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A Concise Route to (−)-Kainic Acid

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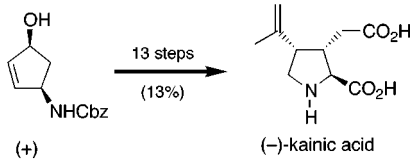
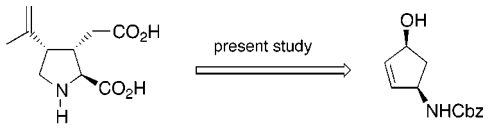
ABSTRACT



A concise route to (−)-kainic acid from enantiopure (+)-*cis*-4-carbobenzoxyamino-2-cyclopentenol has been devised by employing concurrent Chugaev *syn*-elimination and intramolecular ene reaction as the key step.

(−)-Kainic acid[1] (**1**), first isolated with the C4-epimer allokainic acid from the marine algae *Digenea simplex* and used as an anthelmintic in Japan, is the parent member of kainoid amino acids exhibiting excitatory neurotransmitting activity[2] in the mammalian central nervous system. Since the activity is strongly owed to their *trans*-C2/C3:*cis*-C3/C4 stereochemistry with 2-carboxy and 3-carboxymethyl functionalities, it is most important to avoid generation of an allokainic-acid type diastereomer having *trans*-C3/C4-stereochemistry in the stereocontrolled construction of the kainoid amino acid type molecules.[3,4] We report here a facile construction of an all-*cis*-substituted pyrrolidine on a cyclopentane framework sharing its C2/C3 stereogenic centers from chiral *cis*-4-carbobenzoxyamino-2-cyclopentenol[5] (+)-**2** and the diastereoselective conversion of the pyrrolidine product into (−)-kainic acid (**1**) unaccompanied with an allo-type byproduct (Scheme 1).

Scheme 1



(−)-kainic acid (**1**) (+)-**2**

The enantiopure starting material *cis*-4-carbobenzoxyamino-2-cyclopentenol (+)-**2** was prepared on the basis of the established procedure by Miller and co-workers[5] involving hetero-Diels−Alder reaction[6] and lipase-mediated kinetic resolution. Thus, the racemic alcohol (±)-**2** was first prepared in two steps from *N*-carbobenzoxyhydroxylamine by exactly following the original procedure through an azoxabicyclo-[2.2.1]heptane intermediate (±)-**3** by concurrent oxidation to an acylnitroso intermediate and its cycloaddition with cyclopentadiene in the same reaction medium, followed by reductive cleavage of the nitrogen−oxygen bond using molybdenum hexacarbonyl. In the lipase-mediated resolution, the Miller group obtained the enantiomerically enriched acetate (−)-**4** with 92% ee in 40% yield under transesteri-

(1) Takemoto, T. *Jikken Kagaku Koza* **1958**, *23*, 2081.
(2) Hashimoto, K.; Shirahama, H. *Trends Org. Chem.* **1991**, *2*, 1 and references therein.
(3) Pertinent reviews for the synthesis of the kainoid amino acids, see: (a) Reference 2. (b) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149. (c) Molony, M. G. *Nat. Prod. Rep.* **1999**, *16*, 485 and previous reports.
(4) Enantiocontrolled synthesis of (−)-kainic acid reported after ref 3, see: (a) Hanessian, S.; Ninkovic, S. *J. Org. Chem* **1996**, *61*, 5418. (b) Kawamura, M.; Ogasawara, K. *Heterocycles* **1997**, *44*, 129. (c) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896. (d) Nakada, Y.; Sugahara, T.; Ogasawara, K. *Tetrahedron Lett.* **1997**, *38*, 857. (e) Miyata, O.; Ozawa, Y.; Ninomiya, I.; Naito, T. *Synlett* **1997**, 275. (f) Rubio, A.; Ezquerra, J.; Escribano, A.; Remuinan, M. J.; Vanquero, J. J. *Tetrahedron Lett.* **1998**, *39*, 2171. (g) Cossy, J.; Cases, M.; Pardo, D. G. *Synlett* **1998**, 507 and *Tetrahedron* **1999**, *55*, 6153. (h) Cheviliakov, M. V.; Montgomery, J. *J. Am. Chem. Soc.* **1999**, *121*, 11139. (i) Campbell, A. D.; Raynhan, T. M.; Taylor, R. J. K. *Chem Commun.* **1999**, 245.
(5) Mulvihill, M. J.; Gage, J. L.; Miller, M. J. *J. Org. Chem.* **1998**, *63*, 3357
(6) Pertinent review for the hetero-Diels−Alder reaction involving a nitroso dienophile, see: (a) Streith, J.; Defoin, A. *Synthesis* **1994**, 1107. (b) Vogt, P. F.; Miller, M. J. *Tetrahedron* 1998, *54*, 1317.

