UNIVERSITY OF SOUTHAMPTON

Faculty of Science
School of Chemistry

THE TOTAL SYNTHESIS OF OKARAMINE ALKALOIDS

by

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Thesis for the Degree of Doctor of Philosophy

January 2004

UNIVERSITY OF SOUTHAMPTON

ABSTRACT

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The okaramines are a series of indole alkaloids isolated from *Penicillium simplicissimum* fermented on okara, the residue from ground soybeans. The first total synthesis of okaramines J and C, and studies towards the synthesis of okaramine A are described.

Okaramines J and C were synthesised from derivatives of L-tryptophan. Alkylation of a sterically hindered hexahydropyrroloindoline with an alkynyl bromide, followed by hydrogenation gave a key *N*-reverse prenyl intermediate. A facile acid-catalysed *N*-reverse prenyl to *C*-prenyl aza-Claisen rearrangement of this intermediate led to the total synthesis of okaramine J. Alternative conditions were found that avoided this rearrangement to enable the synthesis of okaramine C.

Two strategies have been explored for the formation of an 8-membered ring like that present in okaramine A. Acid-catalysed cyclisation of an alkene onto an indole has been investigated and the cyclisation achieved in low yield with $AlCl_3$. A general route to vinyl amides has been developed using ethanolamine as the alkene precursor. This methodology has been used to prepare substrates for ring-closing metathesis, which has been investigated as an alternative means of forming an 8-membered ring.

CONTENTS

PREFACE

The research described in this thesis was carried out under the supervision of Dr A. Ganesan at the University of Southampton between October 2000 and October 2003. No part of this thesis has previously been submitted for a degree.

ACKNOWLEDGEMENTS

There are many people without whom this work would not have been possible. Firstly, I would like to thank the EPSRC for funding and Pfizer for a CASE studentship. I would then like to thank my supervisor, Dr Ganesan and my industrial supervisor Dr Richard Webster for all their support, advice and encouragement.

I would like to thank all members of the Ganesan group, past and present, especially Alex, Helen, Jeff and Paul for all their help. There has never been a dull moment and it's been a great lab to work in. Thanks to my advisor, Dr. Peter Roach, especially for adding extra entertainment to group meetings. Thanks to Allison Carley for spending her 3rd year project trying out ideas for minimal results. Thanks to the Harrwoven, Brown and Whitby groups for being friendly and letting me borrow things. Thanks to everyone at Pfizer Veterinary Medicine for making me feel at home and being extremely helpful during my CASE placement. I would also like to thank Joan Street and Neil Wells (NMR) and John Langley and Julie Herniman (MS) for a great spectroscopic service.

Finally there are all the people who have supported me in the background. I would like to thank my family for always being there. Thanks to Henry, Jenny, Pete, Ben, Marianne, Helen and Steve who have had to put up with living with me for anything between 6 days and 6 years. Thanks to everyone at Swaythling Baptist Church for giving me lots to do when I wasn't doing chemistry as well as lots to eat. Thanks to John for being there when I was writing up and not minding being told to go away. Last of all, thanks to God who is constant and without whom I would not have lasted the distance.

ABBREVIATIONS

Ac	acetyl
Ar	aryl
9-BBN	9-borabicyclo[3.1.1]nonane
Boc	*tert*-butoxycarbonyl
Boc_2O	di-*tert*-butyl dicarbonate
BOP-Cl	bis(2-oxo-3-oxazolidinyl)phosphinic chloride
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMDO	dimethyldioxirane
DMSO	dimethyl sulfoxide
EDAC	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EDTA	ethylenediaminetetraacetic acid
Fmoc-Cl	9-fluorenylmethyl chloroformate
HBTU	*O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate
HPLC	high performance liquid chromatography
hv	ultraviolet irradiation
IR	infrared
m/z	mass to charge ratio
m-CPBA	*m*-chloroperbenzoic acid
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NBS	*N*-bromosuccinimide

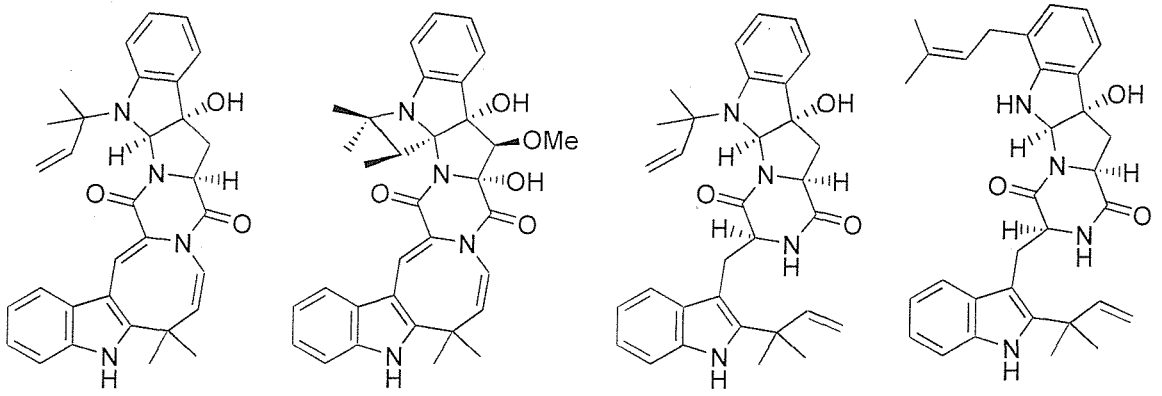
NMR	nuclear magnetic resonance
δ	chemical shift in parts per million
b	broad
d	doublet
J	coupling constant
m	multiplet
q	quartet
t	triplet
Ph	phenyl
PPA	polyphosphoric acid
PPE	polyphosphate ester
PPSE	trimethylsilylpolyphosphate
PPTS	pyridinium *p*-toluene sulfonate
PTSA	*p*-toluenesulfonic acid
PyBOP	benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate
PyBrop	bromo-tris-pyrrolidino-phosphonium hexafluorophosphate
RT	room temperature
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMSI	trimethylsilyl iodide
TMSOTf	trimethylsilyl triflate
Ts	*p*-toluenesulfonyl

1.0 INTRODUCTION

1.1 Okaramines

The objective of this project was to devise a total synthesis of okaramine alkaloids that was also amenable to analogue preparation. The okaramines are a series of indole alkaloids isolated from *Penicillium simplicissimum* and *Aspergillus aculeatus* fermented on okara (Figure 1). Okara is the residue from ground soybeans used in the production of soymilk and tofu. One of its many uses is as a medium for microbial fermentation[1].

Figure 1. Examples of okaramine alkaloids.

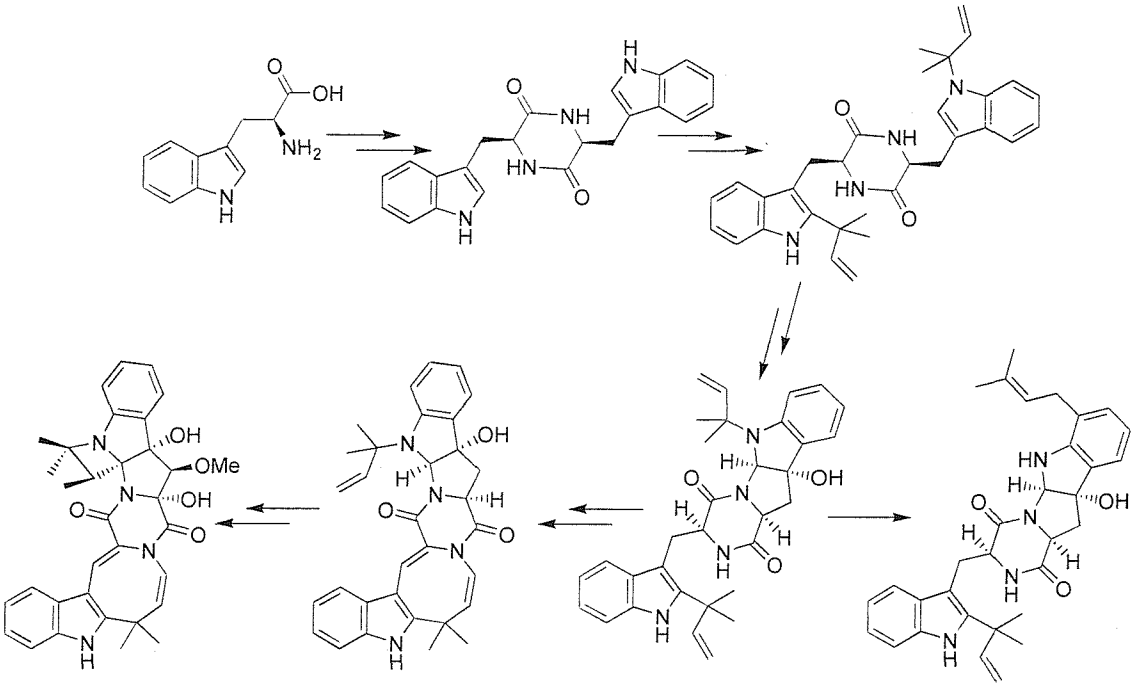


The first two compounds were isolated from *Penicillium simplicissimum* AK-40 by Hayashi's group in 1988 and were named okaramine A and B[2]. In subsequent years, many new okaramines have been isolated using okara as a fermentation base. Okaramine C was isolated from *Penicillium simplicissimum* AHU 8402[3], okaramines D - G from *Penicillium simplicissimum* ATCC 90288[4, 5], okaramines H and I from *Aspergillus aculeatus* KF-428[6] and okaramines J - R from *Penicillium simplicissimum* ATCC 90288[7, 8].

1.2 Biosynthesis of the okaramines

The okaramines are derived from the diketopiperazine of two molecules of L-tryptophan and the isoprene unit[7]. Although the precise sequence of events is not yet known, the biosynthesis proceeds through a series of prenylations, structural reorganization and oxidations (Figure 2).

Figure 2. Proposed biosynthetic pathway for okaramines.



1.3 Insecticidal activity of okaramines

The insecticidal activity of the okaramines has been investigated by oral administration to the 3rd instar larvae of silkworms[2]. The LD_{50} values for okaramines A-R are shown in Table 1. Okaramines A, B, C, D, G and Q showed potent insecticidal activity against silkworm larvae.

Table 1. Insecticidal Activity of Okaramines A-R[2-8]

Okaramine	LD_{50} μg/g of diet	Okaramine	LD_{50} μg/g of diet
A	8	J	>100
B	0.2	K	>100
C	8	L	>100
D	20	M	>100
E	>100	N	>100
F	>100	O	>100
G	40	P	>100
H	>100	Q	8
I	>100	R	>100

The effect of the 4-membered azetidine and 8-membered azocine rings on insecticidal activity has been investigated for okaramine B[9]. Hydrogenation of okaramine B provided degradation products with the azetidine ring opened and the azocine ring reduced to form dihydro and tetrahydro derivatives. The ring-opened products showed no insecticidal activity. Dihydrookaramine B had an LD_{50} of 6 μg/g of diet whereas the tetrahydro derivative had an LD_{50} reduced to 80 μg/g of diet. This indicated that the azetidine ring was the main requirement for insecticidal activity but the conformation of the azocine ring was also important.

1.4 Austamide

Despite their unusual functionality and biological activity there were no reports of synthetic efforts towards the okaramines at the start of this project. There are, however, examples of the synthesis of natural products bearing some structural similarities.

Austamide (Figure 3) was first isolated by Steyn from *Aspergillus ustus*[10]. This was shortly followed by the isolation of four other related diketopiperazine metabolites[11]. One of these metabolites (Figure 4), a biogenetic precursor to austamide, shares the indole, azocine and diketopiperazine ring system with the okaramines.

Figure 3. Austamide.

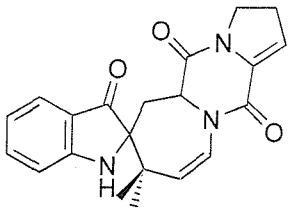
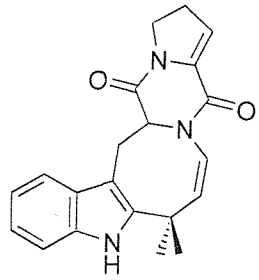
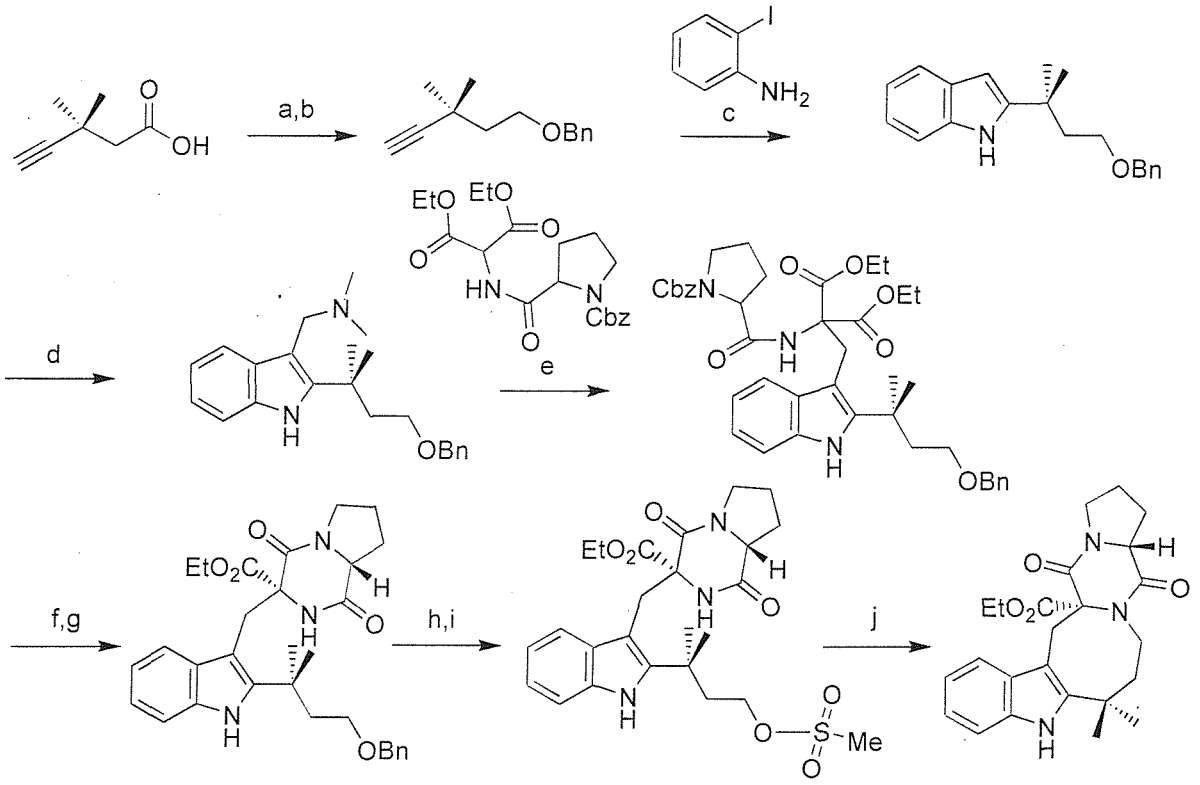


Figure 4. *A. ustus* metabolite.



Hutchison and Kishi, in their synthesis of tetrahydroaustamide[12] and *dl*-austamide[13] prepared similar intermediates containing the indole and diketopiperazine rings joined by an 8-membered azocine ring (Scheme 1). An indole containing a protected precursor to the prenyl unit was formed by coupling *o*-iodoaniline with 3,3-dimethyl-5-benzyloxy-1-pentyne in the presence of cuprous iodide and triethylamine. This was converted to a gramine derivative, which was coupled with a protected prolylaminomalonate unit. The diketopiperazine ring was formed by deprotection of the prolyl nitrogen followed by heating. The prenyl alcohol was deprotected and converted to the mesylate. Cyclisation to form the 8-membered ring took place on treatment with NaH in benzene. The resultant intermediate was then converted to tetrahydroaustamide.

Scheme 1. Synthesis of tetrahydroaustamide precursor [a].

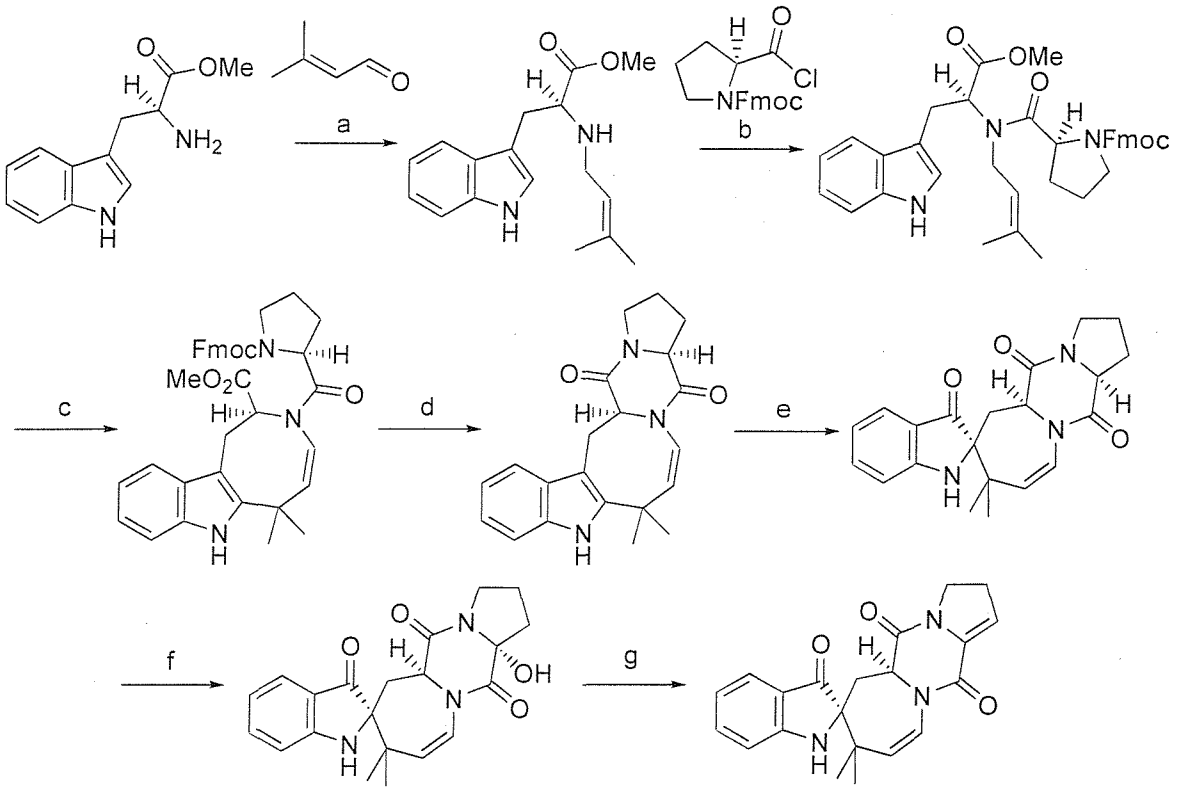


[a] Conditions: (a) $LiAlH_4$, Et_2O; (b) $PhCH_2Br$, NaH, THF, 54%; (c) CuI, Et_3N, DMF, 145 °C, 68%; (d) $NHMe_2$, formaldehyde, AcOH, MeOH, 81%; (e) NaOH powder, 59%; (f) hydrogenolysis, MeOH; (g) xylene, reflux, 91%; (h) hydrogenolysis, 1:1 MeOH:AcOH; (i) $MeSO_2Cl$, 85%; (j) NaH, PhH, 65%.

Recently, while undertaking this project, Baran and Corey published a synthesis of austamide[14]. This used tryptophan as a starting material and therefore provided a stereoselective and much shorter route, not requiring the synthesis of the gramine derivative. Again, this synthesis passed through an intermediate with the same indoleazocine diketopiperazine ring system (Scheme 2). Tryptophan methyl ester was prenylated by reductive alkylation with 3-methyl-2-butenal then coupled with a protected proline derivative. This intermediate was treated with $Pd(OAc)_2$ under O_2 to give the desired 8-membered ring in modest yield. Deprotection and heating gave the diketopiperazine in good yield. The synthesis of austamide was completed in a similar fashion to the Kishi synthesis[13]. The indole ring was converted to a 3-hydroxyindoline with m-CPBA followed by formation of the spirocycle with NaOMe. Radical-initiated

hydroxylation of the proline subunit with benzoyl peroxide under O_2, then dehydration with MsCl gave (+)-austamide.

Scheme 2. Synthesis of austamide [a].



[a] Conditions: (a) mol sieves, CH_2Cl_2, 3 h then $NaBH_4$, MeOH, 0 °C, 30 min; (b) CH_2Cl_2, 2 h, 98%; (c) $Pd(OAc)_2$, AcOH/THF/H_2O, O_2, 36 h, 29%; (d) Et_2NH, THF, 0 °C, 3 h then PhH reflux, 2 h, 95%; (e) m-CPBA then NaOMe, MeOH, reflux, 45 min, 54%; (f) benzoyl peroxide, O_2, THF, 55 °C then Me_2S, 32%; (g) MsCl, Et_3N, CH_2Cl_2, 2 h, 63%.

1.5 Brevianamide E and Deoxybrevianamide E

Brevianamide E (Figure 5) is a member of a group of natural products isolated by Birch and Wright from *Penicillium brevicompactum*[15]. Deoxybrevianamide E (Figure 6) was first isolated by Steyn from *Aspergillus ustus*[11]. Like the okaramines, these natural products are diketopiperazines where one half is a reverse-prenylated tryptophan derivative. Brevianamide E also shares the hexahydropyrroloindoline skeleton present in okaramines.

Figure 5. Brevianamide E

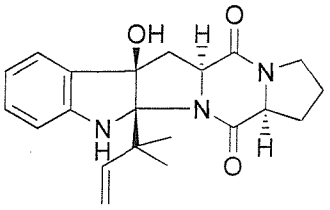
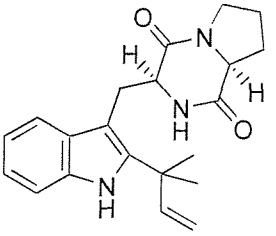
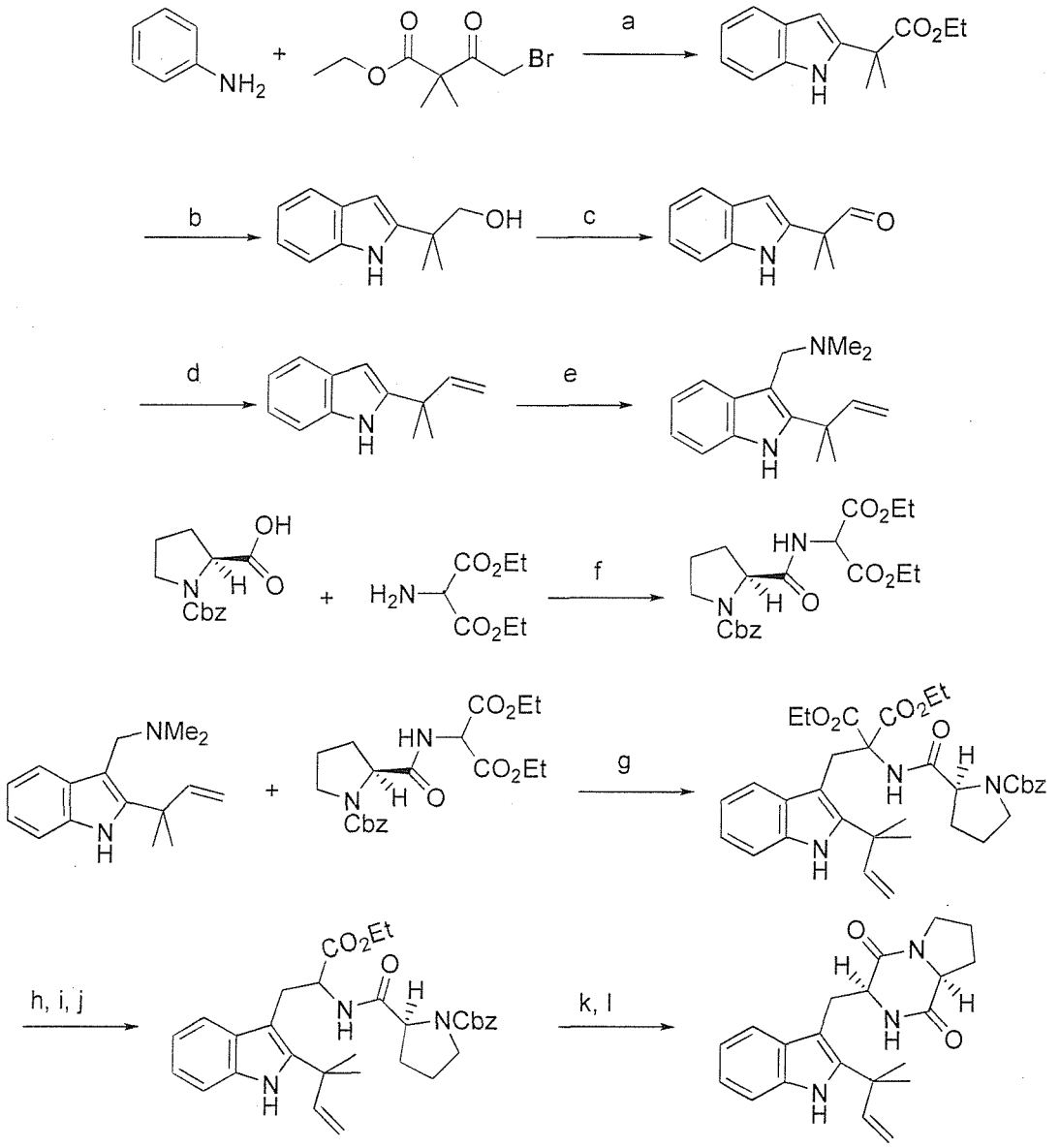


Figure 6. Deoxybrevianamide E



Deoxybrevianamide E was first prepared by Ritchie and Saxton[16]. This synthesis began with 3-(indol-2-yl)-3-methylbut-1-ene, which was prepared by the reaction of ethyl 4-bromo-2,2-dimethylacetoacetate with aniline[17] (Scheme 3). Reduction of the resultant ester with $LiAlH_4$ gave the alcohol, which was oxidised to the aldehyde. A Wittig reaction then gave the desired prenylated indole derivative. This was converted to a gramine derivative *via* a Mannich reaction[18]. This piece was coupled with a prolylaminomalonate. Decarboxylation and deprotection followed by heating gave the desired diketopiperazine as a mixture of diastereoisomers which were separated by preparative TLC to give deoxybrevianamide E.

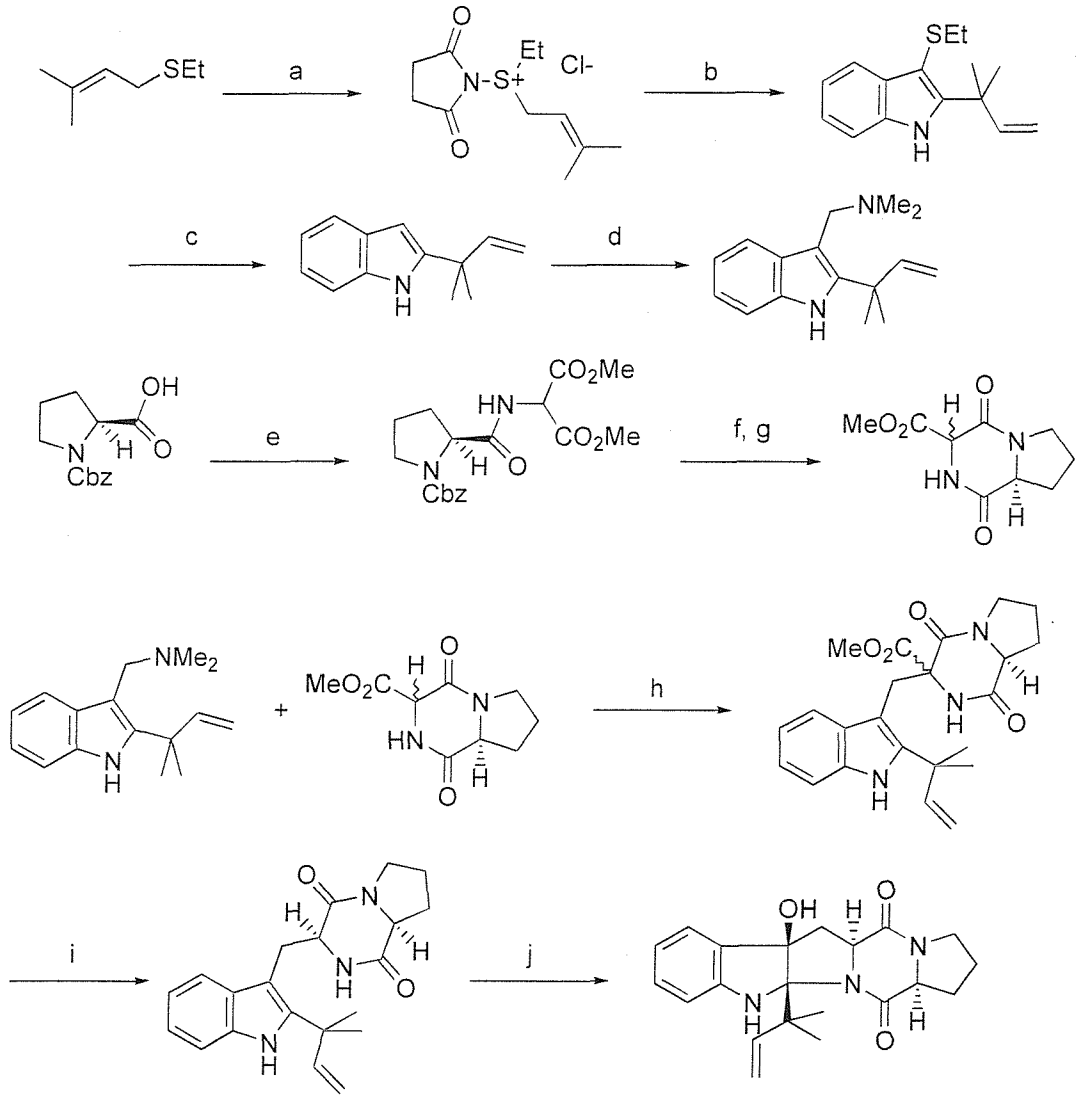
Scheme 3. Synthesis of deoxybrevianamide E [a].



[a] Conditions: (a) 150 °C, 4 h, 50%; (b) $LiAlH_4$, Et_2O, reflux, 2 h, 95%; (c) DMSO, pyridine, TFA, dicyclohexylcarbodiimide, PhH, 16 h, 80%; (d) CH_2PPh_3, THF, reflux, 16 h, 60%; (e) $NHMe_2$, formaldehyde, AcOH, MeOH, 20 h, 84%; (f) dicyclohexylcarbodiimide, THF, 16 h, 76%; (g) Na, EtOH, 30 min then dimethyl sulfate, reflux, 2 h, 42%; (h) NaOH, MeOH, 16 h; (i) H_2O, reflux, 2 h; (j) $SOCl_2$, EtOH, 16 h, 52%; (k) HBr, AcOH, 2 h; (l) Et_3N, toluene, reflux, 18 h, 20%.

Kametani's group produced the first total synthesis of brevianamide E[19,20] (Scheme 4). A 2-reverse prenyl indole derivative was prepared using the method of Tomita[21].

Scheme 4. Synthesis of brevianamide E [a].

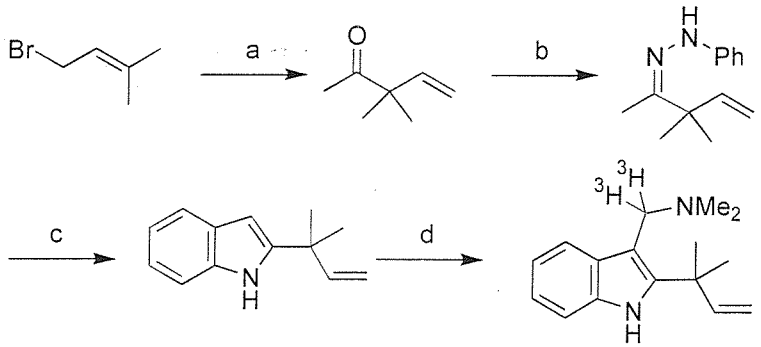


[a] Conditions: (a) *N*-chlorosuccinimide, CH_2Cl_2, -30 °C; (b) indole, CH_2Cl_2, 1 h, 58%; (c) Zn, AcOH, 60 °C, 10 h, 61%; (d) $NHMe_2$, formaldehyde, AcOH, MeOH, 20 h, 84%; (e) $SOCl_2$, PhH, reflux, 2 h then 2-aminodimethylmalonate, Et_2O, 15 °C, 1.5 h, 69%; (f) H_2, Pd/C, MeOH, 70 °C, 1 h; (g) 2-hydroxypyridine, 70 °C, 1 h, 93%; (h) NaH, DMF, 60 °C, 6 h, 74%; (i) $MgCl_2.6H_2O$, DMSO, 130 °C, 2.5 h, 59%; (j) rose bengal, O_2, MeOH, hυ, -8 to –10 °C, 3 h then Me_2S, -10 °C, 16 h, 63%.

Prenyl ethyl sulfide was reacted with *N*-chlorosuccinimide and indole added to the resulting intermediate. This gave the reverse prenylated indole in moderate yield. The sulfide was removed with zinc and acetic acid then converted to a gramine derivative using the method of Houghton and Saxton[18]. This was coupled to a diketopiperazine unit prepared from the coupling of a protected proline derivative with 2-aminodimethylmalonate followed by deprotection then cyclisation by heating in 2-hydoxypyridine. Decarboxylation with $MgCl_2$ in DMSO gave deoxybrevianamide E as well as its epimer in a ratio of 1.5:1. This was converted to brevianamide E by photo-oxygenation. Irradiation of a solution of deoxybrevianamide E in methanol in the presence of rose bengal and oxygen followed by treatment with dimethyl sulfide gave brevianamide E in a 2:1 mixture with its epimer.

Williams and co-workers synthesised a tritium labelled analogue of brevianamide E[22]. This synthesis followed the Kametani route but used an alternate synthesis of the key prenylated gramine derivative (Scheme 5). Reaction of prenyl bromide with acetonitrile and Zn(Ag) gave 3,3-dimethylpent-4-en-2-one which was converted to the phenyl hydrazone. Reflux with $ZnCl_2$ in diglyme gave the desired indole, which was converted to the gramine derivative.

Scheme 5. Preparation of tritium labelled gramine derivative [a].

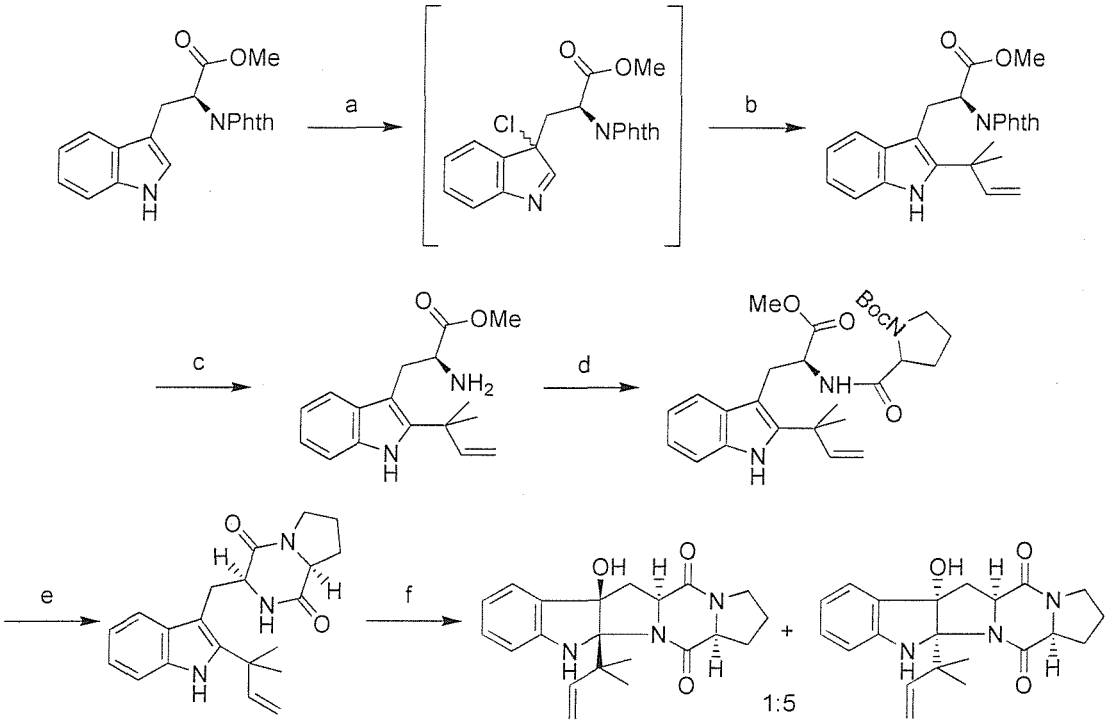


[a] Conditions: (a) Zn(Ag), MeCN, THF, 36 h, 63%; (b) $PhNHNH_2$, toluene, reflux, 30 min; (c) $ZnCl_2$, diglyme, reflux, 9 h, 45%; (d) H_2O, formaldehyde, [^{3} H_2]formaldehyde, Me_2NH, AcOH, 18 h, 83%

The most recent synthesis of deoxybrevianamide E and brevianamide E was by Danishefsky's group[23]. A reverse prenyl group was introduced to phthaloyl protected

tryptophan methyl ester by nucleophilic attack of prenyl 9-BBN on a 3-chloroindolenine derivative (Scheme 6). After removal of the phthaloyl protecting group with hydrazine, the tryptophan unit was coupled with Boc-protected proline. Removal of the Boc group followed by treatment with ammonia gave deoxybrevianamide E. Reaction with dimethyldioxirane gave brevianamide E as a 1:5 mixture with its epimer.

Scheme 6. Synthesis of brevianamide E [a].

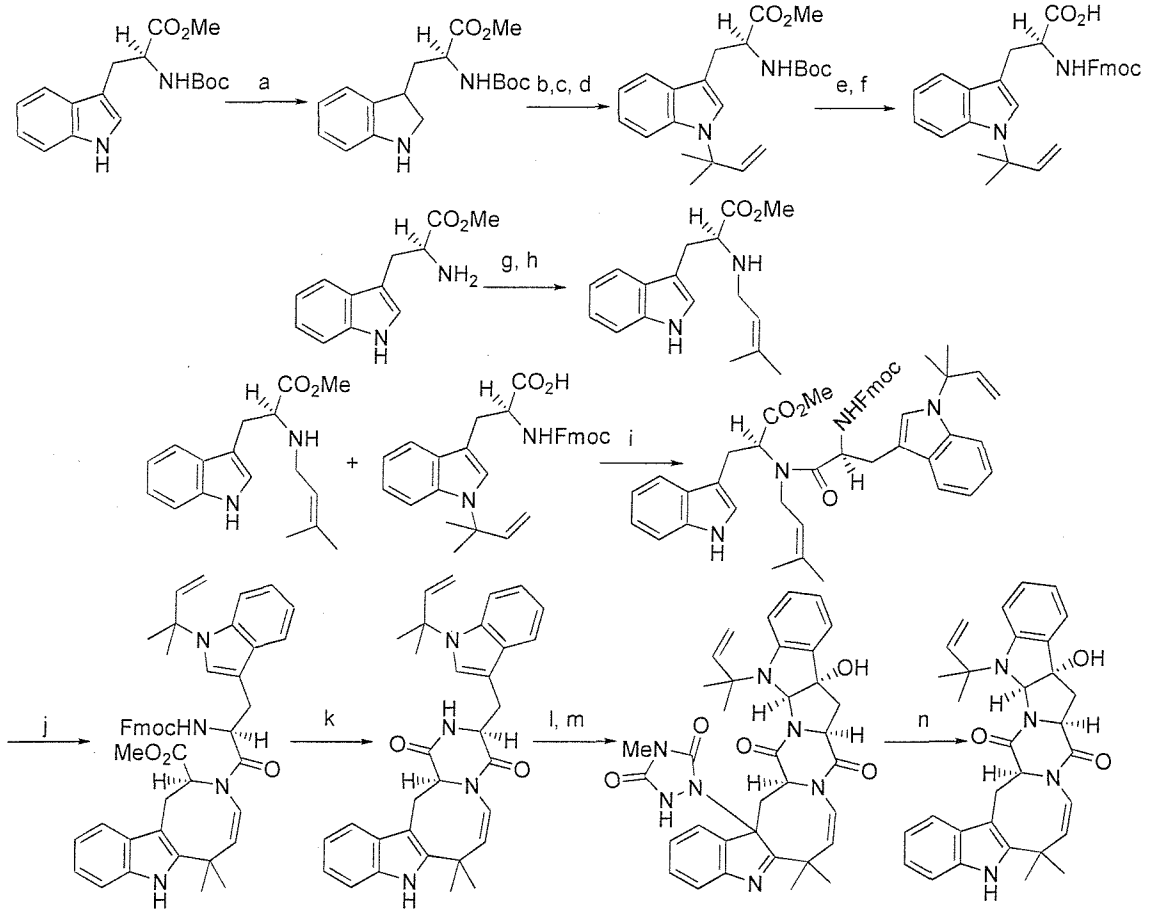


[a] Conditions: (a) *tert*-butyl hypochlorite, Et_3N, THF, -78 °C, 30min; (b) prenyl 9-BBN, -78 °C to rt over 6 h, 95%; (c) NH_2NH_2, EtOH, 3 d, 65%; (d) Boc-L-proline, BOP-Cl, CH_2Cl_2, -78 to 0 °C over 1 h; (e) TFA, CH_2Cl_2, 2 h then NH_3, MeOH, reflux, 12 h, 52%; (f) dimethyldioxirane, acetone, CH_2Cl_2, -78 to 0 °C, 1 h, 76%.

1.6 Okaramine N

Baran, Guerrero and Corey's total synthesis of okaramine N[24] (Scheme 7) was published very recently, almost simultaneously with our own total synthesis of okaramine J (Chapter 2).

Scheme 7. Synthesis of okaramine N [a].



[a] Conditions: (a) $NaBH_3CN$, AcOH, 0 °C, 12 h, 60%; (b) 2-acetoxy-2-methyl-3-butyne, CuCl, $^iPr_2NEt$, THF, 8 h, 93%; (c) DDQ, CH_2Cl_2, 0 °C, 20 min; (d) H_2, Pd/C, quinoline, MeOH, 3 h, 87%; (e) $SOCl_2$, MeOH, 50 °C, 2 h; (f) LiOH, THF, H_2O, 0 °C, 2 h, then FmocCl, CH_2Cl_2, 10% aq. Na_2CO_3, 10 min, 81%; (g) 2-methyl-3-butenal, mol. sieves, CH_2Cl_2, 3 h; (h) $NaBH_4$, MeOH, 30 min; (i) BOP-Cl, $^iPr_2NEt$, CH_2Cl_2, 0 °C, 3 h, 70%; (j) $Pd(OAc)_2$, O_2, dioxane, AcOH, H_2O, 16 h, 38%; (k) Et_2NH, THF, 6 h, 95%; (l) *N*-methyltriazolinedione, CH_2Cl_2, 0 °C, 10 min; (m) O_2, methylene blue, MeOH, hυ, -28 °C, 7.5 h then Me_2S, -28 to -10 °C over 3 h; (n) heat, 110 °C, 30 min, 36%.

Boc-protected tryptophan was reduced to the indoline then alkylated with 2-acetoxy-2-methyl-3-butyne and CuCl. This piece was oxidised back up to the indole with DDQ and the Boc protecting group exchanged for Fmoc. This unit was then coupled to an *N*-prenyl tryptophan derivative prepared by reductive alkylation of tryptophan methyl ester with 2-methyl-3-butenal. The 8-membered ring was formed using $Pd(OAc)_2$, then treatment with base gave the diketopiperazine. The unsubstituted indole was selectively protected with *N*-methyltriazolinedione *via* a thermally reversible ene reaction[25]. This enabled photooxidation and cyclisation at the *N*-substituted indole to give the desired octacycle. Finally, loss of *N*-methyltriazolinedione on heating gave okaramine N.

References

[1] O'Toole, D. K. *J. Agric. Food Chem.* **1999**, *47*, 363-371.

[2] Hayashi, H.; Takiuchi, K.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1989**, *53*, 461-469.

[3] Hayashi, H.; Fujiwara, T.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1991**, *55*, 3143-3145.

[4] Hayashi, H.; Asabu, Y.; Murao, S.; Arai, M. *Biosci. Biotechnol. Biochem.* **1995**, *59*, 246-250.

[5] Hayashi, H.; Sakaguchi, A. *Biosci. Biotechnol. Biochem.* **1998**, *62*, 804-806.

[6] Hayashi, H.; Furutsuka, K.; Shiono, Y. *J. Nat. Prod.* **1999**, *62*, 315-317.

[7] Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1910-1920.

[8] Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **2000**, *64*, 103-110.

[9] Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem*, **2000**, ***64***, 1519-1521.

[10] Steyn, P. S. *Tetrahedron Lett.* **1971**, *12*, 3331-3334.

[11] Steyn, P. S. *Tetrahedron* **1973**, *29*, 107-120.

[12] Hutchison, A. J.; Kishi, Y. *Tetrahedron Lett.* **1978**, *19*, 539-542.

[13] Hutchison, A. J.; Kishi, Y. *J. Am. Chem. Soc.* **1979**, *101*, 6786-6788.

[14] Baran, P. S.; Corey, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 7904-7905.

[15] Birch, A. J.; Wright, J. J. *J. Chem. Soc., Chem. Commun.* **1969**, 644-645.

[16] Ritchie, R.; Saxton, J. E. *Tetrahedron*, **1981**, *37*, 4296-4293.

[17] Houghton, E.; Saxton, J. E. *J. Chem. Soc. (C)* **1969**, 595-599.

[18] Houghton, E.; Saxton, J. E. *J. Chem. Soc. (C)* **1969**, 1003-1012.

[19] Kametani, T.; Kanaya, N.; Ihara, M. *J. Am, Chem. Soc.* **1980**, *102*, 3974-3975.

[20] Kametani, T.; Kanaya, N.; Ihara, M. *J. Chem. Soc., Perkin Trans. 1* **1981**, 959-963.

[21] Tomita, K.; Terada, A.; Tachikawa, R. *Heterocycles*, **1976**, *4*, 733-737.

[22] Sanz-Cervera, J. F.; Glinka, T.; Williams, R. M. *Tetrahedron* **1993**, *49*, 8471-8482.

[23] Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964-11975.

[24] Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628-5629.

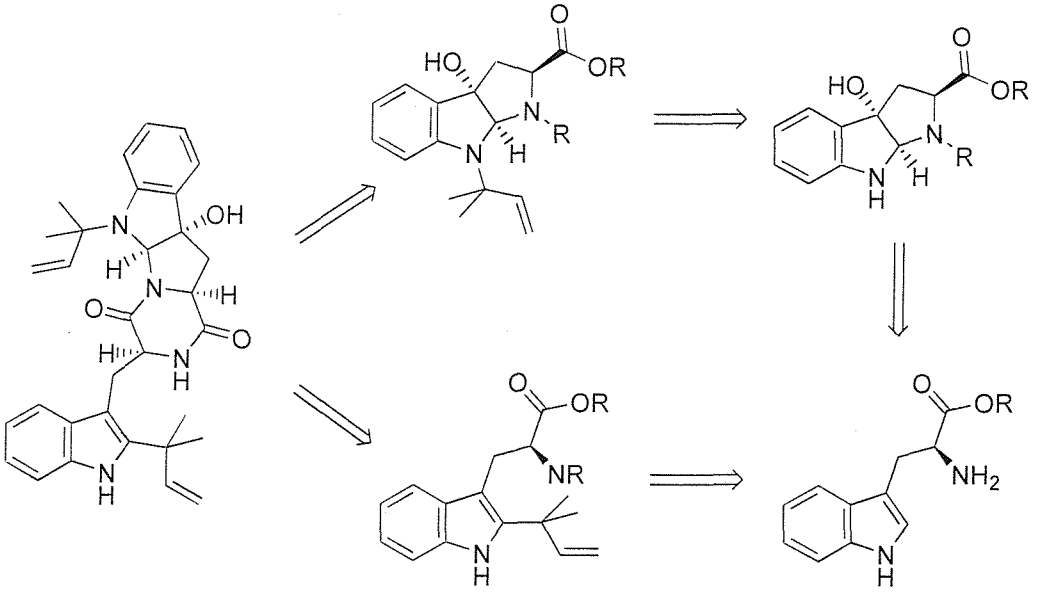
[25] Baran, P. S.; Guerrero, C. A.; Corey, E. J. *Org. Lett.* **2003**, *5*, 1999-2001.

2.0 TOTAL SYNTHESIS OF OKARAMINE J AND C

2.1 Retrosynthesis of okaramine C

The first synthetic target for this project was okaramine C[1]. This was chosen because it is the simplest of this group of alkaloids with biological activity. Retrosynthetic analysis showed that disconnection through the diketopiperazine ring would divide the molecule into two halves, both derived from L-tryptophan (Figure 1). The half containing the hexahydropyrroloindoline substructure could be formed by cyclisation of tryptophan followed by alkylation of the indole nitrogen. The second half requires introduction of a reverse prenyl group at the C-2 position of the indole ring.

Figure 1. Retrosynthesis of okaramine C.

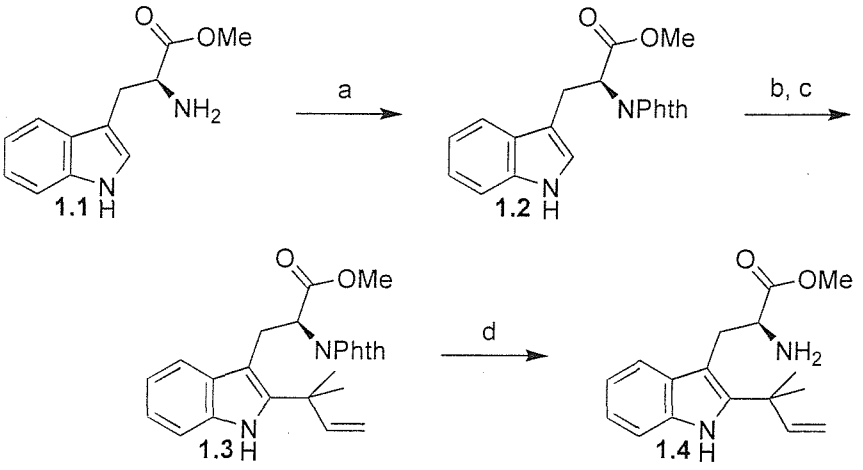


2.2 Preparation of reverse prenyl tryptophan

For the preparation of reverse prenyl tryptophan **1.4** we adopted the method employed by Danishefsky in his synthesis of gypsetin[2] and brevianamide E[3] (Scheme 1). Of the various methods available for the synthesis of reverse prenylated indoles mentioned in the previous

chapter, this is the shortest and highest yielding, and provides enantiomercially pure material.

Scheme 1. Synthesis of reverse prenyl tryptophan derivative [a].

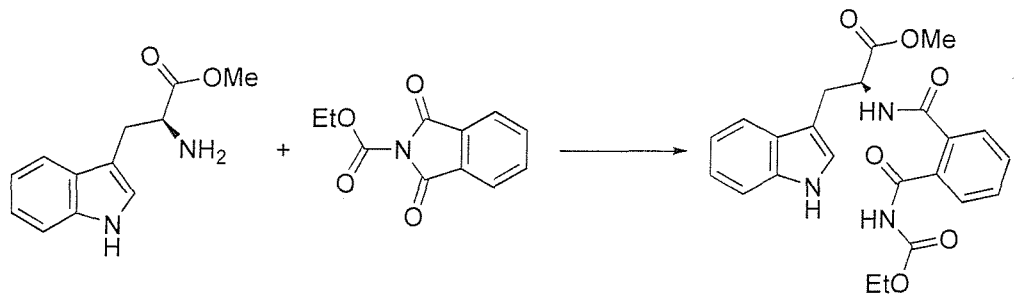


[a] Conditions: (a) phthalic anhydride, Et_3N, toluene, reflux, 7 h, 82%; (b) ^tBuOCl, Et_3N, THF, -78 °C, 30 min; (c) prenyl 9-BBN, 1M in THF, -78 to 0 °C over 5 h, 85%; (d) hydrazine, EtOH, 3 d, 50%.

This synthesis first required protection of tryptophan as the phthalate **1.2**. The method of protection was not described in detail in the Danishefsky paper, and a modified procedure whereby an amino acid is reacted with *N*-carbethoxyphthalimide in water was referred to. This reaction was carried out according to the procedure given in the literature[4]. However, in our hands the reaction failed to give the desired product. The major product was a white solid, which was insoluble in most solvents. An alternative method was attempted using *N*-carbethoxyphthalimide with THF as the solvent and addition of catalytic DMAP[5]. Again, the only isolable product was a white solid, which was recrystallised from hot methanol.

The failure of this method was attributed to the precipitation of an intermediate before complete reaction had occurred. Nucleophilic attack of tryptophan would cause ring opening of the phthalimide to give an intermediate with a large number of amide bonds (Figure 2). It is likely that this intermediate would be highly insoluble resulting in its precipitation before ring closure and elimination of ethyl carbamate could take place.

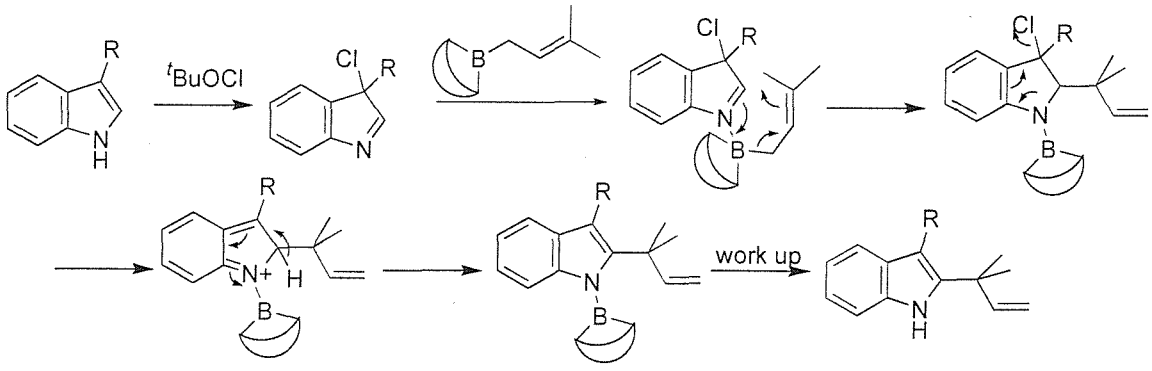
Figure 2. Probable outcome of the reaction of L-tryptophan methyl ester with *N*-carbethoxyphthalimide.



As the use of *N*-carbethoxyphthalimide to afford protected tryptophan methyl ester was unsuccessful, an alternative route was sought. Reaction of tryptophan methyl ester with phthalic anhydride in the presence of triethylamine in toluene[6] gave the desired phthalate in 82% yield. Refluxing of the material from the previous failed reactions in acetonitrile gave the same product as obtained by the phthalic anhydride reaction. This would indicate that this material was indeed an insoluble intermediate.

With the phthalate in hand, prenyl 9-BBN[7] and *tert*-butyl hypochlorite[8] were prepared and reacted with **1.2** to give prenylated tryptophan **1.3** in 85% yield. A proposed mechanism for the addition of prenyl 9-BBN to a chloroindolenine to give a reverse prenylated indole is shown in Figure 3.

Figure 3. Proposed mechanism for the formation of a reverse prenylated indole.



Removal of the phthaloyl protecting group was accomplished with hydrazine to give tryptophan derivative **1.4** in 50% yield, thus completing the synthesis of one half of the okaramine C diketopiperazine.

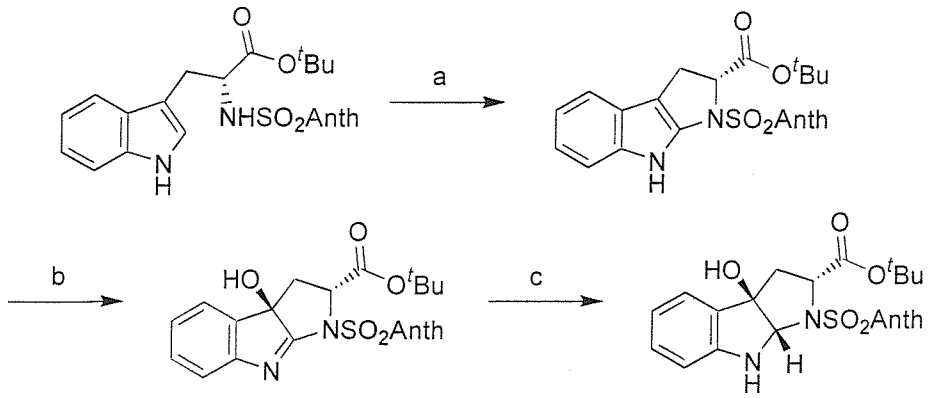
Alkylation of C=N compounds with allylindium species have been reported[9,10]. Introduction of a reverse prenyl group using prenylindium bromide was attempted as an alternative to using prenyl 9-BBN. The reaction was tried with *N*-phthaloyl tryptophan methyl ester **1.2** and the chloroindolenine intermediate from the reaction of **1.2** with *tert*-butylhypochlorite. Neither method showed any reaction. This was due partly to the unreactivity of the indole moiety and also the difficulty in forming prenylindium bromide.

2.3 Preparation of hexahydropyrroloindoline core

Initially, attempts were made to form the hexahydropyrroloindoline ring system by epoxidising the indole ring followed by intramolecular cyclisation. Oxidations with *meta*-chloroperbenzoic acid were attempted on tryptophan and tryptophan methyl ester without success. Sharpless asymmetric epoxidation of tryptophol to form 3a-hydroxyfuroindoline has been reported[11]. This reaction was carried out on tryptophan methyl ester and Fmoc-tryptophan to see if the epoxidation would work on a tryptophan substrate to give the desired pyrroloindoline ring system. However, although the reactions showed some change by TLC, only starting material was isolated on work up.

A route to the hexahydropyrroloindoline substructure has been developed by Danishefsky and Kamenecka as part of their synthesis of himastatin[12]. Anthracenyl sulfonamide protected tryptophan *tert*-butyl ester is cyclised using *N*-bromosuccinimide (NBS) to form a dihydropyrroloindole. This is oxidized using dimethyldioxirane (DMDO) in acetone followed by reduction of the intermediate imine to give the hexahydropyrroloindoline (Scheme 2). This route has the added advantage that the hexahydropyrroloindoline can be prepared with the desired stereochemistry through the careful choice of protecting groups.

Scheme 2. Preparation of a pyrroloindoline [a].

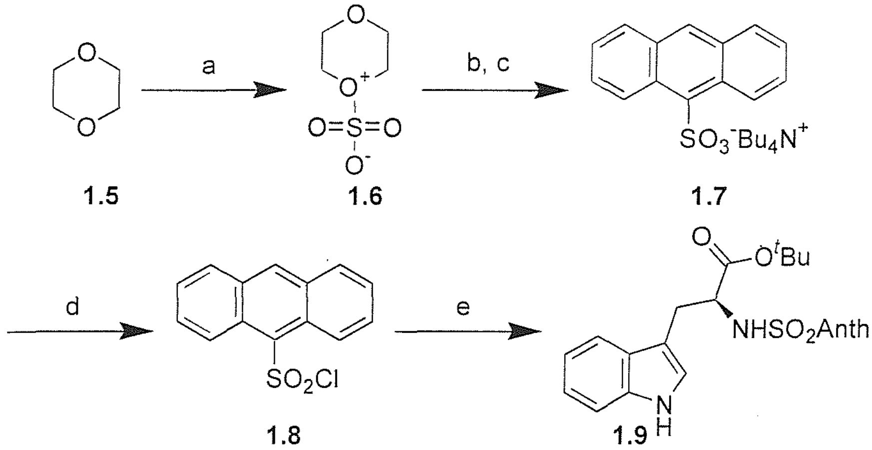


[a] Conditions: (a) NBS, Et_3N, CH_2Cl_2, 0 °C to RT, 30 min; (b) DMDO solution in acetone, CH_2Cl_2, -78 °C, 10 min; (c) $NaBH_4$, MeOH, 0 °C to RT, 4 h, 75% (3 steps).

Since anthracene sulfonyl chloride was not commercially available, the synthesis was attempted with 2,4-dinitrobenzenesulfonamide as the protecting group. The sulfonamide was prepared from tryptophan *tert*-butyl ester in 76% yield. A solution of DMDO in acetone was prepared[13] and the oxidation attempted. The reaction was tried on a small scale (100 mg) and only starting material was obtained. Reaction on a larger scale (1 g) gave a complex mixture of products as well as starting material. It was decided to abandon this protecting group and make the anthracenyl sulfonamide protected tryptophan **1.9** (Scheme 3).

Trimethylsilylchlorosulfonate was reacted with dioxane to give a dioxane-SO_3 complex and TMS-Cl, which was removed by distillation. The dioxane-SO_3 complex was reacted with anthracene to give the sulfate, which was isolated as the tetrabutylammonium salt **1.7**[14]. The sulfonyl chloride **1.8** was prepared in 94% yield from the reaction of **1.7** with $POCl_3$[15]. This was reacted with L-tryptophan *tert*-butyl ester to give **1.9** in 64% - 68% yield after column chromatography. A small amount of less pure material was also obtained.

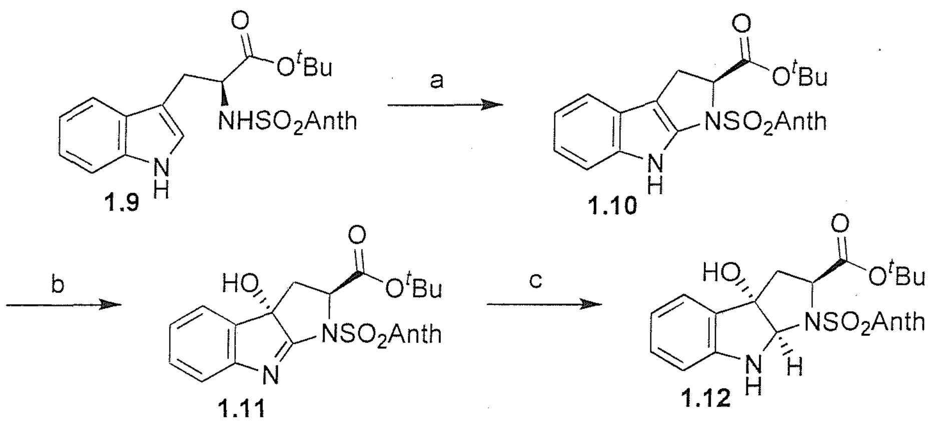
Scheme 3. Preparation of anthracenyl sulfonamide protected tryptophan [a].



[a] Conditions: (a) $TMSOSO_2Cl$, 5 min; (b) anthracene, 2 h; (c) Bu_4NHSO_3, NaOH, H_2O, 50%; (d) $POCl_3$, sulfolane, CH_3CN, 10 min, 94%; (e) L-Trp-O^{t}Bu, pyridine, CH_2Cl_2, 5 h, 78%.

The pyrroloindoline was made by reaction of **1.9** with *N*-bromosuccinimide to form dihydropyrroloindole **1.10** followed by oxidation with DMDO, then reduction with $NaBH_4$ (Scheme 4). Stereochemical assignment of hexahydropyrroloindoline **1.12** was made based on correlation of the ^{1}H NMR data with that reported by Kamenecka and Danishefsky[12] for its enantiomer.

Scheme 4.Preparation of hexahydropyrrolindole [a]



[a] Conditions: (a) NBS, Et_3N, CH_2Cl_2, 0 °C, 30 min, 83%; (b) DMDO solution in acetone, CH_2Cl_2, -78 °C, 10 min; (c) $NaBH_4$, MeOH, 0 °C to RT over 4 h, 71% .

Formation of the dihydropyrroloindole **1.10** was achieved by reacting the tryptophan sulfonamide **1.9** with NBS then adding triethylamine. This reaction did not proceed in the expected manner[12]. Initial attempts at this reaction gave two products as well as unreacted starting material. The major product was a yellow solid. The minor product, an orange solid, was shown to be the desired material by MS and NMR. When the undesired product was investigated further, MS showed peaks at 577 and 579 in a 1:1 ratio indicating incorporation of bromine. ^{1}H NMR showed only three protons in the aromatic region in addition to those due to the anthracene system, showing that bromination of **1.10** had occurred in the indole ring. However, due to overlap of these signals between 7.00 and 7.35 ppm, it was impossible to determine the exact position of the bromine atom.

Many attempts were made to improve the overall yield and selectivity of the NBS reaction. NBS was recrystallised before use but this did not make a significant difference. The time of addition of triethylamine and NBS, the number of equivalents of NBS added and the length of reaction time were investigated. It was found that a longer reaction time did not improve the yield. Use of more than 1 equivalent of NBS consumed more starting material but did not improve selectivity. The time of addition of triethylamine did not make a significant difference when an excess of NBS was used. A large excess of triethylamine did not give better results. The reaction was tried using solvents that had been degassed with Ar before use and 1 equivalent of NBS. This gave fewer products but a low yield. The best yield (88%) and purity was obtained using degassed solvents with 1.3 equivalents of NBS. Unfortunately, when these conditions were tried on a larger (1 g) scale the results were not as good as the small scale reactions, although better than previous attempts.

At this stage Professor Samuel Danishefsky and Dr. Ted Kamenecka were consulted, who gave helpful suggestions. The key to the NBS reaction was to carry it out in the dark. Under these conditions the desired dihydropyrroloindole **1.10** was obtained in good yield on multigram scale without significant amounts of the brominated by-product.

As solutions of DMDO in acetone had been cumbersome to prepare, it was thought that an *in situ* method of forming a dioxirane might be easier to carry out. A method of generating

a dioxirane *in situ* using trifluoroacetone, oxone and $NaHCO_3$ in a mixture of acetonitrile and EDTA.Na_2 solution was attempted on **1.10**[16]. The oxidation appeared to proceed cleanly by TLC. However, when the reduction step was carried out TLC showed a complex mixture of products.

It was considered that the reaction might have had too much water present. The reduction was repeated using distilled MeOH. A large amount of starting material remained after 4 hours. A further excess of $NaBH_4$ was added and the reaction left overnight. There was still starting material present. After work up and purification a yellow solid was obtained in 12% yield. MS and NMR appeared to be consistent with the desired product, although impurities were still present.

The oxidation step was repeated and rather than continuing with the reduction, the intermediate was purified by column chromatography to give a 15% yield of clean product as well as a further 32% of less pure material. This was characterised by MS and ^1H NMR and was found to be consistent with the imine intermediate **1.11**. Although TLC had shown this reaction to be complete the yield was poor. This indicated it was the oxidation conditions rather than the reduction conditions that were low yielding. The *in situ* dioxirane oxidation uses a large excess of trifluoroacetone and, therefore, dioxirane. It was considered that this might have been the cause of the low yields.

A solution of DMDO in acetone was prepared and the concentration estimated by oxidation of thioanisole to phenyl methyl sulfoxide then ^1H NMR of the products[17]. Dr. Kamenecka recommended the use of 'aged' DMDO that had been stored over molecular sieves for at least 1 week. The oxidation of **1.10** was repeated using 1.1 equivalents of DMDO followed by reduction with $NaBH_4$. This gave the desired product in 75% yield.

An alternative method of *in situ* dioxirane formation was attempted. This used 0.05 equivalents of tetrahydothiopyran-4-one as a source of dioxirane instead of a large excess of trifluoroacetone[18]. After reduction with $NaBH_4$ the desired product was obtained in 48%

yield. This was an improvement on the trifluoroacetone method but still not as good as using preformed DMDO in acetone.

2.4 Reverse prenylation of hexahydropyrroloindoline

Having made the hexahydropyrroloindoline core **1.12** it was now necessary to find a method to incorporate an *N*-reverse prenyl group. Initially, it was thought that the free hydroxyl group of **1.12** should be protected. Several attempts were made to attach a silyl protecting group without success and only starting material was obtained in significant yield. Since this hydroxyl seemed to be quite hindered it was decided to attempt the prenylation without protection.

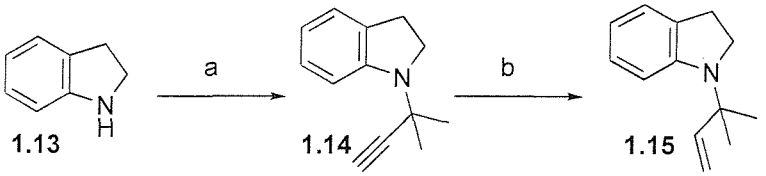
Introduction of an *N*-reverse prenyl group to indoline has been reported by CuCl catalysed addition of 2-methyl-3-butynyl-2-acetate followed by reduction with Lindlar's catalyst[19]. The acetate was prepared and the reaction carried out on **1.12**. However, only starting material was obtained on all attempts.

