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Recent Developments in Kainoid Amino Acid Chemistry

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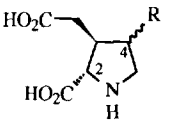
1. Introduction to Kainic, Allokainic, Domoic and the Acromelic Acids

1.1. Structure and Isolation

The kainoid amino acids are a unique group of non-proteinogenic pyrrolidine dicarboxylic acids. They all have three asymmetric centres at positions 2, 3 and 4 of the pyrrolidine ring with the relative configuration *S*, *S* and *S* or *R* respectively (see below). The substituent at the C-4 position of the ring can vary in nature, although generally contains π-unsaturation, and it is this which gives rise to various members of the kainoid family.



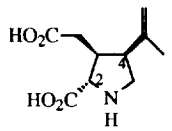
The parent member, (-)-α-kainic acid **(1)** (originally known as digenic acid) was first isolated in 1953 from the Japanese marine algae *Digenea simplex*[1] along with its C-4 epimer (+)-allokainic acid **(2)**. Since then **(1)** has been found to occur in the related algae *Centrocerus clavulatum*[2a] and in the Corsican moss, *Alsidium helminthocorton*.[2b,c] The structure was originally assigned as 3-carboxymethyl-4-isopropenyl-pyrrolidine-2-carboxylic acid in a series of classical chemical degradations and syntheses of degradative products by several Japanese groups[3] in the mid 1950's. Among the early and important degradative reactions were a soda-lime distillation that led to the isolation of a pyrrole, and an ozonolysis which yielded formaldehyde.[3] Morimoto[4] was the first to deduce the relative stereochemistry of the pyrrolidine ring substituents by chemical studies, and this has been supported by X-ray evidence.[5] Since then a rigorous assignment of the absolute stereochemistry has been provided by Oppolzer and Thirring[6] in their concise synthesis of (-)-α-kainic acid **(1)** (section 2.2). In a similar manner, the structure of the C-4 epimer, (+)-α-allokainic acid **(2)** has been established on the basis of chemical[7] and X-ray[8] evidence.

(-)-Domoic acid **(3)** was originally isolated by Daigo *et. al.*[9] from another Japanese marine algae - the warm water algae *Chondria armata*. Since then it has been found in the Canadian phytoplankton *Nitzschia pungens*[10] and the algae *Alsidium corallinum*.[2] Levels in excess of 1% dry weight of the plankton have been observed. There is also a high probability that other phytoplankton such as *Amphora coffaeformis*[10] are primary producers of domoic acid **(3)**. Domoic acid **(3)** has an octadienoic side chain at C-4 and this was originally determined by a combination of classical degradations and spectral techniques.[11a] This led to a proposed (*trans-*, *trans-*) diene geometry with undefined stereochemistry at C-5'.[11a] This was later redefined as (*cis-*, *trans-*) and the absolute stereochemistry at C-5' was established (as *R*) by Ohfune and Tomita[12] in their total synthesis of (-)-domoic acid **(3)** (Section 2.4.). More recently an X-ray crystallographic analysis has been reported which has confirmed this assignment.[11b]

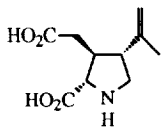
A number of kainoids related to domoic acid **(3)** have also been isolated from the same algae. This includes the isodomoic acids A-F **(4)**-**(9)**,[13,14] the C-5' domoic acid diastereomer **(10)**[15] and the domoilactones A **(11)** and B **(12)**.[16]

The acromelic acids A **(13)** and B **(14)**, in which the C-4 substituent is a functionalised 2-pyridone, were first isolated in sub-milligram quantities in 1983.[17,18] They were found in a quite different organism to the previously described kainoids, namely the poisonous Japanese mushroom *Clitocybe acromelalga*. Due to the limited sample quantity only ^{1}H n.m.r., C.D. and U.V. spectra data were available for structural assignment. From this data, the structure of the acromelates A **(13)** and B **(14)** was deduced by comparison with those of related compounds [including kainic **(1)** and domoic acid **(3)**]. Since then both acromelate structures have been confirmed by total synthesis (section 2.5.).[18]

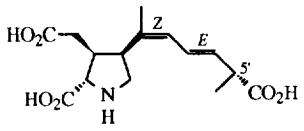
Since the isolation of the acromelates **(13)** and **(14)**, numerous other kainoid amino acids have been shown to be minor constituents of *Clitocybe acromelalga*, including the acromelic acids C, D and E **(15)**-**(17)**.[19,20]



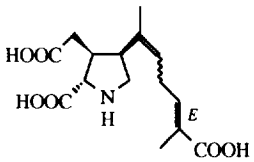
(1) (-)-α-KAINIC ACID



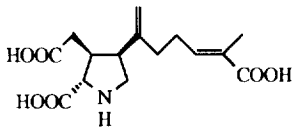
(2) (+)-α-ALLOKAINIC ACID



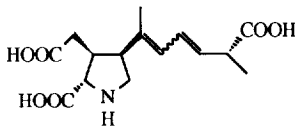
(3) (-)-DOMOIC ACID



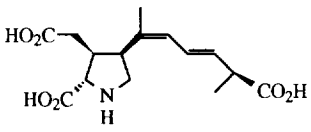
(4) ISODOMOIC ACID A (*Z*, *E*)
(5) ISODOMOIC ACID B (*E*, *E*)



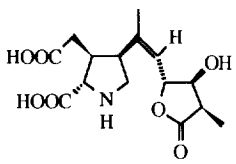
(6) ISODOMOIC ACID C



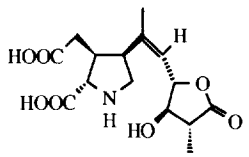
(7) ISODOMOIC ACID D (*Z*, *Z*)
(8) ISODOMOIC ACID E (*E*, *E*)
(9) ISODOMOIC ACID F (*E*, *Z*)



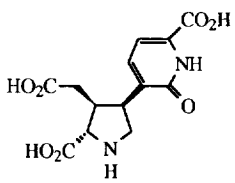
(10)



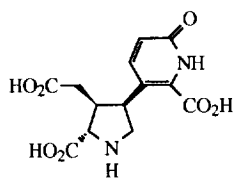
(11) DOMOILACTONE A



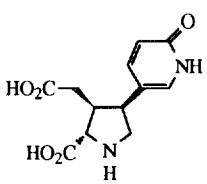
(12) DOMOILACTONE B



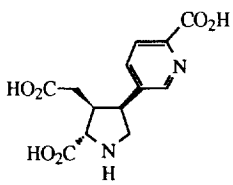
(13) ACROMELIC ACID A



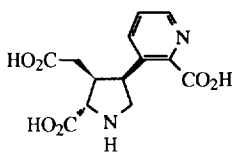
(14) ACROMELIC ACID B



(15) ACROMELIC ACID C



(16) ACROMELIC ACID D



(17) ACROMELIC ACID E

1.2. Biological Properties

The kainoid amino acids have attracted considerable interest largely because of their pronounced insecticidal, anthelmintic and principally neuroexcitatory properties.

The ability of the kainoids to act as insecticides has long been utilised by inhabitants of Yakushima Island, Japan.[13] They used an extract of red algae, from which kainic (**1**) and domoic acid (**3**) have since been isolated for its fly-killing properties. Since then, domoic acid (**3**) and the isodomoic acids A-C (**4**)-(**6**) have been shown to be potent insecticides when injected subcutaneously into the abdomens of the American cockroach (*Periplaneta americana*).[13] This insecticidal activity[21a] is found to be strongly dependent on the nature of the side chain at the C-4 position of the pyrrolidine ring. Thus, domoic acid (**3**) is 23 times more active on the American cockroach than isodomoic acid C (**6**). For comparison, the activity of domoic acid (**3**) was also compared with that of the well known pesticide 1,1,1-trichloro-2,2-bis(4-chlorophenyl)ethane [or DDT], and it was found to be 14 times more active.[13] This illustrates the extremely strong insecticidal activity of domoic acid (**3**).

The algae *Digenea simplex*, from which kainic acid (**1**) was first isolated (Section 1.1.), has been used for its anthelmintic (anti-intestinal worm) properties for more than a thousand years in Japan. Since then the active component, kainic acid (**1**), has been found to have an intense anthelmintic effect, about 10 times that of santonin without side effects.[5b] The *cis*- stereochemistry of the C-3 and C-4 substituents appears to be crucial to the anthelmintic function, as the C-4 epimer, allokainic acid (**2**), is said to have a very weak anthelmintic effect, if any. Indeed, of the known stereoisomers of kainic acid (**1**), all show considerably reduced anthelmintic activity compared with that of kainic acid itself.[21b] The anthelmintic behaviour of domoic acid (**3**) has also been demonstrated. Thus Daigo[9] found that oral administration (of 20mg) of domoic acid (**3**) was extremely effective in expelling ascaris and pinworm, without any observable side effects, in Japanese children.

