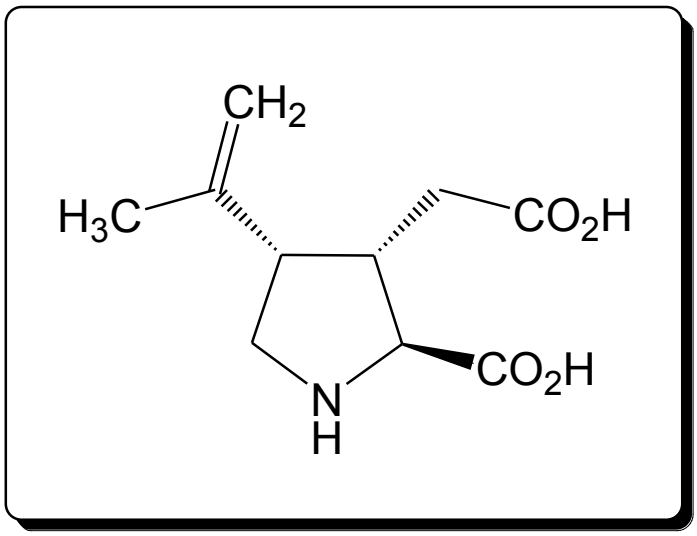
University of Sussex

School of Life Sciences

Department of Chemistry

Studies Towards the Total Synthesis of (-)-α-Kainic Acid



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Master of Philosophy

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I dedicate this thesis to my mum, dad, wife and sister. Without their help and support, I wouldn't never got this far.

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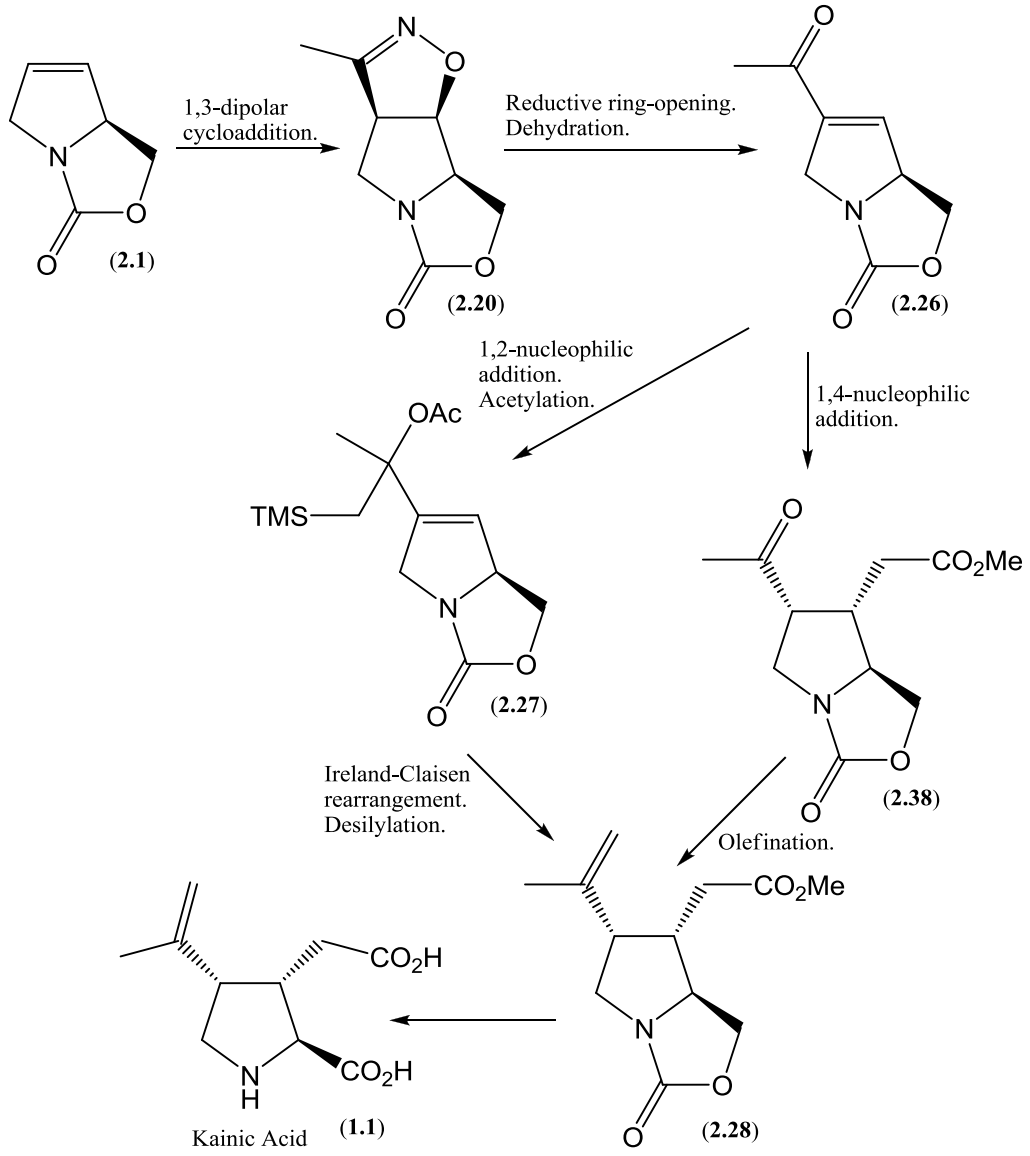
Abstract



trans-4-Hydroxy-L-proline (**2.2**) was converted to a key oxazolidinone precursor (**2.1**) by an improved Greenwood's procedure.[47,48] The diastereofacial selective property of (**2.1**) led to a stereo-controlled 1,3-dipolar cycloaddition and gave a single tricyclic

diastereomer (**2.20**). The N-O bond of the resulting isoxazoline (**2.20**) was cleaved by a reductive ring-opening, followed by an elimination to give enone (**2.26**). The enone (**2.26**) was converted to a *β*-silanol (**2.33**) by a nucleophillic addition with $LiCH_2Si(CH_3)_3$ and then an acetylation to (**2.27**) was attempted.

Addition of Gilman reagent to the enone (**2.26**) resulting a diastereoselective 1,4-nucleophillic addition and afforded the C-2,C-3 *trans*, C-3,C-4 *cis* sterically favoued bicyclic pyrrolidine (**2.38**) as the only diastereomer. All that remains for the synthesis of kainic acid (**1.1**) are olefination, ring-opening of carbamate, oxidation and deprotection.

Abbreviations

Ac…….……..……. acetyl

Aq……..……...…… aqueous

Ar…….……... aromatic

Bn……..……..benzyl

Boc……...……. *tert*-butoxycarbonyl

b.p…….…… boiling point

Bz …….……...…… benzoyl

Bu……..……..…..… butyl

^{n}Bu…… butyl

^{t}Bu…….....… *tert*-butyl

cat…….……..……. catalytic

Cbz……..……benzyloxycarbonyl

cm……. centimetre

conc……..……. concentrated

*m*CPBA…… *meta*-chloroperbenzoic acid

Cy…….……... cyclohexyl

DAST……..…….……. diethylamino sulfurtrifluoride

DBU …….……...… 1,8-diazobicyclo[5.4.0]undec-7-ene

DCM…….…….. dichloromethane

DIBAL-H ……..... di-*iso*-butylaluminium hydride

DMAP ……..... 4-dimethylaminopyridine

DMDO…….dimethyl dioxirane

DME ……. dimethoxyethane

DMF ……. *N,N*-dimethylformamide

DMSO……...……..……. dimethylsulfoxide

EI^+…….……..……. electron impact

ESI ……..……. electrospray ionization

Et……..…. ethyl

Ether…….……. diethyl ether

equiv…….….. equivalents

FTIR……...…….....…..... Fourier transform infrared spectroscopy

g……...……..…… gram(s)

h..……..…….. hour(s)

HRMS……...……..... high resolution mass spectrometry

M ……. molar

Me……..…… methyl

MeOH……...…….. methanol

min……...……..…. minute(s)

mol……...…… mole

mmol……..…… millimole

m.p……..... melting point

Ms …….. methanesulfonyl

M.S……....…. molecular sieves

MW…….…….. molecular weight

NCS……..…….. *N*-chlorosuccinimide

NMR…….…..… nuclear magnetic resonance

NMO……..*N*-Methylmorpholine *N*-oxide

n.Ö.e……. nuclear Överhauser enhancement

Nu^-……...……... nucleophile

Petrol……..…….……... 40-60^oC petroleum

Ph…….….. phenyl

ppm……..... parts per million

PTSA……...……...…….. *para*-toluenesulfonic acid

^{i}Pr ……..…….….. *iso*-propyl

pyr……..….. pyridine

Rf……..…… retention factor

rt ……... room temperature

SM ……..… starting material

TFA……..... trifluoroacetic acid

TFAA…….…... trifluoroacetic anhydride

THF…….……. tetrahydrofuran

TLC……..……...…… thin layer chromatography

TMANO……Triethylamine *N*-oxide

TMS……..... trimethylsilyl

Tol……..……... toluene

Ts……..……. tosyl

Acknowledgements

Firstly, I would like to offer my special appreciation to Professor Phil Parsons for his supervision and support whilst I was carrying research at the University of Sussex. He has provided me with the opportunity, not only to carry out this M.Phil degree, but also an invaluable experience in my life, which will be very important for my future. I will always feel grateful to converse with him as a friend.

I must also give my gratitude to Dr. Clive Penkett for his help and support over the previous years, without his invaluable encouragement and patience, I would never got this far. I also appreciate his friendly treats either inside or outside the lab.

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1. Introduction

1.1 Structure and Isolation

(-)-α-Kainic acid (**1.1**) (figure 1.1) (originally known as digenic acid) is a five membered cyclic amino dicarboxylic acid, which consists of a pyrrolidine ring with 3 asymmetric centres – C-2,C-3 & C-4, with the *S*, *S* and *S* or *R* related configuration respectively. Different substituents at C-4 gives rise to a series of the kainoid members (figure 1.2).[1]

(-)-α-Kainic acid (**1.1**) was the earliest kainoid member to be isolated by Murakami in 1953 from the Japanese marine alga *Digenea simplex*[2], together with its C-4 epimer (+)-α-Allokainic acid (**1.2**). It has also been found in the related alga *Centrocerus clavulatum*[3] and in the *Alsidium Helminthocorton* (known as Corsican moss).[4,5] The structure was deduced by Japanese chemistry groups by classical chemical degradation methods in the mid 1950's,[6,7,8]. The stereochemistry of the pyrrolidine ring was deduced by Morimoto in 1955 using chemical studies,[9] and also confirmed by single crystal X-ray analysis.[10,11] Subsequently the absolute stereochemistry was established by Oppolzer and Thirring from their total synthesis of (-)-α-Kainic acid (**1.1**).[12]

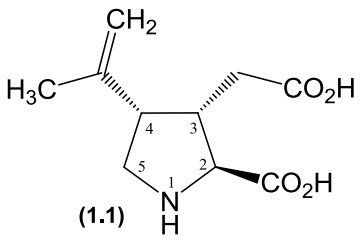
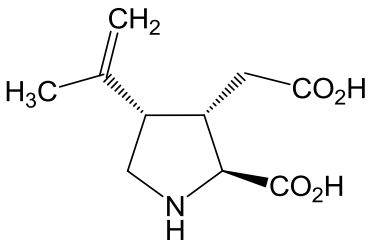
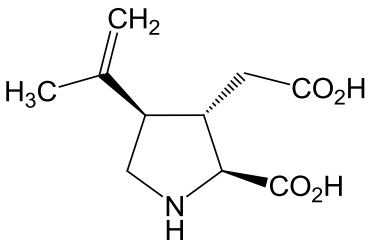


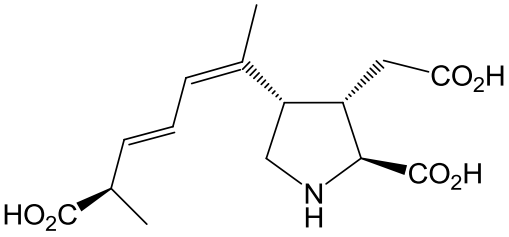
Figure 1.1: (-)-α-kainic acid



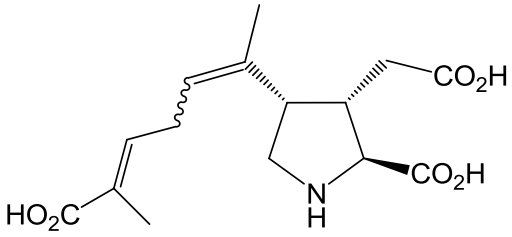
(**1.1**) (-)-α-Kainic acid



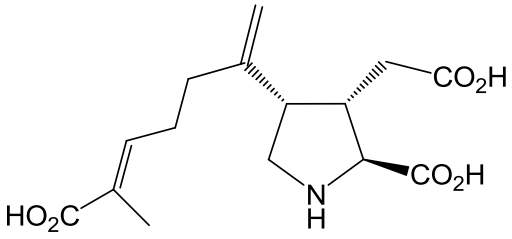
(**1.2**) (+)-α-Allokainic acid



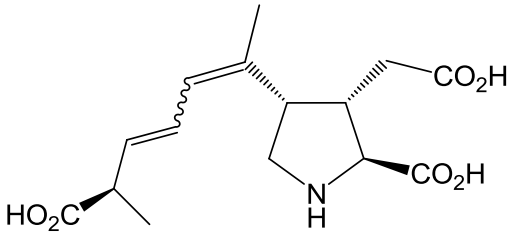
(**1.3**) (-)-a-Domoic acid



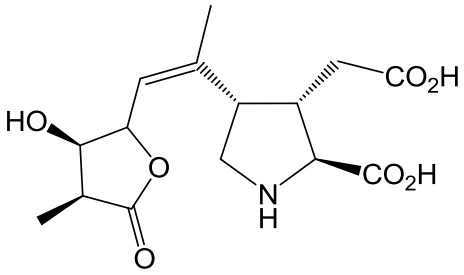
(**1.4**) Isodomoic acid A (*Z*, *E*)
(**1.5**) Isodomoic acid B (*E*, *E*)



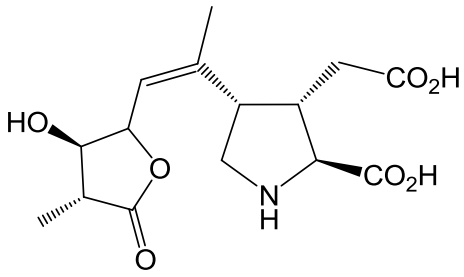
(**1.6**) Isodomoic acid C



(**1.7**) Isodomoic acid D (*Z*, *Z*)
(**1.8**) Isodomoic acid E (*E*, *E*)
(**1.9**) Isodomoic acid F (*E*, *Z*)



(**1.10**) Domoilactone A



(**1.11**) Domoilactone B

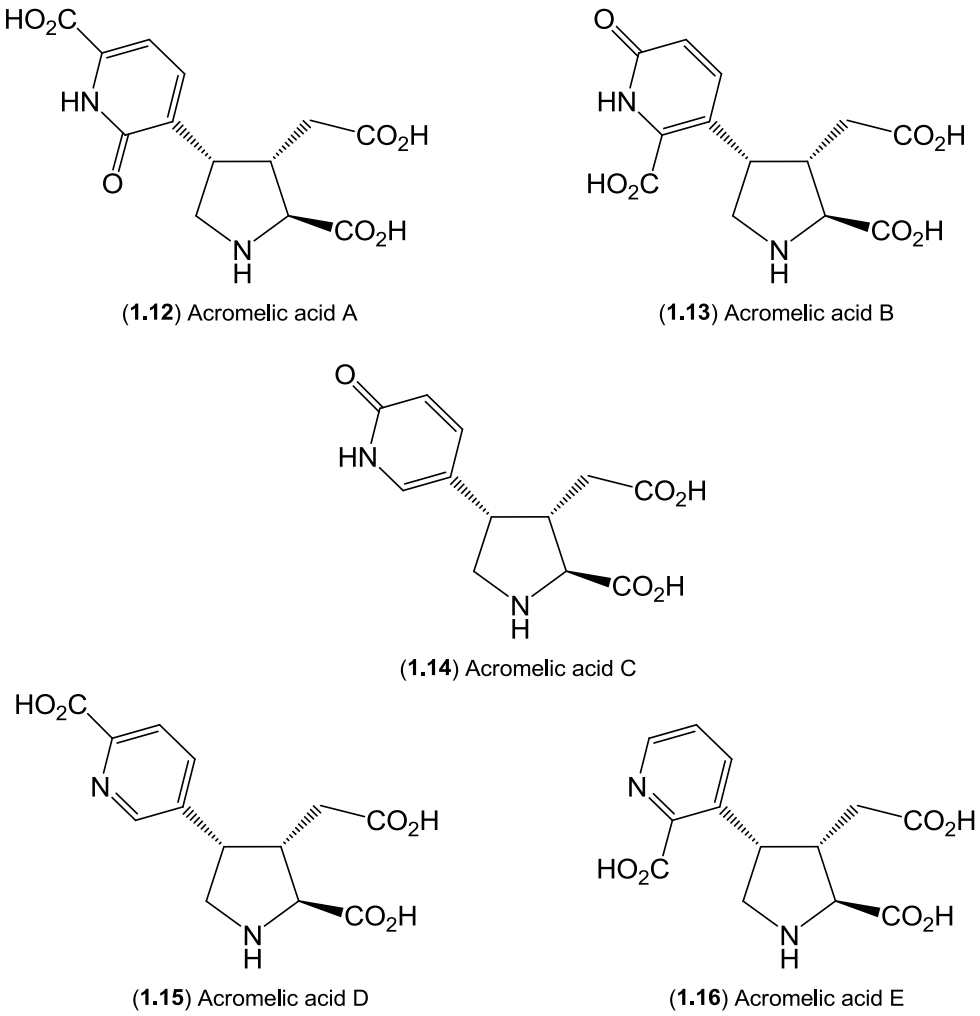


Figure 1.2: Members of Kainoid amino acid.[1]

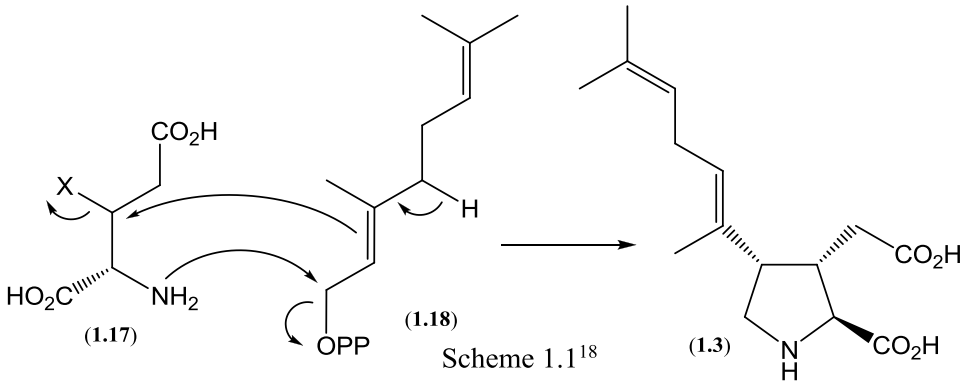
1.2 Biological Properties

Kainoid amino acids have notable insecticidal, anthelmintic and neuroexcitatory properties. Kainic acid (**1.1**) acts as the key active component in the alga *Digenea simplex*, which has been used as an anthelmintic in Japan for more than a thousand years. Its anthelmintic effect is about 10 times more potent than santonin (an anti-ascarid drug).[10] The anthelmintic function of kainic acid (**1.1**) depends on the stereochemistry of the C-3 and C-4 substituents; the anthelmintic effect of allokainic acid (**1.2**) is very weak. The anthelmintic activity of all known stereoisomers of kainic acid (**1.1**) is also very weak compared with (-)-α-kainic acid (**1.1**) itself.[13]

Kainic acid (**1.1**) is used for neuroscience research. The pharmacological effects observed after injection of kainoids is similar to that of patients suffering from neurodegenerative diseases such as epilepsy,[14] Huntington's chorea[15,16] and Alzheimer's disease.[17] In 2000, the price of kainic acid (**1.1**) rose significantly due to shortage of supply.

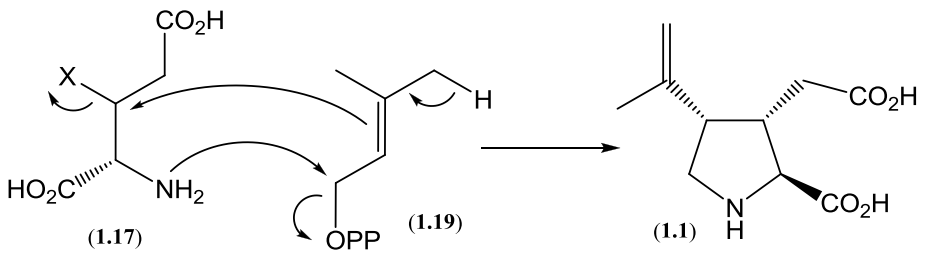
1.3 Biosynthesis

Wright has investigated the biosynthesis pathway of domoic acid (**1.3**),[18] by performing labelling experiments. [1-^{13}C] Acetate and [1,2-^{13}C] acetate proved the pyrrolidine rings of the kainoids were formed by a novel condensation of an isoprenoid unit with a glutamic acid derivative. For instance, domoic acid (**1.3**), is formed by cyclisation of a glutamic acid derivative (**1.17**) (where X is a leaving group), with a geranyl pyrophosphate (**1.18**) (Scheme 1.1).



Scheme 1.1[18]

Wright also suggested kainic acid (**1.1**) was generated in a similar manner (from isopentenyl pyrophosphate (**1.19**) instead of geranyl pyrophosphate (**1.18**)) (Scheme 1.2).[18]



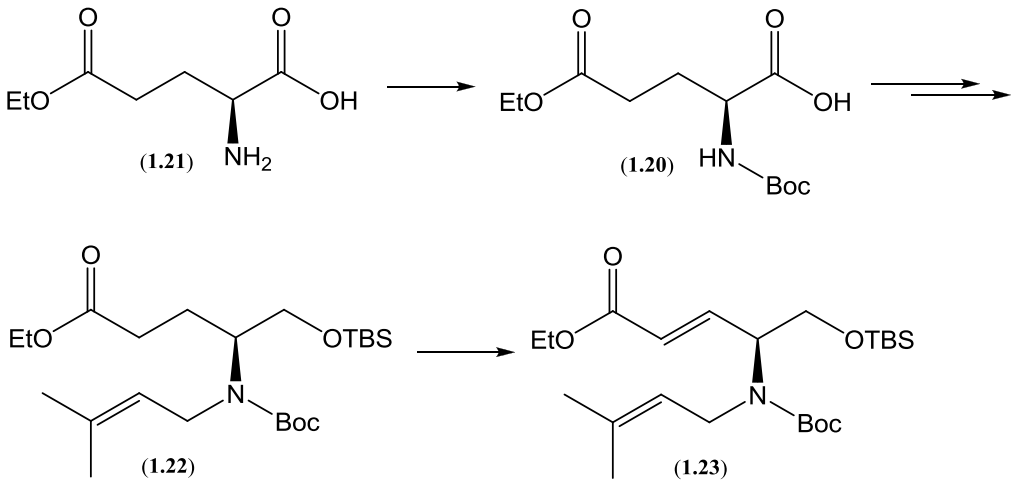
(1.17) (1.19) (1.1)

Scheme 1.2

1.4 Previous Syntheses

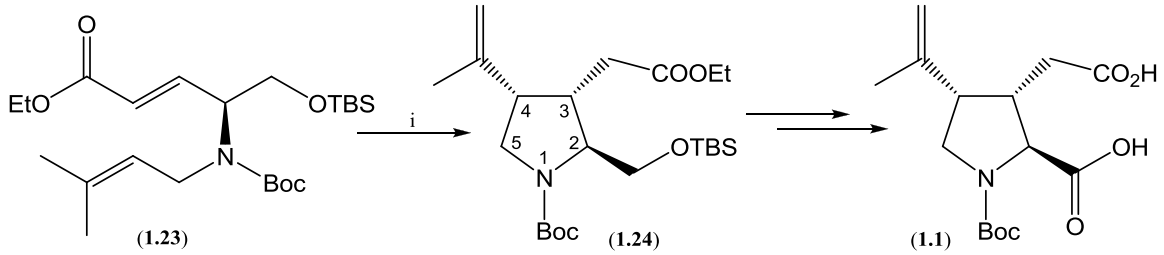
Early syntheses of kainic acid (**1.1**) were inefficient and nonstereoselective,[19,20] the need for stereocontrol of the C-2, C-3 and C-4 of the pyrrolidine makes the synthesis of (-)-α-kainic acid challenging. To date, more than 50 synthetic routes have been developed. Some of these have been reviewed by Parsons.[1] A numbers of these syntheses involved a stereocontrolled intramolecular ene reaction as a key step for the formation of the tri-substituted pyrrolidine framework. Some of the stereocontrolled syntheses will be discussed in this chapter.

The first enantioselective total synthetic route to kainic acid (**1.1**) was developed by Oppolzer and Thirring in 1982.[12] The carbamate (**1.20**) was prepared by Boc protecting commercially available (*S*)-(+)-5-ethyl glutamate (**1.21**). After silylation and alkylation of carbamate (**1.20**), the saturated ester (**1.22**) then eliminated to a 1,6-diene intermediate (**1.23**) (Scheme 1.3).



Scheme 1.3

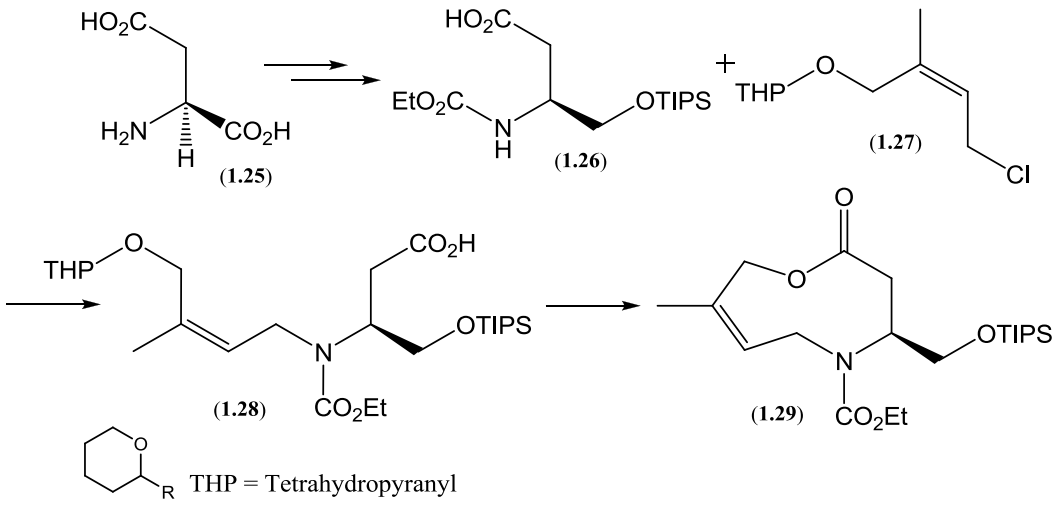
The 1,6-diene intermediate (**1.23**) was then cyclised to a kainoid pyrrolidine skeleton (**1.24**) by an intramolacular ene-reaction, forming a new C-3,C-4 bond. ^{1}H NMR analysis proved the configurations of the isopropenyl group and ethoxy carboyl on C-3 and C-4 were *cis* related. After the removal of the protecting groups and oxidation of the alcohol, the desired (-)-α-kainic acid (**1.1**) was afforded in 5% overall yield from (*S*)-(+)-5-ethyl glutamate (**1.21**) (Scheme 1.4). This remains one of the shortest synthetic routes for kainic acid (**1.1**), with only 6 steps involved.



Reagents: i. Toluene, 140°C, 40hr, 75%

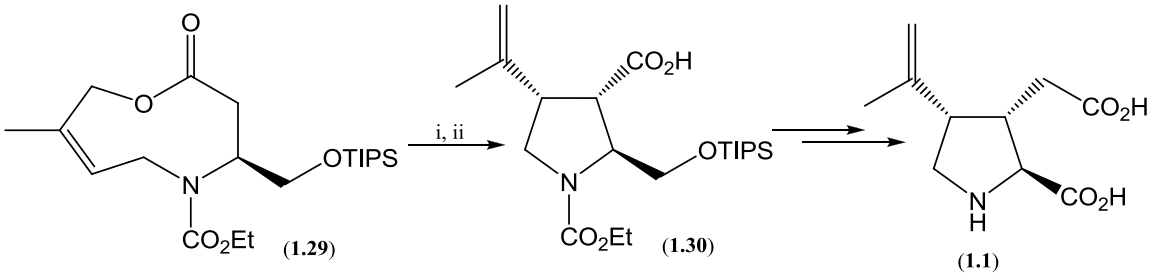
Scheme 1.4

Five years later, Knight and co-workers reported the second total synthetic route to kainic acid (**1.1**).[21,22] L-Aspartic acid (**1.25**) was converted to a protected *β*-amino acid derivative (**1.26**) in five steps, then it was coupled with a tetrahydropyranyl protected chloride fragment (**1.27**) to afford adduct (**1.28**). After removal of the tetrahydropyranyl protecting group and lactonisation, the azalactone precursor (**1.29**) was prepared (Scheme 1.5).



Scheme 1.5

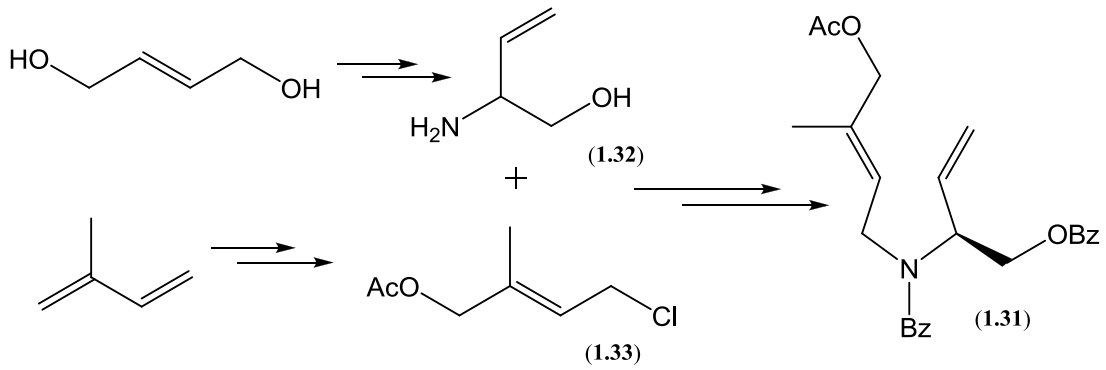
The key Claisen rearrangement step resulted in stereoselective formation of the new C-3,C-4 bond, to afford a tri-substituted pyrrolidine carboxylic acid (**1.30**) in 55% yield, without any other isomers being detected. After carrying out an Arndt-Eistert homologation, desilylation, oxidation and removal of the carbamate, kainic acid (**1.1**) was successfully synthesised (Scheme 1.6).



Reagents: i. LDA, TBSCl, THF, -100 to 20 ^{o}C; ii. K_2CO_3, MeOH/H_2O (55% over 2 steps).

