

https://dspace.org/

Enaminones in the synthesis of azabicyclic models for alkaloids

Mthembu, Siyanda Thabani

2008-10-06T13:36:45Z
http://hdl.handle.net/10539/5725

Downloaded from a DSpace repository. https://dspace.org/

ENAMINONES IN THE SYNTHESIS OF AZABICYCLIC MODELS FOR ALKALOIDS

SIYANDA THABANI MTHEMBU

FEBRUARY 2008

SUPERVISED BY PROF. J. P. MICHAEL AND PROF. C. B. DE KONING

AN MSc DISSERTATION SUBMITTED TO THE FACULTY OF SCIENCE AT THE UNIVERSITY OF THE WITWATERSRAND,JOHANNESBURG IN FULFILMENT OF THE REQUIREMENTS FOR DEGREE OF MASTER OF SCIENCE

DECLARATION

I declare that this work presented in this dissertation was carried out exclusively by me under the supervision of Prof. J. P. Michael and Prof. C. B. de Koning and with the assistance of the acknowledged individuals. It is being submitted for the degree of Master of Science in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination in any other University

Siyanda Thabani Mthembu

February 2008

ABSTRACT

The purpose of this project was to investigate whether methodology developed in these laboratories for preparing 5/6 and 6/6 azabicyclic systems with bridged head nitrogen can be extended to 7/6, 8/6, 9/6 and 13/6 azabicyclic systems. The methodology entails the use of enaminones as central to the formation of the azabicyclic systems.

The synthetic route adopted began with the Beckmann rearrangement reaction and/or the Schmidt reaction of cyclic ketones to make lactams, which were then thionated by Curphy or Brillon procedures. The Michael reaction of NH thiolactams with *tert*-butyl acrylate was followed by Eschenmoser sulfide contraction to afford the enaminones **132** which were utilised in the ring-closing step. This involved hydrolysis of the *tert*-butyl ester and cyclisation via a mixed anhydride. Ethyl 7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **170b**, 1-(4-nitrobenzoyl)-3,4,6,7,8,9-hexahydroquinolizin-2-one **172a**, 1-benzoyl-3,4,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-2(6*H*)-one **173d**, 1-(4-nitrobenzoyl)-3,4,6,7,8,9,10,11-octahydropyrido[1,2-*a*]azocin-2-one **174a**, and 1-(4-nitrobenzoyl)-3,4,7,8,9,10,11,12,13,14,17,16-dodecahydropyrido[1,2-*a*]azacyclo-tridecin-2(6*H*)-one **176a** were synthesised in good yields, but yields of 8-(4-nitrobenzoyl)-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **171a** and 1-(4-nitrobenzoyl)-3,4,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-2(6*H*)-one **175a** were not satisfactory.

In a much shorter synthetic route that involves enaminone chemistry as well, NH vinylogous amides were synthesised by the Eschenmoser sulfide contraction and used in the aza-annulation reaction with acryloyl chloride. Structural isomers (to compounds mentioned above) 8-(4-nitrobenzoyl)-2,3,6,7-tetrahydroindolizin-5(1*H*)-one **178a**, 1-(4-nitrobenzoyl)-2,3,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-4(6*H*)-one **180a**, 1-benzoyl-2,3,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-4(6H)-one **180b**, 1-(4-nitrobenzoyl)-2,3,6,7,8,9,10,11-octahydropyrido[1,2-*a*]azocin-4-one

181a, 1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-one **182a** and 1-(4-nitrobenzoyl)-2,6,7,8,9,10,11,12,13,14,15,16-dodecahydropyrido[1,2-*a*]azacyclo-tridecin-4(3*H*)-one **183a** were synthesised in good yields. 1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one **179a** was obtained in low yield, and apparently as two conformational isomers.

ACKNOWLEDGEMENTS

I would like to acknowledge the following individuals for their contribution towards the success of this project.

- Prof. J. P. Michael for intellectual and financial support
- Prof. C. B. de Koning for intellectual support
- The NRF for financial support
- Mr R. Mampa for all NMR data and his patience
- Mr M. Brits and Dr. A. Dinsmore for all MS data
- Mr G. Morgans for his support
- The organic group for the good working environment
- My mother for her love and support
- God for ALL

TABLE OF CONTENTS

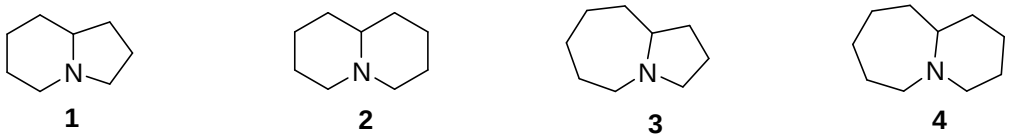
CHAPTER 1: BACKGROUND TO THE PROJECT 1
1.1 Introduction 1
1.2 Alkaloids with seven and larger-membered rings.....2
1.2.1 Lehmizidines 2
1.2.2 *Stemona* alkaloids.....3
1.2.3 *Securinega* alkaloids.....7
1.2.4 Manzamine alkaloids 9
1.3 Reported synthetic approaches to pyrrolo[1,2-*a*]azepine and pyrido[1,2-*a*]azepine systems: selected examples.....11
1.3.1 A short synthesis of racemic (3,10*Z*)-3-butyllehmizidine 56 and (3,10*E*)-3-butyllehmizidine 14 11
1.3.2 Mercury-promoted Schmidt reactions 12
1.3.3 Novel synthesis of octahydro-1H-pyrrolo[1,2-a]azepine and decahydropyrido[1,2-*a*]azepine.....15
1.3.4 Synthesis of 5/7-, 5/8- and 5/9-bicyclic lactams 16
1.4 The Wits Background.....19
1.4.1 Introduction to enaminones.....19
1.4.2 Alkaloid synthesis via enaminones: Selected Wits examples 22
1.5 Aims.....29
CHAPTER 2: RESULTS AND DISCUSSION 33
2.1 Synthesis of azacyclotridecane-2-one by the Beckmann rearrangement 33
2.2 Synthesis of lactams by the Schmidt reaction.....34
2.3 Synthesis of NH thiolactams 36
2.3.1 Synthesis by the Curphey procedure 36
2.3.2 Synthesis by the Brillon procedure.....39
2.4 Synthesis of N-alkylated thiolactams 40
2.5 Eschenmoser sulfide contraction 44
2.5.1 Synthesis of N-alkyl vinylogous urethanes.....44
2.5.2 Synthesis of N-alkyl vinylogous amides 48

2.5.3 Synthesis of NH vinylogous amides.....51
2.6 Synthesis of azabicyclic systems by intramolecular cycloacylation.....54
2.7 Synthesis of azabicyclic systems by aza-annulation.....60
2.8 Conclusion.....65
2.9 Future work.....67
CHAPTER 3.....71
3.1 General experimental methods.....71
3.2 General procedure for synthesizing lactams using the Beckmann rearrangement method.....72
3.3 General procedure: The Schmidt reaction.....73
3.4 Thionation of lactams.....75
3.4.1 The Curphey procedure.....75
3.4.2 The Brillon procedure.....75
3.5 General procedure for the N-alkylation of thiolactams with acrylate asters.....79
3.6 General procedure for the preparation of N-alkyl vinylogous urethanes from N-alkylthiolactams.....83
3.7 General procedure for the preparation of N-alkyl vinylogous amides from N-alkylthiolactams.....89
3.8 General procedure for the preparation of NH vinylogous amides from thiolactams.....96
3.9 Synthesis of azabicyclic systems by intramolecular cycloacylation.....101
3.10 Reactions of N-H vinylogous amides with acryloyl chloride.....108
REFERENCES.....115
APPENDIX: NMR DATA.....119

CHAPTER 1: BACKGROUND TO THE PROJECT

1.1 Introduction

The organic group at the University of the Witwatersrand (Wits) has devoted considerable effort to making azabicyclic alkaloids containing the indolizidine **1** and quinolizidine **2** ring systems, which are very common in natural products. Other azabicyclic systems such as **3** and **4** are much less common in nature, and the Wits research group has paid almost no attention to them up to now (Figure 1). The purpose of this project is to investigate whether methodology developed in these laboratories for smaller azabicyclic systems can be extended to analogues in which at least one of the rings is seven-membered or larger.



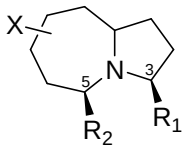
1 **2** **3** **4**

Figure 1. Azabicyclic systems with small and medium rings

This discussion will begin with a short survey of some natural products containing azabicyclic systems with seven-membered and larger rings. The second part will be a short survey on how other groups make these azabicyclic systems. The Wits approach to alkaloid synthesis via enaminone intermediates will then be introduced. The specific aims of this project and strategies to be followed will then be presented.

1.2 Alkaloids with seven and larger-membered rings

1.2.1 Lehmizidines



Lehmizidines	R_1	R_2	X
5	$(CH_2)_7C{\equiv}CH$	CH_3	H
6	$(CH_2)_5CH{=}CHCH{=}CH_2$	CH_3	H
7	$(CH_2)_7CH{=}CH_2$	CH_3	H
8	$C_9H_{13}O$ (=O, $C{\equiv}CH$)	CH_3	H
9	$(CH_2)_5CH{=}CHC{\equiv}CH$	CH_3	OH
10	$C_9H_{15}O$	CH_3	H
11	$(CH_2)_7C{\equiv}CH$	CH_3	OH
12	$C_9H_{17}O$ (=O)	CH_3	H
13	$(CH_2)_7CH{=}CH_2$	CH_3	OH
14	$(CH_2)_3CH_3$	H	–

Table 1. Lehmizidines[1,2]

Lehmizidine alkaloids originate from a group of Colombian dendrobatid frogs, known as *Dendrobates lehmanni*.[1] Ten alkaloids, **5** – **14**, belonging to this group have been reported. Their structures were elucidated by mass spectral analysis. The mass spectrum of lehmizidines revealed the presence of a substituent at C-3, indicated by a base peak; and a methyl substituent at C-5, indicated by a small fragment. The relative structural configuration of all lehmizidines is unknown,

except for compound **5**, which is shown with the relative configuration. Positions of the OH groups are also unknown. No toxicity or biological activity data have been reported.[1] Unlike the frog lehmizidines with a methyl group, (3*R*)-3-butyl-octahydro-1*H*-pyrrolo[1,2-*a*]azepine **14**, isolated together with some indolizidine alkaloids from an ant *Myrmicaria melanogaster* from Brunei Darussalam, has a butyl side as the only substituent at C-3.[2]

1.2.2 Stemona alkaloids

Stemona alkaloids are another group of alkaloids that contain the azabicyclic nucleus **3** of interest. They are found in the family Stemonaceae, which occurs from southern Asia and Malaysia to northern Australia.[3] The pyrrolo[1,2-*a*]azepine nucleus, also known as perhydroazaazulene and 4-azaazulene, is at the heart of most *Stemona* alkaloids (**A**, Figure 2). The *Stemona* alkaloids have been classified by Pilli and de Oliveira into five groups according to their structural features, namely stenine **I**, stemoamide **II**, tuberostemonine **III**, stemonamine **IV** and tuberostemoamide **V** (Figure 2).[3]

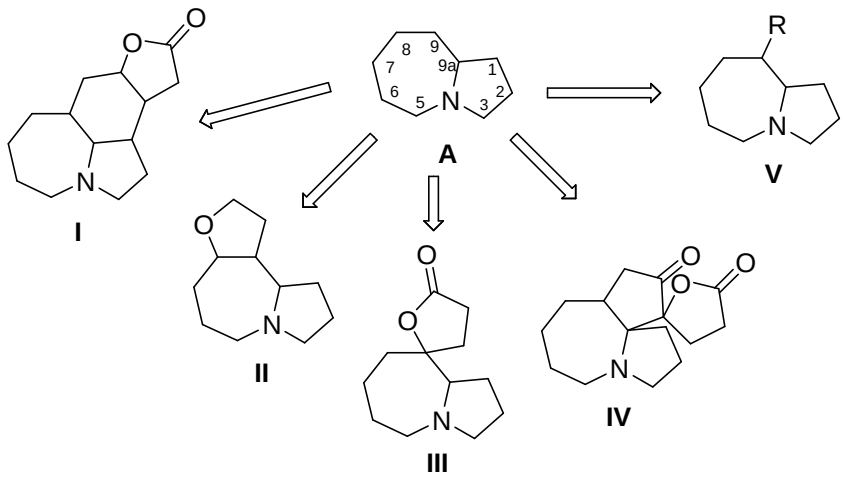


Figure 2. Main classes of *Stemona* alkaloids.[3]

Some specific examples of classes (**I**) – (**V**) are shown in Figure 3. They include stenine **15**, tuberostemonine **16** and tuberostemonine A **17**, which can be structurally represented by the tetracyclic furo[2,3-*h*]pyrrolo[3,2,1-*jk*][1]benzazepin-10(*2H*)-one nucleus (**I**); stemoamide **18** and neostemodiol **19**, which display the tricyclic *2H*-furo[3,2-*c*]pyrrolo[1,2-*a*]azepine nucleus (**II**); tuberostemospironine **20** and didehydrocroomine **21**, which are structurally characterized by a *2H*-spiro[furan-2,9'[9*H*]pyrrolo[1,2-*a*]azepin-5-one nucleus (**III**); stemonamine **22**, which is structurally characterized by a 2'*H*,11*H*-spiro[1*H*-cyclopenta[*b*]pyrrolo[1,2-*a*]azepine-1,2'furan]-5',10-dione nucleus (**IV**) and didehydroparvistemonine **23**, which is characterized by the lack of the B-C ring fusion and a hexahydro-2,6-dimethyl-5-oxofuro[3,2,-*b*]furan-3-yl]moiety attached to C-9 in the pyrrolo[1,2-*a*]azepine nucleus (**V**). [3]

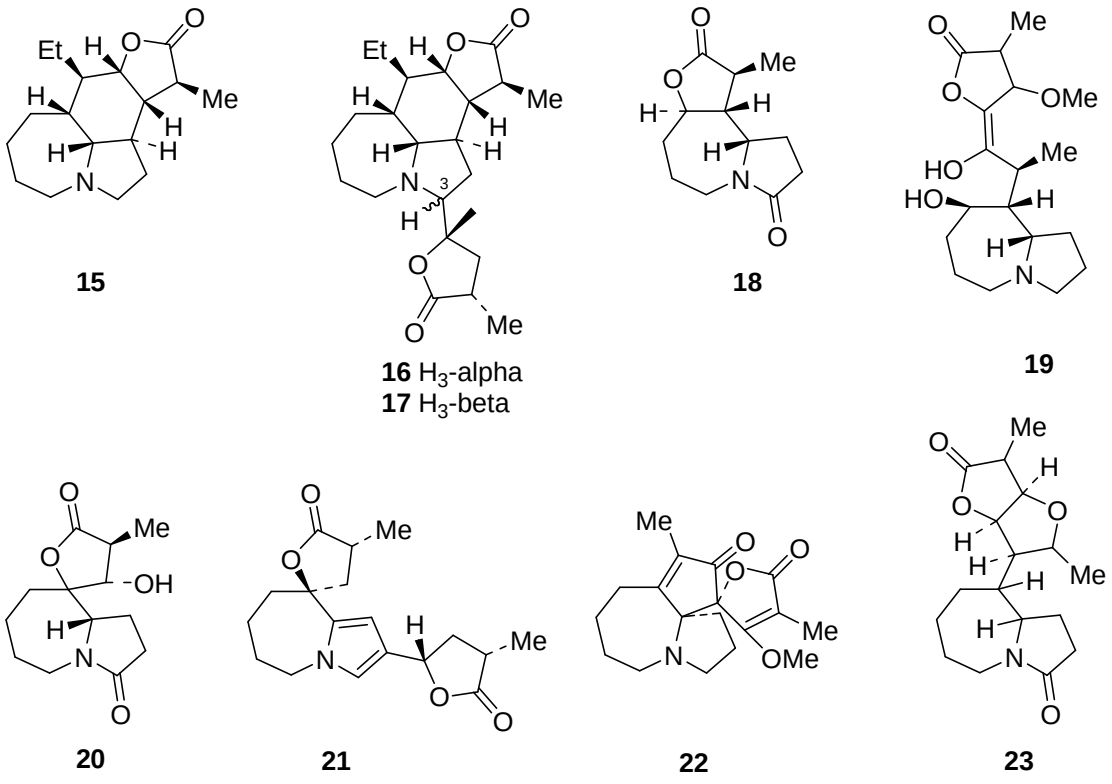


Figure 3. Examples of *Stemona* alkaloids.[3]

Of interest to this project are alkaloids in which the azabicyclic system is not fused to other carbocyclic rings. These include most members of the stemoamide, tuberostemospironine and parvistemoline families. The representative examples in these groups are neostemodiol **19**, didehydrocroomine **21** and didehydroparvistemonine **23** respectively.

The crude extracts of Stemonaceae species have been used by the Chinese and Japanese as insecticides, vermifuges and in the treatment of respiratory diseases. They have also shown antitubercular and antitussive activities. Tuberostemonine **16** has shown activity when tested against *Angiostrongylus cantonensis, Dipylidium caninum* and *Fasciola hepatica*, with an effect of motility of these helminthic worms. Tuberostemonine has also been shown by Shinozaki and Ishida to depress glutamate-induced responses at similar concentrations to those of established glutamate inhibitors. This has been shown on the neuromuscular transmission in crayfish, which is considered a model for studying the mechanism of drug action in the mammalian central nervous system. A few other *Stemona* alkaloids have also been reported to show insect anti-feeding activity, but it seems that no other biological activity has been reported.[3]

The stemocurtisine group of the *Stemona* alkaloids containing the pyrido[1,2-*a*]azepine nucleus (**B**, Figure 4) has been isolated mainly from the roots *S. kerrii*, collected in North and Northwest Thailand.[4] The specific alkaloids are stemokerrin **24**, methoxystemokerrin-*N*-oxide **25**, oxystemokerrin **26**, oxystemokerrin-*N*-oxide **27** and pyridostemin **28** (Figure 4). Oxystemokerrin **26** has an oxygen bridge between C-1 and C-9, while stemokerrin **24** is unsaturated between C-8 and C-9. Pyridostemin **28** lacks the substituent at C-4 of oxystemokerrin **26**.[4]

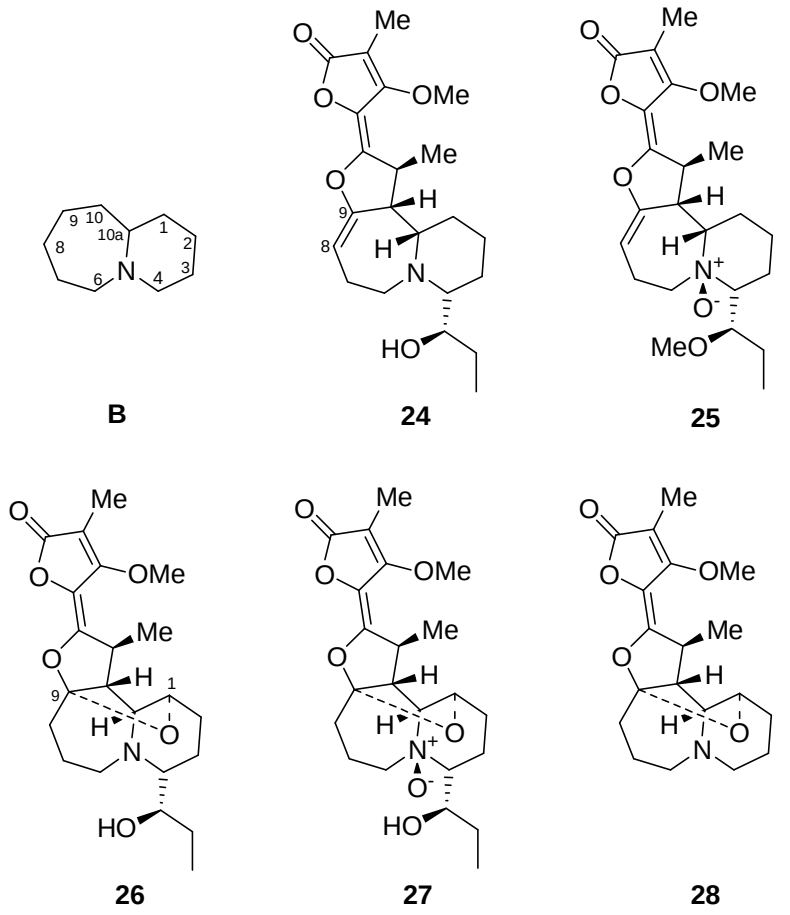


Figure 4. Pyridoazepine alkaloids.[4]

A common biogenetic origin may be suggested by the occurrence of both the pyrrolo- and pyridoazepine alkaloids in the same plant species. For example, protostemonine **29** (Figure 5) is a likely biosynthetic precursor of the pyridoazepine alkaloids. The butyl side chain at C-3 of compound **30** might be interpreted as a result of hydrolysis of the lactone ring of compound **29** followed by decarboxylation. The propyl side chain at C-4 of compound **31** might also be interpreted as the cleavage of the C-3–N bond, followed by the formation of C-18–N (Figure 5) [also labeled as C-4–N bond on (**B**, Figure 4)].[4]

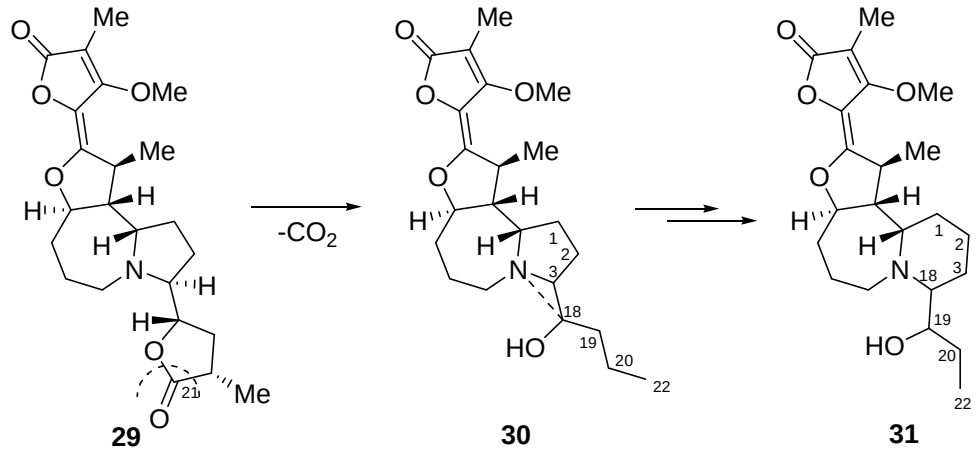


Figure 5. Proposed biosynthetic connection between pyrrolo- and pyridoazepines.[4]

The strongest insecticidal activity was found for oxystemokerrin **26**, which had a LC_{50} value of 5.9 ppm. *N*-Oxidation in oxystemokerrin-*N*-oxide **27** or insertion of double bond in stemokerrin **24** resulted in decreased activities to LC_{50} values of 12.5 ppm and 58 ppm, respectively. The biggest drop in activity was due to loss of the side chain in **28** (LC_{50} = 149) or *O*-methylation in **25** (LC_{50} > 100 ppm). In general compounds **24**, **26**, **27**, **28** and **29** were characterized by the paralysis and softening of the larval bodies.[4]

1.2.3 Securinega alkaloids

The *Securinega* alkaloids include four well-known natural occurring alkaloids, which occur in plants of the family Euphorbiaceae. They are securinine **32**, virosecurinine **33**, allosecurinine **34** and viroallosecurinine **45** (Figure 6).[5] Securinine **32** and allosecurinine **34** occur in *Securinega suffruticosa*, whilst virosecurinine **33** and viroallosecurinine **35** occur in *S. virosa*.[5] In addition to these alkaloids (–)-norsecurinine **36** and (–)-allonorsecurinine **37** are naturally occurring, and the rare alkaloids phyllanthidine **38** and *ent*-phyllanthidine **39** were isolated from *Phyllanthus discoides* and *Securinega suffruticosa*.[6,7]

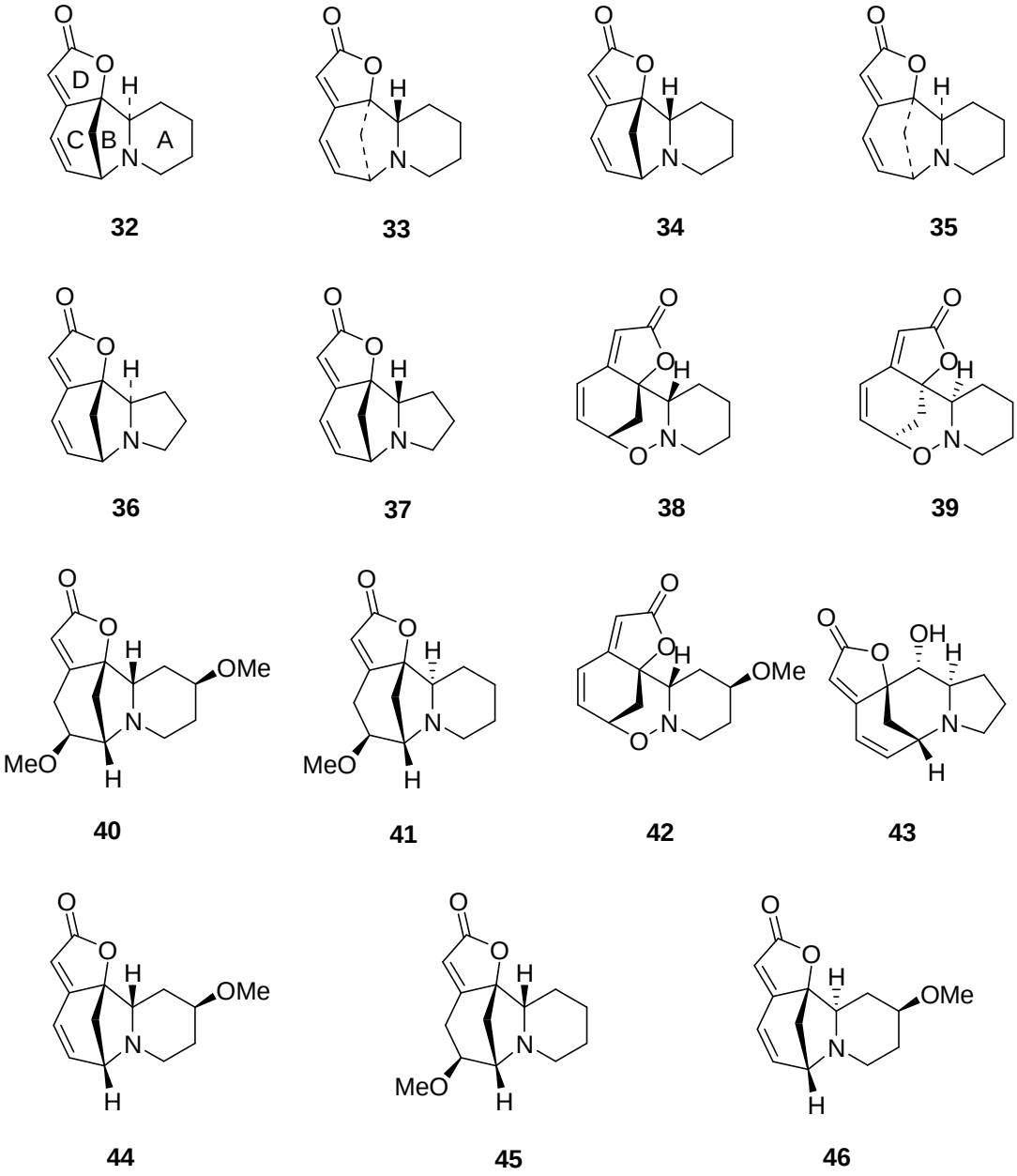


Figure 6. *Securinega* alkaloids.[5-8]

Securinine **32** was the first to have its structure elucidated in 1962 by degradation and spectroscopic studies. The structure was confirmed in 1965 by X-ray crystallography.[5] The *Securinega* alkaloids present a tetracyclic structure formed by an α,ß-butenolide (ring D), a 6-azabicyclo[3.2.1]octane system (rings

B and C), and a piperidine or pyrrolidine (ring A) (**32**, Figure 6).[5] Rings A and C together constitute the pyridoazepine skeleton that is of interest for this project.

The biological activity of securinine **32** is of interest as the compound has been used in Russia as a CNS stimulating drug, acting as a stereospecific antagonist at the GABA binding site of the $GABA_A$–receptor complex. Its rigidity might aid in understanding the shape of the $GABA_A$ receptor site.[5]

Recently, new Securinega alkaloids have been discovered from the wood of *Securinega suffruticasa* var. *amamiensis* which occurs in the Ryukyu Islands in the subtropical area of Japan.[8] They have been found with the relatively known *Securinega* alkaloids securinine **32** and phyllanthidine **38**. The new alkaloids are secu'amamine A **43**, 4-epiphyllanthine **44**, securitinine **45**, 15α-methoxy-14,15-dihydrophyllochrysine **46** and they are secu' amamines B **40**, C **41**, D **42**.[8]

Their structures as shown in Figure 6 contain methoxy groups compared to securinine **32** with no methoxy group. The *Securinega* alkaloids are of interest to this project because they contain the 5,7, 6,7 and 5,8 ring systems.

1.2.4 Manzamine alkaloids

The manzamine alkaloids, which include ircinal A **47**, manzamine A **48**, 8-hydroxymanzamine A **49**, 6-hydroxymanzamine A **50**, 6-deoxymanzamine X **51**, manzamine E **52** and manzamine F **53**, were isolated from the Indonesian marine sponge *Acanthostrongylophora* (Figure 7).[9,10] Their structure is characterized by the decahydropyrrolo[1,2-*a*]azocine nucleus **C** fused to a octahydroisoquinoline at C-25 and C-26 and a 13-membered ring fused with octahydroisoquinoline nucleus between C-12 and N-21.

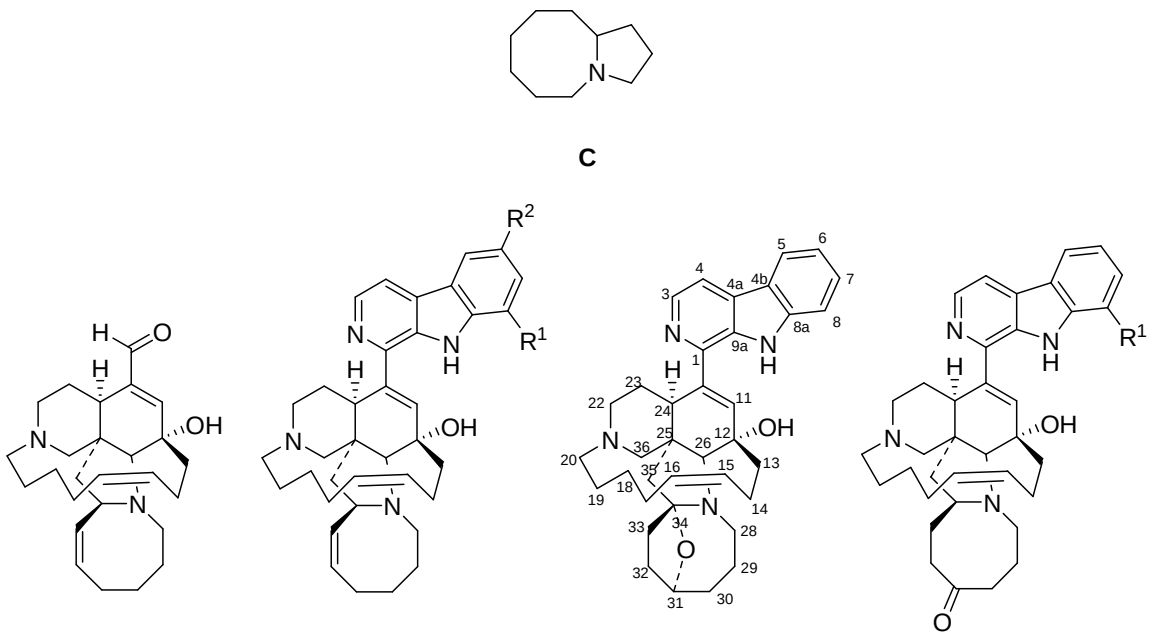


Figure 7. Manzamine alkaloids.[9,10]

Biological activities such as insecticidal, antiparasitic, anti-inflammatory, cytotoxic and antibacterial activities have been previously reported for manzamine alkaloids. In addition to this, the manzamine alkaloids have recently shown biological activities against *M. tuberculosis* (H37Rv), chloroquine sensitive D6 clone and chloroquine resistant W2 clone of *P. falciparum* and *Leishmania donovani*, AIDS opportunistic pathogens and HIV-1.[9] They have also shown activity in GSK3 inhibition in vitro, one of the two kinase implicated in tau hyperphosphorylation, the other being CDK-5.[10] The decreasing activity against *M. tuberculosis* was in the order from 6-hydroxymanzamine A **50**, 8-hydroyxmanzamine A **49**, manzamine A **48**, manzamine F **53** to manzamine E **52**. The higher activity in this case maybe due to the position of the OH group at R^2. The decreasing activity against chloroquine sensitive D6 clone and chloroquine resistant W2 clone of *P.falciparum* was in the order from manzamine A **48**, 8-hydroxymanzamine A **49**, 6-hydroxymanzamine A **50**, manzamine F **53** to manzamine E **52**. There is a great difference between the activity of 8-

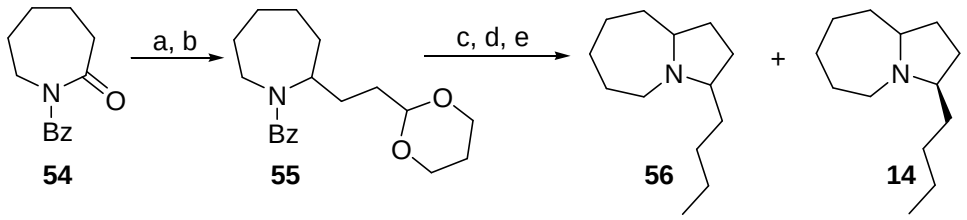
hydroyxmanzamine A **49** and 6-hydroxymanzamine A **50** that might be due to the preference of the OH group to be at R^1 for higher activity. The decreasing activity against *Leishmania donovani* was in the order from manzamine A **48**, 6-hydroxymanzamine A **50**, manzamine E **52**, manzamine F **53** to 8-hydroyxmanzamine A **49**. Generally, the decreasing activity against AIDS opportunistic pathogens, namely *S. aureus*, MRS, *C. neoformans* and *M. intracellulare* was in the order from manzamine A **48**, 8-hydroxymanzamine A **49**, 6-hydroxymanzamine A **50**, manzamine F **53** to manzamine E **52** with some compounds showing no activity or not tested. The decreasing activity against HIV-1 was in the order from 8-hydroyxmanzamine A **49**, manzamine A **48**, manzamine F **53** to manzamine E **52**. The decreasing activity in GSK3 inhibition was in the order from 8-hydroyxmanzamine A **49**, manzamine A **48**, manzamine E **52** to manzamine F **53**.[9] The manzamine alkaloids can be used as a building block for the synthesis of more potent and selective GSK-3 inhibitors for the control of diabetes and Alzheimer's disease.[10]

1.3 Reported synthetic approaches to pyrrolo[1,2-a]azepine and pyrido[1,2-a]azepine systems: selected examples

1.3.1 A short synthesis of racemic (3,10Z)-3-butyllehmizidine 56 and (3,10E)-3-butyllehmizidine 14

Jones and co-workers synthesised (3,10*Z*)-3-butyllehmizidine **56** and (3,10*E*)-3-butyllehmizidine **14** in a bid to compare compound **14** to a naturally occurring diastereomer **14** found in the ant *Myrmicaria melanogaster* from Brunei (**Scheme 1**).[2] {2-[2-(1,3-dioxan-2-yl)ethyl]azepan-1-yl}(phenyl)methanone **55** was prepared in a Grignard reaction of 1-benzoylazepan-2-one **54** with a three fold excess of the Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane that was stirred overnight at room temperature (a, **Scheme 1**), followed by addition of sodium cyanoborohydride and acetic acid at 0 ℃. The reaction mixture was

worked-up and the resulting crude product distilled at 150 – 160 ℃ to give the desired compound **55** at 47% yield that was 81% pure by GC analysis (b, **Scheme 1**).



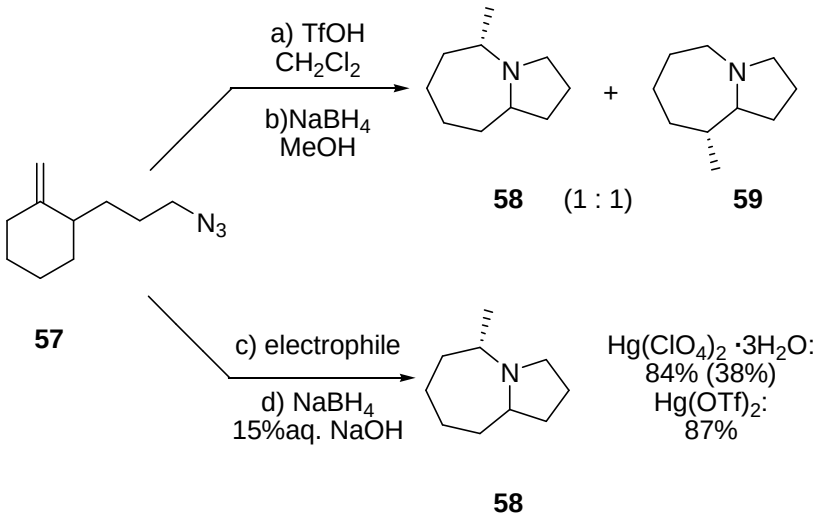
Scheme 1. (*a*) Excess Grignard reagent prepared from 2-(2-bromoethyl)-1,3-dioxane, THF, 0 ℃ to rt, overnight; (*b*) 1.24 $NaCNBH_3$, 8 ml CH_3COOH, 0 ℃; (*c*) 1 g Ammonium formate, 1g 10% Pd/C, methanol, reflux, overnight; (*d*) 5ml 10% HCl, 1 drop 70% $HClO_4$ (v/v), THF, rt, 3 days; (*e*) KCN, excess *n*-butylmagnesium bromide.[2]

Compound **55** was deprotected refluxing with ammonium formate and Pd/C in THF to yield crude 2-[2-(1,3-dioxan-2-yl)ethyl]azepane in a 70% yield (c, **Scheme 1**). The crude azepane stirred for 3 days with 10% hydrochloric acid and one drop of 70% perchloric acid (v/v) in THF, followed by sequential addition of potassium cyanide and excess of *n*-butylmagnesium bromide to yield a 1:1 mixture of the isomers of **14**. Jones and co-workers confirmed the synthetic (3,10*E*)-3-butyllehmizidine **14** to be identical to the naturally occurring compound **14**.[2]

1.3.2 Mercury-promoted Schmidt reactions

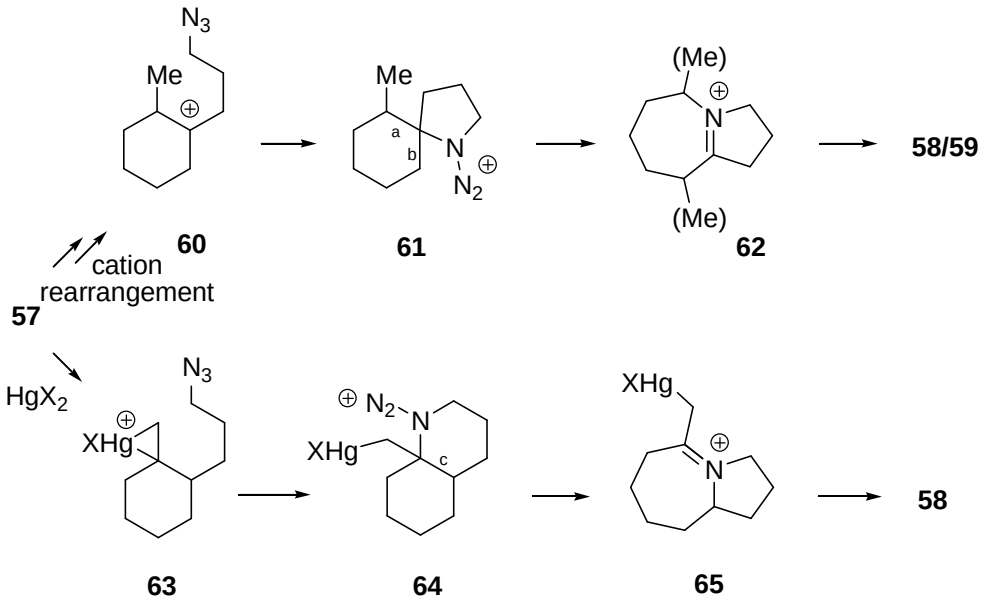
Pearson and co-workers reported the mercury-promoted Schmidt reaction of the 1-(3-azidopropyl)-2-methylenecyclohexane **57** to be more regioselective compared to the proton-promoted Schmidt reaction.[11] The lack of regioselectivity in the proton-promoted Schmidt reaction is due to carbocation rearrangement prior to cyclisation (top path, **Scheme 3**). The yields for **58**/**59** were a modest 40% affected by isolation problems (top path, **Scheme 2**). A reaction of compound **57** with stoichiometric amount of mercuric perchlorate trihydrate or

mercuric trifluoromethanesulfonate, followed by reduction with sodium borohydride gave **58** in 84% and 87% yields, respectively, as determined by GC against an internal decane standard, calibrated for relative response. Again, isolation difficulties resulted in a 38% yield of **58**.[11]

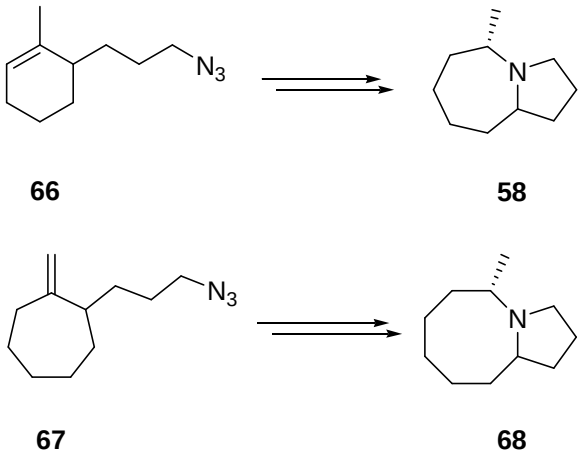


Scheme 2. Proton- vs mercury-promoted Schmidt reactions.[11]

The proton-promoted Schmidt reaction proceeds as shown (top path, **Scheme 3**). Compound **60** results from protonation of the alkene in compound **57**, followed by migration of the tertiary carbocation. Cyclisation to the aminodiazonium ion affords compound **61**, in which bonds *a* or *b* nonregioselectively migrate to form two regioisomeric iminium ions **62**. The reduction by sodium borohydride affords regioisomers **58**/**59**.[11] In the mercury-promoted Schmidt reaction (bottom path, **Scheme 3**), a mercuronium ion **63** is formed instead of the carbocation when compound **57** is treated with an electrophile. Ring-closing by nucleophilic azide attack opens the mercuronium ion **63** without rearrangement affording compound **64**, in which bond *c* rearranges and the reduction by sodium borohydride gives **58** as the only regioisomer.[11]



Scheme 3. Proposed mechanisms for Proton-and mercury-promoted Schmidt reactions.[11]

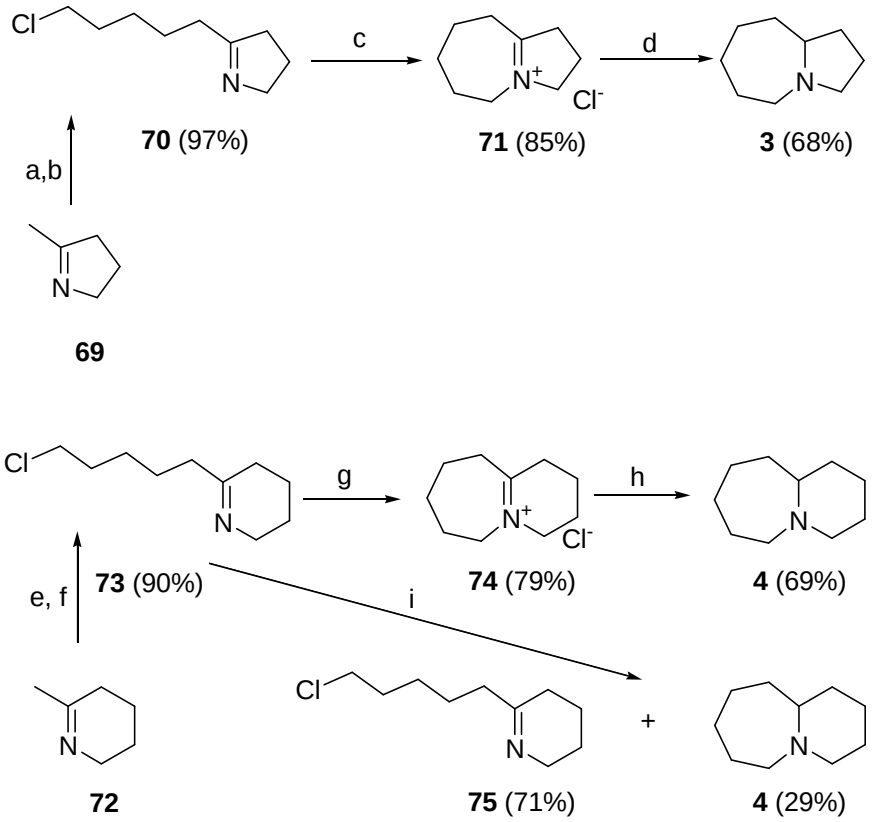


Scheme 4. Additional mercury-promoted Schmidt reactions.[11]

Compound **58** and (5*S*)-5-methyl-decahydropyrrolo[1,2-*a*]azocine **68** were also synthesised in a mercury-promoted Schmidt reaction from 6-(3-azidopropyl)-1-methylcyclohex-1-ene **66** and 1-(3-azidopropyl)-2-methylenecycloheptane **67** respectively, both in 31% isolated yield.[11]

1.3.3 Novel synthesis of octahydro-1H-pyrrolo[1,2-a]azepine and decahydropyrido[1,2-a]azepine

De Kimpe and co-workers recently reported a short, reliable synthesis of 1-azabicyclic rings, including examples containing an azepine ring. To achieve 1-azabicyclo[5.4.0]decane **3** (a,b,c,d, **Scheme 5**) they reacted 1-bromo-4-chlorobutane with 2-methyl-1-pyrroline **69**, resulting in the stable intermediate 2-(5-chloropentyl)-1-pyrroline **70** which was isolated. The formation of the iminium salt **71** was catalyzed by heat upon distillation of 2-(5-chloropentyl)-1-pyrroline **70**. Iminium salt **71** was then reduced to the desired product **3**. To achieve 1-azabicyclo[5.4.0]undecane **4** (e,f,g,h, **Scheme 5**) they reacted 1-bromo-4-chlorobutane with 6-methyl-2,3,4,5-tetrahydropyridine **72** resulting in the stable intermediate 6-(5-chloropentyl)-2,3,4,5-tetrahydropyridine **73**. The formation of the iminium salt **74** was catalysed by heating 6-(5-chloropentyl)-2,3,4,5-tetrahydropyridine **73** (neat). The iminium salt **70** was then reduced to the desired product **4**. It was also observed that treatment of 6-(5-chloropentyl)-2,3,4,5-tetrahydropyridine **73** directly with sodium borohydride resulted in a mixture of major 2-(5-chloro-pentyl)piperidine **75** and minor desired 1-azabicyclo[5.4.0]undecane **4**.[12]

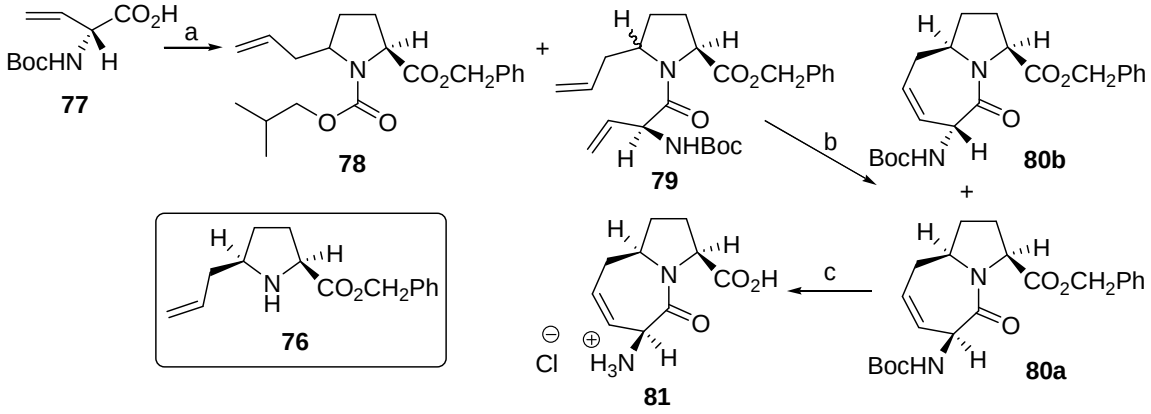


Scheme 5. The synthesis of azabicyclic alkaloids (**3**)and(**4**) with larger rings. (*a*) 1.1 equiv. LDA, THF, N_2, -78 ℃, 1 h; (*b*) 1.05 equiv. $Br(CH_2)_4Cl$, -78 ℃, 1 h + rt, 15 h; (*c*) 120 ℃; (*d*) 1 equiv. $LiAlH_4$, Et_2O, rt, 45 min; (*e*) 1.1 equiv. LDA, THF, N_2, -78 ℃, 2 h; (*f*) 1.05 equiv. $Br(CH_2)_4Cl$, -78 ℃ - rt, 15 h; (*g*) 115 ℃; (*h*) 1.5 equiv. $LiAlH_4$, Et_2O, heat, 3 h; (*i*) 2 equiv. $NaBH_4$, MeOH, heat, 3 h.[12]

1.3.4 Synthesis of 5/7-, 5/8- and 5/9-bicyclic lactams

Young and co-workers have synthesised 5/7-, 5/8- and 5/9-bicyclic lactam templates as constraints for external *β*-turns, by a route involving ring closing metathesis. The reverse turns occur on the surface of a large functional protein, and connect elements of protein secondary structure. They form an important design for molecular recognition. Synthetic *β*-turns that mimic these turns are less liable to proteolysis than natural turns, owing to the ability not to be part of a large protein to be constrained in appropriate stable conformations.[13,14]

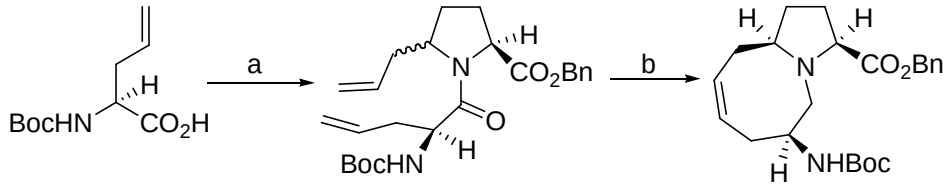
(2*S*,5*R*)-Benzyl 5-allylpyrrolidine-2-carboxylate **76** (common in all of their synthetic routes) was synthesised by a route by Scolastico *et al*. from (*S*)-2-benzyl 1-tert-butyl 5-oxopyrrolidine-1,2-dicarboxylate over four steps in an overall 79% yield.[13,15] In preparation for 5/7-bicyclic lactam they required (*R*)-2-(*tert*-butoxycarbonyl)but-3-enoic acid **77**, which was prepared by the method of Rapaport and Afzali-Ardakani from L-vinylglycine prepared from L-methionine.[16] A mixed anhydride made from compound **77** and isobutyl chloroformate was condensed and reacted with compound **76** at 0 ℃ resulting in unwanted (2 *S*)-2-benzyl-1-isobutyl-5-allylpyrrolidine-1,2-dicarboxylate **78** and desired (2*S*)-benzyl 5-allyl-1-[(*S*)-2-(*tert*-butoxycarbonyl)but-3-enoyl]pyrrolidine-2-carboxylate **79** in poor yields (a, **Scheme 6**). A ring closing methatesis by the Grubbs catalyst resulted in (3*S*,6*S*,9a*R*,*Z*)-benzyl 6-(*tert*-butoxycarbonyl)-5-oxo-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **80a** and (3*S*,6*R*,9a*R*,*Z*)-benzyl 6-(*tert*-butoxycarbonyl)-5-oxo-2,3,5,6,9,9a-hexahydro-1*H*-pyrrolo[1,2-*a*]azepine-3-carboxylate **80b** (b, **Scheme 6**). Compound **80a** was hydrolysed to the amino acid hydrochloride **81** in a quantitative yield (c, **Scheme 6**).[13]



Scheme 6. (*a*) (i) $ClCO_2{}^{i}Bu$, pyridine, THF, 0 ℃, 15 min, (ii) **76**, THF, rt, 3 h (23% **78**, 20% **79**); (*b*) ([*c*-$C_6H_{10})_3$]P)$_2Cl_2$Ru=CHPh, CH_2Cl_2, reflux, 24 h (58% **80a**, 9% **80b**); (*c*) 6 N HCl, 60 ℃, overnight (quant.).[13]

(*S*)-2-(*tert*-Butoxycarbonyl)pent-4-enoic acid **82** was prepared by the *in situ* Wittig reaction of (*S*)-*tert*-butyl 2-(*tert*-butoxycarbonyl)-4-oxobutanoate with

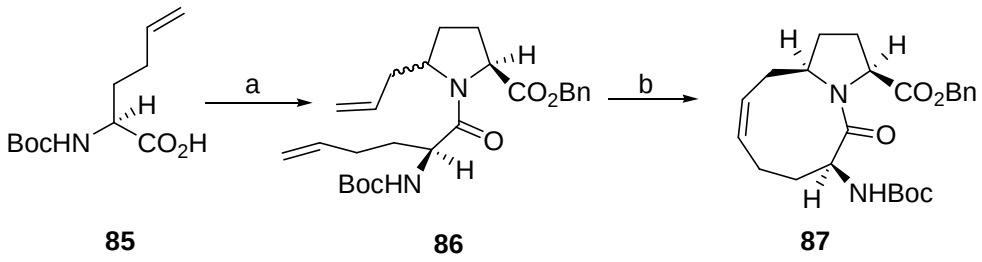
methyltriphenylphosphonium ylide, followed by hydrolysis of the alkene using 6 N hydrochloric acid and treatment of the resultant amino acid with di-*tert*-butyl dicarbonate under Schotten-Baumann conditions. The mixed anhydride formed on reacting compound **82** with isobutyl chloroformate was reacted with compound **76** at –78 ℃ affording unwanted compound **78** and the desired (*S*)-benzyl 5-allyl-1-[(*S*)-2-(*tert*-butoxycarbonyl)pent-4-enoyl]pyrrolidine-2-carboxylate **83** in poor yield (a, **Scheme 7**). Ring closing metathesis gave 5/8-bicyclic lactam **84** as a single diastereoisomer in good yield (b, **Scheme 7**).[13]



82 **83** **84**

Scheme 7. (*a*) (i) $ClCO_2{}^{i}Bu$, pyridine, THF, -78 ℃, 15 min, (ii) **76**, CH_2Cl_2, rt, 3 h (33% **78**, 15% **83**); (*b*) ([*c*-$C_6H_{10})_3$]P)$_2Cl_2$Ru=CHPh, CH_2Cl_2, reflux, 24 h (65%).[13]

In making (*S*)-2-(*tert*-butoxycarbonyl)hex-5-enoic acid **85** (*S*)-*tert*-butyl 2-(*tert*-butoxycarbonyl)-5-[methoxy(methyl)amino]-5-oxopentanoate was reduced to (*S*)-*tert*-butyl 2-(*tert*-butoxycarbonyl)-5-oxopentanoate (an aldehyde) using tri-*tert*-butoxyaluminium hydride followed by Wittig reaction. (*S*)-*tert*-Butyl 2-(*tert*-butoxycarbonyl)hex-5-enoate was hydrolysed to the corresponding amino acid and protected with the Boc group to afford compound **85**. Compound **86** was accompanied by compound **78** as products in the reaction between the mixed anhydride and compound **76** (a, **Scheme 8**). Ring closing metathesis gave 5/9-bicyclic lactam **87** as a single diastereoisomer in good yield (b, **Scheme 8**).[13]



Scheme 8. (*a*) (i) $ClCO_2{}^{i}Bu$, pyridine, THF, -78 ℃, 15 min, (ii) **76**, CH_2Cl_2, rt, 3 h (36% **78**, 27% **86**); (*b*) $([c\text{-}C_6H_{10})_3]P)_2Cl_2Ru{=}CHPh$, CH_2Cl_2, reflux, 24 h (84%).[13]

There are many other literature examples dedicated to the making of 5/7 azabicyclic alkaloids.[17-21]

1.4 The Wits Background

1.4.1 Introduction to enaminones

An enaminone is a α,β aminoenone in which the lone pair is in conjugation with the unsaturated system (see Figure 8). The acyl group stabilises and monitors the reactivity of the enamine unit. The electron-withdrawing group (EWG) may either influence or overwhelm the reactivity of the enaminone core. The kinds of enaminones this group has explored are the vinylogous amides, urethanes, cyanamides, ureas, sulfonamides and nitramines (see Figure 8).[22] In virtually all work from this group, the nitrogen is part of a heterocyclic ring.

