

Studies on the generation of chemical diversity using hetero Diels Alder reactions and polyfunctional scaffolds

A thesis for the degree of Doctor of Philosophy

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By

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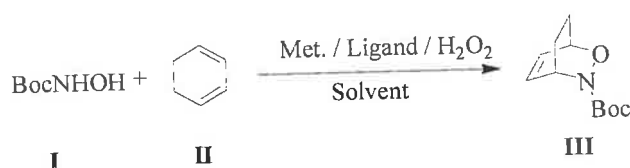
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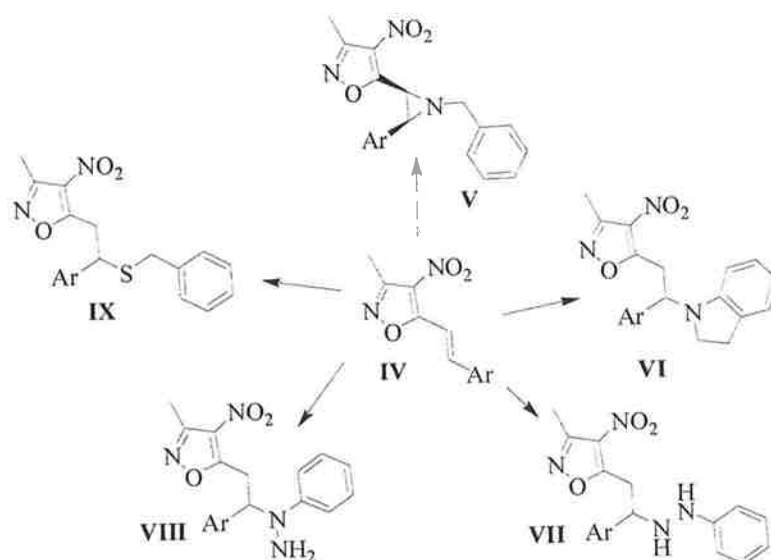
Abstract

In the first part of this work we developed four novel methodologies for the generation of nitroso dienophile from commercially available hydroxamic acid **I** which is trapped with appropriate diene through a hetero-Diels-Alder (HDA) reaction (**Scheme 1**). These procedures afforded cycloadduct in good yields, employing reagents in a 1:1 ratio and only 5 mol.% catalyst loading. Remarkably, the crude reaction mixture showed the HDA adduct as the only compound present: this renders the reactions described herein as ideal for the development of tandem processes. Moreover, we demonstrated that these new methodologies can be applied to a large number of dienes.



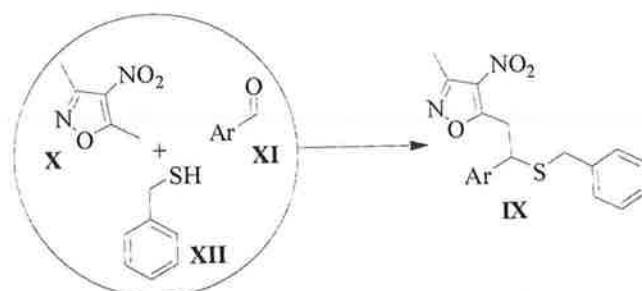
Scheme 1: synthesis of cycloadduct **III** using Ru^{III} , Fe^{III} , Cu^{I} , Cu^{II} as metal catalyst.

In the second part we demonstrated the synthetic usefulness of styrylisoxazole **IV** which was used to access a number of compounds. Herein we describe the syntheses of aziridines **V**, *N*-Michael adducts **VI**, **VII** and **VIII** and *S*-Michael adducts **IX** which were obtained by reacting styrylisoxazole **IV**, with the corresponding nucleophile (**Scheme 2**).



Scheme 2: synthesis of aziridines and Michael adducts from styrylisoxazole **IV**.

We also report the one-pot preparation of *S*-Michael adducts **IX** from commercially available isoxazole **X**, an aromatic aldehyde **XI** and benzyl mercaptan **XII** (Scheme 3).



Scheme 3: one-pot synthesis of *S*-Michael adducts **IX**.

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Chapter 1: Nitroso and acylnitroso hetero Diels-Alder reactions in organic chemistry

1.1 Introduction

The Diels-Alder reaction emerged as a key step in organic synthesis as in one step two new C-C bonds are formed often in a stereoselective fashion. The scope of reaction is wide and several enantioselective methodologies were developed in the recent past.¹ Hetero-Diels-Alder reactions (HDA) constitute an important variant that allows incorporating heteroatoms (O, N, S) in a carbon framework.² In particular, the HDA reaction of nitroso and acylnitroso species with dienes has been subject of intensive investigation in the recent past.³

Several nitroso species have been used in HDA reactions. These included acylnitroso **2**, α -chloronitroso **3**, aryl nitroso **4** and iminonitroso **5**. In these compounds, the reactivity of the nitroso group correlates with the electron-withdrawing character of the group attached. For example a higher reactivity is observed for nitrosocarbonyl compounds **2** and nitrosoformate esters **1** over aryl nitroso **4** while a lower reactivity is observed for iminonitroso compounds **5** (Figure 1). Clearly conjugation imparted a higher stability to nitroso species.

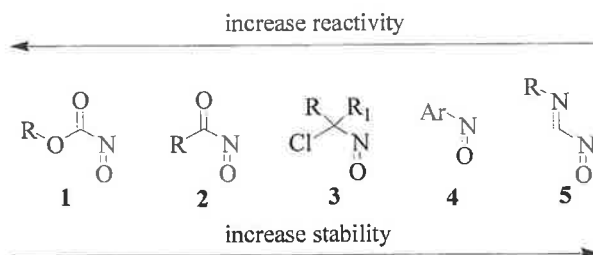
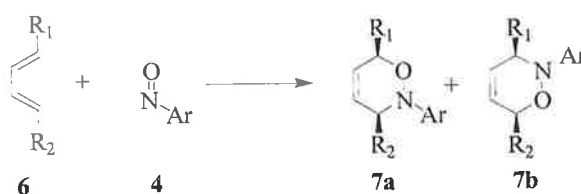


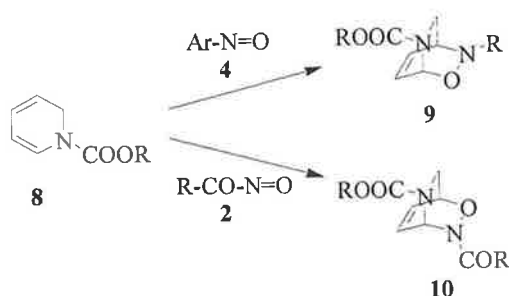
Figure 1

The HDA reaction of nitroso species with dienes is a concerted process⁴ that occurs with complete stereoselectivity: for example when aryl nitroso **4** was generated in the presence of an appropriate 1,3-diene the corresponding 3,6-dihydro-1,2-oxazines **7a** and **7b** were obtained in good yields (**Scheme 1**).⁵ Additionally, when the diene component was electronically dissymmetric, the reaction occurred with high degree of regioselectivity.



Scheme 1

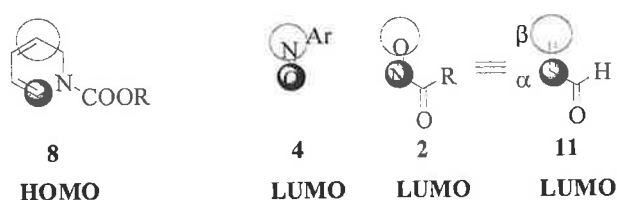
Aryl nitroso **4** and acyl nitroso **2** displayed an opposite regioselectivity when reacted with dissymmetric dienes. For instance, the reaction of 1,2-dihydropyridine **8** with **4** ($\text{Ar}-\text{N}=\text{O}$) gave cycloadduct **9** as the only regioisomer and in high isolated yield.⁶ When **8** was reacted with acyl nitroso compound **2** ($\text{R}-\text{CO}-\text{N}=\text{O}$), the reaction gave adduct **10** as the exclusive regioisomer (**Scheme 2**).⁷



Scheme 2

This result could be explained considering the FMO of aryl nitroso **4** and acyl nitroso species **2** (**Figure 2**) and assuming the reaction to occur through an overlap of the HOMO (diene) with the LUMO (dienophile).⁸ The LUMO of species **4** is

characterized by a larger orbital coefficient on the *N*-atom. This could be explained taking into consideration the difference of electronegativity between nitrogen and oxygen. On the contrary, the LUMO of acylnitroso species **2** presents a larger orbital coefficient on the oxygen. This could be explained by invoking the effect of conjugation with the acyl group that renders the *O*-terminus of the nitroso species electron deficient. A similar effect was observed in α,β -unsaturated carbonyls **11** that displayed a high electrophilic character at their β position (**Figure 2**).



Arylnitroso Acylnitroso

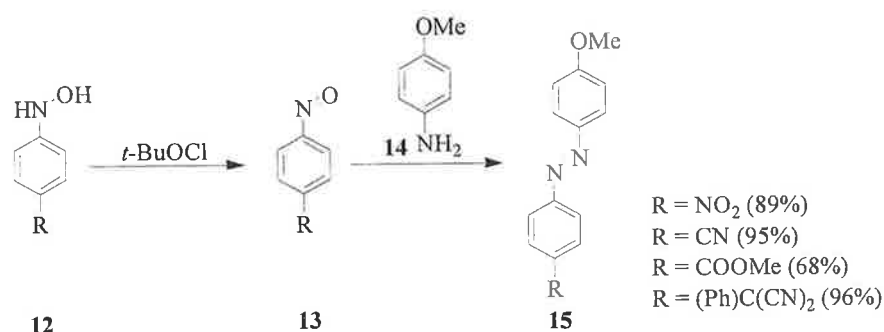
Figure 2

1.2. C-Nitroso dienophiles

1.2.1. Arylnitroso dienophiles

Arylnitroso derivatives as **13** (**Scheme 3**) have been described as very stable compounds that could be isolated and stored for long time. Nitroso derivatives **13** were originally preformed by oxidation of the corresponding arylhydroxylamine **12**, under heterogeneous conditions using $\text{Mo}(\text{O})-(\text{O}_2)_2(\text{H}_2\text{O})(\text{hmpa})$ as the catalyst and H_2O_2 as the terminal oxidant.⁹ Later pyridinium chlorochromate has been reported as an efficient reagent for the conversion of **12** to **13**.¹⁰ Considering that heterogeneous oxidations frequently required several hours to achieve a full conversion a few oxidations running under homogeneous catalysis have been developed. Nowadays, the most frequently used protocol for the oxidation of hydroxylamine **12** to the corresponding aryl nitroso species **13** involves *tert*-butyl hypochlorite as the oxidant.¹¹ Under these conditions,

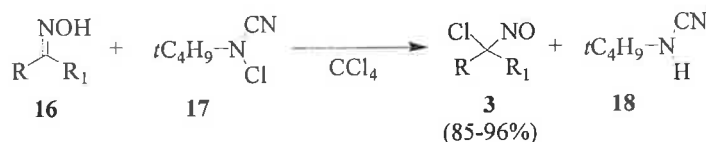
hydroxylamine was converted to its nitroso derivative once the oxidant was added. The yields of this reaction were calculated from the isolation of aza coupled compound **15** obtained in a subsequent Mills coupling (**Scheme 3**).



Scheme 3

1.2.2. α -Chloronitroso dienophiles

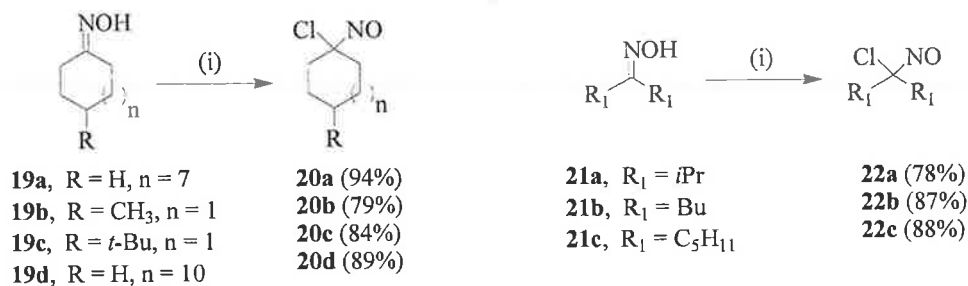
α -Chloronitroso compounds **3** (**Scheme 4**) are among the first nitroso dienophiles used.¹² Some of these species were poorly stable and of consequence their reactions with dienes were usually sluggish. For this reason, their use has been described requiring low temperature and their generation carried out *in situ*. Conversely, other types of α -chloronitroso species were described as stable compounds and isolated in good yields. Chlorine,¹³ aqueous hypochlorous acid,¹⁴ *N*-halo-compounds¹⁵ or an alkyl hypochlorite¹⁶ could be equally employed as the oxidant, however their use did often result in the formation of over-oxidized nitro derivatives. In the recent past, a new method was developed for the oxidation of oximes **16** where *N*-*tert*-butyl-*N*-chlorocyanamide **17** was used as the oxidant (**Scheme 4**).¹⁷



Scheme 4

This method has several advantages including high yields, shorter reaction times (< 1 min.) and ease of work up. In addition, the reduced byproduct **18** was recycled to **17** for further use.

Terent'ev *et al.* described a process in which oximes were oxidised using aqueous $\text{H}_2\text{O}_2/\text{HCl}$ in a biphasic system (Scheme 5).¹⁸ This oxidation was carried out in $\text{H}_2\text{O}_2/\text{HCl}/\text{DCM}$. In this procedure a solution of **19a-d** or **21a-c** in DCM was firstly treated with conc. HCl and then with 37% H_2O_2 . The desired α -chloronitroso compounds **20a-d** and **22a-c** were obtained in 20 minutes in excellent yields (up to 94%). In this study, cyclic and acyclic oximes were transformed to their corresponding α -chloronitroso species.

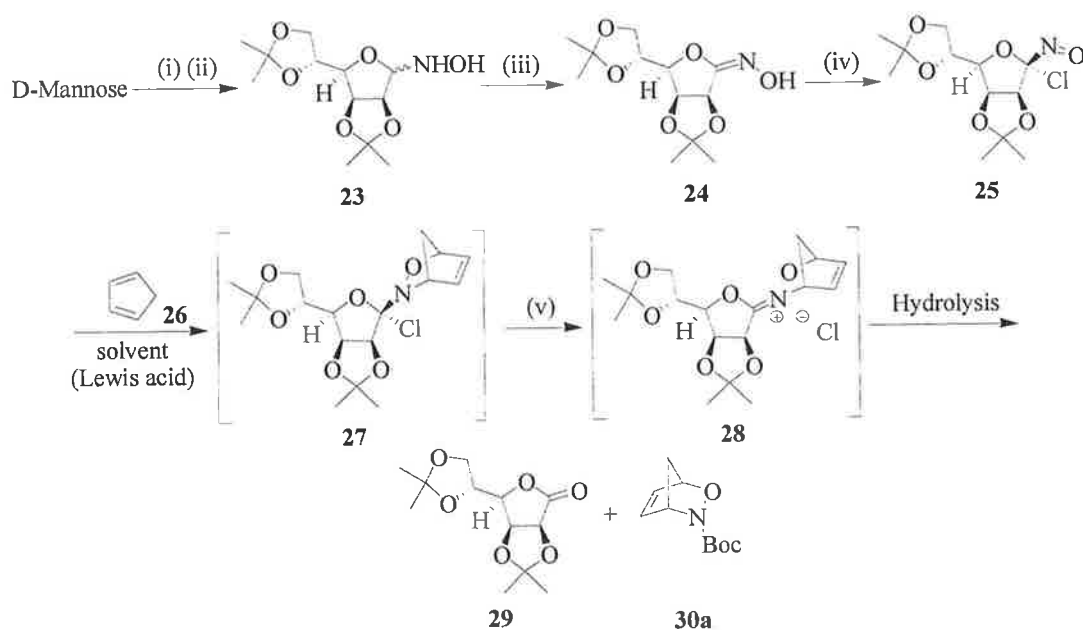


Reagents: (i) aq. $\text{H}_2\text{O}_2/\text{HCl}/\text{DCM}$, 20 min., 40 °C.

Scheme 5

Miller *et al.* carried out extensive studies on the HDA reaction using a D-mannose-derived chloronitroso **25** (Scheme 6).¹⁹ Compound **25** was synthesised in good overall yield. The synthesis required four steps from commercially available D-mannose. D-Mannose was firstly reacted with acetone and a Lewis acid, then with hydroxylamine to afford derivative **23**. Subsequent oxidation of **23** with MnO_2 furnished oxime **24** that in turn was converted to α -chloronitroso **25** by reaction with *t*-BuOCl. The

yield of **25** was excellent (83% yield after recrystallization). The reaction of **25** with cyclopentadiene was studied in polar and apolar solvents. The effect of Lewis acid on the cycloaddition was also investigated. Best results were obtained reacting **25** with cyclopentadiene in toluene as a solvent and in the presence of titanium salt (**Table 1**).



Reagents: (i) acetone, P_2O_5 , $\text{Ca}(\text{OH})_2$, carbon; (ii) $\text{NH}_2\text{OH}\cdot\text{HCl}$, NaOAc , EtOH , reflux; (iii) MnO_2 , MeOH (70%, three steps); (iv) $t\text{-BuOCl}$, EtOH ; (v) Boc_2O , NaHCO_3 .

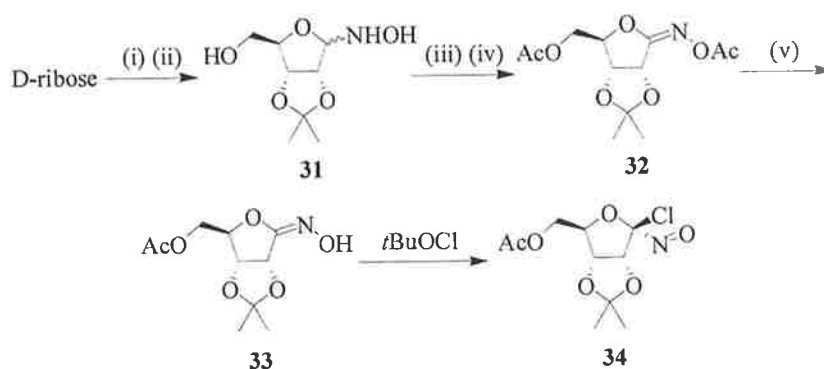
Scheme 6

Table 1

| Solvent | Lewis acid (eq.) | Yield of 30a (%) | ee (%) |
|---------|--|------------------|--------|
| THF | Et_2AlCl (0.2) | 25 | 73 |
| Toluene | - | 52 | 75 |
| Toluene | Et_2AlCl (0.2) | 61 | 84 |
| Toluene | $\text{Ti}(\text{O}i\text{Pr})_3\text{Cl}$ (0.3) | 76 | 78 |
| Toluene | $\text{Ti}(\text{O}i\text{Pr})_4/\text{D-DET}$ (1.0) | 80 | 75 |

Under these conditions, adduct **30a** was obtained in high yield and good enantioselectivity with lactone **29** as the only side product. Importantly **29** was recovered from the reaction mixture and used to regenerate **23**.

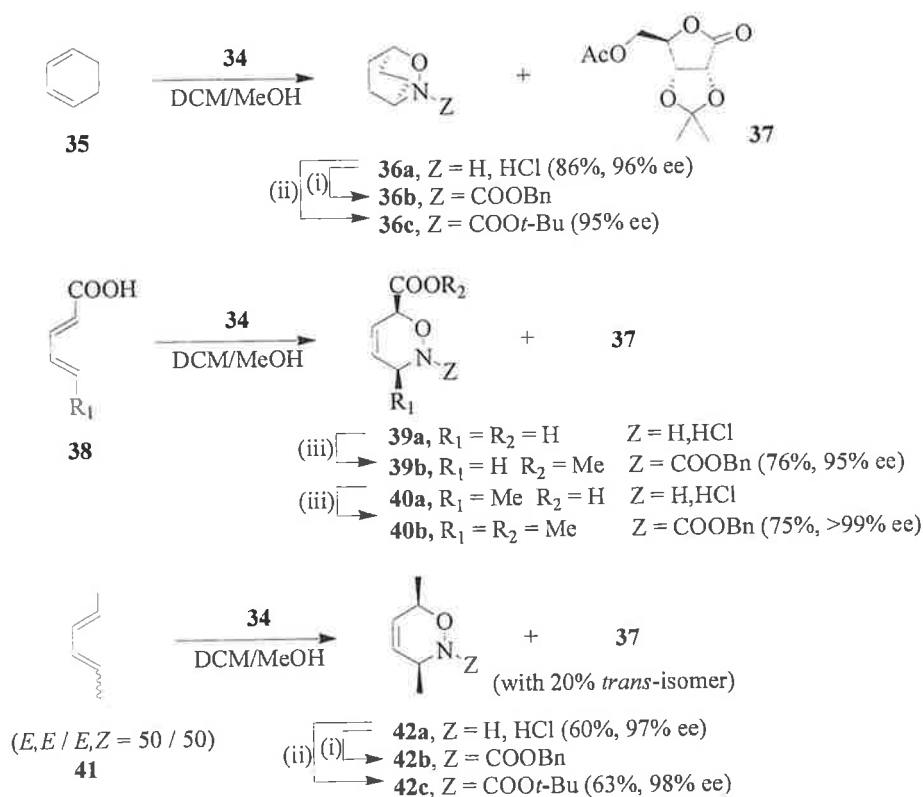
Defoin and co-workers described the synthesis of the α -chloronitroso **34** from D-ribose (**Scheme 7**).²⁰ The synthesis of **34** was achieved in six steps. Initial treatment of D-ribose with acetone and P_2O_5 was followed by addition of hydroxylamine and furnished compound **31**. In turn, compound **31** was oxidised and acetylated to give **32**. Finally, compound **32** was subjected to selective hydrolysis and the resulting **33** converted to **34** by oxidation of cyclic lactone oxime **33** by reaction with *t*-BuOCl.



Reagents: (i) acetone, P_2O_5 , $Ca(OH)_2$, carbon; (ii) $NH_2OH \cdot HCl$, $EtOH/H_2O$, reflux; (iii) $NaIO_4$, $NaOAc$, $EtOH/H_2O$, reflux; (iv) AcO_2 , Py; (v) $NaHCO_3$, $EtOH$, reflux.

Scheme 7

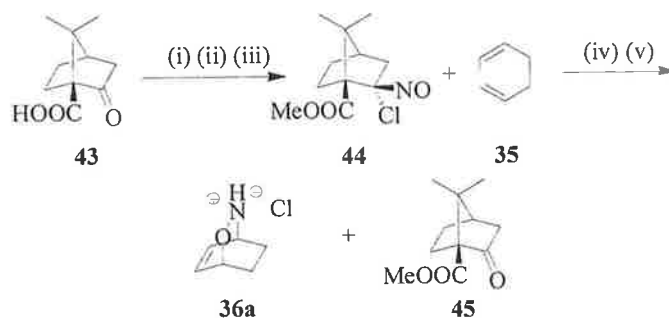
The same authors reacted **34** with cyclic and acyclic dienes providing cycloadducts **36**, **39**, **40** and **42** in good yields and excellent enantioselectivity (**Scheme 8**). In this reaction the corresponding lactone **37** was recovered and recycled to cyclic oxime **33**.



Reagents: (i) ClCOOBn/NaHCO₃; (ii) (*t*-BuCOO)₂O/NaCO₃; (iii) ClCOOBn/NaHCO₃/H₂O, then dry HCl/MeOH

Scheme 8

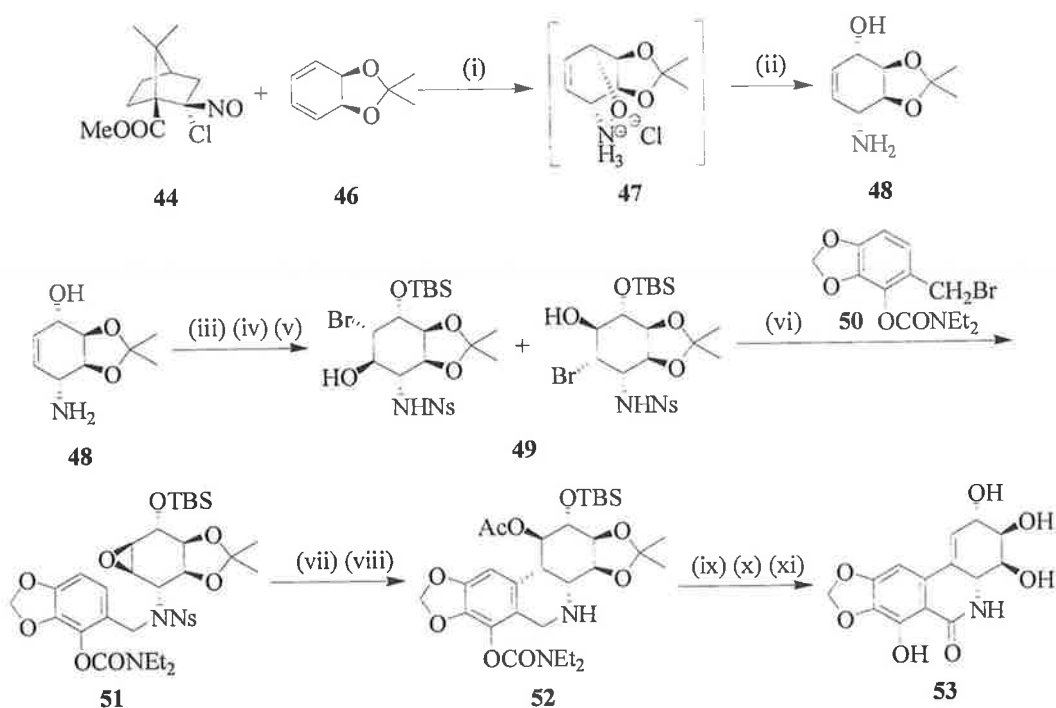
In order to study the effect of the camphor scaffold on the diastereoselectivity of α -chloronitroso HDA, Yan and co-workers prepared the α -chloronitroso compound **44** (Scheme 9).²¹ The synthesis of **44** was achieved in three steps from Ketopinic acid **43**: esterification of acid **43** with thionyl chloride in MeOH, followed by treatment with hydroxylamine hydrochloride and oxidation by *t*-BuOCl afforded **44** in 88% overall yield. The reaction of nitroso compound **44** and 1,3-cyclohexadiene occurred in good yield (88%) and the expected cycloadduct **36a** obtained in excellent enantiomeric excess (>98% e.e.).



Reagents: (i) SOCl_2 , MeOH; (ii) $\text{NH}_2\text{OH}\cdot\text{HCl}$, MeOH, NaOAc; (iii) $t\text{-BuOCl}$, DCM; (iv) DCM, 0 °C; (v) $i\text{-PrOH}/\text{H}_2\text{O}$.

Scheme 9

The same group exploited compound **44** in the synthesis of (+)-Narciclasine alkaloid **53**²² (Scheme 10).



Reagents: (i) DCM, 0 to 25 °C; (ii) $\text{Al}(\text{Hg})$, MeCN, 86% (two steps); (iii) NsCl , Et_3N , CH_3CN ; (iv) TBSCl , DBU (78%, two steps); (v) NBS , $\text{H}_2\text{O}/\text{acetone}$ (98%); (vi) K_2CO_3 , CH_3CN , 60 °C (88%); (vii) SnCl_4 (20mol %), DCM then Ac_2O , K_2CO_3 (98%); (viii) HSCH_2COOH , LiOH , DMF (78%); (ix) Boc_2O , CH_3CN then RuCl_3 , NaIO_4 , H_2O (67%); (x) DBU , benzene, 70 °C (96%); (xi) HCOOH , THF, 60 °C then concentration, LiAlH_4 , THF (65%).

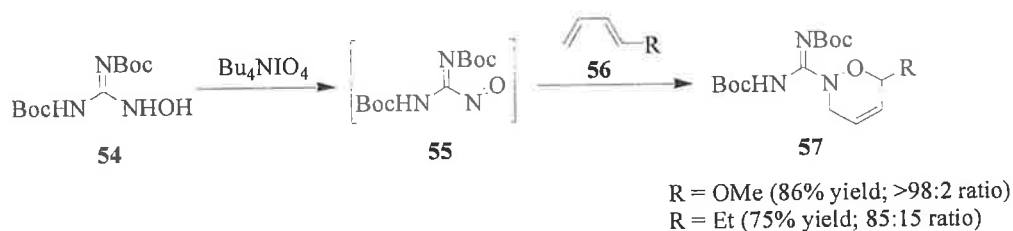
Scheme 10

The cycloaddition of **44** with diene **46** afforded chloride salt **47** which was converted to **48**. Acetonide **48** was then used to prepare (+)-Narciclasine **53**. This involved protecting **48** on its amino and hydroxyl groups and transforming the resulting species into **49**. Reaction of **49** with pyperonyl bromide **50** in the presence of K_2CO_3 led to compound **51**. Compound **52** arose from a *N*-alkylation and concomitant S_N2 reaction of the bromohydrine moiety to furnish epoxide **51**. Exposure of **51** to $SnCl_4$ followed by addition of Ac_2O and treatment with mercaptoacetic acid in alkaline ambient furnished the free amine **52**. Compound **52** was then reacted with $(Boc)_2O$ and $NaIO_4/RuCl_3$ to convert the secondary amine into a lactam. This was treatment with DBU to remove the acetyl group and form the double bond. The final deprotection of the hydroxyls was achieved using formic acid followed by reduction with $LiAlH_4$.

1.2.3. Iminonitroso dienophiles

Iminonitroso derivatives display a lower reactivity compared to acylnitroso species. The reactivity of iminonitroso species can be augmented by attaching an appropriated electron withdrawing group. This usually lowers the LUMO energy of nitroso and renders its reaction with a diene faster.

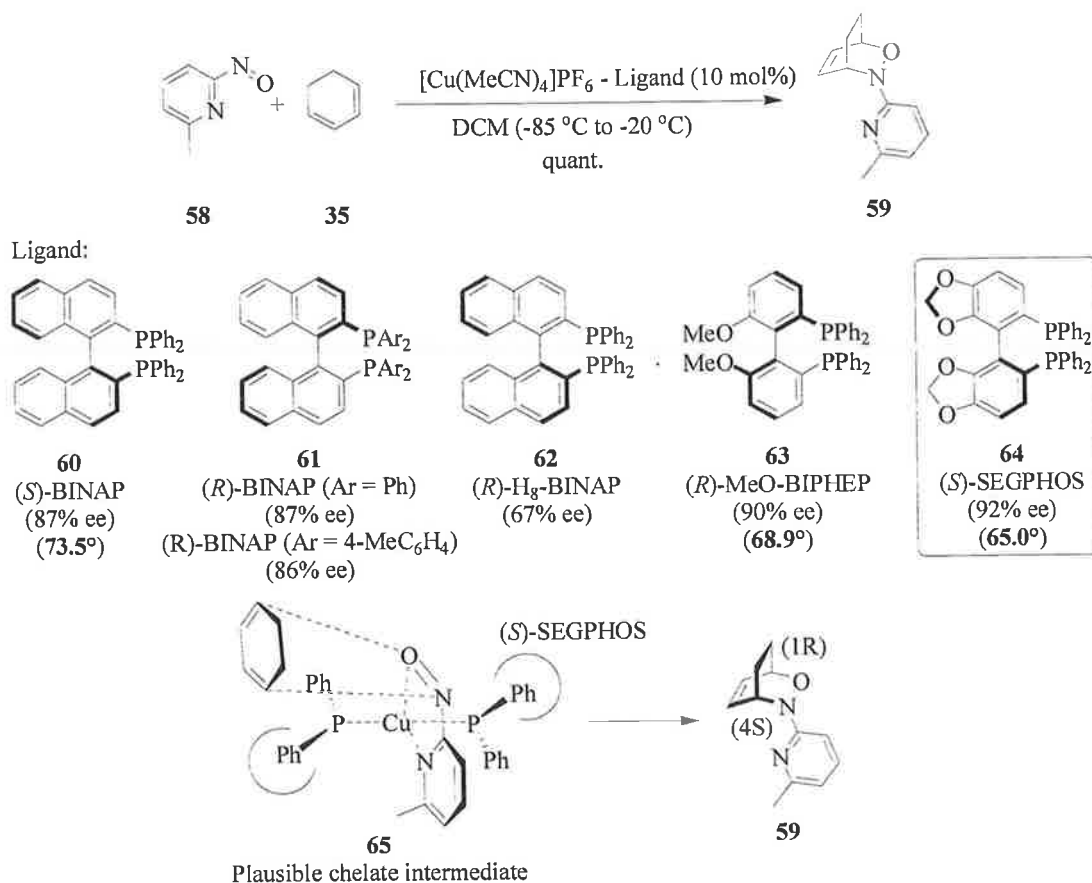
Batey and Miller reported a high level of regioselectivity in HDA reactions of iminonitroso derivatives with dienes (Scheme 11).²³



Scheme 11

N-protected guanidine **54** was oxidized with Bu_4NIO_4 to nitroso intermediate **55** in the presence of 1,3-dienes. When unsymmetrical dienes **56** were used a strong preference for the proximal isomers **57** was observed. The regioselectivity is similar to the one observed for acylnitroso species and predicted calculating the energy of the possible transition states.²⁴

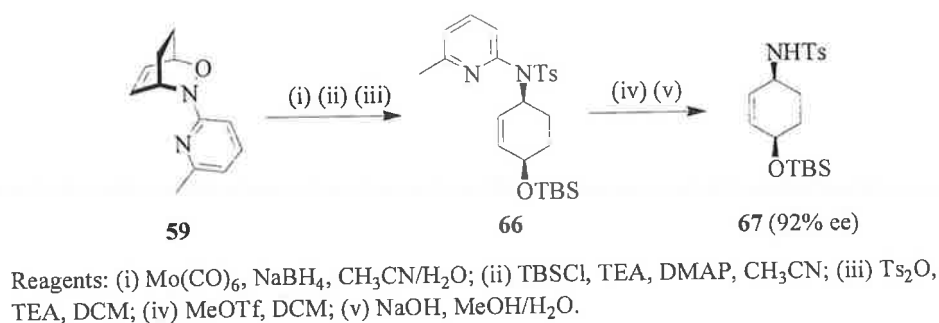
Yamamoto reported a high level of enantio and diastereo-selectivity using iminonitroso species **58** (Scheme 12).²⁵ 6-Methyl-2-nitrosopyridine **58** was reacted with 1,3-cyclohexadiene in the presence of 10 mol % of $[\text{Cu}(\text{MeCN})_4]\text{PF}_6$ and a chiral ligand **60-64** providing the nitroso Diels-Alder adduct **59** in quantitative yield and excellent enantioselectivity (67-92% ee).



Scheme 12

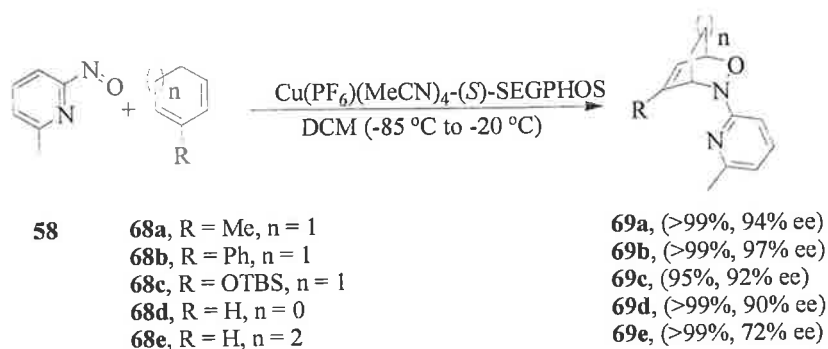
The authors linked the level of enantioselectivity observed to the dimension of the dihedral angle of phosphine ligand.²⁶ It was established that a greater enantioselectivity was obtained using atropoisomer phosphines possessing a narrow dihedral angle. The best result was obtained using (*S*)-SEGPHOS **64** which gave **59** in 92% yield. Yamamoto explained the enantioselectivity observed by preferential formation of stable complex **65** in which one face of the nitroso compound **59** was selectively shielded.

The Diels-Alder cycloadduct **59** was then converted to alcohol **67** in five steps (Scheme 13). The transformation of **59** to **66** entailed cleavage of N-O bond using Mo(CO)_6 and NaBH_4 , followed by TBSCl protection of resulting alcohol and tosylation of the amine functionality to obtain **66**. Intermediate **66** was then converted to desired **67** by pyridine *N*-methylation followed by alkaline hydrolysis. Importantly, the conversion of **59** to **67** occurred without loss of enantioselectivity.



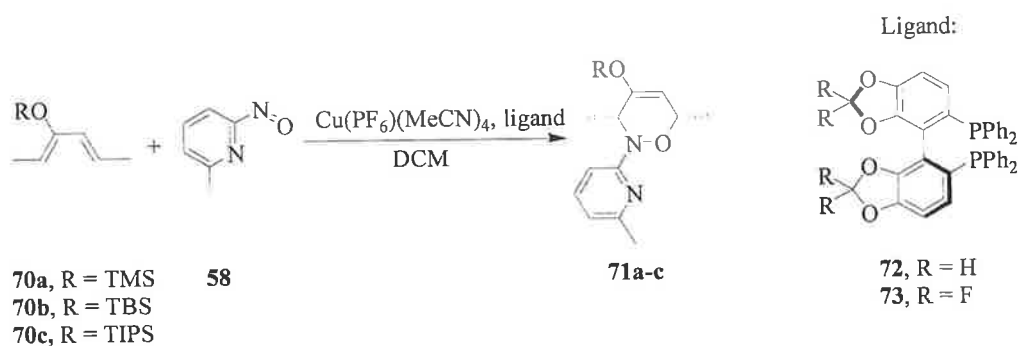
Scheme 13

The same authors carried out the reaction of **58** with cyclic unsymmetrical dienes **68a-e** using $\text{Cu(PF}_6\text{)(MeCN)}_4$ -(*S*)-SEGPHOS as catalyst (Scheme 14). These reactions proceeded with total regioselectivity and adducts **69a-e** were obtained in excellent yields and enantioselectivity.



Scheme 14

Iminonitroso species **58** reacted with acyclic dienes **70a-c** in the presence of Cu^I and (*S*)-SEGPHOS affording the expected adducts **71a-c** in high yields, regioselectivity and enantioselectivity (Scheme 15).²⁷ When 6-methyl-2-nitrosopyridine **58** was reacted with (2*Z*,4*E*)-3-substituted-silyloxy-2,4-hexadienes **70a-c** in the presence of Cu(PF₆)(MeCN)₄-(*S*)-SEGPHOS **72** or Cu(PF₆)(MeCN)₄-(*S*)-DIFLUOROPHOS **73** (10 mol%) the corresponding cycloadducts **71a-c** were obtained with variable enantioselectivity (16% to >99% ee). The authors showed that the enantioselectivity is severely improved by increasing the size of the silyl group (R) present on the diene. Small (R) groups gave low enantioselectivity while larger (R) groups as TIPS ensured an optimal level of enantioselectivity (Table 2).

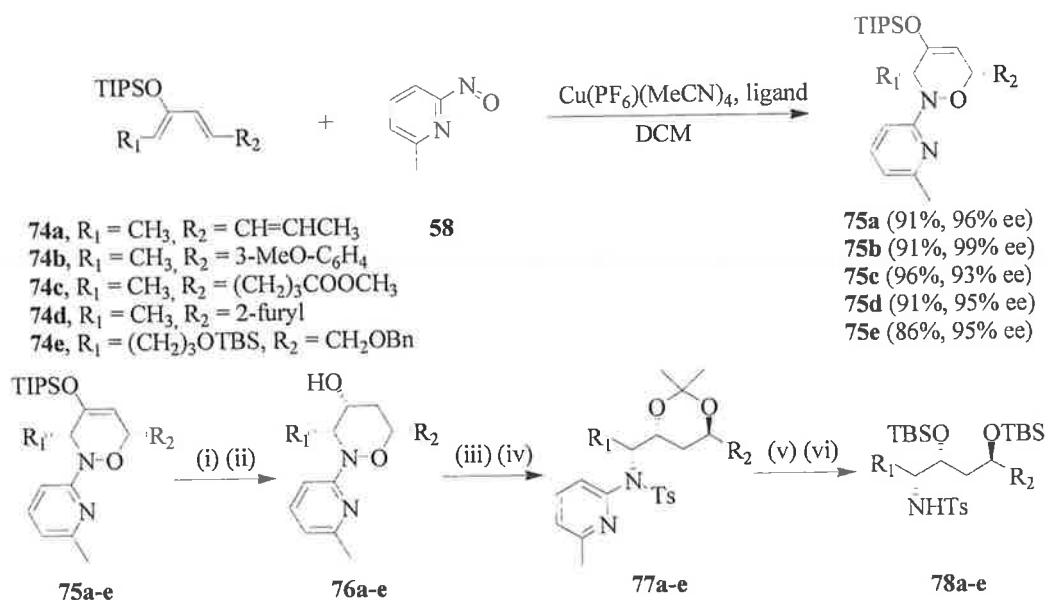


Scheme 15

Table 2

| Diene | Ligand | Yield of 71 (%) | ee (%) |
|-------|--------|-----------------|--------|
| 70a | 72 | 86 | 16 |
| 70b | 72 | 88 | 84 |
| 70c | 72 | 93 | 98 |
| 70c | 73 | 95 | >99 |

The large scope of this reaction was then demonstrated by reacting several functionalized dienes **74a-e** (Scheme 16). Alkyl, aryl, heteroaryl substituted dienes and trienes gave the expected cycloadducts **75a-e** in high yields and enantioselectivity. Compounds **75a-e** were then converted in six steps into protected amino alcohols **78a-e** which were found in many important natural products.²⁸



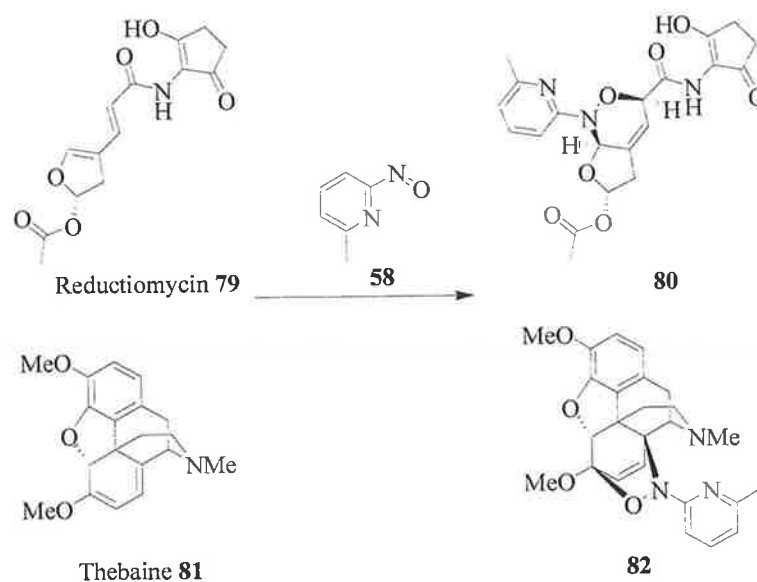
Reagents: (i) TBAF/AcOH; (ii) NaBH_4 (up to 98%, two steps); (iii) Pd/C, H_2 , then 2,2-dimethoxypropane, TsOH; (iv) Ts_2O , diethylisopropylamine, 1,2-dichloroethane; (v) TsOH, MeOH, then TBSOTf, 2,6-lutidine, DCM; (vi) MeOTf, DCM, then 10 N KOH, MeOH.

Scheme 16

Hydrolysis of the silyl group in **75a-e** using TBAF/AcOH and reduction of ketone gave the corresponding alcohols **76a-e** as a single diastereomer. The reductive

cleavage of N-O bond using H_2 and Pd/C followed by protection of the diol and tosylation with Ts_2O afforded ketals **77a-e**. Deprotection of the acetonide in **77a-e**, successive treatment with TBSOTf and final removal of pyridine ring using MeOTf and NaOH furnished the protected amino alcohols **78a-e**.

Iminonitroso Diels-Alder reactions were also used as an efficient method to derivatize natural products containing a diene system.²⁹ Cyclic and acyclic dienes reacted efficiently with 6-methyl-2-nitrosopyridine **58** (Scheme 17). For example, Reductionmycin **79** was reacted with **58** in THF at 0 °C to obtain the cycloadduct **80** as a single isomer (yield >90%). Analgesic Thebaine **81** reacted with **58** in 10 min to give cycloadduct **82** in 99% yield as a single isomer.



Scheme 17

1.3. Acylnitroso dienophiles

Acylnitroso dienophiles **2** are less stable and much more reactive compared to C-nitroso dienophiles **2**, **3**, **4** and **5**. It has been observed that the lifetime of benzoacylnitroso species **83** (Figure 3) is on the order of 1 ms.³⁰

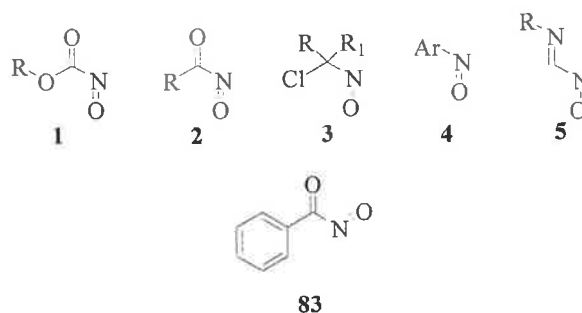
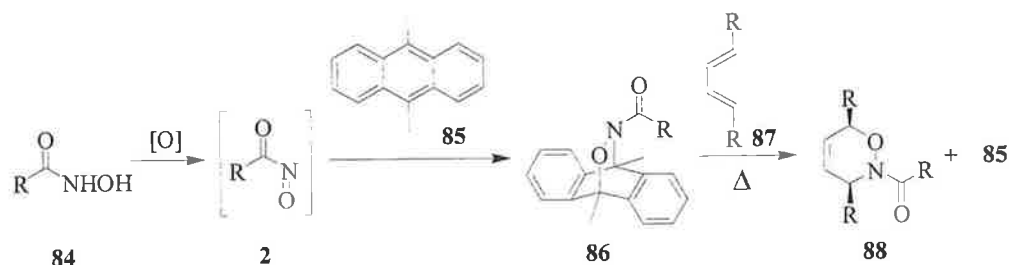


Figure 3

For this reason acylnitroso dienophiles are usually generated *in situ* and consequently trapped by a diene. These compounds have been widely used as efficient hetero dienophiles in cycloaddition reactions with conjugated dienes.³¹

1.3.1. Synthesis of acylnitroso species

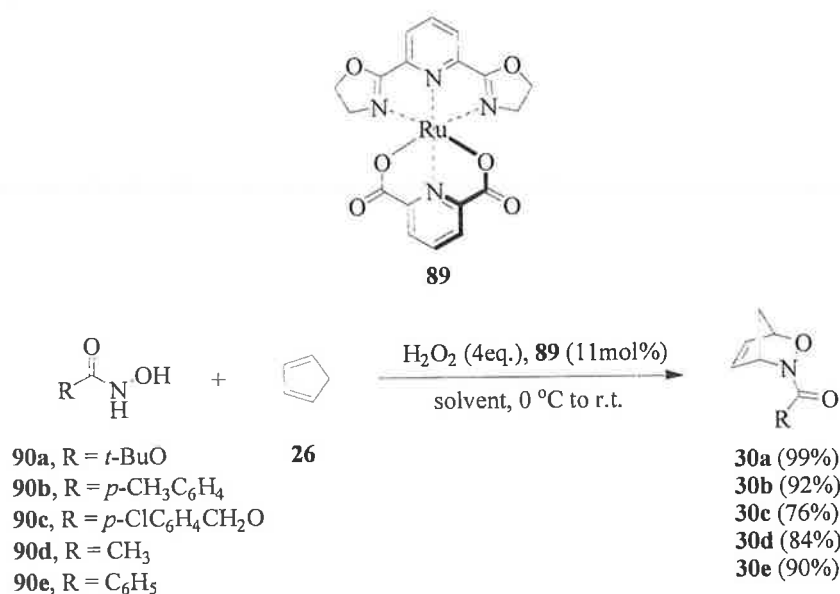
The work on the generation of acylnitroso species was pioneered by Kirby.⁵ Acylnitroso species were generated by oxidation of the parent hydroxamic acid using organic oxidants such as periodate salts,^{5, 32} Dess-Martin periodinane,³² NMO-nitrile oxides,³³ Swern-Moffan reagent,³⁴ *t*-BuOOH³⁵ or inorganic reagents such as PCC³⁶ and hypochlorite.³⁷ Very often these conditions were severe as they did not tolerate the presence of oxygen containing functionalities. For this reason acylnitroso species **2** was trapped with 9,10-dimethylantracene **85** in the form of cycloadducts **86** and readily regenerated by warming (Scheme 18). This strategy allowed the generation of acylnitroso in the presence of sensitive groups without using oxidants. Moreover this method allowed storage of nitroso species for a long time.



Scheme 18

The methodologies relying on general oxidants have the drawback of leaving considerable amounts of inorganic or organic side products. In order to obviate this, several groups have investigated the use of hydrogen peroxide as the terminal oxidant as water would be formed as the only side product.³⁸

Iwasa *et al.* reported that acylnitroso intermediates were generated using $\text{Ru}^{\text{II}}(\text{pybox-dh})(\text{pydic})$ **89** as the catalyst and hydrogen peroxide³⁹ as oxidant (Scheme 19).

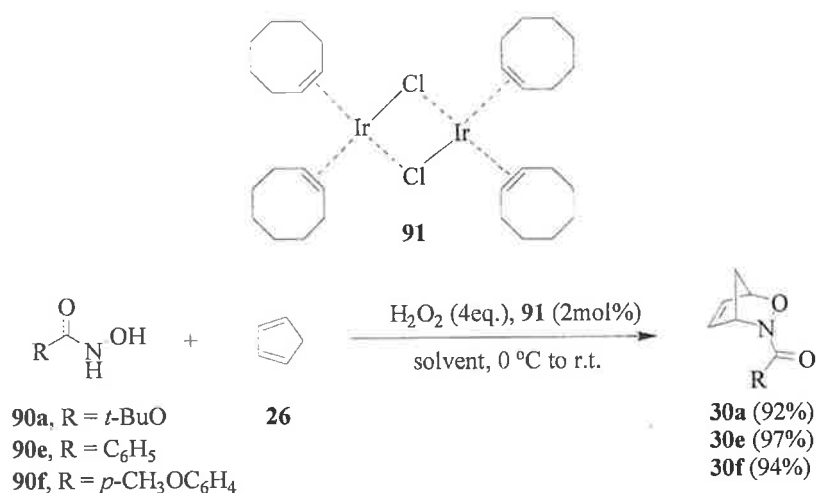


Scheme19

The method was mild, used only small excesses of hydrogen peroxide and afforded desired adducts **30a-e** in good isolated yields. The oxidation of a number of hydroxamates **90a-e** was reported to proceed well at catalyst loading of 11 mol% in

either THF and MeOH/H₂O as the solvent. Particularly reactive hydroxamate **90a** (R = *t*-BuO) was efficiently oxidised at 1 mol% catalyst loading affording **30a** in 91% yield.

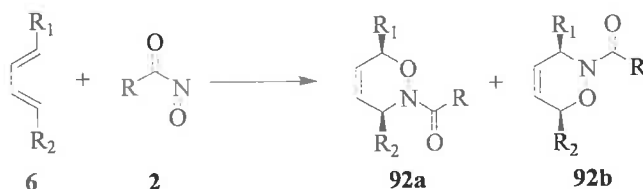
More recently the same group described an Ir^I based catalyst that could be employed for the oxidation of hydroxamates **90a**, **90e**, and **90f** (Scheme 20).⁴⁰ In this report, acylnitroso species were generated from **78** using [Ir(coe)₂Cl]₂ **91** and hydrogen peroxide in THF and trapped *in situ* by dienes to obtain the corresponding 1,2-oxazines **30a,e,f** in high yields.



Scheme 20

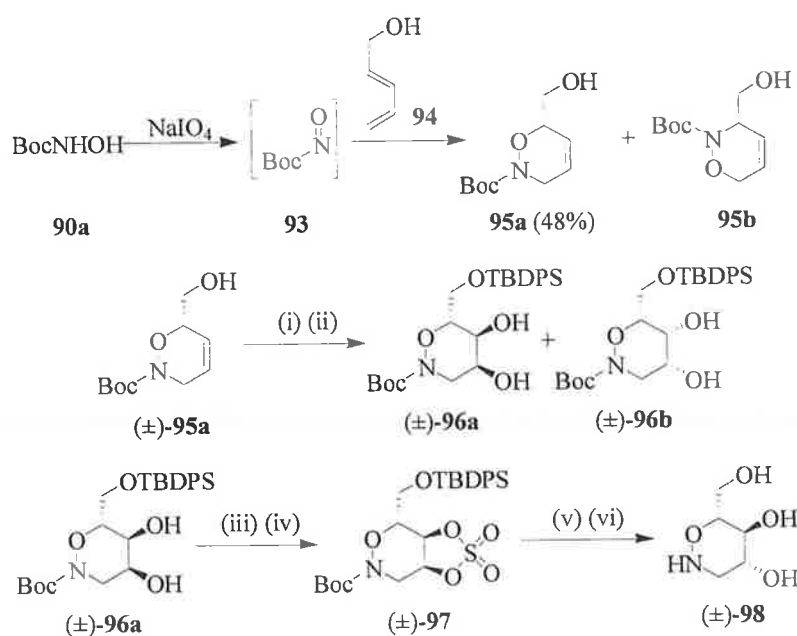
1.3.2. Applications in organic synthesis

Diels-Alder reactions with heterodienophiles have provided entry into a number of important ring systems. The early Kirby studies established that the use of *N*-acylnitroso dienophiles **2** offered an efficient route to access the 3,6-dihydro-1,2-oxazine ring system (**92a,b**) (Scheme 21).⁵



Scheme 21

Elaboration of **92a** or **92b** provided a means to prepare sugar analogues. Bach showed that 3,6-dihydro-1,2-oxazines **95a,b** could be prepared by [4+2] cycloaddition between BocNHOH **90a** and 2,4-pentadienol **94** (Scheme 22).⁴¹



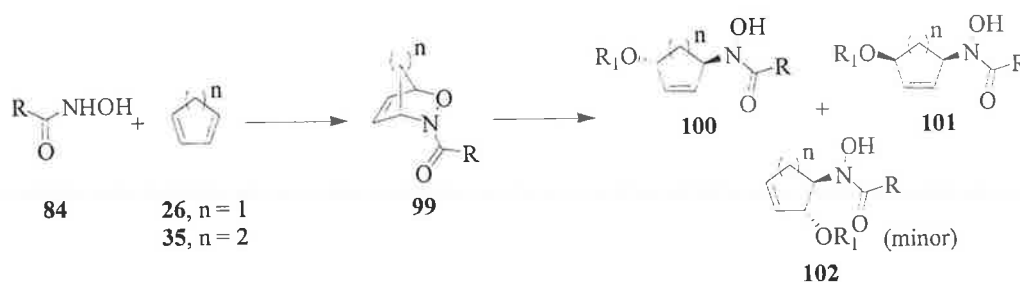
Reagents: (i) TBDPSCl, imidazole, DMF (90%); (ii) OsO₄, acetone/H₂O/*t*-BuOH; (iii) SOCl₂, Et₃N, DCM (67%); (iv) RuO₄, NaIO₄, CHCl₃/CH₃CN/H₂O (67%); (v) NaOBz, DMF; (vi) H₂SO₄, H₂O/dioxane, then Na₂CO₃, MeOH (50% two steps).

Scheme 22

3,6-Dihydro-1,2-oxazine **95a,b** were obtained as a mixture of two regioisomers in a 2 : 1 ratio. Compound **95a** was converted to 1-azagluco analogue **98** in six steps. The alcohol in **95a** was protected using TBDPSCl and then the alkene dihydroxylated to diol **96a,b** with good diastereoselectivity (**96a** : **96b** = 95 : 5). Diol **96a** was then

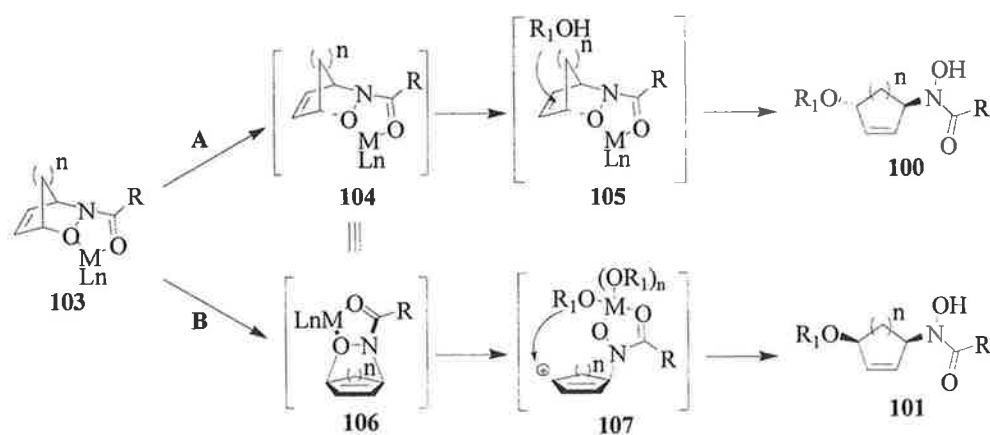
converted to the cyclic sulphate **97** through reaction with thionyl chloride and subsequent oxidation with RuO_4 . **97** was reacted with sodium benzoate and hydrolysed to give 1-azagluco analogue **98**. Compound **98** showed high affinity for β -glucosidase with a K_i of 60 μM .

Miller found that the treatment of HDA adducts **99** with an appropriate Lewis acids led to a ring opening reaction to give *anti*-1,4 and *syn*-1,4-hydroxamic acid **100** or **101** that differ for the relative stereochemistry of the 1,3 aminoalcohol moiety (**Scheme 23**).⁴² Two protocols were established to obtain **100** or **101** in a selective fashion. It was found that the solvent had a major impact on the distribution of products. Treatment of cycloadducts **99** with Fe^{III} or Cu^{II} in an alcohol solvent induced ring opening to afford predominantly *anti*-1,4-hydroxamic acids **100**, while treatment of **99** with Cu^{II} in toluene afforded *syn*-1,4-hydroxamic acids **101**. Compounds **100** and **101** were obtained in yields up to 95%.



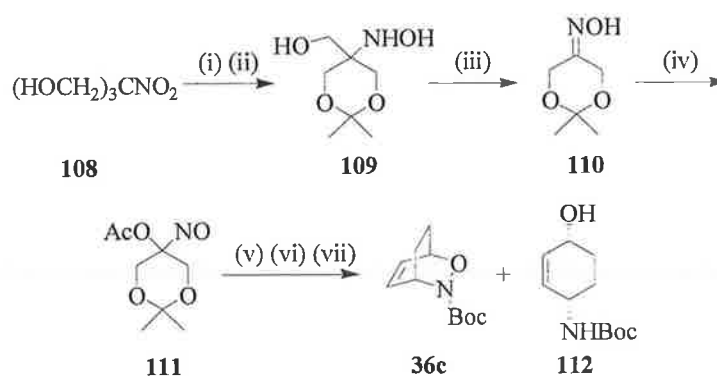
Scheme 23

The effect of solvent on the diastereoselectivity of the reaction was explained as follows. 1,2-Oxazines contain Lewis basic centres that form complex **103** with opportune Lewis acids (**Scheme 24**). The nature of reaction of complex **103** depended on the nature of solvent. In small nucleophilic solvents (such as methanol) an $\text{S}_{\text{N}}2$ pathway lead to inversion of configuration to give mainly an *anti* aminoalcohol **100** (**Scheme 24**, path A). When the nucleophile was sterically demanding an $\text{S}_{\text{N}}1$ pathway prevailed and carbocation **107** was formed. In this case, the addition of nucleophile occurred with retention of configuration due to the directing effect of the hydroxamate metal complex (**Scheme 24**, path B).



Scheme 24

Kouklovsky *et al.* have reported the first example of HDA reaction using α -acetoxynitroso species **111** as dienophile (Scheme 25).⁴³



Reagents: (i) acetone, *p*-TsOH, benzene, reflux; (ii) Al/Hg; (iii) NaIO₄, KH₂PO₄, MeOH/H₂O, (37%, three steps); (iv) PhI(OAc)₂, DCM (67%); (v) 1,3-cyclohexadiene, Lewis acid (20 mol%), toluene, 0 °C; (vi) HCl (1N); (vii) NaOH, Boc₂O.

Scheme 25

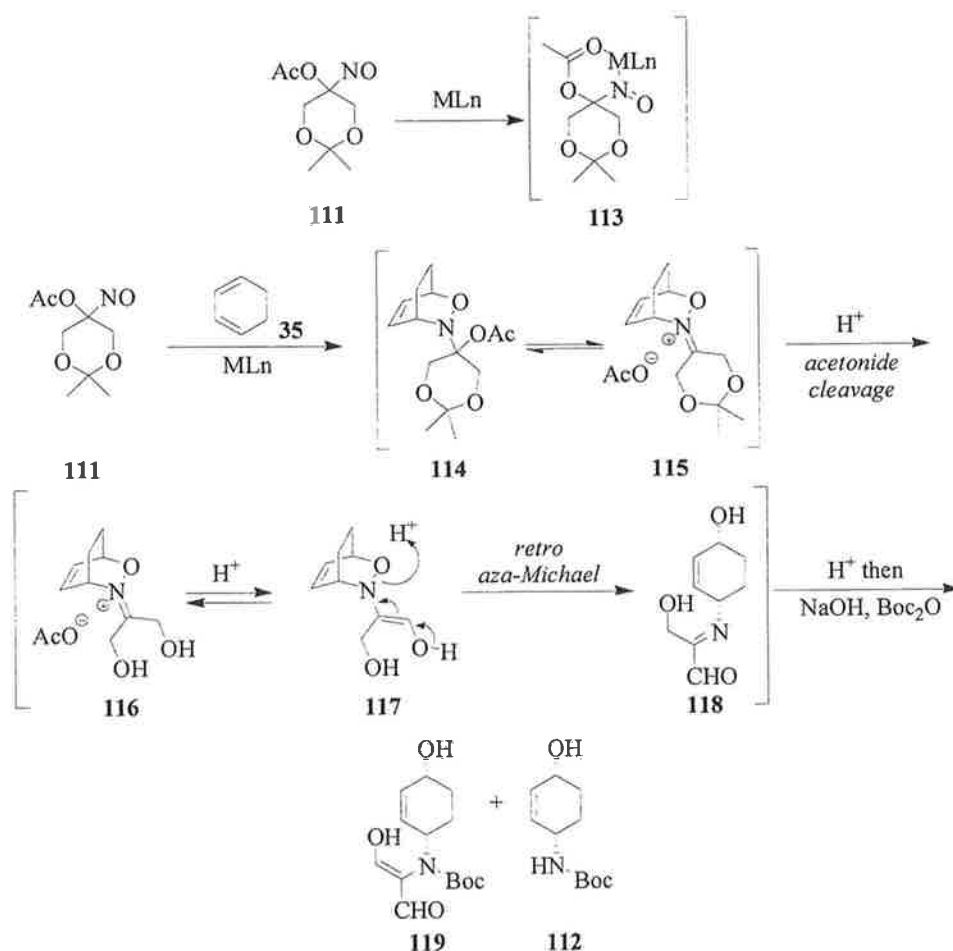
Compound **111** was obtained in four steps from commercially available tris(hydroxymethyl)nitromethane **108**.⁴⁴ Condensation of **108** with acetone in the presence of TsOH followed by reduction with Al(Hg) furnished a corresponding hydroxylamine **109**. The product obtained was converted into oxime **110** by NaIO₄ oxidation. Nitroso species **111** was finally synthesized by oxidation with PhI(OAc)₂. The reaction of **111**

with Lewis acid followed by acidic hydrolysis, neutralization and treatment with (Boc)₂O afforded the expected oxazine **36c** and hydroxycarbamate **112** (ratio **36c** : **112** = 2 : 98). A screening of Lewis acids revealed that Mg(OTf)₂, Cu(OTf)₂ and CrCl₃ were the best enhancers for this reaction (Table 3).

Table 3

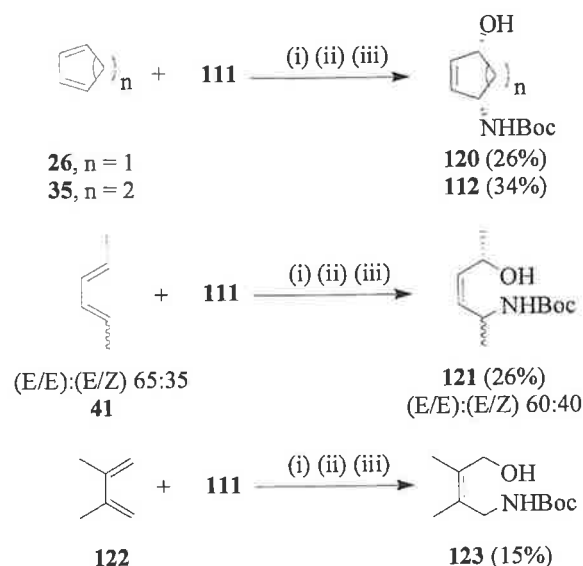
| Lewis acid | 36c/112 ratio | Yields 112 (% three steps) |
|----------------------|---------------|----------------------------|
| - | 2/98 | 14 |
| Mg(OTf) ₂ | 2/98 | 41 |
| CrCl ₃ | 2/98 | 41 |
| Cu(OTf) ₂ | 2/98 | 41 |

The effect of the Lewis acid on the reaction yield was explained by the formation of a six-membered ring complex **113** which was formed by treatment of α -acetoxynitroso compound **111** with a metal (Scheme 26). The formation of **112** could be explained as shown in Scheme 26. Compounds **114** and **115** arose from the cycloaddition of **111** and 1,3-cyclohexadiene. It is believed that **114** and **115** are in equilibrium. Acid hydrolysis of the acetonide moiety lead to 1,3-diol **116**, which equilibrated to the corresponding enaminol **117**. Retro aza-Michael reaction of **117** followed by hydrolysis of the resulting imine and protection of the amino group as a *tert*-butylcarbamate finally lead to product **112**. Support for this mechanism was obtained by isolating traces of **119** in the reaction mixture.



Scheme 26

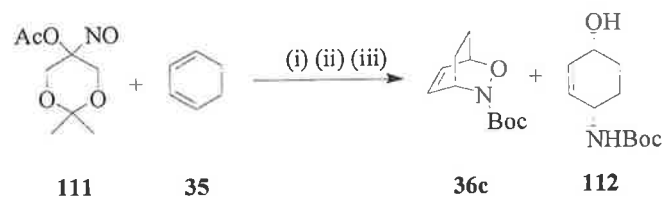
The reaction of **111** with cyclic **26**, **35** and acyclic **41**, **122** 1,3 dienes using $\text{Cu}(\text{OTf})_2$ and CrCl_3 as Lewis acids gave the corresponding hydroxycarbamates **120**, **112**, **121** and **123** in moderate yields (**Scheme 27**). This procedure was interesting giving directly protected amino alcohols without using toxic or expensive reagents such as $\text{Mo}(\text{CO})_6$ and $\text{Na}(\text{Hg})$ amalgam, used to cleave the N-O bond in 1,2 oxazines.



Reagents: (i) $\text{Cu}(\text{OTf})_2$ (20 mol%), toluene; (ii) HCl (1N); (iii) NaOH , Boc_2O ; (iv) CrCl_3 (20 mol %).

Scheme 27

It was observed that traces of water led to a dramatic reversal of oxazine **36c** : hydroxycarbamate **112** ratio (**Scheme 28**). The pioneering studies of Breslow explained that reaction rates, and regio- and stereochemistry of Diels-Alder reactions could be influenced by the presence of water.⁴⁵ In this case the addition of just 2 equiv of water inverted the product ratio **36c** : **112**.⁴⁶ Therefore the HDA cycloaddition of **111** in the presence of 20 mol% of $\text{Zn}(\text{OTf})_2$ was conducted in pure water, in absence of any organic solvent or in pure water without the addition of a Lewis acid where it gave the optimal oxazine/hydroxycarbamate ratio (**36c/112**) (**Table 4**).



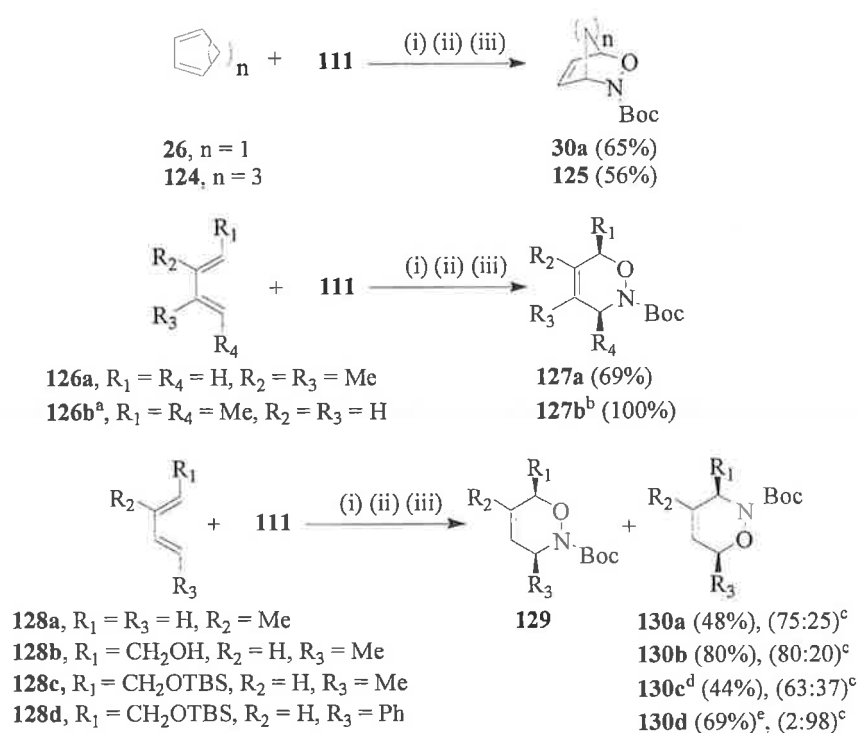
Reagents: (i) $\text{Zn}(\text{OTf})_2$, H_2O , Toluene; (ii) HCl ; (iii) NaOH , Boc_2O .

Scheme 28

Table 4

| Zn(OTf) ₂ (mol%) | Water (eq.) | Yield (%) | 36c/112 ratio |
|-----------------------------|-----------------------|-----------|---------------|
| 20 | - | 40 | 8/92 |
| 20 | 2 | 39 | 60/40 |
| 20 | 10 | 53 | 85/15 |
| 20 | H ₂ O only | 78 | 90/10 |
| - | H ₂ O only | 74 | >98/2 |

Cyclodienes **26** and **124** reacted similarly affording the corresponding cycloadducts **30a**, **125** in 65 and in 56% yield respectively (**Scheme 29**).



Reagents: (i) H₂O; (ii) HCl; (iii) NaOH, Boc₂O; ^a (E,E)/(Z,E) = 70:30 mixture; ^b containing 20% of trans-isomer; ^c ratio **129/130**; ^d 50% H₂O/THF; ^e based on 84% conversion.

