Enantioselective Synthesis of (-)-Kainic Acid

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Abstract: Novel diastereoselectivity in the intramolecular Diels-Alder reaction of the heterodiene **18** has been observed. The structure of the cycloadduct was determined to be **20**, possessing cis-5/6 ring juncture by converting it into (-)-kainic acid (**1**) and kainic acid lactone (**25**).

The unique structures and novel biological activities (anthelmintic,[1] insecticidal,[2] and neuroexcitory[3]) of kainic acid (**1**) and allokainic acid (**2**), isolated from the marine alga *Digenea simplex*,[4] have led to the development of several interesting synthetic strategies.[5,6] Recently, we showed a novel example of diastereoselective intramolecular Diels-Alder reaction of the heterodienes in which the stereochemistry of the cycloadducts is controlled by the configuration of the dienophile olefin.[7] Thus, when both isomeric heterodienes **7a** and **b** were generated from diethyl L-tartrate (**8**), the spontaneous intramolecular cycloaddition took place to give the adduct **5** with cis-5/6 juncture from the *E* olefin **7a** and the adduct **6** with trans-5/6 juncture from the *Z* olefin **7b** selectively, both with complete reflection of the stereochemistry of the chiral starting material **8** (Scheme I). This finding appeared to be ideally suited for the diastereoselective synthesis of both kainic acid (**1**) and allokainic acid (**2**) in optically active forms, since the reaction can selectively produce 2,3,4-trisubstituted tetrahydrofuran ring systems that correspond to the relative configuration of these amino acids. As an application, we report here an experiment using the nitrogen substrate **18** containing a trisubstituted dienophile moiety that selectively furnished the single adduct **20** leading to a synthesis of natural (-)-kainic acid (**1**) in the intramolecular cycloaddition reaction.

Treatment of the epoxy alcohol **9**,[8] prepared from diethyl L-tartrate (**8**), with diphenylphosphoryl azide in the presence of diisopropyl azodicarboxylate and triphenylphosphine[9] gave the epoxy azide **10** with inversion of chirality. Treatment of **10** with acetone in the presence of Lewis acid allowed conversion of the oxirane moiety into the dioxolane ring with the azide group intact to give rise to the compound **11**. On hydride reduction **11** yielded the primary amine **12**, which then was transformed to the carbamate **13** in 47% overall yield from **9**. Alkylation of **13** with prenyl chloride gave the tertiary amide **14**, which in turn was converted into the disubstituted glyceraldehyde **16** on sequential hydrolysis and oxidative cleavage. Reaction of **16** with Meldrum's acid[10] was accompanied by intramolecular cycloaddition of the condensation product **18** at 0 °C to room temperature to furnish a single adduct **20**, which was refluxed in aqueous dioxane (2:1) to give the bicyclic lactone **22** in 54% overall yield from **13** (Scheme II). Since we already observed that the carbon analogue **27** of **18** furnished the single adduct **28** with trans-5/6 juncture[11] selectively, the present adduct was initially assumed to have the same trans-5/6 stereochemistry (Scheme III). However, conflicting experimental results have been reported[12] with allokainic acid (**2**), which failed to form the δ-lactone with trans-5/6 juncture. The compound **22** was accordingly converted into amino acid **25** in 62% overall yield via the primary alcohol **23** and the carboxylic acid **24** on sequential debenzylation, Jones oxidation, and debenzyloxycarbonylation. The compound **25** as well as its methyl ester **26** was in all respects identical with kainic acid lactone[13] (**25**) and its methyl ester **26** obtained from natural kainic acid (**1**). These clearly revealed that the adduct **20** should have cis-5/6 juncture with the same configuration as that of natural kainic acid (**1**).