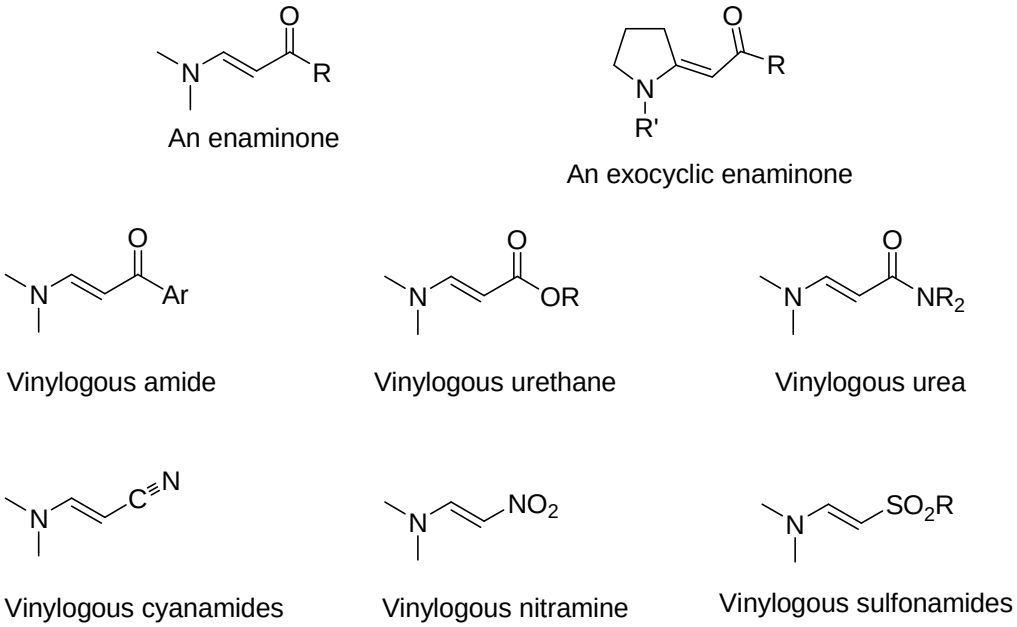
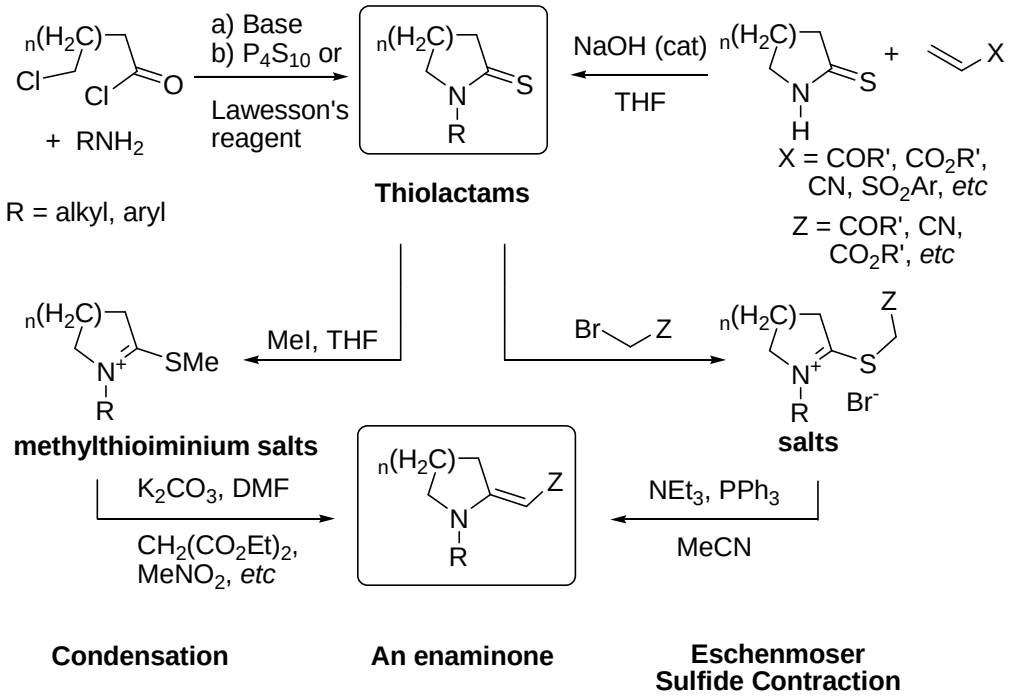


Figure 8. Examples of enaminones.[22]

The cyclic enaminones needed for this project are easily obtained from thiolactams. The thiolactams are prepared in a thionation reaction from lactams made from primary amine and bifuctional reagents (e.g. 4-chlorobutanoyl chloride) or by a Michael addition reaction of secondary thiolactams (e.g. pyrrolidine-2-thione) to methyl vinyl ketone-like acceptors (e.g. acrylate esters). The alkylidene substituent is either introduced in a Knoevenagel like condensation of a relatively acidic component (e.g. nitromethane) with methylthioiminium salts or in an Eschenmoser sulfide contraction reaction, with a loss of sulfur from the salt that results when thiolactams react with α-halocarbonyl compounds (**Scheme 9**).[22]



Scheme 9. General approach to enaminones.[22]

Enaminones can react as both electrophiles and as nucleophiles. As nucleophiles, the enaminone's expected nucleophilicity at N (**I**, Figure 9) and C (**ii**, Figure 9) is extended to the carbonyl O group (**iii**, Figure 9) through conjugation. Strong bases can deprotonate the carbon β to N or acid induced tautomerism to give further nucleophilicity (**iv**, Figure 9). As electrophiles, enaminones can participate in 1,2-and 1,4-additions (**v**, **vi**, Figure 9). We intend to explore the 'enamine' nucleophilicity at C (**ii**, Figure 9) to access azabicyclic alkaloid scaffolds.[22]

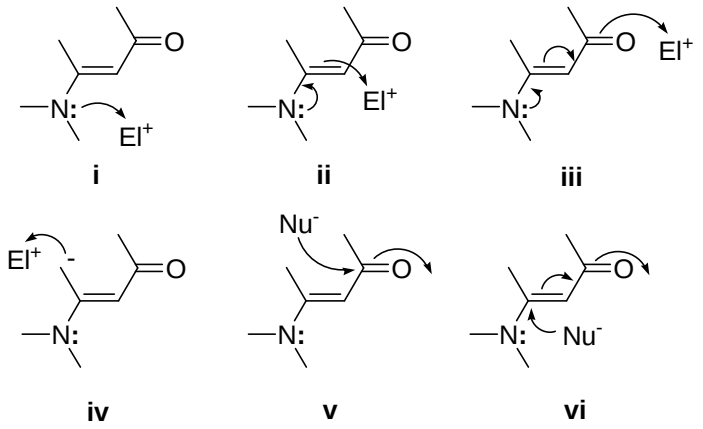
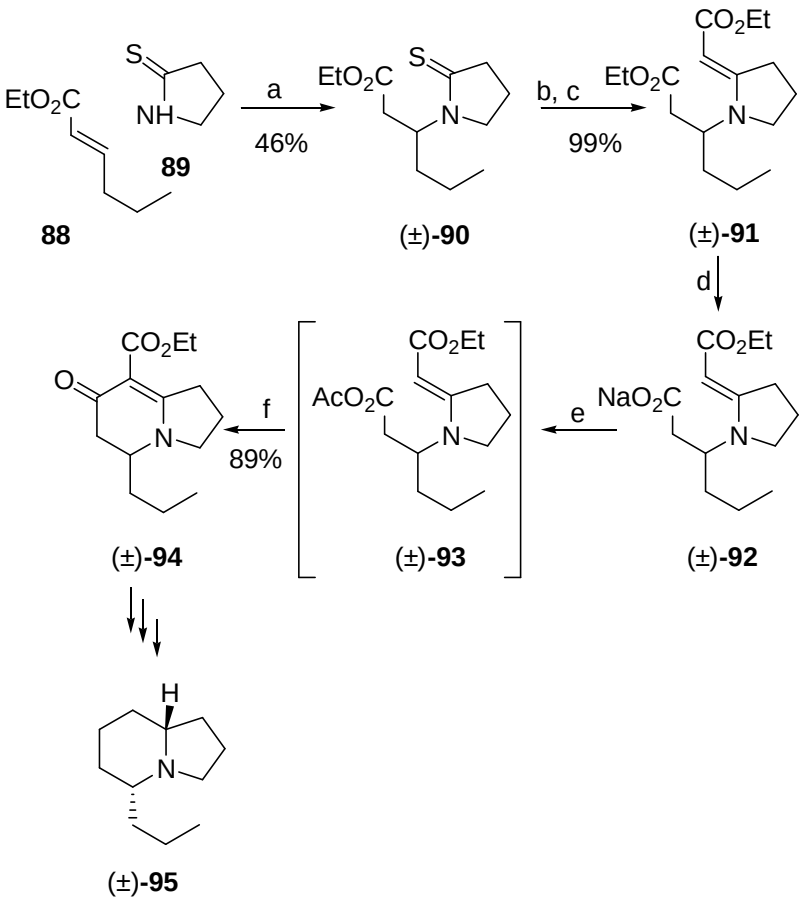


Figure 9. Enaminone rectivity.[22]

1.4.2 Alkaloid synthesis via enaminones: Selected Wits examples

Michael and Gravestock have reported the synthesis of alkaloid 167B (±)**-95** in eight steps with an overall yield of 7.2% based on pyrrolidine-2-thione **89**. Their synthesis started with the Michael addition of pyrrolidine-2-thione **89** to the Michael acceptor **88** to yield ethyl 3-(2-thioxopyrrolidin-1-yl)hexanoate (±)**-90** in moderate yield, which they could not improve (a, **Scheme 10**). They then took 3-(2-thioxopyrrolidin-1-yl)hexanoate (±)**-90** through an Eschenmoser reaction with ethyl 2-bromoacetate, resulting exclusively in the formation (*E*)-ethyl 3-[2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]hexanoate (±)**-91** with excellent yield (b, c. **Scheme 10**). Compound (±)**-91** could form the basis the desired acylative cyclisation, but they had to convert compound (±)**-91** into an anhydride (±)**-93** owing to inefficiency of the saturated ester as an acylating agent. This they did through a chemoselective hydrolysis of compound (±)**-91** with sodium hydroxide refluxing in water. They then followed with the reaction of the resulting salt sodium (*E*)-3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)hexanoate (±)**-92** with acetic anhydride *in situ* at ambient temperature. The enaminone chemistry then took centre stage when the temperature was raised to reflux with a spontaneous cyclisation of the anhydride, yielding the ethyl 7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (±)**-94** in excellent yield over three steps. The

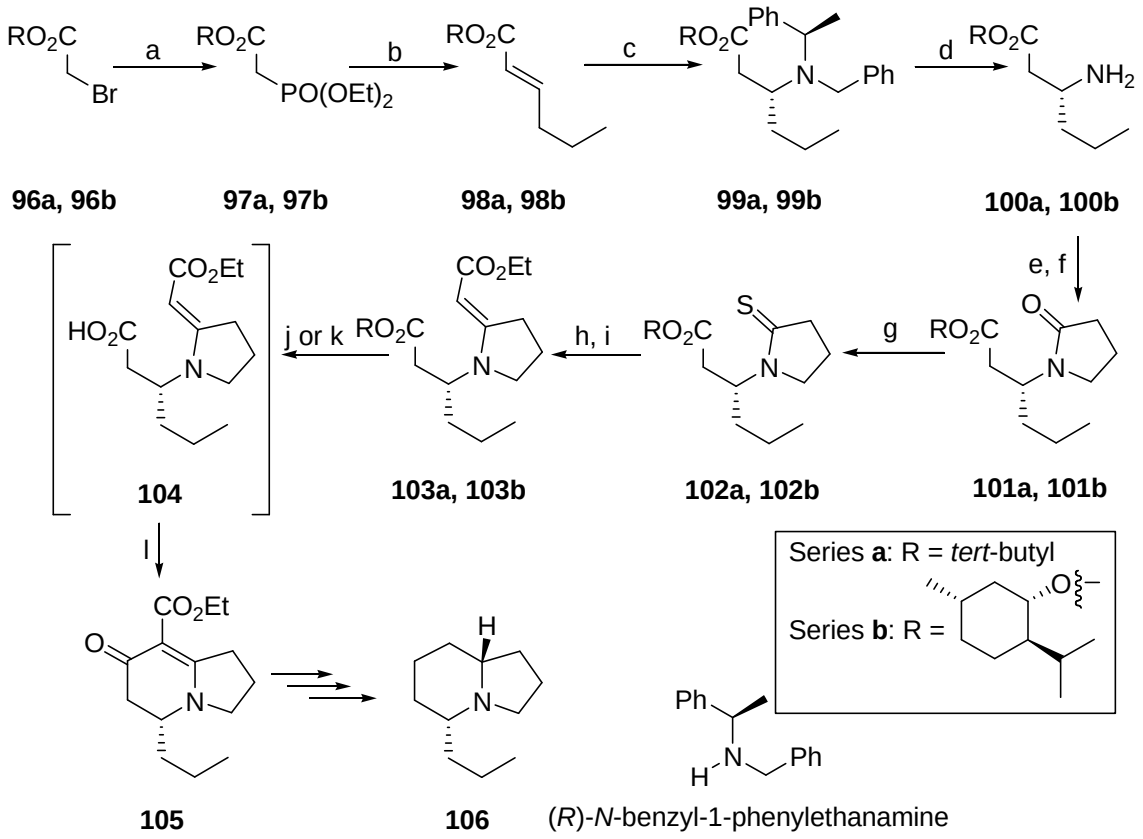
synthesis was completed by hydrolysis and decarboxylation of the ester and reduction of the remaining functional groups.[23]



Scheme 10. (*a*) NaOH (cat.), THF, reflux; (*b*) $BrCH_2CO_2Et$, MeCN, rt; (*c*) PPh_3, NEt_3, MeCN, rt; (*d*) NaOH, H_2O, reflux; (*e*) Ac_2O, MeCN, rt; (*f*) MeCN, reflux.[23]

Michael and Gravestock extended this work to include an enantioselective synthesis of (–)-indolizidine 167B **106**.[24] They achieved this by using the optically pure chiral amine *N*-benzyl-1-phenylethylamine in the conjugate addition to α,ß-unsaturated esters, a procedure demonstrated by Davies and Ichihara.[25] To begin, they had to prepare (*E*)-tert-butyl hex-2-enoate **98a** using the Horner-Wadsworth-Emmons variation of the Wittig reaction. They treated *tert*-butyl 2-bromoacetate **96a** with triethyl phosphite at 110 ℃ achieving *tert*-butyl 2-(diethoxyphosphoryl)acetate **97a**, which they then treated with butanal in the

presence of 1,5-diazabicyclo[5.4.0]undec-7-ene and lithium chloride, giving (*E*)-*tert*-butyl hex-2-enoate **98a** in 63% yield and 99:1 diastereoselectivity (a, b, **Scheme 11**, Series a). Michael addition of the (*R*)-N-benzyl-1-phenylethanamine anion to (*E*)-*tert*-butyl hex-2-enoate **98a** gave them the optically active (*R*)-*tert*-butyl 3-{benzyl[(*R*)-1-phenylethyl]amino}hexanoate **99a** in 74% yield (c, **Scheme 11**, Series a). Compound **99a** was debenzylated in a catalytic reduction reaction giving (*R*)-*tert*-butyl 3-aminohexanoate **100a** in 70% yield (d, **Scheme 11**, Series a). (*R*)-*tert*-Butyl 3-(2-oxopyrrolidin-1-yl)hexanoate **101a** was made by first forming an uncyclised amide intermediate using 4-chlorobutanoyl chloride and sodium hydrogen carbonate as proton scavenger, which was cyclised by addition of freshly sublimed potassium *tert*-butoxide in 56% yield over two steps (e, f, **Scheme 11**, Series a). Compound **101a** was thionated using Lawesson's reagent to achieve (*R*)-*tert*-butyl 3-(2-thioxopyrrolidin-1-yl)hexanoate **102a** in 85% yield (g, **Scheme 11**, Series a) . The vinylogous urethane (*R*,*E*)-tert-butyl 3-[2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl]hexanoate **103a** was prepared in 79% yield over two steps, first by *S*-alkylating compound **102a** with ethyl bromoacetate followed by the Eschenmoser sulphide contraction (h, i, **Scheme 11**, Series a). The *tert*-butyl ester was not a suitable acylating agent for a ß-aminoacrylate **103a**. (*R*,*E*)-3-[2-(2-Ethoxy-2-oxoethylidene)pyrrolidin-1-yl]hexanoic acid **104** was synthesised using trimethylsilyl iodide to cleave the *tert*-butyl group of compound **103a** in variable yields (17%–95%) (j, **Scheme 11**, Series a). This they attributed to extensive decomposition of the labile vinylogous urethane under acid hydrolysis conditions. Michael and co-workers managed to make indolizidine (*R*)-ethyl 7-oxo-5-propyl-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **105** in 55% yield over two steps from the impure acid **104** in a reaction with acetic anhydride (l, **Scheme 11**, Series a). The unsuccessful cyclisation step made them recall that cyclisation under basic conditions gave better success. But using the less hindered ethyl ester would result in far less diastereoselectivity as determined by the Davies procedure.[25] They then replaced the *tert*-butyl group with a sterically demanding *secondary* alcohol, (+)-menthol.[24]



Scheme 11. (*a*) $P(OEt)_3$, 110℃; (*b*) butanal, DBU, LiCl, MeCN, rt; (*c*) (*R*)-*N*-benzyl-1-phenyl-ethanamine, BuLi, THF, -78℃; (*d*) H_2 (7 atm), 10 % Pd-C, HOAc, rt; (*e*) $Cl(CH_2)_3COCl$, $NaHCO_3$, CHCl, RT; (*f*) $KOBu^t$, Bu^tOH; (*g*) Lawesson's reagent, toluene, reflux; (*h*) $BrCH_2CO_2Et$, MeCN, rt (for R = Bu^t); (*i*) Ph_3P, Et_3N, MeCN, rt; (*j*) Me_3SiI, CCl_4, rt (for R = Bu^t); (*k*) KOH, EtOH, reflux (for R = menthyl); (*l*) Ac_2O, MeCN, 50 ℃. [24]

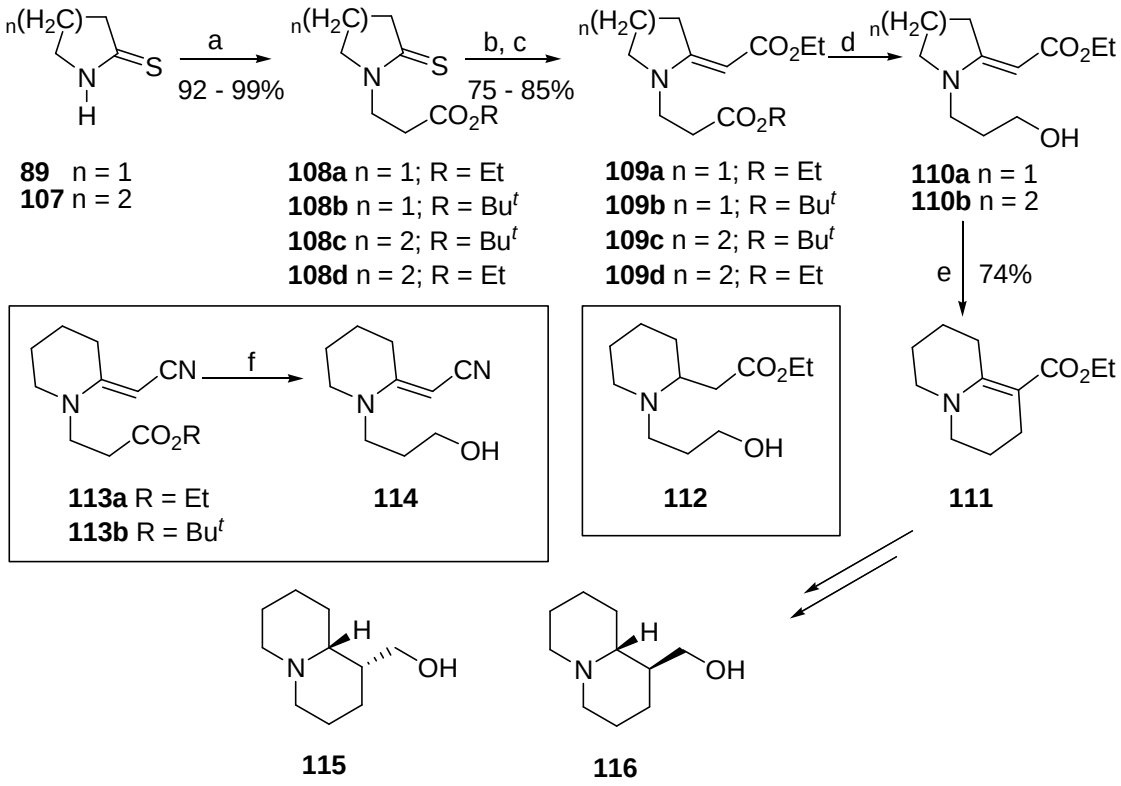
(1*S*,2*R*,5*S*)-2-Isopropyl-5-methylcyclohexyl 2-bromoacetate **96b** was quantitatively prepared following a procedure described by Vandewalle and co-workers from (+)-menthol, sodium hydroxide and bromoacetyl bromide in toluene.[26] The rest of the synthesis from compound **96b** to compound **103b** was analogous to that described for the *tert*-butyl series. These compound were prepared with the accompanying yields, **97b**, **98b** (92%), amine **99b** (93%), **100b** (91%), **101b** (66%), **102b** (83%) and **103b** (89%) (a, b, c, d, e, f, g, h, i, **Scheme 11**, Series b). Then they hydrolysed **103b** in a reaction with potassium hydroxide refluxing in methanol, followed by the cyclisation of the unpurified acid using acetic anhydride and potassium carbonate in dry acetonitrile to give compound

105 in 87% yield over two steps. They achieved the enantioselective synthesis of (–)-indolizidine 167B **106** over four steps from compound **105**. [24]

The previous synthesis illustrated the formation of an azabicyclic system by an intramolecular acylation of an enaminone. Michael's team has also made azabicyclic systems by an intramolecular alkylation of an enaminone.[25] For example; they used six-membered vinylogous urethanes in the synthesis of (±)-lupinine **115** and (±)-epilupinine **116**. This work also showed interesting differences in the behavior of 5-and 6-membered vinylogous urethanes. Their synthesis began with the Michael addition reaction of thiolactams **89** and **107** to *tert*-butyl acrylate or ethyl acrylate in dry tetrahydrofuran at 40 ℃ giving *N*-alkyl-thiolactams **108a**–**d** in excellent yield (a, **Scheme 12**). The *N*-alkyl-thiolactams **108a**–**d** were converted into vinylogous urethane **109a**–**d** in good yields in a two-step Eschenmoser sulfide contraction reaction with ethyl bromoacetate in acetonitrile at room temperature and followed by triphenylphosphine and triethylamine in acetonitrile at room temperature (b, c, **Scheme 12**).[27]

Brown's observation ("*Reactions which involve the loss of an exo double bond will be favored in the 6-ring as compared to the corresponding 5-ring derivative*")[28] about the stability and reactivity of double bonds that are exocyclic or endocyclic to rings of varying size applied to their vinylogous urethanes.[27] The loss of the exo double bond in their attempted reduction of the saturated ester of the vinylogous urethanes **109c** and **109d** resulted in compound **112**, while their reduction of the saturated ester of the vinylogous urethanes **109a** and **109b** resulted in compound **110a** (d, **Scheme 12**) that retained the exo double bond. Michael and co-workers took their study further to investigate the lability of piperidinylidene vinylogous urethane towards conjugate reduction by using the vinylogous cyanamide. They found that the reduction of vinylogous cyanamides **113a** and **113b** gave product **114** in good yields of 74% and 60% respectively, with no presence of over reduced product (f, **Scheme 12**). Compound **109d** was best reduced with lithium aluminium hydride in a 4:1 ratio combination of solvents

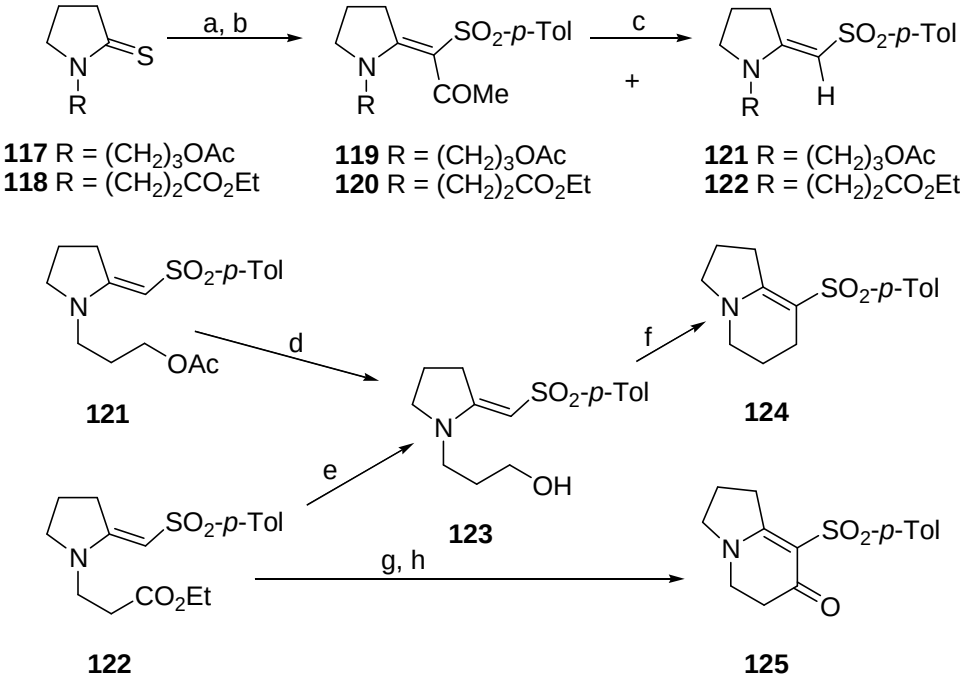
toluene and diethyl ether at 0 ℃, yielding compoun d **110b** (62%) and compound **112** (13%). Michael's team converted the alcohol into a good leaving group by substituting it with iodine in the presence of triphenylphosphine and imidazole, making alkyl iodide, which formed *in situ* and immediately cyclised to give ethyl 3,4,6,7,8,9-hexahydro-2*H*-quinolizine-1-carboxylate **111** in 74% yield, when the reactants were heated in a 2:1 mixture of toluene and acetonitrile. (±)-Lupinine **115** was achieved in two more steps and (±)-epilupinine **116** was made in three more steps from compound **111** in excellent yields.[27]



Scheme 12. (*a*) CH_2CHCO_2R, NaOH or NaH, THF, 40 ℃, 16 h; (*b*) $BrCH_2CO_2Et$, MeCN, rt, 16 h; (*c*) Ph_3P, NEt_3, MeCN, rt, 16 h; (*d*)$LiAlH_4$, THF, rt, 2 h; (*e*) Ph_3P, imizadole, I_2, toluene, 120 ℃, 80 min; (*f*) $LiAlH_4$, THF, rt, 48 h.[27]

Michael and co-workers have recently prepared azabicyclo type compound using vinylogous sulfonamides instead of the usual vinylogous urethane.[29] The thiolactams were activated with iodomethane and the resulting thioiminium salt was transformed to ß-substituted enamines in the presence of an activated

methylene system. The thiolactams **117** and **118** were prepared in a thionation reaction of corresponding lactams in good yields. 1-[(4-Methylphenyl)sulfonyl]propan-2-one was also prepared in a reaction of sodium 4-methylbenzenesulfinate with chloroacetone using procedures in literature in excellent yields.[30] The thiolactams **117** and **118** were reacted with 1-[(4-methylphenyl)sulfonyl]propan-2-one resulting in the (*E*)-3-[2-(2-oxo-1-tosylpropylidene)pyrrolidin-1-yl]propyl acetate **119** and (*E*)-ethyl 3-[2-(2-oxo-1-tosylpropylidene)pyrrolidin-1-yl]propanoate **120** they expected plus the vinylogous sulfonamides (*E*)-3-[2-(tosylmethylene)pyrrolidin-1-yl]propyl acetate **121** and (*E*)-ethyl 3-[2-(tosylmethylene)pyrrolidin-1-yl]propanoate **122** (with the illustrated (*E*) geometry) that they did not expect (a, b, **Scheme 13**). This was as a result of spontaneous deacylation of products due to increasing reaction time. Compounds **121** and **125** were made by treating **119** and **120** with trifluoroacetic acid in acceptable yields (c, **Scheme 13**). In order to get higher yields, it proved to be better to separate the mixture of product first and do the deacylation step on compounds **119** and **120** rather than forcing complete deacylation of the mixture.[24] (*E*)-3-[2-(Tosylmethylene)pyrrolidin-1-yl]propan-1-ol **123** was prepared from compound **121** in a reaction with potassium carbonate (d, **Scheme 13**) and from compound **122** in a reaction with lithium aluminium hydride (e, **Scheme 13**). Compound **123** was ring-closed using triphenylphosphine, imidazole and iodine (f, **Scheme 13**) resulting in 8-tosyl-1,2,3,5,6,7-hexahydroindolizine **124** in good yield, while they also achieved 8-tosyl-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **125** over two steps in good yield using potassium carbonate and acetic anhydride (g, h, **Scheme 13**).[29] This work is now being extended to the synthesis of 3,5-disubstituted indolizidine alkaloids [S Travis, PhD].

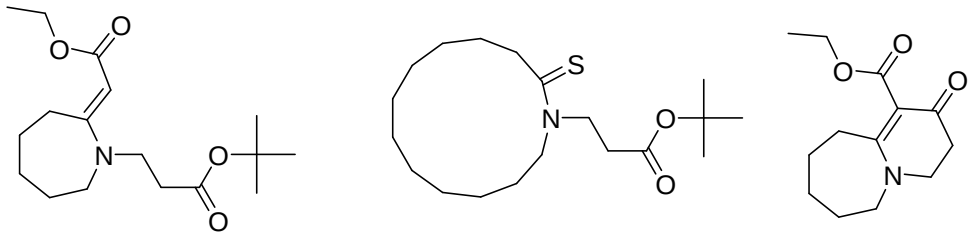


Scheme 13. (*a*) MeI, THF, 0 ℃, 1-17 h; (*b*) $MeOCCH_2SO_2^-p^-Tol$, NEt_3, CH_2Cl_2, rt, 72 h (yields:**120** + **122**, 5% + 81%; **121** + **123**, 5% + 70%); (*c*) TFA, 80-90 ℃, 30 min (yields: **122**, 87%; **123**, 92%); (*d*) K_2CO_3, MeOH, rt, 1 h (96%); (*e*) $LiAlH_4$, THF, rt, 15 h (94%); (*f*) PPh_3, Im, I_2, MeCN, reflux, 2 h (80%); (*g*) KOH, EtOH, reflux, 30 min, then HCl; (*h*) K_2CO_3, AcO, MeCN, 50 ℃, 2 h, rt, 21 h (71% over 2 steps).[29]

1.5 Aims

This MSc project is a continuation of the Honours projects of Ramsuran and Madeley.[31,32] Ramsuran attempted the synthesis of azabicyclic systems **3** and **4** using well established methods within our laboratories for the synthesis of azabicyclic systems such as **1** and **2**. Owing to time limitation she could not get to the all-important ring closing-step that utilizes enaminone chemistry, but successfully made (*E*)-*tert*-butyl 3-(2-(2-ethoxy-2-oxoethylidene)azepan-1-yl)propanoate **126**. On the other hand Madeley synthesized the scaffold for the azabicyclic system **4**, namely ethyl 2-oxo-2,3,4,6,7,8,9,10-octahydropyrido[1,2-*a*]azepine-1-carboxylate **128**. He also attempted to synthesise azabicyclic

systems in which one of the rings was 13-membered fused to a 6-membered ring **131**, but managed to make compound **127**.

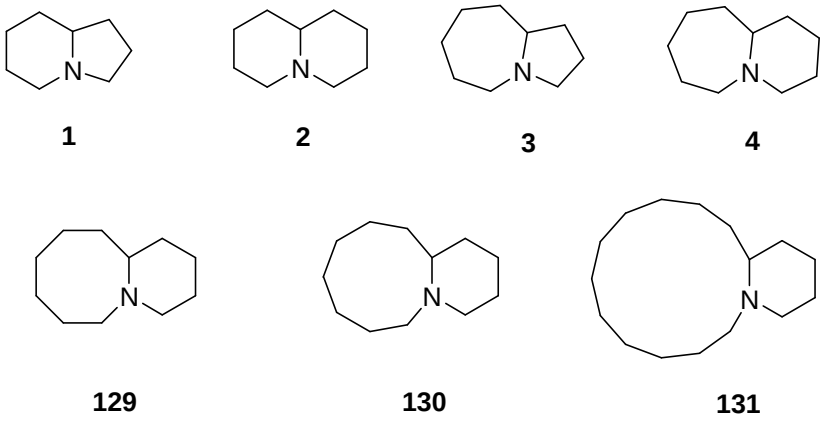


126 **127** **128**

FIgure 10. Ramsuran's compound **126** and Madeley's compounds **127** and **128**

Before we could extend the methodology for making azabicyclic systems **1** and **2** to larger rings, we had to make these azabicyclic systems first, to make sure the methodology works in my hands.

We aimed to synthesise scaffolds from which we could make the azabicyclic systems octahydroindolizine **1**, octahydro-1*H*-quinolizine **2**, decahydropyrido[1,2-*a*]azepine **4**, decahydro-1*H*-pyrido[1,2-*a*]azocine **129**, dodecahydropyrido[1,2-*a*]azonine **130** and **131** (Figure 11).



1 **2** **3** **4**

129 **130** **131**

Figure 11. Azabicyclic systems with small, medium and large rings

Thus, the principal aim of my MSc is to make 1-azabicyclic systems in which a 7-membered or larger ring is fused to a six-membered ring where they share one common nitrogen atom. These could then be analogues of the 5,6 (indolizidines) and 6,6 (quinolizidines) ring systems, which as shown previously, can easily be made by cycloalkalation or cycloacylation of suitable enamine precursors. Therefore, in this work, the idea is to start with a large-ring enaminones (**132**, Figure 12), onto which a six-membered ring can be fused by utilizing a variety of methods. It is thus necessary to prepare suitable enaminones, which we intended would be derived from lactam precursors, as described in Section 1.4.1.

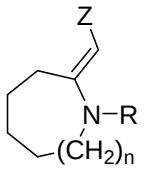
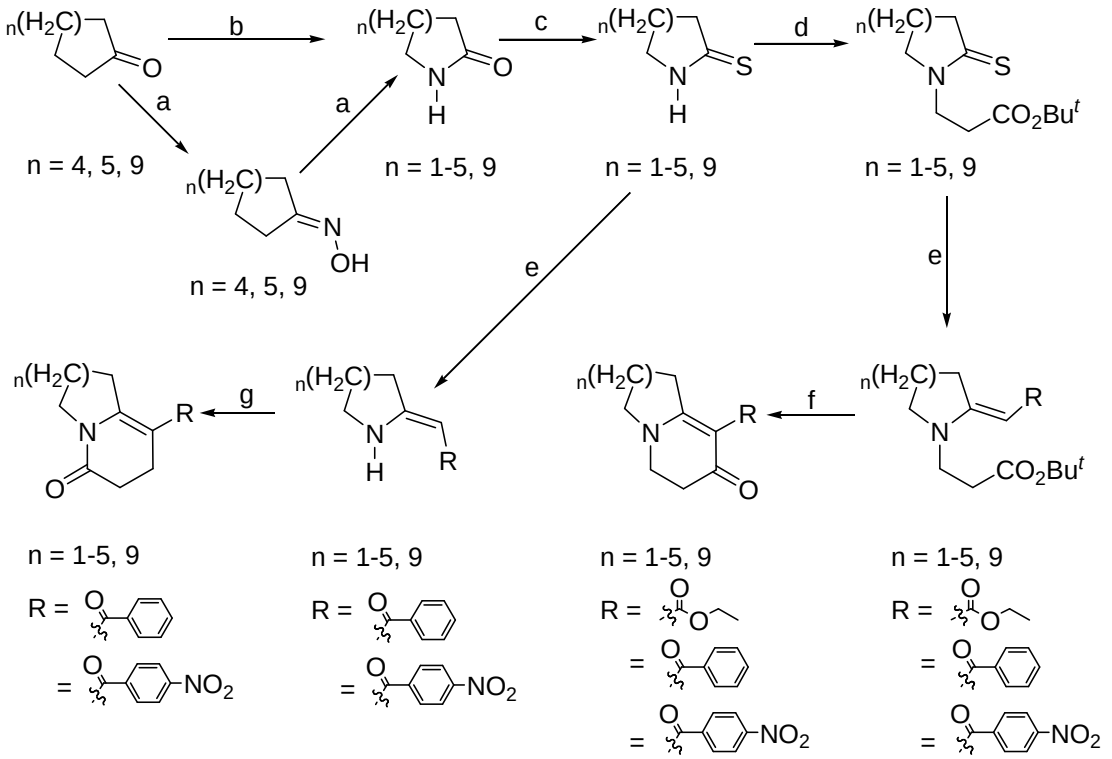


Figure 12. **132** n = 1, 2, 3 and 7

The synthetic strategy we wish to adopt begins with the Beckmann rearrangement reaction (a, **Scheme 14**) or the Schmidt reaction for making lactams from ring ketones that were relatively expensive (b, **Scheme 14**). The Beckmann rearrangement reaction is a two-step reaction starting from cyclic ketone, resulting in the formation of a ketoxime in the first step and the second step is the rearrangement of the ketoxime to a lactam. The lactams are converted into thiolactams utilising a thionation reaction (c, **Scheme 14**). The *N*-Alkylated thiolactams are formed are a result of a Michael reaction between NH thiolactams and *tert*-butyl acrylate (d, **Scheme 14**).

The enaminones formed can be achieved by using an Eschenmoser sulfide contraction reaction of *N*-alkylated thiolactams or N-H thiolactams with good electron withdrawing groups (e, **Scheme 14**). For this project, we decided to prepare vinylogous urethanes (R = CO_2Et) and vinylogous amides (R = COC_6H_4-*p*-NO_2 or COPh). This is a two step reaction which starts with *S*-alkylation of the

electron withdrawing group which is followed by the extrusion of the sulfur substituent.



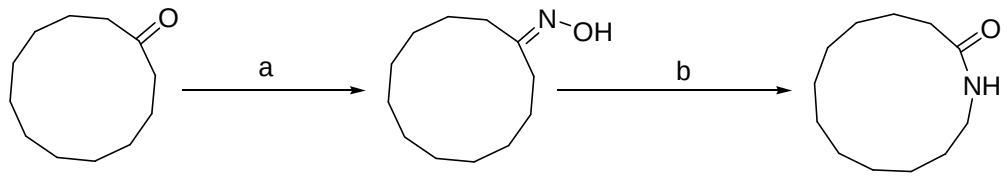
Scheme 14. (*a*) Beckmann rearrangement reaction; (*b*) Schmidt reaction; (*c*) Thionation reaction; (*d*) Michael addition reaction; (*e*) Eschenmoser sulfide contraction reaction; (*f*) Ring-closing step 1; (*g*) Ring-closing step 2.

The next step was to explore two different methods for building the six-membered ring onto the enaminone scarffold. In the first, we would use the N-alkylated products in intramolecular acylation reactions by first hydrolyzing the *tert*-butyl ester to an acid, and then exploiting a previously developed cyclisation via a mixed anhydride to give the desired products (f, **Scheme 14**). In the second approach, we planned to investigate an aza-annulation process introduced by Stille and co-workers in which secondary enamines are treated with acryloyl chloride to give isomeric azabicycles (g, **Scheme 14**).[33]

CHAPTER 2: RESULTS AND DISCUSSION

2.1 Synthesis of azacyclotridecane-2-one by the Beckmann rearrangement

Although commercially available and cheap, azacyclotridecane-2-one **135** was initially synthesized by a known Beckmann rearrangement reaction.[34] This is a two step reaction in which the first step is the formation of ketoxime and the second step is the rearrangement of the ketoxime to a lactam. Cyclododecanone oxime **134** was prepared in 96% yield from cyclododecanone **133** and hydroxylamine hydrochloride (a, **Scheme 15**). Its melting point of 117 – 118 ℃ was different to that of cyclododecanone 59 – 61 ℃ .[35a]



133 **134** **135**

Scheme 15. (*a*) 2.3 eq. $NH_2OH.HCl$, 2.5 eq. $C_2H_3O_2Na.3H_2O$, MeOH, 90 ℃, 3 h; (*b*) 0.05 eq. Cyanuric chloride, MeCN, relfux, 2.33 h.

The IR spectrum had a broad peak at ν_{max} = 3413 cm^{-1} for an OH group, ν_{max} = 1642 cm^{-1} for a C=N group and no indication of the carbonyl group at ν_{max} = 1720 cm^{-1} from cyclododecanone. ^1H NMR spectroscopy indicated the presence of the OH group at δ = 7.80 ppm. The ^{13}C NMR spectrum showed the up-field shift of the quaternary carbon peak from $\delta \approx$ 200 ppm to δ = 161.2 ppm, indicating the disappearance of the carbonyl carbon in cyclododecanone **133** and the appearance of the C=N group in cyclododecanone oxime **134**. There were no competing side reactions; this can be seen by the exceptionally high yield for this reaction. The elevated melting point is presumably due to the strong hydrogen

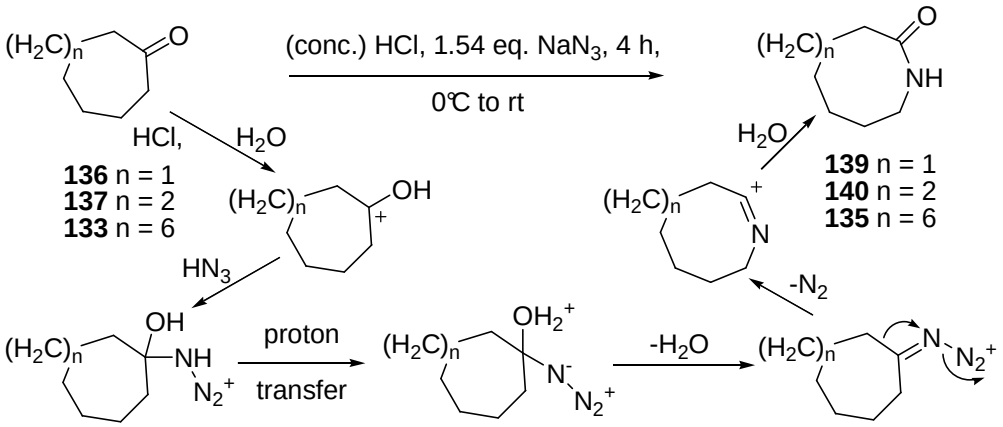
bonding between the N···HO in cyclododecanone oxime **134** as compared to dipole-dipole forces in cyclododecanone.

In the second step of the Beckmann rearrangement reaction a mixture of cyclododecanone oxime **134** and cyanuric chloride in acetonitrile was refluxed followed by base treatment with sodium hydrogen carbonate. The crude product was recrystallised from a mixture of ethyl acetate and hexane, giving the pure azacyclotridecane-2-one **135** in 98% yield (b, **Scheme 15**). Its melting point of 151 ℃ was comparable to the literature value [35b] of 150 – 153 ℃ and higher than that of cyclododecanone oxime **134**. The IR spectrum had a broad peak at ν_{max} = 3307 cm^{-1} for the NH group and strong peak at ν_{max} = 1639 cm^{-1} for the amide carbonyl group. ^{1}H NMR spectroscopy indicated the presence of the NH group at δ = 5.53 ppm, which is an up-field shift of about δ = 2.27 ppm from the OH peak of cyclododecanone oxime **134**. The ^{13}C NMR spectrum showed the down-field shift of the quaternary carbon peak from δ = 161.2 ppm to δ = 173.8 ppm, indicating an amide type carbonyl group. There were also no competing side reactions. This two-step Beckmann reaction was a success with an overall yield of 95%.

2.2 Synthesis of lactams by the Schmidt reaction

The azocan-2-one **139** and azonan-2-one **140** are also relatively expensive when compared to pyrrolidin-2-one, piperidin-2-one and azepan-2-one. Attempted synthesis of compounds **139** and **140** from their respective ketooximes in the Beckmann rearrangement were unsuccessful, which is in line with the finding of Furuya and co-workers, except that they managed to make compound **140**.[34] However, the Schmidt reaction, in which the ketone is treated with sodium azide under acidic conditions, gave the three lactams in good yield (**Scheme 16**).[36] The

products were purified by recrystallisation. The mechanism is also shown in the Scheme.



Scheme 16. The Schmidt reaction and its mechanism.[36]

Azocan-2-one **139** was synthesised in 83% yield from cycloheptanone **136**. Its melting point of 35 – 36 ℃ was comparable to liter ature value of 35 – 38 ℃. [35c] The IR spectrum had a broad peak at ν_{max} = 3291 cm^{-1} for an NH group and strong peak at ν_{max} = 1659 cm^{-1} for the amide carbonyl group. ^{1}H NMR spectroscopy indicated the presence of NH group at δ = 6.48 ppm. The ^{13}C NMR spectrum showed the up-field shift of the quaternary carbon peak from $\delta \approx$ 200 ppm to δ = 173.4, indicating a change from ketone type quaternary to an amide type quaternary. The reaction had no observable side reaction by NMR spectroscopy.

Azonan-2-one **140** was synthesised in 96% yield from cyclooctanone **137**. Its melting point of 75 – 76 ℃ is clearly different to that of cyclooctanone **137** 32 – 41 ℃ and was comparable to the literature value of 74 – 76 ℃. [35d] The IR spectrum had a broad peak at ν_{max} = 3301 cm^{-1} for an NH group and strong peak at ν_{max} = 1651 cm^{-1} for the amide carbonyl group. ^{1}H NMR spectroscopy indicated the presence of NH group at δ = 6.36 ppm. The ^{13}C NMR spectrum showed the up-field shift of the quaternary carbon peak from $\delta \approx$ 200 ppm to δ =

178.0, indicating a change from ketone type to an amide type carbonyl group. The high yield suggests few side reactions. Azacyclotridecan-2-one **135** was synthesised in 81% yield from cyclododecanone. The data were comparable to those obtained on the product from the Beckmann rearrangement.

We preferred the Schmidt reaction over the Beckmann rearrangement because it was employable in the synthesis of all lactams we required. The Schmidt reaction was time efficient compared to the two-step Beckmann rearrangement. The cyclooximes were also not easy to handle owing to their fluffy nature.

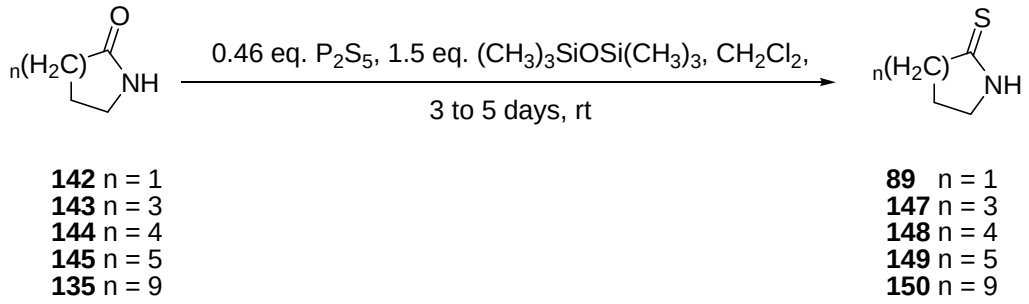
2.3 Synthesis of NH thiolactams

The required thiolactams were prepared by the Curphey and Brillon procedures.[37,38] The products are needed as starting materials for a Michael addition reaction or an Eschenmoser sulfide contraction reaction (See sections 2.4 and 2.5.3).

2.3.1 Synthesis by the Curphey procedure

Curphey's method makes use of hexamethyldisiloxane (HMDO) with phosphorus pentasulfide (P_2S_5) in the thionation of esters, lactones, 3-oxoesters, amides, lactams and ketones.[37] This P_2S_5/HMDO combination has become a popular method for effecting thionation, in some cases equaling or exceeding the yields produced by Lawesson's reagent (LR). Reagent-derived byproducts can be removed by a simple extractive or chromatographic workup, while the use of LR entails the use of large columns, even on small scale owing to LR's high equivalent weight.[37] Of relevance to our project Curphey made pyrrolidine-2-thione **89** and azepane-2-thione **147** in 91% (83% isolated) and 100% (92% isolated) yields, respectively. We made five NH thiolactams by this procedure

and purified them by column chromatography and recrystallisation (**Scheme 17** and Table 2).



142 n = 1
143 n = 3
144 n = 4
145 n = 5
135 n = 9

89 n = 1
147 n = 3
148 n = 4
149 n = 5
150 n = 9

Scheme 17. The Curphey procedure

Table 2.

Compound	Yield / %	m. p. / ℃	Significant IR signal ν_{max} / cm^{-1}	Significant ^{1}H NMR signal δ / ppm	Significant ^{13}C NMR signal δ / ppm
89	36	103 – 105 (Lit. 103 – 106)[39]	3135 (NH)	8.59 (N*H*)	206.0 (*C*=S)
147	73	102 – 104 (Lit. 103 – 104)[38]	3423 (NH)	8.84 (N*H*)	210.7 (*C*=S)
148	71	69 – 72 (Lit. 79 – 82 ℃) [39]	3425 (NH)	8.59 (N*H*)	209.2 (*C*=S)
149	50	72 – 75 (Lit. 84 – 87 ℃) [39]	3407 (NH)	8.30 (N*H*)	209.6 (*C*=S)
150	93	104 (Lit. 102 – 104 ℃) [39]	3327 (NH)	7.21 (N*H*)	205.4 (*C*=S)

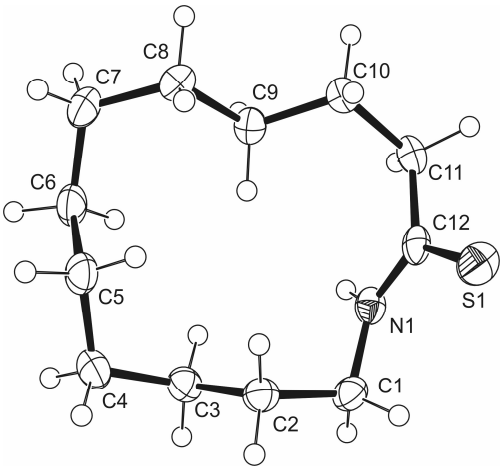
One example is discussed in detail here. Pyrrolidine-2-thione **89** was synthesised from 2-pyrrolidinone **142** in a poor 36% yield as cream crystals. Compound **89** had a melting point of 103 – 105 ℃ (Lit. 103 – 106 ℃) [39] which is clearly different from that of 2-pyrrolidinone **142** (23 – 25 ℃). [35e] The IR spectrum had a broad

peak at ν_{max} = 3135 cm^{-1} for an NH group and no peak for the amide carbonyl group at ν_{max} = 1650 cm^{-1}. ^{1}H NMR spectroscopy indicated the presence of an NH group at δ = 8.59 ppm. The ^{13}C NMR spectrum showed a quaternary carbon peak at δ = 206.0 ppm, indicating a *C*=S carbonyl group. Compound **142** was not recovered after work-up. There may have been competing side reaction owing to the low yield of compound **89**.

Yields and significant data for the remaining products **147**–**150** are present in Table 2. The isolated yields of compound **89** and azepane-2-thione **147** are low compared to those obtained by Curphey for the same compounds. These compounds, including azonane-2-thione **149** may have been lost in the purification step. The lactams were not recovered in all five reactions, indicating either that the reaction went to completion or there were competing side reactions. In all cases except **150**, a downfield shift of the N*H* signal from about δ ≈ 6 ppm to δ ≈ 8 ppm in the ^{1}H NMR spectrum was observed, indicating stronger deshielding effects of the sulfur atom. Again, the expected disappearance of the amide carbonyl (*C*=O) at δ ≈ 175 ppm and appearance of the thiolactam carbonyl (*C*=S) at δ ≈ 209 ppm was visible on the ^{13}C NMR spectra in all cases.

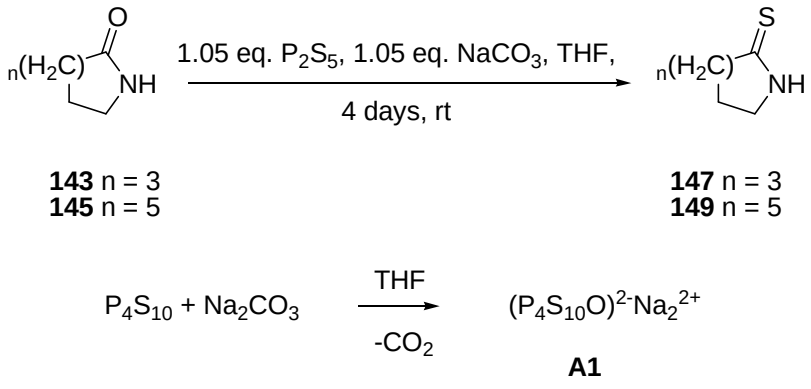
The crystal structure of azacyclotridecane-2-thione **150** (Figure 12) carried out by Dr C. Perry had its N*H* group pointing inwards, which may explain its low melting point as compared to 150 – 153 ℃ of azacyclotridec an-2-one **135**. Its N*H* singal at δ ≈ 7.21 ppm is also different from the others owing to its conformation. We could not compare crystal structures of compounds **135** and **150**, because attempted recrystallisation of **135** was not successful in all solvents we used. Generally, other thiolactams had higher melting points than their respective lactams.

Figure 12. Azacyclotridecane-2-thione **150**



2.3.2 Synthesis by the Brillon procedure

Brillon's method makes use of a more electrophilic *in situ* reagent, sodium carbonate/phosphorus pentasulfide **A1** (1:1 ratio), in the thionation of amides, peptides and lactams.[38] This is a modification of a procedure described by Scheeren,[40] which uses the *in situ* reagent bicarbonate/phosphorus pentasulfide (6:1 ratio). Brillon's *in situ* reagent is both soluble in THF and water which made for an easy workup procedure. Brillon prepared pyrrolidine-2-thione **89**, piperidine-2-thione and azepane-2-thione **147** using condition **A1** at 25 ℃ for 2 h in yields of 88%, 85% and 84%, respectively (**Scheme 18**).

