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Stereocontrolled Synthesis of (−)-Kainic Acid from *trans*-4-Hydroxy-L-proline†

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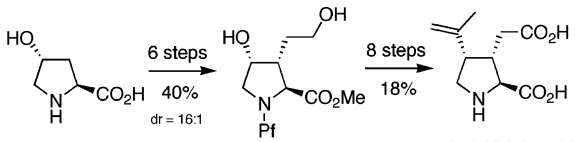
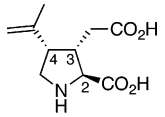


trans-4-Hydroxy-L-proline (−)-Kainic acid

A highly stereoselective synthesis of (−)-kainic acid has been achieved in 14 steps and >7% overall yield starting from inexpensive *trans*-4-hydroxy-L-proline. The key steps are diastereoselective enolate alkylation and cuprate substitution reactions.

Isolated in 1953 from *Digenea simplex*,[1] (−)-kainic acid (**1**, Figure 1) is the parent member of the kainoid class of marine natural products. This class of compounds exhibits a wide range of biological activities, and members have found use as anthelmintics and insecticides.[2] Kainic acid, itself, is currently used by brain researchers to reproduce neuronal death for the study of important neuronal disorders such as Alzheimer's disease and epilepsy.[3] A halt in the commercial extraction of kainic acid in 1999 created a shortage,[4a] which led to the development of numerous total syntheses, thus adding significantly to the many already existent in 1999.[5] The natural product, however, is once again available from algae, and the supply problem appears to be largely resolved.[4b]

Many of the successful kainic acid syntheses have relied on a Pauson−Khand, Ireland−Claisen, ene, or radical reaction for the formation of the C3−C4 bond with



(−)-Kainic Acid **1**

FIGURE 1.

the often problematic C3−C4 cis substitution. Other approaches have made use of a 3 + 2 cyclization or have started from pyroglutamic acid. Surprisingly, inexpensive *trans*-4-hydroxy-L-proline (**2**, eq 1) has not been used to date as the starting material for a preparation of (−)-kainic acid.[6] While the structure and absolute configuration of this hydroxy amino acid would seem to make it an ideal substance for this purpose, the difficulty in controlling the relative stereochemistry at the three contiguous stereogenic centers on the pyrrolidine has apparently so far thwarted or dissuaded synthetic chemists.[7]

We hoped to be able to achieve such a synthesis through regio- and stereoselective alkylation of a keto derivative of hydroxyproline (**I**), followed by stereoselective reduction of the keto function and displacement of a derivative of the resulting hydroxyl group by an isopro-

† This paper is dedicated to a friend and colleague, Dr. Yanyun Wang, deceased March 5, 2005.

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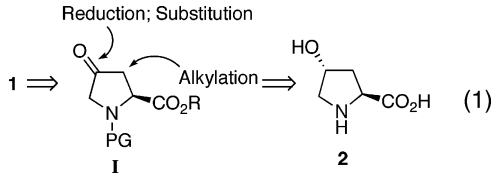


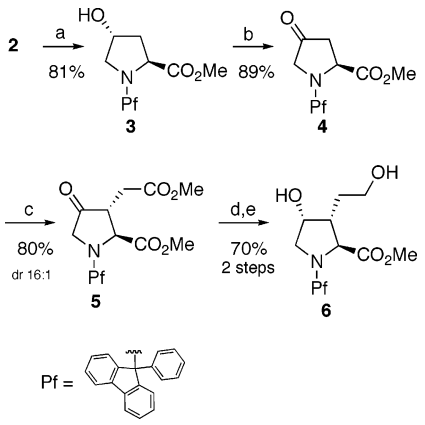
penyl. The choice of the nitrogen protecting group loomed crucial to the success of the approach: the *N*-benzoyl enamine was known to undergo selective alkylation, but in modest yield,[8] and the *N*-phenylfluorenyl ketone efficient regioselective alkylation, but with little diastereoselectivity.[9,10] A further consideration was that with carbamate derivatives cuprate substitution with retention of configuration had been reported and carbamate participation was proposed to explain the unusual result.[5aa,11]