During other work in the group on the introduction of a prenyl unit at the C-3 position of indole using zinc triflate and prenyl bromide, the *N*-prenyl derivative had been observed as a by-product.[20] This method was explored to introduce a reverse prenyl group to indoline as a model for **1.12**. As indoline does not possess the double bond present in indole, alkylation at the 2 or 3 position is not possible. The reaction with 2-methyl-3-butynyl-2-acetate was investigated, however only starting material was observed. When 2-methyl-3-butynyl-2-bromide[21] was used, a small amount of a new product was obtained. NMR showed this was not the desired product. MS showed the product contained bromine so could be consistent with addition of indoline across the triple bond. When these reaction conditions were investigated further by varying solvents and bases, no significant yield of the desired alkylated product was obtained.

As zinc triflate was giving unsatisfactory results, the reaction was repeated with 2-methyl-3-butynyl-2-bromide returning to CuCl as the catalyst[22]. This gave propargyl indoline **1.14**

in 55% yield (Scheme 5). Varying the equivalents of reagents, as well as heating the reaction at reflux and in a microwave reactor was investigated but the yield could not be improved beyond a moderate 65%. These optimised conditions used 10 mol % of catalyst with a slight excess of the bromide and $^{i}Pr_2NEt$ for 3 hours at RT. The reverse prenylated indoline **1.15** was obtained from **1.14** in 95% yield by reduction with Lindlar's catalyst[18].

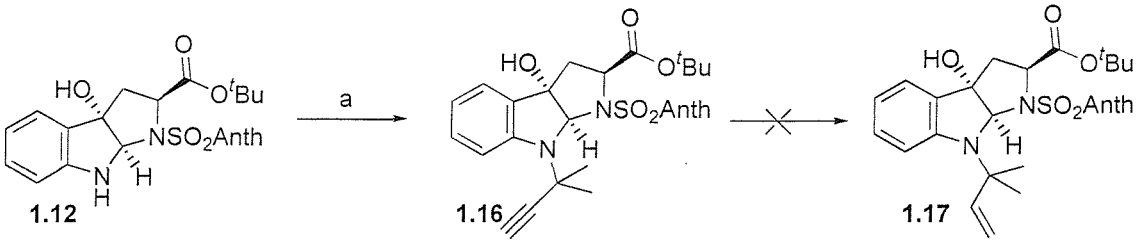
Scheme 5. Preparation of *N*-reverse prenyl indoline [a].



[a] Conditions: (a) $HC{\equiv}CC(CH_3)_2Br$, CuCl, $^{i}Pr_2NEt$, THF, 3 h, 65%; (b) H_2 (1 atm), Lindlar's catalyst, EtOAc, 3 h, 95%.

The reaction of 2-methyl-3-butynyl-2-bromide and CuCl with hexahydropyrroloindoline **1.12** was investigated (Scheme 6). This gave a mixture of the desired product **1.16** (37%), starting material (44%) and a small amount of a dialkylated product (4%). Heating the reaction in a microwave reactor was explored. At lower temperatures and times, the yields were less than at room temperature but higher temperatures and times led to decomposition of starting materials. The reaction was carried out on a larger scale (1 g) and gave a similar ratio of products. Although the yield was less than desirable, starting material could easily be recycled to give sufficient product for the continuation of the synthesis.

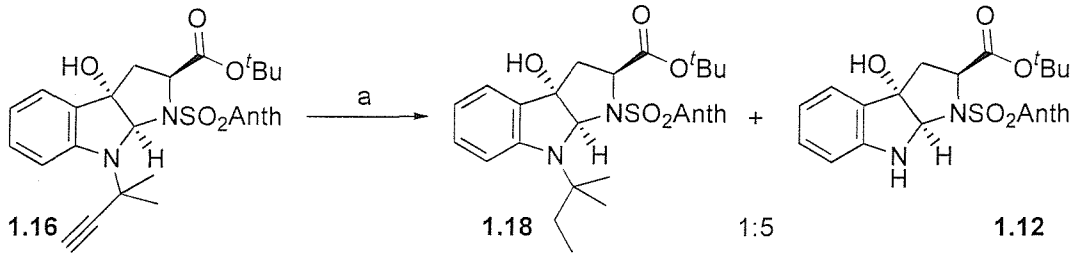
Scheme 6. Alkylation and attempted hydrogenation of hexahydropyrroloindoline [a].



[a] Conditions: (a) $HC{\equiv}CC(CH_3)_2Br$, CuCl, $^{i}Pr_2NEt$, THF, 16 h, 55%.

The hydrogenation of the triple bond to form **1.17** was attempted using Lindlar's catalyst. Although the reaction worked well with model **1.14**, only starting material was recovered when the reaction was attempted on **1.16**, even after several days under H_2. It was considered that the alkyne might be too hindered, requiring harsher conditions for the reduction. This reaction was repeated at a higher pressure (50 psi), however only starting material was observed by NMR. Use of a more active catalyst, Pd/Al_2O_3, gave a mixture of two products after 24 h at 50 psi, corresponding to the over-reduced alkane **1.18** and hexahydropyrroloindoline **1.12** (Scheme 7).

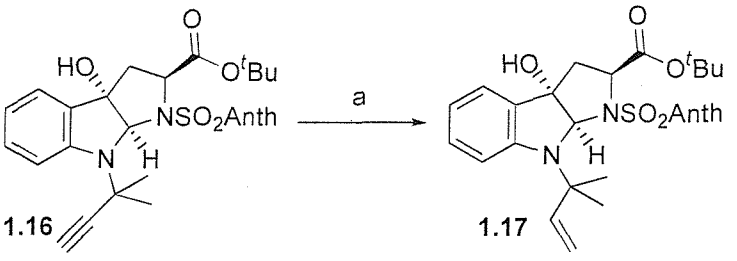
Scheme 7. Over-reduction of alkyne [a]



[a] Conditions: (a) Pd/Al_2O_3, H_2 (50 psi), EtOH, 24 h, >99%.

The reaction was repeated under atmospheric pressure and with a greatly decreased reaction time of 10 min (Scheme 8). This time only the desired alkene **1.17** was obtained.

Scheme 8. Reduction of alkyne to alkene [a].



[a] Conditions: (a) Pd/Al_2O_3, H_2 (1 atm), EtOAc, 10 min, >99%.

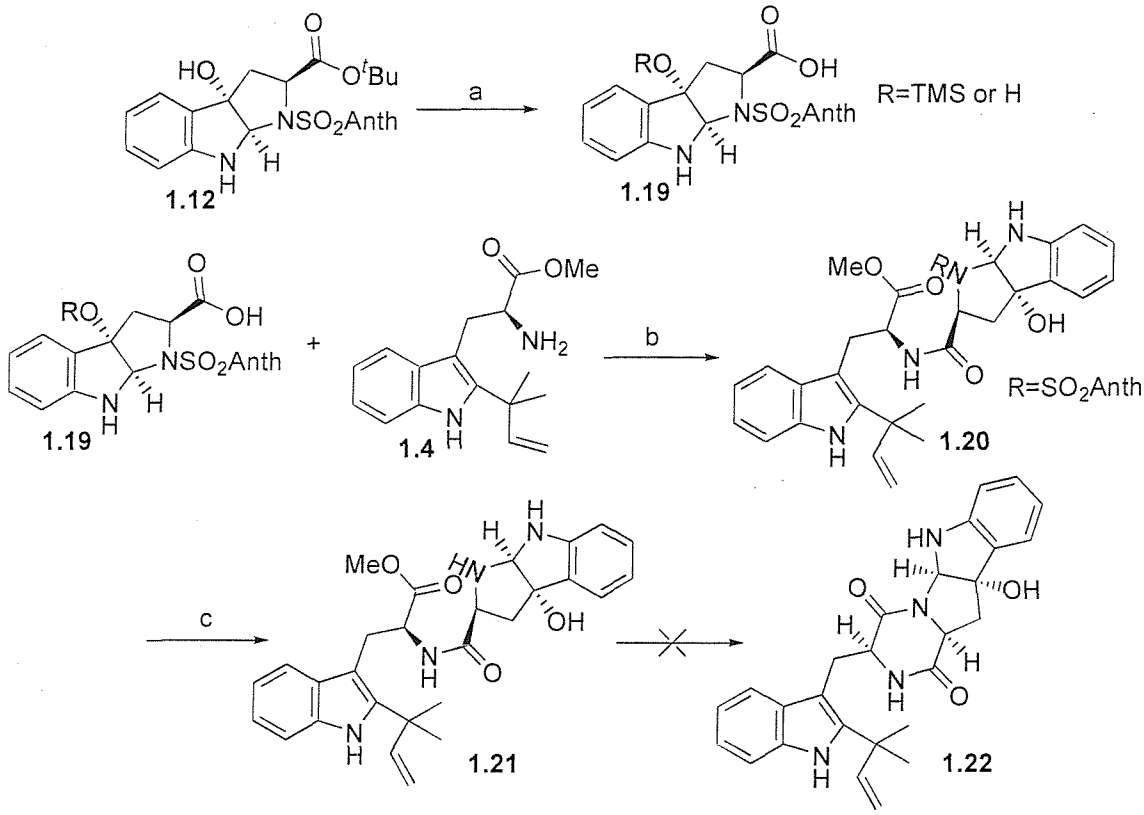
When this reaction was repeated on a larger scale under the same conditions, ^1H NMR showed a mixture of product and starting material in approximately 2:1 ratio. These compounds were very close by TLC and inseparable by column chromatography. On further investigation, it was found that increasing the amount of catalyst from 10 wt % to

20 wt % with a reaction time of 1.5 h reliably gave the desired product in quantitative yield without the need for chromatography.

2.5 Formation of the diketopiperazine ring

With the two halves of the okaramine skeleton in hand, it was necessary to find a method of joining them together to form a diketopiperazine. Initial studies were conducted on the unprenylated hexahydropyrroloindoline **1.12** (Scheme 9).

Scheme 9. Attempted preparation of diketopiperazine ring [a].



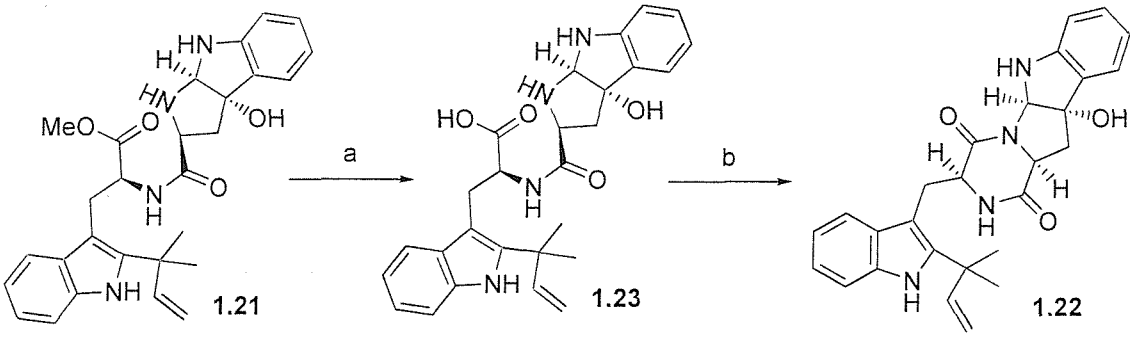
[a] Conditions: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 24 h; (b) PyBOP, NEt_3, THF, 0 °C, 24 h, 79%; (c) Al(Hg), THF/H_2O, 5 h, 86%.

The *tert*-butyl ester of **1.12** was removed using trimethlysilyl triflate (TMSOTf) buffered with 2,6-lutidine[23] to give a mixture of products where the alcohol was either free or TMS protected. This was used without further purification in a coupling step with **1.4**, which

gave amide **1.20** in 79% yield over the two steps. It was hoped that the diketopiperazine would form spontaneously on deprotection of the anthracene sulfonamide. However, when **1.20** was treated with an aluminium/mercury amalgam[24], the deprotected but uncyclised product **1.21** was obtained in 89% yield. Refluxing of **1.21** with $^{i}Pr_2NEt$ or DBU did not induce diketopiperazine cyclisation. The reaction was also carried out in a microwave reactor at various temperatures but only starting material was observed and this route was abandoned. The cyclisation was attempted on methyl ester **1.21** using TMSI[25]. This gave a complex mixture of products, which did not include the desired diketopiperazine.

As it was not possible to form the diketopiperazine ring with the methyl ester in place, it was hydrolysed to the acid **1.23** with KOH. This would enable the use of various peptide coupling reagents to effect the cyclisation. Intramolecular coupling was attempted using PyBOP and Et_3N. After 24 h a single product was obtained in moderate yield. However, NMR showed this to be a mixture of diketopiperazine **1.22** and tricyclohexylphosphine oxide. No starting material could be recovered. The coupling was repeated using a water-soluble carbodiimide (EDAC) and HOBt to avoid formation of inseparable by-products (Scheme 10). After 2 days the reaction was worked up and after purification by column chromatography the diketopiperazine **1.22** was obtained in 33% yield.

Scheme 10. Preparation of diketopiperazine ring [a].

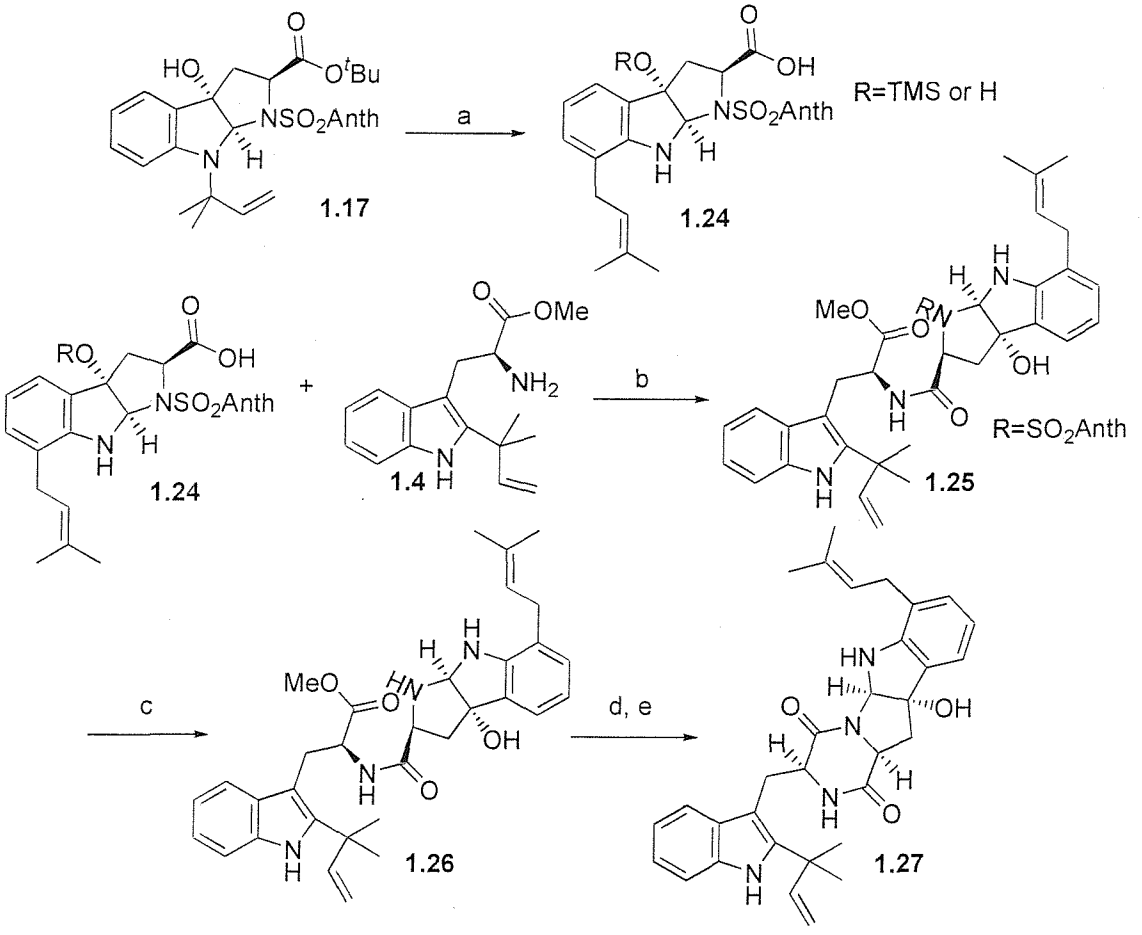


[a] Conditions: (a) 10% KOH in MeOH, 1,4-dioxane, 16 h; (b) EDAC, HOBt, Et_3N, THF, 48 h, 33% (2 steps).

2.6 Attempted preparation of okaramine C

Having found a method for forming a diketopiperazine ring with unalkylated hexahydropyrroloindoline **1.12**, the route was attempted with *N*-reverse prenyl hexahydropyrroloindoline **1.17** (Scheme 11).

Scheme 11. Attempted synthesis of okaramine C [a].



[a] Conditions: (a) TMSOTF, 2,6-lutidine, THF, 24 h; (b) PyBOP, Et_3N, THF, 0 °C, 4 h, 27%; (c) Al/Hg, THF/H_2O, 16 h, 70%; (d) 10% KOH in MeOH, 1,4-dioxane, 16 h; (e) PyBrop, Et_3N, THF, 2 d, 35% (2 steps).

The *tert*-butyl ester was deprotected with TMSOTf and acid **1.24** coupled to tryptophan derivative **1.4** in a surprisingly low 27% yield compared to 79% for the unalkylated case. The anthracenyl sulfonamide and methyl ester protecting groups were removed and the

diketopiperazine ring formed in 35% yield with PyBrop. This was comparable to the 33% yield obtained previously with EDAC and HOBt.

Comparison of the ^{1}H NMR spectra of the isolated compound with that reported for okaramine C[1] showed this was not the desired product, despite having the same mass. However, the NMR data did correspond exactly to those reported for okaramine J **1.27**[26]. This compound had resulted from an aza-Claisen rearrangement of the *N*-reverse prenyl group onto the aromatic ring. Further study of the NMR data for the intermediates showed this transfer had occurred during the *tert*-butyl ester deprotection. In all ^{1}H NMR spectra after this step a signal at approximately 5.3 ppm ($CH_2C\mathbf{H}=C(CH_3)_2$) and two signals at approximately 3.2 ppm ($C\mathbf{H}_2CH=C(CH_3)_2$) were present. The absence of the aromatic proton on the indole ring was difficult to see due to the large amount of signals in the aromatic region. Rearrangement at this step meant an alternative deprotection strategy would be required to make okaramine C. However, the first total synthesis of okaramine J has been achieved as a result of this "undesired" rearrangement.

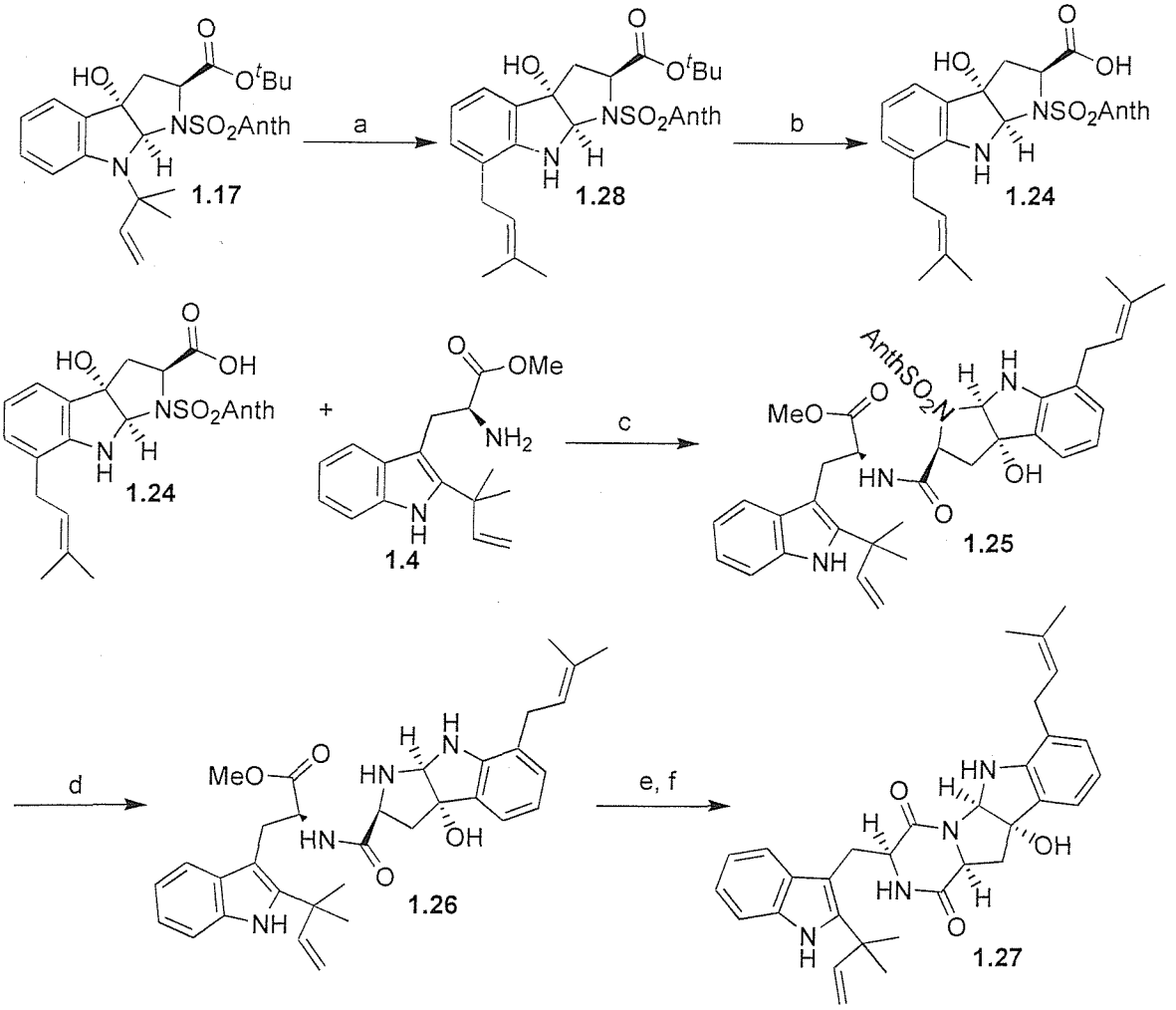
2.7 Aza-Claisen rearrangements of aromatic allylamines

The aza-Claisen rearrangement of aromatic allylamines is precedented in the literature, although not under as mild conditions as those used for the synthesis of okaramine J. Carnahan and Hurd first studied this rearrangement, subjecting *N*-allylaniline to pyrolysis[27]. This attempt was unsuccessful, however, a later study into this rearrangement by Hurd and Jenkins gave *o*-allylaniline in 42% yield by refluxing *N*-allylaniline in xylene and zinc chloride[28]. Most recent examples[29,30] of aromatic aza-Claisen rearrangements have used either protic or Lewis acid catalysis or quaternary anilinium substrates and reactions are conducted at temperatures greater than 100 °C.

2.8 Total synthesis of okaramine J

Since the aza-Claisen rearrangement and deprotection of *N*-reverse prenyl hexahydropyrroloindoline **1.17** with TMSOTf had proceeded in low yield, an alternative method was sought to improve the synthesis of okaramine J (Scheme 12).

Scheme 12. Preparation of okaramine J [a].



[a] Conditions: (a) TFA, CH_2Cl_2, 16 h, 84%; (b) TMSOTf, 2,6-lutidine, CH_2Cl_2, 16 h, 75%; (c) PyBOP, Et_3N, THF, 0 °C, 5 h, 82%; (d) Al/Hg, THF/H_2O, 16 h, 73%; (e) 10% KOH in MeOH, 1,4-dioxane, 16 h; (f) HBTU, $^iPr_2NEt$, CH_2Cl_2, 7 d, 49%.

As both the rearrangement and the deprotection step are acid catalysed, it was hoped that both could be achieved in the same step. Hexahydropyrroloindoline **1.17** was heated in a microwave reactor for 30 min at 60 °C with 5 equivalents of TFA in CH_2Cl_2. NMR spectra of the crude material showed the rearrangement had occurred without the removal of the ester. The reaction was repeated at 100 °C, however, at this temperature the material started to decompose. Reaction of **1.17** with TFA at room temperature gave the rearranged product **1.28** in 84% yield without ester deprotection. This material was treated with TMSOTf to remove the ester and coupled with **1.4** to give diketopiperazine precursor **1.25** in 82% yield compared to 27% for the previous attempt. Following removal of the anthracenyl sulfonamide and methyl ester, the final diketopiperazine formation was achieved using HBTU to give okaramine J in 49% yield.

2.9 Total synthesis of okaramine C

Having completed the synthesis of okaramine J, it was time to return to the original target of okaramine C. This required finding an alternative method for removal of the *tert*-butyl ester without the undesired rearrangement occurring. Various methods were investigated for the deprotection of the *tert*-butyl ester **1.17** under non-acidic conditions. Base hydrolysis of the ester was attempted with KOH in MeOH. At RT no reaction was observed, however, addition of 18-crown-6 and heating to reflux in toluene[31] led to decomposition of starting material and product. Enzymatic removal of the ester with pig liver esterase[32] was attempted but no reaction was observed. Thermolysis[33] was also attempted but resulted in decomposition.

Two alternative strategies were explored: removal of the *tert*-butyl ester prior to the hydrogenation step forming the reverse prenyl moiety and converting the *tert*-butyl ester to an ethyl ester which could be removed under basic conditions.

Alkyne **1.16** was deprotected with TMSOTf and submitted to the hydrogenation conditions. Although this reaction was not very clean, a small amount of the alkene was obtained. This material was coupled with **1.4** and submitted to the same conditions used to

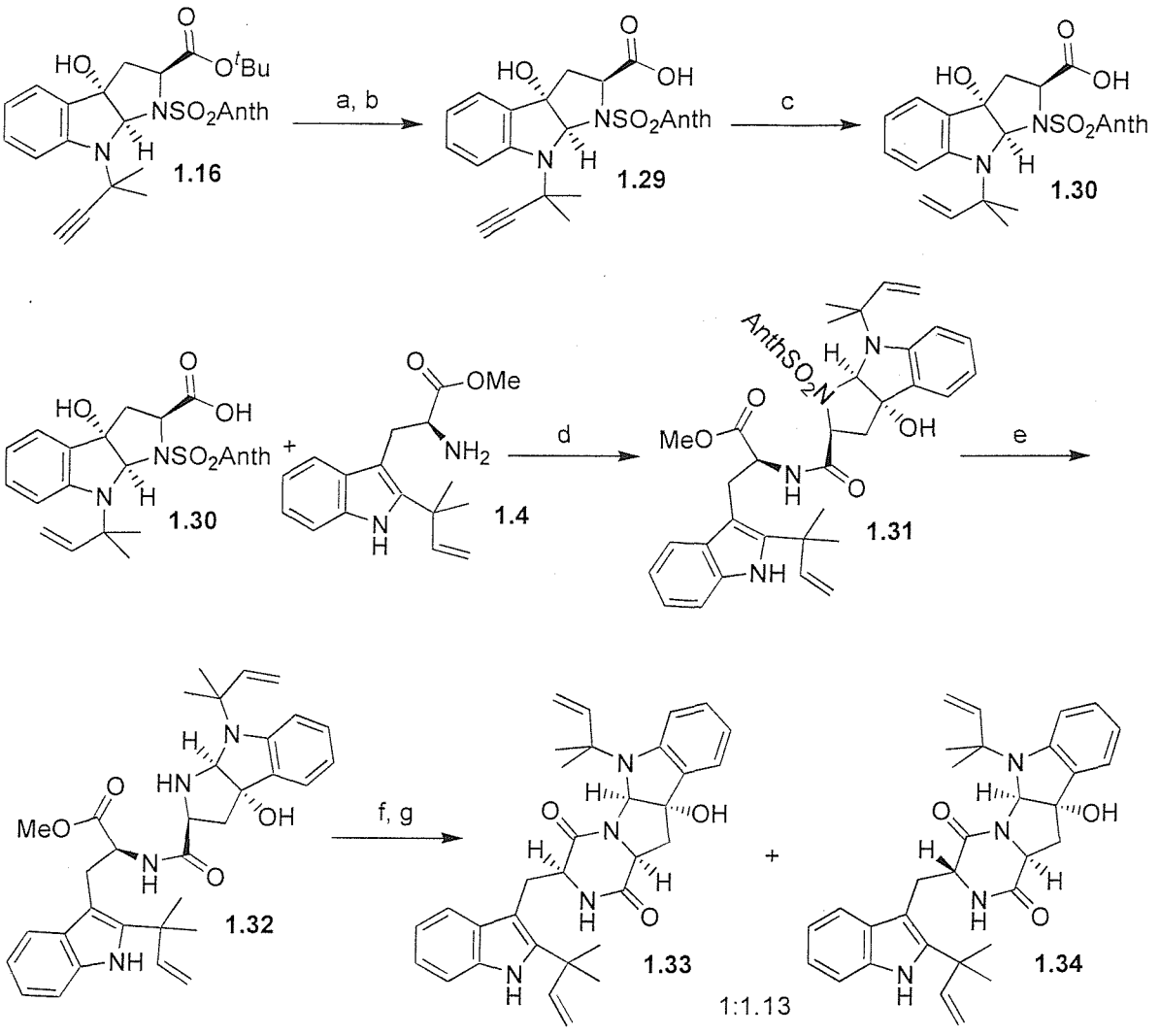
form okaramine J. This gave a mixture of okaramine C and another product. NMR and MS showed this was a mixture of alkene and alkyne, which could not be separated by column chromatography.

As the deprotection then hydrogenation strategy did not seem as simple as hoped, the alternative change of protecting group was investigated. The *tert*-butyl ester was removed as above then treated with TBAF as TLC showed a mixture of free and TMS protected OH. Formation of the ethyl ester was attempted using EtOH, DCC and DMAP[34] as strongly acidic ester formation conditions were unsuitable for this sensitive molecule. Unfortunately the coupling did not proceed cleanly and only gave a low yield of the desired product.

It was decided to attempt the hydrogenation of the free acid again on a larger scale. Alkyne **1.16** was treated with TMSOTf (Scheme 13). TLC showed a mixture of free and TMS protected OH. The crude product was passed through a column of silica to remove impurities at the solvent front and on the baseline. The mixture was then treated with TBAF and purified by column chromatography to give acid **1.29** in 73% yield. This was smoothly hydrogenated to give alkene **1.30** in quantitative yield.

Having successfully completed the synthesis of the hexahydropyrroloindoline half of okaramine C, it could be coupled with reverse prenyl tryptophan derivative **1.4** prior to deprotection and the final diketopiperazine formation. Initially the PyBOP coupling looked like it had proceeded cleanly and quantitatively. However, NMR and MS showed the material was heavily contaminated with the alkyl phosphine oxide by-product from the PyBOP coupling. This was removed by passing the material through a pad of alumina in EtOAc to give the clean product **1.31** in a more disappointing 50% yield. HBTU was used to bring about the coupling in greater yield but only achieved 29%. Use of two equivalents of amine **1.4** improved the yield to 57% with PyBOP and 62% with HBTU. The best result in terms of yield and economy of starting materials was using EDAC and HOBt with a slight excess of **1.4**. This gave the desired product in 59% yield. Use of resin-bound EDAC gave a comparable 61% yield.

Scheme 13. Synthesis of okaramine C [a].



[a] Conditions: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, 16 h; (b) TBAF, THF, 1 h, 92%; (c) H_2 (1 atm), Pd/Al_2O_3, EtOAc, 2 h, 99%; (d) EDAC, HOBt, Et_3N, THF, 4 d, 59%; (e) Al/Hg, THF/H_2O, 7 h, 78%; (f) 10% KOH in MeOH, 1,4-dioxane, 8 h; (g) HBTU, $^iPr_2NEt$, CH_2Cl_2, 24 h, 32%.

Finally, the anthracenyl sulfonamide protecting group was removed and the methyl ester hydrolysed before diketopiperazine formation with HBTU. After purification by column chromatography, ^1H NMR showed a mixture of products with the same functional groups as in okaramine C. These were separated by preparative TLC on alumina to give two

compounds: okaramine C **1.33** and an unknown compound in a ratio of 1:1.3. MS showed the unknown compound had the same mass as okaramine C. The ^{1}H NMR spectrum was consistent with okaramine C and dd signals at 6.50 and 6.13 ppm showed both reverse prenyl groups were still present so the unknown compound could not be okaramine J. It seemed most likely that racemisation had occurred during the coupling step to give epi-okaramine C **1.34**. The optical rotations of **1.33** and **1.34** (+3.0 and +112.5 respectively) were significantly different as would be expected for two different diastereomers.

Two other coupling agents were investigated for the final coupling step in order to avoid epimerisation. Coupling with PyBrop was attempted but this did not give a significant yield of clean product. As work up and purification of the final step had proved difficult, a resin bound carbodiimide was employed. After reacting for 48 h the resin was washed and removed by filtration. The filtrate was concentrated, then purified by preparative TLC to give okaramine C in 57% yield as a single isomer.

2.10 Summary

The first total synthesis of okaramine alkaloids J and C has been achieved. This has involved the alkylation of a sterically hindered hexahydropyrroloindoline with an alkynyl bromide, followed by hydrogenation to an alkene using Pd/Al_2O_3 catalyst. This *N*-reverse prenyl hexahydropyrroloindoline was used in the synthesis of okaramine J as a result of a facile acid-catalysed *N*-reverse prenyl to *C*-prenyl aza-Claisen rearrangement[35]. A similar reaction was observed by Corey in his recently published synthesis of okaramine N[36]. Conditions have been found that avoid this rearrangement, enabling the total synthesis of okaramine C. The final diketopiperazine cyclisation involved reaction of a highly hindered and electronically deactivated amine with an activated ester. As this process was slow, epimerisation occurred and okaramine C was obtained together with its diastereomer in approximately equal quantity. When this cyclisation was repeated using a resin bound coupling agent okaramine C was obtained as a single diastereomer.

2.11 Experimental

2.11.1 General Methods

All chemicals were obtained from commercial suppliers and used without further purification except where stated. CH_2Cl_2 and MeOH were distilled from CaH_2. THF was distilled over Na wire and benzophenone. TLC was carried out on precoated plates: analytical (Merck; Kieselgel 60 F_{254}, aluminium backed), spots visualised with UV light and phosphomolybdic acid solution or $KMnO_4$ solution. Column chromatography was performed with silica (Apollo Scientific; 40-63 micron) unless stated otherwise. Infrared spectra (IR) were recorded on a Nicolet 400 FT-IR fitted with a Thunderdome HATR Ge crystal or NaCl plates and absorptions labelled as strong (s), medium (m) or weak (w). Mass spectra were recorded on a Navigator open access Electrospray (positive ionisation unless stated otherwise). NMR spectra were recorded on a Bruker AC300 (^{1}H, 300 MHz; ^{13}C, DEPT, 75MHz; solvent $CDCl_3$) unless stated otherwise where they were recorded on a Bruker DPX400. Optical rotations were recorded on an Optical Activity POLAAR 2001. Melting points are uncorrected.

2.11.2 N- *Phthaloyltryptophan methyl ester* **1.2**

A solution of L-tryptophan methyl ester (12.4 g, 57 mmol) and phthalic anhydride (9.3 g, 63 mmol) in Et_3N (12 mL) and toluene (60 mL) was refluxed for 7 h. The solvent was evaporated and the residual yellow oil dissolved in EtOAc (150 mL), washed with 5% HCl (2 x 50 mL) and water (50 mL), dried over Na_2SO_4, filtered and the solvent evaporated to give a yellow foam. This was dissolved in EtOH, ice/water added and the mixture shaken. The resultant solid was removed by filtration and recrystallised from EtOH/water to give **1.2** as a yellow solid (11.5 g, 58%): mp 62-64 °C (lit. 119-120 °C[6]); IR ν_{max} 3389w, 1740s, 1708s cm^{-1}; ^{1}H NMR δ 8.04 (1H, bs, N**H**), 7.75 (2H, dd, *J* = 5.5, 2.9 Hz, Ar**H**), 7.66 (2H, dd, *J* = 5.5, 2.9 Hz, Ar**H**), 7.61 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.27 (1H, d, *J* = 6.3 Hz, Ar**H**), 7.14 (1H, td, *J* = 7.9, 1.1 Hz, Ar**H**), 7.06 (1H, td, *J* = 7.9, 1.1 Hz, Ar**H**), 7.00 (1H, d, *J* = 2.2 Hz, Ar**H**), 5.29 (1H, dd, *J* = 9.2, 6.6 Hz, C**H**), 3.81 (3H, s, C**H**$_3$), 3.76 (2H, dd, *J* = 9.6, 6.6 Hz, C**H**$_2$); ^{13}C NMR δ 169.9 (**C**), 167.8 (**C**), 136.2 (**C**), 134.2 (**C**), 131.8 (**C**), 127.3

(**C**), 123.6 (**C**H), 122.7 (**C**H), 122.2 (**C**H), 119.7 (**C**H), 118.6 (**C**H), 111.3 (**C**H), 111.2 (**C**H), 53.0 (**C**H), 52.7 (**C**H_3), 24.9 (**C**H_2); MS *m/z* 387 $[M+K]^+$.

*2.11.3 3-[2-(1,1-Dimethylallyl)-1*H*-indol-3-yl]-2-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-propionic acid methyl ester* **1.3**

To a solution of **1.2** (3.1 g, 8.9 mmol) in Et_3N (1.49 mL, 10.7 mmol) and THF (40 mL) at –78 °C was added *t*-BuOCl[8] (1.27 mL, 10.7 mmol) and the solution stirred for 30 min. Prenyl 9-BBN[7] (1M in THF, 17.8 mL, 17.8 mmol) was added and the reaction allowed to warm to RT over 5 h. The reaction was quenched with saturated aqueous Na_2CO_3 (20 mL), the layers separated and the aqueous layer extracted with EtOAc (2 x 20 mL). The organic phases were combined, dried over Na_2SO_4, filtered and the solvent evaporated to give the crude product as a brown oil. This was purified by column chromatography (150 g silica, eluent 15% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **1.3** as a yellow foam (3.16 g, 85%): ^{1}H NMR δ 7.95 (1H, bs, N**H**), 7.70 (2H, dd, *J* = 5.5, 3.3 Hz, Ar**H**), 7.62 (2H, dd, *J* = 5.5, 3.3 Hz, Ar**H**), 7.29 (1H, d, *J* = 8.5 Hz, Ar**H**), 7.13 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.91 (1H, dd, *J* = 8.1, 6.1 Hz, Ar**H**), 6.72 (1H, dd, *J* = 8.5, 6.1 Hz, Ar**H**), 6.21 (1H, dd, *J* = 17.4, 10.4 Hz, C**H**), 5.13-5.27 (3H, m, CH_2, C**H**), 3.88 (1H, dd, *J* = 15.1, 3.9 Hz, CH_2), 3.79 (3H, s, CH_3), 3.69 (1H, dd, *J* = 15.1, 11.4 Hz, C**H**), 1.60 (6H, s, 2 x CH_3). The spectroscopic properties were consistent with that reported in the literature (ref 3).

*2.11.4 2-Amino-3-[2-(1, 1-dimethyl-allyl)-1*H*-indol-3-yl]-propionic acid methyl ester* **1.4**

To a solution of **1.3** (4.0 g, 9.6 mmol) in EtOH (60 mL) was added hydrazine monohydrate (1.4 mL, 28.8 mmol) and the solution was stirred for 3 d at RT. After this time a white precipitate had formed. The mixture was diluted with water (100 mL) and extracted with EtOAc (3 x 75 mL). The organic phases were combined, washed with water (75 mL) and brine (75 mL), dried over $MgSO_4$, filtered and the solvent evaporated to give the crude product as a yellow oil. This was purified by column chromatography (200 g silica, eluent 30 - 70% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **1.4** as a pale yellow viscous oil (1.72 g, 70%): ^{1}H NMR δ 8.01 (1H, bs,

N**H**), 7.58 (1H, d, J = 7.7 Hz, Ar**H**), 7.30 (1H, d, J = 7.4 Hz, Ar**H**), 7.15 (1H, dd, J = 7.4, 6.8 Hz, Ar**H**), 7.10 (1H, dd, J = 7.7, 6.8 Hz, Ar**H**), 6.17 (1H, dd, J = 17.6, 10.3 Hz, C**H**), 5.27-5.31 (2H, m, C$\mathbf{H}_2$), 3.91 (1H, dd, J = 9.6, 5.2 Hz, C$\mathbf{H}_2$), 3.70 (3H, s, C$\mathbf{H}_3$), 3.36 (1H, dd, J = 14.3, 4.8 Hz, C$\mathbf{H}_2$), 3.09 (1H, dd, J = 14.7, 9.6 Hz, C**H**), 1.58 (6H, s, 2 x C$\mathbf{H}_3$). The spectroscopic properties were consistent with that reported in the literature (ref 3).

2.11.5 Tetrabutylammonium anthracene-9-sulfonate **1.7**

A solution of trimethylsilylchlorosulfonate (27 mL, 180 mmol) in dioxane (75 mL) was stirred at RT for 5 min then TMS-Cl was removed by vacuum distillation. Anthracene (27.4 g, 150 mmol) was added and the resultant yellow slurry stirred for 2 h. The reaction mixture was filtered and the filtrate poured onto ice/water (200 mL) then treated with 50% NaOH (40 mL) and tetrabutylammonium hydrogen sulfate (51 g, 150 mmol). The yellow mixture was extracted with CH_2Cl_2 (3 x 100 mL) and washed with water (100 mL), dried over $MgSO_4$, filtered and the solvent evaporated to give a brown, viscous oil. This was recrystallised from hot EtOAc to give **1.7** as a pale yellow solid (41.9 g, 56%): mp 168-170 °C; ^{1}H NMR δ 9.78 (2H, d, J = 9.2 Hz, Ar**H**), 8.38 (1H, s, Ar**H**), 7.89 (2H, d, J = 7.4 Hz, Ar**H**), 7.39 (4H, m, Ar**H**), 2.81 (8H, dd, J = 8.5, 8.5 Hz C$\mathbf{H}_2$), 1.23 (8H, m, C$\mathbf{H}_2$), 1.02 (8H, quintet, J = 7.4 Hz, C$\mathbf{H}_2$), 0.75 (8H, t, J = 7.0 Hz, C$\mathbf{H}_3$). The spectroscopic properties were consistent with that reported in the literature (ref 14).

2.11.6 Anthracene-9-sulfonyl chloride **1.8**

To a suspension of **1.7** (25 g, 50 mmol) in CH_3CN (40 mL) and sulfolane (24 mL, 250 mmol) at 0°C was added dropwise $POCl_3$ (19 mL, 200 mmol) and the resultant orange solution stirred for 10 min. Water (200 mL) was added dropwise and the resultant orange precipitate filtered and washed with water (100 mL) to give **1.8** as an orange solid (13.0 g, 99%): mp 131-133 °C; IR ν_{max} 1365s, 1165s cm^{-1}; ^{1}H NMR δ 9.38 (2H, d, J = 9.2 Hz, Ar**H**), 8.82 (1H, s, Ar**H**), 8.09 (2H, d, J = 8.5 Hz, Ar**H**), 7.78 (2H, t, J = 6.6 Hz, Ar**H**), 7.60 (2H, t, J = 7.4 Hz, Ar**H**). ^{13}C NMR δ 139.0 (**C**H), 134.1 (**C**), 131.1 (**C**), 130.6 (**C**H), 129.9 (**C**), 129.8 (**C**H), 126.1 (**C**H), 124.5 (**C**H).

*2.11.7 2-(Anthracene-9-sulfonylamino)-3-(1*H*-indol-3-yl)-propionic acid tert-butyl ester* **1.9**

To a solution of L-tryptophan *tert*-butyl ester (15.7 g, 60 mmol) in CH_2Cl_2 (250 mL) and pyridine (5.8 mL, 72 mmol) was added **1.8** (16.6 g, 60 mmol). The reaction mixture was stirred for 5 h at RT then washed with water (2 x 250 mL). The aqueous phase was washed with CH_2Cl_2 (100 mL), the organic phases combined, dried over $MgSO_4$, filtered and the solvent evaporated. The resultant orange foam was purified by column chromatography (400 g silica; eluent 1:1 - 3:1 Et_2O:hexane). The relevant fractions were combined and the solvent evaporated to give **1.9** as a yellow solid (23.3 g, 78%): mp 168-170 °C; ^{1}H NMR δ 9.22 (2H, d, J = 9.2 Hz, Ar**H**), 8.55 (1H, s, Ar**H**), 7.95 (2H, d, J = 8.5 Hz, Ar**H**), 7.73 (1H, bs, indole N**H**), 7.60 (2H, t, J = 7.7 Hz, Ar**H**), 7.48 (2H, t, J = 7.0 Hz, Ar**H**), 7.21 (1H, d, J = 9.6 Hz, Ar**H**), 7.16 (1H, d, J = 8.1 Hz, Ar**H**), 7.06 (1H, dd, J = 9.6, 6.3 Hz, Ar**H**), 6.88 (1H, dd, J = 8.1, 6.3 Hz, Ar**H**), 6.77 (1H, d, J = 2.2 Hz, Ar**H**), 5.72 (1H, d, J = 8.1 Hz, sulfonamide N**H**), 4.19 (1H, ddd, J = 6.6, 6.4, 5.9 Hz, C**H**), 3.09 (1H, dd, J = 14.7, 5.9 Hz, C**H**$_2$), 3.00 (1H, dd, J = 14.7, 6.6 Hz, C**H**$_2$), 0.95 (9H, s, C**H**$_3$). The spectroscopic properties were consistent with that reported for the enantiomer in the literature (ref 12).

*2.11.8 1-(Anthracene-9-sulfonyl)-1,2,3,8-tetrahydro-pyrrolo[2,3-*b*]indole-2-carboxylic acid tert-butyl ester* **1.10**

To a solution of **1.9** (5 g, 10.0 mmol) in CH_2Cl_2 (500 mL) at 0 °C in a foil covered flask was added *N*-bromosuccinimide (1.8 g, 10 mmol) and triethylamine (4.2 mL, 30 mmol). The reaction mixture was stirred for 30 min then concentrated under vacuum and the resultant orange oil quickly purified by column chromatography (100 g silica; eluent 3:1 – 1:1 hexane:Et_2O). The relevant fractions were combined and the solvent evaporated to give **1.10** as an orange solid (4.13 g, 83%): mp 144-146 °C; IR ν_{max} 3333w, 1744w, 1715w, 1616w cm^{-1}; ^{1}H NMR δ 9.41 (2H, d, J = 9.2 Hz, Ar**H**), 8.78 (1H, s, Ar**H**), 8.03 (2H, d, J = 8.1 Hz, Ar**H**), 7.65 (2H, t, J = 7.7 Hz, Ar**H**), 7.52 (2H, t, J = 7.0 Hz, Ar**H**), 7.46 (1H, m,

ArH), 7.38 (1H, m, ArH), 7.11 (2H, m, ArH), 5.05 (1H, dd, J = 9.9, 5.5 Hz, CH), 3.36 (1H, dd, J = 14.0, 9.9 Hz, CH_2), 2.94 (1H, dd, J = 14.0, 5.5 Hz, CH_2), 0.87 (9H, s, CH_3); ^{13}C NMR δ 168.7 (C), 141.8 (C), 138.5 (C), 137.7 (CH), 131.9 (C), 131.4 (C), 129.5 (CH), 125.8 (CH), 125.5 (CH), 125.3 (CH), 123.8 (C), 120.8 (CH), 117.8 (CH), 112.1 (CH), 102.2 (C), 81.9 (C), 68.5 (CH), 29.7 (CH_2), 27.3 (CH_3); MS *m/z* 499 $[M+H]^+$.

2.11.9 1-(Anthracene-9-sulfonyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-b] indole-2-carboxylic acid tert-butyl ester **1.12**

To a solution of **1.10** (3.5 g, 7.0 mmol) in CH_2Cl_2 (40 mL) at –78 °C was added DMDO in acetone (82 mL, 7.7 mmol). The solution was stirred for 10 min then the solvent evaporated. The resultant yellow foam was dissolved in MeOH (40 mL), cooled to 0 °C and $NaBH_4$ (794 mg, 21 mmol) added. The reaction was allowed to warm to RT over 4 h then concentrated *in vacuo*. The residue was diluted with EtOAc (50 mL), washed with 1M HCl (2 x 50 mL) then brine (50 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The resultant yellow solid was recrystallised from hot EtOH to give **1.12** as a yellow solid (1.45 g). The filtrate was concentrated then purified by column chromatography (50 g silica; eluent 1:3 – 1:1 – 3:1 Et_2O:hexane). The relevant fractions were combined and the solvent evaporated to give a further 1.11 g **1.12** (total mass 2.56 g, 71%): mp 191-193 °C; ^1H NMR δ 9.45 (2H, d, J = 9.6 Hz, ArH), 8.73 (1H, s, ArH), 8.08 (2H, d, J = 8.5 Hz, ArH), 7.70 (2H, t, J = 7.7 Hz, ArH), 7.55 (2H, t, J = 7.0 Hz, ArH), 7.18 (2H, m, ArH), 6.72 (1H, t, J = 7.4 Hz, ArH), 6.58 (1H, d, J = 7.7 Hz, ArH), 5.06 (1H, s, NH-CH-NR), 4.87 (1H, dd, J = 9.0, 1.5 Hz, CH), 2.77 (1H, dd, J = 12.9, 1.5 Hz, CH_2), 2.61 (1H, dd, J = 12.9, 9.0 Hz, CH_2), 0.94 (9H, s, CH_3). The spectroscopic properties were consistent with that reported for the enantiomer in the literature (ref 12).

2.11.10 1-(1,1-Dimethyl-prop-2-ynyl)-2,3-dihydro-1H-indole **1.14**

To a solution of indoline (0.94 mL, 8.4 mmol), CuCl (83 mg, 0.8 mmol), and diisopropylethylamine (1.74 mL, 10.0 mmol) in THF (50 mL) was added 2-methyl-3-butynyl-2-bromide[20] (1.14 mL, 10.0 mmol), followed by stirring for 3 h. The solvent was

then evaporated and the resultant brown residue dissolved in CH_2Cl_2 (50 mL), washed with saturated aq NH_4Cl (20 mL), brine (20 mL), dried over Na_2SO_4, filtered and concentrated. The residue was purified by column chromatography (75 g silica; eluent 2% - 5% Et_2O in hexane). The relevant fractions were combined and the solvent evaporated to give **1.14** as a brown oil (996 mg, 65%): IR ν_{max} 1602m, 1484s, cm^{-1}; ^1H NMR δ 7.22 (1H, d, J = 7.7 Hz, ArC**H**), 7.08 (2H, m, ArC**H**), 6.73 (1H, t, J = 7.7 Hz, ArC**H**), 3.39 (2H, t, J = 8.1 Hz, C**H**$_2$), 2.92 (2H, t, J = 8.1 Hz, C**H**$_2$), 2.40 (1H, s, ≡C**H**), 1.61 (6H, s, 2 x C**H**$_3$); ^{13}C NMR δ 150.0 (**C**), 131.7 (**C**), 126.8 (**C**H), 124.4 (**C**H), 118.5 (**C**H), 111.8 (**C**H), 87.6 (**C**), 70.9 (**C**H), 51.1 (**C**), 49.5 (**C**H$_2$), 28.2 (**C**H$_2$), 27.1 (**C**H$_3$); MS *m/z* 186 $[M+H]^+$. The spectroscopic properties were consistent with the assigned structure of this known compound (ref 18) although no data was reported.

2.11.11 1-(1,1-Dimethyl-allyl)-2,3-dihydro-1H-indole **1.15**

A solution of **1.14** (100 mg, 0.54 mmol) and Lindlar's catalyst (5 mg) in EtOAc (5 mL) under H_2 (1 atm) was stirred for 3 h. The reaction mixture was filtered through a pad of silica and the solvent evaporated. The resultant yellow oil was purified by column chromatography (10 g silica; eluent hexane – 2% Et_2O in hexane). The relevant fractions were combined and the solvent evaporated to give **1.15** as a pale yellow oil (96 mg, 95%): IR ν_{max} 1607w, 1484m cm^{-1}; ^1H NMR δ 7.07 (1H, dd, J = 7.4, 1.1 Hz, ArC**H**), 6.97 (1H, dd, J = 7.4, 7.0 Hz, ArC**H**), 6.81 (1H, d, J = 8.1 Hz, ArC**H**), 6.64 (1H, dd, J = 8.1, 7.0 Hz, ArC**H**), 6.15 (1H, dd, J = 17.7, 10.7 Hz, CH_2=C**H**), 5.24 (1H, dd, J = 17.7, 1.1 Hz, C**H**$_2$=CH), 5.14 (1H, dd, J = 10.7, 1.1 Hz, C**H**$_2$=CH), 3.44 (2H, t, J = 8.1 Hz, C**H**$_2$), 2.92 (2H, t, J = 8.1 Hz, C**H**$_2$), 1.36 (6H, s, 2 x C**H**$_3$); ^{13}C NMR δ 150.8 (**C**), 147.2 (**C**H), 131.6 (**C**), 126.6 (**C**H), 124.3 (**C**H), 117.3 (**C**H), 112.2 (**C**H$_2$), 111.3 (**C**H), 57.4 (**C**), 49.2 (**C**H$_2$), 28.2 (**C**H$_2$), 24.2 (**C**H$_3$); MS *m/z* 188 $[M+H]^+$. The spectroscopic properties were consistent with the assigned structure of this known compound (ref 18) although no data was reported.

2.11.12 1-(Anthracene-9-sulfonyl)-8-(1,1-dimethyl-prop-2-ynyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrolo[2,3-b]indole-2-carboxylic acid tert-butyl ester **1.16**

To a solution of **1.12** (600 mg, 1.16 mmol), CuCl (23 mg, 0.23 mmol), diisopropylethylamine (242 μL, 1.39 mmol) in THF (25 mL) was added 2-methyl-3-butyn-2-bromide (204 mg, 1.39 mmol). The reaction mixture was stirred for 16 h and the solvent evaporated. The residue was dissolved in CH_2Cl_2 (20 mL), washed with saturated aq NH_4Cl (2 x 20 mL) then brine (20 mL), dried over Na_2SO_4, filtered and the solvent evaporated. The resultant brown oil was purified by column chromatography (50 g silica; eluent 20% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **1.16** as a yellow solid (372 mg, 55%): mp 80 – 82 °C; $[\alpha]^{22}_D$ = +11.6 (*c* = 0.33 in MeOH); IR ν_{max} 3281m, 2364w, 1716s cm^{-1}; ^1H NMR δ 9.52 (2H, d, *J* = 9.0 Hz, ArC**H**), 8.68 (1H, s, ArC**H**), 8.01 (2H, d, *J* = 8.5 Hz, ArC**H**), 7.68 (2H, dt, *J* = 5.6, 1.1 Hz, ArC**H**), 7.52 (2H, t, *J* = 8.1 Hz, ArC**H**), 7.31 (2H, m, ArC**H**), 7.20 (1H, t, *J* = 7.7 Hz, ArC**H**), 6.96 (1H, t, *J* = 7.4 Hz, ArC**H**), 6.03 (1H, s, NC**H**N), 4.65 (1H, dd, *J* = 6.2, 4.4 Hz, C**H**CO_2R), 3.01 (1H, bs, O**H**), 2.92 (1H, d, *J* = 4.4 Hz, CH_2), 2.89 (1H, d, *J* = 6.2 Hz, CH_2), 2.41 (1H, s, C≡C**H**), 1.93 (3H, s, CH_3), 1.88 (3H, s, CH_3), 0.32 (9H, s, 3 x CH_3); ^{13}C NMR δ 168.9 (**C**), 136.6 (**C**H), 134.5 (**C**), 131.6 (**C**), 131.2 (**C**), 129.9 (**C**H), 129.8 (**C**), 129.2 (**C**H), 128.8 (**C**H), 125.9 (**C**H), 125.6 (**C**H), 124.2 (**C**H), 123.2 (**C**H), 119.0 (**C**H), 89.8 (**C**), 88.2 (**C**H), 86.3 (**C**), 81.3 (**C**), 60.9 (**C**H), 55.0 (**C**), 40.8 (**C**H_2), 31.9 (**C**H_3), 29.4 (**C**H_3), 27.4 (**C**H), 26.8 (**C**H_3) 14.3 (**C**); MS *m/z* 583 $[M+H]^+$, 605 $[M+Na]^+$.

2.11.13 1-(Anthracene-9-sulfonyl)-8-(1,1-dimethyl-allyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-b]indole-2-carboxylic acid tert-butyl ester **1.17**

To a solution of **1.16** (1.0 g, 1.72 mmol) in EtOAc (75 mL) was added Pd/Al_2O_3 catalyst (200 mg) and the reaction mixture stirred under H_2 (1 atm) for 1.5 h. The reaction mixture was filtered through a pad of celite and the solvent evaporated to give **1.17** as a yellow foam (969 mg, 96%): $[\alpha]^{22}_D$ = +3.8 (*c* = 0.33 in MeOH); IR ν_{max} 3468bm, 1751m, 1479m cm^{-1}; ^1H NMR δ 9.50 (2H, d, *J* = 9.3 Hz, ArC**H**), 8.71 (1H, s, ArC**H**), 8.02 (2H, d, *J* = 8.3 Hz, ArC**H**), 7.72 (1H, dd, *J* = 6.7, 1.5 Hz, ArC**H**), 7.69 (1H, dd, *J* = 6.7, 1.5 Hz, ArC**H**), 7.54 (2H, t, *J* = 7.4 Hz, ArC**H**), 7.21 (1H, d, *J* = 7.4 Hz, ArC**H**), 7.09 (1H, dd, *J* = 8.1, 7.8

Hz, ArC**H**), 7.02 (1H, d, J = 8.1 Hz, ArC**H**), 6.80 (1H, dd, J = 7.8, 7.4 Hz, ArC**H**), 6.23 (1H, dd, J = 17.6, 10.7 Hz, CH_2=C**H**), 6.01 (1H, s, NC**H**N), 5.18 (1H, d, J = 17.7 Hz, CH=C$\mathbf{H}_2$), 5.08 (1H, d, J = 10.7 Hz, CH=C$\mathbf{H}_2$), 4.62 (1H, d, J = 9.3 Hz, CHC$\mathbf{H}_2$), 2.89 (1H, d, J = 12.8 Hz, CHC$\mathbf{H}_2$), 2.74 (1H, dd, J = 12.8, 9.3 Hz, C**H**CH_2), 1.56 (3H, s, C$\mathbf{H}_3$), 1.42 (3H, s, C$\mathbf{H}_3$), 0.53 (9H, s, 3 x C$\mathbf{H}_3$); ^{13}C NMR δ 168.5 (**C**), 149.9 (**C**), 147.3 (**C**H), 136.7 (**C**H), 132.3 (**C**), 131.7 (**C**), 131.2 (**C**H), 129.7 (**C**H), 129.6 (**C**H), 125.7 (**C**H), 125.5 (**C**H), 123.5 (**C**H), 120.6 (**C**H), 115.9 (**C**H), 112.1 (**C**H_2), 88.5 (**C**H), 81.3 (**C**), 61.5 (**C**H), 60.2 (**C**), 41.8 (**C**H_2), 29.7 (**C**), 28.4 (**C**H_3), 27.2 (**C**H_3); MS *m/z* 584 $[M+H]^+$, 607 $[M+Na]^+$.

2.11.14 2-{[1-(Anthracene-9-sulfonyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrolo[2,3-b] indole-2-carbonyl]-amino}-3-[2-(1,1-dimethyl-allyl)-1H-indol-3-yl]-propionic acid methyl ester **1.20**

To a solution of **1.12** (150 mg, 0.29 mmol) and 2,6-lutidine (1.7 mL, 14.5 mmol) in CH_2Cl_2 (2.5 mL) at 0 °C was added dropwise trimethylsilyl triflate (1.2 mL, 5.8 mmol). After stirring for 24 h the reaction mixture was quenched with saturated aq $NaHCO_3$ (ca. 2 mL). The reaction mixture was diluted with EtOAc (50 mL), then acidified with 1N HCl (ca. 25 mL). The phases were separated and the organic phase washed with brine (20 mL), dried over $MgSO_4$, and the solvent evaporated. The resultant yellow solid **1.19** was used in the next step without further purification.

To a solution of **1.19** (164 mg, 0.29 mmol), **1.4** (92 mg, 0.32 mmol) and NEt_3 (0.12 mL, 0.87 mmol) in THF (5 mL) at 0 °C was added PyBOP (307 mg, 0.59 mmol), followed by stirring for 24 h. Water (5 mL) was added and the reaction mixture washed with EtOAc (2 x10 mL). The organic phase was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvent evaporated. The resultant brown residue was purified by column chromatography (25 g silica; eluent 1:1 – 3:1 Et_2O:hexane). The relevant fractions were combined and the solvent evaporated to give **1.20** as a yellow solid (167 mg, 79%): mp 136 – 138 °C; IR ν_{max} 3399bs, 3049m, 2349m, 1734s, 1655s cm^{-1}; ^{1}H NMR δ 9.47 (2H, d, J = 9.6 Hz, ArC**H**), 8.80 (1H, s, ArC**H**), 8.10 (2H, d, J = 8.1 Hz, ArC**H**), 7.96 (1H,

s, indole NH), 7.76 (2H, ddd, J = 9.6, 6.6 Hz, ArCH), 7.58 (2H, dd, J = 6.8, 6.6 Hz, ArCH), 7.46 (2H, t, J = 6.6 Hz, ArCH), 7.30 (1H, dd, J = 6.6, 3.7 Hz, ArCH), 7.09-7.18 (3H, m, ArCH), 6.98 (1H, t, J = 7.7 Hz, ArCH), 6.65 (1H, t, J = 7.7 Hz, ArCH), 6.18 (1H, d, J = 8.1 Hz, $CHCH_2$), 6.05 (1H, dd, J = 17.3, 10.7 Hz, CH_2=CH), 5.59 (1H, s, NCHN), 5.14 (2H, m, CH=CH_2), 4.51 (1H, d, J = 9.2 Hz, NH), 4.04 (1H, dd, J = 15.4, 7.0 Hz, $CHCH_2$), 3.27 (3H, s, CO_2CH_3), 2.81 (1H, d, J = 12.9 Hz, NH), 2.63 (1H, dd, J = 14.5, 7.0 Hz, $CHCH_2$), 2.46 (1H, dd, J = 14.3, 8.8 Hz, $CHCH_2$), 2.22 (2H, dd, J = 13.1, 9.4 Hz, $CHCH_2$), 1.48 (3H, s, CH_3), 1.47 (3H, s, CH_3); ^{13}C NMR δ 171.9 (C), 170.0 (C), 148.8 (C), 145.7 (CH), 140.5 (C), 137.4 (CH), 134.0 (C), 131.6 (C), 131.5 (C), 131.2 (CH), 130.0 (C), 128.5 (C), 126.5 (C), 125.8 (CH), 125.0 (CH), 124.5 (C), 121.7 (CH), 120.3 (CH), 119.6 (CH), 118.6 (CH), 112.6 (CH_2), 110.5 (CH), 110.4 (CH), 105.6 (C), 88.2 (C), 84.9 (CH), 66.0 (CH), 62.4 (CH), 54.8 (CH), 52.0 (CH_3), 40.8 (CH_2), 39.2 (C), 30.5 (C), 27.7 (CH_3), 27.4 (CH_2), 15.4 (CH); MS *m/z* 729 $[M+H]^+$, 751 $[M+Na]^+$.

2.11.15 3-[2-(1,1-Dimethyl-allyl)-1H-indol-3-yl]-2-[(3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrolo[2,3-b]indole-2-carbonyl)-amino]-propionic acid methyl ester **1.21**

To a solution of **1.20** (146 mg, 0.2 mmol) in THF/H_2O (5:1, 5 mL) was added freshly prepared Al(Hg) amalgam (ca 600 mg Al). The reaction mixture was stirred for 5 h then filtered through a pad of celite and washed with EtOAc (20 mL). The solvent was evaporated then the residue purified by column chromatography (10 g silica; eluent 1:1 – 1:0 EtOAc:hexane). The relevant fractions were combined and the solvent evaporated to give **1.21** as a white foam (84 mg, 86%): IR ν_{max} 3348bs, 1734s, 1656s cm^{-1}; ^{1}H NMR δ 8.29 (1H, s, indole NH), 7.91 (1H, d, J = 6.3 Hz, ArCH), 7.52 (1H, d, J = 7.7 Hz, ArCH), 7.32 (1H, d, J = 8.1 Hz, ArCH), 7.06-7.13 (2H, m, ArCH), 6.93-7.02 (2H, m, ArCH), 6.67 (1H, t, J = 6.6 Hz, ArCH), 6.08 (1H, dd, J = 17.7, 10.7 Hz, CH_2=CH), 6.05 (1H, s, NCHN), 5.13 (2H, m, CH=CH_2), 4.62 (1H, s, NH), 4.28 (1H, td, J = 9.2, 6.6 Hz, $CHCH_2$), 3.86 (1H, dd, J = 8.5, 6.6 Hz, $CHCH_2$), 3.51 (3H, s, CO_2CH_3), 3.04 (1H, dd, J = 14.7, 6.6 Hz, $CHCH_2$), 2.86 (1H, dd, J = 14.7, 9.2 Hz, $CHCH_2$), 2.36 (1H, dd, J = 13.2, 8.5 Hz, $CHCH_2$), 2.28 (1H, dd, J = 13.2, 4.8 Hz, $CHCH_2$), 2.04 (6H, s, 2 x CH_3); ^{13}C NMR δ 174.0 (C), 173.3 (C), 171.4 (C), 148.9 (C), 145.6 (CH), 140.9 (C), 134.2 (C), 130.6 (C),

130.0 (**C**H), 124.1 (**C**H), 121.6 (**C**H), 119.5 (**C**H), 119.3 (**C**H), 118.4 (**C**H), 112.5 (**C**H_2), 110.8 (**C**H), 109.9 (**C**H), 105.8 (**C**), 89.4 (**C**), 85.9 (**C**H), 61.7 (**C**H), 54.2 (**C**H), 52.3 (**C**H_3), 42.5 (**C**H_2), 39.2 (**C**), 27.7 (**C**H_3), 27.5 (**C**H_2); MS *m/z* 489 $[M+H]^+$, 977 $[2M+H]^+$.

*2.11.15 3-[2-(1,1-Dimethyl-allyl)-1*H*-indol-3-ylmethyl]-10b-hydroxy-2,3,6,10b,11,11a-hexahydro-5a*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4-dione* **1.22**

To a solution of **1.21** (75 mg, 0.15 mmol) in 1,4-dioxane (1.5 mL) was added 10% KOH in MeOH (1.5 mL). The reaction mixture was stirred for 16 h then acidified to pH 5 with 1N HCl and extracted with Et_2O (3 x 10 mL). The organics were combined, washed with water (2 x 10 mL), dried over Na_2SO_4 filtered and the solvent evaporated to give **1.23** as a white glass which was used in the next step without further purification.

To a solution of **1.23** (62 mg, 0.31 mmol) in THF (5 mL) was added Et_3N (20 μL, 0.14 mmol) and HOBt (19 mg, 0.14 mmol). The reaction mixture was stirred for 15 min then EDAC (27 mg, 0.14 mmol) was added and the reaction mixture stirred for a further 48 h. The reaction mixture was extracted with EtOAc (5 mL) and water (5 mL), the organic phase separated, washed with water (5 mL) and brine (5 mL), dried over $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography (5 g silica; eluent 1%-2% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **1.22** as a white glass (20 mg, 33%): IR ν_{max} 3356bs, 1688s, 1614m cm^{-1}; ^{1}H NMR δ 8.11 (1H, s, indole N**H**), 7.49 (1H, d, *J* = 7.8 Hz, ArC**H**), 7.33 (1H, d, *J* = 8.0 Hz, ArC**H**), 7.28 (1H, d, *J* = 7.3 Hz, ArC**H**), 7.19 (2H, m, ArC**H**), 7.11 (1H, dd, *J* = 7.4, 7.3 Hz, ArC**H**), 6.81 (1H, d, *J* = 8.0, 7.4 Hz, ArC**H**), 6.67 (1H, d, *J* = 7.9 Hz, ArC**H**), 6.13 (1H, dd, *J* = 17.5, 10.4 Hz, =C**H**), 5.78 (1H, s, NC**H**N), 5.51 (1H, s, N**H**), 5.17 (2H, d, d , *J* = 17.5, 10.4 Hz, =C**H**$_2$), 4.55 (1H, dd, *J* = 10.9, 6.7 Hz, C**H**CH$_2$), 4.46 (1H, dd, *J* = 11.5, 3.8 Hz, C**H**CH$_2$), 3.76 (1H, dd, *J* = 15.2, 3.8 Hz, CHC**H**$_2$), 3.19 (1H, dd, *J* = 15.2, 11.5 Hz, CHC**H**$_2$), 2.72 (1H, dd, *J* = 13.6, 6.7 Hz, CHC**H**$_2$), 2.35 (1H, dd, *J* = 13.5, 10.9 Hz, CHC**H**$_2$), 1.55 (6H, s, 2 x C**H**$_3$); ^{13}C NMR δ 168.6 (**C**), 167,5 (**C**), 147.5(**C**), 145.6 (**C**H), 141.6 (**C**), 134.4 (**C**), 130.3 (**C**H), 129.5 (**C**), 129.5 (**C**), 129.0 (**C**), 123.0 (**C**H), 122.2 (**C**H), 120.2 (**C**H), 119.7 (**C**H), 117.8 (**C**H), 112.8 (**C**H_2), 110.9 (**C**H), 110.3 (**C**H), 104.3

(**C**), 87.0 (**C**), 85.0 (**C**H), 59.0 (**C**H), 55.0 (**C**H), 40.9 (**C**H_2), 39.0 (**C**), 27.9 (**C**H_3), 26.1 (**C**H_2); MS *m/z* 457 $[M+H]^+$.

