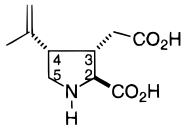
# Enantioselective Total Synthesis of (−)-α-Kainic Acid through Free Radical Cyclization of an Alkenyl Monothioformimide

Mario D. Bachi* and Artem Melman

*Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel*

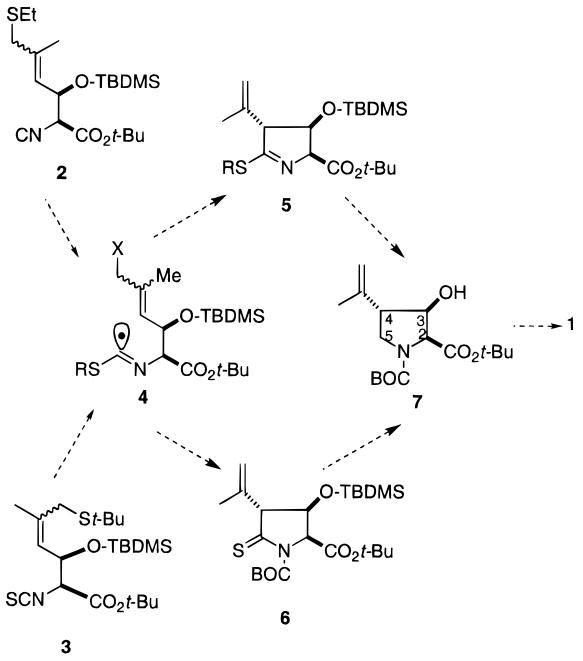
*Received November 11, 1996*

(−)-α-Kainic Acid **1** is the prototype of a group of neuroexcitatory amino acids which activate particular subtypes of glutamic acid receptors. These amino acids are important substrates for physiological and pharmacological studies of the central nervous system,[1] and their synthesis continues to attract widespread interest.[2−12] Recently we reported on a new strategy for the synthesis of α-kainic acid **1** and described its application to the synthesis of (±)-α-kainic acid.[13,14] This synthesis consist of two stages: (a) preparation of either racemic isocyanide **2** or racemic isothiocyanate **3**, their stereoselective cyclization, through free radicals **4**, to a pyrroline **5** or a pyrrolidinethione **6**, and subsequent reduction to the racemic tetra-substituted pyrrolidine **7**; (b) conversion of key racemic compound **7** into racemic α-kainic acid through a series of stereospecific reactions identical to those described in Scheme 2 for the nonracemic compounds. It was reasoned that, provided enantiomerically pure key compound **7** become available, this strategy can be applied to the synthesis of (−)-α-kainic acid **1**. We describe herein the synthesis of enantiomerically pure key compound **7**, by a new free radical cyclization, and its employment in the synthesis of (−)-α-kainic acid **1**.

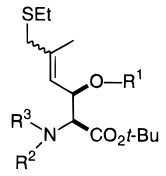


**1**

Compounds **2** and **3** are allylglycine derivatives which were deliberately designed for the synthesis of pyrrolidine **7** with its particular array of substituents at positions 2, 3, and 4.[14] We looked for a method for the preparation of either nonracemic **2** and **3** or another synthetically equivalent allylglycine derivative **8**. Of the numerous methods available for the stereoselective synthesis of optically active α-amino acids[15,16] Hayashi's reaction for catalytic addition of aldehydes and alkyl isocyanoacetates[17] seemed most compatible with the particular



