ORGANIC LETTERS

2007
Vol. 9, No. 9
1635−1638

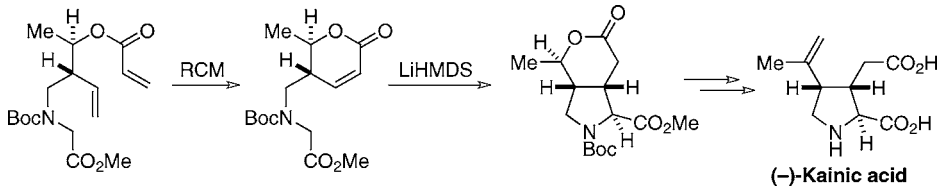
Stereocontrolled Total Synthesis of (−)-Kainic Acid

Hiroshi Sakaguchi,[†] Hidetoshi Tokuyama,[‡] and Tohru Fukuyama*

Graduate School of Pharmaceutical Sciences, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
fukuyama@mol.f.u-tokyo.ac.jp

Received December 25, 2006

ABSTRACT



A stereocontrolled total synthesis of (−)-kainic acid is described. A fully functionalized trisubstituted pyrrolidine ring was constructed by ring-closing metathesis of an acrylate derivative followed by an intramolecular Michael addition of the resultant α,β-unsaturated lactone with high diastereoselectivity. Two alternative protocols for the construction of the α,β-unsaturated lactone were also developed.

(−)-Kainic acid (**1**), first isolated in 1953 from the Japanese marine alga *Digenea simplex*[1] and later found in a related algae as well,[2] is the parent member of the kainoid family.[3] Kainoids display potent anthelmintic properties[4] and neurotransmitting activities[5] in the mammalian central nervous system, and kainic acid in particular has been widely used as a tool in neuropharmacology[6] for stimulation of nerve cells and the mimicry of disease states such as epilepsy,[7] Alzheimer's disease, and Huntington's chorea.[8] A recent shortage in the supply of **1** had become a serious problem for researchers, but even after a recent recovery in the supply of **1**, it continues to be a costly compound.[9]

From a synthetic point of view, the structural features of **1**, namely, a highly functionalized trisubstituted pyrrolidine ring with three contiguous chiral centers, has attracted considerable attention from synthetic chemists. A number of total syntheses and synthetic approaches have been reported,[10,11] including one from this laboratory featuring a regio- and stereoselective lithiation of a pyrrolidine ring.[12] However, there have been few synthetic routes amenable to large-scale preparation with comparable efficiency to the current method of isolation from algae. Herein, we describe an efficient synthetic route to **1**, featuring a ring-closing metathesis (RCM) reaction[13] of an acrylate derivative and an intramolecular Michael addition for the stereoselective construction of the functionalized pyrrolidine ring.

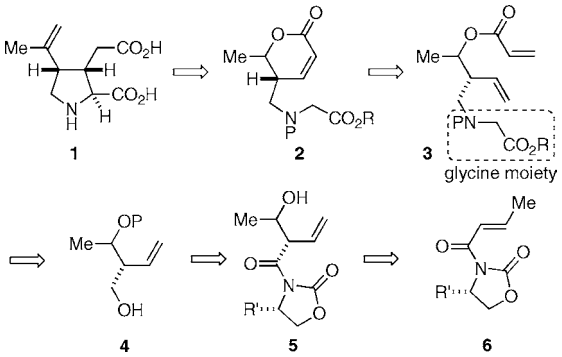
Our synthetic strategy is outlined in Scheme 1. For the stereoselective construction of the 3,4-*cis*-pyrrolidine ring, we planned to perform an intramolecular Michael addition of the glycine moiety to the α,β-unsaturated lactone.[14] The α,β-unsaturated lactone **2** could be formed by RCM of an acrylate derivative **3**. Installation of the acrylate and glycine

[†] Visiting researcher from Sumitomo Chemical Co., Ltd.
[‡] Current Address: Graduate School of Pharmaceutical Sciences, Tohoku University, Aramaki, Aoba, Sendai, 980-8578, Japan.

