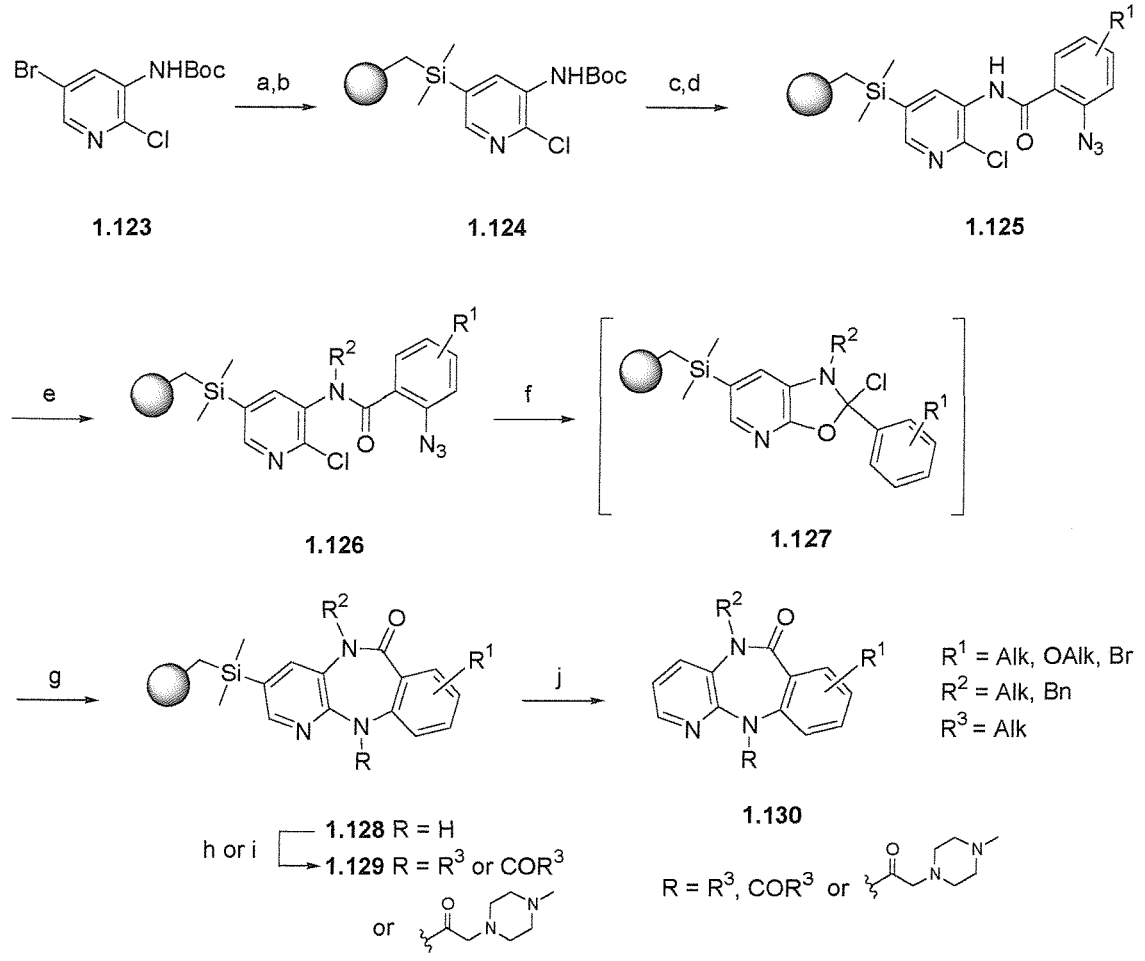
The applicability of the linker was demonstrated in the synthesis of a series of benzodiazepines, [69] a well know class of pharmaceutically important compounds. After

N-deprotection, the free amino group was reacted with an amino acid fluoride, affording **1.120**. Nitrogen deblocking with piperidine and cyclodehydration gave the immobilized benzodiazepines, which were then *N*-alkylated and finally cleaved from the support upon protodesilylation with dry HF, to afford final compound **1.122** (Scheme 1.23).



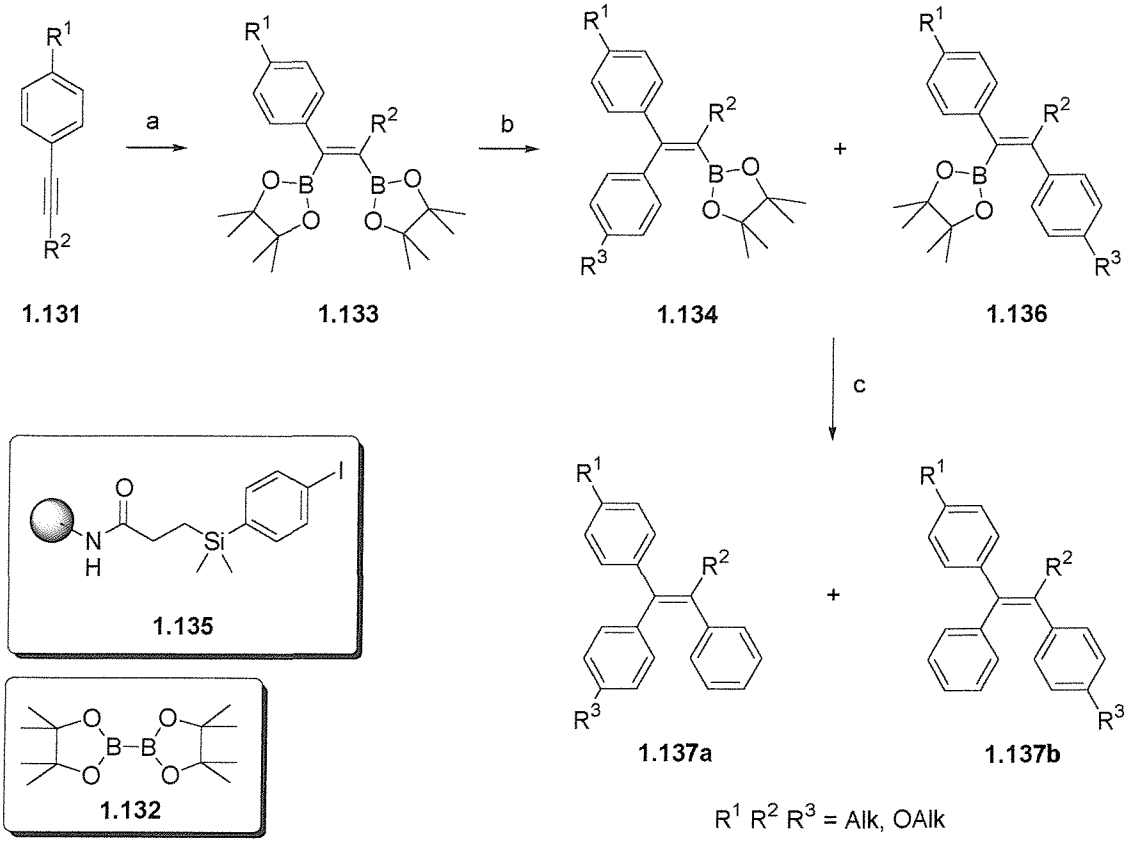
Scheme 1.23 (a) R^1COCl, $Pd_2(dba)_3{\cdot}CHCl_3$ **(b)** 3% CF_3COOH **(c)** Fmoc aminoacid fluoride **(d)** 20% piperidine in DMF **(e)** i. 5% AcOH, 65 °C ii. Lithiated oxazolidinone, then R^3X, DMF **(f)** Anydrous HF

In 1997 the same author extended this strategy with the SPOS of pyridine based tricyclic compounds. [71] Lithiation of pyridine **1.123** and immobilization onto polystyrene dimethylsilyl chloride derivative **1.25b** (see page 9) afforded resin **1.124**. Boc group removal followed by coupling with a variety of azidobenzoyl chlorides gave resin bound precursors **1.125**, which then cyclized to the corresponding tricyclic compounds **1.128** or **1.129**. Traceless release from the support was accomplished with TBAF in THF, to afford final compounds **1.130** (Scheme 1.24).



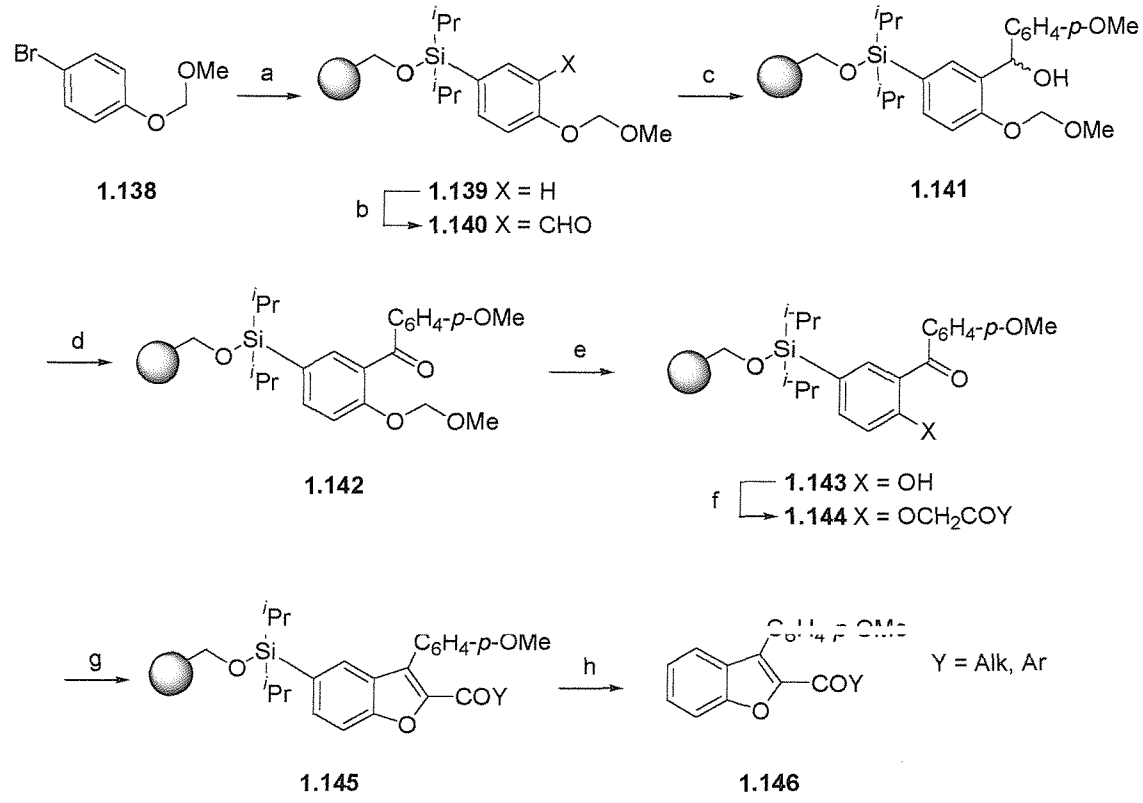
Scheme 1.24 (a) KH, THF, then ^{t}BuLi **(b) 1.25b (c)** 85% TFA in CH_2Cl_2 **(d)** 2-azidobenzoyl chloride, CH_2Cl_2/Pyridine 9:1 **(e)** Lithiated acetanilide, THF, then R_2X **(f)** $SnCl_2$/PhSH/Et_3N (1:4:5) **(g)** DMF/TFA/H_2O (7:2:1) **(h)** Lithiated *N*- ^{t}Butylbenzamide, THF, then R_3X or $R_3(CO)_2O$ **(i)** i. Chloroacetyl chloride, Et_3N, dioxane ii. *N*-Methylpyrazine CH_2Cl_2 **(j)** TBAF, THF

In 1997 Armstrong employed the traceless release during the construction of a Tamoxifen analogues library. [72] The approach adopted the use of monoboryl alkenes as a key fragments. This was accomplished by reaction between bisboryl alkenes **1.133** and a variety of aryl halides. However, considerable amounts of byproducts were also detected, along with the key fragments **1.134** and **1.136**. To avoid a tiresome purification, the crude reaction mixture was reacted with silyl resin **1.135** via a Suzuki coupling. Only the key fragments **1.134** and **1.136** were immobilized, whereas the byproducts were simple washed away. Final traceless release followed by passage through a plug of basic alumina afforded final compounds **1.137a** and **1.137b** in purity greater than 90% (Scheme 1.25).



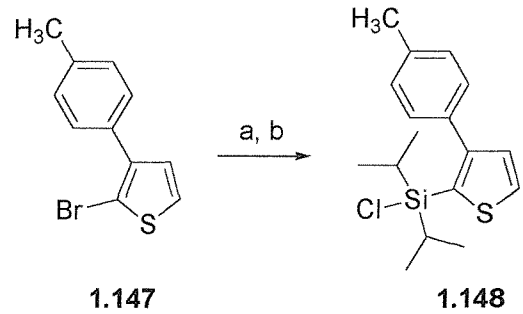
Scheme 1.25 (a) 1.132, Pd $(PPh_3)_4$, DMF, 80 °C **(b)** R^3-ArX, Pd $(dppf)Cl_2$, 3,5-dimethoxyphenol, KOH 6M, DME, rt **(c)** i. **1.135**, KOH 6M, rt ii. 30% TFA in CH_2Cl_2

In 1996 H. D. Showalter *et al* used silicon linkers for the traceless release of benzofurans. [73] According to their approach, lithiation of **1.138** followed by exposure with diisopropyldichlorosilane and coupling with Wang resin **1.2** (see page 3) afforded silyl resin **1.139**. Formylation followed by reduction of the resulting aldehyde with a Grignard reagent gave resin **1.141**. Subsequent alcohol oxidation with DMP and MOM group cleavage afforded phenol **1.143**, which was then alkylated to give resin bound acyclic precursor **1.144**. Ring closure of this latter was carried out in DBU at 80 °C to afford resin bound benzofurans **1.145**, which released the final compounds **1.146** upon treatment with TBAF in THF (Scheme 1.26).



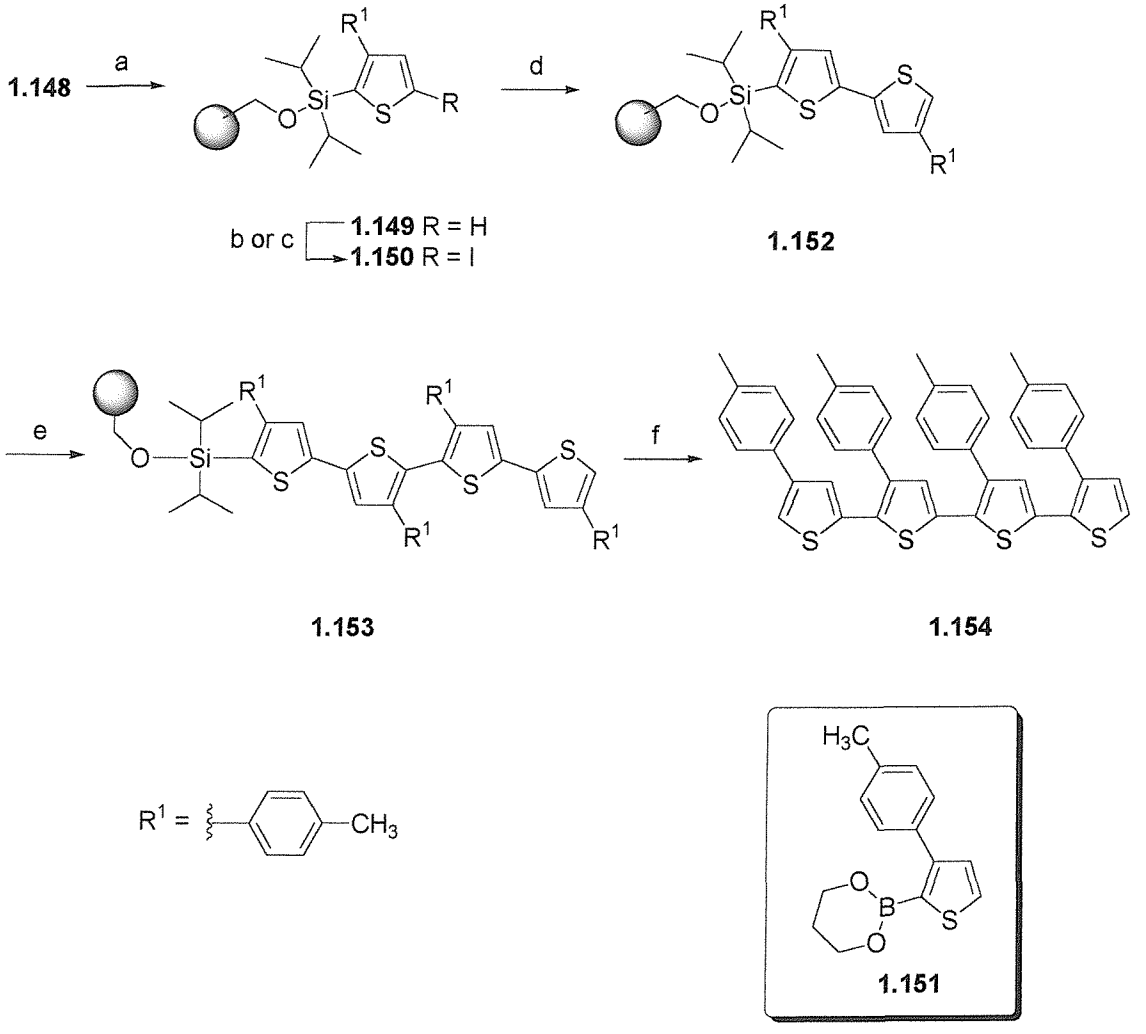
Scheme 1.26 (a) i. ^{n}BuLi, THF, -78 °C ii. $^{i}Pr_2SiCl_2$, -78 °C to rt iii. Wang resin, imidazole, DMF, rt **(b)** i. ^{n}BuLi, TMEDA, Et_2O, 0 °C ii. DMF, 0 °C **(c)** i. 4-bromoanisole, ^{n}BuLi, THF, -78 °C ii. **1.140 (d)** DMP, DMSO/THF, rt **(e)** 5% TFA in CH_2Cl_2, 0 °C **(f)** $BrCH_2COY$, DIPEA, NMP, 80 °C **(g)** DBU, NMP, 80 °C **(h)** TBAF, THF, 65 °C

In 2000 P. Baüerle *et al* employed the silicon linkers for the synthesis and the traceless release of oligo-3-arylthiophenes. [74] After validation of the chemistry with an extensive solution phase model, bromothiophene **1.147** was lithiated and the resulting anion quenched with diisopropyldichlorosilane, affording silyl chloride **1.148** (Scheme 1.27).



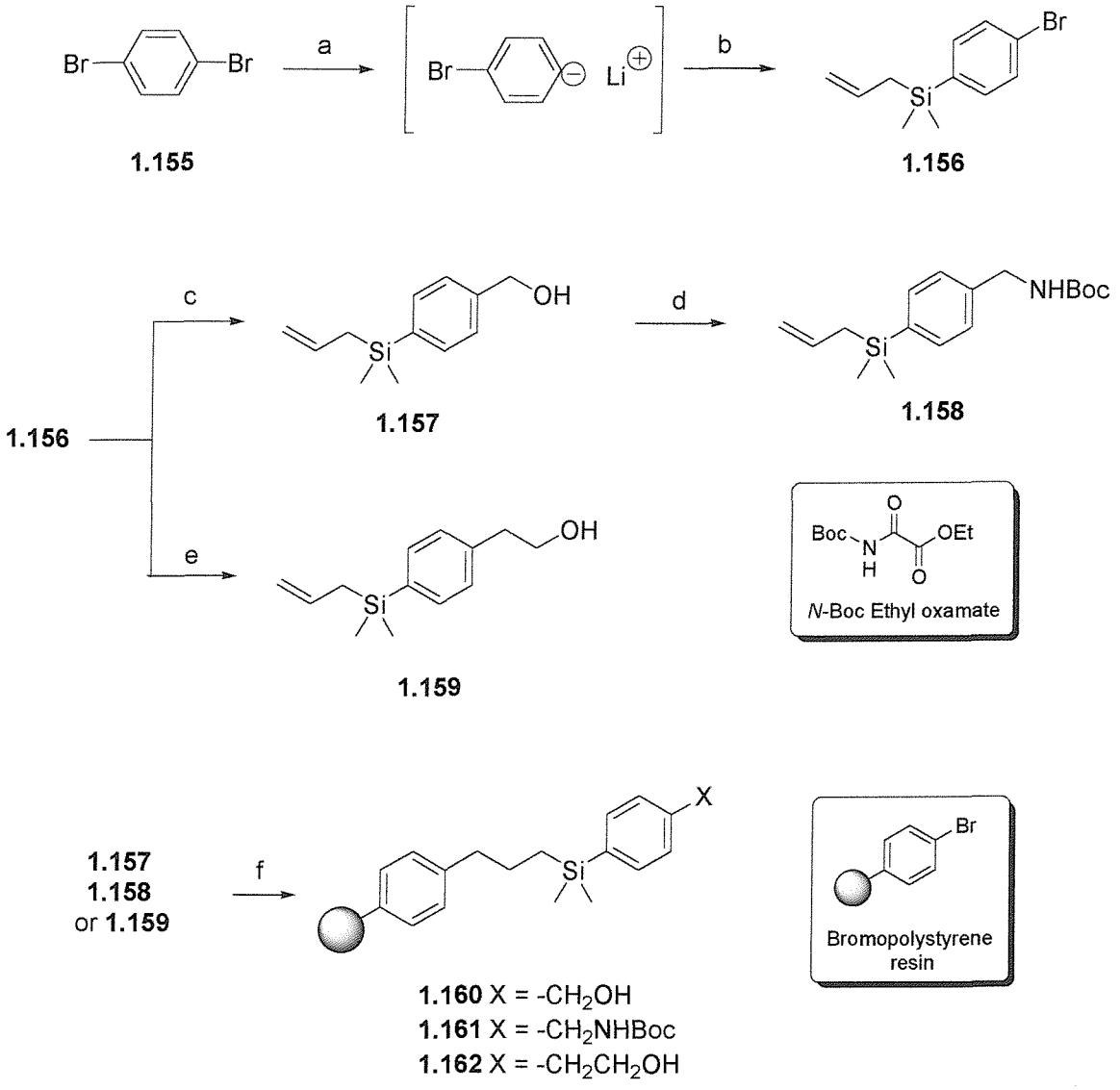
Scheme 1.27 (a) ^{n}BuLi, Et_2O **(b)** $^{i}Pr_2SiCl_2$, Et_2O

Compound **1.148** was then reacted with Wang resin **1.2** to afford polymer bound silyl ether **1.149**. *O*-lithiation with LDA and iodine quench gave **1.150** which underwent a Suzuki coupling with **1.151** to afford resin **1.152**. Reiteration of the last two steps on the resin gave the immobilized tetrathiophene resin **1.153**, which released the final compound **1.154** upon TBAF exposure and purification (Scheme 1.28).



Scheme 1.28 (a) Wang resin, imidazole, DMF **(b)** i. LDA, THF ii. I_2 **(c)** i. $Hg(OCOC_5H_{11})_2$, CH_2Cl_2 ii. I_2 **(d) 1.151**, $Pd(PPh_3)_4$ cat., $NaHCO_3$, THF **(e)** Repeat steps c and d **(f)** TBAF, THF

The traceless release strategy was also employed by Silverman *et al.* [75] Preliminary monolithiation of 1,4-dibromobenzene **1.155** with ^{n}BuLi followed by quench with allyldimethylsilyl chloride afforded intermediate **1.156**. Different elaborations of **1.156** (Scheme 1.29) gave building blocks **1.157**, **1.158** and **1.159**, which were loaded on bromopolystyrene resin in one pot two step procedure, involving hydroboration and *in situ* Suzuki coupling, to afford resins **1.160**, **1.161** and **1.162**.



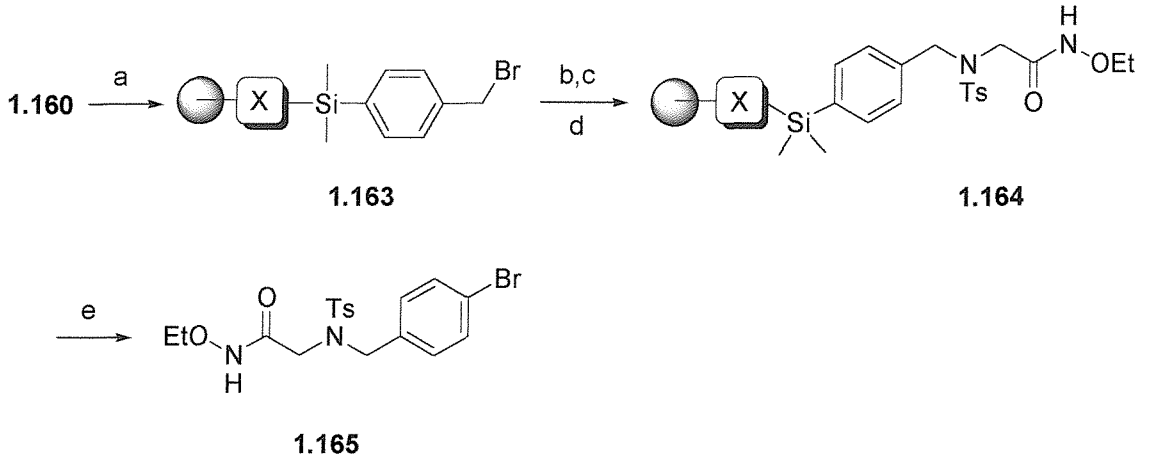
Scheme 1.29 (a) ^{n}BuLi **(b)** (allyl)$SiMe_2Cl$ **(c)** i. Mg, THF ii. $(CHO)_n$ **(d)** i. *N*-Boc ethyl oxamate, PPh_3, DEAD ii. LiOH, THF/H_2O (4:1) **(e)** i. ^{n}BuLi, THF, –78 °C ii. Ethylene oxide **(f)** i. 9-BBN, THF ii. bromopolystyrene, $Pd(PPh_3)_4$, K_2CO_3, 60 °C, DMF, 24h

Treatment of resin **1.160** with PPh_3 and CBr_4 afforded the corresponding bromide **1.163**; subsequent immobilization of glycine ethyl ester followed by *N*-tosylation, hydrolysis of the ethyl ester and coupling with *O*-ethyl hydroxylamine gave resin **1.164**. Final release of the product **1.165** was accomplished with Br_2 (Scheme 1.30).

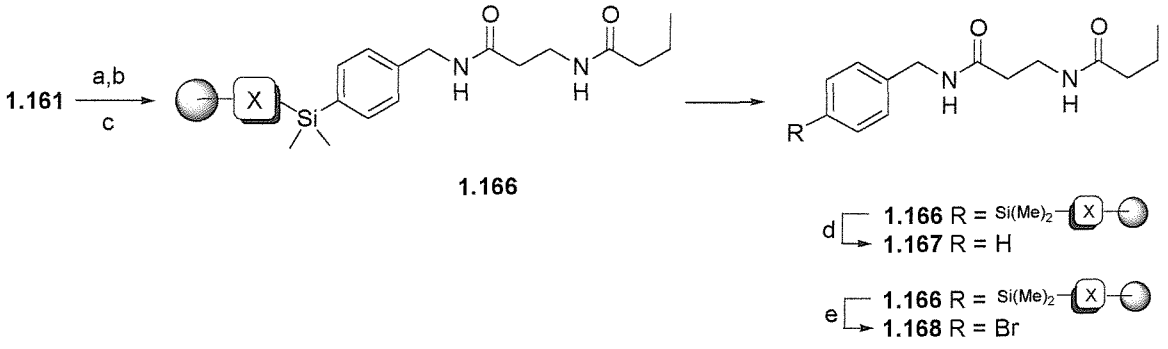
After *N*-deblocking with TFA (Scheme 1.31), resin **1.161** was coupled with β-Fmoc-alanine and butyric acid to give resin **1.166**, which released the final compounds **1.167** and **1.168** upon treatment with TFA or Br_2 respectively.

In a last example (Scheme 1.32) resin **1.162** was converted in the *N*-Boc derivative **1.169** after Mitsunobu reaction with *N*-Boc-Ethyl oxamate and hydrolysis. Couplings

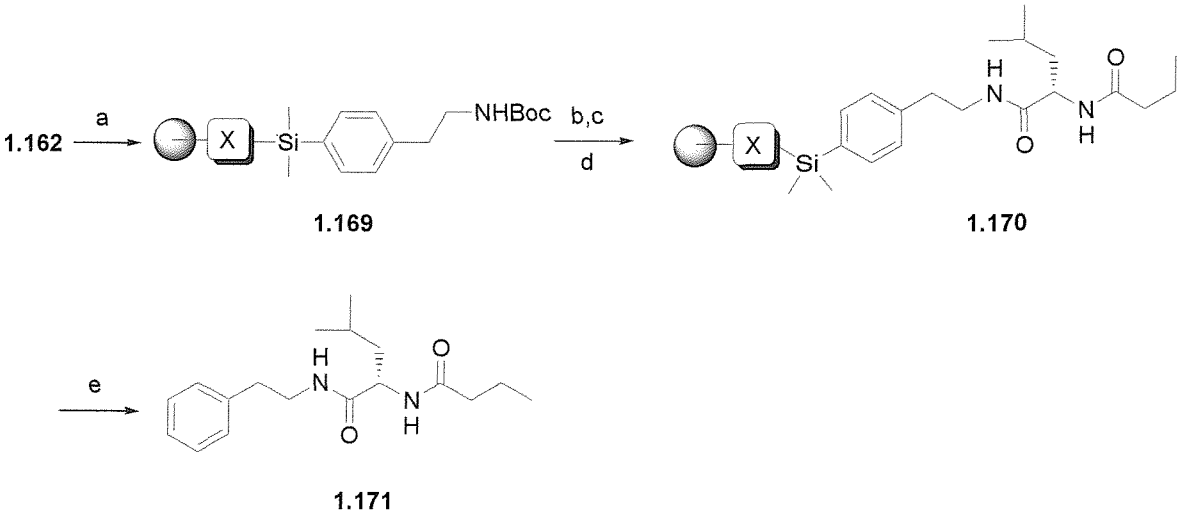
with Fmoc leucine and butyric acid gave resin **1.170** which released the product **1.171** after TFA exposure.



Scheme 1.30 (a) PPh_3, CBr_4, CH_2Cl_2 **(b)** H-Gly-OEt, DMF **(c)** TsCl, Et_3N, DMAP cat **(d)** i. LiOH, THF/H_2O (8:1) ii. NH_2OEt, EDC, HOBt, Et_3N, DMF **(e)** Br_2, CH_2Cl_2

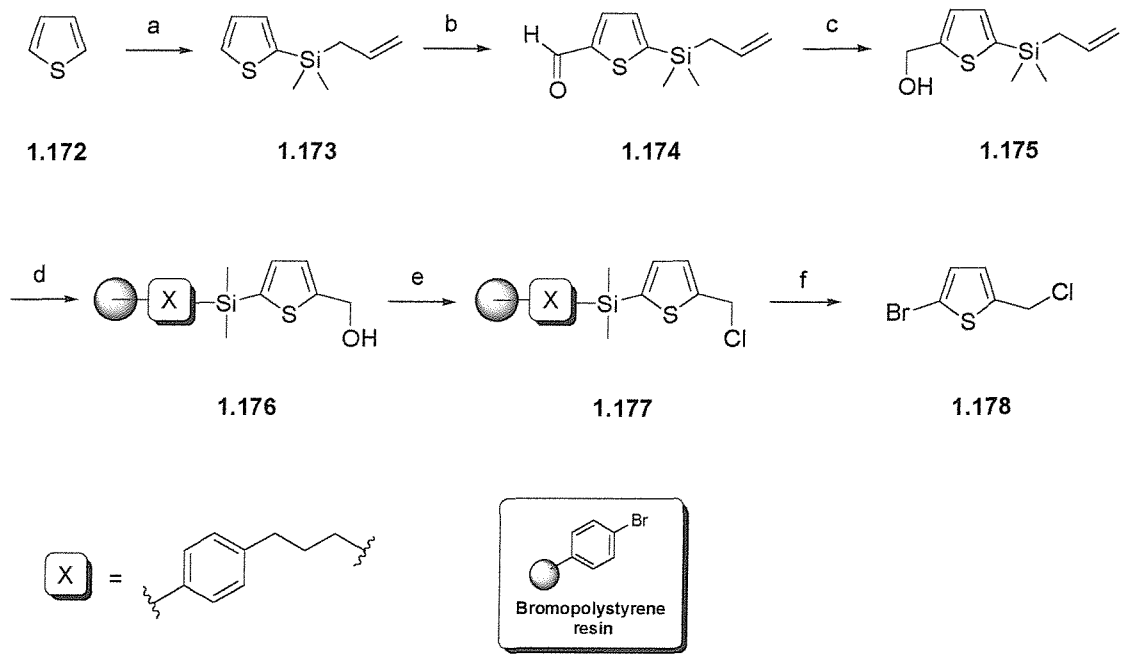


Scheme 1.31 (a) 50% TFA in CH_2Cl_2 5 min **(b)** β-Fmoc-Ala-OH, EDC, HOBt, Et_3N, DMF **(c)** i. 20% Piperidine, DMF ii. Butyric acid, EDC, HOBt, Et_3N **(d)** 50% TFA in CH_2Cl_2, 24h, rt **(e)** Br_2, CH_2Cl_2



Scheme 1.32 (a) i. *N*-Boc ethyl oxamate, PPh_3, DEAD ii. LiOH, THF/H_2O (8:1) **(b)** i. TFA, CH_2Cl_2 ii. Fmoc-Leu-OH, EDC, HOBt, Et_3N, DMF **(c)** 20% Piperidine, DMF **(d)** Butyric acid, EDC, HOBt, Et_3N, DMF **(e)** 50% TFA in CH_2Cl_2, 24h, rt

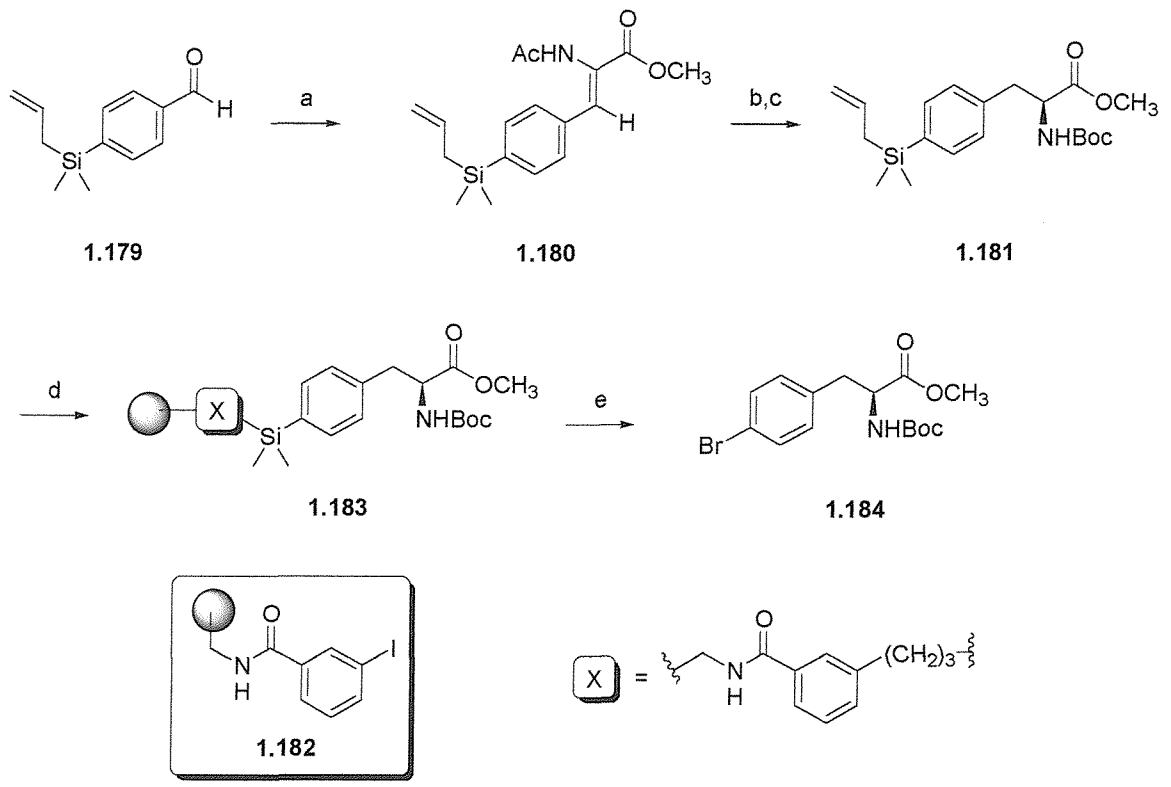
In a similar fashion, the authors showed that also heteroaromatic substrates can be attached and cleaved using the same approach. As an example, monolithiation of thiophene **1.172** followed by quenching with allyldimethylsilyl chloride afforded **1.173**; further lithiation and treatment with DMF gave **1.174**. Reduction of the aldehyde afforded **1.175**, which was then coupled to bromopolystyrene resin using the same method previously reported (see Scheme 1.29, step f, page 28). Chlorination of alcohol **1.176** followed by Br_2 mediated cleavage afforded the 1,5-difunctionalized thiophene **1.178** (Scheme 1.33).



Scheme 1.33 (a) i. ^{n}BuLi, THF, -78 °C ii. (allyl)$SiMe_2Cl$ **(b)** i. ^{n}BuLi, THF, -78 °C, ii. DMF **(c)** $NaBH_4$, EtOH **(d)** i. 9-BBN, THF ii. bromopolystyrene, $Pd(PPh_3)_4$, K_2CO_3, 75 °C, DMF, 24h. **(e)** Cl_3CCl_3, PPh_3 CH_2Cl_2 **(f)** Br_2, CH_2Cl_2

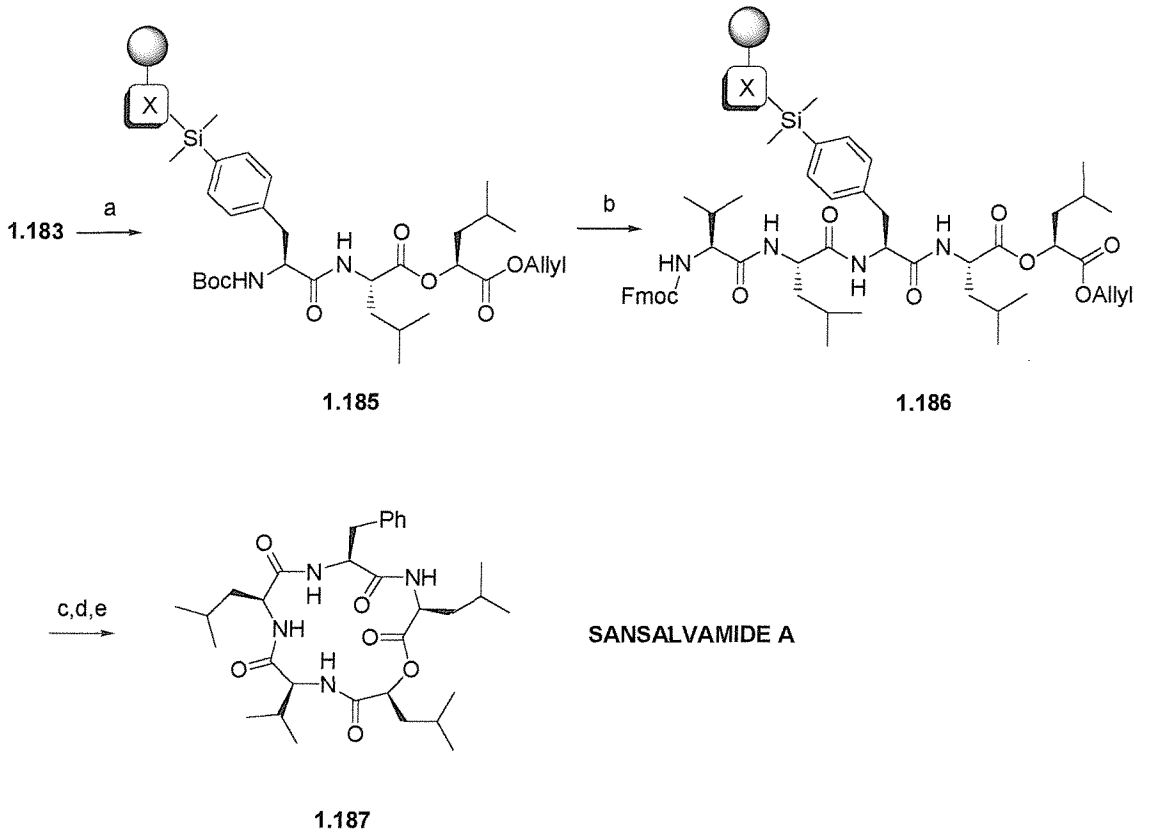
In a series of papers, Silverman showed that the traceless release can also be employed for the synthesis of natural products. As a proof, his team synthesized the antitumor antibiotic cyclopeptide Sansalvamide A using a silicon side-chain-tethered phenylalanine building block. [76] After obtainment of **1.156** (see Scheme 1.29, steps a and b, page 28), subsequent lithiation and quench with DMF gave substrate **1.179**. TMG mediated Horner Emmons reaction afforded exclusively the *Z*-enamide ester **1.180**, which was subjected to an asymmetric hydrogenation to give compound **1.181**. The authors observed a high regioselectivity for this last step, as no reduction of the terminal

double bond was detected. Compound **1.181** was then hydroborated and coupled *in situ* with resin **1.182** to afford the silyl linker **1.183**. The loading level of this latter was determined by its exposure to Br_2 and quantification of the released *p*-bromophenylalanine derivative **1.184** (Scheme 1.34).



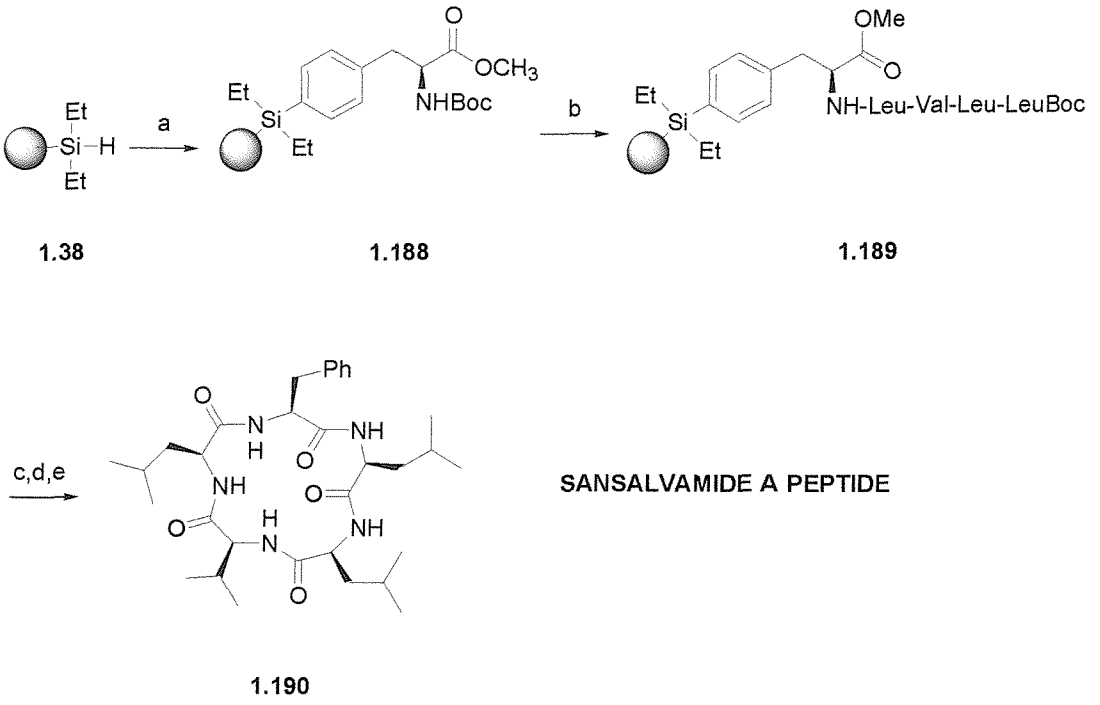
Scheme 1.34 (a) Methyl 2 acetamido-2-(dimethoxyposphinyl)acetate, TMG, THF, -78 °C to rt **(b)** [((*S, S*)-Et-DuPHOS)-Rh]$^+$ (1 mol%), H_2 (1 atm), CH_2Cl_2, 23h. **(c)** i. Boc_2O, DMAP cat., THF, reflux ii. Hydrazine MeOH, 4h **(d)** i. 9-BBN, THF, rt ii. **1.182**, $Pd(PPh_3)_4$, K_2CO_3, 75 °C, DMF, 24h.

The solid phase synthesis began with the deprotection of the ester in **1.183**, followed by coupling with *O*-All-Leu-*O*-Leu-NH_2, which gave resin **1.185**. After Boc removal, chain elongation on the other side was performed with the Fmoc chemistry, to give the linear precursor **1.186**. After deprotection of the *N* and *C* termini, the cyclization was accomplished with HTBU. TFA mediated cleavage afforded Sansalvamide A **(1.187)** in 67% yield and excellent purity (Scheme 1.35).



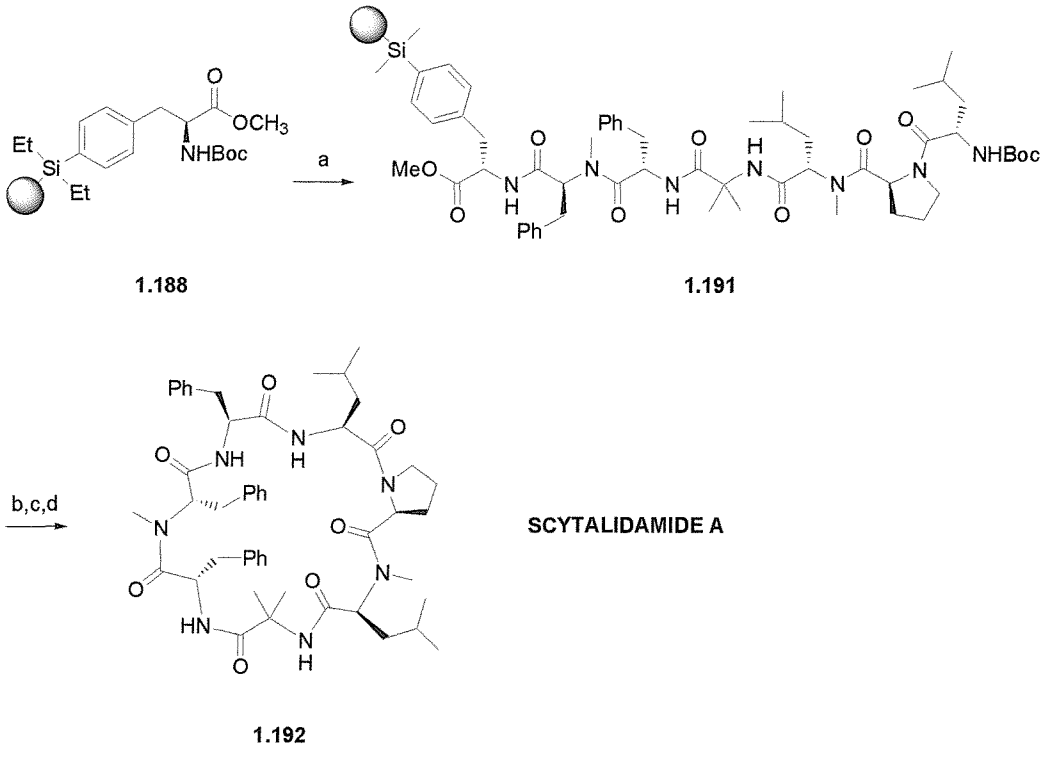
Scheme 1.35 (a) i. LiOH THF/H_2O (7:1) rt, 16h. ii. *O*-All-Leu-*O*-LeuNH$_2$, HBTU, DIPEA, NMP, 16h **(b)** i. 50% TFA, 2% thioanisole, CH_2Cl_2, 15 min. ii. 20% piperidine, DMF, then Fmoc-AA-OH, HBTU, DIPEA, NMP, 16h **(c)** $Pd(PPh_3)_4$, $CHCl_3$/AcOH/NMM (37:2:1) **(d)** i. 20% piperidine, DMF ii. HBTU, DIPEA, NMP, 16h **(e)** 50% TFA, 2% thioanisole, CH_2Cl_2, 36h.

In another paper, [77] the same authors reported the solid phase synthesis of an analogue of Sansalvamide A, namely the Sansalvamide A peptide. In this case the phenylalanine linker was more conveniently prepared by palladium mediated coupling between a *p*-iodophenylalanine derivative and the commercially available PSDES resin. The loading of resin **1.188** was kept low (0.1 mmol/g) to minimize oligomerization problems during the cyclization. The immobilized ester **1.188** was then used for the peptide chain elongation employing the Boc chemistry, which gave resin bound acyclic precursor **1.189**. Cyclization with PyBop and final protodesilylation with neat TFA afforded peptide **1.190** in 66% yield and 95% purity, as judged from HPLC analysis (Scheme 1.36). The analogue **1.190** was found to be 10 times more potent than the Sansalvamide A against the HCT-116 colon cancer cells.



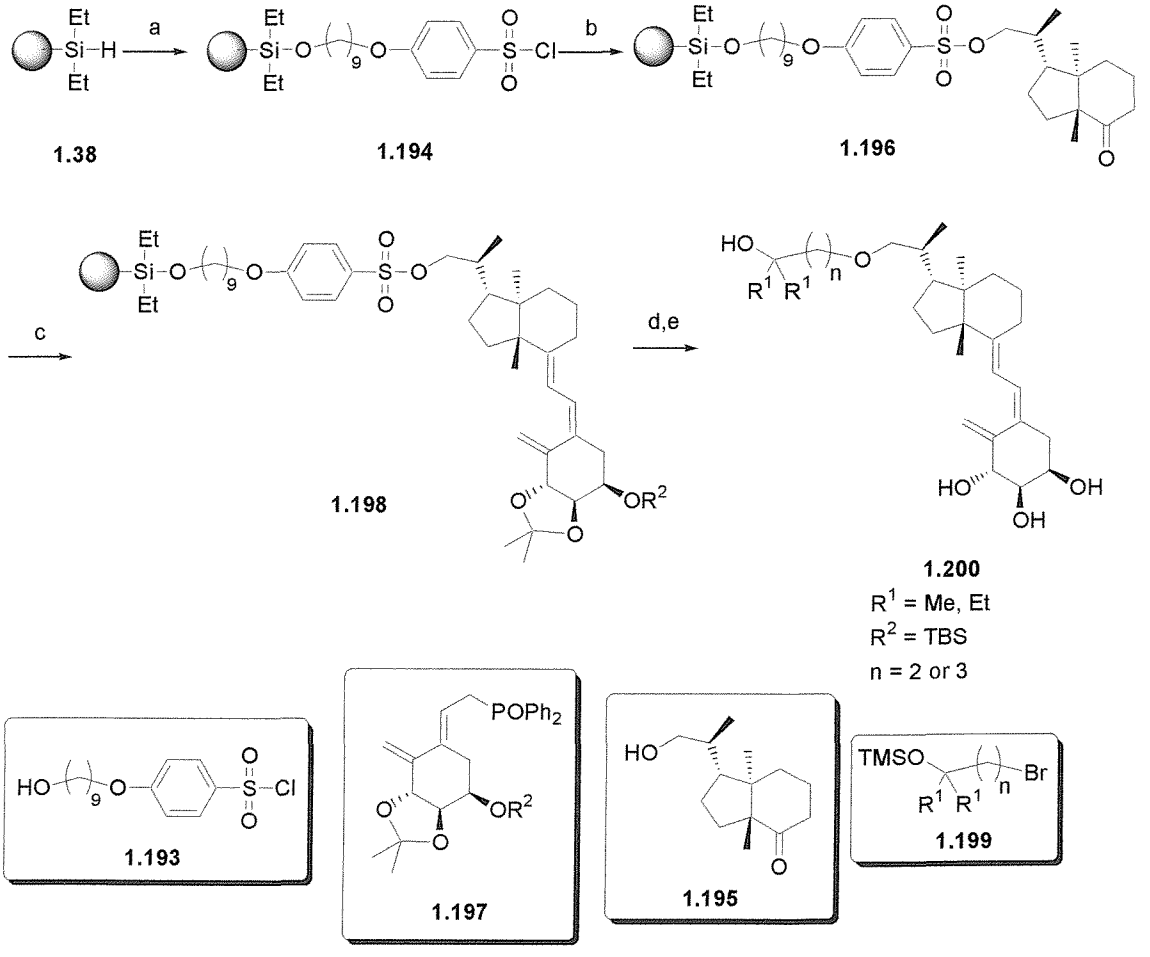
Scheme 1.36 (a) *N*-Boc-4-iodophenylalanine methyl ester, $Pd_2(dba)_3 \cdot CHCl_3$, P(*O*-tol)$_3$, DIPEA, NMP, rt or 105 °C **(b)** i. 50% TFA in CH_2Cl_2, 15 min. ii. Boc-AA-OH, HATU, DIPEA, NMP, 6h **(c)** i. LiOH, THF/H_2O (7:1) ii. 50% TFA in CH_2Cl_2, 15 min **(d)** PyBop, DIPEA, NMP, 24h **(e)** Neat TFA, rt, 24h

The authors further used the same approach for the synthesis of another cyclopeptide, the Scytalidamide A. [78] Always starting from resin **1.188**, chain elongation was performed with the Boc chemistry (Scheme 1.37). Final cyclization and cleavage afforded the cycloheptapeptide **1.192** in 20% overall yield.



