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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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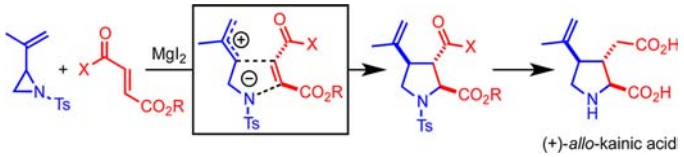
ABSTRACT



3-Methyl vinyl aziridine undergoes a mild MgI_2-promoted S_N2' ring opening and concomitant cyclization with fumarate Michael acceptors to give trisubstituted 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, nonproteinogenic 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 corea[2] and Alzheimer's disease.[3] Their significant biological activity, coupled with an alarming global shortage,[4] has fueled 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]

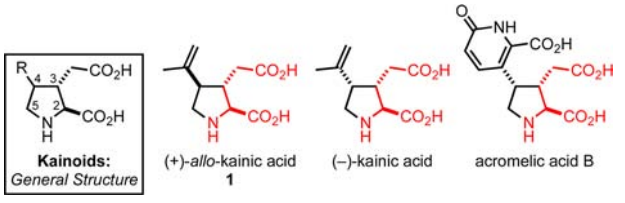


Figure 1. Structures of kainoids. The red color highlights the analogy with L-glutamic acid.

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(6) For the isolation of **1** from *Digenea simplex*, see: (a) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026. (b) Marimoto, H. *J. Pharm. Soc. Jpn.* **1975**, *75*, 766. (c) Murakami, S.; Daigo, K.; Takagi, N.; Takemoto, T.; Tei, Z. *J. Pharm. Soc. Jpn.* **1955**, *75*, 1252. (d) Watase, H. *Bull. Chem. Soc. Jpn.* **1958**, *31*, 932. (e) Nitta, I.; Watase, H.; Tomiie, Y. *Nature* **1958**, *181*, 761.

(7) Ene reaction: (a) Oppolzer, W.; Robbiani, C. *Helv. Chim. Acta* **1980**, *63*, 2010. (b) Oppolzer, W.; Robbiani, C.; Battig, K. *Helv. Chim. Acta* **1980**, *63*, 2015. (c) Oppolzer, W.; Robbiani, C.; Battig, K. *Tetrahedron* **1984**, *40*, 1391. Ni-catalyzed cyclization: (d) Montgomery, J.; Chevliakov, M. V. *Angew. Chem., Int. Ed.* **1998**, *37*, 3144. Allyl silane cyclization: (e) Mooiweer, H. H.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1991**, *47*, 3451. Isonitrile cyclization: (f) Murakami, M.; Hasegawa, N.; Hayashi, M.; Ito, Y. *J. Org. Chem.* **1991**, *56*, 7356. Allyl-Pd: (g) Cook, G. R.; Sun, L. *Org. Lett.* **2004**, *6*, 2481.

(8) [3 + 2] Cycloaddition: (a) Kraus, G. A.; Nagy, J. O. *Tetrahedron* **1985**, *41*, 3537. (b) DeShong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, *27*, 3979. Aza-Cope: (c) Agami, C.; Cases, M.; County, F. *J. Org. Chem.* **1994**, *59*, 7937. (d) Agami, C.; County, F.; Lin, J.; Mikaeloff, A.; Poursoulis, M. *Tetrahedron* **1993**, *49*, 7239.

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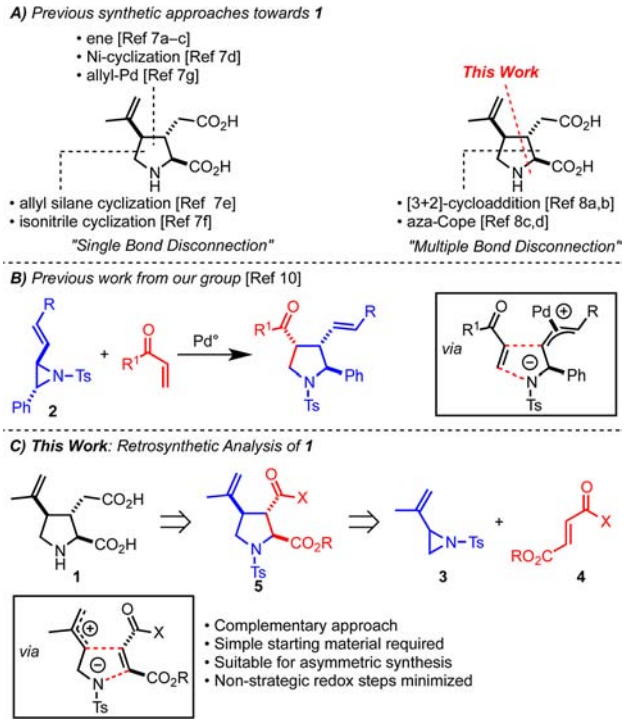
As outlined in Scheme 1A, these synthetic efforts can be divided into "single bond disconnections" and "multiple bond disconnections". The former approaches are based on the formation of the pyrrolidine ring and control of the three contiguous stereocenters while forming a single C−C bond on an advanced 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