*2.11.16 1-(Anthracene-9-sulfonyl)-3a-hydroxy-7-(3-methyl-but-2-enyl)-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole-2-carboxylic acid* tert-*butyl ester* **1.28**

To a solution of **1.17** (650 mg, 1.11 mmol) in CH_2Cl_2 (50 mL) was added trifluoroacetic acid (171 μL, 2.22 mmol) and the reaction mixture stirred for 16 h. The reaction mixture was washed with water (2 x 50 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The resultant brown oil was purified by column chromatography (40 g silica; eluent 1 – 5% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **1.28** as a yellow foam (543 mg, 84%): $[\alpha]^{22}_D$ = +98.6 (*c* = 0.33 in MeOH); IR ν_{max} 3594bs, 1739s, 1715s, 1602s, 1482s cm^{-1}; ^1H NMR δ 9.39 (2H, d, *J* = 9.6 Hz, ArC**H**), 8.73 (1H, s, ArC**H**), 8.05 (2H, d, *J* = 8.1 Hz, ArC**H**), 7.70 (2H, dd, *J* = 6.6, 1.5 Hz, ArC**H**), 7.54 (2H, t, *J* = 7.4 Hz, ArC**H**), 7.04 (1H, d, *J* = 7.7 Hz, ArC**H**), 6.98 (1H, d, *J* = 7.4 Hz, ArC**H**), 6.72 (1H, dd, *J* = 7.7, 7.4 Hz, ArC**H**), 5.22 (1H, td, *J* = 7.4, 1.5 Hz, $C(CH_3)_2$=C**H**), 5.15 (1H, s, NC**H**N), 4.84 (1H, dd, *J* = 9.2, 1.8 Hz, CH_2C**H**), 3.10 (2H, d, *J* = 7.4 Hz), 2.75 (1H, dd, *J* = 12.9, 1.8 Hz, CHC$\mathbf{H}_2$), 2.64 (1H, dd, *J* = 12.8, 9.2 Hz, CHC$\mathbf{H}_2$), 1.78 (3H, s, C$\mathbf{H}_3$), 1.73 (3H, s, C$\mathbf{H}_3$), 0.85 (9H, s, 3 x C$\mathbf{H}_3$); ^{13}C NMR δ 169.2 (**C**), 148.3 (**C**), 136.5 (**C**H), 133.7 (**C**), 131.4 (**C**), 131.3 (**C**), 130.3 (**C**H), 129.6 (**C**H), 129.1 (**C**H), 128.2 (**C**), 128.1 (**C**), 125.5 (**C**H), 125.2 (**C**H), 123.6 (**C**H), 121.5 (**C**H), 120.9 (**C**H), 120.1 (**C**H), 88.6 (**C**), 83.2 (**C**H), 81.3 (**C**), 62.0 (**C**H), 41.1 (**C**H_2), 30.0 (**C**H_2), 27.2 (**C**H_3), 25.7 (**C**H_3), 17.9 (**C**H_3); MS *m/z* 584 $[M+H]^+$, 607 $[M+Na]^+$.

*2.11.17 1-(Anthracene-9-sulfonyl)-3a-hydroxy-7-(3-methyl-but-2-enyl)-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole-2-carboxylic acid* **1.24**

To a solution of **1.28** (258 mg, 0.44 mmol) and 2,6-lutidine (2.5 mL, 22 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added dropwise trimethylsilyl triflate (1.8 mL, 8.8 mmol). After stirring for 16 h the reaction mixture was quenched with saturated aq $NaHCO_3$ (ca. 2 mL). The reaction mixture was diluted with EtOAc (10 mL), washed with 1N HCl (2 x 10 mL)

then brine (10 mL), dried over $MgSO_4$, and the solvent evaporated. The resultant yellow oil was purified by column chromatography (25 g silica; eluent 1 – 5% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **1.24** as a yellow foam (175 mg, 75%): $[\alpha]^{22}_D$ = +149.2 (*c* = 0.33 in MeOH); IR ν_{max} 3395bs, 3139s, 3054s, 1731s, 1713s, 1602m, 1484s cm^{-1}; ^1H NMR δ 9.36 (2H, d, *J* = 9.2 Hz, ArC**H**), 8.79 (1H, s, ArC**H**), 8.10 (2H, d, *J* = 8.5 Hz, ArC**H**), 7.70 (2H, t, *J* = 7.5 Hz, ArC**H**), 7.58 (2H, t, *J* = 7.5 Hz, ArC**H**), 6.98 (1H, d, *J* = 7.4 Hz, ArC**H**), 6.95 (1H, d, *J* = 6.6 Hz, ArC**H**), 6.67 (1H, dd, *J* = 7.4, 6.6 Hz, ArC**H**), 5.30 (1H, s, NC**H**N), 5.09 (1H, t *J* = 7.0 Hz, $C(CH_3)_2$=C**H**), 4.72 (1H, dd, *J* = 8.8, 2.6 Hz, CH_2C**H**), 3.01 (2H, d, *J* = 7.0 Hz), 2.64 (1H, dd, *J* = 13.2, 2.6 Hz, CHC$\mathbf{H}_2$), 2.56 (1H, dd, *J* = 13.2, 8.8 Hz, CHC$\mathbf{H}_2$), 1.74 (3H, s, C$\mathbf{H}_3$), 1.68 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR δ 172.9 (**C**), 147.0 (**C**), 137.3 (**C**H), 134.0 (**C**), 131.4 (**C**), 131.2 (**C**), 130.9 (**C**H), 129.8 (**C**H), 129.6 (**C**H), 128.2 (**C**), 126.3 (**C**), 125.6 (**C**H), 124.8 (**C**H), 124.5 (**C**), 121.4 (**C**H), 121.1 (**C**H), 120.7 (**C**H), 88.3 (**C**H), 84.2 (**C**), 61.0 (**C**H), 41.8 ($\mathbf{C}H_2$), 30.1 ($\mathbf{C}H_2$), 25.7 ($\mathbf{C}H_3$), 17.8 ($\mathbf{C}H_3$); MS *m/z* 529 $[M+H]^+$, 551 $[M+Na]^+$.

2.11.18 2-{[1-(Anthracene-9-sulfonyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrolo[2,3-b] indole-2-carbonyl]-amino}-3-[2-(1,1-dimethyl-allyl)-1H-indol-3-yl]-propionic acid methyl ester **1.25**

To a solution of **1.24** (100 mg, 0.19 mmol), **1.4** (60 mg, 0.21 mmol) and Et_3N (79 μL, 0.57 mmol) in THF (5 mL) at 0 °C was added PyBOP (193 mg, 0.38 mmol) and the reaction mixture stirred for 5 h. The reaction mixture was diluted with EtOAc, (10 mL), washed with water (2 x 10 mL) then brine (10 mL), dried over $MgSO_4$, filtered, and the solvent evaporated. The resultant brown residue was purified by column chromatography (10 g silica; eluent 3:1 - 1:1 – 1:3 hexane:Et_2O). The relevant fractions were combined and the solvent evaporated to give **1.25** as a yellow solid (124 mg, 82%): mp 136 – 138 °C; $[\alpha]^{22}_D$ = +9.0 (*c* = 0.33 in MeOH); IR ν_{max} 3376bs, 3049m, 1772w, 1738s, 1660s, 1520s, 1456s cm^{-1}; ^1H NMR δ 9.44 (2H, d, *J* = 9.5 Hz, ArC**H**), 8.81 (1H, s, ArC**H**), 8.04 (2H, d, *J* = 8.51 Hz, ArC**H**), 7.85 (1H, s, indole N**H**), 7.76 (2H, td, *J* = 9.2, 1.5 Hz, ArC**H**), 7.58 (2H, t, *J* = 7.4 Hz, ArC**H**), 7.46 (1H, d, *J* = 4.4 Hz, N**H**), 7.15-7.30 (3H, m, ArC**H**), 6.96-7.15 (3H, m, ArC**H**), 6.72 (1H, t, *J* = 7.7 Hz, ArC**H**), 6.02 (1H, dd, *J* = 17.3, 10.7 Hz, C**H**=CH_2), 5.68

(1H, s, NC**H**N), 5.31 (1H, m, C**H**=C), 5.12 (1H, d, J = 10.7 Hz, CH=C$\mathbf{H}_2$), 5.09 (1H, d, J = 17.3 Hz, CH=C$\mathbf{H}_2$), 4.62 (1H, d, J = 9.2 Hz, CH_2C**H**), 4.12 (1H, tt, J = 7.0, 4.4 Hz, C**H**CH_2), 3.37 (1H, dd, J = 15.8, 7.0 Hz, CHC$\mathbf{H}_2$), 3.25 (1H, J = 15.8, 5.9 Hz, CHC$\mathbf{H}_2$), 3.07 (3H, s, $CO_2C\mathbf{H}_3$), 2.96 (1H, s, N**H**), 2.61 (1H, dd, J = 13.1, 9.7 Hz, CHC$\mathbf{H}_2$), 2.39 (1H, dd, J = 14.3, 4.8 Hz, CHC$\mathbf{H}_2$), 2.01 (1H, d, J = 13.1 Hz, CHC$\mathbf{H}_2$), 1.92 (1H, d, J = 13.1 Hz, CHC$\mathbf{H}_2$), 1.81 (3H, s, C$\mathbf{H}_3$), 1.79 (3H, s, C$\mathbf{H}_3$), 1.44 (3H, s, C$\mathbf{H}_3$), 1.43 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR δ 169.8 (**C**), 170.0 (**C**), 148.8 (**C**), 145.9 (**C**H), 140.5 (**C**), 137.5 (**C**H), 133.9 (**C**), 131.5 (**C**), 131.3 (**C**H), 129.9 (**C**H), 128.9 (**C**), 126.5 (**C**), 125.8 (**C**H), 125.8 (**C**H), 124.9 (**C**H), 124.3 (**C**), 122.2 (**C**), 121.4 (**C**H), 121.1 (**C**H), 119.2 (**C**H), 118.5 (**C**H), 112.5 (**C**H_2), 110.3 (**C**H), 105.2 (**C**), 88.6 (**C**), 84.7 (**C**H), 66.0 (**C**H), 62.6 (**C**H), 53.7 (**C**H), 51.9 (**C**H_3), 41.2 (**C**H_2), 39.2 (**C**), 30.7 (**C**H_2), 30.5 (**C**), 27.7 (**C**H_3), 27.4 (**C**H_2), 25.9 (**C**H_3), 18.1 (**C**H_3), 15.4 (**C**H); MS *m/z* 797 $[M+H]^+$, 819 $[M+Na]^+$.

*2.11.19 3-[2-(1,1-Dimethyl-allyl)-1*H*-indol-3-yl]-2-[(3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrolo[2,3-*b*]indole-2-carbonyl)-amino]-propionic acid methyl ester* **1.26**

To a solution of **1.25** (420 mg, 0.53 mmol) in THF/H_2O (5:1, 20 mL) was added freshly prepared Al(Hg) amalgam (ca 1.8 g Al). The reaction mixture was stirred for 16 h then filtered through a pad of celite, washed with EtOAc (50 mL) and the solvent evaporated. The resultant pale yellow residue was purified by column chromatography (30 g silica; eluent 2% – 5% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **1.26** as a white glass (216 mg, 73%): $[\alpha]^{22}_D$ = -24.0 (c = 0.33 in MeOH); IR ν_{max} 3348bs, 1732s, 1659s, 1651s, 1597m, 1519s, 1456s cm^{-1}; ^{1}H NMR δ 7.97 (1H, s, indole N**H**), 7.91 (1H, d, J = 8.1 Hz, N**H**), 7.41 (1H, d, J = 8.1 Hz, ArC**H**), 7.21 (1H, d, J = 7.7 Hz, ArC**H**), 7.10 (1H, d, J = 7.4 Hz, ArC**H**), 7.02 (1H, dd, J = 7.7, 6.9 Hz, ArC**H**), 6.95 (1H, d, J = 7.4 Hz, ArC**H**), 6.86 (1H, dd, J = 8.1, 6.9 Hz, ArC**H**), 6.67 (1H, t, J = 7.4 Hz, ArC**H**), 6.08 (1H, dd, J = 17.3, 10.3 Hz, CH_2=C**H**), 5.30 (1H, m, C=C**H**), 5.14 (2H, m, CH=C$\mathbf{H}_2$), 4.92 (1H, s, NC**H**N), 4.57 (1H, q, J = 8.1 Hz, C**H**CH_2), 3.95 (1H, dd, J = 8.8, 5.5 Hz, C**H**CH_2), 3.36 (3H, s, $CO_2C\mathbf{H}_3$), 3.22 (1H ,dd, J = 16.2, 6.6 Hz, C$\mathbf{H}_2$CH), 3.14 (1H, dd, J = 15.4, 6.6 Hz, C$\mathbf{H}_2$CH), 2.75 (2H, dd, J = 8.1, 2.1 Hz, CHC$\mathbf{H}_2$), 2.50 (1H, dd, J = 13.2, 8.8 Hz, CHC$\mathbf{H}_2$), 2.24 (1H, dd, J = 13.2, 5.5 Hz, CHC$\mathbf{H}_2$), 1.80 (3H, s, C$\mathbf{H}_3$),

1.77 (3H, s, C**H**$_3$), 1.55 (1H, d, J = 2.2 Hz, N**H**), 1.52 (1H, d, J = 2.2 Hz, N**H**), 1.50 (3H, s. C**H**$_3$), 1.48 (3H, s, C**H**$_3$); ^{13}C NMR δ 173.6 (**C**), 173.4 (**C**), 171.4 (**C**), 147.4 (**C**), 145.9 (**C**H), 140.5 (**C**), 134.0 (**C**), 130.7 (**C**), 129.9 (**C**H), 123.6 (**C**), 121.6 (**C**H), 121.4 (**C**H), 120.0 (**C**H), 119.4 (**C**H), 118.4 (**C**H), 112.4 (**C**H$_2$), 110.4 (**C**H), 105.7 (**C**), 89.4 (**C**), 86.2 (**C**H), 61.7 (**C**H), 53.3 (**C**H), 52.2 (**C**H$_3$), 42.6 (**C**H$_2$), 39.2 (**C**), 30.2 (**C**H$_2$), 28.5 (**C**H$_2$), 27.7 (**C**H$_3$), 27.6 (**C**H$_3$), 25.9 (**C**H$_3$), 18.2 (**C**H$_3$); MS *m/z* 557 $[M+H]^+$, 579 $[2M+H]^+$.

*2.11.20 3-[2-(1,1-Dimethyl-allyl)-1*H*-indol-3-ylmethyl]-10b-hydroxy-2,3,6,10b,11,11a-hexahydro-5a*H*-pyrazino[1',2':1,5]pyrrolo[2,3-*b*]indole-1,4-dione* **1.27** *(okaramine J)*

To a solution of **1.26** (330 mg, 0.59 mmol) in 1,4-dioxane (3 mL) was added 10% KOH in MeOH (3 mL). The reaction mixture was stirred for 16 h then acidified to pH 5 with 1N HCl, extracted with EtOAc (3 x 10 mL), washed with water (10 mL), dried over $MgSO_4$, filtered and the solvent evaporated to give the carboxylic acid as a white glass which was used in the next step without further purification.

To a solution of the carboxylic acid (50 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was added diisopropylethylamine (47 μL, 0.27 mmol) and HBTU (38 mg, 0.10 mmol). The reaction mixture was stirred for 7 d then the solvent evaporated. The residue was purified by column chromatography (5 g silica; eluent 1% – 5% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **1.27** as a white glassy solid (23 mg, 49%): $[\alpha]^{22}_D$ = +24.6 (c = 0.33 in MeOH, lit +31); IR ν_{max} 3367bs, 1667s, 1605m cm^{-1}; ^{1}H NMR (400MHz, $(CD_3)_2CO$) δ 9.85 (1H, s, indole N**H**), 7.42 (1H, d, J = 8.0 Hz, Ar**CH**), 7.22 (1H, d, J = 8.0 Hz, Ar**CH**), 7.01 (1H, d, J = 7.3 Hz, Ar**CH**), 6.95 (1H, dd, J = 7.3, 6.4 Hz, Ar**CH**), 6.88 (1H, dd, J = 8.0, 6.4 Hz, Ar**CH**), 6.84 (1H, d, J = 7.5 Hz, Ar**CH**), 6.58 (1H, dd, J = 8.0, 7.5 Hz, Ar**CH**), 6.12 (1H, dd, J = 17.3, 10.5 Hz, CH$_2$=**CH**), 5.56 (1H, s, NC**H**N), 5.39 (1H, d, J = 3.8 Hz, N**H**), 5.31 (1H, d, J = 3.8 Hz. N**H**), 5.16 (1H, td, J = 7.3, 1.3, C=C**H**), 5.01 (1H, d, J = 17.5 Hz, CH=C**H**$_2$), 4.94 (1H, d, J = 10.5 Hz, CH=C**H**$_2$), 4.55 (1H, dd, J = 11.0, 6.7 Hz, C**H**CH$_2$), 4.44 (1H, dd, J = 11.0, 4.0 Hz, C**H**CH$_2$), 3.59 (1H, dd, J = 15.0, 4.0 Hz, CHC**H**$_2$), 3.15 (1H, dd, J = 16.1, 7.5 Hz, CHC**H**$_2$), 3.09 (1H, dd, J = 16.2, 7.3 Hz, CHC**H**$_2$), 2.45 (1H, dd, J = 13.3, 7.0 Hz,

CHC**H**$_2$), 2.03 (1H, dd, J = 13.0, 11.0 Hz, CHC**H**$_2$), 1.74 (6H, s, 2 x C**H**$_3$), 1.47 (3H, s, C**H**$_3$), 1.47 (3H, s, C**H**$_3$); ^{13}C NMR (100 MHz, $(CD_3)_2CO$) δ 170.0 (**C**), 168.7 (**C**), 147.5 (**C**), 142.7 (**C**H), 136.4 (**C**), 133.8 (**C**), 131.9 (**C**), 130.4 (**C**), 130.0 (**C**H), 124.1 (**C**), 122.8 (**C**H), 122.4 (**C**H), 121.6 (**C**H), 120.3 (**C**H), 120.2 (**C**H), 118.7 (**C**H), 112.4 (**C**H$_2$), 112.2 (**C**H), 105.7 (**C**), 87.6 (**C**), 85.6 (**C**H), 59.8 (**C**H), 56.4 (**C**H), 42.5 (**C**H$_2$), 40.2 (**C**), 29.5 (**C**H$_2$), 28.7 (**C**H$_3$), 28.6 (**C**H$_3$), 26.9 (**C**H$_2$), 26.1 (**C**H$_3$), 18.1(**C**H$_3$); MS *m/z* 525 $[M+H]^+$, 547 $[M+Na]^+$. The spectroscopic properties were consistent with that reported in the literature (ref 25).

2.11.21 1-(Anthracene-9-sulfonyl)-8-(1,1-dimethyl-prop-2-ynyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-b]indole-2-carboxylic acid **1.29**

To a solution of **1.17** (1.45 g, 2.5 mmol) and 2,6-lutidine (14.4 mL, 125 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added dropwise trimethylsilyl triflate (10.2 mL, 50 mmol). After stirring for 16 h the reaction mixture was cooled to 0 °C and quenched with saturated aq $NaHCO_3$ (ca. 10 mL). The reaction mixture was washed with 1N HCl (2 x 25 mL) then brine (25 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The resultant brown oil was purified by column chromatography (100 g silica; eluent 2% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give a yellow foam. This was dissolved in THF (50 mL) and treated with TBAF (1M solution in THF 3.75 mL, 3.75 mmol). After stirring for 1 h the reaction mixture was washed with saturated aq NH_4Cl (25 mL), saturated aq $NaHCO_3$ (25 mL), then brine (25 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The resultant yellow foam was purified by column chromatography (100 g silica; eluent 2% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **1.29** as a yellow foam (1.20 g, 92%): $[\alpha]^{22}_D$ = -19.1 (c = 0.2 in MeOH); ^{1}H NMR δ 9.47 (2H, d, J = 9.2 Hz, ArC**H**), 8.77 (1H, s, ArC**H**), 8.06 (2H, d, J = 8.5 Hz, ArC**H**), 7.76 (2H, dd, J = 9.2, 6.6 Hz, ArC**H**), 7.58 (2H, dd, J = 8.5, 6.6 Hz, ArC**H**), 7.22 (1H, d, J = 8.5 Hz, ArC**H**), 7.19 (1H, d, J = 8.1 Hz, ArC**H**), 7.14 (1H, dd, J = 8.5, 7.0 Hz, ArC**H**), 6.93 (1H, dd, J = 8.1, 7.0 Hz, ArC**H**), 6.04 (1H, s, NC**H**N), 4.34 (1H, dd, J = 8.8, 1.5 Hz, C**H**CH$_2$), 2.83 (1H, dd, J = 12.9, 1.5 Hz, CHC**H**$_2$), 2.74 (1H, dd, J = 12.9, 8.8 Hz, CHC**H**$_2$), 2.41 (1H, s, C≡C**H**), 1.85 (3H, s, C**H**$_3$), 1.84 (3H,

s, CH_3); ^{13}C NMR δ 171.0 (**C**), 148.8 (**C**), 138.1 (**C**H), 133.2 (**C**), 131.5 (**C**), 131.2 (**C**), 130.5 (**C**H), 130.0 (**C**H), 125.8 (**C**H), 124.6 (**C**H), 124.4 (**C**H), 123.8 (**C**H), 119.3 (**C**H), 89.0 (**C**), 88.2 (**C**H), 86.2 (**C**), 72.2 (**C**), 60.9 (**C**H), 55.1 (**C**), 41.2 (CH_2), 31.4 (**C**H), 29.5 (CH_3); IR ν_{max} 3508bs, 3286s, 3134m, 3045m, 1727s, 1602s, 1517m, 1479m cm^{-1}; MS *m/z* 526 $[M+H]^+$, 549 $[M+Na]^+$.

*2.11.22 1-(Anthracene-9-sulfonyl)-8-(1,1-dimethyl-allyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole-2-carboxylic acid* **1.30**

To a solution of **1.29** (500 mg, 0.95 mmol) in EtOAc (25 mL) was added Pd/Al_2O_3 catalyst (100 mg) and the reaction mixture stirred under H_2 (1 atm) for 2 h. The reaction mixture was filtered through a pad of celite and the solvent evaporated to give **1.30** as a yellow foam (502 mg, 99%): $[\alpha]^{22}_D$ = +9.6 (*c* = 0.2 in MeOH); IR ν_{max} 3478bs, 3394bs, 3144w, 3082m, 1725s, 1607s, 1517m, 1481s cm^{-1}; ^1H NMR δ 9.43 (2H, d, *J* = 9.2 Hz, ArC**H**), 8.79 (1H, s, ArC**H**), 8.07 (2H, d, *J* = 8.5 Hz, ArC**H**), 7.75 (2H, dd, *J* = 9.2, 6.6, Hz, ArC**H**), 7.58 (2H, dd, *J* = 8.5, 6.6 Hz, ArC**H**), 7.17 (1H, d, *J* = 7.4 Hz, ArC**H**), 7.05 (1H, dd, *J* = 7.4, 6.6 Hz, ArC**H**), 7.02 (1H, d, *J* = 7.7 Hz, ArC**H**), 6.83 (1H, dd, *J* = 7.7, 6.6 Hz, ArC**H**), 6.11 (1H, dd, *J* = 17.6, 10.7 Hz, CH_2=C**H**), 6.01 (1H, s, NC**H**N), 5.15 (1H, d, *J* = 18.0 Hz, CH=C$\mathbf{H}_2$), 5.10 (1H, d, *J* = 11.4 Hz, CH=C$\mathbf{H}_2$), 4.46 (1H, d, *J* = 8.8 Hz, CHC$\mathbf{H}_2$), 2.82 (1H, d, *J* = 12.9 Hz, CHC$\mathbf{H}_2$), 2.67 (1H, dd, *J* = 12.9, 9.2 Hz, C**H**CH$_2$), 1.49 (3H, s, C$\mathbf{H}_3$), 1.41 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR δ 174.7 (**C**), 171.3 (**C**), 148.9 (**C**), 146.5 (**C**H), 138.1 (**C**H), 131.8 (**C**), 131.6 (**C**), 131.2 (**C**H), 130.3 (**C**H), 130.0 (**C**H), 125.9 (**C**H), 124.7 (**C**), 124.4 (**C**H), 123.9 (**C**H), 122.0 (**C**H), 116.9 (**C**H), 112.9 (CH_2), 89.1 (**C**H), 86.8 (**C**), 61.4 (**C**H), 60.9 (**C**), 42.4 (CH_2), 28.6 (CH_3), 24.3 (CH_3); MS *m/z* 529 $[M+H]^+$.

*2.11.23 2-{[1-(Anthracene-9-sulfonyl)-8-(1,1-dimethyl-allyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-*b*]indole-2-carbonyl]-amino}-3-[2-(1,1-dimethyl-allyl)-1*H*-indol-3-yl]-propionic acid methyl ester* **1.31**

Method 1: To a solution of **1.30** (150 mg, 0.28 mmol), **1.4** (89 mg, 0.31 mmol) and Et_3N (43 μL, 0.31 mmol) in THF (10 mL) was added HOBt (42 mg, 0.31 mmol) and the

reaction mixture stirred for 15 min. EDAC (59 mg, 0.31 mmol) and the reaction mixture stirred for 4 d. The reaction mixture was concentrated under vacuum, diluted with CH_2Cl_2, (10 mL), washed with water (3 x 10 mL) then brine (10 mL), dried over $MgSO_4$, filtered, and the solvent evaporated. The resultant brown residue was purified by column chromatography (15 g silica; eluent 10% - 50% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **1.31** as a yellow glass (132 mg, 59%): $[\alpha]^{22}_D$ = -7.9 (*c* = 0.2 in MeOH); IR ν_{max} 3389s, 3078w, 1740s, 1667s, 1621w, 1616w, 1519s, 1479s cm^{-1}; ^1H NMR δ 9.53 (2H, d, *J* = 9.2 Hz, ArC**H**), 8.81 (1H, s, ArC**H**), 8.09 (2H, d, *J* = 8.5 Hz, ArC**H**), 7.85 (1H, s, indole N**H**), 7.77 (2H, dd, *J* = 9.2, 6.6 Hz, ArC**H**), 7.56 (2H, dd, *J* = 8.5, 6.6 Hz, ArC**H**), 6.99-7.26 (6H, m, ArC**H**), 6.80-6.90 (2H, m, ArC**H**), 6.46 (1H, dd, *J* = 17.5, 10.8 Hz, C**H**=CH_2), 6.19 (1H, s, NC**H**N), 5.99 (1H, dd, *J* = 17.5, 10.5 Hz, C**H**=CH_2), 5.36 (1H, d, *J* = 17.6 Hz, CH=C**H**$_2$), 5.28 (1H, d, *J* = 10.6 Hz, CH=C**H**$_2$), 5.11 (1H, d, *J* = 10.3 Hz, CH=C**H**$_2$), 5.07 (1H, d, *J* = 17.3 Hz, CH=C**H**$_2$), 4.36 (1H, d, *J* = 8.8 Hz, C**H**CH_2), 3.75 (1H, m, C**H**CH_2), 3.02 (2H, d, *J* = 14.0 Hz, CHC**H**$_2$), 2.86 (3H, s, $CO_2C\mathbf{H}_3$), 2.72 (1H, dd, *J* = 12.7, 9.0 Hz, CHC**H**$_2$), 2.28 (1H, dd, *J* = 14.3, 5.2 Hz, CHC**H**$_2$), 2.21 (1H, s, N**H**), 1.87 (3H, s, C**H**$_3$), 1.60 (3H, s, C**H**$_3$), 1.39 (3H, s, C**H**$_3$), 1.38 (3H, s, C**H**$_3$); ^{13}C NMR δ 171.0 (**C**), 168.7 (**C**), 150.2 (**C**), 147.6 (**C**H), 145.8 (**C**H), 140.2 (**C**), 137.6 (**C**H), 133.9 (**C**), 132.2 (**C**), 131.7 (**C**), 131.3 (**C**), 130.5 (**C**H), 129.9 (**C**H), 129.5 (**C**), 125.7 (**C**H), 124.8 (**C**H), 124.6 (**C**H), 121.6 (**C**H), 121.4 (**C**H), 121.4 (**C**H), 119.1 (**C**H), 118.5 (**C**H), 116.4 (**C**H), 112.5 (**C**H$_2$), 112.5 (**C**H$_2$), 110.3 (**C**H), 104.8 (**C**), 88.5 (**C**H), 87.0 (**C**), 63.1 (**C**H), 61.2 (**C**), 53.6 (**C**H), 51.5 (**C**H), 40.7 (**C**H$_2$), 39.1 (**C**), 29.3 (**C**H), 27.8 (**C**H), 27.7 (**C**H$_2$), 27.5 (**C**H$_3$), 25.2 (**C**H$_3$); MS *m/z* 797 $[M+H]^+$.

Method 2: To a solution of **1.30** (100 mg, 0.19 mmol) and **1.4** (60 mg, 0.20 mmol) in THF was added HOBt (27 mg, 0.2 mmol) followed by resin-bound EDAC (loading 1.45 mmol/g, 655 mg, 0.95 mmol). The reaction mixture was stirred for 24 h at RT then filtered and the resin washed with THF. The solvent was evaporated and the residue dissolved in EtOAc (10 mL), washed with water (3 x 10 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by column chromatography (10 g silica; eluent 1:1 – 3:1 Et_2O:hexane). The relevant fractions were combined and the solvent evaporated to give **1.31** as a yellow glass (93 mg, 61%).

2.11.24 2-{[8-(1,1-Dimethyl-allyl)-3a-hydroxy-1,2,3,3a,8,8a-hexahydro-pyrrolo[2,3-b]indole-2-carbonyl]-amino}-3-[2-(1,1-dimethyl-allyl)-1H-indol-3-yl]-propionic acid methyl ester **1.32**

To a solution of **1.31** (150 mg, 0.19 mmol) in THF/H_2O (5:1, 5 mL) was added freshly prepared Al(Hg) amalgam (ca 0.6 g Al). The reaction mixture was stirred for 7 h then filtered through a pad of celite, washed with EtOAc (50 mL) and the solvent evaporated. The resultant pale yellow residue was purified by column chromatography (25 g alumina; eluent 1% – 2% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **1.32** as a white foam (83 mg, 78%): $[\alpha]^{22}_D$ = +13.2 (*c* = 0.2 in MeOH); IR ν_{max} 3338s, 3077w, 1737s, 1658s, 1602m, 1515s, 1478s cm^{-1}; ^1H NMR δ 7.93 (1H, d, *J* = 3.7 Hz, indole N**H**), 7.91 (1H, d, *J* = 5.1 Hz, N**H**), 7.40 (1H, d, *J* = 7.7 Hz, ArC**H**), 7.21 (2H, d, *J* = 7.4 Hz, ArC**H**), 7.01-7.08 (2H, m, ArC**H**), 6.96 (1H, dd, *J* = 8.1, 7.0 Hz, ArC**H**), 6.82 (1H, d, *J* = 8.1 Hz, ArC**H**), 6.64 (1H, dd, *J* = 7.4, 7.0 Hz, ArC**H**), 6.24 (1H, dd, *J* = 17.6, 10.7 Hz, CH_2=C**H**), 6.07 (1H, dd, *J* = 17.5, 10.5 Hz, CH_2=C**H**), 5.30 (1H, dd, *J* = 17.3, 0.7 Hz, CH=C$\mathbf{H}_2$), 5.23 (1H, dd, *J* = 10.7, 0.7 Hz, CH=C$\mathbf{H}_2$), 5.15 (1H, dd, *J* = 17.6, 1.1 Hz, CH=C$\mathbf{H}_2$), 5.15 (1H, dd, *J* = 10.3, 1.1 Hz, CH=C$\mathbf{H}_2$), 5.04 (1H, s, NC**H**N), 4.57 (1H, m, C**H**CH_2), 3.90 (1H, t, *J* = 6.4 Hz, C**H**CH_2), 3.25 (3H, s, $CO_2C\mathbf{H}_3$), 2.63 (1H, d, *J* = 12.1 Hz, C$\mathbf{H}_2$CH), 2.58 (1H, dd, *J* = 5.3, 5.3 Hz, C$\mathbf{H}_2$CH), 2.47 (2H, dd, *J* = 14.5, 6.1 Hz, CHC$\mathbf{H}_2$), 1.68 (3H, s, C$\mathbf{H}_3$), 1.51 (3H, s, C$\mathbf{H}_3$), 1.50 (3H, s. C$\mathbf{H}_3$), 1.48 (3H, s, C$\mathbf{H}_3$); ^{13}C NMR δ 173.2 (**C**), 173.1 (**C**), 148.5 (**C**), 146.5 (CH), 145.8 (CH), 140.3 (**C**), 134.0 (**C**), 131.4 (**C**), 130.0 (CH), 129.7 (**C**), 124.1 (CH), 121.4 (CH), 119.3 (CH), 118.4 (CH), 117.9 (CH), 112.9 (CH_2), 112.3 (CH_2), 111.7 (CH), 110.3 (CH), 105.5 (**C**), 87.1 (CH), 86.1 (**C**), 60.9 (CH), 57.3 (**C**), 52.7 (CH), 52.0 (CH), 41.2 (CH_2), 39.1 (**C**), 28.9 (CH_2), 27.7 (CH_3), 27.5 (CH_3), 26.7 (CH_3), 25.6 (CH_3); MS *m/z* 557 $[M+H]^+$.

2.1.25 6-(1,1-Dimethyl-allyl)-3-[2-(1,1-dimethyl-allyl)-1H-indol-3-ylmethyl]-10b-hydroxy-2,3,6,10b,11,11a-hexahydro-5aH-pyrazino[1',2':1,5]pyrrolo[2,3-b]indole-1,4-dione **1.33** *(okaramine C)*

To a solution of **1.32** (60 mg, 0.11 mmol) in 1,4-dioxane (1 mL) was added 10% KOH in MeOH (1 mL). The reaction mixture was stirred for 8 h then acidified to pH 5 with 1N

HCl, extracted with EtOAc (2 x 10 mL), washed with water (2 x 10 mL), dried over $MgSO_4$, filtered and the solvent evaporated to give the carboxylic acid as a white glass which was used in the next step without further purification.

Method 1: To a solution of the carboxylic acid (50 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) was added diisopropylethylamine (47 μL, 0.27 mmol) and HBTU (38 mg, 0.10 mmol). The reaction mixture was stirred for 24 h, diluted with CH_2Cl_2 (5 mL), washed with water (2 x 5 mL), the aqueous phases combined, washed with CH_2Cl_2 (5 mL), the organics combined, dried over $MgSO_4$ then the solvent evaporated. The residue was purified by column chromatography (5 g alumina; eluent 1% – 2% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated. The residue was purified by preparative TLC (neutral alumina, aluminium backed plates; eluent EtOAc) to give **1.33** as a white glass (7 mg, 15%): $[\alpha]^{22}_D$ = +3.0 (*c* = 0.2 in MeOH, lit +19); IR ν_{max} 3361s, 1682s, 1602m, 1476s, 1462m cm^{-1}; ^1H NMR (400 MHz) δ 8.00 (1H, s, indole N**H**), 7.40 (1H, d, *J* = 7.8 Hz, ArC**H**), 7.32 (1H, d, *J* = 7.7 Hz, ArC**H**), 7.29 (1H, d, *J* = 8.0 Hz, ArC**H**), 7.17 (1H, dd, *J* = 7.7, 7.2 Hz, ArC**H**), 7.15 (1H, dd, *J* = 8.0, 7.3 Hz, ArC**H**), 7.07 (1H, dd, *J* = 8.0, 7.2 Hz, ArC**H**), 7.04 (1H, d, *J* = 8.0 Hz, ArC**H**), 6.85 (1H, dd, *J* = 7.8, 7.3 Hz, ArC**H**), 6.45 (1H, dd, *J* = 17.6, 10.8 Hz, CH_2=C**H**), 6.03 (1H, dd, *J* = 17.3, 10.5 Hz, CH_2=C**H**), 5.44 (1H, s, NC**H**N), 5.41 (1H, s, O**H**), 5.19 (1H, dd, *J* = 17.9, 1.0 Hz, CH=C$\mathbf{H}_2$), 5.15 (1H, dd, *J* = 10.8, 1.0 Hz, CH=C$\mathbf{H}_2$), 5.07 (1H, dd, *J* = 17.3, 0.7 Hz, CH=C$\mathbf{H}_2$), 5.02 (1H, dd, *J* = 10.5, 0.7 Hz, CH=C$\mathbf{H}_2$), 4.24-4.27 (2H, m, C**H**CH_2), 3.66 (1H, dd, *J* = 15.3, 4.5 Hz, $CHC\mathbf{H}_2$), 3.21 (1H, dd, *J* = 13.7, 4.4 Hz, $C\mathbf{H}_2CH$), 3.08 (1H, dd, *J* = 15.2, 11.4 Hz, $C\mathbf{H}_2CH$), 2.59 (1H, dd, *J* = 13.8, 10.3 Hz, $CHC\mathbf{H}_2$), 1.73 (3H, s, $C\mathbf{H}_3$), 1.55 (3H, s, $C\mathbf{H}_3$), 1.47 (6H, s, 2 x $C\mathbf{H}_3$) ^{13}C NMR δ 168.9 (**C**), 168.6 (**C**), 148.8 (**C**), 147.3 (**C**H), 145.6 (**C**H), 141.5 (**C**), 134.4 (**C**), 132.9 (**C**), 130.2 (**C**H), 129.2 (**C**), 123.9 (**C**H), 122.3 (**C**H), 120.5 (**C**H), 120.3 (**C**H), 118.0 (**C**H), 115.7 (**C**H), 112.8 ($\mathbf{C}H_2$), 112.1 ($\mathbf{C}H_2$), 110.9 (**C**H), 104.8 (**C**), 85.0 (**C**H), 84.0 (**C**), 59.5 (**C**), 57.5 (**C**H), 55.3 (**C**H), 39.0 (**C**), 32.9 ($\mathbf{C}H_2$), 27.9 ($\mathbf{C}H_3$), 26.0 ($\mathbf{C}H_3$), 25.7 ($\mathbf{C}H_2$); MS *m/z* 525 $[M+H]^+$. The spectroscopic properties were consistent with that reported in the literature (ref 1).

Epi-okaramine C **1.34** was obtained as a white glass (8 mg, 17%): $[\alpha]^{22}_{D}$ = +112.5 (*c* = 0.2 in MeOH); IR ν_{max} 3347s, 3078w, 1681s, 1607m, 1474w, 1462m cm^{-1}; ^{1}H NMR (400 MHz) δ 8.01 (1H, s, indole N**H**), 7.55 (1H, d, *J* = 7.8 Hz, ArC**H**), 7.28 (1H, d, *J* = 8.0 Hz, ArC**H**), 7.25 (1H, d, *J* = 7.5 Hz, ArC**H**), 7.06-7.17 (3H, m, ArC**H**), 7.02 (1H, d, *J* = 8.0 Hz, ArC**H**), 6.81 (1H, dd, *J* = 7.8, 7.3 Hz, ArC**H**), 6.50 (1H, dd, *J* = 17.8, 10.8 Hz, CH_2=C**H**), 6.13 (1H, dd, *J* = 17.3, 10.5 Hz, CH_2=C**H**), 5.44 (1H, d, *J* = 3.8 Hz, O**H**), 5.31 (1H, s, NC**H**N), 5.12-5.21 (4H, m, CH=C$\mathbf{H}_2$), 4.18 (1H, dt, *J* = 9.8, 4.0 Hz, C**H**CH_2), 4.07 (1H, dd, *J* = 10.5, 6.0 Hz, C**H**CH_2), 3.44 (1H, dd, *J* = 14.6, 4.0 Hz, CHC$\mathbf{H}_2$), 3.35 (1H, dd, *J* = 14.6, 9.8 Hz, C$\mathbf{H}_2$CH), 3.07 (1H, dd, *J* = 13.9, 6.0 Hz, C$\mathbf{H}_2$CH), 2.56 (1H, dd, *J* = 13.9, 10.4 Hz, CHC$\mathbf{H}_2$), 1.75 (3H, s, C$\mathbf{H}_3$), 1.52 (9H, s, 2 x C$\mathbf{H}_3$) ^{13}C NMR δ 168.3 (**C**), 167.6 (**C**), 148.9 (**C**), 147.4 (**C**H), 146.3 (**C**H), 141.6 (**C**), 134.5 (**C**), 133.8 (**C**), 130.1 (**C**H), 128.8 (**C**), 123.8 (**C**H), 122.2 (**C**H), 120.6 (**C**H), 120.0 (**C**H), 118.7 (**C**H), 115.8 (**C**H), 112.0 ($\mathbf{C}H_2$), 112.0 ($\mathbf{C}H_2$), 110.8 (**C**H), 105.4 (**C**), 85.8 (**C**H), 83.3 (**C**), 59.7 (**C**), 58.7 (**C**H), 55.4 (**C**H), 39.8 (**C**), 34.4 ($\mathbf{C}H_2$), 29.1 ($\mathbf{C}H_2$), 28.2 ($\mathbf{C}H_3$), 28.0 ($\mathbf{C}H_3$), 27.9 ($\mathbf{C}H_3$), 26.2 ($\mathbf{C}H_3$); MS *m/z* 525 $[M+H]^+$.

Method 2: To a solution of carboxylic acid (40 mg, 0.07 mmol) in THF (3 mL) was added HOBt (10 mg, 0.077 mmol) followed by resin-bound EDAC (loading 1.45 mmol/g, 145 mg, 0.21 mmol). The reaction mixture was stirred for 5 d at RT then filtered and the resin washed with THF. The solvent was evaporated and the residue dissolved in CH_2Cl_2 (5 mL), washed with water (3 x 5 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by preparative TLC (eluent 5% MeOH in CH_2Cl_2), extracted with EtOAc and the solvent evaporated to give **1.33** as a white glass (22 mg, 57%).

References

[1] Hayashi, H.; Fujiwara, T.; Murao, S.; Arai, M. *Agric. Biol. Chem.* **1991**, *55*, 3143-3145.

[2] Schkeryantz, J. M.; Woo, J. C. G.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 7025-7026.

[3] Schkeryantz, J. M.; Woo, J. C. G.; Siliphaivanh, P.; Depew, K. M.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1999**, *121*, 11964-11975.

[4] Bodansky, M; Bodansky, A. *The Practice of Peptide Synthesis*; Springer-Verlag: Berlin, 1984, p10.

[5] Kolasa, T.; Miller, M. J. *J. Org. Chem.* **1990**, *55*, 1718-1721.

[6] Ohki, S.; Nagasaka, T. *Chem. Pharm. Bull.* **1971**, *19*, 545-551.

[7] Kramer, G. W.; Brown, H. C. *J Organomet. Chem.* **1977**, *132*, 9-27.

[8] Mintz, M. J.; Walling, C. *Org. Syntheses*, **1969**, *49*, 9-12.

[9] Kumar, H. M. S.; Anjaneyulu, S.; Reddy, E. J.; Yadav, J. S. *Tetrahedron Lett.* **2000**, *41*, 9311-9314.

[10] Tussa, L.; Lebreton C.; Mosset, P. *Chem. Eur. J.* **1997**, *3*, 1064-1070.

[11] Sanazuka, T.; Hirose, T.; Shirahata, T.; Harigaya, Y.; Hayashi, M.; Komiyama, K.; Omura, S. *J. Am.Chem. Soc.* **2000**, *122*, 2122-2123.

[12] Danishefsky, S. J.; Kamenecka, T. M. *Chem. Eur. J.* **2001**, *7*, 41-63.

[13] Murray, R.W.; Singh, M. *Org. Syntheses* **1997**, *74*, 91-100.

[14] Wuts, P. G. M. *J. Org. Chem.* **1997**, *62*, 430.

[15] Robinson, A. J.; Wyatt, P. B. *Tetrahedron* **1993**, *49*, 11329-11340.

[16] Yang, D.; Wong, M.; Yip, Y. *J. Org. Chem.* **1995**, *60*, 3887-3889.

[17] A modified version of method in Murray, R.W.; Singh, M. *Org. Syntheses* **1997**, *74*, 91-100.

[18] Yang, D.; Yip, Y.; Jiao, G.; Wang, M. *Org. Syntheses* **2000**, *78*, 225-233.

[19] Sugiyama, H.; Yokokawa, F.; Aoyama, T.; Shiori, T. *Tetrahedron Lett.* **2001**, *42*, 7277-7280.

[20] Zhu, X. *PhD Thesis*, University of Southampton, 2001, 73-89.

[21] Rank, E.; Bruckner, R.; *Eur. J. Org. Chem.* **1998**, 1045-1053.

[22] For examples of propargylations with halides and esters see: (a) Hennion, G. F.; Hanzel, R. S. *J. Am. Chem. Soc.* **1960**, *82*, 4908-4912. (b) Wipf, P.; Venkatraman, S. *J. Org. Chem.* **1996**, *61*, 6517-6522. (c) Imada, Y.; Yuasa, M.; Nakamura, I.; Murahashi, S-I. *J. Org. Chem.* **1994**, *59*, 2282-2284.

[23] Borgulya, J.; Bernauer, K. *Synthesis*, **1980**, 545-547.

[24] Arenzo, H. B.; Kemp, D. S. *Synthesis*, **1998**, 33-36.

[25] Schiavi, B. M.; Richard, D. J.; Joullie, M. M. *J. Org. Chem.* **2002**, *67*, 620-624.

[26] Shiono, Y.; Akiyama, K.; Hayashi, H. *Biosci. Biotechnol. Biochem.* **1999**, *63*, 1910-1920.

[27] Carnahan, F. L.; Hurd, C. D. *J. Am. Chem. Soc.* **1930**, *52*, 4586-4595.

[28] Hurd, C. D.; Jenkins, W. W. *J. Org. Chem.* **1957**, *22*, 1418-1423.

[29] For thermal rearrangements of aromatic allyl or propargylamines see: (a) Marcinkiewicz, S.; Green, J.; Mamalis, P. *Tetrahedron*, **1961**, *14*, 208-222. (b) Scheurer, H.; Zsindely, J.; Schmid, H. *Helv. Chim. Acta*

1973, *56*, 478-489. (c) Prasad, D. V.; Darbarwar, M. *Synth. Commun.* **1988**, *18*, 881-887. (d) Majumdar, K. C.; Bhattacharyya, T. *Tetrahedron Lett.* **2001**, *42*, 4231-4233.

[30] For charge accelerated aza-Claisen rearrangements see: (a) Takamatsu, N.; Inoue, S.; Kishi, Y. *Tetrahedron Lett.* **1971**, *12*, 4661-4664. (b) Schmid, M.; Hansen, H.-J. *Helv. Chim. Acta* **1973**, *56*, 105-124. (c) Jolidon, S.; Hansen, H.-J. *Helv. Chim. Acta* **1977**, *60*, 978-1032. (d) Barmettler, P.; Hansen, H.-J. *Helv. Chim. Acta* **1990**, *73*, 1515-1573. (e) Lai, G.; Anderson, W. K. *Tetrahedron Lett.* **1993**, *34*, 6849-6852. (f) Beholz, L. G.; Stille, J. R. *J. Org. Chem.* **1993**, *58*, 5095-5100. (g) Anderson, W. K.; Lai, G. *Synthesis* **1995**, 1287-1289. (h) Lai, G.; Anderson, W. K. *Tetrahedron* **2000**, *56*, 2583-2590. (i) Cooper, M. A.; Lucas, M. A.; Taylor, J. M.; Ward, A. D.; Williamson, N. M. *Synthesis* **2001**, 621-625.

[31] Pedersen, C. J. *J. Am. Chem. Soc.* **1967**, *89*, 7017-7036.

[32] Stein, K. A.; Toogood, P. L. *J. Org. Chem.* **1995**, *60*, 8110-8112.

[33] Klemm, L. H.; Antoniades, E. P.; Lind, C. D. *J. Org. Chem.* **1967**, *27*, 519-526.

[34] Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, *19*, 4475-4478.

[35] Roe, J. M.; Webster, R. A. B.; Ganesan, A. *Org. Lett.* **2003**, *5*, 2825-2827.

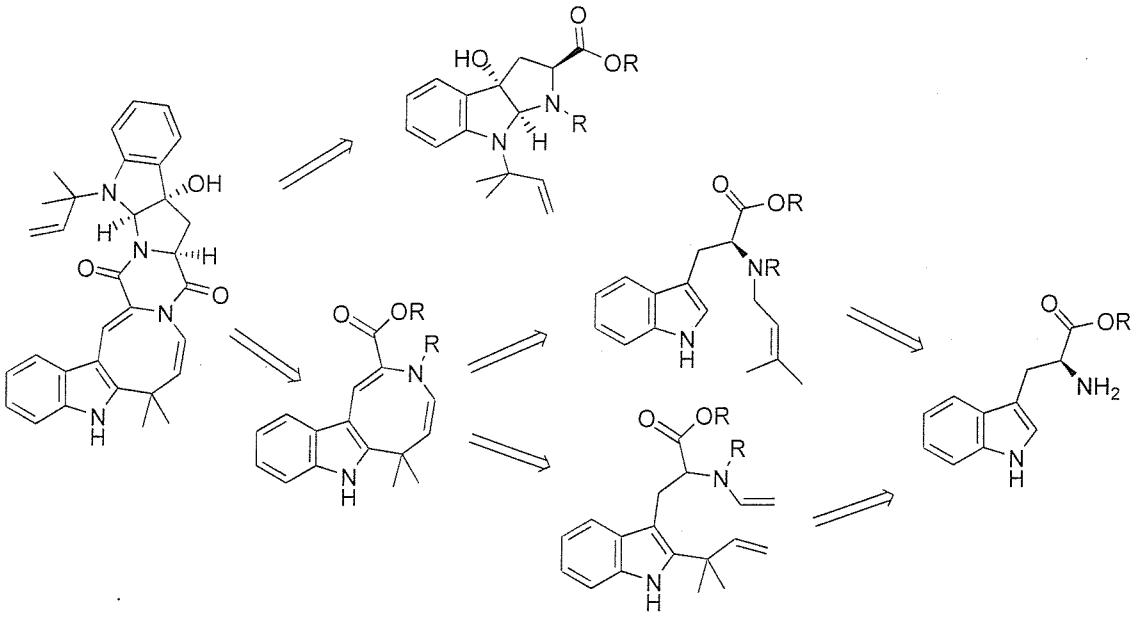
[36] Baran, P. S.; Guerrero, C. A.; Corey, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5628-5629.

3.0 Studies Towards the Synthesis of Okaramine A

3.1 Retrosynthesis of okaramine A

The previous chapter detailed the successful total syntheses of okaramine J and C. Many of the okaramines contain an 8-membered azocine. Here we describe model studies directed towards this ring system. Okaramine A, for example, can be split in two through the diketopiperazine ring, the hexahydropyrroloindoline half being identical to that used in the synthesis of okaramine C (Figure 1). Two strategies were considered for the formation of the azocine ring, again both starting from tryptophan. The first was to form an 8-membered ring by acid-catalysed cyclisation of a prenyl group onto the indole ring of tryptophan. Further oxidation would then be required to introduce the double bonds present in okaramine A. The alternative strategy was to form the 8-membered ring by ring-closing metathesis between a reverse prenylated tryptophan and a vinyl amine.

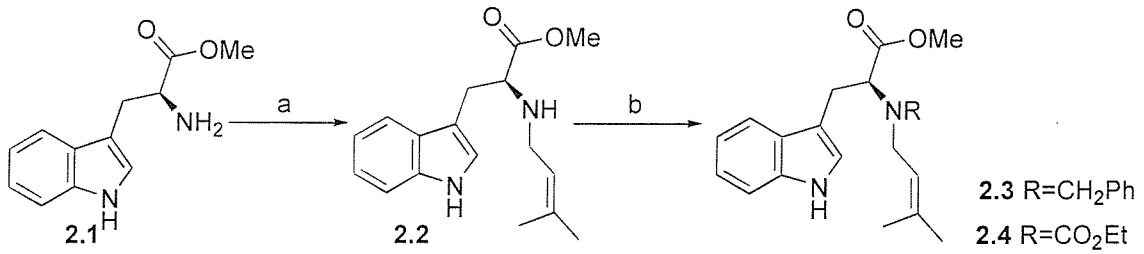
Figure 1. Retrosynthesis of okaramine A.



3.2 Formation of 8-membered ring via acid catalysed cyclisation

A model substrate was chosen to investigate the possibility of forming an 8-membered ring by acid catalysed cationic cyclisation. A carbamate protected *N*-prenyl tryptophan derivative was prepared by reductive alkylation of L-tryptophan methyl ester followed by reaction with a chloroformate (Scheme 1).

Scheme 1. Preparation of carbamate protected *N*-prenyl tryptophan derivative [a].



[a] Conditions: (a) 3-methyl-2-butenal, $NaBH(OAc)_3$, 1% AcOH in CH_2Cl_2, 2 h, 49%; (b) Et_3N, CH_2Cl_2, benzyl chloroformate, 24 h, 2%; ethyl chloroformate, 3 d, 94%.

Reductive alkylation of **2.1** with 3-methyl-2-butenal yielded 49% of pure material after column chromatography with an additional 25% of material with one impurity by TLC. Secondary amine **2.2** was protected as a carbamate. Initially **2.2** was reacted with benzyl chloroformate in an attempt to form the benzyl carbamate **2.3**. Monitoring by TLC showed complete disappearance of the chloroformate, although a small amount of starting material remained. After workup and purification by column chromatography the majority of material recovered was the starting amine. A new product was obtained in very low yield due to alkylation of **2.2** on nitrogen with benzyl chloride, a known impurity in the starting chloroformate. MS was consistent with addition of a benzyl group and ^1H NMR showed alkylation had occurred on nitrogen to give **2.3**.

Ethyl chloroformate was used as an alternative to benzyl chloroformate. MS and IR indicated formation of the desired product **2.4** in 49% yield. The yield was increased to 94% when a larger excess of the chloroformate was used. Some of the peaks in the ^1H NMR spectrum were broad with unresolved coupling. The integration and chemical shift

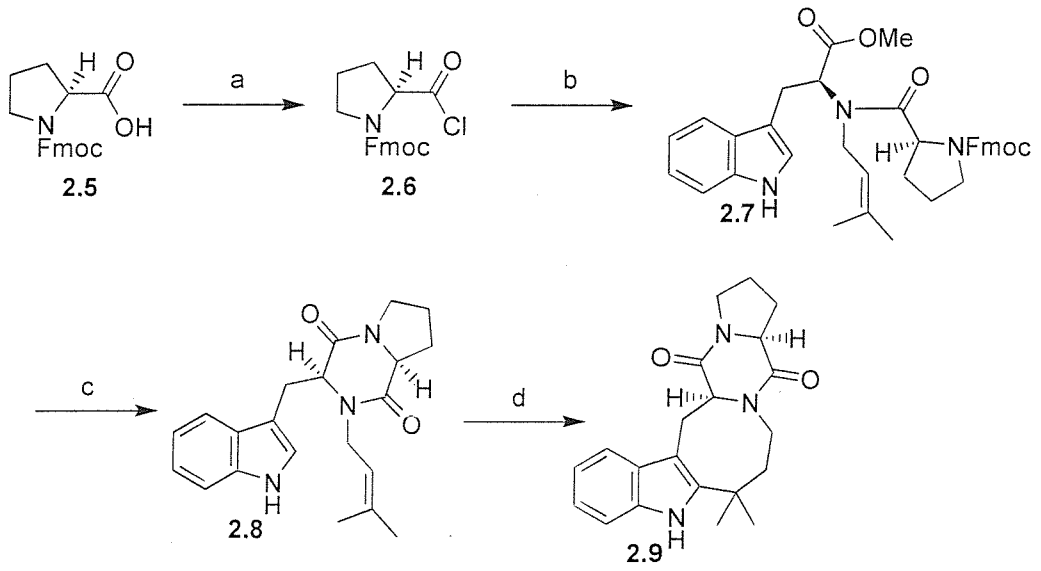
were consistent with the desired product but were not absolutely conclusive. The unusual broadening of these peaks was indicative of the presence of amide rotamers. This was confirmed by recording ^{1}H NMR spectra over a range of temperatures. Spectra were recorded at 300, 323, 353 and 373 K. As the temperature was increased, the peaks narrowed and the coupling became visible. At 353 K all the coupling had resolved and the spectrum was consistent with the desired product.

Cationic cyclisation of **2.4** was attempted using pyridinium *p*-toluene sulfonate (PPTS), *p*-toluenesulfonic acid (PTSA) and polyphosphoric acid (PPA). Reactions were monitored by TLC and HPLC. The first reaction with PPTS was attempted under mild conditions in CH_2Cl_2 at RT. However, no reaction was observed. Reactions with PPTS and PTSA were performed in refluxing toluene over several days but again no change was observed by TLC or HPLC and only starting material was present. Reaction of **2.4** with PPA were the only conditions to show any change by TLC. The new component was isolated by preparative TLC. ^{1}H NMR showed no cyclisation had occurred, as the characteristic doublet at 7.01 ppm due to the proton at the 2 position of the indole ring was still present. However, the exact structure of the new product could not be determined.

After these unsuccessful trials, we considered moving from a carbamate to a diketopiperazine. This would restrict the rotation of the prenylated N-C bond, keeping the prenyl group in a more favourable position for the cyclisation. Wang and Ganesan prepared diketopiperazine **2.8** during the synthesis of demethoxyfumitremorgin C analogues[1]. Diketopiperazine **2.8** was prepared in 76% yield from **2.2** and Fmoc-proline acid chloride (Scheme 2).

Cationic cyclisation was attempted with PTSA, TFA and PPA. Only PPA showed any reaction. Two new products were obtained, each in 5% yield. MS for both compounds showed peaks corresponding to M+H of the desired product. ^{1}H NMR of the first compound appeared to be consistent with the desired product. ^{1}H NMR of the other product was inconclusive. Due to the limited amount of material further characterisation was not attempted

Scheme 2. Preparation and cyclisation of diketopiperazine [a].



[a] Conditions: (a) $SOCl_2$, CH_2Cl_2, reflux, 30 min, 80%; (b) **2**, Na_2CO_3 (aq), CH_2Cl_2, 2 h, 100%; (c) piperidine, CH_2Cl_2, 40 min, 76%; (d) $AlCl_3$, CH_2Cl_2, 2 h, 22%.

It has been reported that use of xylene as a co solvent can improve yields of reactions using PPA[2]. The cationic cyclisation of **2.8** was attempted under these conditions, but this did not improve the reaction and none of the desired product was formed.

Polyphosphate ester (PPE) can be used as an alternative to PPA. Attempts were made to make PPE by refluxing P_2O_5 in chloroform and ether for 4 days[3]. After this time a brown viscous oil was obtained indicating moisture had entered the reaction vessel during reflux. Trimethylsilyl polyphosphate (PPSE) can be used as an alternative to PPE[4]. This was prepared by refluxing P_2O_5 and hexamethyldisiloxane in CH_2Cl_2 for 30 min. Cyclisation was attempted by refluxing **2.8** in the PPSE solution. However, TLC showed no change in the reaction mixture, even after several days.

A further attempt was made to make PPE. This time the reaction was successful and a cyclisation was carried out. None of the desired product was observed, however, a new

product **X** had formed. This was similar to the product observed on reaction of **2.4** with PPA. The cyclisation was repeated with PPA. The same product was obtained. NMR of the products from the PPE and PPA reactions seemed to indicate the product was formed from quenching of the initial carbocation with water or phosphate as the proton from the prenyl double bond at 5.21 ppm in the ^{1}H NMR was no longer present and there were two additional protons arising from CH_2. However, it was not possible to determine conclusively the structure of product **X**.

A final attempt at cyclisation of **2.8** was carried out using $AlCl_3$ as the acid. This time a new product was obtained in 22% yield. NMR was consistent with the desired product **2.9**. Although the desired cyclisation had taken place to form an 8-membered ring, because the yield was low and the material would still need further oxidation to give the correct degree of unsaturation, this route was abandoned.

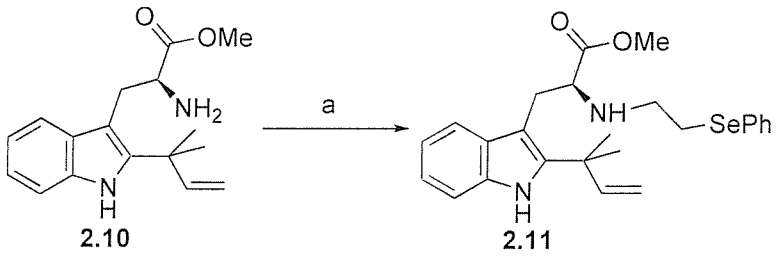
3.3 Investigation of ring-closing metathesis to make cyclic enamides

Preparation of substituted vinyl amines as precursors of metathesis reactions has been reported[5]. An imine is prepared which, on reaction with an acylating agent or sulfonyl chloride, rearranges to give a protected enamide[6]. These compounds then successfully underwent ring-closing metathesis.

This route was attempted with previously prepared prenylated tryptophan derivative **2.10**. Acetaldehyde was reacted with **2.10** to form the imine. TLC appeared to show a new product, however, on workup only starting material was obtained. This was most likely due to the instability of the imine. The reaction was repeated without an aqueous workup and the crude material reacted with di-*tert*-butyl dicarbonate (Boc_2O) to make the enamide. However after workup and purification by column chromatography only starting material was obtained. In the literature too, metathesis precursors prepared by this method were only available in low yield when acetaldehyde was used to form the imine[5].

To overcome these difficulties, we devised a new route to protected enamides. Although it requires more steps, each of these steps proceeds in high yield. Our premise was that a selenide would function as a latent olefin. The selenide was introduced by reductive amination of **2.10** with phenylselanylacetaldehyde (Scheme 3). Initially preparation of the aldehyde was attempted by formation of $PhSeCl_3$ and reaction with acetaldehyde[7]. Although the $PhSeCl_3$ was prepared in good yield the subsequent reaction with acetaldehyde was unsuccessful. There were problems with solubility of the $PhSeCl_3$ in the reaction solvent and none of the colour changes described in the literature were observed. Despite several attempts the reaction only gave the desired product on one occasion in 15% yield. This material was used in the reductive amination of **2.10** and gave the desired product **2.11** in 81% yield.

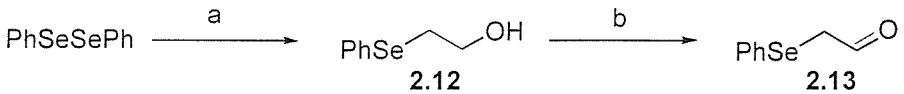
Scheme 3. Preparation of selenide [a].



[a] Conditions: (a) $PhSeCH_2CHO$, $NaBH(OAc)_3$, 1% AcOH in CH_2Cl_2, 3 h, 81%.

An alternative route to the aldehyde was sought (Scheme 4). Alcohol **2.12** was prepared from diphenyldiselenide and ethylene oxide in 96% yield[8]. This was oxidised to the aldehyde with Dess-Martin periodinane in 36% yield. Swern oxidation instead gave the aldehyde in 20% yield. Low yields were due in part to the difficulty in isolation of the volatile phenylselanylacetaldehyde.

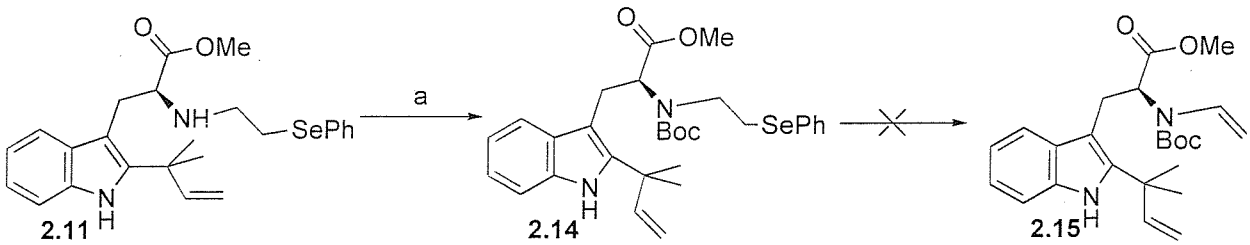
Scheme 4. Preparation of phenylselanylacetaldehyde [a].



[a] Conditions: (a) ethylene oxide, $NaBH_4$, EtOH, -20 °C, 30 min, 96%; (b) DMP, CH_2Cl_2, 15 min, 36%.

Protection of the amine followed by oxidation and elimination of the selenide would give an enamide that could be used in a ring-closing metathesis reaction to give an 8-membered ring. An attempt to protect **2.11** with Fmoc-Cl gave only starting material. Reaction of **2.11** with Boc_2O gave the desired product **2.14** in 61% yield (Scheme 5). Oxidation of **2.14** with m-CPBA gave only starting material.

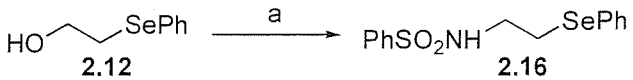
Scheme 5. Protection and attempted oxidation of selenide [a].



[a] Conditions: (a) Boc_2O, NEt_3, CH_2Cl_2, 24 h, 61%.

Due to a limited supply of the reverse prenyl tryptophan starting material, a more general model system for the metathesis reaction was sought. One possibility was to couple benzenesulfonamide with 2-phenylselanylethanol *via* a Mitsunobu reaction, alkylate with an appropriate alkene, then oxidise the selenide and eliminate to give the enamine. Although Mitsunobu reactions with sulfonamides have been reported[9], examples with compounds containing selenium could not be found.

Scheme 6. Coupling of benzenesulfonamide with 2-phenylselanyl ethanol [a].

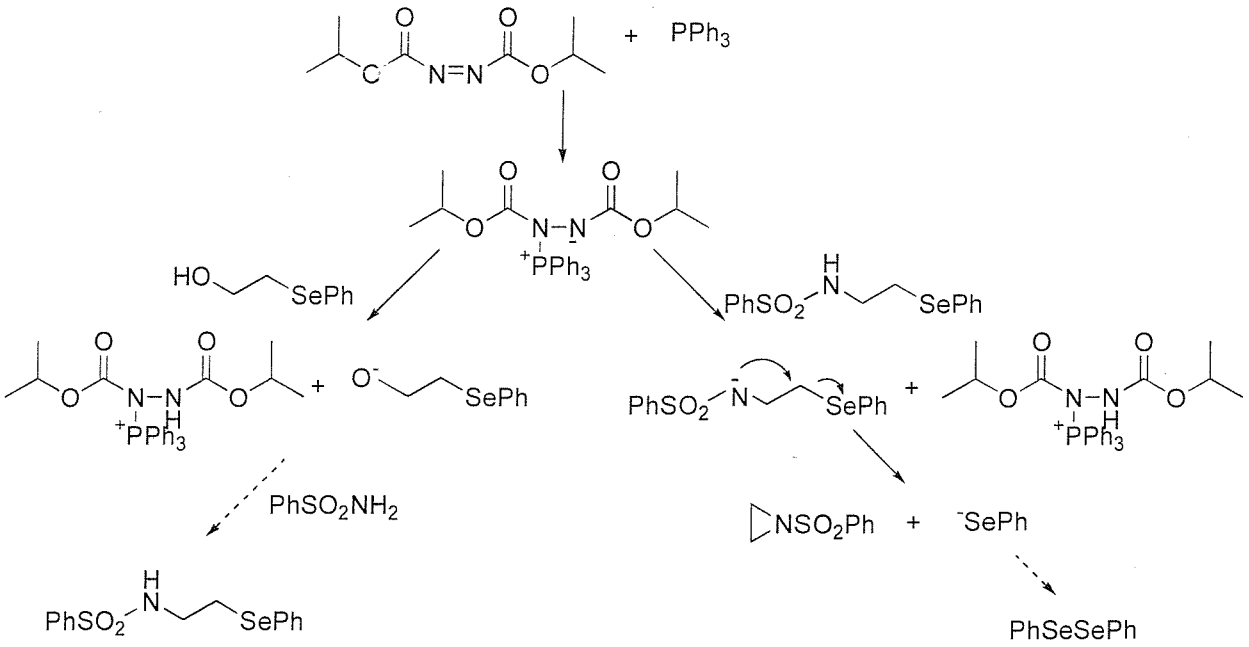


[a] Conditions: (a) Benzenesulfonamide, PPh_3, DIAD, THF, 24 h, 11%

Initial attempts to couple benzenesulfonamide with 2-phenylselanylethanol gave only starting material (Scheme 6). When the amount of diisopropyl azodicarboxylate was increased from 1 to 2 equivalents the reaction occurred in 11%, however, the major

product was diphenyldiselenide indicating side reactions had taken place. A possible explanation for this (Figure 2) is that the anion from the initial triphenylphosphine diisopropyl azodicarboxylate intermediate can either deprotonate the alcohol to form the alkoxide which can then react in the usual fashion to give the desired product (left-hand pathway) or it can deprotonate the sulfonamide product (right-hand pathway). This could then be followed by elimination of phenylselenide to form an aziridine. The selenide can then either be protonated or react with phenylselenol to give diphenyldiselenide.