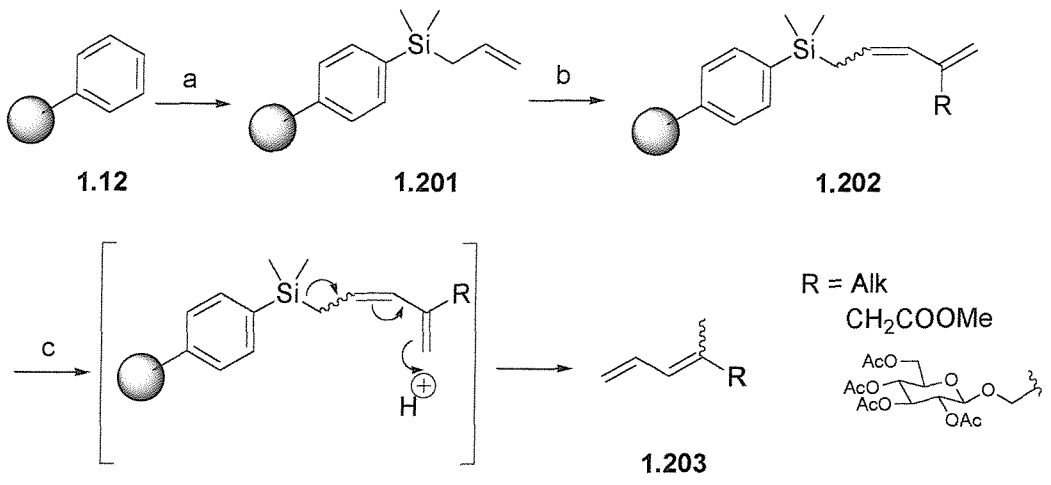
Scheme 1.37 (a) i. 50% TFA in CH_2Cl_2, 30 min ii. Boc-AA-OH, HATU, DIPEA, 6h **(b)** LiOH/H_2O (7:1) rt, 12h **(c)** 50% TFA in CH_2Cl_2, 30 min **(d)** i. PyBOP, DIPEA, NMP, 24 ii. Neat TFA, rt 24h

Silicon linkers were also employed by Takahashi *et al* during the solid phase synthesis of a library of Vitamin D_3 analogues. [79] According to their approach compound **1.193** was loaded on PSDES chloride resin to give **1.194**. Coupling with **1.195** afforded resin **1.196**, which underwent Horner Wadsworth Emmons reaction with lithiated **1.197** to afford the immobilized triene **1.198**. Release from the sulphonate linker was accomplished via a Cu^I catalyzed reaction with **1.199**. The cleaved product was treated with a CSA solution in methanol and water to give final compound **1.200** in 47% yield from resin **1.38**. Originally the authors decided to carry out the synthesis employing a resin where the sulphonyl chloride moiety was linked directly to the polymeric core, but attempts to perform the corresponding Horner Emmons reaction proved to be unsuccessful; the authors hypothesized that this failure was due to the proximity of the substrate to the polymeric matrix. The use of a long spacer, employing a silicon linker, overcame this problem, simultaneously allowing attachment of alcohol **1.193** without affecting the sulphonyl chloride moiety (Scheme 1.38).



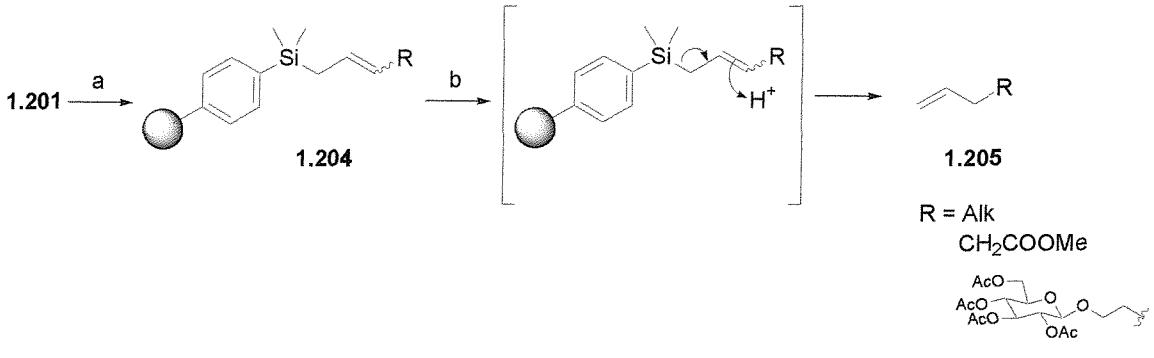
Scheme 1.38 (a) i. 1,3-Dichloro-5,5-dimethylhydantoin, CH_2Cl_2, rt 1h ii. **1.193**, imidazole, CH_2Cl_2, rt, 6h **(b) 1.195**, DMAP, CH_2Cl_2, rt 2h **(c) 1.197**, ^{n}BuLi, THF, -40 to –10 °C, 3h **(d) 1.199**, Mg, CuBr·SMe_2, THF, rt **(e)** CSA, MeOH/H_2O, 30 °C, 6h

Silyl linkers were also used by Blechert *et al.* [80] Lithiated polystyrene (prepared in the way depicted in Scheme 1.4, page 8) was quenched with allyldimethylsilyl chloride to afford resin **1.201**. Cross metathesis of this latter with a range of alkynes and traceless electrophilic cleavage gave the 1,3-dienes **1.203** (Scheme 1.39).



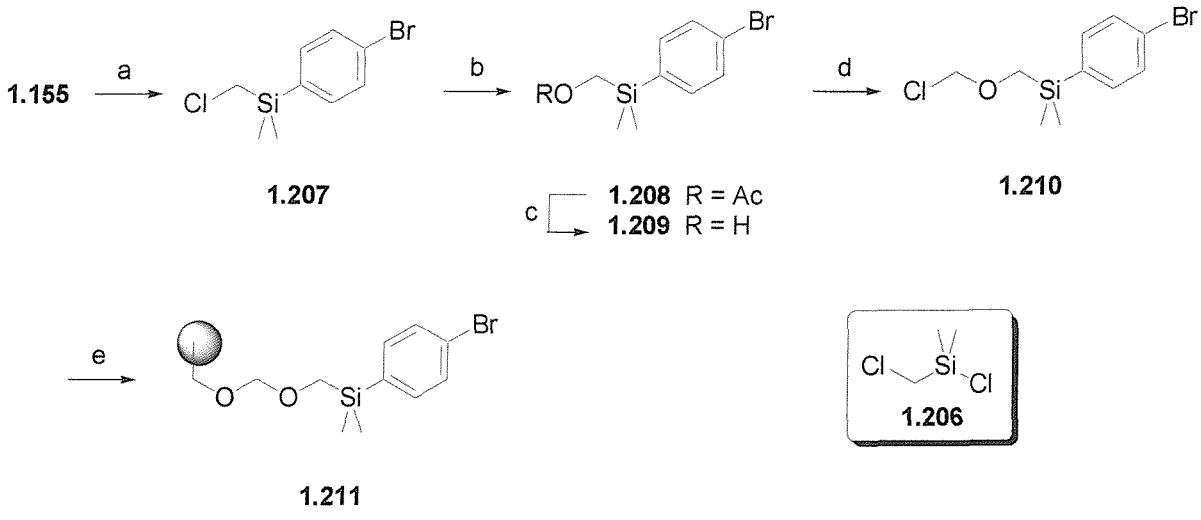
Scheme 1.39 (a) i. ^{n}BuLi, TMEDA ii. (Allyl)$SiMe_2Cl$ **(b)** Alkyne, $Cl_2(PCy_3)_2Ru$=CHPh cat., CH_2Cl_2, reflux **(c)** 1.5% TFA in CH_2Cl_2

In a similar fashion, the authors also demonstrated that alkenes can be immobilized on the same resin **1.201**. [81] In this case the electrophilic release from **1.204** with TFA afforded the homologized olefins (Scheme 1.40).



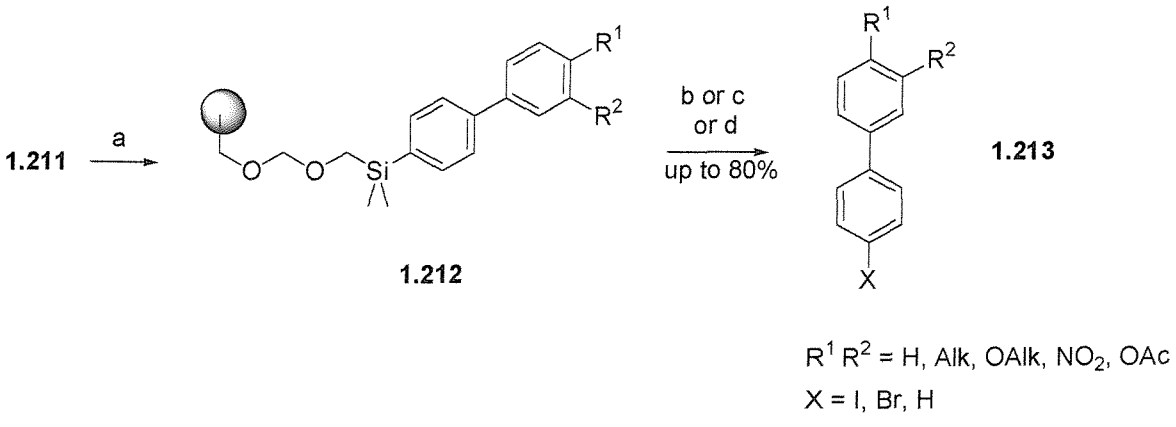
Scheme 1.40 (a) Alkene, $Cl_2(PCy_3)_2Ru$=CHPh cat., CH_2Cl_2, reflux **(b)** 3% TFA in CH_2Cl_2

Haan and Coworkers also employed silicon linkers quite successfully. [82] Here, monolithiation of 1,4-dibromobenzene **1.155** (see page 28) followed by quenching with silyl chloride **1.206** afforded **1.207**. Acetate displacement and reduction gave **1.209** which was reacted with trioxane in HCl, affording substrate **1.210**. This latter was loaded on Wang resin to give silyl linker **1.211** (Scheme 1.41).



Scheme 1.41 (a) i. ^{n}BuLi, THF, -78 °C ii. **1.206**, -78 °C **(b)** NaOAc, DMF, $^{n}Bu_4I$, 80 °C, 24h **(c)** DIBAL-H, toluene, -78 to 0 °C, 2h **(d)** Trioxane, HCl **(e)** Wang resin, DIPEA, DMF, 40-50 °C, o.n.

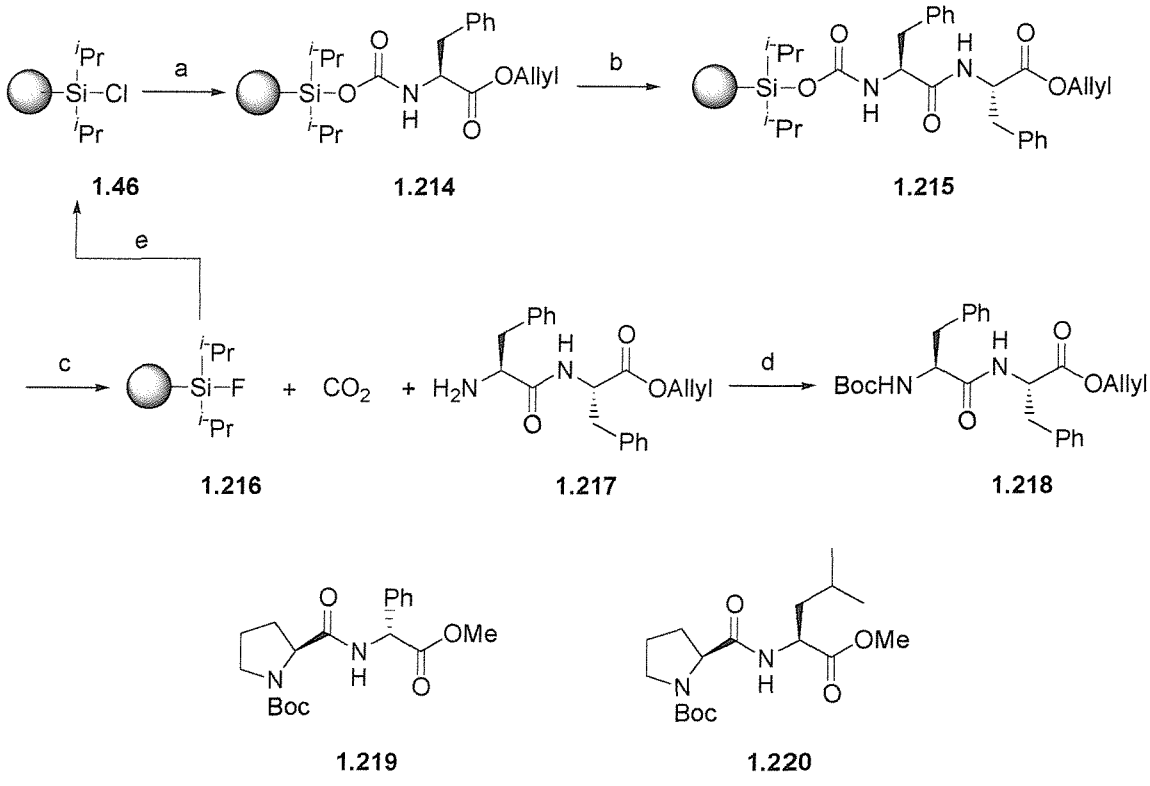
To demonstrate the utility of the linker **1.211**, it was subjected to a series of Suzuki couplings, giving a variety of differently functionalized biphenyls **1.213**, which were released from the support with ICl, Br_2 or TFA in yields typically higher than 80% (Scheme 1.42).



Scheme 1.42 (a) $ArB(OH)_2$ Et_3N/DMF (1:1), 80-90 °C, 24h **(b)** ICl, CH_2Cl_2 **(c)** Br_2, CH_2Cl_2 **(d)** TFA, CH_2Cl_2

1.4.4 Miscellaneous

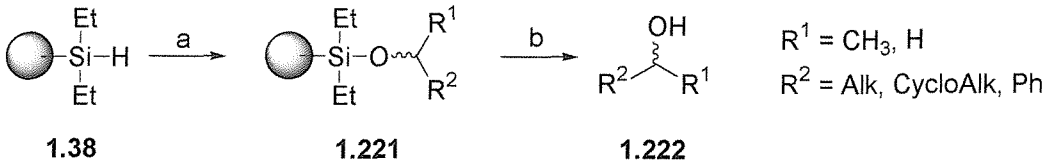
Lipshutz and coworkers developed a linker based on the Tsoc as a supported protecting group for the nitrogen in the reversed SPPS. [83] In their approach, silyl chloride resin **1.46** was reacted with a range of aminoacids derivatives, including proline, in presence of CO_2 and Et_3N, to give the immobilized silyl carbamate **1.214**. Carboxyl unblocking and coupling with the *N*-free amino acids afforded resin bound dipeptide **1.215**, which was then treated with HF in acetonitrile to afford **1.217**, along with resin **1.216** and CO_2. Boc protection of **1.217** gave compound **1.218** in good overall yield. Analysis of the optical rotatory powers showed minimal epimerization during the peptide coupling. In a similar fashion compounds **1.219** and **1.220** were prepared. Desiderable features included the formation of gaseous byproducts and the possibility to recycle resin **1.216** into the corresponding chloride **1.46** (Scheme 1.43).



Scheme 1.43 (a) H-PheOAllyl, CO_2, Et_3N, –78 °C to rt **(b)** i. $Pd(PPh_3)_4$, $Me_2NH{\cdot}BH_3$ ii. ^{t}Bu-chloroformate NMM, 0 °C to rt iii. H-PheOAllyl **(c)** HF (aq), CH_3CN **(d)** $(Boc)_2O$, Et_3N **(e)** BCl_3, CH_2Cl_2

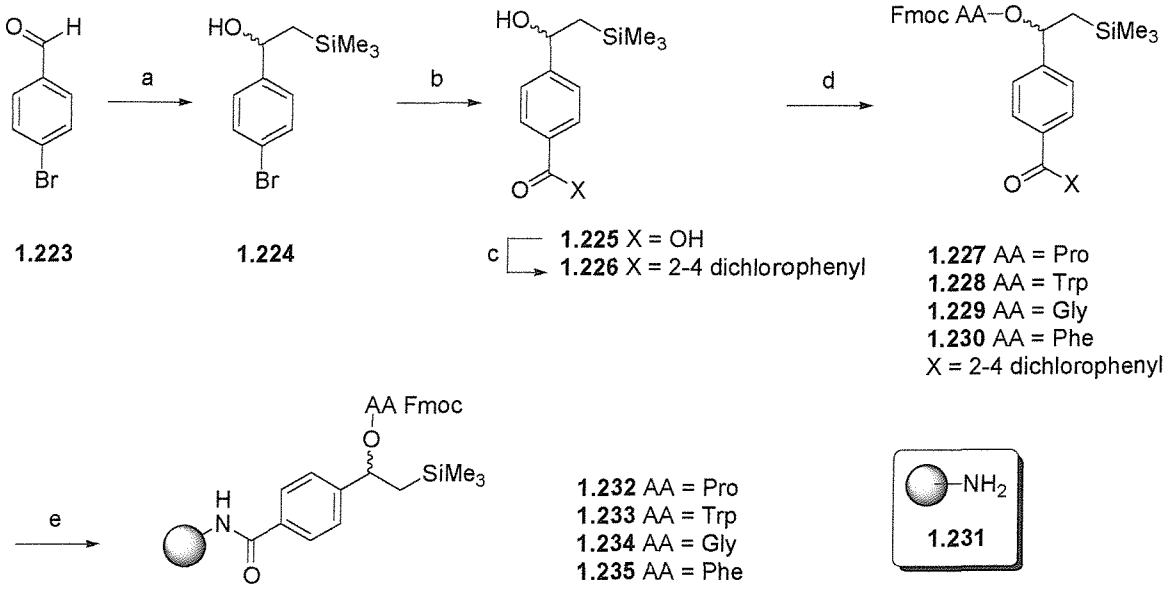
The silyl resins have also been employed as a supported reducing agent; for example Porco *et al* reported the reduction of carbonyl compounds. [84] In this approach,

aldehydes and ketones were hydrosilylated with the commercially available PSDES resin, to afford resin bound silyl ethers **1.221**. TBAF exposure gave the alcohols **1.222** in good yields (Scheme 1.44).



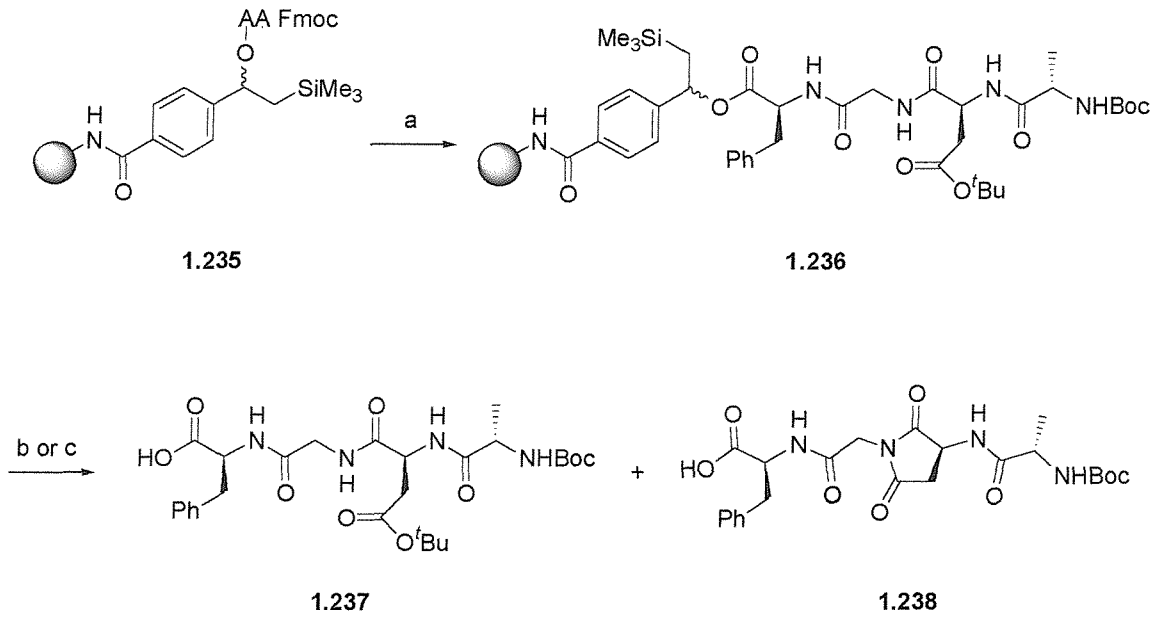
Scheme 1.44 (a) Aldehyde or ketone, $RhCl(PPh_3)$, NMP, 60 °C 0.5-3h **(b)** i. HF· Pyr THF ii. $MeOSiMe_3$

In a paper Chao *et al* described a linker based on the TMSE ester as a supported protecting group for the carboxylic acids. [85] *p*-Bromobenzaldehyde **1.223** was reacted with ((trimethylsilyl)methyl)magnesium chloride to give alcohol **1.224** in quantitative yield. Lithiation of this and quench with CO_2 afforded acid **1.225** which was esterificated with 2,4-dichlorophenol to afford **1.226**. Final esterification with a variety of amino acids afforded linkers **1.227**, **1.228**, **1.229** and **1.230**. The resulting linkers were then attached to amino methyl resin **1.231** to afford resins **1.232**, **1.233**, **1.234** and **1.235** (Scheme 1.45).



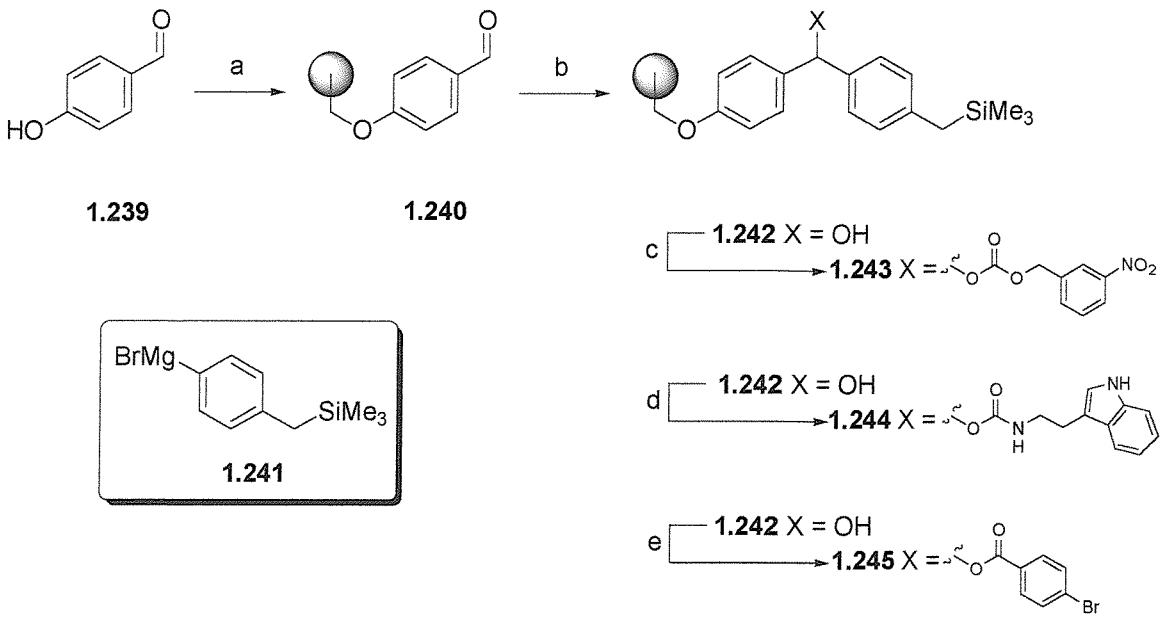
Scheme 1.45 (a) Me_3SiCH_2MgCl, Et_2O, 0 °C **(b)** i. ^nBuLi, -78 °C ii. CO_2 **(c)** 2,4-dichlorophenol, DCC, THF **(d)** Fmoc-AA-OH, DCC, DMAP, THF **(e)** Aminomethyl resin, HOBT, DIPEA, DMF, rt

To show the potential of the application, the linkers were employed in the solid phase synthesis of a range of peptides, employing the Fmoc chemistry, as illustrated in Scheme 1.46. Final cleavage of the products occurred by acidolysis with 1% TFA in CH_2Cl_2 or alternatively with TBAF. However, when TBAF was employed, side reactions were also observed, like the formation of succinimide **1.238**.



Scheme 1.46 (a) i. 20% Piperidine, DMF ii. Fmoc-AA-OH, HOBt, DIPEA, rt, 5h **(b)** TBAF, THF **(c)** 1% TFA, CH_2Cl_2

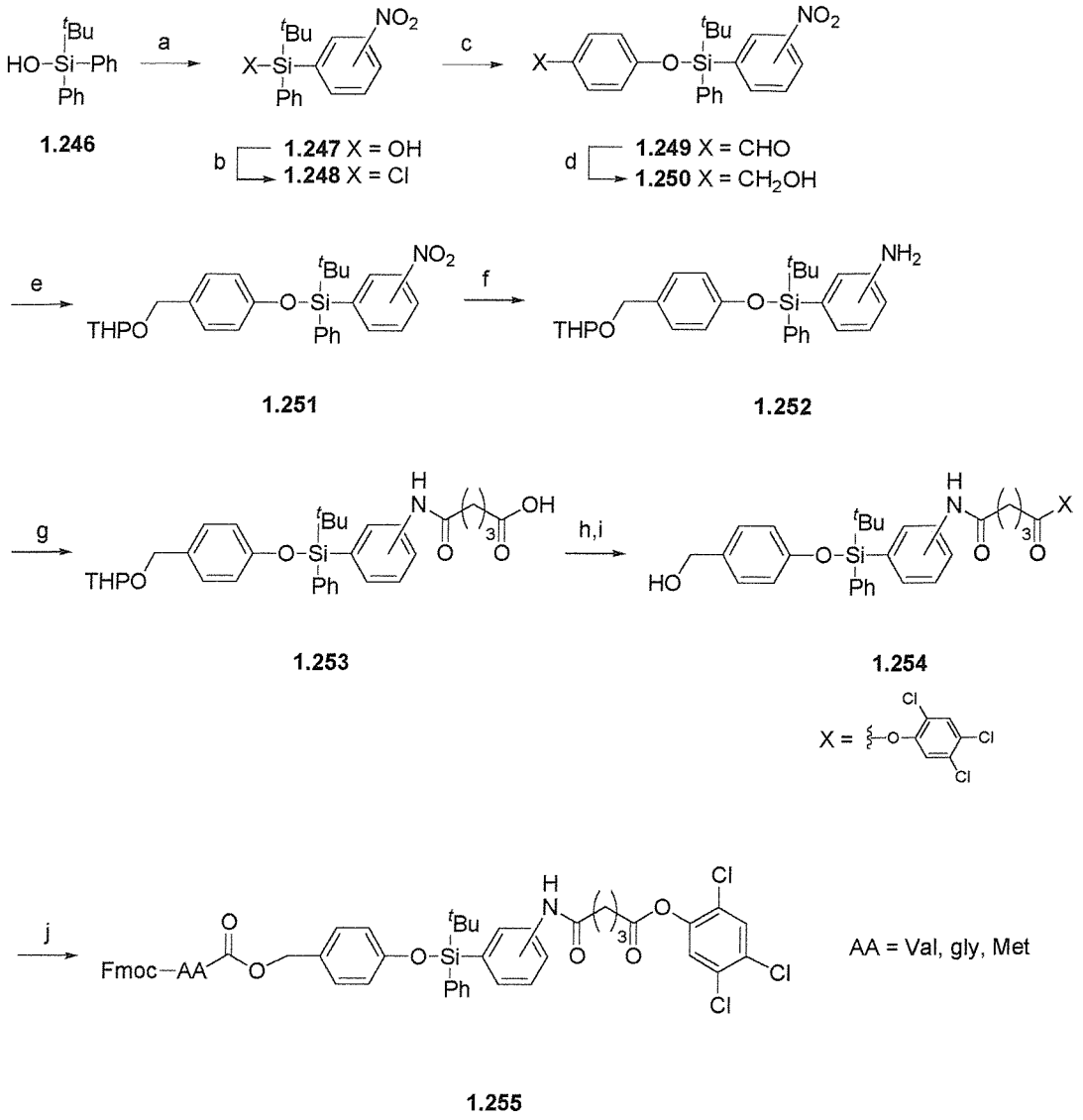
A different silyl linker was synthesized by Turner and coworkers. [86] Here, Merrifield resin **1.1** was reacted with *p*-hydroxybenzaldehyde **1.239** to give **1.240**. Subsequent action of the Grignard reagent **1.241** afforded silyl resin **1.242**. Once formed, the utility of **1.242** was demonstrated as supported protecting group for alcohols, carboxylic acids and amines, as depicted in Scheme 1.47



Scheme 1.47 (a) i. *p*-hydroxybenzaldehyde, NaH, DMF ii. Merrifield resin, 18h, rt **(b) 1.241 (c)** i. CDI, pyridine, CH_2Cl_2, 1h, rt ii. *m*-nitrobenzyl alcool, DBU, CH_2Cl_2, rt, 15 min **(d)** i. CDI, pyridine, CH_2Cl_2, 1h, rt ii. tryptamine, pyridine, DMF, rt, 18h **(e)** i. *p*-Bromobenzoic acid, DIC, pyridine, DMAP cat., HOBT cat., DMF, rt, 18h

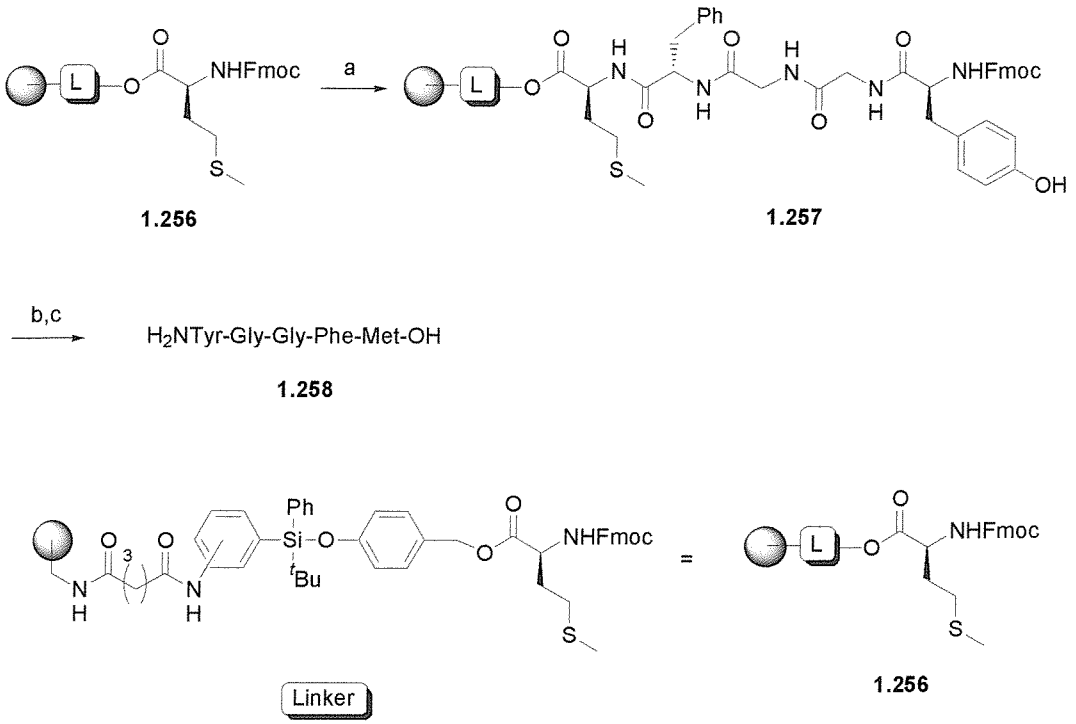
Exposure of resins **1.243**, **1.244** and **1.245** either with TBAF, CsF or TFA in CH_2Cl_2 released the *m*-nitrobenzyl alcohol, the tryptanine and *p*-bromobenzoic acid, respectively.

A silicon linker for the protection of carboxylic acids was also synthesized by Barany and coworkers. [87] According to their approach, nitration of silanol **1.246** with ammonium nitrate in TFAA afforded **1.247**, which was converted in the chloride **1.248** with oxalyl chloride and DMAP. Coupling with *p*-hydroxybenzaldehyde afforded **1.249**, which was then reduced to **1.250**. Subsequent alcohol protection as a THP ether, followed by reduction of the nitrogroup and ring opening with glutaric anhydride afforded **1.253**. Carboxyl activation with 2,4,5-trichlorophenol, THP ether deprotection and esterification with the first amino acid afforded final linker **1.255** (Scheme 1.48).

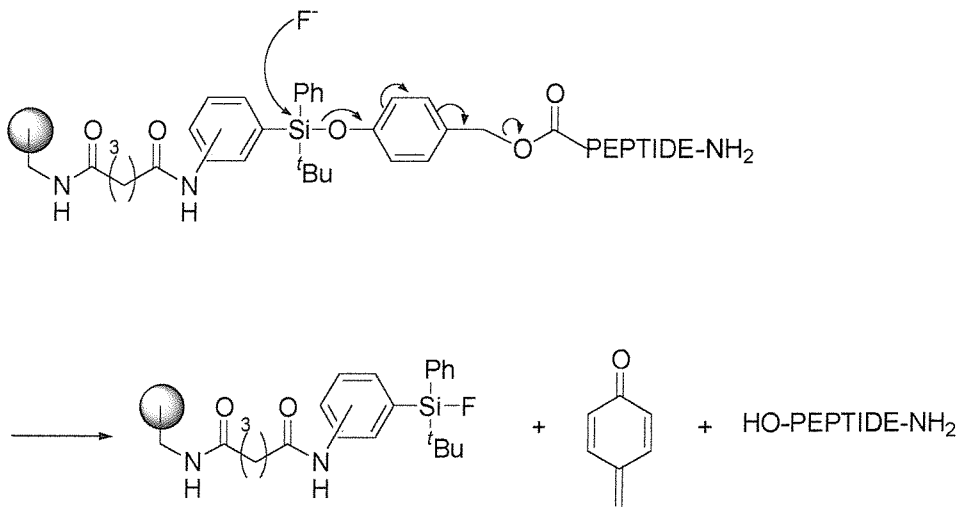


Scheme 1.48 (a) NH_4NO_3, TFAA **(b)** $(ClCO)_2$, DMAP **(c)** *p*-hydroxybenzaldehyde, DIPEA, CH_2Cl_2 **(d)** BH_3·THF **(e)** Dihydropyran, pyridinium tosylate, CH_2Cl_2 **(f)** Pd/C, ammonium formate, MeOH **(g)** Glutaric anhydride, CH_2Cl_2 **(h)** 2,4,5-trichlorophenol, DCC, CH_2Cl_2 **(i)** Pyridinium tosylate, EtOH, 50 °C **(j)** Fmoc-AA-OH, *N, N*-dimethylformamide dineopenthylacetal, 3 days.

Attachment of linker **1.255** on the polymer was performed with amino methyl resin **1.231**, and the Fmoc amino acid was used to construct a range of different peptides, like **1.258**, which were finally cleaved with TBAF in DMF or with a mixture of TFA and CH_2Cl_2, employing dimethylsulphide as scavenger (Scheme 1.49). Importantly, the linker was found to be totally stable during all of the conditions required for the SPPS. The proposed mechanism for the fluoride assisted cleavage of peptides from resin **1.256** is illustrated in Scheme 1.50.



Scheme 1.49 (a) i. 20% Piperidine, DMF ii. Fmoc-AA-OH, DCC, HOBt **(b)** 20% Piperidine, DMF **(c)** TBAF, DMF rt



Scheme 1.50 Fluoride mediated cleavage of peptides from linker **1.256**

1.5 Conclusion and aims of the project

In summary, this overview demonstrated the importance of silicon linkers in solid phase organic synthesis. They have found diverse applications for the synthesis of a large variety of compounds such as oligosaccarides, peptides, poliketides and benzodiazepines. In addition silicon linkers proved to be successful as polymer bound reducing reagents for aldehydes and ketones, and they have been successfully employed for the synthesis of γ-δ unsaturated esters using a catch and release strategy.

Despite their success, silicon linkers in solid phase synthesis remain a relatively unexplored field. One possible reason could lie in the lack of convenient methods for their synthesis: as previously shown, some authors (see section 1.4.3, page 22) synthesized the whole linkers in solution prior to attachment to the solid support. This strategy proved to be tedious, both in the number of the steps involved and in terms of the purification of intermediate compounds. In addition, the overall yields of the linkers obtained were sometimes low and required the use of reagents that are not readily available. [69]
However, some of these problems were partially solved by Darling [54] and Hu. [55] By performing the whole synthesis of the linkers directly on the polymer, all the analogous solution phase intermediate purification steps were avoided. In addition, the simplicity of the syntheses and the variety of the reagents involved made this approach suitable for the rapid generation of differently functionalised silyl linkers. However, this approach also presented some drawbacks in that some reactions were found to be low yielding or extremely time-consuming, even when high temperatures or a large excess of reagents were employed.

After consideration of these drawbacks observed from the literature, it was decided to extend the repertoire of the available silyl resins and to develop a synthesis of novel silicon linkers for use in solid phase synthesis. For this purpose, the new linkers to be developed must represent a valuable alternative to those already available and thus this feature has two important consequences:

1. They have to be easily and rapidly synthesized, using high-yielding procedures from cheap starting materials.

2. They should present excellent stability under a broad variety of reaction conditions.

With these ideas in mind the general structures depicted in Figure 1.4 were chosen as potential candidates.

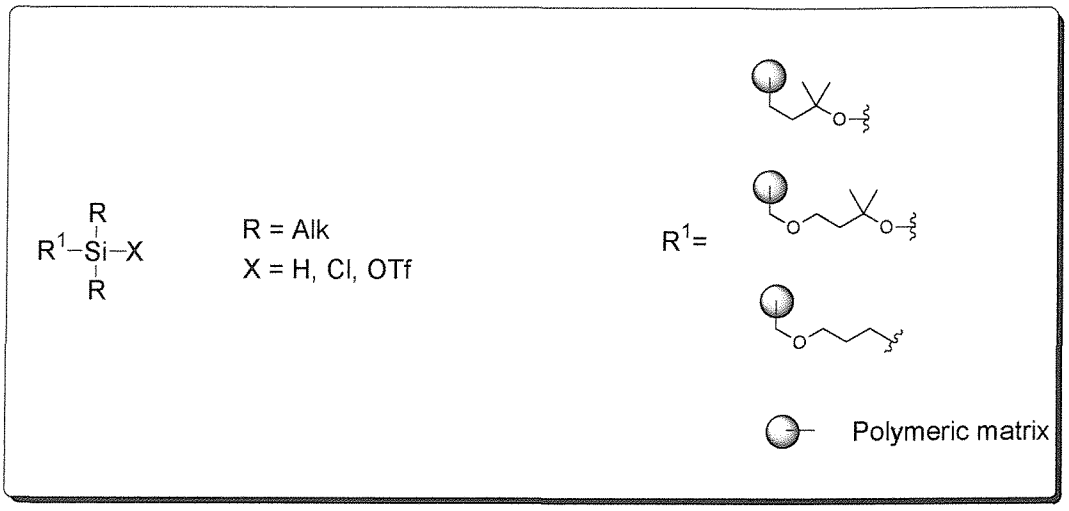


Figure 1.4 General structures of the silyl linkers investigated

The structures depicted also offered the possibility of performing the synthesis of the whole linker on the solid phase, avoiding its preparation in solution. It was felt that these linkers would fulfil all the requirements cited above and would offer the possibility to be employed for a wide variety of solid phase reactions. As an example, the silyl chlorides or triflates could be used as supported protecting groups for hydroxyl containing compounds, whereas the corresponding silanes could be conveniently employed as polymer bound reducing agents.

For each of the linkers reported, a high-yielding synthetic methodology was required. Hence it was proposed to conduct the initial validation and optimization of the chemistry in solution before being applied to the solid phase. All of these investigations will be the subject of the next chapter.

CHAPTER 2. RESIN PREPARATION AND LOADING

2.1 Synthesis of linkers 2.1a and 2.1b

2.1.1 General considerations and retrosynthetic analysis

The first generation of linkers investigated is presented by the general structure **2.1** as shown in Figure 2.1

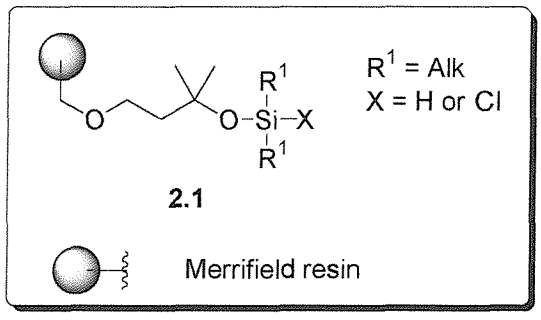
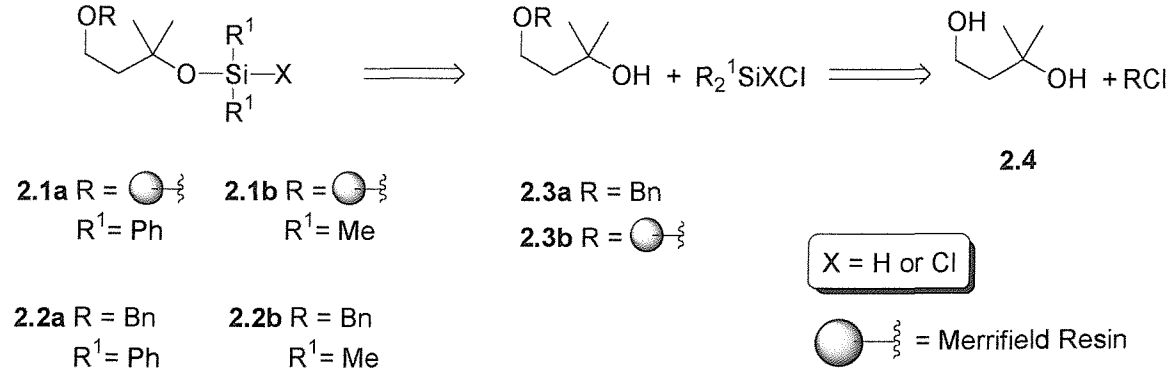


Figure 2.1 General structures of the linkers investigated

The retrosynthetic analysis for its synthesis is shown in Scheme 2.1



Scheme 2.1 Retrosynthetic analysis for the linkers investigated

According to Scheme 2.1, the proposed targets can be obtained from a dialkyl monochloro or dichloro silane and the tertiay alcohol resin **2.3b**. This latter could be

obtained via a reaction between 3-methyl-1,3-butanediol **2.4** and Merrifield resin. It was felt this provided a convenient route for the preparation of the proposed targets employing very cheap starting materials. The great attraction of this strategy relies upon the selective attachment of the primary alcohol of **2.4** to afford resin **2.3b**, which would therefore afford a rapid access to variety of differently functionalised silyl resins of general structure **2.1**, simply by reaction with appropriate dialkyl monochloro or dichloro silanes.

Differently from the trialkylsilyl chloride linkers already reported (see introduction, section 1.4.1.2, page 8), a novel feature of **2.1a** and **2.1b** is the presence of a silyloxy chloride moiety. This latter could be advantageous, as it should result in an enhanced reactivity of **2.1a** and **2.1b** with alcohols.

2.1.2 Solution phase model for linker 2.1a

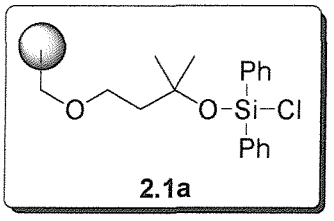
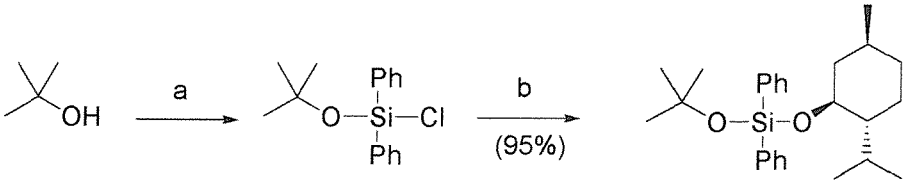


Figure 2.2 Structure of the first silyl linker investigated

Our initial investigations involved the synthesis of linker **2.1a**, which is closely related to *tert*-butoxydiphenylsilyl chloride **2.5** (for its structure see Scheme 2.2), which is known undergo reaction with alcohols in excellent yields. [50] Therefore, the analogous resin **2.1a** should display similar reactivity with alcohols, and the resulting siloxanes should have good stability to a range of reactions commonly employed in SPOS.

Initial investigations commenced with the preparation of a solution phase version of **2.1a** as a model. Before attempting the synthesis of a model, siloxane **2.7** was synthesized following a literature procedure, to verify that the literature chemistry proceeded as reported. [50] According to Scheme 2.2, *tert*-butanol **2.6** was reacted with diphenyldichlorosilane employing CH_2Cl_2 as solvent and Et_3N as base. DMAP was also included in the reaction mixture to enhance the silylation rate of **2.6**. In the literature work, DMAP had not been employed, resulting in very slow reaction times, such as 36 hours in refluxing CH_2Cl_2, for the reaction to reach completion. In our case, **2.6**

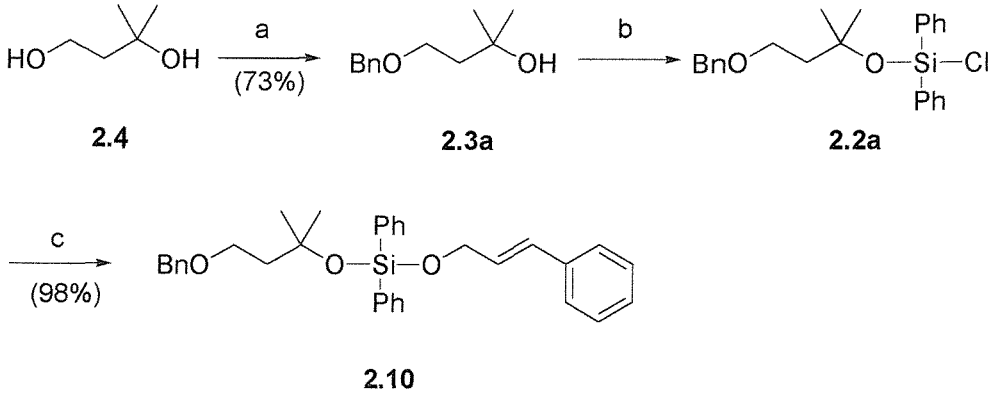
disappeared completely after 10 minutes and to confirm that formation of silyl chloride **2.5** had occurred the crude reaction mixture was treated with menthol, an excess of Et_3N and one equivalent of DMAP, affording **2.7** in excellent purity, as judged by ^1H NMR. Chromatography afforded pure **2.7** in near quantitative yield.



2.6 **2.5** **2.7**

Scheme 2.2 (a) Ph_2SiCl_2, Et_3N, DMAP, rt **(b)** Menthol, Et_3N, DMAP, rt

Having established adequate high yielding conditions for the formation of a simple siloxane **2.7**, the synthesis of **2.2a** was attempted (Scheme 2.3). Using benzyl chloride as a surrogate for Merrifield resin, the Williamson reaction [88] with the sodium salt of 3-methyl-1,3-butanediol in dry DMF at 0 °C gave **2.3a** in 73% yield, along with some unreacted diol. This important result suggested that no cross-linking problems should arise in the corresponding step of the solid phase synthesis, as no reaction at the tertiary alcohol was observed.



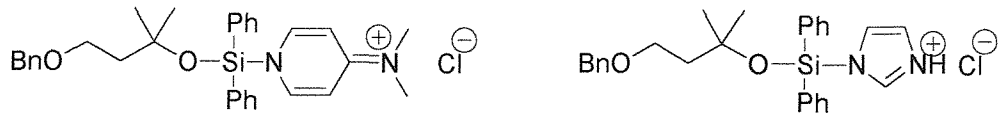
2.4 **2.3a** **2.2a**

2.10

Scheme 2.3 (a) NaH, DMF, 0 °C, then BnCl, 0 °C to rt **(b)** Ph_2SiCl_2, Et_3N, DMAP, rt **(c)** *trans*-cinnamyl alcohol, Et_3N, DMAP, rt

In order to obtain the presumed silyloxy chloride **2.2a**, **2.3a** was reacted with diphenyldichlorosilane in presence of Et_3N with either DMAP or imidazole (Scheme 2.3); in both cases TLC analysis showed the total disappearance of substrate **2.3a** within 10 minutes at room temperature, along with the formation of a new major compound.

As was encountered previously, very slow reaction times were observed in absence of DMAP or imidazole, requiring up to 24 hours for the consumption of the starting material. In all the three cases examined, the TLC analysis showed the formation of the same compound, suggesting also that the formation of intermediates **2.8** and **2.9** is unlikely (Figure 2.3).



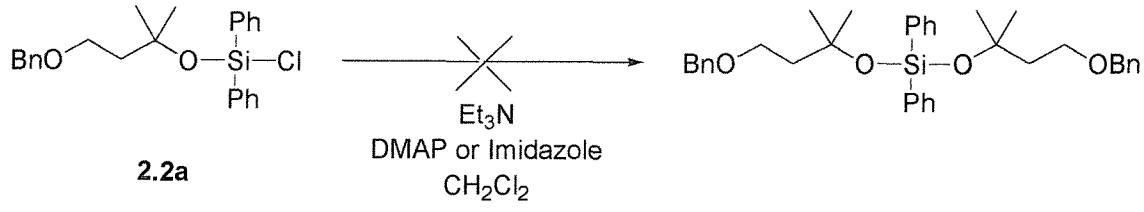
2.8 **2.9**

Figure 2.3 Possible intermediates of silyl chloride **2.2a**

In addition, compound **2.2a** was found to be reasonably stable under acidic and basic aqueous workup conditions, TLC analysis showing only slight decomposition.

To further ensure the formation of **2.2a**, the crude reaction mixture was reacted with *trans*-cinnamyl alcohol, affording siloxane **2.10** in 98% overall yield from **2.3a** (Scheme 2.3, page 47).

Interestingly, no further reaction between silyl chloride **2.2a** and the 3° alcohol **2.3a** was observed using the experimental conditions employed.



2.2a

Scheme 2.4 Possible further silylation of alcohol **2.3a**

It was encouraging to discover that silyl chloride **2.2a** was effectively unreactive towards 3° alcohol **2.3a** (even if DMF was employed as solvent), as this suggested that no cross-linking problems should arise during the corresponding step of the solid phase synthesis.

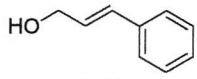
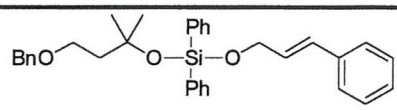
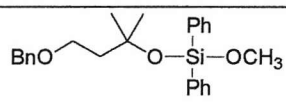
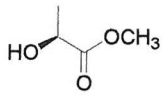
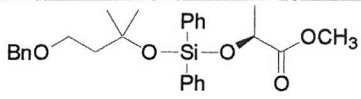
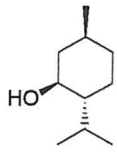
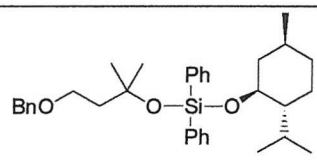
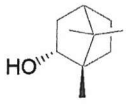
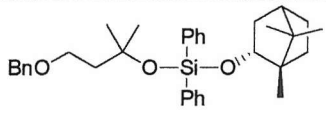
Having established an effective access to **2.2a**, several aspects of its formation had been elucidated. Firstly, the influence of the solvent in the rate formation of **2.2a** had been analysed. The solvents of choice were CH_2Cl_2 and DMF, as they are commonly employed in the silylation of alcohols; whenever CH_2Cl_2 or DMF were used no substantial difference was observed in the formation of **2.2a**, the reaction being complete in less than 30 minutes in both the cases. However it was decided to carry out all the reactions in CH_2Cl_2; this choice lies on its easier removal than DMF and, importantly, it is also less hygroscopic, as silylations of alcohols are usually performed under dry conditions.

Finally, the role of the catalyst was investigated. DMAP and imidazole were employed in two different experiments, and a faster reaction rate was observed with DMAP. Having optimized the conditions for the formation of silyl chloride **2.2a**, its reactivity with alcohols was investigated. Thus **2.2a** was reacted with a number of different alcohols in CH_2Cl_2 in the presence of DMAP at room temperature. In all cases excellent reactivity was observed with primary, secondary and bulky secondary alcohols, the silylations being complete in less than one hour, as examined by TLC analysis. After aqueous workup and chromatography, pure siloxanes **2.10-2.14** were obtained in excellent yield over two steps, starting from tertiary alcohol **2.3a**. For convenience, the silyl chloride **2.2a** was not isolated, and the crude reaction mixture was directly exposed to alcohols **2.15-2.19**, with Et_3N and DMAP. The results are summarized in Table 2.1

2.2a **2.10-2.14**

Scheme 2.5 (a) ROH, Et_3N, DMAP, CH_2Cl_2 rt

TABLE 2.1 Siloxanes obtained between reaction of silyl chloride **2.2a** and various alcohols

Alcohol employed	Siloxane	Yield[a, b]
 **2.15**	 **2.10**	98
CH_3OH **2.16**	 **2.11**	90
 **2.17**	 **2.12**	93
 **2.18**	 **2.13**	90
 **2.19**	 **2.14**	94

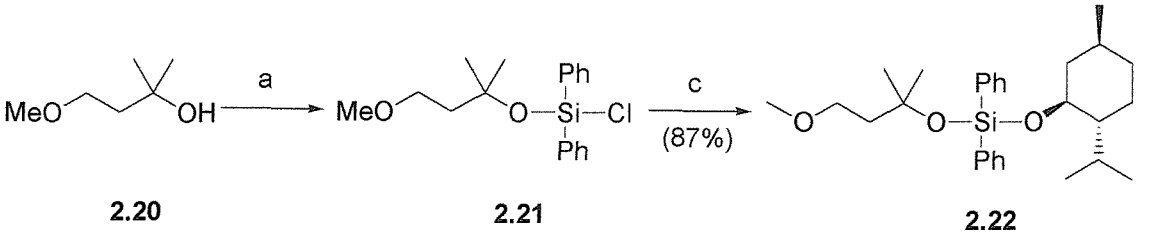
[a] All yields refer to the isolated compound (purified by column chromatography)
[b] Overall yield starting from alcohol **2.3a**

In addition, all the siloxanes **2.10-2.14** were found to be extremely stable to TLC analysis, and no decomposition was observed thus allowing their purification by column chromatography.

