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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 kainoids³ that display potent anthelmintic properties⁴ and neurotransmitting activities⁵ in the mammalian central nervous system. Thus, kainic acid has been widely used as a tool in neuropharmacology⁶ for the stimulation of the nerve cells and the mimicry of disease states such as epilepsy,⁷ Alzheimer's disease, and

(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.

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.

^{(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.

⁽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.



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

Synthesis of (–)-kainic acid (1) commenced with a largescale 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 ylide¹⁴ took place smoothly upon treatment of a mixture of **8** and **9** with 10 mol % of TFA¹⁵ 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 Et₃SiH 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).



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. (1) 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).



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.



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).



 a The ratio of regioisomers (*) was determined by HPLC analysis after conversion to the corresponding benzyl ester (BnBr, K₂CO₃, 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

^{(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.



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 ¹H and ¹³C 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.