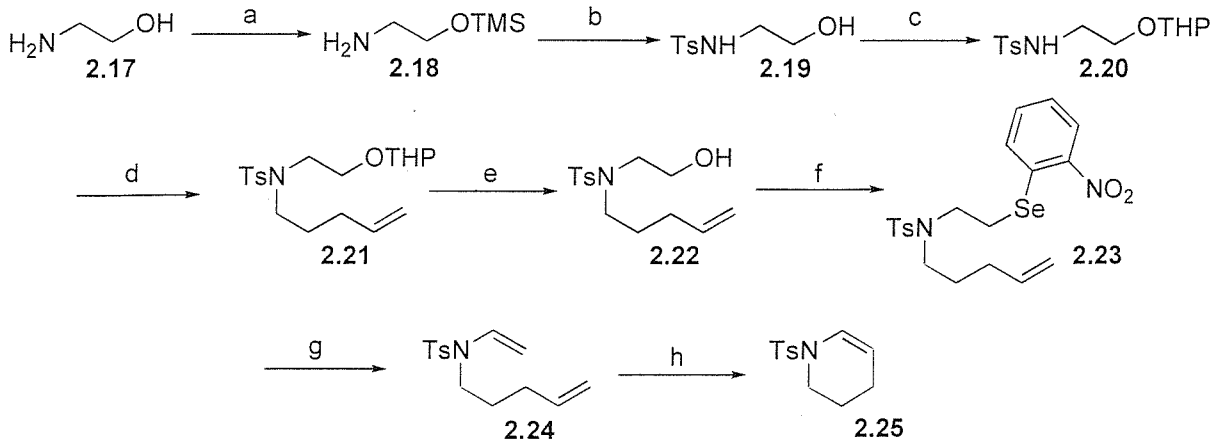
Figure 2. Proposed mechanism for formation of diphenyldiselenide.



An alternative route to a selenide precursor was sought (Scheme 7). Ethanolamine was reacted with hexamethyldisilazane to give the TMS protected alcohol **2.18** in 60% yield[10]. This was reacted with TsCl to give sulfonamide **2.19** in 85% yield[11]. MS and NMR showed loss of the TMS protecting group in this step. The alcohol was reprotected with dihydropyran to give **2.20** in quantitative yield. A Mitsunobu reaction with penten-1-ol gave alkene **2.21** in 88% yield. Removal of the THP protecting group gave **2.22** in 62% yield as well as a significant amount of an unidentifiable by-product. The alcohol was converted to selenide **2.23** with *o*-nitrophenylselenocyanate and tributylphosphine in quantitative yield[12]. Reaction of **2.23** with m-CPBA gave vinyl sulfonamide **2.24** in 71%

yield. The previously reported conditions for ring-closing metathesis of enamides with Grubbs' second-generation catalyst[5] were used to convert **2.24** to the 6-membered cyclic enamide **2.25** in quantitative yield.

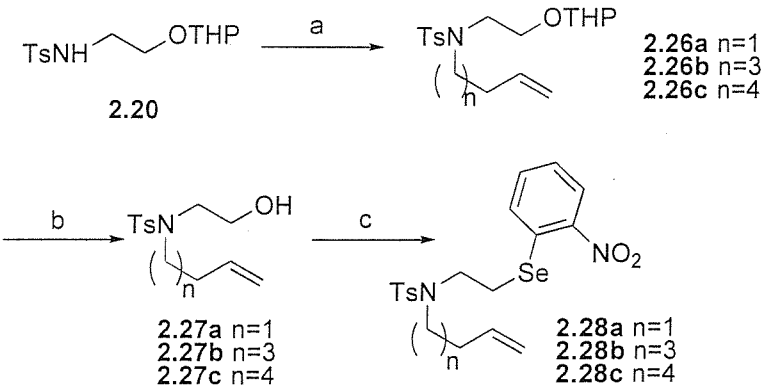
Scheme 7. Preparation of a 6-membered cyclic enamide by ring-closing metathesis [a].



[a] Conditions: (a) $(TMS)_2NH$, TMSCl, reflux, 2 h, 60%; (b) TsCl, pyridine, 24 h, 85%; (c) dihydropyran, PPTS, CH_2Cl_2, 3 h, >99%; (d) $H_2C{=}CH(CH_2)_3OH$, PPh_3, DIAD, THF, 5 h, 88%; (e) $pTsOH.H_2O$, MeOH, 5 h, 62%; (f) *o*-nitrophenylselenocyanate, PBu_3, THF, 5 h, >99%; (g) m-CPBA, CH_2Cl_2, 1 h, 71%; (h) Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, 24 h, >99%.

Having successfully formed a 6-membered cyclic enamide *via* ring-closing metathesis, the formation of other ring sizes was investigated. The selenide precursors to the acyclic enamides were prepared from THP-protected sulfonamide **2.20** (Scheme 8).

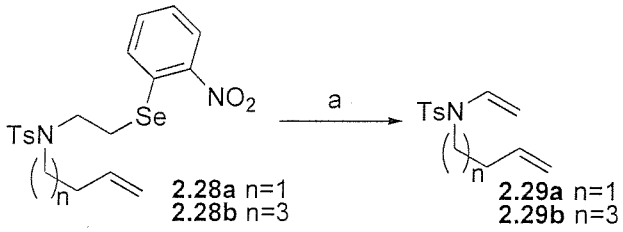
Scheme 8. Preparation of selenide precursors [a].



[a] Conditions: (a) $H_2C{=}CH(CH_2)_nOH$, PPh_3, DIAD, THF, 5 h, 42-88%; (b) $pTsOH.H_2O$, MeOH, 3 h, 60-89%; (c) *o*-nitrophenylselenocyanate, PBu_3, THF, 1 h, 81-99%.

Oxidative elimination of the selenides **2.28a-c** was carried out with m-CPBA to prepare the precursors for 5, 7 and 8-membered cyclic enamides. This gave the desired enamides **2.29a-b** in good yield for the 5 and 7-membered ring precursors (Scheme 9).

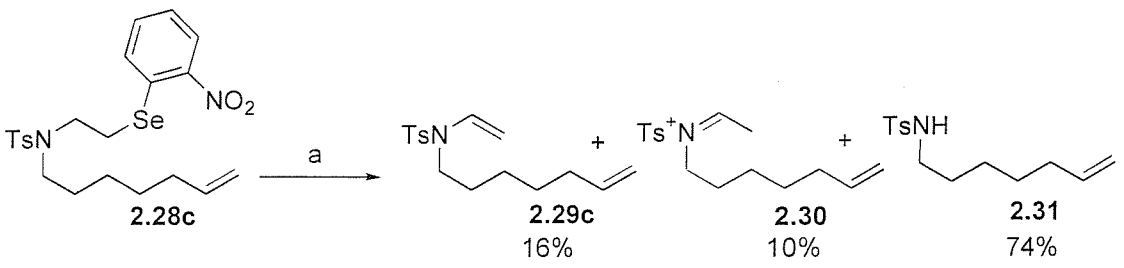
Scheme 9. Oxidative elimination of selenides [a].



[a] Conditions: (a) m-CPBA, CH_2Cl_2, 1 h, 67-70%.

Oxidation of selenide **2.28c**, the 8-membered ring precursor, gave only a small amount of the desired enamide **2.29c**. A very small amount of what seemed to be the iminium species **2.30** by NMR was also obtained. The major product was alkene **2.31** arising from hydrolysis of this iminium salt (Scheme 10).

Scheme 10. Oxidative elimination of 8-membered ring precursor [a].



[a] Conditions: (a) *m*-CPBA, CH_2Cl_2, 1 h.

The 5 and 7-membered cyclic enamide precursors were reacted with Grubbs' second-generation catalyst in refluxing CH_2Cl_2 under N_2. Under these conditions the reactions

were significantly slower than in 6-membered case and the reactions did not go to completion. The first time the reaction to form the cyclic enamide **2.32** was carried out, after 26 h a mixture of two products were isolated in 63% yield as well as 36% starting material. This was reacted again and after 48 h 69% yield was obtained (Scheme 11). The mixture seemed to contain the desired 7-membered cyclic enamide **2.32** as well as a 6-membered cyclic enamide **2.25** in approximately 3:1 ratio by ^{1}H NMR. A similar result was observed by Rutjes, although only the 6-membered ring was seen under his conditions[5]. One explanation for this reduction in ring size is isomerisation of the terminal alkene prior to metathesis[13].

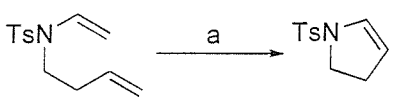
Scheme 11. Preparation of 7-membered cyclic enamide [a].

2.29b **2.32** **2.25**

[a] Conditions: (a) Grubbs' 2nd generation catalyst, CH_2Cl_2, reflux, 4 d, 69%.

The reaction to form the 5-membered cyclic enamide was even slower (Scheme 12). After 24 h a second aliquot of catalyst was added. After 48 h there was still a large amount of staring material remaining. After 72 h only a small amount of product was isolated in low purity by NMR. It is possible that there may have been a problem with the reaction conditions as this reaction to form the 5-membered cyclic enamide has been reported as occurring in good yield[5]. The metathesis reaction was repeated using Grubbs' 2nd generation catalyst in refluxing CH_2Cl_2. The reaction was also attempted using Grubbs' catalyst without a significant difference in yield[5]. Unfortunately the excellent yields achieved for the 6-membered cyclic enamide could not be repeated in this case.

Scheme 12. Preparation of 5-membered cyclic enamide [a].

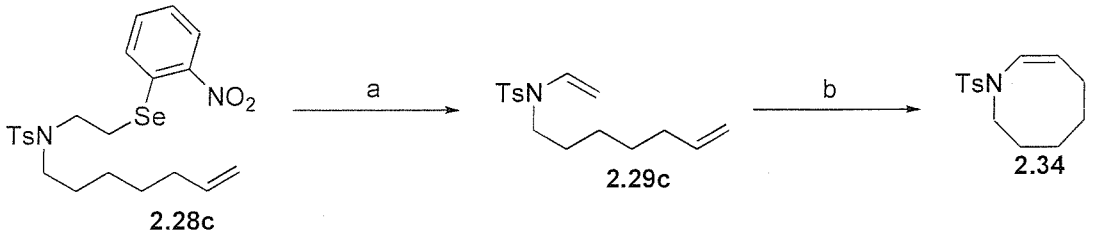


2.29a **2.33**

[a] Conditions: (a) Grubbs' catalyst, CH_2Cl_2, 24 h, 50%.

The acyclic enamide precursor to the 8-membered ring was prepared from selenide **2.28c** using $NaIO_4$ as the oxidising agent[14]. This gave the desired product **2.29c** in 82% yield, compared to 16% when m-CPBA was used. Metathesis was carried out using Grubbs' 2nd generation catalyst in refluxing dichloroethane (Scheme 13). A small amount of the desired cyclic enamide **2.34** was observed by NMR, however traces of other inseparable impurities were present and the overall yield was low. Despite the low yield for this model system it was hoped the additional conformational rigidity present in the okaramine A precursor would make formation of the 8-membered ring more favourable for the real system[15].

Scheme 13. Preparation of 8-membered cyclic enamide [a].



2.28c 2.29c 2.34

[a] Conditions: (a) $NaIO_4$, $NaHCO_3$, 6:1 MeOH:H_2O, 3 h, 82%; (b) Grubbs' 2nd generation catalyst, $C_2H_4Cl_2$, reflux, 24 h, 11%.

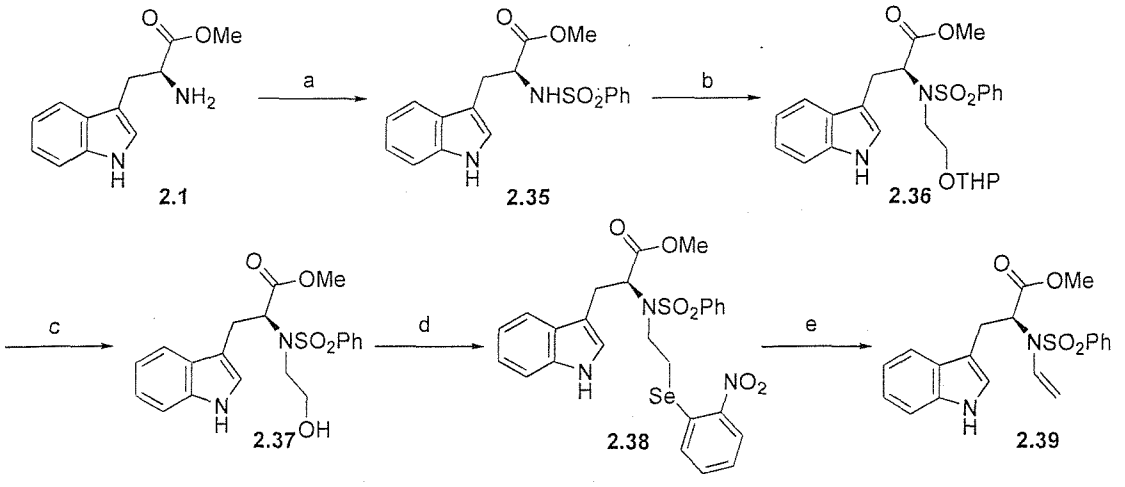
Since a carbamate protecting group would be easier to remove than a sulfonamide for the synthesis of okaramine A, the preparation of a vinyl carbamate was investigated. *N*-Boc ethanolamine was protected with TBDMSCl, then attempts were made to introduce the alkene side chain by coupling a series of alcohols *via* a Mitsunobu reaction. However, the carbamate was not reactive enough and no reaction was observed. When *N*-Boc ethanolamine was deprotected with NaH and reacted with 1-bromo-4-butene under various conditions, none of the desired product was observed. Starting material was obtained as well as a small amount of deprotected starting material and a small amount of unprotected alkylated material. Addition of alkyl side chains *via* reductive alkylation was also investigated but proved unsuccessful. As the desired precursors proved difficult to

synthesise, this route was abandoned and preparation of a metathesis precursor conducted on a sulfonamide.

3.4 Attempted preparation of an okaramine A precursor via ring-closing metathesis

Having established a general route for the construction of cyclic vinyl sulfonamides, it was possible to use this methodology on a substrate more closely resembling okaramine A. Construction of the desired vinyl sulfonamide was first attempted with readily available tryptophan methyl ester (Scheme 14). Sulfonylation and a Mitsunobu reaction with THP protected ethylene glycol gave **2.36**. The triphenylphosphine oxide by-product could not be separated from the desired product, so the crude material was carried through to the subsequent deprotection step. This method gave the alcohol **2.37** in 52% yield over the two steps. Alcohol **2.37** was then converted to an aryl selenide **2.38** as before. Various methods were investigated for the oxidative elimination of the selenide. Oxidation with m-CPBA occurred rapidly but in moderate yield with some decomposition of starting materials. Oxidation with $NaIO_4$ was much slower, requiring days rather than minutes, but gave cleaner reactions and higher yields. H_2O_2 oxidation was also attempted[16] but did not proceed cleanly and none of the desired product was isolated.

Scheme 14. Preparation of enamide [a].

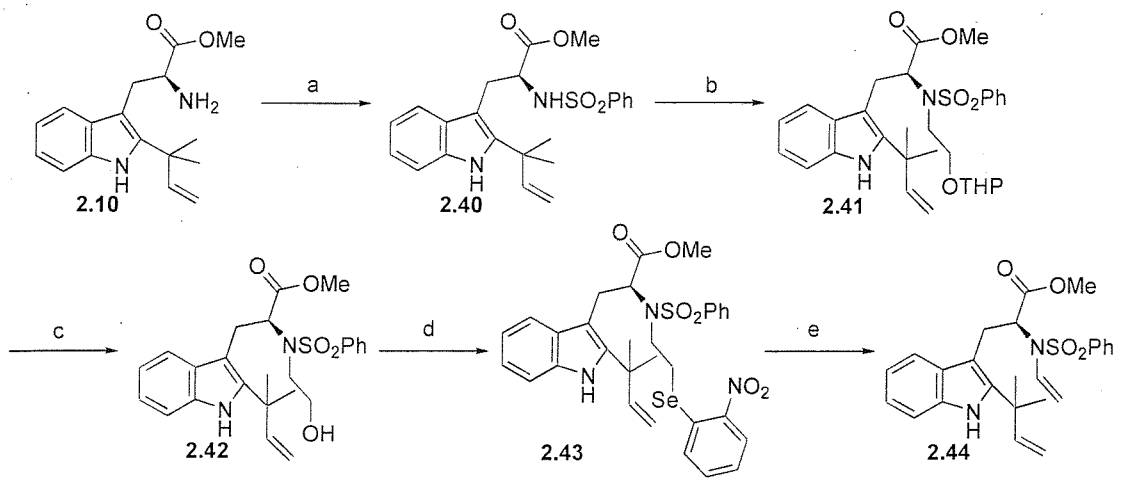


[a] Conditions: (a) $PhSO_2Cl$, pyridine, CH_2Cl_2, 4 h, 52%; (b) $THPOCH_2CH_2OH$, PPh_3, DIAD, THF, 24 h.; (c) pTsOH.H_2O, MeOH, 3.5 h, 52% (2 steps); (d) *o*-nitrophenylselenocyanate, PBu_3, THF, 2 h, 66%; (e) $NaIO_4$, $NaHCO_3$, MeOH, H_2O, 24 h, 78%.

Having shown the general procedure could be applied to tryptophan to make a vinyl sulfonamide, the synthesis of a ring-closing metathesis precursor was carried out (Scheme 15). Alkylation of reverse prenyl tryptophan derivative **2.10** with benzenesulfonyl chloride occurred in good yield. Introduction of the ethanolamine side chain proceeded well giving **2.42** in 78% overall yield for the alkylation and deprotection steps. The selenide was introduced successfully and then eliminated to give enamide **2.44** in 71% yield.

The metathesis reaction was attempted with Grubbs' first generation catalyst in CH_2Cl_2 at RT, then at reflux. It was also attempted with Grubbs' second-generation catalyst in refluxing dichloroethane. However, even after several days no reaction was observed and only starting material was recovered.

Scheme 15. Preparation of ring-closing metathesis precursor [a].



[a] Conditions: (a) $PhSO_2Cl$, pyridine, CH_2Cl_2, 4 h, 75%; (b) $THPOCH_2CH_2OH$, PPh_3, DIAD, THF 24 h; (c) pTsOH.H_2O, MeOH, 5 h, 78% (2 steps); (d) *o*-nitrophenylselenocyanate, PBu_3, THF, 2.5 h, 82%; (e) $NaIO_4$, $NaHCO_3$, MeOH, H_2O, CH_2Cl_2 5 d, 71%.

3.5 Summary

Two strategies have been explored for the formation of an 8-membered ring like that present in okaramine A. Acid catalysed cyclisation of an alkene onto an indole to form an 8-membered ring has been investigated on first a carbamate then a diketopiperazine. A range of conditions was tried and $AlCl_3$ successfully found to give an 8-membered ring, albeit in a low yield of 22%.

Ring-closing metathesis has been explored as a possible route to an 8-membered ring containing an enamide. A general route to vinyl amides has been developed using ethanolamine as the alkene precursor. Side chains were introduced onto nitrogen *via* a Mitsunobu reaction then the alcohol was converted to a selenide. Oxidative elimination then gave the alkene in good yield. These vinyl amides have undergone ring-closing metathesis with varying degrees of success, dependent on the size of the ring being formed.

This methodology has been successfully used to introduce the vinyl amide functionality to tryptophan derivatives. It was hoped that the additional conformational rigidity arising from the indole ring system and steric bulk would make formation of an 8-membered ring more favourable. However, when the vinyl amide precursor was subjected to ring-closing metathesis conditions no reaction took place. Unfortunately, for this substrate, this additional conformational rigidity prevents the molecule from reaching the desired conformation for reaction rather than assisting it.

3.6 Experimental

3.6.1 General methods

See section 2.11.1

3.6.2 3-(1H-Indol-3-yl)-2-(3-methyl-but-2-enylamino)-propionic acid methyl ester **2.2**

To a suspension of L-tryptophan methyl ester (500 mg, 2.29 mmol) and $NaBH(OAc)_3$ (971 mg, 4.58 mmol) in 1% AcOH in CH_2Cl_2 (50 mL) was added 3-methyl-2-butenal (0.24 mL, 2.52 mmol) and the mixture stirred at RT for 2 h. Saturated Na_2CO_3 solution (25 mL) was added and the mixture stirred until effervescence ceased. The reaction mixture was extracted with CH_2Cl_2 (3 x 25 mL), washed with water (25 mL), the organic phases combined, dried over Na_2SO_4, filtered and the solvent evaporated. The resultant pale yellow oil was purified by column chromatography (15 g silica, eluent 50% EtOAc in hexane). The fractions containing product also contained an impurity by TLC. These fractions were combined and concentrated under vacuum. The resultant oil was purified by column chromatography (30 g silica, eluent 1% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **2.2** as an off white crystalline solid (304 mg, 46%): ^{1}H NMR δ 8.35 (1H, bs, N**H**), 7.61 (1H, d, J = 6.9 Hz, Ar**H**), 7.34 (1H, d, J = 7.7 Hz, Ar**H**), 7.21 (1H, dd, J = 6.9, 6.4 Hz, Ar**H**), 7.11 (1H, dd, J = 7.7, 6.4 Hz, Ar**H**), 7.05 (1H, s), 5.17 (1H, t, J = 7.0 Hz, C**H**), 3.68 (1H, t, J = 6.6 Hz, C**H**), 3.64 (3H, s, C**H**$_3$), 3.23 (1H, dd, J = 13.0, 7.0 Hz, C**H**$_2$), 3.17 (2H, d, J = 6.6 Hz, C**H**$_2$), 3.12 (1H, dd, J = 13.0, 7.0 Hz, C**H**$_2$), 1.68 (3H, s, C**H**$_3$), 1.57 (3H, s, C**H**$_3$). The spectroscopic properties were consistent with that reported in the literature (ref 1).

3.6.3 2-(Ethoxycarbonyl-(3-methyl-but-2-enyl)-amino)-3-(1H-indol-3-yl)-propionic acid methyl ester **2.4**

To a solution of **2.2** (500 mg, 1.75 mmol) in CH_2Cl_2 (20 mL) and Et_3N (0.54 mL, 3.8 mmol) at 0 °C was added ethyl chloroformate (0.23 mL, 2.4 mmol) and the reaction stirred at RT for 3 d. A further aliquot of ethyl chloroformate (0.23 mL, 2.4 mmol) was added and the reaction stirred for 2 h. The reaction mixture was washed with water (2 x 20 mL), dried

over Na_2SO_4, filtered and the solvent evaporated. The resultant reddish brown oil was purified by column chromatography (70 g silica, eluent 10% EtOAc in toluene). The relevant fractions were combined and the solvent removed under vacuum to give **2.4** as a pale yellow oil (589 mg, 94%): IR ν_{max} 3332w, 1740s, 1684s cm^{-1}; ^1H NMR (273 K) δ 8.23 (1H, bs), 7.59 (1H, bt), 7.37 (1H, d), 7.19 (1H, t), 7.12 (1H, t), 7.04 (1H, bd), 4.88 (1H, bm), 4.49 (1H, bm), 4.17 (2H, bm), 3.85 (1H, bm), 3.74 (3H, s), 3.54 (2H, bm), 3.32 (1H, bm), 1.52 (3H, s), 1.41 (3H, bd), 1.24 (3H, bm); ^1H NMR (400 MHz, DMSO, 373 K) δ 10.51 (1H, bs, N**H**), 7.51 (1H, d, J = 8.0 Hz, Ar**H**), 7.36 (1H, d, J = 8.0 Hz, Ar**H**), 7.08 (1H, dd, J = 8.0, 6.0 Hz, Ar**H**), 7.06 (1H, d, J = 2.0 Hz, Ar**H**), 7.00 (1H, dd, J = 8.0, 6.0 Hz, Ar**H**), 4.88 (1H, d, J = 6.8 Hz, C**H**), 4.51 (1H, dd, J = 9.0, 5.8 Hz, C**H**), 4.05 (2H, q, J = 7.0 Hz, C$\mathbf{H}_2$), 3.76 (1H, dd, J = 15.6, 6.5 Hz, C$\mathbf{H}_2$), 3.68 (3H, s, C$\mathbf{H}_3$), 3.61 (1H, dd, J = 15.6, 6.9 Hz, C$\mathbf{H}_2$), 3.39 (1H, ddd, J = 14.8, 5.8, 0.8 Hz, C$\mathbf{H}_2$), 3.23 (1H, dd, J = 14.8, 9.0 Hz, C$\mathbf{H}_2$), 1.52 (3H, s, C$\mathbf{H}_3$), 1.47 (3H, s, C$\mathbf{H}_3$), 1.16 (3H, t, J = 7.0 Hz, C$\mathbf{H}_3$); ^{13}C NMR δ 172.2 (**C**), 136.3 (**C**), 123.3 (**C**), 123.0 (**C**), 122.1 (**C**H), 120.7 (**C**), 120.3 (**C**H), 119.5 (**C**H), 118.7 (**C**H), 111.3 (**C**H), 111.2 (**C**), 61.7 (**C**H), 52.3 (**C**H_3), 45.6 (**C**H_2), 26.1 (**C**H_2), 25.8 (**C**H_3), 25.2 (**C**H_2), 17.6 (**C**H_3), 14.8 (**C**H_3); MS *m/z* 359 $[M+H]^+$.

3.6.4 3-(1H-Indol-3-ylmethyl)-2-(3-methyl-but-2-enyl)-hexahydro-pyrrolo[1,2-a]pyrazine-1,4-dione **2.8**

To a suspension of Fmoc-L-proline (5 g, 14.8 mmol) in CH_2Cl_2 (20 mL) was added thionyl chloride (10 mL). The mixture was refluxed for 30 min then the solvent evaporated. To the residue was added CH_2Cl_2 (20 mL) and the solvent evaporated. This was repeated a further 2 times to give a sticky white solid which was dissolved in diethyl ether. Hexane was added and the resultant white solid collected by filtration and washed with hexane to give crude **2.6** (4.2 g, 80%), which was used without further purification.

To a solution of **2.2** (950 mg, 3.3 mmol) in CH_2Cl_2 (20 mL) at RT was added **2.6** (1.3 g, 4.3 mmol) and the reaction stirred for 2 min. Na_2CO_3 solution (1M, 20 mL) was added then the reaction stirred for 2 h. The phases were separated, the organic phase dried over

Na_2SO_4, filtered and the solvent evaporated to give **2.7** as a pale yellow foam (2.4 g, >100%) which was used without further purification.

A solution of **2.7** (1.1 g, 1.8 mmol) in CH_2Cl_2 (10 mL) and piperidine (2.5 mL) was stirred for 40 min at RT. The solvent was evaporated to give an off-white solid, which was purified by column chromatography (50 g silica 220-440 mesh, eluent 1:2 EtOAc: $CHCl_3$). The relevant fractions were combined and the solvent evaporated to give an off-white solid which was recrystallised from hot ethanol/water to give **2.8** as a white solid (492 mg, 76%): ^{1}H NMR δ 8.76 (1H, s, N**H**), 7.64 (1H, d, *J* = 7.7 Hz, Ar**H**), 7.31 (1H, d, *J* = 8.1 Hz, Ar**H**), 7.14 (1H, dd, *J* = 7.7, 6.5 Hz, Ar**H**), 7.08 (1H, dd, *J* = 8.1, 6.5 Hz Ar**H**), 6.91 (1H, d, *J* = 2.2 Hz, NHC**H**), 5.21 (1H, bt, *J* = 5.9 Hz, C**H**), 4.88 (1H, dd, *J* = 14.7, 5.9 Hz C**H**$_2$), 4.37 (1H, bs, C**H**), 3.61-3.72 (3H, m, C**H**$_2$), 3.49 (1H, m, C**H**$_2$), 3.22 (1H, dd, *J* = 14.7, 4.4 Hz, C**H**$_2$), 2.91 (1H, td, *J* = 10.7, 5.2 Hz, C**H**$_2$), 1.78 (6H, s, 2 x C**H**$_3$), 1.68 (1H, m, C**H**$_2$), 1.30 (1H, m, C**H**$_2$), 0.69 (1H, m, C**H**$_2$), –0.26 (1H, quintet, *J* = 11.8 Hz C**H**$_2$). The spectroscopic properties were consistent with that reported in the literature (ref 1).

3.6.5 (10aS,15aS)-6,6-Dimethyl-6,7,8,10a,11,12,13,15,15a,16-decahydro-5H,10H-pyrrolo[1″2″:4′,5′]pyrazino[1′,2′:1,2]azocino[5,4-6]indole-10,15-dione **2.9**

To a solution of **2.8** (64 mg, 0.18 mmol) in CH_2Cl_2 (3 mL) was added $AlCl_3$ (121 mg, 0.91 mmol) and the reaction stirred for 2 h. Ice (5 g) was added, the phases separated and the aqueous phase washed with CH_2Cl_2 (2 x 3 mL). The organic phases were combined, dried over Na_2SO_4, filtered and the solvent evaporated. The resultant pale yellow glass was purified by preparative TLC (eluent EtOAc) to give **2.9** as a colourless glass (14 mg, 22 %): IR ν_{max} 2926m, 2354w, 1737s, 1645s cm^{-1}; ^{1}H NMR (400 MHz) δ 8.07 (1H, bs, N**H**), 7.52 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.25 (1H, d, *J* = 7.8 Hz, Ar**H**), 7.08 (1H, dd, *J* = 7.8, 7.0 Hz, Ar**H**), 7.01 (1H, dd, *J* = 7.8, 7.0 Hz, Ar**H**), 4.41 (1H, ddd, *J* = 14.6, 8.0, 3.8 Hz, C**H**), 4.28 (1H, d, *J* = 7.3 Hz, C**H**$_2$), 3.96 (1H, d, *J* = 15.6 Hz, C**H**$_2$), 3.67 (1H, dd, *J* = 15.3, 7.3 Hz, C**H**), 3.58 (2H, m, C**H**$_2$), 3.09 (2H, m, C**H**$_2$), 2.29 (1H, ddd, *J* = 15.3, 8.3, 4.0 Hz, C**H**$_2$), 2.09 (1H, ddd, *J* = 15.1, 8.0, 3.3 Hz, C**H**$_2$), 1.75 (1H, m, C**H**$_2$), 1.58 (3H, s, C**H**$_3$), 1.43 (1H, m, C**H**$_2$), 1.46 (3H, s, C**H**$_3$), 1.10 (1H, m, C**H**$_2$), -0.03 (1H, quintet, *J* = 11.5 Hz,

CH_2); ^{13}C (100 MHz) δ 166.4 (**C**), 165.0 (**C**), 143.1 (**C**), 134.3 (**C**), 129.1 (**C**), 121.7 (**C**H), 119.8 (**C**H), 119.1 (**C**H), 110.6 (**C**H), 104.8 (**C**), 63.3 (**C**H), 59.0 (**C**), 45.3 (CH_2), 43.7 (CH_2), 41.5 (CH_2), 35.2 (**C**), 30.1 (2 x CH_3), 29.4 (CH_2), 29.3 (CH_2), 29.1 (CH_2); MS *m/z* 352 $[M+H]^+$, 725 $[2M+Na]^+$.

3.6.6 Unknown product **X** *(see p61).*

A solution of **2.8** (100 mg, 0.28 mmol) in PPE (5 g) was stirred at for 24 h at RT. The reaction mixture was dissolved in water (5 mL), saturated Na_2CO_3 solution (5 mL) added, then the mixture extracted with CH_2Cl_2 (4 x 5 mL), the organic phases combined, dried over Na_2SO_4, filtered and the solvent evaporated. The residue was purified by column chromatography (5 g silica, eluent EtOAc). The relevant fractions were combined and the solvent evaporated to give **X** as a colourless glass (54 mg): IR ν_{max} 2926m, 2359w, 1730m, 1649s cm^{-1}; ^1H NMR (400 MHz) δ 9.02 (1H, bs, N**H**), 7.57 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.33 (1H, d, *J* = 8.0 Hz, Ar**H**), 7.16 (1H, dd, *J* = 8.0, 7.0 Hz, Ar**H**), 7.09 (1H, dd, *J* = 8.0, 7.0 Hz, Ar**H**), 6.91 (1H, d, *J* = 2.3 Hz, Ar**H**), 4.28 (1H, dd, *J* = 5.0, 3.3 Hz, C**H**CH_2), 4.11 (1H, m, C**H**$_2$), 3.53 (1H, dd, *J* = 14.8, 3.3 Hz, CHC**H**$_2$), 3.44 (1H, m, C**H**$_2$), 3.28 (1H, dd, *J* = 14.8, 5.0 Hz, C**H**$_2$), 3.07 (1H, m, C**H**$_2$), 3.00 (1H, m, C**H**$_2$), 2.20 (1H, dd, *J* = 10.9, 6.1 Hz, C**H**CH_2), 1.90 (1H, m, C**H**$_2$), 1.67-1.80 (3H, m, C**H**$_2$), 1.56 (1H, m, C**H**$_2$), 1.23 (6H, s, 2 x CH_3), 1.18 (1H, m, C**H**$_2$); ^{13}C (100 MHz) δ 168.5 (**C**), 165.9 (**C**), 136.6 (**C**), 127.7 (**C**), 124.8 (**C**H), 122.7 (**C**H), 120.1 (**C**H), 119.1 (**C**H), 111.8 (**C**H), 109.2 (**C**), 69.9 (**C**), 63.5 (**C**H), 58.3 (**C**H), 45.3 (CH_2), 41.1 (CH_2), 41.0 (CH_2), 30.1 (2 x CH_3), 29.6 (CH_2), 27.8 (CH_2), 22.0 (CH_2).

3.6.7 3-[2-(1,1-Dimethyl-allyl)-1H-indol-3-yl]-2-(2-phenylselanyl-ethylamino)-propionic acid methyl ester **2.11**

To a solution of **2.10**[17] (78 mg, 0.27 mmol) in 1% AcOH in CH_2Cl_2 (5 mL) was added $NaBH(OAc)_3$ (127 mg, 0.6 mmol) followed by phenylselanylacetaldehyde (60 mg, 0.33 mmol) and the mixture stirred for 3 h. The reaction mixture was quenched with saturated Na_2CO_3 solution (5 mL), extracted with CH_2Cl_2 (2 x 5 mL), the organic phases combined,

dried over Na_2SO_4, filtered and the solvent evaporated. The resultant colourless oil was purified by column chromatography (10 g silica; eluent 20% Et_2O in hexane). The relevant fractions were combined and the solvent evaporated to give **2.11** as a colourless oil (103 mg, 81%): IR ν_{max} 1729s, 1463m, 1432m cm^{-1}; ^1H NMR (400 MHz) δ 7.94 (1H, bs, N**H**), 7.56 (1H, d, J = 7.7 Hz, Ar**H**), 7.25-7.32 (3H, m, Ar**H**), 7.06-7.21 (5H, m, Ar**H**), 6.17 (1H, dd, J = 17.3, 10.7 Hz, CH_2=C**H**), 5.20 (1H, d, J = 17.3 Hz, C**H**$_2$=CH), 5.18 (1H, d, J = 10.7 Hz, C**H**$_2$=CH), 3.64 (1H, t, J = 7.4 Hz, CH_2C**H**), 3.57 (3H, s, C**H**$_3$), 3.24 (2H, d, J = 7.4 Hz, C**H**$_2$CH), 2.79-2.95 (3H, m, C**H**$_2$), 2.55 (1H, dt, J = 11.8, 6.6 Hz, C**H**$_2$), 1.88 (1H, bs, N**H**), 1.59 (6H, s, C**H**$_3$); ^{13}C NMR (100 MHz) δ 175.6 (**C**), 146.2 (**C**H), 140.6 (**C**), 134.3 (**C**), 133.6 (**C**H), 129.7 (**C**), 129.1 (**C**H), 127.2 (**C**H), 121.7 (**C**H), 119.5 (**C**H), 118.8 (**C**H), 112.3 (**C**H_2), 110.5 (**C**H), 106.7 (**C**), 62.7 (**C**H), 52.0 (**C**H_3), 47.5 (**C**H_2), 39.4 (**C**), 29.5 (**C**H_2), 28.6 (**C**H_2), 28.1 (**C**H_3); MS *m/z* 471 $[M+H]^+$.

*3.6.8 2-[*tert*-Butoxycarbonyl-(2-phenylselenyl-ethyl)-amino]-3-[2-(1,1-dimethyl-allyl)-1H-indol-3-yl]-propionic acid methyl ester* **2.14**

To a solution of **2.11** (160 mg, 0.34 mmol) and NEt_3 (95 μL, 0.68 mmol) in CH_2Cl_2 (5 mL) was added Boc_2O (74 mg, 0.34 mmol) and the reaction mixture stirred for 24 h. The solvent was evaporated and the residue purified by column chromatography (10 g silica; eluent 20% Et_2O in hexane). The relevant fractions were combined and the solvent evaporated to give **2.14** as a colourless oil (118 mg, 61%): IR ν_{max} 1730m, 1682m cm^{-1}; ^1H NMR δ 7.90 (1H, s, indole N**H**), 7.43 (1H, t, J = 8.1 Hz, ArC**H**), 7.02-7.32 (8H, m, ArC**H**), 6.07 (1H, dd, J = 17.3, 10.3 Hz, C**H**=CH_2), 5.17 (1H, d, J = 17.3 Hz, CH=C**H**$_2$), 5.14 (1H, d, J = 10.3 Hz, CH=C**H**$_2$), 4.15 + 4.04 (1H, dd, J = 10.3, 3.7 Hz, C**H**CH_2), 3.73 + 3.74 (3H, s, CO_2C**H**$_3$), 3.40-3.69 (2H, m, CHC**H**$_2$), 3.30 + 3.18 (1H, dd, J = 13.0, 5.5 Hz, CH_2C**H**$_2$), 2.99 + 2.94 (1H, dd, J = 11.8, 5.1 Hz, CH_2C**H**$_2$), 2.73 + 2.38 (1H, dt, J = 12.1, 5.1 Hz, CH_2C**H**$_2$), 2.62 + 2.51 (1H, dt, J = 11.8, 5.5 Hz, CH_2C**H**$_2$), 1.52 + 1.49 (6H, s, 2 x C**H**$_3$), 1.51 + 1.42 (9H, s, 3 x C**H**$_3$); ^{13}C NMR δ 171.9 (**C**), 150.0 (**C**H), 134.2 (**C**), 132.3 (**C**H), 131.9 (**C**H), 129.2 (**C**H), 126.9 (**C**H), 126.6 (**C**), 121.6 (**C**H), 119.7 (**C**H), 119.5 (**C**), 118.6 (**C**H), 118.3 (**C**), 112.2 (**C**H_2), 110.5 (**C**H), 107.6 (**C**), 81.1 (**C**), 80.6 (**C**), 63.6 (**C**H), 52.3 (**C**H_3), 51.2 (**C**H_2), 38.8 (**C**), 27.8 (**C**H_3), 27.7 (**C**H_3), 24.6 (**C**H_2), 24.2 (**C**H_2); MS *m/z* 571 $[M+H]^+$, 1163 $[2M+H]^+$.

3.6.9 2-Trimethylsilanyloxy-ethylamine **2.18**

Hexamethyldisilazane (9 mL, 45 mmol) was added dropwise to ethanolamine (4.9 mL, 82 mmol) followed by trimethylsilyl chloride (1 drop) and the reaction mixture heated at reflux for 2 h. The reaction mixture was purified by distillation to give **2.18** as a colourless oil (6.5 g, 60%): ^{1}H NMR δ 3.59 (2H, dd, J = 5.2, 5.5 Hz, C**H**$_2$), 2.78 (2H, dd, J = 5.2, 5.5 Hz, C**H**$_2$), 1.41 (2H, s, N**H**), 0.12 (9H, s, 3 x SiC**H**$_3$). The spectroscopic properties were consistent with that reported in the literature (ref 10).

3.6.10 N-*(2-Hydroxy-ethyl)-4-methyl-benzenesulfonamide* **2.19**

To a stirred solution of **2.18** (6.5 g, 49 mmol) in pyridine (10 mL) at 0 °C was added portionwise *p*-toluenesulfonyl chloride (10 g, 54 mmol). The reaction mixture was stirred for 24 h, then H_2O (2 mL) was added and the reaction mixture poured onto ice. The reaction mixture was acidified with AcOH, then the mixture extracted with EtOAc (2 x 100 mL). The organic phase was washed with saturated aq $NaHCO_3$ (100 mL), dried over $MgSO_4$, and the solvent evaporated. The residue was purified by column chromatography (70 g silica; eluent 2:1 EtOAc:hexane). The relevant fractions were combined and the solvent evaporated to give **2.19** as a pale yellow solid (8.9 g, 85%) mp 53-54 °C: IR ν_{max} 3513bs, 3267s cm^{-1}; ^{1}H NMR δ 7.76 (2H, d, J = 8.1 Hz, ArC**H**), 7.12 (2H, d, J = 8.1 Hz, ArC**H**), 5.22 (1H, bt, J = 5.9 Hz, N**H**), 3.70 (2H, dd, J = 5.5, 4.4 Hz, C**H**$_2$), 3.09 (2H, q, J = 5.5 Hz, C**H**$_2$), 2.45 (3H, s, ArC**H**$_3$); ^{13}C NMR δ 143.8 (**C**), 130.0 (**C**H), 127.3 (**C**H), 61.4 (**C**H$_2$), 45.3 (**C**H$_2$), 21.7 (**C**H$_3$); MS (ES-) *m/z* 328 [M+TFA]$^-$.

3.6.11 4-Methyl-N-*[2-(tetrahydro-pyran-2-yloxy)-ethyl]-benzenesulfonamide* **2.20**

To a solution of **2.19** (8.8 g, 41 mmol) and dihydropyran (4.8 mL, 61.5 mmol) in CH_2Cl_2 (100 mL) was added pyridinium *p*-toluene sulfonate (1.0 g, 4 mmol). The reaction mixture was stirred for 3 h, then washed with saturated aq $NaHCO_3$ (2 x 50 mL). The organic phase was dried over Na_2SO_4, filtered and the solvent evaporated to give **2.20** as a pale yellow oil (14 g, >99%): IR ν_{max} 3276bm, 2936s, 2874w, 1323m, 1161s cm^{-1}; ^{1}H NMR δ 7.76 (2H, d, J = 8.1 Hz, ArC**H**), 7.32 (2H, d, J = 8.1 Hz, ArC**H**), 5.19 (1H, t, J = 5.9 Hz, N**H**), 4.45

(1H, m, CH_2CH), 3.80 (1H, m, CH_2), 3.69 (1H, dt, J = 10.3, 5.2 Hz, CH_2), 3.54 (1H, m, CH_2), 3.47 (1H, m, CH_2), 3.17 (2H, dd, J = 10.3, 5.2 Hz, CH_2), 2.43 (3H, s, $ArCH_3$), 1.72 (2H, m, CH_2), 1.51 (4H, m, 2 x CH_2); ^{13}C NMR δ 143.5 (C), 137.1 (C), 129.8 (CH), 127.3 (CH), 99.8 (CH), 66.7 (CH_2), 63.2 (CH_2), 43.4 (CH_2), 30.7 (CH_2), 25.3 (CH_2), 21.7 (CH_3), 19.9 (CH_2); MS *m/z* 300 $[M+H]^+$, 317 $[M+NH_4]^+$.

*3.6.12 4-Methyl-*N*-pent-4-enyl-*N*-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-benzenesulfonamide* **2.21**

To a solution of **2.20** (500 mg, 1.7 mmol), penten-1-ol (172 μL, 1.7 mmol) and PPh_3 (535 mg, 2.0 mmol) in THF (10 mL) was added dropwise diisopropylazodicarboxylate (401 μL, 2.0 mmol). The reaction mixture was stirred for 5 h, then filtered through a pad of silica and washed with EtOAc. The solvent was evaporated and the residue purified by column chromatography (75 g silica; eluent 20% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **2.21** as a colourless oil (552 mg, 88%): IR ν_{max} 3328bm, 3078s, 1749s, 1711s cm^{-1}; ^1H NMR δ 7.71 (2H, d, J = 8.1 Hz, ArCH), 7.29 (2H, d, J = 8.1 Hz, ArCH), 5.79 (1H, m, $CH_2CH=CH_2$), 4.93-5.07 (2H, m, $CH=CH_2$), 4.45 (1H, m, CH_2CH), 3.74-3.88 (2H, m, CH_2), 3.41-3.60 (2H, m, CH_2), 3.25-3.40 (2H, m, CH_2), 3.19 (2H, dt, J = 8.1, 3.4 Hz, CH_2), 2.42 (3H, s, $ArCH_3$), 1.98-2.14 (2H, m, CH_2), 1.62-1.75 (2H, m, CH_2), 1.40-1.60 (2H, m, CH_2), 1.18-1.29 (4H, m, 2 x CH_2); ^{13}C NMR δ 143.2 (C), 137.7 (C), 129.8 (CH), 127.3 (CH), 115.3 (CH_2), 99.2 (CH), 66.7 (CH_2), 62.5 (CH_2), 49.2 (CH_2), 48.1 (CH_2), 30.9 (CH_2), 30.7 (CH_2), 27.9 (CH_2), 25.5 (CH_2), 22.2 (CH), 21.6 (CH_3), 19.6 (CH_2); MS *m/z* 368 $[M+H]^+$, 390 $[M+Na]^+$.

3.6.13 N*-(2-Hydroxyethyl)-4-methyl-*N*-pent-4-enyl-benzenesulfonamide* **2.22**

To a solution of **2.21** (800 mg, 2.2 mmol) in MeOH (15 mL) was added *p*-toluenesulfonic acid (46 mg, 0.22 mmol). The reaction mixture was stirred for 5 h, then the solvent evaporated. The residue was diluted in Et_2O (10 mL) and H_2O (10 mL), then the organic phase washed with saturated aq $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and the solvent evaporated. The residue was purified by column chromatography

(40 g silica; eluent 1:1 – 2:1 Et_2O: hexane). The relevant fractions were combined and the solvent evaporated to give **2.22** as a colourless oil (382 mg, 62%): IR ν_{max} 3532bs, 3068m, 1749s, 1635m, 1692m cm^{-1}; ^1H NMR δ 7.71 (2H, d, J = 8.1 Hz, ArC**H**), 7.32 (2H, d, J = 8.1 Hz, ArC**H**), 5.77 (1H, ddt, J = 16.9, 10.3, 6.6 Hz, CH_2CH=CH_2), 5.05 (2H, m, CH=CH_2), 3.77 (2H, q, J = 5.5 Hz, CH_2), 3.24 (2H, t, J = 5.5 Hz, CH_2), 2.92 (2H, m, CH_2), 2.44 (3H, s, ArCH_3), 2.39 (1H, t, J = 5.7 Hz, CH_2O**H**), 2.07 (2H, q, J = 7.4 Hz, CH_2), 1.67 (2H, m, CH_2); ^{13}C NMR δ 143.7 (**C**), 137.7 (**C**H), 136.1 (**C**), 129.9 (**C**H), 127.4 (**C**H), 115.6 (**C**H_2), 61.6 (**C**H_2), 51.2 (**C**H_2), 48.8 (**C**H_2), 30.8 (**C**H_2), 28.1 (**C**H_2), 21.7 (**C**H_3); MS (ES-) *m/z* 396 $[M+TFA]^-$.

*3.6.14 4-Methyl-*N*-[2-(2-nitro-penylselanyl)-ethyl]-*N*-pent-4-enyl-benzenesulfonamide*

2.23

To a solution of **2.22** (360 mg, 1.27 mmol) and *o*-nitrophenylselenocyanate (577 mg, 2.5 mmol) in THF (5 mL) was added dropwise tributylphosphine (950 μL, 3.8 mmol). The reaction mixture was stirred for 5 h, then the solvent evaporated. The resultant brown residue was purified by column chromatography (100 g silica; eluent 3:1 – 1:1 – 1:3 hexane: Et_2O). The relevant fractions were combined and the solvent evaporated to give **2.23** as a yellow oil (668 mg, >99%): IR ν_{max} 3078w, 1588w, 1512s cm^{-1}; ^1H NMR δ 8.32 (1H, d, J = 8.5 Hz, ArC**H**), 7.79 (1H, d, J = 8.1 Hz, ArC**H**), 7.66 (2H, d, J = 8.5 Hz, ArC**H**), 7.49 (1H, m, ArC**H**), 7.38 (1H, t, J = 8.5 Hz, ArC**H**), 7.28 (2H, d, J = 8.5 Hz, ArC**H**), 5.78 (1H, ddt, J = 16.9, 10.3, 6.6 Hz, CH_2CH=CH_2), 4.98-5.08 (2H, m, CH=CH_2), 3.31-3.38 (2H, m, CH_2), 3.15-3.22 (4H, m, 2 x CH_2), 2.52 (3H, s, ArCH_3), 2.08 (2H, q, J = 6.6 Hz, CH_2), 1.68 (2H, quintet, J = 7.7 Hz, CH_2); ^{13}C NMR δ 143.7 (**C**), 137.3 (**C**), 136.3 (**C**), 134.2 (**C**H), 129.9 (**C**H), 129.2 (**C**H), 127.2 (**C**H), 126.8 (**C**H), 126.1 (**C**H), 115.8 (**C**H_2), 49.1 (**C**H_2), 48.3 (**C**H_2), 30.8 (**C**H_2), 28.3 (**C**H_2), 25.3 (**C**H_2), 21.7 (**C**H_3); MS *m/z* 469 $[M+H]^+$.

*3.6.15 4-Methyl-*N*-pent-4-enyl-*N*-vinyl-benzenesulfonamide* **2.24**

To a solution of **2.23** (640 mg, 1.27 mmol) in CH_2Cl_2 (10 mL) was added *m*-chloroperbenzoic acid (548 mg, 3.18 mmol) and the reaction mixture stirred for 1 h. The reaction mixture was quenched with 10% sodium thiosulfate solution (10 mL) and the phases separated. The organic phase was washed with saturated aq $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered and the solvent evaporated. The resultant yellow oily solid was treated with hexane and the solid removed by filtration. The filtrate was evaporated and the residue purified by column chromatography (30 g alumina; eluent hexane – 5% -10% Et_2O in hexane). The relevant fractions were combined and the solvent evaporated to give **24** as a pale yellow oil (238 mg, 71%): ^{1}H NMR δ 7.67 (2H, d, J = 8.1 Hz, ArC**H**), 7.31 (2H, d, J = 8.1 Hz, ArC**H**), 6.89 (1H, dd, J = 15.8, 9.2 Hz, CH_2=C**H**), 5.79 (1H, ddt, J = 17.3, 10.3, 6.6 Hz, CH_2=C**H**), 4.97-5.08 (2H, m, C**H**$_2$=CH), 4.34 (1H, dd, J = 9.2, 1.1 Hz, C**H**$_2$=CH), 4.24 (1H, dd, J = 15.8, 1.1 Hz, C**H**$_2$=CH), 3.31 (2H, dd, J = 7.7, 7.4 Hz, C**H**$_2$), 2.42 (3H, s, ArC**H**$_3$), 2.69 (2H, dd, J = 7.7, 7.4 Hz, C**H**$_2$), 1.71 (2H, m, C**H**$_2$). The spectroscopic properties were consistent with that reported in the literature (ref 5).

3.6.16 1-(Toluene-4-sulfonyl)-1,2,3,4-tetrahydro-pyridine **2.25**

To a solution of **2.24** (200 mg, 0.75 mmol) in dry, degassed CH_2Cl_2 (40 mL) under Ar was added Grubbs' 2nd generation catalyst (32 mg, 0.04 mmol). The reaction mixture was heated at reflux for 24 h then the solvent evaporated. The residue was purified by column chromatography (15 g alumina; eluent 20% Et_2O in hexane). The relevant fractions were combined and the solvent evaporated to give **2.25** as a pale yellow solid (184 mg, >99%) mp 50-52 °C: ^{1}H NMR δ 7.67 (2H, d, J = 8.1 Hz, ArC**H**), 7.32 (2H, d, J = 8.1 Hz, ArC**H**), 6.63 (1H, d, J = 8.1 Hz, NC**H**=CH), 4.97 (1H, dt, J = 8.1, 4.0 Hz, CH=C**H**CH$_2$), 3.36 (2H, t, J = 5.5 Hz, C**H**$_2$), 2.42 (3H, s, ArC**H**$_3$), 1.91 (2H, m, C**H**$_2$), 1.65 (2H, m, C**H**$_2$). The spectroscopic properties were consistent with that reported in the literature (ref 5).

3.6.17 General procedure for protected sulfonamides **2.26**: *4-Methyl*-N-*hex-5-enyl*-N-*[2-(tetrahydro-pyran-2-yloxy)-ethyl]-benzenesulfonamide* **2.26b**

To a solution of **2.20** (500 mg, 1.7 mmol), hexen-1-ol (204 μL, 1.7 mmol) and PPh_3 (535 mg, 2.0 mmol) in THF (10 mL) was added dropwise diisopropylazodicarboxylate (401 μL, 2.0 mmol). The reaction mixture was stirred for 5 h, then filtered through a pad of silica and washed with EtOAc. The solvent was evaporated and the residue purified by column chromatography (75 g silica; eluent 20% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **2.26b** as a colourless oil (571 mg, 88%): IR ν_{max} 3319bm, 1734s, 1716s cm^{-1}; ^1H NMR δ 7.72 (2H, d, J = 8.1 Hz, ArC**H**), 7.28 (2H, d, J = 8.1 Hz, ArC**H**), 5.78 (1H, ddt, J = 17.1, 10.3, 7.0 Hz, CH_2CH=CH_2), 4.91-5.04 (2H, m, CH=C$\mathbf{H}_2$), 3.45 (1H, m, CH_2C**H**), 3.74-3.88 (4H, m, 2 x C$\mathbf{H}_2$), 3.35 (2H, q, J = 5.9 Hz, C$\mathbf{H}_2$), 3.18 (2H, t, J = 5.5 Hz, C$\mathbf{H}_2$), 2.42 (3H, s, ArC$\mathbf{H}_3$), 1.98-2.14 (2H, m, C$\mathbf{H}_2$), 1.55-1.85 (4H, m, C$\mathbf{H}_2$), 1.37 (2H, q, J = 7.0 Hz, C$\mathbf{H}_2$), 1.19-1.30 (4H, m, 2 x C$\mathbf{H}_2$); ^{13}C NMR δ 143.2 (**C**), 138.5 (**C**H), 137.1 (**C**), 129.7 (**C**H), 127.3 (**C**H), 114.9 (**C**H_2), 99.2 (**C**H), 66.7 (**C**H_2), 62.5 (**C**H_2), 49.4 (**C**H_2), 47.9 (**C**H_2), 33.4 (**C**H_2), 30.6 (**C**H_2), 28.1 (**C**H_2), 26.0 (**C**H_2), 25.5 (**C**H_2), 22.2 (**C**H), 21.6 (**C**H_3), 19.6 (**C**H_2); MS *m/z* 404 $[M+Na]^+$.

4-Methyl-N-*but-3-enyl*-N-*[2-(tetrahydro-pyran-2-yloxy)-ethyl]-benzenesulfonamide* **2.26a**

Colourless oil (253 mg, 42%): IR ν_{max} 3305bm 1704s cm^{-1}; ^1H NMR δ 7.70 (2H, d, J = 8.1 Hz, ArC**H**), 7.29 (2H, d, J = 8.1 Hz, ArC**H**), 5.72 (1H, ddt, J = 17.1, 10.2, 6.3 Hz, CH_2CH=CH_2), 4.91-5.04 (2H, m, CH=C$\mathbf{H}_2$), 4.52 (1H, m, CH_2C**H**), 3.75-3.88 (2H, m, C$\mathbf{H}_2$), 3.44-3.59 (4H, m, 2 x C$\mathbf{H}_2$), 3.34-3.41 (2H, m, C$\mathbf{H}_2$), 3.24-3.31 (2H, m, C$\mathbf{H}_2$), 2.42 (3H, s, ArC$\mathbf{H}_3$), 2.35 (2H, dd, J = 14.4, 7.4 Hz, C$\mathbf{H}_2$), 1.40-1.85 (2H, m, C$\mathbf{H}_2$), 1.19-1.33 (2H, m, 2 x C$\mathbf{H}_2$); ^{13}C NMR δ 143.1 (**C**), 137.1 (**C**), 134.8 (**C**H), 129.6 (**C**H), 127.3 (**C**H), 116.9 (**C**H_2), 99.1 (**C**H), 66.5 (**C**H_2), 62.3 (**C**H_2), 48.8 (**C**H_2), 47.9 (**C**H_2), 33.1 (**C**H_2), 30.5 (**C**H_2), 25.3 (**C**H_2), 22.0 (**C**H), 21.4 (**C**H_3), 19.4 (**C**H_2); MS *m/z* 418 $[M+Na]^+$.

*4-Methyl-*N*-hept-6-enyl-*N*-[2-(tetrahydro-pyran-2-yloxy)-ethyl]-benzenesulfonamide*

2.26c

Colourless oil (472 mg, 70%): IR ν_{max} 1744s, 1718s cm^{-1}; ^1H NMR δ 7.71 (2H, d, *J* = 8.2 Hz, ArC**H**), 7.29 (2H, d, *J* = 8.2 Hz, ArC**H**), 5.78 (1H, ddt, *J* = 17.0, 10.3, 6.7 Hz, CH_2CH=CH_2), 4.96 (1H, d, *J* = 17.0 Hz, CH=C$\mathbf{H}_2$), 4.94 (1H, d, *J* = 10.3 Hz, CH=C$\mathbf{H}_2$), 4.52 (1H, m, CH_2C**H**), 3.76-3.87 (4H, m, 2 x C$\mathbf{H}_2$), 3.35 (2H, dd, *J* = 12.0, 6.2 Hz, C$\mathbf{H}_2$), 3.17 (2H, dd, *J* = 7.6,7.6 Hz, C$\mathbf{H}_2$), 2.42 (3H, s, ArC$\mathbf{H}_3$), 2.03 (2H, m, C$\mathbf{H}_2$), 1.24-1.82 (10H, m, 5 x C$\mathbf{H}_2$); ^{13}C NMR δ 143.0 (**C**), 138.7 (**C**H), 137.1 (**C**), 129.5 (**C**H), 127.2 (**C**H), 114.4 (**C**H_2), 99.1 (**C**H), 66.5 (**C**H_2), 62.3 (**C**H_2), 49.3 (**C**H_2), 47.7 (**C**H_2), 33.6 (**C**H_2), 30.5 (**C**H_2), 28.5 (**C**H_2), 28.5 (**C**H_2), 26.1 (**C**H_2), 25.3 (**C**H_2), 22.0 (**C**H), 21.4 (**C**H_3), 19.5 (**C**H_2); MS *m/z* 418 $[M+Na]^+$.

3.6.18 General procedure for sulfonamides **2.27**: N*-(2-Hydroxyethyl)-4-methyl-*N*-hex-5-enyl-benzenesulfonamide* **2.27b**

To a solution of **2.26b** (530 mg, 1.4 mmol) in MeOH (10 mL) was added *p*-toluene sulfonic acid (26 mg, 0.1 mmol). The reaction mixture was stirred for 3 h, then the solvent evaporated. The residue was diluted in Et_2O (10 mL) and H_2O (10 mL), then the organic phase washed with saturated aq $NaHCO_3$ (10 mL), brine (10 mL), dried over Na_2SO_4, filtered and the solvent evaporated. The residue was purified by column chromatography (25 g silica; eluent 1:1 Et_2O: hexane). The relevant fractions were combined and the solvent evaporated to give **2.27b** as a colourless oil (275 mg, 66%): IR ν_{max} 3532bs, 3073m, 1640m, 1597m cm^{-1}; ^1H NMR δ 7.61 (2H, d, *J* = 8.3 Hz, ArC**H**), 7.31 (2H, d, *J* = 8.3 Hz, ArC**H**), 5.75 (1H, ddt, *J* = 17.1, 10.3, 6.6 Hz, CH_2CH=CH_2), 4.99 (2H, m, CH=C$\mathbf{H}_2$), 3.76 (2H, q, *J* = 5.6 Hz, C$\mathbf{H}_2$), 3.22 (2H, t, *J* = 5.6 Hz, C$\mathbf{H}_2$), 3.16, (2H, dd, *J* = 7.6 Hz, C$\mathbf{H}_2$), 2.43 (3H, s, ArC$\mathbf{H}_3$), 2.30 (1H, t, *J* = 5.8 Hz, CH_2O**H**), 2.04 (2H, q, *J* = 7.1 Hz, C$\mathbf{H}_2$), 1.56 (2H, quintet, *J* = 7.1 Hz, C$\mathbf{H}_2$) 1.38 (2H, quintet, *J* = 7.6 Hz, C$\mathbf{H}_2$); ^{13}C NMR δ 143.5 (**C**), 138.2 (**C**H), 136.0 (**C**), 129.7 (**C**H), 127.3 (**C**H), 114.9 (**C**H_2), 61.5 (**C**H_2), 50.9 (**C**H_2), 49.9 (**C**H_2), 33.1 (**C**H_2), 28.1 (**C**H_2), 25.8 (**C**H_2), 21.5 (**C**H_3); MS(ES-) *m/z* 410 $[M+TFA]^-$.

N-*(2-Hydroxyethyl)-4-methyl*-N-*but-4-enyl-benzenesulfonamide* **2.27a**

Colourless oil (55 mg, 89%): IR ν_{max} 3322bs, 1722w, 1645w, 1595w cm^{-1}; ^1H NMR δ 7.72 (2H, d, *J* = 8.2 Hz, ArC**H**), 7.32 (2H, d, *J* = 8.2 Hz, ArC**H**), 5.73 (1H, ddt, *J* = 17.1, 10.3, 6.8 Hz, $CH_2C\mathbf{H}{=}CH_2$), 5.06 (2H, m, $CH{=}C\mathbf{H}_2$), 3.76 (2H, t, *J* = 5.6 Hz, $C\mathbf{H}_2$), 3.21-3.26 (4H, m, $C\mathbf{H}_2$), 2.44 (3H, s, $ArC\mathbf{H}_3$), 2.33 (2H, q, *J* = 7.3 Hz, $C\mathbf{H}_2$) 2.16 (1H, bs, **OH**); ^{13}C NMR δ 143.5 (**C**), 136.0 (**C**), 134.5 (**C**H), 129.7 (**C**H), 127.2 (**C**H), 117.3 ($\mathbf{C}H_2$), 61.3 ($\mathbf{C}H_2$), 51.1 ($\mathbf{C}H_2$), 49.3 ($\mathbf{C}H_2$), 33.2 ($\mathbf{C}H_2$), 21.5 ($\mathbf{C}H_3$); MS *m/z* 292 $[M+Na]^+$.

N-*(2-Hydroxyethyl)-4-methyl*-N-*hept-6-enyl-benzenesulfonamide* **2.27c**

Colourless oil (159 mg 61%): ^1H NMR δ 7.70 (2H, d, *J* = 8.2 Hz, ArC**H**), 7.32 (2H, d, *J* = 8.2 Hz, ArC**H**), 5.78 (1H, ddt, *J* = 17.1, 10.3, 6.7 Hz, $CH_2C\mathbf{H}{=}CH_2$), 4.99 (1H, d, *J* = 17.0 Hz, $CH{=}C\mathbf{H}_2$), 4.95 (1H, d, *J* = 10.3 Hz, $CH{=}C\mathbf{H}_2$), 3.76 (2H, t, *J* = 5.5 Hz, $C\mathbf{H}_2$), 3.23 (2H, t, *J* = 5.5 Hz, $C\mathbf{H}_2$), 3.15, (2H, dd, *J* = 7.5 Hz, $C\mathbf{H}_2$), 2.43 (3H, s, $ArC\mathbf{H}_3$), 2.18 (1H, bs, **OH**), 2.04 (2H, dd, *J* = 13.7, 6.8 Hz, $C\mathbf{H}_2$), 1.55 (2H, quintet, *J* = 7.5 Hz, $C\mathbf{H}_2$) 1.25-1.43 (2H, m, 2 x $C\mathbf{H}_2$); ^{13}C NMR δ 143.4 (**C**), 138.6 (**C**H), 136.1 (**C**), 129.7 (**C**H), 127.2 (**C**H), 114.5 ($\mathbf{C}H_2$), 61.4 ($\mathbf{C}H_2$), 50.8 ($\mathbf{C}H_2$), 50.0 ($\mathbf{C}H_2$), 33.5 ($\mathbf{C}H_2$), 28.6 ($\mathbf{C}H_2$), 28.4 ($\mathbf{C}H_2$), 26.1 ($\mathbf{C}H_2$), 21.5 ($\mathbf{C}H_3$); IR ν_{max} 3515bs cm^{-1}; MS *m/z* 312 $[M+Na]^+$.

3.6.19 General procedure for selenides **2.28**: *4-Methyl*-N-*[2-(2-nitro-phenylselanyl)-ethyl]*-N-*hex-5-enyl-benzenesulfonamide* **2.28b**

To a solution of **2.27b** (100 mg, 0.36 mmol) and *o*-nitrophenylselenocyanate (200 mg, 0.72 mmol) in THF (3 mL) was added dropwise tributylphosphine (269 μL, 1.08 mmol). The reaction mixture was stirred for 1 h, then the solvent evaporated. The resultant brown residue was purified by column chromatography (10 g silica; eluent 3:1 – 1:1 – 1:3 hexane:Et_2O). The relevant fractions were combined and the solvent evaporated to give **2.28b** as a yellow oil (166 mg, 95%): IR ν_{max} 3073w, 1588m, 1512s cm^{-1}; ^1H NMR δ 8.36 (1H, dd, *J* = 8.5, 1.5 Hz, ArC**H**), 7.79 (1H, dd, *J* = 8.1, 1.5 Hz, ArC**H**), 7.65 (2H, d, *J* = 8.5 Hz, ArC**H**), 7.63 (1H, t, *J* = 8.6 Hz, ArC**H**), 7.38 (1H, t, *J* = 8.5 Hz, ArC**H**), 7.28 (2H, d, *J* = 8.5 Hz, ArC**H**), 5.78 (1H, ddt, *J* = 17.1, 10.3, 7.0 Hz, $CH_2C\mathbf{H}{=}CH_2$), 5.01 (1H, dq, *J* =

17.1, 1.1 Hz, CH=C**H**$_2$), 4.96 (1H, dq, J = 10.3, 1.1 Hz, CH=C**H**$_2$), 3.35 (2H, m, C**H**$_2$), 3.18 (4H, dd, J = 7.7, 7.7 Hz, 2 x C**H**$_2$), 2.41 (3H, s, ArC**H**$_3$), 2.06 (2H, q, J = 7.0 Hz, C**H**$_2$), 1.58 (2H, m, C**H**$_2$), 1.41 (2H, quintet, J = 7.0 Hz, C**H**$_2$); ^{13}C NMR δ 147.1 (**C**), 143.7 (**C**), 138.3 (**C**H), 136.3 (**C**), 134.2 (**C**H), 131.7 (**C**), 129.9 (**C**H), 129.2 (**C**H), 127.8 (**C**H), 127.2 (**C**H), 126.8 (**C**H), 126.1 (**C**H), 115.2 (**C**H$_2$), 48.4 (**C**H$_2$), 48.1 (**C**H$_2$), 33.3 (**C**H$_2$), 28.4 (**C**H$_2$), 25.9 (**C**H$_2$), 25.1 (**C**H$_2$), 21.7 (**C**H$_3$); MS *m/z* 483 [M+H]$^+$.

4-Methyl-N-*[2-(2-nitro-phenylselanyl)-ethyl]*-N-*but-3-enyl-benzenesulfonamide* **2.28a**

Yellow oil (79 mg, 87%): IR ν_{max} 3062w, 1590m, 1511s cm^{-1}; ^{1}H NMR δ 8.31 (1H, dd, J = 8.2, 1.2 Hz, ArC**H**), 7.78 (1H, d, J = 8.2 Hz, ArC**H**), 7.67 (2H, d, J = 8.2 Hz, ArC**H**), 7.64 (1H, t, J = 8.2 Hz, ArC**H**), 7.38 (1H, t, J = 8.3 Hz, ArC**H**), 7.29 (2H, d, J = 8.3 Hz, ArC**H**), 5.73 (1H, ddt, J = 17.1, 10.3, 6.4 Hz, CH$_2$C**H**=CH$_2$), 5.09 (2H, m, CH=C**H**$_2$), 3.37 (2H, m, C**H**$_2$), 3.27 (2H, dd, J = 7.8, 7.8 Hz, 2 x C**H**$_2$), 2.41 (3H, s, ArC**H**$_3$), 2.33 (2H, dd, J = 14.3, 7.5 Hz, C**H**$_2$); ^{13}C NMR δ 143.6 (**C**), 136.3 (**C**), 134.3 (**C**H), 133.9 (**C**), 131.5 (**C**), 129.8 (**C**H), 129.1 (**C**H), 127.1 (**C**H), 126.5 (**C**H), 125.8 (**C**H), 117.5 (**C**H$_2$), 48.8 (**C**H$_2$), 48.2 (**C**H$_2$), 33.5 (**C**H$_2$), 26.9 (**C**H$_2$), 24.8 (**C**H$_2$), 21.5 (**C**H$_3$); MS *m/z* 477 [M+Na]$^+$.