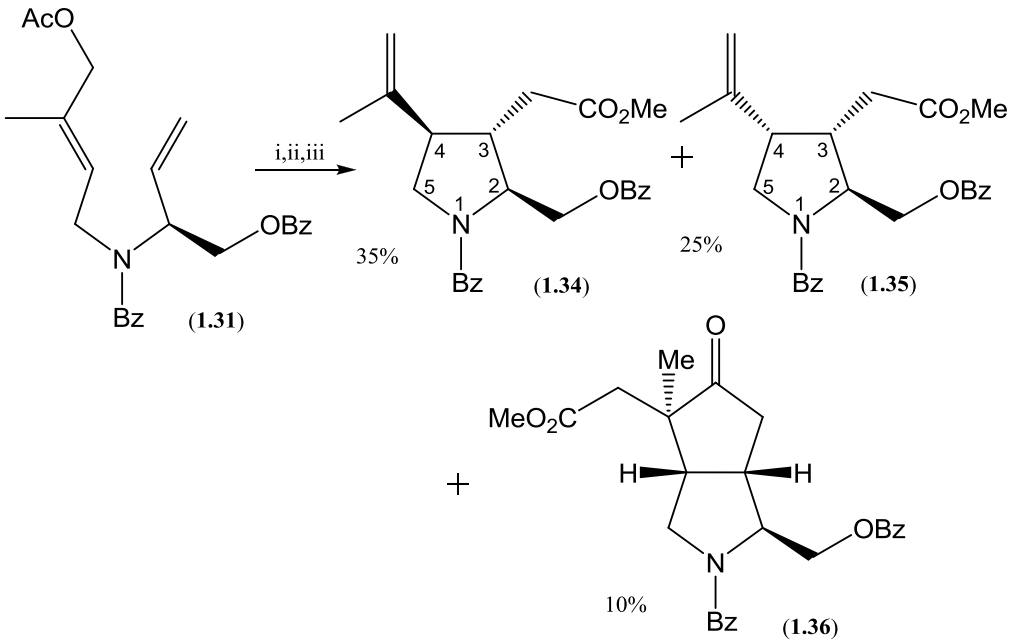
Scheme 1.6

Yoo has developed a synthetic route for kainic acid (**1.1**) which also involved the use of an ene-reaction in 1990.[23] The key vinyl allylic acetate precursor (**1.31**) was prepared by coupling vinylamino alcohol (**1.32**) with allylic chloride (**1.33**), followed by benzoylation (Scheme 1.7).



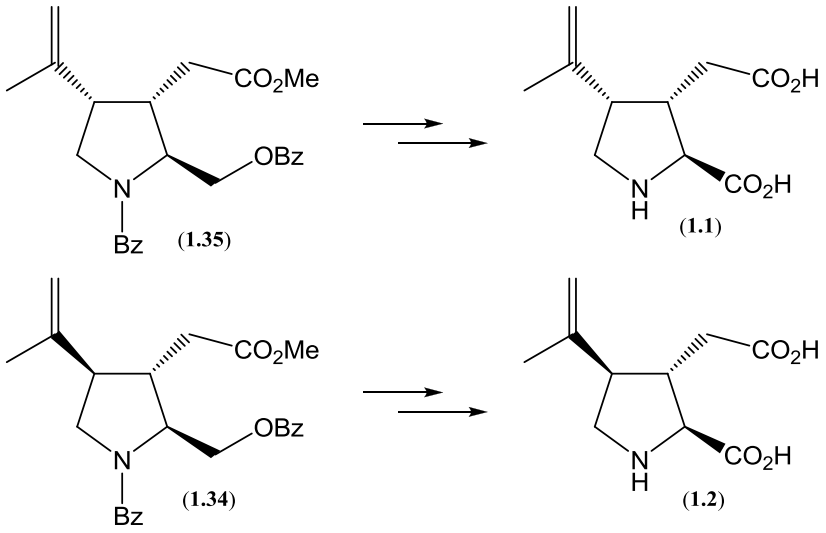
Scheme 1.7

The intramolecular cyclisation of vinyl allylic acetate precursor (**1.31**) and subsequent carbonylation were catalysed by $Pd(dba)_2$, and, after hydrolysis with H_2O and esterification with CH_2N_2, two major pyrrolidine isomers (**1.34**) and (**1.35**) were formed in 35% and 25% yield, respectively (Scheme 1.8). One minor bicyclic product (**1.36**) was also obtained in 10% yield, due to a second cyclisation of the C-3 acyl onto the alkene double bond. After the elaboration of isomers (**1.34**) and (**1.35**), allokainic acid (**1.2**) and kainic acid (**1.1**) were formed respectively (Scheme 1.9).



Reagents: i. $Pd(dba)_2$, CO, PPh_3, acetic acid, 80 ^oC; ii. H_2O; iii. CH_2N_2.

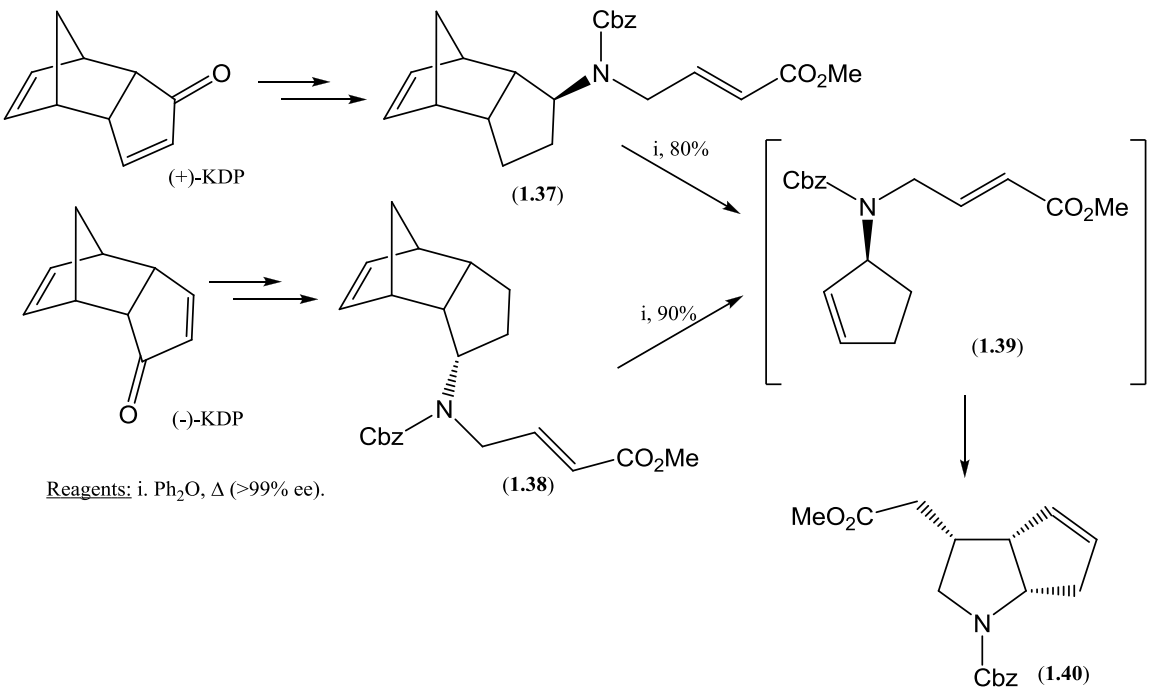
Scheme 1.8



Scheme 1.9

The synthesis of kainic acid developed by Ogasawara also involved the use of an intramolecular ene-reaction.[24] The (+) or (-) - enantiomers of optically pure ketodicyclo-

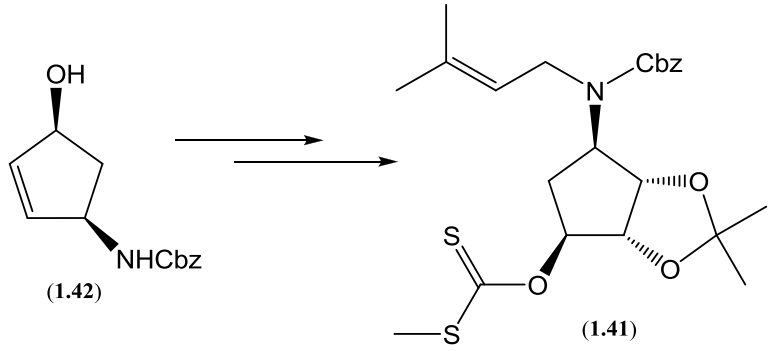
pentadiene (KDP) were used as starting materials for the preparation of the tricyclic precursors (**1.37**) and (**1.38**). A one-pot retro-Diels Alder reaction gave the monocyclic carbamate intermediate (**1.39**) containing a 1,6-diene system which underwent spontaneous conversion to a *cis* trisubstituted pyrrolidine (**1.40**) via an intramolecular ene-reaction under the same conditions (Scheme 1.10). The bicyclic pyrrolidine (**1.40**) was used as a framework for the synthesis of kainic acid (**1.1**).



Scheme 1.10

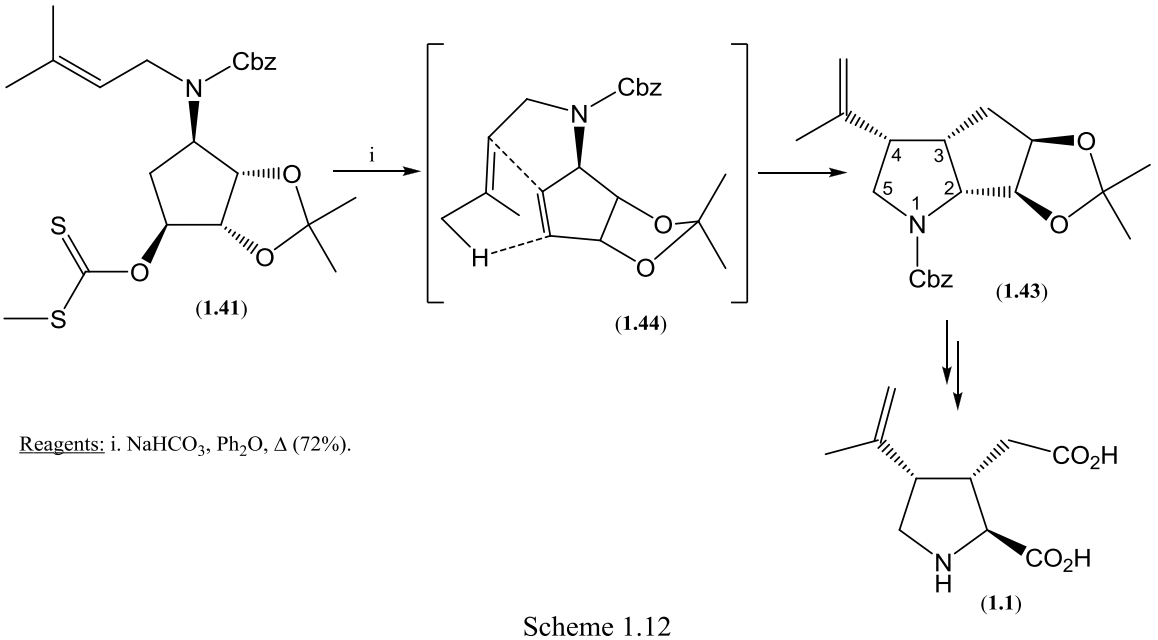
Ogasawara reported another synthesis of kainic acid in 2000,[25] which consisted of a Chugaev *syn*-elimination and intramolecular ene-reaction. The key xanthate precursor

(**1.41**) was prepared from an enantiopure (+)-*cis*-4-carbobenzoxyamino-2-cyclopentenol (**1.42**) in 58% overall yield in six steps (Scheme 1.11).



Scheme 1.11

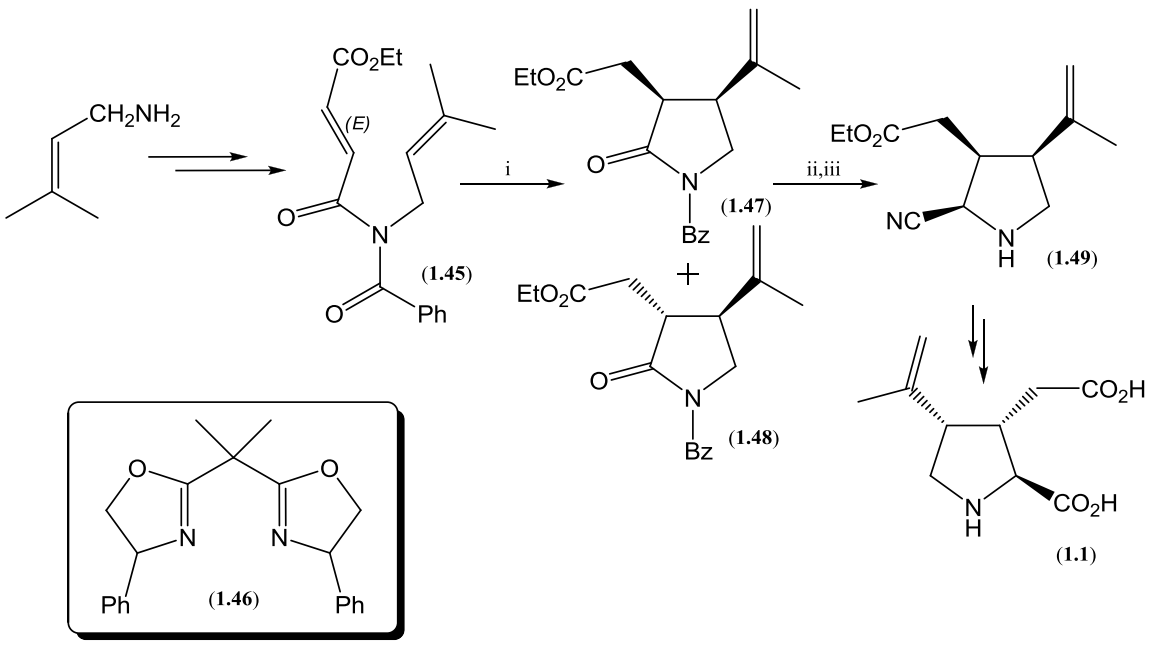
Then the xanthate (**1.41**) was converted to a trisubstituted pyrrolidine (**1.43**) by employing a Chugaev *syn*-elimination and intramolecular ene-reaction via the transient 1,6-diene intermediate (**1.44**) in one-pot. N.Ö.e experiments proved that only one diastereomer had been formed and all substituents on C-2, C-3 and C-4 were *cis* related. After elaboration of the pyrrolidine framework (**1.43**), kainic acid (**1.1**) was obtained in 13% overall yield from alcohol (**1.42**) (Scheme 1.12).



Reagents: i. $NaHCO_3$, Ph_2O, Δ (72%).

Scheme 1.12

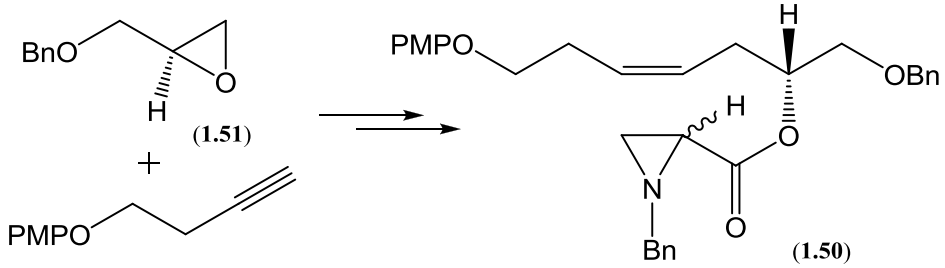
Ganem has developed a total synthesis of kainic acid (**1.1**) which involves the use of an asymmetric,[26] magnesium bis-oxazoline catalyzed ene-cyclisation as a key step for the construction of the pyrrolidine framework. Pure stereoisomer 1,6-diene (**1.45**) was prepared from *N*-prenylamine in two steps and the intramolecular ene-cyclisation of (**1.45**) in the presence of ligand (**1.46**) occurred with high diastereoselectivity, favouring pyrrolidine (**1.47**) over its *trans* isomer (**1.48**) (>20:1). The mixture of pyrrolidine (**1.47**) and (**1.48**) was then hydrolysed and converted to nitrile (**1.49**) by using Schwartz's reagent and nitrilation. After the hydrolysis of both nitrile and ester, followed by epimerization with base, kainic acid (**1.1**) was afforded in a high overall yield exceeding 20% (Scheme 1.13).



Reagents: i.$Mg(ClO_4)_2$, CH_2Cl_2 (72%); ii. Cp_2ZrHCl, THF. iii. TMSCN, CH_2Cl_2 (70% over 2 steps).

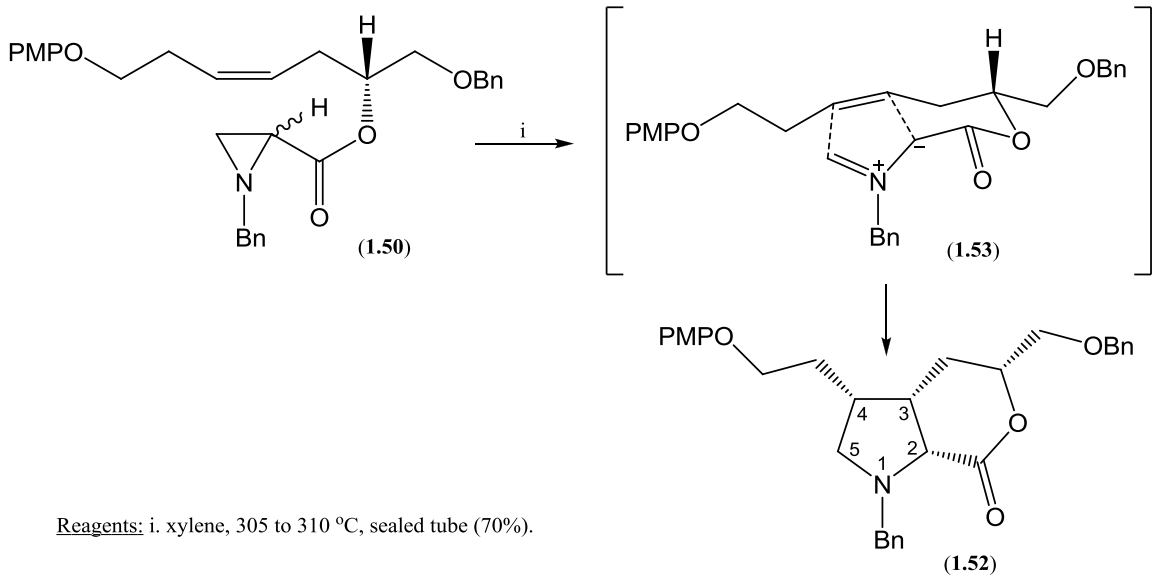
Scheme 1.13

Takano has shown great interest in the synthesis of kainic acid by developing a total of four enantioselective approaches. The first synthetic approach involved an enantio- and diastereo-selective intramolecular 1,3-dipolar cyclisation as a key step.[27] The key aziridine ester precursor (**1.50**) was prepared from (*S*)-2-(benzyloxymethyl)oxirane (**1.51**) in 4 steps (Scheme 1.14).



Scheme 1.14

The intramolecular 1,3-dipolar cyclisation was performed by heating the aziridine ester precursor (**1.50**) in xylene at 310 ^{o}C for 5 min, to give the bicyclic pyrrolidine (**1.52**) with all *cis* configuration. The authors postulate that the ylid adopts conformation (**1.53**), placing the benzyloxymethyl substituent in a pseudoequatorial orientation (Scheme 1.15).



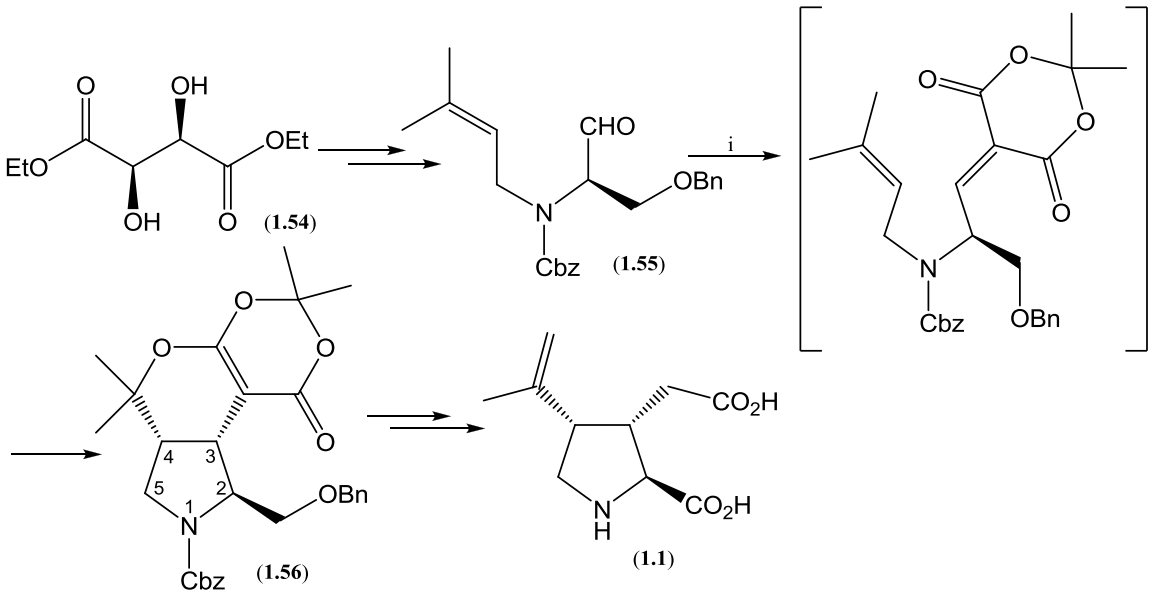
Reagents: i. xylene, 305 to 310 ^{o}C, sealed tube (70%).

Scheme 1.15

Following further elaboration of pyrrolidine (**1.52**) including the epimerisation at C-2 by using base, kainic acid (**1.1**) was prepared.

In the same year, Takano reported the second synthesis of kainic acid (**1.1**).[28] Starting from diethyl L-tartrate (**1.54**) to generate the aldehyde (**1.55**) key precursor, followed by a diastereoselective intramolecular Diels-Alder reaction to give the tricyclic adduct (**1.56**) with *cis* C-3/C-4 juncture, caused by the carbamate sp^2-like planar configuration at

nitrogen allowing [4π+2π] overlap only in the *endo* conformation. After elaboration to the tricyclic pyrrolidine (**1.56**), kainic acid (**1.1**) was achieved (Scheme 1.16).

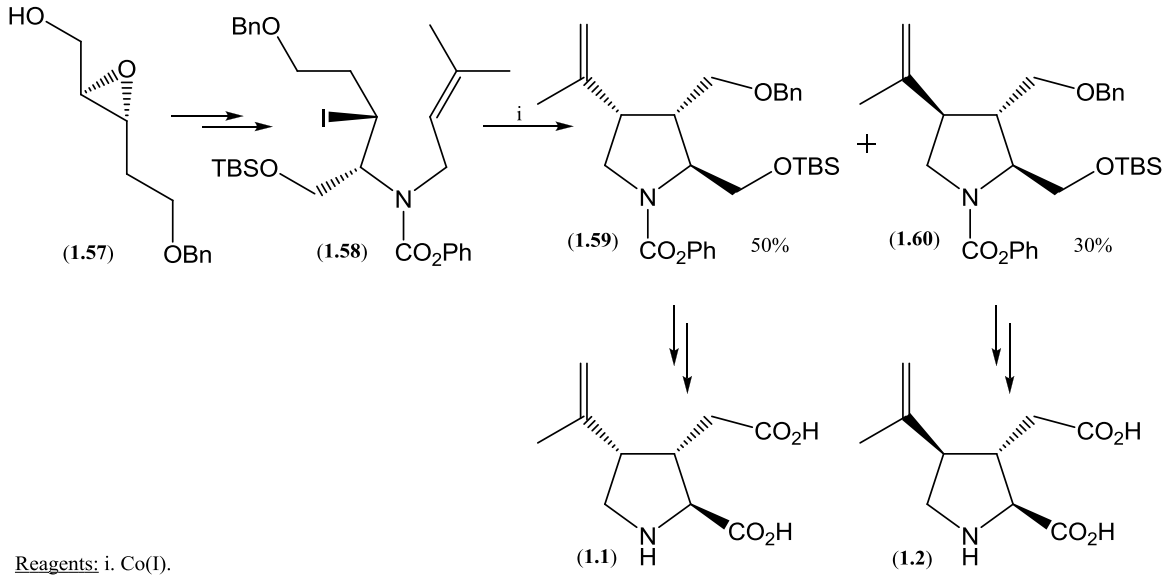


Reagents: i. Meldrum's acid, $(CH_2NH_3)_2{\cdot}2AcO^-$, 0°C to r.t.

Scheme 1.16

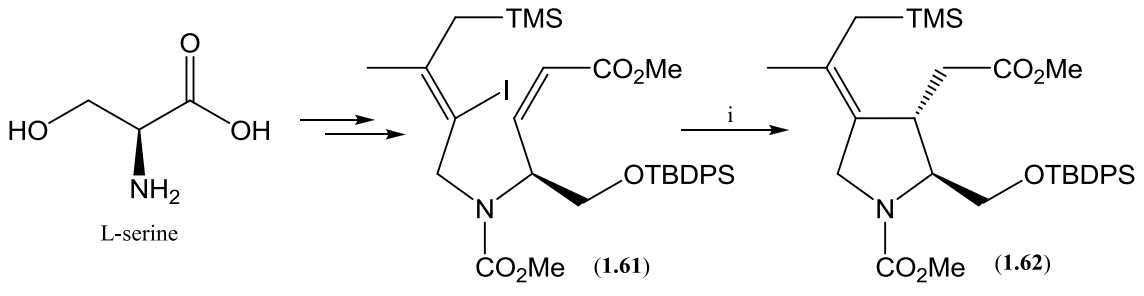
Baldwin has developed a synthetic route to kainic acid (**1.1**) based on a cobalt-mediated cyclisation as a key step,[29] for the stereoselective construction of the pyrrolidine structure. Starting from epoxide (**1.57**) (which is readily accessible through the corresponding allylic alcohol by the Sharpless epoxidation) convertion to the key acyclic iodide precursor (**1.58**) was carried out in six steps.[30,31] Carrying out a cobaloxime mediated cyclisation on (**1.58**) led to the formation of a novel C-3,C-4 bond, which gave the separable stereoisomers (**1.59**) and (**1.60**) in a 50% and 30% yield respectively. Both pyrrolidine frameworks (**1.59**) and (**1.60**) were deprotected then oxidised to give (-)-α-

kainic acid (**1.1**) and (+)-allokainic acid (**1.2**) respectively (Scheme 1.17).



Scheme 1.17

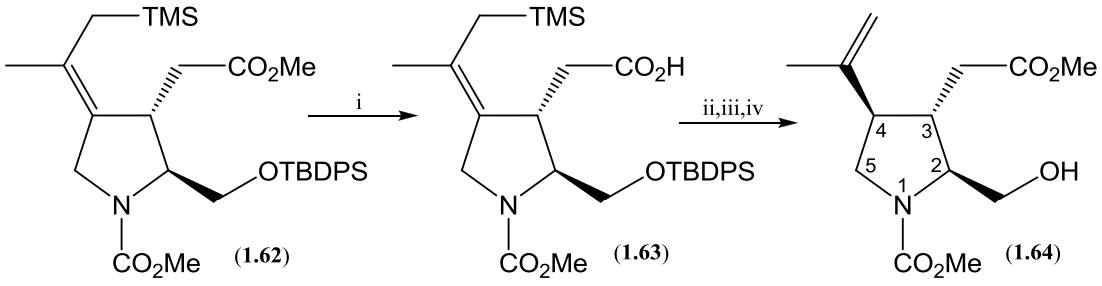
In 1993, Takano also reported a synthetic route for both kainic acid (**1.1**) and allokainic acid (**1.2**).[32] This synthesis employed a radical based enantioselective cyclisation to construct the C-3,C-4 bond of the pyrrolidine ring. The key vinyl iodide precursor (**1.61**) was obtained from L-serine. A highly diastereoselective radical intramolecular cyclisation of the precursor (**1.61**) using tributyltin hydride and AIBN led to the formation of pyrrolidine (**1.62**) in an excellent yield of 86% (scheme 1.18).



Reagents: i. Bu_3SnH, AIBN, C_6H_6, Δ (86%).

Scheme 1.18

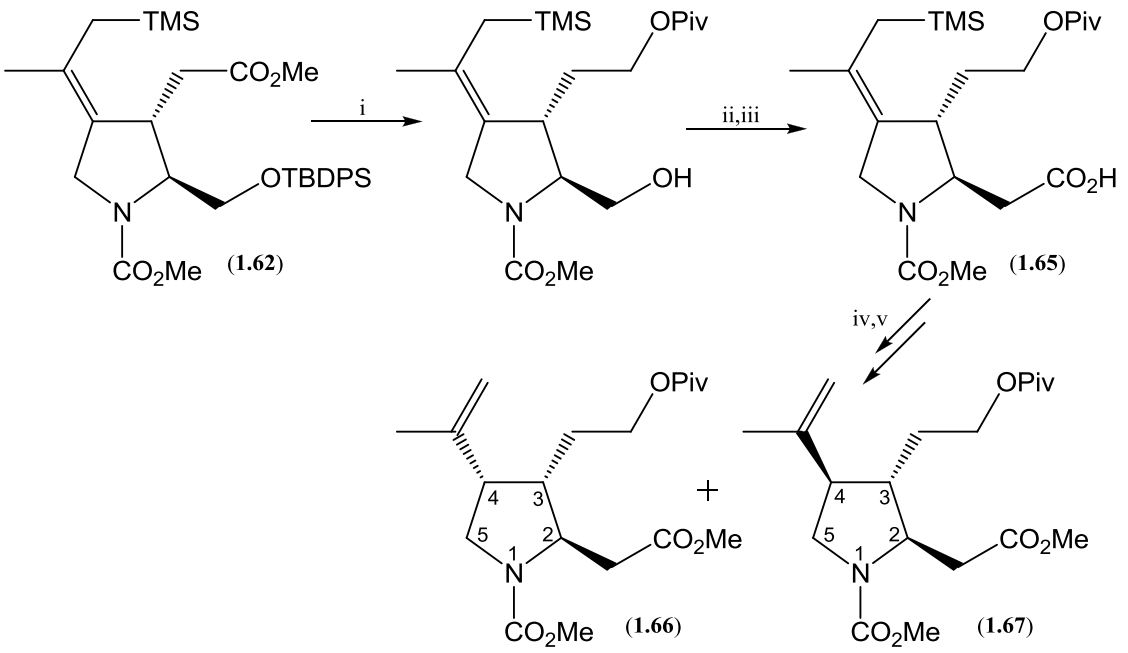
After the hydrolysis of pyrrolidine (**1.62**), carboxylic acid (**1.63**) was then treated with $BF_3{\cdot}OEt_2$ in dichloromethane, when concommitant C-3 directed intramolecular protodesilylation, methylation and deprotection led to a single diastereomer (**1.64**) , an allokainic acid precursor, in 57% yield (Scheme 1.19).



