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Concise Synthesis of (+)-allo-Kainic Acid via MgI₂-Mediated Tandem Aziridine Ring Opening-Formal [3+2] Cycloaddition

Giada Arena, C. Chun Chen, Daniele Leonori and Varinder K. Aggarwal

School of Chemistry, University of Bristol, Catock’s Close, Bristol, BS8 1TS, U.K.

v.aggarwal@bristol.ac.uk, daniele.leonori@bristol.ac.uk

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ABSTRACT

3-Methyl vinyl aziridine undergoes a mild MgI₂-promoted S₉2′ 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).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 corea² and Alzheimer’s disease.³ Their significant biological activity, coupled with an alarming global shortage⁴ has fuelled intense interest in the synthesis of this class of compounds.⁵ Among the kainoids, (+)-allo-kainic acid 1,⁶ has received considerably less attention than its C3-C4 diastereomer, (−)-kainic acid.⁷,⁸

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

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.\(^7\)

The latter, and more direct approaches assemble the highly substituted pyrrolidine ring by forming two C–C bonds simultaneously.\(^8\) 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.\(^9\)

### Scheme 1.

A) Previous synthetic approaches towards 1

- allyl silane cyclization \([Ref \ 7a-c]\)
- Ni-cyclization \([Ref \ 7d]\)
- allyl-Pd \([Ref \ 7g]\)

\[\text{Single Bond Disconnection}\]

B) Previous work from our group \([Ref \ 10]\)

\[\text{Multiple Bond Disconnection}\]

C) This Work: Retrosynthetic Analysis of 1

\[\text{Complementary approach} \quad \text{Simple starting material required} \quad \text{Suitable for asymmetric synthesis} \quad \text{Non-strategic redox steps minimised}\]

We have recently reported the Pd°-mediated annulation of vinyl aziridines 2 with Michael acceptors in the stereocentrered synthesis of substituted pyrrolidines and we have applied this methodology to a short formal synthesis of \((-\text{kainic acid} (\text{Scheme 1B})\).\(^{10,11}\) 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, stereocontrolled 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 3\(^{12}\) 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 stereochemistry for \((\text{-allo-})\text{kainic acid 1.}\)

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, \([\text{Pd}(\text{dbaz})\cdot \text{CHCl}_3],^{13}\) P(furyl)\(_3\) and TBAC\(^{14}\) in THF\(^{10}\) 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

\[\text{Other work from our group, see: (a) Fontana, F.; Chun Chen, C.; Lawrence, P. G.; Fontana, F.; Calabrese, A. A.; Aggarwal, V. K. Angew. Chem. Int. Ed. 2011, 50, 6370.}^{11}\]


\[\text{For the Pd°-mediated opening of activated aziridines, see: (c) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. Synlett 2001, 1596.}\]

\[\text{The addition of TBAC is aided to prevent ion pairing of the amide}\]


\[\text{BF}_3\cdot\text{Et}_2\text{O} (1.5 \text{ equiv}) \quad \text{Cl}_2\text{C}=	ext{C} \cdot \text{Cl}_2 \cdot \text{CO}_2 \cdot \text{H}^{-78} \text{°C} + \text{rt} \]

\[\text{For the Pd°-mediated opening of activated aziridines, see: (c) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. Synlett 2001, 1596.}\]

\[\text{The addition of TBAC is aided to prevent ion pairing of the amide}\]

occurring but that the Michael acceptor was not reactive enough to undergo the addition process. They 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 5Ca–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).

These 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 $\text{S}_{\text{N}}\text{2'}$ process). We were particulary intrigued by early reports from Carreira and Lautens where MgI$_2$ has been found to be a competent electrophilic/nucleophilic promoter in the opening of cyclopropanes. We thus speculated that addition of equinomial amounts of MgI$_2$ to our reaction would both open the aziridine and activate the fumurate derivative. Our plan was not without potential problems since M–X salts (M = Mg, Li, In; X = I, Br, Cl) have been reported to open (vinyl)-aziridines at the less substituted position.

### Table 1. Optimization of the tandem aziridine opening-formal

<table>
<thead>
<tr>
<th>Entry</th>
<th>4 additive (1.0 equiv)</th>
<th>Yield (%)</th>
<th>$dr$ (A:B:C)</th>
<th>$dr$ (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>a</td>
<td>TBAC</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>b</td>
<td>TBAC</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>c</td>
<td>TBAC</td>
<td>59%</td>
<td>5:2:3:8:1</td>
</tr>
<tr>
<td>4</td>
<td>c</td>
<td>TBAC</td>
<td>11%</td>
<td>2:5:1:7:1</td>
</tr>
<tr>
<td>5</td>
<td>c</td>
<td>TBAC</td>
<td>52%</td>
<td>4:2:1:4:1</td>
</tr>
<tr>
<td>6</td>
<td>d</td>
<td>TBAC</td>
<td>66%</td>
<td>1:1:0</td>
</tr>
<tr>
<td>7</td>
<td>d</td>
<td>TBAC + LA</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Entry</th>
<th>4 additive (1.0 equiv)</th>
<th>Yield (%)</th>
<th>$dr$ (A:B:C)</th>
<th>$dr$ (A)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>a</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>9</td>
<td>a</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>c</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>d</td>
<td>63%</td>
<td>9:1:0</td>
<td>99:1:1</td>
</tr>
<tr>
<td>12</td>
<td>e</td>
<td>–</td>
<td>62%</td>
<td>1:5:1:0</td>
</tr>
<tr>
<td>13$^a$</td>
<td>d</td>
<td>traces</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

### Footnotes

16 $^{a}$ Yield after column chromatography for the mixture of diastereomers. $^b$ Determined by $^{1}H$ NMR spectroscopy of the crude mixture. $^c$ Determined by chiral SFC. $^d$ Determined after removal of the chiral auxiliary. $^e$ 6 was used instead of P(furyl)$_3$. $^f$ Yield for the 5a. $^g$ 0.1 eq. of MgI$_2$ was used.

### Scheme

Whilst reactions with fumarate derivatives 4a and 4c were not successful, they did give the aziridine ring-opened product 7 showing that the $\text{S}_{\text{N}}\text{2'}$ with MgI$_2$ had occurred in the desired manner (entries 8-10 and Scheme 2A).
Having found the right charge-affinity pattern and the 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).

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 S22-type cyclisation of the intermediate enolate in the all-anti conformation (minimizing non-bonded interactions) results in the observed stereochemistry.

The complete total synthesis of (+)-allo-kainic acid. (+)-1 is shown in Scheme 4. Having found the appropriate conditions to access pyrrolidine 5dA, the auxiliary was removed by base hydrolysis to afford acid 8. Treatment of 8 with oxalyl chloride and TMS-diazomethane gave the corresponding diazoketone in 63% yield. This compound proved to be stable under silica gel chromatography and could be easily purified. Sonication of this intermediate in the presence of silver benzoate promoted the required Arndt-Eistert homologation. The resulting diester did not require any further purification and the two final deprotections could be performed on the crude material. Thus, saponification of the ethyl esters and removal of the tosyl group gave (+)-allo-kainic acid (+)-1 \( ([\alpha]_D +7.1 \text{ (c 0.1, H}_2\text{O}) \); Lit. \([\alpha]_D +7.7 \text{ (c 0.2, D}_2\text{O})\).7a

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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