R = alkyl or *n*-$Bu_3Sn$; X = EtS or *t*-BuS

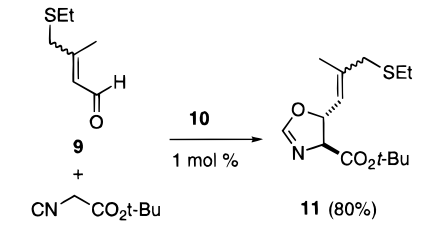


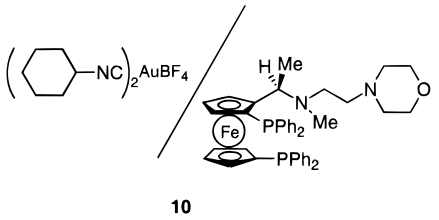
**8**

pattern and character of functionalities on compounds **8**. Indeed, under the mediation of Hayashi's optically active gold(I) catalyst **10**, aldehyde **9**[14] and *tert*-butyl isocyanoacetate afforded oxazoline **11** in very good yield and diasteroselectivity.[18] Oxazoline **11** can be hydrolyzed to an α-amino-β-hydroxy derivative **8** ($R^1 = R^2 = R^3 = H$)[15−17] or to an α-formylamino-β-hydroxy derivative **8** ($R^1 = R^2 = H$; $R^3 = HCO$).[19] Both compounds were considered as possible intermediates for the preparation of **8** ($R^1$ = TBDMS; $R^2$ and $R^3$ = CN or SCN), namely nonracemic compounds **2** and **3**.[20] Searching for additional, possibly superior, precursors of pyrrolidine **7** compounds of type **8** ($R^3$ = HCS) were conceived. These compounds may be obtained through the hydrothiolysis

(1) Shinozaki, H. In *Exitatory Amino Acid Receptors. Desigen of Agonists and Antagonists*; Krogsgaard-Larsen, P., Hansen, J. J., Eds.; Ellis Horwood: New York, 1992; pp 261−191.
(2) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4978.
(3) Takano, S.; Iwabuhi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204.
(4) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467.
(5) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1990**, *46*, 7263.
(6) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169.
(7) Barco, A.; Benetti, S.; Spalluto, G.; Casolari, A.; Pollini, G. P.; Zanirato, V. *J. Org. Chem.* **1992**, *57*, 6279.
(8) Cooper, J.; Knight, D. W.; Gallagher, P. T. *J. Chem. Soc., Perkin Trans. I* **1992**, 553.
(9) Hatakeyama, S.; Sugawara, K.; Takano, S. *J. Chem. Soc., Chem. Commun.* **1993**, 125.
(10) Monn, J. A.; Valli, M. J. *J. Org. Chem.* **1994**, *59*, 2773.
(11) Yoo, S. E.; Lee, S. H. *J. Org. Chem.* **1994**, *59*, 6968.
(12) Hanessian, S.; Ninkovic, S. *J. Org. Chem.* **1996**, *61*, 5418.
(13) Bachi, M. D.; Melman, A. *Synlett* **1996**, 60.
(14) Bachi, M. D.; Bar-Ner, N.; Melman, A. *J. Org. Chem.* **1996**, *61*, 7116.
(15) Williams, R. M. *Synthesis of Optically Active α-Amino Acids*; Pergamon Press: Oxford, 1989.
(16) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.
(17) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405.
(18) Acceptable enantioselectivity in the formation of oxazoline **11** was assumed on the grounds of reports on similar reactions (see refs 17 and 15 pp 49−53, and ref 16 pp 1597−1598) and was corroborated *a posteriori* by the isolation of enantiomerically pure pyrrolidine **7**.
(19) Melman, A. Ph.D. Thesis, The Weizmann Institute of Science, 1996, Manuscript in preparation.
(20) In a preliminary experiment, oxazoline **11** was hydrolyzed to formamide **8** ($R^1 = R^2 = H$; $R^3 = HCO$), O-protected to give **8** ($R^1$ = TBDMS; $R^2 = H$; $R^3 = HCO$) which was subsequently dehydrated to isonitrile **2** in low overall yield (not optimized).[19]