4-Methyl-N-*[2-(2-nitro-phenylselanyl)-ethyl]*-N-*hept-6-enyl-benzenesulfonamide* **2.28c**

Yellow oil (284 mg, 90%): IR ν_{max} 3069w, 1591m, 1510s cm^{-1}; ^{1}H NMR δ 8.31 (1H, dd, J = 8.3, 1.5 Hz, ArC**H**), 7.78 (1H, d, J = 8.0 Hz, ArC**H**), 7.66 (2H, d, J = 8.4 Hz, ArC**H**), 7.63 (1H, t, J = 8.0 Hz, ArC**H**), 7.38 (1H, t, J = 8.2 Hz, ArC**H**), 7.29 (2H, d, J = 6.7 Hz, ArC**H**), 5.79 (1H, ddt, J = 17.1, 10.3, 6.7 Hz, CH$_2$C**H**=CH$_2$), 4.99 (2H, m, CH=C**H**$_2$), 3.35 (2H, m, C**H**$_2$), 3.15-3.21 (4H, dd, J = 8.0, 8.0 Hz, 2 x C**H**$_2$), 2.42 (3H, s, ArC**H**$_3$), 2.04 (2H, q, J = 7.0 Hz, C**H**$_2$), 1.57 (2H, quintet, J = 7.4 Hz, C**H**$_2$), 1.28-1.45 (2H, m, C**H**$_2$); ^{13}C NMR δ 147.1 (**C**), 143.5 (**C**), 138.5 (**C**H), 136.3 (**C**), 131.5 (**C**), 129.7 (**C**H), 129.1 (**C**H), 127.1 (**C**H), 126.5 (**C**H), 125.9 (**C**H), 114.6 (**C**H$_2$), 49.3 (**C**H$_2$), 48.0 (**C**H$_2$), 33.5 (**C**H$_2$), 28.8 (**C**H$_2$), 28.4 (**C**H), 26.0 (**C**H$_2$), 25.0 (**C**H$_2$), 21.5 (**C**H$_3$); MS *m/z* 519 [M+Na]$^+$.

3.6.20 General procedure for enamides **2.29**: *4-Methyl*-N-*hex-5-enyl*-N-*vinyl-benzenesulfonamide* **2.29b**

To a solution of **2.28b** (160 mg, 0.33 mmol) in CH_2Cl_2 (5 mL) was added *m*-chloroperbenzoic acid (143 mg, 0.83 mmol) and the reaction mixture stirred for 1 h. The reaction mixture was quenched with 10% sodium thiosulfate solution (10 mL) and the phases separated. The organic phase was washed with saturated aq $NaHCO_3$ (10 mL), dried over Na_2SO_4, filtered and the solvent evaporated. The resultant yellow oily solid was treated with hexane and the solid removed by filtration. The filtrate was evaporated and the residue purified by column chromatography (10 g alumina; eluent hexane - 5% -10% Et_2O in hexane). The relevant fractions were combined and the solvent evaporated to give **2.29b** as a pale yellow oil (62 mg, 67%): IR ν_{max} 3073m, 1624s cm^{-1}; ^1H NMR δ 7.66 (2H, d, J = 8.5 Hz, ArC**H**), 7.31 (2H, d, J = 8.5 Hz, ArC**H**), 6.89 (1H, dd, J = 15.8, 9.2 Hz, CH_2=C**H**), 5.77 (1H, ddt, J = 17.1, 10.3, 7.0 Hz, CH_2=C**H**), 5.00 (2H, dq, J = 17.1, 1.5 Hz, C**H**=CH_2), 4.96 (2H, dq, J = 10.3, 1.5 Hz, C**H**$_2$=CH), 4.34 (1H, dd, J = 9.2, 1.5 Hz, C**H**$_2$=CH), 4.24 (1H, dd, J = 15.8, 1.1 Hz, C**H**$_2$=CH), 3.30 (2H, dd, J = 7.5, 7.5 Hz, C**H**$_2$), 2.43 (3H, s, ArC**H**$_3$), 2.06 (2H, q, J = 7.4 Hz, C**H**$_2$), 1.61 (2H, quintet, J = 7.4 Hz, C**H**$_2$), 1.41 (2H, quintet, J = 8.1 Hz, C**H**$_2$); ^{13}C NMR δ 143.9 (**C**), 138.5 (**C**H), 136.4 (**C**), 132.3 (**C**H), 129.9 (**C**H), 127.0 (**C**H), 115.0 (**C**H_2), 44.9 (**C**H_2), 33.4 (**C**H_2), 26.4 (**C**H_2), 26.2 (**C**H_2), 21.7 (**C**H_3).

4-Methyl-N-*but-3-enyl*-N-*vinyl-benzenesulfonamide* **2.29a**

Pale yellow oil (30 mg, 70%): ^1H NMR δ 7.67 (2H, d, J = 8.2 Hz, ArC**H**), 7.30 (2H, d, J = 8.2 Hz, ArC**H**), 6.90 (1H, dd, J = 15.9, 9.3 Hz, CH_2=C**H**), 5.76 (1H, ddt, J = 17.3, 10.3, 6.8 Hz, CH_2=C**H**), 5.08 (1H, dd, J = 10.3, 1.1 Hz, CH=C**H**$_2$), 5.07 (2H, d, J = 17.1 Hz, C**H**$_2$=CH), 4.35 (1H, dd, J = 9.3, 1.4 Hz, C**H**$_2$=CH), 4.27 (1H, dd, J = 15.9, 1.2 Hz, C**H**$_2$=CH), 3.38 (2H, dd, J = 5.8, 5.8 Hz, C**H**$_2$), 2.42 (3H, s, ArC**H**$_3$), 2.34 (2H, dd, J = 15.3, 6.8 Hz, C**H**$_2$). The spectroscopic properties were consistent with that reported in the literature (ref 5).

*3.6.21 4- methyl-*N*-Hept-6-enyl-*N*-vinyl-benzenesulfonamide* **2.29c**

To a solution of **2.28c** (25 mg, 0.05 mmol) in MeOH:H_2O (6:1, 2 mL) was added $NaHCO_3$ (6 mg, 0.08 mmol) and $NaIO_4$ (27 mg, 0.13 mmol). The reaction mixture was stirred for 3 h then the solvent evaporated. The residue was dissolved in Et_2O (5 mL) and H_2O (5 mL), the aqueous phase separated and washed with Et_2O (2 x 5 mL), the organics combined, washed with H_2O (5 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by column chromatography (3 g alumina; eluent 5%-25% Et_2O in hexane), the relevant fractions combined and the solvent evaporated to give **2.29c** as a yellow oil (12 mg, 82%): IR ν_{max}/cm^{-1} 3288s, 3073w, 1639m, 1624s, 1593m, 1446s cm^{-1}; ^1H NMR δ 7.65 (2H, d, *J* = 8.3 Hz, ArC**H**), 7.32 (1H, d, *J* = 8.3 Hz, ArC**H**), 6.89 (1H, dd, *J* = 15.8, 9.2 Hz, C**H**=CH_2), 5.78 (1H, ddt, *J* = 16.9, 10.3, 6.6 Hz, C**H**=CH_2), 4.99 (1H, d, *J* = 16.9 Hz, C$\mathbf{H}_2$=CH), 4.94 (1H, d, *J* = 10.3 Hz, C$\mathbf{H}_2$=CH), 4.33 (1H, dd, *J* = 9.2, 1.5 Hz, C$\mathbf{H}_2$=CH), 4.23 (1H, dd, *J* = 15.8, 1.5 Hz, C$\mathbf{H}_2$=CH), 2.99 (2H, t, *J* = 7.7 Hz, C$\mathbf{H}_2$), 2.43 (3H, s, ArC$\mathbf{H}_3$), 2.04 (2H, q, *J* = 6.6 Hz, C$\mathbf{H}_2$), 1.60 (2H, quintet, *J* = 7.5 Hz, C$\mathbf{H}_2$), 1.12-1.42 (4H, m, 2 x C$\mathbf{H}_2$); ^{13}C NMR δ 143.8 (**C**), 138.8 (**C**H), 136.5 (**C**), 132.3 (**C**H), 129.9 (**C**H), 127.0 (**C**H), 114.7 (**C**H_2), 92.9 (**C**H_2), 45.0 (**C**H_2), 33.7 (**C**H_2), 28.6 (**C**H_2), 26.7 (**C**H_2), 26.4 (**C**H_2), 21.7 (**C**H_3).

*3.6.22 2-Benzenesulfonylamino-3-(1*H*-indol-3-yl)-propionic acid methyl ester* **2.35**

To a solution of tryptophan methyl ester (1 g, 4.6 mmol) in pyridine (545 μL, 5.5 mmol) and CH_2Cl_2 (50 mL) was added benzenesulfonyl chloride (702 μL, 5.5 mmol). The reaction mixture was stirred for at RT for 4 h, washed with water (2 x 25 mL), saturated aq $NaHCO_3$ (25 mL) then brine (25 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by column chromatography (25 g silica; eluent 50% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **2.35** as an off white foam (854 mg, 52%): IR ν_{max} 3395s, 3281s, 3054w, 1737s, 1447s cm^{-1}; ^1H NMR (400 MHz) δ 8.13 (1H, bs, indole N**H**), 7.73 (2H, d, *J* = 7.3 Hz, ArC**H**), 7.50 (1H, t, *J* = 7.3 Hz, ArC**H**), 7.45 (1H, d, *J* = 7.8 Hz, ArC**H**), 7.39 (2H, t, *J* = 7.3 Hz, ArC**H**), 7.33 (1H, d, *J* = 8.0 Hz, ArC**H**), 7.17 (1H, dd, *J* = 8.0, 7.9 Hz, ArC**H**), 7.08 (1H, dd, *J* = 7.9, 7.8 Hz, ArC**H**), 7.01 (1H, d, *J* = 2.3 Hz, ArC**H**), 5.21 (1H, d, *J* = 9.0 Hz, N**H**),

4.29 (1H, dt, J = 9.0, 5.5 Hz, CH_2CH), 3.41 (3H, s, CH_3), 3.23 (2H, d, J = 5.5 Hz, CH_2CH); ^{13}C NMR (100 MHz) δ 171.7 (**C**), 139.7 (**C**), 136.2 (**C**), 132.8 (**CH**), 129.0 (**CH**), 127.3 (**C**), 127.1 (**CH**), 123.5 (**CH**), 122.4 (**CH**), 119.8 (**CH**), 118.6 (**CH**), 111.4 (**CH**), 109.1 (**C**), 56.2 (**CH**), 52.6 (CH_3), 29.4 (CH_2); MS *m/z* 359 $[M+H]^+$, 376 $[M+NH_4]^+$.

3.6.23 2-[Benzenesulfonyl-(2-hydroxy-ethyl)-amino]-3-(1H-indol-3-yl)-propionic acid methyl ester **2.37**

To a solution of **2.35** (800 mg, 2.2 mmol), 2-(tehrahydro-2H-pyran-2-yloxy)ethanol (299 μL, 2.2 mmol) and PPh_3 (682 mg, 2.6 mmol) in THF (15 mL) was added DIAD (512 μL, 2.6 mmol) and the reaction mixture stirred at RT for 24 h. On completion, the reaction mixture was filtered through a pad of silica, washed through with EtOAc and the solvent evaporated. The residue was purified by column chromatography (20 g silica; eluent 30% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **2.36** as a pale yellow oil, which was used in the next step without further purification.

To a solution of **2.36** in MeOH (10 mL) was added *p*-toluenesulfonic acid (84 mg, 0.44 mmol). The reaction mixture was stirred for 3.5 h at RT then the solvent evaporated. The residue was partitioned between Et_2O (10 mL) and water (10 mL), the phases separated, the organics washed with water (10 mL), saturated aq $NaHCO_3$ (10 mL), then brine (10 mL), dried over $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography (35 g silica; eluent 30% - 50% EtOAc in hexane). Relevant fractions were combined and the solvent evaporated to give **2.37** as a colourless glass (454 mg, 52%): IR ν_{max} 3522m, 3402s, 3054m, 1737s, 1447s cm^{-1}; ^1H NMR δ 8.12 (1H, bs, indole N**H**), 7.68 (2H, dd, J = 8.1, 1.1 Hz, ArC**H**), 7.48-7.56 (2H, m, ArC**H**), 7.33-7.41 (3H, m, ArC**H**), 7.22 (1H, td, J = 7.0, 1.1 Hz, ArC**H**), 7.14 (1H, td, J = 7.0, 1.1 Hz, ArC**H**), 7.00 (1H, d, J = 2.2 Hz, ArC**H**), 4.97 (1H, dd, J = 9.2, 5.9 Hz, CH_2CH), 3.63-3.82 (2H, m, CH_2), 3.57 (3H, s, CH_3), 3.40-3.54 (3H, m, CH_2), 3.23 (1H, dd, J = 15.3, 9.4 Hz, CH_2CH), 3.04 (1H, t, J = 6.6 Hz, O**H**); ^{13}C NMR δ 172.6 (**C**), 139.2 (**C**), 136.2 (**C**), 132.8 (**CH**), 128.9 (**CH**), 127.4 (**CH**), 127.0 (**C**), 122.8 (**CH**), 122.5 (**CH**), 119.9 (**CH**), 118.4 (**CH**), 111.5 (**CH**), 110.1

(**C**), 62.2 ($\mathbf{C}H_2$), 59.9 (**C**H), 52.6 ($\mathbf{C}H_3$), 48.1 ($\mathbf{C}H_2$), 26.3 ($\mathbf{C}H_2$); MS *m/z* 403 $[M+H]^+$, 420 $[M+NH_4]^+$.

3.6.24 2-{Benzenesulfonyl-[2-(2-cyano-phenylselanyl)-ethyl]-amino}-3-(1H-indol-3-yl)-propionic acid methyl ester **2.38**

To a stirred solution of **2.37** (500 mg, 1.24 mmol) and *o*-nitrophenylselenocyanate (572 mg, 2.52 mmol) in THF (10 mL) was added dropwise PBu_3 (942 μL, 3.78 mmol). The reaction mixture was stirred at RT for 2 h then the solvent evaporated. The residue was purified by column chromatography (50 g silica; eluent 10% - 30% EtOAc in hexane). Relevant fractions were combined and the solvent evaporated to give **2.38** as a yellow foam (479 mg, 66%): IR ν_{max} 3408s, 3059w, 1739s, 1628s, 1503m 1447s cm^{-1}; ^1H NMR δ 8.31 (1H, dd, *J* = 8.5, 1.5 Hz, ArC**H**), 8.11 (1H, bs, indole N**H**), 7.74 (1H, dd, *J* = 8.1, 1.1 Hz, ArC**H**), 7.69 (2H, dd, *J* = 8.1, 1.5 Hz, ArC**H**), 7.49-7.60 (3H, m, ArC**H**), 7.32-7.43 (4H, m, ArC**H**), 7.22 (1H, td, *J* = 7.0, 1.1 Hz, ArC**H**), 7.16 (1H, d, *J* = 2.6 Hz, ArC**H**), 7.14 (1H, td, *J* = 7.0, 1.1 Hz, ArC**H**), 4.97 (1H, dd, *J* = 7.0, 8.5 Hz, CH_2C**H**), 3.51-3.71 (2H, m, $\mathbf{C}H_2$), 3.44 (1H, dd, *J* = 15.1, 7.0 Hz, $\mathbf{C}H_2$CH), 3.42 (3H, s, $\mathbf{C}H_3$), 3.32 (1H, td, *J* = 11.8, 5.2 Hz, $\mathbf{C}H_2$), 3.16 (1H, dd, *J* = 15.1, 8.5 Hz, $\mathbf{C}H_2$CH), 2.95 (1H, dd, *J* = 12.5, 5.2 Hz, $\mathbf{C}H_2$); ^{13}C NMR δ 171.2 (**C**), 147.0 (**C**), 139.1 (**C**), 136.1 (**C**), 134.1 (**C**H), 132.9 (**C**H), 131.8 (**C**), 129.3 (**C**H) 129.0 (**C**H), 127.3 (**C**H), 127.1 (**C**), 126.7 (**C**H), 125.9 (**C**H), 123.0 (**C**H), 122.5 (**C**H), 119.9 (**C**H), 118.3 (**C**H), 111.5 (**C**H), 110.0 (**C**), 59.7 (**C**H), 52.3 ($\mathbf{C}H_3$), 45.2 ($\mathbf{C}H_2$), 27.1 ($\mathbf{C}H_2$), 25.8 ($\mathbf{C}H_2$); MS *m/z* 605 $[M+NH_4]^+$.

3.6.25 2-(Benzenesulfonyl-vinyl-amino)-3-(1H-indol-3-yl)-propionic acid methyl ester **2.39**

To a solution of **2.38** (50 mg, 0.086 mmol) in MeOH (5 mL) was added $NaHCO_3$ (10 mg, 0.13 mmol) in water (1 mL) followed by $NaIO_4$ (46 mg, 0.21 mmol). The reaction mixture was stirred for 24 h at RT then the solvent evaporated. The residue was partitioned between Et_2O (5 mL) and water (5 mL). The phases were separated and the organic phase washed with water (2 x 5 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by column chromatography (10 g alumina; eluent 10% - 20% EtOAc in hexane). Relevant fractions were combined and the solvent evaporated to give **2.39** as a

yellow oil (30 mg, 78%): IR ν_{max} 3404s, 3054m, 1741s, 1630w, 1447s cm^{-1}; ^1H NMR δ 8.04 (1H, bs, indole N**H**), 7.66 (1H, dd, *J* = 8.1, 1.1 Hz, ArC**H**), 7.57 (2H, d, *J* = 7.4 Hz, ArC**H**), 7.49 (1H, t, *J* = 7.4 Hz, ArC**H**), 7.38 (1H, d, *J* = 8.1 Hz, ArC**H**), 7.35 (2H, t, *J* = 7.4 Hz, ArC**H**), 7.22 (1H, dd, *J* = 8.1, 6.6 Hz, ArC**H**), 7.15 (1H, dd, *J* = 7.4, 6.6 Hz, ArC**H**), 7.05 (1H, d, *J* = 2.2 Hz, ArC**H**), 6.62 (1H, dd, *J* = 15.8, 9.6 Hz, CH_2=C**H**), 5.18 (1H, dd, *J* = 8.1, 6.4 Hz, CH_2C**H**), 4.61 (1H, dd, *J* = 15.8, 1.5 Hz, C**H**$_2$=CH), 4.58 (1H, dd, *J* = 9.6, 1.5 Hz, C**H**$_2$=CH), 3.65 (1H, dd, *J* = 14.7, 6.4 Hz, C**H**$_2$CH), 3.51 (3H, s, C**H**$_3$), 3.32 (1H, dd, *J* = 14.7, 8.1 Hz, C**H**$_2$CH); ^{13}C NMR δ 170.6 (**C**), 139.3 (**C**), 136.1 (**C**), 132.8 (**C**H), 129.9 (**C**H), 128.7 (**C**H), 127.4 (**C**H), 127.2 (**C**), 123.5 (**C**H), 122.2 (**C**H), 119.7 (**C**H), 118.7 (**C**H), 111.4 (**C**H), 111.0 (**C**), 98.6 (**C**H_2), 59.5 (**C**H), 52.4 (**C**H_3), 24.6 (**C**H_2); MS *m/z* 385 $[M+H]^+$, 402 $[M+NH_4]^+$.

3.6.26 2-Benzenesulfonylamino-3-[2-(1,1-dimethyl-allyl)-1H-indol-3-yl]-propionic acid methyl ester **2.40**

To a solution of **2.10** (247 mg, 0.86 mmol) in pyridine (143 μL, 1.44 mmol) and CH_2Cl_2 (20 mL) was added benzene sulfonyl chloride (185 μL, 1.44 mmol). The reaction mixture was stirred for at RT for 4 h, washed with water (2 x 20 mL), saturated aq $NaHCO_3$ (20 mL) then brine (20 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by column chromatography (25 g silica; eluent 20% EtOAc in hexane). The relevant fractions were combined and the solvent evaporated to give **2.40** as a white foam (276 mg, 75%): IR ν_{max} 3404s, 3276s, 3059w, 1739s, 1447s cm^{-1}; ^1H NMR δ 7.90 (1H, bs, indole N**H**), 7.52 (2H, d, *J* = 7.4 Hz, ArC**H**), 7.41 (1H, td, *J* = 7.4, 1.1 Hz, ArC**H**), 7.34 (1H, d, *J* = 7.4 Hz, ArC**H**), 7.23-7.30 (3H, m, ArC**H**), 7.12 (1H, t, *J* = 7.0, 1.1 Hz, ArC**H**), 7.04 (1H, td, *J* = 7.0, 1.1 Hz, ArC**H**), 6.02 (1H, dd, *J* = 18.0, 10.3 Hz, CH_2=C**H**), 5.22 (1H, d, *J* = 9.2 Hz, N**H**), 5.17 (1H, dd, *J* = 10.3, 0.7 Hz, C**H**$_2$=CH), 5.15 (1H, dd, *J* = 18.0, 0.7 Hz, C**H**$_2$=CH), 4.22 (1H, dt, *J* = 9.2, 7.0 Hz, CH_2C**H**), 3.38 (3H, s, C**H**$_3$), 3.24 (2H, dd, *J* = 7.0, 2.4 Hz, C**H**$_2$CH), 1.47 (6H, s, 2 x C**H**$_3$); ^{13}C NMR δ 172.7 (**C**), 145.8 (**C**H), 140.8 (**C**) 139.4 (**C**), 134.1 (**C**), 132.6 (**C**H), 129.4 (**C**), 128.7 (**C**H), 127.1 (**C**H), 121.7 (**C**H), 119.8 (**C**H), 118.0 (**C**H), 112.5 (**C**H_2), 110.6 (**C**H), 104.8 (**C**),

56.8 (**C**H), 52.5 (CH_3), 39.1 (**C**), 29.4 (CH_2), 27.7 (CH_3); MS *m/z* 427 $[M+H]^+$, 444 $[M+NH_4]^+$.

*3.6.27 2-[Benzenesulfonyl-(2-hydroxy-ethyl)-amino]-3-[2-(1,1-dimethyl-allyl)-1*H*-indol-3-yl]-propionic acid methyl ester* **2.42**

To a solution of **2.40** (250 mg, 0.58 mmol), 2-(tehrahydro-2H-pyran-2-yloxy)ethanol (95 μL, 0.70 mmol) and PPh_3 (184 mg, 0.70 mmol) in THF (5 mL) was added DIAD (138 μL, 0.70 mmol) and the reaction mixture stirred at RT for 24 h. On completion, the reaction mixture was filtered through a pad of silica, washed through with EtOAc and the solvent evaporated. The residue was purified by column chromatography (25 g silica; eluent 1% MeOH in CH_2Cl_2). The relevant fractions were combined and the solvent evaporated to give **2.41** as a pale yellow oil, which was used in the next step without further purification.

To a solution of **2.41** in MeOH (10 mL) was added *p*-toluenesulfonic acid (23 mg, 0.58 mmol). The reaction mixture was stirred for 5 h at RT then the solvent evaporated. The residue was dissolved in Et_2O (5 mL), washed saturated aq $NaHCO_3$ (2 x 5 mL), then brine (5 mL), dried over $MgSO_4$ and the solvent evaporated. The residue was purified by column chromatography (20 g silica; eluent 20% - 30% EtOAc in hexane). Relevant fractions were combined and the solvent evaporated to give **2.42** as a colourless oil (215 mg, 78%): IR ν_{max} 3532m, 3409s, 3324s, 3054w, 1739s, 1446s cm^{-1}; ^1H NMR δ 7.96 (1H, bs, indole N**H**), 7.79 (2H, d, *J* = 7.4 Hz, ArC**H**), 7.58 (1H, tt, *J* = 7.4, 1.1 Hz, ArC**H**), 7.48 (2H, td, *J* = 7.4, 1.1 Hz, ArC**H**), 7.25-7.31 (2H, m, ArC**H**), 7.12 (1H, t, *J* = 7.0, 1.1 Hz, ArC**H**), 7.03 (1H, td, *J* = 7.0, 1.1 Hz, ArC**H**), 6.07 (1H, dd, *J* = 17.7, 10.3 Hz, CH_2=C**H**), 5.15 (1H, dd, *J* = 17.6, 0.7 Hz, C**H**$_2$=CH), 5.14 (1H, dd, *J* = 10.3, 0.7 Hz, C**H**$_2$=CH), 4.77 (1H, dd, *J* = 11.0, 4.8 Hz, CH_2C**H**), 3.88-4.01 (3H, m, C**H**$_2$), 3.62 (1H, m, C**H**$_2$), 3.53 (1H, dd, *J* = 14.0, 11.0 Hz, C**H**$_2$CH), 3.37 (1H, t, *J* = 6.6 Hz, O**H**), 3.22 (1H, dd, *J* = 14.0, 4.8 Hz, C**H**$_2$CH), 3.10 (3H, s, C**H**$_3$), 1.48 (3H, s, C**H**$_3$), 1.47 (3H, s, C**H**$_3$); ^{13}C NMR δ 173.1 (**C**), 145.6 (**C**H), 140.5 (**C**) 139.0 (**C**), 134.1 (**C**), 133.0 (**C**H), 129.2 (**C**), 129.1 (**C**H), 127.6 (**C**H), 121.7 (**C**H), 119.6 (**C**H), 118.2 (**C**H), 112.5 (CH_2), 110.5 (**C**H), 104.8 (**C**), 63.3 (CH_2),

59.6 (**C**H), 52.0 (**C**H_3), 39.3 (**C**), 27.7 (**C**H_3), 27.6 (**C**H_3), 27.5 (**C**H_2); MS *m/z* 471 $[M+H]^+$, 488 $[M+NH_4]^+$.

*3.6.28 2-{Benzenesulfonyl-[2-(2-cyano-phenylselanyl)-ethyl]-amino}-3-[2-(1,1-dimethyl-allyl)-1*H*-indol-3-yl]-propionic acid methyl ester* **2.43**

To a stirred solution of **2.42** (193 mg, 0.41 mmol) and *o*-nitrophenylselenocyanate (186 mg, 0.82 mmol) in THF (5 mL) was added dropwise PBu_3 (306 μL, 1.23 mmol). The reaction mixture was stirred at RT for 2.5 h then the solvent evaporated. The residue was purified by column chromatography (25 g silica; eluent 10% - 20% EtOAc in hexane). Relevant fractions were combined and the solvent evaporated to give **2.43** as a yellow foam (221 mg, 82%): IR ν_{max} 3414s, 3064w, 1738s, 1590m, 1564m, 1512s, 1446s cm^{-1}; ^{1}H NMR δ 8.35 (1H, dd, *J* = 8.5, 1.5 Hz, ArC**H**), 8.00 (1H, dd, *J* = 8.1, 1.1 Hz, ArC**H**), 7.95 (1H, bs, indole N**H**), 7.63-7.74 (3H, m, ArC**H**), 7.53 (1H, tt, *J* = 7.4, 1.1 Hz, ArC**H**), 7.33-7.45 (4H, m, ArC**H**), 7.27 (1H, d, *J* = 8.1 Hz, ArC**H**), 7.12 (1H, t, *J* = 7.0, 1.1 Hz, ArC**H**), 7.05 (1H, td, *J* = 7.0, 1.1 Hz, ArC**H**), 6.09 (1H, dd, *J* = 17.7, 10.7 Hz, CH_2=C**H**), 5.19 (1H, dd, *J* = 17.7, 0.7 Hz, C**H**$_2$=CH), 5.19 (1H, dd, *J* = 10.7, 0.7 Hz, C**H**$_2$=CH), 4.84 (1H, dd, *J* = 11.0, 4.8 Hz, CH_2C**H**), 3.96 (1H, dd, *J* = 12.1, 5.1 Hz, C**H**$_2$), 3.78 (1H, td, *J* = 12.1, 4.4 Hz, C**H**$_2$), 3.62 (1H, td, *J* = 12.5, 4.8 Hz, C**H**$_2$), 3.52 (1H, dd, *J* = 13.6, 11.0 Hz, C**H**$_2$CH), 3.33 (1H, dd, *J* = 13.9, 4.8 Hz, C**H**$_2$CH), 3.21 (1H, dd, *J* = 12.5, 5.1 Hz, C**H**$_2$), 3.01 (3H, s, C**H**$_3$), 1.53 (3H, s, C**H**$_3$), 1.52 (3H, s, C**H**$_3$); ^{13}C NMR δ 171.4 (**C**), 147.0 (**C**), 145.5 (**C**H), 140.6 (**C**) 138.8 (**C**), 134.0 (**C**H), 132.9 (**C**H), 131.9 (**C**), 129.4 (**C**H), 129.1 (**C**), 129.0 (**C**H), 127.3 (**C**H), 126.7 (**C**H), 125.9 (**C**H), 121.7 (**C**H), 119.6 (**C**H), 118.0 (**C**H), 112.5 (**C**H_2), 110.4 (CH), 104.5 (**C**), 59.4 (**C**H), 51.7 (**C**H_3), 45.1 (**C**H_2), 39.2 (**C**), 28.0 (**C**H_2), 27.6 (**C**H_3), 27.5 (**C**H_3), 26.6 (**C**H_2); MS *m/z* 656 $[M+H]^+$, 672 $[M+NH_4]^+$.

*3.6.29 2-(Benzenesulfonyl-vinyl-amino)-3-[2-(1,1-dimethyl-allyl)-1*H*-indol-3-yl]-propionic acid methyl ester* **2.44**

To a solution of **2.43** (43 mg, 0.065 mmol) in MeOH (1 mL) and CH_2Cl_2 (1 mL) was added $NaHCO_3$ (27 mg, 0.32 mmol) in water (1 mL) followed by $NaIO_4$ (112 mg, 0.52

mmol). The reaction mixture was stirred for 5 d at RT then the solvent evaporated. The residue was dissolved in Et_2O (5 mL) washed with water (2 x 5 mL), dried over $MgSO_4$, filtered and the solvent evaporated. The residue was purified by column chromatography (5 g alumina; eluent 10% - 20% EtOAc in hexane). Relevant fractions were combined and the solvent evaporated to give **2.44** as a pale yellow oil (21 mg, 71%): IR ν_{max} 3418s, 3054w, 1737s, 1629m, 1447m cm^{-1}; ^1H NMR δ 7.88 (1H, bs, indole N**H**), 7.47 (1H, d, J = 8.1 Hz, ArC**H**), 7.38-7.44 (3H, m, ArC**H**), 7.22-7.26 (3H, m, ArC**H**), 7.11 (1H, td, J = 7.0, 1.1 Hz, ArC**H**), 7.01 (1H, td, J = 7.0, 1.1 Hz, ArC**H**), 6.68 (1H, dd, J = 16.2, 9.6 Hz, CH_2=C**H**), 6.13 (1H, dd, J = 17.3, 10.7 Hz, CH_2=C**H**), 5.33 (1H, dd, J = 8.8, 4.8 Hz, CH_2C**H**), 5.20 (1H, dd, J = 17.3, 0.7 Hz, C**H**$_2$=CH), 5.15 (1H, dd, J = 10.7, 0.7 Hz, C**H**$_2$=CH), 4.61 (1H, dd, J = 9.6, 1.8 Hz, C**H**$_2$=CH), 4.58 (1H, dd, J = 16.2, 1.8 Hz, C**H**$_2$=CH), 3.70 (1H, dd, J = 15.1, 4.8 Hz, C**H**$_2$CH), 3.47 (3H, s, C**H**$_3$), 3.46 (1H, dd, J = 15.4, 8.8 Hz, C**H**$_2$CH), 1.50 (3H, s, C**H**$_3$), 1.49 (3H, s, C**H**$_3$); ^{13}C NMR δ 170.9 (**C**), 145.9 (**C**H), 140.3 (**C**) 139.1 (**C**), 134.2 (**C**), 132.6 (**C**H), 130.4 (**C**H), 129.8 (**C**), 128.5 (**C**H), 127.2 (**C**H), 121.6 (**C**H), 119.4 (**C**H), 118.7 (**C**H), 112.2 (**C**H_2), 110.5 (**C**H), 106.8 (**C**), 97.5 (**C**H_2), 59.8 (**C**H), 52.4 (**C**H_3), 39.2 (**C**), 27.7 (**C**H_3), 27.7 (**C**H_3), 23.7 (**C**H_2); MS *m/z* 453 $[M+H]^+$, 470 $[M+NH_4]^+$.

References

[1] Wang, H.; Usui, T.; Osada, H.; Ganesan, A. *J. Med. Chem.* **2000**, *43*, 1577-1585.

[2] Guy, G.; Guette, J. *Synthesis* **1980**, 222-223.

[3] Cava, M. P.; Lakshmikantham, M. V.; Mitchell, M. J. *J. Org. Chem.* **1969**, *34*, 2665.

[4] Yokoyama, M.; Yoshida, S.; Imamoto, T. *Synthesis* **1982**, 591-592.

[5] Kinderman, S. S.; van Marseveen, J. H.; Schoemaker, H. E.; Hiemstra H.; Rutjes F. P. J. T. *Org. Lett.* **2001**, *3*, 2045-2048.

[6] Bach, T.; Schroder, J. *J. Org. Chem.* **1999**, *64*, 1265-1273.

[7] Houltemare, D.; Ponthieux, S.; Outurguin, F.; Paulmier, C. *Synthesis* **1997**, 101-106.

[8] Rollin, P.; Verez Bencomo, V.; Sinay, P. *Synthesis*, **1984**, 134-135.

[9] Leit, S. M.; Paquette, L. A. *J. Org. Chem.* **1999**, *64*, 9225-9229.

[10] Mormann, W.; Leukel, G. *Synthesis*, **1988**, 990-992.

[11] Hope, D. B.; Horncastle, K. C. *J. Chem. Soc.* **1966**, 1098-1101.

[12] Honda, T.; Ishikawa F.; Yamana, S. *J. Chem. Soc, Perkin Trans. 1*, **1996**, 1125-1130.

[13] Joe, D.; Overman, L. E. *Tetrahedron Lett.* **1997**, *38*, 8635-8638.

[14] Winkler, J. D.; Kim, H. S.; Kim, S.; Ando, K.; Houk, K.N. *J. Org. Chem.* **1997**, *62*, 2957-2962.

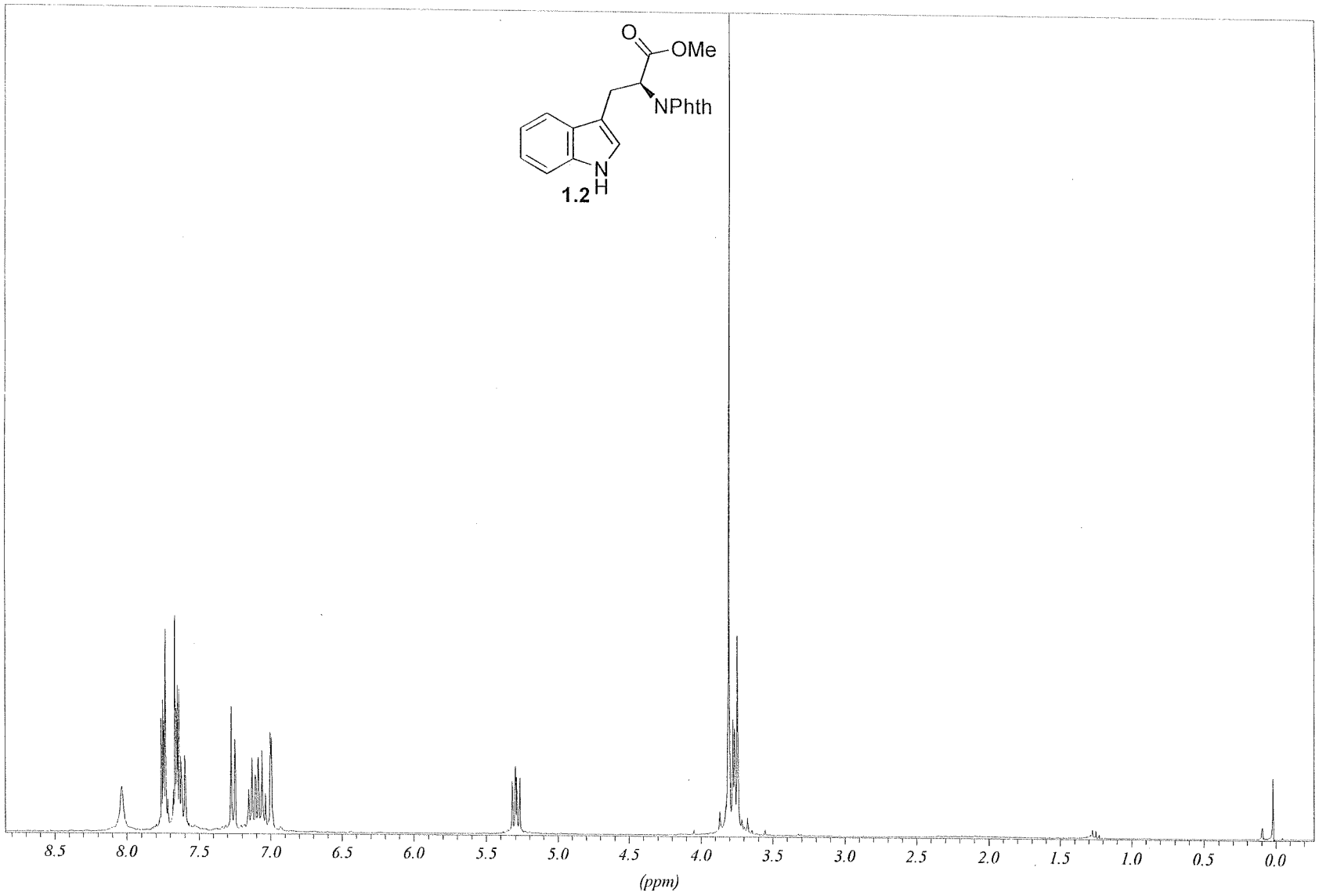
[15] Maier, M. E. *Angew. Chem. Int. Ed,* **2000**, *39*, 2073-2077.

[16] Gerlach, B.; Brantley, S. E.; Smith, K. M. *J. Org. Chem.* **1998**, *63*, 2314-2320.

[17] See section 2.11.4.

APPENDIX 1

^{1}H NMR Spectra for compounds in section 2.11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N
H
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8.0
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6.5
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4.0
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2.5
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1.5
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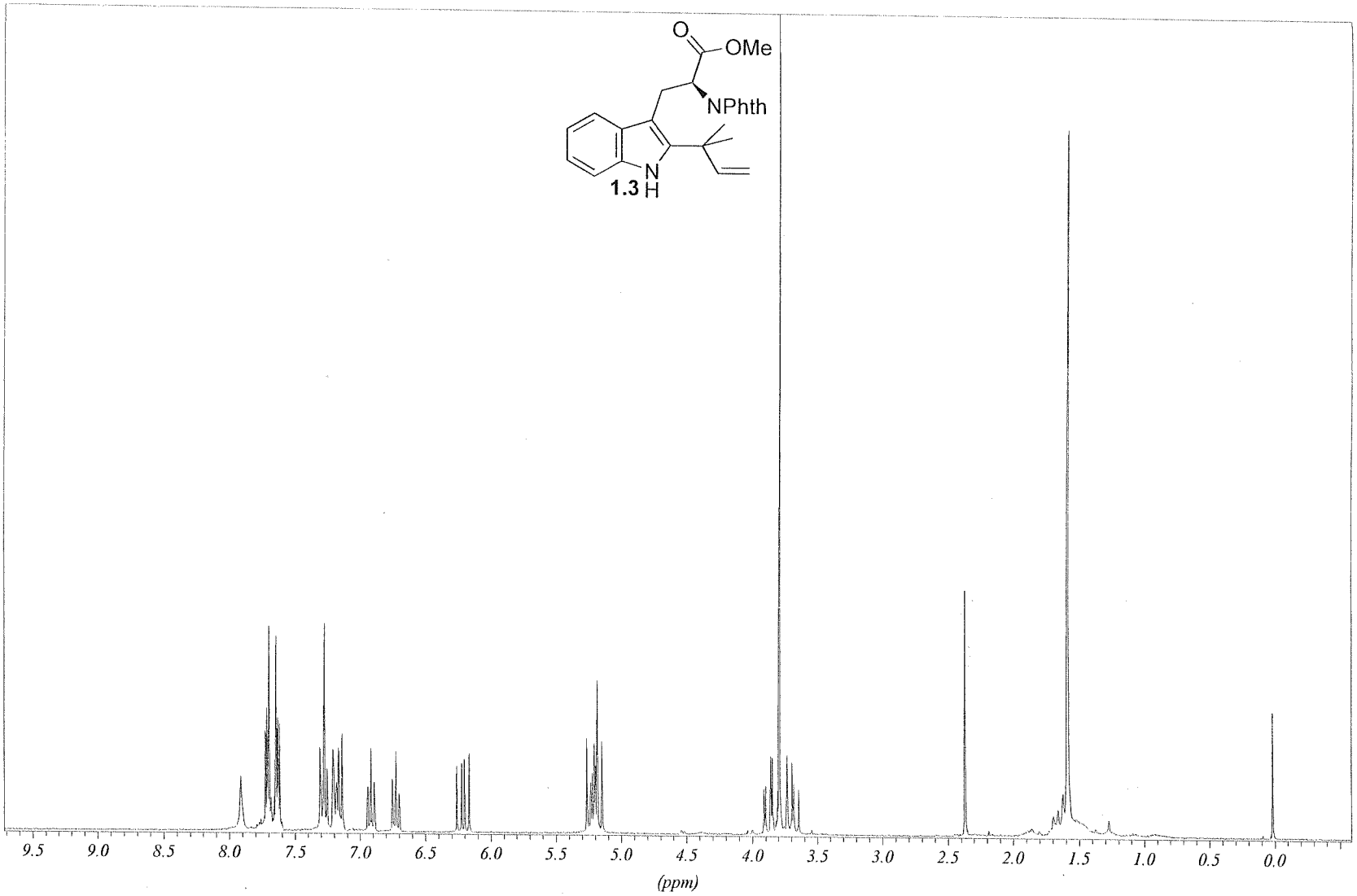
0.0
(ppm)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N
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9.0
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7.5
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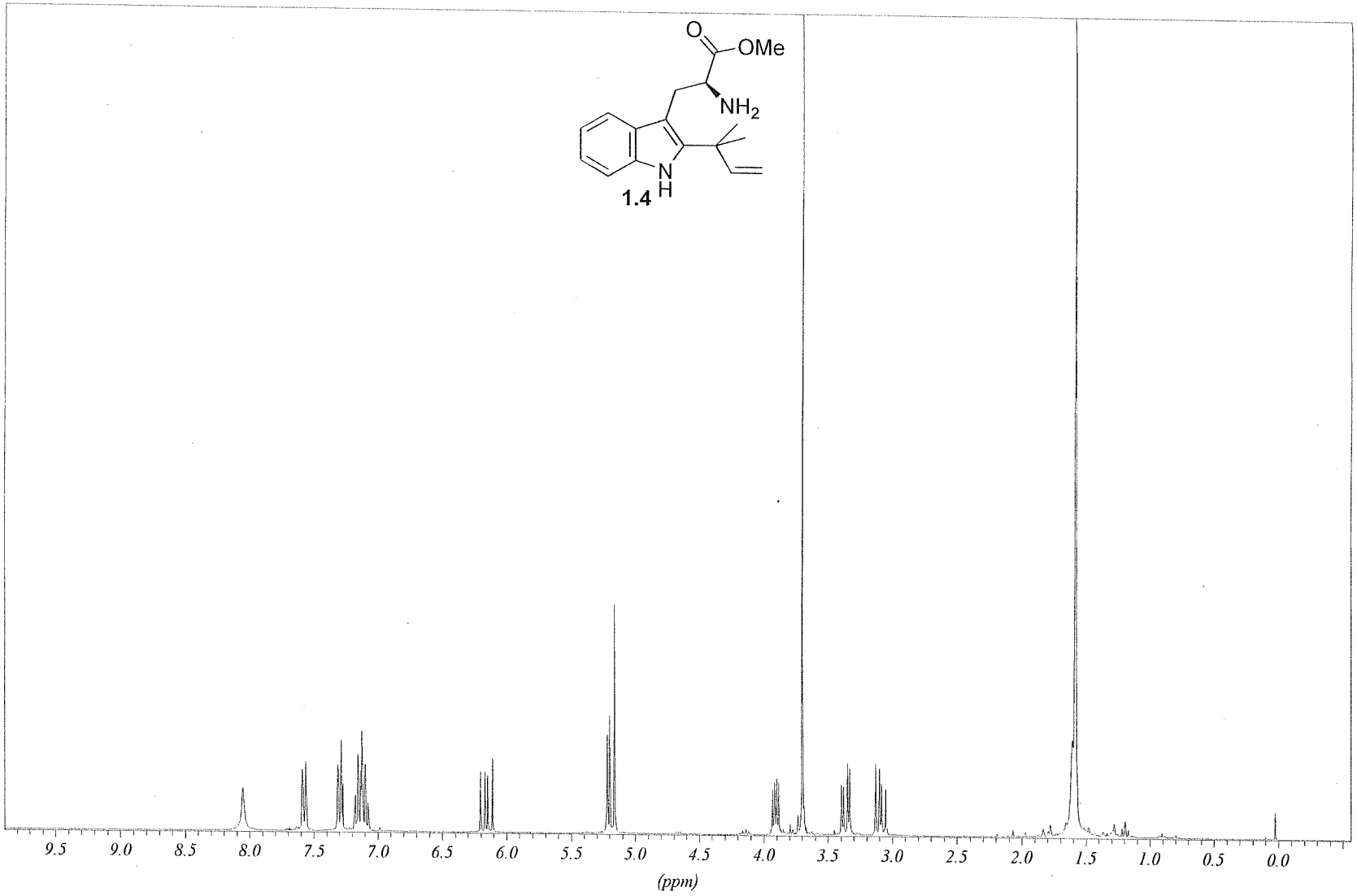
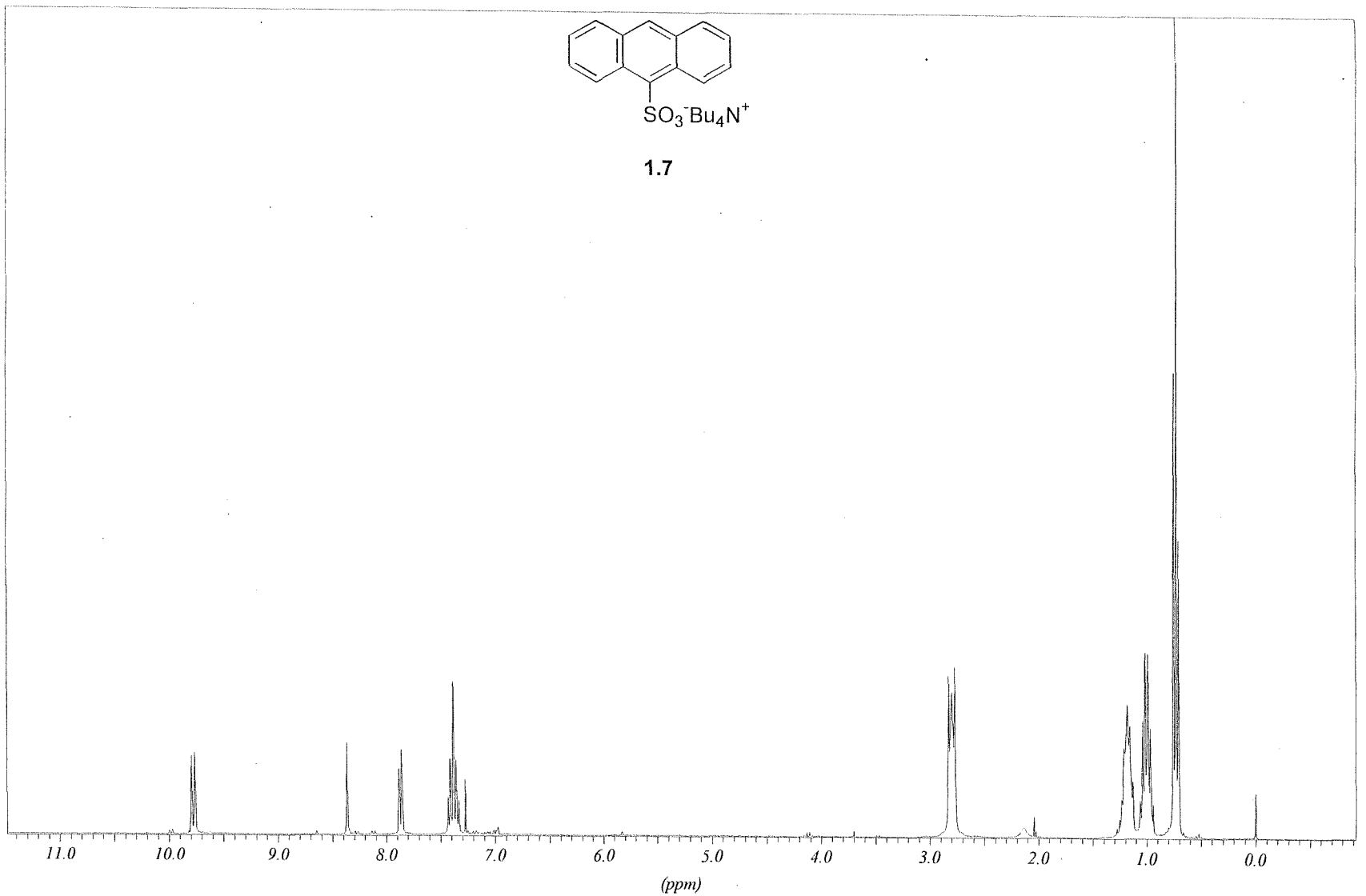
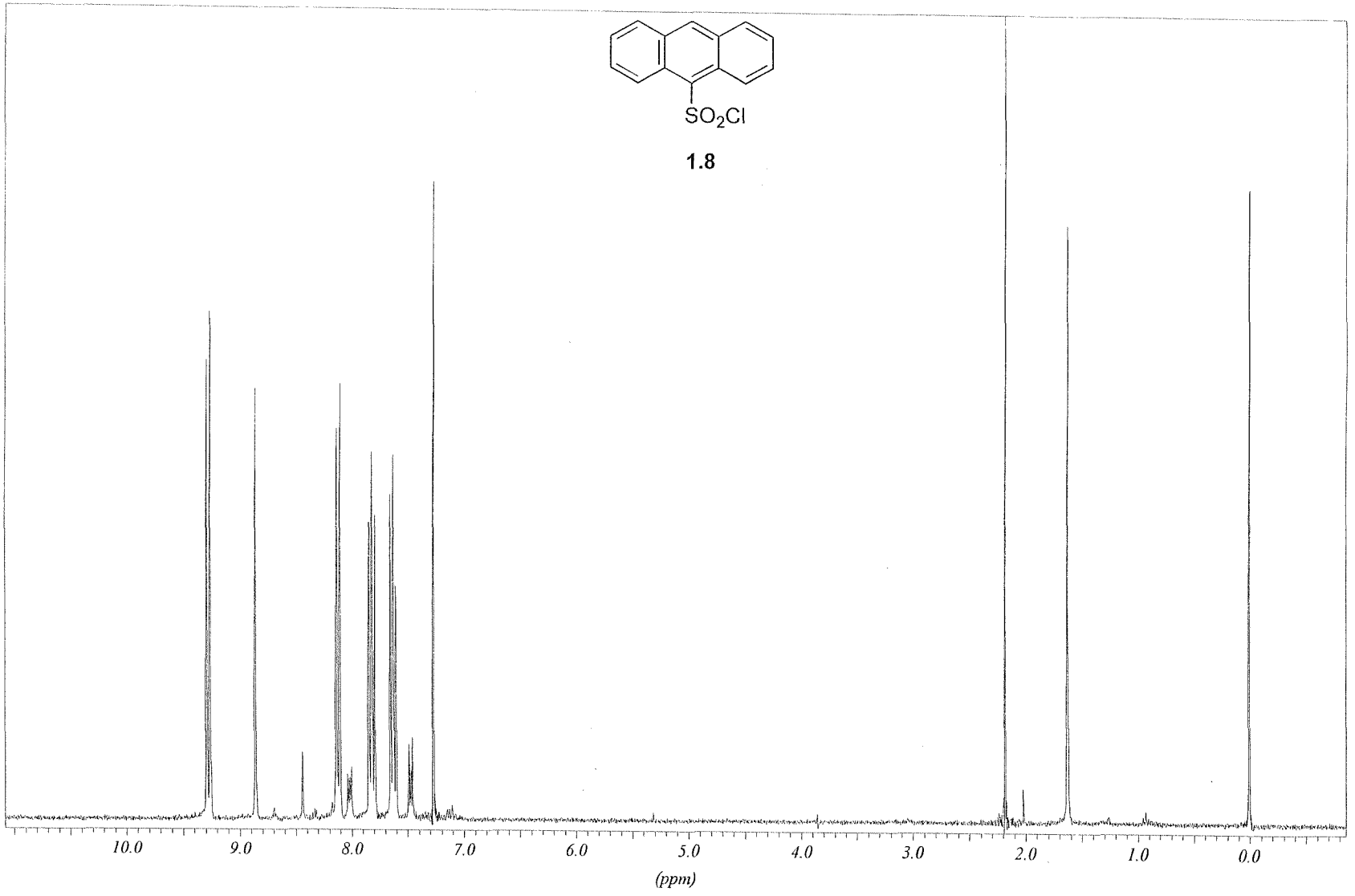
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

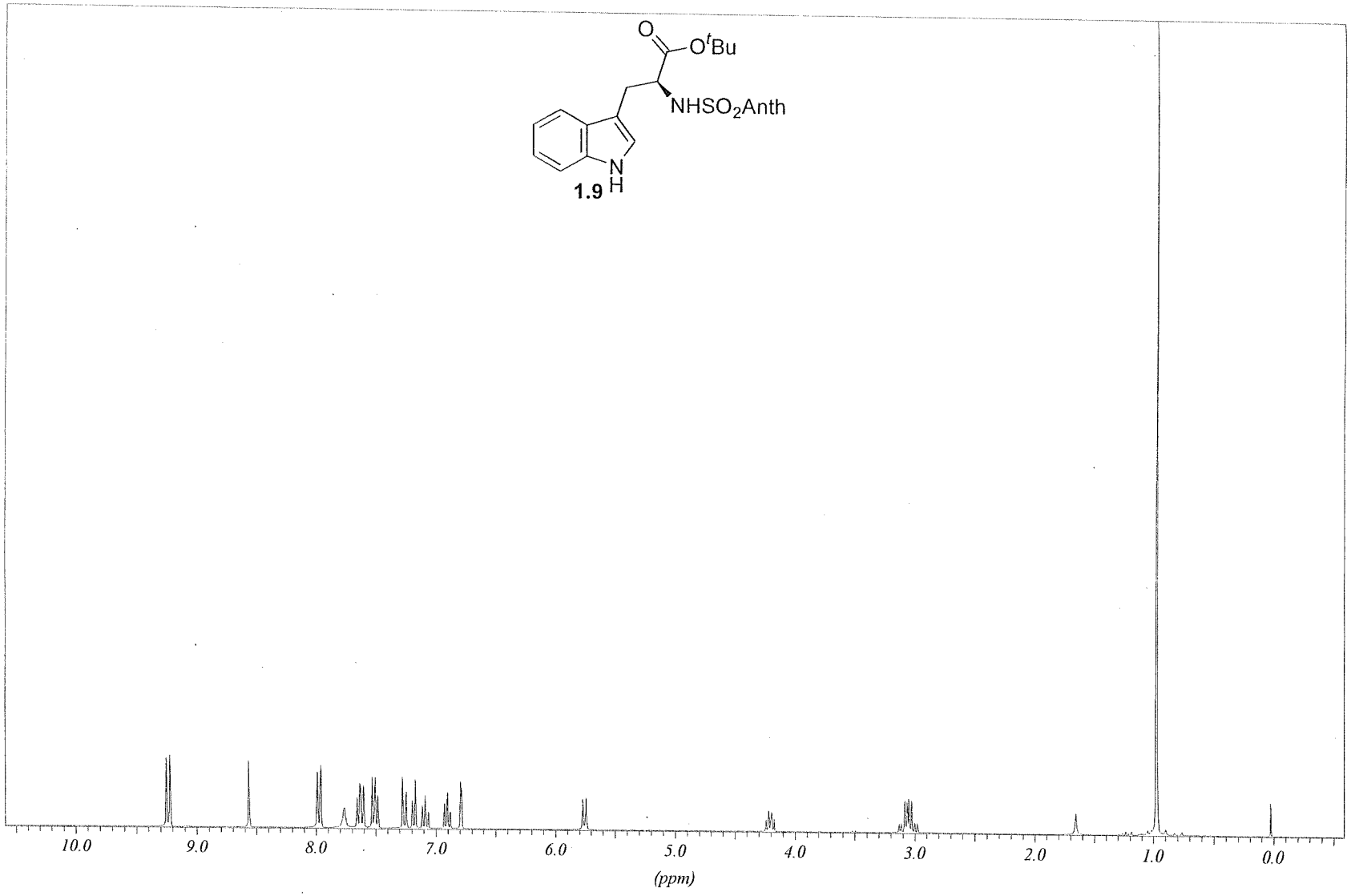

O
OMe
NH2
N
H
1.4
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

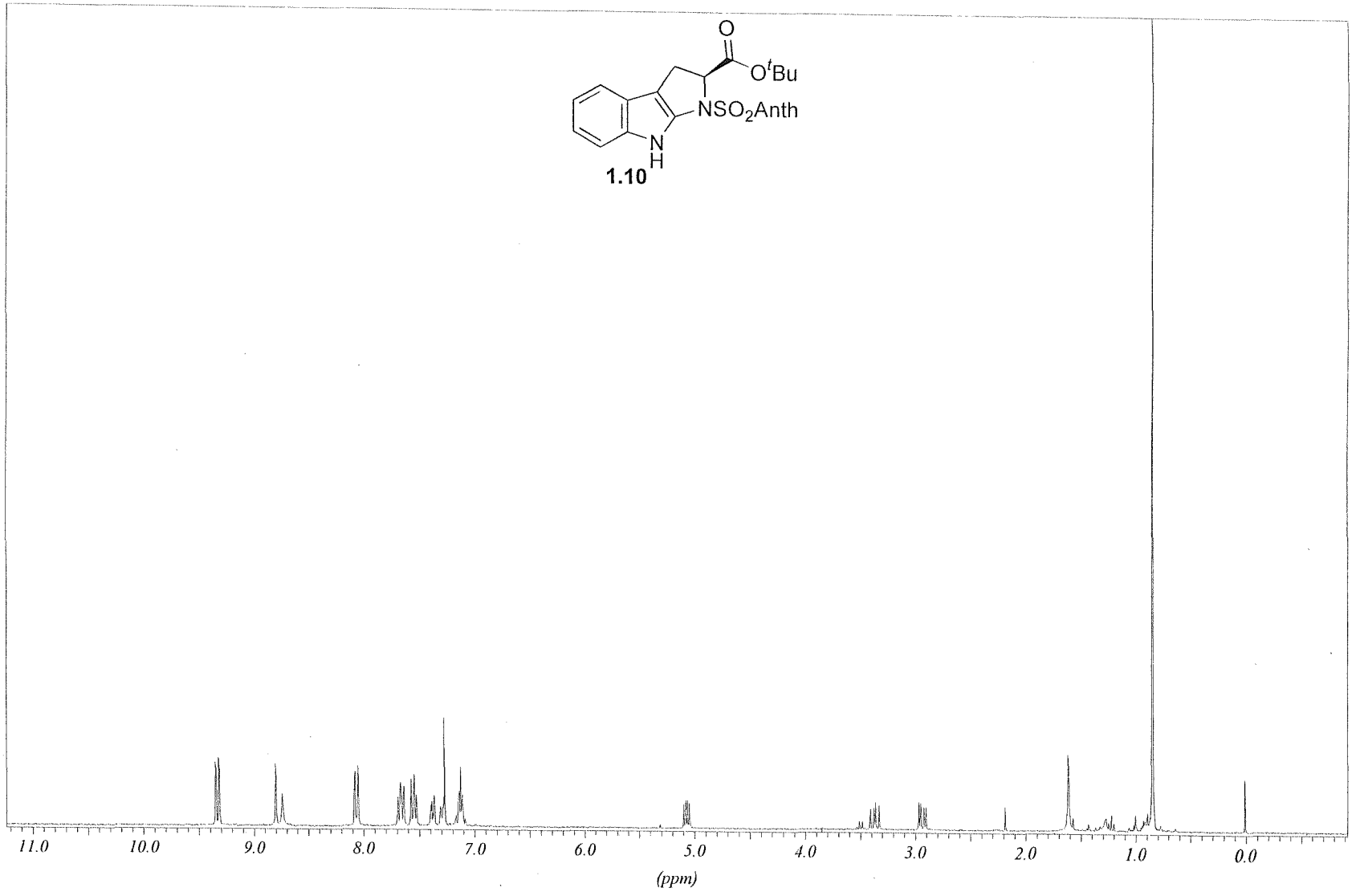


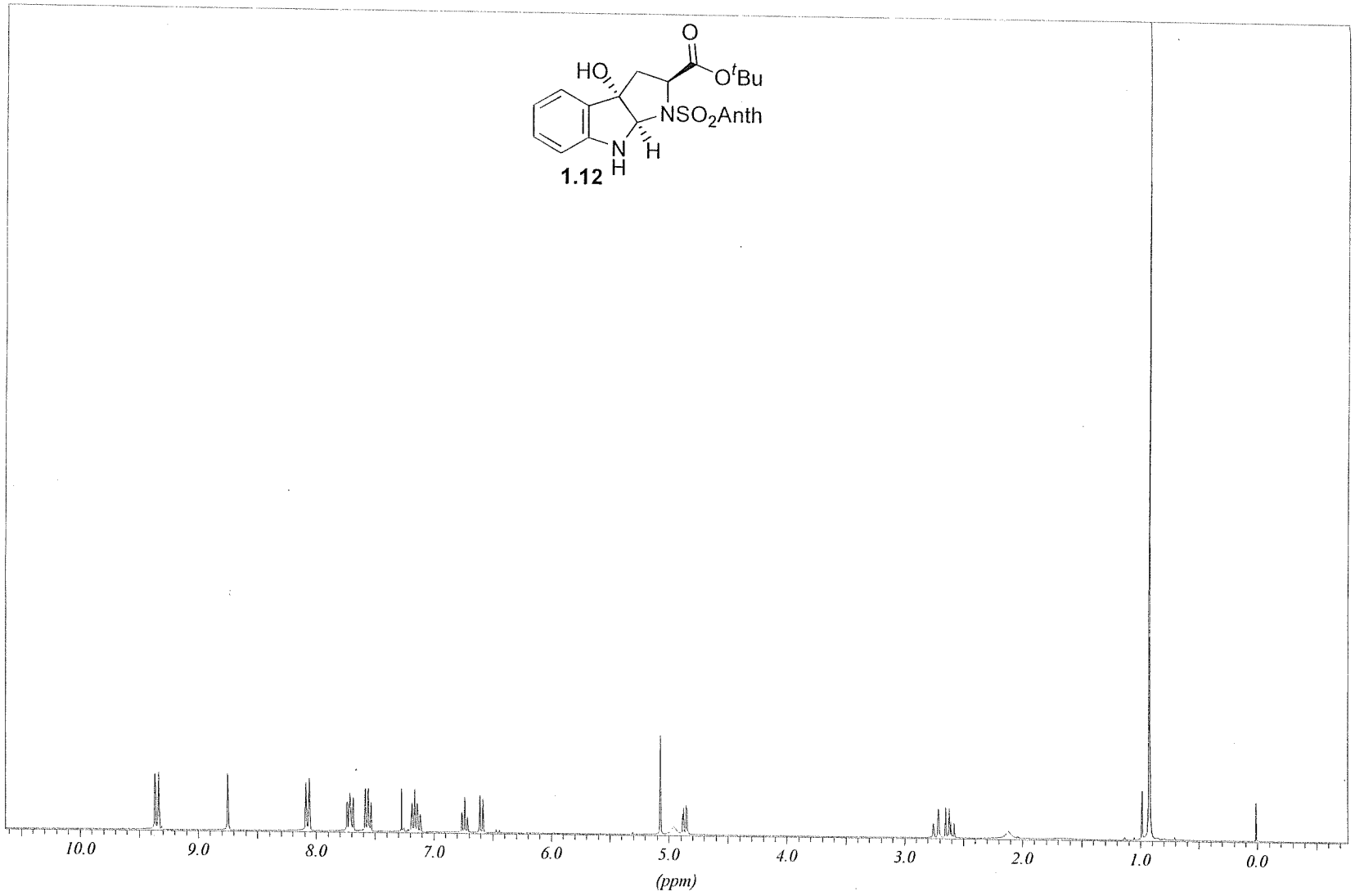
1.7

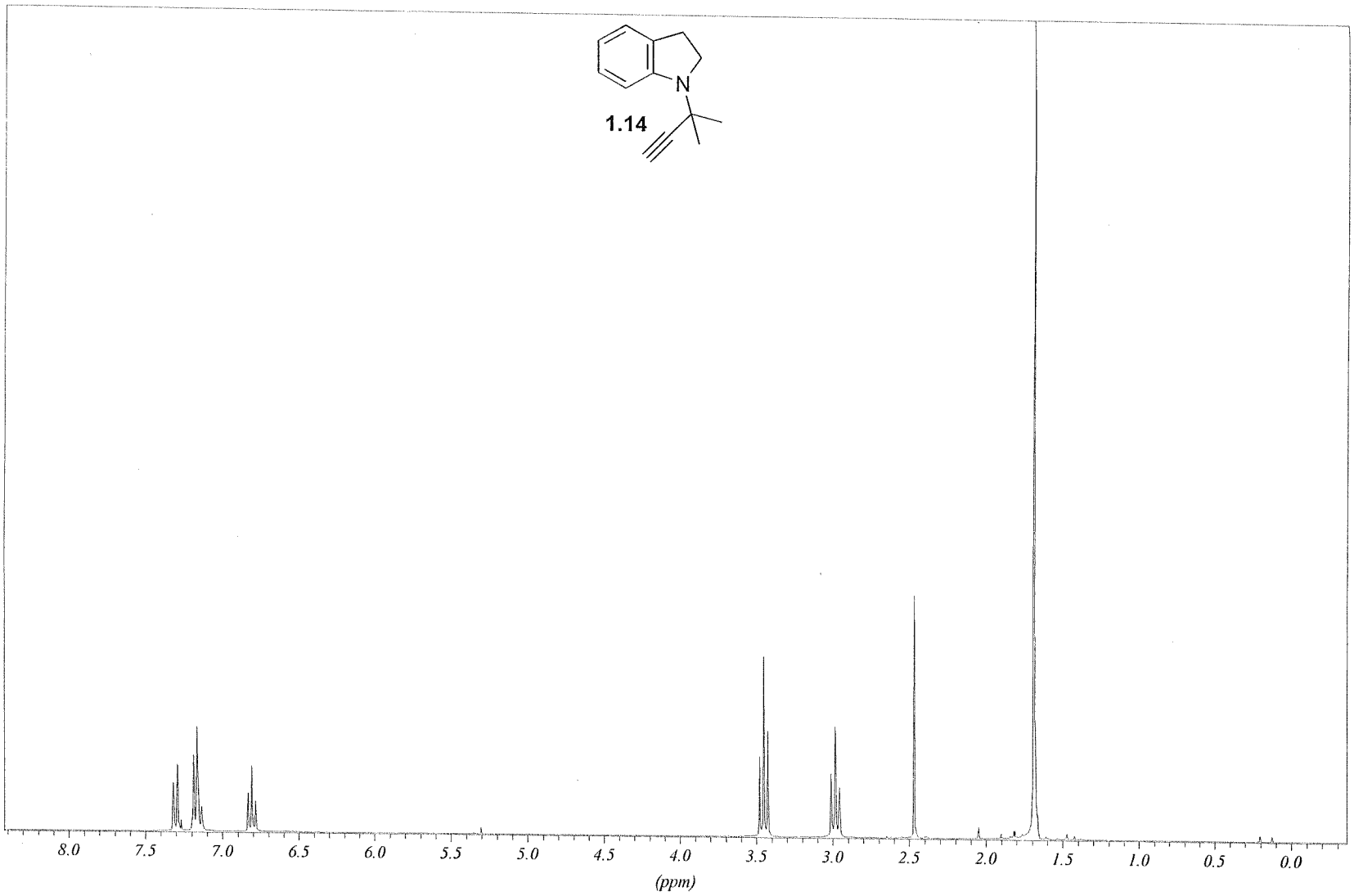


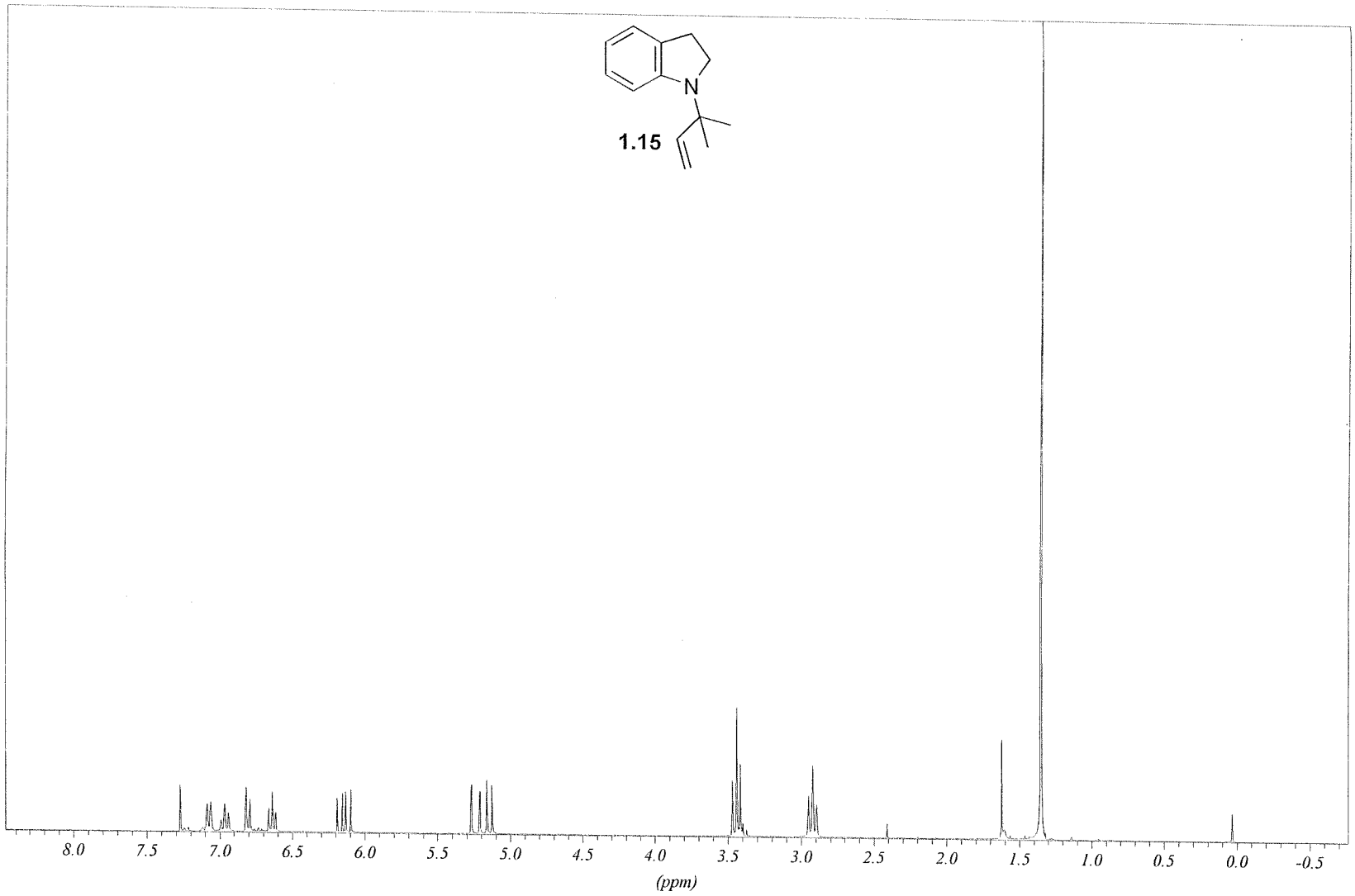
1.8

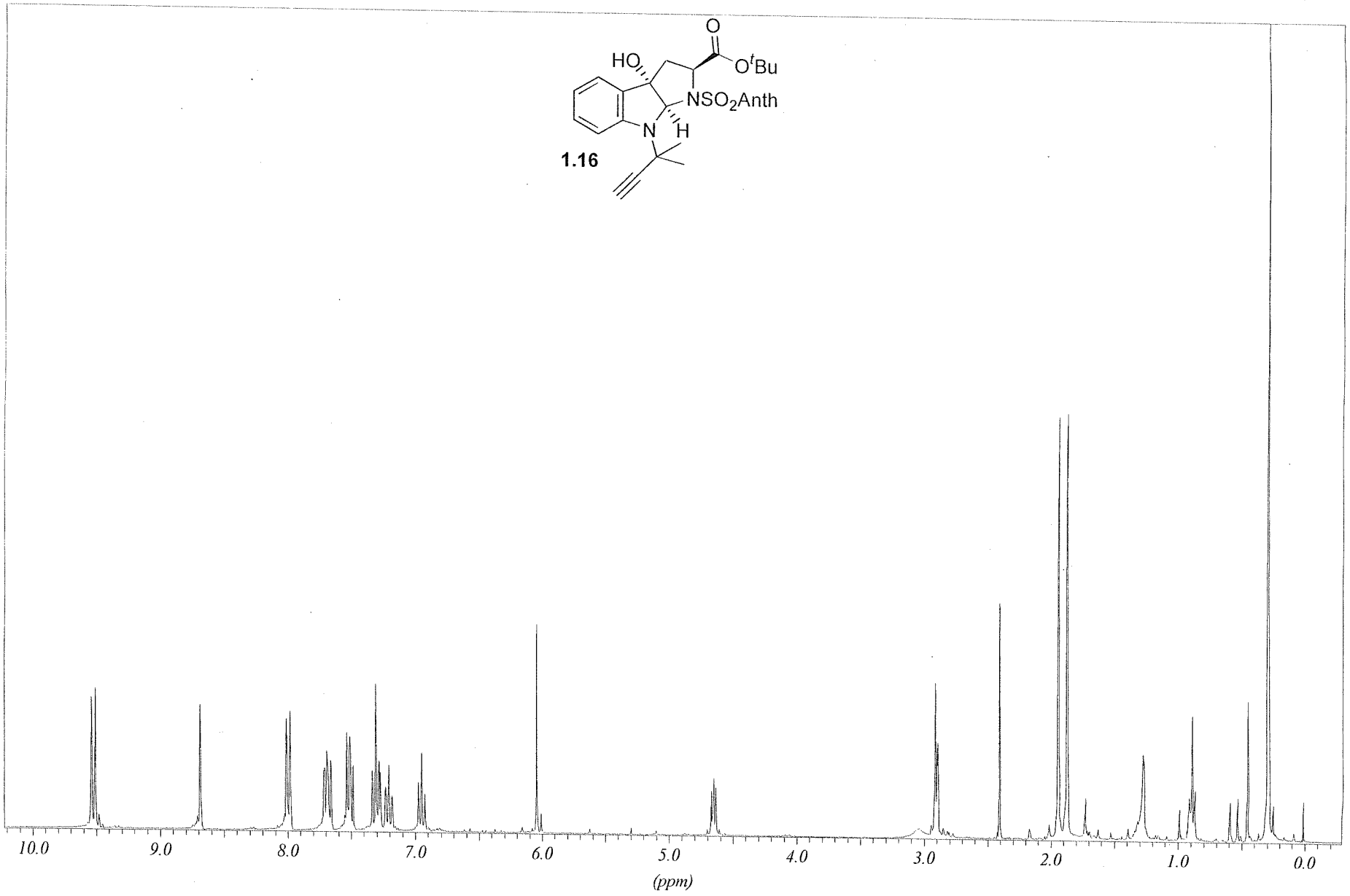

O
O^{t}Bu
NHSO$_2$Anth
N
H
1.9
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