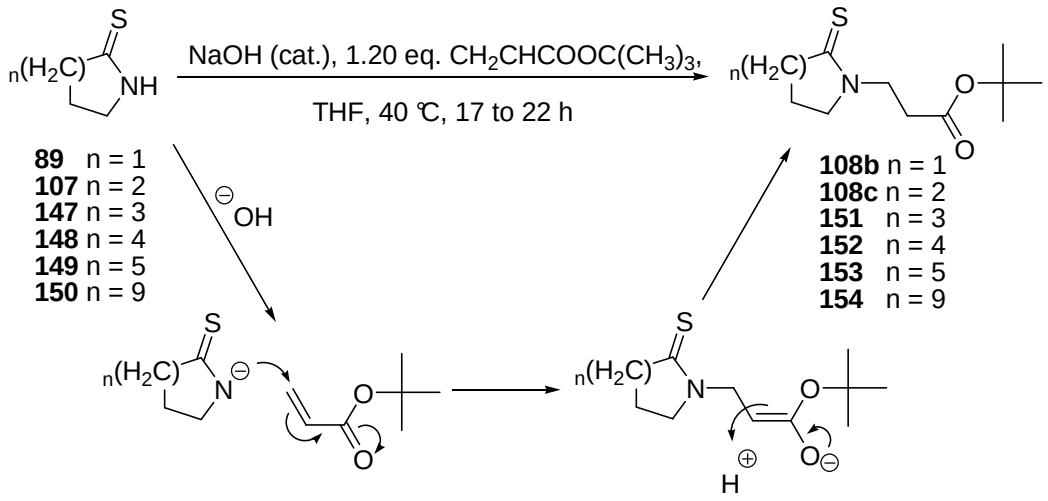


Scheme 18. The Brillon procedure

We made two thiolactams by this procedure to compensate for the moderate yields from the Curphey procedure. They were also purified by column chromatography and recrystallisation. Thiolactams **147** and **149** were synthesised from lactams **143** and **145** in good yields of 91% and 84% respectively, as colourless crystals. The data were comparable to those obtained on the products from the Curphey procedure.

2.4 Synthesis of N-alkylated thiolactams

One approach to making our bicyclic systems is to start with a functionalised 3-carbon chain on nitrogen, and our way of doing this is to attach the chain at the thiolactam stage. *N*-Alkylated thiolactams were synthesised in a Michael reaction of NH thiolactam to *tert*-butyl acrylate as shown in **Scheme 19**. In this reaction, sodium hydroxide is used to deprotonate the nitrogen atom, which then engages in a 1,4 addition to *tert*-butyl acrylate. The electron density travels the conjugated system, picking up the acidic proton from the base and resulting in the *N*-alkylated thiolactams.[27] The products were purified by recrystallisation from ethyl acetate:hexane solvent mixture. The following six compounds were synthesised by this method (**Scheme 19** and Table 3).



Scheme 19. Michael addition reaction and proposed mechanism.[41]

Table 3

Com-pound	Yield / %	m. p. / ℃	Significant IR signal ν_{max} / cm^{-1}	Significant ^{1}H NMR signals δ / ppm	Significant ^{13}C NMR signals δ / ppm
108b	85	48 – 49	1716 (C=O)	3.98 $Bu^tCO_2CCH_2CH_2N$ and 3.02 $Bu^tCO_2CCH_2CH_2N$	171.2 (*C*=O) and 201.9 (*C*=S)
108c	73	54 – 55 (Lit. 55 – 56)[27]	1716 (C=O)	3.95 $Bu^tCO_2CCH_2CH_2N$ and 2.75 $Bu^tCO_2CCH_2CH_2N$	171.1 (*C*=O) and 199.9 (*C*=S)
151	82	60 – 62	1725 (C=O)	4.23 $Bu^tCO_2CCH_2CH_2N$ and 3.12 $Bu^tCO_2CCH_2CH_2N$	171.5 (*C*=O) and 206.8 (*C*=S)

Table 3 (continued)

Com-pound	Yield / %	m. p. / ℃	Significant IR signal ν_{max} / cm^{-1}	Significant ^{1}H NMR signals δ / ppm	Significant ^{13}C NMR signals δ / ppm
152	82	66 – 69	1727 (C=O)	4.13 $Bu^tCO_2CCH_2CH_2N$ and 3.07 $Bu^tCO_2CCH_2CH_2N$	171.3 (*C*=O) and 205.7 (*C*=S)
153	94	64 – 66	1726 (C=O)	4.12 $Bu^tCO_2CCH_2CH_2N$ and 3.05 $Bu^tCO_2CCH_2CH_2N$	171.7 (*C*=O) and 206.8 (*C*=S)
154	60	86 – 88	1727 (C=O)	4.10 $Bu^tCO_2CCH_2CH_2N$ and 2.77 $Bu^tCO_2CCH_2CH_2N$	171.6 (*C*=O) and 205.1 (*C*=S)

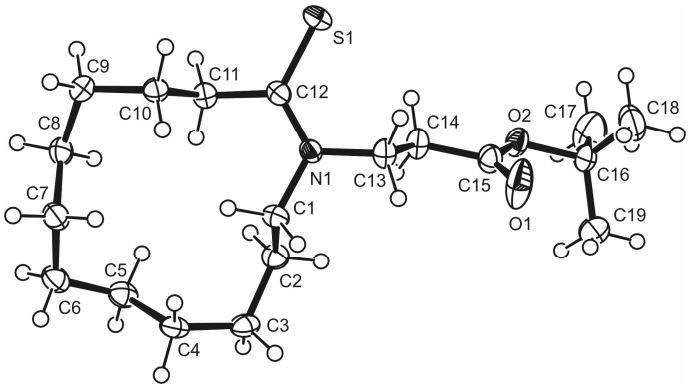
One example is discussed in detail here. *tert*-Butyl 3-(2-thioxopyrrolidin-1-yl)propanoate **108b** was synthesised from 2-pyrrolidine-2-thione **89** in a good 85% yield as colourless crystals. *N*-Alkylated thiolactam **108b** had a melting point of 48 – 49 ℃ which is clearly different and lower to that pyrrolidine-2-thione 103 – 105 ℃. The IR spectrum had no broad peak above ν_{max} = 3000 cm^{-1} for an NH group and had a peak for the ester carbonyl group at ν_{max} = 1716 cm^{-1}. ^{1}H NMR spectroscopy indicated the disappearance of the N*H* peak at δ = 8.59 ppm. The presence of a *tert* butyl group at δ = 1.46 ppm and two new peaks at δ = 3.98 ppm and δ = 3.02 ppm for $[(CH_3)_3COOCCH_2CH_2N]$ and $[(CH_3)_3COOCCH_2CH_2N]$, respectively, were evidence for the formation of compound **108b**. The ^{13}C NMR spectrum showed three quaternary carbon peaks with the first peak at δ = 206.0 ppm for *C*=S, the second peak at δ = 171.2 ppm for the ester carbonyl group and

the third peak at δ = 81.6 ppm for *tert* butyl group. Pyrrolidine-2-thione **89** was not recovered after work-up and the high yield suggests few side reactions.

The data for the remaining products is summarised in Table 3, and the spectroscopic details are similar to those for **108b**. *N*-Alkylated thiolactams **108c**, **151**, **152** and **153** were also synthesised from their respective unprotected thiolactams in good yield as colourless crystals. The reaction went to completion as determined by a TLC test. Varying reaction conditions like increasing the temperature to 60 ℃, longer reaction times and inc reasing the equivalence of the acrylate ester did not improve the yield of *tert*-butyl 3-(2-thioxoazacyclotridecan-1-yl)propanoate **154**.

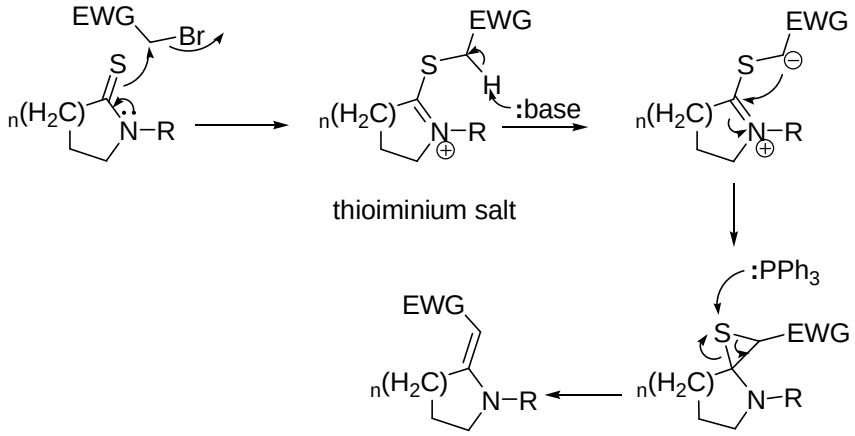
Azacyclotridecane-2-thione **150** was always recovered after the reaction was terminated, owing to the steric hindrance around the nitrogen atom. Looking at the crystal structure of **154** (Figure 13) (carried out by Dr C. Perry) we can see that the *N*-alkyl group points away from the ring. Generally, the melting point decreased in all *N*-alkylated thiolactams as compared to their respective unprotected thiolactams, owing to the loss of hydrogen bonding present in the unprotected thiolactams. The IR spectra had no broad peak for an NH group but had a peak for the ester carbonyl group.

Figure 13. *tert*-butyl 3-(2-thioxoazacyclotridecan-1-yl)propanoate **154**



2.5 Eschenmoser sulfide contraction

Enaminones are central to the project because they are scaffolds on which we are going to build new rings. So, having prepared thiolactams we are now in a position to use them in Eschenmoser sulfide contractions to give a variety of enaminones. The reaction mechanism is believed to begin when the electron density from the nitrogen atom is delocalised onto the sulfur atom, making it nucleophilic enough to engage in a substitution reaction replacing the bromine atom from the α-position of a compound with a good electron withdrawing group (EWG). The thioiminium salt that had been formed is then treated with a base, resulting in a compound with a thiirane group. Triphenylphosphine is then introduced to scavenge the sulfur atom affording a carbon-carbon double bond (**Scheme 20**).[41] This reaction has been reported to be efficient with EWG containing compounds such as methyl 2-bromoacetate and methyl 2-bromo-2-phenylacetate.[42,43]

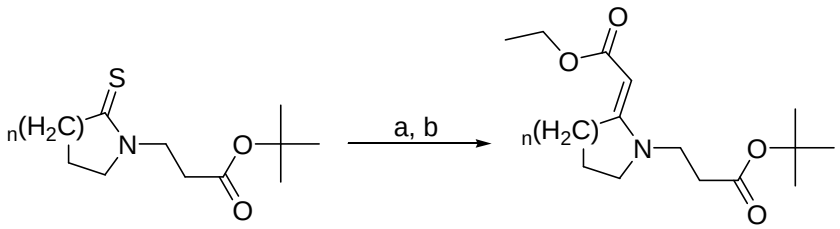


Scheme 20. Eschenmoser sulfide contraction mechanism.[41]

2.5.1 Synthesis of N-alkyl vinylogous urethanes

Practically, the vinylogous urethanes were prepared by reacting *N*-alkyl thiolactams with ethyl bromoacetate at room temperature, after which *S*-

alkylation was thought to be complete (followed by the disappearance of starting material on a TLC plate), followed by sulfur extrusion using either triphenylphosphine or triethyl phosphite with triethylamine acting as the base at room temperature.[27] The resulting residues were worked-up and purified by column chromatography on silica gel. The following five compounds were synthesised by this method (**Scheme 21** and Table 4).



108b n = 1
151 n = 3
152 n = 4
153 n = 5
154 n = 9

109b n = 1
155 n = 3
156 n = 4
157 n = 5
158 n = 9

Scheme 21. (*a*) 1.10 eq. $BrCH_2COOCH_2CH_3$, MeCN, rt, 42 h; (*b*) 1.10 eq. PPh_3 or 1.10 eq. $P(OEt)_3$, 1.10 eq. Et_3N, rt, 25 h.

Table 4

Compo-und	Yield / %	Significant IR signals ν_{max} / cm^{-1}	Significant ^{1}H NMR signals δ / ppm	Significant ^{13}C NMR signals δ / ppm
109b	88	1725 (sat, C=O), 1682 (unsat, C=O) and 1588 (alkene)	4.46 (NC=C*H*), 4.03 (OCH_2CH_3) and 1.21 (OCH_2CH_3)	169.0 (N*C*=C), 166.4 (CO_2Et) and 80.8 (NC=*C*)
155	30	1727 (sat. C=O), 1683 (unsat. C=O) and 1573 (alkene)	4.46 (NC=C*H*), 4.03 (OCH_2CH_3) and 1.21 (OCH_2CH_3)	169.0 (N*C*=C), 166.4 (CO_2Et) and 80.8 (NC=*C*)

Table 4 (continued)

Compo-und	Yield / %	Significant IR signals ν_{max} / cm^{-1}	Significant ^{1}H NMR signals δ / ppm	Significant ^{13}C NMR signals δ / ppm
156	21	1728 (sat. C=O), 1683 (unsat. C=O) and 1567 (alkene)	4.52 (NC=C*H*), 4.08 (OC*H*$_2$CH$_3$) and 1.25 (OCH$_2$C*H*$_3$)	167.5 (N*C*=C), 164.6 (*C*O$_2$Et) and 79.8 (NC=*C*)
157	8	1727 (sat. C=O), 1683 (unsat. C=O) and 1561 (alkene)	4.49 (NC=C*H*), 4.01 (OC*H*$_2$CH$_3$) and 1.20 (OCH$_2$C*H*$_3$)	168.9 (N*C*=C), 167.4 (*C*O$_2$Et) and 81.3 (NC=*C*)
158	20	1728 (sat. C=O), 1682 (unsat. C=O) and 1569 alkene)	4.54 (NC=C*H*), 4.07 (OC*H*$_2$CH$_3$) and 1.31 (OCH$_2$C*H*$_3$)	169.0 (N*C*=C), 164.8 (*C*O$_2$Et) and 81.4 (NC=*C*)

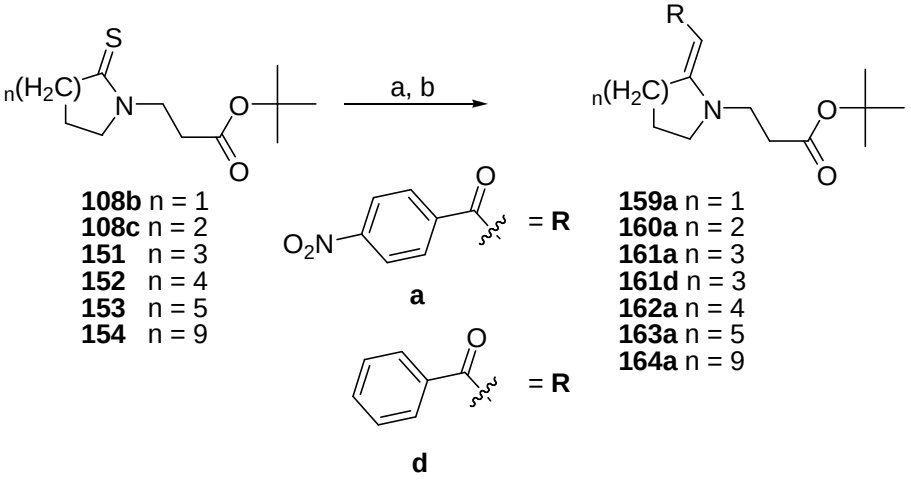
One example is discussed in detail here. (*E*)-*tert*-Butyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate **109b** was synthesised from *tert*-butyl 3-(2-thioxopyrrolidin-1-yl)propanoate **108b** in a good yield of 88% as a red oil. The IR spectrum had a stretching band for the saturated ester carbonyl group at ν_{max} = 1725 cm^{-1}, a peak for the unsaturated ester carbonyl group at ν_{max} = 1682 cm^{-1} and another signal at ν_{max} =1588 for the alkene. ^{1}H NMR spectroscopy indicated the presence of a new vinyl proton peak at δ = 4.53 ppm accompanied by two new peaks at δ = 4.09 ppm for (O*C*H$_2$CH$_3$) and δ = 1.25 ppm for the methyl group, representative of the ethyl ester. The peak for *tert* butyl group at δ = 1.45 ppm and two peaks at δ = 3.42 ppm and δ = 3.13 ppm for Bu^{t}CO$_2$CCH$_2$C*H*$_2$N and Bu^{t}CO$_2$CC*H*$_2$CH$_2$N were still present in compound **109b**. The ^{13}C NMR spectrum showed four quaternary carbon peaks with the disappearance of a peak at δ = 206.0 ppm for (*C*=S) and appearance of a peak at δ = 169.7 ppm for (N*C*=C), at

δ = 171.1 ppm for the *tert*-butyl ester carbonyl group, at δ = 164.8 ppm for the ethyl ester carbonyl group and at δ = 81.4 ppm for *tert* butyl group. The peak for (NC=*C*) was at δ = 78.6 ppm. Compound **108b** was not recovered during purification.

The second compound *tert*-Butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azepan-1-yl}propanoate **155** was synthesised from *tert*-butyl 3-(2-thioxoazepan-1-yl)propanoate **151** in a poor 30% yield as a yellow oil. The thioiminium salt visibly formed within 1 h of stirring and was supported by a baseline spot, but spots for starting material **151** and triphenylphosphine were present in the reaction mixture even when the reaction was left overnight to force complete salt formation. The crude product was purified by column chromatography on silica gel and appeared to decompose (on the base line of the TLC plate). We found that *tert*-butyl 3-(2-oxoazepan-1-yl)propanoate (an *N*-alkylated lactam) was formed and was almost always recovered mixed with *tert*-butyl 3-(2-thioxoazepan-1-yl)propanoate **151**. This could only happen if moisture was hydrolysing the salt before the sulfur extrusion step. We also recovered more unused triphenylphosphine than triphenylphosphine sulfide and some triphenylphosphine oxides. We suspected that ethyl 2-bromoacetate might have decomposed with age, but even after using freshly distilled ethyl bromoacetate yields never improved. Many other attempts were taken to make *tert*-butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azepan-1-yl}propanoate **155**, which included salt formation without solvent, raising the temperature to 40 ℃ in the sulfur extrusion step and an acid work-up, all of which resulted in either low yield or no product recovery. Vinylogous urethane **155** therefore became the main focus in our study in order to pave the way for the synthesis of vinylogous urethanes **156**, **157** and **158**, their synthesis was met with similar difficulties as for **155**. All products were obtained as yellow oils. Their spectroscopic data were similar to those of product **109b**, and significant signals are included in Table 4.

2.5.2 Synthesis of N-alkyl vinylogous amides

Since we were not able to make vinylogous urethanes in sufficient quantity for cyclisation studies, we decided to make a range of vinylogous amides instead, for ease of synthesis of vinylogous amides. The vinylogous amides were prepared similarly to vinylogous urethanes.[27] The resulting residues were worked-up and purified by column chromatography on silica gel. The following seven compounds were synthesised by this method (**Scheme 22**, Table 5).



Scheme 22. (*a*) 1.05 eq. $BrCH_2CO(C_6H_4)$-*p*-NO_2 **a** or 1.05 eq. $BrCH_2CO(C_6H_5)$ **d**, MeCN, rt, 22 to 30 h; (*b*) 1.05 eq. PPh_3 or 1.05 eq. $P(OEt)_3$, 1.05 eq. Et_3N, rt, 2 to 24 h.

Table 5

Com-pound	Yield / %	m.p. / ℃	Significant IR signals ν_{max} / cm^{-1}	Significant ^{1}H NMR signals δ / ppm	Significant ^{13}C NMR signals δ / ppm
159a	89	128 – 129	1728 (C=O) and 1678 (alkene)	5.73 (NC=C*H*), 8.23 and 8.00 (arom.)	185.2 (C=O), 168.6 (N*C*=C), 149.0 and 148.0 (arom.) and 87.0 (NC=*C*)

160a	32	116 – 117	1722 (C=O) and 1610 (alkene)	5.68 (NC=C*H*), 8.22 and 7.96 (arom.)	185.0 (C=O), 166.0 (N*C*=C), 149.1 and 148.9 (arom.) and 90.7 (NC=*C*)
161a	72	oil	1711 (C=O) and 1622 (alkene)	5.62 (NC=C*H*), 8.22 and 7.96 (arom.)	185.0 (C=O), 170.8 (N*C*=C), 149.1 and 149.0 (arom.) and 90.6 (NC=*C*)
161d	32	oil	1724 (C=O) and 1622 (alkene)	5.65 (NC=C*H*), 7.87, 7.38 and 7.38 (arom.)	188.5 (C=O), 169.2 (N*C*=C), 143.3 (arom.) and 91.9 (NC=*C*)
162a	87	71 – 73	1720 (C=O) and 1616 (alkene)	5.71 (NC=C*H*), 8.21 and 7.99 (arom.)	184.4 (C=O), 169.7 (N*C*=C), 149.2 and 148.9 (arom.) and 91.0 (NC=*C*)
163a	67	111 – 112	1711 (C=O) and 1615 (alkene)	5.72 (NC=C*H*), 8.22 and 8.00 (arom.)	184.4 (C=O), 168.6 (N*C*=C), 149.1 and 148.9 (arom) and 91.7 (NC=*C*)
164a	4	amorphous solid	1725 (C=O) and 1625 (alkene)	5.67 (NC=C*H*), 8.23 and 7.97 (arom.)	184.8 (C=O), 170.6 (N*C*=C), 149.0 and 148.1 (arom.) and 91.7 (NC=*C*)

One example is discussed in detail here. (*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]pyrrolidin-1-yl}propanoate **159a** was synthesised from *tert*-butyl 3-(2-thioxopyrrolidin-1-yl)propanoate **108b** in a good 89% yield as orange crystals. Compound **159a** had a melting point of 128 – 129 ℃ is clearly dif ferent and higher than that of compound **108b** of 48 – 49 ℃. The IR spectrum had a peak for the ester and conjugated ketone group at ν_{max} = 1726 cm^{-1} and at ν_{max} = 1678 cm^{-1}, a peak at ν_{max} = 1595 cm^{-1} for an alkene and N–O aromatic peaks at ν_{max} = 1514 cm^{-1} and ν_{max} = 1342 cm^{-1}. ^{1}H NMR spectroscopy indicated the presence of a new vinyl proton peak at δ = 5.73 ppm accompanied by two new peaks at δ = 8.23 ppm and δ = 8.00 ppm for the aromatic group. The (*E*) geometry is apparent from chemical shieft of CH_2 adjacent to C=C (3.40 ppm) which is deshielded through space by the C=O group; in (2) analogues this position is upfield by 0.5 – 0.8 ppm.[27] The ^{13}C NMR spectrum showed six quaternary carbon peaks with the disappearance of a peak at δ = 201.9 ppm for (*C*=S) and appearance of a peak at δ = 168.6 ppm for (N*C*=C), at δ = 185.2 ppm for the ketone group, at δ = 170.8 ppm for the *tert*-butyl ester carbonyl group, at δ = 149.0 ppm and δ = 148.0 ppm for the aromatic group and at δ = 81.8 ppm for *tert* butyl group. The peak for (NC=*C*) was at δ = 87.0 ppm. Compound **108b** was not recovered after purification and the high yield suggest few side products.

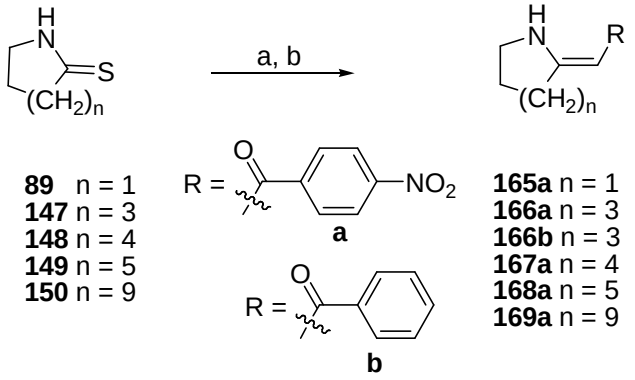
Vinylogous amides **161a**, **162a** and **163a** were also synthesised from their respective *N*-alkylthiolactams and the phenacyl bromide in good yield. Generally, the salt precipitation occured within 2 h and this was supported by a base line spot on a thin layer chromatography test plate. The vinylogous amides were afforded with little or no *N*-alkylthiolactams after purification. However (*E*)-*tert*-Butyl 3-(2-(2-(4-nitrophenyl)-2-oxoethylidene)piperidin-1-yl)propanoate **160a** was synthesised from *tert*-butyl 3-(2-thioxopiperidin-1-yl)propanoate **108c** in a poor 32% yield as yellow crystals. Thin layer chromatography showed that the thioiminium salt had partially formed after 6 h by a spot on the base line with a bright yellow spot at R_f = 0.54 for *p*-nitrophenacyl bromide. The reaction was

stirred for 11 h and a triphenylphosphine and triethylamine solution in acetonitrile was added resulting in a dark green colour change. The reaction mixture was stirred for an extra 22 h, worked-up and purified by column chromatography on silica gel. Compound **108c** was recovered together with *p*-nitrophenacyl bromide in significant amounts. We were not able to investigate the cause of failure for this reaction owing to time limitations. To our surprise, (*E*)-*tert*-butyl 3-(2-(2-oxo-2-phenylethylidene)azepan-1-yl)propanoate **161d** was synthesised from *tert*-butyl 3-(2-thioxoazepan-1-yl)propanoate **151** in a poor 32% yield as yellow oil as well. The salt had visibly formed after 2 h was supported by a spot on the base line on a TLC plate. Compound **151** was the major component recovered after purification. (*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azacyclotridecan-1-yl}propanoate **164a** was synthesised from *tert*-butyl 3-(2-thioxoazacyclotridecan-1-yl)propanoate **154** in a very poor 4% yield as yellow amorphous solid. The thin layer chromatography test plate showed that the salt had formed after 2 h by a spot on the base line and had precipitated. After purification we mainly recovered (*Z*)-2-(azacyclotridecan-2-ylidene)-1-(4-nitrophenyl)ethanone **169a** (**Scheme 23**). It seemed that the acrylate ester was no longer present and the Eschenmoser sulfide contraction reaction occurred on azacyclotridecane-2-thione **150** (**Scheme 23**). The IR spectra were not so different to those of the *N*-alkylthiolactams except they had stretching band for the aromatic ring. The vinyl proton accompanied by two peaks for the aromatic group in the ^{1}H NMR spectra were evidence enough that the reaction was successful and this was confirmed by the ^{13}C NMR spectra with peaks for all quaternary carbons.

2.5.3 Synthesis of NH vinylogous amides

Another approach to making our bicyclic systems is to start with NH vinylogous amides in an aza-annulation reaction with acryloyl chloride. These were prepared as described in the previous section.[27] The resulting residues were worked-up

and purified by column chromatography on silica gel. The following six compounds were synthesised by this method (**Scheme 27**, Table 6).



Scheme 23. (*a*) 1.05 eq. $BrCH_2CO(C_6H_4)pNO_2$ **a** or 1.05 eq. $BrCH_2CO(C_6H_5)$ **b**, MeCN, rt, 4 to 30 h; (*b*) 1.05 eq. PPh_3, 1.05 eq. Et_3N, rt, 2 to 24 h.

Table 6

Com-pound	Yield / %	m.p. / ℃	Significant IR signals ν_{max} / cm^{-1}	Significant ^{1}H NMR signals δ / ppm	Significant ^{13}C NMR signals δ / ppm
165a	79	160 – 161	3280 (NH) and 1739 (C=O)	5.65 (NC=C*H*), 11.8 (N*H*), 8.23 and 7.99 (arom.)	185.4 (C=O), 173.2 (N*C*=C), 149.2 and 146.6 (arom.) and 92.1 (NC=*C*)
166a	82	124 – 127	3280 (NH) and 1739 (C=O)	5.65 (NC=C*H*), 11.8 (N*H*), 8.23 and 7.99 (arom.)	185.4 (C=O), 173.2 (N*C*=C), 149.2 and 146.6 (arom.) and 92.1 (NC=*C*)

Table 6 (continued)

Com-pound	Yield / %	m.p. / ℃	Significant IR signals ν_{max} / cm^{-1}	Significant ^{1}H NMR signals δ / ppm	Significant ^{13}C NMR signals δ / ppm
166b	66	64 – 66	3200 – 3400 (NH) and 1739 (C=O)	5.66 (NC=C*H*), 11.5 (N*H*), 7.86, 7.37 and 7.37 (arom.)	186.7 (C=O), 170.2 (N*C*=C), 139.4 (arom.) and 89.8 (NC=*C*)
167a	76	128 – 129	3200 – 3400 (NH) and 1739 (C=O)	5.67 (NC=C*H*), 11.7 (N*H*), 8.24 and 7.99 (arom.)	184.5 (C=O), 172.2 (N*C*=C), 148.7 and 146.3 (arom.) and 92.4 (NC=*C*)
168a	88	128 – 129	3200 – 3400 (NH) and 1739 (C=O)	5.52 (NC=C*H*), 11.6 (N*H*), 8.10 and 7.88 (arom.)	184.7 (C=O), 173.3 (N*C*=C), 149.3 and 147.0 (arom.) and 92.3 (NC=*C*)
169a	83	104 – 105	3200 – 3400 (NH) and 1738 (C=O)	5.65 (NC=C*H*), 11.8 (N*H*), 8.23 and 7.98 (arom.)	184.3 (C=O), 170.5 (N*C*=C), 148.8 and 146.3 (arom.) and 92.5 (NC=*C*)

One example is discussed in detail here. (*Z*)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone **165a** was synthesised from pyrrolidine-2-thione **89** in a good 79% yield as yellow crystals. Compound **165a** had a melting point of 160 – 161 ℃ which is clearly different and higher than that of pyrrolidine-2-thione of 103 – 105 ℃. The IR spectrum had a broad peak at ν_{max} = 3280 cm^{-1} for an NH group,

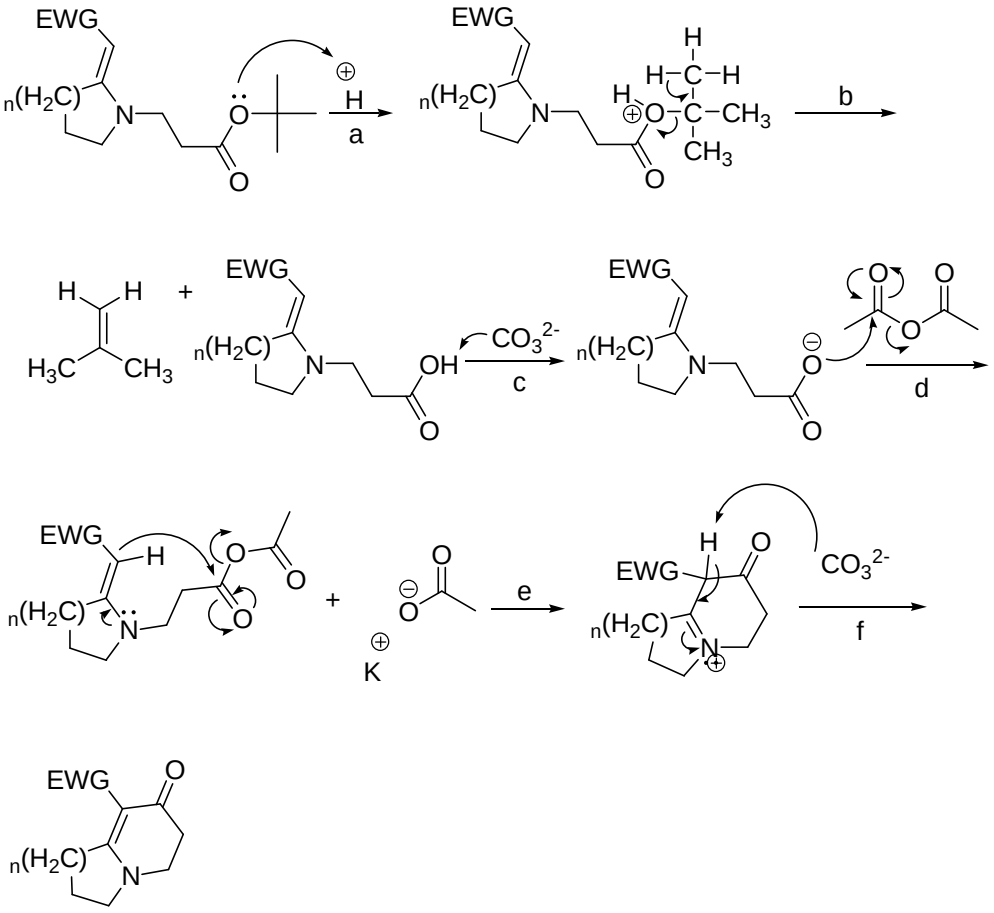
a peak for the ketone carbonyl group at ν_{max} = 1739 cm^{-1}, a peak at ν_{max} = 1596 cm^{-1} for an alkene, a peak at ν_{max} = 1478 $cm^{-1}$for the aromatic alkene and N–O aromatic peaks at ν_{max} = 1534 cm^{-1} and ν_{max} = 1335 cm^{-1}. ^{1}H NMR spectroscopy indicated the presence of NH group at δ = 11.5 ppm and the presence of a new vinyl proton peak at δ = 5.66 ppm accompanied by two new peaks at δ = 7.86 ppm and δ = 7.37 ppm for the aromatic group. The (*Z*) geometry was apparent from chemical shieft of CH_2 adjacent to C=C (2.35 – 2.78 ppm); in (*E*) analogues, this position is deshielded through space by the carbonyl group.[27] The ^{13}C NMR spectrum showed four quaternary carbon peaks with the disappearance of a peak at δ = 206.0 ppm for (*C*=S) and appearance of a peak at δ = 170.6 ppm, δ = 185.0 ppm, δ = 148.8 ppm and δ = 146.0 ppm for the (N*C*=C), ketone group and aromatic group, respectively. The peak for (NC=*C*) was at δ = 87.0 ppm. Compound **89** was recovered after purification and there were no competing side reactions determined by NMR spectroscopy.

The remaining NH vinylogous amides **166a**, **166b**, **167a**, **168a** and **169a** were synthesised from their respective NH thiolactams in good yields as yellow crystals. The reaction never went to completion even though the salt completely formed (salt precipitated and base line spot on TLC plate), owing to the recovery of NH thiolactams in low yield after purification. Specific data are similar to that for **165a** and significant signals are included in Table 6.

2.6 Synthesis of azabicyclic systems by intramolecular cycloacylation

Having prepared the vinylogous urethanes and amides, now we are in a position to utilise the enaminone reactivity to achieve azabicyclic models for alkaloids. The ring acylative closing mechanism utilises the nucleophilicity at α-carbon to the EWG. Trifluoroacetic acid hydrolyses the ester to a carboxylic acid with 2-methylprop-1-ene as a by-product (a, b **Scheme 24**). Potassium carbonate

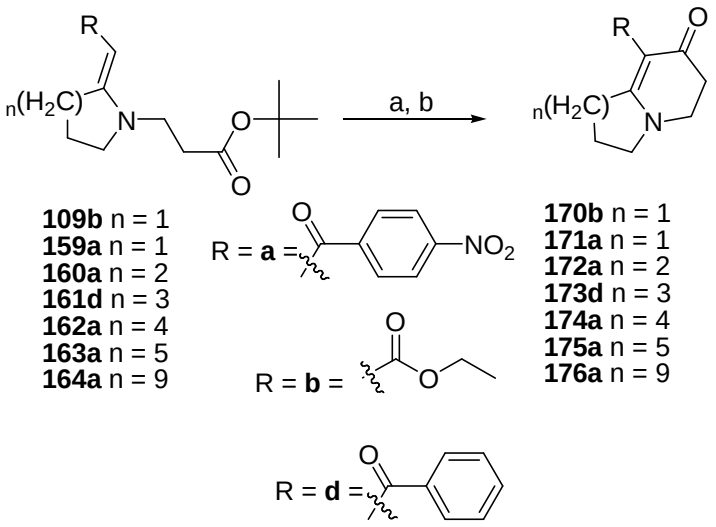
deprotonates the carboxylic acid leading to a nucleophilic attack on acetic anhydride by the resultant oxygen nucleophile, affording a mixed anhydride which is a good leaving group (c, d, **Scheme 24**). Enaminone chemistry takes over from here, with a nucleophilic attack on an electrophile of the mixed anhydride, forming a six-membered ring with loss of acetate group (e, **Scheme 24**). Potassium carbonate deprotonates the α-hydrogen to EWG affording the azabicyclic compounds (f, **Scheme 24**).[32]



Scheme 24. Acylative ring-closing reaction mechanism.[32]

Azabicyclic systems were prepared by reacting the *tert*-butyl-containing vinylogous urethanes or amides with trifluoroacetic acid at room temperature which resulted in the conversion of the *tert*-butyl group to the free carboxylic acid

group. After removing trifluoroacetic acid in *vacuo*, the free carboxylic acid was converted to an anhydride group in a reaction with potassium carbonate and acetic anhydride, which *in situ* (in acetonitrile at 60 ℃) transformed to azabicyc lic systems in an acylative ring-closing reaction propagated by the enaminone nucleophilicity losing the anhydride as a good leaving group.[43] The following seven compounds were prepared by this method (**Scheme 25**, Table 7).



Scheme 25. (*a*) 26.9 eq. Trifluoroacetic acid, rt, 4 to 5 h; (*b*) 2.00 eq. K_2CO_3, 2.00 eq. acetic anhydride, 60 ℃, 14 to 20 h.

Table 7

Compound	Yield / %	m.p. / ℃	Significant IR signals ν_{max} / cm^{-1}	Significant ^{13}C NMR signals δ / ppm
170b	79	149 – 150	1726 (C=O) and 1478 (conj. alkene)	187.6 (ring, C=O), 173.9 (N*C*=C) and 98.9 (NC=*C*)
171a	31	230	1739 (C=O) and 1631 (conj. alkene)	192.2 (ring, C=O), 174.9 (N*C*=C) and 106.8 (NC=*C*)
171a (isomer?)	65	230	1739 (C=O) and 1631 (conj. alkene)	184.1 (ring, C=O), 170.0 (N*C*=C) and 128.0 (NC=*C*)

Table 7 (continued)

Compound	Yield / %	m.p. / ℃	Significant IR signals ν_{max} / cm^{-1}	Significant ^{13}C NMR signals δ / ppm
172a	99	116 – 117	1723 (C=O) and 1645 (conj. alkene)	194.3 (ring, C=O), 169.3 (N*C*=C) and 110.0 (NC=*C*)
173d	73	amorphous solid	1738 (C=O) and 1613 (conj. alkene)	197.9 (ring, C=O), 170.7 (N*C*=C) and 112.2 (NC=*C*)
174a	89	175	1738 (C=O) and 1637 (conj. alkene)	195.6 (ring, C=O), 172.9 (N*C*=C) and 111.0 (NC=*C*)
175a	90	131 – 132	1739 (C=O) and 1631 (conj. alkene)	195.3 (ring, C=O), 173.1 (N*C*=C) and 111.0 (NC=*C*)
176a	90	108 – 110	1738 (C=O) and 1618 (conj. alkene)	192.9 (ring, C=O), 169.3 (N*C*=C) and 109.3 (NC=*C*)

One example is discussed in detail here. Ethyl 7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate **170b**[44] was synthesised from (*E*)-*tert*-butyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate **109b** in a good 79% yield as colourless crystals. Compound **170b** had a melting point of 149 – 150 ℃. The IR spectrum had a peak for the ketone and e ster carbonyl group at ν_{max} = 1726 cm^{-1}, two peaks at ν_{max} = 1478 cm^{-1} for a conjugated alkene and alkene peak at ν_{max} = 1432 cm^{-1}. ^{1}H NMR spectroscopy indicated the expected disappearance of the *tert*-butyl group at δ = 1.45 ppm and the vinyl proton at δ = 4.53 ppm, while the rest of the peaks still remained. The ^{13}C NMR spectrum showed four quaternary carbon peaks at δ = 187.6 ppm, δ = 173.9 ppm, δ = 166.5 ppm, δ = 98.9 ppm for the ketone, (N*C*=C), ester and (NC=*C*), respectively. (*E*)-*tert*-Butyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate **109b** was not recovered after purification. Data were comparable with those reported elsewhere.[44]

Attempted synthesis of azabicyclic compounds **128** (Figure 10), **170b** (n = 4,5 and 9) resulted in formation of what seemed to be polymeric material mixed with starting material. We tried longer reaction times and longer trifluoroacetic acid evaporation times, but all came to nothing. The poor yields of starting materials **155**, **156**, **157** and **158** for making compounds similar to compound **170b** were also a stumbling block in our synthesis. We suspect that failed attempts in synthesising azabicyclic scaffolds from **155**, **156**, **157** and **158** may have been due to preferential protonation of the enamine system, giving a charged intermediate that is no longer nucleophilic enough for the cyclisation to take place. Also, larger rings may have low reactivity owing to constrained conformation resulting in highly hindered reactive sites.

Compounds **172a**, **176a**, **174a**, **175a** and **173d** were synthesised from their respective vinylogous amides in good yields as yellow solids. Specific data are similar to that for **170b** and significant signals are included in Table 7.

8-(4-Nitrobenzoyl)-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **171a** was synthesised from (*E*)-*tert*-butyl 3-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)propanoate **159a** in a poor 31% yield as yellow crystals. The poor yield was due to the recovery of what seemed to be a conformational isomer in a 65% yield (b, Figure 15). There is a significant difference between the positions of the (NC=*C*) signal in the ^{13}C NMR spectra for **171a** and **171a** (isomer) at δ = 106.8 and δ = 128.0, respectively (Table 7 and a, b Figure 15), but the NMR and MS (HRMS (EI): found, 286.09385 ($C_{15}H_{14}O_4N_2$ requires 286.09536)) data of both could fit the desired structure and that is why we suspect conformation isomers. We were not able to compare the crystal structures of **171a** and its isomer?, because of the isomer? could not be recrystallised properly. The crystal structure of 8-(4-Nitrobenzoyl)-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **171a** (Figure 14) (carried out by Dr C. Perry) shows oxygen atoms O1 and O2 far from each other,

resulting in a conformation that can also be expected for compound **170b**, **172a**, **173d**, **174a**, **175a** and **176a**.

Figure 14. 8-(4-Nitrobenzoyl)-2,3,5,6-tetrahydroindolizin-7(1*H*)-one **171a**

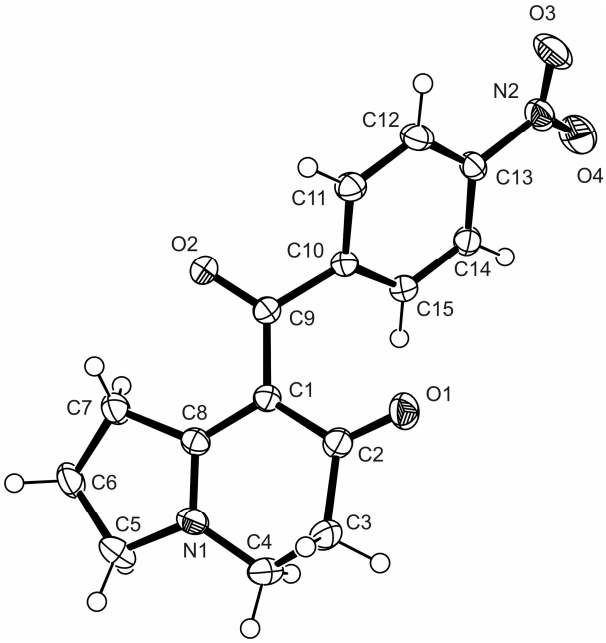
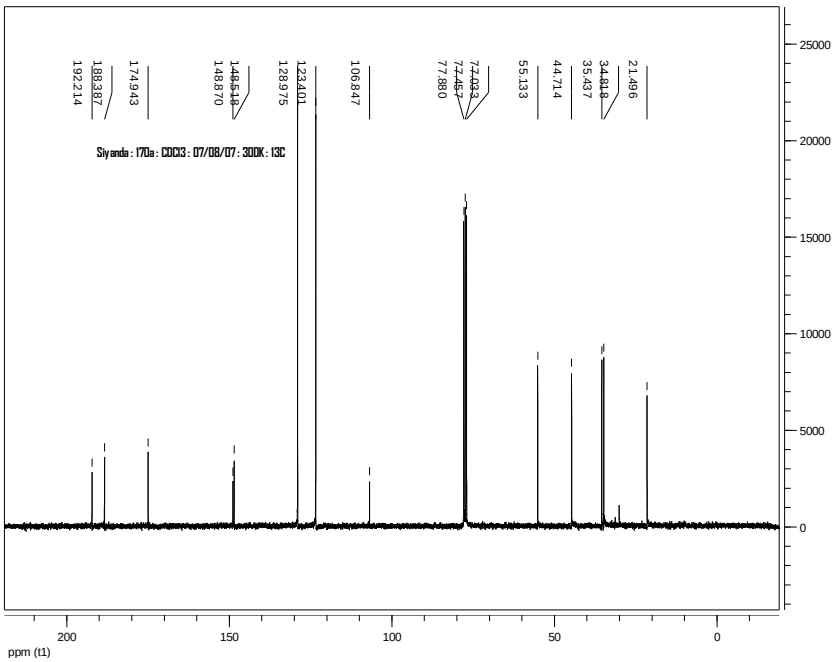
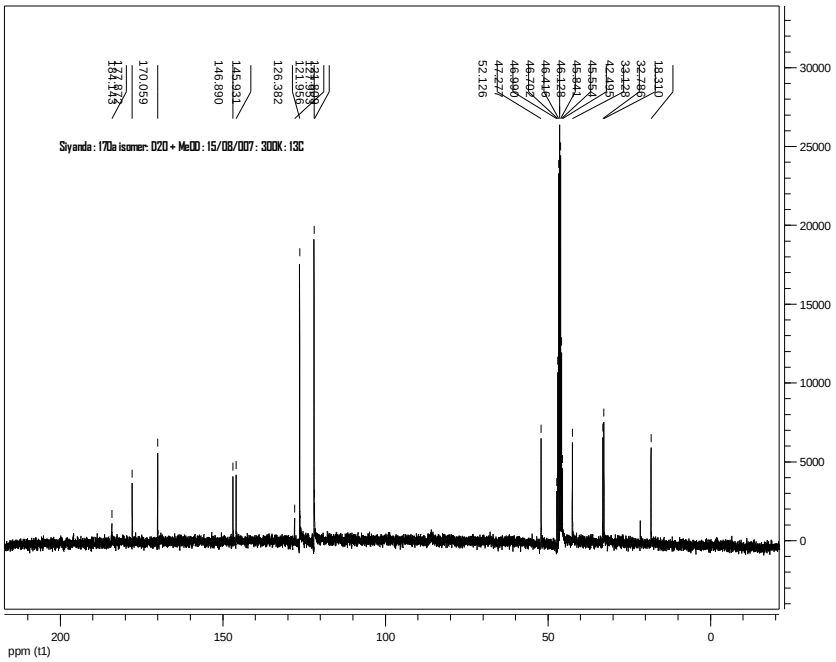


Figure 15. (a) ^{13}C NMR spectrum for 171a, (b) ^{13}C NMR spectrum for 171a (isomer?).



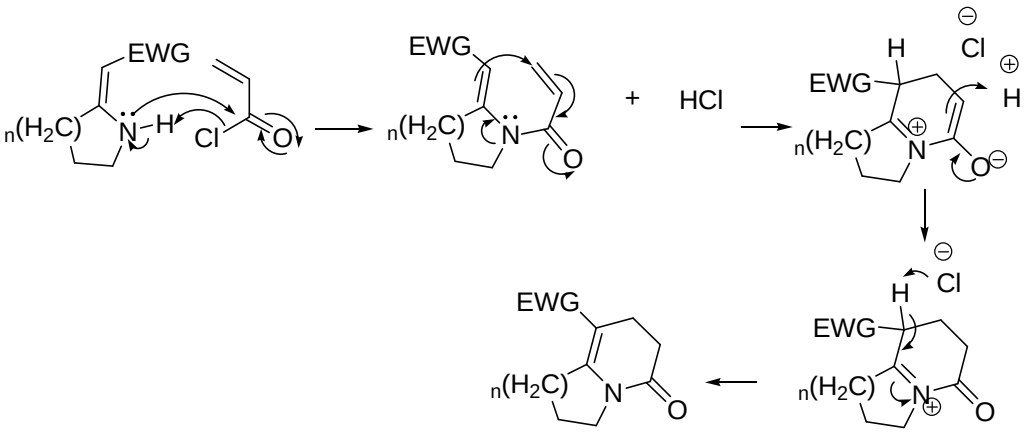
(a)

(b)



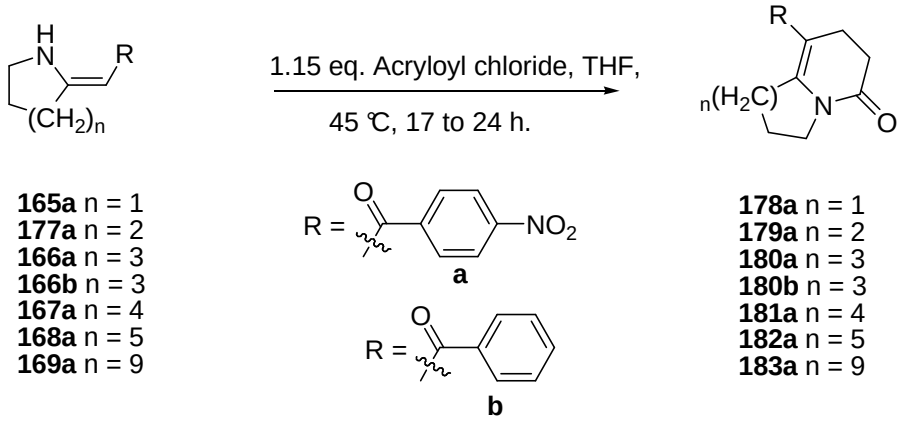
2.7 Synthesis of azabicyclic systems by aza-annulation

Azabicyclic structures were prepared by reacting vinylogous amides with acryloyl chloride in dry tetrahydrofuran according to a procedure by Stille.[45] The aza-annulation reaction begins with a 1,2 addition of nitrogen atom to acryloyl chloride followed by the elimination of the hydrogen chloride. A Michael type, 1,4 addition to the acryloyl group by the α-carbon to the EWG (enaminone nucleophilicity) resulted. The chloride anion then deprotonate α-hydrogen to EWG affording the azabicyclic compounds (**Scheme 26**).



Scheme 26. Proposed aza-annulation reaction mechanism.

The resulting products were purified by recrystallisation from ethyl acetate: hexane solvent mixture. The following seven compounds were prepared by this method (**Scheme 27**, Table 8).



165a n = 1
177a n = 2
166a n = 3
166b n = 3
167a n = 4
168a n = 5
169a n = 9

178a n = 1
179a n = 2
180a n = 3
180b n = 3
181a n = 4
182a n = 5
183a n = 9

Scheme 27. Aza-annulation reactions.

Table 8

Com-pound	Yield / %	m.p. / ℃	Significant IR signals ν_{max} / cm^{-1}	Significant ^{13}C NMR signals δ / ppm
178a	100	120 –121	1683 (C=O) and 1599 (conj. alkene)	169.6 (amide *C*=O), 149.3 (N*C*=C) and 109.5 (NC=*C*)
179a	49	126 – 127	1673 (C=O) and 1597 (conj. alkene)	168.7 (amide *C*=O), 148.1 (N*C*=C) and 112.2 (NC=*C*)
179a (isomer?)	23	Amorphous solid	1673 (C=O) and 1597 (conj. alkene)	168.7 (amide *C*=O), 150.8 (N*C*=C) and 108.4 (NC=*C*)
180a	99	130 – 131	1687 (C=O) and 1597 (conj. alkene)	170.7 (amide *C*=O), 150.1 (N*C*=C) and 114.7 (NC=*C*)
180b	95	103 – 105	1726 (C=O) and 1677 (conj. alkene)	168.9 (amide *C*=O), 136.9 (N*C*=C) and 113.7 (NC=*C*)
181a	99	59 – 61	1682 (C=O) and 1573 (conj. alkene)	169.2 (amide *C*=O), 148.5 (N*C*=C) and 113.3 (NC=*C*)
182a	90	110 – 112	1686 (C=O)and 1582 (conj. alkene)	169.4 (amide *C*=O), 148.5 (N*C*=C) and 114.4 (NC=*C*)
183a	97	107 – 108	1693 (C=O) and 1567 (conj. alkene)	169.4 (amide *C*=O), 148.5 (N*C*=C) and 113.3 (NC=*C*)

One example is discussed in detail here. 8-(4-Nitrobenzoyl)-2,3,6,7-tetrahydroindolizin-5(1*H*)-one **178a** was synthesised from (*Z*)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone **165a** in a good 100% yield as yellow crystals. Compound **178a** had a melting point of 120 – 121 ℃ which is clear ly different and lower than that of (*Z*)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone of 160 – 161 ℃. The IR spectrum had a peak for the ke tone carbonyl group at ν_{max} = 1683 cm^{-1}, a peaks at ν_{max} = 1599 cm^{-1} for a conjugated alkene and N–O aromatic peaks at ν_{max} = 1516 cm^{-1} and ν_{max} = 1345 cm^{-1}. ^{1}H NMR spectroscopy indicated the expected disappearance of the vinyl proton at δ = 5.73 ppm and of

the NH peak at δ = 10.4 ppm and two new peaks at δ = 2.65 ppm for (ArCC*H*$_2$CH$_2$CON and ArCCH$_2$C*H*$_2$CON). The rest of the peaks still remained. The ^{13}C NMR spectrum showed six quaternary carbon peaks at δ = 193.4 ppm, δ = 169.6 ppm, δ = 149.3 ppm, (δ = 156.3 ppm and 146.7) and δ = 109.5 ppm for the ketone, carbonyl of the amide group, (N*C*=C), the aromatic group and (NC=*C*), respectively. (*Z*)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone **178a** was not recovered after column and there were no competing side reactions.

Compounds **180a**, **180b**, **181a**, **182a** and **183d** were synthesised from their respective NH vinylogous amides in good yields as yellow crystals. Specific data is similar to that for **178a** and significant signals are included in Table 8.

1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one **179a** was synthesised from (*Z*)-1-(4-nitrophenyl)-2-(piperidin-2-ylidene)ethanone **177a** in a poor 49% yield as yellow crystals. Compound **179a** was synthesised with what we suspected to be a conformational isomer which had a yield of 23% (Table 8 and b, Figure 17). There is a significant difference between signals in the ^{1}H NMR spectra for **179a** and **179a** (isomer) (Table 8 and a, b Figure 17), but the NMR and MS (**179a**, HRMS (EI): found, 300.10836 ($C_{16}H_{16}O_4N_2$ requires 300.11101) and **179a** (isomer), HRMS (EI): found, 300.11080 ($C_{16}H_{16}O_4N_2$ requires 300.11101)) data of both could fit the desired structure and that is why we suspect conformation isomers. We were not able to compare the crystal structures of **171a** and its isomer?, because of the isomer? was an amorphous solid. The crystal structure of 1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one **179a** (Figure 16) (carried out by Dr. C. Perry) has its Ar group in a position similar to that of O2 of compound **171a** (Figure 14).