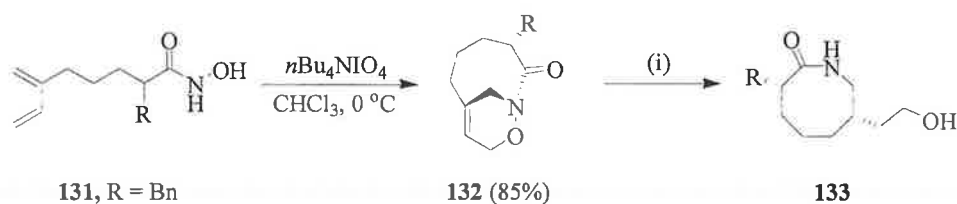
Scheme 29

Dissymmetric acyclic dienes **126**, **128** gave the corresponding adducts **127**, **130** in moderate to good yields with a variable regioisomeric ratio. Importantly in these

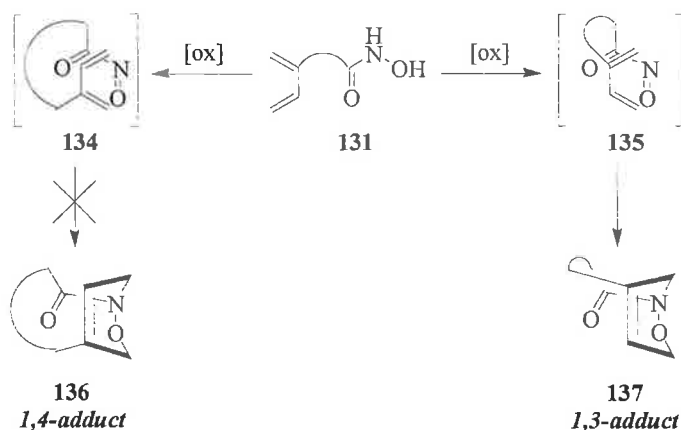
experiments no corresponding hydroxycarbamates were observed. Therefore it was possible to use the same α -acetoxynitroso species **111** to access two different classes of compounds namely the 1,2-oxazine or the hydroxycarbamate simply operating in different solvent media and in the presence of a suitable Lewis acid.

An important extension of nitroso HDA reaction includes the intramolecular version of this reaction which has been applied in the synthesis of nitrogen containing heterocycles.

Medium-ring lactam as **133** is present in a large number of natural and unnatural bioactive compounds. In particular lactams **133** were used as sedative or anti-hypertensive agents.⁴⁷ The conventional cyclization method of acyclic precursor for the preparation of this class of compounds was shown to be difficult in terms of regio and stereo control. The use of intramolecular cycloaddition then provided an opportunity to control the regio- and the stereo-chemistry of the products obtained. For example Shea reported an elegant synthesis of azocin-2-one **133** *via* HDA reaction (Scheme 30).⁴⁸



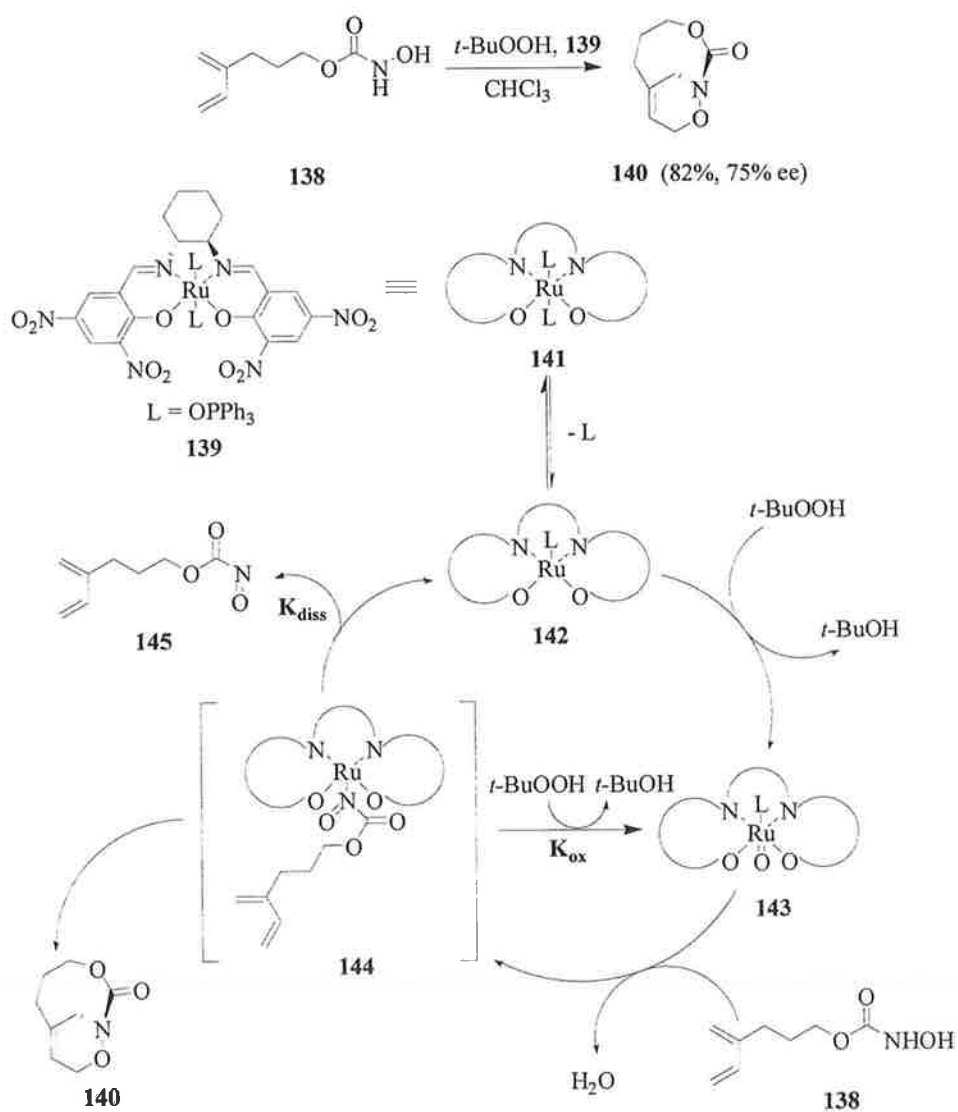
Reagents: (i) Na(Hg), Na₂HPO₄, EtOH (80%)



Scheme 30

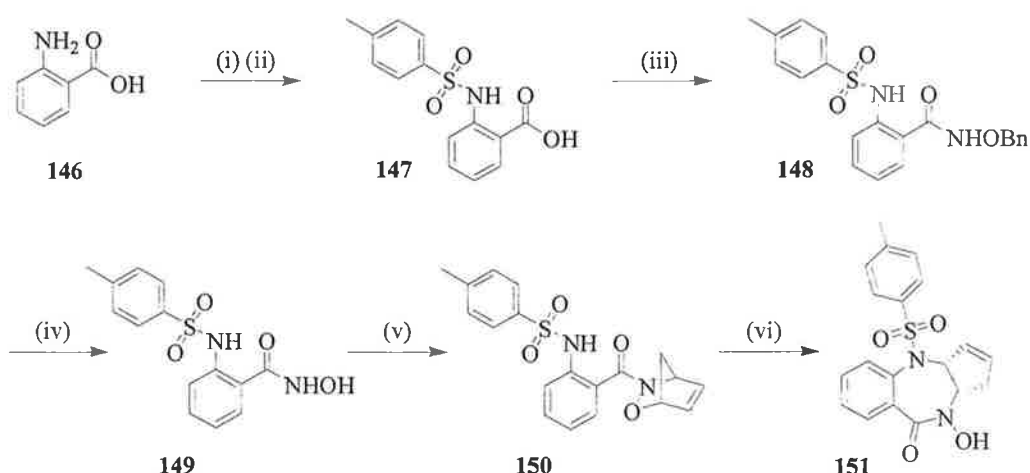
The synthetic plan involved the preparation of hydroxamate **131**, that was then oxidised to the corresponding acyl nitroso using periodate. 1,3-Adduct **132** was obtained as a single diastereomer (**Scheme 30**). The regiochemical outcome is consistent with the estimated energies of regioisomeric cycloadducts. In the bicyclo[5.n.n.]alkene series, the estimated energy of the 1,3-regioisomer (bicyclo[5.3.1]alkene **137**) is 8.5 kcal mol⁻¹ lower than of analogues 1,4-regioisomers (**136**). Cleavage of N-O bond using Na(Hg) amalgam, provided *cis*-3,7-disubstituted azocin-2-one **133** in good yield.

A total synthesis of oxazinolactam **140** *via* nitroso HDA was also reported (**Scheme 31**).⁴⁹ In analogy with their synthesis of azocin-2-one **133** Shea and co-workers prepared the *N*-hydroxy formate ester **140** which was then treated with *t*-BuOOH in the presence of Ru^{II}SALEN complex **139** to give the expected oxazinolactam **140** in good yield (up to 82%) and enantioselectivity (up to 75% ee). Shea noted that the lifetime of chiral complex **144** is dependent of its rate of reoxidation to Ru-oxo species **143** (K_{ox}) and also on the dissociation of acylnitroso **145** from complex **144** (K_{diss}). This was a crucial point as **145** could undergo cycloaddition without the chiral complex being involved, leading to loss of enantioselectivity. In order to decrease the extent of reoxidation of **144** to **143**, this reaction was carried out at high dilution, with the optimal formation of **140** achieved at 7.2×10^{-2} M.



Scheme 31

Miller reported an application of nitroso HDA reaction in which the medically relevant 1,4-benzodiazepine core was obtained.⁵⁰ In this synthesis, the appropriate functionalized cycloadduct **150** was prepared from anthranilic acid **146** (**Scheme 32**).

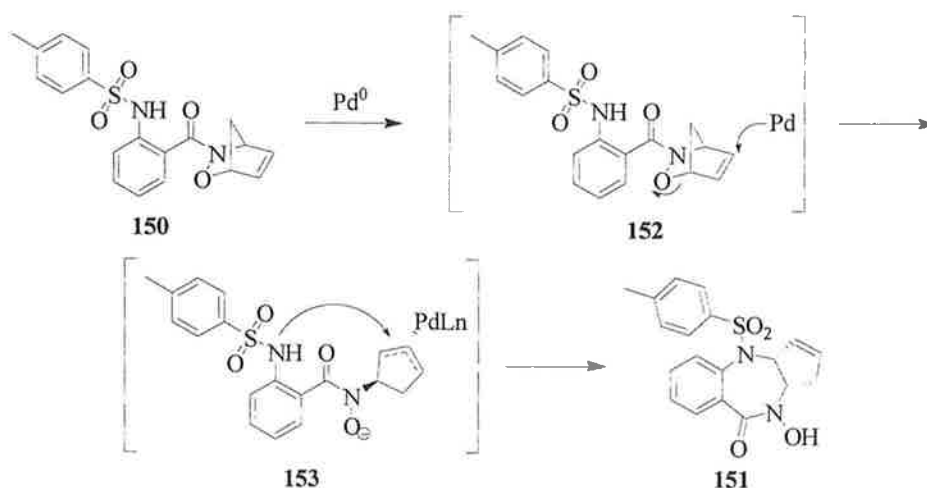


Reagents: (i) TsCl, Na₂CO₃, H₂O, 60 °C; (ii) HCl (69% two steps); (iii) BnONH₂, EDC, DCM (81%); (iv) H₂, Pd/C, MeOH (99%); (v) cyclopentadiene, NaIO₄, MeOH, H₂O, 79%; (vi) Pd(PPh₃)₄, THF, reflux (20%).

Scheme 32

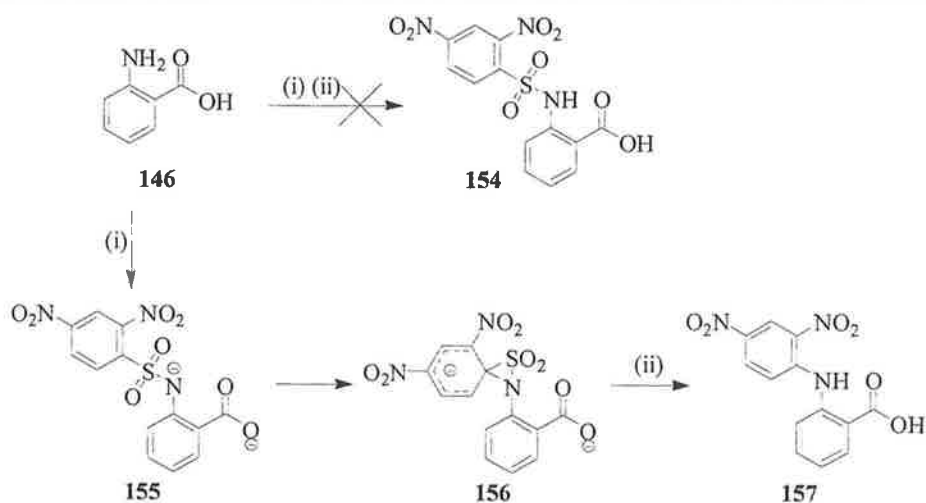
The synthesis of **151** started with a selective tosylation to obtain the *N*-tosyl anthranilic acid **147** in two steps. Compound **147** was then reacted with EDC (1-Ethyl-3-[3-dimethylaminopropyl]carbodiimide) and coupled with *O*-benzyl hydroxylamine to provide *O*-benzyl hydroxamate **148**. Removal of benzyl group by hydrogenolysis gave hydroxamic acid **149** in quantitative yield. Oxidation of **149** in the presence of cyclopentadiene induced the acylnitroso HDA reaction to give the desired *N*-tosyl cycloadduct **150**. Treatment of **150** with Pd⁰ provided the target benzodiazepine **151** in modest yield (20%).

The conversion of **150** to **151** proceeded through a nucleophilic attack brought by Pd⁰ to the π system of cycloadduct **150** (Scheme 33). The resulting π -allyl complex in **153** was then a substrate for a nucleophilic attack by the sulfonamide moiety, resulting in the formation of **151**.



Scheme 33

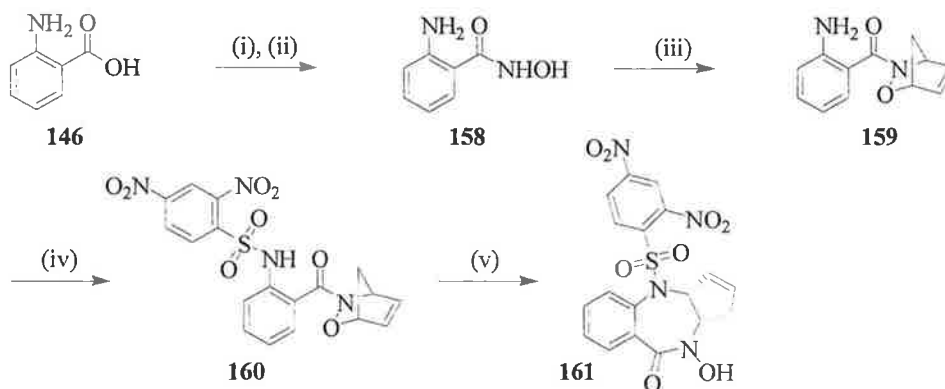
The pK_a of the sulfonamide group had an effect on the reaction yields that was increased with the decrease of nitrogen pK_a . Consequently, the presence of two nitro groups on the sulfonamide ring ensured high yields. The inclusion of additional nitro group imposed a revision of the synthetic strategy. When reacted with a 2,4-dinitrobenzenesulfonyl chloride and base, anthranilic acid **146** did not furnish desired **154** but the aniline derivative **157** (Scheme 34).



Reagents: (i) 2,4-dinitrobenzenesulfonyl chloride, Na_2CO_3 , H_2O , 60°C ; (ii) HCl .

Scheme 34

It was believed that the presence of two nitro groups favoured an intramolecular rearrangement of the sulfonamide moiety. Therefore hydroxamic acid **158** was prepared from antranilic acid **146** using BnONH_2 and EDC followed by hydrogenation (Scheme 35).

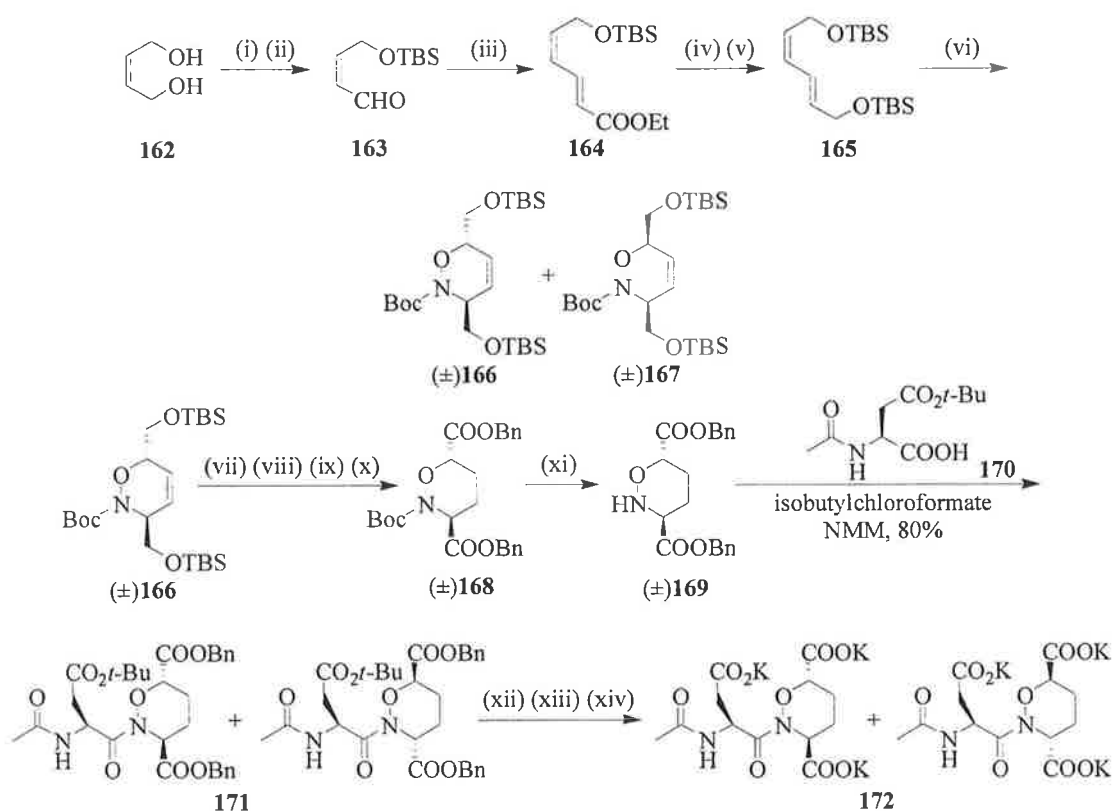


Reagents: (i) BnONH_2 , EDC, DCM (71%); (ii) H_2 , Pd/C, MeOH (99%); (iii) cyclopentadiene, NaIO_4 , MeOH, H_2O , (58%); (iv) 2,4-dinitrobenzenesulfonyl chloride, pyridine, DCM (56%); (v) $\text{Pd(PPh}_3)_4$, THF, reflux (56%).

Scheme 35

Compound **158** was oxidised to its nitroso intermediate using NaIO_4 and trapped by cyclopentadiene to cycloadduct **159**. The treatment of **159** with 2,4-dinitrobenzenesulfonyl chloride and pyridine afforded compound **160** in moderate yield. Exposure of **160** to Pd^0 furnished 1,4-benzodiazepine **161** in 56% yield.

A further synthetic application of nitroso HDA reaction involved the preparation of peptidomimetic scaffolds which showed remarkable activity as inhibitors of *N*-acetylated- α -linked-acidic-dipeptidase (NAALADase).⁵¹ In this report, a diastereomeric mixture of oxazines **166** and **167** was obtained submitting diene **165** to HDA reaction (Scheme 36).

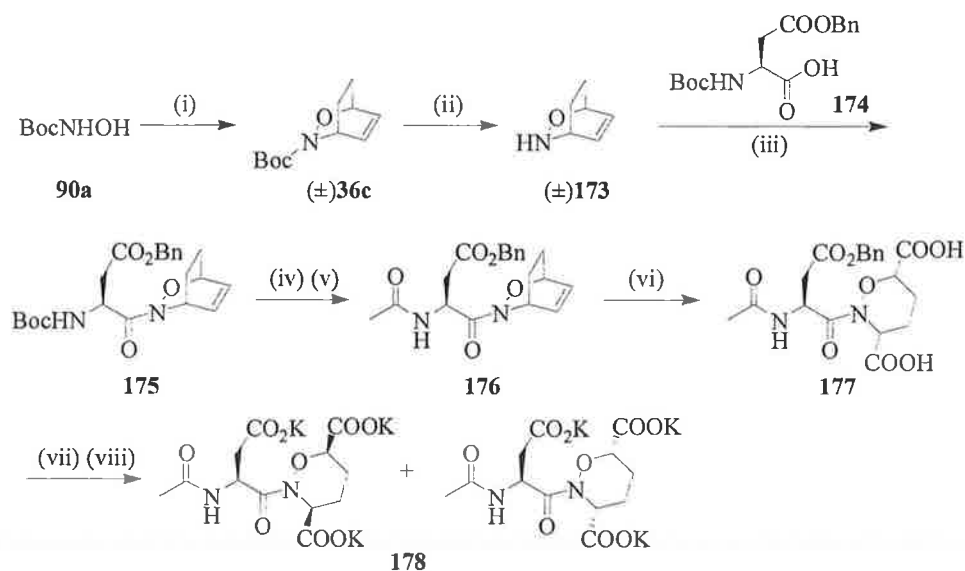


Scheme 36

Diene **165** was prepared in five steps from diol **162**. Thus, commercially available *cis*-diol **162** was protected as TBS ether and then oxidized to corresponding aldehyde **163** using the Dess-Martin reagent. The resulting aldehyde was transformed to ester **164** *via* a Wittig reaction. Subsequent reduction and protection provided the desired (*E,Z*)-diene **165**. Diene **165** reacted with Boc-nitroso to provide a 1 : 1 mixture of *trans* and *cis* adducts **166** and **167** respectively. The *trans* isomer **166** was separated and carried through the synthesis of **168**. This involved cleavage of the silyl ether by TBAF, hydrogenation of the alkene moiety, oxidation of the resulting alcohols to carboxylates and protection of the acids as benzyl esters. The Boc protection in **168** was cleaved by

treatment with TFA to give the corresponding free amine **169**. The use of isobutyl chloroformate and NMM as coupling reagent afforded **171** as an inseparable mixture of diastereomers. Removal of *tert*-butyl group followed by hydrogenolytic cleavage of the benzyl protecting groups and ion exchange chromatography, gave the *trans*-potassium salts **172** as a diastereomeric mixture.

The *cis*-potassium salt **178** was obtained by a diverse reaction sequence (Scheme 37).



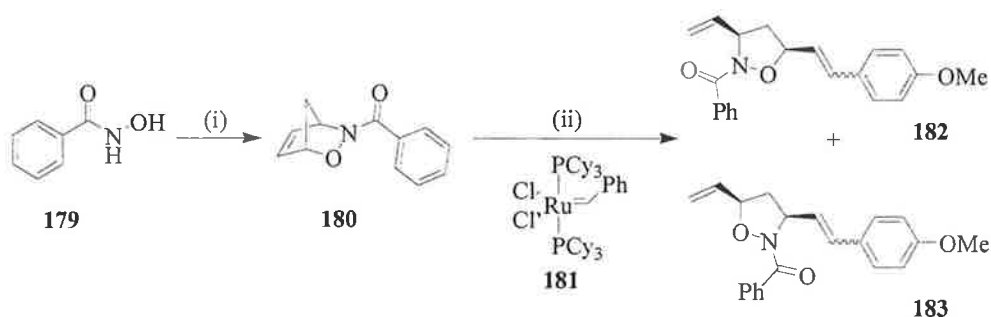
Reagents: (i) 1,3-cyclohexadiene, NaIO₄, MeOH/H₂O (82%); (ii) TFA, DCM, then Na₂CO₃; (iii) EDC·HCl, AtOH, Na₂CO₃; (iv) TFA, Na₂CO₃; (v) Ac₂O, Py (92%); (vi) KMnO₄, K₂CO₃ (92%); (vii) H₂, Pd/C, MeOH; (viii) ion exchange column (80% two steps).

Scheme 37

Diels-Alder adduct **36c** was obtained by oxidation of BocNHOH in the presence of 1,3-cyclohexadiene. **36c** was then treated with TFA to provide free amine **173**, which was coupled with a suitably protected aspartic acid unit **174** using EDC and AtOH as coupling reagents. This reaction afforded desired **175** in good yield. The Boc group in **175** was removed and the resulting free amine treated with acetic anhydride in the presence of pyridine to give **176**. Oxidative cleavage of the double bond in **176** with KMnO₄ in a basic media produced diacid **177**. Hydrogenolysis of benzyl ester in **177**,

followed by ion exchange chromatography, provided the desired *cis*-potassium salt **178** as a mixture of diastereomers.

The HDA reaction was also combined⁵² with ring opening metathesis/cross metathesis reaction (ROM/CM).⁵³ In this context, cycloadduct **180**, prepared by the periodate oxidation of benzohydroxamic acid in the presence of 1,3-cyclopentadiene, was reacted with Grubbs' catalyst **181** to forms a mixture of *E* and *Z* regioisomers **182** and **183** in moderate yield (**Scheme 38**).

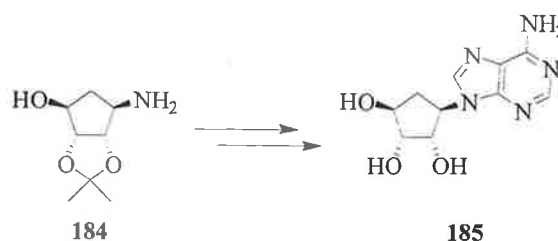


Reagents: (i) 1,3-cyclopentadiene, IO_4^- ; (ii) 1-Methoxy-4-vinyl-benzene, DCM (57%).

Scheme 38

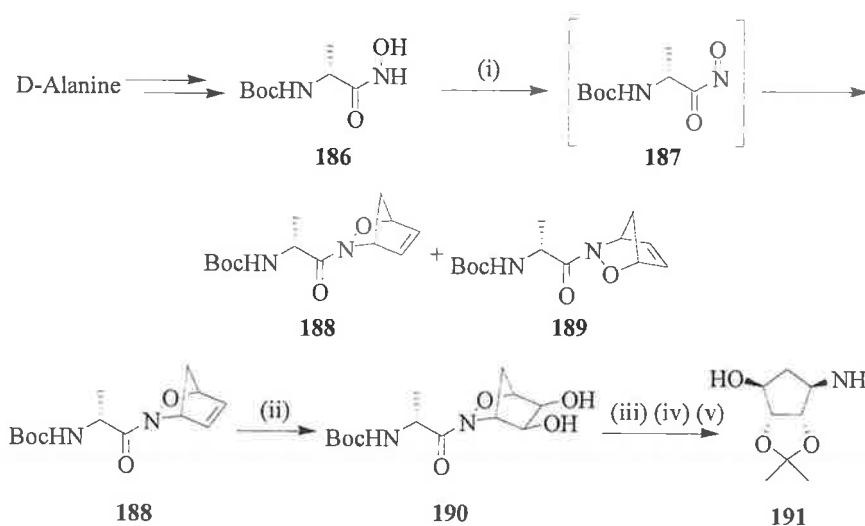
1.4. Asymmetric acylnitroso Diels-Alder reactions

Considering what was exposed so far the cycloaddition of acylnitroso compounds to cyclic and acyclic dienes represents a versatile and synthetically important reaction. The cleavage of the N-O bond of HDA cycloadducts led to protected amino alcohols which could be employed to prepare a large number of compounds. For example, amino alcohol **184** has been used as in the synthesis of antiviral carbocyclic nucleosides **185** (**Scheme 39**).⁵⁴



Scheme 39

Miller reported a simplified preparation of enantiomerically pure **191** (Scheme 40).⁵⁵

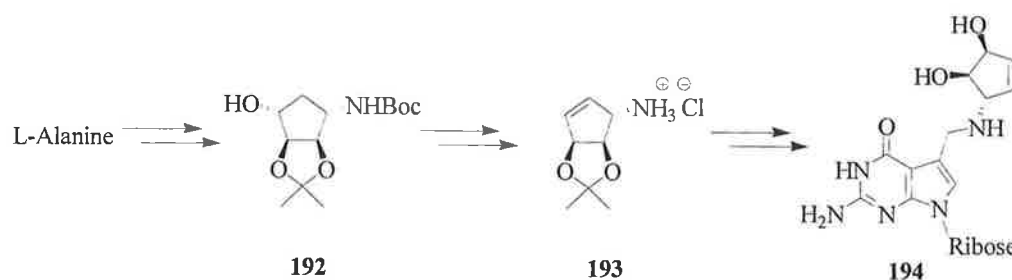


Reagents: (i) (COCl)₂, DCM, cyclopentadiene, DCM, then pyridine; (ii) OsO₄, NMO, (CH₃)₂C(OCH₃)₂, TsOH; (iii) NaBH₄; (iv) H₂, Pd/C.

Scheme 40

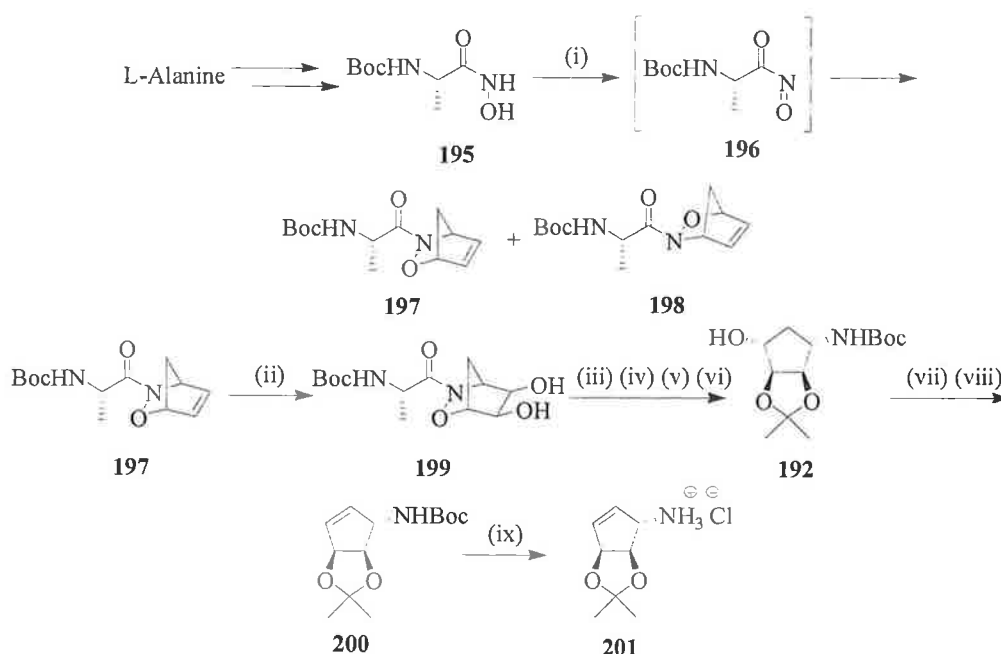
This synthesis relied on hydroxamic acid **186**, which was obtained from D-alanine. The transient acylnitroso intermediate **187** was trapped with cyclopentadiene generating cycloadducts **188** and **189** as a 5.9 : 1 mixture of diastereomers. Dihydroxylation of **188** provided a single diastereomer **190** resulting from an *exo* approach of OsO₄ to the alkene. Diol **190** was protected as an acetonide, the chiral auxiliary reductively removed and the N-O bond cleaved. Amino alcohol **191** was obtained in 36% overall yield from Boc-D-ala-NHOH **186**.

Alcohol **192**, which possesses the opposite absolute stereochemistry of **184**, was obtained starting from L-alanine using the same reaction sequence. Compound **192** was a key intermediate in the synthesis of **193** which is a fragment of Nucleoside Q **194** (Scheme 41).⁵⁶



Scheme 41

Nucleoside Q, known also as queuosine, is present in several tRNA of plants and animals. The interest in Nucleoside Q arose from its ability to affect the rate of tumor growth.⁵⁷ The synthetic route to amino cyclopentene **193** is shown below (Scheme 42). Hydroxamic acid **195**, readily accessible from L-alanine, was oxidized to the acylnitroso species **196**, which was trapped with cyclopentadiene to produce cycloadducts **197** and **198** as 5 : 1 mixture of separable diastereomers. The major diastereomer **197** was then transformed into enantiopure diol **199** by dihydroxylation. Compound **199** was protected as acetonide, the chiral auxiliary removed using mild conditions, the N-O bond cleaved by hydrogenation and followed by treatment with (Boc)₂O to provide protected aminoalcohol **192**. Compound **192** was converted into the corresponding mesylated derivative and dehydrated to **200**. Desired compound **193** was finally prepared from **200** by treatment with diluted aqueous HCl.

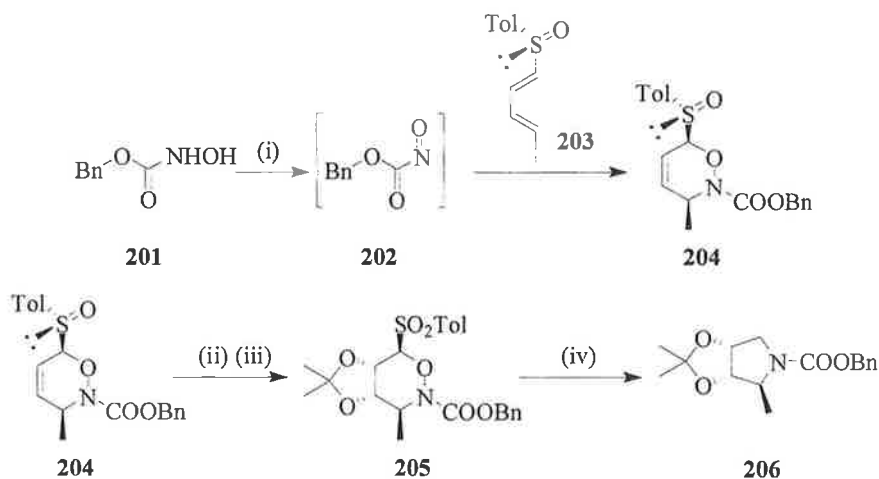


Reagents: (i) (COCl)₂, DMSO, DCM, Py, cyclopentadiene, 70%; (ii) OsO₄, NMO, THF/H₂O; (iii) (CH₃)₂C(OMe)₂, TsOH; (iv) NaBH₄, MeOH; (v) H₂, Pd/C, MeOH; (vi) Boc₂O, Na₂CO₃, THF/H₂O, 64% five steps; (vii) MsCl, Et₃N, DCM, 95%; (viii) DBU, toluene, reflux, 76%; (ix) 3M HCl, Et₂O.

Scheme 42

Asymmetric HDA reactions can also be carried out using optically pure 1,3-dienes as chiral auxiliaries. For instance, chiral 1-sulfinyl-1,3-butadienes **203** were used efficiently in asymmetric HDA reaction.⁵⁸ These reactions often displayed a high level of stereoselectivity. Additionally, the ease of transformation of their adducts through highly stereocontrolled rearrangements made these reactions a valuable tool for the construction of stereodefined molecules.⁵⁹ The first asymmetric HDA reaction of [(*S*)-*R*]-1(*E*,3*E*)-1-*p*-tolylsulfinyl-1,3-pentadiene **203** with benzyl nitrosoformate **202** was reported by Garcia Ruano *et al.* (Scheme 43).⁶⁰ In this report, the dienophile **202** was generated *in situ* by oxidation of *N*-benzyloxycarbonyl hydroxamic acid **201** with Bu₄NIO₄. Acylnitroso **202** was then trapped by diene **203** and the corresponding cycloadduct **204** was isolated in 54% yield. The reaction proceeded with complete regioselectivity and high stereoselectivity. Successive transformations of **204** led to enantiomerically pure acetone **205** through dihydroxylation with OsO₄ followed by

treatment with DMP and PTSA. The sulfinyl group was oxidized to sulfone in this process. Compound **205** was converted with a one-pot transformation into enantiopure dihydroxypyrrolidine **206** with hydrogenolysis followed by treatment with benzyl chloroformate in aqueous NaHCO_3 .



Reagents: (i) Bu_4NIO_4 , DCM (54%); (ii) OsO_4 , NMO, acetone/ H_2O (42%); (iii) DMP, PTSA, acetone (89%); (iv) H_2 , Pd/C, then ClCOOBn , NaHCO_3 , H_2O (96%, two steps).

Scheme 43

The stereochemical course of the HDA reaction could be explained considering that the heterodienophile approached the less hindered face of diene with the $\text{S}=\text{O}$ bond in *s-trans* conformation respect to $\text{C}(1)=\text{C}(2)$ (**Figure 4**).

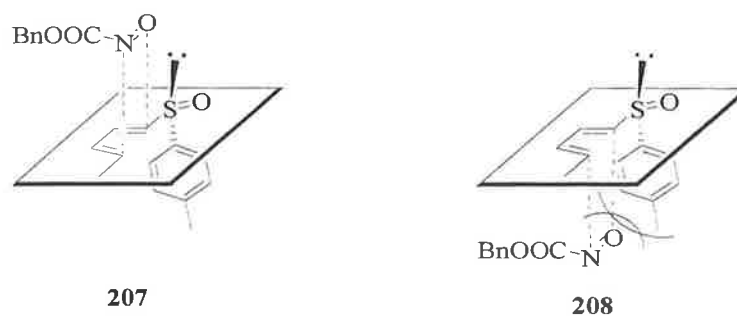
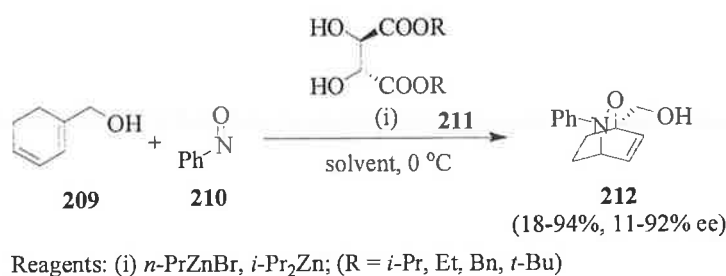


Figure 4

Electrostatic repulsion between the carbonyl and sulfinyl oxygens in the transition state was invoked to justify the high reactivity of the *s-trans* conformation of sulfinyl oxygen. The nitroso species could approach the diene from the face containing the lone pair (**Figure 4, 207**) or from the one containing the tosyl ring (**Figure 4, 208**). In the first case the nitroso did not experience steric hindrance being the lone pair small. In the second case the steric hindrance of tosyl group prevented the approach of the nitroso to the diene.

Development of asymmetric HDA reactions of nitroso compounds has been for a long time restricted to only diastereoselective reactions using chiral dienes or chiral nitroso compounds. Recently, Ukaji and Inomata have elaborated the first example of nitroso HDA reaction utilizing tartatic acid ester as chiral ligand.⁶¹ In the experiment described, (cyclohex-1,3-dienyl)methanol **209** was reacted with nitrosobenzene **210**, in the presence of (*R,R*)-tartrate ester **211** and an alkyl zinc. This reaction proceeded to give cycloadduct **212** with a complete regioselectivity, excellent yield and high enantioselectivity (**Scheme 44**).

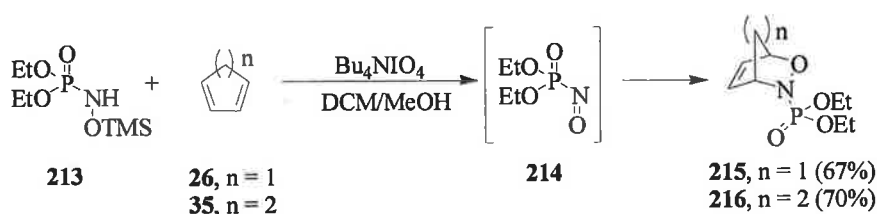


Scheme 44

The enantioselectivity of this reaction was profoundly influenced by the type of solvent and the tartrate ester: *tert*-butyl methyl ether and di-*tert*-butyl tartrate gave the best results (94% yield, 92% ee). The role of alkyl zinc derivatives was not established, but it was postulated that it was involved in a complex together the diene, the tartaric ester and the nitroso species.

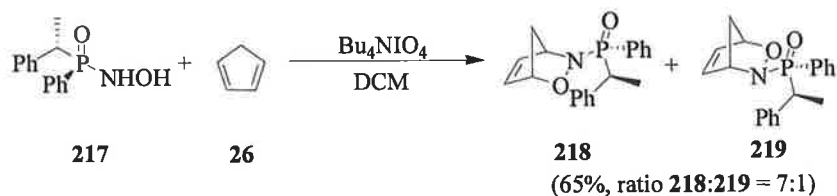
1.5. *P*-Nitroso dienophiles

Nitrosophosphates represent an alternative class of nitroso intermediates that can be used as efficient dienophiles. Periodate oxidation of *N*-(diethylphosphoryl)-*O*-(trimethylsilyl) hydroxylamine **213** in the presence of 1,3-cyclopentadiene or 1,3-cyclohexadiene produced cycloadduct **215** and **216** respectively in good yield (Scheme 45).⁶²



Scheme 45

Asymmetric *N*-hydroxyphosphinamides reacted with dienes to give a mixture of products enriched in a single diastereomer. Reaction of chiral phosphine oxide **217** with 1,3-cyclopentadiene in the presence of Lewis acid resulted in 7 : 1 ratio of diastereomers **218** : **219** (Scheme 46).⁶³

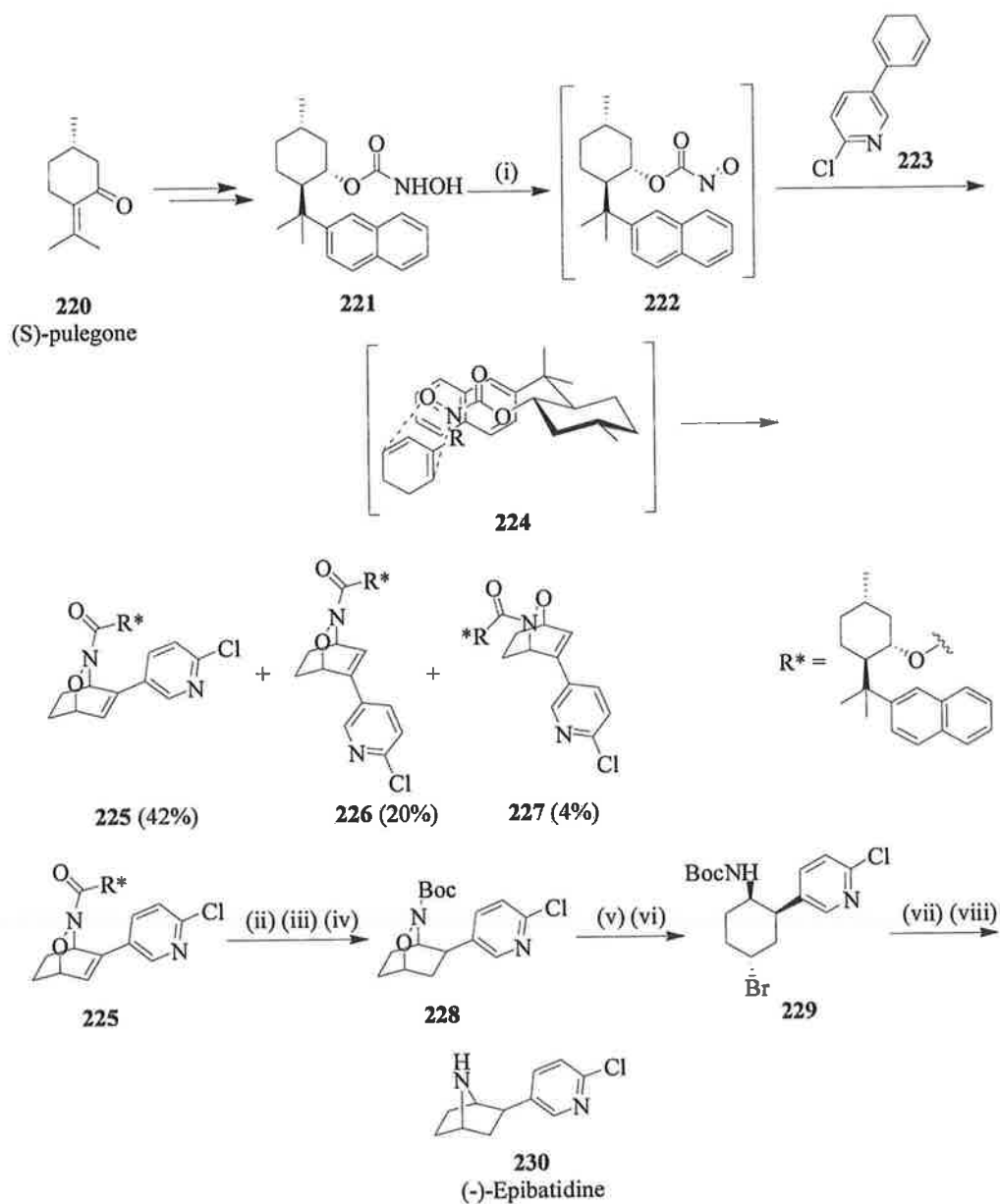


Scheme 46

1.6. Synthesis of natural products

Several natural products were synthesized using HDA cycloadducts as key intermediates. This includes (-)-Epibatidine, (+)-Azimine, (+)-Carpaine, (-)-Lepadine A, B and C, (+)-Loline, (-)-Kainic acid and (+)-Streptazoline.

Kibayashi and co-workers described a total synthesis of (-)-Epibatidine **230** that employed an asymmetric HDA reaction as a key step (**Scheme 47**).⁶⁴ Chiral acylnitroso dienophile **222** derived from (*S*)-Pulegone **220** was obtained by oxidising the parent hydroxamate **221** under Swern condition and subsequently trapped by 2-chloro-5-(1,5-cyclohexadienyl)pyridine **223**. This reaction did not proceed with high regio and diastereoselectivity, affording three stereoisomers (**225**, **226**, **227**). These results indicated that the *meta-aza* regioisomer was favoured over the *para-aza* one an effect due to the presence of an electron-withdrawing substituent at position 2 of the diene moiety. The facial selectivity observed was explained by transition state **224**. In this model, the acylnitroso group rested in its *s-cis* conformation with respect to the C-N bond and the naphthyl group shielded selectively one face of the nitroso group. This forced the diene to an "*endo* approach". Thus, the desired cycloadduct **225** was obtained as the major compound and isolated by chromatography. Hydrogenation over PtO₂, removal of chiral auxiliary using LiNH₂·BH₃ and treatment with (Boc)₂O furnished *exo* adduct **228** as single diastereomer. N-O cleavage and bromination of **228** led to halo derivate **229**. Removal of Boc group using TFA and prolonged heating provided the desired (-)-Epibatidine **230**.



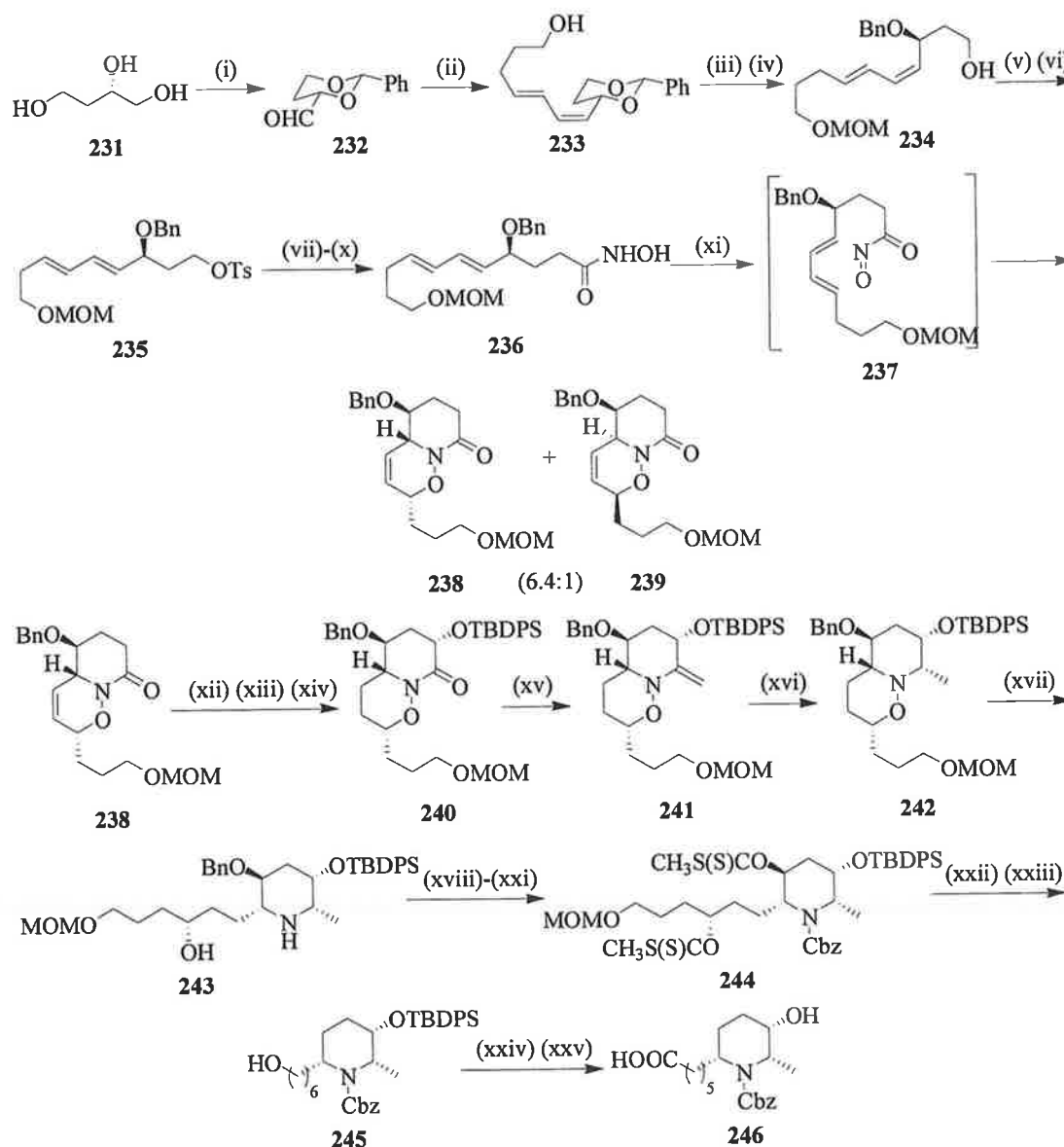
Reagents: (i) $(\text{COCl})_2$, DMSO, Et_3N , DCM; (ii) H_2 , PtO_2 , dioxane (81%); (iii) LiNH_2BH_3 , THF; (iv) Boc_2O , Na_2CO_3 (58% two steps); (v) $\text{Mo}(\text{CO})_6$, $\text{CH}_3\text{CN}/\text{H}_2\text{O}$, reflux (85%); (vi) PPh_3 , CBr_4 , CH_3CN (42%); (vii) TFA, DCM, reflux (96%); (viii) reflux, CH_3Cl , three days (97%).

Scheme 47

(+)-Azimine **247** and (+)-Carpaine **250**, two macrocyclic dilactones containing a 2,3,6-trisubstituted piperidine skeleton, were recently obtained using bicyclic compound **238** as a key intermediate (Scheme 48, 49).⁶⁵ These syntheses occurred *via* an

intramolecular HDA reaction of nitroso intermediate **237**. The synthesis began with (*S*)-1,2,4-butanetriol **231** as a single source of chirality. Compound **231** was converted to 2,4-dihydroxybutanal which was then protected as benzylidene acetal **232**. Wittig reaction of aldehyde **232** using LiHMDS as base, produced derivative **233** as a 6 : 1 unseparable mixture of 6-(*Z,E*) isomers. Protection of the hydroxyl group as MOM ether followed by DIBAL-H reduction, gave alcohol **234** which was protected as tosyl ester and photolysed in the presence of I₂ to give pure (*E,E*) isomer **235**. Conversion to hydroxamic acid **236** was accomplished by a sequence of reactions involving nucleophilic displacement of the tosylate by cyanide ion, alkaline hydrolysis, esterification with diazometane and treatment with hydroxylamine. Upon oxidation of **236** with NaIO₄, the *in situ* generated acylnitroso compound **237** underwent intramolecular Diels-Alder reaction to afford a 6.4 : 1 mixture of *trans* and *cis* adducts **238** and **239** in 69% total yield. Olefin **238** was then hydrogenated and submitted to α -keto hydroxylation using Davis' reagent.⁶⁶ Thus, the lactam enolate formed by treatment with LiHMDS was oxidized using (+)-[(8,8-dichlorocamphoryl)-sulfonyl]oxaziridine to furnish exclusively the secondary alcohol which was protected as silyl ether **240**. Compound **240** was treated with methylmagnesium bromide to give the enamine **241**, which was reduced with NaBH₃CN to yield the desired methylated product **242** in 76% overall yield as the only stereoisomer. Reductive N-O bond cleavage of **242** provided the amino alcohol **243**, which was converted into thionocarbonate **244** *via* hydrogenolytic removal of the benzyl protecting group, benzylcarbonilation of free amine and treatment with CS₂ followed by MeI. Transformation of **244** to **245** was accomplished using the Barton-McCombie deoxygenation reaction followed by deprotection of the MOM group. PDC oxidation followed by removal of the silyl protecting group transformed **245** into acid **246**.

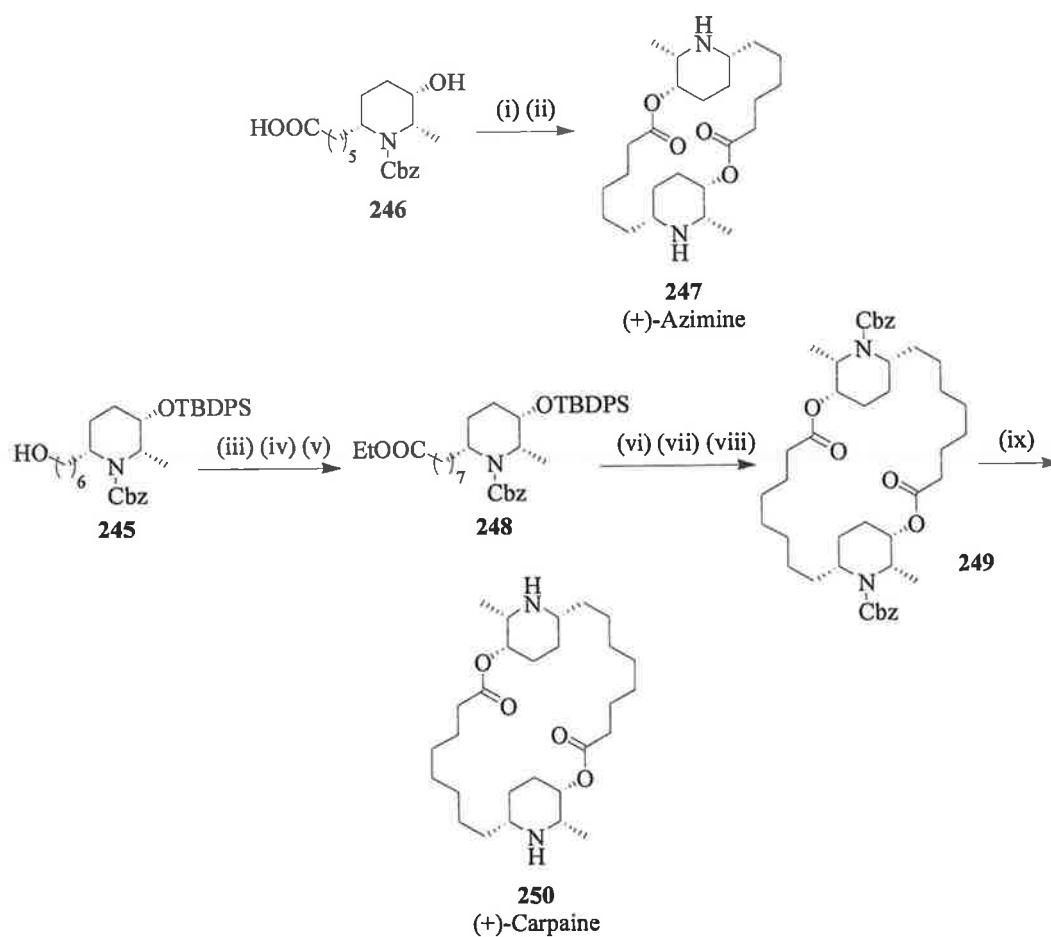
Compounds **246** and **245** were used as intermediate in the synthesis of (+)-Azimine **247** and (+)-Carpaine **250** respectively (Scheme 49).



Reagents: (i) PhCHO, TsOH, then Swern oxidation; (ii) $\text{BrPh}_3\text{P}^+\text{CH}_2\text{CH}=\text{CH}(\text{CH}_2)_3\text{OH}$, LiHMDS, HMPA, THF (66%); (iii) MOMCl, $i\text{-Pr}_2\text{NEt}_3$, DCM, 60 °C (93%); (iv) DIBAL-H, DCM (84%); (v) TsCl, Et_3N , DMAP, DCM (91%); (vi) irradiation, I_2 , benzene (94%); (vii) NaCN, DMSO, 50 °C (95%); (viii) NaOH, MeOH/ H_2O , reflux; (ix) CH_2N_2 , Et_2O , 0 °C (94% two steps); (x) $\text{NH}_2\text{OH}\cdot\text{HCl}$, KOH, MeOH, 0 °C (88%); (xi) NaIO_4 , $\text{H}_2\text{O}/\text{DMF}$ (50:1), 0 °C (69%); (xii) H_2 , Pd/C (97%); (xiii) LiHMDS, (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine, THF (99%); (xiv) TBDPSCl, imidazole, DMF (73%); (xv) MeMgBr, THF; (xvi) NaBH_3CN , AcOH, THF (76% two steps); (xvii) Zn, AcOH, 60 °C (93%); (xviii) H_2 , Pd(OH) $_2$, MeOH; (xix) CbzCl, Na_2CO_3 ; (xx) 1M NaOH, MeOH (45% three steps); (xxi) CS_2 , NaH, imidazole, THF, reflux then MeI, reflux (93%); (xxii) Bu_3SnH , AIBN, benzene, reflux (99%); (xxiii) PPTS, $t\text{-BuOH}$, reflux (73%); (xxiv) PDC, DMF; (xxv) Bu_4NF , THF (82% two steps).

Scheme 48

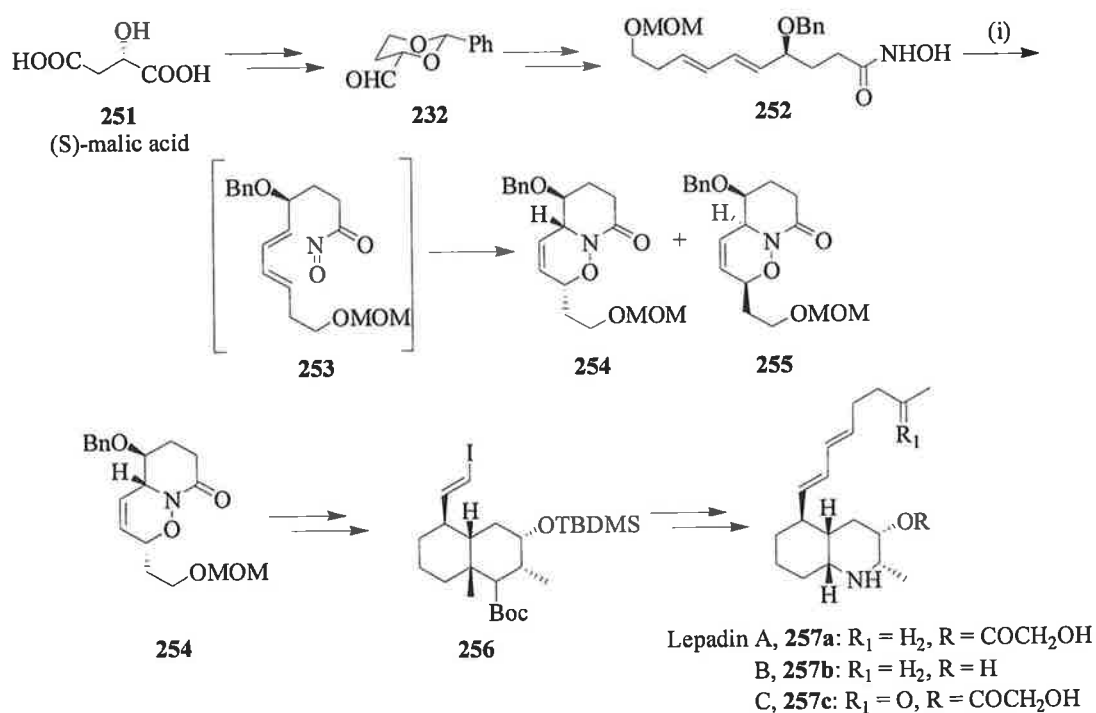
Cyclization of **246** was carried out using the Yamaguchi method.⁶⁷ Hydrogenolysis of the Cbz group provided desired (+)-Azimine **247**. (+)-Carpaine **250** was obtained from piperidine **245**. Compound **245** was submitted to Swern oxidation, the resulting aldehyde subjected to Horner-Wadsworth-Emmons homologation and the olefin obtained hydrogenated to give **248**. Deprotection of the silyl group, hydrolysis of the ester and lactonization of resulting *N*-Cbz acid under Yamaguchi macrocyclization condition provided intermediate **249**. Finally, deprotection of Cbz group led to target (+)-Carpaine **250**.



Reagents: (i) 2,4,6-Cl₃C₆H₂COCl, Et₃N, THF then DMAP, toluene, reflux (71%); (ii) H₂, Pd(OH)₂, MeOH (76%). (iii) (COCl)₂, DMSO, Et₃N, DCM; (iv) (EtO)₂P(O)CH₂COOEt, NaH, THF (91% two steps); (v) H₂, PrO₂, AcOEt (76%); (vi) Bu₄NF, THF (97%); (vii) Ba(OH)₂·8H₂O, MeOH (97%); (viii) 2,4,6-Cl₃C₆H₂COCl, Et₃N, THF then DMAP, toluene, reflux (71%); H₂, Pd(OH)₂, MeOH (87%).

Scheme 49

Kibayashi reported the synthesis of (-)-Lepadin A, B and C (**257a,b,c**, Scheme 50).⁶⁸



Reagents: (i) Pr_4NIO_4 , $\text{H}_2\text{O}/\text{DMF}$ (50:1) (90%).

Scheme 50

These compounds possess a decahydroquinoline core and have shown a significant cytotoxicity against some human cancer cell lines.⁶⁹ **257a,b,c** were obtained through an intramolecular HDA reaction. The chiral hydroxamate **252** was employed to prepare desired bicycle-[4.4.0]-1,2-oxazine **254** (analogue of **238**) in good yield and diastereoselectivity. Compound **252** was prepared from (S)-malic acid **251** via the formation of aldehyde **232**. Compound **232** was then converted into hydroxamic acid **252** in ten steps. The oxidation of **257** using Pr_4NIO_4 , generated the intermediate **253** which underwent an intramolecular HDA reaction to furnish cycloadducts **254** and **255**. The best diastereomeric ratio was obtained by carrying the reaction out in a mixture $\text{H}_2\text{O}/\text{DMF}$ at 0 °C (Table 5).

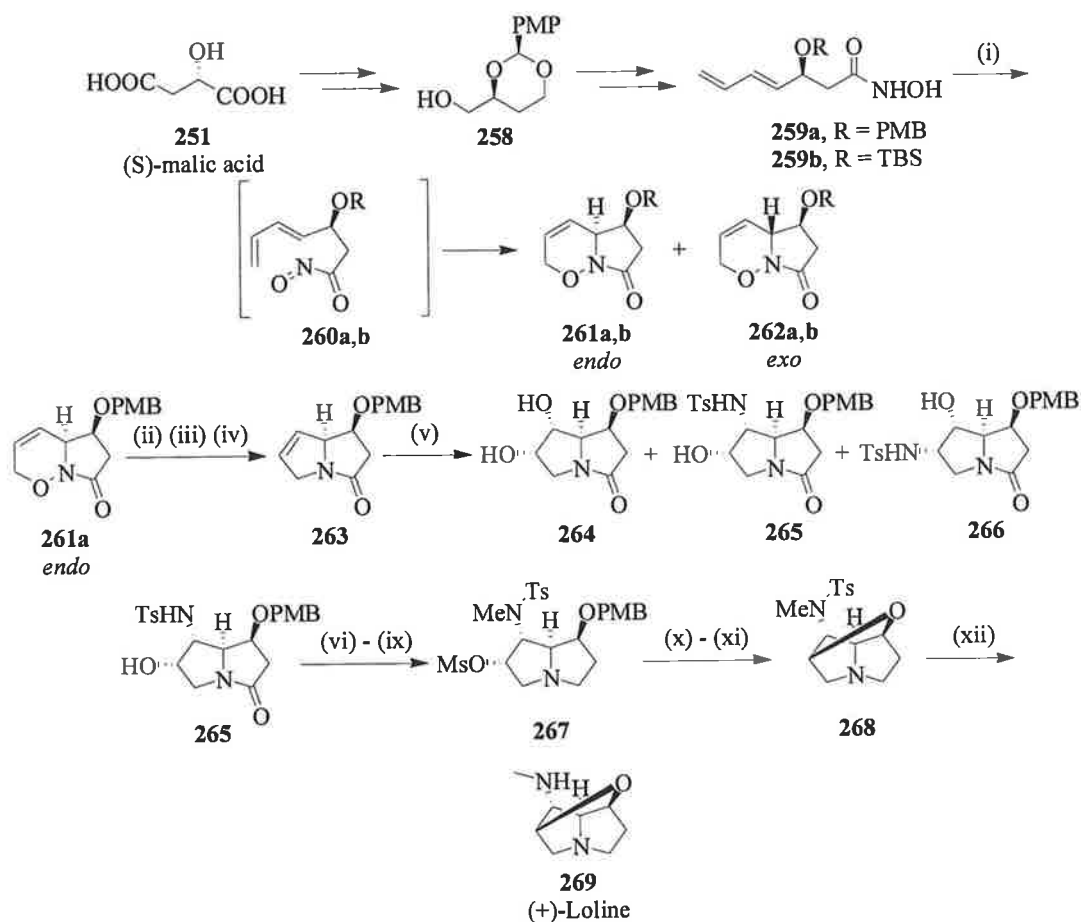
Table 5

| Solvent | (254:255) ratio | Yield (%) |
|-----------------------------|-----------------|-----------|
| CHCl ₃ | 1.7:1 | 81 |
| MeOH | 2.6:1 | 96 |
| H ₂ O/THF (50:1) | 4.3:1 | 88 |
| H ₂ O/DMF (50:1) | 6.6:1 | 90 |

The major isomer **254** was then converted into intermediate **256** which was finally converted into (-)-Lepadine A, B and C.

The wide use of **238** and **254** demonstrates the importance and the high versatility of intramolecular nitroso HDA reaction in the synthesis of natural compounds.

Unfortunately, high diastereoselectivity was not observed in White's synthesis of (+)-Loline **269** (Scheme 51).⁷⁰



Reagents: (i) periodate salt, solvent; (ii) Na(Hg), Na₂HPO₄, EtOH; (iii) MsCl, Et₃N, DCM; (iv) LDA, THF; (v) TsNClNa, Os. cat., solvent; (vi) MeI, *t*-BuOK, *t*-BuOH, 50 °C (76%); (vii) MsCl, Et₃N, DCM, 0 °C (99%); (viii) BH₃·SMe₂, THF; (ix) Pd(OH)₂/C, MeOH (73% two steps); (x) DDQ, DCM/H₂O (20/1) (70%); (xi) 1,2-di-ClC₆H₄, 180 °C (75%); (xii) sodium naphthalenide, DME, -60 °C (48%).

Scheme 51

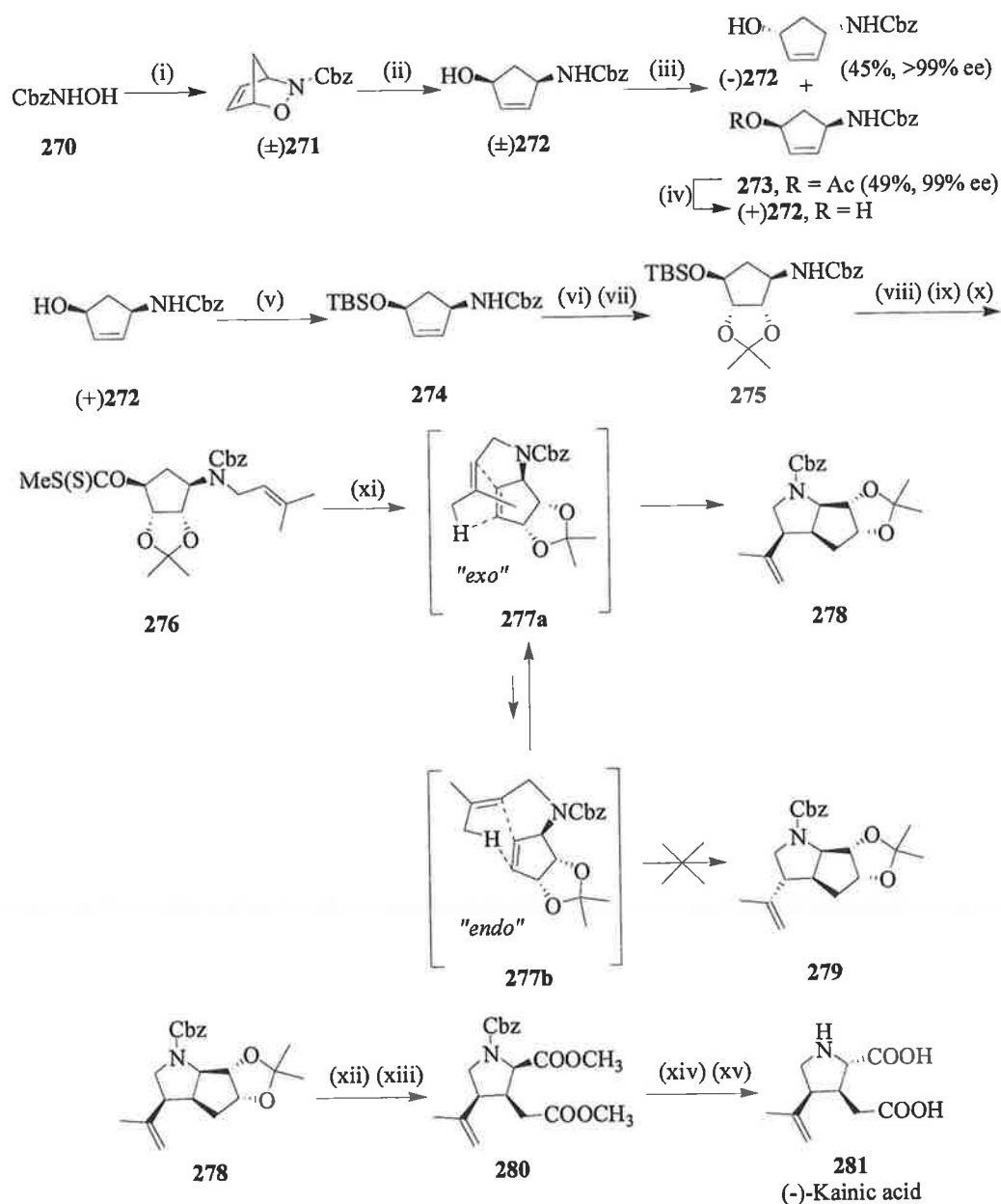
The precursor chiral hydroxamic acid **259a,b** was synthesized from commercially available (S)-malic acid **251** in ten steps. Oxidation of **259a,b** was carried out with Bu₄NIO₄ under a variety of conditions. The resultant nitrosodiene **260a,b** in each case underwent spontaneous intramolecular cycloaddition to give bicyclic dihydrooxazines **261a,b** and **262a,b** with poor diastereoselectivity. It was found that in benzene or toluene **259a,b** gave predominantly the *endo* isomer **261a,b**, with the yield increasing but selectivity decreasing as the temperature of the reaction was raised from -20 to 80 °C (Table 6). A reversal of selectivity was observed when the oxidation was

carried out in aqueous THF: in this case the *exo* cycloadduct was the major compound. The *endo* hydrooxazine **261a** was reduced with Na(Hg), mesylated and treated with LDA to furnish bicyclic **263**. Osmylation of **263** in the presence of excess chloramine-T⁷¹ yielded principally diol **264** together with small amounts of amino alcohols **265** and **266**. Screening of reaction conditions established that K₂OsO₂(OH)₄, (DHQD)₂PHAL in *t*-BuOH/H₂O mixture gave the best result (47% total yield **265** + **266**, **265:266** = 80:20). Compound **265** was then treated with MeI, MsCl in presence of Et₃N, BH₃·SMe₂ and Pearlman catalyst to afford protected bicyclic **267**. Removal of PMB ether from **267** with DDQ followed by thermal cyclization at 180 °C in presence of 1,2-di-chlorobenzene furnished the tricycle **268**. Removal of the tosyl group using sodium naphthalenide afforded desired (+)-Loline **269**.