(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.; Timond-David, P.; Gasquent, M. *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) Maloney, M. G. *Nat. Prod. Rep.* **2002**, *19*, 597. (d) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. (d) Hashimoto, K.; Shirahama, H. *J. Synth. Org. Chem. Jpn.* **1989**, *47*, 212.
(4) Nitta, I.; Watase, H.; Tomiie, Y. *Nature (London)* **1958**, *181*, 761.
(5) (a) Hashimoto, K.; Shirahama, H. *Trends Org. Chem.* **1991**, *2*, 1. (b) 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) Tremblay, J.-F. *Chem. Eng. News* **2000**, Jan 3, 14. (b) Tremblay, J.-F. *Chem. Eng. News* **2000**, Mar 6, 31. (c) Tremblay, J.-F. *Chem. Eng. News* **2001**, Jan 29, 19.
(10) For recent reviews, see ref 3.

10.1021/ol0631197 CCC: $37.00
Published on Web 03/30/2007

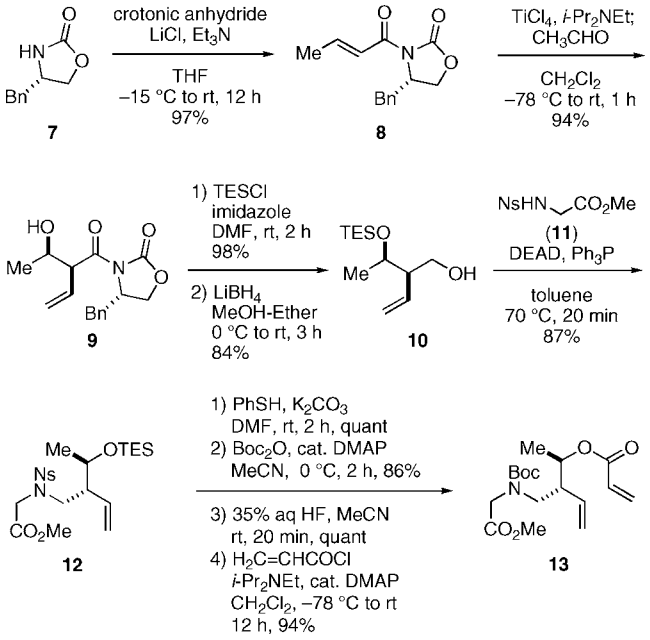
Scheme 1. Synthetic Strategy for (−)-Kainic Acid (**1**)



functionalities could be carried out on monoprotected diol **4**. Enantioselective synthesis of **4** would be possible by reduction of the Evans aldol reaction[15] product **5**, available from crotonic acid derivative **6** and acetaldehyde.

Preparation of the substrate for RCM reaction started with the acylation of oxazolidinone **7** with crotonic anhydride[16] (Scheme 2). A diastereoselective Evans aldol reaction between crotonamide detivative **8** and acetaldehyde proceeded in the presence of 1.05 equiv of $TiCl_4$ and 2.5 equiv of *i*-Pr_2NEt to give the aldol product **9** as a single isomer.[17]

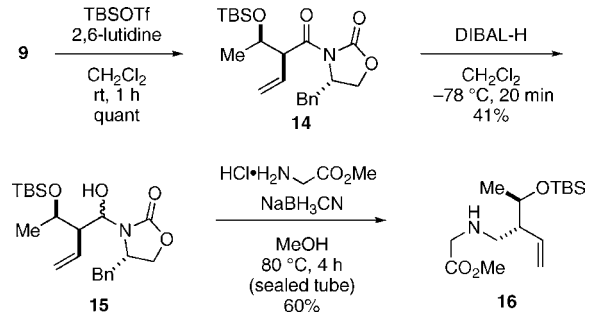
Scheme 2. Synthesis of RCM Precursor **12**



After protection of the hydroxyl group as the TES ether, the chiral auxiliary was reductively cleaved to provide homoallylic alcohol **10**. Introduction of the glycine moiety was then carried out by Mitsunobu reaction[18] of **10** with Nosyl (Ns)-activated glycine methyl ester **11**.[19] Exchanging the Ns with the Boc group by the standard conditions was followed by desilylation and acylation with acryloyl chloride to afford the desired precursor **13** for RCM reaction.