Figure 16. 1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one **179a**

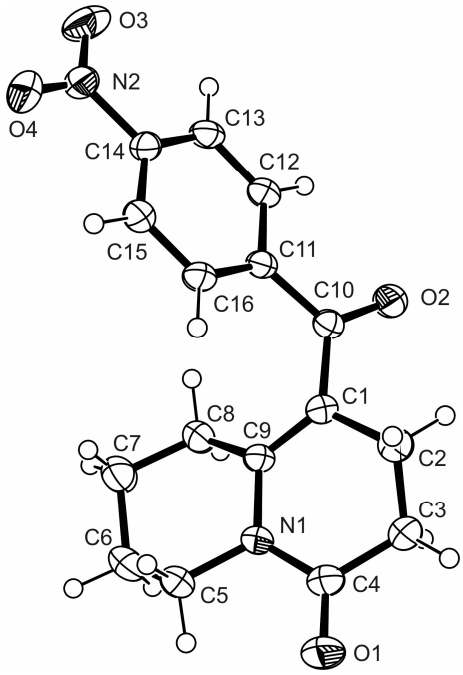
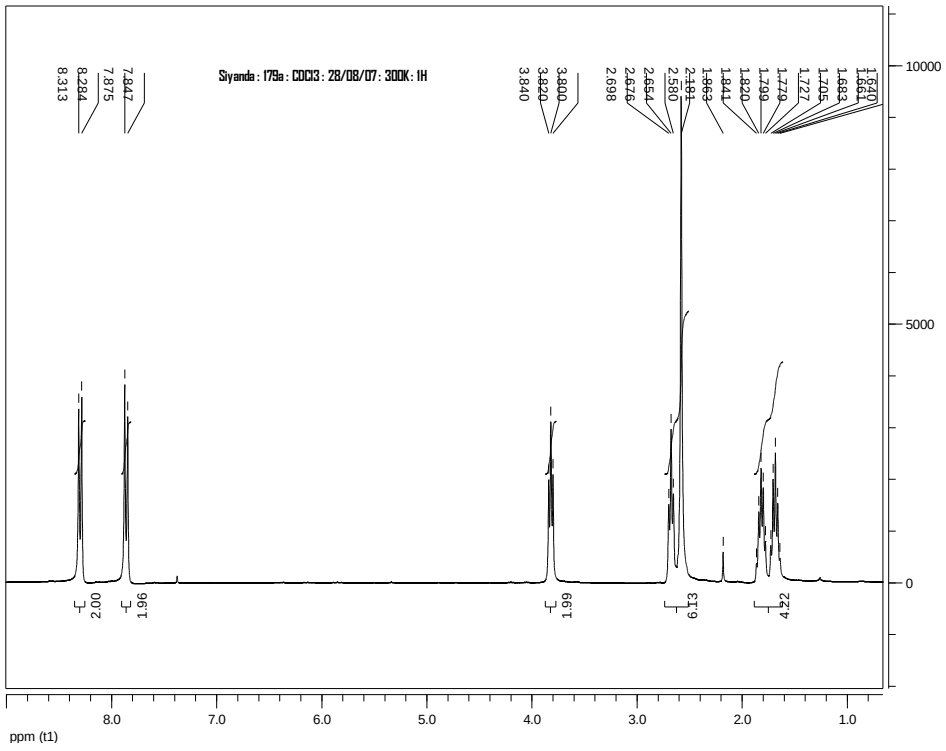
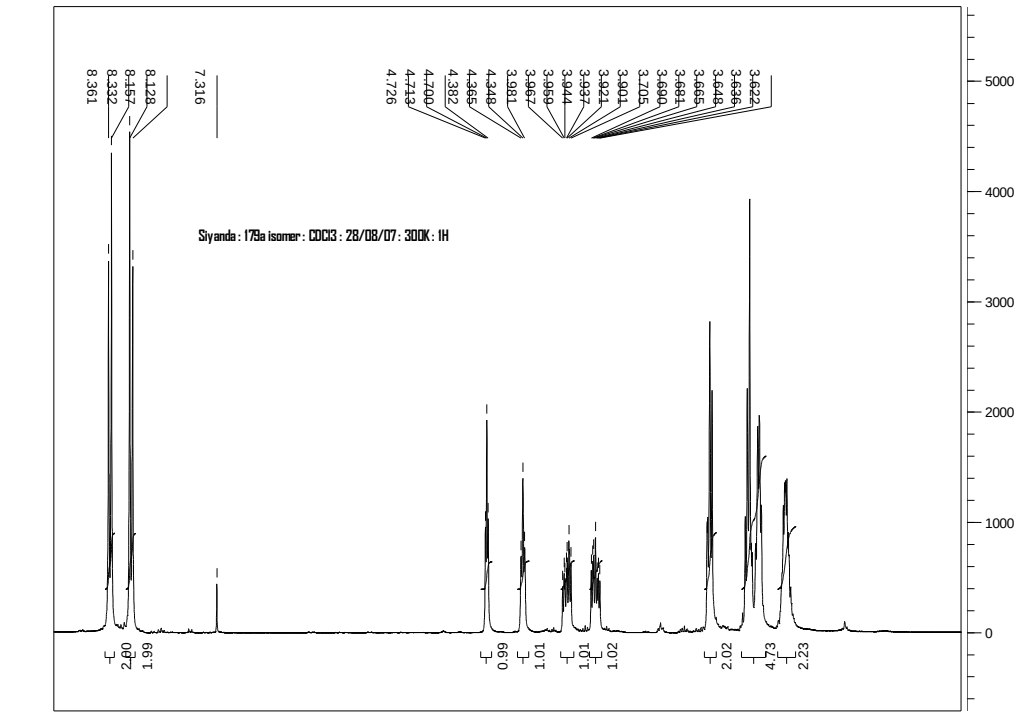


Figure 17. (a) ^{1}H NMR spectrum for 179a, (b) ^{1}H NMR spectrum for 179a (isomer?).



(a)



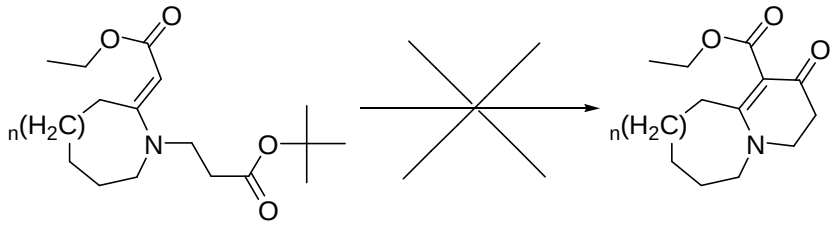
(b)

2.8 Conclusion

Vinylogous urethanes and amides were synthesised by the Eschenmoser sulfide contraction reaction. Large ringed vinylogous urethanes **155**, **156**, **157** and **158** were obtained in relatively low yields, as compared to small ringed vinylogous urethane **109b**. This was not the general case in the synthesis of vinylogous amides, as they were produced in relatively high yields. A number of attempts to improve the yields of large ringed vinylogous urethanes were unsuccessful.

Enaminones **132** (Figure 12) were then subjected to ring-closing conditions. Azabicyclic models for alkaloids were synthesised in good yields from vinylogous amides under the acylative ring-closing conditions and by the new aza-annulation conditions. The key step in the acylative ring-closing conditions is the efficient hydrolysis of the *tert*-butyl ester with trifluoroacetic acid over long periods of time followed by cyclisation via a mixed anhydride. The key step in aza-annulation

ring-closing conditions is a Michael type, 1,4 addition to the acryloyl group by the α-carbon to the EWG utilising enaminone nucleophilicity.



155 n = 1
156 n = 2
157 n = 3
158 n = 7

Scheme 28. Attempted synthesis of azabicyclic scaffolds.

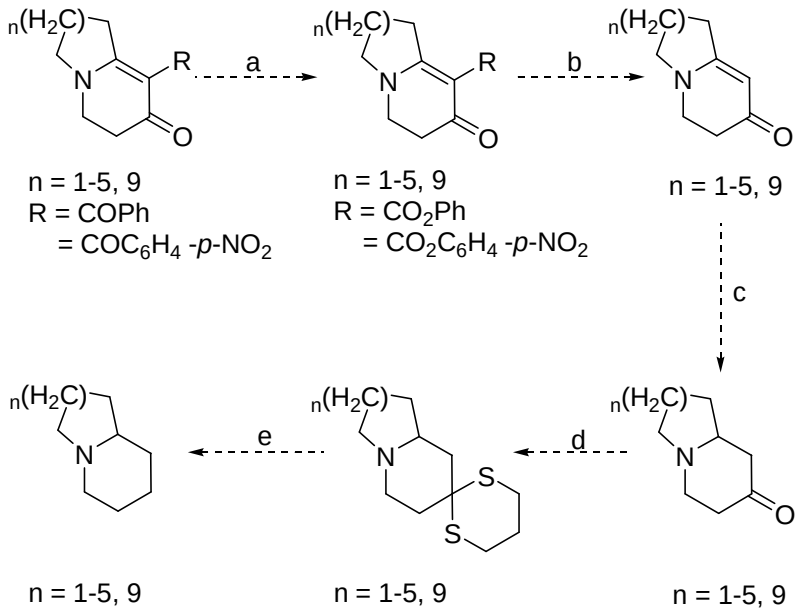
To our surprise, 1-(4-nitrobenzoyl)-3,4,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-2(6*H*)-one was obtained in a poor yield from **161a**. A number of attempts always resulted in compound(s) with NMR data that we were not able to interpret. Compounds **171a** and **179a** were obtained in low yields with what appeared to be their conformational isomers. Nuclear Overhauser experiments were not decisive in giving us the answer to how these isomers differed in structure. We were also not able to compare crystal structure as a result of recrystallisation difficulties on the isomers. The aza-annulation conditions were more efficient with reduced number of synthetic steps to the azabicyclic models for alkaloids and generally high yields.

In conclusion, we were able to extend the methodology developed in our laboratories for the synthesis of indolizidines and quinolizidines to analogues in which at least one of the rings was seven-, eight-, nine- and thirteen-membered.

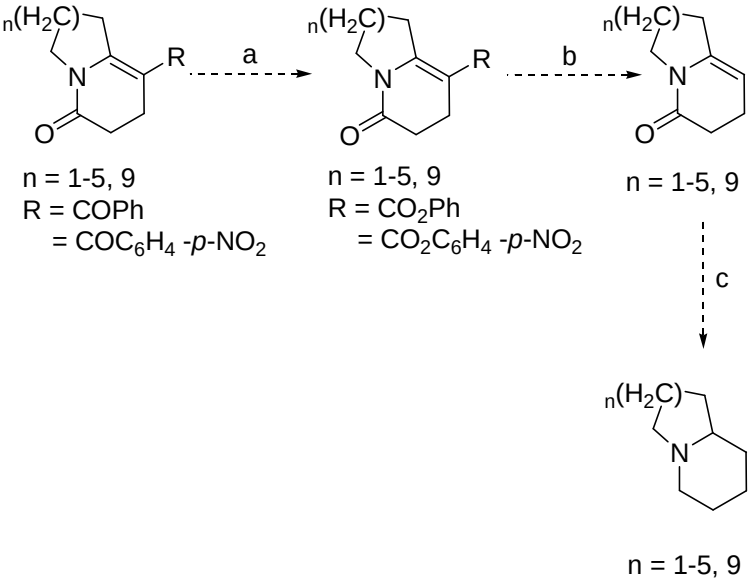
2.9 Future work

Our synthetic strategy needs to be improved for the Michael reaction of azacyclotridecane-2-thione **150** with *tert*-butyl acrylate. Compound **150** behaves differently in solution compared to solid state. Maybe doing the reaction at low temperatures might restrict compound **150** to a steady conformation, increasing the probability for reaction sites to find each other. The Eschenmoser sulfide contraction reaction needs a separate study, to investigate the contributions of different types of electron withdrawing in the reaction.

The azabicyclic systems **1**, **2**, **4**, **129**, **130** and **131** can be achieved by the proposed synthetic strategies in **Scheme 29** and **Scheme 30**. First, we would have to oxidise the ketone carbonyl to an ester group in a Baeyer-Villager oxidation reaction (a, **Scheme 29 and 30**). This substituent can then be removed by hydrolysis and decarboxylation reaction using potassium hydroxide at 100 ℃ (b, **Scheme 29 and 30**).[24] A reduction with lithium aluminium hydride has been found to be selective for the exo-double bond to the ring containing nitrogen for azabicyclic scaffold where n = 1 or 2.[27] This can be tried for the reduction for the reduction of larger rings as well (c, **Scheme 29**), although there is a tendency for decreased reactivity of the exo-double bond in larger ringed systems.[27] We would hope that the same reduction method reduces both the alkene and amide carbonyl groups, to afford the desired products (c, **Scheme 30**).[24] The ketone group can be removed by protecting the compound without the exo-double bond with propane-1,3-dithiol and later removing the whole group using Raney nickel (d, e, **Scheme 29**),[24] to achieve azabicyclic systems such as **1**, **2**, **4**, **129**, **130** and **131** (Figure11).

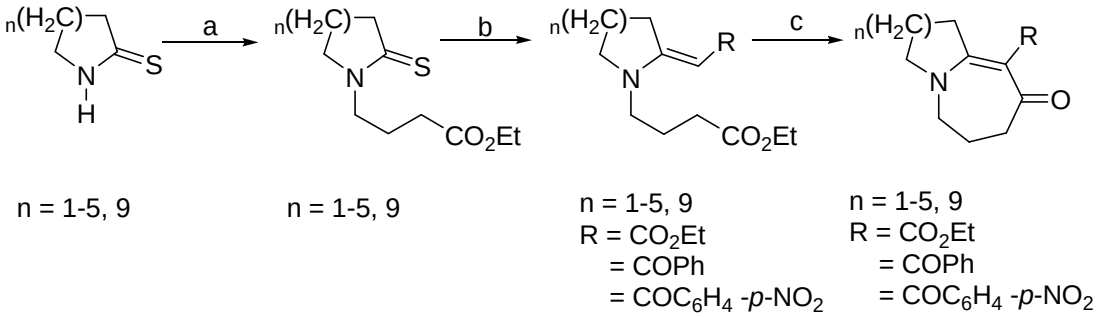


Scheme 29. Proposed synthetic strategy to azabicyclic systems **1**, **2**, **4**, **129**, **130** and **131**. (*a*) Baeyer-Villager oxidation, (*b*) Hydrolysis and decarboxylation, (*c*) Alkene reduction, (*d*) and (*e*) Ketone reduction



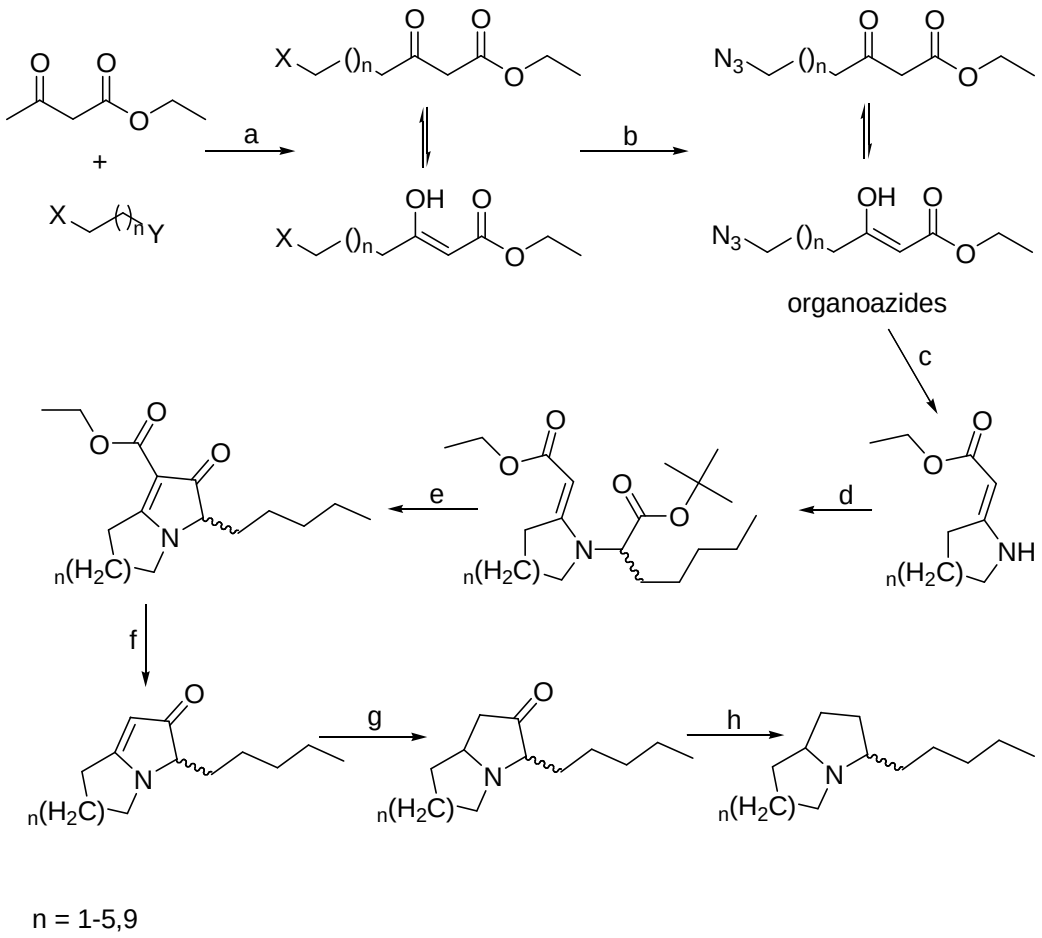
Scheme 30. Proposed synthetic strategy to azabicyclic systems **1**, **2**, **4**, **129**, **130** and **131**

Another approach to the azabicyclic scaffolds is to build a seven-membered ring instead of the six-membered ring. The seven-membered ring can be accessed from the *N*-alkylation of thiolactams with ethyl 4-bromobutanoate and ring-closing under basic conditions (a, c, **Scheme 31**).[29]



Scheme 31. (*a*) *N*-Alkylation reaction; (*b*) Eschenmoser sulfide contraction reaction and (*c*) Ring-closing step

In applying the Wits approach to naturally occurring compounds, we would attempt a racemic synthesis of 3-pentyl-octahydro-1*H*-pyrrolo[1,2-*a*]azepine (n = 3) and its analogues (n = 1-5, 9, **Scheme 32**). This method uses the intramolecular aza-Wittig reaction to vinylogous urethanes and amides instead of the Eschenmoser sulfide contraction reaction.[46] Organoazides (n = 1-5,7) could be synthesised in two steps in a γ-monoalkylation of the dianions with an α,ω-dihaloalkane followed by a nucleophilic displacement of X by NaN_3 (a, b, **Scheme 32**).



Scheme 32. Proposed synthetic route to racemic 3-pentyl-octahydro-1*H*-pyrrolo[1,2-*a*] azepine (n = 3) and its analogous. (*a*) gamma-Monoalkylation of the dianions with an alpha, omega-dihaloalkane, (*b*) Substitution, (*c*) Organoazide reaction, (*d*) *N*-Alkylation reaction.

The vinylogous urethanes could be accessed by treating the organoazides with 1 equivalent of triphenylphosphine in ether of benzene (c, **Scheme 32**).[46] *N*-Alkylation of vinylogues urethanes with *tert*-butyl 2-bromoheptanoate would result in racemic (*E*)-*tert*-butyl 2-(2-(2-ethoxy-2-oxoethylidene)azepan-1-yl)heptanoate and its analogous (d, **Scheme 32**),[47] which would the be subjected to acidic ring-closing conditions to give ethyl racemic 2-oxo-4-pentyl-2,3,4,6,7,8,9,10-octahydropyrido[1,2-*a*]azepine-1-carboxylate and its analogues. The reaction to follow then would be similar to those mentioned (**Scheme 29**) to afford desired racemic products.

CHAPTER 3

3.1 General experimental methods

Glassware was pre-dried by an open flame or in an oven at 150 ℃. All reactions except the Schmidt reaction were done under nitrogen atmosphere. All solvents used in reactions except methanol were distilled prior to use. Tetrahydrofuran was pre-dried over calcium chloride and distilled under nitrogen from benzophenone and sodium. Dichloromethane and acetonitrile were distilled under nitrogen from calcium hydride and sodium, respectively. The organic extracts from an aqueous phase were either dried over magnesium sulfate or sodium sulfate. Solvents and volatiles were removed (*in vacuo*) using a rotary evaporator, followed by an oil vacuum pump at pressures below 1.0 mmHg.

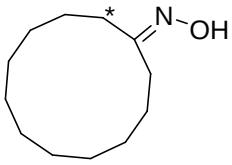
Products were purified by either recrystallisation or column chromatography. Solids were recrystallised in an ethyl acetate:hexane solvent mixture while column chromatography was carried out using silica gel (Merck, 60-230). Melting points were measured on a Reichert hot-stage microscope apparatus, and are uncorrected. The solvents used in column chromatography were distilled for better purity. Thin layer chromatography was performed on aluminium-backed Alugram Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60 and separation patterns were visualised using ultraviolet light, potassium permanganate developing reagent or iodine vapour.

Nuclear magnetic resonance (NMR) spectra were recorded using the Brucker WM-300 at 300 MHz for proton (^{1}H) NMR and at 75 MHz for carbon (^{13}C) NMR spectra. Deuteriated chloroform ($CDCl_3$) was used as a solvent and tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are reported in parts per million (ppm) relative to TMS. The multiplicity is abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet and m = multiplet. Infrared (IR) spectra were recorded using thin film or product pellets on a Varian Vector 800

FTIR spectrometer. MS spectroscopy conditions: EIMS data were obtained on a VG70SEQ or a Thermo DSF spectrometer at 70 eV.

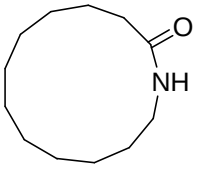
3.2 General procedure for synthesizing lactams using the Beckmann rearrangement method

3.2.1 Synthesis of Cyclododecanone oxime (134)



Cyclododecanone **133** (5.042 g, 27.66 mmol), hydroxyamine hydrochloride (4.431 g, 63.76 mmol, 2.3 equiv) and sodium acetate trihydrate (9.411 g, 69.14 mmol, 2.5 equiv) were reacted in methanol (100 ml) in the manner which has been described by a general procedure in the reference.[34] A solution of sodium acetate trihydrate in distilled water was added to a solution of ketone and hydroxylamine hydrochloride in methanol at room temperature. A white precipitate was formed. The reaction mixture was reflux heated for 3 h. The reaction mixture was then neutralised with saturated aqueous sodium hydrogen carbonate solution. The neutralised reaction mixture was extracted with diethyl ether. The organic layer was washed with a saturated sodium chloride solution and dried over anhydrous magnesium sulphate. The solvent was removed in *vacuo*. The product which solidified on cooling was purified by recrystallisation from an ethyl acetate: hexane solvent mixture to give *cyclododecanone oxime* **134** (5.211 g, 96%) as a white solid, m.p. 117 – 118 ℃; ν_{max} (NaCl; Thin Film)/cm^{-1} 3413 (s, br, OH); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.80 (1H, s, br, O*H*), 2.42 (2H, m, C*H*$_2$C=NOH), 2.26 (2H, m, C*H*$_2$C=NOH), 1.62 (4H, m, C*H*$_2$CH$_2$C=NOH) and 1.33 (14H, m, CH$_2$C*H*$_2$CH$_2$); δ_C (75 MHz; $CDCl_3$) 161.2 (*C*=NOH), 30.7 (*C**H$_2$C=NOH), 26.5 (*C*H$_2$C=NOH), 25.9, 25.4, 25.2, 24.4, 23.9, 23.7, 23.6, 23.6 and 23.1 (remaining *C*H$_2$).

3.2.2 Synthesis of Azacyclotridecane-2-one (135)



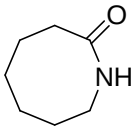
Cyclododecanone oxime **134** (397 mg, 2.01 mmol) and cyanuric chloride (25.2 mg, 0.14 mmol, 0.07 equiv) were reacted in acetonitrile (6.50 ml) in the manner which has been described by a procedure in the reference.[34] A mixture of ketoxime and cyanuric chloride in dry acetonitrile was refluxed under nitrogen atmosphere for 2.5 h. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution. Ethyl acetate was added to the neutralised reaction mixture in the separator funnel to extract the organic content. The organic layer was dried over anhydrous magnesium sulphate and evaporated in *vacuo*. The product which solidified was purified by recrystallisation from an ethyl acetate: hexane solvent mixture to give *azacyclotridecane-2-one* **135** (388 mg, 98%) as colourless crystals, m.p. 151 ℃, Lit.[35b] m.p. 150 – 153 ℃; ν_{max} (NaCl; Thin Film)/cm^{-1} 3307 (s, br, N-H), 2934 (s, C-H) and 1639 (s, C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 5.53 (1H, s, br, N*H*), 3.30 (2H, m, CH_2N), 2.20 (2H, m, CH_2C=O), 1.67 (2H, m, CH_2CH_2N), 1.50 (2H, m, CH_2CH_2C=O) and 1.33 (7×2H, m CH_2CH_2CH_2); δ_C (75 MHz; $CDCl_3$) 173.8 (*C*=O), 39.5 (*C*H_2N), 37.4 (*C*H_2C=O), 28.7, 27.2, 26.8, 26.6, 26.1, 25.6, 25.3, 25.1 and 24.3 (remaining *C*H_2).

3.3 General procedure: The Schmidt reaction

The lactams were prepared by a procedure in the reference.[36] Sodium azide was added (as rapidly as the evolution of nitrogen would permit) into a mixture of concentrated hydrochloric acid and ketone in an ice-bath. The reaction mixture was stirred for 4 h. Sodium carbonate was added until the mixture was slightly alkaline. Distilled water was added to dissolve the inorganic salts, and the oil which had separated was extracted with dichloromethane. The organic extracts

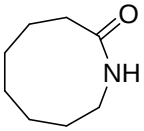
were dried over anhydrous magnesium sulphate and the solvent was removed in *vacuo*. The crystals which were formed on cooling were purified by re-crystallisation in an ethyl acetate: hexane solvent mixture. The following three compounds were prepared by this method

(a) Azocan-2-one (139)



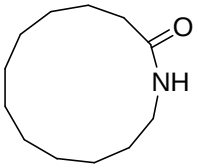
A mixture of cycloheptanone **136** (10.000 g, 89.13 mmol) and concentrated hydrochloric acid (20.00 ml) was treated with sodium azide (8.924 g, 137.27 mmol, 1.54 equiv) as described above to give *azocan-2-one* **139** (9.452 g, 83%) as colourless crystals, m.p. 35 – 36 ℃, Lit.[35c] m.p. 35 – 38 ℃; ν_{max} (NaCl; Thin Film)/cm^{-1} 3291 (s, br, N-H), 2928 (s, C-H) and 1659 (s, C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.84 (1H, s, br, N*H*), 3.32 (2H, t, *J* 6.0, CH_2N), 2.42 (2H, t, *J* 5.4, CH_2C=O), 1.81 (2H, m, CH_2CH_2N) and 1.58 (3×2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 173.4 (*C*=O), 46.0 (*C*H_2N), 32.5 (*C*H_2C=O), 32.3, 28.3, 26.1 and 25.2 (remaining *C*H_2's)

(b) Azonan-2-one (140)



A mixture of cyclooctanone **137** (2.250 g, 17.84 mmol) and concentrated hydrochloric acid (10.00 ml) was treated with sodium azide (1.781 g, 27.40 mmol, 1.54 equiv) as described above to give *azonan-2-one* **140** (2.520 g, 96%) as colourless crystals, m.p. 75 – 76 ℃, Lit.[35d] m.p. 74 – 76 ℃; ν_{max} (NaCl; Thin Film)/cm^{-1} 3301 (s, br, N-H), 2930 (s, C-H) and 1651 (s, C=O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 6.36 (1H, s, br, N*H*), 3.36 (2H, m , CH_2N), 2.43 (2H, t, *J* 6.35, CH_2C=O), 1.81 (2H, m, CH_2CH_2N) and 1.62 – 1.40 (4×2H, m $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 178.0 (*C*=O), 43.3 (*C*H_2N), 33.0 (*C*H_2C=O), 30.0, 27.8, 25.4, 24.5 and 23.1 (remaining *C*H_2's)

(c) Azacyclotridecan-2one (141)



A mixture of cyclotridecanone **133** (10.000 g, 54.84 mmol) and concentrated hydrochloric acid (20.00 ml) was treated with sodium azide (5.491 g, 84.46 mmol, 1.54 equiv) in the manner which has been described above to give *azacyclotridecane-2-one* **135** (8.750 g, 81%) as colourless crystals. The data is the same as reported above.

3.4 Thionation of lactams

3.4.1 The Curphey procedure

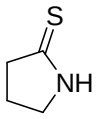
The thiolactams were prepared by a procedure in the reference.[37] A mixture of lactam, phosphorus pentasulfide and hexamethyldisiloxane in dry dichloromethane was stirred at room temperature under nitrogen atmosphere for 3 to 5 days. Saturated aqueous potassium carbonate was carefully added to the reaction mixture which was stirred for another 5 min before being transferred to a separator funnel. The organic layer was extracted repeatedly with dichloromethane. The organic extracts were dried over anhydrous magnesium sulphate and the solvent was evaporated in *vacuo*. The crude products which were formed were either purified by recrystallisation in an ethyl acetate: hexane solvent mixture or purified by column chromatography on silica gel using EtOAc: Hexane {(0.5:9.5), (1:9), (2:8) and (3:7)} solvent mixture as eluent.

3.4.2 The Brillon procedure

The thiolactams were prepared by a procedure in the reference.[38] Sodium carbonate was added portion-wise over 5 min to a vigorously stirred suspension

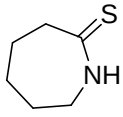
of phosphorus pentasulfide in dry tetrahydrofuran and left to stir at room temperature for 15 min. The lactam was added to the clear yellow solution and the reaction was left stirring at room temperature for 4 days. The reaction was quenched by the cautious addition of aqueous sodium carbonate solution. After stirring for 5 min, the mixture was extracted repeatedly with dichloromethane and the combined organic extracts were dried over anhydrous magnesium sulphate, evaporated in *vacuo* and purified by recrystallisation from ethyl acetate: hexane solvent mixture.

(a) Pyrrolidine-2-thione (89)



A mixture of pyrrolidin-2-one **142** (5.600 g, 85.10 mmol), phosphorus pentasulfide (6.728 g, 30.27 mmol, 0.46 equiv) and hexamethyldisiloxane (16.027 g, 98.70 mmol, 1.5 equiv) in dry dichloromethane (150.00 ml, 1.77 ml per mmol) were reacted according to general procedure 1 to give *pyrrolidine-2-thione* **89** (2.420 g, 36%) as cream crystals, m.p. 103 – 105 ℃ , Lit[39] m.p. 103 – 106 ℃; R_f 0.40 (EtOAc: Hex, 6:4); ν_{max} (NaCl; Thin Film)/cm^{-1} 3135 (w, br, N-H), 2947 (vw, C-H); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.59 (1H, s, br, N*H*), 3.67 (2H, t, *J* 7.2, CH_2N), 3.92 (2H, t, *J* 7.9, CH_2C=S) and 2.23 (2H, m $CH_2CH_2CH_2N$); δ_C (75 MHz; $CDCl_3$) 206.0 (*C*=S), 49.7 (*C*H_2N), 43.3 (*C*H_2C=S) and 23.0 (*C*H_2CH_2N); HRMS (EI): found, 101.02938 (C_4H_7NS requires 101.02992).

(b) Azepane-2-thione (147)

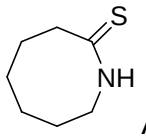


(i) A mixture of azepan-2-one **143** (10.000 g, 88.36 mmol), phosphorus pentasulphide (9.034 g, 40.64 mmol, 0.46 equiv) and hexamethyldisiloxane (21.521 g, 135.533 mmol, 1.5 equiv) in dry dichloromethane (154.62 ml, 1.75 ml per mmol) were reacted according to general procedure 1 to give *azepane-2-thione* **147** (8.306 g, 73%) as colourless crystals, m.p. 102 – 104 ℃, Lit. [38] m.p.

103 – 104 ℃; R_f 0.25 (EtOAc:Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 3423 (m, br, N-H), 2936 (vw, C-H); δ_H (300MHz; $CDCl_3$; Me_4Si) 8.84 (1H, s, br, N*H*), 3.38 (2H, dd, *J* 5.6 and 9.7, C*H*$_2$N), 2.99 (2H, m, C*H*$_2$C=S) and 1.81 – 1.71 (3×2H, m $CH_2CH_2CH_2$); δ_C (300MHz; $CDCl_3$) 210.7 (*C*=S), 47.4 (*C*H_2N), 45.2 (*C*H_2C=S), 30.6, 28.4 and 24.8 (remaining *C*H_2's); HRMS (EI): found, 129.06067 ($C_6H_{11}NS$ requires 129.06122).

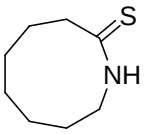
(ii) A mixture of azepan-2-one **143** (5.008 g, 44.25 mmol), phosphorus pentasulphide (10.320 g, 46.42 mmol, 1.05 equiv) and sodium carbonate (6.152 g, 58.02 mmol, 1.3 equiv) in dry tetrahydrofuran (150 ml, 3.39 ml per mmol) were reacted according to general procedure 2 to give *azepane-2-thione* **147** (5.207 g, 91%) as colourless crystals. The data is the same as reported above.

(c) Azocane-2-thione (148)



A mixture of azocan-2-one **144** (9.453 g, 74.30 mmol), phosphorus pentasulphide (7.597 g, 34.18 mmol, 0.46 equiv) and hexamethyldisiloxane (18.097 g, 111.45 mmol, 1.5 equiv) in dry dichloromethane (130 ml, 1.75 ml per mmol) were reacted according to general procedure 1 to give *azocane-2-thione* **148** (7.513 g, 71%) as colourless crystals, m.p. 69 – 72 ℃, Lit. [39] m.p. 79 – 82 ℃; R_f 0.69 (EtOAc:Hex, 4:1); ν_{max} (NaCl; Thin Film)/cm^{-1} 3425 (m, br, N-H), 2927 (vw, C-H); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.59 (1H, s, br, N*H*), 3.46 (2H, m, C*H*$_2$N), 2.92 (2H, t, *J* 6.3, C*H*$_2$C=S), 1.93 (2H, m, C*H*$_2$$CH_2$N) 1.68 (2H, m, C*H*$_2$$CH_2$C=S) and 1.57 (2×2H, m $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 209.2 (*C*=S), 45.7 (*C*H_2N), 39.6 (*C*H_2C=S), 32.1, 30.7, 25.3 and 25.0 (remaining *C*H_2's); HRMS (EI): found, 143.07631 ($C_7H_{13}NS$ requires 143.07687).

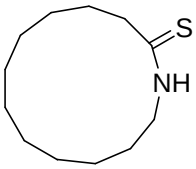
(d) Azonane-2-thione (149)



(i) A mixture of azonan-2-one **145** (2.520 g, 17.84 mmol), phosphorus pentasulphide (1.825 g, 8.21 mmol, 0.46 equiv) and hexamethyldisiloxane (4.345 g, 26.76 mmol, 1.5 equiv) in dry dichloromethane (32 ml, 1.79 ml per mmol) were reacted according to general procedure 1 to give *azonane-2-thione* **149** (1.260 g, 50%) as colourless crystals, m.p. 72 – 75 ℃, Lit.[39] m.p. 84 – 87 ℃; R_f 0.77 (EtOAc:Hex, 4:1); ν_{max} (NaCl; Thin Film)/cm^{-1} 3407 (m, br, N-H); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.30 (1H, s, br, N*H*), 3.51 (2H, m, C*H*$_2$N), 2.92 (2H, m, C*H*$_2$C=S), 1.95 (2H, m, C*H*$_2$CH$_2$N), 1.68 (2H, m, C*H*$_2$CH$_2$C=S) and 1.57 (3×2H, m, CH$_2$C*H*$_2$CH$_2$); δ_C (75 MHz; $CDCl_3$) 209.6 (*C*=S), 48.0 (*C*H$_2$N), 41.4 (*C*H$_2$C=S), 29.2, 28.4, 27.7, 24.7 and 24.1 (remaining *C*H$_2$'s); HRMS (EI): found, 157.09199 ($C_8H_{15}NS$ requires 157.09252).

(ii) a mixture of azonan-2-one **145** (2.692 g, 19.06 mmol), phosphorus pentasulphide (4.498 g, 20.01 mmol, 1.05 equiv) and sodium carbonate (2.626 g, 24.78 mmol, 1.3 equiv) in dry tetrahydrofuran (150 ml, 8.31 ml per mmol) were reacted according to general procedure 2 to give *azonane-2-thione* **149** (2.998 g, 84%) as colourless crystals. The data is the same as reported above.

(e) Azacyclotridecane-2-thione (150)



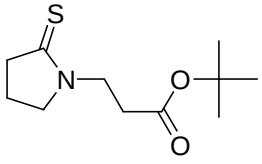
A mixture of azacyclotridecan-2-one **135** (5.000 g, 25.33 mmol), phosphorus pentasulphide (2.604 g, 11.72 mmol, 0.46 equiv) and hexamethyldisiloxane (16.170 g, 38.00 mmol, 1.5 equiv) in dry dichloromethane (22.76 ml, 0.90 ml per mmol) were reacted according to general procedure 1 to give *azacyclotridecane-2-thione* **150** (5.050 g, 93 %) as colourless crystals, m.p. 104 ℃, Lit.[39] m.p. 102 – 104 ℃; R_f 0.53 (EtOAc:Hex, 3:7); ν_{max} (NaCl; Thin

Film)/cm^{-1} 3327 (m, br, N-H); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.21 (1H, s, br, N*H*), 3.77 (2H, m, CH_2N), 2.73 (2H, m, CH_2C=S), 1.81 (2H, m, CH_2CH_2N), 1.68 (2H, m, CH_2CH_2C=S) and 1.43 – 1.33 (7×2H, m $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 205.4 (*C*=S), 46.8 (*C*H_2N), 45.3 (*C*H_2C=S), 27.5, 26.6, 26.4, 25.9, 25.5, 25.2, 24.5, 24.2 and 23.9 (remaining *C*H_2's); HRMS (EI): found, 213.15460 ($C_{12}H_{23}NS$ requires 213.15512).

3.5 General procedure for the N-alkylation of thiolactams with acrylate esters

The *N*-alkylthiolactams were prepared by a procedure in the reference.[27] To a stirred solution of the thiolactam in dry tetrahydrofuran was added a catalytic amount of sodium hydroxide, followed by the dropwise addition of *tert*-butyl acrylate. The mixture was stirred at 40 ^oC for 17 - 22 h, before evaporating the solvent in *vacuo*. The residue was dissolved in dichloromethane, and the resulting solution was washed with distilled water and saturated sodium chloride solution. The organic layer was dried over anhydrous magnesium sulphate, filtered and evaporated in *vacuo* to yield oil which solidified on cooling at room temperature. The product was purified by recrystallisation from ethyl acetate: hexane solvent mixture. The following compounds were prepared by this method.

(a) *tert*-Butyl 3-(2-thioxopyrrolidin-1-yl)propanoate (108b)

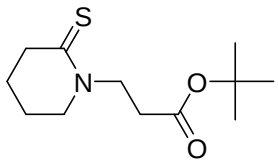


Pyrrolidine-2-thione **89** (626 mg, 5.73 mmol), *tert*-butyl acrylate (882 mg, 6.88 mmol, 1.20 equiv) and a catalytic amount of sodium hydroxide in dry tetrahydrofuran (50.00 ml) were reacted as described above to give tert-*butyl 3-(2-thioxopyrrolidin-1-yl)propanoate* **108b** (1.125 g, 85%) as colourless crystals, m.p. 48 – 49 ℃; R_f 0.34 (EtOAc:Hex, 3:7); ν_{max} (NaCl; Thin

Film)/cm^{-1} 2981 (m, C-H), 1716 (s, C=O) and 1151 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.98 (2H, t, *J* 6.7, $(CH_3)_3COOCCH_2CH_2N$), 3.79 (2H, t, *J* 7.3, $CH_2CH_2CH_2N$), 3.02 (2H, t, *J* 7.9, $CH_2C=S$), 2.67 (2H, t, *J* 6.7, $(CH_3)_3COOCCH_2CH_2N$), 2.05 (2H, m, $CH_2CH_2CH_2$) and 1.46 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 201.9 (*C*=S), 171.2 (*C*=O), 81.6 ($(CH_3)_3C$), 56.2 ($CH_2CH_2CH_2N$), 45.4 ($(CH_3)_3COOCCH_2CH_2N$), 44.3 ($CH_2CH_2CH_2C=S$), 32.8 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($(CH_3)_3C$) and 20.3 ($CH_2CH_2C=S$); HRMS (EI): found, 229.11310 ($C_{11}H_{19}O_2NS$ requires 229.11365).

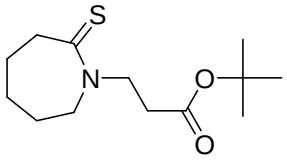
(b) *tert*-butyl 3-(2-thioxopiperidin-1-yl)propanoate (108c)

27



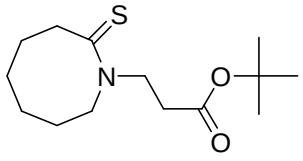
Piperidine-2-thione **107** (376 mg, 3.26 mmol), *tert*-butyl acrylate (501 mg, 3.91 mmol, 1.20 equiv) and a catalytic amount of sodium hydroxide in dry tetrahydrofuran (5.70 ml) were reacted as described above to give tert-*butyl 3-(2-thioxopiperidin-1-yl)propanoate* **108c** (0.579 g, 73%) as colourless crystals, m.p. 54 – 55 ℃, Lit m.p. 55 – 56 ℃; [22] R_f 0.45 (EtOAc:Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} ; δ_H (300 MHz; $CDCl_3$; Me_4Si) 3.95 (2H, t, *J* 6.9, $(CH_3)_3COOCCH_2CH_2N$), 3.34 (2H, t, *J* 5.7, $CH_2CH_2CH_2N$), 2.75 (2H, t, *J* 6.2, $CH_2C=S$), 2.55 (2H, t, *J* 6.9, $(CH_3)_3COOCCH_2CH_2N$), 1.68 (2H, m, $CH_2CH_2CH_2N$), 1.52 (2H, m, $CH_2CH_2CH_2N$) and 1.45 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 199.9 (*C*=S), 171.1 (*C*=O), 81.0 ($(CH_3)_3C$), 52.0 ($CH_2CH_2CH_2N$), 51.1 ($(CH_3)_3COOCCH_2CH_2N$), 42.1 ($CH_2CH_2CH_2C=S$), 32.1 ($(CH_3)_3COOCCH_2CH_2N$), 23.2 ($CH_2CH_2CH_2N$), 28.3 ($(CH_3)_3C$) and 20.7 ($CH_2CH_2C=S$).

(c) *tert*-Butyl 3-(2-thioxoazepan-1-yl)propanoate (151)



Azepane-2-thione **147** (2.000 g, 15.47 mmol), *tert*-butyl acrylate (2.379 g, 18.56 mmol, 1.20 equiv) and a catalytic amount of sodium hydroxide in dry tetrahydrofuran (27.00 ml) were reacted as described above to give tert-*butyl 3-(2-thioxoazepan-1-yl)propanoate* **151** (3.267 g, 82%) as colourless crystals, m.p. 60 – 62 ℃; R_f 0.57 (EtOAc:Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2932 (m, C-H), 1725 (s, C=O) and 1156 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.23 (2H, t, *J* 6.9, $(CH_3)_3COOCCH_2CH_2N$), 3.74 (2H, m, $CH_2CH_2CH_2N$), 3.12 (2H, m, $CH_2C{=}S$), 2.72 (2H, t, *J* 6.9, $(CH_3)_3COOCCH_2CH_2N$), 1.73 – 1.65 (3×2H, m, $CH_2CH_2CH_2$) and 1.45 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 206.8 (*C*=S), 171.5 (*C*=O), 81.4 ($(CH_3)_3C$), 55.4 ($CH_2CH_2CH_2N$), 53.3 ($(CH_3)_3COOCCH_2CH_2N$), 47.6 ($CH_2CH_2CH_2C{=}S$), 33.0 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($(CH_3)_3C$), 29.6, 27.6 and 25.0 (remaining CH_2's); HRMS (EI): found, 257.14705 ($C_{13}H_{23}O_2NS$ requires 257.144954).

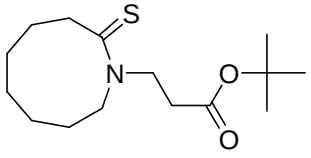
(d) *tert*-Butyl 3-(2-thioxoazocan-1-yl)propanoate (152)



Azocane-2-thione **148** (2.000 g, 13.96 mmol), *tert*-butyl acrylate (2.147 g, 16.75 mmol, 1.20 equiv) and a catalytic amount of sodium hydroxide in dry tetrahydrofuran (24.00 ml) were reacted as described above to give tert-*butyl 3-(2-thioxoazocan-1-yl)propanoate* **152** (3.541 g, 93%) as crystals, m.p. 66 – 69 ℃; R_f 0.64 (EtOAc:Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2929 (m, C-H), 1727 (s, C=O) and 1154 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.13 (2H, t, *J* 6.9, $(CH_3)_3COOCCH_2CH_2N$), 3.81 (2H, m, $CH_2CH_2CH_2N$), 3.07 (2H, m, $CH_2C{=}S$), 2.81 (2H, t, *J* 7.0, $(CH_3)_3COOCCH_2CH_2N$), 1.94 (2H, m, $CH_2CH_2CH_2N$), 1.75 (2H, m, $CH_2CH_2CH_2C{=}S$), 1.45 (3×3H, s, $(CH_3)_3C$) and 1.58 – 1.48 (2×2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 205.7 (*C*=S), 171.3 (*C*=O),

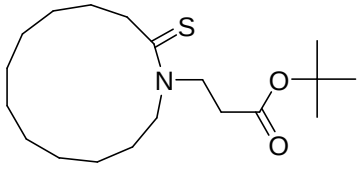
81.0 ($(CH_3)_3C$), 52.2 ($CH_2CH_2CH_2N$), 49.5 ($(CH_3)_3COOCCH_2CH_2N$), 32.2 ($CH_2CH_2CH_2C=S$), 44.9 ($(CH_3)_3COOCCH_2CH_2N$), 28.1 ($(CH_3)_3C$), 31.4, 25.9, 29.6 and 24.7 (remaining CH_2's); HRMS (EI): found, 271.15878 ($C_{14}H_{25}O_2NS$ requires 271.1606).

(e) *tert*-Butyl 3-(2-thioxoazonan-1-yl)propanoate (153)



Azonane-2-thione **149** (0.799 g, 5.08 mmol), *tert*-butyl acrylate (0.782 g, 6.10 mmol, 1.20 equiv) and a catalytic amount of sodium hydroxide in dry tetrahydrofuran (9.00 ml) were reacted as described above to give tert-*butyl 3-(2-thioxoazonan-1-yl)propanoate* **153** (1.367 g, 94%) as colourless crystals, m.p. 64 – 66 ℃; R_f 0.62 (EtOAc:Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2927 (m, C-H), 1726 (s, C=O) and 1155 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.12 (2H, m, $(CH_3)_3COOCCH_2CH_2N$), 3.81 (2H, m, $CH_2CH_2CH_2N$), 3.05 (2H, m, $CH_2C=S$), 2.82 (2H, t, *J* 7.0, $(CH_3)_3COOCCH_2CH_2N$), 1.95 (2H, m, $CH_2CH_2CH_2N$), 1.77 (2H, m, $CH_2CH_2CH_2C=S$), 1.45 (3×3H, s, $(CH_3)_3C$) and 1.57 – 1.51 (3×2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 206.8 (*C*=S), 171.7 (*C*=O), 81.4 ($(CH_3)_3C$), 54.2 ($CH_2CH_2CH_2N$), 49.4 ($(CH_3)_3COOCCH_2CH_2N$), 45.4 ($CH_2CH_2CH_2C=S$), 32.3 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($(CH_3)_3C$), 29.1, 27.1, 28.1, 25.1 and 22.8 (remaining CH_2's); HRMS (EI): found, 285.17625 ($C_{15}H_{27}O_2NS$ requires 285.17625).

(f) *tert*-Butyl 3-(2-thioxoazacyclotridecan-1-yl)propanoate (154)



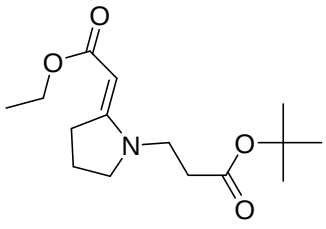
Azacyclotridecane-2-thione **150** (1.013 g, 4.75 mmol), *tert*-butyl acrylate (0.731 g, 5.70 mmol, 1.20 equiv) and a catalytic amount of sodium hydroxide in dry tetrahydrofuran (8.00 ml) were reacted as described

above to give tert-*butyl 3-(2-thioxoazacyclotridecan-1-yl)propanoate* **154** (0.978 g, 60%) as colourless crystals, m.p. 86 – 88 ℃; R_f 0.72 (EtOAc:Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2931 (m, C-H), 1727 (s, C=O) and 1155 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.10 (2H, m, $(CH_3)_3COOCCH_2CH_2N$), 3.49 (2H, m, $CH_2CH_2CH_2N$), 2.77 (2x2H, m, $(CH_3)_3COOCCH_2CH_2N$ and $CH_2C=S$), 1.81 (2×2H, m, $CH_2CH_2CH_2N$ and $CH_2CH_2CH_2C=S$), 1.45 (3×3H, s, $(CH_3)_3C$) and 1.60 – 1.26 (7×2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 205.1 (*C*=S), 171.6 (*C*=O), 81.4 ($(CH_3)_3C$), 51.8 ($CH_2CH_2CH_2N$), 50.0 ($(CH_3)_3COOCCH_2CH_2N$), 42.8 ($CH_2CH_2CH_2C=S$), 32.6 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($(CH_3)_3C$), 26.8, 26.7, 26.3, 24.6, 24.5, 24.3, 24.3, 23.5 and 23.2 (remaining CH_2's); HRMS (EI): found, 341.23908 ($C_{19}H_{35}O_2NS$ requires 341.23885).

3.6 General procedure for the preparation of N-alkyl vinylogous urethanes from N-alkylthiolactams

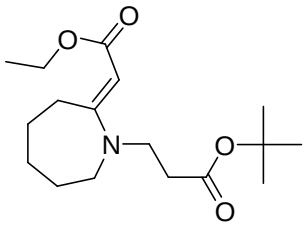
The vinylogous urethanes were prepared by a procedure in the reference.[27] Ethyl bromoacetate was added dropwise to a stirred solution of *N*-alkylthiolactams in dry acetonitrile. The resulting solution was stirred at room temperature for 42 h, after which the *S*-alkylation was complete. The volatiles were removed in *vacuo*. The salt was then re-dissolved in dry acetonitrile, after which triphenylphosphine or triethylphosphite and triethylamine were added to induce sulphur extrusion. The resulting solution was left to stir at ambient temperature for 25 h. Distilled water was added and the resulting solution was extracted with dichloromethane. The organic extracts were dried over anhydrous magnesium sulphate, filtered and evaporated in *vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate: hexane (0.5:9.5) solvent mixture as eluent. The following compounds were prepared by this method.

(a) (*E*)-*tert*-Butyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate (109b)



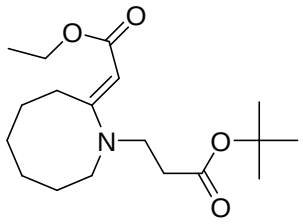
tert-Butyl 3-(2-thioxopyrrolidin-1-yl)propanoate **108b** (236 mg, 1.03 mmol) and ethyl bromoacetate (252 mg, 1.31 mmol, 1.30 equiv) in dry MeCN (10.00 ml) were reacted as described above, followed by the addition of $P(OEt)_3$ (199 mg, 1.20 mmol, 1.20 equiv) and Et_3N (221 mg, 2.18 mmol, 2.10 equiv) in dry MeCN (10.00 ml) (Specific reaction conditions: **Scheme 21.** (*a*) rt, 8 h, (*b*) rt, 1.5 h) to give *(*E*)*-tert-*butyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate* **109b** (257 mg, 88%) as a red oil. R_f 0.36 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2974 (vw, =C-H), 1725 (m, sat, C=O), 1682 (m, unsat, C=O), 1588 (s, C=C) and 1125 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.53 (1H, s, C=C*H*COOEt), 4.09 (2H, q, *J* 7.1, COOC*H*$_2$CH$_3$), 3.42 (2×2H, m, $(CH_3)_3COOCCH_2CH_2N$ and $CH_2CH_2CH_2N$), 3.13 (2H, t, *J* 7.8, C*H*$_2$C=C), 2.49 (2H, t, *J* 7.0, $(CH_3)_3COOCCH_2CH_2N$), 1.92 (2H, p, *J* 7.4, $CH_2CH_2CH_2$), 1.45 (3×3H, s, $(CH_3)_3C$) and 1.25 (3H, t, *J* 7.1, CH_2CH_3) ; δ_C (75 MHz; $CDCl_3$) 171.1 ($(CH_3)_3COOCCH_2CH_2N$), 169.7 (N*C*=C), 164.8 (CH_3CH_2OOC), 81.4 ($(CH_3)_3C$), 78.6 (NC=*C*), 58.6 (CH_3CH_2), 53.1 ($CH_2CH_2CH_2N$), 42.4 ($(CH_3)_3COOCCH_2CH_2N$), 32.9 ($CH_2CH_2CH_2C=C$), 32.6 ($(CH_3)_3COOCCH_2CH_2N$), 28.4 ($(CH_3)_3C$), 21.5 ($CH_2CH_2CH_2$) and 15.1 (CH_2CH_3); HRMS (EI): found, 283.17781 ($C_{15}H_{25}O_4N$ requires 283.17836).

(b) *tert*-Butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azepan-1-yl}propanoate (155)



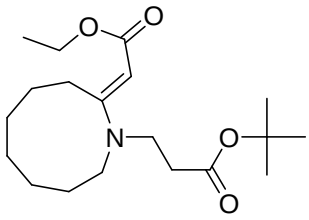
tert-Butyl 3-(2-thioxoazepan-1-yl)propanoate **151** (1.274 g, 4.95 mmol) and ethyl bromoacetate (0.910 g, 5.45 mmol, 1.10 equiv) in dry MeCN (8.60 ml) were reacted as described above, followed by the addition of PPh_3 (0.551 g, 5.45 mmol, 1.10 equiv) and Et_3N (1.429 g, 5.45 mmol, 1.10 equiv) in dry MeCN (8.60 ml) (Specific reaction conditions: **Scheme 21.** (*a*) rt, 23.5 h, (*b*) rt, 1 h) to give tert-*butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azepan-1-yl}propanoate* **155** (0.290 g, 19%) as a yellow oil. R_f 0.52 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2931 (vw, =C-H), 1727 (m, sat, C=O), 1683 (m, unsat, C=O), 1573 (s, C=C) and 1136 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.46 (1H, s, C=C*H*COOEt), 4.03 (2H, q, *J* 7.1, COOC*H*$_2$CH$_3$), 3.48 (2H, t, *J* 7.0, (CH$_3$)$_3$COOCCH$_2$C*H*$_2$N), 3.40 (2H, m, CH$_2$CH$_2$C*H*$_2$N), 3.20 (2H, m, C*H*$_2$C=C), 2.50 (2H, t, *J* 7.0, (CH$_3$)$_3$COOCC*H*$_2$CH$_2$N), 1.60 (2×2H, m, CH$_2$C*H*$_2$CH$_2$), 1.52 (2H, m, CH$_2$C*H*$_2$CH$_2$), 1.42 (3×3H, s, (C*H*$_3$)$_3$C) and 1.21 (3H, t, *J* 7.1, CH$_2$C*H*$_3$) ; δ_C (75 MHz; $CDCl_3$) 170.8 ((CH$_3$)$_3$COO*C*CH$_2$CH$_2$N), 169.0 (N*C*=C), 166.4 (CH$_3$CH$_2$OO*C*), 82.7 ((CH$_3$)$_3$*C*), 80.8 (NC=*C*), 58.1 (CH$_3$*C*H$_2$), 52.9 (CH$_2$CH$_2$*C*H$_2$N), 48.5 ((CH$_3$)$_3$COOCCH$_2$*C*H$_2$N), 29.2 (CH$_2$CH$_2$*C*H$_2$C=C), 32.8 ((CH$_3$)$_3$COOC*C*H$_2$CH$_2$N), 27.9 ((*C*H$_3$)$_3$C), 28.7, 27.0, 25.9 (remaining *C*H$_2$'s) and 14.6 (CH$_2$CH$_3$); HRMS (EI): found, 311.20906 ($C_{17}H_{29}O_4N$ requires 311.20966).