We presumed that the observed, rather surprising, stereochemical outcome may be due to the nature of the carbamate nitrogen of which sp^2-like planar configuration allows efficient $[4\pi + 2\pi]$ overlap only in the endo conformer **18a** to generate the cis adduct **20** with the kainic acid configuration. In contrast, no such overlap can be expected in the alternative exo conformer **18b**, which failed to generate the trans adduct **29** with the allokainic acid configuration (Scheme IV). In order to confirm this assumption, we examined the same reaction using the sp^3 counterpart **19** of **18** generating in situ from the tertiary amine **15** via the aldehyde **17**. However, neither the adduct **21** nor its isomer could be isolated under the same conditions or more forcing conditions as decomposition of the substrates prevailed.

Although direct transformation of **25** into (-)-kainic acid (**1**) could not be achieved owing to preferential exocyclic isopropylidene bond formation, a seven-step sequence leading to (-)-kainic acid (**1**) from **23** was devised. The alcohol **23** was silylated, and the resulting ether **30** was reduced with sodium borohydride in boiling 2-propanol to give the diol **31**. After several frustrating attempts, which mostly resulted in formation of the isopropylidene group, we finally found that the reaction took place in the desired way when **31** was heated with acetic anhydride at 270 °C in a sealed tube to furnish the isopropenyl acetate **32** exclusively in 85% yield. Sequential deacetylation and desilylation of **32** followed by Jones oxidation of the resulting diol **34** gave the diacid **35** as well as its dimethyl ester **36**, which were identical with authentic materials prepared from natural (-)-kainic acid (**1**). (-)-Kainic acid (**1**) could be obtained by saponification of **36** with methanolic sodium hydroxide. Overall yield of **1** from **22** was 22% (Scheme V).

The stereochemical outcome observed may be advantageous in both pharmacological and synthetic points of view since other kainoid congeners possessing kainic acid configuration were re-