Reagents: i. 5% KOH, MeOH; ii. $BF_3{\cdot}OEt_2$, CH_2Cl_2; iii. CH_2N_2, Et_2O; iv. HF, MeCN

Scheme 1.19

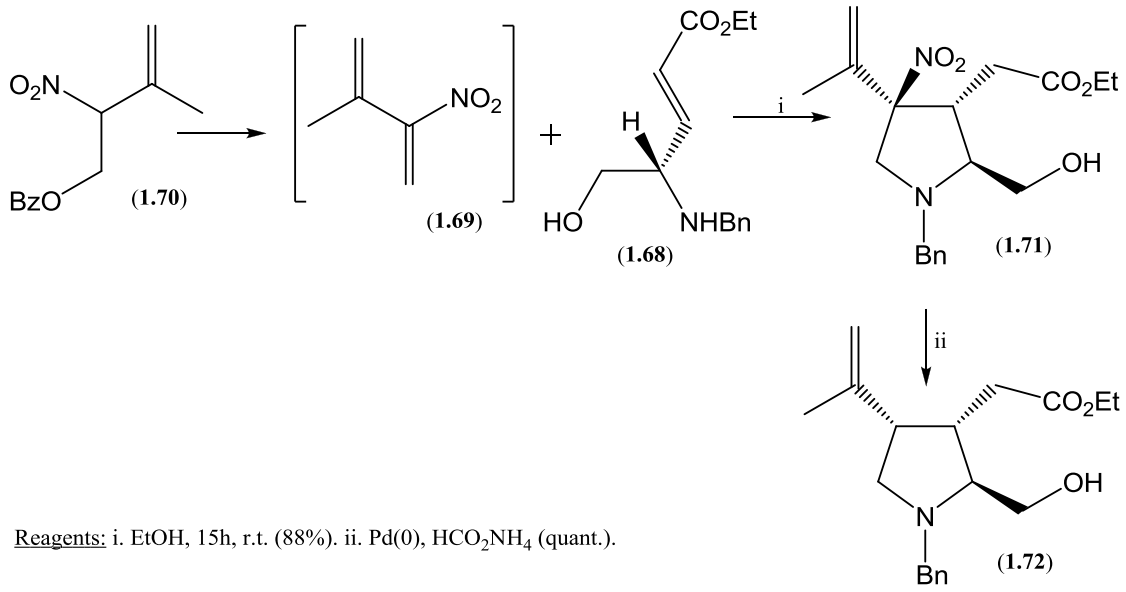
Pyrrolidine (**1.62**) was elaborated to carboxylic acid (**1.65**) and treatment with $BF_3{\cdot}OEt_2$ in dichloromethane similarly led to a C-2 directed intramolecular proto-desilylation. After methylation, the kainic acid precursor (**1.66**) was prepared in 58% yield (together with its C-4 epimer (**1.67**) in 11%). (Scheme 1.20)



Reagents: i. (a) diisobutylaluminium hydride (DIBAL), CH_2Cl_2, -78 °C, (b) Bu^{t}COCl, Et_3N, DMAP (catalyst), CH_2CI_2, (c) 46% HF, MeCN. ii. $(COCl)_2$, DMSO, CH_2Cl_2, -60 °C then Et_3N. iii. $NaClO_2$, $NaHPO_4$, CH_2=C(CH_3)CH_2CH_3. iv. BF_3·OEt_2, CH_2Cl_2. v. CH_2N_2, Et_2O

Scheme 1.20

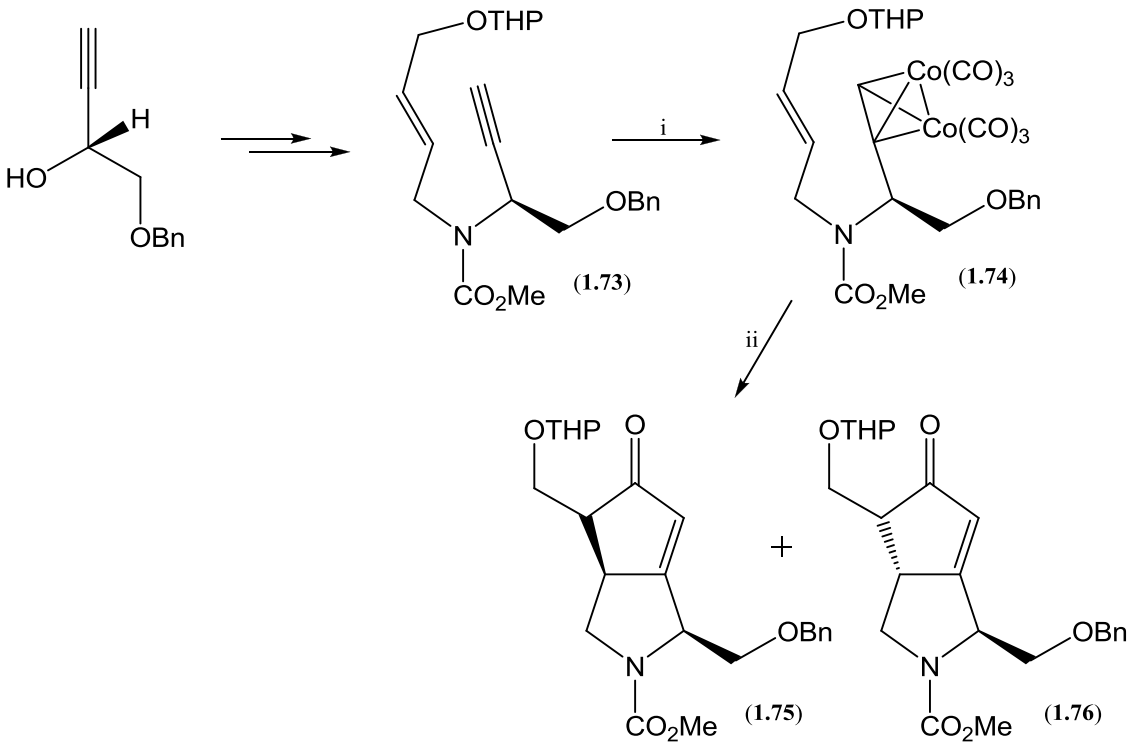
Benetti developed a synthetic route for kainic acid in 1991,[33] which involved the construction of the pyrrolidine C-3 and C-4 bond by tandem Michael reactions. By cyclising a secondary amine (**1.68**) (which was generated from D-serine) with an electron-withdrawing diene (**1.69**) generated from the nitro compound (**1.70**) *in situ*, a trisubstituted pyrrolidine adduct (**1.71**) with a *trans* C-2,C-3 and *cis* C-3,C-4 configuration was formed in 88% yield. The allylic nitro group was removed regio- and stereo- selectively by a hydride transfer reaction with a palladium(0) catalyst developed by Ono, to give kainic acid precursor (**1.72**) in quantitative yield (Scheme 1.21).[34]



Reagents: i. EtOH, 15h, r.t. (88%). ii. Pd(0), HCO_2NH_4 (quant.).

Scheme 1.21

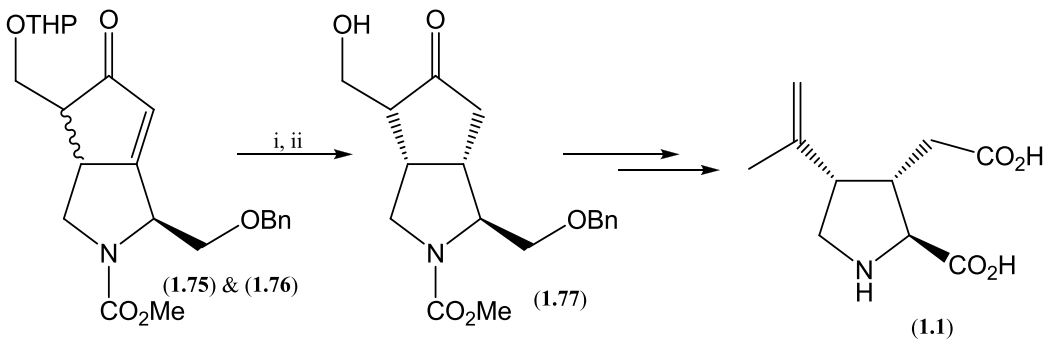
An enantioselective route to kainic acid (**1.1**) involving a Pauson-Khand reaction as the key step was developed by Takano in 1993.[35] (*R*)-4-Benzyloxy-1-butyn-3-ol was converted to the tertiary carbamate (**1.73**) in four steps. Treatment of (**1.73**) with dicobalt octacarbonyl gave the cobalt complex (**1.74**). Treatment of (**1.74**) with *N*-methylmorpholine *N*-oxide (NMO) gave the bicyclic enones (**1.75**) and (**1.76**) as an inseparable mixture in 85% yield. After reduction and removal of the THP group to form the mixture (**1.75**) and (**1.76**) (Scheme 1.22), the desired bicyclic adduct (**1.77**) was formed in 60% yield.



Reagents: i. $Co_2(CO)_8$, C_6H_6; ii. NMO, CH_2Cl_2, 0 ^oC (85% over 2 steps).

Scheme 1.22

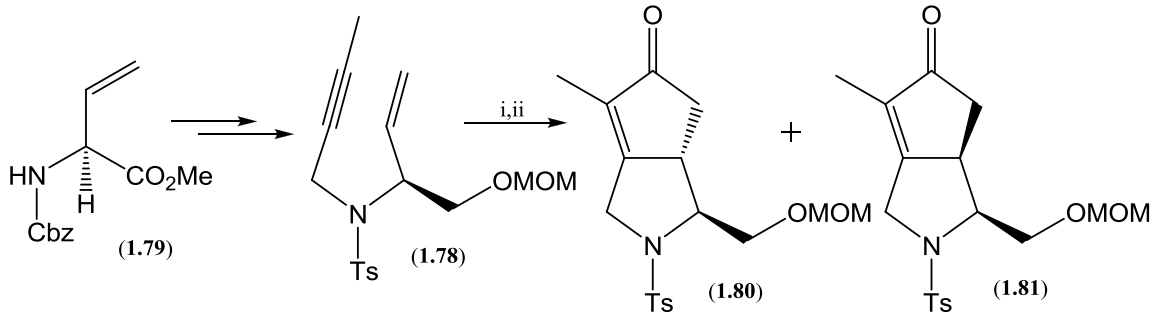
The subsequent elaboration of the bicyclic ketone (**1.77**), included lactone formation and then a facile cleavage of the cyclic lactone, led to kainic acid (**1.1**) being prepared in 5 steps (Scheme 1.23).



Reagents: i. $LiAlH_4$, CuI, THF, HMPA, -78 ^oC; ii. *p*TsOH, MeOH.

Scheme 1.23

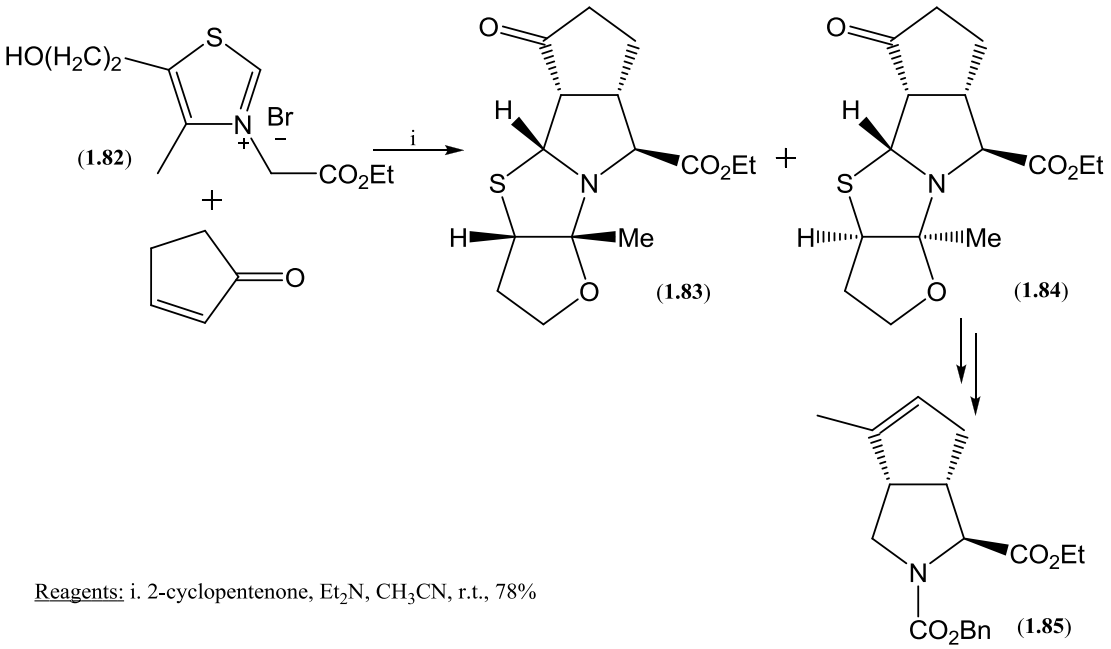
Yoo has also developed a similar pathway towards kainic acid based on the Pauson-Khand reaction.[36] The key intermediate (**1.78**) was prepared from the vinyl glycine derivative (**1.79**), followed by the Pauson Khand reaction with dicobalt octacarbonyl, which formed an inseparable mixture of two bicyclic enone diastereoisomers (**1.80**) and (**1.81**) (1.7:1) in 95% yield (Scheme 1.24). The mixture of (**1.80**) and (**1.81**) was converted to kainic acid (**1.1**) in six steps.



Reagents: i. $Co_2(CO)_8$, CH_2Cl_2, r.t.; ii. NMO or TMANO, CH_2Cl_2, 0 ^oC (95%)

Scheme 1.24

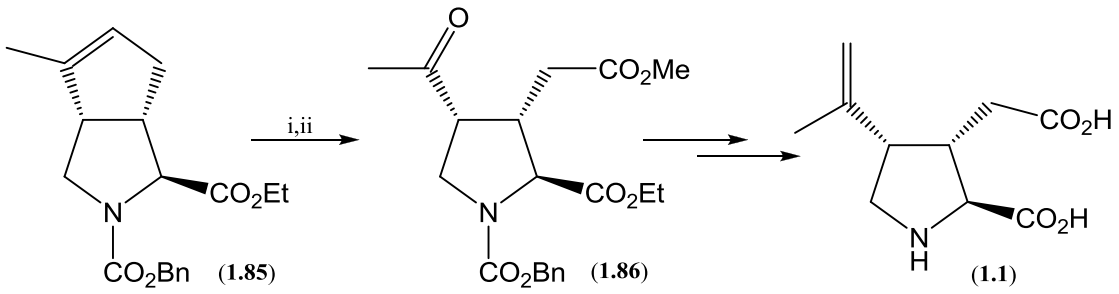
Monn has developed a synthetic route to kainic acid (**1.1**) which involved a stereocontrolled thiazolium ylide dipolar cycloaddition approach.[37,38] The pyrrolidine C-3,C-4 bond was constructed by the cyclisation of thiazolium ylide bromide (**1.82**) (prepared from thiazolium *in situ*) with 2-cyclopentenone to give a separable mixture of tetracyclic isomers (**1.83**) and (**1.84**) in good yield (70-80%). By means of reductive cleavage of the C-S bond with tri-*n*-butyltin hydride followed by hydrolysis *in situ*, protection of the nitrogen, methylation and elimination, the bicyclic *trans* C-2,C-3, *cis* C-3,C-4 pyrrolidine framework (**1.85**) was constructed (Scheme 1.25).



Scheme 1.25

After the oxidative ring opening of (**1.85**) with RuO_4 under Sharpless conditions, followed by elaboration to the pyrrolidine (**1.86**), kainic acid (**1.1**) was prepared in 8%

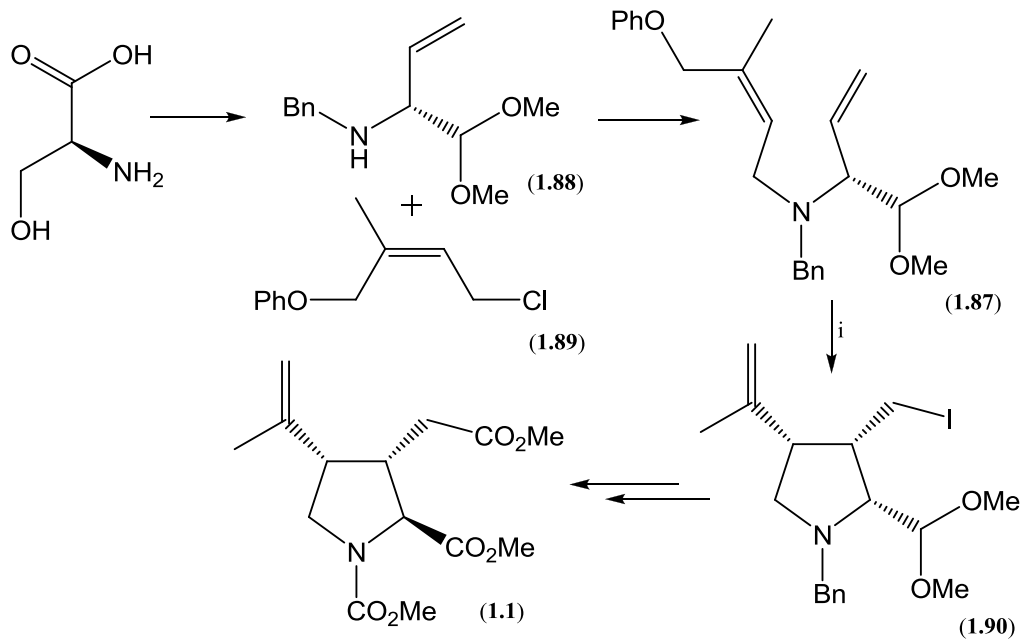
overall yield from 2-cyclopentenone (Scheme 1.26).



Reagents: i. RuO_2, $NaIO_4$, CCl_4, CH_3CN, H_2O, r.t.; ii. MeI, K_2CO_3, DMF, r.t., 51 %

Scheme 1.26

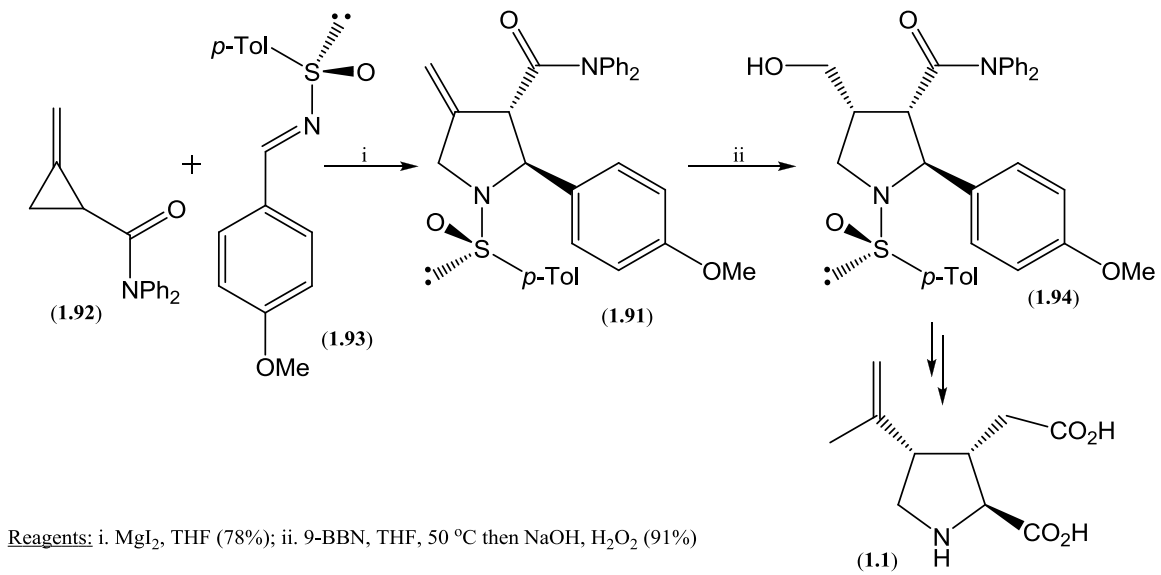
A synthesis of kainic acid (**1.1**) employing titanium-mediated diene metallabicyclisation was developed by Taylo.[39,40] The key 1,6 diene precursor (**1.87**) was obtained by reacting the alkene (**1.88**) (generated from L-serine) with allylic chloride (**1.89**), followed by a diastereoselective cyclisation in the presence of $Ti(O^iPr)_4$ and iodination to give all *cis* trisubstituted pyrrolidine (**1.90**) in 56% yield. After elaboration to the pyrrolidine (**1.90**) including an epimerisation at C-2 with base, kainic acid (**1.1**) was formed in 3.5% yield over 12 steps (Scheme 1.27).



Reagents: i. $Ti(O^iPr)_4$, ^iPrMgCl, Et_2O, -50 °C to r.t. then I_2, 0 °C (56%).

Scheme 1.27

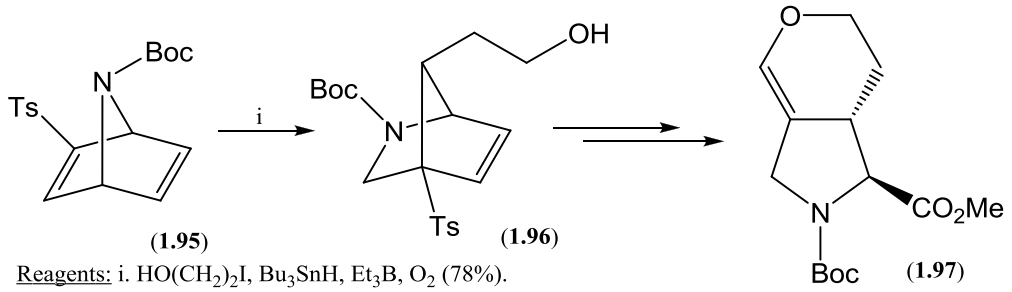
Lautens has used a diastereoselective methylenecyclopropane ring expansion method for the total synthesis of kainic acid (**1.1**).[41] The desired diastereomer (**1.91**) was prepared by a MgI_2-mediated ring expansion of methylene cyclopropylamide (**1.92**) in the presence of chiral sulfinimine (**1.93**), followed by a stereocontrolled hydroboration with 9-BBN and oxidative workup to give pyrrolidine (**1.94**).[47] By this approach kainic acid (**1.1**) was successfully synthesized in 13 steps, with an overall yield of 15% from methylene cyclopropylamide (**1.92**) (Scheme 1.28).



Reagents: i. MgI_2, THF (78%); ii. 9-BBN, THF, 50 ^oC then NaOH, H_2O_2 (91%)

Scheme 1.28

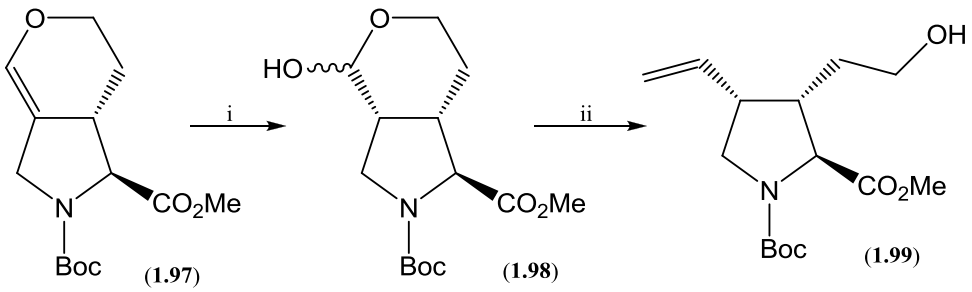
Hodgson has developed a synthetic route for kainic acid (**1.1**) which involves a radical rearrangement.[43] The dienyl sulfone radical acceptor (**1.95**) was generated from commercially available materials (*N*-Boc pyrrole and tosyl ethyne) in one step. Treatment of (**1.95**) with 2-iodoethanol in the presence of Bu_3SnH and Et_3B led to a radical mediated addition and rearrangement to give sulfone (**1.96**) in 78% yield. Sulfone (**1.96**) was then converted to enol ether (**1.97**) by ozonolysis, Swern oxidation, Boc replacement and Julia elimination (Scheme 1.29).



Reagents: i. $HO(CH_2)_2I$, Bu_3SnH, Et_3B, O_2 (78%).

Scheme 1.29

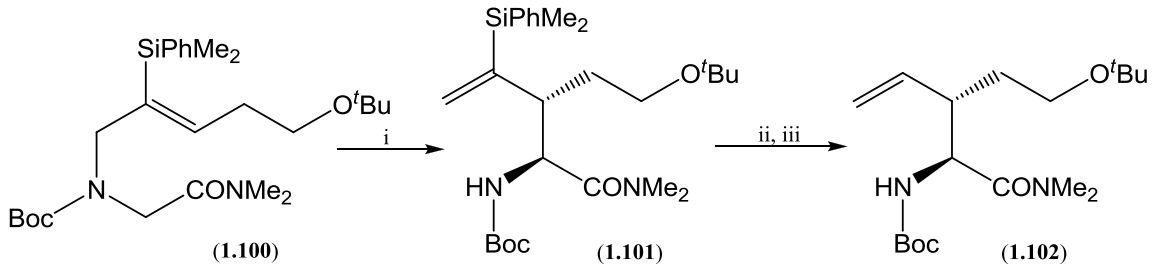
After the acid-catalysed hydration of enol ether (**1.97**), lactol (**1.98**) was formed with the desired *trans* C-2,C-3, *cis* C-3,C-4 configuration for kainoids. A further ring opening led to the formation of trisubstituted kainic acid precursor (**1.99**) (Scheme 1.30).



Reagents: i. HCl (6 equiv), THF, 20 °C, 5 h; ii. PPh_3MeBr (11 equiv), KHMDS (11 equiv), PhMe, THF, 20 °C, 2 h.

Scheme 1.30

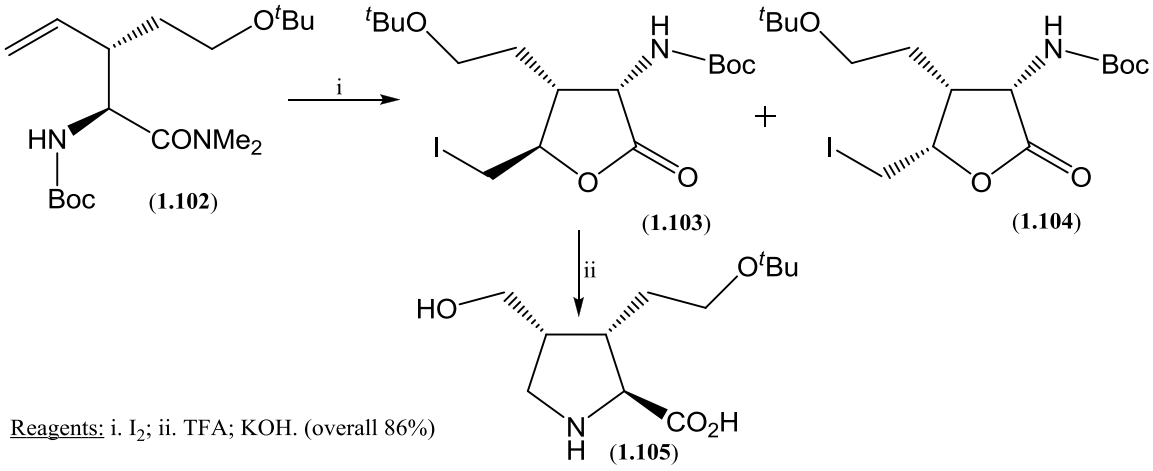
Anderson achieved a total synthesis of kainic acid (**1.1**),[44] by using an aza-[2,3]-Wittig sigmatropic rearrangement as the key step. Beginning with commercially available 3-butyne-1-ol, the key achiral aza-[2,3]-Wittig precursor (**1.100**) was synthesized in five steps. Treatment of (**1.100**) with LDA led to aza-[2,3]-Wittig rearrangement and formed amino acid derivative (**1.101**) in 78% yield. After protodesilylation of (**1.101**) with H_2O under basic conditions and a further treatment with TBAF, alkene (**1.102**) was obtained in 59% overall yield (Scheme 1.31).



Reagents: i. LDA, -78 °C to 0 °C (78%); ii. ^{t}BuOK, 18-crown-6, H_2O; iii. TBAF.

Scheme 1.31

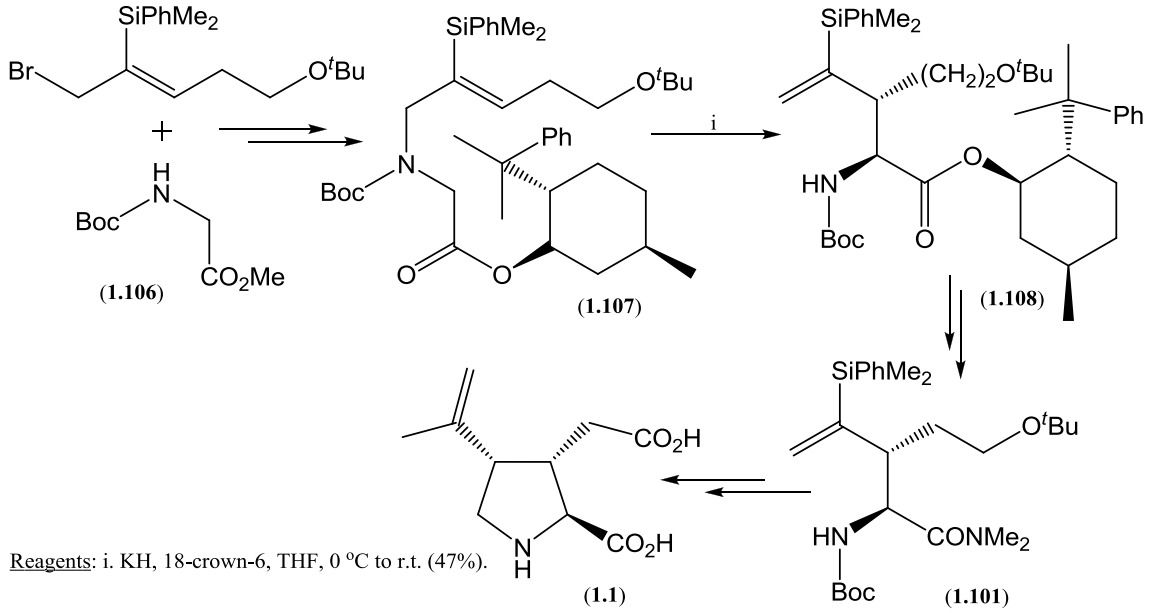
Iodolactonization provided a mixture of diastereomers of the lactone (**1.103**) and (**1.104**) in a 7:1 ratio. The stereo configurations of C-2,C-3 and C-4 of the major diastereomer (**1.103**) were verified by n.Ö.e analysis, and shown to be the same as the pyrrolidine ring of kainic acid (**1.1**). Deprotection and base-induced ring opening of the lactone followed by a 5-*exo*-tet cyclization gave the pyrrolidine kainic acid precursor (**1.105**) in 86% yield (Scheme 1.32).



Reagents: i. I_2; ii. TFA; KOH. (overall 86%)

Scheme 1.32

Two years later the same group reported a stereocontrolled approach to (-)-kainic acid. Starting with *N*-Boc glycine methyl ester (**1.106**),[47] the rearrangement precursor (**1.107**) was prepared in three steps, followed by an aza-[2,3]-Wittig rearrangement which was initiated with KH and 18-crown-6 in THF to give a diastereomerically pure product (**1.108**) in 47% yield. Then (**1.108**) was converted to the amino acid derivative (**1.101**) (an intermediate in the previous synthesis) in 4 steps. Kainic acid (**1.1**) was successfully synthesized by means of his earlier procedure (scheme 1.33).

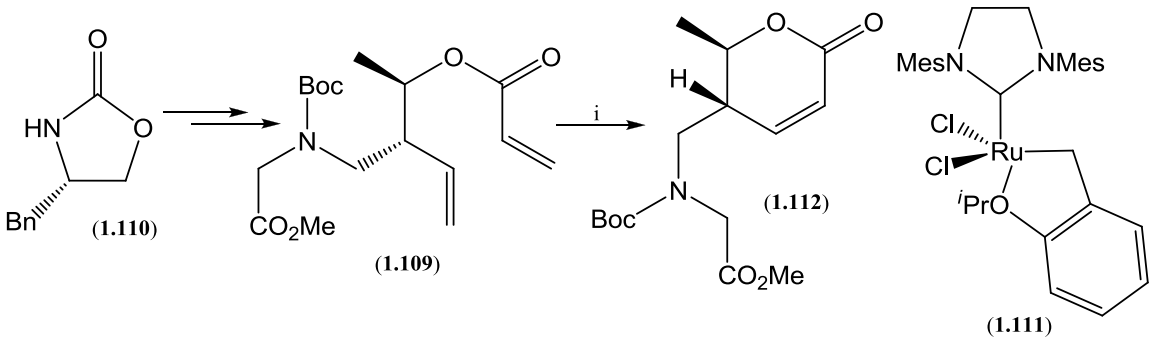


Reagents: i. KH, 18-crown-6, THF, 0 °C to r.t. (47%).