The pronounced neuroexcitatory properties of the kainoids have been well investigated.[22] The kainoids have been shown to selectively block neuronal processes and as a consequence are valuable tools in the study of neurofunctioning. Their extremely potent activity (in both the vertebrate and invertebrate glutamergic system[23]) leads to specific neuronal death in the brain. The pharmacological effects and patterns of neuronal degeneration observed after injection of kainoids have been shown to mimic the symptoms observed in patients suffering from neuronal diseases such as epilepsy[24] and Huntington's chorea.[25] In addition, there is a possibility that neuronal death caused by kainoids is a good experimental model for neuronal cell loss in senile dementia.[22]

The potent neuroexcitatory activity of the kainoids is attributed to their action as conformationally restricted analogues of the neurotransmitter glutamic acid and numerous structure-activity investigations[26,27] of the kainoids and analogues have been carried out. From these results it can be safely assumed that the C-4 stereochemistry [*i.e.* allokainic acid (**2**) is less of a neuroexcitant than (**1**)[26b]], the nature of the C-4 substituent (a double bond is essential for excitatory activity[26c]) and its conformation,[26d] play a critical role in binding and functional activation at the recognition site. This is further supported by the observation that domoic acid (**3**) is even more neuroexcitatory than kainic acid (**1**).[28] Domoic acid (**3**) has been identified as the toxin in paralytic shellfish poisons (PSPs) and was believed to be responsible for an outbreak of mussel

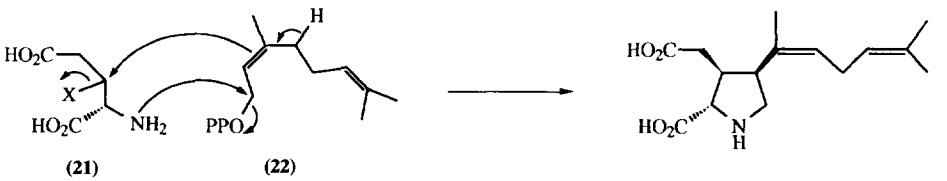
poisoning in Canada, which resulted in three deaths and 153 cases of intoxication.[10,29] The contamination of the mussel was thought to occur by ingestion of domoic acid (**3**) through its main food source, *Nitzschia pungens*, which is a primary producer of the toxin (Section 1.1.). More recently, domoic acid (**3**) intoxication of brown pelicans and cormorants in California has been reported.[30]

The acromelic acids A (**13**) and B (**14**) were originally isolated from the mushroom *Clitocybe acromelalga* (Section 1.1.). Ingestion of the mushroom results in a sharp pain and a reddish oedema in the hand and foot after several days, which generally continues for up to a month. Since their isolation, the acromelates (**13**) and (**14**) have been tested for neuroexcitatory activity.[23c,d] Both were found to be even more potent than domoic acid (**3**), the acid B (**14**) being slightly less potent than acid A (**13**). The acromelates also showed a different mode of action to kainic acid (**1**).[23e] More recently, the lethal toxicity of acromelic acid C (**15**) to mice was reported at a dose of 10mg/kg.[19] Similar lethal doses of 7 and 8mg/kg were observed for acromelic acid A (**13**) and B (**14**) respectively. Acromelic acid D (**16**) has also been investigated and shown to be as potent a neuroexcitant as kainic acid (**1**).[31]

Synthetic acromelate analogues such as (**18**)-(**20**) have also been tested, and the phenyl derivative (**18**) showed comparable activity to kainic acid (**1**).[32] The phenol derivative (**19**) exhibited more potent activity than acromelic acid B (**14**) or domoic acid (**3**). Recently four stereoisomers (2*S*, 3*S* or *R*, 4*S* or *R*) of the phenol derivative have been examined and the (2*S*, 3*S*, 4*S*)-isomer (**19**) [which has the same configuration as kainic acid (**1**)] shown the most potent biological activity.[33a] However, the methoxyphenyl derivative (**20**) was 3- to 5- fold more potent than acromelic acid A (**13**), and is the most potent excitatory reagent known so far. The powerful neuroexcitatory properties of acromelate analogues[33b] has stimulated considerable synthetic interest in this area (section 2.6.).

1.3. Biosynthesis

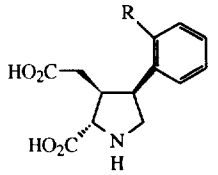
The biosynthesis of domoic acid (**3**) has been investigated by Wright and co-workers.[34] Labelling experiments with [1-^{13}C]acetate and [1,2-^{13}C]acetate provided evidence for a novel condensation of a glutamic acid derivative (**21**) (where X is a leaving group) with a geranyl pyrophosphate (**22**) and subsequent cyclisation to form a proline ring (scheme 1). It is likely that this route provides a general biosynthetic pathway to all the kainoids.



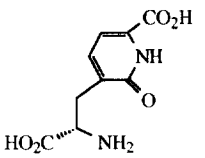
(**21**) (**22**)

Scheme 1

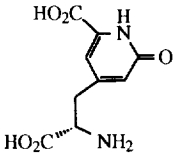
A biosynthetic outline to the synthesis of the acromelates has been proposed in which the pyridone moieties are derived from L-DOPA.[18] The recent isolation of proposed biosynthetic intermediates **(23)**-**(25)** from *Clitocybe acromelalga* lends support to this pathway.[35]



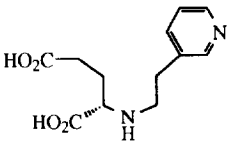
(18) R=H
(19) R=OH
(20) R=OMe



(23)



(24)



(25)

2. Kainoid Synthesis

2.1. Synthetic Challenge

The kainoid amino acids represent a considerable synthetic challenge. A kainoid synthesis needs to address the formation of a pyrrolidine-2-carboxylic acid with defined stereochemistry at the three contiguous chiral centres of the ring. The *cis*- stereochemistry of the 3 and 4 positions [except for allokainic acid **(2)**] needs special consideration. In addition an ideal synthesis would allow the ability to introduce various side chains at the C-4 position in a convergent manner to afford all the known kainoids and various kainoid analogues. This review will now give an account of various total syntheses of the kainoids and kainoid analogues.[36]

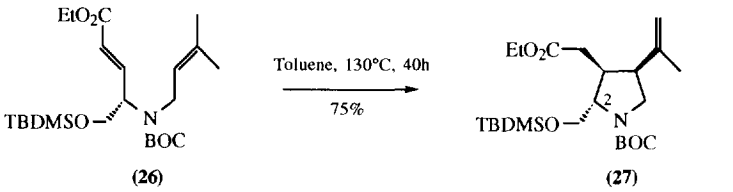
2.2. Kainic acid (1)

Kainic acid **(1)**, being the parent kainoid, has attracted the most synthetic attention amongst the kainoids to-date. The early syntheses of kainic acid **(1)** were relatively inefficient and nonstereoselective.[37] Since then, a number of stereoselective syntheses have been achieved which in general have involved the construction of the C-3 to C-4 bond under the steric control of the C-2 substituent.

The first enantioselective synthesis of kainic acid **(1)** was developed by Oppolzer and Thirring.[6] The key step was a stereocontrolled intramolecular ene reaction (scheme 2). The key diene **(26)** was prepared in good yield from L-glutamic acid and subjected to thermolysis in hot toluene. The ene cyclisation reaction proceeded in 75% yield to furnish the desired trisubstituted pyrrolidine **(27)** under the steric control of the chiral C-2 centre. The relative stereochemistry of **(27)** was rigorously ascertained by conversion of this compound to kainic acid **(1)** in six straightforward steps. A related approach to (±)-kainic acid **(1)** has since been reported.[38]

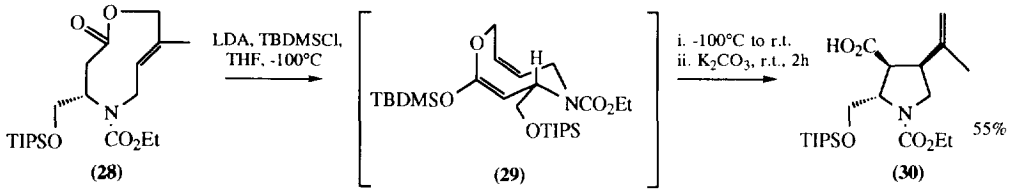
Knight and associates have developed an enantioselective synthesis of kainic acid **(1)** starting from the amino acid L-aspartic acid (scheme 3).[39] The key feature of their strategy is the use of a stereocontrolled enolate Claisen rearrangement to control the relative stereochemistry at the 3,4-positions. The key 9-

membered azalactone **(28)** was prepared from L-aspartic acid in modest overall yield. Enolate formation in the presence of the silyl trapping agent, followed by rearrangement afforded (after silyl ester hydrolysis) the pyrrolidine **(30)**, presumably *via* the boat-like transition state **(29)**, in 55% yield. It is noted that the pseudoequatorial protected alcohol (CH_2OTIPS) gives rise to the high diastereomeric purity obtained. Homologation of the acid **(30)** followed by oxidation furnished **(1)** in seven additional steps and good overall yield.