Table 6

| Hydroxamic acid | Oxidant | Solvent | Temp. (°C) | 261/262 ratio | Yield (%) |
|-----------------|----------------------------------|----------------------------|------------|---------------|-----------|
| 259b | Bu ₄ NIO ₄ | Toluene | -20 | 70/30 | 49 |
| 259b | Bu ₄ NIO ₄ | Benzene | 0 | 71/29 | 60 |
| 259b | Bu ₄ NIO ₄ | Benzene | 80 | 60/40 | 80 |
| 259b | Bu ₄ NIO ₄ | DCM | -78 | 50/50 | 86 |
| 259b | Bu ₄ NIO ₄ | CHCl ₃ | 22 | 55/45 | 91 |
| 259a | Bu ₄ NIO ₄ | CHCl ₃ | 22 | 57/43 | 87 |
| 259b | NaIO ₄ | H ₂ O/THF (1:1) | 0 | 27/73 | 97 |

Ogasawara reported the synthesis of (-)-Kainic acid **281** via formation of (+)-*cis*-4-carbobenzoxymino-2-cyclopentenol (**272**) from *N*-carbobenzoxymino-2-cyclopentenol (**270**) through the use of an HDA reaction (Scheme 52).⁷²



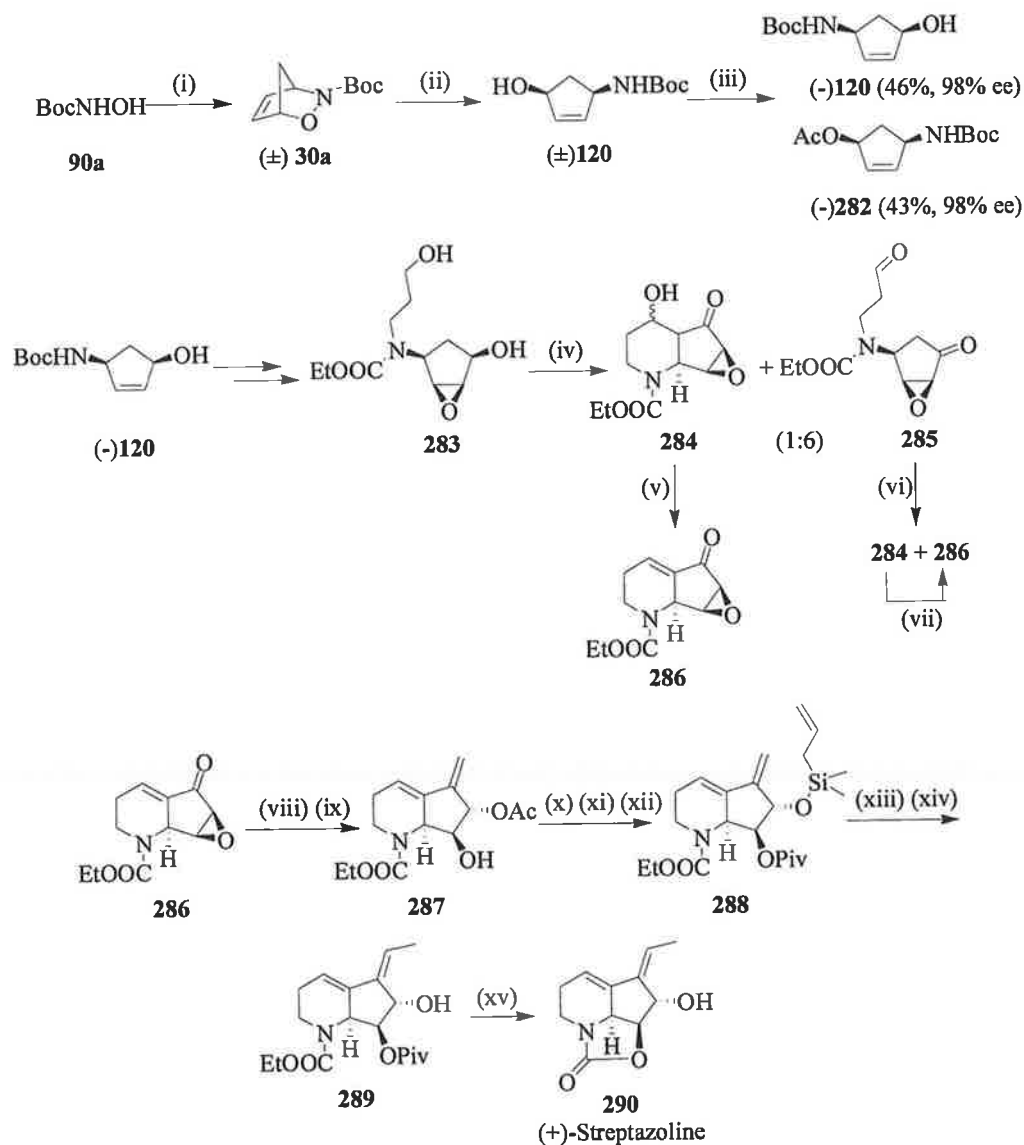
Reagents: (i) cyclopentadiene, NaIO₄, MeOH/H₂O (3:1); (ii) Mo(CO)₆, MeCN/H₂O (15:1) (52% two steps); (iii) Lipase AK, vinyl acetate, DCM; (iv) K₂CO₃, MeOH (98%); (v) TBSCl, imidazole, DMF (91%); (vi) OsO₄, NMO, THF/H₂O (2:1); (vii) Me₂C(OMe)₂, PPTS, DMF (87%); (viii) prenyl-Cl, NaI, NaH, THF; (ix) TBAF, THF (80%); (x) CS₂, MeI, NaH, THF (92%); (xi) NaHCO₃, Ph₂O, reflux (72%); (xii) 1N HCl/THF (3:2), reflux; (xiii) NaIO₄, THF/H₂O (2:1) then Jones oxidation then CH₂N₂ (48%); (xiv) NaH, DBU, benzene; (xv) 40% NaOH/MeOH (1:1) (63% two steps).

Scheme 52

The oxidation of **270** generated the correspondent nitroso species which was trapped with cyclopentadiene to give cycloadduct **271** which in turn was converted into racemic protected aminoalcohol (\pm)**272** by reductive cleavage of N-O bond. The enzymatic resolution with lipase AK afforded compound **273** in moderate yield and excellent enantioselectivity (49%, 99% ee). Deacetylation of **273** afforded (+)-*cis*-4-carbobenzoxyamino-2-cyclopentenol (+)**272** in excellent yield. The subsequently treatment with TBSCl gave the corresponding protected aminoalcohol **274** which was dyhydroxylated and protected as acetonide to furnish **275**. The secondary carbamate of **275** was next alkylated to give the tertiary prenyl carbamate and after desilylation with TBAF, it was transformed into xanthate ester **276** by treatment with CS₂ and MeI. The subsequent Chugaev elimination and intramolecular ene reaction afforded compound **278** as a single diastereomer in good yield presumably through intermediate **277a**. The complete control of the stereochemistry was due to the preference of the *exo* transition state **277a** over the *endo* transition state **277b**. the acetonide group of **278** was removed under acidic hydrolysis, the resulting diol cleaved with sodium periodate, oxidized with Jones' reagent and treated with diazomethane to form the trisubstituted pyrrolidine ester **280** having an all *cis* stereochemistry. Compound **280** was epimerized at C-2 to give the *trans* C2/C3 and the *cis* C3/C4 diastereomer, which on alkaline hydrolysis afforded (-)-Kainic acid **281** in 13% overall yield.

Recently, novel enzymatic resolutions were developed to prepare key intermediates for natural product synthesis.⁷³ In particular, Miller *et al.* obtained the antibiotic (+)-Streptazoline **290** using enantiopure aminoalcohol (-)**120** as key intermediate (Scheme 53).⁷⁴ Racemic aminocyclopentenol **120** was obtained from cycloadduct **30a**, which was synthesized by oxidation of BocNHOH **90a** in presence of cyclopentadiene. The subsequent N-O reductive cleavage using Mo(CO)₆ afforded **120**. Kinetic resolution of racemic alcohol **120** was achieved using commercially available immobilized *Candida antartica* B lipase. The enantiopure acetate (-)**282** and alcohol (-)**120** were obtained in 43%, and 46% yield, respectively, with 98% ee after

recrystallization. Enantiopure (-)-**120** was subsequently transformed into epoxide **283** in eight steps.



Reagents: (i) cyclopentadiene, NaIO_4 , $\text{MeOH}/\text{H}_2\text{O}$; (ii) $\text{Mo}(\text{CO})_6$, NaBH_4 , $\text{MeCN}/\text{H}_2\text{O}$; (iii) *C. Antartica B*, vinyl acetate, DCM, eptane; (iv) $(\text{COCl})_2$, DMSO, DCM (82%); (v) Et_3N , MsCl , DMAP (86%); (vi) Al_2O_3 (83%); (vii) Et_3N , MsCl , DMAP (86%); (viii) NaH , $\text{Ph}_3\text{PCH}_2\text{Br}$, THF (71%); (ix) AcOH , NaOAc (87%); (x) $\text{O}(\text{CO}(\text{CH}_3)_3)_2$, TMSOTf , 0°C (80%); (xi) K_2CO_3 , MeOH ; (xii) $\text{Me}_2\text{ClSiCH}_2\text{CH}=\text{CH}_2$ (74% two steps); (xiii) Grubbs II (2 mol%), DCM, reflux (100%); (xiv) KF , KHCO_3 , MeOH/THF 1:1 (50%); (xv) NaOMe , MeOH , reflux, (76%).

Scheme 53

Swern oxidation carried out on **283** gave bicyclic **284** and aldehyde **285** as 1 : 6 mixture. **284** was then transformed into compound **286** by dehydration of water using MsCl in basic media. Aldehyde **285** was converted to **286** in two steps using Al₂O₃ followed by MsCl in present of Et₃N and DMAP. Wittig reaction carried out on **286** and treatment with NaOAc in AcOH afforded the mono protected diol **287** in good yield. Protection of free alcohol as pivaloyl derivate, deacetylation and treatment with chlorosilyl derivative, afforded the corresponding silyl ether **288**. Derivative **288** was reacted with Grubbs' second generation catalyst and KF to give allylic alcohol **289**. Compound **289** was then converted to (+)-Streptazoline **290** by cyclization in basic conditions.

1.7. References

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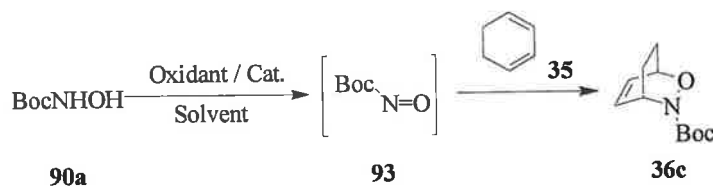
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Chapter 2: Generation of acylnitroso dienophiles: a study of metal catalysis

2.1. Introduction

Acylnitroso compounds have been widely used since the 1940s as efficient hetero dienophiles in [4 + 2]-cycloaddition reactions with conjugated dienes.¹ As explained in *Chapter 1*, the acylnitroso species could be obtained from the oxidation of a hydroxamic acid using either an organic or an inorganic oxidant.

As a part of our ongoing research on the generation of chemical diversity, we became interested in the generation of acylnitroso species. Our approach to the development of diversity oriented syntheses is based on the generation of building blocks that contain multiple functionalities that could be selectively reacted (polyfunctional scaffolds).² We hypothesized that a reagent containing a number of functionalities m , which could be selectively reacted in a number of n directions, will generate diversity in $D = (mn)$ directions. We identified cycloadduct **36c** (**Scheme 1**) as an example of a polyfunctional scaffold, which contains four contiguous chemodifferentiable functionalities.



Scheme 1: synthesis of cycloadduct **36c**.

In this respect, the [4 + 2] cycloaddition of acylnitroso dienophile **93** to a diene **35** is an ideal transformation to initiate structural divergence. We reasoned that if **36c**

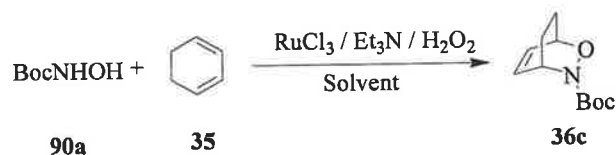
could be prepared from a mild oxidation of 1 equiv. of **90a** and 1 equiv. of **35**, then the HDA reaction could be run in tandem with other transformations involving the functionalities formed in **36c**.

2.2.1. Results and discussion

As first step, we focused our attention to metal catalyzed oxidations of **90a**, as metals were often involved in the transformation of alkenes bearing proximal heteroatom functionalities.³

In the choice of the oxidant, hydrogen peroxide was selected since water was the only side product formed. A literature survey revealed that Ru^{II}⁴ and Cu^I⁵ were reported as catalysts for the oxidation of hydroxamic acid **90a**. In particular, Iwasa *et al.* reported the oxidation of **90a** using hydrogen peroxide as the oxidant.^{4a} This method exploited a preformed Ru^{II}(pybox-dh)(pydic) catalyst that was employed at 1 mol % loading. However, Iwasa's catalyst was soluble only in mixtures of methanol/water or THF, and this poor solubility profile was not ideal for the development of tandem catalyses. Nicholas and co-workers reported that Cu^I salts catalyzed the oxidation of **90a** to **93** with hydrogen peroxide as the oxidant: 15 mol % CuCl was necessary to convert **90a** to **93**; the reaction occurred in 7 hours and required an excess of the diene component to ensure a high yield of cycloadduct **36c**.^{5b} In a related work, Cu^I and Cu^{II} salts were described as catalysts for the oxidation of phenylhydroxylamine to PhN=O, which was subsequently trapped with a diene.⁶ This process required high temperatures and long reaction times and gave a cycloadduct related to **36c** in low yield and contaminated by several side products. Whiting *et al.* reported a few Ru^{II} complexes as catalysts for the oxidation of **90a** to **93** using *t*-BuOOH as an oxidant.^{4b,c} A Ru^{II}-SALEN complex was described to be active at 0.1 mol % loading. The preparation of the Ru^{II}-SALEN catalyst required two steps. To find a metal catalyzed oxidation of **90a** to **93** based on truly commercially available sources, we decided to screen a number of metal salts.

Considering that ligands have repeatedly influenced the reactivity of the metal catalyst (ligand accelerated catalysis),⁷ we carried out the screening in the presence of ligands, which could also facilitate the solubility of the catalyst. In a test experiment, we used RuCl₃ and Et₃N. We were delighted to observe that the metal/amine couple Ru^{III}/Et₃N showed a remarkable catalytic activity (**Scheme 2** and **Table 1**).



Scheme 2: synthesis of cycloadduct **36c** using Ru catalyst.

Table 1: yield of adducts **36c** obtained using catalytic amount of Ru^{III}.

| Entry | % Ru ^{III} | Amine | Solvent | Yield % ^a |
|-------|---------------------|-------------------|--------------------|----------------------|
| 1 | - | Et ₃ N | DCM | - |
| 2 | 10 | - | DCM | 9 |
| 3 | 10 | Et ₃ N | DCM | 71 ^b |
| 4 | 5 | Et ₃ N | DCM | 76 ^b |
| 5 | 5 | Et ₃ N | THF | 74 ^b |
| 6 | 5 | Et ₃ N | CH ₃ CN | 78 ^b |
| 7 | 1 | Et ₃ N | DCM | 34 |

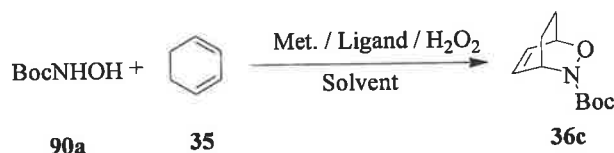
^a Isolated yield after chromatography.

^b ¹H NMR of crude reaction mixture showed a complete conversion of **90a** and the presence of adduct **36c** as only product.

When BocNHOH **90a** was reacted with hydrogen peroxide in the presence of sub-stoichiometric amounts of RuCl₃ and Et₃N, cycloadduct **36c** was obtained in good isolated yield (**Scheme 2**), showing that Ru^{III} is an efficient catalyst for this reaction. When neither Ru^{III} or Et₃N was present, no reaction had occurred (**Table 1**, entries 1 and 2). However, with just 5 mol % Ru^{III} catalyst, cycloadduct **36c** was obtained in 74-78% isolated yield (**Table 1**, entries 4-6). The reaction proceeded equally well in a variety of solvents including DCM, THF, and CH₃CN, and complete conversion of **90a**

was typically observed in 20-30 min. Importantly, the crude reaction mixture contained only adduct **36c**, as evidenced by ^1H NMR.

We then turned our attention to other potentially useful metal/amine catalysts, with commercially available CuCl and CuCl_2 being an obvious choice. We also included in this study FeCl_3 and NiCl_2 , as Fe^{III} and Ni^{II} were repeatedly reported as good catalysts for the oxidation of amines⁸ or alkenes⁹ using H_2O_2 (**Scheme 3**).



Scheme 3: synthesis of cycloadduct **36c** using metal catalyst.

Ethanol amine, ethylene diamine, and triethylamine were selected as the ligands considering that enantiopure amino alcohols, diamines, and tertiary amines are easy to obtain. These choices were placed in an experimental setup in which equimolar amounts of **90a** and **35** were reacted with H_2O_2 in the presence of 5 mol % metal salt and 15 mol % ligand. As a solvent was needed, we selected THF and DCM. We were interested in comparing the catalytic efficiency of the metal/amine catalyst in solvents able (THF) or unable (DCM) to participate in metal ligation.

These studies revealed three novel and efficient catalysts for the generation of acylnitroso species that work under a set of mild reaction conditions (**Table 2**).

Table 2: yield of **36c** obtained using a Metal/Amine catalyst.

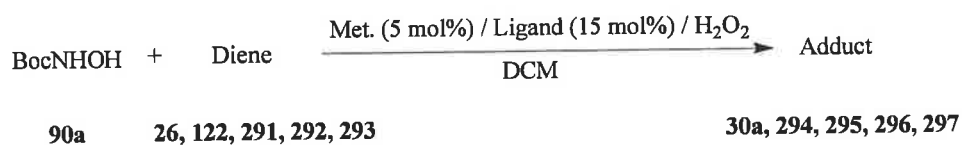
| Entry | Metal | Amine | Solvent | Time (min) ^a | Yield % ^{b,c} |
|-------|-------------------|---|---------|-------------------------|------------------------|
| 1 | CuCl | - | DCM | 390 | 76 |
| 2 | CuCl | - | THF | 300 | 95 |
| 3 | CuCl | HOCH ₂ CH ₂ NH ₂ | DCM | 30 | 83 |
| 4 | CuCl | HOCH ₂ CH ₂ NH ₂ | THF | 180 | 95 |
| 5 | CuCl | Et ₃ N | DCM | 720 | 80 |
| 6 | CuCl | H ₂ NCH ₂ CH ₂ NH ₂ | DCM | 300 | 32 |
| 7 | CuCl ₂ | - | DCM | 255 | 58 |
| 8 | CuCl ₂ | - | THF | 45 | 94 |
| 9 | CuCl ₂ | HOCH ₂ CH ₂ NH ₂ | DCM | 20 | 84 |
| 10 | CuCl ₂ | HOCH ₂ CH ₂ NH ₂ | THF | 30 | 95 |
| 11 | CuCl ₂ | Et ₃ N | DCM | 120 | 77 |
| 12 | CuCl ₂ | H ₂ NCH ₂ CH ₂ NH ₂ | DCM | 180 | 27 |
| 13 | FeCl ₃ | - | DCM | 30 | 48 |
| 14 | FeCl ₃ | - | THF | 30 | 95 |
| 15 | FeCl ₃ | HOCH ₂ CH ₂ NH ₂ | DCM | 35 | 62 |
| 16 | FeCl ₃ | HOCH ₂ CH ₂ NH ₂ | THF | 1800 | 89 |
| 17 | FeCl ₃ | Et ₃ N | DCM | 30 | 69 |
| 18 | FeCl ₃ | H ₂ NCH ₂ CH ₂ NH ₂ | DCM | 20 | 76 |
| 19 | NiCl ₂ | - | DCM | 5760 | 52 |
| 20 | NiCl ₂ | - | THF | 11520 | 78 |
| 21 | NiCl ₂ | HOCH ₂ CH ₂ NH ₂ | DCM | 1080 | 71 |
| 22 | NiCl ₂ | HOCH ₂ CH ₂ NH ₂ | THF | 10080 | 71 |
| 23 | NiCl ₂ | Et ₃ N | DCM | 4560 | 81 |
| 24 | NiCl ₂ | H ₂ NCH ₂ CH ₂ NH ₂ | DCM | 4680 | 60 |

^a Time required to observe complete conversation of **1**.^b Isolated yield after column chromatography.^c ¹H NMR of crude reaction mixture showed a complete conversation of **1** and the presence of adduct **4** as the only product.

The reactions were very simple to set up and did not require either controlled atmosphere or controlled temperature. A mixture of the required metal salt and ligand


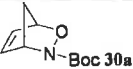

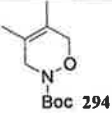
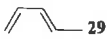
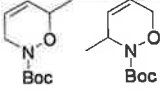

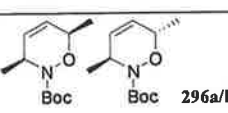

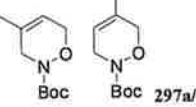

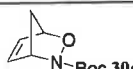

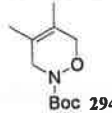
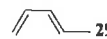
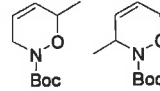

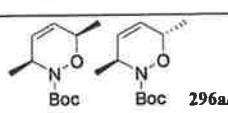

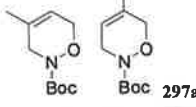

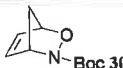

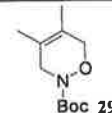
was usually premixed prior to the addition of the diene. We noticed that to ensure high yields and fast reaction rates, the sequence of addition of the reagents was crucial. Particularly, it was important to add the oxidant as the last component. The data collected (**Table 2**) pointed out the following facts: (a) faster reaction rates were observed in DCM versus THF in the presence of a ligand; (b) Cu^I, Cu^{II}, and Fe^{III} showed a high level of activity even in the absence of a ligand (**Table 2**, entries 1, 7, 8, 13, and 14); this is in line with the previous reports,^{5,6} although our procedure worked well using a reduced catalyst loading and a 1:1 ratio of hydroxamic acid/diene; (c) the reaction proceeded also in the absence of ligand, which was due to the ability of THF to act as a ligand, although the role of BocNHOH **90a** as a ligand could not be ruled out; (d) in the absence of the ligand, the reactions of Cu^I and Cu^{II} were faster in THF as compared to DCM, but this was reverted in the presence of the ligand (**Table 2**, entries 1 and 2 and 3 and 4 or entries 7 and 8 and 9 and 10); (e) amino alcohols were the best ligands for Cu^I and Cu^{II}, to which they imparted a significant acceleration (**Table 2**, entries 1 and 3 or 7 and 9); (f) although Ni^{II} catalyzed reactions gave a high yield of **36c**, these reactions appeared to be significantly slower.

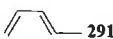
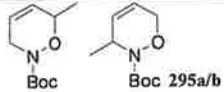

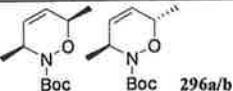

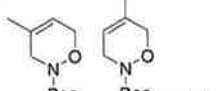
Having established four new methodologies for the generation of **36c**, we explored the scope of the reaction by using different dienes (**Scheme 4** and **Table 3**).



Scheme 4: synthesis of cycloadducts using HDA reaction.

Table 3: Cu^I, Cu^{II}, Fe^{III} catalyzed HDA reactions of cyclic and acyclic dienes.

| Entry | Catalyst | Diene | Product | Yield % ^a | Time (m) |
|-------|---|---|---|----------------------|----------|
| 1 | Cu ^I / HOCH ₂ CH ₂ NH ₂ |  26 |  Boc 30a | 63 | 20 |
| 2 | Cu ^I / HOCH ₂ CH ₂ NH ₂ |  122 |  Boc 294 | 74 | 30 |
| 3 | Cu ^I / HOCH ₂ CH ₂ NH ₂ |  291 |  Boc 295a/b | 70 ^b | 30 |
| 4 | Cu ^I / HOCH ₂ CH ₂ NH ₂ |  292 |  Boc 296a/b | 64 ^c | 30 |
| 5 | Cu ^I / HOCH ₂ CH ₂ NH ₂ |  293 |  Boc 297a/b | 58 ^d | 30 |
| 6 | Cu ^{II} / HOCH ₂ CH ₂ NH ₂ |  26 |  Boc 30a | 64 | 20 |
| 7 | Cu ^{II} / HOCH ₂ CH ₂ NH ₂ |  122 |  Boc 294 | 70 | 30 |
| 8 | Cu ^{II} / HOCH ₂ CH ₂ NH ₂ |  291 |  Boc 295a/b | 54 ^b | 30 |
| 9 | Cu ^{II} / HOCH ₂ CH ₂ NH ₂ |  292 |  Boc 296a/b | 70 ^c | 30 |
| 10 | Cu ^{II} / HOCH ₂ CH ₂ NH ₂ |  293 |  Boc 297a/b | 65 ^d | 30 |
| 11 | Fe ^{III} / H ₂ NCH ₂ CH ₂ NH ₂ |  26 |  Boc 30a | 78 | 20 |
| 12 | Fe ^{III} / H ₂ NCH ₂ CH ₂ NH ₂ |  122 |  Boc 294 | 76 | 30 |

| | | | | | |
|----|---|---|---|-----------------|----|
| 13 | $\text{Fe}^{\text{III}} / \text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$ |  291 |  295a/b | 54 ^b | 30 |
| 14 | $\text{Fe}^{\text{III}} / \text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$ |  292 |  296a/b | 58 ^c | 30 |
| 15 | $\text{Fe}^{\text{III}} / \text{H}_2\text{NCH}_2\text{CH}_2\text{NH}_2$ |  293 |  297a/b | 64 ^d | 30 |

^a Isolated yield after chromatography.

^b Obtained as a 1:1.6 mixture of regioisomers.

^c Obtained as a 1:3 mixture of diastereoisomers.

^d Obtained as 1:1 mixture of regioisomers.

Both cyclic and acyclic dienes gave the corresponding adducts in good yields (Table 3). Complete conversion of **90a** was typically observed in 20-30 min.

2.2.2. Studies towards the optimisation of an enantioselective acyl nitroso Diels Alder reaction

In the previous section we have illustrated the discovery of four novel metal catalysed oxidations of hydroxamic acids. These reactions used H_2O_2 as the oxidant and it has been demonstrated that reactions were faster when in the presence of metal ligand. For this reason, these oxidations constitute a further example of ligand accelerated catalysis. Ligand accelerated catalysis is an effect that is often linked to asymmetric catalysis. Sharpless, for instance, demonstrated how the use of cinchona alkaloids and its derivatives have an effect on the overall reaction rate of OsO_4 catalysed dihydroxylation and on its enantiomeric excess.¹⁰ We reasoned that the oxidations we have discovered were sensibly accelerated by amines or aminoalcohols which could be found in large variety as enantiopure materials. We have therefore selected a few amines and aminoalcohols and we have studied their effect on the oxidation of BocNHOH and on the enantioselectivity of the cycloaddition between nitroso species and cyclohexadiene.

We firstly examined the effect of chiral ligands on the RuCl_3 catalysed reaction (**Figure 1**).

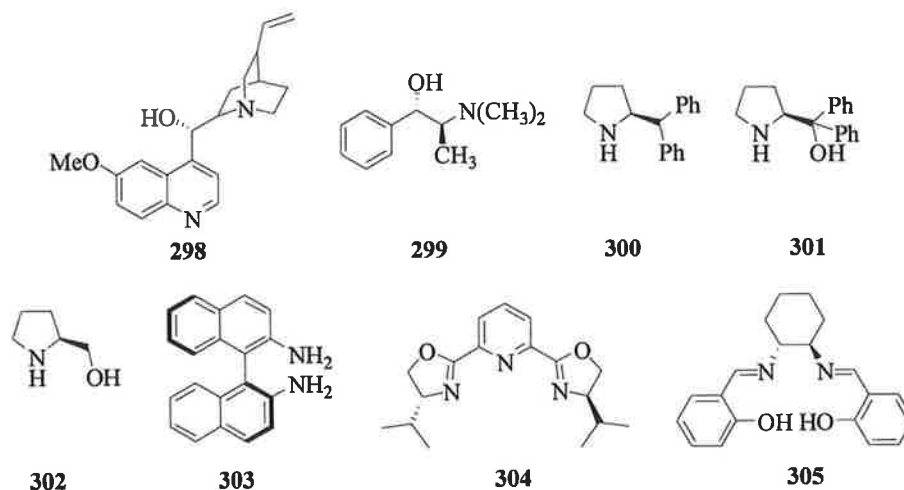
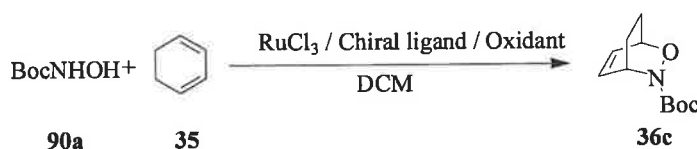


Figure 1: chiral ligands employed in HDA reactions.

Chiral ligands **298-304** were selected as commercially available, while **305** was reported by Zhu.¹¹ The reactions were carried out using 1 equiv. of BocNHOH **90a** and 1 equiv. of 1,3-cyclohexadiene **35**, DCM used as the solvent and RuCl_3 added in 5 mol %. We have identified in 3 equiv. the amount of ligand required and for this reason we kept this number constant (**Scheme 5**).



Scheme 5: synthesis of cycloadduct **36c** using chiral ligands and Ru catalyst.

The results obtained are shown in **Table 4**. These catalytic systems worked well giving cycloadduct **36c** as the only product present in the crude reaction mixture. Tertiary (**Table 4**, entry 1) and secondary amines (**Table 4**, entry 4), amino alcohols (**Table 4**, entries 2, 5-11) and SALEN **305** (**Table 4**, entry 3) afforded cycloadducts **36c** in good yields. Instead, PYBOX ligand **304** (**Table 4**, entry 14) gave **36c** in moderate yield. This is probably due to the limited propensity of PIBOX to bind Ru cations. RuCl_3

could be used at 1 mol% together with 3 mol% of 2-pyrrolidinemethanol **302** as the ligand to afford adduct **4** in 60% yield (Table 4, entry 10). Primary chiral diamine BINAP **303** (Table 4, entry 13) gave the best result at 0 °C giving desired adduct **36c** in 94% isolated yield. Despite the high yields obtained no enantiomeric excess were observed in these reactions.

Table 4: Ru^{III} catalyzed HDA reaction using chiral ligands in the synthesis of **36c**.

| Entry | Ligand (15 mol%) | Oxidant | Yield % ^a | ee % |
|-------------------|------------------|-------------------------------|----------------------|------|
| 1 | 298 | H ₂ O ₂ | 67 | 0 |
| 2 | 299 | H ₂ O ₂ | 67 | 0 |
| 3 | 305 | H ₂ O ₂ | 78 | 0 |
| 4 | 300 | H ₂ O ₂ | 75 | 0 |
| 5 | 301 | H ₂ O ₂ | 52 | 0 |
| 6 | 302 | H ₂ O ₂ | 56 | 0 |
| 7 ^b | 302 | H ₂ O ₂ | 40 | 0 |
| 8 ^c | 302 | H ₂ O ₂ | 58 | 0 |
| 9 ^d | 302 | H ₂ O ₂ | 54 | 0 |
| 10 ^{d,e} | 302 | H ₂ O ₂ | 60 | 0 |
| 11 | 302 | <i>t</i> -BuOOH | 75 | 0 |
| 12 | 303 | H ₂ O ₂ | 72 | 0 |
| 13 ^f | 303 | H ₂ O ₂ | 94 | 0 |
| 14 | 304 | H ₂ O ₂ | 46 | 0 |

^a Isolated yield after chromatography.

^b The reaction was carried out at -78 °C.

^c 50 mol% of ligand.

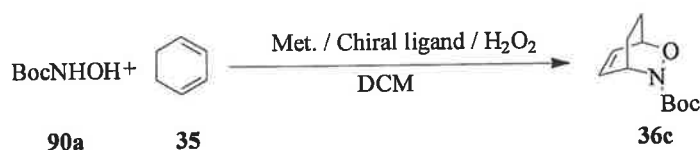
^d 1 mol% of Ru^{III}, 3 mol% of ligand.

^e The reaction was carried out in THF.

^f The reaction was carried out at 0 °C.

A possible explanation was that Ru^{III} nitroso complexes were not stable enough to ensure an efficient chirality transfer from the ligand to the substrate. In order to correct this, it was thought that a stronger Lewis acid would have complexed the nitroso more tightly leading to an asymmetric induction. For this reason we turned our attention

to Cu^{I} , Cu^{II} , Fe^{III} , Ni^{II} catalyzed reactions (**Scheme 6**). The oxidation of **90a** was carried out in the presence of metal and an opportune chiral ligand, the adduct **36c** obtained was then analysed by chiral HPLC.



Scheme 6: synthesis of cycloadduct **36c** using chiral ligands and metal catalysts.

The reaction of Cu^{I} and Cu^{II} and PYBOX (15 mol%) gave good yields of **36c**. Equally good results in term of yield were obtained at room and at low (0 °C) temperature (**Table 5**, entries 3, 4, 7, 8). 2-Pyrrolidinemethanol **302** gave a good acceleration to Cu^{I} , Cu^{II} , Fe^{III} and Ni^{II} reactions (**Table 5**, entries 1, 2, 6, 8-11, 14, 15). Remarkably, the reactions of Cu^{I} , Cu^{II} , Fe^{III} and Ni^{II} with pyrrolidinemethanol gave an optimal turnover, giving adduct **36c** in high yields also when used at 1 mol %. Cu^{I} , Fe^{III} oxidation proceeded well in presence of **301** and SALEN **305** (**Table 5**, entries 5, 12). Unfortunately, despite the good yields of adduct obtained, no enantiomeric excess was observed.

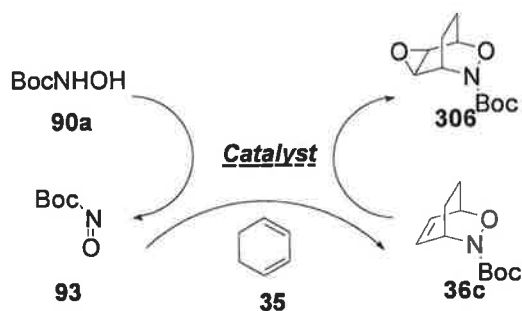
Table 5: Cu^I, Cu^{II}, Fe^{III}, Ni^{II} catalyzed HDA reactions using chiral ligands in the synthesis of **36c**.

| Entry | Metal (5 mol%) | Ligand (15 mol%) | Yield % ^a | ee % |
|-------------------------|-------------------|------------------|----------------------|------|
| 1 | Cu ^I | 302 | 84 | 0 |
| 2^b | Cu ^I | 302 | 73 | 0 |
| 3 | Cu ^I | 304 | 73 | 0 |
| 4^c | Cu ^I | 304 | 73 | 0 |
| 5 | Cu ^I | 301 | 72 | 0 |
| 6 | Cu ^{II} | 302 | 72 | 0 |
| 7 | Cu ^{II} | 304 | 67 | 0 |
| 8^c | Cu ^{II} | 304 | 84 | 0 |
| 9 | Fe ^{III} | 302 | 64 | 0 |
| 10^b | Fe ^{III} | 302 | 39 | 0 |
| 11^{b,d} | Fe ^{III} | 302 | 38 | 0 |
| 12 | Fe ^{III} | 305 | 73 | 0 |
| 13 | Fe ^{III} | 304 | 33 | 0 |
| 14 | Ni ^{II} | 302 | 80 | 0 |
| 15^b | Ni ^{II} | 302 | 21 | 0 |

^a Isolated yield after chromatography.^b 1 mol% of Metal, 3 mol% of ligand.^c The reaction was carried out at 0 °C.^d The reaction was carried out in THF.

2.2.3. Studies towards the development of a tandem HAD-epoxidation process

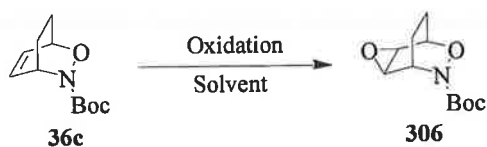
We envisaged the possibility of exploiting the functionality generated in adduct **36a** (alkene) and the metal present to build tandem consecutive processes. For example, we became interested in the preparation of epoxide **306**, through a tandem one-pot reaction in which **36c** was generated and subsequently transformed into **306**. In this plan, the catalyst would have supported three consecutive steps (**Scheme 7**).



Scheme 7: tandem process involving metal catalyst.

Unfortunately, the use of a strong excess of oxidant (H_2O_2 , *m*-CPBA, *t*-BuOOH, Oxone[®]) in the HDA reaction employing all metals (Ru^{III} , Cu^{I} , Cu^{II} , Fe^{III}) was not sufficient to promote the formation of desired epoxide **306**.

The synthesis of **306** was also attempted from isolated **36c** (Scheme 8). Oxone[®], *m*-CPBA, *t*-BuOOH and MTO were used with or without additives and in different reaction conditions but in all cases only starting material was recovered even after prolonged times (Table 6). MTO/ H_2O_2 in presence of pyridine gave epoxide **306** in very low yield ($\approx 5\%$).



Scheme 8: synthesis of epoxide **306**.

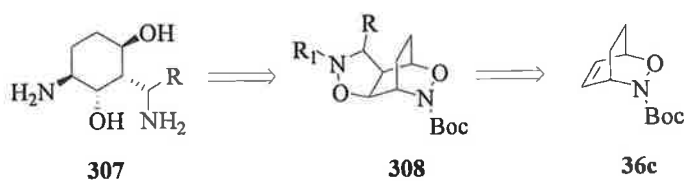
Table 6: epoxidation of cycloadduct **36c**.

| Entry | Oxidant | Additives | Solvent | Yield % ^a |
|----------------|-----------------------------------|--------------------------------|-------------------------------------|----------------------|
| 1 | Oxone [®] | NaHCO ₃ | Acetone | 0 |
| 2 | Oxone [®] | NaHCO ₃ /Morpholine | CH ₃ CN/H ₂ O | 0 |
| 3 | <i>t</i> -BuOOH | RuCl ₃ /DIPEA | DCM | 0 |
| 4 | <i>t</i> -BuOOH | RuCl ₃ /DIPEA | CH ₃ CN | 0 |
| 5 ^b | <i>m</i> -CPBA | - | DCM | 0 |
| 6 | <i>m</i> -CPBA | NaHCO ₃ | Toluene | 0 |
| 7 | <i>m</i> -CPBA | - | Benzene | 0 |
| 8 | MTO/H ₂ O ₂ | Pyridine | DCM | ≈ 5% |

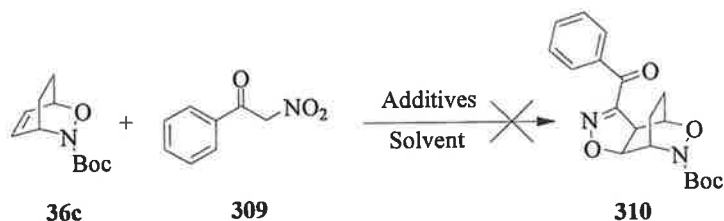
^a After NMR analysis of reaction crude.^b The reaction was carried out at 40 °C.

2.2.4. Reaction of adduct **36a** as a dipolarophile in 1,3-dipolar cycloadditions

The cycloadduct **36c** represent a versatile synthon in organic chemistry because it could undergo several transformations. As shown in **Scheme 9**, we envisaged a synthesis of carbosugar **307** starting from **36c**. Carbosugar **307** represents an important target in organic chemistry.¹² Compound **36c** would serve as a key intermediate to prepare **308** which in turn could be transformed to **307** by cleavage of the two N-O moieties. Crucial for this plan was the establishment of a 1,3-dipolar cycloaddition between **36c** and nitron.

**Scheme 9:** retrosynthesis of carbosugar **307**.

In a test experiment, **36c** was reacted with benzyl nitromethane **309** (Scheme 10). Several reaction conditions were screened but unfortunately only starting material was recovered (Table 7).



Scheme 10: 1,3-dipolar reaction involving **36c**.

Table 7: synthesis of **310** through 1,3-dipolar reactions.

| Entry | Additives | Solvent | Yield % |
|-------|---------------------------|-------------------|---------|
| 1 | DABCO | CHCl ₃ | 0 |
| 2 | (Boc) ₂ O/DMAP | CHCl ₃ | 0 |
| 3 | CAN | CHCl ₃ | 0 |
| 4 | PPh ₃ | Toluene | 0 |

We also reacted **36c** with some preformed nitrones such as 3,4-dihydro-2H-pyrrole 1-oxide **311**, 3,6-dihydro-2H-[1,4]oxazine 4-oxide **312**, 2,3,4,5-tetrahydro-pyridine 1-oxide **313** and *tert*-butyl-(2,4,6-trimethoxy-benzylidene)-amine *N*-oxide **314** (Figure 2) but these experiments did not give the desired isoxazolidines.

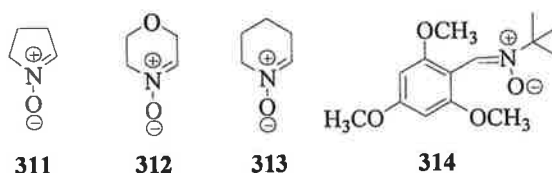
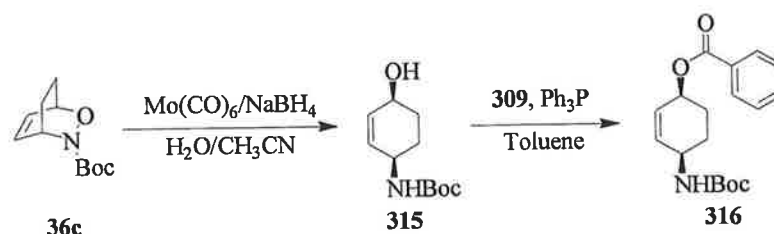


Figure 2

It was reasoned that the low reactivity of **36c** was due to the strained conformation of the cycloadduct. The steric hindrance of the ethylenic bridge would

then decrease the reactivity of the double bond. In respect of that, we decided to carry out the reaction on derivative **315** which could be prepared by reductive cleavage of the N-O bond by using $\text{Mo(CO)}_6/\text{NaBH}_4$ (Scheme 10).¹³ With compound **315** in hands, we attempted its reaction with different reagents such as CAN in acetone, nitrolic acids in THF, α -chloroximes in DCM and benzyl nitromethane **309** in toluene. All these methodologies, suitable for the *in situ* generation of nitron, gave only starting material after prolonged reaction time. Instead, using **315** and **309** in presence of Ph_3P in toluene at reflux for 12 hours, we obtained a new compound that it was identified as benzoyl derivated **316**.



Scheme 10: formation of benzoyl derivated **316**.

2.3. Conclusions

In conclusion, we have developed four novel methodologies for the generation of nitroso dienophiles. These reactions were practical and executable from truly commercially starting materials and afforded synthetically useful products in good to excellent yields. As compared with existing methodologies, these procedures afforded cycloadducts in similar yields, employing reagents in a 1:1 ratio and a reduced catalyst loading.^{5,6} Remarkably, the crude reaction mixture showed the HDA adduct as the only compound present: this renders the reactions described herein as ideal for the development of tandem processes. Experiments run using several enantiopure ligands gave racemic **36c**, suggesting that the nitroso species was released from the metal after

oxidation and this is in line with the observation reported by Whiting^{4c} using chiral Ru^{II} salen catalysts.

2.4. References

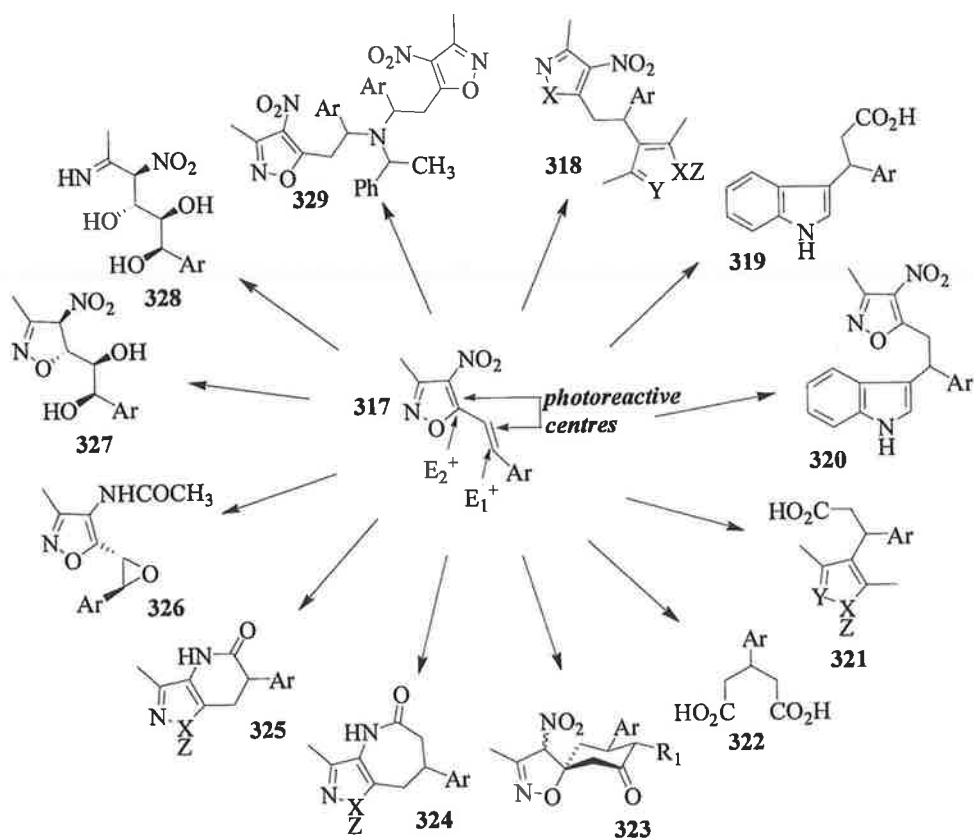
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Chapter 3: Aziridination of 3-methyl-4-nitro-5-styrylisoxazoles

3.1. Synthetic applications of 3-methyl-4-nitro-5-styrylisoxazole

Our group has recently reported some applications in synthesis of 3-methyl-4-nitro-5-styrylisoxazoles **317** (Scheme 1). Our approach to the development of diversity oriented syntheses is based on the generation of building blocks that contain multiple functionalities which could be selectively reacted.¹⁻⁹



Scheme 1: Synthetic applications of 3-methyl-4-nitro-5-styrylisoxazoles **317**.

We worked on the hypothesis that a product containing a number of functionalities m , which could be selectively reacted in a number of n directions, will generate diversity in $D = (m \times n)$ directions.

In this respect, 3-methyl-4-nitro-5-styrylisoxazoles **317** (Scheme 1) represent a class of poly-functional scaffolds, which hold great potential for the generation of diversity.

Compound **317** contains two different electrophilic centres, both of which can be selectively reacted. We have shown that soft nucleophiles, such as enolates, are selective for the soft electrophilic centre E_1^+ , whereas hard nucleophiles such as (OH^-) reacted exclusively at the hard electrophilic centre E_2^+ . Indeed, when reacted with excess of NaOH, the 4-nitroisoxazol-5-yl core revealed a carboxylic acid. Therefore compounds **317** should be considered as equivalent to cinnamate **330** (Figure 1).

Importantly, **317** possesses the following advantages compared to cinnamate esters: it could be generated *in situ* using mild conditions (0.1 equiv. piperidine in ethanol at 50-60 °C, for 1-2 h) and through an operationally simple methodology which does not require a controlled atmosphere or dry conditions. This is not true for cinnamates which are usually prepared either by malonic synthesis which require harsh conditions; by Wittig-Horner reaction which require a controlled atmosphere or by Heck reaction which require expensive Pd catalyst.

Considering that compounds **317** could be prepared from the condensation of commercially available 3,5-dimethyl-4-nitroisoxazole **331** and an aromatic aldehyde **332** (Figure 1), we reasoned that a number of multicomponent tandem procedures could be devised by coupling the generation of **317** with a subsequent reaction that involved the formed double bond. Additionally, the isoxazole core is of considerable value in total synthesis.

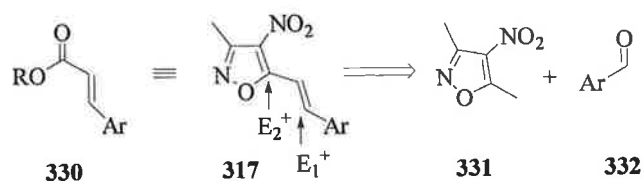


Figure 1: 3-Methyl-4-nitro-5-styrylisoxazole **317** as cinnamate equivalent.

In the present study, we report the synthesis of aziridines **333**, *N*-Michael adducts **334-336** and thia-Michael adducts **337** (**Figure 2**).

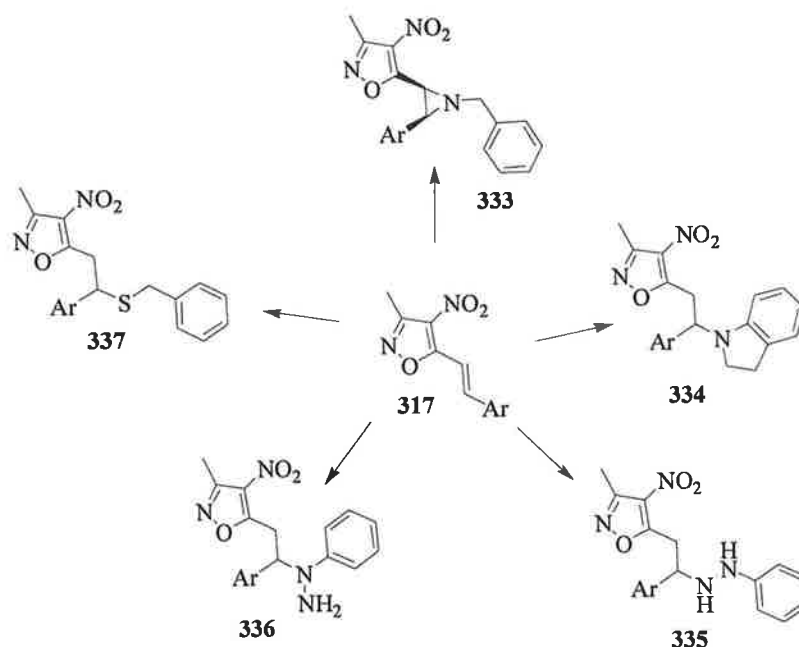


Figure 2

3.2. Introduction

The aziridine nucleus is present in several natural products exhibiting biological activity such as antitumor agents and antibiotics.¹⁰ Since these are the nitrogen analogues of epoxides, they also display similar electrophilic reactivity: aziridines undergo various nucleophilic ring-opening reactions and serve as synthetic intermediates for nitrogen-containing compounds.¹¹ For instance aziridines were used for the synthesis of amino acids and alkaloids,¹² substituted amines, diamines, amino alcohols, and α - or β -amino acids.^{12a, 13}

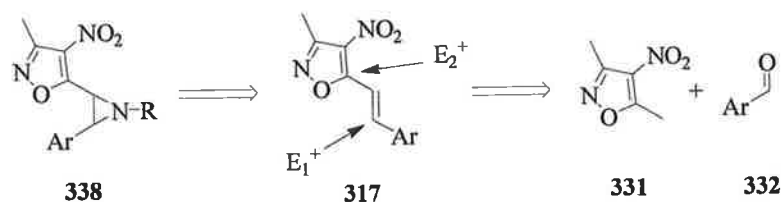
Various synthetic methods have been developed to prepare aziridines, typically starting from alkenes or imines.¹⁴ Copper,¹⁵ rhodium,¹⁶ manganese,¹⁷ and rhenium,¹⁸

were equally used to catalyse the conversion of olefins to aziridines. Among these metals, copper in conjunction with tosylimino-phenyliodane¹⁹ has been widely used as the nitrogen transfer reagent. Chloramine-T²⁰ or bromamine-T²¹ have also been employed in aziridination reactions. A combination of bromamine-T with porphyrin complexes of transition metals such as Mn, Fe, Ru, and Co was also shown to yield aziridines.²² Polymers incorporating Mn and Fe were found to be efficient in aziridination reactions with bromamine-T.²³ Recently, the use of *N*-tosyloxycarbamates was reported as an alternative to produce rhodium²⁴ or copper²⁵ nitrenes that can undergo C-H insertion and azyridination reactions.

Several methods are available for the preparation of enantiomerically enriched aziridines. However, most involve multi-step procedures, employing either optically active starting materials or stoichiometric quantities of a chiral auxiliary.²⁶ Direct approaches to aziridines involve the cycloaddition of a nitrene fragment to an olefin, or a carbene to an imine. The latter approach has been studied by a number of groups. Most noteworthy are efforts by Evans,²⁷ Jacobsen²⁸ and Scott²⁹ towards the development of an efficient catalytic asymmetric version of a nitrene transfer from *N*-(*p*-toluenesulfonyl)imino]phenyliodinane (PhI=NTs) with a variety of chiral copper Lewis acids. Katsuki and Nishikori also showed that manganese salens were excellent catalytic promoters of the enantioselective aziridination of a series of styrene derivatives in very high yields and enantioselectivities.³⁰ Aggarwal reported the catalytic asymmetric aziridination of imines with *in situ* generated diazo compounds as carbene sources in the presence of chiral sulfides.³¹

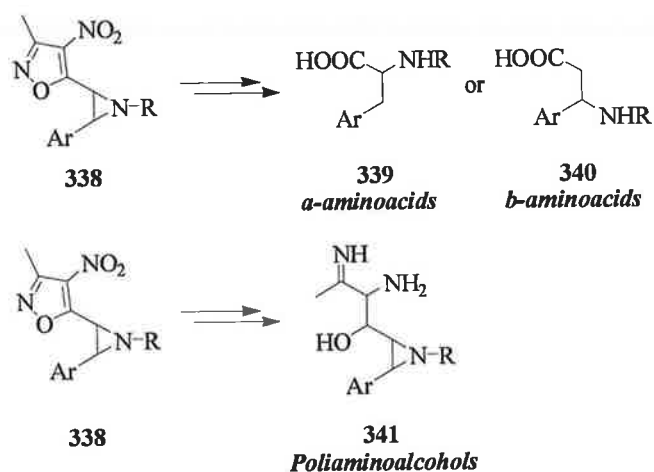
3.3. Results and discussion

As part of our ongoing studies on the generation of chemical diversity using polyfunctional scaffolds, we became interested in the preparation of aziridine **338** (Scheme 2). In analogy to compound **317**, aziridine **338** possesses two electrophilic centres that we hoped to react selectively.



Scheme 2: retrosynthetic analysis of target **338**.

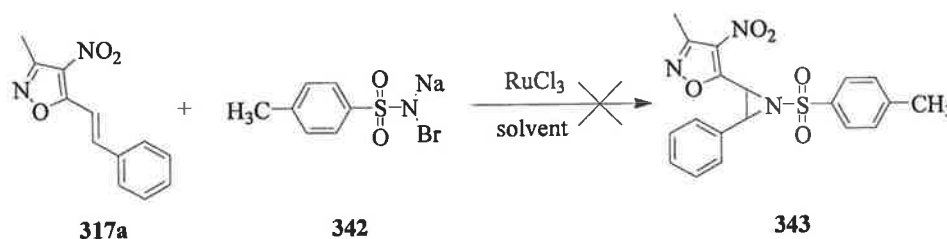
α,β -Aziridines are versatile synthons that can be regio and stereoselectively ring opened when reacted with suitable nucleophiles.³² Therefore, compounds **338** constitute a stereospecific version of scaffolds **317** that we hope to employ to generate diversity in a stereoselective fashion. Considering that the 4-nitroisoxazole core represents a masked carboxylate or a protected β -diketone, it is easy to envisage the potential of compound **338** in synthesis. For example, aziridine ring opening followed by transformation of isoxazole core to acid would furnish the corresponding aminoacids **339-340** (Scheme 3). Alternatively, reductive ring opening of the 4-nitroisoxazole core could lead to polyaminoalcohols **341** (Scheme 3).



Scheme 3: transformation of aziridine-isoxazole **338**.

We started investigating the aziridination of **317a** by using bromamine-T **342**. Bromamine-T has been extensively used as a source of nitrene.³³ When styrylisoxazole

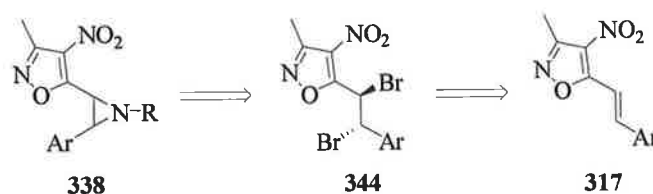
317a was reacted with bromamine-T **342** in the presence of RuCl_3 as the catalyst, formation of the corresponding aziridine **343** was not observed (**Scheme 4**). We studied extensively this reaction by varying the nature of catalyst, solvent, temperature but only starting material was recovered.



Scheme 4: reactivity of **317a** using bromamine-T.

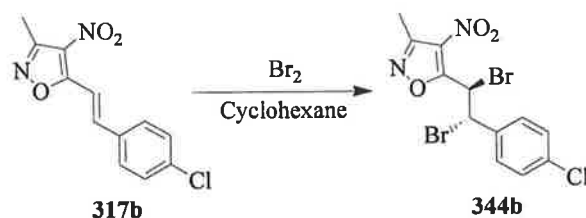
We then investigated the reaction of **317a** and sulfonyl azide with RuCl_3 as catalyst and also in this case only starting material was observed.

A possible reason for the resistance of **317a** to undergo aziridination was the electron deficiency of the double bond in **317a**. Therefore we designed a novel strategy in which the exocyclic alkene would be converted to dibromide derivatives **344**³⁴ which in turn could be used to prepare **338** (**Scheme 5**). The preparation of compound **344** was reported.³⁵



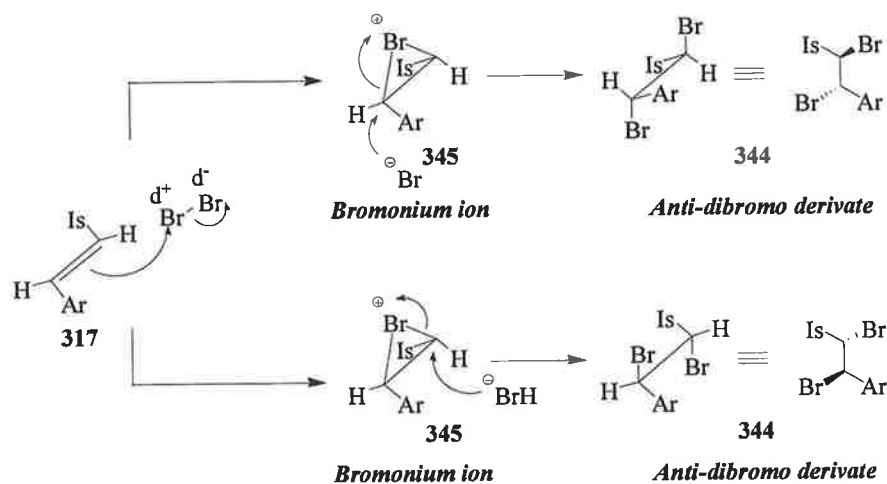
Scheme 5: retrosynthetic analysis of target **338**.

When **317b** was reacted with 1 equiv. of bromine in cyclohexane, pure dibromide derivative **344b** was obtained as a racemic mixture in half an hour and in quantitative yield (**Scheme 6**). This is in line with the report of Sarti-Fantoni *et al.*³⁵



Scheme 6: synthesis of dibromoderivate **344b**.

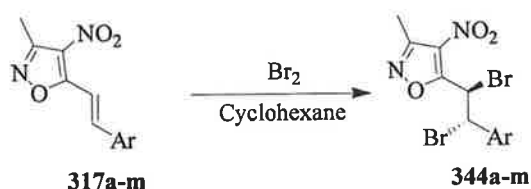
As widely described,³⁶ the halogen addition to *trans*-alkenes lead to *anti*-dibromo derivatives through an *anti*-addition where two atoms or substituents are added to opposite faces of a double bond (**Scheme 7**). In the first step of reaction, a bromine molecule approaches the electron-rich alkene C-C double bond of compound **317** and the bromine atom closer to the bond takes on a partial positive charge as its electrons are repelled by the electrons of the double bond (*polarization*). This bromine atom is electrophilic at this time and the alkene double bond attacks it to form a three-membered ring where the bromine atom binds to both carbon atoms of alkene π -system. The bromine ion acquires a positive charge, which it shares slightly with the two carbon atoms (*bromonium ion*, **345**). When the first bromine atom is attacked by the C-C π -bond, it leaves behind one of its electrons with the other bromine that it was bonded to in Br_2 .



Scheme 7: mechanism of synthesis of dibromo derivate **344**.

That other atom is now a negative bromine anion which is attracted to the slight positive charge on the carbon atom. It is blocked from nucleophilic attack on one side of the carbon chain by the first bromine atom and only attacks on the other side. As it attacks and forms a bond with one of the carbons, the bond between the first bromine atom and the other carbon atom breaks, leaving each carbon atom with a halogen substituent (**344**).

Several *anti*-dibromo derivatives were preformed in quantitative yields using this procedure (**Scheme 8** and **Table 1**). Only the *p*-NO₂ derivative required a larger excess of bromine for its synthesis (**Table 1**, entry 12).



Scheme 8: synthesis of dibromo isoxazoles derivatives **344a-m**.

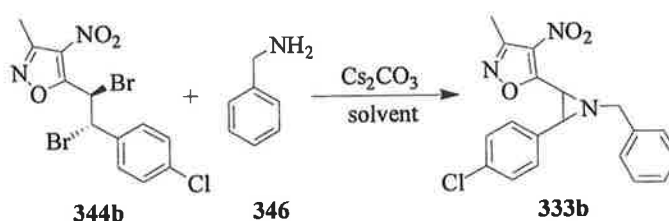
Table 1: synthesis of dibromo derivatives **344a-m**.

| Entry | Compound | Ar | Yield (%) ^a |
|-------|-------------|--|------------------------|
| 1 | 344a | C ₆ H ₅ | 98 |
| 2 | 344b | <i>p</i> -Cl-C ₆ H ₄ | 98 |
| 3 | 344c | <i>p</i> -F-C ₆ H ₄ | 98 |
| 4 | 344d | <i>p</i> -Br-C ₆ H ₄ | 98 |
| 5 | 344e | <i>m</i> -Cl-C ₆ H ₄ | 98 |
| 6 | 344f | 2-Pyridine | 98 |
| 7 | 344g | <i>p</i> -MeO-C ₆ H ₄ | 98 |
| 8 | 344h | 2-naftyl | 98 |
| 9 | 344i | 2-quinoline | 77 |
| 10 | 344j | <i>p</i> -CH ₃ -C ₆ H ₄ | 98 |
| 11 | 344k | 2-thiophenyl | 98 |
| 12 | 344l | <i>p</i> -NO ₂ -C ₆ H ₄ | 98 ^b |
| 13 | 344m | 2,4-di-Cl-C ₆ H ₃ | 98 |

^a Isolated yield.

^b Sealed tube, 27 eq. of Br₂, reflux, 12h.

With compounds **344a-m** in hand, we studied their reactivity towards benzylamine in order to synthesize an aziridine ring. When **344b** was reacted with benzylamine in CH₃CN the reaction afforded a mixture of isomeric aziridines. The use of bases such as Na₂CO₃ or pyridine did not lead to improvement. It has been reported that Cs₂CO₃ had beneficial effects on the conversion of 1,2-dibromo derivatives to aziridines.³⁷ Following this report we undertook a screening of reaction conditions to identify an optimum experimental set up (**Scheme 9**). Results are shown in **Table 2**.



Scheme 9: synthesis of aziridine.

Table 2: screening of reaction conditions in aziridination.

| Entry | Benzylamine (eq.) | Cs ₂ CO ₃ (eq.) | Solvent | Yield % ^a |
|-------|-------------------|---------------------------------------|--------------------|----------------------|
| 1 | 1 | 1.2 | CH ₃ CN | mix ^b |
| 2 | 1 | 3.5 | DCM | - |
| 3 | 1 | 3.5 | CH ₃ CN | 50 |
| 4 | 1 | 3.5 | CH ₃ CN | - ^c |
| 5 | 1 | 3.5 | Toluene | mix ^b |
| 6 | 1 | 5 | CH ₃ CN | 31 |
| 7 | 3 | 3.5 | CH ₃ CN | 49 |
| 8 | 3 | 6 | CH ₃ CN | - |

^a Isolated yield after chromatography.

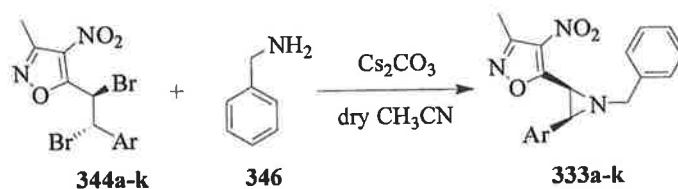
^b Not understandable mixture of isomers.

^c Reaction was carried out at 60 °C.

Best results were obtained using 3.5 equiv. of Cs₂CO₃ in dry acetonitrile (**Table 2**, entry 3). Large excess of Cs₂CO₃ did not lead to improvement of the reaction yield (**Table 2**, entry 6) as well as the use of an excess of benzylamine (**Table 2**, entry 7). DCM, toluene and CH₃CN were examined with the latter giving better results.

Therefore, it was confirmed that best procedure involved the use of 1 equiv of benzylamine, 3.5 equiv. of Cs_2CO_3 and dry CH_3CN as the solvent (Table 2, entry 3).

A number of aryl substituted dibromoisoxazoles **344a-k** were then submitted to reaction with benzylamine **346** in the presence of Cs_2CO_3 (Scheme 10) and results are summarised in Table 3.



Scheme 10: synthesis of aziridines **333a-k**.

Table 3: synthesis of aziridines.

| Entry | Compound | Ar | Yield % ^a |
|-------|-------------|---|----------------------|
| 1 | 333a | C_6H_5 | 30 |
| 2 | 333b | <i>p</i> -Cl- C_6H_4 | 50 |
| 3 | 333c | <i>p</i> -F- C_6H_4 | 40 |
| 4 | 333d | <i>p</i> -Br- C_6H_4 | 46 |
| 5 | 333e | <i>m</i> -Cl- C_6H_4 | 36 |
| 6 | 333f | 2-Pyridine | 41 |
| 7 | 333g | <i>p</i> -CH ₃ O- C_6H_4 | - |
| 8 | 333h | 2-naphtyl | - |
| 9 | 333i | 2-quinoline | - |
| 10 | 333j | <i>p</i> -CH ₃ - C_6H_4 | - |
| 11 | 333k | 2-thiophenyl | - |

^a Isolated yield after chromatography.

Compounds **344** bearing an electron withdrawing group reacted promptly giving desired aziridines in good isolated yields (Table 3, entries 2-5). Conversely, compounds bearing an electron donating group did not react and starting materials were recovered after prolonged reaction time. These results were explained considering that the presence of electron withdrawing groups made the benzylic bromide more reactive towards

nucleophilic attack. The analysis of the crude reaction $^1\text{H-NMR}$ showed that only one isomer was obtained. The *cis* stereochemistry was assigned by estimation of constant coupling between $\text{H}_6\text{-H}_7$ and N.O.E. experiments. In compound **333a-f**, J_{6-7} appeared to be 6.4 Hz which is typical for *cis* aziridine ring (**Figure 3**).

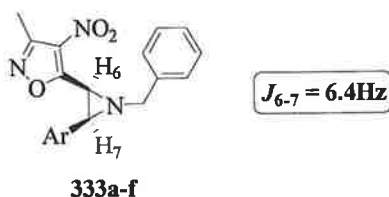
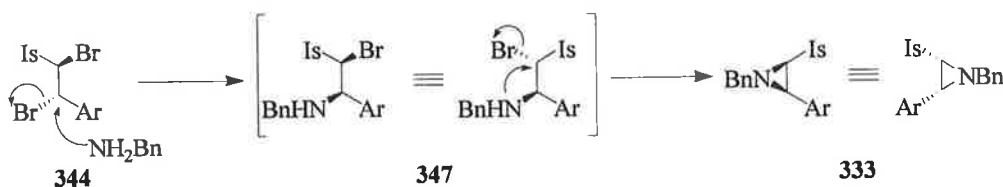


Figure 3: NMR constant coupling in aziridine **333a-f**.

The complete stereoselective formation of *cis* aziridines could be explained considering that the reaction mechanism consists of two $\text{S}_{\text{N}}2$ nucleophilic additions of amine to the *anti*-dibromo derivate (**Scheme 11**). In the first step the amine attacks on the atom bearing bromine atom and bromide ion is eliminated to form the intermediate **347**. The followed intramolecular $\text{S}_{\text{N}}2$ reaction gives the elimination of another bromide ion and affords the only *cis* isomer.



Scheme 11: plausible mechanism in the synthesis of *cis*-aziridines.

3.4. Conclusions

In conclusion we have reported a methodology to synthesize 4-nitroisoxazolylaziridines **333**. The reaction afforded the corresponding adducts in

moderate yields and with complete stereoselectivity as only *cis* stereoisomers were obtained.