Since alkylation attempts on the *N*-Boc ketone failed to produce satisfactory results, the corresponding phenylfluorenyl (Pf) derivative **4**[12] was prepared (Scheme 1). This ketone could be easily obtained from *trans*-4-hydroxy-L-proline in good yield on a multigram scale by sequential esterification (99%), phenylfluorenyl introduction (82%), and oxidation (89%). Although achievable under Swern conditions, the oxidation was more conveniently carried out with IBX in refluxing ethyl acetate.[13]

Concordant with Sardina and co-workers' results,[10b] it was initially found that the enolate of **4** in the presence of bromoacetate at −40 °C slowly formed the desired alkylation product, but on prolonged reaction or allowing the reaction mixture to warm to 0 °C, it underwent epimerization. Fortunately, however, by keeping the reaction temperature at −40 °C and using a catalytic amount of sodium iodide to generate in situ the more reactive iodoacetate, the desired trans product **5** could be secured highly selectively (dr 16:1) and in 80% yield.[14] Similar diastereoselectivity was observed with benzyl and *tert*-butyl bromoacetates and methyl and allyl iodides.[15]

The next difficulty was to regenerate selectively the C-4 hydroxyl group with the *R* configuration. Sodium borohydride afforded the undesired C-4 *S* isomer as a single product.[16] L-Selectride (2.1 equiv), however, selectively produced a lactol (not shown), which could be further reduced with sodium borohydride to give cleanly diol **6** in 70% yield on a gram scale. The use of 3 equiv of L-Selectride led directly to the diol, but in lower yield. The sterochemistry in diol **6** was confirmed by X-ray analysis.[17]

SCHEME 1. Diastereoselective Alkylation and Reduction[a]



[a] Reaction conditions: (a) (i) MeOH, $SOCl_2$, reflux; (ii) TMSCl, Et_3N, CH_2Cl_2, 35 °C, then MeOH, 0 °C, then PfBr, $Pb(NO_3)_2$, Et_3N, 20 °C; (b) IBX, EtOAc, reflux. (c) *n*-BuLi, HMPA, THF, −78 °C, then $BrCH_2CO_2CH_3$, cat. NaI, −40 °C (dr 16:1); (d) L-Selectride, THF, −78 °C; (e) $NaBH_4$, EtOH, 0 °C.

In preparation for the upcoming cuprate substitution, the bulky phenylfluorenyl protecting group, having played its crucial role in the alkylation, was replaced with a benzyloxycarbonyl (Cbz) group. This was accomplished through palladium-catalyzed hydrogenolysis of the phenylfluorenyl group in **6**, followed by carbamate formation with BCN,[18] which provided **7a** in 76% overall yield (Scheme 2). Selective acetylation of the primary hydroxyl in **7a** to give **7b** (82%) then allowed tosylation of the secondary hydroxyl to be efficiently achieved through reaction with tosylimidazole activated with MeOTf (79%).[19] Treatment of the resultant tosylate **8** with sodium hydroxide produced double ester cleavage to afford **9** in 92% yield.

The substitution reaction using a high order cyanocuprate proved very sensitive to reaction conditions, as reported previously.[5aa] However, by strictly following the procedure reported in the Experimental Section, reproducible yields of the substitution product **10** could be realized. The mechanism of this intriguing reaction is unclear and deserves study.

The denouement of the synthesis was straightforward: oxidation of the primary alcohol with Jones re-

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(14) Epimerization of **5** is so facile that purification on silica gel pretreated with triethylamine (2.5%, v/v) was sufficient to produce the cis isomer.