(26) **(27)**

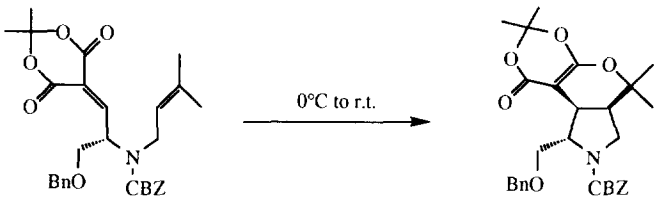
Scheme 2



(28) **(29)** **(30)**

Scheme 3

Takano and co-workers[40] have employed an interesting intramolecular hetero-Diels-Alder cyclisation to construct (-)-kainic acid **(1)** (scheme 4). The key [4+2] cyclisation intermediate **(31)**, which was not isolated, was obtained originally from diethyl L-tartrate. This species spontaneously cyclised to the tricyclic adduct **(32)** on heating from 0°C to ambient temperature with the desired facial selectivity. The sp^2-like planar configuration of the carbamate nitrogen was thought to allow for efficient [4π+2π] orbital overlap only in the *endo* conformer which gives rise to **(32)**. Ketal hydrolysis, hydrogenation, amine reprotection and manipulation of the 3,4-appendages gave kainic acid **(1)**.

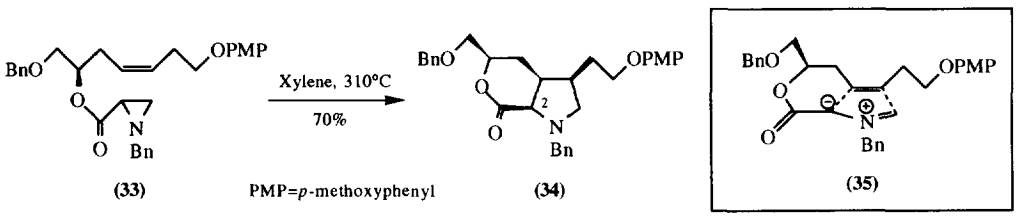


(31) **(32)**

Scheme 4

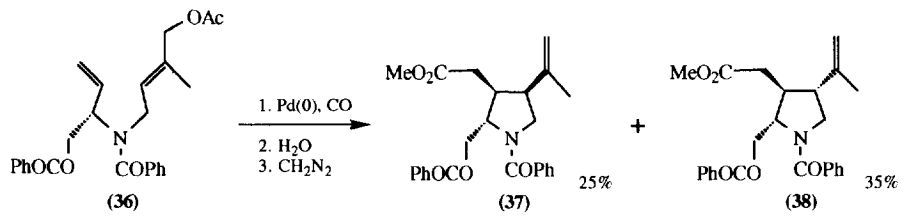
The same research group have utilitised a [1,3] dipolar cycloaddition reaction of an azomethine ylide in an enantioselective approach to kainic acid **(1)** (scheme 5).[41] Thus aziridine **(33)**, prepared from (*S*)-2-(benzyloxymethyl)oxirane, was heated to 310°C in xylene in a sealed tube to produce the all *syn*- adduct **(34)** in 70% yield. The authors postulate that the azomethine ylide adopts conformation **(35)** which places the

substituents in a pseudoequatorial disposition resulting in the observed all *syn*- stereochemistry. The adduct **(34)** was elaborated to kainic acid **(1)** in a number of steps including inversion of stereochemistry at C-2 by treatment with sodium hydride and DBU. A similar approach has been utilised in the synthesis of acromelic acids A **(13)** and B **(14)** (section 2.5.).



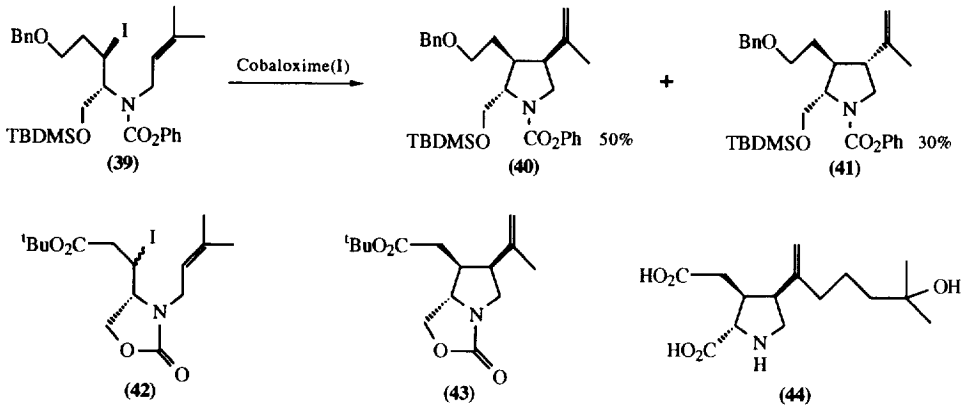
Scheme 5

A racemic synthesis of kainic acid **(1)** and its C-4 epimer, allokainic acid **(2)**, using a palladium(0) mediated olefin insertion-carbonylation reaction, has recently been reported by Yoo.[42] As illustrated in scheme 6, on carbonylation of allylic acetate **(36)**, the diastereomers **(37)** and **(38)** were isolated in 25% and 35% yield, respectively. The C-2 substituent thus controls the stereochemistry at C-3 but not at C-4. The transformation of **(37)** and **(38)** into kainic **(1)** and allokainic acid **(2)** respectively, was performed in five further steps.

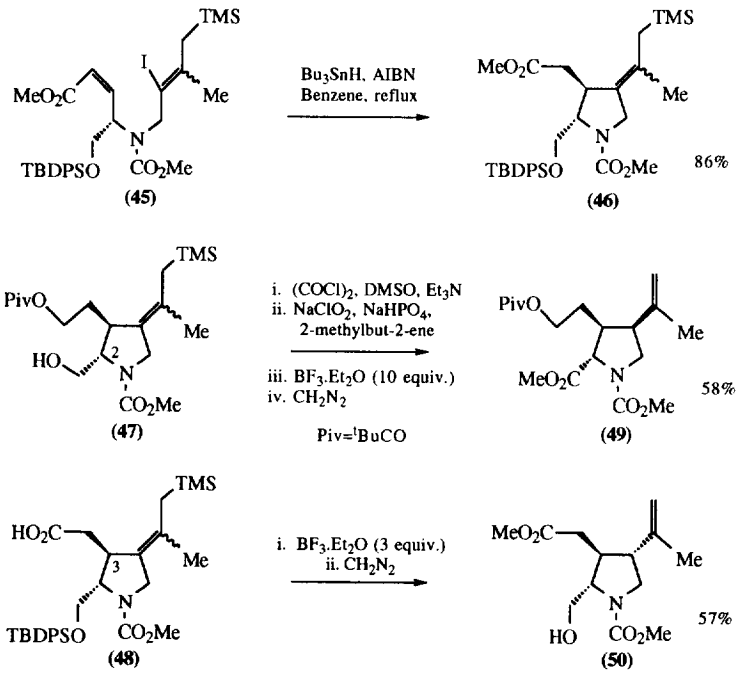


Scheme 6

Baldwin and co-workers have applied a cobalt-mediated cyclisation reaction to kainoid synthesis. Two approaches to (-)-kainic acid **(1)** have been reported, the first of which involved the cyclisation of iodide **(39)** (scheme 7).[43] On treatment of **(39)** with cobaloxime(I), cyclisation afforded a 5:3 mixture of the separable *syn*- and *anti*- pyrrolidines **(40)** and **(41)** in 80% yield. Significantly, in addition to pyrrolidine ring formation, the cobalt reaction introduces a double bond at the C-4 side chain (*via* a dehydrocobaltation process). Compound **(40)** was elaborated to kainic acid **(1)** in six further steps, while the *anti*- isomer **(41)** was transformed in a similar manner to allokainic acid **(2)**. The second approach centred on the cyclisation of the D-serine-derived iodide **(42)**.[44] The presence of the oxazolidinone ring was shown to provide a better (4*S*:4*R*) stereocontrol [4:1 compared to 1.7:1 for **(39)**] in the cobaloxime(I) ring closure. The resultant pyrrolidine **(43)** was elaborated to kainic acid **(1)** by a six step sequence in 18% overall yield. The same group have also prepared the domoic acid analogue **(44)**[45] and acromelic acid A **(13)**[46] (see section 2.5.) using the same methodology.



