UNIVERSITY OF SOUTHAMPTON

FACULTY OF ENGINEERING, SCIENCE & MATHEMATICS

School of Chemistry

Towards the Synthesis of the Ergot Alkaloids and Analogues of FK-506

by

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Thesis for the degree of Doctor of Philosophy

September 2007

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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The ergot alkaloids are an important subgroup of indole alkaloids as they show a wide range of biological activity. A synthesis of the ergot alkaloid skeleton was attempted from the amino acid tryptophan, the biosynthetic precursor. We anticipated that the C ring of the skeleton would be constructed by an intramolecular Friedel-Crafts type acylation of an aziridine onto the C-4 position of the indole ring. The more reactive C-2 position of the ring would be blocked due to the electron acceptance and steric hindrance of a pivaloyl protecting group on the indole nitrogen. The amino acid was converted to its corresponding aziridine *via* a Grignard addition to the amino aldehyde, followed by a Mitsunobu reaction. Through a sequence of protecting group manipulations, a range of precursors to the Freidel-Crafts acylation were synthesised and the cyclisations attempted, mediated by the Lewis acid $BF_3 \cdot OEt_2$.

FK-506 is a powerful immunosuppressant used for the prevention and treatment of organ transplant rejection. A synthesis of the C-26-C-34 fragment of the macrocycle was achieved from an acyclic precursor where the cyclohexyl ring was constructed *via* an intramolecular cyclisation. The chirality of the molecule was set prior to ring closure using Evans aldol chemistry. Following the boron-mediated aldol condensation the molecule was protected as a TIPS ether and the chiral auxiliary reductively removed with sodium borohydride. Conversion of the alcohol to a tosylate was achieved to furnish the precursor to the cyclisation. The intramolecular S_N2 displacement was optimized using microwave conditions.

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Acknowledgements

My appreciation goes to my supervisor Ganesan for all his help and guidance during my PhD.

Thanks to all past and present members of the Ganesan group who made coming into university everyday such an enjoyable experience. In particular thanks to Sally, Helen and Krystle for being great neighbours and for having a good gossip, Alex for the downloads and showing us how things should be done, Wendy for the endless supply of sweets, Tom for being such an easy target, Shijun for all his help in labs and Lauren for letting me share her fume hood and desk.

Thanks to Neil and Joan from NMR, Julie and John from mass spec, Karl and Tony from stores and Pat for supplying the tea.

Special thanks to all my friends and family, in particular my Mum and Dad who made it possible for me to go to university and for showing their support at all times.

A big thank you to Paul for providing a roof over my head during my most poverty-stricken period, I don't know what I would have done if you hadn't let me come and stay!

Finally special thanks to Simon for helping me both emotionally and financially and for putting up with me during the low times. I couldn't have done this without your support and encouragement and I will be eternally grateful for all your lovely cooking!

Abbreviations

Ac	Acetyl
AIBN	Azoisobutyronitrile
app	Apparent
aq.	Aqueous
Bn	Benzyl
Bz	Benzoyl
Boc	*tert*-Butoxycarbonyl
br	Broad
conc	Concentrated
m-CPBA	*meta*-Chloroperoxybenzoic acid
d	Doublet
DBU	1,8-Diazobicyclo[5.4.0]undec-7-ene
DCC	1,3-Dicyclohexylcarbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	Diisopropylazodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N'*-Dimethylformamide
DMSO	Dimethyl sulfoxide
EDC	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
Equiv	Equivalents
h	Hours
HMDS	Hexamethyl disilazide
HMPA	Hexamethylphosphoramide
HOBt	1-Hydroxybenzotriazole
IR	Infrared
LDA	Lithium diisopropylamide
LRMS	Low resolution mass spectrometry
m	Multiplet
Ms	Methanesulfonyl

MS	Mass spectrometry
Mts	2,4,6-trimethylbenzenesulfonyl
NBS	*N*-Bromosuccinimide
NMO	*N*-methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
Ns	4-Nitrobenzenesulfonyl
PCC	Pyridinium chlorochromate
Piv	Pivaloyl
PMA	phosphomolybdic acid
PMB	*p*-methoxybenzyl
ppm	Parts per million
PPTS	Pyridinium *p*-toluenesulfonate
PTSA	*p*-Toluenesulfonic acid
q	Quartet
quant.	Quantitative yield
s	Singlet
rt	room temperature
t	Triplet
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TFA	Trifluoroacetic acid
Tf (OTf)	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin layer chromatography
TOSMIC	Toluenesulphonylmethyl isocyanide
TMS	Trimethylsilyl
Ts	*p*-Toluenesulphonyl
UV	Ultraviolet
WSC	Water-soluble carbodiimide

1. Towards the Synthesis of the Ergot Alkaloids.

1.1. Introduction.

The ergot alkaloids are an important subgroup of indole alkaloids as they show a wide range of biological activity.[1] They can be found in scattered species of fungi belonging to different groups. Their main occurrence however, is in *Claviceps purpurea*, the parasitic fungus found on the ears of rye and other grasses.[2] The ergot alkaloids can be categorised into two structural groups; the lysergamide alkaloids and the clavine alkaloids. Both classes have a tetracyclic ring structure constituting the main skeleton. The water soluble lysergamide alkaloids, are amides of lysergic acid **1.1**, and the clavine alkaloids **1.2** are 6,8-dimethylergolines where the lysergic acid carboxyl appears in reduced form, R', R'' and R''' can be combinations of either H or OH and the double bond is in either the 8-9 or the 9-10 position. Lysergic acid **1.1**, originally isolated by Jacobs *et al.*[3,4] is one of the most important compounds of the ergot alkaloid family. Its derivatives, particularly carboxamide analogues, show remarkable pharmacological effects. For example, lysergic acid diethylamide (LSD) **1.3** is a potent hallucinogenic drug[5] and methysergide **1.4** is used in the treatment of migraine headaches.[6]

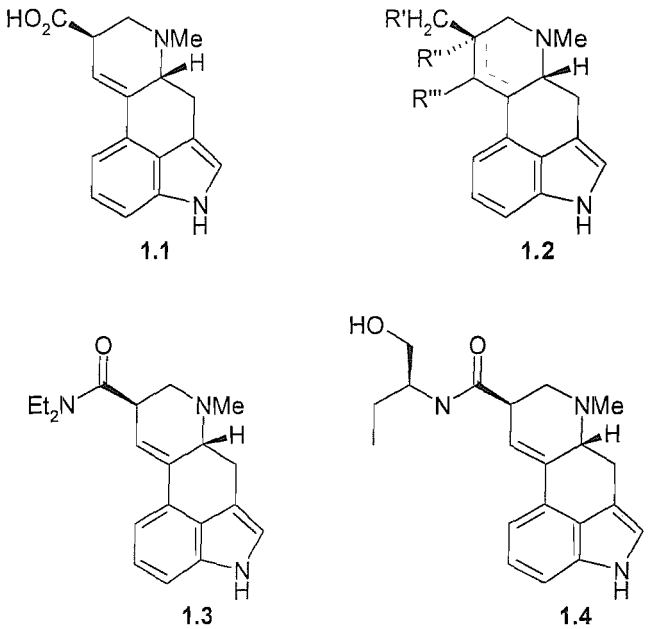
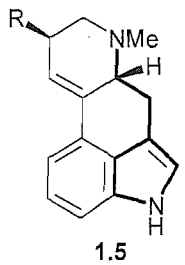


Figure 1.1 Lysergic acid, clavine alkaloids and derivatives of lysergic acid

1.1.1. Biological Activity.

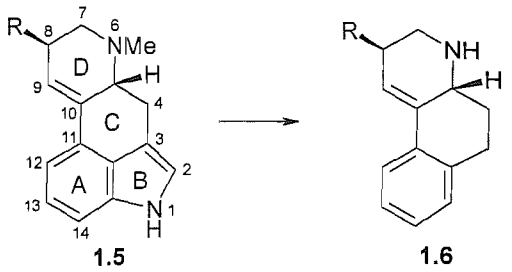
Natural ergot alkaloids and various synthetic derivatives exhibit a considerable spectrum of pharmacological activity. Their range of activity includes vasoconstrictor, oxytocic, α-blocking, serotonin antagonist and hallucinogenic properties.[1] Small variations in the substituents present on the core tetracycle change the biological response. The ergot alkaloids have received considerable attention as a number of them act as potent dopamine agonists with use as anti-Parkinson drugs or as prolactin inhibitors.[7] The main characteristic of the ergot alkaloids is their non-selective interaction with monoaminergic receptors, e.g. dopamine, serotonin, norepinephrine and histamine recognition sites, to produce their complex spectrum of pharmacological activities. Therefore the main challenge found in the development of the ergot alkaloids into pharmaceuticals is the identification of compounds that are suitably selective at the recognition site.[8] A number of compounds have been identified which are selective and these have been used to treat a number of conditions. Therefore the synthesis of the ergot alkaloid skeleton is of great value as drugs for the treatment of a variety of disorders.

Recently the dopamine agonist activity of the ergot alkaloids has been discovered and intensively studied. It was proposed that the structural moiety of the ergolines responsible for dopamine antagonism was the rigid pyrroleethylamine portion including an aromatic NH feature as a hydrogen bond donating group shown (Figure 1.2).[9] Kornfield *et al.* proved this hypothesis by degrading the active ergoline dopamine agonist **1.5** to the depyrrolo derivative **1.6** and testing the activity of **1.6** in comparison to **1.5**. They found that removal of the pyrrole ring from dopaminergic ergolines resulted in a loss of dopamine agonist activity (Scheme 1.1).[10]



1.5

Figure 1.2 The rigid pyrroleethylamine portion.



1.5 1.6

Scheme 1.1

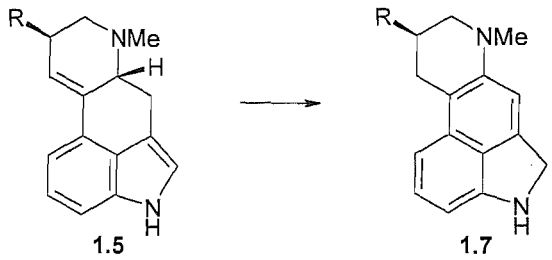
Great interest has developed in the possibility of using ergot alkaloid derivatives in the treatment of prolactin dependent conditions based on the discovery that compounds of this class can inhibit the secretion of the pituitary hormone prolactin.[11] In order for an ergot alkaloid to show prolactin inhibitory activity there are a number of structural requirements. It was found that the entire tetracyclic ergoline skeleton with *trans* C, D ring fusion was necessary, substituents can be accommodated at the 2, 6 and 8 positions but not in the 7 and 9 positions, reduction of the 2-3 double bond diminished activity and that a compound with an 8-9 double bond shows greater activity than the 9-10 double bond isomer.

In order for an ergot alkaloid to show hallucinogenic or similar psychedelic or behavioural effects it acts as a serotonin agonist. Serotonin receptors have been shown to be accountable for a number of psychiatric disorders such as anxiety and depression as well as physiological processes such as sleep and regulation of mood.[8] Therefore the receptors for serotonin have been the target for a number of therapeutic reagents.

1.1.2. Synthetic Approaches.

The early approaches to the synthesis of the ergot alkaloids were designed to confirm the unique 4-substituted indole structure, the position of the carboxylic acid and the position of the 9-10 double bond in lysergic acid. These approaches encountered a number of problems: 1. the regiospecific construction of 4-substituted indoles; 2. the high level of strain introduced on forming the 6-membered ring in the 4-position of indole and 3. the instability of the ergoline skeleton which contains a 9-10 double bond, more likely to isomerise to the resonance stable benzindoline (Scheme 1.2).[12]

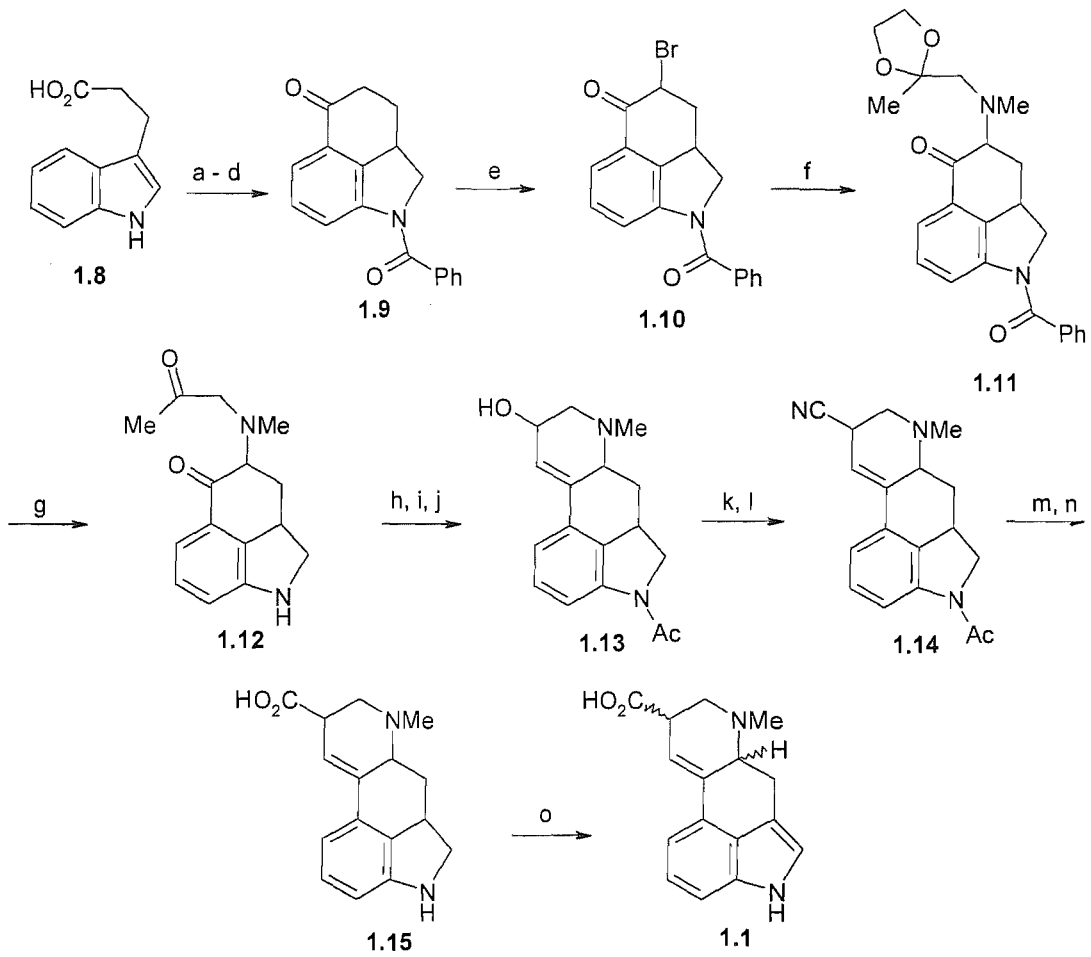
Therefore the total synthesis of the ergoline nucleus has long been viewed as a challenging target with attempts dating back to Uhle and culminating in the synthesis of lysergic acid by Woodward and co-workers in 1956.[13]



Scheme 1.2

1.1.2.1. Synthesis from Kornfield's Ketone.

The first synthesis of racemic lysergic acid was accomplished by Woodward *et al.* (Scheme 1.3).[13] Their route avoided the problems of ergoline isomerisation to the benzindoline by protecting the indole ring as the benzoyl indoline, with regeneration of the indole as the final step of the synthesis. They began their synthesis from indole propionic acid **1.8** which was reduced to the corresponding indoline and converted by thionyl chloride to the corresponding acid chloride and directly cyclised regioselectively to ketone **1.9** by the Friedel-Crafts reaction with aluminium chloride. This cyclisation occurred only at the C-4 position of the indoline ring as reduction of the indole prevented cyclisation onto the labile C-2 position. Ketone **1.9** would later become known as Kornfield's ketone and is one of the most versatile intermediates to the ergot alkaloids as it has all the elements necessary for the further synthesis to all oxidation levels found in natural lysergamide and clavine alkaloids.[12]



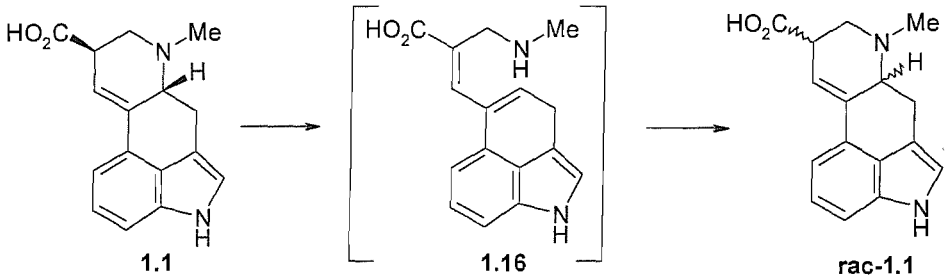
Reagents and conditions: a) NaOH-Raney nickel; b) NaOH, PhCOCl; c) $SOCl_2$, Et_2O; d) $AlCl_3$, CS_2, 77%; e) AcOH, pyridine HBr perbromide, 69%; f) methylaminoacetone ethylene ketal, benzene, 71%; g) conc. HCl, 77%; h) EtOH, NaOMe, -15°C, 69%; i) Ac_2O, 0 °C, 76%; j) $NaBH_4$, MeOH, H_2O, 85%; k) $SOCl_2$, SO_2; l) NaCN, HCN, 54%; m) MeOH, H_2O, conc. H_2SO_4, 100 °C, 53%; n) conc. HCl, H_2O; o) 1.5% KOH, $Na_2HAsO_4.H_2O$, deactivated Raney nickel, reflux, 30%.

Scheme 1.3

As ketone **1.9** had an activated methylene group at the C-4 position, Woodward anticipated that the construction of the D ring of lysergic acid might be performed by the attachment of the requisite nitrogen atom at the reactive position. They therefore synthesised bromo derivative **1.10** as a suitable intermediate. Ketal ketone **1.11** was synthesised by the alkylation with methylaminoacetone ethylene ketal, which contained all the functional groups necessary for formation of the D ring of lysergic acid. The protecting group was removed by hydrolysis with hydrochloric acid. The diketone was then cyclised to the α,β-unsaturated ketone with sodium methoxide in absolute ethanol which after protection with acetic anhydride and reduction with sodium borohydride afforded unsaturated alcohol **1.13**. The cyano compound **1.14**

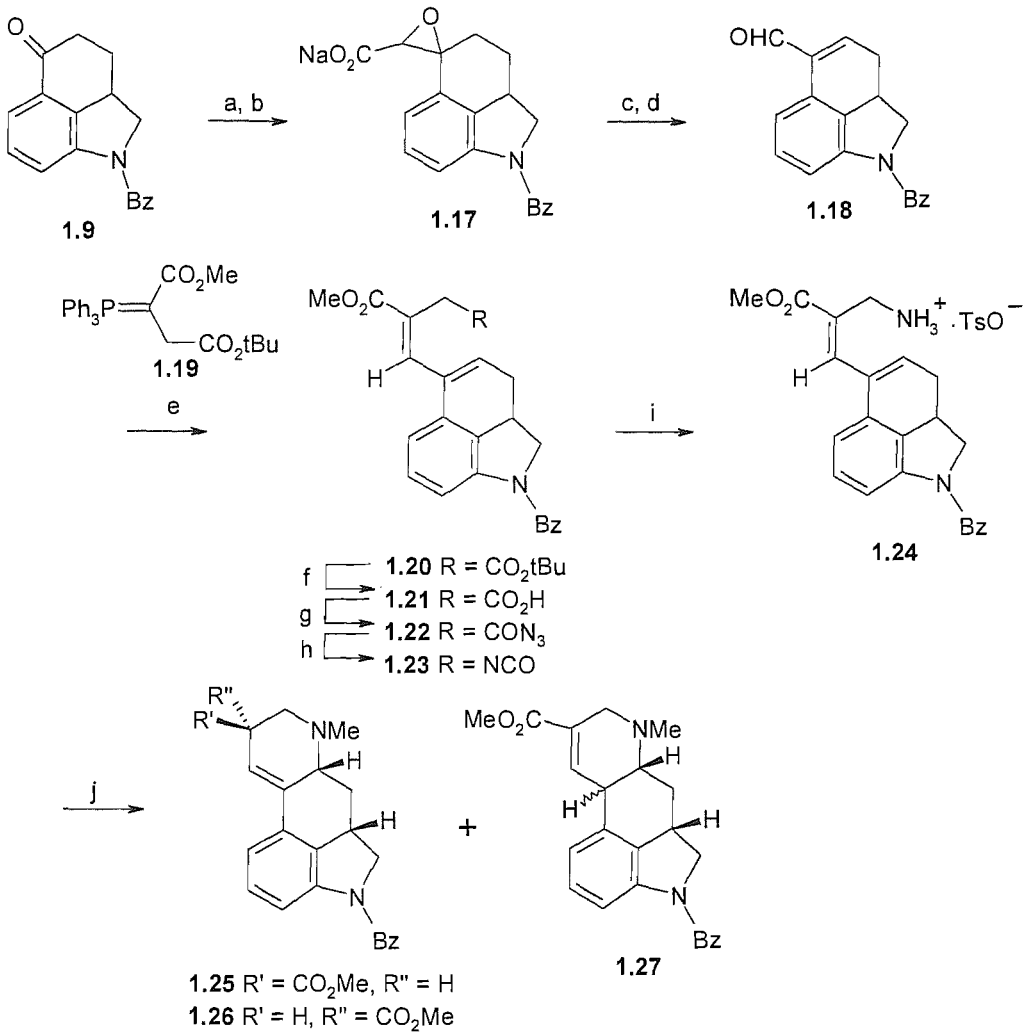
was synthesised *via* the chloride and methanolysis afforded the ester which was readily hydrolysed to the corresponding carboxylic acid **1.15**. In the final step lysergic acid **1.1** was synthesised by dehydrogenation of **1.15** with heat-deactivated Raney nickel. At this point the diastereoselectivity of all the transformations were unknown.

Ramage *et al.* also began their synthesis from Kornfield's ketone (Scheme 1.5).[14,15] They planned their route retrosynthetically based on the observation that (+)-lysergic acid could be converted to racemic lysergic acid by barium hydroxide in aqueous solution at high temperatures (Scheme 1.4).



Scheme 1.4 The racemisation of (+)-lysergic acid

It was discovered that racemisation occurred at both the C-5 and C-8 positions, which appeared surprising as only the carboxyl substituent at the C-8 position would be expected to epimerise. In order to explain this epimerisation at the supposedly unreactive C-5 position it was proposed that the racemisation process proceeded through the achiral tricyclic intermediate **1.16** which could be formed from lysergic acid *via* a retro-Michael reaction.[13] Therefore, if this explanation for the racemisation was correct, the synthesis of intermediate **1.16** would produce racemic lysergic acid by a spontaneous cyclisation. To prevent tautomerisation to the more stable benzindoline Ramage focused on synthesising the modified target **1.25** in which lysergic acid could be formed in the last step by oxidation of the indoline. Aldehyde **1.18** was readily prepared from Kornfield's ketone **1.9** through the corresponding glycidate **1.17**.



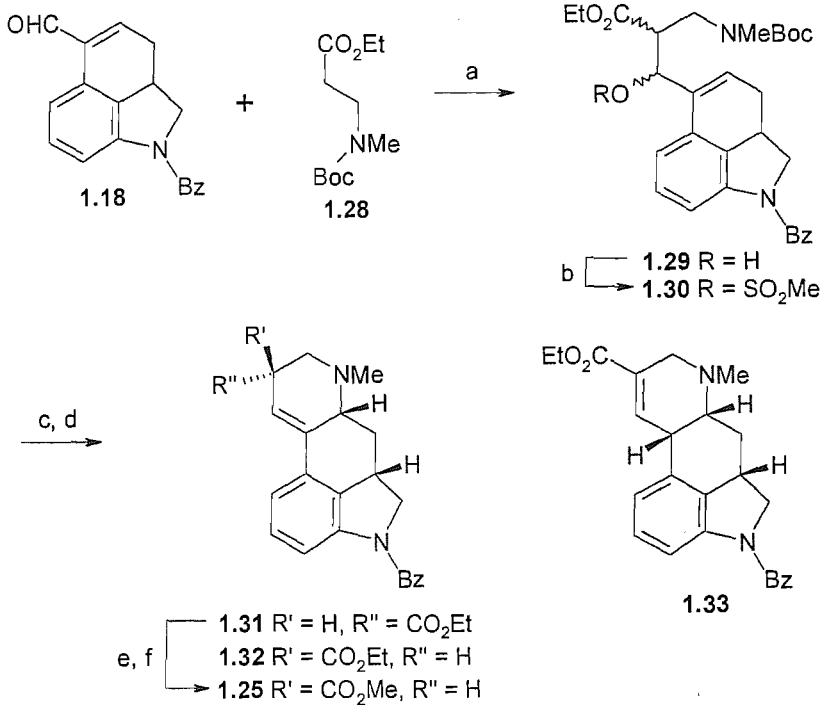
Reagents and conditions: a) *t*-BuOK, ethyl chloroacetate, benzene, toluene, 75 °C; b) 50% NaOH, EtOH, 0 °C, 80% from **1.9**; c) pyridinium HBr perbromide, MeCN, 40 °C, then semicarbazide HCl, $NaOAc.3H_2O$, H_2O, 40 °C, 79%; d) $MeCO.CO_2H$, *p*-TsOH, $CHCl_3$, 94%; e) **1.19**, benzene/ *t*-BuOH, reflux, 79%; f) 90% TFA, benzene, 88%; g) NMO, diphenylphosphonyl chloride, CH_2Cl_2, -40 °C, tetramethylguanidinium azide, MeCN, 0 °C; h) benzene, reflux; i) *p*-$TsOH.H_2O$, Et_2O, benzene, 80%; j) K_2CO_3, CH_2Cl_2, then HCO_2H, HCHO, 62%.

Scheme 1.5

A Wittig reaction between **1.18** and the stabilised ylid **1.19** afforded adduct **1.20** with the predominant stereoisomer having the carbonyl function *trans* to the larger group at the β-position. The amine functionality was introduced by selective degradation of the carboxyl group using the Curtius rearrangement. It was anticipated that hydrolysis and decarboxylation to afford the free amine would cause undesired hydrolytic side reactions, therefore to overcome this *p*-toluene sulfonic acid monohydrate in anhydrous solvent was employed as this contained sufficient water

to perform the hydrolysis and the decarboxylation was driven by formation of the amine salt. The cyclisation to form the D ring of the ergoline structure was performed using an Eschweiler-Clarke reaction involving hydride reduction of the intermediate imonium species. Although this reaction would usually form the dimethylated species, in this case the intermediate secondary amine preferred to cyclise rather than undergo the second methylation step. Tetracyclic isomers were isolated in a ratio of 9:3:2 which were determined to be **1.25**, **1.26** and **1.27** respectively. The stereochemistry at C-3 and C-5 was determined during the cyclisation; it was thought that the π-overlap between the 9-10 double bond and the aromatic ring would lead to the C-3 and C-5 C-H bonds being *cis* as depicted in **1.25, 1.26** and **1.27**. As shown by Woodward *et al.* the tetracyclic methyl esters could be further manipulated to synthesise lysergic acid.

Kurihara and co-workers made modifications to Ramage's synthesis in their route to lysergic acid (Scheme 1.6).[16,17] An aldol condensation between aldehyde **1.18** and the anion of **1.28** afforded alcohol **1.29** as a diastereoisomeric mixture. Transformation to the mesylate followed by treatment with base furnished tetracyclic isomers **1.31** and **1.32** as a 2:1 ratio in 42% yield and **1.33** in 7% yield.

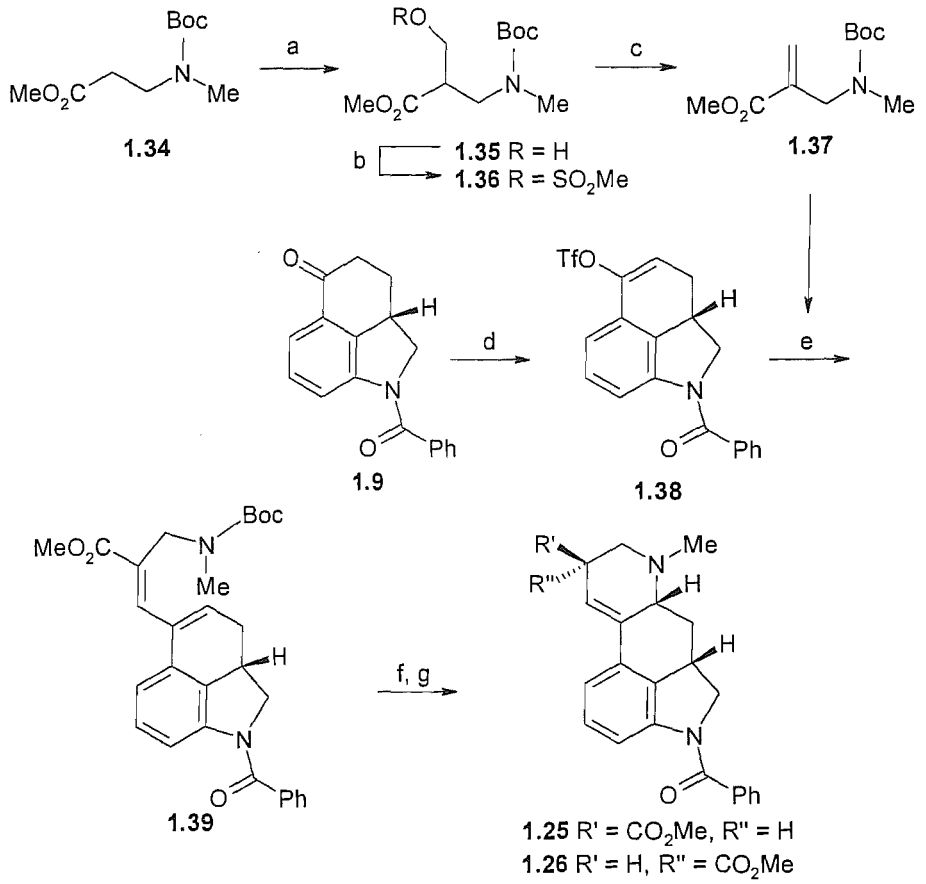


Reagents and conditions: a) LDA, THF, -78 °C, 99%; b) MsCl, Et_3N, CH_2Cl_2; c) HCl, EtOAc; d) DBU, DMSO, 42% from **1.29**; e) MeOH, conc. HCl, reflux; f) BzCl, MeOH.

Scheme 1.6

Recrystallision of the mixture of **1.31** and **1.32** in ethyl acetate afforded pure **1.31** which after hydrolysis and esterification with HCl in methanol followed by mild benzoylation afforded **1.25**. A deprotection, oxidation and saponification sequence could be employed to afford lysergic acid.

Ortar and co-workers utilised Kornfield's ketone as an impropriate intermediate in their synthesis of lysergic acid (Scheme 1.7).[18]



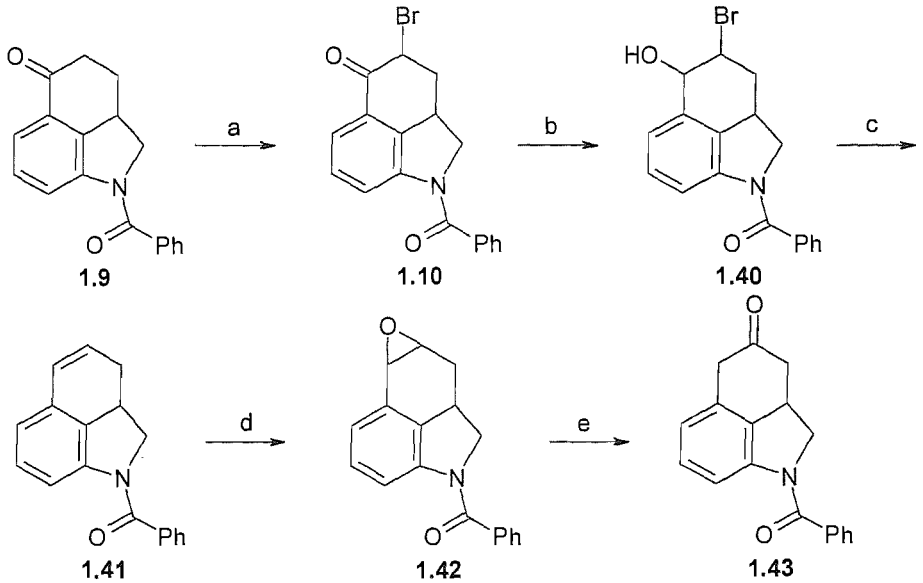
Reagents and conditions: a) LDA, THF, -78 °C, formaldehyde, 53%; b) MsCl, Et_3N, CH_2Cl_2; c) DBU, benzene, 74% from **1.17**; d) triflic anhydride, 2,6-di-*t*-butyl-4-methylpyridine, 91%; e) $Pd(OAc)_2$, PPh_3, Et_3N, DMF, 60 °C, 26%; f) 2.5 N HCl in EtOAc; g) $NaHCO_3$, 60%.

Scheme 1.7

Kornfield's ketone was converted to the vinyl triflate **1.38** which underwent a Heck type reaction with alkene **1.37**, palladium (II) acetate and triphenylphosphine to afford adduct **1.39**. Alkene **1.37** was synthesised from **1.34** by a three step sequence comprising trapping of the anion of **1.34** with formaldehyde, conversion to mesylate **1.36** with mesyl chloride and elimination with DBU. Cleavage of the Boc protecting

group under acidic conditions followed by treatment with $NaHCO_3$ afforded a 1.7:1 ratio of **1.25**:**1.26** which could be separated by recrystallisation from ethyl acetate. The 8β ester **1.25** could be further elaborated following the procedure of Kornfield to give (±)- lysergic acid.

Ninomiya *et al.*[19] also began their synthesis from Kornfield's ketone (Scheme 1.9) but in this case it was isomerised to tricyclic ketone **1.43** following the five step sequence of Woodward *et al.* (Scheme 1.8).[13,20,21] Bromohydrin **1.40** was obtained from the bromination of ketone **1.9** followed by reduction with sodium borohydride. Elimination with zinc in acetic acid afforded alkene **1.41** which was oxidised with perbenzoic acid to epoxide **1.42** and finally rearranged using magnesium bromide to afford tricyclic ketone **1.43**.

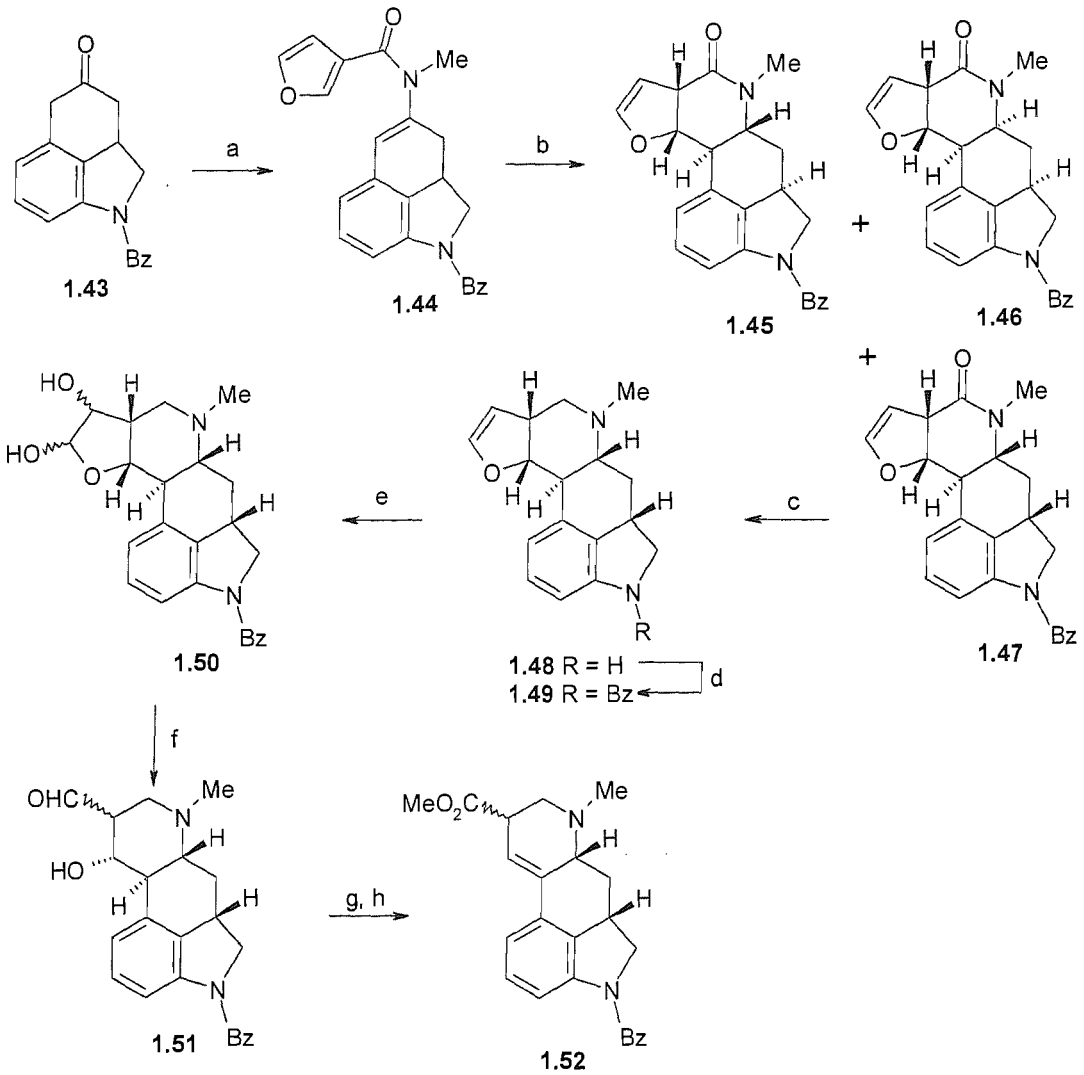


Reagents and conditions: a) AcOH, pyridine HBr perbromide, 69%; b) $NaBH_4$, Et_2O, MeOH, 60%; c) Zn dust, AcOH, reflux, 60%; d) Perbenzoic acid, $CHCl_3$, 81%; e) Mg, Et_2O, Br_2, 75%.

Scheme 1.8

Ninomiya *et al* prepared enamide **1.44** by reacting isomerised Kornfield's ketone **1.43** with methylamine and 3-furoyl chloride in the presence of triethylamine. Irradiation of enamide **1.44** in benzene-methanol in the presence of sodium borohydride with a high pressure mercury lamp afforded a mixture of **1.45**, **1.46** and **1.47** in 1:4:10 ratio which could be separated by repeated crystallisation and column chromatography. As lactam **1.47** was the predominant product this was used for the

synthesis of lysergic acid. Ring opening of the dihydrofuran ring was accomplished by reduction with lithium aluminium hydride to diamine **1.48** which was re-benzoylated and dehydroxylated with osmium tetraoxide to afford a 3:2 ratio of *cis*-glycols **1.49**. The mixture was then oxidised to cleave the glycol and provide aldehyde **1.51** in a 1:1 ratio of diastereoisomers. In the presence of base this gave only the 8β diastereoisomer as it brought about the complete isomerisation of the unstable 8α isomer to the stable 8β isomer.



Reagents and conditions: a) $MeNH_2$, 3-furoyl chloride, Et_3N, 96%; b) $NaBH_4$, benzene-MeOH, irradiation, 81%; c) Et_2O-THF, $LiAlH_4$, 74%; d) Benzene, BzCl, Et_3N, 74%; e) OsO_4, trimethylamine *N*-oxide dehydrate, pyridine, H_2O, *t*-BuOH, reflux, 83%; f) sodium metaperiodate, MeOH-H_2O; g) 4.0 M CrO_3-H_2SO_4, MeOH-acetone, 38%; h) 85% H_2PO_4, phosphoryl trichloride, pyridine, 60 °C, 55%.

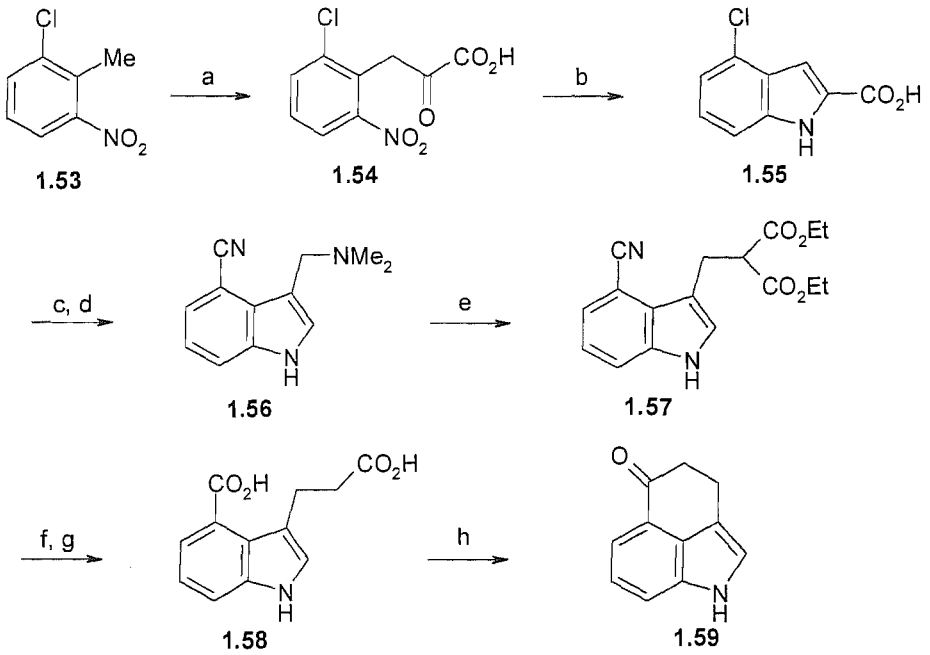
Scheme 1.9

Oxidation of aldehyde **1.51** with chromium trioxide and sulfuric acid in methanol-acetone solution afforded a 1:1 ratio of esters which were separable by preparative layer chromatography. Oxidation of the enantiomerically pure 8β aldehyde **1.51** gave the 8β ester in 38% yield. Dehydration of the 8β ester by heating with phosphoryl trichloride and phosphoric acid in pyridine afforded a 3:1 ratio of 8β:8α esters **1.52** which could be converted to (±)-lysergic acid according to the procedure of Woodward *et al.*

1.1.2.2. Synthesis from Uhle's Ketone.

Many approaches to the synthesis of the C ring of the ergoline skeleton have concentrated on working with indole instead of indoline derivatives. Uhle's ketone **1.59**, first synthesised in eight steps by Uhle in 1949 (Scheme 10),[22] is a key intermediate to the synthesis of the ergot alkaloids. It has advantages over starting from Kornfield's ketone as with the latter, four extra steps in the synthesis are required. The first to hydrogenate the indole, the second to benzoyl protect the unstable indoline, and at the end of the synthesis deprotection by hydrolysis and dehydrogenation to re-form the indole ring which has low and variable yields.

Uhle's synthesis of the ketone **1.59** began with 2-nitro-6-chlorotoluene which was transformed to indole **1.55** *via* a Reissert synthesis (Scheme 1.10). Decarboxylation followed by replacement of the chloride by a cyano group and introduction of the amine functionality afforded the Mannich base **1.56** which was converted through the malonic ester derivative **1.57** to dicarboxylic acid **1.58**. The final cyclisation with acetic anhydride and potassium cyanide yielded Uhle's ketone. Uhle's route was found to be long-winded and unsuitable for scale up; therefore improvements to Uhle's synthesis have been documented.

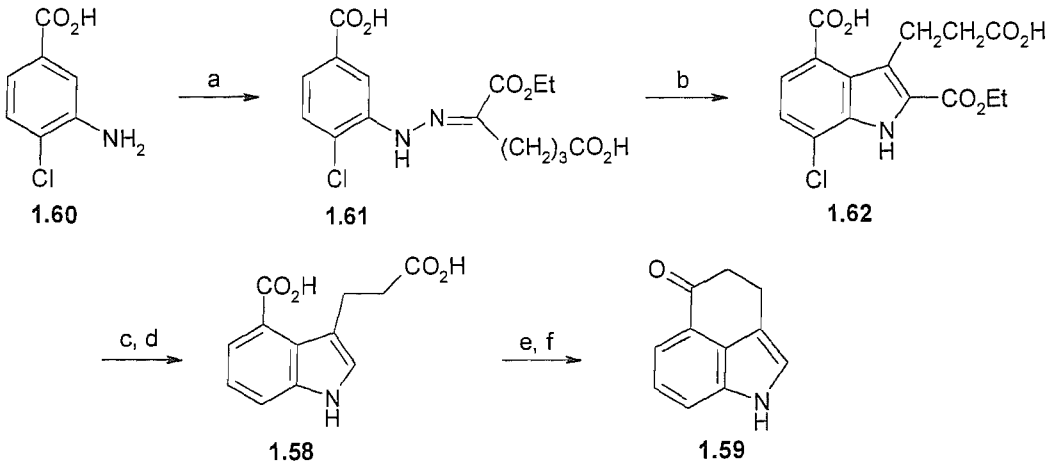


1.53 1.54 1.55 1.56 1.57 1.58 1.59

Reagents and conditions: a) NaOEt, $(CO_2Et)_2$, 42%; b) $Fe(OH)_2$, NH_4OH, reflux, 92%; c) CuCN, quinoline, 237 °C, 51%; d) AcOH, HCOH, $HNMe_2$, 95%; e) NaOEt, $CH_2(CO_2Et)_2$, $(CH_3)_2SO_2$, 65%; f) 10% NaOH, EtOH, H_2O, 200 °C, 81%; g) 30% KOH, reflux, 90%; h) Ac_2O, KCN, reflux, 80%.

Scheme 1.10

Bowman *et al.* formed Uhle's ketone using a Fischer indole synthesis (Scheme 1.11).[23,24] The Fischer cyclisation had to occur *ortho* to the 3-carboxylic acid functional group as the 6 position was blocked with a chlorine atom. The chloride was removed at a later stage by a catalytic reduction. The final cyclisation gave Uhle's ketone in reasonable yield.

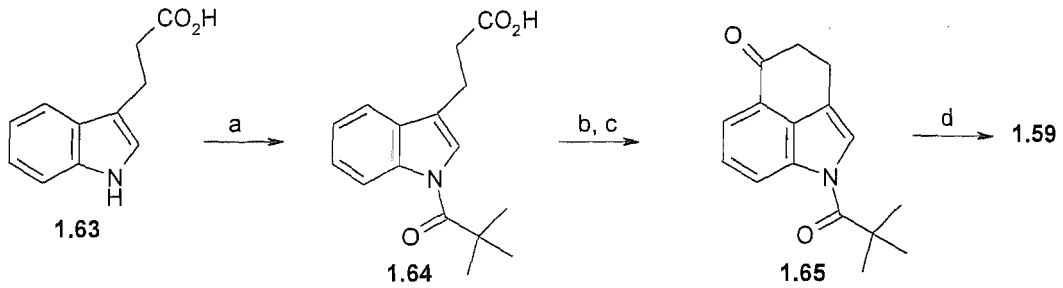


1.60 1.61 1.62 1.58 1.59

Reagents and conditions: a) i) $NaNO_2$, HCl, NaOAc, ethyl-2-oxocyclopentanecarboxylate, H_2O; ii) AcOH, H_2O, 95-100 °C, 63%; b) BF_3.HOAc, 81%; c) KOH; d) H_2/Pd/C, 66%; e) KCN, Ac_2O; f) NaOH, MeOH, 71%.

Scheme 1.11

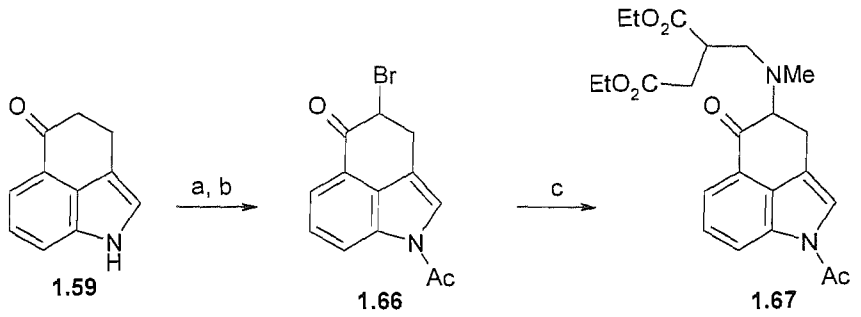
Goto and co-workers reported the synthesis of Uhle's ketone by a regioselective Friedel-Crafts cyclisation (Scheme 1.12).[25] They showed how a pivalamide protected acid chloride can undergo a regioselective cyclisation onto the C-4 position of the indole ring using chloroacetyl chloride and aluminium chloride as a donor-acceptor complex species. The pivalamide protecting group worked to inhibit the cyclisation at the more reactive C-2 position due to electron acceptance from the pyrrole ring and steric hindrance effects. Goto's procedure is now the most commonly used method for the synthesis of Uhle's ketone.



Reagents and conditions: a) *n*-BuLi, PivCl, THF, -78 °C, 91%; b) $SOCl_2$, 15 °C; c) $AlCl_3$, chloroacetyl Cl, 1,2-dichloroethane, 78%; d) NaOMe, MeOH, 15 °C, 95%.

Scheme 1.12

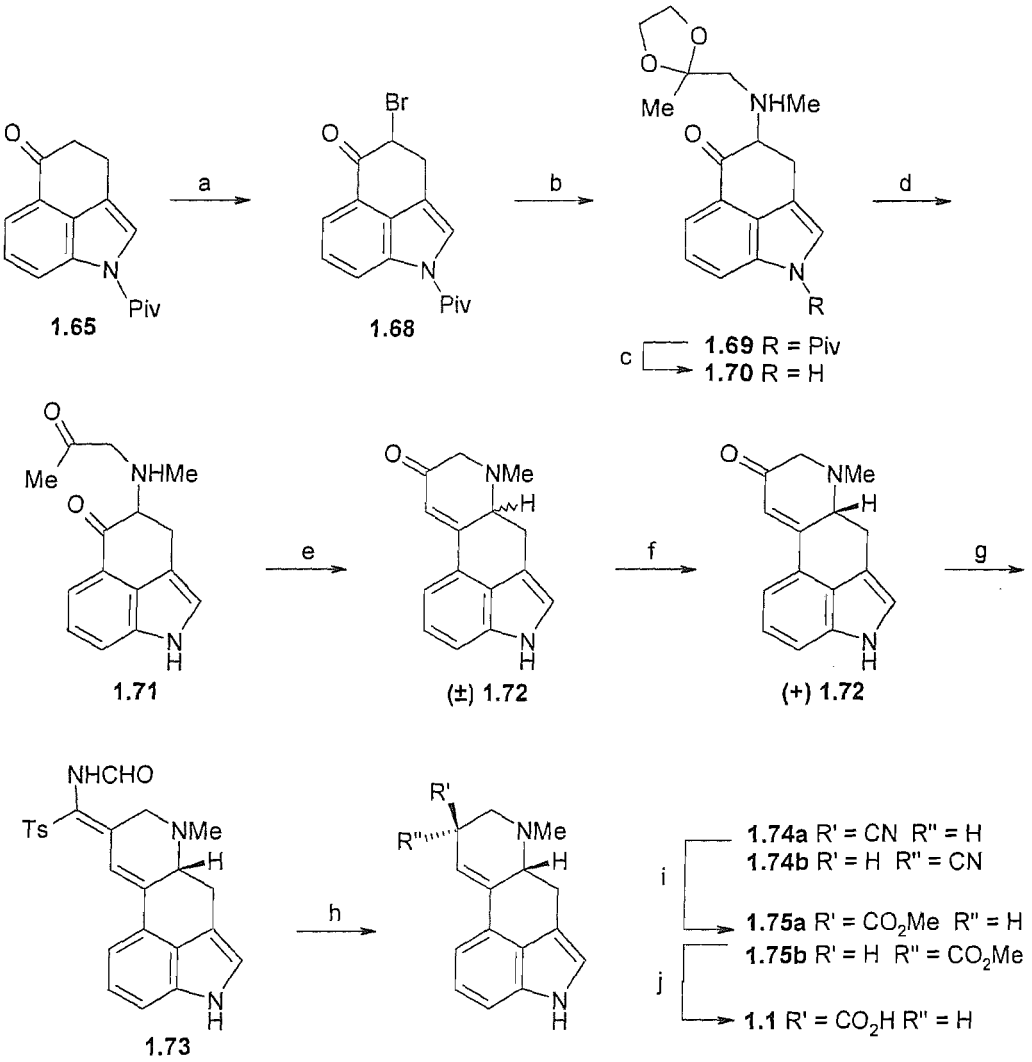
Constructing the D-ring from Uhle's ketone proved problematic. Bowman's results showed that while the 4-bromo derivative of Kornfield's ketone **1.10** reacted smoothly with methylaminoacetone ethyl ketone yielding tertiary amine **1.11**, the corresponding indole derivative did not afford any basic material using the same reaction conditions.[23] Although Uhle reported in 1954 the tetracycle had been synthesised, attempts by Bowman to reproduce these results failed. Uhle reported that the ketone could be acetylated and brominated and then reacted to give intermediate **1.67** which should have been appropriate for an intramolecular Stobbe condensation (Scheme 1.13).[26] Uhle's approach was described in a preliminary communication,[27] but the final version has never been published.



Reagents and conditions: a) Br_2; b) Ac_2O; c) $MeNHCH_2CH(CO_2Et)CH_2CO_2Et$.

Scheme 1.13

Szántay and co-workers later reported the first synthesis of lysergic acid from Uhle's ketone (Scheme 1.14).[28] They discovered that contrary to Bowman's results, bromoketone **1.68** could be subjected to a substitution reaction with an amine to afford **1.69**, if the reaction was left to proceed at ambient temperature in toluene. After deprotection of the pivalamide and ketone functionalities intermediate **1.71** was isolated. Although previously reported for the indoline derivative Szántay's attempts to form the D-ring by an intramolecular aldol condensation with a number of well established reagents failed. However, this reaction was achieved with LiBr and triethylamine to afford racemic unsaturated ketone **1.72** which could be resolved with dibenzoyltartaric acid. Optically pure unsaturated ketone **1.72** was reacted with an isonitrile derivative in the presence of base to give **1.73** which could be directly hydrolysed to afford lysergic acid as a mixture of diastereoisomers. In order to synthesise pure (+)-lysergic acid, intermediate **1.73** was treated with base to afford nitriles **1.74a** and **b** in a 1:1 ratio. The mixture was converted by a Pinner reaction into lysergic acid methyl ester diastereoisomers **1.75a** and **b** in a 3:2 ratio respectively, followed by basic hydrolysis to obtain chirally pure (+)-lysergic acid **1.1** through concurrent hydrolysis and epimerisation.



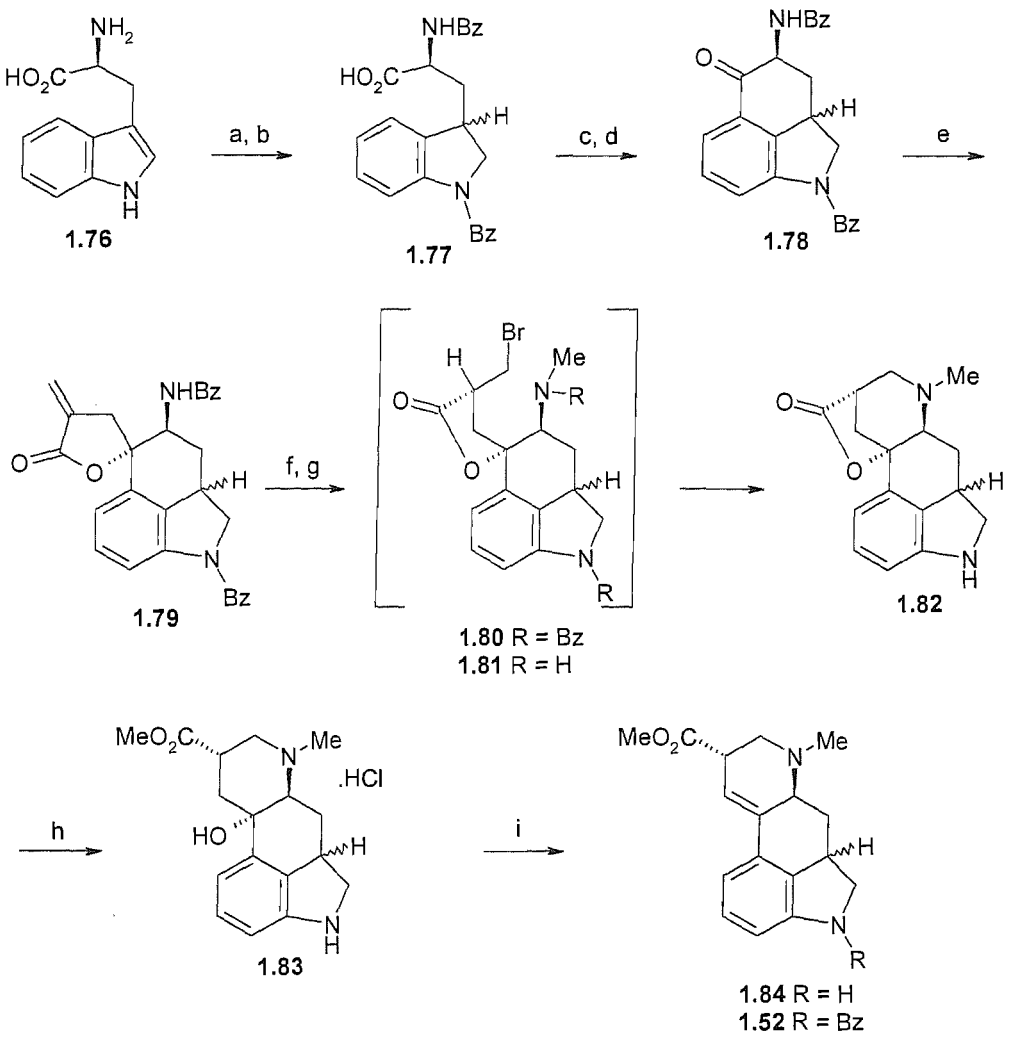
Reagents and conditions: a) Br_2, 1,4-dioxane, CCl_4, $CHCl_3$, Et_2O, 5-10 °C, 77%; b) methylaminoacetone ethylene ketal, toluene, 35%; c) $MeNH_2$, benzene, 10-15 °C, 80%; d) 6 M HCl (aq), 35-40 °C; e) LiBr, Et_3N, $CHCl_3$, 0-5 °C, 60% from **1.70**; f) (-)-dibenzoyl-L-tartaric acid, CH_3CN, H_2O, 38%; g) TOSMIC, *t*-BuOK, THF, *t*-BuOH, 0 °C then H_2O, -5 °C, 77%; h) NaOMe, MeOH, 70-75 °C, 70%; i) 6.7 M HCl/MeOH, 75-80 °C, 72%; j) 5 M NaOH (aq), MeOH, 70-80 °C, then 6 M HCl (aq), 54%.

Scheme 1.14

1.1.2.3. Synthesis from Tryptophan.

Rebek *et al.*[29,30] synthesised lysergic acid from tryptophan **1.76**, the biosynthetic precursor (Scheme 1.15). Rebek anticipated that as with Uhle's and Kornfield's ketones, tryptophan may participate in an intramolecular Friedel-Crafts acylation to construct the C ring of lysergic acid. As the amine functionality is already in place

the route would require less synthetic transformations and can take advantage of the set chirality of the amino acid.



Reagents and conditions: a) 1 N HCl, 10% Pd/C, H_2, 25%; b) BzCl, NaOH, 33%; c) Ac_2O, 100 °C; d) $ClCH_2CH_2Cl$, $AlCl_3$, 57%; e) Zn, THF, ethyl α-(bromomethyl)acrylate, 83%; f) MeI, NaH, DMF, 80%; g) HBr, CH_2Cl_2, $Et_3O^+BF_4^-$, CH_2Cl_2, Na_2CO_3, 55%; h) $SOCl_2$, MeOH, 100%; i) P_2O_5, CH_3SO_3H, 95%.

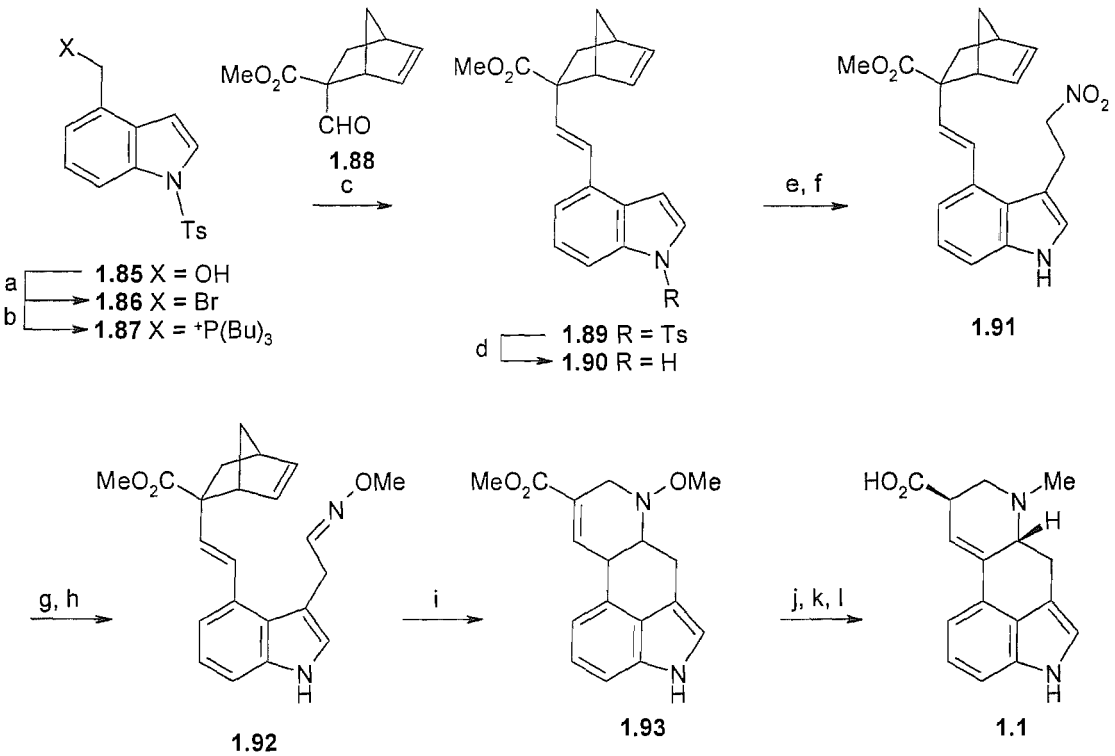
Scheme 1.15

It is well documented that acyl amino acids form azlactones on treatment with dehydrating agents and that azlactones are suitable acylating agents in intermolecular Friedel-Crafts reactions. Therefore after reduction to the corresponding indoline and protection with benzyl chloride, Rebek synthesised the azlactone derivative of tryptophan and subjected this to Friedel-Crafts conditions with aluminium chloride to afford tricyclic ketone **1.78**. Treatment of tricyclic ketone **1.78** with ethyl α-

(bromomethyl)acrylate afforded lactone **1.79**. Alkylation with MeI followed by treatment with HBr afforded the addition product **1.80** which on deprotection spontaneously cyclised to **1.82** during workup. The lactone was opened with $SOCl_2$/ MeOH to the ester **1.83** which after dehydration with P_2O_5 afforded **1.84** which as previously reported by Ramage after benzoyl protection could be converted to lysergic acid.

1.1.2.4. Synthesis from Indole Derivatives.

Oppolzer and co-workers synthesised lysergic acid from the sulfonamide protected 4-substituted indole derivative **1.85** (Scheme 1.16).[31] The ergot skeleton was formed *via* an intramolecular Diels-Alder reaction followed by isomerisation of the C-8-9 double bond to the more stable C-9-10 position. The indole nucleus was kept intact throughout the entire reaction sequence.

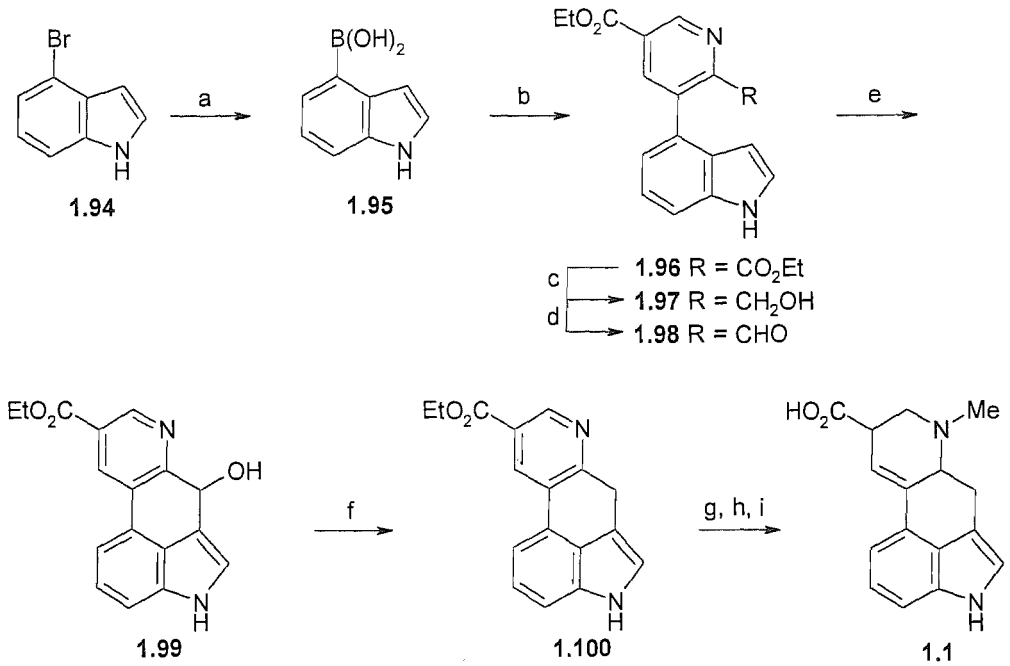


Reagents and conditions: a) CBr_4, PPh_3, DMF, 97%; b) PBu_3, C_6H_6, 80 °C, 100%; c) NaH, DMSO, 62%; d) NaOH, MeOH, 95%; e) aq. CH_2O, Me_2NH; f) $MeNO_2$, MeO_2C-C≡C-CO_2Me, 20 °C, 48% from **1.90**; g) NaOMe, MeOH; h) $TiCl_3/NH_4OAc$, H_2N-OMe, MeOH/H_2O 3:1, 64% from **1.91**; i) trichlorobenzene, 200 °C, 67%; j) $MeOSO_2F$, CH_2Cl_2, 20 °C; k) Al/Hg, THF/H_2O 2:1; l) 0.5 N KOH, EtOH/H_2O, reflux, 33% from **1.93**.

Scheme 1.16

Due to the instability of 2-carbomethoxydienes the diene functionality was introduced in protected form by the Wittig reaction of the phosphorane derived from **1.87** with the bicycloheptene derivative **1.88**. After removal of the *N*-tosyl group **1.90** was subjected to the Mannich reaction with acetic acid, dimethylamine and aqueous formaldehyde followed by treatment with nitromethane and dimethyl acetylenedicarboxylate to furnish nitro compound **1.91**. After conversion to the oxime ether, thermolysis led to the retro Diels-Alder reaction and release of the diene unit which preferentially added to the imino bond affording **1.93** as a 2:3 mixture of diastereoisomers. Replacement of the methoxy functional group with a methyl group was accomplished by methylation with methylfluorosulfonate. Hydrogenolysis of the resulting salt with amalgamated aluminium followed by a saponification afforded lysergic acid.

Hendrickson *et al.* synthesised lysergic acid *via* a Suzuki coupling between a simple indole and a nicotinic acid derivative, both retaining their aromaticity until the end of the synthesis (Scheme 1.17). [32]



Reagents and conditions: a) KH, BuLi, $B(OBu)_3$, 88%; b) 3-Chloro-pyridine-2,5-dicarboxylic acid diethyl ester, $Pd(PPh_3)_4$, Na_2CO_3 (aq), EtOH, 91%; c) $NaBH_4$, $CaCl_2$, EtOH, 85%; d) MnO_2, $CHCl_3$, 92%; e) NaOH, MeOH, 91%; f) $NaBH_4$, TFA, CH_2Cl_2; g) MeI, CH_2Cl_2, 41%; h) $NaBH_4$, MeOH; i) NaOH, EtOH, 62% from **1.100**.

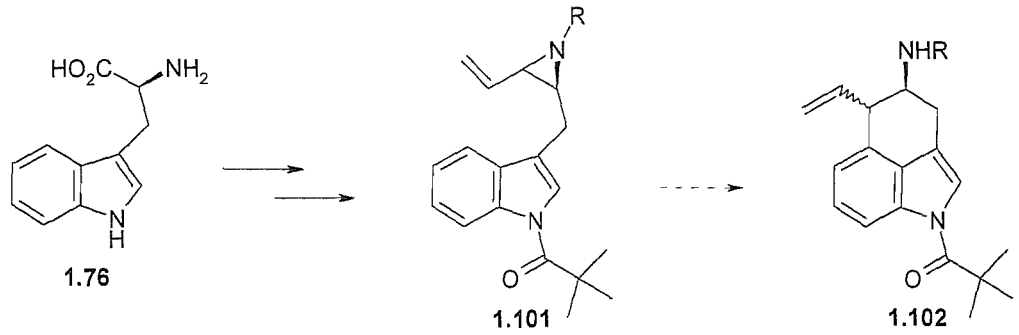
Scheme 1.17

4-Bromoindole was transformed to its corresponding boronic acid and allowed to participate in a Suzuki coupling with the nicotinic acid derivative. After reduction and subsequent oxidation to aldehyde **1.98** the molecule was cyclised under basic conditions to form the C-ring of lysergic acid. The alcohol was reductively cleaved and following methylation was reduced to afford lysergic acid ethyl ester which was hydrolysed to afford lysergic acid.

1.2. Results and Discussion.

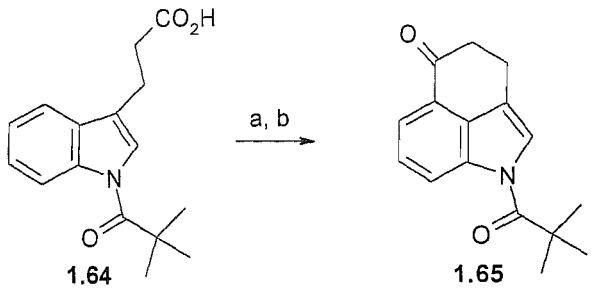
1.2.1. Proposed Synthesis of the Ergot Alkaloid Skeleton.

We were interested in a synthesis of the ergot alkaloid skeleton from the amino acid tryptophan where the amine functionality is already in place and the chirality of the molecule is already set. We proposed that the C ring of the skeleton could be constructed *via* an intramolecular cyclisation of a vinyl aziridine onto the indole ring, anticipating that the aziridine will undergo regioselective ring opening at the activated allylic end (Scheme 1.18).



Scheme 1.18

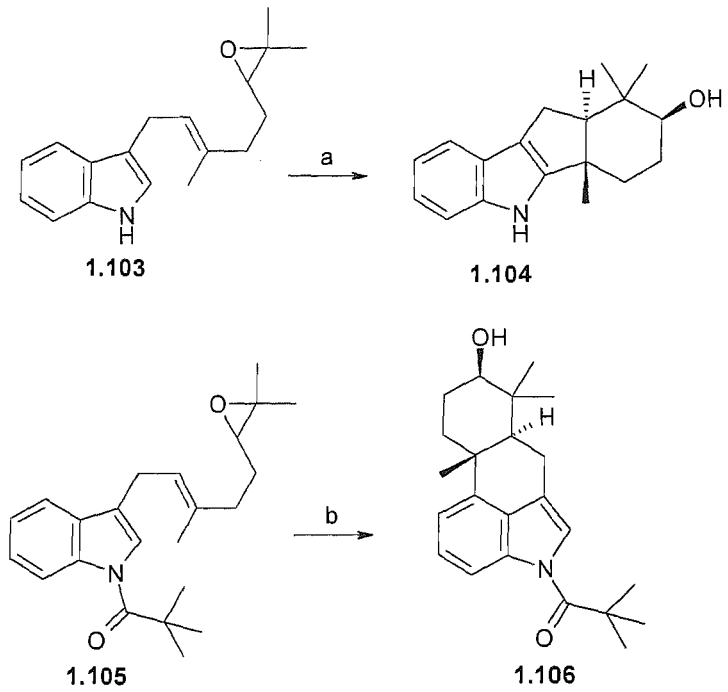
This will take advantage of previous work by Goto which has shown how a pivalamide protected indole will undergo a Friedel-Crafts acylation onto the less reactive C-4 position of the indole ring (Scheme 1.19).[25] The pivalamide protecting group prevents attack onto the C-2 position by electron acceptance from the pyrrole ring and steric encumbering effects.



Reagents: a) $SOCl_2$, 15 °C; b) $AlCl_3$, chloroacetyl chloride, 1,2-dichloroethane.

Scheme 1.19

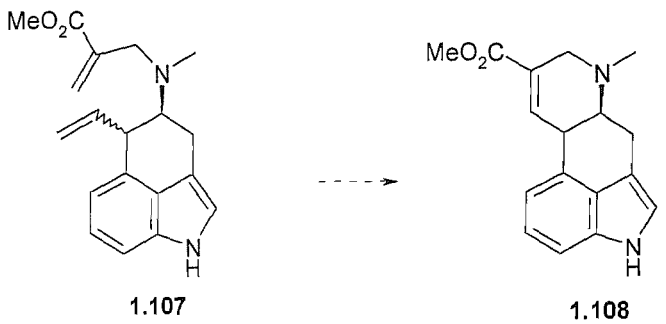
Previous work in the group has used this methodology in controlling the termination of epoxide initiated polyene cyclisations (Scheme 1.20).[33]



Reagents: a) $MeAlCl_2$, CH_2Cl_2, -78 °C; b) $AlCl_3$, CH_2Cl_2.

Scheme 1.20

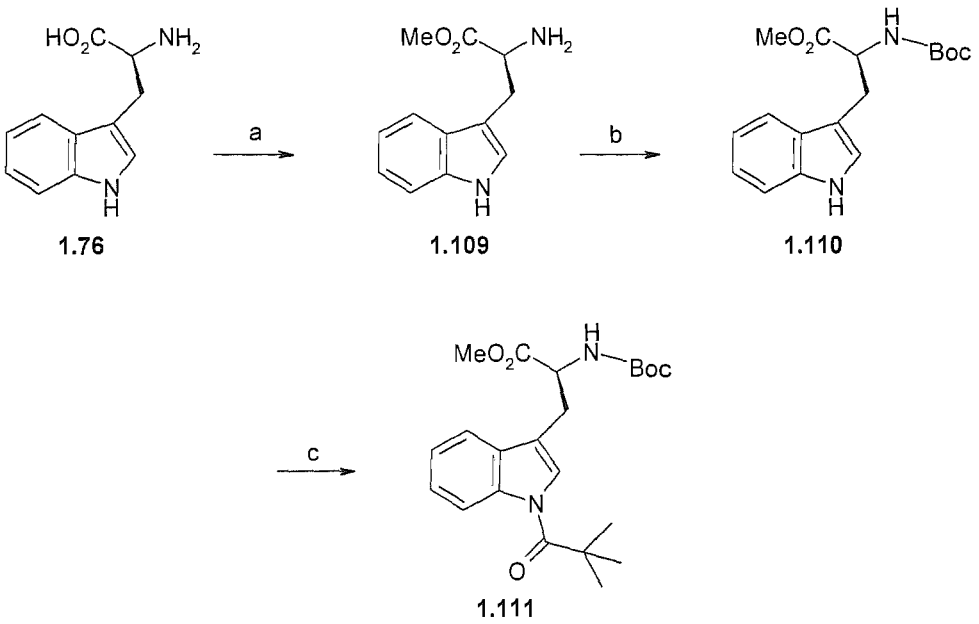
The D ring will be synthesised at a later stage by ring closing metathesis (Scheme 1.21), which following isomerisation will furnish lysergic acid methyl ester.



Scheme 1.21

1.2.2. Synthesis from *N*-Pivaloylindole.

The synthesis began with L-tryptophan which was converted to its corresponding methyl ester (Scheme 1.22). Original attempts with 2,2-dimethoxypropane and aqueous HCl failed as the conditions were too harsh and led to decomposition of the starting material. The reaction was successful under milder conditions with thionyl chloride and methanol,[34,35] affording methyl ester **1.109** in 84% yield. Following Boc protection with Boc anhydride,[36] the molecule was protected as a pivalamide using a two phase procedure with pivaloyl chloride in toluene and 50% NaOH with $Bu_4N^+HSO_4^-$ as a phase catalyst.[37] Adding pivaloyl chloride as a neat solution afforded no desired product, due to the direct hydrolysis of the acid chloride. Yields were improved by adding the pivaloyl chloride dropwise as a dilute solution in toluene.

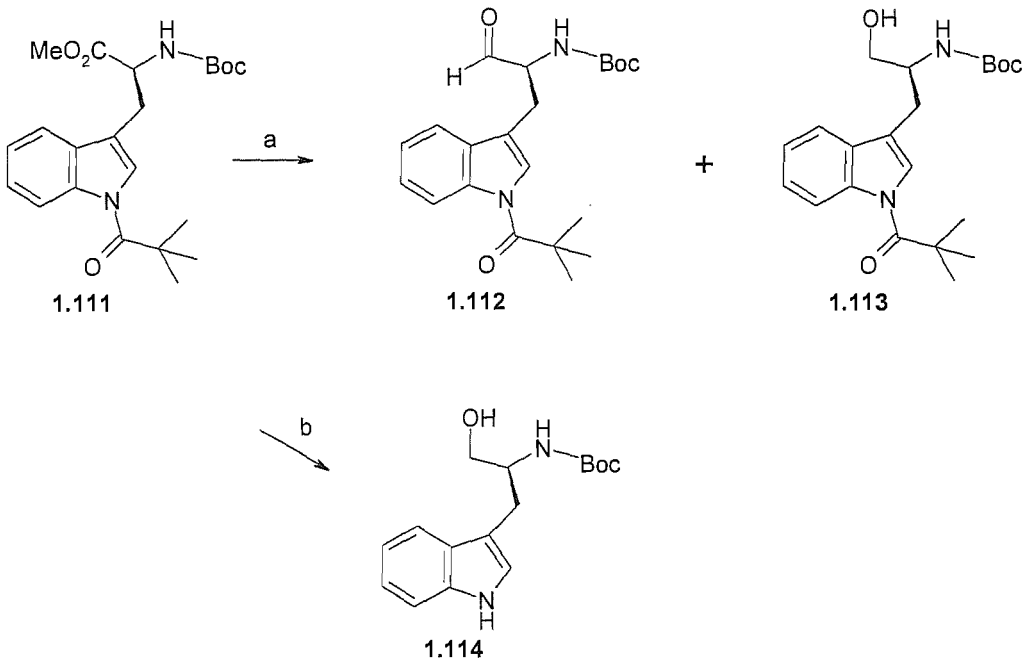


Reagents and conditions: a) $SOCl_2$, MeOH, reflux, 3.5 h, 84%; b) Boc anhydride, K_2CO_3, CH_2Cl_2, 1 h, 99%; c) Pivaloyl chloride, $Bu_4N^+HSO_4^-$, toluene, 50% NaOH (aq), 10 min, 86%.

Scheme 1.22

In order to add the allylic function to the molecule a Grignard addition of a vinylmagnesium halide to the aldehyde of the amino acid had to be performed. It is well documented that aldehydes of amino acids are relatively unstable both chemically and configurationally, particularly in solution.[38] They particularly have a

tendency to racemize due to keto-enol tautomerism during purification by chromatography on silica. It is therefore recommended that these compounds are used immediately after preparation. Attempts to reduce the ester under mild conditions with DIBAL-H were unsuitable as a mixture of products were formed due to over reduction to the corresponding alcohol **1.113** (Scheme 1.23). This was observed on using 1 and 2 equivalents of DIBAL-H at -78 °C.



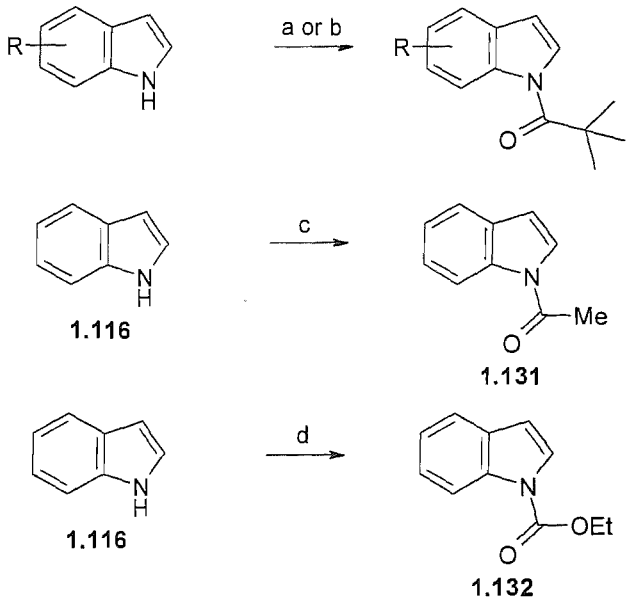
Reagents and conditions: a) DIBAL-H, THF, -78 °C, 3 h, 86%; b) $CaCl_2$, $NaBH_4$, THF, EtOH, 3 h, 90%.

Scheme 1.23

It was therefore considered that the aldehyde could be synthesised from oxidation of the corresponding amino alcohol. On attempting to synthesise the amino alcohol from ester **1.111** by reducing with sodium borohydride-calcium chloride,[39] the reduction was achieved in high yield, but as a side reaction cleavage of the pivalamide was also observed. As the deprotection of *N*-pivaloyl indoles with a mild hydride source was not well precedented, we were interested in investigating the result further.

1.2.3. Deprotection of *N*-Pivaloylindoles with Sodium Borohydride.

As pivalamide cleavage is usually effected by basic hydrolysis we were unaware of the ability of *N*-pivaloylindoles to be deprotected by hydride reagents. Only one example by Kanematsu *et al.* had been noted in passing.[40] They observed during their synthesis of *cis*-trikentrin B that hydride reduction of an indole dialdehyde to the diol also led to cleavage of the *N*-pivaloyl protecting group. Recently Menendez *et al.* observed the deprotection of *N*-pivaloylindoles using an excess of LDA, and explained the results using a Meerwein-Ponndorf-Verley-type mechanism where LDA functions as a hydride source.[41]

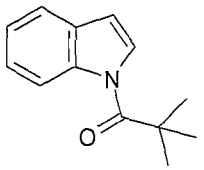
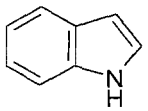
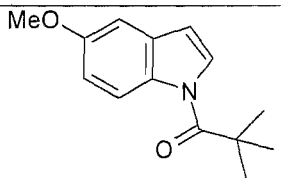
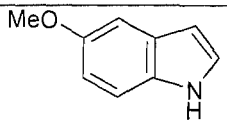
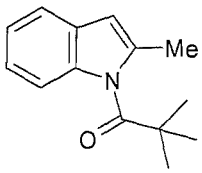
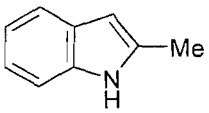
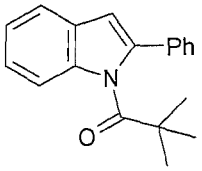
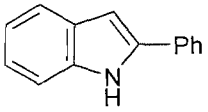
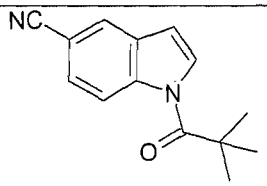
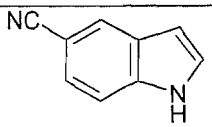


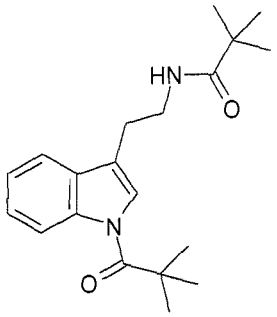
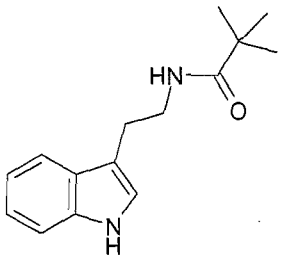
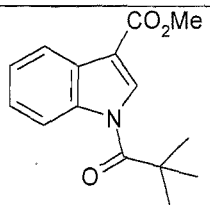
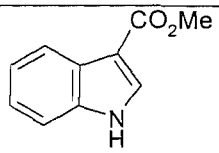
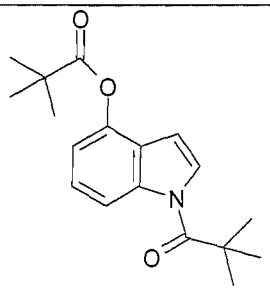
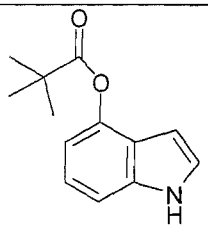
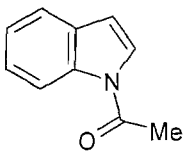
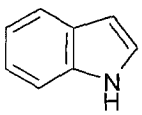
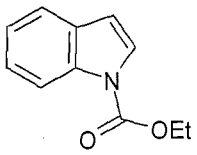
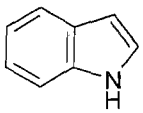
Reagents and conditions: a) $Bu_4N^+HSO_4^-$, toluene, 50% NaOH (aq), 30 min, then pivaloyl chloride in toluene, **1.115**, 10 min, 86%; **1.117**, 3.5 h, 70%; **1.127**, 1.5 h, 84%; b) NaH, THF, 30 min, then pivaloyl chloride, **1.121**, 2h, 92%; **1.119**, 30 min, 92%; **1.123**, 2 h, 91%; **1.125**, 2 h, 87%; **1.129**, 4 days, 46%; c) NaH, THF, 30 min, then acetyl chloride, reflux, 2 days, 63%; d) NaH, THF, 30 min, then ethyl chloroformate, 16 h, 35%.

Scheme 1.24

As pivalamides are very useful protecting groups in indole chemistry, protecting both the N-1 and C-2 positions of the ring, we decided to further investigate the viability of hydride reduction as a general procedure for their removal, which could be of use when more classical procedures involving alkaline hydrolysis are incompatible. We selected sodium borohydride as a mild hydride source and attempted the deprotection

on a range of substituted *N*-acyl and *N*-carbamoyl indoles. The *N*-protected indoles were synthesised as depicted in scheme 1.24 using a two phase procedure with NaOH and $Bu_4N^+HSO_4^-$ as a phase catalyst, or for those requiring slightly more forceful conditions NaH in THF, followed by addition of pivaloyl chloride. The results for the deprotections are summarized in table 1.1.

Reactant	**Product, yield.**[a]
 **1.115**	 **1.116**, 100%
 **1.117**	 **1.118**, 59%
 **1.119**	 **1.120**, 58%
 **1.121**	 **1.122**, 47%
 **1.123**	 **1.124**, 89%

 **1.125**	 **1.126**, 64%
 **1.127**	 **1.128**, 76%
 **1.129**	 **1.130**, 83%
 **1.131**	 **1.116**, 88%
 **1.132**	 **1.116**, 31%

[a]Isolated yield in percentage. Reaction conditions: 1 equiv $NaBH_4$, THF/EtOH, 1 h except for the following deprotections: **1.121** , 48 h; **1.125**, 4 h; **1.132**, 72 h.

Table 1.1. Deprotection of *N*-pivaloylindoles by sodium borohydride.

In all cases, pivalamide cleavage was achieved with sodium borohydride. The reagent also showed wide functional group tolerance. The cyano group in **1.123** and the side chain pivalamide in tryptamine derivative **1.125** were not affected. Similarly,

the esters in **1.127** and **1.129** were left intact, although the latter features a phenolate anion, a good leaving group, upon nucleophilic attack at the ester carbonyl. Finally, we briefly examined the possibility of extending this methodology to other carbonyl or carbamyl indole protecting groups. As shown the reduction was successful for the cleavage of *N*-acetyl indole **1.131** and *N*-carbamoyl indole **1.132**, although low-yielding for the case of **1.132**.

The above reactions used one equivalent of sodium borohydride which equates to four equivalents of hydride. We therefore attempted test reductions using 0.5 equivalents of sodium borohydride (Table 1.2). Although these reactions were also successful, they were significantly slower in the cases where the substituted indole did not have an electron withdrawing substituent (entries 1 and 2).

Entry	Reactant	Conditions	Product, yield
1	**1.115**	0.5 equiv $NaBH_4$, 15 h	**1.116**, 86%
2	**1.119**	0.5 equiv $NaBH_4$, 15 h	**1.120**, 100%
3	**1.123**	0.5 equiv $NaBH_4$, 1 h	**1.124**, 82%
4	**1.127**	0.5 equiv $NaBH_4$, 1 h	**1.128**, 95%
5	**1.121**	3 equiv $NaBH_4$, 15 h	**1.122**, 74%
6	**1.132**	3 equiv $NaBH_4$, 72 h	**1.116**, 69%

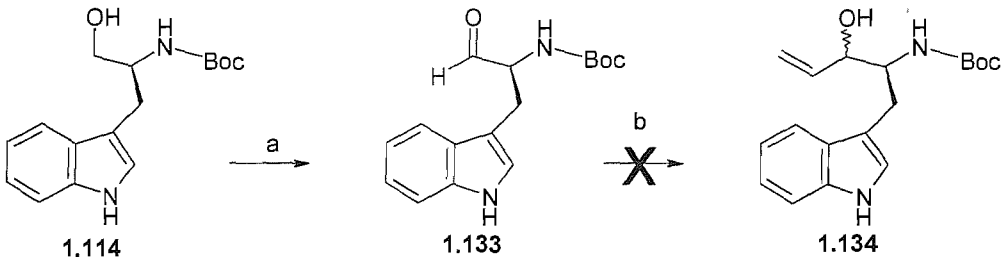
Table 1.2. Variation of sodium borohydride quantities in indole deprotection.

Where originally the reaction was low-yielding on using one equivalent of sodium borohydride, we increased this to three equivalents and observed an increase of yield in both cases and a decrease in reaction time for **1.121**.

We have therefore shown how sodium borohydride can be used as a mild procedure for *N*-pivaloyl, *N*-acetyl and *N*-carbamyl deprotection. The method can be of use when traditional methods for the deprotection are unsuitable.

1.2.4. Synthesis from *N*-Pivaloylindole continued.

The ergot alkaloid synthesis was continued with deprotected alcohol **1.114** as we anticipated that the compound could be re-protected after the Grignard addition. The Swern oxidation[42] of alcohol **1.114** proceeded smoothly, but the Grignard addition of aldehyde **1.133** with vinylmagnesium bromide[43-45] failed, only recovered starting material was isolated from the reaction mixture (Scheme 1.25).

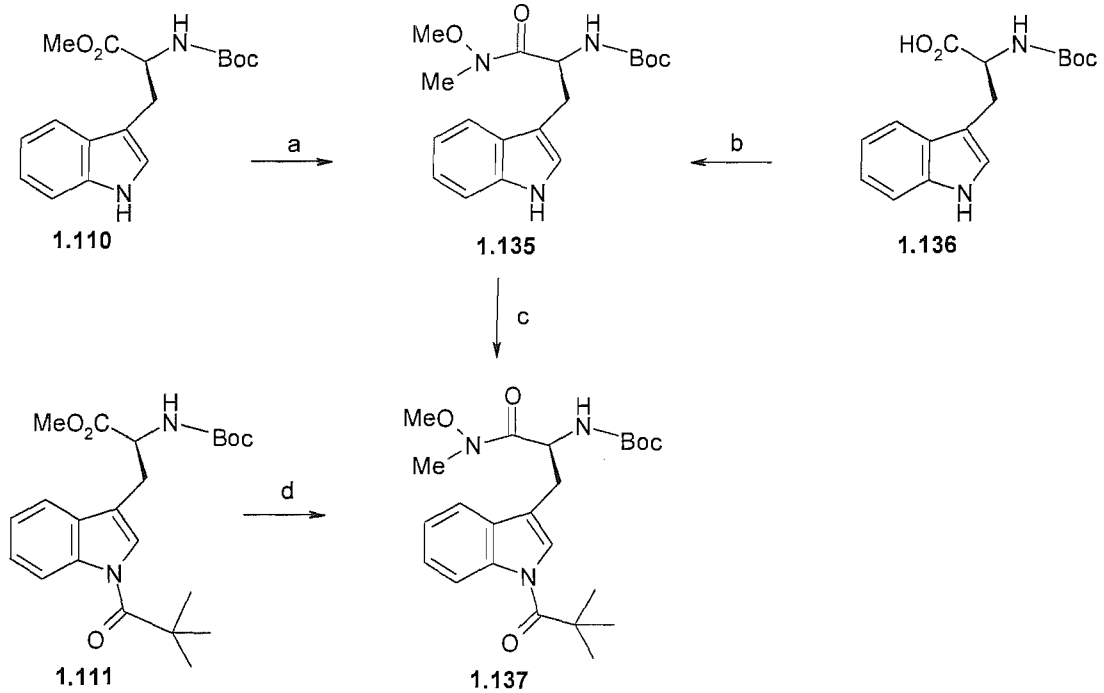


Reagents and conditions: a) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, 30 min, quant; b) vinyl MgBr, THF, 72 h.

Scheme 1.25

As attempts to synthesise the amino aldehyde from the methyl ester had failed we focused our attention on synthesising the aldehyde from the Weinreb amide,[46] which on reduction proceeds through a stable metal-chelated tetrahedral intermediate, collapsing only on work-up and therefore is less likely to be over-reduced to the corresponding alcohol.

Weinreb amide **1.137** was synthesised from esters **1.110** and **1.111** and from Boc tryptophan **1.136** using a range of conditions (Scheme 1.26). Several of the conventional techniques for coupling carboxylic acids to amines were very low-yielding (Table 1.3, entries 2-4). This was presumably due to steric hindrance around the carboxyl group. This was overcome by performing the reaction with methanesulfonyl chloride and *N,O*-dimethylhydroxylamine (entry 5)[47] where the reaction proceeds through the mixed anhydride of methanesulfonic acid.



Reagents and conditions: a) *N,O*-dimethylhydroxylamine·HCl, $AlMe_3$, CH_2Cl_2, reflux, 24 h, 76%; b) *N,O*-dimethylhydroxylamine·HCl, DMAP, DCC, DIPEA, CH_2Cl_2, 24 h, 30%; or methane sulfonyl chloride, Et_3N, *N,O*-dimethylhydroxylamine, THF, 5 h, 83%; or HOBt, WSC.HCl, Et_3N, *N,O*-dimethylhydroxylamine·HCl, CH_2Cl_2, 24 h, 44%; or *N,O*-dimethylhydroxylamine·HCl, DMAP, EDC, DIPEA, CH_2Cl_2, 24 h, 35%; c) NaH, pivaloyl chloride, THF, 2 h, 92%; d) *N,O*-dimethylhydroxylamine·HCl, $AlMe_3$, CH_2Cl_2, reflux, 24 h, 57%.

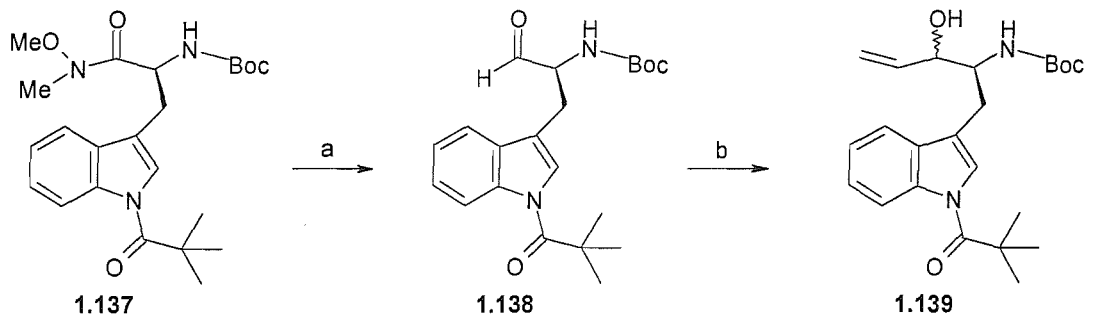
Scheme 1.26

The Weinreb amide could also be formed from methyl esters **1.110** and **1.111** with trimethylaluminium and *N,O*-dimethylhydroxylamine. The reaction was low-yielding with ester **1.111** due to the instability of the pivalamide protecting group. As two steps are required to synthesise Boc-tryptophan methyl ester **1.110** and Boc-tryptophan is commercially available the synthesis from the carboxylic acid was considered to be the most efficient route.

Entry	Starting Material	Conditions	T (°C)	t (h)	Yield of Weinreb amide (%)
1	**1.110**	(MeO)MeNH·HCl $AlMe_3$, CH_2Cl_2.[48]	rt-reflux	24	76
2	**1.111**	(MeO)MeNH·HCl $AlMe_3$, CH_2Cl_2.[48]	rt-reflux	24	57
3	**1.136**	(MeO)MeNH·HCl, DMAP, DCC, DIPEA, CH_2Cl_2.[49]	-30-rt	24	30
4	**1.136**	(MeO)MeNH·HCl, HOBt, WSC·HCl, Et_3N, CH_2Cl_2	rt-reflux	48	44
5	**1.136**	(MeO)MeNH·HCl, DMAP, EDC, DIPEA, CH_2Cl_2	-30-rt	24	35
6	**1.136**	(MeO)MeNH, $MeSO_2Cl$, Et_3N, THF.	0-rt	5	83

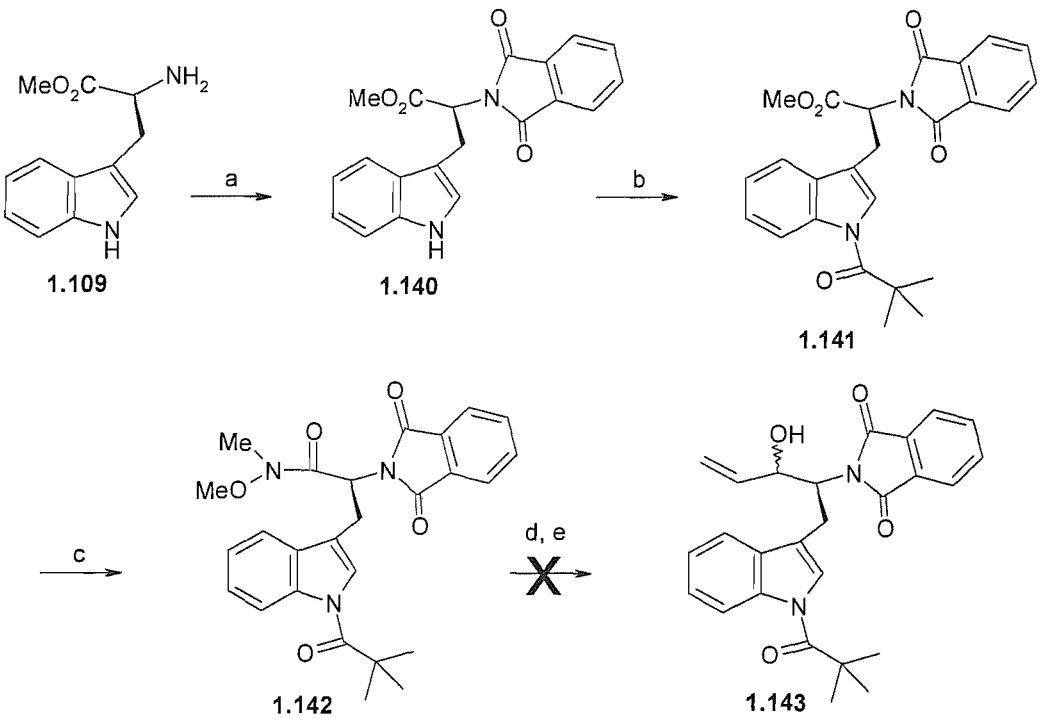
Table 1.3. Coupling conditions to synthesise Weinreb amide **1.134**.

Weinreb amide **1.137** was reduced to aldehyde **1.138** using three equivalents of DIBAL-H.[50] The formation of aldehyde **1.138** was elucidated by the presence of a characteristic aldehyde resonance in the proton NMR. The crude material was continued on without any purification. Treating aldehyde **1.138** with vinylmagnesium bromide was extremely low-yielding and only trace amounts of product were isolated (Scheme 1.27). It was considered that the amide proton may cause interference in the reaction; hence as a comparison the amine was protected as a phthalimide.



Reagents and conditions: a) DIBAL-H, THF, -78 °C, 1h, quant.; b) vinyl MgBr, THF, 0 °C, 3 h.

Scheme 1.27

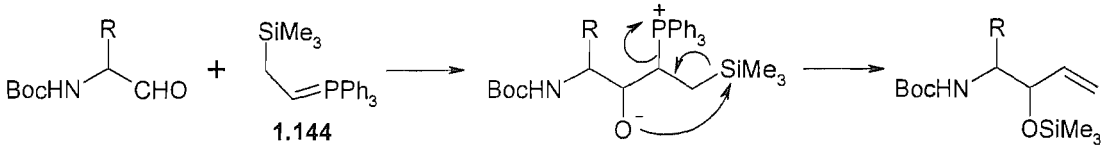


Reagents and conditions: a) Phthalic anhydride, Et_3N, toluene, reflux, 6 h, 84%; b) pivaloyl chloride, $Bu_4N^+HSO_4^-$, toluene, 50% NaOH (aq), 1 h, 81%; c) *N,O*-dimethylhydroxylamine·HCl, $AlMe_3$, CH_2Cl_2, reflux, 24 h, 62%; d) DIBAL-H, THF, -78 °C, 1.5 h; e) vinyl MgBr, THF, 2 days.