(15) The following yields and disatereoselectivities were obtained: benzyl bromoacetate (92%, 14:1), *tert*-butyl bromoacetate (83%, 16:1), methyl iodide (66%, 8:1), allyl iodide (80%, 14:1).

(16) The C-4 *S* isomer (benzyl acetate) could be converted to diol **6** by hydrogenolysis, lactonization under Mitsunobu conditions, and reduction.

(17) Crystal data for $C_{27}NO_4H_{27}\cdot H_2O$: monoclinic $P2_1$, a = 9.921(5) Å, b = 27.47(1) Å, c = 10.021(5) Å, β = 118.67(5)°, V = 2396(2) Å^3, Z = 4, d_{calcd} = 1.241 mg/m^3, $F(000)$ = 952.00, λ Cu Kα = 1.54178 Å, Θ_{max} range 3.22−74.89°, 5344 measured reflections, 4438 [R(int) = 0.03897] independent reflections, $R(1)$ [$1 > 2\sigma(I)$] = 0.0652, wR2 [all data] = 0.0924, GoF (all data) = 1.962. The crystallographic information file (CIF) has been deposited at the Cambridge Crystallographic Data Centre as CCDC 276163. These data can be obtained from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CBZ 1EZ, UK.; fax (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk.

(18) Benzyl 5-norborbene-2,3-dicarboximido carbonate. Henklein, P.; Heyne, H.-U.; Halatsch, W.-R.; Niedrich, H. *Synthesis* **1987**, 166−167.

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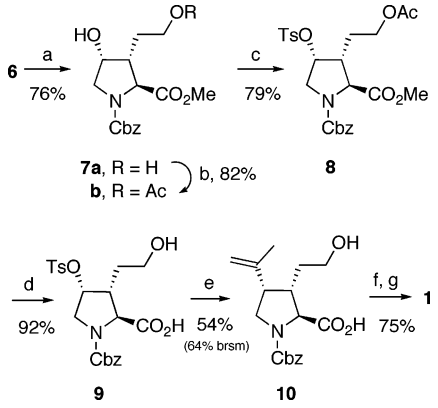
SCHEME 2. Synthesis of (−)-Kainic Acid[a]



[a] Reaction conditions: (a) (i) H_2, Pd/C, AcOH, EtOAc, 20 °C; (ii) BCN,[18] Et_3N, dioxane−H_2O, 20 °C; (b) AcCl, collidine, CH_2Cl_2, −78 °C; (c) tosylimidazole, MeOTf, *N*-methylimidazole, THF, 30 °C; (d) NaOH, THF−H_2O, 20 °C; (e) $[CH_2{=}C(CH_3)]_2CuCNLi_2$, THF, −78 → 25 °C; (f) Jones reagent, acetone, 20 °C, 87%; (g) NaOH, reflux, 86%.

agent led in 87% yield to the corresponding acid, which was refluxed in aqueous sodium hydroxide to afford (−)-kainic acid (mp 239−243 °C, $[\alpha]^{20}_D$ −13.9 (*c* 0.35, H_2O)), indistinguishable spectroscopically and chromatographically from an authentic sample of the natural product (mp 241−243 °C, $[\alpha]^{20}_D$ −13.9 (*c* 0.31, H_2O)).

In summary, we have described the first synthesis of (−)-kainic acid starting from *trans*-4-hydroxy-L-proline. The synthesis proceeds in >7% yield for 14 steps with essentially total stereochemical control at the three contiguous stereogenic centers, which places it among the most effective reported to date. A highlight of the work is the diastereoselective alkylation of ketone **4**, the apparent generality of which should make *trans*-4-hydroxy-L-proline an even more attractive starting material for synthesis.