Scheme 7

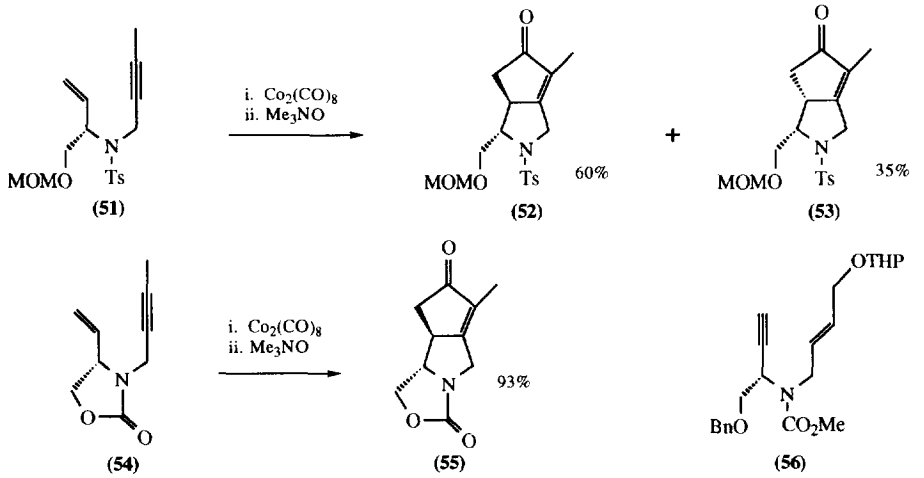


Scheme 8

The synthesis of kainic acid (**1**), and allokainic acid (**2**), from L-serine has recently been reported by Takano and co-workers.[47] In this approach, the vinyl iodide (**45**) was treated with the radical generating agent tributyltin hydride, in the presence of AIBN, to promote a diastereoselective radical cyclisation leading to (**46**) in an excellent 86% yield (scheme 8). Pyrrolidine (**46**) was found to be a useful intermediate and was readily elaborated to (**47**) and (**48**). Two-step oxidation of the primary alcohol of (**47**) followed by reaction with 10 equivalents of $BF_3.Et_2O$ under dilute conditions (CH_2Cl_2, 1.7×10^{-3} mol dm^{-3}) promoted a C-2

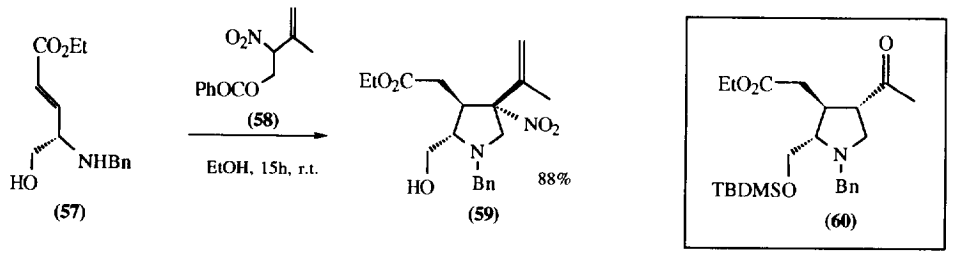
directed intramolecular protodesilylation and, after esterification, gave the kainic acid precursor (**49**) in 58% yield (together with 11% of the C-4 epimer). On treatment of (**48**) with 3 equivalents of $BF_3.Et_2O$ (CH_2Cl_2, 3-5x10^{-2} mol dm^{-3}) a C-3 directed intramolecular protodesilylation yielded the allokainic acid precursor (**50**) after reaction with diazomethane.

The Pauson-Khand reaction has also been utilised as the key step in the synthesis of (-)-kainic acid (**1**). On reaction of the glutamic acid derived ene-yne (**51**) with dicobalt octacarbonyl, followed by trimethylamine *N*-oxide (or 4-methylmorpholine *N*-oxide), the enone diastereomers (**52**) and (**53**) (1.7:1 ratio) were isolated as an inseparable mixture in 95% yield (scheme 9).[48] Enone (**52**), which possesses the desired *trans*- C-2:C-3 stereochemistry, was then converted into kainic acid (**1**) in 41% yield. Subsequent studies by the same group have shown that a more diastereoselective cyclisation can be achieved using the oxazolidinone precursor (**54**), the desired kainic acid precursor (**55**) being formed in 93% yield.[49] A related approach to (**1**) involving the Pauson-Khand reaction of ene-yne (**56**) has been reported by Takano and co-workers.[50]



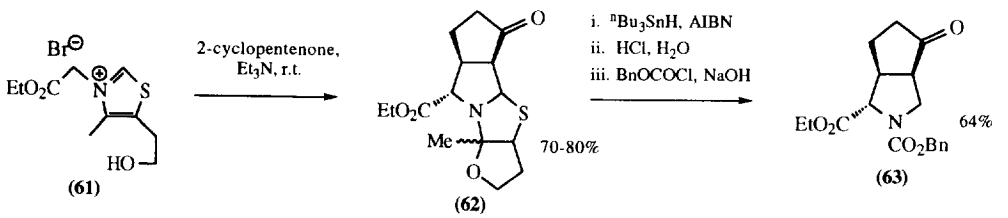
Scheme 9

Benetti and co-workers have employed a tandem Michael reaction strategy in kainoid synthesis. Reaction of the secondary amine (**57**), derived from D-serine, with the electrophilic alkene 2-nitro-3-methyl-buta-1,3-diene generated *in situ* from (**58**), in ethanol at room temperature for 15h yielded the desired pyrrolidine (**59**) in 88% yield (scheme 10).[51] For the synthesis of kainic acid (**1**), the nitro group needed to be regio- and stereoselectively removed and this was achieved by a hydride transfer reaction (in quantitative yield) in the presence of a palladium catalyst. The nitro diene, generated from (**58**), was required to exert a stereocontrolling influence as previous studies had showed that reaction of O-silylated (**57**) with methyl vinyl ketone gave the all *trans*- allokainoid precursor (**60**) in quantitative yield [which was elaborated to allokainic acid (**2**)[52]]. The nitro group thus offered sufficient steric interaction so that cyclisation afforded product (**59**) with a *syn*- relationship of the C-3:C-4 side chains. This methodology has recently been applied to the enantioselective formal synthesis of acromelic acid A (**13**) (see section 2.5.).[53]



Scheme 10

One further racemic synthesis of kainic acid (**1**) which deserves a special mention involves a concise stereocontrolled thiazolium ylide approach recently reported by Monn and Valli.[54] This centres on a tandem cycloaddition-cyclisation of the ylide derived from (**61**) with 2-cyclopentenone to afford the tetracycle as a 6.8:1 mixture of diastereomers (**62**) (scheme 11). Kraus and Nagy have previously made use of a similar 1,3-dipolar cycloaddition in the synthesis of racemic allokainic acid (**2**) (see section 2.3.).[55] The diastereomers (**62**), which could be prepared on a large scale (up to 1.5 mol) were isolated in 70-80% yield. Reductive cleavage of the thiazoline C-S bond with Bu_3SnH followed by hydrolysis of the resulting hemiaminal and *N*-protection gave (**63**) in 64% yield. The bicycle (**63**) was then converted to racemic (**1**) in 16% yield *via* a concise six-step sequence. This approach represents an extremely short and efficient method and the key intermediate (**63**), which has potential application in the synthesis of other kainoids, can be prepared on a large scale.