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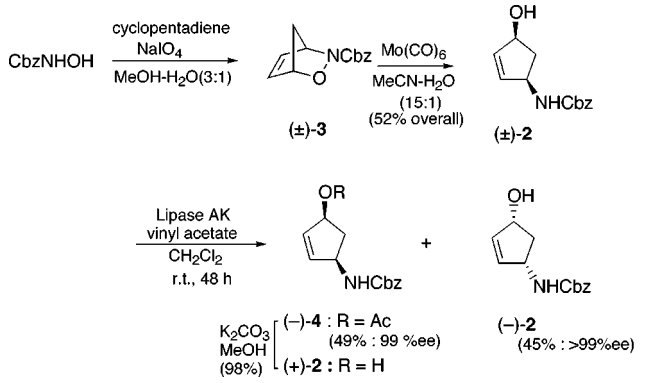
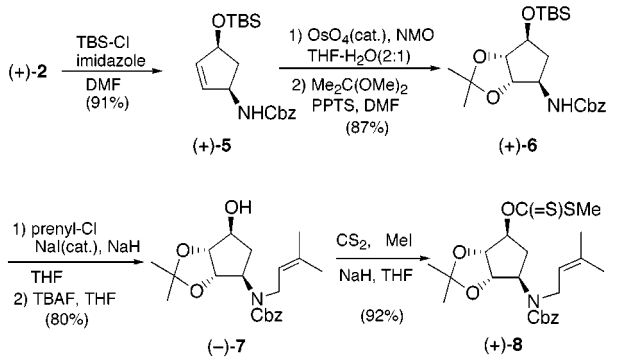
fication conditions in the presence of a lipase of *Pseudomonas* sp. However, the fate of the unreacted starting material was not mentioned at all. We therefore reinvestigated the lipase-mediated resolution more extensively so as to improve the optical yield of the acetate (−)-**4** and to know the fate of the other enantiomer in the racemic starting material (±)-**2**. Among the lipases examined, it was found that clear-cut resolution occurred under transesterification conditions in the presence of an immobilized lipase-on-Celite, Lipase AK (*Pseudomonas fluorescens*, Amano). Thus, when the racemic alcohol (±)-**2** was stirred with vinyl acetate in dichloromethane at room temperature for 2 days in the presence of Lipase AK, the highly enantiomerically enriched[7] (99% ee) acetate (−)-**4**, mp 85.0−86.0 °C, $[\alpha]^{25}_D$ −8.8 (*c* 0.6, $CHCl_3$), was obtained in 49% yield, leaving the enantiopure[7] (>99% ee) alcohol (−)-**2**, mp 79−83 °C, $[\alpha]^{27}_D$ −60.6 (*c* 0.5, $CHCl_3$), in 45% recovery yield.[8] The acetate (−)-**4** gave the alcohol (+)-**2**, mp 79−82 °C, $[\alpha]_D^{30}$+60.9 (*c* 0.4, $CHCl_3$), on alkaline methanolysis (Scheme 2).

Scheme 2



To explore further utilization of the resolved products, we examined the conversion of (+)-alcohol (+)-**2** into (−)-kainic acid (**1**) by concurrent Chugaev *syn*-elimination[9] and intramolecular ene reaction[10] as the key step, though such a combination of reactions in thermolysis conditions has not been reported so far. To install C2-carboxy and C3-carboxymethyl functionalities of (−)-kainic acid (**1**) without difficulty in the later stage, the compound (+)-**2** was transformed to (+)-**5**, $[\alpha]^{29}_D$ +7.0 (*c* 0.7, $CHCl_3$) (TBSCl, imidazole, DMF), and the olefin functionality was dihydroxylated and protected as the acetonide (+)-**6**, $[\alpha]^{31}_D$ +19.8 (*c* 0.5, $CHCl_3$). The secondary carbamate of (+)-**6** was next alkylated to give the tertiary prenyl carbamate (−)-**7**, $[\alpha]^{30}_D$ −18.4 (*c* 0.6, $CHCl_3$), after desilylation, which was next transformed into the key xanthate ester (+)-**8**, $[\alpha]_D^{31}$ +30.5 (*c* 0.8, $CHCl_3$), under standard conditions (NaH, CS_2, THF, then MeI, −30 °C). Overall yield of (+)-**8** from (+)-**2** was 58% in six steps (Scheme 3).