Scheme 1.28

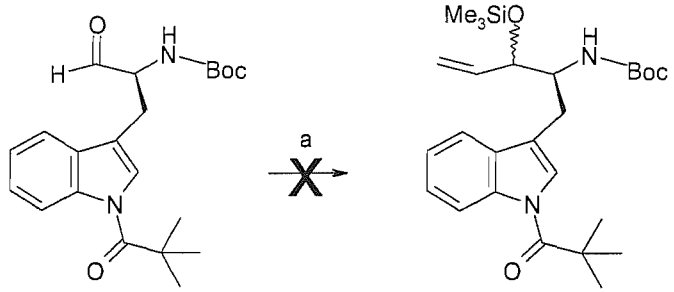
Phthalimide protected Weinreb amide **1.142** was synthesised according to scheme 1.28. Treatment with DIBAL-H afforded the corresponding aldehyde but again the Grignard addition with vinylmagnesium bromide was unsuccessful.

We therefore considered an alternative approach, whereby the allyl amino alcohol would be synthesised by treating the aldehyde with 2-trimethylsilylethylidenetriphenylphosphorane **1.144**.[51] Vinylation occurs *via* the migration of the silyl group to the oxygen and subsequent elimination of triphenylphosphine (Scheme 1.29).



Scheme 1.29

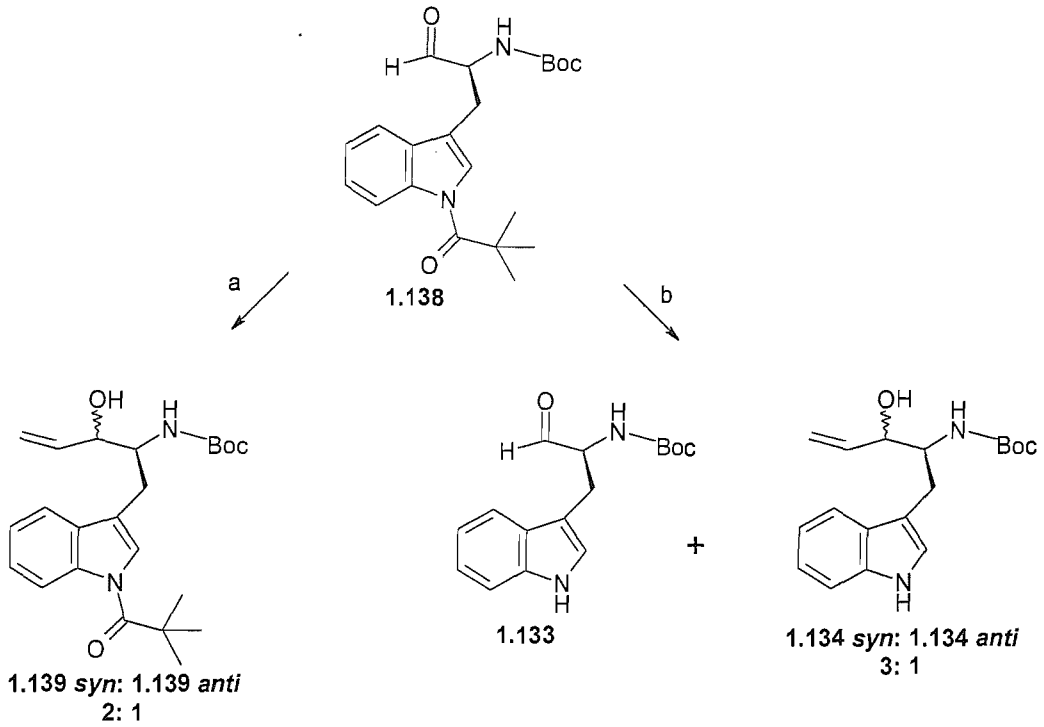
We applied this reaction to aldehyde **1.138**, with no success (Scheme 1.30).



Reagents and conditions: a) Methyltriphenylphosphonium bromide, *t*-BuLi, iodomethyltrimethylsilane, THF, -78 °C-rt, 24 h.

Scheme 1.30

Ibuka and co-workers reported during their synthesis of (*E*)-alkene dipeptide isosteres that on treating Boc-(*S*)-alaninal with a vinylmagnesium halide only the chloride gave them high yields of the desired product.[52] Treating aldehyde **1.138** with 3.5 equivalents of vinylmagnesium chloride afforded allyl alcohol **1.139** in 62% yield.

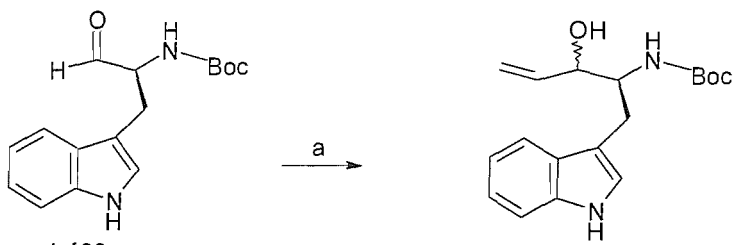


Reagents and conditions: a) vinyl MgCl (3.5 equiv.), THF, 0 °C, 20 h, 62%; b) vinyl MgCl (5 equiv.), THF, 0 °C, 20 h, **1.133**, 18%, **1.134**, 40%.

Scheme 1.31

The reaction did not go to completion due to the competing side reaction of enolization of the aldehyde. It was found that the aldehyde co-eluted with the desired allyl alcohol and therefore efforts to isolate the desired product by column chromatography always gave an inseparable mixture of alcohol **1.139** and trace amounts of aldehyde **1.138**. On using five equivalents of Grignard reagent cleavage of the pivalamide was observed, 18% of deprotected aldehyde **1.133** and 40% of deprotected allyl alcohol **1.134** were isolated from the reaction (Scheme 1.31).

As the pivalamide was seemingly unstable when attempting to drive the reaction to completion using a large excess of the Grignard reagent, we envisioned that the reaction could be performed on unprotected aldehyde **1.133** and the pivalamide could be set in place prior to the synthesis of the aziridine. Hence, aldehyde **1.133** was treated with 3.5 equivalents of vinylmagnesium chloride at -78 °C, affording 52% of allyl alcohol **1.134** as a ratio of 1: 1, *syn*: *anti* (Scheme 1.32).



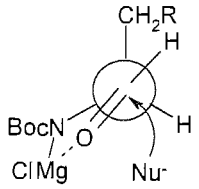
1.133

1.134 *syn*: 1.134 *anti*
1: 1

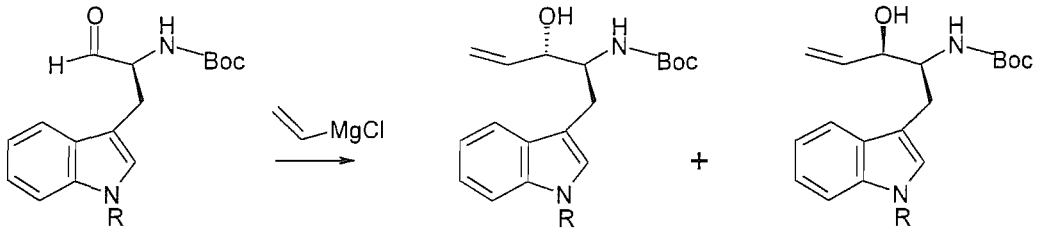
Reagents and conditions: a) vinyl MgCl (3.5 equiv.), THF, -78 °C, 20 h, 52%.

Scheme 1.32

The stereochemical outcome of the Grignard addition was dependent on the temperature at which the reaction was performed. At higher temperatures a greater proportion of NH protons should be removed and the reaction will proceed in favour of the chelation controlled Cram product, the *syn* alcohol (Scheme 1.33).[38,43]



Cram-chelate model



1.146 1.147:*syn* 1.147:*anti*

Scheme 1.33

Temp (°C)	Ratio *syn: anti*	Yield
-78	1: 1	52%
0	3: 1	62%
rt	5: 1	40%

Table 1.4. Ratio of Grignard reaction products.

As the *syn: anti* diastereoisomers were inseparable by column chromatography the ratio was determined from the ratio of allylic protons observed in the proton NMR (Figure 1.1). As shown from table 1.4 performing the addition at -78 °C gave a 1: 1 ratio of *syn: anti* diastereoisomers. As predicted increasing the temperature to 0 °C gave an increase in the ratio to 3: 1 and increasing the temperature further to room temperature afforded a 5: 1 ratio of diastereoisomers. As the stereochemical outcome would not affect the overall synthesis, as the chirality at this position is destroyed later in the route to the ergot alkaloid skeleton, the optimum conditions for the reaction was to perform the addition at 0 °C, this giving the highest yield. At higher temperatures the yield is lower presumably due to the competing reaction of aldehyde epimerization.

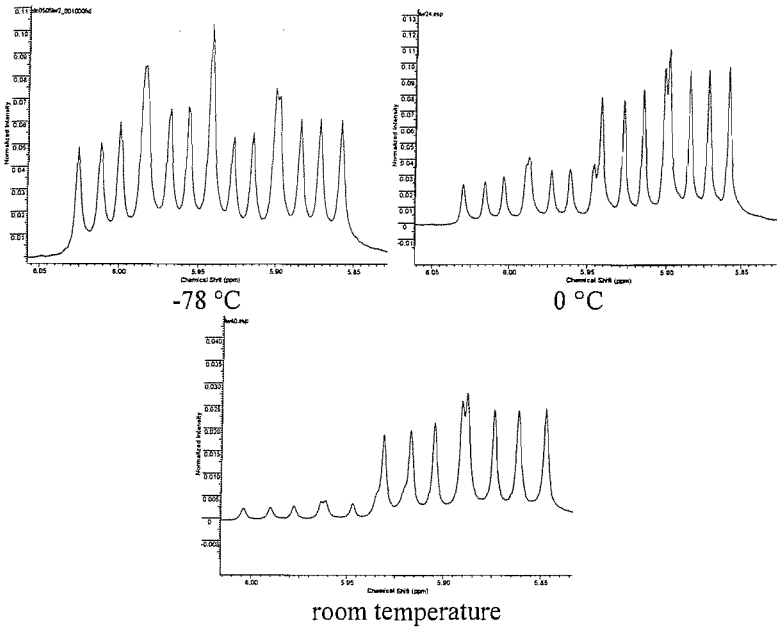
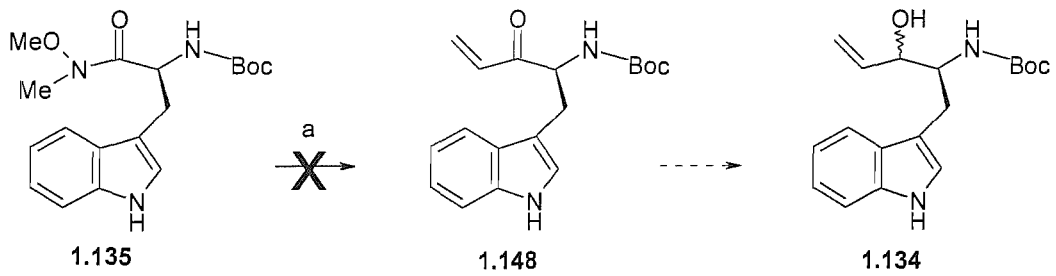


Figure 1.1. NMR of Grignard reaction products

In order to optimise the reaction we considered changing the reaction sequence and performing the Grignard addition prior to the DIBAL-H reduction. This reaction was unsuccessful and no α,β-unsaturated ketone was isolated from the reaction (Scheme 1.34).

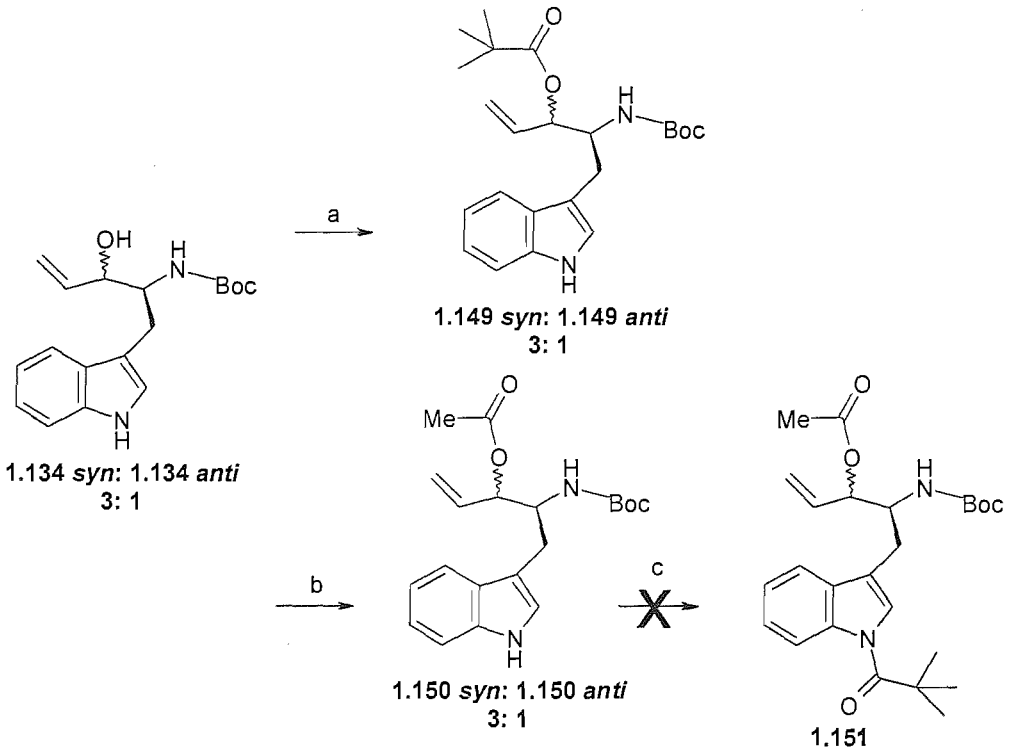


Reagents and conditions: a) vinyl MgCl, THF, 20 h.

Scheme 1.34

With amino alcohol **1.134** in hand we attempted to protect the indole as a pivalamide (Scheme 1.35). Treating the alcohol with pivaloyl chloride afforded product **1.149** in which the hydroxyl group had been protected. We therefore had to protect the free alcohol before the indole functionality with a protecting group that could be selectively cleaved. An acetyl protecting group was considered as this could also be used as an effective leaving group for the formation of the aziridine. The protection

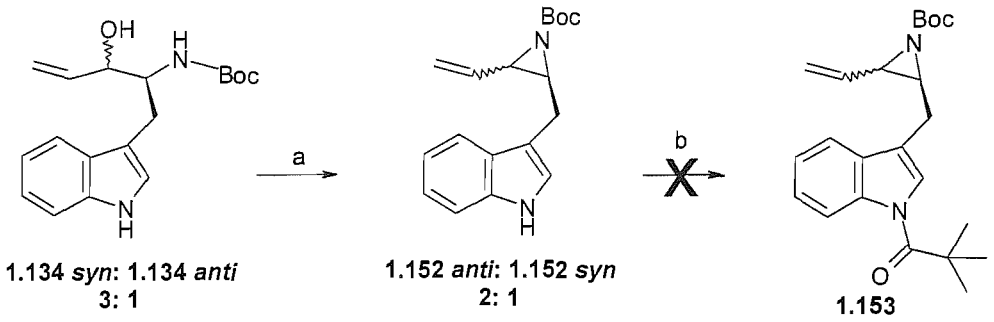
was accomplished with acetic anhydride, triethylamine and catalytic DMAP. Efforts to protect with acetyl chloride failed, due to the fast hydrolysis of the acid chloride. Under the aqueous basic conditions of the pivalamide protection two products were isolated from the reaction. Alcohol **1.134** resulting from cleavage of the acetyl group was observed in 73% yield and alcohol **1.149** was isolated in 24% yield where the acetyl group had been removed and re-protected as a pivalamide.



Reagents and conditions: a) PivCl, 50% NaOH (aq), $Bu_4N^+HSO_4^-$, toluene, 1 h, 41%; b) acetic anhydride, DMAP, Et_3N, CH_2Cl_2, 2 h, 72%; c) PivCl, 50% NaOH (aq), $Bu_4N^+HSO_4^-$, toluene.

Scheme 1.35

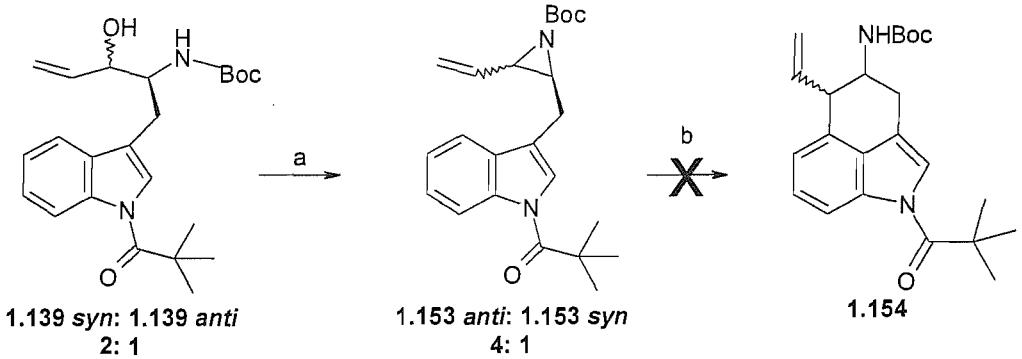
It was also envisioned that the pivalamide protecting group could be put in place after formation of the aziridine. Hence, aziridine **1.152** was synthesised from allyl alcohol **1.134** *via* a Mitsunobu reaction[53,54] with PPh_3 and DIAD (Scheme 1.36). Efforts to protect at this point using both NaH and biphasic procedures were unsuccessful with the basic conditions leading to decomposition of the starting material.



Reagents and conditions: a) PPh_3, DIAD, THF, 20 h, 74%; b) PivCl, NaH, THF.

Scheme 1.36

As protecting the indole after the Grignard addition was proving to be cumbersome, the route was continued from **1.139**, with protection prior to the DIBAL-H reduction. Aziridine **1.153** was synthesised from amino alcohol **1.138** in 54% yield. The structure of aziridine **1.153** was confirmed from the crystal structure (Figure 1.3)



Reagents and conditions: a) PPh_3, DIAD, THF, 48 h, 54%; b) $AlCl_3$, CH_2Cl_2.

Scheme 1.37

On treating aziridine **1.153** with a Lewis acid we anticipated that the molecule would take part in a Friedel-Crafts type alkylation onto the C-4 position of the indole ring. Performing the reaction with aluminium chloride resulted in no desired product being produced, suggesting that the Boc protecting group was unstable to the acidic conditions, and its cleavage leading to decomposition of the molecule. We therefore had to consider an alternative protecting group which would be stable to the Lewis acidic conditions, and decided on the use of a sulfonamide protecting group which due to strong electron acceptance will facilitate the cyclisation.

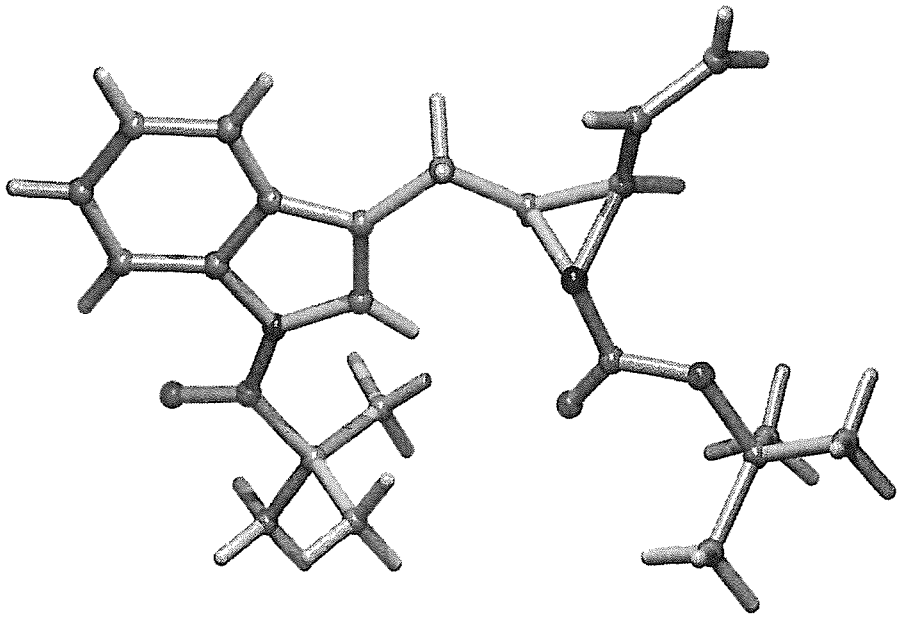
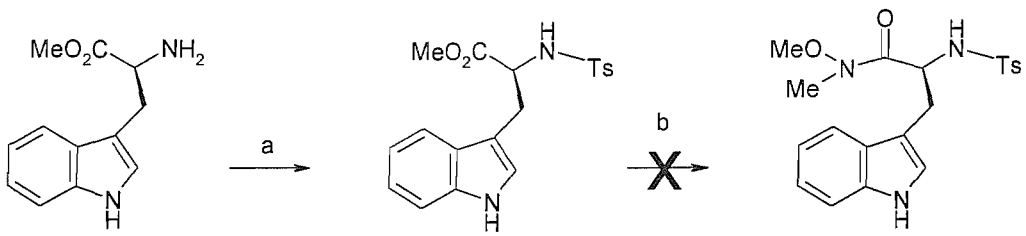


Figure 1.3. Crystal structure of **1.153** ***syn***

Tryptophan methyl ester was protected as a tosamide under basic conditions with triethylamine and tosyl chloride in 98% yield (Scheme 1.38). Efforts to synthesise the Weinreb amide with trimethylaluminium failed. Only recovered starting material was isolated from the reaction.

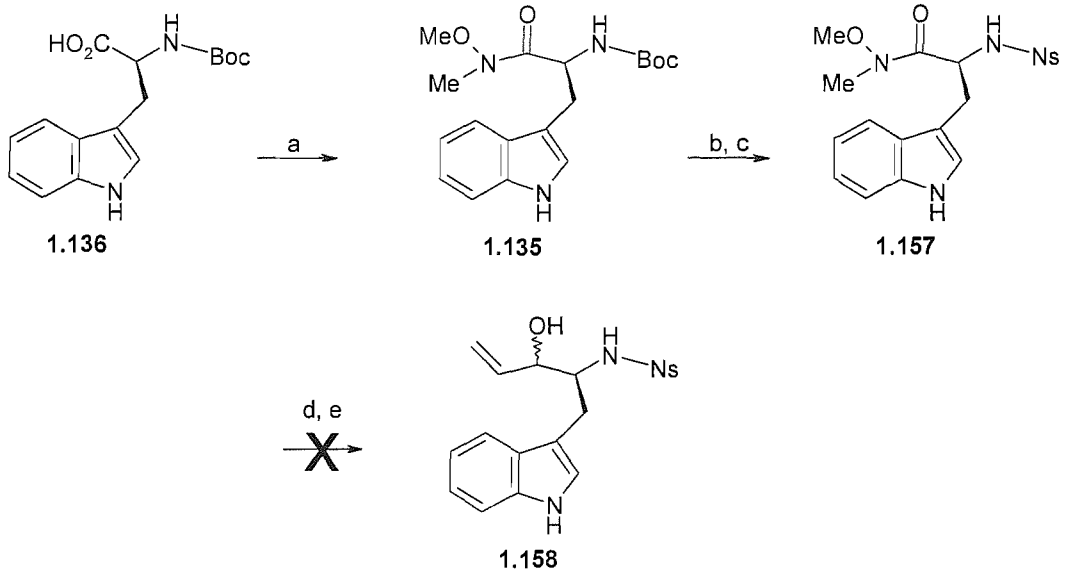


Reagents and conditions: a) TsCl, Et_3N, CH_2Cl_2, 0 °C, 3.5 h, 98%; b) $AlMe_3$, *N,O*-dimethylhydroxyamine·HCl, CH_2Cl_2, reflux, 24 h.

Scheme 1.38

We envisioned that the Boc protecting group could be changed for a sulfonamide protecting group after formation of the Weinreb amide. We decided on the use of a nitrophenylsulfonyl (nosyl) protecting group as Far *et al.* had shown how it can be effectively used to facilitate the opening of aziridines by indoles mediated by boron trifluoride.[55,56] This was accomplished by removal with TFA followed by protection with nosyl chloride. Attempts to form allyl alcohol **1.158** using the same reduction,

Grignard addition sequence failed. This was presumably due to the increased acidity due to increased electron acceptance of the nosyl group.

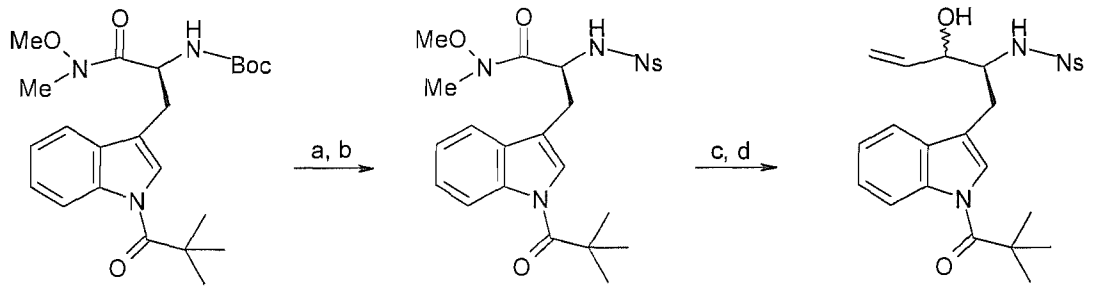


1.136 **1.135** **1.157** **1.158**

Reagents and conditions: a) MsCl, Et_3N, *N,O*-dimethylhydroxylamine, THF, 5 h, 83%; b) TFA, CH_2Cl_2, 1 h; c) NsCl, Et_3N, CH_2Cl_2, 2 h, 63%; d) DIBAL-H, THF, -78 °C, 1.5 h; e) vinyl MgCl, THF, 0 °C, 20 h.

Scheme 1.39

The DIBAL-H reduction and Grignard addition were also attempted on the pivalamide protected precursor **1.159** (Scheme 1.40).



1.137 **1.159** **1.160 *syn*: 1.160 *anti* 3: 1**

Reagents and conditions: a) TFA, CH_2Cl_2, 1 h; b) NsCl, Et_3N, CH_2Cl_2, 2 h, 92%, c) DIBAL-H, THF, -78 °C, 1.5 h; d) vinyl MgCl, THF, 0 °C, 20 h, 15%.

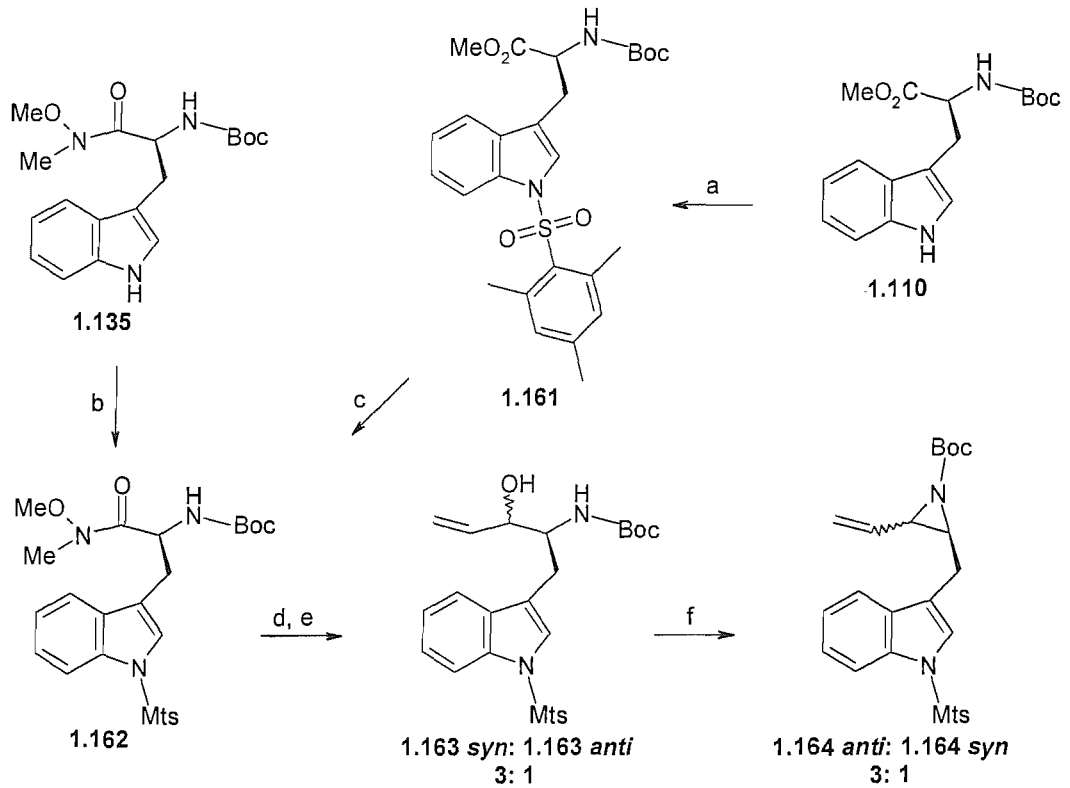
Scheme 1.40

The synthesis of **1.159** was accomplished from **1.137** by deprotecting with TFA followed by re-protecting with nosyl chloride. The DIBAL-H reduction proceeded

smoothly, as evident from the proton NMR. The Grignard addition was again problematic; only 15% of the desired product was isolated and the proton NMR showed a complex mix of products. As the acidity of the molecule is increased by the presence of the nosyl protecting group more of the competing side reaction of enolization of the aldehyde would be expected, hence forming a complex mixture of diastereoisomers.

1.2.5. Synthesis from *N*-Mesitylenesulfonyl indole.

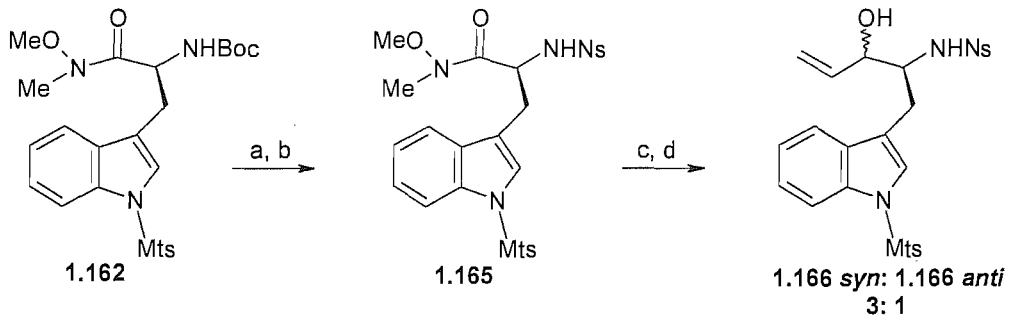
Due to the labile nature of the pivalamide, we investigated in parallel the use of a mesitylenesulfonyl protecting group which we anticipated would show the same steric effect in blocking the C-2 position of the indole ring.



Reagents and conditions: a) 2-mesitylenesulfonyl chloride, 50% NaOH (aq), $Bu_4N^+HSO_4^-$, toluene, 2 h, 95%; b) 2-mesitylenesulfonyl chloride, 50% NaOH (aq), $Bu_4N^+HSO_4^-$, toluene, 2 h, 92%; c) $AlMe_3$, *N, O*-dimethylhydroxylamine·HCl, CH_2Cl_2, reflux, 20 h, 53%; d) DIBAL-H, THF, -78 °C, 1 h; e) vinyl MgCl, THF, 0 °C, 20 h, 83%; f) DIAD, PPh_3, THF, 16 h, 60%.

Scheme 1.41

The protected Weinreb amide **1.162** was synthesised according to scheme 1.40 from tryptophan methyl ester or by the protection of Weinreb amide **1.135** derived from Boc-tryptophan **1.136**. As the synthesis from the carboxylic acid resulted in a greater overall yield, this was considered the most efficient route. Treatment of Weinreb amide **1.162** with DIBAL-H followed by the Grignard reaction with vinylmagnesium chloride afforded amino alcohol **1.163** in 83% yield as a 3: 1 ratio of *syn: anti* (Scheme 1.42). Due to the greater stability of the mesitylenesulfonyl protecting group in comparison with the pivalamide, the yield of the Grignard addition was improved. Treatment of allyl alcohol **1.163** with DIAD and PPh_3 gave aziridine **1.164** in 60% yield.



Reagents and conditions: a) TFA, CH_2Cl_2, 0 °C, 1 h; b) NsCl, Et_3N, CH_2Cl_2, 2 h, 85%; c) DIBAL-H, THF, -78 °C, 1.5 h; d) vinyl MgCl, THF, 0 °C, 20 h, 15%.

Scheme 1.42

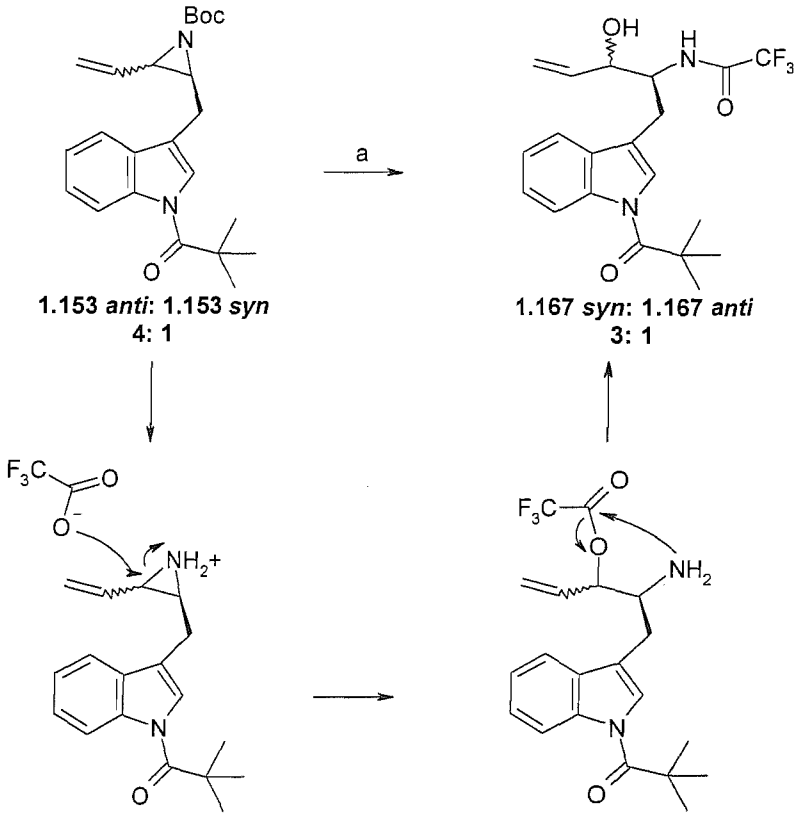
The Grignard addition of the aldehyde derived from Weinreb amide **1.165** was also low-yielding, suggesting that the nosyl protecting group would have to be set in place following the Grignard addition.

1.2.6. Exchanging the Protecting Groups.

As the Grignard addition was proving problematic with the nosyl protecting group in place, we envisaged that the Boc group could be changed for the nosyl group following the Grignard reaction. Efforts to exchange the Boc aziridine for a nosyl aziridine were made under a range of conditions.

On treating aziridine **1.153** with TFA, cleavage of the carbamate was observed. However, the product isolated appeared also to possess a trifluoroacetyl moiety. The

NMR and mass spectometry data were consistent with the structure of **1.167**. A proposed mechanism for its formation is depicted in scheme 1.43.



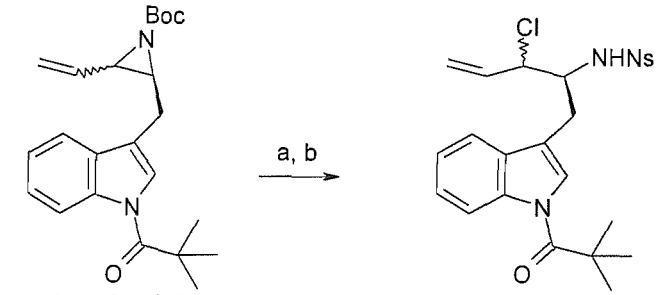
Reagents and conditions: a) TFA, CH_2Cl_2, 4 h, 50%.

Scheme 1.43

Treatment of aziridine **1.153** with HCl in methanol led to the formation of a product in which the proton NMR was extremely complicated but mass spectrometry detected a mass of deprotected aziridine + MeOH, suggesting that the aziridine was opened by methanol. On performing the deprotection with *p*-TsOH in CH_2Cl_2 the NMR and mass were consistent with the addition of a *p*-toluenesulfonate group to the molecule, again suggesting opening of the aziridine by nucleophilic attack of the counter-ion.

On performing the reaction with HCl in a non-nucleophilic solvent, in this case dioxane,[57] with anisole as a scavenger, the deprotection appeared to proceed smoothly according to the mass spectrum and proton NMR. On treating the free amine with NsCl, product **1.168** was isolated in which the aziridine had been opened by the chloride present in the reaction mixture, clearly showing the activating effect

of the nosyl group (Scheme 1.44). This result was also shown by Bonnet-Delpon *et al.* during their synthesis of fluorinated α,β-diamino esters by ring opening of activated 3-trifluoromethyl aziridine-2-carboxylates.[58,59] This opening was both regio- and stereo-selective. The opening occurred at the activated allylic end of the aziridine and only one diastereoisomer was obtained, of which the stereochemistry was unknown.

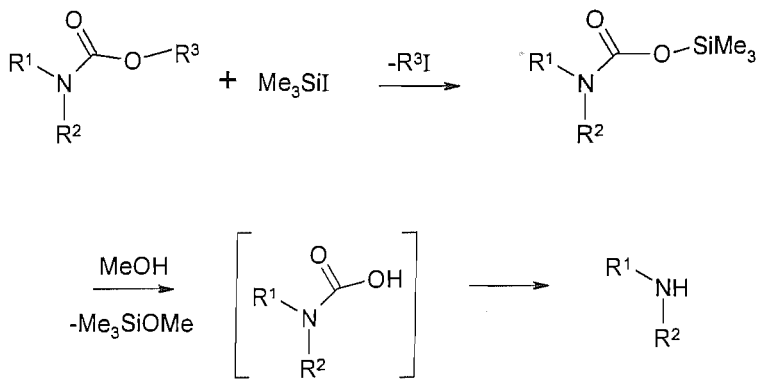


1.153 *anti*: 1.153 *syn* **4: 1** **1.168**

Reagents and conditions: a) 4 M HCl in dioxane, anisole, 2 h; b) NsCl, Et_3N, CH_2Cl_2, 16 h, 16%.

Scheme 1.44

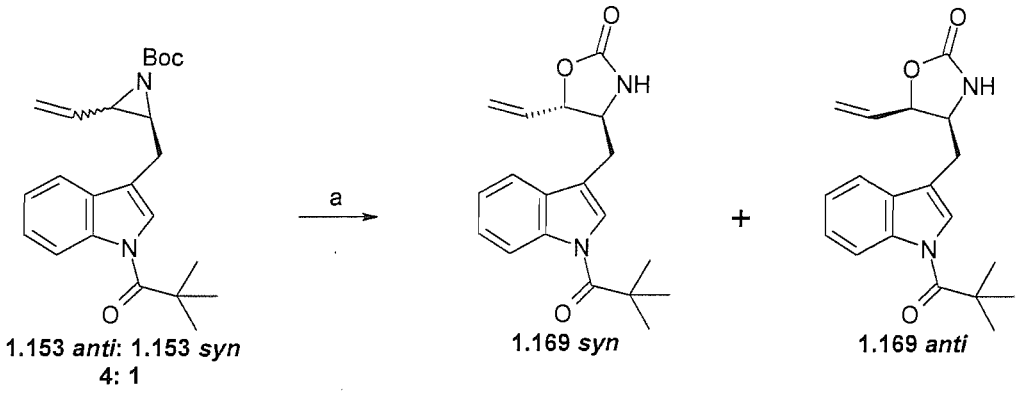
The deprotection was also attempted using iodotrimethylsilane as a milder neutral reagent.[60,61] The reaction proceeds *via* the trimethylsilyl carbamate. Treatment with methanol provides the free carbamic acid which spontaneously loses CO_2 to form the free amine (Scheme 1.45).



Scheme 1.45

Performing the reaction in the presence of base led to the formation of oxazolidinone **1.169** where instead of losing CO_2 to form the free amine, the molecule takes place in

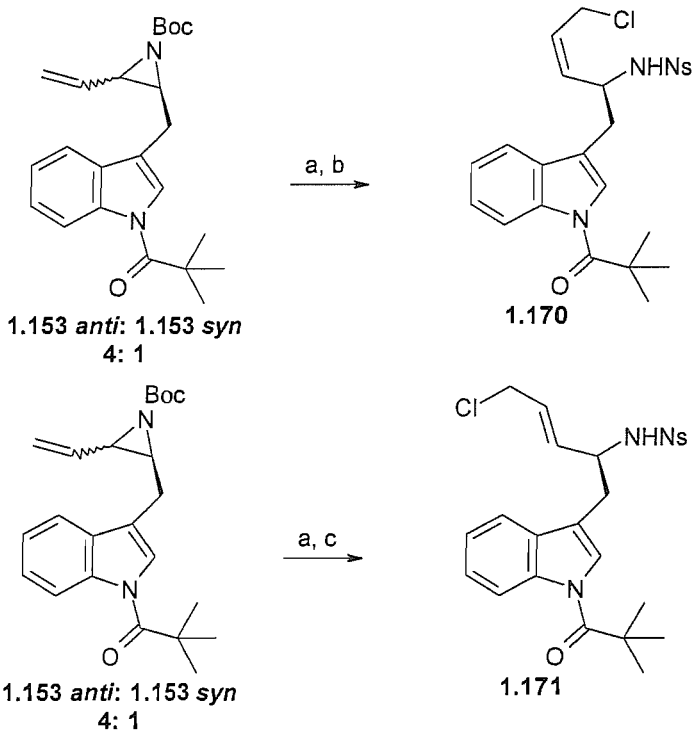
an intramolecular cyclisation (Scheme 1.46). The cyclisation resulted in two diastereoisomers which were separable by column chromatography.



Reagents and conditions: a) Me_3SiI, 2, 6-lutidine, CH_2Cl_2, 0 °C, 1 h, **1.169** ***syn*** 17%, **1.169** ***anti*** 10%.

Scheme 1.46

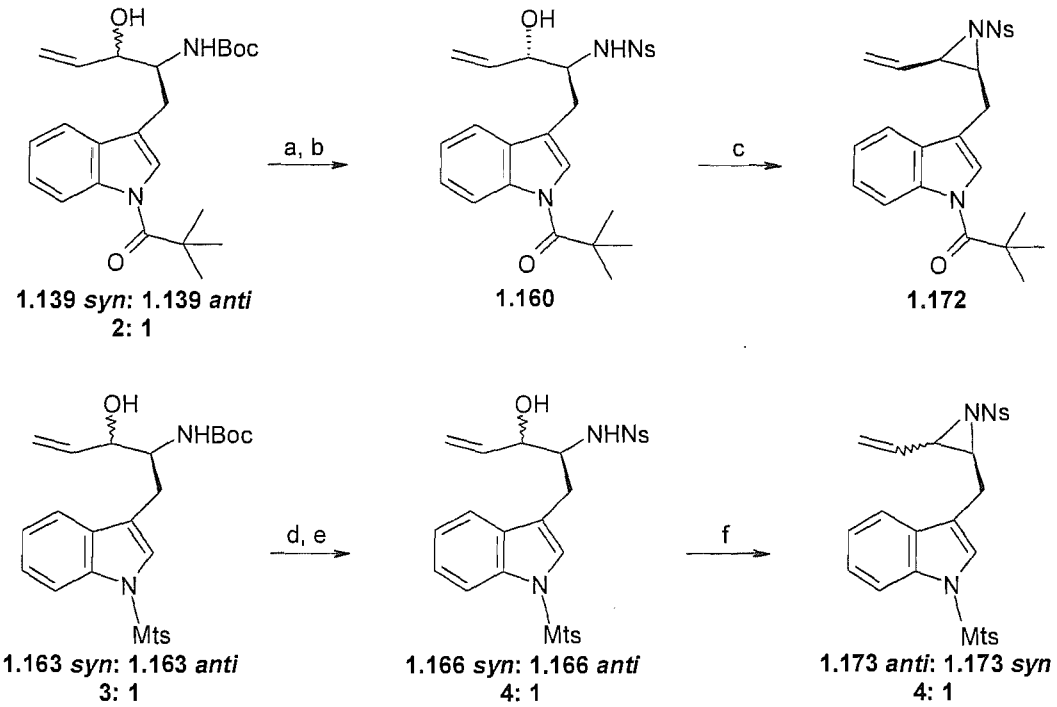
On reacting the crude deprotected product with nosyl chloride under basic conditions the free chloride took part in an S_N2' addition, resulting in opening of the aziridine. The reaction was under thermodynamic control. On performing the reaction at 0 °C the *cis* isomer was formed, at room temperature the *trans* isomer was formed (Scheme 1.47).



Reagents and conditions: a) Me_3SiI, 2,6-lutidine, CH_2Cl_2, 0 °C, 2 h; b) NsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h, 52%; c) NsCl, Et_3N, CH_2Cl_2, 2 h, 33%.

Scheme 1.47

As difficulties were encountered due to the ease with which the aziridine is opened under acidic conditions,[62,63] it was anticipated that the nosyl protecting group could be set in place prior to synthesising the aziridine. Efforts were made to substitute the Boc group for the nosyl group of the allyl alcohol.[64]



Reagents and conditions: a) 4 M HCl in dioxane, anisole, 2 h; b) NsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 h, 34%; c) DIAD, PPh_3, THF, 2 h, 58%; d) TFA, CH_2Cl_2, 0 °C, 1 h; e) NsCl, Et_3N, CH_2Cl_2, 2 h, 62%; f) DIAD, PPh_3, THF, 2 h, 67%.

Scheme 1.48

Initially the Boc deprotection was attempted with TFA as earlier work had shown it to be an efficient procedure for its removal. With the mesitylene sulfonate protected substrate **1.163** the deprotection occurred smoothly with both steps proceeding in 62% overall yield (Scheme 1.48). With the pivalamide protected indole the transformation occurred in 25% yield due to the instability of the pivalamide under the strong acidic conditions. Attempting the deprotection under milder conditions with Me_3SI resulted in no desired product. The best result was observed when deprotecting with 4 M HCl in dioxane in the presence of anisole as a scavenger, providing the nosyl protected product in 34% overall yield, in which only the *syn* diastereoisomer was isolated.

With the nosyl protected alcohols in hand the aziridines were formed effectively using Mitsunobu conditions. The crystal structure of **1.173** ***anti*** is shown in figure 1.4.

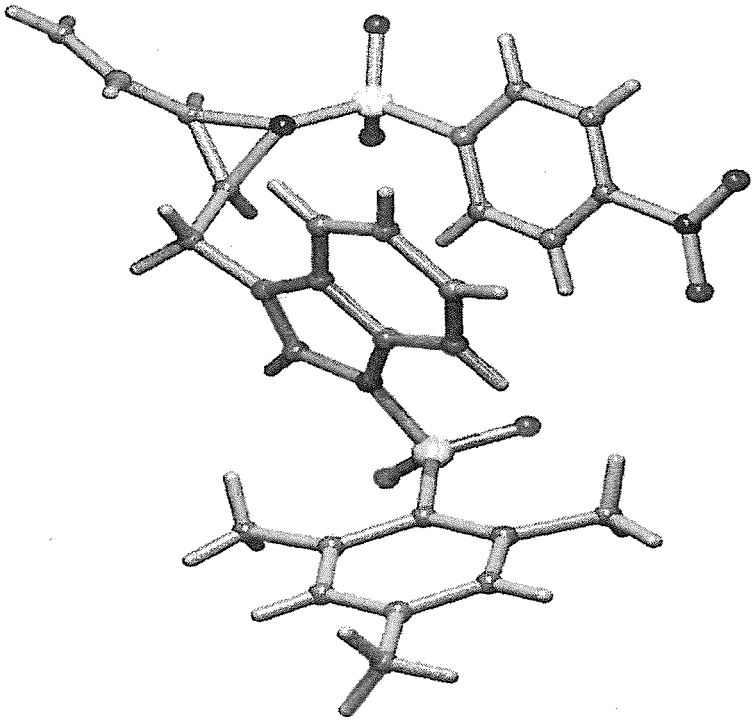
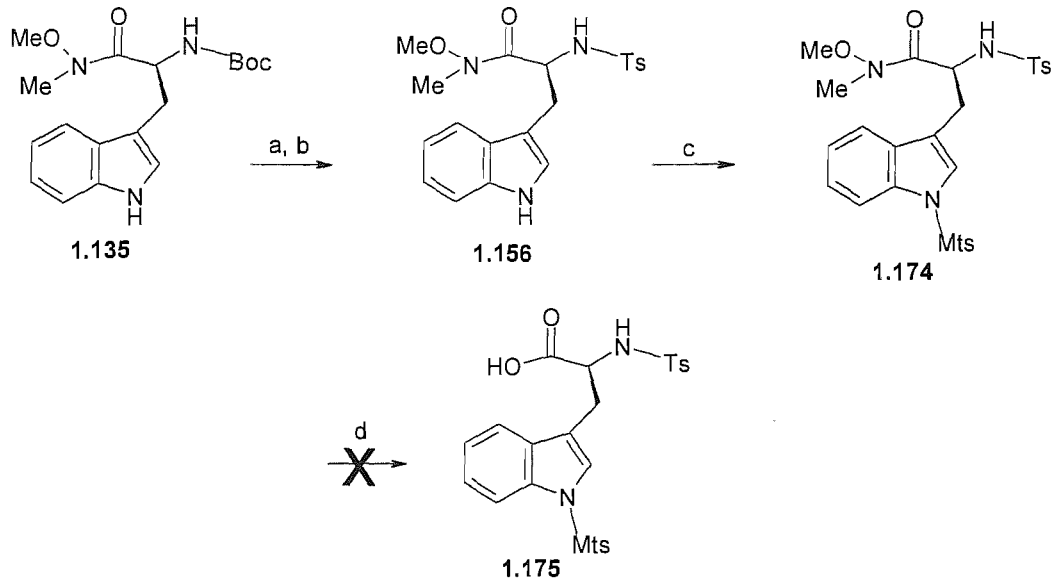


Figure 1.4. Crystal structure of **1.173** ***anti***

1.2.7. Synthesis from the Acid chloride.

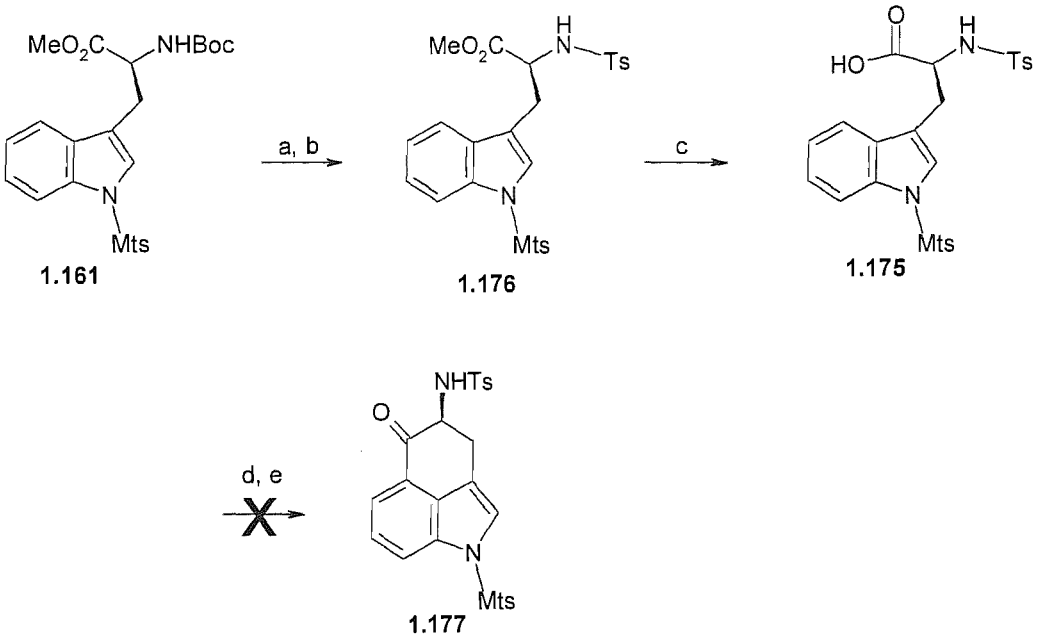
Goto and co-workers have shown how an acid chloride can take part in an intramolecular cyclisation onto the C-4 position of a pivalamide-protected indole.[25] We anticipated that the acid chloride of tryptophan could be cyclised onto the C-4 position of the indole ring.

As we had the Weinreb amide in hand we attempted to form the carboxylic acid from hydrolysis of the amide. This was unsuccessful due to the stability of the Weinreb amide (Scheme 1.49).



Reagents and conditions: a) TFA, CH_2Cl_2, 2 h; b) TsCl, Et_3N, CH_2Cl_2, 68%; c) 50% NaOH (aq), $Bu_4N^+HSO_4^-$, 2-mesitylenesulfonyl chloride, toluene, 16 h, 36%; d) LiOH, 30% H_2O_2, THF, H_2O, 3 days.

Scheme 1.49



Reagents and conditions: a) TFA, CH_2Cl_2, 1 h; b) TsCl, Et_3N, CH_2Cl_2, 16 h, 89%; c) LiOH, H_2O, THF, 16 h, 92%; d) $SOCl_2$, CH_2Cl_2, 25 min; e) $AlCl_3$, CH_2Cl_2, 0 °C.

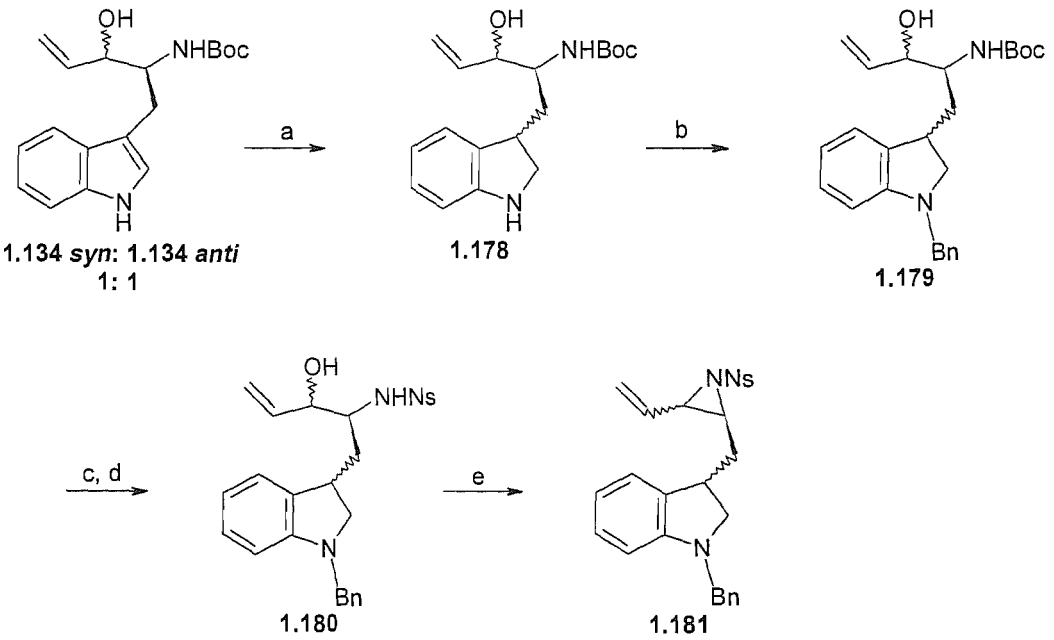
Scheme 1.50

We therefore synthesised the carboxylic acid by saponification of the methyl ester (Scheme 1.50). After protection of the indole and exchanging the Boc protecting group for a tosyl group the methyl ester was hydrolysed to the corresponding

carboxylic acid with LiOH. Various attempts were made to form the acid chloride. Thionyl chloride,[65] oxalyl chloride[66] and hexachloroacetone[67] were all unsuccessful; no desired product was isolated from the reaction, presumably due to the instability of the acid chlorides of amino acids. Performing the Friedel-Crafts acylation with aluminium chloride on the crude material without attempting to isolate the acid chloride was also unsuccessful.

1.2.8. Synthesis from the Indoline Derivative.

In order to prevent cyclisation onto the C-2 position of the indole ring many of the previous synthesise of the ergot alkaloids have started from indoline derivatives. We therefore synthesised indoline **1.181** to be used as a comparison for the protected indoles.



Reagents and conditions: a) $NaCNBH_3$, acetic acid, 16 h, 89%; b) $NaHCO_3$, BnCl, H_2O, 95 °C, 3 h, 81%; c) TFA, CH_2Cl_2, 16 h; d) NsCl, Et_3N, CH_2Cl_2, 2 h, 97%; e) PPh_3, DIAD, THF, 16 h, 42%.

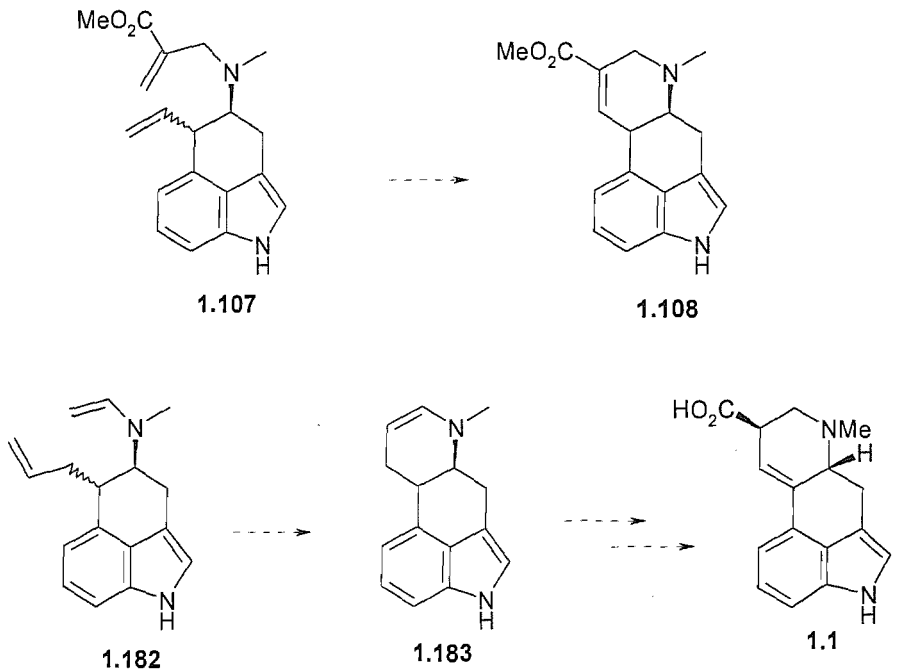
Scheme 1.51

The reduction of indole **1.134** with sodium cyanoborohydride[68] proceeded smoothly to afford indoline **1.178** (Scheme 1.51) as a complex mixture of four diastereoisomers. Attempts to exchange the Boc protecting group for the nosyl group without protecting the indoline nitrogen were low-yielding. The desired product was

formed in 13% yield. Exchanging the protecting groups on the benzyl protected substrate[69] was very efficient, providing the nosyl protected product in 97% overall yield.

The Mitsunobu reaction with DIAD and triphenylphosphine was in this case low-yielding. On nosyl protecting the free amines only one equivalent of nosyl chloride was used to prevent diprotection. As the nosylate would effectively be a good leaving group we anticipated that reacting the amine with two equivalents of nosyl chloride would lead to the dinosylated amino alcohol and subjecting the adduct to basic conditions would result in an intramolecular displacement of the nosylate by the amine to produce the aziridine.[70] Treatment of the free amine with 2.2 equivalents of nosyl chloride was problematic as the reaction was extremely slow and longer reaction times led to undesirable decompositions. Hence, the route was continued with formation of the aziridine *via* the Mitsunobu reaction.

1.2.9. Synthesis from the Homoallylic Alcohol.

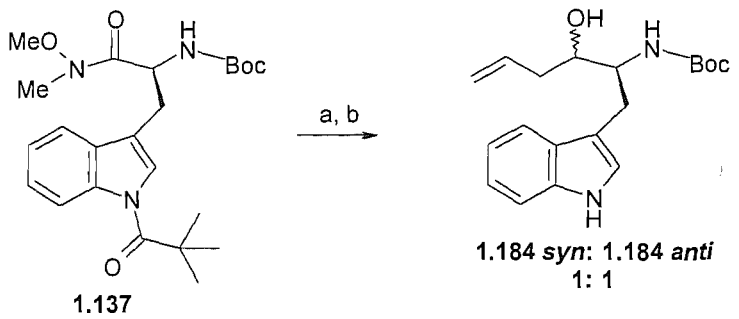


Scheme 1.52

Due to the difficulties encountered in attempting to exchange the protecting groups of the allylic alcohol we considered an alternative route from the homoallylic

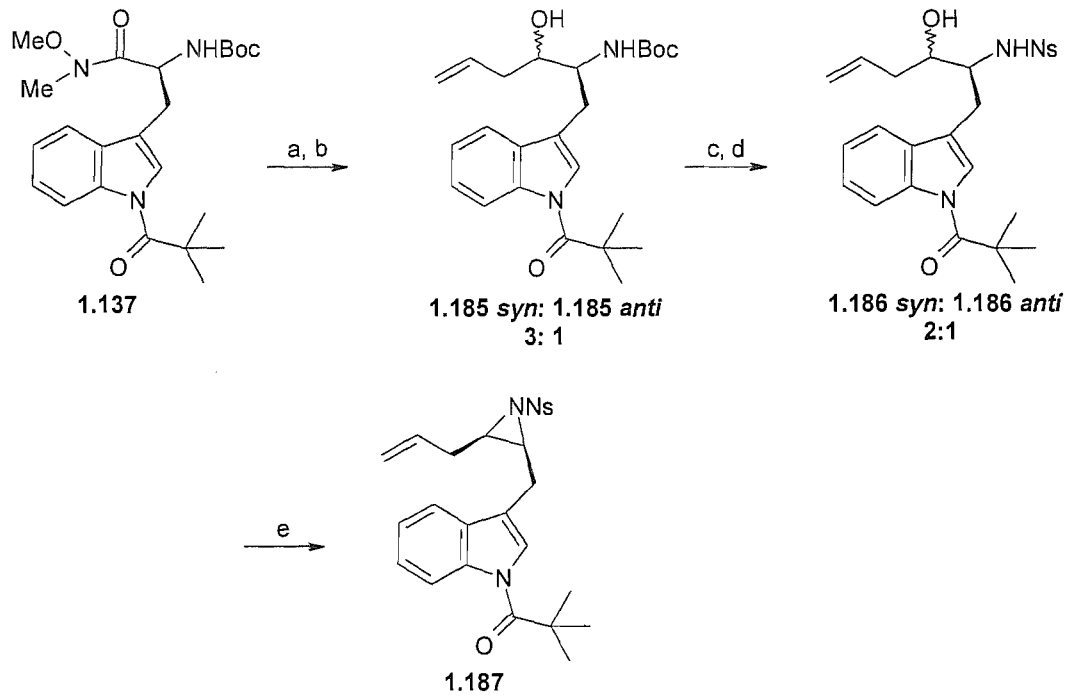
alcohol. The double bond will be employed later in the synthesis to construct the fourth ring of the ergot alkaloid skeleton *via* ring closing metathesis. Therefore the position of the double bond would not affect the overall synthesis (Scheme 1.52).

Attempts to form the homoallylic alcohol by the Grignard addition to the amino aldehyde[71] resulted in cleavage of the pivalamide protecting group to give the known homoallylic alcohol **1.184**[72] (Scheme 1.53).



Reagents and conditions: a) DIBAL-H, THF, -78 °C, 1 h; b) allyl MgCl (3.5 equiv), THF, 20 h, 37%.

Scheme 1.53



Reagents and conditions: a) DIBAL-H, THF, -78 °C, 1 h; b) $CrCl_2$, allyl bromide, THF, 2 h, 59%; c) 4 M HCl in dioxane, anisole, 0 °C, 2 h; d) NsCl, Et_3N, CH_2Cl_2, 16 h, 53%; e) DIAD, PPh_3, THF, 16 h, 48%.

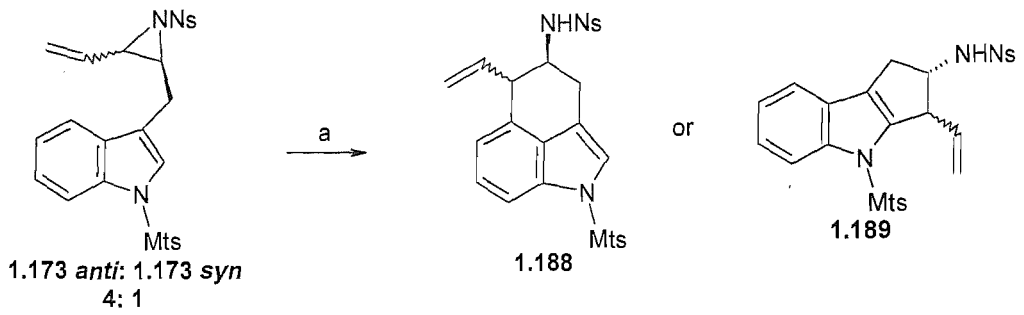
Scheme 1.54

On using two equivalents of Grignard reagent the desired homoallylic alcohol was isolated in 26% yield. We therefore considered an alternative route using $CrCl_2$ mediated addition of allyl bromide to the amino aldehyde.[72] The allyl bromide and anhydrous chromium (II) chloride react *in situ* with the aldehyde to form the corresponding homoallylic alcohol (Scheme 1.54). The reaction occurred in 59% yield with a ratio of 3:1 *syn: anti* as the reaction proceeds in favour of the chelation controlled Cram product. Treating **1.185** with HCl in dioxane followed by nosyl chloride in the presence of base generated alcohol **1.186** in 53% yield. The Mitsunobu reaction occurred in 48% yield to afford nosyl protected allylic aziridine **1.187**, in which only the *anti* diastereomer was isolated.

1.2.10. Attempted Cyclisations.

With a range of nosyl aziridines in hand we attempted the Lewis acid mediated cyclisations, anticipating that the cyclisation would occur onto the less reactive C-4 position of the indole ring. As Far *et al.* had reported the enantioselective and regioselective opening of nosyl aziridines by indoles mediated by boron trifluoride,[55] this was our Lewis acid of choice for the transformations.

Our first attempted cyclisation was with mesitylenesulfonyl protected indole **1.173**. We predicted that the mesitylenesulfonyl protecting group would show the same steric effect as the pivalamide in blocking the C-2 position of the indole ring and that the cyclisation would occur onto the C-4 position.



Reagents and conditions: a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 16 h, 20%.

Scheme 1.55

Aziridine **1.173** was treated with 1.5 equivalents of boron trifluoride affording cyclised material in 20% yield, in which only one diastereoisomer was isolated, suggesting that one of the diastereoisomers was more reactive in the cyclisation (Scheme 1.55). The crystal structure of the product showed that the cyclisation had occurred onto the C-2 position and that the *syn* diastereomer had been isolated. Therefore the mesitylenesulfonyl did not show the same steric blocking effect as the pivalamide.

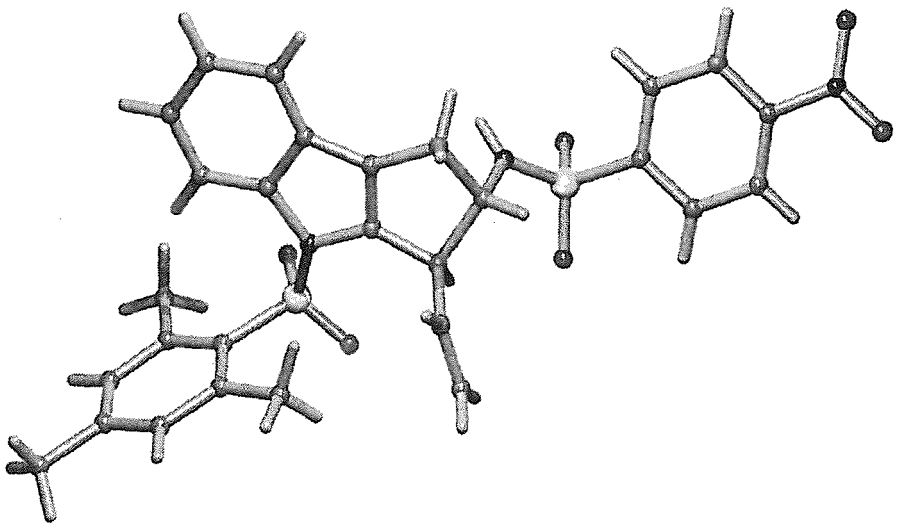
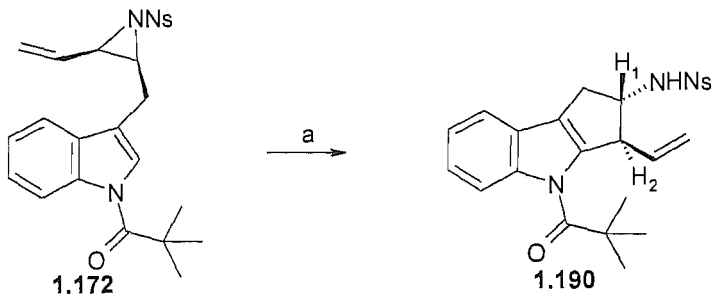


Figure 1.5 Crystal structure of **1.189** ***syn***

Efforts to cyclise the pivalamide protected nosyl aziridine with boron trifluoride resulted in cyclised material in 25% yield. According to the proton NMR the singlet corresponding to the C-2 proton of the indole ring had disappeared. This suggested that the unprecedented result of cyclisation onto the C-2 position had occurred and the pivalamide protecting group in this case did not effectively block the position. Only one diastereoisomer was observed, the coupling constant of H_1-H_2 was 2.4 Hz, corresponding to the *syn* diastereoisomer.

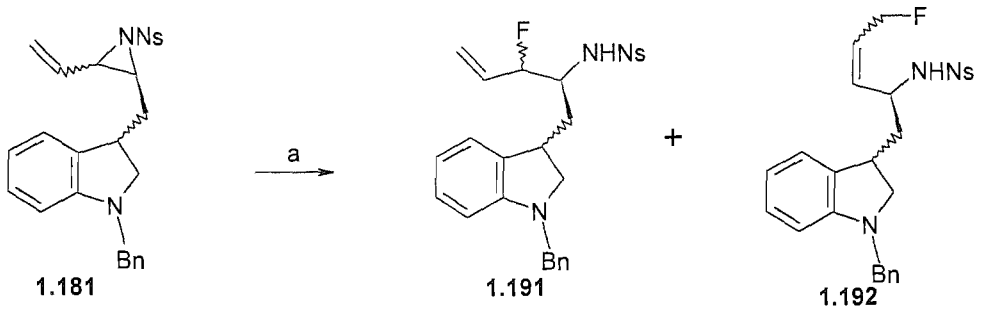


Reagents and conditions: a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 16 h, 25%.

Scheme 1.56

Attempts to perform the cyclisation with aluminium chloride and chloroacetyl chloride as an additive resulted in an unidentifiable product being isolated. The chloroacetyl chloride reacts with aluminium chloride *in situ* to generate a donor-acceptor complex species, which increases the steric bulk and hence the positional selectivity of the reaction.[73] Five aromatic resonances corresponding to the indole were present in the proton NMR, suggesting that no cyclisation had occurred. The resonances due to the vinyl protons had disappeared; therefore an isomerisation had taken place under the reaction conditions.

On attempting to cyclise the indoline derivative with boron trifluoride a complex mixture of products were formed in which fluorides **1.191** and **1.192** were isolated in trace amounts resulting from boron trifluoride acting as a nucleophilic source of fluoride. Indeed, Duhamel *et al.* have shown how boron trifluoride can be used as a fluorinating reagent in the opening of epoxides.[74] No cyclisation onto the C-4 position was observed.



Reagents and conditions: a) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 16 h.

Scheme 1.57

Efforts to cyclise allylic aziridine **1.186** resulted in an unidentifiable product. Due to the slightly increased steric encumbrance cyclisation onto the C-4 position was prevented but, according to the proton NMR all five protons from the indole were present, therefore no cyclisation had occurred. The resonances due to the olefin had changed to a 1:1 ratio, signifying that a rearrangement had occurred.

In the case with nosyl protected aziridines cyclisation onto the C-4 position of the ring is seemingly extremely unlikely. This result is apparent when cyclising indoline **1.181**. Even though there is no nucleophilic C-2 position, cyclisation onto the C-4 position of the indoline ring was not observed. Also in other examples where the

steric bulk is increased with chloroacetyl chloride as an additive or with allylic aziridine **1.187** no intramolecular cyclisation was detected.

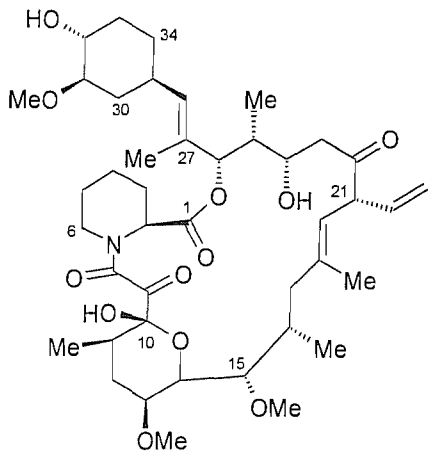
1.3. Conclusion and Future Work.

In conclusion a synthesis of the ergot alkaloid skeleton has been attempted from the amino acid tryptophan. We anticipated that the intramolecular Friedel-Crafts acylation of an *N*-pivaloyl indole would occur onto the unreactive C-4 position of the indole ring. In order to synthesise the precursor to the cyclisation a number of protecting group manipulations were required. An alternative to the Boc group was necessary due to the instability of the carbamate to the Lewis acid conditions of the cyclisation. A nosyl protecting group was chosen as it would facilitate the opening of the aziridine, but proved problematic in reactions preceding the Grignard addition. The cyclisation of nosyl aziridine **1.172** gave the unprecedented result of cyclisation onto the C-2 position of the indole ring. In the case with nosyl protected aziridines the C-4 position is apparently extremely unreactive. This was exemplified by the attempted cyclisation of indoline **1.181**. Instead of cyclisation onto the C-4 position the aziridine ring was opened by $BF_3{\cdot}OEt_2$ in which the Lewis acid acts as a source of fluoride. Also in further examples using chloroacetyl chloride and aluminium chloride, whereby the acid chloride reacts with aluminium chloride *in situ* to generate a donor-acceptor complex species as an electron acceptor, due to the increased steric bulk no reaction onto the C-2 position was observed. Instead of cyclising onto the C-4 position of the indole ring an isomerisation occurred. This was also observed when attempting to cyclise allylic aziridine **1.187**. Due to the slightly increased steric bulk compared to the vinyl aziridine, cyclisation onto the C-2 position was prevented, but instead of the predicted result of cyclisation onto the C-4 position, another type of isomerisation occurred. These results could be investigated further by changing the protecting group of the aziridine. The increased electron acceptance of the nosyl protecting group make the aziridine extremely labile to nucleophilic attack and isomerisation, this could be preventing cyclisation onto the unreactive C-4 position of the indole ring. Also attempting the reaction with a range of non-nucleophilic Lewis acids may lead to desired product formation. Efforts could also be made to change the indole protecting group for one which is more sterically encumbered. If successful the fourth ring could be composed *via* ring closing metathesis and following isomerisation will yield the ergot alkaloid skeleton.

2. Towards the Synthesis of Analogues of FK506.

2. 1. Introduction.

FK506 **2.1** is a powerful immunosuppressant used for the prevention and treatment of tissue rejection following organ transplant surgery. The complex 23-membered macrolide has been isolated from the fermentation broth of the soil actinomycete *Streptomyces tsukubaensis*.[75] The isolation and structure elucidation of FK-506 were reported by Tanaka and co-workers.[76] They discovered the macrocycle contained fourteen asymmetric centres, two trisubstituted olefins, amino acid and hemiketal-masked α,β-diketoamide functionalities. This array of challenging structural features as well as its biological potency have stimulated a considerable amount of interest in the synthetic community, rendering FK506 an ideal target for the development of new enantioselective processes in organic synthesis. To date, numerous total syntheses of FK-506 have been reported.[77-83] Although being a potent immunosuppressant the macrocycle has a level of toxicity that discourages its use as a drug.[84] Therefore a versatile synthesis of the immunosuppressant will provide a ready access to analogues that may be lower in toxicity.



2.1

Figure 2.1 FK506

2.1.1. Biological Activity.

FK506 produces its immunosuppressive effect by inhibiting T-cell activation.[85] The drug inhibits calcium dependent T cell growth induced by antigens using a receptor-mediated signal transduction pathway.[86] The receptor for FK506 is the immunophilin FKBP12, an enzyme which catalyses the interconversion of *cis* and *trans* amide bond rotamers adjacent to proline residues in peptidic substrates (Figure 2.2).[87] Once bound to the proline-binding site of FKBP12, FK506 inhibits its enzymatic activity. Enzymes which show this rotamase activity are known to play roles in a variety of cellular processes, for example the regulation of hetero-oligomeric complexes and protein trafficking.[88]

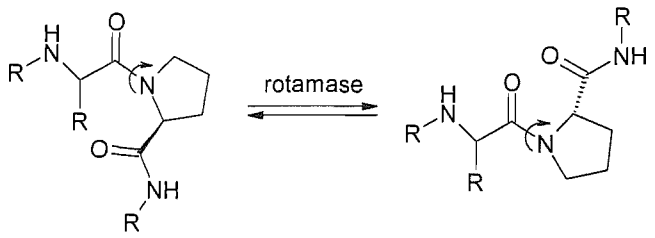


Figure 2.2 The interconversion of *cis* and *trans* amide bond rotamers

It was originally believed that FK506 achieved its immunosuppressive characteristics by inhibiting the rotamase activities of the FKBP12 enzyme alone. It is now known that the enzyme binds to FK506 and mediates its interactions with secondary protein targets. It is the complex of the drug with FKBP12 which is the active species.[87,88] Crystallographic and NMR analysis of FK506 and the binding protein, FKBP12, have shown the following observations 1) The conformation of FKBP12 is unchanged once bound to FK506; 2) The conformation of FK506 in complex with FKBP12 is extremely different to the conformation of the unbound drug observed in solution; 3) FK506 is not soluble in aqueous solution, but the complex is soluble, suggesting the bound complex may alter the intracellular dispersal of the drug; 4) Approximately half of FK506 is bound to FKBP12, the other half is exposed on the surface of the complex, where it can interact with target molecules.[85] Therefore FK506 contains two binding regions; an immunophilin binding region which binds to FKBP12 and an effector region which mediates interaction of the complex with the secondary protein target (Figure 2.3).[88]

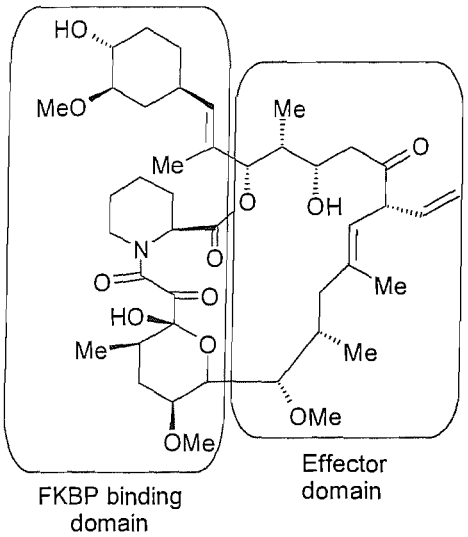


Figure 2.3 The two domains of FK506

It has been discovered that the FKBP12 enzyme is present in the brain at levels nearly 50 times higher than in the immune system.[89] The extraordinary high concentrations of the enzyme in the brain imply that neural functions of FK506 may be as important as its immunosuppressive activity, suggesting the drug could also be utilized for treating neurological disorders such as Parkinson's and Alzheimer's diseases.[89] Although FK506 shows activity against a range of disorders it has a level of toxicity that reduces its broader use as a drug. This toxicity includes nephrotoxicity, diabetogenic effects and neurological effects, for example headache, insomnia, tremors and lethargy.[85] Therefore interest has now focused on the synthesis of analogues of FK506 which may have increased activity and lower toxicity.

2.1.2. Synthetic Approaches.

It has been shown that FK-506 might be best constructed using a convergent synthesis where the molecule is divided into smaller fragments that can be synthesised separately and then joined together. Retrosynthetically, the trisubstituted olefins (C-19-C-20 and C-27-C-28) and the amide/ ester linkages are appropriate disconnection points. The cyclohexyl fragment, masked tricarbonyl portion and stereochemically complex C-21-C-26 and C-10-C-17 subunits have been popular synthetic targets. We were interested in a synthetic route to the C-26-C-34

cyclohexyl portion **2.2** which would be suitable as an appropriate building block to analogues of FK-506.

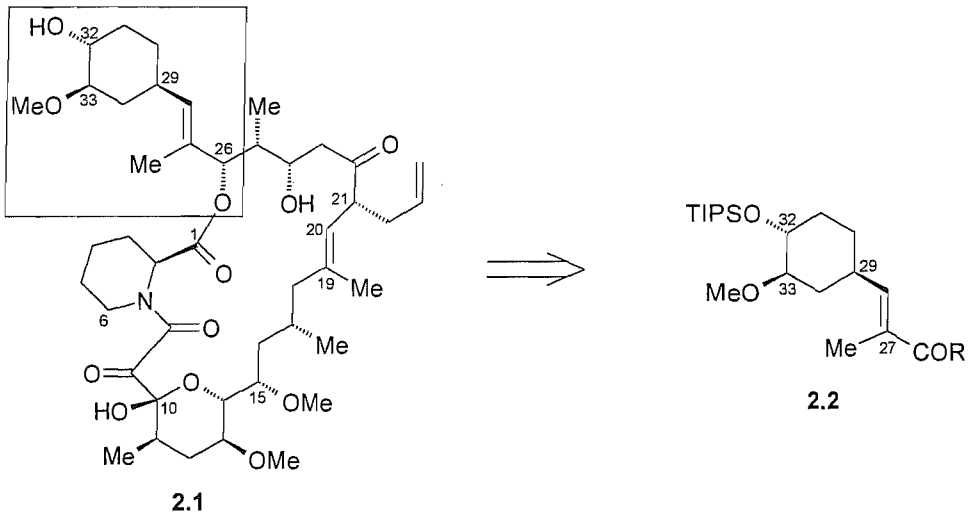


Figure 2.4 FK506 and the C-26-C-34 cyclohexyl fragment

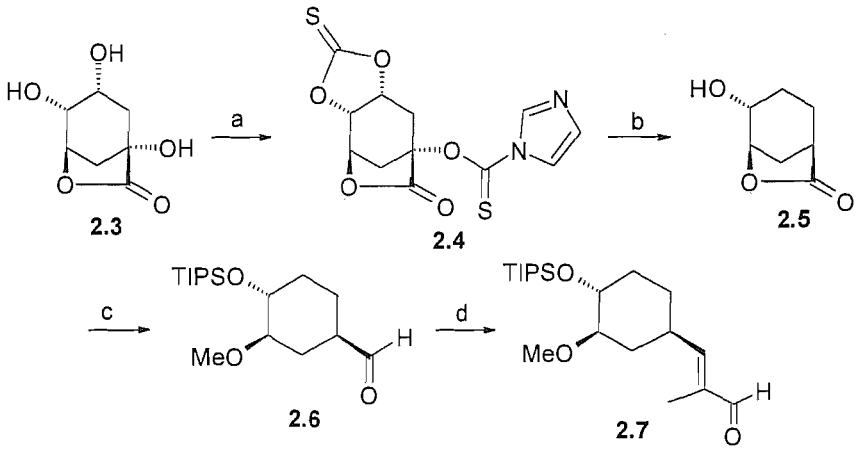
The fragment is composed of a 1,3,4-trisubstituted cyclohexyl ring which contains three chiral centres and is attached to the macrocycle through a trisubstituted alkene.

2.1.3. Previous Approaches to the C-26-C-34 Cyclohexyl Fragment.

2.1.3.1. Synthesis from Quinic acid.

The Merck process group devised a synthesis of the fragment utilizing D-(-)-quinic acid lactone **2.3** as an appropriate starting material (Scheme 2.1).[90] They observed that the stereochemistry of the C-29, C-31 and C-32 substituents of FK-506 corresponded to that of D-(-)-quinic acid, an inexpensive chiral starting material from nature. The unrequired hydroxyl groups at positions C-29 and C-33 could be stereospecifically and regioselectively cleaved under free radical conditions. Thus, lactone **2.3**, which is readily available from quinic acid,[91] was reacted with thiocarbonyl diimidazole to provide bis-adduct **2.4**. Reduction under free radical conditions with tributyltin hydride-AIBN afforded alcohol **2.5** in 40% yield. After protection as a TIPS ether, the lactone was opened with Weinreb's reagent, followed by methylation with methyl triflate and reduction with DIBAL-H to afford aldehyde

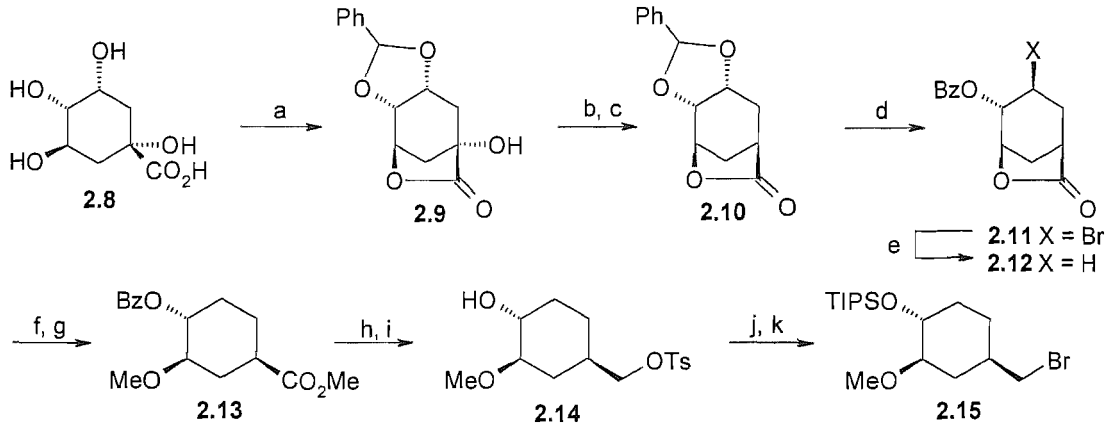
2.6. After reacting the aldehyde with 2-lithio-2-triethylsilylpropanal *t*-butylimine the C-26-C-34 fragment **2.7** was formed. It was later discovered that this procedure proved problematic on large scale, particularly in the radical reaction.[83]



Reagents and conditions: a) 1-1'-thiocarbonyldiimidazole, dichloroethane, reflux, 74%; b) tributyltin hydride, AIBN, xylene, reflux, 40%; c) i) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; ii) Me(MeO)NAlCl(Me), toluene; iii) MeOTf, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, 22-24 °C; iv) DIBAL-H, THF, -78 °C, 85% from **2.5**; d) 2-lithio-2-triethylsilylpropanal *t*-butylimine, THF, -78 °C to -10 °C, 78%.

Scheme 2.1

Rao and co-workers also synthesised the fragment using D-(-)-quinic acid as an appropriate starting material (Scheme 2.2).[92] Reacting D-(-)-quinic acid **2.8** with benzaldehyde under acidic conditions with catalytic PTSA led to the formation of both the benzylidene and the five membered lactone in a single step. Deoxygenation under radical conditions yielded lactone **2.10** which after regioselective opening of the benzylidene ring with *N*-bromosuccinimide and tin hydride reduction of the resulting bromide produced compound **2.12**. Opening of the lactone with methanol and catalytic potassium carbonate followed by functional group manipulation afforded tosylate **2.14**. Protection of the secondary hydroxyl group as a silyl ether and conversion of the primary tosylate to a bromide gave **2.15** which could be further reacted to compose the C-27-C-28 alkene.



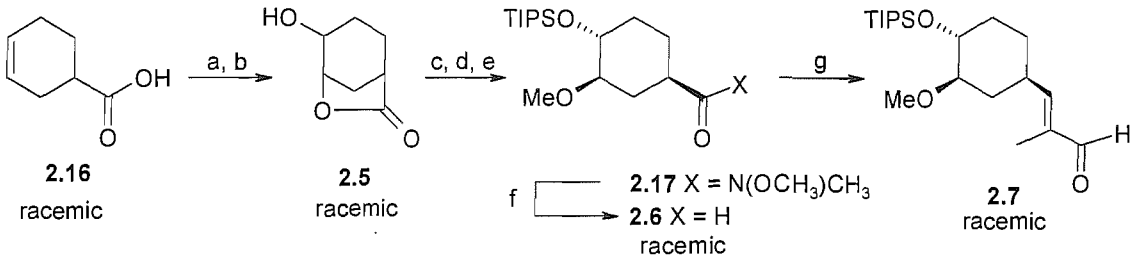
Reagents and conditions: a) PhCHO, PTSA, toluene, 70%; b) KH, CS_2, MeI, THF, 85%; c) Bu_3SnH, toluene, AIBN, 75%; d) NBS, benzene, AIBN, 80 °C, 85%; e) Bu_3SnH, AIBN, 80 °C, 80%; f) K_2CO_3, MeOH, 0 °C, 5 min, 85%; g) $MeOSO_2CH_3$, 2,4,6-*t*-butyl pyridine, $CHCl_3$, 89%; h) $LiAlH_4$, diethyl ether, 84%; i) TsCl, pyridine, CH_2Cl_2, 75%; j) TIPSOTf, 2,6-lutidine, 0 °C, 95%; K) LiBr, $NaHCO_3$, 95%.

Scheme 2.2

2.1.3.2. Synthesis from 3-Cyclohexenecarboxylic acid.

Many syntheses of the fragment involved starting from 3-cyclohexenecarboxylic acid **2.16**. This could be obtained in optically pure form either by resolution of the racemate or by an enantioselective Diels-Alder reaction.[84,93-95]

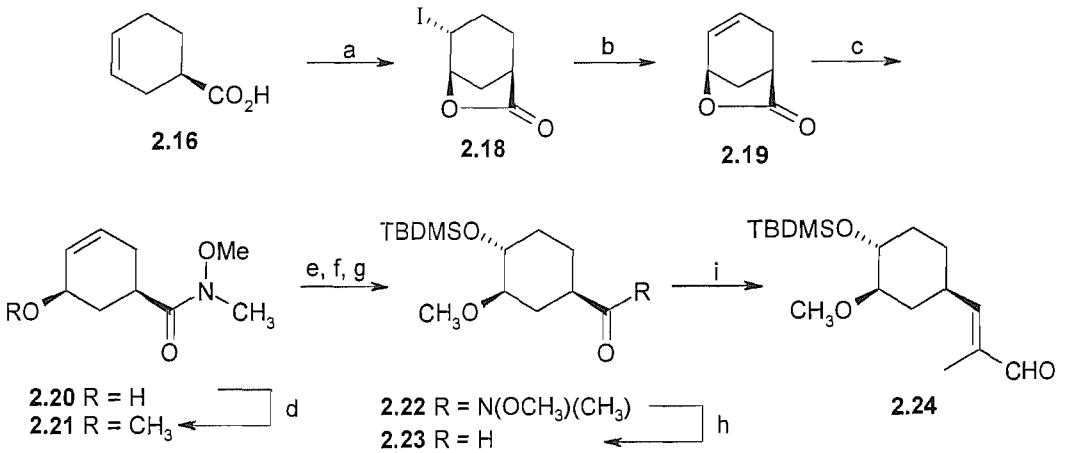
The Merck process group reported a convenient route to the fragment involving the *m*-CPBA epoxidation of commercially available racemic 3-cyclohexenecarboxylic acid **2.16** followed by high-dilution thermolysis in chlorobenzene (Scheme 2.3).[83] Under these conditions the *trans* epoxy acid cyclised to hydroxylactone **2.5**, which was separated from acidic side products by extraction. The synthesis of α,β-unsaturated aldehyde **2.7** was achieved following the same procedure as their original synthesis from quinic acid. The diastereoisomers were separated by flash chromatography at a later point following connection to the macrocyclic backbone.



Reagents and conditions: a) *m*-CPBA, CH_2Cl_2, 0 °C; b) chlorobenzene, 130 °C; 30% from **2.16**; c) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C; d) Me(MeO)NAl(Me)Cl, toluene, 20 °C; e) CH_3OTf, 2,6-di-*t*-butyl-4-methylpyridine, CH_2Cl_2, 20 °C; f) DIBAL-H, THF, -78 °C; g) 2-lithio-2-(triethylsilyl)propanal, *N*-cyclohexylimine, THF, -20 °C, TFA, THF, 0 °C, 68% from **2.5**.

Scheme 2.3

It was later discovered that the epoxidation of optically pure 3-cyclohexenecarboxylic acid **2.16** gave a 3:1 ratio of diastereoisomers,[85] which would later prove problematic to separate, whereas iodolactonisation of optically pure **2.16** gave only one product. Kocienski *et al.* utilised this procedure in their synthesis of the fragment (Scheme 2.4).[96]



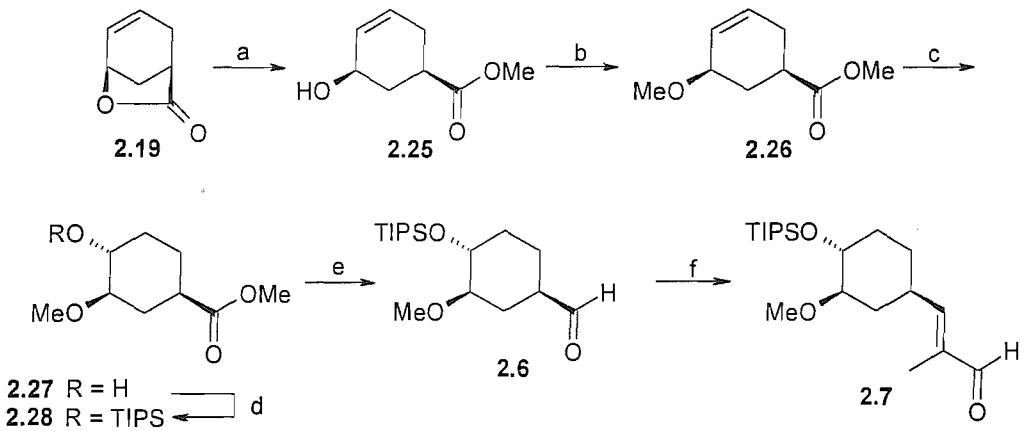
Reagents and conditions: a) I_2, KI, 96%; b) DBU, THF, 92%; c) Me(MeO)NAlCl(Me), benzene, 91%; d) CH_3OTf, 2,6-di-*t*-butyl-4-methylpyridine, 77%; e) BH_3·THF, THF; f) NaOH, H_2O_2; g) TBDMSOTf, 2,6-lutidine, 48% from **2.21**; h) DIBAL-H, THF, -78 °C, 98%; i) 2-lithio-2-(triethylsilyl)propanal, *N*-cyclohexylimine, THF, -20 °C, TFA, 73%.

Scheme 2.4

Kocienski's synthesis began with (*R*)-cyclohexenecarboxylic acid **2.16** obtained in optically pure form using an enzymatic resolution with pig liver esterase. After iodolactonisation with iodine and potassium iodide and elimination with DBU,

lactone **2.19** was opened with Weinreb's reagent followed by methylation with methyl triflate. The C-32 hydroxyl was introduced *via* a hydroboration reaction, this occurred both with high regio- and stereoselectivity where only minor amounts (<5%) of stereoisomeric side products were obtained. Protection as a TBDMS ether followed by reduction with DIBAL-H furnished aldehyde **2.23** which when reacted with 2-lithio-2-(triethylsilyl)propenal, *N*-cyclohexylimine followed by isomerisation with TFA to afford the C-26-C-34 fragment **2.24**.

Marshall *et al.*[93] devised a synthesis similar to that of Kocienski and co-workers (Scheme 2.5). Carboxylic acid **2.16** was obtained by an enantioselective Diels-Alder reaction, which after the same iodolactonisation and elimination sequence afforded lactone **2.19**. Opening of the lactone with sodium carbonate in methanol followed by methylation, hydroboration and protection as a TIPS ether afforded ester **2.28** which was reduced with DIBAL-H to its corresponding aldehyde **2.6** and reacted with 2-lithio-2-(triethylsilyl)propenal, *N*-*t*-butylimine to yield the C-26-C-34 fragment of FK-506.

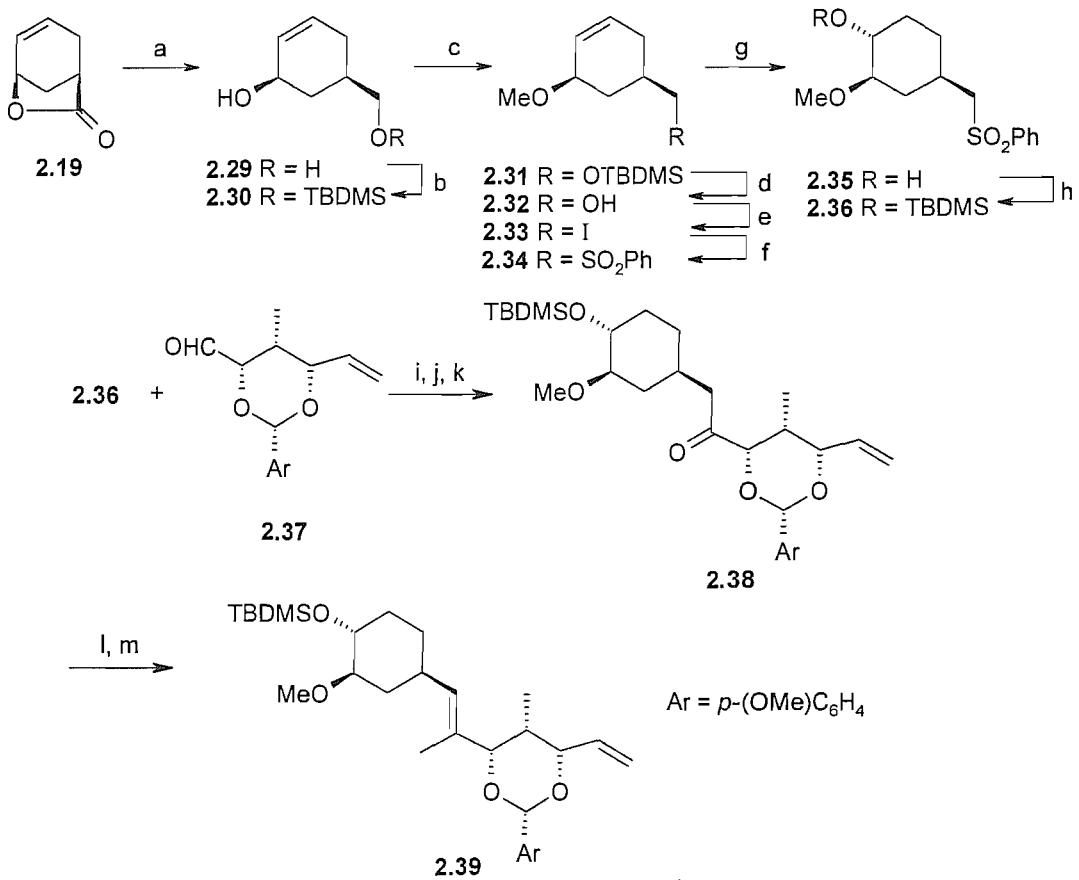


Reagents and conditions: a) $NaHCO_3$, MeOH, 94%; b) 2,6-di-*t*-butyl-4-methylpyridine, MeOTf, CH_2Cl_2, 0 °C, 86%; c) BH_3·THF, H_2O_2, NaOH, 87%; d) TIPSOTf, Et_3N, CH_2Cl_2, 0 °C, 91%; e) DIBAL-H, 89%; f) 2-lithio-2-(triethylsilyl)propenal, *N*-*t*-butylimine, THF, TFA, 93%.