S0022-3263(96)02100-7 CCC: $14.00 



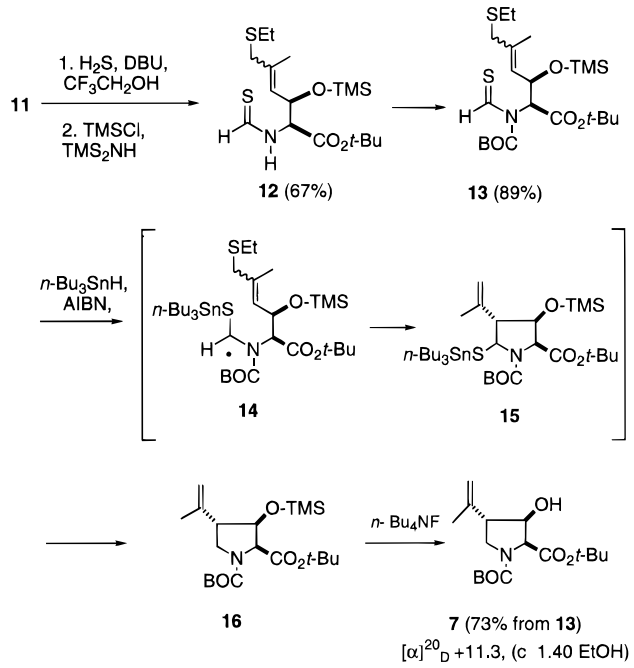

of oxazoline **11**. Their use as substrates in *n*-$Bu_3SnH$/AIBN mediated free radical cyclizations requires some attention.

Highly reactive ene-radicals like the thioimidoyl radicals **4** are intermediates in various synthetically useful free radical cyclizations.[21,22] In contrast adducts of organostannyl radicals and the thiocarbonyl group of thioamides, *e.g.*, of **8** ($R^2$ = alkyl, $R^3$ = HCS), are highly stabilized by the two adjacent heteroatoms and may fail to maintain a viable chain reaction required to support an efficient ring closure.[23] The radical stabilizing power of the nitrogen atom can be suppressed by the introduction of an electron-attracting substituent like a sulfonyl group[23,24] or a carbonyl group.[23] This role was given in the case of the designed radical intermediate **14** to the N-BOC substituent. Accordingly monothioformimide **13** which is equivalent to **8** ($R^1$ = TMS; $R^2$ = BOC; $R^3$ = HCS) was chosen as an intermediate compound for the synthesis of pyrrolidine **7**.

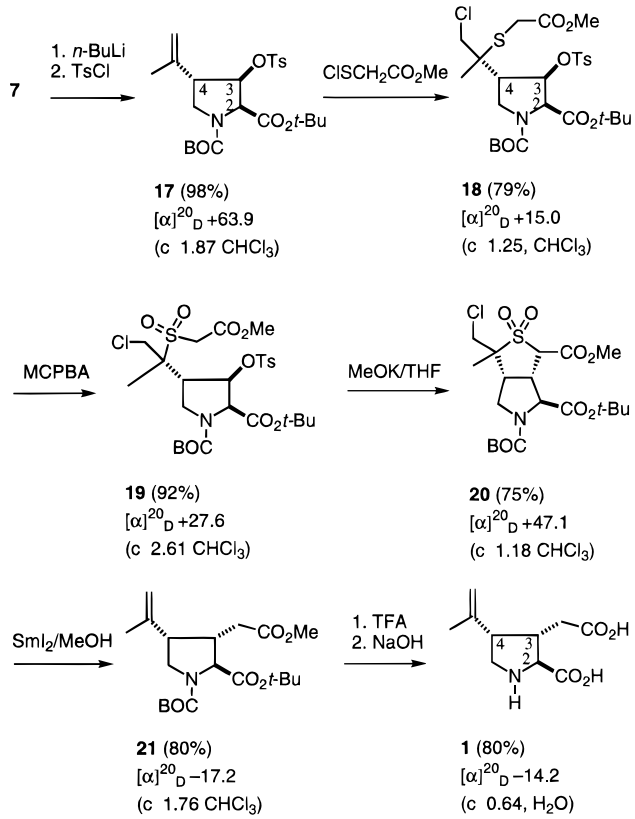
Thus, base-catalyzed hydrothiolysis of oxazoline **11** followed by O-silylation afforded thioformamide **12** which was subsequently converted into the highly functionalyzed monothioformimide **13**. Free radical cyclization of monothioformimide **13**, mediated by 2 equiv of *n*-$Bu_3SnH$, afforded the tetrasubstituted pyrrolidine **16** and after desilylation and recrystallization the enantiomerically pure key compound **7** (Scheme 1). The NMR data of key compound **7** is identical to that of racemic pyrrolidine **7** whose relative configuration was corroborated by crystallographic analysis.[14] Key compound **7** was converted into (−)-α-kainic acid **1** following the same sequence of reactions previously reported[14] for the synthesis of (±)-α-kainic acid from racemic pyrrolidine **7** and described in Scheme 2 for optically active compounds. Noteworthy is the effective method for temporary sulfur connection of the acetic acid moiety to the 4-isopropenyl group.[13,14]