(c) *tert*-Butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azocan-1-yl}propanoate (156)



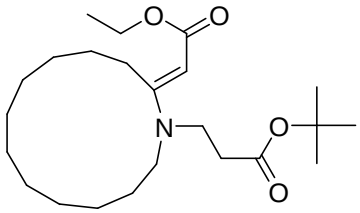
tert-Butyl 3-(2-thioxoazocan-1-yl)propanoate **152**(3.472 g, 12.71 mmol) and ethyl bromoacetate (2.350 g, 14.07 mmol, 1.10 equiv) in dry acetonitrile (22.40 ml) were reacted as described above, followed by the addition of PPh_3 (3.690 g, 14.07 mmol, 1.10 equiv) and Et_3N (1.424 g, 14.07 mmol, 1.10 equiv) in dry MeCN (22.40 ml) (Specific reaction conditions: **Scheme 21.** (*a*) rt, 23 h, (*b*) rt, 22 h) to give tert-*butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azocan-1-yl}propanoate* **156** (1.178 g, 21%) as a yellow oil. R_f 0.61 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2929 (vw, =C-H), 1728 (m, sat, C=O), 1683 (m, unsat, C=O), 1567 (s, conj, C=C) and 1133 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.52 (1H, s, C=C*H*COOEt), 4.08 (2H, q, *J* 7.1, COOC*H*$_2$CH$_3$), 3.46 (2H, m, $(CH_3)_3COOCCH_2CH_2N$), 3.46 (2H, m, $CH_2CH_2CH_2N$), 3.07 (2H, m, C*H*$_2$C=C), 2.57 (2H, t, *J* 7.1, $(CH_3)_3COOCCH_2CH_2N$), 1.78 (2H, m, CH_2CH_2N), 1.60 (2H, m, C*H*$_2$CH$_2$C=C), 1.58 (2×2H, m, $CH_2CH_2CH_2$), 1.58 (3×3H, s, $(CH_3)_3C$) and 1.25 (3H, t, *J* 7.1, CH_2CH_3) ; δ_C (75 MHz; $CDCl_3$) 169.9 ($(CH_3)_3COOCCH_2CH_2N$), 167.5 (N*C*=C), 164.6 (CH_3CH_2OOC), 81.1 ($(CH_3)_3C$), 79.8 (NC=*C*), 57.0 (CH_3CH_2), 44.7 ($CH_2CH_2CH_2N$), 47.7 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($CH_2CH_2CH_2C$=C), 31.3 ($(CH_3)_3COOCCH_2CH_2N$), 26.9 ($(CH_3)_3C$), 29.2, 25.3, 24.9, 23.5 (remaining CH_2's) and 13.5 (CH_2CH_3); HRMS (EI): found, 325.22465 ($C_{18}H_{31}O_4N$ requires 325.22531).

(d) *tert*-Butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azonan-1-yl}propanoate (157)



tert-Butyl 3-(2-thioxoazonan-1-yl)propanoate **153** (1.326 g, 4.64 mmol) and ethyl bromoacetate (0.852 g, 5.10 mmol, 1.10 equiv) in dry MeCN (8.10 ml) were reacted as described above, followed by the addition of PPh_3 (1.337 g, 5.10 mmol, 1.10 equiv) and Et_3N (0.516 g, 5.10 mmol, 1.10 equiv) in dry MeCN (8.10 ml) (Specific reaction conditions: **Scheme 21.** (*a*) rt, 23 h, (*b*) rt, 22 h) to give tert-*butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azonan-1-yl}propanoate* **157** (0.175 g, 8%) as an yellow oil. R_f 0.62 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2932 (vw, =C-H), 1727 (m, sat, C=O), 1683 (m, unsat, C=O), 1561 (s, C=C) and 1136 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.49 (1H, s, C=C*H*COOEt), 4.01 (2H, q, *J* 7.1, $COOCH_2CH_3$) 3.42 (2H, m, $(CH_3)_3COOCCH_2CH_2N$), 3.35 (2H, t, *J* 7.0, $CH_2CH_2CH_2N$), 3.05 – 2.79 (2H, m, $CH_2C=C$), 2.51 (2H, t, *J* 7.0, $(CH_3)_3COOCCH_2CH_2N$), 1.74 (2H, m, CH_2CH_2N), 1.38 (3×3H, s, $(CH_3)_3C$), 1.20 (3H, t, *J* 3.6, CH_2CH_3) and 1.59 – 1.16 (4×2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 171.6 ($(CH_3)_3COOCCH_2CH_2N$), 168.9 (NC=C), 167.4 (CH_3CH_2OOC), 84.2 ($(CH_3)_3C$), 81.3 (NC=*C*), 58.6 (CH_3CH_2), 50.6 ($CH_2CH_2CH_2N$), 45.3 ($(CH_3)_3COOCCH_2CH_2N$), 30.0 ($CH_2CH_2CH_2C=C$), 32.5 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($(CH_3)_3C$), 15.1 (CH_2CH_3), 28.2, 27.6, 26.2, 27.1 and 21.6 (remaining CH_2's); HRMS (EI): found, 339.24046 ($C_{19}H_{33}O_4N$ requires 339.24096).

(e) *tert*-Butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azacyclotridecan-1-yl}propanoate (158)

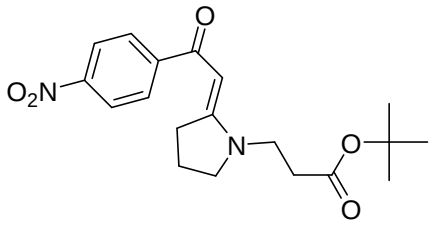


tert-Butyl 3-(2-thioxoazacyclotridecan-1-yl)propanoate **158** (0.978 g, 2.86 mmol) and ethyl bromoacetate (0.526 g, 3.15 mmol, 1.10 equiv) in dry MeCN (10.00 ml) were reacted as described above, followed by the addition of PPh_3 (0.826 g, 3.15 mmol, 1.10 equiv) and Et_3N (0.319 g, 3.15 mmol, 1.10 equiv) in dry MeCN (10.00 ml) (Specific reaction conditions: **Scheme 21.** (*a*) rt, 23 h, (*b*) rt, 22 h) to give tert-*butyl 3-{(2*E*)-2-[(ethoxycarbonyl)methylene]azacyclotridecan-1-yl}propanoate* **154** (249 mg, 20%) as a yellow oil. R_f 0.72 (EtOAc: Hexane,); ν_{max} (NaCl; Thin Film)/cm^{-1} 2932 (vw, =C-H), 1728 (m, sat, C=O), 1682 (m, unsat, C=O), 1569 (s, C=C) and 1152 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.54 (1H, s, C=C*H*COOEt), 4.07 (2H, q, *J* 6.1, COOC*H*$_2$CH$_3$), 3.46 (2H, t, *J* 7.4, $(CH_3)_3COOCCH_2CH_2N$), 3.25 (2H, m, $CH_2CH_2CH_2N$), 2.76 (2H, t, *J* 7.2, C*H*$_2$C=C), 2.50 (2H, t, *J* 7.4, $(CH_3)_3COOCCH_2CH_2N$), 1.81 (2H, m, C*H*$_2$CH$_2$N), 1.46 (3×3H, s, (C*H*$_3$)$_3$C) 1.31 (3H, t, *J* 3.6, CH$_2$C*H*$_3$) and 1.65 – 1.22 (8×2H, m, CH$_2$C*H*$_2$CH$_2$); δ_C (75 MHz; $CDCl_3$) 171.4 ($(CH_3)_3COOCCH_2CH_2N$), 169.0 (N*C*=C), 164.8 (CH_3CH_2OOC), 84.2 ($(CH_3)_3C$), 81.4 (NC=*C*), 58.6 (CH_3CH_2), 51.8 ($CH_2CH_2CH_2N$), 50.0 ($(CH_3)_3COOCCH_2CH_2N$), 46.2 ($CH_2CH_2CH_2C=C$), 49.0 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($(CH_3)_3C$), 15.1 (CH_2CH_3), 33.1, 32.6, 26.8, 26.7, 25.2, 24.8, 24.5, 24.3 and 23.2 (remaining *C*H$_2$'s); HRMS (EI): found, 395.30302 ($C_{23}H_{41}O_4N$ requires 395.30356).

3.7 General procedure for the preparation of N-alkyl vinylogous amides from N-alkylthiolactams

The vinylogous amides were prepared by a procedure in reference.[27] *p*-Nitrophenacyl bromide or phenacyl bromide was added to a stirred solution of *N*-alkylthiolactams in dry acetonitrile. The resulting solution was stirred at room temperature for 22 – 30 h, after which the *S*-alkylation was complete shown by formation of the thioiminium salt. This was then followed by the addition of triphenylphosphine and triethylamine to induce sulphur extrusion. The resulting solution was left to stir at ambient temperature for 2 – 24 h. Distilled water was added and the resulting solution was extracted with dichloromethane. The organic extracts were dried over anhydrous sodium sulphate, filtered and evaporated in *vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate: hexane (0.5:9.5) solvent mixture as eluent. The following compounds were prepared by this procedure.

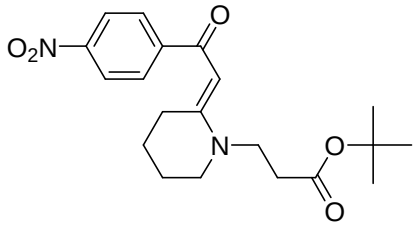
(a) (*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]pyrrolidin-1-yl}propanoate (159a)



tert-Butyl 3-(2-thioxopyrrolidin-1-yl)propanoate **108b** (504 mg, 2.20 mmol) and *p*-nitrophenacyl bromide (564 mg, 2.31 mmol, 1.05 equiv) in dry MeCN (45.00 ml) were reacted as described above, followed by the addition of PPh_3 (606 mg, 2.31 mmol, 1.05 equiv) and Et_3N (234 mg, 2.31 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 22.** (*a*) rt, 22 h, (*b*) rt, 2 h) to give *(*E*)*-tert-*butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]pyrrolidin-1-yl}propanoate* **159a** (758 mg, 89%) as orange crystals, m.p. 128 – 129 ℃; R_f 0.076 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2987 (vw, =C-H), 1726 (m, C=O), 1678 (m, conj, C=C), 1595 (s, C=C), 1514 (m, aromatic, N-O), 1342 (m, aromatic, N-O) and 1148 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.23 (2×1H,

d, *J* 8.7, C*H*CNO_2), 8.00 (2×1H, d, *J* 8.7, C*H*CHCNO_2) 5.73 (1H, s, C=C*H*COAr), 3.67 (2H, t, *J* 6.8 $(CH_3)_3COOCCH_2CH_2N$), 3.57 (2H, t, *J* 7.3, $CH_2CH_2CH_2N$), 3.40 (2H, t, *J* 7.8, CH_2C=C), 2.61 (2H, t, *J* 6.8, $(CH_3)_3COOCCH_2CH_2N$), 2.05 (2H, p, *J* 7.6, $CH_2CH_2CH_2$) and 1.45 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 185.2 (CH*C*OAr), 170.8 ($(CH_3)_3COOCCH_2CH_2N$), 168.6 (N*C*=C), 149.0 (CH*C*NO_2), 148.0 (*C*CHCHCNO_2), 128.5 (*C*HCHCNO_2), 123.7 (*C*HCNO_2), 81.8 ($(CH_3)_3C$), 87.0 (NC=*C*), 53.6 ($CH_2CH_2CH_2N$), 42.8 ($(CH_3)_3COOCCH_2CH_2N$), 34.5 ($CH_2CH_2CH_2C$=C), 33.0 ($(CH_3)_3COOCCH_2CH_2N$), 28.4 ($(CH_3)_3C$) and 21.2 ($CH_2CH_2CH_2$); HRMS (EI): found, 360.16797 ($C_{19}H_{24}O_5N_2$ requires 360.16852).

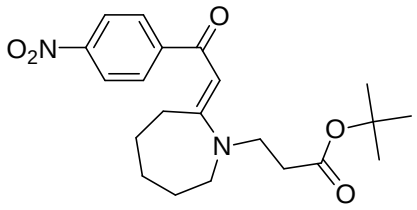
(b) (*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]piperidin-1-yl}propanoate (160a)



tert-Butyl 3-(2-thioxopiperidin-1-yl)propanoate **108c** (297 mg, 1.22 mmol) and *p*-nitrophenacyl bromide (312 mg, 1.28 mmol, 1.05 equiv) in dry MeCN (15.00 ml) were reacted as described above, followed by the addition of PPh_3 (336 mg, 1.28 mmol, 1.05 equiv) and Et_3N (130 mg, 1.28 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 22.** (*a*) rt, 11 h, (*b*) rt, 22 h) to give *(*E*)*-tert-*butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]piperidin-1-yl}propanoate* **160a** (146 mg, 32%) as yellow crystals, m.p. 116 – 117 ℃ ; R_f 0.13 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2970 (vw, =C-H), 2360 (w, R_3-N^+ ions), 1722 (m, C=O), 1610 (m, conj, C=C), 1588 (s, C=C), 1514 (m, aromatic, N-O), 1346 (m, aromatic, N-O) and 1142 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.22 (2×1H, d, *J* 8.5, C*H*CNO_2), 7.96 (2×1H, d, *J* 8.5, C*H*CHCNO_2) 5.68 (1H, s, C=C*H*COAr), 3.67 (2H, t, *J* 6.9 $(CH_3)_3COOCCH_2CH_2N$), 3.44 (2H, t, *J* 5.8, $CH_2CH_2CH_2N$), 3.34 (2H, t, *J* 6.3, CH_2C=C), 2.65 (2H, t, *J* 6.9, $(CH_3)_3COOCCH_2CH_2N$), 1.84 (2H, m, $CH_2CH_2CH_2$), 1.72 (2H, m, $CH_2CH_2CH_2$) and 1.45 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 185.0 (CH*C*OAr), 170.9

((CH_3)$_3$COO*C*CH_2CH_2N), 166.0 (N*C*=C), 149.1 (CH*C*NO_2), 148.9 (*C*CHCHCNO_2), 128.4 (*C*HCHCNO_2), 123.7 (*C*HCNO_2), 81.9 ((CH_3)$_3$*C*), 90.7 (NC=*C*), 51.3 (CH_2CH_2*C*H_2N), 48.7 ((CH_3)$_3$COOCCH_2*C*H_2N), 32.6 (CH_2CH_2*C*H_2C=C), 28.9 ((CH_3)$_3$COOC*C*CH_2CH_2N), 28.4 ((CH_3)$_3$C) 23.2 (CH_2*C*H_2CH_2) and 19.3 (CH_2*C*H_2CH_2); HRMS (EI): found, 374.18361 ($C_{20}H_{26}O_5N_2$ requires 374.18417).

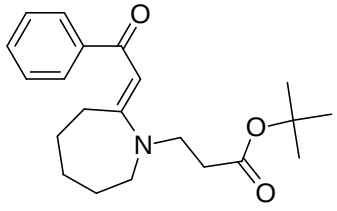
(c) (*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azepan-1-yl}propanoate (161a)



tert-Butyl 3-(2-thioxoazepan-1-yl)propanoate **151** (746 mg, 2.90 mmol) and *p*-nitrophenacyl bromide (744 mg, 3.05 mmol, 1.05 equiv) in dry MeCN (40.00 ml) were reacted as described above, followed by the addition of PPh_3 (800 mg, 3.05 mmol, 1.05 equiv) and Et_3N (309 mg, 3.05 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 22.** (*a*) rt, 23 h, (*b*) rt, 4 h) to give *(*E*)*-tert-*butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azepan-1-yl}propanoate* **161a** (812 mg, 72%) as yellow oil. R_f 0.23 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2981 (vw, =C-H), 2360 (w, R_3-N^+ ions), 1711 (m, C=O), 1622 (m, conj, C=C), 1591 (s, C=C), 1514 (m, aromatic, N-O), 1341 (m, aromatic, N-O) and 1152 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.22 (2×1H, d, *J* 8.7, C*H*CNO_2), 7.96 (2×1H, d, *J* 8.7, C*H*CHCNO_2), 5.62 (1H, s, C=C*H*COAr), 3.72 (2H, t, *J* 6.9 (CH_3)$_3$COOCCH_2C*H*$_2$N), 3.61 (2H, m, CH_2CH_2C*H*$_2$N), 3.51 (2H, m, C*H*$_2$C=C), 2.64 (2H, t, *J* 6.9, (CH_3)$_3$COOCC*H*$_2CH_2$N), 1.74 (2×2H, m, CH_2C*H*$_2CH_2$), 1.67 (2H, m, CH_2C*H*$_2CH_2$) and 1.46 (3×3H, s, (C*H*$_3$)$_3$C); δ_C (75 MHz; $CDCl_3$) 185.6 (CH*C*OAr), 170.8 ((CH_3)$_3$COO*C*CH_2CH_2N), 170.8 (N*C*=C), 149.1 (CH*C*NO_2), 149.0 (*C*CHCHCNO_2), 128.5 (*C*HCHCNO_2), 123.6 (*C*HCNO_2), 81.8 ((CH_3)$_3$*C*), 91.6 (NC=*C*), 53.9 (CH_2CH_2*C*H_2N), 49.5 ((CH_3)$_3$COOCCH_2*C*H_2N), 33.5 (CH_2CH_2*C*H_2C=C), 29.7 ((CH_3)$_3$COOC*C*H_2CH_2N), 28.4 ((CH_3)$_3$C), 28.5, 28.4 and

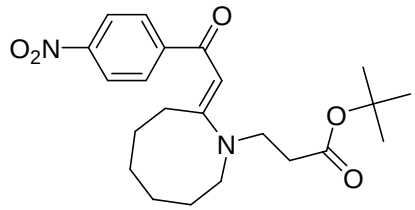
25.5 (remaining *C*H_2's); HRMS (EI): found, 388.19928 ($C_{21}H_{28}O_5N_2$ requires 388.19982).

(d) (*E*)-*tert*-Butyl 3-[2-(2-oxo-2-phenylethylidene)azepan-1-yl]propanoate (161d)



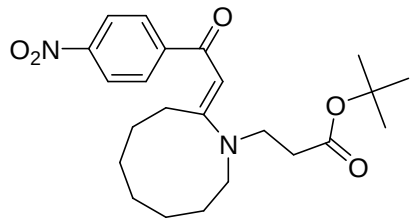
tert-Butyl 3-(2-thioxoazepan-1-yl)propanoate **151** (509 mg, 1.97 mmol) and phenacyl bromide (412 mg, 2.07 mmol, 1.05 equiv) in dry MeCN (15.00 ml) were reacted as described above, followed by the addition of PPh_3 (535 mg, 2.07 mmol, 1.05 equiv) and Et_3N (206 mg, 2.07 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 22.** (*a*) rt, 20 h, (*b*) rt, 4 h) to give *(*E*)*-tert-*butyl 3-[2-(2-oxo-2-phenylethylidene)azepan-1-yl]propanoate* **161d** (216 mg, 32%) as yellow oil. R_f 0.25 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2911 (vw, =C-H), 2360 (w, R_3-N^+ ions), 1724 (m, C=O), 1622 (m, conj, C=C), 1574 (s, C=C), 1529 (s, aromatic, C=C), 1450 (m, aromatic, C=C) and 1151 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.87 (2×1H, dd, *J* 1.8, *J* 7.4, COCC*H*CH), 7.38 (2×1H, m, COCCHC*H*), 7.38 (1H, m, COCCHCHC*H*), 5.65 (1H, s, C=C*H*COAr), 3.67 (2H, t, *J* 7.0, $(CH_3)_3COOCCH_2CH_2N$), 3.54 (2H, m, $CH_2CH_2CH_2N$), 3.48 (2H, m, CH_2C=C), 2.61 (2H, t, *J* 7.0, $(CH_3)_3COOCCH_2CH_2N$), 1.71 (2×2H, m, $CH_2CH_2CH_2$), 1.62 (2H, m, $CH_2CH_2CH_2$) and 1.46 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 188.5 (CHCOAr), 171.1 ($(CH_3)_3COOCCH_2CH_2N$), 169.2 (NC=C), 143.3 (COCCHCHCH), 130.7 (COCCHCHC*H*), 128.4 (COCC*H*CHCH), 127.7 (COCCHC*H*CH), 81.7 ($(CH_3)_3C$), 91.9 (NC=*C*), 53.7 ($CH_2CH_2CH_2N$), 49.5 ($(CH_3)_3COOCCH_2CH_2N$), 33.5 ($CH_2CH_2CH_2C$=C), 29.9 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($(CH_3)_3C$), 28.8, 28.3 and 25.9 (remaining *C*H_2's); HRMS (EI): found, 343.21421 ($C_{21}H_{28}O_3N$ requires 343.21474).

(e) (*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azocan-1-yl}propanoate (162a)



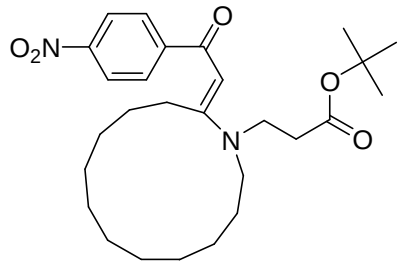
tert-Butyl 3-(2-thioxoazocan-1-yl)propanoate **152** (582 mg, 2.14 mmol) and *p*-nitrophenacyl bromide (549 mg, 2.25 mmol, 1.05 equiv) in dry MeCN (40.00 ml) were reacted as described above, followed by the addition of PPh_3 (591 mg, 2.25 mmol, 1.05 equiv) and Et_3N (228 mg, 2.25 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 22.** (*a*) rt, 23 h, (*b*) rt, 4 h) to give *(*E*)*-tert-*butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azocan-1-yl}propanoate* **162a** (750 mg, 87%) as yellow crystals, m.p. 71 – 73 ℃; R_f 0.30 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2921 (vw, =C-H), 2360 (w, R_3-N^+ ions), 1720 (m, C=O), 1616 (m, conj, C=C), 1586 (s, C=C), 1513 (s, aromatic, N-O), 1462 (m, aromatic, C=C), 1336 (s, aromatic, N-O) and 1159 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.21 (2×1H, d, *J* 8.7, C*H*CNO_2), 7.99 (2×1H, d, *J* 8.7, C*H*$CHCNO_2$) 5.71 (1H, s, C=C*H*COAr), 3.69 (2H, m, $(CH_3)_3COOCCH_2CH_2N$), 3.69 (2H, m, $CH_2CH_2CH_2N$), 3.30 (2H, m, CH_2C=C), 2.69 (2H, t, *J* 7.1, $(CH_3)_3COOCCH_2CH_2N$), 1.92 (2H, m, $CH_2CH_2CH_2N$), 1.71 (2H, m, $CH_2CH_2CH_2C$=C), 1.50 (2×2H, m, $CH_2CH_2CH_2CH_2C$=C) and 1.47 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 184.4 (CHCOAr), 170.8 ($(CH_3)_3COOCCH_2CH_2N$), 169.7 (NC=C), 149.2 ($CHCNO_2$), 148.9 ($CCHCHCNO_2$), 128.5 ($CHCHCNO_2$), 123.6 ($CHCNO_2$), 81.9 ($(CH_3)_3C$), 91.0 (NC=*C*), 50.0 ($CH_2CH_2CH_2N$), 47.1 ($(CH_3)_3COOCCH_2CH_2N$), 38.1 ($CH_2CH_2CH_2C$=C), 33.1 ($(CH_3)_3COOCCH_2CH_2N$), 28.4 ($(CH_3)_3C$), 30.2, 29.9, 26.6 and 25.2 (remaining CH_2's); HRMS (EI): found, 402.21493 ($C_{22}H_{30}O_5N_2$ requires 402.21547).

(f) (*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azonan-1-yl}propanoate (163a)



tert-Butyl 3-(2-thioxoazonan-1-yl)propanoate **153** (601 mg, 2.11 mmol) and *p*-nitrophenacyl bromide (542 mg, 2.22 mmol, 1.05 equiv) in dry MeCN (40.00 ml) were reacted as described above, followed by the addition of PPh_3 (582 mg, 2.22 mmol, 1.05 equiv) and Et_3N (225 mg, 2.22 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 22.** (*a*) rt, 23 h, (*b*) rt, 4 h) to give *(*E*)*-tert-*butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azonan-1-yl}propanoate* **163a** (620 mg, 67%) as yellow crystals, m.p. 111 – 112 ℃; R_f 0.30 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2931 (vw, =C-H), 1711 (m, C=O), 1615 (w, conj, C=C), 1587 (m, C=C), 1513 (s, aromatic, N-O), 1466 (m, aromatic, C=C), 1338 (s, aromatic, N-O) and 1153 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.22 (2×1H, d, *J* 8.8, C*H*CNO_2), 8.00 (2×1H, d, *J* 8.8, C*H*$CHCNO_2$) 5.72 (1H, s, C=C*H*COAr), 3.67 (2H, m, $(CH_3)_3COOCCH_2CH_2N$), 3.67 (2H, m, $CH_2CH_2CH_2N$), 3.24 (2H, m, CH_2C=C), 2.70 (2H, t, *J* 7.0, $(CH_3)_3COOCCH_2CH_2N$), 1.94 (2H, m, $CH_2CH_2CH_2N$), 1.75 (2H, m, $CH_2CH_2CH_2C$=C), 1.60 (2H, m, $CH_2CH_2CH_2CH_2N$), 1.51 (2H, m, $CH_2CH_2CH_2CH_2C$=C) and 1.47 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 184.4 (CHCOAr), 170.8 ($(CH_3)_3COOCCH_2CH_2N$), 170.6 (NC=C), 149.1 ($CHCNO_2$), 148.9 ($CCHCHCNO_2$), 128.5 ($CHCHCNO_2$), 123.6 ($CHCNO_2$), 81.8 ($(CH_3)_3C$), 91.7 (NC=*C*), 51.4 ($CH_2CH_2CH_2N$), 46.2 ($(CH_3)_3COOCCH_2CH_2N$), 32.7 ($CH_2CH_2CH_2C$=C), 30.8 ($(CH_3)_3COOCCH_2CH_2N$), 28.4 ($(CH_3)_3C$), 29.6, 27.6, 26.7, 25.9 and 21.8 (remaining CH_2's); HRMS (EI): found, 416.23060 ($C_{23}H_{32}O_5N_2$ requires 416.23112).

(g) (*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azacyclotridecan-1-yl}propanoate (164a)

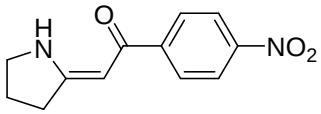


tert-Butyl 3-(2-thioxoazacyclotridecan-1-yl)propanoate **154** (581 mg, 1.70 mmol) and *p*-nitrophenacyl bromide (437 mg, 1.79 mmol, 1.05 equiv) in dry MeCN (40.00 ml) were reacted as described, followed by the addition of PPh_3 (469 mg, 1.79 mmol, 1.05 equiv) and Et_3N (181 mg, 1.79 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 22.** (*a*) rt, 24 h, (*b*) rt, 5 h) to give *(*E*)*-tert-*butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azacyclotridecan-1-yl}propanoate* **164a** (30 mg, 4%) as yellow amorphous solid. R_f 0.60 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2929 (vw, =C-H), 2360 (w, R_3N^+ ions), 1725 (m, C=O), 1625 (w, conj, C=C), 1594 (m, C=C), 1523 (s, aromatic, N-O), 1467 (m, aromatic, C=C), 1342 (s, aromatic, N-O) and 1150 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.23 (2×1H, d, *J* 8.6, C*H*CNO_2), 7.97 (2×1H, d, *J* 8.5, C*H*CHCNO_2), 5.67 (1H, s, C=C*H*COAr), 3.64 (2H, m, $(CH_3)_3COOCCH_2CH_2N$), 3.34 (2H, m, $CH_2CH_2CH_2N$), 2.97 (2H, m, CH_2C=C), 2.61 (2H, t, *J* 6.0, $(CH_3)_3COOCCH_2CH_2N$), 1.89 – 1.26 (9×2H, m, $CH_2CH_2CH_2$) and 1.46 (3×3H, s, $(CH_3)_3C$); δ_C (75 MHz; $CDCl_3$) 184.8 (CHCOAr), 170.9 ($(CH_3)_3COOCCH_2CH_2N$), 168.6 (NC=C), 149.0 (CHCNO_2), 128.1 (CCHCHCNO_2), 128.5 (CHCHCNO_2), 123.8 (CHCNO_2), 82.0 ($(CH_3)_3C$), 91.7 (NC=C), 49.6 ($CH_2CH_2CH_2N$), 46.9 ($(CH_3)_3COOCCH_2CH_2N$), 33.2 ($CH_2CH_2CH_2C$=C), 28.0 ($(CH_3)_3COOCCH_2CH_2N$), 28.5 ($(CH_3)_3C$), 27.2, 27.1, 25.2, 24.9, 24.7, 24.1, 24.1, 23.0 and 22.9 (remaining CH_2's); HRMS (EI): found, 472.29318 ($C_{27}H_{40}O_5N_2$ requires 472.29372). Compound **164a** was recovered with *(Z)-2-(azacyclotridecan-2-ylidene)-1-(4-nitrophenyl)ethanone* **169a** (108 mg, 13%) as yellow crystals. Data is to follow on page 99.

3.8 General procedure for the preparation of NH vinylogous amides from thiolactams

The vinylogous amides were prepared by a procedure in reference.[27] *p*-Nitrophenacyl bromide or phenacyl bromide was added to a stirred solution of thiolactams in dry acetonitrile. The resulting solution was stirred at room temperature for 4 – 30 h, after which the *S*-alkylation was complete shown by formation of the thioiminium salt. This was then followed by the addition of triphenylphosphine and triethylamine to induce sulphur extrusion. The resulting solution was left to stir at ambient temperature for 2 – 24 h. Distilled water was added and the resulting solution was extracted with dichloromethane. The organic extracts were dried over anhydrous sodium sulphate, filtered and evaporated in *vacuo*. The crude product was purified by column chromatography on silica gel using ethyl acetate: hexane (0.5:9.5) solvent mixture as eluent. The following compounds were prepared by this method.

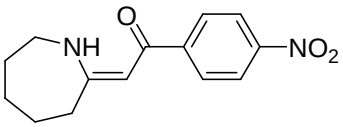
(a) (*Z*)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone (165a)



Pyrrolidine-2-thione **89** (653 mg, 6.45 mmol) and *p*-nitrophenacyl bromide (1.65 g, 6.77 mmol, 1.05 equiv) in dry MeCN (60.00 ml) were reacted as described above, followed by the addition of PPh_3 (1.78 g, 6.77 mmol, 1.05 equiv) and Et_3N (685 mg, 6.77 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 23.** (*a*) rt, 4 h, (*b*) rt, 3 h) to give *(Z)-1-(4-nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone* **165a** (1.176 g, 79%) as yellow crystals, m.p. 160 – 161 ℃; R_f 0.15 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 3280 (m, N-H), 2891 (vw, =C-H), 1739 (w, C=O), 1596 (m, C=C), 1534 (s, aromatic, N-O), 1478 (m, aromatic, C=C) and 1335 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 10.44 (N*H*), 8.23 (2×1H, dd, *J* 8.8 and *J* 1.05, C*H*CNO_2), 7.99 (2×1H, dd, *J* 8.8, C*H*$CHCNO_2$), 5.80 (1H, s, C=C*H*COAr), 3.71 (2H, t, *J* 7.1, $CH_2CH_2CH_2N$), 2.78 (2H, t, *J* 7.9, CH_2C=C) and 2.10 (2H, m, $CH_2CH_2CH_2N$); δ_C (75 MHz; $CDCl_3$)

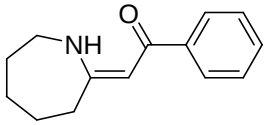
185.0 (CH*C*OAr), 170.6 (N*C*=C), 148.8 (CH*C*NO_2), 146.0 (*C*CHCHCNO_2), 127.9 (*C*HCHCNO_2), 123.5 (*C*HCNO_2), 87.0 (NC=*C*), 48.1 ($CH_2CH_2CH_2N$), 33.1 ($CH_2CH_2CH_2C$=C) and 21.3 ($CH_2CH_2CH_2N$); HRMS (EI): found, 232.08524 ($C_{12}H_{12}O_3N_2$ requires 232.08479). Compound **165a** was recovered with *pyrrolidine-2-thione* **89** (0.283 g, 19%) as cream crystals. Data is above on page 76.

(b) (*Z*)-2-(Azepan-2-ylidene)-1-(4-nitrophenyl)ethanone (166a)



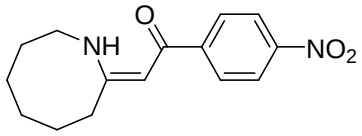
Azepane-2-thione **147** (502 mg, 3.88 mmol) and *p*-nitrophenacyl bromide (995 mg, 4.08 mmol, 1.05 equiv) in dry MeCN (30.00 ml) were reacted as described above, followed by the addition of PPh_3 (1.069 g, 4.08 mmol, 1.05 equiv) and Et_3N (413 mg, 4.08 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 23.** (*a*) rt, 19 h, (*b*) rt, 2 h) to give *(Z)-2-(azepan-2-ylidene)-1-(4-nitrophenyl)ethanone* **166a** (829 mg, 82%) as yellow crystals, m.p. 125 – 127 ℃; R_f 0.16 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 3280 (m, N-H), 2919 (vw, =C-H), 1739 (w, C=O), 1587 (m, C=C), 1505 (s, aromatic, N-O), 1450 (m, aromatic, C=C) and 1317 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 11.7 (N*H*), 8.23 (2×1H, d, *J* 8.8, C*H*CNO_2), 7.99 (2×1H, m, C*H*CHCNO_2), 5.67 (1H, s, C=C*H*COAr), 3.47 (2H, dd, *J* 9.9 and *J* 5.8, $CH_2CH_2CH_2N$), 2.54 – 2.43 (2H, m, CH_2C=C) and 1.80 – 1.65 (3×2H, m, $CH_2CH_2CH_2CH_2N$); δ_C (75 MHz; $CDCl_3$) 185.4 (CH*C*OAr), 173.2 (N*C*=C), 149.2 (CH*C*NO_2), 146.6 (*C*CHCHCNO_2), 128.1 (*C*HCHCNO_2), 123.8 (*C*HCNO_2), 92.1 (NC=*C*), 45.0 ($CH_2CH_2CH_2N$), 35.8 ($CH_2CH_2CH_2C$=C), 31.0, 29.3 and 25.9 (remaining CH_2's); HRMS (EI): found, 260.11554 ($C_{14}H_{16}O_3N_2$ requires 260.11609).

(c) (*Z*)-2-(Azepan-2-ylidene)-1-phenylethanone (166b)



Azepane-2-thione **147** (700 mg, 5.42 mmol) and phenacyl bromide (1.133 g, 5.69 mmol, 1.05 equiv) in dry MeCN (40.00 ml) were reacted as described above, followed by the addition of PPh_3 (1.492 g, 5.69 mmol, 1.05 equiv) and Et_3N (576 mg, 5.69 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 23.** (*a*) rt, 30 h, (*b*) rt, 24 h) to give *(Z)-2-(azepan-2-ylidene)-1-phenylethanone* **166b** (770 mg, 66%) as yellow crystals, m.p. 64 – 66 ℃; R_f 0.40 (EtOAc: Hexane, 3:7) ν_{max} (NaCl; Thin Film)/cm^{-1} 3200 – 3400 (v br, N-H), 2924 (m, =C-H), 1739 (w, C=O), 1585 (m, C=C), 1548 (s, aromatic, C=C), and 1434 (m, aromatic, C=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 11.5 (N*H*), 7.86 (2×1H, m, COCC*H*CH), 7.37 (3×1H, m, COCCHC*HCH*), 5.66 (1H, s, C=C*H*COAr), 3.36 (2H, m, $CH_2CH_2CH_2N$), 2.40 (2H, m, CH_2C=C) and 1.68 – 1.60 (3×2H, m, $CH_2CH_2CH_2CH_2N$); δ_C (75 MHz; $CDCl_3$) 186.7 (CH*C*OAr), 170.2 (N*C*=C), 139.4 (CO*C*CHCH), 129.1 (COCCHCH*C*H), 126.9 (COCCHC*H*CH), 125.6 (COCC*H*CHCH), 89.8 (NC=*C*), 43.1 ($CH_2CH_2CH_2N$), 34.1 ($CH_2CH_2CH_2C$=C), 29.3, 28.1 and 24.6 (remaining CH_2's); HRMS (EI): found, 215.13095 ($C_{14}H_{17}ON$ requires 215.13101).

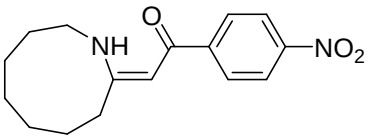
(d) (*Z*)-2-(Azocan-2-ylidene)-1-(4-nitrophenyl)ethanone (167a)



Azocane-2-thione **148** (501 mg, 3.50 mmol) and *p*-nitrophenacyl bromide (898 mg, 3.68 mmol, 1.05 equiv) in dry MeCN (40.00 ml) were reacted as described above, followed by the addition of PPh_3 (965 mg, 3.68 mmol, 1.05 equiv) and Et_3N (372 mg, 3.68 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 23.** (*a*) rt, 20 h, (*b*) rt, 2.5 h) to give *(Z)-2-(azocan-2-ylidene)-1-(4-nitrophenyl)ethanone* **167a** (726 mg, 76%) as yellow crystals, m.p. 128 – 129 ℃; R_f 0.33 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 3200 – 3400

(v br, N-H), 2928 (m, =C-H), 1739 (w, C=O), 1586 (m, C=C), 1548 (s, aromatic, N-O), 1472 (m, aromatic, C=C) and 1338 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 11.8 (N*H*), 8.24 (2×1H, d, *J* 8.8, C*H*CNO_2), 7.99 (2×1H, d, *J* 8.8, C*H*C*H*CNO_2), 5.65 (1H, s, C=C*H*COAr), 3.52 (2H, dd, *J* 7.2 and *J* 11.6, $CH_2CH_2CH_2N$), 2.47 (2H, m, CH_2C=C), 1.86 – 1.79 (2H, m, $CH_2CH_2CH_2CH_2N$), 1.75 – 1.68 (2H, m, $CH_2CH_2CH_2CH_2C$=C) and 1.62 – 1.51 (2×2H, m, $CH_2CH_2CH_2CH_2N$); δ_C (75 MHz; $CDCl_3$) 184.5 (CH*C*OAr), 172.2 (N*C*=C), 148.7 (CH*C*NO_2), 146.3 (*C*CHCHCNO_2), 127.7 (*C*HCHCNO_2), 123.4 (*C*HCNO_2), 91.4 (NC=*C*), 41.7 ($CH_2CH_2CH_2N$), 32.2 ($CH_2CH_2CH_2C$=C), 31.0, 30.9, 25.5 and 24.6 (remaining *C*H_2's); HRMS (EI): found, 274.13120 ($C_{15}H_{18}O_3N_2$ requires 274.13174).

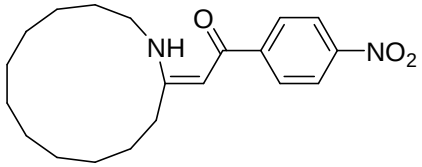
(e) (*Z*)-2-(Azonan-2-ylidene)-1-(4-nitrophenyl)ethanone (168a)



Azonane-2-thione **149** (530 mg, 3.37 mmol) and *p*-nitrophenacyl bromide (864 mg, 3.54 mmol, 1.05 equiv) in dry MeCN (40.00 ml) were reacted as described above, followed by the addition of PPh_3 (929 mg, 3.54 mmol, 1.05 equiv) and Et_3N (358 mg, 3.54 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 23.** (*a*) rt, 20 h, (*b*) rt, 2.5 h) to give *(Z)-2-(azonan-2-ylidene)-1-(4-nitrophenyl)ethanone* **168a** (860 mg, 88%) as yellow crystals, m.p. 128 – 129 ℃; R_f 0.41 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 3200 – 3400 (v br, N-H), 2927 (m, methane, =C-H), 1739 (w, C=O), 1586 (m, C=C), 1555 (s, aromatic, N-O), 1474 (m, aromatic, C=C) and 1338 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 11.8 (N*H*), 8.10 (2×1H, d, *J* 8.7, C*H*CNO_2), 7.88 (2×1H, d, *J* 8.7, C*H*C*H*CNO_2), 5.52 (1H, s, C=C*H*COAr), 3.42 (2H, dd, *J* 6.9 and *J* 11.5, $CH_2CH_2CH_2N$), 2.35 (2H, m, CH_2C=C), 1.70 (2H, m, $CH_2CH_2CH_2CH_2N$), 1.61 (2H, m, $CH_2CH_2CH_2CH_2C$=C) and 1.50 – 1.41 (3×2H, m, $CH_2CH_2CH_2CH_2CH_2N$); δ_C (75 MHz; $CDCl_3$) 184.7 (CH*C*OAr), 173.3 (N*C*=C), 149.3 (CH*C*NO_2), 147.0 (*C*CHCHCNO_2), 128.4 (*C*HCHCNO_2), 124.0 (*C*HCNO_2), 92.3 (NC=*C*), 44.7

($CH_2CH_2CH_2N$), 33.4 ($CH_2CH_2CH_2C=C$), 30.6, 29.0, 27.7, 25.9 and 23.2 (remaining CH_2's); HRMS (EI): found, 288.14685 ($C_{16}H_{20}O_3N_2$ requires 288.14739).

(f) (*Z*)-2-(Azacyclotridecan-2-ylidene)-1-(4-nitrophenyl)ethanone (169a)



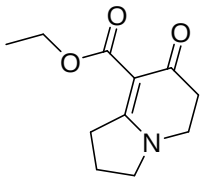
Azacyclotridecane-2-thione **150** (614 mg, 2.88 mmol) and *p*-nitrophenacyl bromide (737 mg, 3.02 mmol, 1.05 equiv) in dry MeCN (50.00 ml) were reacted as described above, followed by the addition of PPh_3 (792 mg, 3.02 mmol, 1.05 equiv) and Et_3N (306 mg, 3.02 mmol, 1.05 equiv) (Specific reaction conditions: **Scheme 23.** (*a*) rt, 16 h, (*b*) rt, 2 h) to give *(Z)-2-(azacyclotridecan-2-ylidene)-1-(4-nitrophenyl)ethanone* **169a** (991 mg, 83%) as yellow crystals, m.p. 104 – 105 ℃; R_f 0.54 (EtOAc: Hexane, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 3200 – 3400 (v br, N-H), 2930 (m, =C-H), 1738 (w, C=O), 1589 (m, C=C), 1552 (s, aromatic, N-O), 1464 (m, aromatic, C=C) and 1338 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 11.6 (N*H*), 8.23 (2×1H, d, *J* 8.9, C*H*CNO_2), 7.98 (2×1H, d, *J* 8.9, C*H*$CHCNO_2$), 5.65 (1H, s, C=C*H*COAr), 3.42 (2H, dd, *J* 7.0 and *J* 13.8, $CH_2CH_2CH_2N$), 2.39 (2H, m, $CH_2C=C$), 1.78 – 1.68 (2×2H, m, $CH_2CH_2CH_2CH_2N$ and $CH_2CH_2CH_2CH_2C=C$) and 1.56 – 1.32 (7×2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 184.3 (CHCOAr), 170.5 (NC=C), 148.8 ($CHCNO_2$), 146.3 ($CCHCHCNO_2$), 127.7 ($CHCHCNO_2$), 123.4 ($CHCNO_2$), 92.5 (NC=C), 41.4 ($CH_2CH_2CH_2N$), 31.6 ($CH_2CH_2CH_2C=C$), 28.3, 25.7, 25.5, 25.4, 25.3, 24.8, 24.4, 24.3 and 23.2 (remaining CH_2's); HRMS (EI): found, 344.20943 ($C_{20}H_{28}O_3N_2$ requires 344.20999).

3.9 Synthesis of azabicyclic systems by intramolecular cycloacylation

The ring closed compounds were prepared by a procedure in reference.[44] A mixture of vinylogous urethanes or amides and trifluoroacetic acids at room temperature, was stirred for 4 – 5 h. Trifluoroacetic acid was removed under high vacuum for a period of about 2 – 24 h. The resulting carboxylic acid was dissolved in acetonitrile, followed by the addition of potassium carbonate and acetic anhydride. The resulting solution was stirred at 60 ℃ for 14 – 20 h. The solvent was removed in *vacuo*. Water was added and the resulting solution was extracted with dicloromethane. The organic extracts were dried over anhydrous sodium sulphate, filtered and evaporated in *vacuo*. The crude product was purified by column chromatography on silica gel using methanol: ethyl acetate (2:8) solvent mixture as eluent. The following compounds were prepared by this method.

(a) Ethyl 7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate (170b)

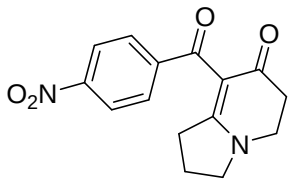
[39,48]



(*E*)-*tert*-Butyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate **109b** (240 mg, 0.847 mmol) and trifluoroacetic acid (2.597 g, 22.8 mmol, 26.9 equiv) were reacted as described above, followed by the addition of potassium carbonate (104 mg, 1.02 mmol, 1.20 equiv) and acetic anhydride (234 mg, 1.69 mmol, 2.00 equiv) in acetonitrile (2.82 ml) (Specific reaction conditions: **Scheme 25.** (*a*) rt, 4 h, (*b*) 60 ℃, 20 h) to give *ethyl 7-oxo-1,2,3,5,6,7-hexahydroindolizine-8-carboxylate* **170b** [39,48] (177 mg, 79%) as colourless crystals, m.p. 73 – 75 ℃ (Lit. m.p. 74.5 – 75.5 ℃); R_f 0.24 (MeOH: EtOAc, 2:8); ν_{max} (NaCl; Thin Film)/cm^{-1} 3055 (w, methylene, C-H), 1726 (m, C=O), 1478 (m, conj, C=C), 1432 (s, C=C) and 1098 (s, C-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 4.22

(2H, q, *J* 7.1, COOC*H*$_2$CH$_3$), 3.57 (2×2H, m, (COCCH$_2$C*H*$_2$N and CH$_2$CH$_2$C*H*$_2$N), 3.28 (2H, t, *J* 7.8, (COCC*H*$_2$CH$_2$N), 2.58 (2H, t, *J* 7.7, C*H*$_2$C=C), 2.14 (2H, m, CH$_2$C*H*$_2$CH$_2$) and 1.32 (3H, t, *J* 7.1, CH$_2$C*H*$_3$); δ_C (75 MHz; CDCl$_3$) 187.6 (CH$_3$CH$_2$OOCC(=C)O*C*CH$_2$CH$_2$N), 173.9 (N*C*=C), 166.5 (CH$_3$CH$_2$OO*C*), 98.9 (NC=*C*), 59.9 (CH$_3$*C*H$_2$), 55.0 (CH$_2$CH$_2$*C*H$_2$N), 44.4 (C(=C)OCH$_2$*C*H$_2$N), 36.1 (C(=C)OC*C*H$_2$CH$_2$N), 35.3 (CH$_2$*C*H$_2$CH$_2$), 21.5 (CH$_2$CH$_2$*C*H$_2$C=C) and 14.9 (CH$_2$*C*H$_3$); HRMS (EI): found, 209.10467 ($C_{11}H_{15}O_3N$ requires 209.10519).

(b) 8-(4-Nitrobenzoyl)-2,3,5,6-tetrahydroindolizin-7(1*H*)-one (171a)

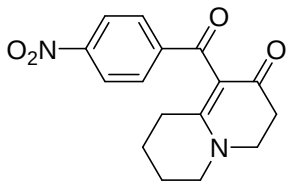


(i) (*E*)-*tert*-Butyl 3-(2-(2-(4-nitrophenyl)-2-oxoethylidene)pyrrolidin-1-yl)propanoate **159a** (307 mg, 0.852 mmol) and trifluoroacetic acid (2.611 g, 22.9 mmol, 26.9 equiv) were reacted as described above, followed by the addition of potassium carbonate (104 mg, 1.02 mmol, 1.20 equiv) and acetic anhydride (236 mg, 1.70 mmol, 2.00 equiv) in acetonitrile (40.00 ml) (Specific reaction conditions: **Scheme 25.** (*a*) rt, 4 h, (*b*) 60 ℃, 19.5 h) to give *8-(4-nitrobenzoyl)-2,3,5,6-tetrahydroindolizin-7(1*H*)-one* **170a** (75 mg, 31%) as yellow crystals, m.p. 230 ℃; R_f 0.39 (MeOH: EtOAc, 2:8); ν_{max} (NaCl; Thin Film)/cm^{-1} 2970 (w, methylene, C-H), 2360 (w, R_3N^+ ions), 1739 (m, C=O), 1631 (w, conj, C=C), 1595 (m, C=C), 1512 (s, aromatic, N-O), 1462 (m, aromatic, C=C) and 1342 (s, aromatic, N-O); δ_H (300 MHz; CDCl$_3$; Me$_4$Si) 8.19 (2×1H, d, *J* 8.8, C*H*CNO$_2$), 7.62 (2×1H, d, *J* 8.8, C*H*CHCNO$_2$), 3.69 (2×2H, m, (COCCH$_2$C*H*$_2$N and CH$_2$CH$_2$C*H*$_2$N)), 3.39 (2H, t, *J* 7.8, (COCC*H*$_2$CH$_2$N), 2.62 (2H, t, *J* 7.7, C*H*$_2$C=C) and 2.22 (2H, m, CH$_2$C*H*$_2$CH$_2$); δ_C (75 MHz; CDCl$_3$) 192.2 (ArC(=C)O*C*CH$_2$CH$_2$N), 188.4 (*C*OCCHCHCNO$_2$), 174.9 (N*C*=C), 148.9 (COCCHCH*C*NO$_2$), 148.5 (CO*C*CHCHCNO$_2$), 129.0 (COCCH*C*HCNO$_2$), 123.4 (COC*C*HCHCNO$_2$), 106.8 (NC=*C*), 55.1 (CH$_2$CH$_2$*C*H$_2$N), 44.7 (C(=C)OCCH$_2$*C*H$_2$N), 35.4 (C(=C)OC*C*H$_2$CH$_2$N), 34.8 (CH$_2$CH$_2$*C*H$_2$C=C) and

21.5 ($CH_2CH_2CH_2$); HRMS (EI): found, 286.09385 ($C_{15}H_{14}O_4N_2$ requires 286.09536).

(ii) *8-(4-Nitrobenzoyl)-2,3,5,6-tetrahydroindolizin-7(1*H*)-one* isomer (160 mg, 65%) was synthesised as yellow crystals, m.p. 230 °C; R_f 0.16 (MeOH: EtOAc, 2:8); ν_{max} (NaCl; Thin Film)/cm^{-1} 2970 (w, methylene, C-H), 2360 (w, R_3N^+ ions), 1739 (m, C=O), 1631 (w, conj, C=C), 1595 (m, C=C), 1512 (s, aromatic, N-O), 1462 (m, aromatic, C=C) and 1342 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.25 (2×1H, d, *J* 8.8, C*H*CNO_2), 8.04 (2×1H, d, *J* 8.8, C*H*$CHCNO_2$), 3.69 (2×2H, m, ($COCCH_2CH_2N$ and $CH_2CH_2CH_2N$)), 3.39 (2H, t, *J* 7.9, ($COCCH_2CH_2N$), 2.53 (2H, t, *J* 7.4, CH_2C=C) and 2.08 (2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 184.1 (ArC(=C)O*C*CH_2CH_2N), 177.9 (*C*$OCCHCHCNO_2$), 170.0 (N*C*=C), 146.9 ($COCCHCHCNO_2$), 145.9 ($COCCHCHCNO_2$), 126.4 ($COCCHCHCNO_2$), 122.0 ($COCCHCHCNO_2$), 128.0 (NC=*C*), 52.1 ($CH_2CH_2CH_2N$), 42.5 ($C(=C)OCCH_2CH_2N$), 33.1 ($C(=C)OCCH_2CH_2N$), 32.8 ($CH_2CH_2CH_2C$=C) and 18.3 ($CH_2CH_2CH_2$); HRMS (EI): found, 286.09385 ($C_{15}H_{14}O_4N_2$ requires 286.09536).

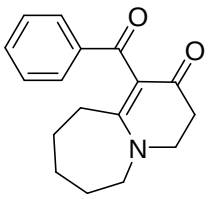
(c) 1-(4-Nitrobenzoyl)-3,4,6,7,8,9-hexahydroquinolizin-2-one (172a)



(*E*)-*tert*-Butyl 3-(2-(2-(4-nitrophenyl)-2-oxoethylidene)piperidin-1-yl)propanoate **160a** (116 mg, 0.320 mmol) and trifluoroacetic acid (982 mg, 8.61 mmol, 26.9 equiv) were reacted as described above, followed by the addition of potassium carbonate (65 mg, 0.640 mmol, 2.00 equiv) and acetic anhydride (88 mg, 0.640 mmol, 2.00 equiv) in acetonitrile (14.00 ml) (Specific reaction conditions: **Scheme 25.** (*a*) rt, 4 h, (*b*) 60 ℃, 20 h) to give *1-(4-nitrobenzoyl)-3,4,6,7,8,9-hexahydroquinolizin-2-one* **172a**(95 mg, 99%) as yellow crystals, m.p. 138 – 139 ℃; R_f 0.41 (MeOH: EtOAc, 2:8); ν_{max}

(NaCl; Thin Film)/cm^{-1} 2930 (w, methylene, C-H), 2360 (w, R_3N^+ ions), 1723 (vw, C=O), 1645 (w, conj, C=C), 1607 (m, C=C), 1552 (s, aromatic, N-O), 1508 (m, aromatic, C=C) and 1343 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.19 (2×1H, d, *J* 8.6, C*H*CNO_2), 7.74 (2×1H, d, *J* 8.6, C*H*$CHCNO_2$), 3.65 (2H, t, *J* 7.3, ($COCCH_2CH_2N$), 3.52 (2H, t, *J* 6.0, $CH_2CH_2CH_2N$), 2.95 (2H, t, *J* 6.1, ($COCCH_2CH_2N$), 2.54 (2H, t, *J* 7.5, CH_2C=C) 1.96 (2H, m, $CH_2CH_2CH_2N$) and 1.74 (2H, m, $CH_2CH_2CH_2C$=C); δ_C (75 MHz; $CDCl_3$) 194.3 (ArC(=C)OCCH_2CH_2N), 188.8 ($COCCHCHCNO_2$), 169.3 (N*C*=C), 149.1 ($COCCHCHCNO_2$), 147.9 ($COCCHCHCNO_2$), 129.3 ($COCCHCHCNO_2$), 123.6 ($COCCHCHCNO_2$), 110.0 (NC=*C*), 52.0 ($CH_2CH_2CH_2N$), 50.9 (C(=C)OCCH_2CH_2N), 35.2 (C(=C)OCCH_2CH_2N), 28.6 ($CH_2CH_2CH_2C$=C), 22.6 ($CH_2CH_2CH_2N$) and 18.8 ($CH_2CH_2CH_2C$=C); HRMS (EI): found, 300.10710 ($C_{16}H_{16}O_4N_2$ requires 300.11101).