O
O^{t}Bu
NSO$_2$Anth
N
H
1.10
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

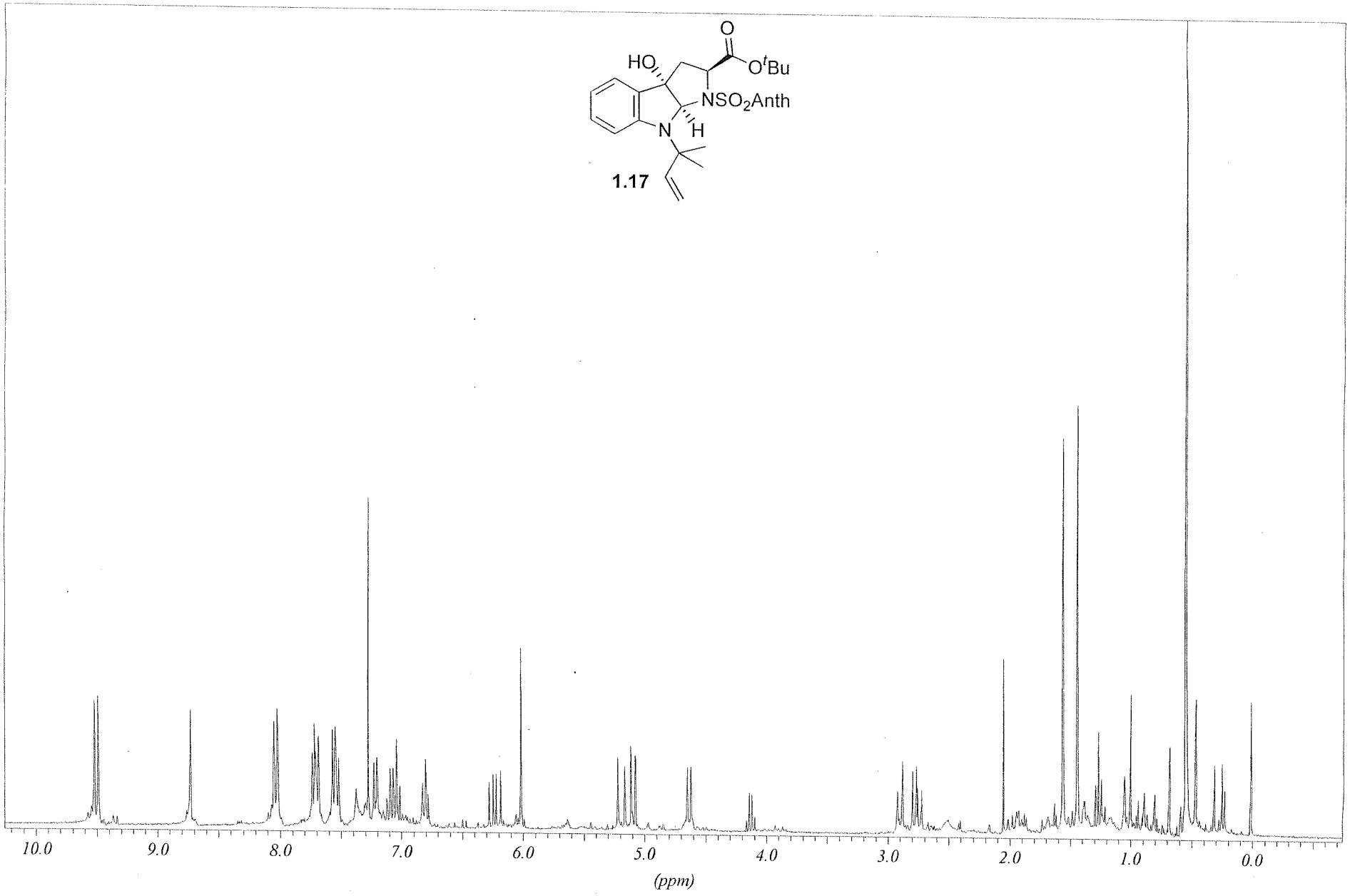

HO
O
O^{t}Bu
NSO$_2$Anth
N
H
H
1.12
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


N
1.14
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
(ppm)

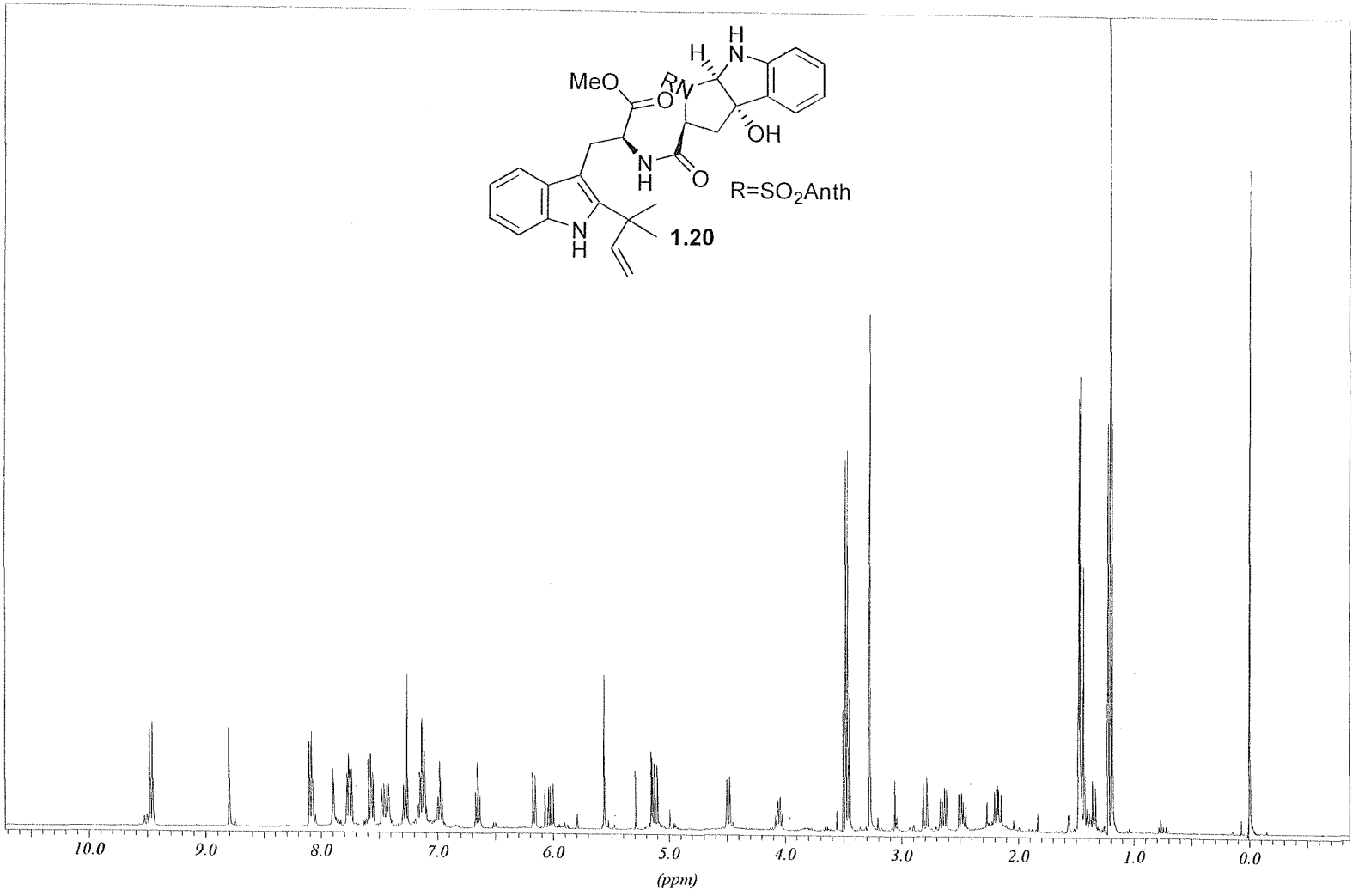

N
1.15
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

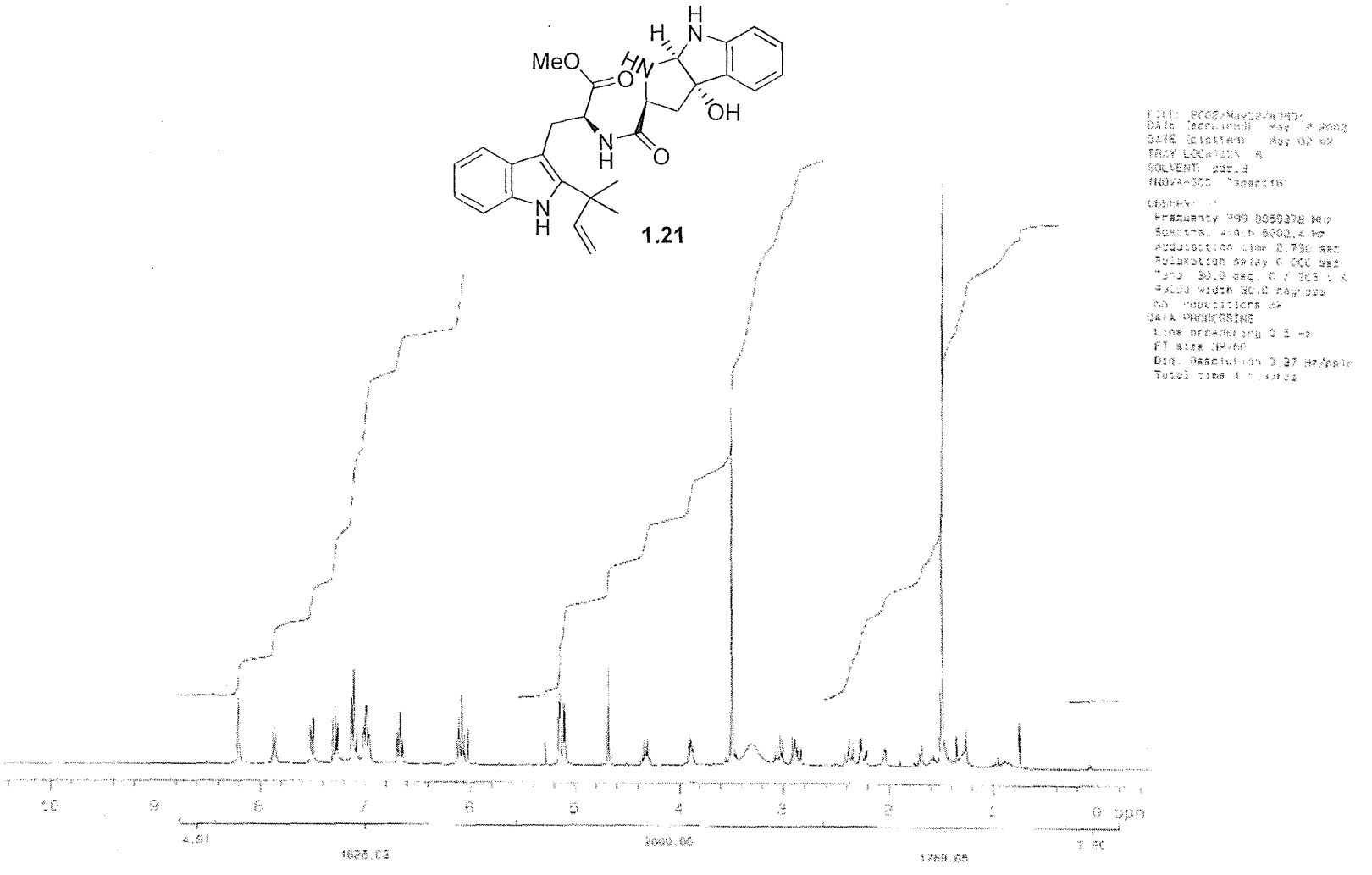


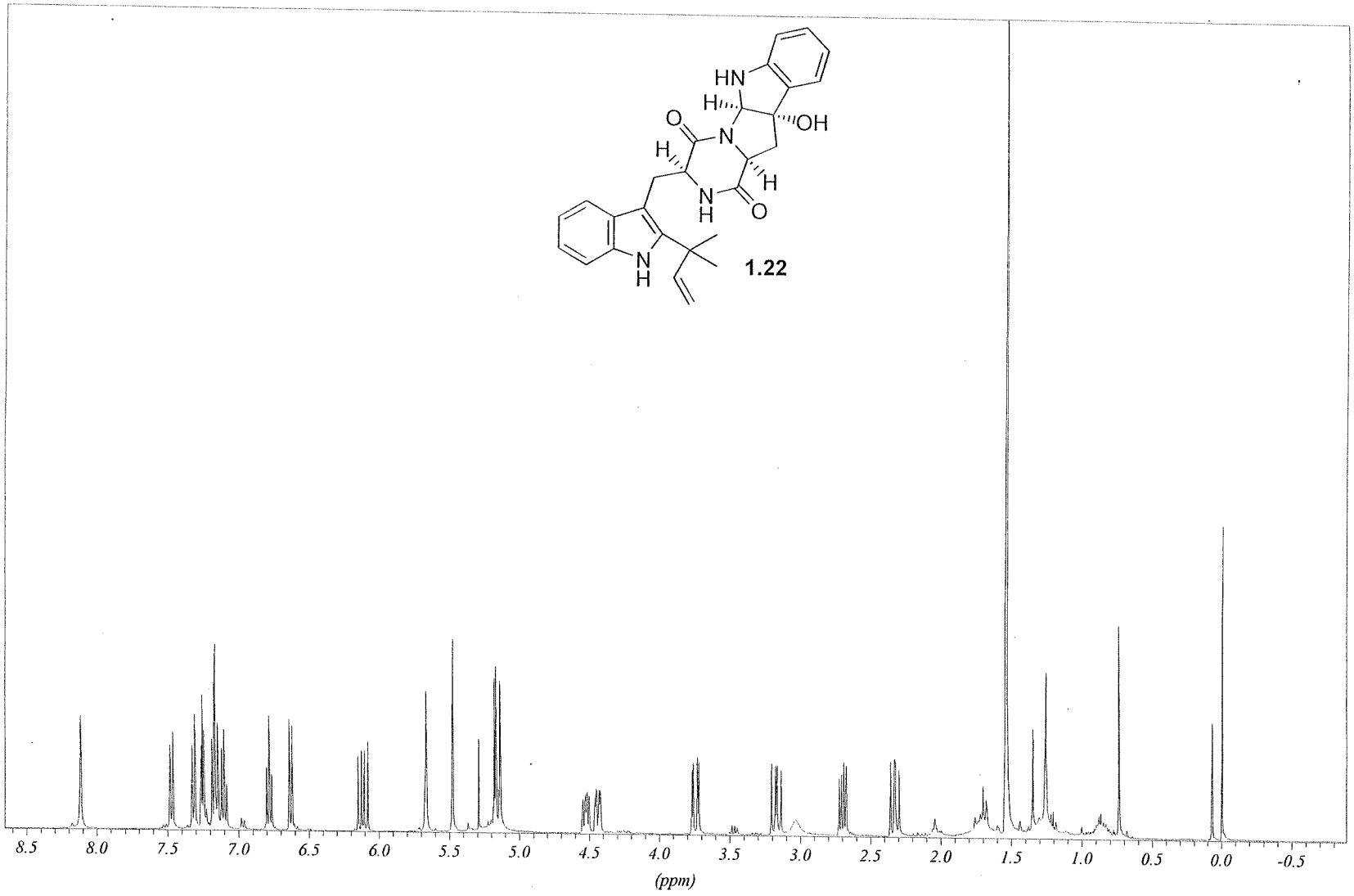
1.16

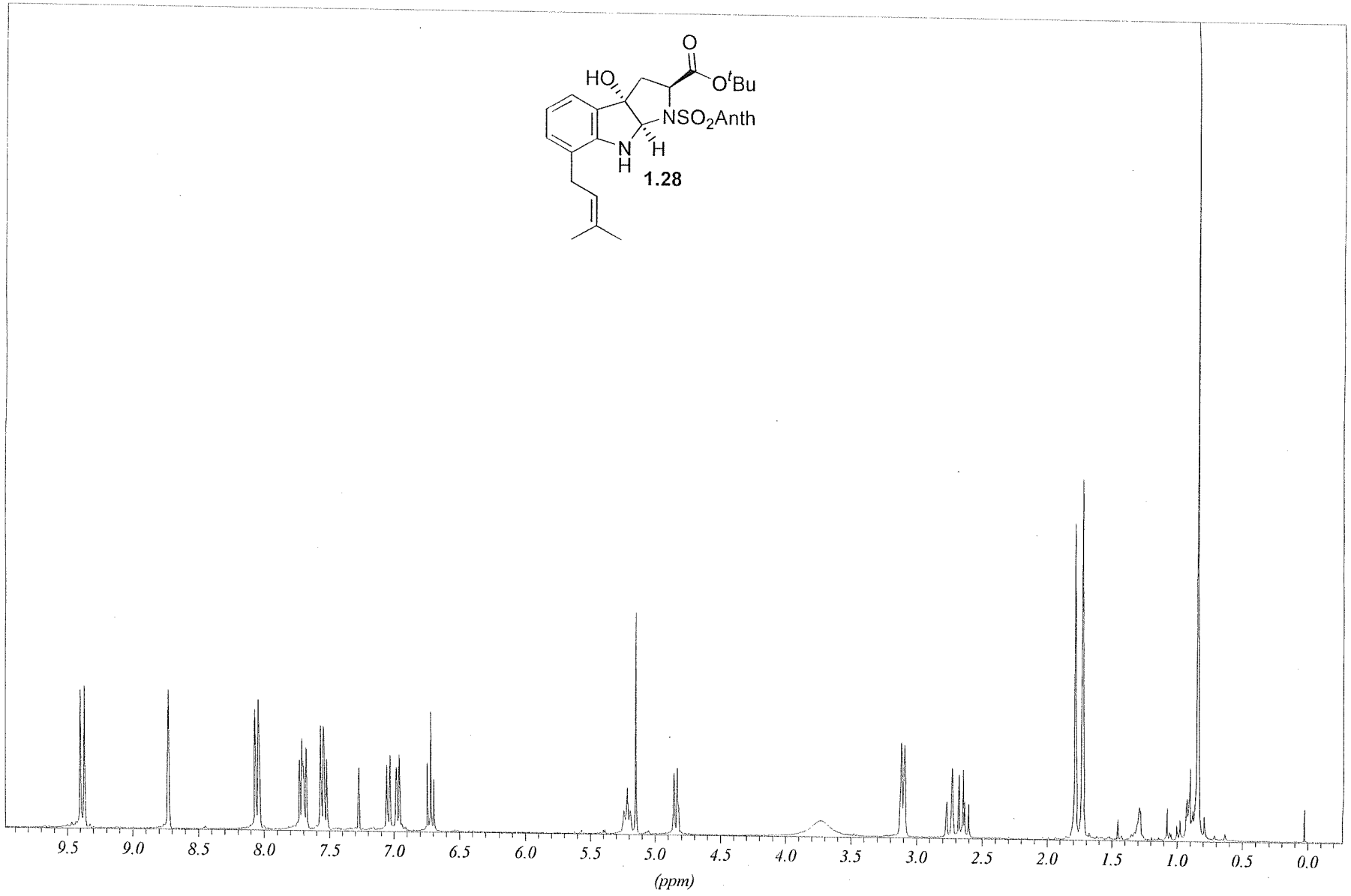


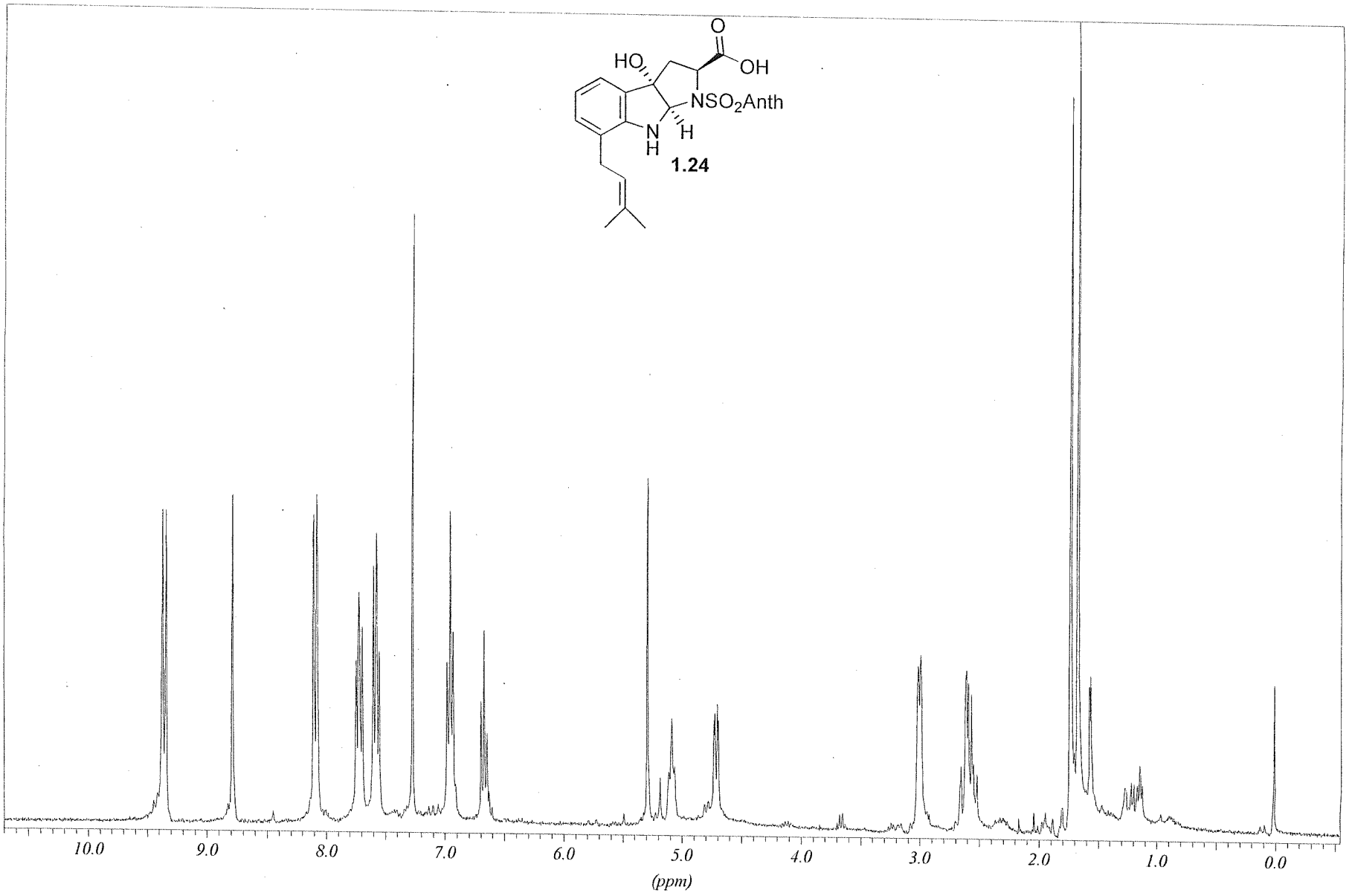
1.17

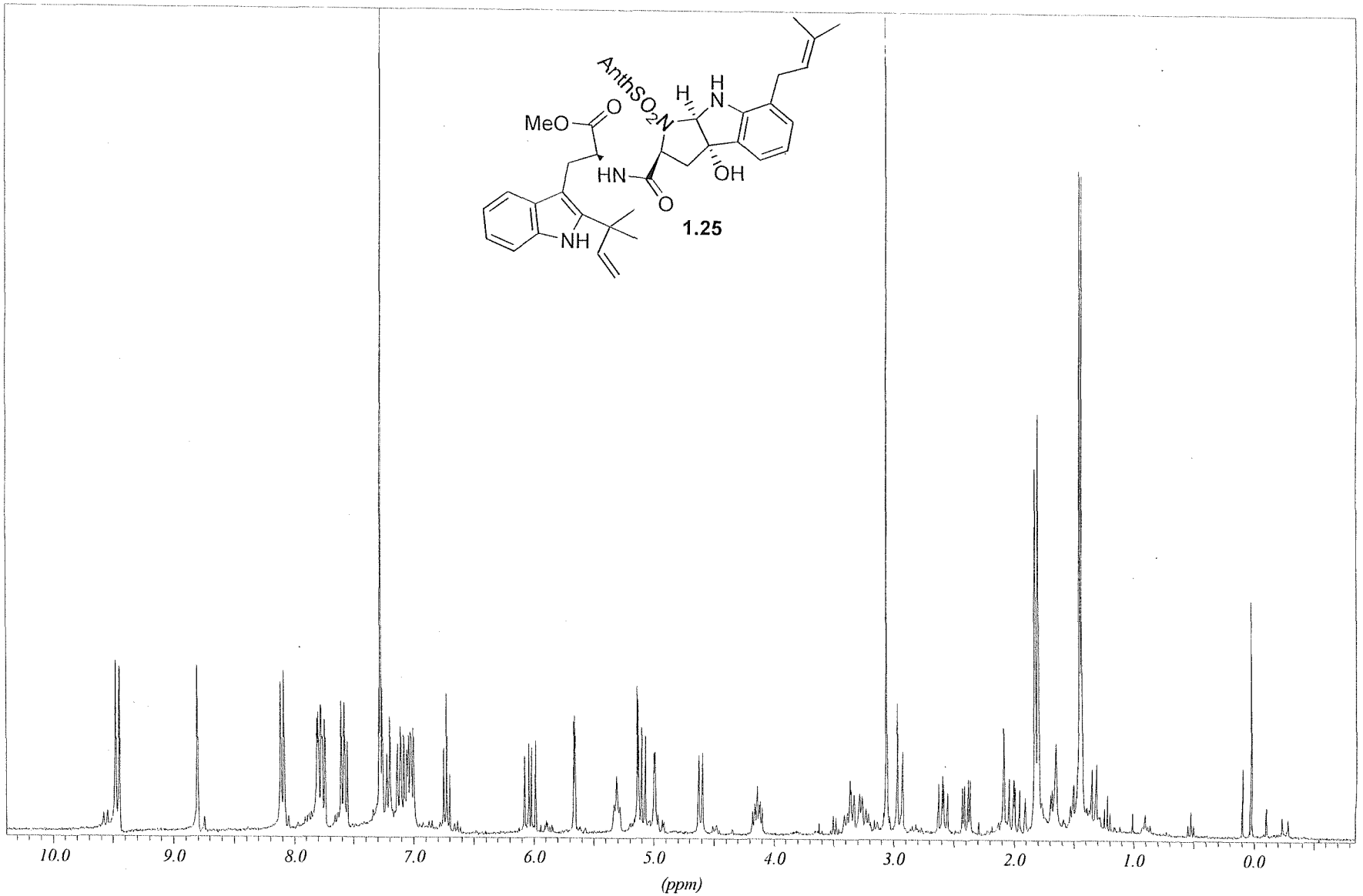

MeO
O
R
N
H
N
H
OH
O
N
H
R=SO2Anth
1.20
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

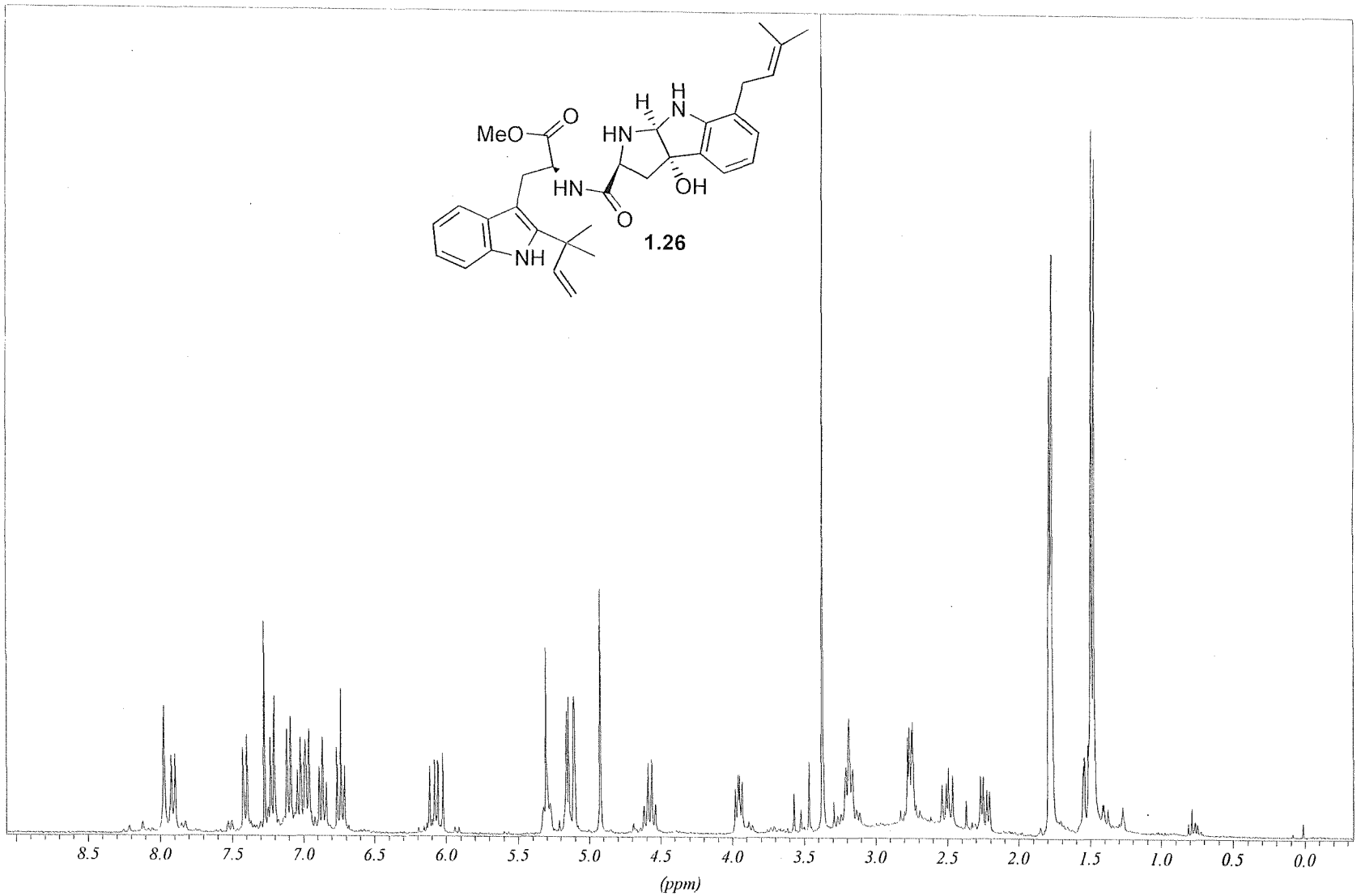

MeO
O
HN
H
N
H
N
H
N
O
OH
1.21
10
9
8
7
6
5
4
3
2
1
0 ppm
4.91
1625.03
2000.00
1788.65
7.80

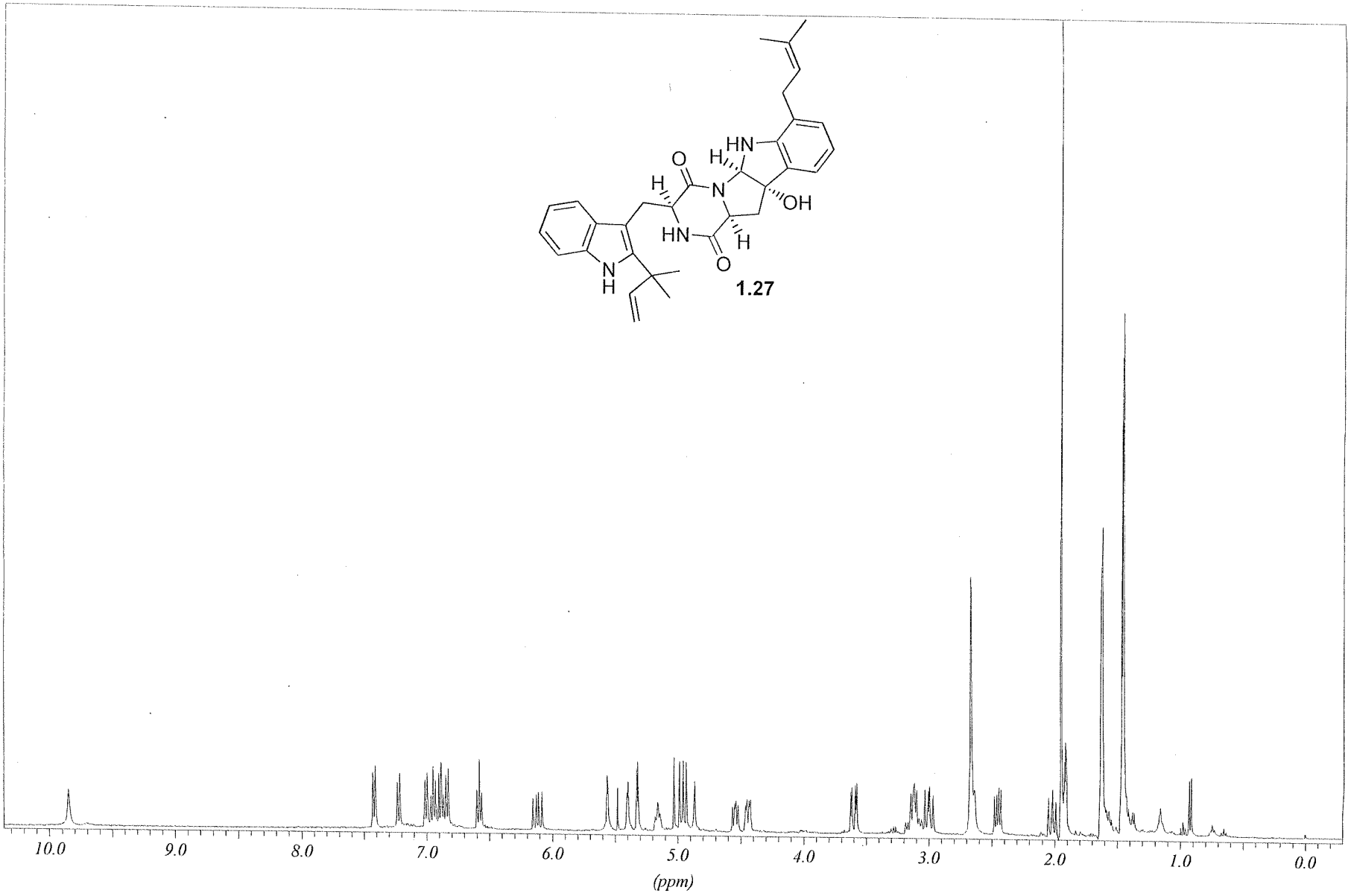

HN
H
OH
O
N
H
H
N
H
O
N
H
1.22
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


HO
O
O^{t}Bu
NSO$_2$Anth
N
H
H
1.28
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
(ppm)

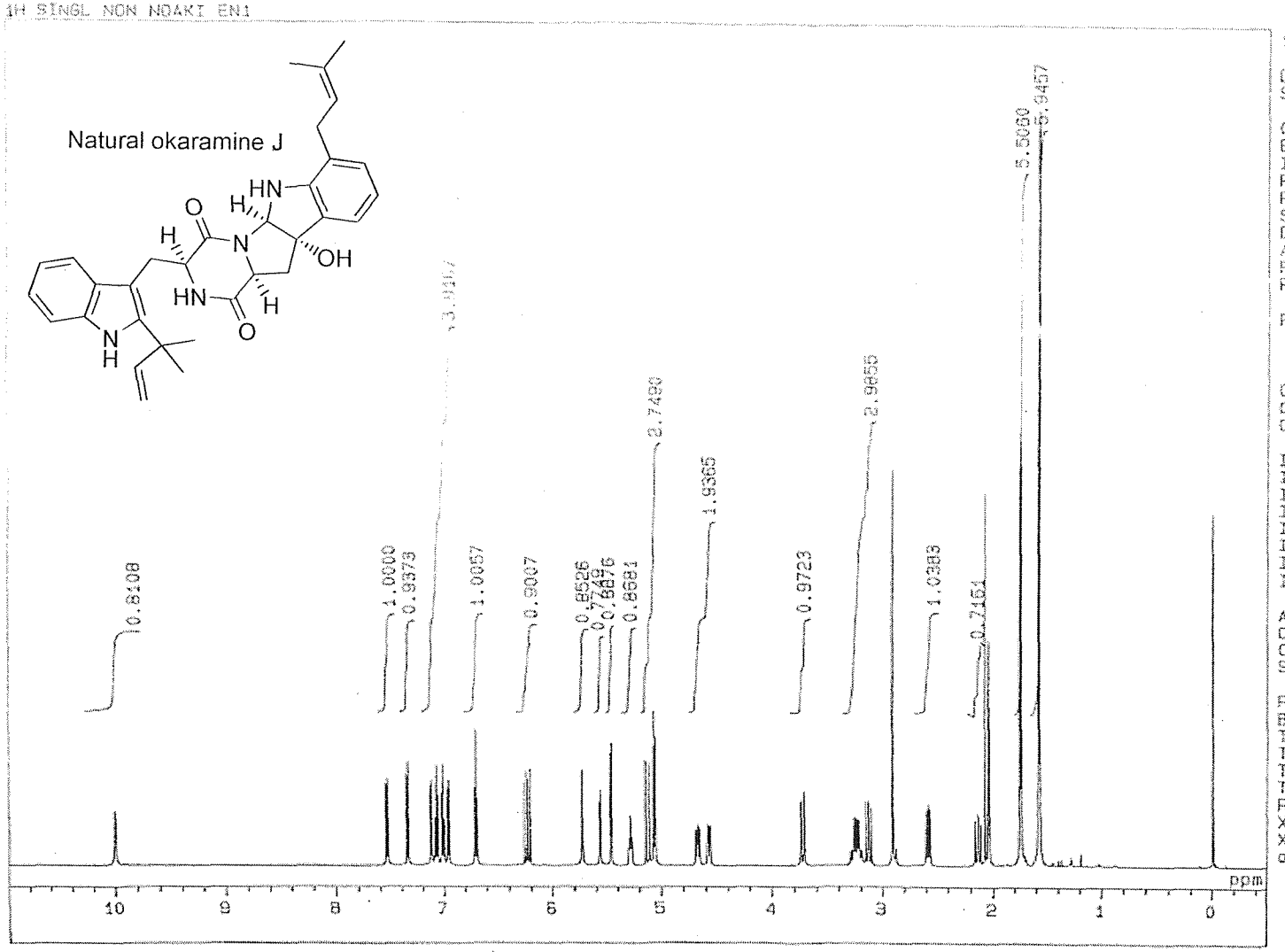

HO
O
OH
NSO2Anth
N
H
H
1.24
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


AnthSO2N
H
N
MeO
O
HN
O
OH
NH
1.25
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)


MeO
O
HN
H
N
HN
OH
O
NH
1.26
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
(ppm)


HN
H
O
H
N
OH
HN
H
O
N
H
1.27
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

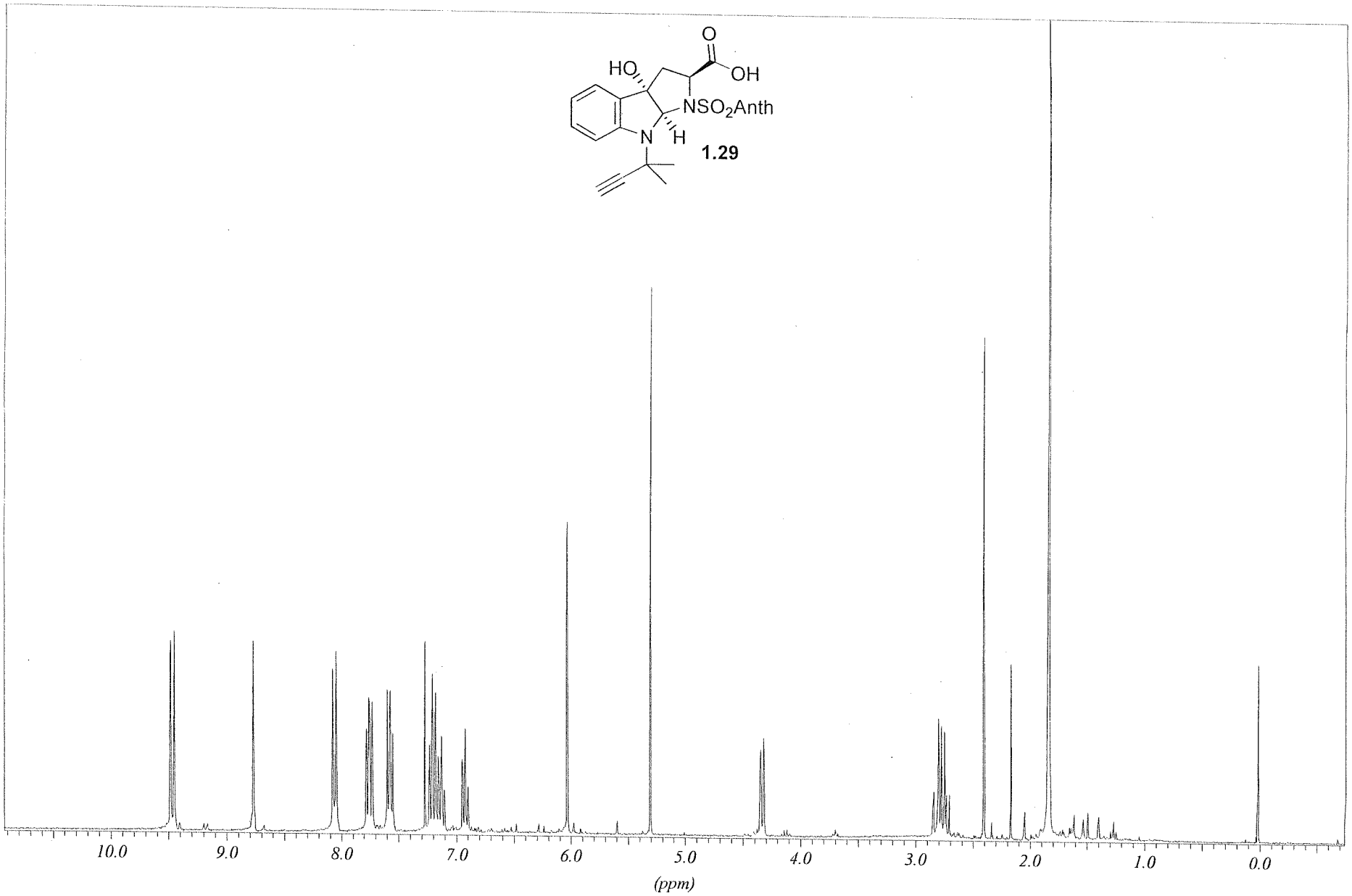
1H SINGL NON NOAKI EN1

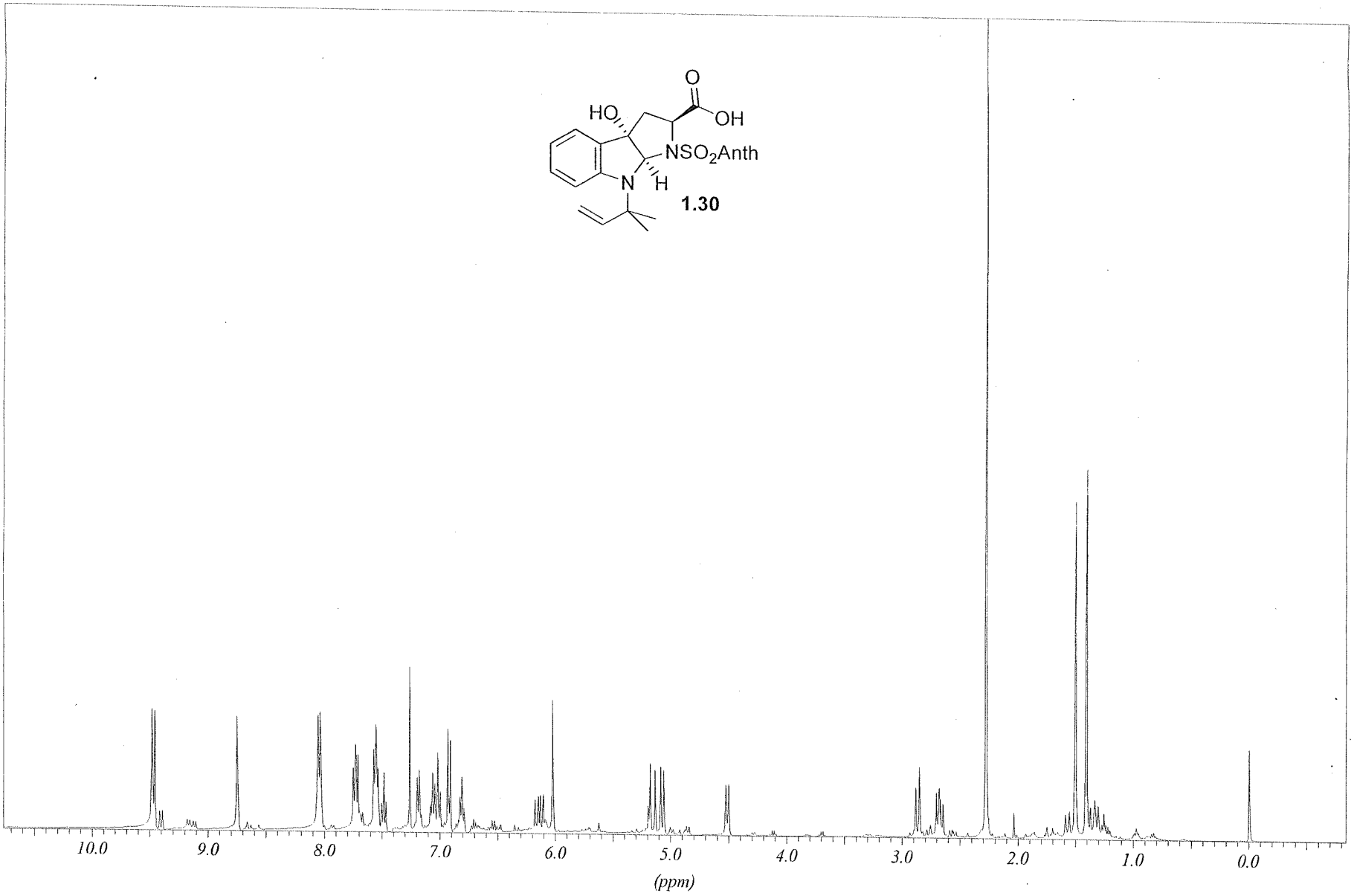


16-APR-1997 10:50:50.49

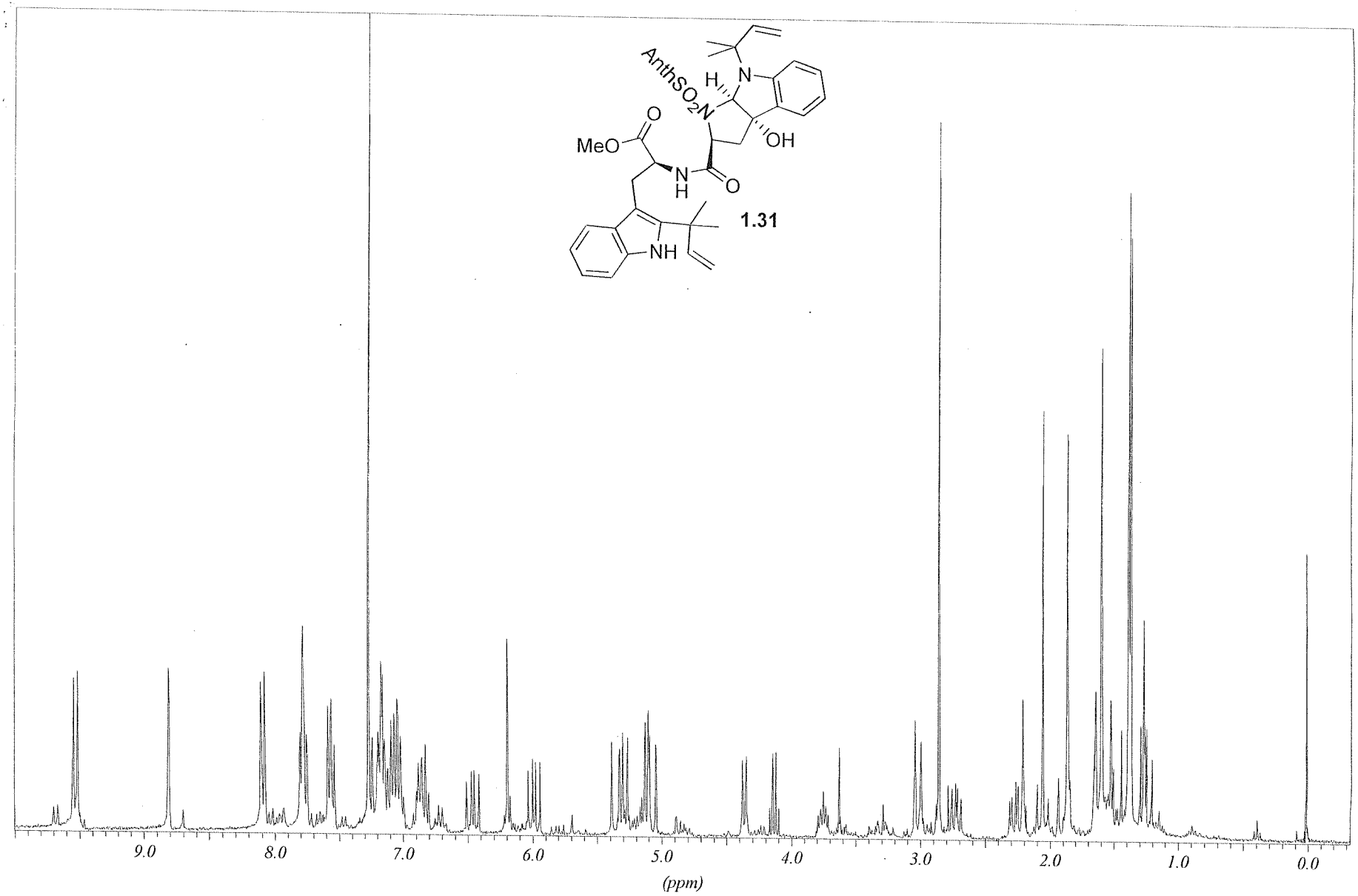
```
DFILE : ALPHA
SFILE : NOAKI2NON_E1

COMNT : 1H SINGL NON NOAKI EN1
EXMOD : SINGL
IRMOD : NON
POINT :    32768
FREQU : 10000.00 Hz
SCANS :       32
DUMMY :        4
ACQTM :    3.2768 sec
PD    :    3.7232 sec
RGAIN :       14

PW1   :   12.40 usec


OBNUC : 1H
OBFRQ :  500.00 MHz
OBSET : 162410.00 Hz

IRNUC : 1H
IRFRQ :  500.00 MHz
IRSET : 162410.00 Hz
IRATN :      511
IRRPW :    50.0 usec
IRBP1 :       21
IRBP2 :        6
IRRNS :        0

ADBIT :       16
CTEMP :     25.2 c
CSPED :       12 Hz
SLVNT : ACETN

RESOL :     0.31 Hz
BF    :     0.10 Hz
T1    :     0.00 %
T2    :     0.00 %
T3    :    90.00 %
T4    :   100.00 %
REFVL :     0.00 ppm
XE    :  5751.65 Hz
XS    :  -133.51 Hz
operator
```

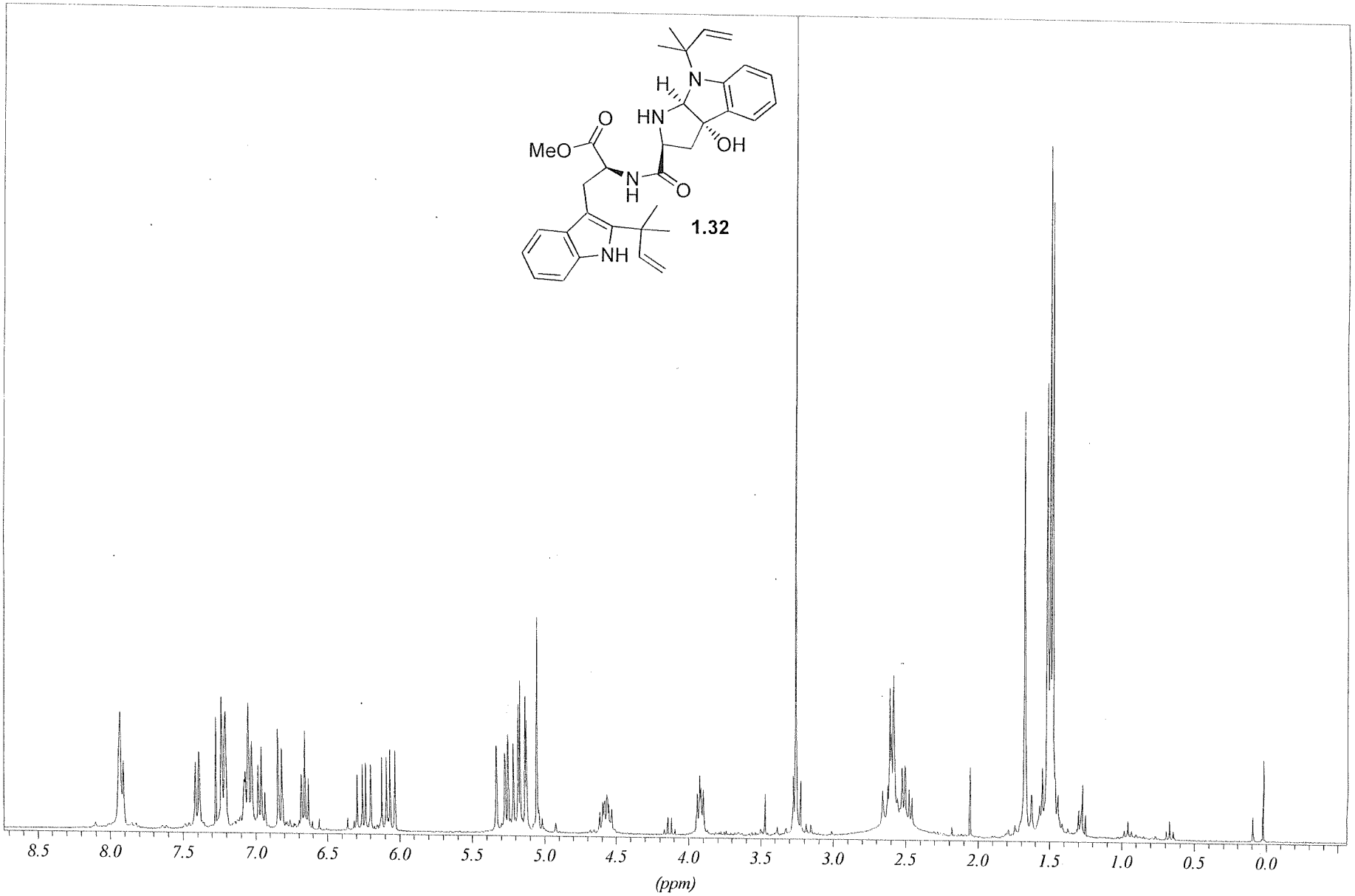
JR-3474-38



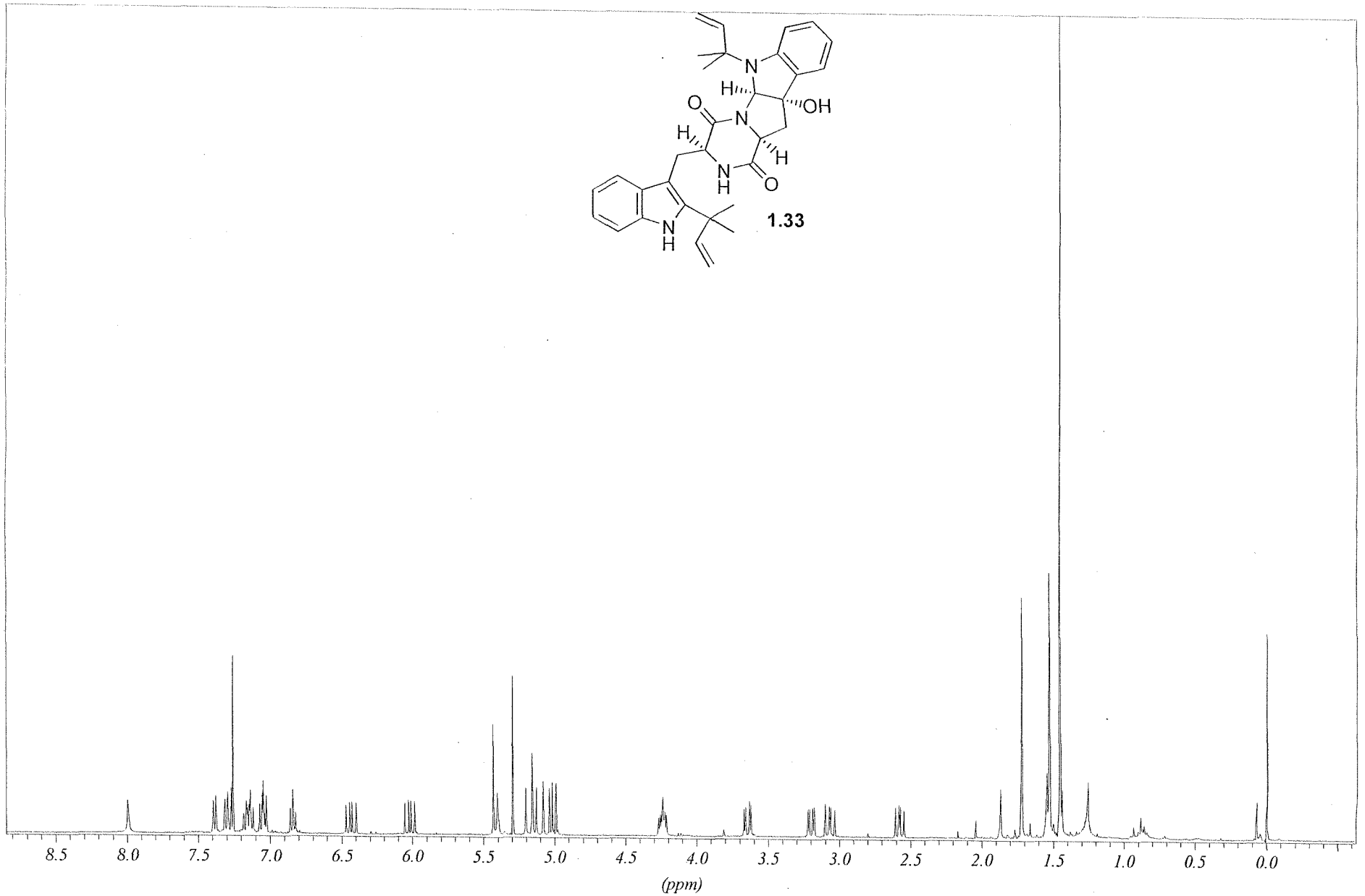

HO
O
OH
NSO2Anth
N
H
1.30
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)

JR-3474-40/2



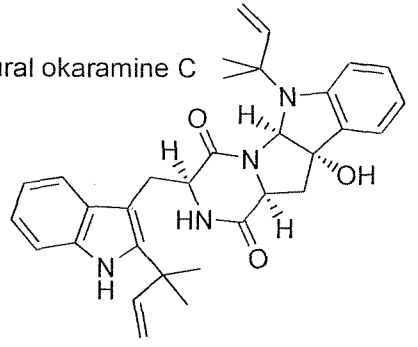

MeO
O
HN
OH
N
H
O
N
H
NH
1.32
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