Scheme 1.33

The most recent total synthesis of kainic acid (**1.1**) was developed by Fukyama in 2007.[46] The trisubstituted pyrrolidine ring was constructed by a ring-closing metathesis of an acrylate diene (**1.109**) (generated from oxazolidinone (**1.110**)) by a Hoveyda Grubbs'

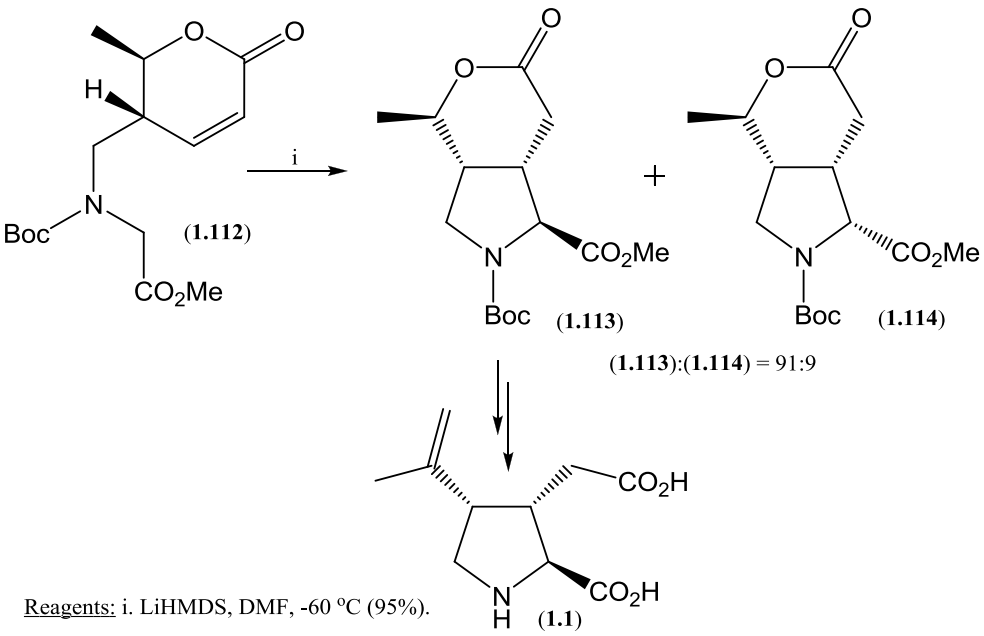
second generation catalyst (**1.111**) to give the α,β-unsaturated lactone (**1.112**) (scheme 1.34).



Reagents: i. (**1.111**), $(CH_2Cl)_2$, Δ, (99%).

Scheme 1.34

Treatment with LiHMDS in DMF initiated an intramolecular Michael addition to (**1.112**), forming the desired pyrrolidine derivative (**1.113**) together with its C-2 epimer (**1.114**) in a 91:9 ratio respectively, in 95% yield. After ring-opening to the bicyclic pyrrolidine (**1.113**), followed by elaboration including oxidation, olefination and deprotections, kainic acid (**1.1**) was successfully made in 13% yield from (**1.110**) (scheme 1.35).


O
O
H
i
N
Boc
(1.112)
CO2Me
O
O
N
CO2Me
Boc
(1.113)
+
O
O
N
CO2Me
Boc
(1.114)
(1.113):(1.114) = 91:9
CO2H
CO2H
N
H
(1.1)
Reagents: i. LiHMDS, DMF, -60 °C (95%).

Scheme 1.35

2. Results and Discussion

2.1 Introduction to This Project.

The intention of this project was to follow the work of Greenwood and Murray:[47,48,53,57]

1. To carry out and improve Greenwood's synthesis of the oxazolidinone kainoid precursor (**2.1**).[47,48]

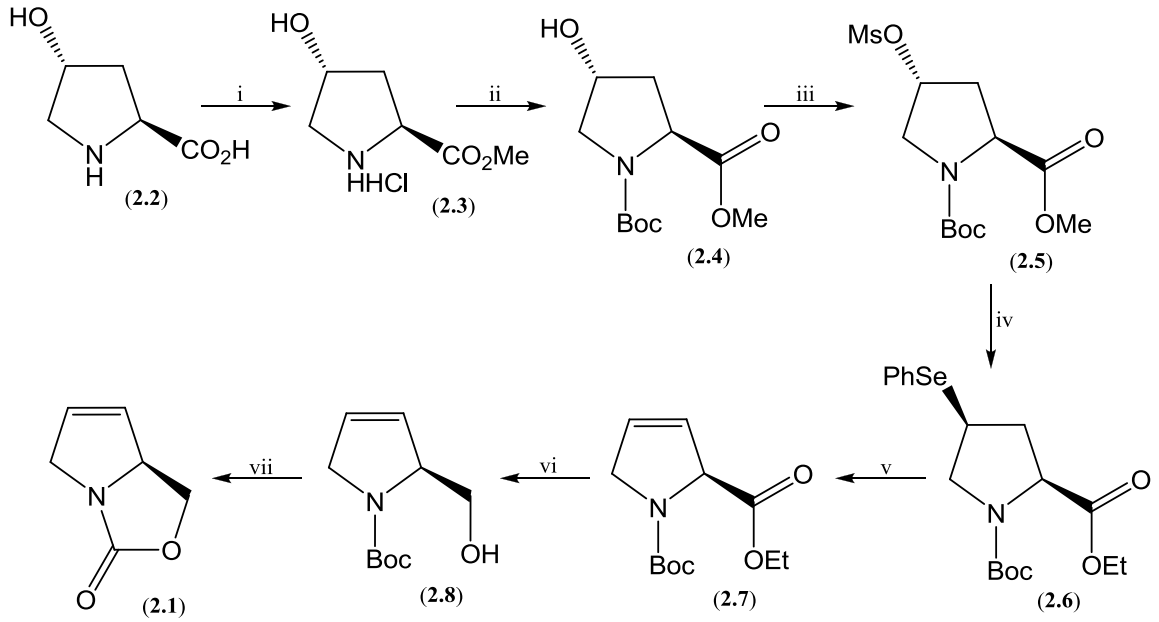
2. To investigate further the diastereofacial selectivity of the oxazolidinone precursor (**2.1**) by carrying out 1,3-dipolar cycloadditions.

3. To utilise the oxazolidinone precursor (**2.1**) to develop a novel synthetic route to kainic acid (**1.1**).

2.2 Introduction of Oxazolidinone (**2.1**).

2.2.1 Formation of oxazolidinone precursor (**2.1**).

The synthetic route to an important oxazolidinone precursor (**2.1**), originally developed by Greenwood is shown in scheme 2.1.[47,48]



Reagents: i. $SOCl_2$, MeOH, Δ; ii. Boc_2O, $^iPr_2(Et)N$, DMAP, dioxane (96%); iii. MsCl, DMAP, Et_3N, CH_2Cl_2 (95%); iv. $(PhSe)_2$, $NaBH_4$, EtOH, Δ; v. H_2O_2, pyr., CH_2Cl_2, -78 ^oC to r.t. (65 % over 2 steps); vi. DIBAL-H, Et_2O, -78 to 0 ^oC (57%); vii. DAST, CH_2Cl_2, (79%).

Scheme 2.1

The carboxylic acid group of *trans*-4-hydroxy-L-proline (**2.2**) was converted to a methyl ester by Fischer esterification.[49] The resulting hydrochloride salt (**2.3**) was protected with Boc (*tert*-butyl carbonate ester) to give Boc protected ester (**2.4**) in 96% yield over 2

steps. The protected amine (**2.4**) was then transferred to the mesylate (**2.5**) by treatment with mesyl chloride in 95% yield, then the mesyl group was replaced by a phenyl selenide with stereochemical inversion via SN_2 mechanism,[50] forming phenyl selenide (**2.6**) which was used without any purification. During this conversion, the methyl ester on the C-2 position was converted to an ethyl ester. Elimination, by conversion of the phenyl selenide (**2.6**) to its selenoxide with H_2O_2, gave alkene (**2.7**) in 65% yield over 2 steps. The resultant ethyl ester (**2.7**) was reduced to an alcohol (**2.8**), and finally the alcohol (**2.8**) was cyclised to form a bicyclic oxazolidinone precursor (**2.1**) by the treatment with diethylamino sulfur trifluoride in 79% yield.[51]

Some of the steps were improved by an alternative procedure in order to maximise the amount of oxazolidinone (**2.1**) capable of being prepared by this route.

- Replacement of dioxane with DCM as the solvent for Boc protection of hydrochloride salt (**2.3**).

  Reasons: Better solubility for both reactant and product.

  Results: Yield has increased from 34% to 69% for my trial.

- Eliminate mesylate (**2.5**) directly to alkene (**2.7**) with DBU, to avoid the selenation step.

Reasons: To simplify the synthesis of oxazolidinone (**2.1**), avoid the use of highly toxic organoselenium compound and increase the yield.

Results: Mesylate (**2.5**) was successfully eliminated to an alkene directly in satisfactory yield (61%). However the stereo centre at C-2 of the resultant alkene was found to have racemised.

- To reduce ester (**2.7**) to primary alcohol (**2.8**) with $NaBH_4$ in the presence of methanol,[52] instead of using DIBAL-H.

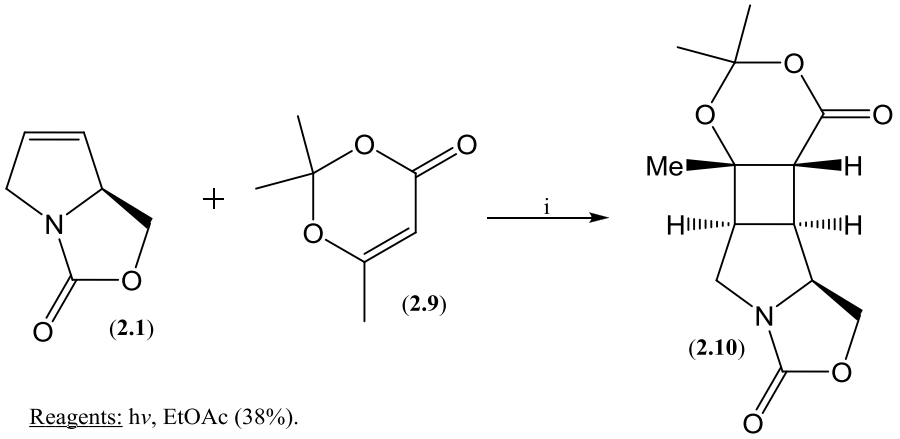
  Reasons: Increase the yield of the water soluble alcohol (**2.8**) by avoiding an aqueous work-up.

  Results: Yield has increased from 49% to 98% after purification.

2.2.2 Diastereofacial selectivity of the oxazolidinone precursor (**2.1**).

The diastereofacial selectivity of the oxazolidinone (**2.1**) was first discovered by Greenwood.[47,48] A [2+2] photocycloaddition was performed by irradiating a solution of oxazolidinone (**2.1**) with dioxinone (**2.9**). Interestingly, the photolysis gave just one photoadduct (**2.10**), although only in 38% yield, together with isolated starting materials. This indicated the photocycloaddition occurred regio- and stereoselectively. The structure

of the cyclobutane (**2.10**) was defined by X-ray crystallographic analysis and surprisingly it showed the all-*cis* arrangement around the pyrrolidine ring, which indicated the dioxinone (**2.9**) had added onto the sterically hindered face of the oxazolidinone (**2.1**) (Scheme 2.2).

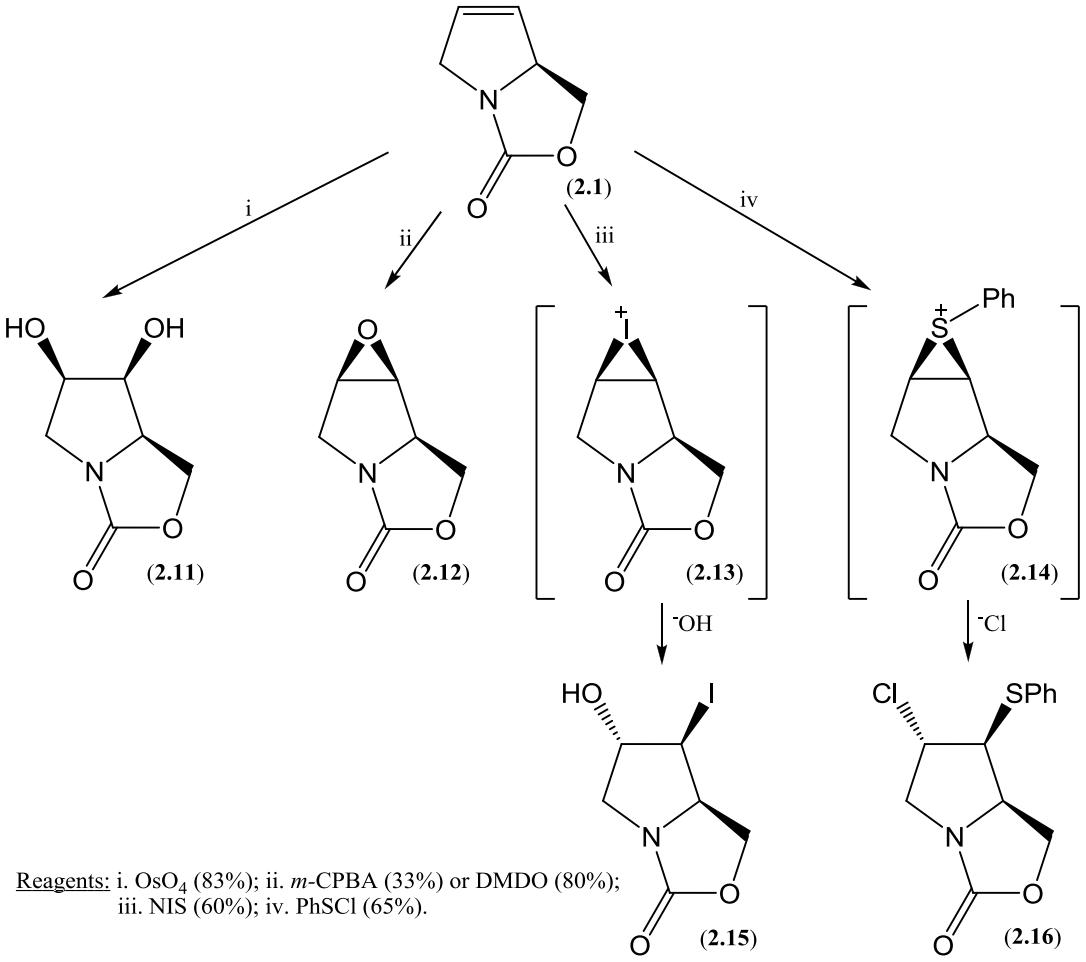


Reagents: h*v*, EtOAc (38%).

Scheme 2.2

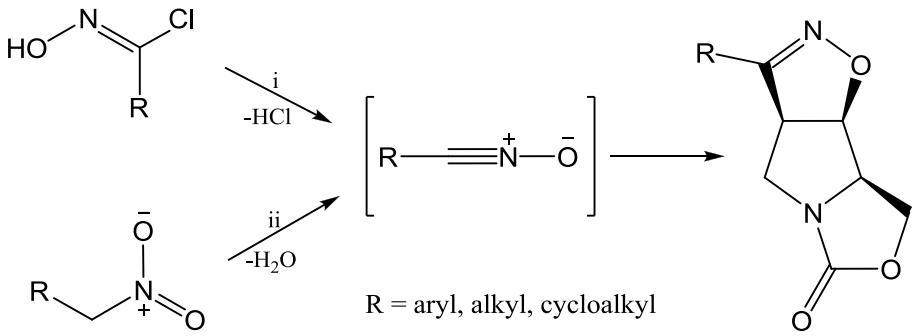
Further investigations of the diastereofacial selectivity were carried by Greenwood, Murray[53] and then later on by myself.

Greenwood and Murray showed that this diastereofacial selectivity effect applied not only for [2+2] photocycloaddition. They treated a series of electrophiles with the oxazolidinone (**2.1**) (scheme 2.3).[53]



Scheme 2.3[53]

My investigation involved an intermolecular 1,3-dipolar cycloaddition, treating oxazolidinone (**2.1**) with a range of nitrile oxides as the electrophiles, to provide a series of isoxazolines.[54] The nitrile oxides used in these cycloadditions were generated *in situ* by either γ-elimination of α-chloro-oximes or dehydration of primary nitro compounds, both in the presence of Et_3N (scheme 2.4).

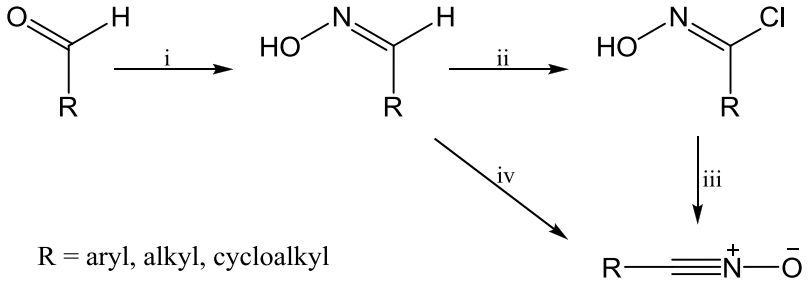


Reagents: i. (**2.1**), Et_3N, C_6H_6, r.t.; ii. (**2.1**), PhNCO or TsCl, Et_3N, C_6H_6, r.t..

Scheme 2.4

Due to aldehydes being more commercially accessible than nitro compounds, most of the nitrile oxides used in this 1,3-dipolar cycloaddition were generated by the classical method (γ-elimination of α-chloro-oximes).

Condensation of aldehydes with hydroxylamine hydrochloride under basic conditions gave the corresponding aldoximes. These aldoximes were chlorinated to α-chloro-oximes by the treatment with NCS in DCM (scheme 2.5).[55]

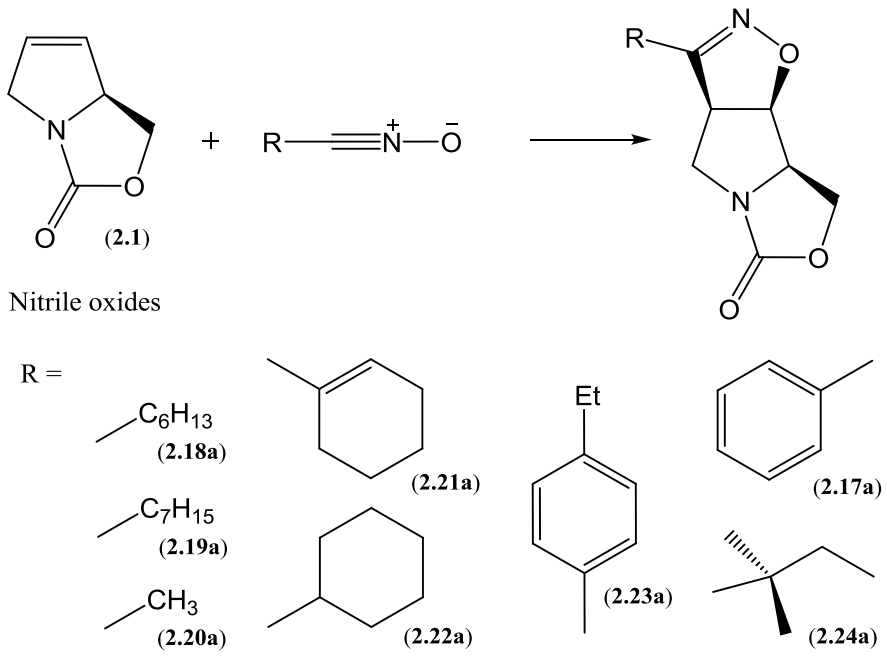


Reagents: i. $NH_2OH{\cdot}HCl$, H_2O, Na_2CO_3, r.t.; ii. NCS, DCM, r.t.;
iii. Et_3N, C_6H_6, r.t.; iv. 8% NaOCl(aq), Et_3N, C_6H_6, r.t..

Scheme 2.5

However, in many cases, α-chloro-oximes are not sufficiently stable to isolate for use in the 1,3-dipolar cycloaddition, hence one pot synthesis of isoxazolines (developed by Lee) was employed,[56] which involved the chlorination of aldoximes, γ-elimination of α-chloro-oximes and 1,3 dipolar cycloaddition. Addition of an 8% aqueous sodium hypochlorite solution to a solution of α-chloro-oximes, Et_3N and alkenes in benzene provided the corresponding isoxazolines in good yields.

A series of isoxazolines (figure 2.1) was made by the treatment of oxazolidinone (**2.1**) with various nitrile oxides with different substituents (scheme 2.6).



Scheme 2.6

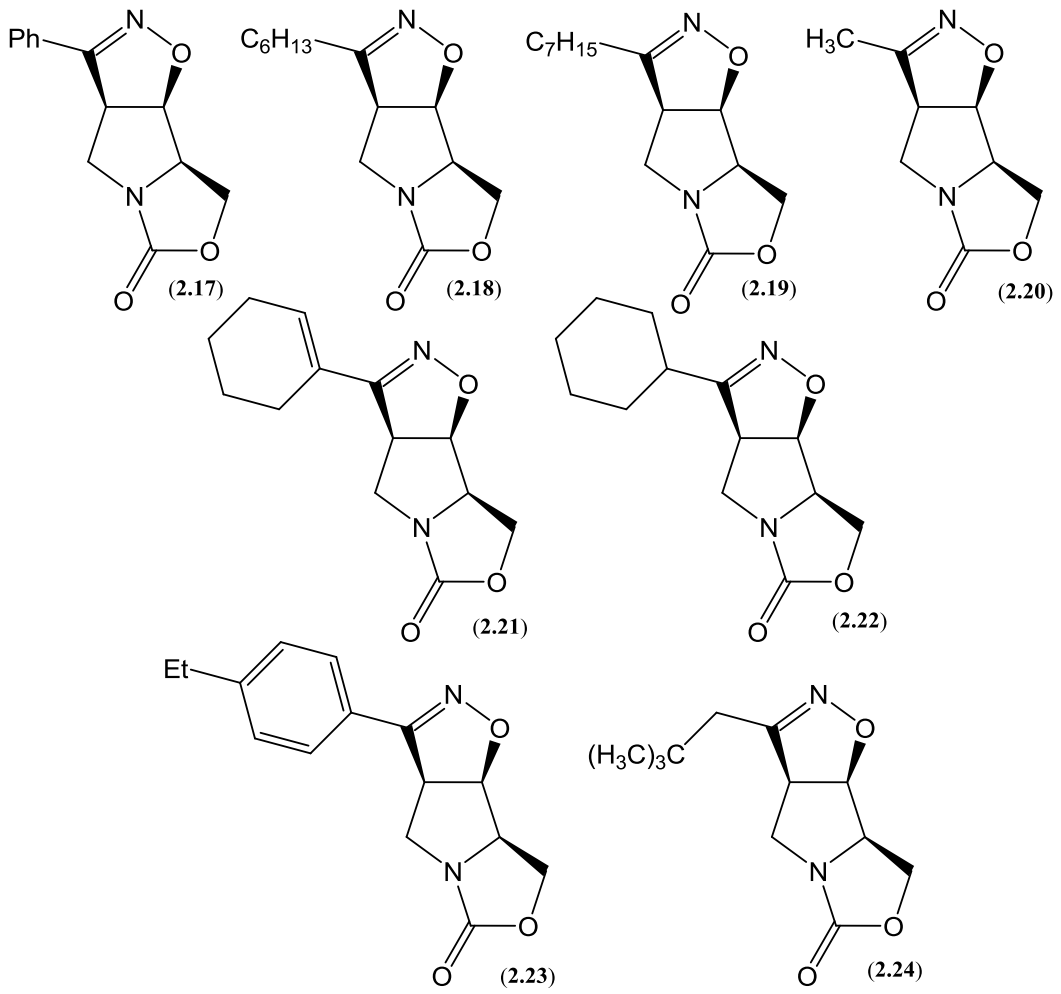
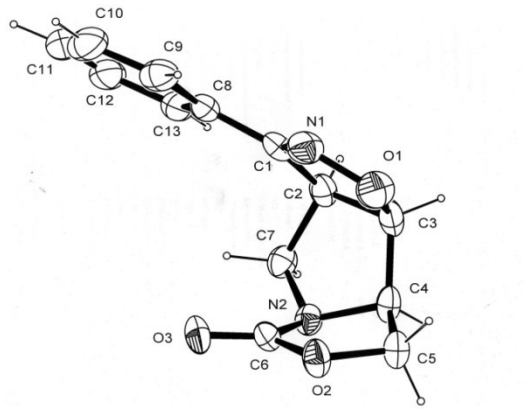


Figure 2.1: List of Isoxazolines

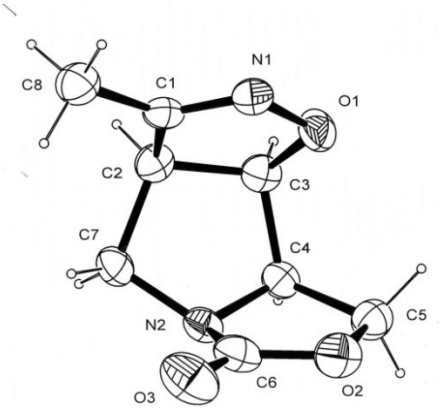
Table I: 1,3-dipolar cycloadditions with nitrile oxides.

Nitrile Oxides	Alkene	Isoxazolines	Yield (%)
(2.17a)	**(2.1)**	**(2.17)**	68
(2.18a)	**(2.1)**	**(2.18)**	11
(2.19a)	**(2.1)**	**(2.19)**	40
(2.20a)	**(2.1)**	**(2.20)**	39
(2.21a)	**(2.1)**	**(2.21)**	95
(2.22a)	**(2.1)**	**(2.22)**	26
(2.23a)	**(2.1)**	**(2.23)**	36
(2.24a)	**(2.1)**	**(2.24)**	24

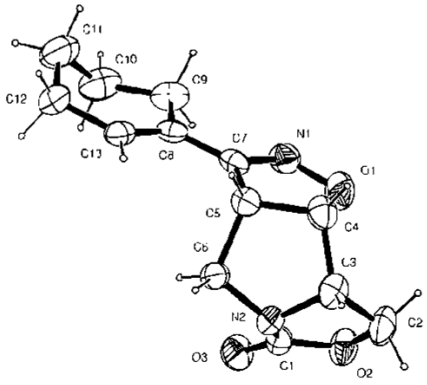
Although some of the isoxazolines were not obtained in good yield, interestingly, the X-ray crystallographic analyses by Hitchcock showed all of the crystallisable isoxazolines (**2.17**), (**2.20**) and (**2.21**) were found to be *cis* at C-2, C-3 and C-4. Figure 2.2 showed the C-1 and O-1 of isoxazolines (**2.17**) and (**2.20**), C-7 and O-1 of (**2.21**) were located at the sterically hidden position of the corresponding isoxazolines. This showed that the corresponding 1,3-dipoles attacked on the sterically hidden concave face of oxazolidinone (**2.1**). In addition, no other stereo- and regio- isomers of (**2.17**), (**2.20**) and (**2.21**) were found by X-ray crystallographic analyses.



(**2.17**)



(**2.20**)



(**2.21**)

Figure 2.2: X-ray crystallographic analyses of (**2.17**), (**2.20**) and (**2.21**) by Hitchcock

NMR analyses showed that the structure of rings A, B and C for all 1,3-dipolar cycloadducts (**2.17-2.24**) are very similar. The coupling constants for H_{a-e} are almost identical between each isoxazolines: for instance J_{He} ~ 2.4, 8.8 Hz, J_{Hb} ~ 8.1, 12.6 Hz, J_{Ha} ~ 8.3 Hz and J_{Hc} ~ 4.3, 8.4 Hz (Figure 2.3).

This indicated that only one isoxazoline isomer had been obtained, showing that these 1,3-dipolar cycloadditions were occurring both regio- and stereoselectivity in each case.

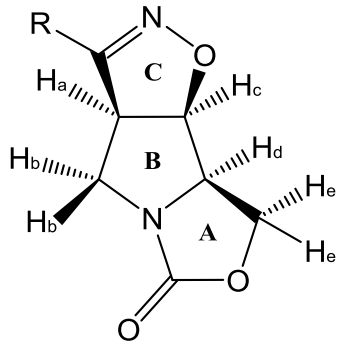


Figure 2.3

These results coincided with Greenwood and Murray's explanation,[48,53,58] that the diastereofacial selectivity was influenced by the distribution of electron density within the alkene (**2.1**).[53] In our group, Viseux investigated this effect by molecular mechanics conformational searching and *ab initio* studies at the 6-31G* level, which show the preferred conformation (as calculated with MM+ set) of ozazolidinone (**2.1**) in Figure 2.4.

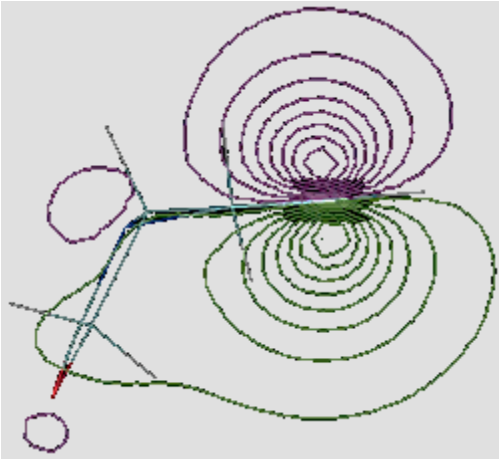


Figure 2.4: 6-31G* representation of the HOMO of oxazolidinone (**2.1**).[53]

According to the investigation, Viseux suggested:[53]

1. The lone pair electrons of the nitrogen in the oxazolidinone (**2.1**) is not in conjugation with the adjacent carbonyl group. This was supported by the observed IR stretch frequency of the C=O bond at 1751 cm^{-1}, which is at the higher end of what would be expected for such a carbamate system.
2. The HOMO shows the electron density of the unsymmetrical π system is higher on

the *endo* face of the oxazolidinone (**2.1**), thus leading to electrophiles approaching the concave face.

Pyne has also reported the same phenomenon when dihydroxylating oxazolidinone (**2.1**) with osmium tetraoxide,[58] and has rationalized that the pseudo-axial protons H-10 and H-12 cause the *exo* face of oxazolidinone (**2.1**) to be sterically hidden from electrophilic attack (figure 2.5).

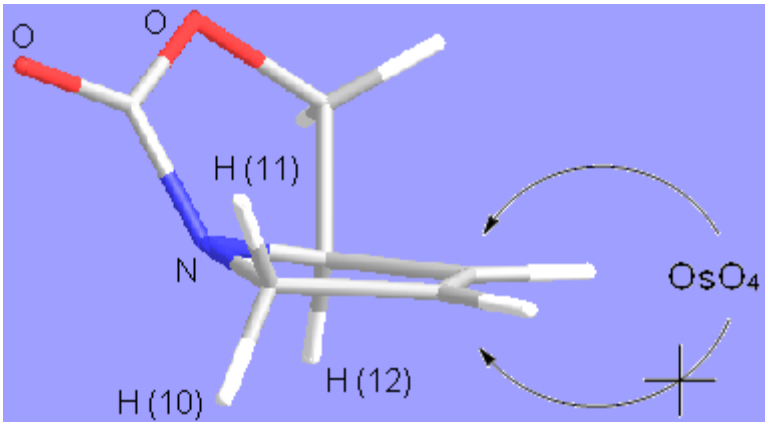
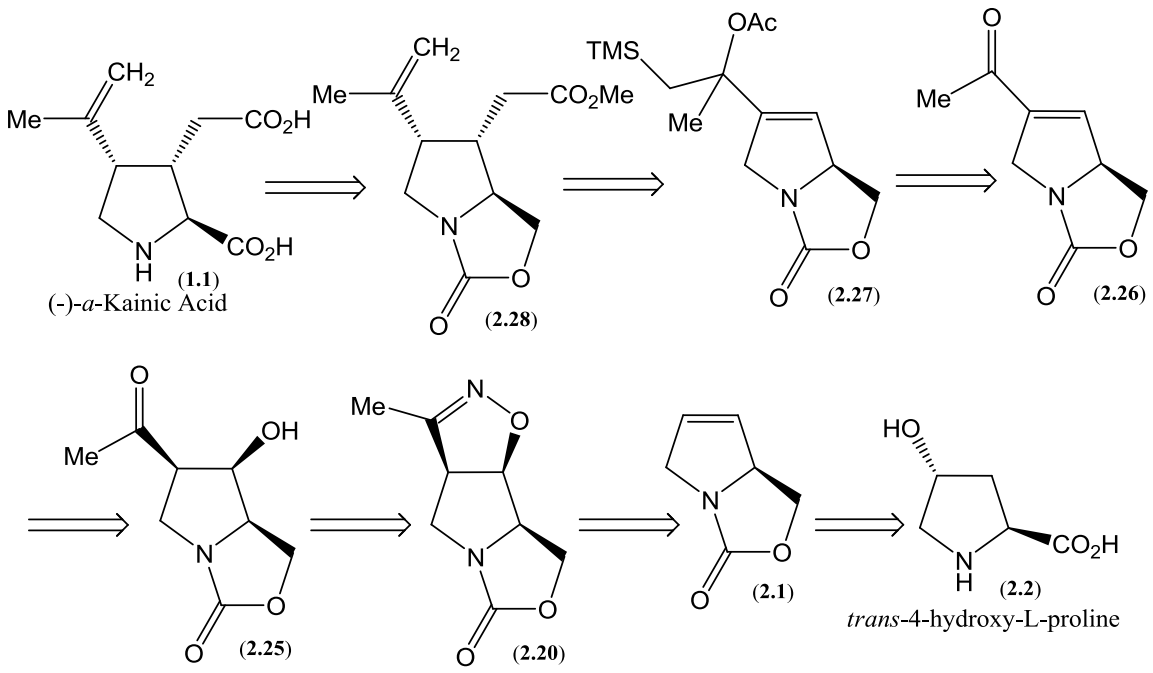


Figure 2.5: Stereochemical model (Spartan AM1) of oxazolidinone (**2.1**).[58]

2.3 The Synthesis of Kainic Acid (**1.1**).

2.3.1 Proposed Synthetic Route

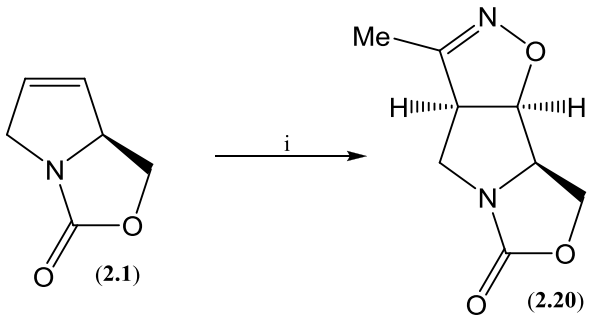
Utilising oxazolidinone (**2.1**) as a key precursor, a regio- and diastereoselective 1,3-dipolar cycloaddition with ethyl nitrile oxide would give the tricyclic isoxazoline (**2.20**). Reducing (**2.20**) (by treatment with Raney Ni under H_2 atmosphere) to the β-hydroxy ketone (**2.25**), and subsequent elimination would lead to the enone (**2.26**). Performing a 1,2-nucleophilic addition with trimethylsilyl-lithium followed by an acetylation would provide the acetate (**2.27**). After the Ireland Claisen rearrangement, the resulting silane would be eliminated to the desired C-2,C-3 *trans*, C-3,C-4 *cis* pyrrolidine (**2.28**) with fluoride. Final carbamate ring opening, oxidation and deprotection would yield kainic acid (**1.1**) (scheme 2.7).



