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Stereocontrolled Total Synthesis of (−)-Kainic Acid. Regio- and Stereoselective Lithiation of Pyrrolidine Ring with the (+)-Sparteine Surrogate

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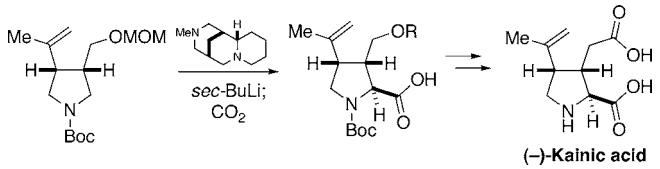
ABSTRACT



A stereocontrolled total synthesis of (−)-kainic acid is described. *cis*-3,4-Disubstituted pyrrolidine ring was constructed by [3 + 2] cycloaddition of azomethine ylide with chiral butenolide. The crucial introduction of carboxyl group at the C-2 position was executed by regio- and stereoselective lithiation of the pyrrolidine ring in the presence of a (+)-sparteine surrogate followed by trapping with carbon dioxide.

(−)-Kainic acid (**1**), first isolated in 1953 from the Japanese marine alga *Digenea simplex*[1] and later found in the related algae as well,[2] is the parent member of the kainoids[3] that display potent anthelmintic properties[4] and neurotransmitting activities[5] in the mammalian central nervous system. Thus, kainic acid has been widely used as a tool in neuropharmacology[6] for the stimulation of the nerve cells and the mimicry of disease states such as epilepsy,[7] Alzheimer's disease, and Huntington's chorea.[8] On the other hand, the structural feature of **1**, namely, a highly functionalized trisubstituted pyrrolidine ring with three contiguous chiral centers, has received considerable attention from synthetic chemists. Since Oppolzer's first enantioselective total synthesis,[9] a number of total syntheses and synthetic approaches have been reported to date.[10]

In view of the recent depletion of supply of the natural kainic acid,[11] we developed a research program to develop an efficient synthetic route to **1**. Our synthetic strategy is outlined in Scheme 1. The carboxyl group on the C-3 substituent would be introduced in the last stage of the synthesis. We planned to construct the α-amino acid moiety by regio- and diastereoselective lithiation at the C-2 position of the pyrrolidine **3** followed by carboxylation. The propenyl group at the C-4 position would be installed by nucleophilic addition to the γ-lactone. Stereoselective construction of the lactone-fused pyrrolidine ring would be performed by a substrate-controlled diastereoselective 1,3-

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(1) Murakami, S.; Takemoto, T.; Shimizu, Z. *J. Pharm. Soc. Jpn.* **1953**, *73*, 1026.

(2) (a) Impellizzeri, G.; Mangiafico, S.; Oriente, G.; Piatelli, M.; Sciuto, S.; Fattorusso, E.; Magno, S.; Santacroce, C.; Sica, D. *Phytochemistry* **1975**, *14*, 1549. (b) Balansard, G.; Gayte-Sorbier, A.; Cavalli, C. *Ann. Pharm. Fr.* **1982**, *40*, 527. (c) Balansard, G.; Pellegrini, M.; Cavalli, C.; Timon-David, P.; Gasquet, M.; Boudon, G. *Ann. Pharm. Fr.* **1983**, *41*, 77.

(3) (a) Maloney, M. G. *Nat. Prod. Rep.* **1998**, *15*, 205. (b) Maloney, M. G. *Nat. Prod. Rep.* **1999**, *16*, 485. (c) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149.

(4) Nitta, I.; Watase, H.; Tomiie, Y. *Nature (London)* **1958**, *181*, 761.

(5) (a) Hashimoto, K.; Shirahama, H. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 212. (b) Hashimoto, K.; Shirahama, H. *Trends Org. Chem.* **1991**, *2*, 1. (c) Cantrell, B. E.; Zimmerman, D. M.; Monn, J. A.; Kamboj, R. K.; Hoo, K. H.; Tizzano, J. P.; Pullar, I. A.; Farrell, L. N.; Bleakman, D. *J. Med. Chem.* **1996**, *39*, 3617.

(6) MacGeer, E. G.; Olney, J. W.; MacGeer, P. L. *Kainic Acid as a Tool in Neurogiology*; Raven: New York, 1978.