Scheme 2.5

Danishefsky and co-workers employed the same iodolactonisation/ elimination route to afford lactone **2.19** (Scheme 2.6).[97] The reductive opening of lactone **2.19** with $LiAlH_4$ followed by the selective protection of the primary alcohol as a TBDMS ether provided alcohol **2.30**. After methylation of the secondary alcohol, cleavage of

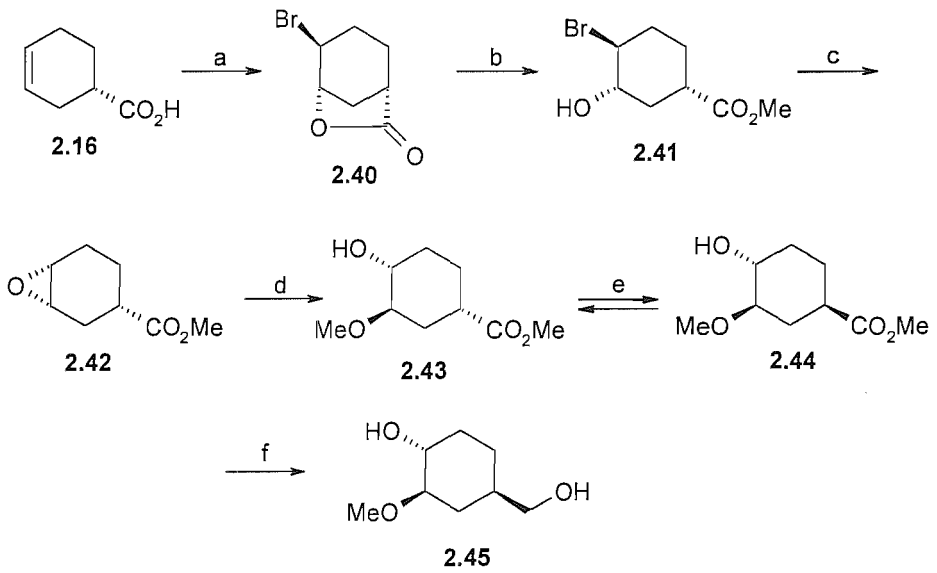
the silyl protecting group afforded alcohol **2.32**. The alcohol was converted to an iodide with triphenylphosphine, iodine and imidazole which when reacted with sodium phenylsulfinate in DMF yielded sulfone **2.34**. The C-32 hydroxyl was introduced regio and stereoselectively by a hydroboration reaction which following protection as a silyl ether provided sulfone **2.36**. Compound **2.36** was coupled with aldehyde **2.37**, which following Dess-Martin oxidation and reduction with lithium naphthalide gave ketone **2.38.** The tertiary alcohol obtained from the addition of methylmagnesium bromide to **2.39** was eliminated using Burgess' reagent to the C-27-C-28 olefin.[78]



Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 81%; b) TBDMSCl, DMF, imidazole, 0 °C, 65%; c) NaH, MeI, THF, 82%; d) HF-CH_3CN, Et_2O, 82%; e) PPh_3, I_2, imidazole, benzene, 75%; f) $PhSO_2Na$, DMF, 80%; g) $BH_3 \cdot SMe_2$, THF, H_2O_2, NaOH, 60%, h) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 77%; i) BuLi, THF, -78 °C; j) Dess-Martin periodinane, pyridine, CH_2Cl_2; k) lithium naphthalenide, THF, 58% from **2.36**; l) MeMgBr, THF, 0 °C; m) Burgess' salt, benzene, 40 °C, 76% from **2.38**.

Scheme 2.6

Crotti and co-workers began their synthesis of the fragment from (*S*)-3-cyclohexanecarboxylic acid instead of the commonly used (*R*) form, and utilised an epimerisation reaction to give the required stereochemistry (Scheme 2.7).[98] The (*S*) carboxylic acid was synthesised by an asymmetric Diels-Alder reaction. Treatment of **2.16** with bromine in the presence of Et_3N gave bromolactone **2.40** in 80% yield. Reacting **2.40** with acidic methanol provided bromohydrin **2.41** which following base treatment with NaOH afforded the *cis* epoxide **2.42**. The epoxide was opened by acid methanolysis followed by epimerisation to afford **2.44** in which all substituents of the ring are in the most stable equatorial conformation. Ester **2.44** was reduced to diol **2.45** which as shown by Danishefsky, could be further elaborated to provide the C-27-C-28 olefin.



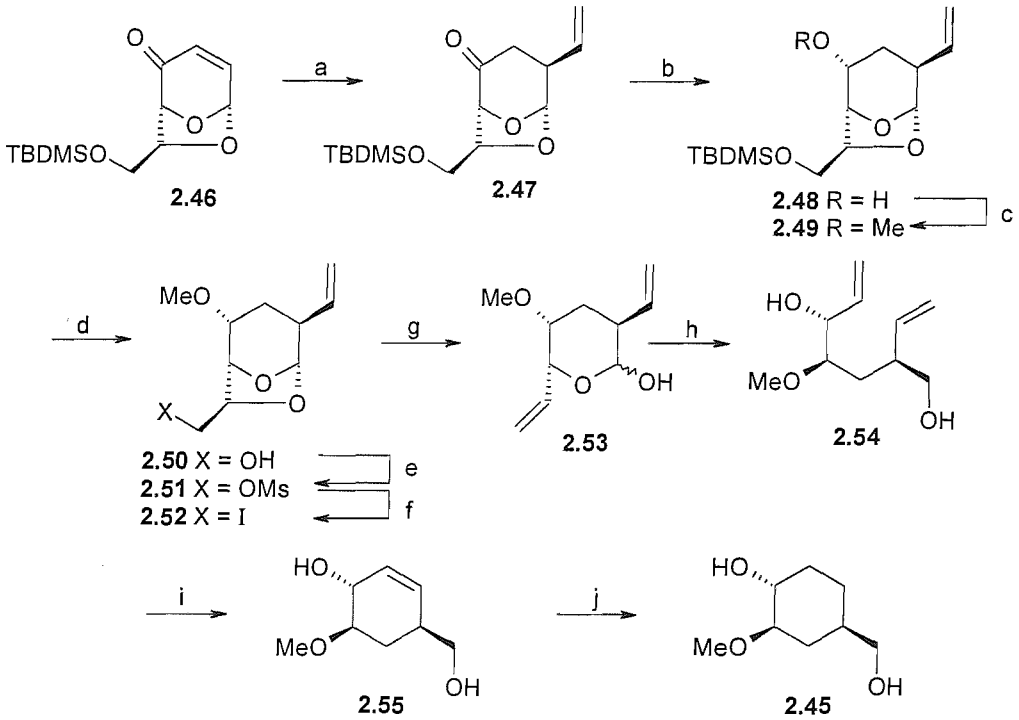
Reagents and conditions: a) Br_2, $CHCl_3$, Et_3N, 0 °C, 80%; b) H_2SO_4, CH_3OH, reflux, 95%; c) NaOH, *i*-PrOH, 85%; d) H_2SO_4, CH_3OH, 70 %; e) CH_3ONa, CH_3OH, 140 °C, 65%; f) $LiAlH_4$, diethyl ether, 100%.

Scheme 2.7

2.1.3.3. Synthesis from an Acyclic Precursor.

The C-26-C-34 fragment of FK506 has also been synthesised from acyclic precursors where the cyclohexyl ring is constructed by an intramolecular cyclisation and the chirality is set before ring closure.

Ogasawara and co-workers developed a synthesis of the fragment using ring closing metathesis (Scheme 2.8) to compose the cyclohexyl ring.[99] The building block **2.46** was synthesised using either a catalytic or enzymatic procedure.

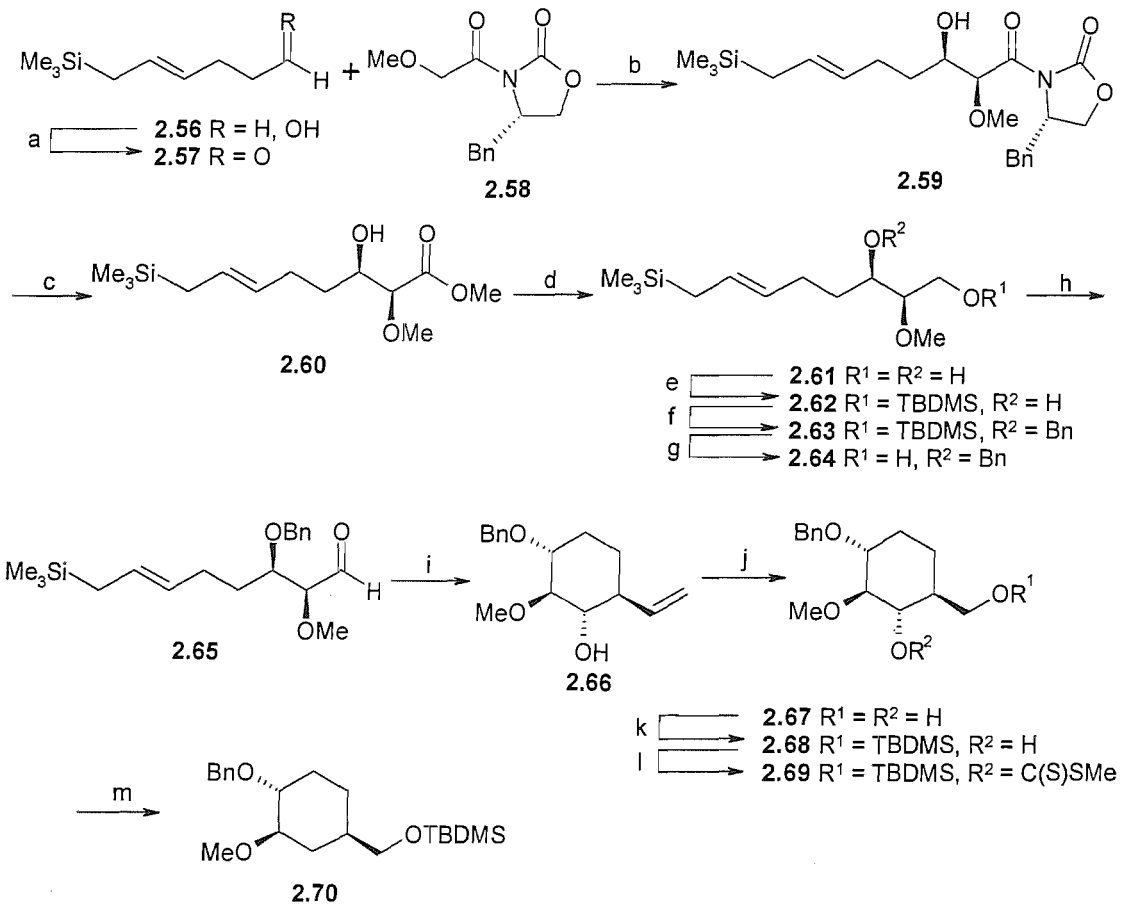


Reagents and conditions: a) Vinyl MgCl, $CuBr{\cdot}SMe_2$, HMPA, THF, -78 °C, 77%; b) $NaBH_4{\cdot}CeCl_3.7H_20$, MeOH, -30 °C; c) MeI, NaH, THF, 0 °C-rt, 77% from **2.47**; d) TBAF, THF, 95%; e) MsCl, Et_3N, CH_2Cl_2, 0 °C-rt; f) LiI, THF, reflux, 90% from **2.50**; g) Zn, AcOH: MeOH (1:10 v/v); h) $LiAlH_4$, THF, 0 °C, 81% from **2.52**; i) Grubbs' reagent (10 mol%), CH_2Cl_2, reflux; j) H_2, PtO_2, EtOAc, 87% from **2.54**.

Scheme 2.8

The conjugate addition with vinyl cuprate occurred on the unhindered convex face of the molecule to provide ketone **2.47** as the major product. The reduction with sodium borohydride was also diastereoselective due to the steric effect of the vinyl group. Methylation with methyl iodide followed by cleavage of the silyl protecting group and conversion of the alcohol to the iodide *via* the mesylate afforded **2.52**. Reductive cleavage with zinc in methanolic acetic acid gave **2.53** which was reduced with $LiAlH_4$ to yield diol **2.54** with two vinyl functionalities. Ring closing metathesis with Grubbs's catalyst generated **2.55** which after reduction to diol **2.45** could be further manipulated to afford the C-27-C-28 olefin.

Maier *et al.*[100] formed the cyclohexyl ring *via* an intramolecular ene-type cyclisation of an allylsilane aldehyde (Scheme 2.9). The chirality was set prior to ring closure using Evans aldol chemistry.

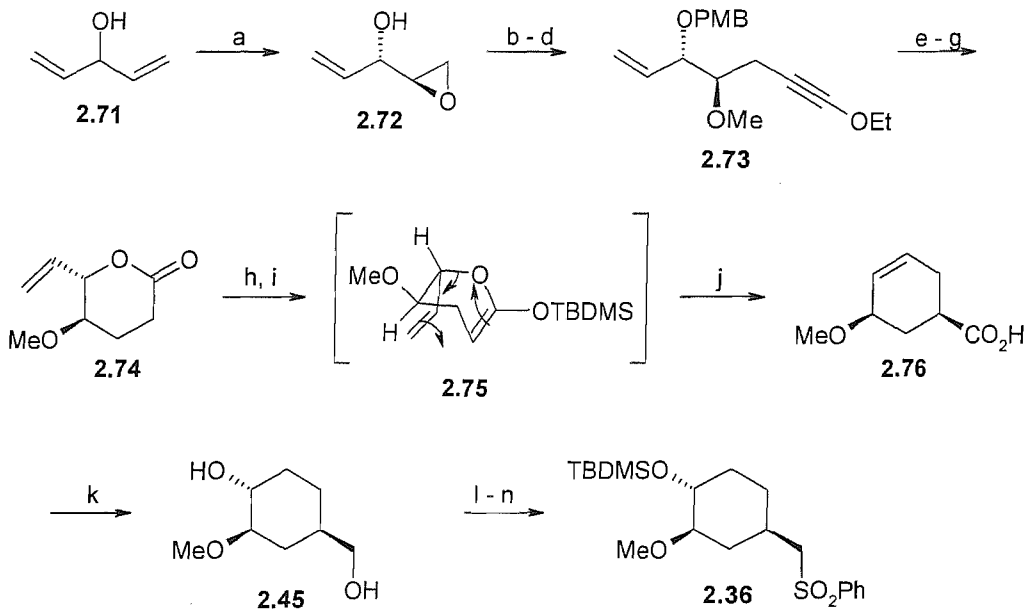


Reagents and conditions: a) DMSO, $(COCl)_2$, NEt_3, -70 °C, 90%; b) **2.58** , Et_3N, Bu_2OTf, CH_2Cl_2, -78 °C, add **2.57**, -78 to -40 °C, 89%; c) MeMgBr, MeOH, 0 °C, 82%; d) $LiAlH_4$, Et_2O, 0-20 °C, 84%; e) imidazole, TBDMSCl, CH_2Cl_2, 96%; f) BnBr, NaH, DMF, 0-20 °C, 73%; g) PPTS, MeOH, 50 °C, 84%; h) DMSO, $(COCl)_2$, NEt_3, CH_2Cl_2, -60 °C, quant; i) $BF_3{\cdot}OEt_2$, CH_2Cl_2, -78 °C, 82%; j) O_3, CH_2Cl_2/MeOH (4:1), -78 °C, then $NaBH_4$ in H_2O/MeOH, 0-40 °C, 90%; k) imidazole, TBDMSCl, CH_2Cl_2, 88%; l) NaH, CS_2, MeI, 70 °C, 87%; m) Bu_3SnH, AIBN, toluene, 110 °C, 92%.

Scheme 2.9

The boron mediated aldol condensation between aldehyde **2.57** and oxazolidinone **2.58** occurred in 89% yield with greater than 96% diastereoselectivity. The auxiliary was cleaved by transesterification of adduct **2.59** with magnesium methoxide in methanol, which was then reduced to diol **2.61** with $LiAlH_4$. After protection of the primary alcohol as a silyl ether the secondary alcohol was protected as a benzyl ether. Following selective cleavage of the primary silyl ether, the resulting alcohol was oxidised to its corresponding aldehyde which under Lewis acid conditions with $BF_3{\cdot}OEt_2$ underwent an intramolecular ene-type cyclisation to afford the cyclohexane ring **2.66**. After ozonolysis and subsequent reduction with $NaBH_4$, the resulting alcohol was protected as a TBDMS ether. The unrequired alcohol at C-30 was reductively cleaved under free radical conditions to afford the cyclohexyl fragment of FK506 **2.70**.

Schreiber *et al.*[101] synthesised the C-26-C-34 fragment of FK506 using a stereospecific Ireland-Claisen rearrangement (Scheme 2.10). The correct chirality was introduced by a Sharpless asymmetric epoxidation of divinyl carbinol **2.71**. The epoxy alcohol was protected as a *p*-methoxybenzyl ether and the epoxide was regioselectively opened with ethoxyacetylene and methylated to afford **2.73**. After ethanolysis with ethanol and catalytic $HgCl_2$ the *p*-methoxybenzyl ether was oxidatively deprotected to give the δ-hydroxy ester which was cyclised to lactone **2.74** with *p*-TsOH. The Ireland-Claisen rearrangement was induced by treating with TBDMSOTf followed by heating in toluene to provide carboxylic acid **2.76**. Hydroboration both regio and stereoselectively introduced the C-32 hydroxyl group and reduced the carboxylic acid to diol **2.45**. After conversion of the primary alcohol to the phenyl sulfone *via* the iodide the secondary alcohol was protected as a silyl ether to give **2.36** which as previously shown could be elaborated to construct the C-27-C-28 olefin.



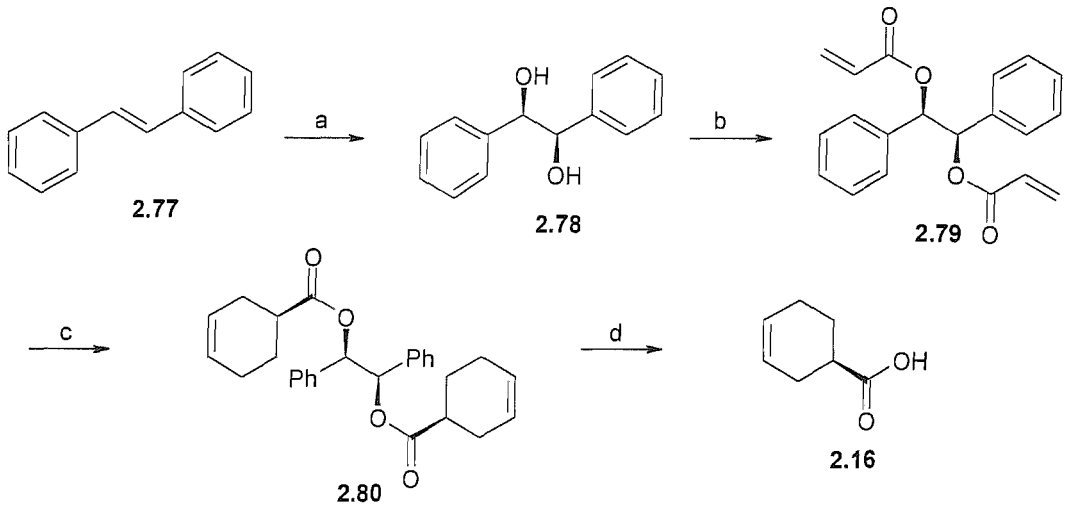
Reagents and conditions: a) Sharpless asymmetric epoxidation, 55%; b) PMBBr, NaH, THF, 95%; c) EtOCCLi, $BF_3 \cdot OEt_2$, d) MeI, NaH, 87%; e) $HgCl_2$, EtOH; f) DDQ, 78%; g) *p*-TsOH, benzene, 85%; h) TBDMSOTf, Et_3N; i) toluene, 110 °C; j) THF, HCl, 71% from **2.74**; k) $BH_3 \cdot THF$, H_2O_2, 79%; l) I_2, PPh_3; m) $PhSO_2Na$; n) TBDMSOTf, Et_3N, 59% from **2.45**.

Scheme 2.10

2.2. Results and Discussion.

2.2.1. Synthesis from (*R*)-3-Cyclohexenecarboxylic acid.

Our initial synthesis of the C-26-C-34 fragment of FK506 began following the procedure of Marshall *et al.*[93] (*R*)-3-cyclohexenecarboxylic acid **2.16** was prepared in optically pure form by an asymmetric Diels-Alder reaction of bis-acrylate **2.79** with 1,3-butadiene followed by saponification of bis-adduct **2.80** (Scheme 2.11).

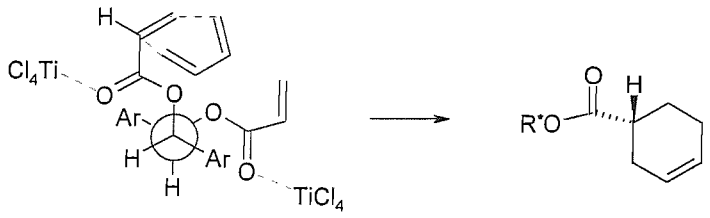


Reagents and conditions: a) $(DHQD)_2$-PHAL, $K_2OsO_2(OH)_4$, NMO, *t*-BuOH, 3 h, 97%; b) acryloyl chloride, CH_2Cl_2, 0 °C, 20 min; c) 1,3-butadiene, $TiCl_4$, CH_2Cl_2, -20 °C, 3 days, 44%; d) LiOH, MeOH, H_2O, 7 h, 91%.

Scheme 2.11

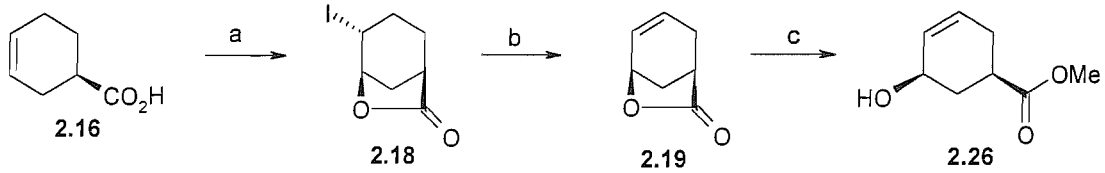
The requisite diol **2.78** was prepared by the dihydroxylation of *trans*-stilbene **2.77**, following the procedure of Sharpless *et al.*, with potassium osmate (VI) dihydrate and the chiral ligand $(DHQD)_2$-PHAL.[102] *N*-methylmorpholine-*N*-oxide was used as a co-oxidant allowing potassium osmate (VI) dihydrate to be used in catalytic quantity. The reaction is enantioselective; the chiral alkaloid directs the OsO_4 to dihydroxylate from the top face of the double bond, leading to the formation of (*R, R*)-hydrobenzoin in 97% yield. On obtaining diol **2.78** the route to ester **2.32** was continued following the synthesis of Marshall *et al.*[93] Bis-acrylate **2.79** was prepared by the esterification of (*R,R*)-hydrobenzoin **2.78** with acryloyl chloride. This resulted in a yield greater than 100% as the product was contaminated with $Et_3N{\cdot}HCl$. The

crude product could not be purified, due to the instability of bis-acrylate **2.79**. The diastereoselective Diels-Alder reaction of **2.79** with 1,3-butadiene using titanium tetrachloride as a Lewis acid gave bis-adduct **2.80** in low yield. The low temperatures suggested in the literature could not be achieved for a period of three days. This was essential as bis-acrylate **2.79** polymerises at room temperature and 1,3-butadiene boils at –5 °C and is very low in polarity. It escapes easily even at sub-boiling point during a multiple day process. The correct conditions are also critical for the selectivity of the reaction. Due to steric encumbrance the phenyl groups prefer an *anti* conformation, therefore a transition state depicted in scheme 2.12 accounts for the facial selectivity of the cycloaddition.



Scheme 2.12

Saponification of bis-adduct **2.80** with LiOH in aqueous methanol provided carboxylic acid **2.16** in 91% yield. Iodolactonisation[103] of carboxylic acid **2.16** with iodine and potassium iodide followed by elimination of the axial iodide with DBU gave lactone **2.19** in 85% yield (Scheme 2.13).

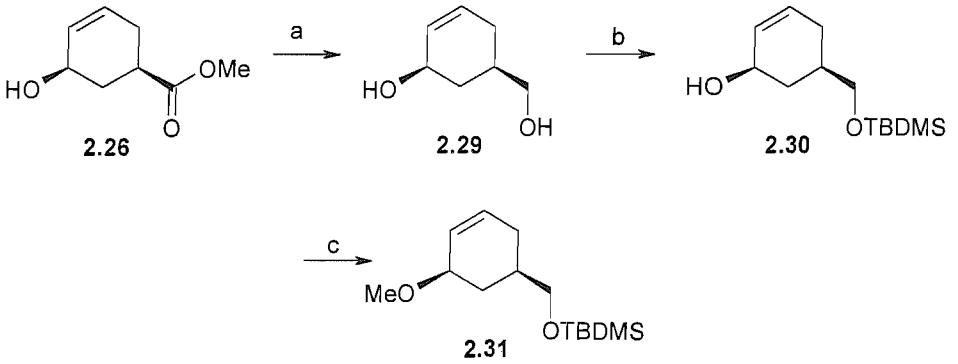


Reagents and conditions: a) $NaHCO_3$, I_2, KI, 24 h, 84%; b) DBU, THF, reflux, 7 h, 85%; c) $NaHCO_3$, MeOH, 15 h, 30%.

Scheme 2.13

Lactone **2.19** was opened by treatment with $NaHCO_3$ and methanol, providing ester **2.26** in 30% yield. Ester **2.26** was reduced with lithium aluminium hydride forming the crude diol **2.29** which was used in the next reaction without purification. Diol **2.29** was selectively protected with *t*-butyldimethylsilyl chloride before being

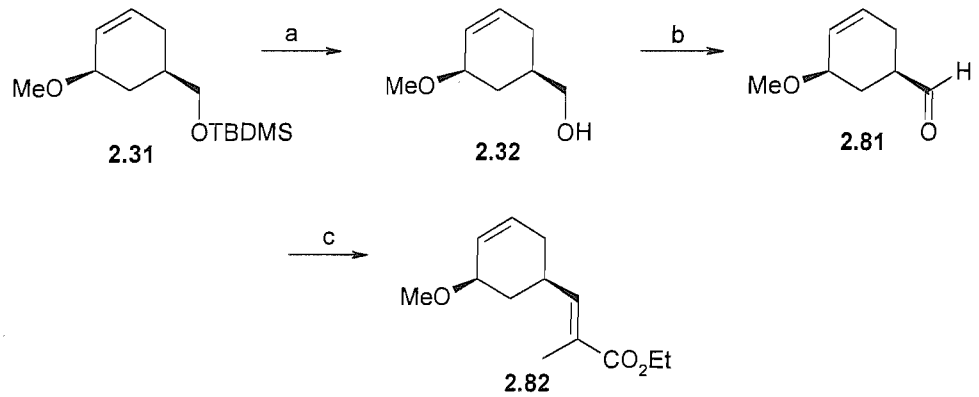
methylated with methyl iodide and sodium hydride to provide methyl ether **2.31** in modest yield (Scheme 2.14).



Reagents and conditions: a) $LiAlH_4$, THF, 0 °C, 1 h; b) imidazole, TBDMSCl, DMF, 5 h, 47% from **2.26**; c) NaH, MeI, THF, 4.5 h, 84%.

Scheme 2.14

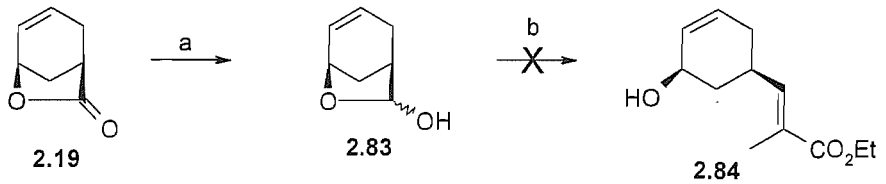
Cleavage of the silyl protecting group using TBAF[93] was accomplished to afford alcohol **2.32** in 77% yield (Scheme 2.15). Alcohol **2.32** was oxidised to the corresponding aldehyde using Swern oxidation[104] conditions. The Wittig reaction[105] of **2.81** with the stabilised ylid, (1-ethoxycarbonyethylidene)triphenylphosphorane, was *E* selective, providing **2.82** in 60% yield.



Reagents and conditions: a) TBAF, THF, 5 h, 77%; b) Oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -30 °C, 4 h, 33%; c) (1-ethoxycarbonyethylidene)triphenylphosphorane, THF, reflux, 3 days, 60%.

Scheme 2.15

Attempts were made to decrease the length of the overall synthesis by reducing lactone 2.19 with DIBAL-H followed by the Wittig reaction of lactol 2.83 with (1-ethoxycarbonyethylidene)triphenylphosphorane (Scheme 2.16).



2.19 2.83 2.84

Reagents and conditions: a) DIBAL-H, CH_2Cl_2, -78 °C, 17 h; b) (1-ethoxycarbonyethylidene) triphenylphosphorane, CH_2Cl_2, reflux, 24 h.

Scheme 2.16

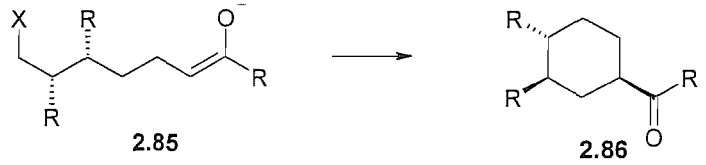
Performing the reaction without isolating lactol **2.83** gave a small amount of product, although spectroscopic data was not consistent with the structure of diene **2.84**. ^{13}C NMR and infrared data showed the presence of two carbonyl resonances. When attempting to isolate **2.83** prior to the Wittig reaction it was found that lactone **2.19** was also over reduced to diol **2.29**. This occurred on using both one and two equivalents of DIBAL-H. The ^{1}H and ^{13}C NMR spectra of lactol **2.83** were very complex as the compound exists as both the aldehyde and epimerized lactols.

In summary, while the majority of literature routes employ optically pure carboxylic acid **2.16** a lengthy sequence of steps is needed to introduce the alcohol functional group into the ring. The route was also not convenient as the conditions required for the synthesis of **2.16** could not be achieved. For these reasons we decided to investigate a new strategy for the synthesis of the fragment from an acyclic precursor.

2.2.2. Synthesis from an Acyclic Precursor.

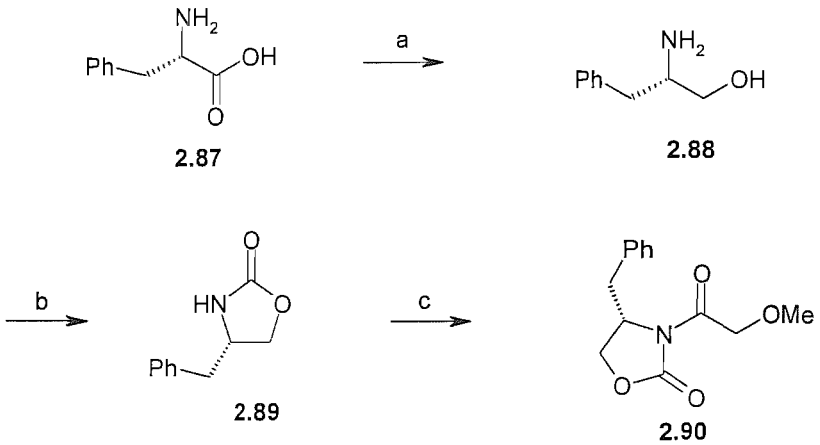
We envisaged that the C-22 to C-34 fragment of FK-506 could be synthesised in a different fashion with the cyclohexyl ring being constructed at the end by an intramolecular S_N2 displacement. Thus, powerful modern methods for acyclic stereoselection would be used to set the chiral centres prior to ring closure. In particular, we planned to employ Evans aldol chemistry. Maier *et al.* used Evans

aldol chemistry in their synthesis of the fragment although their route was lengthy due to a long sequence of protecting group manipulations and cleavage of the unrequired hydroxyl group at C-30 (Scheme 2.9).[100] We intended to compose the cyclohexyl ring by an intramolecular S_N2 alkylation of an enolate. It was anticipated that the molecule would epimerize to the most stable conformation with all substituents in equatorial positions (Scheme 2.17), if successful no unrequired functional groups would have to be cleaved and no long sequence for protecting group manipulations would be required.



Scheme 2.17

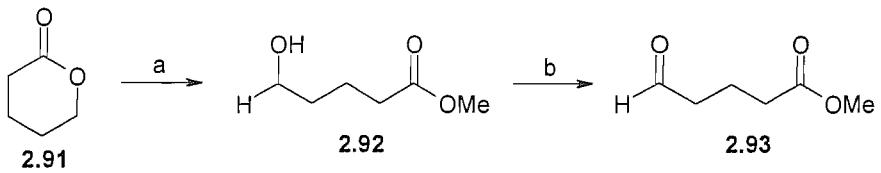
The prerequisite oxazolidinone was prepared according to scheme 2.18, following the procedure of Evans *et al.*[106,107]



Reagents and conditions: a) $BF_3{\cdot}OMe_2$, $BH_3{\cdot}SMe_2$, THF, reflux, 14 h, 70 %; b) $CO(OEt)_2$, K_2CO_3, reflux, 2 h, 70%.

Scheme 2.18

Acylated oxazolidinone **2.90** was reacted with ester **2.93**, prepared by the opening of δ-valerolactone **2.91** with methanol in the presence of sulfuric acid, followed by oxidation by PCC (Scheme 2.19).[108,109]



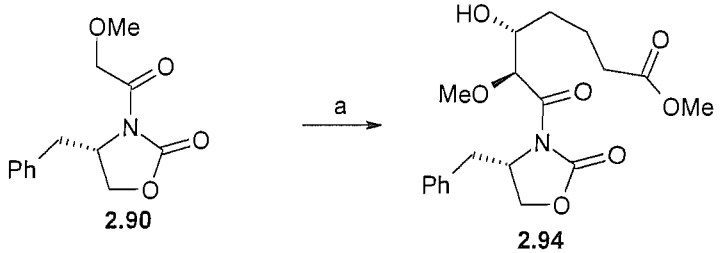
2.91 2.92 2.93

Reagents and conditions: a) MeOH, H_2SO_4, reflux, 4 h, quant; b) PCC, CH_2Cl_2, 2 h, 83%.

Scheme 2.19

On our first attempt at opening δ-valerolactone **2.91** with methanol, an aqueous workup with sat. $NaHCO_3$ was employed which caused lactonisation of the product. Therefore the reaction was quenched with anhydrous $NaHCO_3$ and the crude material was carried on to the next reaction without purification, as distillation would also have led to the re-formation of δ-valerolactone **2.91**. The formation of hydroxyester **2.92** was elucidated by the presence of an O-H stretch in the infrared spectrum. The oxidation of hydroxyester **2.92** with PCC proceeded smoothly providing aldehyde **2.93** in 83% yield.

The boron-mediated aldol condensation[106,110] between oxazolidinone **2.90** and aldehyde 2.**93** occurred in 81% yield. Only one diastereoisomer was observed according to the ^{1}H NMR (Scheme 2.20).

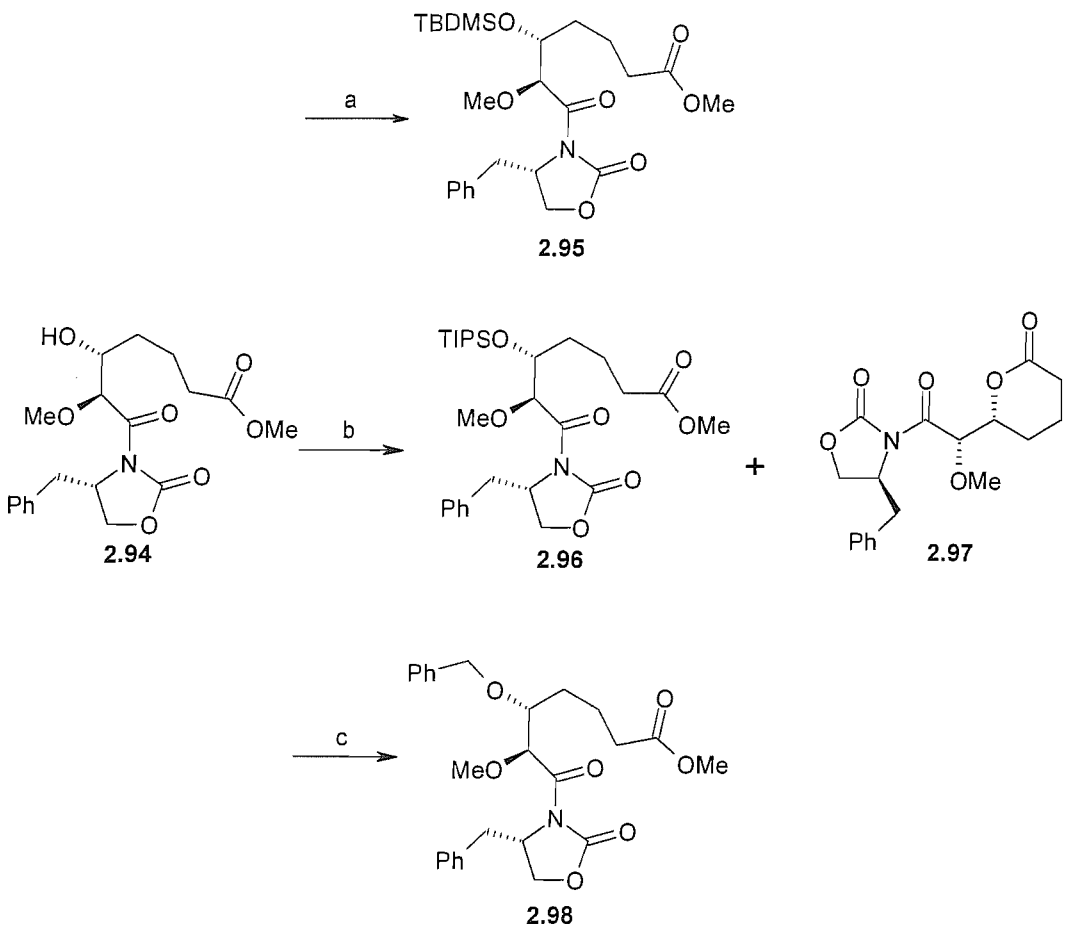


2.90 2.94

Reagents and conditions: a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C then **2.93**, -65 °C 20 minutes, then 0 °C, 1 h, 81%.

Scheme 2.20

Before reductively removing the chiral auxiliary, the free hydroxyl group of **2.94** had to be protected to prevent interference in further reactions (Scheme 2.21). Attempts to protect with *t*-butyldimethylsilyl chloride in the presence of imidazole[111] were unsuccessful. Protected product **2.95** was afforded in only 2% yield, suggesting more forceful conditions would be required.



Reagents and conditions: a) imidazole, TBDMSCl, CH_2Cl_2, 15 h, 2%; b) 2,6-lutidine, TIPSOTf, CH_2Cl_2, 0 °C, 30 minutes, then, rt 1 h, **2.96** 18%, **2.97** 17%; c) benzyl-2,2,2-trichloroacetimidate, triflic acid, 3 days, 35%.

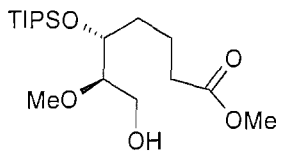
Scheme 2.21

Attempting to protect the free alcohol with triisopropylsilyl triflate under basic conditions with 2,6-lutidine[112] led to the formation of two products, silyl protected **2.96** and lactone **2.97**. The ^{13}C NMR spectrum of silyl ether **2.96** showed several resonances had doubled up, implying that the molecule may have epimerised or contain rotamers. Under the basic conditions of the reaction an intramolecular cyclisation also occurred producing lactone **2.97**. The lactone co-eluted with the starting material and consequently only 17% was isolated in pure form along with a small amount present in a mixture with recovered staring material. The inseparable mixture was heated in methanol with catalytic sulfuric acid,[108,109] from which starting material **2.94** was recovered in 40% yield. Attempts were made to protect **2.94** as a triethylsilyl ether using both TESCl[113] and TESOTf.[113,114] These procedures were also unsuccessful and no protected product was isolated. In order to prevent the

intramolecular cyclisation under basic conditions oxazolidinone **2.94** was protected as a benzyl ether under acidic conditions. The reaction with benzyl-2,2,2-chloroacetimidate in the presence of catalytic triflic acid[115] afforded protected product **2.98** in 35% yield.

The opening of oxazolidinone **2.97** with methanol and concentrated sulfuric acid was also performed on the pure isolated cyclised product affording oxazolidinone **2.94** in 83% yield, hence proving that cyclised product can easily be recycled.

Efforts were made to reductively cleave the chiral auxiliary from oxazolidinone **2.96** with aqueous sodium borohydride in THF.[116] The ^{1}H and ^{13}C NMR spectra corresponding to **2.99** were very complicated, some of the resonances had doubled up and there were many peaks corresponding to the silyl ether. This may be due to migration of the protection group, or presence of an impurity difficult to remove by column chromatography.

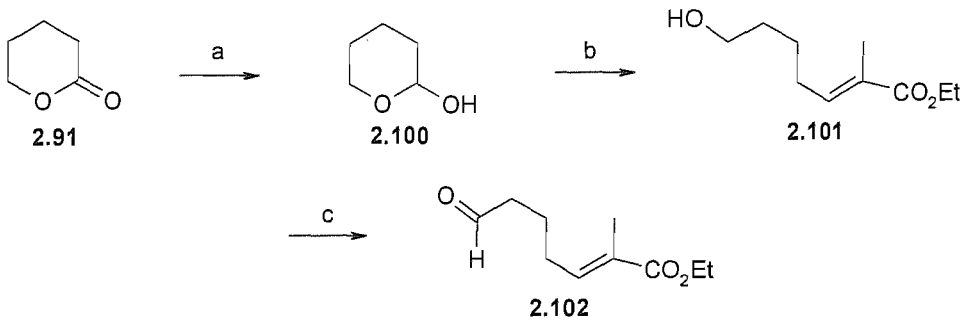


2.99

Figure 2.5

Due to the difficulties encountered attempting to protect oxazolidinone **2.94** as a silyl ether an alternative approach to the fragment was considered. We envisioned that if the aldehyde required for the boron mediated aldol condensation contained an α,β-unsaturated ester instead of a methyl ester the molecule would be less likely to participate in an intramolecular cyclisation under basic conditions.

Thus, aldehyde **2.102** was synthesised from δ-valerolactone **2.91** (Scheme 2.22). The reduction of δ-valerolactone **2.91** with DIBAL-H[117] gave lactol **2.100** in 82% yield. The Wittig reaction[104,118] of lactol **2.100** with the stabilised ylid (1-ethoxycarbonyethylidene)triphenylphosphorane provided alcohol **2.101** in the required *trans* configuration. The Swern oxidation[105] of alcohol **2.101** was highly effective affording aldehyde **2.102** in 92% yield.

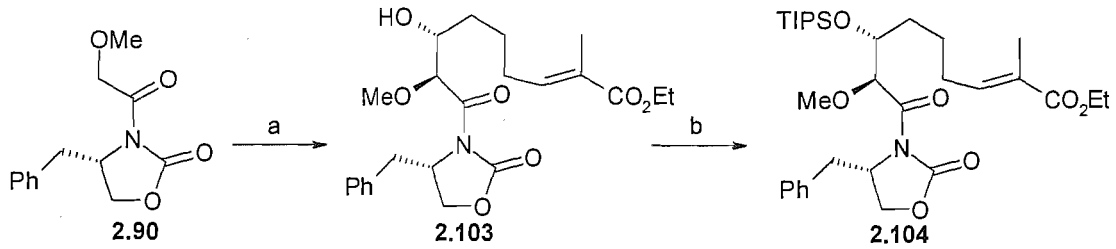


2.91 2.100 2.101 2.102

Reagents and conditions: a) DIBAL-H, CH_2Cl_2, -78 °C, 30 min, 82%; b) (1-ethoxycarbonyethylidene) triphenylphosphorane, benzene, 90 °C, 48 h, 85%; c) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, -78 °C, 15 min, 92%.

Scheme 2.22

The boron-mediated aldol condensation of acylated oxazolidinone **2.90** with aldehyde **2.102** provided **2.103** in 76% yield as a single diastereoisomer according to the ^1H NMR spectrum (Scheme 2.23). The protection of oxazolidinone **2.103** with TBDMSCl[111] was unsuccessful suggesting that more forceful conditions would be required. Protection with TIPS triflate under basic conditions with 2,6-lutidine[112] afforded protected oxazolidinone **2.104** in 89% yield. This time no intramolecular cyclisation occurred.



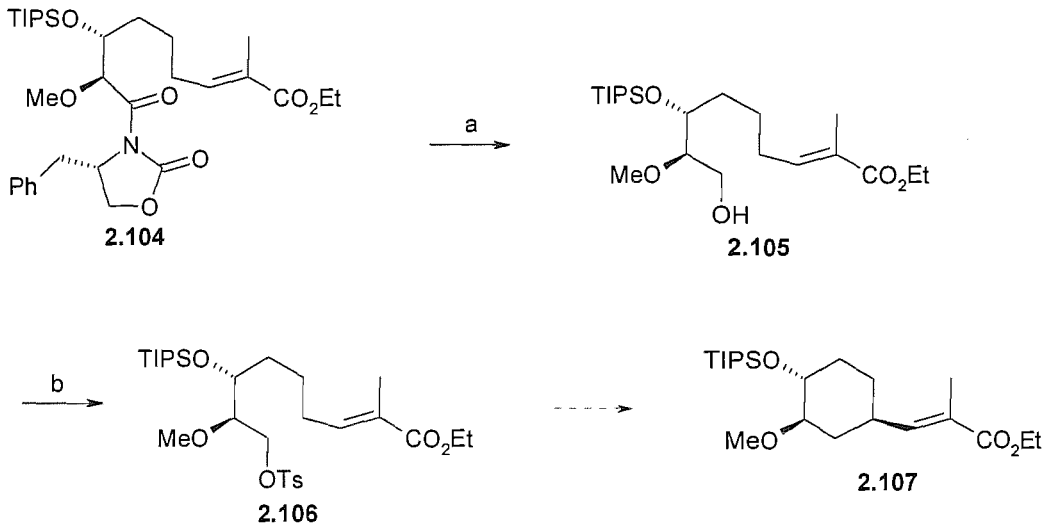
2.90 2.103 2.104

Reagents and conditions: a) Bu_2BOTf, Et_3N, CH_2Cl_2, 0 °C then **2.102**, -65 °C 20 minutes, then 0 °C, 1 h, 76%; b) TIPSOTf, 2,6-lutidine, CH_2Cl_2, 1 h, 89%.

Scheme 2.23

The chiral auxiliary was cleaved by reduction with sodium borohydride,[116] this proceeded in 81% yield (Scheme 2.24). Triturating the crude product with diethyl ether/hexane afforded recovered oxazolidinone **2.89** in 71% yield. Alcohol **2.105** was converted to tosylate **2.106** by the reaction with *p*-toluenesulfonyl chloride and pyridine.[119] On first attempt only two equivalents of *p*-toluenesulfonyl chloride was

employed, this gave a low yield of 27%. Increasing the amount of *p*-toluenesulfonyl chloride to four equivalents and using catalytic DMAP gave an improvement of yield to 70%. Stirring the crude with ammonia removed any by-product of *p*-toluenesulfonic acid present.

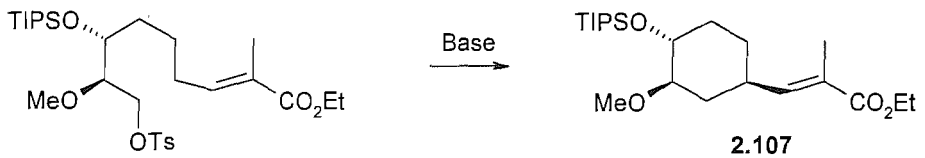


Reagents and conditions: a) $NaBH_4$, THF, H_2O, 6 h, 81%; b) TsCl, pyridine, DMAP, CH_2Cl_2, 40 h, 70 %.

Scheme 2.24

It was anticipated that under basic conditions tosylate **2.106** would participate in an intramolecular cyclisation to form the C-26-C-34 cyclohexyl fragment of FK505 **2.107**. For the cyclisation to occur a non nucleophilic base had to be employed. Hence, the cyclisation was attempted with range of non nucleophilic bases (table 2.1). Efforts with LDA, sodium-HMDS and sodium hydride in toluene were unsuccessful; no cyclised product was isolated from the reaction. Corey *et al.* demonstrated during their synthesis of (±)-α- and (±)-β-copanes how an intramolecular cyclisation *via* the displacement of a tosylate with an enolate could be achieved using sodium hydride in DMSO.[120] Under these same conditions the cyclisation of tosylate **2.106** was accomplished in 33% yield. Heating the reaction to 80 °C and 100 °C led to decomposition of the starting material, implying that the conditions were too harsh. The cyclisation was also endeavoured using BEMP resin; this gave no result with 100% starting material being recovered. According to the literature the displacement of a tosylate with an enolate had been achieved using sodium hydride in DMF.[121] Efforts under these conditions afforded cyclised material

although NMR and mass spectroscopy data were consistent with the structure of carboxylic acid **2.108**, formed *via* hydrolysis of the cyclised ester. Attempts to form the methyl ester from **2.108** with thionyl chloride were unsuccessful. It was considered that using more than one equivalent of base may be detrimental to the reaction, leading to decomposition of the starting material or aiding the hydrolysis to carboxylic acid **2.108**. Therefore the cyclisation of tosylate **2.106** was performed using 0.9 equivalents of sodium hydride in DMSO. This resulted in cyclised ester **2.107**, recovered tosylate and carboxylic acid **2.108** in 40%, 17% and 9% yields respectively.

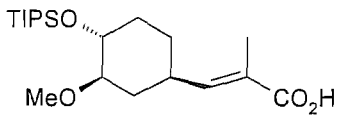


2.106 **2.107**

Scheme 2.25

Base	Equivalents	Temp/ °C	Time/ h	Yield/ %
LDA	1.2	rt	24	X
NaHMDS	1.5	rt	48	X
NaH in toluene	1.5	rt	20	X
NaH in DMSO	1.5	rt	20	33
NaH in DMSO	0.9	rt	20	40
NaH in DMSO	1.5	100	2	X
NaH in DMSO	1.5	80	1.5	X
BEMP resin	1.2	rt	24	X
NaH in DMF	4	rt	15	46, cyclised acid

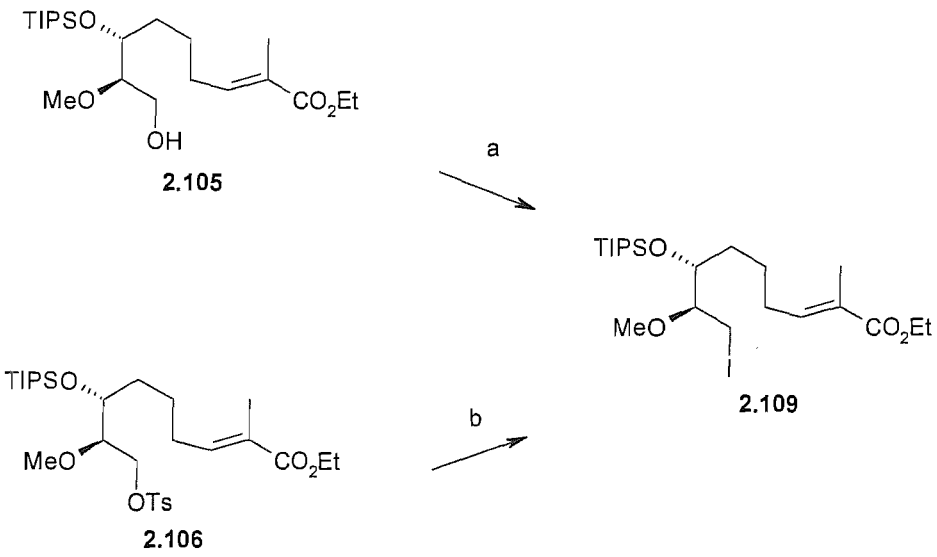
Table 2.1 Attempted cyclisations of tosylate **2.106**



2.108

Figure 2.6

It was considered that attempting the intramolecular cyclisation with the iodide analogue of tosylate **2.106** may lead to an improvement of yield. Thus, iodide **2.109** was synthesised from alcohol **2.105** by treating with iodine and triphenylphosphine under basic conditions with imidazole[122] and from tosylate **2.106** by reacting with NaI in acetone[123] (Scheme 2.26).

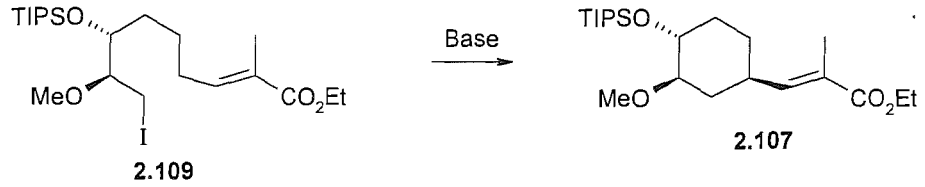


Reagents and conditions and conditions: a) I_2, PPh_3, imidazole, benzene, 24 h, 86%; b) NaI, acetone, 14 days, 69%.

Scheme 2.26

The cyclisation of iodide **2.109** was attempted with a range of non nucleophilic bases (Table 2.2). On reacting iodide **2.109** with sodium-HMDS in THF it was found that the cyclised product co-eluted with the starting material, forming an inseparable mixture impossible to purify by column chromatography. According to the NMR spectrum mostly starting material was recovered. Reacting iodide **2.109** with sodium hydride in DMSO at room temperature provided cyclised material in 25% yield. This was a decreased yield compared to the cyclisation of tosylate **2.106**. Heating the

cyclisation to 100 °C gave no product or recovered starting material. Heating to 80 °C provided carboxylic acid **2.108** in 21% yield, BEMP resin gave 100% recovered starting material and sodium hydride in DMF afforded cyclised carboxylic acid in 31% yield.



2.109 **2.107**

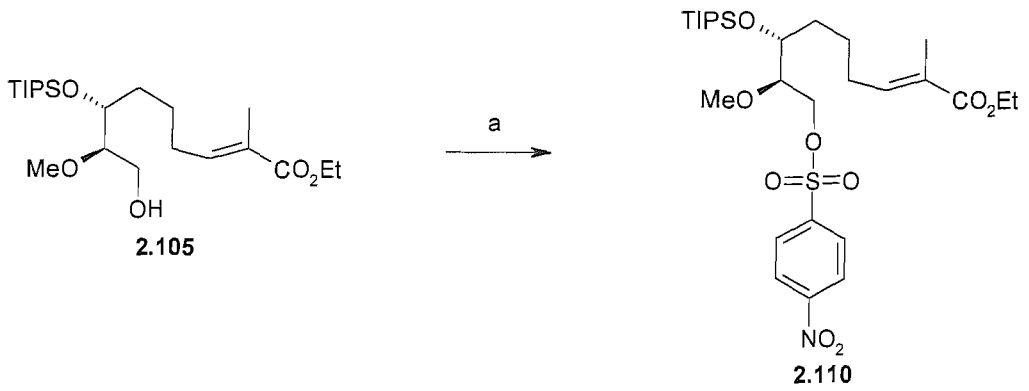
Scheme 2.27

Base	Equivalents	Temp/ °C	Time/ h	Yield/ %
NaHMDS	3	rt	48	X
NaH in DMSO	1.5	rt	72	25
NaH in DMSO	1.5	100	2	X
NaH in DMSO	1.5	80	1.5	21, cyclised acid
BEMP resin	1.2	rt	24	X
NaH in DMF	4	rt	15	31, cyclised acid

Table 2.2 Attempted cyclisations of iodide **2.109**

As the iodide analogue of tosylate **2.106** did not give an improvement in yield for the cyclisation, it was anticipated that converting alcohol **2.105** to the more reactive *p*-nitrobenzene sulfonate equivalent would lead to an improvement of yield. Therefore, *p*-nitrobenzene sulfonate **2.110** was synthesised by reacting alcohol **2.105** with nosyl chloride under basic conditions.[124]

Attempts to perform the cyclisation of nosylate **2.110** with NaH in DMSO at room temperature were unsuccessful. No product or starting material were isolated indicating that nosylate rapidly decomposes.

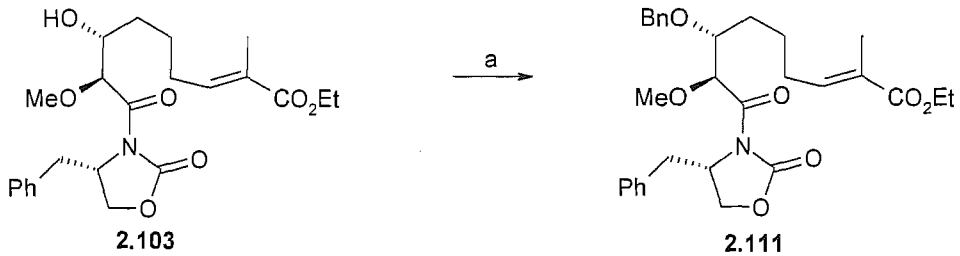


2.105 2.110

Reagents and conditions and conditions: a) *p*-nitrobenzenesulfonyl chloride, pyridine, DMAP, CH_2Cl_2, 3 days, 85%.

Scheme 2.28

The protecting group used may have a steric affect on the cyclisation. Hence, as a comparison, alcohol **2.103** was protected as the less sterically encumbering benzyl ether. Efforts under basic conditions with benzyl bromide[125] were unsuccessful. Therefore, protections under acidic conditions were employed. The reaction with 2,2,2-trichloroacetimidate and catalytic triflic acid,[126] providing benzyl ether **2.111** in 33% yield (Scheme 2.29). Alternatives with catalytic $BF_3{\cdot}OMe_2$[127] were ineffective. As the yield for protecting alcohol **2.103** as a benzyl ether was very low compared to protection as a TIPS ether, work was continued using substrate **2.104**.

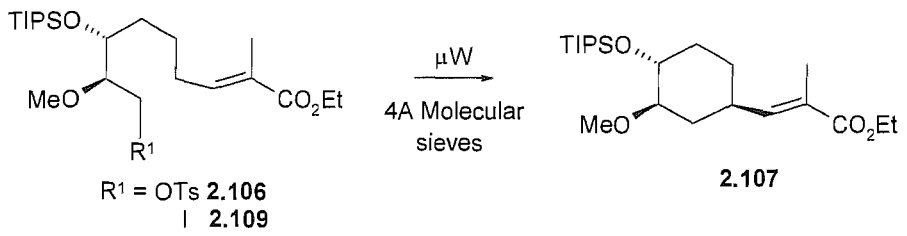


2.103 2.111

Reagents and conditions: a) 2,2,2-trichloroacetimidate, TfOH, hexane, 0 °C, 33%.

Scheme 2.29

It was anticipated that shorter reaction times and elevated temperatures may lead to an improvement of yield for the cyclisation. Therefore in order to optimise the reaction microwave conditions were investigated, with the use of molecular sieves to eliminate water and circumvent hydrolysis to carboxylic acid **2.108**. The results are shown in table 2.3.



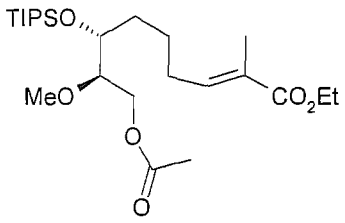
Scheme 2.30

Substrate	Equivalents NaH in DMSO	Temp/ °C	Time/ min	Product /Yield
OTs	0.9	100	15	**2.107** / 11% **2.106** / 44%
OTs	1.5	120	60	**2.107** / 29% **2.112** / 12%
OTs	1.0	150	15	**2.107** / 14%
OTs	1.5	150	60	**2.107** / 49% **2.112** / 17%
OTs	1.5	200	60	**2.107** / 32%
I	0.9	100	15	Mix of **2.109** and **2.107**
I	1.5	150	30	**2.107** / 45% **2.112**/ 9%
I	2.0	150	60	**2.107** / 37%

Table 2.3

Since iodide **2.109** co-eluted with cyclised **2.107** and it was difficult to isolate the cyclised material from the reaction work mainly focused on the cyclisation of tosylate **2.106**. Under the microwave conditions another product was isolated from the reaction mixture, NMR and mass spectrometry data were consistent with the structure of acetate **2.112**, considered to be formed *via* the microwave assisted

degradation of DMSO,[128] although a mechanism for this transformation is unknown (Figure 2.7).



2.112

Figure 2.7

Using less than one equivalent of base led to large amounts of recovered starting material being isolated. At higher temperatures no starting material was isolated but the yield of cyclised product was still modest. At temperatures above 150 °C the yield of cyclised product was decreased, possibly due to decomposition of the starting material. The highest yielding reactions were found at 150 °C and at longer reaction times. It was also found that the presence of molecular sieves did prevent the hydrolysis to carboxylic acid **2.109**.

Previously the cyclisation with sodium hydride in DMF afforded carboxylic acid **2.108** in 46% yield. It was anticipated that performing this reaction under microwave conditions with molecular sieves would prevent the hydrolysis taking place, however, this reaction was unsuccessful for both iodide **2.109** and tosylate **2.106.** None of the desired product was isolated.

2.3. Conclusion and Future Work.

In conclusion, a stereoselective, novel synthesis of the C-26-C-34 fragment of FK-506 in eight steps and an overall 12% yield has been achieved. Previous attempts involving utilizing (*R*)-3-cyclohexenecarboxylic acid as appropriate starting materials were found to be lengthy; therefore an alternative approach from an acyclic precursor was investigated. Using Evans aldol chemistry, chirality was introduced into the molecule prior to cyclisation. On first attempt the aldol condensation between aldehyde **2.93** and oxazolidinone **2.90** was accomplished, but attempts to protect the free hydroxyl group as a silyl ether led to an intramolecular cyclisation, forming lactone **2.97**. This was overcome by performing the boron-mediated aldol condensation with oxazolidinone **2.90** and aldehyde **2.102**, which contained an α,β-unsaturated ester, therefore less likely to cyclise under basic conditions. This also proceeded smoothly forming adduct **2.103**. Protection as a silyl ether followed by reduction with sodium borohydride afforded alcohol **2.105** which when transformed into the corresponding tosylate and subjected to sodium hydride in DMSO under microwave conditions provided the C-26-C-34 fragment **2.107** in 49% yield. Although this step occurred in only moderate yield, the overall route represents a significant improvement over previous syntheses in terms of length and simplicity. Throughout, inexpensive reagents are used and undesired functionality does not need to be removed. This fragment can now be used as a building block for analogues of FK506.

3. Experimental.

3.1. General Experimental.

Melting points were determined using a Reichert heated stage apparatus equipped with a Comark digital probe and were uncorrected.

Infrared spectra were recorded using a Bio-Rad FTS 135 Fourier transform infrared spectrometer equipped with a Golden Gate Single Reflection Diamond ATR.

NMR spectra were recorded on a Bruker AC300 (operating at 300 MHz for ^{1}H and at 75 MHz for ^{13}C) or a Bruker DPX400 instrument (operating at 400 MHz for ^{1}H and at 100 MHz for ^{13}C). Proton and carbon NMR were taken in $CDCl_3$ unless otherwise stated, using tetramethylsilane as an internal standard and are reported as parts per million. Multiplicities are described using the abbreviations s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; app, apparent; and br, broad.

Mass spectra were obtained on a Thermoquest Trace MS and Micromass Platform II instruments.

Optical rotations were recorded on an Optical Activity POLAAR 2001 polarimeter operating at 589 nm, c = g/100 mL

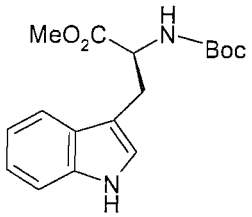
Column chromatography was performed using MN Kieselgel 60, 0.04-0.063 mm 230-400 mesh ASTM silica.

Reactions were monitored by thin layer chromatography using pre-coated aluminium backed sheets coated with Sil G/UV_{254} 0.14 mm Silica gel 60 and were visualised with UV light and a PMA dip.

THF was dried and degassed by distillation from sodium benzophenone ketyl; CH_2Cl_2, dichloroethane, MeOH and xylene were distilled from calcium hydride, toluene was distilled from sodium. All other solvents and reagents were used directly as supplied unless stated otherwise.

3.2. Experimental.

(*S*)-2-*t*-Butoxycarbonylamino-3-(1*H*-indol-3-yl)propionic acid methyl ester (1.110).

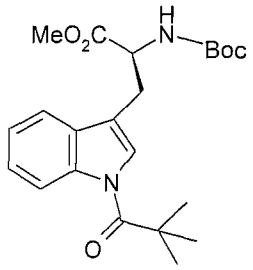


1.110

A solution of K_2CO_3 (4.56 g, 33.0 mmol) in water (45 mL) was added to L-Trp(OMe)·HCl (6.0 g, 23.5 mmol) in CH_2Cl_2 (45 mL). The reaction was stirred at rt for 2 h then brine (30 mL) and CH_2Cl_2 (20 mL) were added. The aqueous phase was extracted with CH_2Cl_2 (2 x 30 mL) and the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give a white solid. Recrystallisation from EtOAc/ hexane afforded **1.110** as a white crystalline solid (7.5 g, 99%).

$[\alpha]_D^{27}$ +45.3 (*c* 0.5, $CHCl_3$); mp. 146-148 °C; IR ν 3381, 3313, 2975, 2949, 1735, 1689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.23 (1 H, br s, indole N**H**), 7.56 (1 H, app d, *J* = 7.9 Hz, Ar-**H**), 7.34 (1 H, app d, *J* = 7.9 Hz, Ar-**H**), 7.19 (1 H, td, *J* = 7.9, 1.1 Hz, Ar-**H**), 7.12 (1 H, td, *J* = 7.9, 1.1 Hz, Ar-**H**), 6.99 (1 H, m, Ar-**H**), 5.10 (1 H, br d, *J* = 7.4 Hz, N**H**), 4.65 (1 H, m, NHC**H**), 3.68 (3 H, s, CO_2CH_3), 3.29 (2 H, app d, *J* = 4.8 Hz, CH_2), 1.43 (9 H, br s, $C(CH_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9 (C), 155.4 (C), 136.3 (C), 127.8 (C), 122.9 (CH), 122.3 (CH), 119.7 (CH), 118.8 (CH), 111.3 (CH), 110.3 (C), 80.0 (C), 54.3 (CH), 52.3 (CH_3), 28.5 (CH_3), 28.1 (CH_2) ppm; LRMS ES^+ *m/s* (%) 341 ($[M + Na]^+$, 100), 357 ($[M + K]^+$, 30).

(*S*)-2-*t*-Butoxycarbonylamino-3-[1-(2,2-dimethylpropionyl)-1*H*-indol-3-yl]-propionic acid methyl ester (1.111).

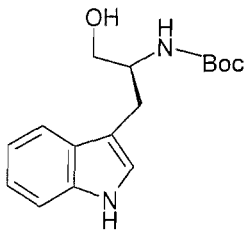


1.111

To a solution of **1.110** (100 mg, 0.3 mmol) and $Bu_4N^+HSO_4^-$ (11 mg, 0.03 mmol) in toluene (1.5 mL) was added 50% NaOH (aq) (0.5 mL). The reaction mixture was stirred for 10 min then a solution of pivaloyl chloride (60 μL, 0.47 mmol) in toluene (1 mL) was added dropwise. After stirring at rt for 2 h the organic phase was washed with water (2 x 1 mL) then brine (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-40% EtOAc in hexane) afforded **1.111** as a pale yellow oil (108 mg, 86%).

$[\alpha]_D^{27}$ +53.3 (*c* 0.5, $CHCl_3$); IR ν 3368, 2977, 1744, 1690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.49 (1 H, d, *J* = 7.8 Hz, Ar-**H**), 7.56 (1 H, s, Ar-**H**), 7.48 (1 H, d, *J* = 7.8 Hz, Ar-**H**), 7.34 (1 H, t, *J* = 7.8 Hz, Ar-**H**), 7.27 (1 H, t, *J* = 7.8 Hz, Ar-**H**), 5.13 (1 H, d, *J* = 6.7 Hz, N**H**), 4.70 (1 H, m, NHC**H**), 3.69 (3 H, s, CO_2CH_3), 3.29 (1 H, dd, *J* = 14.9, 5.5 Hz, CH**H**), 3.19 (1 H, m, CH**H**), 1.51 (9 H, s, Piv $C(CH_3)_3$), 1.43 (9 H, br s, Boc $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (C), 172.4, (C), 155.2 (C), 137.1 (C), 129.6 (C), 125.6 (CH), 124.0 (CH), 123.6 (CH), 118.5 (CH), 117.6 (CH), 116.1 (C), 80.2 (C), 53.5 (CH), 52.5 (CH_3), 41.3 (C), 28.8 (CH_3), 28.4 (CH_3), 27.9 (CH_2) ppm; LRMS ES^+ *m/s* (%) 425 ($[M + Na]^+$, 100), 827 ($[2M + Na]^+$, 80).

[(*S*)-1-Hydroxymethyl-2-(1*H*-indol-3-yl)ethyl]-carbamic acid *t*-butyl ester (1.114).

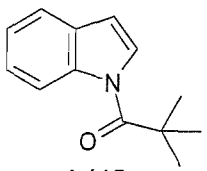


1.114

To a solution of **1.111** (0.1 g, 0.25 mmol) and $CaCl_2$ (58 mg, 0.52 mmol) in THF (1 mL) and EtOH (1.5 mL) at 0 °C under argon was added $NaBH_4$ (39 mg, 1.0 mmol). The reaction mixture was warmed to rt and stirred for 3 h then poured into 5% citric acid (aq) (2 mL) and extracted with diethyl ether (2 x 2 mL). The combined extracts were washed with sat. $NaHCO_3$ (aq) (2 mL), water (2 mL) and brine (2 mL), dried over $MgSO_4$, and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 80% EtOAc in hexane) afforded alcohol **1.114** as a white solid (65 mg, 90%).

$[\alpha]_D^{27}$ -14.4 (*c* 1.0, $CHCl_3$) (Lit. $[\alpha]_D^{23}$ -19.1 (*c* 1.0, CH_2Cl_2));[65] mp. 114-116 °C (Lit. 118-120 °C);[65] IR ν 3418, 3358, 2980, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.12 (1 H, br s, indole N-**H**), 7.65 (1 H, d, *J* = 7.7 Hz, Ar-**H**), 7.36 (1 H, d, *J* = 7.7 Hz, Ar-**H**), 7.20 (1 H, t, *J* = 7.7 Hz, Ar-**H**), 7.13 (1 H, t, *J* = 7.7 Hz, Ar-**H**), 7.04 (1 H, m, Ar-**H**), 4.81 (1 H, br s, N**H**), 3.99 (1 H, m, C**H**NH), 3.70 (1 H, m, CH**H**), 3.61 (1 H, m, C**H**H), 3.00 (2 H, app d, *J* = 6.8 Hz, C**H**$_2$), 2.47 (1 H, br s, O**H**), 1.43 (9 H, s, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.5 (C), 136.5 (C), 127.8 (C), 122.8 (CH), 122.3 (CH), 119.7 (CH), 119.0 (CH), 112.0 (C), 111.3 (CH), 79.8 (C), 65.1 (CH_2), 53.2 (CH), 28.5 (CH_3), 27.2 (CH_2) ppm; LRMS ES^+ *m/s* (%) 313 ($[M + Na]^+$, 100), 603 ($[2M + Na]^+$, 20). Data consistent with lit.[65]

1-Indol-1-yl-2,2-dimethylpropan-1-one (1.115).



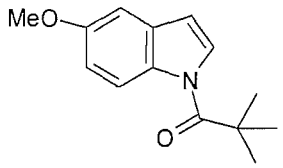
1.115

To a solution of indole (500 mg, 4.3 mmol) and $Bu_4N^+HSO_4^-$ (0.14 g, 0.4 mmol) in toluene (10 mL) was added 50% NaOH (aq) (6.5 mL). The reaction mixture was stirred for 30 min then pivaloyl chloride (0.79 mL, 6.4 mmol) in toluene (5 mL) was added dropwise. After 10 min the organic phase was washed with water (5 mL) and brine (5 m), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% EtOAc in hexane) afforded **1.115** as a pink crystalline solid (0.75 g, 86%).

mp. 62-64 °C (Lit. 65-66 °C);[129] IR ν 2977, 2934, 1678 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (1 H, app d, *J* = 7.6 Hz, Ar-**H**), 7.74 (1 H, d, *J* = 4.0 Hz, Ar-**H**), 7.56 (1 H, app d, *J* = 7.6 Hz, Ar-**H**), 7.35 (1 H, td, *J* = 7.6, 1.0 Hz, Ar-**H**), 7.27 (1 H,

td, J = 7.6, 1.0 Hz, Ar-**H**), 6.62 (1 H, d, J = 4.0 Hz, Ar-**H**), 1.52 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (C), 136.9 (C), 129.5 (C), 125.8 (CH), 125.2 (CH), 123.7 (CH), 120.6 (CH), 117.5 (CH), 108.4 (CH), 41.4 (C), 28.9 (CH_3) ppm; LRMS ES$^+$ *m/s* (%) 224 ([M + Na]$^+$, 100). Data consistent with lit.[129]

1-(5-Methoxyindol-1-yl)-2,2-dimethylpropan-1-one (1.117).

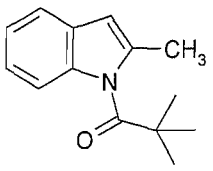


1.117

To a solution of 5-methoxyindole (0.24 g, 1.6 mmol) and $Bu_4N^+HSO_4^-$ (54 mg, 0.16 mmol) in toluene (10 mL) was added 50% NaOH (aq) (3 mL). The reaction mixture was stirred for 30 min then pivaloyl chloride (0.30 mL, 2.4 mmol) in toluene (5 mL) was added dropwise. After 3.5 h the organic phase was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% EtOAc in hexane) afforded **1.117** as a white solid (0.32 g, 70%).

mp. 85-89 °C; IR ν 3174, 2932, 1672 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.41 (1 H, d, J = 9.1 Hz, Ar-**H**), 7.71 (1 H, d, J = 3.9 Hz, Ar-**H**), 7.02 (1 H, d, J = 2.7 Hz, Ar-**H**), 6.96 (1 H, dd, J = 9.1, 2.7 Hz, Ar-**H**), 6.55 (1 H, d, J = 3.9 Hz, Ar-**H**), 3.86 (3 H, s, OC**H**$_3$), 1.51 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (C), 156.5 (C), 131.6 (C), 130.5 (C), 126.4 (CH), 118.2 (CH), 113.5 (CH), 108.2 (CH), 103.4 (CH), 55.8 (CH_3), 41.2 (C), 28.9 (CH_3) ppm; LRMS ES$^+$ *m/s* (%) 254 ([M + Na]$^+$, 100).

2,2-Dimethyl-1-(2-methylindol-1-yl)propan-1-one (1.119).



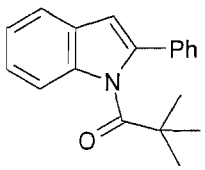
1.119

To a suspension of NaH (60% in mineral oil, 0.16 g, 4.0 mmol) in THF (2.5 mL) under argon was added 2-methylindole (0.26 g, 2.0 mmol) in THF (2.5 mL). The mixture was stirred for 30 min then pivaloyl chloride (0.25 mL, 2.0 mmol) was added. After stirring at rt for 2 h sat. NH_4Cl (aq) (5 mL) was added, the phases were

separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (SiO_2, 5% EtOAc in hexane) afforded **1.119** as a white solid (0.39 g, 92%).

mp. 38-40 °C; IR ν 3015, 2963, 2918 1704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) 7.50 (1 H, m, Ar-**H**), 7.29 (1 H, m, Ar-**H**), 7.16 (1 H, td, J = 7.2, 1.5 Hz, Ar-**H**), 7.12 (1 H, td, J = 7.2, 1.5 Hz, Ar-**H**), 6.33 (1 H, m, Ar-**H**), 2.40 (3 H, d, J = 1.0 Hz, C**H**$_3$), 1.42 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 186.5 (C), 136.3 (C), 136.2 (C), 128.9 (C), 121.9 (CH), 121.1 (CH), 120.1 (CH), 112.2 (CH), 104.6 (CH), 44.4 (C), 28.4 (CH_3), 14.1 (CH_3) ppm; LRMS ES^+ *m/s* (%) 254 ($[M + K]^+$, 100), 286 ($[M + K + MeOH]^+$, 60).

2,2-Dimethyl-1-(2-phenylindol-1-yl)propan-1-one (1.121).

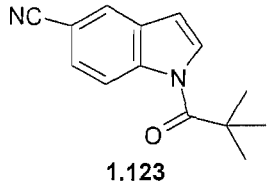


1.121

To a suspension of NaH (60% in mineral oil, 99 mg, 2.5 mmol) in THF (3 mL) under argon was added 2-phenylindole (0.24 g, 1.2 mmol) in THF (3 mL). The mixture was stirred for 30 min then pivaloyl chloride (0.15 mL, 1.2 mmol) was added. After stirring at rt for 2 h sat. NH_4Cl (aq) (3 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (SiO_2, 10% EtOAc in hexane) afforded **1.121** as yellow oil (0.32 g, 92%).

IR ν 3060, 2969, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (1 H, m, Ar-**H**), 7.58-7.52 (2 H, m, Ph Ar-**H**), 7.40-7.34 (4 H, m, 3 x Ph Ar-**H** + Ar-**H**), 7.26 (1 H, td, J = 7.5, 1.4 Hz, Ar-**H**), 7.20 (1 H, td, J = 7.5, 1.4 Hz, Ar-**H**), 6.70 (1 H, d, J = 0.6 Hz, Ar-**H**), 0.98 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.5 (C), 139.6 (C), 137.4 (C), 134.1 (C), 129.2 (CH), 128.5 (C), 128.4 (CH), 128.0 (CH), 123.6 (CH), 121.7 (CH), 120.8 (CH), 111.4 (CH), 104.8 (CH), 45.3 (C), 28.1 (CH_3) ppm; LRMS ES^+ *m/s* (%) 300 ($[M + Na]^+$, 100).

1-(2,2-Dimethylpropionyl)-1*H*-indole-5-carbonitrile (1.123).

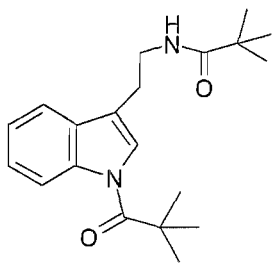


1.123

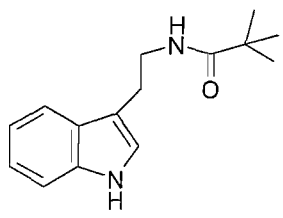
To a suspension of NaH (60% in mineral oil, 0.16 g, 4.0 mmol) in THF (2.5 mL) under argon was added 5-cyanoindole (0.28 g, 2.0 mmol) in THF (2.5 mL). The mixture was stirred for 30 min then pivaloyl chloride (0.25 mL, 2.0 mmol) was added. After stirring at rt for 2 h sat. NH_4Cl (aq) (2 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (SiO_2, 5% EtOAc in hexane) afforded **1.123** as a white solid (0.41 g, 91%).

mp. 158-161 °C; IR ν 3168, 2959, 2910, 2218, 1682 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.58 (1 H, d, J = 8.8 Hz, Ar-**H**), 7.89 (1 H, dd, J = 1.6, 0.5 Hz, Ar-**H**), 7.86 (1 H, d, J = 3.9 Hz, Ar-**H**), 7.58 (1 H, dd, J = 8.8, 1.6 Hz, Ar-**H**), 6.68 (1 H, dd, J = 3.9, 0.5 Hz, Ar-**H**), 1.53 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.3 (C), 138.7 (C), 129.5 (C), 128.2 (CH), 127.9 (CH), 125.4 (CH), 119.8 (C), 118.2 (CH), 107.9 (CH), 107.0 (C), 41.6 (C), 28.6 (CH_3) ppm; LRMS ES^+ *m/s* (%) 249 ($[M + Na]^+$, 25), 290 ($[M + Na + MeCN]^+$, 100).

N-{2-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-yl]-ethyl}-2,2-dimethylpropion amide (1.125) and N-[2-(1*H*-Indol-3-yl)ethyl]-2,2-dimethylpropionamide (1.126).



1.125



1.126

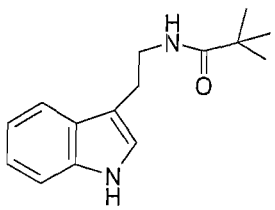
To a suspension of NaH (60% in mineral oil, 0.32 g, 8.0 mmol) in THF (2.5 mL) under argon was added tryptamine (0.32 g, 2.0 mmol) in THF (2.5 mL). The mixture was stirred for 30 min then pivaloyl chloride (0.50 mL, 4.0 mmol) was added. After stirring at rt for 2 h sat. NH_4Cl (aq) (2 mL) was added, the phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined extracts

were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-50% EtOAc in hexane) yielded di-protected **1.125** as a pale yellow solid (0.57 g, 87%) and mono-protected **1.126** as a yellow solid (50 mg, 10%).

1.125: mp. 131-135 °C; IR ν 3389, 2968, 1687, 1633 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (1 H, app d, J = 7.6 Hz, Ar-**H**), 7.57 (1 H, s, Ar-**H**), 7.55 (1 H, dd, J = 7.6, 1.2 Hz, Ar-**H**), 7.36 (1 H, td, J = 7.6, 1.2 Hz, Ar-**H**), 7.29 (1 H, td, J = 7.6, 1.2 Hz, Ar-**H**), 5.76 (1 H, br s, N**H**), 3.62 (2 H, td, J = 7.0, 6.0 Hz NHC**H**$_2$), 2.95 (2 H, td, J = 7.0, 0.6 Hz, indole-C**H**$_2$), 1.50 (9 H, s, indole Piv $C(CH_3)_3$), 1.15 (9 H, s, NH Piv $C(CH_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.7 (C), 177.0 (C), 137.5 (C), 129.4 (C), 125.6 (CH), 123.6 (CH), 123.1 (CH), 118.8 (C), 118.6 (CH), 117.7 (CH), 41.3 (C), 39.1 (CH_2), 38.8 (C), 28.8 (CH_3), 27.7 (CH_3), 25.5 (CH_2) ppm; LRMS ES^+ *m/s* (%) 351 ($[M + Na]^+$, 100).

1.126: mp. 124-130 °C; IR ν 3336, 3252, 2965, 1609 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.36 (1 H, br s, indole N**H**), 7.63 (1 H, app d, J = 7.7 Hz, Ar-**H**), 7.38 (1 H, app d, J = 7.7 Hz, Ar-**H**), 7.21 (1 H, td, J = 7.7, 1.1 Hz, Ar-**H**), 7.13 (1 H, td, J = 7.7, 1.1 Hz, Ar-**H**), 7.01 (1 H, d, J = 2.3 Hz, Ar-**H**), 5.75 (1 H, br s, N**H**), 3.59 (2 H, td, J = 6.7, 5.9 Hz, NHC**H**$_2$), 2.98 (2 H, app t, J = 6.7 Hz, indole-C**H**$_2$), 1.14 (9 H, s, Piv $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.6 (C), 136.6 (C), 127.5 (C), 122.3 (CH), 122.2 (CH), 119.5 (CH), 118.9 (CH), 113.2 (C), 111.4 (CH), 40.0 (CH_2), 38.8 (C), 27.7 (CH_3), 25.4 (CH_2) ppm; LRMS ES^+ *m/s* (%) 267 ($[M + Na]^+$, 100).

_N_-[2-(1_H_-Indol-3-yl)ethyl]-2,2-dimethylpropionamide (1.126).

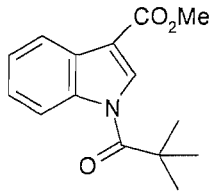


1.126

To a solution of **1.125** (99 mg, 0.16 mmol) in THF (1 mL) and EtOH (1.5 mL) at rt under argon was added $NaBH_4$ (11 mg, 0.3 mmol). After 1 h the reaction mixture was poured into 5% citric acid (aq) (1 mL) and extracted with diethyl ether (2 x 1 mL). The combined extracts were washed with sat. $NaHCO_3$ (aq) (1 mL), water (1 mL) and brine (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by

column chromatography (SiO_2, 40-60% EtOAc in hexane) afforded **1.126** as a yellow solid (47 mg, 64%). For spectroscopic data see above.

1-(2,2-Dimethylpropionyl)-1*H*-indole-3-carboxylic acid methyl ester (1.127).

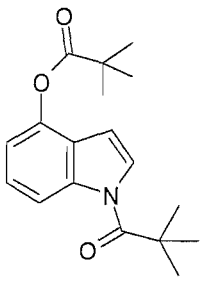


1.127

To a solution of methyl indole-3-carboxylate (0.35 g, 2.0 mmol) and $Bu_4N^+HSO_4^-$ (68 mg, 0.2 mmol) in toluene (10 mL) was added 50% NaOH (aq) (3 mL). The reaction mixture was stirred for 30 min then pivaloyl chloride (0.37 mL, 3.0 mmol) in toluene (5 mL) was added dropwise. After 1.5 h the organic phase was washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$, concentrated *in vacuo.* Purification by column chromatography (SiO_2, 5% EtOAc in hexane) afforded **1.127** as a white solid (0.43 g, 84%).

mp. 101-105 °C; IR ν 3201, 2989, 1716, 1704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.47 (1 H, m, Ar-**H**), 8.16 (1 H, m, Ar-**H**), 8.41 (1 H, s, Ar-**H**), 7.44-7.35 (2 H, m, Ar-**H**), 3.96 (3 H, s, CO_2CH_3), 1.55 (9 H, s, Piv $(CH_3)_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.4 (C), 164.7 (C), 137.4 (C), 131.6 (C), 126.6 (C), 126.0 (CH), 124.8 (CH), 121.4 (CH), 117.2 (CH), 113.1 (CH), 51.7 (CH_3), 41.8 (C), 28.8 (CH_3) ppm; LRMS ES^+ *m/s* (%) 282 ($[M + Na]^+$, 95), 323 ($[M + Na + MeCN]^+$, 100).

2,2-Dimethylpropionic acid 1-(2,2-dimethylpropionyl)-1*H*-indol-4-yl ester (1.129).



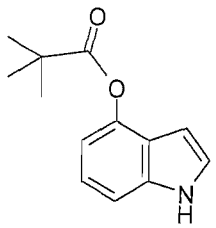
1.129

To a suspension of NaH (60% in mineral oil, 37 mg, 0.9 mmol) in THF (2.5 mL) under argon was added **1.130** (100 mg, 0.5 mmol) in THF (2.5 mL). The mixture was stirred for 30 min then pivaloyl chloride (60 μL, 0.5 mmol) was added. After stirring

overnight a further equivalent of pivaloyl chloride (60 μL, 0.5 mmol) was added and the reaction mixture was stirred for a further 3 days then quenched with sat. NH_4Cl (aq) (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5-20% EtOAc in hexane) afforded **1.129** as a colourless oil (64 mg, 46%) and recovered starting material **1.130** as a white solid (45 mg, 45%).

IR ν 2976, 1753, 1699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (1 H, d, J = 8.2 Hz, Ar-**H**), 7.71 (1 H, d, J = 3.9 Hz, Ar-**H**), 7.33 (1 H, t, J = 8.2 Hz, Ar-**H**), 7.00 (1 H, dd, J = 8.2, 0.7 Hz, Ar-**H**), 6.47 (1 H, dd, J = 3.9, 0.7 Hz, Ar-**H**), 1.51 (9 H, s, N-Piv C(C**H**$_3$)$_3$), 1.44 (9 H, s, O-Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.2 (C), 176.9 (C), 143.6 (C), 138.4 (C), 125.9 (CH), 125.7 (CH), 122.8 (C), 116.1 (CH), 115.2 (CH), 104.6 (CH), 41.4 (C), 39.5 (C), 28.8 (CH_3), 27.4 (CH_3) ppm; LRMS ES^+ *m/s* (%) 324 ($[M + Na]^+$, 15), 365 ($[M + Na + MeCN]^+$, 100), 625 ($[2M + Na]^+$, 40).

2,2-Dimethylpropionic acid 1*H*-indol-4-yl ester (1.130).



1.130

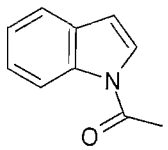
Method A: To a solution of 4-hydroxyindole (0.1 g, 0.75 mmol) in THF (2 mL) at -78 °C under argon was added NaHMDS (1.0 M in THF, 0.75 mL, 0.75 mmol). The reaction mixture was stirred for 15 min then pivaloyl chloride (0.11 mL, 0.9 mmol) was added. After stirring for 1 h the reaction mixture was quenched with sat. NH_4Cl (aq) (2 mL) and extracted with EtOAc (5 x 5 mL). The combined extracts were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 50% EtOAc in hexane) afforded **1.130** as a white solid (82 mg, 50%).

Method B: To a solution of **1.129** (50 mg, 0.16 mmol) in THF (1 mL) and EtOH (1.5 mL) was added $NaBH_4$ (6 mg, 0.16 mmol) at rt under argon. After 1 h the reaction mixture was poured into 5% citric acid (aq) (1 mL) and extracted with diethyl ether (2 x 1 mL). The combined extracts were washed with sat. $NaHCO_3$ (aq) (2 mL),

water (2 mL) and brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10-30% EtOAc in hexane) afforded **1.130** as a white solid (30 mg, 83%).

mp. 100-103 °C; IR ν 3402, 2970, 2927, 2870, 1730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.28 (1 H, br s, indole N**H**), 7.19 (1 H, br d, J = 7.7 Hz, Ar-**H**), 7.14 (1 H, t, J = 7.7 Hz, Ar-**H**), 7.06 (1 H, m, Ar-**H**), 6.85 (1 H, dd, J = 7.7, 1.1 Hz, Ar-**H**), 6.37 (1 H, t, J = 2.2 Hz, Ar-**H**), 1.47 (9 H, s, Piv C($C\mathbf{H_3}$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C), 144.2 (C), 137.8 (C), 124.5 (CH), 122.3 (CH), 121.4 (C), 111.9 (CH), 109.0 (CH), 99.3 (CH), 39.5 (C), 27.5 (CH_3) ppm; LRMS ES^+ *m/s* (%) 240 ($[M + Na]^+$, 100), 281 ($[M + Na + MeCN]^+$, 50).

1-Indol-1-ylethanone (1.131).

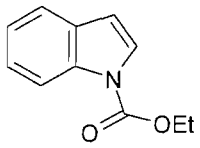


1.131

To a solution of indole (200 mg, 1.7 mmol) in THF (2 mL) under argon was added NaH (60% in mineral oil, 82 mg, 2.0 mmol). The mixture was stirred for 30 min then acetyl chloride (0.12 mL, 2.0 mmol) was added. The reaction mixture was heated at reflux for 2 days then quenched with sat. NH_4Cl (aq) (2 mL). The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc in hexane) afforded **1.131** as a colourless oil (0.17 g, 63%).

IR ν 2979, 2937, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.44 (1 H, app d, J = 7.8 Hz, Ar-**H**), 7.57 (1 H, dd, J = 7.8, 0.5 Hz, Ar-**H**), 7.43 (1 H, d, J = 3.8 Hz, Ar-**H**), 7.36 (1 H, td, J = 7.8, 1.3 Hz, Ar-**H**), 7.28 (1 H, td, J = 7.8, 1.3 Hz, Ar-**H**), 6.65 (1 H, dd, J = 3.8, 0.5 Hz, Ar-**H**), 2.65 (3 H, s, $C\mathbf{H_3}$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.7 (C), 135.5 (C), 130.4 (C), 125.2 (CH), 125.1 (CH), 123.7 (CH), 120.8 (CH), 116.5 (CH), 109.2 (CH), 24.0 (CH_3) ppm; LRMS ES^+ *m/s* (%) 182 ($[M + Na]^+$, 100). Data consistent with lit.[130]

Indole-1-carboxylic acid ethyl ester (1.132).

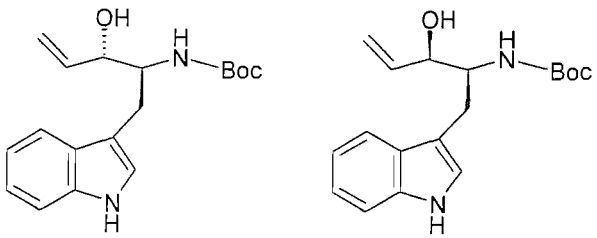


1.132

To a solution of indole (200 mg, 1.7 mmol) in DMF (3 mL) at 0 °C under argon was added NaH (60% in mineral oil, 0.14 g, 3.4 mmol) portionwise. After stirring for 30 min ethyl chloroformate (0.24 mL, 2.6 mmol) was added and the reaction mixture was stirred at rt overnight. Water (6.5 mL) was added and the aqueous phase was extracted with EtOAc (3 x 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5-20% EtOAc in hexane) afforded **1.132** as a colourless oil (0.11 g, 35%) and recovered indole (81 mg, 41%).

IR ν 2982, 1731 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.19 (1 H, app d, J = 7.8 Hz, Ar-**H**), 7.63 (1 H, d, J = 3.8 Hz, Ar-**H**), 7.57 (1 H, app d, J = 7.8 Hz, Ar-**H**), 7.33 (1 H, td, J = 7.8, 1.2 Hz, Ar-**H**), 7.25 (1 H, td, J = 7.8, 1.2 Hz, Ar-**H**), 6.60 (1 H, d, J = 3.8 Hz, Ar-**H**), 4.50 (2 H, q, J = 7.1 Hz, $OC\mathbf{H}_2CH_3$), 1.48 (3 H, t, J = 7.1 Hz, $OCH_2C\mathbf{H}_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.9 (C), 130.7 (C), 125.7 (CH), 124.6 (CH), 123.1 (CH), 121.1 (CH), 116.4 (C), 115.3 (CH), 108.1 (CH), 63.3 (CH_2), 14.6 (CH_3) ppm; LRMS ES^+ *m/s* (%) 212 ($[M + Na]^+$, 100).

[(*S*)-2-Hydroxy-1-(1*H*-indol-3-ylmethyl)but-3-enyl]carbamic acid *t*-butyl ester (1.134).



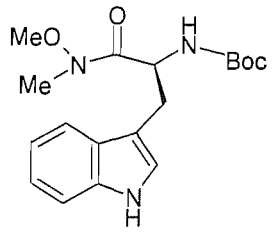
1.134 *syn* **1: 1** **1.134 *anti***

To a solution of **1.135** (0.50 g, 1.4 mmol) in THF (10 mL) at -78 °C under argon was added DIBAL-H (1.0 M in toluene, 4.3 mL, 4.3 mmol) at a rate so the temperature did not exceed -65 °C. After stirring at -78 °C for 1.5 h MeOH (2 mL) was added dropwise followed by the addition of sat. Rochelle's salt (aq) (20 mL). After stirring for 1 h the reaction mixture was extracted with EtOAc (2 x 20 mL). The combined

extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide crude aldehyde **1.133** (0.46 g, quant.) which was reacted on without purification. To a solution of aldehyde **1.133** (0.46 g, 1.4 mmol) in THF (10 mL) at -78 °C under argon was added vinyl MgCl (1.6M in THF, 4.5 mL, 7.2 mmol). The reaction mixture was warmed to rt over 20 h then quenched with sat. NH_4Cl (aq) (10 mL) followed by water (10 mL) then extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.134** as a white solid. Recrystallisation from EtOAc/ hexane afforded **1.134** as a white crystalline solid (0.23 g, 52%) isolated as a 1:1 mixture of diastereoisomers.

$[\alpha]_D^{28}$ -17.0 (*c* 0.3, $CHCl_3$); mp 111-115 °C; IR ν 3412, 3350, 2978, 2931, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1 H, br s, indole N**H**), 7.68 (1 H, app d, *J* = 7.7 Hz, *syn*: Ar-**H**), 7.62 (1 H, app d, *J* = 7.7 Hz, *anti*: Ar-**H**), 7.35 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.20 (1 H, td, *J* = 7.7, 1.2 Hz, Ar-**H**), 7.12 (1 H, td, *J* = 7.7, 0.9 Hz, Ar-**H**), 7.05 (1 H, m, *syn*: Ar-**H**), 7.04 (1 H, m, *anti*: Ar-**H**), 6.0 (1 H, ddd, *J* = 17.0, 10.6, 5.7 Hz, *anti*: CH_2=C**H**), 5.90 (1 H, ddd, *J* = 17.3, 10.6, 5.5 Hz, *syn*: CH_2=C**H**), 5.37 (1 H, app dt, *J* = 17.0, 1.5 Hz, *anti*: C**H**H=CH), 5.29 (1 H, app dt, *J* = 10.6, 1.5 Hz, *anti*: CH**H**=CH), 5.27 (1 H, app dt, *J* = 17.3, 1.4 Hz, *syn*: C**H**H=CH), 5.17 (1 H, app dt, *J* = 10.6, 1.4 Hz, *syn*: CH**H**=CH), 4.91 (1 H, br s, *syn*: N**H**), 4.67 (1 H, br s, *anti*: N**H**), 4.27 (1 H, m, *anti*: C**H**OH), 4.18 (1 H, m, *syn*: C**H**OH), 4.09 (1 H, m, *anti*: C**H**NH), 3.91 (1 H, m, *syn*: C**H**NH), 3.12 (1 H, dd, *J* = 14.6, 7.7 Hz, C**H**H), 2.98 (1 H, m, CH**H**), 2.41 (1 H, br s, O**H**), 1.41 (9 H, br s, Boc $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9 (*anti* C), 156.5 (*syn* C), 138.7 (*syn* CH), 137.4 (*anti* CH), 136.5 (*anti* C), 136.4 (*syn* C), 127.9 (*syn* C), 127.8 (*anti* C), 122.8 (*syn* CH), 122.3 (*anti* CH), 122.2 (*syn* CH), 122.0 (*anti* CH), 119.6 (*syn* CH), 119.4 (*anti* CH), 119.0 (*syn* CH), 119.0 (*anti* CH), 117.0 (*syn* CH_2), 116.0 (*anti* CH_2), 112.4 (*syn* C), 111.9 (*anti* C), 111.3 (*anti* CH), 111.2 (*syn* CH), 80.0 (*anti* C), 79.5 (*syn* C), 75.0 (*anti* CH), 73.1 (*syn* CH), 55.9 (*anti* CH), 55.4 (*syn* CH), 28.6 (*anti* CH_3), 28.5 (*syn* CH_3), 27.7 (*syn* CH_2), 26.1 (*anti* CH_2) ppm; LRMS ES^+ *m/s* (%) 339 ($[M + Na]^+$, 100).

[(*S*)-2-(1*H*-Indol-3-yl)-1-(methoxymethylcarbamoyl)ethyl]carbamic acid *t*-butyl ester (1.135).



1.135

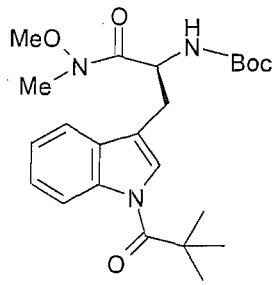
Method A: To a solution of *N,O*-dimethylhydroxylamine·HCl (0.46 g, 4.7 mmol) in CH_2Cl_2 (15 mL) under argon was added $AlMe_3$ (2M in toluene, 3.1 mL, 6.3 mmol). After stirring at rt for 30 min a solution of **1.110** (0.5 g, 1.6 mmol) in CH_2Cl_2 (5 mL) was added and the reaction mixture was heated at reflux. After 24 h 0.5M HCl (aq) (25 mL) was added dropwise and the organic phase was washed with sat. $NaHCO_3$ (aq) (25 mL), water (25 mL) then brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 0-100% EtOAc in hexane) afforded a white solid, recrystallisation from EtOAc/ hexane afforded **1.135** as a white crystalline solid (0.41 g, 76%).

Method B: To a solution of Boc-L-Trp-OH (20 g, 65.4 mmol) in THF (480 mL) at 0 °C under argon was added Et_3N (27 mL, 196 mmol) followed by the dropwise addition of methanesulfonyl chloride (5.6 mL, 72 mmol). After stirring at 0 °C for 10 min *N,O*-dimethylhydroxylamine (7.2 mL, 98 mmol) was added. The reaction mixture was stirred at rt for 5 h then water (250 mL) was added and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined extracts were washed with brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (SiO_2, 50% EtOAc in hexane) afforded a white solid, recrystallisation from EtOAc/ hexane afforded **1.135** as a white crystalline solid (18.9 g, 83%).

$[\alpha]_D^{27}$ -12.1 (*c* 0.5, $CHCl_3$) (Lit. $[\alpha]_D^{23}$ -11.2 (*c* 1, MeOH))[131]; mp. 132-134 °C (Lit. 129-130 °C);[131] IR ν 3324, 2985, 2933, 2850, 1694, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.35 (1 H, br s. indole N**H**), 7.59 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.32 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.16 (1 H, td, *J* = 7.7, 0.9 Hz, Ar-**H**), 7.10 (1 H, td, *J* = 7.7, 1.1 Hz, Ar-**H**), 7.00 (1 H, m, Ar-**H**), 5.26 (1 H, br s, N**H**), 5.01 (1 H, m, C**H**NH), 3.63 (3 H, br s, OCH_3), 3.24 (1 H, dd, *J* = 14.6, 5.7 Hz, C**H**H), 3.14 (3 H, s, NCH_3), 3.10 (1 H, m, CH**H**), 1.41 (9 H, br s, $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz,

$CDCl_3$) δ 172.8 (C), 155.5 (C), 136.3 (C), 127.9 (C), 123.0 (CH), 122.1 (CH), 119.5 (CH), 118.8 (CH), 111.3 (CH), 110.7 (C), 79.4 (C), 61.5 (CH_3), 51.2 (CH), 32.3 (CH_3), 28.5 (CH_3 + CH_2) ppm; LRMS ES^+ *m/s* (%) 370 ($[M + Na]^+$, 100).

[(*S*)-2-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-yl]-1-(methoxymethylcarbamoyl) ethyl]carbamic acid *t*-butyl ester (1.137).



1.137

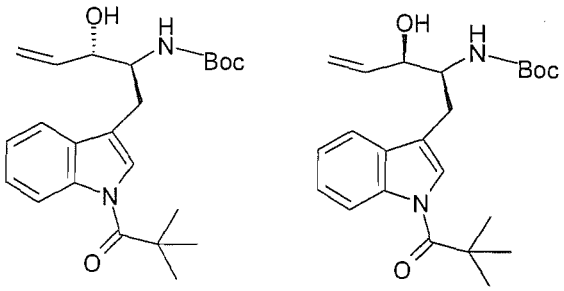
Method A: To a solution of *N,O*-dimethylhydroxylamine·HCl (73 mg, 0.75 mmol) in CH_2Cl_2 (2 mL) under argon was added $AlMe_3$ (2M in toluene, 0.37 mL, 0.75 mmol). The reaction mixture was stirred at rt for 30 min then **1.111** (0.1 g, 0.25 mmol) in CH_2Cl_2 (1 mL) was added and the reaction mixture was heated at reflux. After 24 h 0.5 M HCl (5 mL) was added dropwise and the organic phase was washed with sat. $NaHCO_3$ (aq) (5 mL), water (5 mL) then brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil (94 mg). Purification by column chromatography (SiO_2, 40% EtOAc in hexane) afforded **1.137** as a yellow oil (61 mg, 57%).

Method B: To a solution of **1.135** (16.9 g, 49 mmol) in THF at rt under argon was added NaH (60% in mineral oil, 3.9 g, 97 mmol). The reaction mixture was stirred for 30 minutes the pivaloyl chloride (9 mL, 73 mmol) was added. The reaction mixture was stirred for 2 h at rt then quenched with sat. NH_4Cl (aq) (50 mL) and extracted with CH_2Cl_2 (2 x 100 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 70% EtOAc in hexane) afforded **1.137** as a yellow oil (19.2 g, 92%).