Due to the impracticality of the Mitsunobu reaction for large-scale preparation, we examined a reductive amination approach to incorporate the glycine moiety (Scheme 3).

Scheme 3. Reductive Amination Approach To Introduce the Glycine Moiety



Treatment of the TBS-protected aldol product **14** with DIBAL-H at −78 °C gave the corresponding hemiaminal **15** as a mixture of diastereomers in modest yield. Reductive amination of **15** with glycine methyl ester hydrochloride

(11) For selected examples, see: (a) Ueno, Y.; Tanaka, K.; Ueyanagi, J.; Nawa, H.; Sanno, Y.; Honjo, M.; Nakamori, R.; Sugawa, T.; Uchibayashi, M.; Osugi, K.; Tatsuoka, S. *Proc. Jpn. Acad.* **1957**, *33*, 53. (b) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978. (c) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204. (d) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467. (e) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1990**, *46*, 7263. (f) Jeong, N.; Yoo, S.-E.; Lee, S. J.; Lee, S. H.; Chung, Y. K. *Tetrahedron Lett.* **1991**, *32*, 2137. (g) Barco, A.; Benetti, S.; Pollini, G. P.; Spalluto, G.; Zanirato, V. *J. Chem. Soc., Chem. Commun.* **1991**, 390. (h) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. 1* **1992**, 553. (i) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169. (j) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125. (k) Yoo, S.-E.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968. (l) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418. (m) Nakada, Y.; Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 857. (n) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896. (o) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Synlett* **1997**, 275. (p) Rubio, A.; Ezquerra, J.; Escribano, A.; Remuinan, M. J.; Vaquero, J. J. *Tetrahedron Lett.* **1998**, *39*, 2171. (q) Cossy, J.; Cases, M.; Pardo, D. G. *Tetrahedron* **1999**, *55*, 6153. (r) Campbell, A. D.; Taylor, R. J. K.; Raynham, T. M. *Chem. Commun.* **1999**, 245. (s) Chevliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139. (t) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Tetrahedron* **2000**, *56*, 6199. (u) Nakagawa, H.; Sugahara, T.; Ogasawara, K. *Org. Lett.* **2000**, *2*, 3181. (v) Xia, Q.; Ganem, B. *Org. Lett.* **2001**, *3*, 485. (w) Hirasawa, H.; Taniguchi, T.; Ogasawara, K. *Tetrahedron Lett.* **2001**, *42*, 7587. (x) Clayden, J.; Menet, C. J.; Tchabanenko, K. *Tetrahedron* **2002**, *58*, 4727. (y) Martínez, M. M.; Hoppe, D. *Eur. J. Org. Chem.* **2005**, *7*, 1427. (z) Anderson, J. C.; O'Loughlin, J. M. A.; Tornos, J. A. *Org. Biomol. Chem.* **2005**, *3*, 2741. (aa) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763. (bb) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045. (cc) Poisson, J.-F.; Orellana, A.; Greene, A. E. *J. Org. Chem.* **2005**, *70*, 10860.

(12) Morita, Y.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2005**, *7*, 4337.

(13) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.

(14) For the construction of the pyrrolidine ring system by intramolecular Michael addition reaction, see: Yoo, S.-E.; Lee, S.-H.; Kim, N.-J. *Tetrahedron Lett.* **1988**, *29*, 2195.

(15) (a) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127. (b) Evans, D. A.; Takacs, J. M.; McGee, L. R.; Ennis, M. D.; Mathre, D. J.; Bartroli, J. *Pure Appl. Chem.* **1981**, *53*, 1109.

(16) Ho, G.-J.; Mathre, D. J. *J. Org. Chem.* **1995**, *60*, 2271.

(17) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.