(7) Sperk, G. *Prog. Neurobiol. (Oxford)* **1994**, *42*, 1.

(8) Coyle, J. T.; Schwarcz, R. *Nature (London)* **1976**, *263*, 244.

(9) (a) Racemic synthesis: Oppolzer, W.; Andres, H. *Helv. Chim. Acta* **1979**, *62*, 2282. (b) Enantioselective synthesis: Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978.

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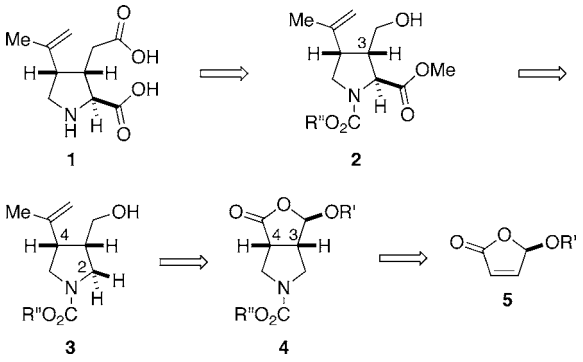
Scheme 1. Synthetic Strategy for (−)-Kainic Acid (**1**)

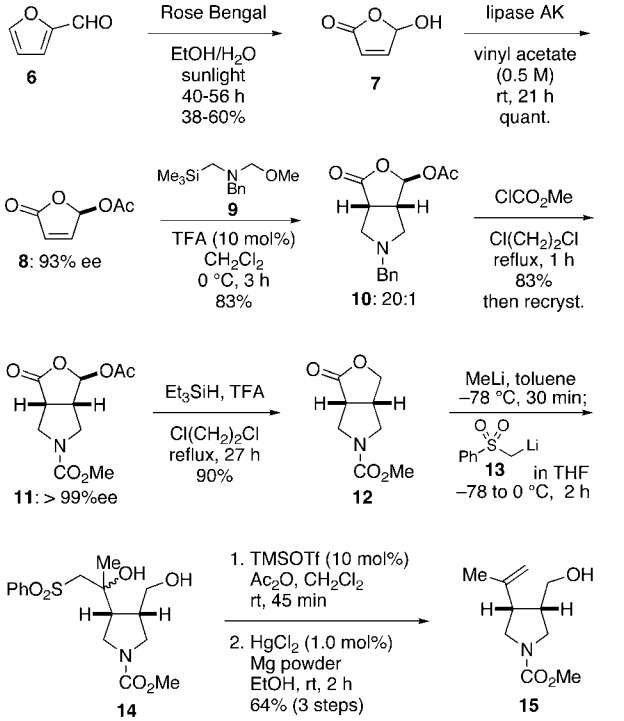


dipolar cycloaddition of an azomethine ylide to the chiral butenolide **5**.

Synthesis of (−)-kainic acid (**1**) commenced with a large-scale preparation of chiral butenolide **8** by a modification of the reported methods. We have found that photooxygenation of furfural (**6**) proceeded with bubbling air under sunlight instead of bubbling oxygen under irradiation with a high-pressure mercury lamp.[12] Thus, bubbling air through an ethanolic solution of furfural in the presence of Rose Bengal under the sun gave the desired butenolide **7**. We have also improved the subsequent enzymatic dynamic kinetic resolution of **7**.[13] When the reaction was carried out with lipase AK in a higher concentration of **7** in vinyl acetate as solvent, the reaction time was dramatically shortened and the desired acetoxy butenolide **8** (93% ee) was obtained in a quantitative yield.

The crucial 1,3-dipolar cycloaddition of the chiral butenolide **8** with the azomethine ylide[14] took place smoothly upon treatment of a mixture of **8** and **9** with 10 mol % of TFA[15] to afford the desired cycloadduct **10** in 83% yield with high diastereoselectivity (20:1). After a one-pot conversion of the *N*-benzyl group into the *N*-carbomethoxy group, the optically pure γ-lactone **11** (>99% ee) was obtained by recrystallization. Subsequent reduction of the acetal with Et_3SiH and TFA furnished lactone **12**. Construction of the 4-propenyl group was then achieved by a three-step transformation involving a modified Julia olefination. Thus, after treatment of **12** with methyllithium in toluene, a THF solution of α-lithiated methyl phenyl sulfone **13** was added to the reaction mixture to provide the desired diol **14** as a diastereomeric mixture. Neither epimerization at the C-4 position nor a formation of dimethylcarbinol was observed. TMSOTf-catalyzed acetylation of **14** to the corresponding diacetate, followed by reductive treatment with catalytic amount of mercury chloride and magnesium powder,[16] gave **15** bearing the isopropenyl group in high yield (Scheme 2).