$[\alpha]_D^{27}$ +18.3 (*c* 0.5, $CHCl_3$); IR ν 3307, 2967, 2936, 2876, 1689, 1660 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.48 (1 H, d, *J* = 7.6 Hz, Ar-**H**), 7.61 (1 H, s, Ar-**H**), 7.51 (1 H, d, *J* = 7.6 Hz, Ar-**H**), 7.33 (1 H, t, *J* = 7.6 Hz, Ar-**H**), 7.26 (t, 1 H, *J* = 7.6 Hz, Ar-**H**), 5.35 (1 H, d, *J* = 8.4 Hz, N**H**), 5.01 (1 H, m, NHC**H**), 3.65 (3 H, s, NOC**H**$_3$), 3.13 (3 H, s, NC**H**$_3$), 3.05 (1 H, br dd, *J* = 14.8, 6.0 Hz, C**H**H), 3.05 (1 H,

dd, J = 14.8, 6.5 Hz, CHH), 1.50 (9 H, s, Piv C(CH_3)$_3$), 1.41 (9 H, s, Boc C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0 (C), 172.3, (C), 155.4 (C), 137.1 (C), 129.8 (C), 125.4 (CH), 123.8 (CH), 123.5 (CH), 118.4 (CH), 117.5 (CH), 116.6 (C), 79.9 (C), 61.7 (CH_3), 50.1 (CH), 41.3 (C), 32.2 (CH_3), 28.8 (CH_3), 28.5 x 2 (CH_3 + CH_2) ppm; LRMS ES$^+$ *m/s* (%) 454 ([M + Na]$^+$, 100).

{(*S*)-1-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-ylmethyl]-2-hydroxybut-3-enyl}carbamic acid *t*-butyl ester (1.139).



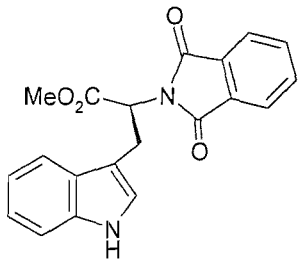
1.139 *syn* **2: 1** **1.139 *anti***

To a solution of Weinreb amide **1.137** (0.21 g, 0.5 mmol) in THF (5 mL) at -78 °C under argon was added DIBAL-H (1.0 M in toluene, 1.45 mL, 1.45 mmol) at a rate so the temperature did not exceed -65 °C. After stirring at -78 °C for 1.5 h MeOH (1 mL) was added dropwise, followed by the addition of sat. Rochelle's salt (aq) (10 mL). After stirring for 1 h the reaction mixture was extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide crude aldehyde **1.138** (0.20 g, quant.) which was used without purification. To a solution of aldehyde **1.138** (0.20 g, 0.5 mmol) in THF (5 mL) at 0 °C under argon was added vinyl MgCl (1.6M in THF, 1.1 mL, 1.7 mmol). The reaction mixture was stirred at 0 °C for 20 h then quenched with sat. NH_4Cl (aq) (5 mL) followed by water (5 mL) then extracted with EtOAc (2 x 10 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.139** as a white foam (0.12 g, 62% for 2 steps) isolated as an inseparable 2:1 mixture of diastereoisomers and recovered aldehyde. Data reported for major (*syn*) diastereoisomer.

$[\alpha]_D^{28}$ -14.5 (*c* 0.5, $CHCl_3$); IR ν 3368, 2977, 1684, 1504 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (1 H, app d, J = 7.8 Hz, Ar-**H**), 7.70-7.45 (2 H, m, 2 x Ar-**H**), 7.35 (1 H, td, J = 7.8, 1.2 Hz, Ar-**H**), 7.27 (1 H, app t, J = 7.8 Hz, Ar-**H**), 5.93 (1 H,

ddd, J = 17.2, 10.5, 5.6 Hz, CH_2=C**H**), 5.31 (1 H, app dt, J = 17.2, 1.3 Hz, CH**H**=CH), 5.22 (1 H, app dt, J = 10.5, 1.3 Hz, CH**H**=CH), 4.91 (1 H, d, J = 7.8 Hz, N**H**), 4.35-4.17 (2 H, m, C**H**NH + C**H**OH), 3.10-2.81 (2 H, m, CH_2), 1.51 (9 H, s, Piv C(CH_3)$_3$), 1.40 (9 H, br s, Boc C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C), 156.4 (C), 138.6 (CH), 137.3 (C), 137.2 (CH), 129.8 (C), 125.5 (CH), 123.6 (CH), 118.6 (CH), 117.6 (CH), 117.3 (CH_2), 116.5 (C), 80.0 (C), 73.7 (CH), 54.2 (CH), 41.3 (C), 28.8 (CH_3), 28.5 (CH_3), 27.6 (CH_2) ppm; LRMS ES$^+$ *m/s* (%) 423 ([M + Na]$^+$, 100).

(*S*)-2-(1,3-Dioxo-1,3-dihydroisoindol-2-yl)-3-(1*H*-indol-3-yl)propionic acid methyl ester (1.140).



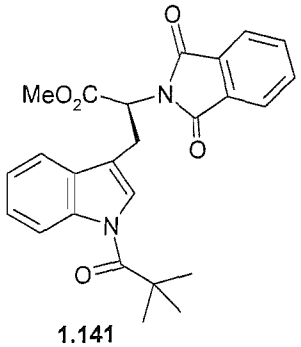
1.140

To a solution of L-Trp(OMe)·HCl (1.36 g, 6.2 mmol) and phthalic anhydride (1.02 g, 6.9 mmol) in toluene (10 mL) under argon was added Et_3N (1.32 mL, 9.5 mmol). The reaction mixture was heated at reflux for 6 h then concentrated *in vacuo*. The resulting oil was dissolved in EtOAc (15 mL), washed with 5% HCl (aq) (2 x 5 mL) and water (5 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The resulting yellow solid was triturated with EtOAc and diethyl ether to afford recovered phthalic anhydride as a white solid (0.29 g, 28% recovery). The filtrate was concentrated *in vacuo* and purified by column chromatography (SiO_2, 90:9:1 CH_2Cl_2, MeOH, Et_3N) to afford **1.140** as a yellow foam (1.83 g, 84%).

$[\alpha]_D^{28}$ -174.3 (*c* 0.5, $CHCl_3$); mp. 56-58 °C; IR ν 3402, 2953, 1774, 1740, 1702 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (1 H, br s, indole N**H**), 7.75 (2 H, dd, J = 5.5, 3.1 Hz, phthalimide Ar-**H**), 7.65 (2 H, dd, J = 5.5, 3.1 Hz, phthalimide Ar-**H**), 7.60 (1 H, app d, J = 7.7 Hz, Ar-**H**), 7.26 (1 H, app d, J = 7.7 Hz, Ar-**H**), 7.12 (1 H, td, J = 7.7, 1.2 Hz, Ar-**H**), 7.05 (1 H, td, J = 7.7, 1.2 Hz, Ar-**H**), 6.99 (1 H, d, J = 2.4 Hz, Ar-**H**), 5.28 (1 H, dd, J = 9.1, 6.8 Hz, C**H**N), 3.80 (3 H, s, OCH_3), 3.78-3.72 (2 H, m, CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (C), 167.7 (C), 136.2 (C), 134.1 (CH), 131.8 (C), 127.3 (C), 125.4 (C), 123.5 (CH), 122.7 (CH), 122.2 (CH),

119.6 (CH), 118.6 (CH), 111.2 (CH), 52.9 (CH_3), 52.7 (CH), 24.9 (CH_2) ppm; LRMS ES^+ *m/s* (%) 371 ($[M + Na]^+$, 100).

(*S*)-3-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-yl]-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)propionic acid methyl ester (1.141).

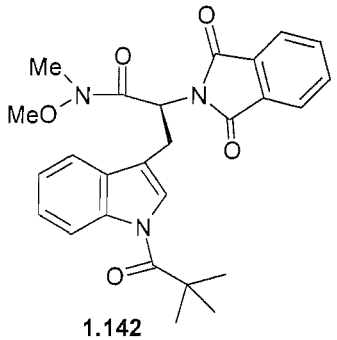


1.141

To a solution of **1.140** (1.7 g, 4.9 mmol) and $Bu_4N^+HSO_4^-$ (0.17 g, 0.5 mmol) in toluene (30 mL) was added 50% NaOH (aq) (7.5 mL). The reaction mixture was stirred for 5 min then pivaloyl chloride (0.9 mL, 7.3 mmol) in toluene (15 mL) was added. After 1 h the phases were separated and the organic phase was washed with water (2 x 10 mL) then brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5-50% EtOAc in hexane) afforded **1.141** as a colourless oil (1.7 g, 81%).

$[\alpha]_D^{28}$ -82.4 (*c* 1.0, $CHCl_3$); IR ν 2953, 1775, 1746, 1712, 1687 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.42 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.78 (2 H, dd, *J* = 5.5, 3.1 Hz, phthalimide Ar-**H**), 7.68 (2 H, dd, *J* = 5.5, 3.1 Hz, phthalimide Ar-**H**), 7.55 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.52 (1 H, s, Ar-**H**), 7.31 (1 H, td, *J* = 7.7, 1.2 Hz, Ar-**H**), 7.25 (1 H, td, *J* = 7.7, 1.2 Hz, Ar-**H**), 5.32 (1 H, dd, *J* = 10.8, 5.4 Hz, C**H**N), 3.81 (3 H, s, OC**H**$_3$), 3.75 (1 H, dd, *J* = 15.6, 10.8 Hz, C**H**H), 3.68 (1 H, app ddd, *J* = 15.6, 5.4, 1.0 Hz, CH**H**), 1.35 (9 H, s, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (C), 169.4 (C), 167.6 (C), 137.2 (C), 134.4 (CH), 131.7 (C), 129.2 (C), 125.6 (CH), 123.7 (CH), 123.6 (2 x CH), 118.3 (CH), 117.5 (CH), 116.7 (C), 53.1 (CH_3), 51.4 (CH), 41.1 (C), 28.5 (CH_3), 24.7 (CH_2) ppm; LRMS ES^+ *m/s* (%) 455 ($[M + Na]^+$, 100).

(*S*)-3-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-yl]-2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-*N*-methoxy-*N*-methylpropionamide (1.142).

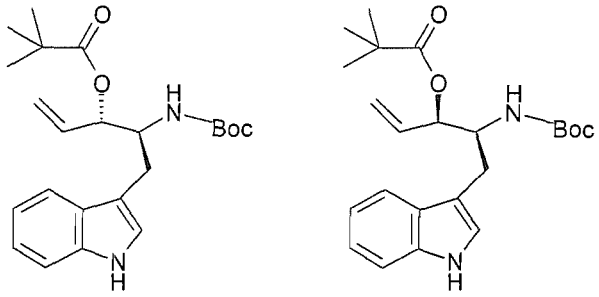


1.142

To a solution of *N,O*-dimethylhydroxylamine·HCl (0.68 g, 7.0 mmol) in CH_2Cl_2 (15 mL) under argon was added $AlMe_3$ (2M in toluene, 3.5 mL, 7.0 mmol). The reaction mixture was stirred at rt for 30 min then **1.141** (1.0 g, 2.3 mmol) in CH_2Cl_2 (10 mL) was added and the reaction mixture was heated at reflux. After 24 h 0.5M HCl (aq) (25 mL) was added dropwise and the organic phase was washed with sat. $NaHCO_3$ (aq) (25 mL), water (25 mL) then brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 20-100% EtOA*c* in hexane) afforded a yellow solid, recrystallisation from EtOAc afforded **1.142** as a pale yellow solid (0.67 g, 62%).

$[\alpha]_D^{28}$ +2.7 (*c* 1.0, $CHCl_3$); mp 84-86 °C; IR ν 3307, 2974, 2935, 1642 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.47 (1 H, d, *J* = 7.9 Hz, Ar-**H**), 7.72 (1 H, s, Ar-**H**), 7.58 (1 H, app d, *J* = 7.7 Hz, phthalimide Ar-**H**), 7.51 (1 H, d, *J* = 7.9 Hz, Ar-**H**), 7.48, (1 H, td, *J* = 7.7, 1.2 Hz, phthalimide Ar-**H**), 7.40 (1 H, app t, *J* = 7.7 Hz, phthalimide Ar-**H**), 7.31 (1 H, t, *J* = 7.9 Hz, Ar-**H**), 7.24 (1 H, t, *J* = 7.9 Hz, Ar-**H**), 7.11 (1 H, app d, *J* = 7.7 Hz, phthalimide Ar-**H**), 5.47 (1 H, m, C**H**N), 3.70 (3 H, s, OC**H**$_3$), 3.32 (1 H, dd, *J* = 14.7, 6.3 Hz, C**H**H), 3.25 (1 H, dd, *J* = 14.7, 5.9 Hz, CH**H**), 3.13 (3 H, s, NC**H**$_3$), 1.42 (9 H, s, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.2 (C), 2 x 171.3 (C), 167.0 (C), 137.1 (C), 135.5 (C), 133.4 (C), 130.7 (CH), 129.8 (C), 129.3 (CH), 127.5 (CH), 127.4 (CH), 125.4 (CH), 124.5 (CH), 123.5 (CH), 118.4 (CH), 117.6 (CH), 116.0 (C), 61.8 (CH_3), 59.8 (CH), 41.3 (C), 32.3 (CH_3), 28.6 (CH_3), 27.7 (CH_2) ppm; LRMS ES^+ *m/s* (%) 462 ($[M + H]^+$, 100).

2,2-Dimethylpropionic acid 1-[(*S*)-1-*t*-butoxycarbonylamino-2-(1*H*-indol-3-yl)ethyl]allyl ester (1.149).

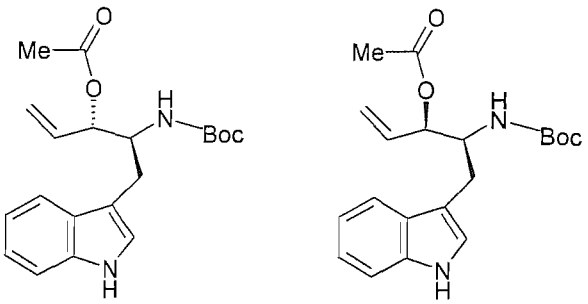


1.149 *syn* **3: 1** **1.149 *anti***

To a solution of **1.134** (100 mg, 0.32 mmol) and $Bu_4N^+HSO_4^-$ (11 mg, 0.03 mmol) in toluene (2 mL) was added 50% NaOH (aq) (0.5 mL). The reaction mixture was stirred for 5 min then pivaloyl chloride (58 μL, 0.5 mmol) in toluene (1 mL) was added. After 1 h the organic phase was washed with water (2 x 2 mL) then brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.149** as a pale yellow oil (52 mg, 41%) isolated as an inseparable 3:1 mixture of diastereoisomers and recovered starting material **1.134** (52 mg, 52%). Data reported for major (*syn*) diastereoisomer.

$[\alpha]_D^{28}$ -25.2 (*c* 1.3, $CHCl_3$); IR ν 3369, 2975, 2932, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.15 (1 H, br s, indole N**H**), 7.66 (1 H, d, *J* = 7.6 Hz, Ar-**H**), 7.35 (1 H, d, *J* = 7.6 Hz, Ar-**H**), 7.19 (1 H, t, *J* = 7.6 Hz, Ar-**H**), 7.12 (1 H, t, *J* = 7.6 Hz, Ar-**H**), 6.99 (1 H, m, Ar-**H**), 5.81 (1 H, ddd, *J* = 17.0, 10.9, 5.7 Hz, CH_2=C**H**), 5.34 (1 H, m, C**H**OPiv), 5.29-5.15 (2 H, m, CH_2=CH), 4.68 (1 H, d, *J* = 9.2 Hz, N**H**), 4.21 (1 H, m, C**H**NH), 2.98 (1 H, dd, *J* = 14.6, 6.9 Hz, C**H**H), 2.91 (1 H, dd, *J* = 14.6, 7.5 Hz, CH**H**), 1.41 (9 H, s, Boc-C($C\mathbf{H}_3$)$_3$), 1.29 (9 H, s, Piv-C($C\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.4 (C), 155.7 (C), 136.4 (C), 134.2 (CH), 127.8 (C), 122.8 (CH), 122.2 (CH), 119.6 (CH), 119.1 (CH), 117.9 (CH_2), 111.6 (C), 111.2 (CH), 79.5 (C), 74.1 (CH), 53.6 (CH), 39.2 (C), 28.5 (CH_3), 28.1 (CH_2), 27.5 (CH_3) ppm; LRMS ES^+ *m/s* (%) 423 ($[M + Na]^+$, 100), 824 ($[2M + Na]^+$, 20).

Acetic acid 1-[(*S*)-1-*t*-butoxycarbonylamino-2-(1*H*-indol-3-yl)ethyl]allyl ester (1.150).

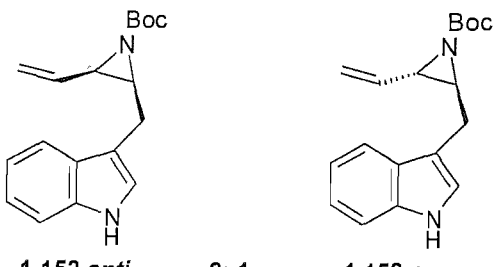


1.150 *syn* **3: 1** **1.150 *anti***

To a solution of **1.134** (100 mg, 0.3 mmol), DMAP (4 mg, 0.03 mmol) and Et_3N (71 μL, 0.5 mmol) in CH_2Cl_2 (1 mL) under argon was added acetic anhydride (45 μL, 0.5 mmol). The reaction mixture was stirred for 2 h then concentrated *in vacuo*. Purification by column chromatography (SiO_2, 40% EtOAc in hexane) afforded **1.150** as a colourless oil (84 mg, 72%) isolated as an inseparable 3:1 mixture of diastereoisomers. Data reported for major (*syn*) diastereoisomer.

$[\alpha]_D^{28}$ -14.7 (*c* 1.0, $CHCl_3$); IR ν 3349, 2978, 2931, 1741, 1694, 1503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (1 H, br s, indole NH), 7.67 (1 H, d, J = 7.6 Hz, Ar-H), 7.35 (1 H, d, J = 7.6 Hz, Ar-H), 7.19 (1 H, t, J = 7.6 Hz, Ar-H), 7.12 (1 H, m, Ar-H), 7.01 (1 H, m, Ar-H), 5.80 (1 H, ddd, J = 17.5, 10.7, 5.9 Hz, CH_2=CH), 5.35 (1 H, m, CHOAc), 5.27 (1 H, app d, J = 17.5 Hz, CHH=CH), 5.22 (1 H, app d, J = 10.7 Hz, CHH=CH), 4.77 (1 H, d, J = 9.0 Hz, NH), 4.35 (1 H, m, CHNH), 3.08 (1 H, m, CHH), 2.91 (1 H, dd, J = 14.0, 7.8 Hz, CHH), 2.12 (3 H, s, Ac-CH_3), 1.42 (9 H, br s, Boc-C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.0 (C), 155.7 (C), 136.4 (C), 134.0 (CH), 127.7 (C), 122.8 (CH), 122.2 (CH), 119.6 (CH), 119.1 (CH), 118.1 (CH_2), 111.6 (C), 111.3 (CH), 79.5 (C), 74.7 (CH), 53.4 (CH), 28.5 (CH_3), 28.2 (CH_2), 21.2 (CH_3) ppm; LRMS ES^+ *m/s* (%) 381 ($[M + Na]^+$, 100).

(*S*)-2-(1*H*-Indol-3-ylmethyl)-3-vinylaziridine-1-carboxylic acid *t*-butyl ester (1.152).

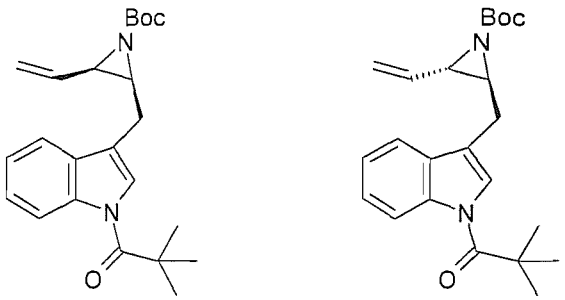


1.152 *anti* **2: 1** **1.152 *syn***

To a solution of **1.134** (100 mg, 0.3 mmol) in THF (1 mL) at 0 °C under argon was added PPh_3 (0.17 g, 0.63 mmol) and DIAD (0.12 mL, 0.63 mmol). The reaction mixture was warmed to rt and stirred overnight then concentrated *in vacuo*. Column chromatography (SiO_2, 30-50% EtOAc in hexane) afforded **1.152** as a yellow oil (70 mg, 74%) isolated as an inseparable 2:1 mixture of diastereoisomers. Data reported for major (*anti*) diastereoisomer.

$[\alpha]_D^{28}$ -2.0 (*c* 2.4, $CHCl_3$); IR 3380, 2980, 2933, 1698 ν cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.09 (1 H, br s, indole N**H**), 7.62 (1 H, app d, *J* = 7.8 Hz, Ar-**H**), 7.36 (1 H, app d, *J* = 7.8 Hz, Ar-**H**), 7.24 (1 H, d, *J* = 2.2 Hz, Ar-**H**), 7.20 (1 H, td, *J*, = 7.8, 1.0 Hz, Ar-**H**), 7.12 (1 H, td, *J* = 7.8, 1.0 Hz, Ar-**H**), 5.84 (1 H, ddd, *J* = 17.2, 10.5, 6.7 Hz, CH_2=C**H**), 5.53 (1 H, app d, *J* = 17.2, C**H**H=CH), 5.38 (1 H, dd, *J* = 10.5, 0.8 Hz, CH**H**=CH), 3.22-2.96 (2 H, m, 2 x C**H**N), 2.96-2.73 (2 H, m, CH_2), 1.44 (9 H, s, Boc-C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.6 (C), 136.3 (C), 134.3 (CH), 132.4 (CH), 127.6 (C), 122.1 (CH), 119.9 (CH_2), 119.4 (CH), 118.9 (CH), 112.9 (C), 111.2 (CH), 81.3 (C), 43.8 (CH), 43.5 (CH), 28.0 (CH_3), 24.1 (CH_2) ppm; LRMS ES^+ *m/s* (%) 321 ($[M + Na]^+$, 80).

(*S*)-2-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-ylmethyl]-3-vinylaziridine-1-carboxylic acid *t*-butyl ester (1.153).

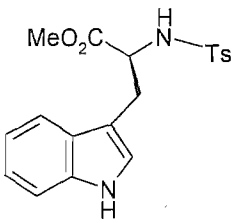


1.153 ***anti*** **4: 1** **1.153** ***syn***

To a solution of **1.139** (454 mg, 1.1 mmol) in THF (5 mL) at 0 °C under argon was added PPh_3 (0.59 g, 2.3 mmol) and DIAD (0.45 mL, 2.3 mmol). The reaction mixture was warmed to rt, stirred for 48 h and concentrated *in vacuo*. Column chromatography (SiO_2, 0-30% EtOAc in hexane) afforded **1.153** as a colourless oil which when left to stand became a white crystalline solid (0.23 g, 54%) isolated as an inseparable 4:1 mixture of diastereoisomers. Data reported for major (*anti*) diastereoisomer.

$[\alpha]_D^{27}$ -6.1 (*c* 0.5, $CHCl_3$); mp. 65-68 °C; IR ν 2981, 2935, 1702, 1685 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.51 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.95 (1 H, s, Ar-**H**), 7.50 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.35 (1 H, td, *J* = 7.7, 1.0 Hz, Ar-**H**), 7.27 (2 H, td, *J* = 7.7, 1.1 Hz, Ar-**H**), 5.81 (1 H, ddd, *J* = 17.2, 10.4, 6.5 Hz, CH_2=C**H**), 5.53 (1 H, app d, *J* = 17.2 Hz, C**H**H=CH), 5.39 (1 H, app d, *J* = 10.4 Hz, CH**H**=CH), 3.08 (1 H, app t, *J* = 6.5 Hz, NC**H**CH_2=CH), 2.94 (1 H, m, C**H**N), 2.88-2.81 (2 H, m, CH_2), 1.52 (9 H, s, Piv-C(CH_3)$_3$), 1.43 (9 H, s, Boc-C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.3 (C), 162.6 (C), 137.3 (C), 132.3 (CH), 129.7 (C), 125.4 (C), 125.4 (CH), 123.4 (2 x CH), 120.3 (CH_2), 118.4 (CH), 117.6 (CH), 81.5 (C), 43.6 (CH), 42.0 (CH), 41.3 (C), 28.7 (CH_3), 28.0 (CH_3), 23.9 (CH_2) ppm; LRMS ES^+ *m/s* (%) 405 ($[M + Na]^+$, 100); Anal. Calcd for $C_{23}H_{30}N_2O_3$: C, 72.22; H, 7.91; N, 7.32. Found: C, 71.92; H, 7.56; N, 7.14.

(*S*)-3-(1*H*-Indol-3-yl)-2-(toluene-4-sulfonylamino)propionic acid methyl ester (1.155).



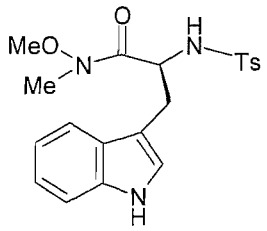
1.155

To a solution of L-Trp(OMe)·HCl (0.50 g, 2 mmol) in CH_2Cl_2 (1 mL) at 0 °C under argon was added TsCl (0.39 g, 2.1 mmol) followed by Et_3N (0.82 mL, 5.9 mmol). The reaction mixture was stirred at 0 °C for 3.5 h then water (1 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined extracts were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 100% EtOAc) afforded a white solid. Recrystallisation from EtOAc/ hexane afforded **1.155** as a white crystalline solid (0.72 g, 98%).

$[\alpha]_D^{28}$ +11.8 (*c* 0.5, $CHCl_3$); mp. 126-128 °C; IR ν 3404, 3310, 1736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.14 (1 H, br s, indole N**H**), 7.60 (2 H, d, *J* = 8.3 Hz, Ts Ar-**H**), 7.42 (1 H, app d, *J* = 7.8 Hz, Ar-**H**), 7.31 (1 H, app d, *J* = 7.8 Hz, Ar-**H**), 7.21-7.11 (3 H, m, Ts Ar- **H** + Ar-**H**), 7.06 (1 H, td, *J* = 7.8, 0.9 Hz, Ar-**H**), 7.00 (1 H, d, *J* = 2.3 Hz, Ar-**H**), 5.19 (1 H, d, *J* = 8.8 Hz, N**H**), 4.25 (1 H, dt, *J* = 8.8, 5.8 Hz,

CHNH), 3.44 (3 H, s, CO_2CH_3), 3.23 (2 H, app d, J = 5.8 Hz, CH_2), 2.36 (3 H, s, Ts CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8 (C), 143.6 (C), 136.7 (C), 136.2 (C), 129.6 (CH), 127.3 (C), 127.2 (CH), 123.6 (CH), 122.3 (CH), 119.8 (CH), 118.6 (CH), 111.4 (CH), 109.1 (C), 56.2 (CH), 52.5 (CH_3), 29.3 (CH_2), 21.6 (CH_3) ppm; LRMS ES^+ *m/s* (%) 395 ($[M + Na]^+$, 100), 767 ($[2M + Na]^+$, 80).

(*S*)-3-(1*H*-Indol-3-yl)-*N*-methoxy-*N*-methyl-2-(toluene-4-sulfonylamino) propionamide (1.156).



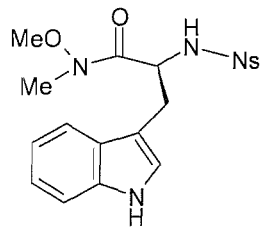
1.156

To a solution of **1.135** (1 g, 2.9 mmol) in CH_2Cl_2 (20 mL) under argon was added TFA (5 mL). The reaction mixture was stirred for 2 h then sat. $NaHCO_3$ (aq) was added until gas evolution ceased. The aqueous phase was extracted with CH_2Cl_2 (5 x 20 mL) and the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude amine (0.65 g, 91%) which was used without any purification. To a solution of amine (100 mg, 0.4 mmol) in CH_2Cl_2 (1 mL) under argon was added TsCl (81 mg, 0.42 mmol) followed by Et_3N (0.17 mL, 1.2 mmol). After stirring for 3.5 h water (2 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 2 mL). The combined extracts were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded a white solid. Recrystallisation from EtOAc/ hexane provided **1.156** as a white crystalline solid (0.11 g, 68%).

$[\alpha]_D^{28}$ +39.8 (*c* 0.5, $CHCl_3$); mp. 74-75 °C; IR ν 3396, 3310, 1651 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.17 (1 H, br s, indole NH), 7.53 (2 H, d, J = 7.8 Hz, Ts Ar-H), 7.43 (1 H, app d, J = 7.8 Hz, Ar-H), 7.29 (1 H, app d, J = 7.8 Hz, Ar-H), 7.14 (1 H, td, J = 7.8, 1.0 Hz, Ar-H), 7.08 (2 H, d, J = 7.8 Hz, Ts Ar-H), 7.07 (1 H, m, Ar-H), 7.01 (1 H, d, J = 2.3 Hz, Ar-H), 5.60 (1 H, d, J = 8.5 Hz, NH), 4.60 (1 H, td, J = 8.5, 5.4 Hz, CHNH), 3.45 (3 H, s, OCH_3), 3.16 (1 H, dd, J = 14.6, 5.4 Hz, CHH), 3.02 (1 H, dd, J = 14.6, 8.5 Hz, CHH), 2.97 (3 H, s, NCH_3), 2.33 (3 H, s, Ts CH_3) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.7 (C), 143.2 (C), 136.9 (C), 136.2 (C), 129.3

(CH), 127.5 (C), 127.2 (CH), 123.6 (CH), 122.0 (CH), 119.5 (CH), 118.3 (CH), 111.4 (CH), 109.9 (C), 61.4 (CH_3), 53.4 (CH), 32.2 (CH_3), 29.5 (CH_2), 21.6 (CH_3) ppm; LRMS ES^+ *m/s* (%) 424 ($[M + Na]^+$, 100), 825 ($[2M + Na]^+$, 50).

(*S*)-3-(1*H*-Indol-3-yl)-*N*-methoxy-*N*-methyl-2-(4-nitrobenzenesulfonylamino) propionamide (1.157).

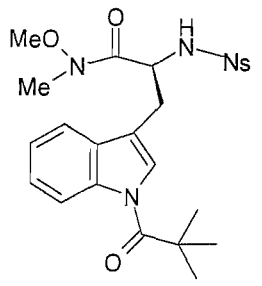


1.157

To a solution of **1.135** (200 mg, 0.57 mmol) in CH_2Cl_2 (5 mL) under argon was added TFA (0.95 mL). The reaction mixture was stirred for 1 h then sat. $NaHCO_3$ (aq) was added until gas evolution ceased. The phases were separated and the aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude amine (0.5 g, quant.) which was used without any purification. To a solution of amine (0.5 g, 0.57 mmol) in CH_2Cl_2 (5 mL) under argon was added NsCl (0.13 g, 0.6 mmol) followed by Et_3N (0.24 mL, 1.7 mmol). After stirring for 2 h water (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-100% EtOAc in hexane) afforded **1.157** as a yellow foam (0.16 g, 63%).

$[\alpha]_D^{27}$ -69.4 (*c* 0.25, MeOH: $CHCl_3$); IR ν 3396, 3234, 1652 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 10.67 (1 H, br s, indole N**H**), 8.69 (1 H, br s, N**H**), 7.84 (2 H, d, *J* = 8.7 Hz, Ns Ar-**H**), 7.44 (2 H, d, *J* = 8.7 Hz, Ns Ar-**H**), 7.22 (1 H, m, Ar-**H**), 7.07 (1 H, m, Ar-**H**), 7.01 (1 H, d, *J* = 2.2 Hz, Ar-**H**), 6.94-6.81 (2 H, m, Ar-**H**), 4.44 (1 H, m, C**H**NH), 3.73 (3 H, s, OC**H**$_3$), 3.09 (3 H, s, NC**H**$_3$), 2.92 (1 H, dd, *J* = 14.3, 3.6 Hz, C**H**H), 2.72 (1 H, dd, *J* = 14.3, 10.5 Hz, CH**H**) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.1 (C), 147.5 (C), 135.2 (C), 125. 9 (CH), 125.6 (C), 123.4 (CH), 119.9 (CH), 117.5 (CH), 116.6 (C), 110.4 (CH), 107.8 (C), 60.6 (CH_3), 52.2 (CH), 31.0 (CH_3), 26.8 (CH_2) ppm; LRMS ES^+ *m/s* (%) 455 ($[M + Na]^+$, 100).

(*S*)-3-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-yl]-*N*-methoxy-*N*-methyl-2-(4-nitrobenzenesulfonylamino)propionamide (1.159).

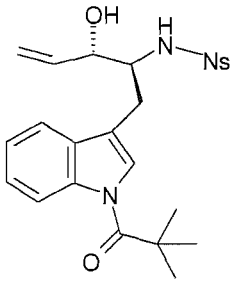


1.159

To a solution of **1.137** (0.19 g, 0.5 mmol) in CH_2Cl_2 (5 mL) under argon was added TFA (0.8 mL). The reaction mixture was stirred for 1 h then sat. $NaHCO_3$ (aq) was added until gas evolution ceased. The aqueous phase was extracted with CH_2Cl_2 (5 x 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude amine (0.16g, quant.) which was used without any purification. To a solution of amine (0.16 g, 0.5 mmol) in CH_2Cl_2 (5 mL) under argon was added NsCl (0.11 g, 0.5 mmol) followed by Et_3N (0.19 mL, 1.4 mmol). After stirring for 2 h water (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-100% EtOAc in hexane) afforded **1.159** as a white foam (0.22 g, 92%).

$[\alpha]_D^{28}$ +12.2 (*c* 0.5, $CHCl_3$); IR ν 3269, 3178, 2978, 2939, 1689, 1646 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.34 (1 H, app d, *J* = 7.8 Hz, Ar-**H**), 7.94 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.63 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.57 (1 H, s, Ar-**H**), 7.35 (1 H, m, Ar-**H**), 7.30 (1 H, m, Ar-**H**), 7.23 (1 H, td, *J* = 7.8, 1.1 Hz, Ar-**H**), 5.98 (1 H, d, *J* = 9.7 Hz, N**H**), 4.71 (1 H, td, *J* = 9.7, 4.3 Hz, C**H**NH), 3.74 (3 H, s, OC**H**$_3$), 3.15 (3 H, s, NC**H**$_3$), 3.12 (1 H, dd, *J* = 14.7, 4.3 Hz, C**H**H), 2.90 (1 H, dd, *J* = 14.7, 9.7 Hz, CH**H**), 1.49 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.7 (C), 171.1, (C), 149.8 (C), 145.4 (C), 137.1 (C), 128.7 (C), 127.8 (CH), 125.7 (CH), 124.6 (CH), 123.8 (CH), 123.6 (CH), 117.8 (CH), 117.7 (CH), 115.4 (C), 61.9 (CH_3), 53.1 (CH), 41.4 (C), 32.4 (CH_3), 29.2 (CH_2), 28.8 (CH_3) ppm; LRMS ES^+ *m/s* (%) 517 ($[M + H]^+$, 80), 539 ($[M + Na]^+$, 100).

***N*-{(1*S*,2*S*)-1-[1-(2,2-Dimethylpropionyl)-1H-indol-3-ylmethyl]-2-hydroxybut-3-enyl}-4-nitrobenzenesulfonamide (1.160).**

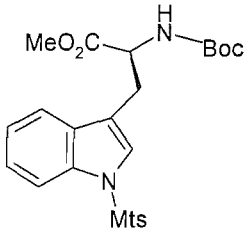


1.160

To a mixture of alcohol **1.139** (2.8 g, 7.0 mmol) and anisole (0.76 mL, 7.0 mmol) at 0 °C, under argon was added HCl (4 M in dioxane, 20 mL). The reaction mixture was stirred at rt for 2 h then concentrated under reduced pressure to give the crude amine (2.2 g, quant.) which was used without any purification. To a solution of the amine (2.2 g, 7.0 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon was added NsCl (1.63 g, 7.4 mmol) followed by Et_3N (1.96 mL, 14.0 mmol). After stirring at 0 °C for 2 h water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.160** as a yellow powder (1.157 g, 34%).

$[\alpha]_D^{24}$ -61.7 (*c* 0.5, MeOH); mp 211-213 °C; IR ν 3526, 3276, 2975, 2924, 2874, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, CD_3OD (5%)) δ 8.07 (1 H, app d, *J* = 7.6 Hz, Ar-**H**), 7.65 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.37 (1 H, s, Ar-**H**), 7.38 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.16 (1 H, dd, *J* = 7.6, 1.1 Hz, Ar-**H**), 7.13 (1 H, td, *J* = 7.6, 1.1 Hz, Ar-**H**), 7.08 (1 H, td, *J* = 7.6, 1.3 Hz, Ar-**H**), 5.80 (1 H, ddd, *J* = 17.2, 10.7, 5.7 Hz, CH_2=C**H**), 5.26 (1 H, app dt, *J* = 17.2, 1.5 Hz, C**H**H=CH), 5.12 (1 H, app dt, *J* = 10.7, 1.5 Hz, CH**H**=CH), 4.20 (1 H, dd, *J* = 5.7, 4.0 Hz, C**H**OH), 3.56 (1 H, ddd, *J* = 10.2, 4.3, 4.0 Hz, C**H**NH), 2.93 (1 H, dd, *J* = 14.9, 4.3 Hz, C**H**H), 2.55 (1 H, dd, *J* = 14.9, 10.2 Hz, CH**H**), 1.37 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$, CD_3OD (5%)) δ 176.8 (C), 148.9 (C), 145.9 (C), 136.9 (C), 136.5 (CH), 128.7 (C), 126.8 (CH), 125.2 (CH), 124.1 (CH), 123.3 (CH), 123.1 (CH), 118.3 (CH), 117.3 (CH), 117.2 (C), 117.1 (CH_2), 73.9 (CH), 57.9 (CH), 41.1 (C), 28.3 (CH_3), 26.3 (CH_2) ppm; LRMS ES^+ *m/s* (%) 486 ($[M + H]^+$, 30), 508 ($[M + Na]^+$, 50).

(*S*)-2-*t*-Butoxycarbonylamino-3-[1-(2,4,6-trimethylbenzenesulfonyl)-1*H*-indol-3-yl]propionic acid methyl ester (1.161).

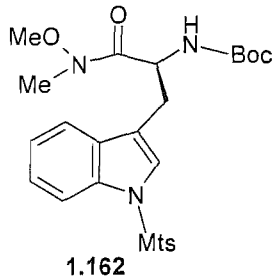


1.161

To a solution of **1.135** (8.0 g, 25 mmol) and $Bu_4N^+HSO_4^-$ (0.85 g, 2.5 mmol) in toluene (90 mL) was added 50% NaOH (aq) (40 mL). The reaction mixture was stirred for 5 min then 2-mesitylenesulfonyl chloride (8.2 g, 3.8 mmol) in toluene (30 mL) was added. After stirring for 2 h the phases were separated and the organic phase was washed with water (2 x 20 mL) then brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.161** as a yellow solid (11.8 g, 95%).

$[\alpha]_D^{28}$ +32.7 (*c* 0.5, $CHCl_3$); mp 119-121 °C; IR ν 3354, 2974, 1739, 1704 cm^{-1}; 1H NMR (300 MHz, $CDCl_3$) δ 7.51 (1 H, m, Ar-**H**), 7.39 (1 H, s, Ar-**H**), 7.33 (1 H, m, Ar-**H**), 7.24-7.14 (2 H, m, Ar-**H**), 6.95 (2 H, s, Mts Ar-**H**), 5.09 (1 H, d, J = 7.1 Hz, N**H**), 4.64 (1 H, m, C**H**NH), 3.66 (3 H, s, OC**H**$_3$), 3.30 (1 H, dd, J = 14.7, 5.5 Hz, C**H**H), 3.20 (1 H, dd, J = 14.7, 5.0 Hz, CH**H**), 2.52 (6 H, s, 2 x Mts C**H**$_3$), 2.28 (3 H, s, Mts CH_3), 1.44 (9 H, s, Boc C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.2 (C), 155.1 (C), 144.2 (C), 140.4 (C), 134.9 (C), 133.1 (C), 132.5 (CH), 130.4 (C), 124.8 (CH), 124.5 (CH), 122.7 (CH), 119.7 (CH), 114.6 (C), 112.6 (CH), 80.2 (C), 53.9 (CH_3), 52.4 (CH), 28.5 (CH_3), 27.9 (CH_2), 22.8 (CH_3), 21.1 (CH_3) ppm; LRMS ES^+ *m/s* (%) 523 ($[M + Na]^+$, 100).

(*S*)-1-(Methoxymethylcarbamoyl)-2-[1-(2,4,6-trimethylbenzenesulfonyl)-1*H*-indol-3-yl]ethyl}carbamic acid *t*-butyl ester (1.162).

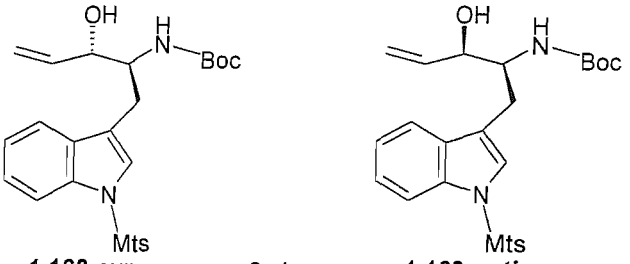


1.162

To a solution of **1.135** (0.1 g, 0.29 mmol) and $Bu_4N^+HSO_4^-$ (10 mg, 0.03 mmol) in toluene (2 mL) was added 50% NaOH (aq) (0.5 mL). The reaction mixture was stirred for 5 min then 2-mesitylenesulfonyl chloride (94 mg, 0.43 mmol) in toluene (1 mL) was added. After 2 h the phases were separated and the organic phase was washed with water (2 x 1 mL) then brine (1 mL), dried over $MgSO_4$ then concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-100% EtOAc in hexane) afforded **1.162** as a colourless oil (141 mg, 92%).

$[\alpha]_D^{27}$ +15.3 (*c* 0.5, $CHCl_3$); IR ν 3420, 3325, 2977, 2938, 1705, 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (1 H, d, *J* = 7.5 Hz, Ar-**H**), 7.40 (1 H, s, Ar-**H**), 7.34 (1 H, d, *J* = 7.5 Hz, Ar-**H**), 7.23-7.09 (2 H, m, 2 x Ar-**H**), 6.94 (2 H, s, 2 x Mts Ar-**H**), 5.26 (1 H, d, *J* = 8.0 Hz, N**H**), 4.97 (1 H, m, NHC**H**), 3.64 (3 H, s, OC**H**$_3$), 3.17 (1 H, dd, *J* = 14.4, 6.2 Hz, C**H**H), 3.11 (3 H, s, NC**H**$_3$), 3.04 (1 H, dd, *J* = 14.4, 6.6 Hz, CH**H**), 2.52 (6 H, s, 2 x Mts-C**H**$_3$), 2.28 (3 H, s, Mts-C**H**$_3$), 1.41 (9 H, s, C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1 (C), 155.3 (C), 144.0 (C), 140.4 (C), 135.0 (C), 133.2 (C), 132.5 (CH), 130.5 (C), 124.7 (CH), 124.4 (CH), 122.7 (CH), 119.6 (CH), 115.2 (CH), 112.7 (C), 80.4 (C), 62.0 (CH_3), 50.9 (CH), 32.5 (CH_3), 28.8 (CH_3), 28.6 (CH_2), 23.1 (CH_3), 21.5 (CH_3) ppm; LRMS ES^+ *m/s* (%) 552 ($[M + Na]^+$, 100).

{(*S*)-2-Hydroxy-1-[1-(2,4,6-trimethylbenzenesulfonyl)-1*H*-indol-3-ylmethyl]but-3-enyl}carbamic acid *t*-butyl ester (1.163).



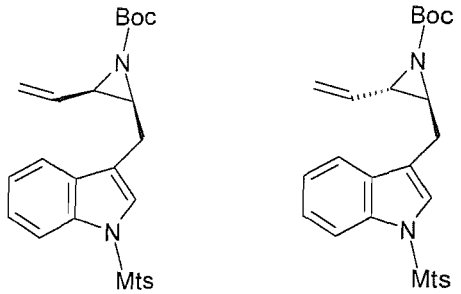
1.163 *syn* **3: 1** **1.163 *anti***

To a solution of **1.162** (2.67 g, 5.0 mmol) in THF (50 mL) at -78 °C under argon was added DIBAL-H (1.0 M in toluene, 15.1 mL, 15.1 mmol) at a rate so the temperature did not exceed -65 °C. After stirring at -78 °C for 1.5 h MeOH (10 mL) was added dropwise, followed by the addition of sat. Rochelle's salt (aq) (100 mL). After stirring for 1 h the reaction mixture was extracted with EtOAc (2 x 50 mL). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide crude aldehyde (2.75 g, quant.) which was reacted on without purification. To a solution of the aldehyde (2.75 g, 5.0 mmol) in THF (50 mL) at 0 °C under argon was added vinyl MgCl (1.6M in THF, 11.0 mL, 17.6 mmol). After stirring at 0 °C for 20 h the reaction mixture was quenched with sat. NH_4Cl (aq) (25 mL) followed by water (25 mL). The mixture was extracted with EtOAc (2 x 50 mL) and the combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-40% EtOAc in hexane) afforded **1.163** as a yellow oil (2.09 g, 83% for 2 steps) isolated as an inseparable 3:1 mixture of diastereoisomers and recovered aldehyde. Data reported for major (*syn*) diastereoisomer.

$[\alpha]_D^{27}$ -10.4 (*c* 0.5, $CHCl_3$); IR ν 3437, 3016, 2980, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (1 H, d, *J* = 7.2 Hz, Ar-**H**), 7.47 (1 H, s, Ar-**H**), 7.35 (1 H, td, *J* = 7.2, 1.6 Hz, Ar-**H**), 7.24-7.13 (2 H, m, Ar-**H**), 6.93 (2 H, s, Mts Ar-**H**), 5.89 (1 H, ddd, *J* = 17.2, 10.6, 5.6 Hz, CH_2=C**H**), 5.26 (1 H, app dt, *J* = 17.2, 1.4 Hz, C**H**H=CH), 5.18 (1 H, app dt, *J* = 10.6, 1.4 Hz, CH**H**=CH), 4.93 (1 H, d, *J* = 8.9 Hz, N**H**), 4.17 (1 H, m, C**H**OH), 3.90 (1 H, m, C**H**NH), 3.05 (1 H, dd, *J* = 14.5, 7.5 Hz, C**H**H), 3.97 (1 H, m, CH**H**), 2.52 (6 H, s, 2 x Mts CH_3), 2.27 (3 H, s, Mts CH_3), 1.38 (9 H, br s, Boc $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.3 (C), 144.0 (C), 140.3 (C), 138.3 (CH), 135.1 (C), 133.3 (C), 132.5 (CH), 130.5 (C), 124.5 (CH), 123.9 (CH), 122.7 (CH), 119.9 (CH), 116.8 (C), 116.4 (CH_2), 112.6 (CH), 79.7 (C),

72.9 (CH), 54.6 (CH), 28.5 (CH_3), 27.4 (CH_2), 22.8 (CH_3), 21.1 (CH_3) ppm; LRMS ES^+ *m/s* (%) 521 ($[M + Na]^+$, 100).

(*S*)-2-[1-(2,4,6-Trimethylbenzenesulfonyl)-1*H*-indol-3-ylmethyl]-3-vinyl aziridine-1-carboxylic acid *t*-butyl ester (1.164).

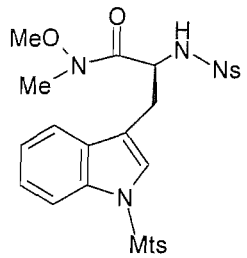


1.164 *anti* **3: 1** **1.164 *syn***

To a solution of **1.163** (2.0 g, 4.0 mmol) in THF (25 mL) at 0 °C under argon was added PPh_3 (2.1 g, 8.0 mmol) and DIAD (1.58 mL, 8.0 mmol). The reaction mixture was warmed to rt and stirred for 16 h then concentrated *in vacuo*. Column chromatography (SiO_2, 0-30% EtOAc in hexane) afforded **1.164** as a pale yellow oil (1.15 g, 60%) isolated as an inseparable 3:1 mixture of diastereoisomers. Data reported for major (*anti*) diastereoisomer.

$[\alpha]_D^{27}$ -7.2 (*c* 0.5, $CHCl_3$); IR ν 3018, 2982, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1H NMR (400 MHz, $CDCl_3$) δ 7.62-7.50 (2 H, m, Ar-**H**), 7.39 (1 H, m, Ar-**H**), 7.25-7.28 (2 H, m, Ar-**H**), 6.94 (2 H, s, Mts Ar-**H**), 5.70 (1 H, ddd, *J* = 17.1, 10.5, 6.4 Hz, CH_2=C**H**), 5.52 (1 H, app ddd, *J* = 17.1, 1.6, 0.9 Hz, C**H**H=CH), 5.36 (1 H, app ddd, *J* = 10.5, 1.6, 0.6 Hz, CH**H**=CH), 3.09 (1 H, t, *J* = 6.4 Hz, C**H**N), 3.05-2.72 (3 H, m, C**H**N, + CH_2), 2.54 (6 H, s, 2 x Mts CH_3), 2.28 (3 H, s, Mts CH_3), 1.41 (9 H, s, Boc $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.2 (C), 160.3 (C), 143.9 (C), 140.3 (C), 135.0 (C), 132.4 (CH), 132.0 (CH), 130.3 (C), 124.4 (CH), 123.9 (CH), 122.5 (CH), 120.2 (CH_2), 119.7 (CH), 117.0 (C), 112.6 (CH), 81.4 (C), 43.2 (CH), 42.6 (CH), 27.9 (CH_3), 23.9 (CH_2), 22.8 (CH_3), 21.1 (CH_3) ppm; LRMS ES^+ *m/s* (%) 405 ($[M + Na]^+$, 100); Anal. Calcd for $C_{27}H_{32}N_2O_4S$: C, 67.47; H, 6.71; N, 5.83. Found: C, 67.43; H, 6.51; N, 5.61.

(*S*)-*N*-Methoxy-*N*-methyl-2-(4-nitrobenzenesulfonylamino)-3-[1-(2,4,6-trimethylbenzenesulfonyl)-1*H*-indol-3-yl]propionamide (1.165).

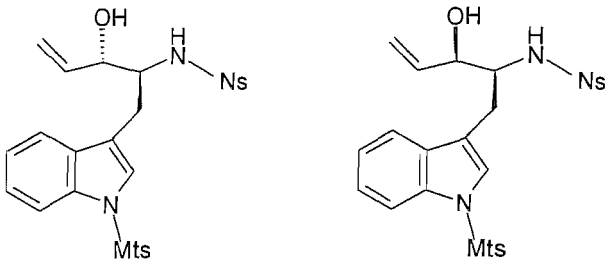


1.165

To a solution of **1.162** (0.25 g, 0.5 mmol) in CH_2Cl_2 (5 mL) under argon was added TFA (0.8 mL). The reaction mixture was stirred for 1 h then sat. $NaHCO_3$ (aq) was added until gas evolution ceased. The aqueous phase was extracted with CH_2Cl_2 (10 x 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude amine (0.21 g, quant.) which was used without any purification. To a solution of the amine (0.21 g, 0.5 mmol) in CH_2Cl_2 (5 mL) under argon was added NsCl (0.11 g, 0.5 mmol) followed by Et_3N (0.19 mL, 1.4 mmol). After stirring for 2 h water (5 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-100% EtOAc in hexane) afforded **1.165** as a white foam (0.25 g, 85%).

$[\alpha]_D^{27}$ -14.2 (*c* 1.0, $CHCl_3$); IR ν 3188, 2983, 2929, 1648 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92 (2 H, d, *J* = 8.8 Hz, Ns Ar-**H**), 7.59 (2 H, d, *J* = 8.8 Hz, Ar-**H**), 7.43 (1 H, s, Ar-**H**), 7.33 (1 H, m, Ar-H), 7.17-7.02 (3 H, m, Ar-**H**), 6.94 (2 H, s, Mts Ar-**H**), 6.15 (1 H, d, *J* = 10.0 Hz, N**H**), 4.64 (1 H, td, *J* = 10.0, 3.8 Hz, C**H**NH), 3.80 (3 H, s, OC**H**$_3$), 3.22 (3 H, s, NC**H**$_3$), 3.09 (1 H, dd, *J* = 14.5, 3.8 Hz, C**H**H), 2.85 (1 H, dd, *J* = 14.5, 10.0 Hz, CH**H**), 2.49 (6 H, s, 2 x Mts C**H**$_3$), 2.27 (3 H, s, Mts C**H**$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3 (C), 149.7 (C), 145.3 (C), 144.5 (C), 140.5 (C), 134.7 (C), 132.7 (C), 132.6 (CH), 129.5 (C), 127.6 (CH), 125.6 (CH), 124.5 (CH), 124.0 CH), 122.8 (CH), 118.9 (CH), 114.1 (C), 112.7 (CH), 61.9 (CH_3), 53.5 (CH), 32.4 (CH_3), 28.8 (CH_2), 22.8 (CH_3), 21.2 (CH_3) ppm; LRMS ES^+ *m/s* (%) 637 ($[M + Na]^+$, 100).

***N*-{(*S*)-2-Hydroxy-1-[1-(2,4,6-trimethylbenzenesulfonyl)-1*H*-indol-3-ylmethyl]but-3-enyl}-4-nitrobenzenesulfonamide (1.166).**

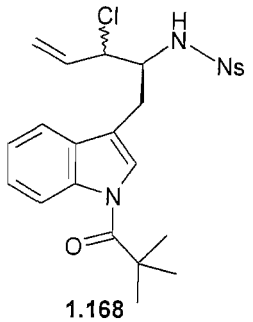


1.166 ***syn*** **4: 1** **1.166** ***anti***

To a solution of **1.163** (2.16 g, 4.3 mmol) in CH_2Cl_2 (20 mL) at 0 °C under argon was added TFA (5 mL). After stirring at 0 °C for 1 h sat. $NaHCO_3$ (aq) was added until gas evolution ceased. The aqueous phase was extracted with CH_2Cl_2 (10 x 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude amine (1.88 g, quant.) which was used without any purification. To a solution of the crude amine (1.88 g, 4.3 mmol) in CH_2Cl_2 (20 mL) under argon was added NsCl (0.96 g, 4.3 mmol) followed by Et_3N (1.21 mL, 8.7 mmol). After stirring for 2 h water (20 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 20 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.166** as a pale yellow foam (1.56 g, 62%) isolated as an inseparable 4:1 ratio of diastereoisomers. Data reported for major (*syn*) diastereoisomer.

$[\alpha]_D^{27}$ -19.0 (*c* 0.5, $CHCl_3$); IR v 3286, 3108, 2966, 1603, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.90 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.58 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.36 (1 H, s, Ar-**H**), 7.32 (1 H, m, Ar-**H**), 7.16-6.97 (3 H, m, Ar-**H**), 6.92 (2 H, s, Mts Ar-**H**), 5.91 (1 H, ddd, *J* = 17.1, 10.6, 6.0 Hz, CH_2=C**H**), 5.40 (1 H, app d, *J* = 17.1 Hz, C**H**H=CH), 5.27 (1 H, app d, *J* = 10.6 Hz, CH**H**=CH), 5.14 (1 H, d, *J* = 7.5 Hz, N**H**), 4.39 (1 H, m, C**H**OH), 3.62 (1 H, m, C**H**NH), 3.10 (1 H, dd, *J* = 14.6, 4.8 Hz, C**H**H), 2.60-2.95 (1 H, dd, *J* = 14.6, 9.9 Hz, CH**H**), 2.47 (6 H, s, 2 x Mts C**H**$_3$), 2.27 (3 H, s, Mts C**H**$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.5 (C), 145.1 (C), 144.5 (C), 140.4 (C), 136.5 (CH), 134.8 (C), 132.6 (CH + C), 129.4 (C), 127.4 (CH), 124.9 (CH), 124.6 (CH), 124.1 (CH), 122.8 (CH), 119.3 (CH), 118.3 (CH_2), 115.1 (C), 112.6 (CH), 74.2 (CH), 58.1 (CH), 27.1 (CH_2), 22.7 (CH_3), 21.2 (CH_3) ppm; LRMS ES^+ *m/s* (%) 606 ($[M + Na]^+$, 100).

***N*-{(*S*)-2-Chloro-1-[1-(2,2-dimethylpropionyl)-1*H*-indol-3-ylmethyl]but-3-enyl}-4-nitrobenzenesulfonamide (1.168).**

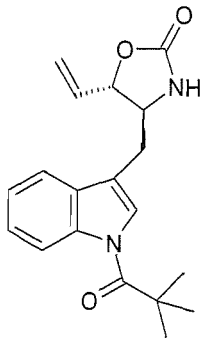


1.168

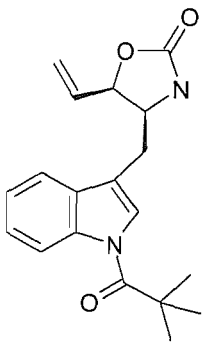
To a mixture of **1.153** (100 mg, 0.3 mmol) and anisole (28 mL, 0.3 mmol) at 0 °C was added 4M HCl in dioxane (0.4 mL). After stirring at rt for 2 h the reaction mixture was quenched with sat. $NaHCO_3$ (aq) and extracted with CH_2Cl_2 (2 x 1 mL). The combined extracts were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the free amine (0.12 g, quant.) which was used without purification. To a solution of the amine (0.12 g, 0.3 mmol) in CH_2Cl_2 (2 mL) at 0 °C under argon was added NsCl (58 mg, 0.3 mmol) and Et_3N (73 μL, 0.06 mmol). The reaction mixture was stirred overnight then water (2 mL) was added. The organic phase was washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-30% EtOAc in hexane) afforded **1.168** as a yellow solid (21 mg, 16%).

$[\alpha]_D^{25}$ -21.7 (*c* 0.5, $CHCl_3$); mp. 182-185 °C; IR ν 3301, 2995, 1690, 1609, 1529 cm^{-1}; 1H NMR (400 MHz, $CDCl_3$) δ 8.29 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.87 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.57 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.43 (1 H, s, Ar-**H**), 7.35 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.30 (1 H, td, *J* = 7.7, 1.2 Hz, Ar-**H**), 7.22 (1 H, td, *J* = 7.7, 1.2 Hz, Ar-**H**), 5.88 (1 H, ddd, *J* = 16.8, 10.3, 7.7 Hz, CH_2=C**H**), 5.44 (1 H, app d, *J* = 16.8 Hz, C**H**H=CH), 5.30 (1 H, app d, *J* = 10.3 Hz, CH**H**=CH), 5.09 (1 H, d, *J* = 9.2 Hz, N**H**), 4.68 (1 H, dd, *J* = 7.7, 2.9 Hz, C**H**Cl), 3.93 (1 H, tdd, *J* = 9.2, 5.4, 2.9 Hz, C**H**NH), 3.22 (1 H, dd, *J* = 14.6, 5.4 Hz, C**H**H), 2.78 (1 H, dd, *J* = 14.6, 9.2 Hz, CH**H**), 1.47 (9 H, s, Piv C($C\mathbf{H}_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.5 (C), 149.6 (C), 145.1 (C), 137.2 (C), 133.1 (CH), 128.3 (C), 127.4 (CH), 125.9 (CH), 124.1 (CH), 123.8 (CH), 123.7 (CH), 120.7 (CH_2), 118.2 (CH), 117.8 (CH), 115.8 (C), 64.3 (CH), 58.3 (CH), 41.3 (C), 28.8 (CH_3), 27.8 (CH_2) ppm; ES^+ *m/s* (%) 504 ($[M + H]^+$, 90), ($[M + NH_4]^+$, 100).

(4*S*,5*S*)-4-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-ylmethyl]-5-vinyloxazolidin-2-one (1.169 *syn*) and (4*S*,5*R*)-4-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-ylmethyl]-5-vinyloxazolidin-2-one (1.169 *anti*).



1.169 *syn*



1.169 *anti*

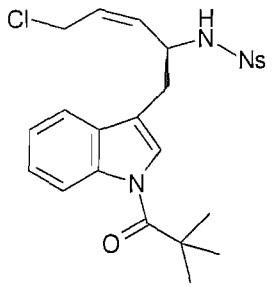
To a solution of **1.153** (100 mg, 0.26 mmol) in CH_2Cl_2 (1 mL) at 0 °C under argon was added Me_3SiI (93 μL, 0.65 mmol). The reaction mixture was stirred at 0 °C for 2 h then warmed to rt and stirred for a further 2 h. After this time Me_3SiI (37 μL, 0.26 mmol) was added and the reaction mixture was stirred at rt for a further 1 h then MeOH (0.5 mL) was added and the mixture was washed with water (1 mL) and brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.169 *syn*** as a brown oil (23 mg, 17%) and **1.169 *anti*** as a yellow oil (13 mg, 10%).

1.169 *syn*: $[\alpha]_D^{27}$ -5.8 (*c* 0.25, $CHCl_3$); IR ν 3272, 2929, 1748, 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.53 (1 H, app d, *J* = 7.8 Hz, Ar-**H**), 7.61 (1 H, s, Ar-**H**), 7.47 (1 H, app d, *J* = 7.8 Hz, Ar-**H**), 7.39 (1 H, td, *J* = 7.8, 1.2 Hz, Ar-**H**), 7.31 (1 H, td, *J* = 7.8, 1.2 Hz, Ar-**H**), 5.90 (1 H, ddd, *J* = 17.1, 10.4, 6.0 Hz, CH_2=C**H**), 5.41 (1 H, app dt, *J* = 17.1, 1.0 Hz, C**H**H=CH), 5.33 (1 H, app dt, *J* = 10.4, 1.0 Hz, CH**H**=CH), 5.14 (1 H, s, N**H**), 4.73 (1 H, t, *J* = 6.0 Hz, C**H**O), 3.90 (1 H, dtd, *J* = 8.4, 6.0, 1.0 Hz, C**H**NH), 3.06 (1 H, ddd, *J* = 14.5, 6.0, 0.6 Hz, C**H**H), 2.96 (1 H, dd, *J* = 14.5, 8.4 Hz, CH**H**), 1.52 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.9 (C), 158.1 (C), 137.5 (C), 133.9 (CH), 128.8 (C), 126.1 (CH), 123.9 (CH), 123.8 (CH), 119.6 (CH_2), 118.2 (CH), 118.0 (CH), 115.8 (C), 82.6 (CH), 58.1 (CH), 41.4 (C), 30.7 (CH_2), 28.9 (CH_3) ppm; LRMS ES^+ *m/s* (%) 344 ($[M + NH_4]^+$, 100), 349 ($[M + Na]^+$, 90).

1.169 *anti*: $[\alpha]_D^{27}$ -17.8 (*c* 0.5, $CHCl_3$); IR ν 3272, 2980, 1748, 1686 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.52 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.62 (1 H, s, Ar-**H**), 7.46 (1 H, dt, *J* = 7.7, 1.0 Hz, Ar-**H**), 7.38 (1 H, td, *J* = 7.7, 1.0 Hz, Ar-**H**), 7.30 (1 H,

td, J = 7.7, 1.0 Hz, Ar-H), 5.87 (1 H, ddd, J = 17.1, 10.4, 6.6 Hz, CH_2=CH), 5.70 (1 H, s, NH), 5.38 (1 H, app dt, J = 17.1, 1.0 Hz, CHH=CH), 5.31 (1 H, app dt, J = 10.4, 1.0 Hz, CHH=CH), 4.71 (1 H, tt, J = 6.6, 0.8 Hz, CHO), 3.91 (1 H, m, CHNH), 3.05 (1 H, ddd, J = 14.6, 5.5, 0.8 Hz, CHH), 2.97 (1 H, dd, J = 14.6, 7.6 Hz, CHH), 1.51 (9 H, s, Piv C(CH_3)$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.9 (C), 158.5 (C), 137.4 (C), 134.0 (CH), 128.9 (C), 126.0 (CH), 123.9 (CH), 123.8 (CH), 119.5 (CH_2), 118.2 (CH), 117.9 (CH), 115.7 (C), 82.5 (CH), 58.1 (CH), 41.4 (C), 30.5 (CH_2), 28.8 (CH_3) ppm; LRMS ES$^+$ *m/s* (%) 349 ([M + Na]$^+$, 100), 675 ([2M + Na]$^+$, 20).

_N_-{(_Z_)-(_S_)-4-Chloro-1-[1-(2,2-dimethylpropionyl)-1_H_-indol-3-ylmethyl]but-2-enyl}-4-nitrobenzenesulfonamide (1.170).



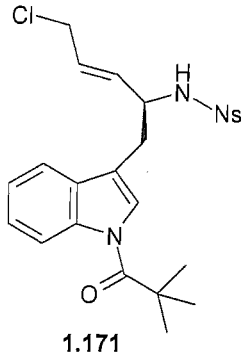
1.170

To a solution of **1.153** (100 mg, 0.26 mmol) in CH_2Cl_2 (1 mL) at 0 °C under argon was added Me_3SiI (93 μL, 0.65 mmol). The reaction mixture was stirred at 0 °C for 2 h then warmed to rt and stirred for a further 2 h. After this time Me_3SiI (37 μL, 0.26 mmol) was added and the reaction mixture was stirred at rt for a further 1 h then MeOH (0.5 mL) was added, the mixture was washed with water (1 mL) and brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo* (0.15 g). To a solution of the crude material (0.15 g, 0.26 mmol) in CH_2Cl_2 (1 mL) at 0 °C under argon was added NsCl (64 mg, 0.29 mmol) followed by Et_3N (73 μL, 0.52 mmol). The reaction mixture was stirred at 0 °C for 2 h then water (1 mL) was added, the phases were separated and aqueous phase was extracted with CH_2Cl_2 (2 x 1 mL). The combined extracts were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 0-20% EtOAc in hexane) afforded **1.170** as a yellow solid (68 mg, 52%).

$[\alpha]_D^{27}$ -31.6 (*c* 0.25, MeOH: $CHCl_3$); mp. 188-190 °C; IR ν 3271, 2982, 1681, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (1 H, app d, J = 7.9 Hz, Ar-H), 7.99

(2 H, d, J = 8.9 Hz, Ns Ar-**H**), 7.66 (2 H, d, J = 8.9 Hz, Ns Ar-**H**), 7.52 (1 H, s, Ar-**H**), 7.34-7.24 (2 H, m, Ar-**H**), 7.20 (1 H, td, J = 7.9, 1.0 Hz, Ar-**H**), 5.85-5.74 (2 H, m, C**H**=C**H**), 4.94 (1 H, d, J = 7.9 Hz, N**H**), 4.25 (1 H, m, C**H**NH), 3.99-3.94 (2 H, m, ClC**H**$_2$), 3.03 (1 H, dd, J= 14.9, 5.1 Hz, C**H**H), 2.84 (1 H, dd, J = 14.9, 8.8 Hz, CH**H**), 1.49 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (C), 149.8 (C), 145.7 (C), 137.2 (C), 133.7 (CH), 128.7 (C), 128.5 (CH), 127.7 (CH), 125.8 (CH), 124.3 (CH), 124.0 (CH), 123.7 (CH), 118.2 (CH), 117.8 (CH), 115.6 (C), 54.9 (CH), 43.7 (CH_2), 41.4 (C), 31.6 (CH_2), 28.8 (CH_3) ppm; LRMS ES$^+$ *m/s* (%) 504 ([M + H]$^+$, 30), 526 ([M + Na]$^+$, 100); Anal. Calcd for $C_{24}H_{26}N_3O_5SCl$: C, 57.20; H, 5.20; N, 8.33. Found: C, 56.98; H, 5.13; N, 7.95.

_N_-{(_E_)-(_S_)-4-Chloro-1-[1-(2,2-dimethylpropionyl)-1_H_-indol-3-ylmethyl]but-2-enyl}-4-nitrobenzenesulfonamide (1.171).



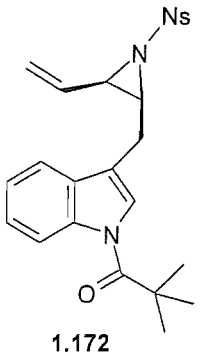
1.171

To a solution of **1.153** (25 mg, 0.08 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C under argon was added Me_3SiI (23 μL, 0.16 mmol). The reaction mixture was stirred at 0 °C for 2 h then MeOH (0.5 mL) was added, the mixture was washed with water (1 mL) and brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo* (35 mg). To a solution of the crude material (18 mg, 0.07 mmol) in CH_2Cl_2 (0.5 mL) at rt under argon was added NsCl (16 mg, 0.08 mmol) followed by Et_3N (18 μL, 0.14 mmol). The reaction mixture was stirred at rt for 2 h then water (0.5 mL) was added, the phases were separated and aqueous phase was extracted with CH_2Cl_2 (2 x 0.5 mL). The combined extracts were washed with brine (1 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.171** as a pale yellow oil (11 mg, 33%).

$[\alpha]_D^{27}$ -28.9 (*c* 0.5, $CHCl_3$); IR ν 3277, 2975, 2928, 1690, 1606, 1530 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (1 H, d, J = 7.8 Hz, Ar-**H**), 8.02 (2 H, d, J = 8.9 Hz, Ns Ar-**H**), 7.68 (2 H, d, J = 8.9 Hz, Ns Ar-**H**), 7.52 (1 H, s, Ar-**H**), 7.33-7.29 (2

H, m, Ar-**H**), 7.21 (1 H, td, J = 7.8, 1.0 Hz, Ar-**H**), 5.88 (1 H, dtd, J = 15.2, 7.9, 1.3 Hz, $ClCH_2CH$=CH), 5.65 (1 H, dd, J = 15.2, 6.4 Hz, $ClCH_2CH$=C**H**), 4.82 (1 H, d, J = 7.9 Hz, N**H**), 4.24 (1 H, m, C**H**NH), 3.75 (2 H, d, J = 7.9 Hz, $ClCH_2$), 3.00 (1 H, dd, J = 14.8, 5.1 Hz, CH**H**), 2.83 (1 H, dd, J = 14.8, 8.7 Hz, CH**H**), 1.50 (9 H, s, Piv $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (C), 149.9 (C), 145.7 (C), 137.3 (C), 132.7 (CH), 130.4 (CH), 128.7 (C), 127.7 (CH), 125.9 (CH), 124.3 (CH), 124.1 (CH), 123.8 (CH), 118.2 (CH), 117.8 (CH), 115.6 (C), 54.8 (CH), 41.4 (C), 31.6 (CH_2), 28.8 (CH_3), 3.1 (CH_2) ppm; LRMS ES^+ *m/s* (%) 526 ($[M + Na]^+$, 100); Anal. Calcd for $C_{24}H_{26}N_3O_5SCl$: C, 57.20; H, 5.20; N, 8.33. Found: C, 57.31; H, 5.10; N, 7.88.

2,2-Dimethyl-1-{3-[(2*S*,3*R*)-1-(4-nitrobenzenesulfonyl)-3-vinylaziridin-2-ylmethyl]indol-1-yl}propan-1-one (1.172).



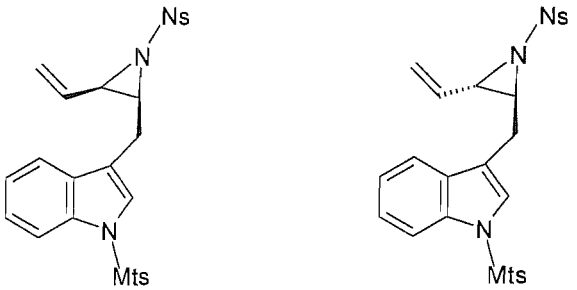
1.172

To a solution of **1.160** (0.11 g, 0.20 mmol) in THF (1 mL) at rt under argon was added PPh_3 (80 mg, 0.30 mmol) and DIAD (50 μL, 0.26 mmol). The reaction mixture was stirred for 2 h and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-30% EtOAc in hexane) afforded **1.172** as a pale yellow foam (62 mg, 58%).

$[\alpha]_D^{27}$ -11.9 (*c* 0.5, $CHCl_3$); IR ν 2980, 1689, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.37 (1 H, app d, J = 7.8 Hz, Ar-**H**), 7.98 (2 H, d, J = 8.9 Hz, Ns Ar-**H**), 7.76 (2 H, d, J = 8.9 Hz, Ns Ar-**H**), 7.52 (1 H, s, Ar-**H**), 7.38-7.29 (2 H, m, Ar-**H**), 7.21 (1 H, td, J = 7.8, 0.8 Hz, Ar-**H**), 5.83 (1 H, ddd, J = 17.1, 10.4, 6.9 Hz, CH_2=C**H**), 5.61 (1 H, app d, J = 17.1 Hz, C**H**H=CH), 5.49 (1 H, app d, J = 10.4 Hz, CH**H**=CH), 3.69 (1 H, t, J = 6.9 Hz, CH_2=CHC**H**N), 3.34 (1 H, ddd, J = 9.4, 6.9, 4.4 Hz, NC**H**CH_2), 2.98 (1 H, dd, J = 15.4, 4.4 Hz, C**H**H), 2.71 (2 H, dd, J = 15.4, 9.4 Hz, CH**H**), 1.49 (9 H, s, Piv $C(CH_3)_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (C), 150.3 (C), 143.1 (C), 137.1 (C), 129.1 (CH), 128.7 (C), 128.7 (CH), 125.7 (CH),

123.7 (CH), 123.6 (CH), 123.2 (CH), 122.8 (CH_2), 118.4 (CH), 117.7 (CH), 117.0 (C), 46.3 (CH), 46.0 (CH), 41.3 (C), 28.7 (CH_3), 22.9 (CH_2) ppm; LRMS ES^+ *m/s* (%) 490 ($[M + Na]^+$, 100); Anal. Calcd for $C_{24}H_{25}N_3O_5S$: C, 61.66; H, 5.39; N, 8.99. Found: C, 61.33; H, 5.23; N, 8.78.

3-[(*S*)-1-(4-Nitrobenzenesulfonyl)-3-vinylaziridin-2-ylmethyl]-1-(2,4,6-trimethylbenzenesulfonyl)-1*H*-indole (1.173).

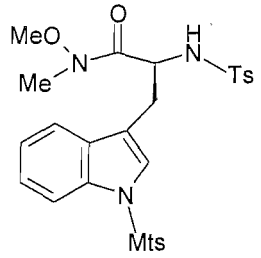


1.173 ***anti*** **4: 1** **1.173** ***syn***

To a solution of **1.166** (92 mg, 0.16 mmol) in THF (1 mL) at 0 °C under argon was added PPh_3 (83 mg, 0.3 mmol) and DIAD (62 μL, 0.3 mmol). The reaction mixture was warmed to rt and stirred for 16 h then concentrated *in vacuo*. Column chromatography (SiO_2, 0-30% EtOAc in hexane) afforded **1.173** as a cream solid (60 mg, 67%) isolated as an inseparable 4:1 mixture of diastereoisomers. Data reported for major (*anti*) diastereoisomer.

$[\alpha]_D^{27}$ -25.6 (*c* 1.0, $CHCl_3$); mp. 153-155 °C; IR ν 3106, 2964, 1747, 1605, 1531 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.88 (2 H, d, *J* = 9.0 Hz, Ns Ar-**H**), 7.66 (2 H, d, *J* = 9.0 Hz, Ns Ar-**H**), 7.36 (1 H, s, Ar-**H**), 7.24 (1 H, m, Ar-**H**), 7.12-6.99 (3 H, m, Ar-**H**), 6.94 (2 H, s, Mts Ar-**H**), 5.87 (1 H, ddd, 17.1, 10.4, 6.9 Hz, CH_2=C**H**), 5.66 (1 H, app d, *J* = 17.1 Hz, C**H**H=CH), 5.52 (1 H, app d, *J* = 10.4 Hz, CH**H**=CH), 3.73 (1 H, t, *J* = 6.9 Hz, C**H**NCH=CH_2), 3.22 (1 H, ddd, *J* = 9.6, 6.9, 4.3 Hz, C**H**N), 2.93 (1 H, dd, 15.1, 4.3 Hz, C**H**H), 2.66 (1 H, dd, *J* = 15.1, 9.6 Hz, CH**H**), 2.49 (6 H, s, 2 x Mts CH_3), 2.28 (3 H, s, Mts CH_3) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (C), 144.5 (C), 142.7 (C), 140.4 (C), 134.6 (C), 132.7 (C), 132.6 (CH), 129.5 (C), 129.1 (CH), 128.5 (CH), 124.5 (CH), 124.2 (CH), 124.2 (CH), 123.8 (CH), 122.7 (CH_2), 119.5 (CH), 115.5 (C), 112.4 (CH), 47.5 (CH), 45.3 (CH), 22.7 (CH_3), 22.6 (CH_2), 21.2 (CH_3) ppm; LRMS ES^+ *m/s* (%) 588 ($[N + Na]^+$, 100); Anal. Calcd for $C_{28}H_{27}N_3O_6S_2$: C, 59.45; H, 4.81; N, 7.42. Found: C, 59.05; H, 4.84; N, 7.30.

(*S*)-*N*-Methoxy-*N*-methyl-2-(toluene-4-sulfonylamino)-3-[1-(2,4,6-trimethyl benzenesulfonyl)-1*H*-indol-3-yl]propionamide (1.174).

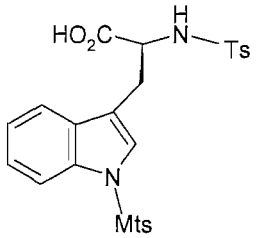


1.174

To a solution of **1.156** (100 mg, 0.25 mmol) and $Bu_4N^+HSO_4^-$ (9 mg, 0.03 mmol) in toluene (2 mL) was added 50% NaOH (aq) (0.5 mL). The reaction mixture was stirred for 5 min then 2-mesitylenesulfonyl chloride (82 mg, 0.37 mmol) in toluene (1 mL) was added. After stirring overnight the phases were separated and the organic phase was washed with water (2 x 2 mL) then brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.174** as an orange solid (52 mg, 36%) and recovered starting material **1.156** (55 mg, 55%).

$[\alpha]_D^{28}$ +10.4 (*c* 1.0, $CHCl_3$); mp. 139-140 °C; IR ν 3247, 2940, 1654, 1601 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (2 H, d, *J* = 8.1 Hz. Ts Ar-**H**), 7.42 (1 H, m, Ar-**H**), 7.35 (1 H, s, Ar-**H**), 7.32 (1 H, m, Ar-**H**), 7.19-7.13 (2 H, m, Ar-**H**), 7.11 (2 H, d, *J* = 8.1 Hz, Ts Ar-**H**), 6.94 (2 H, s, Mts Ar-**H**), 5.56 (1 H, d, *J* = 8.5 Hz, N**H**), 4.55 (1 H, td, *J* = 8.5, 5.4 Hz, C**H**NH), 3.49 (3 H, s, OC**H**$_3$), 3.07 (1 H, dd, *J* = 14.5, 5.4 Hz, C**H**H), 2.98 (3 H, s, NC**H**$_3$), 2.94 (1 H, dd, *J* = 14.5, 8.5 Hz, CH**H**), 2.52 (6 H, s, 2 x Mts C**H**$_3$), 2.33 (3 H, s, Ts C**H**$_3$), 2.28 (3 H, s, Mts C**H**$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1 (C), 144.1 (C), 143.2 (C), 140.4 (C), 136.7 (C), 135.0 (C), 133.1 (C), 132.5 (CH), 130.0 (C), 129.5 (CH), 127.2 (CH), 125.2 (CH), 124.3 (CH), 122.7 (CH), 119.3 (CH), 114.4 (C), 112.7 (CH), 61.5 (CH_3), 52.9 (CH), 32.2 (CH_3), 29.3 (CH_2), 22.8 (CH_3), 21.6 (CH_3), 21.2 (CH_3) ppm; LRMS ES^+ *m/s* (%) 606 ($[M + Na]^+$, 100).

(*S*)-2-(Toluene-4-sulfonylamino)-3-[1-(2,4,6-trimethylbenzenesulfonyl)-1-indol-3-yl]propionic acid (1.175).

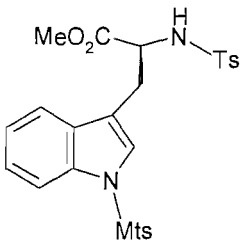


1.175

To a solution of **1.176** (1.57 g, 2.8 mmol) in THF (20 mL) was added a solution of LiOH (0.27 g, 11.3 mmol) in water (10 mL). After stirring overnight the reaction mixture was quenched with 5% citric acid (aq) and extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-20% MeOH in CH_2Cl_2) afforded **1.175** as a pale yellow powder (1.4 g, 92%).

$[\alpha]_D^{27}$ -3.0 (*c* 0.25, MeOH: $CHCl_3$); mp 172-175 °C; IR v 3270, 2978, 2927, 1723 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6) δ 12.93 (1 H, br s, CO_2**H**), 8.32 (1 H, d, *J* = 7.9 Hz, Ar-**H**), 7.69 (1 H, s, Ar-**H**), 7.56 (2 H, d, *J* = 8.2 Hz, Ts Ar-**H**), 7.53 (1 H, d, *J* = 7.9 Hz, Ar-**H**), 7.34-7.24 (3 H, m, Ar-**H**), 7.22 (2 H, s, Mts Ar-**H**), 7.16-7.23 (2 H, m, Ts Ar-**H**), 4.04 (1 H, m, C**H**NH), 3.44 (1 H, br s, N**H**), 3.19 (1 H, dd, *J* = 14.6, 5.3 Hz, C**H**H), 2.99 (1 H, dd, *J* = 14.6, 8.8 Hz, CH**H**), 2.56 (6 H, s, 2 x Mts CH_3), 2.37 (3 H, s, Ts CH_3), 2.36 (3 H, s, Mts CH_3) ppm; ^{13}C NMR (100 MHz, DMSO-d_6) δ 172.2 (C), 144.3 (C), 142.1 (C), 139.4 (C), 137.7 (C), 134.0 (C), 132.3 (CH), 132.2 (C), 129.4 (C), 129.1 (CH), 126.1 (CH), 125.2 (CH), 124.1 (CH), 122.5 (CH), 119.4 (CH), 114.7 (C), 111.7 (CH), 55.5 (CH), 27.4 (CH_2), 22.1 (CH_3), 20.9 (CH_3), 20.4 (CH_3) ppm; LRMS ES^+ *m/s* (%) 563 ($[M + Na]^+$, 100); LRMS ES^- *m/s* (%) 539 ($[M - H]^-$, 20).

(*S*)-2-(Toluene-4-sulfonylamino)-3-[1-(2,4,6-trimethylbenzenesulfonyl)-1*H*-indol-3-yl]propionic acid methyl ester (1.176).

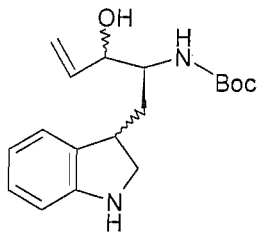


1.176

To a solution of **1.161** (1.70 g, 3.4 mmol) in CH_2Cl_2 (40 mL) under argon was added TFA (5.95 mL). The reaction mixture was stirred for 1 h then sat. $NaHCO_3$ (aq) was added until gas evolution ceased. The aqueous phase was extracted with CH_2Cl_2 (10 x 40 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude amine (1.5 g, quant.) which was used without any purification. To a solution of the amine (1.5 g, 3.4 mmol) in CH_2Cl_2 (20 mL) under argon was added TsCl (1.0 g, 5.3 mmol) and Et_3N (1.42 mL, 10.2 mmol). After stirring overnight water (40 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 40 mL). The combined extracts were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-40% EtOAc in hexane) afforded **1.176** as a white foam (1.7 g, 89%).

$[\alpha]_D^{28}$ +1.5 (*c* 1.0, $CHCl_3$); IR ν 3312, 3109, 2955, 1759, 1746 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (2 H, d, *J* = 8.3 Hz, Ts Ar-**H**), 7.47 (1 H, m, Ar-**H**), 7.43 (1 H, s, Ar-**H**), 7.32 (1 H, m, Ar-**H**), 7.20 (2 H, d, *J* = 8.3 Hz, Ts Ar-**H**), 7.18-7.14 (2 H, m, Ar-**H**), 6.95 (2 H, s, Mts Ar-**H**), 5.21 (1 H, d, *J* = 8.8 Hz, N**H**), 4.25 (1 H, dt, *J* = 8.8, 5.8 Hz, C**H**NH), 3.46 (3 H, s, OC**H**$_3$)), 3.20 (1 H, dd, *J* = 14.7, 5.8 Hz, C**H**H), 3.13 (1 H, dd, *J* = 14.7, 5.8 Hz, CH**H**), 2.50 (6 H, s, 2 x Mts C**H**$_3$), 2.37 (3 H, s, Ts C**H**$_3$), 2.28 (3 H, s, Mts C**H**$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4 (C), 144.2 (C), 143.8 (C), 140.3 (C), 136.6 (C), 135.0 (C), 133.0 (C), 132.5 (CH), 130.0 (C), 129.8 (CH), 127.2 (CH), 125.2 (CH), 124.5 (CH), 122.8 (CH), 119.6 (CH), 113.7 (C), 112.7 (CH), 55.9 (CH_3), 52.7 (CH), 29.2 (CH_2), 22.8 (CH_3), 21.6 (CH_3), 21.2 (CH_3) ppm; LRMS ES^+ *m/s* (%) 572 ($[M + NH_4]^+$, 100), 577 ($[M + Na]^+$, 30).

[(*S*)-1-(2,3-Dihydro-1*H*-indol-3-ylmethyl)-2-hydroxy-but-3-enyl]carbamic acid *t*-butyl ester (1.178).



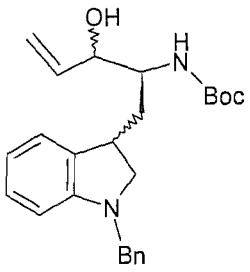
1.178

To a solution of **1.134** (100 mg, 0.3 mmol) in acetic acid (1.5 mL) at 0 °C under argon was added sodium cyanoborohydride (0.20 g, 3.2 mmol). The reaction mixture was stirred at rt overnight then diluted with CH_2Cl_2 (5 mL) and water (5 mL). The

pH of the mixture was adjusted to >12 with 10% NaOH (aq). The organic phase was separated and washed with water (2 x 5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-100% EtOAc in hexane) afforded **1.178** as a colourless oil (90 mg, 89%) isolated as an inseparable mixture of diastereoisomers. Data reported for major diastereoisomer.

$[\alpha]_D^{26}$ -15.5 (*c* 0.5, $CHCl_3$); IR ν 3434, 3011, 2979, 1694, 1664 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.06 (1 H, d, *J* = 7.5 Hz, Ar-**H**), 7.02 (1 H, t, *J* = 7.5 Hz, Ar-**H**), 6.71 (1 H, t, *J* = 7.5 Hz, Ar-**H**), 6.63 (1 H, d, *J* = 7.5 Hz, Ar-**H**), 5.90 (1 H, ddd, *J* = 17.1, 10.5, 6.1 Hz, CH_2=C**H**), 5.30 (1 H, app dt, *J* = 17.1, 1.3 Hz, C**H**H=CH), 5.20 (1 H, app d, *J* = 10.5 Hz, CH**H**=CH), 4.78 (1 H, d, *J* = 9.3 Hz, N**H**), 4.10 (1 H, m, C**H**OH), 3.79-3.51 (3 H, m, C**H**NH + indoline N**H** + CH**H**NH), 3.37 (1 H, m, CH_2CHCH_2), 3.24 (1 H, m, CH**H**NH), 1.85-1.63 (2 H, m, C**H**$_2$), 1.45 (9 H, s, Boc C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6 (C), 151.4 (C), 138.0 (CH), 132.8 (C), 127.7 (CH), 123.7 (CH), 118.8 (CH), 116.8 (CH_2), 109.8 (CH), 79.7 (C), 75.4 (CH), 53.3 (CH_2), 53.0 (CH), 39.0 (CH), 38.8 (CH_2), 28.5 (CH_3) ppm; LRMS ES^+ *m/s* (%) 319 ($[M + H]^+$, 100).

[(S)-1-(1-Benzyl-2,3-dihydro-1H-indol-3-ylmethyl)-2-hydroxybut-3-enyl] carbamic acid *t*-butyl ester (1.179).



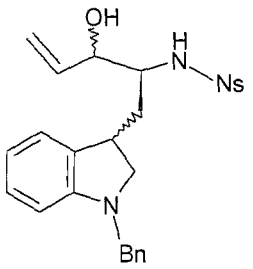
1.179

To a solution of **1.178** (0.1 g, 0.31 mmol) and $NaHCO_3$ (35 mg, 0.42 mmol) in water (2 mL) at 95 °C was added BnCl (40 μL, 0.35 mmol) dropwise. The reaction mixture was heated at 95 °C for 3 h then cooled to rt and extracted with EtOAc (2 x 5 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.179** as a colourless oil (0.10 g, 81%) isolated as an inseparable mix of diastereoisomers. Data reported for major diastereoisomer.

$[\alpha]_D^{26}$ -10.3 (*c* 0.5, $CHCl_3$); IR ν 3434, 3010, 2979, 1694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42-7.19 (5 H, m, Bn Ar-**H**), 7.11-6.95 (2 H, m, 2 x Ar-**H**), 6.69 (1

H, m, Ar-**H**), 6.48 (1 H, m, Ar-**H**), 5.88 (1 H, ddd, J = 17.1, 10.7, 6.3 Hz, CH_2=C**H**), 5.30 (1 H, app dt, J = 17.1, 1.3 Hz, CH**H**=CH), 5.20 (1 H, app dt, J = 10.7, 1.3 Hz, CH**H**=CH), 4.70 (1 H, br s, N**H**), 4.37-4.15 (2 H, m, C**H**$_2$Ph), 4.09 (1 H, m, C**H**OH), 3.62 (1 H, m, C**H**NH), 3.49 (1 H, td, J = 8.7, 1.9 Hz, C**H**HNBn), 3.30 (1 H, m, CH_2C**H**CH_2), 3.03 (1 H, m, CH**H**NBn), 2.01 (1 H, m, C**H**H), 1.76 (1 H, m, CH**H**), 1.42 (9 H, br s, Boc C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6 (C), 152.4 (C), 138.5 (C), 138.0 (CH), 133.4 (C), 128.6 (CH), 127.9 (CH), 127.9 (CH), 127.2 (CH), 123.5 (CH), 117.7 (CH), 116.8 (CH_2), 107.2 (CH), 79.7 (C), 75.5 (CH), 59.6 (CH_2), 53.3 (CH_2), 53.1 (CH), 37.6 (CH), 36.9 (CH_2), 28.5 (CH_3) ppm; LRMS ES$^+$ *m/s* (%) 409 ([M + H]$^+$, 30), 431 ([M + H]$^+$, 100).

_N_-[(S)-1-(1-Benzyl-2,3-dihydro-1_H_-indol-3-ylmethyl)-2-hydroxybut-3-enyl]-4-nitrobenzenesulfonamide (1.180).



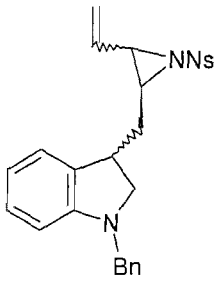
1.180

To a solution of **1.179** (29 mg, 0.07 mmol) in CH_2Cl_2 (0.5 mL) under argon was added TFA (26 μL). The reaction mixture was stirred overnight then sat. $NaHCO_3$ (aq) was added until gas evolution ceased. The aqueous phase was extracted with CH_2Cl_2 (5 x 1 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give the crude amine (30 mg, quant.) which was used without any purification. To a solution of the amine (30 mg, 0.07 mmol) in CH_2Cl_2 (0.5 mL) under argon was added NsCl (16 mg, 0.07 mmol) and Et_3N (20 μL, 0.14 mmol). After stirring for 2 h water (1 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 1 mL). The combined extracts were washed with brine (2 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.180** as a brown oil (34 mg, 97%) isolated as an inseparable mixture of diastereoisomers. Data reported for major diastereoisomer.

$[\alpha]_D^{27}$ +8.1 (*c* 0.5, $CHCl_3$); IR ν 3527, 3288, 3027, 2923, 1604, 1528 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (2 H, d, J = 8.9 Hz, Ns Ar-**H**), 7.89 (2 H, d, J = 8.9

Hz, Ns Ar-**H**), 7.43-7.19 (5 H, m, Bn Ar-**H**), 7.08 (1 H, m, Ar-**H**), 6.97 (1 H, d, J = 7.2 Hz, Ar-**H**), 6.68 (1 H, m, Ar-**H**), 6.50 (1 H, m, Ar-**H**), 5.69 (1 H, ddd, J = 17.1, 10.5, 6.3 Hz, CH_2=C**H**), 5.22 (1 H, app d, J = 17.1 Hz, C**H**H=CH), 5.06 (1 H, m, N**H**), 5.09 (1 H, app d, J = 10.5 Hz, CH**H**=CH), 4.26-4.11 (2 H, m, C**H**$_2$Ph), 4.08 (1 H, m, C**H**OH), 3.45 (1 H, m, C**H**NH), 3.30 (1 H, t, J = 8.7 Hz, C**H**HNBn), 3.16(1 H, m, CH_2C**H**CH_2), 2.93 (1 H, m, CH**H**NBn), 2.00-1.64 (2 H, m, C**H**$_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.2 (C), 150.0 (C), 147.0 (C), 138.3 (C), 137.0 (CH), 132.4 (C), 128.7 (CH), 128.3 (CH), 128.3 (CH), 127.9 (CH), 127.4 (CH), 124.3 (CH), 123.8 (CH), 118.0 (CH_2), 117.9 (CH), 107.5 (CH), 74.2 (CH), 59.4 (CH_2), 56.6 (CH), 53.3 (CH_2), 37.3 (CH_2), 37.2 (CH) ppm; LRMS ES$^+$ *m/s* (%) 494 ([M + H]$^+$, 100).

1-Benzyl-3-[(*S*)-1-(4-nitrobenzenesulfonyl)-3-vinylaziridin-2-ylmethyl]-2,3-dihydro-1*H*-indole (1.181).



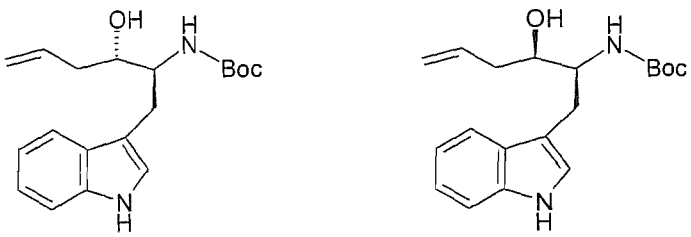
1.181

To a solution of **1.180** (0.17 g, 0.30 mmol) in THF (2 mL) at 0 °C under argon was added PPh_3 (96 mg, 0.40 mmol) and DIAD (72 μL, 0.40 mmol). The reaction mixture was warmed to rt and stirred for 16 h then PPh_3 (43 mg, 0.15 mmol) and DIAD (33μL, 0.15 mmol) were added. After stirring for a further 2 h the reaction mixture was concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-30% EtOAc in hexane) afforded **1.181** as a brown oil (66 mg, 42%) isolated as an inseparable mixture of diastereoisomers. Data reported for major diastereoisomer.

$[\alpha]_D^{26}$ +21.0 (*c* 0.5, $CHCl_3$); IR ν 3028, 2920, 2828, 1605, 1529 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (2 H, d, J = 8.9 Hz, Ns Ar-**H**), 8.09 (2 H, d, J = 8.9 Hz, Ns Ar-**H**), 7.40-7.27 (5 H, m, Bn Ar-**H**), 7.08 (1 H, app t, J = 7.6 Hz, Ar-**H**), 7.00 (1 H, app d, J = 7.6 Hz, Ar-**H**), 6.67 (1 H, td, J = 7.6, 0.7 Hz, Ar-**H**), 6.52 (1 H, app d, J = 7.6 Hz, Ar-**H**), 5.54 (1 H, ddd, J = 17.1, 10.4, 6.9 Hz, CH_2=C**H**), 5.37 (1 H, app d, 17.1 Hz, C**H**H=CH), 5.29 (1 H, app d, J = 10.4 Hz, CH**H**=CH), 4.23 (2 H,

s, CH_2Ph), 3.44 (1 H, t, J = 6.9 Hz, CH_2=CHCHN), 3.39 (1 H, t, J = 8.8 Hz, NCHH), 3.21(1 H, m, CH_2CHCH_2), 3.13 (1 H, dt, 7.3, 6.9 Hz, $NCHCH_2$), 3.01 (1 H, dd, J = 8.8, 6.5 Hz, NCHH), 1.93 (1 H, ddd, J = 14.6, 7.3, 4.5 Hz, CHH), 1.75 (1 H, ddd, J = 14.6, 9.0, 6.9 Hz, CHH) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.9 (C), 150.4 (C), 143.9 (C), 137.9 (C), 131.6 (C), 128.9 (CH), 128.7 (CH), 128.4 (CH), 128.0 (CH), 127.8 (CH), 127.1 (CH), 124.1 (CH), 123.5 (CH), 121.9 (CH_2), 117.7 (CH), 107.2 (CH), 58.4 (CH_2), 53.1 (CH_2), 46.7 (CH), 44.1 (CH), 38.5 (CH), 30.8 (CH_2) ppm; LRMS ES^+ *m/s* (%) 476 ($[M + H]^+$, 100); Anal. Calcd for $C_{26}H_{25}N_3O_4S$: C, 65.67; H, 5.30; N, 8.84. Found: C, 65.22; H, 5.13; N, 8.68.

[(*S*)-2-Hydroxy-1-(1*H*-indol-3-ylmethyl)pent-4-enyl]carbamic acid *t*-butyl ester (1.184).

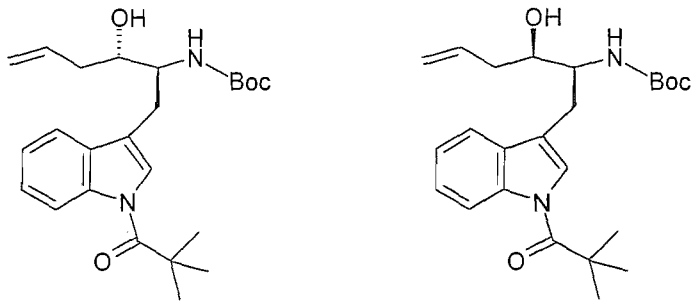


1.184 *syn* **1: 1** **1.184 *anti***

To a solution of **1.137** (0.50 g, 1.2 mmol) in THF (10 mL) at -78 °C under argon was added DIBAL-H (1.2M in toluene, 2.9 mL, 3.5 mmol) at a rate so the temperature did not exceed -65 °C. After stirring at -78 °C for 1 h MeOH (5 mL) was added dropwise, followed by the addition of sat. Rochelle's salt (aq) (50 mL). After stirring for 1 h the reaction mixture was extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide the crude aldehyde (0.50 g, quant.) which was used without purification. To a solution of the crude aldehyde (0.50 g, 1.2 mmol) in THF (10 mL) at -78 °C under argon was added allyl MgCl (2.0 M in THF, 2.0 mL, 4.1 mmol). The reaction mixture was warmed to rt over 20 h then quenched with sat. NH_4Cl (aq) (10 mL) followed by water (10 mL) then extracted with EtOAc (2 x 20 mL). The combined extracts were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.184** as a white solid (0.14 g, 37%) isolated as an inseparable 1:1 ratio of diastereoisomers.

$[\alpha]_D^{27}$ -24.1 (*c* 0.5, $CHCl_3$); mp. 127-129 °C; IR ν 3417, 3359, 2979, 2931, 1682, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.14 (1 H, d, *J* = 7.0 Hz, indole N**H**), 7.70 (1 H, app d, *J* = 7.7 Hz, *syn* Ar-**H**), 7.63 (1 H, app d, *J* = 7.7 Hz, *anti* Ar-**H**), 7.35 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.19 (1 H, td, *J* = 7.7, 1.4 Hz, Ar-**H**), 7.12 (1 H, app t, *J* = 7.7 Hz, Ar-**H**), 7.05 (1 H, m, Ar-**H**), 5.88 (1 H, ddt, *J* = 17.2, 9.8, 7.1 Hz, *anti* CH_2=C**H**), 5.74 (1 H, ddt, *J* = 17.2, 9.6, 7.2 Hz, *syn* CH_2=C**H**), 5.18 (1 H, app d, *J* = 17.2 Hz, *anti* C**H**H=CH), 5.16 (1 H, app d, *J* = 9.8 Hz, *anti* CH**H**=CH), 5.11 (1 H, app d, *J* = 17.2 Hz, *syn* C**H**H=CH), 5.09 (1 H, app d, *J* = 9.6 Hz, *syn* CH**H**=CH), 4.97 (1 H, m, *syn* N**H**), 4.67 (1 H, br s, *anti* N**H**), 3.92 (1 H, m, C**H**OH), 3.71 (1 H, m, C**H**NH), 3.11-2.98 (2 H, m, CH_2=CHC**H$_2$**), 2.47-2.11 (3 H, m, C**H$_2$** + O**H**), 1.44 (9 H, br s, *syn* Boc C(C**H$_3$**)$_3$), 1.37 (9 H, br s, *anti* Boc C(C**H$_3$**)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.4 (*syn* and *anti* C), 136.4 (*syn* and *anti* C), 135.0 (*syn* CH), 134.7 (*anti* CH), 128.0 (*syn* C), 127.9 (*anti* C), 122.7 (*syn* and *anti* CH), 122.2 (*syn* CH), 122.2 (*anti* CH), 119.6 (*syn* and *anti* CH), 119.0 (*syn* CH), 119.0 (*anti* CH), 118.4 (*syn* CH_2), 118.3 (*anti* CH_2), 112.7 (*syn* C), 112.1 (*anti* C), 111.3 (*syn* and *anti* CH), 79.7 (*syn* C), 79.4 (*anti* C), 72.8 (*anti* CH), 70.6 (*syn* CH), 55.4 (*syn* CH), 54.6 (*anti* CH), 39.5 (*syn* CH_2), 38.5 (*anti* CH_2), 28.5 (*syn* and *anti* CH_3), 25.5 (*anti* CH_2), 25.5 (*syn* CH_2) ppm; LRMS ES^+ *m/s* (%) 331 ($[M + H]^+$, 100), 353 ($[M + Na]^+$, 80).