Scheme 2.7

2.3.2 1,3-dipolar cycloaddition of oxazolidinone (**2.1**)

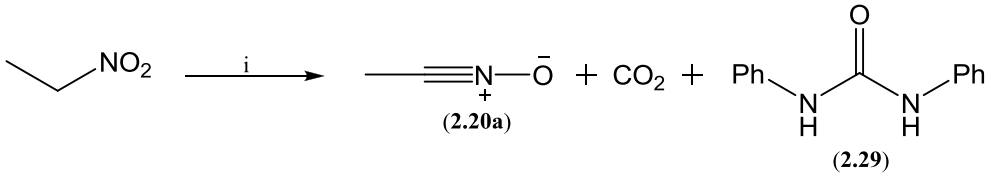
By carrying out Greenwood's modified procedure for the preparation of oxazolidinone (**2.1**),[47,48] we were able to subject the oxazolidinone (**2.1**) to the 1,3-dipolar cycloaddition conditions. Addition of triethylamine to a solution of oxazolidinone (**2.1**) and nitroethane in the presence of PhNCO or *p*TsCl gave just one isoxazoline (**2.20**) (Scheme 2.8). The structure of the resulting adduct was confirmed by X-ray crystallographic analysis (Figure 2.2).



Reagents: i. $EtNO_2$, PhNCO or *p*TsCl, Et_3N, C_6H_6, 12 Hr, 39%.

Scheme 2.8

In the first attempt, ethyl nitrile oxide (**2.20a**) was generated *in situ* by the Mukaiyama-Hoshino procedure,[59] dehydrating nitroethane with phenyl isocyanate in the presence of triethylamine. However, the diphenyl urea (**2.29**) by-product that precipitated from the 1,3-dipolar cycloaddition solution was difficult to separate from the desired isoxazoline (**2.20**) due to their similar solubilities. Further purification by flash column chromatography still failed to separate them completely (Scheme 2.9).

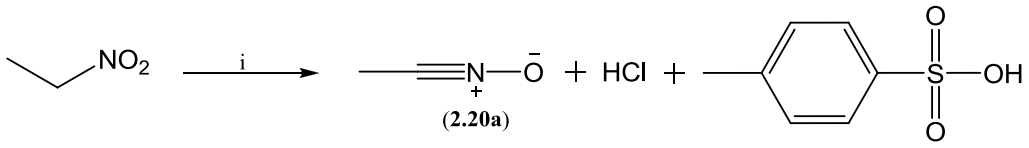


Reagents: i. PhNCO, Et_3N, Δ, C_6H_6.

Scheme 2.9

The second attempt employed a procedure reported by Shimizu,[60] which involved generating nitrile oxides *in situ* by dehydration of the primary nitro compounds with aryl sulfonyl chlorides or ethyl chloroformate in the presence of triethylamine.

Addition of triethylamine to a solution of *p*TsCl, oxazolidinone (**2.1**) and nitroethane in benzene gave isoxazoline (**2.20**) in 39% yield. The by-products of this procedure (*p*TsOH and HCl) can be removed easily by an aqueous wash (Scheme 2.10).



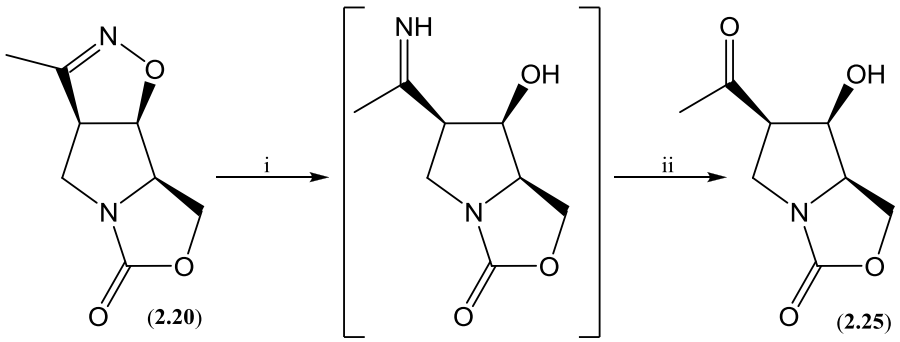
Reagents: i. *p*TsCl, Et_3N, C_6H_6.

Scheme 2.10

2.3.3 Ring-opening of isoxazoline (**2.20**) and formation of *β*-unsaturated ketone (**2.25**)

With the isoxazoline (**2.20**) in hand, we could now move forward to investigation of the ring-opening.

Curran was the first to use Raney nickel to reduce isoxazolines into *β*-hydroxy ketones in1983.[61] The N-O bond of the isoxazoline ring was cleaved by hydrogenation with a Raney nickel catalyst in the presence of methanol and water, under acidic conditions (Scheme 2.11).



Reagents: i. Raney Ni, H_2, $B(OH)_3$, MeOH; ii. H_2O.

Scheme 2.11

In the first attempt, I used phenyl substituted isoxazoline (**2.17**) as a study model to determine a suitable condition for this reduction. Acetic acid was used as the acid catalyst for this reductive ring-opening, without the use of any buffer, but no desired *β*-hydroxy ketone (**2.30**) was obtained. The ^{1}H NMR and M/*z* analyses showed that the isolated material was the saturated ketone (**2.31**) (Figure 2.6).

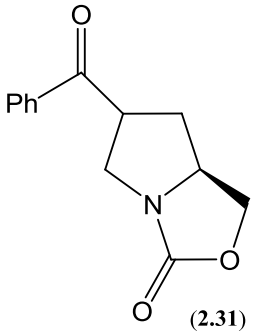
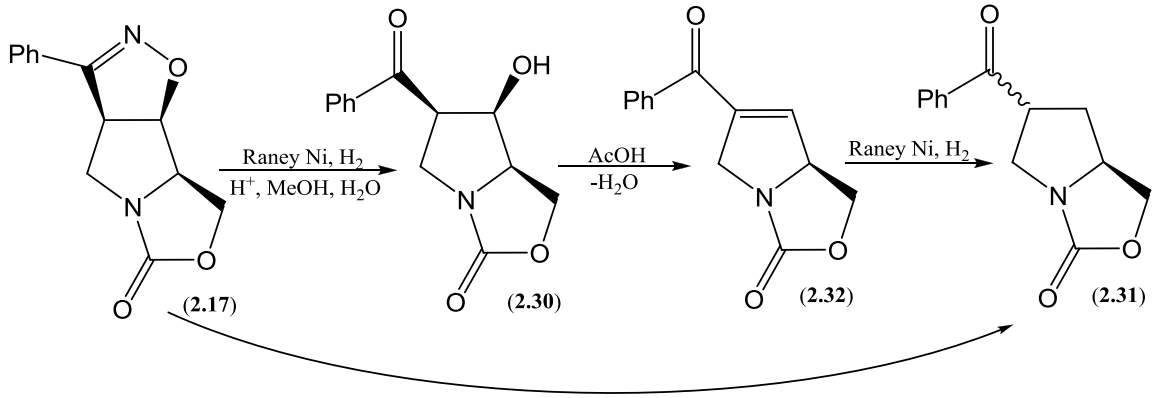


Figure 2.6: An unexpected saturated ketone.

Believing that the conditions used were too acidic for this ring-opening reduction, it was assumed that, whilst the desired *β*-hydroxy ketone (**2.30**) has been formed, it then

eliminated to an enone (**2.32**) by an acid catalysed dehydration. However, when the enone (**2.32**) was exposed to a hydrogen atmosphere in the presence of Raney nickel, this led to an unwanted hydrogenation, giving the unexpected saturated ketone (**2.31**) (Scheme 2.12).

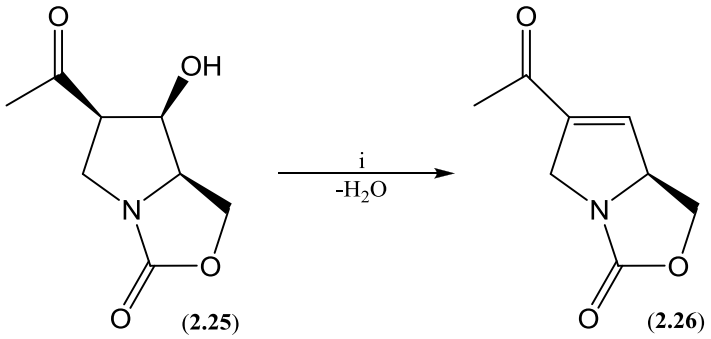


Scheme 2.12

In the second attempt, methyl substituted isoxazoline (**2.20**) was used for ring-opening reduction. Boric acid was used as the acid catalyst, in order to avoid the elimination taking place, and then desired *β*-hydroxy ketone (**2.25**) was obtained smoothly as a green oil.

The resultant *β*-hydroxy ketone (**2.25**) was then eliminated to enone (**2.26**) by an acid catalysed dehydration. A catalytic amount of *p*TsOH was added to a mixture of (**2.25**) and toluene, followed by reflux for 2 hours. Water was collected by a Dean-Stark

apparatus and the enone (**2.26**) was obtained after the usual workup in 42% yield (Scheme 2.13).



Reagents: i. *p* TsOH, toluene, 110 ^{o}C, 2 Hr, 42%.

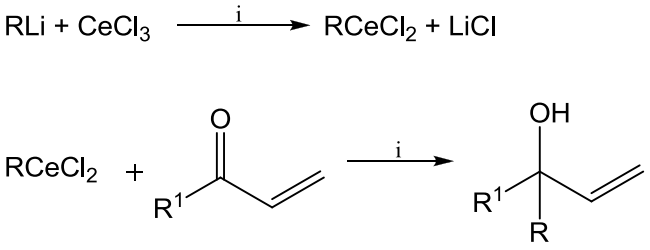
Scheme 2.13

2.3.4 1,2-Nucleophilic addition of *β*-unsaturated ketone (**2.26**)

β-Unsaturated ketone (**2.26**) was subjected to 1,2-nucleophilic addition conditions, to yield *β*-silanol (**2.33**).[62,63] Addition of $TMSCH_2Li$ to a solution of *β*-unsaturated ketone (**2.26**) in THF at -78 ^{o}C formed *β*-silanol (**2.33**) successfully. However, the desired adduct (**2.33**) was obtained in only 38% yield.

Imamoto found that treatment of readily-enolisable enones such as (**2.26**) with organo-lithium results primarily in the formation of enolates due to the strong basicity of the organolithium reagents.[64] This author reported conversion of organolithium or Grignard reagents to the corresponding organocerium reagents with anhydrous cerium (III) chloride. These reacted cleanly with enolisable enones to provide the 1,2-nucleophilic

adducts in good to excellent yields (scheme 2.14).[64]

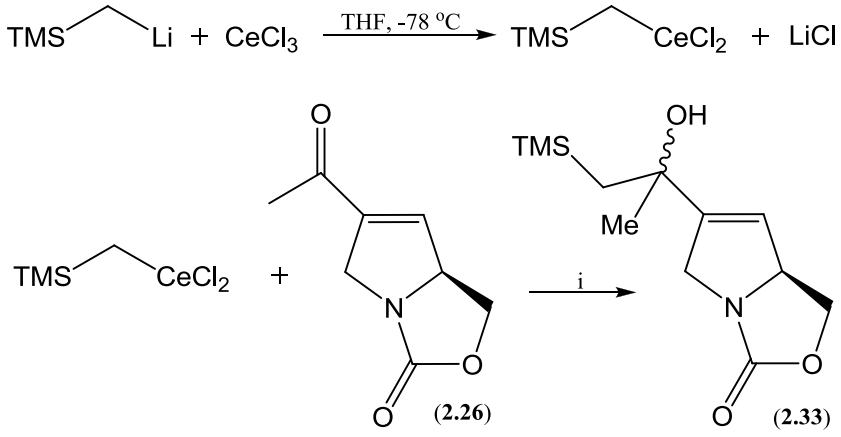


Reagents: i. THF, -78 °C.

Scheme 2.14

By employing the organocerium procedure in the second attempt, the yield of *β*-silanol (**2.33**) was significantly increased to 68% (scheme 2.15).

NMR analysis showed that the chiral carbon adjacent to the hydroxyl group of *β*-silanol (**2.33**) is racemic, this was supported by the appearance of an extra singlet peaks for both the TMS group (δ at 0.05) and its adjacent CH_2 (δ at 1.13).



Reagents: i. THF, -78 °C, 3 hr, 68 %.

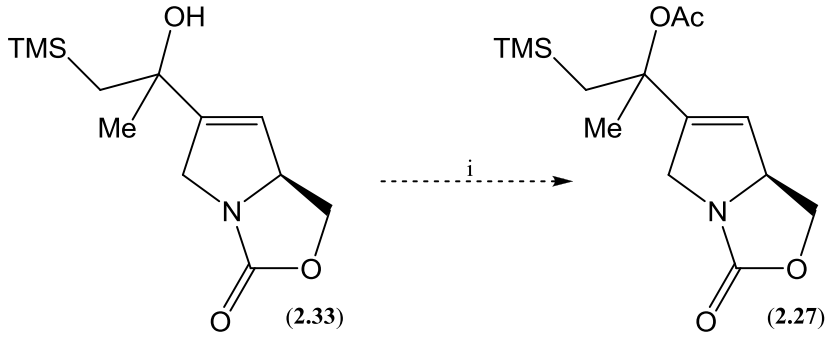
Scheme 2.15

2.3.5 Formation of Ireland-Claisen rearrangement precursors (**2.27**)

In order to carry out an Ireland-Claisen rearrangement for the formation of C-2,C-3 *trans*, C-3,C-4 *cis* pyrrolidine ring, the preparation of (**2.27**) was targeted.

In the first attempt, acetic anhydride was selected to acetylate *β*-silanol (**2.33**) in pyridine. However, it was found that the tertiary alcohol (**2.33**) was inert to this reagent, with TLC analysis showing no evidence for any reaction.

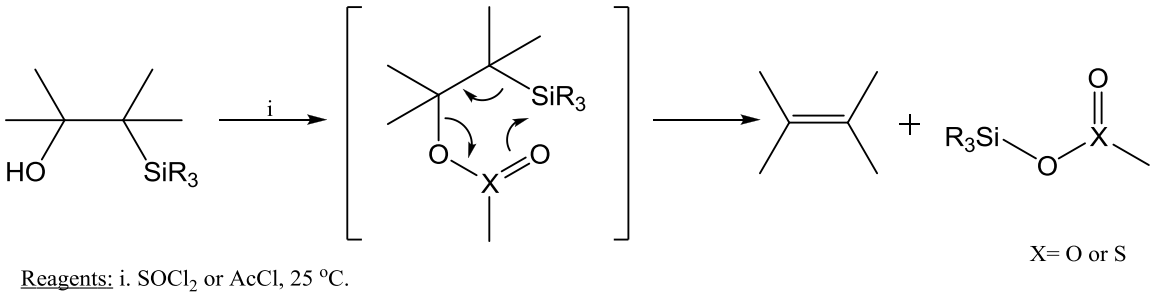
In the second attempt, treatment of a solution of *β*-silanol (**2.33**) in pyridine in the presence of DMAP with acetyl chloride, led to disappearance of starting material as indicated by TLC. Unfortunately, NMR and mass spectrometric analysis showed none of the desired acetate (**2.27**) had been formed (scheme 2.16).



Reagents: i. Ac_2O or AcCl, DMAP, pyridine.

Scheme 2.16

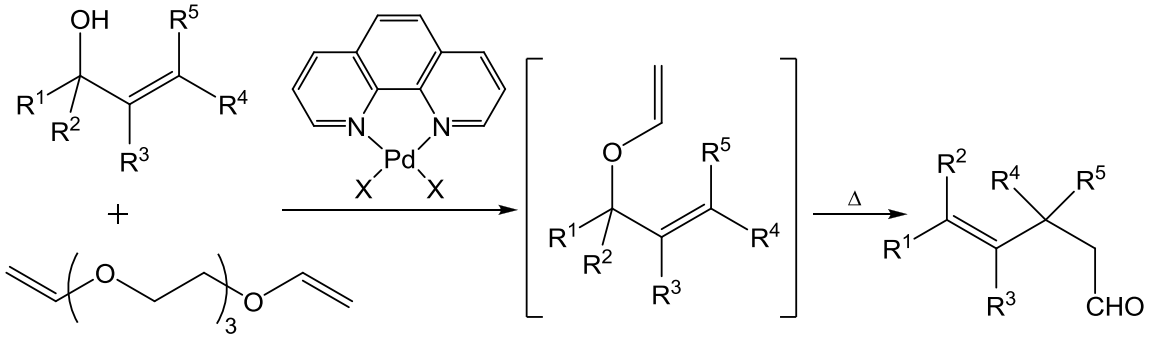
Chan has found that acetylation of the β-silylcarbinols with either acetyl chloride or thionyl chloride will gave a β-silyl esters that will self-eliminate to an alkene by Peterson olefination (Scheme 2.17).[65]



Reagents: i. $SOCl_2$ or AcCl, 25 ^oC.

Scheme 2.17

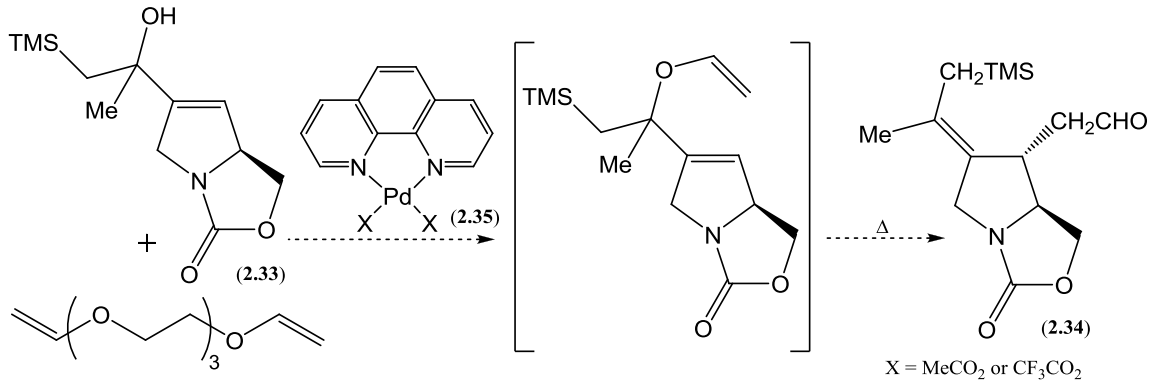
Wei developed a new procedure for the Claisen rearrangement in 2007,[66] involving Pd(II)-catalyzed vinyl ether exchange-Claisen rearrangement approach to give γ,δ-unsaturated aldehydes. Thus allylic alcohols could be converted to the corresponding γ,δ-unsaturated aldehydes under mild conditions, without using the toxic Hg(II) catalysts (Scheme 2.18).



X = $MeCO_2$ or CF_3CO_2

Scheme 2.18

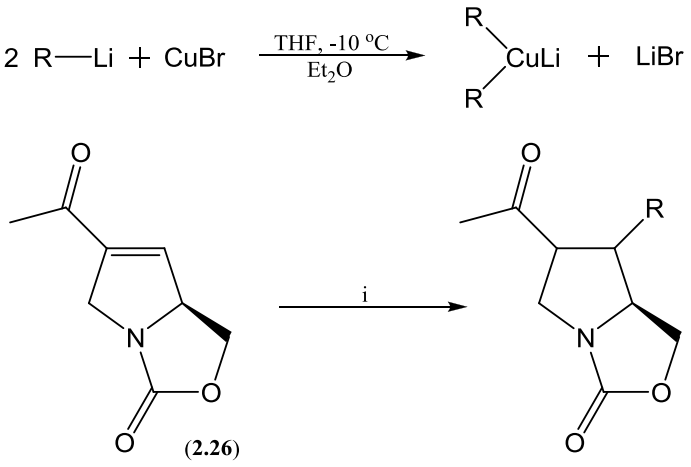
We hoped that applying this procedure to the *β*-silanol (**2.33**) would lead to the formation of aldehyde (**2.34**). However, as heating the mixture of *β*-silanol (**2.33**) and a commercially available triethylene glycol divinyl ether (TGDV) in the presence of 1,10-phenathroline $Pd(OAc)_2$ complex (**2.35**) at 80 ^oC, TLC analysis showed no reaction had taken place, even when the temperature was increased to 130 ^oC (Scheme 2.19).



Scheme 2.19

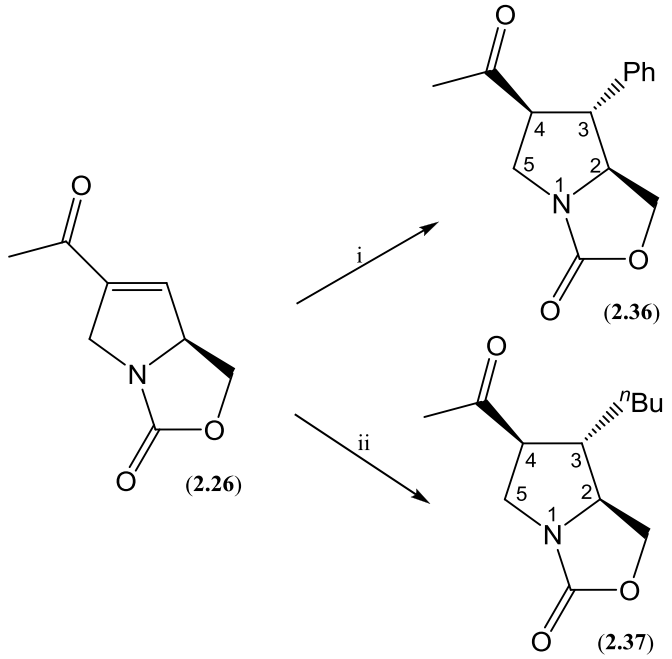
2.3.6 1,4-nucleophilic addition of *β*-unsaturated ketone (**2.26**)

In an attempt to insert a functional group into the C-3 position of *β*-unsaturated ketone (**2.26**), in order to form an pyrrolidine ring, a 1,4-nucleophilic addition was employed. Treatment of Gilman reagents (generated from an addition of organolithiums to a suspension of copper (I) bromide in THF *in situ*) with enone (**2.26**), led to the bicyclic pyrrolidines (**2.36**) and (**2.37**) being obtained (Scheme 2.20).[67]



Scheme 2.20

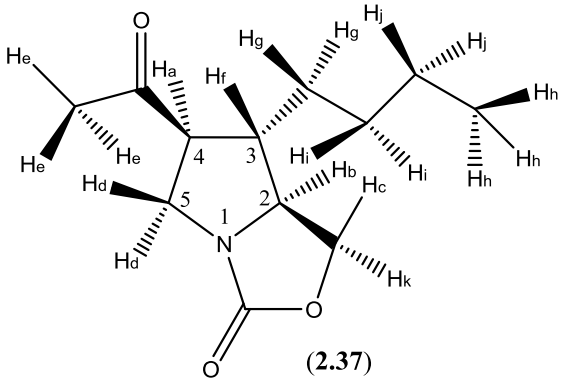
The 1,4-nucleophilic additions proceeded in a diastereofacially selective manner, to give the pyrrolidines (**2.36**) and (**2.37**) with only the C-2,C-3 *trans*, C-3,C-4 *trans* configuration (scheme 2.21), as supported by Day's NMR analyses.



Scheme 2.21

The ^{1}H NMR of (**2.37**) showed that $J_{Hc\text{-}Hb}$ = 3.5 Hz, which is smaller compared to $J_{Hk\text{-}Hb}$ = 7.8 Hz, this showed that H_c is attached to the concave face of the bicyclic pyrrolidine (**2.37**) and H_k is almost eclipsed with H_b.

ROESY experiments showed that H_f and H_c are closer in space than H_f and H_k, and also no correlation between H_b and H_f, which indicated H_f is attached to the sterically hidden concave face of (**2.37**). No correlation was observed between H_a and H_c, however H_a was correlated with H_g, which showed that H_a and the butyl group are likely attached to the same face of the bicyclic pyrrolidine (**2.37**) (figure 2.7).



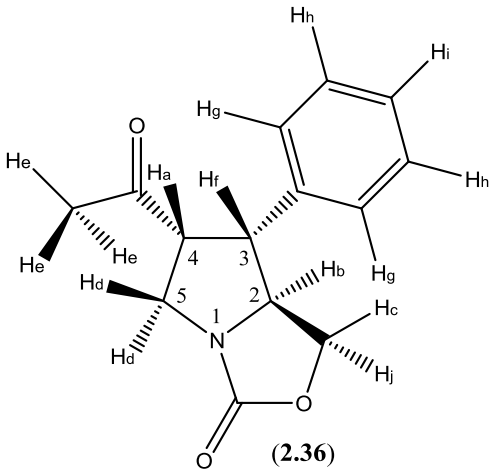
(**2.37**)

Figure 2.7

The ^{1}H NMR of (**2.36**) also showed that $J_{Hc\text{-}Hb}$ = 2.5 Hz is smaller than $J_{Hj\text{-}Hb}$ = 7.6 Hz, hence H_c is attached to the concave face of (**2.36**) and H_j is *cis* related to H_b.

ROESY experiments showed that H_f and H_c are closer in space compared to H_f and H_j,

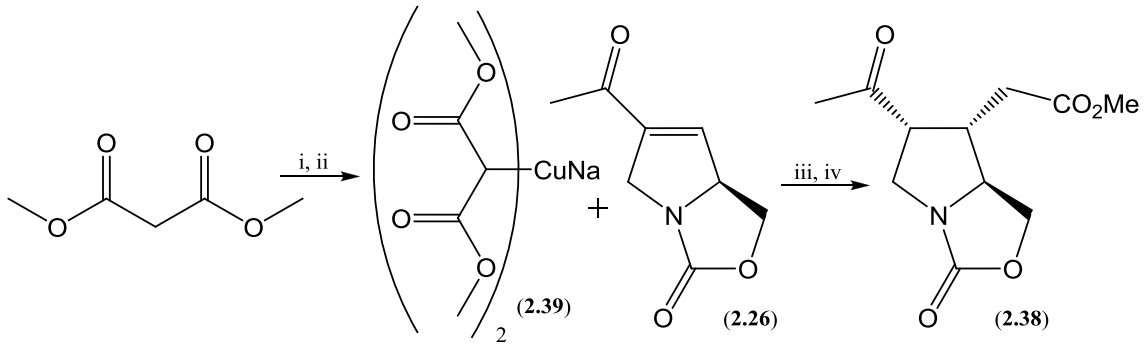
also only weak correlation was observed between H_g and H_c, this indicated the phenyl group of (**2.36**) is *cis* related to H_b. No correlation was observed between H_e and H_g, however the spectrum showed that H_a and H_g, H_e and H_c are close in space, which showed that the ketone group was attached to the concave face of (**2.36**) (figure 2.8).



(**2.36**)

Figure 2.8

By modifying this procedure, we hoped that the C-2,C-3 *trans*, C-3,C-4 *cis* kainic acid framework (**2.38**) would be generated by treating the *β*-unsaturated ketone (**2.26**) with copper (I) dimethyl malonate (**2.39**) followed by a thermal decarboxylation (Scheme 2.22).[68]



Reagents: i. NaOMe; ii. CuBr, Et_2O, -10 °C; iii. Et_2O, -78 °C; iv, Δ.

Scheme 2.22

If it proved possible to achieve the kainic acid framework (**2.38**), olefination of the ketone, ring-opening of the carbamate, oxidation and deprotection would led to kainic acid (**1.1**) in 14 steps from *trans*-4-hydroxy-L-proline (**2.2**).

2.4 Conclusion

The formation of oxazolidinone precursor (**2.1**) has been achieved by repeating the literature apposed of Greenwood. Some of the steps were improved by using alternative procedures or reagents in order to increase the amount of oxazolidinone (**2.1**) obtained.

Various nitrile oxides were utilised as the electrophiles, to investigate the diastereofacial selectivity of oxazolidinone precursor (**2.1**) by carrying out a series of 1,3 dipolar cycloadditions. The results coincided with previous investigations;[48,53,57] the stereo configurations of C-2, C-3 and C-4 being *cis* related for all isoxazolines, which demonstrated that the electrophiles favoured approach to the concave face of the oxazolidinone (**2.1**).

The formation of β-silanol (**2.33**) was successfully achieved, although the conversion of (**2.33**) to the Ireland-Claisen rearrangement precursor (**2.27**) was not successful.

In addition, the diastereofacially selective 1,4-nucleophilic addition to enone (**2.26**) was also attempted. However, only sterically unfavoured C-2,C-3 *trans*, C-3,C-4 *trans* configured (**2.36**) and (**2.37**) were obtained.

If it proved possible to achieve the sterically favoured kainic acid framework (**2.38**), a further 4-step elaboration would lead the formation of (-)-α-kainic Acid (**1.1**).

3. Experimental Section

3.1 General Experimental Procedures

All reactions were conducted under a nitrogen atmosphere, using oven dried glassware. Reactions requiring anhydrous conditions were carried out under a nitrogen atmosphere using flame-dried glassware.

Purification by flash column chromatography was performed using Merk Kieselgel 60 silica gel (particle size less than 0.063 nm) eluting with the stated solvents purchased from Fisher scientific. Thin layer chromatography analyses were performed using Merk glass backed plates precoated with a 0.25 mm layer of 60 F_{254} silica gel. Visualization of the TLC plates was under ultra violet radiation (254 nm) and by potassium permanganate or vanillin dip.

Melting points were recorded using a Gallenkamp melting point apparatus without correction.

1H NMR spectra were recorded on a Bruker Advance AC-300 instrument at 300 MHz or a Bruker AMX 500 at 500 MHz. Samples were run in deuterochloroform or deuteromethanol at ambient temperature and were referenced to deuterochloroform or deuteromethanol internal standard. Chemical shifts are quoted in ppm on the δ scale and

coupling constants *J* are measured in Hz. The following abbreviations were used to describe multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dddd, doublet of doublet of doublet of doublets; dt, doublet of triplets.

13C NMR spectra were recorded on a Bruker Advance AC-300 instrument at 75 MHz or a Bruker AMX 500 instrument at 125 MHz. Samples were run in deuterochloroform or deuteromethanol at ambient temperature and are referenced to deuterochloroform or deuteromethanol internal standard. Chemical shifts are quoted in ppm on the δ scale.

