An Enantioselective Synthesis of (-)-α-Kainic Acid via Thiyl Radical Addition-Cyclization-Elimination Reaction

Okiko Miyata, Yoshiki Ozawa, Ichiya Ninomiya, and Takeaki Naito*

Kobe Pharmaceutical University, Motoyamakita, Higashinada, Kobe 658, Japan

Fax 078 441 7556; E-mail: taknaito@kobepharma-u.ac.jp

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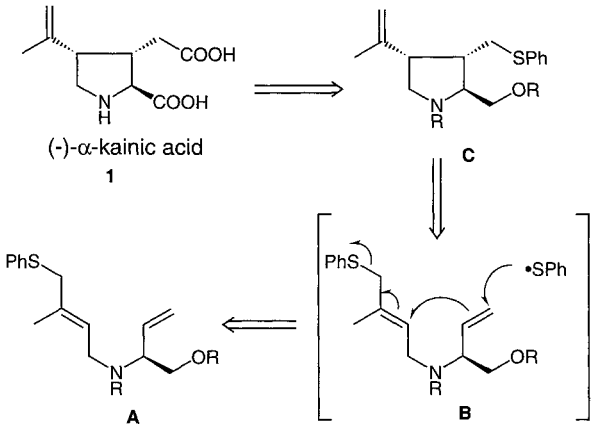
Abstract: An enantioselective synthesis of (-)-α-kainic acid has been achieved via the route involving thiyl radical addition-cyclization-elimination reaction.

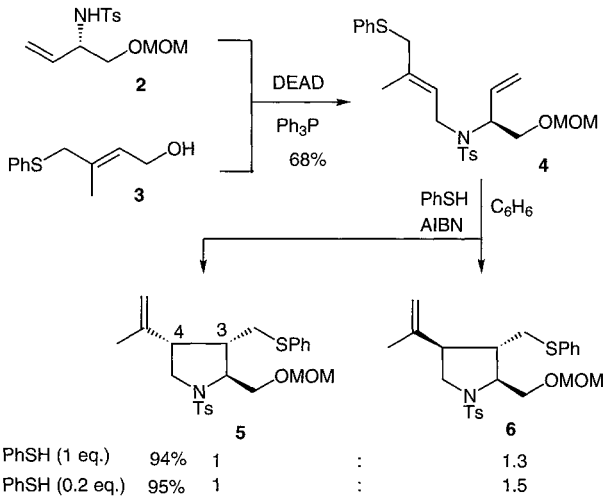
The marine product (-)-α-kainic acid (**1**) has attracted considerable interest since it was first isolated by Takemoto[1] in 1953, principally because of its potent neurotransmitting activity in the central nervous system. Several total syntheses of kainic acid and the related compounds have been achieved during the last decade,[2] since Oppolzer[3] reported an enantioselective synthesis of α-kainic acid via an intramolecular ene reaction. We report a concise enantioselective synthesis of (-)-α-kainic acid, employing the newly developed thiyl radical addition-cyclization-elimination reaction (**A**→**C**) as a key step, which involves the sequential two bonds formation and one bond cleavage in one-pot procedure; intermolecular addition of thiyl radical to olefin;[4,5] 5-exo-trig cyclization of the resulting carbon radical; β-elimination of the thiyl radical. This synthetically useful reaction would be expected to realize "one-pot" construction of the trisubstituted pyrrolidine ring **C** comprising the kainic acid.



Scheme 1

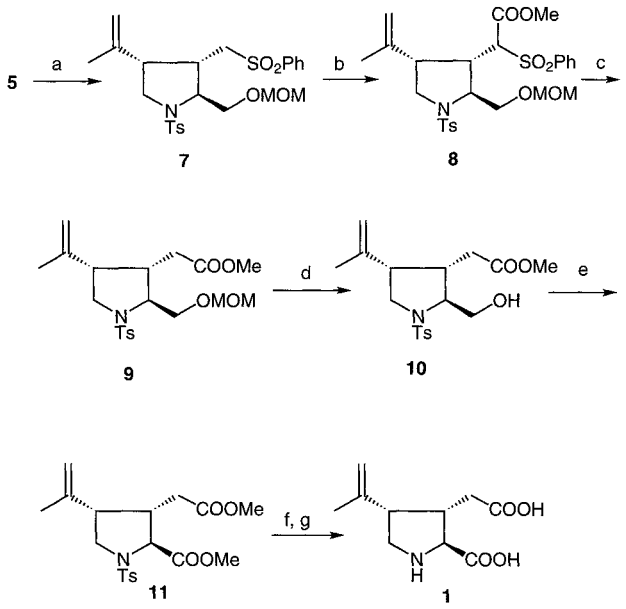
The requisite diene **4** for the radical cyclization was prepared through Mitsunobu reaction of the (*S*)-vinylglycinol **2**[6] with the hydroxy sulfide **3**.[8] We investigated the thiyl radical addition-cyclization-elimination reaction of **4** in the presence of thiophenol and AIBN. A benzene solution containing thiophenol (1 equiv.) and AIBN (0.5 equiv.) was added dropwise by a syringe pump over 2 h to a solution of **4** in boiling benzene while stirring under nitrogen. The solution was then refluxed for further 6 h. The products were found to be 3,4-*cis*-**5**[10] and 3,4-*trans*-**6**[11] in 41 and 53% yields, respectively, after separation by chromatography. Interestingly, when a catalytic amount (0.2 equiv.) of thiophenol was used, the reaction also proceeded smoothly to give **5** and **6** in 38 and 57% yields, respectively. Thus, we have now succeeded in extending the thiyl radical addition-cyclization-elimination reaction to a catalytic version which would be a potential synthetic weapon.