{(*S*)-1-[1-(2,2-Dimethylpropionyl)-1*H*-indol-3-ylmethyl]-2-hydroxypent-4-enyl}carbamic acid *t*-butyl ester (1.185).



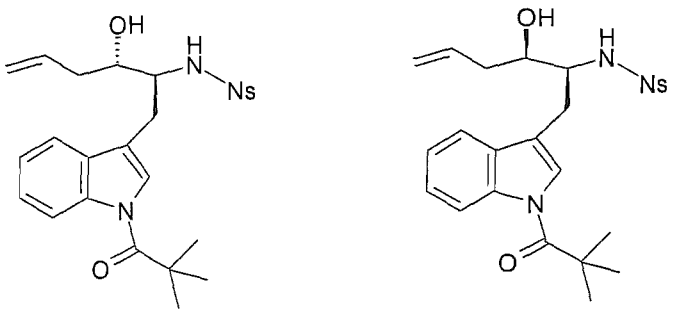
1.185 *syn* **3: 1** **1.185 *anti***

To a solution of **1.137** (5.0 g, 11.6 mmol) in THF (100 mL) at -78 °C under argon was added DIBAL-H (1.2M in toluene, 29.0 mL, 35.0 mmol) at a rate so the temperature did not exceed -65 °C. After stirring at -78 °C for 1 h MeOH (20 mL) was added dropwise, followed by the addition of sat. Rochelle's salt (aq) (100 mL). After stirring for 1 h the reaction mixture was extracted with EtOAc (2 x 50 mL).

The combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to provide the crude aldehyde (4.51 g, quant.) which was used without purification. $CrCl_2$ (4.3 g, 35 mmol) was placed in a round bottomed flask and heated to 200 °C *in vacuo* for 25 min. After cooling under argon a solution of the crude aldehyde (4.51 g, 11.6 mmol) in THF (50 mL) was added followed by allyl bromide (2.0 mL, 23 mmol). After stirring at rt for 2 h diethyl ether (50 mL) and sat. NH_4Cl (aq) (50 mL) were added. The organic phase was washed with water (50 mL) then brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **1.185** as a colourless oil (2.83 g, 59%) isolated as an inseparable 3:1 ratio of diastereoisomers and recovered aldehyde. Data reported for major (*syn*) diastereoisomer.

$[\alpha]_D^{27}$ -4.0 (*c* 0.5, $CHCl_3$); IR ν 3436, 3017, 2979, 1685, 1606, 1501 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.50 (1 H, app d, *J* = 7.7 Hz, Ar-**H**), 7.71-7.44 (2 H, m, Ar-**H**), 7.34 (1 H, td, *J* = 7.7, 1.3 Hz, Ar-**H**), 7.27 (1 H, app t, *J* = 7.7 Hz, Ar-**H**), 5.77 (1 H, ddt, *J* = 16.9, 9.8, 7.3 Hz, CH_2=C**H**), 5.26-5.06 (2 H, m, C**H**$_2$=CH), 5.00 (1 H, d, *J* = 9.2 Hz, N**H**), 4.08 (1 H, m, C**H**NH), 3.72 (1 H, m, C**H**OH), 3.05 (1 H, dd, *J* = 14.7, 5.8 Hz, indole-C**H**H), 2.98 (1 H, dd, *J* = 14.7, 7.4 Hz, indole-CH**H**), 2.50-2.06 (2 H, m, CH_2=CHC**H**$_2$), 1.51 (9 H, s, Piv C(C**H**$_3$)$_3$), 1.43 (9 H, s, Boc C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.1 (C), 156.3 (C), 137.3 (C), 134.4 (CH), 129.9 (C), 125.4 (CH), 123.6 (CH), 123.5 (CH), 118.9 (CH_2), 118.7 (CH), 118.3 (C), 117.5 (CH), 79.6 (C), 71.2 (CH), 53.5 (CH), 41.3 (C), 39.4 (CH_2), 28.8 (CH_3), 28.5 (CH_3), 28.4 (CH_2) ppm; LRMS ES^+ *m/s* (%) 478 ($[M + Na + MeCN]^+$, 60), 851 ($[2M + Na]^+$, 50).

_N_-{(_S_)-1-[1-(2,2-Dimethylpropionyl)-1_H_-indol-3-ylmethyl]-2-hydroxypent-4-enyl}-4-nitrobenzenesulfonamide (1.186).

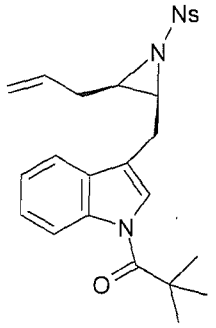


1.186 *syn* 2: 1 1.186 *anti*

To a mixture of **1.185** (2.68 g, 6.5 mmol) and anisole (0.7 mL, 6.5 mmol) at 0 °C under argon was added 4M HCl in dioxane (40 mL). After stirring at rt for 2 h the reaction mixture was quenched with sat. $NaHCO_3$ (aq) and extracted with CH_2Cl_2 (5 x 20 mL). The combined extracts were washed with brine (40 mL), dried over $MgSO_4$ and concentrated *in vacuo* to afford the crude amine (2.50 g, quant.) which was used without purification. To a solution of the crude amine (2.50 g, 6.5 mmol) in CH_2Cl_2 (40 mL) at 0 °C under argon was added NsCl (1.5 g, 6.8 mmol) and Et_3N (1.8 mL, 12.9 mmol). The reaction mixture was stirred at rt overnight then water (20 mL) was added. The organic phase was washed with brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 25-100% EtOAc in hexane) afforded **1.186** as a yellow foam (1.67 g, 53%) isolated as an inseparable 2:1 ratio of diastereoisomers. Data reported for major (*syn*) diastereoisomer.

$[\alpha]_D^{27}$ -45.6 (*c* 0.25, MeOH: $CHCl_3$); IR ν 3286, 2978, 1688, 1607, 1528 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + CD_3OD (5%)) δ 8.09 (1 H, d, *J* = 8.3 Hz, Ar-**H**), 7.58 (2 H, d, *J* = 8.6 Hz, Ns Ar-**H**), 7.41 (1 H, s, Ar-**H**), 7.29 (2 H, d, *J* = 8.6 Hz, Ns Ar-**H**), 7.23-7.05 (3 H, m, Ar-**H**), 5.91 (1 H, ddt, *J* = 17.1, 10.2, 6.9 Hz, CH_2=C**H**), 5.24 (1H, app d, *J* = 17.1 Hz, CH**H**=CH), 5.21 (1 H, app d *J* = 10.2 Hz, CH**H**=CH), 4.11 (1 H, m, C**H**OH), 3.57 (1 H, app d, *J* = 11.8 Hz, C**H**NH), 2.84 (1 H, m, indole-CH**H**), 2.65 (1 H, dd, *J* = 14.7, 11.8 Hz, indole-CH**H**), 2.53-2.22 (2 H, m, CH_2=CHC**H**$_2$), 1.42 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ and CD_3OD (5%)) δ 176.6 (C), 148.9 (C), 145.2 (C), 136.9 (C), 134.3 (CH), 128.5 (C), 126.6 (CH), 125.3 (CH), 124.3 (CH), 123.3 (CH), 123.1 (CH), 118.2 (CH_2), 117.9 (CH), 117.5 (CH), 116.8 (C), 73.9 (CH), 57.3 (CH), 41.2 (C), 38.4 (CH_2), 28.5 (CH_3), 23.2 (CH_2) ppm; LRMS ES^+ *m/s* (%) 522 ($[M + Na]^+$, 100).

1-{3-[(2*S*,3*R*)-3-Allyl-1-(4-nitrobenzenesulfonyl)aziridin-2-ylmethyl]indol-1-yl}-2,2-dimethylpropan-1-one (1.187).

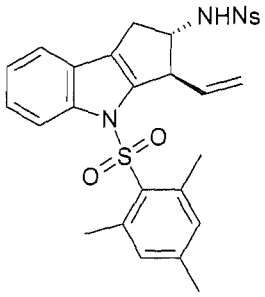


1.187

To a solution of **1.186** (1.0 g, 2.0 mmol) in THF (10 mL) at rt under argon was added PPh_3 (0.68 g, 2.6 mmol) and DIAD (0.43 mL, 2.2 mmol). The reaction mixture was stirred overnight then concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-30% EtOAc in hexane) afforded **1.187** as a yellow oil (0.47 g, 48%).

$[\alpha]_D^{27}$ +33.9 (*c* 0.5, $CHCl_3$); IR ν 3417, 2980, 1688, 1607, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (1 H, app d, *J* = 7.9 Hz, Ar-**H**), 8.03 (2 H, d, *J* = 9.0 Hz, Ns Ar-**H**), 7.77 (2 H, d, *J* = 9.0 Hz, Ns Ar-**H**), 7.47 (1 H, s, Ar-**H**), 7.37 (1 H, app d, *J* = 7.9 Hz, Ar-**H**), 7.32 (1 H, td, *J* = 7.9, 0.9 Hz, Ar-**H**), 7.21 (1 H, td, *J* = 7.9, 0.9 Hz, Ar-**H**), 5.78 (1 H, ddt, *J* = 17.2, 10.3, 6.6 Hz, CH_2=C**H**), 5.13 (1 H, app dq, *J* = 17.2, 1.4 Hz, CH**H**=CH), 5.08 (1 H, app dq, *J* = 10.3, 1.4 Hz, CH**H**=CH), 3.27 – 3.16 (2 H, m, C**H**N + indole-CH**H**), 2.99-2.85 (2 H, m, C**H**N + indole-CH**H**), 2.76-2.64 (2 H, m, CH_2=CHC**H**$_2$), 1.47 (9 H, s, Piv C(C**H**$_3$)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7 (C), 150.1 (C), 145.4 (C), 137.1 (C), 133.3 (CH), 128.7 (C), 128.4 (CH), 125.7 (CH), 123.8 (CH), 123.6 (CH), 123.4 (CH), 118.4 (CH), 118.2 (C), 117.7 (CH_2), 117.1 (CH), 50.5 (CH), 49.2 (CH), 41.3 (C), 33.6 (CH_2), 28.7 (CH_3), 26.6 (CH_2) ppm; LRMS ES^+ *m/s* (%) 482 ($[M + H]^+$, 70); Anal. Calcd for $C_{25}H_{27}N_3O_5S$: C, 62.35; H, 5.65; N, 8.72. Found: C, 62.08; H, 5.70; N, 8.66.

4-Nitro-*N*-[(2S,3R)-4-(2,4,6-trimethylbenzenesulfonyl)-3-vinyl-1,2,3,4-tetrahydrocyclopenta[b]indol-2-yl]benzenesulfonamide (1.189).

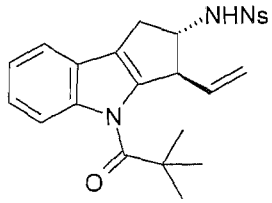


1.189

To a solution of **1.173** (30 mg, 0.05 mmol) in CH_2Cl_2 (2 mL) under argon was added $BF_3{\cdot}OEt_2$ (10 μL, 0.08 mmol) over a period of 10 min. The reaction mixture was stirred at rt overnight then quenched by the addition of 5% $NaHCO_3$ (aq) (1 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) gave a white solid which was recrystallised from diethyl ether to give **1.189** as a white crystalline solid (6 mg, 20%).

$[\alpha]_D^{27}$ -24.2 (*c* 0.25, $CHCl_3$); mp. 175-178 °C; IR ν 3286, 3026, 2924, 1604, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 8.07 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.44 (1 H, m, Ar-**H**), 7.36 (1 H, m, Ar-**H**), 7.20 (1 H, td, *J* = 7.3, 1.6 Hz, Ar-**H**), 7.17 (1 H, td, *J* = 7.3, 1.6 Hz, Ar-**H**), 6.92 (2 H, s, Mts Ar-**H**), 5.59 (1 H, ddd, *J* = 17.2, 10.2, 7.2 Hz, CH_2=C**H**), 5.16 (1 H, d, *J* = 9.2 Hz, N**H**), 4.87 (1 H, app d, *J* = 10.2 Hz, C**H**H=CH), 4.71 (1 H, app d, *J* = 17.2 Hz, CH**H**=CH), 4.21 (1 H, m, C**H**NH), 3.72 (1 H, app d, *J* = 7.2 Hz, C**H**CH=CH_2), 3.19 (1 H, ddd, *J* = 15.9, 6.4, 0.8 Hz, C**H**H), 2.59 (1 H, dd, *J* = 15.9, 1.4 Hz, CH**H**), 2.40 (6 H, s, 2 x Mts CH_3), 2.30 (3 H, s, Mts CH_3); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.3 (C), 146.9 (C), 144.4 (C), 142.2 (C), 140.8 (C), 140.2 (C), 134.5 (CH), 133.7 (C), 132.4 (CH), 128.4 (CH), 125.5 (C), 124.7 (CH), 124.4 (CH), 123.3 (CH), 122.3 (C), 119.6 (CH), 117.0 (CH_2), 114.3 (CH), 64.8 (CH), 53.4 (CH), 32.1 (CH_2), 22.5 (CH_3), 21.2 (CH_3); LRMS ES^+ *m/s* (%) 588 ($[M + Na]^+$, 100); Anal. Calcd for $C_{28}H_{27}N_3O_6S_2$: C, 59.45; H, 4.81; N, 7.43. Found: C, 59.16; H, 4.93; N, 7.11.

***N*-[(2*S*,3*R*)-4-(2,2-Dimethylpropionyl)-3-vinyl-1,2,3,4-tetrahydrocyclopenta [b]indol-2-yl]-4-nitrobenzenesulfonamide (1.190).**

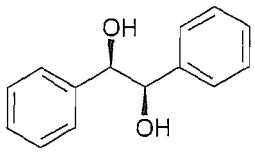


1.190

To a solution of **1.172** (47 mg, 0.1 mmol) in CH_2Cl_2 (2 mL) under argon was added $BF_3{\cdot}OEt_2$ (26 μL, 0.2 mmol) over a period of 10 min. The reaction mixture was stirred at rt overnight then quenched by the addition of 5% $NaHCO_3$ (aq) (1 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (SiO_2, 0-40% EtOAc in hexane) afforded **1.190** as a yellow oil (12 mg, 25%).

$[\alpha]_D^{26}$ +12.5 (*c* 0.30, $CHCl_3$); IR ν 2981, 1689, 1530 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.38 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 8.10 (2 H, d, *J* = 8.9 Hz, Ns Ar-**H**), 7.67 (1 H, d, *J* = 7.9 Hz, Ar-**H**), 7.37 (1 H, m, Ar-**H**), 7.27 (1 H, m, Ar-**H**), 7.20 (1 H, td, *J* = 7.9, 0.9 Hz, Ar-**H**), 5.70 (1 H, ddd, *J* = 17.2, 10.2, 7.2 Hz, CH_2=C**H**), 5.27 (1 H, d, *J* = 9.3 Hz, N**H**), 5.00 (1 H, app d, *J* = 10.2 Hz, C**H**H=CH), 4.71 (1 H, app d, *J* = 17.2 Hz, CH**H**=CH), 4.25 (1 H, ddt, *J* = 9.3, 6.9, 2.4 Hz, C**H**NH), 3.96 (1 H, m, C**H**CH=CH_2), 3.17 (1 H, dd, *J* = 15.8, 6.9 Hz, C**H**H), 2.61 (1 H, dd, *J* = 15.8, 2.4 Hz, CH**H**), 1.40 (9 H, s, Piv C(CH_3)$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.7 (C), 150.4 (C), 147.0 (C), 141.9 (C), 140.7 (C), 135.6 (CH), 128.5 (CH), 125.5 (C), 124.7 (CH), 123.8 (CH), 122.6 (CH), 122.2 (C), 119.5 (CH), 117.7 (CH_2), 115.4 (CH), 64.3 (CH), 54.4 (CH), 42.0 (C), 32.3 (CH_2), 28.0 (CH_3) ppm; LRMS ES^+ *m/s* (%) 490 ($[M + Na]^+$, 100).

(1*R*,2*R*)-1,2-Diphenylethane-1,2-diol (2.78).



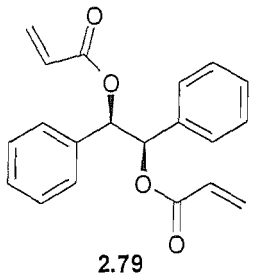
2.78

Diol **2.78** was prepared following the procedure of Wang *et al.*[102] Thus, to a suspension of $(DHQD)_2$-PHAL (1.09 g, 1.0 mmol), *trans*-stilbene **2.77** (100 g, 0.55 mol) and *N*-methyl-morpholine-*N*-oxide (50% in water, 168 mL, 0.72 mol) in *t*-butyl

alcohol (224 mL) was added potassium osmate (VI) dihydrate (0.41 g, 1.0 mmol). The mixture was stirred at rt for 15 h then quenched by the addition of 4,5-dihydroxy-1,3-benzenedisulfonic acid, disodium salt monohydrate (1.0 g, 3.0 mmol). After stirring for 3 h the mixture was poured into water (300 mL) and stirred for a further 3 h. The resulting precipitate was collected by filtration and washed with water until colourless. After drying *in vacuo*, diol **2.78** (105 g, 88%) was obtained as a white solid. The filtrate was stirred with EtOAc (400 mL) for 3 h, then the organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to a yellow solid which on triturating with hexane afforded additional diol **2.78** (11 g, 10%) for an overall yield of 97%.

mp. 151-153 °C (Lit. 148-150 °C);[102] IR ν 3496, 3385, 2895 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.23 (6 H, m, Ar-**H**), 7.17-7.12 (4 H, m, Ar-**H**), 4.72 (2 H, s, O**H**), 2.98 (2 H, s, C**H**OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.9 (C), 128.3 (CH), 128.0 (CH), 127.1 (CH), 79.2 (CH) ppm; LRMS ES^- *m/s* (%) 249 ([M + HCl - H]$^-$, 100). Data consistent with lit.[102]

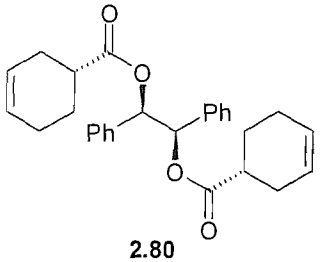
Acrylic acid (1*R*,2*R*)-2-acryloyloxy-1,2-diphenylethyl ester (2.79).



2.79

Bis-acrylate **2.79** was synthesised following the procedure of Marshall *et al.*[93] Thus, to a suspension of (*R,R*)-hydrobenzoin **2.78** (0.50 g, 2.34 mmol) in CH_2Cl_2 (11.6 mL) under argon was added Et_3N (1.4 mL, 9.8 mmol). The solution was cooled to 0 °C and acryloyl chloride (0.6 mL, 7.0 mmol) was added over a period 10 min. After stirring for 20 min the reaction mixture was poured into water (5.8 mL), the aqueous phase was extracted with CH_2Cl_2 (2 x 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give bis-acrylate **2.79** as a brown oil (1.0 g, >100%, contaminated with $Et_3N.HCl$). The crude product was used without purification.

Bis-(*R*)-3-Cyclohexenecarboxylate of (1*R*,2*R*)-1,2-Diphenylethane-1,2-diol (2.80).

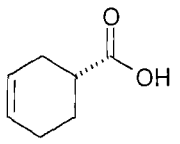


2.80

Diester **2.80** was prepared following the procedure of Marshall *et al.*[93] Thus, to a solution of bis-acrylate **2.79** (2.22 g, 4.7 mmol) in CH_2Cl_2 (23.1 mL) at -50 °C under argon was added $TiCl_4$ (1M in CH_2Cl_2, 4.7 mL, 4.7 mmol). After stirring for 15 min 1,3-butadiene (2.26 mL, 28 mmol) was added by cannula. The reaction mixture was stirred at ~ -20 °C for 3 days then warmed to rt and poured into water (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 x 25 mL); the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow solid. Purification by column chromatography (SiO_2, 10% diethyl ether in hexane) afforded diester **2.80** as a white solid (0.89 g, 44%).

$[\alpha]_D^{26}$ +37.5 (*c* 1.5, $CHCl_3$) (Lit. $[\alpha]_D^{24}$ +41.1 (*c* 1.34, $CHCl_3$);[93] mp. 97-99 °C (Lit. 99 °C);[93] IR ν 3350, 3028, 2928, 2839, 1725 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.13 (10 H, m, Ar-**H**), 6.10 (2 H, s, **CH**Ph), 5.72-5.63 (4 H, m, **CH**=**CH**), 2.60 (2 H, m, **CH**CO_2), 2.24-2.22 (4 H, m, CH=CH**CH_2**$CHCO_2$), 2.10-2.06 (4 H, m, CH_2**CH_2**CH=CH), 2.00-1.95 and 1.68-1.58 (4 H, m, **CH_2**CH_2CH=CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6 (C), 136.5 (C), 128.4 (CH), 128.3 (CH), 127.5 (CH) 126.9 (CH), 125.2 (CH), 76.7 (CH), 39.5 (CH), 27.4 (CH_2), 25.0 (CH_2), 24.5 (CH_2) ppm. Data consistent with lit.[93]

(*R*)-3-Cyclohexenecarboxylic Acid (2.16).



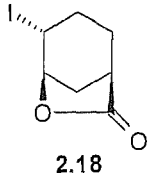
2.16

Carboxylic acid **2.16** was prepared following the method of Marshall *et al.*[93] To a suspension of diester **2.80** (12.0 g, 28 mmol) in MeOH (70 mL) under argon was added LiOH (2.67 g, 0.11 mol). After stirring for 7 h water (34 mL) was added and the reaction mixture was stirred for a further 1 h. Approximately half of the solvent was removed *in vacuo* with slight heating and the resulting slurry was diluted with

50% $NaHCO_3$ (aq) (300 mL). The mixture was extracted with diethyl ether (2 x 300 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to a white solid. Recrystallisation from diethyl ether/ hexane afforded recovered (*R*,*R*)-hydrobenzoin **2.78** as a white solid (5.21 g). The aqueous layer was acidified with 3 N HCl (aq) and extracted with diethyl ether (3 x 200 mL). The extracts were combined, washed with brine (300 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography on (SiO_2, 80% diethyl ether in hexane) afforded carboxylic acid **2.16** as a pale yellow oil (6.4 g, 91%).

$[\alpha]_D^{27}$ +75.8 (*c* 6.56, MeOH) (lit. +89.6 (*c* 6.45, MeOH));[93] IR ν 3027, 2919, 2842, 1699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74-5.65 (2 H, m, C**H**=C**H**), 2.62 (1 H, m, C**H**CO_2H), 2.31-2.27 (2 H, m, CH=CHC**H**$_2$CHCO_2H), 2.16-2.03 (3 H, m, C**H**HC**H**$_2$CH=CH), 1.71 (1 H, m, CH**H**CH_2CH=CH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 182.7 (C), 126.9 (CH), 125.1 (CH), 39.3 (CH), 27.3 (CH_2), 25.1 (CH_2), 24.4 (CH_2); LRMS ES^- *m/s* (%) 125 ($[M - H]^-$, 100) ppm. Data consistent with lit.[93]

(1*R*,4*R*,5*R*)-4-Iodo-6-oxabicyclo[3.2.1]octan-7-one (2.18).



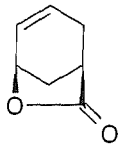
2.18

Iodolactone **2.18** was prepared following the method of Marshall *et al.*[93] A solution of $NaHCO_3$ (3.75 g, 45 mmol) in water (66 mL) was added to carboxylic acid **2.16** (1.94 g, 15 mmol) with ice cooling. After the suspension had dissolved, a solution of potassium iodide (14.77 g, 89 mmol) and iodine (4.12 g, 16 mmol) in water (33 mL) was added, the reaction mixture was warmed to rt and stirred for 24 h. Chloroform (50 mL) was added, the phases were separated and the aqueous layer was extracted with chloroform (4 x 50 mL). The combined extracts were washed with 50% sodium thiosulfate (aq) (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow solid. The crude product was dissolved in ethanol with slight heating. After standing for 3 days iodolactone **2.18** was afforded as a white crystalline solid (3.25 g, 84%).

$[\alpha]_D^{26}$ +37.0 (*c* 2.0, $CHCl_3$) (Lit. $[\alpha]_D^{24}$ +40.9 (*c* 2.49, $CHCl_3$));[93] mp. 132-135 °C (Lit. 132 °C);[93] ^1H NMR (300 MHz, $CDCl_3$) δ 4.83 (1 H, t, *J* = 5.1 Hz, C**H**OC(O)), 4.51 (1 H, t, *J* = 4.4 Hz, C**H**I), 2.80 (1 H, d, *J* = 12.0 Hz, C**H**CO_2), 2.68

(1 H, m, OCHCHHCHCO), 2.52-2.36 (2 H, m, CHICHH + $CO_2CHCHHCH_2$), 2.12 (1 H, app dd, J = 16.6, 5.1 Hz, OCHCHHCHCO), 1.93 (1 H, m, CHICHH) 1.83 (1 H, m, $CO_2CHCHHCH_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.9 (C), 80.3 (CH), 38.7 (CH), 34.6 (CH_2), 29.8 (CH_2), 23.9 (CH), 23.2 (CH_2) ppm. Data consistent with lit.[93]

(1*R*,5*R*)-6-Oxabicyclo[3.2.1]oct-3-en-7-one (2.19).

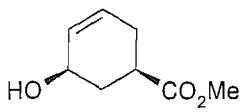


2.19

Lactone **2.19** was prepared following the method of Marshall *et al.*[93] To a solution of iodolactone **2.18** (3.50 g, 13.9 mmol) in THF (98 mL) under argon was added DBU (3.15 mL, 21 mmol). The reaction mixture was heated at reflux for 7 h then cooled to rt, poured into HCl (aq) (0.5 N, 100 mL) and extracted with diethyl ether (3 x 50 mL). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 80% diethyl ether in hexane) afforded lactone **2.19** as a pale yellow oil (1.46 g, 85%).

$[\alpha]_D^{26}$ +150.0 (*c* 3.0, $CHCl_3$) (Lit. $[\alpha]_D^{24}$ +191 (*c* 3.18, $CHCl_3$));[93] ^1H NMR (300 MHz, $CDCl_3$) δ 6.25 (1 H, m, OCHCH=CH), 5.85 (1 H, m, OCHCH=CH) 4.76 (1 H, t, J = 7.2 Hz, OCH), 2.91 (1 H, m, $CHCO_2$), 2.55-2.41 (3 H, m, $CH=CHCH_2CHCO_2$ + OCHCHHCHCO), 2.09 (1 H, d, J = 11.2 Hz, OCHCHHCHCO) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.4 (C), 130.4 (CH), 129.5 (CH), 73.4 (CH), 38.2 (CH), 34.6 (CH_2), 29.3 (CH_2) ppm; CIMS *m/s* (%) 125 ($[M + H]^+$, 100). Data consistent with lit.[93]

(1*R*,5*R*)-5-Hydroxycyclohex-3-enecarboxylic acid methyl ester (2.26).



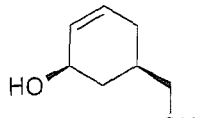
2.26

Ester **2.26** was prepared following the procedure of Marshall *et al.*[93] To a solution of lactone **2.19** (2.80 g, 23 mmol), in anhydrous MeOH (80 mL) under argon was added $NaHCO_3$ (1.89 g, 23 mmol). The reaction mixture was stirred at rt for 15 h. The solvent was removed *in vacuo* with slight heating and the residue was diluted with

water (250 mL) and extracted with diethyl ether (3 x 250 mL). The combined extracts were washed with brine (250 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 70% diethyl ether in hexane) afforded ester **2.26** as a yellow oil (1.08 g, 30%).

$[\alpha]_D^{26}$ -3.1 (*c* 2.0, $CHCl_3$) (Lit. $[\alpha]_D^{24}$ -4.6 (*c* 2.25, $CHCl_3$));[93] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.81-5.72 (2 H, m, C**H**=C**H**), 4.29 (1 H, m, C**H**OH), 3.70 (3 H, s, OC**H$_3$**), 2.74 (1 H, m, C**H**CO$_2$CH$_3$), 2.31-2.26 (4 H, m, CH=CHC**H$_2$** + O**H** + OHCHC**H**HCHCO$_2$), 1.74 (1 H, ddd, *J* = 12.9, 10.5, 7.9 Hz, HOCHCH**H**CHCO$_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.8 (C), 130.9 (CH), 127.0 (CH), 66.1 (CH_3), 52.1 (CH), 37.8 (CH), 34.3 (CH_2), 27.5 (CH_2) ppm. Data consistent with lit.[93]

(1*R*,5*R*)-5-Hydroxymethylcyclohex-2-enol (2.29).

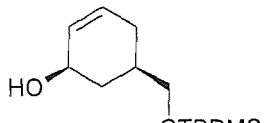


2.29

A solution of ester **2.26** (0.80 g, 5.0 mmol) in THF (10 mL) was added dropwise to a suspension of $LiAlH_4$ (0.19 g, 5.0 mmol) in THF (40 mL) at 0 °C under argon. After 1 h water (0.22 mL), 15% NaOH (aq) (0.22 mL) followed by water (0.66 mL) were added, the reaction mixture was warmed to rt and stirred for 2 h. The solid was filtered and the filtrate was dried over $MgSO_4$ and concentrated *in vacuo* to give diol **2.29** as a white solid (0.87 g, quant.).

$[\alpha]_D^{26}$ +18.5 (*c* 2.0, MeOH) (Lit. $[\alpha]_D^{23}$ +20.3 (*c* 2.25, MeOH));[97] mp. 81-83 °C (Lit. 84 °C);[97] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85-5.79 (1 H, m, HOCHCH=C**H**), 5.72 (1 H, m, HOCHC**H**=CH), 4.34 (1 H, m, C**H**OH), 3.59 (2 H, d, *J* = 7.4 Hz, C**H$_2$**OH), 2.19-2.12 (2 H, m, CH=CHC**H$_2$**), 2.01-1.75 (2 H, m, HOCHC**H$_2$**), 1.68 (br s, H_2O and OH peaks), 1.32 (1 H, ddd, *J* = 12.3, 11.0, 7.4 Hz, C**H**CH$_2$OH) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.0 (CH), 128.5 (CH), 67.5 (CH_2), 67.1 (CH), 35.3 (CH_2), 35.2 (CH), 26.2 (CH_2) ppm. Data consistent with lit.[97]

(1*R*,5*R*)-5-(*t*-Butyldimethylsilanyloxymethyl)cyclohex-2-enol (2.30).

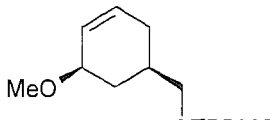


2.30

Protected diol **2.30** was prepared following the procedure of Danishefsky *et al.*[97] Thus, to a solution of diol **2.29** (0.72 g, 5.6 mmol) in anhydrous DMF (20 mL) under argon was added imidazole (0.70 g, 10 mmol) and the reaction mixture was cooled to 0 °C. *t*-Butyldimethylsilyl chloride (0.77 g, 5 mmol) was added and the reaction mixture was warmed to rt. After stirring for 5 h the reaction mixture was quenched by the addition of pH 7 buffer (25 mL). The mixture was extracted with diethyl ether (3 x 25 mL) and the combined extracts were washed with brine (25 mL) dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (SiO_2, 10% EtOAc in hexane) yielded protected diol **2.30** as a pale yellow oil (0.64 g, 47%).

$[\alpha]_D^{26}$ +1.9 (*c* 1.5, CH_2Cl_2) (Lit. $[\alpha]_D^{23}$ +2.7 (*c* 1.7, CH_2Cl_2));[97] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.72 (1 H, m, HOCHCH=C**H**), 5.63 (1 H, app d, *J* = 10.0 Hz, HOCHC**H**=CH), 4.26 (1 H, m, C**H**OH), 3.47 (2 H, dd, *J* = 5.5, 2.0 Hz, C**H**$_2$OSi), 2.11-1.68 (5 H, m, CH=CHC**H**$_2$C(CH_2)HC**H**$_2$ and OH), 1.17 (1 H, m, C**H**CH_2OSi), 0.85 (9 H, s, SiC(C**H**$_3$)$_3$), 0.00 (6 H, s, Si(C**H**$_3$)$_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 131.3 (CH), 128.5 (CH), 67.7 (CH_2), 67.6 (CH), 35.9 (CH_2), 35.7 (CH), 28.3 (CH_2), 26.0 (CH_3), 18.5 (C), -5.3 (CH_3) ppm. Data consistent with lit.[97]

***t*-Butyl-((1*R*,5*R*)-5-methoxycyclohex-3-enylmethoxy)dimethylsilane (2.31).**

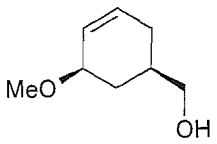


2.31

Protected methyl ether **2.31** was prepared following the method of Danishefsky *et al.*[97] A solution of alcohol **2.30** (0.55 g, 2.3 mmol) in THF (2 mL) was added to a suspension of NaH (60% in mineral oil, 0.27 g, 7 mmol) in THF (8 mL) under argon. Methyl iodide (1.40 mL, 23 mmol) was added and the reaction mixture was stirred at rt. After 4.5 h the mixture was quenched by the addition of water (25 mL) and extracted with diethyl ether (3 x 25 mL). The combined extracts were dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography (SiO_2, 0-50% EtOAc in hexane) afforded **2.31** as a pale yellow oil (0.50 g, 84%).

$[\alpha]_D^{26}$ -6.1 (*c* 1.5, CH_2Cl_2) (Lit. $[\alpha]_D^{23}$ -5.3 (*c* 1.59, CH_2Cl_2));[97] ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.75 (1 H, m, MeOCHCH=C**H**), 5.68 (1 H, app br d, *J* = 10.8 Hz, MeOCHC**H**=CH), 3.86 (1 H, m, C**H**OMe), 3.46 (2 H, dd, *J* = 6.0, 1.0 Hz, C**H**$_2$OSi), 3.33 (3 H, s, OC**H**$_3$), 2.13-1.99 (2 H, m, CH=CHC**H**$_2$), 1.80-1.70 (2 H, m, MeOCHC**H**$_2$), 1.15 (1 H, m, C**H**CH$_2$OSi), 0.85 (9 H, s, SiC(C**H**$_3$)$_3$), 0.00 (6 H, s, Si(C**H**$_3$)$_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.9 (CH), 128.8 (CH), 76.5 (CH_3), 67.9 (CH_2), 55.6 (CH), 36.0 (CH), 31.8 (CH_2), 26.7 (CH_2), 26.1 (CH_3), 18.5 (C), -5.2 (CH_3) ppm. Data consistent with lit.[97]

((1*R*,5*R*)-5-Methoxycyclohex-3-enyl)methanol (2.32).

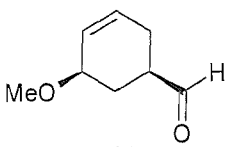


2.32

To a solution of **2.31** (0.45 g, 1.8 mmol) in THF (25 mL) at 0 °C under argon was added TBAF (1M in THF, 5.1 mL, 5.1 mmol) over 5 min. The reaction mixture was warmed to rt and stirred for 5 h then cooled to 0 °C, poured into ice water (~25 mL) and extracted with diethyl ether (3 x 25 mL). The combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 40% EtOAc in hexane) afforded alcohol **2.32** as a yellow oil (0.20 g, 77%).

$[\alpha]_D^{26}$ +16.3 (*c* 1.5, CH_2Cl_2) (Lit. $[\alpha]_D^{23}$ +18.1 (*c* 1.62, CH_2Cl_2));[97] ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.83 (1 H, m, MeOCHCH=C**H**), 5.77 (1 H, app d, *J* = 10.3 Hz, MeOCHC**H**=CH), 3.87 (1 H, m, C**H**OMe), 3.61-3.55 (2 H, m, C**H**$_2$OH), 3.39 (3 H, s, OC**H**$_3$), 2.17-2.10 (2 H, m, CH=CHC**H**$_2$), 1.96-1.74 (3 H, m, MeOCHC**H**$_2$ + OH), 1.32 (1 H, ddd, *J* = 12.5, 11.0, 8.8 Hz, C**H**CH$_2$OH) ppm; ^{13}C NMR (75MHz, $CDCl_3$) δ 129.0 (CH), 128.2 (CH), 75.4 (CH_3), 67.4 (CH_2), 55.8 (CH), 35.0 (CH), 31.2 (CH_2), 28.3 (CH_2) ppm. Data consistent with lit.[97]

(1*R*,5*R*)-5-Methoxycyclohex-3-enecarbaldehyde (2.81).

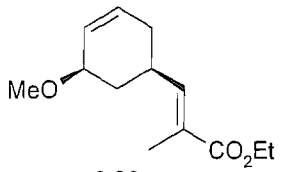


2.81

To a solution of oxalyl chloride (0.12 mL, 1.3 mmol) in CH_2Cl_2 (20 mL) at -78 °C under argon was added DMSO (0.19 g, 1.3 mmol). After 30 min alcohol **2.32** (0.19 g, 1.3 mmol) dissolved in CH_2Cl_2 (5 mL) was added dropwise and the mixture was stirred for a further 30 min. Et_3N (0.37 mL, 2.6 mmol) was added and the reaction mixture was warmed to -30 °C. After 4 h the reaction mixture was warmed to rt and quenched with 50% NaCl (aq) (25 mL). The aqueous phase was extracted with EtOAc (2 x 25 mL) and the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to a white oily solid. Addition of EtOAc: hexane (1:1) induced the formation of a precipitate which was collected by filtration ($Et_3N.HCl$) and the filtrate was concentrated *in vacuo* purification by column chromatography (SiO_2, 40% EtOAc in hexane) afforded aldehyde **2.81** as a pale yellow oil (0.06 g, 33%).

$[\alpha]_D^{27}$ -2.5 (*c* 0.1, $CHCl_3$); IR ν 2933, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.69 (1 H, s, C**H**O), 5.88-5.77 (2 H, m, C**H**=C**H**), 3.89 (1 H, m, C**H**OMe), 3.37 (3 H, s, OC**H₃**), 2.54 (1 H, m, C**H**COH), 2.34-2.22 (2 H, m, CH=CHC**H₂**), 1.73 (2 H, ddd, J = 13.0, 10.1, 7.5 Hz, MeOCHC**H₂**) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.0 (CH), 128.4 (CH), 128.0 (CH), 74.1 (CH_3), 55.9 (CH), 44.9 (CH), 28.1 (CH_2), 24.4 (CH_2) ppm.

(*E*)-3-((1*R*,5*R*)-5-Methoxycyclohex-3-enyl)-2-methylacrylic acid ethyl ester (2.82).

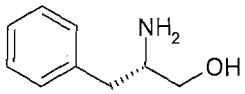


2.82

To a solution of aldehyde **2.81** (54 mg, 0.4 mmol) in THF (5 mL) at 0 °C under argon was added a solution of (1-ethoxycarbonyethylidene)triphenylphosphorane (0.21 g, 0.6 mmol) in THF (20 mL). The reaction mixture was stirred at 0 °C for 6 h then a further 1.5 equiv. of (1-ethoxycarbonyethylidene)triphenylphosporane (0.21 g, 0.6 mmol) was added and the reaction mixture was stirred at rt overnight, and then heated at reflux. After 3 days at reflux the reaction mixture was cooled to rt, water (25 mL) was added and the reaction mixture was extracted with diethyl ether (2 x 25 mL). The combined extracts were washed with brine (25 mL), dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% EtOAc in hexane) afforded diene **2.82** as a yellow oil (52 mg, 60%).

$[\alpha]_D^{27}$ +18.2 (*c* 1.0, $CHCl_3$); IR ν 3019, 2983, 2927, 2820, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.63 (1 H, dq, *J* = 10.3, 1.5 Hz, C**H**=C(CH_3)), 5.83-5.74 (2 H, m, C**H**=C**H**), 4.21 (2 H, q, *J* = 7.0 Hz, OC**H**$_2$$CH_3$), 3.97 (1 H, m, C**H**OMe), 3.38 (3 H, s, OC**H**$_3$), 2.69 (1 H, m, C**H**CH=C(CH_3)), 2.11-2.03 (2 H, m, CH=CHC**H**$_2$), 1.97-1.90 (2 H, m, MeOCHC**H**$_2$), 1.87 (3 H, d, *J* = 1.5 Hz, CH=C(C**H**$_3$)), 1.31 (3 H, t, *J* = 7.0 Hz, OCH_2C**H**$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 144.9 (CH), 128.7 (CH), 128.3 (CH), 127.4 (C), 75.1 (CH_3), 60.7 (CH_2), 55.74 (CH), 33.8 (CH_2), 32.9 (CH), 30.6 (CH_2), 14.4 (CH_3), 12.6 (CH_3) ppm.

(*S*)-Phenylalanol (2.87).

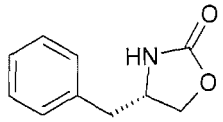


2.87

(*S*)-Phenylalanol **2.87** was prepared following the procedure of Evans *et al.*[107] To a suspension of phenylalanine **2.87** (20 g, 0.12 mol) in THF (60 mL) under argon was added BF_3·OEt_2 (11.13 mL, 0.12 mol) over 30 min. The mixture was heated at reflux under argon for 2 h then BH_3·SMe_2 complex (10 M in THF, 14 mL, 0.14 mol) was added dropwise *via* dropping funnel over 1.5 h to the refluxing solution. The reaction mixture was heated at reflux for 6 h then quenched by the dropwise addition of THF: water (1:1, 15 mL) followed by 5M NaOH (aq) (90 mL). The mixture was heated at reflux for 14 h, cooled to rt and filtered. The residue solids were washed with THF (2 x 3 mL). The filtrate was concentrated *in vacuo* and the slurry was extracted with CH_2Cl_2 (3 x 30 mL), the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo.* The resulting solid was re-crystallised from EtOAc/ diethyl ether to afford (*S*)-phenylalanol **2.88** as a white solid (12.75 g, 70%).

$[\alpha]_D^{27}$ -18.5 (*c* 0.5, EtOH) (Lit. $[\alpha]_D^{24}$ -22.4 (*c* 1.03, EtOH);[107] mp. 89-92 °C (Lit. 88.5-91 °C).[107] IR ν 3161, 3139, 3120, 1807, 1530 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.27-7.15 (5 H, m, Ar-**H**), 3.28 (1 H, dd, *J* = 10.4, 4.9 Hz, C**H**H(OH)), 3.17 (1 H, dd, *J* = 10.4, 6.4 Hz, CH**H**(OH)), 2.86 (1 H, m, C**H**NH_2), 2.67 (1 H, dd, *J* = 13.2, 5.5 Hz, C**H**HPh), 2.42 (1 H, dd, *J* = 13.2, 7.7 Hz, CH**H**Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 139.8 (C), 129.1 (CH), 128.1 (CH), 125.7 (CH), 65.8 (CH_2), 54.4 (CH), 40.2 (CH_2) ppm; LRMS ES^+ *m/s* (%) 152 ($[M + H]^+$, 100), 193 ($[M + H + MeCN]^+$, 20). Data consistent with lit.[107]

(*S*)-4-(Phenylmethyl)-2-oxazolidinone (2.89).

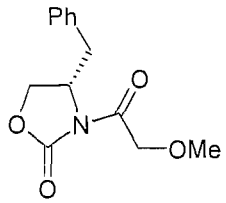


2.89

Oxazolidinone **2.89** was prepared following the procedure of Evans *et al.*[107] Phenylalanol **2.88** (12.0 g, 79.4 mmol), diethyl carbonate (19.81 mL, 0.16 mol) and anhydrous K_2CO_3 (1.10 g, 7.9 mmol) were heated at reflux with removal of ethanol by distillation for 2 h. CH_2Cl_2 (100 mL) was added and the solution was washed with water (100 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was recrystallised from EtOAc: hexane (2:1, 50 mL) to give **2.89** as a white crystalline solid (9.43 g, 71%).

$[\alpha]_D^{27}$ +6.0 (*c* 1.0, EtOH) (Lit. $[\alpha]_D^{23}$ +4.9 (*c* 1.10, EtOH));[107] mp. 88-90 °C (Lit. 84.5-86.5 °C);[107] IR ν 3283, 2925, 2361, 1745, 1706 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.77 (1 H, br s, N**H**), 7.33-7.23 (5 H, m, Ar-**H**), 4.25 (1 H, t, *J* = 8.0 Hz, C**H**HO), 4.05 (1 H, m, C**H**NH) 3.97 (1 H, dd, *J* = 8.0, 5.6 Hz, CH**H**O), 2.82 (1 H, dd, *J* = 13.5, 5.2 Hz, C**H**HPh), 2.74 (1 H, dd, *J* = 13.5, 6.9 Hz, CH**H**Ph) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.6 (C), 136.5 (C), 129.3 (CH), 128.4 (CH), 126.5 (CH), 68.0 (CH_2), 52.5 (CH), 40.2 (CH_2) ppm; LRMS ES^+ *m/s* (%) 377 ($[2M + Na]^+$, 45). Data consistent with lit.[107]

(*S*)-4-Benzyl-3-(2-methoxyacetyl)oxazolidin-2-one (2.90).



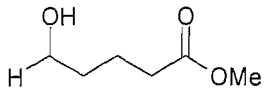
2.90

To a suspension of oxazolidinone **2.89** (9.0 g, 51 mmol), in THF (153 mL) at -78 °C under argon was added BuLi (2.56M in hexane, 20.15 mL, 52 mmol) over a period of 10 min. Methoxyacetyl chloride (5.14 mL, 56 mmol) was added and the reaction mixture was stirred at -78 °C for 30 min. The reaction mixture was warmed to rt then quenched with sat. NH_4Cl (aq) (30 mL). The solution was concentrated *in vacuo* and the resulting slurry was extracted with CH_2Cl_2 (2 x 50 mL). The extracts were combined, washed with sat. NaOH (aq) (40 mL) and brine (40 mL), dried over

$MgSO_4$ and concentrated *in vacuo* to a yellow oil. This was cooled to -20 °C overnight and triturated with cold hexane/ diethyl ether to give acylated oxazolidinone **2.90** as a white solid (11.9 g, 94%).

$[\alpha]_D^{27}$ +71.5 (*c* 1.5, $CHCl_3$) (Lit. $[\alpha]_D^{23}$ +72.3 (*c* 1.48, $CHCl_3$));[132] mp. 51-53 °C (Lit. 52 °C);[132] IR ν 2911, 2359, 1771, 1713 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.20 (5 H, m, Ar-**H**), 4.71 (1 H, m, C**H**N), 4.63 (2 H, app d, *J* = 1.9 Hz, C**H**$_2$OCH$_3$), 4.30 (1 H, t, *J* = 9.2 Hz, CO_2CH**H**), 4.24 (1 H, dd, *J* = 9.2, 3.4 Hz, CO_2C**H**H), 3.52 (3 H, s, OC**H**$_3$), 3.33 (1 H, dd, *J* = 13.4, 3.2 Hz, C**H**HPh), 2.83 (1 H, dd, *J* = 13.4, 9.4 Hz, CH**H**Ph) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C), 153.5 (C), 135.0 (C), 129.5 (CH), 129.1 (CH), 127.6 (CH), 72.3 (CH_2), 67.4 (CH_2), 59.6 (CH_3), 54.9 (CH), 37.9 (CH_2); CIMS *m/s* (%) 250 ($[M + H]^+$, 100) ppm. Data consistent with lit.[132]

5-Hydroxypentanoic acid methyl ester (2.92).

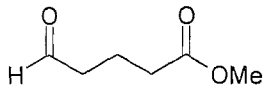


2.92

Hydroxylactone **2.92** was prepared following the method of Huckstep *et al.*[109] δ-valerolactone **2.91** (10 mL, 92.6 mmol), anhydrous MeOH (200 mL) and conc. H_2SO_4 (10 drops) were heated at reflux under argon for 5 h. After this time the reaction mixture was cooled in an ice/salt bath and $NaHCO_3$ (1.0 g) was added. The mixture was stirred for a further 10 min and then filtered. The filtrate was concentrated *in vacuo* to give hydroxyester **2.92** as a colourless liquid (14.97 g, quant.) which was used without further purification.

IR ν 3409, 2951, 2874, 1735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.68 (3 H, s, OC**H**$_3$), 3.65 (2 H, t, *J* = 5.9 Hz, C**H**$_2$OH), 2.37 (2 H, t, *J* = 7.1 Hz, C**H**$_2$CO$_2$Me), 1.78-1.58 (4 H, m, C**H**$_2$C**H**$_2$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3 (C), 62.2 (CH_2), 51.5 (CH_3), 33.6 (CH_2), 32.0 (CH_2), 21.1 (CH_2) ppm. Data consistent with lit.[109]

5-Oxopentanoic acid methyl ester (2.93).

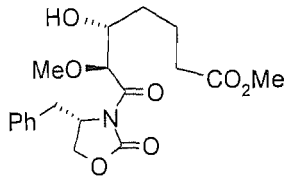


2.93

Aldehyde **2.93** was prepared following the procedure of Huckstep *et al.*[109] Hydroxyester **2.92** (12.23 g, 92.5 mmol) in CH_2Cl_2 (80 mL) was added to a stirred suspension of PCC (29.5 g, 1.14 mmol) in CH_2Cl_2 (120 mL). The reaction mixture was stirred for 2 h under argon then diethyl ether (200 mL) was added. The solution was decanted from the black residue and the residue was washed with diethyl ether (3 x 50mL) and the combined extracts were filtered through florisil® and concentrated *in vacuo* to a green oil. Purification by column chromatography (SiO_2, 1:1 EtOAc hexane) afforded ester **2.93** as a pale yellow oil (9.98g, 83%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.76 (1 H, app s, C**H**O), 3.67 (3 H, s, OC**H**$_3$), 2.52 (2 H, t, J = 7.0 Hz, HCOC**H**$_2$)), 2.36 (2 H, t, J = 7.0 Hz, C**H**$_2$CO$_2$CH$_3$), 1.94 (2 H, quintet, J = 7.0 Hz, C**H**$_2$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 201.6 (CH), 173.4 (C), 51.7 (CH_3), 43.0 (CH_2), 33.1 (CH_2), 17.5 (CH_2) ppm. Data consistent with lit.[109]

(5*R*,6*S*)-7-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-6-methoxy-7-oxo heptanoic acid methyl ester (2.94).



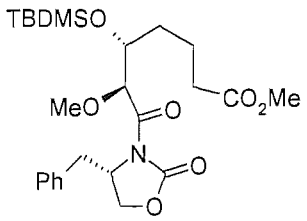
2.94

A solution of acylated oxazolidinone **2.90** (4.0 g, 16 mmol) in CH_2Cl_2 (45 mL) was cooled to 0 °C under argon. Dibutylboron triflate (1.0 M in CH_2Cl_2, 4.1 mL, 4 mmol) was added followed by the dropwise addition of Et_3N (2.92 mL, 21 mmol). The solution was cooled to -65 °C then 5-oxo-pentanoic acid methyl ester **2.93** (2.28 g, 18 mmol) was added over 5 min. The mixture was stirred at -65 °C for 20 min then at 0 °C for 1 h. The reaction mixture was quenched by the addition of pH 7 phosphate buffer (20 mL) followed by MeOH (60 mL), then MeOH: 30% H_2O_2 (2:1, 60 mL) was added dropwise. The reaction mixture was concentrated *in vacuo* and the slurry was extracted with diethyl ether (3 x 150 mL). The combined extracts were washed with 5% NaHCO3 (aq) (150 mL), then brine (150 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2,

50-100% EtOAc in hexane) afforded oxazolidinone **2.94** (4.97 g, 81%) as a colourless oil which on standing became a white waxy solid.

$[\alpha]_D^{27}$ +15.2 (*c* 1.0, $CHCl_3$); IR ν 3481, 2950, 1773, 1730, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.29-7.14 (5 H, m, Ar-**H**), 4.92 (1 H, d, *J* = 2.4 Hz, C**H**OCH_3), 4.71 (1 H, ddt, *J* = 9.6, 7.2, 2.9 Hz, C**H**N), 4.26 (1 H, dd, *J* = 9.1, 7.2 Hz, C**H**HO), 4.21 (1 H, dd, *J* = 9.1, 2.9 Hz, CH**H**O), 3.88 (1 H, m, C**H**OH), 3.64 (3 H, s, CO_2CH_3), 3.47 (3 H, s, $CHOCH_3$), 3.35 (1 H, dd, *J* = 13.3, 2.9 Hz, C**H**HPh), 2.85 (1 H, dd, *J* = 13.3, 9.6 Hz, CH**H**Ph), 2.29-2.26 (2 H, m, $CH_2C(=O)$), 1.77-1.61 (4 H, m, CH_2CH_2) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.0 (C), 170.7 (C), 153.6 (C), 135.1 (C), 129.5 (CH), 129.1 (CH), 127.5 (CH), 81.8 (CH), 72.0 (CH), 67.2 (CH_2), 58.8 (CH_3), 55.8 (CH), 51.6 (CH_3), 37.9 (CH_2), 33.8 (CH_2), 33.4 (CH_2), 21.2 (CH_2) ppm; LRMS ES^+ *m/s* (%) 402 ($[M + Na]^+$, 100), 443 ($[M + Na + MeCN]^+$, 35), 781 ($[2M + Na]^+$, 40); Anal. Calcd for $C_{19}H_{25}NO_7$: C, 60.15; H, 6.64; N, 3.69. Found: C, 60.27; H, 6.64; N, 3.69.

(*S*)-7-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-(*t*-butyldimethylsilanyloxy)-6-methoxy-7-oxoheptanoic acid methyl ester (2.95).



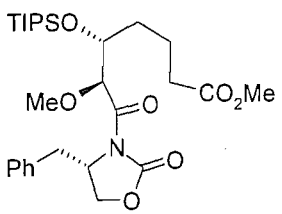
2.95

To a solution of **2.94** (0.5 g, 1.3 mmol) in CH_2Cl_2 (20 mL) under argon was added imidazole (0.19 g, 2.8 mmol). The solution was cooled to 0 °C and *t*-butyldimethylsilyl chloride (0.42 g, 2.8 mmol) was added. The reaction mixture was stirred at rt for 15 h then quenched by the addition of HCl (aq) (pH 5, 3 x 20 mL). The organic phase was dried over $MgSO_4$ and concentrated *in vacuo* to a colourless oil. Purification by column chromatography (SiO_2, 40-100% EtOAc in hexane then 10% MeOH in CH_2Cl_2) afforded protected oxazolidinone **2.95** as a colourless oil (13 mg, 2%).

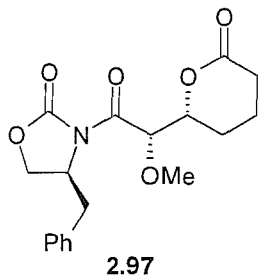
$[\alpha]_D^{27}$ +30.5 (*c* 0.5, MeOH); ^1H NMR (300 MHz, DMSO-d_6) δ 7.30-7.21 (5 H, m, Ar-**H**), 4.88 (1 H, d, *J* = 4.4 Hz, C**H**OCH_3), 4.67 (1 H, m, C**H**N), 4.35 (1 H, m, C**H**HO), 4.34 (1 H, dd, *J* = 12.8, 9.3 Hz, CH**H**O), 3.97 (1 H, td, *J* = 5.9, 4.4 Hz, C**H**OSi), 3.57 (3 H, s, CO_2CH_3), 3.33 (3 H, s, $CHOCH_3$), 3.06 (2 H, app d, *J* = 5.1

Hz, CH_2Ph), 2.30 (2 H, t, J = 6.8 Hz, $CH_2CO_2CH_3$) 1.61-1.35 (4 H, m, CH_2CH_2), 0.83 (9 H, s, $SiC(CH_3)_3$), -0.18 (6 H, app d, J = 9.5 Hz, $Si(CH_3)_2$) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.1 (C), 170.1 (C), 153.1 (C), 135.3 (C), 129.5 (CH), 128.6 (CH), 127.0 (CH), 80.8 (CH), 71.9 (CH), 66.8 (CH_2), 58.0 (CH_3), 54.9 (CH), 51.1 (CH_3), 36.3 (CH_2), 33.0 (CH_2), 32.2 (CH_2), 20.3 (CH_2), 17.7 (C), -4.7 (CH_3), -5.0 (CH_3) ppm; LRMS ES^+ *m/s* (%) 516 ($[M + Na]^+$, 80). Anal. Calcd for $C_{25}H_{39}NO_7$: C, 60.82; H, 7.96; N, 2.84. Found: C, 60.79; H, 7.89; N, 2.84.

(5*R*,6*S*)-7-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-6-methoxy-7-oxo-5-triisopropylsilanyloxyheptanoic acid methyl ester (2.96) and (*S*)-4-Benzyl-3-[(*S*)-2-methoxy-2-((*R*)-6-oxotetrahydropyran-2-yl)acetyl]oxazolidin-2-one (2.97).



2.96



2.97

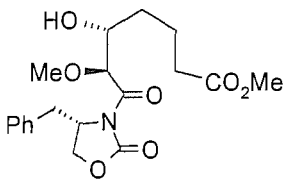
To a solution of oxazolidinone **2.94** (2.0 g, 5.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C under argon was added 2, 6-lutidine (3.7 mL, 32 mmol) followed by the dropwise addition of triisopropylsilyl triflate (5.7 mL, 21 mmol). The reaction mixture was stirred at 0 °C for 30 min then at rt for 2 h then 2, 6-lutidine (0.61 mL, 5.3 mmol) and triisopropylsilyl triflate (5.7 mL, 21 mmol) were added. After 30 min the reaction mixture was washed with 10% HCl (aq) (100 mL), then 5% NaHCO3 (aq) (100 mL) and brine (100 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 10-100% EtOAc in hexane) afforded protected oxazolidinone **2.96** as a colourless oil (0.50 g, 18%) and **2.97** as a white solid (0.3 g, 17%). Any mixed fractions were combined, concentrated *in vacuo*, refluxed with anhydrous MeOH (10 mL) and conc. H_2SO_4 (1 drop) for 6 h. After this time the mixture was cooled and $NaHCO_3$ (10 mg) was added. The mixture was filtered, concentrated *in vacuo* and purified by column chromatography (SiO_2, 5% MeOH in CH_2Cl_2) to give recovered starting material **2.94** as a colourless oil (0.81 g, 40%, for spectroscopic data see above)

2.96: $[\alpha]_D^{27}$ +26.9 (*c* 1.0, $CHCl_3$); IR ν 2954, 2866, 1778, 1734 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.22 (5 H, m, Ar-H), 5.07 (1 H, app t, J = 5.7 Hz,

C**H**OCH$_3$), 4.65 (1 H, m, C**H**N), 4.28-4.17 (3 H, m, C**H$_2$**O- and C**H**OSi), 3.64 (3 H, s, CO$_2$C**H$_3$**), 3.46 (3 H, s, CHOC**H$_3$**), 3.38 (1 H, dd, *J* = 12.3, 1.9 Hz, C**H**HPh), 2.86 (1 H, dd, *J* = 12.3, 9.5 Hz, CH**H**Ph), 2.33 (2 H, q, *J* = 4.9 Hz, C**H$_2$**CO$_2$CH$_3$), 1.82-1.34 (4 H, m, C**H$_2$C H$_2$**), 1.05 - 0.94 (21 H, m, TIPS-**H**) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 174.0 (C), 171.2 (C), 153.5 (C), 135.3 (C), 129.6 (CH), 129.1 (CH), 127.6 (CH), 81.4 (CH), 72.7 (CH), 66.8 (CH$_2$), 58.9 (CH$_3$), 56.2 (CH), 51.6 (CH$_3$), 37.8 (CH$_2$), 33.9 (CH$_2$), 33.4 (CH$_2$), 20.3 (CH$_2$) 18.3 (CH), 13.0 (CH$_3$) ppm; LRMS ES$^+$ *m/s* (%) 558 ([M + Na]$^+$, 100); Anal. Calcd for $C_{28}H_{45}NO_7Si$: C, 62.77; H, 8.47; N, 2.61. Found: C, 62.74; H, 8.47; N, 2.58.

2.97: [α]$_D^{27}$ +13.7 (*c* 1.0, CHCl$_3$); mp. 43-45 °C; IR ν 2945, 1769, 1730, 1710 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37-7.21 (5 H, m, Ar-**H**), 5.03 (1 H, d, *J* = 3.2 Hz, C**H**OCH$_3$), 4.79 (1 H, app ddd, *J* = 7.3, 3.2, 2.7 Hz, C**H**N), 4.76 (1 H, ddd, *J* = 9.9, 6.8, 3.2 Hz, C**H**OC(=O)), 4.30 (1 H, dd, *J* = 9.2, 7.3 Hz, C**H**HO), 4.24 (1 H, dd, *J* = 9.2, 2.7 Hz, CH**H**O), 3.52 (3 H, s, OC**H$_3$**), 3.38 (1 H, dd, *J* = 13.4, 3.2 Hz, C**H**HPh), 2.88 (1 H, dd, *J* = 13.4, 9.4 Hz, CH**H**Ph), 2.61-2.38 (2 H, m, C**H$_2$**C(=O)), 2.09-1.77 (4 H, m, C**H$_2$C H$_2$**) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.4 (C), 168.4 (C), 153.9 (C), 135.0 (C), 129.6 (CH), 129.2 (CH), 127.7 (CH), 80.8 (CH), 79.1 (CH), 67.4 (CH$_2$), 59.3 (CH$_3$), 55.9 (CH), 37.8 (CH$_2$), 29.9 (CH$_2$), 23.7 (CH$_2$), 18.6 (CH$_2$); LRMS ES$^+$ *m/s* (%) 365 ([M + Na]$^+$, 100) ppm; Anal. Calcd for $C_{18}H_{21}NO_6$: C, 62.24; H, 6.09; N, 4.03. Found: C, 62.04; H, 6.09; N, 3.98.

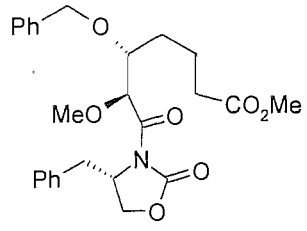
(5*R*,6*S*)-7-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-6-methoxy-7-oxo heptanoic acid methyl ester (2.94).



2.94

To a solution of lactone **2.97** (50 mg, 0.15 mmol) in MeOH (5 mL) was added conc. H_2SO_4 (1 drop). The reaction mixture was heated at reflux under argon for 6 h, then cooled to 0 °C and $NaHCO_3$ (5 mg) was added. The reaction mixture was filtered, concentrated *in vacuo*. Purification by column chromatography (SiO_2, 5% MeOH in CH_2Cl_2) afforded **2.94** as a colourless oil (46 mg, 83%, for spectroscopic data see above).

(*S*)-7-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-benzyloxy-6-methoxy-7-oxoheptanoic acid methyl ester (2.98).

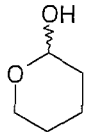


2.98

To a solution of oxazolidinone **2.94** (0.1 g, 0.3 mmol) in CH_2Cl_2/ hexane (2:1, 3 mL) under argon was added benzyl-2,2,2-trichloroacetimidate (60 μL, 0.3 mmol). The solution was cooled to 0 °C then triflic acid (5 μL, 0.05 mmol) was added. The reaction mixture was stirred at 0 °C for 1 h then at rt for 1 h. The mixture was filtered through celite, washed with sat. $NaHCO_3$ (aq) (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil (0.30 g). Purification by column chromatography (SiO_2, 40-100% EtOAc in hexane) afforded benzyl ether **2.98** as a colourless oil (43 mg, 35%).

$[\alpha]_D^{26}$ +33.1 (*c* 1.0, $CHCl_3$); IR ν 2948, 1775, 1732, 1709 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.14 (10 H, m, Ar-**H**), 5.10 (1 H, d, *J* = 3.4 Hz, C**H**OCH_3), 4.58 (1 H, d, *J* = 11.7 Hz, OC**H**HPh), 4.42 (1 H, d, *J* = 11.7 Hz, OCH**H**Ph), 4.36 (1 H, m, C**H**N), 4.02 (1 H, app d, *J* = 9.0 Hz, OC**H**HCHN), 3.82 (1 H, t, *J* = 9.0 Hz, OCH**H**CHN), 3.77 (1 H, m, C**H**OCH_2Ph)), 3.63 (3 H, s, CO_2CH_3), 3.44 (3 H, s, $CHOCH_3$), 3.26 (1 H, dd, *J* = 13.4, 2.8 Hz, C**H**HPh), 2.76 (1 H, dd, *J* = 13.4, 9.6 Hz, CH**H**Ph), 2.30 (2 H, d, *J* = 6.0 Hz, CH_2CO_2Me), 1.77-1.58 (4 H, m, CH_2CH_2) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.0 (C), 170.5 (C), 153.4 (C), 138.3 (C), 135.2 (C), 129.5 (CH), 129.1 (CH), 128.7 (CH), 128.4 (CH), 127.9 (CH), 127.5 (CH), 80.5 (CH), 77.5 (CH), 71.9 (CH_2), 66.8 (CH_2), 59.0 (CH_3), 55.9 (CH), 51.7 (CH_3), 37.7 (CH_2), 34.0 (CH_2), 29.3 (CH_2), 21.1 (CH_2) ppm; LRMS ES^+ *m/s* (%) 508 ($[M + K]^+$, 100); Anal. Calcd for $C_{26}H_{31}NO_7$: C, 66.51; H, 6.65; N, 2.98. Found: C, 66.50; H, 6.49; N, 2.85.

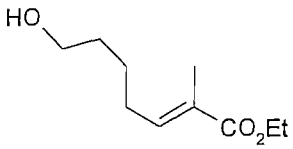
Tetrahydropyran-2-ol (2.100).



2.100

Lactol **2.100** was prepared following the procedure of Rousseau and co-workers.[117] To a solution of δ-valerolactone **2.91** (2 g, 20 mmol) in CH_2Cl_2 (50 mL) at -78 °C under argon was added DIBAL-H (1.0 M in CH_2Cl_2, 20 mL, 20 mmol). The reaction mixture was stirred for 30 min then IPA in toluene (2M, 11 mL) was added and the reaction mixture was stirred for 30 min. The reaction mixture was warmed to 0 °C then water (3 mL), followed by THF (50 mL) was added and the reaction mixture was warmed to rt. Silica gel (12 g) and Na_2SO_4 (20 g) were added and the reaction mixture was stirred for 30 min, filtered and concentrated *in vacuo* to give lactol **2.100** as a colourless oil (1.67 g, 82%). The crude product was used without purification.

(*E*)-7-Hydroxy-2-methylhept-2-enoic acid ethyl ester (2.101).

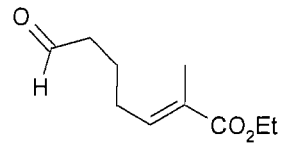


2.101

Enone **2.101** was prepared following the procedure of Hayashi *et al.*[118] To a solution of (1-ethoxycarbonyethylidene)triphenylphosporane (19.87 g, 55 mmol) in benzene (60 mL) under argon was added lactol **2.100** (2.8 g, 27 mmol). The reaction mixture was heated at 90 °C for 48 h then concentrated *in vacuo.* Purification by column chromatography (SiO_2, 1:1 EtOAc: hexane) afforded **2.101** as a pale yellow oil (4.32 g, 85%).

IR ν 3397, 2935, 2856, 1707 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.75 (1 H, tq, J = 7.1, 1.4 Hz, C**H**=C), 4.18 (2 H, q, J = 6.9 Hz, O**CH$_2$**CH$_3$), 3.65 (2 H, m, **CH$_2$**OH), 2.21 (2 H, q, J = 7.1 Hz, **CH$_2$**CH=C), 1.83 (3 H, d, J = 1.4 Hz, **CH$_3$**C=CH), 1.65-1.47 (4 H, m, **CH$_2$CH$_2$**), 1.29 (3 H, t, J = 6.9 Hz, OCH$_2$**CH$_3$**) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 141.9 (CH), 128.2 (C), 62.9 (CH_2), 60.6 (CH_2), 32.5 (CH_2), 28.5 (CH_2), 25.0 (CH_2), 14.4 (CH_3), 12.3 (CH_3) ppm; CIMS *m/s* (%) 187 ($[M + H]^+$, 66). Data consistent with lit.[118]

(*E*)-2-Methyl-7-oxohept-2-enoic acid ethyl ester (2.102).

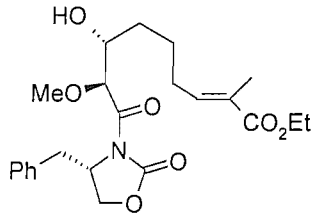


2.102

To a solution of oxalyl chloride (4.13 mL, 47 mmol) in CH_2Cl_2 (100 mL) under argon at -78 °C was added DMSO (6.72 mL, 95 mmol) in CH_2Cl_2 (50 mL) dropwise over 5 min. The reaction mixture was stirred for 10 min then **2.101** (4.32 g, 24 mmol) in CH_2Cl_2 (50 mL) was added over 5 min. The reaction mixture was warmed to -60 °C, stirred for 15 min then Et_3N (26.4 mL, 189 mmol) was added. The reaction mixture was warmed to rt then water (120 mL) was added and the reaction mixture was stirred for 10 min. The organic phase was washed with 2 N HCl (aq) (160 mL), water (160 mL) then sat. $NaHCO_3$ (aq) (160 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 30% EtOAc in hexane) afforded aldehyde **2.102** as a colourless oil (3.94 g, 92%).

IR ν 2937, 2724, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (1 H, t, J = 1.5 Hz, **H**C=O), 6.71 (1 H, tq, J = 7.4, 1.2 Hz, C**H**=C), 4.19 (2 H, q, J = 7.1 Hz, OC**H**$_2$CH$_3$), 2.47 (2 H, td, J = 7.4, 1.5, C**H**$_2$C=O), 2.22 (2 H, q, J = 7.4 Hz, C**H**$_2$CH=C), 1.82 (3 H, d, J = 1.2 Hz, C**H**$_3$C=CH), 1.79 (2 H, quintet, J = 7.4 Hz, CH$_2$C**H**$_2$CH$_2$), 1.29 (3 H, t, J = 7.1 Hz, OCH$_2$C**H**$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 201.9 (CH), 168.1 (C), 140.5 (CH), 129.0 (C), 60.6 (CH_2), 43.3 (CH_2), 27.9 (CH_2), 21.1 (CH_2), 14.4 (CH_3), 12.5 (CH_3) ppm.

(*E*)-(7*R*,8*S*)-9-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-7-hydroxy-8-methoxy-2-methyl-9-oxonon-2-enoic acid ethyl ester (2.103).



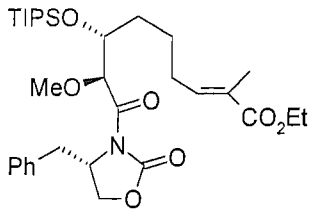
2.103

To a solution of acylated oxazolidinone **2.90** (0.37 g, 1.5 mmol) in CH_2Cl_2 (5 mL) at 0 °C under argon was added dibutylboron triflate (1.0 M in CH_2Cl_2, 1.7 mL, 1.7 mmol) followed by Et_3N (0.27 mL, 1.9 mmol). The solution was cooled to -65 °C then aldehyde **2.102** (0.30 g, 1.6 mmol) was added dropwise over 5 min. The

reaction mixture was stirred at -65 °C for 20 min then at 0 °C for 1 h then quenched by the addition of pH 7 phosphate buffer (5 mL) followed by MeOH, (10 mL) then MeOH: 30% H_2O_2 (aq) (2:1, 10 mL). The mixture was stirred for 1 h then concentrated *in vacuo* and the slurry was extracted with diethyl ether (3 x 20 mL)). The combined extracts were washed with 5% $NaHCO_3$ (aq) (20 mL) and brine (20 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 50-100% EtOAc in hexane) afforded oxazolidinone **2.103** as a colourless oil (0.49 g, 76%).

$[\alpha]_D^{26}$ +22.4 (*c* 1.0, $CHCl_3$); IR ν 3475, 2931, 1776, 1704 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.21-7.04 (5 H, m, Ar-**H**), 6.57 (1 H, tq, *J* = 6.9, 1.1 Hz, C**H**=C), 4.76 (1 H, d, *J* = 2.2 Hz, C**H**OCH$_3$), 4.56 (1 H, m, C**H**N), 4.14-4.05 (2 H, m, C**H**$_2$OCON), 4.01 (2 H, q, *J* = 7.1 Hz, OC**H**$_2$CH$_3$), 3.71 (1 H, m, C**H**OH), 3.32 (3 H, s, OC**H**$_3$), 3.20 (1 H, dd, *J* = 13.4, 3.1 Hz, C**H**HPh), 2.70 (1 H, dd, *J* = 13.4, 9.3 Hz, CH**H**Ph), 2.04 (2 H, q, *J* = 6.9 Hz, C**H**$_2$CH=C), 1.66 (3 H, d, *J* = 1.1 Hz, C**H**$_3$C=CH), 1.51-1.33 (4 H, m, C**H**$_2$C**H**$_2$), 1.12 (3 H, t, *J* = 7.1 Hz, OCH$_2$C**H**$_3$) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7 (C), 168.3 (C), 153.7 (C), 141.8 (CH), 135.1 (C), 129.5 (CH), 129.2 (CH), 128.3 (C), 127.6 (CH), 81.9 (CH), 72.2 (CH), 67.2 (CH_2), 60.5 (CH_2), 58.9 (CH_3), 55.8 (CH), 37.9 (CH_2), 33.9 (CH_2), 28.6 (CH_2), 24.8 (CH_2), 14.4 (CH_3), 12.5 (CH_3) ppm; LRMS ES^+ *m/s* (%) 456 ($[M + Na]^+$, 100); Anal. Calcd for $C_{23}H_{31}NO_7$: C, 65.63; H, 6.83; N, 3.06. Found: C, 65.78; H, 7.17; N, 3.35.

(*E*)-(7*R*,8*S*)-9-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-8-methoxy-2-methyl-9-oxo-7-triisopropylsilanyloxynon-2-enoic acid ethyl ester (2.104).



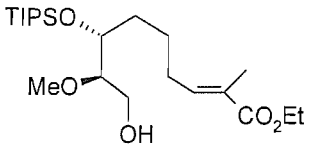
2.104

To a solution of oxazolidinone **2.103** (3 g, 6.9 mmol) in CH_2Cl_2 (50 mL) at 0 °C under argon was added 2,6-lutidine (5.2 mL, 45 mmol) followed by the dropwise addition of triisopropylsilyl triflate (12.1 mL, 45 mmol). The reaction mixture was stirred at 0 °C for 30 min then at rt for 1 h then washed with 10% HCl (aq) (50 mL), 5% $NaHCO_3$ (aq) (50 mL) and brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 10-100%

EtOAc in hexane) afforded protected oxazolidinone **2.104** as a colourless oil (3.59 g, 89%).

$[\alpha]_D^{26}$ +22.0 (*c* 1.0, $CHCl_3$); IR ν 2942, 2866, 1779, 1705 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (5 H, m, Ar-**H**), 6.73 (1 H, tq, *J* = 7.2, 1.0 Hz, C**H**=C), 5.03 (1 H, d, *J* = 3.8 Hz, C**H**OCH_3), 4.63 (1 H, m, C**H**N), 4.27 (1 H, m, **H**COSi), 4.21-4.11 (2 H, m, CH_2OCON), 4.17 (2 H, q, *J* = 7.0 Hz, OCH_2CH_3), 3.47 (3 H, s, OCH_3), 3.38 (1 H, dd, *J* = 13.6, 3.0 Hz, CHHPh), 2.86 (1 H, dd, *J* = 13.6, 9.4 Hz, CHHPh), 2.20 (2 H, q, *J* = 7.2 Hz, CH_2CH=C), 1.82 (3 H, d, *J* = 1.0 Hz, CH_3C=CH), 1.58-1.52 (4 H, m, CH_2CH_2), 1.28 (3 H, t, *J* = 7.0 Hz, OCH_2CH_3), 1.04 - 0.99 (21 H, m, TIPS-**H**) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (C), 168.3 (C), 153.4 (C), 141.8 (CH), 135.3 (C), 129.6 (CH), 129.2 (CH), 128.4 (C), 127.6 (CH), 81.7 (CH), 73.1 (CH), 66.9 (CH_2), 60.5 (CH_2), 59.0 (CH_3), 56.2 (CH), 37.9 (CH_2), 33.7 (CH_2), 28.8 (CH_2), 24.4 (CH_2), 18.3 (CH_3), 14.4 (CH_3), 13.1 (CH), 12.5 (CH_3) ppm; LRMS ES^+ *m/s* (%) 629 ($[M + K]^+$, 100); Anal. Calcd for $C_{32}H_{51}NO_7Si$: C, 65.16; H, 8.71; N, 2.37. Found: C, 65.32; H, 8.81; N, 2.33.

(*E*)-(7*R*,8*R*)-9-Hydroxy-8-methoxy-2-methyl-7-triisopropylsilanyloxynon-2-enoic acid ethyl ester (2.105).



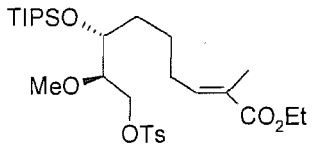
2.105

A solution of $NaBH_4$ (0.64 g, 17 mmol) in water (4.75 mL) was added dropwise to a solution of protected oxazolidinone **2.104** (2 g, 3.4 mmol) in THF (40 mL). The reaction mixture was stirred at rt for 6 h then water (20 mL) was added. The mixture was extracted with EtOAc (3 x 50 mL). The combined extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. The crude was triturated with diethyl ether/ hexane and filtered to give recovered oxazolidinone **2.89** as a white solid (042 g, 71%). Purification of the filtrate by column chromatography (SiO_2, 40% EtOAc in hexane) afforded alcohol **2.105** as a colourless oil (1.15 g, 81%).

$[\alpha]_D^{27}$ +13.9 (*c* 1.0, $CHCl_3$); IR ν 3460, 2942, 2866, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.74 (1 H, tq, *J* = 7.4, 1.4 Hz, C**H**=C), 4.18 (2 H, q, *J* = 7.1 Hz, OCH_2CH_3), 4.03 (1 H, dt, *J* = 6.5, 4.6 Hz, **H**COSi), 3.82 (1 H, dd, *J* = 11.5, 4.6 Hz,

CHHOH), 3.63 (1 H, dd, J = 11.5, 6.5 Hz, CHHOH), 3.44 (3 H, s, OCH_3), 3.36 (1 H, td, J = 6.5, 4.6 Hz, $CHOCH_3$), 2.17 (2 H, q, J = 7.4 Hz, CH_2CH=C), 1.91 (1 H, br s, OH), 1.82 (3 H, d, J = 1.4 Hz, CH_3C=CH), 1.71-1.38 (4 H, m, CH_2CH_2), 1.29 (3 H, t, J = 7.1 Hz, OCH_2CH_3), 1.07 - 0.98 (21 H, m, TIPS-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.4 (C), 141.9 (CH), 128.2 (C), 84.1 (CH), 71.9 (CH), 61.2 (CH_2), 60.6 (CH_2), 58.5 (CH_3), 32.7 (CH_2), 29.1 (CH_2), 25.0 (CH_2), 18.3 (CH_3), 14.4 (CH_3), 12.8 (CH), 12.5 (CH_3) ppm; LRMS ES$^+$ *m/s* (%) 439 ([M + Na]$^+$, 100); Anal. Calcd for $C_{22}H_{44}O_5Si$: C, 63.42; H, 10.64. Found: C, 63.26; H, 10.82.

(*E*)-(7*R*,8*R*)-8-Methoxy-2-methyl-9-(toluene-4-sulfonyloxy)-7-triisopropylsilanyloxynon-2-enoic acid ethyl ester (2.106).



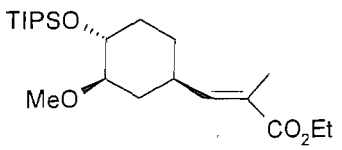
2.106

To a stirred solution of alcohol **2.105** (0.2 g, 0.5 mmol) in CH_2Cl_2 (5 mL) under argon was added pyridine (0.16 mL, 1.9 mmol), DMAP (6 mg, 0.05 mmol) and a solution of TsCl (0.37 g, 1.9 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at rt for 40 h then diethyl ether (8 mL) and water (4 mL) were added. The organic phase was washed with 2 N HCl (aq) (8mL), sat. $NaHCO_3$ (aq) (8 mL) and water (8 mL). The extracts were dried over $MgSO_4$ and concentrated *in vacuo* to a white solid. The crude was stirred with NH_3 (aq) (8 mL) extracted with diethyl ether (2 x 10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 20% EtOAc in hexane) afforded tosylate **2.106** as a colourless oil (0.19 g, 70%).

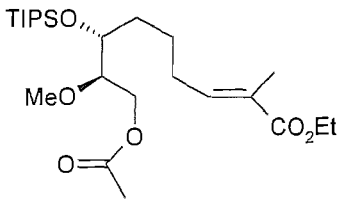
$[\alpha]_D^{27}$ +17.2 (*c* 1.0, $CHCl_3$); IR ν 2944, 2867, 1706 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (2 H, d, J = 8.4 Hz, Ar-H), 7.35 (2 H, d, J = 8.4 Hz, Ar-H), 6.70 (1 H, tq, J = 7.3, 1.3 Hz, CH=C), 4.26 (1 H, dd, J = 10.2, 2.2 Hz, CHHOS), 4.19 (2 H, q, J = 7.2 Hz, OCH_2CH_3), 4.05 (1 H, dd, J = 10.2, 7.7 Hz, CHHOS), 3.90 (1 H, dt, J = 7.3, 4.6 Hz, CHOSi), 3.45 (1 H, m, $HCOCH_3$), 3.37 (3 H, s, OCH_3), 2.44 (3 H, s, $ArCH_3$), 2.12 (2 H, q, J = 7.3 Hz, CH_2CH=C), 1.80 (3 H, d, J = 1.3 Hz, CH_3C=CH), 1.62-1.38 (4 H, m, CH_2CH_2), 1.29 (3 H, t, J = 7.2 Hz, OCH_2CH_3), 0.99 - 0.93 (21 H, m, TIPS-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3 (C) 144.9 (C), 141.7 (CH), 133.0 (C), 130.0 (CH), 128.3 (C), 128.1 (CH), 82.1 (CH), 71.4 (CH), 70.5 (CH_2),

60.6 (CH_2), 59.0 (CH_3), 32.4 (CH_2), 29.0 (CH_2), 25.2 (CH_2), 21.8 (CH_3), 18.2 (CH_3), 14.4 (CH_3), 12.7 (CH), 12.5 (CH_3) ppm; LRMS ES^+ *m/s* (%) 609 ($[M + K]^+$, 100); Anal. Calcd for $C_{29}H_{50}O_7SSi$: C, 61.02; H, 8.83; S, 5.62. Found: C, 60.63; H, 9.06; S, 5.89.

(*E*)-3-((1*R*,3*R*,4*R*)-3-Methoxy-4-triisopropylsilanyloxycyclohexyl)-2-methylacrylic acid ethyl ester (2.107) and (*E*)-(7*R*,8*R*)-9-Acetoxy-8-methoxy-2-methyl-7-triisopropylsilanyloxynon-2-enoic acid ethyl ester (2.112).



2.107



2.112

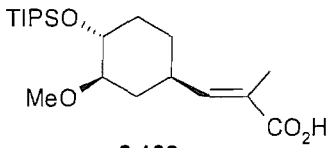
NaH (60% in mineral oil, 5 mg, 0.13 mmol) under argon was washed with hexane (2 x 2 mL). Anhydrous DMSO (2 mL) was added and the reaction mixture was stirred for 30 min then transferred to a microwave tube containing 4 Å molecular sieves. Tosylate **2.106** (50 mg, 0.09 mmol) in anhydrous DMSO (2 mL) was added and the reaction mixture was heated in the microwave at 150 °C for 1 h. Water (3 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 x 5 mL). The combined extracts were washed with brine (5 mL) dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (SiO_2, 10% EtOAc in hexane) afforded ester **2.107** as a pale yellow oil (17 mg, 49%) and acetate **2.112** as a colourless oil (7 mg, 17%).

Cyclised 2.107: $[\alpha]_D^{27}$ -11.6 (*c* 1.0, $CHCl_3$); IR ν 2941, 2867, 1707 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.56 (1 H, d, *J* = 9.5 Hz, C**H**=C), 4.19 (2 H, q, *J* = 7.1 Hz, O**CH**$_2$CH$_3$), 3.98 (1 H, m, **CH**OSi), 3.38 (3 H, s, O**CH**$_3$), 3.35 (1 H, m, **H**COCH$_3$), 2.69 (1 H, m, **CH**CH=C), 1.85 (3 H, s, **CH**$_3$C=CH), 1.80-1.36 (6 H, m, 3 x **CH**$_2$), 1.30 (3 H, t, *J* = 7.1 Hz, OCH$_2$**CH**$_3$), 1.07-1.06 (21 H, m, TIPS-**H**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7 (C), 147.0 (CH), 126.6 (C), 79.2 (CH), 67.1 (CH), 60.6 (CH_2), 56.7 (CH_3), 31.4 (CH), 29.5 (CH_2), 28.1 (CH_2), 25.1 (CH_2), 18.2 (CH_3), 14.5 (CH_3), 12.6 (CH), 12.4 (CH_3) ppm; CIMS *m/s* (%) 399 ($[M + H]^+$, 38); Anal. Calcd for $C_{22}H_{42}O_4Si$: C, 66.28; H, 10.62. Found: C, 66.05; H, 11.02.

Acetate 2.112: $[\alpha]_D^{27}$ +16.5 (*c* 0.5, $CHCl_3$); IR ν 2943, 2866, 1743, 1710 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (1 H, tq, *J* = 7.5, 1.5 Hz, C**H**=C), 4.36 (1 H, dd, *J* =

11.6, 2.5 Hz, CHHCOCH$_3$), 4.18 (2 H, q, J = 7.0 Hz, OCH$_2$CH$_3$), 4.09 (1 H, dd, J = 11.6, 7.3 Hz, CHHCOCH$_3$), 3.98 (1 H, dt, J = 6.5, 4.5 Hz, HCOSi), 3.44 (1 H, m, CHOCH$_3$), 3.43 (3 H, s, OCH$_3$), 2.17 (2 H, q, J = 7.5 Hz, CH$_2$CH=C), 2.07 (3 H, s, C(=O)CH$_3$), 1.82 (3 H, d, J = 1.5 Hz, CH$_3$C=CH), 1.72-1.35 (4 H, m, CH$_2$CH$_2$), 1.29 (3 H, t, J = 7.0 Hz, OCH$_2$CH$_3$), 1.09-1.05 (21 H, m, TIPS-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.1 (C), 168.3 (C), 141.8 (CH), 128.3 (C), 82.3 (CH), 71.7 (CH), 64.2 (CH_2), 60.5 (CH_2), 58.7 (CH_3), 32.7 (CH_2), 29.1 (CH_2), 25.1 (CH_2), 21.1 (CH_3), 18.3 (CH_3), 14.4 (CH_3), 12.9 (CH_3), 12.5 (CH) ppm; LRMS ES$^+$ *m/s* (%) 481 ([M + Na]$^+$, 100), 459 ([M + H]$^+$, 15).

(*E*)-3-((1*R*,3*R*,4*R*)-3-Methoxy-4-triisopropylsilanyloxycyclohexyl)-2-methyl acrylic acid (2.108).

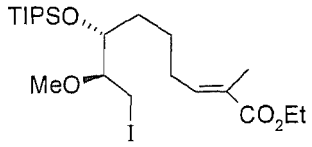


2.108

NaH (60% in mineral oil, 14 mg, 0.35 mmol) under argon was washed with hexane (2 x 2 mL). Anhydrous DMF (2 mL) was added and the reaction mixture was stirred for 30 min. After cooling to 0 °C tosylate **2.106** (50 mg, 0.09 mmol) in anhydrous DMF (1 mL) was added dropwise. After stirring for 15 h water (3 mL) was added and the solution was extracted with diethyl ether (4 x 5 mL). The combined extracts were washed with brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil. Purification by column chromatography (SiO_2, 10% EtOAc in hexane) afforded carboxylic acid **2.108** as a colourless oil (15 mg, 46%).

$[\alpha]_D^{26}$ -3.8 (*c* 0.45, $CHCl_3$); IR ν 2940, 2866, 1686 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.72 (1 H, dq, J = 9.5, 1.3 Hz, CH=C), 3.99 (1 H, app d, J = 2.2 Hz, CHOSi), 3.36 (3 H, s, OCH$_3$), 3.35 (1 H, m, HCOCH$_3$), 2.64 (1 H, m, CHCH=C), 1.86 (3 H, d, J = 1.3 Hz, CH$_3$C=CH), 1.82-1.26 (6 H, m, 3 x CH$_2$), 1.07-1.06 (21 H, m, TIPS-H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.6 (C), 149.8 (CH), 125.8 (C), 79.1 (CH), 67.0 (CH), 56.7 (CH_3), 31.6 (CH), 29.3 (CH_2), 28.0 (CH_2), 25.0 (CH_2), 18.3 (CH_3), 12.5 (CH), 12.3 (CH_3) ppm; LRMS ES$^-$ *m/s* (%) 369 ([M - H]$^-$, 100).

(*E*)-(7*R*,8*S*)-9-Iodo-8-methoxy-2-methyl-7-triisopropylsilanyloxynon-2-enoic acid ethyl ester (2.109).



2.109

From alcohol 2.105

To a stirred solution of alcohol **2.105** (0.50 g, 1.2 mmol) in benzene (15 mL) under argon was added imidazole (0.16 g, 2.4 mmol), PPh_3 (0.63 g, 2.4 mmol) and iodine (0.61 g, 2.4 mmol). The reaction mixture was stirred for at rt under argon for 24 h then quenched with sat. $NaHCO_3$ (aq): $Na_2S_2O_3$ (1:1, 20 mL). The aqueous phase was extracted with diethyl ether (3 x 10 mL) and the combined extracts were dried over Na_2SO_4 and concentrated *in vacuo* to a white solid. Purification by column chromatography (SiO_2, 10% EtOAc in hexane) afforded iodide **2.109** as a colourless oil (0.55 g, 86%).

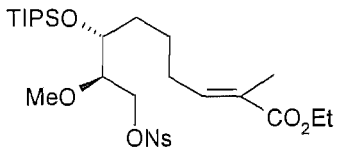
From tosylate 2.106

To a solution of NaI (53 mg, 0.35 mmol) in anhydrous acetone (0.5 mL) under argon was added tosylate **2.106** (50 mg, 0.09 mmol) in anhydrous acetone (0.5 mL). After 24 h NaI (53 mg, 0.35 mmol) in acetone (0.5 mL) was added and the reaction mixture was stirred for 2 weeks. After this time water (5 mL) was added and the reaction mixture was extracted with hexane (3 x 5 mL). The combined extracts were washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil (49 mg). Purification by column chromatography (SiO_2, 10% EtOAc in hexane) afforded iodide **2.109** as a colourless oil (32 mg, 69%).

$[\alpha]_D^{27}$ +5.0 (*c* 0.5, $CHCl_3$); IR ν 2943, 2866, 1709 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.73 (1 H, t, *J* = 7.3 Hz, C**H**=C), 4.19 (2 H, q, *J* = 7.0 Hz, OC**H**$_2$CH$_3$), 3.97 (1 H, dt, *J* = 6.5, 4.5 Hz, **H**COSi), 3.47 (1 H, m, C**H**HI), 3.46 (3 H, s, OC**H**$_3$), 3.13 (1 H, dd, *J* = 10.0, 8.0 Hz, CH**H**I), 3.37 (1 H, m, C**H**OCH$_3$), 2.17 (2 H, q, *J* = 7.3 Hz, C**H**$_2$CH=C), 1.82 (3 H, s, C**H**$_3$C=CH), 1.67-1.31 (4 H, m, C**H**$_2$C**H**$_2$), 1.27 (3 H, t, *J* = 7.0 Hz, OCH$_2$C**H**$_3$), 1.08-1.05 (21 H, m, TIPS-**H**) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.3 (C), 141.7 (CH), 128.4 (C), 85.2 (CH), 72.7 (CH), 60.6 (CH_2), 58.9 (CH_3),

31.9 (CH_2), 29.0 (CH_2), 25.0 (CH_2), 18.3 (CH_3), 14.4 (CH_3), 12.9 (CH), 12.5 (CH_3), 5.3 (CH_2) ppm; LRMS ES^+ *m/s* (%) 549 ($[M + Na]^+$, 100).

(*E*)-(7*R*,8*R*)-8-Methoxy-2-methyl-9-(4-nitrobenzenesulfonyloxy)-7-triisopropyl silanyloxynon-2-enoic acid ethyl ester (2.110).

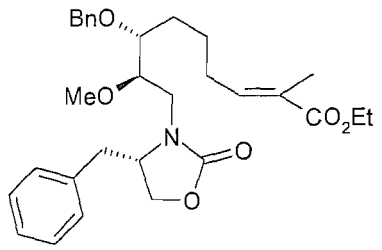


2.110

To a solution of alcohol **2.105** (0.7 g, 1.7 mmol) in CH_2Cl_2 (20 mL) under argon was added pyridine (0.54 mL, 6.7 mmol), DMAP (21 mg, 0.17 mmol) and a solution of *p*-nitrobenzenesulfonyl chloride (1.49 g, 6.7 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was stirred at rt for 3 days then diethyl ether (10 mL) and water (5 mL) were added. The organic phase was washed with 2 N HCl (aq) (10 mL), sat. $NaHCO_3$ (aq) (10 mL) and water (10 mL). The extracts were concentrated *in vacuo* and stirred with NH_3 (aq) (15 mL) overnight. The reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL), the combined extracts were dried over $MgSO_4$ and concentrated *in vacuo* to a yellow oil. Purification by column chromatography (SiO_2, 20% EtOAc in hexane) afforded **2.110** as a pale yellow oil (0.82 g, 85%).

$[\alpha]_D^{27}$ +21.3 (*c* 0.5, $CHCl_3$); IR ν 2941, 2864, 1704, 1532 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.40 (2 H, d, *J* = 9.0 Hz, Ar-**H**), 8.12 (2 H, d, *J* = 9.0 Hz, Ar-**H**), 6.69 (1 H, tq, *J* = 7.2, 1.5 Hz, C**H**=C), 4.41 (1 H, dd, *J* = 10.3, 2.0 Hz, C**H**HOS), 4.19 (2 H, q, *J* = 7.0 Hz, OC**H**$_2$CH$_3$), 4.17 (1 H, dd, *J* = 10.3, 7.5 Hz, CH**H**OS), 3.95 (1 H, dt, *J* = 7.0, 4.5 Hz, C**H**OSi), 3.48 (1 H, ddd, *J* = 7.5, 4.5, 2.0 Hz, **H**COCH$_3$), 3.34 (3 H, s, OC**H**$_3$), 2.14 (2 H, q, *J* = 7.2 Hz, C**H**$_2$CH=C), 1.81 (3 H, s, C**H**$_3$C=CH), 1.63-1.42 (4 H, m, C**H**$_2$C**H**$_2$), 1.30 (3 H, t, *J* = 7.0 Hz, OCH$_2$C**H**$_3$), 1.02-0.92 (21 H, m, TIPS-**H**) ppm; ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3 (C), 150.8 (C), 142.1 (C), 141.4 (CH), 129.4 (CH), 128.5 (C), 124.5 (CH), 82.3 (CH), 71.8 (CH_2), 71.1 (CH), 60.6 (CH_2), 58.9 (CH_3), 32.4 (CH_2), 28.9 (CH_2), 25.2 (CH_2), 18.2 (CH_3), 14.4 (CH_3), 12.8 (CH_3), 12.5 (CH) ppm; LRMS ES^+ *m/s* (%) 624 ($[M + Na]^+$, 100).

(*E*)-(7*R*,8*R*)-9-((*S*)-4-Benzyl-2-oxooxazolidin-3-yl)-7-benzyloxy-8-methoxy-2-methylnon-2-enoic acid ethyl ester (2.111).



2.111

To a solution of alcohol **2.103** (0.10 g, 0.23 mmol) in CH_2Cl_2 (2 mL) and hexane (1 mL) under argon was added benzyl-2, 2, 2-trichloroacetimidate (64 μL, 0.35 mmol). The solution was cooled to 0 °C then triflic acid (4 μL, 0.05 mmol) was added and the reaction mixture was stirred for 30 min then filtered through celite. The filtrate was washed with sat. $NaHCO_3$ (aq) (10 mL), then brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo* to a white solid (194 mg). Column chromatography (SiO_2, 1:1 EtOAc: hexane) afforded benzyl ether **2.111** as a colourless oil (40 mg, 33%).

$[\alpha]_D^{27}$ +24.0 (*c* 0.5, $CHCl_3$); IR ν 2938, 1775, 1704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.14 (10 H, m, Ar-**H**), 6.71 (1 H, tq, *J* = 7.3, 1.5 Hz, C**H**=C) 5.09 (1 H, app d, *J* = 3.7 Hz, C**H**OCH$_3$), 4.58 (1 H, d, *J* = 11.7 Hz, OC**H**HPh), 4.41 (1 H, d, *J* = 11.7 Hz, OCH**H**Ph), 4.35 (1 H, m, C**H**N), 4.15 (2 H, q, *J* = 7.2 Hz, OC**H**$_2$CH$_3$), 4.02 (1 H, dd, *J* = 9.1, 1.8 Hz, C**H**HO), 3.82 (1 H, t, *J* = 9.1 Hz, CH**H**O), 3.75 (1 H, m, C**H**OCH$_2$Ph)), 3.44 (3 H, s, CHOC**H**$_3$), 3.26 (1 H, dd, *J* = 13.5, 3.3 Hz, C**H**HPh), 2.78 (1 H, dd, *J* = 13.5, 9.5 Hz, CH**H**Ph), 2.16 (2 H, q, *J* = 7.3 Hz, C**H**$_2$CH=C), 1.86 (3 H, d, *J* = 1.5 Hz, C**H**$_3$C=CH), 1.82-1.41 (4 H, m, C**H**$_2$C**H**$_2$), 1.26 (3 H, t, *J* = 7.2 Hz, OCH$_2$C**H**$_3$) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C), 168.3 (C), 153.4 (C), 141.8 (CH), 138.4 (C), 135.2 (C), 129.5, (CH), 129.1 (C), 128.8 (CH), 128.4 (CH), 128.2 (CH), 127.9 (CH), 127.5 (CH), 80.7 (CH), 77.8 (CH), 72.0 (CH_2), 66.8 (CH_2), 60.5 (CH_2), 59.0 (CH_3), 55.9 (CH), 37.8 (CH_2), 29.7 (CH_2), 28.7 (CH_2), 24.8 (CH_2), 14.4 (CH_3), 12.5 (CH_3) ppm; LRMS ES^+ *m/s* (%) 546 ([M + Na]$^+$, 100).

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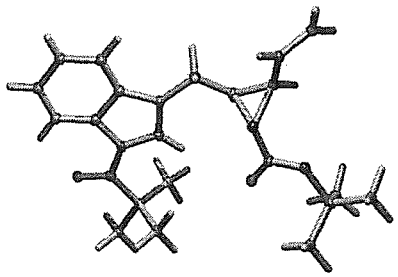
Appendix

Crystal structure data for compound 1.153

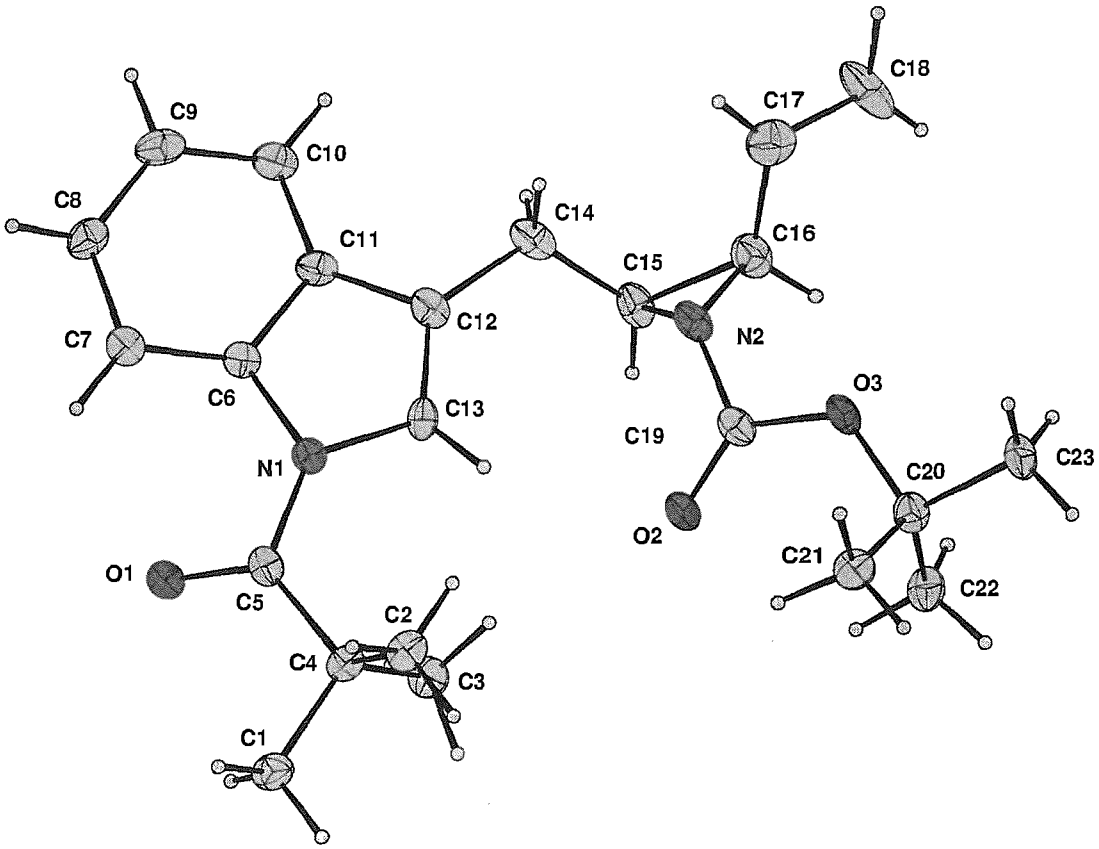
Table 1. Crystal data and structure refinement details.