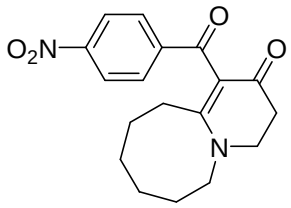
(d) 1-Benzoyl-3,4,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-2(6*H*)-one (173d)



(*E*)-*tert*-Butyl 3-(2-(2-oxo-2-phenylethylidene)azepan-1-yl)propanoate **161d** (110 mg, 0.321 mmol) and trifluoroacetic acid (952 mg, 8.35 mmol, 26.9 equiv) were reacted as described above, followed by the addition of potassium carbonate (65.5 mg, 0.642 mmol, 2.00 equiv) and acetic anhydride (88,7 mg, 0.642 mmol, 2.00 equiv) in acetonitrile (20.00 ml) (Specific reaction conditions: **Scheme 25.** (*a*) rt, 4 h, (*b*) 60 ℃, 20 h) to give *1-benzoyl-3,4,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-2(6*H*)-one* **173d** (63 mg, 73%) as yellow amorphous solid. R_f 0.47 (MeOH: EtOAc, 2:8); ν_{max} (NaCl; Thin Film)/cm^{-1} 2922 (w, methylene, C-H), 2360 (vw, R_3N^+ ions), 1738 (m, C=O), 1613 (w, conj, C=C), 1538 (m, C=C), 1467 (s, aromatic, C=C) and 1387 (m, aromatic, C=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.77 (2×1H, m, COCC*H*CHCH), 7.45 – 7.38 (3×1H, m,

COCCHC*H*C*H*), 3.70 – 3.61 (2×2H, m, $(CH_3)_3COOCCH_2CH_2N$ and $CH_2CH_2CH_2N$), 2.56 (2×2H, m, $(CH_3)_3COOCCH_2CH_2N$ and $CH_2C{=}C$) and 1.71 (3×2H, m, $CH_2CH_2CH_2N$ and $CH_2CH_2CH_2C{=}C$); δ_C (75 MHz; $CDCl_3$) 197.9 (ArC(=C)O*C*CH_2CH_2N), 189.5 (*C*OC_6H_5), 170.7 (N*C*=C), 140.5 (CO*C*CHCHCH), 132.5 (COCCHCH*C*H), 129.4 (COC*C*HCHCH), 128.5 (COCCH*C*HCH), 112.2 (NC=*C*), 55.6 ($CH_2CH_2CH_2N$), 52.1 ($C(=C)OCCH_2CH_2N$), 36.3 ($C(=C)OCCH_2CH_2N$), 31.5 ($CH_2CH_2CH_2C{=}C$), 29.3, 27.4 and 25.6 (remaining CH_2's); HRMS (EI): found, 269.13829 ($C_{17}H_{19}O_2N$ requires 269.14158).

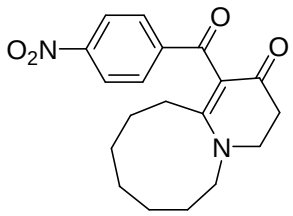
(e) 1-(4-Nitrobenzoyl)-3,4,6,7,8,9,10,11-octahydropyrido[1,2-*a*]azocin-2-one (174a)



(*E*)-*tert*-Butyl 3-(2-(2-(4-nitrophenyl)-2-oxoethylidene)azocan-1-yl)propanoate **162a** (549 mg, 1.36 mmol) and trifluoroacetic acid (4.173 g, 36.6 mmol, 26.9 equiv) were reacted as described given, followed by the addition of potassium carbonate (208 mg, 2.04 mmol, 1.50 equiv) and acetic anhydride (376 mg, 2.72 mmol, 2.00 equiv) in acetonitrile (20.00 ml, 14.71 ml per mmol) (Specific reaction conditions: **Scheme 25.** (*a*) rt, 4.5 h, (*b*) 60 ℃, 20 h) to give *1-(4-nitrobenzoyl)-3,4,6,7,8,9,10,11-octahydropyrido[1,2-*a*]azocin-2-one* **174a** (398 mg, 89%) as yellow crystals, m.p. 175 ℃; R_f 0.083 (EtOAc: Hex, 7:3); ν_{max} (NaCl; Thin Film)/cm^{-1} 2919 (w, methylene, C-H), 2360 (vw, R_3N^+ ions), 1738 (m, C=O), 1637 (w, conj, C=C), 1602 (m, C=C), 1549 (s, aromatic, N-O), 1514 (m, aromatic, C=C) and 1338 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.20 (2×1H, d, *J* 8.1, C*H*CNO_2), 7.78 (2×1H, d, *J* 8.1, C*H*$CHCNO_2$), 3.70 (2×2H, m, $COCCH_2CH_2N$ and $CH_2CH_2CH_2N$), 2.82 (2H, m, $COCCH_2CH_2N$), 2.52 (2H, m, $CH_2C{=}C$), 1.96 – 1.81 (2×2H, m, $CH_2CH_2CH_2N$ and $CH_2CH_2CH_2C{=}C$) and 1.57 (2×2H, m, $CH_2CH_2CH_2N$ and $CH_2CH_2CH_2C{=}C$); δ_C (75 MHz; $CDCl_3$) 195.6

(ArC(=C)O*C*CH_2CH_2N), 190.1 (*C*OCCHCHCNO_2), 172.9 (N*C*=C), 149.7 (COCCHCH*C*NO_2), 148.1 (CO*C*CHCHCNO_2), 129.7 (COCCH*C*HCNO_2), 124.1 (COC*C*HCHCNO_2), 111.0 (NC=*C*), 52.1 ($CH_2CH_2CH_2$N), 49.8 (C(=C)OCCH_2*C*H_2N), 36.0 (C(=C)OC*C*H_2CH_2N), 31.8 ($CH_2CH_2CH_2$C=C), 29.6, 29.6, 26.7 and 25.4 (remaining *C*H_2's); HRMS (EI): found, 328.14479 ($C_{18}H_{20}O_4N_2$ requires 328.14231).

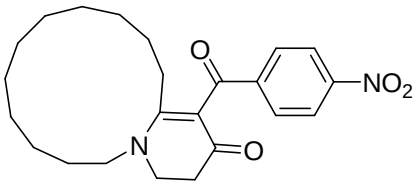
(f) 1-(4-Nitrobenzoyl)-3,4,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-2(6*H*)-one (175a)



(*E*)-*tert*-Butyl 3-(2-(2-(4-nitrophenyl)-2-oxoethylidene)azonan-1-yl)propanoate **163a** (310 mg, 0.744 mmol) and trifluoroacetic acid (2.280 g, 20.0 mmol, 26.9 equiv) were reacted as described above, followed by the addition of potassium carbonate (114 mg, 1.12 mmol, 1.50 equiv) and acetic anhydride (206 mg, 1.49 mmol, 2.00 equiv) in acetonitrile (20.00 ml) (Specific reaction conditions: **Scheme 25.** (*a*) rt, 4.5 h, (*b*) 60 ℃, 20 h) to give *1-(4-nitrobenzoyl)-3,4,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-2(6*H*)-one* **175a** (256 mg, 90%) as yellow crystals, m.p. 131 – 132 ℃ ; R_f 0.083 (EtOAc: Hex, 7:3); ν_{max} (NaCl; Thin Film)/cm^{-1} 2919 (w, methylene, C-H), 2360 (w, R_3N^+ ions), 1739 (m, C=O), 1631 (w, conj, C=C), 1595 (m, C=C), 1512 (s, aromatic, N-O), 1462 (m, aromatic, C=C) and 1342 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.21 (2×1H, d, *J* 8.4, C*H*CNO_2), 7.76 (2×1H, d, *J* 8.6, C*H*CHCNO_2), 3.76 (2H, m, COCCH_2C*H*$_2$N), 3.67 (2H, m, CH_2CH_2C*H*$_2$N), 2.81 (2H, m, (COCC*H*$_2$$CH_2$N), 2.53 (2H, m, C*H*$_2$C=C), 1.86 – 1.84 (2×2H, m, CH_2C*H*$_2$$CH_2$N and CH_2C*H*$_2$$CH_2$C=C), 1.68 (2H, m, C*H*$_2$$CH_2CH_2$N) and 1.56 (2×2H, m, C*H*$_2$$CH_2CH_2$C=C and C*H*$_2$$CH_2CH_2CH_2$N); δ_C (75 MHz; $CDCl_3$) 195.3 (ArC(=C)O*C*CH_2CH_2N), 189.7 (*C*OCCHCHCNO_2), 173.1 (N*C*=C), 149.3 (COCCHCH*C*NO_2), 147.6 (CO*C*CHCHCNO_2), 129.3 (COCCH*C*HCNO_2), 123.8

(COC*C*HCHCNO$_2$), 111.0 (NC=*C*), 53.2 ($CH_2CH_2CH_2N$), 48.7 (C(=C)OCCH$_2$*C*H$_2$N), 35.4 (C(=C)OC*C*H$_2$CH$_2$N), 31.5 ($CH_2CH_2CH_2C$=C), 29.0, 27.3, 26.8, 26.4 and 21.2 (remaining *C*H$_2$'s); HRMS (EI): found, 342.15385 ($C_{19}H_{22}O_4N_2$ requires 342.15796).

(g) 1-(4-Nitrobenzoyl)-3,4,7,8,9,10,11,12,13,14,17,16-dodecahydropyrido[1,2-*a*]azacyclotridecin-2(6*H*)-one (176a)



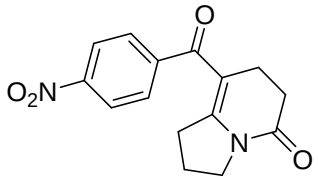
(*E*)-*tert*-Butyl 3-(2-(2-(4-nitrophenyl)-2-oxoethylidene)azacyclotridecan-1-yl)propanoate **164a** (20 mg, 0.0423 mmol) and trifluoroacetic acid (130 mg, 1.14 mmol, 26.9 equiv) were reacted as described above, followed by the addition of potassium carbonate (8.64 mg, 0.0846 mmol, 2.00 equiv) and acetic anhydride (11.7 mg, 0.0846 mmol, 2.00 equiv) in acetonitrile (20.00 ml) (Specific reaction conditions: **Scheme 25.** (*a*) rt, 4 h, (*b*) 60 ℃, 20 h) to give *1-(4-nitrobenzoyl)-3,4,7,8,9,10,11,12,13,14,17,16-dodecahydropyrido[1,2-*a*]azacyclotridecin-2(6*H*)-one* **176a** (6 mg, 36%) as yellow crystals, m.p. 108 – 110 ℃; R_f 0.78 (MeOH: EtOAc, 2:8); ν_{max} (NaCl; Thin Film)/cm^{-1} 2925 (m, methylene, C-H), 2360 (w, R_3N^+ ions), 1738 (m, C=O), 1618 (w, conj, C=C), 1618 (m, C=C), 1536 (s, aromatic, N-O), 1445 (m, aromatic, C=C) and 1343 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.21 (2×1H, d, *J* 8.7, C*H*CNO$_2$), 7.74 (2×1H, d, *J* 8.7, C*H*CHCNO$_2$), 3.68 (2H, m, COCCH$_2$C*H*$_2$N), 3.48 (2H, m, $CH_2CH_2CH_2N$), 2.58 – 2.48 (2×2H, m, COCC*H*$_2$CH$_2$N and C*H*$_2$C=C), 1.86 – 1.81 (2×2H, m, CH$_2$C*H*$_2$CH$_2$N and CH$_2$C*H*$_2$CH$_2$C=C), 1.60 – 1.55 (2×2H, m, C*H*$_2$CH$_2$CH$_2$N and C*H*$_2$CH$_2$CH$_2$C=C) and 1.34 (7×2H, m, CH$_2$C*H*$_2$CH$_2$); δ_C (75 MHz; $CDCl_3$) 192.9 (ArC(=C)O*C*CH$_2$CH$_2$N), 187.4 (*C*OCCHCHCNO$_2$), 169.3 (N*C*=C), 147.2 (COCCHCH*C*NO$_2$), 145.6 (CO*C*CHCHCNO$_2$), 127.2 (COCCH*C*HCNO$_2$), 121.6 (COC*C*HCHCNO$_2$), 109.3 (NC=*C*), 49.3 ($CH_2CH_2CH_2N$), 47.2 (C(=C)OCCH$_2$*C*H$_2$N), 33.7

(C(=C)OCCH_2CH_2N), 28.0 ($CH_2CH_2CH_2$C=C), 27.2, 24.7, 23.0, 22.5, 22.3, 22.1, 21.7, 21.1 and 20.7 (remaining CH_2's); HRMS (EI): found, 398.21860 ($C_{23}H_{30}O_4N_2$ requires 398.22056).

3.10 Reactions of N-H vinylogous amides with acryloyl chloride

The ring closed compounds were prepared by a procedure in reference.[45] Acryloyl chloride was added dropwise to a solution of vinylogous amide in tetrahydrofuran. The resulting solution was left stirring at 45 ℃ for 17 – 24 h. Saturated sodium hydrogen carbonate was added the reaction mixture, followed by the addition distilled water. The resulting solution was extracted with dichloromethane. The organic extracts were dried over Na_2SO_4 and evaporated in *vacuo*. The crude product was purified by column recrystallisation. The following compounds were prepared by this procedure.

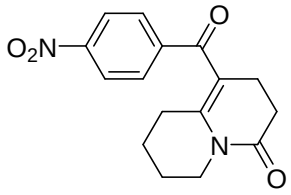
(a) 8-(4-Nitrobenzoyl)-2,3,6,7-tetrahydroindolizin-5(1*H*)-one (178a)



(*Z*)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone **165a** (826 mg, 3.56 mmol) and acryloyl chloride (370 mg, 4.09 mmol, 1.15 equiv) were reacted in tetrahydrofuran (50.00 ml) as described above to give *8-(4-nitrobenzoyl)-2,3,6,7-tetrahydroindolizin-5(1*H*)-one* **178a** (1.019 g, 100%) as yellow crystals, m.p. 120 – 121 ℃; R_f 0.04 (EtOAc: Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2880 (m, methylene, C-H), 2854 (w, methine, C-H), 1683 (m, aromatic ketones, C=O), 1599 (s, conj, C=C), 1516 (s, aromatic, N-O) and 1345 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.18 (2×1H, d, *J* 8.6, C*H*CNO_2), 7.63 (2×1H, d, *J* 8.6, C*H*CHCNO_2), 3.66 (2H, t, *J* 7.2, $CH_2CH_2CH_2$N), 2.65 (2×2H,

m, ArCCH_2CH$_2$CON and ArCCH$_2$CH_2CON), 2.50 (2H, t, *J* 7.3, CH_2C=C) and 1.89 (2H, p, *J* 7.4, CH$_2$CH_2CH$_2$); δ_C (75 MHz; $CDCl_3$) 193.4 (*C*OCCHCHCNO$_2$), 169.6 (ArCCH$_2$CH$_2$*C*ON), 156.3 (COCCHCH*C*NO$_2$), 149.3 (N*C*=C), 146.7 (CO*C*CHCHCNO$_2$), 128.9 (COCCH*C*HCNO$_2$), 124.0 (COC*C*HCHCNO$_2$), 109.5 (NC=*C*), 46.3 (CH$_2$CH$_2$*C*H$_2$N), 33.2 (CH$_2$*C*H$_2$CH$_2$N), 31.6 (C(=C)OCCH$_2$*C*H$_2$CON), 23.4 (CH$_2$CH$_2$*C*H$_2$C=C) and 22.0 (C(=C)OC*C*H$_2$CH$_2$CON); HRMS (EI): found, 286.09379 ($C_{15}H_{14}O_4N_2$ requires 286.09536).

(b) 1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one (179a)

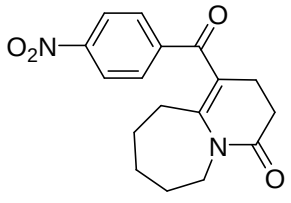


(i) (*Z*)-1-(4-Nitrophenyl)-2-(piperidin-2-ylidene)ethanone **177a** (533 mg, 2.16 mmol) and acryloyl chloride (224 mg, 2.48 mmol, 1.15 equiv) were reacted in tetrahydrofuran (40.00 ml) as described above to give *1-(4-nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one* **179a** (319 mg, 49%) as yellow crystals, m.p. 126 – 127 ℃; R_f 0.59 (EtOAc: Hex, 7:3); ν_{max} (NaCl; Thin Film)/cm^{-1} 2947 (w, methylene, C-H), 1673 (m, aromatic ketones, C=O), 1597 (s, conj, C=C), 1520 (s, aromatic, N-O) and 1346 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.30 (2×1H, d, *J* 8.6, C*H*CNO$_2$), 7.86 (2×1H, d, *J* 8.6, C*H*CHCNO$_2$), 3.82 (2H, t, *J* 6.1, CH$_2$CH$_2$CH_2N), 2.68 (2H, t, *J* 6.5, ArCCH_2CH$_2$CON), 2.58 (2×2H, m, ArCCH$_2$CH_2CON and CH_2C=C), 1.82 (2H, m, CH$_2$CH_2CH$_2$N) and 1.68 (2H, m, CH$_2$CH_2CH$_2$C=C); δ_C (75 MHz; $CDCl_3$) 192.9 (*C*OCCHCHCNO$_2$), 168.7 (ArCCH$_2$CH$_2$*C*ON), 150.8 (N*C*=C), 140.8 (COCCHCH*C*NO$_2$), 134.2 (CO*C*CHCHCNO$_2$), 130.0 (COCCH*C*HCNO$_2$), 124.4 (COC*C*HCHCNO$_2$), 108.4 (NC=*C*), 47.2 (CH$_2$CH$_2$*C*H$_2$N), 40.8 (C(=C)OCCH$_2$*C*H$_2$CON), 30.2 (CH$_2$CH$_2$*C*H$_2$C=C), 23.0 (CH$_2$*C*H$_2$CH$_2$C=C), 22.9

($CH_2CH_2CH_2N$), and 21.8 ($C(=C)OCCH_2CH_2CON$); HRMS (EI): found, 300.10836 ($C_{16}H_{16}O_4N_2$ requires 300.11101).

(ii) *1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one* isomer ? (150 mg, 23%) was synthesised as an amorphous solid; R_f 0.36 (EtOAc: Hex, 7:3); ν_{max} (NaCl; Thin Film)/cm^{-1} 2947 (w, methylene, C-H), 1673 (m, aromatic ketones, C=O), 1597 (s, conj, C=C), 1520 (s, aromatic, N-O) and 1346 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.35 (2×1H, d, *J* 8.8, C*H*CNO_2), 8.14 (2×1H, d, *J* 8.8, C*H*$CHCNO_2$), 4.71 (1H, t, *J* 3.9, $CH_2CH_2CH_2N$), 4.36 (1H, t, *J* 5.2, $CH_2CH_2CH_2N$), 3.94 (1H, m, $ArCCH_2CH_2CON$), 3.66 (1H, m, $ArCCH_2CH_2CON$) 2.57 (2H, m, $ArCCH_2CH_2CON$), 2.18 (2H, m, $CH_2C=C$), 2.09 (2H, m, $CH_2CH_2CH_2N$) and 1.82 (2H, m, $CH_2CH_2CH_2C=C$); δ_C (75 MHz; $CDCl_3$) 198.2 ($COCCHCHCNO_2$), 167.4 ($ArCCH_2CH_2CON$), 149.1 ($COCCHCHCNO_2$), 148.1 (N*C*=C), 143.7 ($COCCHCHCNO_2$), 127.8 ($COCCHCHCNO_2$), 122.4 ($COCCHCHCNO_2$), 112.2 (NC=*C*), 38.8 ($CH_2CH_2CH_2N$), 30.0 ($C(=C)OCCH_2CH_2CON$), 25.6 ($CH_2CH_2CH_2C=C$), 22.1 ($CH_2CH_2CH_2C=C$), 20.6 ($CH_2CH_2CH_2N$), and 18.4 ($C(=C)OCCH_2CH_2CON$); HRMS (EI): found, 300.11080 ($C_{16}H_{16}O_4N_2$ requires 300.11101).

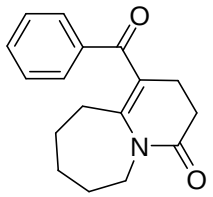
(c) 1-(4-Nitrobenzoyl)-2,3,7,8,9,10-hexahydropyrido[1,2-a]azepin-4(6*H*)-one (180a)



(*Z*)-2-(Azepan-2-ylidene)-1-(4-nitrophenyl)ethanone **166a** (473 mg, 1.82 mmol) and acryloyl chloride (189 mg, 2.09 mmol, 1.15 equiv) were reacted in tetrahydrofuran (11.62 ml) as described above to give *1-(4-nitrobenzoyl)-2,3,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-4(6*H*)-one* **180a** (563 mg, 99%) as yellow crystals, m.p. 130 – 131 ℃; R_f 0.20 (EtOAc: Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2896 (w, methine, C-H), 1687 (m, aromatic ketones,

C=O), 1597 (s, conj, C=C), 1516 (s, aromatic, N-O) and 1344 (s, aromatic, N-O) ; δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.22 (2×1H, d, *J* 8.7, C*H*CNO_2), 7.80 (2×1H, d, *J* 8.7, C*H*CHCNO_2), 3.85 (2H, m, $CH_2CH_2CH_2$*H*$_2$N), 2.56 (2H, m, ArCC*H*$_2CH_2CON$), 2.52 – 2.41 (2×2H, m, $ArCCH_2CH_2$*H*$_2$CON and C*H*$_2$C=C), 1.57 (3×2H, m, CH_2CH_2*H*$_2CH_2$N, CH_2CH_2*H*$_2CH_2$C=C) and CH_2CH_2*H*$_2CH_2$N); δ_C (75 MHz; $CDCl_3$) 195.5 (*C*OCCHCHCNO_2), 170.7 ($ArCCH_2CH_2$*C*ON), 152.7 (COCCHCH*C*NO_2), 150.1 (N*C*=C), 144.9 (CO*C*CHCHCNO_2), 129.8 (COCCH*C*HCNO_2), 124.8 (COC*C*HCHCNO_2), 114.7 (NC=*C*), 42.8 (CH_2CH_2*C*H$_2$N), 32.0 (C(=C)OCCH_2*C*H$_2$CON), 30.4 (CH_2CH_2*C*H$_2$C=C), 29.2, 29.0, 27.6 (remaining CH_2's) and 24.0 (C(=C)OC*C*H_2CH_2CON); HRMS (EI): found, 314.12329 ($C_{17}H_{18}O_4N_2$ requires 314.12666).

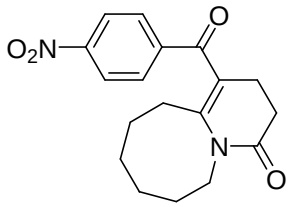
(d) 1-Benzoyl-2,3,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-4(6*H*)-one (180b)



(*Z*)-2-(Azepan-2-ylidene)-1-phenylethanone **166b** (607 mg, 2.82 mmol) and acryloyl chloride (293 mg, 3.24 mmol, 1.15 equiv) were reacted in tetrahydrofuran (40.00 ml) as described above to give *1-benzoyl-2,3,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-4(6*H*)-one* **180b** (722 mg, 95%) as yellow crystals, m.p. 103 – 105 ℃; R_f 0.23 (EtOAc: Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2930 (m, methylene, C-H), 2850 (w, methine, C-H), 1726 (w, C=O), 1677 (m, aromatic ketones, C=O) and 1605 (s, conj, C=C); δ_H (300 MHz; $CDCl_3$; Me_4Si) 7.78 (2×1H, t, *J* 7.7, COCC*H*CHCH), 7.55 (1H, t, *J* 7.7, COCCHCHC*H*), 7.46 (2×1H, t, *J* 7.4, COCCHC*H*CH), 3.89 (2H, m, $CH_2CH_2CH_2$*H*$_2$N), 2.58 (3×2H, m, ArCC*H*$_2CH_2CON$, $ArCCH_2CH_2$*H*$_2$CON and C*H*$_2$C=C), 1.65 (3×2H, m, CH_2CH_2*H*$_2CH_2$N, CH_2CH_2*H*$_2CH_2$C=C) and CH_2CH_2*H*$_2CH_2$N); δ_C (75 MHz; $CDCl_3$) 195.8 (*C*OCCHCHCH), 168.9 ($ArCCH_2CH_2$*C*ON), 146.8 (CO*C*CHCHCH), 136.9 (N*C*=C), 130.9 (COCCHCH*C*H), 127.1 (COC*C*HCHCH), 126.8 (COCCH*C*HCH), 113.7 (NC=*C*), 40.5 (CH_2CH_2*C*H$_2$N), 29.9 (C(=C)OCCH_2*C*H$_2$CON), 28.2 (CH_2CH_2*C*H$_2$C=C),

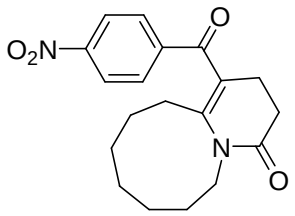
27.2, 27.1, 25.6 (remaining *C*H_2's) and 21.9 (C(=C)OC*C*H_2CH_2CON); HRMS (EI): found, 269.13866 ($C_{17}H_{19}O_2N$ requires 269.14158).

(e) 1-(4-Nitrobenzoyl)-2,3,6,7,8,9,10,11-octahydropyrido[1,2-*a*]azocin-4-one (181a)



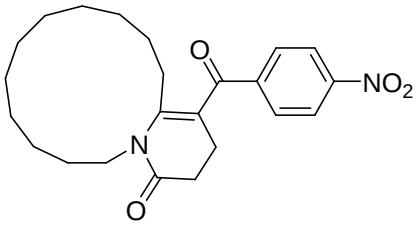
(*Z*)-2-(Azonan-2-ylidene)-1-(4-nitrophenyl)ethanone **167a** (482 mg, 1.76 mmol) and acryloyl chloride (183 mg, 2.02 mmol, 1.15 equiv) were reacted in tetrahydrofuran (20.00 ml) as described above to give *1-(4-nitrobenzoyl)-2,3,6,7,8,9,10,11-octahydropyrido[1,2-*a*]azocin-4-one* **181a** (578 mg, 99%) as yellow crystals, m.p. 59 – 61 ℃; R_f 0.24 (EtOAc: Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2920 (m, methylene, C-H), 2855 (w, methine, C-H), 1682 (m, aromatic ketones, C=O), 1573 (s, conj, C=C), 1516 (s, aromatic, N-O) and 1348 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.19 (2×1H, d, *J* 8.5, C*H*CNO_2), 7.73 (2×1H, d, *J* 8.5, C*H*CHCNO_2), 3.86 (2H, m, $CH_2CH_2CH_2$N), 2.72 (2H, m, ArCCH_2CH_2CON), 2.44 – 2.39 (2×2H, m, ArCCH_2CH_2CON and CH_2C=C), 1.74 (2H, m, $CH_2CH_2CH_2$N), 1.64 (2H, m, $CH_2CH_2CH_2$C=C) 1.46 (2×2H, m, C$H_2CH_2CH_2$N and C$H_2CH_2CH_2$C=C); δ_C (75 MHz; $CDCl_3$) 193.4 (*C*OCCHCHCNO_2), 169.2 (ArCCH_2CH_2*C*ON), 152.8 (COCCHCH*C*NO_2), 148.5 (N*C*=C), 143.6 (CO*C*CHCHCNO_2), 128.2 (COCCH*C*HCNO_2), 122.7 (COC*C*HCHCNO_2), 113.3 (NC=*C*), 40.8 ($CH_2CH_2CH_2$N), 30.9 (C(=C)OCCH_2CH_2CON), 30.1 ($CH_2CH_2CH_2$C=C), 27.8, 26.2, 24.4, 24.1 (remaining *C*H_2's) and 23.0 (C(=C)OC*C*H_2CH_2CON); HRMS (EI): found, 328.14505 ($C_{18}H_{20}O_4N_2$ requires 328.14231).

(f) 1-(4-Nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-one (182a)



(*Z*)-2-(Azonan-2-ylidene)-1-(4-nitrophenyl)ethanone **168a** (401 mg, 1.39 mmol) and acryloyl chloride (145 mg, 1.60 mmol, 1.15 equiv) were reacted in tetrahydrofuran (20.00 ml) as described above to give *1-(4-nitrobenzoyl)-2,3,7,8,9,10,11,12-octahydropyrido[1,2-*a*]azonin-4(6*H*)-one* **182a** (476 mg, 90%) as yellow crystals, m.p. 110 – 112 ℃ ; R_f 0.26 (EtOAc: Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2929 (m, methylene, C-H), 2851 (w, methine, C-H), 1686 (m, aromatic ketones, C=O), 1582 (s, conj, C=C), 1517 (s, aromatic, N-O) and 1347 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.22 (2×1H, d, *J* 8.7, C*H*CNO_2), 7.72 (2×1H, d, *J* 8.7, C*H*$CHCNO_2$), 3.79 (2H, m, $CH_2CH_2CH_2N$), 2.72 (2H, m, $ArCCH_2CH_2CON$), 2.44 – 2.45 (2H, m, $ArCCH_2CH_2CON$) 2.39 – 2.35 (2H, m, $CH_2C{=}C$), 1.82 – 1.71 (2×2H, m, $CH_2CH_2CH_2N$ and $CH_2CH_2CH_2C{=}C$) 1.55 – 1.46 (3×2H, m, $CH_2CH_2CH_2N$, $CH_2CH_2CH_2C{=}C$ and $CH_2CH_2CH_2CH_2N$); δ_C (75 MHz; $CDCl_3$) 193.2 (*C*O$CCHCHCNO_2$), 169.4 ($ArCCH_2CH_2CON$), 153.9 ($COCCHCHCNO_2$), 148.5 (N*C*=C), 143.8 ($COCCHCHCNO_2$), 128.0 ($COCCHCHCNO_2$), 122.8 ($COCCHCHCNO_2$), 114.4 (NC=*C*), 43.3 ($CH_2CH_2CH_2N$), 31.3 ($C(=C)OCCH_2CH_2CON$), 28.7 ($CH_2CH_2CH_2C{=}C$), 28.6, 28.1, 26.8, 23.1, 23.0 (remaining CH_2's) and 22.7 ($C(=C)OCCH_2CH_2CON$); HRMS (EI): found, 342.15738 ($C_{19}H_{22}O_4N_2$ requires 342.15796).

(g) 1-(4-Nitrobenzoyl)-2,6,7,8,9,10,11,12,13,14,15,16-dodecahydropyrido[1,2-*a*]azacyclotridecin-4(3*H*)-one (183a)



(*Z*)-2-(Azacyclotridecan-2-ylidene)-1-(4-nitrophenyl)ethanone **169a** (489 mg, 1.42 mmol) and acryloyl chloride (148 mg, 1.63 mmol, 1.15 equiv) were reacted in tetrahydrofuran (40.00 ml) as described above to give *1-(4-nitrobenzoyl)-2,6,7,8,9,10,11,12,13,14,15,16-dodecahydropyrido[1,2-*a*]azacyclotridecin-4(3*H*)-one* **183a** (563 mg, 97%) as yellow crystals, m.p. 107 – 108 ℃; R_f 0.40 (EtOAc: Hex, 3:7); ν_{max} (NaCl; Thin Film)/cm^{-1} 2923 (m, methylene, C-H), 2850 (w, methine, C-H), 1693 (m, aromatic ketones, C=O), 1567 (s, conj, C=C), 1520 (s, aromatic, N-O) and 1350 (s, aromatic, N-O); δ_H (300 MHz; $CDCl_3$; Me_4Si) 8.20 (2×1H, d, *J* 8.5, C*H*CNO_2), 7.72 (2×1H, d, *J* 8.4, C*H*$CHCNO_2$), 3.60 (2H, m, $CH_2CH_2CH_2N$), 2.55 – 2.49 (2H, m, $ArCCH_2CH_2CON$), 2.46 – 2.43 (2H, m, $ArCCH_2CH_2CON$) 2.38 – 2.35 (2H, m, $CH_2C{=}C$), 1.69 – 1.56 (2×2H, m, $CH_2CH_2CH_2N$ and $CH_2CH_2CH_2C{=}C$) 1.49 (2H, m, $CH_2CH_2CH_2N$), 1.40 (2H, m, $CH_2CH_2CH_2C{=}C$) and 1.24 (5×2H, m, $CH_2CH_2CH_2$); δ_C (75 MHz; $CDCl_3$) 193.6 ($COCCHCHCNO_2$), 169.4 ($ArCCH_2CH_2CON$), 152.4 ($COCCHCHCNO_2$), 148.5 ($NC{=}C$), 143.9 ($COCCHCHCNO_2$), 128.0 ($COCCHCHCNO_2$), 122.8 ($COCCHCHCNO_2$), 113.3 ($NC{=}C$), 40.4 ($CH_2CH_2CH_2N$), 30.8 ($C(=C)OCCH_2CH_2CON$), 26.4 ($CH_2CH_2CH_2C{=}C$), 25.7, 25.6, 25.1, 23.7, 23.5, 23.1, 22.6, 22.4, 21.6 (remaining CH_2's) and 21.6 ($C(=C)OCCH_2CH_2CON$); HRMS (EI): found, 398.22000 ($C_{23}H_{30}O_4N_2$ requires 398.22056).

REFERENCES

1. J. W. Daly, T. F. Spande, and H. M. Garraffo. *J*. *Nat*. *Prod*. **68**, 1556–1575 (2005).
2. T. H. Jones, H. L. Voegtle, H. M. Miras, R. G. Weatherford, T. F. Spande, H. M. Garraffo, J. W. Daly, D. W. Davidson, and R. R. Snelling. *J*. *Nat*. *Prod*. **70**, 160–168 (2007).
3. R. A. Pilli, and M. F. de Oliveira. *Nat*. *Prod*. *Rep*. **17**, 117–127 (2000).
4. E. Kaltenegger, B. Brem, K. Mereiter, H. Kalchhauser, H. Kählig, O. Hofer, S. Vajrodaya and H. Greger. *Phytochemistry* **63**, 803–816 (2003).
5. T. Honda, H. Namiki, K. Kaneda, and H. Mizutani. *Org*. *Lett*. **6**, 87–89 (2004).
6. R. Alibés, P. Bayón, P. de March, M. Figueredo, J. Font, E. García-García, and D. González-Gálvez. *Org*. *Lett*. **22**, 5107–5109 (2005).
7. N. H. Lajis, O. B. Guan, M. V. Sargent, B. W. Skelton and A. H. White. *Aust*. *J*. *Chem*. **45**, 1893–1897 (1992).
8. A. Ohsaki, Y. Kobayashi, K. Yoneda, A. Kishida, and H. Ishiyama. *J*. *Nat*. *Prod*. **70**, 2003–2005 (2007).
9. K. V. Rao, M. S. Donia, J. Peng, E. Garcia-Palomero, D. Alonso, A. Martinez, M. Medina, S. G. Franzblau, B. L. Tekwani, S. I. Khan, S. Wahyuono, K. L. Willett, and M. T. Hamann. *J*. *Nat*. *Prod*. **69**, 1034–1040 (2006).
10. M. Hamann, D. Alonso, E. Martín-Aparicio, A. Fuertes, M. José Pérez-puerto, A. Castro, S. Morales, M. L. Navarro, M. del Monte-Millán, M. Medina, H. Pennaka, A. Balaiah, J. Peng, J. Cook, S. Wahyuono, and A. Martínez. *J*. *Nat*. *Prod*. **70**, 1397–1405 (2007).
11. W. H. Pearson, D. A. Hutta, and W. Fang. *J*. *Org*. *Chem*. **65**, 8326–8332 (2000).
12. K. P. Tehrani, M. D'hooghe, and N. De Kimpe. *Tetrahedron* **59**, 3099–3108 (2003).

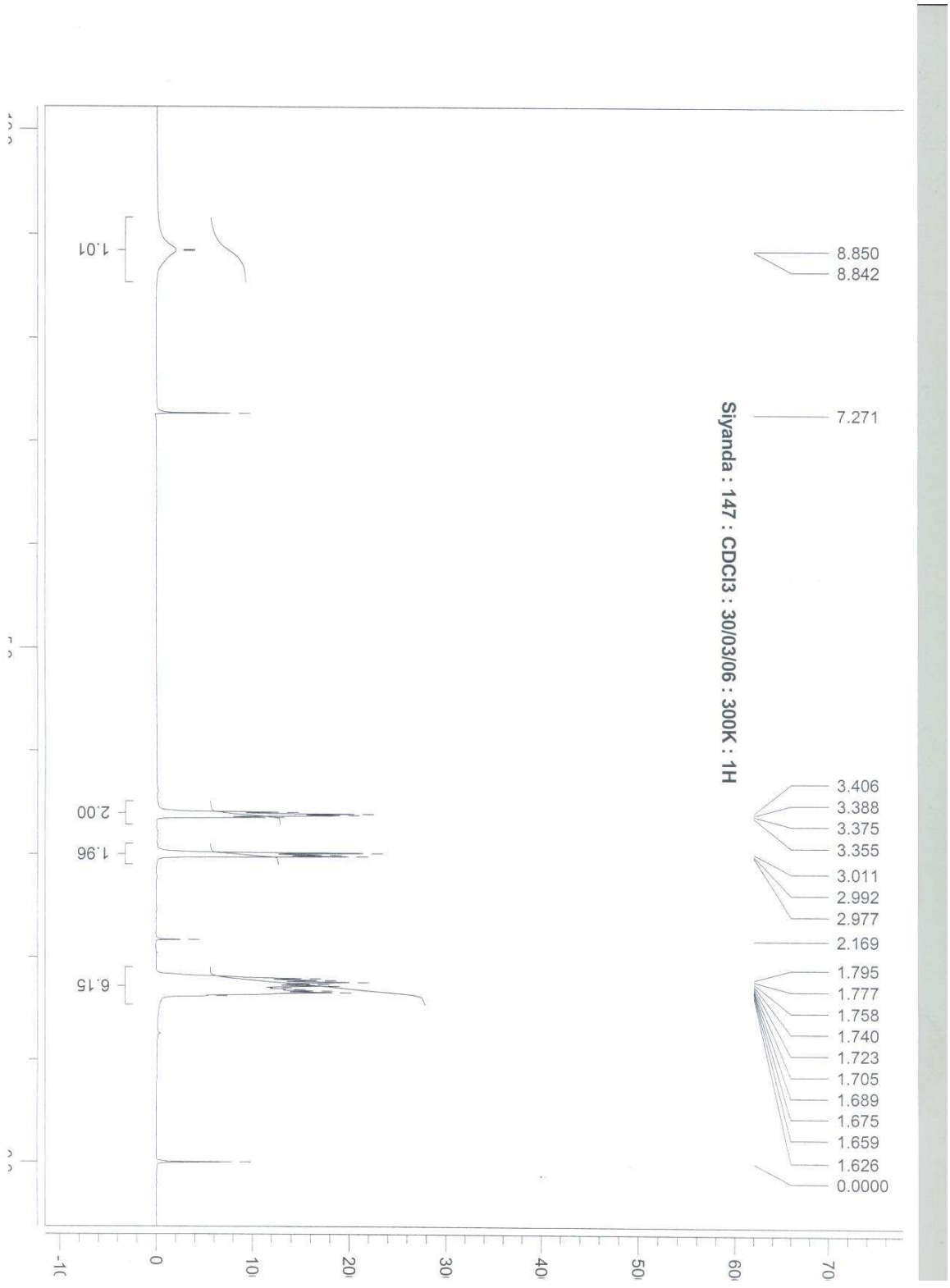
13. H. M. E. Duggan, P. B. Hitchcock, and D. W. Young. *Org*. *Biomol*. *Chem*. **3**, 2287–2295 (2005).
14. D. E. Davies, P. M. Doyle, R. D. Hill, and D. W. Young. *Tetrahedron* **61**, 301–312 (2005).
15. M. V. Chiesa, L. Manzoni, and C. Scolastico. *Synlett* 441–443 (1996).
16. A. Afzali-Ardakani and H. Rapoport. *J*. *Org*. *Chem*. **45**, 4817–4820 (1980).
17. A. S. Kende, J. I. Martin Hernando, and J. B. J. Milbank. *Tetrahedron* **58**, 61–74 (2002).
18. R. Alibés, P. Blanco, E. Casas, M. Closa, P. de March, M. Figueredo, J. Font, E. Sanfeliu, and Á. Álvarez-Larena. *J. Org. Chem.* **70**, 3157–3167 (2005).
19. L. Zhu, R. Lauchli, M. Loo, and K. J. Shea. *Org. Lett.* **9**, 2269–2271 (2007).
20. S. Torssell, E. Wanngren, and P. Somfai. *J. Org. Chem.* **72**, 4246–4249 (2007).
21. N. Bogliotti, P. I. Dalko, and J. Cossy. *J. Org. Chem.* **71**, 9528–9531 (2006).
22. J. P. Michael, C. B. de Koning, D. Gravestock, G. D. Hosken, A. S. Horward, C. M. Jungmann, R. W. M. Krause, A. S. Parsons, S. C. Pelly, and T. V. Stanbury. *Pure Appl*. *Chem*. **71**, 979–988 (1999).
23. J. P. Michael and D. Gravestock. *Eur*. *J*. *Org*. *Chem*. 865–870 (1998).
24. J. P. Michael and D. Gravestock. *S*. *Afr*. *J*. *Chem*. **51**, 146–157 (1998).
25. S. G. Gavies and O. Ichihara. *Tetrahedron: Asymmetry* **2**, 183 (1991).
26. M. Vandewalle, J. van de Eycken, W. Oppolzer, and C. Vulliod. *Tetrahedron* **42**, 4035 (1991).
27. J. P. Michael, C. B. de Koning, C. San Fat and G. L. Nattrass. *Arkivoc* **ix**, 62–77 (2002).
28. (*a*) H. C. Brown, H. J. Brewster, H. J. Shechter. *J*. *Am*. *Chem*. *Soc*. **76**, 467. (*b*) H. C. Brown. *J*. *Org*. *Chem*. **22**, 439 (1957).

29. J. P. Michael, C. B. de Koning, T. J. Malefetse, and I. Yillah. *Org*. *Biomol*. *Chem*. **2**, 3510–3517 (2004).
30. G. E. Vennstra and B. Zwaneburg. *Synthesis* 519–520 (1975).
31. N. Ramsuran, BSc Honours project, University of the Witwatersrand, 2004.
32. L. Madeley, BSc Honours project, University of the Witwatersrand, 2005.
33. K. Paulvannan and J. R. Stille. *J*. *Org*. *Chem*. **59**, 1613–1620 (1994).
34. Y. Furuya, K. Ishihara, and H. Yamamoto. *J*. *Am*. *Chem*. *Soc*. **127**, 11240–11241 (2005).
35. Aldrich catalogoue, 2005-2006, (a) page 749, (b) page 178, (c) page 250, (d) page 249, (e) page 2084
36. S. Lang and J. A. Murphy. *Chem*. *Soc*. *Rev*. **35**, 146–156 (2006).
37. T. J. Curphey. *J*. *Org*. *Chem*. **67**, 6461–6473 (2002).
38. D. Brillon. *Synth*. *Commun*. **20**, 3085–3095 (1990).
39. D. Pienaar, PhD thesis, University of the Witwatersrand, 2005.
40. J. W. Scheeren, P. H. J. Ohms, and R. J. F. Nivard. *Synthesis* 149–151 (1973).
41. B. P. Mundy, M. G. Ellerd, and F. G. Favaloro. In *Name Reactions and Reagents in Organic Synthesis*, 2nd Ed. page 228. Wiley-Interscience, A John Wiley & Sons, Inc (2005).
42. J. S. Petersen, G. Fels, and Rapoport, *J*. *Am*. *Chem*. *Soc*. **106**, 4359 (1984).
43. D. Russowsky and B. A. da Silveira Neto. *Tetrahedron Letters* **45**, 1437 (2004).
44. G. L. Nattrass, MSc dissertation, University of the Witwatersrand, 2002.
45. K. Paulvannan and J. R. Stille. *Tetrahedron Letters* **34**, 8197 (1993).
46. P. H. Lambert, M. Vaultier, and R. Carrié. *J*. *Org*. *Chem*. **50**, 5352–5356 (1985).
47. D. W. Knight, N. Lewis, A. C. Share, and D. Haigh. *J. Chem. Soc.,Perkin Trans. 1*, 3673–3684 (1998).

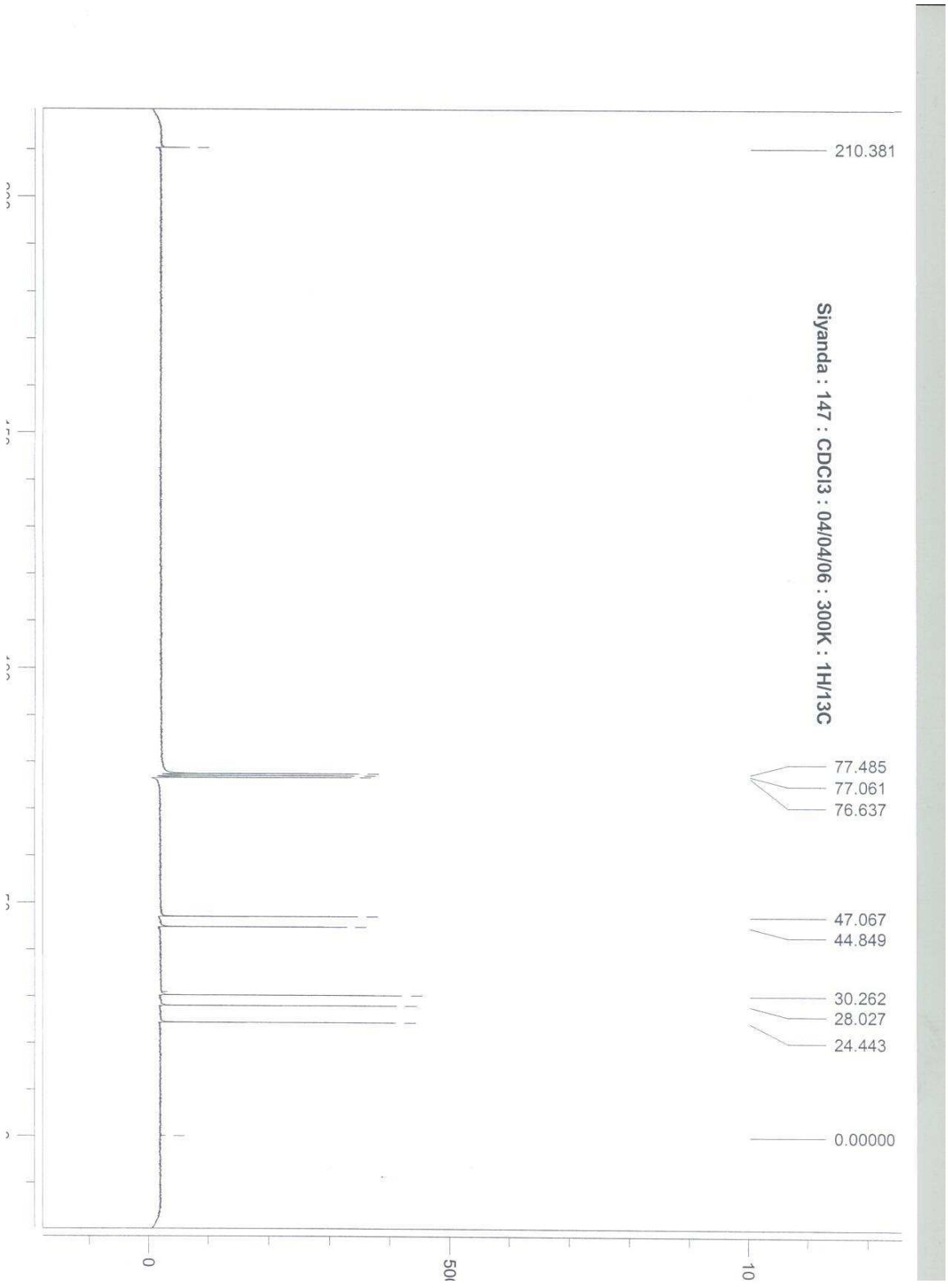
48. A. S. Howard, G. C. Gemans and C. A. Meerhalz. *Tetrahedron Letters* **21**, 1373–374 (1980).

APPENDIX: NMR DATA

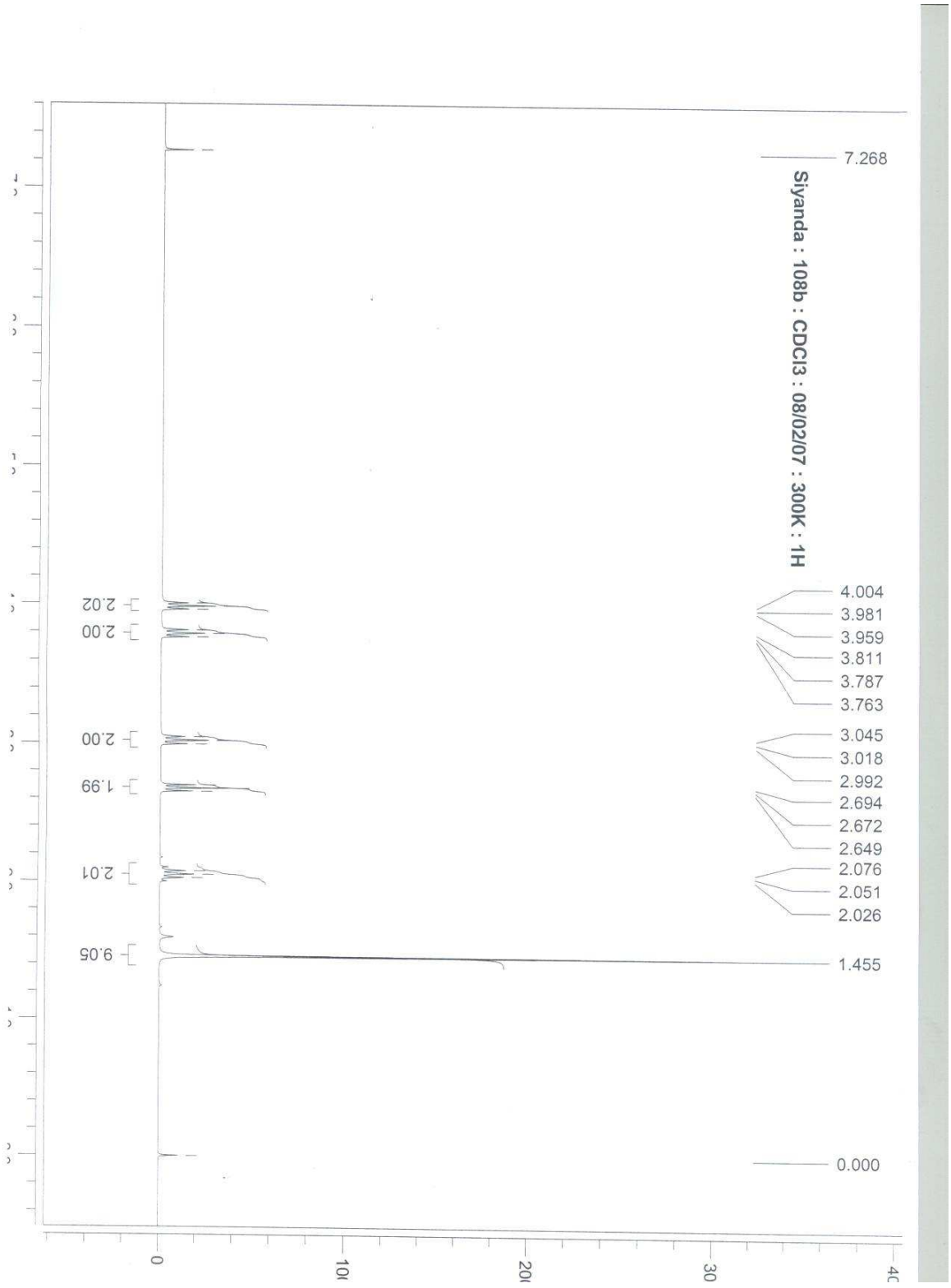
Azepane-2-thione (147)



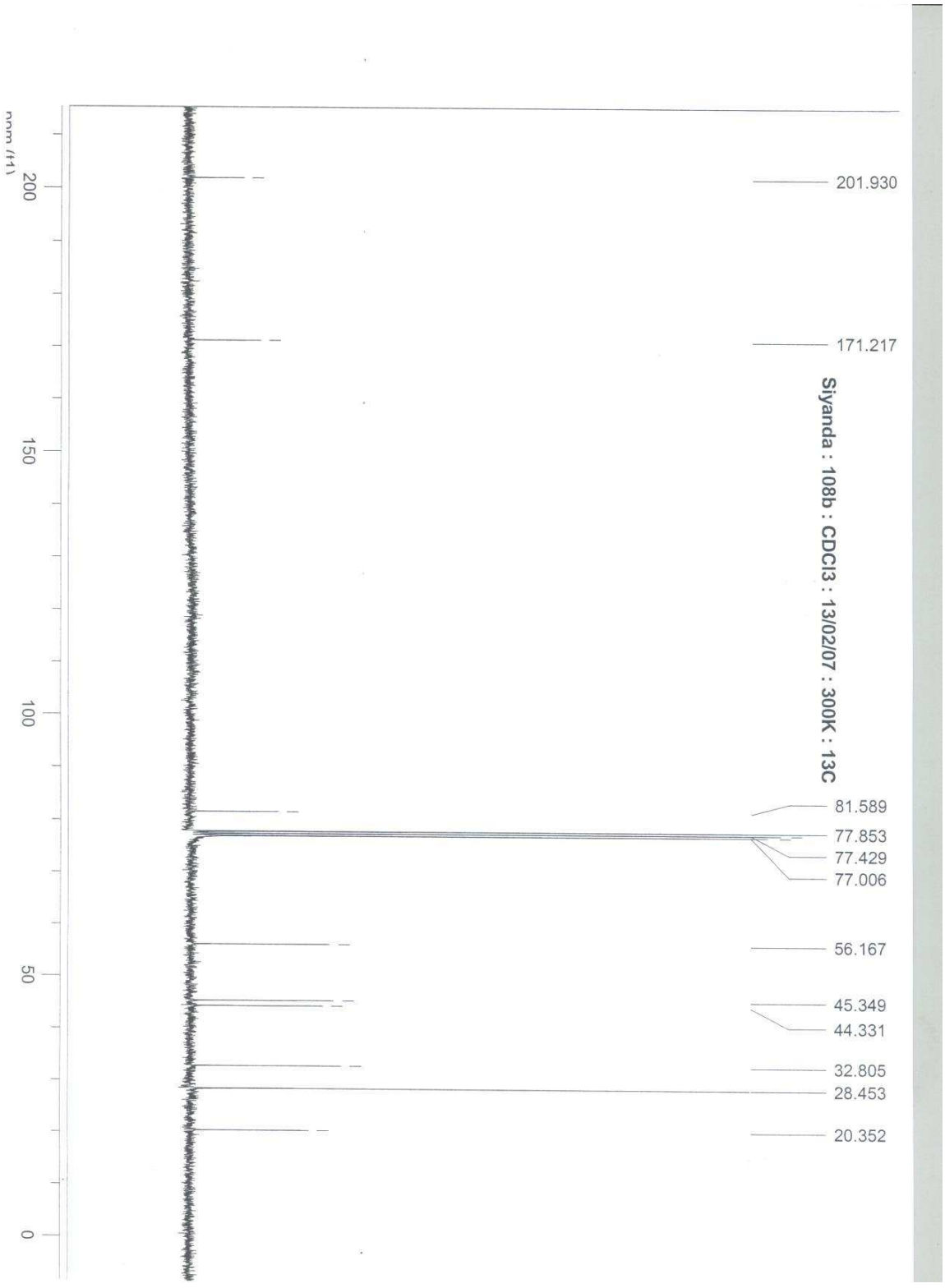
Azepane-2-thione (147)