Infrared spectra were recorded on Perkin-Elmer Spectrum One Fourier transform spectrometer, with a universal ATR sampling accessory, with υ_{max} measured in cm^{-1}.

Low resolution and high resolution mass spectra were recorded on a Fisons Instrument VG Autospec mass spectrometer. The following abbreviations were used to represent the experiment: EI - electron impact, ESI - electron spray ionization, HRMS - high resolution mass spectrometry, LRMS - low resolution mass spectrometry.

Specific rotations were measured on a BS ADP 440 polarimeter at ambient temperature and 589 nm.

All organic solvents were distilled under a nitrogen atmosphere from an appropriate drying agent, see below.

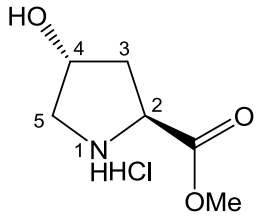
Solvent	Drying Reagent
Acetonitrile	Calcium hydride
Benzene	Calcium hydride
Diethyl ether	Sodium in the presence of benzophenone
Dichloromethane	Calcium hydride
Ethanol	Magnesium turnings*
Methanol	Magnesium turnings*
Pyridine	Calcium hydride
Tetrahydrofuran	Sodium in the presence of benzophenone

*Magnesium turnings were activated by heating with a crystal of I_2 under a nitrogen atmosphere.

All compounds in the experimental detail section are numbered to aid identification of protons and carbons in the relevant spectra. This numbering may not always correspond with that of the I.U.P.A.C. guidelines.

3.2 Experimental Detail.

3.2.1 Methyl (4*R*)-4-hydroxy-L-prolinate hydrochloride (**2.3**)

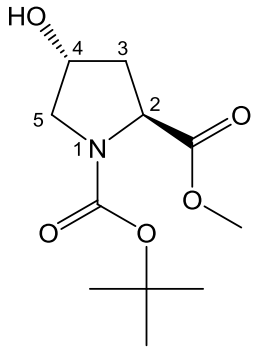


The title compound was prepared by a modification of the procedure of Greenwood.[47,48]

A suspension of *trans*-4-hydroxy-L-proline (**2.2**) (10.0 g, 76.0 mmol) in methanol (40 mL) was stirred and cooled to 0^{o}C. Thionyl chloride (2.49 mL, 34.31 mmol) was added to the reaction mixture dropwise at 0 ^{o}C. The reaction mixture was stirred at 0 ^{o}C for 1 hour before heated to reflux for 24 hours, then being allowed to re-cool to 0 ^{o}C. Diethyl ether (80 mL) added, the white precipitate was filtered, washed with diethyl ether (2 x 20 mL) and dried under reduced pressure to give methyl (4*R*)-4-hydroxy-L-prolinate hydrochloride (**2.3**) as a white solid (11.288 g).

Spectroscopic data identical to literature values.[47,48]

3.2.2 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (**2.4**)



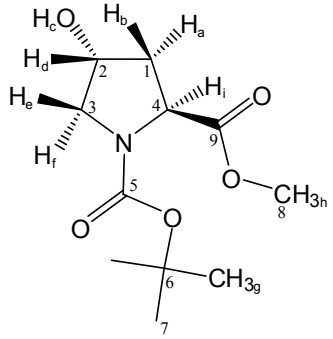
The title compound was prepared by a modification of the procedure of Greenwood.[47,48]

Diisopropylethylamine (23.86 mL, 136.56 mmol) and di-*tert*-butyl dicarbonate (14.9 g, 68.28 mmol) were added to a suspension of methyl (4*R*)-4-hydroxy-L-prolinate hydrochloride (**2.3**) (11.288 g) in DCM (80 mL) at 0^{o}C. The reaction mixture was stirred and allowed to warm to room temperature for 24 hours before being concentrated under reduced pressure. The residue was diluted with ethyl acetate (50 mL), then washed with 1M citric acid solution (50 mL). The aqueous phase was further extracted with ethyl acetate (3 x 100mL). The organic phases were combined then washed with saturated sodium hydrogen carbonate solution (300 mL) and brine (300 mL), dried over magnesium sulfate and concentrated *in vacuo* to give 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (**2.4**) as a yellow oil. No further purification was required. Overall yield for experiments 3.2.1 and 3.2.2 (9.063 g, 48 %).

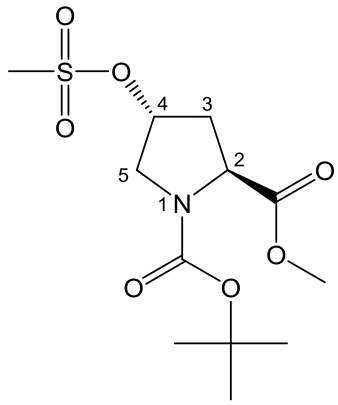
^{1}H NMR (300MHz, $CDCl_3$) δ: 1.38 and 1.43 (2 x s, 9H, *g*), 2.03 (ddd, 1H, J = 12.6, 8.3, 4.3 Hz, *b*), 2.27 (dd, 1H, J = 12.2, 20.0 Hz, *a*), 2.79 (brs, 1H, *c*), 3.63-3.41 (m, 2H, *e, f*), 3.71 (s, 3H, *h*), 4.41 – 4.35 (m, 1H, *i*), 4.46 -4.45 (m, 1H, *d*).

^{13}C NMR (75.5MHz, $CDCl_3$) δ: 28.2 and 28.3 (*7*), 38.4 and 39.0 (*1*), 52.0 (*8*), 54.6 (*3*), 57.4 and 57.9 (*4*), 69.3, 70.0 (*2*), 80.3 and 80.4 (*6*), 154.0 (*5*), 173.6 (*9*).

Spectroscopic data identical to literature values.[47,48]



3.2.3 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-(methylsulfonyloxy)pyrrolidine-1,2-dicarboxylate (**2.5**)



The title compound was prepared by a modification of the procedure of Greenwood.[47,48]

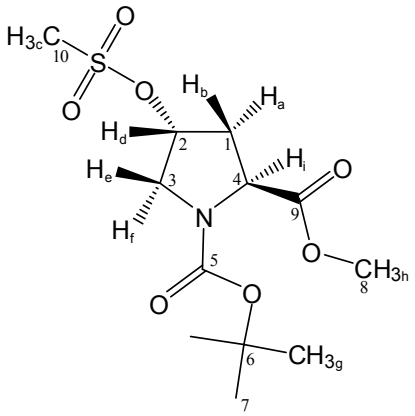
Methanesulfonyl chloride (21.560 g, 188.22 mmol) and 4-dimethylaminopyridine (2.09 g, 17.111 mmol) were added to a stirred solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (**2.4**) (41.922 g, 171.11 mmol) and triethylamine (25.71 mL, 184.80 mmol) in dichloromethane (600 mL) at 0^{o}C. The reaction mixture was stirred and allowed to warm to room temperature for 15 hours before cooling to 0^{o}C and adding water (300 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 200 mL). The organic extracts were combined and washed with 1M citric acid solution, saturated sodium hydrogen carbonate solution and dried over magnesium sulfate. The extract was concentrated under reduced pressure and the

crude product was purified by flash column chromatography on silica gel, eluting with 50 % ethyl acetate / petrol to give 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-[(methylsulfonyl)oxy]pyrrolidine-1,2-dicarboxylate (**2.5**) as a white solid (45.213 g, 82 %).

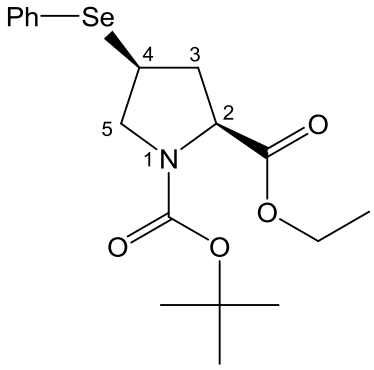
^{1}H NMR (300MHz, $CDCl_3$) δ: 1.44 and 1.40 (2 x s, 9H, *g*), 2.28 -2.19 (m, 1H, *b*), 2.68 - 2.52 (m, 1H, *a*), 3.04 (s, 3H, *c*), 3.73 (s, 3H, *h*), 3.86 – 3.67 (m, 2H, *e, f*), 4.47 – 4.35 (m, 1H, *i*), 5.24 (m, 1H, *d*).

^{13}C NMR (75.5MHz, $CDCl_3$) δ: 28.1 and 28.3 (*7*), 36.2 and 37.4 (*1*), 38.6 and 38.7 (*10*), 52.1 and 52.4 (*3*), 52.3 and 52.5 (*8*), 57.0 and 57.4 (*4*), 78.1 and 77.9 (*2*), 80.9 (*6*), 153.3 and 153.8 (*5*), 172.5 and 172.7 (*9*).

Spectroscopic data identical to literature values.[47,48]



3.2.4 1-*tert*-butyl 2-ethyl (2*S*,4*S*)-4-(phenylseleno)pyrrolidine-1,2-dicarboxylate (**2.6**)

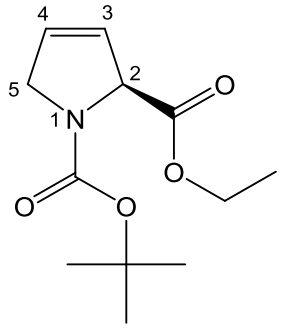


The title compound was prepared by a modification of the procedure of Greenwood.[47,48]

Sodium borohydride (6.349 g, 167.84 mmol) was added to a stirred suspension of diphenyl diselenide (26.922 g, 76.93 mmol) in anhydrous ethanol (750 mL) at 0^{o}C portionwise. The reaction mixture was allowed to warm to room temperature and stirred for 1 hour before re-cooling to 0^{o}C. The solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-(methylsulfonyloxy)pyrrolidine-1,2-dicarboxylate (**2.5**) (45.213 g, 139.87mmol) in anhydrous ethanol (250mL) was added to the reaction mixture followed by heating under reflux for 24 hours. The reaction mixture was contracted under reduced pressure, re-diluted with diethyl ether (1000 mL) and washed with water (600 mL). The phases were separated and the aqueous phase was extracted with diethyl ether (3 x 500 mL). The organic phases were combined and further washed with saturated sodium chloride solution (600 mL), dried over magnesium sulfate then concentrated *in vacuo* to give the

crude 1-*tert*-butyl 2-ethyl (2*S*,4*S*)-4-(phenylseleno)pyrrolidine-1,2-dicarboxylate (**2.6**) as a brown oil (55.50 g).

3.2.5 1-*tert*-butyl 2-ethyl (2*S*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (**2.7**)



The title compound was prepared by a modification of the procedure of Greenwood.[47,48]

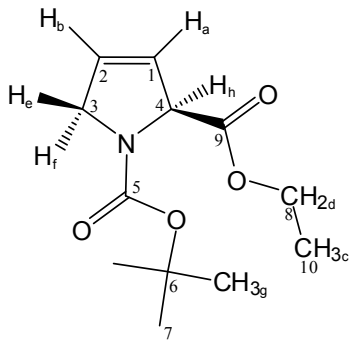
Hydrogen peroxide solution (35 wt. %, 74.53 mL, 766.44 mmol) was added to a vigorously stirred solution of crude 1-*tert*-butyl 2-ethyl (2*S*,4*S*)-4-(phenylseleno) pyrrolidine-1,2-dicarboxylate (**2.6**) (55.50 g) and pyridine (24.26 mL, 64.57 mmol) in dichloromethane (1000 mL) dropwise over 30 minutes at -78^{o}C. The reaction mixture was stirred and allowed slowly to warm to room temperature for 18 hours. After adding saturated ammonium chloride solution (500 mL), the phases were separated and the aqueous phase extracted with dichloromethane (3 x 250 mL). The organic phases were combined, washed with saturated ammonium chloride solution (500 mL) and saturated

sodium chloride solution (500 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 20 % diethyl ether / petrol, then 50 % diethyl ether / petrol to give 1-*tert*-butyl 2-ethyl (2*S*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (**2.7**) as a brown oil (19.841 g, 59 %).

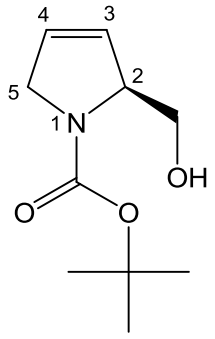
^{1}H NMR (300MHz, $CDCl_3$) δ: 1.21 - 1.28 (m, 3H, *c*), 1.41 and 1.46 (2 x s, 9H, *g*), 4.10 - 4.30 (m, 4H, *d,e,f*), 4.90 - 5.01 (m, 1H, *h*), 5.68 - 5.75 (m, 1H, *a*), 5.90 - 5.98 (m, 1H, *b*).

^{13}C NMR (75.5MHz, $CDCl_3$) δ: 14.1 and 14.2 (*10*), 28.2 and 28.3 (*7*), 53.2 and 53.5 (*3*), 66.1 (*8*), 66.3 and 66.6 (*4*), 80.0 and 80.1 (*6*), 124.7 and 124.8 (*2*), 129.1 and 129.2 (*1*), 153.4 and 153.8 (*5*), 170.2 and 170.6 (*9*).

Spectroscopic data identical to literature values.[47,48]



3.2.6 *tert*-butyl (2*S*)-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**2.8**)



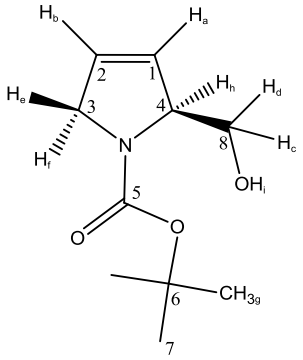
Sodium borohydride (376 mg, 9.948 mmol) was added to a stirred solution of 1-*tert*-butyl 2-ethyl (2*S*)-2,5-dihydro-1*H*-pyrrole-1,2-dicarboxylate (**2.7**) (400 mg, 1.658 mmol) in tetrahydrofuran (20 mL). The reaction mixture was heated to 65^{o}C for 15 min before adding methanol (4 mL) dropwise over 15 min and the reaction was then heated under reflux for 2 hr before cooling to room temperature. The reaction mixture was then concentrated *in vacuo* and the residue was purified by flash column chromatography on

silica gel, eluting with neat ether to give *tert*-butyl (2*S*)-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**2.8**) as a yellow oil (305 mg, 92 %).

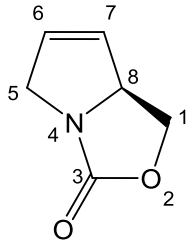
^{1}H NMR (300MHz, $CDCl_3$) δ: 1.49 (s, 9H, *g*), 3.57 (t, 1H, J = 8.1, *f*), 3.78 (t, 1H, J = 9.7 Hz, *e*), 4.08 (m, 1H, *d*), 4.18 (d, 1H, J = 14.4 Hz, *c*), 4.59 (s, 1H, *i*), 4.74 (s, 1H, *h*), 5.65 (d, 1H, J = 8.6 Hz, *a*), 5.67 (m, 1H, *b*).

^{13}C NMR (75.5MHz, $CDCl_3$) δ: 28.4 (*7*), 54.1 (*8*), 67.1 (*3*), 67.5 (*4*), 80.5 (*6*), 126.6 (*1*), 126.7 (*2*), 156.4 (*5*).

Spectroscopic data identical to literature values.[47,48]



3.2.7 (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**)



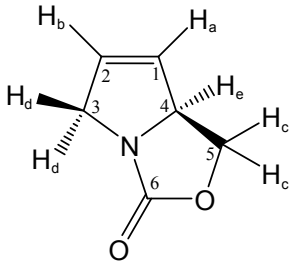
The title compound was prepared by a modification of the procedure of Greenwood.[47,48]

Diethylamino sulfur trifluoride (2.83mL, 12.05 mmol) was added to a stirred solution of *tert*-butyl (2*S*)-2-(hydroxymethyl)-2,5-dihydro-1*H*-pyrrole-1-carboxylate (**2.8**) (1.847 g, 9.27 mmol) in dichloromethane (60 mL) at 0^{o}C. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours, then re-cooled to 0^{o}C before adding water (50 mL). The phases were separated, the aqueous phase was extracted with dichloromethane (3 x 100 mL), the organic phases were combined, washed with saturated sodium chloride solution (100 mL), dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 70 % diethyl ether / petrol to give (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) as a yellow oil (0.958 g, 83 %).

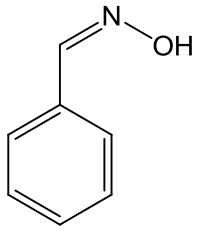
^{1}H NMR (300MHz, $CDCl_3$) δ: 3.76 - 3.82 (m, 1H, *d*), 4.23 (dd, 1H, J = 5.1, 8.6$_c$ Hz, *c*), 4.40 - 4.33 (m, 1H, *d*), 4.59 (d, 1H, J = 8.6$_c$ Hz, *c*), 4.76 – 4.66 (m, 1H, *e*), 5.88 - 5.90 (m, 1H, *a*), 6.02 – 6.04 (m, 1H, *b*).

^{13}C NMR (75.5MHz, $CDCl_3$) δ: 54.8 (*3*), 64.6 (*5*), 68.7 (*4*), 128.9 (*1*), 130.8 (*2*), 163.3 (*6*).

Spectroscopic data identical to literature values.[47,48]



3.2.8 benzaldehyde oxime



The title compound was prepared by a modification of the procedure of Liu.[55]

A solution of sodium carbonate (6.0 g, 56.6 mmol) in water (50mL) was added to a stirred solution of hydroxylamine hydrochloride (7.87 g, 113.00 mmol) and benzaldehyde

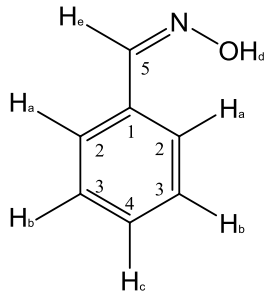
(10.00 g, 94.3 mmol) in water (50 mL) dropwise at 0°C, the reaction mixture was allowed to warm to room temperature for 2 hours, followed by extraction with ether (3 x 100 mL). The organic phases were combined, washed with water (200 mL), dried over magnesium sulfate and concentrated *in vacuo* and the crude product was purified by fractional distillation to give benzaldehyde oxime as a white solid (10.959 g, 96 %).

^{1}H NMR (300MHz, $CDCl_3$) δ: 3.42 (d, 1H, J = 7.03 Hz, *e*), 7.24 - 7.98 (m, 4H, *a,b*), 8.1 (m, 1H, *c*), 9.17 (s, 1H, *d*).

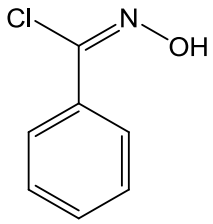
^{13}C NMR (75.5MHz, $CDCl_3$) δ: 128.0 (*2*), 129.3 (*3*), 130.3 (*4*), 130.7 (*1*), 145.5 (*5*).

FTIR υ_{max} cm^{-1}: 1679, 2558, 2842

LRMS (ES+): 122 ($[MH]^+$)



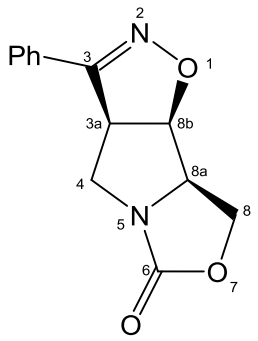
3.2.9 *N*-hydroxybenzenecarboximidoyl chloride



The title compound was prepared by a modification of the procedure of Liu.[55]

N-chlorosuccinimide (21.282 g, 136.9 mmol) was added to a stirred solution of benzaldehyde oxime (13.800 g, 114.0 mmol) in dichloromethane (150 mL). The reaction mixture was allowed to stir for 15 hours before being poured into ice water (600 mL). The organic phase was washed with water (3 x 50 mL), dried over magnesium sulfate and concentrated *in vacuo* to give the crude *N*-hydroxybenzenecarboximidoyl chloride as a white solid (14.610 g, 82 %) that was used for the next reaction without any purification.

3.2.10 (3a*S*,8a*R*,8b*R*)-3-phenyl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5]pyrrolo[3,4-*d*]isoxazol-6-one (**2.17**)



N-hydroxybenzenecarboximidoyl chloride (2.0 g, 10.0 mmol), (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) (1.256 g, 10.0 mmol) was dissolved in benzene (25 mL). To this stirring solution, triethylamine (1.212 g, 12.0 mmol) was added dropwise before stirring for 18 hours. The white solid was filtered, rinsed with cold ether (30 mL) and recrystallised from dichloromethane to give (3a*S*,8a*R*,8b*R*)-3-phenyl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5]pyrrolo[3,4-*d*]isoxazol-6-one (**2.17**) as colourless crystals (1.633 g, 68 %).

Melting range: 225.2 – 226.3 ^{o}C

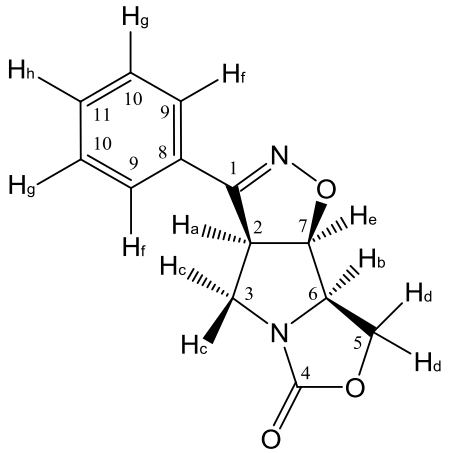
$[\alpha]_{D}^{25}$ = -197 (c= 0.60, MeOH)

^{1}H NMR (300MHz, CD_3OD) δ: 3.66 (dd, 1H, J = 8.2, 12.7$_c$ Hz, *c*) , 4.25 (dd, 1H, J = 1.8, 12.7$_c$ Hz, *c*) , 4.41 (m, 1H, *b*) , 4.55 (td, 1H, J = 2.1, 8.5$_a$ Hz, *e*) , 4.73 (t, 1H, J = 8.5$_e$ Hz, *a*) , 4.94 (dd, 1H, J = 2.5, 8.7$_d$ Hz, *d*) , 5.54 (dd, 1H, J = 4.3, 8.7$_d$ Hz, *d*) , 7.56 (d,1H, J = 1.9$_g$ Hz, *h*) 7.69 (d, 2H, J = 1.9$_g$ Hz, *f*), 7.75 - 7.78 (tt, 2H, J = 1.9$_f$, 5.2 Hz, *g*).

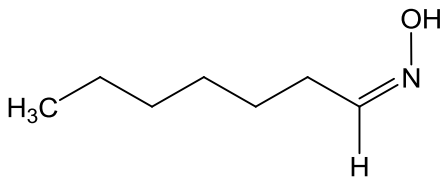
^{13}C NMR (75.5MHz, CD_3OD) δ: 49.9 (*3*), 55.0 (*2*), 63.1 (*6*), 64.9 (*5*), 85.9 (*7*), 127.5 (*9*), 129.4 (*10*), 131.0 (*8*), 131.2 (*11*), 147.6 (*1*), 157.3 (*4*).

FTIR υ_{max} cm^{-1}: 1745 (s), 2974 (s)

HRMS (ESI): calcd. for $C_{13}H_{12}N_2O_3$ $[M+Na]^+$ 267.0745 found 267.0735



3.2.11 heptanal oxime



The title compound was prepared by a modification of the procedure of Liu.[55]

A solution of sodium carbonate (3.250 g, 30.65 mmol) in water (20mL) was added to a stirred solution of hydroxylamine hydrochloride (3.80 g, 54.73 mol) and heptanal (5.0 g, 43.79 mmol) in water (30 mL) added dropwise at 0^{o}C. The reaction mixture was allowed to warm to room temperature for 2 hours, followed by extraction with ether (3 x 100 mL). The organic phases were combined, washed with water (200 mL), dried over magnesium sulfate and concentrated *in vacuo*, to give the crude heptanal oxime as a white solid (5.48 g, 97 %).

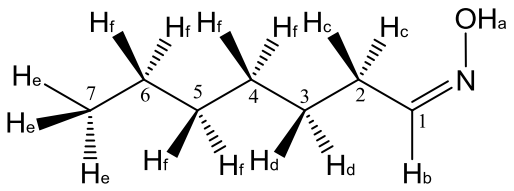
Melting range: 44.7 - 46.0^{o}C.

^{1}H NMR (300MHz, $CDCl_3$) δ: 0.86 (td, 3H, J = 2.3, 6.7 Hz, *e*), 1.23-1.35 (m, 6H, *f*), 1.46 (m, 2H, *d*), 2.17 (q, 1H, J = 7.2$_c$ Hz, *c*), 2.35 (q, 1H, J = 7.2$_c$, *c*), 7.39 (t, 1H, J = 6.2 Hz, *b*), 9.65 (s, 1H, *a*).

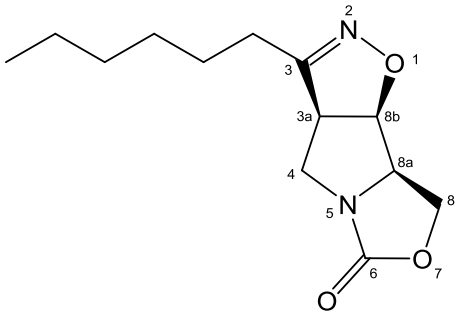
^{13}C NMR (75.5MHz, $CDCl_3$) δ: 13.8 (*7*), 22.4 (*6*), 26.5 (*3*), 28.9 (*4*), 29.3 (*2*), 31.4 (*5*), 152.0 (*1*).

FTIR υ_{max} cm^{-1}: 1666, 2924

HRMS (ESI): calcd. for $C_7H_{15}NO$ $[M+Na]^+$ 152.1051 found 152.1037



3.2.12 (3a*S*,8a*R*,8b*R*)-3-hexyl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5]pyrrolo[3,4-*d*]isoxazol-6-one (**2.18**)



To a stirred solution of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) (100 mg, 0.800 mmol), heptanal oxime (100.3 mg, 0.879 mmol) and triethylamine (0.134 mL, 0.960 mmol) in dichloromethane (20 mL), 8 % aqueous sodium hypochlorite (10 mL,

12.3 mmol) was added dropwise over 15 min at 0°C, then the reaction mixture was allowed to stir for 12 hour. The aqueous phase was separated before extraction with dichloromethane (3 x 50 mL), the organic phases were combined and washed with water (2 x 50 mL), then dried over magnesium sulfate and concentrated *in vacuo.* Diethyl ether (30 mL) was added to the residue and then filtered, the solid residue was rinsed with diethyl ether (30 mL) and then recrystallised from methanol give (3a*S*,8a*R*,8b*R*)-3-hexyl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5] pyrrolo[3,4-*d*] isoxazol-6-one (**2.18**) as a white solid (23 mg, 11 %).

Melting range: 139.9 – 141.5°C.

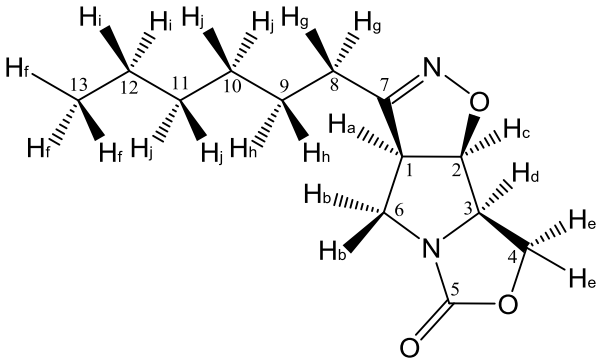
$[\alpha]_{D}^{28}$ = -81.0 (c= 0.58, $CHCl_3$)

^{1}H NMR (500MHz, $CDCl_3$) δ: 0.87 (t, 3H, J = 5.8_i Hz, *f*), 1.29 (m, 4H, *j*), 1.34 (m, 2H, *i*), 1.53 (m, 1H, *h*), 1.61 (m, 1H, *h*), 2.25 (m, 1H, *g*), 2.44 (m, 1H, *g*), 3.25 (dd, 1H, J = 7.9_a, 12.8_b Hz, *b*), 3.85 (t, 1H, J = 7.9_b Hz, *a*), 3.99 (d, 1H, J = 12.8_b Hz, *b*), 4.05 (m, 1H, *d*), 4.46 (t, 1H, J = 8.6_e Hz, *e*), 4.64 (dd, 1H, J = 2.2, 8.6_e Hz, *e*), 5.02 (dd, 1H, J = 4.7, 8.3 Hz, *c*).

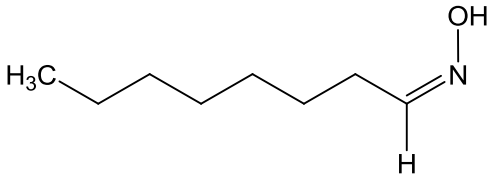
^{13}C NMR (125.7MHz, $CDCl_3$) δ: 13.9 (*13*), 22.4 (*12*), 25.9 (*9*), 26.0 (*10*), 28.8 (*11*), 31.3 (*8*), 48.1 (*6*), 56.8 (*1*), 62.7 (*3*), 64.2 (*4*), 83.4 (*2*), 158.8 (*7*), 160.8 (*5*).

FTIR υ_{max} cm^{-1}: 1724, 2932

HRMS (ESI): calcd. for $C_{13}H_{20}N_2O_3$ $[M+Na]^+$ 275.1371 found 275.1358



3.2.13 octanal oxime



The title compound was prepared by a modification of the procedure of Liu.[55]

A solution of sodium carbonate (2.00 g, 18.88 mmol) in water (20mL) was added to a stirring solution of hydroxylamine hydrochloride (2.343 g, 33.71 mol) and octanal (3.457

g, 26.97 mmol) in water (30 mL) dropwise at 0°C. Then the reaction mixture was then allowed to warm to room temperature for 2 hours, followed by extraction with ether (3 x 100 mL). The organic phases were combined, washed with water (200 mL), dried over magnesium sulfate and concentrated *in vacuo*. No purification was required to give octanal oxime as a white solid (2.322 g, 60 %).

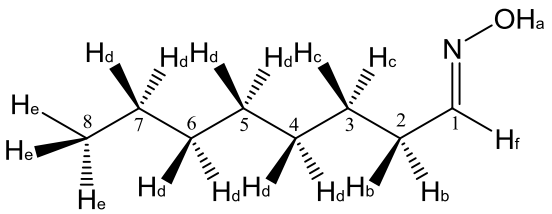
Melting range: 52.2 - 52.8°C.

^{1}H NMR (300MHz, $CDCl_3$) δ: 0.86 (td, 3H, J = 2.3, 6.7 Hz, *e*), 1.21-1.37 (m, 8H, *d*), 1.45 (m, 2H, *c*), 2.18 (q, 1H, J = 7.1_b Hz, *b*), 2.37 (q, 1H, J = 7.1_b, *b*), 7.37 (t, 1H, J = 6.2 Hz, *f*), 9.65 (s, 1H, *a*).

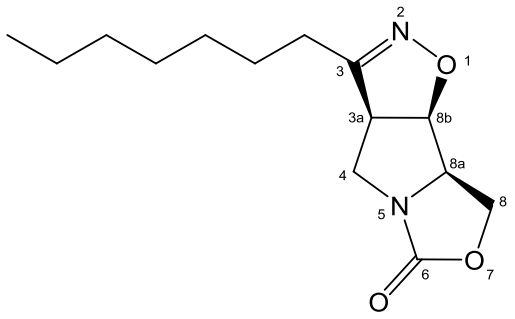
^{13}C NMR (75.5MHz, $CDCl_3$) δ: 13.9 (*8*), 22.4 (*7*), 25.9 (*2*), 26.5 (*3*), 28.9 (*4*), 29.3 (*5*), 31.4 (*6*), 152.1 (*1*).

FTIR υ_{max} cm^{-1}: 1667, 2919

HRMS (ESI): calcd. for $C_8H_{17}NO$ $[M+Na]^+$ 166.1280 found 166.1268



3.2.14 (3a*S*,8a*R*,8b*R*)-3-heptyl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5]pyrrolo[3,4-*d*]isoxazol-6-one (**2.19**)



To a stirred solution of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) (100 mg, 0.800 mmol), octanal oxime (127 mg, 0.879 mmol) and triethylamine (0.134 mL, 0.960 mmol) in dichloromethane (20 mL), 8 % aqueous sodium hypochlorite (10 mL, 12.3 mmol) was added dropwise over 15 min at 0^{o}C. The reaction mixture was allowed to stir for 12 hours, the aqueous phase was separated before extraction with dichloromethane (3 x 50 mL). The organic phases were combined and washed with water (2 x 50 mL), then dried over magnesium sulfate and concentrated *in vacuo.* Diethyl ether (30 mL) was added to the residue and then filtered, the solid residue was rinsed with diethyl ether (30 mL) and then recrystallised from methanol give (3a*S*,8a*R*,8b*R*)-3-heptyl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5] pyrrolo[3,4-*d*] isoxazol-6-one (**2.19**) as a white solid (85 mg, 40 %).