JR-3474-47 okaramine C



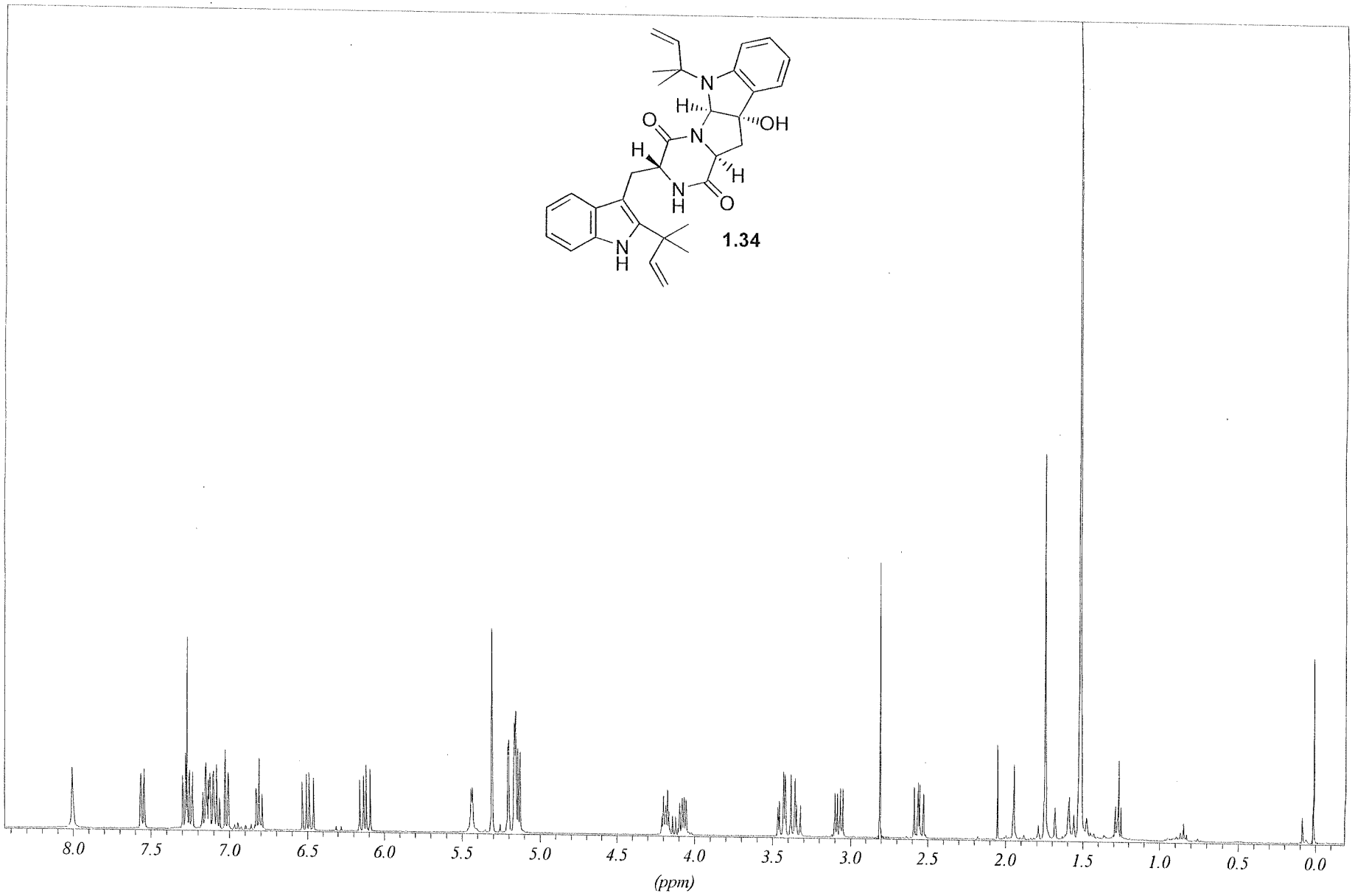
okaramine C/CDCl3

Natural okaramine C



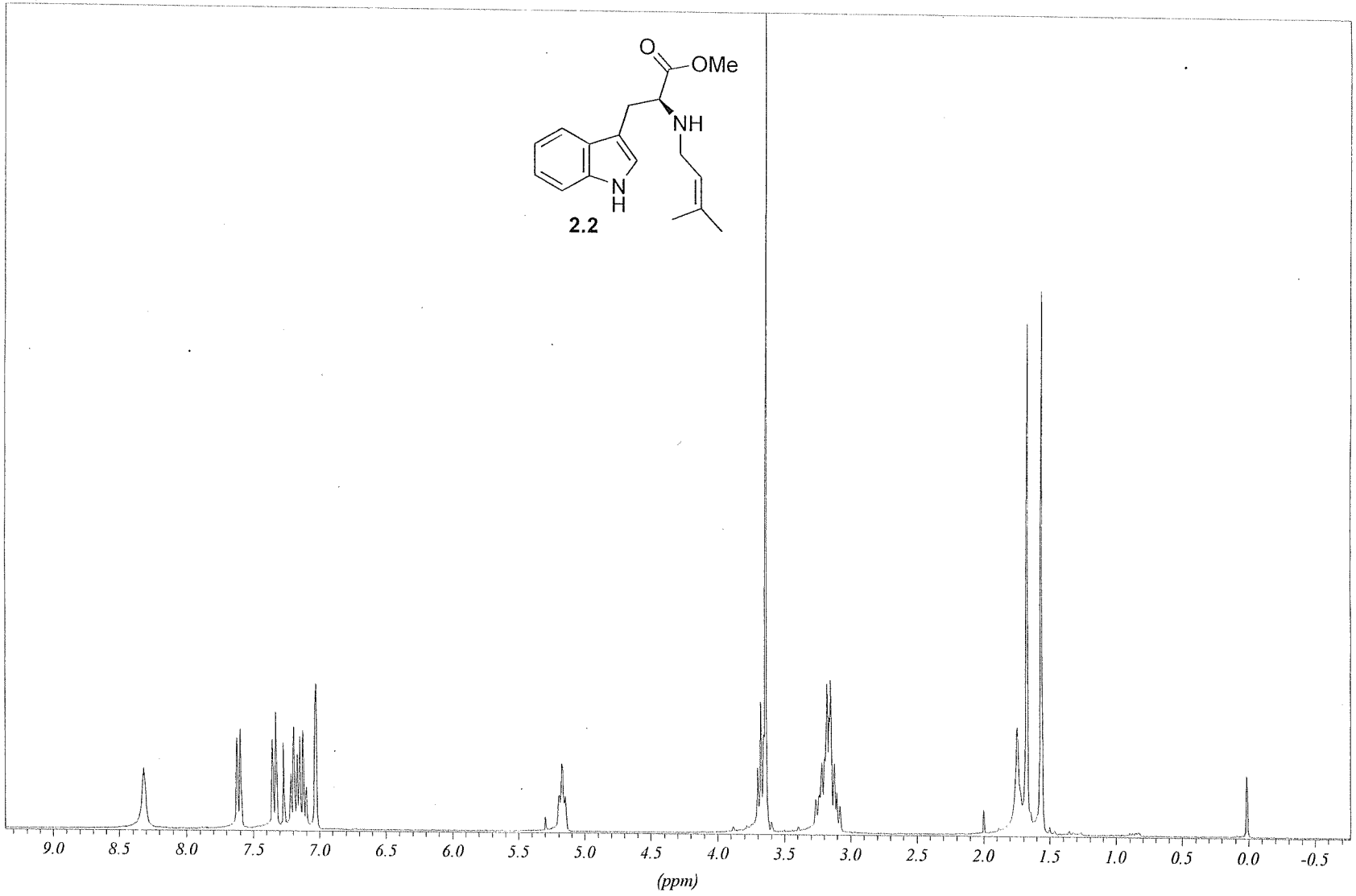

```
24-DEC-87 13:49:56
OBNUC 1H
OBFRQ          270.05 MHz
OBSET          112.00 kHz
OBFIN         5280.0 Hz
PW1              6.6 us
PW2             20.0 us
PW3             20.0 us
PI1           1.000 ms
PI2           1.000 ms
DEADT          116.7 us
PREDL        0.2000 ms
INIWT            1.0 sec
POINT          16384
SAMPO          16384
TIMES             90
SCANS             80
DUMMY              0
FREQU        5000.0 Hz
FILTR          2500 Hz
DELAY           80.0 us
ACQTM          1.638 sec
PD             0.600 sec
ADBIT     12
RGAIN     18
NGAIN             17
YG             18.92
BF              0.20 Hz
EXMOD SGNON
IRNUC 1H
IRFRQ          270.05 MHz
IRSET          112.00 kHz
IRFIN         5400.0 Hz
IRPW              50 us
MENUF N1H
DFILE DY:AHUA1HCL3
SHMFL CHS
SLVNT CDCL3
LKLEV            180
LGAIN             22
LKPHS              0 deg
LKSIG           1200
SPEED             15 Hz
COMNT AHU-A-1H-CDCL3
```

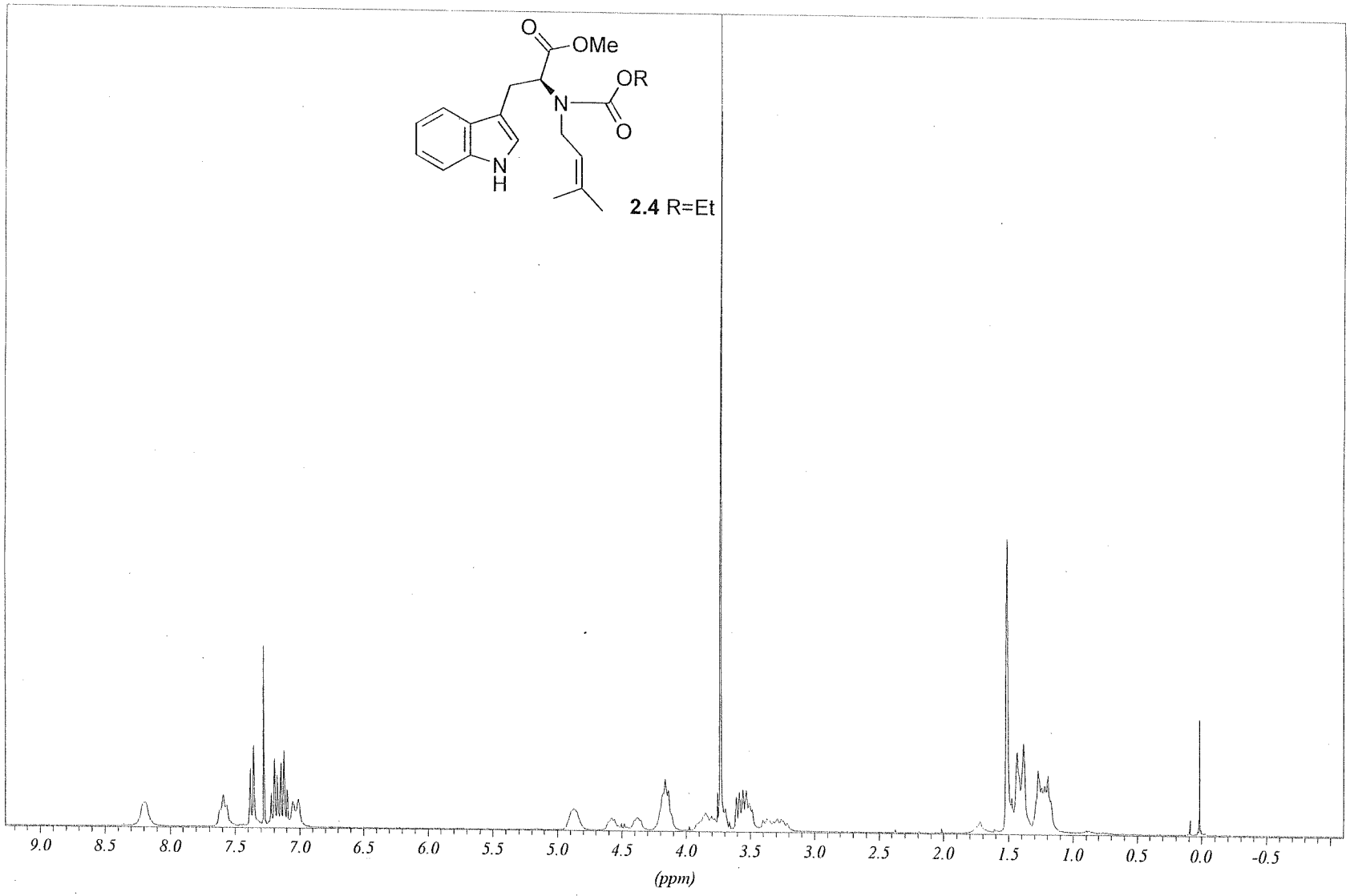
JR-3474-47b

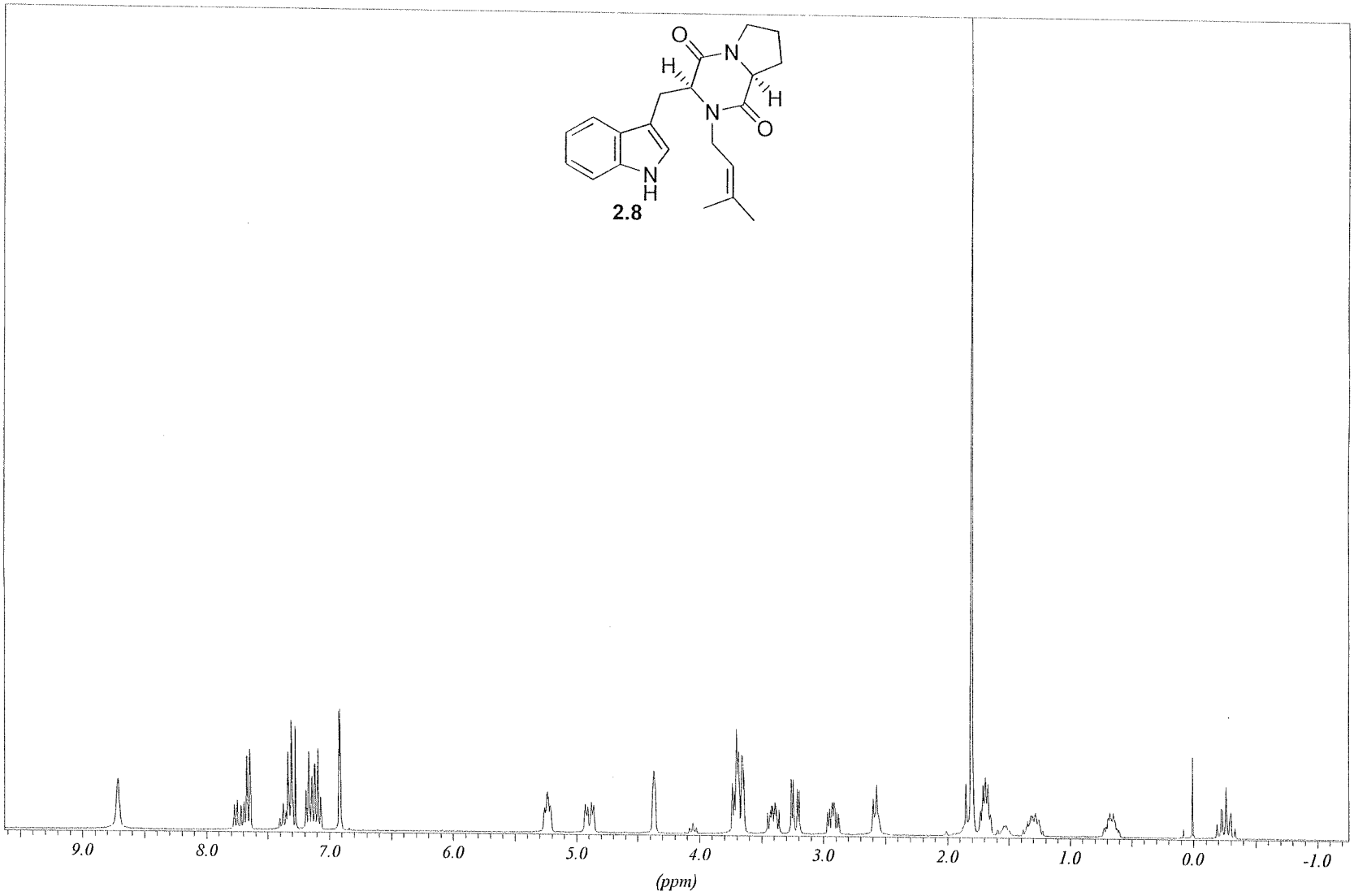


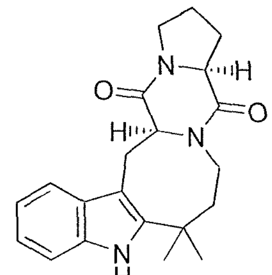
APPENDIX 2

^{1}H NMR Spectra for compounds in section 3.6

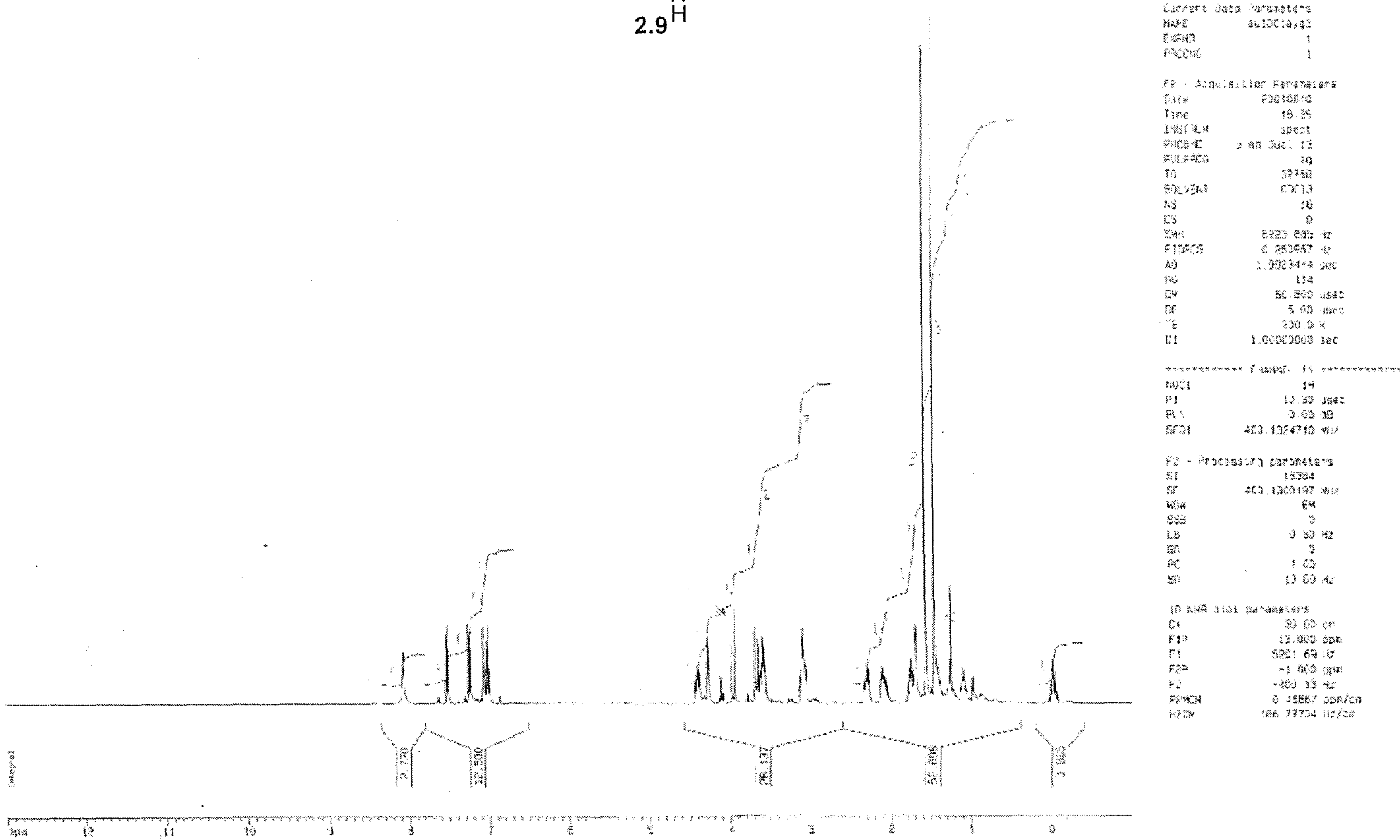

O
OMe
NH
N
H
2.2
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


O
OMe
OR
N
O
N
H
2.4 R=Et
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)


O
N
H
H
N
O
N
H
2.8
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0
(ppm)

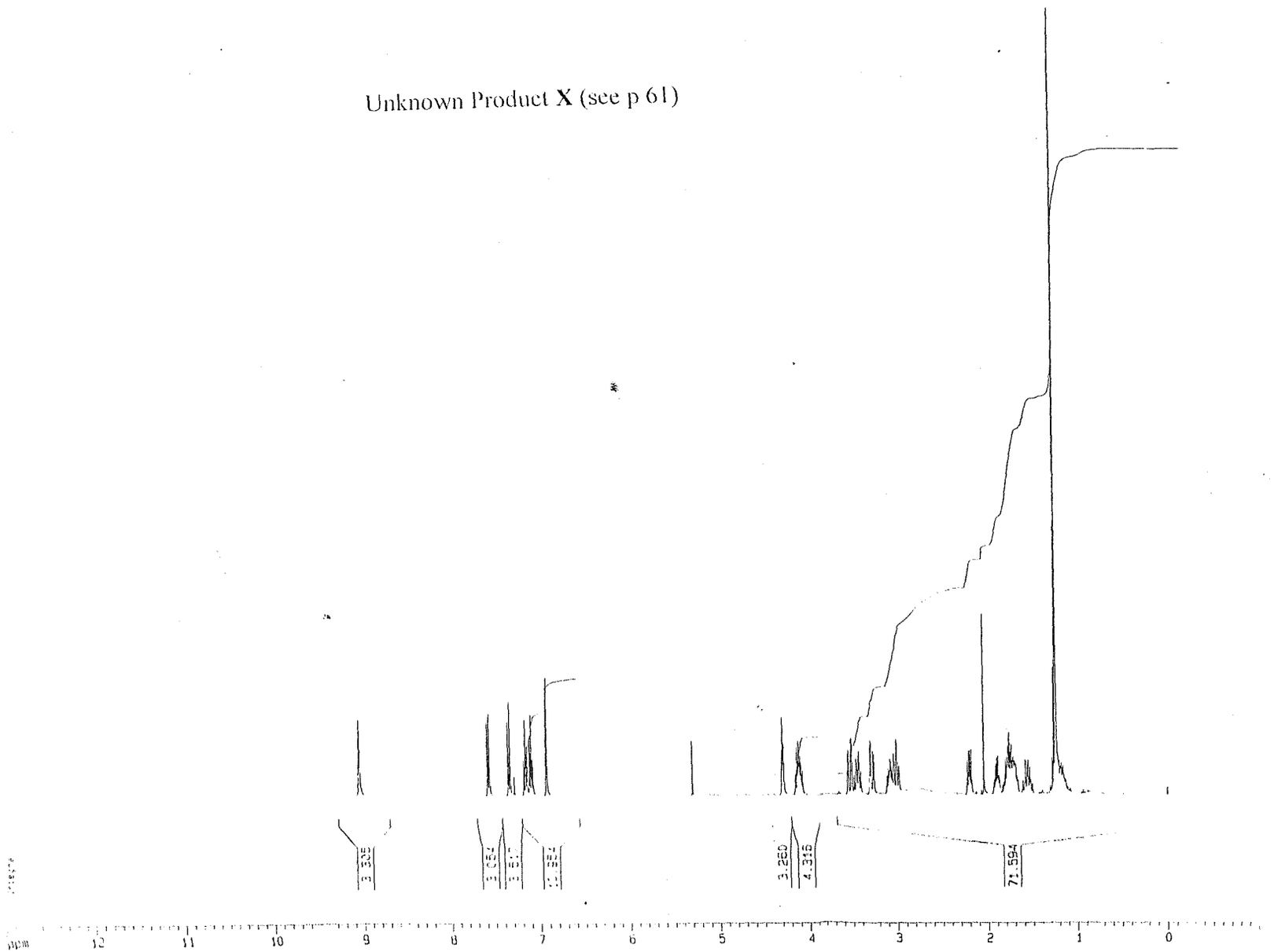


2.9

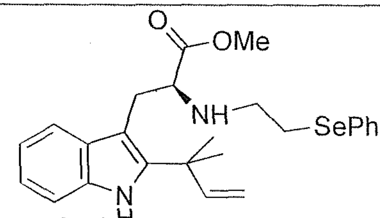

Current Data Parameters
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
INSTRUM spect
PULPROG zg
SOLVENT CDCl3
NS 16
DS 0
F2 - Processing parameters
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1D NMR plot parameters
F2P -1.000 ppm
ppm

JR-2878-238

Unknown Product **X** (see p 61)

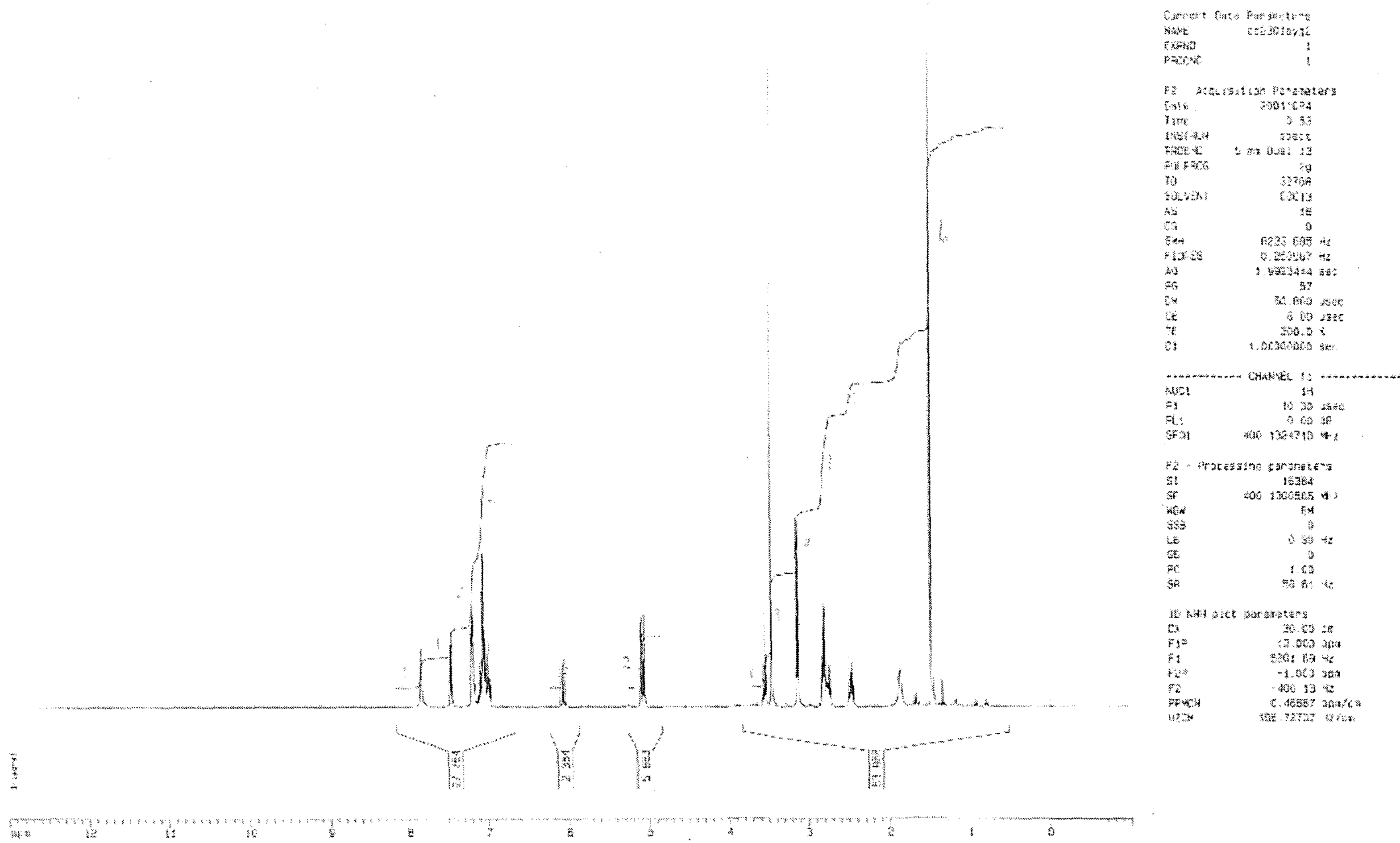



```
Current Data Parameters
NAME                  jy1101ayg4
EXPNO                          1
PROCNO                         1

F2 - Acquisition Parameters
Date_                  20010712
Time                       0.49
INSTRUM                   spect
PROBHD          5 mm Dual 13
PULPROG                      zg
TD                        32768
SOLVENT                   CDCl3
NS                            16
DS                             0
SWH                 6223.665 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                  400.130013[illegible] MHz
WDW                           [illegible]
SSB
LB                            [illegible] Hz
GB
PC                         1.[illegible]
SR                        13.1[illegible] Hz

1D NMR plot parameters
CX                        30.00 cm
F1P                      13.000 ppm
F1                     5201.65 Hz
F2P                      -1.000 ppm
F2                      400.13 Hz
PPMCM                 0.46667 ppm/cm
HZCM                186.72734 Hz/cm
```

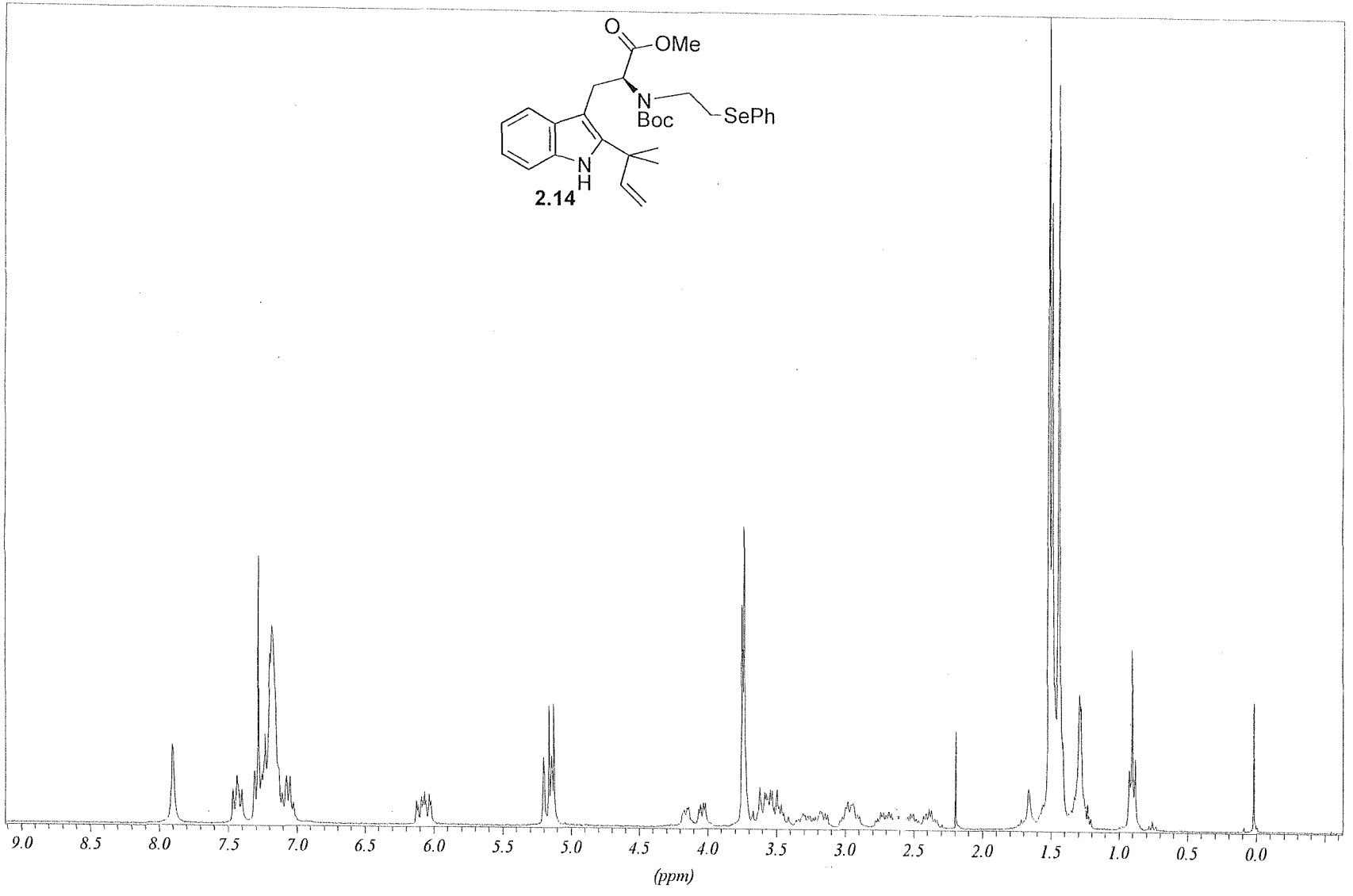


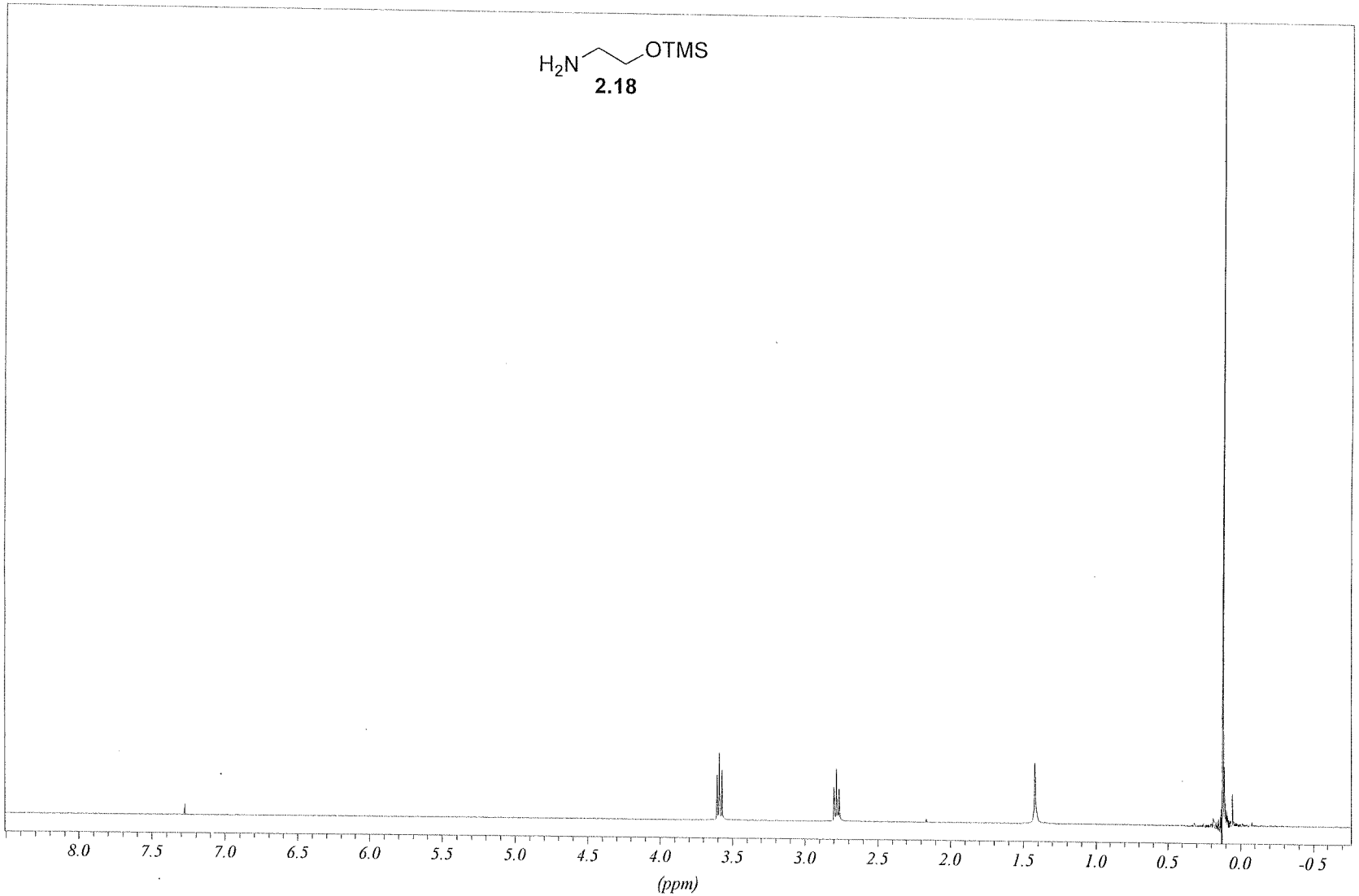
OMe
NH
SePh
N
H

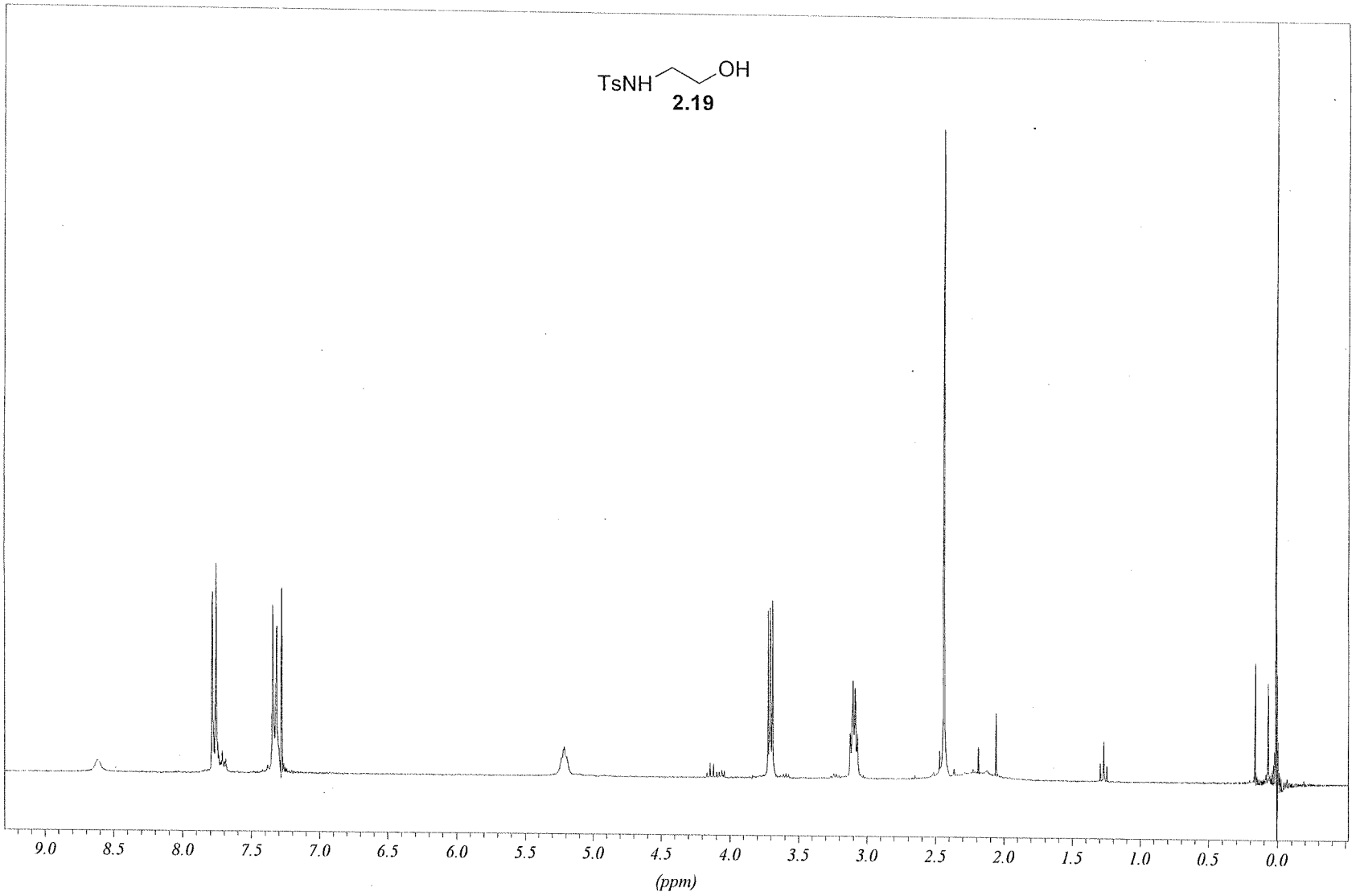
2.11

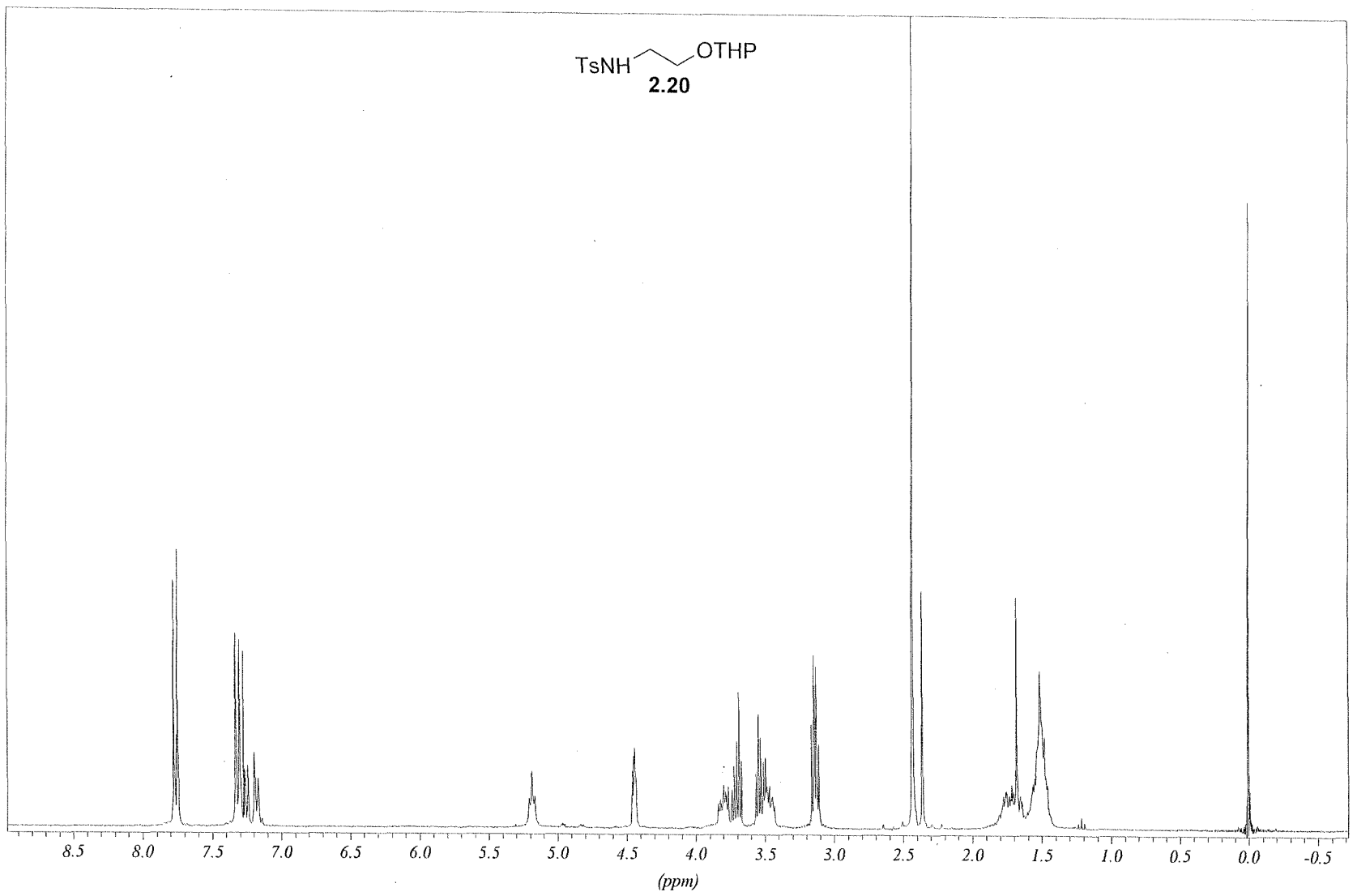


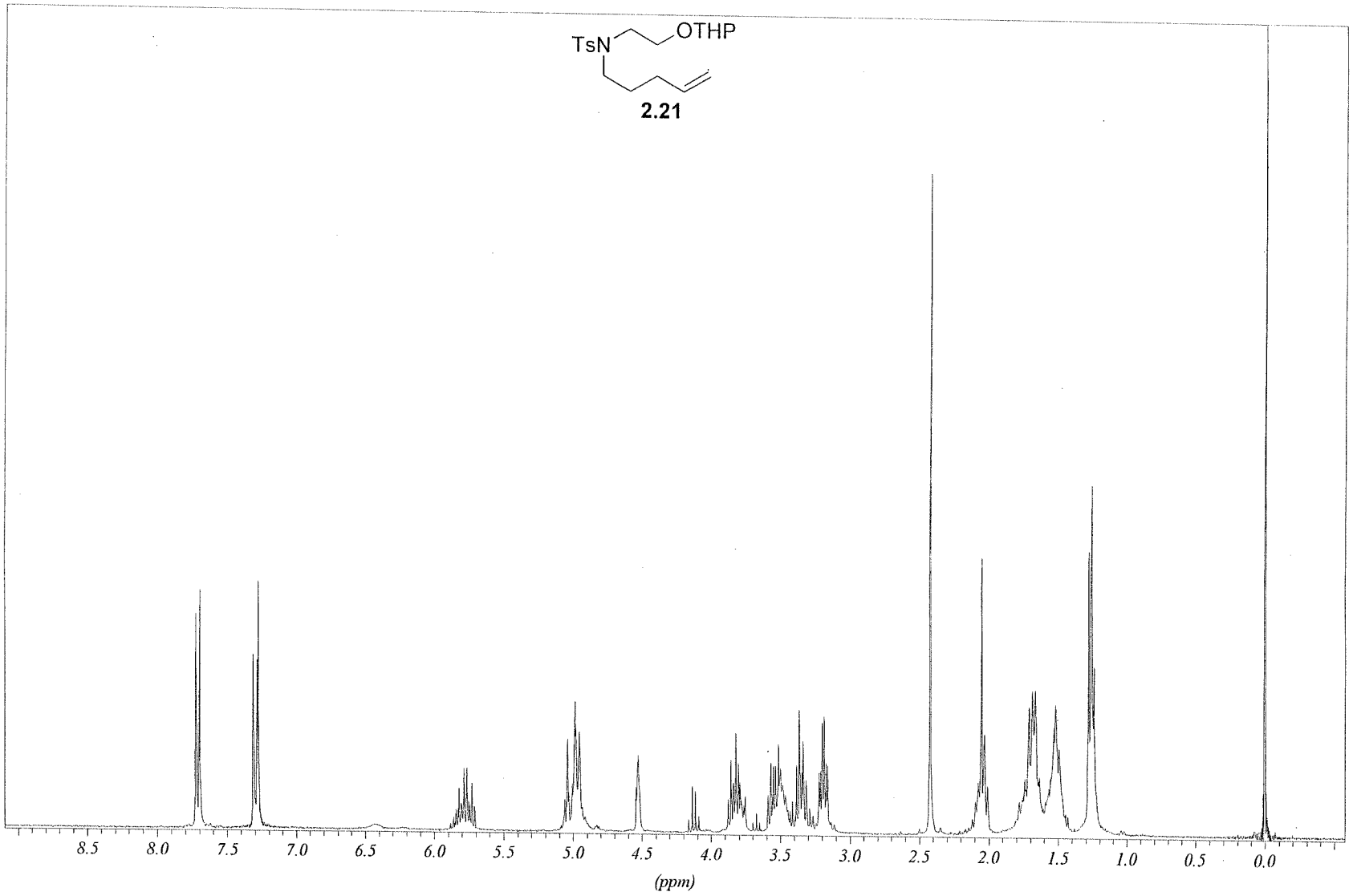
Current Data Parameters
F2 - Acquisition Parameters
CHANNEL f1
F2 - Processing parameters
1D NMR plot parameters
ppm
12
11
10
9
8
7
6
5
4
3
2
1
0

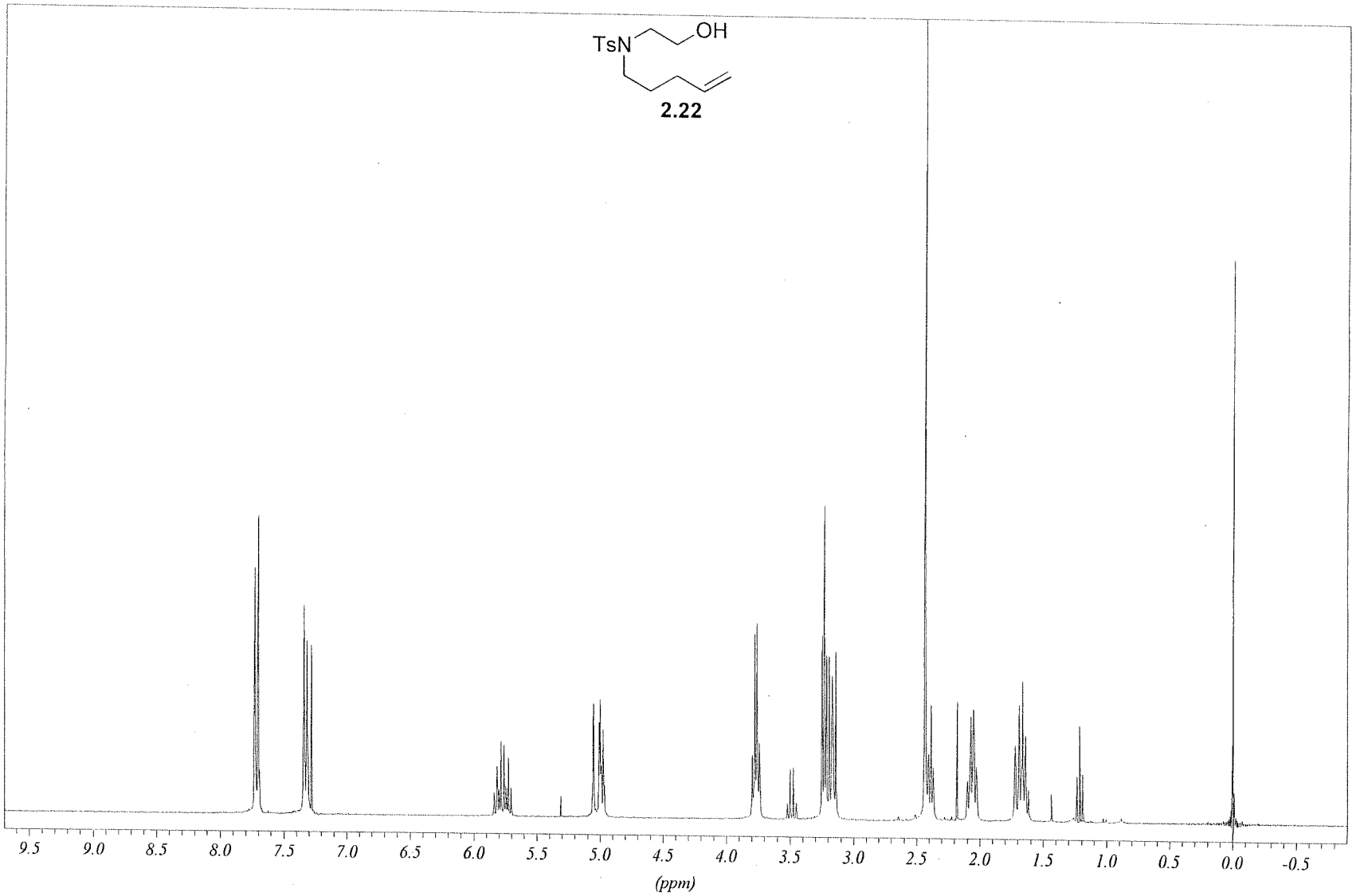

O
OMe
N
Boc
SePh
N
H
2.14
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

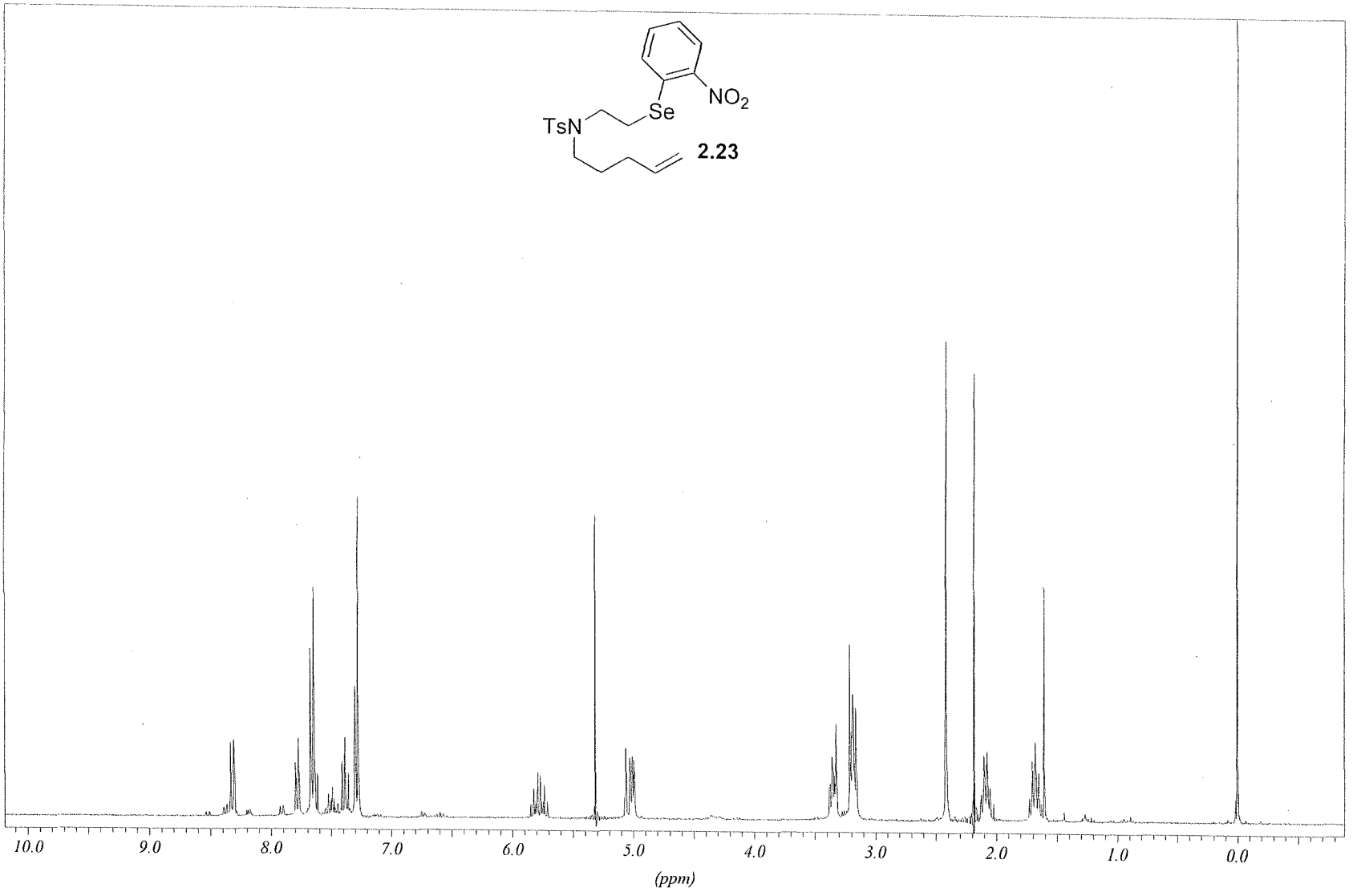

H2N
OTMS
2.18
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0 5
(ppm)

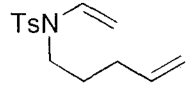

TsNH
OH
2.19
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


TsNH
OTHP
2.20
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)

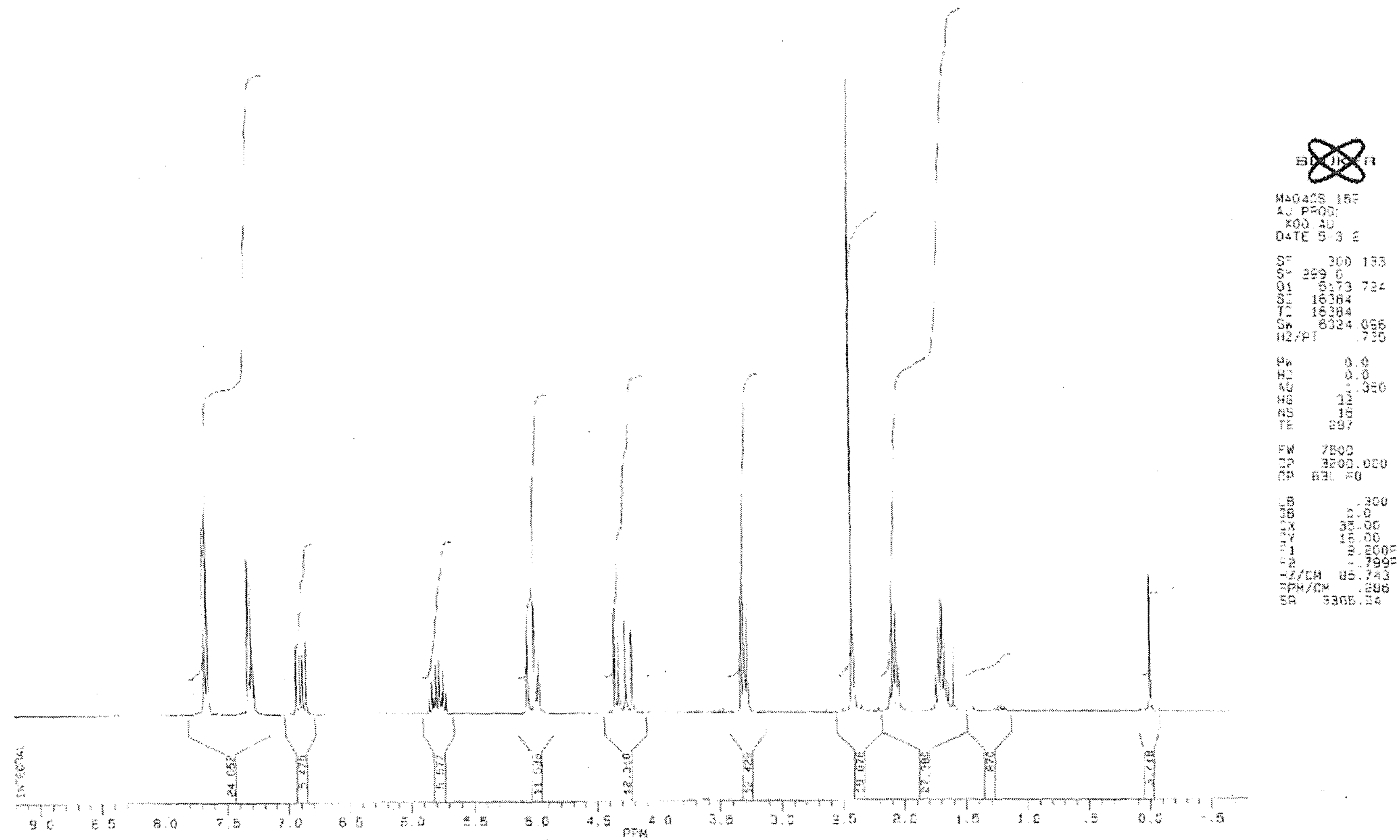

TsN
OTHP
2.21
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)

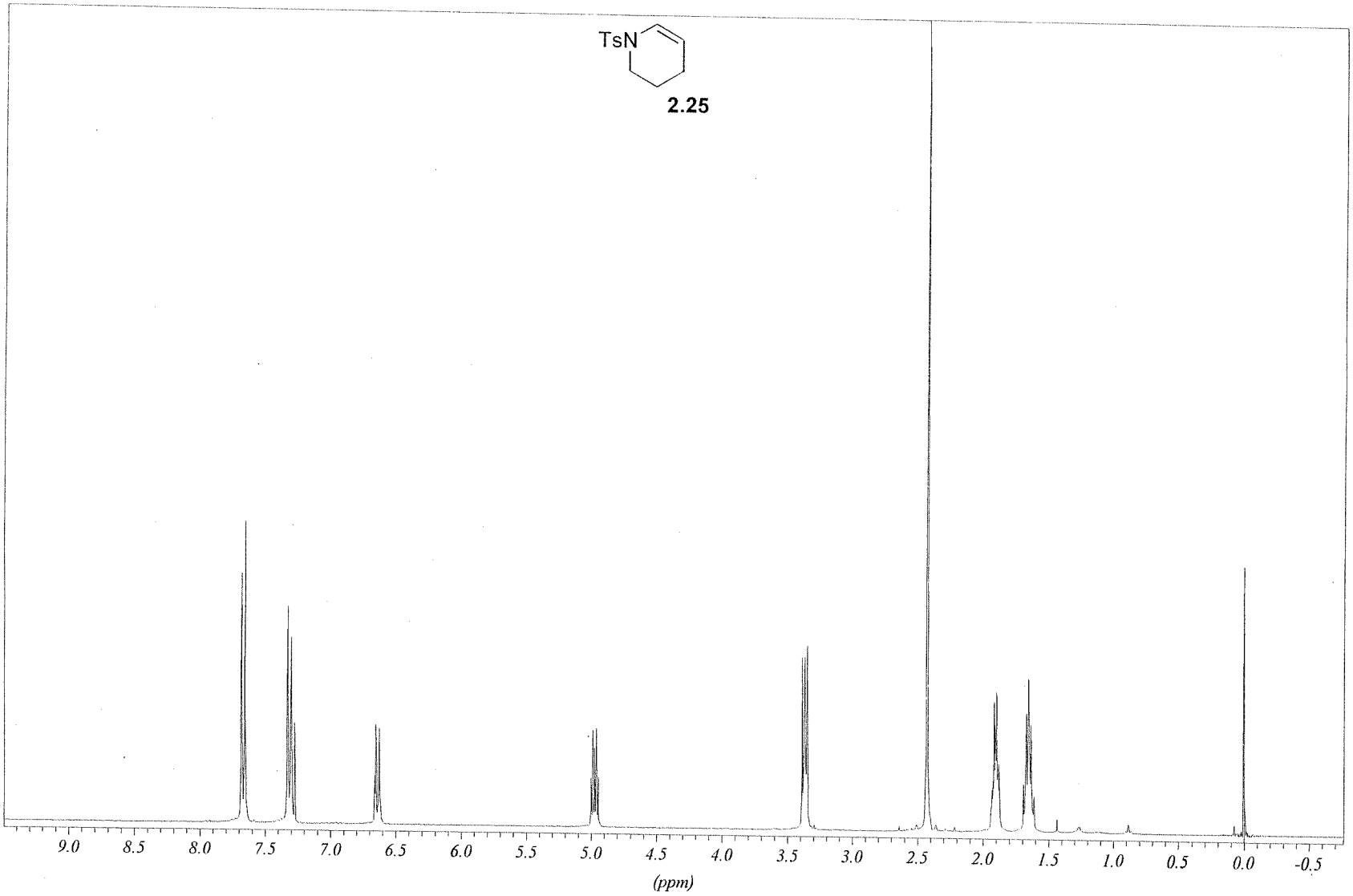

TsN
OH
2.22
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)

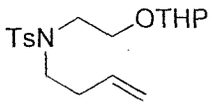

NO2
Se
TsN
2.23
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
(ppm)



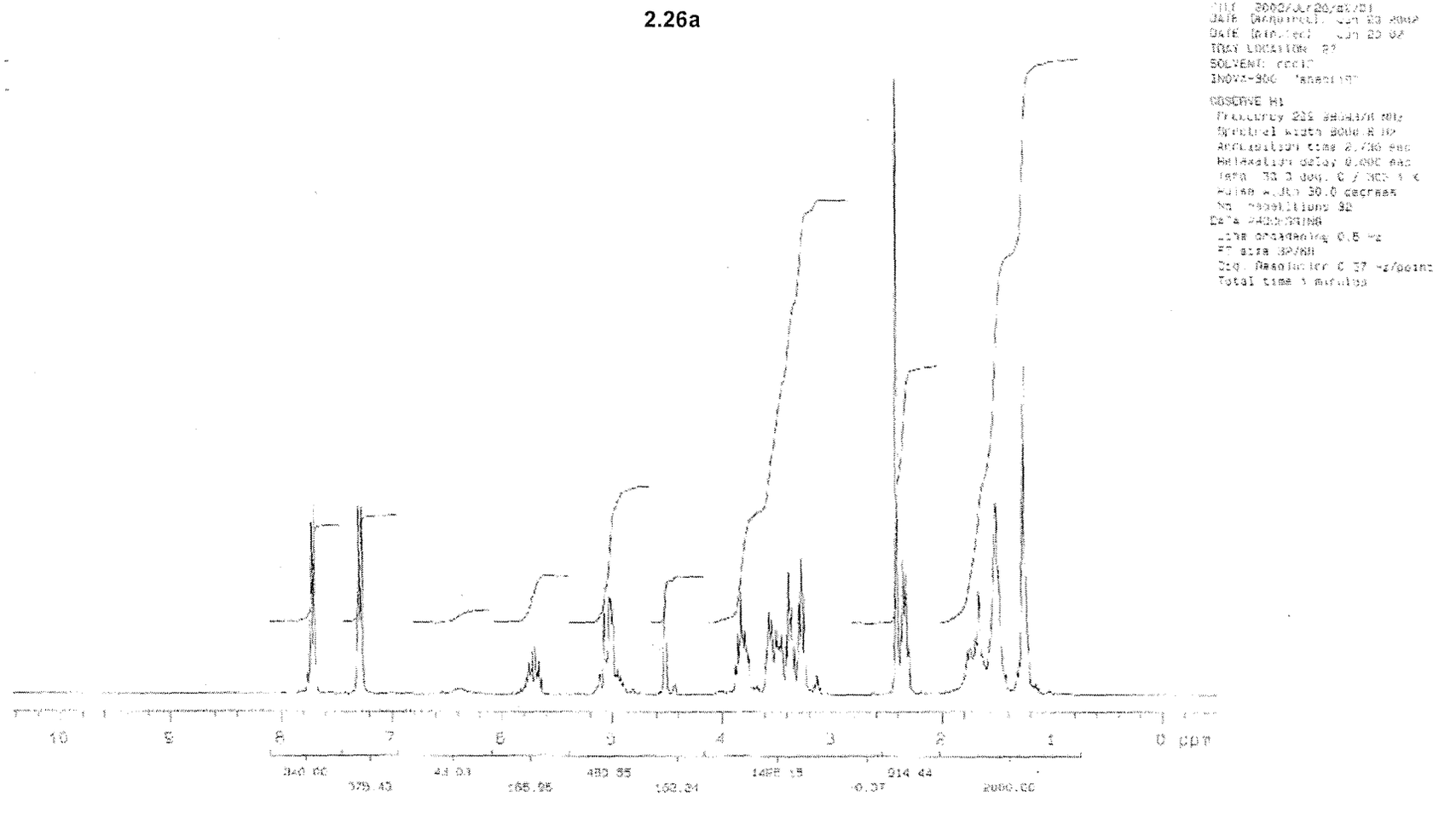
2.24

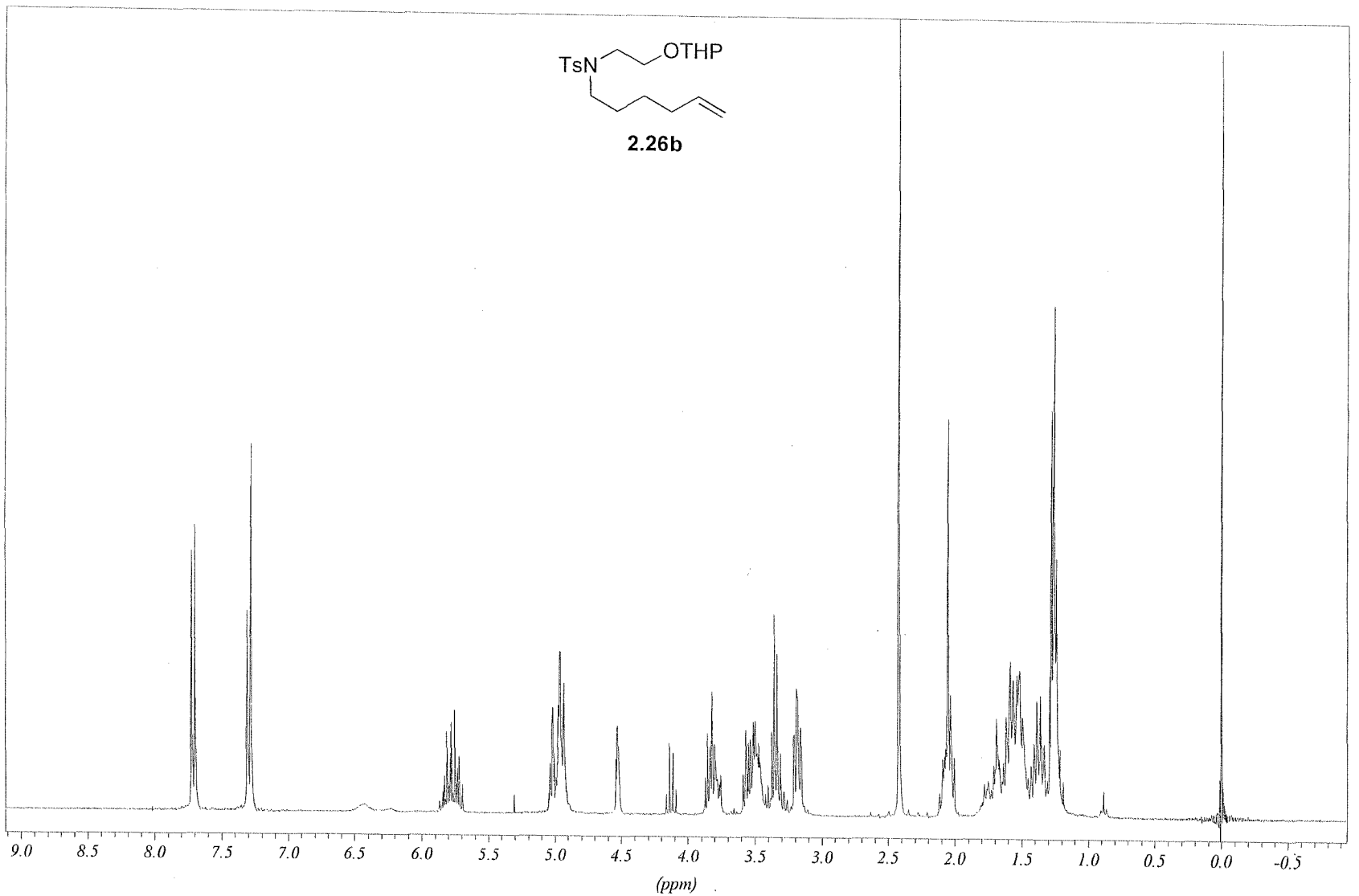


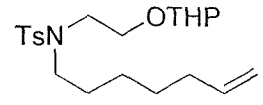

TsN
2.25
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)