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(6) For some leading references to synthesis of allokainic acid, see: (a) Miyamoto, M.; Sugawa, T.; Morimoto, H.; Uchibayashi, M.; Tanaka, K.; Tatsuoka, S. *J. Pharm. Soc. Jpn* **1957**, *77*, 580. (b) Miyamoto, M.; Honjo, M.; Sanno, Y.; Uchibayashi, M.; Tanaka, K.; Tatsuoka, S. *Ibid.* **1957**, *77*, 586. (c) Honjo, M. *Ibid.* **1957**, *77*, 598. (d) Oppolzer, W.; Robbiani, C.; Battig, K. *Helv. Chim. Acta* **1980**, *63*, 2015. (e) Kraus, G. A.; Nagy, J. O. *Tetrahedron* **1985**, *41*, 3537. (f) DeShong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, *27*, 3979. (g) Reference 5c.
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(12) Morimoto, H.; Nakamori, R. *J. Pharm. Soc. Jpn* **1956**, *76*, 294.
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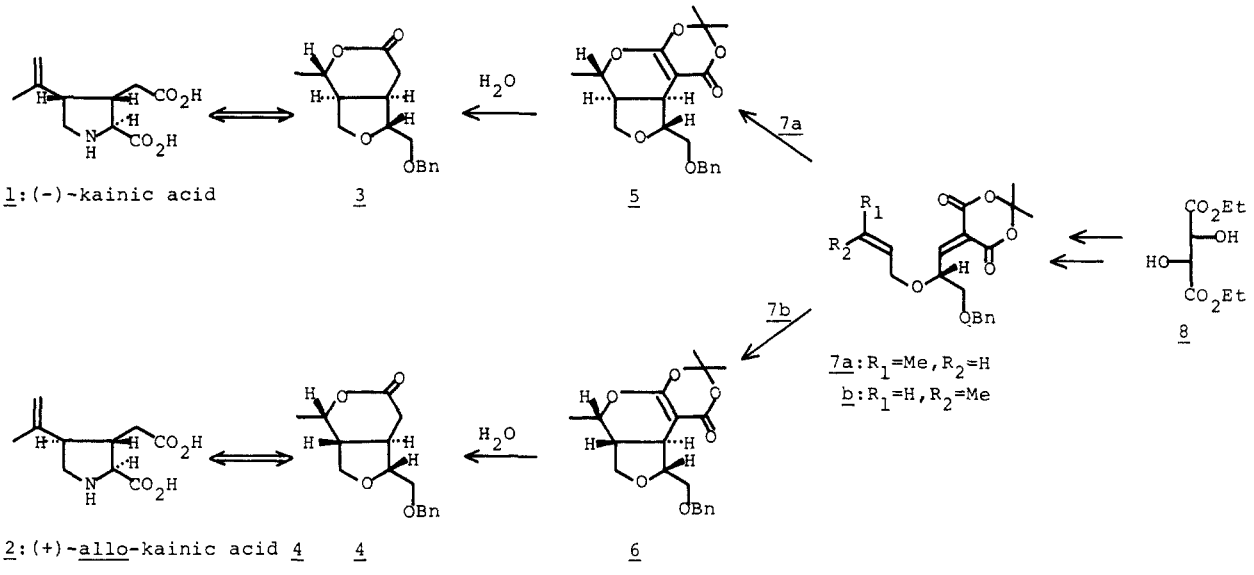
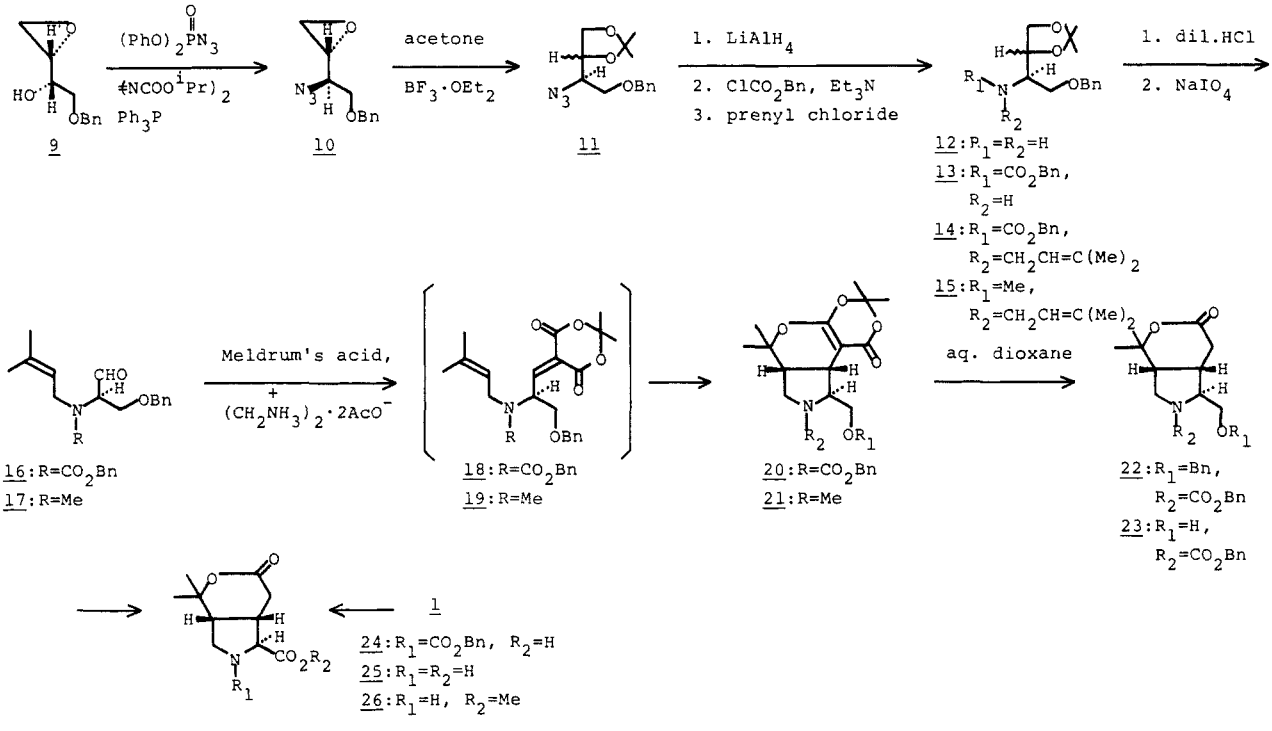
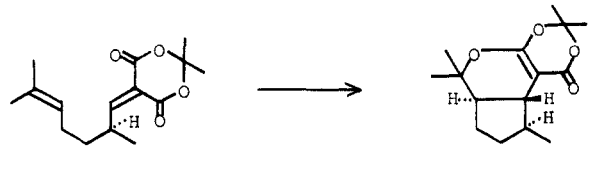
Scheme I



Scheme II



Scheme III



cently found and reported to exhibit more potent physiological activities.[14]

Experimental Section

All reactions except hydrogenation were carried out under argon.