Melting range: 141.8 - 145.7°C.

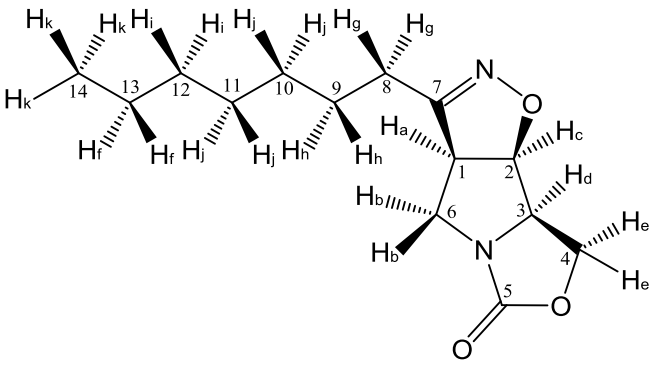
$[\alpha]_D^{28}$ = -96.8 (c= 0.25, $CHCl_3$)

^{1}H NMR (500MHz, $CDCl_3$) δ: 0.86 (t, 3H, J = 6.6 Hz, *k*), 1.28 (m, 4H, *f*, *i*), 1.39 (t, 4H, J = 7.3 Hz, *j*), 1.54 (m, 1H, *h*), 1.61 (m, 1H, *h*), 2.25 (m, 1H, *g*), 2.44 (m, 1H, *g*), 3.25 (dd, 1H, J = 7.8_a, 12.8_b Hz, *b*), 3.85 (t, 1H, J = 7.8_b Hz, *a*), 3.99 (d, 1H, J = 12.8_b Hz, *b*), 4.06 (m, 1H, *d*), 4.46 (t, 1H, J = 8.7_e Hz, *e*), 4.65 (dd, 1H, J = 2.2, 8.7_e Hz, *e*), 5.02 (dd, 1H, J = 4.7, 8.5 Hz, *c*).

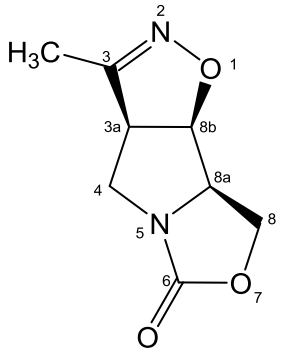
^{13}C NMR (125.7MHz, $CDCl_3$) δ: 14.0 (*14*), 22.5 (*13*), 26.0 (*9*), 28.8 (*11*), 29.1 (*10*), 31.6 (*12*), 45.9 (*8*), 48.1 (*6*), 56.8 (*1*), 62.7 (*3*), 64.2 (*4*), 83.4 (*2*), 158.7 (*7*), 160.7 (*5*).

FTIR υ_{max} cm^{-1}: 1725, 2930

HRMS (ESI): calcd. for $C_{14}H_{22}N_2O_3$ $[M+Na]^+$ 289.1528 found 289.1513



3.2.15 ethyl (3a*S*,8a*R*,8b*R*)-6-oxo-3a,8,8a,8b-tetrahydro-4*H*[1,3]oxazolo[3',4':1,5]pyrrolo [3,4-*d*]isoxazole-3-carboxylate (**2.20**)



Triethylamine (484 mg, 4.795 mmol) was added to a stirred solution of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) (300 mg, 2.398 mmol), nitroethane **(**216 mg, 2.877 mmol) and *p*-toluenesulfonyl chloride (913 mg, 4.795 mmol) in benzene (25 mL) at 0 ^{o}C. The reaction mixture was allowed to warm room temperature for 12 hours before

washing with water (3 x 50 mL). The organic phase was dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 9:1 diethyl ether/petrol then neat ethyl acetate to give ethyl (3a*S*,8a*R*,8b*R*)-6-oxo-3a,8,8a,8b-tetrahydro-4*H*[1,3]oxazolo[3',4':1,5]pyrrolo[3,4-*d*] isoxazole-3-carboxylate (**2.20**) as colourless crystals (170 mg, 39 %).

Melting range: 123.6 - 126.4^{o}C.

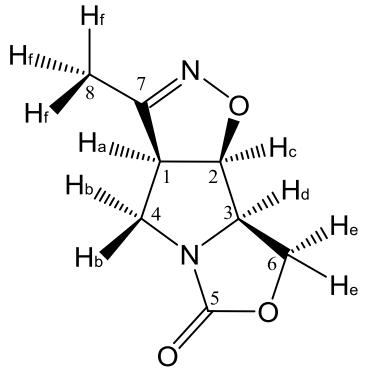
$[\alpha]_{D}^{28}$ = -150.3 (c= 0.93, MeOH)

^{1}H NMR (300MHz, $CDCl_3$) δ: 2.01 (s, 3H, *f*), 3.26 (dd, 1H, J = 7.5_a, 13.1_b Hz, *b*), 3.83 (t, 1H, J = 7.5_b Hz, *a*), 4.02 (d, 1H, J = 13.1_b Hz, *b*), 4.06 (m, 1H, *d*), 4.47 (td, 1H, J = 3.4, 8.7_e Hz, *e*), 4.66 (dd, 1H, J = 3.0, 8.7_e Hz, *e*), 5.05 (m, 1H, *c*).

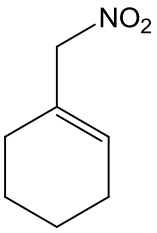
^{13}C NMR (75.5MHz, $CDCl_3$) δ: 11.3 (*8*), 48.0 (*4*), 58.0 (*1*), 62.7 (*3*), 64.3 (*6*), 84.7 (*2*), 155.2 (*7*), 176.9 (*5*).

FTIR υ_{max} cm^{-1}: 1732(s), 2964 (s)

HRMS (ESI): calcd. for $C_8H_{10}N_2O_3$ $[M+Na]^+$ 205.0589 found 205.0581



3.2.16 1-(nitromethyl)cyclohexene

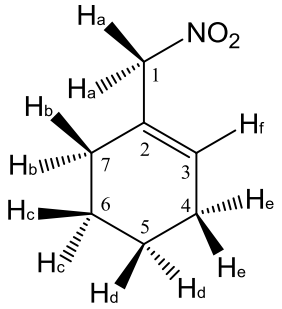


In a round-bottomed flask fitted with a Dean and Stark trap was placed a solution of cyclohexanone (3.0 g, 30.57 mmol), *N*,*N* dimethylethylenediamine (1.776 g, 15.29 mmol) and nitromethane (7.463 g, 122.2 mmol) in benzene (75 mL). The solution was heated under reflux for 18 hours, then cooled, washed with 2M hydrochloric acid (20 mL) and water (20 mL), dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 20 % diethyl ether / petrol give 1-(nitromethyl)cyclohexene as a yellow oil (301 mg, 7 %).

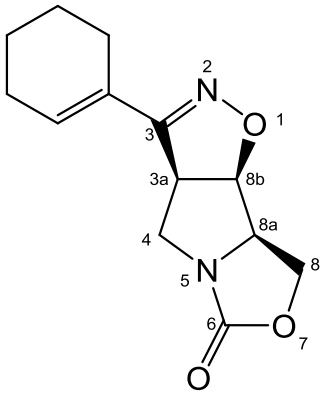
^{1}H NMR (300MHz, $CDCl_3$) δ: 1.57 – 1.68 (m, 4H, *c, d*) , 2.08 (m, 4H, *b, e*) , 4.78 (s, 2H, *a*), 5.92 (s, 1H, *f*).

^{13}C NMR (75.5MHz, $CDCl_3$) δ: 21.4 (*6*), 22.1 (*5*), 25.3 (*7*), 26.5 (*4*), 82.8 (*1*), 128.5 (*3*), 133.1 (*2*).

Spectroscopic data identical to literature values.[69]



3.2.17 (3a*S*,8a*R*,8b*R*)-3-cyclohex-1-en-1-yl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5]pyrrolo[3,4-*d*]isoxazol-6-one (**2.21**)



Triethylamine (221 mg, 2.192 mmol) was added to a stirred solution of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) (137 mg, 1.096 mmol), 1-(nitromethyl) cyclohexene **(**170 mg, 1.206 mmol) and *p*-toluenesulfonyl chloride (418 mg, 2.192 mmol) in chloroform (25 mL) at 0 ^{o}C. The reaction mixture was allowed to warm room temperature for 15 hours before being washed with water (3 x 50 mL). The organic phase was dried over magnesium sulfate, and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 7:1 diethyl ether / petrol give (3a*S*,8a*R*,8b*R*)-3-cyclohex-1-en-1-yl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5] pyrrolo[3,4-*d*]isoxazol-6-one (**2.21**) as colourless crystals (284 mg, 95 %).

Melting range: 228.4 - 231.5^{o}C.

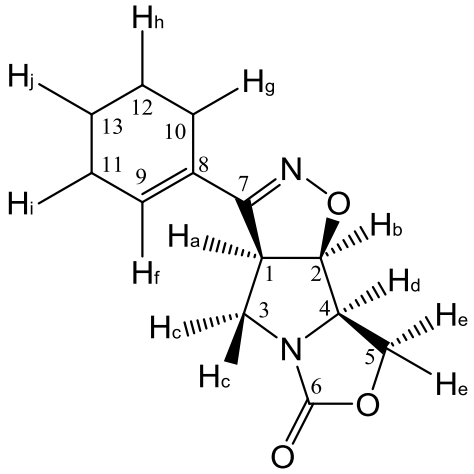
$[\alpha]_{D}^{27}$ = -288.4 (c= 0.95, MeOH)

^{1}H NMR (300MHz, $CDCl_3$) δ: 1.59 (m, 4H, *h*, *j*), 2.20 (m, 4H, *g*, *i*), 3.31 (dd, 1H, J = 8.3, 12.5_c Hz, *c*), 3.93 (dd, 1H, J = 2.0_a, 12.5_c Hz, *c*) 4.00 (td, 1H, J = 2.0_c, 8.5_b Hz, *a*), 4.09 (m, 1H, *d*), 4.42 (t, 1H, J = 8.5_a Hz, *b*), 4.61 (dd, 1H, J = 2.5, 8.6_e Hz, *e*), 5.01 (dd, 1H, J = 4.1, 8.6_e Hz, *e*), 5.94 (t, 1H, J = 3.9 Hz, *f*).

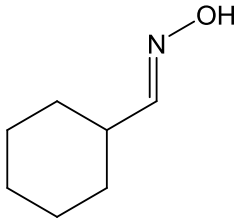
^{13}C NMR (75.5MHz, $CDCl_3$) δ: 22.1, 22.3, 25.3, 26.4, 50.5, 54.1, 63.2, 64.9, 85.5, 133.9.

FTIR υ_{max} cm^{-1}: 1742, 2924

HRMS (ESI): calcd. for $C_{13}H_{16}N_2O_3$ $[M+Na]^+$ 271.1058 found 271.1045



3.2.18 cyclohexanecarboxaldehyde oxime



The title compound was prepared by a modification of the procedure of Liu.[55]

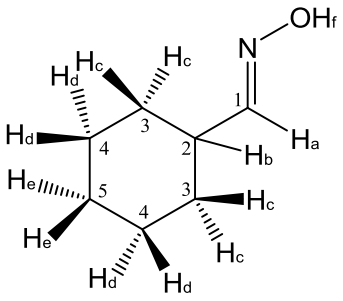
A solution of sodium carbonate (1.988 g, 18.75 mmol) in water (30mL) was added dropwise to a stirred solution of hydroxylamine hydrochloride (2.327 g, 33.48 mol) and

cyclohexanecarboxaldehyde (3.00 g, 26.80 mmol) in water (20 mL). The reaction mixture was allowed to stir for 2 hours, followed by extraction with ether (3 x 80 mL). The organic phases were combined, washed with water (50 mL), dried over magnesium sulfate and concentrated *in vacuo* and used directly for the next step (3.115 g, 92 %).

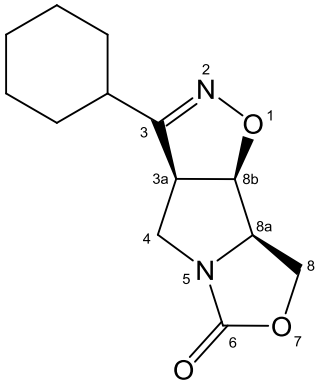
^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.15-1.34 (m, 4H, *c*, *d*), 1.44 (m, 2H, *e*), 1.69-1.79 (m, 4H, *c*, *d*), 2.22 (m, 1H, *b*), 7.31 (d, 1H, J = 5.1 Hz, *a*), 9.12 (s, 1H, *f*).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 25.5 (*4*), 25.9 (*5*), 30.2 (*3*), 38.5 (*2*), 156.1 (*1*).

LRMS (ES+): 127 ($[MH]^+$)



3.2.19 (3a*S*,8a*R*,8b*R*)-3-cyclohexyl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5] pyrrolo[3,4-*d*]isoxazol-6-one (**2.22**)



To a stirred solution of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) (100 mg, 0.800 mmol), cyclohexanecarboxaldehyde oxime (112 mg, 0.880 mmol) and triethylamine (0.134 mL, 0.960 mmol) in dichloromethane (10 mL), 8 % aqueous sodium hypochlorite (10 mL) was added dropwise over 15 min at 0^{o}C. The reaction mixture was allowed to stir for 12 hours, the aqueous layer was separated before extraction with dichloromethane (3 x 50 mL). The organic phases were combined and washed with water (2 x 50 mL), then dried over magnesium sulfate and concentrated *in vacuo.* Diethyl ether (30 mL) was added to the residue and then filtered, the solid residue was rinsed with diethyl ether (30 mL) and then recrystallised from methanol to give (3a*S*,8a*R*,8b*R*)-3-cyclohexyl-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5]pyrrolo[3,4-*d*]isoxazol-6-one (**2.22**) as a white solid (52 mg, 26 %).

Melting range: 230.4 - 232.7 ^{o}C.

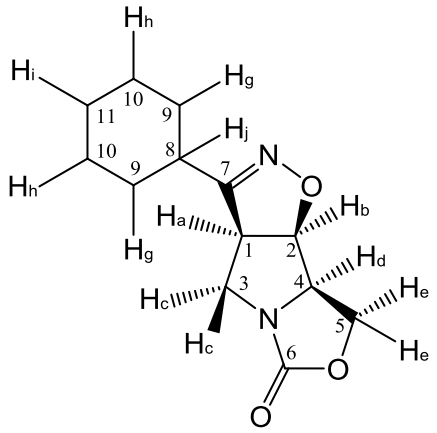
$[\alpha]_{D}^{30}$ = -184.4 (c= 0.95, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.20 - 1.26 (td, 2H, J = 2.5, 12.0_h Hz, *i*), 1.29 - 1.34 (td, 2H, J = 3.0_h, 12.3_h Hz, *g*), 1.48 (qd, 1H, J = 3.0_g, 12.3_g Hz, *h*), 1.68 (d, 1H, J = 12.9 Hz, *h*), 1.78 (m, 2H, *g*), 1.92 (d, 2H, 12.0_i Hz, *h*), 2.37 (tt, 1H, 3.3, 11.2 Hz, *j*), 3.26 (dd, 1H, J = 8.1_a, 12.8_c Hz, *c*), 3.90 (t, 1H, J = 8.1_c Hz, *a*), 4.01 (d, 1H, J = 12.8_c Hz, *c*), 4.05 (m, 1H, *d*), 4.46 (t, 1H, J = 8.5 Hz, *b*), 4.65 (dd, 1H, J = 2.4_d, 8.7_e Hz, *e*), 5.00 (dd, 1H, J = 4.6_d, 8.7_e Hz, *e*).

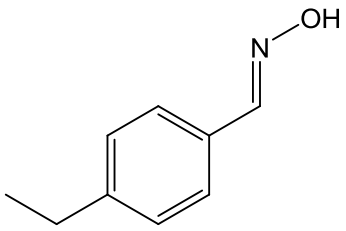
^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 25.8 (*10*), 30.0 (*11*), 31.2 (*9*), 35.9 (*8*), 48.4 (*3*), 55.7 (*1*), 62.7 (*4*), 64.1 (*5*), 83.6 (*2*), 160.8 (*7*), 162.4 (*6*).

FTIR υ_{max} cm^{-1}: 1726, 2854, 2927.

HRMS (ESI): calcd. for $C_{13}H_{18}N_2O_3$ $[M+Na]^+$ 273.1215 found 273.1201



3.2.20 4-ethyl benzaldehyde oxime



The title compound was prepared by a modification of the procedure of Liu.[55]

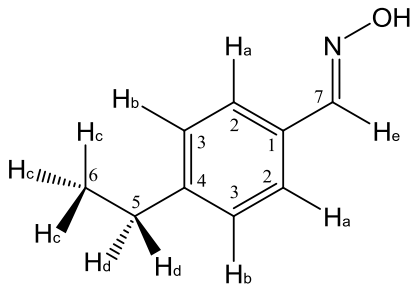
A solution of sodium carbonate (820 mg, 7.731 mmol) in water (20mL) was added to a stirred solution of hydroxylamine hydrochloride (959 mg, 13.80 mol) and 4-ethyl benzaldehyde (1.480 g, 11.40 mmol) in water (30 mL) dropwise. The reaction mixture was allowed to stir for 2 hours, followed by extraction with ether (3 x 50 mL). The organic phases were combined, washed with water (50 mL), dried over magnesium sulfate, concentrated *in vacuo* and used directly for the next step (1.583 g, 96 %).

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.26 (t, 3H, J = 7.6$_d$ Hz, *c*), 2.68 (q, 2H, J = 7.6$_c$ Hz, *d*), 7.23 (app. d, 2H, J = 7.4$_a$ Hz, *b*), 7.51 (app. d, 2H, J = 7.4$_b$ Hz, *a*), 8.16 (s, 1H, *e*).

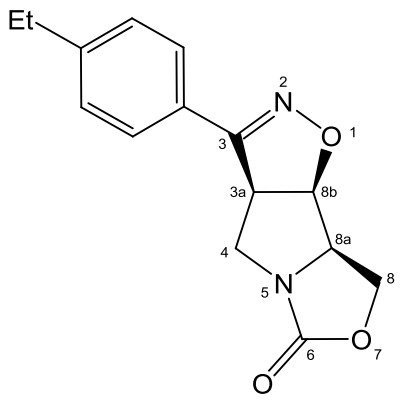
^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 15.3 (*6*), 28.8 (*5*), 127.1 (*3*), 128.3 (*1*), 129.4 (*2*), 146.6 (*4*), 150.3 (*7*).

FTIR υ_{max} cm^{-1}: 1679, 2557, 2844

LRMS (ES+): 149 ($[MH]^+$)



3.2.21 (3a*S*,8a*R*,8b*R*)-3-(4-ethylphenyl)-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5] pyrrolo[3,4-*d*]isoxazol-6-one (**2.23**)



To a stirred solution of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) (164 mg, 1.311 mmol), ethyl benaldehyde oxime (234 mg, 1.573 mmol) and triethylamine (0.220 mL, 1.573 mmol) in dichloromethane (10 mL), 8 % aqueous sodium hypochlorite (10 mL) was added dropwise over 15 min at 0 ^{o}C. The reaction mixture was allowed to stir for 12 hours, the aqueous layer was separated before extraction with dichloromethane (3 x 50 mL). The organic phases were combined and washed with water (2 x 50 mL), then dried over magnesium sulfate and concentrated *in vacuo.* Diethyl ether (30 mL) was added to the residue and then filtered, the solid residue was rinsed with diethyl ether (30 mL), and then recrystallised from methanol to give (3a*S*,8a*R*,8b*R*)-3-(4-ethylphenyl)-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5]pyrrolo [3,4-*d*]isoxazol-6-one (**2.23**) as a white solid (128 mg, 36 %).

Melting range: 260.2 – 263.6 ^{o}C.

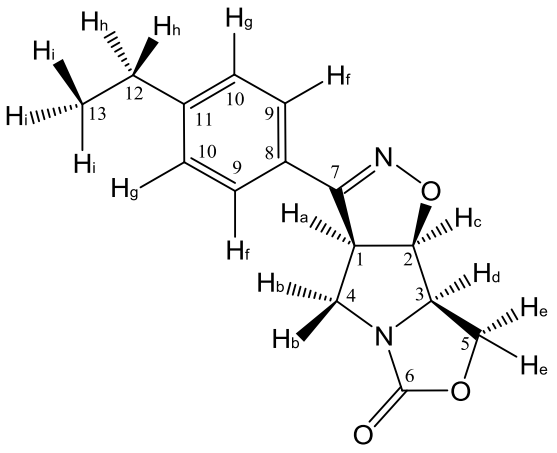
$[\alpha]_D^{28}$ = -318.3 (c= 0.35, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 1.25 (t, 3H, J = 7.5_h Hz, *i*), 2.68 (q, 2H, J = 7.5_i Hz, *h*), 3.45 (dd, 1H, J = 8.2_a, 12.6_b Hz, *b*), 4.05 (d, 1H, 12.6_b Hz, *b*), 4.19 (m, 1H, *d*), 4.33 (t, 1H, J = 8.2_b Hz, *a*), 4.52 (t, 1H, J = 8.7_e Hz, *e*), 4.74 (d, 1H, J = 8.7_e Hz, *e*), 5.22 (dd, 1H, J = 4.1, 8.2 Hz, *c*), 7.25 (app. d, 2H, J = 8.1_f Hz, *g*), 7.53 (app. d, 2H, J = 8.1_g Hz, *f*).

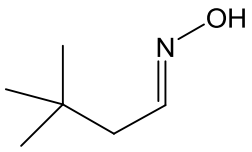
^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 15.1 (*13*), 28.6 (*12*), 49.3 (*4*), 54.5 (*1*), 62.5 (*3*), 64.3 (*5*), 85.1 (*2*), 109.8 (*8*), 124.7 (*11*), 126.9 (*9*), 128.3 (*10*), 147.0 (*7*), 157.5 (*6*).

FTIR υ_{max} cm^{-1}: 1736, 2968.

HRMS (ESI): calcd. for $C_{15}H_{16}N_2O_3$ $[M+Na]^+$ 295.1059 found 295.1043



3.2.22 3,3-dimethylbutanal oxime

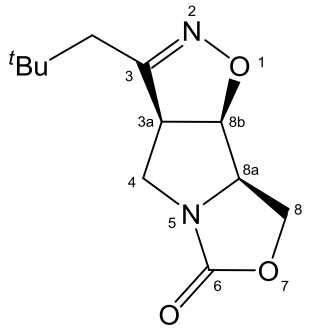


The title compound was prepared by a modification of the procedure of Liu.[55]

A solution of sodium carbonate (371 mg, 3.50 mmol) in water (20mL) was added dropwise to a stirred solution of hydroxylamine hydrochloride (434 mg, 6.25 mmol) and 3,3-dimethylbutanal (500 mg, 5.00 mmol) in water (10 mL). The reaction mixture was allowed to warm to room temperature for 2 hours, followed by extraction with ether (3 x 50 mL). The organic phases were combined, washed with water (50 mL), dried over

magnesium sulfate, concentrated *in vacuo* and used directly for the next step (428 mg, 74 %).

3.2.23 (3a*S*,8a*R*,8b*R*)-3-(2,2-dimethylpropyl)-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo [3', 4':1,5]pyrrolo[3,4-*d*]isoxazol-6-one (**2.24**)



To a stirred solution of (*S*)-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.1**) (100 mg, 0.800 mmol), 3,3-dimethylbutanal oxime (129 mg, 1.119 mmol) and triethylamine (0.134 mL, 0.960 mmol) in dichloromethane (10 mL), 8 % aqueous sodium hypochlorite (10 mL) was added dropwise over 15 min at 0^{o}C. The reaction mixture was allowed to stir for 12 hours, the aqueous phase was separated before extraction with dichloromethane (3 x 50 mL). The organic phases were combined, washed with water (2 x 50 mL), then dried over magnesium sulfate and concentrated *in vacuo.* Diethyl ether (30 mL) was added to the residue and then filtered, the solid residue was rinsed with diethyl ether (30 mL) and then recrystallised from methanol give (3a*S*,8a*R*,8b*R*)-3-(2,2-

dimethylpropyl)-3a,8,8a,8b-tetrahydro-4*H*-[1,3]oxazolo[3',4':1,5] pyrrolo[3,4-*d*] isoxazol -6-one (**2.24**) as a white solid (45 mg, 24 %).

Melting range: 199.5 – 205.2 ^{o}C.

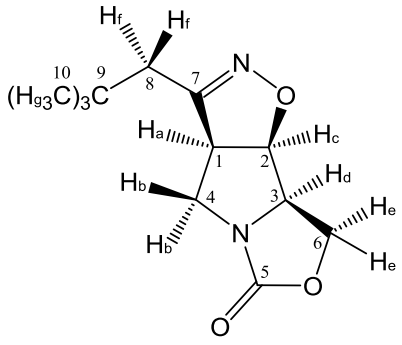
$[\alpha]_{D}^{27}$ = -162 (c= 0.40, $CHCl_3$)

^{1}H NMR (300MHz, $CDCl_3$) δ: 1.03 (s, 9H, *g*), 2.17 (d, 1H, J = 14.8_f Hz, *f*), 2.45 (d, 1H, J = 14.8_f Hz, *f*), 3.26 (dd, 1H, J = 7.9_a, 12.8_b Hz, *b*), 3.91 (t, 1H, J = 7.9_b Hz, *a*), 4.02 - 4.08 (m, 2H, *d, b*), 4.48 (t, 1H, J = 8.7_e Hz, *e*), 4.69 (dd, 1H, J = 2.4, 8.7_e Hz, *e*), 5.02 (dd, 1H, J = 4.8, 8.5 Hz, *c*).

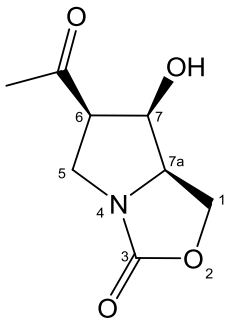
^{13}C NMR (75.5MHz, $CDCl_3$) δ: 29.8 (*10*), 31.4 (*9*), 39.1 (*4*), 48.3 (*1*), 58.6 (*8*), 62.7 (*3*), 64.5 (*6*), 83.0 (*2*), 125.2 (*7*), 157.0 (*5*).

FTIR υ_{max} cm^{-1}: 1730, 2955

HRMS (ESI): calcd. for $C_{12}H_{18}N_2O_3$ $[M+Na]^+$ 261.1215 found 261.1202

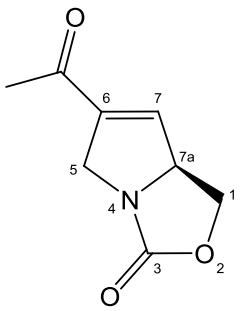


3.2.24 (6*R*,7*R*,7a*R*)-6-acetyl-7-hydroxytetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.25**)



Raney nickel (1 spatula, approx. 10-20 mg) was added to a stirred solution of ethyl (3a*S*,8a*R*,8b*R*)-6-oxo-3a,8,8a,8b-tetrahydro-4*H*[1,3]oxazolo[3',4':1,5]pyrrolo[3,4-*d*] isoxazole-3-carboxylate (**2.20**) (680 mg, 3.732 mmol) and boric acid (485 mg, 7.838 mmol) in a 5:1 mixture of methanol and water (30 mL). The reaction mixture was allowed to stir for 8 hours under hydrogen atmosphere. The Raney nickel was removed by filtration, the solution was concentrated *in vacuo* and used directly for the next step (406 mg, 40 %). R_f (EtOAc) = 0.16

3.2.25 (7a*S*)-6-acetyl-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.26**)



p-Toluenesulfonic acid monohydrate (3.5 mg, 18.5 umol) was added to a stirred mixture of (6*R*,7*R*,7a*R*)-6-acetyl-7-hydroxytetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.25**) (171 mg, 0.924 mmol) and toluene (15 mL). The reaction was heated under reflux for 2 hours with a Dean-Stark apparatus. The reaction mixture was concentrated *in vacuo* and the residue was purified by flash column chromatography on silica gel, eluting with neat diethyl ether to give (7a*S*)-6-acetyl-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.26**) as a brown oil (64 mg, 42 %).

R_f (Et_2O) = 0.09

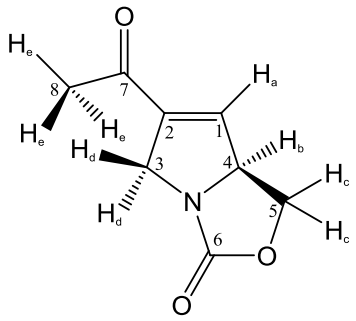
$[\alpha]_D^{28}$ = -93.4 (c= 0.69, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 2.34 (s, 3H, *e*), 3.97 (d, 1H, J = 15.6$_d$ Hz, *d*), 4.33 (dd, 1H, J = 4.9, 8.7$_c$ Hz, *c*), 4.56 (d, 1H, J = 15.6$_d$ Hz, *d*), 4.63 (t, 1H, J = 8.7$_c$ Hz, *c*), 4.90 (m, 1H, *b*), 6.67 (s, 1H, *a*).

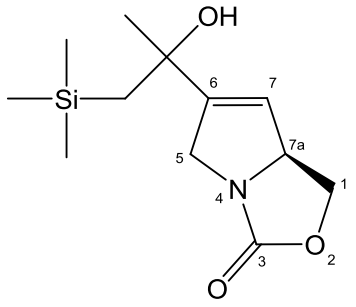
^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 26.9 (*8*), 53.5 (*3*), 65.4 (*4*), 67.3 (*5*), 138.0 (*1*), 145.0 (*2*), 162.5 (*6*), 193.8 (*7*).

FTIR υ_{max} cm^{-1}: 1666, 1732, 2919.

HRMS (ESI): calcd. for $C_8H_9NO_3$ $[M+Na]^+$ 190.0475 found 190.0483.



3.2.26 (7a*S*)-6-[1-hydroxy-1-methyl-2-(trimethylsilyl)ethyl]-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.33**)



Trimethylsilylmethyl lithium (1.0 M in pentane, 1.08 mL, 1.079 mmol) was added to a stirred suspension of anhydrous $CeCl_3$ (310 mg, 1.258 mmol) in THF (10 mL) at -78 ^oC,

the suspension was allowed to stir for a further 1 hour before adding (7a*S*)-6-acetyl-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.26**) (120 mg, 0.719 mmol) in dry THF (10 mL). The reaction was allowed to warm to room temperature over 1 hour followed by stirring for a further 2 hours. The resulting mixture was concentrated *in vacuo* and re-diluted in DCM (30 mL) then washed with H_2O (30 mL). The aqueous layer was extracted with DCM (3 x 30 mL), the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 2:1 diethyl ether / *n*-hexane to give (7a*S*)-6-[1-hydroxy-1-methyl-2-(trimethylsilyl)ethyl]-5,7a-dihydro-1*H*-pyrrolo[1,2*c*][1,3]oxazol-3-one (**2.33**) as a brown oil (124 mg, 68 %).

R_f (Et_2O / *n*-hexane 2:1) = 0.19

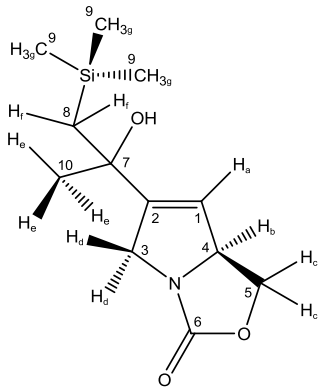
$[\alpha]_D^{25}$ = +32.8 (c= 0.67, $CHCl_3$)

^{1}H NMR (500 MHz, $CDCl_3$) δ: 0.05 (2 x s, 9H, *g*), 1.13 (2 x s, 2H, *f*), 1.44 (s, 3H, *e*), 3.86 (d, 1H, J = 15.4$_d$ Hz, *d*), 4.21 (m, 1H, *c*), 4.38 (d, 1H, J = 15.4$_d$ Hz, *d*), 4.56 (t, 1H, J = 8.3 Hz, *c*), 4.73 (m, 1H, *b*), 5.64 (s, 1H, *a*).