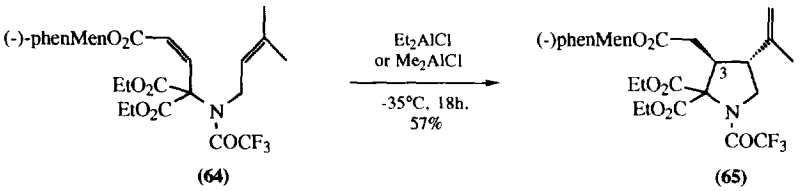
Scheme 11

2.3. Allokainic Acid (2)

As described in section 2.2., the non-stereoselective synthetic procedures used for kainic acid (**1**) have often also been utilised for allokainic acid (**2**).[42,43,47,52] Other synthetic approaches to (**2**) which have not yet been mentioned are discussed below.

A synthesis of (+)-allokainic acid (**2**) from (*Z*)-β-chloroacrylic acid has been reported by Oppolzer and associates in which they make use of the high asymmetric induction obtained in a Lewis acid-promoted intramolecular ene-type reaction.[56] The chiral precursor, (*Z*)-8-phenylmenthyl ester (**64**), was treated with a mild Lewis acid (*e.g.* 3 mole equivalents of Me_2AlCl or Et_2AlCl in dry CH_2Cl_2 at -35°C) to afford the 3*S*,4*R* pyrrolidine (**65**) in 57% yield (scheme 12). The 3*R*,4*S* diastereomer was also evident, but only in 3% yield. It is noted that the use of the corresponding (*E*)-phenylmenthyl ester led to an opposite sense of induction and

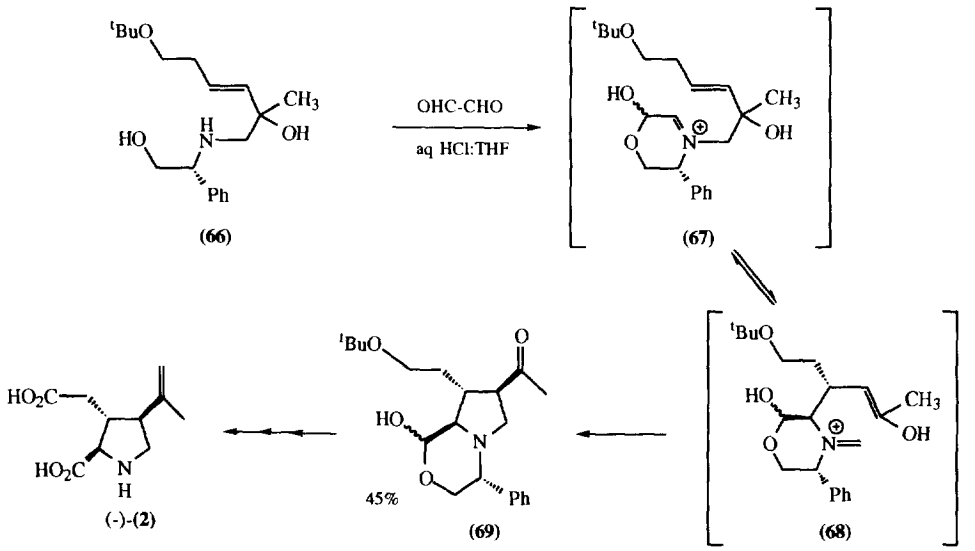
(65) was only formed in 9% yield (while the 3*R*,4*S* diastereomer was found in 72% yield). Subsequent saponification and decarboxylation of **(65)** afforded enantiomerically pure allokainic acid **(2)**, in which the configuration at C-2 was determined by the stereochemistry at the C-3 centre.



(64) **(65)**

Scheme 12

An enantioselective synthesis of the (-)-enantiomer of allokainic acid **(2)** has recently been reported using a tandem aza-Cope/Mannich reaction.[57] The (*E*)-alkene **(66)**, formed from (*R*)-phenylglycinol, was reacted with glyoxal in a slightly acidic (pH 4-5) aqueous medium to afford the desired bicyclic hemiacetal **(69)** (in 45% yield as a 70:30 mixture of epimers) *via* the iminium ions **(67)** and **(68)** (scheme 13). The three contiguous stereocentres are thus introduced in a one-pot reaction using (*R*)-phenylglycinol as a chiral template. The axial attack of the double bond on iminium ion **(67)** establishes the stereochemistry at the C-2 position while the (*E*)-stereochemistry of the double bond is responsible for the stereospecific formation of the C-3 centre. The elaboration of **(68)** to (-)-**(2)** was accomplished in a further ten steps.

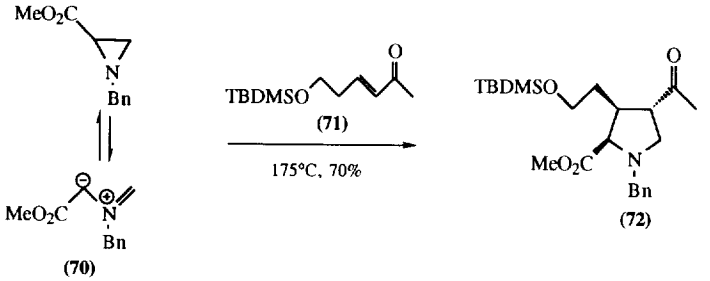


(66) **(67)** **(68)** **(69)** (-)-**(2)**

Scheme 13

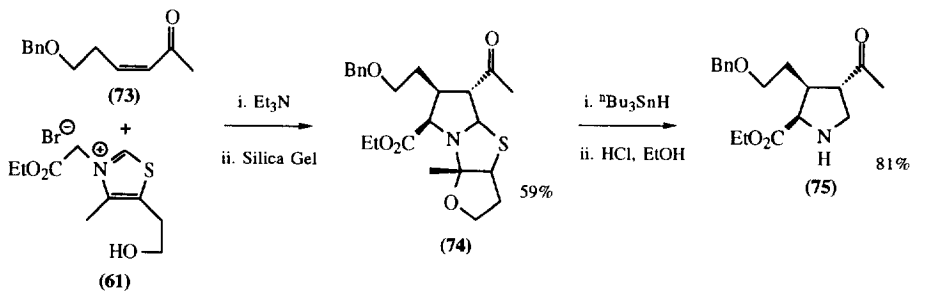
DeShong[58] has synthesised racemic allokainic acid **(2)** using a [3+2] dipolar cycloaddition of an azomethine ylide to establish the requisite pyrrolidine stereochemistry as shown in scheme 14. Thus on heating aziridine **(70)** with enone **(71)** in a sealed tube at 175°C, the trisubstituted pyrrolidine **(72)** was

obtained (together with a minor isomer impurity) in 70% yield. This was elaborated to (±)-allokainic acid (**2**) in six steps including Wittig olefination (to introduce the C-4 isopropenyl moiety) and C-2 epimerisation using aqueous sodium hydroxide.

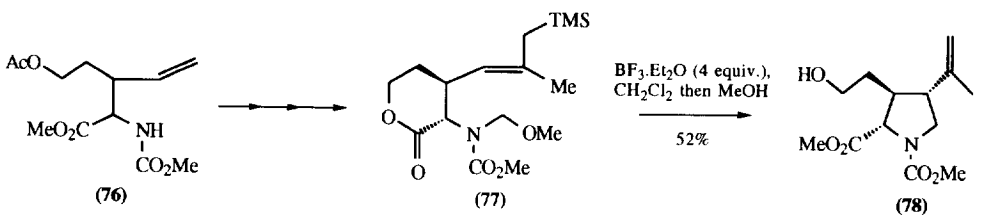


Scheme 14

Kraus and Nagy[55] have made use of the 1,3-dipolar cycloaddition of an azomethine ylide to synthesise (±)-allokainic acid (**2**) (scheme 15). They reacted the disubstituted olefin (**73**) with the ylide derived from (**61**) and the tricyclic compound (**74**) was isolated in 59% yield. Reaction of (**74**) with Bu_3SnH followed by treatment with acidic ethanol afforded pyrrolidine (**75**) in good yield (see scheme 11), which was then elaborated to allokainic acid (**2**) in eight steps (including epimerisation of the C-2 position).



Scheme 15

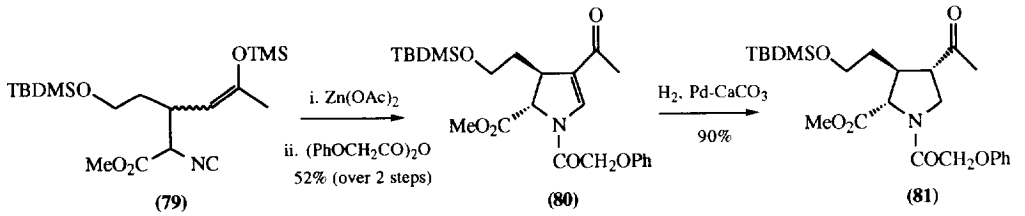


Scheme 16

A recent racemic synthesis of (**2**) has been reported which centres on two allylsilane *N*-acyliminium ion reactions.[59] An initial intermolecular *N*-acyliminium coupling reaction was employed in the synthesis of (**76**) which was subsequently elaborated to the key allylsilane intermediate (**77**) in four steps (scheme 16).