Scheme 3



To initiate concurrent Chugaev *syn*-elimination and intramolecular ene reaction, (+)-**8** was heated in refluxing diphenyl ether in the presence of sodium hydrogen carbonate.[11,12] Gratifyingly, the expected concurrent reaction did take place to give the tricyclic product (−)-**10**, $[\alpha]^{31}_D$ −8.0 (*c* 1.0, $CHCl_3$), bearing the trisubstituted pyrrolidine framework in 72% yield as a single diastereomer presumably via the transient 1,6-diene intermediate **9** in this single operation. At this point, though the product (−)-**10** could not be distinguished unambiguously from its diastereomer **11** owing to its presence as the carbamate rotamers, significant NOEs between C2−H and C3−H, C2−H and C4−H, and C3−H and C4−H were observed to support diastereospecific generation of the former product having all-*cis*-configuration (Figure 1). The assigned stereochemistry was consistent with

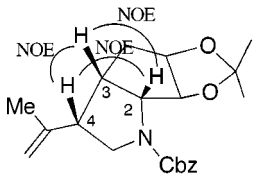


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Figure 1.

the preference of the *exo*-transition state **9a** over the *endo*-transition state **9b** as has been observed in some precedents[10] (Scheme 4).

To confirm the assigned stereochemistry of (−)-**10** and to convert (−)-**10** into (−)-kainic acid (**1**), it was transformed first into the known all-*cis*-diester[13] (+)-**12** on the basis of

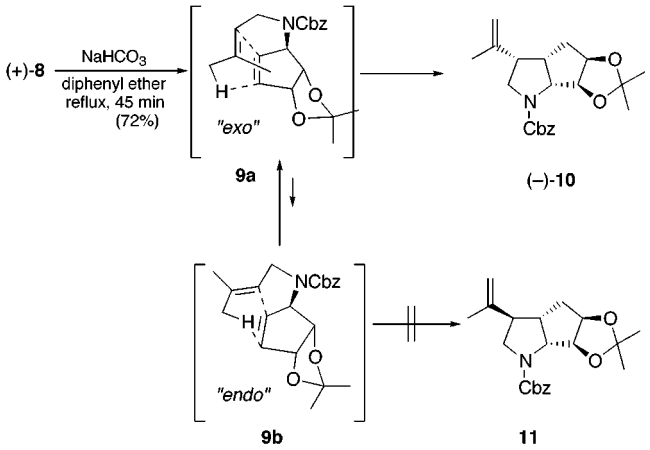
(7) Optical purity of the products was determined by HPLC using a column with a chiral stationary phase (CHIRALCEL OD, elution with *i*-PrOH/hexane 20:80 v/v for **4** and *i*-PrOH/hexane 10:90 v/v for **2**).

(8) **Typical Procedure for the Lipase-Mediated Transesterification.** A suspension of (±)-**2** (503 mg, 2.16 mmol), vinyl acetate (0.2 mL, 2.16 mmol), and Lipase AK (100 mg) in dichloromethane (10 mL) was stirred at room temperature for 48 h. After filtration through a Celite pad, the filtrate was evaporated under reduced pressure and chromatographed (silica gel, elution with AcOEt/hexane, 1:4 to 1:1 v/v) to give (−)-**4** (293 mg, 49%) and (−)-**2** (225 mg, 45%).

(9) Nace, H. R. *Org. React.* **1962**, *12*, 57.

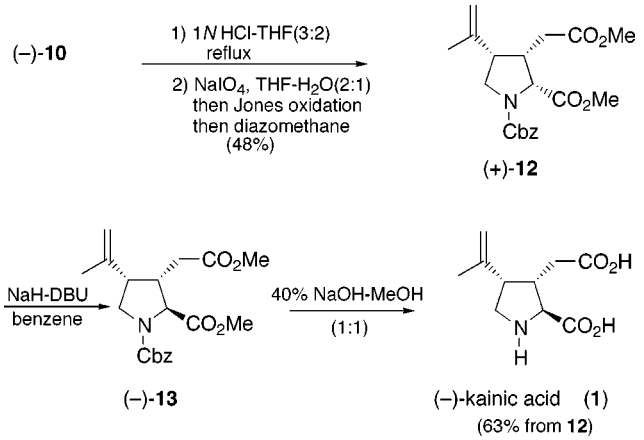
(10) Oppolzer, W.; Snieckus, V. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 476. (b) Curruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon Press: Oxford, 1990; pp 252−264.