The next route of investigation was the reactivity dependence on the presence of a phenyl group in the chain, as this could interact with the two aromatic substituents on the silicon, with the result of a decreased reactivity.

To evaluate this second possibility, silyl chloride **2.21** was prepared using the same protocol employed to prepare **2.2a**. Thus **2.20** (obtained via a Williamson reaction between **2.4** and methyl iodide) was reacted with diphenyldichlorosilane to afford intermediate **2.21**, which was then exposed to menthol in the presence of Et_3N and

DMAP to give siloxane **2.22** in good yield in less than 1 hour (Scheme 2.6). This result suggested that the rate of silylation of the alcohols is unaffected by the presence of different substituents on the alkyl chain.



2.20 **2.21** **2.22**

Scheme 2.6 (a) Ph_2SiCl_2, Et_3N, DMAP, rt **(b)** Menthol Et_3N, DMAP, rt

The second aspect investigated was the reactivity dependence of silyl chloride **2.2a** on the presence of oxygen in the aliphatic chain. More precisely, it was postulated that the presence of the oxygen in the benzyl ether moiety could somewhat decrease the reaction rate of silylation via formation of an Lewis acid-Lewis base interaction between the oxygen of the linker model and the silicon, with the formation of a six membered structure, as illustrated in Figure 2.4

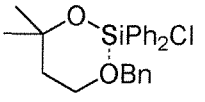
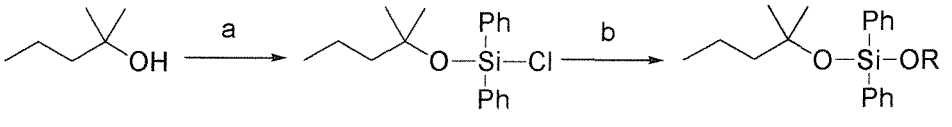


Figure 2.4 Possible Lewis acid-Lewis base interaction between the ether oxygen and the silicon atom

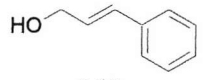
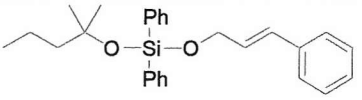
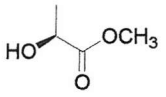
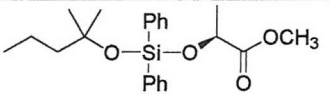
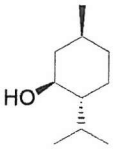
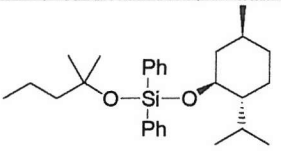
To evaluate this, an "all carbon chain" silyl chloride **2.24** was prepared by reacting **2.23** with diphenyldichlorosilane, and subsequently reacting with a variety of alcohols under the same experimental conditions previously reported (see Scheme 2.7), affording siloxanes **2.25-2.27** in excellent yields over 2 steps. This demonstrated that the reactivity of the original silyl chloride **2.2a** is not significantly affected by the presence of the heteroatom in the chain.



2.23 **2.24** **2.25-2.27**

Scheme 2.7 (a) Ph_2SiCl_2, Et_3N, DMAP, rt **(b)** ROH, Et_3N, DMAP, rt

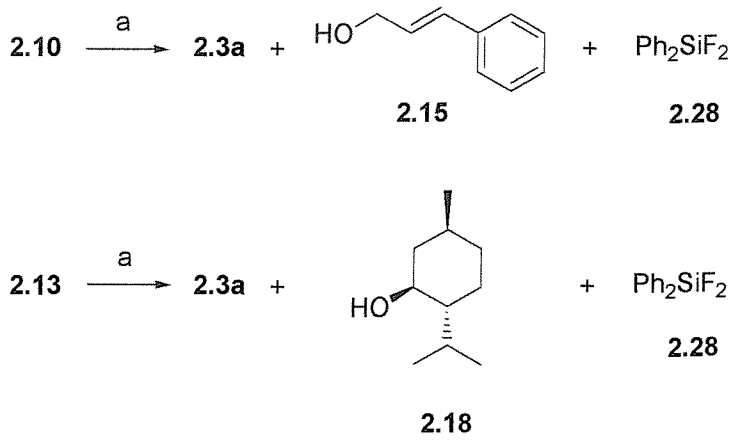
TABLE 2.2 Siloxanes obtained from reaction of silyl chloride **2.24** and various alcohols

Alcohol employed	Siloxane	Yield[a,b]
 **2.15**	 **2.25**	98
 **2.17**	 **2.26**	88
 **2.18**	 **2.27**	90

[a] All yields refer to the isolated compound (purified by column chromatography)
[b] Overall yield starting from alcohol **2.23**

Once a procedure for the silylation of alcohols had been determined and optimized, stability studies of the siloxane moiety were performed. In particular, the reactivity with the fluoride anion was investigated, as silyl ethers are known to be sensitive under these conditions.

Substrates **2.10** and **2.13** were chosen as a models and TBAF was employed as the fluoride source as it displays good solubility in THF, which will become important later in the development of the related solid phase chemistry. Siloxanes **2.10** and **2.13** were dissolved in THF and reacted with 2 equivalents of TBAF at room temperature. TLC analysis showed that complete decomposition of the substrates occurred within 10 minutes, along with the formation of the two alcohols **2.15** and **2.18** and the tertiary alcohol **2.3a**. Purification furnished alcohols **2.15**, **2.18** and **2.3a** in quantitative yield, along with the diphenyldifluorosilane **2.28**. The formation of this latter demonstrated that the fluoride anion cleaved both the Si-O bonds of the siloxane, showing at the same time that both primary and secondary hindered alcohols can be deprotected very rapidly.



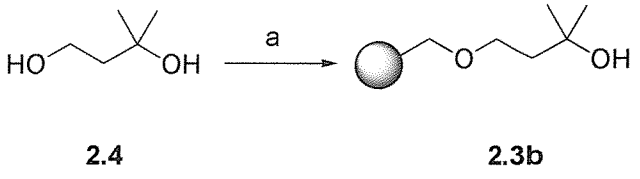
Scheme 2.8 (a) TBAF, THF, rt

To summarize, an extensive investigation was carried out using a solution phase model of linker **2.1a**. An excellent protocol for the synthesis of silyl chloride **2.2a** was developed from cheap and readily available starting materials. It was discovered that alcohol **2.3a** is silylated rapidly only once and the resulting silyl chloride readily silylates a broad variety of alcohols, including some secondary hindered ones, but does not react readily with tertiary alcohols.

The following part of the chapter will describe the synthesis of the diphenylsilyloxychloride resin **2.1a**, by adaptation of the experimental procedures successfully employed in the solution phase model.

2.1.3 Solid phase synthesis of linker 2.1a

Once the solution phase model was successfully completed, attention was focused to the solid phase synthesis of **2.1a**. A Williamson reaction between the sodium salt of **2.4** and Merrifield resin afforded **2.3b**, as shown in Scheme 2.9



Scheme 2.9 (a) NaH, DMF, 0 °C, then Merrifield resin, 0 °C to rt

The formation of **2.3b** was supported by the FT IR of one dried sample of beads and from the gel phase ^{13}C NMR.

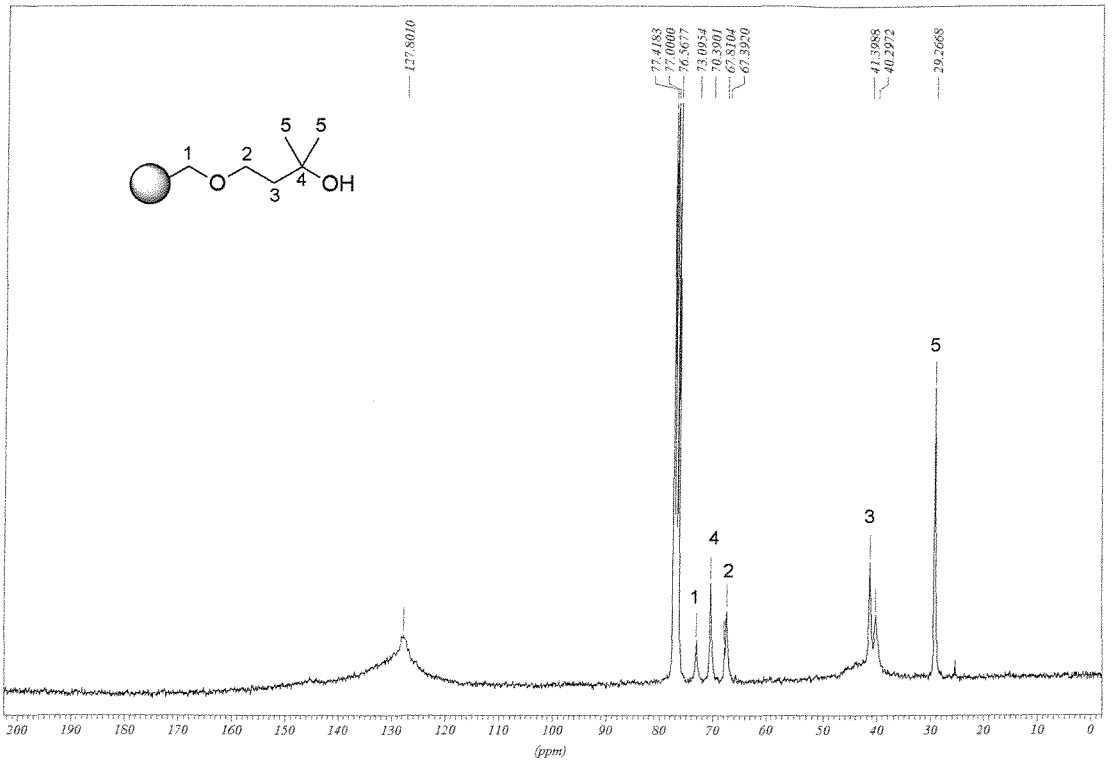
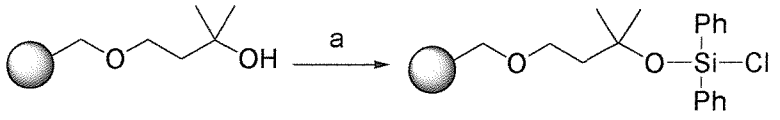


Figure 2.5 Gel phase ^{13}C NMR of intermediate resin **2.3b**

In order to obtain the silyl chloride resin, **2.3b** was treated with Ph_2SiCl_2 in dry CH_2Cl_2 as solvent, in the presence of Et_3N and DMAP (Scheme 2.10).

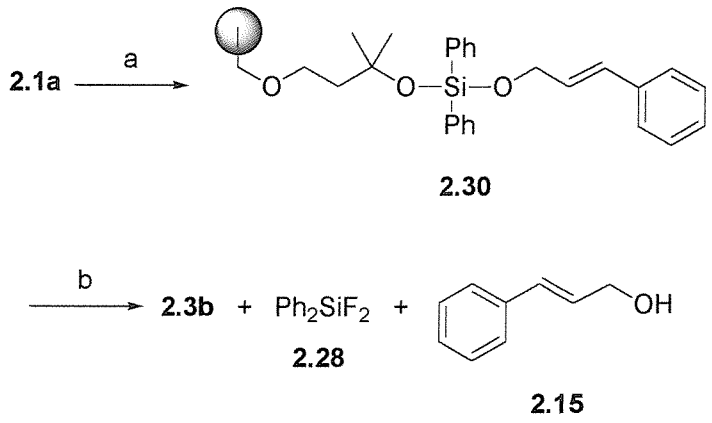


2.3b **2.1a**

Scheme 2.10 (a) Ph_2SiCl_2, Et_3N, DMAP, rt

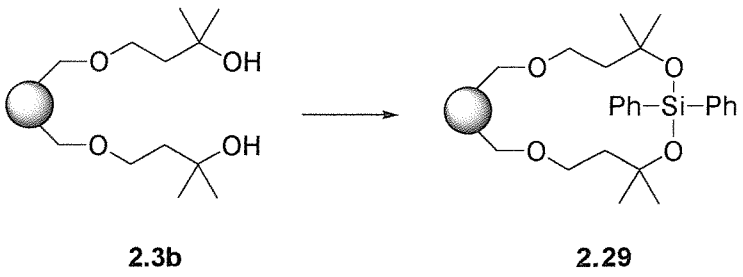
The resulting intermediate resin **2.1a** was rinsed with dry CH_2Cl_2, and reacted with *trans*-cinnamyl alcohol in presence of Et_3N and DMAP (Scheme 2.11). We were pleased to observe that subsequent exposure of **2.30** to TBAF in THF at room temperature led to the recovery of the *trans*-cinnamyl alcohol **2.15**, along with **2.28**, as

shown by the TLC analysis. This inferred the formation of the silyl chloride resin **2.1a** and its successful reaction with the alcohol.



Scheme 2.11 (a) *trans*-cinnamyl alcohol, Et_3N, DMAP, rt **(b)** TBAF, THF, rt

Importantly, this last result demonstrated also the absence of any crosslinking problems that could have arisen after reaction between Ph_2SiCl_2 and and two neighbouring alcohols onto the resin to form **2.29**, as illustrated in Scheme 2.12. The possible absence of this problem was also anticipated from the extensive solution phase investigation (Section 2.2.2, page 47).



Scheme 2.12 Possible crosslinking of resin **2.3b** with diphenyldichlorosilane

In order to check the complete deprotection of the alcohol **2.15**, the resin recovered from the cleavage reaction was re-exposed to the same amount of TBAF under the same experimental conditions. No further alcohol cleaved was detected, demonstrating that the deprotection occurred completely with the first TBAF treatment.

2.1.4 Loading determination of linker 2.1a

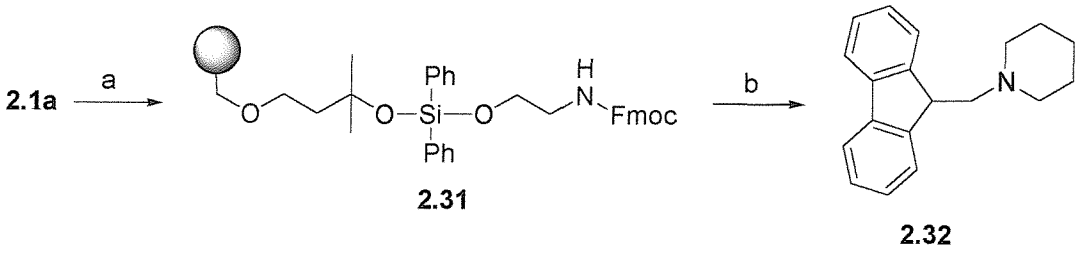
Having established the synthesis of **2.1a**, a major priority was the determination of the loading of silyl resin **2.1a**. This goal was achieved in two different ways.

2.1.4.1 GC quantification of cleaved material

In this method the resin bound silyl chloride **2.1a** was reacted with *trans*-cinnamyl alcohol to afford siloxane resin **2.30** following the sequence previously described (see Scheme 2.11). Then a known amount of dried resin **2.30** was taken and treated with TBAF. The reaction was allowed to run for 2 hours and after workup the organic solution was analysed by GC and the released *trans*-cinnamyl alcohol was quantified with standard solutions.

2.1.4.2 Quantification by Fmoc Assay

In this method an *N*-Fmoc amino alcohol was attached to the silyl chloride resin **2.1a** under the usual conditions to afford siloxane **2.31**. It is important to underline that under these coupling conditions no cleavage of the Fmoc was detected. A known amount of the dried resin **2.31** was then treated with a 20% solution of piperidine in DMF and the piperidine fulvene adduct released **2.32** was quantified by UV absorbance at 302 nm (Scheme 2.13). The simplest available amino alcohol, *N*-Fmoc aminoethanol, was chosen for this study.



2.31 **2.32**

Scheme 2.13 (a) *N*-Fmoc glycinol, Et_3N, CH_2Cl_2, DMAP, rt **(b)** 20% piperidine, DMF

Both methods were applied to the loading determination of the silyl chloride resin **2.1a** and a value of 0.2 mmol/g was initially found. This value was found to be quite low with respect to the theoretical loading (1.1 mmol/g, starting from the commercially

available Merrifield resin of 1.6 mmol/g). Therefore the resin loading was the subject of further investigation.

2.1.5 Preparation of silyl chloride resin 2.1a with an improved loading

The solution phase model had shown clearly that Ph_2SiCl_2 rapidly silylates alcohol **2.3a** only once, to afford **2.2a**, suggesting that cross linking problems during the silylation of resin **2.3b** in the second step of the solid phase synthesis would be unlikely. In addition, it has been observed that the formation of alcohol **2.3a** in solution did not reach the completion as some unreacted starting material was recovered (see Section 2.1.2, page 47). Combining these pieces of experimental evidence, it was proposed that the low loading of **2.1a** could be due to an inefficiency of the first step, possibly increased by the low solubility of the sodium salt of **2.4** in DMF at room temperature. The overall synthesis of resin **2.1a** was therefore repeated, performing the first step at 60 °C; the other steps were performed in the same way as previously described (see Section 2.1.3, Schemes 2.10 and 2.11, pages 54 and 55). However no substantial increase in the final resin loading was observed (still 0.2 mmol/g).

It was then decided to change the experimental conditions for the ether formation. Following a literature procedure,[89] diol **2.4** was reacted with Merrifield resin in the presence of potassium *tert*-butoxide in dry THF at room temperature for 3.5 days. All the subsequent reactions were carried out in the usual way. It was encouraging to observe that the modified ether bond formation was more efficient; after the two steps, a loading of 0.6 mmol/g was found, demonstrating the inefficiency of the original ether forming conditions. In a third experiment, the first step was performed with 18-crown-6 **(2.33)** (see Figure 2.6) as phase transfer catalyst, resulting in a final loading of 0.65 mmol/g for resin **2.1a** which corresponded to 60%, with respect to the theoretical loading.

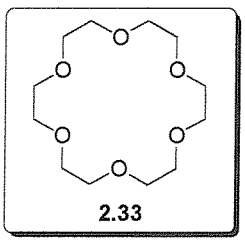


Figure 2.6 Structure of 18-Crown-6

In a second instance attention was turned to enhance the reaction rate. Originally, immobilization of the diol **2.4** on Merrifield resin was performed over 3.5 days at room temperature, resulting in a very time consuming reaction. However, this long period was necessary to obtain the loading previously reported. This was realized by performing the attachment of diol **2.4** on Merrifield resin over 1 or 2 days, and using **2.3b** for the preparation of the silyl chloride (see Section 2.1.3, Schemes 2.9 and 2.10, pages 53 and 54): in both cases a lower loading of **2.1a** was found. With this in mind, attention was paid to enhance the reaction rate. In particular the use of microwave irradiation was investigated. [90] Attachment of diol **2.4** was carried out at 120 °C employing two different reaction times. The other steps were performed as usual (see Section 2.1.3, Scheme 2.11, page 55). This further modification proved to be successful, as the loading of the corresponding silyl chloride resin was found to be 0.7 mmol/g in both the cases, now corresponding to a 65% of the theoretical loading.

To summarize, the results for the loading of **2.1a** prepared under various reaction conditions on the first step of the synthesis are illustrated in Table 2.3

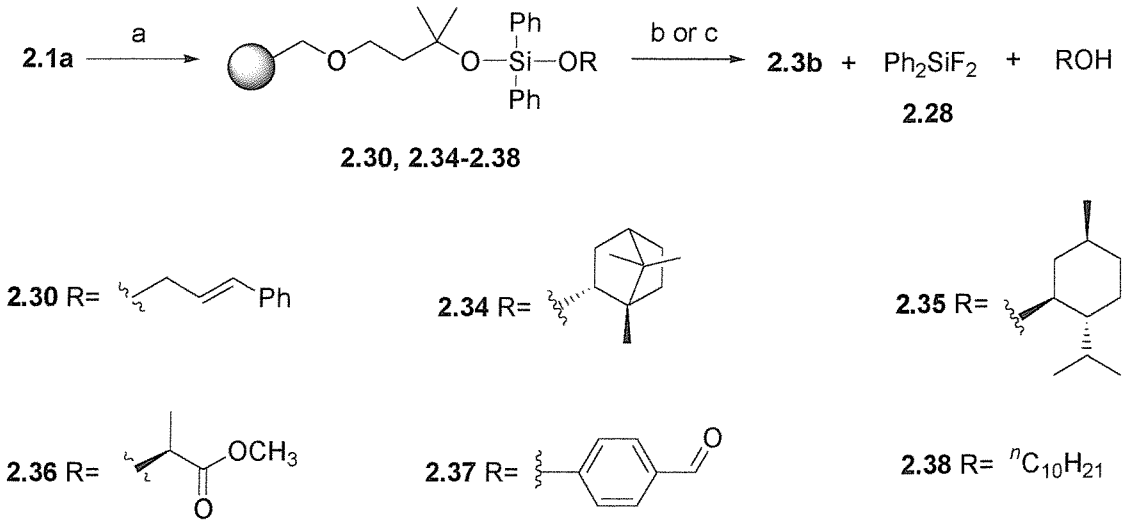
TABLE 2.3 Improvements in the loading of **2.1a** after modification of the first step of the synthesis (Scheme 2.9, page 51).

Base	Solvent	Temp (°C), Time	PTC	Loading (mmol/g)
NaH	DMF	rt, 24h	No	0.20
NaH	DMF	60, 24h	No	0.23
^{t}BuOK	THF	rt, 3.5 days	No	0.60
^{t}BuOK	THF	rt, 3.5 days	Yes	0.65
^{t}BuOK	THF	μω, 120, 5 min	Yes	0.70
^{t}BuOK	THF	μω 120, 10 min	Yes	0.70

2.1.6 Investigation of the reactivity of resin 2.1a with different alcohols

As discussed previously (see Introduction, Section 1.4.1.2), one of the principal roles of silyl linkers is their ability to act as a supported protecting group for the immobilization of alcohols. With this in mind a detailed study of the reactivity of linker **2.1a** with a range of hydroxyl containing compounds was carried out. To demonstrate its versatility, silyl chloride resin **2.1a** was reacted with primary, hindered secondary and tertiary

alcohols (Scheme 2.14). The reactions were performed under the previously described conditions (see Section 2.1.3, Scheme 2.11, page 55) and afforded the corresponding siloxanes resins **2.30** and **2.34-2.38**, as determined by FT IR and gel phase ^{13}C NMR studies of some of the resins.



Scheme 2.14 (a) ROH, Et_3N, DMAP, CH_2Cl_2 rt **(b)** TBAF, THF **(c)** KF, 18-Crown-6, THF

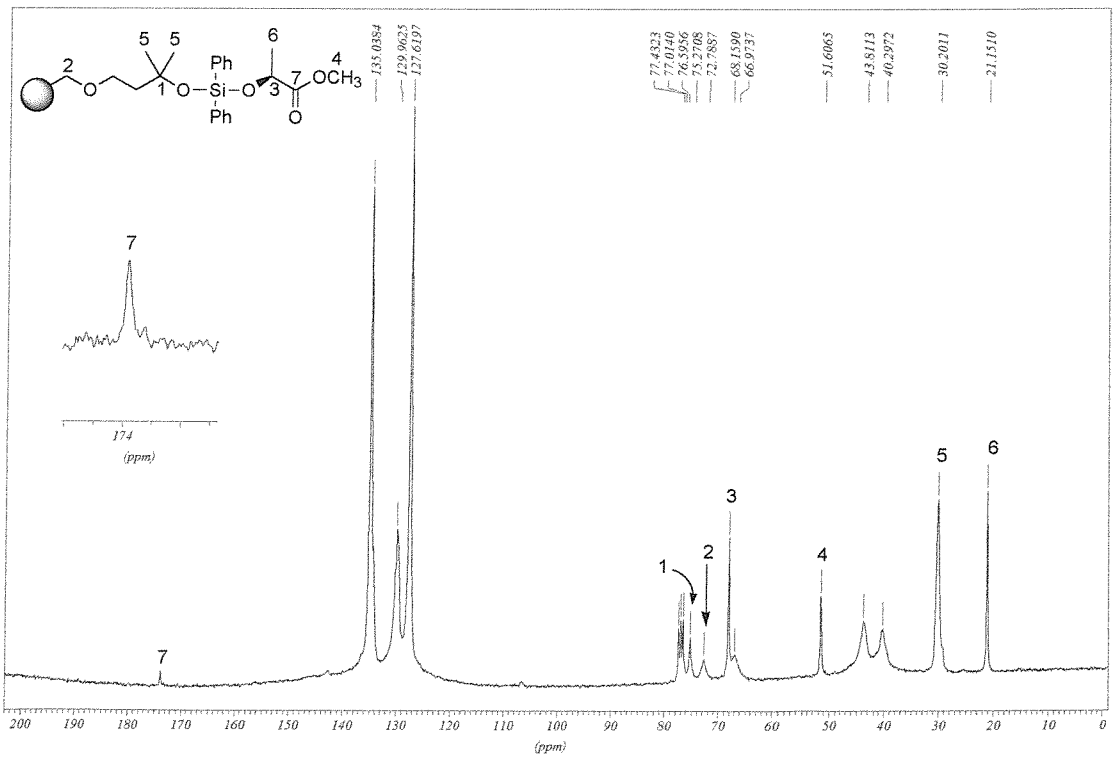
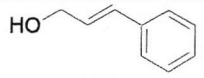
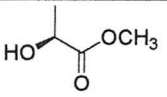
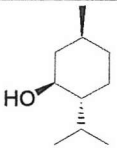
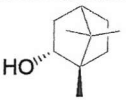
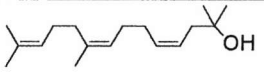
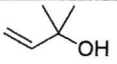
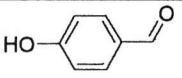


Figure 2.7 Gel phase ^{13}C NMR of ester bound resin **2.36**

In order to quantify the yield of the coupling, resins were treated with TBAF and the cleaved solutions were analysed by GC analysis. In most of the cases an aqueous workup was required to eliminate the TBAF from the reaction mixture. However, in the case of water-soluble compounds, such as *S*-methyl lactate, this procedure was avoided. In this case the cleavage mixture was concentrated under reduced pressure and the compound purified by passage through a short silica gel column. Alternatively, to avoid workup, the release of the alcohol can be effectively accomplished using potassium fluoride in THF, using a catalytic amount of 18-Crown-6 as a phase transfer catalyst. In this way the solution can be collected and analysed directly by GC analysis.

Under the conditions reported, primary and hindered secondary alcohols such as menthol, were found to react readily with the silyl chloride resin **2.1a** in high yields within one hour (Table 2.4). A different result was found with tertiary alcohols. In this case immobilization did not occur at all, even after running the coupling reaction in DMF for 24 hours at room temperature. This result suggested that tertiary alcohols are unreactive towards **2.1a**.

TABLE 2.4 Alcohols attached to resin **2.1a** and quantified after exposure of siloxanes **2.30** and **2.34-2.38** to TBAF

Alcohol	Cleavage reagent	Yield
 **2.15**	TBAF or KF 18-Crown-6	Quant. [a]
 **2.17**	TBAF	95
 **2.18**	TBAF	96
 **2.19**	TBAF	95
$^{n}C_{10}H_{21}OH$ **2.39**	TBAF	70
 **2.40**	TBAF	0
 **2.41**	TBAF	0
 **2.42**	TBAF	96

[a] Based on the assumption that *trans*-cinnamyl alcohol reacted completely with **2.1a**

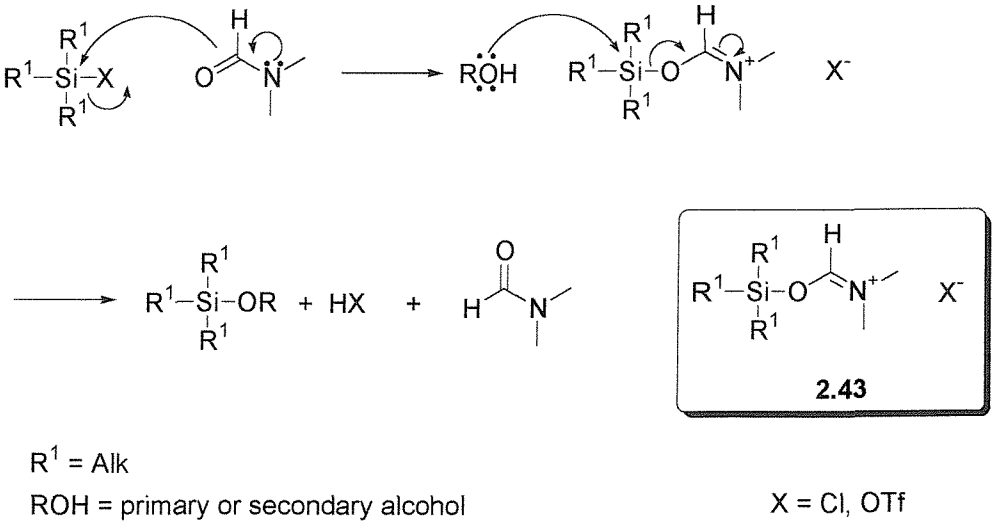
2.1.7 Silylation of diols

One important application of silicon linkers is their ability to preferentially protect primary alcohols over the secondary alcohols. This mainly lies in the difference in reactivity between primary and secondary alcohols and on the steric hindrance of the groups on the silicon; as a rule, the greater the bulkiness of the substituents, the greater is the selectivity. For example, as previously stated (see Introduction, Section 1.4.1.2,

page 8) polystyrene diphenylsilyl chloride is reported to silylate primary alcohols in good yields and selectivity.

As already mentioned, linker **2.1a** closely resembles *tert*-butoxydiphenylsilyl chloride **2.5**, which, in the absence of DMAP, readily silylates primary alcohols in good yields and selectivity due to the presence of the two bulky phenyl groups on the silicon. [50] On the basis of this information it was felt that resin **2.1a** could be employed for the selective protection of primary alcohols under "DMAP-free" silylation conditions.

For our purpose a range of functionalised diols **2.53-2.55** was chosen (Scheme 2.16). We chose to carry out reactions in CH_2Cl_2 because previous studies showed that silylating agents can react with the DMF to afford intermediate **2.43** (Scheme 2.15), [91] which is more reactive than the silyl chloride and can react with both primary and secondary alcohols at a comparable rate. [50]

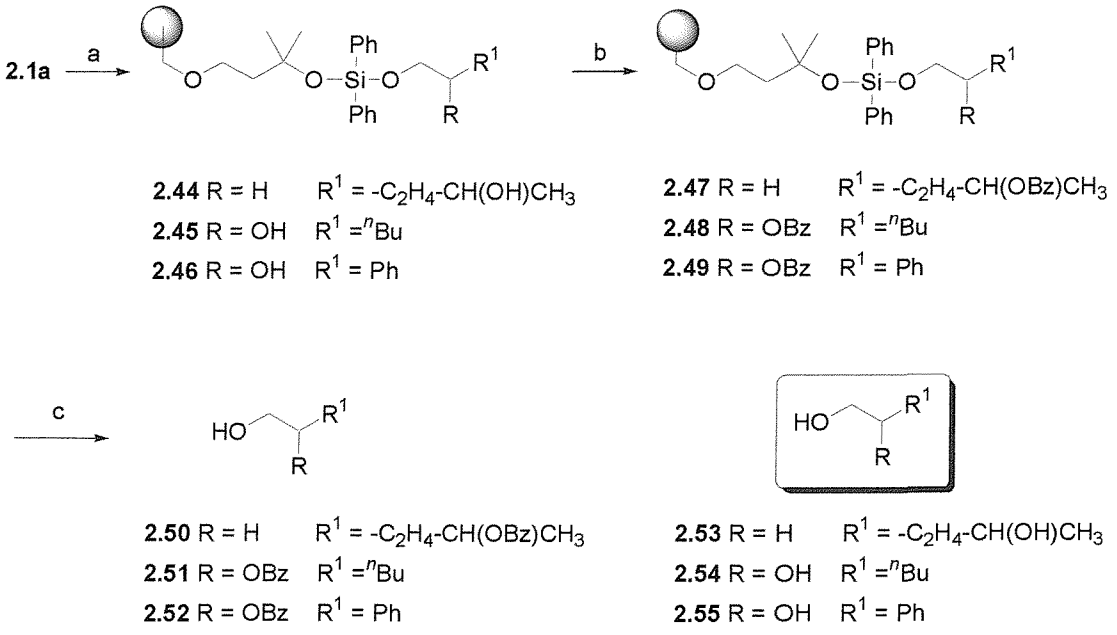


Scheme 2.15 Silylation of primary and secondary alcohols via formation of postulated intermediate **2.43**

After generation of resin **2.1a** and repeated washing with dry CH_2Cl_2 to remove any trace of DMAP, the attachment of the diols was then performed in CH_2Cl_2 and Et_3N. The reactions were monitored by FT IR spectroscopy and in all the cases the dried resins showed a broad band tentatively assigned to the presence of a hydroxyl group. At this point a method to test the selectivity of resin **2.1a** was required. It was felt that the acylation of the free remaining OH followed by cleavage and quantification of the corresponding secondary monoesters would provide a useful means to achieve this (Scheme 2.16). However, attention had to be paid to the stability of the corresponding

products under the cleavage conditions, as the fluoride anion has been observed to promote transesterification of monoesters of diols, which would make the selectivity study meaningless. [92] Treatment of resin **2.47** with either TBAF and KF/18-crown-6 afforded a mixture of the primary and secondary monobenzoylated esters (See Table 2.6, page 62) and the absence of 1,5-hexanediol **2.53**, suggesting that transesterification had occurred.

In order to overcome to this problem the cleavage conditions were modified. The adapted cleavage protocol involved the use of HF·Pyr, as monoesters of diols are less prone to transesterification under acidic conditions. Resins **2.47-2.49** were treated with HF·Pyr and the crude products purified, affording compounds **2.50-2.52** in 80, 81 and 75% yield, respectively, based on the loading of the silyl chloride resin **2.1a** (Scheme 2.16 and Table 2.5).



2.44 R = H R^1 = $-C_2H_4$-CH(OH)CH_3
2.45 R = OH R^1 = ^{n}Bu
2.46 R = OH R^1 = Ph

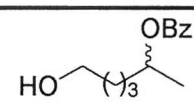
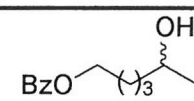
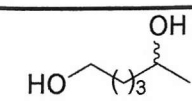
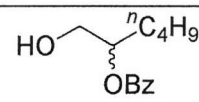
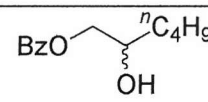
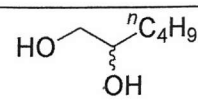
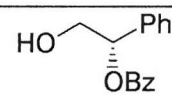
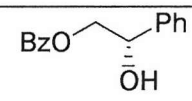
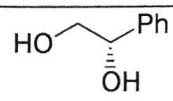
2.47 R = H R^1 = $-C_2H_4$-CH(OBz)CH_3
2.48 R = OBz R^1 = ^{n}Bu
2.49 R = OBz R^1 = Ph

2.50 R = H R^1 = $-C_2H_4$-CH(OBz)CH_3
2.51 R = OBz R^1 = ^{n}Bu
2.52 R = OBz R^1 = Ph

2.53 R = H R^1 = $-C_2H_4$-CH(OH)CH_3
2.54 R = OH R^1 = ^{n}Bu
2.55 R = OH R^1 = Ph

Scheme 2.16 (a) 2.53 2.54, or **2.55**, Et_3N, CH_2Cl_2, rt **(b)** BzCl, pyridine, CH_2Cl_2, rt **(c)** HF·Pyr, rt

TABLE 2.5 Selective silylation of resin **2.1a** with a variety of diols

Diol	Products[a]		
2.53			
	2.50 80%	none	**2.53** none
2.54			
	2.51 81%	**2.56** 8%	**2.54** 9%[b]
2.55			
	2.52 75%	**2.57** 13%	**2.55** 10%[b]

[a] All yields refer to the isolated purified compound
[b] Recovered after cleavage with HF·Pyr

In the case of resin **2.47**, only **2.50** was obtained after column chromatography, with no other products detected. Further confirmation was obtained from gel phase ^{13}C NMR analysis of resin **2.44** (Figure 2.8).

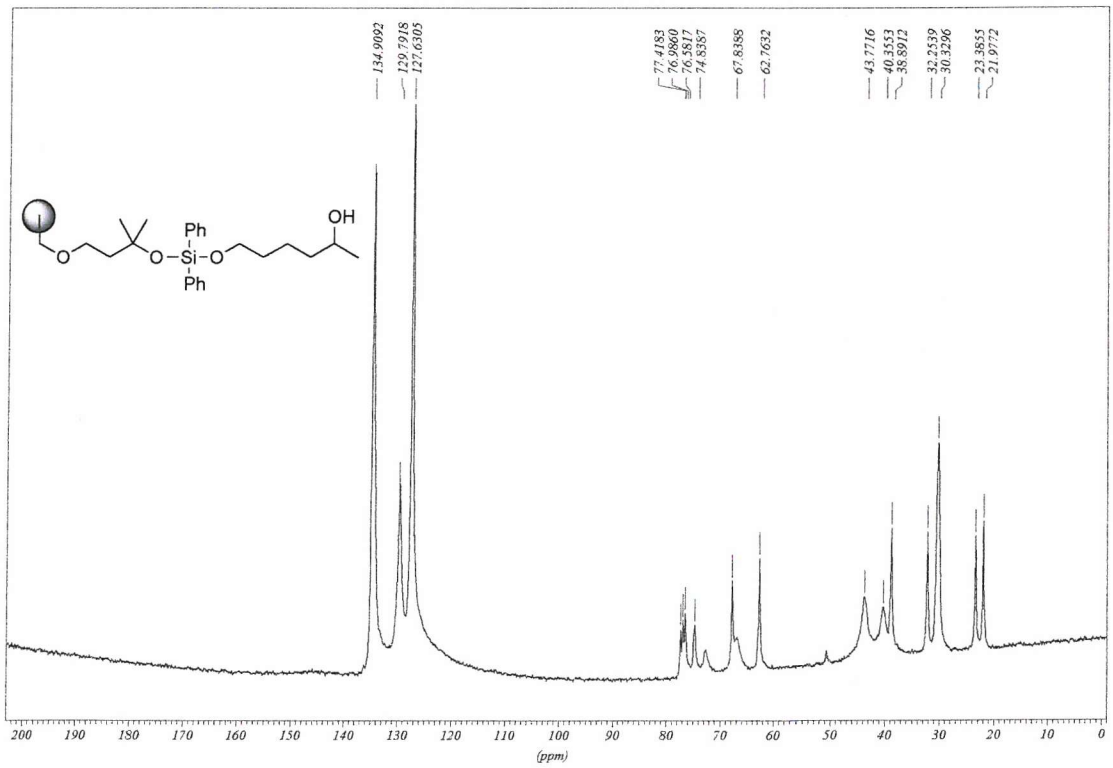
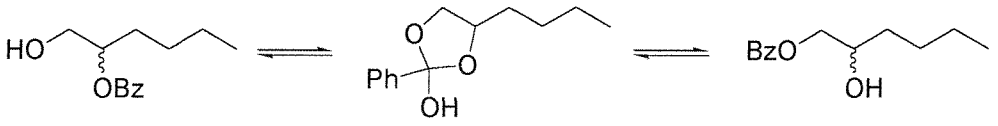


Figure 2.8 Gel phase ^{13}C NMR of intermediate resin **2.44**

In the case of 1,2-diols slightly different results were found: cleavage from **2.48** and **2.49** gave **2.51** and **2.52**, respectively, as main compounds, along with a small percentage of the other regioisomers **2.56** and **2.57** and the original 1,2-diol. However the only signal in the gel phase ^{29}Si NMR of resin **2.49** suggested that a lack of selectivity was unlikely. It was then postulated that compounds **2.51** and **2.52** can undergo transesterification even during these cleavage conditions. This behavior is quite common for monoesters of 1,2-diols, as the isomerization occurs via the 5-member ring intermediate **2.58**. [92]



2.51 **2.58** **2.56**

Figure 2.9 Five-membered intermediate involved in the transesterification of mobenzoyl esters of the 1,2-hexanediol

This behavior has not been encountered for the monoester of the 1,5-hexanediol: isomerization in this case is much slower as it does not occur via the same transition state. In summary in this section it has been elucidated that silyl resin **2.1a** may be employed for the selective silylation of primary alcohols.

2.1.8 Long term stability studies of resin 2.1a

To date, little was known about the long term stability of silyl chloride resin **2.1a**. As a consequence, it was generated immediately before the alcohol attachment step. This was found to be an extremely reliable method, though quite time consuming, especially when resin **2.1a** was required for the protection of several different alcohols. Consequently, a study into the long term stability of **2.1a** is extremely attractive as it opens up the possibility of preparing **2.1a** in larger quantities. Therefore a batch of resin **2.1a** was prepared and, after removal of the impurities, the resin was dried for 24 hours and stored in the freezer. In order to check the long term stability, the loading of **2.1a** was calculated on the same batch every month using the methods reported above (see Sections 2.1.4.1 and 2.1.4.2, page 56). The results are summarized in Table 2.6

TABLE 2.6 Loading values of resin **2.1a** after fixed amounts of time

Time	Loading found (mmol/g)
After 1 month	0.65
After 2 months	0.65
After 3 months	0.65
After 4 months	0.65
After 5 months	0.64

The experimental data displayed in Table 2.6 inferred the long term stability of silyl chloride resin **2.1a**. The consequence of this last result means a more simplified procedure for the alcohol attachments, as the need to generate **2.1a** immediately before the alcohol protection can be avoided.

2.1.9 Stability studies of the siloxane moiety

The next priority was to evaluate the degree of stability of the siloxane linker under conditions usually employed for the SPOS. The stability of the linker with acids, such as acetic acid and TFA, and strong bases, such as LDA and ^{t}BuOK was investigated. This choice lies on their extensive employment in the field of solid phase chemistry: as an example, LDA has been successfully used for the formation of supported enolates, [17, 93-96] whereas TFA has been used to remove trityl ethers in presence of a Tentagel type linker. [97] *Trans*-cinnamyl alcohol bound resin **2.30** was chosen as substrate, and in a first reaction was treated with a known amount of TBAF; the alcohol released was then quantified by GC analysis. As the deprotection was shown to be quantitative under these conditions (see Section 2.1.3, page 55), the amount of alcohol coming off from the resin was taken as standard for the successive measurements. Resin **2.30** was subsequently treated with various acids and bases in different concentrations, and after

fixed amounts of time the solution was collected and analysed by GC in comparison with the standard solution. All the results obtained are summarized in Table 2.7

TABLE 2.7 Results obtained from the kinetic studies of the diphenylsiloxane linker with different acids and bases

Reagent	Solvent	Quantity	Time	T(°C)	Alcohol cleaved
LDA	THF	1 eq	2.5h	0	0
LDA	THF	2.5 eq	2.5h	0	0
^{t}BuOK	THF	1 eq	2.5h	0	0
^{t}BuOK	THF	2.5 eq	2.5h	0	0
HCOOH	CH_2Cl_2	1% v/v	24h	rt	0
TFA	CH_2Cl_2	1% v/v	2 min	rt	53%

The results obtained were quite good. In fact in all the cases investigated an excellent stability of the linker was observed, apart from the last case, in which the TFA cleaved the linker considerably, only after 2 minutes.

To confirm further, the resin coming from the treatment with 2.5 equivalents of LDA was thoroughly washed, dried and treated with TBAF, affording exactly the theoretical amount of alcohol expected, and definitely demonstrating that no cleavage at all occurred during LDA exposure.

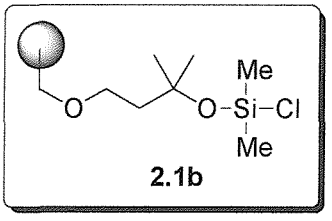
2.1.10 Conclusions

In conclusion, in this part of the work a novel silyl chloride resin **2.1a** was successfully synthesized. The key step is the regioselective attachment of the diol **2.4** to the Merrifield resin, to afford tertiary alcohol resin **2.1a**. The resulting supported tertiary alcohol can be easily employed to obtain a silyl chloride resin in a concise and straightforward way. The optimized conditions initially developed in solution were readily transferred to the solid phase, with excellent and consistent results. In addition, considerable improvements in the loading and on the reaction times were achieved. The resulting resin **2.1a** proved stable to prolonged storage and showed excellent reactivity with primary and secondary alcohols. [98] The resulting siloxane moiety was shown to be

stable to a variety of acids and bases. Finally, resin **2.1a** preferentially silylates primary alcohols over secondary ones; this last feature could be useful, as silyl chloride **2.1a** can be conveniently employed as a supported reagent for the scavenging of mixture of primary and secondary alcohols in solution.

Despite all of these good results, some drawbacks of resin **2.1a** were encountered, such as the loading value, the lack of reactivity with tertiary alcohols and finally its sensitivity to strong acids such as TFA, even if present in very low concentrations. With this in mind, we went on to try to overcome each of these drawbacks by synthesizing different linkers. The next sections will then cover the synthesis of these other linkers.

2.2 Synthesis of linker 2.1b



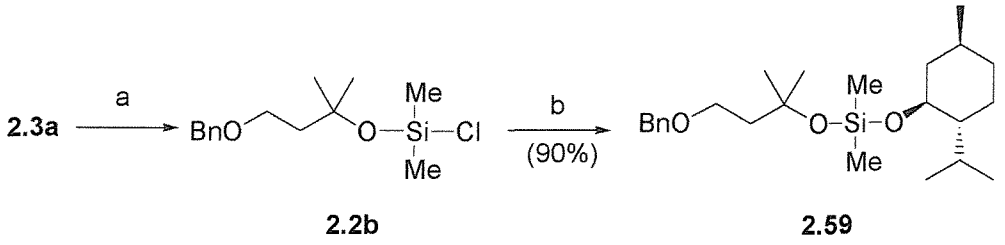
2.1b

It was outlined above that the reactivity of linker **2.1a** with tertiary alcohols was low; this feature is due to the presence of two bulky substituents on the silicon. On this basis it was felt that the dimethyl analogue **2.1b** should display enhanced reactivity with tertiary alcohols. An added benefit of linker **2.1b** respect to **2.1a** is the easy removal of the byproducts after fluoride cleavage, as the resulting Me_2SiF_2 is a gas, whereas Ph_2SiF_2 is an high boiling liquid.

To allow further investigation, resin **2.1b** was prepared and its reactivity investigated.

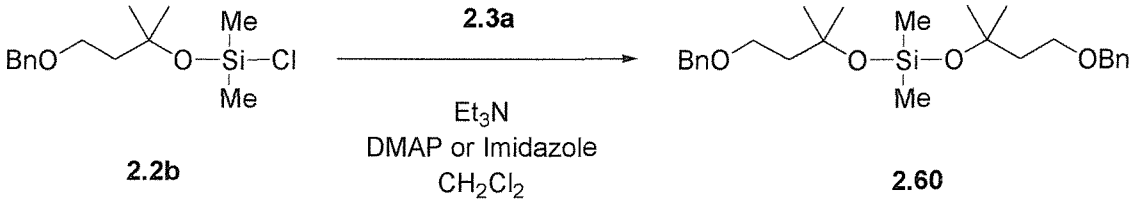
2.2.1 Solution phase synthesis for linker 2.1b

Before attempting any solid phase synthesis, a short preliminary investigation in solution was carried out, in order to validate the chemistry. Alcohol **2.3a** was reacted with dimethyldichlorosilane, in dry CH_2Cl_2 using Et_3N as base and DMAP as catalyst. The resulting silyl chloride **2.2b** was directly reacted with menthol to afford the corresponding siloxane in 90% yield over the last two steps (Scheme 2.17).



2.2b **2.59**

Scheme 2.17 (a) Me_2SiCl_2, Et_3N, DMAP, CH_2Cl_2 **(b)** Et_3N, menthol, DMAP, CH_2Cl_2, rt



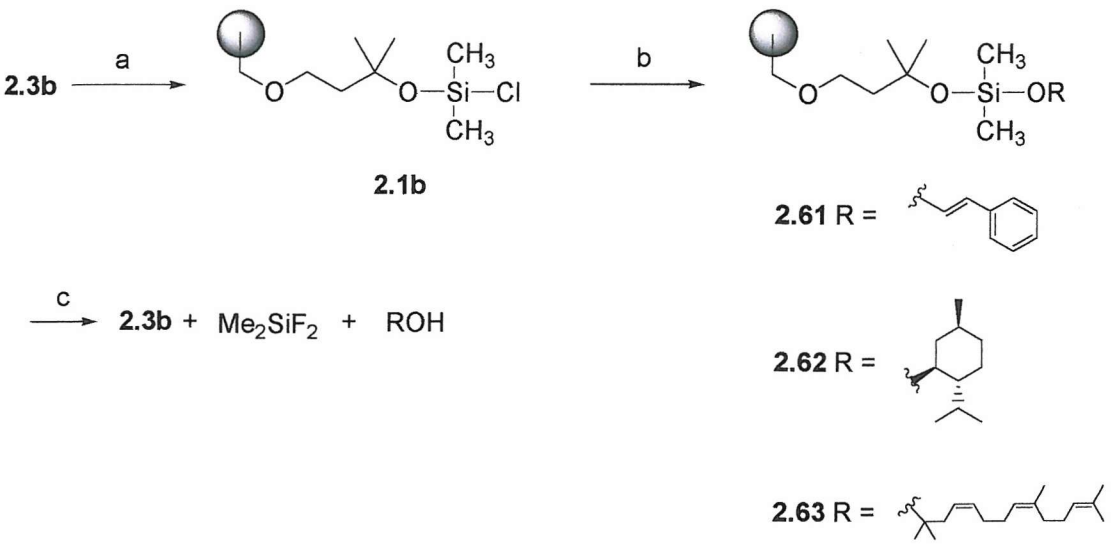
2.2b **2.60**

Scheme 2.18 Further silylation of alcohol **2.3a**

The formation of the silyl chloride **2.2b** occurred less cleanly than the corresponding diphenyl analogue. The reason lies in the double silylation of alcohol **2.3a** with the dimethyldichlorosilane, to afford **2.60**, as indicated by the crude ^1H NMR of the reaction mixture. Importantly, **2.59** was observed to be stable during column chromatography.

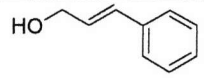
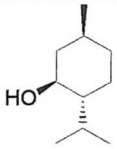
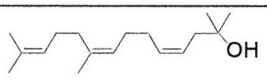
2.2.2 Solid phase synthesis and reactivity with alcohols

The solid phase synthesis of **2.1b** is very similar to that of resin **2.1a**. The action of an excess of dimethyldichlorosilane on **2.3b** with Et_3N and DMAP afforded resin **2.1b** which was then reacted with primary, secondary and tertiary alcohols (Scheme 2.19). The loading of **2.1b** was determined using the two methods previously reported for the linker **2.1a** (see Sections 2.1.4.1 and 2.1.4.2, page 56) and was found to be 0.37 mmol/g.



Scheme 2.19 (a) Me_2SiCl_2, Et_3N, DMAP, rt **(b)** ROH, Et_3N, DMAP, rt **(c)** TBAF, THF, rt

TABLE 2.8 Alcohols attached to resin **2.1b** and subsequently cleaved

Alcohol	Cleavage reagent	Yield
 **2.15**	TBAF or KF 18 Crown 6	Quant. [a]
 **2.18**	TBAF	96
 **2.40**	TBAF	95

[a] Based on the assumption that *trans*-cinnamyl alcohol reacted completely with **2.1b**

Gratifyingly tertiary alcohols were successfully immobilized with excellent yields in the conditions reported (Table 2.8), along with primary and secondary ones. Further confirmations arose from the gel phase ^{13}C NMR of some of the resins. Here, the

dimethylsiloxane moiety present in the resin is clearly indicated by the two peaks near 0 ppm (Figure 2.10).