Identification code	**2005sot1394 (LW4358/96)**
Empirical formula	$C_{23}H_{30}N_2O_3$
Formula weight	382.49
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 5.7705(2) Å
	b = 14.7570(11) Å
	c = 25.395(2) Å
Volume	2162.6(2) Å^3
Z	4
Density (calculated)	1.175 Mg / m^3
Absorption coefficient	0.078 mm^{-1}
F(000)	824
Crystal	Lath; Colourless
Crystal size	0.3 × 0.03 × 0.01 mm^3
θ range for data collection	3.19 – 25.03°
Index ranges	$-6 \le h \le 6$, $-17 \le k \le 17$, $-30 \le l \le 30$
Reflections collected	17826
Independent reflections	2214 [R_{int} = 0.1049]
Completeness to θ = 25.03°	99.3 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9984 and 0.9708
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2214 / 0 / 260
Goodness-of-fit on F^2	1.146
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0645, $wR2$ = 0.1339
R indices (all data)	$R1$ = 0.0992, $wR2$ = 0.1481
Absolute structure parameter	Not reliably determined
Extinction coefficient	0.010(2)
Largest diff. peak and hole	0.445 and –0.192 e Å^{-3}

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

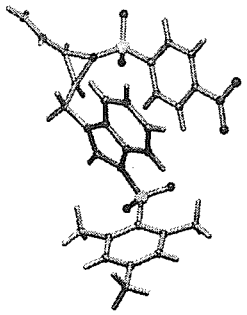
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	3503(8)	3282(3)	846(2)	39(1)	1
C2	4139(9)	1673(3)	595(2)	40(1)	1
C3	7306(8)	2588(4)	1031(2)	42(1)	1
C4	4698(8)	2393(3)	1011(2)	33(1)	1
C5	3729(8)	2122(3)	1547(2)	32(1)	1
C6	3536(8)	965(3)	2261(2)	30(1)	1
C7	1640(8)	1238(3)	2567(2)	36(1)	1
C8	1149(9)	725(3)	3008(2)	41(1)	1
C9	2472(10)	−35(4)	3141(2)	47(1)	1
C10	4339(10)	−299(3)	2840(2)	44(1)	1
C11	4871(8)	198(3)	2393(2)	35(1)	1
C12	6623(8)	76(3)	1997(2)	36(1)	1
C13	6298(7)	731(3)	1640(2)	34(1)	1
C14	8485(10)	−640(3)	1997(2)	46(1)	1
C15	10176(8)	−555(3)	1555(2)	42(1)	1
C16	11779(10)	−1314(4)	1374(2)	49(2)	1
C17	11871(11)	−2150(4)	1631(2)	56(2)	1
C18	13879(11)	−2621(4)	1689(3)	70(2)	1
C19	9958(8)	−656(3)	581(2)	35(1)	1
C20	11590(8)	−976(3)	−290(2)	39(1)	1
C21	9361(8)	−827(3)	−593(2)	41(1)	1
C22	13158(8)	−162(3)	−291(2)	41(1)	1
C23	12869(9)	−1814(3)	−482(2)	47(1)	1
N1	4450(6)	1304(2)	1784(2)	30(1)	1
N2	9634(7)	−1065(3)	1074(2)	38(1)	1
O1	2349(6)	2586(2)	1780(1)	42(1)	1
O2	9236(6)	89(2)	483(1)	42(1)	1
O3	11033(5)	−1230(2)	264(1)	37(1)	1



Thermal ellipsoids drawn at the 30% probability level

Crystal structure data for compound 1.173

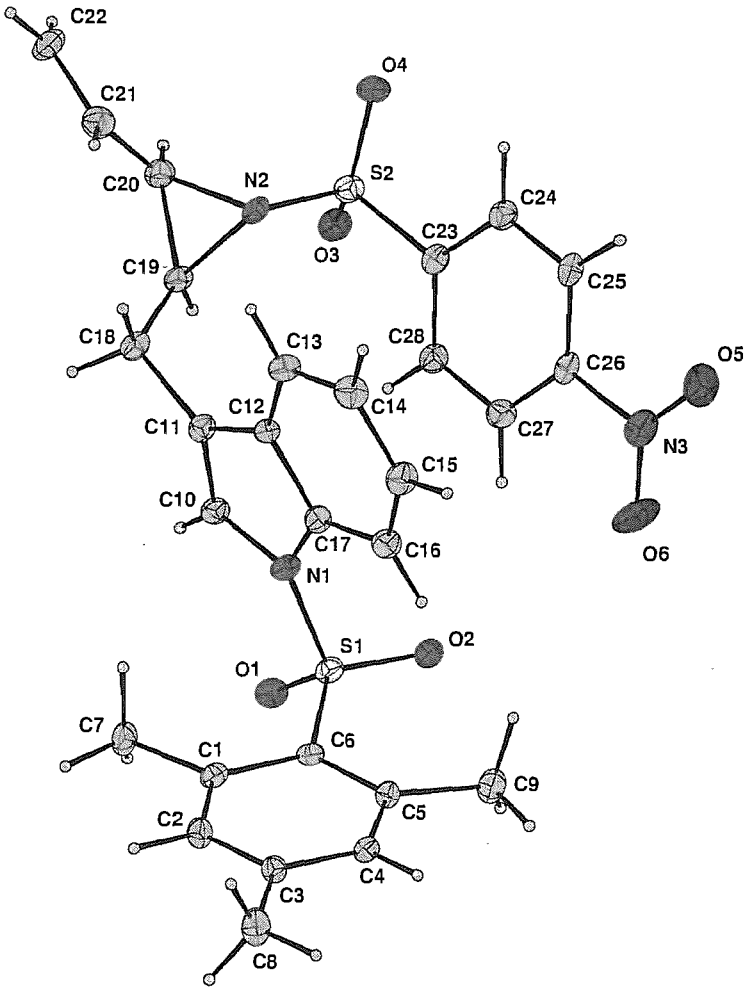
Table 1. Crystal data and structure refinement details.



Identification code	**2006sot0345 (LW4481/94)**
Empirical formula	$C_{28}H_{27}N_3O_6S_2$
Formula weight	565.65
Temperature	120(2) K
Wavelength	0.71073 Å
Crystal system	Monoclinic
Space group	$P2_1$
Unit cell dimensions	a = 7.8308(5) Å
	b = 9.4520(4) Å β = 99.707(2)°
	c = 18.3031(11) Å
Volume	1335.34(13) Å^3
Z	2
Density (calculated)	1.407 Mg / m^3
Absorption coefficient	0.248 mm^{-1}
F(000)	592
Crystal	Plate; Colourless
Crystal size	0.3 × 0.1 × 0.02 mm^3
θ range for data collection	3.04 – 27.48°
Index ranges	$-10 \le h \le 10$, $-12 \le k \le 9$, $-23 \le l \le 23$
Reflections collected	13129
Independent reflections	5717 [R_{int} = 0.0611]
Completeness to θ = 27.48°	99.7 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9951 and 0.9193
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5717 / 1 / 356
Goodness-of-fit on F^2	1.018
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0547, $wR2$ = 0.1048
R indices (all data)	$R1$ = 0.0839, $wR2$ = 0.1155
Absolute structure parameter	0.05(7)
Extinction coefficient	0.0057(13)
Largest diff. peak and hole	0.322 and –0.346 e Å^{-3}

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

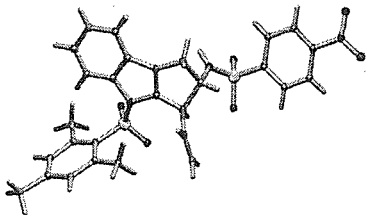
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
C1	2474(4)	6044(3)	8879(2)	24(1)	1
C2	1568(4)	6562(3)	9406(2)	26(1)	1
C3	2341(4)	7279(4)	10034(2)	25(1)	1
C4	4120(4)	7429(4)	10144(2)	26(1)	1
C5	5150(4)	6918(3)	9653(2)	25(1)	1
C6	4303(4)	6263(3)	9003(2)	24(1)	1
C7	1473(5)	5299(4)	8211(2)	33(1)	1
C8	1293(5)	7901(4)	10570(2)	39(1)	1
C9	7078(5)	7086(4)	9889(2)	39(1)	1
C10	3870(5)	6401(4)	6876(2)	25(1)	1
C11	3467(4)	7548(4)	6434(2)	25(1)	1
C12	3964(4)	8778(3)	6879(2)	23(1)	1
C13	3847(5)	10228(4)	6728(2)	30(1)	1
C14	4428(5)	11169(4)	7287(2)	36(1)	1
C15	5139(5)	10699(4)	7996(2)	35(1)	1
C16	5287(5)	9267(4)	8167(2)	32(1)	1
C17	4671(4)	8318(4)	7603(2)	25(1)	1
C18	2722(4)	7573(4)	5625(2)	28(1)	1
C19	4083(4)	7294(4)	5143(2)	26(1)	1
C20	4034(5)	7889(3)	4383(2)	33(1)	1
C21	2668(5)	8830(4)	4019(2)	36(1)	1
C22	2185(5)	8847(4)	3280(2)	42(1)	1
C23	8216(4)	8763(3)	5945(2)	26(1)	1
C24	9024(4)	10071(4)	6039(2)	29(1)	1
C25	9693(5)	10547(4)	6744(2)	31(1)	1
C26	9519(4)	9680(4)	7336(2)	27(1)	1
C27	8747(4)	8375(4)	7255(2)	33(1)	1
C28	8081(5)	7902(4)	6548(2)	30(1)	1
N1	4612(4)	6841(3)	7591(2)	26(1)	1
N2	5240(4)	8505(3)	5043(2)	28(1)	1
N3	10198(4)	10201(4)	8095(2)	41(1)	1
O1	5007(3)	4373(2)	8027(1)	30(1)	1
O2	7227(3)	6141(2)	8488(1)	31(1)	1
O3	7681(3)	6705(2)	4984(1)	33(1)	1
O4	7845(3)	9140(3)	4511(1)	36(1)	1
O5	10877(4)	11382(3)	8146(2)	54(1)	1
O6	10011(4)	9451(3)	8616(2)	59(1)	1
S1	5441(1)	5774(1)	8288(1)	25(1)	1
S2	7322(1)	8190(1)	5043(1)	29(1)	1



Thermal ellipsoids drawn at the 35% probability level.

Crystal structure data for compound 1.188

Table 1. Crystal data and structure refinement details.

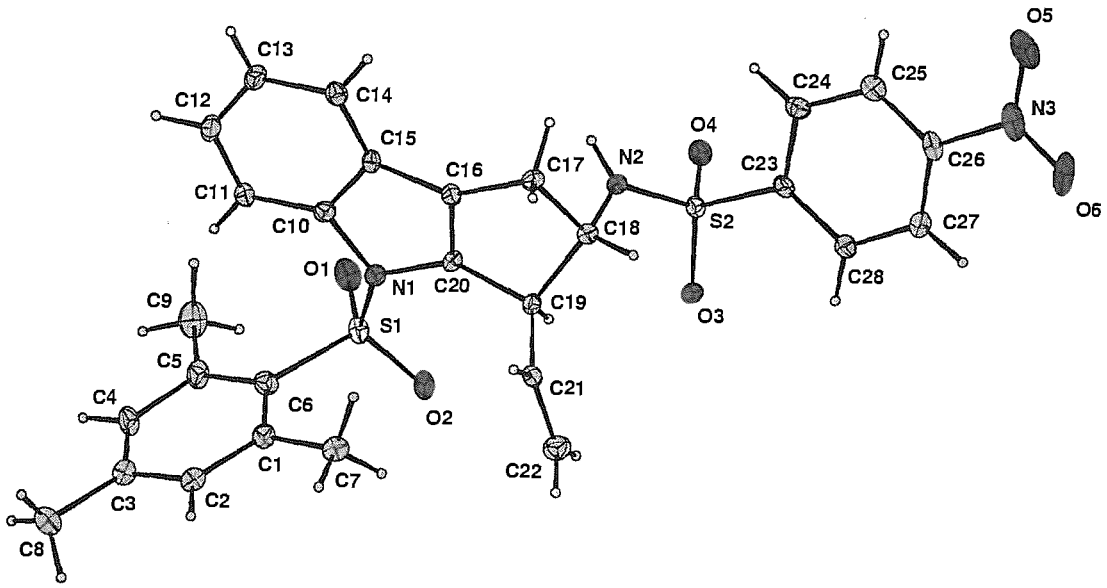


Identification code	**2006sot0346 (LW4481/97)**
Empirical formula	$C_{28}H_{27}N_3O_6S_2$
Formula weight	565.65
Temperature	120(2) K
Wavelength	0.71069 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	a = 10.1170(2) Å
	b = 13.9880(3) Å
	c = 37.7880(10) Å
Volume	5347.6(2) Å^3
Z	8
Density (calculated)	1.405 Mg / m^3
Absorption coefficient	0.248 mm^{-1}
F(000)	2368
Crystal	Plate; Colourless
Crystal size	0.3 × 0.2 × 0.02 mm^3
θ range for data collection	2.91 – 27.48°
Index ranges	$-13 \le h \le 13$, $-18 \le k \le 17$, $-49 \le l \le 43$
Reflections collected	37321
Independent reflections	12099 [R_{int} = 0.0778]
Completeness to θ = 27.48°	98.9 %
Absorption correction	Semi–empirical from equivalents
Max. and min. transmission	0.9951 and 0.9194
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	12099 / 828 / 709
Goodness-of-fit on F^2	1.011
Final R indices [$F^2 > 2\sigma(F^2)$]	$R1$ = 0.0630, $wR2$ = 0.1335
R indices (all data)	$R1$ = 0.1006, $wR2$ = 0.1531
Absolute structure parameter	0.08(7)
Largest diff. peak and hole	0.415 and –0.431 e Å^{-3}

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

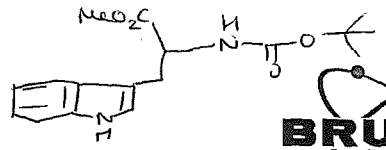
Atom	*x*	*y*	*z*	U_{eq}	*S.o.f.*
S4	6654(1)	7465(1)	10084(1)	22(1)	1
S3	7020(1)	9012(1)	8491(1)	26(1)	1
S1	6337(1)	3167(1)	8561(1)	26(1)	1
S2	6166(1)	2401(1)	10102(1)	22(1)	1
O10	5338(2)	7808(2)	10013(1)	28(1)	1
O4	6665(3)	1444(2)	10113(1)	28(1)	1
O9	6957(3)	6483(2)	10029(1)	29(1)	1
O7	7016(3)	9841(2)	8275(1)	37(1)	1
O1	6957(3)	2258(2)	8515(1)	35(1)	1
N5	7661(3)	8077(2)	9849(1)	23(1)	1
O3	4875(2)	2593(2)	9959(1)	28(1)	1
O2	5114(3)	3221(2)	8746(1)	34(1)	1
O8	5849(3)	8750(2)	8681(1)	30(1)	1
N1	7378(3)	3846(2)	8798(1)	23(1)	1
N2	7203(3)	3024(2)	9881(1)	23(1)	1
O11	8679(3)	7644(2)	11748(1)	41(1)	1
C29	7633(4)	8029(3)	8248(1)	26(1)	1
C20	7238(4)	4020(3)	9164(1)	20(1)	1
C48	7943(4)	9253(3)	9169(1)	22(1)	1
C15	9396(4)	4292(3)	9026(1)	21(1)	1
C17	8275(4)	4510(3)	9694(1)	23(1)	1
N6	7654(4)	7978(3)	11628(1)	34(1)	1
C19	6120(4)	4036(3)	9426(1)	21(1)	1
C51	6977(4)	7699(3)	10539(1)	21(1)	1
N4	8160(3)	9182(2)	8805(1)	24(1)	1
O6	5081(4)	3434(2)	11788(1)	51(1)	1
C21	5277(4)	4918(3)	9396(1)	23(1)	1
C44	9092(4)	9426(3)	9340(1)	22(1)	1
C14	10738(4)	4469(3)	9018(1)	24(1)	1
C43	10123(4)	9470(3)	9083(1)	24(1)	1
C18	6935(4)	4028(3)	9778(1)	23(1)	1
C47	6744(4)	9226(3)	9407(1)	23(1)	1
C24	7350(4)	2776(3)	10735(1)	27(1)	1
C16	8408(4)	4289(3)	9302(1)	21(1)	1
C23	6158(4)	2806(3)	10547(1)	21(1)	1
C54	7425(4)	7908(3)	11245(1)	27(1)	1
C11	9394(4)	3878(3)	8401(1)	27(1)	1
C27	4974(4)	3190(3)	11077(1)	26(1)	1
O5	7172(4)	3106(3)	11803(1)	56(1)	1
C25	7336(4)	2939(3)	11092(1)	31(1)	1
C46	7466(4)	9102(3)	9774(1)	23(1)	1
C49	5897(4)	10106(3)	9401(1)	30(1)	1
C4	6392(5)	3822(4)	7518(1)	39(1)	1
C10	8732(4)	3986(3)	8716(1)	23(1)	1

C28	4969(4)	3035(3)	10713(1)	23(1)	1
C34	7905(4)	7171(3)	8431(1)	26(1)	1
C38	9530(4)	9318(3)	8751(1)	26(1)	1
C32	8710(4)	6473(3)	7878(1)	30(1)	1
C2	5604(4)	5183(4)	7831(1)	39(1)	1
C56	5997(4)	8069(3)	10752(1)	27(1)	1
C26	6149(4)	3131(3)	11255(1)	28(1)	1
C12	10731(4)	4070(3)	8394(1)	30(1)	1
C5	6563(4)	3302(3)	7833(1)	33(1)	1
N3	6128(5)	3241(3)	11644(1)	39(1)	1
C13	11399(4)	4359(3)	8700(1)	29(1)	1
C52	8215(4)	7451(3)	10675(1)	26(1)	1
C1	5731(4)	4710(3)	8153(1)	31(1)	1
C55	6229(4)	8169(3)	11109(1)	31(1)	1
O12	6833(4)	8389(3)	11806(1)	68(1)	1
C53	8436(4)	7553(3)	11033(1)	29(1)	1
C6	6218(4)	3768(3)	8152(1)	29(1)	1
C30	7862(5)	8104(3)	7879(1)	33(1)	1
C31	8383(4)	7317(3)	7711(1)	33(1)	1
C39	10251(4)	9301(3)	8436(1)	34(1)	1
C37	7677(4)	7025(3)	8822(1)	30(1)	1
C40	11603(4)	9435(3)	8463(1)	37(1)	1
C36	9323(5)	5660(3)	7683(1)	39(1)	1
C7	5324(4)	5251(3)	8485(1)	35(1)	1
C22	3988(4)	4894(3)	9373(1)	33(1)	1
C50	6035(5)	10841(3)	9187(1)	38(1)	1
C3	5939(4)	4751(4)	7512(1)	42(1)	1
C42	11500(4)	9600(3)	9100(1)	31(1)	1
C45	8852(4)	9569(3)	9728(1)	26(1)	1
C33	8443(4)	6406(3)	8239(1)	27(1)	1
C41	12221(4)	9579(3)	8789(1)	37(1)	1
C9	7104(5)	2303(3)	7799(1)	48(1)	1
C35	7546(6)	8969(4)	7654(1)	53(1)	1
C8	5816(5)	5309(5)	7168(2)	61(2)	1



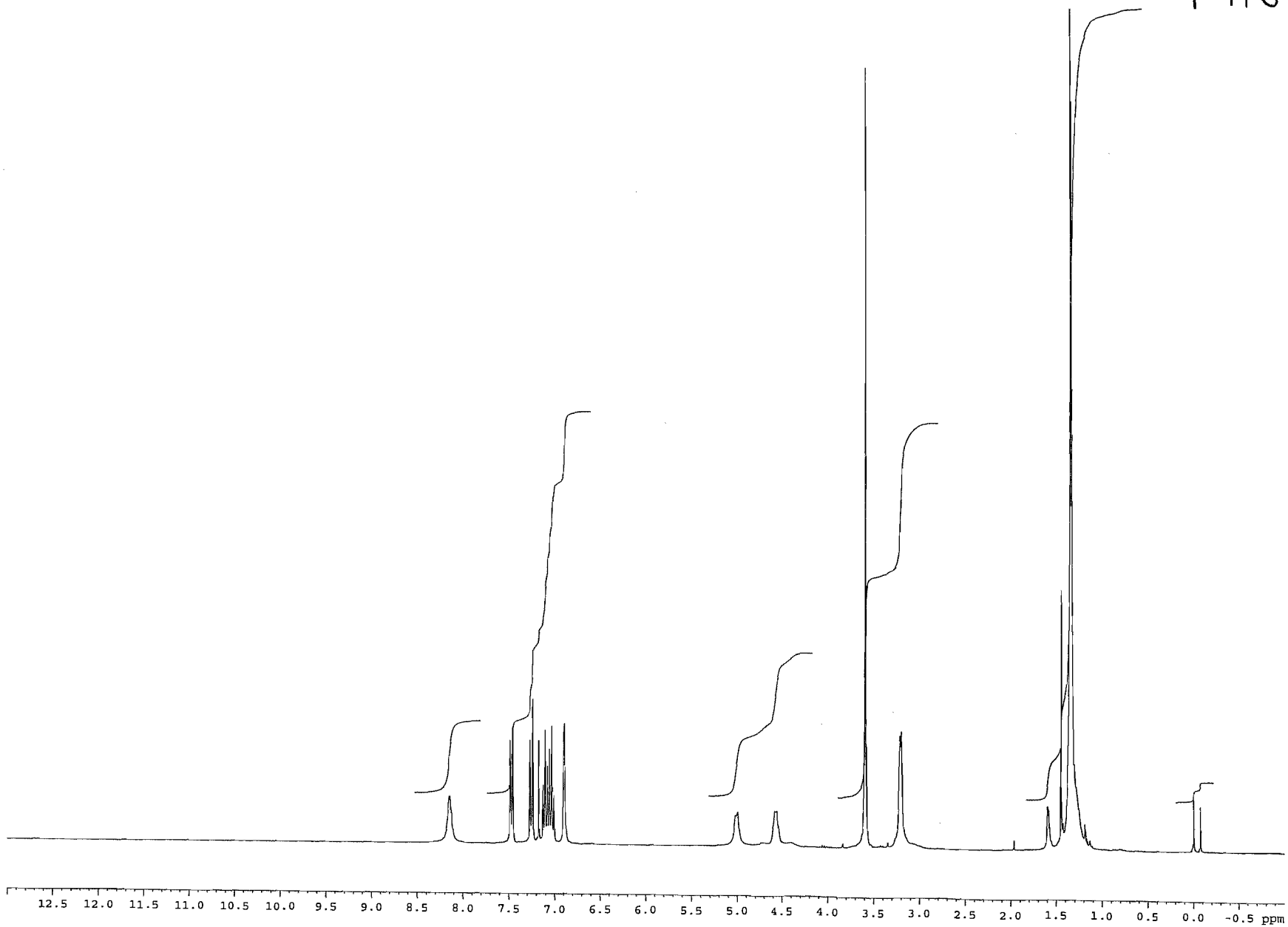
One of the 2 independent molecules in the asymmetric unit. Thermal ellipsoids drawn at the 35% probability level.

LW4358-3



BRUKER

1-110



Current Data Parameters
NAME ap29051w1
EXPNO 10
PROCNO 1

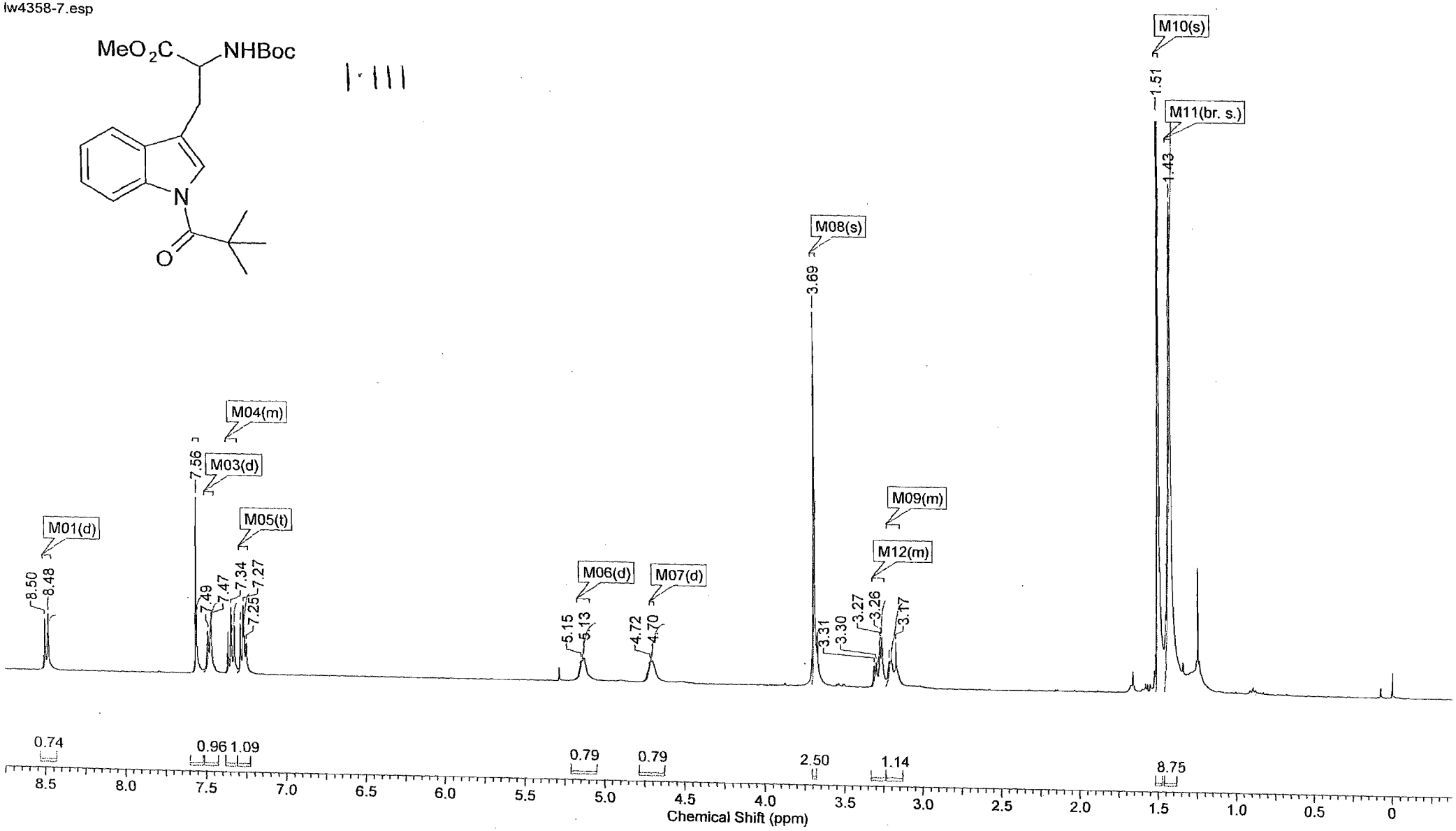
F2 - Acquisition Parameters
Date_ 20050429
Time 12.16
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 256
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

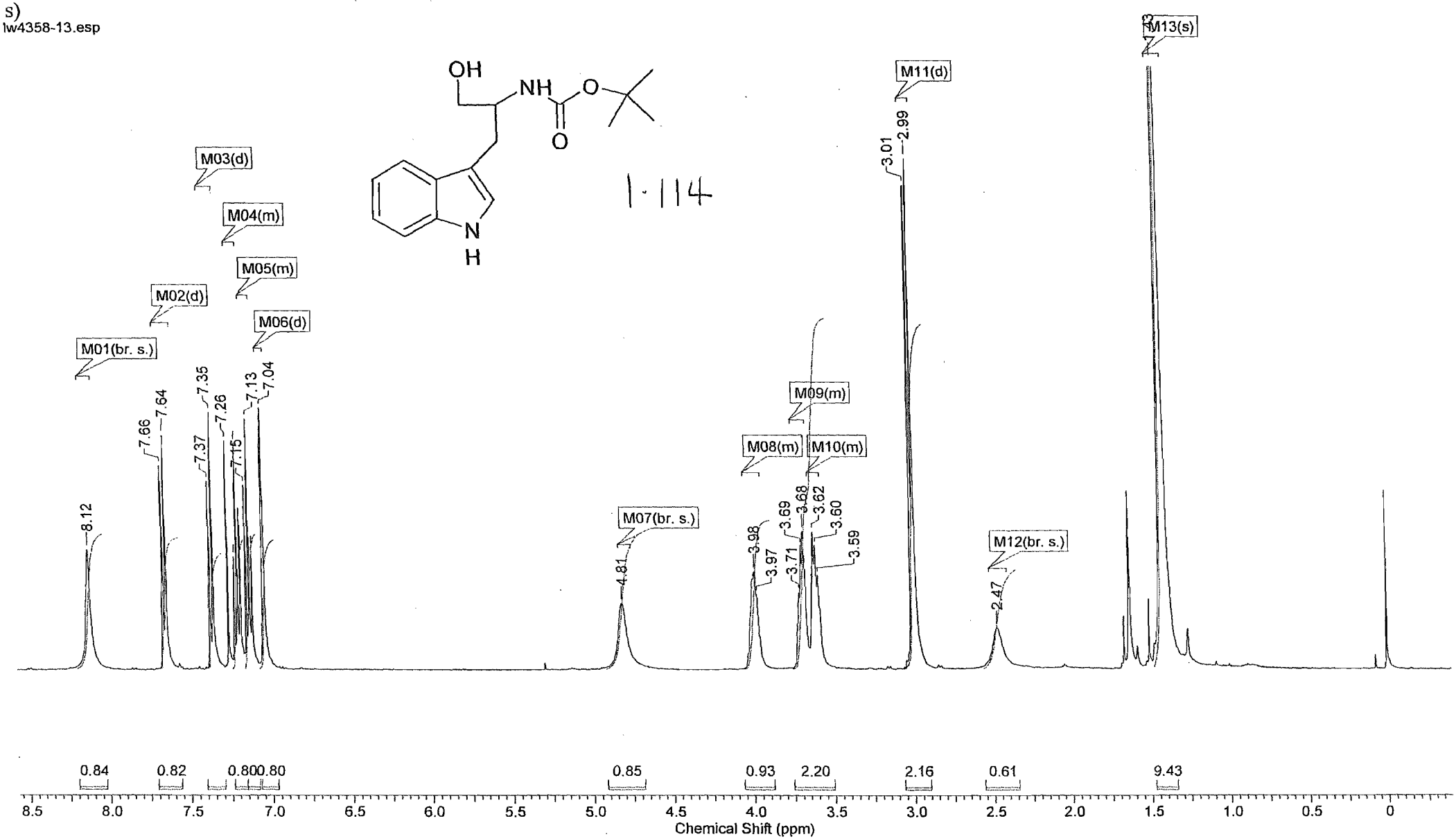
F2 - Processing parameters
SI 16384
SF 300.1300308 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 30.82 Hz

1-110

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.43 (br. s., 9 H) 1.51 (s, 9 H) 3.15 - 3.23 (m, 1 H) 3.25 - 3.32 (m, 1 H) 3.69 (s, 3 H) 4.71 (d, *J*=5.40 Hz, 1 H) 5.14 (d, *J*=6.65 Hz, 1 H) 7.27 (t, *J*=7.40 Hz, 1 H) 7.31 - 7.38 (m, 1 H) 7.48 (d, *J*=7.65 Hz, 1 H) 7.56 (s, 1 H) 8.49 (d, *J*=8.28 Hz, 1 H)



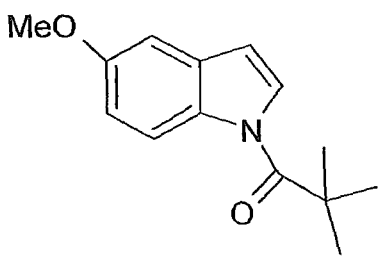
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.12 (1 H, br. s.), 7.65 (1 H, d, *J*=7.8 Hz), 7.36 (1 H, d, *J*=8.0 Hz), 7.17 - 7.24 (1 H, m), 7.09 - 7.16 (1 H, m), 7.04 (1 H, d, *J*=1.5 Hz), 4.81 (1 H, br. s.), 3.94 - 4.04 (1 H, m), 3.65 - 3.74 (1 H, m), 3.57 - 3.64 (1 H, m), 3.00 (2 H, d, *J*=6.8 Hz), 2.47 (1 H, br. s.), 1.43 (9 H, s)



18/09/2006 14:45:54

1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.51 (s, 9 H) 3.86 (s, 3 H) 6.55 (d, *J*=3.84 Hz, 1 H) 6.95 (dd, *J*=9.10, 2.61 Hz, 1 H) 7.02 (d, *J*=2.47 Hz, 1 H) 7.71 (d, *J*=3.75 Hz, 1 H) 8.41 (d, *J*=9.06 Hz, 1 H)

ju2805lw4_010000fid

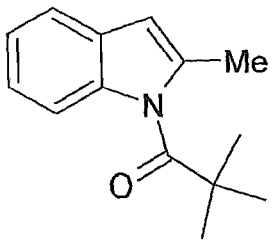


1·117

21/09/2006 11:29:43

1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 7.46 - 7.54 (1 H, m), 7.26 - 7.33 (1 H, m), 7.16 (1 H, td), 7.11 (1 H, td), 6.33 (1 H, s), 2.40 (3 H, d, *J*=0.9 Hz), 1.42 (9 H, s)

jy0805lw4.esp

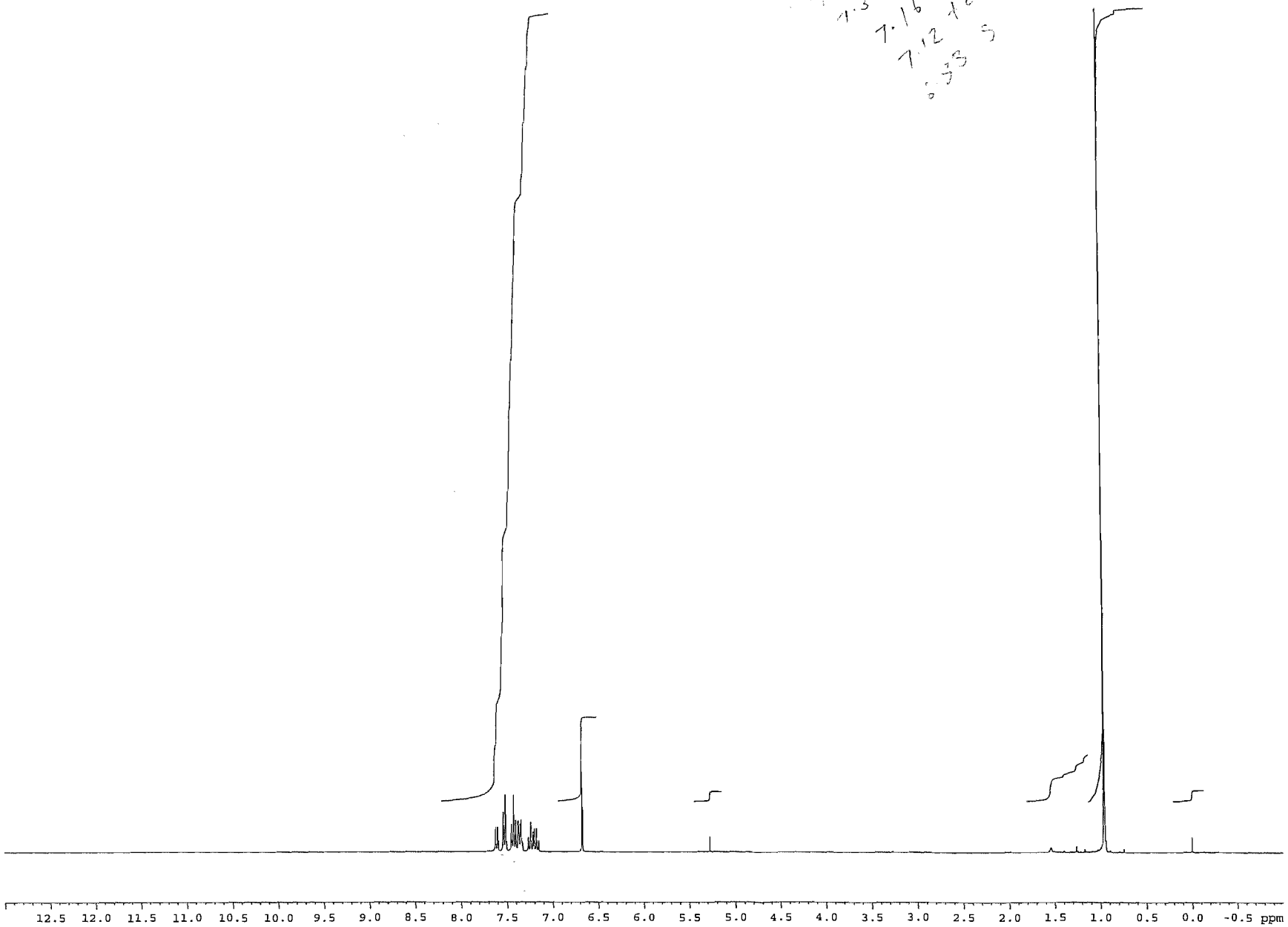


1·119

lw4358/46

1.121

7.51-7.45
7.30-7.25
7.16 td
7.12 td
5.33 s



BRUKER

Current Data Parameters

NAME	jy08051w1
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20050708
Time	12.41
INSTRUM	av300
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5995.204 Hz
FIDRES	0.182959 Hz
AQ	2.7329011 sec
RG	228.1
DW	83.400 usec
DE	6.00 usec
TE	300.2 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

NUC1	1H
P1	12.10 usec
PL1	3.00 dB
SFO1	300.1315006 MHz

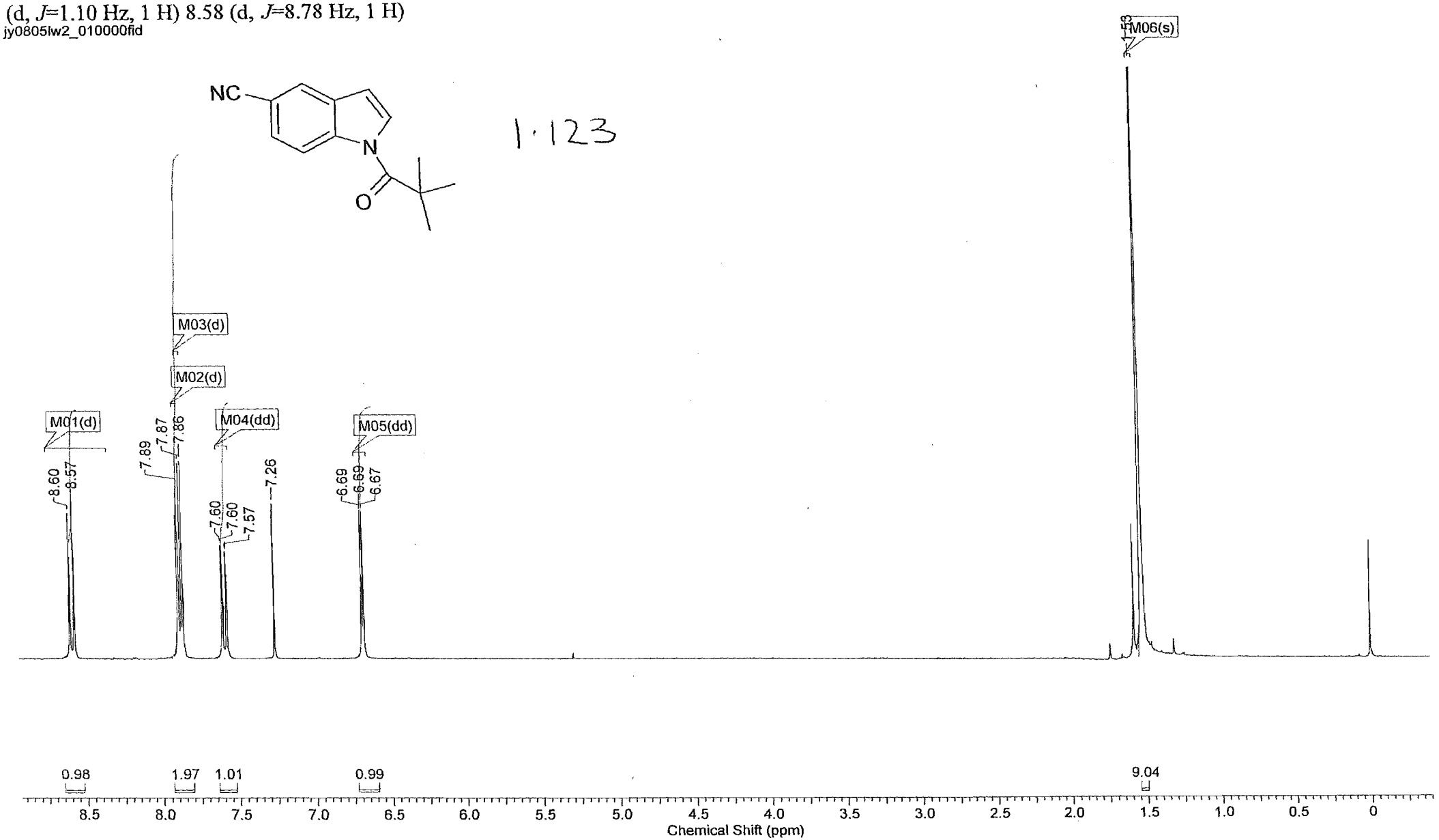
F2 - Processing parameters

SI	16384
SF	300.1300125 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	12.46 Hz

1.12

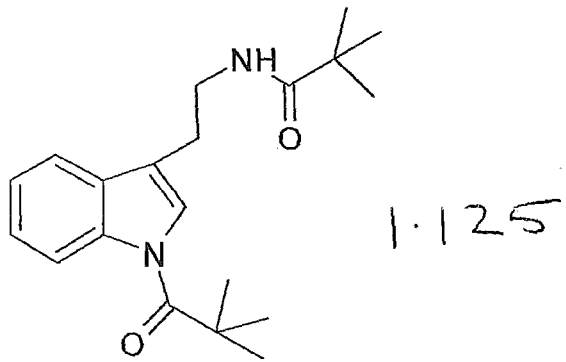
1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.53 (s, 9 H) 6.68 (dd, *J*=3.84, 0.46 Hz, 1 H) 7.58 (dd, *J*=8.69, 1.65 Hz, 1 H) 7.86 (d, *J*=3.93 Hz, 1 H) 7.89 (d, *J*=1.10 Hz, 1 H) 8.58 (d, *J*=8.78 Hz, 1 H)

jy0805lw2_010000fid



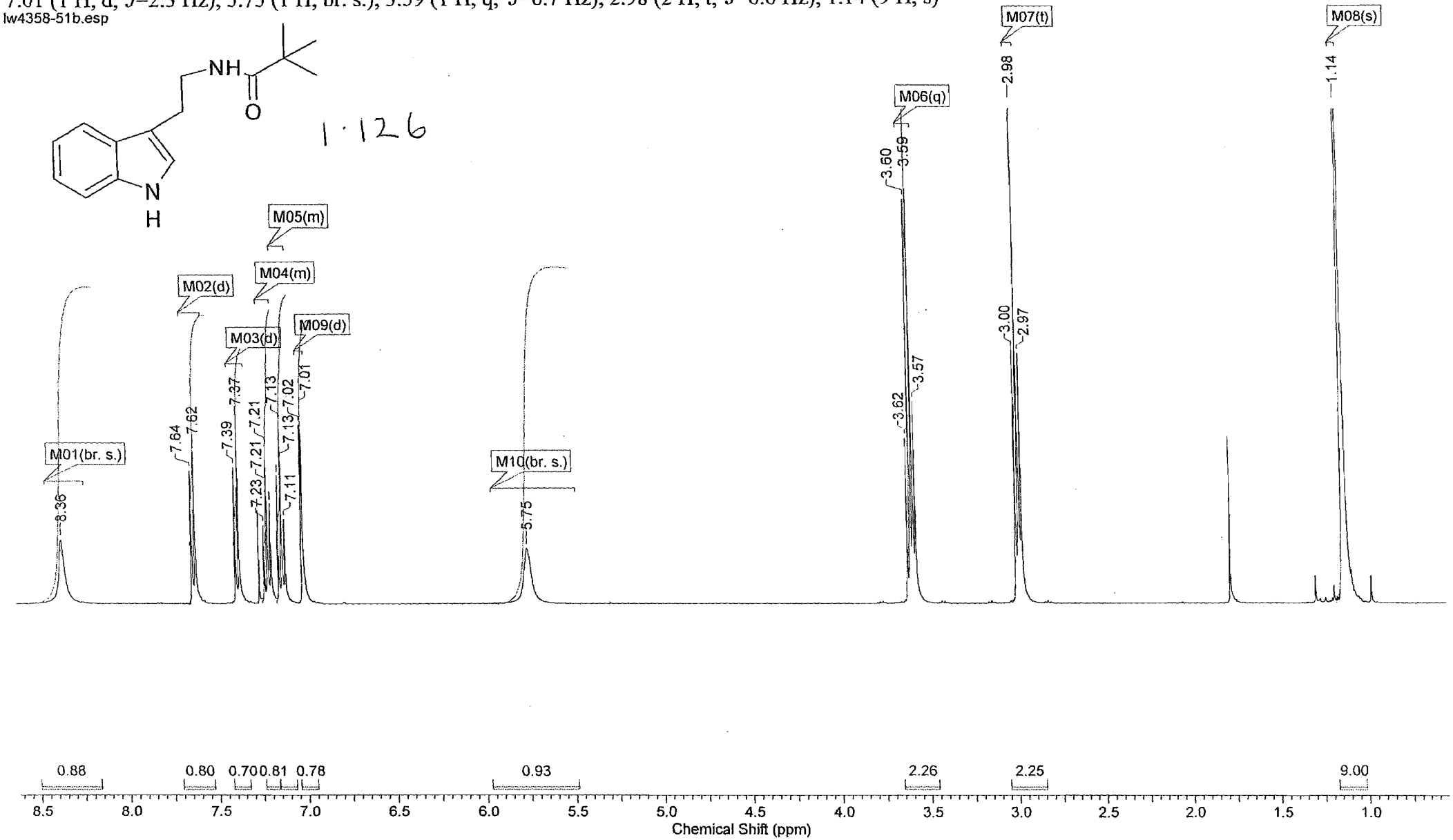
1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.52 (1 H, d, *J*=8.0 Hz), 7.57 (1 H, s), 7.54 (1 H, d, *J*=0.9 Hz), 7.36 (1 H, dt), 7.24 - 7.32 (1 H, m), 3.57 - 3.67 (2 H, m), 2.90 - 2.98 (2 H, m), 1.50 (9 H, s), 1.15 (9 H, s)

lw4358-47e1.esp



1.125

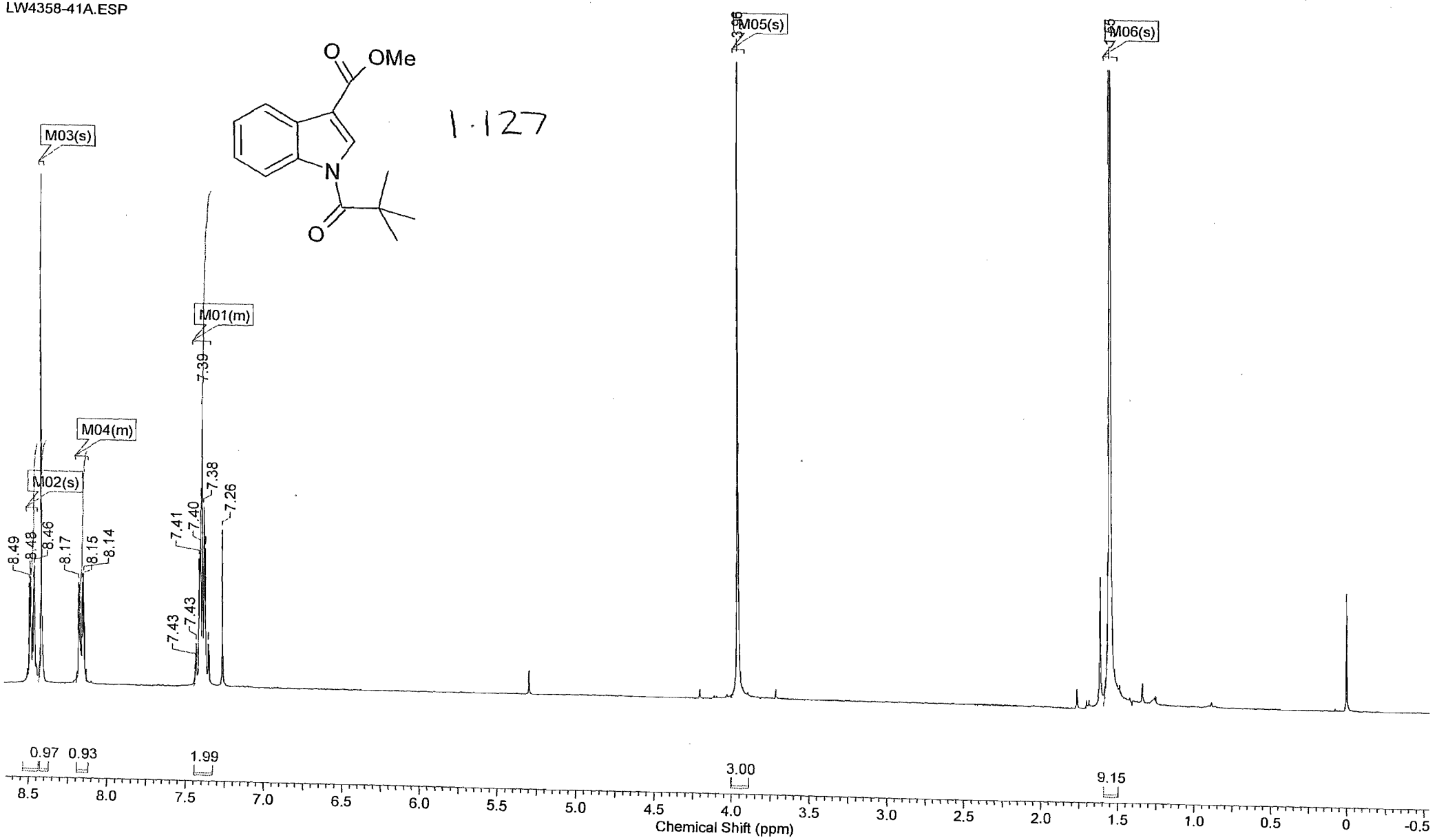
1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.36 (1 H, br. s.), 7.63 (1 H, d, *J*=7.8 Hz), 7.38 (1 H, d, *J*=8.2 Hz), 7.17 - 7.25 (1 H, m), 7.08 - 7.16 (1 H, m), 7.01 (1 H, d, *J*=2.3 Hz), 5.75 (1 H, br. s.), 3.59 (1 H, q, *J*=6.7 Hz), 2.98 (2 H, t, *J*=6.6 Hz), 1.14 (9 H, s)



19/09/2006 15:41:45

1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 8.47 (1 H, s), 8.41 (1 H, s), 8.11 - 8.20 (1 H, m), 7.33 - 7.45 (2 H, m), 3.96 (3 H, s), 1.55 (9 H, s)

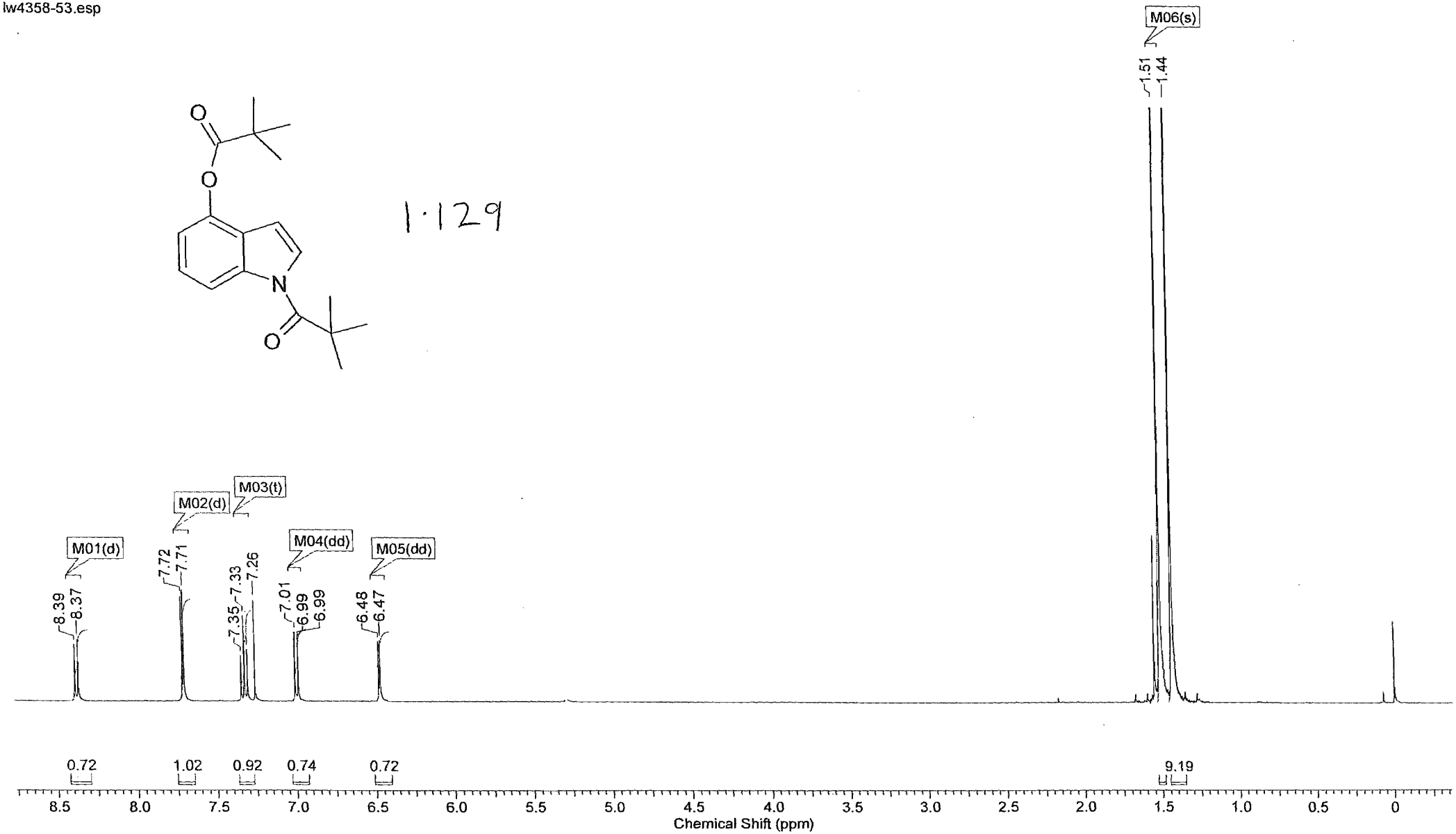
LW4358-41A.ESP



1.127

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 1.44 (s, 9 H) 1.51 (s, 9 H) 6.47 (dd, *J*=3.89, 0.63 Hz, 1 H) 7.00 (dd, *J*=7.91, 0.75 Hz, 1 H) 7.33 (t, *J*=8.16 Hz, 1 H) 7.71 (d, *J*=3.89 Hz, 1 H) 8.38 (d, *J*=8.41 Hz, 1 H)

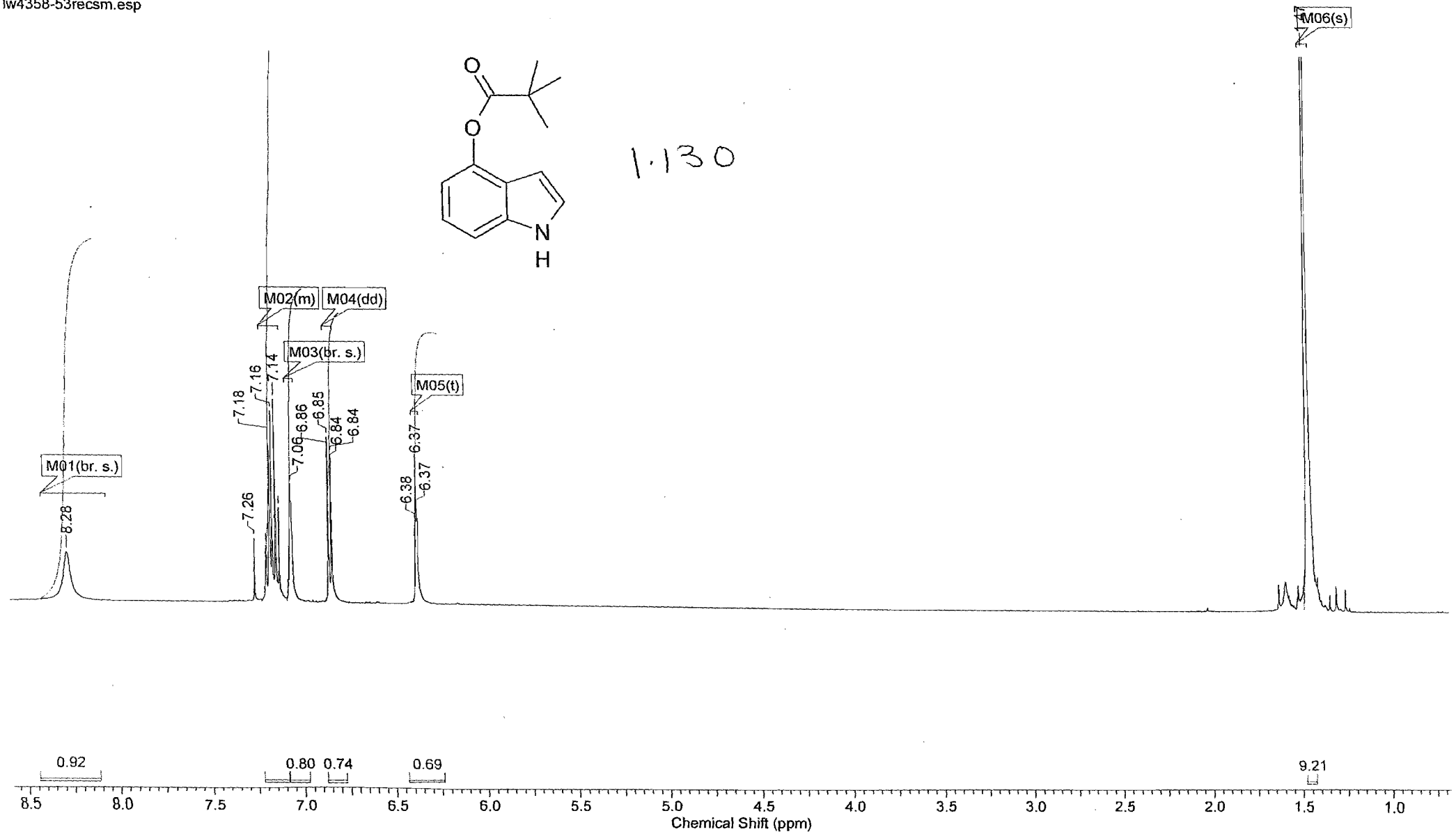
lw4358-53.esp



1·129

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.28 (1 H, br. s.), 7.11 - 7.22 (2 H, m), 7.06 (1 H, br. s.), 6.85 (1 H, dd, *J*=7.3, 1.1 Hz), 6.37 (1 H, t, *J*=2.2 Hz), 1.47 (9 H, s)

lw4358-53recsm.esp



lw4358/65

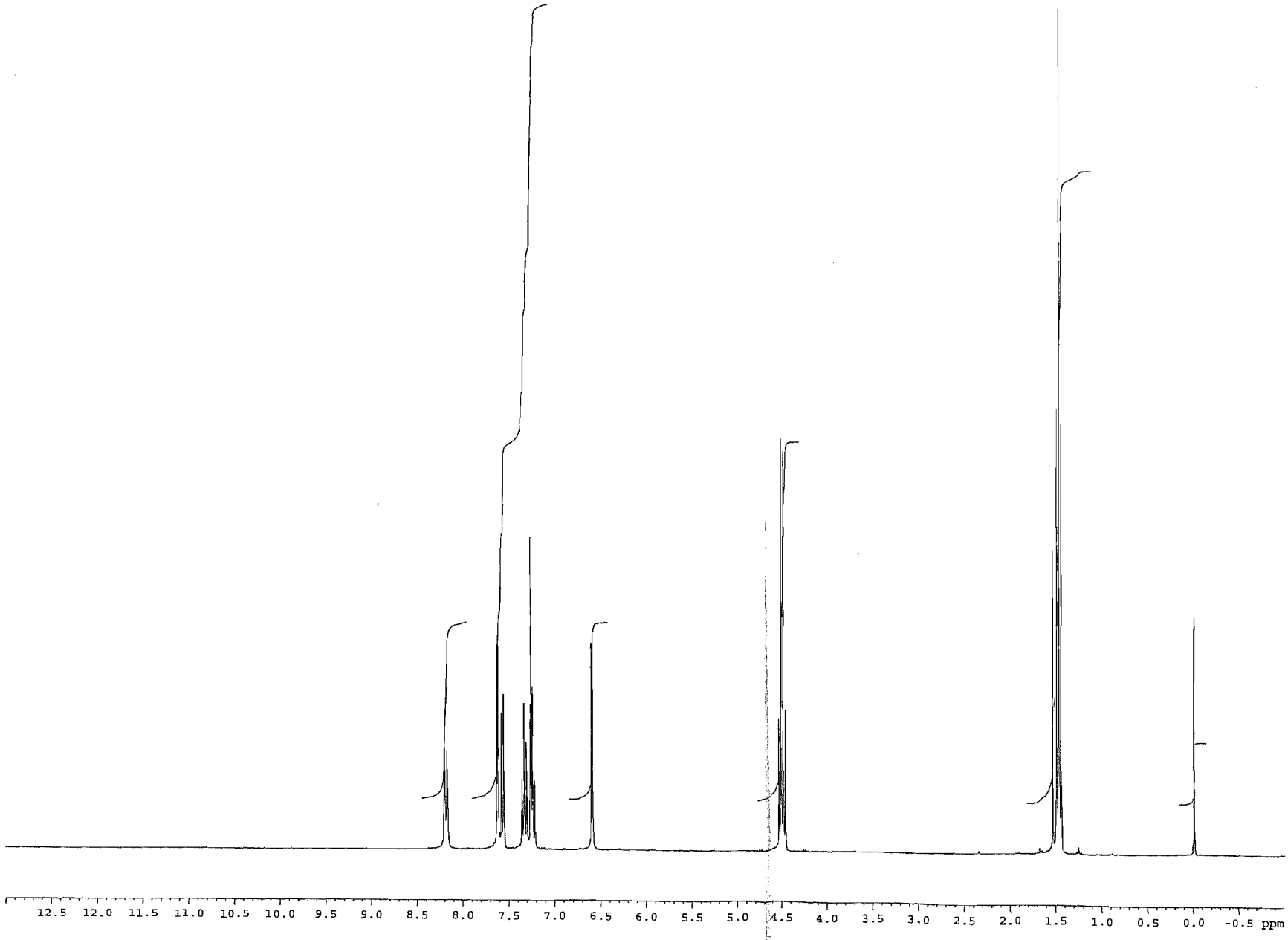
1-132

Current Data Parameters
NAME au01051w1
EXPNO 10
PROCNO 1

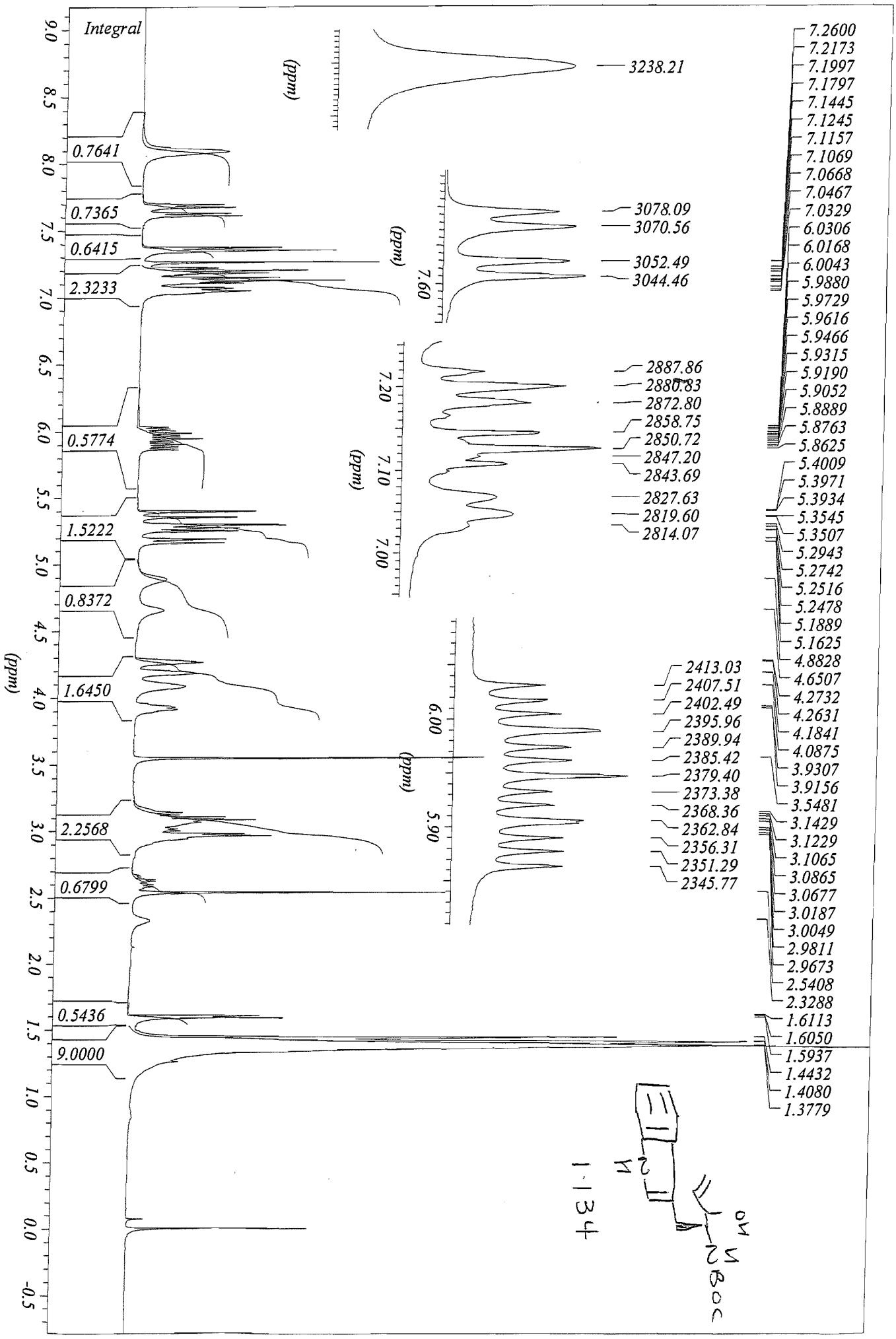
F2 - Acquisition Parameters
Date_ 20050801
Time 10.53
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 912.3
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300084 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 8.45 Hz

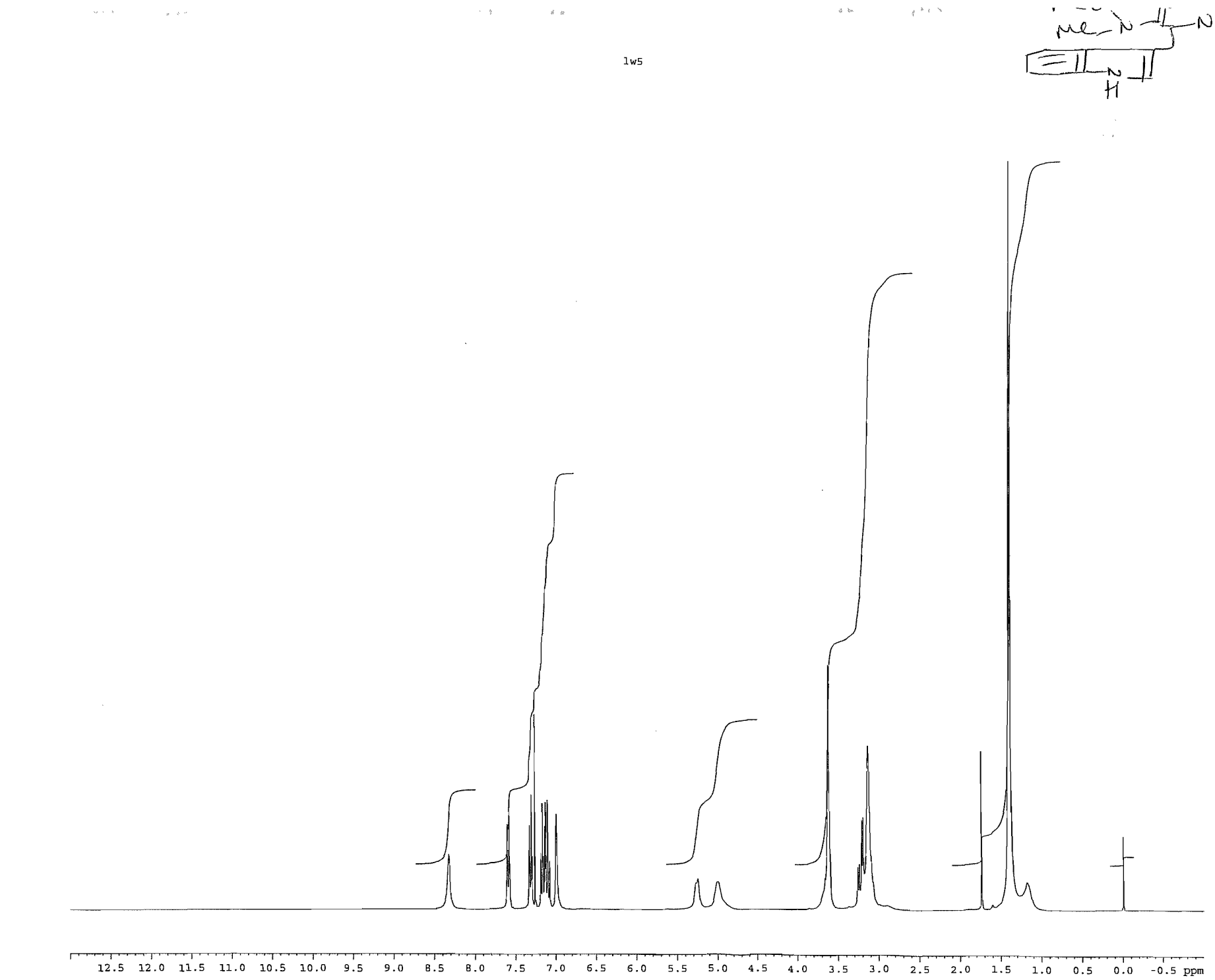


1-132



lw4358/94□

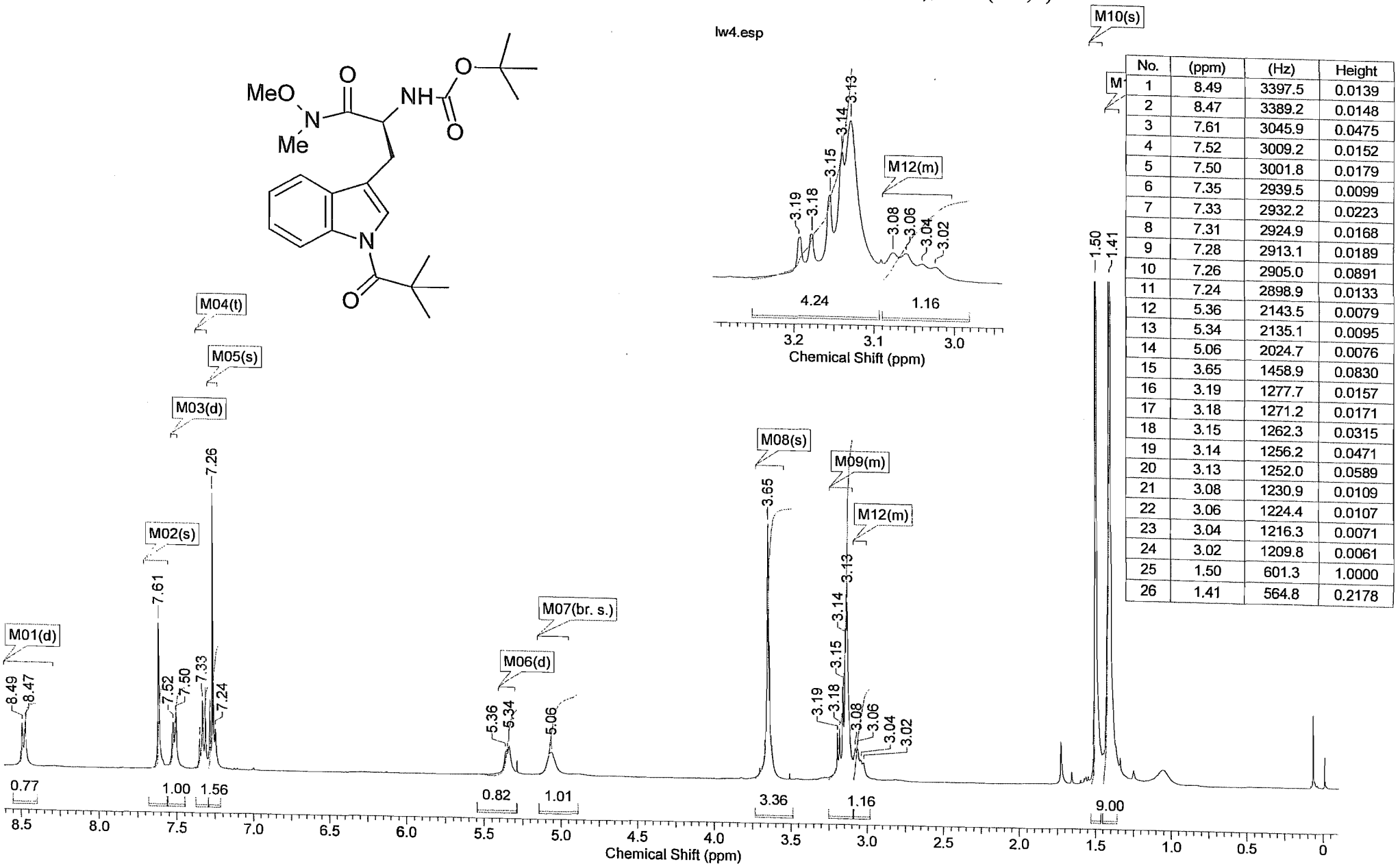
1.134


lw5
Me
NHBOC
N
H
1.135
BRUKER
Current Data Parameters
NAME se1606lw1
EXPNO 10
PROCNO 1
F2 - Acquisition Parameters
Date_ 20060916
Time 14.23
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 256
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz
F2 - Processing parameters
SI 16384
SF 300.1300084 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 8.38 Hz
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 ppm
1.135

20/09/2006 16:56:14

1H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 8.48 (1 H, d, *J*=8.3 Hz), 7.61 (1 H, s), 7.51 (1 H, d, *J*=7.4 Hz), 7.33 (1 H, t, *J*=7.3 Hz), 7.26 (1 H, s), 5.35 (1 H, d, *J*=8.4 Hz), 5.06 (1 H, br. s.), 3.65 (3 H, s), 3.09 - 3.24 (4 H, m), 3.00 - 3.09 (1 H, m), 1.50 (9 H, s), 1.41 (9 H, s)

lw4.esp



No.	(ppm)	(Hz)	Height
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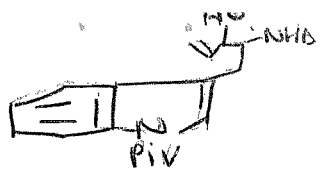
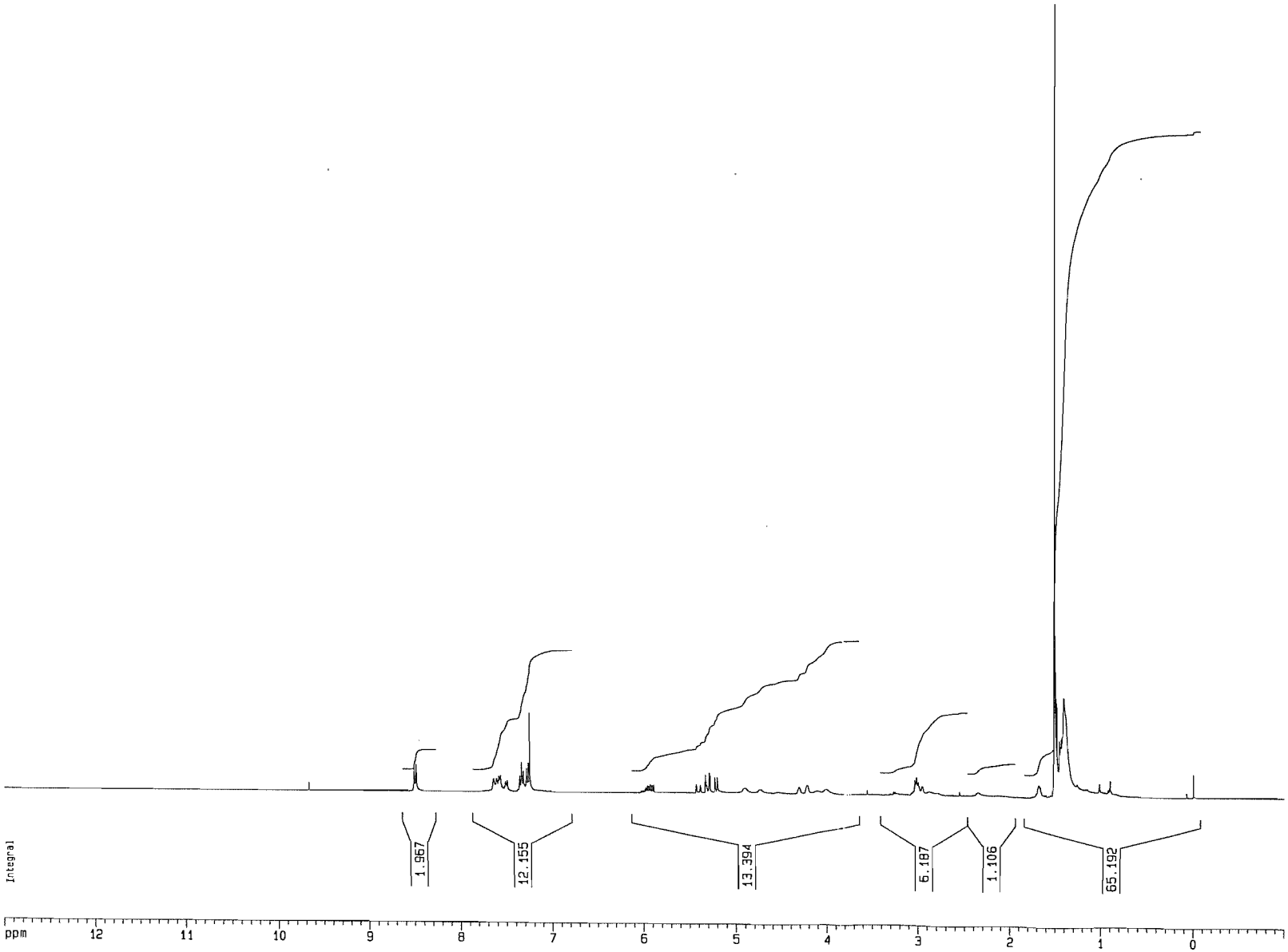
2	8.47	3389.2	0.0148
3	7.61	3045.9	0.0475
4	7.52	3009.2	0.0152
5	7.50	3001.8	0.0179
6	7.35	2939.5	0.0099
7	7.33	2932.2	0.0223
8	7.31	2924.9	0.0168
9	7.28	2913.1	0.0189
10	7.26	2905.0	0.0891
11	7.24	2898.9	0.0133
12	5.36	2143.5	0.0079
13	5.34	2135.1	0.0095
14	5.06	2024.7	0.0076
15	3.65	1458.9	0.0830
16	3.19	1277.7	0.0157
17	3.18	1271.2	0.0171
18	3.15	1262.3	0.0315
19	3.14	1256.2	0.0471
20	3.13	1252.0	0.0589
21	3.08	1230.9	0.0109
22	3.06	1224.4	0.0107
23	3.04	1216.3	0.0071
24	3.02	1209.8	0.0061
25	1.50	601.3	1.0000
26	1.41	564.8	0.2178

1·137

1-139



LW23



Current Data Parameters

NAME	se14061w4
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060914
Time	19.12
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

SI	16384
SF	400.1300210 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.96 Hz

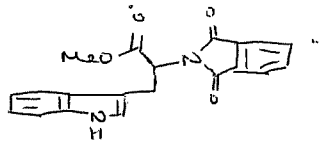
1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

1-139

1.140

lw4358/59



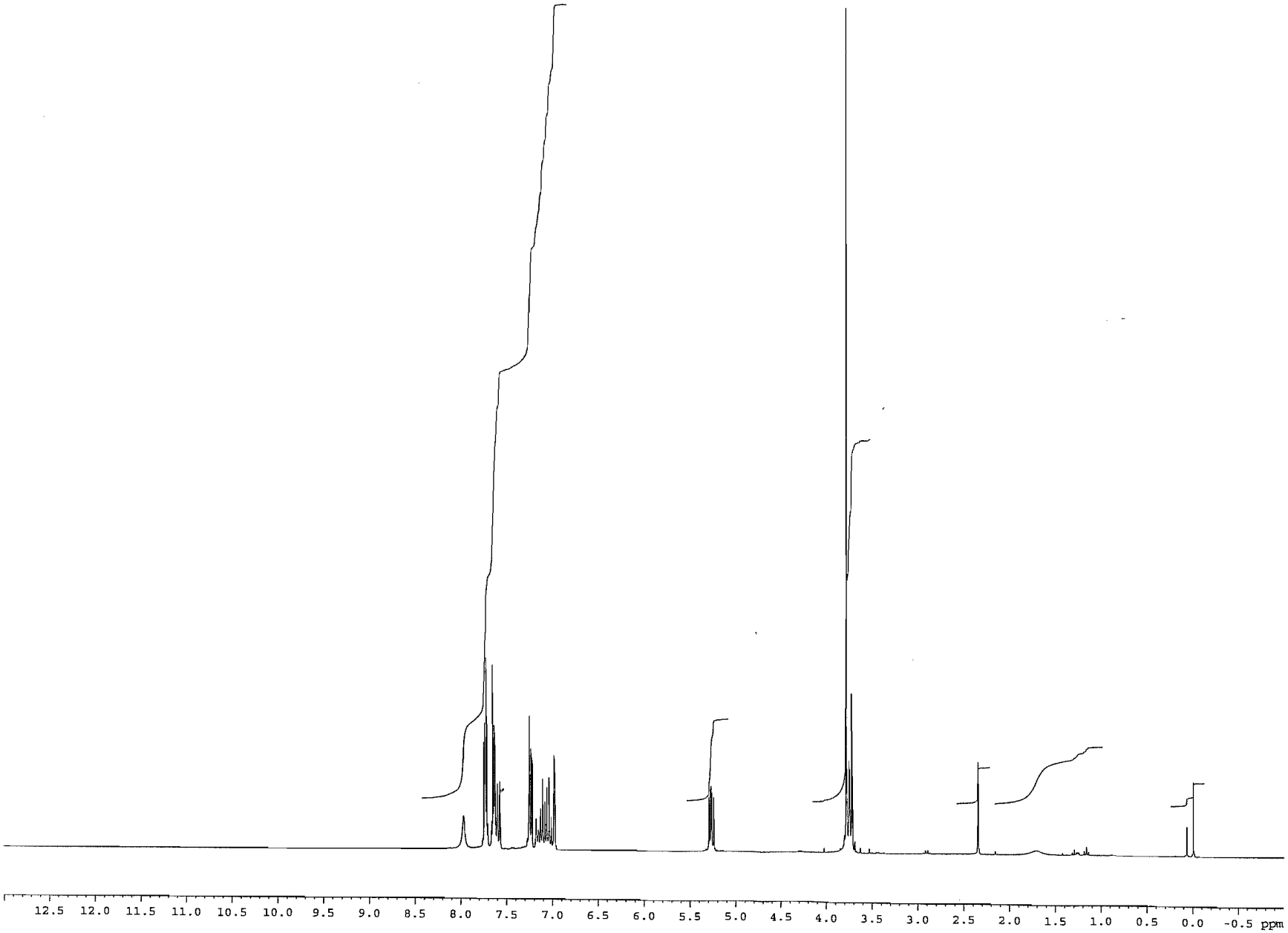
BRUKER

Current Data Parameters
NAME jy2505lw8
EXPNO 10
PROCNO 1

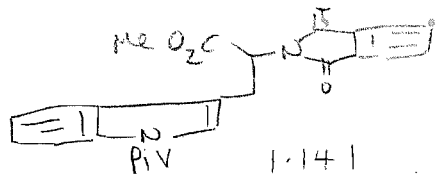
F2 - Acquisition Parameters
Date_ 20050725
Time 21.21
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 406.4
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300092 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 9.22 Hz

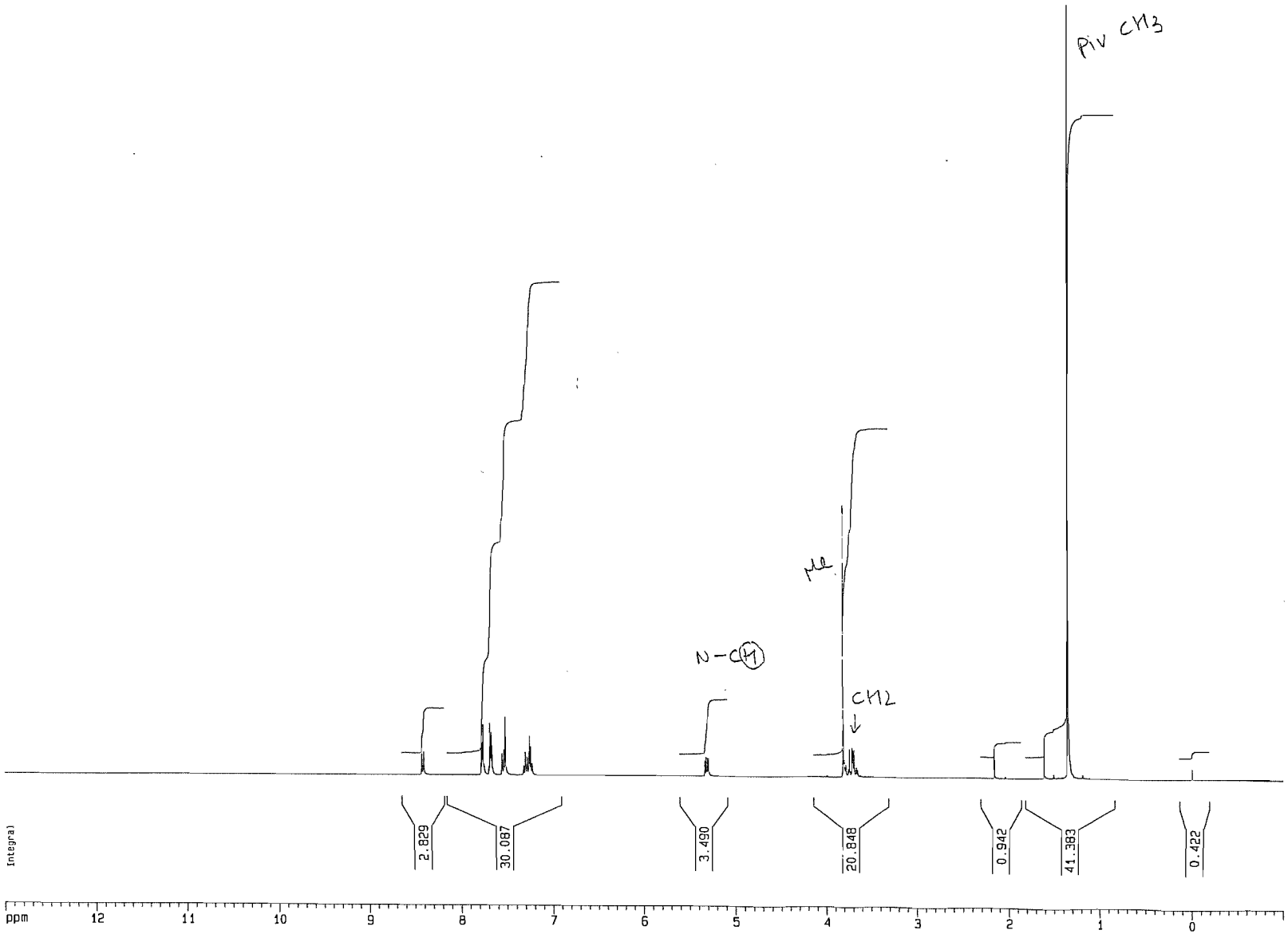


1 of 1



1.141

lw20



Current Data Parameters

NAME	se1306lw3
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060914
Time	8.32
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

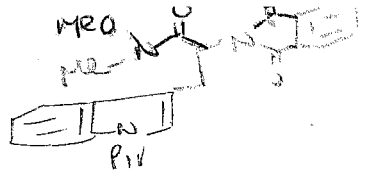
F2 - Processing parameters

SI	16384
SF	400.1300209 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.89 Hz

1D NMR plot parameters

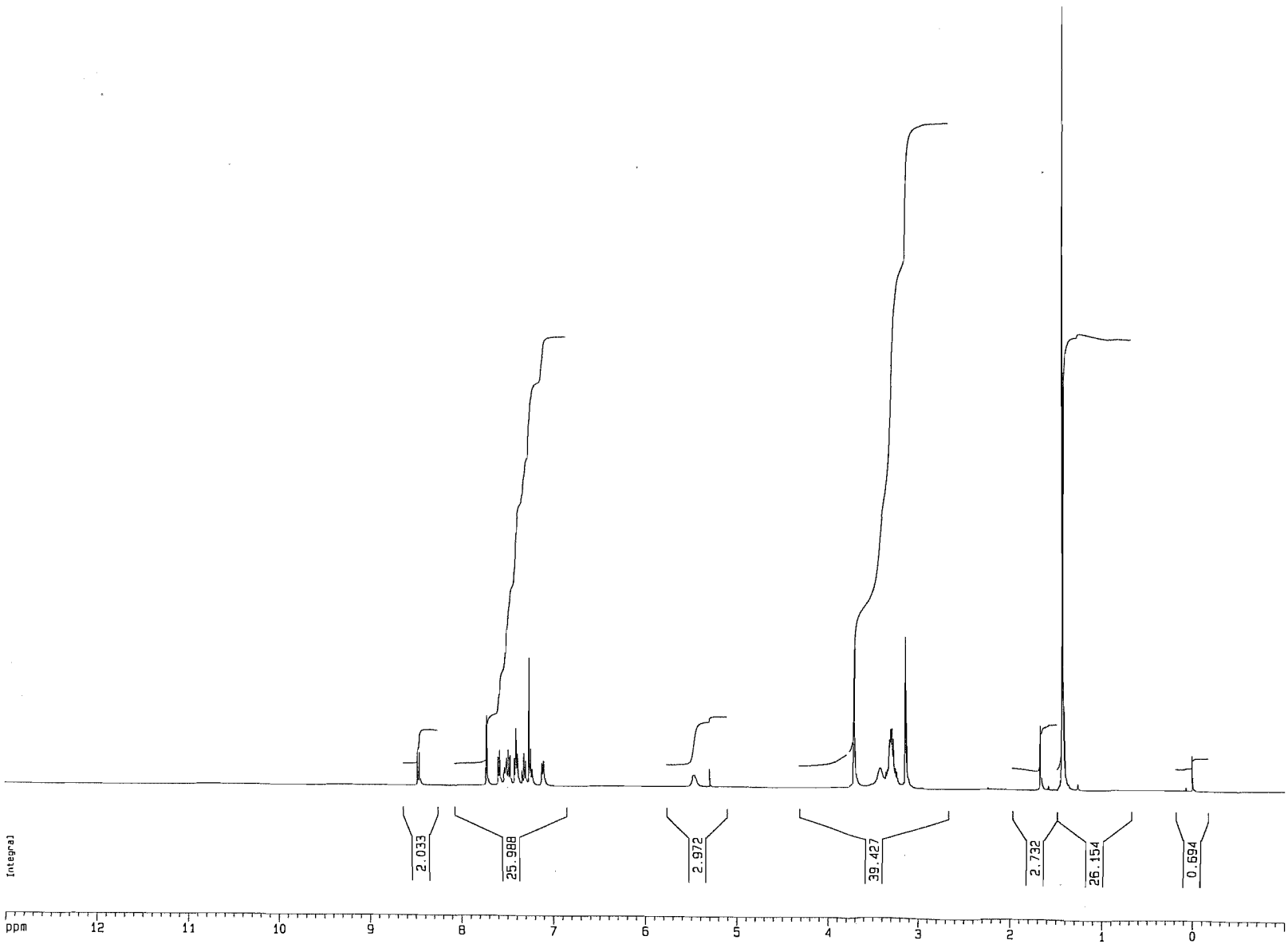
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

1.141



LW21

1.142



Current Data Parameters

NAME	se14061w2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060914
Time	16.23
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

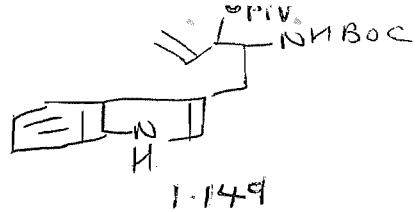
F2 - Processing parameters

SI	16384
SF	400.1300195 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	19.51 Hz

1D NMR plot parameters

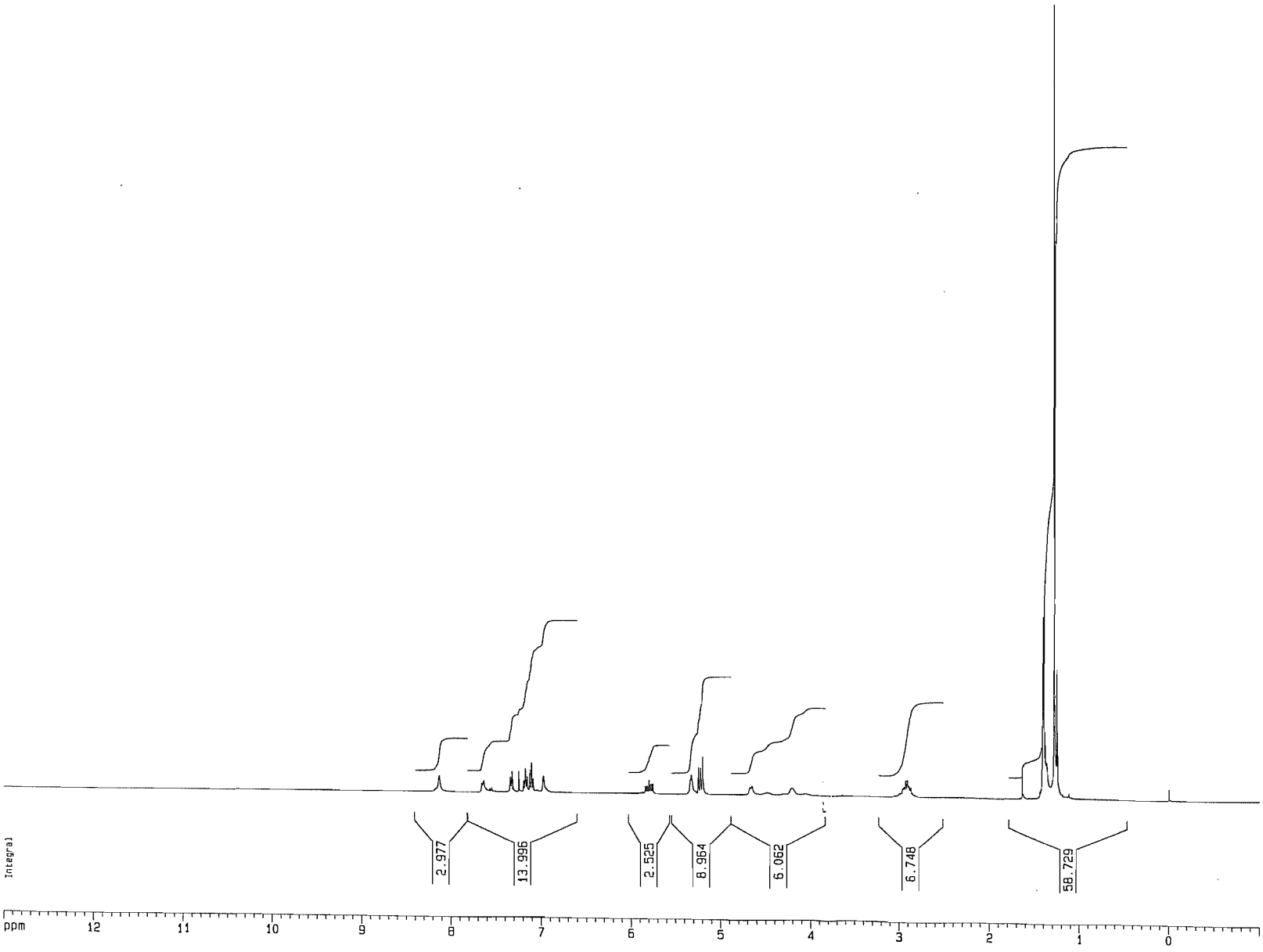
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm

1.142



1.149

lw25



Current Data Parameters

NAME	se16061w2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060917
Time	15.57
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	COC13
NS	64
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

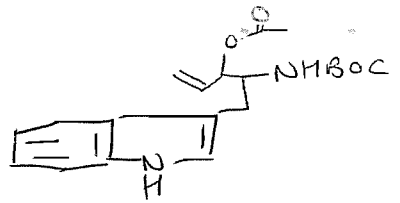
F2 - Processing parameters

SI	16384
SF	400.1300240 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	23.96 Hz

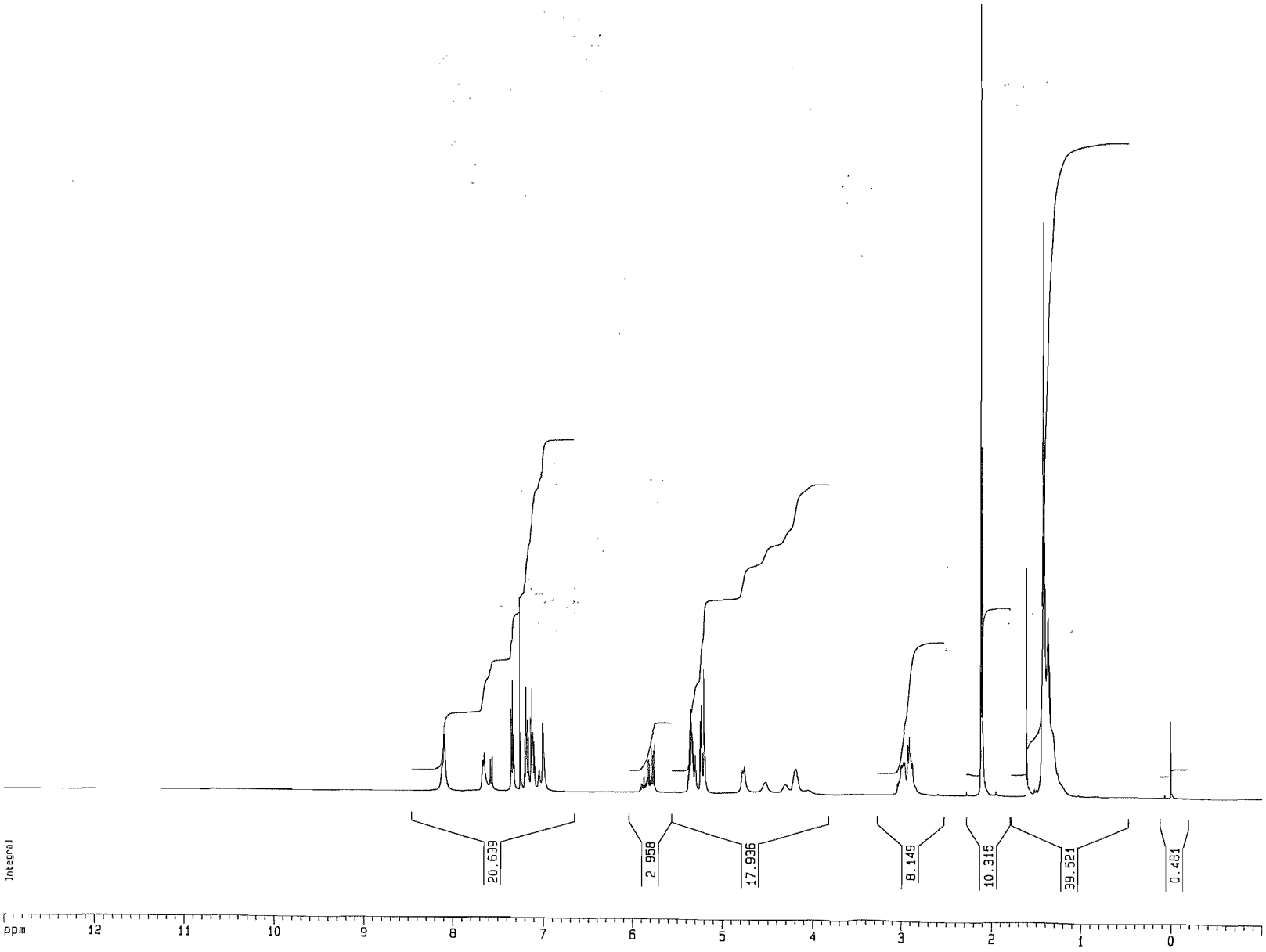
1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