Scheme 4



the 1,2-glycol functionality installed in the early stage. Thus, after removal of the acetonide protecting group of (−)-**10** under acid-hydrolysis conditions, the resulting diol was sequentially cleaved with sodium periodate and further oxidized with Jones' reagent to give the trisubstituted pyrrolidine diester[13] (+)-**12**, $[\alpha]^{25}_D$ +21.6 (*c* 0.2, $CHCl_3$) [ref:[13] $[\alpha]^{24}_D$ +19.3 (*c* 0.8, $CHCl_3$)], having all-*cis* stereochemistry after treatment with diazomethane. Since we have previously obtained (+)-**12** by employing a different method[13] and have established its transformation into (−)-kainic acid (**1**) through an α-epimerization, the confirmation of the stereochemistry of the thermolysis product (−)-**10**, as well as a formal synthesis of the target amino acid, was achieved at this point. Actually, (+)-**12** was epimerized at the C2-stereogenic center with the base treatment[13] to give the *trans*-C2/C3:*cis*-C3/C4 diastereomer (−)-**13**, $[\alpha]^{29}_D$ −21.3 (*c* 0.5, $CHCl_3$) [ref:[13] $[\alpha]^{26}_D$ −22.5 (*c* 1.0, $CHCl_3$)], which on alkaline hydrolysis afforded (−)-kainic acid (**1**), $[\alpha]^{26}_D$ −13.5 (*c* 0.5, H_2O) [natural:[14] $[\alpha]^{20}_D$ −14 (*c* 1, H_2O)], to complete an alternative enantioselective synthesis. Overall yield of (−)-kainic acid (**1**) was 13% in 13 steps from the enantiopure starting material (+)-**2**, which was obtained from the racemic precursor (±)-**2** in 48% yield by sequential lipase-mediated transesterification and methanolysis (Scheme 5).

Scheme 5



In conclusion, we have devised a new synthesis of (−)-kainic acid (**1**) on the basis of the stereochemical outcome of the thermolysis of the xanthate (+)-**8**, which produced diastereoselectively all-*cis*-substituted pyrrolidine on the cyclopentane ring by concurrent Chugaev *syn*-elimination and intramolecular ene reaction. In connection with this synthesis, we have also established an excellent lipase-mediated kinetic resolution to give the enantiopure alcohol (+)-**2** and its enantiomer.

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(11) Addition of sodium hydrogen carbonate was found to suppress decomposition of the substrate, cf. Kamikubo, T.; Ogasawara, K. *Chem. Commun.* **1995**, 1951.

(12) **Typical Procedure for the Thermolysis Reaction.** A mixture of **8** (65.2 mg, 0.14 mmol) and sodium hydrogen carbonate (58 mg, 0.70 mmol) in diphenyl ether (2 mL) was heated in an oil bath at 280 °C for 45 min. After cooling, the mixture was chromatographed (silica gel, elution with AcOEt/hexane, 1:8 v/v) to give (−)-**10** (38.2 mg, 72%), $[\alpha]^{31}_D$ −8.0 (*c* 1.0, $CHCl_3$); IR (film) 1707 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$, 60 °C) δ 1.26 (3H, s), 1.44 (3H, s), 1.49 (1H, m), 1.75 (3H, s), 1.83 (1H, dd, J = 14.7, 7.5 Hz), 2.77 (1H, m), 3.14 (1H, m), 3.31 (1H, t, J = 11.1 Hz), 3.74 (1H, br.s), 4.10 (1H, d, J = 6.5 Hz), 4.63 (3H, m), 4.83 (1H, s), 5.14 (2H, m), 7.20−7.50 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$, 60 °C) δ 22, 24, 26, 31, 44, 45, 47, 66, 70, 81, 85, 110, 111, 127, 128, 137, 141, 154; mass *m*/*z* 357 (M^+), 91 (100%); HRMS calcd for $C_{21}H_{27}NO_4$ 357.1939, found 357.1920.

(13) Takano S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204.

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