(2*R*,3*R*)-2-Azido-1-(benzyloxy)-3,4-epoxybutane (10). To a stirred mixture of the alcohol **9** (202 mg, 1.04 mmol) and Ph_3P (328 mg, 1.25 mmol) in THF (3 mL) was added diphenylphosphoryl azide (0.27 mL, 1.25 mmol) followed by diisopropyl azodicarboxylate (0.25 mL, 1.27 mmol) at 0 °C, and the mixture was stirred for 10 min at the same temperature and for 1.5 h at room temperature. The mixture was condensed in vacuo to give an oily residue, which was chromatographed on a silica gel column (AcOEt–hexane, 1:8 v/v) to give the azide **10**: 137 mg, 61%; $[\alpha]^{30}_D$ −30.2° (*c* 1.00, $CHCl_3$); IR (film) 2100 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.67 (m, 2 H), 2.98–3.22 (m, 1 H), 3.35–3.80 (m, 3 H), 4.60 (s, 2 H), 7.35 (s, 5 H); MS, *m/e* 219 (M^+), 91 (100). Anal. Calcd for $C_{11}H_{13}N_3O_2$: C, 60.26; H, 5.98; N, 19.15. Found: C, 60.01; H, 5.80; N, 19.37.

(2*R*,3*RS*)-2-Azido-1-(benzyloxy)-3,4-(isopropylidenedioxy)butane (11). To a stirred solution of **10** (137 mg, 0.625 mmol) in acetone (3 mL) was added boron trifluoride etherate (6.0 mL, 0.049 mmol) at 0 °C, and the mixture was refluxed for 13 h. After being cooled, the mixture was neutralized by addition of 5% $NaHCO_3$ and most of the solvent was removed in vacuo. After the residue was diluted with water and ether, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were washed (brine), dried ($MgSO_4$), and evaporated to leave a yellow oil, which was chromatographed on a silica gel column (AcOEt–hexane, 1:15 *v/v*) to give **11** (140 mg, 81%) as a mixture of epimers: IR (film) 2100 cm^{-1}; ^1H NMR ($CDCl_3$)