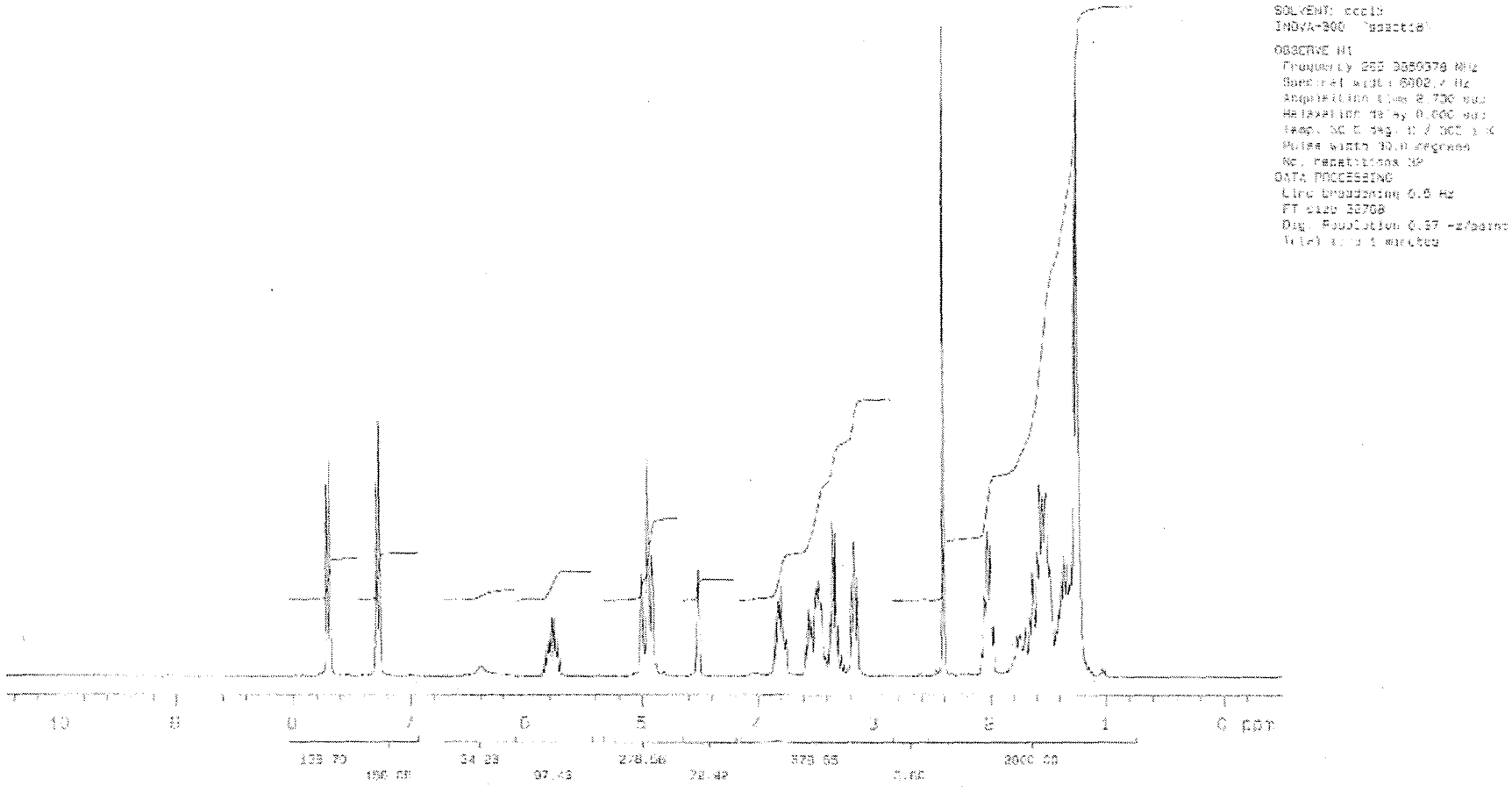
2.26a

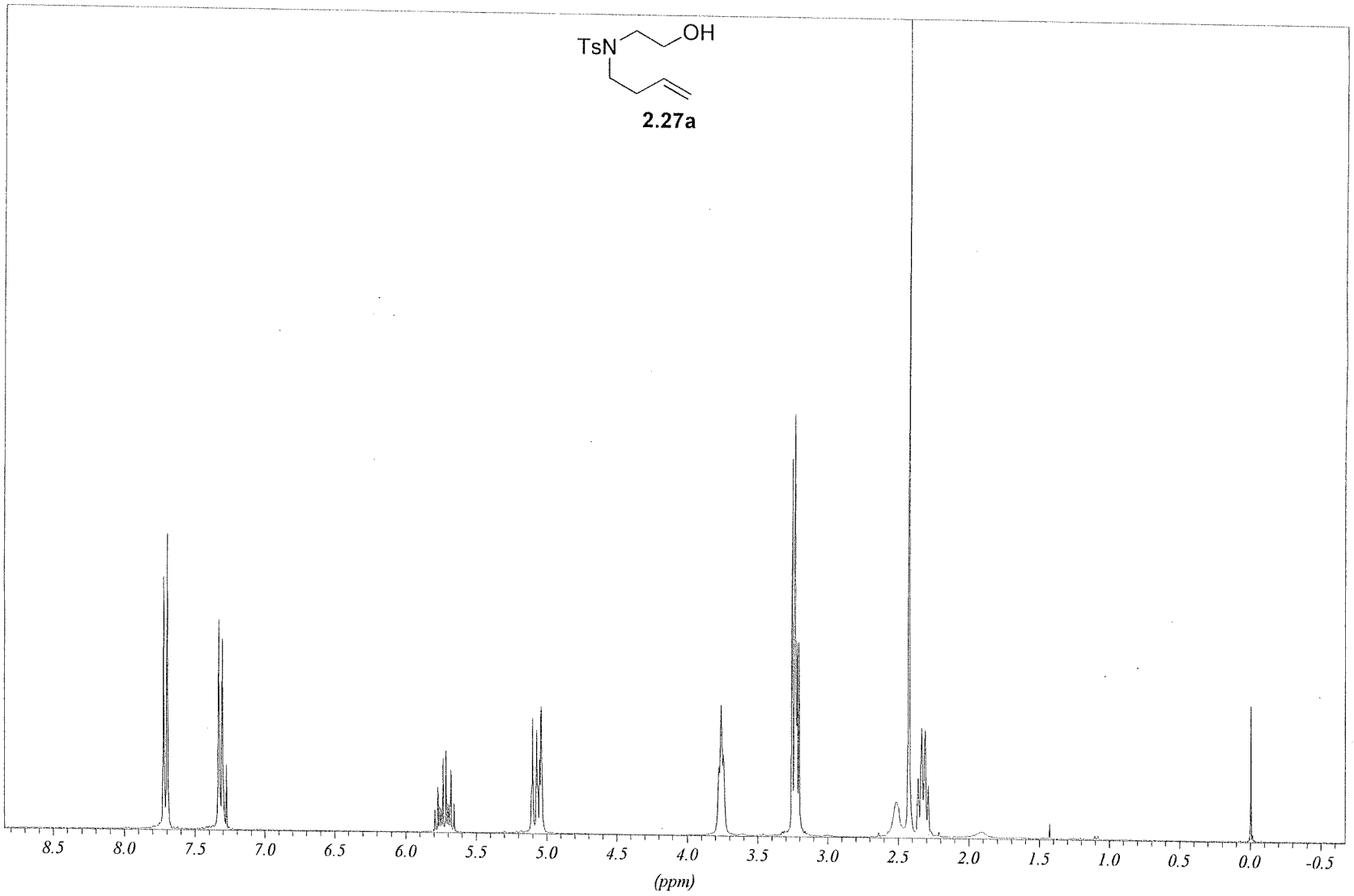


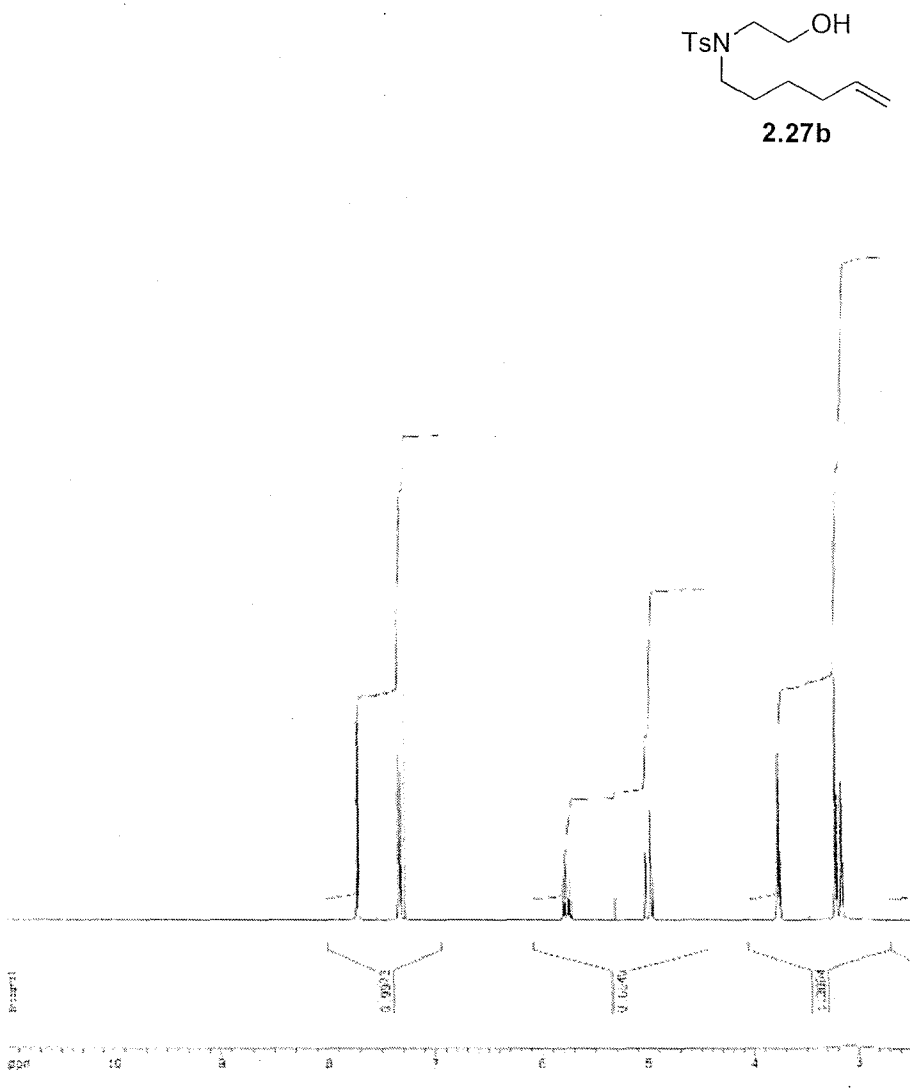

TsN
OTHP
2.26b
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


TsN
OTHP

2.26c

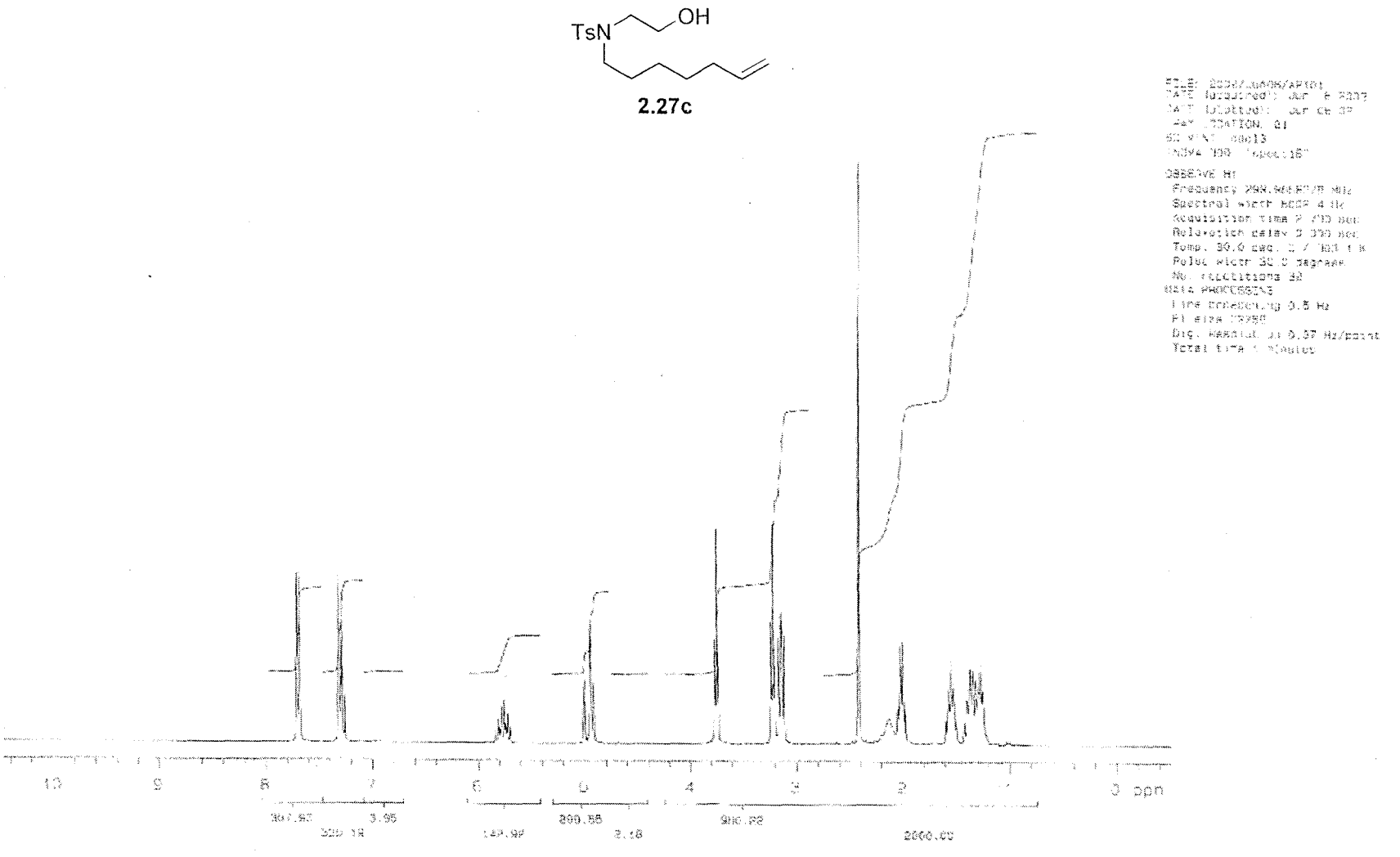

DATE (acquired) May 28 2002
DATE (plotted) May 28 09
TRAY LOCATION: 3
SOLVENT: cdcl3
INOVA-300 "gasc18"
OBSERVE H1
Pulse Width 30.0 degrees
DATA PROCESSING
Line Broadening 0.6 Hz
FT size 32768
10
9
8
7
6
5
4
3
2
1
0 ppm
103.70
34.29
278.56
373.65
2000.00

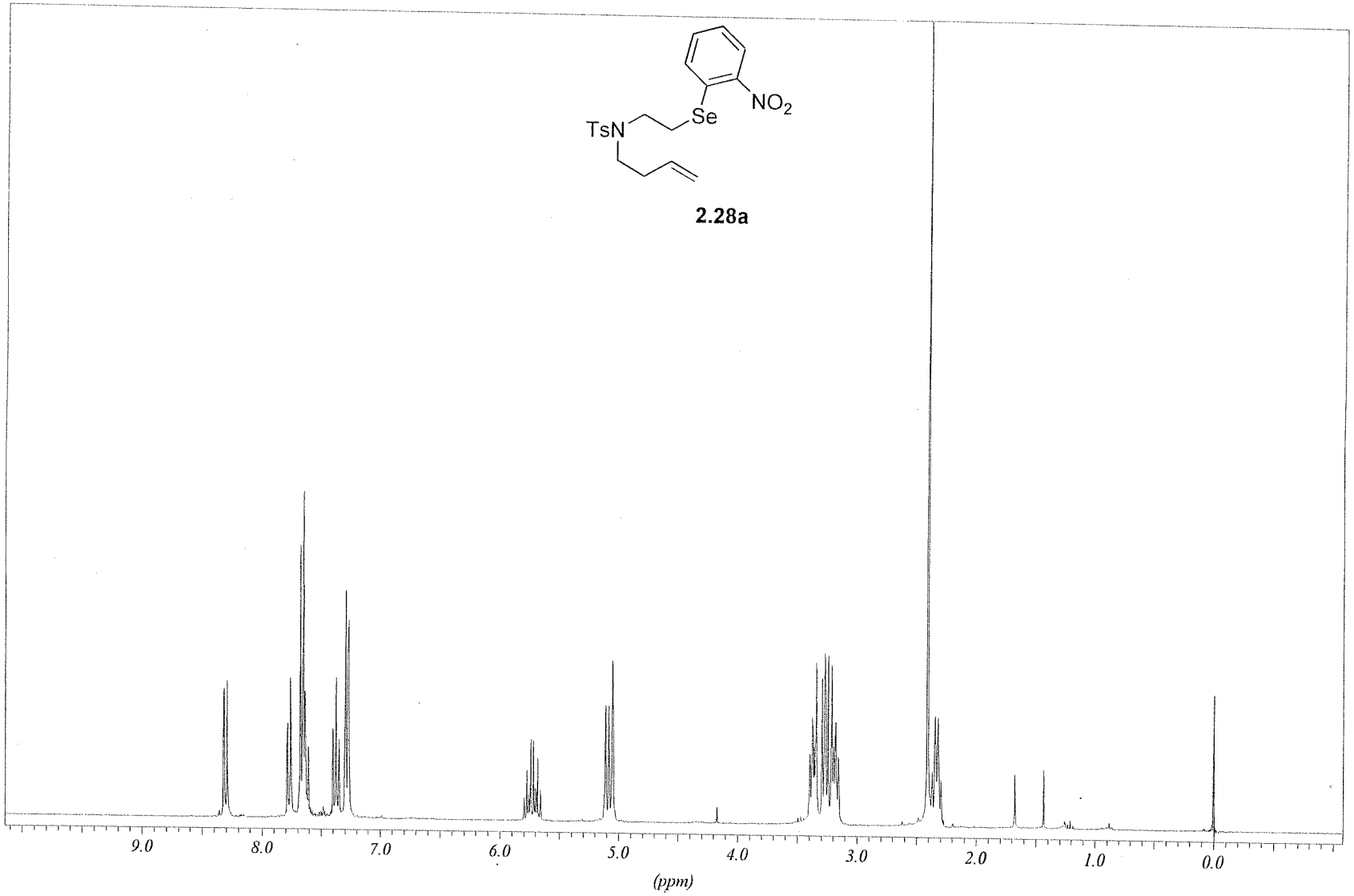

TsN
OH
2.27a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)



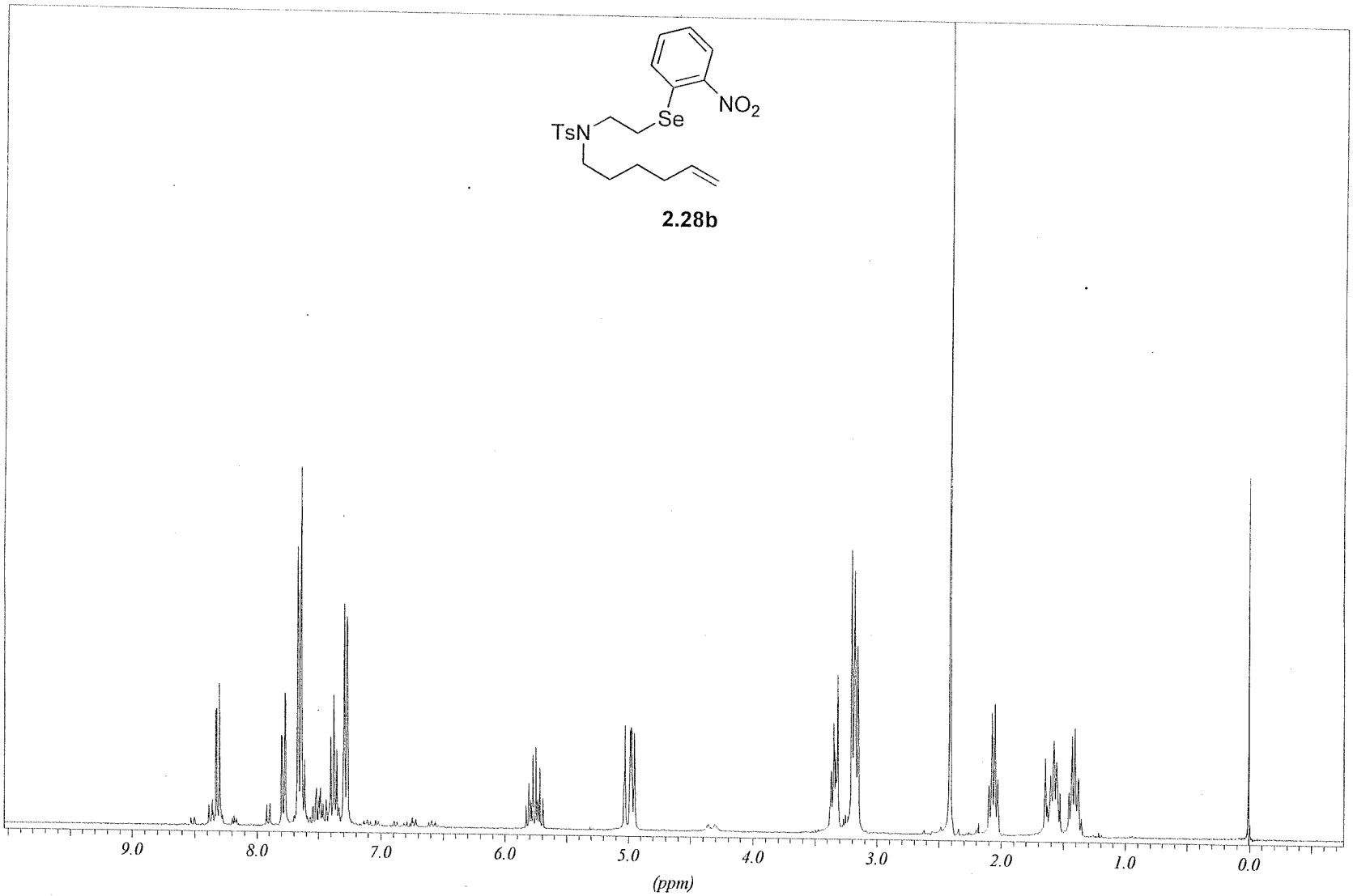
2.27b


```
Current Data Parameters
NAME          mr140(1)mgjr2
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_      20070314
Time              12.31
INSTRUM           dqx400
PROBHD     5 mm CXI 13C
PULPROG           zg30
TD                32768
SOLVENT           CDCl3
NS                   16
DS                    2
SWH           6278.196 Hz
FIDRES        0.382826 Hz
AQ            2.6738272 sec
RG                  230
DW             80.400 usec
DE              6.00 usec
TE                300.0 K
D1          1.00000000 sec

======== CHANNEL f1 ========
NUC1                1H
P1               8.30 usec
PL1             -8.00 dB
SFO1          400.1324710 MHz

F2 - Processing parameters
SI                 15384
SF          400.1300073 MHz
WDW                   EM
SSB                    0
LB                0.30 Hz
GB                     0
PC                 1.00
BP                 7.27 Hz

1H NMR plot parameters
CX                20.65 cm
F1P              11.000 ppm
F1               4401.73 Hz
F2P              -1.000 ppm
F2               -400.13 Hz
PPMCM          0.45003 ppm/cm
HZCM          180.05303 Hz/cm
```

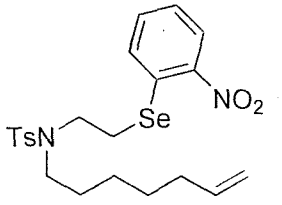

TsN
OH
2.27c
10
9
8
7
6
5
4
3
2
1
0 ppm
3.95
2.18



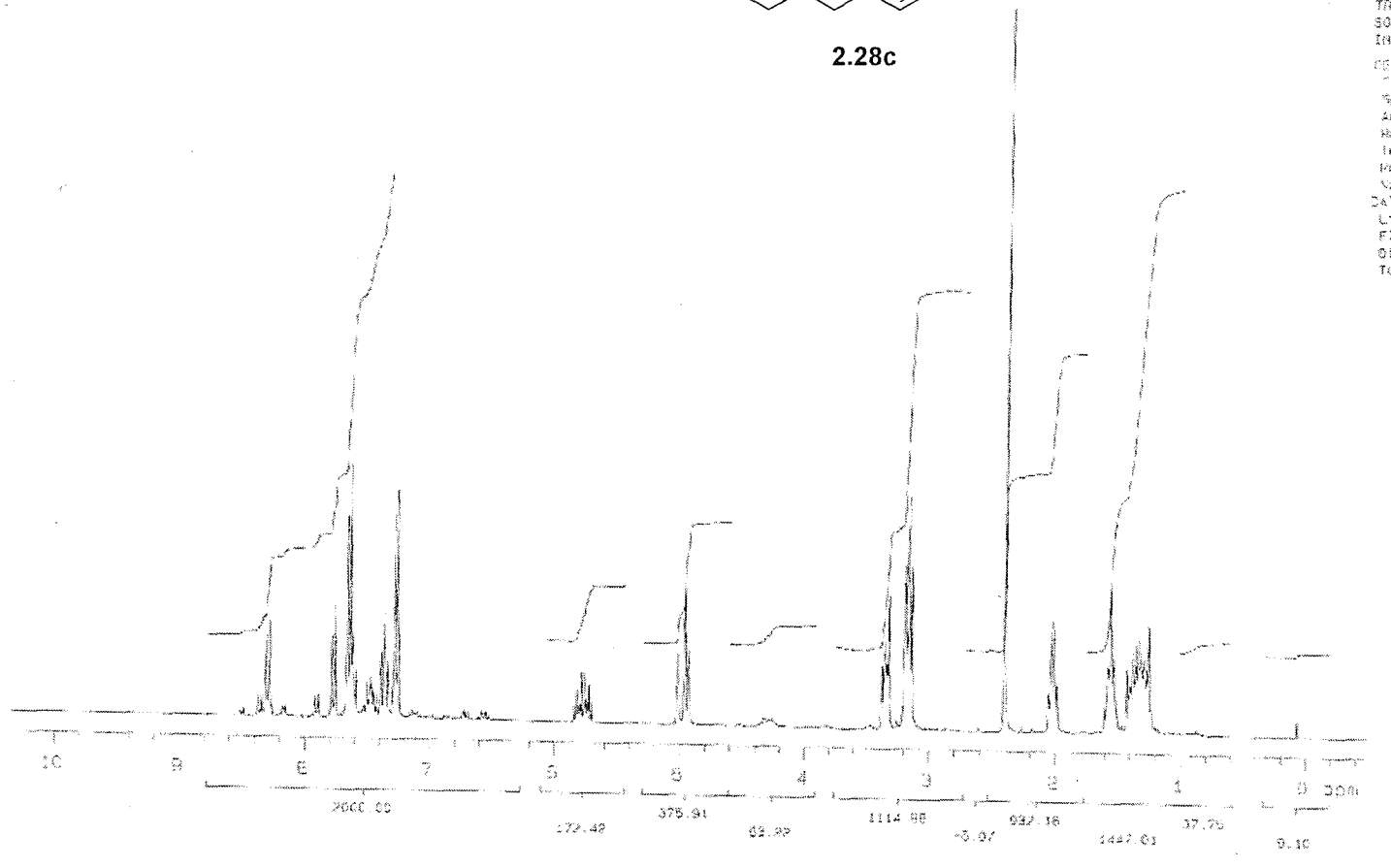
2.28a

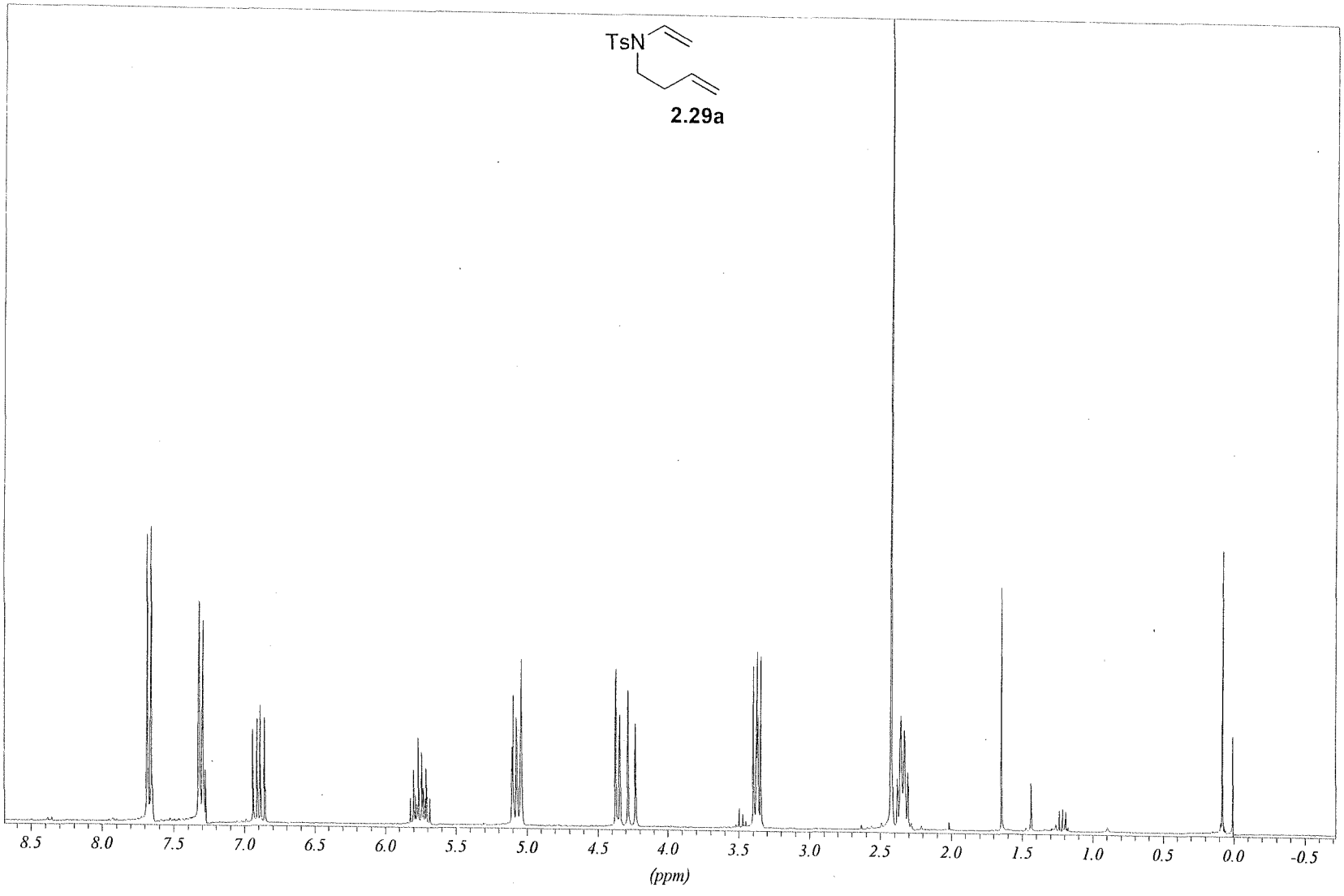


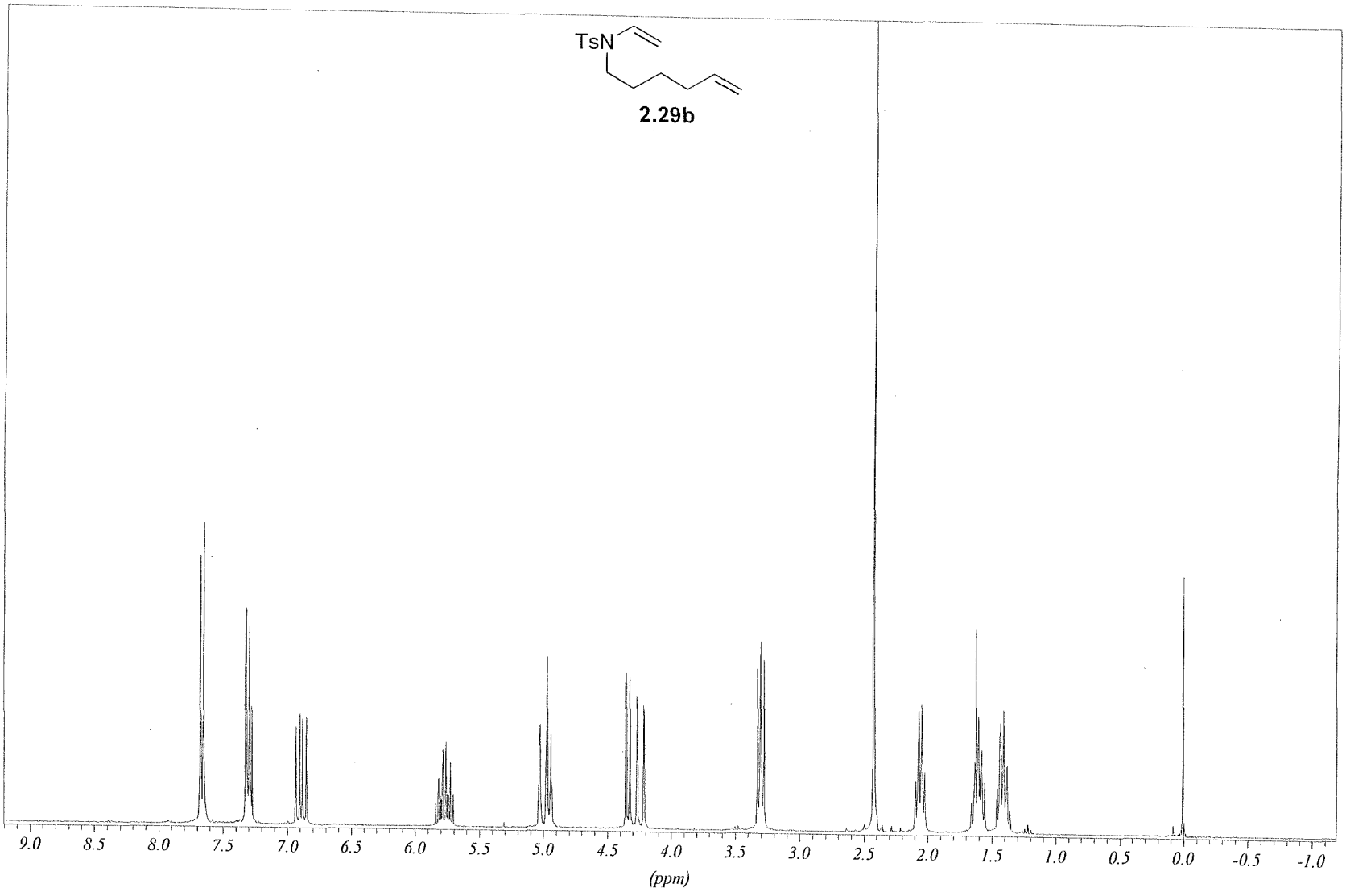
2.28b

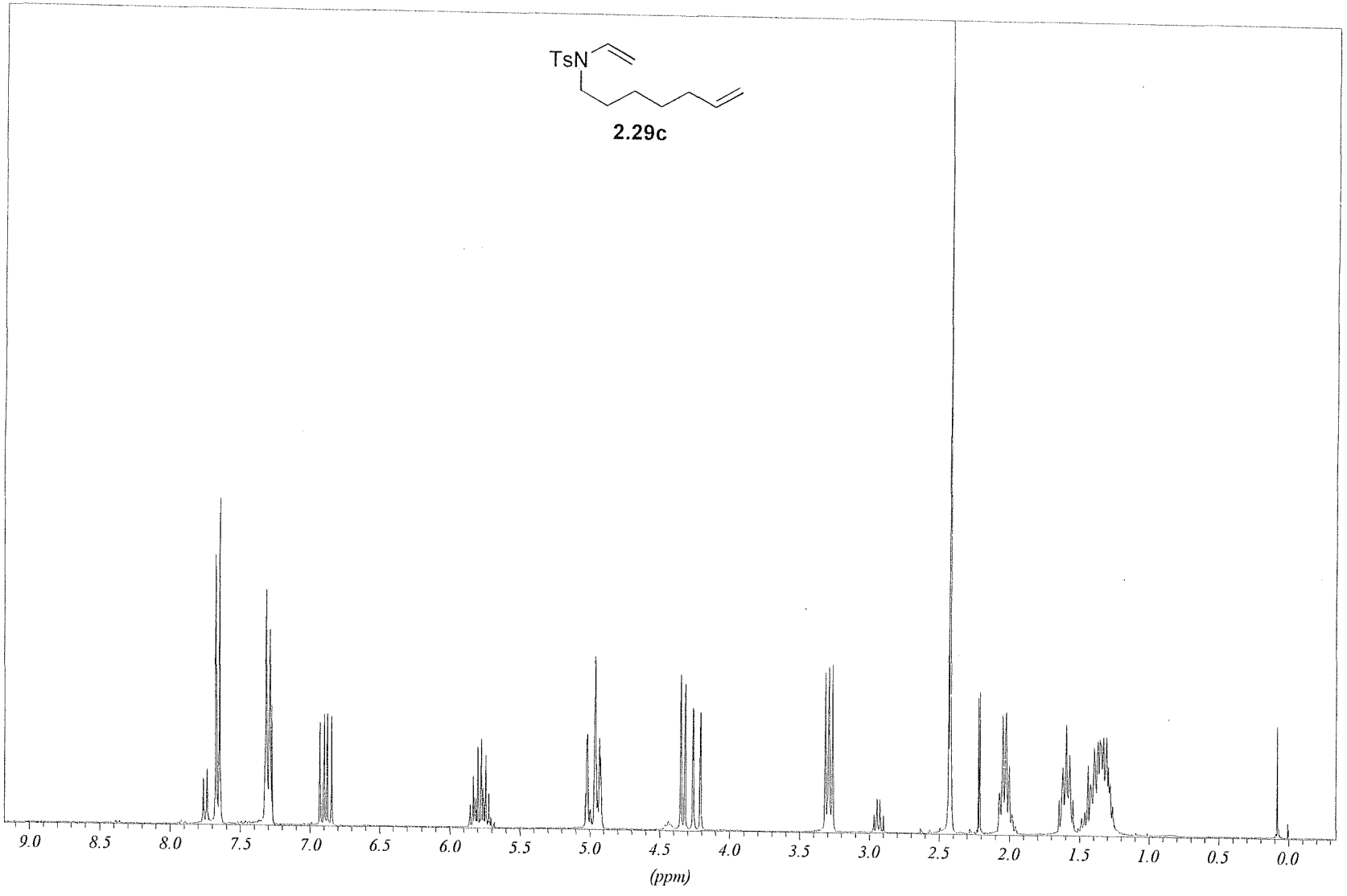

TsN
Se
NO2

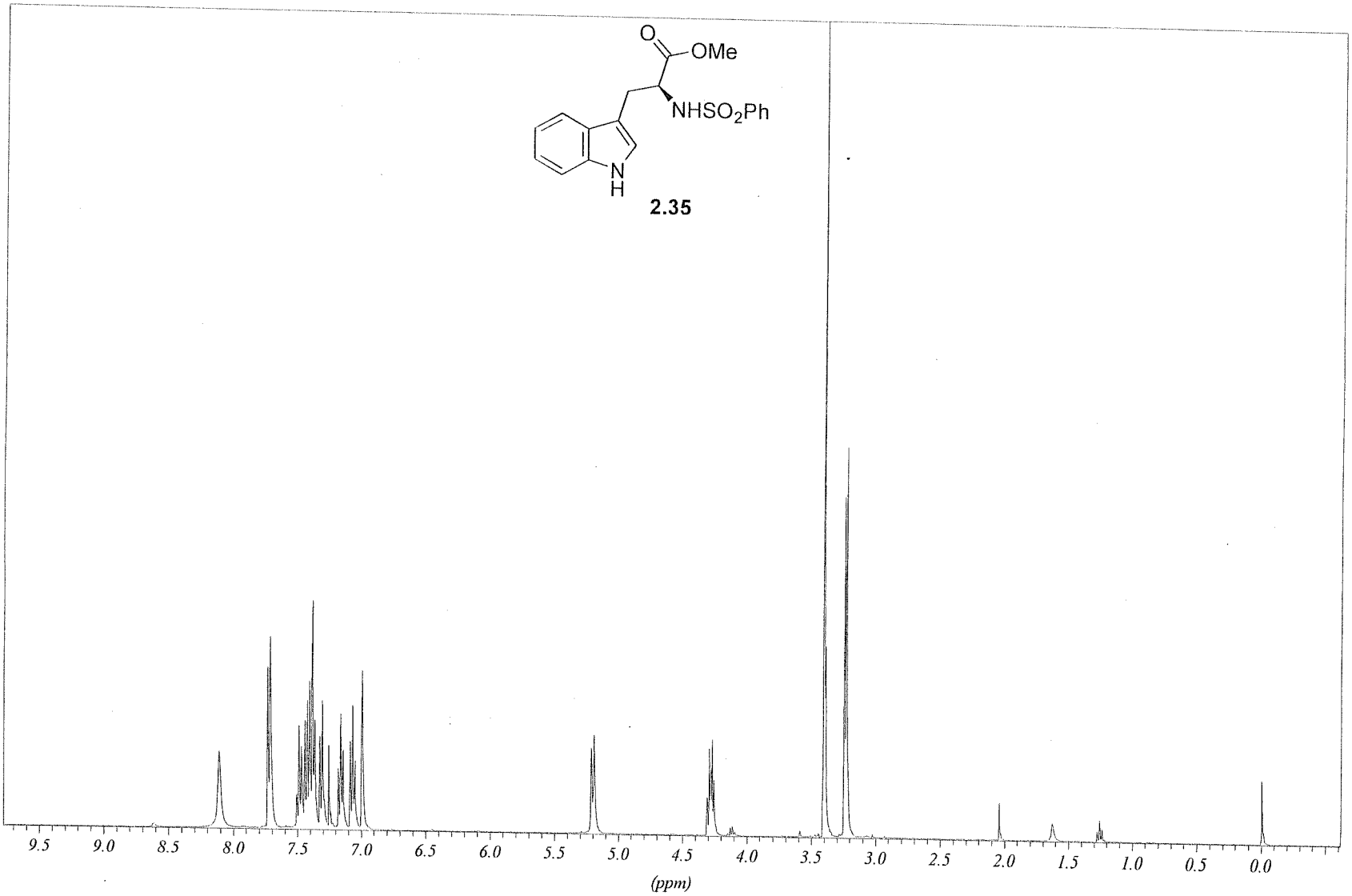
2.28c


10
9
8
7
6
5
4
3
2
1
0 ppm
9000.00
172.49
375.91
82.99
1114.88
<0.07
932.16
1487.63
37.75
9.10

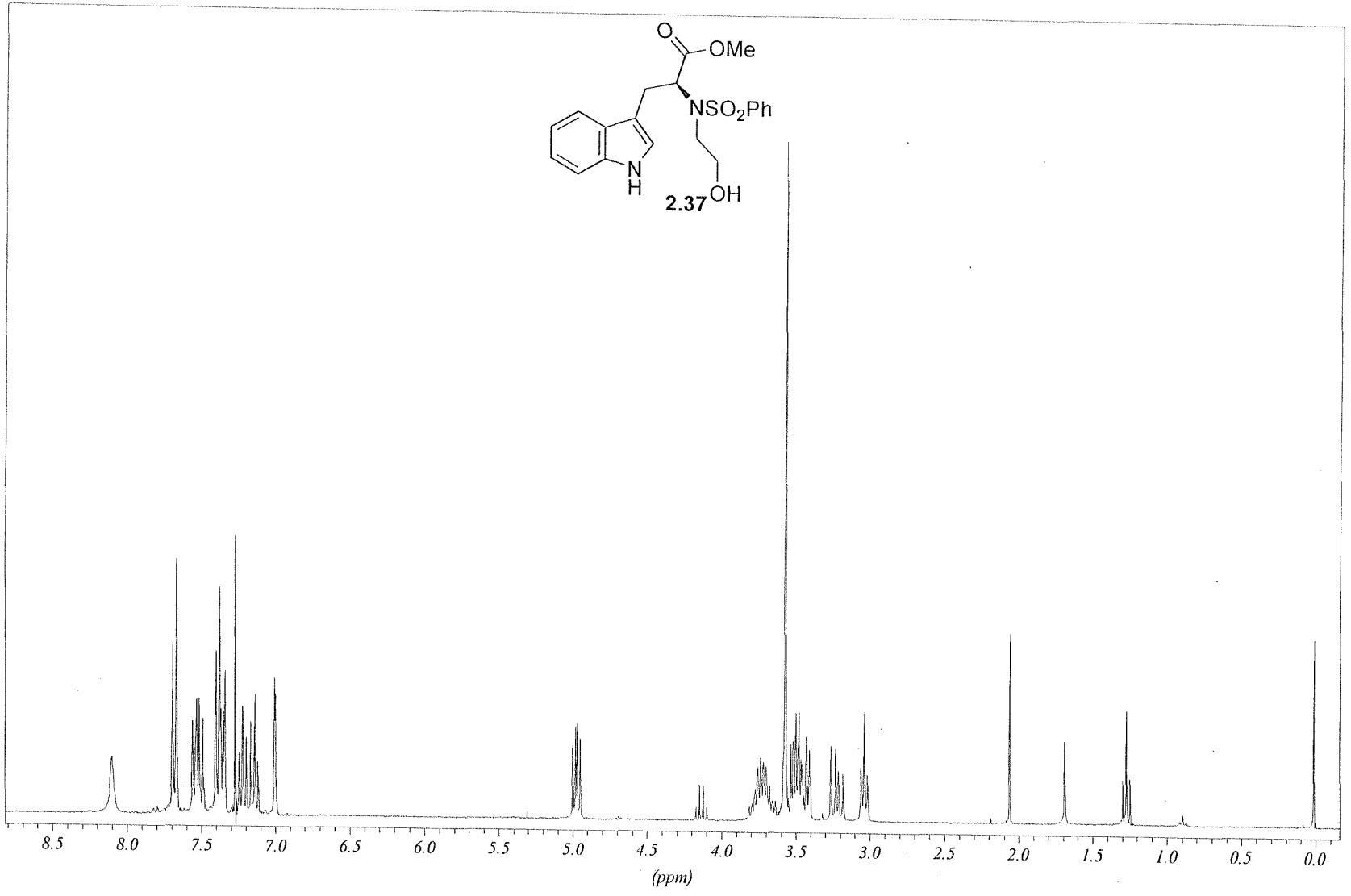

TsN
2.29a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
(ppm)


TsN
2.29b
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
-1.0
(ppm)

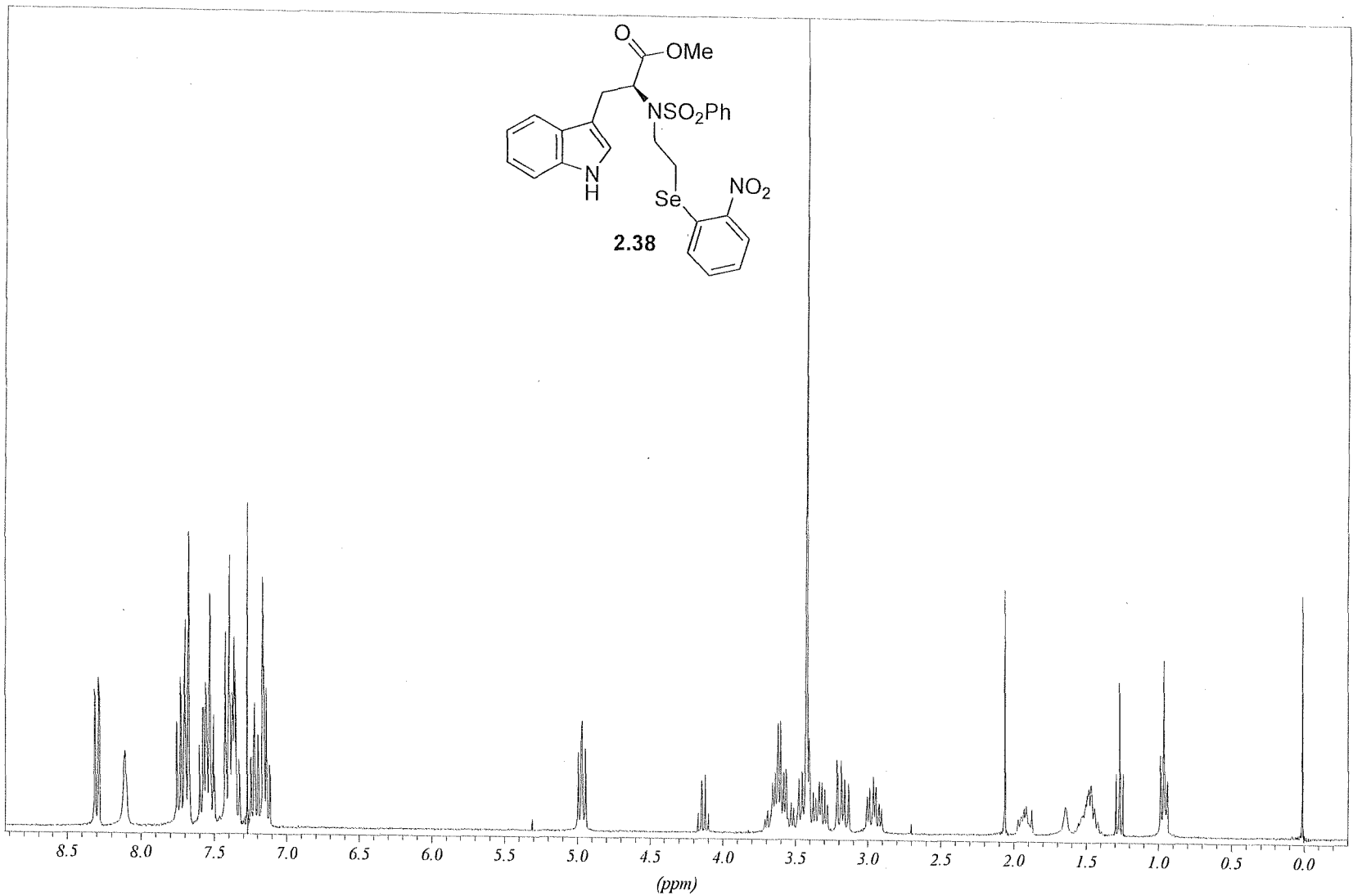

TsN
2.29c
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
(ppm)


O
OMe
NHSO2Ph
N
H
2.35
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
(ppm)

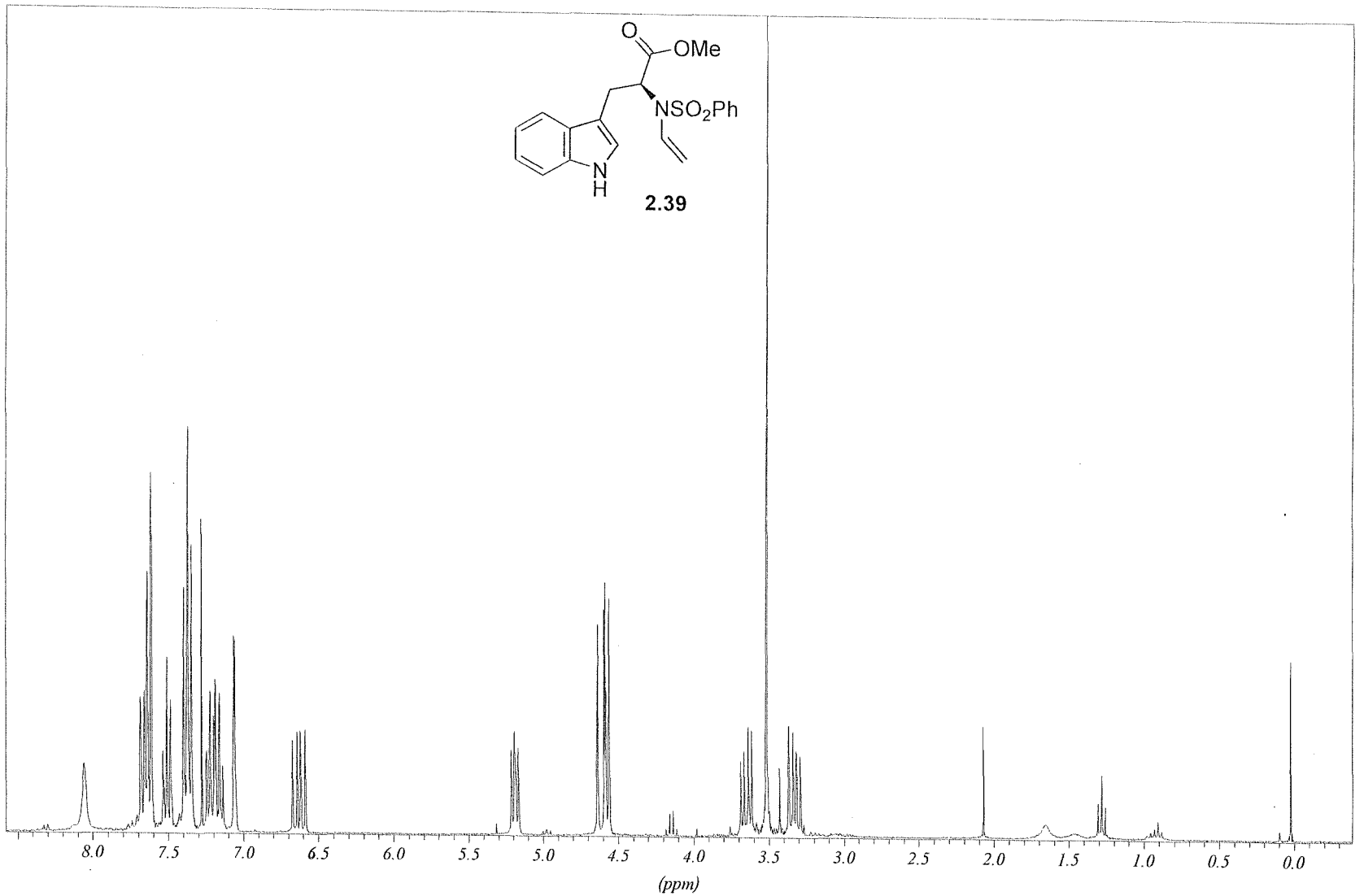
JR-3474-69


O
OMe
NSO2Ph
N
H
2.37
OH
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
(ppm)

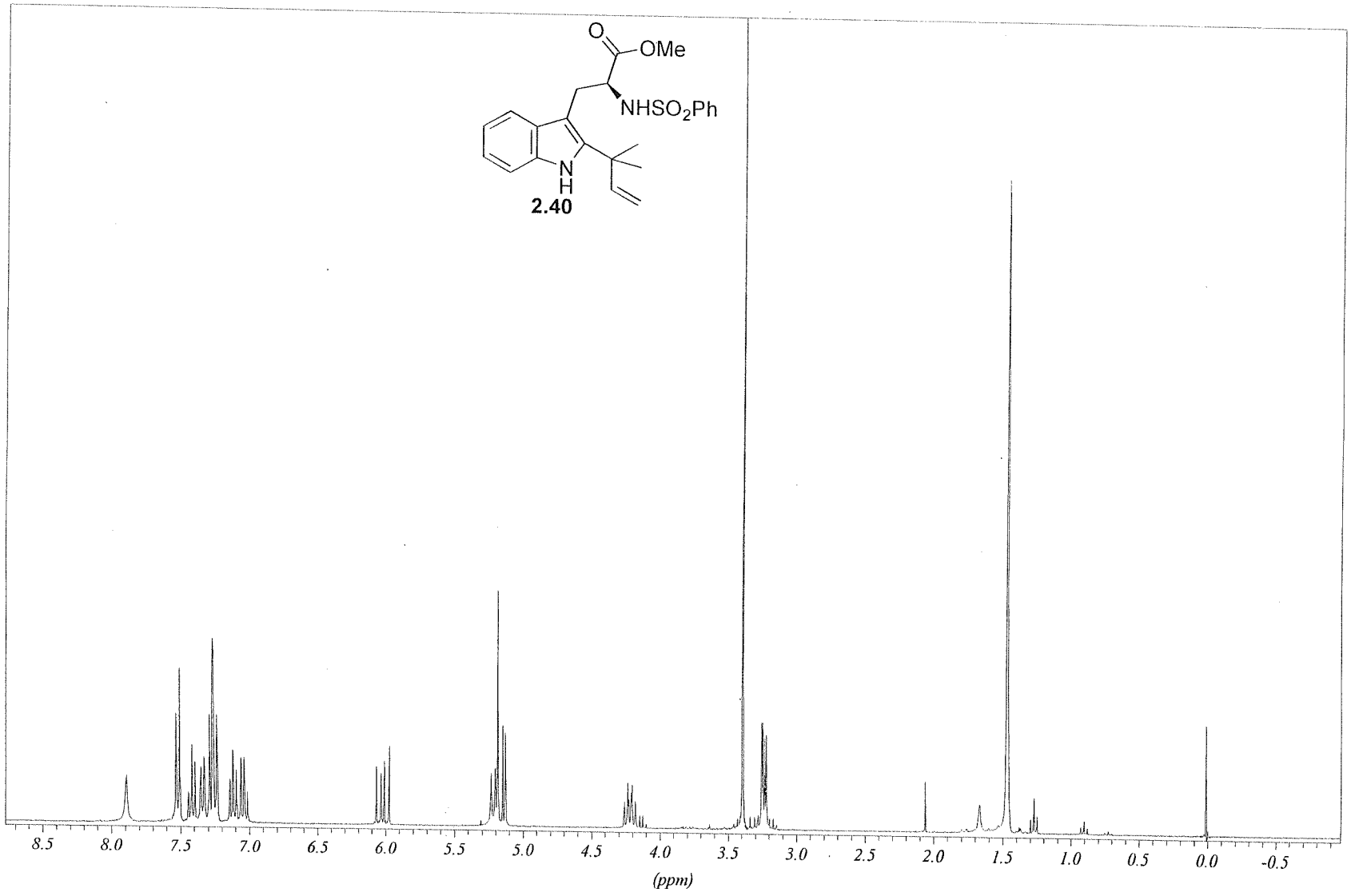
JR-3474-71


O
OMe
NSO2Ph
N
H
Se
NO2
2.38
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
(ppm)

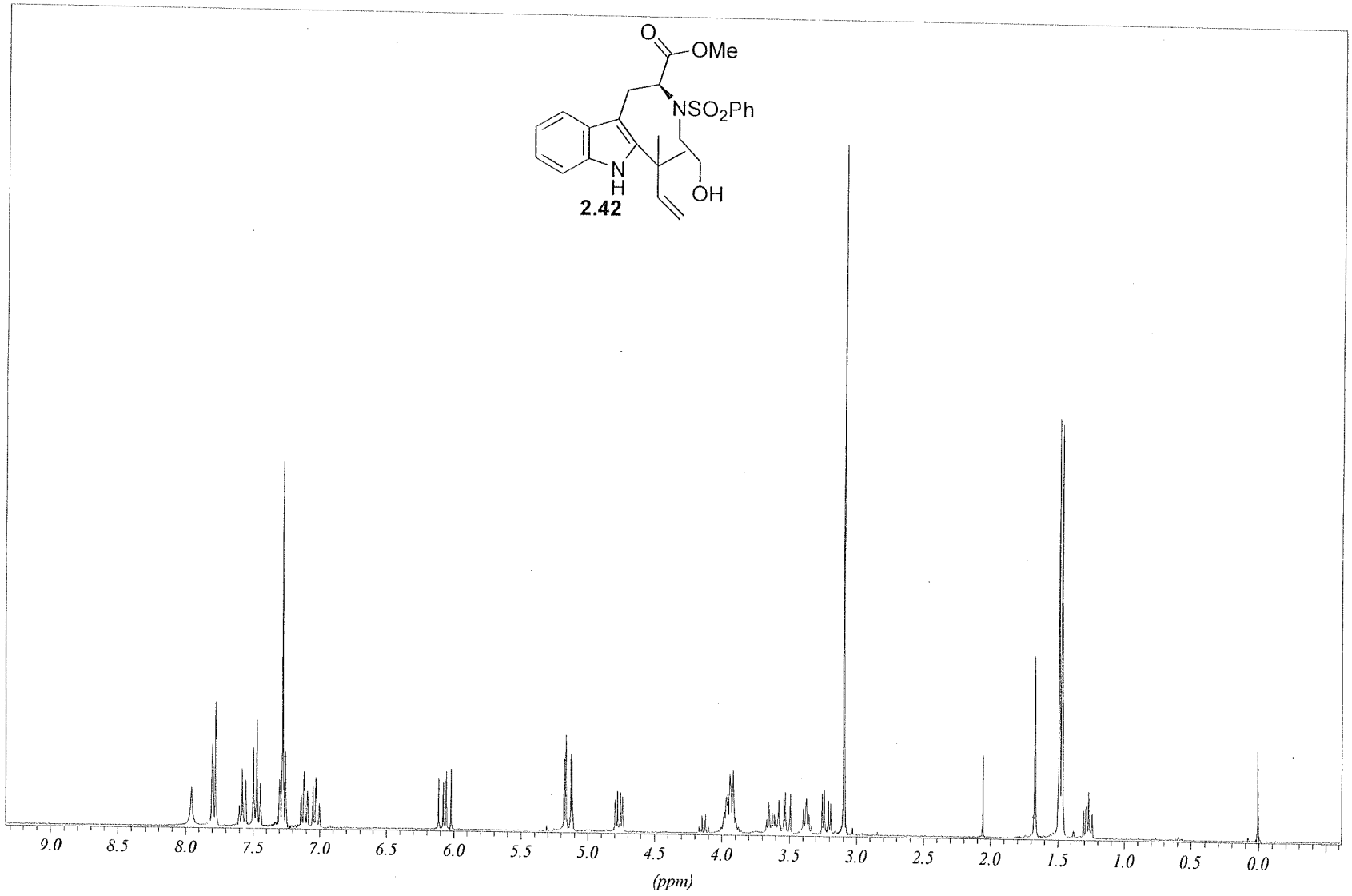
JR-3474-76


O
OMe
NSO2Ph
N
H
2.39
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
(ppm)

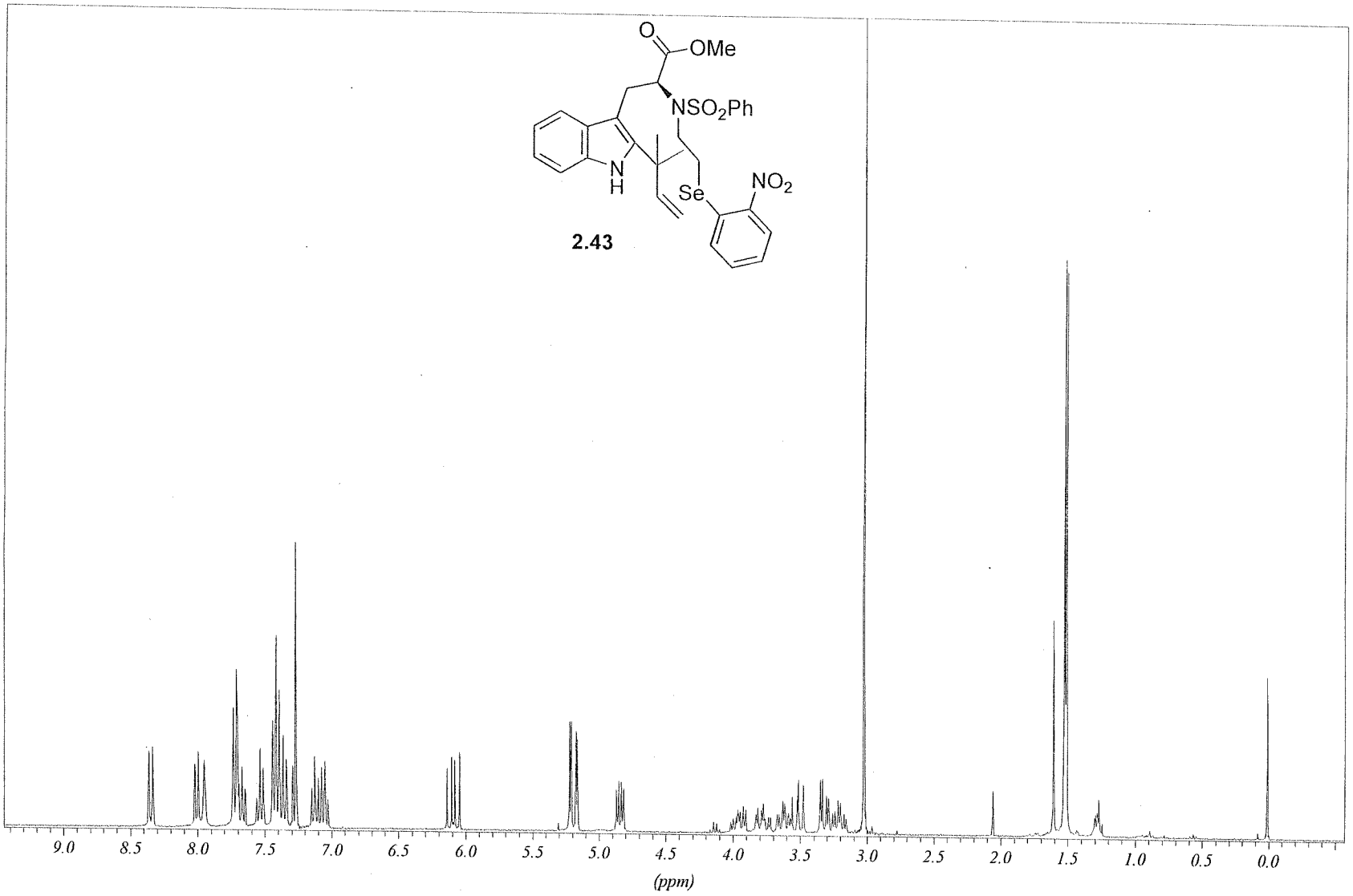
JR-3474-77


O
OMe
NHSO2Ph
N
H
2.40
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)

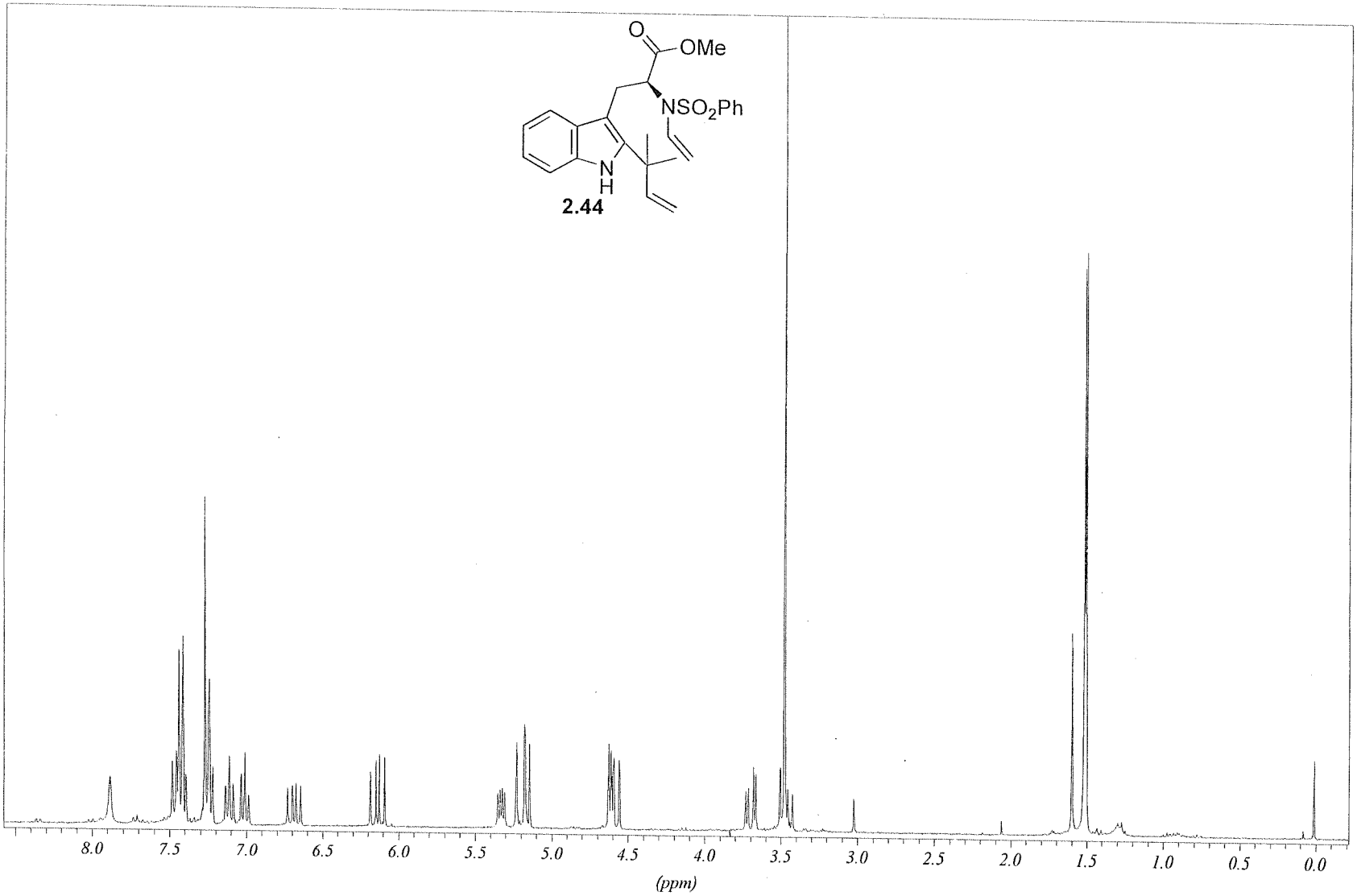
JR-3474-80


O
OMe
NSO2Ph
N
H
OH
2.42
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
(ppm)

JR-3474-80


O
OMe
NSO2Ph
N
H
Se
NO2
2.43
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
(ppm)

JR-3474-82


O
OMe
NSO2Ph
N
H
2.44
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
(ppm)