3.5. References

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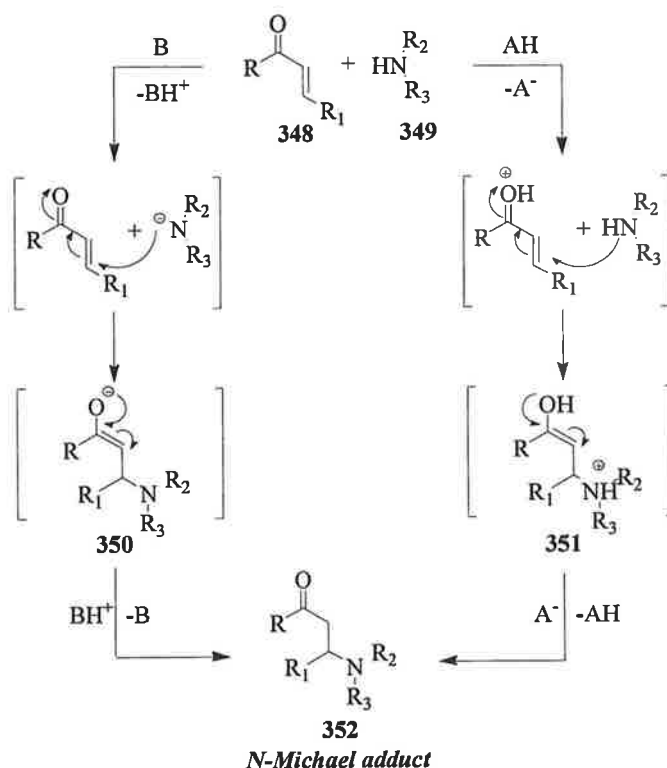
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Chapter 4: Studies on the reactivity of 3-methyl-4-nitro-5-styrylisoxazoles with *N*-nucleophiles

4.1. Introduction

The addition of nitrogen nucleophiles to alkenes is of great interest in organic synthesis.¹ In particular the addition of amines to α,β -unsaturated carbonyl compounds (aza-Michael) attracted much interest as β -amino ketones are obtained. The classic method for the synthesis of β -amino ketones is the Mannich reaction of methyl ketones, amines and paraformaldehyde.² This reaction often suffers from drawbacks of long reaction time and harsh reaction conditions, which impair the applicability in the synthesis of complex molecules.^{2,3} In the recent past novel efficient methods leading to chiral β -amino ketones, β -amino acids and their derivatives have been developed.⁴ In general, the nucleophilic addition of amine to α,β -unsaturated carbonyl compounds requires either basic conditions⁵ (B) or an acid catalyst⁶ (AH) (**Scheme 1**) which can be detrimental to the desired synthesis.



Scheme 1: aza-Michael reactions.

In order to overcome some of these limitations, a number of alternative procedures have been reported using a variety of metal catalysts such as $\text{Bi}(\text{NO}_3)_3$,⁷ $\text{Bi}(\text{OTf})_3$,⁸ $\text{CeCl}_3 \cdot \text{H}_2\text{O}/\text{NaI}$,⁹ boric acid¹⁰ and CAN .¹¹ The advantage of these methodologies are an oxygen and moisture stability, a low toxicity and cost of the catalyst. Moreover, both cyclic and acyclic α,β -unsaturated carbonyl compounds can be used with these catalysts.

Recently, $\text{FeCl}_3 \cdot 7\text{H}_2\text{O}$, $\text{CrCl}_3 \cdot 6\text{H}_2\text{O}$ and $\text{SnCl}_4 \cdot 4\text{H}_2\text{O}$ have shown the ability to catalyze aza-Michael reactions under mild conditions in aqueous solution, where both aliphatic and aromatic amines could be used as the nucleophiles.¹² This is an important finding as usually arylamines are poor nucleophiles compared to aliphatic ones. It was also demonstrated that β -cyclodextrin promoted addition of arylamines to olefins.¹³ A high by efficient base ionic liquid catalysis of aromatic amines and *N*-heterocycles to

α,β -unsaturated cyclic and acyclic ketones under solvent-free condition to produce the desired Michael adduct has been reported.¹⁴ This process was simple and generated a diverse range of aromatic amino carbonyl derivatives using an easily accessible and recyclable catalyst.

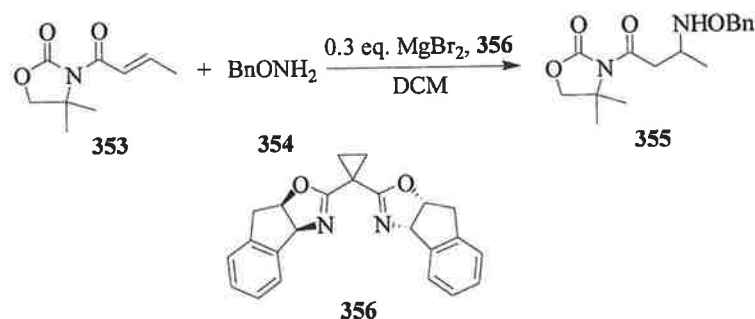
In the recent past, a wide variety of amines and their synthetic equivalents were examined as nucleophiles in 1,4-addition to α,β -unsaturated carbonyl moiety to develop a novel and more efficient synthetic method leading to β -amino ketones and β -amino acids. Advance in this direction include the conjugate addition of aldoximes,¹⁵ hydrazoic acids,¹⁶ trimethylsilyl azide¹⁷ and hydroxilamines.¹⁸ The catalytic addition of carbamates using metal catalysis was also reported. In particular, Cu^{II} ¹⁹ and $\text{In}^{\text{III}}/\text{TMSCl}$ ²⁰ were able to catalyze the nucleophilic addition of weak basic nitrogen to enones and induce a moderate stereoselectivity when chiral ligands were used.

Addition of amines to cinnamate derivatives in aza-Michael reactions has also been studied. In particular, LiClO_4 ²¹ and $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ or montmorillonite K10²² accelerated Michael addition of amines to α,β -unsaturated ester under solvent-free and mild conditions were reported. Using LiClO_4 , primary aliphatic amines reacted with cinnamate esters to give only the 1,4-adduct and no side product was observed even by using the excess of reagents. Unfortunately, aromatic amines gave the desired adducts in low yield under these reaction conditions. Moreover, this method is temperature dependent. When the reaction was carried out at room temperature, only Michael adducts were formed. By elevating the temperature to 60 °C, the corresponding amides were obtained. Instead, Hashemi *et al.* reported the conjugate addition reaction of different aliphatic amines to cinnamates in the presence of $\text{ZrOCl}_2 \cdot 8\text{H}_2\text{O}$ /montmorillonite K10. In both methodologies catalytic systems could be easily recovered and used again after reactivation by heating.

Enantioselective aza-Michael reactions have also received considerable attention. Jorgensen described the first example of enantioselective aza-Michael reaction which was catalyzed by a TiCl_2 BINOL complex.²³

In an alternative approach, Lewis acid and homochiral bisoxazolines were used to catalyze the addition of nucleophile amine to α,β -unsaturated amides. Cu^{II} ^{19a} and

Mg^{II}²⁴ resulted to be the best metals used in combination with chiral bisoxazolines **356** to catalyze aza-Michael additions to unsaturated 2-oxazolidinones derivatives **353** (Scheme 2). These methodologies afforded the desired Michael adducts in good yields and excellent enantioselectivity. The face selectivity of the procedure was shown to be dependant on the temperature although a comprehensive explanation for this effect was not given (Scheme 2, Table 1).



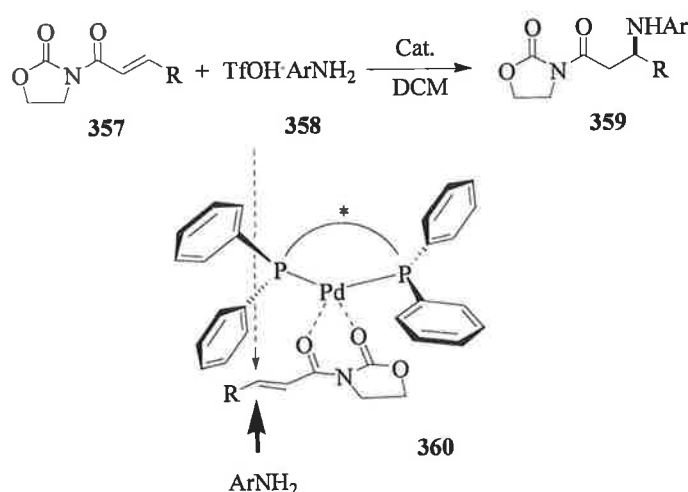
Scheme 2: enantioselective aza-Michael reaction.

Table 1: enantioselective aza-Michael reaction.

| R | T (°C) | Yield (%) | ee (%) |
|--------------------------------|--------|-----------|--------|
| Et | rt | 87 | 35 (-) |
| Et | 0 | 82 | 28 (-) |
| Et | -60 | 83 | 53 (+) |
| Pr | rt | 56 | 40 (-) |
| Pr | 0 | 76 | 31 (-) |
| Pr | -60 | 66 | 81 (+) |
| C ₅ H ₁₁ | rt | 69 | 22 (-) |
| C ₅ H ₁₁ | 0 | 79 | 35 (-) |
| C ₅ H ₁₁ | -60 | 87 | 26 (+) |

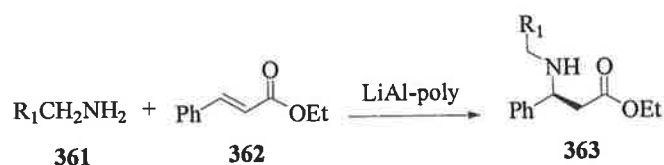
Addition of amine to unsaturated 2-oxazolidinones derivatives was also catalyzed by Pd^{II}-BINAP complex.²⁵ The reactions proceeded with good yields and high enantioselectivity with both benzyl and aromatic amines. Sodeoka *et al.* developed a combination of Pd^{II}-BINAP complex and amine salt capable to release free nucleophilic

amine.²⁶ Under these conditions, an efficient catalytic conjugate addition of various aromatic amines **358** was achieved to afford β -amino addition to unsaturated 2-oxazolidinones **357** (Scheme 3). The proposed transition complex **360** ensures that the free amines would attack on the bottom face of the double bond because the other one was blocked preferentially by one of the phenyl groups of BINAP.



Scheme 3: enantioselective aza-Micheal reaction.

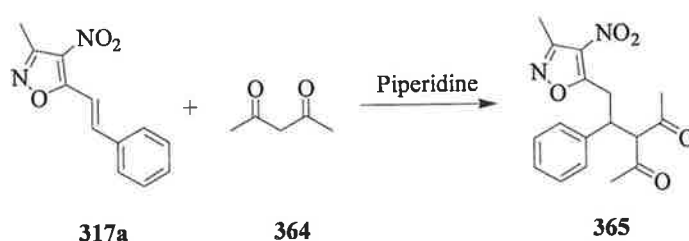
An asymmetric aza-Michael addition of benzylamine to ethylcinnamate was studied by Sundararajan and co-workers.²⁷ Polymer-anchored chiral catalyst (LiAl-poly) was prepared from monomer (*R,R*)-3-aza-3-(*p*-vinylbenzyl)-1,5-diphenyl-1,5-dihdropentane when polymerized with divinylbenzene, onto which lithium and aluminium are incorporated *via* reaction with lithium aluminium hydride. LiAl-poly catalyzed enantioselective conjugate addition of benzyl amines **361** to ethylcinnamate **362** afforded the Michael adduct **363** with good yield and enantioselectivity (Scheme 4).



Scheme 4: enantioselective aza-Michael reaction.

4.2. Results and discussion

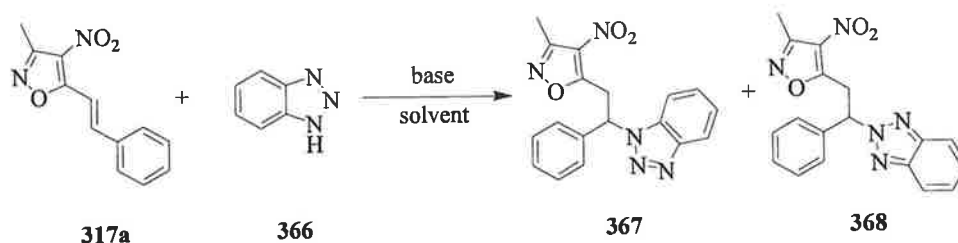
As a part of our ongoing efforts in exploring the synthetic potentials of styrylisoxazoles **317**, we became interested in studying the reactivity of **317** towards *N*-nucleophiles. We have previously reported that **317a** is an excellent Michael acceptor reacting efficiently with acetylacetone **364** to afford Michael adduct **365** in high isolated yield (**Scheme 5**).²⁸



Scheme 5: Michael reaction.

This data and our interest in developing chemical diversity from **317** prompted us in reacting **317a** with standard *N*-nucleophiles. Benzotriazole has been extensively shown to be an excellent nucleophile²⁹ and was selected to run preliminary studies. Additionally, some benzotriazole containing molecules have shown medicinal properties such as antiemetic and gastroprokinetic.³⁰

In a test experiment styrylisoxazole **317a** was reacted with 1.1 equiv. of benzotriazole **366** in DCM at room temperature (**Scheme 6**). Under these conditions no Michael addition took place and reactants were recovered quantitatively at the end of the reaction. In order to promote the Michael reaction of **317a** and **366**, several combination of solvents and bases were tested (**Scheme 6**, **Table 2**).



Scheme 6: aza-Michael reaction using benzotriazole **366**.

Table 2: base and solvent screening.

| Entry | Solvent | Base (eq.) | Yield % ^a |
|-----------------|--------------------|------------------------------|----------------------|
| 1 | DCM | - | - |
| 2 | DCM | DMAP | 32 |
| 3 | DCM | DMAP, thiourea-derivate | 38 |
| 4 | DCM | Tetrabutylammonium hydroxide | - |
| 5 | DCM | Pyrrolidinemethanol | - |
| 6 | CH ₃ CN | Tetrabutylammonium hydroxide | - |
| 7 ^b | CH ₃ CN | DMAP, thiourea-derivate | 64 |
| 8 | <i>i</i> -PrOH | Pyrrolidinemethanol | - |
| 9 ^c | DCM | DMAP | 38 |
| 10 ^d | CH ₃ CN | DMAP | 80 |
| 11 | EtOH | DMAP | - |
| 12 | THF | DMAP | - |
| 13 | Et ₂ O | DMAP | - |
| 14 | Toluene | Quinine | 15 |

^a Isolated yields after chromatography.

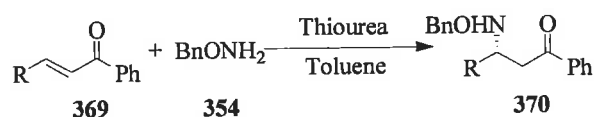
^b 5eq. base, 5eq. 1,2,3-benzotriazole, 1eq. thiourea-derivate.

^c 3eq. DMAP, 3eq. 1,2,3-benzotriazole.

^d 5eq. DMAP, 5eq. 1,2,3-benzotriazole.

Data collected showed that the reaction of **317a** and **366** depended on the solvent and base employed. Pyrrolidinemethanol (Table 2, entry 8) and tetrabutylammonium hydroxide (Table 2, entries 4, 6) failed to catalyse this reaction. Conversely, DMAP promoted the addition of **366** to **317a** but only in selected solvents. The reaction gave only low quantities of adducts **367** and **368** in DCM and no reaction occurred when run

in EtOH, THF or Et₂O (**Table 2**, entries 11-13). Quinine was also shown to promote the formation of Michael adduct **367** and **368** in very low yields (**Table 2**, entry 14). Best results were obtained using a large excess (5 equiv.) of DMAP in CH₃CN and an excess of benzotriazole **366** (**Table 2**, entry 10). We have also explored the additional catalysis of thiourea derivatives. Thiourea compounds have been shown to act as co-catalysts for base promoted reactions. For example they have been used in enantioselective aza-Michael reactions on α,β -unsaturated ketones **369** (**Scheme 7**).³¹



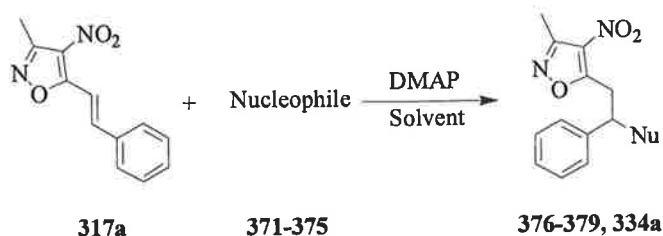
Scheme 7:aza-Michael reactions using thiourea.


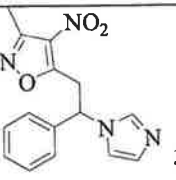

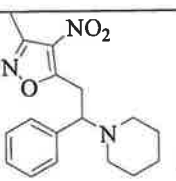
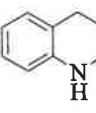
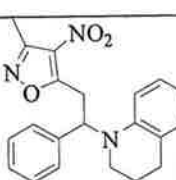
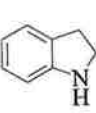
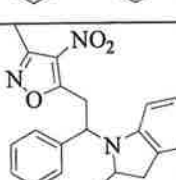
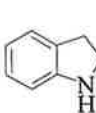
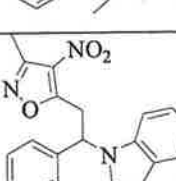
Thiourea is capable of enhancing the basic media created by DMAP. For this reason we thought that the presence of thiourea could be beneficial. Data collected showed that this was not true in our case (**Table 2**, entries 2, 3). A ¹H-NMR analysis of the product revealed the presence of two products **367** and **368**. This is in accordance with an other report.²⁹

Typically, in the reaction of **317a** and 5 equiv. of **366** in the presence of 5 equiv. of DMAP, adducts **367** and **368** were obtained in 73% and 7% isolated yield respectively.

In addition we studied the effect of the temperature on the reaction rate. We observed that heating the reaction mixture did not improve the reaction rate and yield: a retro Michael reaction was observed when the reaction was heated and only starting material was recovered.

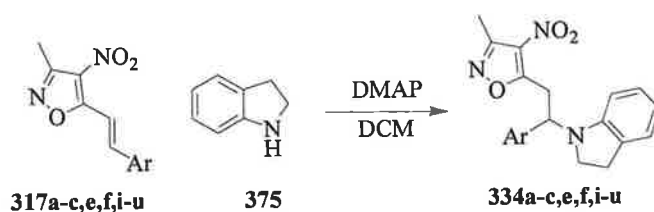
Having studied the reactivity of **317a** and benzotriazole we decided to explore the range of amine nucleophiles (**Scheme 8**). Therefore, compound **317a** was reacted with imidazole **371**, piperidine **372**, 1,2,3,4-tetrahydroquinoline **373**, 2-methylindoline **374** and indoline **375**.

**Scheme 8:** aza-Michael reaction.**Table 3:** aza-Michael additions.

| Entry | Nucleophile | Product | Yield % |
|-------|--|---|---------|
| 1 |  371 |  376 | - |
| 2 |  372 |  377 | - |
| 3 |  373 |  378 | - |
| 4 |  374 |  379 | - |
| 5 |  375 |  334a | 89 |

The reaction of **317a** with **371-374** failed to give the desired Michael adduct. With our delight indoline **375** showed to be a good nucleophile and corresponding adduct **334a** was obtained in good yield. The reaction proceeded at room temperature in 24 hours with 5 equiv. of indoline **375** and catalytic amount (0.2 equiv.) of DMAP as the

base. The generality of this reaction was demonstrated by preparing a family of compounds **334** (Scheme 9 and Table 4).



Scheme 9: aza-Michael reaction using indoline **375**.

Table 4: aza-Michael reaction with indoline **375**.

| Entry | Compound | Ar | Yield % ^a |
|-------|-------------|--|----------------------|
| 1 | 334a | C ₆ H ₅ | 89 ^b |
| 2 | 334b | <i>p</i> -Cl-C ₆ H ₄ | 84 |
| 3 | 334c | <i>p</i> -F-C ₆ H ₄ | 86 |
| 4 | 334e | <i>m</i> -Cl-C ₆ H ₄ | 89 |
| 5 | 334f | 2-pyridine | 98 |
| 6 | 334i | 2-quinoline | 95 |
| 7 | 334j | <i>p</i> -CH ₃ -C ₆ H ₄ | 61 |
| 8 | 334k | 2-thiophenyl | 82 |
| 9 | 334l | <i>p</i> -NO ₂ -C ₆ H ₄ | 41 |
| 10 | 334m | 2,4-di-Cl-C ₆ H ₃ | 91 |
| 11 | 334n | <i>p</i> -CN-C ₆ H ₄ | 93 |
| 12 | 334o | <i>m</i> -CH ₃ -C ₆ H ₄ | 73 |
| 13 | 334p | 2-furyl | 52 |
| 14 | 334q | 2,3-di-Cl-C ₆ H ₃ | 90 |
| 15 | 334r | 3-pyridine | 94 |
| 16 | 334s | 4-pyridine | 94 |
| 17 | 334t | <i>o</i> -Cl-C ₆ H ₄ | 92 |
| 18 | 334u | 4-quinoline | 86 |

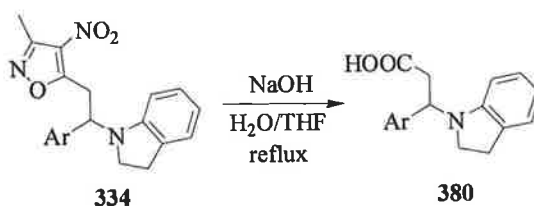
^a NMR yields.

^b Isolated yield after flash chromatography.

The data collected showed that pyridine (**Table 4**, entries 5-16) and quinoline (**Table 4**, entries 6, 18) isoxazoles were the most reactive substrates for this reaction as well as chlorine containing ones (**Table 4**, entries 2, 4, 10, 14, 17), which gave quantitative yields.

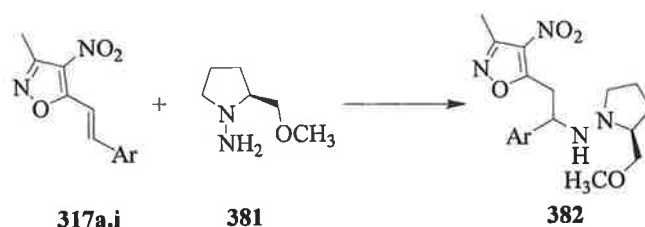
The yields were estimated by integration of the ^1H -NMR peak relative to an internal standard. Compounds **334** could be obtained pure by column chromatography. The chromatographic purification was laborious and often led to a much decreased yield. The main problem laid in the fact that a full conversion of arylisoxazoles **317** was only observed in few cases (**Table 4**, entries 5, 6) and that starting material R_f was too close to the R_f of **334**. This rendered the chromatographic purification laborious. Crystallization of crude product afforded pure compounds in typically 50-60% yields.

With compounds **334** in hand we studied their conversion to acid **380** (**Scheme 10**). We have recently reported an efficient procedure in which the 4-nitroisoxazole core was transformed into a carboxylate.^{32, 33} In our plan, this reaction would have provided a means to prepare β -aminoacids. Recently, we reported the use of KMnO_4 in a mixture of acetone/water as a new method for the hydrolysis of isoxazole in the synthesis of aryl-glutaric acids³⁴ but unfortunately this procedure failed. The preparation of **380** was attempted by submitting **334** to reaction with 5 equiv. of NaOH in $\text{H}_2\text{O}/\text{THF}$ mixture at reflux. Although a full conversion of starting material was observed, recovery of the acid was achieved only for **380u**, which was isolated in 10% yield. For this reason the conversion of **334** to **380** was also studied by using several oxidising agents, including Oxone[®], $t\text{-BuOOH}$ and $m\text{-CPBA}$ without success.



Scheme 10: synthesis of indolinpropionic acids **380**.

We have also studied the reactivity of isoxazoles **317** and hydrazines. Substituted hydrazines are important synthones as they could be used for the synthesis of heterocycles, drugs, polymers and dyestuffs.³⁵ It has been recently shown that chiral hydrazines reacted efficiently in aza-Michael reactions.³⁶ This encouraged us in applying this procedure to isoxazole **317** (**Scheme 11**). Isoxazole **317a-i** were selected as probes and reacted with chiral hydrazine **381** under standard reported conditions. Unfortunately, these experiments gave negative results and the expected adduct **382** was not observed (**Table 5**).

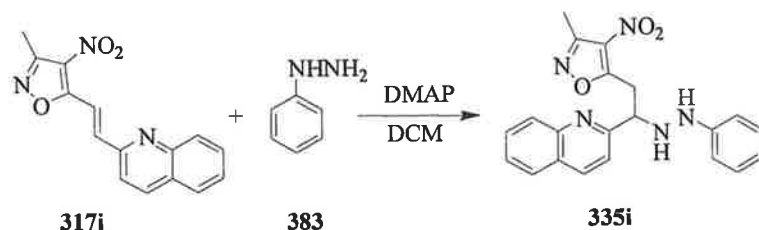


Scheme 11: reaction of styrylisoxazoles with chiral hydrazine **381**.

Table 5: reactivity of styrylisoxazoles with chiral hydrazine **381**.

| Entry | Styrylisoxazole | Ar | 381 (eq) | Base | Solvent | Yield % |
|-------|-----------------|-------------------------------|----------|------|---------|---------|
| 1 | 317a | C ₆ H ₅ | 2 | - | DCM | - |
| 2 | 317a | C ₆ H ₅ | 0.6 | - | THF | - |
| 3 | 317i | 2-quinoline | 2 | - | DCM | - |
| 4 | 317i | 2-quinoline | 1 | DMAP | DCM | - |

We then focussed our attention on the reactivity of other hydrazines with styryl isoxazoles. We tried reacting isoxazole **317i** with benzyl hydrazine **383** in presence of a catalytic amount of base. This procedure allowed us to isolate compound **335i** in good yield (**Scheme 12**). The reaction proceeded at room temperature and required 24 hours. To establish the optimal reaction conditions we tried to vary the amount of hydrazine and base (**Table 6**).



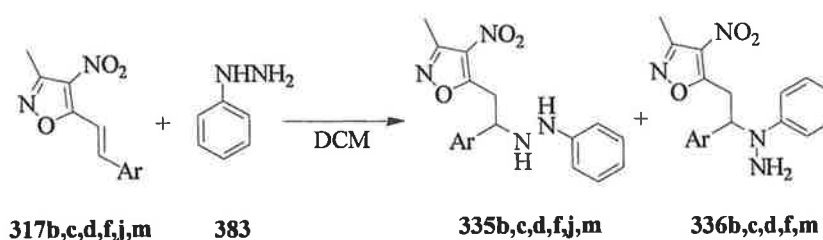
Scheme 12: aza-Michael reaction with phenylhydrazine **383**.

Table 6: screening of reaction conditions in the synthesis of **335i**.

| Entry | 385 (eq) | Base | Yield % ^a |
|-------|----------|-------------------|----------------------|
| 1 | 4 | DMAP | 68 |
| 2 | 1 | DMAP | 30 |
| 3 | 4 | - | 65 |
| 4 | 4 | Et ₃ N | 61 |

^a Isolated yield after chromatography.

This work identified 4 equiv. of hydrazine **383** as the optimal amount and importantly that no base was needed. With an optimal procedure in hand we have generated a small family of hydrazine adducts (**Scheme 13**). All reactions were carried out in DCM using 4 equiv. of hydrazine **383** until complete disappearance of starting material was observed that usually occurs in 24 hours. In all cases the crude NMR showed one isomer (only product **335b,c,d,f,j,m**, **Scheme 8**). However upon chromatography purification we observed the formation of a second isomer that we identified as compound **336b,c,d,f,m**. Purification by crystallization of crude reaction product with Ar = *p*-CH₃ afforded adduct **336j** as the only product. All reaction yields were excellent and results obtained are listed in **Table 7**.



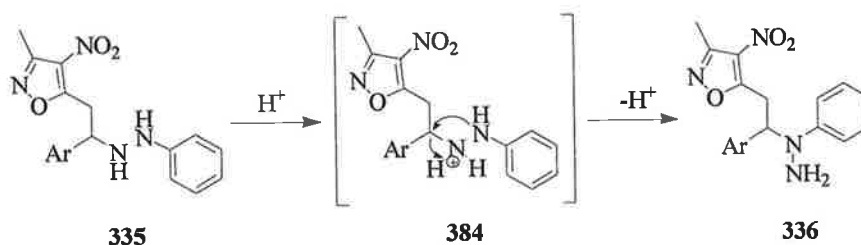
Scheme 13: formation of adducts **335b,c,d,f,j,m** and **336b,c,d,f,m**.

Table 7: synthesis of aza-Michael adducts **335b,c,d,f,j,m** and **336b,c,d,f,m**.

| Entry | Styrylisoxazole | Ar | Yield % ^a (335:336 ratio) |
|-------|-----------------|--|--------------------------------------|
| 1 | 317b | <i>p</i> -Cl-C ₆ H ₄ | 81 (1:1.9) |
| 2 | 317c | <i>p</i> -F-C ₆ H ₄ | 81 (1:0.6) |
| 3 | 317d | <i>p</i> -Br-C ₆ H ₄ | 90 (1:0.5) |
| 4 | 317f | 2-pyridine | 85 ^b |
| 5 | 317j | <i>p</i> -CH ₃ -C ₆ H ₄ | 55 ^{b,c} |
| 6 | 317m | 2,4-di-Cl-C ₆ H ₃ | 90 (1:1) |

^a Total yield after chromatography.^b Only isomer **386j** was observed.^c Yield after crystallization.

The formation of compounds **336** during the chromatography purification could be explained considering the acidity of silica used for this procedure (**Scheme 14**). More basic nitrogen in compound **335** could be protonated to form intermediate **384** which undergoes an intramolecular Sn2 reaction. This reaction generates compound **336** which is recovered together **335** in variable ratio.

**Scheme 14:** plausible mechanism of formation of **336**.

4.3. Conclusions

In conclusion we have reported the synthesis of several aza-Michael adducts using indoline as Michael donor. All reactions were carried out in the presence of catalytic amount of base to furnish desired adducts in good yields without the use of chromatography purification. In the same reaction the use of phenyl hydrazine as

nucleophile affords compound **335** without the use of base catalyst. Yields of reactions were good and the formation of isomer **336** was observed when the purification was carried out using chromatography.

4.4. References

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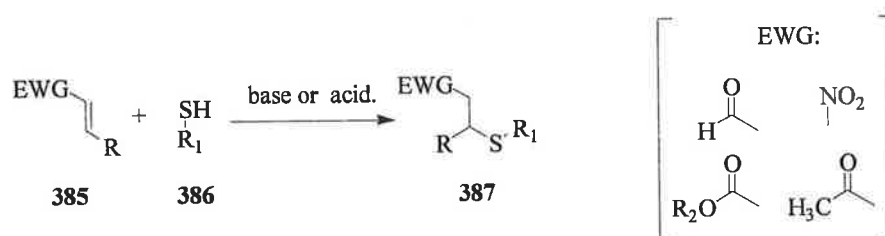
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Chapter 5: Studies on the reactivity of 3-methyl-4-nitro-5-styrylisoxazoles with *S*-nucleophiles

5.1. Introduction

The conjugate addition of thiols to electron deficient olefins, leading to the formation of C-S bonds (**Scheme 1**), is a key reaction in the synthesis of organosulfur compounds as well as in biological synthesis¹ and in the synthesis of bioactive compounds.² Organosulfur compounds have multiple applications³ thereby providing additional impetus to the study of thia-Michael reactions. Strategically, the success of the addition of mercaptans to conjugated alkenes lie in the activation of either the acceptor olefins with acids or the thiols by a base.⁴ Unfortunately, the use of either strongly acidic or basic condition typically leads to the formation of undesirable side products owing to side reaction.



Scheme 1: thia-Michael reaction.

In the recent past several synthetic organic methodologies were reported using a Lewis acid catalyst for thia Michael addition reactions. Typical Lewis acids described were zeolites,⁵ Hf(OTf)₃,⁶ alumina,⁷ InBr₃,⁸ InCl₃,⁹ Bi(NO₃)₃,¹⁰ Bi(OTf)₃,¹¹ Nafion SAC-13,¹² Cu(BF₄)₂·xH₂O,¹³ Zn(ClO₄)₂·6H₂O¹⁴ and boric acid.¹⁵

Yadav and co-workers described a simple, convenient and efficient protocol for the 1,4-conjugate additions of thiols to α,β -unsaturated ketones using ionic liquids as solvent under mild and neutral conditions.¹⁶ In this reaction the ionic liquids play a dual role of solvent and promoter reducing the reaction time and improving the yield significantly.

Cerium ammonium nitrate (CAN) was found to be an excellent catalyst in thia-Michael reaction to both cyclic and acyclic α,β -unsaturated ketones.¹⁷ This methodology was economic and could be applied to a wide variety of substrates with excellent product yields. This catalyst not only offers advantage such as high catalytic activity but also stands as an alternative to conventional methods, which involve the use of expensive, toxic and air sensitive catalyst.

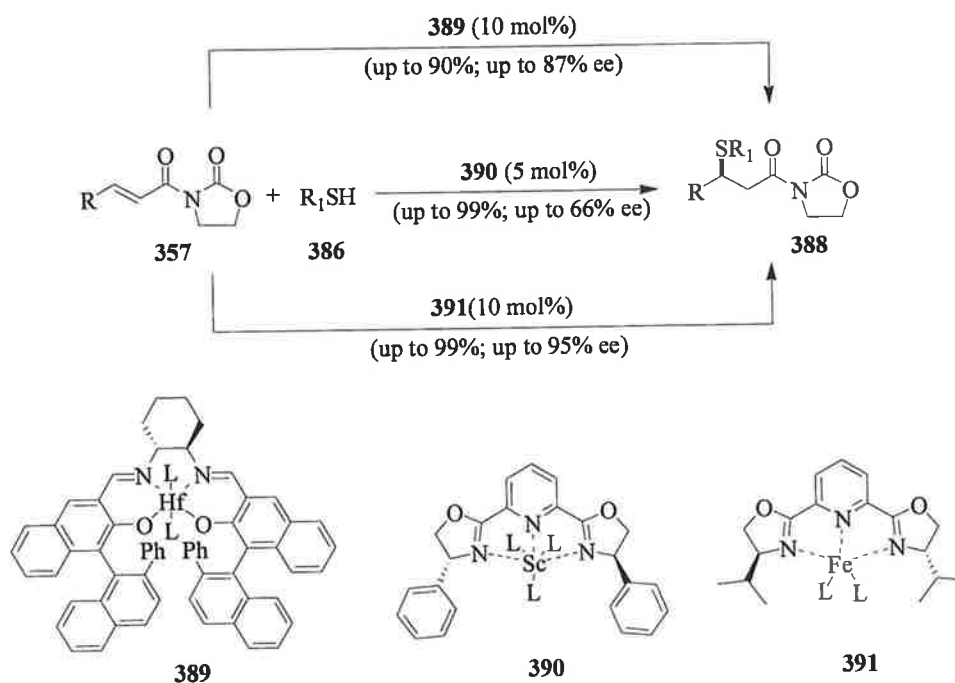
Recently, polyethylene glycol (PEG),¹⁸ $\text{HClO}_4/\text{SiO}_2$ ¹⁹ and azaphosphatrane nitrate²⁰ have been used for the thia-Michael reactions. In particular, catalytic amount of azaphosphatrane nitrate salt were used to react amines and thiols with a wide variety of Michael acceptors. This catalyst operated at room temperature and promoted the Strecker and coupling reactions.

An asymmetric version of the thia-Michael reaction would be desirable as it would give access to enantiopure β -thio ketones and esters which represent an important target in organic chemistry.²¹ The use of chiral bases to promote an asymmetric addition of thiols to Michael acceptor has been reported. For example, cinchona alkaloids,²² proline²³ and its derivatives²⁴ were widely used for this purpose.

Recently, chiral amino ethers were used to react thio derivatives with a variety of α,β -unsaturated ketones and esters in enantioselective fashion.²⁵ This methodology furnished desired Michael adducts with excellent yields and good enantioselectivity.

The use of metal catalyst in thia-Michael addition has received wide attention in the last years. Nakajima and co-workers, reported the use of chiral N,N' -dioxide cadmium iodide complex in the addition of thiols to cyclic enones and enals.²⁶ They can be employed as acceptors, utilizing 1 mol % catalyst loading, to afford the sulfides in high yields and good enantioselectivity. Other different Lewis acids in combination with chiral ligands were studied as catalysts in 1,4-addition to unsaturated 2-oxazolidinones

357 to form the corresponding thio derivatives **388** (Scheme 2). Hf-SALEN **389**,²⁷ Sc-PYBOX **390**²⁸ and Fe-PYBOX **391**²⁹ complex given the best results.



Scheme 2: enantioselective thia-Michael reaction.

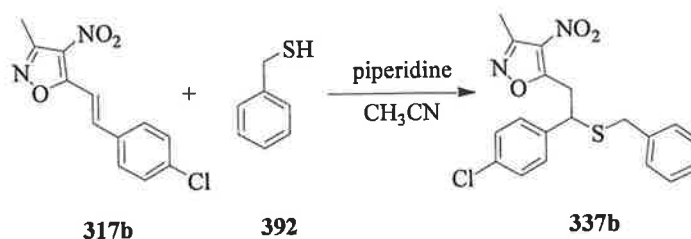
These complexes showed a high ability to catalyze thia-Michael reactions of thiols to α,β -unsaturated amide **357** with 5-10 mol % loading and the reactions afforded thia-adducts in good yields and high enantioselectivity. The Fe-PYBOX complex **391** gave better results in term of both yield and enantioselectivity (up to 99% yield, up to 95 % ee).

5.2. Results and discussion

In the recent past our group reported the addition of enolates to styrylisoxazole and in *Chapter 4* of this thesis we have discussed the addition of aza nucleophiles to

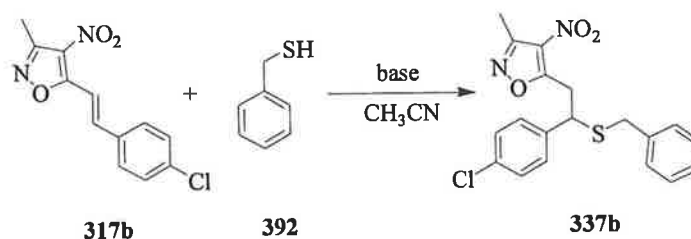
317. Considering the reactivity of **317** as a Michael acceptor, we became interested in studying the behaviour of **317** towards sulfur nucleophiles.

In a test experiment styrylisoxazole **317b** was reacted with small excess of thiol **392** and a catalytic amount of base. We were delighted to observe that under these conditions a full conversion of **317b** was achieved in 4 hours and that the desired compound **337b** was formed in high yield (**Scheme 3**).



Scheme 3: thia-Michael reaction on styrylisoxazole.

Encouraged by the result obtained, we have embarked in an optimization study (**Scheme 4**). As a first step, we have screened several bases (**Table 1**). All reactions in table 1 were carried out using 2 equiv. of mercaptan **392** and 0.3 equiv. of base and CH₃CN was used as the solvent. This study established that secondary and tertiary amines were efficient catalysts and that L-proline was particularly efficient. Typically 0.3 equiv. of L-proline were necessary to convert **317b** in **337b** in 20 min (**Table 1**, entry 8). Even using 10 mol % catalyst loading, the reaction furnished the desired adduct in high yield (**Table 1**, entry 9).



Scheme 4: screening base in thia-Michael reaction.

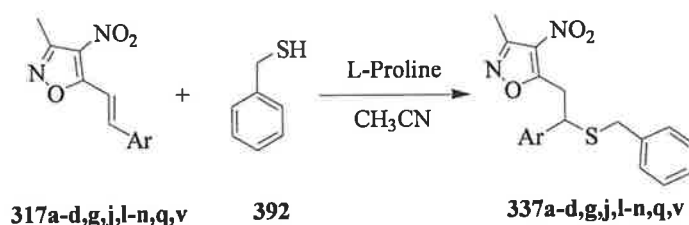
Table 1: screening base in thia-Michael reaction.

| Entry | Base | Time (h) | Yield % ^a |
|----------------|-------------------|----------|----------------------|
| 1 | - | 24 | - |
| 2 | Piperidine | 2 | 76 |
| 3 | Pyrrolidine | 4 | 71 |
| 4 | Et ₃ N | 0.5 | 80 |
| 5 | DBU | 24 | 55 |
| 6 | DMAP | 1.5 | 78 |
| 7 | Pyridine | 24 | 50 |
| 8 | L-proline | 0.3 | 84 |
| 9 ^b | L-proline | 24 | 78 |

^a Isolated yield after crystallization.^b 0.1eq. of base.

Having established that L-proline was the best base for this reaction, we have studied the effect of solvent. This study determined that MeOH and EtOH were not good solvents which was mainly due to a poor solubility of **317b**. DCM and toluene were good solvents but the reaction in these media was significantly slower.

Having determined an appropriate set of reaction conditions, we carried out the synthesis of a small family of thia-Michael adducts **337** (**Scheme 5**). Styryl isoxazoles **317a-d,g,j,l-n,q,v** were reacted with 2 equiv. of benzyl mercaptan **392** and 0.3 equiv. of L-proline in CH₃CN to afford desired adducts in good to excellent isolated yields. Compounds **337a-d,g,j,l-n,q,v** were obtained pure by crystallization from MeOH without the intervention of chromatography. Only in case of Ar = 3,5-di-Cl-C₆H₃ and Ph, it was necessary to involve chromatography for their purification (**Table 2**, entries 1, 11).



Scheme 5: thia-Michael reaction on styrylisoxazole.

Table 2: synthesis of thia-Michael adducts **337a-d,g,j,l-n,q,v**.

| Entry | Compound | Ar | Time (h) | Yield % ^a |
|-------|-------------|---|----------|----------------------|
| 1 | 337a | C ₆ H ₅ | 1 | 85 ^{b,c} |
| 2 | 337b | <i>p</i> -Cl-C ₆ H ₄ | 0.3 | 84 |
| 3 | 337c | <i>p</i> -F-C ₆ H ₄ | 0.3 | 83 |
| 4 | 337d | <i>p</i> -Br-C ₆ H ₄ | 2 | 84 |
| 5 | 337g | <i>p</i> -CH ₃ O-C ₆ H ₄ | 2.5 | 80 |
| 6 | 337j | <i>p</i> -CH ₃ -C ₆ H ₄ | 48 | 78 |
| 7 | 337l | <i>p</i> -NO ₂ -C ₆ H ₄ | 4 | 88 |
| 8 | 337m | 2,4-di-Cl-C ₆ H ₃ | 1.5 | 86 |
| 9 | 337n | <i>p</i> -CN-C ₆ H ₄ | 0.3 | 81 |
| 10 | 337q | 2,3-di-Cl-C ₆ H ₃ | 2 | 81 |
| 11 | 337v | 3,5-di-Cl-C ₆ H ₃ | 1 | 78 ^b |

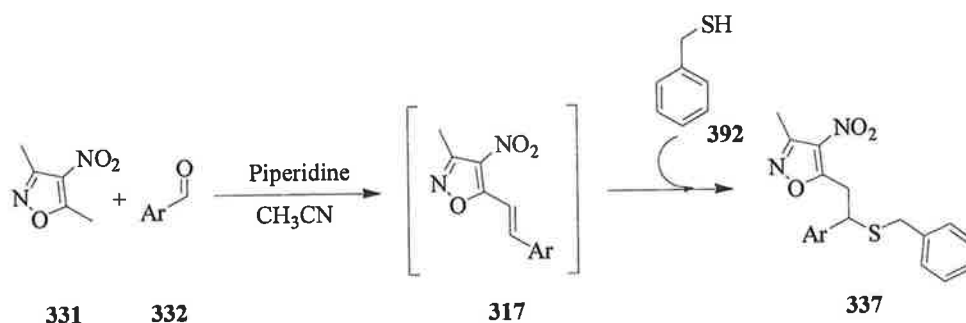
^a Isolated yield after crystallization.

^b Isolated yield after chromatography.

^c 1.2 equivalent of benzyl mercaptan **392**.

In case of Ar = Ph the reaction was particularly efficient and proceeded to completion in 1 h with just 1.2 equiv. of **392**.

Having determined a basic catalysis for the conversion of **317** to **337** and considering that the generation of **317** requires similar basic conditions, we decided to investigate the possibility of preparing **337** directly from **331**, an aldehyde and **392** (**Scheme 6**). We obtained the best result using piperidine as catalyst and CH₃CN as the solvent. The results obtained are summarised in **Table 3**.



Scheme 6: one-pot thia-Michael reaction.

Table 3: one-pot synthesis of compounds **337**.

| Enty | Compound | Ar | Yield % ^a |
|------|-------------|---|----------------------|
| 1 | 337a | C ₆ H ₅ | 70 ^b |
| 2 | 337b | <i>p</i> -Cl-C ₆ H ₄ | 65 |
| 3 | 337c | <i>p</i> -F-C ₆ H ₄ | 63 |
| 4 | 337d | <i>p</i> -Br-C ₆ H ₄ | 81 |
| 5 | 337g | <i>p</i> -CH ₃ O-C ₆ H ₄ | 64 |
| 6 | 337j | <i>p</i> -CH ₃ -C ₆ H ₄ | 69 |
| 7 | 337l | <i>p</i> -NO ₂ -C ₆ H ₄ | 80 |
| 8 | 337m | 2,4-di-Cl-C ₆ H ₃ | 68 |
| 9 | 337n | <i>p</i> -CN-C ₆ H ₄ | 63 |
| 10 | 337q | 2,3-di-Cl-C ₆ H ₃ | 65 |
| 11 | 337v | 3,5-di-Cl-C ₆ H ₃ | 68 ^b |

^a Isolated yield after crystallization.^b Isolated yield after chromatography.

Isoxazole **331** and 1 equiv. of aromatic aldehyde **332** were reacted in refluxing CH₃CN in the presence of 0.1 equiv. of piperidine for 4 h. Then a further 0.2 equiv. of piperidine was added at room temperature followed by 1.2 equiv. of **392** and the reaction protracted until compound **317** was finished (20 min – 5 h).

As for the synthesis of **337** from styrylisoxazole **317**, products **337b-d,g,j,l-n,q**, synthesized in a one-pot reaction were isolated by a simple crystallization method from MeOH and the use of chromatography for purification was involved only for compounds **337a,v**.

Having established a protocol for the addition of thiols to alkenes which is catalysed by an amine, we decided to investigate the effect of chiral amines on the reaction outcome. Therefore, L-proline, (-)-ephedrine **393**, (+)-2-pyrrolidinemethanol **394**, *trans*-4-hydroxy-L-proline **395**, hydroquinine **396** and thiourea derivate **397** were employed to catalyse the conversion of **317b** to **337b** (Figure 1 and Scheme 7). Then **337b** were isolated and analysed by chiral HPLC.

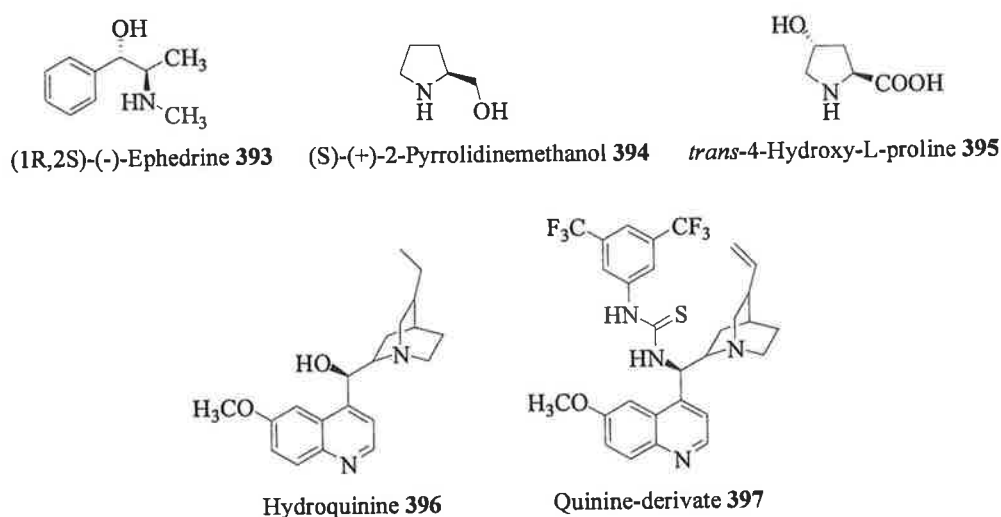
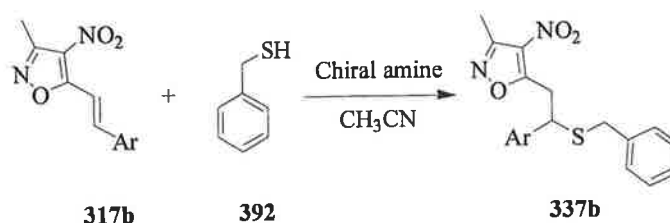


Figure 1: chiral amines, amino alcohols and amino acid tested in thia-Michael reactions.

In all cases, reactions afforded the corresponding adducts in excellent yields and very short reaction time (Table 3). We have explained this by the higher capacity of aminoalcohols in creating a basic environment compared to tertiary amines. The stronger basic media then favoured the deprotonation of the thiol. Unfortunately, e.e. was not observed for these experiments. We have also tried to reduce the temperature (-78 °C) but unfortunately no e.e. was observed.



Scheme 7: enantioselective one-pot thia-Michael reaction.

Table 3: synthesis of thia-Michael adducts using chiral amines.

| Entry | Amines | Time (h) | Yield % ^a | ee % ^b |
|----------------|--------|----------|----------------------|-------------------|
| 1 | 393 | 0.2 | 80 | 0 |
| 2 ^c | 393 | 2 | 80 | 0 |
| 3 | 394 | 0.3 | 87 | 0 |
| 4 | 395 | 0.2 | 84 | 0 |
| 5 | 397 | 0.2 | 84 | 0 |
| 6 ^c | 397 | 4 | 83 | 0 |
| 7 | 396 | 24 | - | - |

^a Isolated yield after crystallization.

^b e.e. was determinate by chiral HPLC using OD column and eptane/IPA 95/5 as solvent.

^c The reaction was carried out at -78 °C.

5.3. Conclusions

In conclusion we reported a one-pot procedure to prepare thia-Micheal adducts **337** in good to excellent yields. The compounds were prepared from inexpensive starting materials and under mild conditions. This synthesis is modular and benefits from a simple method of purification, which does not require chromatography.

5.4. References

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General Experimental Details

Melting points were determined using a Stuart scientific melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded as KBr discs using a Bruker Tensor27 FT-IR instrument. Absorption maximum (ν_{\max}) was reported in wave numbers (cm^{-1}) and only selected peaks are reported. NMR experiments were performed on a Bruker Avance 400 instrument and samples were prepared in CDCl_3 (referenced to 7.26 ppm for ^1H and 77.16 for ^{13}C) and in $\text{DMSO}-d_6$ (referenced to 2.52 and 3.3 ppm for ^1H and 40.0 for ^{13}C). Coupling constants (J) are in Hertz (Hz) and corrected to the nearest 0.5Hz. Multiplicities are reported as follows: s, singlet, d, doublet, dd, doublets of doublets, t, triplet, q, quartet, m, multiplet, c, complex, and br, broad. ^1H NMR spectral assignments are supported by ^1H - ^1H COSY and ^{13}C - ^1H COSY where necessary. Carbon spectra are supported by DEPT analysis where necessary. High resolution mass spectra were obtained on a Waters Micro mass LCT and low resolution mass spectra were recorded on Waters Micro mass Quattro LCMS spectrometers at 70 eV.

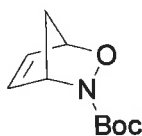
Tetrahydrofuran was freshly distilled over sodium benzophenone prior to use according to standard procedure. All other reagents and solvents were used as purchased from Aldrich. Reactions were checked for completion by TLC (EM Science, silica gel 60 F₂₅₄) which were visualized by quenching of u.v. fluorescence ($\lambda_{\max} = 254 \text{ nm}$) or by staining with either 10% w/v ammonium molybdate in 2M sulphuric acid or basic potassium permanganate solution (followed by heat) as appropriate. Retention factors (R_f) are reported to ± 0.05 . Flash chromatography was performed using *silica gel 60* (0.040-0.063 mm, 230-400 mesh).

Experimental details Chapter 2

General procedure for the preparation of cycloadducts 30a, 36c, 294-297.

To a solution of BocNHOH (200 mg, 1.5 mmol, 1.0 eq.) in appropriate solvent (2.5 mL) were added a metal salt (0.05 eq.) and an opportune amine (0.15 eq.). A diene (1.0 eq.) was added to the resulting solution, and the reaction mixture was stirred for 10 min before H₂O₂ (30%) (0.84 mL, 7.0 eq.) was added dropwise. The reaction was quenched by the addition of water (5 mL) when the starting material disappeared. The crude product was extracted with DCM (2 x 20 mL), the organic layer was dried over anhydrous Na₂SO₄, and the solvent was removed in vacuo. The crude material was purified by flash chromatography on silica gel using PE/EA (3:1).

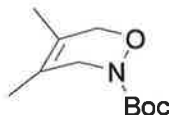
2-Oxa-3-aza-bicyclo[2.2.1]hept-5-ene-3-carboxylic acid *tert*-butyl ester 30a:



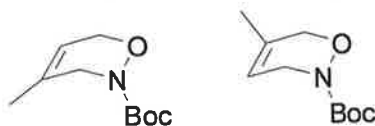
pale yellow oil (78%); R_f = 0.6 (PE/EA v/v 3:1); ¹H-NMR δ : (400 MHz, CDCl₃): 6.13-6.07 (m, 2H), 4.88 (s, 1H), 4.67 (s, 1H), 1.67-1.63 (m, 1H), 1.41 (d, J = 8, 1H), 1.16 (s, 9H); ¹³C-NMR δ : (100MHz, CDCl₃): 157.8, 133.3, 132.1, 82.7, 81.0, 64.3, 47.3, 27.4.

2-Oxa-3-aza-bicyclo[2.2.2]oct-5-ene-3-carboxylic acid *tert*-butyl ester 36c:

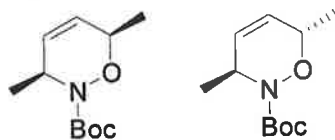
pale yellow oil (95%); $R_f = 0.6$ (PE/EA v/v 3:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 6.50-6.48 (m, 2H), 4.69 (s, 2H), 2.18-2.02 (m, 2H), 1.42 (s, 9H), 1.35-1.27 (m, 2H); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 157.3, 131.2, 131.1, 81.1, 70.2, 49.7, 27.7, 23.1, 20.1.

4,5-Dimethyl-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester 294:

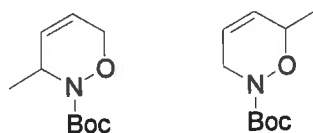
pale yellow oil (76%); $R_f = 0.4$ (PE/EA v/v 3:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 4.19 (s, 2H), 3.88 (s, 2H), 1.65 (s, 3H), 1.58 (s, 3H), 1.49 (s, 9H); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 154.5, 122.6, 121.4, 80.9, 70.7, 48.0, 27.8, 14.8, 13.3.

5-Methyl-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester; 4-methyl-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester 295a,b:

pale yellow oil (70%); $R_f = 0.4$ (PE/EA v/v 3:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 5.48 (m, 1H, isomer A), 4.60-4.59 (m, 1H, isomer B), 4.33 (m, 2H, isomer A), 4.23 (m, 2H, isomer B), 4.00 (m, 2H, isomer A), 3.91 (m, 2H, isomer B), 1.70 (s, 3H, isomer B), 1.63 (s, 3H, isomer A), 1.49-1.46 (m, 18H, isomer A and B); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 154.4, 154.3, 130.9, 129.6, 117.5, 115.9, 80.8, 70.4, 67.3, 53.0, 48.0, 44.2, 27.6, 19.1, 17.6.

3,6-Dimethyl-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester 296a,b:

pale yellow oil (70%); $R_f = 0.4$ (PE/EA v/v 3:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 5.78-5.74 (m, 1.5H), 5.66 (d, $J = 10$, 1H), 4.63 (br, 1H), 4.46-4.39 (m, 1.5H), 1.49 (s, 9H), 1.33 (d, $J = 7$, 1H), 1.29 (d, $J = 7$, 3.3H), 1.25 (d, $J = 7$, 3.3H); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 153.8, 128.3, 127.9, 127.4, 126.6, 80.5, 80.3, 74.3, 72.8, 49.5, 49.3, 27.8, 18.2, 18.0, 17.5, 16.7.

6-Methyl-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester; 3-methyl-3,6-dihydro-[1,2]oxazine-2-carboxylic acid *tert*-butyl ester 297a,b:

pale yellow oil (65%); $R_f = 0.4$ (PE/EA v/v 3:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 5.71-5.64 (m, 4H), 4.55-4.46 (m, 2H), 4.34-4.32 (m, 1H), 4.11-4.02 (m, 2H), 3.86-3.81 (m, 1H), 1.42-1.39 (m, 18H), 1.21 (d, $J = 6$, 3H), 1.17 (d, $J = 7$, 3H); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 155.3, 154.3, 153.9, 152.9, 128.9, 127.6, 122.9, 121.6, 84.3, 82.0, 80.7, 73.1, 67.8, 50.0, 44.0, 27.8, 27.7, 27.5, 27.0, 18.1, 17.1.

Experimental details Chapter 3

General procedure for the preparation of dibromide compounds 344.

A mixture of styrylisoxazole **317** (1 g, 1.0 eq.) in cyclohexane (40 mL) was heated to reflux with heatgun. Bromine (1.0 eq.) was added dropwise and the mixture was slowly cooled down to room temperature and stirred for 15 min. The solution was quenched with 10% aqueous Na₂S₂O₃ solution (40 mL) and extracted with DCM (2 x 50 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The crude product thus obtained was used in the next reaction without further purification.

General procedure for the preparation of dibromide 344l.

A sealed tube was filled with a mixture of styrylisoxazole **317l** (200 mg, 0.726 mmol, 1.0 eq.) in cyclohexane (10 mL). Bromine (27.0 eq., 19.51 mmol, 1 mL) was added and the mixture was heated to 80 °C for 12h. The solution was quenched with 10% aqueous Na₂S₂O₃ solution (10 mL) and extracted with DCM (2 x 15 mL). The combined organic extracts were dried over anhydrous Na₂SO₄, filtered and the solvent was removed under vacuum. The crude product thus obtained was used in the next reaction without further purification.

General procedure for the preparation of aziridines 333.

To a solution of dibromide **344** (200 mg, 1.0 eq.) in dry CH₃CN (6 mL) at 0 °C was added benzylamine (1.0 eq.) followed immediately by Cs₂CO₃ (3.5 eq.). The solution was slowly warmed to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (10 mL) and extracted with DCM (2 x 15 mL). The combined organic extracts were dried over anhydrous

Na₂SO₄, filtered and the solvent was removed under vacuum. The crude product was purified by silica-gel chromatography with appropriate eluent to afford the *cis*-aziridine **333a-f**.

5-(1,2-Dibromo-2-phenyl-ethyl)-3-methyl-4-nitro-isoxazole 344a:



white solid (98%); m.p.: 167-170 °C; ¹H-NMR δ: (400 MHz, CDCl₃): 7.52 (2H, dd, *J* = 8.0, *J* = 1.6), 7.48-7.42 (3H, m), 6.33 (1H, d, *J* = 12.0), 5.60 (1H, d, *J* = 12.0), 2.65 (3H, s); ¹³C-NMR δ: (100MHz, CDCl₃): 169.0, 156.2, 137.4, 130.0, 129.3, 128.2, 50.0, 39.8, 11.9; IR: ν_{max} (KBr)/cm⁻¹: 3015, 2925, 1613, 1523, 1374, 1140, 822, 688; HRMS: Calcd. for C₁₂H₁₀Br₂N₂O₃ ([M]⁺): 387.9058, found: 387.9068.

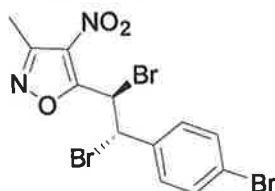
5-[1,2-Dibromo-2-(4-chloro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 344b:



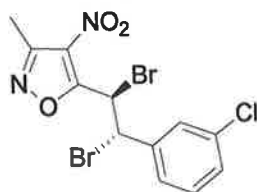
white solid (98%); m.p.: 170-173 °C; ¹H-NMR δ: (400 MHz, CDCl₃): 7.46 (2H, d, *J* = 8.4), 7.43 (2H, d, *J* = 8.4), 6.27 (1H, d, *J* = 12.0), 5.57 (1H, d, *J* = 11.6), 2.65 (3H, s); ¹³C-NMR δ: (100MHz, CDCl₃): 168.6, 156.3, 136.0, 135.9, 129.6, 129.5, 49.0, 39.6, 11.9; IR: ν_{max} (KBr)/cm⁻¹: 3020, 2881, 1613, 1523, 1374, 1140, 827, 593; HRMS: Calcd. for C₁₂H₉Br₂ClN₂O₃ ([M]⁺): 421.8668, found: 421.8665.

5-[1,2-Dibromo-2-(4-fluoro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 344c:

white solid (98%); m.p.: 160-163 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.53-7.50 (2H, m), 7.17-7.13 (2H, m), 6.27 (1H, d, $J = 12.0$), 5.59 (1H, d, $J = 12.0$), 2.65 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 168.7, 162.1, 156.3, 133.5, 133.4, 130.2, 130.0, 116.5, 116.3, 49.2, 40.0, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3075, 3011, 1603, 1528, 1379, 1230, 827; HRMS: Calcd. for $\text{C}_{12}\text{H}_9\text{Br}_2\text{FN}_2\text{O}_3$ ($[\text{M}]^+$): 405.8964, found: 405.8954.

5-[1,2-Dibromo-2-(4-bromo-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 344d:

white solid (98%); m.p.: 170-173 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.59 (2H, d, $J = 8.8$), 7.40 (2H, d, $J = 8.4$), 6.26 (1H, d, $J = 12.0$), 5.55 (1H, d, $J = 12.0$), 2.65 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 168.6, 156.3, 136.5, 132.6, 129.8, 124.1, 49.0, 39.5, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3095, 3021, 1613, 1523, 1379, 1140, 827, 589; HRMS: Calcd. for $\text{C}_{12}\text{H}_9\text{Br}_3\text{N}_2\text{O}_3$ ($[\text{M}]^+$): 465.8163, found: 465.8170.

5-[1,2-Dibromo-2-(3-chloro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 344e:

white solid (98%); m.p.: 164-167 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.52-7.51 (1H, m), 7.42-7.39 (3H, m), 6.26 (1H, d, $J = 12.0$), 5.53 (1H, d, $J = 12.0$), 2.65 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 168.6, 156.3, 139.3, 135.1, 130.6, 130.2, 128.4,

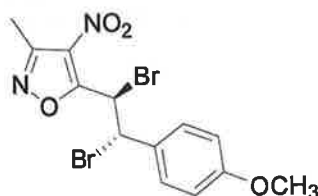
126.4, 48.7, 39.5, 11.9; IR: ν_{\max} (KBr)/ cm^{-1} : 3021, 2877, 1608, 1528, 1374, 1140, 827, 693; HRMS: Calcd. for $\text{C}_{12}\text{H}_9\text{Br}_2\text{ClN}_2\text{O}_3$ ($[\text{M}]^+$): 421.8668, found: 421.8677.

2-[1,2-Dibromo-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-pyridine 344f:

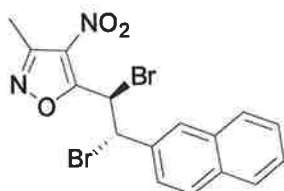


white solid (98%); m.p.: 133-136 °C; ^1H -NMR δ : (400 MHz, CDCl_3): 8.74-8.73 (1H, m), 7.79-7.75 (1H, m), 7.42 (1H, dd, $J = 7.6$, $J = 0.8$), 7.36-7.32 (1H, m), 6.76 (1H, d, $J = 11.2$), 5.70 (1H, d, $J = 11.6$), 2.64 (3H, s); ^{13}C -NMR δ : (100MHz, CDCl_3): 168.9, 156.3, 155.2, 150.7, 137.4, 125.1, 125.0, 124.4, 123.7, 49.1, 37.7, 12.0, 11.9; IR: ν_{\max} (KBr)/ cm^{-1} : 3018, 1961, 1603, 1519, 1369, 1140, 832; HRMS: Calcd. for $\text{C}_{11}\text{H}_9\text{Br}_2\text{N}_3\text{O}_3$ ($[\text{M}]^+$): 388.9011, found: 388.9014.

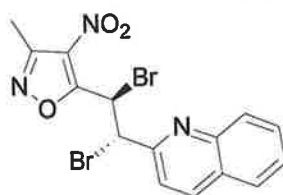
5-[1,2-Dibromo-2-(4-methoxy-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 344g:



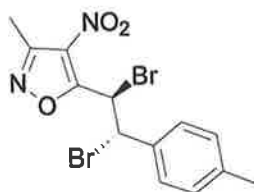
white solid (98%); m.p.: 130-133 °C; ^1H -NMR δ : (400 MHz, CDCl_3): 7.47-7.43 (2H, m), 6.98-6.96 (2H, m), 6.31 (1H, d, $J = 12.0$), 5.61 (1H, d, $J = 12.0$), 3.85 (3H, s), 2.65 (3H, s); ^{13}C -NMR δ : (100MHz, CDCl_3): 169.1, 160.7, 156.2, 129.5, 129.4, 114.6, 55.6, 50.4, 40.2, 11.89; IR: ν_{\max} (KBr)/ cm^{-1} : 3011, 2941, 2847, 1608, 1533, 1265, 827, 593; HRMS: Calcd. for $\text{C}_{13}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_4$ ($[\text{M}]^+$): 417.9164, found: 417.9170.

5-(1,2-Dibromo-2-naphthalen-2-yl-ethyl)-3-methyl-4-nitro-isoxazole 344h:

yellow solid (98%); m.p.: 175-176 °C (dec.); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.99-7.96 (2H, m), 7.92-7.88 (2H, m), 7.64-7.62 (1H, m), 7.61-7.55 (2H, m), 6.46 (1H, d, $J = 12.0$), 5.79 (1H, d, $J = 12.0$), 2.67 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 169.0, 156.3, 134.4, 133.9, 133.0, 129.7, 128.5, 128.4, 128.0, 127.5, 127.2, 124.2, 50.6, 39.7, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3011, 2926, 1608, 1528, 1374, 1135, 822, 752; HRMS: Calcd. for $\text{C}_{16}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_3$ ($[\text{M}]^+$): 437.9215, found: 437.9209.

2-[1,2-Dibromo-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-quinoline 344i:

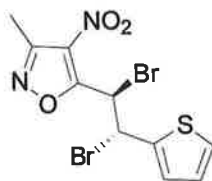
white solid (77%); m.p.: 164-167 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.29-8.24 (1H, m), 8.21-8.18 (1H, m), 7.85-7.83 (1H, m), 7.79-7.77 (1H, m), 7.64-7.60 (1H, m), 7.54 (1H, d, $J = 8.4$), 6.95 (1H, d, $J = 11.6$), 5.91 (1H, d, $J = 11.6$), 2.67 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 169.1, 156.3, 155.1, 148.0, 137.9, 130.5, 129.9, 127.8, 127.7, 120.6, 49.3, 37.3, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3084, 2922, 1689, 1520, 1365, 830; HRMS: Calcd. for $\text{C}_{15}\text{H}_{11}\text{Br}_2\text{N}_3\text{O}_3$ ($[\text{M}]^+$): 438.9167, found: 438.9199.

5-(1,2-Dibromo-2-p-tolyl-ethyl)-3-methyl-4-nitro-isoxazole 344j:

white solid (98%); m.p.: 116-119 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.41 (2H, d, $J = 8.4$), 7.27-7.25 (2H, m), 6.33 (1H, d, $J = 11.6$), 5.59 (1H, d, $J = 12.0$), 2.65 (3H, s);

s), 2.40 (3H, s); ^{13}C -NMR δ : (100MHz, CDCl_3): 169.0, 156.2, 140.2, 134.4, 130.0, 129.9, 128.6, 128.0, 50.2, 39.9, 21.5, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3021, 2932, 1609, 1521, 1389, 1156, 829; HRMS: Calcd. for $\text{C}_{13}\text{H}_{12}\text{Br}_2\text{N}_2\text{O}_3$ ($[\text{M}]^+$): 401.9215, found: 401.9203.

5-(1,2-Dibromo-2-thiophen-2-yl-ethyl)-3-methyl-4-nitro-isoxazole 344k:

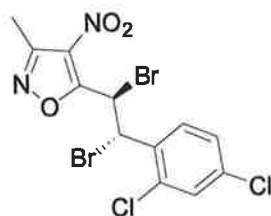


yellow solid (98%); m.p.: 137-140 °C; ^1H -NMR δ : (400 MHz, CDCl_3): 7.47 (1H, d, $J = 4.8$), 7.27-7.25 (2H, m), 7.32-7.31 (1H, m), 7.04-7.02 (1H, m), 6.27 (1H, d, $J = 11.6$), 5.95 (1H, d, $J = 11.6$), 2.64 (3H, s); ^{13}C -NMR δ : (100MHz, CDCl_3): 168.6, 156.3, 140.9, 128.9, 128.1, 127.3, 44.8, 41.1, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3100, 2995, 1613, 1523, 1379, 1135, 827, 713; HRMS: Calcd. for $\text{C}_{10}\text{H}_8\text{Br}_2\text{N}_2\text{O}_3\text{S}$ ($[\text{M}]^+$): 393.8622, found: 393.8618.

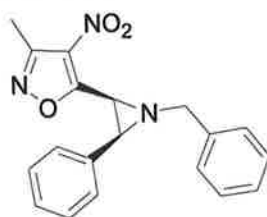
5-[1,2-Dibromo-2-(4-nitro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 344l:



brown solid (98%); m.p.: 184-186 °C; ^1H -NMR δ : (400 MHz, CDCl_3): 8.32 (2H, d, $J = 6.4$), 7.71 (2H, d, $J = 6.8$), 6.30 (1H, d, $J = 12.0$), 5.66 (1H, d, $J = 12.0$), 2.66 (3H, s); ^{13}C -NMR δ : (100MHz, CDCl_3): 168.0, 156.4, 148.6, 144.2, 129.3, 124.6, 47.6, 39.0, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3084, 2916, 1619, 1519, 1346, 1146, 831, 694, 589; HRMS: Calcd. for $\text{C}_{12}\text{H}_9\text{Br}_2\text{N}_3\text{O}_5$ ($[\text{M}]^+$): 432.8909, found: 432.8916.

5-[1,2-Dibromo-2-(2,4-dichloro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 344m:

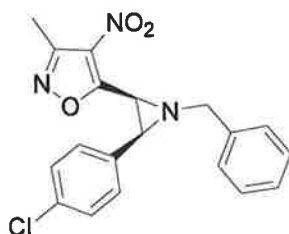
white solid (98%); m.p.: 141-144 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.58 (1H, br), 7.48 (1H, d, $J = 2.0$), 7.41 (1H, d, $J = 8.0$), 6.31 (1H, br), 6.19 (1H, br), 2.66 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 168.3, 156.3, 136.3, 134.8, 130.2, 129.5, 128.6, 43.8, 38.6, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3015, 2920, 1608, 1523, 1369, 1135, 827, 598; HRMS: Calcd. for $\text{C}_{12}\text{H}_8\text{Br}_2\text{Cl}_2\text{N}_2\text{O}_3$ ($[\text{M}]^+$): 455.8279, found: 455.8276.

Cis-5-(1-Benzyl-3-phenyl-aziridin-2-yl)-3-methyl-4-nitro-isoxazole 333a:

yellow oil (30%); R_f : 0.2 (PE/EA v/v 15:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.47 (2H, d, $J = 7.2$), 7.37-7.19 (8H, m), 3.99 (1H, d, $J = 13.6$), 3.92 (1H, d, $J = 14.0$), 3.68 (1H, d, $J = 6.4$), 3.49 (1H, d, $J = 6.4$), 2.39 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 170.3, 155.4, 137.4, 134.2, 128.7, 128.4, 128.1, 128.0, 127.9, 127.4, 63.9, 50.5, 42.8, 11.5; IR: ν_{max} (KBr)/ cm^{-1} : 3056, 2932, 2851, 1599, 1402, 1379, 832; HRMS: Calcd. for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_3$ ($[\text{M}]^+$): 335.1270, found: 335.1265.