Scheme 2. Synthesis of the Disubstituted Pyrrolidine Ring



With the key *cis*-3,4-disubstituted pyrrolidine intermediate in hand, we next focused our attention on the stereoselective introduction of carboxyl group at the C-2 position. For this purpose, we initially tested a directing effect of the C-3 substituent on the selective lithiation of *N*-Boc-protected pyrrolidine.[17] Thus, the nitrogen and hydroxyl groups of **15** were protected with Boc and MOM groups, respectively, and

(10) For a recent review, see ref 3. For selected examples, see: (a) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204. (b) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467. (c) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1990**, *46*, 7263. (d) Jeong, N.; Yoo, S.-E.; Lee, S. J.; Lee, S. H.; Chung, Y. K. *Tetrahedron Lett.* **1991**, *32*, 2137. (e) Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *J. Chem. Soc., Chem. Commun.* **1991**, 390. (f) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 553. (g) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169. (h) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125. (i) Yoo, S.-E.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968. (j) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (k) Nakada, Y.; Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 857. (l) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896. (m) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Synlett* **1997**, 275. (n) Rubio, A.; Ezquerra, J.; Escribano, A.; Remuinan, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1998**, *39*, 2171. (o) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron* **1999**, *55*, 6153. (p) Campbell, A. D.; Taylor, R. J. K.; Raynham, T. M. *Chem. Commun.* **1999**, 245. (q) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139. (r) Hirasawa, H.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 7587. (s) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727. (t) Trost. B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 1467. (u) Anderson, J. C.; Whiting, M. *J. Org. Chem.* **2003**, *68*, 6160.

(11) (a) Tremblay, J.-F. *Chem. Eng. News* **2000**, *78*(1), 14. (b) Tremblay, J.-F. *Chem. Eng. News* **2000**, *78*(10), 31.

(12) (a) Moradei, O. M.; Paquette, L. A. *Org. Synth.* **2003**, *80*, 66. (b) Gollnick, K.; Griesbeck, A. *Tetrahedron* **1985**, *41*, 2057.

(13) (a) Brinksma, J.; Deen van der, H.; Oeveren van, A.; Feringa, B. L. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4159. (b) Deen van der, H.; Cuiper, A. D.; Hof, R. P.; Oeveren van, A.; Feringa, B. L.; Kellogg, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 3801.

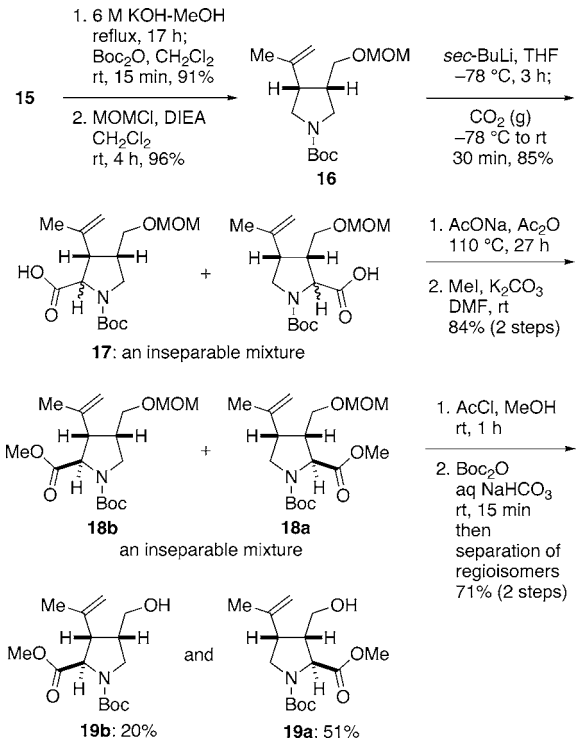
(14) (a) Hosomi, A.; Sakata, Y.; Sakurai, H. *Chem. Lett.* **1984**, 1117. (b) Padwa, A.; William, D. *Organic Syntheses*; Wiley: New York, 1993; Collect. Vol. VIII, p 231.