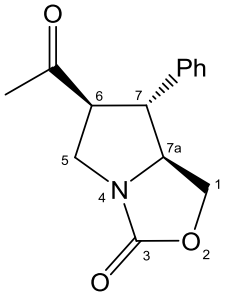
^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 0.1 (*9*), 29.6 (*10*), 30.3 (*8*), 31.9 (*3*), 54.1 (*4*), 64.8 (*5*), 68.8 (*7*), 120.3 (*1*), 125.4 (*2*), 154.2 (*6*).

FTIR υ_{max} cm^{-1}: 1741, 2921, 3450.

HRMS (ESI): calcd. for $C_{12}H_{21}NO_3Si$ $[M+Na]^+$ 190.0475 found 190.0483.



3.2.28 (6*S*,7*R*,7a*S*)-6-acetyl-7-phenyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.36**)



Phenyllithium solution (2.0 M in dibutyl ether, 1.26 mL, 2.515 mmol) was added to a stirred suspension of copper bromide (180 mg, 1.257 mmol) in anhydrous diethyl ether (10 mL) dropwise at -10 ^{o}C. The suspension was allowed to stir for 15 minutes before cooling to -78 ^{o}C. A solution of (7a*S*)-6-acetyl-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.26**) (100 mg, 0.599 mmol) in anhydrous diethyl ether (10 mL) was added to the reaction mixture dropwise before allowing to warm to room temperature for 12 hours, the resulting mixture was poured into an ice / saturated ammonium chloride solution mixture. The organic phase was washed with saturated ammonium chloride solution (2 x 50 mL) and the combined aqueous phases were extracted with diethyl ether (2 x 50 mL). The organic phases were combined and washed with saturated sodium chloride solution (50 mL), then dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash column chromatography on silica gel, eluting with 3:1 diethyl ether / *n*-hexane to give (6*S*,7*R*,7a*S*)-6-acetyl-7-phenyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.36**) as a brown oil (32 mg, 22 %). R_f (Et_2O / *n*-hexane 3:1) = 0.15

$[\alpha]_D^{26}$ = +92.4 (c= 0.52, $CHCl_3$)

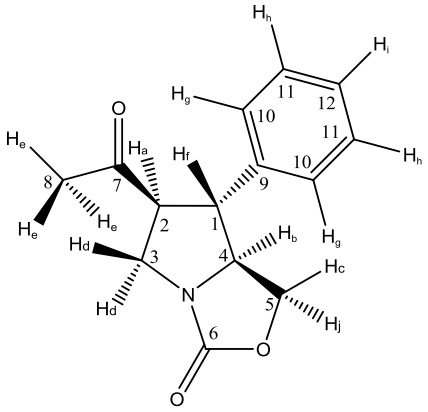
^{1}H NMR (600 MHz, $CDCl_3$) δ: 1.94 (s, 3H, *e*), 3.09 (t, 1H, J = 10.1_b Hz, *f*), 3.48 (td, 1H, J = 7.4_d, 9.9_d Hz, *a*), 3.62 (dd, 1H, J = 9.9_a, 11.8_d Hz, *d*),

3.90 (dd, 1H, J = 7.4_a, 11.8_d Hz, *d*), 3.99 (ddd, 1H, J = 2.5_c, 7.6_j, 10.1_f Hz, *b*), 4.15 (dd, 1H, J = 2.5_b, 9.3_j Hz, *c*), 4.32 (dd, 1H, J = 7.6_b, 9.3_c Hz, *j*), 7.20 (d, 2H, J = 4.7 Hz, *g*), 7.25 (t, 1H, J = 7.5_h Hz, *i*), 7.31 (t, 2H, J = 7.5_i Hz, *h*).

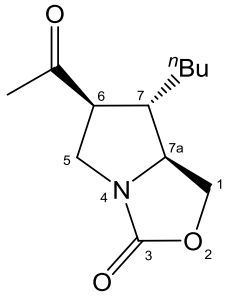
^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 30.0 (*8*), 48.0 (*1*), 52.6 (*3*), 60.2 (*2*), 65.9 (*4*), 66.5 (*5*), 127.7 (*10*), 128.1 (*12*), 129.3 (*11*), 136.8 (*9*), 160.9 (*6*), 204.9 (*7*).

FTIR υ_{max} cm^{-1}: 1708, 1746, 2912.

HRMS (ESI): calcd. for $C_{14}H_{15}NO_3$ $[M+Na]^+$ 268.0944 found 268.0940.



3.2.27 (6*S*,7*S*,7a*S*)-6-acetyl-7-butyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.37**)



n-Butyllithium (2.5 M in pentane, 1.00mL, 2.515 mmol) was added to a stirred suspension of copper bromide (180 mg, 1.257 mmol) in anhydrous diethyl ether (10 mL) dropwise at -10 ^{o}C. The suspension was allowed to stir for 15 minutes before cooling to -78 ^{o}C, a solution of (7a*S*)-6-acetyl-5,7a-dihydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.26**) (100 mg, 0.599 mmol) in anhydrous diethyl ether (10 mL) was added to the reaction mixture dropwise before allowing to warm to room temperature for 12 hours. The resulting mixture was poured into an ice / saturated ammonium chloride solution mixture and the organic phase was washed with saturated ammonium chloride solution (2 x 50 mL). The combined aqueous phases were extracted with diethyl ether (2 x 50 mL), the organic phases were combined and washed with saturated sodium chloride solution (50 mL), then dried over magnesium sulfate and concentrated *in vacuo.* The residue was purified by flash column chromatography on silica gel, eluting with 2:1 diethyl ether / *n*-

hexane to give (6*S*,7*S*,7a*S*)-6-acetyl-7-butyltetrahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazol-3-one (**2.37**) as a brown oil (70 mg, 52 %). R_f (Et_2O / *n*-hexane 3:1) = 0.18

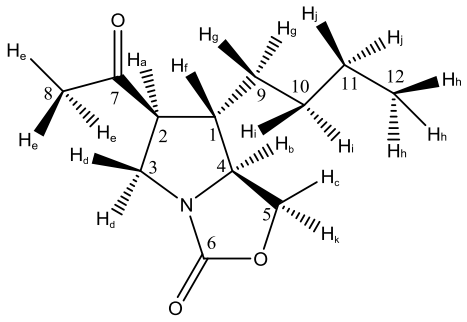
$[\alpha]_D^{26}$ = +77.3 (c= 0.65, $CHCl_3$)

^{1}H NMR (600 MHz, $CDCl_3$) δ: 0.85 (t, 3H, J = 7.3_i Hz, *h*), 1.12 – 1.24 (m, 2H, *i*), 1.24 – 1.32 (m, 2H, *j*) 1.34 (dddd, 1H, J = 5.4_i, 8.2_f, 10.8_i, 13.6_g Hz, *g*) 1.49 (dddd, 1H, J = 5.1_i, 6.0_f, 11.4_i, 13.5_g Hz, *g*), 2.18 (s, 3H, *e*), 2.17 – 2.22 (m, 1H, *f*), 2.94 (ddd, 1H, J = 6.7_d, 8.8_f, 9.8_d Hz, *a*), 3.47 (dd, 1H, J = 9.8_a, 11.9_d Hz, *d*), 3.63 (ddd, 1H, J = 3.5_c, 7.8_k, 9.0_g Hz, *b*), 3.68 (dd, 1H, J = 6.6_a, 11.9_d Hz, *d*), 4.22 (dd, 1H, J = 3.5_b, 9.1_k Hz, *c*), 4.50 (dd, 1H, J = 7.9_b, 9.1_c Hz, *k*).

^{13}C NMR (125.7 MHz, $CDCl_3$) δ: 13.8 (*12*), 22.8 (*11*), 29.1 (*8*), 30.2 (*10*), 31.8 (*9*), 46.5 (*1*), 47.7 (*3*), 58.9 (*2*), 64.8 (*4*), 67.5 (*5*), 160.6 (*6*), 206.3 (*7*).

FTIR υ_{max} cm^{-1}: 1707, 1747, 2926.

HRMS (ESI): calcd. for $C_{12}H_{19}NO_3$ $[M+Na]^+$ 248.1257 found 248.1248.


O
He
Ha
Hf
Hg
Hg
Hj
Hj
8
7
9
10
11
12
Hh
He
He
2
1
Hi
Hi
Hb
Hh
Hh
Hd
3
4
Hc
N
5
Hd
Hk
6
O
O

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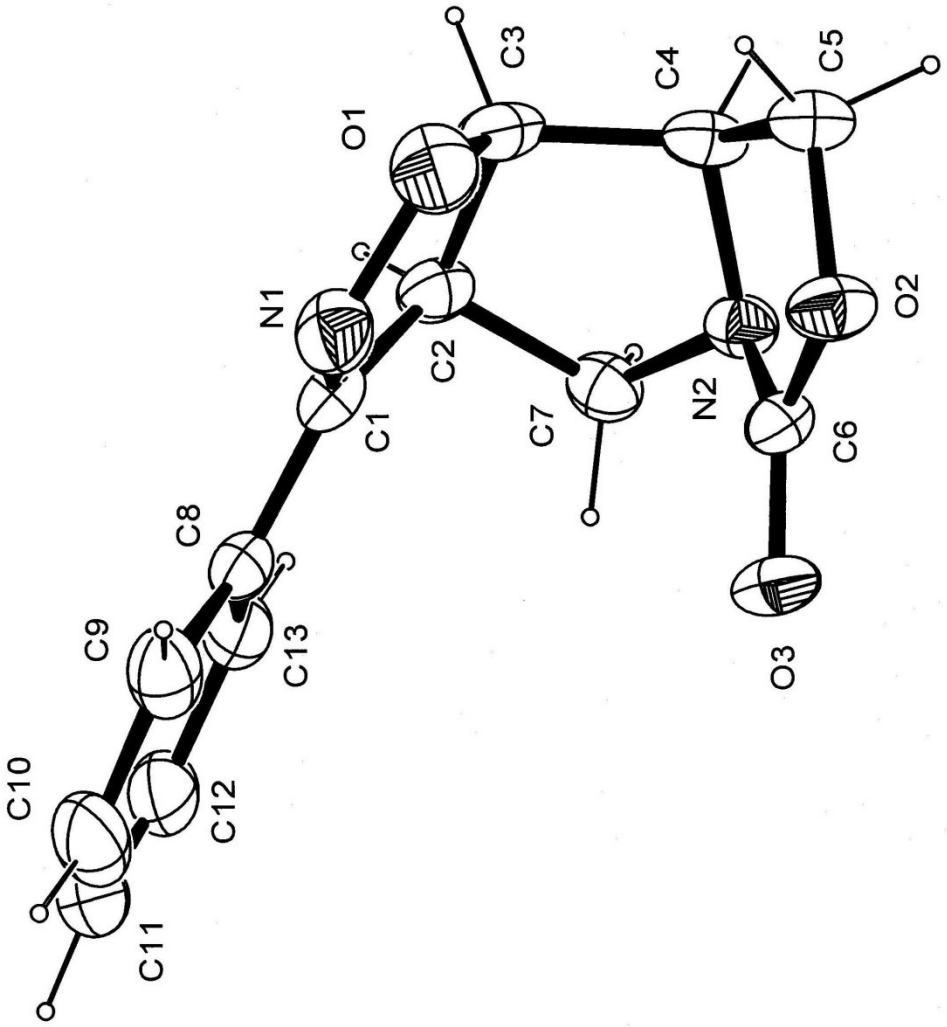
5. Appendices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C4
C5
O1
N1
C2
C7
N2
O2
C1
C6
C8
O3
C9
C13
C10
C12
C11

Table 1. Crystal data and structure refinement .

Identification code	apr1507	
Empirical formula	C13 H12 N2 O3	
Formula weight	244.25	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$ (No.19)	
Unit cell dimensions	a = 6.2349(2) Å	α= 90°.
	b = 10.1260(4) Å	β= 90°.
	c = 17.9768(7) Å	γ = 90°.
Volume	1134.96(7) $Å^3$	
Z	4	
Density (calculated)	1.43 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	512	
Crystal size	0.35 x 0.10 x 0.05 mm^3	
Theta range for data collection	3.46 to 26.01°.	
Index ranges	-7<=h<=7, -12<=k<=12, -19<=l<=22	
Reflections collected	7062	
Independent reflections	1320 [R(int) = 0.048]	
Reflections with I>2sigma(I)	1154	
Completeness to theta = 26.01°	99.5 %	
Tmax. and Tmin.	0.9948 and 0.9647	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1320 / 0 / 163	
Goodness-of-fit on F^2	1.066	
Final R indices [I>2sigma(I)]	R1 = 0.034, wR2 = 0.075	
R indices (all data)	R1 = 0.042, wR2 = 0.080	
Absolute structure parameter	-1.2(17)	
Largest diff. peak and hole	0.14 and -0.16 $e.Å^{-3}$	

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for apr1507. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5456(3)	5939(2)	7770(1)	45(1)
O(2)	7690(2)	5816(1)	6219(1)	34(1)
O(3)	10912(2)	5221(2)	6667(1)	41(1)
N(1)	7199(3)	6165(2)	8251(1)	38(1)
N(2)	7917(3)	3886(2)	6809(1)	27(1)
C(1)	8037(3)	5064(2)	8441(1)	27(1)
C(2)	7025(3)	3872(2)	8087(1)	30(1)
C(3)	5199(3)	4530(2)	7641(1)	36(1)
C(4)	5625(3)	4195(2)	6823(1)	31(1)
C(5)	5516(3)	5303(2)	6252(1)	33(1)
C(6)	9023(3)	4985(2)	6586(1)	28(1)
C(7)	8489(3)	3210(2)	7499(1)	30(1)
C(8)	9932(3)	5015(2)	8928(1)	29(1)
C(9)	10939(4)	6180(2)	9153(1)	41(1)
C(10)	12807(5)	6120(3)	9568(1)	55(1)
C(11)	13672(4)	4921(3)	9766(1)	54(1)
C(12)	12672(4)	3770(3)	9562(1)	45(1)
C(13)	10809(3)	3812(2)	9141(1)	35(1)

Table 3. Bond lengths [Å] and angles [°] for apr1507.

O(1)-N(1)	1.408(2)
O(1)-C(3)	1.453(3)
O(2)-C(6)	1.355(2)
O(2)-C(5)	1.453(2)
O(3)-C(6)	1.210(2)
N(1)-C(1)	1.278(3)
N(2)-C(6)	1.369(3)
N(2)-C(7)	1.462(2)
N(2)-C(4)	1.463(3)
C(1)-C(8)	1.472(3)
C(1)-C(2)	1.504(3)
C(2)-C(3)	1.544(3)
C(2)-C(7)	1.549(3)
C(3)-C(4)	1.534(3)
C(4)-C(5)	1.522(3)
C(8)-C(13)	1.389(3)
C(8)-C(9)	1.396(3)
C(9)-C(10)	1.385(3)
C(10)-C(11)	1.375(4)
C(11)-C(12)	1.371(4)
C(12)-C(13)	1.387(3)
N(1)-O(1)-C(3)	110.06(15)
C(6)-O(2)-C(5)	109.28(15)
C(1)-N(1)-O(1)	109.73(17)
C(6)-N(2)-C(7)	120.39(16)
C(6)-N(2)-C(4)	108.88(16)
C(7)-N(2)-C(4)	108.91(16)
N(1)-C(1)-C(8)	121.15(19)
N(1)-C(1)-C(2)	114.59(17)
C(8)-C(1)-C(2)	124.13(18)
C(1)-C(2)-C(3)	100.49(16)
C(1)-C(2)-C(7)	112.89(16)
C(3)-C(2)-C(7)	105.52(17)

O(1)-C(3)-C(4)	110.53(18)
O(1)-C(3)-C(2)	105.06(17)
C(4)-C(3)-C(2)	105.94(17)
N(2)-C(4)-C(5)	100.93(16)
N(2)-C(4)-C(3)	103.45(17)
C(5)-C(4)-C(3)	118.45(18)
O(2)-C(5)-C(4)	104.46(15)
O(3)-C(6)-O(2)	122.2(2)
O(3)-C(6)-N(2)	128.0(2)
O(2)-C(6)-N(2)	109.77(16)
N(2)-C(7)-C(2)	103.46(15)
C(13)-C(8)-C(9)	118.98(19)
C(13)-C(8)-C(1)	120.67(19)
C(9)-C(8)-C(1)	120.3(2)
C(10)-C(9)-C(8)	119.8(2)
C(11)-C(10)-C(9)	120.5(3)
C(12)-C(11)-C(10)	120.2(2)
C(11)-C(12)-C(13)	120.0(3)
C(12)-C(13)-C(8)	120.4(2)

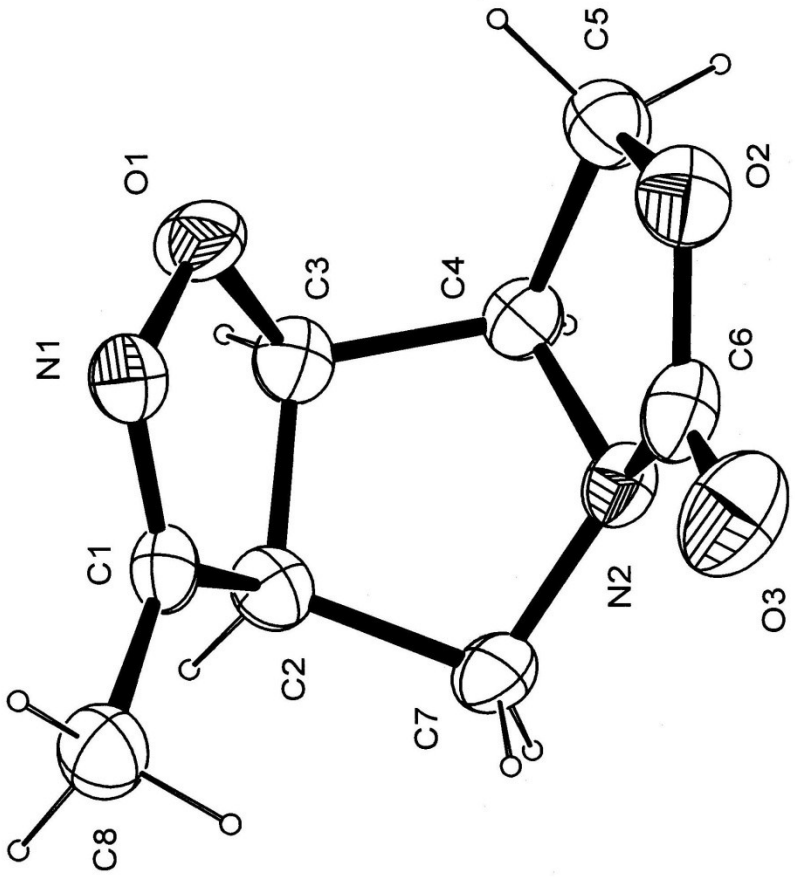
C5
O1
O2
C3
C4
N1
C6
C1
N2
O3
C2
C7
C8

Table 1. Crystal data and structure refinement .

Identification code	jun1007	
Empirical formula	C8 H10 N2 O3	
Formula weight	182.18	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/n$ (No.14)	
Unit cell dimensions	a = 5.4551(4) Å	α= 90°.
	b = 16.1862(12) Å	β= 101.417(5)°.
	c = 9.3683(6) Å	γ = 90°.
Volume	810.83(10) $Å^3$	
Z	4	
Density (calculated)	1.49 Mg/m^3	
Absorption coefficient	0.12 mm^{-1}	
F(000)	384	
Crystal size	0.20 x 0.02 x 0.02 mm^3	
Theta range for data collection	4.01 to 26.00°.	
Index ranges	-6<=h<=6, -13<=k<=19, -11<=l<=9	
Reflections collected	5536	
Independent reflections	1578 [R(int) = 0.095]	
Reflections with I>2sigma(I)	932	
Completeness to theta = 26.00°	98.8 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1578 / 0 / 119	
Goodness-of-fit on F^2	1.063	
Final R indices [I>2sigma(I)]	R1 = 0.061, wR2 = 0.104	
R indices (all data)	R1 = 0.128, wR2 = 0.124	
Largest diff. peak and hole	0.21 and -0.24 $e.Å^{-3}$	

Data collection KappaCCD , Program package WinGX , Abs correction not applied,
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jun1007. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	786(4)	6587(1)	9388(2)	37(1)
O(2)	1242(3)	7570(1)	6475(2)	38(1)
O(3)	1599(4)	6492(1)	5019(2)	52(1)
N(1)	2152(4)	5860(1)	9196(2)	32(1)
N(2)	-1865(4)	6655(1)	6072(2)	28(1)
C(1)	710(5)	5346(2)	8406(3)	27(1)
C(2)	-1919(5)	5648(2)	7895(3)	29(1)
C(3)	-1779(5)	6510(2)	8592(3)	30(1)
C(4)	-2318(5)	7123(2)	7326(3)	28(1)
C(5)	-517(5)	7848(2)	7358(3)	34(1)
C(6)	418(5)	6856(2)	5791(3)	35(1)
C(7)	-2554(5)	5795(2)	6225(3)	33(1)
C(8)	1650(5)	4530(2)	8044(3)	37(1)

Table 3. Bond lengths [Å] and angles [°] for jun1007.

O(1)-N(1)	1.422(3)
O(1)-C(3)	1.455(3)
O(2)-C(6)	1.355(3)
O(2)-C(5)	1.456(3)
O(3)-C(6)	1.212(3)
N(1)-C(1)	1.277(3)
N(2)-C(6)	1.362(4)
N(2)-C(7)	1.457(3)
N(2)-C(4)	1.460(3)
C(1)-C(8)	1.480(4)
C(1)-C(2)	1.501(3)
C(2)-C(3)	1.535(4)
C(2)-C(7)	1.552(3)
C(3)-C(4)	1.530(4)
C(4)-C(5)	1.526(4)
N(1)-O(1)-C(3)	109.86(18)
C(6)-O(2)-C(5)	109.7(2)
C(1)-N(1)-O(1)	109.5(2)
C(6)-N(2)-C(7)	120.8(2)
C(6)-N(2)-C(4)	109.8(2)
C(7)-N(2)-C(4)	109.2(2)
N(1)-C(1)-C(8)	120.9(2)
N(1)-C(1)-C(2)	114.3(2)
C(8)-C(1)-C(2)	124.8(2)
C(1)-C(2)-C(3)	101.4(2)
C(1)-C(2)-C(7)	112.3(2)
C(3)-C(2)-C(7)	105.8(2)
O(1)-C(3)-C(4)	111.1(2)
O(1)-C(3)-C(2)	104.9(2)
C(4)-C(3)-C(2)	105.9(2)
N(2)-C(4)-C(5)	101.8(2)
N(2)-C(4)-C(3)	104.5(2)
C(5)-C(4)-C(3)	117.4(2)

O(2)-C(5)-C(4)	104.2(2)
O(3)-C(6)-O(2)	122.1(3)
O(3)-C(6)-N(2)	127.8(3)
O(2)-C(6)-N(2)	110.1(3)
N(2)-C(7)-C(2)	103.58(19)

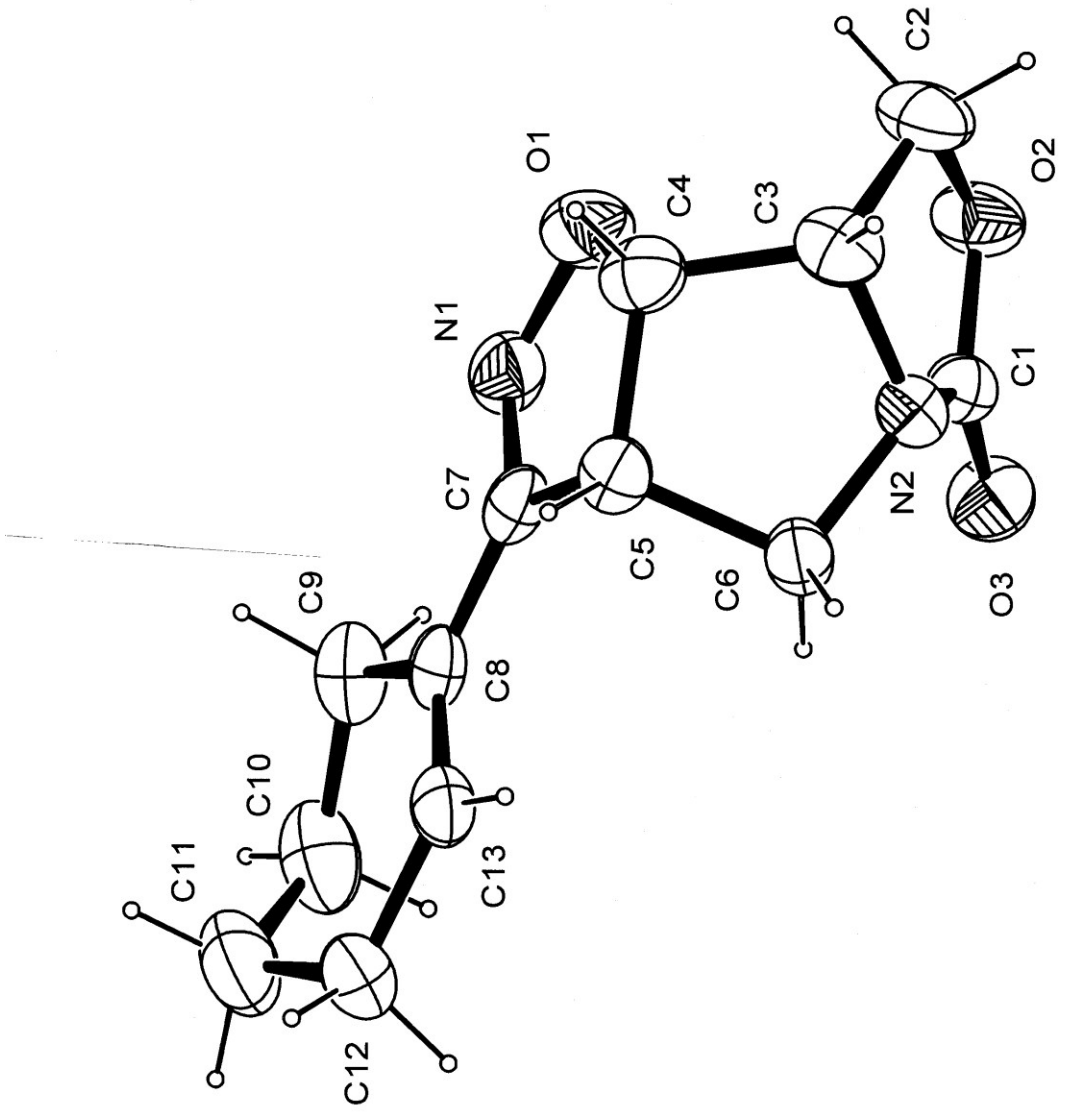
C2
O1
O2
C4
C3
N1
C1
C7
N2
C5
C6
O3
C9
C8
C10
C11
C13
C12

Table 1. Crystal data and structure refinement for jla33.

Identification code	jun107	
Empirical formula	C13 H16 N2 O3	
Formula weight	248.28	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$ (No.19)	
Unit cell dimensions	a = 6.3669(3) Å	α= 90°.
	b = 9.9102(4) Å	β= 90°.
	c = 19.6176(8) Å	γ = 90°.
Volume	1237.82(9) Å^3	
Z	4	
Density (calculated)	1.33 Mg/m^3	
Absorption coefficient	0.10 mm^{-1}	
F(000)	528	
Crystal size	0.30 x 0.30 x 0.02 mm^3	
Theta range for data collection	3.73 to 26.00°.	
Index ranges	-7<=h<=5, -12<=k<=9, -24<=l<=24	
Reflections collected	7828	
Independent reflections	1418 [R(int) = 0.060]	
Reflections with I>2sigma(I)	1267	
Completeness to theta = 26.00°	98.8 %	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1418 / 0 / 163	
Goodness-of-fit on F^2	0.980	
Final R indices [I>2sigma(I)]	R1 = 0.038, wR2 = 0.091	
R indices (all data)	R1 = 0.044, wR2 = 0.095	
Largest diff. peak and hole	0.14 and -0.15 e.Å^{-3}	

Data collection KappaCCD , Program package WinGX , Abs correction not applied ,
Refinement using SHELXL-97 , Drawing using ORTEP-3 for Windows

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for jun107. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5110(3)	5639(2)	2901(1)	49(1)
O(2)	6409(3)	5264(2)	1382(1)	44(1)
O(3)	9842(3)	5109(2)	1615(1)	45(1)
N(1)	6675(3)	5165(2)	3359(1)	42(1)
N(2)	7968(3)	7024(2)	1872(1)	30(1)
C(1)	8236(4)	5750(2)	1631(1)	32(1)
C(2)	4754(4)	6246(3)	1502(1)	48(1)
C(3)	5731(4)	7260(3)	1986(1)	38(1)
C(4)	5462(4)	7058(3)	2754(1)	41(1)
C(5)	7623(4)	7364(2)	3068(1)	33(1)
C(6)	9157(4)	7512(3)	2456(1)	36(1)
C(7)	8010(4)	6099(2)	3470(1)	32(1)
C(8)	9757(4)	5885(2)	3941(1)	34(1)
C(9)	9948(5)	4528(3)	4284(1)	47(1)
C(10)	12127(6)	4344(3)	4603(1)	60(1)
C(11)	12732(6)	5563(3)	5017(1)	62(1)
C(12)	12871(4)	6804(3)	4566(1)	51(1)
C(13)	11102(4)	6885(3)	4064(1)	38(1)

Table 3. Bond lengths [Å] and angles [°] for jun107.

O(1)-N(1)	1.422(3)
O(1)-C(4)	1.452(3)
O(2)-C(1)	1.350(3)
O(2)-C(2)	1.454(3)
O(3)-C(1)	1.204(3)
N(1)-C(7)	1.276(3)
N(2)-C(1)	1.359(3)
N(2)-C(6)	1.457(3)
N(2)-C(3)	1.461(3)
C(2)-C(3)	1.515(4)
C(3)-C(4)	1.531(3)
C(4)-C(5)	1.537(3)
C(5)-C(7)	1.502(3)
C(5)-C(6)	1.553(3)
C(7)-C(8)	1.461(3)
C(8)-C(13)	1.332(4)
C(8)-C(9)	1.508(3)
C(9)-C(10)	1.533(5)
C(10)-C(11)	1.506(4)
C(11)-C(12)	1.518(4)
C(12)-C(13)	1.498(3)
N(1)-O(1)-C(4)	109.69(18)
C(1)-O(2)-C(2)	109.12(17)
C(7)-N(1)-O(1)	109.62(19)
C(1)-N(2)-C(6)	121.15(19)
C(1)-N(2)-C(3)	108.9(2)
C(6)-N(2)-C(3)	109.44(18)
O(3)-C(1)-O(2)	122.3(2)
O(3)-C(1)-N(2)	127.3(2)
O(2)-C(1)-N(2)	110.4(2)
O(2)-C(2)-C(3)	104.32(18)
N(2)-C(3)-C(2)	101.44(19)
N(2)-C(3)-C(4)	103.83(19)

C(2)-C(3)-C(4)	119.0(2)
O(1)-C(4)-C(3)	109.8(2)
O(1)-C(4)-C(5)	104.5(2)
C(3)-C(4)-C(5)	105.5(2)
C(7)-C(5)-C(4)	101.11(19)
C(7)-C(5)-C(6)	112.44(19)
C(4)-C(5)-C(6)	105.82(17)
N(2)-C(6)-C(5)	104.47(18)
N(1)-C(7)-C(8)	120.7(2)
N(1)-C(7)-C(5)	113.9(2)
C(8)-C(7)-C(5)	125.35(19)
C(13)-C(8)-C(7)	119.8(2)
C(13)-C(8)-C(9)	122.0(2)
C(7)-C(8)-C(9)	118.2(2)
C(8)-C(9)-C(10)	111.2(2)
C(11)-C(10)-C(9)	110.9(2)
C(10)-C(11)-C(12)	110.4(2)
C(13)-C(12)-C(11)	112.5(2)
C(8)-C(13)-C(12)	124.3(2)

Symmetry transformations used to generate equivalent atoms: