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Concise Synthesis of (+)-allo-Kainic Acid via MgI$_2$-Mediated Tandem Aziridine Ring Opening-Formal [3+2] Cycloaddition

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ABSTRACT

3-Methyl vinyl aziridine undergoes a mild MgI$_2$-promoted S$_2$2′ ring-opening and concomitant cyclization with fumarate Michael acceptors to give tri-substituted pyrrolidines. The process is efficient and highly diastereoselective. This methodology has been applied to a concise asymmetric synthesis of (+)-allo-kainic acid.

The kainoids are a class of natural, non-proteinogenic amino acids with interesting structural and biological properties (Figure 1). They are characterized by a densely functionalized pyrrolidine ring bearing three contiguous stereogenic centers and two carboxylic acid units. These structural features make them conformationally restricted analogues of glutamic acid and as such they have been extensively used in studies of several neurological diseases such as Huntington corea and Alzheimer’s disease. Their significant biological activity, coupled with an alarming global shortage has fuelled intense interest in the synthesis of this class of compounds. Among the kainoids, (+)-allo-kainic acid 1, has received considerably less attention than its C3-C4 diastereomer, (−)-kainic acid 2.

Figure 1. Structures of kainoids. The red color highlights the analogy with L-glutamic acid.

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As outlined in Scheme 1A, these synthetic efforts can be divided into “single bond disconnections” and “multiple bond disconnections”. The former approaches are based on the formation of the pyrrolidine ring and the control of the three contiguous stereocentres while forming a single C–C bond on an advanced intermediate. The latter, and more direct approaches assemble the highly substituted pyrrolidine ring by forming two C–C bonds simultaneously. Upon inspection of these methods we were intrigued that attention has been almost exclusively given to the disconnection across the C2-C3 and C4-C5 bonds.

Scheme 1.

A) Previous synthetic approaches towards 1

- [ene] Ref [7a-c]
- Ni-cyclization [Ref 7d]
- allyl-Pd [Ref 7g]

"Single Bond Disconnection"

B) Previous work from our group [Ref 10]

C) This Work: Retrosynthetic Analysis of 1

We have recently reported the Pd°-mediated annulation of vinyl aziridines 2 with Michael acceptors in the stereocentrer-controlled synthesis of substituted pyrrolidines and we have applied this methodology to a short formal synthesis of (–)-kainic acid (Scheme 1B). Whilst the methodology resulted in rapid construction of the pyrrolidine ring, it required additional functional group interconversion and redox chemistry to reach the target. We recognized that a similar reaction manifold, but with the correct juxtaposition of functional groups in the two reacting components could result in formation of the kainoids with minimal downstream manipulation. In this communication we describe our success in achieving a short, stereocentrer-controlled total synthesis of 1 using this strategy.

In our retrosynthetic analysis we envisioned the disconnection of 1 via a single key step (Scheme 1C). We reasoned that opening of vinyl aziridine 312 and concomitant annulation with a suitable fumarate derivative 4 would lead to the pyrrolidine ring with the functionality required for the kainic acids and the correct stereocentrer for (–)-allo-kainic acid 1. From pyrrolidine 5, a single functional group manipulation, namely the Arndt-Eistert homologation, and subsequent deprotection would complete the total synthesis.

Initial efforts at promoting reaction between aziridine 3 and Michael acceptors 4a (R = H) and 4b (R = OEt) using our previously optimized conditions, however, {[Pd(2dbc)Cl2]}, P(furyl)3 and TBAC14 in THF10 were fruitless (Table 1, entries 1–2). The reactions were usually characterised by complete decomposition of 3 and quantitative recovery of the acceptor. These observations indicated that the activation of the aziridine was indeed

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occurred but that the Michael acceptor was not reactive enough to undergo the addition process. We reasoned that the use of a more activating group such as a thioester or an oxazolidinone would promote the initial nucleophilic attack. Pleasingly, when thioester 4c was used, the reaction gave a mixture of diastereoisomers 5a–C in good yield but with poor diastereorecontrol (entry 3). The diastereoisomers were separated and their structure elucidated on the basis of their characteristic J values and nOe experiments. At this point the reaction parameters were further explored. The use of alternative halides was not effective (entry 4). Attempts to control both relative and absolute stereochemistry were explored initially using chiral ligands. However, the Trost ligand 6 gave the product in 52% yield but similar dr and without any enantioinduction (entry 5). We then explored chiral auxiliaries. When oxazolidinone-based acceptor 4d was used the formation of diastereomer 5dC was suppressed but a 1:1 mixture of 5dA and 5dB isomers was obtained but again with no control from the chiral auxiliary (i.e. after removal of the auxiliary the product was racemic) (entry 6). We believed that the poor diastereorecontrol from the auxiliary was due to two competing isoenergetic pathways arising from the fast interconversion of the syn-s-cis and anti-s-cis conformations around the auxiliary (Scheme 2A). Attempts to control this using chelating Lewis acids was however unsuccessful and no product was obtained (entry 7).