(15) Terao, Y.; Kotaki, H.; Imai, N.; Achiwa, K. *Chem. Pharm. Bull.* **1985**, *33*, 2762.

(16) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833. (b) Lee, G. H.; Lee, H. K.; Choi, E. B.; Kim, B. T.; Pak, C. S. *Tetrahedron Lett.* **1995**, *36*, 5607.

the compound thus obtained was treated with *s*-BuLi at −78 °C and then with gaseous carbon dioxide. Disappointingly, however, the trisubstituted pyrrolidine derivative **17** was obtained as an inseparable mixture of regio- and diastereoisomers. At this point, we could epimerize the undesired α−carboxyl isomers to the thermodynamically more stable *β*-epimers via their mixed anhydrides and then converted to methyl esters **18a** and **18b**. After removal of the MOM group, the regioisomers could be separated to give the desired **19a** and the undesired **19b** in a 2.6:1 ratio (51% and 20% overall yield from **16**). This result indicated that the directing effects of the substituents at the 3-position were not sufficient for the differentiation of the regio- and stereochemistry in the lithiation process (Scheme 3).

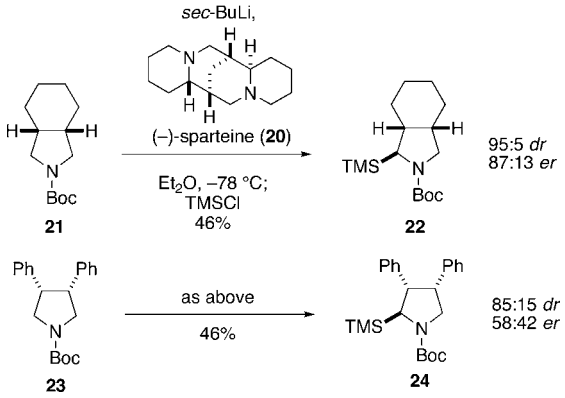
Scheme 3. MOM Group-Directed Lithiation of **19**[a]



We then decided to utilize external chiral ligands to achieve regio- and diastereoselective lithiation. However, (−)-sparteine (**20**), the most representative chiral amine established by Beak and co-workers, could not be adopted in our case. Beak reported that (−)-sparteine-mediated lithiation/silylation of bicyclic *cis*-3,4-disubstituted *N*-Boc-pyrrolidine **21** gave the corresponding silylated product **22** with excellent diastereo- and enantioselectivity although the stereochemistry of the product is opposite to what we desired (Scheme 4). In addition, rather poor diastereo- and enantioselectivity was observed with the monocyclic compound **23**.

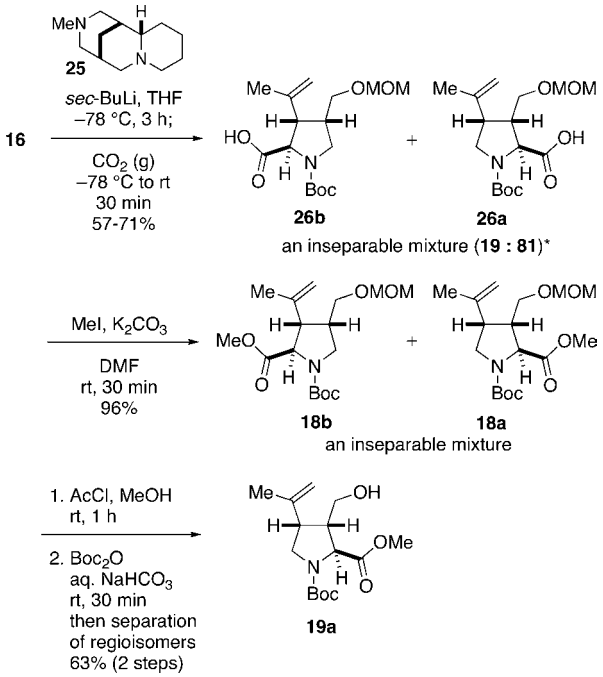
(17) (a) For a review, see: Beak, P.; Zajdel, W. J. *Chem. Rev.* **1984**, *84*, 471. (b) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. (c) Beak, P.; Basu, A.; Gallagher, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552. (d) Johnson, T. A.; Jang, D. O.; Slafer, B. W.; Curtis, M. D.; Beak, P. *J. Am. Chem. Soc.* **2002**, *124*, 11689, references therein.