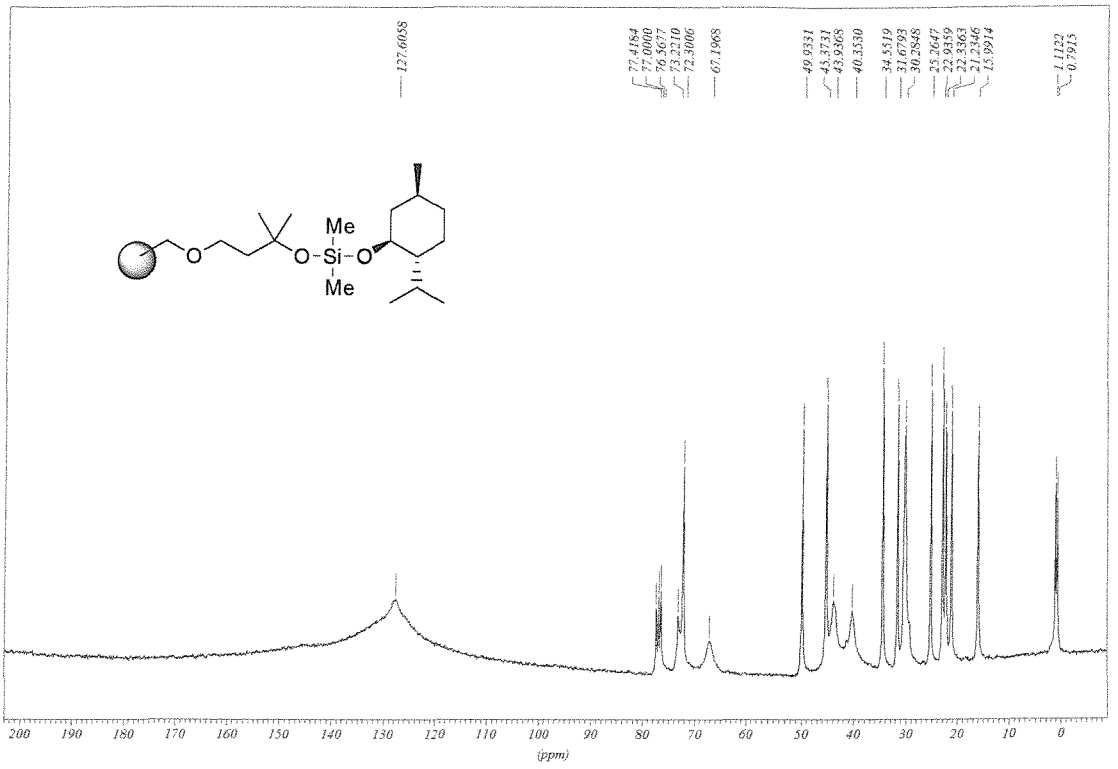


Figure 2.10 Gel phase ^{13}C NMR of menthol bound resin **2.62**

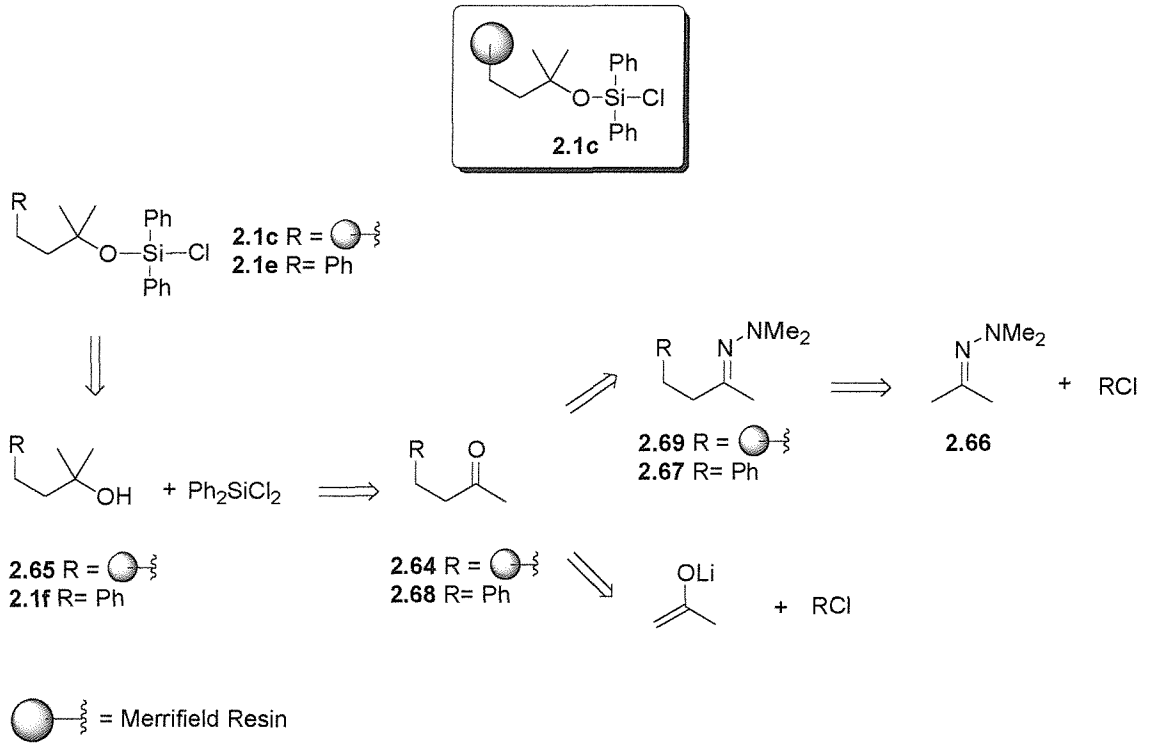
In conclusion, the problem of the reactivity between resin **2.1a** and tertiary alcohols was overcome by using the dimethyl resin **2.1b**, which showed excellent reactivity with all the alcohols considered.

However, despite the excellent results obtained, a low loading for **2.1b** was observed with respect to the theoretical one. This could have been due to the lower stability of the silyl chloride resin **2.1b** or to crosslinking during the second step of the synthesis, although the ^{13}C and ^{29}Si spectroscopy on resin **2.62** showed that this last possibility was unlikely. For these main reasons it was decided not to investigate this linker any further.

2.3 Synthesis of linker 2.1c

It has been previously shown that resin **2.1a** undergoes preferential silylation of primary alcohols over secondary ones. This selectivity could make resin **2.1a** quite interesting, as it could be employed as a supported scavenger for primary alcohols in solution. In

this context a higher value of loading (typically not less than 1 mmol/g) would be desirable. For these reasons several attempts to increase the loading were carried out (see Section 2.1.5, pages 57 and 58), but the loading values were still significantly lower than the theoretical value. It was felt that to overcome these problems an alternative 3° alcohol resin **2.1c** could be prepared (Scheme 2.20).



Scheme 2.20 Retrosynthetic pathways adopted for linker **2.1c** and for its analogue in solution

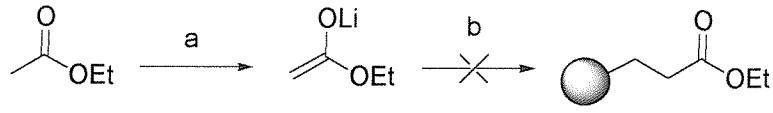
It was hoped that by avoiding the low yielding ether bond formation a higher loading resin could be obtained. The resulting silyl chloride resin **2.1c** should display the same reactivity with alcohols.

2.3.1 Solution phase model

The most straightforward way to obtain intermediate resin **2.65** was to react the enolate of ethyl acetate with benzyl chloride or Merrifield resin in dry THF at –78 °C, followed by hydrolysis, to afford the corresponding ester resin (Scheme 2.21). Then action of methylmagnesium bromide at 0 °C would afford **2.65**.

Although the chemistry required for this approach in solution was simple, it was felt that a lot of potential problems could arise in the corresponding solid phase synthesis.

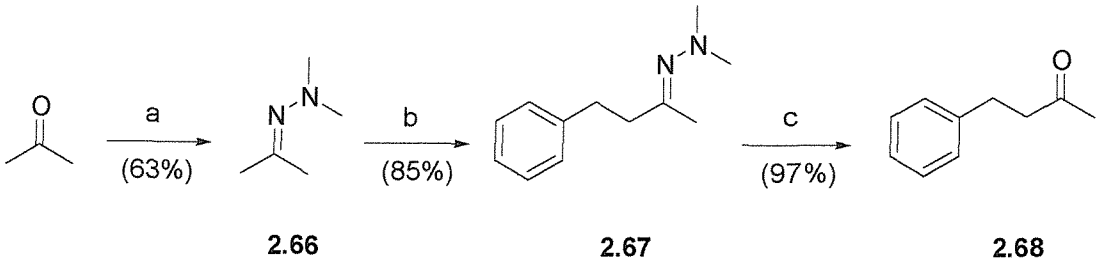
One reason was the inconvenience and expense of working at low temperature (-78°C) to perform the first alkylation step. On the other hand, this temperature was necessary, as the enolate of ethyl acetate is reactive and is known to give self-condensation at temperatures higher than –78 °C. A preliminary investigation was made on the resin. The enolate of ethyl acetate was generated in dry THF using LDA, and the corresponding solution added to Merrifield resin, at –78 °C. Unfortunately, no reaction occurred, as shown by the FT IR, which showed the total absence of an ester signal.



Scheme 2.21 (a) LDA, THF –78 °C **(b)** Merrifield resin

After this preliminary negative result on the solid phase, it was decided to change the approach for the synthesis of **2.65**. Our decision involved the use of the anion of the corresponding acetone *N,N*-dimethylhydrazone derivative. This approach had the main advantage that this anion does not undergo self-condensation. In addition it can be generated at 0 °C using ^{n}BuLi. It was therefore felt that these conditions would be more suitable for the solid phase synthesis.

Having established the modified approach for resin **2.65**, the synthesis in solution was started. Following a literature procedure [99] acetone was condensed with the *N,N*-dimethylhydrazine to afford **2.66** in good yield. Compound **2.66** was then reacted with ^{n}BuLi in dry THF at 0 °C, [100] and the lithium salt reacted with benzyl chloride, to give **2.67** in good yield. The corresponding saturated ketone **2.68** was then obtained quantitatively by action of sodium periodate on **2.67** (Scheme 2.22). [101, 102]

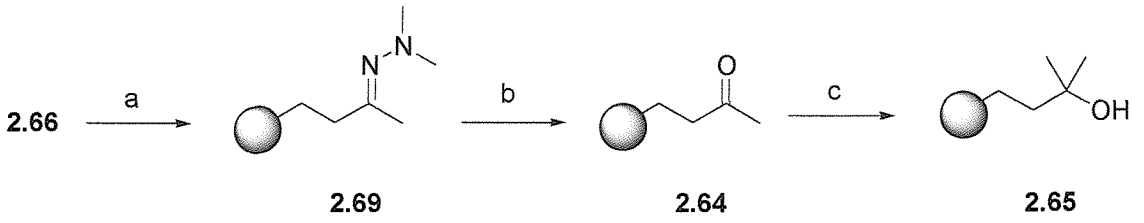


Scheme 2.22 (a) *N,N* Dimethylhydrazine **(b)** ^{n}BuLi, 0 °C, then BnCl, rt, THF **(c)** $NaIO_4$, phosphate buffer, THF-H_2O 4:1

At this point the investigation of the solution phase model was stopped, as the main task of the study was to obtain compound **2.68** in a strategy suitable for its application on the solid phase.

2.3.2 Solid phase synthesis of 2.1c

Once the chemistry had been validated in solution, attention was then turned to the solid phase synthesis (Scheme 2.23). According to the model study, the lithium salt of the acetone *N,N*-dimethylhydrazone was immobilized onto Merrifield resin at 0 °C in dry THF, to afford the hydrazone resin **2.69**. Subsequent oxidation with $NaIO_4$ at room temperature afforded ketone bound resin **2.64**. Exposure of **2.64** to MeMgCl at 0 °C in dry THF afforded resin **2.65**. Formation of intermediate resins **2.69**, **2.64** and **2.65** was successful, as judged by FT IR analysis.



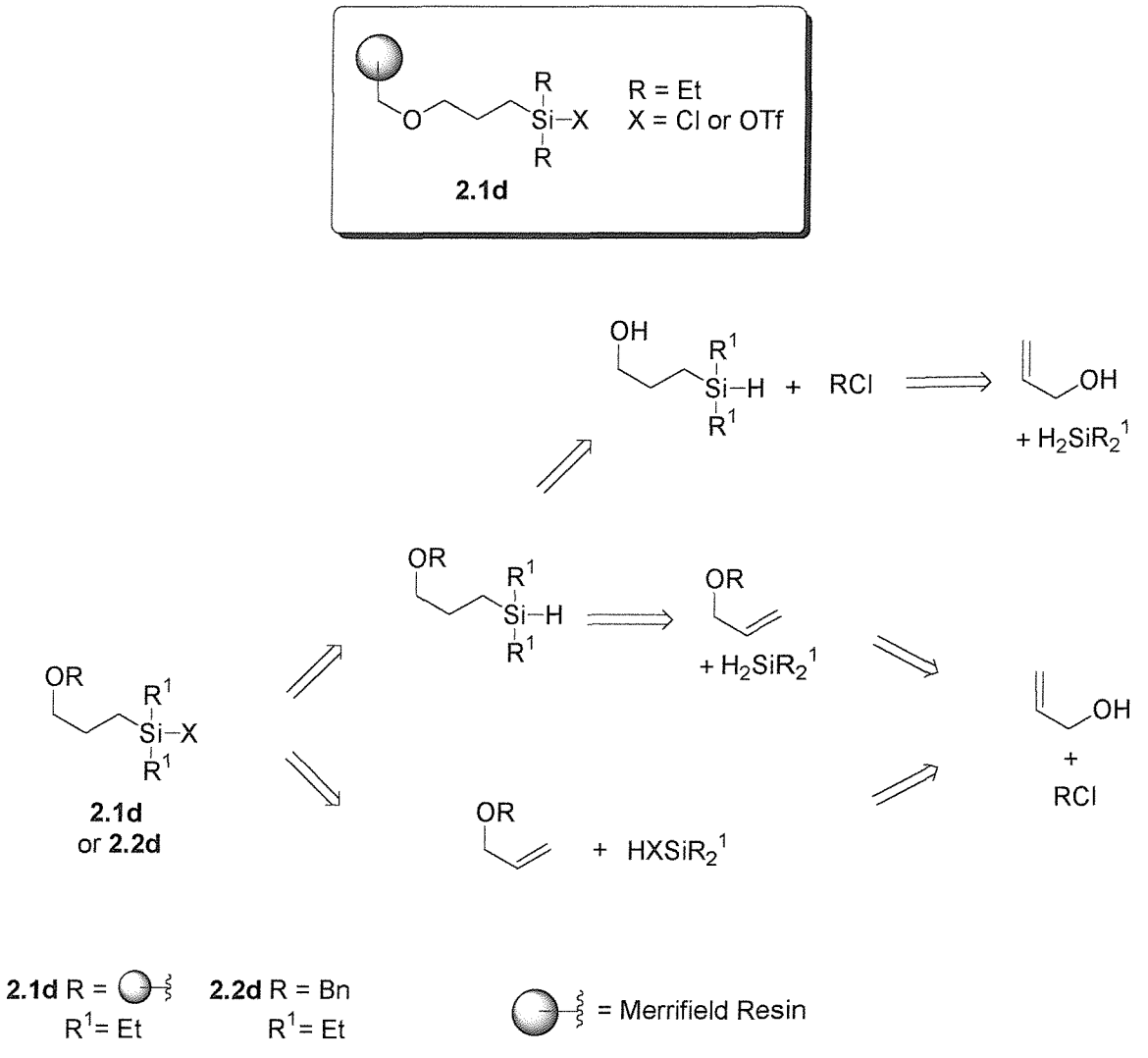
Scheme 2.23 (a) ^{n}BuLi, 0 °C, then Merrifield resin, rt, THF **(b)** $NaIO_4$, phosphate buffer, THF-H_2O 4:1 **(c)** MeMgCl, THF, 0 °C to rt, 24h

In order to obtain silyl chloride resin **2.1c**, **2.65** was reacted with diphenyldichlorosilane in Et_3N and DMAP and the resulting chloride reacted with trans cinnamyl alcohol. Disappointingly, no alcohol was found after TBAF cleavage, suggesting the failure of the formation of the silyl chloride. One of the possible reasons is the inefficiency of the first step. Unfortunately, it was decided to abandon further investigations of this type of linker, due to a lack of time.

2.4 Synthesis of linker 2.1d

2.4.1 General considerations and retrosynthetic analysis

We required an alternative silyl linker that showed the enhanced acid stability relative to the diphenylsiloxane linker **2.1a**. It was postulated that the presence of two Si-O bonds of the siloxane moiety could be responsible of this feature, and for this reason attention was focused on the synthesis of resins having the general structure **2.1d** (Scheme 2.24).



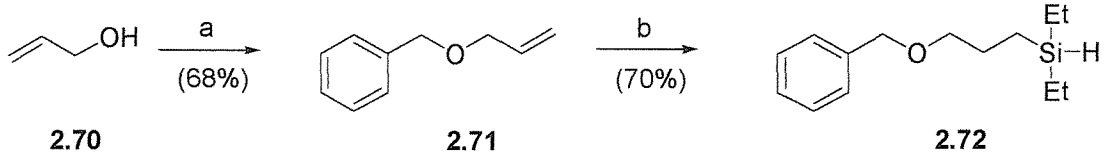
Scheme 2.24 Retrosynthetic analysis adopted for linker **2.1d** and for its solution analogue **2.2d**

According to Scheme 2.24, the key step to obtain a silyl resin of structure **2.1d** is the β-hydrosilylation of the resulting immobilized alkene, which can be prepared via Williamson reaction between Merrifield resin and allyl alcohol. This last feature is attractive, as it was felt that this latter resin could have prepared much easier than the 3 butenyl polystyrene originally reported by Hu *et al.* [55]

A second approach to the general structure **2.1d** could involve the hydrosilylation of an olefin containing resin with a dialkylmonochlorosilane. A third choice initially considered was also the synthesis of the whole linker in solution prior to its attachment to the solid phase. However, high costs, air sensitivity of the dialkylmonochlorosilanes and the time required for the solution phase synthesis of the linker discouraged the investigation of the latter two approaches. Only the first route to the synthesis of model linker **2.1d** was investigated.

2.4.2 Solution phase study

The solution phase study focused on the synthesis of **2.2d** as model compound for linker **2.1d**. Thus, Williamson reaction between the sodium salt of allyl alcohol **2.70** and benzyl chloride in dry DMF at 0 °C gave allyl benzyl ether **2.71** in an unoptimized yield of 68%, along with the unreacted allyl alcohol. Subsequent hydrosilylation with diethylsilane in presence of the Wilkinson's catalyst in toluene, following a literature procedure [103] gave silane **2.72** in good yield (Scheme 2.25). Additionally no decomposition of product **2.72** was observed by TLC.



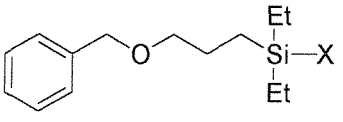
2.70 **2.71** **2.72**

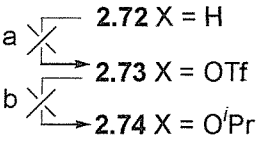
Scheme 2.25 (a) NaH, 0 °C, then BnCl, rt **(b)** Et_2SiH_2, Wilkinson's catalyst, toluene, 70 °C

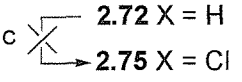
Once silane **2.72** had been obtained, a method for its conversion in the corresponding halide or triflate was required. In order to evaluate this we found a literature method [67] for the conversion of supported silanes to the corresponding triflates, using triflic acid. A first attempt was carried out dissolving **2.72** in dry CH_2Cl_2 and adding slowly one

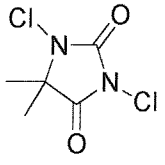
equivalent of the acid at room temperature. TLC analysis showed the disappearance of **2.72** after only 5 minutes, however a very complex mixture of products was observed. This could have been due to the decomposition of the formed silyl triflate **2.73** on the TLC plate. This feature is not surprising as silyl triflates are known to be extremely moisture and acid sensitive. [48] To overcome to this difficulty, the reaction mixture containing the presumed triflate **2.73** was reacted with dry isopropanol in presence of a large excess of 2,6-lutidine. These conditions should afford the more stable siloxane **2.74**, which could have been isolated and characterized. However, no new product was observed by TLC. This experimental evidence suggested the failure of the formation of triflate **2.73**; a possible explanation could be the total cleavage of the benzyl ether promoted by the triflic acid, as such ethers are cleaved under strongly acidic conditions. In addition, ethers are known to be cleaved with silyl triflates; [104] it was then felt that a substrate containing both an ether and a silyl triflate moiety would probably not be stable, even if its formation occurred very rapidly and quantitatively. Further support for these two hypotheses was the presence of benzyl alcohol in the reaction mixture after the first step. For these reasons it was decided to abandon this strategy.

A method for the activation of **2.72** under less harsh conditions was required. As silanes are known to give the corresponding chlorides with 1,3 dichloro-5,5-dimethylhydantoin **2.76**, [105] it was felt that these conditions could be compatible with **2.72**. Therefore, **2.72** was treated with **2.76** in CH_2Cl_2 at room temperature (Scheme 2.26). Again disappointing results were obtained, as TLC analysis showed the presence of a very complex mixture, suggesting that the formation of **2.75** was not clean or that is unstable to TLC analysis.









2.76

Scheme 2.26 (a) TfOH, CH_2Cl_2, rt **(b)** ^{i}PrOH, 2,6-lutidine, CH_2Cl_2 rt **(c) 2.76**, CH_2Cl_2, rt

A further complication which arose during the synthesis was the instability of silane **2.72**, as demonstrated by TLC analysis of **2.72** prepared and stored in the fridge two days.

All of these combined difficulties showed us that the formation of silyl triflate **2.73** or the chloride **2.75** is not straightforward, and suggested that the corresponding resins analogues to **2.72**, **2.73** and **2.75** might not be stable, even if they could be prepared. For the reasons cited and also for lack of time the route towards linker **2.1d** was abandoned.

2.5 Conclusions

In conclusion, in this first part of the work the main goals of our research were achieved. After the successful synthesis of a solution phase model, a diphenyl silyl chloride resin **2.1a** was synthesized in good yield and consistent values of loading (0.65 mmol/g). Excellent reactivity with primary and secondary alcohols was found. [98] In addition resin **2.1a** was stable to prolonged storage. Selective silylations of 1° alcohols was also achieved in presence of 2°.

In the second part of the research attention was paid to solve problems related to resin **2.1a**. In particular its lack of reactivity with tertiary alcohols was successfully overcome by using dimethyl analogue **2.1b**, which proved to react rapidly even with tertiary alcohols. However the low values of loading (0.37 mmol/g) for resin **2.1b** discouraged us to investigate this linker any further. Finally, attempts to produce higher loading siloxane resins, and resins that displayed increased acid stability were investigated. However, problems were encountered both in solution and in the solid phase. Given these last failures and also due to a lack of time the route to linkers **2.1c** and **2.1d** was abandoned.

It was therefore decided to continue the investigation only on resin **2.1a**; the next chapter will describe the applications of the diphenyl linker **2.1a** in the SPOS.

CHAPTER 3. APPLICATIONS OF THE DIPHENYLSILOXANE LINKER IN SOLID PHASE ORGANIC SYNTHESIS

3.1 Aims and objectives

Having established the synthesis of the silyl chloride resins, the second part of the project involved the application of resin **2.1a** in solid phase synthesis. Each application of the linker will be described in detail in a separate section.

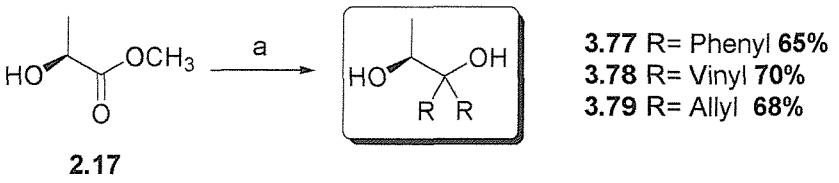
3.2 C-C bond formation on the solid phase

Reactions for C–C bond formation are among the most important classes of reaction in organic synthesis. However, until recently the standard methods required the presence of a strong carbon nucleophile, typically an organolithium salt or a Grignard reagent, to add to an electrophilic substrate, such as an aldehyde, a ketone, or an ester. This approach was sometimes quite complicated, as these reagents are extremely reactive and moisture sensitive, requiring low reaction temperatures and a rigorously dry environment. In addition, robust protecting groups are required in cases where additional functionalities are present, in order to avoid side reactions.
In this context transition metal chemistry offers the unique advantage of forming C-C bonds under mild reaction conditions. Over the last 10 years the interest in performing transition metal catalysed reactions on the solid phase has been growing continuously.[106-109] As a consequence, attention was focused in employing the silyl linker in sequences involving transition metal catalysed steps, in order to evaluate its applicability. The investigation will cover the Sonogashira, Heck, Suzuki, and the ring closing metathesis reactions, which will be described in the ensuing sections.

3.2.1 C-C bond formation with Grignard reagents

The initial study involved the use of Grignard reagents with the siloxane linker, in order to evaluate its stability. Accordingly to these plans, *S*-methyl lactate **2.17** was chosen as substrate and a preliminary study in solution was then carried out to determine the

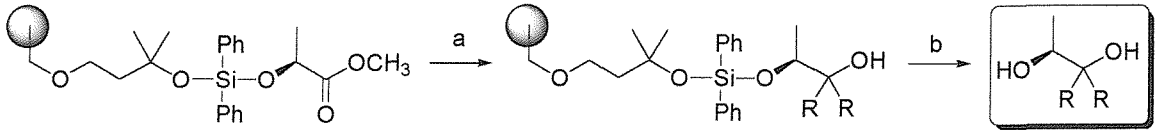
reaction times required. Substrate **2.17** was reacted with phenyl, [110] vinyl [111] and allyl [112] magnesium bromide in dry THF, following a literature procedure, to give compounds **3.77-3.79** in satisfactory yields (Scheme 3.1).



2.17

Scheme 3.1 (a) RMgBr, THF, -78 °C, then NH_4Cl (aq)

According to Scheme 3.2, the immobilized ester **2.36** (obtained by reaction between *S*-methyl lactate **2.17** and silyl chloride resin **2.1a**) was then reacted with phenyl, allyl and vinyl magnesium bromide at –5 °C. Then the compounds were cleaved with TBAF and purified by column chromatography. In all cases the reactions with the Grignard reagents were followed by FT IR analysis on the beads, showing the complete disappearance of the ester band in less than 1 hour. The only exception was isopropylmagnesium chloride in which case the ester band was still present even after 2 hours and at 10 °C. The results are shown in Scheme 3.2 and in Table 3.1

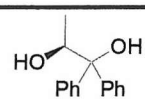
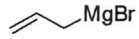
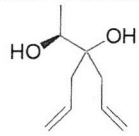


2.36

3.80 R = Ph
3.81 R = Allyl

Scheme 3.2 (a) RMgBr, THF, -5 to 0 °C **(b)** TBAF, THF, rt

TABLE 3.1 Compounds obtained by treatment of resin **2.36** with various Grignard reagents

Grignard reagent	Product	Yield[a,d]
PhMgBr **3.82**	 **3.77**	60
 **3.83**	 **3.79**	53
 **3.84**	-	0[b]
^{i}PrMgBr **3.85**	-	0[c]

[a] All yields refer to the isolated purified compounds
[b] Cleavage of siloxane linker promoted by vinylmagnesium bromide
[c] Recovered *S*-methyl lactate in 97% yield
[d] Overall yield based on the loading of the silyl chloride resin **2.1a**

Disappointingly, vinylmagnesium bromide was found to effect cleavage of the product from the resin. Following purification, product **3.78** was recovered in near quantitative yield. Improved results were observed with phenyl and allyl magnesium bromide, as subsequent cleavage afforded compounds **3.77** and **3.79** in acceptable yield, demonstrating that the siloxane moiety displays some stability to these two Grignard reagents. However, also in this case compounds **3.77** and **3.79** were also found in the reaction mixture, before fluoride cleavage. The last case investigated was represented by isopropylmagnesium chloride and another different result was found. After TBAF treatment, the cleavage mixture, subjected to column chromatography, returned the starting material **2.17** in nearly quantitative yield, demonstrating that the Grignard reagent was unreactive both with the ester group and with the siloxane moiety. This lack of reactivity can be explained by bulkiness of the isopropyl group.

In summary, this study demonstrates that the siloxane moiety was reasonably stable to chemistry with Grignard reagents. However some limitations were encountered, which

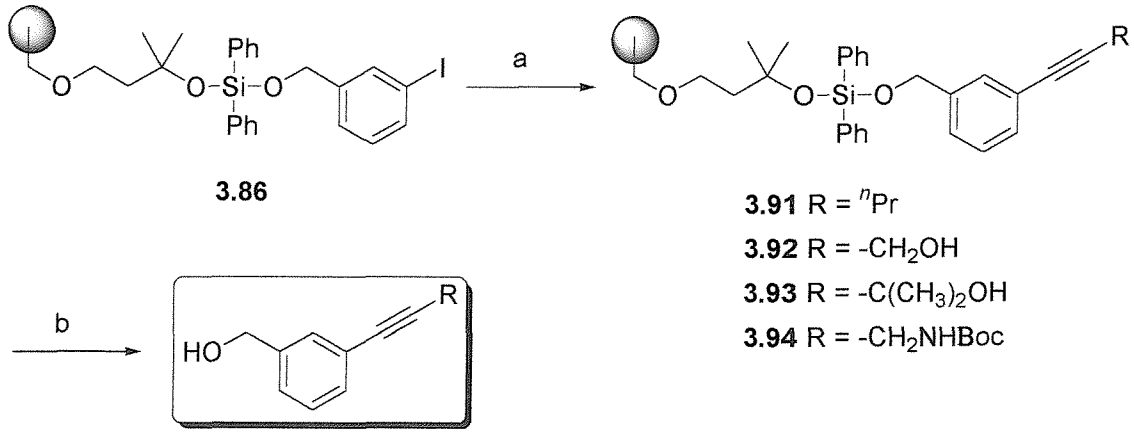
could depend either on the bulkiness of the organometallic reagent used or on the kind substrate employed. As a consequence, the compatibility of the silyl linker was only acceptable with steric demanding organometallic reagents.

3.2.2 Transition metal mediated C-C bond formation

3.2.2.1 Sonogashira reaction

As previously stated, (see Introduction, Section 1.4.1.3, page 20) the Sonogashira reaction involves the coupling between a terminal alkyne and an aryl triflate or halide, typically an iodide. This reaction has the advantage that mild reaction conditions are required, and it has been previously shown to occur with excellent results using other silyl linkers (see Introduction, Section 1.4.1.3, page 20).

Thus, commercially available 3-iodobenzyl alcohol was reacted with the silyl chloride resin **2.1a** to afford polymer bound aryl iodide **3.86**. Subsequent reaction with a variety of terminal alkynes **3.87-3.90** afforded intermediate resins **3.91-3.94**. The reactions were performed following a literature procedure, [113] using a catalytic amount of *trans*-$(PPh_3)_2PdCl_2$ and copper iodide at room temperature, in a mixture of dry Et_3N and dioxane. Subsequent exposure to TBAF and purification by column chromatography afforded compounds **3.95-3.98** in excellent overall yield (3 steps). The operations can be summarized in Scheme 3.3 and the results shown in Table 3.2

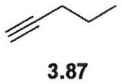
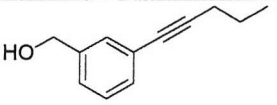
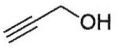
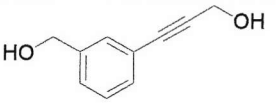
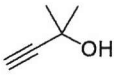
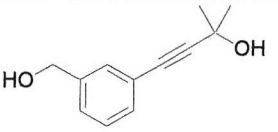
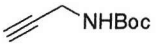
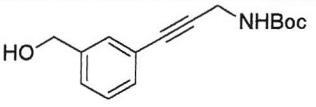


3.86

3.91 R = ^{n}Pr
3.92 R = -CH_2OH
3.93 R = -$C(CH_3)_2OH$
3.94 R = -CH_2NHBoc

Scheme 3.3 (a) 3.87, **3.88**, **3.89** or **3.90**, *trans*-$Pd^{II}(PPh_3)_2Cl_2$, dioxane Et_3N 3:1 (v:v), rt **(b)** TBAF, THF, rt

TABLE 3.2 Products obtained by Sonogashira reaction with various terminal alkynes

Alkyne	Product cleaved	Yield[a,b]
 **3.87**	 **3.95**	93
 **3.88**	 **3.96**	94
 **3.89**	 **3.97**	96
 **3.90**	 **3.98**	97

[a] All yields refer to the isolated purified compounds
[b] Overall yield based on the loading of the silyl chloride resin **2.1a**

All the terminal alkynes were commercially available, with the exception of **3.90**, which was obtained from reaction between propargylamine and di-*tert*-butylpyrocarbonate following a literature protocol. [114] Literature precedents [115, 116] showed that Sonogashira reactions on solid phase could be performed in a period shorter than 24h. However, to check the stability of the linker, all of the reactions were performed at room temperature for 24h. Excellent overall yields were obtained, demonstrating the utility of the linker under this kind of palladium mediated coupling. In addition, some of the compounds cleaved showed an excellent crude purity after TBAF deprotection, as illustrated by the ^{1}H NMR of **3.95** in Figure 3.1

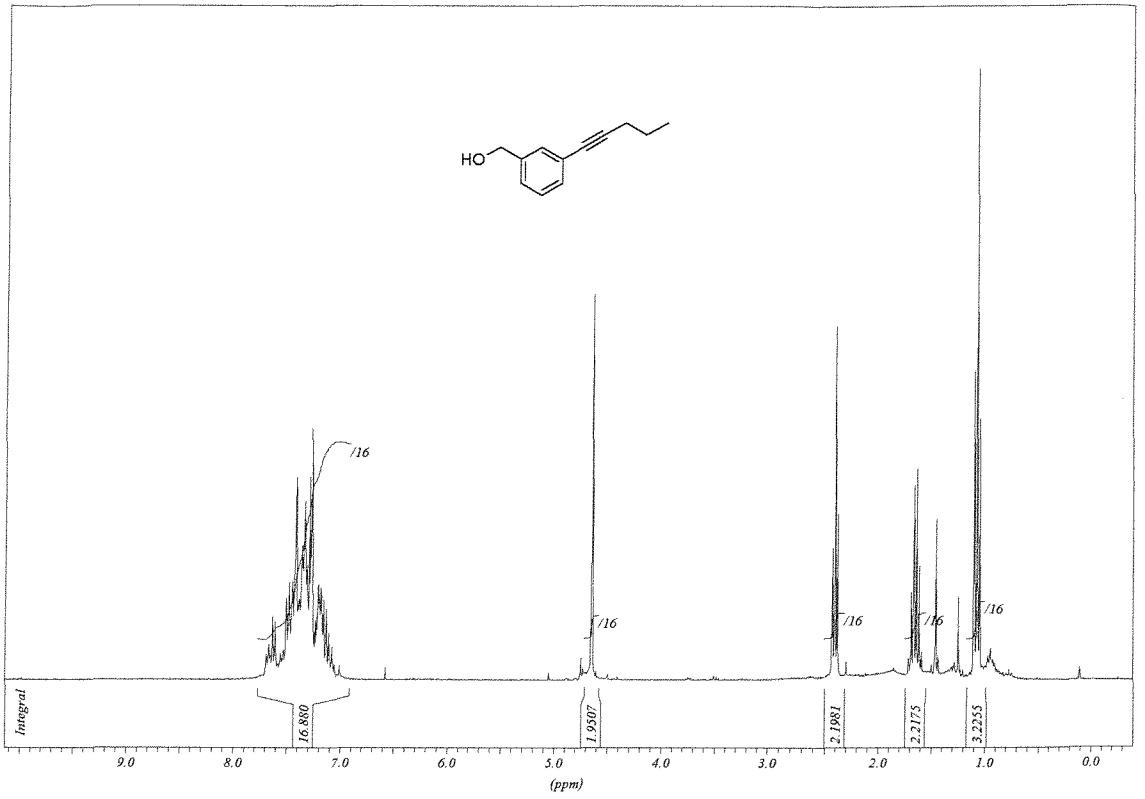
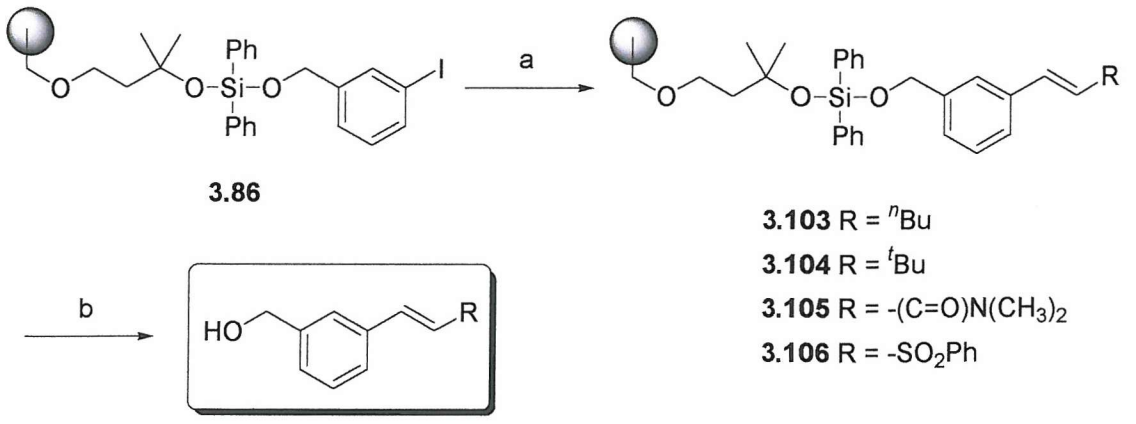


Figure 3.1 ^{1}H NMR of the crude cleaved material **3.95**

3.2.2.2 Heck reactions

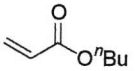
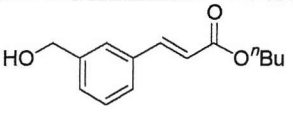
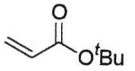
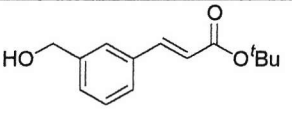
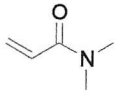
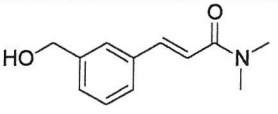
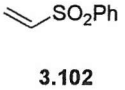
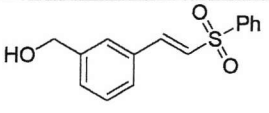
Having shown the excellent stability of the diphenyl siloxane linker towards Sonogashira couplings, our attention was then turned towards the Heck reaction. This palladium mediated reaction involves the use of olefins instead of terminal acetylenes, and could be considered more challenging, as the reaction conditions are typically harsher than those required for Sonogashira reactions.

Polymer bound aryl iodide **3.86** was reacted with a variety of terminal alkenes **3.99-3.102** [113] to afford intermediate resins **3.103-3.106**. Exposure to TBAF and purification afforded compounds **3.107-3.110**, as illustrated in Scheme 3.4 and in Table 3.3



Scheme 3.4 (a) 3.99, **3.100**, **3.101** or **3.102**, $Pd(OAc)_2$, $^{n}BuCl$, NaOAc, DMA, 100 °C **(b)** TBAF, THF, rt

TABLE 3.3 Products obtained by Heck reaction with various terminal alkenes

Alkene	Product	Yield[a,b]
 **3.99**	 **3.107**	70
 **3.100**	 **3.108**	71
 **3.101**	 **3.109**	70
 **3.102**	 **3.110**	67

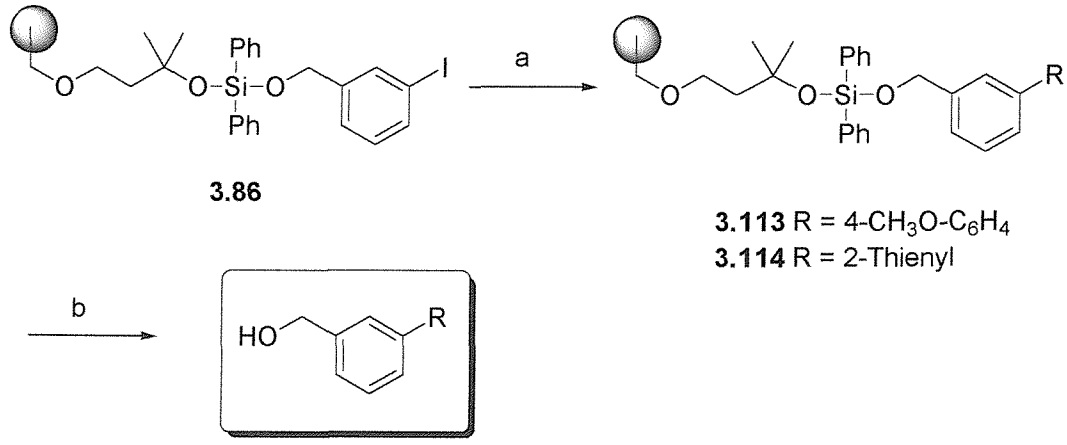
[a] All yields refer to the isolated purified compounds.
[b] Overall yield based on the loading of the silyl chloride resin **2.1a**

Compounds **3.107-3.110** were obtained in good yield. However in all the cases, before fluoride cleavage, some compound was found in the reaction solution, demonstrating that under the coupling conditions the siloxane linker underwent slow cleavage.

3.2.2.3 Suzuki reactions

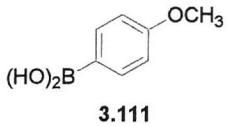
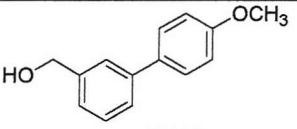
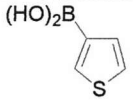
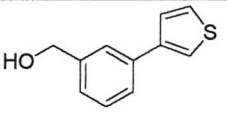
Pd mediated Suzuki couplings with boronic acids or pinacolboranes are important and widely used solid phase reactions. [117] For this reason it was decided to investigate the application of the siloxane linker to this kind of transformation. In a preliminary experiment, resin **3.86** was suspended in dioxane and subsequently treated with the boronic acid **3.111** and *N,N,N',N'*-tetramethylguanidine as base, at 60 °C. It was felt that these conditions would greatly accelerate the reaction rate, as the base was totally soluble in the solvent employed. However no reaction occurred even after 12h. In this case TBAF cleavage quantitatively returned the 3-iodobenzyl alcohol.

After this disappointing result, it was decided to change method used for the coupling. Following a literature procedure, [117] resin **3.86** was suspended in a mixture of dioxane and water and then reacted with 4 equivalents of the arylboronic acids **3.111** and **3.112** and 4 equivalents of potassium carbonate, for 15 h at 100 °C, to afford intermediate resins **3.113** and **3.114**. Exposure to TBAF and purification gave compounds **3.115** and **3.116**. The strategy adopted is illustrated in Scheme 3.5 and the results summarized in Table 3.4



Scheme 3.5 (a) 3.111 or **3.112**, K_2CO_3, Pd(OAc), dioxane/H_2O, 100 °C **(b)** TBAF, THF, rt

TABLE 3.4 Products obtained by Suzuki reaction between polymer bound iodide **3.86** and various boronic acids

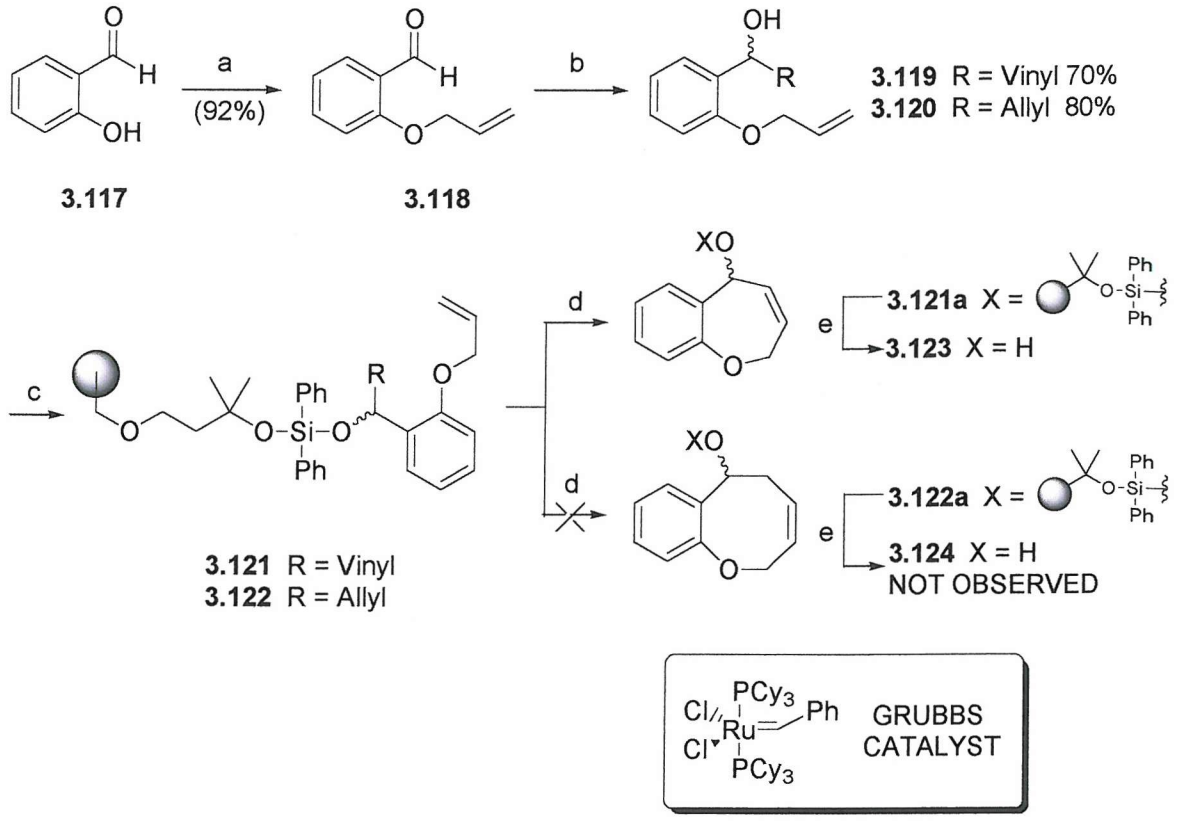
Acid	Product	Yield[a]
 **3.111**	 **3.115**	70
 **3.112**	 **3.116**	67

[a] All yields refer to the isolated purified compounds.

Compounds **3.115** and **3.116** were obtained in good yield, along with some unreacted 4-iodobenzyl alcohol. Gratifyingly, an excellent stability of the siloxane linker under these reaction conditions was seen, as no cleaved product was observed during the coupling, even after 15 hours.

3.2.2.4 Ring closing metathesis

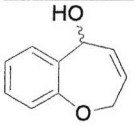
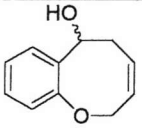
Recently, the ring closing metathesis reaction has became an extremely popular approach for the construction of cyclic molecules of different ring sizes. [118, 119] The main reasons are the mild reaction conditions, which require simple heating of the substrate in refluxing CH_2Cl_2 or DCE in presence of the Grubbs catalyst. RCM has been applied quite successfully in solid phase synthesis [118, 119] with the aid of pseudo dilution effects, especially in the case of the cyclization-cleavage strategy. [120] Having this in mind, the possibility to perform this reaction on the solid phase was investigated. In the first instance attention was given to the solution phase synthesis of the precursors. *O*-alkylation of salicylaldeyde **3.117** with allyl bromide afforded **3.118** which was then reacted with vinyl and allylmagnesium bromide to afford the acyclic precursors **3.119** and **3.120** respectively. Immobilization onto **2.1a** was performed in the usual way (Scheme 3.6).



Scheme 3.6 (a) Allyl bromide, K_2CO_3, DMF, rt **(b)** AllylMgBr or vinylMgBr, THF, -78 °C to rt **(c)** **3.119** or **3.120**, **2.1a**, Et_3N, DMAP, CH_2Cl_2, rt **(d)** Grubbs catalyst, CH_2Cl_2, reflux **(e)** TBAF, THF, rt

The ring closure was performed on resins **3.121** and **3.122** in refluxing CH_2Cl_2 under an inert atmosphere in the presence of 10 mol% of Grubbs catalyst. However, subsequent cleavage from resin and purification afforded only **3.123** as shown in Scheme 3.6 and Table 3.5

TABLE 3.5 Results of the Ring closing metathesis

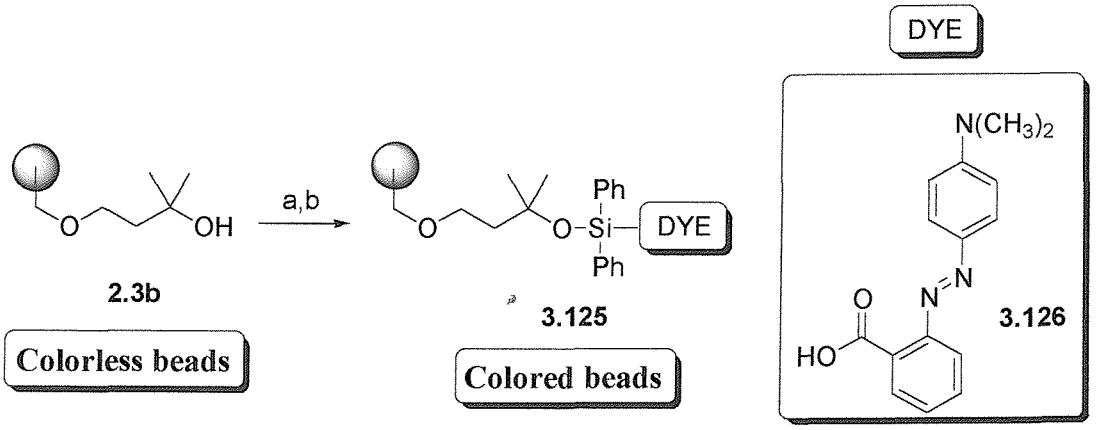
Resin	Product	Yield[a, b]
3.121	 **3.123**	53
3.122	 **3.124**	0

[a] Yield of the isolated compound (purified by chromatography)
[b] Overall yield from the loading of the silyl chloride resin **2.1a**

Under the same conditions, it was not able to obtain **3.124**. In this case, the cleavage did not afford the unreacted precursor, but an extremely complex mixture of compounds which were impossible to separate.

3.3 A new spot test for polymer supported tertiary alcohols

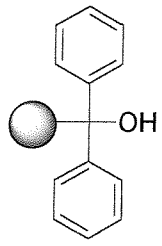
During the development of the silicon linkers, a useful method for the detection of polymer supported tertiary alcohols was discovered. The origin of this relies on the difficulty of checking the formation of resin **2.3b** from Merrifield resin and diol **2.4**. Several spot tests reported in the literature [11, 14] were attempted, but negative results were always obtained, probably due to the lack of reactivity shown by tertiary alcohols. On the other hand, there was other evidence that the immobilization occurred, as shown by the good gel phase ^{13}C NMR (see Chapter 2, page 52) and from the FT IR of **2.3b**. However, as stated in the introduction, all of these analyses were extremely time consuming, as they required the resin to be dried under high vacuum for almost 24h.
During the immobilization of alcohols, it has been previously reported that tertiary alcohol resin **2.3b** reacted only once with diphenyldichlorosilane to afford intermediate resin **2.1a**. Despite the main focus being on alcohols, this overall process can be generalized such that any molecule with a good nucleophilic centre can in theory be linked onto **2.1a**. If, instead of a simple alcohol, a dye was used in the second step, the entire process could have been used to detect the presence of the tertiary alcohol on **2.3b**, simply by observing the colour of the beads. In the absence of any tertiary alcohol, the attachment of the diphenyldichlorosilane would not have been possible, making the immobilization of the dye impossible, and giving colourless beads.



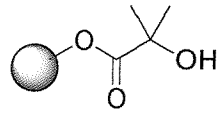
Scheme 3.7 (a) Ph_2SiCl_2, Et_3N, DMAP, rt **(b)** Methyl red, Et_3N, DMAP, rt

Resin **2.3b** was reacted with the diphenyldichlorosilane and subsequently treated with methyl red **(3.126)** under the conditions previously reported for the attachment of alcohols (See Chapter 2, section 2.1.3, page 53). After washing the resin, it was possible to observe the orange color of the beads, demonstrating that the attachment of the dye was successful and showing the presence of the tertiary alcohol on resin **2.3b**. Treatment of the beads with a 1% solution of acetic acid or formic acid in CH_2Cl_2 afforded strongly purple beads.

To extend the potential of the method, several other tertiary alcohol resins were tested, such as **3.127** and **3.128**. After the same treatment, all of them showed positive tests. [13]



3.127



3.128

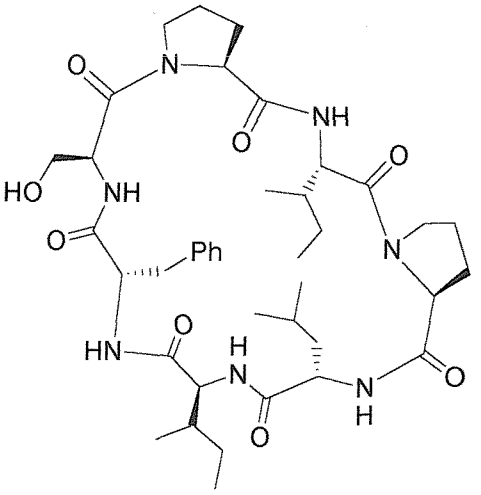
Figure 3.2 Resins found positive to the methyl red test

To check the sensitivity of the test, it was attempted on different batches of resin **2.3b**, having different loadings. In all the times a positive result was found, even with loading of 0.07 mmol/g.

3.4 Solid phase synthesis of Stylopeptide 1

3.4.1 General considerations

As previously shown, some authors (see Introduction, Section 1.4.3, pages 30-33) recently investigated the use of the silicon linkers for the synthesis of cyclic peptides. The reason relies on the great importance of these kind of compounds, as many of them show anticancer properties. This part of the work will deal with the synthesis of the Stylopeptide 1, an heptapeptide containing six hydrophobic residues and one serine moiety (see Figure 3.3)



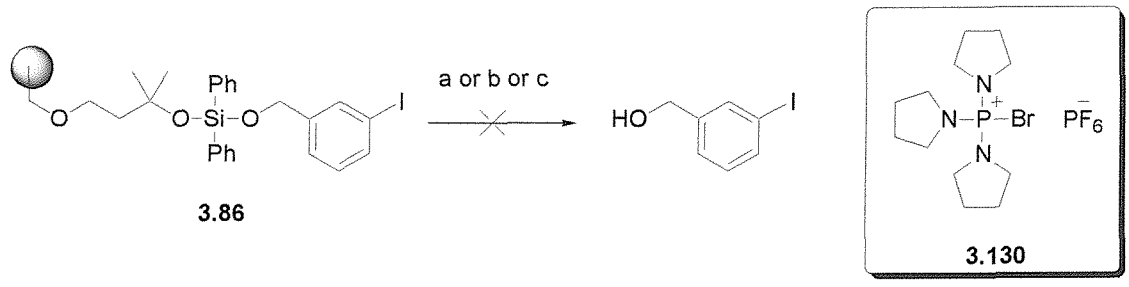
3.129

Figure 3.3 Structure of the Stylopeptide 1

Stylopeptide 1 was originally isolated by Pettit *et al* [121] from a marine sponge, in which it is present in very low amounts. In another paper, [122] the same authors reported its solution phase synthesis. Although the approach was relatively efficient, a serious drawback encountered by the authors were the long reaction times, especially in the final cyclization. Furthermore, a lot of time was taken up in the purification of all the intermediate peptides. In this context the solid phase synthesis would present certain advantages, with the reaction times being drastically reduced and the purification steps avoided. The next section will deal with the solid phase synthesis of the Stylopeptide 1 adopting two different strategies.