Experimental Section

(2*S*,3*R*)-Methyl 3-(2-Methoxy-2-oxoethyl)-4-oxo-1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxylate (5). A solution of *n*-butyllithium (1.6 M in hexane, 3.4 mL, 5.5 mmol) was added dropwise to a solution of ketone **4**[12] (2.00 g, 5.22 mmol) in 10 mL of THF and 2.0 mL of HMPA at −78 °C under argon. The resulting solution was stirred at −78 °C for 0.5 h and then rapidly transferred with a cannula to a solution of sodium iodide (240 mg, 1.60 mmol) and methyl bromoacetate (1.50 mL, 15.84 mmol) in 10 mL of THF at −55 °C. The reaction mixture was allowed to warm to −40 °C, stirred for an additional 1.0 h, and then treated with 10 mL of a 30% aqueous solution of H_3PO_4. Water (10 mL) was added, and the aqueous phase was extracted with EtOAc, which was washed with water and brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure. Purification of the crude product by silica gel flash chromatography (eluant hexane/EtOAc, 7/3) gave keto diester **5** (1.89 g, 80%, dr 16:1) as a pale yellow oil. The spectral data were in accord with the literature values.[10b]

(2*S*,3*R*,4*R*)-Methyl 4-Hydroxy-3-(2-hydroxyethyl)-1-(9-phenyl-9*H*-fluoren-9-yl)pyrrolidine-2-carboxylate (6). A solution of L-Selectride (1 M in THF, 8.7 mL, 8.7 mmol) was added to a solution of keto diester **5** (1.89 g, 4.15 mmol) in THF at −78 °C under argon. The reaction mixture was stirred for 1 h at −78 °C and then treated with 3 N NaOH (2.9 mL, 8.7 mmol), followed by 30% H_2O_2 (2.9 mL, 26.1 mmol), and allowed to warm to 20 °C. After the mixture was stirred for 15 min, water was added and the aqueous phase extracted with ethyl acetate. The organic phase was washed with brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure to leave a pale yellow oil. The oil was taken up in ethanol, the solution was cooled to 0 °C, and $NaBH_4$ (171 mg, 4.51 mmol) was then added. After being stirred at 0 °C for 2.0 h, the mixture was treated with water, followed by a few drops of HCl (1 N). The aqueous phase was extracted with EtOAc, which was washed with brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure. Purification of the crude product by silica gel flash chromatography (eluent CH_2Cl_2/EtOAc, 3/7) afforded diol **6** (1.25 g, 70%) as a white solid: mp 56−57 °C; $[\alpha]^{20}_D$ +230 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.29 (m, 1H), 1.61 (m, 1H), 2.25 (m, 1H), 2.96 (d, J = 8.8 Hz, 1H), 3.14 (dd, J = 2.3, 11.7 Hz, 1H), 3.21 (s, 3H), 3.50 (ddd, J = 4.0, 8.6, 10.5 Hz, 1H), 3.59 (ddd, J = 4.7, 5.5, 10.5 Hz, 1H), 3.69 (dd, J = 4.7, 11.7 Hz, 1H), 4.32 (dt, J = 2.3, 4.7 Hz, 1H), 7.23−7.61 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.7, 48.5, 51.3, 61.2, 65.5, 71.3, 119.7, 119.9, 126.6, 127.0, 127.26, 127.34, 127.47, 127.53, 128.27, 128.32, 128.8, 139.6, 141.7, 142.9, 146.2, 147.4, 176.1, 221.7; MS (ESI$^+$) *m/z* 430 (MH^+). Anal. Calcd for $C_{27}H_{27}NO_4$: C, 75.50; H, 6.34; N, 3.26. Found: C, 75.18; H, 6.43; C, 3.22.