Unproductive avenues prompted us to investigate the use of a different mechanistic pathway for the implementation of this tandem process. We envisaged the use of a bifunctional activator of generic structure M–X where M (metal) would display sufficient Lewis acidity to activate the carbonyl group (via coordination) and X would display appropriate nucleophilicity to open the aziridine regioselectively (via an Sn2’ process). We were particulary intrigued by early reports from Carreira and Lautens where MgI2 has been found to be a competent electrophilic/nucleophilic promoter in the opening of cyclopropanes. We thus speculated that addition of equimolar amounts of MgI2 to our reaction would both open the aziridine and activate the fumarate derivative. Our plan was not without potential problems since M–X salts (M = Mg, Li, In; X = I, Br, Cl) have been reported to suppress the fast opening of the aziridine ring occurring but that the Michael acceptor was not reactive enough to undergo the addition process. We reasoned that the use of a more activating group such as a thioester or an oxazolidinone would promote the initial nucleophilic attack. Pleasingly, when thioester 4c was used, the reaction gave a mixture of diastereoisomers 5a–C in good yield but with poor diastereorecontrol (entry 3). The diastereoisomers were separated and their structure elucidated on the basis of their characteristic J values and nOe experiments. At this point the reaction parameters were further explored. The use of alternative halides was not effective (entry 4). Attempts to control both relative and absolute stereochemistry were explored initially using chiral ligands. However, the Trost ligand 6 gave the product in 52% yield but similar dr and without any enantioinduction (entry 5). We then explored chiral auxiliaries. When oxazolidinone-based acceptor 4d was used the formation of diastereomer 5dC was suppressed but a 1:1 mixture of 5dA and 5dB isomers was obtained but again with no control from the chiral auxiliary (i.e. after removal of the auxiliary the product was racemic) (entry 6). We believed that the poor diastereorecontrol from the auxiliary was due to two competing isoenergetic pathways arising from the fast interconversion of the syn-s-cis and anti-s-cis conformations around the auxiliary (Scheme 2A). Attempts to control this using chelating Lewis acids was however unsuccessful and no product was obtained (entry 7).

Whilst reactions with fumarate derivatives 4a and 4c were not successful, they did give the aziridine ring-opened product 7 showing that the Sn2’ with MgI2 had occurred in the desired manner (entries 8-10 and Scheme


16 5a: \( J^{(1)H-H} = 8 \text{ Hz} \); \( J^{(1)H-H} = 10.5 \text{ Hz} \). 5b: \( J^{(1)H-H} = 1.3 \text{ Hz} \). 5c: \( J^{(1)H-H} = 7.0 \text{ Hz} \). 5d: \( J^{(1)H-H} = 8.2 \text{ Hz} \). 5e: \( J^{(1)H-H} = 11.5 \text{ Hz} \). See the Supporting Information for HPLC conditions.

17 The use of TBAT did not provide any product.

18 Several commercially available ligands have been screened but they were generally ineffective in controlling the diastereoselectivity.

19 For a discussion on chiral oxazolidinones’ conformations in similar systems, see: Davies, S. G.; Herman, G. J.; Sweet, M. J.; Smith A. D. Chem. Commun. 2004, 1128.

20 Lewis Acids screened: Et3AlCl, Se(OTf)2, AgSbF6, Mg(OEt)2.


3). Pleasingly oxazolidinone 5d showed the right charge-affinity pattern and in 2,3,4-trisubstituted pyrrolidine product was obtained in 63% yield, 9:1 dr ( favouring 5dA) and essentially complete enantioselectivity (entry 11). Oxazolidinone 5e has been reported to be superior to 5d in asymmetric 1,4-nucleophilic additions, but in this case only a low diastereoselectivity was obtained (entry 12).

Scheme 2.

The stereochemical model for this new annulation reaction is provided in Scheme 3B and is based on attack of the ring-opened aziridine on the more accessible Si face of chelated syn-s-cis conformation of 4d. Following S$_2$2$^\text{t}$-type cyclisation of the intermediate enolate in the all-anti conformation (minimizing non-bonded interactions) results in the observed stereochemistry.

In summary, we have developed a powerful annulation method for combining readily accessible vinyl aziridines with Evans' fumarates for the stereocontrolled synthesis of densely functionalized pyrrolidines. The methodology has been applied to a concise asymmetric synthesis of (+)-allo-kainic acid.

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Supporting Information Available Synthesis and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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