Scheme 4. (−)-Sparteine-Mediated Lithiation/Silylation of *meso*-3,4-Disubstituted *N*-Boc-pyrrolidine[17d]



O'Brien and co-workers reported that the diamine **25** could serve as a surrogate for (+)-sparteine for enantioselective lithiation of *N*-Boc-pyrrolidine.[18] Thus, we examined the lithiation−carboxylation protocol in the presence of the (+)-sparteine surrogate **25**. To our delight, the reaction in the presence of 2.5 equiv of **25** only gave a mixture of the desired isomer **26a** and its regioisomer **26b** (81:19). Thus, we have successfully controlled the diastereoselectivity, albeit with similar regioselectivity. After conversion to the ester and deprotection of the MOM group, the desired isomer **19a** was chromatographically separated (Scheme 5).

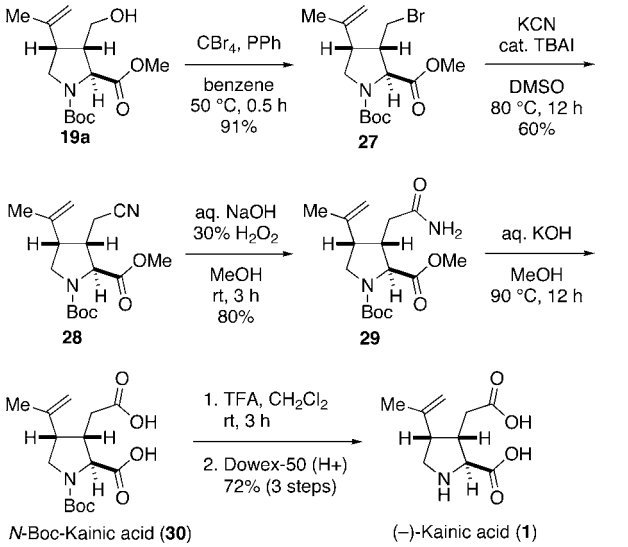
Scheme 5. Lithiation with the (+)-Sparteine Surrogate **25**[a]



[a] The ratio of regioisomers (*) was determined by HPLC analysis after conversion to the corresponding benzyl ester (BnBr, K_2CO_3, DMF, rt, 15 min, quant).

The remaining task toward a total synthesis of (−)-kainic acid was to construct the carboxylmethyl group at the C-3

Scheme 6. Total Synthesis of (−)-Kainic Acid



position of the pyrrolidine ring. After transformation of alcohol **19a** to bromide **27**, nucleophilic substitution with KCN afforded nitrile **28**. Conversion of the nitrile to the carboxylic acid was then executed in a stepwise manner. Thus, treatment of nitrile **28** with alkaline hydrogen peroxide gave amide **29** and the subsequent hydrolysis of both the amide and the methyl ester led to *N*-Boc-kainic acid (**30**). Finally, deprotection of the Boc group with TFA yielded (−)-kainic acid (**1**), which was spectroscopically identical with the natural product[10a,j] (Scheme 6).

In conclusion, an enantioselective total synthesis of (−)-kainic acid (**1**) has been accomplished. The synthesis features (1) a facile construction of the *cis*-3,4-disubstituted pyrroridine ring by a TFA-catalyzed stereoselective 1,3-dipolar cycloaddition of the azomethine ylide and the optically active butenolide prepared by enzymatic dynamic kinetic resolution, (2) a modified Julia olefination for construction of the propenyl group, and (3) the construction of α-amino acid moiety of the trisubstituted pyrrolidine ring by a regio- and stereoselective lithiation-carboxylation sequence.

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Supporting Information Available: Experimental details and ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) (a) Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R. O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870. (b) Hermet, J.-P. R.; Porter, D. W.; Dearden, M. J.; Harrison, J. R.; Koplin, T.; O'Brien, P.; Parmene, J.; Tyurin, V.; Whitwood, A. C.; Gilday, J.; Smith, N. M. *Org. Biomol. Chem.* **2003**, *1*, 3977.