Cis-5-[1-Benzyl-3-(4-chloro-phenyl)-aziridin-2-yl]-3-methyl-4-nitro-isoxazole

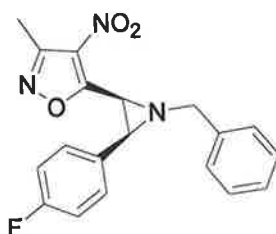
333b:



yellow oil (50%); R_f : 0.2 (PE/EA v/v 15:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.46 (2H, d, $J = 7.2$), 7.37-7.34 (2H, m), 7.31-7.27 (3H, m), 7.20-7.18 (2H, m), 3.97 (1H, d, $J = 14.0$), 3.93 (1H, d, $J = 14.0$), 3.69 (1H, d, $J = 6.4$), 3.44 (1H, d, $J = 6.4$), 2.42 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 169.9, 155.5, 137.2, 133.9, 132.8, 128.8, 128.7, 128.6, 128.1, 127.8, 63.8, 49.6, 42.9, 11.5; IR: ν_{max} (KBr)/ cm^{-1} : 3055, 2920, 2851, 1593, 1454, 1379, 1086, 822; HRMS: Calcd. for $\text{C}_{19}\text{H}_{16}\text{ClN}_3\text{O}_3$ ($[\text{M}]^+$): 369.0880, found: 369.0884.

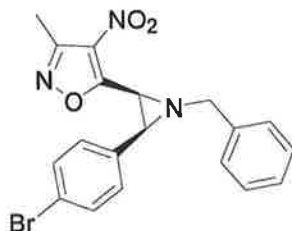
Cis-5-[1-Benzyl-3-(4-fluoro-phenyl)-aziridin-2-yl]-3-methyl-4-nitro-isoxazole

333c:



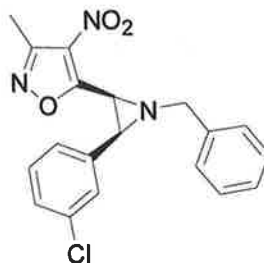
yellow oil (40%); R_f : 0.1 (PE/EA v/v 20:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.46 (2H, d, $J = 7.6$), 7.38-7.29 (5H, m), 6.93-6.89 (2H, m), 3.97 (1H, d, $J = 13.6$), 3.92 (1H, d, $J = 13.6$), 3.67 (1H, d, $J = 6.4$), 3.46 (1H, d, $J = 6.4$), 2.41 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 170.1, 155.5, 137.3, 129.1, 129.0, 128.8, 128.1, 127.8, 63.9, 49.7, 42.8, 11.5; IR: ν_{max} (KBr)/ cm^{-1} : 3060, 2920, 2851, 1603, 1508, 1379, 1225, 827, 693; HRMS: Calcd. for $\text{C}_{19}\text{H}_{16}\text{FN}_3\text{O}_3$ ($[\text{M}]^+$): 353.1176, found: 353.1170.

***Cis*-5-[1-Benzyl-3-(4-bromo-phenyl)-aziridin-2-yl]-3-methyl-4-nitro-isoxazole**
333d:

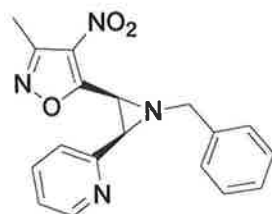


yellow oil (46%); R_f : 0.2 (PE/EA v/v 15:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.46 (2H, d, $J = 7.2$), 7.37-7.34 (4H, m), 7.31-7.29 (1H, m), 7.22 (2H, d, $J = 8.4$), 3.95 (2H, at, $J = 14.4$), 3.69 (1H, d, $J = 6.4$), 3.43 (1H, d, $J = 6.4$), 2.42 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 169.8, 155.5, 137.2, 133.3, 131.5, 129.1, 128.7, 128.0, 127.8, 122.1, 63.8, 49.7, 42.8, 11.5; IR: ν_{max} (KBr)/ cm^{-1} : 3060, 2916, 2851, 1528, 1459, 1374, 1011, 827, 693; HRMS: Calcd. for $\text{C}_{19}\text{H}_{16}\text{BrN}_3\text{O}_3$ ($[\text{M}]^+$): 413.0375, found: 413.0376.

***Cis*-5-[1-Benzyl-3-(3-chloro-phenyl)-aziridin-2-yl]-3-methyl-4-nitro-isoxazole**
333e:



yellow oil (36%); R_f : 0.1 (PE/EA v/v 20:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.46 (2H, d, $J = 7.2$), 7.38-7.31 (3H, m), 7.30 (1H, d, $J = 7.2$), 7.25-7.17 (2H, m), 7.16-7.15 (1H, m), 3.99 (1H, d, $J = 14.0$), 3.90 (1H, d, $J = 13.6$), 3.70 (1H, d, $J = 6.4$), 3.44 (1H, d, $J = 6.0$), 2.42 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 169.8, 155.6, 137.1, 136.4, 134.3, 129.7, 128.8, 128.6, 128.4, 128.2, 127.8, 125.6, 63.8, 49.6, 42.8, 11.6; IR: ν_{max} (KBr)/ cm^{-1} : 3065, 2925, 2851, 1459, 1379, 718; HRMS: Calcd. for $\text{C}_{19}\text{H}_{16}\text{ClN}_3\text{O}_3$ ($[\text{M}]^+$): 369.0880, found: 369.0876.

***Cis*-2-[1-Benzyl-3-(3-methyl-4-nitro-isoxazol-5-yl)-aziridin-2-yl]-pyridine 333f:**

yellow oil (41%); R_f : 0.1 (PE/EA v/v 5:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.42-8.41 (1H, m), 7.59 (1H, td, $J = 8.0$, $J = 1.6$), 7.50-7.45 (3H, m), 7.38-7.33 (2H, m), 7.30-7.26 (1H, m), 7.14-7.11 (1H, m), 4.01 (1H, d, $J = 13.2$), 3.95 (1H, d, $J = 13.6$), 3.86 (1H, d, $J = 6.4$), 3.64 (1H, d, $J = 6.4$), 2.42 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 169.9, 155.6, 154.5, 149.3, 137.1, 136.6, 128.8, 128.3, 127.8, 123.0, 122.3, 63.9, 51.6, 41.9, 11.6; IR: ν_{max} (KBr)/ cm^{-1} : 3060, 2916, 2851, 1603, 1508, 1379, 1150, 698; HRMS: Calcd. for $\text{C}_{18}\text{H}_{16}\text{N}_4\text{O}_3$ ($[\text{M}]^+$): 336.1222, found: 336.1229.

Experimental details Chapter 4

General procedure for the preparation of compounds 334.

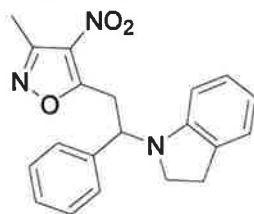
To a solution of styrylisoxazole **317** (1 g, 1.0 eq.) in DCM (25 mL) was added indoline (5.0 eq.) and DMAP (0.2 eq.). The mixture was stirred at room temperature for 24h. The solvent was removed under vacuum and the crude was purified by silica-gel flash chromatography using appropriate eluent. The product was further crystallized from EtOH.

General procedure for the preparation of propionic acid 380u.

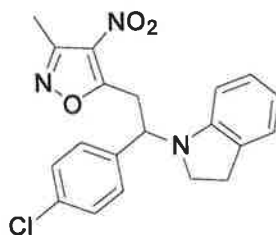
To a solution of adduct **334u** (1.4 g, 3.59 mmol, 1.0 eq.) in THF (20 mL), was added a solution of NaOH (719 mg, 17.98 mmol, 5.0 eq.) in H₂O (20 mL) and the mixture was heated to reflux. After 4 hours the dark solution was cooled to room temperature and washed with CHCl₃ (2 x 30 mL): the water phase was brought to pH = 5 with a 20% aqueous HCl solution and extracted with DCM (2 x 40 mL). The organic phase was dried over anhydrous Na₂SO₄ and the solvent was removed under vacuum. The crude was purified by silica-gel flash chromatography (CHCl₃/MeOH 10:1) to give a brown oil which was crystallized from CHCl₃ to furnished a pale yellow solid **380u**.

General procedure for the preparation of compounds 335, 336.

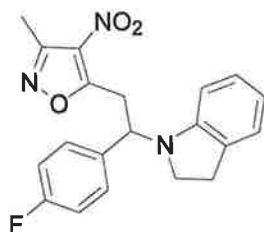
To a solution of styrylisoxazole **317** (200 mg, 1.0 eq.) in DCM (2 mL) was added phenylhydrazine (4.0 eq.). The mixture was stirred at room temperature for 24h. The solvent was removed under vacuum and the crude was purified by silica-gel flash chromatography using appropriate eluent.

1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-phenyl-ethyl]-indoline 334a:

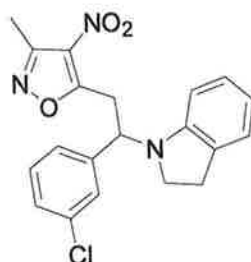
orange solid, m.p. 115-117 °C; R_f : 0.2 (PE-EA v/v 15:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.39-7.32 (5H, m), 7.06-7.02 (2H, m), 6.63 (1H, at, $J = 7.2$), 6.59 (1H, d, $J = 7.6$), 5.49 (1H, dd, $J = 9.2$, $J = 6.8$), 3.99 (1H, dd, $J = 14.4$, $J = 9.2$), 3.86 (1H, dd, $J = 14.4$, $J = 6.8$), 3.58-3.52 (1H, m), 3.19-3.13 (1H, m), 2.99-2.84 (2H, m), 2.50 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.6, 155.6, 150.4, 137.6, 129.6, 128.7, 128.1, 127.7, 127.3, 124.8, 117.8, 106.8, 56.9, 46.7, 28.8, 28.0, 11.64; IR: ν_{max} (KBr)/ cm^{-1} : 3025, 2935, 2826, 1603, 1518, 1255, 743; HRMS: Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_3\text{O}_3$ ($[\text{M}]^+$): 350.1505, found: 350.1489.

1-[1-(4-Chloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-indoline 334b:

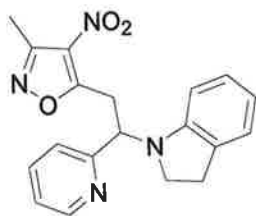
orange solid, m.p. 106-108 °C; R_f : 0.1 (PE/EA v/v 15:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.36-7.31 (4H, m), 7.07-7.03 (2H, m), 6.65 (1H, adt, $J = 7.6$, $J = 0.8$), 6.56 (1H, d, $J = 8.0$), 5.45 (1H, dd, $J = 8.8$, $J = 7.2$), 3.95 (1H, dd, $J = 14.4$, $J = 8.8$), 3.84 (1H, dd, $J = 14.4$, $J = 7.2$), 3.57-3.51 (1H, m), 3.18-3.12 (1H, m), 3.00-2.86 (2H, m), 2.51 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.2, 155.7, 150.1, 136.1, 134.0, 129.7, 129.0, 128.9, 127.3, 124.9, 118.2, 106.9, 56.4, 46.8, 28.8, 28.0, 11.7; IR: ν_{max} (KBr)/ cm^{-1} : 3050, 2920, 2830, 1600, 1515, 1381, 1256, 748; HRMS: Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3\text{Cl}$ ($[\text{M}]^+$): 384.1115, found: 384.1121.

1-[1-(4-Fluoro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-indoline 334c:

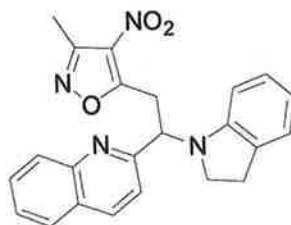
orange solid, m.p. 91-93 °C; R_f : 0.15 (PE/EA v/v 20:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.38-7.34 (2H, m), 7.07-7.03 (4H, m), 6.67-6.63 (1H, m), 6.57 (1H, d, $J = 8.0$), 5.46 (1H, dd, $J = 8.4$, $J = 7.2$), 3.95 (1H, dd, $J = 14.4$, $J = 8.8$), 3.83 (1H, dd, $J = 14.4$, $J = 6.8$), 3.56-3.50 (1H, m), 3.17-3.11 (1H, m), 2.99-2.85 (2H, m), 2.50 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.5, 155.8, 150.3, 129.8, 129.5, 129.4, 127.5, 125.0, 118.2, 115.9, 115.7, 107.0, 56.5, 46.8, 29.0, 28.1, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3028, 2930, 2831, 1598, 1513, 1379, 1225, 827, 743; HRMS: Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3\text{F}$ ($[\text{M}]^+$): 368.1410, found: 368.1404.

1-[1-(3-Chloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-indoline 334e:

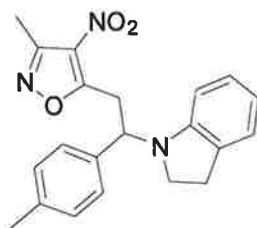
orange solid (89%), m.p. 147-149 °C; crystallized from EtOH; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.36 (1H, s), 7.29-7.23 (3H, m), 7.04-7.00 (2H, m), 6.63 (1H, t, $J = 7.4$), 6.52 (1H, d, $J = 8.0$), 5.42 (1H, dd, $J = 9.2$, $J = 6.4$), 3.95 (1H, dd, $J = 14.4$, $J = 9.2$), 3.79 (1H, dd, $J = 14.4$, $J = 6.4$), 3.57-3.50 (1H, m), 3.18-3.12 (1H, m), 2.98-2.86 (2H, m), 2.48 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.2, 155.8, 150.2, 139.8, 134.9, 130.2, 129.7, 128.5, 128.0, 127.5, 125.9, 125.0, 118.3, 106.9, 56.6, 46.9, 28.9, 28.2, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3050, 2925, 1598, 1513, 1379, 738; HRMS: Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3\text{Cl}$ ($[\text{M}]^+$): 384.1115, found: 384.1121.

1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-pyridin-2-yl-ethyl]-indoline 334f:

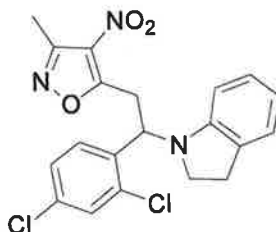
red solid, m.p. 102-104 °C; R_f : 0.1 (PE/EA v/v 10:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.57-8.56 (1H, m), 7.65 (1H, dt, $J = 7.6$, $J = 1.6$), 7.37 (1H, d, $J = 8.0$), 7.24-7.21 (1H, m), 7.06-7.02 (2H, m), 6.64 (1H, at, $J = 7.6$), 6.54 (1H, d, $J = 8.0$), 5.57 (1H, dd, $J = 8.4$, $J = 6.8$), 4.16 (1H, dd, $J = 14.8$, $J = 6.4$), 3.98 (1H, dd, $J = 14.8$, $J = 8.4$), 3.65-3.59 (1H, m), 3.22-3.16 (1H, m), 3.02-2.87 (2H, m), 2.51 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 173.8, 157.3, 155.6, 150.3, 148.9, 136.8, 129.8, 127.3, 124.9, 123.1, 122.9, 118.0, 106.8, 57.8, 47.1, 28.1, 27.9, 11.7; IR: ν_{max} (KBr)/ cm^{-1} : 3045, 2975, 2846, 1598, 1513, 1379, 1255, 738; HRMS: Calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_4\text{O}_3$ ($[\text{M}]^+$): 351.1457, found: 351.1448.

2-[1-(Indoline-1-yl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-quinoline 334i:

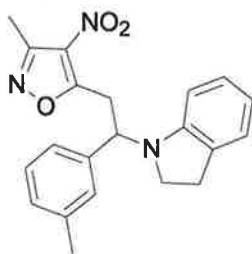
orange solid (95%), m.p. 154-156 °C; crystallized from EtOH; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.10 (1H, d, $J = 8.8$), 7.97 (1H, d, $J = 8.8$), 7.82-7.80 (1H, m), 7.75-7.70 (1H, m), 7.58-7.52 (1H, m), 7.51 (1H, d, $J = 8.4$), 7.08 (2H, at, $J = 7.6$), 6.71-6.67 (1H, m), 6.63 (1H, d, $J = 8.0$), 5.75 (1H, at, $J = 7.6$), 4.48 (1H, dd, $J = 15.2$, $J = 7.2$), 3.88 (1H, dd, $J = 15.2$, $J = 7.2$), 3.58 (1H, at, $J = 8.8$), 3.15-3.08 (1H, m), 3.04-2.89 (2H, m), 2.51 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 174.3, 157.9, 155.7, 150.4, 147.2, 136.9, 129.9, 129.7, 129.6, 127.6, 127.5, 126.9, 125.1, 120.9, 118.3, 106.9, 58.6, 47.5, 28.3, 26.9, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3040, 2935, 2841, 1593, 1513, 1374, 1260, 743; HRMS: Calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_4\text{O}_3$ ($[\text{M}]^+$): 401.1614, found: 401.1620.

1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-p-tolyl-ethyl]-indoline 334j:

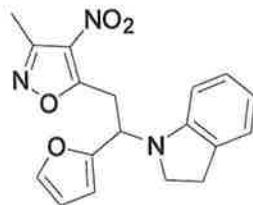
orange solid, m.p. 129-131 °C; R_f : 0.1 (PE/EA v/v 20:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.26 (2H, d, $J = 8.4$), 7.16 (2H, d, $J = 8.4$), 7.06-7.02 (2H, m), 6.64-6.59 (2H, m), 5.45 (1H, dd, $J = 8.8$, $J = 6.8$), 3.96 (1H, dd, $J = 14.4$, $J = 9.2$), 3.84 (1H, dd, $J = 14.4$, $J = 6.8$), 3.56-3.50 (1H, m), 3.18-3.12 (1H, m), 2.97-2.83 (2H, m), 2.49 (3H, s), 2.35 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.8, 155.6, 150.4, 137.9, 134.4, 129.7, 129.4, 127.6, 127.3, 124.7, 117.8, 106.8, 56.7, 46.7, 28.8, 28.0, 21.1, 11.7; IR: ν_{max} (KBr)/ cm^{-1} : 3050, 2920, 2831, 2359, 1603, 1513, 1374, 1260, 738; HRMS: Calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_3$ ($[\text{M}]^+$): 364.1661, found: 364.1663.

1-[1-(2,4-Dichloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-indoline 334m:

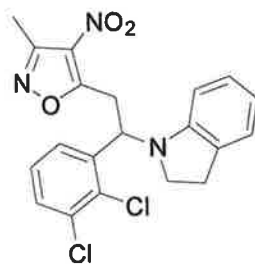
orange solid, m.p. 161-163 °C; R_f : 0.2 (DCM/PE v/v 1:2); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.49-7.45 (2H, m), 7.31-7.26 (1H, m), 7.06-7.02 (2H, m), 6.68-6.64 (1H, m), 6.55 (1H, d, $J = 8.0$), 5.79 (1H, at, $J = 7.6$), 3.97 (1H, dd, $J = 14.4$, $J = 7.6$), 3.80 (1H, dd, $J = 14.4$, $J = 7.6$), 3.52 (1H, aq, $J = 9.6$), 3.26-3.21 (1H, m), 3.05-2.90 (2H, m), 2.48 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 171.4, 155.7, 149.6, 135.5, 134.6, 134.3, 130.2, 129.3, 128.8, 127.4, 127.2, 124.7, 118.2, 106.7, 53.7, 47.3, 28.1, 27.6, 11.6; IR: ν_{max} (KBr)/ cm^{-1} : 3065, 2925, 1603, 1513, 1374, 1270, 822, 753; HRMS: Calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_3\text{Cl}_2$ ($[\text{M}]^+$): 418.0725, found: 418.0713.

1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-m-tolyl-ethyl]-indoline 334o:

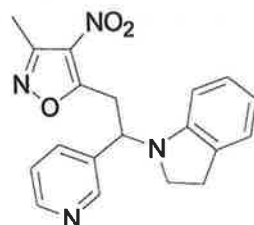
red solid, m.p. 127-129 °C; R_f : 0.1 (PE/EA v/v 35:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.26-7.24 (1H, at, $J = 7.6$), 7.20-7.13 (3H, m), 7.07-7.03 (2H, m), 6.65-6.58 (2H, m), 5.45 (1H, dd, $J = 8.8$, $J = 6.8$), 3.98 (1H, dd, $J = 14.4$, $J = 8.8$), 3.84 (1H, dd, $J = 14.4$, $J = 6.8$), 3.59-3.53 (1H, m), 3.21-3.14 (1H, m), 2.99-2.85 (2H, m), 2.50 (3H, s), 2.37 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.7, 155.6, 150.4, 138.4, 137.5, 129.7, 128.9, 128.5, 127.3, 124.7, 124.6, 117.8, 106.8, 57.0, 46.8, 28.8, 28.0, 21.6, 11.7; IR: ν_{max} (KBr)/ cm^{-1} : 3025, 2920, 2836, 4608, 1518, 1379, 1260, 738; HRMS: Calcd. for $\text{C}_{21}\text{H}_{22}\text{N}_3\text{O}_3$ ($[\text{M}]^+$): 364.1661, found: 364.1656.

1-[1-Furan-2-yl-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-indoline 334p:

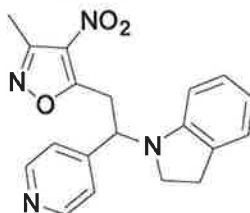
black solid, m.p. 114-116 °C; R_f : 0.15 (PE/EA v/v 30:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.38 (1H, at, $J = 1.0$), 7.10-7.05 (2H, m), 6.69 (1H, at, $J = 7.6$), 6.63 (1H, d, $J = 8.0$), 6.32 (1H, dd, $J = 3.2$, $J = 2.0$), 6.27 (1H, d, $J = 3.2$), 5.47 (1H, dd, $J = 9.2$, $J = 7.2$), 3.94 (1H, dd, $J = 14.4$, $J = 9.2$), 3.85 (1H, dd, $J = 14.8$, $J = 6.8$), 3.62 (1H, aq, $J = 8.0$), 3.18 (1H, aq, $J = 9.2$), 2.93 (2H, at, $J = 8.0$), 2.54 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.1, 155.8, 151.4, 150.2, 142.6, 130.0, 127.4, 124.8, 118.6, 110.3, 108.4, 107.6, 51.6, 47.7, 28.7, 28.2, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3048, 2979, 2845, 1602, 1525, 734; HRMS: Calcd. for $\text{C}_{18}\text{H}_{18}\text{N}_3\text{O}_4$ ($[\text{M}]^+$): 340.1297, found: 340.1289.

1-[1-(2,3-Dichloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-indoline**334q:**

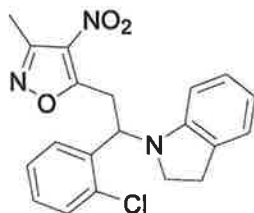
orange solid, m.p. 155-157 °C; R_f : 0.2 (PE/EA v/v 10:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.45-7.43 (2H, m), 7.26-7.22 (1H, m), 7.04-7.00 (1H, m), 6.63 (1H, t, $J = 7.2$), 6.55 (1H, d, $J = 8.0$), 5.85 (1H, at, $J = 8.0$), 3.95 (1H, dd, $J = 14.4$, $J = 7.6$), 3.79 (1H, dd, $J = 14.8$, $J = 7.6$), 3.58-3.47 (1H, m), 3.23-3.17 (1H, m), 3.05-2.88 (2H, m), 2.45 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 171.6, 155.8, 149.7, 138.1, 134.3, 133.3, 130.3, 129.4, 127.5, 127.3, 126.1, 124.8, 118.2, 106.8, 54.8, 47.4, 28.2, 27.6, 11.7; IR: ν_{max} (KBr)/ cm^{-1} : 3040, 2965, 2841, 1598, 1523, 1414, 1250, 743; HRMS: Calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_3\text{O}_3\text{Cl}_2$ ($[\text{M}]^+$): 418.0725, found: 418.0714.

1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-pyridin-3-yl-ethyl]-indoline 334r:

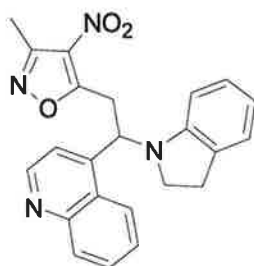
orange solid, m.p. 125-127 °C; crystallized from EtOH; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.66 (1H, d, $J = 2.4$), 8.58 (1H, dd, $J = 4.8$, $J = 1.6$), 7.73 (1H, dt, $J = 8.0$, $J = 2.0$), 7.32 (1H, dd, $J = 8.0$, $J = 4.8$), 7.07-7.04 (2H, m), 6.67 (1H, at, $J = 7.2$), 6.59 (1H, d, $J = 8.0$), 5.52 (1H, dd, $J = 9.2$, $J = 7.2$), 4.01 (1H, dd, $J = 14.4$, $J = 8.8$), 3.87 (1H, dd, $J = 14.4$, $J = 6.8$), 3.58 (1H, aq, $J = 9.2$), 3.19-3.13 (1H, m), 3.02-2.87 (2H, m), 2.50 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.0, 155.8, 149.9, 149.7, 149.3, 135.3, 133.2, 129.7, 127.5, 125.1, 123.7, 118.5, 107.1, 55.1, 46.8, 28.5, 28.1, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3050, 2925, 2846, 1593, 1513, 1379, 1270, 733; HRMS: Calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_4\text{O}_3$ ($[\text{M}]^+$): 351.1457, found: 351.1448.

1-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-pyridin-4-yl-ethyl]-indoline 334s:

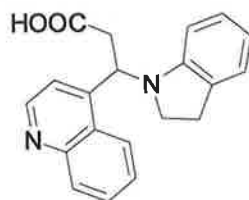
orange solid, m.p. 108-110 °C; R_f : 0.2 (PE/EA v/v 3:2); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.60 (2H, d, $J = 6.2$), 7.30 (2H, d, $J = 6.0$), 7.05-7.01 (2H, m), 6.66 (1H, at, $J = 7.2$), 6.52 (1H, d, $J = 8.0$), 5.46 (1H, dd, $J = 9.2$, $J = 6.8$), 3.98 (1H, dd, $J = 14.8$, $J = 9.2$), 3.86 (1H, dd, $J = 14.8$, $J = 6.4$), 3.56 (1H, aq, $J = 8.8$), 3.19-3.13 (1H, m), 3.02-2.88 (2H, m), 2.48 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 171.8, 155.8, 150.4, 149.9, 146.5, 130.9, 129.5, 127.4, 125.0, 122.5, 118.5, 106.9, 55.9, 46.8, 29.7, 28.3, 28.1, 11.6; IR: ν_{max} (KBr)/ cm^{-1} : 3050, 2925, 2846, 1593, 1513, 1379, 1270, 733; IR: ν_{max} (KBr)/ cm^{-1} : 3045, 2987, 2850, 1597, 1541, 1381, 1264, 735; HRMS: Calcd. for $\text{C}_{19}\text{H}_{19}\text{N}_4\text{O}_3$ ($[\text{M}]^+$): 351.1457, found: 351.1460.

1-[1-(2-Chloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-indoline 334t:

orange solid, m.p. 153-155 °C; R_f : 0.15 (PE/EA v/v 15:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.53 (1H, dd, $J = 7.6$, $J = 2.0$), 7.43 (1H, dd, $J = 7.2$, $J = 2.0$), 7.33-7.26 (2H, m), 7.05-7.01 (2H, m), 6.64 (1H, at, $J = 7.6$), 6.57 (1H, d, $J = 8.0$), 5.85 (1H, at, $J = 7.8$), 3.99 (1H, dd, $J = 14.4$, $J = 7.6$), 3.82 (1H, dd, $J = 14.4$, $J = 7.6$), 3.54 (1H, aq, $J = 9.2$), 3.27-3.21 (1H, m), 3.03-2.89 (2H, m), 2.47 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 171.8, 155.6, 149.8, 135.6, 134.8, 130.4, 129.3, 129.2, 128.0, 127.4, 126.8, 124.6, 117.9, 106.7, 54.0, 47.3, 29.7, 28.1, 27.7, 11.6; IR: ν_{max} (KBr)/ cm^{-1} : 3045, 2930, 2851, 1603, 1523, 1488, 1255, 738; HRMS: Calcd. for $\text{C}_{20}\text{H}_{19}\text{N}_3\text{O}_3\text{Cl}$ ($[\text{M}]^+$): 384.1115, found: 384.1110.

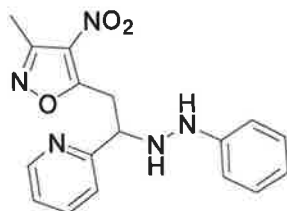
4-[1-(Indoline-1-yl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-quinoline 334u:

orange solid, m.p. 147-149 °C; (PE/EA v/v 3:1→EA); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.95 (1H, d, $J = 4.8$), 8.17 (1H, dd, $J = 8.4$, $J = 0.8$), 8.05 (1H, d, $J = 8.0$), 7.78-7.74 (1H, m), 7.59-7.54 (2H, m), 7.13 (1H, at, $J = 7.6$), 7.08 (1H, d, $J = 7.2$), 6.76-6.70 (2H, m), 6.19 (1H, at, $J = 7.6$), 4.11-4.01 (2H, m), 3.54-3.47 (1H, m), 3.03-2.92 (2H, m), 2.88-2.78 (1H, m), 2.46 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 171.7, 155.8, 149.9, 149.2, 148.7, 143.1, 130.3, 129.7, 129.6, 127.5, 127.4, 126.8, 125.1, 123.3, 118.5, 118.3, 106.0, 52.5, 46.8, 27.9, 25.9, 11.6; IR: ν_{max} (KBr)/ cm^{-1} : 3070, 2920, 1603, 1513, 1374, 1155, 738; HRMS: Calcd. for $\text{C}_{23}\text{H}_{21}\text{N}_4\text{O}_3$ ($[\text{M}]^+$): 401.1614, found: 401.1599.

3-(Indoline-1-yl)-3-quinolin-4-yl-propionic acid 380u:

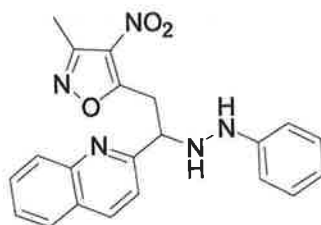
grey-yellow solid; m.p. 220-222 °C; crystallized from CHCl_3 ; $^1\text{H-NMR}$ δ : (400 MHz, DMSO- d_6): 12.50 (1H, s), 8.92 (1H, d, $J = 4.8$), 8.14-8.07 (2H, m), 7.80-7.76 (1H, m), 7.66-7.62 (2H, m), 7.07-7.01 (2H, m), 6.69 (1H, d, $J = 7.6$), 6.60 (1H, at, $J = 7.6$), 5.81 (1H, dd, $J = 9.2$, $J = 6.0$), 3.42-3.33 (1H, m), 3.26 (2H, dd, $J = 16.0$, $J = 8.8$), 2.95-2.83 (3H, m), 2.77-2.68 (1H, m); $^{13}\text{C-NMR}$ δ : (100MHz, DMSO- d_6): 172.4, 150.1, 149.7, 148.1, 144.6, 129.8, 129.5, 129.3, 127.4, 126.9, 126.5, 124.5, 123.5, 118.9, 117.4, 106.4, 50.8, 47.2, 32.3, 27.4; IR: ν_{max} (KBr)/ cm^{-1} : 3060, 3010, 2920, 2851, 2418, 1951, 1603, 1245, 758; HRMS: Calcd. for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2$ ($[\text{M}]^+$): 318.1368, found: 318.1365.

***N*-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-pyridin-2-yl-ethyl]-*N'*-phenyl-hydrazine 335f:**

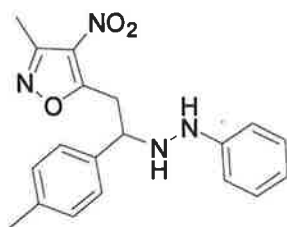


yellow oil (85%); R_f : 0.3 (PE/EA v/v 2:1) $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.66-8.65 (1H, m), 7.74-7.70 (1H, m), 7.31-7.26 (2H, m), 7.15-7.11 (2H, m), 6.75 (1H, t, $J = 7.2$), 6.69-6.66 (2H, m), 5.23 (1H, br), 4.54 (1H, dd, $J = 9.2$, $J = 5.2$), 3.76 (1H, dd, $J = 14.8$, $J = 9.2$), 3.53 (1H, dd, $J = 14.8$, $J = 5.2$), 2.57 (3H, s). $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.7, 158.9, 155.7, 150.1, 148.6, 137.3, 129.5, 123.4, 123.0, 119.5, 113.6, 113.1, 62.7, 32.6, 11.82; IR: ν_{max} (KBr)/ cm^{-1} : 3305, 3256, 3048, 2931, 1599, 1511, 1360, 766; HRMS: Calcd. for $\text{C}_{17}\text{H}_{18}\text{N}_5\text{O}_3$ ($[\text{M}+\text{H}]^+$): 340.1410, found: 340.1417.

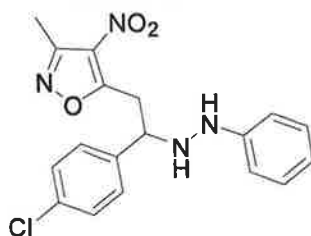
***N*-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-quinolin-2-yl-ethyl]-*N'*-phenyl-hydrazine 335i:**



yellow solid (68%); m.p. 117-121 °C; R_f : 0.2 (PE/EA v/v 15:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.21 (1H, d, $J = 8.4$), 8.10 (1H, d, $J = 8.4$), 7.88-7.85 (1H, m), 7.80-7.76 (1H, m), 7.61-7.57 (1H, m), 7.45 (1H, d, $J = 8.4$), 7.16-7.11 (2H, m), 6.77-6.73 (1H, m), 6.70-6.68 (2H, m), 5.50 (1H, br), 4.89 (1H, br), 4.76 (1H, dd, $J = 9.6$, $J = 5.2$), 3.75 (1H, dd, $J = 14.8$, $J = 9.6$), 3.65 (1H, dd, $J = 14.4$, $J = 4.8$), 2.60 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.8, 159.4, 155.8, 148.8, 148.0, 137.6, 130.2, 129.4, 129.2, 127.9, 127.8, 127.0, 120.5, 119.5, 113.1, 63.2, 32.8, 11.9; IR: ν_{max} (KBr)/ cm^{-1} : 3301, 3269, 3050, 2925, 1598, 1508, 1374, 748; HRMS: Calcd. for $\text{C}_{21}\text{H}_{19}\text{N}_5\text{O}_3$ ($[\text{M}+\text{H}]^+$): 390.1566, found: 390.1564.

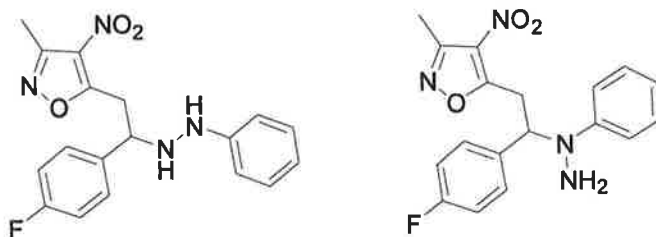
***N*-[2-(3-Methyl-4-nitro-isoxazol-5-yl)-1-*p*-tolyl-ethyl]-*N'*-phenyl-hydrazine 335i:**

orange solid (55%), m.p.: 121-123 °C; crystallized from Et₂O; ¹H-NMR δ: (400 MHz, CDCl₃): 7.26-7.14 (6H, m), 6.78 (1H, t, *J* = 7.2), 6.70 (2H, d, *J* = 8.4), 5.04 (1H, br), 4.44 (1H, at, *J* = 6.8), 3.88 (1H, br), 3.77 (1H, dd, *J* = 14.4, *J* = 8.4), 3.49 (1H, dd, *J* = 14.8, *J* = 6.4), 2.52 (3H, s), 2.37 (3H, s); ¹³C-NMR δ: (100MHz, CDCl₃): 172.8, 155.7, 148.6, 138.7, 136.2, 130.0, 129.3, 127.1, 119.7, 113.0, 62.1, 33.6, 21.3, 11.8; IR: ν_{max} (KBr)/cm⁻¹: 3353, 3249, 3025, 2895, 1605, 1510, 1376, 1131, 828, 743; HRMS: Calcd. for C₁₉H₂₁N₄O₃ ([M+H]⁺): 353.1614, found: 353.1615.

***N*-[1-(4-Chloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-*N'*-phenyl-hydrazine, *N*-[1-(4-Chloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-*N*-phenyl-hydrazine 335b, 336b:**

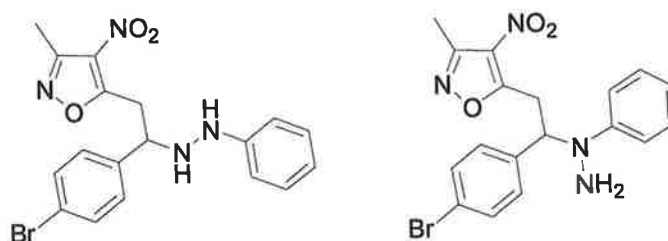
yellow oil (81%); (PE/EA v/v 10:1) ¹H-NMR δ: (400 MHz, CDCl₃): 7.66-7.64 (3.8H, m), 7.46-7.30 (17.3H, m), 7.19-7.15 (2H, m), 6.84-6.78 (1H, m), 6.73-6.69 (2H, m), 5.41 (1.9H, dd, *J* = 8.4, *J* = 6.0); 5.07 (1H, bs), 4.49 (1H, at, *J* = 7.2), 4.07 (1.9H, dd, *J* = 15.2, *J* = 8.8), 3.91 (1.9H, dd, *J* = 15.2, *J* = 6.0), 3.77 (1H, dd, *J* = 14.4, *J* = 8.0), 3.49 (1H, dd, *J* = 14.8, *J* = 6.4), 2.52-2.51 (8.7H, m); ¹³C-NMR δ: (100MHz, CDCl₃): 172.3, 171.7, 155.7, 151.5, 148.4, 137.8, 136.6, 134.6, 134.5, 131.5, 129.4, 129.3, 129.2, 128.6, 122.7, 119.9, 119.7, 113.0, 112.9, 61.7, 33.5, 33.2, 11.8, 11.7; IR: ν_{max} (KBr)/cm⁻¹: 3256, 3023, 2930, 1599, 1509, 1385, 1218, 813; HRMS: Calcd. for C₁₈H₁₈ClN₄O₃ ([M+H]⁺): 373.1067, found: 373.1075.

***N*-[1-(4-Fluoro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-*N'*-phenylhydrazine, *N*-[1-(4-Fluoro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-*N*-phenylhydrazine 335c, 336c:**



yellow oil (81%); (PE/EA v/v 10:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.68-7.65 (1.2H, m), 7.49-7.44 (3H, m), 7.36-7.32 (2H, m), 7.18-7.15 (2.2H, m), 7.11-7.05 (3H, m), 6.81-6.77 (1H, m), 6.74-6.72 (2H, m), 5.44 (0.6H, dd, $J = 8.4$, $J = 6.4$), 5.09 (1H, bs), 4.48 (1H, at, $J = 7.6$), 4.08 (0.6H, dd, $J = 14.8$, $J = 8.4$), 3.91 (0.6H, dd, $J = 15.2$, $J = 6.0$), 3.76 (1H, dd, $J = 14.8$, $J = 8.0$), 3.48 (1H, dd, $J = 14.8$, $J = 6.8$), 2.51 (4.8H, s). $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 172.4, 171.8, 164.0, 161.5, 155.6, 151.4, 148.5, 135.1, 135.0, 133.9, 133.8, 131.4, 129.6, 129.5, 129.2, 129.1, 129.0, 128.9, 122.6, 119.7, 116.2, 116.1, 116.0, 115.9, 112.9, 61.6, 33.5, 33.3, 11.7, 11.6; IR: ν_{max} (KBr)/ cm^{-1} : 3264, 3065, 2920, 2846, 1603, 1508, 1374, 1225, 827; HRMS: Calcd. for $\text{C}_{18}\text{H}_{18}\text{FN}_4\text{O}_3$ ($[\text{M}+\text{H}]^+$): 357.1363, found: 357.1364.

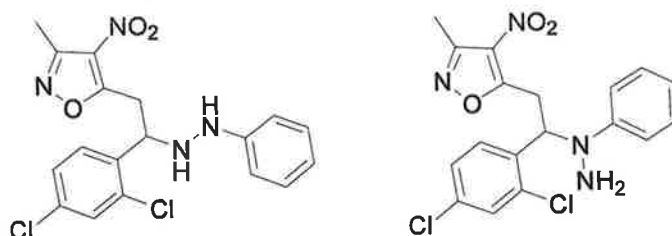
***N*-[1-(4-Bromo-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-*N'*-phenylhydrazine, *N*-[1-(4-Bromo-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-*N*-phenylhydrazine 335d, 336d:**



yellow oil (90%); (PE/EA v/v 9:1); $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.66-7.63 (1.9H, m), 7.54-7.50 (5.8H, m), 7.46-7.44 (2.8H, m), 7.38-7.39 (1.9H, m), 7.27-7.23 (3.9H, m), 7.19-7.15 (4H, m), 6.82-6.78 (2H, m), 6.72-6.70 (3H, m), 5.40 (1H, dd, $J = 8.4$, $J = 6.0$), 4.47 (1.9H, dd, $J = 7.6$, $J = 6.8$), 4.07 (1H, dd, $J = 14.8$, $J = 8.4$), 3.90 (1H, dd, $J = 14.8$, $J = 6.0$), 3.76 (1H, dd, $J = 14.4$, $J = 8.0$), 3.49 (1H, dd, $J = 14.8$,

$J = 6.4$), 2.52-2.51 (8.7H, m). ^{13}C -NMR δ : (100MHz, CDCl_3): 172.2, 171.7, 155.7, 151.5, 148.4, 138.3, 137.1, 132.6, 132.4, 132.3, 131.6, 129.6, 129.4, 129.3, 129.2, 129.0, 122.8, 122.7, 120.0, 113.1, 113.0, 61.8, 33.5, 33.2, 11.8, 11.7; IR: ν_{max} (KBr)/ cm^{-1} : 3271, 3078, 2921, 2856, 1606, 1513, 1389, 812; HRMS: Calcd. for $\text{C}_{18}\text{H}_{18}\text{BrN}_4\text{O}_3$ ($[\text{M}+\text{H}]^+$): 417.0562, found: 417.0565.

***N*-[1-(2,4-Dichloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-*N'*-phenyl-hydrazine, *N*-[1-(2,4-Dichloro-phenyl)-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-*N*-phenyl-hydrazine 335m, 336m:**



yellow oil (90%); (PE/EA v/v 10:1); ^1H -NMR δ : (400 MHz, CDCl_3): 7.67-7.64 (2H, m), 7.50-7.45 (6H, m), 7.41 (1H, d, $J = 2.0$), 7.32-7.29 (2H, m), 7.19-7.15 (2H, m), 6.79 (1H, t, $J = 7.2$), 6.73 (2H, d, $J = 7.6$), 5.95 (1H, dd, $J = 8.4$, $J = 6.0$), 5.00 (1H, dd, $J = 7.6$, $J = 6.4$), 4.11 (1H, dd, $J = 14.8$, $J = 8.4$), 3.84 (1H, dd, $J = 8.4$, $J = 7.6$), 3.78 (1H, dd, $J = 15.2$, $J = 6.0$), 3.50 (1H, dd, $J = 14.4$, $J = 6.0$), 2.53 (3H, s), 2.52 (3H, s). ^{13}C -NMR δ : (100MHz, CDCl_3): 171.8, 171.4, 155.7, 155.6, 151.4, 148.5, 135.2, 134.9, 134.8, 134.5, 134.3, 131.7, 130.2, 130.1, 130.0, 129.3, 129.2, 128.0, 127.8, 122.7, 120.0, 112.9, 72.9, 58.4, 32.2, 32.0, 11.8, 11.7; IR: ν_{max} (KBr)/ cm^{-1} : 3258, 3065, 2943, 2833, 1605, 1499, 1257, 821; HRMS: Calcd. for $\text{C}_{18}\text{H}_{17}\text{Cl}_2\text{N}_4\text{O}_3$ ($[\text{M}+\text{H}]^+$): 407.0678, found: 407.0682.

Experimental details Chapter 5

General procedure for the preparation of compounds 337.

To a solution of styrylisoxazole **317** (200 mg, 1.0 eq.) in CH₃CN (4 mL) was added L-proline (0.3 eq.) followed by benzyl mercaptan **392** (2.0 eq.). The mixture was stirred until the starting material is finished (monitored by TLC). The solvent was removed under vacuum and the crude was purified by crystallization from MeOH.

General procedure for the preparation of compounds 337a,v.

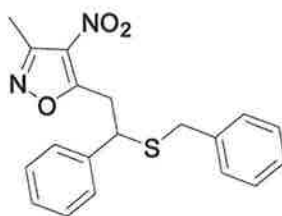
To a solution of styrylisoxazole **317a,v** (200 mg, 1.0 eq.) in CH₃CN (4 mL) was added L-proline (0.3 eq.) followed by benzyl mercaptan **392** (2.0 eq.). The mixture was stirred until the starting material is finished (monitored by TLC). The solvent was removed under vacuum and the crude was purified by flash chromatography using PE/EA as eluent.

General one-pot procedure for the preparation of compounds 337.

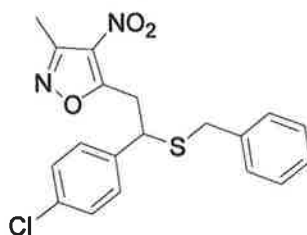
To a solution of 3,5-dimethyl-4-nitroisoxazole **317** (1 g, 7.04 mmol, 1.0 eq.) in CH₃CN (10 mL) was added piperidine (0.1 eq.) and an aromatic aldehyde (1.0 eq.). The reaction mixture was refluxed for 4h and then cooled to room temperature. Piperidine (0.2 eq.) was added followed by benzyl mercaptan **392** (1.2 eq.). The mixture was stirred at room temperature until the styrylisoxazole was not finished (monitored by TLC). The solvent was removed under vacuum and the crude was purified by crystallization from MeOH.

General one-pot procedure for the preparation of compounds 337a,v

To a solution of 3,5-dimethyl-4-nitroisoxazole **317a,v** (1 g, 7.04 mmol, 1.0 eq.) in CH₃CN (10 mL) was added piperidine (0.1 eq.) and an aromatic aldehyde (1.0 eq.). The reaction mixture was refluxed for 4h and then cooled to room temperature. Piperidine (0.2 eq.) was added followed by benzyl mercaptan **392** (1.2 eq.). The mixture was stirred at room temperature until the styrylisoxazole was not finished (monitored by TLC). The solvent was removed under vacuum and the crude was purified by flash chromatography using PE/EA as eluent.

5-[2-Benzylsulfanyl-2-phenyl-ethyl]-3-methyl-4-nitro-isoxazole 337a:

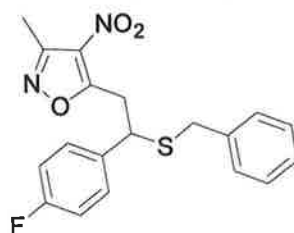
pale yellow oil (85%); *R_f*: 0.2 (PE/EA v/v 12:1); ¹H-NMR δ: (400 MHz, CDCl₃): 7.36-7.25 (8H, m), 7.20-7.18 (2H, m), 4.23 (1H, at, *J* = 8.4), 3.70 (2H, d, *J* = 8.0), 3.61 (1H, d, *J* = 13.2), 3.50 (1H, d, *J* = 13.6), 2.50 (3H, s); ¹³C-NMR δ: (100MHz, CDCl₃): 171.7, 155.5, 140.0, 137.4, 129.0, 128.9, 128.6, 128.1, 127.7, 127.3, 46.2, 35.9, 34.5, 11.7; IR: *v*_{max} (KBr)/cm⁻¹: 3030, 2916, 1603, 1518, 1414, 1379, 1359, 827, 698; HRMS: Calcd. for C₁₉H₁₈N₂O₃S ([M]⁺): 354.1038, found: 354.1042.

5-[2-Benzylsulfanyl-2-(4-chloro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 337b:

white solid (84%); m.p.108-111 °C; ¹H-NMR δ: (400 MHz, CDCl₃): 7.23-7.17 (7H, m), 7.10-7.08 (2H, m), 4.09 (1H, at, *J* = 8.0), 3.57 (2H, dd, *J* = 8.0, *J* = 1.4), 3.52 (1H, d, *J* = 13.6), 3.40 (1H, d, *J* = 13.6), 2.43 (3H, s); ¹³C-NMR δ: (100MHz,

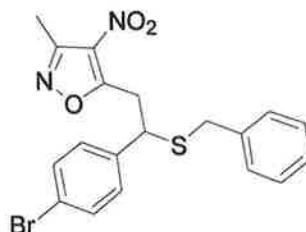
CDCl₃): 171.4, 155.7, 138.7, 137.2, 133.9, 129.2, 129.0, 128.7, 127.5, 45.5, 36.0, 34.5, 11.8; IR: ν_{\max} (KBr)/cm⁻¹: 3031, 2916, 1599, 1515, 1379, 1358, 1090, 823, 707; HRMS: Calcd. for C₁₉H₁₇ClN₂O₃S ([M]⁺): 388.0648, found: 388.0649.

5-[2-Benzylsulfanyl-2-(4-fluoro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 337c:



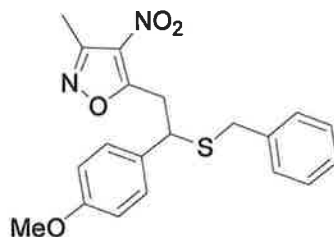
yellow-orange solid (83%); m.p. 102-105 °C; ¹H-NMR δ : (400 MHz, CDCl₃): 7.30-7.24 (5H, m), 7.17-7.15 (2H, m), 7.03-6.99 (2H, m), 4.18 (1H, at, J = 8.0), 3.65 (2H, dd, J = 8.0, J = 1.2), 3.59 (1H, d, J = 13.6), 3.47 (1H, d, J = 13.6), 2.49 (3H, s); ¹³C-NMR δ : (100MHz, CDCl₃): 171.5, 163.6, 161.1, 155.6, 137.2, 135.8, 135.8, 129.5, 129.4, 129.0, 128.7, 127.5, 116.0, 115.8, 45.5, 36.0, 34.7, 11.8; IR: ν_{\max} (KBr)/cm⁻¹: 3031, 2914, 1606, 1517, 1456, 1224, 823, 707; HRMS: Calcd. for C₁₉H₁₇FN₂O₃S ([M]⁺): 372.0944, found: 372.0946.

5-[2-Benzylsulfanyl-2-(4-bromo-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 337d:



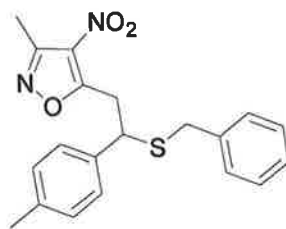
white solid (84%); m.p. 114-117 °C; ¹H-NMR δ : (400 MHz, CDCl₃): 7.46-7.43 (2H, m), 7.28-7.24 (3H, m), 7.20-7.16 (4H, m), 4.15 (1H, at, J = 8.0), 3.64 (2H, dd, J = 8.0, J = 2.0), 3.59 (1H, d, J = 13.6), 3.46 (1H, d, J = 13.6), 2.50 (3H, s); ¹³C-NMR δ : (100MHz, CDCl₃): 171.4, 155.7, 139.2, 137.1, 132.1, 129.5, 129.0, 128.7, 127.5, 122.0, 45.6, 36.0, 34.4, 11.8; IR: ν_{\max} (KBr)/cm⁻¹: 3030, 2911, 1603, 1519, 1414, 1380, 1355, 1071, 828, 708, 509; HRMS: Calcd. for C₁₉H₁₇BrN₂O₃S ([M]⁺): 432.0143, found: 432.0148.

5-[2-Benzylsulfanyl-2-(4-methoxy-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole
337g:

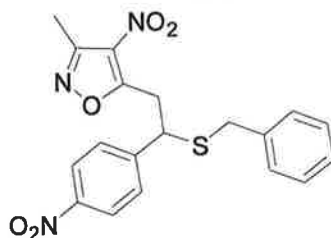


yellow solid (80%); m.p. 128-131 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.30-7.21 (5H, m), 7.19-7.17 (2H, m), 6.84 (2H, d, $J = 8.8$), 4.18 (1H, at, $J = 8.0$), 3.80 (3H, s), 3.72-3.60 (2H, m), 3.58 (1H, d, $J = 13.6$), 3.47 (1H, d, $J = 13.2$), 2.49 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 171.9, 159.3, 155.6, 137.5, 131.9, 129.0, 128.9, 128.6, 127.3, 114.3, 55.4, 45.7, 35.9, 34.7, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3036, 2927, 1604, 1514, 1375, 1250, 823; HRMS: Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_4\text{S}$ ($[\text{M}]^+$): 384.1144, found: 384.1148.

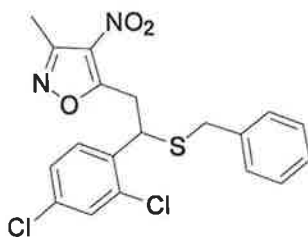
5-[2-Benzylsulfanyl-2-(4-methyl-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 337j:



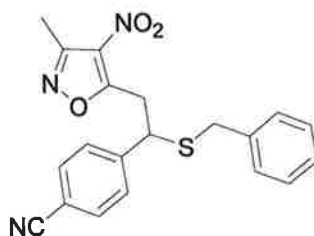
white solid (78%); m.p. 88-91 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.30-7.25 (3H, m), 7.23-7.17 (4H, m), 7.12 (2H, d, $J = 8.0$), 4.18 (1H, at, $J = 8.0$), 3.66 (2H, dd, $J = 8.0$, $J = 1.6$), 3.58 (1H, d, $J = 13.6$), 3.48 (1H, d, $J = 13.2$), 2.49 (3H, s), 2.34 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 171.9, 155.6, 137.9, 137.5, 137.0, 129.6, 129.0, 128.6, 127.6, 127.3, 46.0, 35.9, 34.6, 21.3, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3025, 2920, 1603, 1508, 1414, 1380, 1360, 1111, 827, 708; HRMS: Calcd. for $\text{C}_{20}\text{H}_{20}\text{N}_2\text{O}_3\text{S}$ ($[\text{M}]^+$): 368.1195, found: 368.1193.

5-[2-Benzylsulfanyl-2-(4-nitro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 337l:

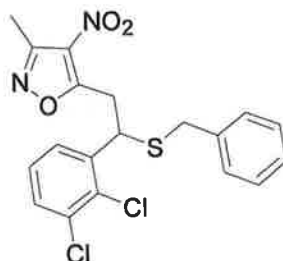
white solid (88%); m.p. 138-141 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 8.19 (2H, d, $J = 8.8$), 7.47 (2H, d, $J = 8.8$), 7.29-7.25 (3H, m), 7.15-7.13 (2H, m), 4.25 (1H, at, $J = 8.0$), 3.68 (2H, d, $J = 8.4$), 3.64 (1H, d, $J = 13.6$), 3.49 (1H, d, $J = 13.6$), 2.51 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 170.8, 155.8, 147.8, 147.6, 136.7, 129.0, 128.8, 128.7, 127.7, 124.3, 45.5, 36.2, 34.2, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3119, 2925, 1613, 1513, 1419, 1344, 1106, 822, 708; HRMS: Calcd. for $\text{C}_{19}\text{H}_{17}\text{N}_3\text{O}_5\text{S}$ ($[\text{M}]^+$): 399.0889, found: 399.0896.

5-[2-Benzylsulfanyl-2-(2,4-dichloro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 337m:

white solid (86%); m.p. 104-107 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.57 (1H, d, $J = 8.4$), 7.31 (1H, d, $J = 2.0$), 7.28-7.22 (4H, m), 7.17-7.15 (2H, m), 4.78 (1H, at, $J = 7.6$), 3.69 (1H, dd, $J = 14.4$, $J = 7.6$), 3.61 (2H, dd, $J = 20.4$, $J = 13.2$), 3.58 (1H, dd, $J = 14.4$, $J = 7.6$), 2.51 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 170.9, 155.7, 137.0, 136.4, 134.3, 134.2, 130.2, 129.6, 129.0, 128.7, 128.0, 127.5, 42.3, 36.5, 33.8, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3060, 2916, 1603, 1513, 1474, 1454, 1414, 1379, 1106, 827; HRMS: Calcd. for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3\text{S}$ ($[\text{M}]^+$): 422.0259, found: 422.0263.

4-[1-Benzylsulfanyl-2-(3-methyl-4-nitro-isoxazol-5-yl)-ethyl]-benzonitrile 337n:

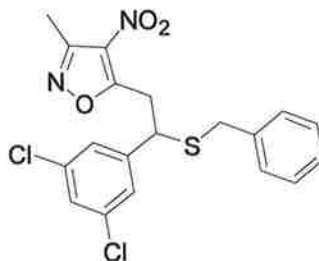
white solid (81%); m.p. 144-147 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.61 (2H, d, $J = 8.4$), 7.41 (2H, d, $J = 8.4$), 7.28-7.24 (3H, m), 7.14-7.12 (2H, m), 4.20 (1H, at, $J = 8.0$), 3.65 (2H, d, $J = 8.0$), 3.62 (1H, d, $J = 13.8$), 3.47 (1H, d, $J = 13.8$), 2.50 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 170.9, 155.7, 145.8, 136.7, 132.8, 128.9, 128.8, 128.6, 127.7, 118.5, 112.0, 45.8, 36.1, 34.2, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 3025, 2916, 2229, 1608, 1518, 1414, 1379, 1359, 1170, 827, 549; HRMS: Calcd. for $\text{C}_{20}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$ ($[\text{M}]^+$): 379.0991, found: 379.0993.

5-[2-Benzylsulfanyl-2-(2,3-dichloro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole 337q:

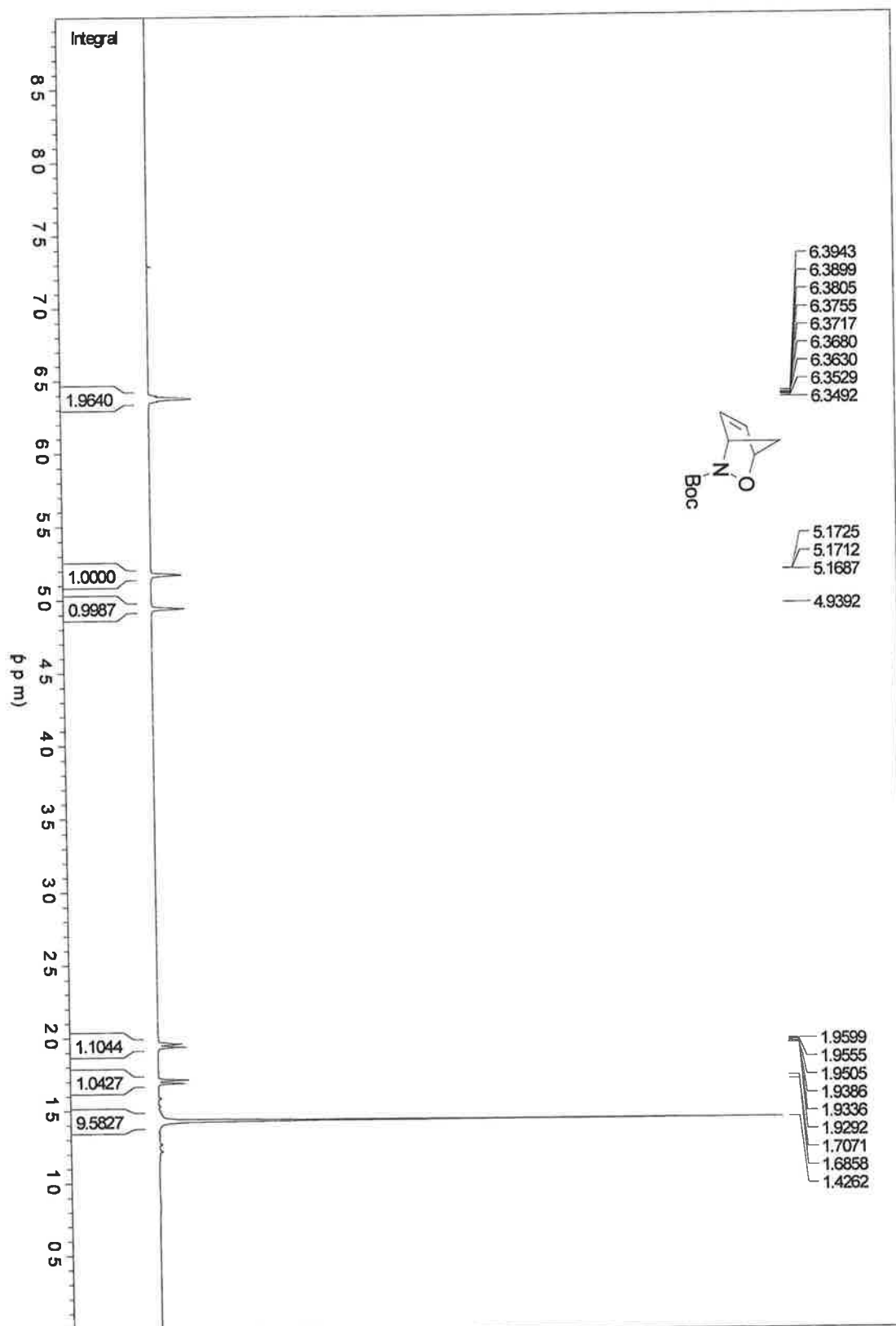
yellow solid (81%); m.p. 136-139 °C; $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.55 (1H, d, $J = 7.6$), 7.37 (1H, dd, $J = 8.4$, $J = 1.6$), 7.28-7.21 (4H, m), 7.17-7.15 (2H, m), 4.87 (1H, at, $J = 7.6$), 3.71 (1H, dd, $J = 14.8$, $J = 8.0$), 3.67-3.58 (3H, m), 2.52 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 171.0, 155.7, 140.1, 137.0, 133.6, 132.0, 130.0, 129.6, 128.7, 128.6, 127.9, 127.5, 127.3, 43.6, 43.4, 36.7, 33.8, 11.8; IR: ν_{max} (KBr)/ cm^{-1} : 2972, 2917, 2354, 1747, 1215, 1041; HRMS: Calcd. for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3\text{S}$ ($[\text{M}]^+$): 422.0259, found: 422.0261.

5-[2-Benzylsulfanyl-2-(3,5-dichloro-phenyl)-ethyl]-3-methyl-4-nitro-isoxazole

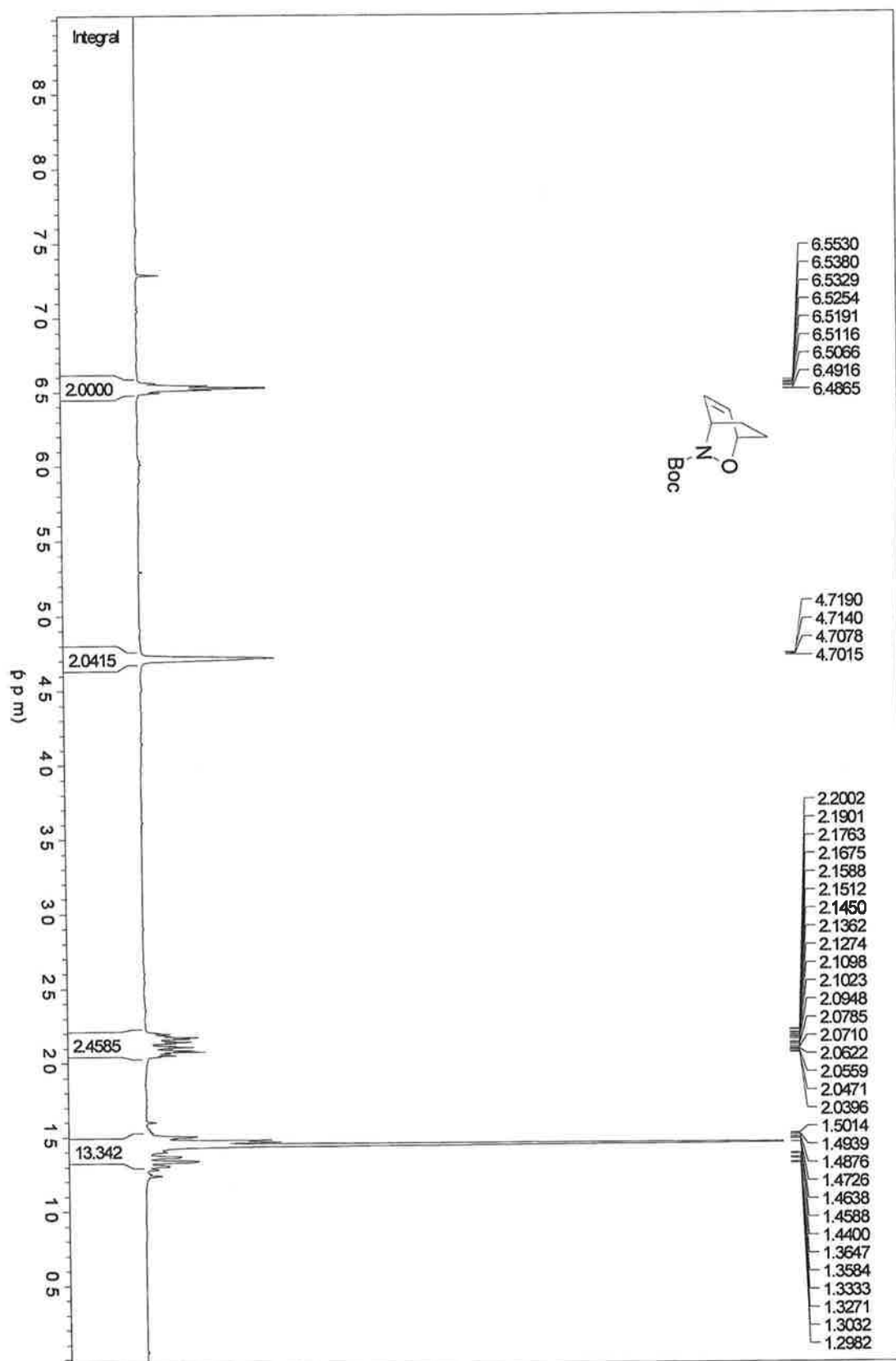
337v:



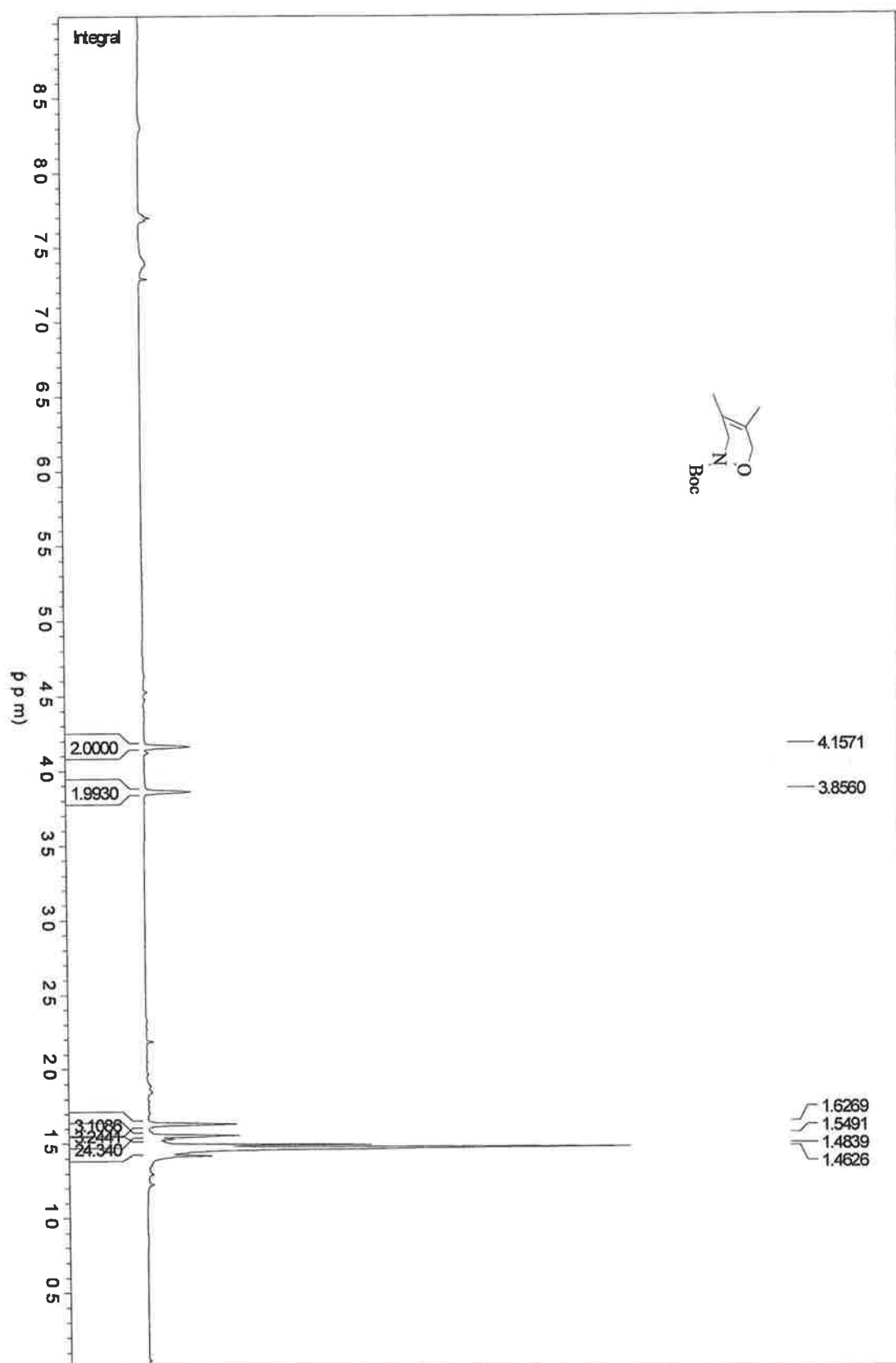
white solid (78%); m.p. 103-106 °C; R_f : 0.1 (PE/EA v/v 16:1), $^1\text{H-NMR}$ δ : (400 MHz, CDCl_3): 7.30-7.25 (4H, m), 7.20 (2H, d, $J = 2.0$), 7.16-7.14 (2H, m), 4.10 (1H, at, $J = 7.6$), 3.67-3.56 (3H, m), 3.50 (1H, d, $J = 13.6$), 2.53 (3H, s); $^{13}\text{C-NMR}$ δ : (100MHz, CDCl_3): 170.9, 155.7, 143.9, 136.7, 135.4, 128.9, 128.7, 128.4, 127.6, 126.3, 45.4, 36.1, 34.4, 11.7; IR: ν_{max} (KBr)/ cm^{-1} : 3065, 2920, 1607, 1514, 1421, 1374, 1360, 699; HRMS: Calcd. for $\text{C}_{19}\text{H}_{16}\text{Cl}_2\text{N}_2\text{O}_3\text{S}$ ($[\text{M}]^+$): 422.0259, found: 422.0258.