1.149



lw26



Current Data Parameters

NAME	se19061w1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060920
Time	2.49
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

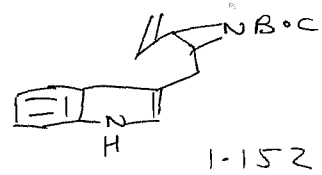
SI	16384
SF	400.1300230 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SA	23.00 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

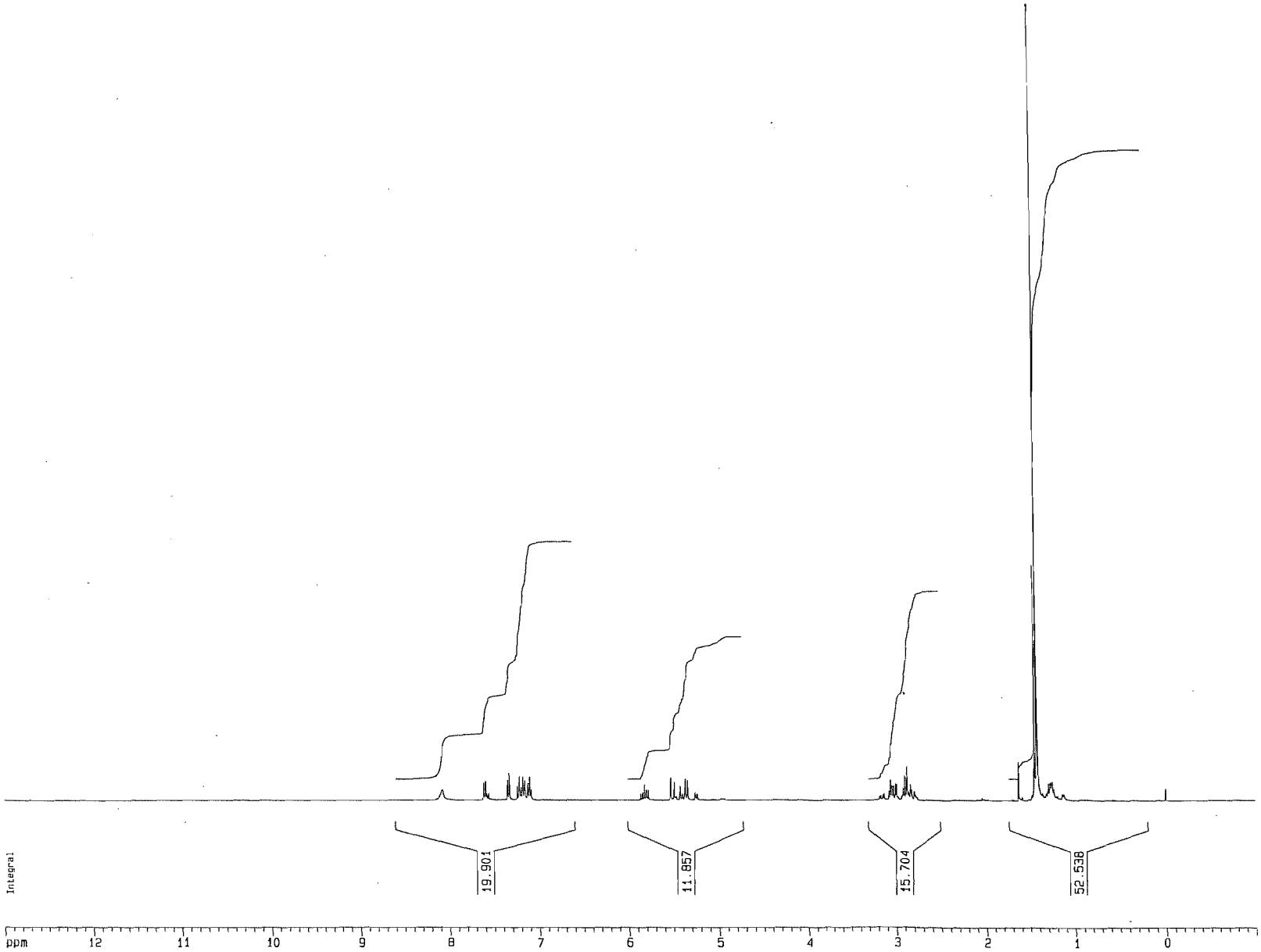
1.150

1.150



1-152

lw4358/87f9-16



Current Data Parameters

NAME	se27051w1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050927
Time	17.21
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

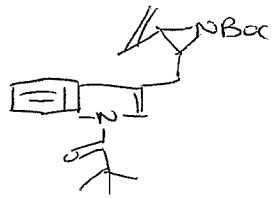
SI	16384
SF	400.1300260 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	26.00 Hz

1D NMR plot parameters

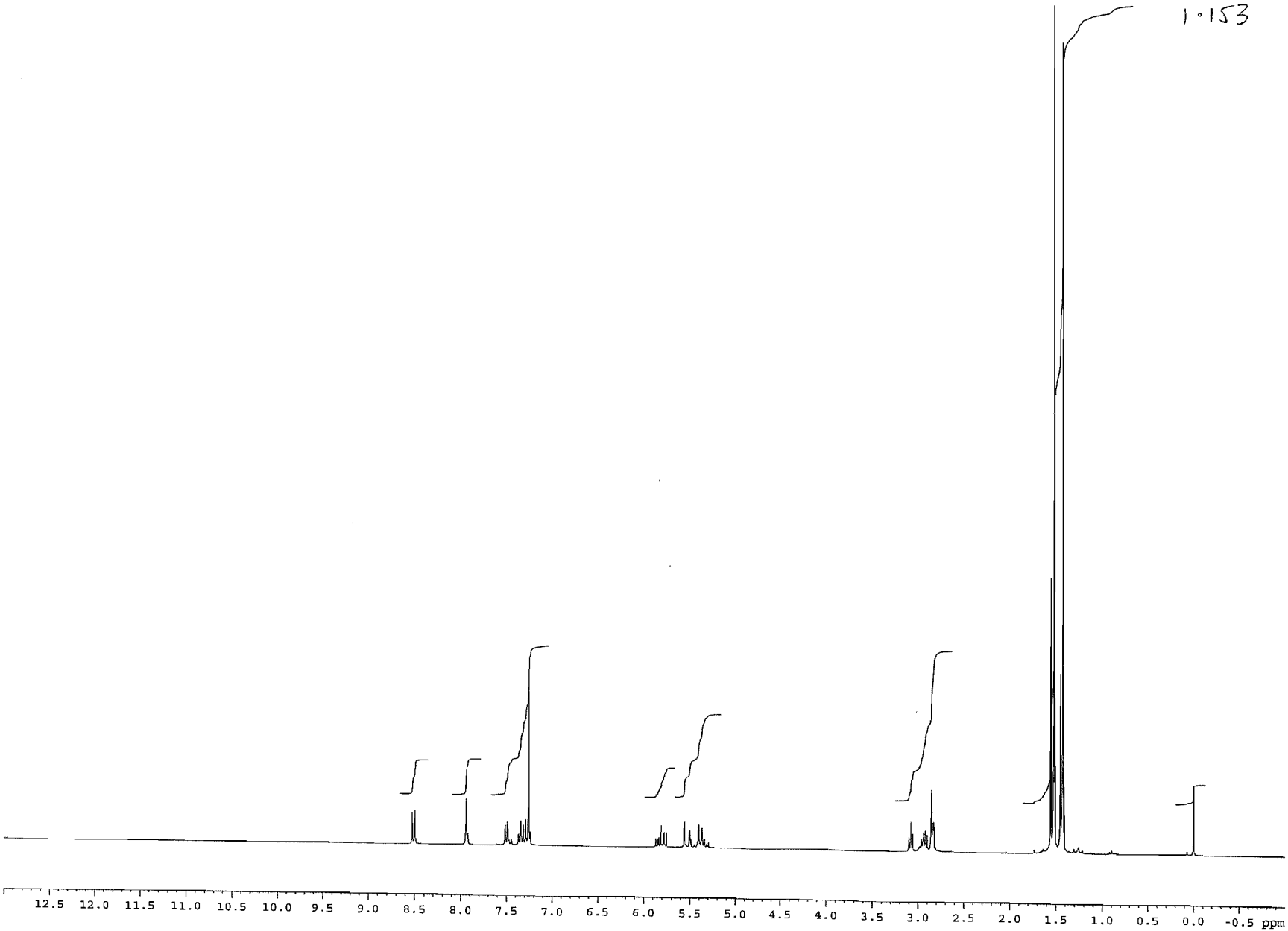
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

2 of 1

lw4358/96



1.153



BRUKER

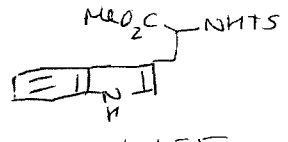
Current Data Parameters
NAME oc11051w3
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20051011
Time 13.29
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 724.1
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300066 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 6.57 Hz

lw4481/10



1-155

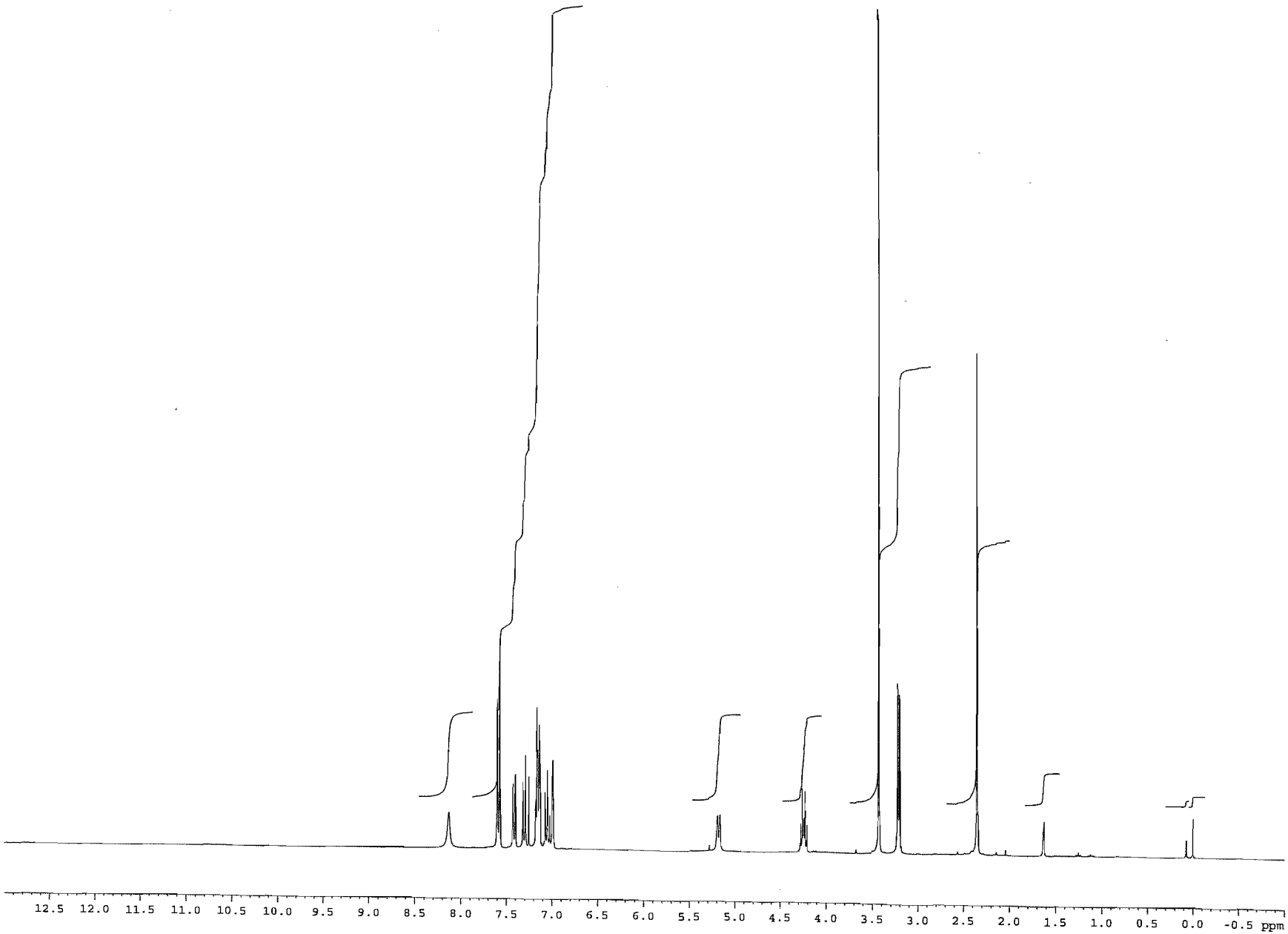
BRUKER

Current Data Parameters
NAME dc05051w5
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20051205
Time 18.10
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 322.5
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

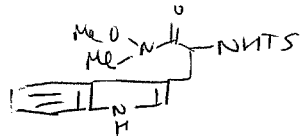
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300091 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 9.06 Hz

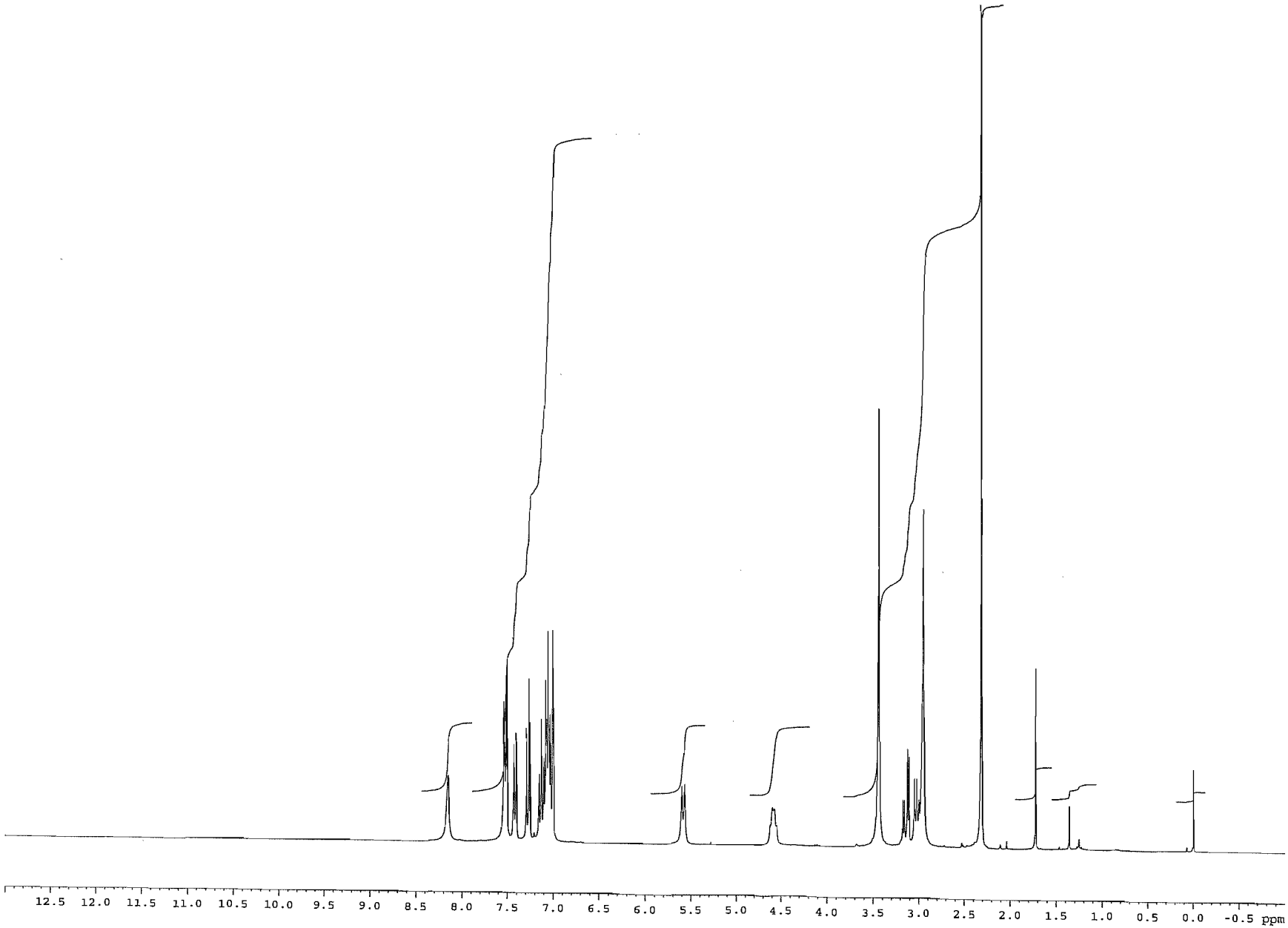


1-155

lw4481/21



1.156



Current Data Parameters
NAME dc05051w6
EXPNO 10
PROCNO 1

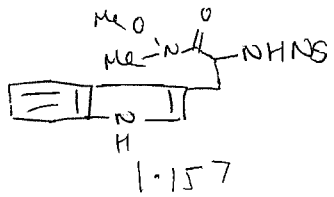
F2 - Acquisition Parameters
Date_ 20051205
Time 18.45
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 287.4
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300081 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 8.12 Hz

1.156

lw4481/51



1.157

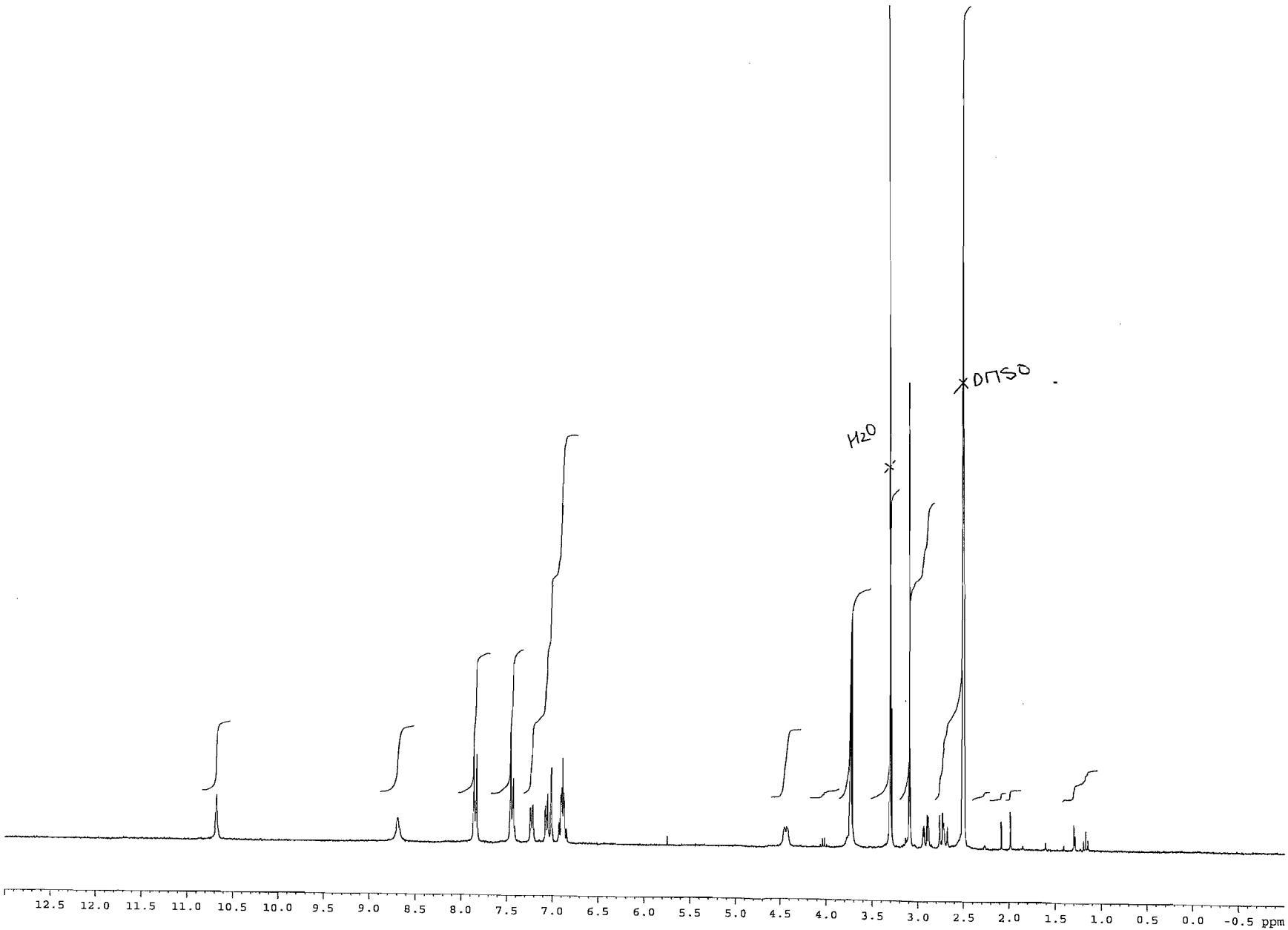
BRUKER

Current Data Parameters
NAME ja09061w1
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20060109
Time 9.43
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 1625.5
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

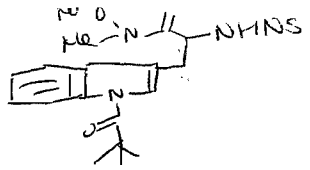
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300000 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 0.00 Hz



1.157

lw4481/52



1.159

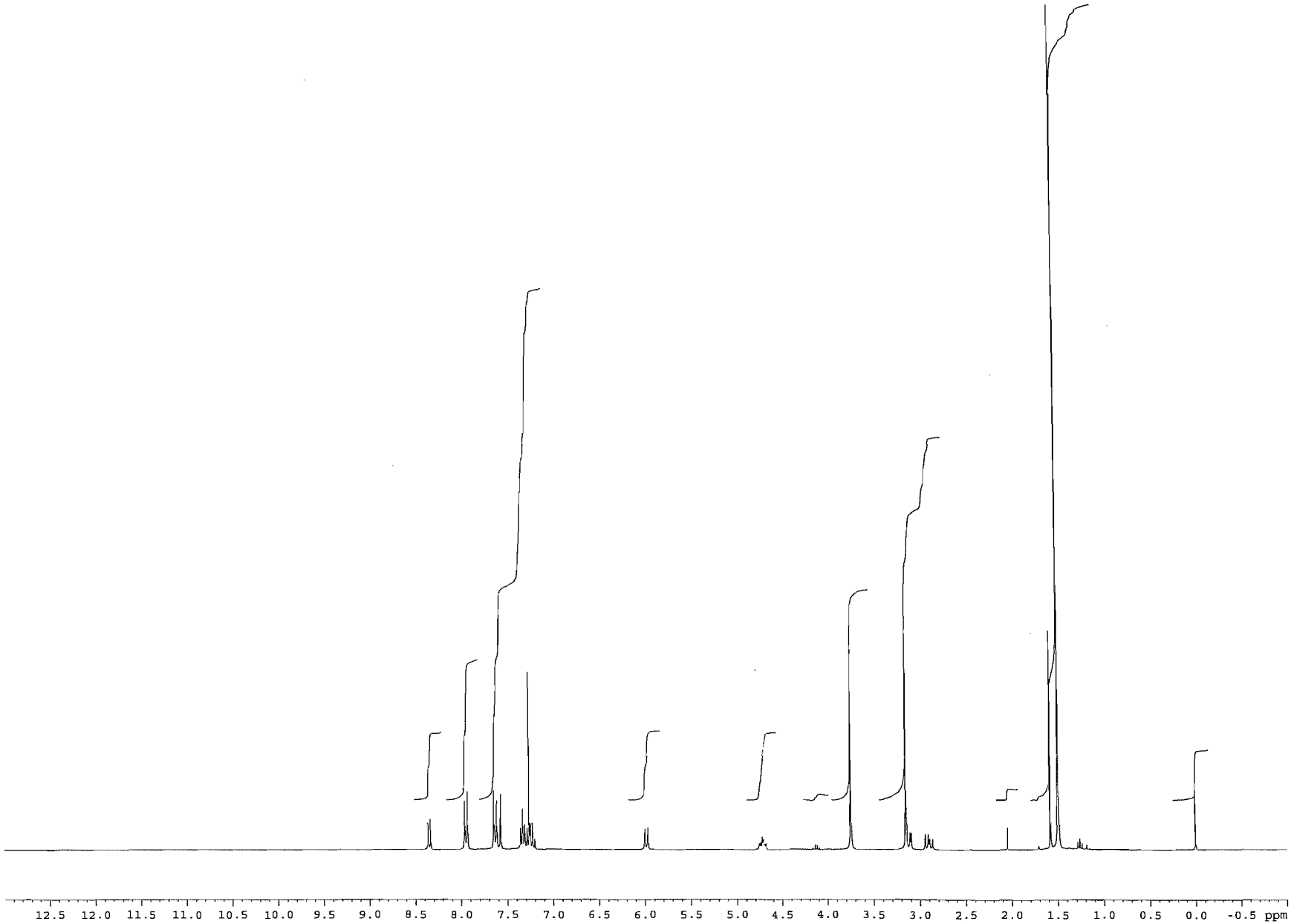
BRUKER

Current Data Parameters
NAME ja09061w2
EXPNO 10
PROCNO 1

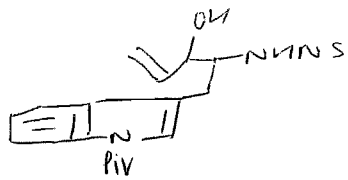
F2 - Acquisition Parameters
Date_ 20060109
Time 9.51
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 812.7
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300060 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 6.04 Hz

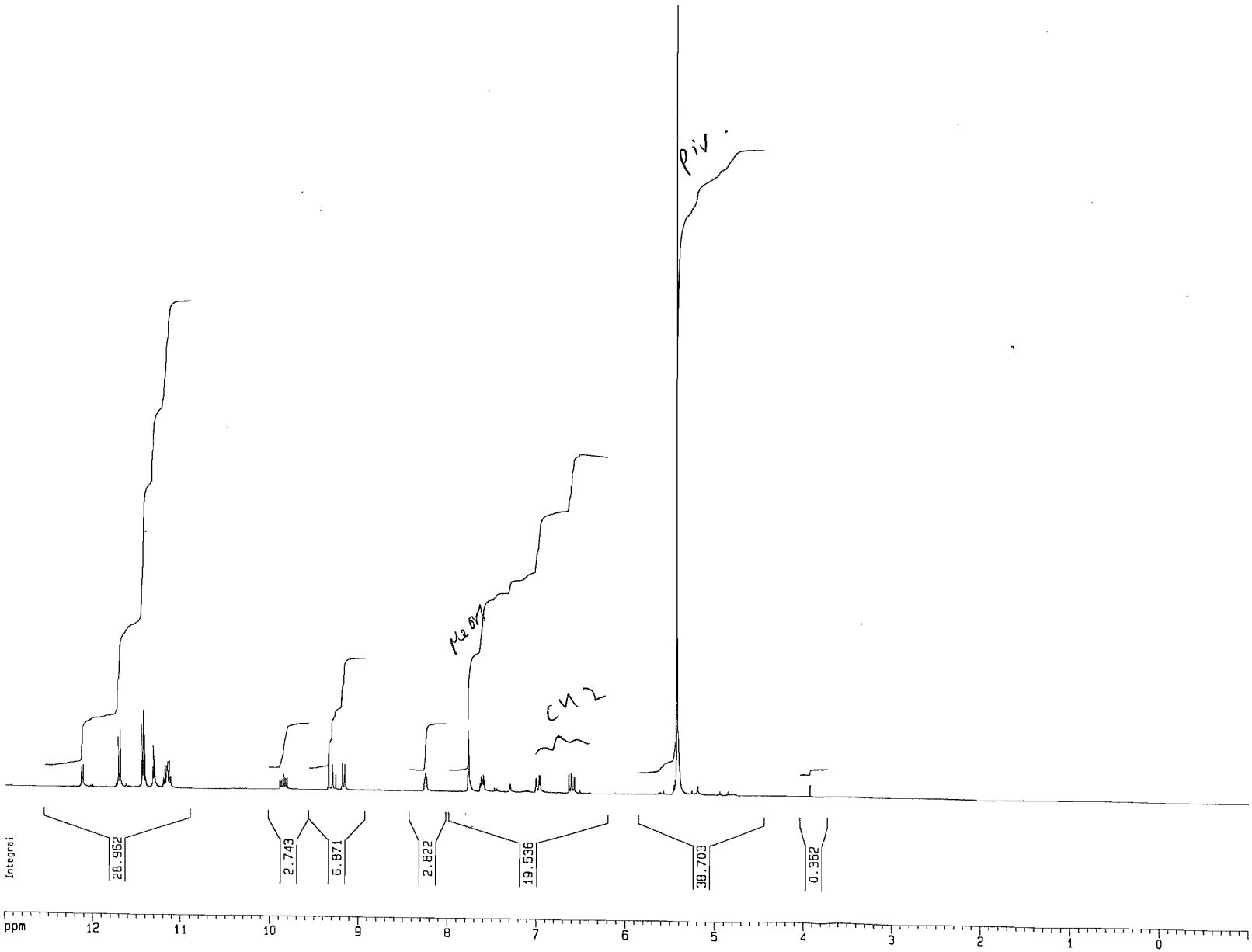


1 of 1



1.160

lw54




```
Current Data Parameters
NAME            se27061w1
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20060927
Time                19.38
INSTRUM             spect
PROBHD     5 mm Dual 13
PULPROG               zg
TD                 32768
SOLVENT           CDCl3
NS                    64
DS                     2
SWH           8223.685 Hz
FIORES        0.250967 Hz
AQ            1.9923444 sec
RG                   114
DW              60.800 usec
DE               6.00 usec
TE               300.0 K
D1            1.00000000 sec

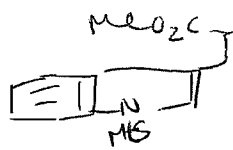
========== CHANNEL f1 ==========
NUC1                  1H
P1              10.30 usec
PL1              0.00 dB
SFO1        400.1324710 MHz

F2 - Processing parameters
SI                 16384
SF          400.1300000 MHz
WDW                   EM
SSB                    0
LB               0.30 Hz
GB                     0
PC                  1.00
SR               0.00 Hz

1D NMR plot parameters
CX              30.00 cm
F1P            13.000 ppm
F1            5201.69 Hz
F2P            -1.000 ppm
F2            -400.13 Hz
PPMCM         0.46667 ppm/cm
HZCM        186.72734 Hz/cm
```

1.160

lw34



1.161

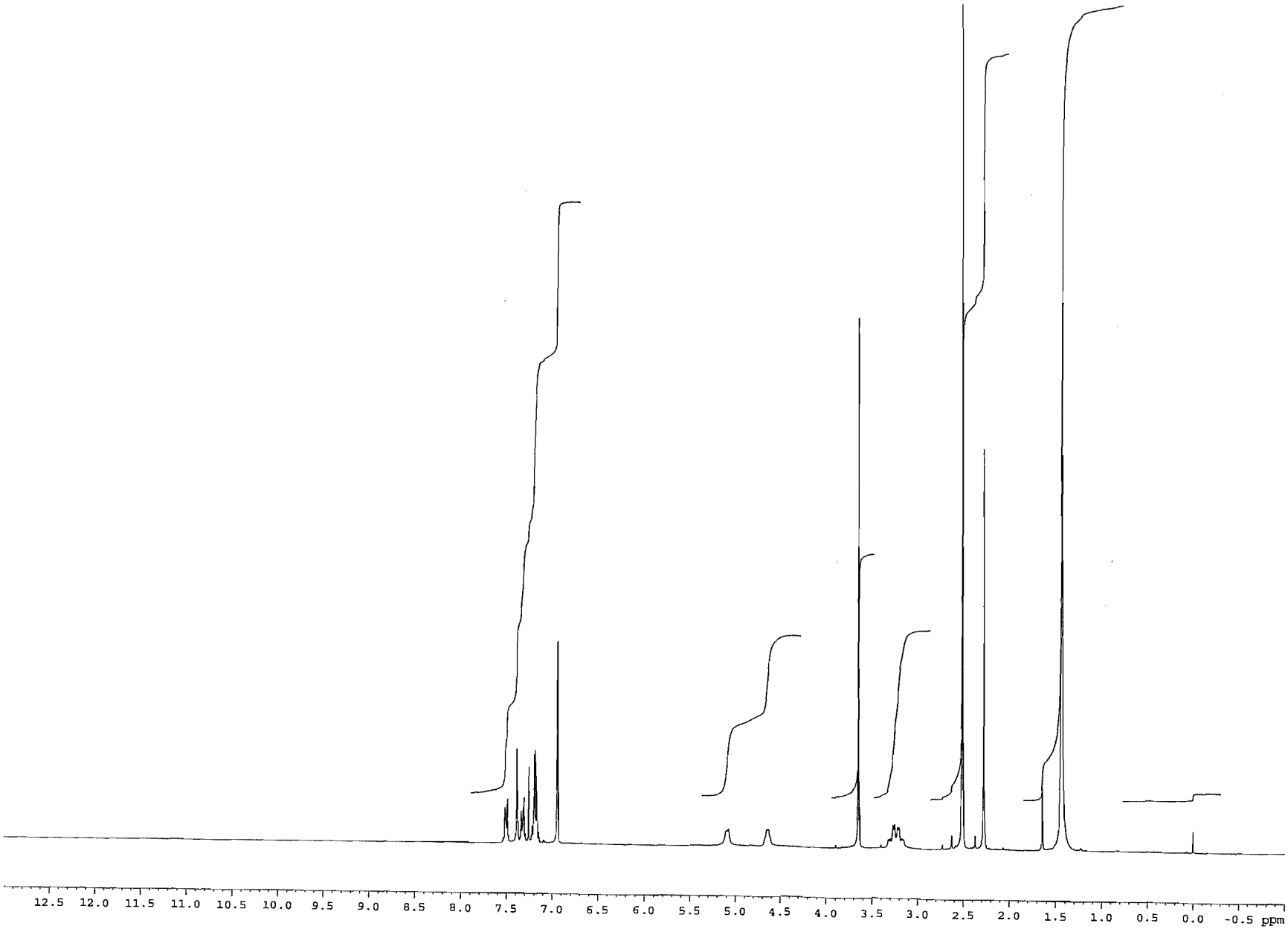
BRUKER

Current Data Parameters
NAME sel606lw2
EXPNO 10
PROCNO 1

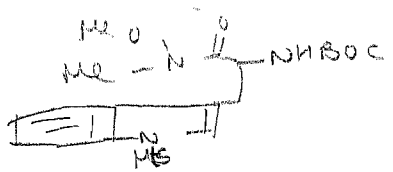
F2 - Acquisition Parameters
Date_ 20060916
Time 14.58
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 228.1
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300067 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 6.74 Hz

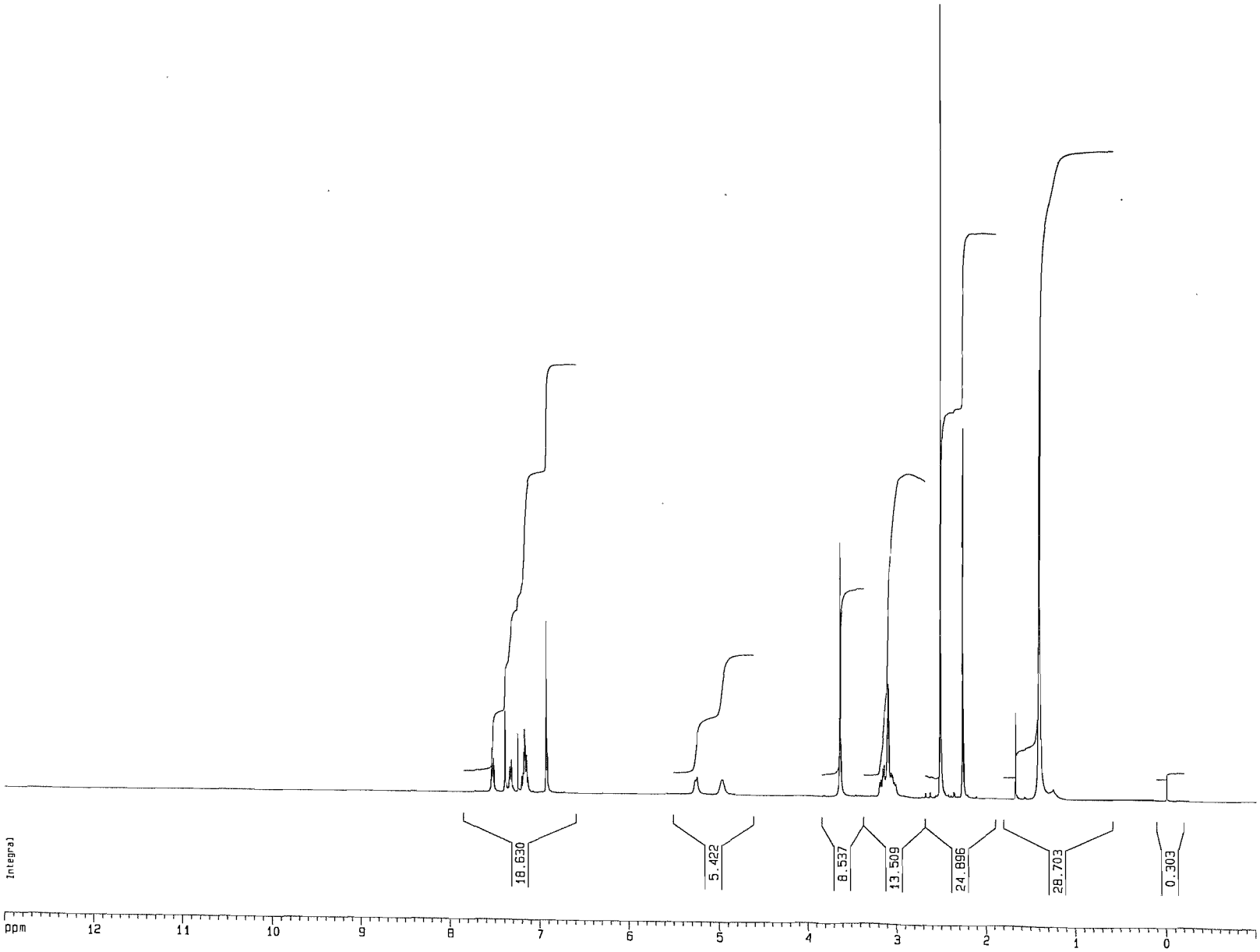


1 of 1



1w6

1.162



Current Data Parameters

NAME	se13061w2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060914
Time	6.45
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SF01	400.1324710 MHz

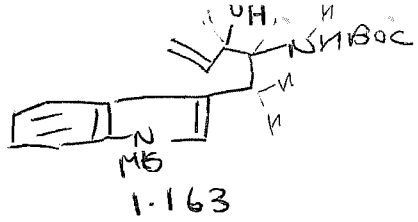
F2 - Processing parameters

SI	16384
SF	400.1300200 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	19.98 Hz

1D NMR plot parameters

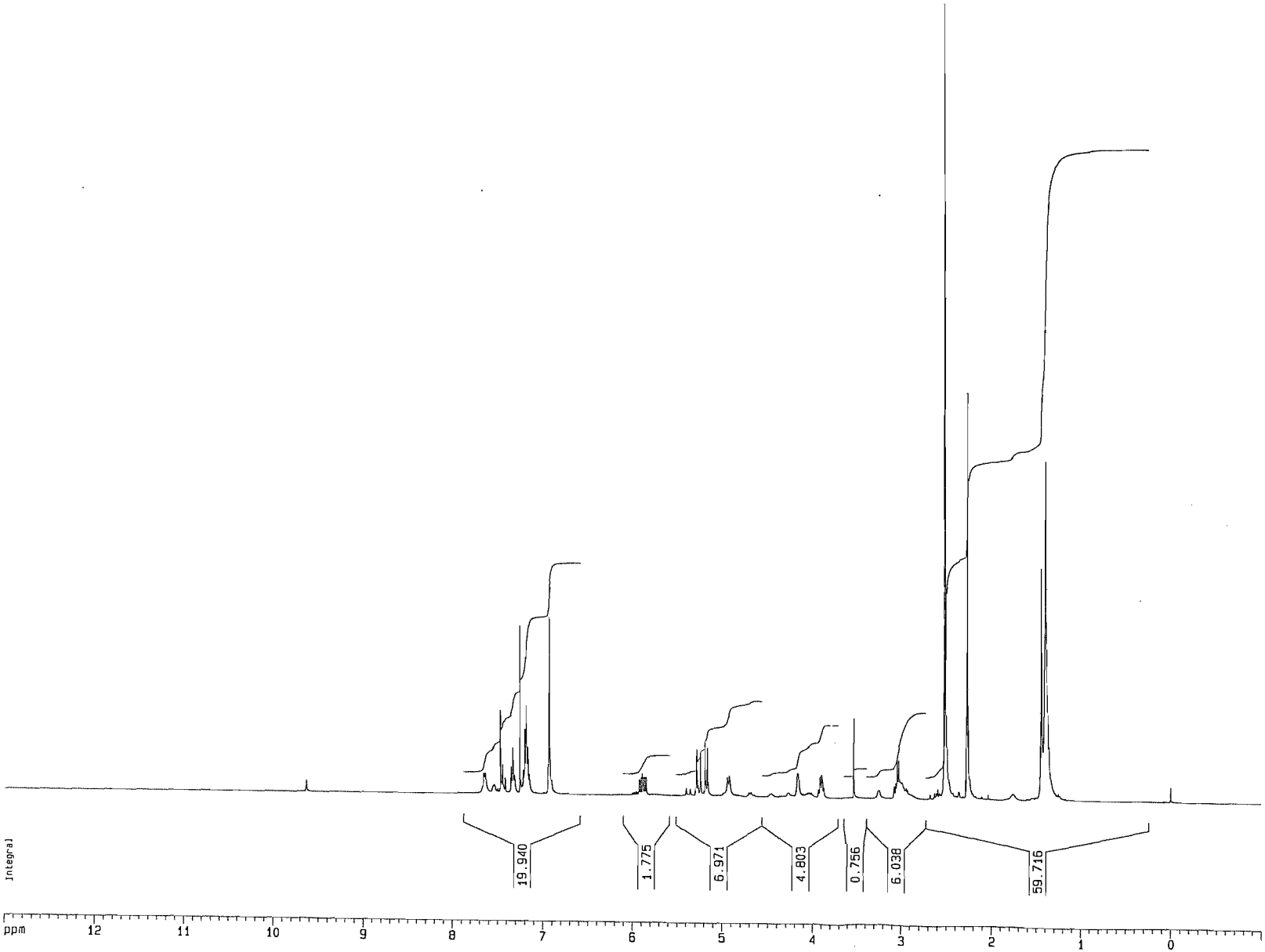
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm

1.162



1.163

lw40



Current Data Parameters

NAME	se16061w6
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060917
Time	21.25
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

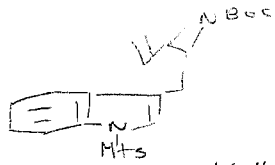
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

SI	16384
SF	400.1300221 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	22.11 Hz

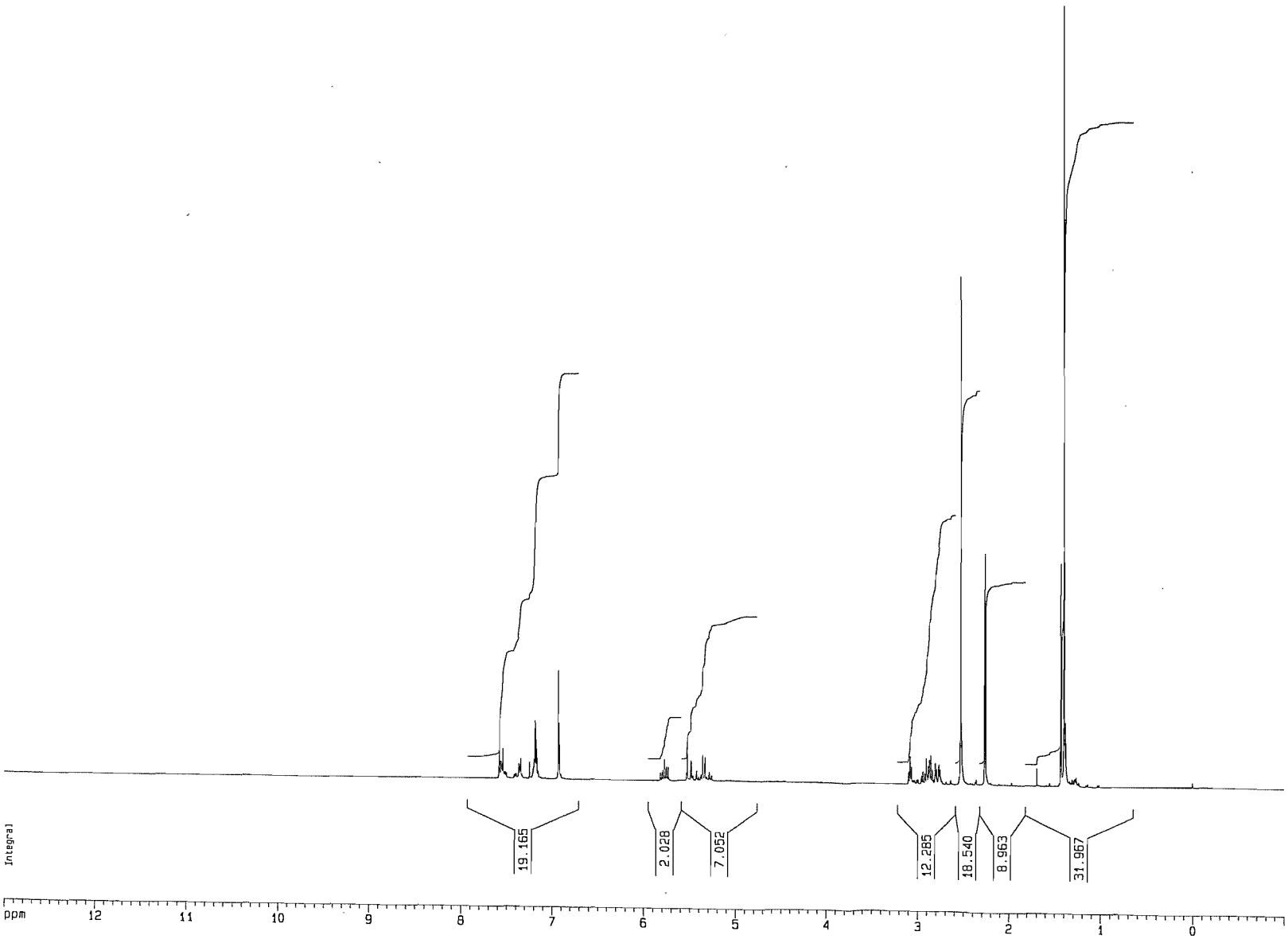
1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm



1.164

lw41



Current Data Parameters

NAME	se19061w2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060920
Time	4.44
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	28.5
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

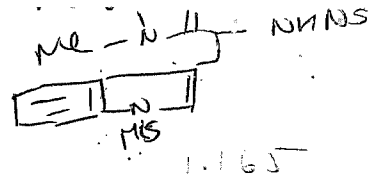
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

SI	16384
SF	400.1300245 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	24.46 Hz

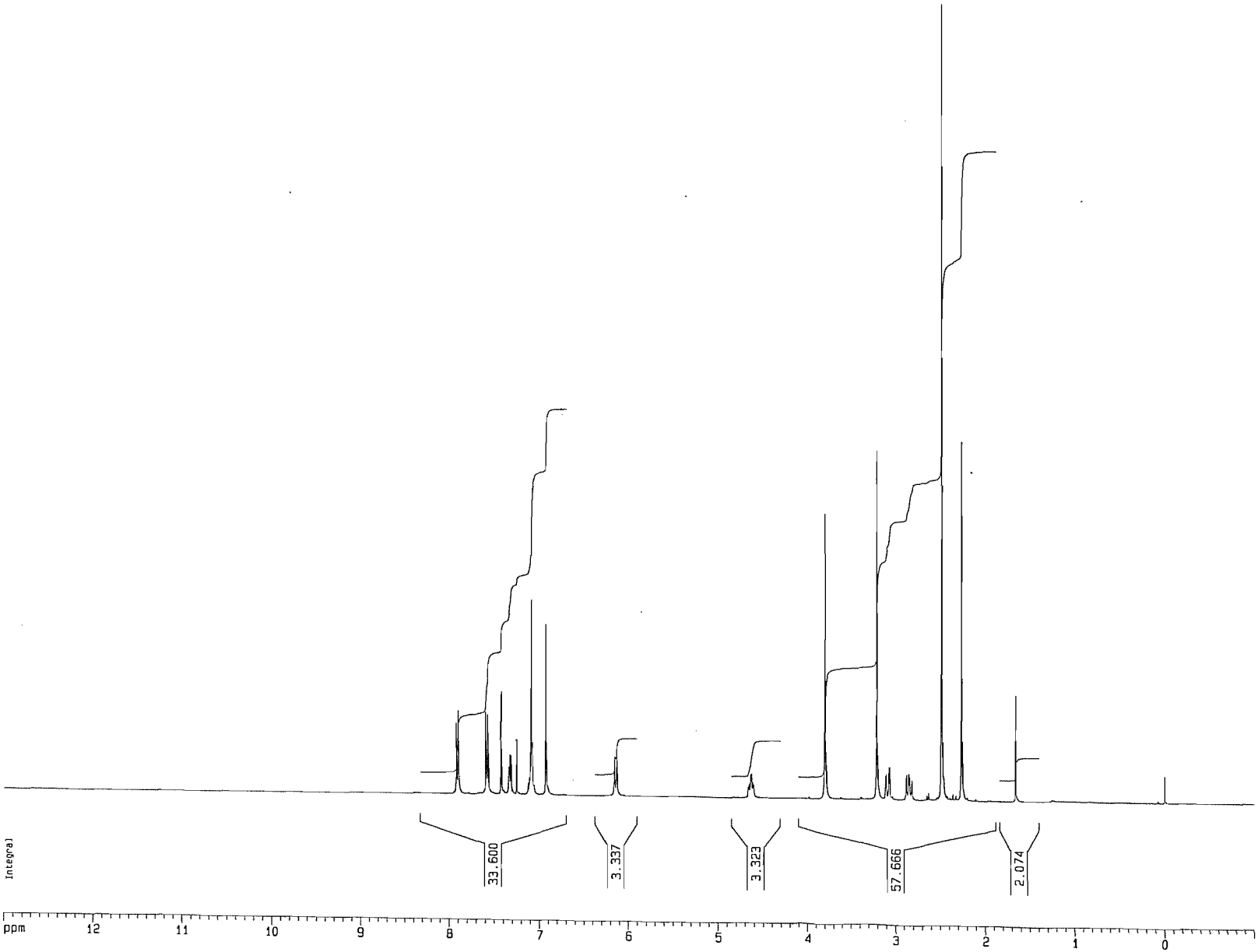
1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm



1.165

lw39



Current Data Parameters

NAME	se16061w5
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060917
Time	19.38
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

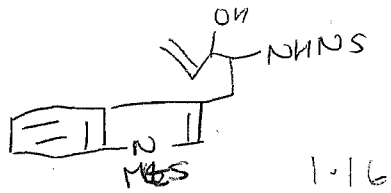
F2 - Processing parameters

SI	16384
SF	400.1300199 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	19.92 Hz

1D NMR plot parameters

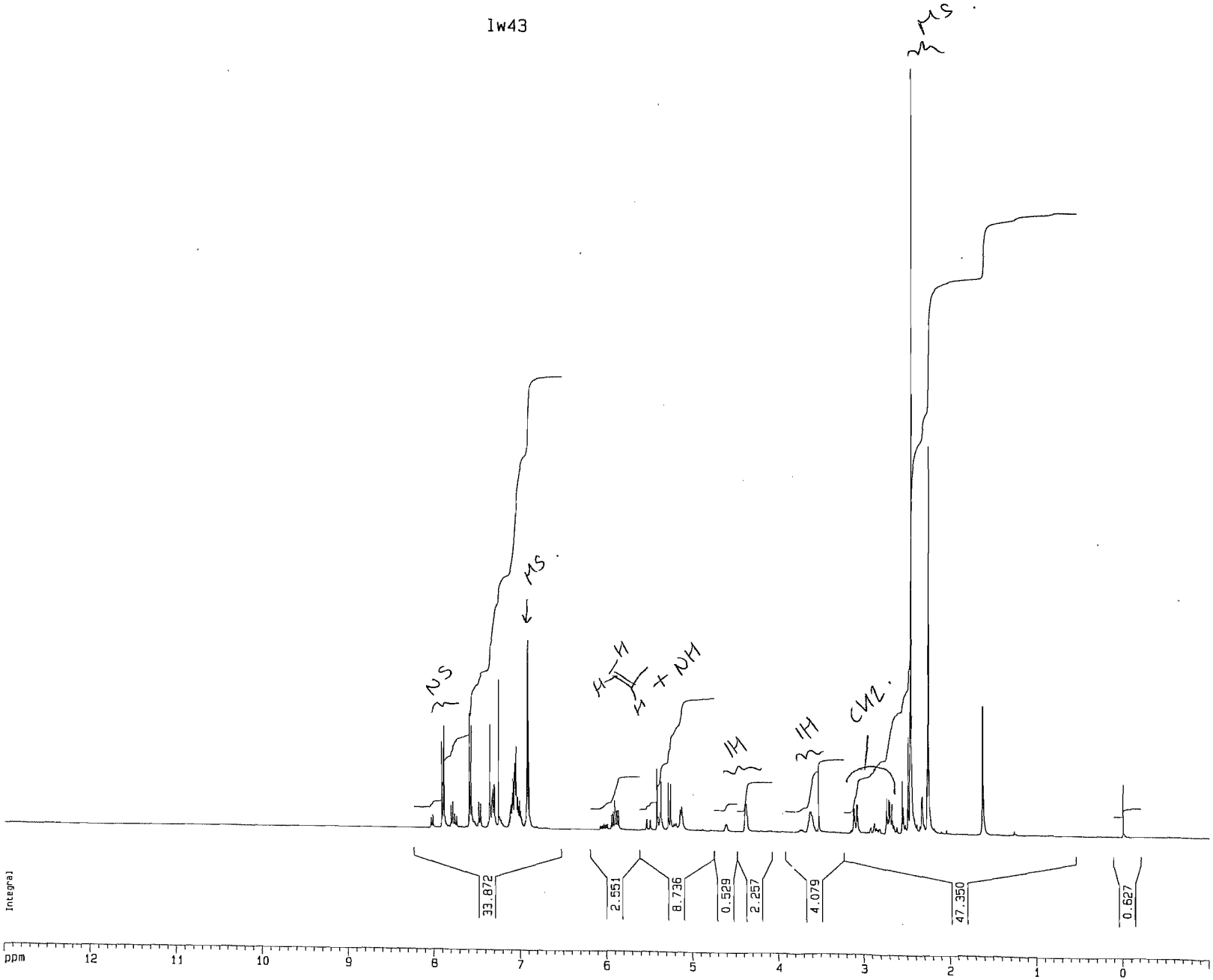
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm

S9



1.166

lw43



Current Data Parameters

NAME	se1806lw3
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060919
Time	3.09
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	64
OS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

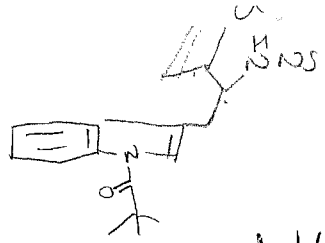
F2 - Processing parameters

SI	16384
SF	400.1300206 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.56 Hz

1D NMR plot parameters

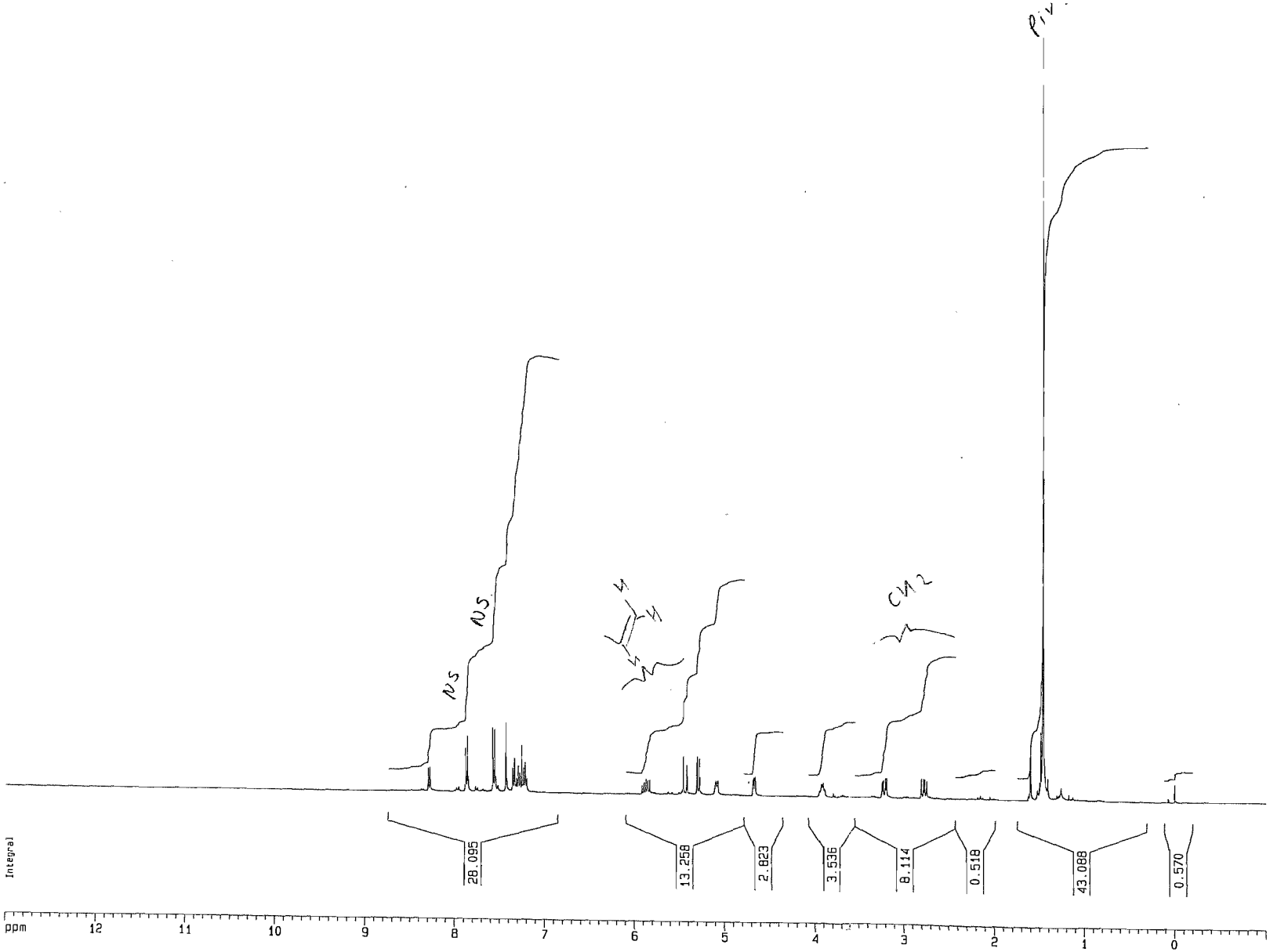
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

Extra → NH



1.168

lw4599/37f13-16



Current Data Parameters

NAME	my1606lw2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060516
Time	18.05
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	32
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	161.3
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

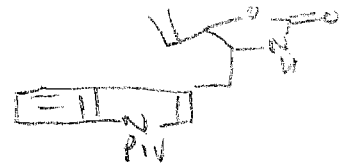
F2 - Processing parameters

SI	16384
SF	400.1300206 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.55 Hz

1D NMR plot parameters

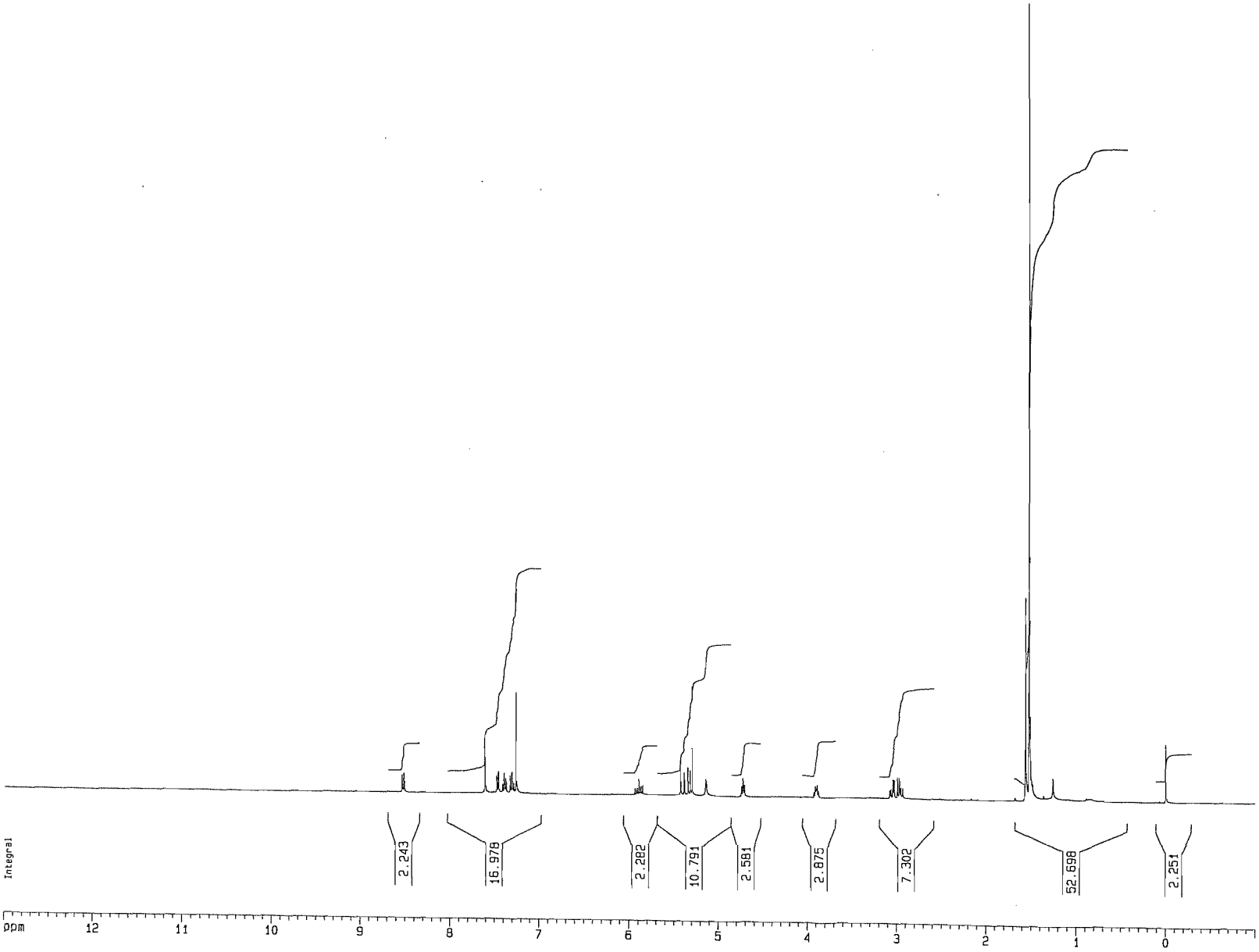
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

2911



1.169

lw4599/51/1 f19

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Current Data Parameters
NAME                oc2006ac8
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20061021
Time                    2.06
INSTRUM                spect
PROBHD      5 mm Dual 13
PULPROG                   zg
TD                     32768
SOLVENT                CDCl3
NS                        64
DS                         2
SWH                8223.685 Hz
FIDRES             0.250967 Hz
AQ                 1.9923444 sec
RG                       362
DW                  60.800 usec
DE                   6.00 usec
TE                   300.0 K
D1                 1.00000000 sec

============ CHANNEL f1 =============
NUC1                       1H
P1                   10.30 usec
PL1                   0.00 dB
SFO1              400.1324710 MHz

F2 - Processing parameters
SI                       16384
SF                400.1300206 MHz
WDW                        EM
SSB                         0
LB                    0.30 Hz
GB                          0
PC                       1.00
SA                    20.59 Hz

1D NMR plot parameters
CX                   30.00 cm
F1P                 13.000 ppm
F1                  5201.69 Hz
F2P                 -1.000 ppm
F2                  -400.13 Hz
PPMCM               0.46667 ppm/cm
HZCM              186.72736 Hz/cm
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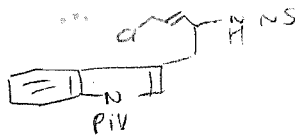
1.169

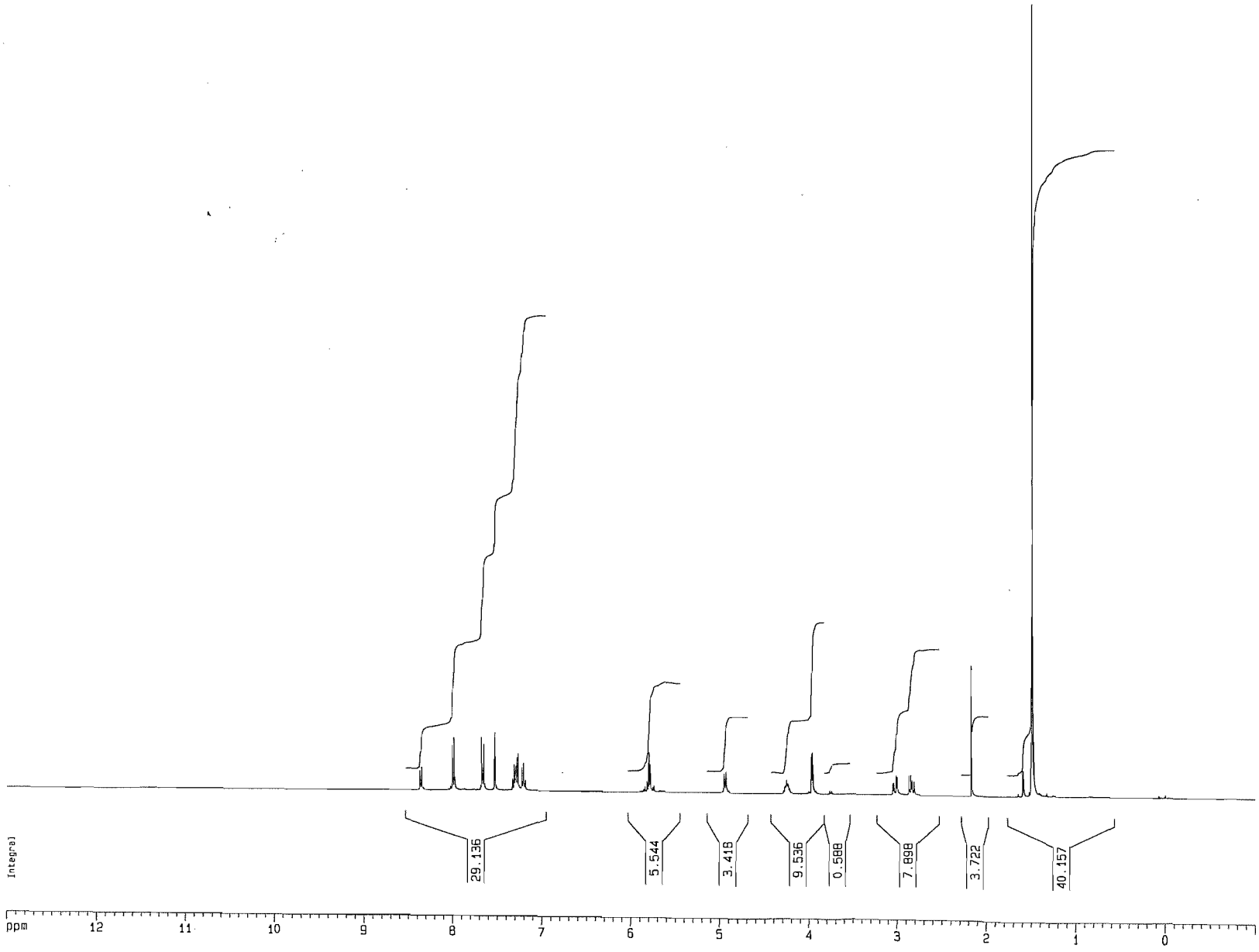


al adduct
aziridine
opened

@ 0 °C

1.17a

lw4599/55



Current Data Parameters

NAME	ju23061w1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060624
Time	0.32
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	161.3
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

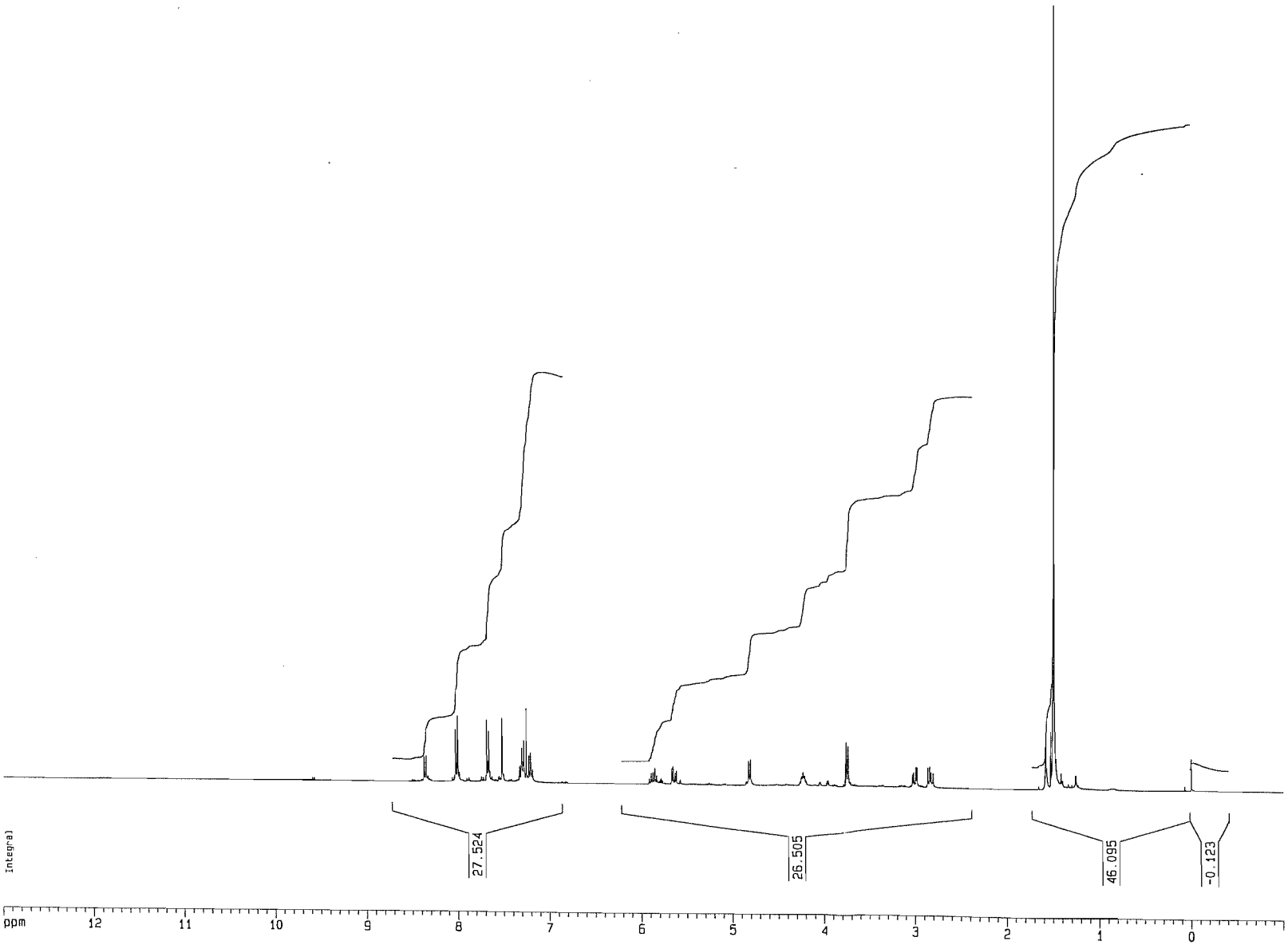
SI	16384
SF	400.1300201 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.12 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm

1.17a

lw4599/51/3



Current Data Parameters

NAME	oc2006ac7
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20061020
Time	21.50
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	228.1
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

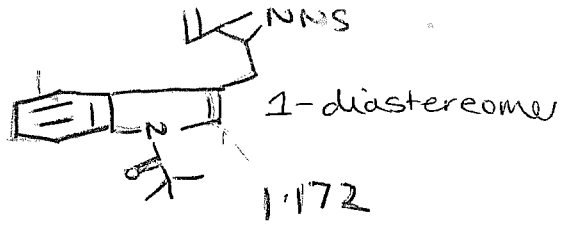
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

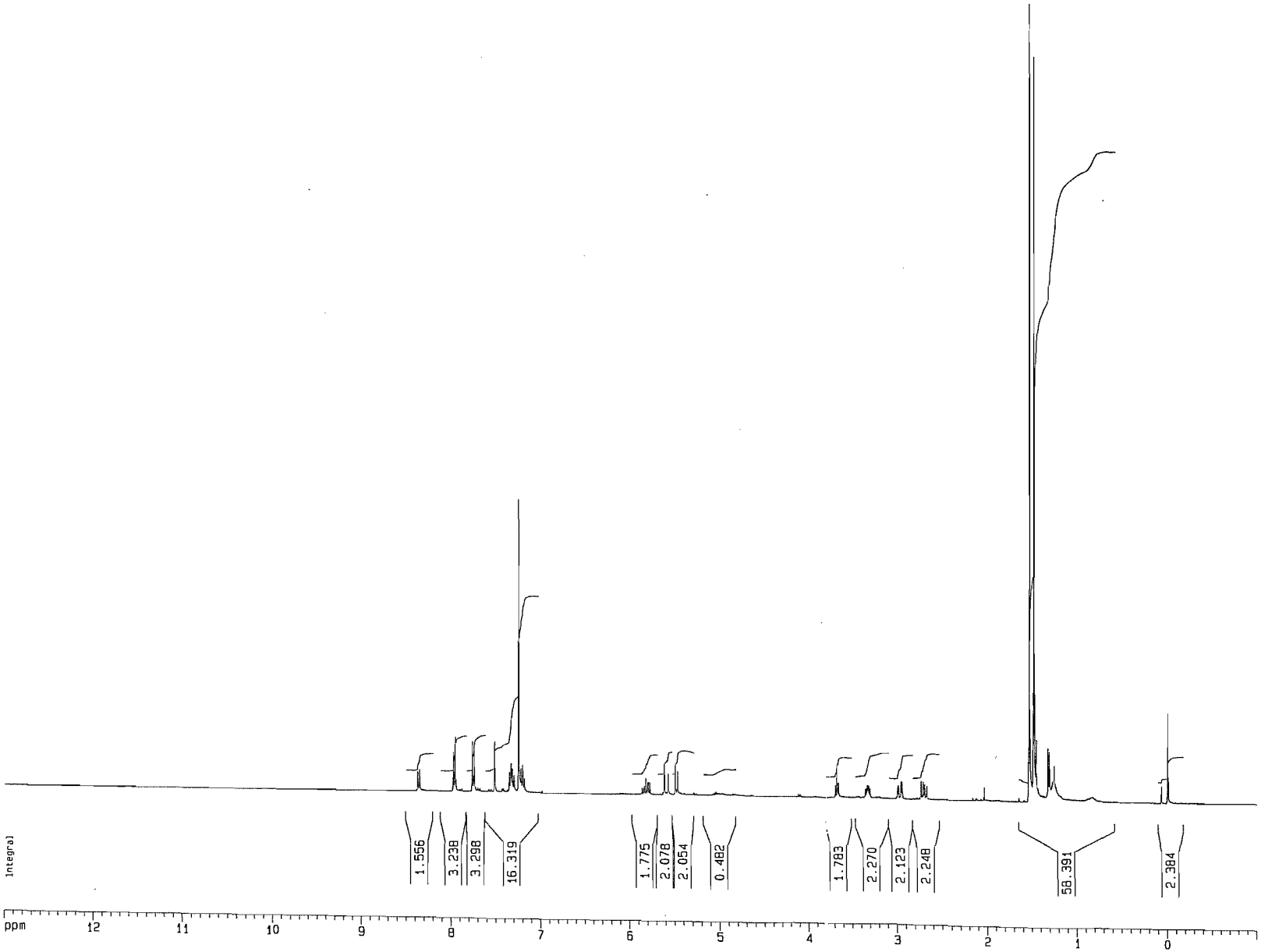
SI	16384
SF	400.1300205 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.49 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm



LW4599/45




```
Current Data Parameters
NAME                  ju07061w1
EXPNO                         1
PROCNO                        1

F2 - Acquisition Parameters
Date_                  20060607
Time                      23.59
INSTRUM                   spect
PROBHD      5 mm Dual 13
PULPROG                     zg
TD                       32768
SOLVENT                  CDCl3
NS                          16
DS                           2
SWH                 8223.685 Hz
FIDRES              0.250967 Hz
AQ                  1.9923444 sec
RG                      456.1
DW                     60.800 usec
DE                      6.00 usec
TE                     300.0 K
D1                  1.00000000 sec

============ CHANNEL f1 =============
NUC1                        1H
P1                     10.30 usec
PL1                     0.00 dB
SFO1              400.1324710 MHz

F2 - Processing parameters
SI                       16384
SF                400.1300209 MHz
WDW                         EM
SSB                          0
LB                      0.30 Hz
GB                           0
PC                        1.00
SR                     20.92 Hz

1D NMR plot parameters
CX                     30.00 cm
F1P                   13.000 ppm
F1                   5201.69 Hz
F2P                  -1.000 ppm
F2                  -400.13 Hz
PPMCM                0.46667 ppm/cm
HZCM               186.72736 Hz/cm
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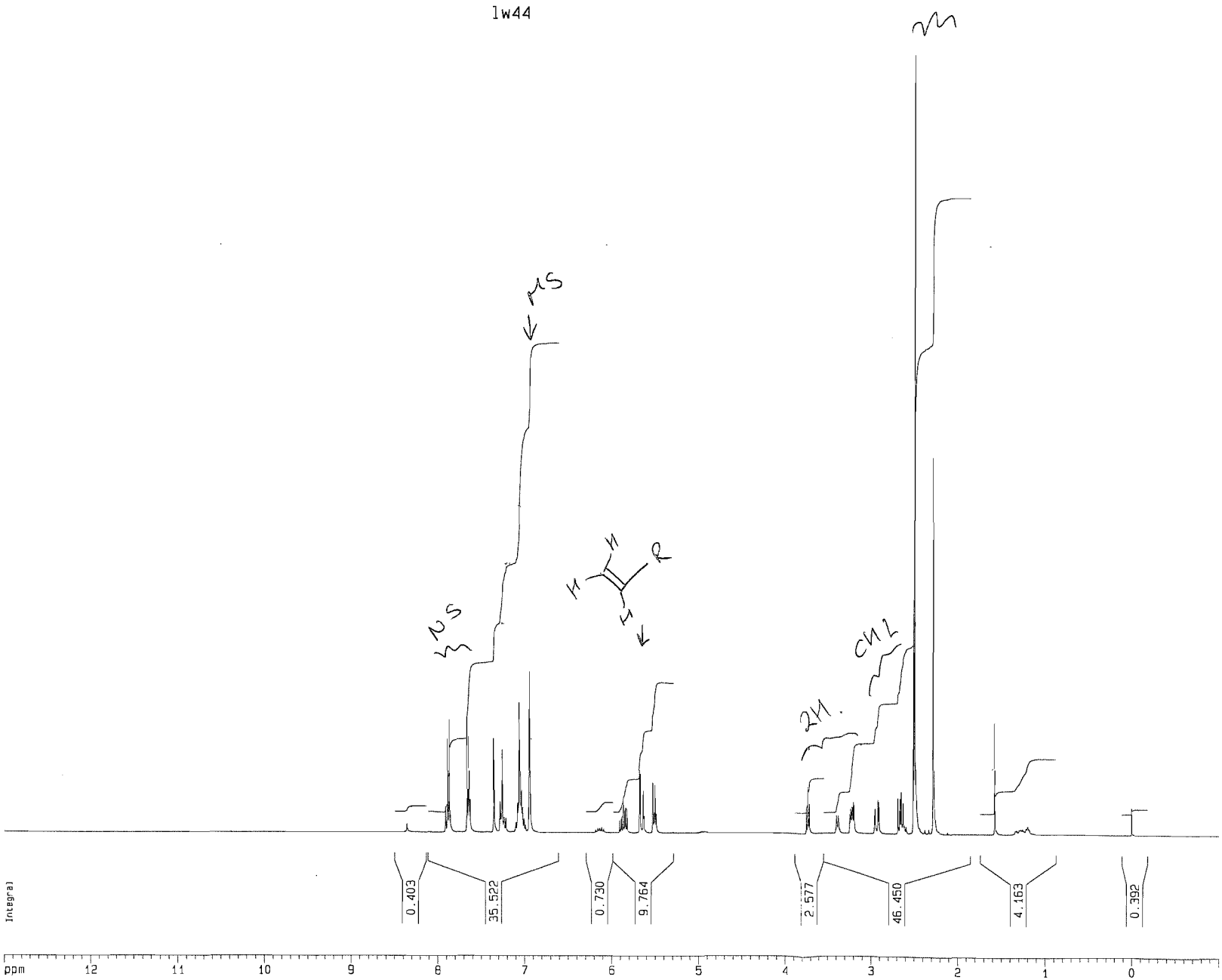
1:172

lw44



Current Data Parameters

NAME	se1806lw4
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060919
Time	5.02
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

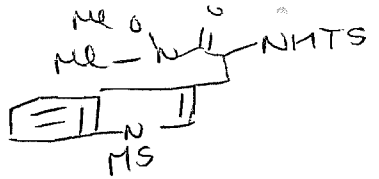
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

SI	16384
SF	400.1300206 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.56 Hz

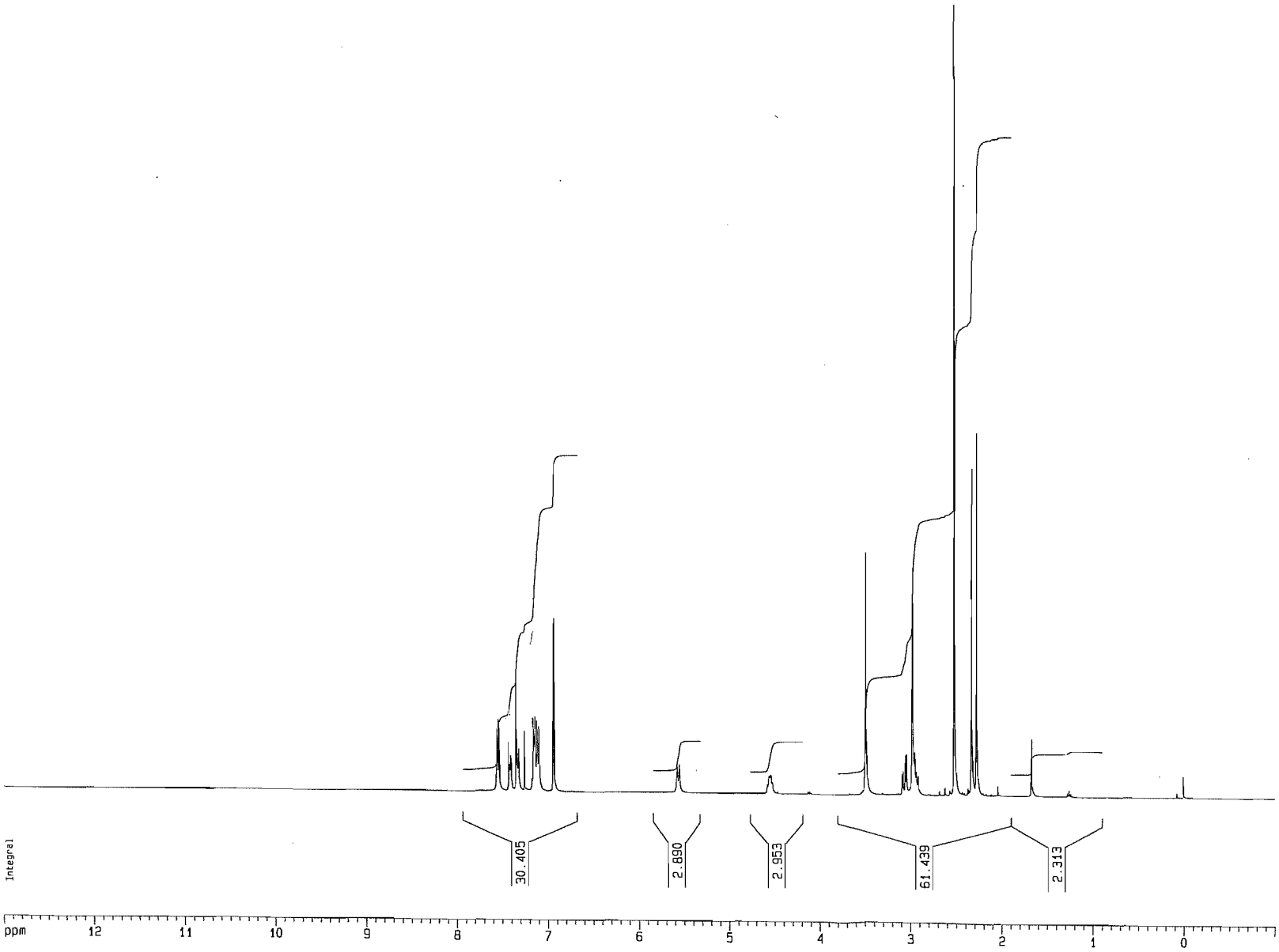
1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm



lw31

1-174



Current Data Parameters

NAME	se1606lw4
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060917
Time	18.44
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIORES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

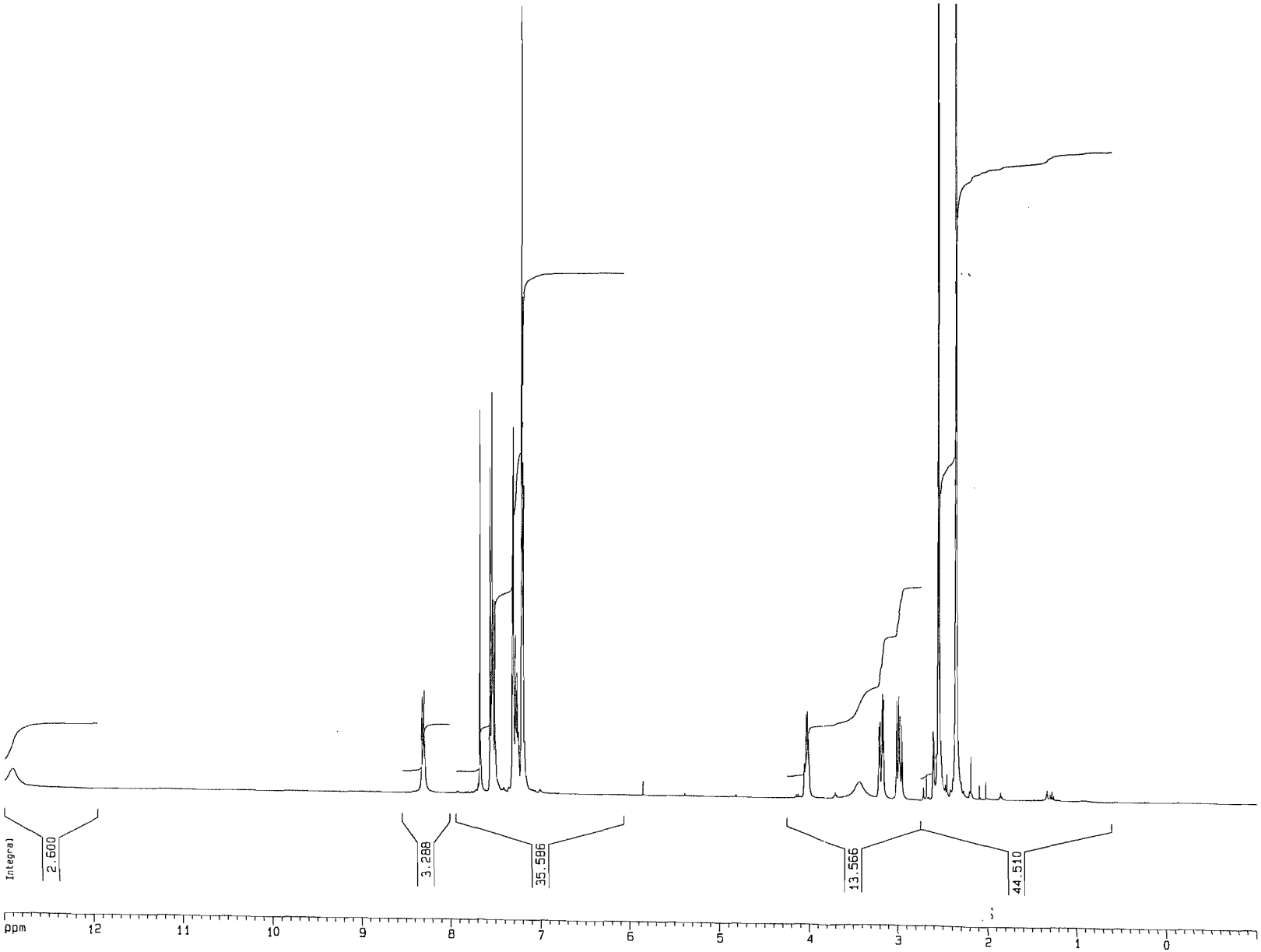
SI	16384
SF	400.1300205 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.54 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

1.175

lw4481/44 (35)



Current Data Parameters

NAME	ap26061w2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060426
Time	20.16
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	DMSO
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

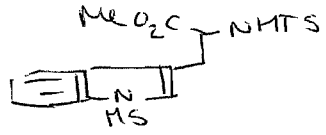
SI	16384
SF	400.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	0.00 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm

SL 1.1

LW32



1.176

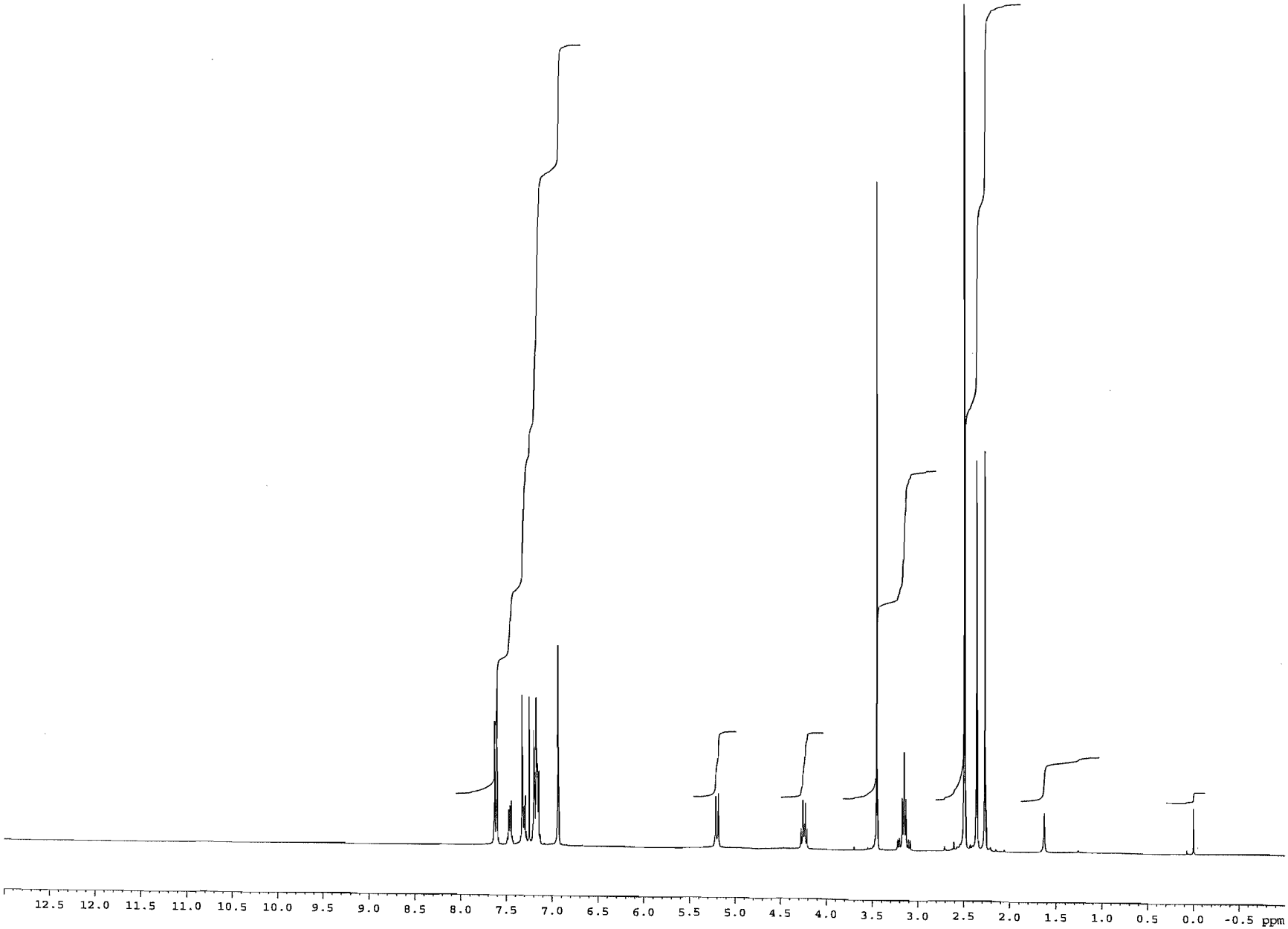
BRUKER

Current Data Parameters
NAME sel406wg3
EXPNO 10
PROCNO 1

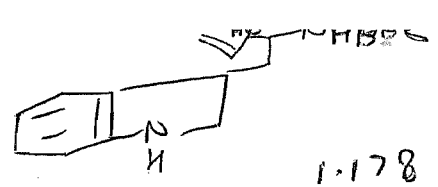
F2 - Acquisition Parameters
Date_ 20060915
Time 2.00
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 256
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300074 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 7.37 Hz

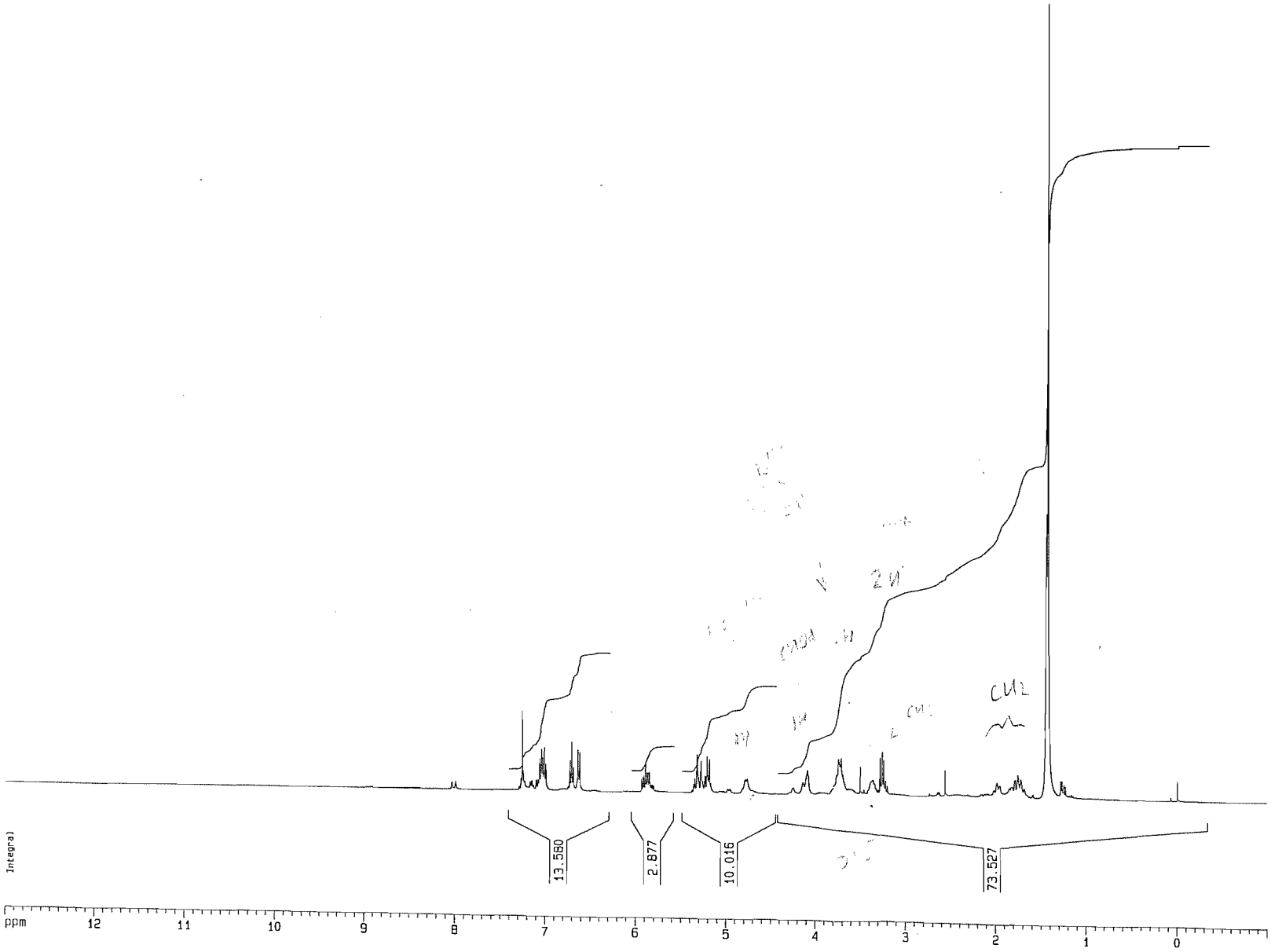


1.176



1.178

lw46

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Current Data Parameters
NAME                se22061w2
EXPNO                       1
PROCNO                      1

F2 - Acquisition Parameters
Date_              20060922
Time                  19.14
INSTRUM               spect
PROBHD     5 mm Dual 13
PULPROG                  zg
TD                    32768
SOLVENT               CDCl3
NS                       64
DS                        2
SWH               8223.685 Hz
FIDRES            0.250967 Hz
AQ                1.9923444 sec
RG                       57
DW                  60.800 usec
DE                   6.00 usec
TE                   300.0 K
D1               1.00000000 sec

============ CHANNEL f1 =============
NUC1                     1H
P1                  10.30 usec
PL1                  0.00 dB
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                    16384
SF              400.1300206 MHz
WDW                      EM
SSB                       0
LB                   0.30 Hz
GB                        0
PC                     1.00
SR                  20.61 Hz

1D NMR plot parameters
CX                  30.00 cm
F1P                13.000 ppm
F1                 5201.69 Hz
F2P                -1.000 ppm
F2                 -400.13 Hz
PPMCM             0.46667 ppm/cm
HZCM            186.72736 Hz/cm
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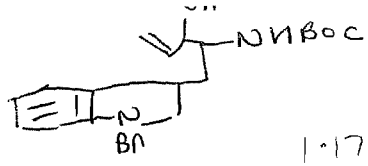
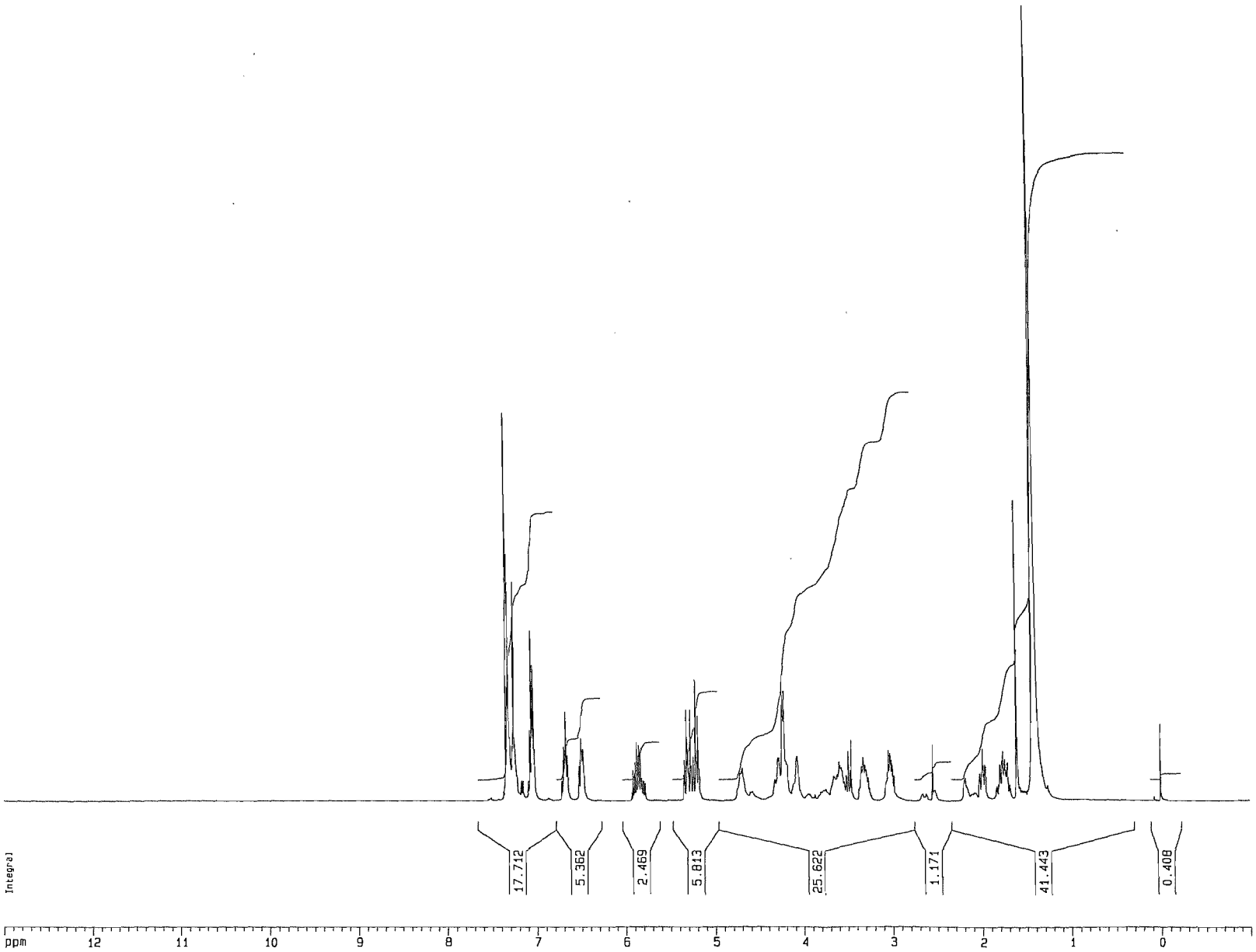
1.178



1.179

lw49



Current Data Parameters

NAME	se24061w1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060924
Time	20.41
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

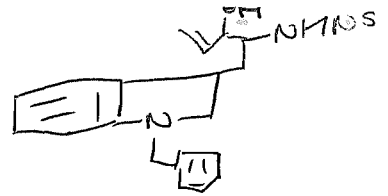
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

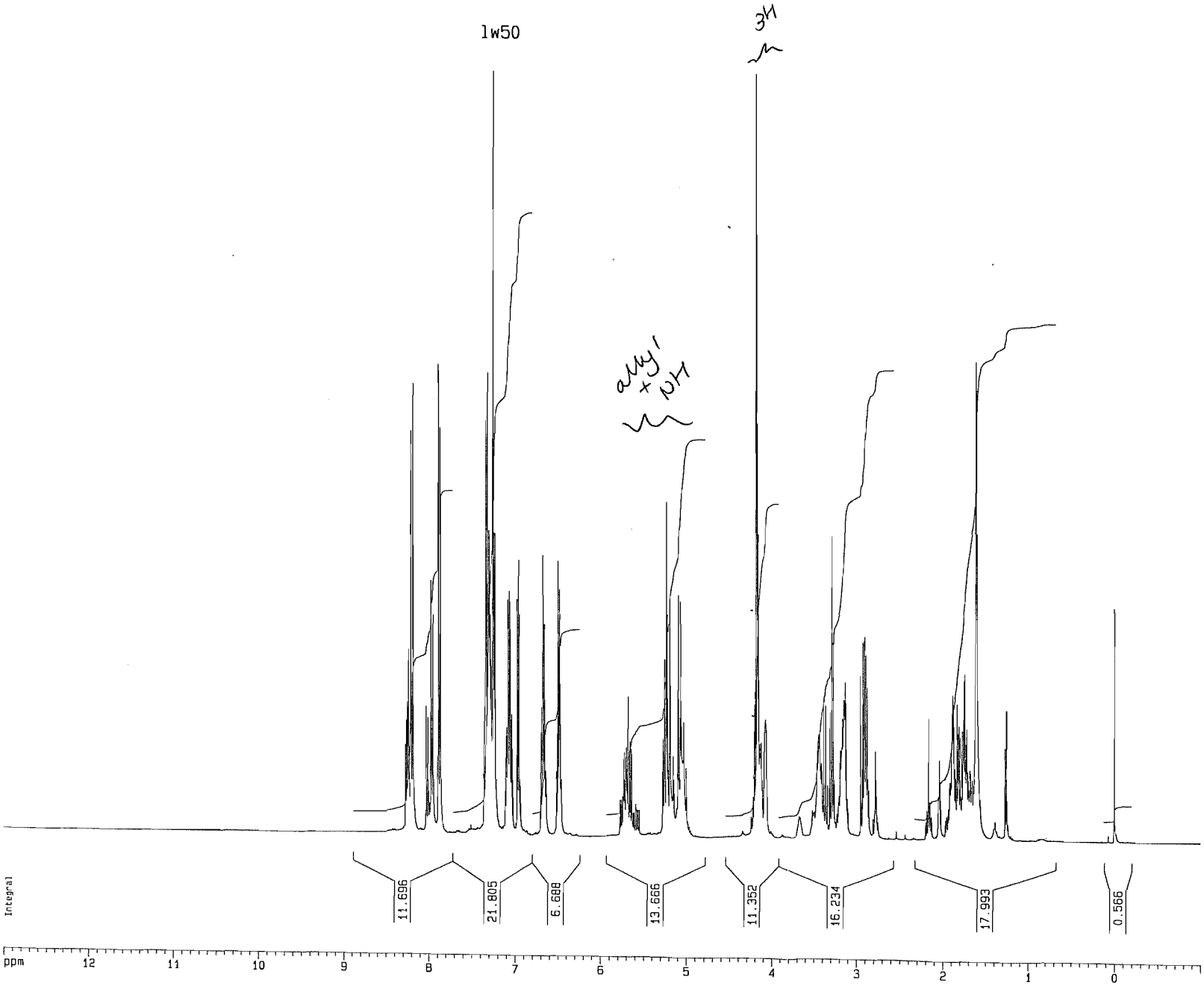
SI	16384
SF	400.1300237 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	23.74 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm



1-180



Current Data Parameters

NAME	se24061w2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060924
Time	23.31
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	. zg
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

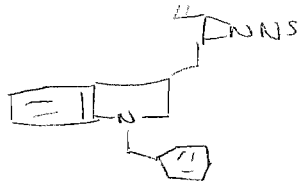
F2 - Processing parameters

SI	16384
SF	400.1300226 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	22.62 Hz

1D NMR plot parameters

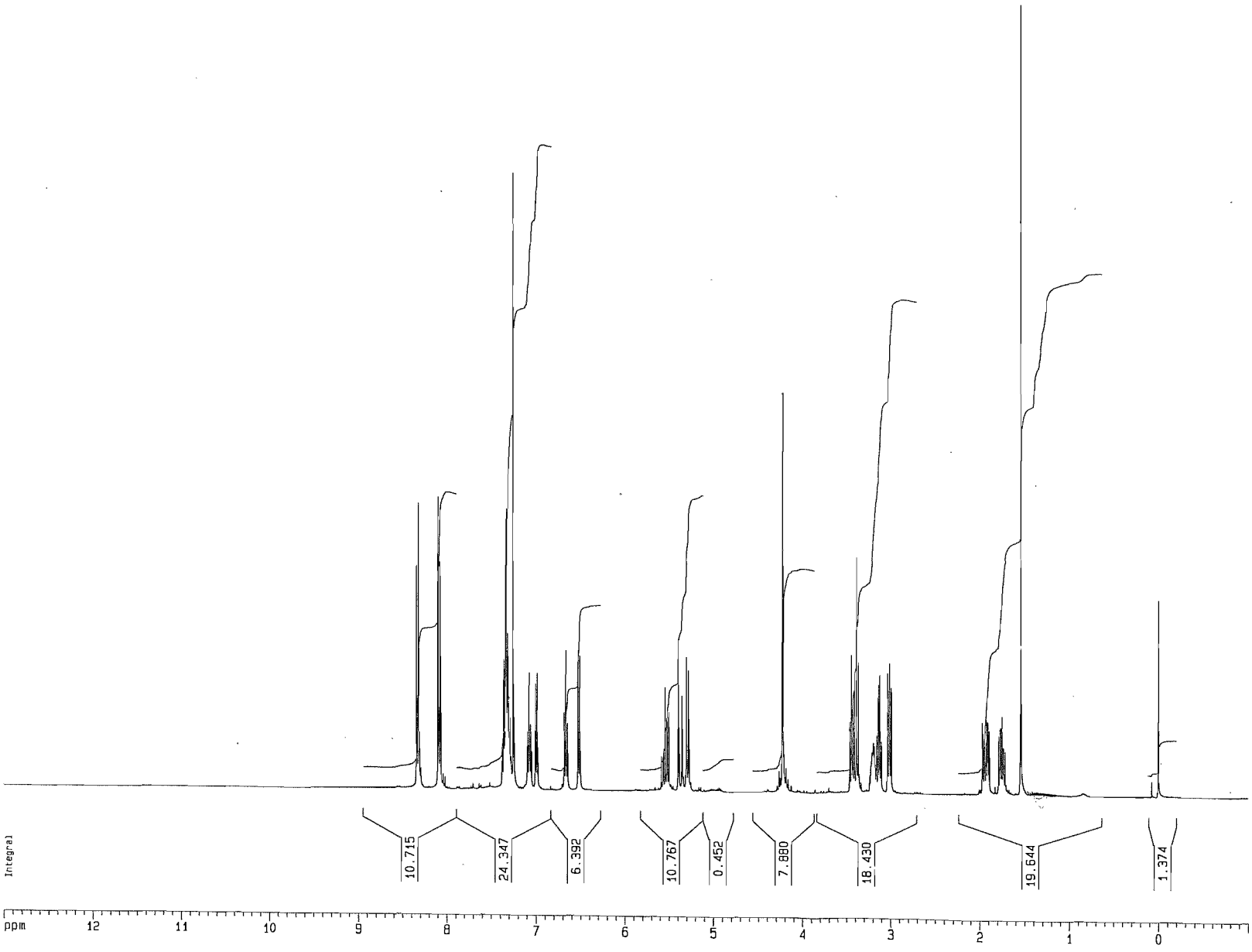
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

1-180



1.181

lw4599/35



Current Data Parameters

NAME	my1506lw2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060515
Time	20.02
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	32
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	228.1
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

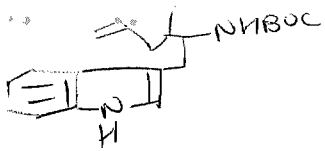
F2 - Processing parameters

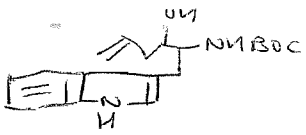
SI	16384
SF	400.1300220 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	22.05 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

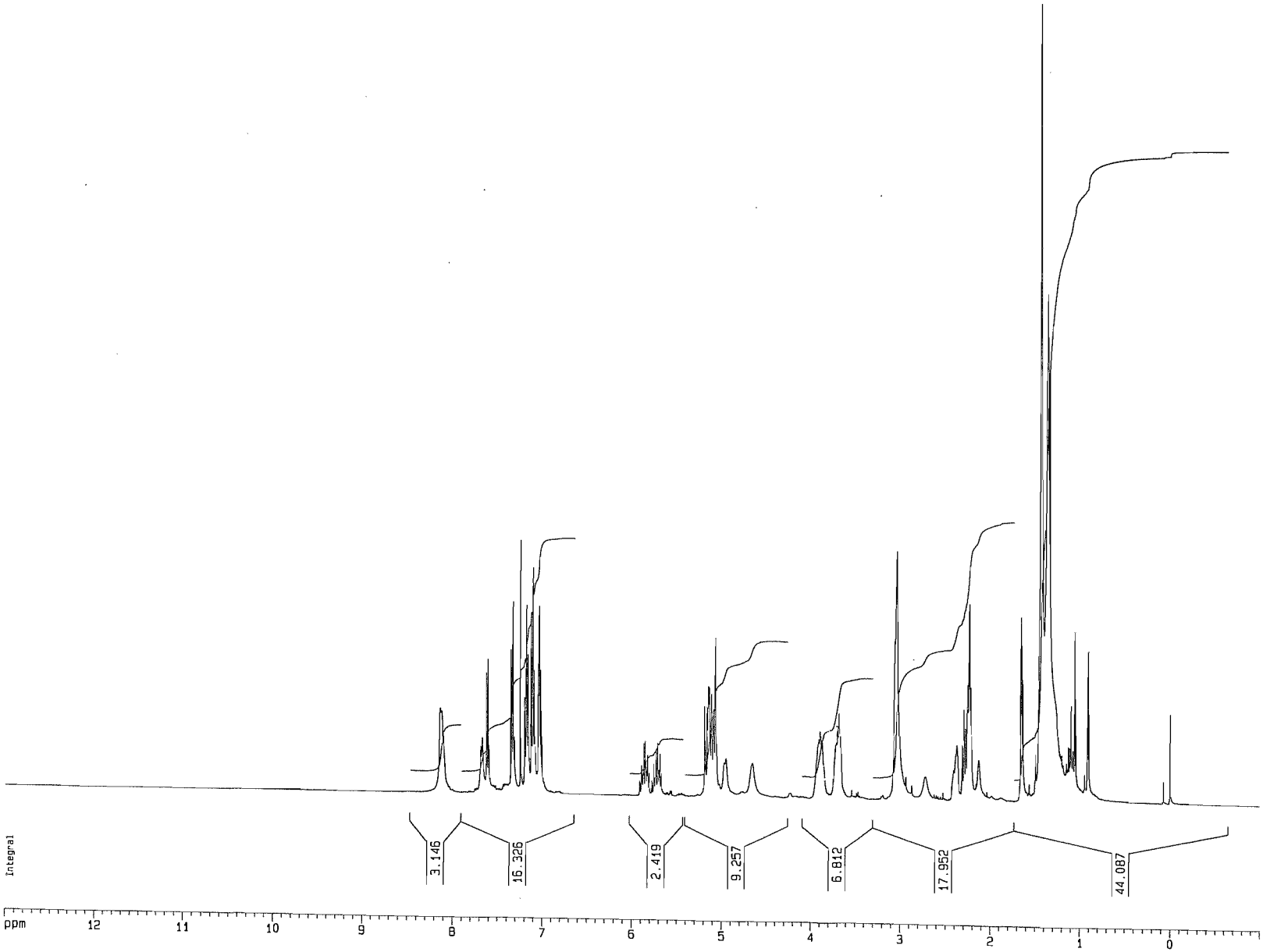
1.181





1.183

lw60



Current Data Parameters

NAME	se29061w1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060929
Time	17.43
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

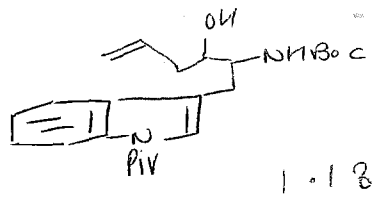
F2 - Processing parameters

SI	16384
SF	400.1300232 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	23.16 Hz

1D NMR plot parameters

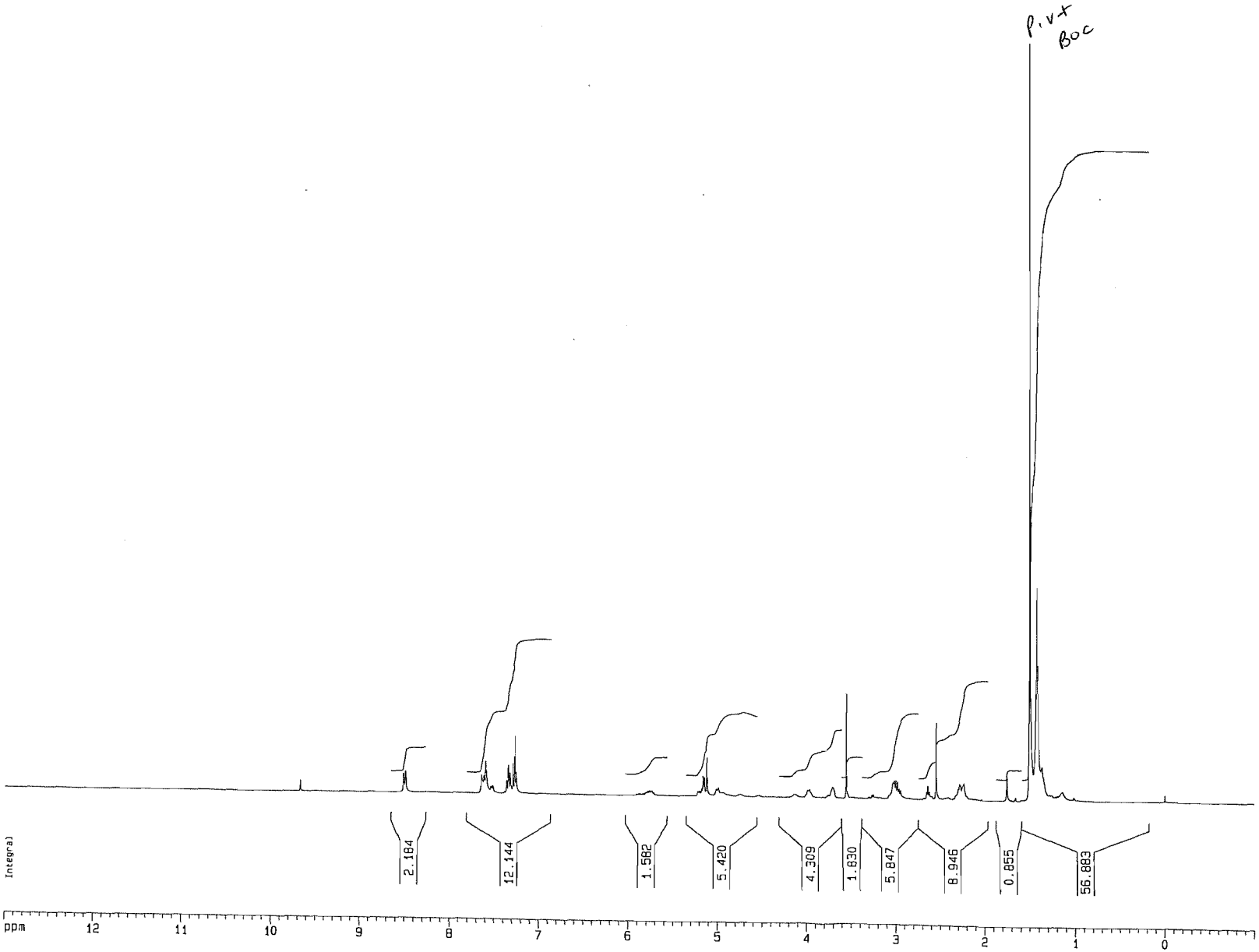
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

1.184



1.184

lw57



Current Data Parameters

NAME	se2706lw2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060927
Time	22.27
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	28.5
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

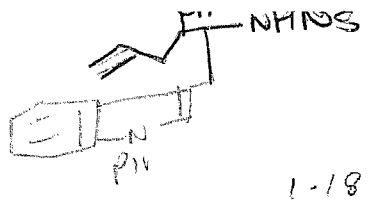
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

SI	16384
SF	400.1300207 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.71 Hz

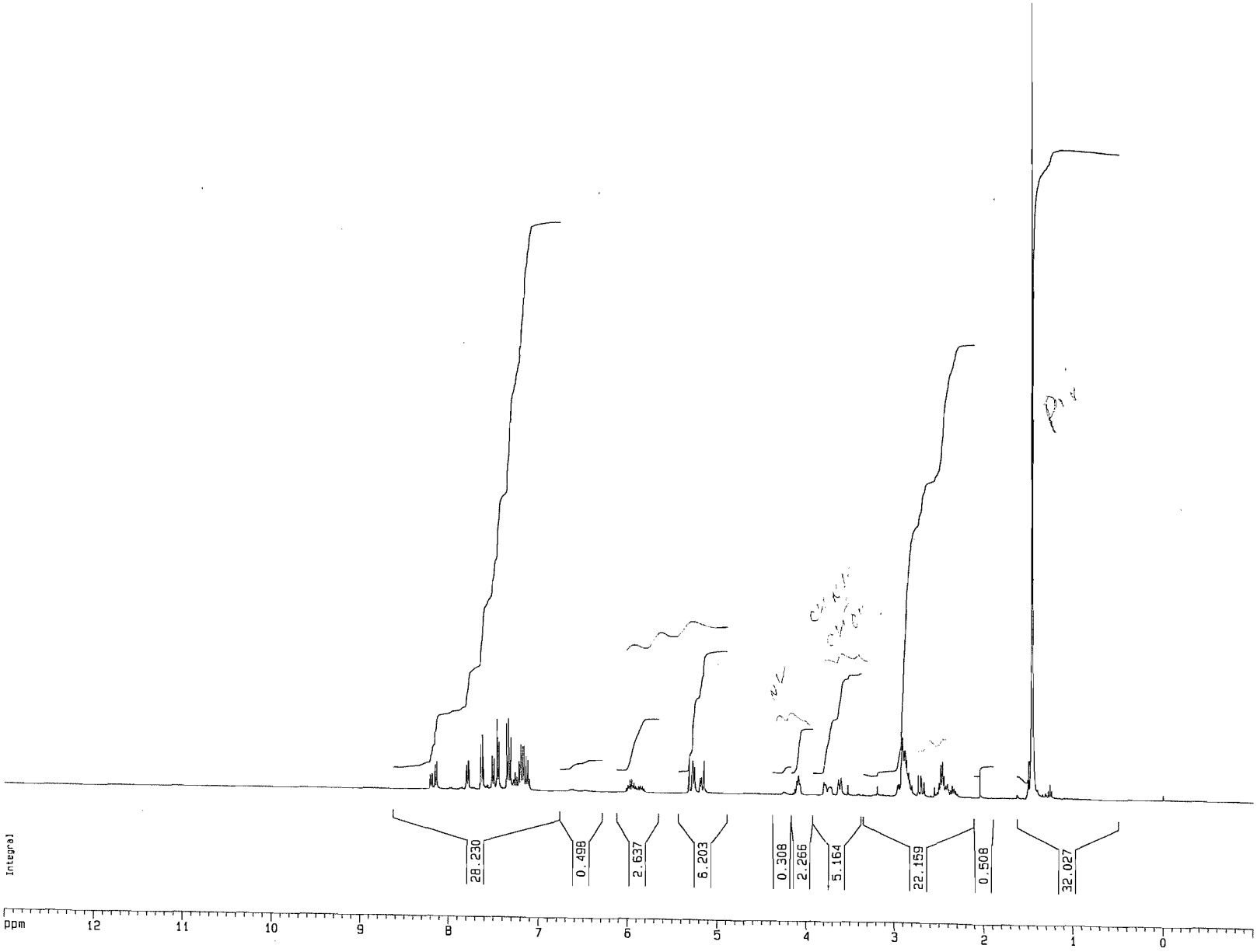
1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm



1-185

lw58



Current Data Parameters

NAME	se21061w3
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060922
Time	3.39
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

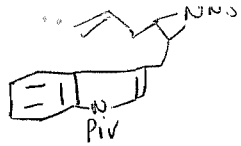
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

SI	16384
SF	400.1299983 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	-1.73 Hz

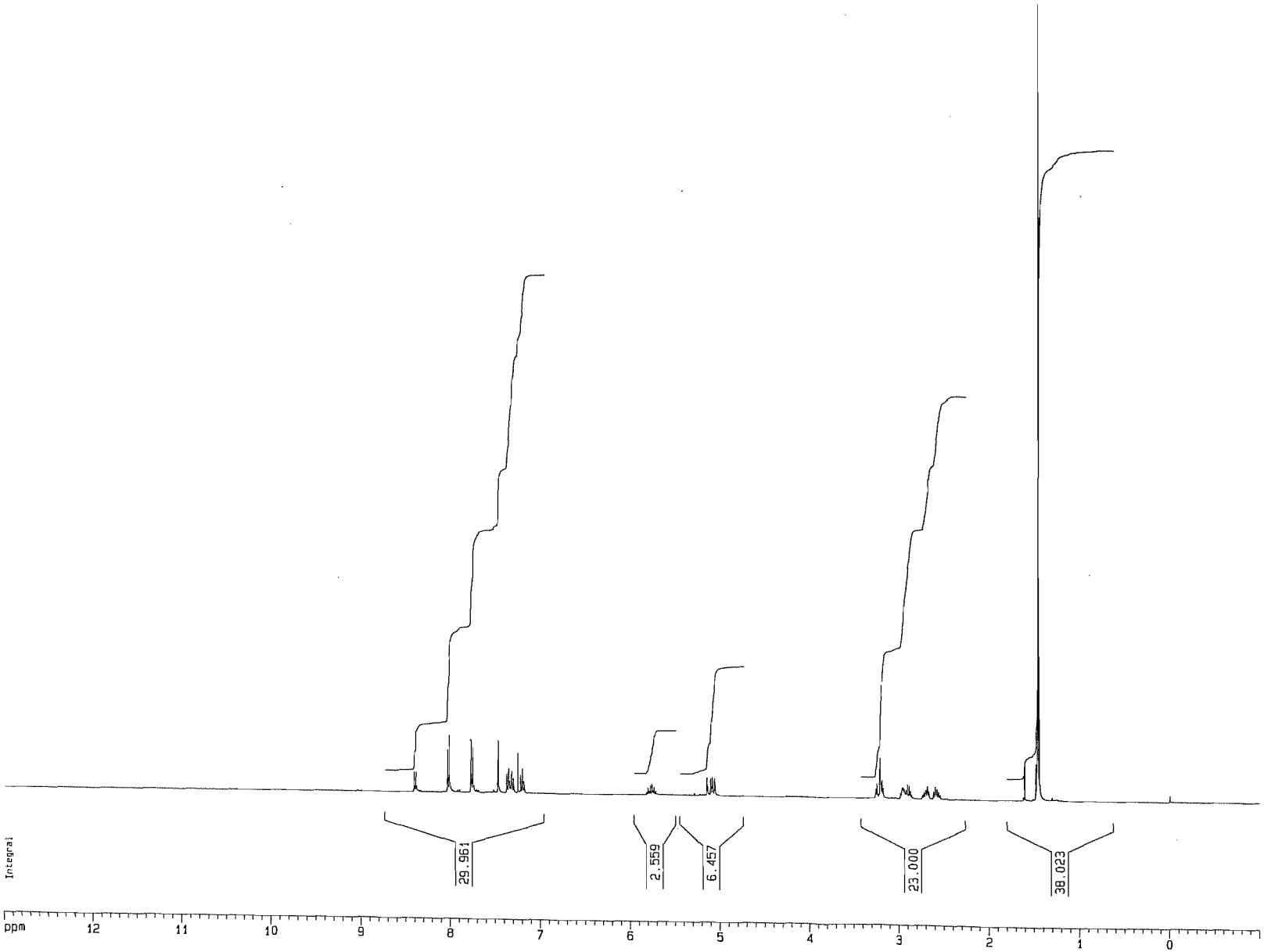
1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm



1.186

lw59



Current Data Parameters

NAME	se27061w3
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20060928
Time	0.05
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

SI	16384
SF	400.1300200 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.02 Hz

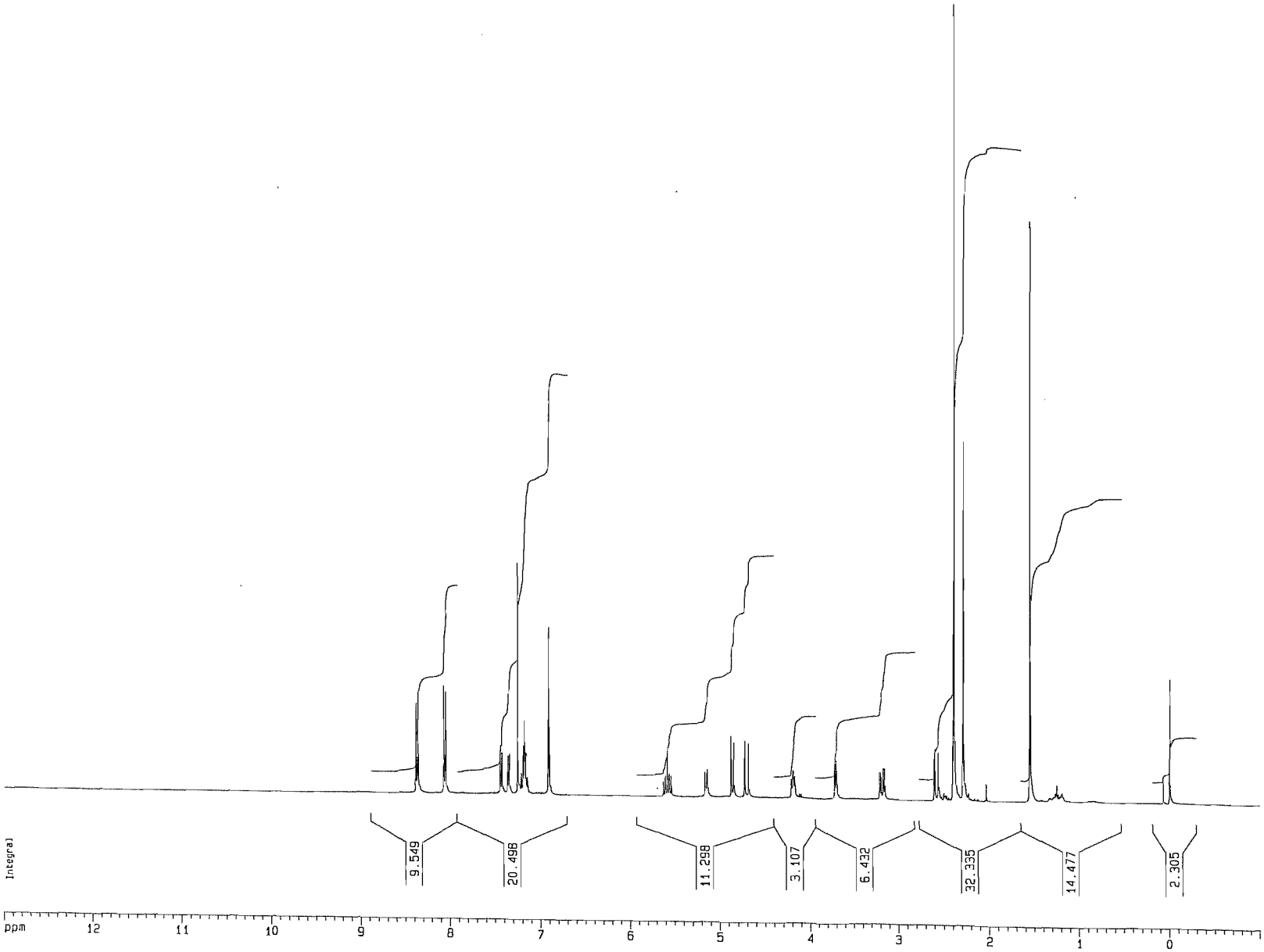
1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72734 Hz/cm

1.187

1.188

lw45



Current Data Parameters
NAME se2206lw1
EXPNO 1
PROCND 1

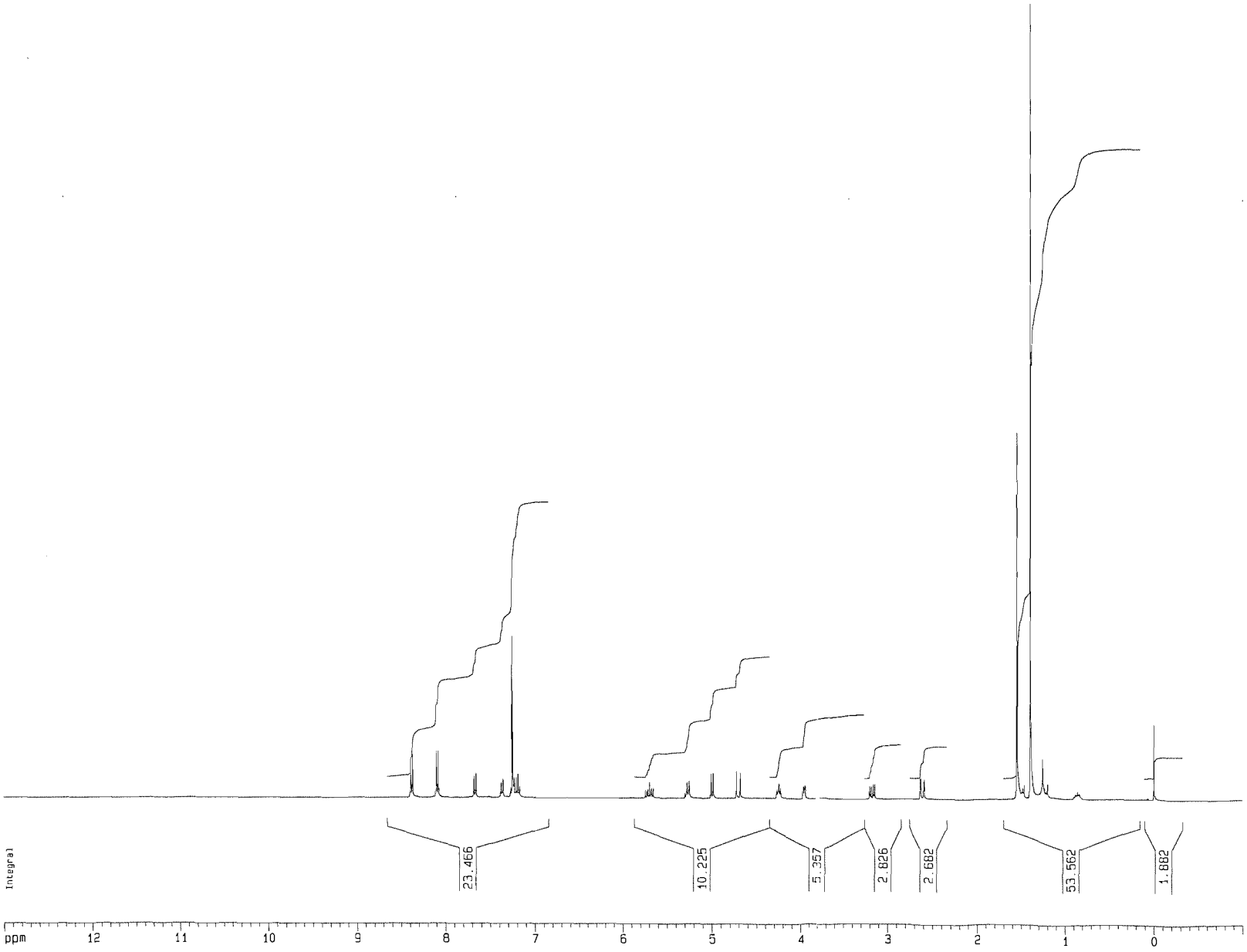
F2 - Acquisition Parameters
Date_ 20060922
Time 15.35
INSTRUM spect
PROBHD 5 mm Dual 13
PULPROG zg
TD 32768
SOLVENT CDCl3
NS 128
DS 2
SWH 8223.685 Hz
FIDRES 0.250967 Hz
AQ 1.9923444 sec
RG 322.5
DW 60.800 usec
DE 6.00 usec
TE 300.0 K
D1 1.00000000 sec

========== CHANNEL f1 ==========
NUC1 1H
P1 10.30 usec
PL1 0.00 dB
SFO1 400.1324710 MHz

F2 - Processing parameters
SI 16384
SF 400.1300209 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 20.93 Hz

1D NMR plot parameters
CX 30.00 cm
F1P 13.000 ppm
F1 5201.69 Hz
F2P -1.000 ppm
F2 -400.13 Hz
PPMCM 0.46667 ppm/cm
HZCM 186.72736 Hz/cm

lw4599/100-1



Current Data Parameters

NAME	oc2406lw1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20061024
Time	23.29
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	128
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	406.4
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

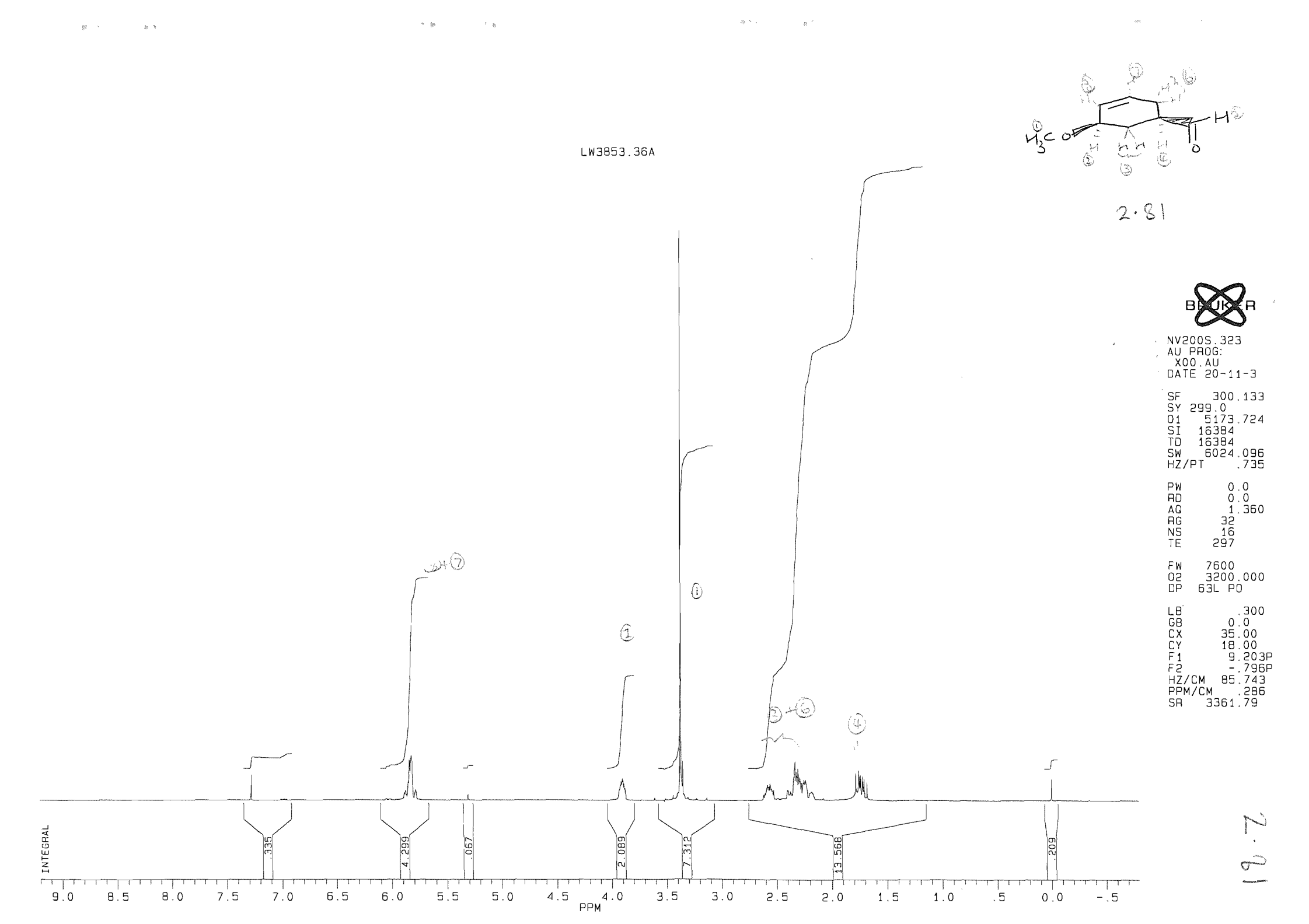
NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SF01	400.1324710 MHz

F2 - Processing parameters

SI	16384
SF	400.1300209 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.93 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm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TD 16384
SW 6024.096
HZ/PT .735
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RD 0.0
AQ 1.360
RG 32
NS 16
TE 297
FW 7600
O2 3200.000
DP 63L PO
LB .300
GB 0.0
CX 35.00
CY 18.00
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F2 -.796P
HZ/CM 85.743
PPM/CM .286
SR 3361.79
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PPM
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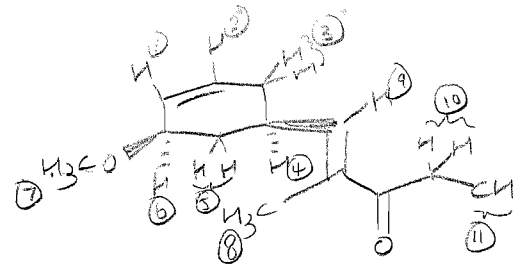

2.82

LW3853.398

BRUKER

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X00.AU
DATE 8-12-3

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TD	16384
SW	6024.096
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PW	0.0
RD	0.0
AQ	1.360
RG	40
NS	16
TE	297
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GB	0.0
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CY	18.00
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F2	-.799P
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PPM/CM	.286
SR	3364.73

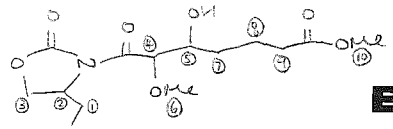
INTEGRAL .643 2.138 4.621 7.979 6.975 2.241 16.202 13.842 .464

9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 .5 0.0 -.5

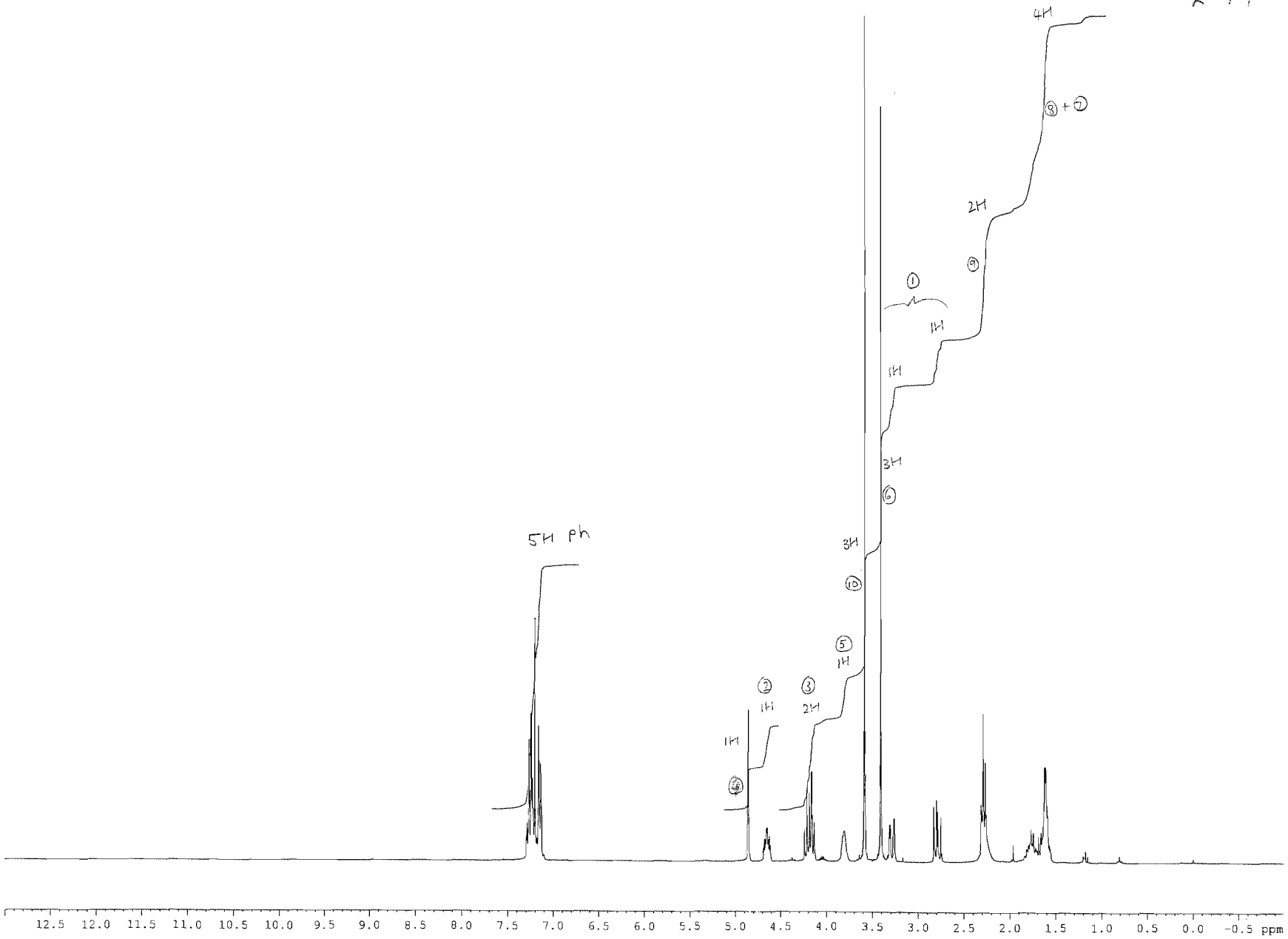
PPM

2.82

lw4031/22



2.94



Current Data Parameters

NAME	myl2041w2
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20040512
Time	21.49
INSTRUM	av300
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5995.204 Hz
FIDRES	0.182959 Hz
AQ	2.7329011 sec
RG	161.3
DW	83.400 usec
DE	6.00 usec
TE	300.2 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

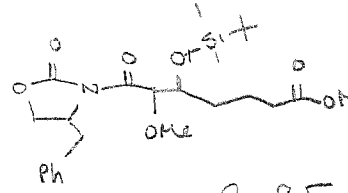
NUC1	1H
P1	12.10 usec
PL1	3.00 dB
SFO1	300.1315006 MHz

F2 - Processing parameters

SI	16384
SF	300.1300234 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	23.36 Hz

2.94

1w4031/27



BRUKER

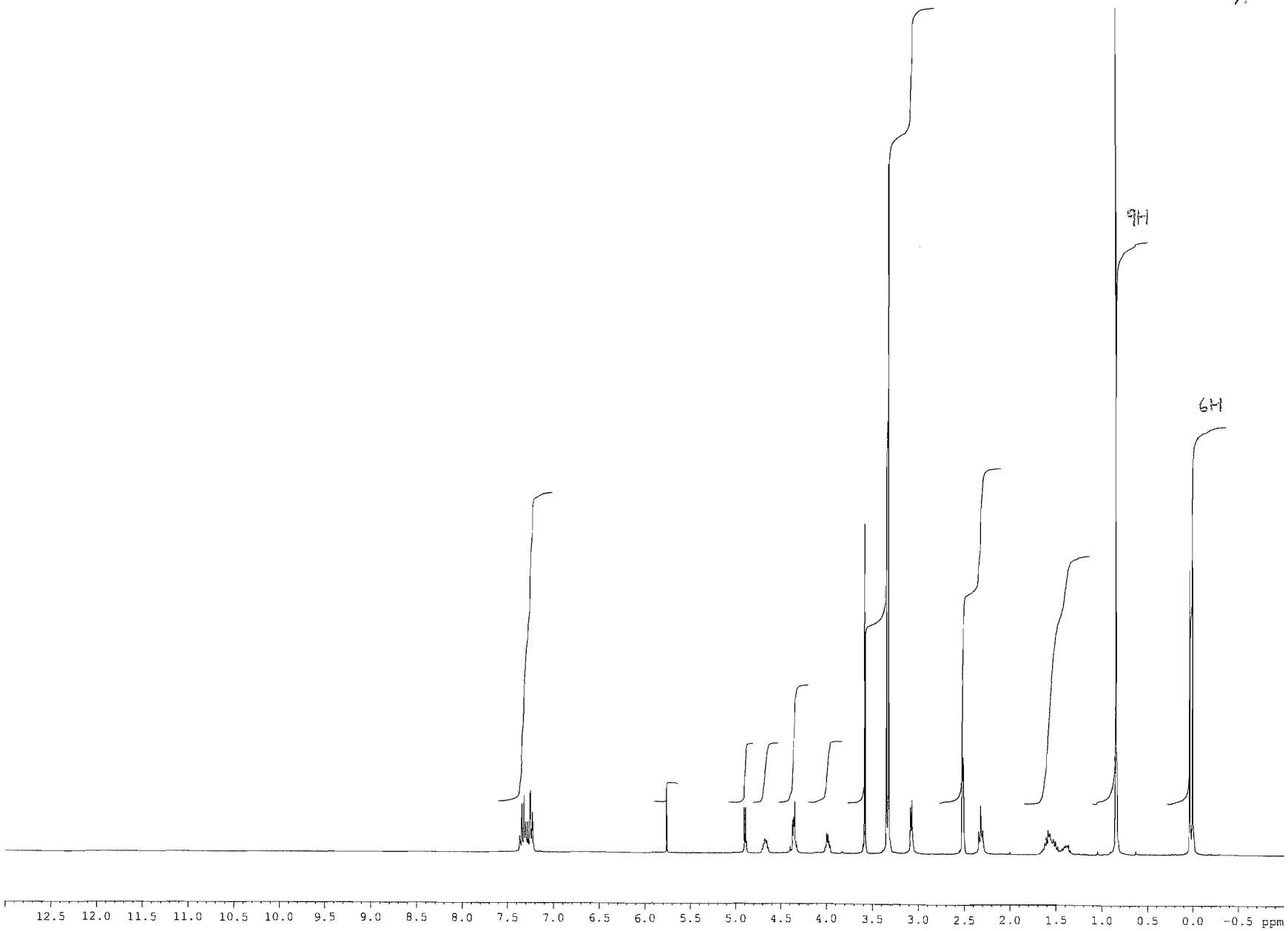
2.95

Current Data Parameters
NAME myl9041w1
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040519
Time 15.55
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT DMSO
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 406.4
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

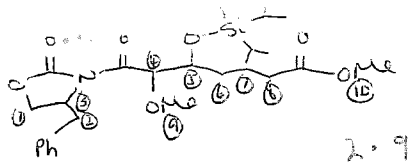
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1299956 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR -4.41 Hz



2.95

1w4031/46-2



2.96

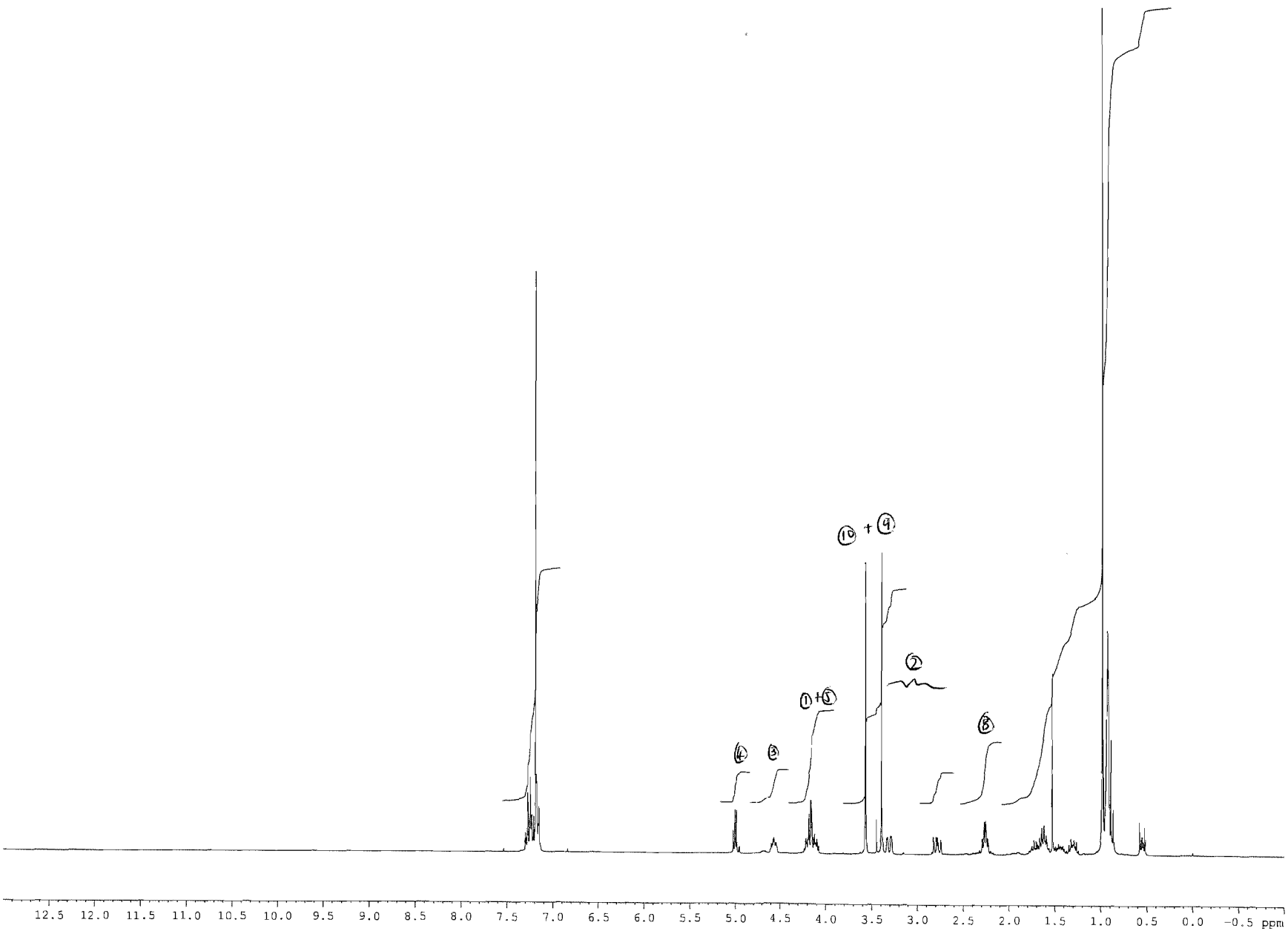
BRUKER

Current Data Parameters
NAME ju15041w4
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20040616
Time 3.13
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 362
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

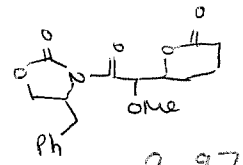
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300265 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 26.49 Hz



2.96

lw4031/42



2.97

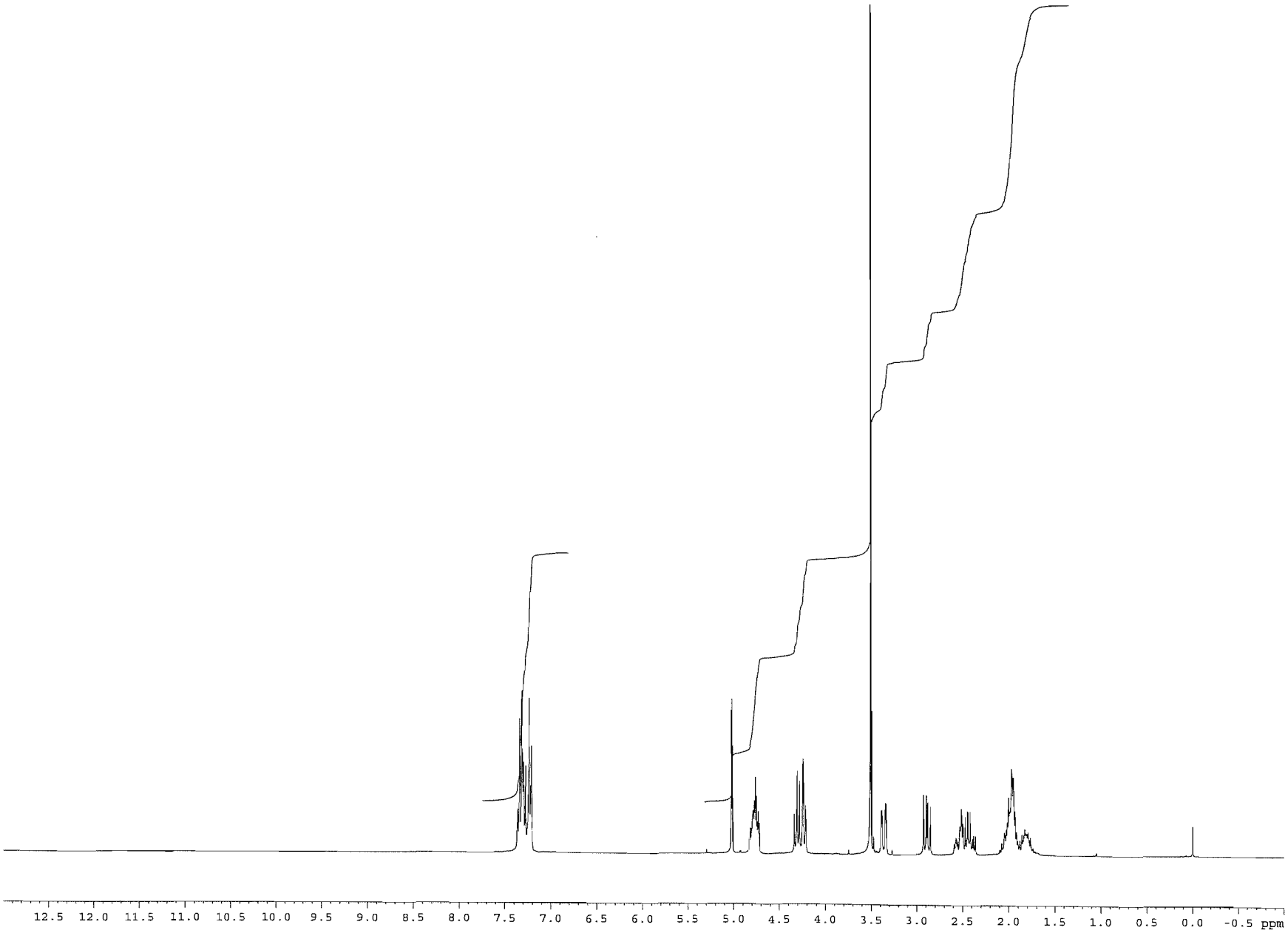
BRUKER

Current Data Parameters
NAME nv2105cpr4
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20051121
Time 23.20
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 203.2
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

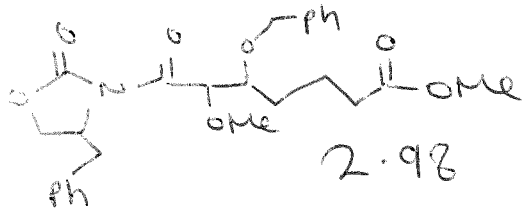
======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300014 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 1.36 Hz

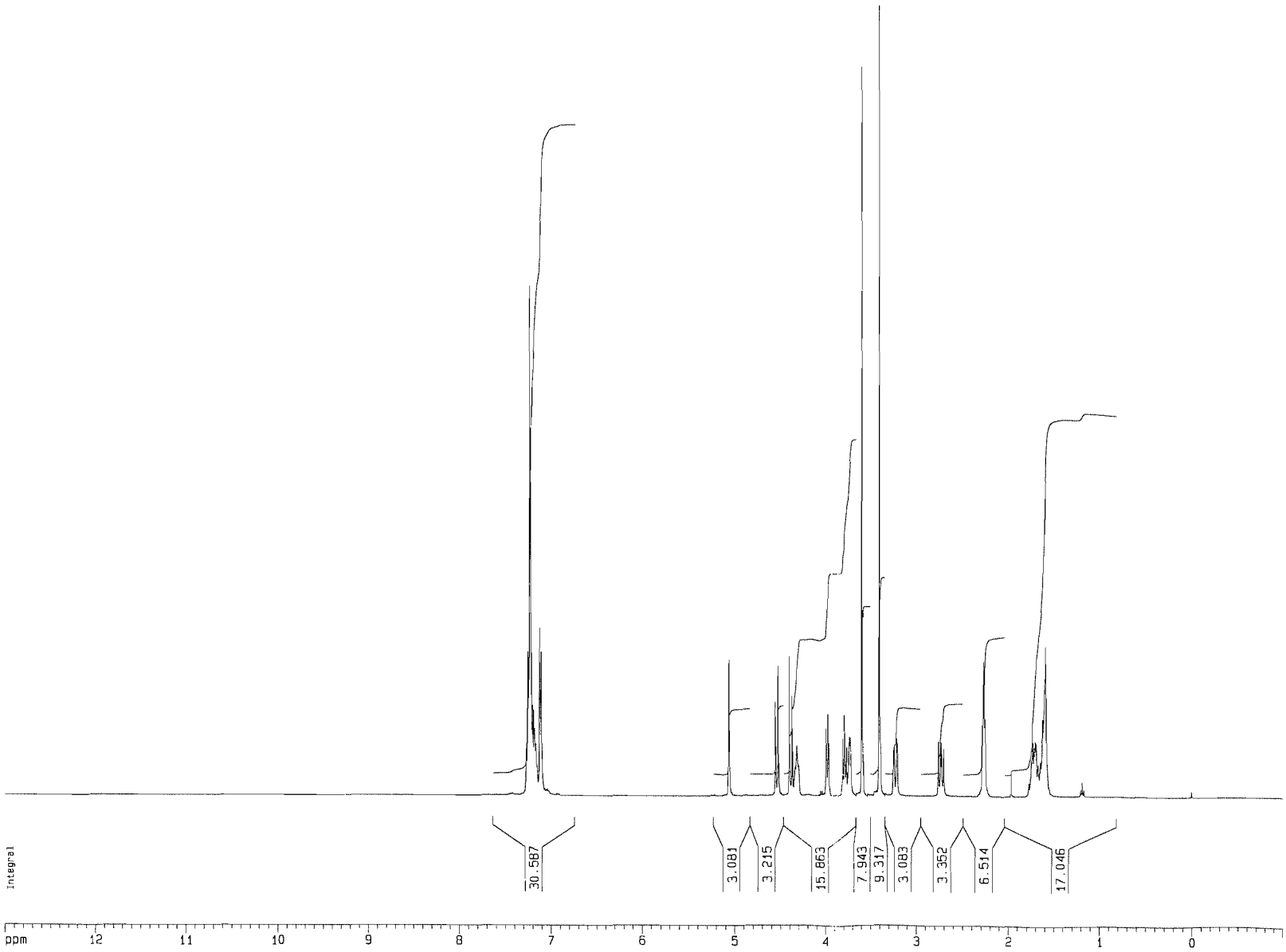


2.97

lw4031/82



2.98



NAME	au1804lw1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20040818
Time	17.14
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIORES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

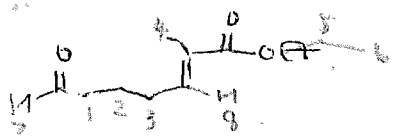
SI	16384
SF	400.1300490 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	49.03 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

26.2

lw4031/74



2.102

BRUKER

Current Data Parameters

NAME	jy2204lw2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

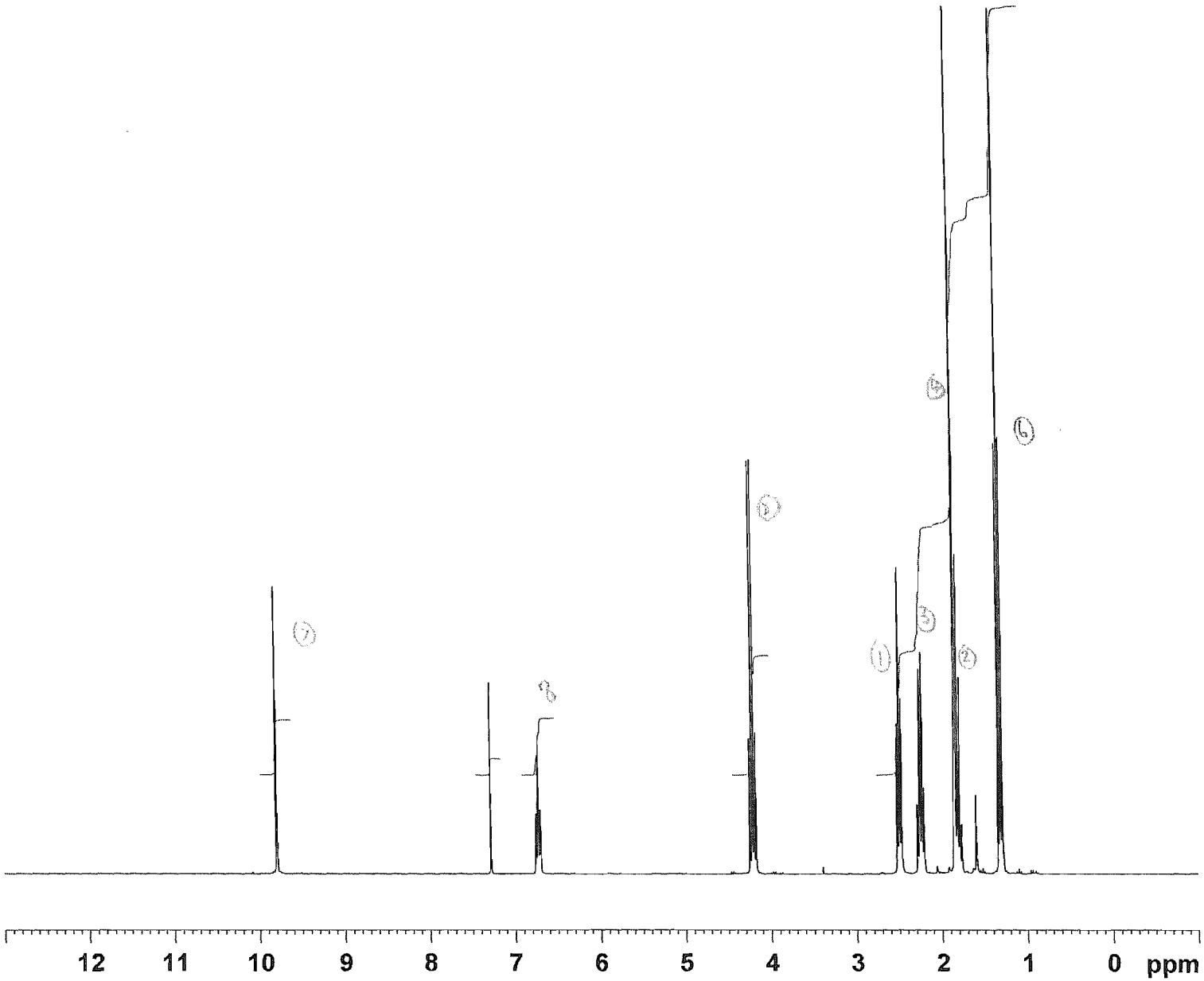
Date_	20040722
Time	16.46
INSTRUM	spect
PROBHD	5 mm Dual 13C/
PULPROG	zg30
TD	32768
SOLVENT	CDC13
NS	8
DS	2
SWH	6172.839 Hz
FIDRES	0.188380 Hz
AQ	2.6542580 sec
RG	322.5
DW	81.000 usec
DE	7.50 usec
TE	300.0 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

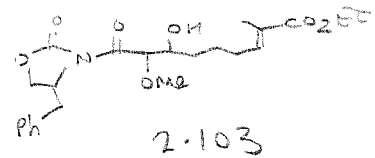
NUC1	1H
P1	9.79 usec
PL1	-2.00 dB
SFO1	300.1318534 MHz

F2 - Processing parameters

SI	16384
SF	300.1300000 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00

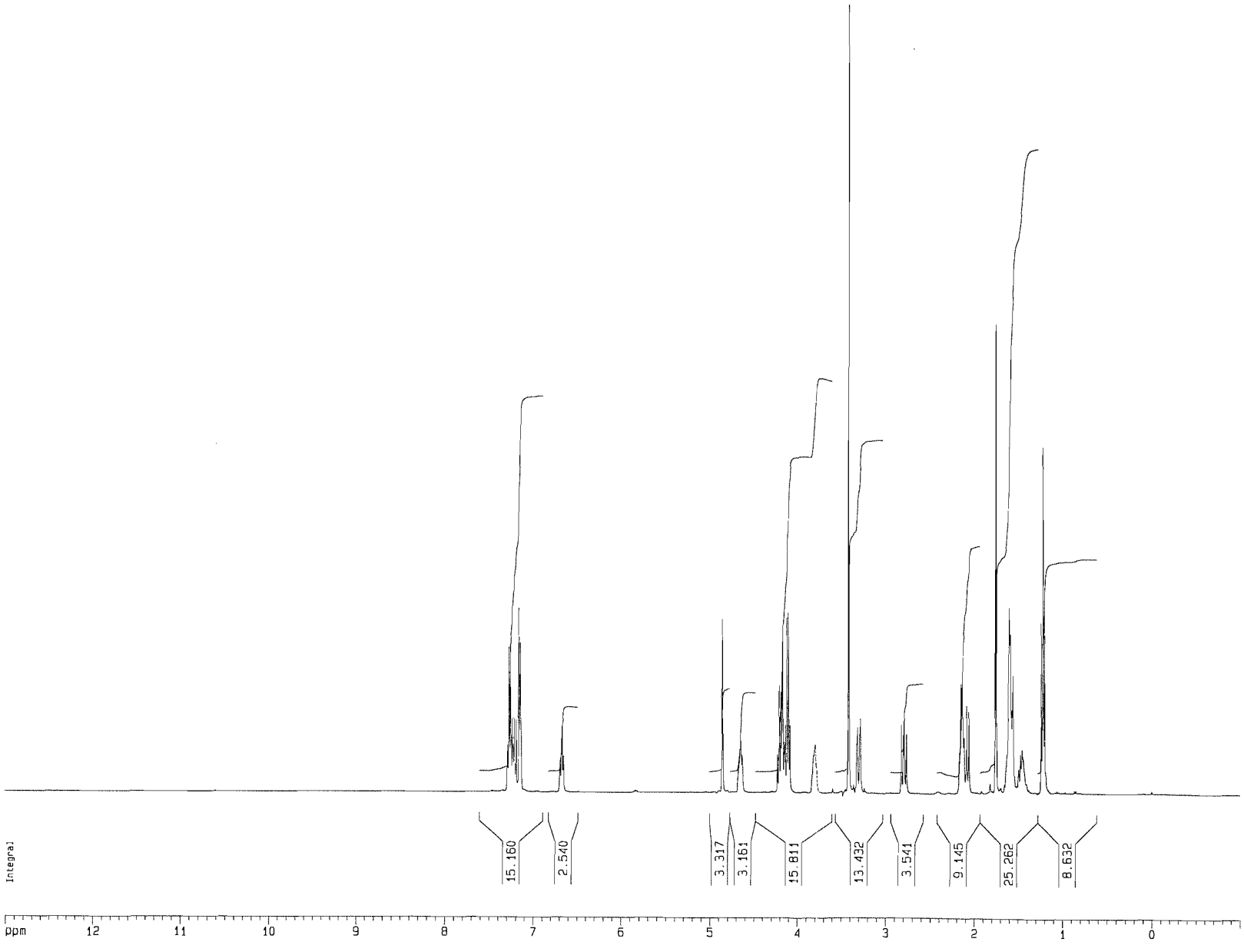


2.102



2.103

lw4031/69



Current Data Parameters

NAME	oc12041w1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041013
Time	13.36
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

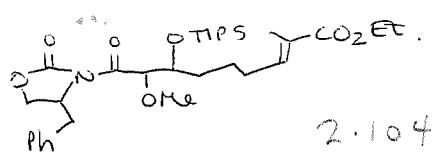
F2 - Processing parameters

SI	16384
SF	400.1300477 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	47.67 Hz

1D NMR plot parameters

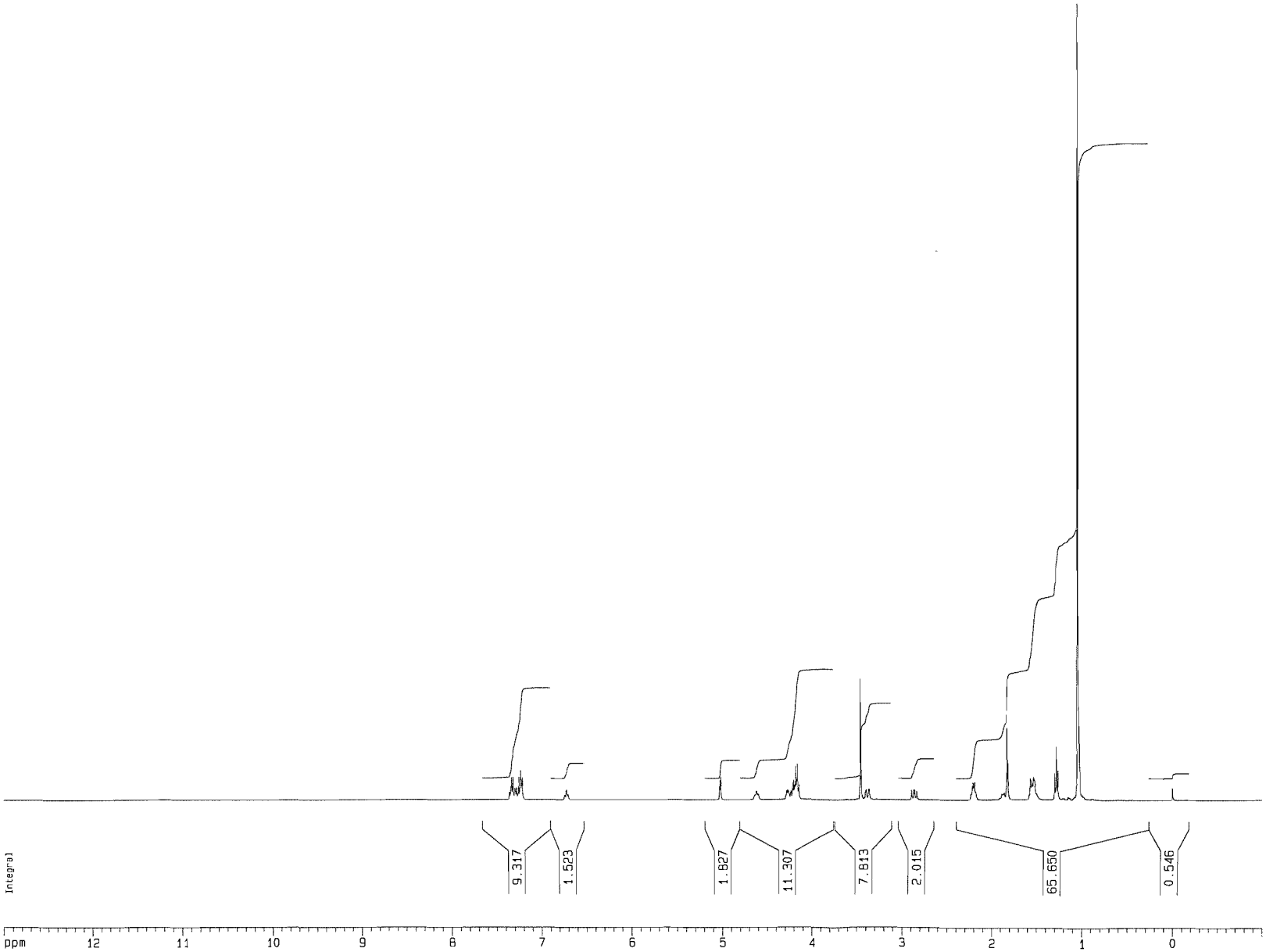
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

2.103



2.104

lw4180/87



Current Data Parameters

NAME	ap0405lw2
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050404
Time	21.19
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

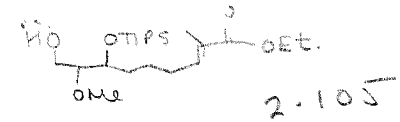
F2 - Processing parameters

SI	16384
SF	400.1300208 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.78 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

1w4031/84-sm



2.105

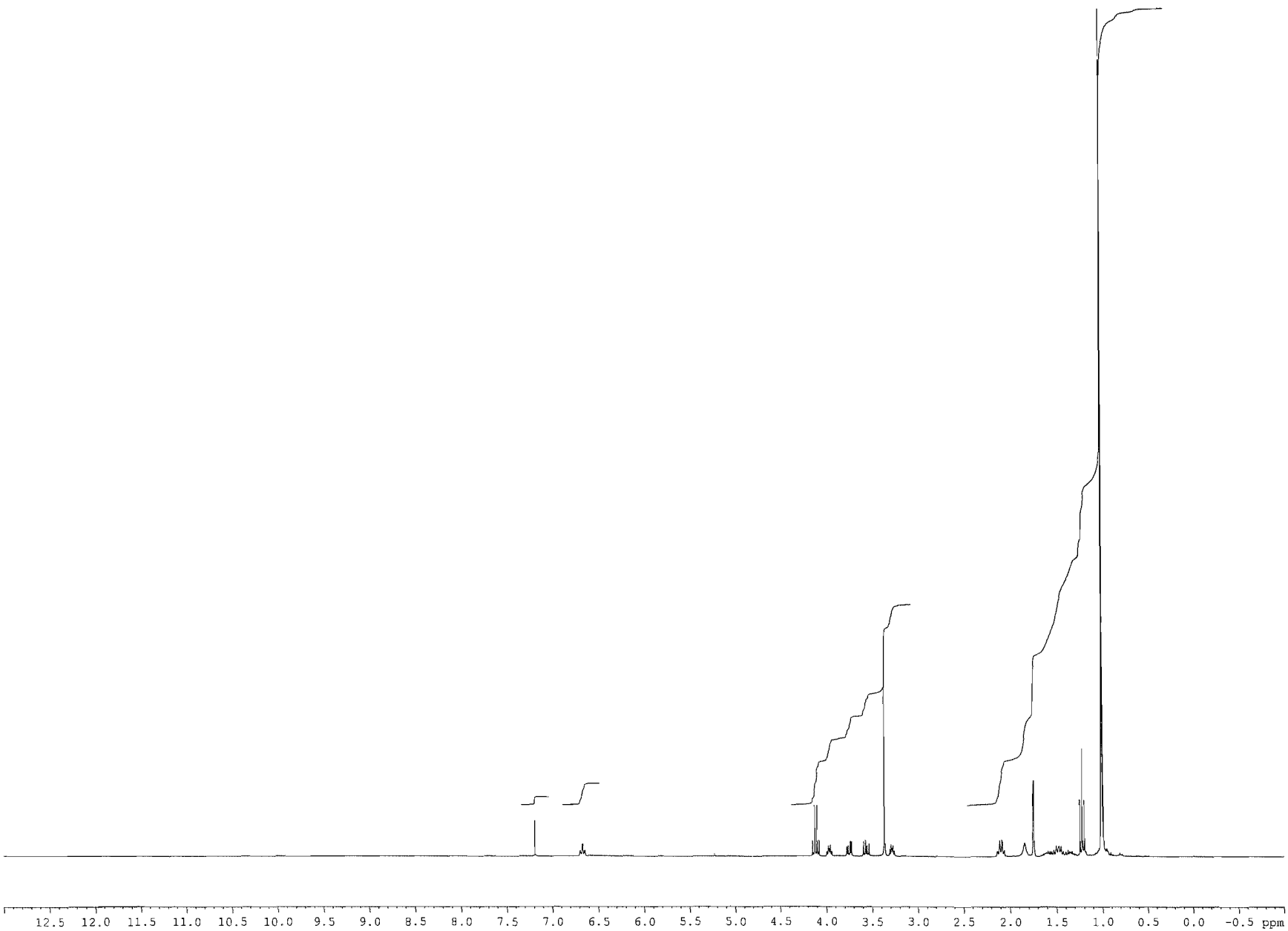
BRUKER

Current Data Parameters
NAME au12041w4
EXPNO 10
PROCNO 1

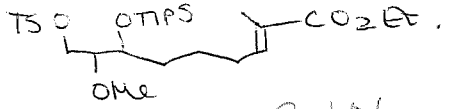
F2 - Acquisition Parameters
Date_ 20040813
Time 1.08
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 287.4
DW 83.400 usec
DE 6.00 usec
TE 295.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300246 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 24.61 Hz

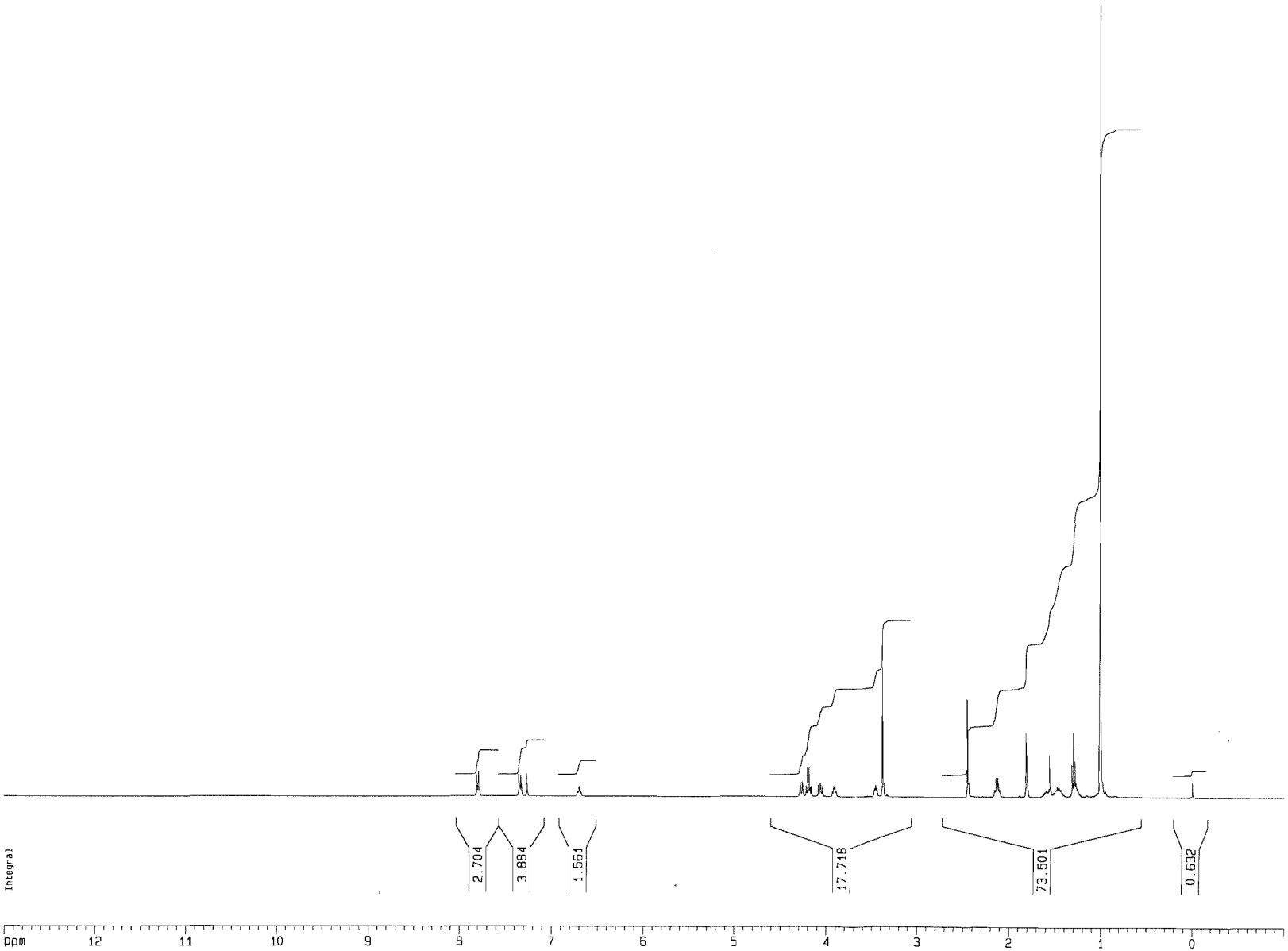


2.105



2.106

lw4180/89



Current Data Parameters

NAME	ap06051w2
EXPND	1
PRDCNO	1

F2 - Acquisition Parameters

Date_	20050406
Time	21.05
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	64
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	114
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

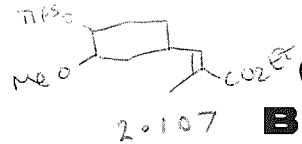
SI	16384
SF	400.1300204 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	20.44 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

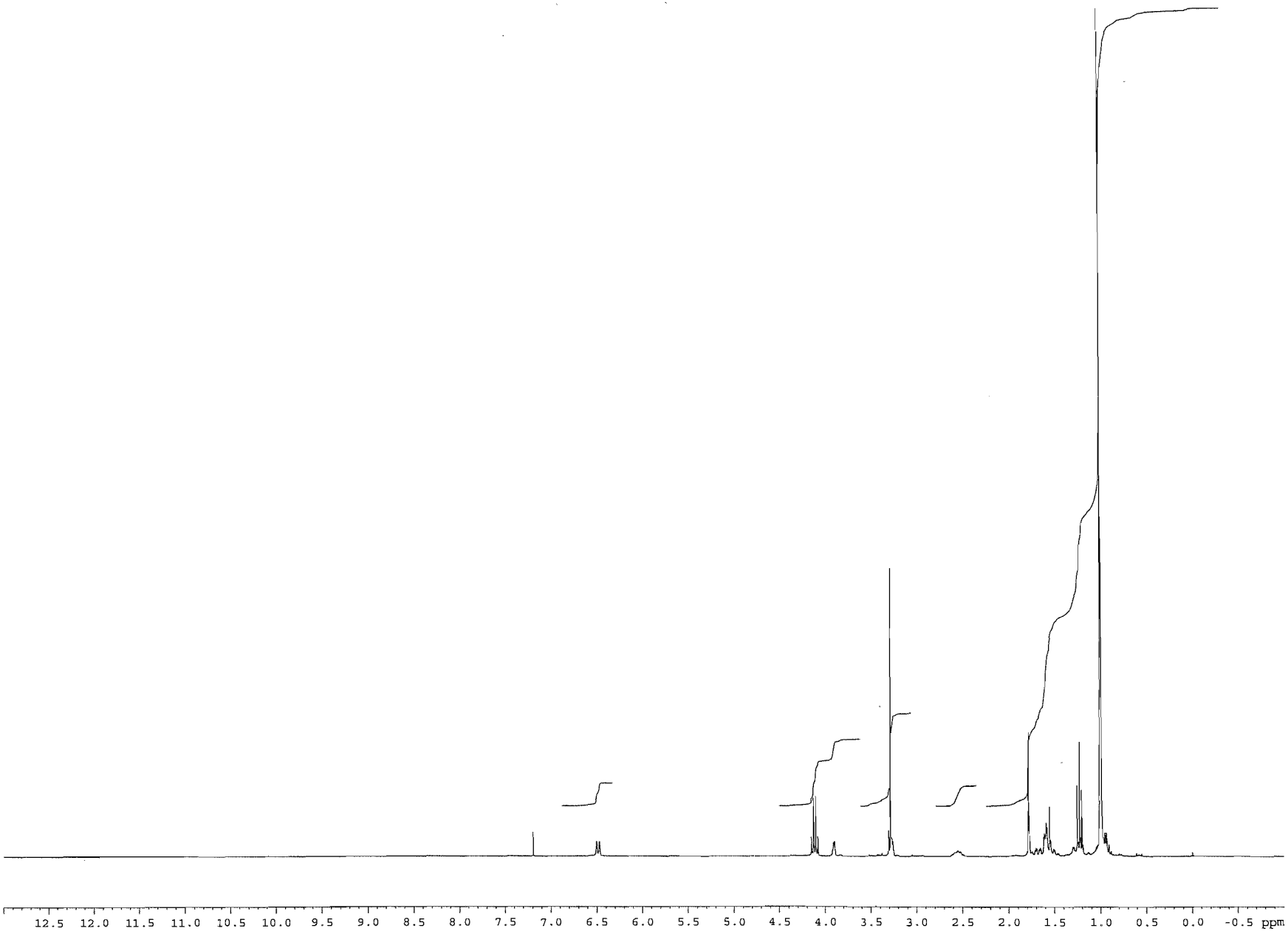
2.106

lw4180/18-1



2.107

BRUKER



Current Data Parameters

NAME	oc2704lw1
EXPNO	10
PROCNO	1

F2 - Acquisition Parameters

Date_	20041027
Time	16.44
INSTRUM	av300
PROBHD	5 mm QNP 1H/13
PULPROG	zg30
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	5995.204 Hz
FIDRES	0.182959 Hz
AQ	2.7329011 sec
RG	161.3
DW	83.400 usec
DE	6.00 usec
TE	300.2 K
D1	1.00000000 sec
MCREST	0.00000000 sec
MCWRK	0.01500000 sec

======== CHANNEL f1 ========

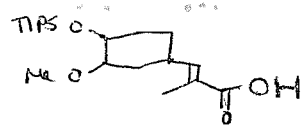
NUC1	1H
P1	12.10 usec
PL1	3.00 dB
SFO1	300.1315006 MHz

F2 - Processing parameters

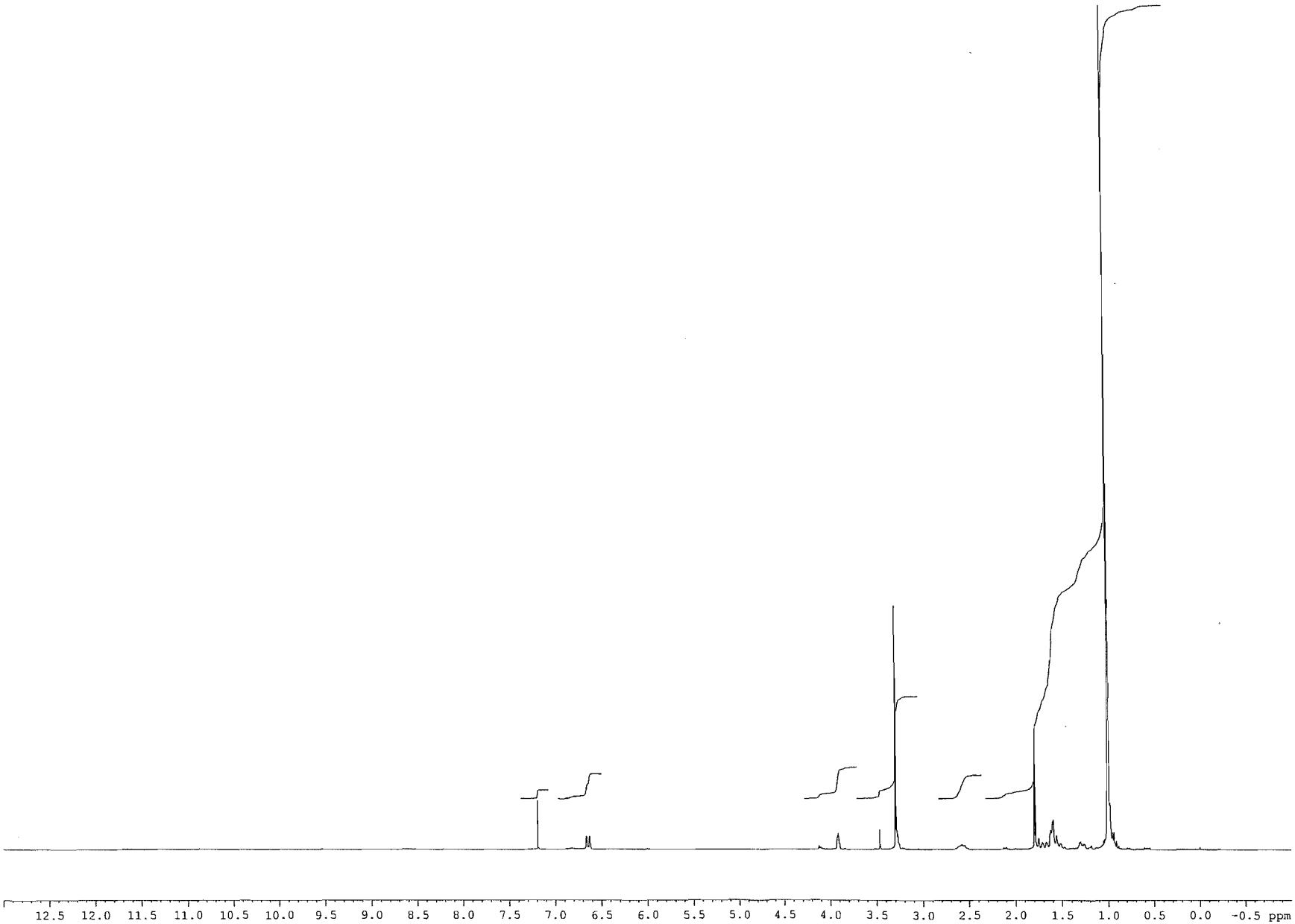
SI	16384
SF	300.1300256 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	25.61 Hz

2.107

lw4180/



2.108



BRUKER

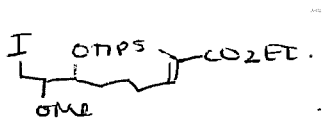
Current Data Parameters
NAME oc1504lw1
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20041015
Time 20.43
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 322.5
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

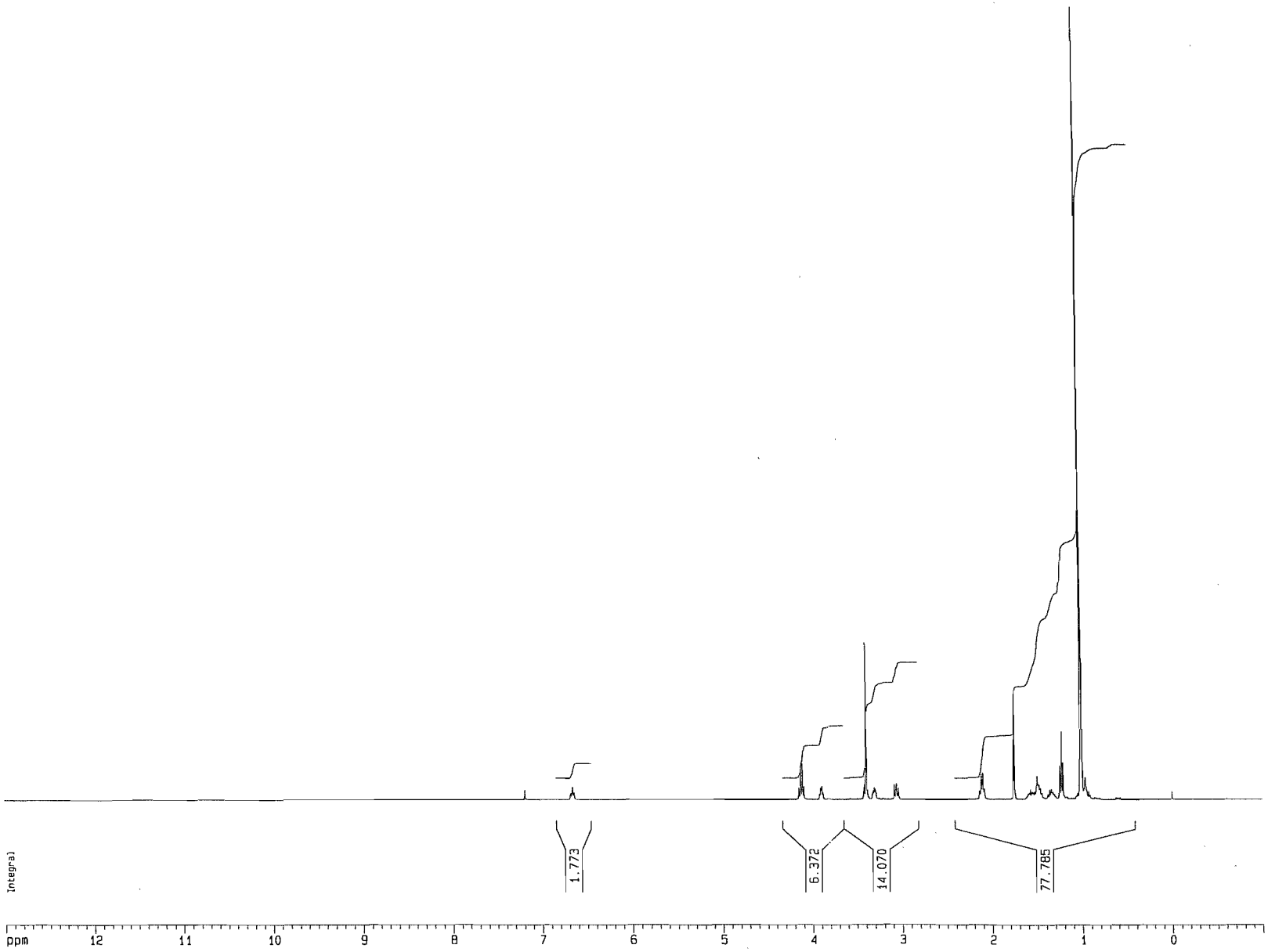
F2 - Processing parameters
SI 16384
SF 300.1300270 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 27.03 Hz

2.108



2.109

lw4180/5



Current Data Parameters

NAME	oc0804lw1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20041009
Time	6.41
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	57
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

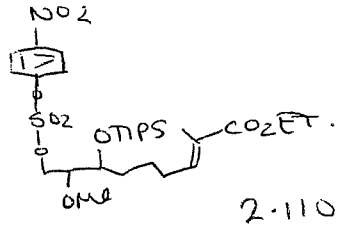
SI	16384
SF	400.1300479 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	47.86 Hz

1D NMR plot parameters

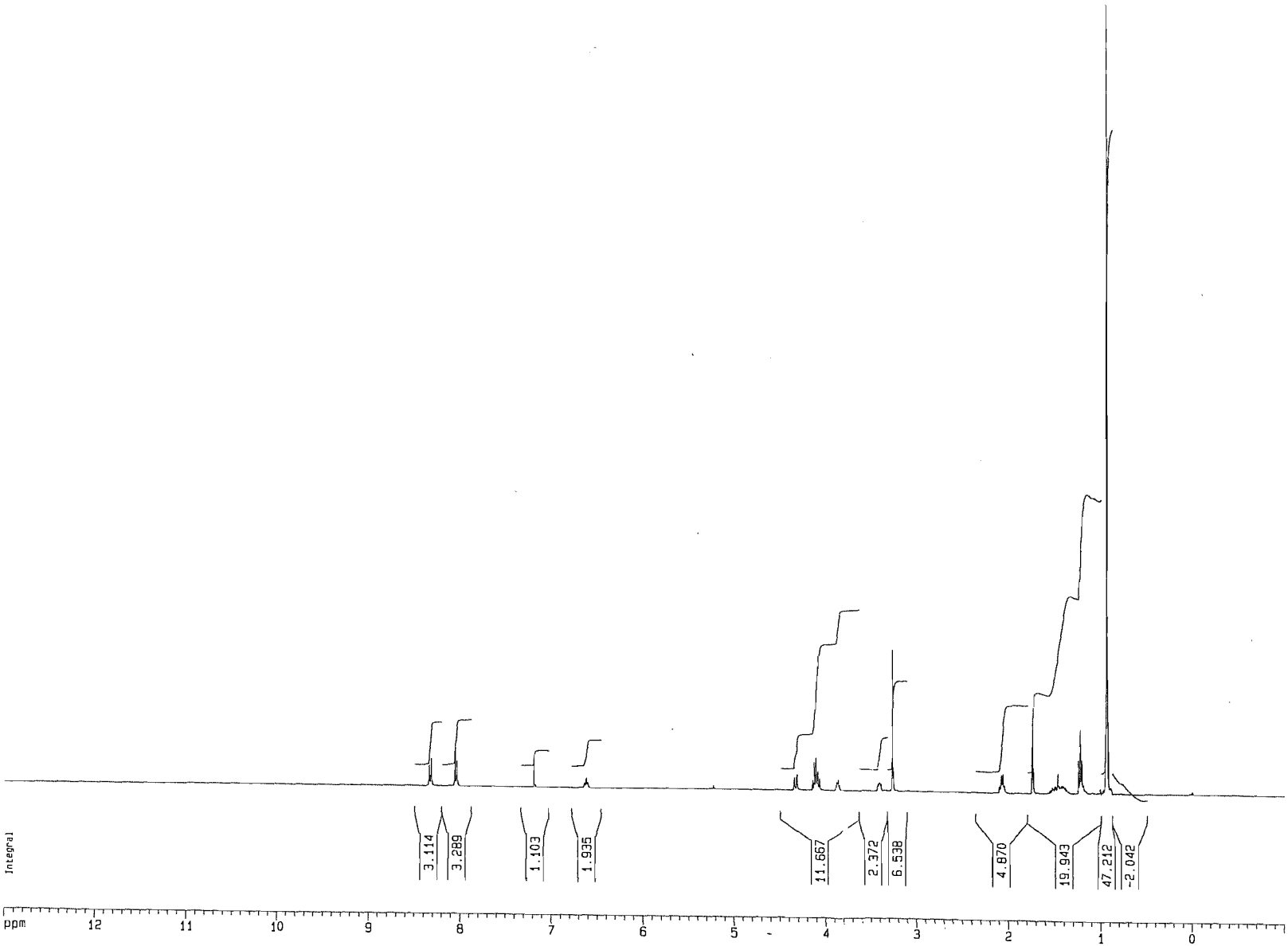
CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

2.109

lw4180/58



2.110



Current Data Parameters

NAME	ja17051w1
EXPNO	1
PROCNO	1

F2 - Acquisition Parameters

Date_	20050117
Time	12.10
INSTRUM	spect
PROBHD	5 mm Dual 13
PULPROG	zg
TD	32768
SOLVENT	CDCl3
NS	16
DS	2
SWH	8223.685 Hz
FIDRES	0.250967 Hz
AQ	1.9923444 sec
RG	181
DW	60.800 usec
DE	6.00 usec
TE	300.0 K
D1	1.00000000 sec

========== CHANNEL f1 ==========

NUC1	1H
P1	10.30 usec
PL1	0.00 dB
SFO1	400.1324710 MHz

F2 - Processing parameters

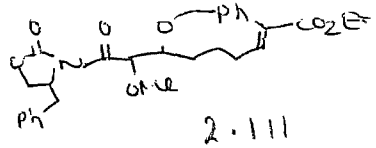
SI	16384
SF	400.1300486 MHz
WDW	EM
SSB	0
LB	0.30 Hz
GB	0
PC	1.00
SR	48.63 Hz

1D NMR plot parameters

CX	30.00 cm
F1P	13.000 ppm
F1	5201.69 Hz
F2P	-1.000 ppm
F2	-400.13 Hz
PPMCM	0.46667 ppm/cm
HZCM	186.72736 Hz/cm

2.110

lw4180/38



2.111

BRUKER

Current Data Parameters
NAME nv2404lw1
EXPNO 10
PROCNO 1

F2 - Acquisition Parameters
Date_ 20041125
Time 1.14
INSTRUM av300
PROBHD 5 mm QNP 1H/13
PULPROG zg30
TD 32768
SOLVENT CDCl3
NS 16
DS 2
SWH 5995.204 Hz
FIDRES 0.182959 Hz
AQ 2.7329011 sec
RG 228.1
DW 83.400 usec
DE 6.00 usec
TE 300.2 K
D1 1.00000000 sec
MCREST 0.00000000 sec
MCWRK 0.01500000 sec

======== CHANNEL f1 ========
NUC1 1H
P1 12.10 usec
PL1 3.00 dB
SFO1 300.1315006 MHz

F2 - Processing parameters
SI 16384
SF 300.1300272 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
SR 27.17 Hz