We have recently reported the Pd°-mediated annulation of vinyl aziridines **2** with Michael acceptors in the stereocontrolled synthesis of substituted pyrrolidines, and we have applied this methodology to a short formal synthesis of (−)-kainic acid (Scheme 1B).[10,11] While 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. Here, 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 (+)-*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 the reaction between aziridine **3** and Michael acceptors **4a** (R = H) and **4b** (R = OEt) using our previously optimized conditions {$[Pd_2(dba)_3 \cdot CHCl_3]$,[13] $P(furyl)_3$, and TBAC[14] in THF},[9] however, were fruitless (Table 1, entries 1−2). The reactions were usually characterized by complete decomposition of **3** and quantitative recovery of the acceptor. These observations indicated that the activation of the aziridine was indeed occurring but that the Michael acceptor was not reactive enough to undergo the addition process.[15] 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 **5cA**−**C** in good yield but with poor diastereocontrol (entry 3). The diastereoisomers were

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(11) For similar work from our group, see: (a) Fontana, F.; Chun Chen, C.; Aggarwal, V. K. *Org. Lett.* **2011**, *13*, 3454. (b) Fontana, F.; Tron, G. C.; Barbero, N.; Ferrini, S.; Thomas, S.; Aggarwal, V. K. *Chem. Commun.* **2010**, *46*, 267.

(12) Aziridine **3** can be obtained in four steps from serine methyl ester hydrochloride; see: (a) Smith, A. B., III; Kim, D.-S. *J. Org. Chem.* **2006**, *71*, 2547. Alternatively, we have developed a one-step, regioselective procedure from isoprene (see Supporting Information). For some relevant work on the aziridination of unsymmetrical dienes, see: (b) Ho, C.-M.; Lau, T.-C.; Kwong, H.-L.; Wong, W.-T. *J. Chem. Soc., Dalton Trans.* **1999**, 2411. (c) Minakata, S.; Ando, T.; Nishimura, M.; Ryu, I.; Komatsu, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 3392. (d) Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* **2002**, *67*, 2101. (e) Nishimura, M.; Minakata, S.; Thongchant, S.; Ryu, T.; Komatsu, M. *Tetrahedron Lett.* **2000**, *41*, 7089. (f) Knight, J. G.; Muldowney, M. P. *Synlett* **1995**, 949. (g) Piangiolino, C.; Gallo, E.; Caselli, A.; Fantauzzi, S.; Ragaini, F.; Cenini, S. *Eur. J. Org. Chem.* **2007**, 743.

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(14) The addition of TBAC is aided to prevent ion pairing of the amide anion with the cationic Pd complex. For discussions on the effects of halide additives in palladium chemistry, see: (a) Reference 7. (b) Reference 10. For a review, see: (c) Fagnou, K.; Lautens, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 26.

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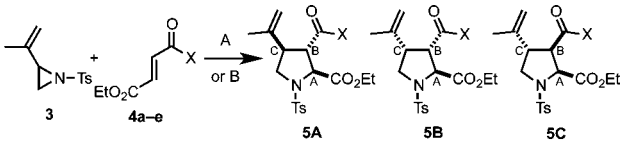
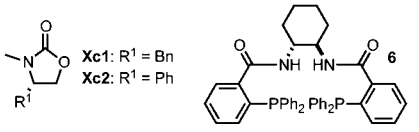
Table 1. Optimization of the Tandem Aziridine Opening–Formal [3 + 2] Cycloaddition Sequence



a : X = H
b : X = OEt
c : X = SEt
d : X = **Xc1**
e : X = **Xc2**



A) *Pd-catalysis:* **3** (1.0 equiv), **4** (1.0 equiv), $Pd_2(dba)_3$•$CHCl_3$ (5 mol%), P(furyl)$_3$ (25 mol%), Et_2O (0.1 M), rt, 24 h

entry	4	additive (1.0 equiv)	yield (%)[a]	dr (A:B:C)[b]	er (A)
1	a	TBAC	–	–	–
2	b	TBAC	–	–	–
3	c	TBAC	59%	5.2:3.8:1	–
4	c	TBAI	11%	2.5:1.7:1	–
5[e]	c	TBAC	52%	4.2:1.4:1	50:50[c]
6	d	TBAC	66%	1:1:0	50:50[d]
7	d	TBAC + LA	–	–	–

B) *Mg-catalysis:* **3** (2.0 equiv), **4** (1.0 equiv), MgI_2 (1.0 equiv), CCl_4 (0.35 M), rt, 16 h

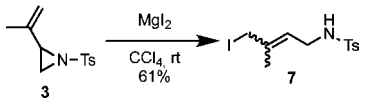
entry	4	additive (1.0 equiv)	yield (%)	dr (A:B:C)	er (A)
8	a	–	–	–	–
9	a	–	–	–	–
10	c	–	–	–	–
11	d	–	63%[f]	9:1:0	99:1[d]
12	e	–	62%	1.5:1:0	n.d.
13[g]	d	–	traces	–	–

[a] Yield after column cromatography 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 5dA. [g] 0.1 equiv of MgI_2 was used.