In summary, a new *n*-$Bu_3SnH$/AIBN mediated stereoselective cyclization of an *N*-alkenyl monothioformimide was developed as a key step in an enantioselective total synthesis of (−)-α-kainic acid **1** (12% overall yield starting from *tert*-butyl isocyanoacetate).

**Scheme 1**




**Scheme 2**




## Experimental Section

For general procedures see ref 25. Optical rotation was measured by Perkin-Elmer 141 polarimeter. Nonracemic chiral compounds **17**−**21** were prepared from enantiomerically pure compound **7** by the same series of reactions employed for the preparation of their racemic mixtures and do exhibit the same IR and $^1H$ NMR spectra.[14] Full experimental data for these compounds are given as Supporting Information.

**(4*S*,5*R*)-4-(*tert*-Butoxycarbonyl)-5-(3-(ethylthio)-2-methyl-1-propenyl)-2-oxazoline (11).** To a solution of (*R*)-*N*-methyl-*N*-[2-(4-morpholino)ethyl)]-1-(*S*)-1′,2-bis(diphenylphosphino)ferrocenyl]ethylamine[26] (72 mg, 0.1 mmol), Au(*c*-$C_6H_{11}$-NC)$_2BF_4$[27] (50 mg, 0.1 mmol), and *tert*-butylisocyanoacetate (1.41

(21) Bachi, M. D.; Bosch, E. *J. Org. Chem.* **1992**, *57*, 4696.
(22) Bachi, M. D.; Balanov, A.; Barner, N. *J. Org. Chem* **1994**, *59*, 7752.
(23) Bachi, M. D.; Bosch, E.; Denenmark, D.; Girsh, D. *J. Org. Chem.* **1992**, *57*, 6803.
(24) Padwa, A.; Nimmesgern, H.; Wong, G. S. K. *J. Org. Chem.* **1985**, *50*, 5620.
(25) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1995**, *60*, 6242.

g, 10 mmol) in $CH_2Cl_2$ (5.5 mL) was added 4-(ethylthio)-3-methylbutenal[14] (1.73 g, 12 mmol). The reaction mixture was stirred under argon at 20 °C for 60 h and evaporated, and the residue was separated by MPLC (medium-pressure liquid chromatography) to afford (4*S*,5*R*)-4-(*tert*-butoxycarbonyl)-5-(3-(ethylthio)-2-methyl-1-propenyl)-2-oxazoline (**11**) (2.28 g, 8 mmol, 80%) as a mixture *E*/*Z* isomers, *ca*. 3:1 ratio: $[\alpha]^{20}_D$ +39.7 (*c* 1.45, $CHCl_3$). IR (neat): 1625, 1686, 1735 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 1.23 (t, *J* = 7.4 Hz, *E*), 1.25 (t, *J* = 7.4 Hz, *Z*), total 3H; 1.50 (s, 9H); 1.88 (s, *E*), 1.91 (s, *Z*), total 3H; 2.42 (q, *J* = 7.4 Hz, *E*), 2.45 (q, *J* = 7.4 Hz, *Z*), total 2H; 3.14 (s, *E*), 3.19, 3.35 (2xd, *J* = 12.8 Hz, *Z*), total 2; 4.24 (m, 1H), 5.34 (m, 2H), 6.93 (d, *J* = 2 Hz, *E*), 6.93 (d, *J* = 2 Hz, *Z*). Anal. Calcd for $C_{14}H_{23}NO_3S$: C, 58.91 H, 8.12; N, 4.91; S, 11.23. Found: C, 58.56; H, 8.33; N, 4.64; S, 10.62.