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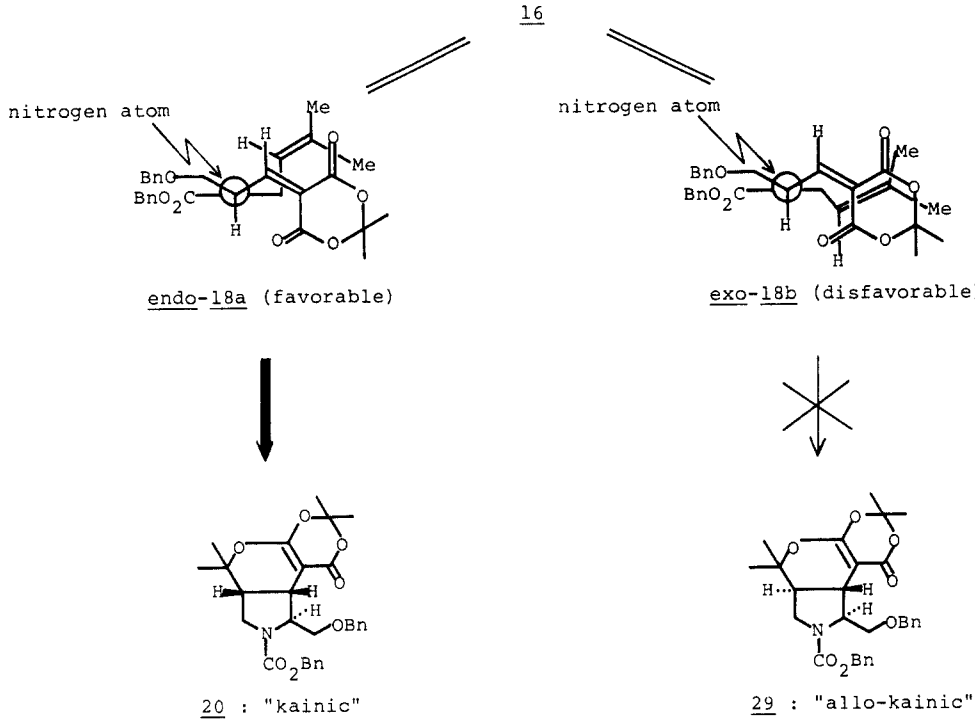
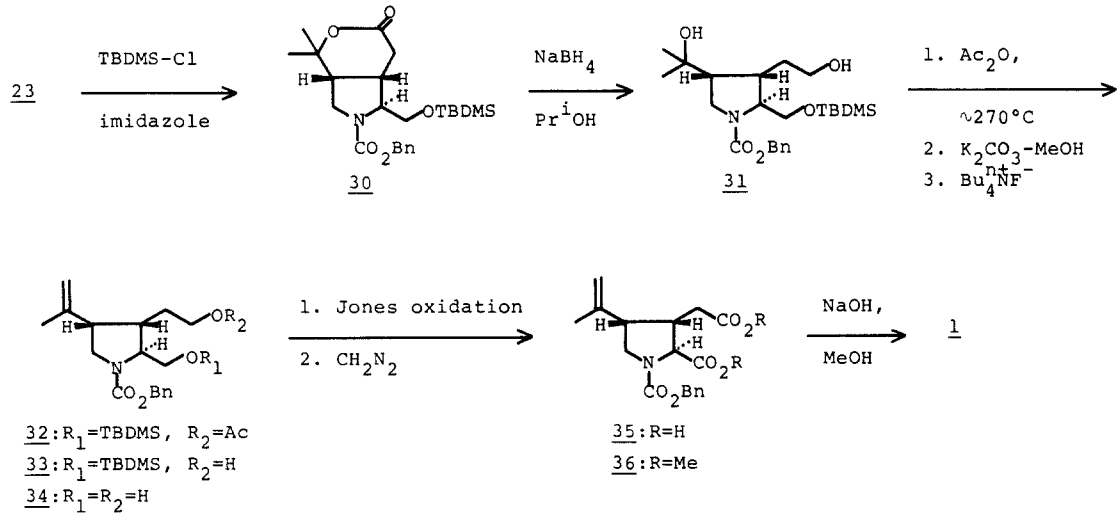
Scheme IV



Scheme V



δ 1.34 (s, 3 H), 1.44 (s, 3 H), 3.45–3.84 (m, 3 H), 3.84–4.22 (m, 3 H), 4.58 (s, 2 H), 7.34 (s, 5 H); MS, *m/e* 277 (M^+), 91 (100). Anal. Calcd for $C_{14}H_{19}N_3O_3$: C, 60.63; H, 6.91; N, 15.15. Found: C, 60.52; H, 7.03; N, 15.39.

(2*R*,3*RS*)-2-[(Benzyloxycarbonyl)amino]-1-(benzyloxy)-3,4-(isopropylidenedioxy)butane (13). To a stirred solution of $LiAlH_4$ (1.32 g, 34.8 mmol) in THF (50 mL) was added **11** (9.66 g, 34.8 mmol) in THF (200 mL) dropwise slowly (40 min) at 0 °C, and the mixture was stirred for 10 h at the same temperature. The mixture was treated with 28% NH_4OH to decompose the hydride complex and, after being stirred overnight, was filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated in vacuo to give the amine **12** (7.76 g) as a yellow oil in a practically pure state, which was used for the next conversion without further purification: IR (film) 3380 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.39 (s, 3 H), 2.23 (br s, 2 H, exchangeable), 2.93–4.27 (m, 6 H), 4.50 (s, 2 H), 7.28 (s, 5 H); MS, *m/e* 251 (M^+), 91 (100).