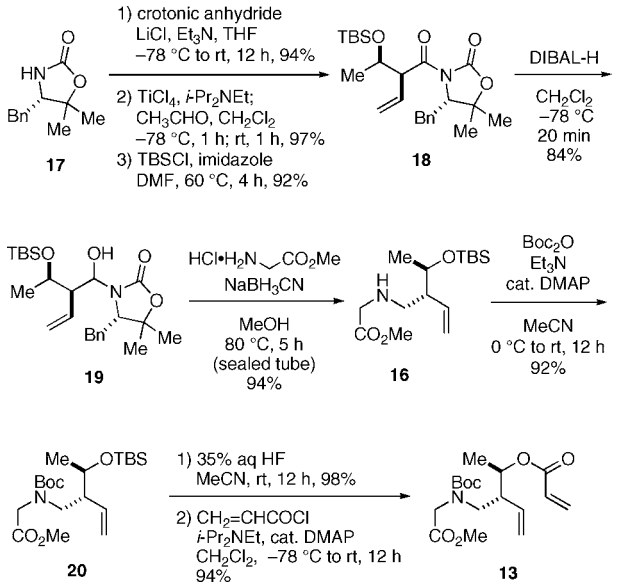
(18) Mitsunobu, O. *Synthesis* **1981**, 1.

(19) For a review of nosyl (2-nitrobenzenesulfonyl) strategies, see: Kan, T.; Fukuyama, T. *Chem. Commun.* **2004**, 353.

proceeded with sodium cyanoborohydride in MeOH at 80 °C (in a sealed tube) to furnish the desired secondary amine **16** in 60% yield.

The low-yielding reductive amination sequence was improved by simply switching the chiral auxiliary to **17** (Scheme 4).[20,21] DIBAL-H reduction of the TBS-protected

Scheme 4. Synthesis of Substrate for RCM



aldol product **18**, which was synthesized from **17** in an analogous manner to the aforementioned route, provided hemiaminal **19** as a single diastereomer in 84% yield. Reductive amination with glycine methyl ester hydrochloride provided the desired secondary amine **16** in 94% yield along with an 85% recovery of chiral auxiliary **17**. Finally, the RCM substrate **13** was obtained by Boc protection, desilylation, and acylation with acryloyl chloride.

With the desired acrylate derivative **13** in hand, we then extensively studied the key RCM reaction (Table 1). After surveying several catalysts, we chose the Hoveyda–Grubbs' second-generation catalyst[22] to find the optimum conditions. Use of 5 mol % of the catalyst in dichloromethane at 80 °C in a sealed tube (entry 5) afforded the desired product in 98% yield. While the yield dropped slightly using 2 mol % or less of the catalyst, a substantial improvement was made by switching the solvent to 1,2-dichloroethane. Under refluxing conditions, sufficient yields were obtained with as low as 0.8 or 0.5 mol % of the catalyst (entries 10 and 11).

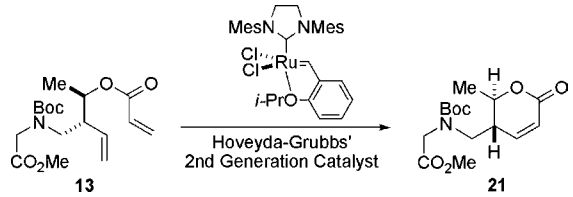
For the construction of the lactone ring, we also established two alternative methods which avoid the use of relatively expensive RCM catalysts (Scheme 5). Ozonolysis of the terminal alkene in **20** afforded aldehyde **22**, which after the

(20) Davies, S. G.; Sanganee, H. J.; Szolcsany, P. *Tetrahedron* **1999**, *55*, 3337.

(21) Bull, S. D.; Davies, S. G.; Nicholson, R. L.; Sanganee, H. J.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 2886.

(22) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168.