3.4.2 Preliminary studies

Before attempting the whole synthesis of the Stylopeptide 1 on solid phase, a preliminary investigation was carried out, to assess the stability of the diphenylsiloxane linker to standard reagents used in SPPS. Polymer bound alcohol **3.86** was suspended in a solution of 20% piperidine in DMF and the solution checked by TLC. Even after 27 h no cleaved alcohol was found, demonstrating the stability of the linker under these conditions. Further investigations were then carried out by treating resin **3.86** with the reagents commonly employed for peptide coupling, such as the DIC/HOBt and PyBrop/DIPEA systems. The stability of the linker to this last reagent has to be carefully checked, as the presence the PF_6 anion of the salt (see structure of the PyBrop **3.130**) might cleave the siloxane, given the sensitivity of the linker to the fluoride ion. These experiments are summarized in Scheme 3.8



3.86 **3.130**

Scheme 3.8 (a) 20% Piperidine in DMF, rt **(b)** DIC, HOBt, CH_2Cl_2 DMF 1:1, rt **(c)** PyBrop, DIPEA, CH_2Cl_2 DMF 1:1, rt

No cleavage of the alcohol was observed, even after 20 h, thus demonstrating the stability of the siloxane linker under peptide coupling conditions.

Having achieved this task, attention then turned to the synthesis of small peptides, to ensure the absence of problems during bond formation. Thus Fmoc L-Serine **3.131a** was reacted with allyl bromide and K_2CO_3 in DMF to afford the corresponding ester **3.132a** in excellent yield. The viability of the esterification was previously verified making **3.132b** as a model compound. Importantly, comparison of the optical rotatory power of **3.132a** with the literature value [123] showed no racemization during the process. Ester **3.132a** was then reacted with the silyl chloride resin **2.1a** under the usual conditions to afford the immobilized ester **3.133**. The successful formation of **3.133** was supported by the FTIR and the gel phase ^{13}C NMR (Figure 3.4).

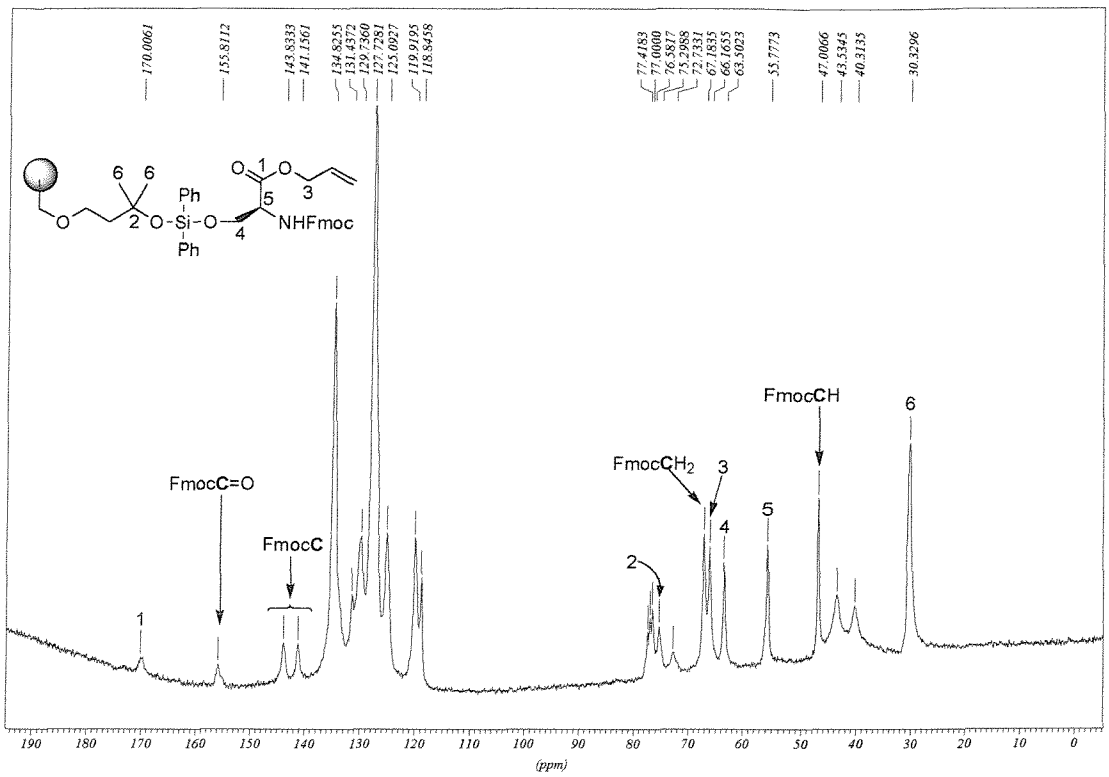
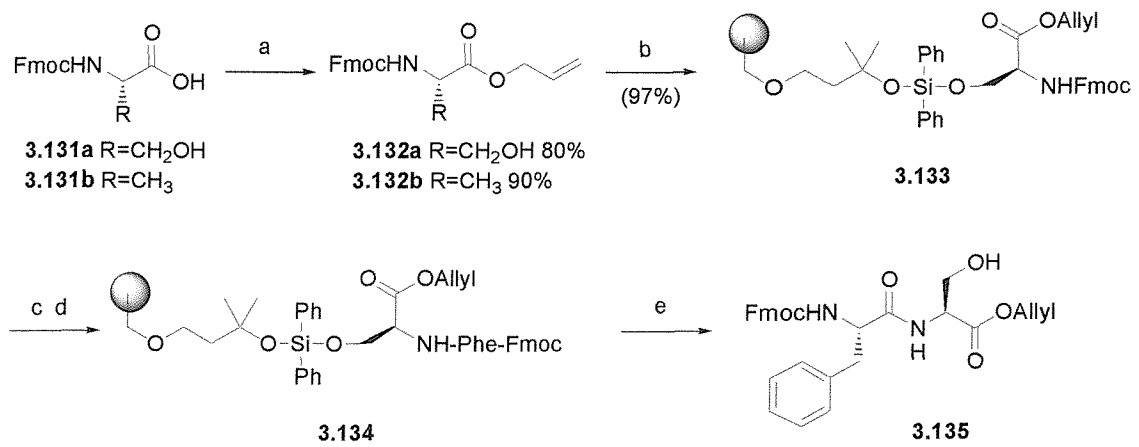


Figure 3.4 Gel phase ^{13}C NMR of intermediate resin **3.133**

The yield of the coupling was 97%, as determined by UV quantification of the piperidine fulvene adduct. After nitrogen deprotection, resin **3.133** was coupled with Fmoc L-Phenylalanine, in presence of DIC and HOBt. Final acidolysis with TFA and purification afforded dipeptide **3.135** (Scheme 3.9). Importantly NMR analysis of **3.135** showed the absence of epimerization during the peptide coupling.



Scheme 3.9 (a) Allyl bromide, K_2CO_3, DMF, rt **(b) 2.1a**, **3.132a**, Et_3N, DMAP, CH_2Cl_2, rt **(c)** 20% Piperidine DMF **(d)** Fmoc L-PheOH, DIC, HOBt, CH_2Cl_2 DMF 9:1 rt **(e)** 30% TFA in CH_2Cl_2, rt

A good overall yield was obtained for **3.135**, but an even better result was observed when double coupling was performed (Table 3.6)

TABLE 3.6 Effects on the yield of dipeptide **3.135** by increasing the number of couplings

Conditions	Yield of 3.135[a,b]
DIC, HOBt, single coupling	80
DIC, HOBt, double coupling	90

[a] Yield refers to the isolated purified compound.
[b] Overall yield based on the loading of silyl chloride resin **2.1a**

In conclusion, a preliminary investigation on the stability of the siloxane linker was carried out successfully, and excellent stability was found under SPPS conditions.
The next sections will describe the attempted solid phase synthesis of Stylopeptide 1, employing two different approaches.

3.4.3 Synthetic strategies

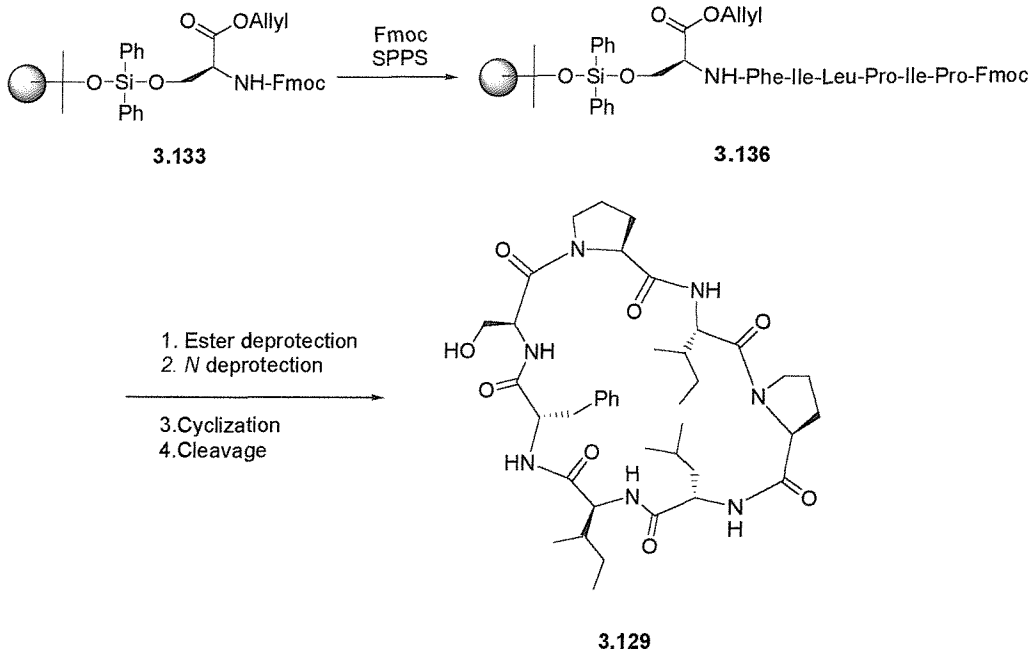
3.4.3.1 General considerations

The presence of the serine residue in the structure of the Stylopeptide 1 was fundamental for our strategy: after attachment of **3.132a** onto the silyl chloride resin, the nitrogen can be used to assemble the whole peptide chain employing standard Fmoc chemistry. Once the peptide sequence was assembled, the deprotection of the carboxyl and the nitrogen termini followed by cyclization would afford Stylopeptide 1, which could be cleaved from the support either with TBAF or by TFA acidolysis. The role of the siloxane linker is to effectively act as a solid supported side chain protecting group. As the serine immobilization onto **2.1a** occurs in mild conditions (Scheme 3.9, page 92), the strategy could also represent a valuable alternative to the one already reported (see Introduction, Section 1.4.3, pages 30-33), in which the Pd mediated attachment of the first aminoacid and the silicon linker occurs under relatively harsh conditions. If successful, the approach could be potentially extended beyond Stylopeptide 1, for the solid phase synthesis of serine containing peptides with potential biological activity. In

our study, two similar approaches were adopted, and to avoid confusion, they will be described separately.

3.4.3.2 Stylopeptide 1: strategy one

The first strategy involved the assembly of the acyclic precursor in one direction, using Fmoc chemistry. The choice of the allyl ester as protecting group lies in its widespread employment in SPPS. [124a-b] Importantly the deprotection step is compatible with the linker. Deprotection of the *N* and *C* termini followed by cyclization and cleavage would afford Stylopeptide 1 (Scheme 3.10)



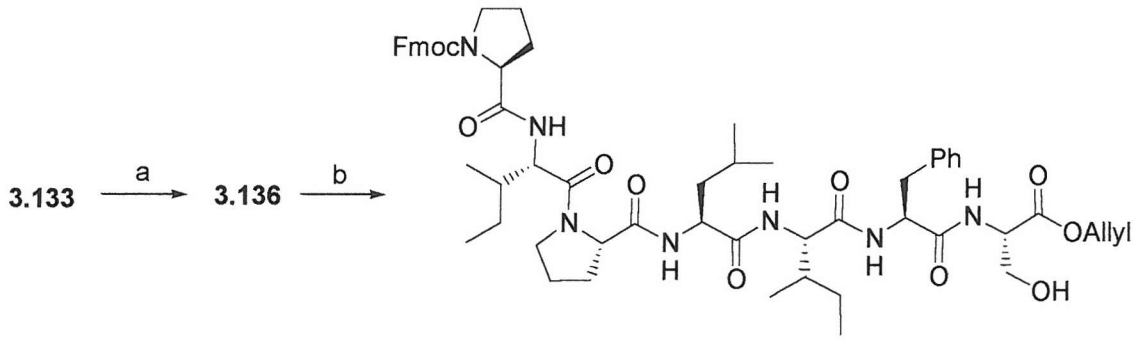
3.133 **3.136** **3.129**

Scheme 3.10 First approach adopted for the synthesis of Stylopeptide 1

The great attraction of the strategy lies in the solid phase macrocyclization involving the proline. This step is difficult, but it was felt that this problem could be overcome with the aid of solid phase synthesis, using a large excess of coupling reagents to drive the cyclization to completion.

Following this approach, immobilized ester **3.133** was initially deprotected with piperidine in DMF and the acyclic precursor was then assembled onto **2.1a** using the solid phase Fmoc chemistry. As previously (see Section 3.4.2, page 93), double couplings with each amino acid were performed to drive all the reactions to

completion. To ensure the presence of the acyclic precursor, resin **3.136** was subjected to TFA acidolysis followed by ether precipitation. Additional chromatography afforded heptapeptide **3.137** in a 60% overall yield, based on the loading of original silyl chloride resin. The peptide showed an excellent HPLC trace and mass spectrum.



3.137

Scheme 3.11 (a) i. 20% Piperidine in DMF ii. Fmoc L-Aminoacid, DIC, HOBt (or PyBrop/DIPEA) CH_2Cl_2 DMF 1:1 rt **(b)** 30% TFA in CH_2Cl_2, rt.

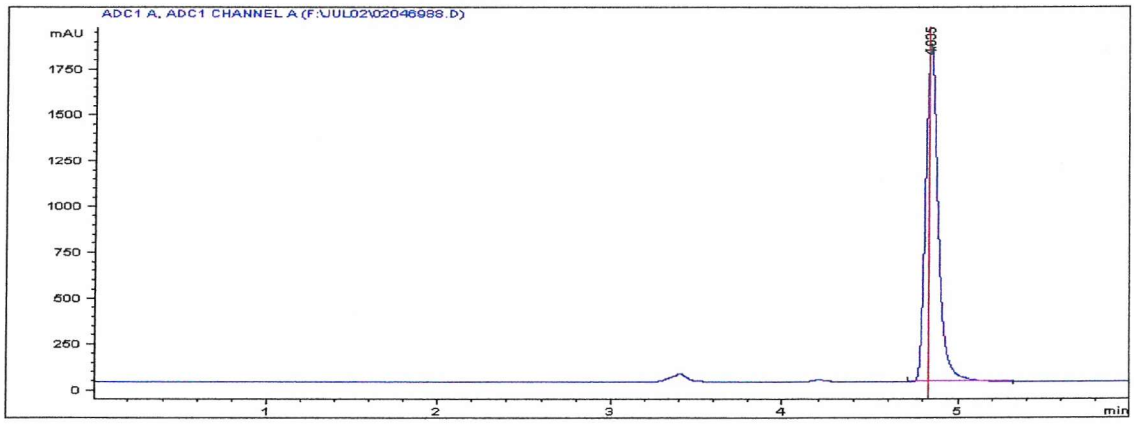
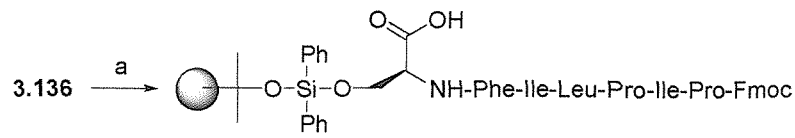
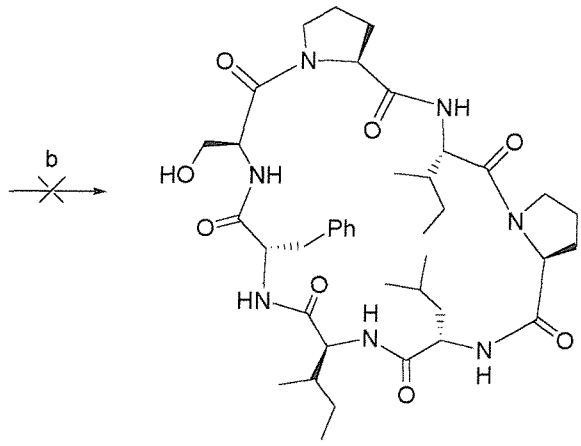


Figure 3.5 HPLC trace of peptide **3.137**

Once the presence of the acyclic precursor on resin **3.136** was confirmed the allyl ester was deprotected following a literature procedure (Scheme 3.12). [125] The reaction was successful, as demonstrated by the mass spectrum of the cleaved material. Subsequent Fmoc cleavage with piperidine in DMF afforded the free amine resin, that was then rinsed with a solution of 1% of acetic acid in CH_2Cl_2. The cyclization was attempted in presence of 6 and 7 equivalents of PyBrop and DIPEA, respectively. The reaction was checked by taking aliquots of resin, cleaving them with TFA and analysing the mixture by mass spectrometry.



3.138



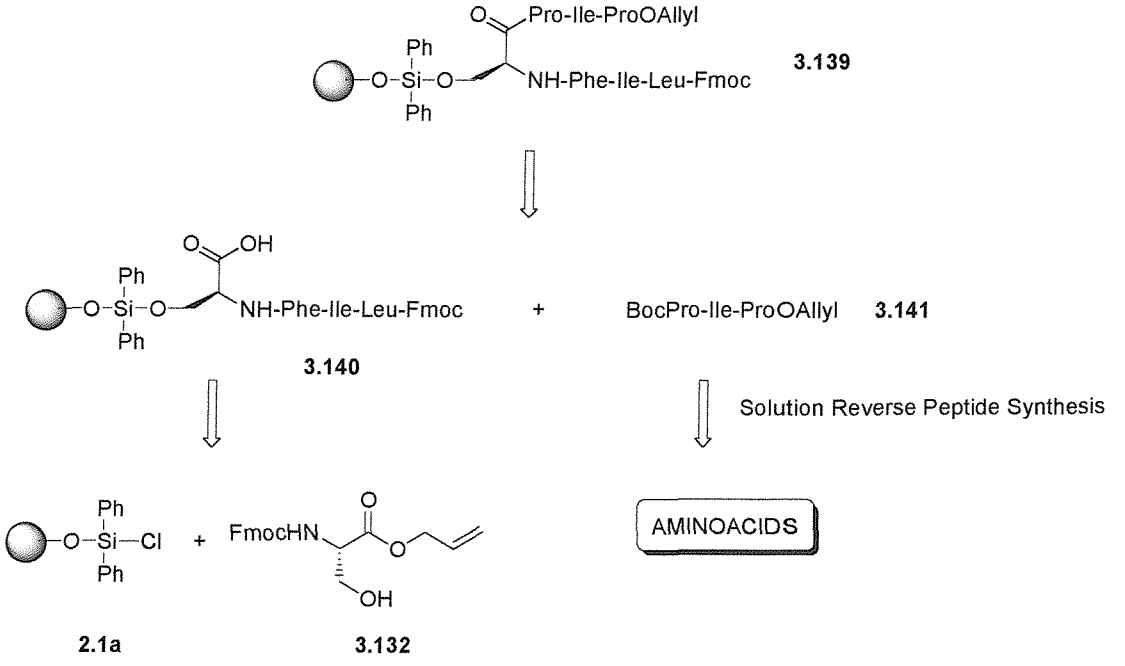
3.129

Scheme 3.12 (a) $Pd(PPh_3)_4$, $CHCl_3$, AcOH, NMM (37:2:1) **(b)** i. 20% Piperidine in DMF ii. PyBrop, DIPEA, CH_2Cl_2 DMF 1:1 rt

Disappointingly, no product was observed at all even after prolonged reaction times. In all cases TLC analysis of the crude cleavage mixture afforded an extremely complex mixture of components, which proved to be very difficult to solubilize and to separate. This last evidence suggested that the oligomerization occurred instead of cyclization. Having observed this failure, a further investigation was made. In particular, after *C* and *N* termini deprotection, the cyclization of **3.137** was attempted in solution, in the high dilution conditions originally reported by Pettit et al. [122] Again, disappointing results were found, as TLC showed the presence of the starting material even after 10 days, with no evidence of other new product. This result suggested that the rate of the macrocyclization at the level of proline was very slow, even when applied on the solid phase. In addition this suggested that the proline may not be considered a good point for the cyclization. As a consequence of these results, it was decided to abandon this route.

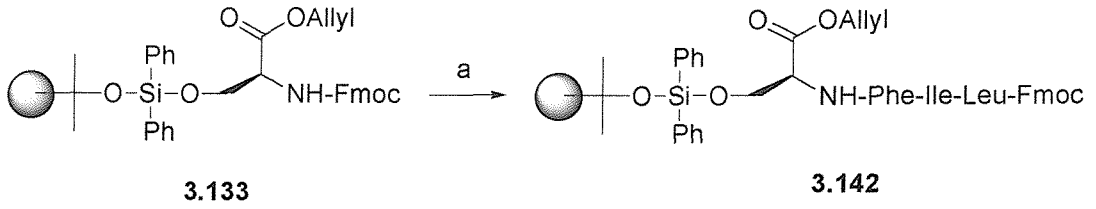
3.4.3.3 Stylopeptide 1: second approach

Following the failure of the first approach, in a second strategy it was decided to carry out the cyclization at the same point as originally reported by Pettit *et al.* [122] In this case, the cyclization was carried out between the carboxyl of the proline and the nitrogen of the leucine. Although the cyclization was slow in solution, a faster cyclization may be possible using a large excess of reagents in the solid phase route. Accordingly to this, it was necessary to build acyclic precursor bound resin **3.139** which would then cyclize under the reported peptide coupling conditions to afford the Stylopeptide 1.



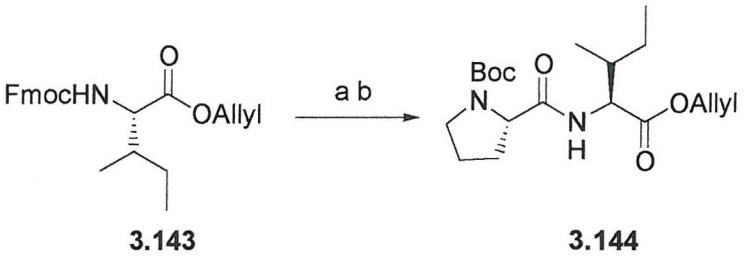
Scheme 3.13 Second approach adopted for the synthesis of Stylopeptide 1

Attention was then directed on the synthesis of resin **3.139**. This can be accomplished using the Fmoc strategy to build resin bound tetrapeptide **3.142** (Scheme 3.14)



Scheme 3.14 (a) i. 20% Piperidine in DMF ii. Fmoc L-Aminoacid, DIC, HOBt, CH_2Cl_2 DMF 1:1, rt

Having synthesized **3.142**, attention was turned to **3.141**. According to Scheme 3.15 Fmoc L-IleOAllyl **3.143**, prepared in the same way adopted for **3.132a**, was *N*-deprotected with diethylamine in acetonitrile; [122] subsequent coupling with Boc L-ProOH [134] afforded dipeptide **3.144** in 87% overall yield, as illustrated in Scheme 3.15



3.143 **3.144**

Scheme 3.15 (a) Et_2N CH_3CN 1:1 (v:v) **(b)** Boc L-ProOH, DCC, CH_2Cl_2, rt

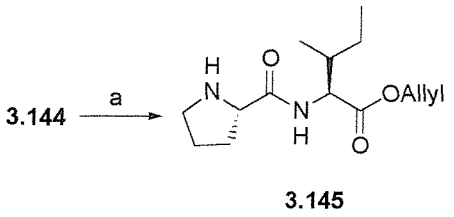
It was found that a 24 h reaction time was necessary to obtain **3.144** in good yield; shorter reaction times gave considerably worse results, as illustrated in Table 3.7

TABLE 3.7 Effect of varying the reaction time on formation of dipeptide **3.144**

Product	Reaction times	Yield[a]
3.144	10h	38
3.144	24h	87

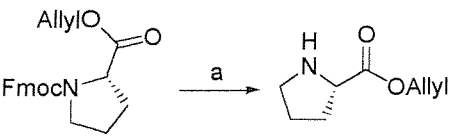
[a] Yield refers to the isolated compound (purified by chromatography)

These experimental results suggested also that the further synthesis of tripeptide **3.141** from the corresponding dipeptide **3.144** could be even slower, as it involved the coupling with the proline. For these reasons it was decided to attach the *N*-free dipeptide **3.145** at this stage onto the resin and then perform the last coupling with the proline on the solid phase.



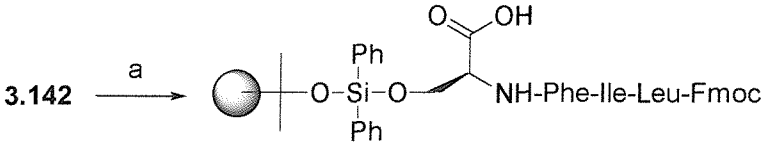
3.145

Scheme 3.16 (a) TFA, CH_2Cl_2, rt

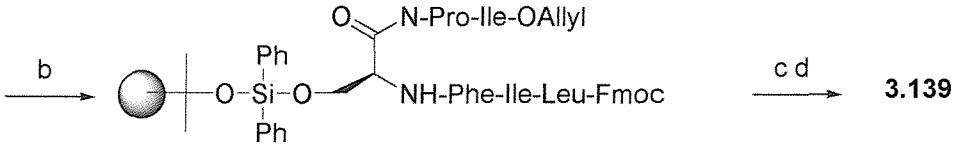


3.146 **3.147**

Scheme 3.17 (a) Et_2N, CH_3CN, rt



3.140



3.148

Scheme 3.18 (a) $Pd(PPh_3)_4$, $CHCl_3$, AcOH, NMM (37:2:1) **(b) 3.145**, PyBrop, DIPEA, CH_2Cl_2 DMF 9:1 (v:v) rt **(c)** Same as in point a **(d) 3.147**, PyBrop, DIPEA, CH_2Cl_2 DMF 9:1 (v:v) rt

In order to achieve these results the allyl ester of resin **3.142** was unblocked using the previously adopted literature procedure. [125] The deprotection was successful, as determined by the positive colour test [12] and from the mass spectrum of the cleaved material. Deprotection of **3.144** with TFA in CH_2Cl_2 afforded **3.145** (Scheme 3.16), which was then coupled with carboxyl resin **3.140** in presence of PyBrop and DIPEA. [126] Final deprotection of the ester from **3.148** and subsequent coupling with crude **3.147** afforded resin bound acyclic precursor **3.139**, as shown by mass spectrometry analysis of the cleaved material from **3.139** (Scheme 3.18). Once resin bound acyclic precursor **3.139** was obtained, the allyl ester was removed and the nitrogen deprotected in the usual way. Before the cyclization, the resin was washed with a 1 % solution of acetic acid in CH_2Cl_2. Then it was suspended in CH_2Cl_2 and then the macrocyclization was carried out under the conditions reported in the literature by Pettit, [122] employing TBTU and DIPEA as coupling system. The reaction was checked by taking a sample of beads and then performing cleavage and analysis by mass spectrometry. As before no

product was detected, even after 6 h, so the reaction was allowed to run for 24 h. Following removal of the solvents and drying, the resin was treated with TFA in CH_2Cl_2. Also in this case, no product was observed, even by crude NMR of the reaction mixture. As before, a very complex mixture was observed, that proved to be extremely insoluble in all the solvents (even in DMSO), suggesting that in this case also oligomerization occurred instead of the cyclization. This probably arose from the loading of the resin employed. The use of **2.1a** with a lower loading may have solved this problem, allowing the macrocyclization to proceed. Unfortunately, time did not allow us to pursue the macrocyclization reaction any further.

3.5 Conclusions

To summarize, this chapter demonstrated that silyl chloride resin **2.1a** can be successfully employed as a supported protecting group for a range of solid phase transformations, such as Grignard and Pd mediated C-C bond formation. In addition linker **2.1a** proved to be versatile for the SPPS, and could be used for the solid phase synthesis of hydroxyl containing peptides.

The project of the synthesis of Stylopeptide 1 has not been completed due to the problems encountered in the cyclization step. In this context the possible solutions could be the use of a silyl resin with a lower loading, or the choice of different cyclization points.

CHAPTER 4. EXPERIMENTAL

4.1 General

Melting points were measured with a Gallenkamp apparatus in open capillary tubes and are uncorrected.

Nuclear magnetic resonance spectra were recorded using a Bruker AC 300 or DPX 400 model FT-NMR spectrometer. Unless stated otherwise, signal assignments are in ppm referenced to TMS as external standard.
^{29}Si NMR spectra were recorded using hexamethyldisilane as external standard.
Gel phase ^{29}Si NMR analyses were performed at the University of Durham.

Infrared spectra were carried out with the following instruments:
1. A Nicolet Impact 400 spectrometer equipped with a Spectra Tech Tundherdome accessory.
2. A Satellite Thermo Mattson with a golden gate screw adaptor.
3. A Perkin Elmer Autoimage FTIR spectrometer equipped with an electronic Microscope.
4. A Bio-Rad FTS 135 spectrometer with a golden gate screw adaptor.
Spectral assignments were recorded in wavenumbers (cm^{-1}) using the following abbreviations: s, strong; w, weak; m, medium; br, broad.

UV measurements were performed with a Hewlett Packard 8452A diode array spectrophotometer.

THF was distilled from sodium/benzophenone under N_2; Et_3N, Pyridine and CH_2Cl_2 were distilled from calcium hydride prior to use. Other solvents were purchased already dry and used without any further purification.

Thin layer chromatography was carried out using Macherey Nagel plates (model: ALUGRAM® SIL G/UV_{254} λ=254 nm). Spots were visualised by UV and/or developed with $KMnO_4$ (1.50 g in 150 mL of water), phosphomolibdic acid (12.00 g in 250 mL of

ethanol), or ninhydrin (0.50 g in 250 mL of ethanol). Flash column chromatography was performed using Merck 60 mesh silica.
Merrifield resin (100-200 mesh, loading 1.6 mmol/g) was purchased from Novabiochem.

GC measurements were recorded using the following instruments:
1. A Varian 3800 chromatograph fitted with a 30 m×0.25 mm DB120 fused silica column and connected to a Hewlett Packard 3396 series integrator.
2. An Hewlett Packard 6890 Plus chromatograph, with the following temperature programs:
Program A: The column was initially heated at 150 °C for 2 min, and its temperature was then increased to 250 °C with a gradient of 20 °C/min.
Program B: The column was initially heated at 40 °C for 2 min; its temperature was then increased to 100 °C with a gradient of 10 °C/min. Then it was further increased to 200 °C with a gradient of 25 °C/min.
Program C: The column was initially heated at 80 °C for 2 min, and its temperature was then increased to 275 °C with a gradient of 25 °C/min.

Low resolution mass spectra were recorded using the following instruments
1. A Fisons VG platform single quadrupole mass spectrometer for ES MS
2. A ThermoQuest Trace single quadrupole GC mass spectrometer for EI MS and CI MS

High resolution mass spectra were recorded with the following instruments
1. A Bruker Apex III for ESMS
2. A VG Analytical 70-250-SE for EI MS and CI MS

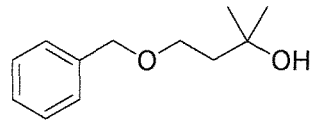
Unless stated otherwise, reactions were conducted in oven-dried glassware under N_2 atmosphere.

Elemental analyses were obtained from Univeristy College, London or MEDAC Ltd, Egham.

HPLC analyses were performed with a Hewlett Packard 1100 system equipped with a Phenomenex Prodigy reverse phase column (150×4.6 mm i.d.) with a flow rate of 1 mL/min.

4.2 Solution phase chemistry

4-(Benzyloxy)-2-methyl-2-butanol (2.3a)



To a rapidly stirred solution of 3-methyl-1,3-butanediol **2.4** (5.33 mL, 0.05 mol) in dry DMF (25 mL) at 0 °C, NaH was added portionwise (2.00 g, 0.05 mol, 60% dispersion in mineral oil). After 10 min benzyl chloride (6.32 g, 0.05 mol) was added and the resulting solution gradually warmed to room temperature. After 6 h crushed ice was added to the mixture, followed by extraction with Et_2O (3×100 mL). The combined organic layers were washed with water (3×200 mL), dried ($MgSO_4$) and concentrated under reduced pressure to give a yellow liquid. Purification was achieved by distillation (87-90°C @ 0.02 mmHg) or by chromatography (hexane AcOEt 3:1), to afford **2.3a** (7.10 g, 36.50 mmol, 73%) as a colourless liquid.

Spectroscopic data were consistent with the literature. [127, 128]

BP: 87-90°C @ 0.02 mmHg (literature: 88-91 °C @ 0.02 mmHg). [128]

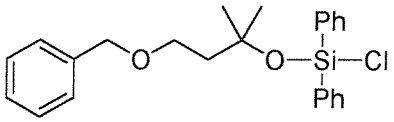
R_f: 0.43 (Hexane AcOEt 3:1)

FTIR (neat) ν_{max}: 3417 (br, O-H), 2969 (m), 2934 (m), 1453 (m), 1364 (s), 1152 (s, C-O), 1095 (s, C-OH), 736 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.41-7.20 (m, 5H, Ph**H**), 4.50 (s, 2H, Ph-C**H$_2$**O-), 3.69 (t, *J*=6.0 Hz, 2H, -O-C**H$_2$**-), 3.44 (br s, 1H, -O**H**), 1.79 (t, *J*=6.0 Hz, 2H, -**CH$_2$**-C(CH_3)$_2$), 1.23 (s, 6H, 2×C**H$_3$**)

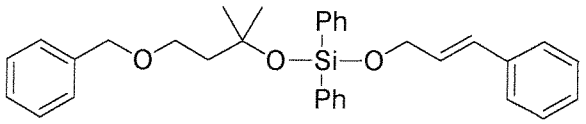
^{13}C NMR (75 MHz, $CDCl_3$) δ: 137.5 (s, Ph**C**) 128.1 (d, Ph**C**H), 127.4 (d, Ph**C**H), 127.3 (d, Ph**C**H), 72.9 (t, Ph-**C**H$_2$O-), 70.0 (s, -**C**(CH$_3$)$_2$-OH), 67.3 (t, -**C**H$_2$OBn), 41.3 (t, -**C**H$_2$-C(CH$_3$)$_2$-O), 29.0 (q, **C**H$_3$)

[3-(Benzyloxy)-1,1-dimethylpropoxy](chloro)diphenylsilane (2.2a)



To a rapidly stirred solution of **2.3a** (710 mg, 3.65 mmol) in CH_2Cl_2 (15 mL) at 0 °C, Et_3N (1.52 mL, 10.96 mmol) was added, followed by dichlorodiphenylsilane (0.77 mL, 3.66 mmol) and DMAP (447 mg, 3.66 mmol). After the complete disappearance of the starting material by TLC (5 min required, R_f: 0.65, hexane AcOEt 3:1) the new product formed was used *in situ* for further transformations. Attempts to purify the silyl chloride **2.2a** proved unsuccessful due to its high reactivity

[3-(benzyloxy)-1,1-dimethylpropoxy]diphenyl{[(*E*)-3-phenyl-2-propenyl]oxy}silane (2.10)



To a rapidly stirred solution containing crude **2.2a** (3.65 theoretical mmol) in CH_2Cl_2 (15 mL) further Et_3N (1.52 mL, 10.96 mmol) was added, followed by *trans*-cinnamyl alcohol (490 mg, 3.66 mmol) and DMAP (446 mg, 3.65 mmol) under N_2. After 20 min the reaction mixture was partitioned between water (100 mL) and Et_2O (150 mL). The

organic phase was then washed with 10% aqueous $KHSO_4$ (2×100 mL), saturated Na_2CO_3 (2×100 mL) and brine (100 mL). Evaporation of the solvent under reduced pressure and chromatography on silica afforded **2.10** as a clear oil (1.80 g, 3.57 mmol, 98%).

Starting from the readily formed **2.2a** and using the same method compounds **2.11**, **2.12**, **2.13**, and **2.14** were obtained from alcohols **2.16**, **2.17**, **2.18** and **2.19**, respectively.

R_f: 0.76 (Hexane AcOEt 3:1)

FTIR (neat) ν_{max}: 3049 (w), 2978 (w), 1943 (w), 1450 (w), 1427 (w), 1365 (w), 1110 (s, C-O), 1058 (s, C-O), 963 (s), 736 (s, Si-O), 712 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.90-7.70 (dt, *J*=5.8, 1.4 Hz, 4H, Ph**H**), 7.40-7.10 (m, 16H, Ph**H**), 6.54 (dt, *J*=15.4, 1.5 Hz, 1H, PhC**H**=CH-), 6.20 (dt, *J*=16.2, 5.1 Hz, 1H, Ph-CH=C**H**-), 4.40 (s, 2H, Ph-C**H$_2$**-O-), 4.34 (dd, *J*=5.1, 1.5 Hz, 2H -O-C**H$_2$**-CH=), 3.62 (t, *J*=7.2 Hz, 2H, Bn-O-C**H$_2$**-), 1.86 (t, *J*=6.8 Hz, 2H, -C**H$_2$**-C(CH$_3$)$_2$-O-), 1.24 (s, 6H, 2×C**H$_3$**)

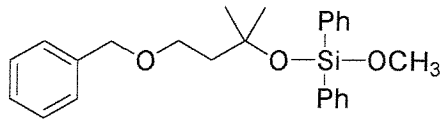
^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (s, Ph**C**), 137.0 (s, Ph**C**), 135.0 (s, Ph**C**), 134.7 (d, Ph**C**H), 130.0 (d, Ph**C**H=CH), 129.9 (d, Ph**C**H), 128.5 (d, Ph**C**H), 128.4 (d, PhCH=**C**H), 128.3 (d, Ph**C**H), 127.7 (d, Ph**C**H), 127.6 (d, Ph**C**H), 127.5 (d, Ph**C**H), 127.4 (d, Ph**C**H), 126.4 (d, Ph**C**H), 75.0 (s, -**C**(CH$_3$)$_2$-), 73.3 (t, Ph-**C**H$_2$-O-), 67.1 (t, **C**H$_2$-OBn), 63.6 (t, =CH-**C**H$_2$-O-), 44.0 (t, -**C**H$_2$-C(CH$_3$)$_2$-), 30.7 (q, **C**H$_3$)

GC CIMS: R_t: 23.01 min; *m/z* (abundance): 315 $[Ph_2Si{=}OCH_2CH{=}CHPh]^+$ (2%), 177 $[BnOCH_2CH_2(CH_3)_2C]^+$ (36%), 117 $[PhCH{=}CH\text{-}CH_2]^+$ (28%), 91 $[C_6H_5CH_2]^+$ (100 %)

^{29}Si NMR (80 MHz, $CDCl_3$) δ: -45.9

Elemental analysis: Anal cal. for $C_{33}H_{36}O_3Si$: C 77.91, H 7.13; found: C 77.72, H 7.16

(3-Benzyloxy-1,1-dimethylpropoxy)methoxydiphenylsilane (2.11) from (2.2a) and (2.16)



Employing the same method (see page 105), compound **2.11** was obtained by reaction between silyl chloride **2.2a** and methanol **2.16**.

Colourless oil (1.33 g, 3.28 mmol, 90%)

R_f: 0.44 (Hexane CH_2Cl_2 1:1)

FTIR (neat) ν_{max}: 3068 (w), 2971 (w), 2937 (w), 1429 (m), 1366 (m), 1113 (s, C-O), 1078 (s, C-O) 1025 (s, C-O), 738 (s)

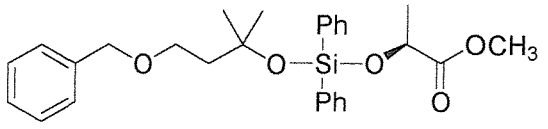
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70-7.50 (m, 4H, Ph**H**), 7.45-7.20 (m, 11H, Ph**H**), 4.46 (s, 2H, Ph-C**H$_2$**-O-), 3.67 (t, *J*=7.3 Hz, 2H, Bn-O-C**H$_2$**-), 3.51 (s, 3H, OC**H$_3$**), 1.89 (t, *J*=7.3 Hz, 2H, -C**H$_2$**-C(CH$_3$)$_2$-O-), 1.27 (s, 6H, 2×C**H$_3$**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (s, Ph**C**), 134.8 (d, Ph**C**H), 134.6 (s, Ph**C**), 129.8 (d, Ph**C**H), 128.2 (d, Ph**C**H), 127.6 (d, Ph**C**H), 127.5 (d, Ph**C**H), 127.4 (d, Ph**C**H), 74.8 (s, -**C**(CH$_3$)$_2$-), 72.9 (t, Ph-**C**H$_2$-O-), 67.0 (t, **C**H$_2$-OBn), 50.0 (q, -O**C**H$_3$), 43.9 (t, -**C**H$_2$-C(CH$_3$)$_2$-), 30.2 (q, **C**H$_3$)

ES MS: *m/z* (abundance): 429 $[(M+Na)]^+$(37%), 445 $[(M+K)]^+$(8%)

HR ESMS: Exact mass calculated for $C_{25}H_{30}O_3SiNa$ [M+Na]: 429.1856; found 429.1851

(2*S*)-[(3-Benzyloxy-1,1-dimethylpropoxy)dimethylsilanoxy]propionic acid methyl ester (2.12) from (2.2a) and (2.17)



Employing the same method (see page 105), compound **2.12** was obtained by reaction between silyl chloride **2.2a** and *S*-(-)-methyl lactate **2.17**.

Colourless oil (1.62 g, 3.39 mmol, 93%)

R_f: 0.50 (Hexane AcOEt 5:1)

$[\alpha]_D$: -1.84° (c=5.2, AcOEt)

FTIR (neat) ν_{max}: 3068 (w), 3035 (w), 2983 (w), 1748 (s, C=O), 1360 (w), 1124 (s, C-O), 1062 (s, C-O), 854 (s), 850 (s), 741 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.65 (m, 4H, PhH), 7.25-7.50 (m, 11H, PhH), 4.46 (s, 2H, Ph-C**H$_2$**-O-), 4.44 (q, *J*=6.6 Hz, 1H, Ph_2SiOCH), 3.66 (t, *J*=7.3 Hz, 2H, BnO-C**H$_2$**), 3.59 (s, 3H, -C(=O)OC**H$_3$**), 1.88 (t, *J*=7.3 Hz, 2H, BnO-CH_2-C**H$_2$**-), 1.37 (d, *J*=6.6 Hz, 3H, C**H$_3$**-CH($COOCH_3$)-O-), 1.27 (s, 3H, -C**H$_3$**), 1.26 (s, 3H, -C**H$_3$**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.0 (s, -**C**(=O)OCH_3), 138.5 (s, Ph**C**), 135,1 (d, Ph**C**H), 134.3 (d, Ph**C**H), 134.1 (d, Ph**C**H), 130.0 (d, Ph**C**H), 128.3 (d, Ph**C**H), 127.6 (d, Ph**C**H), 127.5 (s, Ph**C**), 75.2 (s, -C(**C**H_3)$_2$O-), 72.9 (t, Ph-**C**H_2-O-), 68.2 (d, (CH_3)**C**H($COOCH_3$-O-)), 67.0 (t, -**C**H_2OBn), 51.7 (q, -C(=O)O**C**H_3), 43.8 (t, -**C**H_2-CH_2OBn), 30.2 (q, **C**H_3), 21.2 (q, **C**H_3-CH($COOCH_3$)-O-)

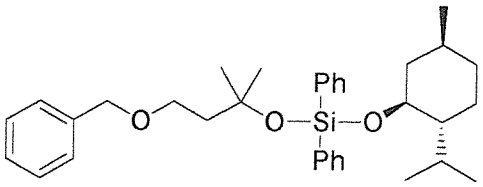
^{29}Si NMR (80 MHz, $CDCl_3$) δ: -56.4

GC CIMS: R_t:17.85 min; *m/z* (abundance): 285 $[Ph_2Si{=}O\text{-}CH(CH_3)(C{=}O)OMe]^+$ (50%), 177 $[BnOCH_2CH_2(CH_3)_2C]^+$ (36%), 91 $[C_6H_5CH_2]^+$ (100%)

HR ESMS: Exact mass calculated for $C_{28}H_{34}O_5SiNa$ [M+Na]: 501.2068; found 501.2080

Elemental analysis: Anal cal. for $C_{28}H_{34}O_5Si$: C, 70.26 H, 7.16; found: C 70.30, H 7.07

(1*R*, 2*S*, 5*R*)-(3-Benzyloxy-1,1-dimethylpropoxy)-(2-isopropyl-4-methylcyclohexyloxy)diphenylsilane (2.13) from (2.2a) and (2.18)



Employing the same method (see page 105), compound **2.13** was obtained by reaction between silyl chloride **2.2a** and (1*R*, 2*S*, 5*R*)-(-)-menthol **2.18**.

Colourless oil (1.74 g, 3.28 mmol, 90%)

R_f: 0.57 (Hexane CH_2Cl_2 1:1)

$[\alpha]_D$: -0.25° (c=1, AcOEt)

FTIR (neat) ν_{max}: 3067 (w), 2953 (w), 2921 (w), 1156 (m), 1111 (s, C-O), 1049 (s, C-O), 740 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.70-7.60 (m, 4H, PhH), 7.45-7.25 (m, 11H, PhH), 4.46 (s, 2H, Ph-C**H$_2$**-O-), 3.68 (t, *J*=7.0 Hz, 2H, BnOC**H$_2$**-), 3.49 (td, *J*=10.0, 4.0 Hz, 1H, -C(CH$_3$)$_2$O(Ph)$_2$SiOC**H**-), 2.32 (apparent quintuple doublet, *J*=7.3, 2.9 Hz, 1H), 2.05-1.85 (m, 1H), 1.86 (t, *J*=7.0 Hz, 2H, BnOCH$_2$-C**H$_2$**), 1.47-1.60 (m, 2H), 1.35-1.00 (m, 9H), 0.86 (d, *J*=7.3 Hz 3H, -C**H$_3$**), 0.81 (d, *J*=6.0 Hz, 3H, -C**H$_3$**, overlapped with 2H, m), 0.49 (d, *J*=6.0 Hz, 3H, -C**H$_3$**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.6 (s, PhC), 136.0 (s, PhC), 135.5 (d, PhCH), 135.1 (d, PhCH), 129.6 (d, PhCH), 128.3 (d, PhCH), 127.6 (d, PhC), 127.4 (d, PhC), 74.7 (s,

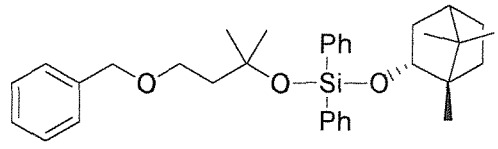
-C$(CH_3)_2$-O-), 73.5 (d, -O-$(Ph)_2$Si-O-CH-), 72.9 (t, Ph-CH_2-O-), 67.2 (t, BnOCH_2-), 50.2 (d, CH), 45.4 (t, CH_2), 43.9 (t, -CH_2-C$(CH_3)_2$-), 34.4 (t, CH_2), 31.5 (d, CH), 30.3 (q, CH_3), 25.2 (d, -CH), 22.6 (t, -CH_2), 22.3 (q, -CH_3), 21.3 (q, -CH_3), 15.6 (q, -CH_3)

^{29}Si NMR (80 MHz, $CDCl_3$) δ: -49.3

GC EIMS: R_t: 19.35 min; *m/z* (abundance): 395 $[(CH_3)_2C{=}OSiPh_2OMenthyl]^+$ (8)%, 337 $[Ph_2Si{=}OMenthyl]^+$ (10%), 199 $[Ph_2Si{=}OH]^+$ (89%), 91 $[C_6H_5CH_2]^+$ (100%)

HR ESMS: Exact mass calculated for $C_{34}H_{46}O_3SiNa$ [M+Na]: 553.3108; found 553.3104

(1*S*)-(3-Benzyloxy-1,1-dimethylpropoxy)diphenyl(1,7,7-trimethylbicyclo [2.2.1]hept-2-yloxy) silane (2.14) from (2.2a) and (2.19)



Employing the same method (see page 105), compound **2.14** was obtained by reaction between silyl chloride **2.2a** and *endo*-(1*S*)-(-)-borneol **2.19**.

Colourless oil (1.81 g, 3.43 mmol, 94%)

R_f: 0.57 (Hexane CH_2Cl_2 1:1)

$[\alpha]_D$: -0.18° (c=5.5, AcOEt)

FTIR (neat) ν_{max}: 3067 (s), 2948 (m), 2871 (w), 1163 (m), 1113 (s, C-O), 1064 (s, C-O), 1037 (s, C-O), 739 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.58 (t, *J*=5.8 Hz, 4H, PhC**H**), 7.45-7.22 (m, 11H, PhC**H**), 4.45 (s, 2H, Ph-C**H$_2$**-O-), 4.12 (ddd *J*=9.5, 2.9, 1.4 Hz, 1H, Ph_2SiOC**H**), 3.67 (t,

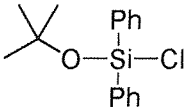
J=6.7 Hz, 2H, Bn-O-C**H**$_2$-), 2.30-2.12 (m, 1H), 1.88 (t, *J*=7.0 Hz, 2H, -C**H**$_2$-C(CH$_3$)$_2$-O-), 1.77-1.58 (m, 1H), 1.56-1.47 (m, 1H), 1.35-1.14 (m, 9H), 0.99 (dd, *J*=13.2, 3.7 Hz, 1H), 0.79 (s, 3H, C**H**$_3$), 0.71 (s, 3H, C**H**$_3$), 0.69 (s, 3H, C**H**$_3$)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (s, Ph**C**), 135.8 (s, Ph**C**), 135.6 (s, Ph**C**), 135.0 (d Ph**C**H), 129.6 (d, Ph**C**H), 128.3 (d, Ph**C**H), 127.6 (d, Ph**C**H), 127.5 (d, Ph**C**H), 127.4 (d, Ph**C**H), 78.0 (d, Ph_2SiOCH-), 74.6 (s, **C**(CH$_3$)$_2$-O), 72.9 (t, Ph**C**H$_2$O-), 67.2 (t, BnO**C**H$_2$-), 50.0 (s, **C**(CH$_3$)$_2$ or **C**(CH$_3$)), 47.2 (s, **C**(CH$_3$)$_2$ or **C**(CH$_3$)), 45.1 (d, **C**H), 44.0 (t, BnOCH$_2$**C**H$_2$), 39.0 (t, **C**H$_2$), 30.0 (s, 2×**C**H$_3$), 28.3 (t, **C**H$_2$), 26.5 (t, **C**H$_2$), 20.2 (q, **C**H$_3$), 18.7 (q, **C**H$_3$), 13.7 (q, **C**H$_3$)

ES MS: *m/z* (abundance): 551 [(M+Na)]$^+$(10%)

HR ESMS: Exact mass calculated for $C_{34}H_{44}O_3SiNa$ [M+Na]: 551.2952; found 551.2953

1-chloro, 1-1-diphenylsilyl(*tert*-butyl)ether (2.5)



To a rapidly stirred solution of ^{t}BuOH **2.6** (1.00 mL, 10.40 mmol) in CH_2Cl_2 (15 mL) at 0 °C, Et_3N (1.60 mL, 11.66 mmol) was added, followed by dichlorodiphenylsilane (2.20 mL, 10.60 mmol) and DMAP (1.30 g, 10.60 mmol). After complete disappearance of the starting material by TLC (15 min required, hexane AcOEt 3:1) the reaction mixture containing crude **2.5** was used directly in the next step.

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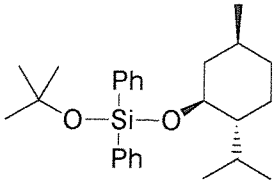
***Tert*-butoxy{[(1*R*, 2*R*, 5*R*)2-isopropyl-5methylcyclohexyl]oxy}diphenylsilane (2.7)**[50]



To a rapidly stirred solution containing crude **2.5** (10.40 theoretical mmol) in CH_2Cl_2 (15 mL) further Et_3N (2.00 mL, 13.78 mmol) was added, followed by (1*R*, 2*S*, 5*R*)-(-)-menthol (1.57 g, 10.00 mmol) and DMAP (1.30 g, 10.60 mmol). After the complete disappearance of the silyl chloride by TLC (1 h required, hexane CH_2Cl_2 9:1) the reaction mixture was partitioned between water (200 mL) and Et_2O (100 mL). The organic phase was then washed with 10% aqueous $KHSO_4$ (100 mL), brine (100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded **2.7** (4.00 g, 9.88 mmol, 95%) as a colourless oil.