On treatment of (**77**) with $BF_3.Et_2O$ (4 equivalents) in CH_2Cl_2 followed by methanol, the trisubstituted pyrrolidine (**78**) was isolated in 52% yield *via* an intramolecular *N*-acyliminium cyclisation reaction. Other Lewis acids, including $SnCl_4$, were found to be less effective for the cyclisation. Pyrrolidine (**78**) was subsequently elaborated to (±)-(**2**) using standard methodology.

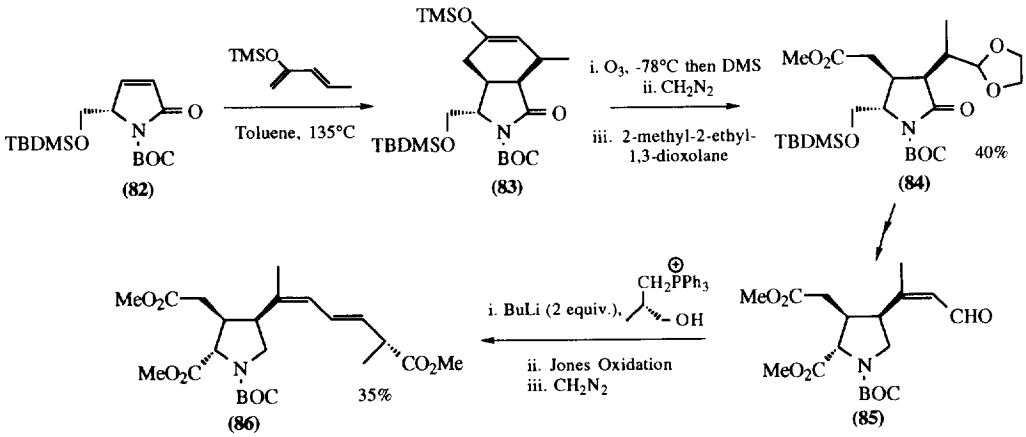
One final racemic synthesis of allokainic acid (**2**) has been reported by Ito and co-workers which employs a zinc acetate catalysed cyclisation of an γ-isocyano silyl enol ether.[60] On reaction of silyl enol ether (**79**) with $Zn(OAc)_2.2H_2O$ in DMSO containing *ca.* 2 equivalents of methanol, cyclisation proceeded smoothly to afford, after *N*-protection, predominantly the *trans*-2-pyrroline (**80**) in 52% yield (scheme 17). The corresponding *cis*- isomer was isolated in 22% yield. Stereoselective hydrogenation of (**80**) was achieved in the presence of 5% $Pd/CaCO_3$ to afford the allokainic acid precursor (**81**).



Scheme 17

2.4. Domoic Acid (3)

To date only one total synthesis of domoic acid (**3**) has appeared in the literature. This was reported by Ohfune and Tomita,[12] who employed a Diels-Alder strategy to control the relative stereochemistry of the appendages at the 3- and 4- positions, as illustrated in scheme 18. Thus pyroglutamic acid was protected and dehydrated to the dienophile (**82**). Subsequent [4+2] cycloaddition with 2-(trimethylsilyl)oxy-1,3-pentadiene proceeded with the expected facial selectivity to give lactam (**83**) as a single adduct in a stereospecific process.

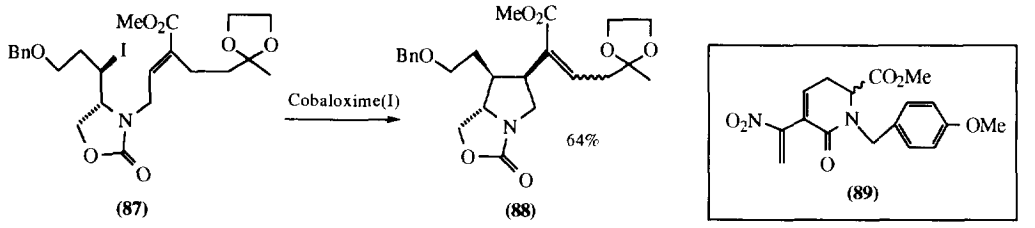


Scheme 18

Oxidative cleavage of the olefin followed by esterification and acetal formation yielded **(84)** in 40% yield [from **(82)**]. Further manipulation of the appendages and lactam reduction afforded (*Z*)-allylic aldehyde **(85)**. Wittig reaction with an unstabilised ylide (of known stereochemistry), followed by oxidation and esterification resulted in the formation of the (2*E*)-diene **(86)**. Subsequent deprotection of **(86)** afforded material, which was identical in all respects (t.l.c., infrared, ^{1}H n.m.r. and ^{13}C n.m.r. spectra) with natural domoic acid **(3)**.

2.5. Acromelic Acids (13)-(17)

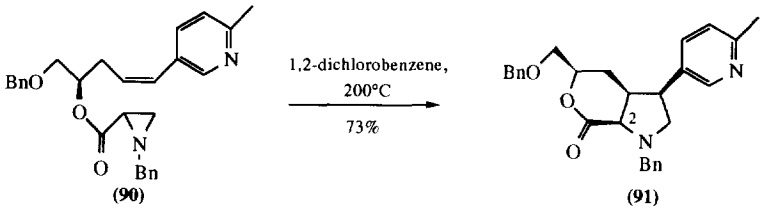
Enantioselective syntheses of acromelic acid A **(13)** have been reported which use the same methodology as that previously employed for the synthesis of kainic acid **(1)** (section 2.2.). Thus Baldwin and Li[46] have employed a similar cobalt-mediated cyclisation reaction using the precursor iodide **(87)** (scheme 19). The resultant pyrrolidine **(88)**, isolated as a 1:1 mixture of double bond isomers, was elaborated to **(13)** in a further 16 steps. Benetti and co-workers[53] have employed a related tandem Michael reaction to that described earlier (scheme 10) using the electrophilic alkene **(89)**, which incorporates a dihydropyridone nucleus. Once again the nitro group was utilised as a stereocontrolling element in the cyclisation.



(87) (88) (89)

Scheme 19

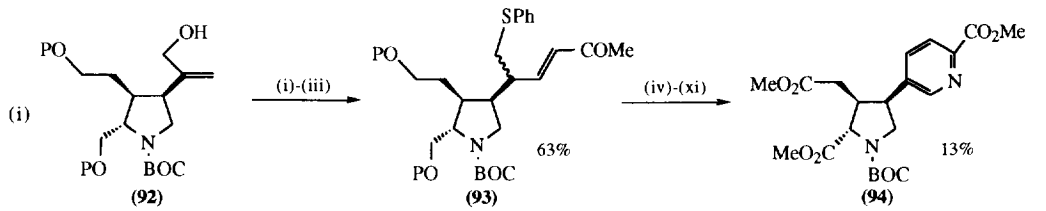
In addition, Takano and co-workers[61] have utilized a similar [1,3] dipolar cycloaddition of an azomethine ylide to that used for kainic acid **(1)** (section 2.2.) in an elegant total synthesis of acromelic acid A **(13)**. As shown in scheme 20, heating of aziridine **(90)** [prepared from (*S*)-*O*-benzylglycidol] in 1,2-dichlorobenzene at 200°C in a sealed tube generates an azomethine ylide which cyclises to the desired lactone **(91)** in 73% yield as a single diastereomer. Manipulation of the lactone appendages, epimerisation at C-2, oxidation of the pyridine ring, esterification and hydrolysis afforded acromelic acid A **(13)**. The same group have reported an enantioselective synthesis of acromelic acid B **(14)** using the same methodology.[62]



(90) (91)