Table 1. Optimization of Ring-Closing Metathesis

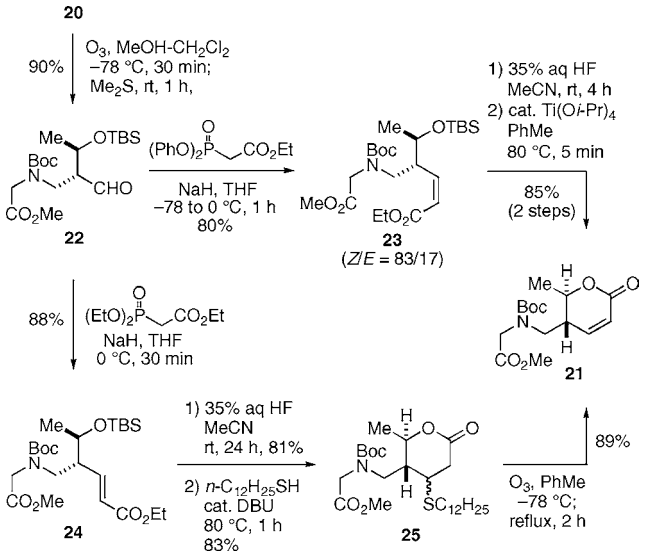


		conditions			
entry	catalyst (mol %)	solvent	T (°C)	time	yield (%)
1	5[a]	toluene	80	3 h	62
2	5	toluene	80	5 h	71
3	5	heptane	80	1 d	66
4	5	PhCl	80	1 d	74
5	5	CH_2Cl_2	80[b]	1 d	98
6	2	CH_2Cl_2	80[b]	2 d	92
7	1	CH_2Cl_2	80[b]	3 d	87
8	1	$Cl(CH_2)_2Cl$	reflux	3 d	97
10	0.8	$Cl(CH_2)_2Cl$	reflux	3 d	99
11	0.5	$Cl(CH_2)_2Cl$	reflux	3 d	92
12	0.2	$Cl(CH_2)_2Cl$	reflux	3 d	61

[a] Grubbs' second-generation catalyst was used. [b] Reaction was conducted in a sealed tube.

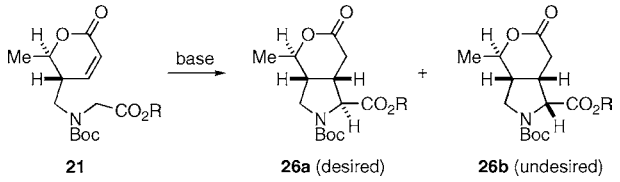
Z-selective Horner–Wadsworth–Emmons reaction[23] gave the corresponding α,β-unsaturated ester **23** (*Z*/*E* ratio based on ^{1}H NMR was 83:17). After removal of the TBS group, lactonization was effected with a catalytic amount of Ti(O-*i*-Pr)$_4$ to provide the desired lactone **21**. Alternatively, the *E*-α,β-unsaturated ester **24**, after deprotection of the TBS group, was treated with dodecanethiol[24] in the presence of a catalytic amount of DBU at 80 °C to afford lactone **25**. Oxidation of the thioether to the sulfoxide with ozone followed by heating in situ in refluxing toluene gave the desired **21**.

Scheme 5. Construction of α,β-Unsaturated Lactone **21** by Horner–Wadsworth–Emmons Reaction



Attention was then focused on the crucial intramolecular Michael addition of the glycine moiety to the α,β-unsaturated lactone ring. The expected reaction took place smoothly upon treatment of **21** with KHMDS in toluene at −78 °C to provide a mixture of the desired pyrrolidine derivative **26a** and its C-2 epimer **26b** in a 71:29 ratio (Table 2, entry 1).

Table 2. Synthesis of the Pyrrolidine Ring by Intramolecular Michael Addition



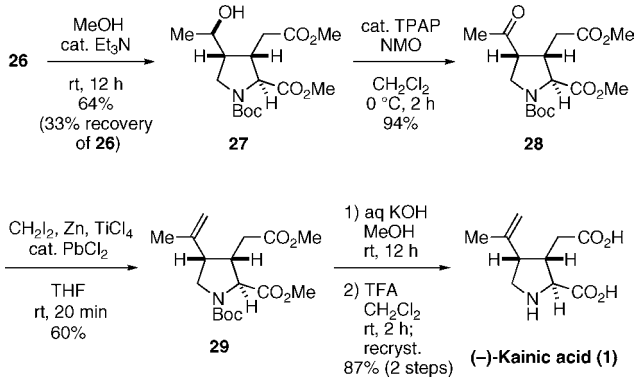
			conditions			
entry	R	base	solvent	T (°C)	**26a/26b**[a]	yield (%)
1	Me	KHMDS	toluene	−78	71:29	89
2	Me	KHMDS	THF	−78	73:24	73
3	Me	KHMDS	DMF	−60	89:11	60
4	Me	NaHMDS	DMF	−60	92:8	79
5	Me	LiHMDS	DMF	−60	91:9	95
6	Et	LiHMDS	DMF	−60	94:6	89
7	*t*-Bu	LiHMDS	DMF	−60	94:6	96