R_f: 0.30 (Hexane CH_2Cl_2 9:1)

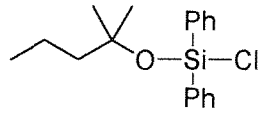
FTIR (neat) ν_{max}: 2973 (w), 2916 (w), 2869 (w), 1426 (w), 1370 (w), 1190 (m), 1114 (s, C-O), 1048 (s, C-O), 868 (w), 703 (s)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.70-7.55 (m, 4H, PhH), 7.43-7.27 (m, 6H, PhH), 3.52 (td, *J*=10.5, 4.5 Hz, 1H, $(CH_3)_3O(Ph)_2$-SiOCH-), 2.38 (sd, *J*=7.0, 2.5 Hz, 1H, $(CH_3)_2$CH-CH)), 2.07-1.98 (m, 1H), 1.61-1.51 (m, 2H), 1.26 (s, 9H, $(CH_3)_3$COSi$(Ph)_2$-), 1.30-1.00 (m, 2H, overlapped with the singlet at 1.26), 0.89 (d, *J*=7.0 Hz, 3H, -CH_3), 0.83 (d, *J*=6.5 Hz, 3H, -CH_3), 0.92-0.77 (m, 3H, overlapped with the singlets at 0.89 and 0.83), 0.54 (d, *J*=7.0 Hz, 3H, -CH_3)

^{13}C NMR (100 MHz, $CDCl_3$) δ: 136.3 (s, PhC), 135.8 (s, PhC), 135.1 (d, PhCH), 129.5 (d, PhCH), 127.4 (d, PhCH), 73.6 (s, $(CH_3)_3$C-O), 73.4 (d, Ph_2SiOCH-), 50.2 (d, CH), 45.5 (t, CH_2), 34.5 (t, CH_2), 31.9 (s, CH_3), 31.5 (d, CH), 25.2 (d, CH), 22.6 (t, CH_2), 22.2 (q, CH_3), 21.3 (q, CH_3), 15.6 (q, CH_3)

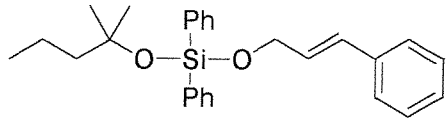
GC CIMS: R_t: 15.21 min; *m/z* (abundance): 395 $[M\text{-}CH_3]^+$ (8%), 199 $[Ph_2Si{=}OH]^+$ (100%), 139 $[C_{10}H_{19}]^+$ (68%)

1-Chloro, 1-1diphenylsilyl (1,1-dimethylbutyl) ether (2.24)



To a rapidly stirred solution of 2-methyl-2-pentanol **2.23** (0.50 mL, 3.96 mmol) in CH_2Cl_2 (15 mL) at 0 °C, Et_3N (0.60 mL, 4.36 mmol) was added, followed by dichlorodiphenylsilane (0.83 mL, 3.96 mmol) and DMAP (0.48 g, 3.96 mmol) under N_2. After the total disappearance of the starting material by TLC (10 min required, hexane AcOEt 3:1) the reaction mixture was used directly for the preparation of **2.25**, **2.26** and **2.27**.

(1,1 Dimethylbutoxy)diphenyl{[(*E*)-3-phenyl-2-propenyl]oxy}silane (2.25)



To a rapidly stirred solution containing **2.24** (3.96 theoretical mmol) in CH_2Cl_2 (15 mL), Et_3N (0.77 mL, 5.54 mmol) was added, followed by *trans*-cinnamyl alcohol (530 mg, 3.96 mmol) and DMAP (483 mg, 3.96 mmol). After the complete disappearance of the starting material by TLC (25 min required, hexane AcOEt 3:1) the reaction mixture was partitioned between water (100 mL) and Et_2O (100 mL). The aqueous phase was extracted with Et_2O (100 mL) and the combined organics were washed with 10% $KHSO_4$ (100 mL), brine (100 mL), saturated aqueous $NaHCO_3$ (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded **2.25** (1.62 g, 3.88 mmol, 98%) as a clear oil.

By adopting the same method, compounds **2.26** and **2.27** were obtained from **2.24** and alcohols **2.17** and **2.18**, respectively.

R_f: 0.40 (Hexane CH_2Cl_2 1:1)

FTIR (neat) ν_{max}: 2968 (w), 1431 (m), 1360 (m), 1114 (s, C-O), 1039 (s, C-O), 963 (m)

^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.78 (d, *J*=6.5 Hz, 4H PhH), 7.52-7.25 (m, 11H, PhH), 6.70 (d, *J*=15.5 Hz, 1H, PhCH=CH-), 6.37 (dt, *J*=16.0, 3.5 Hz, 1H, Ph-CH=CH-), 4.52 (d, *J*=3.5 Hz, 2H, CH_2C=CH-Ph), 1.64-1.46 (m, 4H, -CH_2CH_2-), 1.35 (s, 6H, -$(CH_3)_2$C-O), 0.95 (t, *J*=6.0 Hz, 3H, CH_3)

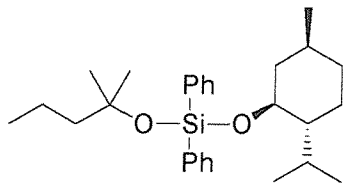
^{13}C NMR (100 MHz, $CDCl_3$) δ: 137.1 (s, PhC), 135.0 (s, PhC), 134.9 (d, PhCH), 134.3 (d, PhCH), 129.9 (d, PhCH=CH-), 129.8 (d, PhCH), 128.4 (d, PhCH=CH-), 127.6 (d, PhCH), 127.3 (d, PhCH), 126.3 (d, PhCH), 75.9 (s, -C$(CH_3)_2$-O-), 63.5 (t, PhCH=CH-CH_2-O-), 47.1 (t, -CH_2-), 29.8 (q, -C$(CH_3)_2$-O-), 17.6 (t, -CH_2-), 14.8 (q, CH_3-CH_2-)

^{29}Si NMR (80 MHz, $CDCl_3$) δ: -49.0

GC EIMS: R_t: 10.66 min; *m/z* (abundance): 416 [M] (16%), 401 $[M\text{-}CH_3]^+$ (4%), 373 $[M\text{-}C_3H_7]^+$ (24%), 315 $[PhCH{=}CHCH_2\text{-}O{=}SiPh_2]^+$ (54%), 199 $[Ph_2Si{=}OH]^+$ (100%), 117 $[PhCH{=}CH\text{-}CH_2]^+$ (85), 91 $[C_6H_5CH_2]^+$ (46%), 77 $[C_6H_5]^+$ (42%), 43 $[C_3H_7]^+$ (42%)

HR EIMS: Exact mass calculated for $C_{27}H_{32}O_2Si$: 416.21791; found: 416.21716

(1,1)dimethylbutoxy{[(1*R*, 2*R*, 3*R*)-2-isopropyl] 5-methylcyclohexyloxy} diphenylsilane (2.27) from (2.24) and (2.18)



Employing the same method (see page 113), compound **2.27** was obtained by reaction between silyl chloride **2.24** and (1*R*, 2*S*, 5*R*)-(-)-menthol **2.18**.

Colourless oil (1.56 g, 3.56 mmol, 90%)

$[\alpha]_D$: -2.01° (c=5.3, AcOEt)

R_f: 0.50 (Hexane CH_2Cl_2 2.5:0.5)

FTIR (neat) ν_{max}: 2954 (w), 2921 (w), 2869 (w), 1171 (m), 1114 (s, C-O), 1072 (s, C-O), 1043 (s), 717 (s), 698 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71 (t, *J*= 8.0 Hz, 2H, Ph**H**), 7.70 (t, *J*= 7.4 Hz, 2H, Ph**H**), 7.47-7.30 (m, 6H, Ph**H**), 3.57 (td, *J*=10.3, 4.4 Hz, 1H, -C(CH_3)$_2$O(Ph)$_2$SiOC**H**-), 2.44 (apparent quintuple doublet, *J*=7.3, 2.9 Hz, 1H), 2.10 (apparent dquin, *J*=11.7, 2.2 Hz, 1H), 1.68-1.56 (m, 2H), 1.55-1.45 (m, 4H), 1.27 (s, 3H, -C**H$_3$**), 1.25 (s, 3H, -C**H$_3$**), 1.40-1.10 (m, 4H, overlapped with the two singlets), 0.95 (d, *J*=6.6 Hz, 3H, -C**H$_3$**), 0.89 (d, *J*=6.0 Hz, 3H, -C**H$_3$**), 1.00-0.80 (m, 4H, overlapped with the previous two doublets), 0.60 (d, *J*=6.6 Hz, 3H, -C**H$_3$**)

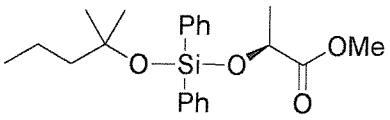
^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.4 (s, Ph**C**), 136.0 (s, Ph**C**), 135.2 (d, Ph**C**H), 129.5 (d, Ph**C**H), 127.4 (d, Ph**C**H), 75.6 (s, -**C**(CH_3)$_2$-O), 73.4 (d, -O-(Ph)$_2$Si-O-**C**H), 50.1 (d, **C**H), 47.2 (t, CH_3-**C**H_2-CH_2 or CH_3-CH_2-**C**H_2), 45.5 (t, -**C**H_2), 34.4 (t, -**C**H_2-), 31.5 (d, **C**H), 29.8 (q, **C**H_3), 25.2 (d, -**C**H-), 22.6 (t, -**C**H_2), 22.2 (q, -**C**H_3), 21.3 (q, -**C**H_3), 17.6 (t, CH_3-**C**H_2-CH_2 or CH_3-CH_2-**C**H_2), 15.6 (q, -**C**H_3), 14.6 (q, **C**H_3CH_2)

^{29}Si NMR (80 MHz, $CDCl_3$) δ: -45.9

GC EIMS: R_t: 9.64 min; *m/z* (abundance): 423 $[M\text{-}CH_3]^+$ (2%), 395 $[M\text{-}C_3H_7]^+$ (8%), 337 $[Ph_2Si{=}O\text{-Menthyl}]^+$ (9%), 199 $[Ph_2Si{=}OH]^+$ (100%), 77 $[C_6H_5]^+$ (8%), 43 $[C_3H_7]^+$ (30%)

HR CIMS: Exact mass calculated for $C_{28}H_{42}O_2Si$: 438.29541; found: 438.29497

(*S*)-2-[(1,1-Dimethyl-butoxy)-diphenylsilanoxyl]propionic acid methyl ester (2.26) from (2.24) and (2.17)



Employing the same method (see page 113), compound **2.26** was obtained by reaction between silyl chloride **2.24** and (*S*)-(-)-methyl lactate **2.17**.

Colourless oil (1.34 g, 3.48 mmol, 88%)

$[\alpha]_D$: -0.56° (c=1.5, AcOEt)

R_f: 0.30 (Hexane CH_2Cl_2 1:1)

FTIR (neat) ν_{max}: 2959 (w), 1758 (s, C=O), 1124 (s, C-O), 1043 (s, C-O), 717 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.80-7.60 (m, 4H, Ph**H**), 7.50-7.25 (m, 6H, Ph**H**), 4.51 (q, *J*=6.6 Hz, 1H, $(CH_3)C\mathbf{H}(COOCH_3)$-O-), 3.62 (s, 3H, -C(=O)O$C\mathbf{H_3}$), 1.55-1.34 (m, 4H, -$C\mathbf{H_2}C\mathbf{H_2}$-), 1.42 (d, *J*=7.0 Hz, 3H, $C\mathbf{H_3}$-CH$(COOCH_3)$-O-), 1.26 (s, $C\mathbf{H_3}$), 1.25 (s, $C\mathbf{H_3}$), 0.89 (t, *J*= 7.3 Hz, 3H, $C\mathbf{H_3}$-CH_2-)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.9 (s, -**C**(=O)OCH_3), 135.0 (d, Ph**C**H), 134.4 (s, Ph**C**), 130.0 (d, Ph**C**H), 127.5 (d, Ph**C**H), 76.1 (s, -**C**$(CH_3)_2$-O-), 68.1 (d, $(CH_3)\mathbf{C}H(COOCH_3$-O-), 51.6 (q, -(C(=O)O$CH_3$), 47.0 (t, CH_3-$\mathbf{C}H_2$-CH_2 or CH_3-CH_2-

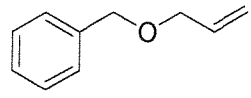
CH_2), 29.7 (q, CH_3), 21.1 (q, CH_3-CH($COOCH_3$)-O-), 17.6 (t, CH_3-CH_2-CH_2 or CH_3-CH_2-CH_2), 14.5 (q, CH_3-CH_2)

^{29}Si NMR (80 MHz, $CDCl_3$) δ: -46.3

GC EIMS: R_t: 9.08 min; *m/z* (abundance): 285 $[Ph_2Si{=}OCH(CH_3)(COOMe)]^+$ (68%), 199 $[Ph_2Si{=}OH]^+$ (48%), 77 $[C_6H_5]^+$ (10%)

Elemental analysis. Anal. calcd. for $C_{22}H_{30}O_4Si$: C, 68.36; H, 7.82; found: C, 68.46 H, 7.59

1-(Allyloxy)methylbenzene (2.71)



To a rapidly stirred solution of allyl alcohol **2.70** (10.30 mL, 0.05 mol) in dry DMF (15 mL) at 0 °C, NaH (6.52 g, 0.16 mol, 60% dispersion in mineral oil) was added portionwise. Benzyl chloride (5.81 mL, 0.05 mol) was added dropwise over 10 min and the reaction gradually warmed to room temperature. After 4 h the mixture was quenched by addition of crushed ice and was extracted with Et_2O (3×100 mL); the combined organics were then dried ($MgSO_4$). Removal of the solvent under reduced pressure followed by chromatography (hexane AcOEt 9.5:0.5) or distillation (100-102°C @ 20 mm) afforded pure **2.71** (5.08 g, 0.03 mol, 68 %) as a colourless liquid.

Spectroscopic data were consistent with the literature. [129]

R_f: 0.50 (Hexane AcOEt 9.5:0.5)

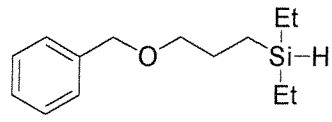
BP: 100-102 °C @ 20 mmHg (literature: 95°C @ 18 mmHg). [129]

FTIR (neat) ν_{max}: 3032 (w), 1495 (w), 1453 (w), 1090 (s, C-O), 923 (s), 736 (s), 697 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60-7.20 (m, 5H, PhH), 6.10-5.90 (m, 1H, H_2C=CH-CH_2O-), 5.38 (d, *J*=17.0 Hz, 1H, *trans* HHC=CH-), 5.27 (d, *J*=10.3 Hz, 1H, *cis* HHC=CH-), 4.58 (s, 2H, Ph-CH_2-O-), 4.09 (d, *J*=5.2 Hz, 2H, H_2C=CH-CH_2O-)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.3 (s, PhCH), 134.8 (d, CH), 128.4 (d, PhCH), 127.7 (d, PhCH), 127.6 (d, PhCH), 117.1 (t H_2C=CH-), 72.1 (t, -CH_2-), 71.2 (t, -CH_2-)

[3-(Benzyloxy)propyl](diethyl)silane (2.72)



To a rapidly stirred solution of **2.71** (1.46 g, 9.84 mmol) in dry toluene (10 mL), diethylsilane (2.00 mL, 15.40 mmol) and Wilkinson's catalyst (4.10 mg, 4.43×10^{-3} mmol) were added. The resulting solution was rapidly stirred and warmed to 40 °C. After 1 h water (30 mL) was added to the mixture and extracted with Et_2O (2×100 mL). The combined organics were collected and dried ($MgSO_4$). Removal of the solvent under reduced pressure and distillation (78-81°C @ 20-22 mmHg for 20 min) afforded **2.72** as a colourless liquid (1.60 g, 6.80 mmol, 70%).

BP: 78-81 °C @ 20-22 mmHg

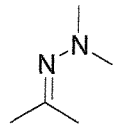
R_f: 0.63 (Hexane AcOEt 9.5:0.5)

FTIR (neat) ν_{max}: 3100 (w), 2953 (s), 2873 (s), 2099 (s, Si-H), 1454 (m), 1099 (s, C-O), 1013 (s, C-O), 970 (m), 813 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.55-7.11 (m, 5H, PhH), 4.57 (s, 2H, Ph-CH_2O-), 3.52 (t, *J*=7.0 Hz, 2H, Bn-O-CH_2), 1.77 (quin, *J*= 8.0 Hz, 2H, -CH_2-), 1.07 (t, *J*=8.0 Hz, 6H, 2×CH_3), 0.90-0.60 (m, 7H)

Further characterisation was not possible due to the instability of **2.72**.

Acetone 2-2 dimethylydrazone (2.66)



The title compound was prepared according to the procedure of Wiley *et al.* [99] *N,N* dimethylhydrazine (6.00 mL, 78.90 mmol) was added to acetone (5.00 mL, 68.00 mmol) and the resulting solution was rapidly stirred and heated to 50 °C for 4 h. During this period the colour of the solution changed from colourless to yellow/green. Solid sodium hydroxide was then added to induce the separation of the two layers and the organic phase was collected; the operation was repeated twice. The combined organics were concentrated and distilled to afford pure **2.66** (4.28 g, 42.80 mmol, 63%) as a pale yellow liquid.

Physical and spectroscopic data were consistent with the literature. [99]

BP: 90-93 °C (literature: 92-94 °C). [99]

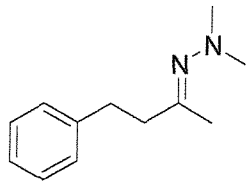
R_f: 0.50 (Hexane AcOEt 9.5:0.5)

FTIR (neat) ν_{max}: 2987 (w), 2950 (w), 2885 (w), 1649 (m C=N), 1464 (m), 1445 (m), 1356 (m), 963 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.33 (s, 6H, -N(CH_3)$_2$), 1.87 (s, 3H, -CH_3), 1.83 (s, 3H, -CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 164.8 (s, (CH_3)$_2$C=N-), 47.0 (q, (CH_3)$_2$N), 25.1 (q, CH_3), 18.0 (q, CH_3)

4-Phenyl-2-butanone-2,2-dimethylhydrazone (2.67)



The title compound was prepared following the protocol of Mitra *et al.* [100] To a rapidly stirred solution of **2.66** (500 mg, 5.00 mmol) in dry THF (25 mL) at 0 °C, ^{n}BuLi (2.00 mL, 5.00 mmol, 2.5 M solution in hexane) was added. After 30 min, benzyl chloride (0.57 mL, 5.00 mmol) was added and the reaction warmed to room temperature. After 2 h the reaction was cooled in an ice bath. Saturated NH_4Cl (100 mL) and Et_2O (100 mL) were then added and the system warmed to room temperature. The aqueous layer was extracted with Et_2O (2×100 mL), and the combined organics were dried ($MgSO_4$). Removal of the solvent under reduced pressure gave **2.67** (810 mg, 4.25 mmol) as a lemon yellow oil. The crude product was found to be pure enough to proceed to next step.

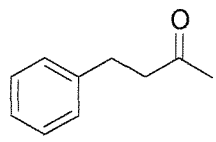
Spectroscopic data were consistent with the literature. [130]

R_f: 0.88 (AcOEt)

FTIR (neat) ν_{max}: 3030 (w), 2950 (w), 1497 (w), 1455 (m), 1356 (w), 745 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40-7.10 (m, 5H, Ph**H**), 2.86 (t, *J*=7.3 Hz, 2H, Ph-C**H$_2$**-), 2.53 (t, *J*= 7.3 Hz, 2H, Ph-CH_2-C**H$_2$**-), 2.43 (s, 6H, -N(C**H$_3$**)$_2$), 1.96 (s, 3H, C**H$_3$**-C(=N)-)

4-Phenyl-2-butanone (2.68)



Substrate **2.67** (190 mg, 1.00 mmol) was dissolved in a mixture of 4:1 THF water (10 mL) and the resulting yellow solution was rapidly stirred. Phosphate buffer was then added (3.00 mL, 1M aqueous solution) followed by $NaIO_4$ (1.32 g, 6.20 mmol) in water (7 mL). The colour of the reaction gradually changed to pink and after 10 min a white precipitate began to form and increased in quantity over 1.5 h. After this period the starting material completely disappeared by TLC (AcOEt). The reaction mixture was then filtered and the liquid partitioned between water and CH_2Cl_2 (100 mL of each). The extraction was repeated and the combined organics dried ($MgSO_4$). Removal of the solvent under reduced pressure gave **2.68** as a pale colourless liquid (144 mg, 0.97 mmol, 97%). No further purification was needed.

Spectroscopic data were consistent with the literature. [131]

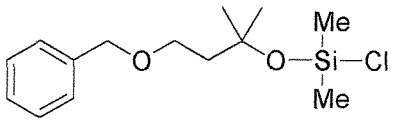
R_f: 0.20 (AcOEt)

FTIR (neat) ν_{max}: 1710 (s), 1597 (w), 1455 (w), 1162 (w), 1034 (w), 750 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.71-7.30 (m, 5H, Ph**H**), 2.80 (t, *J*=8.0 Hz, 2H, Ph-C**H$_2$**-), 2.65 (t, *J*=8.0 Hz, 2H, Ph-CH$_2$-C**H$_2$**-), 2.30 (s, 3H, C**H$_3$**(C=O)-)

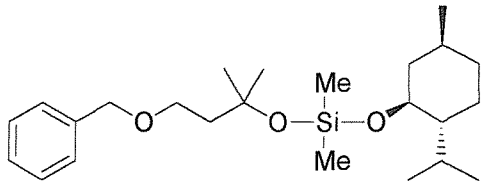
^{13}C NMR (75 MHz, $CDCl_3$) δ: 207.9 (s, **C**(=O)-), 140.8 (Ph**C**), 128.3 (Ph**C**), 128.1 (Ph**C**), 125.9 (Ph**C**), 44.9 (-**C**H$_2$-CH$_2$-(C=O)-), 29.9 (Ph-CH$_2$-**C**H$_2$- or **C**H$_3$-C(C=O)-), 29.5 (Ph-CH$_2$-**C**H$_2$- or **C**H$_3$-C(C=O)-)

(3-Benzyloxy-1, 1-dimethylpropoxy)chlorodimethylsilane (2.2b)



To a rapidly stirred solution of dichlorodimethylsilane (90 μL, 0.73 mmol) in CH_2Cl_2 (15 mL), Et_3N (153 μL, 1.10 mmol) was added, followed by **2.3a** (142 mg, 0.73 mmol) and DMAP (90 mg, 0.73 mmol). After the complete disappearance of the starting material (5 min, TLC hexane AcOEt 3:1) the product was used *in situ* for further transformations.

(1*R*, 2*S*, 5*R*)-(3-Benzyloxy-1,1-dimethylpropoxy)-(2-isopropyl-4-methylcyclohexyloxy)dimethylsilane (2.59)



To the solution containing **2.2b** (0.73 theoretical mmol) in CH_2Cl_2 (15 mL) Et_3N (153 μL, 1.10 mmol) was added followed by (1*R*, 2*S*, 5*R*)-(-)-menthol (103 mg, 0.66 mmol) and DMAP (90 mg, 0.73 mmol). After the complete disappearance of **2.2b** by TLC (hexane AcOEt 3:0.5) the reaction mixture was partitioned between water and Et_2O (100 mL of each). The aqueous phase was extracted with Et_2O (2×100 mL) and the combined organics were washed with 10% $KHSO_4$ (100 mL), brine (100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica (hexane AcOEt 3:0.5) afforded pure **2.59** (268 mg, 0.66 mmol, 90%) as a colourless oil.

R_f: 0.70 (Hexane AcOEt 3:0.5)

FTIR (neat) ν_{max}: 2950 (w), 2916 (w), 1252 (m), 1110 (s, C-O), 1062 (s, C-O), 1048 (s, C-O), 788 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.35-7.22 (m, 5H, Ph**H**), 4.48 (s, 2H, Ph-**CH$_2$**-O-), 3.60 (t, *J*=7.3 Hz, 2H, BnO-**CH$_2$**-), 3.50 (td, *J*=10.3, 4.4 Hz, 1H, -C(CH$_3$)$_2$O(Ph)$_2$SiOC**H**-), 2.17 (apparent quintuple doublet, *J*=7.3, 2.2 Hz, 1H), 1.98-1.87 (m, 1H), 1.83 (t, *J*=7.3 Hz, 2H, BnO-CH$_2$-**CH$_2$**-), 1.70-1.50 (m, 2H), 1.45-1.22 (m, 1H, overlapped with a singlet at 1.27, 6H, 2×**CH$_3$**), 1.18-0.90 (m, 3H), 0.87 (d, *J*=7.3 Hz, 6H, 2×**CH$_3$**), 0.83-0.76 (m, 1H), 0.72 (d, *J*=6.6 Hz, 3H, -**CH$_3$**), 0.10 (s, 3H, Si-**CH$_3$**), 0.08 (s, 3H, Si-**CH$_3$**)

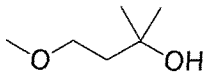
^{13}C NMR (75 MHz, $CDCl_3$) δ: 138.5 (s, Ph**C**), 128.3 (d, Ph**C**H), 127.5 (d, Ph**C**H), 127.4 (d, Ph**C**H), 73.1 (s, -**C**(CH$_3$)$_2$-O-), 72.9 (t, Ph**C**H$_2$O-), 72.2 (d, -O-(Ph)$_2$Si-O-**C**H-), 67.2 (t, BnO**C**H$_2$-), 49.8 (d, **C**H), 45.3 (t, **C**H$_2$), 43.9 (t, BnOCH$_2$-**C**H$_2$-), 34.5 (t, **C**H$_2$), 31.6 (d, **C**H), 30.2 (q, **C**H$_3$), 25.2 (d, -**C**H), 22.8 (t, **C**H$_2$), 22.3 (q, **C**H$_3$), 21.2 (q, -**C**H$_3$), 15.9 (q, -**C**H$_3$), 1.0 (q, Si-**C**H$_3$), 0.7 (q, Si-**C**H$_3$)

GC CIMS: R_t: 9.48 min; *m/z* (abundance): 271 $[Me_2C{=}OSiMe_2\text{-}OMenthyl]^+$ (37%), 251 $[BnOC_2H_4C(CH_3)_2O{=}SiMe_2]^+$ (80%), 91 $[C_6H_5CH_2]^+$, (100%), 75 $[Me_2Si{=}OH]^+$ (34%)

^{29}Si NMR (80 MHz, $CDCl_3$) δ: -15.9

Elemental analysis: Anal.calcd. for $C_{24}H_{42}O_3Si$: C, 70.88; H, 10.41; found C, 70.45, H, 10.81

4-Methoxy-butan-2-ol (2.20)



To a rapidly stirred solution of 3-methyl-1,3-butanediol **2.4** (10 mL, 0.09 mol) in dry DMF (50 mL) at 0 °C, NaH was added portionwise (3.74 g, 0.09 mol, 60% dispersion in mineral oil). After 30 min methyl iodide (5.80 mL, 0.09 mol) was added and the

resulting solution warmed to room temperature. After 3 h the system was cooled to 0 °C and brine (60 mL) was added to the mixture, followed by extraction with Et_2O (3×100 mL); the combined organics were then dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica (hexane AcOEt 1:1) afforded **2.20** (7.12 g, 0.06 mol, 67%) as a colourless liquid.

Physical and spectroscopic data were consistent with the literature. [132]

BP: 141-142 °C (literature: 143-144 °C). [132]

R_f: 0.42 (Hexane AcOEt 1:1)

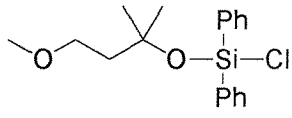
FTIR (neat) ν_{max}: 3444 (br), 2971 (m), 2934 (m), 1465 (m), 1264 (m), 1110 (s), 732 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 3.56 (t, *J*= 6.0 Hz, 2H, CH_3O-C**H$_2$**-), 3.30 (s, 3H, -OC**H$_3$**), 3.20 (s, 1H, O**H**), 1.70 (t, *J*=6.0 Hz, 2H, CH_3O-CH_2-C**H$_2$**-), 1.17 (s, 6H, -C(C**H$_3$**)$_2$OH)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 70.5 (s, -**C**$(CH_3)_2$OH), 70.1 (t, CH_3O-**C**H_2-), 58.8 (q, H_3**C**O-), 41.3 (t, CH_3O-CH_2-**C**H_2-), 29.2 (q, **C**H_3)

GC CIMS: R_t: 5.47 min; *m/z* (abundance): 136 $[M+NH_4]^+$ (6%), 119 $[M+H]^+$ (70%), 101 $[M-OH]^+$ (100%)

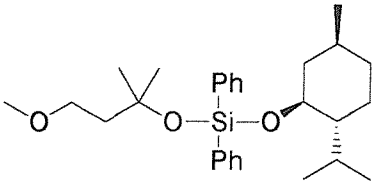
Chloro-(3-methoxy-1,1-dimethylpropoxy)diphenylsilane (2.21)



To a rapidly stirred solution of **2.20** (80 mg, 0.67 mmol) in CH_2Cl_2 (10 mL), Et_3N (113 μL, 0.81 mmol) was added, followed by dichlorodiphenylsilane (142 μL, 0.67 mmol) and DMAP (82 mg, 0.67 mmol). After the complete disappearance of the starting

material by TLC (15 min, hexane AcOEt 1:1) the product was used *in situ* for further transformations.

(1*R*, 2*S*, 5*R*)-(2-Isopropyl-4-methylcyclohexyloxy)-(3-methoxy-1,1-dimethylpropoxy)diphenylsilane (2.22)



To the mixture reaction containing **2.21** (0.67 theoretical mmol), (1*R*, 2*S*, 5*R*)-(-)-menthol (105 mg, 0.67 mmol) was added, followed by DMAP (82 mg, 0.67 mmol). After the complete disappearance of **2.21** by TLC (hexane AcOEt 8:1), water (50 mL) was added to the reaction mixture, followed by extraction with Et_2O (3×100 mL). The combined organics were washed with 10% $KHSO_4$ (100 mL), brine (100 mL), saturated aqueous $NaHCO_3$ (100 mL), brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica (hexane AcOEt 8:1) afforded pure **2.22** (265 mgs, 0.58 mmol, 87%) as a colourless oil.

R_f: 0.62 (Hexane AcOEt 8:1)

FTIR (neat) ν_{max}: 2949 (w), 2911 (w), 1181 (m), 1119 (s, C-O), 1067 (s, C-O), 1062 (s, C-O), 741 (s), 722 (s)

^{1}**H NMR** (300 MHz, $CDCl_3$) δ: 7.59-7.51 (m, 4H, Ph**H**), 7.35-7.22 (m, 6H, Ph**H**), 3.54 (t, *J*=7.3 Hz, 2H, MeO-C**H$_2$**-), 3.48 (td, *J*=10.3, 4.4 Hz, 1H, -C(CH$_3$)$_2$O(Ph)$_2$SiOC**H**-), 3.29 (s, 3H, C**H$_3$**O-), 2.33 (apparent quintuple doublet, *J*=6.6, 2.2 Hz, 1H), 2.02-1.94 (m, 1H), 1.78 (t, *J*=7.3 Hz, 2H, MeO-CH$_2$-C**H$_2$**-), 1.60-1.50 (m, 2H), 1.30 (s, 3H, -C**H$_3$**), 1.20 (s, 3H, -C**H$_3$**), 1.35-1.00 (m, 3H, overlapped with the previous singlets), 0.86 (d, *J*=6.6 Hz, 3H, -C**H$_3$**), 0.81 (d, *J*=6.6 Hz, 3H, -C**H$_3$**), 0.90-0.74 (m, 2H, overlapped with the previous doublets), 0.50 (d, *J*=7.3 Hz, 3H, -C**H$_3$**)

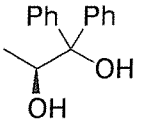
^{13}C NMR (75 MHz, $CDCl_3$) δ: 136.1 (s, Ph**C**), 135.6 (s, Ph**C**), 135.1 (d, Ph**C**H), 129.6 (d, Ph**C**H), 127.4 (d, Ph**C**H), 74.7 (s, -**C**$(CH_3)_2$-O), 73.6 (d, -O-$(Ph)_2$Si-O-**C**H-), 69.5 (t, MeO**C**H_2**C**H_2-), 58.5 (q, **C**H_3O-), 50.1 (d, **C**H), 45.5 (t, **C**H_2), 43.8 (t, MeO**C**H_2**C**H_2-), 34.4 (t, **C**H_2), 31.5 (d, **C**H), 30.2 (q, **C**H_3), 25.2 (d, **C**H), 22.6 (t, **C**H_2), 22.2 (q, -**C**H_3), 21.3 (q, -**C**H_3), 15.6 (q, -**C**H_3)

^{29}Si NMR (80 MHz, $CDCl_3$) δ: -49.3

GC CIMS: R_t: 9.99 min; *m/z* (abundance): 395 $[(Me)_2C{=}O\text{-}SiPh_2OMentyl]^+$, (12%), 337 $[Ph_2Si{=}O\text{-}Menthyl]^+$ (14%), 299 $[Ph_2Si{=}O\text{-}C(CH_3)_2\text{-}C_2H_4OMe]^+$ (59%), 199 $[Ph_2Si{=}OH]^+$ (100%), 45 $[CH_3O{=}CH_2]^+$ (48%)

Elemental analysis: Anal.Calcd for $C_{28}H_{42}O_3Si$: C, 73.96; H, 9.31; found C, 73.86; H, 9.15

(2*S*)-1,1-Diphenyl-1,2-propanediol (3.77)



The title compound was prepared using the method of Mikami *et al.* [110] To an ice cooled, rapidly stirred solution of *S*-methyl lactate **2.17** (1.00 mL, 10.40 mmol) in dry THF (30 mL), phenylmagnesium bromide was added dropwise (8.72 mL, 26.00 mmol, 3M solution in THF). After the complete disappearance of the starting material by TLC (hexane AcOEt 9:1) saturated NH_4Cl (50 mL) was added to the reaction mixture and extracted with AcOEt (50 mL). The organic phase was then washed with brine (3×50 mL) and dried (Na_2SO_4). Removal of the solvent under reduced pressure followed by chromatography on silica (Hexane AcOEt 9:1) and final recrystallization afforded **3.77** as a white solid (1.54 g, 6.76 mmol, 65%).

Spectroscopic data were consistent with the literature. [110]

MP: 89-90°C (Hexane Et_2O) (literature: 91.5-92 °C). [110]

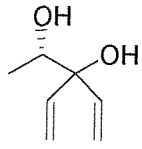
FTIR (neat) ν_{max}: 3567 (s, O-H), 3502 (s, O-H), 2989 (w), 1446 (s), 1265 (s), 1067 (s, C-O), 1010 (s, C-O), 769 (s), 710 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.63 (d, *J*=7.3 Hz, 2H, PhC**H**), 7.45 (d, *J*= 7.3 Hz, 2H, PhC**H**), 7.41-7.14 (m, 6H, PhC**H**), 4.84 (q, *J*=6.5 Hz, 1H, (CH_3)C**H**(OH)-), 3.00 (s, 1H, O**H**), 1.87 (s, 1H, O**H**), 1.12 (d, *J*=6.0 Hz, 3H, CH_3)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 145.5 (s, Ph**C**), 143.8 (s, Ph**C**), 128.6 (d, Ph**C**H), 128.1 (d, Ph**C**H), 127.2 (d, Ph**C**H), 126.7 (d, Ph**C**H), 126.1 (d, Ph**C**H), 125.4 (d, Ph**C**H), 79.8 (s, Ph_2**C**(OH)-), 71.5 (d, **C**HOH), 16.5 (q, **C**H_3)

GC CIMS: R_t: 13.72 min; *m/z* (abundance): 228 $[M]^+$ (8%), 211 $[M\text{-}OH]^+$ (57%), 183 $[(Ph)_2C{=}OH]^+$ (100 %), 105 $[PhC{=}O]^+$ (82%), 77 $[C_6H_5]^+$ (54%)

(2*S*)-3-Vinylpent-4-ene-2,3 diol (3.78)



The title compound was prepared according to the method of Schmidt *et al.* [111] *S*-Methyl lactate **2.17** (0.90 mL, 9.60 mmol) was dissolved in dry THF (60 mL) under N_2. The resulting solution was then rapidly stirred and cooled at –78 °C. Vinylmagnesium bromide (28.00 mL, 1M in THF) was then added dropwise. Stirring was then continued for 1 h at this temperature and for additional 13 h at room temperature. The reaction mixture was then partitioned between aqueous NH_4Cl (60 mL) and AcOEt (150 mL). The organic phase was further washed with brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography afforded **3.78** as colourless oil (860 mg, 6.72 mmol, 70%).

Spectroscopic data were consistent with the literature. [111]

R_f: 0.22 (Hexane AcOEt 3:1)

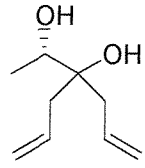
FTIR ($CHCl_3$) ν_{max}: 3404 (br, O-H), 3075 (w), 2979 (w), 1639 (m), 1374 (m), 1046 (s, C=O), 986 (s), 910 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.92 (ddd, *J*=17.0, 11.0, 3.7 Hz, 2H, 2×(-C**H**=CH_2)), 5.36 (d, *J*=9.5 Hz, 1H, *trans*C**H**HC=CH-), 5.30 (d, *J*=9.5 Hz, 1H, *trans*C**H**HC=CH-), 5.20 (dd, *J*= 9.7, 3.7 Hz, 2H, 2×(*cis*C**H**H=CH-)), 3.64 (quartet of doublets, *J*= 6.6, 3.0 Hz, 1H, CH_3-C**H**(OH)-), 2.67 (s, br, O**H**), 2.50 (s, br, O**H**), 1.09 (d, 6.6 Hz, 3H, C**H**$_3$-)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.0 (d, -**C**H=CH_2), 138.0 (d, -**C**H=CH_2), 115.6 (t, -CH=**C**H_2), 115.2 (t, -CH=**C**H_2), 78.3 (s, -C(C_2H_3)$_2$**C**-OH), 72.6 (d, -**C**H(OH)-), 16.8 (q, -**C**H_3)

GC CIMS: R_t: 6.51 min; *m/z* (abundance): 146 $[M+NH_4]^+$ (4%), 128 $[M]^+$ (30%), 111 $[M\text{-}OH]^+$ (22%), 55 $[CH_2=C\text{-}C=O]^+$ (100%)

(2*S*)-3-Allyl-hex-5-ene-2,3-diol (3.79)



The title compound was prepared according to the method of Wallace *et al.* [112] *S*-Methyl lactate **2.17** (0.90 mL, 9.60 mmol) was dissolved in dry THF (60 mL) under N_2. The resulting solution was then cooled to 0 °C and allylmagnesium bromide (28.00 mL, 1M in THF) was added. Stirring continued for 3 h at 0 °C; then the reaction mixture was partitioned between aqueous NH_4Cl (100 mL) and AcOEt (150 mL) and the organic phase was further washed with brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded **3.79** as colourless oil (1.01 g, 6.52 mmol, 68%).

R_f: 0.27 (Hexane AcOEt 3:1)

FTIR ($CHCl_3$) ν_{max}: 3395 (br, O-H), 2982 (w), 1078 (s), 991 (s), 923 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 6.00-5.76 (m, 2H, 2×(-C**H**=CH_2)), 5.24-5.00 (m, 4H, 2×(CH=C**H$_2$**), 3.70 (q, *J*=6.6 Hz, 1H, CH_3-C**H**(OH)-), 2.46-2.04 (m, 6H, 2×(-C**H$_2$**CH=CH_2) and 2×O**H**), 1.15 (d, *J*=6.6 Hz, 3H, C**H$_3$**-)

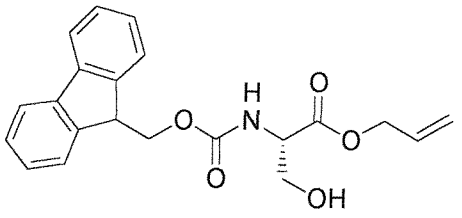
^{13}C NMR (75 MHz, $CDCl_3$) δ: 133.5 (d, 2×(**C**H=CH_2)), 118.9 (t, CH=**C**H$_2$), 118.6 (t, CH=**C**H$_2$), 75.3 (s, (Allyl)$_2$**C**-OH), 71.6 (d, CH_3**C**H(OH)-), 41.0 (t, **C**H$_2$-CH=CH_2), 38.9 (t, **C**H$_2$-CH=CH_2), 16.9 (q, -**C**H$_3$)

GC CIMS: R_t: 8.38 min; *m/z* (abundance): 174 $[M+NH_4]^+$ (90%), 156 $[M]^+$ (6%), 139 $[M-OH]^+$ (100%), 95 $[(CH_2=C-CH_2)_2CH]^+$ (44%), 69 $[CH_2=C-CH_2-C=O]^+$ (64%)

General protocol for esterification of the *N*-Fmoc amino acids with allyl bromide

To a rapidly stirred solution of the Fmoc L-Amino acid (1.00-1.50 g, 3.05-4.80 mmol) in dry DMF (100 mL), K_2CO_3 (422-665 mg, 3.05-4.80 mmol, 1 eq respect to the aminoacid) was added, followed by allyl bromide (284-490 μL, 3.36-5.70 mmol, 1.2 eq respect to the aminoacid). Stirring continued for 3 h, then to the reaction was added AcOEt (200 mL). The organic layer was washed with 10% aqueous $KHSO_4$ (100 mL), brine (100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure and chromatography on silica afforded pure compounds **3.132a**, **3.132b**, **3.143** and **3.146**.

(2*S*)-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-hydroxypropionic acid allyl ester (3.132a)



Starting from Fmoc L-Serine **3.131a** (1.00 g, 3.05 mmol) compound **3.132a** was obtained as a white amorphous solid (0.90 g, 2.44 mmol, 80%).

Spectroscopic data were consistent with the literature. [123]

R_f: 0.34 (Hexane AcOEt 2:1)

$[\alpha]_D$: +0.31° (c=7.5, AcOEt) (literature: +0.30°) (c=7.5, AcOEt). [123]

MP: 81-82°C (Hexane Et_2O) (literature: 82.5-84). [123]

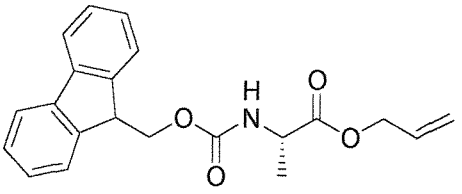
FTIR ($CHCl_3$) ν_{max}: 3404 (s, br, O-H), 3068 (w), 2945 (w), 2883 (w), 1720 (s, C=O), 1195 (s, C-O), 1053 (s, C-O)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.74 (d, *J*=7.3 Hz, 2H, FmocC**H**), 7.60 (d, *J*=4.5 Hz, 2H, FmocC**H**), 7.38 (t, *J*=7.3 Hz, 2H, FmocC**H**), 7.28 (t, *J*=7.3 Hz, 2H, FmocC**H**), 6.00-5.76 (m, 2H, CH_2=C**H**- and N**H**), 5.31 (dd, *J*=17.0, 1.5 Hz, 1H, *trans*C**H**H=CH-), 5.23 (dd, *J*=10.0, 1.5 Hz, 1H, *cis*C**H**H=CH-), 4.65 (d, *J*=5.1 Hz, 2H, CH_2=C-C**H**-), 4.55-4.30 (m, 3H, C_α**H** and FmocC**H$_2$**), 4.20 (t, *J*=6.6 Hz, 1H, FmocC**H**), 4.10-3.80 (m, 2H, C**H$_2$**OH), 2.70 (s, O**H**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.2 (s, **C**(=O)OAllyl), 156.2 (s, Fmoc**C**(=O)), 143.5 (s, Fmoc**C**), 141.2 (s, Fmoc**C**), 131.2 (d, CH_2C=**C**H-), 127.6 (d, Fmoc**C**H), 127.0 (d, Fmoc**C**H), 125.0 (d, Fmoc**C**H), 120.0 (d, Fmoc**C**H), 118.8 (t, **C**H_2C=C), 67.1 (t, Fmoc **C**H_2), 66.2 (t, CH_2=CH-**C**H_2-O), 63.1 (t, **C**H_2OH), 56.0 (d, **C$_\alpha$**H), 46.9 (d, Fmoc**C**H)

ES MS: *m/z* (abundance): 368 $[M+H]^+$ (17%), 390 $[M+Na]^+$ (32%), 406 $[M+K]^+$ (5%), 757 $[2M+Na]^+$ (100%), 773 $[2M+K]^+$ (7%), 1124 $[3M+Na]^+$ (23%)

(2*S*)-(9*H*-Fluoren-9-ylmethoxycarbonylamino)propionic acid allyl ester (3.132b)



Starting from Fmoc L-Alanine **3.131b** (1.50 g, 4.80 mmol) compound **3.132b** was obtained as a white amorphous solid (1.52 g, 4.32 mmol, 90 %).

Spectroscopic data were consistent with the literature. [133]

R_f: 0.33 (Hexane AcOEt 4:1)

$[\alpha]_D$: -5.37° (c=0.53, AcOEt)

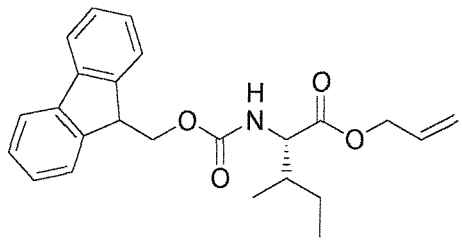
FTIR ($CHCl_3$) ν_{max}: 3321 (m, N-H), 1736 (s, C(=O)OAllyl), 1691 (s, NHC(=O)-), 1536 (s), 1272 (s, C-O)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, *J*= 7.3 Hz, 2H, FmocC**H**), 7.68-7.50 (m, 2H, FmocC**H**), 7.40 (t, *J*=7.3 Hz, 2H, FmocC**H**), 7.30 (t, *J*=7.3 Hz, 2H, FmocC**H**), 6.00-5.80 (m, 1H, -C**H**=CH_2), 5.49 (d, *J*=7.3 Hz, 1H, N**H**), 5.33 (dd, *J*=17.0, 1.5 Hz, 1H, *trans*-CH=C**H$_2$**), 5.25 (dd, *J*=10.0, 1.5 Hz, 1H, *cis*-CH=C**H$_2$**), 4.64 (d, *J*=5.2 Hz, 2H, (-C**H$_2$** -CH=CH_2), 4.52-4.30 (m, 3H, FmocC**H$_2$** and C_α**H**) 4.22 (t, *J*=7.3 Hz, 1H Fmoc-C**H**), 1.44 (d, *J*=7.3 Hz, 3H, C**H$_3$**-C_α)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 172.8 (s, -**C**(=O)OAllyl), 155.7 (s, Fmoc**C**(=O)NH-), 143.8 (s, Fmoc**C**), 141.3 (s, Fmoc**C**), 131.5 (d, CH_2-**C**H=CH_2), 127.7 (d, Fmoc**C**H), 127.1 (d, Fmoc**C**H), 125.1 (d, Fmoc**C**H), 120.0 (d, Fmoc**C**H), 118.8 (t, -CH_2-CH=**C**H_2), 67.0 (t, Fmoc**C**H_2), 66.0 (t, **C**H_2-CH=CH_2), 49.7 (d, **C**$_\alpha$H), 47.1 (d, Fmoc**C**H), 18.7 (q, -**C**H_3)

ES MS: *m/z* (abundance): 374 $[M+Na]^+$ (60%), 725 $[2M+Na]^+$ (100%)

(2*S*, 3*R*)-(9*H*-Fluoren-9-ylmethoxycarbonylamino) 3-methylpentanoic acid allyl ester (3.143)



Starting from Fmoc L-isoleucine (1.50 g, 4.24 mmol) compound **3.143** was obtained as a colourless oil (1.58 g, 4.03 mmol, 95 %)

$[\alpha]_D^{25}$: -1.1° (c=1, $CHCl_3$)

R_f: 0.38 (Hexane AcOEt 4:1)

FTIR ($CHCl_3$) ν_{max}: 3347 (m, br, N-H), 3066 (w), 2964 (m), 1723 (s, C(=O)OAllyl), 1517 (s, NHC(=O)), 1245 (s, C-O), 1194 (s, C-O).

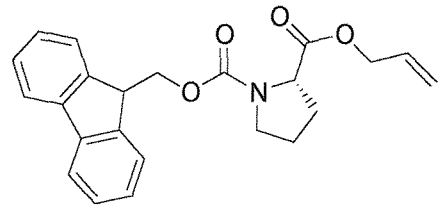
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.75 (d, *J*= 7.3 Hz, 2H, FmocC**H**), 7.58 (d, *J*= 7.3 Hz, 2H, FmocC**H**), 7.40 (t, *J*=7.3 Hz, 2H, FmocC**H**), 7.30 (t, *J*=7.3 Hz, 2H, FmocC**H**), 6.00-5.80 (m, 1H, -C**H**=CH_2), 5.40-5.20 (m, 3H, *trans*-C**H**H=CH, *cis*-C**H**H=CH-, and N**H**), 4.63 (d, *J*=5.1 Hz, 2H, -C**H$_2$** -CH=CH_2), 4.50-4.30 (m, 3H, C_α**H** and FmocC**H$_2$**), 4.21 (t, *J*=7.3 Hz, 1H, FmocC**H**), 2.00-1.82 (m, 1H), 1.53-1.31 (m, 1H), 1.28-1.06 (m, 1H), 1.03-0.74 (m, 6H, 2×C**H$_3$**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 171.8 (s, **C**(=O)OAllyl), 156.0 (s, Fmoc**C**(=O)NH-), 143.7 (s, Fmoc**C**), 141.3 (s, Fmoc**C**), 131.5 (d, -CH_2**C**H=CH_2), 127.7 (d, Fmoc**C**H), 127.0 (d, Fmoc**C**H), 125.1 (d, Fmoc**C**H), 120.0 (d, Fmoc**C**H), 119.0 (t, O-CH_2-CH=**C**H_2), 67.0 (t, Fmoc**C**H_2), 65.8 (t, -O-**C**H_2CH=CH_2), 58.3 (d, **C**$_\alpha$H), 47.1 (d, Fmoc**C**H), 38.1 (d, **C**$_\alpha$H), 25.0 (t, **C**H_2-CH_3), 15.5 (q, **C**H_3), 11.6 (q, **C**H_3)

ES MS: *m/z* (abundance): 416 $[M+Na]^+$ (28%), 809 $[2M+Na]^+$ (100%)

HR ESMS: Calculated for $C_{24}H_{27}NO_4Na$ [M+Na]: 416.1832; found: 416.1836

2(*S*)-Pyrrolidine-1,2-dicarboxylic acid 2-allyl ester 1-(9*H*-fluoren-9-ylmethyl) ester (3.146)



Starting from Fmoc L-proline (1.50 g, 4.44 mmol) compound **3.146** was obtained as a colourless oil (1.51 g, 4.00 mmol, 90 %).

$[\alpha]_D^{25}$: -56.1° (c=1, $CHCl_3$)

R_f: 0.36 (Hexane AcOEt 4:1)

FTIR ($CHCl_3$) ν_{max}: 3064 (w), 2952 (w), 1743 (s, C(=O)OAllyl), 1700 (s, NHC(=O)), 1413 (s), 1169 (s, C-O), 1117 (s, C-O)

NMR analysis complicated by the presence of two conformers

^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.86 (t, *J*=7.0 Hz, 2H, FmocC**H**), 7.60 (dd, *J*=7.5, 3.5 Hz, 1H FmocC**H**), 7.59 (dd, *J*=10.0, 7.5 Hz, 1H, FmocC**H**), 7.45-7.36 (m, 2H, FmocC**H**), 7.35-7.26 (m, 2H, FmocC**H**), 5.95-5.77 (m, 1H, -CH_2-C**H**=CH_2), 5.27 (ddd, *J*=17.5, 10.5, 1.5 Hz, 1H, *trans* CH**H**=CH_2), 5.17 (dd, *J*= 10.0, 2.0 Hz, 1H, *cis* CH**H**=CH_2), 4.62-4.44 (m, 2H), 4.36-4.20 (m, 3H, FmocC**H$_2$** and C_α**H**), 4.15 (t, *J*=6.5 Hz, 1H, FmocC**H**), 3.50-3.28 (m, 2H, >NC**H$_2$**-), 2.29-2.11 (m, 1H), 1.95-1.70 (m, 3H)

^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.0 and 171.9 (s, -**C**(=O)OAllyl), 154.0 and 153.7 (s, Fmoc**C**(=O)NH-), 143.9 and 143.8 (s, Fmoc**C**), 140.9 (s, Fmoc**C**), 132.5 and 132.4 (d, CH_2-**C**H=CH_2), 127.8 (d, Fmoc**C**H), 127.2 (d, Fmoc**C**H), 125.2 and 125.1 (d, Fmoc**C**H), 120.2 (d, Fmoc**C**H), 118.0 and 117.7 (t, -CH_2 -CH=**C**H_2), 66.8 (t,

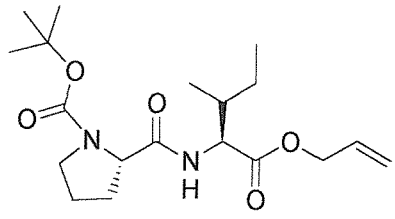
Fmoc**C**H_2), 65.1 and 64.9 (t, -**C**H_2-CH=CH_2), 59.0 and 58.4 (d, **C**$_\alpha$H), 46.8 and 46.2 (t, >N**C**H_2-), 46.7 (d, Fmoc**C**H), 30.6 and 29.5 (t, -**C**H_2-), 24.1 and 23.0 (t, -**C**H_2-)

High temperature NMR studies proved impossible to do due to the thermal instability of the compound. After heating, total cleavage of the Fmoc group was observed.

ES MS: *m/z* (abundance): 400 $[M+Na]^+$ (30%), 777 $[2M+Na]^+$ (100%)

HR ESMS: Calculated for $C_{23}H_{23}NO_4Na$ [M+Na]: 400.1525; found: 400.1519

(2*S*)-(1*S*-Allyloxycarbonyl-2*R*-methylbutylcarbamoyl)pyrrolidine-1-carboxylic acid *tert*-butyl ester (3.144)



For the synthesis of dipeptide **3.144** the following 2-step protocol was employed

Step 1. *N*-Deprotection

The deprotection was carried out employing the procedure of Pettit *et al.* [122] Fmoc L-Ile OAllyl **3.143** (3.00 g, 7.62 mmol) was dissolved in a mixture of acetonitrile and diethylamine (1:1 v/v, 40 mL). The resulting solution was then rapidly stirred at room temperature and the reaction checked by TLC (Hexane AcOEt 4:1). After 2 h the solvent was removed under reduced pressure with the temperature of the water bath not exceeding 35 °C, affording a yellow liquid. The crude *N*-free aminoacid was immediately used in the next step.