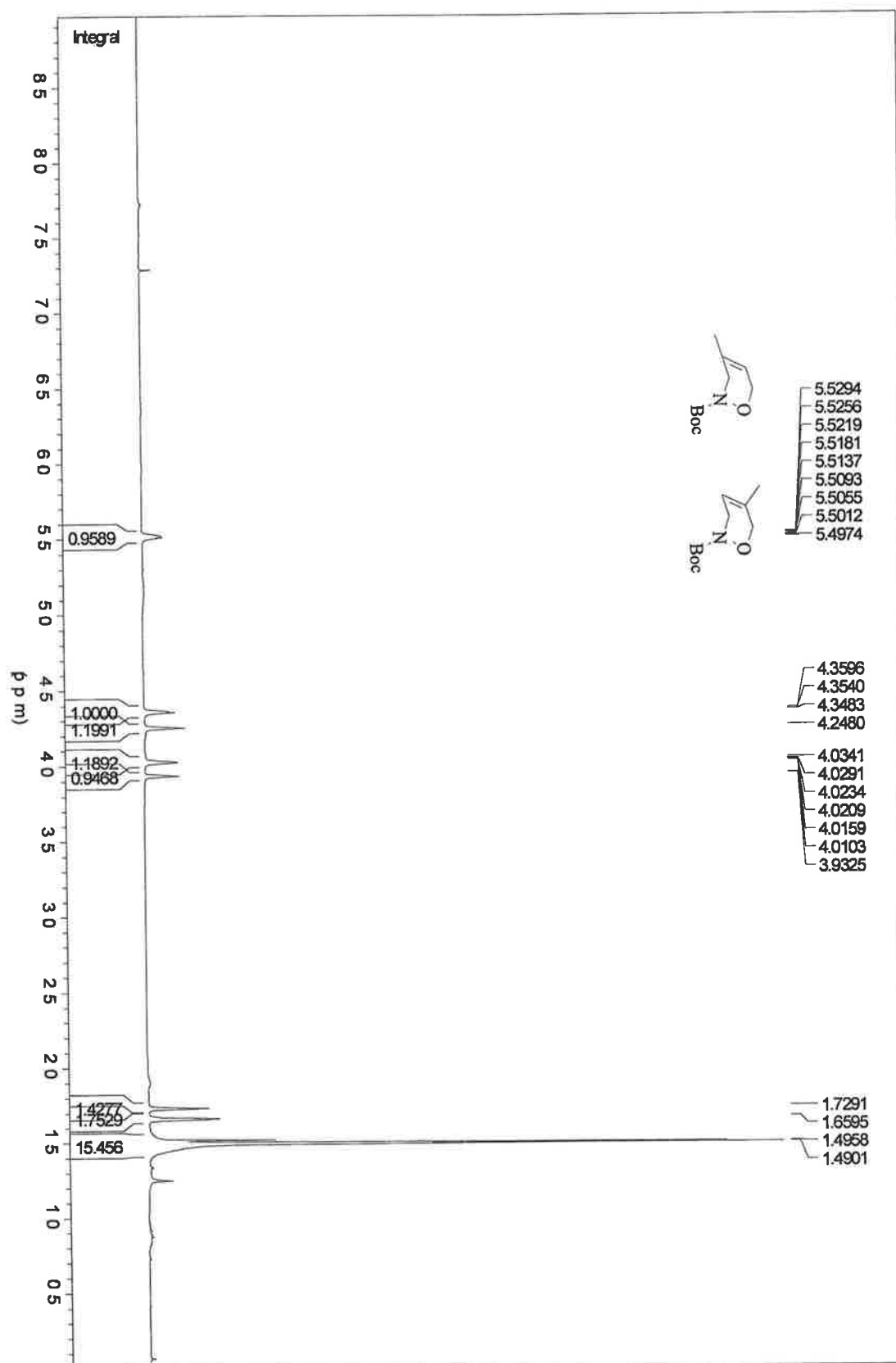
Compound 36c



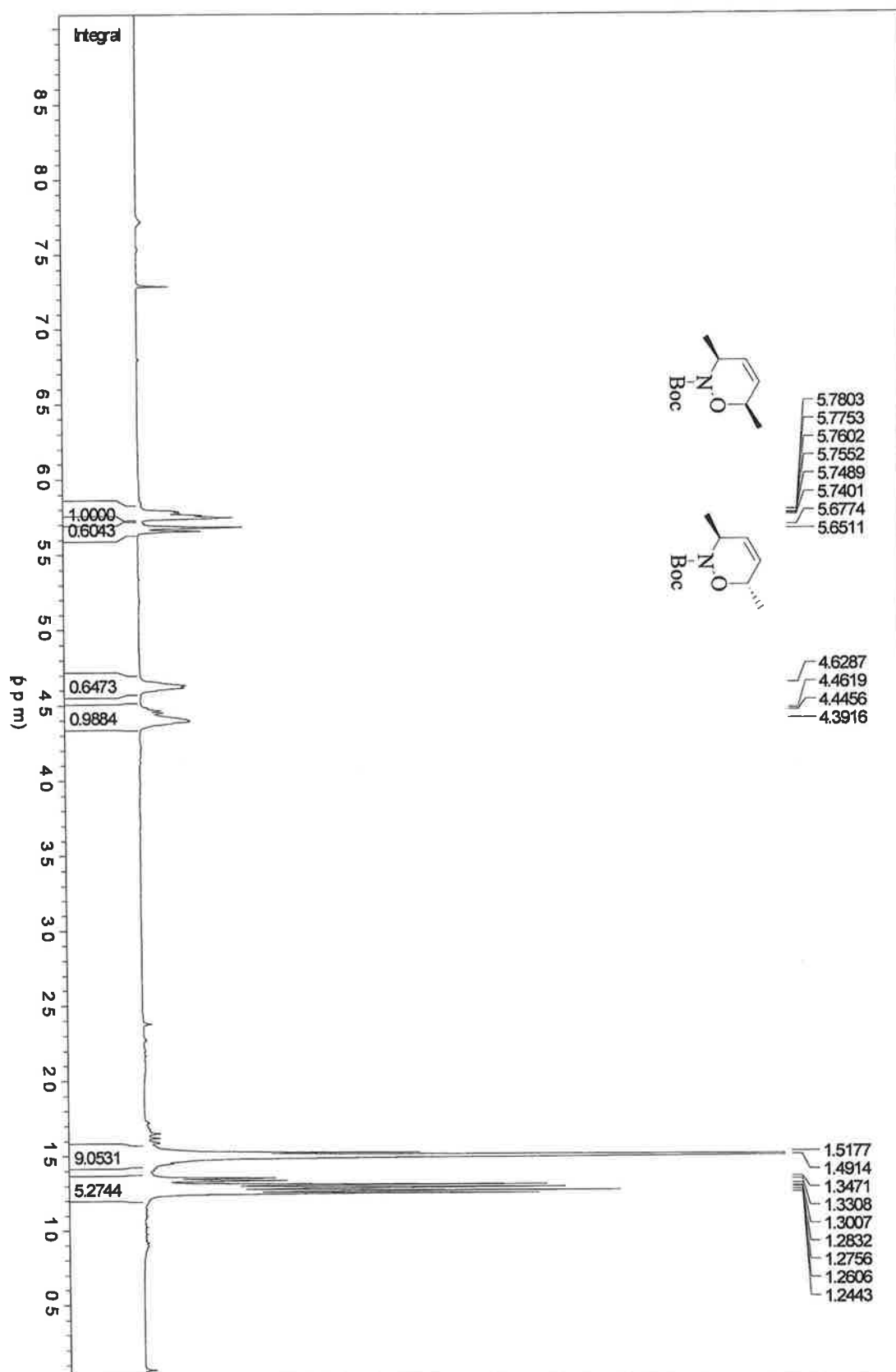
Compound 294



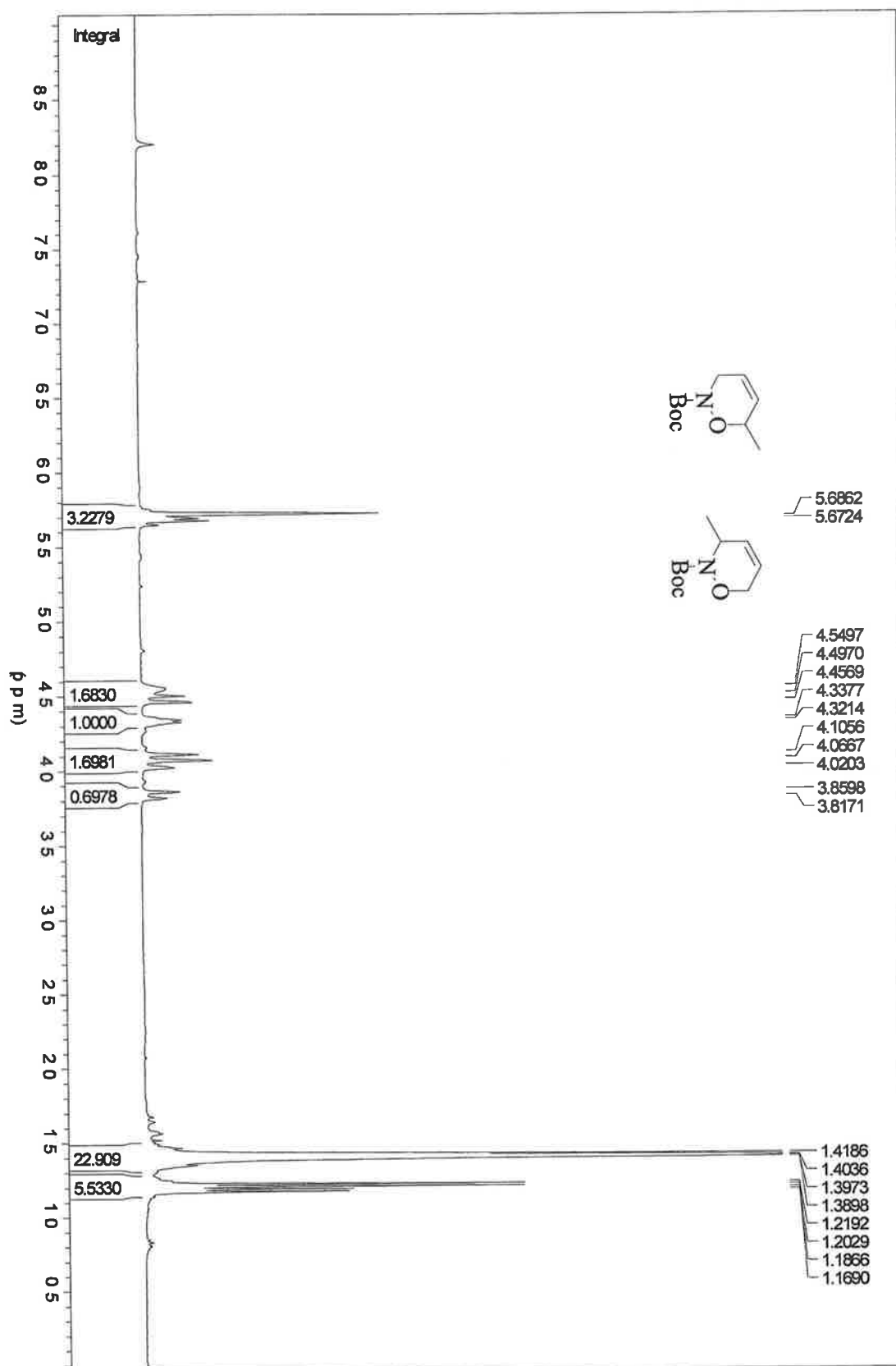
Compound 295a,b



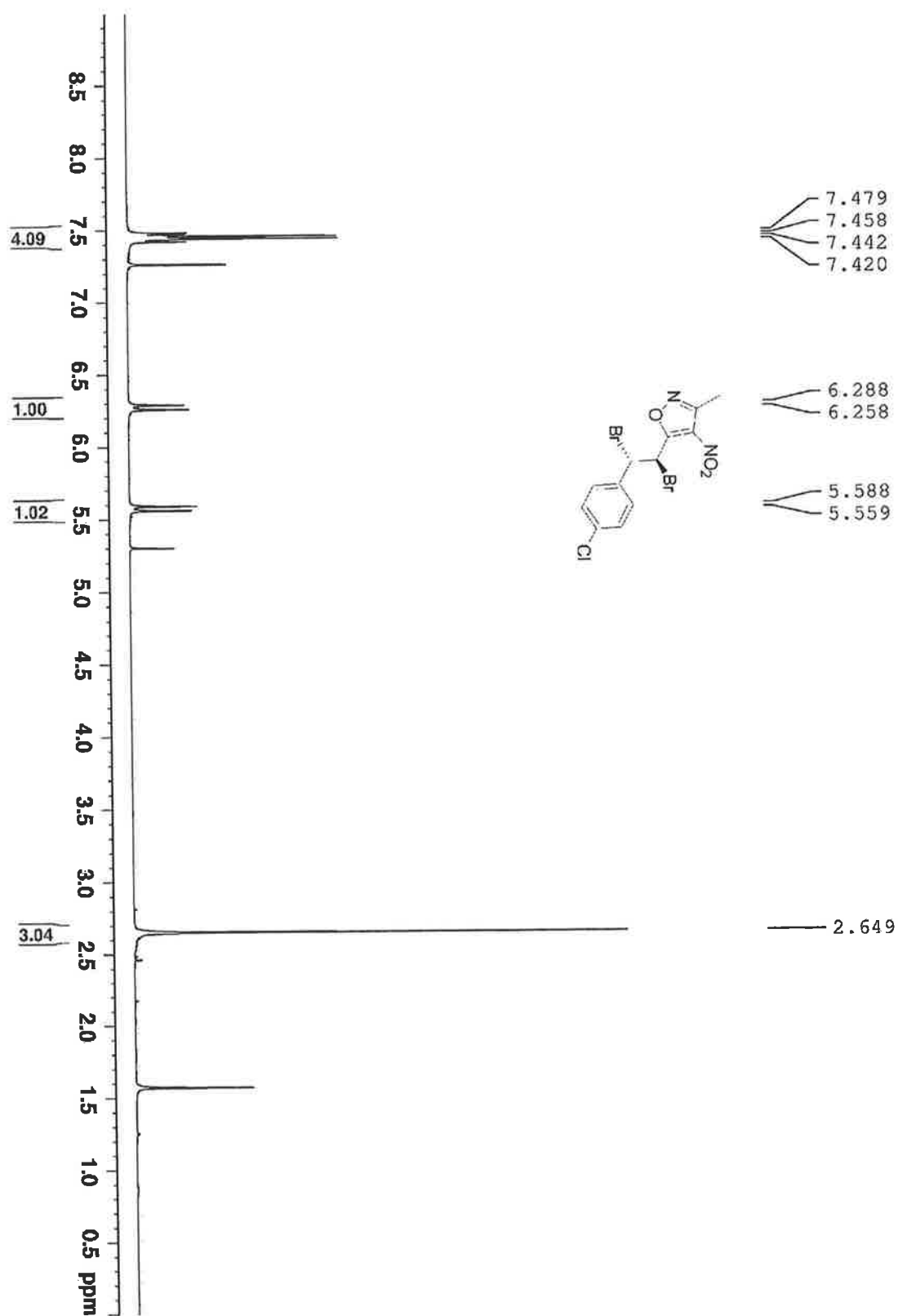
Compound 296a,b



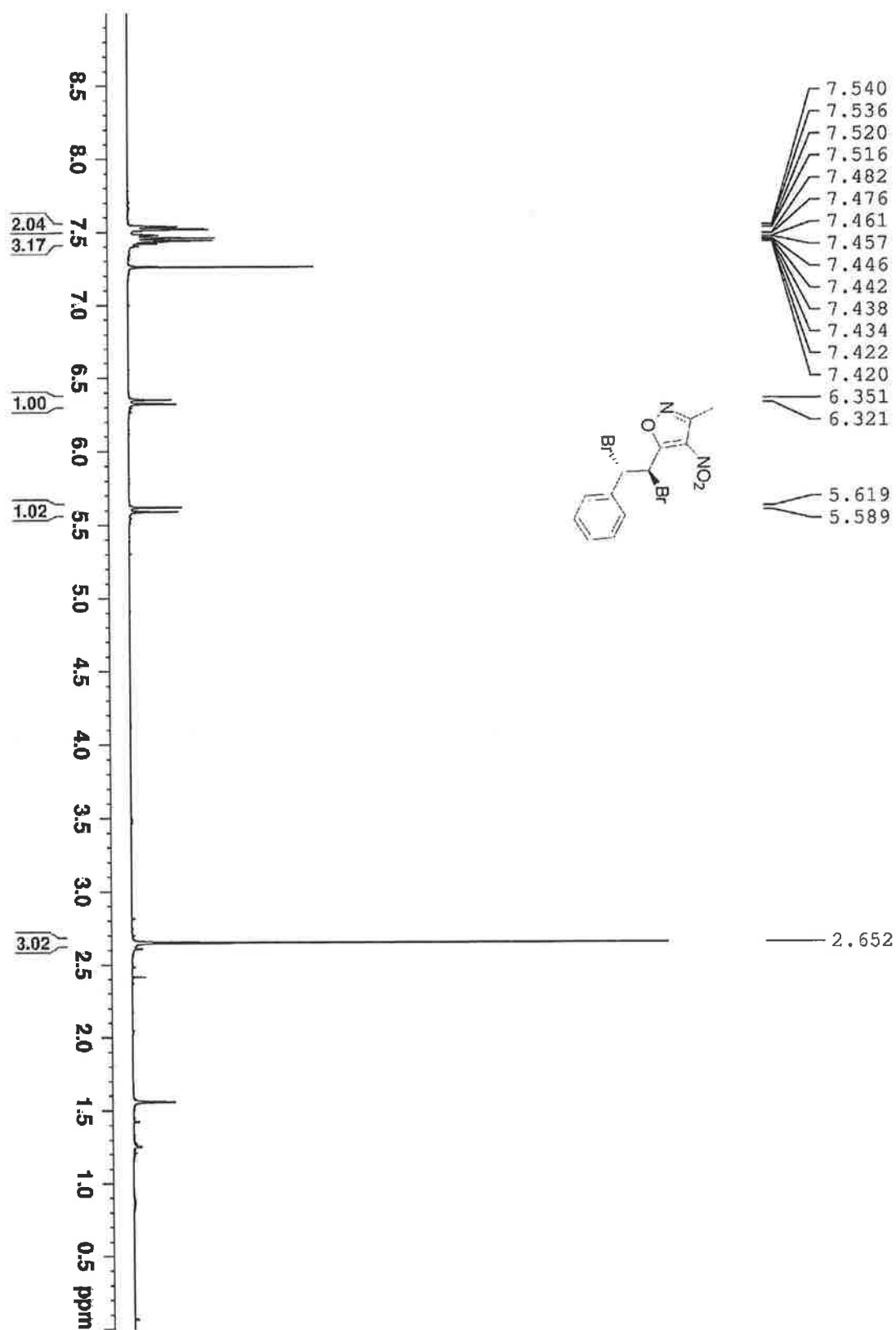
Compound 297a,b



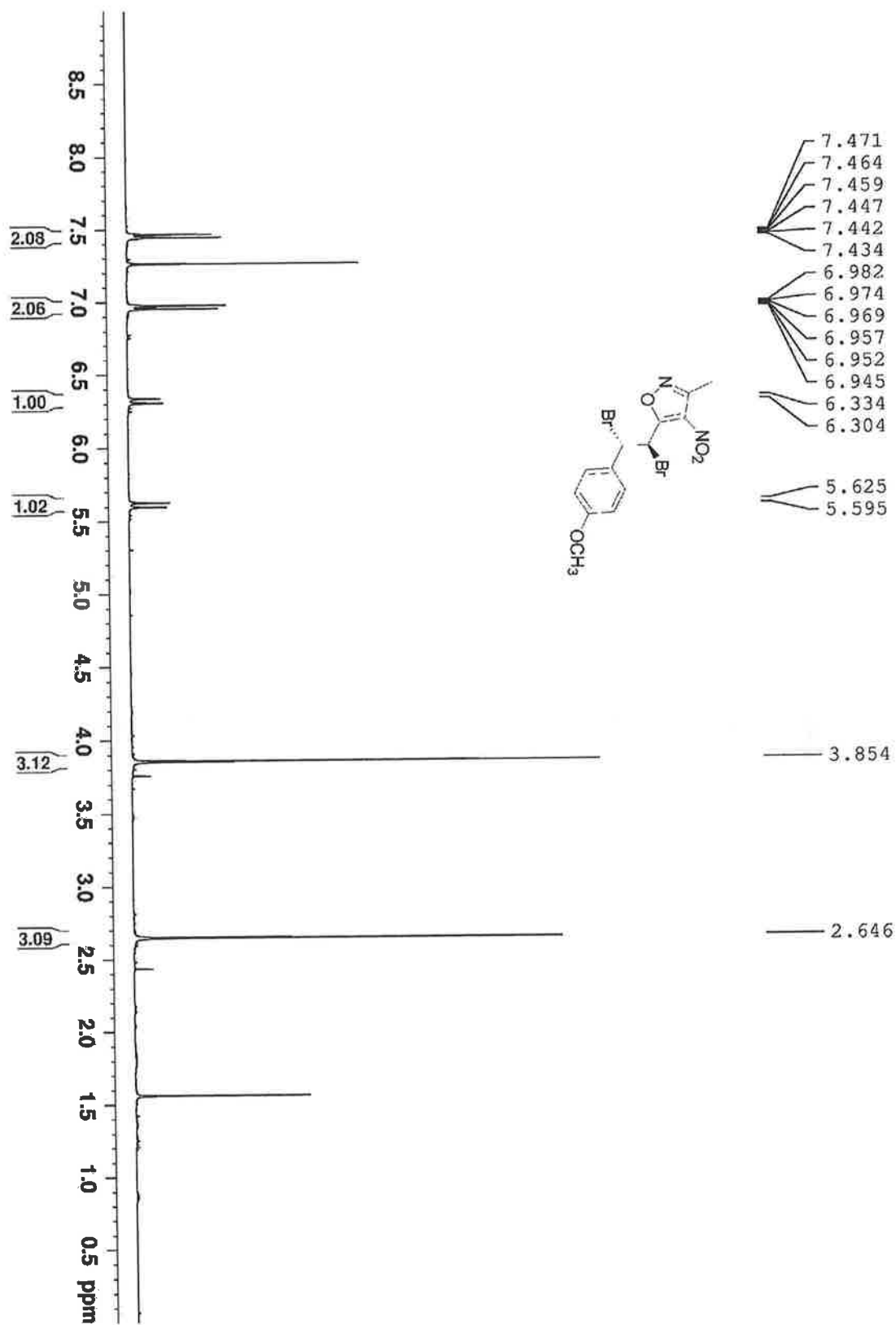
Compound 344b



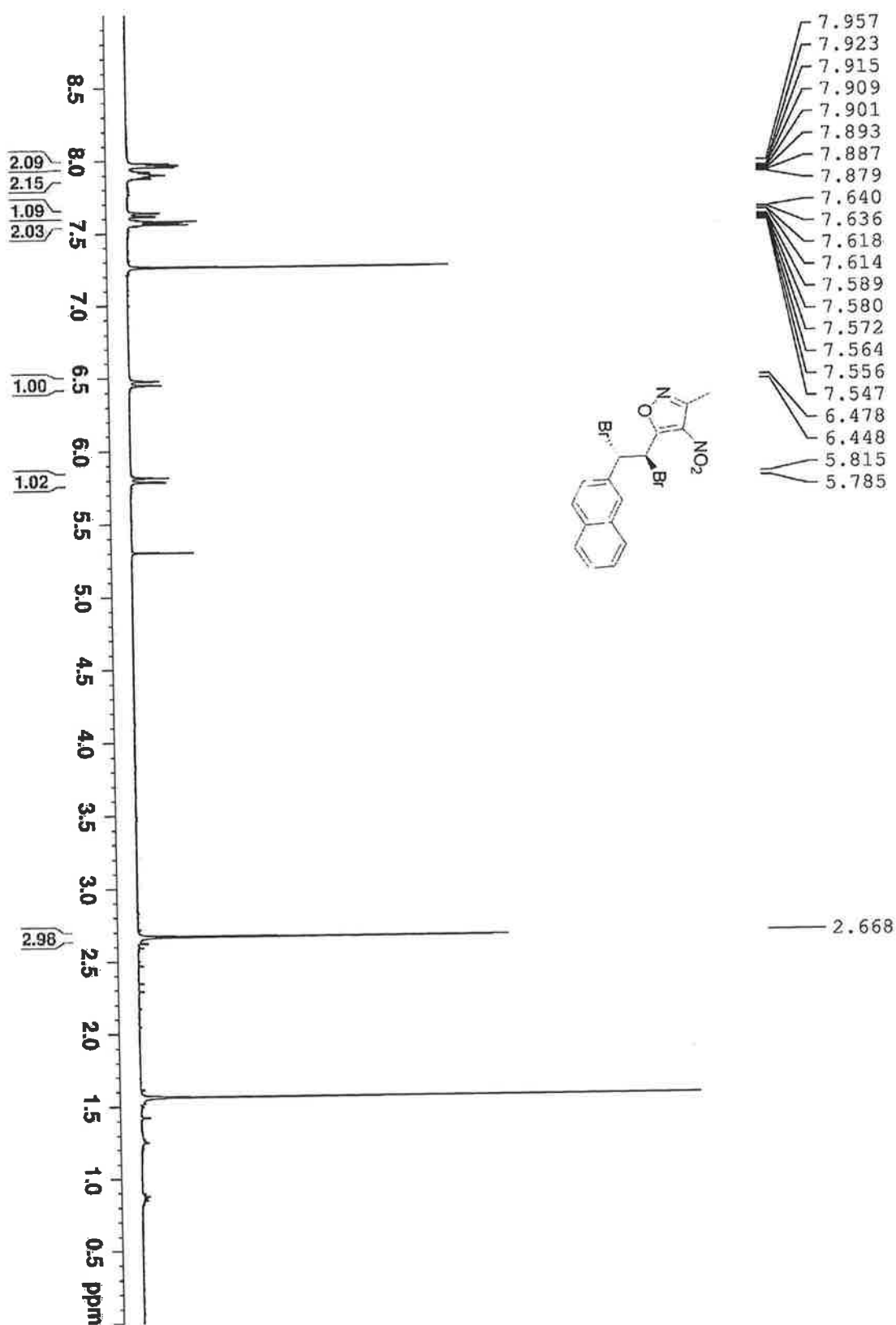
Compound 344a



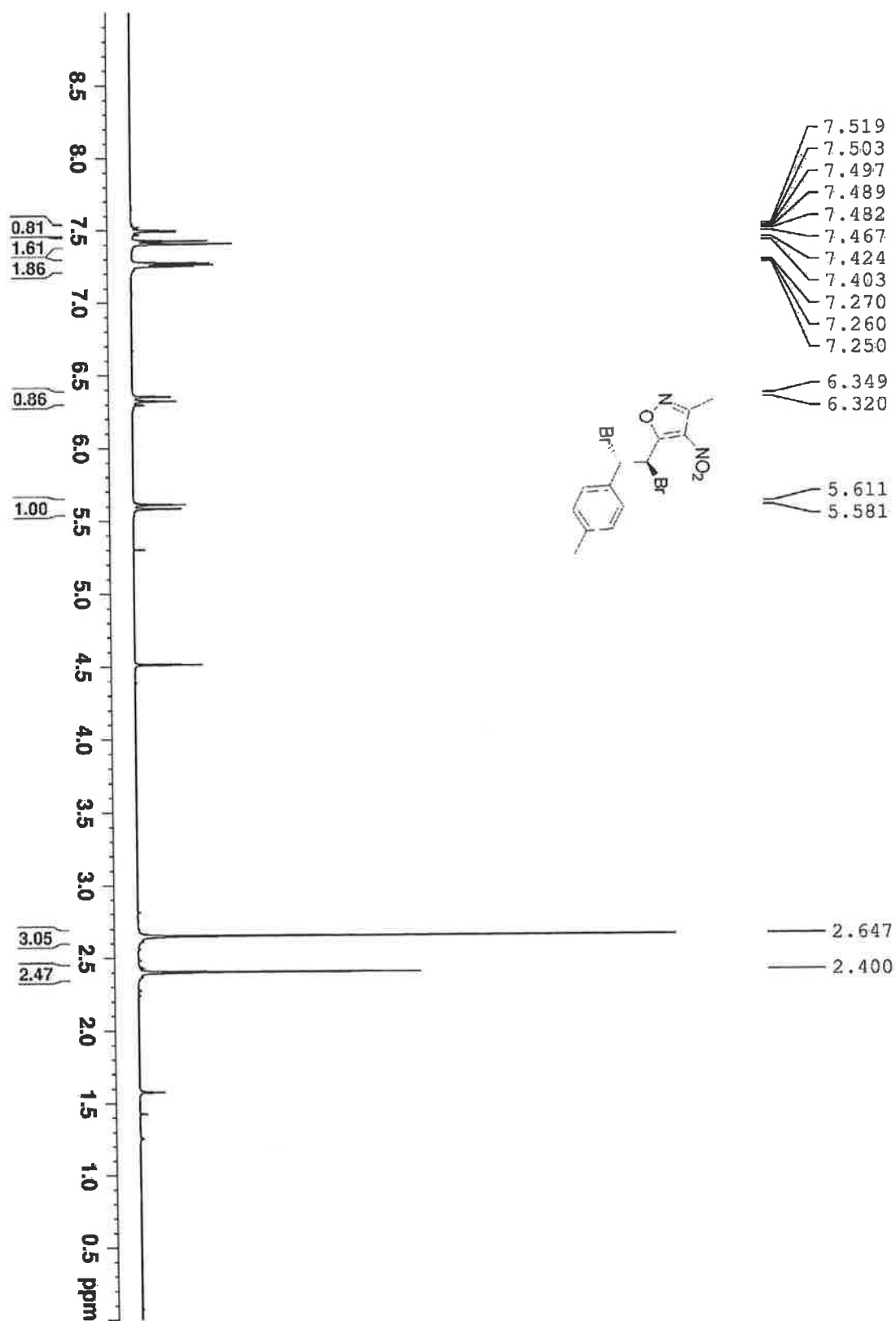
Compound 344g



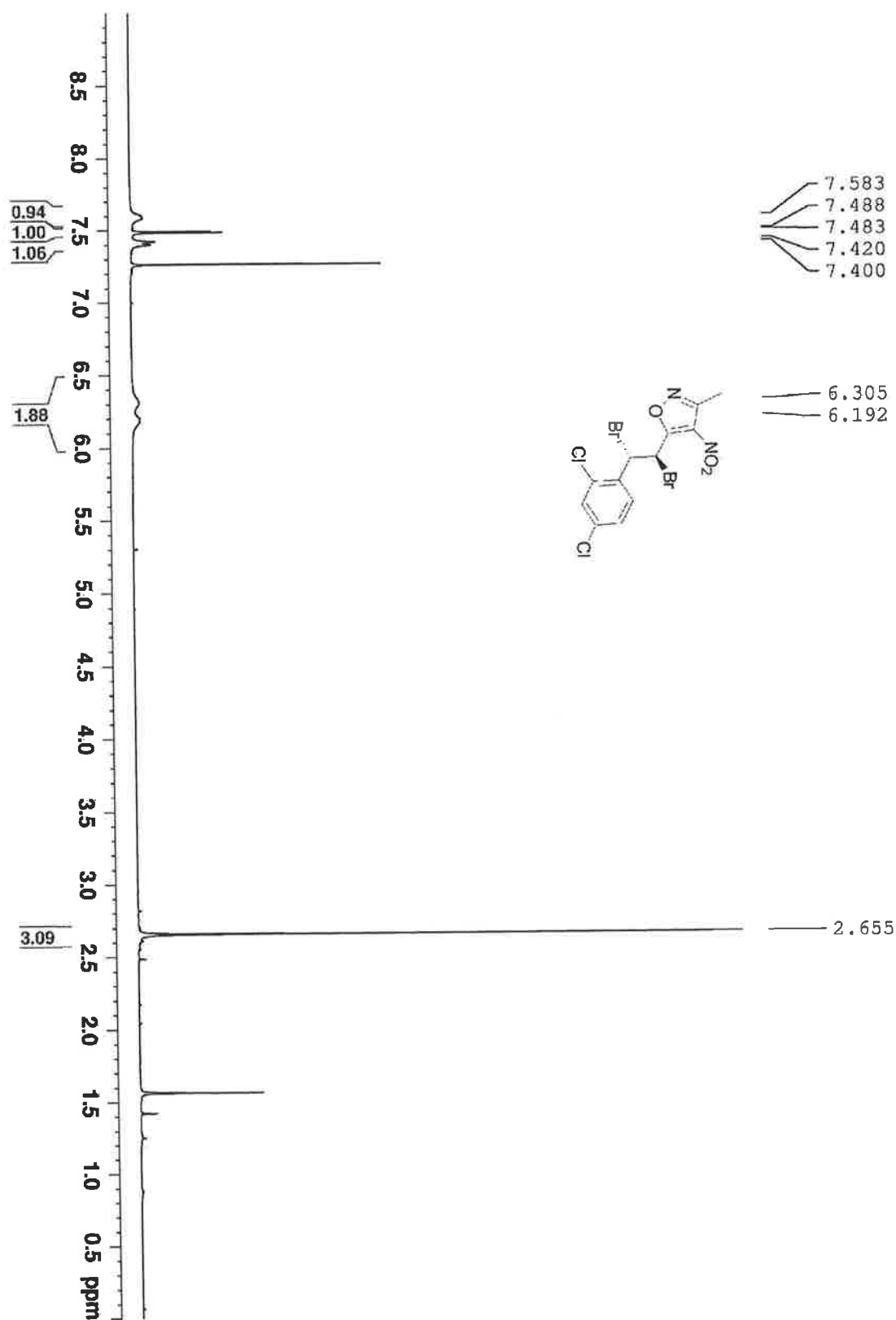
Compound 344h



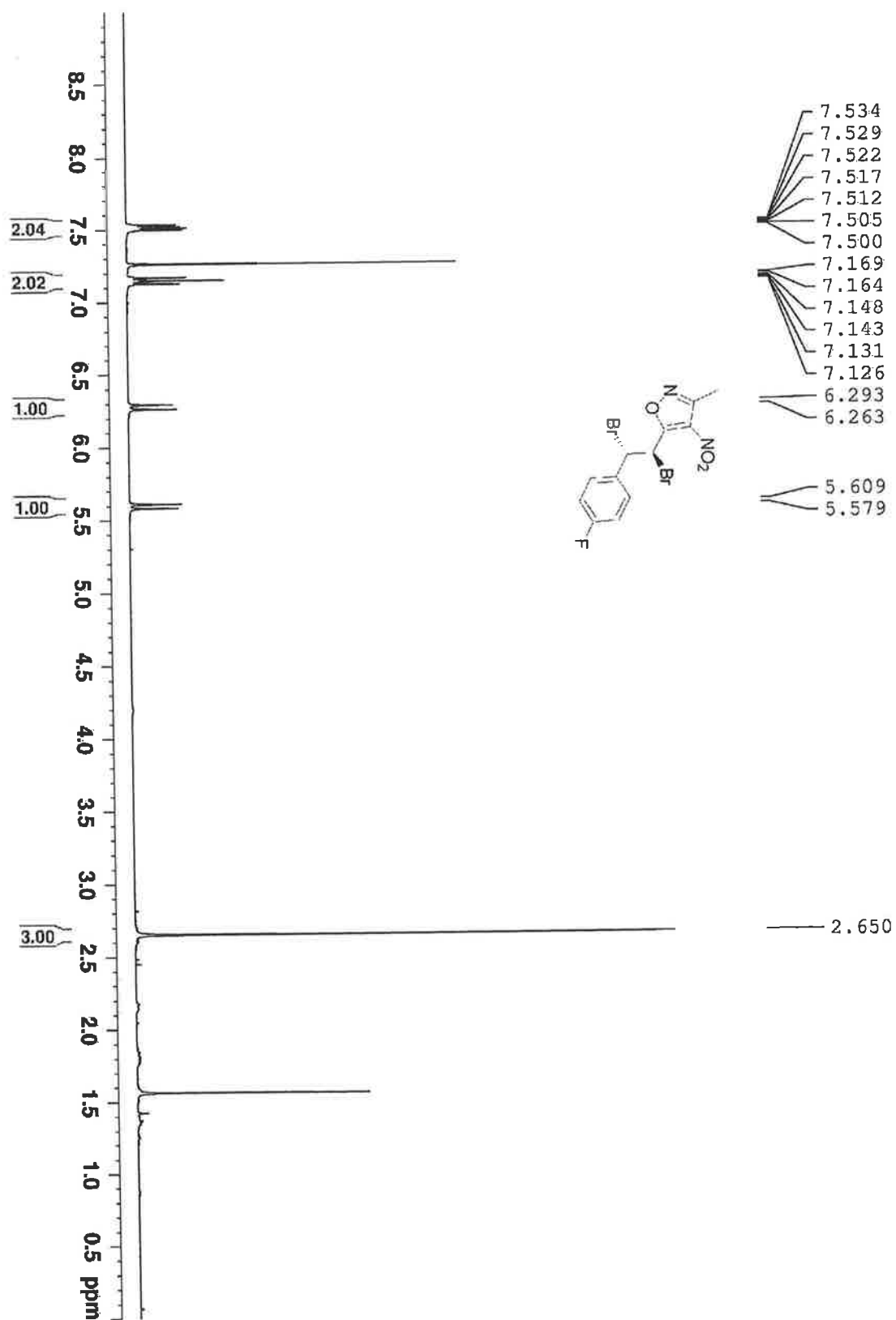
Compound 344j



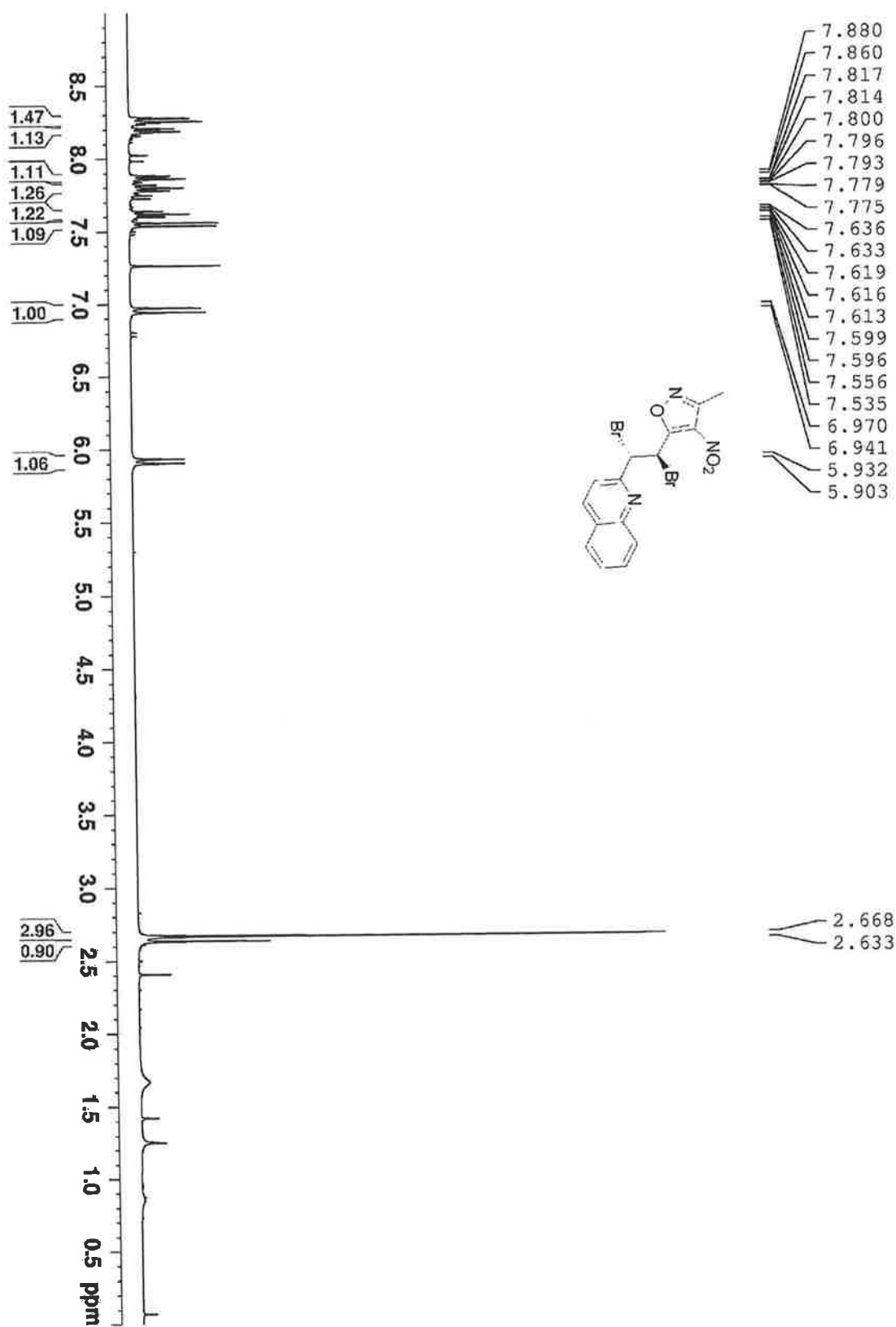
Compound 344m



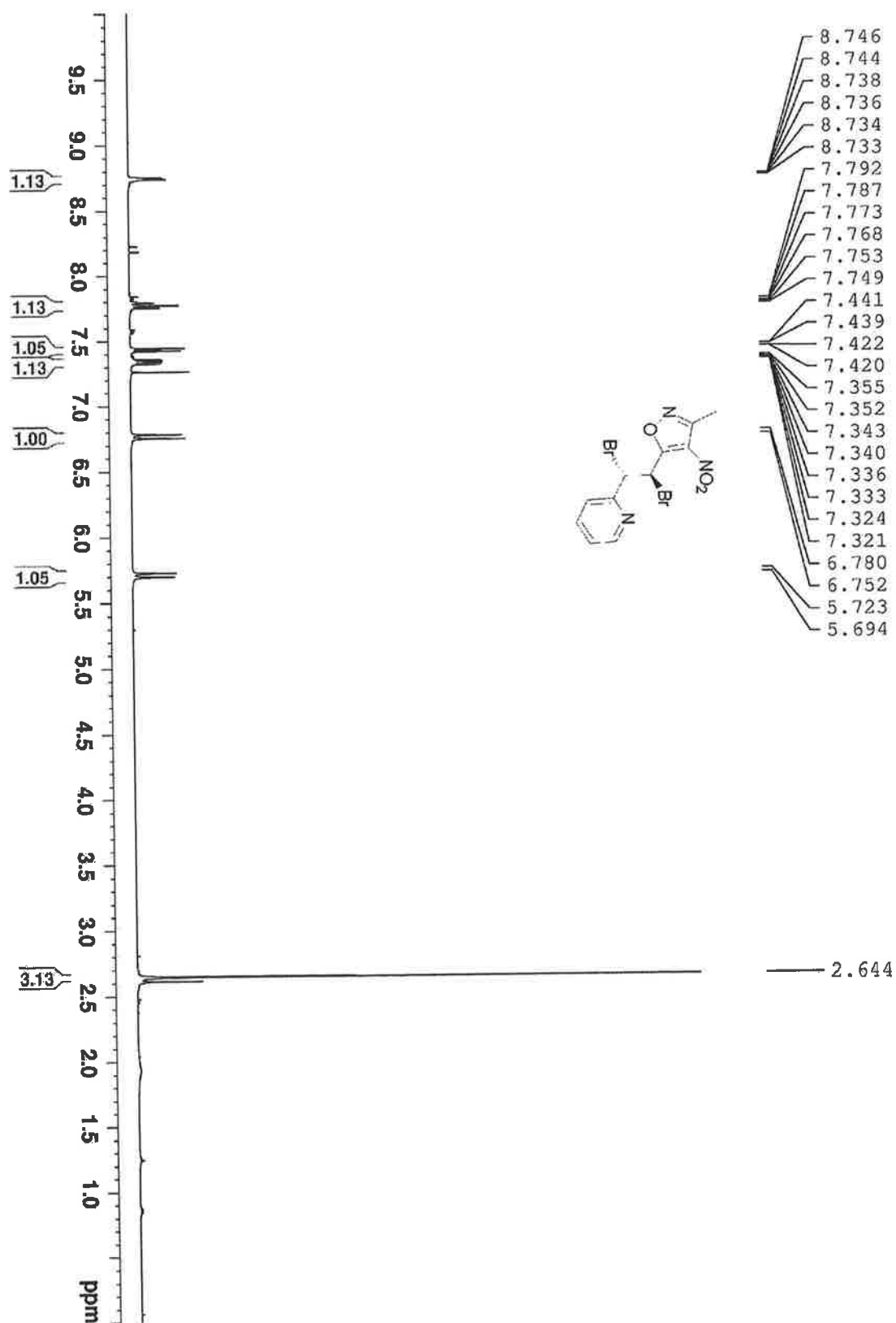
Compound 344c



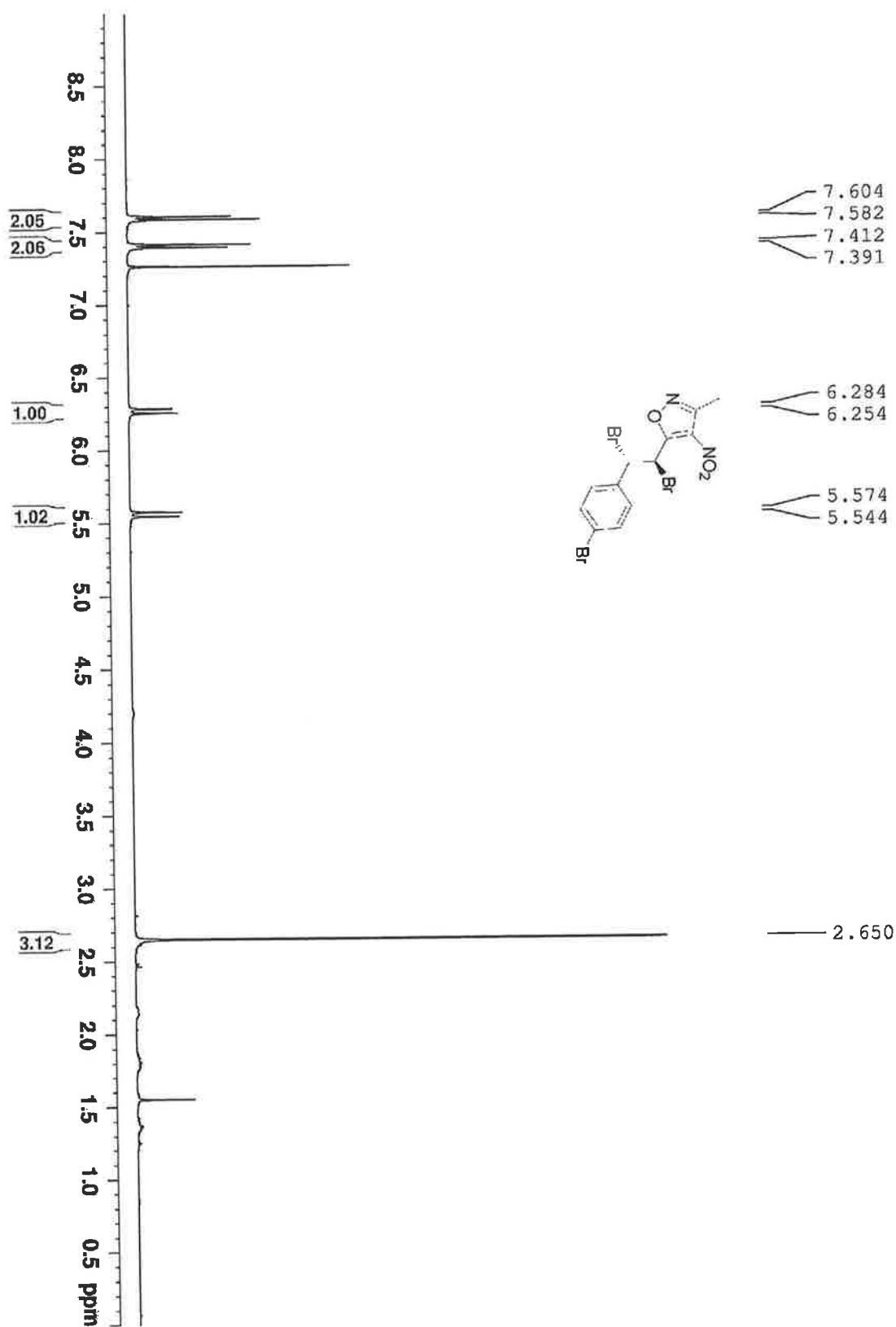
Compound 344i



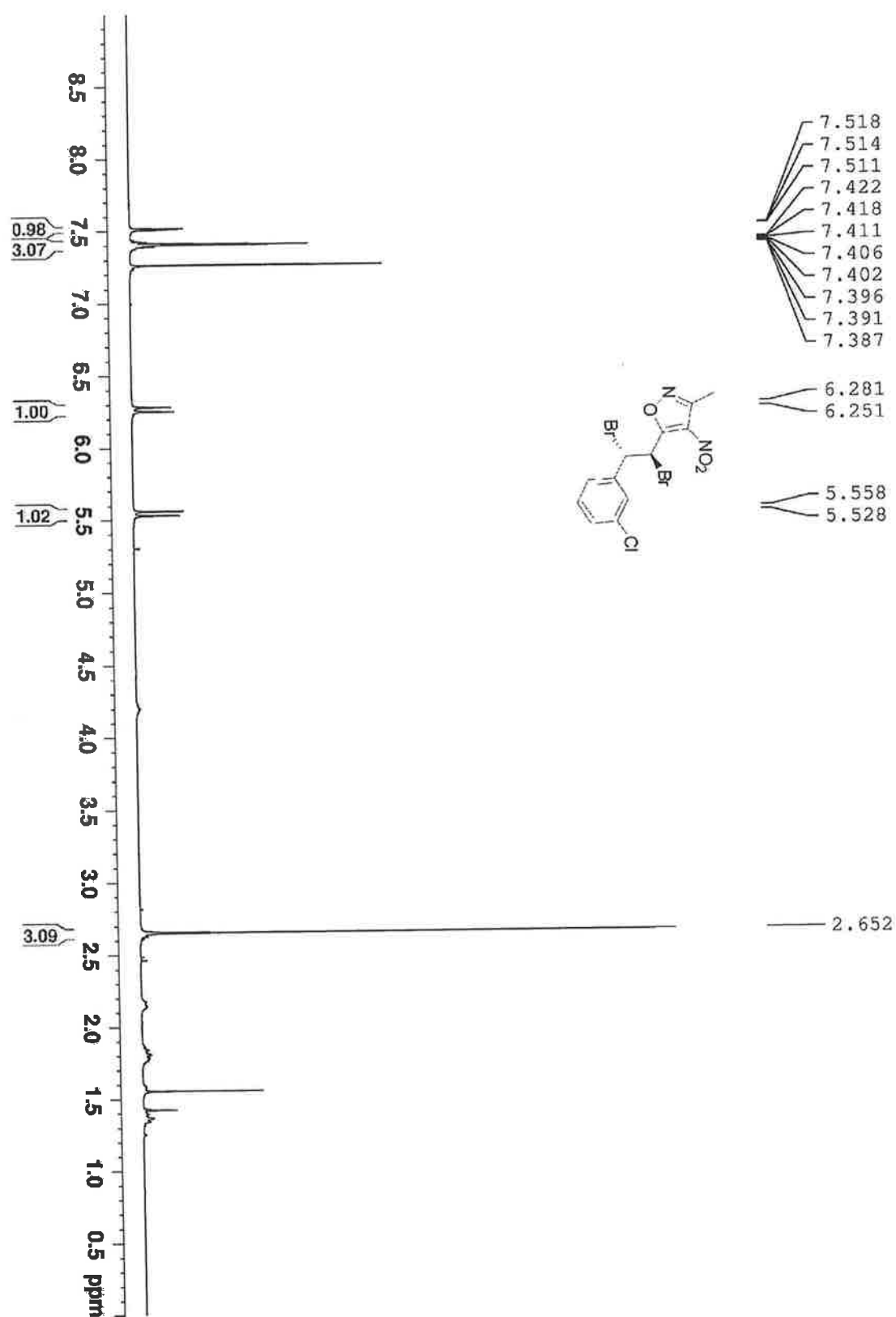
Compound 344f



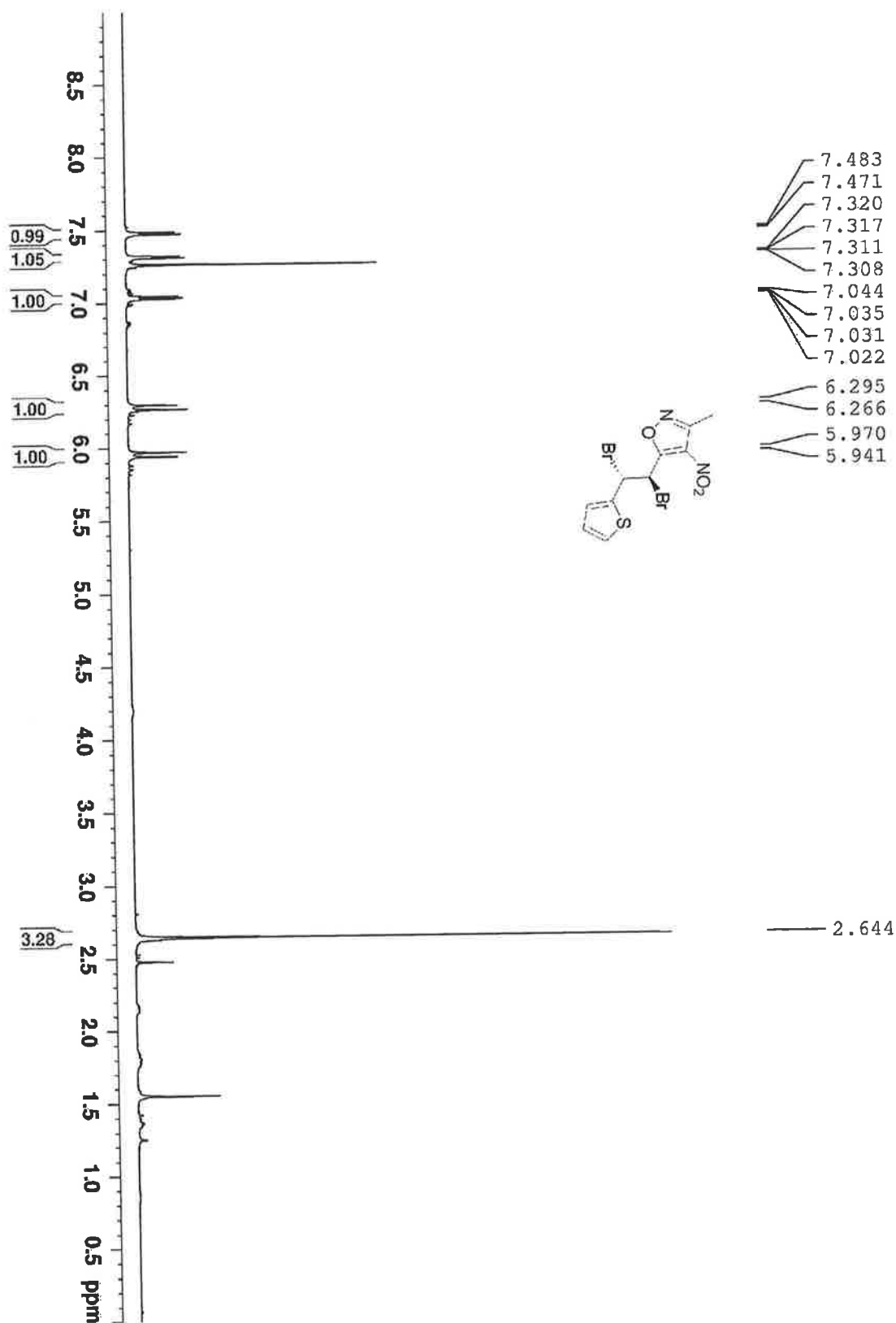
Compound 344d



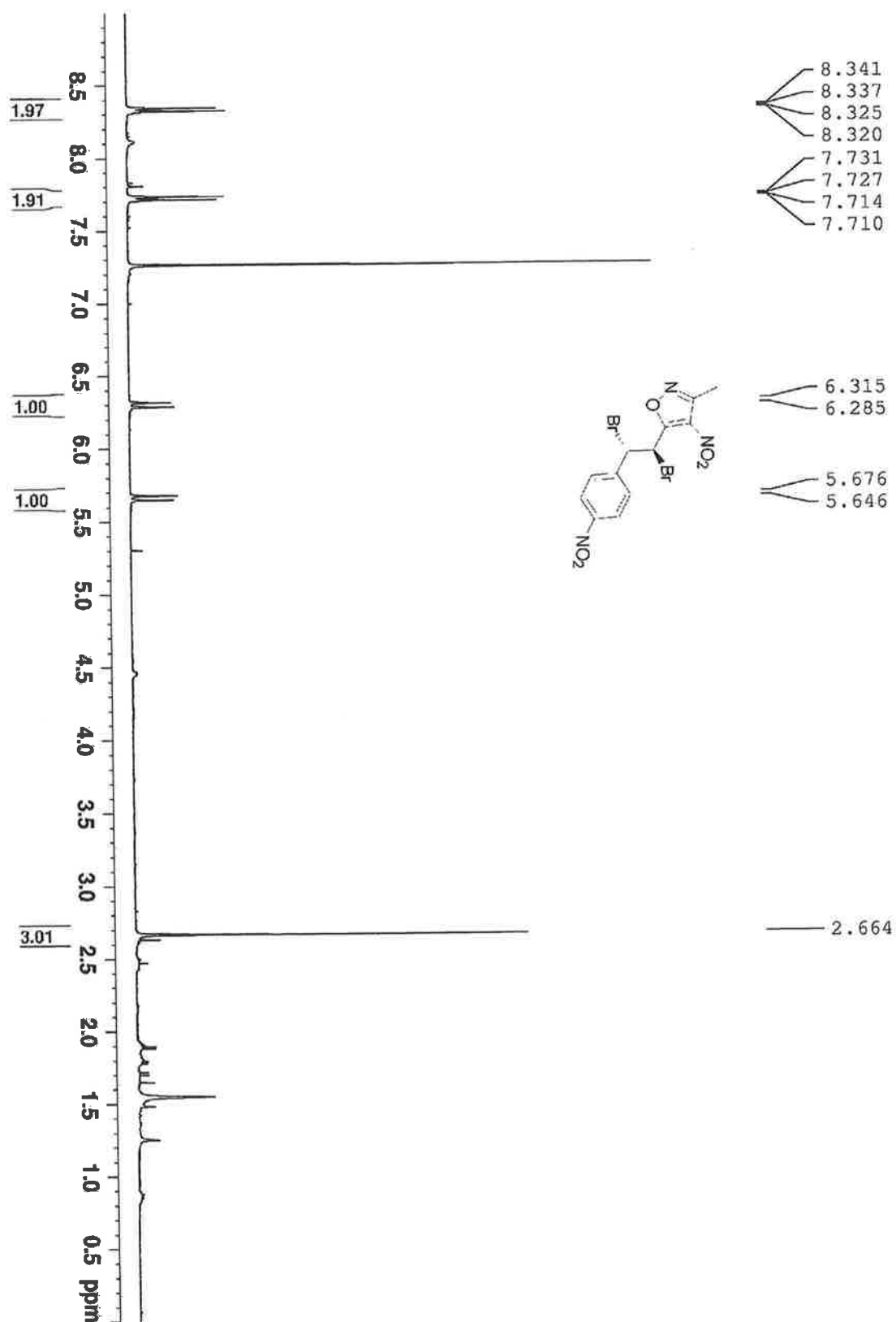
Compound 344e



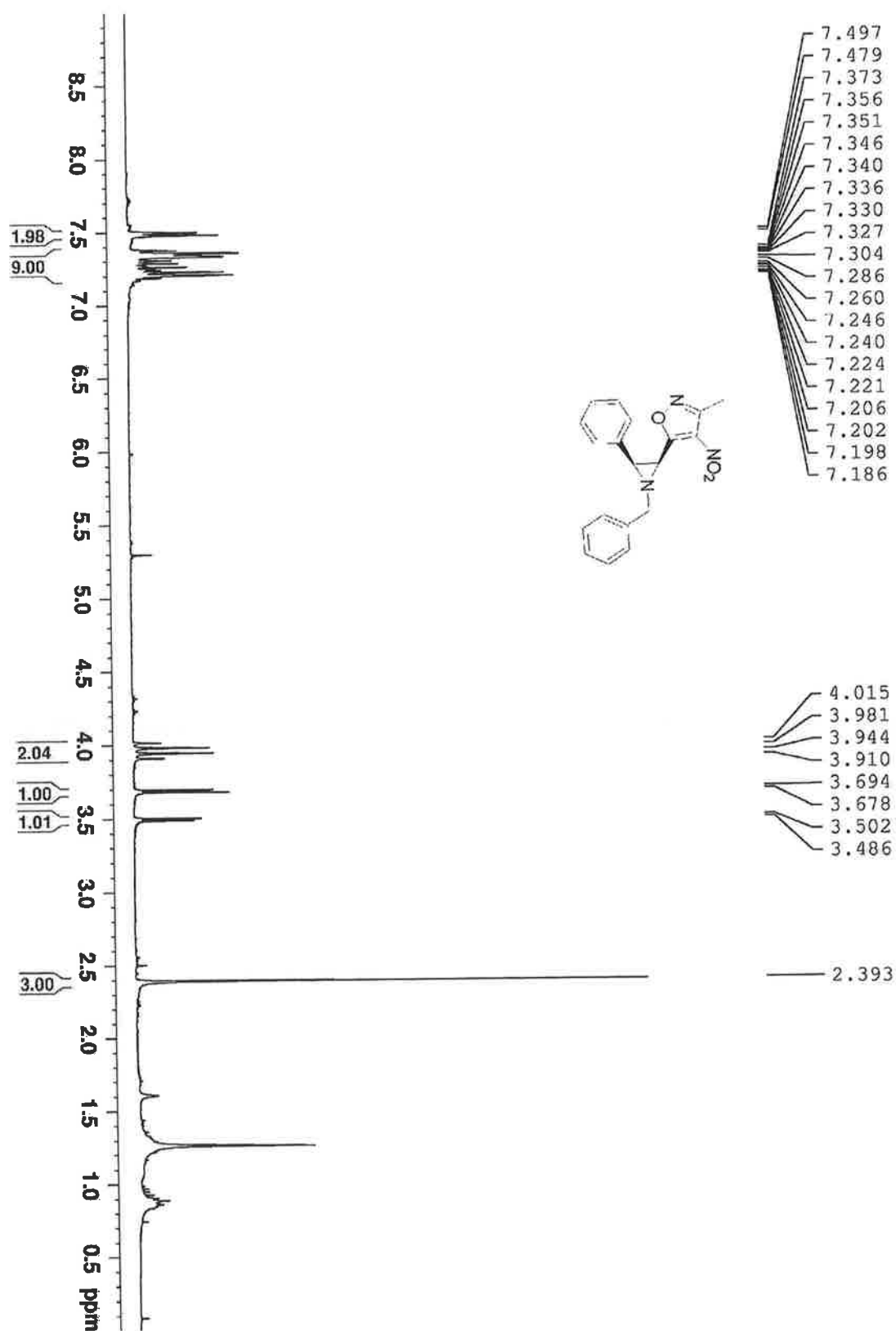
Compound 344k



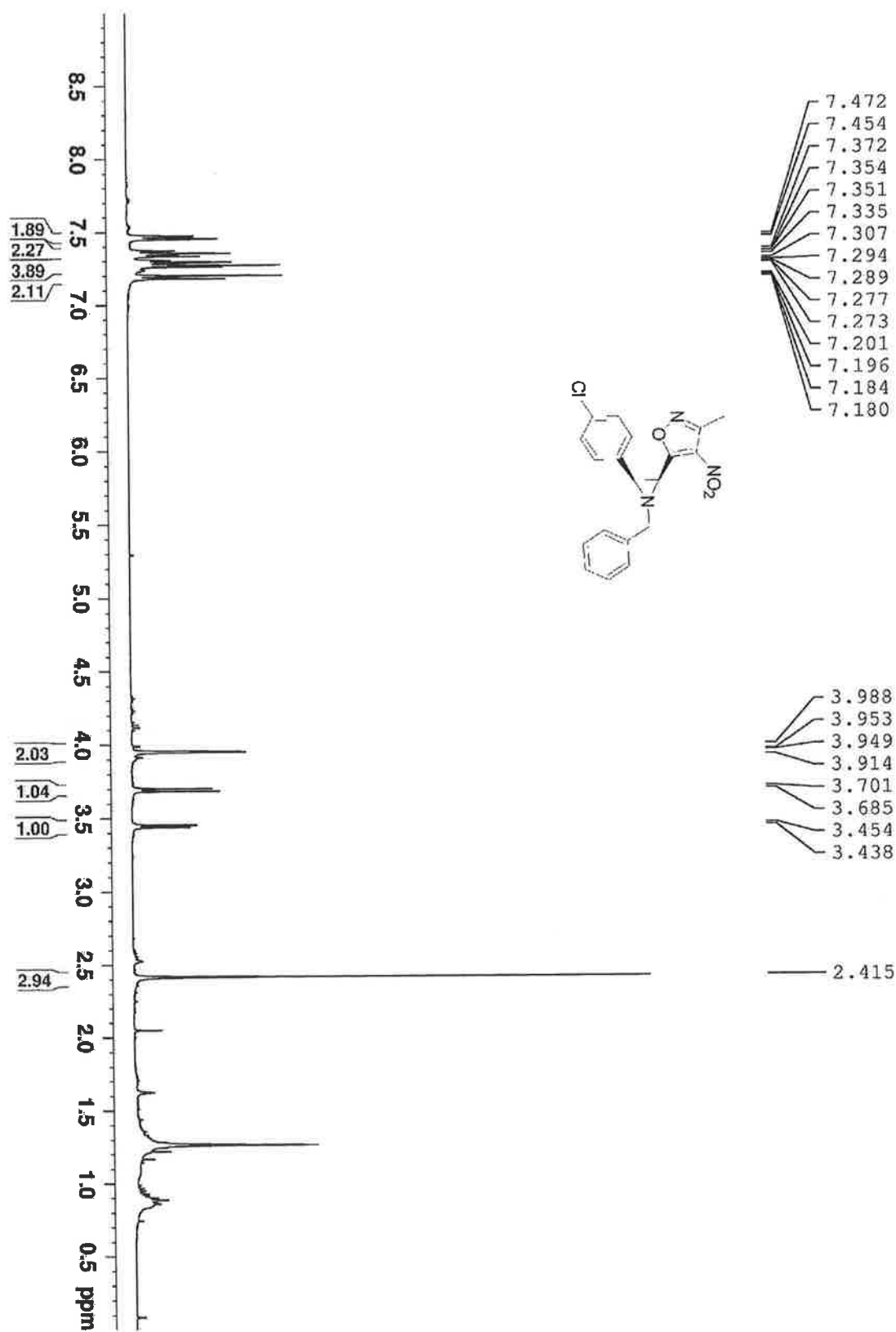
Compound 3441



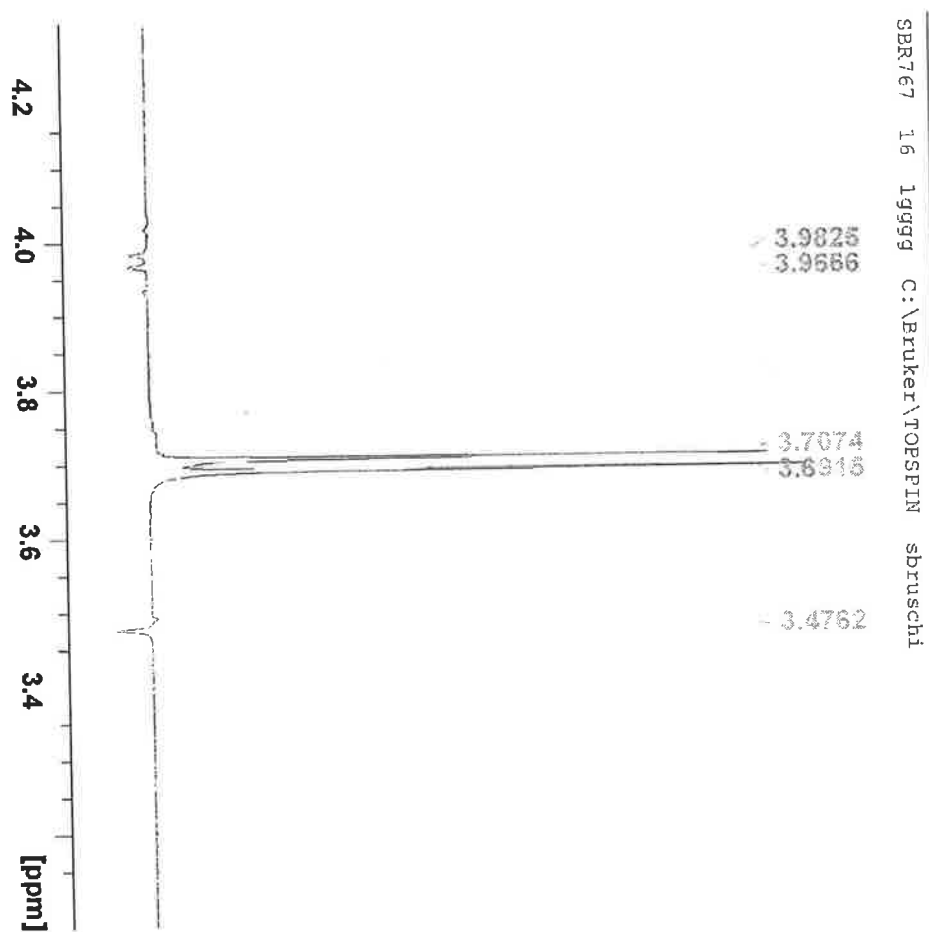
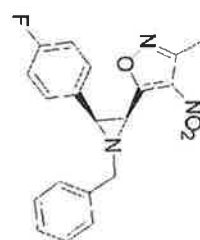
Compound 333a



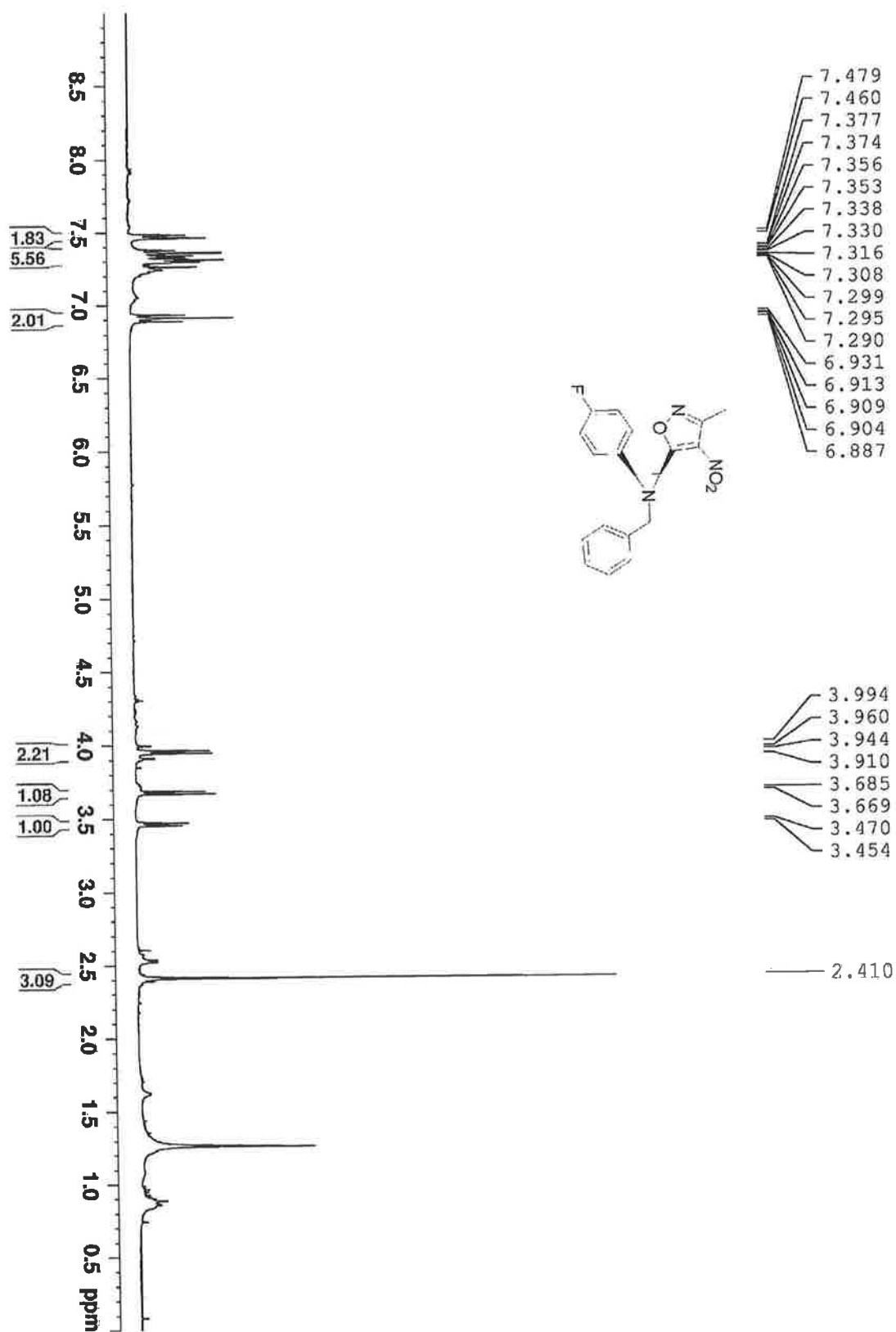
Compound 333b



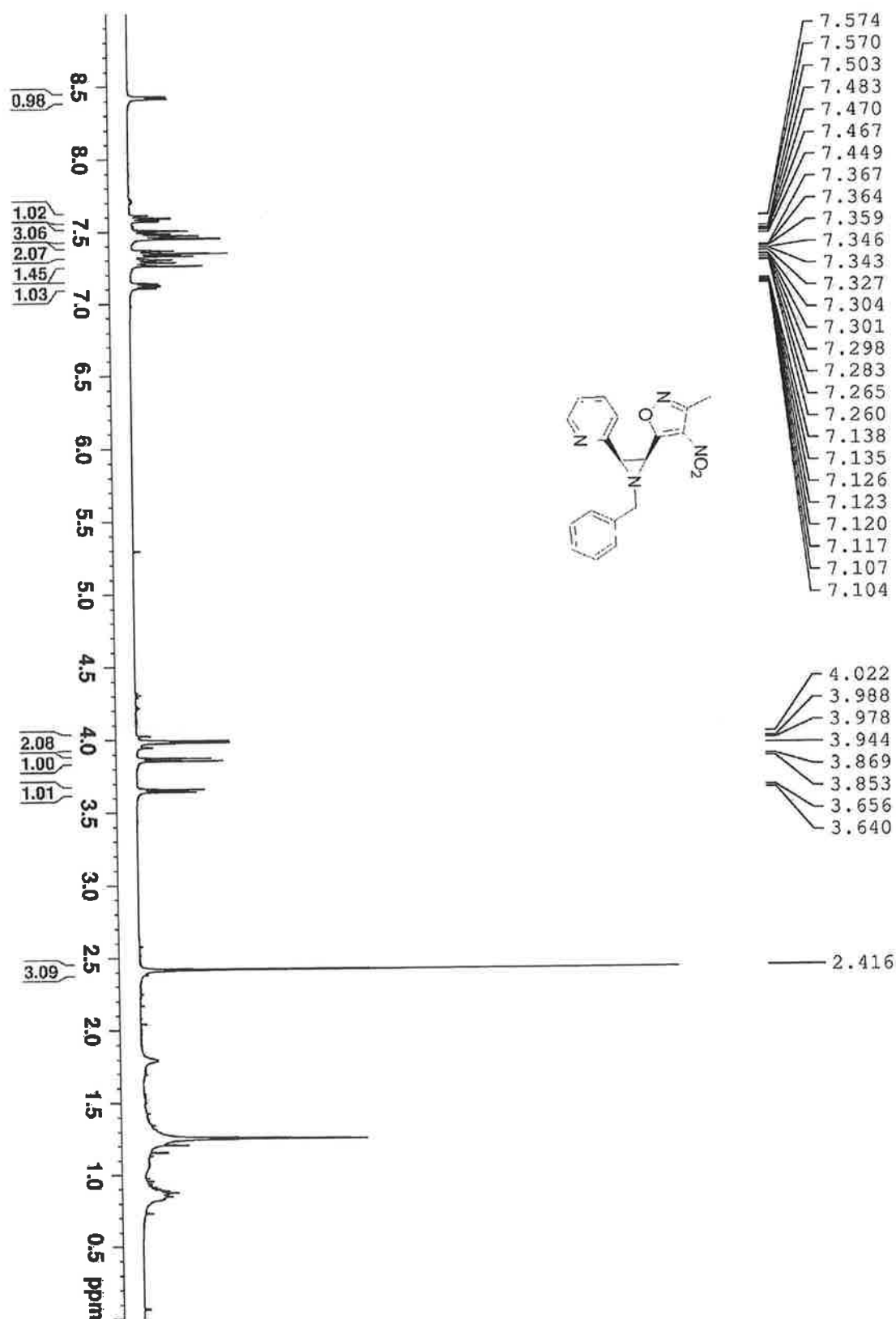
Compound 333c n.O.e.