**(2*S*,3*R*)-*tert*-Butyl 2- (*N*-Thioformylamino)-3-(trimethylsiloxy)-5-methyl-6-(ethylthio)-hex-4-enoate (12).** Through a solution of DBU (100 mg, 0.66 mmol) in trifluoroethanol (5 mL) was passed a slow stream of $H_2S$ gas for 5 min. A solution of oxazoline **11** (2.05 g, 7.2 mmol) in trifluoroethanol (5 mL) was added to the reaction mixture, and saturation with $H_2S$ was continued for an additional 2 h. The reaction mixture was dissolved in EtOAc−hexane (1:1, 100 mL), washed with water, dried, and evaporated. The residue was dissolved in $CH_2Cl_2$ (10 mL), and hexamethyldisilazane (1.18 g, 7.2 mmol), TMSCl (0.78 g, 7.2 mmol), and hexane (5 mL) were added. The reaction mixture was kept for 1 h at 20 °C, dissolved in EtOAc−hexane (1:1, 100 mL), washed with water, dried, and evaporated. The residue was purified by flash-chromatography to afford the title compound **12** (1.89 g, 4.83 mmol, 67% from oxazoline **11**) as a mixture of *E*/*Z* isomers *ca*. 3:1 ratio. $[\alpha]^{20}_D$ +55.4 (*c* 1.50, $CHCl_3$). IR (neat): 1733 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 0.08 (s, 9H), 1.17 (t, *J* = 7.4 Hz, *E*), 1.29 (t, *J* = 7.4 Hz, *Z*), total 3H; 1.48 (s, 9H); 1.82 (d, *J* = 1.3 Hz, *E*), 1.80 (d, *J* = 1.3 Hz, *Z*), total 3H; 2.36 (q, *J* = 7.4 Hz, *E*), 2.52 (q, *J* = 7.4 Hz, *Z*), total 2H; 3.04 (s, *E*), 3.15, 3.27 (2xd, *J* = 12.6 Hz, *Z*), total 2H; 5.04 (dd, *J* = 2.0, 8.8 Hz, 1H); 5.22 (m, 2H); 7.97 (br s, 1H); 9.54 (d, *J* = 6.3 Hz, 1H). Anal. Calcd for $C_{17}H_{33}NO_3S_2Si$: C, 52.17 H, 8.44; N, 3.58; S, 16.37. Found: C, 52.09; H, 8.61; N, 3.58; S, 16.73.

**(2*S*,3*R*)-*tert*-Butyl 2-(*N*-Thioformyl,*N*-((*tert*-butoxycarbonyl)amino)-3-(trimethylsiloxy)-5-methyl-6-(ethylthio)-hex-4-enoate (13).** To a solution of thioformamide **12** (1.70 g, 4.3 mmol) and di-*tert*-butyldicarbonate (1.02 g, 4.7 mmol) in THF (5 mL) was added DMAP (20 mg, 0.16 mmol). The reaction mixture was stirred at 20 °C for 20 min and evaporated, and the residue was dissolved in toluene (150 mL) and boiled under reflux for 5 h. The reaction mixture was evaporated, the residue was purified by flash chromatography to afford the title compound **13** (1.88 g, 3.8 mmol, 89%) as a mixture of *E*/*Z* isomers *ca*. 3:1 ratio. $[\alpha]^{20}_D$ −86.8 (*c* 2.68 $CHCl_3$). IR (neat): 1739 $cm^{-1}$. $^1H$ NMR ($CDCl_3$): 0.03 (s, 9H); 1.21 (t, *J* = 7.2 Hz, *E*), 1.29 (t, *J* = 7.4 Hz, *Z*), total 3H; 1.40, 1.58, 1.59 (3xs, total 18H); 1.94 (d, *J* = 1.2 Hz, *E*), 1.87 (d, *J* = 1.2 Hz, *Z*), total 3H; 2.42 (quartet of doublets, *J* = 7.4 Hz, *J* = 1.4 Hz), 2.60 (quartet of doublets, *J* = 7.4 Hz, *J* = 1.5 Hz), total 2H; 3.09, 3.16 (2xd, *J* = 13.4 Hz, *E*); 3.26, 3.62 (2xd, *J* = 13.0 Hz, *Z*), total 2H; 5.10 (br s, 1H); 5.33 (d, *J* = 9 Hz,1H); 5.9 (br s, 1H); 10.4 (s, *E*), 10.3 (s, *Z*), total 1H. Anal. Calcd for $C_{22}H_{41}NO_5S_2Si$: C, 53.77 H, 8.35; N, 2.85; S, 13.03. Found: C, 53.87; H, 8.50; N, 2.80; S, 13.3.