[a] Inseparable mixture. The ratio of diastereomers was calculated on the basis of ^{1}H NMR after conversion of **26** to **28**.

The more polar solvent DMF afforded **26a** with greater selectivity (89:11) (entry 3), but the choice of base had a significant effect on both the diastereoselectivity and yield. When LiHMDS was used in DMF at −60 °C, a 91/9 mixture (**26a**/**26b**) was obtained in 95% combined yield (entry 5). In order to further improve the diastereoselectivity, substituent effects on the ester moiety were also studied. Although the diastereoselectivity was slightly improved by changing the methyl ester to sterically more bulky ethyl or *tert*-butyl esters (entry 6 and 7),[25] there was a drawback associated with the preparation of these substrates, in that the reductive aminations with the corresponding glycine esters (cf. **19** to **16** in Scheme 4) were not as high yielding as the corresponding methyl ester (85% for the ethyl ester and 32% for the *tert*-butyl ester).

Having successfully constructed the fully functionalized pyrrolidine ring, we proceeded to construct the propenyl group. Methanolysis of the diastereomeric mixture of **26** provided the corresponding diester **27** with 33% recovery of **26** (Scheme 6). TPAP oxidation[26] of secondary alcohol

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



27 gave ketone **28**, which was subjected to an olefination reaction under nonbasic conditions[27] to construct the propenyl group without epimerization at the C-4 position of the pyrrolidine ring. Finally, hydrolysis of both methyl esters, nitrogen deprotection, and recrystallization furnished pure (−)-kainic acid (**1**), which was spectroscopically identical with the natural product.[10a,k]

In conclusion, we have accomplished a stereoselective total synthesis of (−)-kainic acid (**1**). The synthesis features (1) a ring-closing metathesis of an optical active acrylate derivative and (2) a highly diastereoselective intramolecular Michael addition of glycine moiety to an α,β-unsaturated lactone to construct the fully functionalized pyrrolidine ring. The efficiency of the synthetic route, namely 13% overall yield in 13 steps from **17** via the RCM protocol, enabled us to conduct a gram-scale synthesis of (−)-kainic acid (**1**).[28]

Acknowledgment. This work was financially supported in part by a Grant-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology, Japan.

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.

OL0631197

(23) (a) Ando, K. *J. Org. Chem*. **1997**, *62*, 1934. (b) Ando, K. *J. Org. Chem*. **1999**, *64*, 8408.

(24) Node, M.; Kumar, K.; Nishide, K.; Ohsugi, S.; Miyamoto, T. *Tetrahedron Lett*. **2001**, *42*, 9207.

(25) The major isomer **26a** should be obtained through a stransition state which minimize a steric repulsion between the lactone ring and the ester enolate moiety. Substitution effects of the ester moiety support this explanation.

(26) (a) Griffith, W. P.; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun*. **1987**, 1625. (b) Ley, S. V.; Norman, J.; Griffith, W. P.; Marsden, S. P. *Synthesis* **1994**, 639.

(27) (a) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett*. **1985**, *26*, 5579. (b) Takai, K.; Kakiuchi, T.; Kataoka, Y.; Utimoto, K. *J. Org. Chem*. **1994**, *59*, 2668.

(28) While a gram-scale synthesis of **1** reported by Ganem (ref 1v) is quite concise and would be one of the most efficient routes, the synthesis is insufficient for the enantioselectivity of the key step and they utilized optical resolution of **1** using (+)-ephedrine as the final process.