Step 2. Amino acid coupling [134]

The residue of the previous step was dissolved in freshly dried CH_2Cl_2 (150 mL), then Boc L-ProOH (1.50 g, 6.97 mmol) was added, followed by DCC (1.50 g, 7.27 mmol). A precipitate of *N-N* dicyclohexylurea started to form and its amount gradually increased. After 24 h at room temperature the urea was removed by filtration and the organic phase was washed with 1N HCl (100 mL), saturated $NaHCO_3$ (100 mL), brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica (Hexane AcOEt 5:1) afforded **3.144** as a bright yellow oil (2.23 g, 6.06 mmol, 87%).

R_f: 0.55 (Hexane AcOEt 5:1)

FTIR ($CHCl_3$) ν_{max}: 3338 (br, N-H), 2966 (m), 1739 (s, C(=O)OAllyl), 1690 (s, NHC(=O)O^{t}Bu), 1670 (s, NHC(=O), 1392 (s), 1172 (s, C-O)

^{1}H NMR (400 MHz, DMSO-d_6, 100 °C) δ: 7.57 (d, *J*=7.5 Hz, 1H, N**H**) 5.95-5.80 (m, 1H, -CH_2-C**H**=CH_2), 5.31 (dd, *J*=17.0, 1.5 Hz, 1H, *trans*-CH**H**=CH_2), 5.20 (d, *J*=10.0 Hz, 1H, *cis* -CH**H**=CH_2), 4.58 (d, *J*=5.0 Hz, 2H, -C**H$_2$**-CH=CH_2), 4.31 (t, *J*=7.0 Hz, 1H, C_α**H**), 4.26 (dd, *J*= 7.4, 6.8 Hz, 1H, C_α**H**), 3.42-3.25 (m, 2H, >NC**H$_2$**), 2.15-2.00 (m, 1H), 1.95-1.70 (m, 4H), 1.49 (sx, *J*=7.5 Hz, 1H), 1.38 (s, 9H, -C(=O)O(C**H$_3$**)$_3$), 1.24 (sp, *J*=7.1 Hz, 1H), 0.95-0.85 (m, 6H, C**H$_3$**-CH_2- and C**H$_3$**-C_αH-)

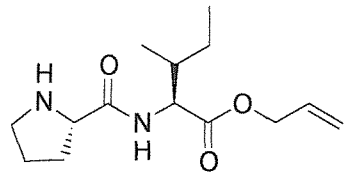
^{13}C NMR analysis complicated by the presence of two conformers

^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.8 (s), 172.3 (s), 171.2 (s), 153.8 and 153.4 (s, ^{t}ButOC(=O)N), 132.4 (d, -CH_2-**C**H=CH_2), 118.1 (t, CH_2-CH=**C**H_2), 78.6 and 78.4 (s, (CH_3)$_3$**C**-O-), 64.8 (t, -O-**C**H_2-CH=CH_2), 59.0 and 58.9 (d, **C**$_\alpha$H), 56.5, (d, **C**$_\alpha$H), 46.6 (t, **C**H_2-N<), 36.4 and 36.2 (d, **C**$_\alpha$H), 31.0 and 29.5 (t, **C**H_2), 28.1 (q, -(C=O)OC(**C**H_3)$_3$), 24.8 (t, **C**H_2), 23.9 and 23.0 (t, **C**H_2), 15.6 (q, **C**H_3), 11.1 (q, **C**H_3)

ES MS: *m/z* (abundance): 369 $[M+H]^+$ (5%), 391 $[M+Na]^+$ (40%), 759 $[2M+Na]^+$ (100%)

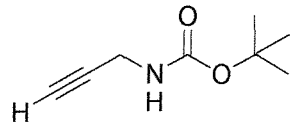
HR ESMS: Calculated for $C_{19}H_{32}N_2O_5Na$ [M+Na]: 391. 2209; found: 391. 2194

(3*R*)-Methyl-(2*S*)-[(pyrrolidine-(2*S*)-carbonyl)amino]pentanoic acid allyl ester (3.145)



Dipeptide **3.144** (2.00 g, 5.42 mmol) was dissolved in a mixture of TFA and CH_2Cl_2 1:1 (100 mL) and the resulting solution rapidly stirred at room temperature. After the total disappearance of the starting material **3.144** by TLC (Hexane AcOEt 5:1) the solvents were removed and cold hexane (100 mL) was added. Formation of a white precipitate was observed instantly. The solid was collected by filtration and used immediately for the successive transformations.

Prop-2-ynyl-carbamic acid *tert*-butyl ester (3.90)



The title compound was prepared employing the method of Krasia *et al.* [114] To a rapidly stirred solution of propargylamine (2.50 mL, 0.03 mol) in THF (50 mL) at 0 °C, di-*tert*-butyldicarbonate (11.00 g, 0.05 mol) was added, followed by DMAP (2.20 g, 0.02 mol). The ice bath was then removed and stirring was continued for 48 h at room temperature. After this period the reaction mixture was partitioned between water (50 mL) and Et_2O (60 mL). The aqueous phase was extracted again with Et_2O (60 mL) and the combined organics washed with 1N HCl (50 mL), brine (50 mL), sat $NaHCO_3$ (50 mL), brine (50 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and

chromatography on silica (Hexane AcOEt 6:3) afforded **3.90** as a white solid (4.42 g, 0.03 mol, 95%).

Spectroscopic data were consistent with the literature. [143, 144]

MP: 43-44°C (Pentane) (literature: 45). [144]

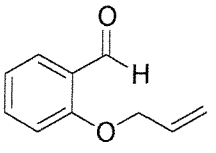
R_f: 0.16 (Hexane AcOEt 6:3)

FTIR ($CHCl_3$) ν_{max}: 3304 (s, C≡C-H or N-H), 3280 (s, C≡C-H or NH), 3050 (w), 2981 (m), 1673 (s, C=O), 1530 (s), 1250 (s), 1157 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.78 (s, br, 1H, N**H**), 3.88 (d, br, *J*=3.0 Hz, 2H, -**CH_2**NH), 2.18 (t, *J*=3.0 Hz, 1H, **H**C≡C-), 1.40 (s, 9H, -C(**CH_3**)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.2 (s, **C**(=O)OC(CH$_3$)$_3$), 80.0 (s), 79.9 (s), 71.2 (d, H**C**≡C-CH_2-), 30.3 (t, -**CH_2**NH-), 28.2 (q, 3×**CH_3**)

2-Allyloxy-benzaldehyde (3.118)



To a rapidly stirred solution of salicylaldehyde (5.00 mL, 47.00 mmol) in dry DMF (100 mL) under N_2, K_2CO_3 (8.43 g, 60.00 mmol) was added, followed by allyl bromide (5.27 mL, 60.00 mmol). After 3 Et_2O (200 mL) was added to the reaction mixture; the organic phase was then washed with 1N HCl (100 mL) saturated $NaHCO_3$ (100 mL), brine (100 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded **3.118** as a yellow oil (7.01 g, 43.24 mmol, 92%).

Spectroscopic data were consistent with the literature. [135]

R_f: 0.27 (Hexane AcOEt 20:1)

FTIR (neat) ν_{max}: 3075 (w), 2863 (w, H-C(=O)), 1682 (s, C=O), 1597 (s), 1284 (s), 1237 (s), 1161 (s, C-O), 993 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 10.50 (s, 1H, C**H**(=O)), 7.84 (dd, *J*=7.3, 1.5 Hz, 1H, PhC**H**), 7.50-7.35 (m, 1H, PhC**H**), 7.08-6.94 (m, 2H, PhC**H**), 6.10-5.90 (m, 1H, CH_2C=C**H**-), 5.55-5.40 (m, 1H, -C**H**H=CH-), 5.38-5.30 (m, 1H, -C**H**H=CH-), 4.66 (dd, *J*=5.1, 1.5 Hz, 2H, -C**H$_2$**-CH=CH_2)

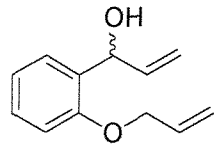
^{13}C NMR (75 MHz, $CDCl_3$) δ: 189.7 (d, H-**C**=O), 160.9 (s, Ph**C**), 135.8 (d, **C**H), 132.3 (d, Ph**C**H), 128.3 (d, Ph**C**H), 125.0 (s, Ph**C**), 120.8 (d, Ph**C**H), 118.0 (t, CH=**C**H_2), 112.8 (d, Ph**C**H), 69.1 (t, -O-**C**H_2CH=CH_2)

GC CIMS: R_t: 11.14 min; *m/z* (abundance): 163 $[M+H]^+$ (64%), 133 $[M-CHO]^+$ (78%), 120 (100%), 105 $[M-(CH_2=CHCH_2O)]^+$ (48%), 77 $[C_6H_5]^+$ (33%)

General protocol for the synthesis of acyclic precursors (3.119) and (3.120)

2-Allyloxybenzaldehyde **3.118** (3.00 g, 18.00 mmol) was dissolved in dry THF (100 mL) under N_2. The resulting solution was then rapidly stirred and cooled at –78 °C. Then allyl magnesium bromide (24.00 mL, 1M solution in Et_2O) or vinyl magnesium bromide (24.00 mL, 1M solution in THF) was added dropwise. After the complete disappearance of the starting material, crushed ice and Et_2O (200 mL) were put into the reaction mixture and then it was gradually warmed at room temperature. The organic phase was further washed with brine (100 mL) and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure and chromatography on silica afforded compounds **3.119** and **3.120**.

1-(2-Allyloxyphenyl)prop-2-en-1-ol (3.119)



Starting from 2-allyloxybenzaldehyde (3.00 g, 18.00 mmol) compound **3.119** was obtained as a colourless oil (2.40 g, 12.60 mmol, 70%)

R_f: 0.29 (Hexane AcOEt 20:3)

FTIR (neat) ν_{max}: 3403 (br, O-H), 3079 (w), 1600 (m), 1232 (s), 1018 (s, C-O), 990 (s), 751 (s)

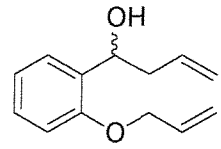
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.31 (dd, *J*=7.3, 1.5 Hz, 1H, Ph**H**), 7.23 (td, *J*=8.0, 2.2 Hz, 1H, Ph**H**), 6.97 (t, *J*=7.3 Hz, 1H, Ph**H**), 6.88 (d, *J*=8.0 Hz, 1H, Ph**H**), 6.21-5.96 (m, 2H, 2×(C**H**=CH_2)), 5.50-5.36 (m, 2H), 5.30-5.23 (m, 2H), 5.16 (dt, *J*=10.3, 1.5 Hz, 1H), 4.58 (dt, *J*=4.4, 2.2 Hz, 2H, -OC**H$_2$**CH=CH_2), 2.89 (d, *J*=4.4 Hz, 1H, O-**H**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.5 (s, Ph**C**), 139.3 (d, **C**H), 132.8 (d, **C**H), 130.9 (s, Ph**C**), 128.6 (d, Ph**C**H), 127.4 (d, Ph**C**H), 121.0 (d, Ph**C**H), 117.6 (t, CH=**C**H_2), 114.4 (t, CH=**C**H_2), 111.8 (d, Ph**C**H), 71.6 (d, -**C**HOH), 68.8 (t, **C**H_2CH=CH_2)

GC CIMS: R_t: 11.72 min; *m/z* (abundance): 190 $[M]^+$ (24%), 173 $[M\text{-}OH]^+$ (85%), 131 (100%), 107 (44%), 91 $[C_6H_5CH_2]^+$ (36%), 77 $[C_6H_5]^+$ (55%)

HR EIMS: Exact mass calculated for $C_{12}H_{14}O_2$: 190.09938; found: 190.09945

1-(2-Allyloxyphenyl)but-3-en-1-ol (3.120)



Starting from 2-allyloxybenzaldehyde (3.00 g, 18.00 mmol) compound **3.120** was obtained as a colourless oil (2.94 g, 14.80 mmol, 80%)

R_f: 0.33 (Hexane AcOEt 20:3)

FTIR ($CHCl_3$) ν_{max}: 3420 (br, O-H), 3075 (w), 2976 (w), 1600 (m), 1232 (s), 915 (s), 751 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.36 (dd, *J*=7.3, 1.5 Hz, 1H, Ph**H**), 7.22 (td, *J*=8.0, 2.2 Hz, 1H, Ph**H**), 6.97 (t, *J*=7.3 Hz, 1H, Ph**H**), 6.86 (d, *J*=8.0 Hz, 1H, Ph**H**), 6.17-6.00 (m, 1H, -C**H**=CH_2), 5.96-5.79 (m, 1H, -C**H**=CH_2), 5.44 (dd, *J*=17.0, 1.5 Hz, 1H, *trans* C**H**H=CH-), 5.31 (dd, *J*=11.0, 1.5 Hz, 1H, *cis*C**H**H=CH-), 5.22-5.08 (m, 2H), 5.03 (dt, *J*= 7.3, 5.1 Hz, 1H), 4.60 (d, *J*=5.1 Hz, 2H, -OC**H$_2$**-CH=CH_2), 2.71-2.45 (m, 3H)

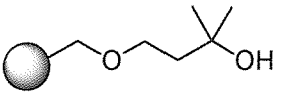
^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.0 (s, Ph**C**), 135.1 (d, **C**H), 132.9 (d, **C**H), 131.9 (s, Ph**C**), 128.1 (d, Ph**C**H), 126.8 (d, Ph**C**H), 120.8 (d, Ph**C**H), 117.6 (d, -CH=**C**H_2), 117.3 (d, -CH=**C**H_2), 111.5 (d, Ph**C**H), 69.6 (d, -**C**HOH), 68.6 (t, O-**C**H_2CH=CH_2), 41.8 (t, **C**H_2CH=CH_2)

GC CIMS: R_t: 12.14 min; *m/z* (abundance): 204 $[M]^+$ (2%), 187 $[M\text{-}OH]^+$ (99%), 163 $[M\text{-}(CH_2CH{=}CH_2)]^+$ (100%), 135 (95%), 107 (92%), 91 $[C_6H_5CH_2]^+$ (24%), 77 $[C_6H_5]^+$ (44%)

HR EIMS: Exact mass calculated for $C_{13}H_{15}O^+$ [M-OH]: 187.11229; found: 187.11219

4.3 Solid phase synthesis

4-Ethoxy-2-methyl-butan-2-ol polymer bound resin (2.3b)



Method 1

3-Methyl 1,3-butanediol (1.70 mL, 16.00 mmol) was dissolved in dry DMF (10 mL) under N_2. NaH (640 mg, 16.00 mmol, 60% dispersion in mineral oil) was then added. When the gas evolution stopped, a slurry of Merrifield resin (1.00 g, loading=1.6 mmol/g) in DMF was added and the reaction continued for 30 h. The resulting yellow resin was then drained, washed with H_2O/THF (5×20 mL, 5 min), DMF (6×5 mL, 5 min), CH_2Cl_2 (1×2 mL, 5 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

Method 2

To a solution of 3-methyl 1,3-butanediol (512 μL, 4.80 mmol) in dry THF (12 mL) at 0 °C, potassium *tert*-butoxide (4.80 mmol, 1M solution in THF) was added followed by 18-crown-6 (1.20 g, 4.80 mmol). The reaction was allowed to run for 1 h at 0 °C and for 3 h at room temperature. The yellow solution was then transferred *via* cannula to a flask containing Merrifield Resin (1.00 g, loading=1.6 mmol/g, preswollen in dry THF for 2 h) under N_2, and the resulting suspension shaken for 3.5 days. The resin was then washed with THF (5×5 mL, 2 min), DMF (5×5 mL, 2 min), 1:1 DMF/H_2O (5×5 mL, 2 min), DMF (5×5 mL, 2 min), THF (5×5 mL, 2 min), CH_2Cl_2 (5×5 mL, 2 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

Method 3. Microwave assisted formation of resin 2.3b

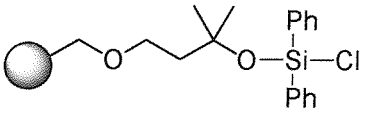
To a solution of 3-methyl 1,3-butanediol (512 μL, 4.80 mmol) in dry THF (12 mL) at 0 °C, potassium *tert*-butoxide (4.80 mmol, 1M solution in THF) was added followed by

18-crown-6 (1.20 g, 4.80 mmol). The reaction was allowed to run for 1 h at 0 °C and for 3 h at room temperature. The yellow solution was then transferred *via* cannula into a vial containing Merrifield Resin (1.00 g, loading=1.6 mmol/g, preswollen in dry THF for 2 h) under N_2. The resulting suspension was then heated in a microwave reactor at 120 °C for 10 min; the resin was then washed with THF (5×5 mL, 2 min), DMF (5×5 mL, 2 min), 1:1 DMF/H_2O (5×5 mL, 2 min), DMF (5×5 mL, 2 min), THF (5×5 mL, 2 min), CH_2Cl_2 (5×5 mL, 2 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

FTIR (on the bead) ν_{max}: 3458 (s, O-H), 3059 (s), 2885 (s), 1153 (s, C-O), 1093 (s, C-O)

Gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 73.0 (t, Ph-**C**H_2-O-), 70.3 (s, -**C**$(CH_3)_2$-OH), 67.4 (t, -**C**H_2-OBn), 41.4 (t, **C**H_2-C$(CH_3)_2$-OH), 29.2 (q, **C**H_3)

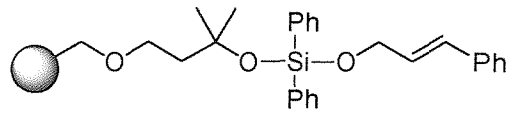
Chloro-(3-ethoxypropoxy)diphenylsilane polymer bound resin (2.1a)



Resin **2.3b** (200 mg) was briefly rinsed with dry CH_2Cl_2 (10 mL, 3 min). Then freshly dried CH_2Cl_2 (10 mL) was added followed by Et_3N (0.27 mL, 1.92 mmol), diphenyldichlorosilane (0.27 mL, 1.30 mmol) and DMAP (40 mg, 0.32 mmol). The resulting suspension was then sealed and shaken at room temperature for 1 h. The resin was then drained and rinsed with dry CH_2Cl_2 (3×5 mL, 1 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h. The loading of resin **2.1a** was determined employing the two methods described in page 146, and it was found to be 0.65 mmol/g.

FTIR (on the bead) ν_{max}: 3058 (s), 2975 (s), 1601 (s, C=C), 1154 (s), 744 (s), 700 (s)

Siloxane resin (2.30)

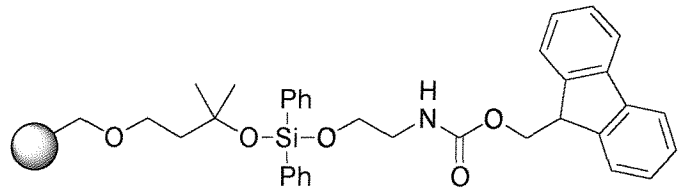


A typical procedure is as follows: resin **2.1a** (200 mg, loading=0.65 mmol/g) was suspended in dry CH_2Cl_2 (10 mL). Then Et_3N (0.27 mL, 1.92 mmol) was added followed by *trans*-cinnamyl alcohol (175 mg, 1.30 mmol) and DMAP (40 mg, 0.32 mmol). The resulting suspension was shaken for 1 h. The resin was then drained and washed with CH_2Cl_2 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min), and dried under high vacuum (40 °C @ 10 mmHg) for 24 h. In the same way resins **2.31** and **2.34-2.38** were obtained.

FTIR (on the bead) ν_{max}: 3026 (s), 2924 (s), 1600 (s, C=C), 1156 (s, C-O), 740 (s)

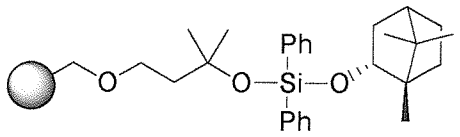
Gel phase ^{13}C NMR (75 MHz, C_6D_6) δ: 75.3 (s, -**C**$(CH_3)_2$-O), 73.0 (t, Ph-**C**H_2-O-), 67.8 (t, O-**C**H_2-C=C), 44.3 (t, **C**H_2-C$(CH_3)_2$-O), 29.2 (q, **C**H_3)

{2-[(3-Ethoxy-1,1-dimethylpropoxy)diphenylsilanoxy]ethyl}carbamic acid 9*H*-fluoren-9-ylmethyl ester polymer bound resin (2.31) from (2.1a) and Fmoc-glycinol



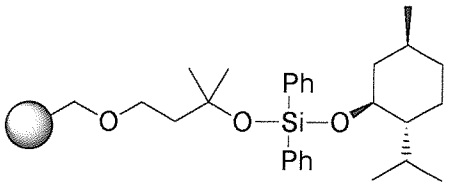
FTIR (on the bead) ν_{max}: 3380 (m, N-H), 3026 (s), 2972 (s), 1724 (C=O), 1156 (s, C-O), 1124 (s, C-O), 909 (s)

Resin (2.34) from (2.1a) and (2.19)



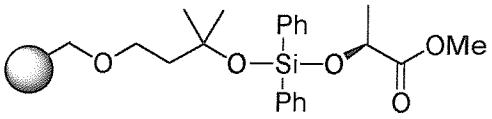
FTIR (on the bead) ν_{max}: 2926 (s), 1601 (m), 1604 (s, C-O), 907 (m), 860 (s)

Resin (2.35) from (2.1a) and (2.18)



FTIR (on the bead) ν_{max}: 3060 (s), 2917 (s), 3027 (s), 1600 (s, C=C), 1068 (s, C-O), 760 (s)

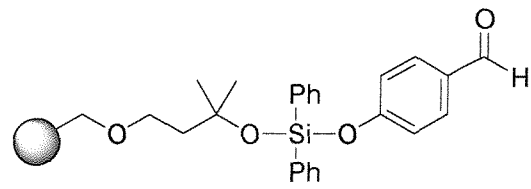
Ester bound resin (2.36) from (2.1a) and (2.17)



FTIR (on the bead) ν_{max}: 3058 (s), 2852 (s), 1758 (s, C=O), 1601 (s, C=C), 1125 (s, C-O)

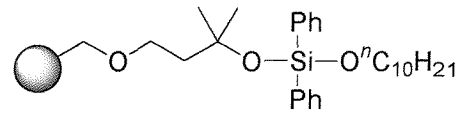
Gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 173.8 (s, (**C**=O)OCH_3), 75.2 (s, -**C**$(CH_3)_2$O-), 72.7 (t, Ph**C**H_2O-), 68.1 (d, (CH_3)**C**H(COOCH_3-O-), 51.6 (q, C=O)O**C**H_3), 30.2 (q, **C**H_3), 21.1 (q, **C**H_3-CH(COOCH_3)-O-)

Aldehyde bound resin (2.37) from (2.1a) and (2.42)



FTIR (on the bead) ν_{max}: 3058 (s), 2923 (s), 2733 (m, H-C=O), 1699 (s, C=O), 1121 (s, C-O), 1059 (s, C-O), 838 (s)

Resin (2.38) from (2.1a) and (2.39)



FTIR (on the bead) ν_{max}: 3058 (w), 2918 (w), 1603 (m), 1153 (s, C-O), 1118 (s, C-O), 1050 (s, C-O), 913 (s)

Loading calculations

The loading of the silyl chloride resin **2.1a** was calculated using two different methods. To avoid confusion, they will be described in two separate sections.

1. Fmoc quantification by UV VIS spectroscopy [136]

A known amount of resin **2.31** (3 mg) was transferred in a screw cap vial and a 20% solution of piperidine in DMF (2 mL) was added. The resulting suspension was then shaken at room temperature for 15 min; the solution was collected and the resin washed with further 20% piperidine in DMF (2×2 mL, 1 min). The original solution and the washings were combined and made up to 25 mL with 20% of piperidine in DMF. The resulting solution was analysed by UV for the presence of the piperidine–fulvene adduct (302 nm). The loading of the resin was calculated with the following equation

$$\text{Loading (mmol/g)} = [(A_{302} \times V) / (\varepsilon_{302} \times W)] \times 10^3$$

Where A_{302} is the absorbance of the piperidyl-fulvene adduct, V the total volume (mL), W the weight of the dried resin sample (mg), and ε_{302} the extinction coefficient of the adduct at 302 nm (7800 $M^{-1}cm^{-1}$).

2. GC measurement of the cleaved alcohol

Resin **2.30** (100 mg) was suspended in THF (5 mL), then TBAF (0.16 mmol, 2.5 eq respect to the loading of the resin **2.1a**) was added and the resulting suspension vigorously stirred at room temperature for 2 h. Then the resin was drained and washed with THF (2×3 mL, 5 min). The original solution and the washings were collected and partitioned between water (10 mL) and Et_2O (15 mL). TLC analysis of the organic phase showed the presence of the *trans*-cinnamyl alcohol, and its amount was then quantified by GC in comparison with standard solutions.

Trans-cinnamyl alcohol: R_t= 4.1 min (GC Program 2)

Stability studies of the diphenylsiloxane linker

The stability studies were carried out employing resin **2.30** as substrate; different procedures were followed, so to aid clarity, they will be discussed in separate sections.

Stability with LDA and KO^{t}Bu

Four oven dried flasks were charged with resin **2.30** (100 mg each), then freshly dried THF (2 mL each) was added under N_2. The resulting suspensions were then rapidly stirred and cooled at 0 °C. At this point the following reagents were added separately.

Flask 1: LDA (1.8M in THF)(40 μL, 0.07 mmol)
Flask 2: LDA (1.8M in THF)(100 μL, 0.18 mmol)
Flask 3: KO^{t}Bu (1M in THF)(65 μL, 0.06 mmol)
Flask 4: KO^{t}Bu (1M in THF)(160 μL, 0.16 mmol)

The suspensions were rapidly stirred at 0 °C for 1 h. Then the four solutions were collected separately, quenched with saturated NH_4Cl (1 mL each) and extracted with Et_2O (4 mL each). The organic phases were then and analysed by GC in comparison with an authentic trace of *trans*-cinnamyl alcohol. No cleaved alcohol **2.15** was found in the 4 cases considered.

Stability with Acetic acid

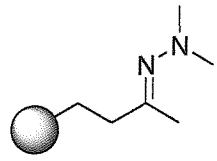
Resin **2.30** (100 mg) was suspended in a 1% solution of acetic acid in CH_2Cl_2 (5 mL) and the resulting suspension rapidly stirred at room temperature for 24 h. The solution was then collected and partitioned between saturated $NaHCO_3$ (2 mL) and Et_2O (4 mL). The organic phase was then analysed by GC in comparison with an authentic trace of *trans*-cinnamyl alcohol; no cleaved alcohol **2.15** was found.

Stability with TFA

Resin **2.30** was suspended in a 1% solution of TFA in CH_2Cl_2 (5 mL, containing 1% of TIS). After 2 min the solution was collected and partitioned between saturated $NaHCO_3$ (2 mL) and Et_2O (4 mL). GC analysis of the organic solution showed that 53% of the alcohol **2.15** had been cleaved from the resin after 2 min.

Trans-cinnamyl alcohol: R_t= 4.1 min (GC Program 2)

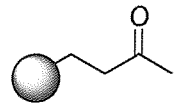
Resin bound hydrazone (2.69)



To a rapidly stirred solution of **2.66** (0.24 g, 2.40 mmol) in dry THF (4 mL) at 0 °C, ^{n}BuLi (1.00 mL, 2.40 mmol, 2.5M solution in hexane) was added. After 30 min the solution was added *via* cannula to a flask containing Merrifield resin (300 mg, 0.48 mmol, loading=1.6 mmol/g, preswollen in THF). The resulting suspension was then shaken at room temperature for 14 h. The bright yellow resin was then collected and washed with THF/H_2O (5×5 mL, 5 min), THF (5×5 mL, 5 min), THF/H_2O (5×5 mL, 5 min), THF (5×5 mL, 5 min), DMF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

FTIR (on the bead) ν_{max}: 3351 (H_2O), 3026 (s), 2974 (s), 1643 (s, C=N), 1603 (s)

Resin bound carbonyl (2.64)

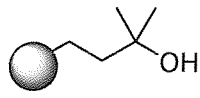


Resin **2.69** (315 mg) was suspended in a mixture of THF/H_2O 4:1 (3 mL). Then phosphate buffer (1.44 mL, 1M solution in H_2O) was added followed by $NaIO_4$ (540 mg, 2.52 mmol) in H_2O (2 mL). The resulting suspension was then shaken at room

temperature for 24 h. During this period the formation of a white precipitate was observed. The resin was collected, washed with DMF/H_2O 1:1 (3×5 mL, 2 min), THF (3×5 mL, 2 min), CH_2Cl_2 (3×5 mL, 2 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

FTIR (on the bead) ν_{max}: 3025 (s), 2852 (s), 1715 (s, C=O), 1631 (s), 1511 (s), 1493 (s), 907 (w)

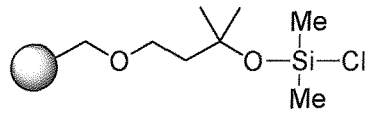
Resin bound tertiary alcohol (2.65)



Resin **2.64** (300 mg) was suspended in dry THF (3 mL). Then methyl magnesium chloride (0.80 mL, 2.40 mmol, 3M solution in THF) was added under N_2. The resulting suspension was then shaken at room temperature for 24 h. The resin was collected, washed with THF/sat NH_4Cl 1:1 (5×5 mL, 2 min), DMF (5×5 mL, 2 min), THF (5×5 mL, 2 min), CH_2Cl_2, (5×5 mL, 2 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

FTIR (on the bead) ν_{max}: 3024 (w), 2919 (w), 1654 (w), 1601 (w), 1560 (w), 1509 (w), 1492 (s), 1451 (s), 1027 (w), 755 (w)

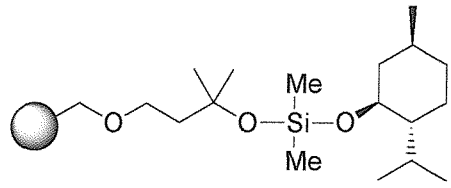
Dimethylsilyloxychloride bound resin (2.1b)



Resin **2.3b** (500 mg) was suspended in a mixture of dichlorodimethylsilane (0.97 mL, 8.00 mmol), and Et_3N (1.67 mL, 12.00 mmol) in dry CH_2Cl_2 (10 mL) under N_2, followed by DMAP (0.97 g, 8.00 mmol); the resulting suspension was shaken at room

temperature for 1 h. The resin was then drained under N_2, rinsed with CH_2Cl_2 (2×5 mL, 1 min) and used immediately for the successive transformations. The loading of resin **2.1b** was determined employing the two methods described in page 146, and it was found to be 0.37 mmol/g.

Siloxane resin (2.62)



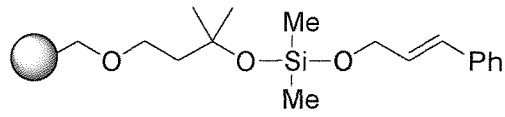
Resin **2.1b** was suspended in dry CH_2Cl_2 (10 mL), then Et_3N (1.67 mL, 12.00 mmol) was added, followed by (1*R*, 2*S*, 5*R*)-(-)-menthol (1.07 g, 8.00 mmol) and DMAP (0.97 g, 8.00 mmol). The suspension was sealed and shaken at room temperature for 1 h. The resin was then drained and washed with CH_2Cl_2 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min), and dried under high vacuum (40 °C @ 10 mmHg) for 24 h. Using the same method, siloxane resins **2.61** and **2.63** were obtained from alcohols **2.15** and **2.40** respectively.

FTIR (on the bead) ν_{max}: 3083 (s), 3060 (s), 1602 (s, C=C), 1161 (s, C-O), 1067 (s, C-O), 881 (s)

Gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 73.8 (s, -**C**$(CH_3)_2$-O-), 73.4 (t, Ph**C**H_2-O-), 72.9 (d, -O-$(Ph)_2$Si-O-**C**H-), 50.6 (d, **C**H), 46.0 (t, **C**H_2), 44.6 (t, BnOCH_2-**C**H_2-), 35.2 (d, **C**H_2), 32.3 (d, **C**H), 30.8 (q, **C**H_3), 25.9 (d, **C**H), 23.6 (t, **C**H_2), 22.9 (q, -**C**H_3), 21.8 (q, -**C**H_3), 16.6 (q, -**C**H_3), 1.7 (q, Si-**C**H_3), 1.4 (q, Si-**C**H_3)

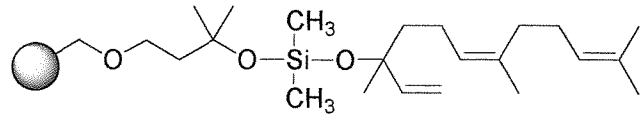
Gel phase ^{29}Si NMR (60 MHz, $CDCl_3$) δ: -12.7

Siloxane resin (2.61) from (2.1b) and (2.15)



FTIR (on the bead) ν_{max}: 3060 (s), 2853 (s), 1601 (s, C=C), 1186 (s, C-O), 1156 (s, C-O), 822 (s)

Siloxane resin (2.63) from (2.1b) and (2.40)

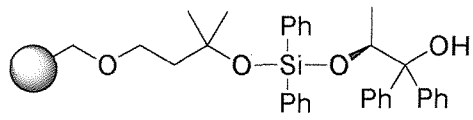


FTIR (on the bead) ν_{max}: 3063 (s), 2924 (s), 1158 (s, C-O), 1116 (s, C-O)

General protocol for the reduction of polymer bound ester (2.36) with Grignard reagents

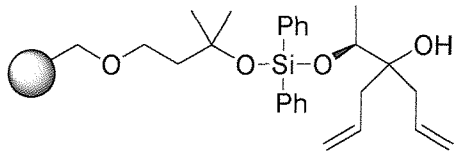
Resin **2.36** (500 mg) was suspended in freshly dried THF (4 mL) under N_2. The resulting suspension was rapidly stirred and cooled to a temperature between –5 and 0 °C. Phenyl magnesium bromide (330 μL, 3M in THF, 3 eq respect to the loading of **2.1a**) or allyl magnesium bromide (980 μL, 1M in THF, 3 eq respect to the loading of **2.1a**) was added dropwise. The system was then gradually allowed to return to room temperature and every 20 min a sample of beads was analysed by FTIR spectroscopy. After the complete disappearance of the ester band (1 h required), the resin was drained, washed extensively with THF/H_2O/Acetone 1:1:1 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

(2*S*)-[(3-Ethoxy-1,1-dimethylpropoxy)diphenylsilanoxy]-1,1-diphenylpropan-1-ol polymer bound resin (3.80)



FTIR (on the bead) ν_{max}: 3412 (s, br, OH), 3026 (s), 2971 (s), 1602 (s, C=C), 1154 (s, C-O), 1116 (s, C-O)

4-{(1*S*)-[(3-Ethoxy-1,1-dimethylpropoxy)diphenylsilanoxy]ethyl}hepta-1,6-dien-4-ol polymer bound resin (3.81)

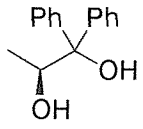


FTIR (on the bead) ν_{max}: 3384 (br, O-H), 2961 (s), 2874 (m), 1608 (m), 1485 (m), 1116 (s, C-O), 1056 (s, C-O)

Fluoride mediated cleavage of diols (3.77) and (3.79) from resins (3.80) and (3.81)

Resins **3.80** and **3.81** (110 and 400 mg respectively) were briefly preswollen in THF (3 mL, 20 min). The resins were drained and fresh THF (7 mL) was added, followed by TBAF (0.18 and 0.65 mmol respectively, 2.5 equivalents respect to the loading of resin **2.1a**). The resulting suspensions were shaken for 1 h at room temperature. The solutions were then collected separately and the resins further washed with THF (3×5 mL, 5 min). The solutions and the washings were combined and Et_2O (25 mL) was added. The organic phases were washed with brine (5×10 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography afforded compounds **3.77** and **3.79**.

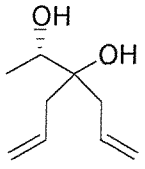
(2*S*)-1,1-Diphenyl-1,2-propanediol (3.77) from resin (3.80)



Starting from resin **3.80** (110 mg) compound **3.77** was obtained as a white solid (9 mg, 0.04 mmol, 60% overall yield over 3 steps, based on the loading of **2.1a**).

Spectroscopic data were consistent with previously reported (see page 126)

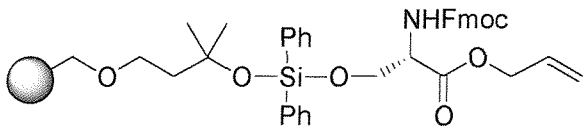
(2*S*)-3-Allyl-hex-5-ene-2,3-diol (3.79) from resin (3.81)



Starting from resin **3.81** (400 mg) compound **3.79** was obtained as a colourless oil (21 mg, 0.13 mmol, 53% overall yield based on the loading of **2.1a**).

Spectroscopic data were consistent with previously reported (see page 128).

3-[diphenyl-silanoxy]-(2*S*)-(9*H*-fluoren-9-ylmethoxycarbonylamino) propionic acid allyl ester polymer bound resin (3.133)



The silyl chloride resin **2.1a** (100 mg, loading=0.65 mmol/g) was suspended in dry CH_2Cl_2 (4 mL) then Et_3N (133 μL, 0.96 mmol) was added, followed by Fmoc L-

SerOAllyl **3.132a** (235 mg, 0.64 mmol) and DMAP (40 mg, 0.32 mmol). The resulting suspension was shaken for 1 h at room temperature. The resin was drained and washed thoroughly with dry CH_2Cl_2 (10×5 mL, 5 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

FTIR (on the bead) ν_{max}: 3440 (s, NH), 3063 (s), 2972 (s), 1727 (s, C(=O)), 1601 (s), 1196 (s, C-O), 1123 (s, C-O)

Gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.0 (s, **C**(=O)OAllyl), 155.8 (s, Fmoc**C**(=O)), 143.8 (s, 2×Fmoc**C**), 141.1 (s, Fmoc**C**), 118.8 (t, $\mathbf{C}H_2C{=}C$), 75.3 (s, $\mathbf{C}(CH_3)_2C$-O), 67.1 (t, Fmoc $\mathbf{C}H_2$), 66.1 (t, $CH_2{=}CH\text{-}\mathbf{C}H_2$-O), 63.5 (t, $\mathbf{C}H_2O$), 55.7 (d, $\mathbf{C}_\alpha H$), 47.0 (d, Fmoc**C**H), 30.3 (s, $\mathbf{C}H_3$)

Peptide bound resins (3.134), (3.136) and (3.142)

For the synthesis of the peptide bound resins **3.134**, **3.136** and **3.142** starting from **3.133,** the following protocol was employed:

1. *N*-Deprotection

The initial resin **3.133** (500 mg) was treated twice with a 20% solution of piperidine in DMF (5.00 mL each, 10 min). Positive ninydrin test [136] on the resin indicated the presence of the free aminogroup. Then the *N*-deprotected amino-resin was washed with DMF (3×5 mL, 5 min) and used immediately for the coupling with the next Fmoc-AA-OH

2. Coupling with Fmoc-AA-OH

To a stirred solution of the Fmoc-AA-OH (3.20 mmol) in a mixture of dry CH_2Cl_2 and DMF (9:1) HOBt (432 mg, 3.20 mmol) was added and stirring continued for 10 min. DIC (500 μL, 3.20 mmol) was added dropwise and the reaction mixture was stirred for additional 10 min. The resulting solution was then added to the previously *N*-

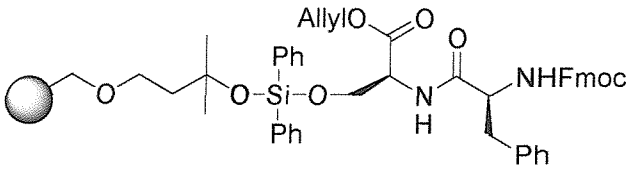
deprotected resin and the corresponding suspension shaken for 3 h. After this period the nynidrin test [136] on the resin was negative, indicating substantially no free aminogroup.

Coupling involving the terminal nitrogen of the L-Proline [126] residue was performed with PyBrop (1.50 g, 3.20 mmol) and DIPEA (700 μL, 4.00 mmol) instead of the DIC/HOBt system, employing the same mixture of solvents. The reaction was allowed to run until chloranyl test was negative. [137]

The described steps were performed onto the initial resin **3.133** with the following aminoacids:

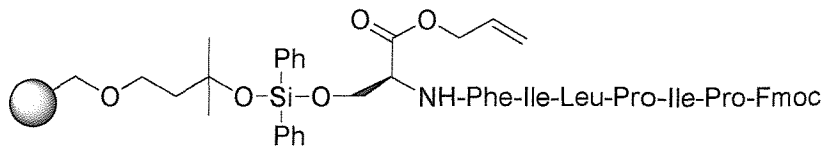
1. Fmoc L-PheOH
2. Fmoc L-IleOH
3. Fmoc L-ProOH
4. Fmoc L-PheOH
5. Fmoc L-IleOH
6. Fmoc L-ProOH

Resin bound dipeptide (3.134)



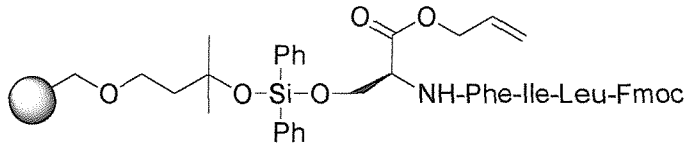
FTIR (on the bead) ν_{max}: 3302 (s, N-H), 3026 (s), 2926 (s), 1643 (s, br, C=O), 1154 (s), 1118 (s)

Acyclic precursor bound resin (3.136)



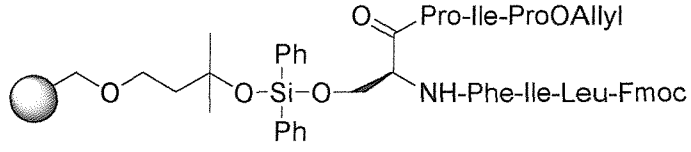
FTIR (on the bead) ν_{max}: 3061 (w), 2921 (s), 1760 (C=O), 1681 (C=O), 1653 (s), 1374 (s), 1110 (s)

Resin bound tetrapeptide (3.142)



FTIR (on the bead) ν_{max}: 3305 (br, N-H), 3026 (s), 2926 (s), 1659 (s, br, C=O), 1191 (s, C-O), 742 (s)

Resin bound acyclic precursor (3.139)



For the synthesis of the acyclic precursor resin **3.139** the following two step procedure was performed.

1. Carboxyl deblocking

The deprotection was carried out employing the procedure originally reported by Albericio *et al.* [125] Resin **3.142** (300 mg) was suspended in a mixture of $CHCl_3$, AcOH and NMM (37:2:1) under N_2 and the resulting suspension vigorously stirred at room temperature. Pd $(PPh_3)_4$ (676 mg, 0.58 mmol) was then added and stirring continued for 4 h. After this period, some beads were collected, rinsed and treated with few drops of a TFA solution (30% v:v in CH_2Cl_2, containing 3% of TIS). The crude cleavage mixture was analysed by ES MS and showed the peak due to the carboxyl free tetrapeptide (FmocLeuIlePheSerOH), demonstrating the success of the deprotection. A further confirmation arose from the positive carboxyl test on the resin. [12]

2. Coupling

The previously deprotected resin was rinsed thoroughly with THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 min) and then suspended in a mixture of CH_2Cl_2 and DMF 1:1 (6 mL). Then a solution of the appropriate substrate **3.145** or **3.147** (0.39 mmol) was added, followed by PyBrop (181 mg, 0.39 mmol) and DIPEA (100 μL, 0.58 mmol). The resulting suspension was then sealed and shaken at room temperature until negative carboxyl test on the resin.

The 2-step protocol was sequentially performed onto the initial resin **3.142** with the following substrates:

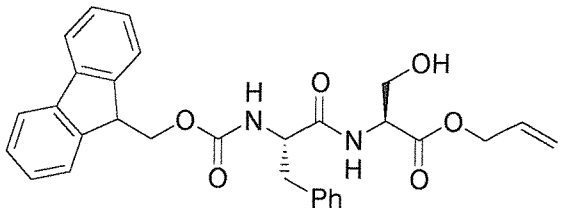
1. HProIleOAllyl **(3.145)**
2. HProOAllyl **(3.147)**

Preparation of **3.145** (as TFA salt) from **3.144** was carried out employing the protocol described in page 136.

Preparation of **3.147** from substrate **3.146** was performed using the same method previously reported for the deprotection of Fmoc L-IleOAllyl (see page 134, step 1). After its formation, crude **3.147** was immediately used for the coupling.

Resin 3.139: **FTIR** (on the bead) ν_{max}: 2950 (w), 1736 (s, C=O), 1657 (s, C=O), 1535 (s), 1391 (s), 1157 (s, C-O), 771 (s)

(2*S*)-[(2*S*)-(9*H*-Fluoren-9-ylmethoxycarbonylamino)-3-phenylpropionylamino]-3-hydroxypropionic acid allyl ester (3.135) from resin (3.134)



Resin **3.134** (524 mg) was briefly preswollen in CH_2Cl_2 (5 mL) and then TFA (30% in CH_2Cl_2 containing 6% of triethylsilane) was added; the resulting suspension was rapidly stirred for 2 h at room temperature. After this period the solution was collected through a glass wool septum and the resin further washed with CH_2Cl_2 (5×5 mL, 5 min). The washings and the original solution were collected and excess of TFA removed under reduced pressure, affording an oily residue. Final chromatography on silica and precipitation with cold Et_2O afforded **3.135** as a white amorphous solid (157 mg, 0.30 mmol, 90% overall yield from the loading of **2.1a**).

$[\alpha]_D^{25}$: -14.00° (c=0.25, MeOH)

R_f: 0.36 (Hexane AcOEt 1:1)

MP: 188-190 °C (Hexane AcOEt)

FTIR ($CHCl_3$) ν_{max}: 3293 (br), 3065 (w), 1741 (s, C=O), 1726 (s, C=O), 1662 (s, C=O), 1545 (s), 1293 (s, C(=O)-O), 1046 (s, C-O)

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.45 (d, *J*=7.5 Hz, 1H, N**H**), 7.86 (d, *J*=7.5 Hz, 2H, FmocC**H**), 7.67-7.56 (m, 3H, 2×FmocC**H** and N**H**), 7.43-7.05 (m, 9H), 5.95-5.81 (m, 1H, -C**H**=CH_2), 5.33 (dd, *J*=17.0, 1.5 Hz, 1H, *trans*CH**H**=CH-), 5.18 (dd, *J*=10.5, 1.5

Hz, 1H, *cis*CHH=CH-), 5.12 (t, *J*=5.5 Hz, 1H, OH), 4.58 (d, *J*=5.0 Hz, 2H, CH_2=C-CH_2-), 4.50-4.32 (m, 2H, 2×CH_α), 4.20-4.00 (m, 3H, Fmoc CH_2 and Fmoc CH), 3.78 (apparent quintet, *J*=5.5 Hz, 1H, CH_aOH), 3.67 (apparent quintet, *J*=5.5 Hz, 1H, CH_bOH), 3.04 (dd, *J*=13.5, 3.0 Hz, 1H, CH_aPh), 2.76 (dd, *J*=13.5, 11.5 Hz, 1H, CH_bPh)

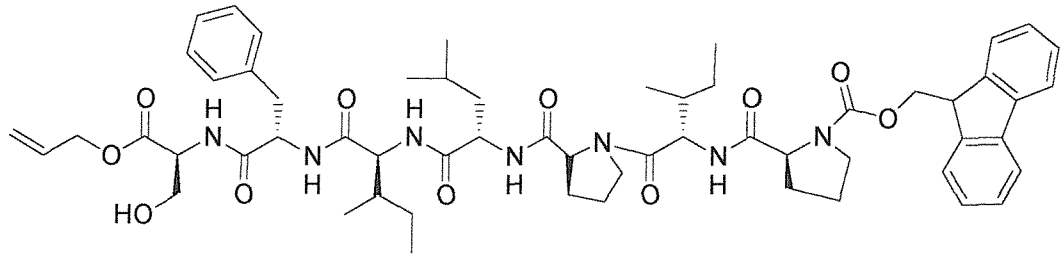
^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.1 (s, C=O), 170.3 (s, C=O), 155.9 (s, Fmoc C(=O)N<), 143.8 (s, ArC), 140.7 (s, ArC), 138.3 (s, ArC), 132.5 (d, -CH=CH_2), 129.4 (d, ArCH), 128.1 (d, ArCH), 127.7 (d, ArCH), 127.2 (d, ArCH), 126.3 (d, ArCH), 125.4 (d, ArCH), 120.2 (d, ArCH), 117.6 (t, -CH=CH_2), 65.8 (t, Fmoc CH_2), 65.0 (t, OCH_2-CH=CH_2), 61.3 (t, CH_2OH), 56.0 (d, $C_\alpha H$), 54.9 (d, $C_\alpha H$), 46.7 (d, FmocCH), 37.6 (t, CH_2Ph)

ES MS: *m/z* (abundance): 537 $[M+Na]^+$ (30%), 553 $[M+K]^+$ (5%)

HR ESMS: Exact mass calculated for $C_{30}H_{30}N_2O_6Na$ $[M+Na]^+$: 537.1996; found: 537.1982

Elemental analysis. Anal. Calcd. For $C_{30}H_{30}N_2O_6$: C, 70.02; H, 5.88; N, 5.44; found: C, 69.27; H, 5.71; N, 5.10

2-{1-[2-(1-{1-[1-(1-Allyloxycarbonyl-2-hydroxy-ethylcarbamoyl)-2-phenyl-ethylcarbamoyl]-2-methyl-butyl carbamoyl}-3-methyl-butylcarbamoyl)-pyrrolidine-1-carbonyl]-2-methyl-butylcarbamoyl}-pyrrolidine-1 -carboxylic acid 9H-fluoren-9-ylmethyl ester (3.137) from resin (3.136)



The cleavage of product **3.137** from resin **3.136** (564 mg) was performed in the same way as reported previously for the cleavage of **3.135** (see page 158). Chromatography

on silica and final precipitation with cold Et_2O afforded **3.137** as a white amorphous solid (230 mg, 0.22 mmol, 60% overall yield from the loading of **2.1a**).
R_f: 0.50 (AcOEt MeOH 60:1)

MP: 150-153 °C (dec) (Hexane AcOEt)

FTIR ($CHCl_3$) ν_{max}: 3300 (br, NH or O-H), 2964 (m), 2878 (m), 1642 (s), 1528 (s), 1188 (s), 1131 (s), 740 (s)

NMR analysis complicated by the presence of different comformers

^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.32 (d, *J*=7.5 Hz, 1H, N**H**), 8.05-7.92 (m, 2H), 7.86 (d, *J*=6.5 Hz, 2H, 2×N**H**) 7.70-7.60 (m, 2H), 7.53 (d, *J*=8.0 Hz, 1H, N**H**), 7.40 (t, *J*= 7.5 Hz, 2H), 7.30 (d, *J*=5.0 Hz, 2H, N**H**), 7.26-7.08 (m, 6H), 5.93-5.80 (m, 1H, -C**H**=CH_2), 5.32 (dd, *J*=17.0, 1.5 Hz, 1H, *trans*C**H**H=CH-), 5.18 (dd, *J*=10.5, 1.5 Hz, 1H, *cis*C**H**H=CH-), 5.12 (t, *J*=5.0 Hz, 1H, O**H**), 4.70-4.60 (m, 1H), 4.57 (d, *J*=5.0 Hz, 2H, CH_2-CH=CH_2), 4.42-4.15 (m, 7H), 4.13-3.95 (m, 2H), 3.79-3.60 (m, 3H), 3.58-3.40 (m, 3H), 3.05 (dd, *J*=14.0, 4.0 Hz, 1H, C**H$_a$**Ph), 2.76 (dd, *J*=14.0, 10.0 Hz, 1H, C**H$_b$**Ph), 2.10-0.91 (m, 17H), 0.89-0.69 (m, 15H), 0.67 (d, *J*=6.5 Hz, 3H)

^{13}C NMR (100 MHz, DMSO-d_6) δ: 172.2 (s), 171.8 (s), 171.6 (s), 171.5 (s), 171.4 (s), 170.7 (s), 170.2 (s), 154.1 and 154.0 (s, Fmoc**C**(=O)NH), 144.1, 143.9 and 143.6 (s, Fmoc**C**), 140.9, 140.8 and 140.7 (s, Fmoc**C**), 137.8 (s), 132.5 (d, -**C**H=CH_2), 129.2 (d, Ar**C**H), 128.1 (d, Ar**C**H), 127.8 (d, Ar**C**H), 127.3 (d, Ar**C**H), 126.3 (d, Ar**C**H), 125.8 (d, Ar**C**H), 125.4 (d, Ar**C**H), 125.3 (d, Ar**C**H), 120.2 (d, Ar**C**H), 117.7 (t, -CH=**C**H_2), 67.1 and 66.7 (t, Fmoc **C**H_2), 65.0 (t, O**C**H_2-CH=CH_2), 61.4 (t), 59.5 (d or q), 59.2 (d or q), 56.9 (d or q), 55.0 (d or q), 54.8 (d or q), 53.4 (d or q), 51.3 (d or q), 47.4 (t), 47.3 (t), 46.8 (d or q), 46.6 (t), 40.0 (t), 37.7 (t), 36.9 (d or q), 36.4 (d or q), 31.6 (t), 30.8 (d or q), 30.0 (t), 29.1 (t), 24.6 (t), 24.4 (t), 24.1 (t), 23.3 (d or q), 21.8 (d or q), 15.3 (d or q), 15.1 (d or q), 15.0 (d or q), 11.0 (d or q), 10.8 (d or q)

High temperature studies proved impossible to perform due to the thermal instability of the compound. After heating, total cleavage of the Fmoc group was observed.