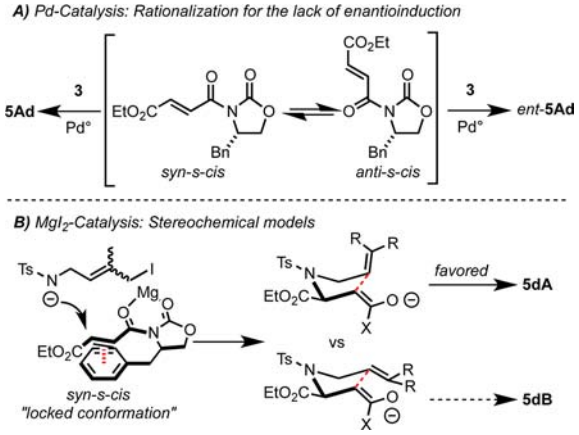
separated, and their structures were elucidated on the basis of their characteristic *J* values and NOE experiments.[16] At this point the reaction parameters were further explored. The use of alternative halides was not effective (entry 4).[17] Attempts to control both the relative and absolute stereochemistry were explored initially using chiral ligands. However, the Trost ligand **6** gave the product in 52% yield but with similar dr and without any enantioinduction (entry 5).[18] 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 diastereocontrol 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 3A).[19] Attempts to control this using chelating Lewis acids was however unsuccessful, and no product was obtained (entry 7).[20]

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 S_N2' process). We were particulary intrigued by early reports from Carreira[21] and Lautens[22] where MgI_2 has been found to be a competent electrophilic/nucleophilic promoter in the opening of cyclopropanes.[23] We thus speculated that addition of equimolar amounts of MgI_2 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 open (vinyl)-aziridines at the less substituted position.[24]

Scheme 2



Scheme 3



While reactions with fumarate derivatives **4a** and **4c** were not successful, they did give the aziridine ring-opened product **7** showing that the S_N2' with MgI_2 had occurred in

(16) **5A**: $J(H^A–H^B) \approx 8.2$ Hz; $J(H^B–H^C) \approx 10.5$ Hz. **5B**: $J(H^A–H^B) \approx 1.3$ Hz; $J(H^B–H^C) \approx 7.0$ Hz. **5C**: $J(H^A–H^B) \approx 8.2$ Hz; $J(H^B–H^C) \approx 11.5$ 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.

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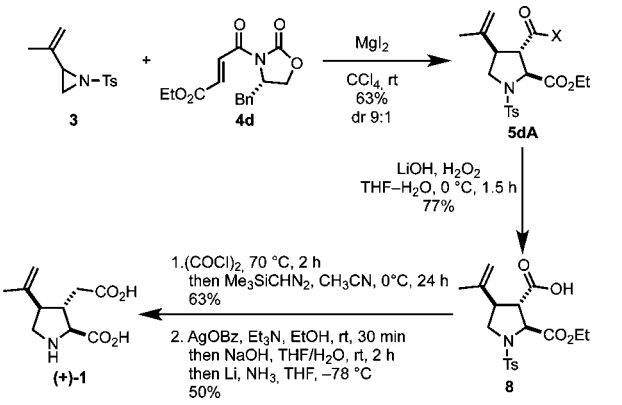
Scheme 4



the desired manner (entries 8−10 and Scheme 2). Pleasingly oxazolidinone **4d** showed the right charge-affinity pattern, and the 2,3,4-trisubstituted pyrrolidine product was obtained in 63% yield, 9:1 dr, (favoring **5dA**) and essentially complete enantioselectivity (entry 11). Oxazolidinone **4e** has been reported to be superior to **4d** in asymmetric 1,4-nucleophilic additions,[25] 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 the chelated *syn-s-cis* conformation of **4d**.[26] Following S_N2'-type cyclization of the intermediate enolate in the all-*anti* conformation (minimizing nonbonded interactions) results in the observed stereochemistry.

The complete total synthesis of (+)-*allo*-kaininc 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*-kaininc acid (+)-**1** {$[\alpha]_D$ +7.1 (*c* 0.1, H_2O); Lit. $[\alpha]_D$ +7.7 (*c* 0.2, H_2O)}.[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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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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The authors declare no competing financial interest.