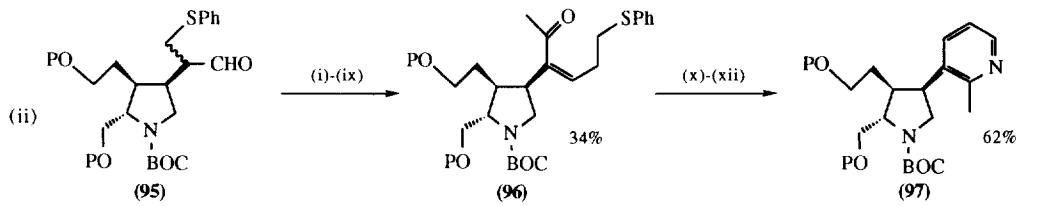
Scheme 20

A semi-synthetic approach to the acromelic acids **(13)**, **(14)** and **(16)**, starting with kainic acid **(1)** has been carried out by Shirahama and associates[18,31,63] as illustrated in schemes 21(i) and (ii). These workers employed a new pyridine synthesis that makes use of a Pummerer reaction as a key step. The kainate isopropenyl moiety is epoxidised and rearranged with strong base to the allylic alcohol **(92)**. Further manipulation to sulphide **(93)** is followed by Pummerer rearrangement and aminolysis resulting in the formation of the pyridine ring. Oxidation of the methyl group using SeO_2, followed by PDC oxidation of the diol and esterification (CH_2N_2) afforded the triester **(94)**. On saponification and N-deprotection of **(94)**, acromelic acid D **(16)** was isolated.[31] Alternatively, oxidation of the pyridine ring of **(94)** to the 2-pyridone [using (i) mCPBA then (ii) TFAA-DMF] followed by deprotection gave acromelic acid A **(13)**.[34,63] Acromelic acid B **(14)** was constructed in a similar fashion from aldehyde **(95)** by a nine-step construction of the regioisomeric enone sulphide **(96)**; Pummerer rearrangement and aminolysis provided the pyridine **(97)**. Conversion of this compound into acromelic acid B **(14)** was achieved in nine steps along the same lines as that used for acromelic acid A **(13)**. Although rather lengthy, the syntheses provided greater than 40mg of **(13)** and greater than 10mg of **(14)**.



(i) MnO_2; (ii) PhSH; (iii) $MeCOCH_2PO(OEt)_2$, NaH; (iv) $NaIO_4$; (v) TFAA; (vi) NH_3; (vii) SeO_2; (viii) CH_2N_2; (ix) TBAF; (x) PDC; (xi) CH_2N_2.

P = TBDMS



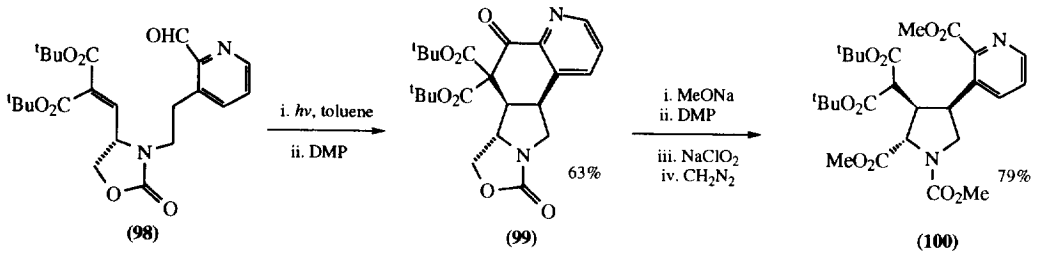
(i) $EtO_2CCH_2PO(OEt)_2$, NaH; (ii) DIBAL-H; (iii) $NaIO_4$; (iv) TFAA; (v) Na_2CO_3; (vi) MsCl; (vii) PhSH; (viii) MeLi; (ix) PDC; (x) $NaIO_4$; (xi) TFAA; (xii) NH_3.

P = TBDMS

Scheme 21

The syntheses of acromelic acids B **(14)** and E **(17)** have recently been reported, the key step of which involved a photochemical intramolecular Diels-Alder reaction.[64] The precursor pyridinecarbaldehyde **(98)**, obtained from (2*S*)-amino-3-butenol, was irradiated using light from a medium pressure mercury lamp in toluene at -78°C to induce enolisation and [4+2] cycloaddition (scheme 22). The reaction proceeded stereoselectively and oxidation of the resulting secondary alcohol using Dess-Martin periodinane (DMP) furnished the desired ketone **(99)** in 63% yield together with its C-4 epimer (10%). Cleavage of the β-ketodiester and cyclic carbamate groups of **(99)**, followed by C-2 oxidation and esterification afforded **(100)**

which was subsequently converted to **(14)** and **(17)**. This methodology has also been applied to the synthesis of kainoid analogues (see section 2.6.).

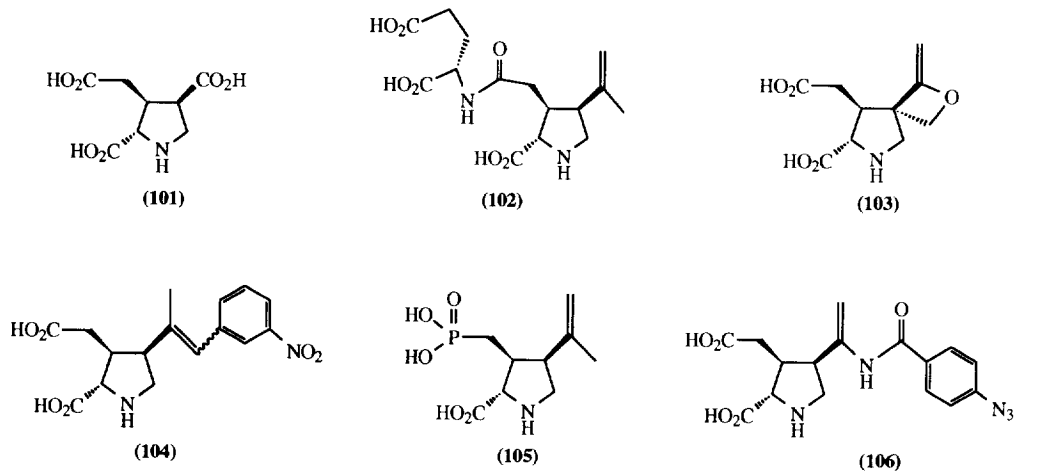


(98) **(99)** **(100)**

Scheme 22

2.6. Kainoid Analogues

A considerable number of semi-synthetic approaches to kainoid analogues starting from kainic acid **(1)** have been reported in the literature.[27] Analogues which have been prepared include tricarboxylic acid **(101)**,[27c] the dipeptide analogue **(102)**,[65] oxetane **(103)**,[27a] the (*Z*) and (*E*)-3-nitrophenyl derivatives **(104)**,[66] ω-phosphonic acid analogue **(105)**,[67] and the photo-activatible amide **(106)**.[68]

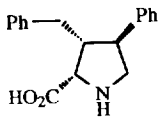


(101) **(102)** **(103)**

(104) **(105)** **(106)**

Other recently reported kainoid analogues not prepared from kainic acid **(1)** include the 4-hydroxyproline derived 3-benzyl derivative **(107)**,[69] the pyroglutamate derived CPAA (2-carboxy-3-pyrrolidineacetic acid) **(108)**[70] and allokainoid **(109)**,[71] lactone **(110)** prepared from (*S*)-2-phenylglycinol,[72] the bicyclo[3.3.0]octane **(111)**[26d] and phosphonic analog **(112)**.[73]

At present however, the most active area of kainoid analogue synthesis centres on the preparation of C-4 aromatic analogues such as **(18)**-**(20)**. These have been targeted because of their extraordinarily potent neuroexcitatory activity (see section 1.2.).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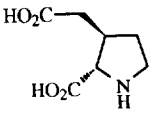
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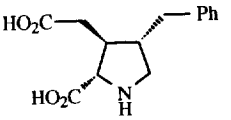
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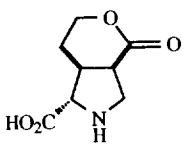
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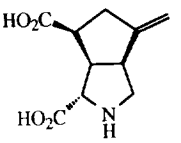
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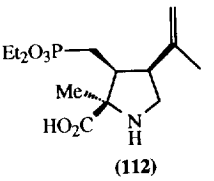
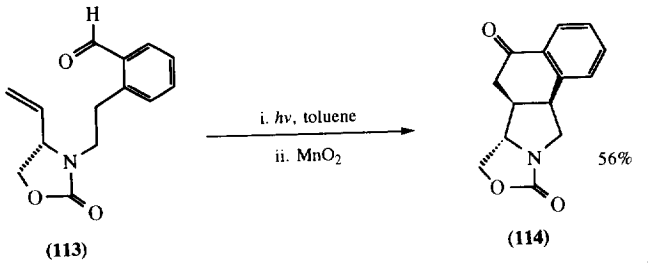

(112)