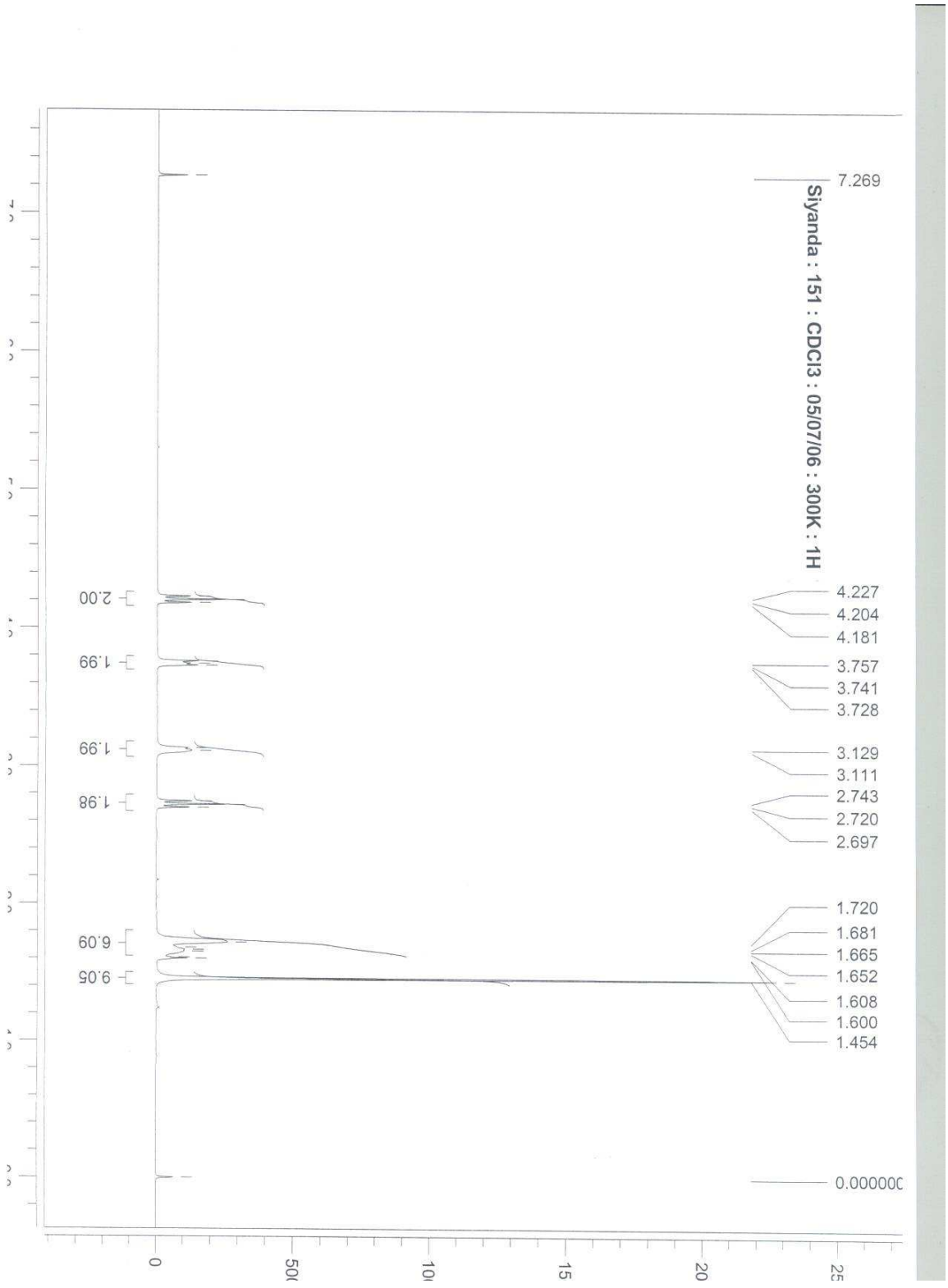
***tert*-Butyl 3-(2-thioxopyrrolidin-1-yl)propanoate (108b)**



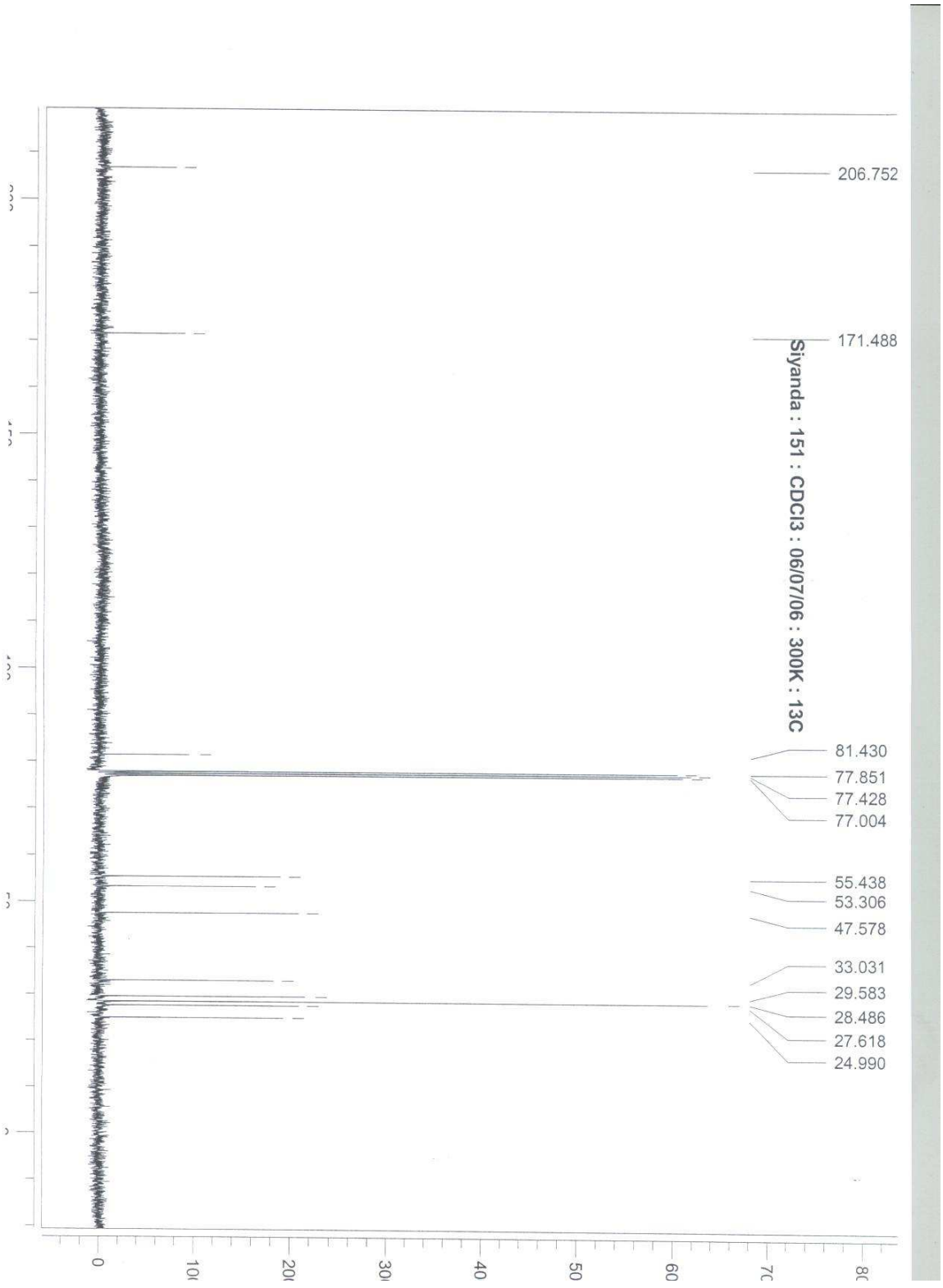
***tert*-Butyl 3-(2-thioxopyrrolidin-1-yl)propanoate (108b)**



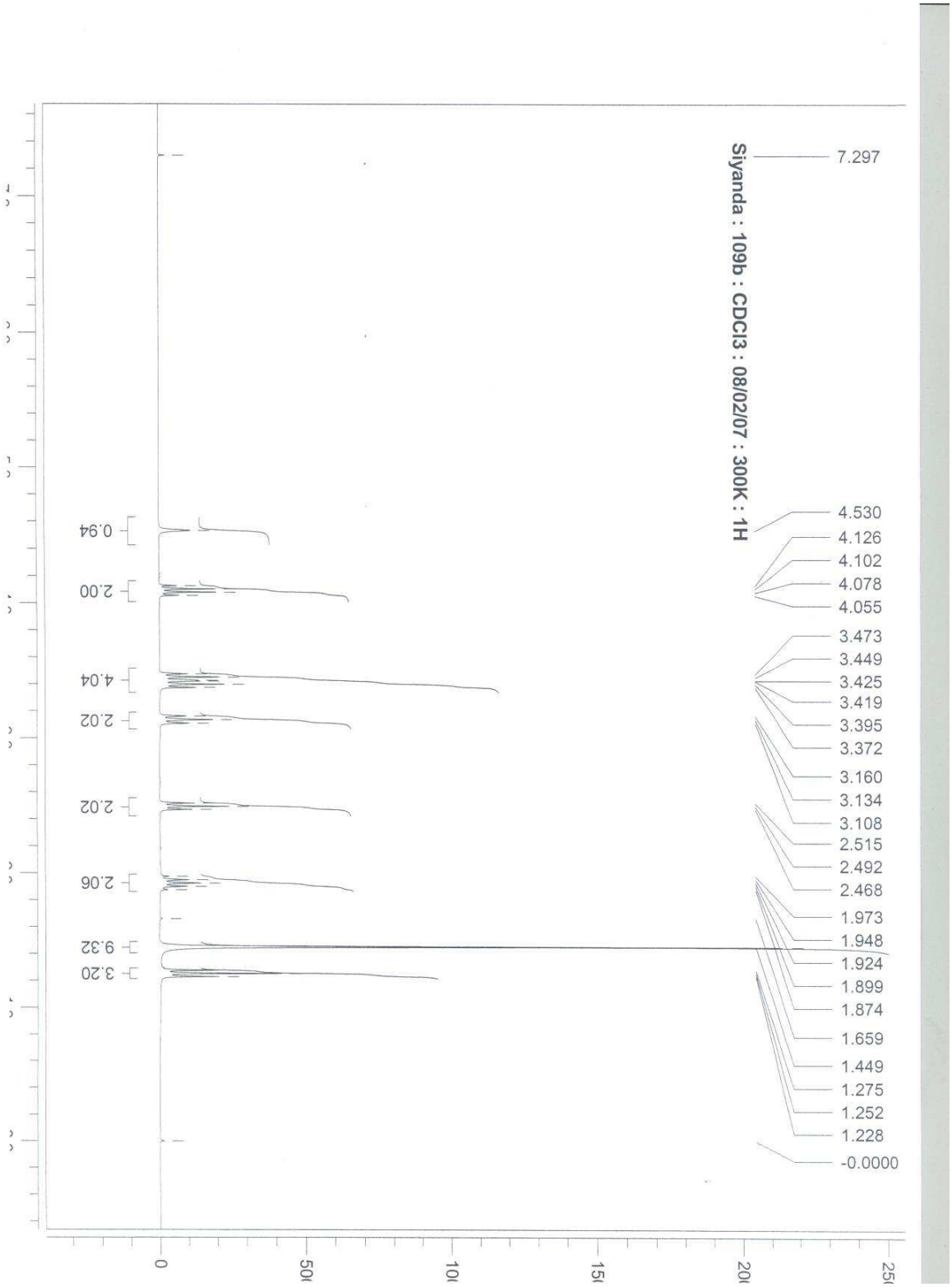
***tert*-Butyl 3-(2-thioxoazepan-1-yl)propanoate (151)**



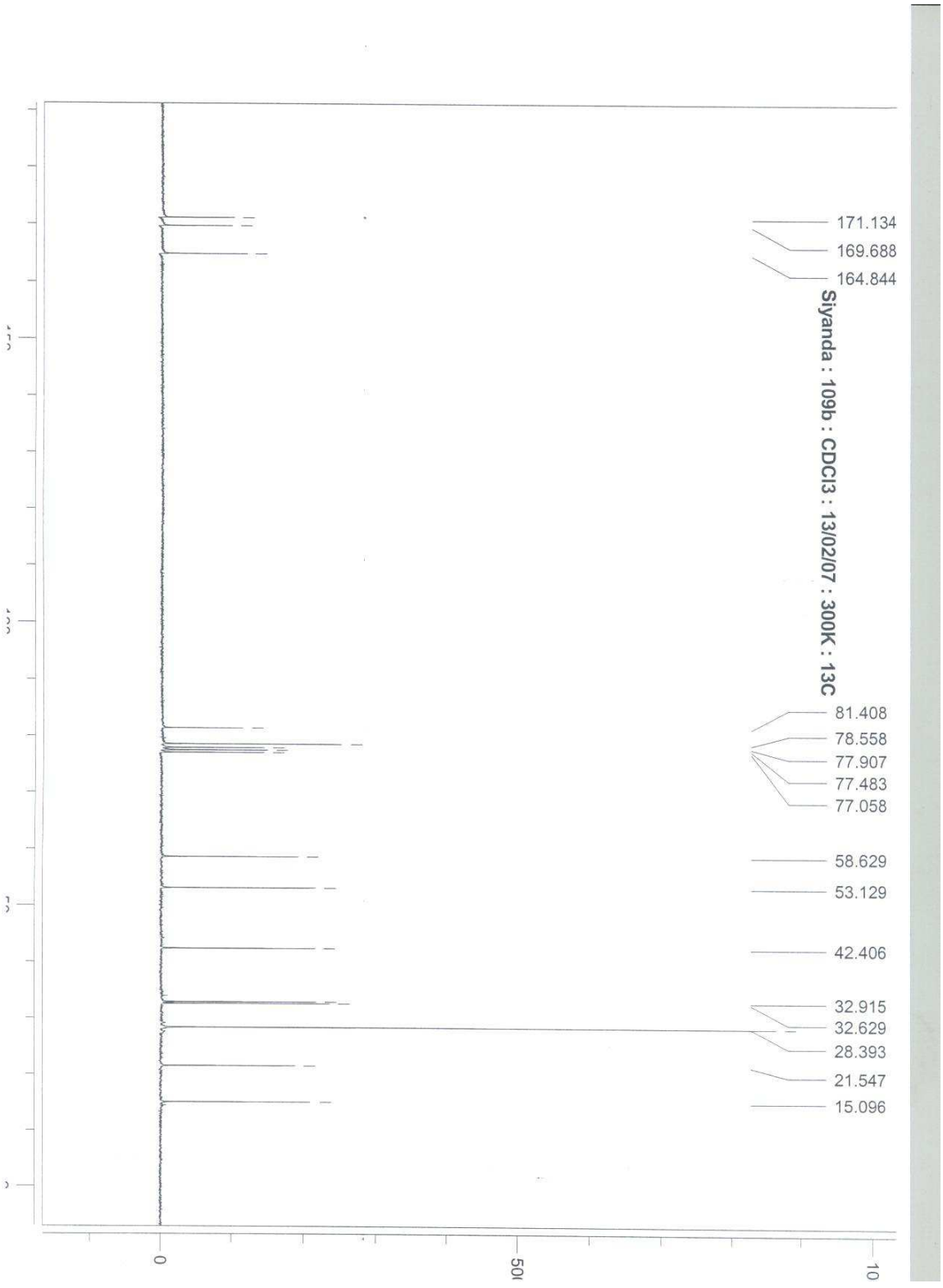
***tert*-Butyl 3-(2-thioxoazepan-1-yl)propanoate (151)**



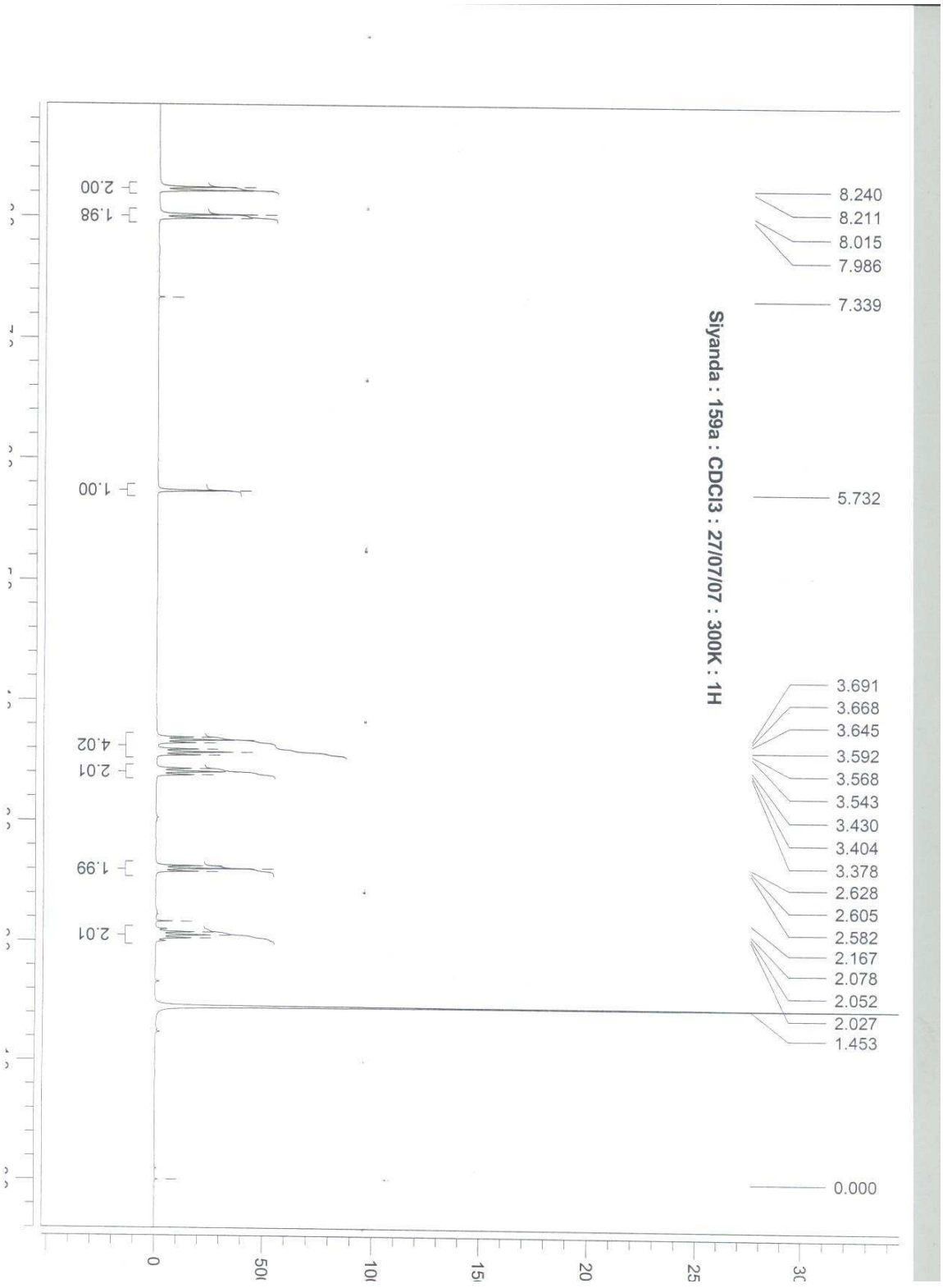
(*E*)-*tert*-Butyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate (109b)



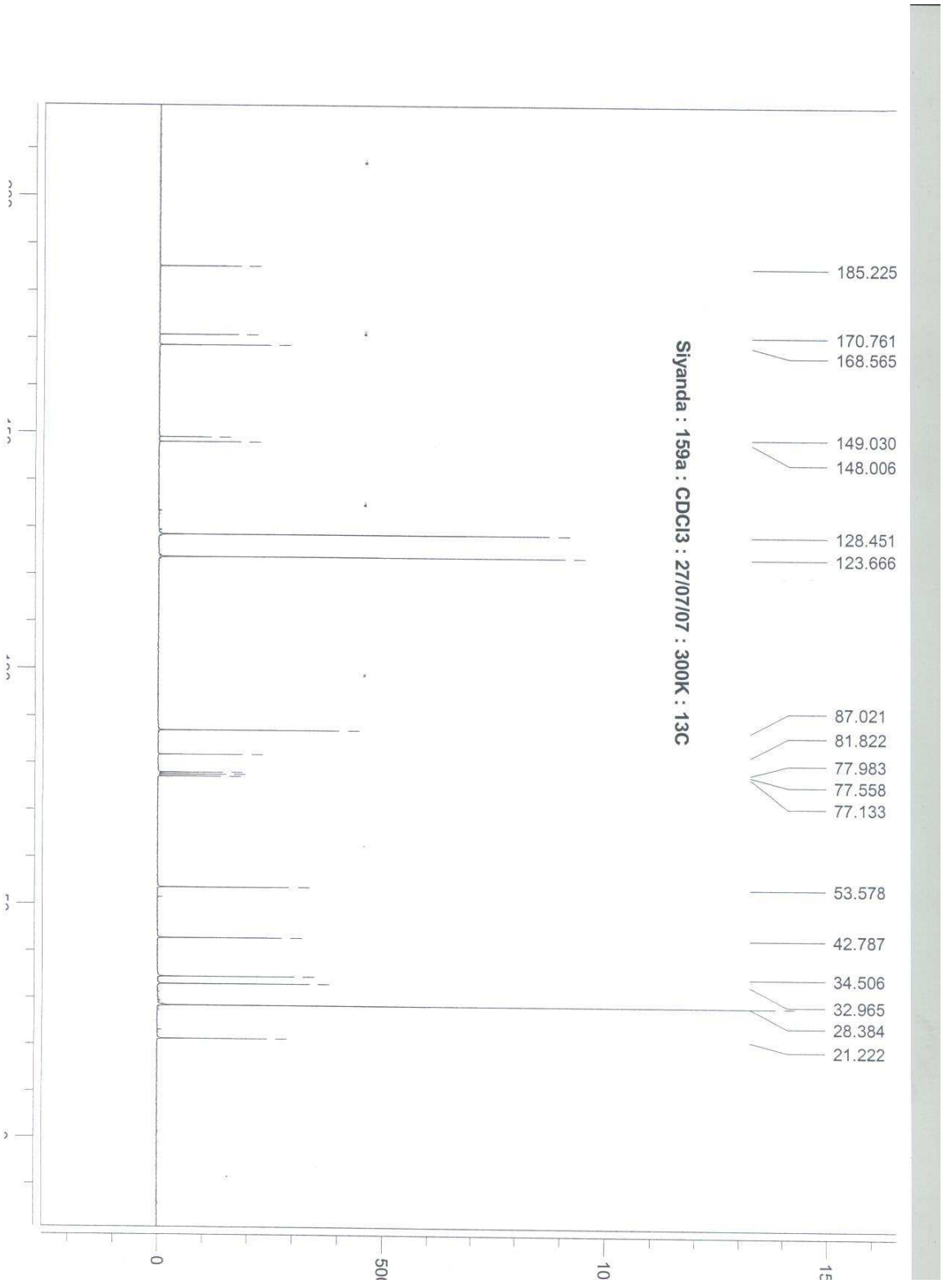
(*E*)-*tert*-Butyl 3-(2-(2-ethoxy-2-oxoethylidene)pyrrolidin-1-yl)propanoate (109b)



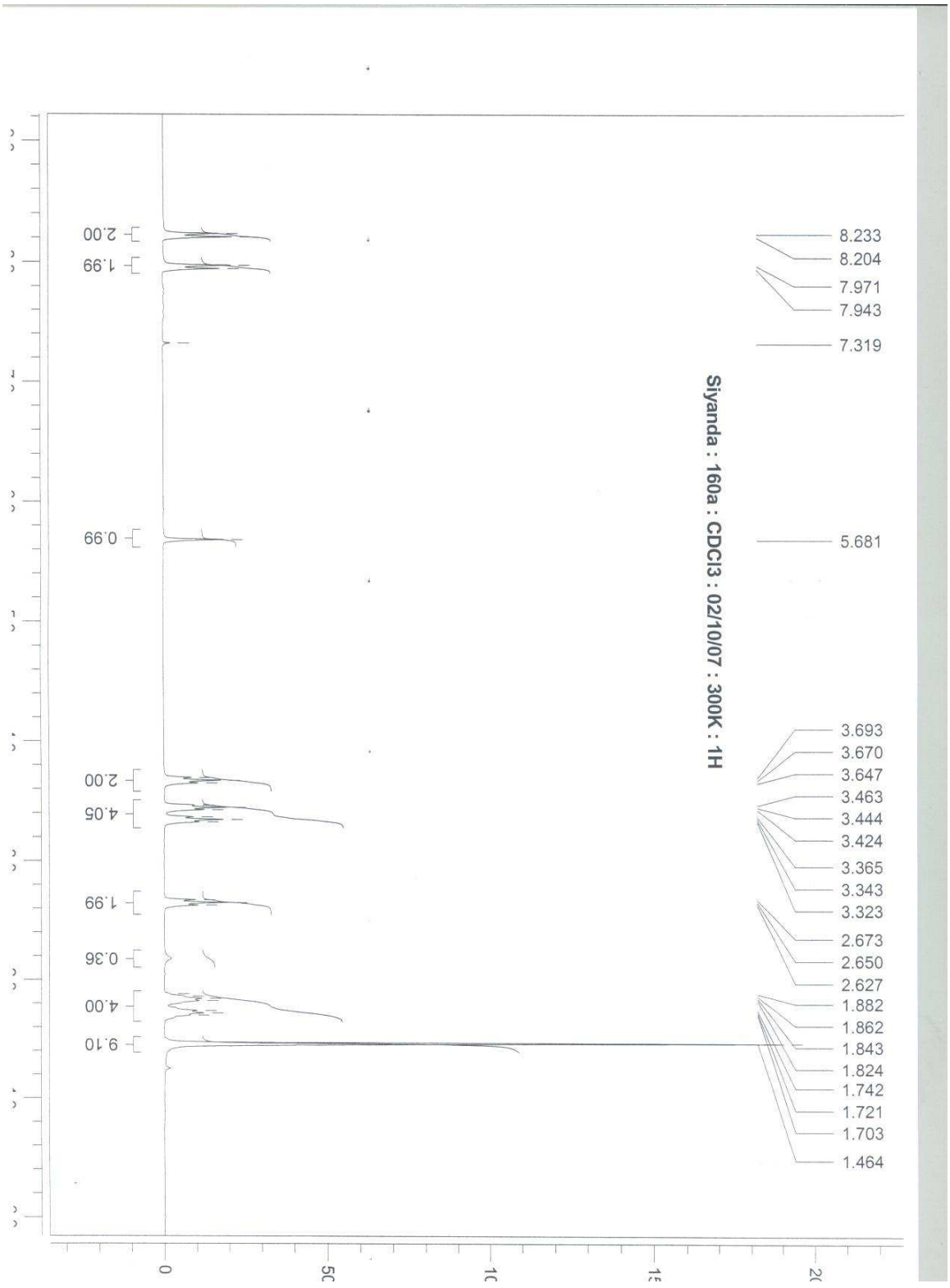
(*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]pyrrolidin-1-yl}propanoate (159a)



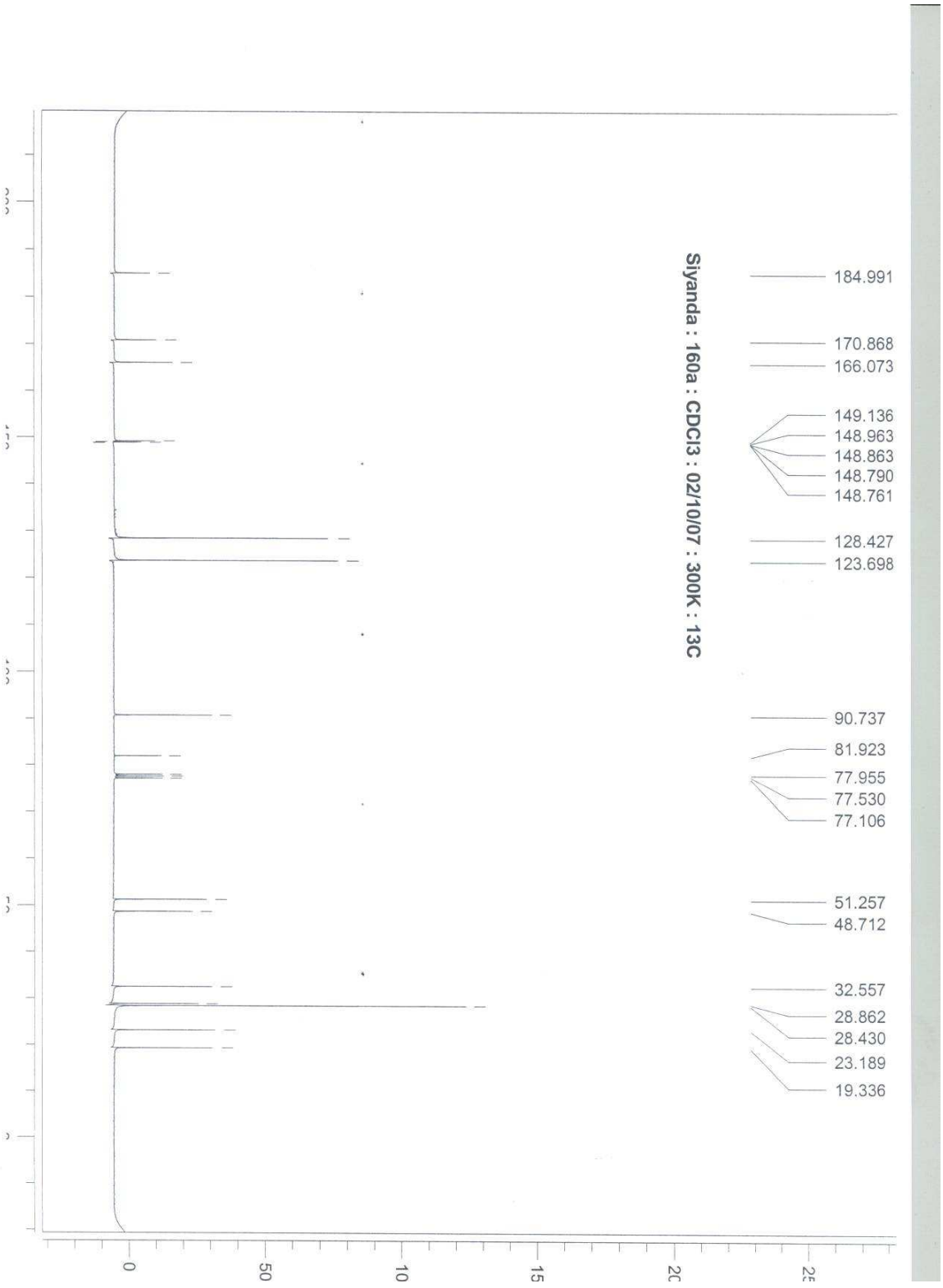
(*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]pyrrolidin-1-yl}propanoate (159a)



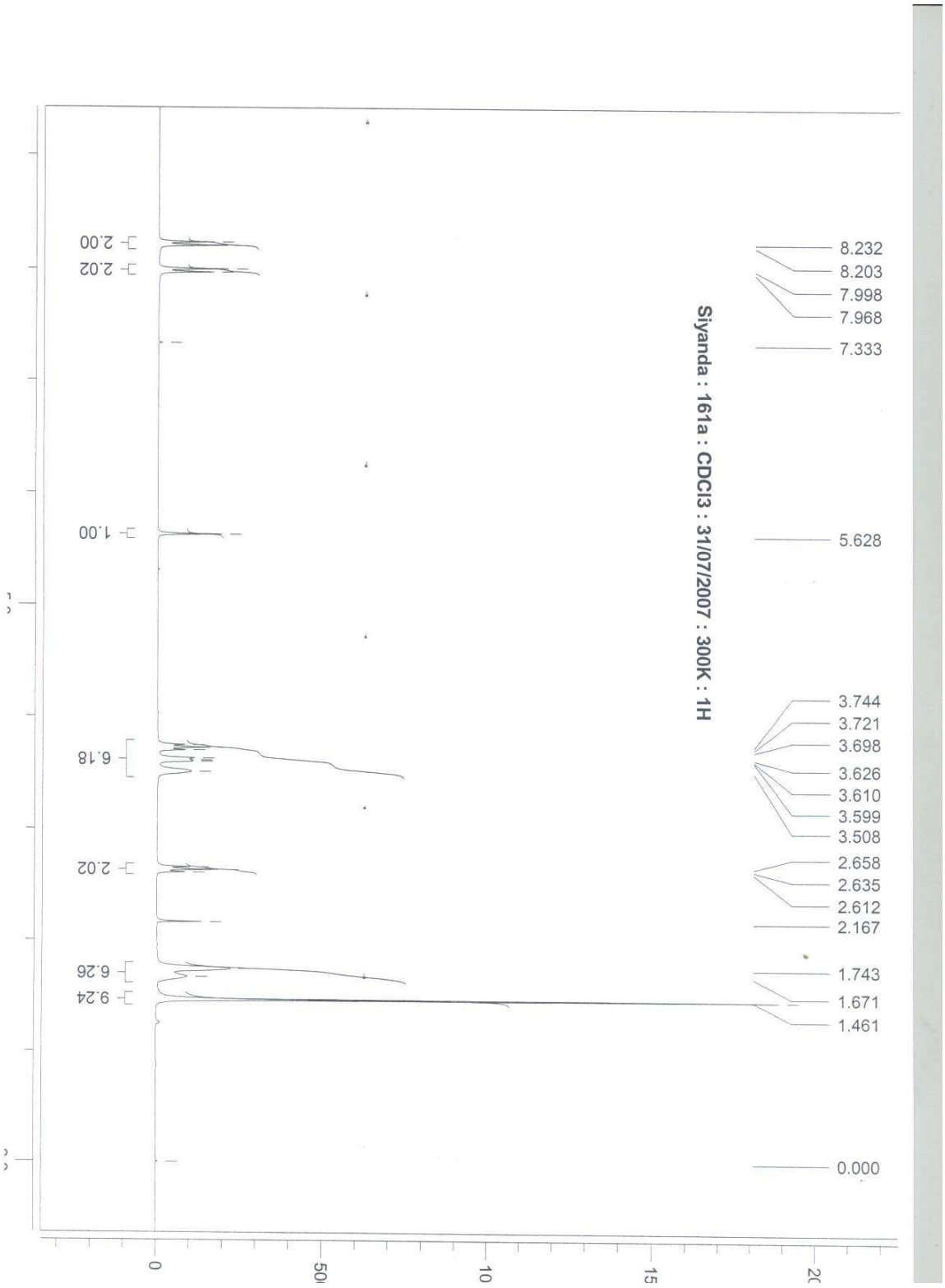
(*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]piperidin-1-yl}propanoate (160a)



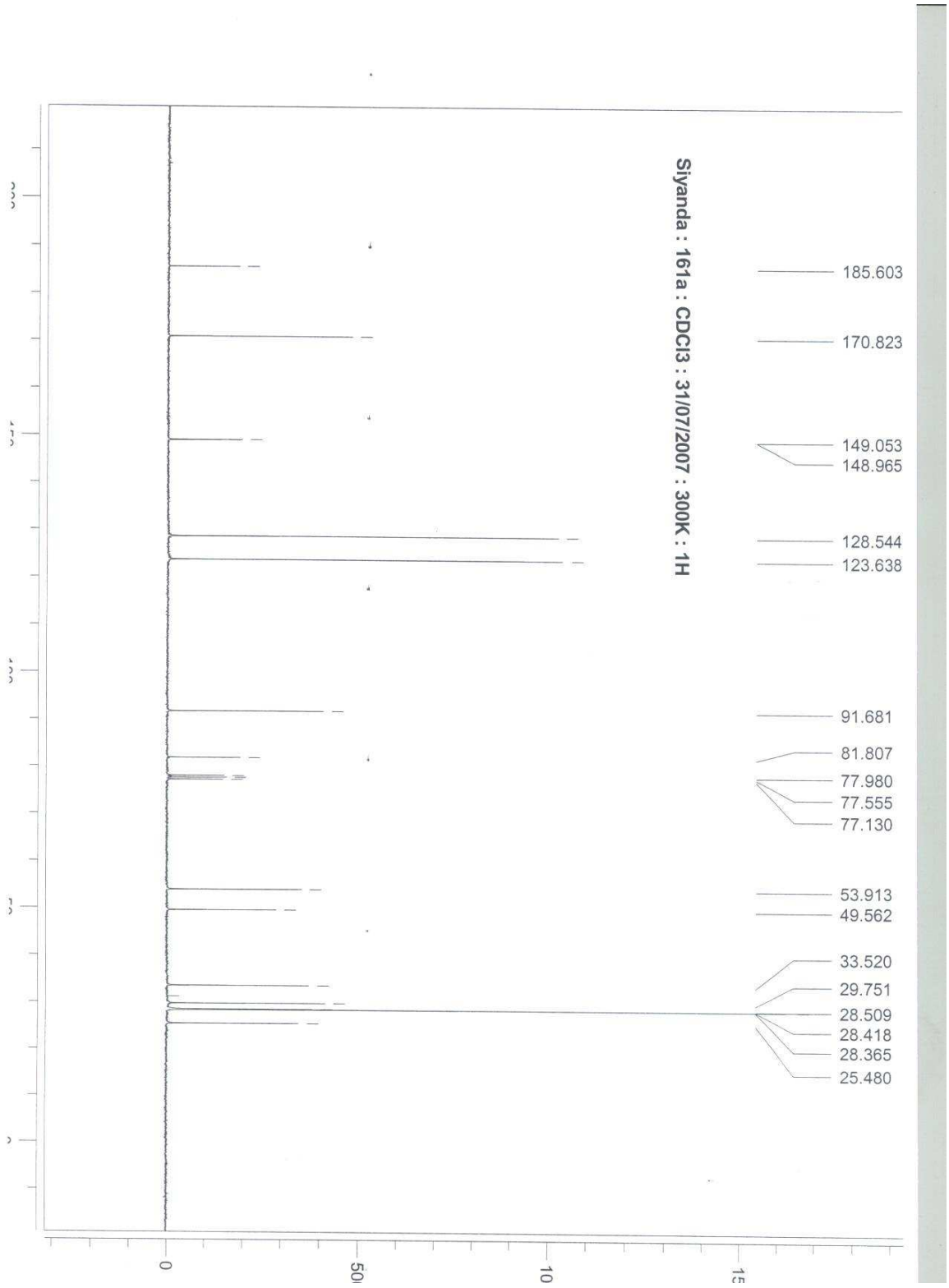
(*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]piperidin-1-yl}propanoate (160a)



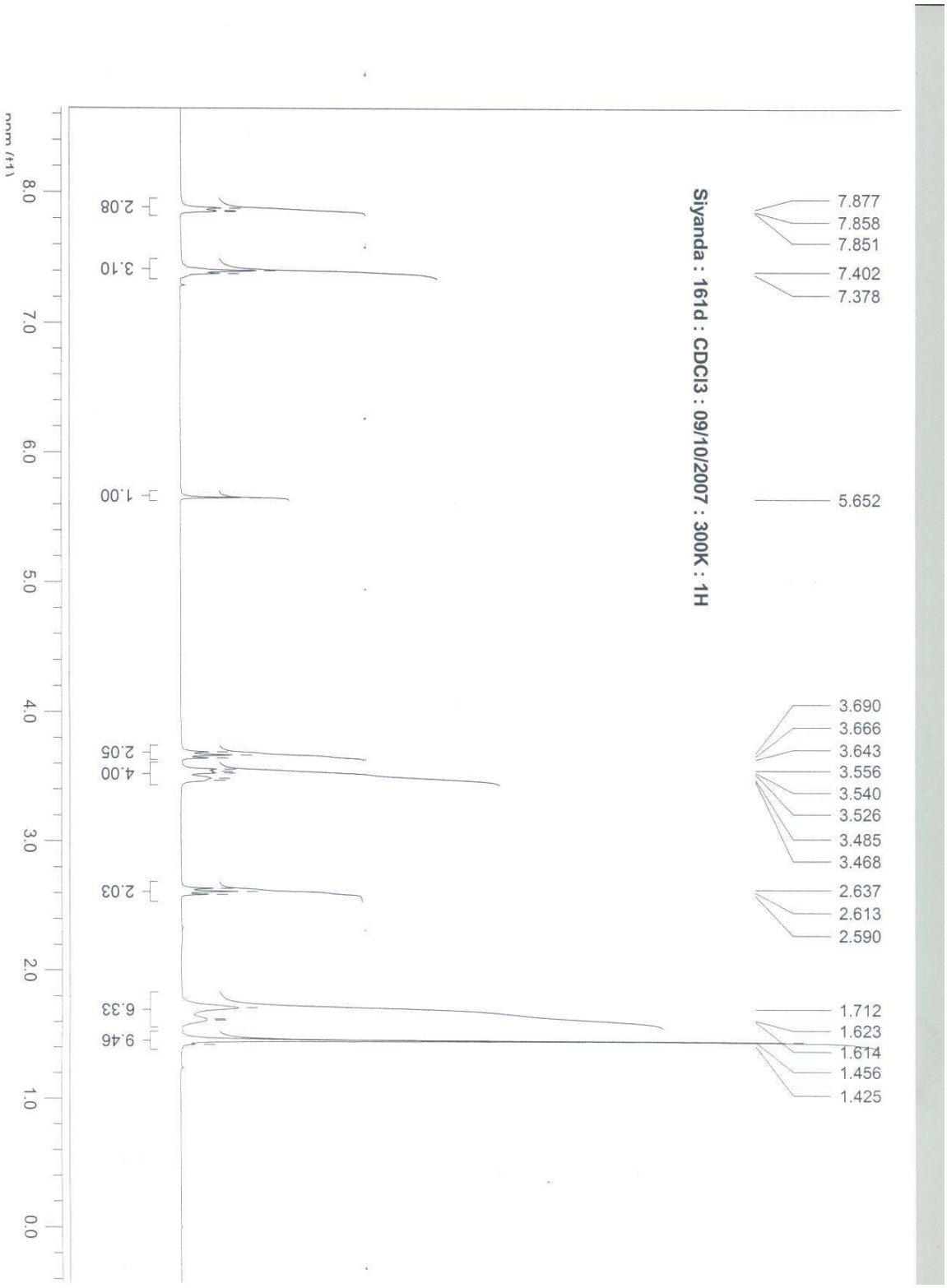
(*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azepan-1-yl}propanoate (161a)



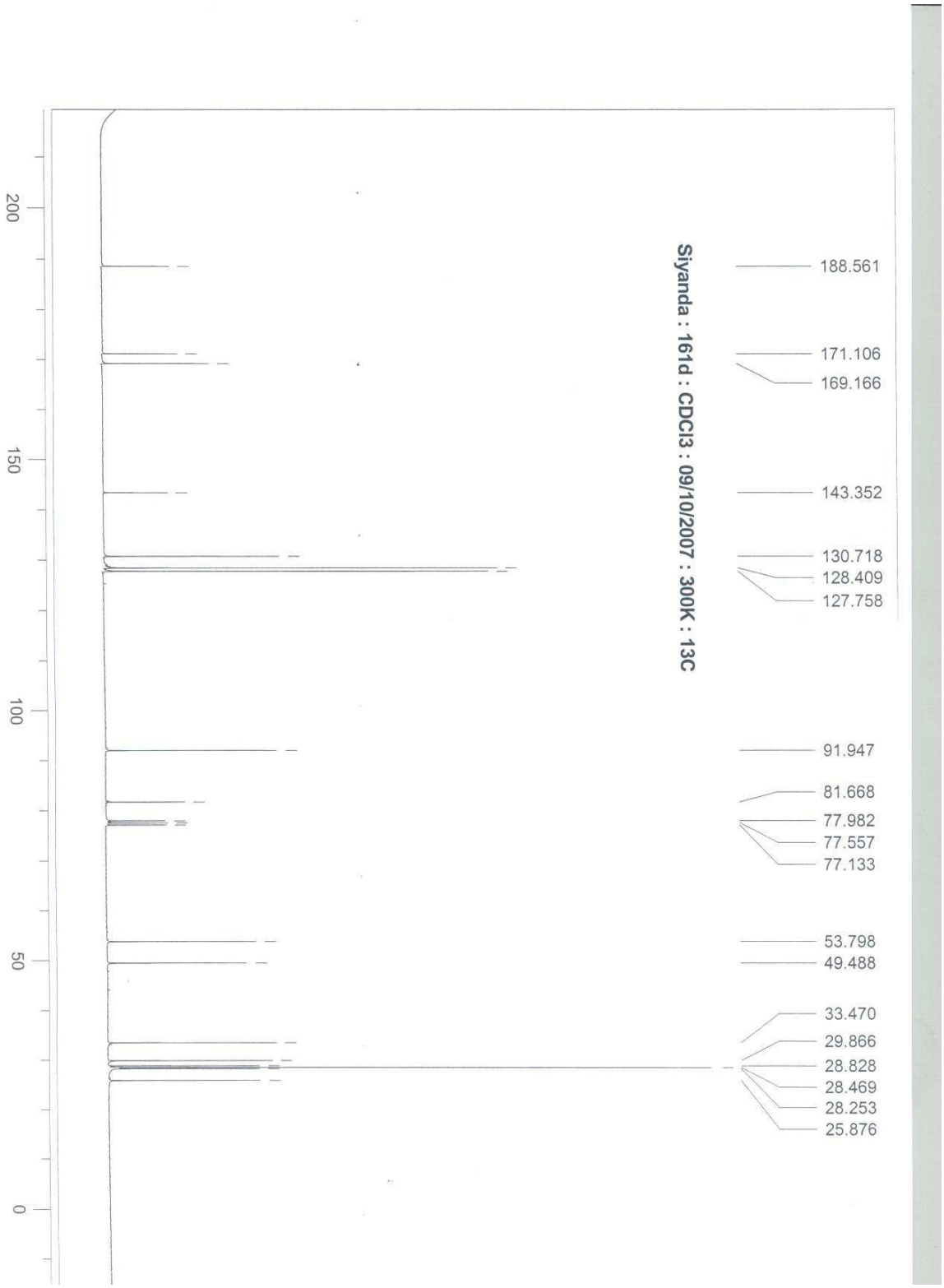
(*E*)-*tert*-Butyl 3-{2-[2-(4-nitrophenyl)-2-oxoethylidene]azepan-1-yl}propanoate (161a)



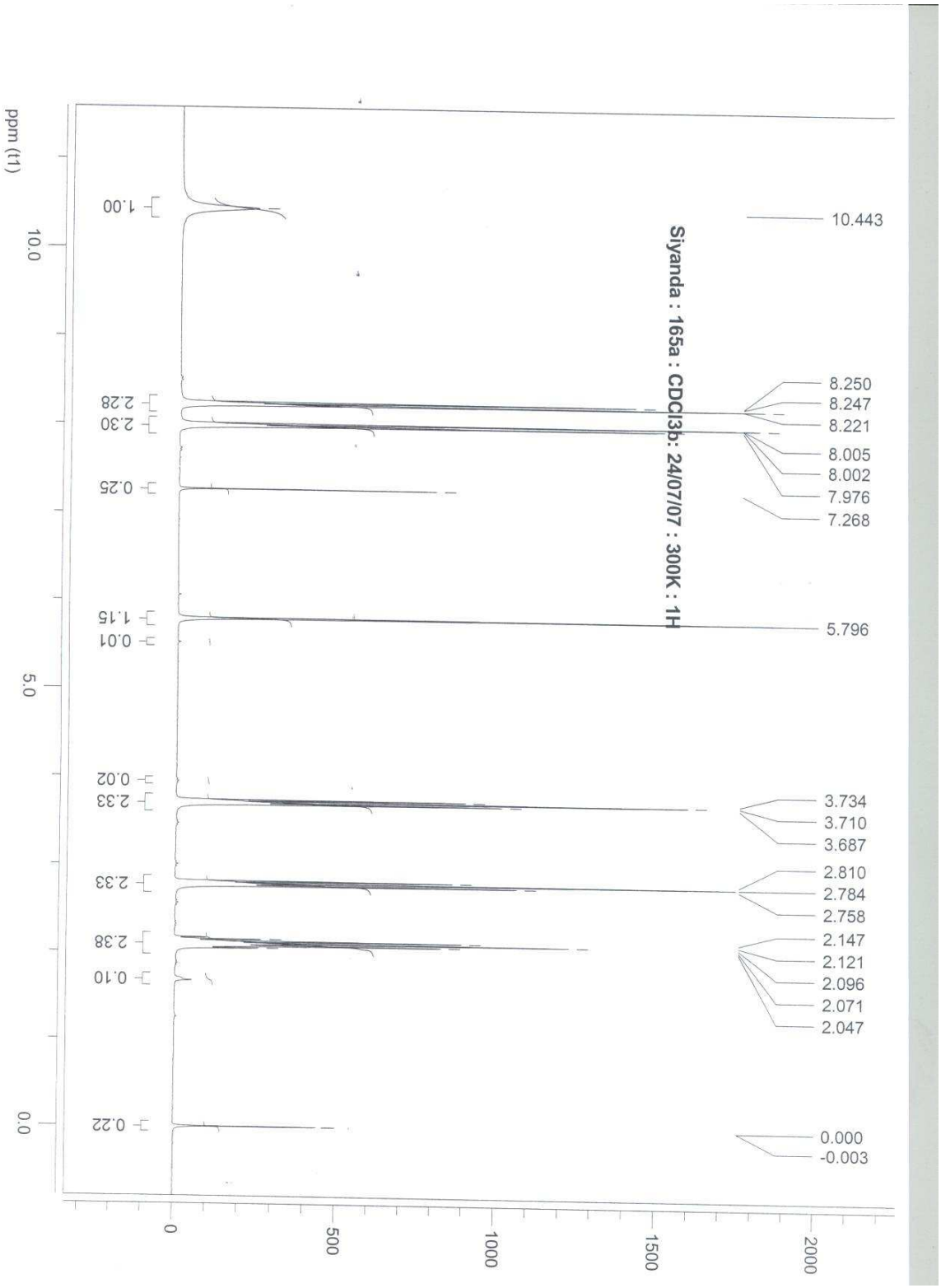
(*E*)-*tert*-Butyl 3-[2-(2-oxo-2-phenylethylidene)azepan-1-yl]propanoate (161d)



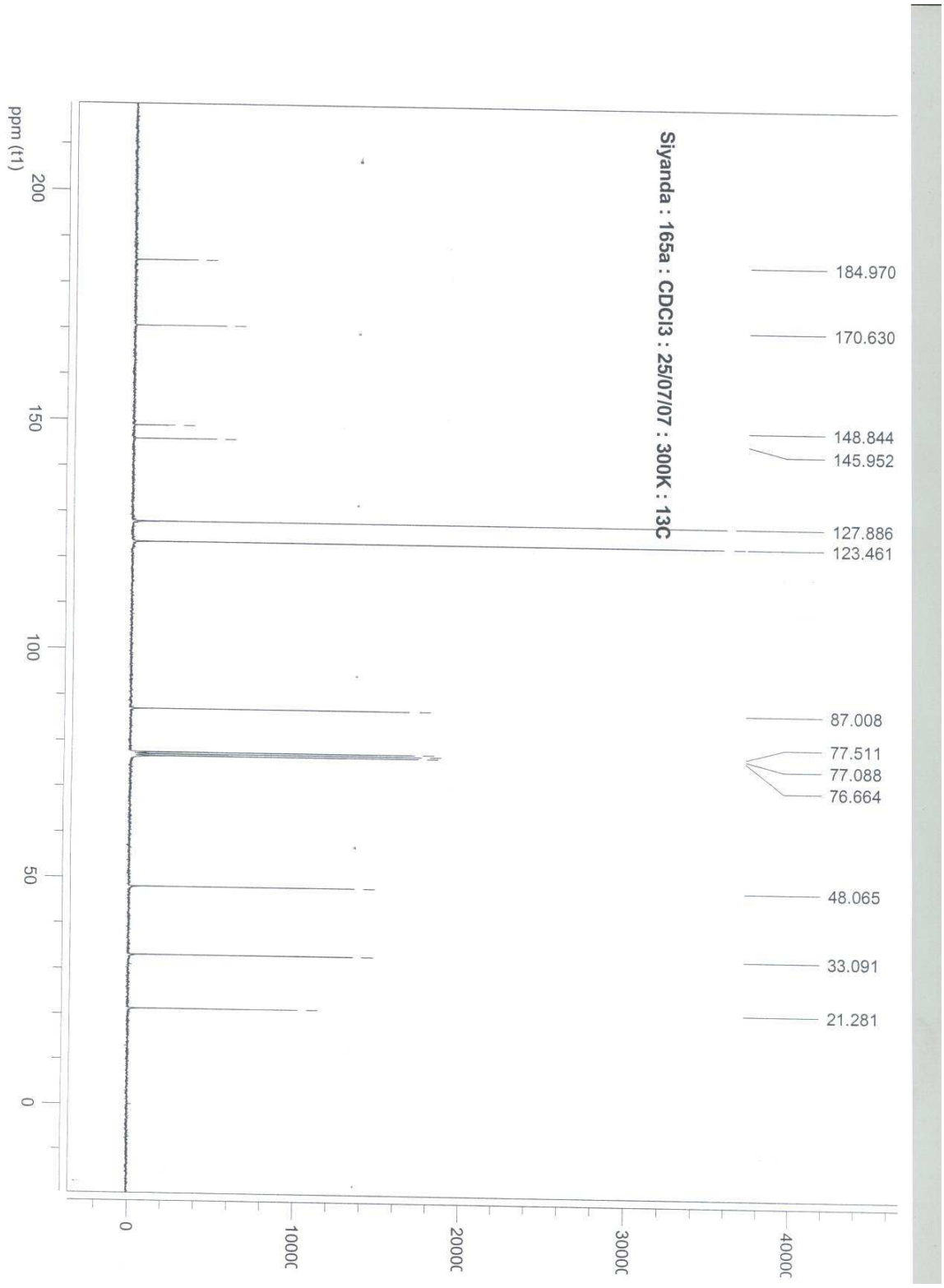
(*E*)-*tert*-Butyl 3-[2-(2-oxo-2-phenylethylidene)azepan-1-yl]propanoate (161d)



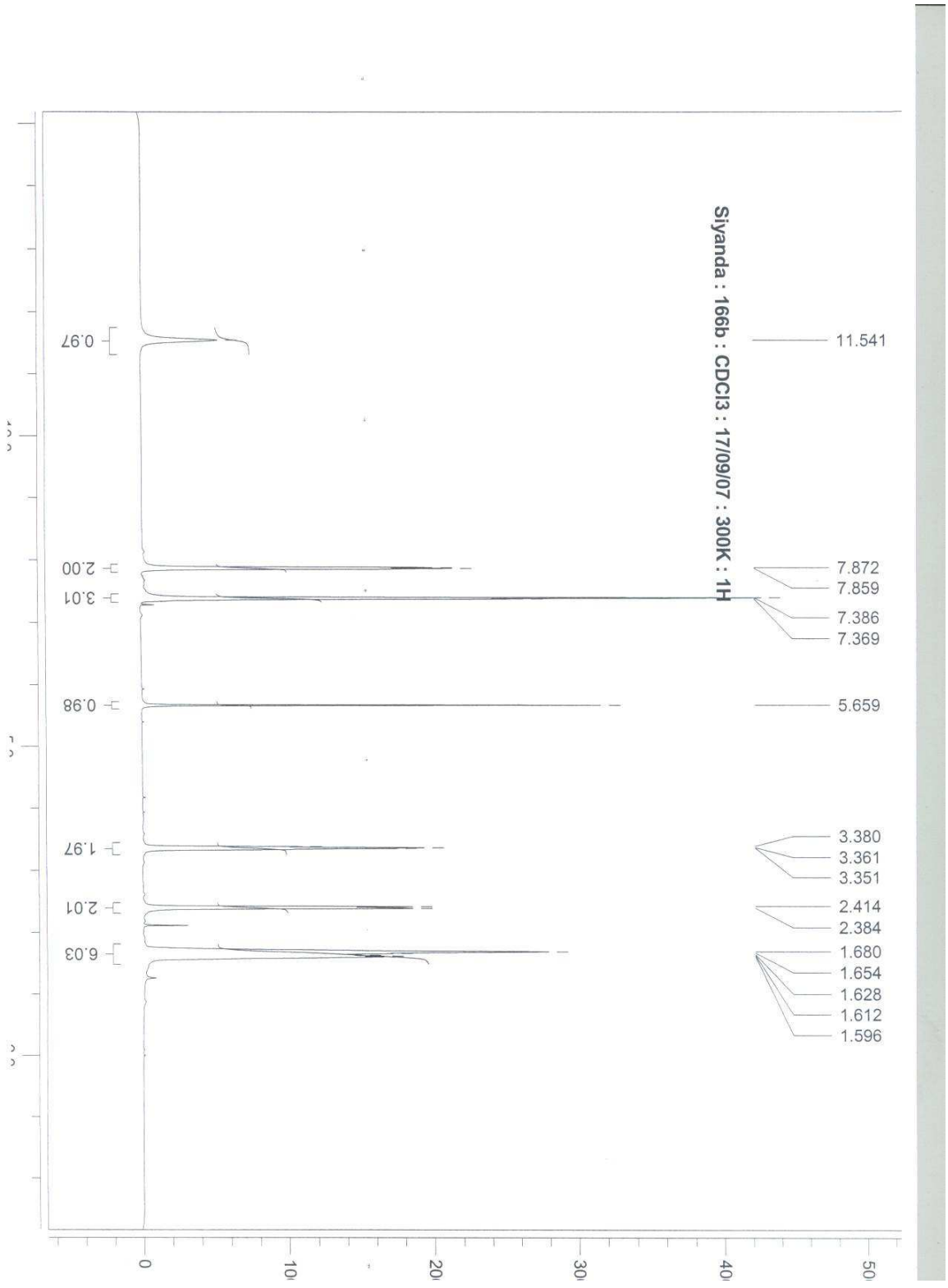
(*Z*)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone (165a)



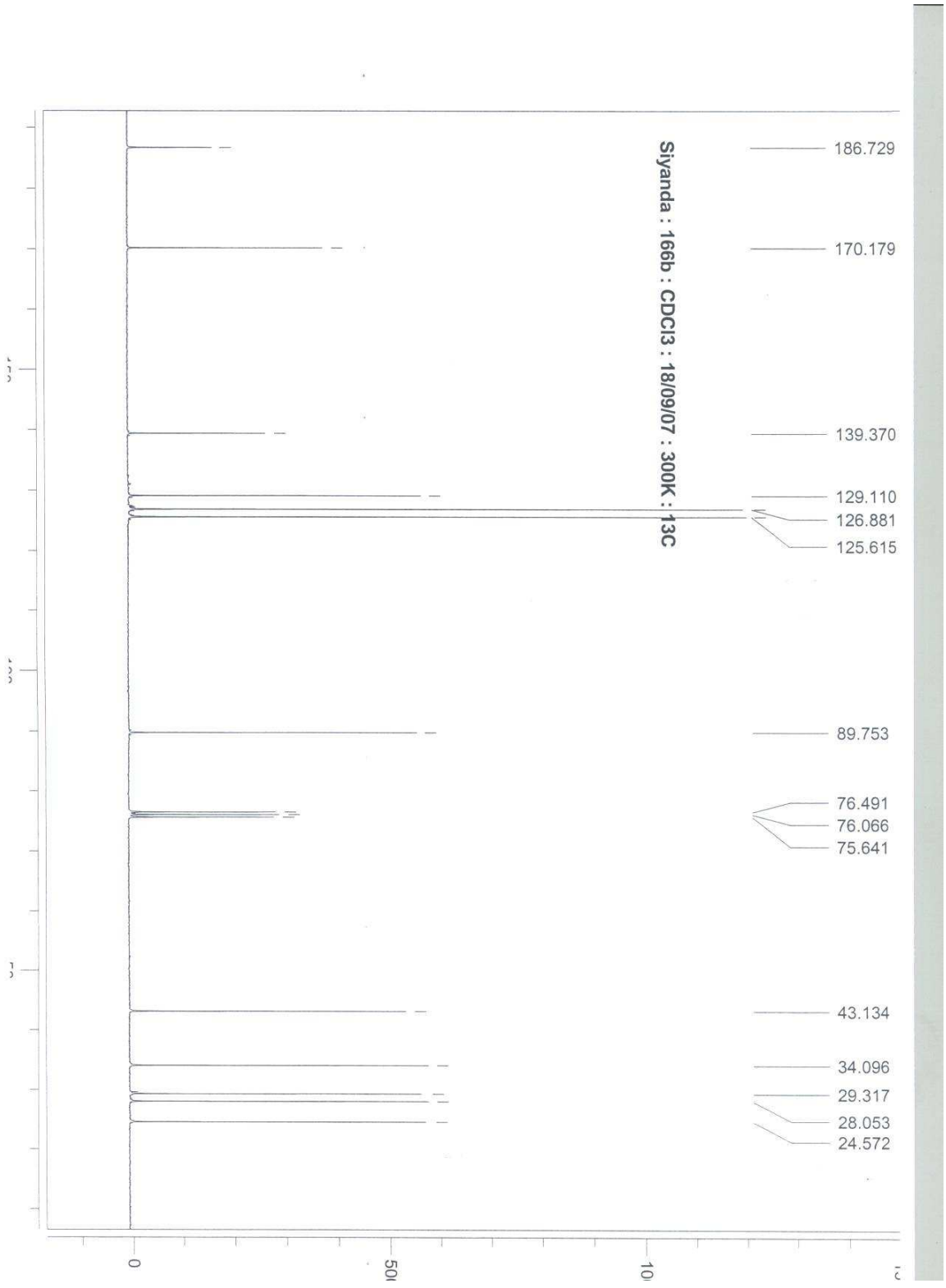
(*Z*)-1-(4-Nitrophenyl)-2-(pyrrolidin-2-ylidene)ethanone (165a)



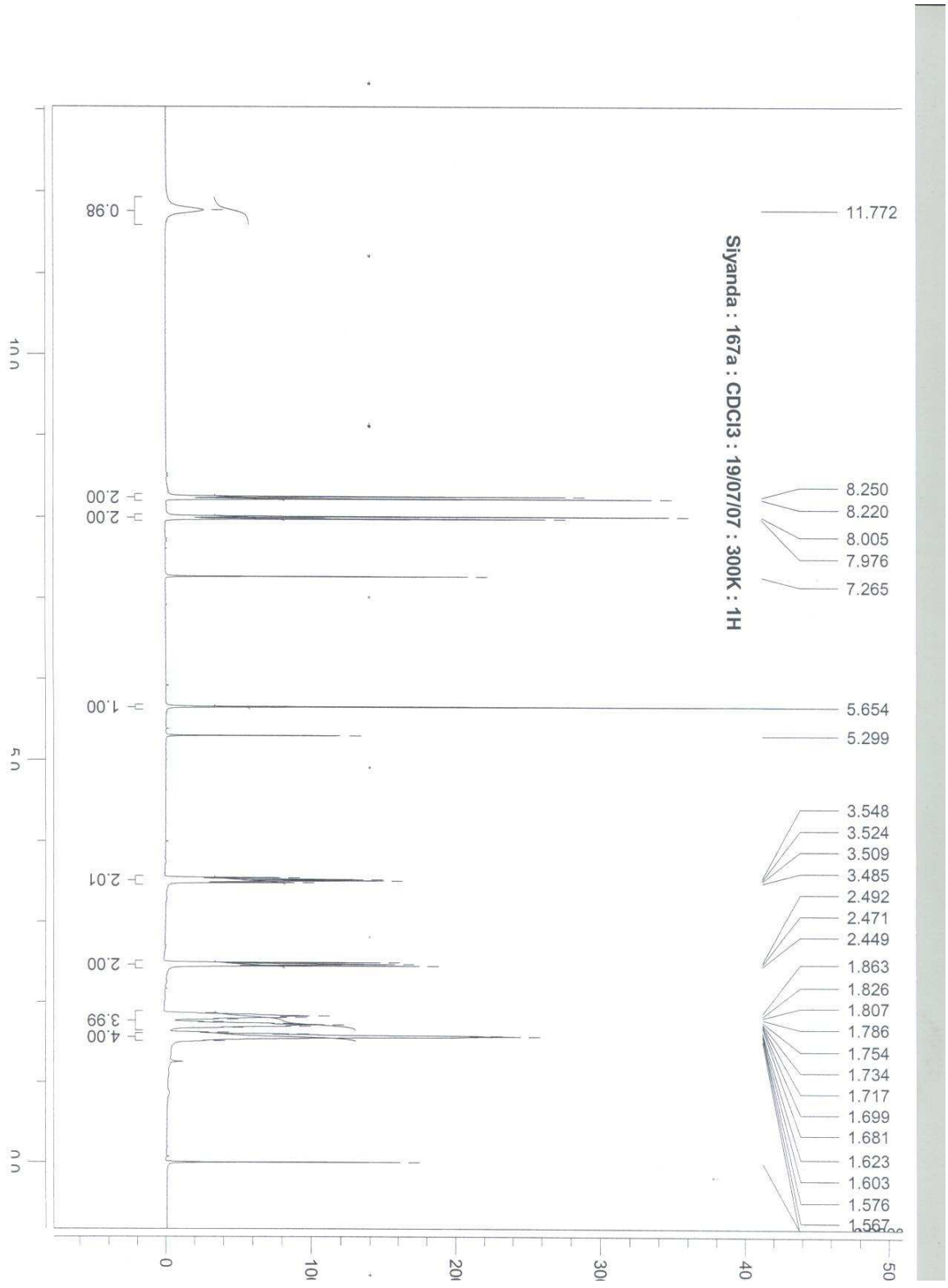
(*Z*)-2-(Azepan-2-ylidene)-1-phenylethanone (166b)



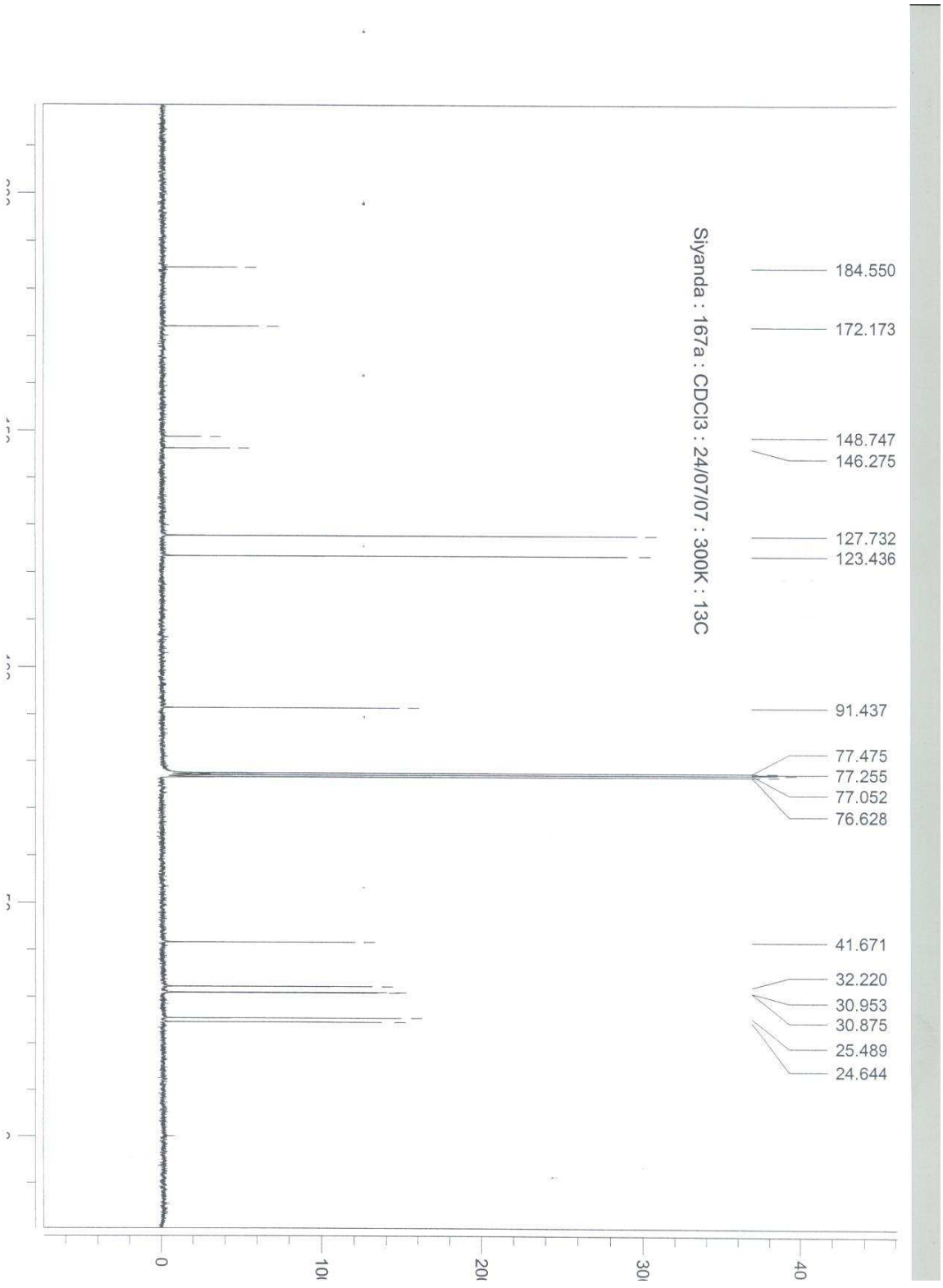
(*Z*)-2-(Azepan-2-ylidene)-1-phenylethanone (166b)



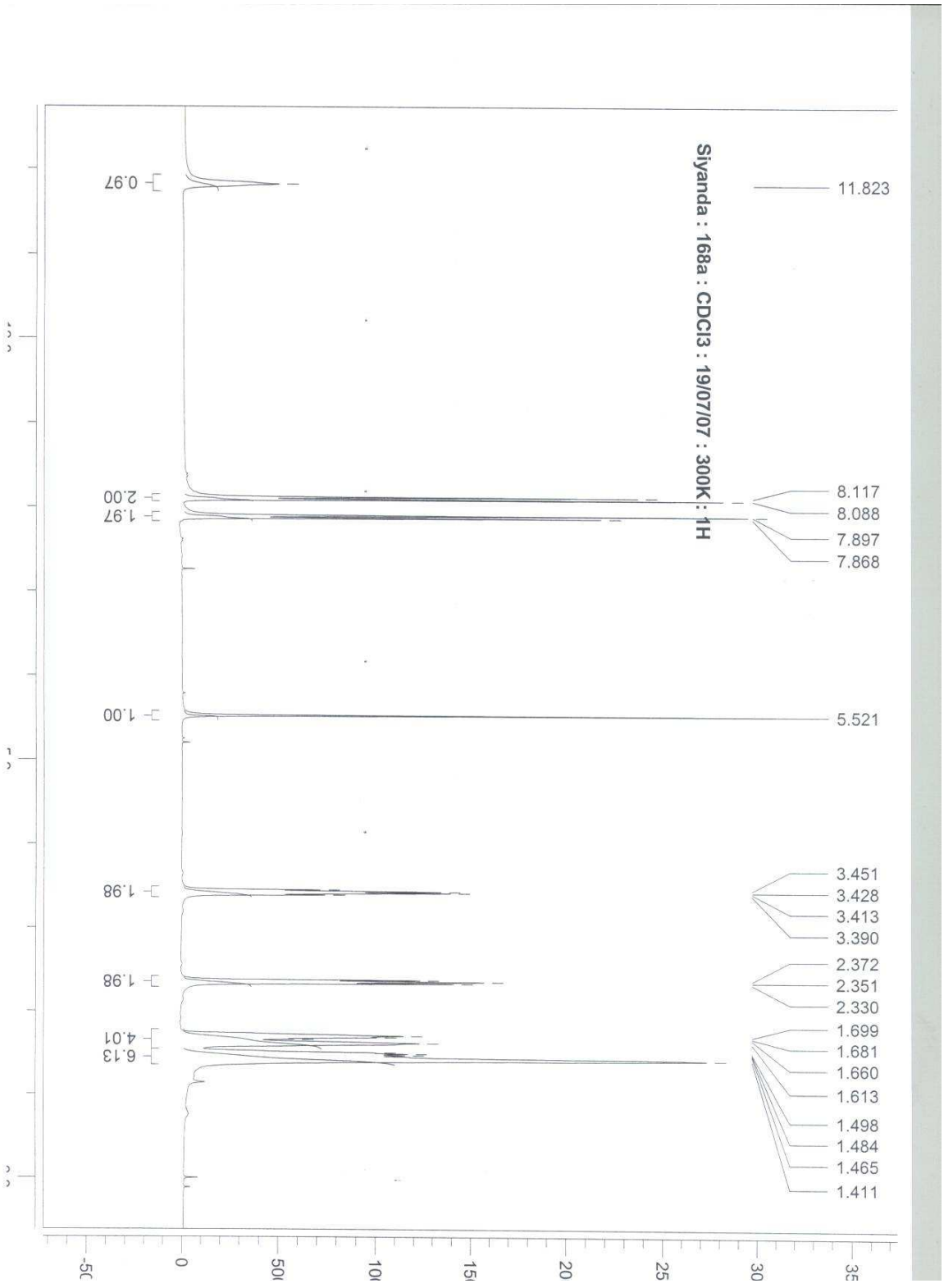
(*Z*)-2-(Azocan-2-ylidene)-1-(4-nitrophenyl)ethanone (167a)



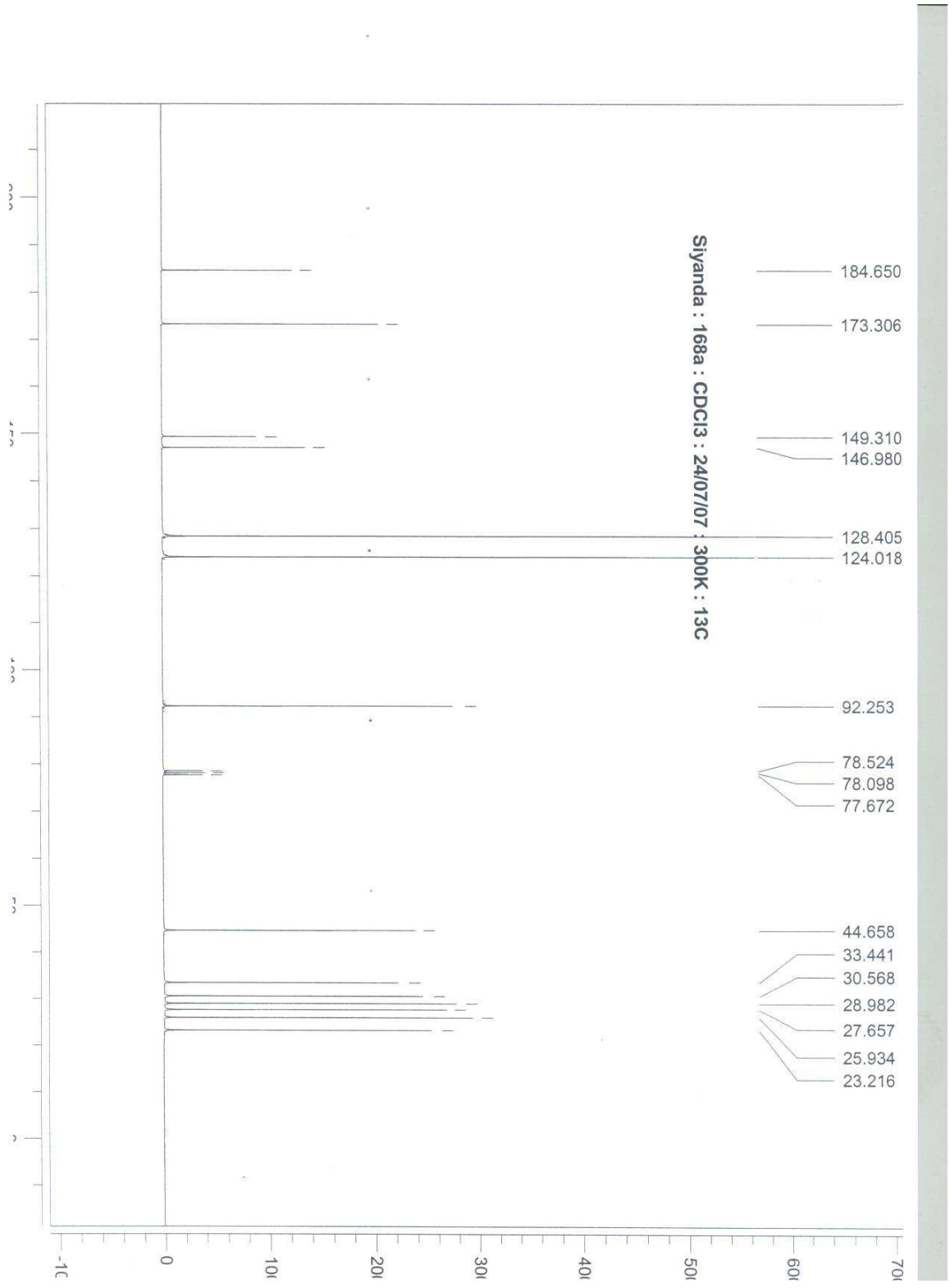
(*Z*)-2-(Azocan-2-ylidene)-1-(4-nitrophenyl)ethanone (167a)



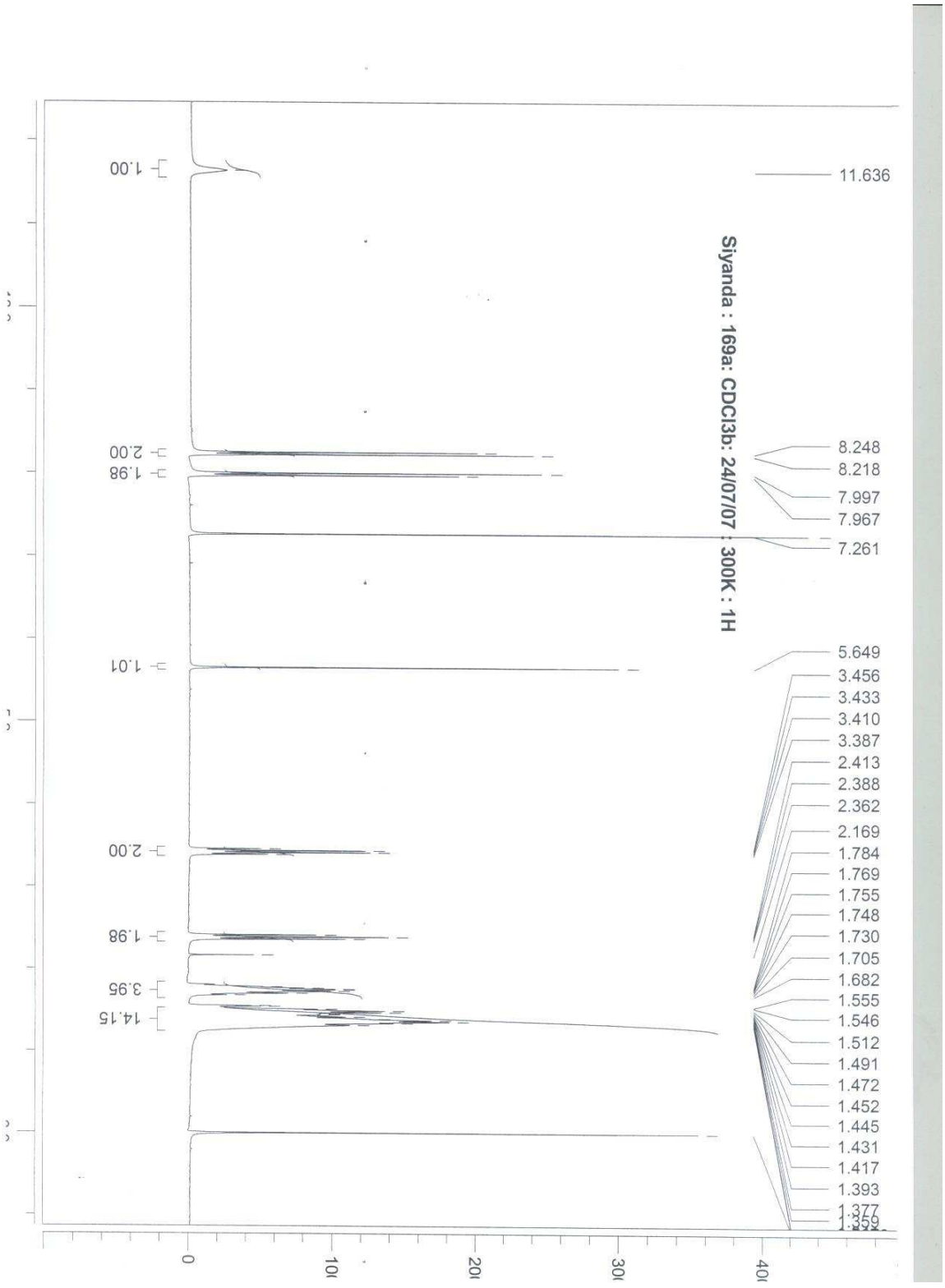
(*Z*)-2-(Azonan-2-ylidene)-1-(4-nitrophenyl)ethanone (168a)



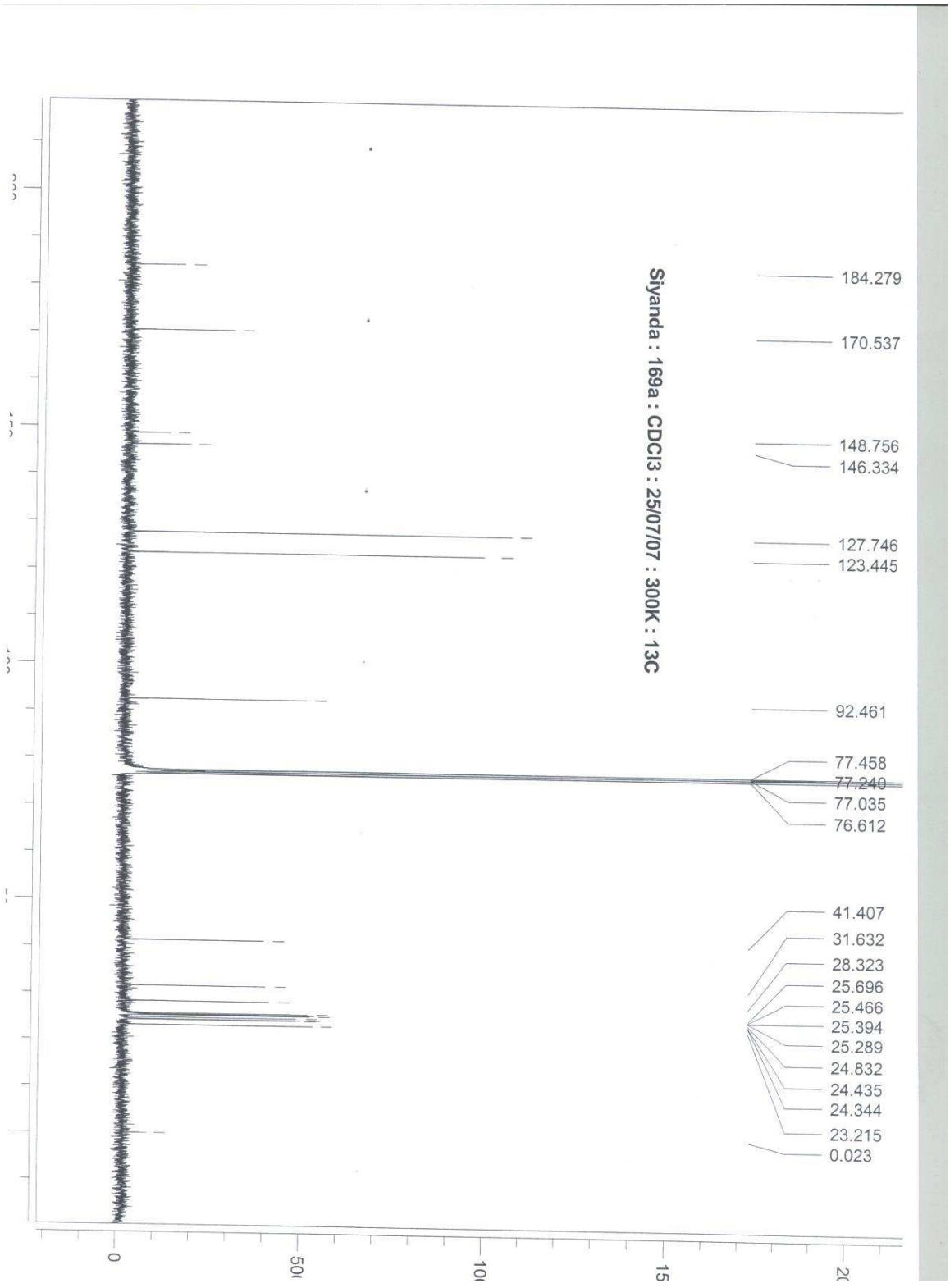
(*Z*)-2-(Azonan-2-ylidene)-1-(4-nitrophenyl)ethanone (168a)



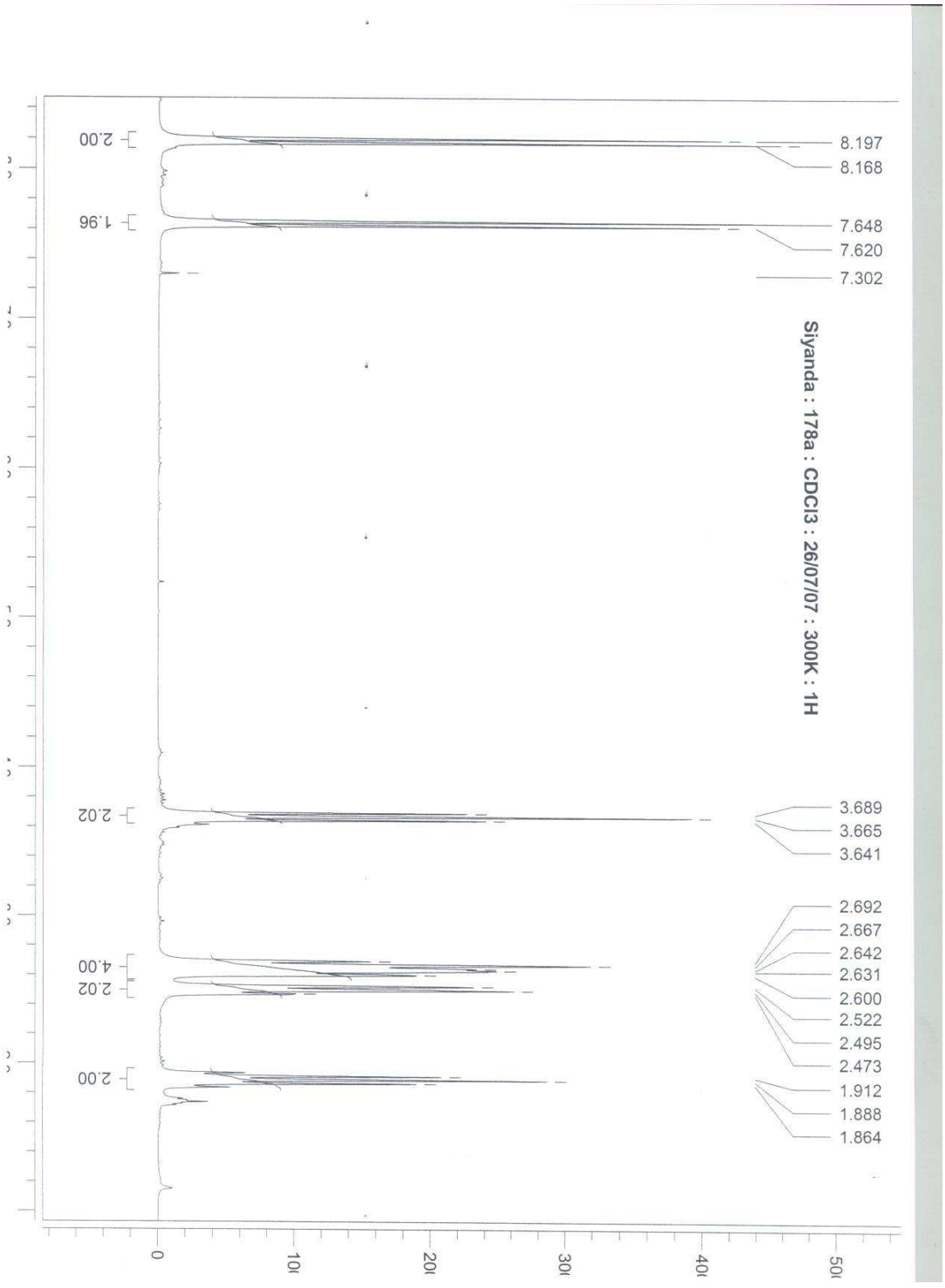
(*Z*)-2-(Azacyclotridecan-2-ylidene)-1-(4-nitrophenyl)ethanone (169a)



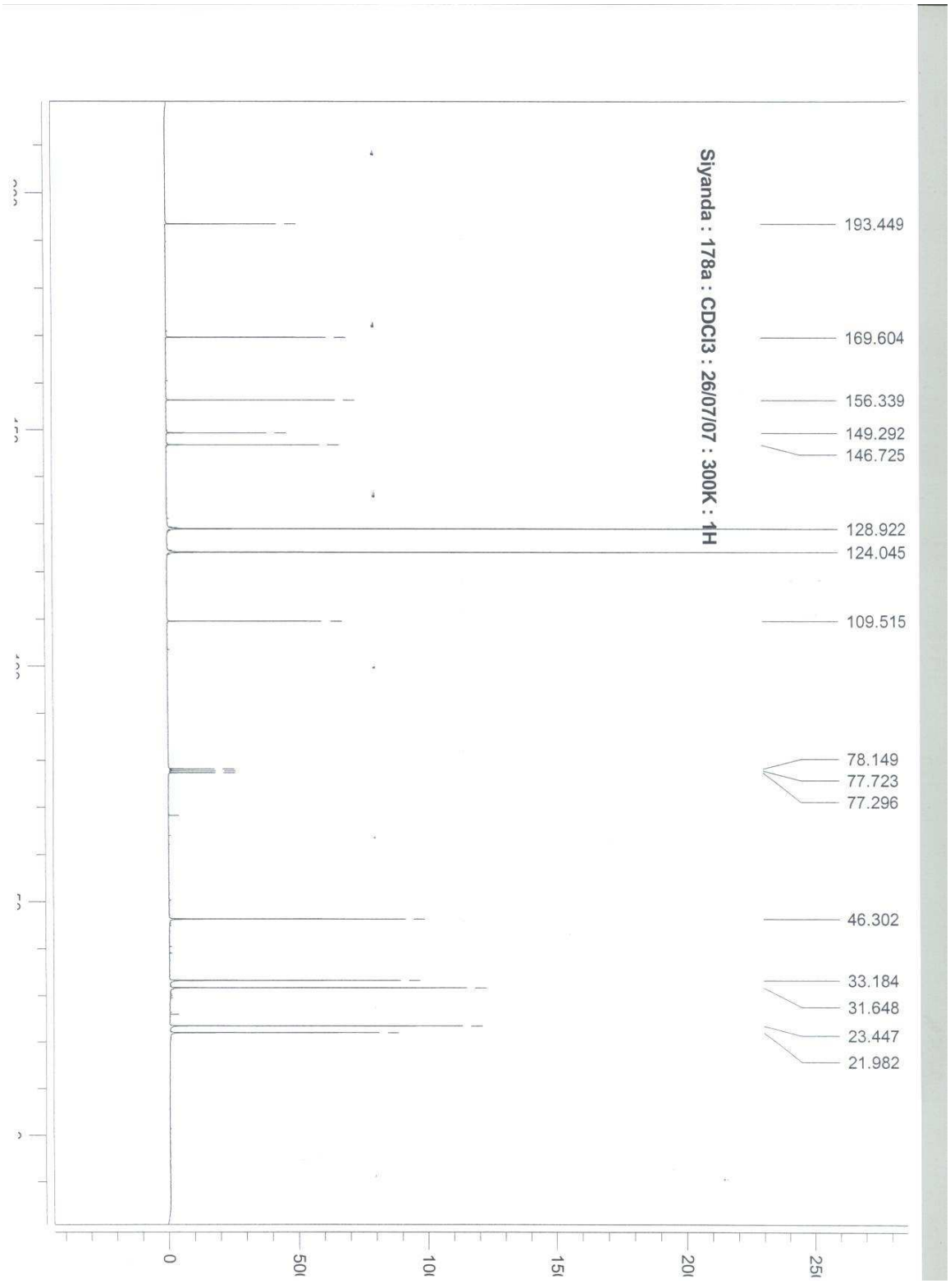
(*Z*)-2-(Azacyclotridecan-2-ylidene)-1-(4-nitrophenyl)ethanone (169a)



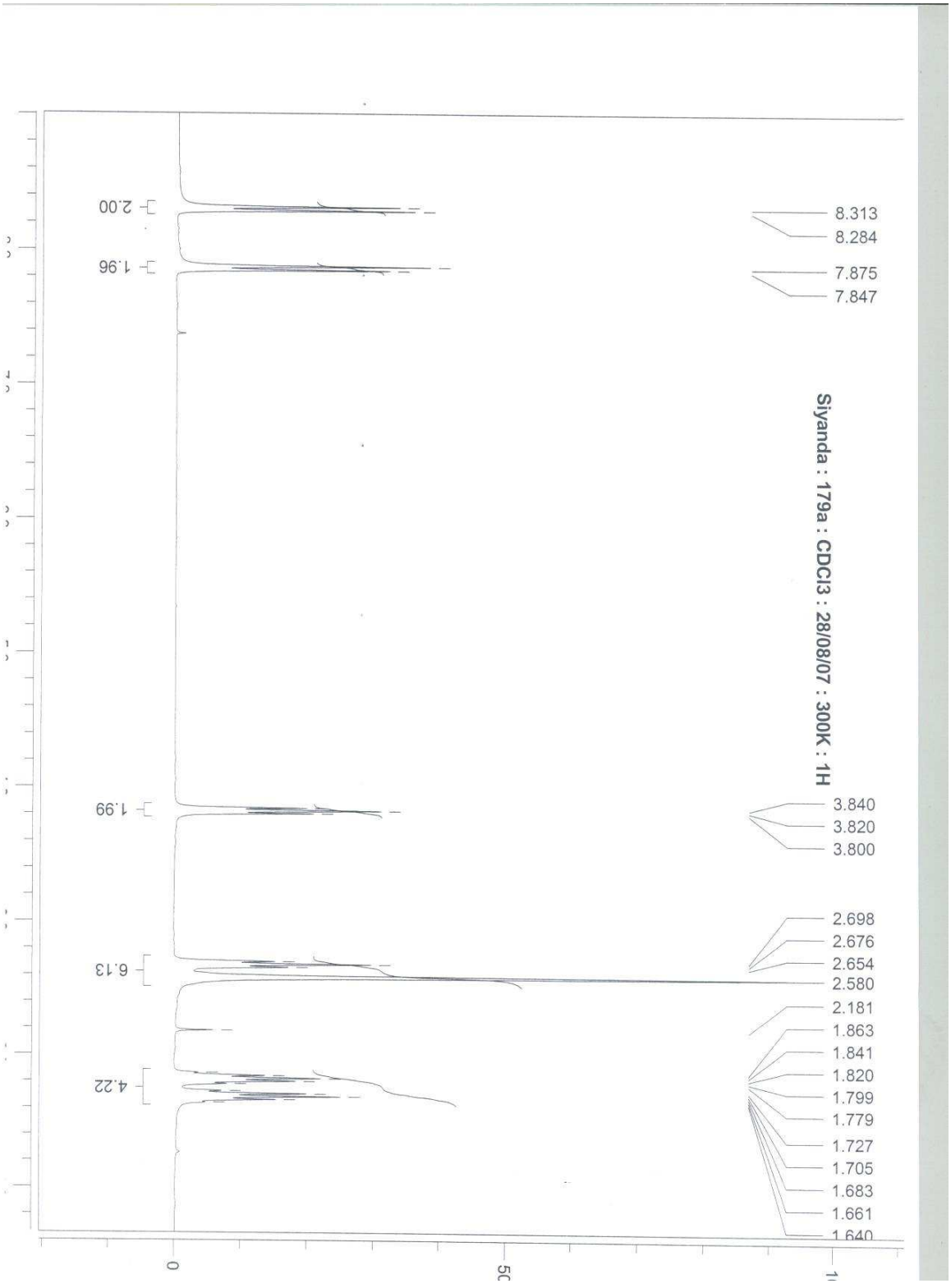
8-(4-Nitrobenzoyl)-2,3,6,7-tetrahydroindolizin-5(1*H*)-one (178a)



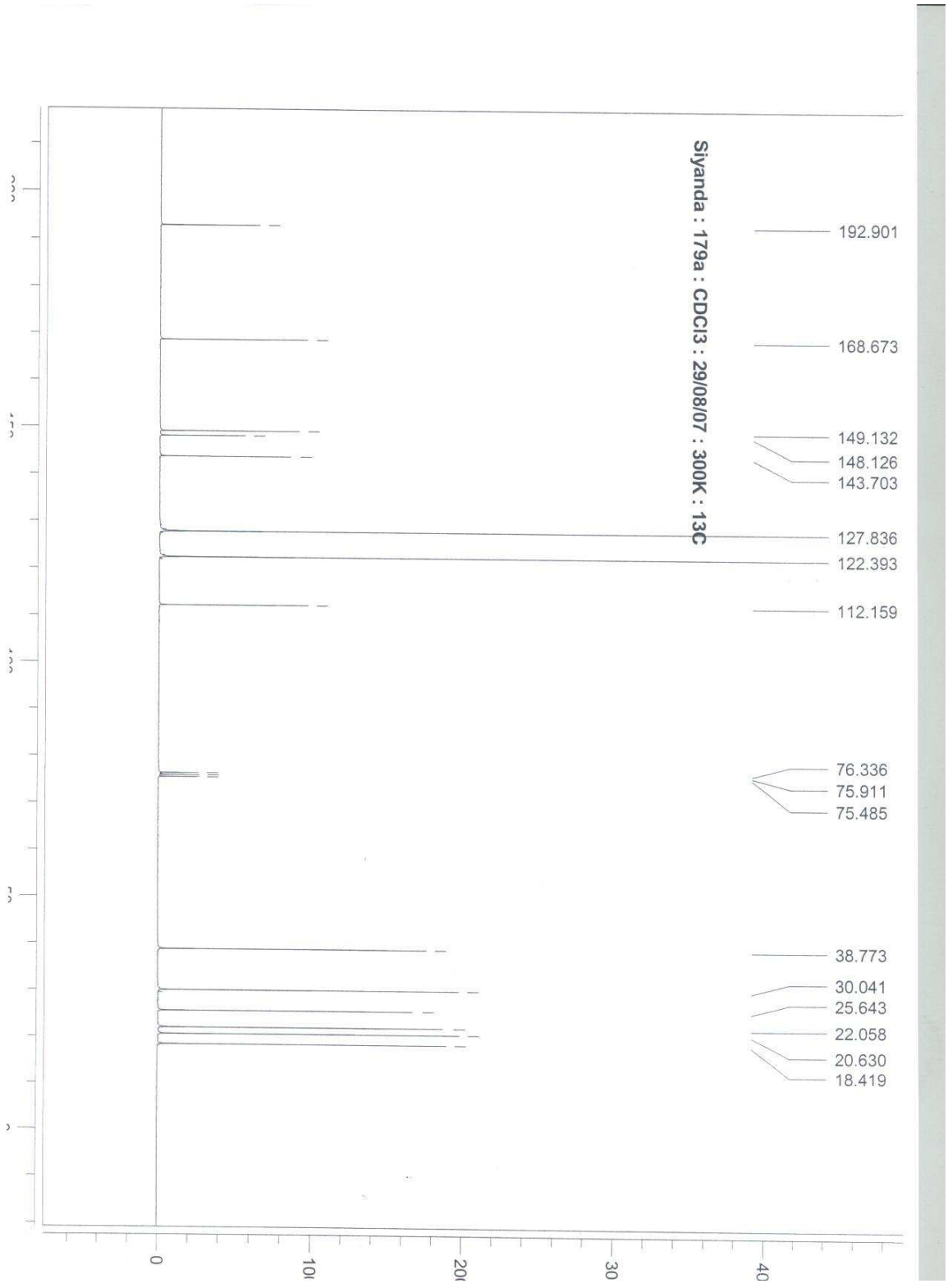
8-(4-Nitrobenzoyl)-2,3,6,7-tetrahydroindolizin-5(1*H*)-one (178a)



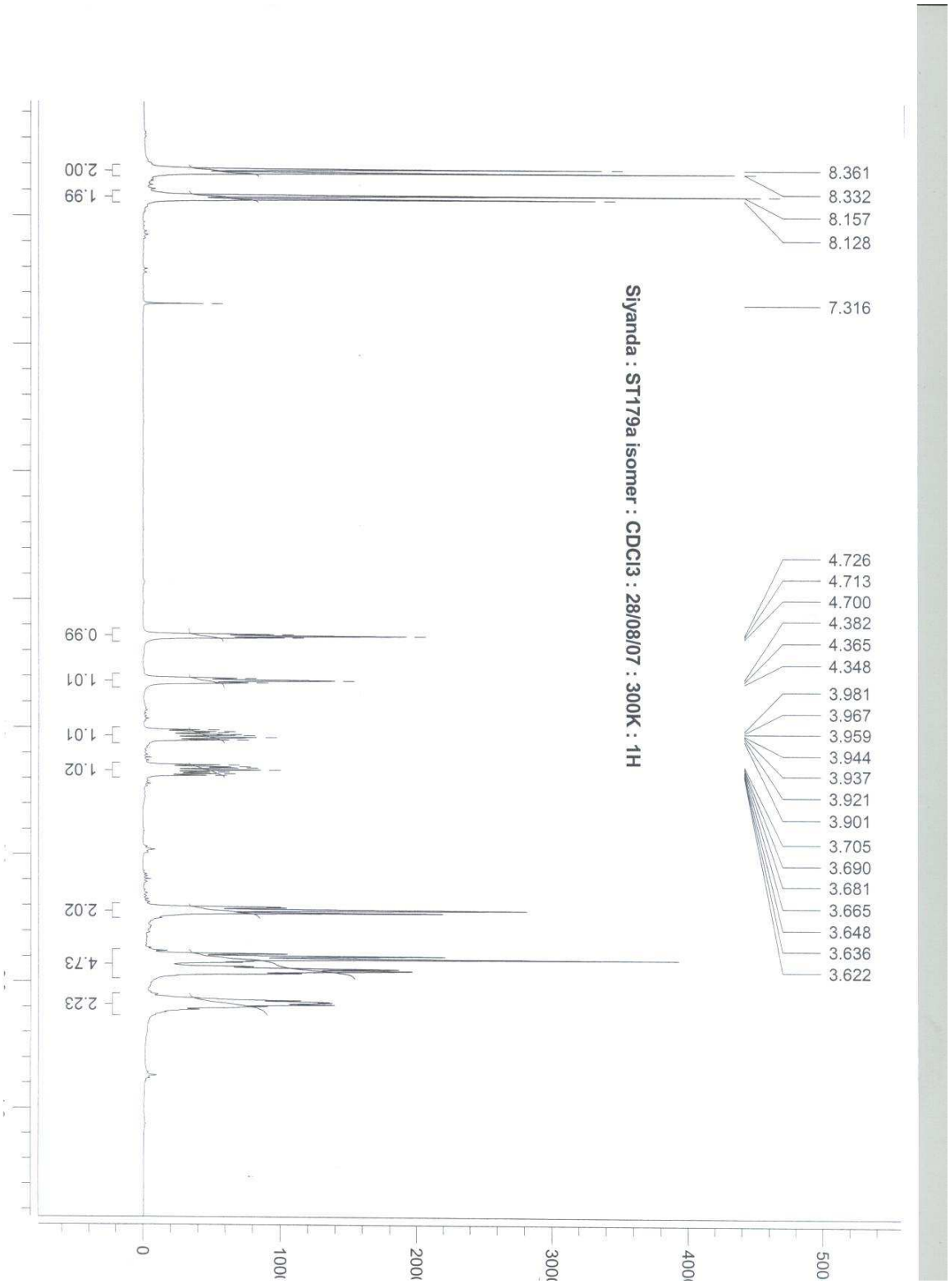
1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one (179a)



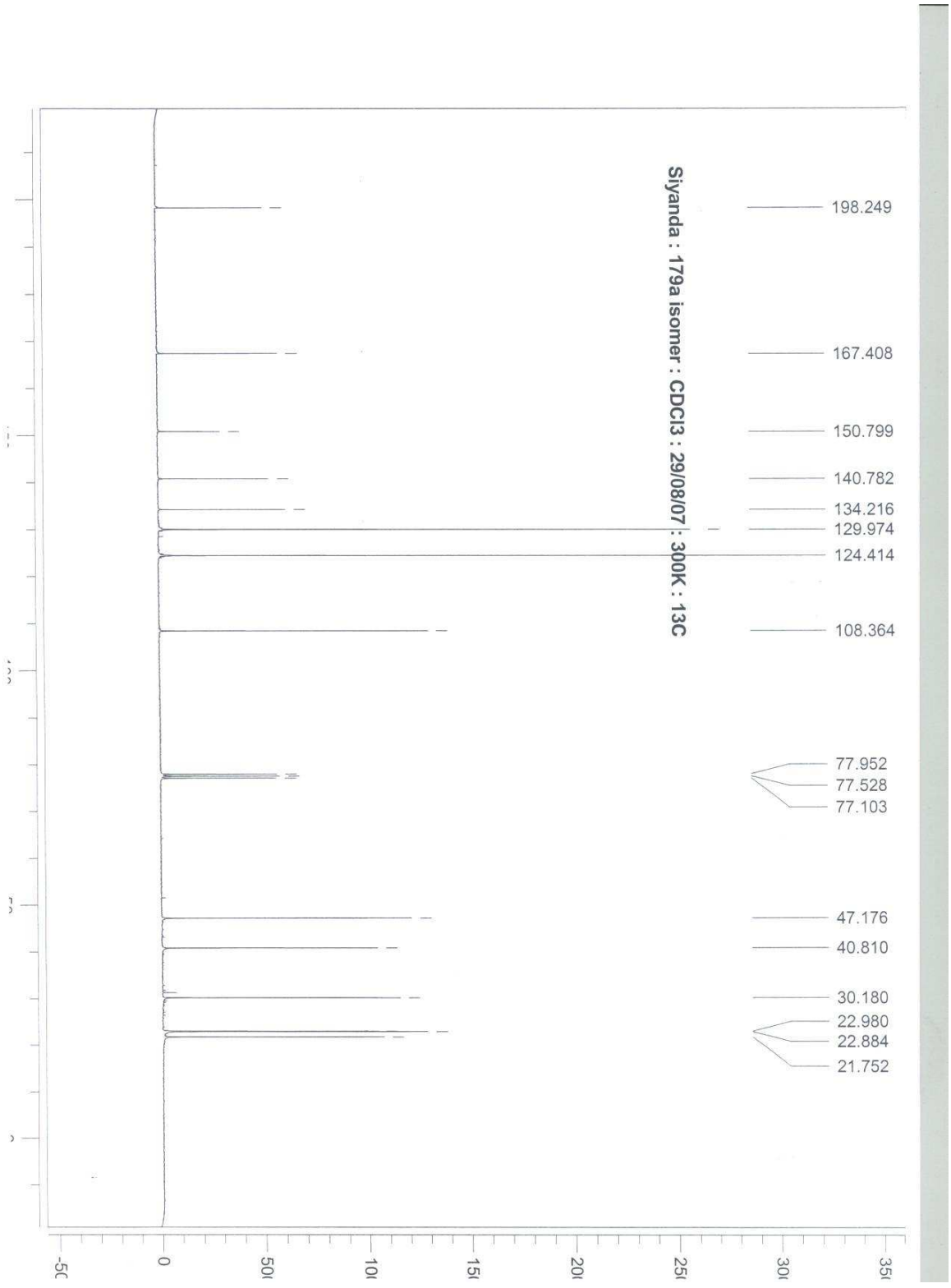
1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one (179a)



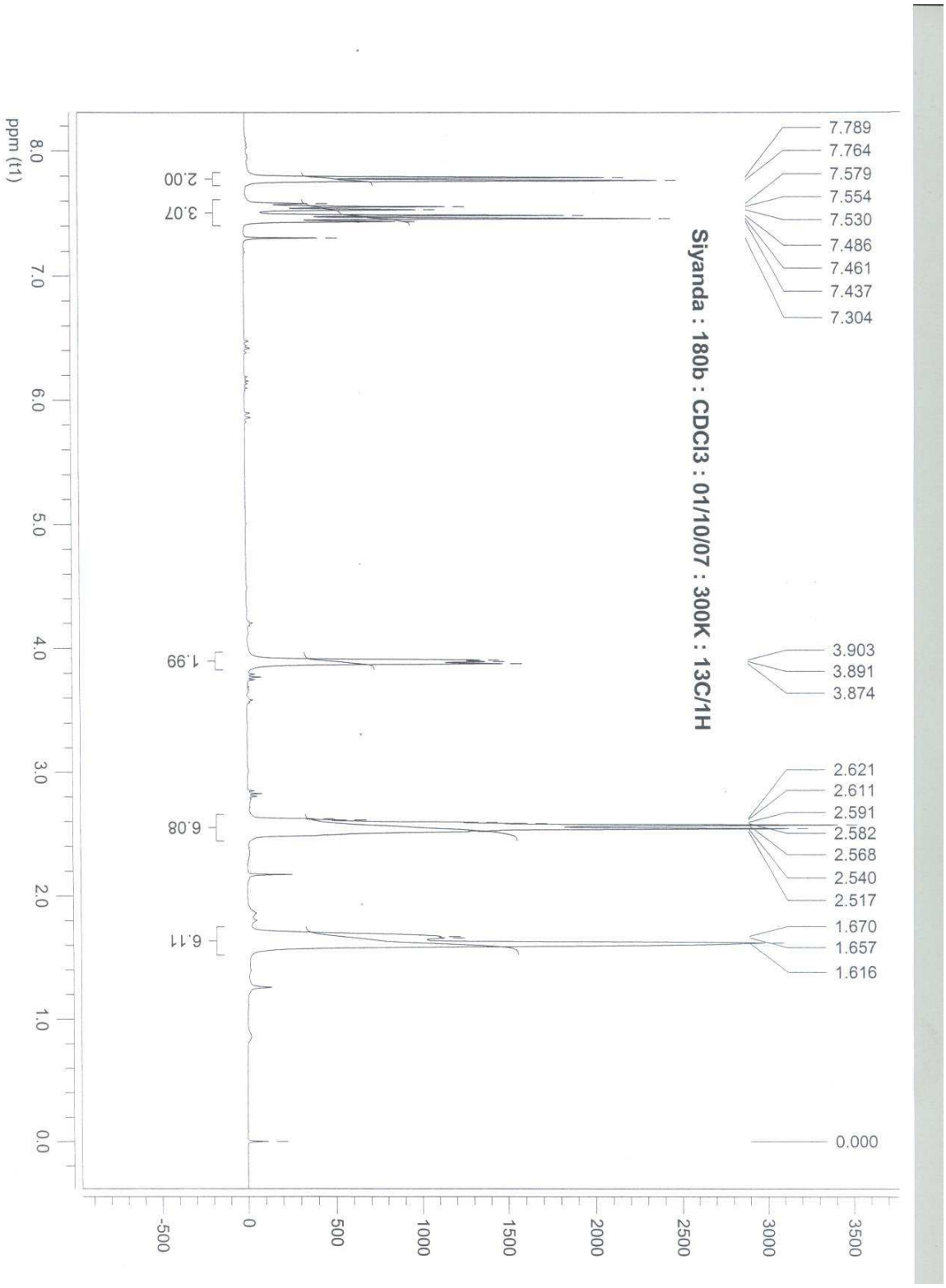
1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one (179a) (isomer?)



1-(4-Nitrobenzoyl)-2,3,6,7,8,9-hexahydroquinolizin-4-one (179a) (isomer?)



1-Benzoyl-2,3,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-4(6*H*)-one (180b)



1-Benzoyl-2,3,7,8,9,10-hexahydropyrido[1,2-*a*]azepin-4(6*H*)-one (180b)