Oxidation of the *cis*-**5** with oxone gave the sulfone **7**, which was then subjected to methoxycarbonylation (MeLi, then ClCOOMe) to afford the sulfone ester **8** in 89% yield. Desulfonylation of **8** by 5% sodium-amalgam followed by demethoxymethylation of the resulting ester **9**[12] with TFA gave the hydroxy ester **10**. Optical purity of **10** was determined to be nearly 100% enantiomeric excess by ^{1}H NMR (500 MHz) spectroscopic analysis of the corresponding (+)-MTPA ester (MTPA= α-methyl-α-(trifluoromethyl)phenylacetic acid) which was derived from **10** by esterification using (+)-α-methyl-α-(trifluoromethyl)phenylacetyl



Scheme 2

chloride. Finally, according to Yoo's procedure,[13] **10** was smoothly converted into (-)-α-kainic acid **1** *via* oxidation to the carboxylic acid, esterification, hydrolysis to the dicarboxylic acids, and finally deprotection under Birch conditions.



(a): oxone (5 eq.), H_2O-MeOH, 0 → 20 °C, 85%; (b): MeLi (8 eq.), -78 °C, then ClCOOMe (20 eq.), THF, -78 → 0 °C, 89%; (c): 5% Na-Hg, MeOH, 0 °C, 60%; (d): TFA (4 eq.), CH_2Cl_2, 20 °C, 97%; (e): PDC, DMF, 20 °C, then CH_2N_2, 20 °C, 87%; (f): LiOH, H_2O-MeOH, 80 °C; (g): Li, liq. NH_3, -78 °C, 88% from **11**.

Scheme 3

The physical (mp. 242-243 °C (dec.); $[\alpha]_{24}^{D}$ -14.0 (c, 0.50, H_2O)) and spectral data of the synthetic (-)-α-kainic acid **1** were identical with those (mp. 243-244 °C (dec.); $[\alpha]_{27}^{D}$ -14.2 (c, 0.23, H_2O)) of the authentic sample reported in the literature.[14] In conclusion, the thiyl radical addition-cyclization-elimination reaction provides a new entry to optically pure kainoids including kainic acids.

Acknowledgements

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References and Notes

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(5) Bertrand and co-workers have reported an attempted synthesis of kainic acid via the tosyl radical mediated cyclization in which tosyl radical is generated from unstable and commercially unavailable Se-phenyl toueneselenosulfonate (PhSeTs). : Bertrand, M.-P.; Gastaldi, S; Nouguier, R. *Tetrahedron Lett.* **1996**, *37*, 1229.

(6) **2** was prepared from L-methionine by the method reported previously.[7]

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(8) **3** was prepared from isoprene by the method reported previously.[9]

(9) a) Oroshinik, W.; Mallory, R. A. *J. Am. Chem. Soc.* **1950**, *72*, 4608. b) Sato, T.; Harayama, K.; Fujisawa, T. *Tetrahedron Lett.* **1988**, *29*, 2197.

(10) *cis*-**5**: colorless crystals; mp. 101.5-102 °C (Et_2O-hexane). IR $\nu_{max}cm^{-1}$ ($CHCl_3$): 1346 and 1164. ^{1}H-NMR ($CDCl_3$, 500MHz) δ: 1.04 (1H, t, *J*=13 Hz), 1.57 (3H, br s), 2.27 (1H, dq, *J*=13, 3 Hz), 2.33 (3H, s), 2.46 (1H, dd, *J*=13, 3 Hz), 3.04 (2H, m), 3.31 (3H, s), 3.56 (1H, m), 3.64 (1H, dd, *J*=10, 8 Hz), 3.77 (1H, dd, *J*=10, 4 Hz), 4.03 (1H, dd, *J*=8, 4 Hz), 4.52 (1H, br s), 4.61 and 4.65 (2H, ABq, *J*=7 Hz), 4.86 (1H, br s), 7.13-7.26 (6H, m), and 7.78 (2H, br d, *J*=8 Hz). HRMS m/z: Calcd $C_{24}H_{31}NO_4S_2$ (M+) 461.1709. Found: 461.1694. $[\alpha]_{25}^{D}$ -31.3 (c, 1.02, $CHCl_3$).

(11) trans-**6**: colorless oil. IR $\nu_{max}cm^{-1}$ ($CHCl_3$): 1345 and 1161. ^{1}H-NMR ($CDCl_3$, 500MHz) δ: 1.57 (3H, br s), 2.05 (1H, td, *J*=11, 8 Hz), 2.45 (3H, s), 2.50 (1H, m), 2.59 (1H, dd, *J*=13, 8 Hz), 2.93 (1H, dd, *J*=13, 5 Hz), 3.25 (1H, dd, *J*=12, 11 Hz), 3.26 (3H, s), 3.63 (1H, dd, *J*=12, 8 Hz), 3.79 (3H, m), 4.55 (2H, br s), 4.67 (1H, br s), 4.79 (1H, br quint. *J*=1 Hz), 7.14-7.28 (5H, m), 7.33 (2H, br d, *J*=8 Hz), and 7.76 (2H, br d, *J*=8 Hz). HRMS m/z: Calcd $C_{24}H_{31}NO_4S_2$ (M+) 461.1703. Found: 461.1694. $[\alpha]_{25}^{D}$ -62.9 (c, 0.81, $CHCl_3$). Relative configuration of **6** was deduced from comparison of the ^{1}H-NMR spectrum with those of the isomer **5** and the related compounds prepared and unpublished.

(12) The ester **9** was identical with the authentic sample[13] upon comparison of their spectral data.

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(14) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467.