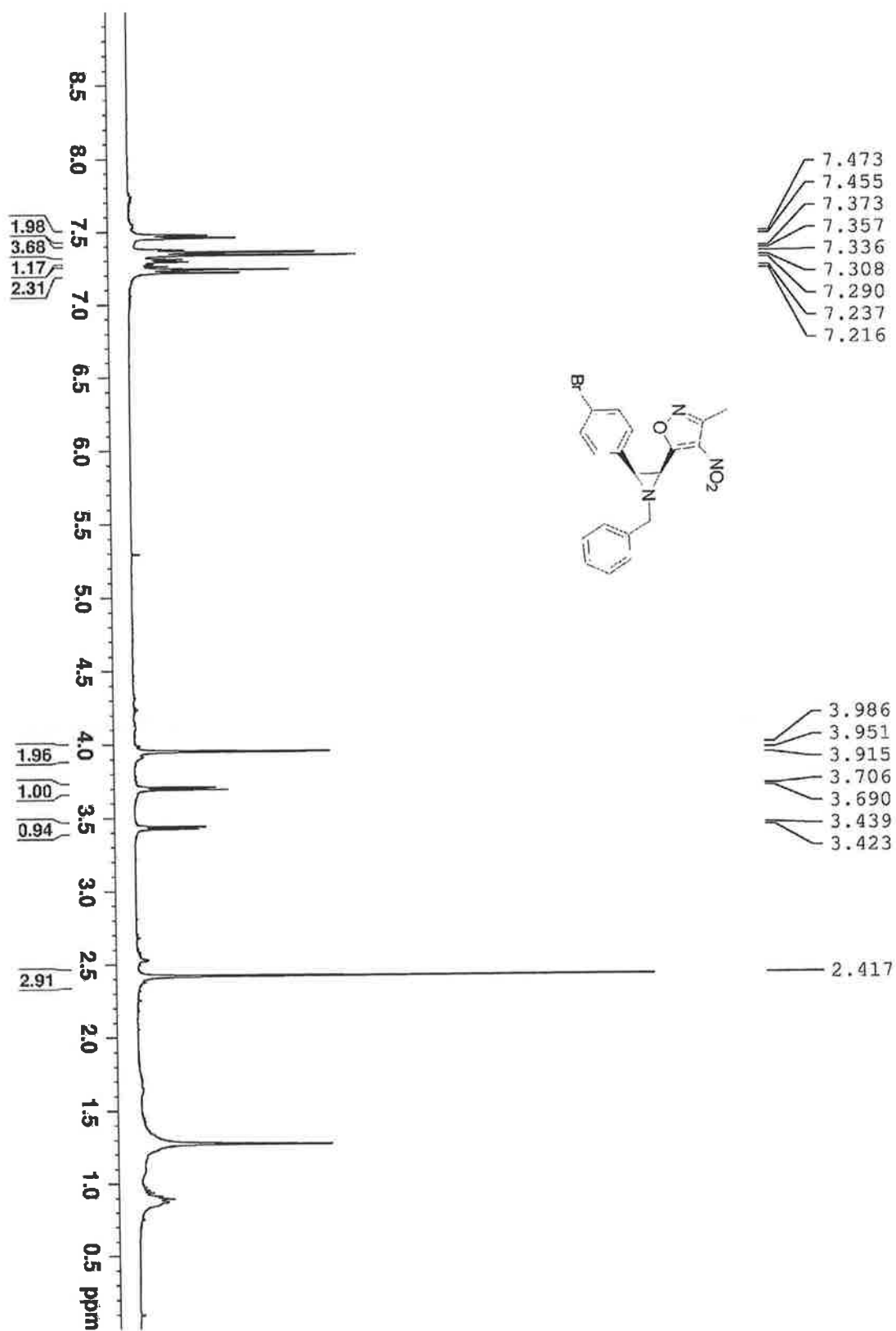
Compound 333c



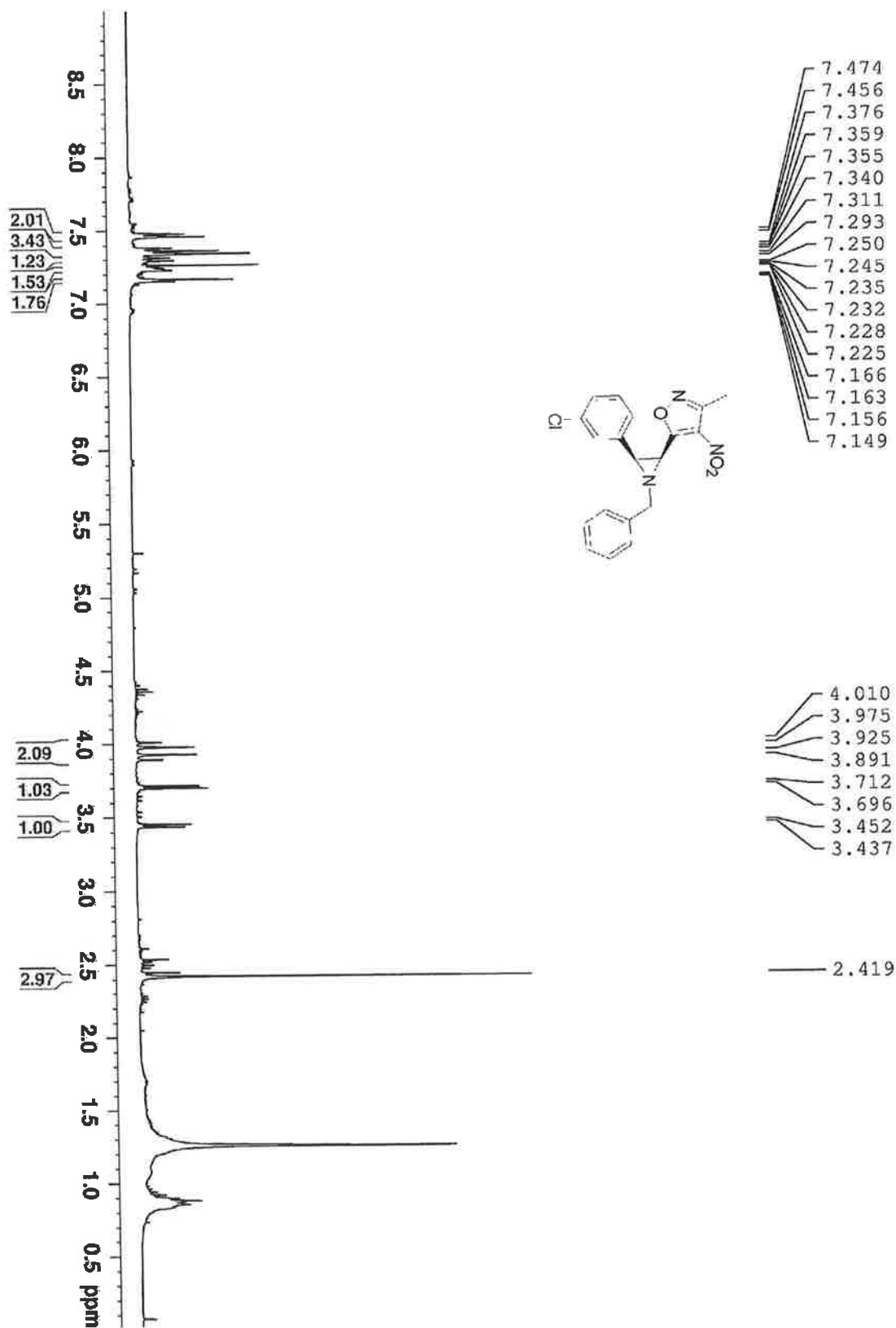
Compound 333f



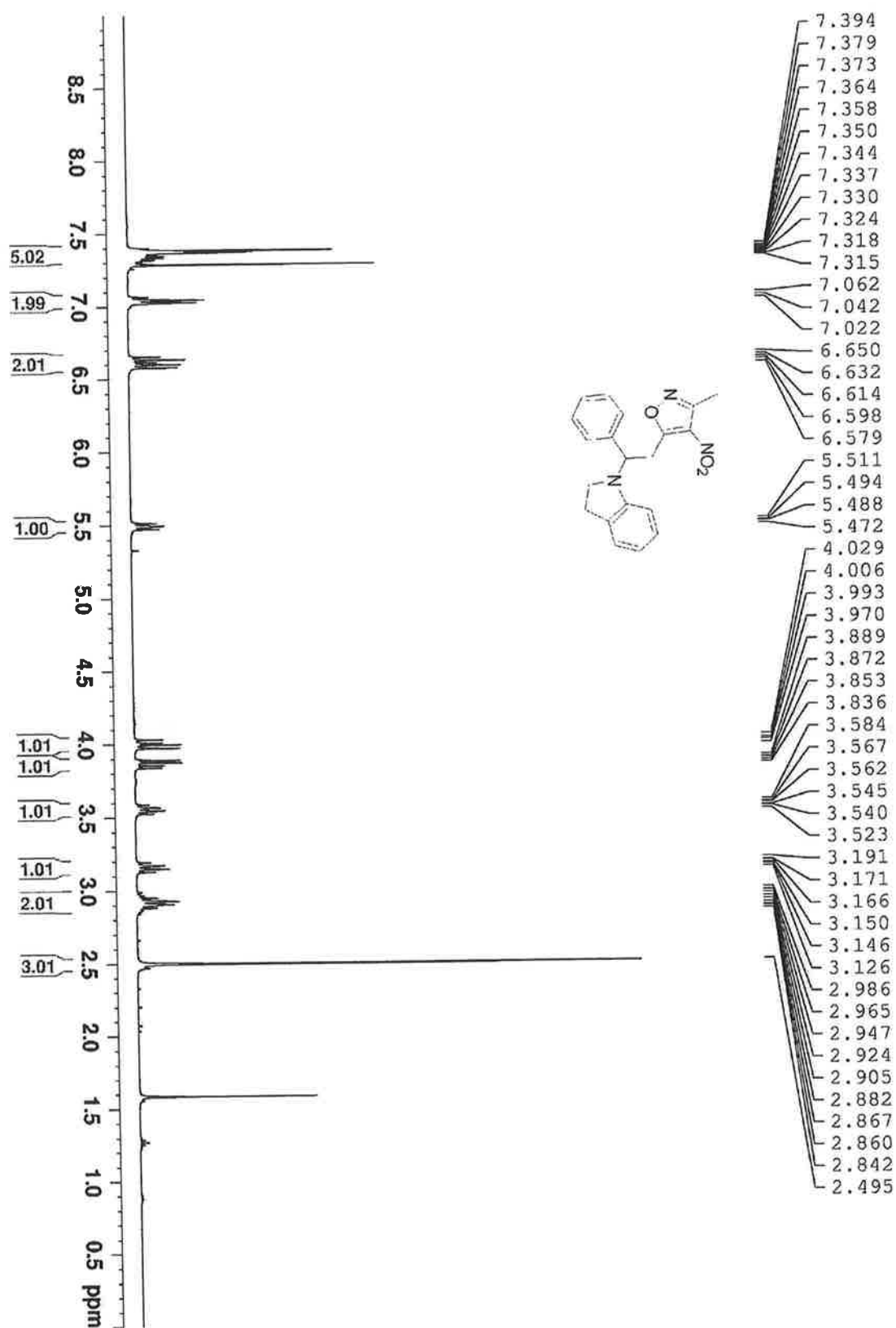
Compound 333d



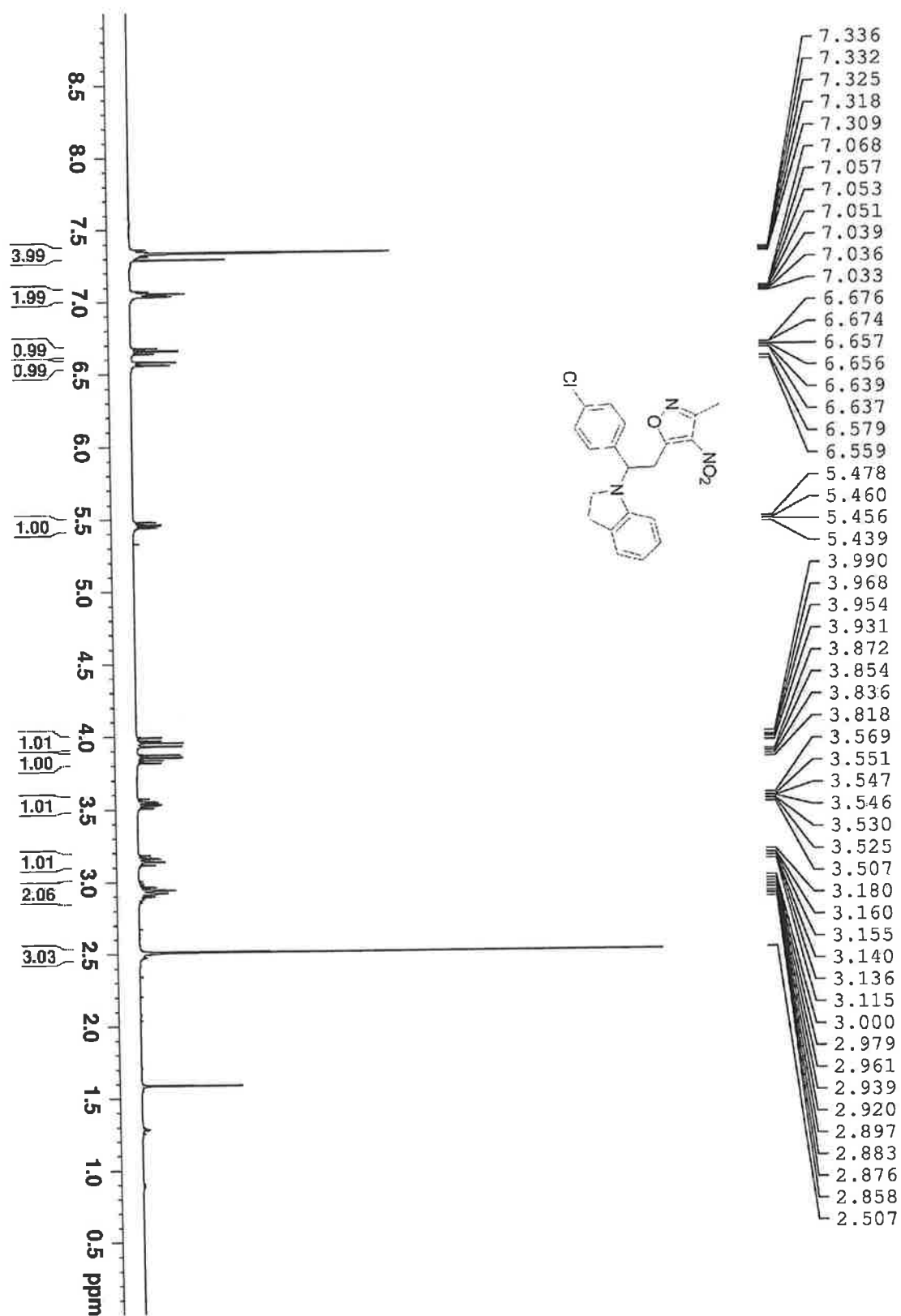
Compound 333e



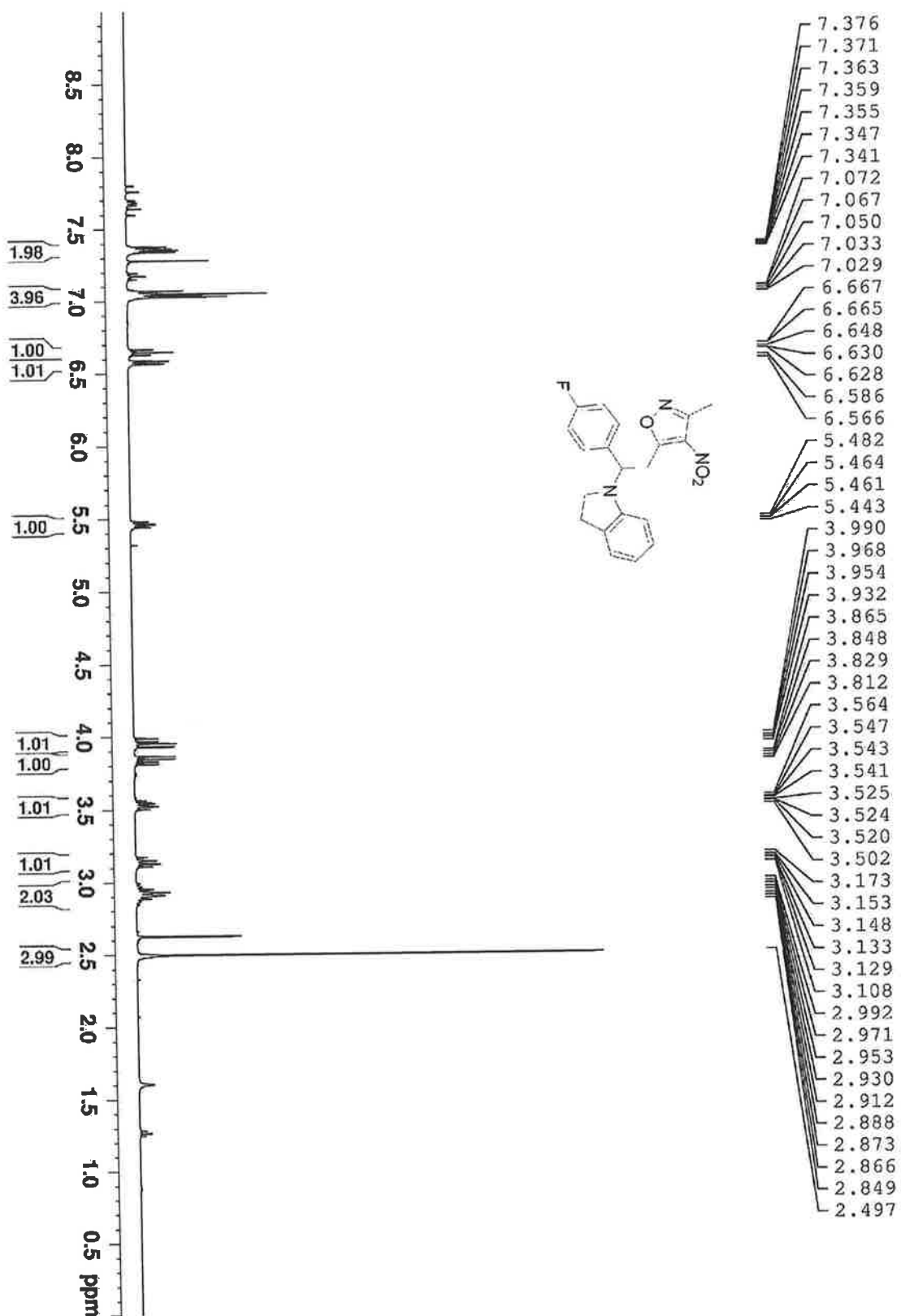
Compound 334a



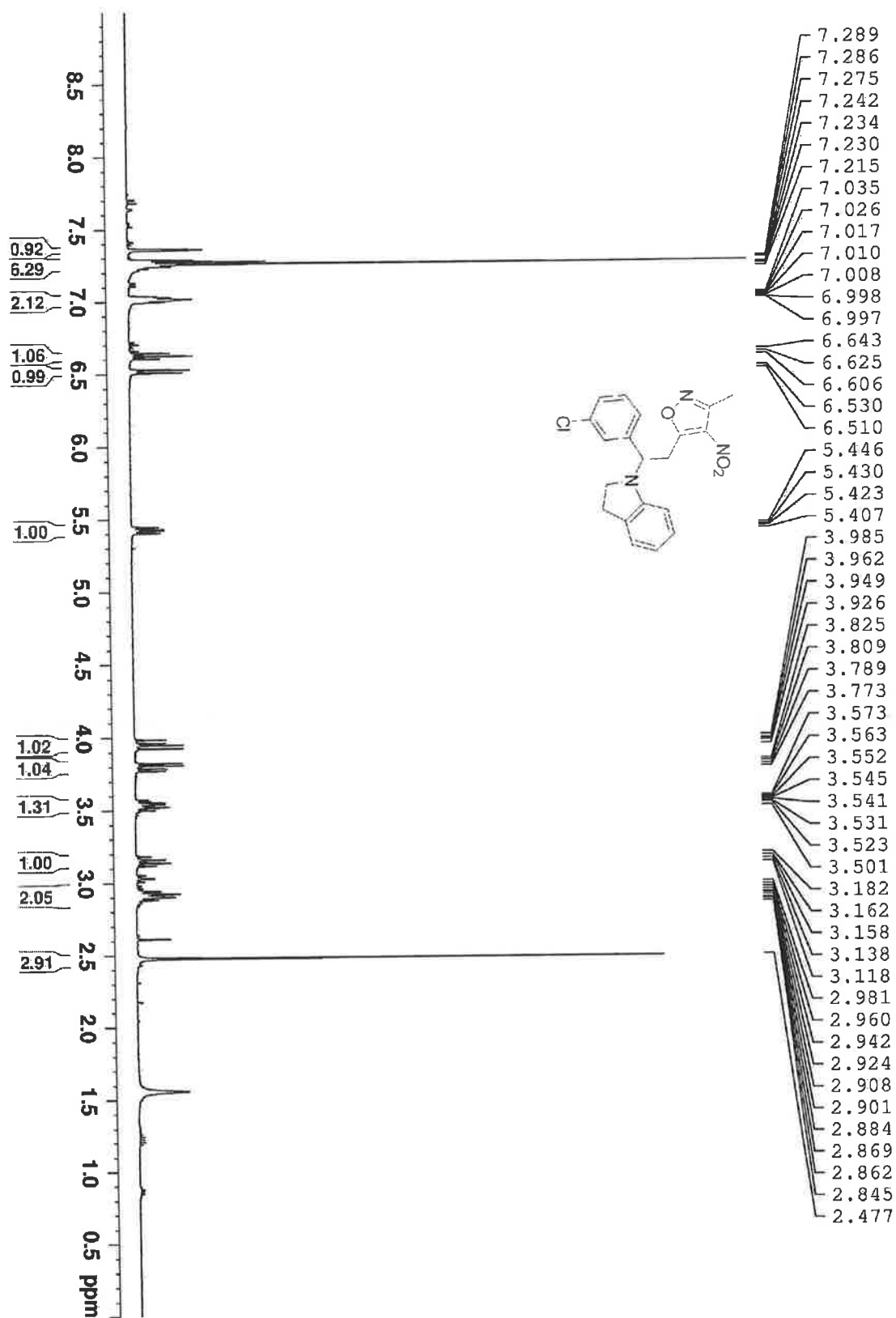
Compound 334b



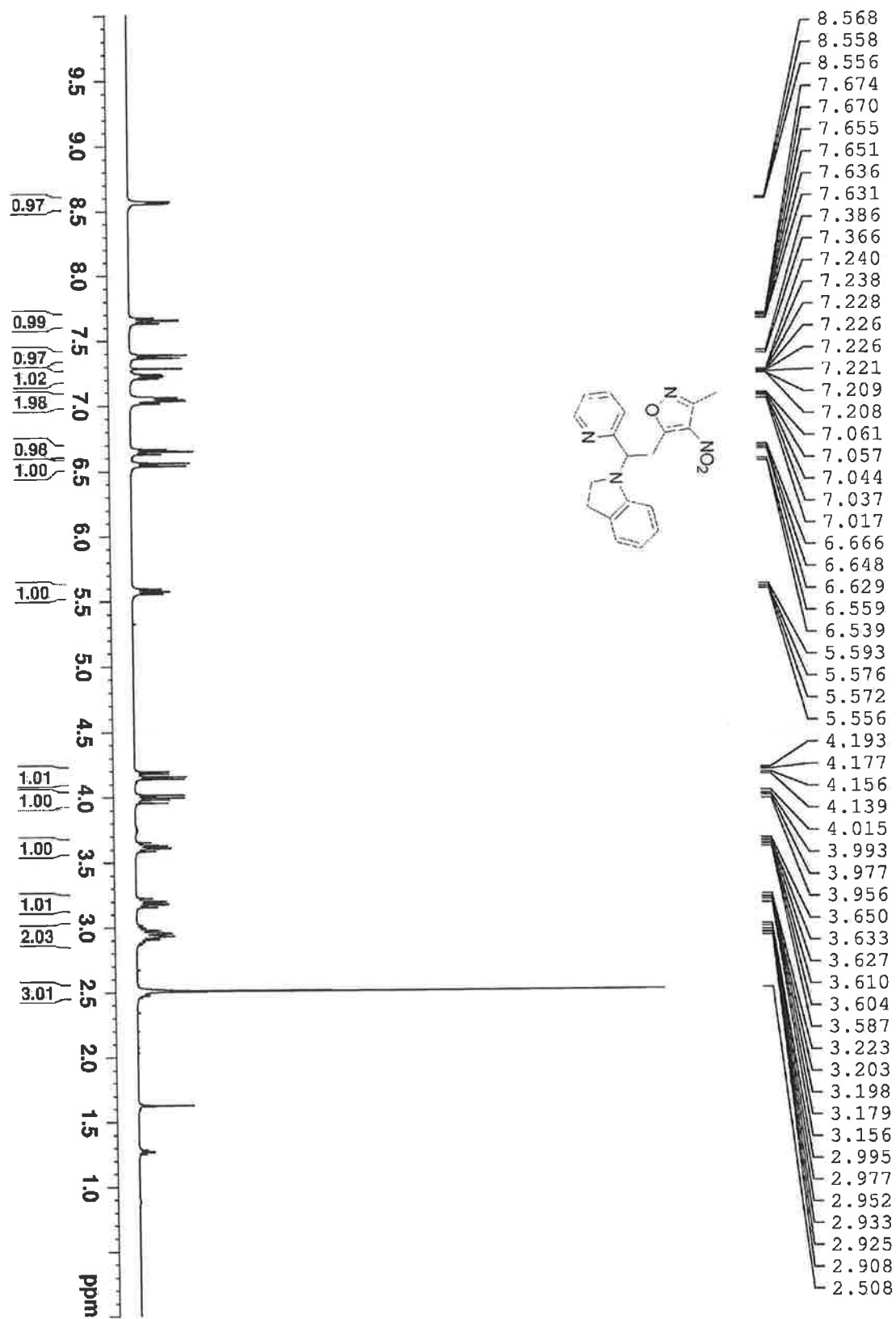
Compound 334c



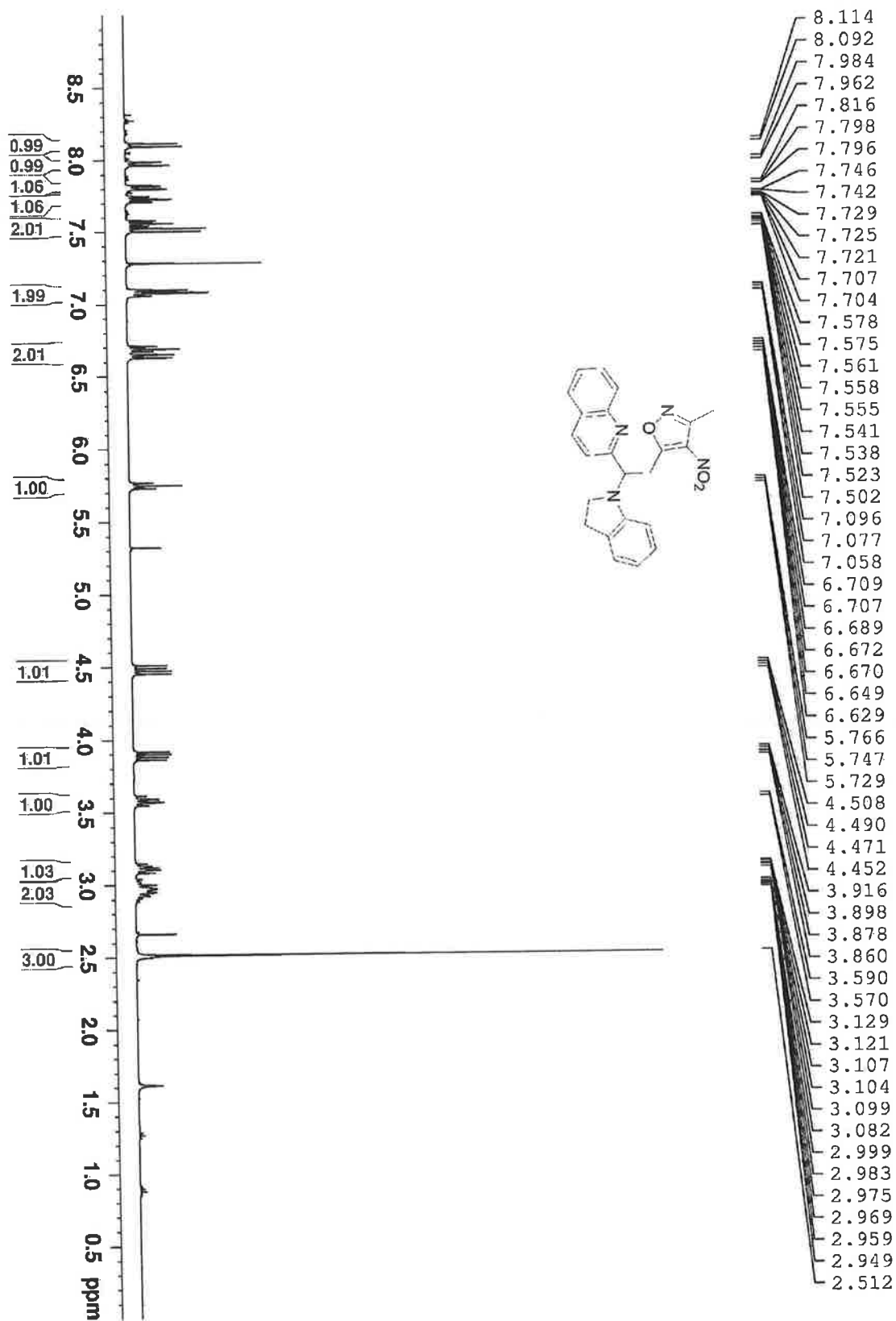
Compound 334e



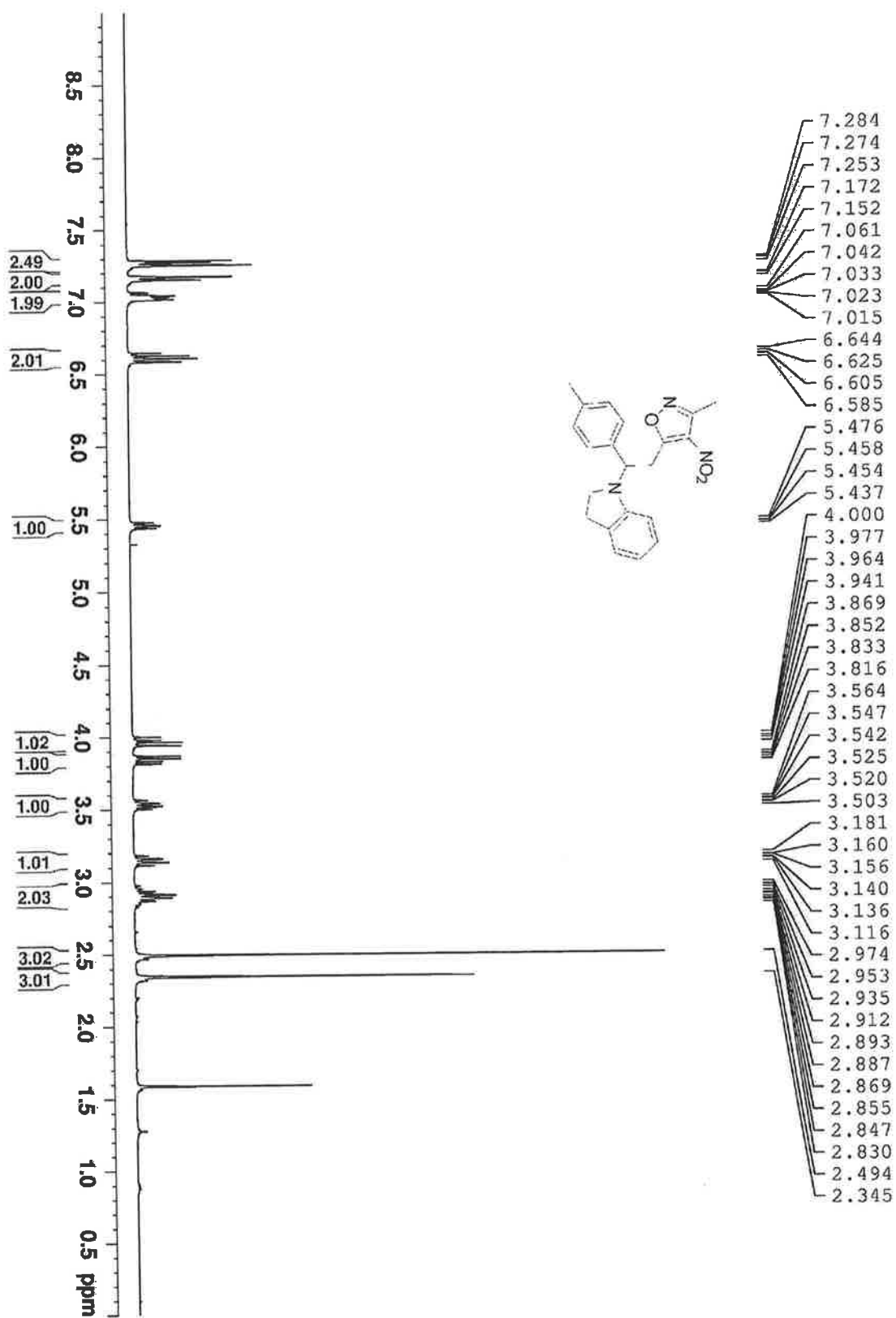
Compound 334f



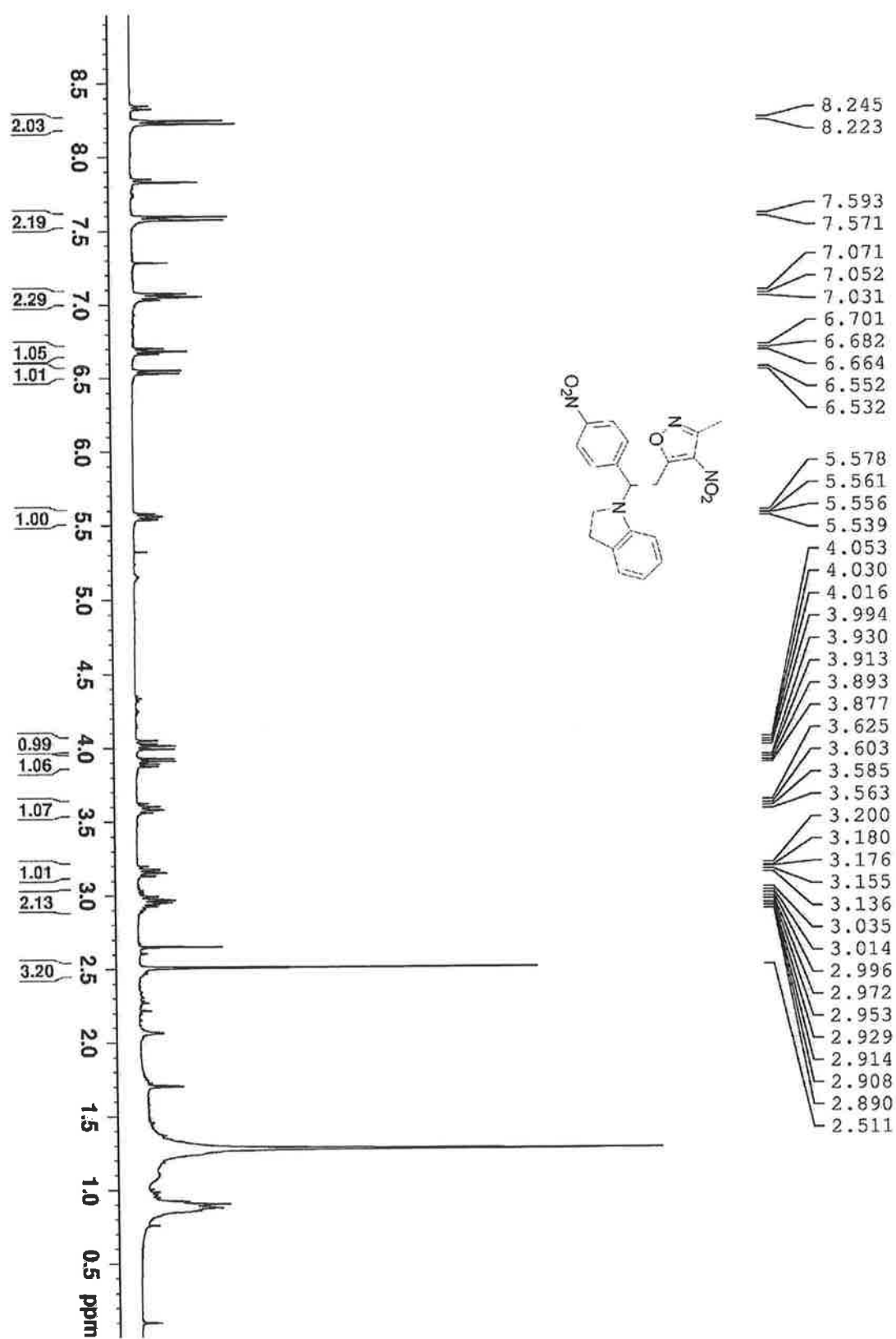
Compound 334i



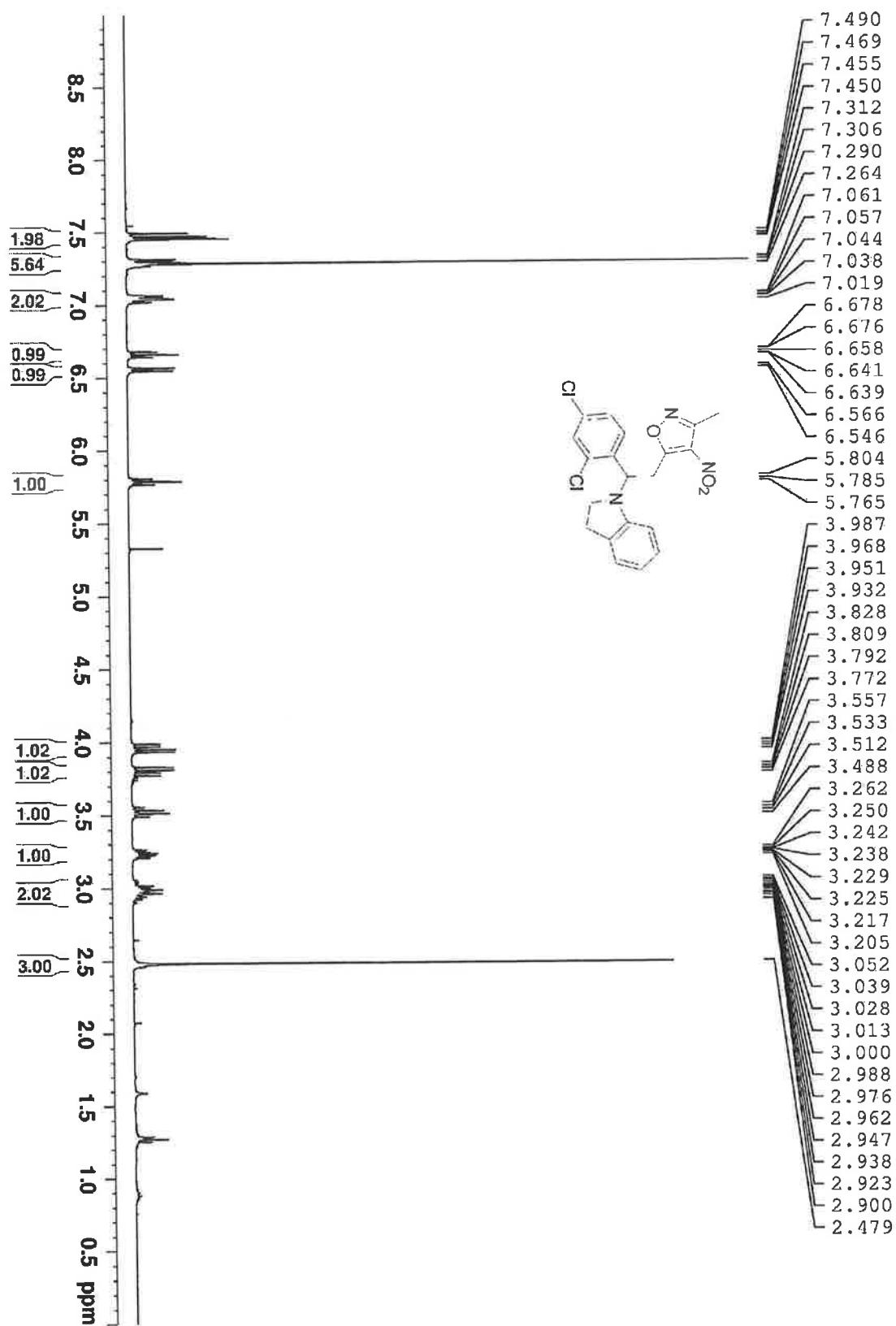
Compound 334j



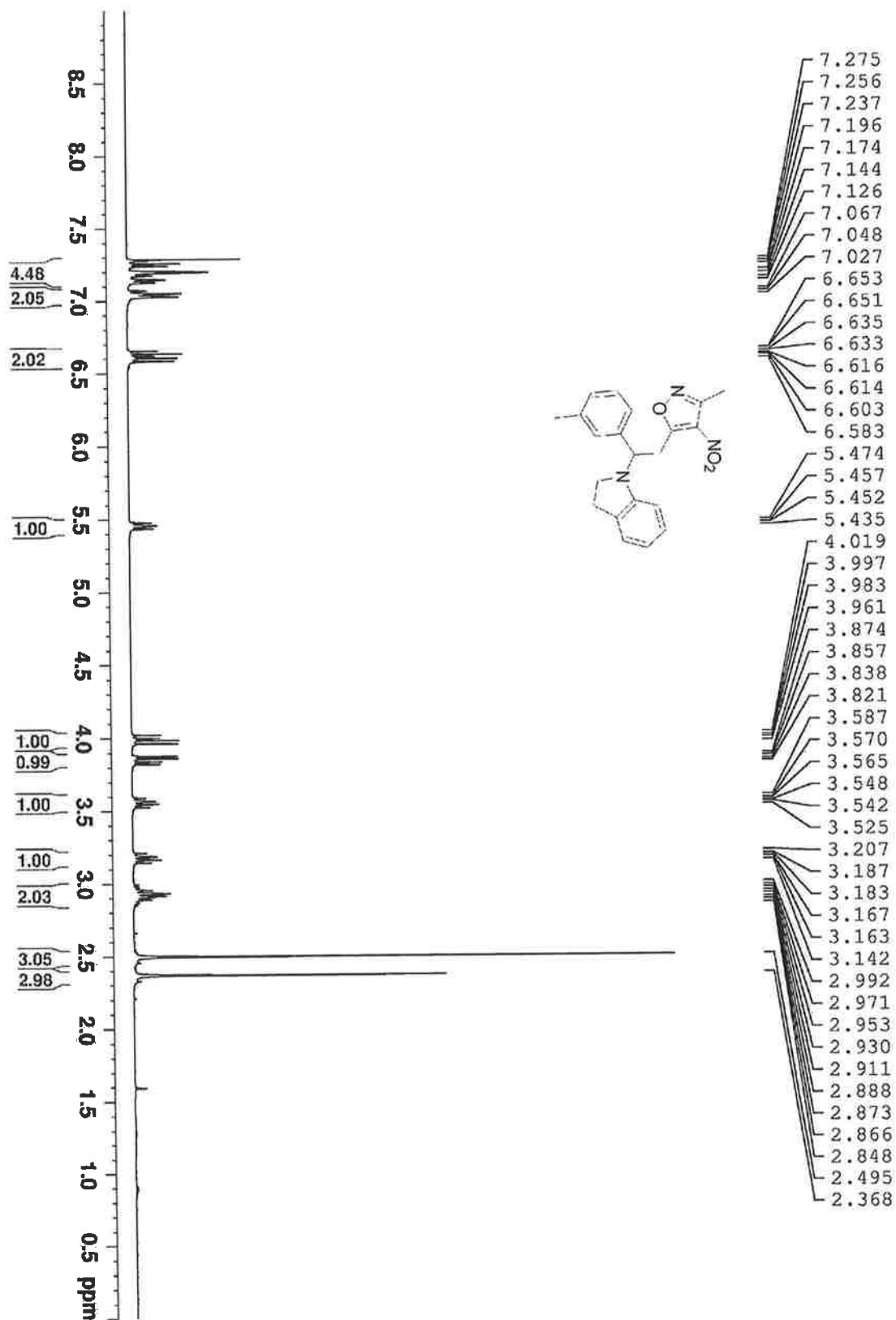
Compound 3341



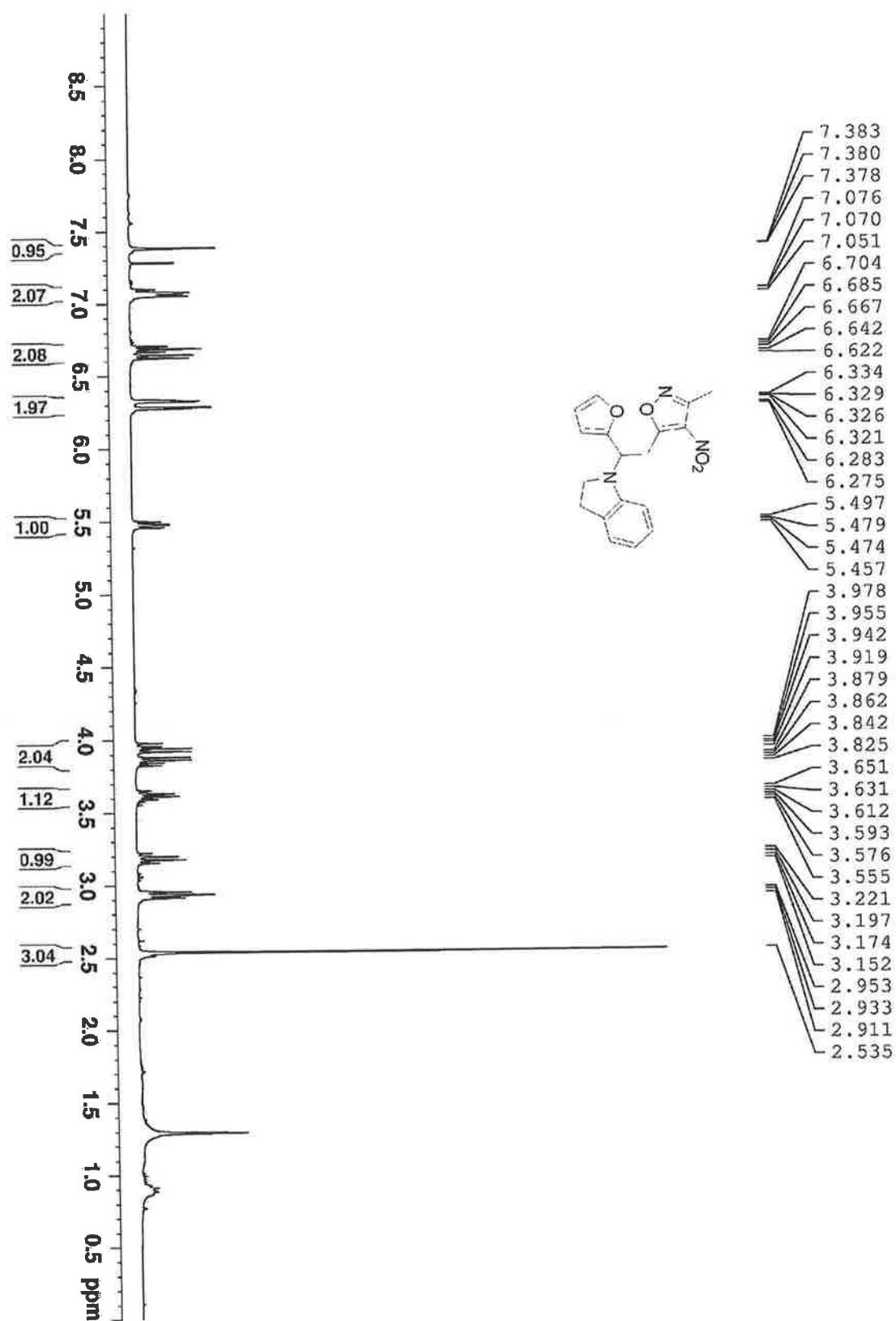
Compound 334m



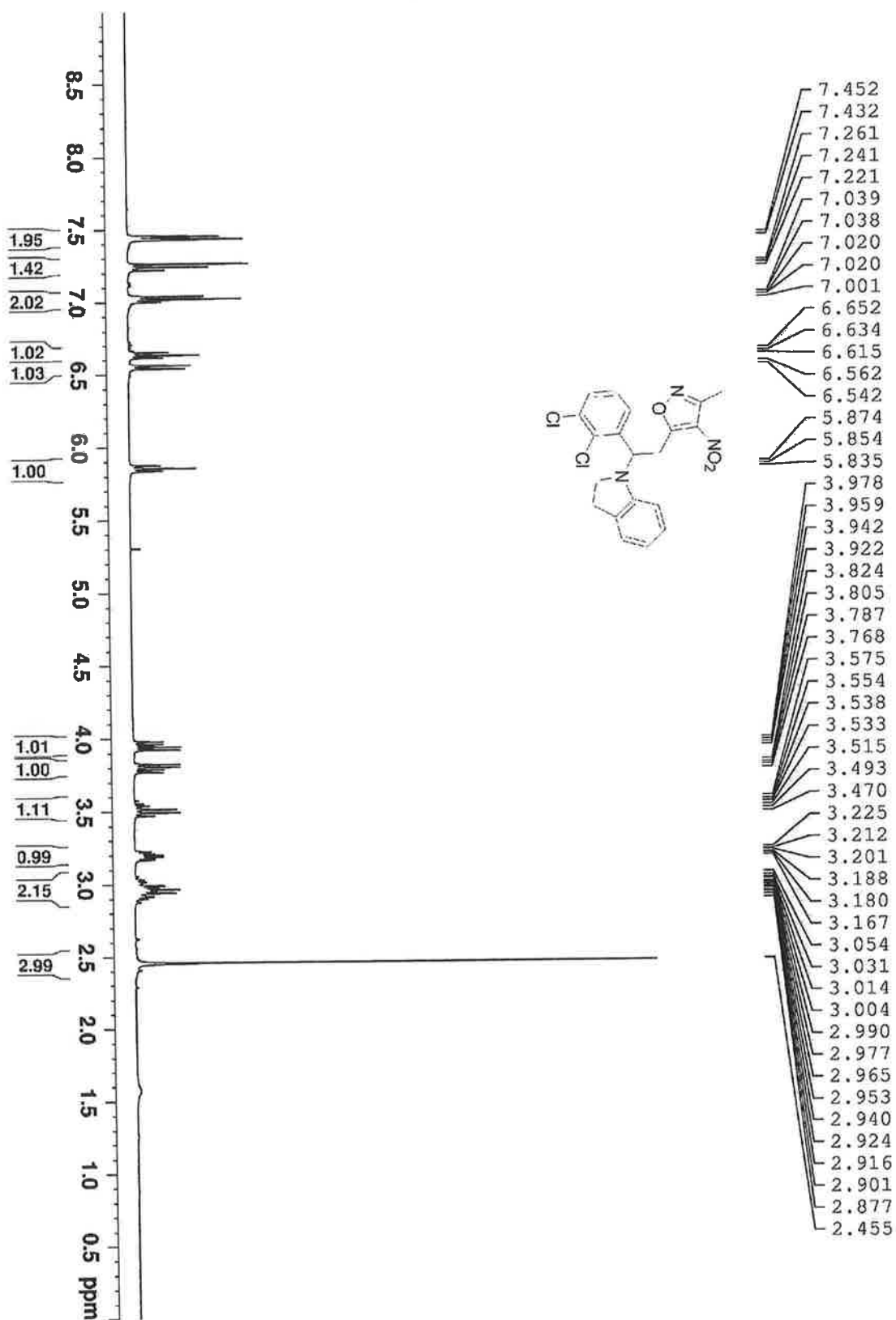
Compound 334o



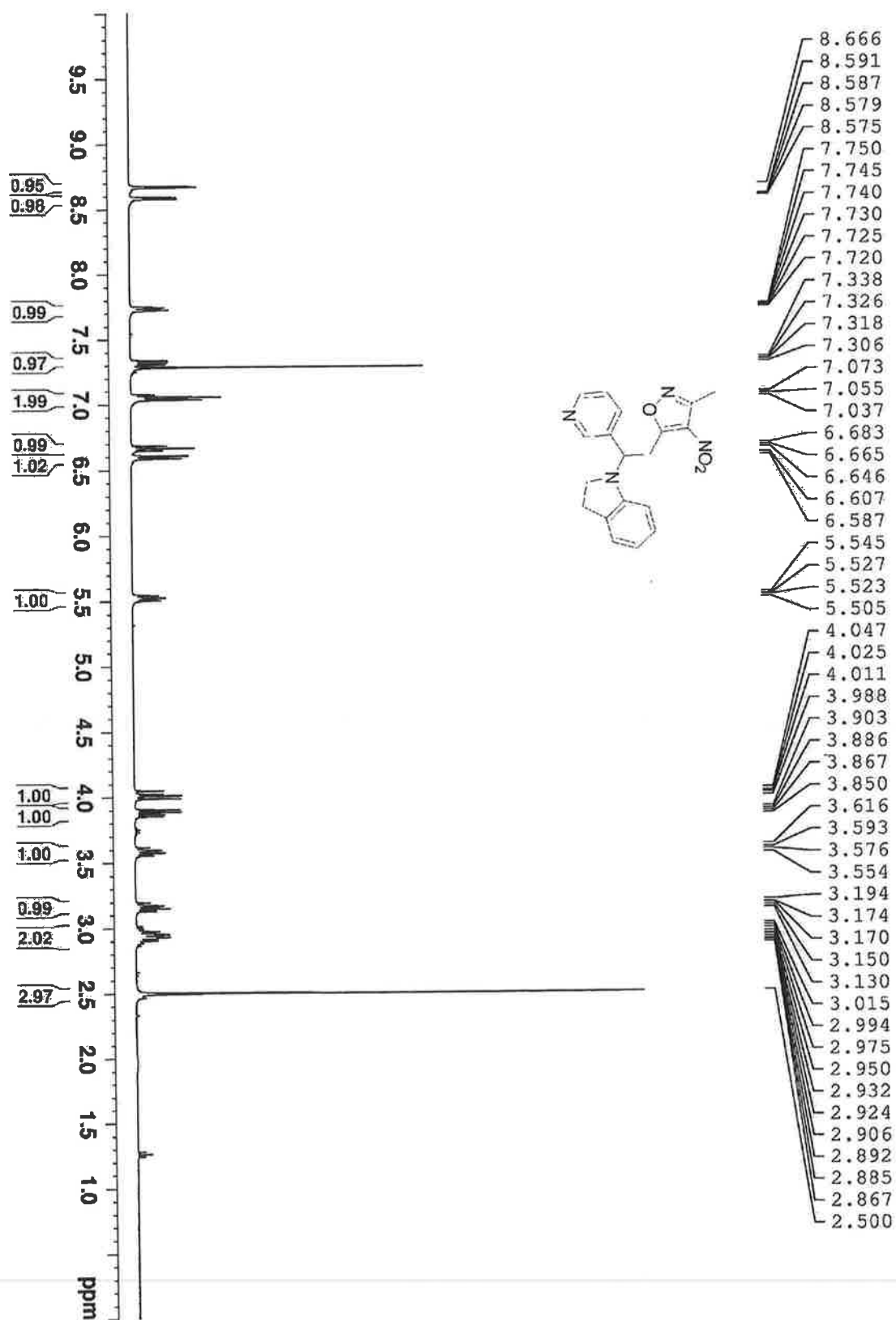
Compound 334p



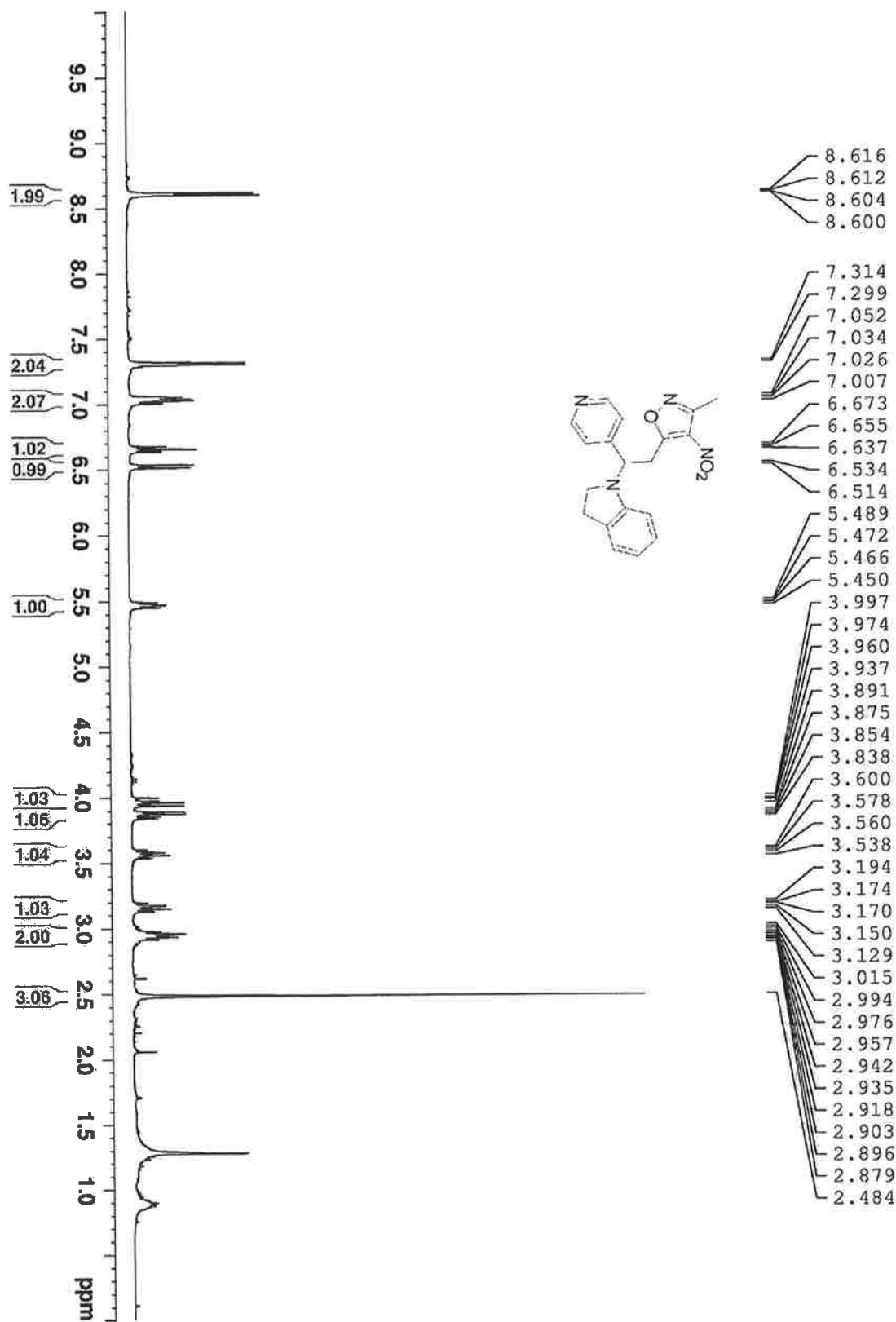
Compound 334q



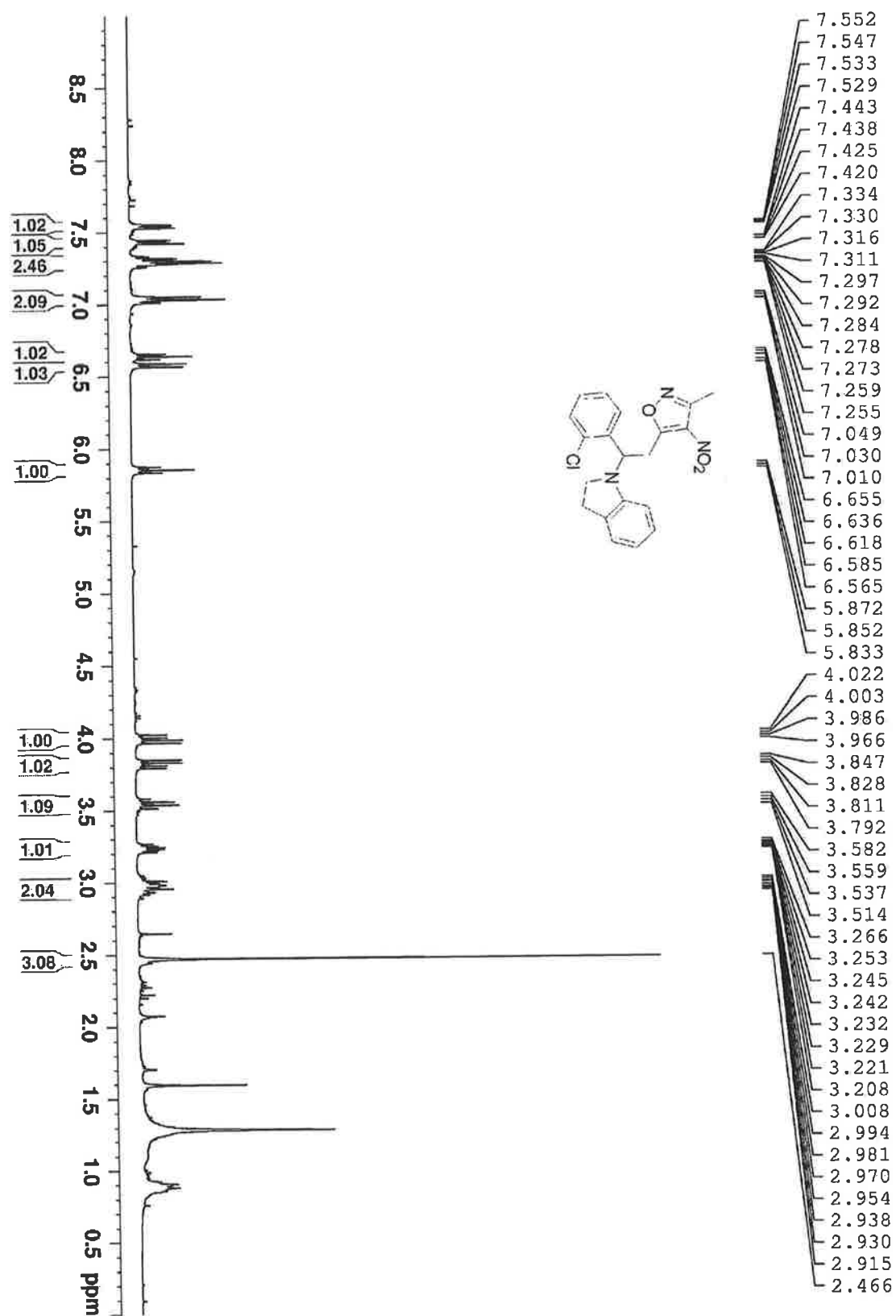
Compound 334r



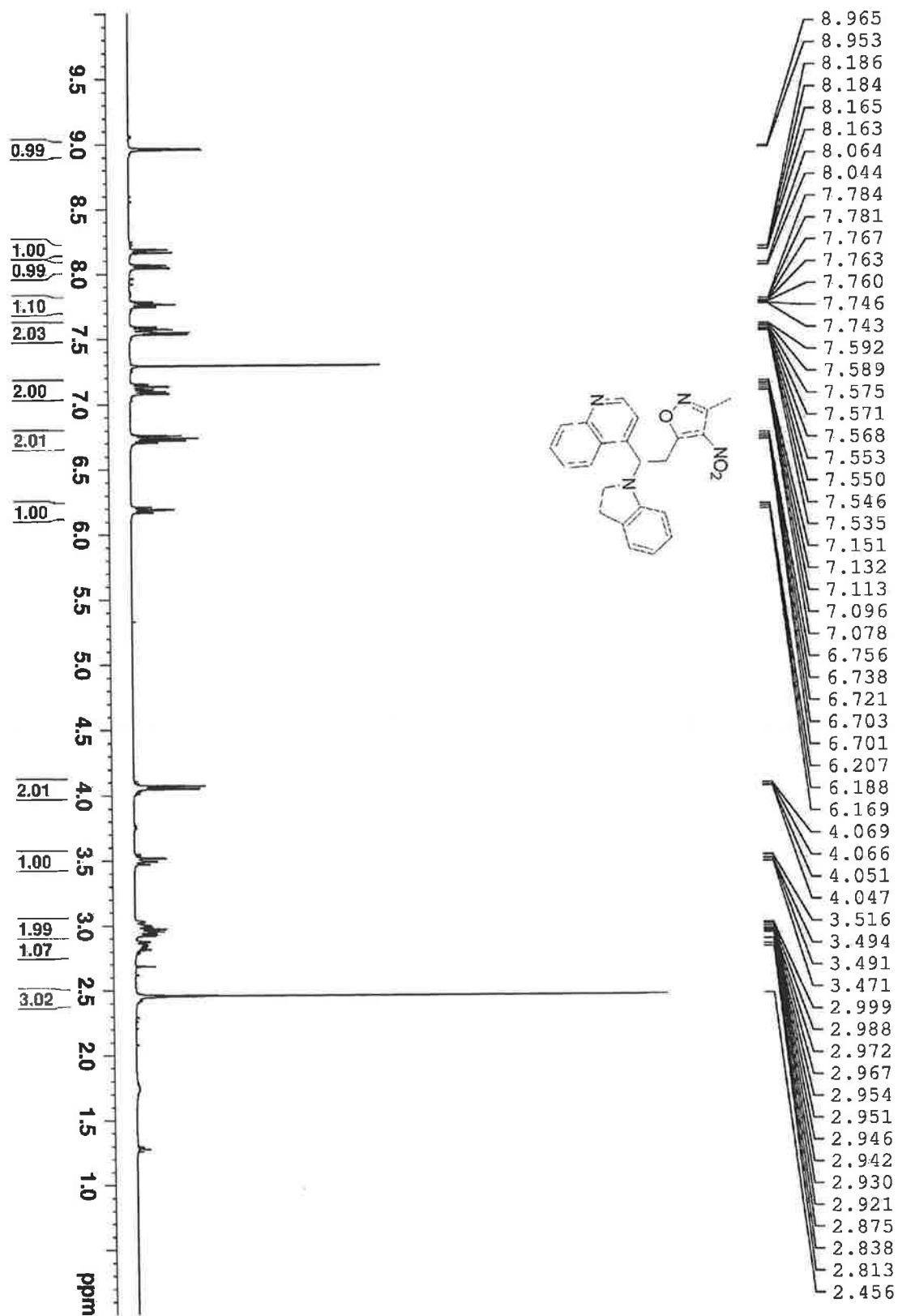
Compound 334s



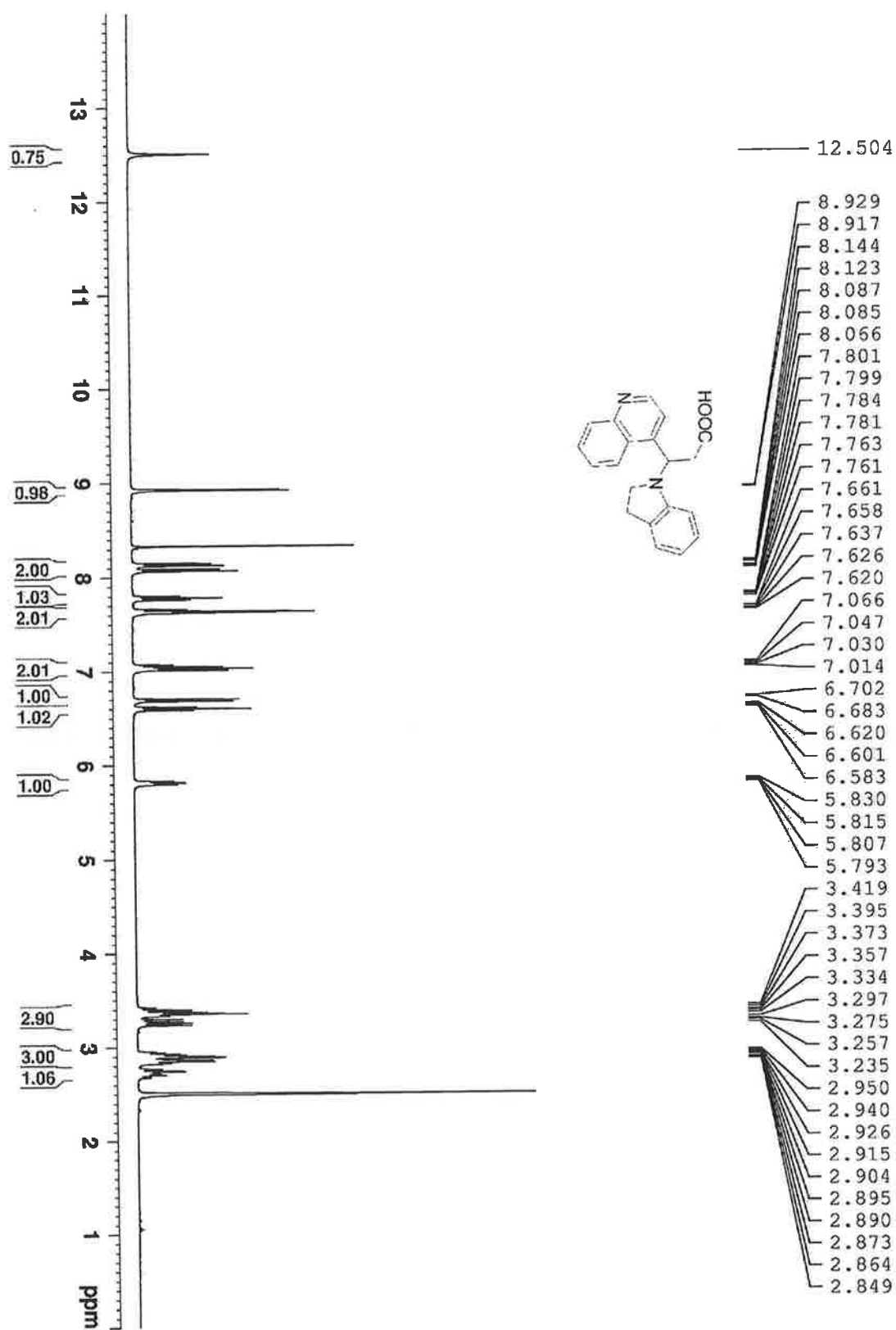
Compound 334t