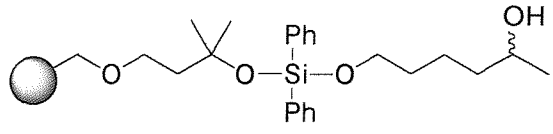
ES MS: *m/z* (abundance): 1070 [M+Na] (15%)

Reverse phase HPLC: R_t: 4.83 min

General protocol for the selective silylation of diols (2.53), (2.54) and (2.55) with resin (2.1a)

Resin **2.1a** (200, 400 and 400 mg, 0.65 mmol/g) was suspended in freshly dried CH_2Cl_2 (4-7 mL), then dry Et_3N (1.92, 3.87 and 5.76 mmol respectively) was added, followed by the diol **2.53**, **2.54** or **2.55** (1.60, 3.22 and 4.48 mmol respectively). The system was purged with N_2 for 5 min and then sealed. The resulting suspension was shaken at room temperature for 1.5 h. Then the resin was drained, rinsed thoroughly with CH_2Cl_2 (5×10 mL) and dried under high vacuum (40 °C @ 10 mmHg) for 48 h. In this way resins **2.44**, **2.45** and **2.46** were obtained.

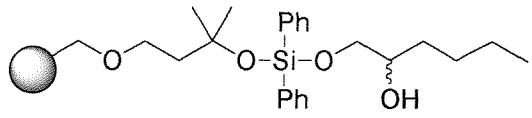
6-[(3-Ethoxy-1,1-dimethylpropoxy)diphenylsilanoxy]hexan-2-ol polymer bound resin (2.44)



FTIR (on the bead) ν_{max}: 3392 (s, O-H), 3063 (s), 2971 (s), 1601 (s), 1157 (s), 1119 (s)

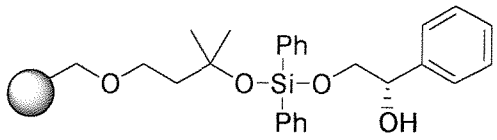
Gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 74.0 (s, -**C**$(CH_3)_2$-O-), 67.8 (t, -**C**H_2-OBn), 62.7 (t, O**C**H_2), 38.8 (t, **C**H_2), 32.2 (t, **C**H_2), 30.3 (s, **C**H_3), 23.3 (t, **C**H_2), 21.9 (q, **C**H_3)

1-[(3-Ethoxy-1,1-dimethyl-propoxy)diphenylsilanyloxy]hexan-2-ol polymer bound resin (2.45)



FTIR (on the bead) ν_{max}: 3467 (s, O-H), 3061 (s), 2913 (s), 1601 (s), 1116 (s, C-O), 818 (s)

2-[(3-Ethoxy-1,1-dimethylpropoxy)diphenylsilanyloxy]-(1*S*)-phenylethanol polymer bound resin (2.46)

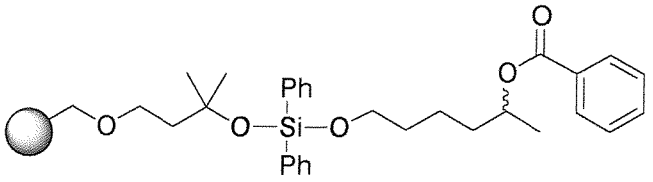


FTIR (on the bead) ν_{max}: 3467 (s, O-H), 3026 (s), 2970 (s), 1601 (s), 1155 (s, C-O), 1116 (s, C-O)

General protocol for benzoylation of polymer supported alcohols (2.44), (2.45) and (2.46)

Resins **2.44**, **2.45** and **2.46** (100, 425 and 593 mg respectively) were suspended in dry CH_2Cl_2 (3-6 mL) under N_2. Then freshly dried pyridine (1.12, 4.68 and 6.64 mmol respectively) was added, followed by benzoyl chloride (0.80, 3.34 and 4.74 mmol respectively). The resulting suspension was then sealed and shaken for 24 h at room temperature. Then the resin was drained, washed thoroughly with dry CH_2Cl_2 (5×5 mL, 5 min) and dried under high vacuum (40 °C @ 10 mmHg) for 48 h. In this way resins **2.47**, **2.48** and **2.49** were obtained.

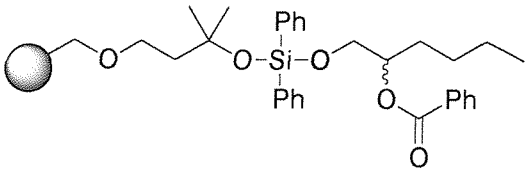
Benzoic acid 5-[(3-ethoxy-1,1-dimethylpropoxy)diphenylsilanoxy]-1-methylpentyl ester polymer bound resin (2.47)



FTIR (on the bead) ν_{max}: 3062 (s), 2974 (s), 1715 (s, C=O), 1601 (s), 1275 (s, C-O), 1156 (s, C-O), 1120 (s, C-O)

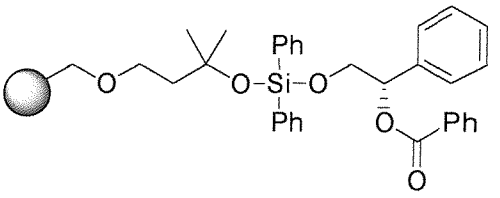
Gel phase ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0 (s, (**C**=O)-O), 74.8 (s, **C**$(CH_3)_2$-O), 71.5 (d, BzO**C**H), 62.6 (t, **C**H_2O-), 35.7 (t, -**C**H_2-), 32.1 (t, -**C**H_2-), 30.3 (s, **C**H_3), 21.7 (t, -**C**H_2-), 20.0 (q, **C**H_3)

Benzoic acid 1-[(3-ethoxy-1,1-dimethylpropoxy)diphenylsilanoxymethyl]pentyl ester polymer bound resin (2.48)



FTIR (on the bead) ν_{max}: 3067 (w), 2926 (m), 1716 (s, C=O), 1271 (s, C(O)-O), 1120 (s, C-O), 1080 (s, C-O)

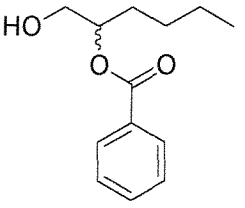
Benzoic acid 2-[(3-ethoxy-1,1-dimethylpropoxy)diphenylsilanoxy] (1*S*)-phenyl ethyl ester polymer bound resin (2.49)



FTIR (on the bead) ν_{max}: 3060 (w), 3027 (w), 2921 (w), 2859 (w), 1721 (s, C=O), 1268 (s, (C=O)-O), 1128 (s, C-O), 1060 (s, C-O)

Gel Phase ^{29}Si NMR (60 MHz, $CDCl_3$) δ: -38.1

Benzoic acid 1-hydroxymethyl-pentyl ester (2.51) from resin (2.48)



Resin **2.48** (414 mg) was suspended in THF (5 mL), then HF·Pyridine complex was added (1.00 mL) and the resulting suspension vigorously stirred at room temperature for 1 h. After this period the solution was collected and resin washed thoroughly with THF (5×5 mL, 5 min). The washings and the original solution were combined and partitioned between saturated $NaHCO_3$ (30 mL) and Et_2O (30 mL). The aqueous phase was then further extracted with Et_2O (5×10 mL) and the organics were dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded **2.51** (48 mg, 0.22 mmol, 81% overall yield from resin **2.1a**), along with the other regioisomer **2.56** (5 mg, 0.02 mmol, 8%) and the 1,2-hexanediol **2.54** (3 mg, 0.02 mmol, 9%).

Spectroscopic data were consistent with the literature. [138]

Benzoic acid 1-hydroxymethyl-pentyl ester (2.51) from resin (2.48)

Using the protocol previously reported (page 164) compound **2.51** was obtained as a colourless oil.

R_f: 0.38 (Hexane AcOEt 7:3)

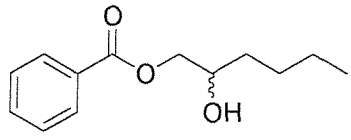
FTIR ($CHCl_3$) ν_{max}: 3446 (br, O-H), 2957 (m), 1715 (s, C=O), 1273 (s, C(=O)-O), 1115 (s, C-OH), 711 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (dd, *J*=8.1, 1.5 Hz, 2H, PhC-**H**), 7.54 (tt, *J*=7.3, 1.5 Hz, 1H, PhC-**H**), 7.42 (t, *J*=8.1 Hz, 2H, PhC-**H**), 5.19-5.08 (m, 1H, -C**H**(OBz)-), 3.80 (dd, *J*=12.0, 3.0 Hz, 1H, -C**H$_a$**OH), 3.73 (dd, *J*=12.0, 6.1 Hz, 1H, -C**H$_b$**OH), 2.31 (s, br, O**H**), 1.87-1.58 (m, 2H, -C**H$_2$**-), 1.46-1.18 (m, 4H, CH_3 C**H$_2$**C**H$_2$**-), 0.87 (t, *J*=7.3 Hz, 3H, C**H$_3$**)
^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.0 (s, -**C**(=O)-O-), 133.0 (d, Ph**C**H), 130.1 (s, Ph**C**), 129.6 (d, Ph**C**H), 128.3 (d, Ph**C**H), 76.3 (d, -**C**H(OBz)-), 64.8 (t, **C**H_2OH), 30.3 (t, **C**H_2), 27.4 (t, **C**H_2), 22.5 (t, **C**H_2), 13.8 (q, **C**H_3)

GC CIMS: R_t: 12.03 min; *m/z* (abundance): 240 $[M+NH_4]^+$ (2%), 223 $[M+H]^+$ (100%), 205 $[M-OH]^+$ (8%), 105 $[Ph(C=O)]^+$ (66%), 77 $[C_6H_5]^+$ (13%)

Benzoic acid 2-hydroxymethyl pentyl ester (2.56)

Using the same protocol previously reported (see page 164) compound **2.56** was obtained as a colourless oil.



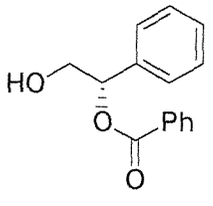
R_f: 0.41 (Hexane AcOEt 7:3)

FTIR ($CHCl_3$) ν_{max}: 3453 (br, O-H), 2955 (m), 1719 (s, C=O), 1272 (s, C(=O)-O), 1114 (s, C-OH), 710 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.03 (d, *J*=6.6, 2H, PhC**H**), 7.56 (tt, *J*=7.3, 1.5 Hz, 1H, PhC**H**), 7.43 (t, *J*=7.3 Hz, 2H, Ph**H**), 4.38 (dd, *J*=11.0, 3.0 Hz, 1H, (BzOC**H**$_a$H$_b$-CH(OH)-), 4.20 (dd, *J*=11.0, 6.6 Hz, 1H, (BzOCH$_a$**H**$_b$-CH(OH)-), 4.02-3.90 (m, 1H, BzOCH$_2$C**H**(OH)-), 2.15 (s, br, 1H, O**H**) 1.66-1.29 (m, 6H), 0.90 (t, *J*=6.6 Hz, 3H, **H**$_3$C-CH$_2$-)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.0 (s, ArC-**C**(=O)O-), 133.1 (d, Ar**C**H), 129.8 (s, Ar**C**-C(=O)O-), 129.6 (d, Ph**C**H), 128.4 (d, Ar**C**H), 70.1 (d, -**C**H(OH)-), 69.2 (t, BzO**C**H$_2$-), 33.1 (t, **C**H$_2$), 27.5 (t, **C**H$_2$), 22.6 (t, **C**H$_2$), 14.0 (q, **C**H$_3$)
GC CIMS: R_t: 12.24 min; *m/z* (abundance): 223 $[M+H]^+$ (12%), 205 $[M-OH]^+$ (2%), 122 (100%), 105 $[Ph(C=O)]^+$ (44%)

Benzoic acid 2-hydroxy-1-phenyl ethyl ester (2.52)
from resin (2.49)



The deprotection was carried out with resin **2.49** (571 mg) employing the same protocol described in page 164. Removal of the solvent under reduced pressure and final chromatography on silica afforded compound **2.52** (67 mg, 0.27 mmol, 75% overall yield from resin **2.1a**) along with the other regioisomer **2.57** (11 mg, 0.05 mmol, 13%) and 1-phenyl-1,2-ethanediol **2.55** (5 mg, 0.04 mmol, 10%).

Spectroscopic data were consistent with the literature. [138, 139]

Benzoic acid 2-hydroxy-1-phenyl ethyl ester (2.52)

White solid

MP: 64-66 °C (Hexane Et_2O) (literature: 65-67). [138]

R_f: 0.25 (Hexane AcOEt 7:3)

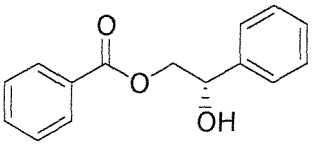
FTIR ($CHCl_3$) ν_{max}: 3438 (br, O-H), 3034 (w), 1703 (s, C=O), 1264 (s, C(=O)-O), 1110 (s, C-O), 1027 (s, C-O)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.12-8.06 (m, 2H, PhH), 7.56 (tt, *J*=7.3, 1.5 Hz, 1H, PhH), 7.48-7.26 (m, 7H, PhH), 6.10 (dd, *J*=7.3, 4.4 Hz, 1H, C_6H_5-CH(OBz)-), 4.02 (dd, *J*=12.5, 8.1 Hz, 1H, HOCH$_a$H$_b$), 3.92 (dd, *J*=12.0, 3.7 Hz, 1H, HOCH$_a$H$_b$), 2.31 (s, br, 1H, OH)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.1 (s, PhC-C(=O)O-), 137.0 (s, PhC), 133.2 (d, PhCH), 129.8 (s, PhC), 129.7 (d, PhCH), 128.6 (d, PhCH), 128.4 (d, PhCH), 128.3 (d, PhCH), 126.5 (d, PhCH), 77.4 (d, PhCH(OBz), 66.1 (t, CH_2OH)
GC CIMS: R_t: 13.97 min; *m/z* (abundance): 243 $[M+H]^+$ (4%), 225 $[M-OH]^+$ (100%), 105 $[Ph(C=O)]^+$ (86%), 91 $[C_6H_5CH_2]^+$ (72%), 77 $[C_6H_5]^+$ (20%), 65 $[C_5H_5]^+$ (12%), 51 $[C_4H_3]^+$ (3%)

Benzoic acid 2-hydroxy-2-phenyl ethyl ester (2.57) [139]

Using the same protocol previously reported (see page 164) compound **2.57** was obtained as a white solid.



MP: 63-64 °C (Hexane Et_2O) (literature: 65-66). [139]

R_f: 0.38 (Hexane AcOEt 7:3)

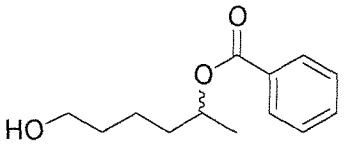
FTIR ($CHCl_3$) ν_{max}: 3297 (s, O-H), 3060 (w), 1717 (s, C=O), 1266 (s, C(=O)-O), 1111 (s, C-O), 1060 (s, C-O)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.04 (d, *J*=7.3 Hz, 2H, PhH), 7.56 (t, *J*=7.3, 1H, PhH), 7.50-7.26 (m, 7H, PhH), 5.10 (dd, *J*=8.1, 3.0 Hz, 1H, Ph-CH(OH)-), 4.51 (dd, *J*=11.7, 3.7 Hz, 1H, BzOCH$_a$H$_b$), 4.40 (dd, *J*=11.0, 8.8 Hz, 1H, BzOCH$_a$H$_b$), 2.77 (s, br, 1H, OH)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.7 (s, PhC-C(=O)O-), 139.8 (s, PhC), 133.2 (d, PhCH), 129.7 (s, PhC), 128.6 (d, PhCH), 128.4 (d, PhCH), 128.2 (d, PhCH), 126.5 (d, PhCH), 126.1 (d, PhCH), 72.5 (d, PhCH(OBz), 69.7 (t, CH_2OBz)

GC CIMS: R_t: 13.99 min; *m/z* (abundance): 243 $[M+H]^+$ (1%), 225 $[M-OH]^+$ (32%), 163 (100%), 105 $[Ph(C=O)]^+$ (89%), 91 $[C_6H_5CH_2]^+$ (30%), 65 $[C_5H_5]^+$ (6%)

Benzoic acid 5-hydroxy-1-methyl pentyl ester (2.50) from resin (2.47)



The deprotection was carried out with resin **2.47** (100 mg) and employing the same protocol described in page 164. Removal of the solvent under reduced pressure and final chromatography on silica afforded compound **2.50** as a colourless oil (12 mg, 0.05 mmol, 80% overall yield from the loading of **2.1a**).

Spectroscopic data were consistent with the literature. [140]

R_f: 0.23 (Hexane AcOEt 7:3)

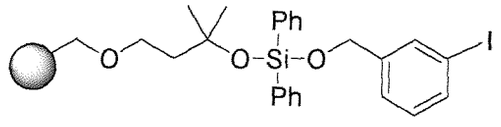
FTIR ($CHCl_3$) ν_{max}: 3413 (br, O-H), 2937 (m), 2866 (w), 1713 (s, C=O), 1276 (s, C-O), 1114 (m), 712 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.05-7.98 (m, 2H, PhH), 7.53 (tt, *J*=7.3, 1.5 Hz, 1H, PhH), 7.40 (t, *J*=7.3 Hz, 2H, PhH), 5.15 (sx, *J*=6.6 Hz, 1H, -CH-OBz), 3.68 (m, br, 2H, -CH_2OH), 1.84-1.37 (m, 6H), 1.32 (d, *J*= 6.0 Hz, 3H, -CH_3), 1.27 (s, br, 1H, OH)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.6 (s, -C(=O)-O-), 133.1 (d, PhCH), 131.2 (s, PhC), 129.9 (d, PhCH), 128.7 (d, PhCH), 71.8 (d, -CH(OBz)-), 63.1 (t, CH_2OH), 36.2 (t, CH_2), 32.9 (t, CH_2), 22.1 (t, CH_2), 20.4 (q, CH_3)

GC CIMS: R_t: 13.15 min; *m/z* (abundance): 223 $[M+H]^+$ (10%), 205 $[M-OH]^+$ (6%), 105 $[Ph(C=O)]^+$ (100%), 82 (59%), 67 (21%)

(3-Ethoxy-1,1-dimethylpropoxy)-(3-iodo-benzyloxy)diphenylsilane polymer bound resin (3.86)



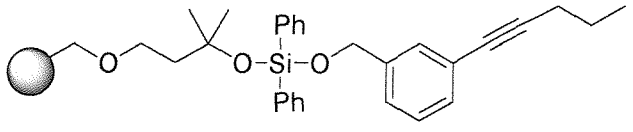
The silyl chloride resin **2.1a** (1.00 g, loading=0.65 mmol/g) was suspended in dry CH_2Cl_2 (9 mL), then Et_3N (1.33 mL, 9.60 mmol) was added, followed by 3-iodobenzyl alcohol (0.80 mL, 6.40 mmol) and DMAP (400 mg, 3.20 mmol). The resulting suspension was shaken at room temperature for 1 h. Then the resin was drained, washed with CH_2Cl_2 (10×5 mL, 5 min) and dried under high vacuum (40 °C @ 10 mmHg) for 24 h.

General protocol for the Sonogashira coupling between polymer bound aryl iodide (3.86) and terminal alkynes [113]

Resin **3.86** (400 mg) was suspended in a mixture of dry dioxane and Et_3N (3:1) (6 mL) under N_2, then CuI (24 mg, 0.13 mmol) and the appropriate alkyne **3.87**, **3.88**, **3.89** or **3.90** (6.60 mmol of each) were sequentially added, followed by *trans*-$(PPh_3)_2PdCl_2$ (0.06 mmol). The system was purged with N_2 for 5 min and sealed; the resulting

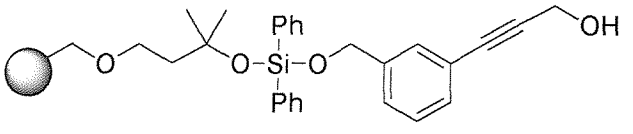
suspension was then wrapped with an alluminium foil and shaken at room temperature for 24 h. The resin was washed thoroughly with dioxane (5×5 mL, 5 min), THF (5×5 mL, 5 min), water (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and then dried under high vacuum (40 °C @ 10 mmHg) for 24 h. In this way resins **3.91**, **3.92**, **3.93** and **3.94** were obtained.

Siloxane resin (3.91)



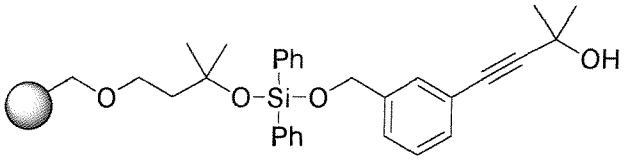
FTIR (on the bead) ν_{max}: 3027 (m), 2918 (s), 1601 (s), 1015 (s, C-O), 753 (s)

Siloxane resin (3.92)



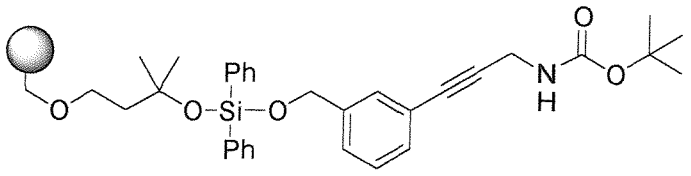
FTIR (on the bead) ν_{max}: 3400 (br, O-H), 3025 (s), 2924 (s), 1601 (s), 1127 (s)

Siloxane resin (3.93)



FTIR (on the bead) ν_{max}: 3414 (s, O-H), 3060 (s), 2977 (s), 1602 (s), 1163 (s, C-O)

Siloxane resin (3.94)

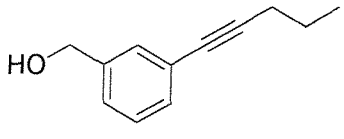


FTIR (on the bead) ν_{max}: 3423 and 3349 (s, NH), 3060 (s), 2975 (s), 1722 (s, C=O), 1602 (s), 1247 (s), 1170 (s, C-O)

General protocol for the cleavage of alkynes (3.95)-(3.98) from resins (3.91)-(3.94)

Resins **3.91-3.94** (371-410 mg) were suspended in THF (5 mL), then TBAF (0.60-0.66 mmol, 2.5 eq respect to the loading of the silyl chloride resin **2.1a**) was added and the resulting suspension stirred at room temperature for 2 h. Then the solution was collected and the resin washed with THF (5×5 ml, 5 min); the original solution and the washings were collected and partitioned between brine (20 mL) and Et_2O (60 mL). The aqueous phase was extracted again with Et_2O (2×30 mL) and the combined organics washed further with brine (30 mL) and dried ($MgSO_4$). Removal of the solvent under reduced pressure and chromatography on silica afforded alkynes **3.95**, **3.96**, **3.97** and **3.98**.

(3-Pent-1-ynylphenyl)methanol (3.95) from resin (3.91)



Starting from resin **3.91** (371 mg), compound **3.95** was obtained as a light yellow oil (39 mg, 0.22 mmol, 93% overall yield from the loading of silyl chloride resin **2.1a**).

R_f: 0.15 (Hexane AcOEt 6:1)

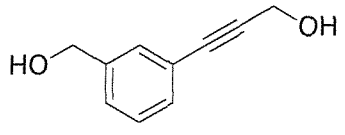
FTIR ($CHCl_3$) ν_{max}: 3324 (br, O-H), 2962 (m), 2932 (m), 2871 (m), 1428 (s), 1126 (s), 1042 (s, C-O), 788 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60-7.00 (m, 4H, Ph**H**), 4.57 (s, 2H, PhC**H$_2$**OH), 2.36 (t, *J*=7.3 Hz, 2H, -C≡CC**H$_2$**-), 2.10 (s, br, 1H, O**H**), 1.60 (sx, *J*=7.3, 2H, -CH_2-C**H$_2$**-CH_3), 1.03 (t, *J*=7.3 Hz, **H$_3$**C-CH_2-)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.0 (s, Ph**C**), 130.6 (d, Ph**C**H), 129.9 (d, Ph**C**H), 128.3 (d, Ph**C**H), 127.6 (d, Ph**C**H), 124.1 (s, Ph**C**), 90.4 (s,-CH_2**C**≡**C**-Ph), 80.4 (s,-**C**≡**C**CH_2-), 64.7 (t, **C**H_2OH), 22.1 (t, **C**H_2), 21.3 (t, **C**H_2), 13.5 (q, **C**H_3)
GC CIMS: R_t: 11.49 min; *m/z* (abundance): 192 $[M+NH_4]^+$ (22%), 174 $[M]^+$ (57%), 145 $[M-C_2H_5]^+$ (64%), 115 (100%), 91 $[C_6H_5CH_2]^+$ (33%), 77 $[C_6H_5]^+$ (20%)

HR CIMS: Exact mass calculated for $C_{12}H_{14}O$: 174.10447; found: 174.10396

3-(3-Hydroxymethylphenyl)propynol (3.96) from resin (3.92)



Starting from resin **3.92** (392 mg), compound **3.96** was obtained as a pink oil (39 mg, 0.24 mmol, 94% overall yield from the loading of silyl chloride resin **2.1a**).

R_f: 0.21 (Hexane AcOEt 6:4)

FTIR ($CHCl_3$) ν_{max}: 3305 (br, O-H), 2920 (w), 2870 (w), 1429 (m), 1026 (s, C-OH), 790 (s)

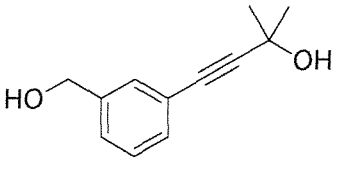
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (apparent singlet, 1H, Ph**H**), 7.37-7.25 (m, 3H, Ph**H**), 4.63 (s, 2H, -C**H$_2$**OH), 4.45 (s, 2H, -C**H$_2$**OH), 2.14 (s, br, 2H, 2×O**H**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.0 (s, Ph**C**), 130.8 (d, Ph**C**H), 130.1 (d, Ph**C**H), 128.5 (d, Ph**C**H), 127.0 (d, Ph**C**H), 122.7 (s, Ph**C**), 87.4 (s, -**C**≡C-), 85.4 (s, -C≡**C**-), 64.7 (t, -**C**H_2OH), 51.5 (t, -**C**H_2OH)

GC CIMS: R_t: 12.27 min; *m/z* (abundance): 180 $[M+NH_4]^+$ (8%), 162 $[M]^+$ (46%), 131 (100%), 91 $[C_6H_5CH_2]^+$ (30%)

HR CIMS: Exact mass calculated for $C_{10}H_{10}O_2$: 162.06808; found: 162.06783

4-(3-Hydroxymethylphenyl)-2-methylbut-3-yn-2-ol (3.97) from resin (3.93)



Starting from resin **3.93** (378 mg), compound **3.97** was obtained as a pink oil (45 mg, 0.23 mmol, 96% overall yield from the loading of silyl chloride resin **2.1a**).

R_f: 0.23 (Hexane AcOEt 6:4)

FTIR ($CHCl_3$) ν_{max}: 3311 (s, O-H), 2981 (m), 2932 (w), 1362 (m), 1153 (s, C-OH)

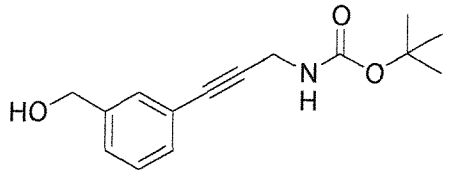
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.40 (apparent singlet, 1H, Ph**H**), 7.36-7.25 (m, 3H, Ph**H**), 4.60 (s, 2H, PhC**H$_2$**OH), 2.65 (s, br, 1H, O**H**), 2.50 (s, br, 1H, O**H**), 1.60 (s, 6H, -C(C**H$_3$**)$_2$OH)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 141.0 (s, Ph**C**), 130.7 (d, Ph**C**H), 130.0 (d, Ph**C**H), 128.4 (d, Ph**C**H), 126.7 (d, Ph**C**H), 122.8 (s, Ph**C**), 94.0 (s, -**C**≡C-), 82.0 (s, -C≡**C**-), 65.5 (s, -**C**$(CH_3)_2$OH), 64.5 (t, HO**C**H_2Ph), 31.4 (q, 2×**C**H_3)

GC CIMS: R_t: 12.00 min; *m/z* (abundance): 190 $[M]^+$ (7%), $[M-OH]^+$ (100%), 132 (97%), 77 $[C_6H_5]^+$ (20%)

HR CIMS: Exact mass calculated for $C_{12}H_{14}O_2$: 190.09938; found: 190.09963

[3-(3-Hydroxymethylphenyl)prop-2-ynyl]carbamic acid *tert*-butyl ester (3.98) from resin (3.94)



Starting from resin **3.94** (410 mg), compound **3.98** was obtained as a yellow oil (67 mg, 0.25 mmol, 97% overall yield from the loading of silyl chloride resin **2.1a**).

R_f: 0.22 (Hexane AcOEt 6:3)

FTIR ($CHCl_3$) ν_{max}: 3398 (s, O-H or N-H), 3306 (s, O-H or N-H), 2980 (w), 1685 (s, C=O), 1513 (s), 1291 (s), 1158 (s, C-O), 1024 (s, C-O)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.39 (apparent singlet, 1H, PhH), 7.35-7.25 (m, 3H, PhH), 4.80 (s, br, 1H, NH), 4.63 (s, 2H, PhCH_2OH), 4.11 (d, br, *J*=5.0 Hz, 2H, -CH_2NH-), 1.97 (s, br, OH), 1.44 (s, 9H, -C(CH_3)$_3$)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 155.3 (s, -C(=O)OC$(CH_3)_3$), 141.1 (s, PhC), 130.8 (d, PhCH), 130.1 (d, PhCH), 128.5 (d, PhCH), 126.9 (d, PhCH), 122.8 (s, PhC), 85.5 (s), 83.0 (s), 80.0 (s), 64.7 (t, PhCH_2OH), 31.1 (t, -CH_2NH-), 28.4 (q, 3×CH_3)

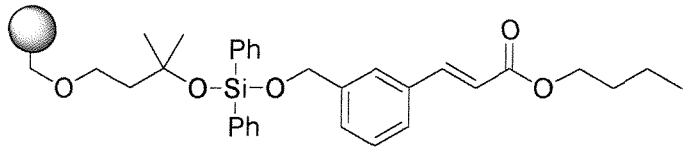
ES MS: *m/z* (abundance): 545 $[2M+Na]^+$ (90%), 806 $[3M+Na]^+$ (33%)

HR ESMS: Exact mass calculated for $C_{15}H_{19}NO_3Na$ [M+Na]: 284.1257; found: 284.1264

General protocol for the Heck reaction between polymer bound aryl iodide 3.86 and terminal alkenes [113]

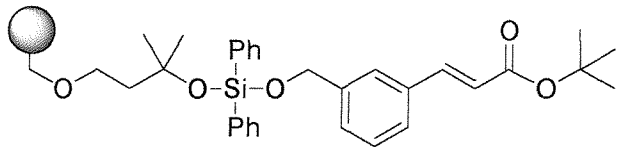
To a vigorously stirred suspension of resin **3.86** (400 mg) in *N, N*-dimethylacetamide (9 mL), NaOAc (106 mg, 0.78 mmol) was added, followed by *N*-tetrabutylammonium chloride (144 mg, 0.52 mmol) and the appropriate alkene **3.99**, **3.100**, **3.101** or **3.102** (2.73 mmol of each). PdOAc (20 mg, 0.08 mmol) was added and the system purged with N_2 for 10 min; the resulting suspension was stirred and heated at 100 °C for 3 h. Then the resin was washed thoroughly with dioxane (5×5 mL, 5 min), THF (5×5 mL, 5 min), water (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and then dried under high vacuum (40 °C @ 10 mmHg) for 24 h. In this way resins **3.103**, **3.104**, **3.105** and **3.106** were prepared. FTIR analysis on the resins showed the presence of an hydroxyl band, due to a partial cleavage of the siloxane under the reaction conditions reported.

Alkene bound resin (3.103)



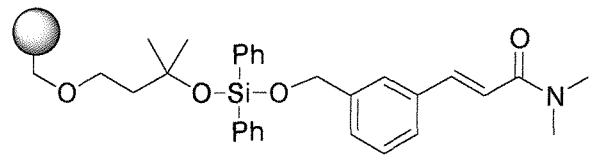
FTIR (on the bead) ν_{max}: 3502 (br, O-H), 3060 (s), 2970 (s), 1712 (s, C=O), 1640 (s, *trans*-C=C-), 1601 (s), 1161 (s, C-O), 1118 (s, C-O), 820 (s)

Alkene bound resin (3.104)



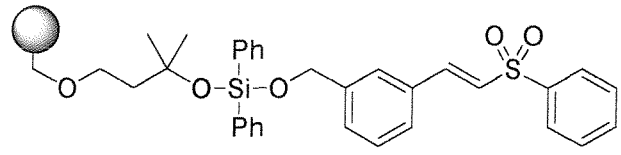
FTIR (on the bead) ν_{max}: 3518 (br, O-H), 3060 (s), 2973 (s), 1710 (s, C=O), 1638 (s, *trans*-C=C), 1602 (s), 1232 (s), 1161 (s, C-O)

Alkene bound resin (3.105)



FTIR (on the bead) ν_{max}: 3332 (br, O-H), 3060 (s), 2972 (s), 1653 (s, C=O), 1602 (s), 1115 (s), 821 (s)

Alkene bound resin (3.106)

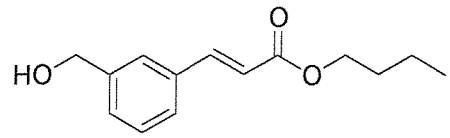


FTIR (on the bead) ν_{max}: 3520 (w, O-H), 3059 (s), 2923 (s), 1616 (s, *trans*-C=C), 1603 (s), 1309 (s, S=O), 1152 (s, C-O), 1117 (s, C-O), 840 (s)

Cleavage of alkenes (3.107)-(3.110) from resins (3.103)-(3.106)

The cleavage was performed in the same way reported in page 171. Additional chromatography and recrystallization afforded compounds **3.107, 3.108, 3.109** and **3.110**.

3-(3-Hydroxymethylphenyl)acrylic acid butyl ester (3.107) from resin (3.103)



Starting from resin **3.103** (316 mg), compound **3.107** was obtained as a colourless oil (33 mg, 0.14 mmol, 70% overall yield from the loading of silyl chloride resin **2.1a**).

R_f: 0.20 (Hexane AcOEt 6:2)

FTIR (neat) ν_{max}: 3420 (br, O-H), 2958 (m), 2872 (w), 1707 (s, C=O), 1636 (s, *trans*-C=C), 1159 (s, C-O), 980 (s)

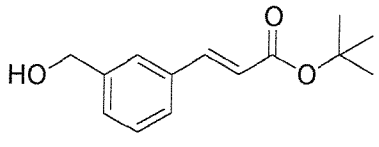
^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (d, *J*=16.0 Hz, 1H, *trans*-Ph-C**H**=CH-), 7.48 (apparent singlet, 1H, Ph**H**), 7.43-7.27 (m, 3H, Ph**H**), 6.40 (d, *J*=16.0 Hz, 1H, *trans*-Ph-CH=C**H**-), 4.65 (s, 2H, PhC**H$_2$**OH), 4.15 (t, *J*=6.6 Hz, 2H, -C(=O)O-C**H$_2$**-), 2.56 (s, br, 1H, -O**H**), 1.65 (quin, *J*=8.0 Hz, 2H, -C(=O)O-CH$_2$-C**H$_2$**-), 1.40 (sx, *J*=8.0 Hz, 2H, -C**H$_2$**-CH$_3$), 0.93 (t, *J*=7.3 Hz, 3H, -C**H$_3$**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.2 (s, **C**(=O)O^{n}Bu), 144.4 (d, Ph**C**H=CH-), 141.7 (s, Ph**C**), 134.6 (s, Ph**C**), 129.0 (d, Ph**C**H), 128.7 (d, Ph**C**H), 127.2 (d, Ph**C**H), 126.3 (d, Ph**C**H), 118.3 (d, PhCH=**C**H-), 64.6 (t, -C(=O)O**C**H$_2$-), 64.5 (t, Ph**C**H$_2$OH), 30.7 (t, -C(=O)O-CH$_2$-**C**H$_2$-), 19.2 (t, -**C**H$_2$-CH$_3$), 13.7 (q, **C**H$_3$)

GC CIMS: R_t: 15.08 min; *m/z* (abundance): 235 $[M+H]^+$ (16%), 103 $[C_5H_{11}O_2]^+$ (70%), 91 $[C_6H_5CH_2]^+$ (32%), 77 $[C_6H_5]^+$ (93%)

HR CIMS: Exact mass calculated for $C_{14}H_{18}O_3$: 234.12559; found: 234.12599

3-(3-Hydroxymethylphenyl)acrylic acid *tert*-butyl ester (3.108) from resin (3.104)



Starting from resin **3.104** (355 mg), compound **3.108** was obtained as a colourless oil (38 mg, 0.16 mmol, 71% overall yield from the loading of silyl chloride resin **2.1a**).

Spectroscopic data were consistent with the literature. [141]

R_f: 0.20 (Hexane AcOEt 6:2)

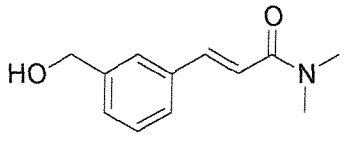
FTIR ($CHCl_3$) ν_{max}: 3404 (br, O-H), 2977 (w), 1704 (s, C=O), 1635 (s, *trans*-C=C-), 1320 (s, C(=O)-O), 1144 (s, C-O), 980 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.57 (d, *J*=16.0 Hz, 1H, *trans*-Ph-C**H**=CH-), 7.50 (apparent singlet, 1H, Ph**H**), 7.43-7.30 (m, 3H, Ph**H**), 6.40 (d, *J*=16.0 Hz, 1H, *trans*-Ph-CH=C**H**-), 4.70 (s, 2H, PhC**H$_2$**OH), 2.20 (s, br, 1H, -O**H**), 1.54 (s, 9H, (C**H$_3$**)$_3$C-O-)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.3 (s, **C**(=O)O^{t}Bu), 143.3 (d, Ph**C**H=CH-), 141.5 (s, Ph**C**), 134.9 (s, Ph**C**), 129.0 (d, Ph**C**H), 128.4 (d, Ph**C**H), 127.2 (d, Ph**C**H), 126.3 (d, Ph**C**H), 120.0 (d, PhCH=**C**H-), 80.6 (s, (CH$_3$)$_3$**C**-O-), 64.9 (t, Ph**C**H$_2$OH), 28.2 (q, 3×**C**H$_3$)

GC CIMS: R_t: 13.33 min; *m/z* (abundance): 252 $[M+NH_4]^+$ (2%), 234 $[M]^+$ (10%), 217 $[M\text{-}OH]^+$ (4%), 196 (100%), 160 $[M\text{-}^t\text{BuOH}]^+$ (72%), 91 $[C_6H_5CH_2]^+$ (13%), 77 $[C_6H_5]^+$ (21%)

3-(3-Hydroxymethylphenyl)-*N*,*N*-dimethylacrylamide (3.109) from resin (3.105)



Starting from resin **3.105** (312 mg), compound **3.109** was obtained as a white solid (29 mg, 0.14 mmol, 70% overall yield from the loading of silyl chloride resin **2.1a**).

R_f: 0.13 (CH_2Cl_2 MeOH 97:3)

MP: 78-80 °C (Hexane AcOEt)

FTIR ($CHCl_3$) ν_{max}: 3254 (s, N-H), 2924 (w), 2852 (w), 1648 (s, C=O), 1588 (s), 1138 (s), 1054 (s), 786 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.50 (d, *J*=15.0 Hz, 1H, *trans*-Ph-C**H**=CH-), 7.48 (apparent singlet, 1H, Ph**H**), 7.40-7.20 (m, 3H, Ph**H**), 6.80 (d, *J*=15.0 Hz, 1H, *trans*-Ph-

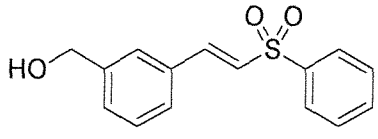
CH=C**H**-), 4.66 (s, 2H, PhC**H**$_2$OH), 3.10 (s, 3H, C**H**$_3$N<), 3.00 (s, 3H, C**H**$_3$N<), 1.89 (s, br, 1H, -O**H**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.8 (s, **C**(=O)-N<), 142.3 (d, **C**H), 141.8 (s, Ph**C**), 135.4 (s, Ph**C**), 128.8 (d, Ph**C**H), 128.1 (d, Ph**C**H), 127.1 (d, Ph**C**H), 125.8 (d, Ph**C**H), 117.3 (d, **C**H), 64.7 (t, Ph**C**H$_2$OH), 37.4 (q, **C**H$_3$N<), 35.9 (q, **C**H$_3$N<)

ES MS: *m/z* (abundance): 411 $[2M+H]^+$ (35%), 616 $[3M+H]^+$ (27%)

HR ESMS: Exact mass calculated for $C_{24}H_{30}N_2O_4Na$ $[2M+Na]^+$: 433.2098; found: 433.2100

[3-(2-Benzenesulfonylvinyl)phenyl]methanol (3.110) from resin (3.106)



Starting from resin **3.106** (327 mg), compound **3.110** was obtained as a white solid (39 mg, 0.14 mmol, 67% overall yield from the loading of silyl chloride resin **2.1a**).

R_f: 0.21 (CH_2Cl_2 MeOH 97:3)

MP: 95-97 °C (Hexane AcOEt)

FTIR (neat) ν_{max}: 3336 (br, O-H), 3048 (w), 2918 (w), 1618 (m, *trans*-CH=CH-), 1296 s, (S=O), 1140 (s, C-O or S=O), 1083 (s, C-O or S=O), 757 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.91 (d, *J*=4.0 Hz, 2H, Ph**H**), 7.70-7.30 (m, 8H), 6.83 (d, *J*=15.0 Hz, 1H, *trans*-Ph-CH=C**H**-), 4.60 (s, 2H, PhC**H**$_2$OH), 2.34 (s, br, 1H, O**H**)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 142.0 (d, **C**H), 141.9 (s, Ph**C**), 140.4 (s, Ph**C**), 133.4 (d, Ph**C**H), 132.4 (s, Ph**C**), 129.5 (d, Ph**C**H), 129.3 (d, Ph**C**H), 129.1 (d, Ph**C**H), 127.8 (d, Ph**C**H), 127.5 (d, Ph**C**H), 127.2 (d, Ph**C**H), 126.5 (d, **C**H), 64.3 (t, Ph$\mathbf{C}H_2$OH)

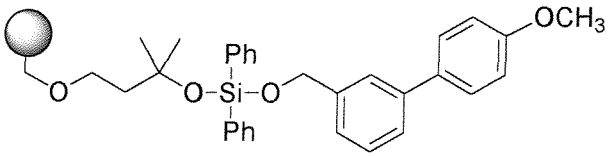
ES MS: *m/z* (abundance): 845 $[3M+Na]^+$ (5%)

HR ESMS: Exact mass calculated for $C_{30}H_{28}O_6S_2Na$ $[2M+Na]^+$: 571.1220; found: 571.1224

General protocol for the Suzuki reaction between polymer bound aryl iodide (3.86) and boronic acids [117]

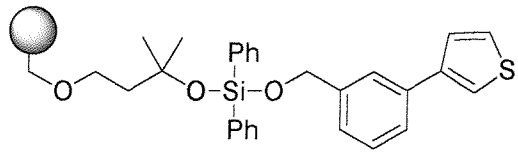
To a vigorously stirred suspension of resin **3.86** (500 mg) in dry dioxane (7 mL), the boronic acid **3.111** or **3.112** (1.30 mmol of each) was added, followed by K_2CO_3 (180 mg, 1.30 mmol, previously dissolved in the minimal amount of H_2O). PdOAc (10 mg, 0.03 mmol) was then added and the resulting suspension rapidly stirred at 100 °C for 15 h. The resin was then drained and rinsed thoroughly with dioxane (5×5 mL, 5 min), THF (5×5 mL, 5 min), THF water 1:1 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min) and then dried under high vacuum (40 °C @ 10 mmHg) for 24 h. In this way resins **3.113** and **3.114** were obtained.

Biphenyl resin (3.113)



FTIR (on the bead) ν_{max}: 3026 (s), 2972 (s), 1602 (s), 1156 (s, C-O), 1060 (s, C-O), 830 (s)

Thiophene resin (3.114)

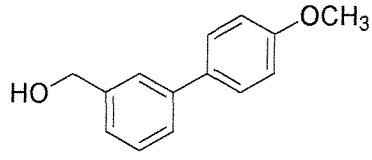


FTIR (on the bead) ν_{max}: 3026 (s), 2973 (s), 1600 (s), 1156 (s, C-O), 1116 (s, C-O), 822 (s)

Cleavage of compounds (3.115) and (3.116) from resins (3.113) and (3.114)

The cleavage was performed using the method previously reported in page 171. Additional chromatography and recrystallization afforded pure compounds **3.115** and **3.116**.

(4'-Methoxybiphenyl-3-yl)methanol (3.115) from resin (3.113)



Starting from resin **3.113** (495 mg), compound **3.115** was obtained as a white solid (48 mg, 0.22 mmol, 70% overall yield from the loading of silyl chloride resin **2.1a**).

Spectroscopic data were consistent with the literature. [141]

R_f: 0.51 (Hexane AcOEt 2:1)

MP: 92-93 °C (Hexane AcOEt) (literature: 94 °C). [141]

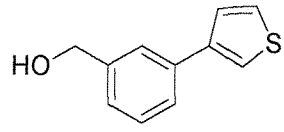
FTIR ($CHCl_3$) ν_{max}: 3267 (br, O-H), 2956 (w), 2911 (w), 1605 (s, C=C), 1250 (s), 1182 (s, C-O), 1025 (s, C-O), 787 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60-7.45 (m, 4H, PhH), 7.40 (t, *J*=7.3 Hz, 1H, PhH), 7.32-7.27 (m, 1H, PhH), 6.96 (dt, *J*=9.0, 3.0 Hz, 2H, PhCH), 4.73 (s, 2H, $PhCH_2OH$), 3.83 (s, 3H, $-OCH_3$), 1.73 (s, br, 1H, O-H)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 159.2 (s, PhC), 141.3 (s, PhC), 141.1 (s, PhC), 133.4 (s, PhC), 129.0 (d, PhCH), 128.1 (d, PhCH), 126.0 (d, PhCH), 125.3 (d, PhCH), 125.2 (d, PhCH), 114.2 (d, PhCH), 65.4 (t, $PhCH_2OH$), 55.3 (q, $-OCH_3$)

GC CIMS: R_t: 14.89 min; *m/z* (abundance): 214 $[M]^+$ (100%), 198 (42%), 183 $[M-CH_3OH]^+$ (17%), 77 $[C_6H_5]^+$ (8%)

(3-Thiophen-3-yl-phenyl)methanol (3.116) from resin (3.114)



Starting from resin **3.114** (476 mg), compound **3.116** was obtained as a white solid (39 mg, 0.20 mmol, 67% overall yield from the loading of silyl chloride resin **2.1a**).

R_f: 0.34 (Hexane AcOEt 3:1)

MP: 88-90 °C (Hexane AcOEt)

FTIR ($CHCl_3$) ν_{max}: 3319 (s, br, O-H), 3102 (w), 2927 (w), 1016 (s, C-O), 770 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60 (apparent singlet, 1H, ArH), 7.56-7.20 (m, 6H, ArH), 4.70 (d, *J*=5.8 Hz, 2H, $PhCH_2OH$), 1.96 (t, *J*=5.8 Hz, 1H, -OH)

^{13}C NMR (75 MHz, $CDCl_3$) δ: 140.8 (s, ArC) 140.1 (s, ArC), 134.9 (s, ArC), 127.8 (d, ArCH), 125.1 (d, ArCH), 125.0 (d, ArCH), 124.6 (d, ArCH), 124.5 (d, ArCH), 123.8 (d, ArCH), 119.2 (d, ArCH), 64.1 (t, $PhCH_2OH$)

GC CIMS: R_t: 13.68 min; *m/z* (abundance): 190 $[M]^+$ (100%), 173 $[M\text{-}OH]^+$ (27%), 161 (48%), 128 (34%), 115 (48%)

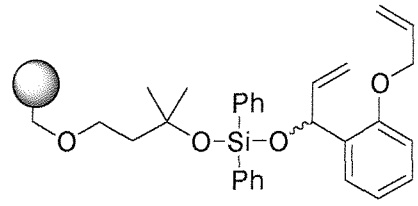
HR EIMS: Exact mass calculated for $C_{11}H_{10}OS$: 190.04524; found: 190.04528

Elemental analysis. Anal. calcd. for $C_{11}H_{10}OS$: C, 69.44; H, 5.30; S, 16.85; found: C, 69.39; H, 5.33; S, 16.97

Resin bound acyclic precursors (3.121) and (3.122)

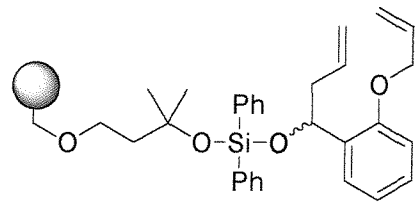
Resin bound acyclic precursors **3.121** and **3.122** were prepared from resin **2.1a** and alcohols **3.119** and **3.120** respectively, using the same protocol previously reported in page 143.

Resin bound acyclic precursor (3.121)



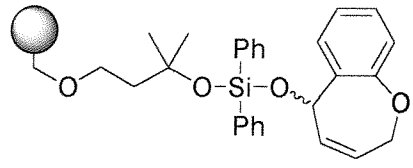
FTIR (on the bead) ν_{max}: 3082 (s), 2816 (s), 1635 (s, C=C), 1601 (s), 1068 (s, C-O), 1023 (s, C-O), 701 (s)

Resin bound acyclic precursor (3.122)



FTIR (on the bead) ν_{max}: 3027 (s), 2974 (s), 2924 (s), 1600 (s), 1239 (s), 1113 (s, C-O), 913 (s)

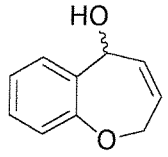
2,5-Dihydro-benzo[*b*]oxepin-5-ol polymer bound resin (3.121a)



Resin **3.121** (400 mg) was suspended in freshly dried CH_2Cl_2 (9 mL) and Grubbs's catalyst (21 mg, 0.02 mmol) was added under N_2. The system was then sealed and the resulting suspension stirred at reflux for 20 h. Then the resin was drained and washed thoroughly with CH_2Cl_2 (5×5 mL, 5 min), THF (5×5 mL, 5 min), CH_2Cl_2 (5×5 mL, 5 min).

FTIR (on the bead) ν_{max}: 3026 (s), 2927 (s), 1601 (s), 1224 (s), 1157 (s, C-O), 1122 (s, C-O), 877 (s)

2,5-Dihydro-benzo[*b*]oxepin-5-ol (3.123) from resin (3.121a)



Cleavage of **3.123** from resin **3.121a** (307 mg) was performed in the same method previously reported in page 171. Chromatography and final recrystallization afforded **3.123** as a colourless solid (17 mg, 0.10 mmol, 53% overall yield from the loading of the silyl chloride resin **2.1a**).

MP: 41-42 °C (CH_3OH) (literature: 41-43 °C). [142]

R_f: 0.27 (Hexane AcOEt 20:5)

FTIR ($CHCl_3$) ν_{max}: 3405 (br, O-H), 3072 (w), 2932 (w), 1483 (s), 1219 (s), 1053 (s, C-O), 732 (s)

^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.43-7.20 (m, 2H, PhC**H**), 7.18-7.06 (m, 2H, PhC**H**), 6.02 (dquin, *J*=11.0, 2.2 Hz, 1H, -C**H**=CH-), 5.60-5.44 (m, 2H, -C**H**OH and -CH=C**H**-), 4.67-4.50 (m, 2H, -O-C**H$_2$**-CH=CH-), 2.56 (d, *J*=7.3 Hz, 1H, O-**H**)

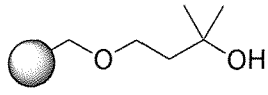
^{13}C NMR (75 MHz, $CDCl_3$) δ: 156.3 (s, Ph**C**), 139.3 (s, Ph**C**), 131.7 (d, **C**H), 129.0 (d, **C**H), 128.0 (d, Ph**C**H), 125.5 (d, Ph**C**H), 124.7 (d, Ph**C**H), 121.7 (d, Ph**C**H), 71.2 (t, -O-**C**H_2CH=CH-), 69.1 (d, -**C**HOH)

GC CIMS: R_t: 11.67 min; *m/z* (abundance): 162 $[M]^+$ (16%), 145 $[M\text{-}OH]^+$ (100%), 131 (74%), 115 (50%), 77 $[C_6H_5]^+$ (20%)

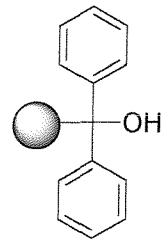
HR EIMS: Exact mass calculated for $C_{10}H_{10}O_2$: 162.06808; found: 162.06832

Detection of polymer bound tertiary alcohols with methyl red, general protocol. [13]

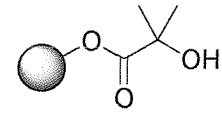
A typical protocol is as follows: resins **2.3b**, **3.127** or **3.128** (5 mg) were suspended in a 10% solution of Et_3N in dry CH_2Cl_2 and treated with diphenyldichlorosilane (100 μL) for 10-20 min. The resin was then drained, washed further with Et_3N (10% solution in CH_2Cl_2) and re-suspended in a solution of methyl red (0.75% w/v in DMF). The resulting suspension was shaken for 10 min, then the resin was drained and washed extensively with DMF (5×500 μL, 1 min), CH_2Cl_2 (5×500 μL, 1 min), until the washings were colourless and an orange/red colour persisted on the beads



2.3b



3.127



3.128

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