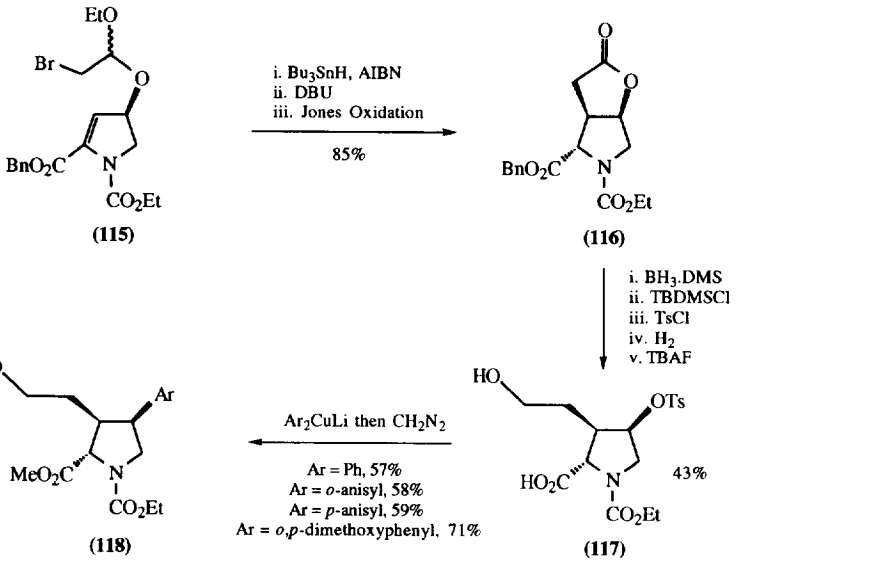
Shirahama[32a] has reported the stereoselective total synthesis of the kainoid analogues **(19)** and **(20)** using a similar intramolecular Diels-Alder reaction to that used for the synthesis of acromelic acids B **(14)** and E **(17)** (scheme 23). Thus on irradiation of aldehyde **(113)** [prepared from (2*S*)-amino-3-butenol] at 15°C, followed by MnO_2 oxidation, the cyclic ketone **(114)** was isolated in 56% yield. The oxazolidinone ring was essential to control the transition state conformation of the Diels-Alder reaction, to give **(114)** with the desired kainoid configuration. Compound **(114)** was then elaborated to the kainoid analogues **(19)** and **(20)** in a number of steps.



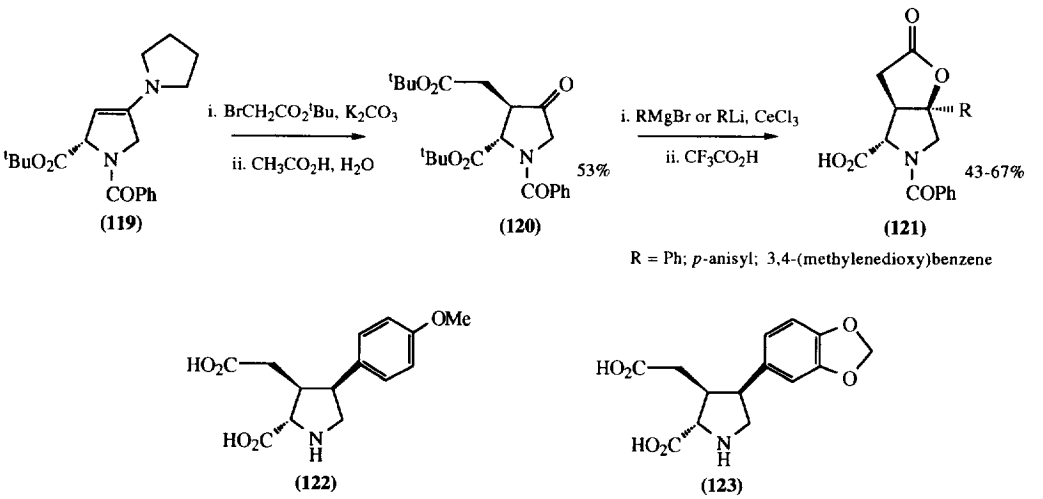
(113) (114)

Scheme 23

More recently, the same group have developed a general synthetic approach to acromelic acid congeners, including **(18)**-**(20)**, based on a substitution reaction of the *trans*-4-tosyloxyproline **(117)** (scheme 24).[32b] This was prepared from *trans*-L-4-hydroxyproline, the C-3 side chain being introduced *via* radical cyclisation of bromoacetal **(115)**. Epimerisation of the C-2 substituent using DBU in hot toluene followed by lactol oxidation then afforded the bicycle **(116)**. Subsequent elaboration of the C-3 and C-4 side chains gave **(117)**. On reaction of **(117)** with various diaryl copper lithium reagents at 0°C to room temperature, substitution at the C-4 position occurred with retention of configuration (in 57-71% yield). Esterification of the C-2 carboxylic acid afforded pyrrolidine **(118)** which could be elaborated to kainoids using standard methodology.



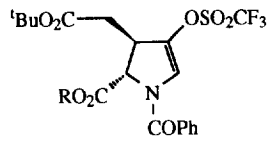
Scheme 24



Scheme 25

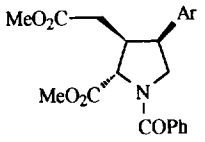
A similar strategy to 4-aryl kainoids has been reported by Baldwin and Rudolph.[74] They utilised ketone **(120)** which was prepared by alkylation of the enamine **(119)** (using *t*-butyl bromoacetate), which in turn was derived from a protected 4-oxoproline derivative (scheme 25). The C-4 side chain was then introduced by reaction with a Grignard reagent or an organocerium reagent and the resultant carbinol (isolated as one diastereomer in *ca.* 50% yield) was treated with TFA to afford the *cis*- fused bicyclic lactone **(121)**. Hydrogenolysis (H_2, Pd/C) of **(121)** proceeded smoothly with inversion and the resultant diacid could be

elaborated to kainoids **(18)**, **(122)** and **(123)**. This approach however, has been found to have limited versatility with some organometallic reagents giving little or no addition to ketone **(120)**.[75] A more versatile approach has since been reported by the same group using ketone **(120)** [or the corresponding C-2 methyl ester], the key step of which involved a Suzuki-type boronate coupling to the vinyl triflate **(124)**.[75] Phenylboronic acid and three anisylboronic acids were found to couple to **(124)** in 46-89% yield. The resultant adducts derived from the C-2 methyl ester could be converted into the kainoid precursor **(125)** *via* a three-step deprotection, esterification, reduction (Et_3SiH, TFA, 60°C) sequence. This approach allowed the preparation of acromelic acid analogues **(18)**, **(20)**, **(122)**, **(126)** and the corresponding allokainoid C-4 epimers.



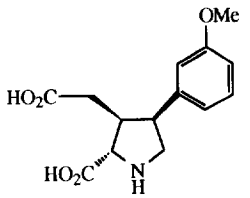
(124)

R=Me or tBu



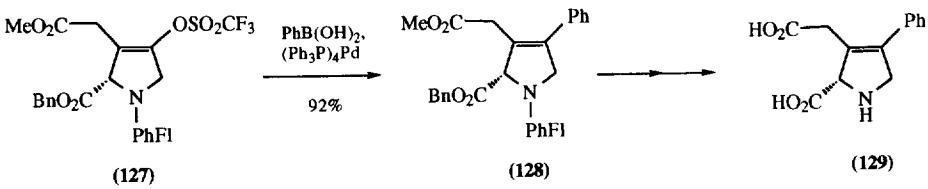
(125)

Ar=Ph, 2-MeOPh, 3-MeOPh or 4-MeOPh



(126)

One final approach, utilising a Pd(0)-catalysed cross-coupling reaction, has recently been reported by Lubell in the synthesis of the (2*S*)-Δ^3-4-phenylkainic acid **(129)** (scheme 26).[76] In this approach, the vinyl triflate **(127)**, derived from L-hydroxyproline, was found to undergo an extremely efficient palladium-catalysed coupling with $PhB(OH)_2$ (at 95°C after 6h in toluene) to yield alkene **(128)** in 92% yield. Deprotection was then accomplished in a further two steps to afford enantiomerically pure **(129)**.



(127) **(128)** **(129)**

PhFl=9-(9-phenylfluorenyl)

Scheme 26

3. Summary

This review has highlighted the considerable number of synthetic approaches which have been reported to natural and unnatural kainoid amino acids (up to mid-September 1995). In addition to the synthetic challenge, the preparation of these compounds has attracted tremendous interest due to their biological activity. The extremely potent neuroexcitatory aromatic acromelate analogues are of particular interest at present and the synthesis of these and related compounds should attract the attention of the synthetic chemist for many years to come.[77]

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