(2*S*,3*R*,4*R*)-1-Benzyl 2-Methyl 4-Hydroxy-3-(2-hydroxyethyl)pyrrolidine-1,2-dicarboxylate (7a). A mixture of diol **6** (1.00 g, 2.33 mmol) and 10% Pd/C (500 mg) in 0.4 mL of acetic acid and 20 mL of ethyl acetate was placed under 5 atm of hydrogen and stirred at 20 °C for 24 h. The reaction mixture was filtered over Celite, which was then washed with methanol and water. The filtrate was concentrated to dryness and the resulting residue dissolved in 20 mL of 4:1 dioxane−water and treated with triethylamine (1.60 mL, 11.5 mmol) followed by BCN[18] (1.40 g, 4.60 mmol). After being stirred for 24 h at 20 °C, the mixture was treated with water and the aqueous phase was extracted with EtOAc. The organic phase was washed with brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. Purification of the crude product by silica gel flash chromatography (eluent EtOAc) gave the Cbz derivative **7a** (574 mg, 76%, two steps) as a thick oil: $[\alpha]^{20}_D$ −29.5 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 1.80−1.98 (m, 2H), 2.22−2.30 (m, 1H), 3.51 (s, 1.5H), 3.60−3.70 (m, 2.5H), 3.75 (s, 1.5H), 3.76−3.85 (m, 1.5H), 4.07 (d, J = 9.2 Hz, 0.5H), 4.10 (d, J = 9.1 Hz, 0.5H), 4.37 (m, 1H), 4.96 (A of AB q, J = 13.7 Hz, 0.5H), 5.09 (app d, J = 1.5 Hz, 1H), 5.19 (B of AB q, J = 13.7 Hz, 0.5H), 7.27−7.35 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of rotamers) δ 29.0, 48.2, 48.9, 52.0, 52.3, 54.4, 54.8, 60.8, 60.9, 62.9, 63.2, 67.2, 67.3, 70.4, 71.3, 127.8, 127.9, 128.3, 128.4, 136.2, 136.3, 154.4, 154.9, 173.0, 173.2; MS (ESI$^+$) *m/z* 346 ($M + Na)^+$. Anal. Calcd for $C_{16}H_{21}NO_6{\cdot}0.5H_2O$: C, 57.82; H, 6.67; N, 4.21. Found: C, 57.87; H, 6.69; N, 4.15.

(2*S*,3*R*,4*R*)-1-Benzyl 2-Methyl 3-(2-Acetoxyethyl)-4-(tosyloxy)pyrrolidine-1,2-dicarboxylate (8). Methyl triflate (0.278 mL, 2.46 mmol) was added dropwise to tosylimidazole (556 mg, 2.50 mmol) in 7 mL of THF at 0 °C under argon. After being stirred for 5 min, a solution of acetate **7b** (415 mg, 1.14 mmol) and *N*-methylimidazole (0.200 mL, 2.51 mmol) in 7 mL of THF was added. The reaction mixture was warmed to 30 °C and stirred for 72 h. The reaction was then quenched by addition of a 5% solution of aqueous $KHSO_4$, diluted with water, and extracted with EtOAc. The organic phase was washed brine and dried over $MgSO_4$, and the volatiles were removed under reduced pressure. The crude product was purified by flash silica gel chromatography (eluent EtOAc/hexane, 6/4 to 1/1) to afford tosylate **8** (464 mg, 79%) as a white powder: mp 91.5 °C; $[\alpha]^{20}_D$ +49.0 (*c* 1.0, $CHCl_3$); IR 2957, 1732, 1711, 1417, 1360, 1240, 1170, 896 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of rotamers) δ 1.80−2.00 (m, 2H), 2.04 (s, 1.5H), 2.05 (s, 1.5H), 2.37−2.54 (m, 1H), 2.44 (s, 1.5H), 2.48 (s, 1.5H), 3.50 (s, 1.5H), 3.59 (dd, J = 3.2, 9.7 Hz, 0.5H), 3.63 (dd, J = 3.2, 9.5 Hz, 0.5H), 3.71−3.85 (m, 1H), 3.78 (s, 1.5H), 3.99 (dq, J = 1.4, 6.2 Hz, 2H), 4.06 (d, J = 9.7 Hz, 0.5H), 4.11 (d, J = 9.5 Hz, 0.5H), 4.98 (A of AB q, J = 12.2 Hz, 0.5H), 5.07 (app t, J = 3.7 Hz, 1H), 5.08 (A′ of A′B′ q, J = 12.5 Hz, 0.5H), 5.13 (B′ of A′B′ q, J = 12.5 Hz, 0.5H), 5.18 (B of AB q, J = 12.2 Hz, 0.5H), 7.28−7.41 (m, 7H), 7.76 (d, J = 8.4 Hz, 1H), 7.80 (d, J = 8.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$,