**(2*S*,3*R*,4*S*)-1,2-Bis-(*tert*-butoxycarbonyl)-3-hydroxy-4-isopropenylpyrrolidine (7).** To a solution of monothioformimide **13** (1.82 g, 3.71 mmol) in toluene (150 mL) at 100 °C under argon were added solutions of $Bu_3SnH$ (2.71 g in 5 mL toluene, 9.78 mmol) and AIBN (164 mg in 5 mL of toluene, 1 mmol), each through a syringe pump, at a rate of 0.15 mL/min for the first 2 mL, followed by 3 mL in one portion. The reaction mixture was kept at 100 °C for an additional 1 h, cooled, and evaporated. The residue was purified by flash chromatography (hexane → EtOAc−hexane mixture, 1:5) to afford crude (2*S*,3*R*,4*S*)-1,2-di(*tert*-butoxycarbonyl)-3-(trimethylsiloxy)-4-isopropenylpyrrolidine (**16**). $^1H$ NMR ($CDCl_3$, two conformers, *ca*. 2:1 ratio) (δ): 0.11 (s, 9H); 1.43 (s, major), 1.44 (s, minor), total 9H; 1.48 (s, major), 1.47 (s, minor), total 9H; 1.72 (s, 3H); 2.98 (m, 1H); 3.23 (t, *J* = 9.8 Hz, major), 3.17 (t, *J* = 10.4 Hz, minor), total 1H; 3.70 (dd, *J* = 8.8, 10.8 Hz, major), 3.66 (dd, *J* = 8.8, *J* = 10.6 Hz, minor), total 1H; 4.13 (d, *J* = 7.7 Hz, major), 4.27 (m, minor), total 1H; 4.27 (m, 1H); 4.88 (m, 2H). Compound **16** was dissolved in THF (5 mL) and AcOH (180 mg, 3 mmol) and TBAF (6 mL of 1 M solution, 6 mmol) were added. After 10 min the reaction mixture was evaporated, dissolved in EtOAc−hexane (1:1, 100 mL), washed with water, dried, and evaporated. The residue was purified by flash chromatography (EtOAc−hexane, 1:5 → 1:3) to afford title alcohol **7**, which was twice crystallized from EtOAc−hexane (0.88 g, 2.71 mmol, 73% from thioformimide **13**), mp 127−129 °C. $[\alpha]^{20}_D$ +11.3 (*c* 1.40 EtOH). IR (neat): 1679, 1704, 1739, 3437 $cm^{-1}$. $^1H$ NMR ($CDCl_3$, two conformers) (d): 1.45 (s, major), 1.47 (s, minor), total 9H; 1.51 (s, major), 1.50 (s, minor), total 9H; 1.77 (s, 3H); 2.3 (br s, major), 2.4 (br s, minor), total 1H; 2.91 (m, 1H); 3.26 (t, *J* = 9.4 Hz, major), 3.15 (t, *J* = 10 Hz, minor), total 1H; 3.78 (dd, *J* = 10.7, 8.6 Hz, major), 3.67 (dd, *J* = 10.3, 8.8 Hz, minor), total 1H; 4.29 (d, *J* = 7.8 Hz, major), 4.36 (m, minor), total 1H; 4.34 (m, 1H); 4.91, 4.93 (2xs, 2H). $^{13}C$ NMR ($CDCl_3$, two conformers, major/minor): 20.25; 28.07, 28.13, 28.30; 47.49, 48.05; 49.99, 50.83; 62.82, 63.20; 73.78, 73.04; 77.1; 80.13, 79.95; 81.87, 82.01; 112.98; 141.59; 153.78; 169.64. Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93; N, 4.28. Found: C, 62.36; H, 9.02; N, 4.44.