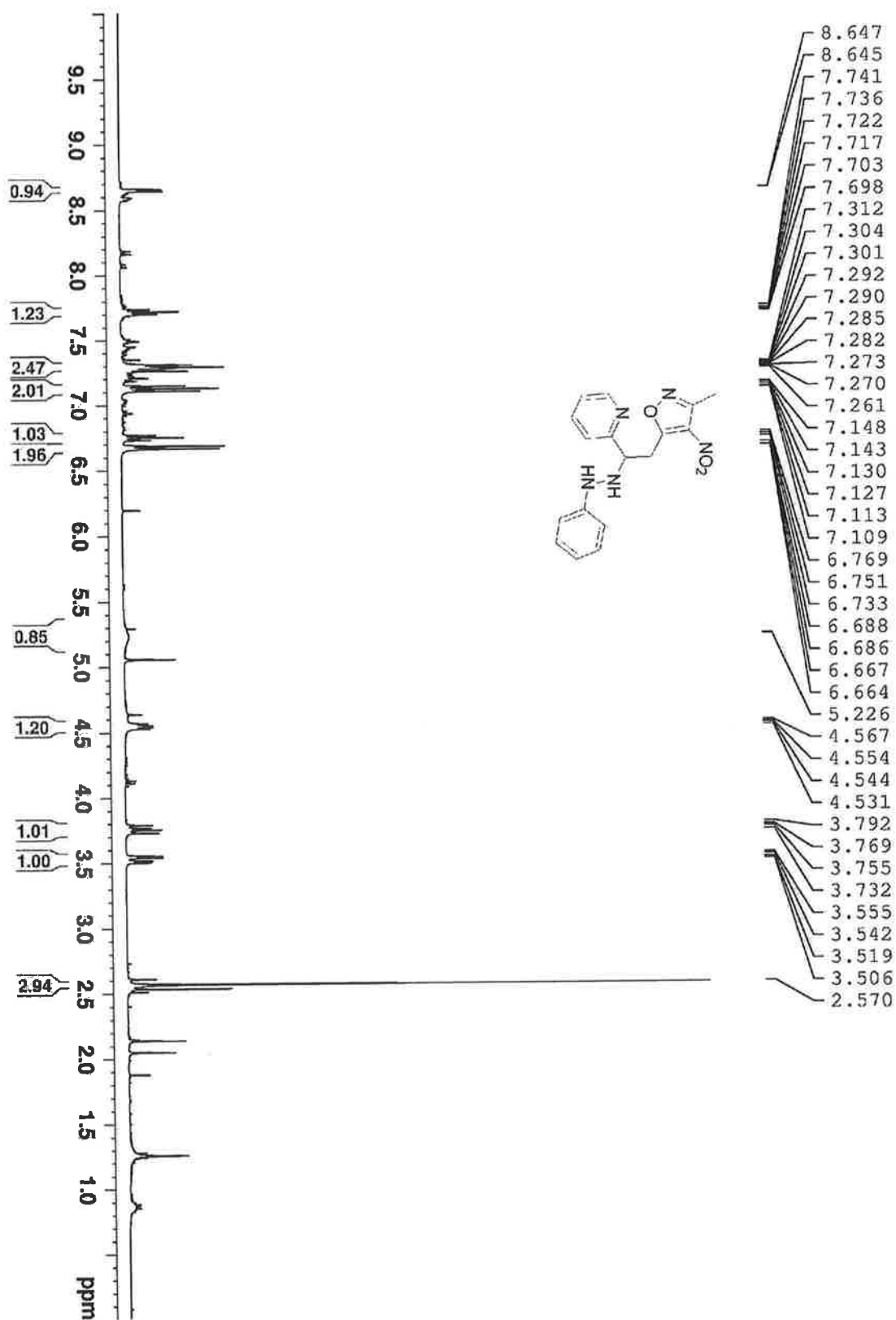
Compound 334u



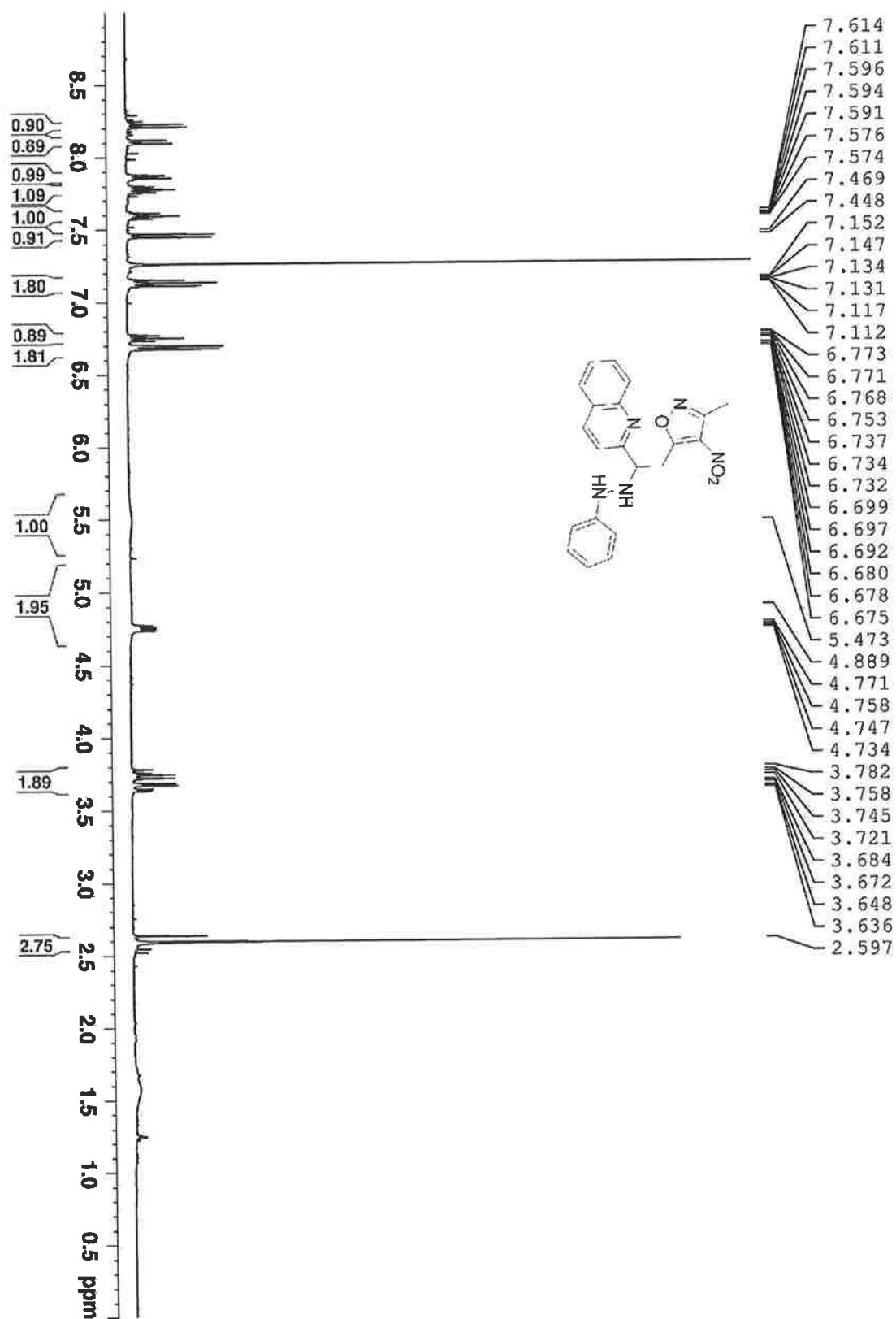
Compound 380u



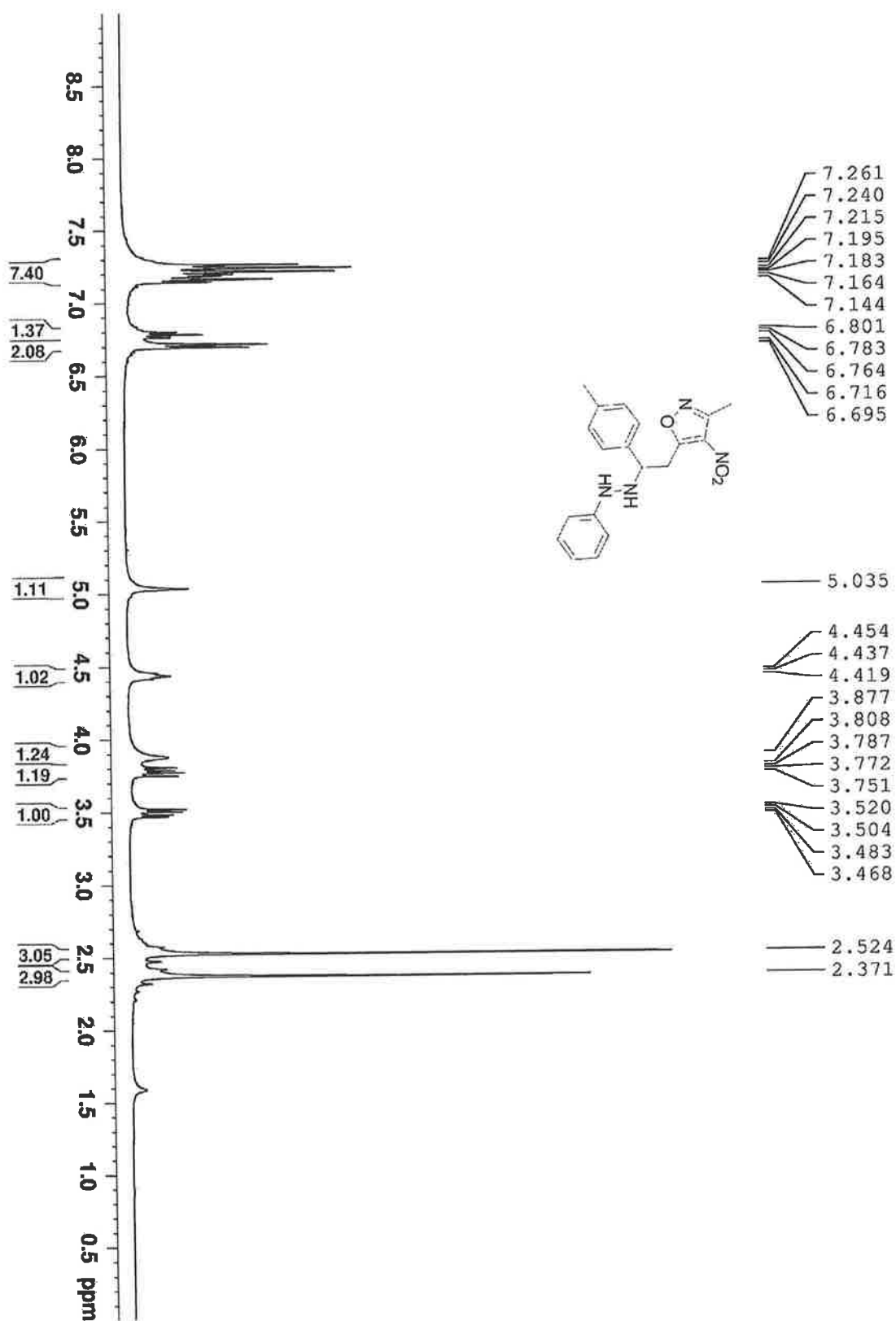
Compound 335f



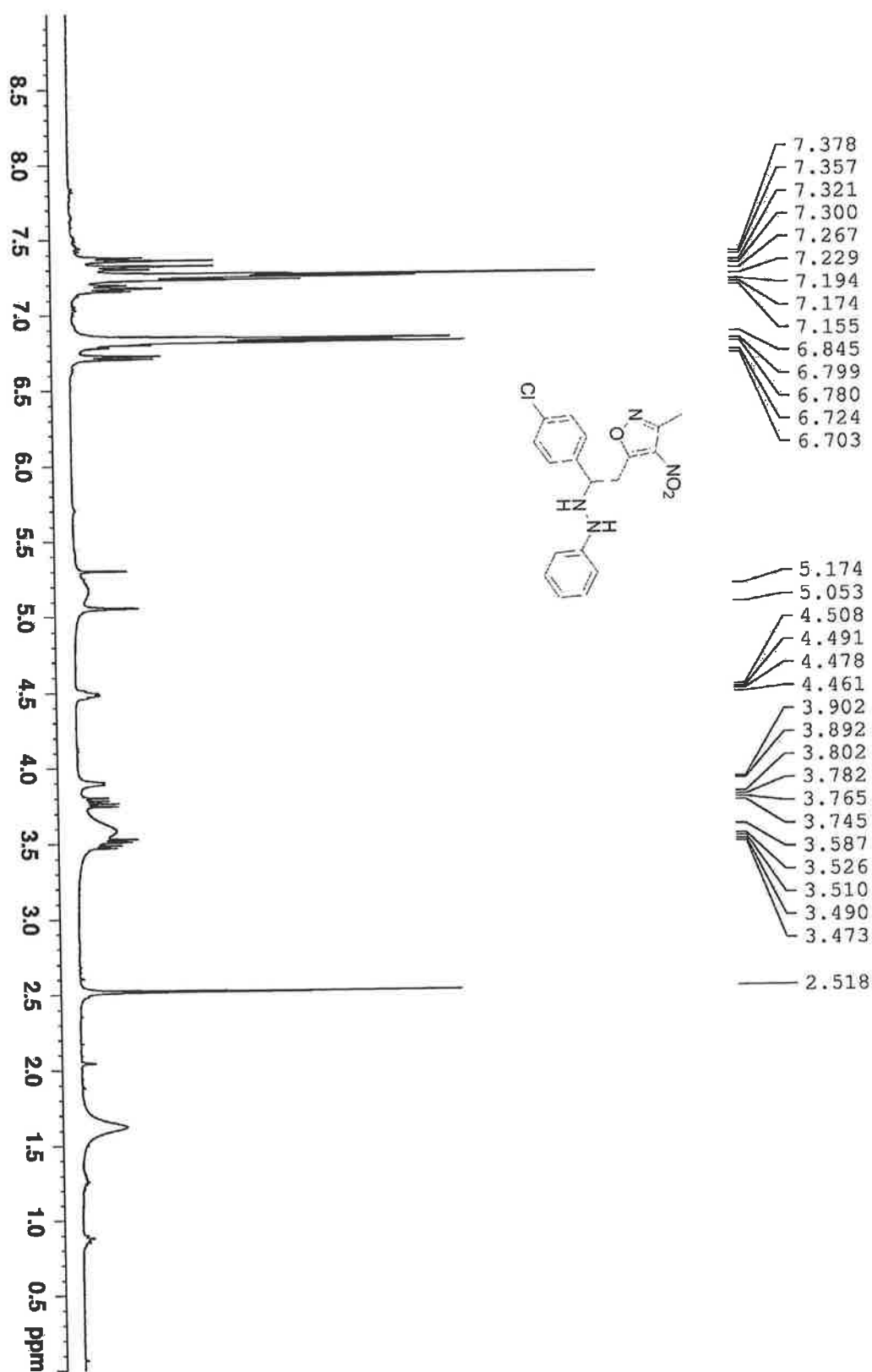
Compound 335i



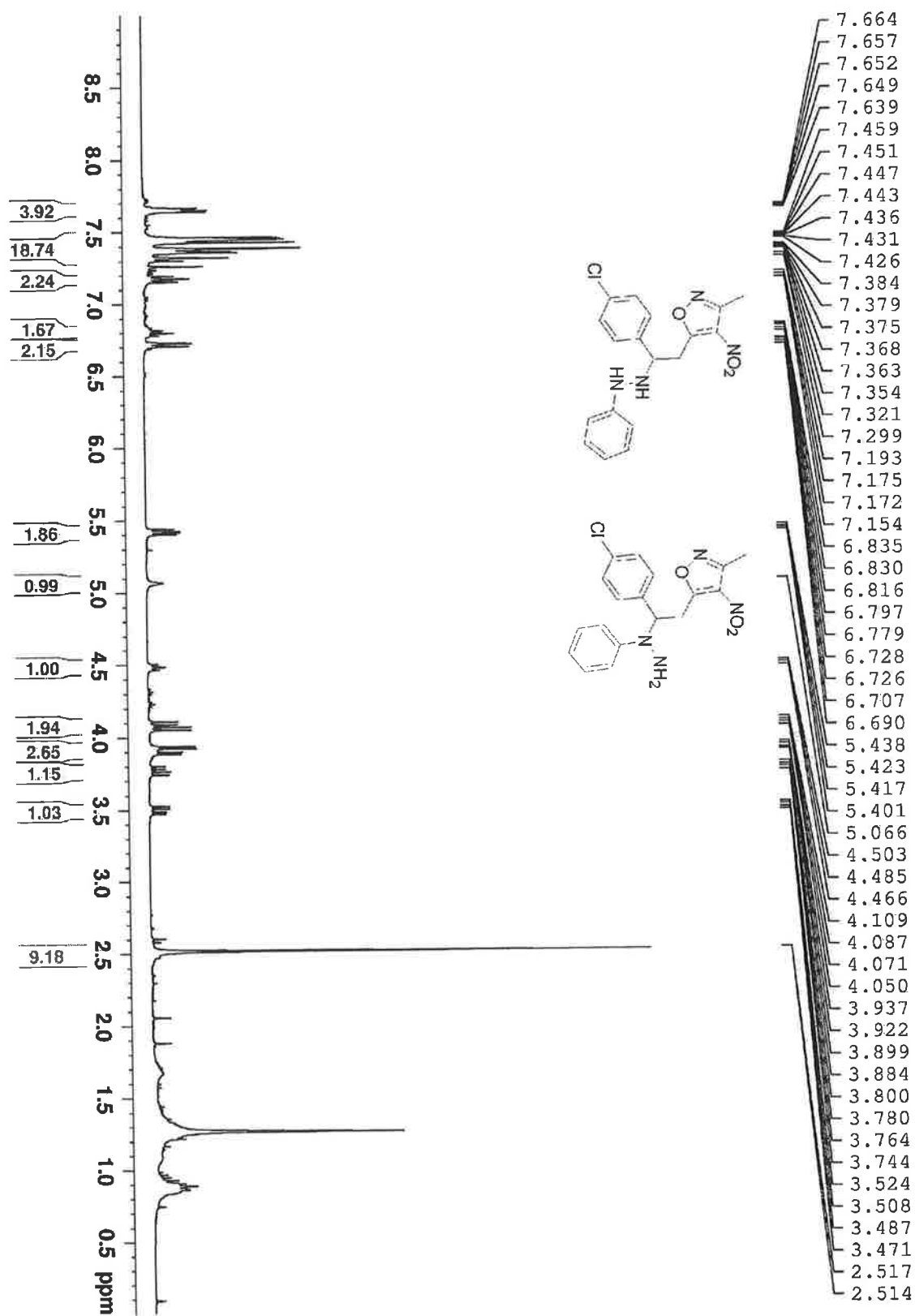
Compound 335j



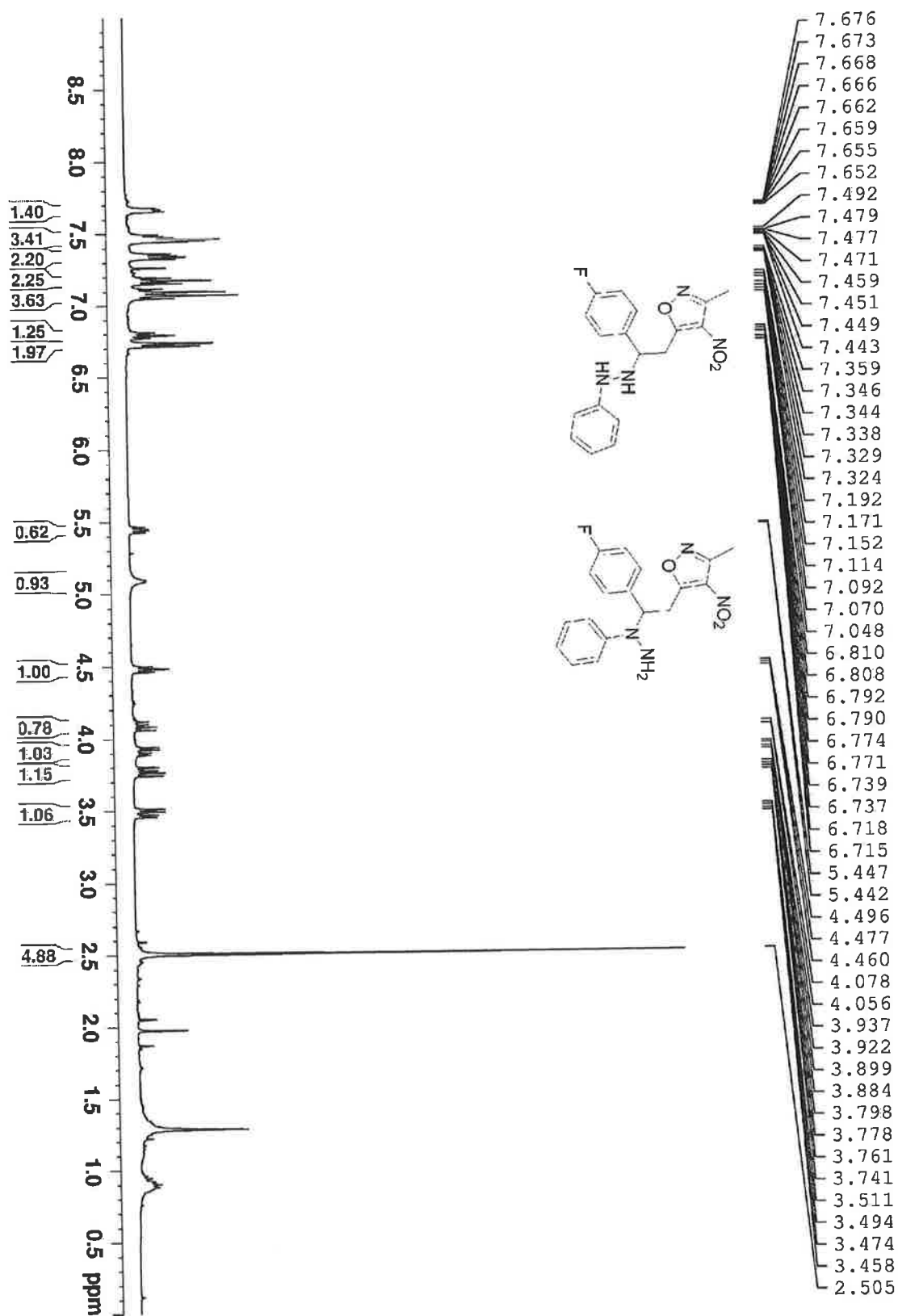
Crude Compound 335b



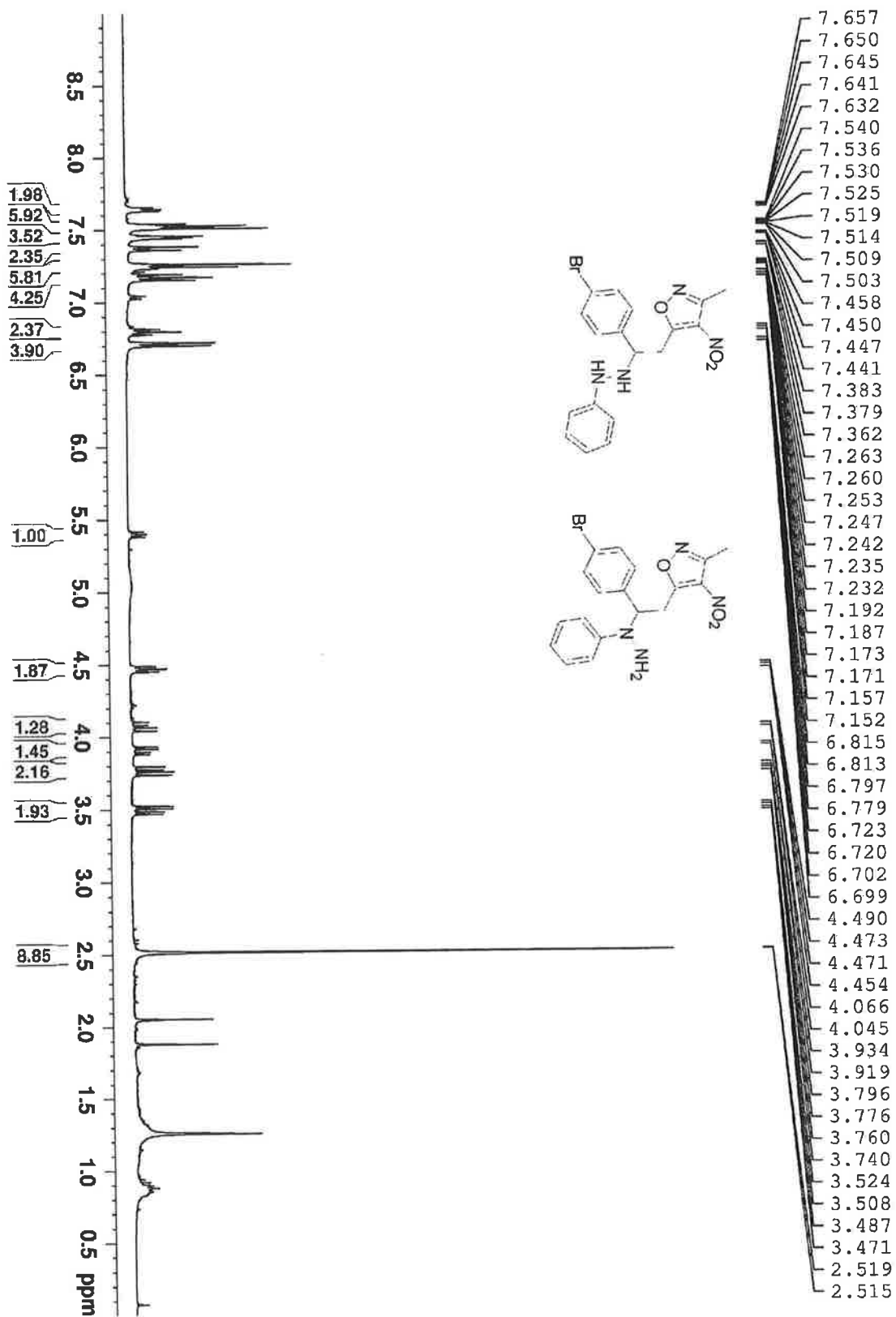
Compounds 335b, 336b



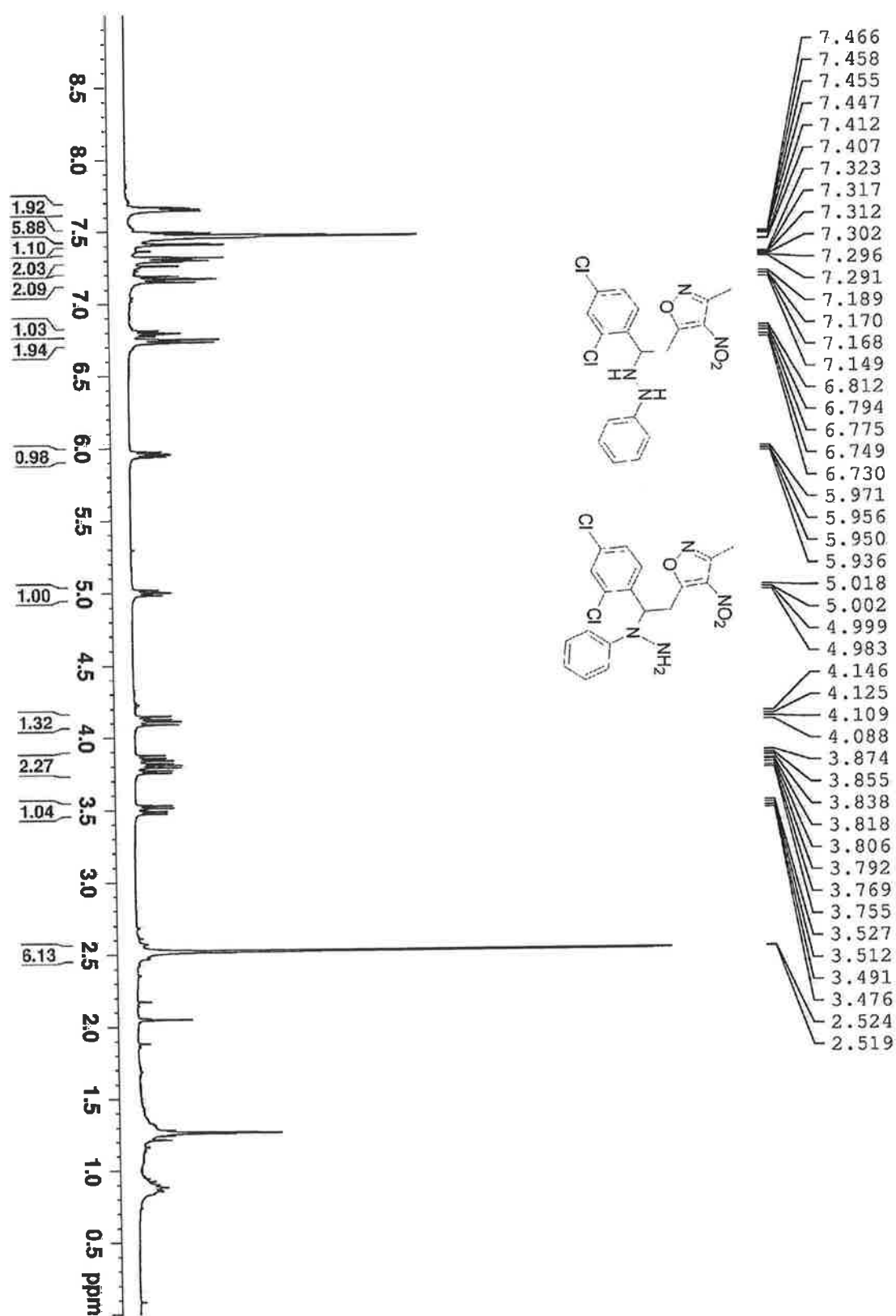
Compounds 335c, 336c



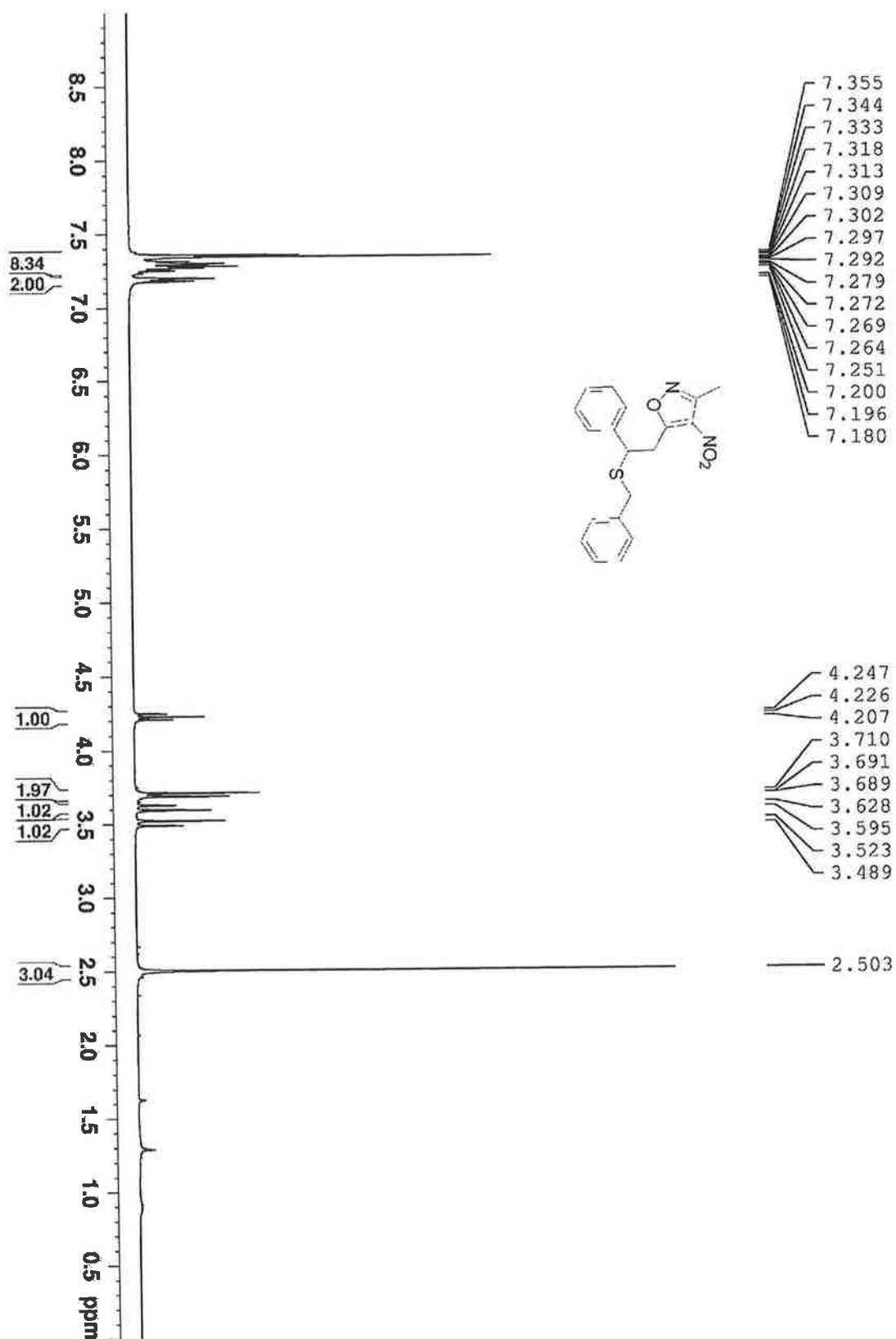
Compounds 335d, 336d



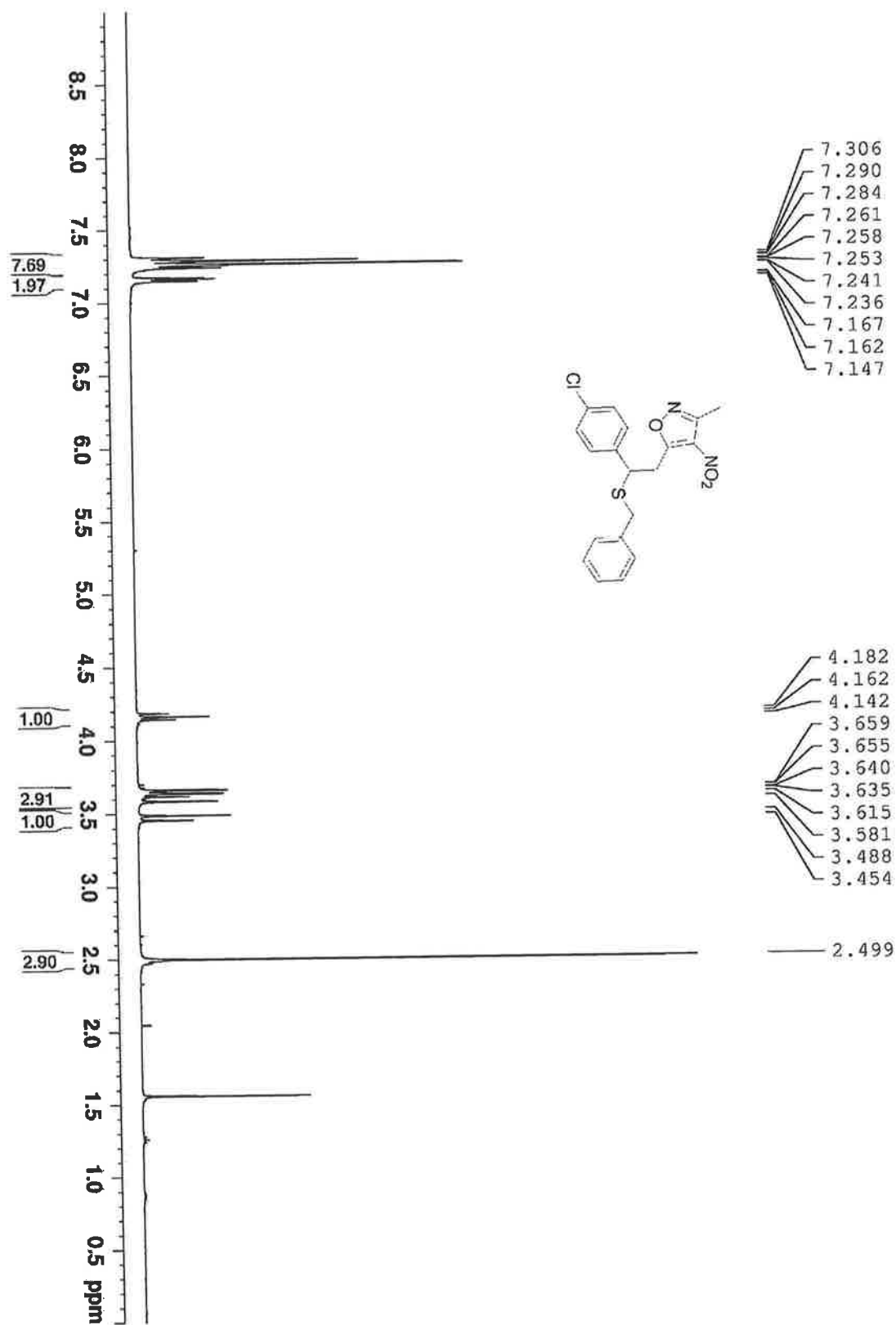
Compounds 335m, 336m



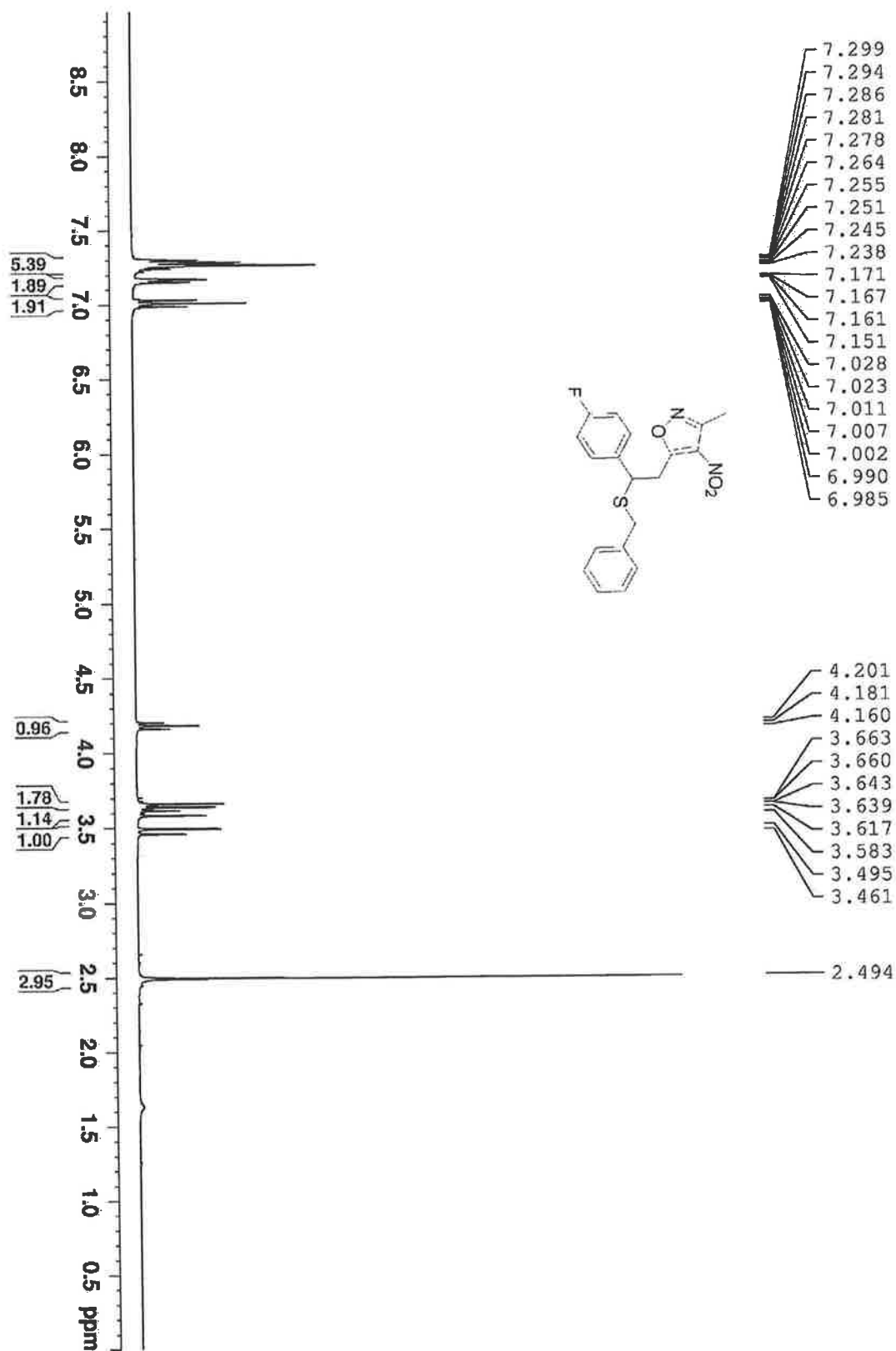
Compound 337a



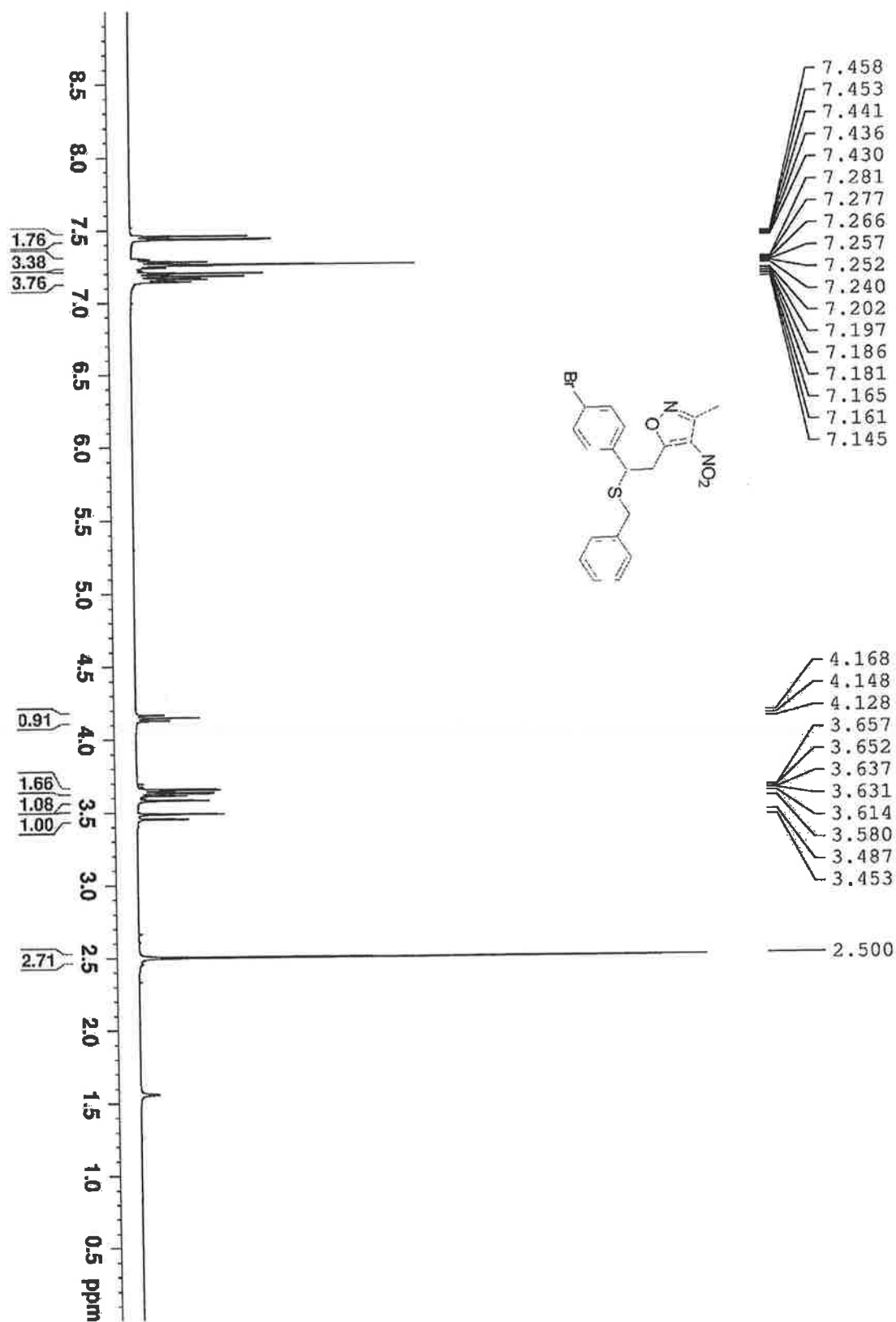
Compound 337b



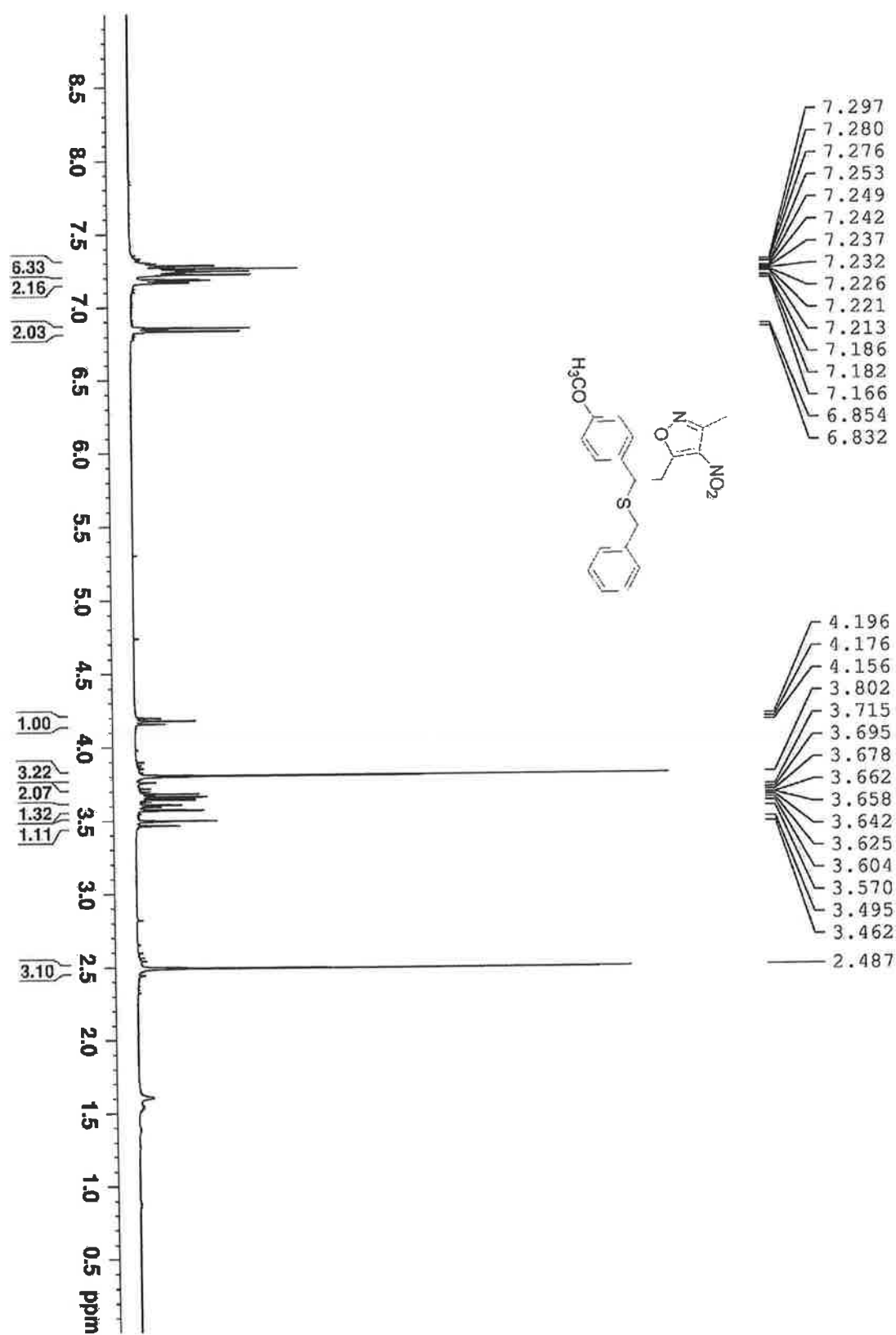
Compound 337c



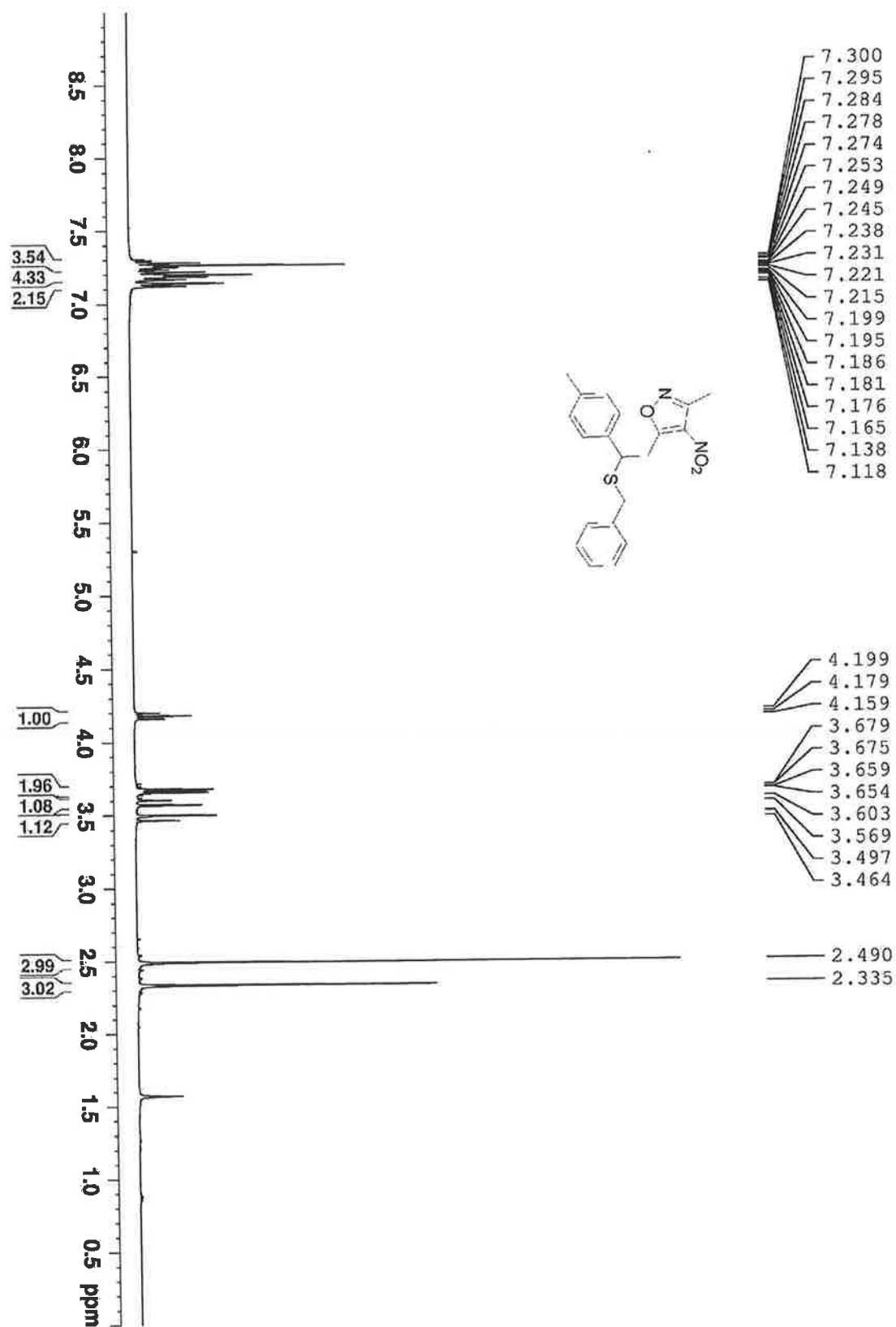
Compound 337d



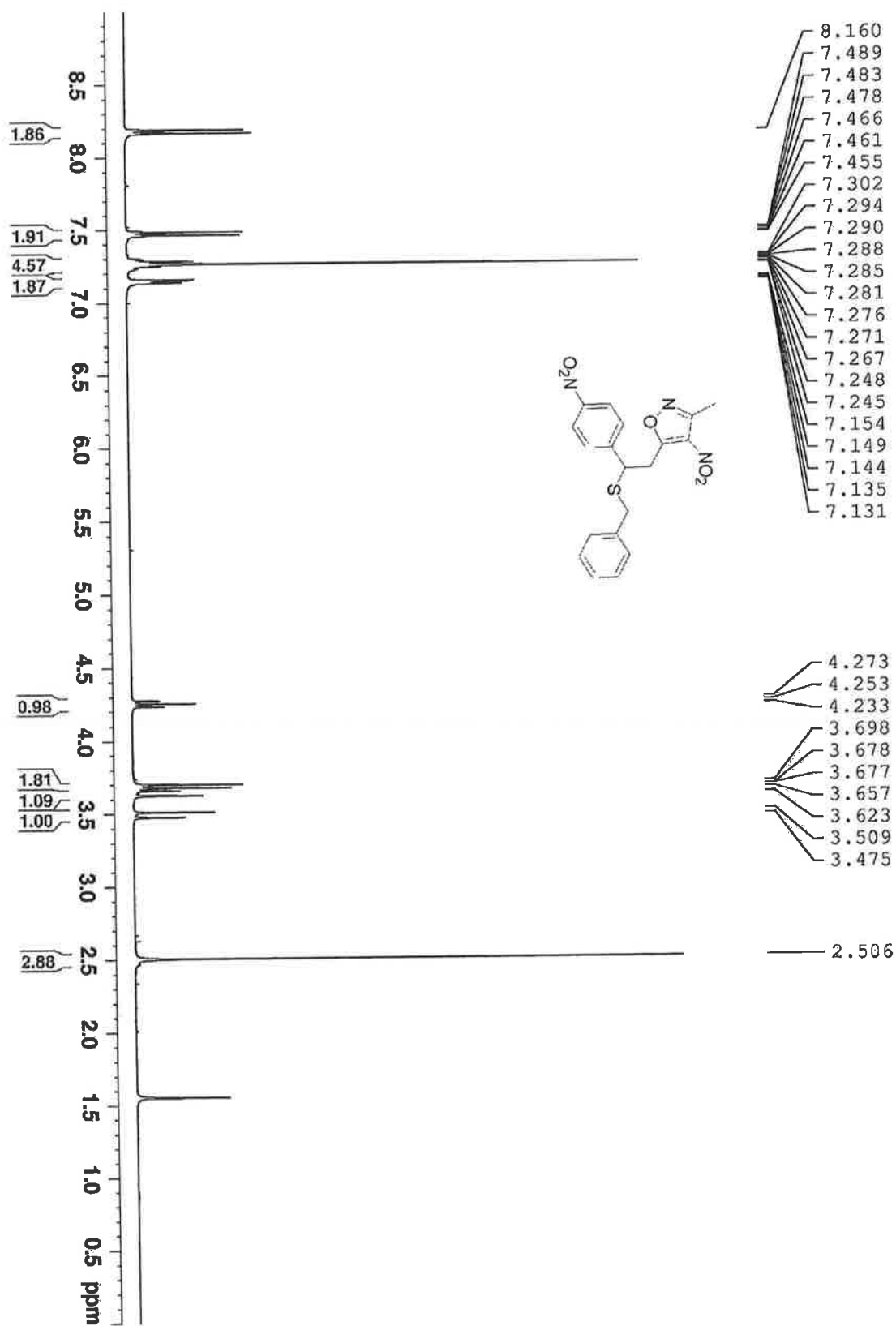
Compound 337g



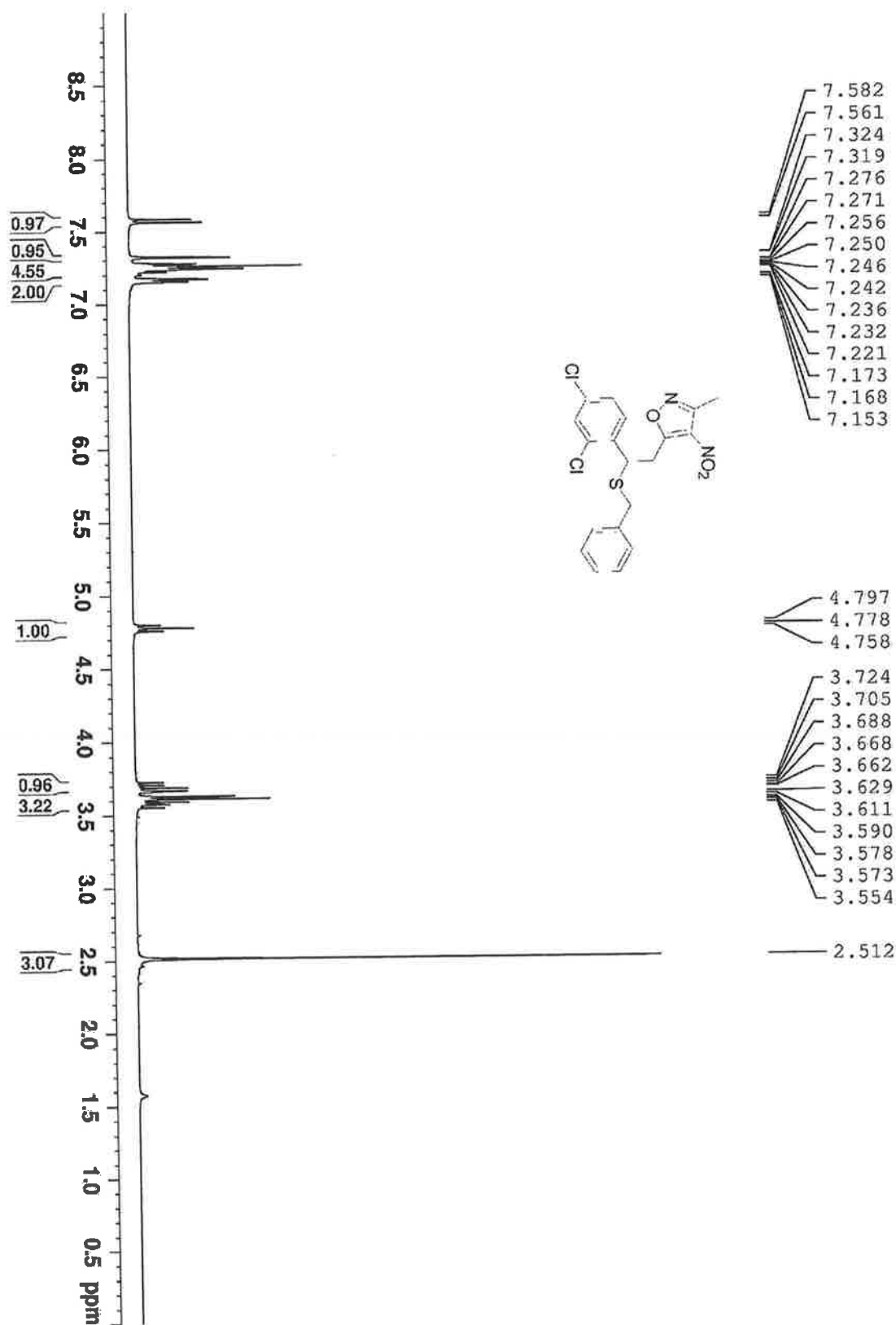
Compound 337j



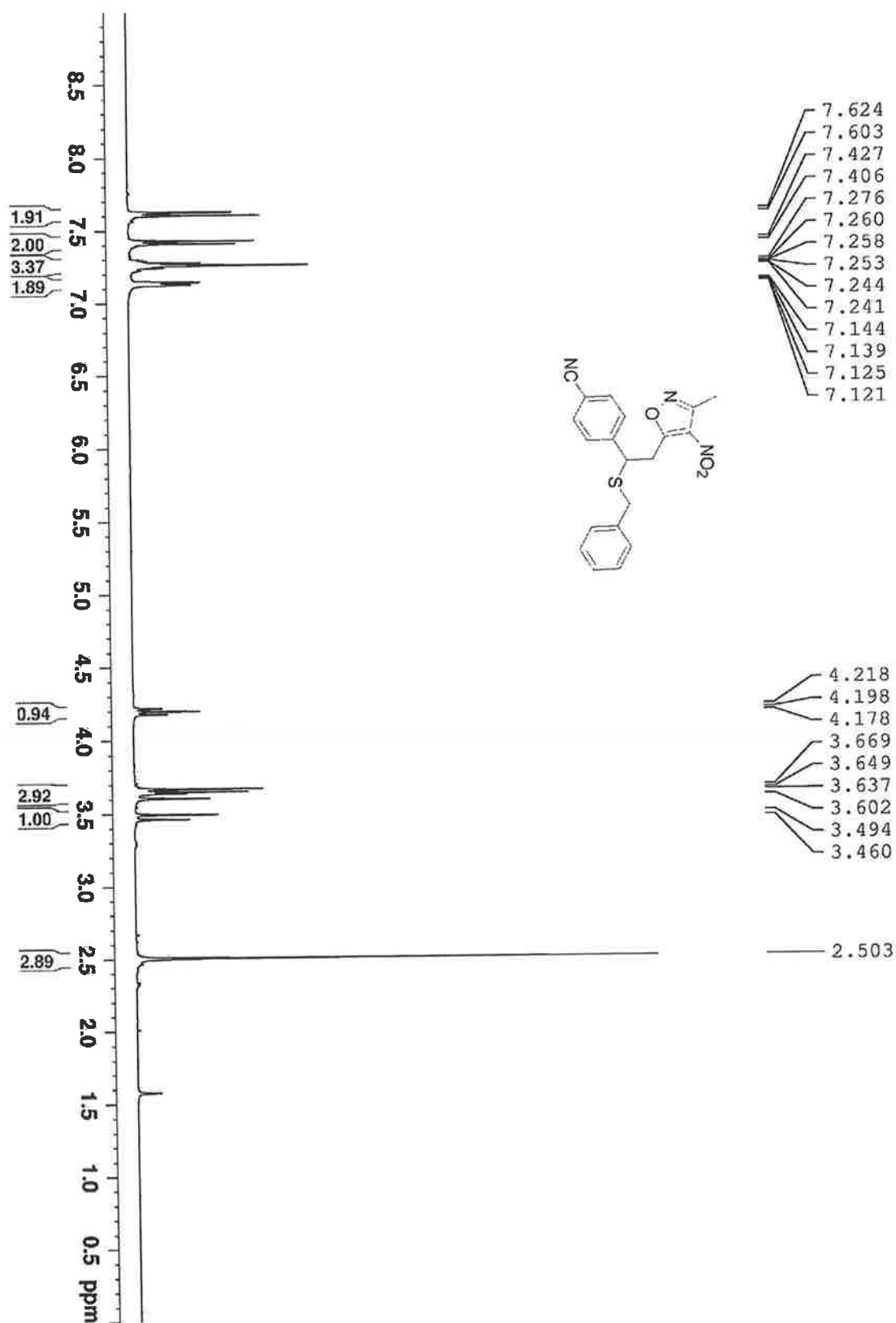
Compound 3371



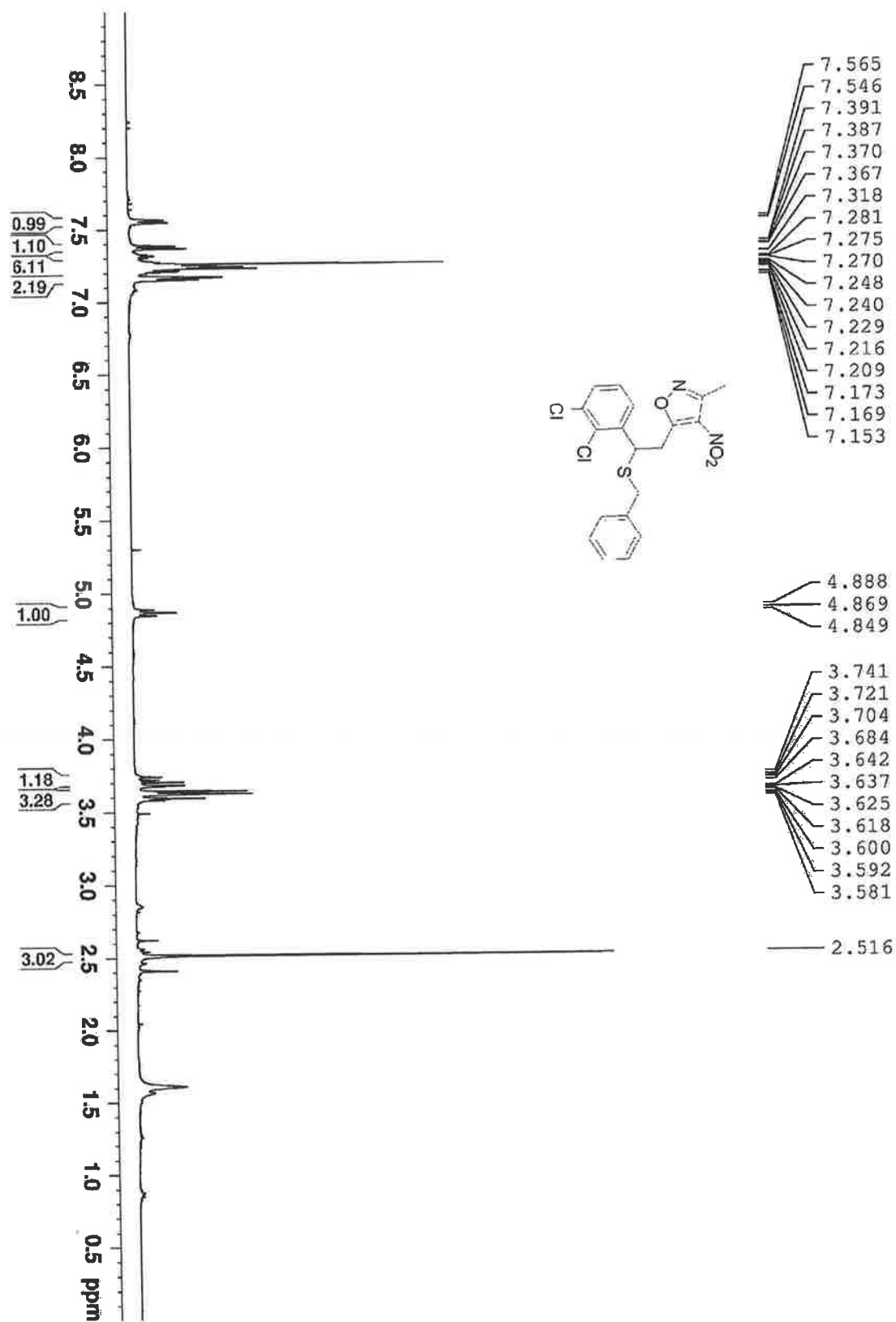
Compound 337m



Compound 337n



Compound 337q



Compound 337v