mixture of rotamers) δ 20.8, 21.6, 25.6, 44.7, 45.6, 52.2, 52.3, 52.5, 52.6, 61.2, 61.3, 62.2, 62.5, 67.4, 67.5, 79.5, 80.0, 127.6, 127.7, 127.8, 127.9, 128.1, 128.4, 128.5, 130.0, 130.1, 133.3, 133.4, 135.9, 136.1, 145.4, 145.5, 153.6, 154.2, 170.7, 172.0, 172.2; MS (CI$^+$) *m/z* 537 $(M + NH_4)^+$. Anal. Calcd for $C_{25}H_{29}NO_9S$: C, 57.79; H, 5.63; N, 2.70. Found: C, 57.50; H, 5.61; N, 2.66.

(2*S*,3*S*,4*S*)-1-(Benzyloxycarbonyl)-3-(hydroxymethyl)-4-(prop-1-en-2-yl)pyrrolidine-2-carboxylic Acid (10). The published procedure[5aa] was slightly modified. *tert*-Butyllithium (1.7 M in pentane, 7.50 mL, 12.7 mmol) was added dropwise to a solution of freshly distilled 2-bromopropene (0.567 mL, 6.4 mmol) in 30 mL of THF under argon, while the internal temperature was maintained below −70 °C. The reaction mixture was stirred at this temperature for an additional 0.5 h and then rapidly transferred with a cannula to a suspension of 286 mg (3.2 mmol) of CuCN (99.99%, dried twice by warming under high vacuum and then kept under argon) in 3 mL of THF at −78 °C. The resulting mixture was stirred for 5 min, after which time it was allowed to warm until complete dissolution of the CuCN (ca. 2 min at −30 °C), which produced a pale yellow, homogeneous solution. A solution of acid **9** (296 mg, 0.64 mmol) in 3 mL of THF was then added at −78 °C, and the reaction mixture was stirred for 5 min before being allowed to warm to 25 °C. After 2.0 h, the reaction mixture was treated with dilute HCl and diluted with water. The aqueous phase was extracted with EtOAc, which was washed with brine and dried over $MgSO_4$. The volatiles were removed under reduced pressure. The crude product was purified by flash silica gel chromatography (gradient hexane/EtOAc/AcOH, 49.5/49.5/1 to EtOAc/AcOH, 99/1) to give adduct **10** (115.8 mg, 54%, 64% brsm) as a clear oil and a second, blue product, which gave acid **9** (42.8 mg, 15% recovery) after base−acid extraction. The spectroscopic data of **10** ($[\alpha]^{20}_D$ −51.5 (*c* 1.0, $CHCl_3$) were in full agreement with those reported.[5aa]

(2*S*,3*S*,4*S*)-4-(Prop-1-en-2-yl)pyrrolidine-2,3-dicarboxylic Acid ((−)-Kainic Acid) (1). The final hydrolysis was performed as previously described:[5aa] 86% yield; $[\alpha]^{20}_D$ −13.9 (*c* 0.35, H_2O). The synthetic material was spectroscopically and chromatographically identical with an authentic sample of the natural product obtained from a commercial source.

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Supporting Information Available: Experimental procedures and characterization data for compounds **7b** and **9**; ^1H and ^{13}C NMR spectra for compound **7b**; CIF and ORTEP diagram for compound **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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