In order to check the enantiomeric purity of product **7** a derivative with chiral amine was prepared. Alcohol **7** (18 mg) was heated with an excess of (*S*)-methylbenzylisocyanate (50 mg, prepared[28] from (*S*)-(−)-α-methylbenzylamine and diphosgene) for 3 h at 140 °C. The reaction mixture was purified by flash chromatography to afford (2*S*,3*R*,4*S*)-1,2-di(*tert*-butoxycarbonyl)-3-[(1*S*-methylbenzyl)aminocarbonyloxy]-4-isopropenylpyrrolidine (26 mg, quantitative yield). Analogously, the racemic derivative was prepared from a sample of racemic alcohol **7**.[14] HPLC (27% EtOAc−hexane, Lichrosorb column, UV detection) showed two peaks of equal integration for the derivative of racemate and just one peak of the derivative of title compound **7**.

**(−)-Kainic Acid (1).** To a solution of chiral pyrrolidine **21** (310 mg, 0.81 mmol, $[\alpha]^{20}_D$ −17.2 (*c* 1.76 $CHCl_3$), prepared in five stages from enantiomerically pure alcohol **7**),[29] in methylene chloride (4 mL) was added trifluoroacetic acid (4 mL). The reaction mixture was left for 2 h at 20 °C, toluene (40 mL) was added, and the reaction mixture was evaporated. The residue was dissolved in methanol (0.5 mL), and aqueous NaOH (3 M, 2 mL) was added. After 15 min the reaction mixture was neutralized with AcOH, washed with ether, and chromatographed on an anion-exchange column (Dowex 1 × 8, charged with acetate-ion; eluent: water → 5% aqueous AcOH) to afford (−)-α-kainic acid **1** as monohydrate (149 mg, 0.65 mmol, 80%). $[\alpha]^{20}_D$ −14.2 (*c* 0.64, $H_2O$) [lit.[30] $[\alpha]^{24}_D$ −14.8 (c 1.01)]. IR (KBr): 1617, 1720, 3450 $cm^{-1}$. $^1H$ NMR ($D_2O$, δ): 1.75 (s, 3H); 2.38 (dd, *J* = 16.8, 8.3 Hz, 1H); 2.47 (dd, *J* = 6.3, 16.8 Hz, 1H); 3.05 (m, 2H); 3.43 (t, *J* = 11.6 Hz, 1H); 3.62 (dd, *J* = 7.2, 11.9 Hz, 1H); 4.10 (d, *J* = 3.3 Hz, 1H); 4.75 (s, 1H); 5.04 (s, 1H), all signals are identical with those of an authentic sample from Sigma. Anal. Calcd for $C_{10}H_{15}NO_4 \cdot H_2O$: C, 51.95; H, 7.36; N, 6.06. Found: C, 51.94; H, 7.36; N, 5.96.

**Supporting Information Available:** Full experimental and spectral data for compounds **17**−**21** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

JO962100M

(26) Hayashi, T.; Mise, T.; Fukushima, M.; Kagotani, M.; Nagashima, N.; Hamada, Y.; Matsumoto, A.; Kawakami, S.; Konishi, M.; Yamamoto, K.; Kumada, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1138.
(27) Bonati, F.; Minghetti, G. *Gazz. Chim. Ital.* **1973**, *103*, 373.
(28) Kurita, K.; Matsumura, T.; Iwakura, Y. *J. Org. Chem.* **1976**, *41*, 2070.
(29) See Supporting Information and ref 14.
(30) *The Merck Index, an Encyclopedia for Chemicals, Drugs, and Biologicals*, 11th ed.; Merck and Co. Inc.: 1989; p 831.