To a solution of **12** (7.76 g) in CH_2Cl_2 (150 mL) was added triethylamine (13.6 mL, 97.5 mmol) followed by carbobenzoxy chloride (90%, 10.0 mL, 63.0 mmol) dropwise (10 min) at 0 °C, and the mixture was stirred at room temperature for 19 h. The mixture was washed (5% HCl, 5% $NaHCO_3$, brine), dried ($MgSO_4$), evaporated in vacuo to leave a yellow oil, which was chromatographed on a silica gel column (AcOEt–hexane, 1:8 v/v) to give **13** (12.8 g, 95%) as a colorless oil: IR (film) 3420, 3330, 1720 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.38 (s, 3 H), 3.27–4.34 (m, 7 H), 4.51 (s, 2 H), 5.10 (s, 2 H), 7.30 (s, 5 H), 7.34 (s, 5 H); MS, *m/e* 385 (M^+), 91 (100). Anal. Calcd for $C_{22}H_{27}NO_5$: C, 68.55; H, 7.06; N, 3.63. Found: C, 68.63; H, 6.78; N, 3.35.

(2*R*,3*RS*)-2-[(Benzyloxycarbonyl)prenylamino]-1-(benzyloxy)-3,4-(isopropylidenedioxy)butane (14). To a suspension of NaH [60% oil dispersion, 749 mg, 18.7 mmol; washed twice with hexane (20 mL)] in DMF (30 mL) was added a solution of **13** (4.68 g, 12.1 mmol) in DMF (50 mL) dropwise at 0 °C, and the mixture was stirred for 1 h at room temperature. To this solution was added prenyl chloride (1.51 g, 14.4 mmol) at 0 °C, and the mixture was stirred at room temperature for 7 h. After the excess hydride was decomposed by addition of 5% $NaHCO_3$, most of the solvent was removed in vacuo. The residue was taken up into ether, and the ether layer was washed (brine), dried ($MgSO_4$), and evaporated in vacuo. The residual oil was chromatographed on a silica gel column (AcOEt–hexane, 1:15 v/v) to give **14** (5.04 g, 92%) as a colorless oil: IR (film) 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.32 (s, 3 H), 1.38 (s, 3 H), 1.47–1.93 (m, 6 H), 3.45–4.87 (m, 10 H), 4.95–5.43 (m, 3 H), 7.25 (s, 10 H); MS, *m/e* 453 (M^+), 91 (100); calcd for $C_{27}H_{35}NO_5$ 453.2515, found 453.2517.

(2*S*,3*S*,4*R*)-[1-(Benzyloxycarbonyl)-2-[(benzyloxy)methyl]-4-(1-hydroxy-1-methylethyl)]-3-pyrrolidineacetic Acid Lactone (22). A solution of **14** (4.12 g, 9.08 mmol) in MeOH (30 mL) was stirred with 10% HCl (15 mL) at room temperature for 9 h. After being neutralized at

0 °C by addition of 5% $NaHCO_3$, the mixture was extracted thoroughly with CH_2Cl_2. The combined extracts were washed (brine), dried ($MgSO_4$), and evaporated in vacuo to give (2*R*,3*RS*)-2-[(benzyloxycarbonyl)prenylamino]-1-(benzyloxy)-3,4-butandiol (3.61 g) as a pale yellow oil: IR (film) 3440, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.43–1.98 (m, 6 H), 2.53–4.35 (m, 10 H, 2 H, exchangeable), 4.50 (s, 2 H), 5.13 (s, 2 H), 5.47–5.93 (m, 1 H), 7.28, 7.29 (each s, 10 H); MS, *m/e* 413 (M^+), 91 (100); calcd for $C_{24}H_{31}NO_5$ 413.2202, found 413.2225.

To a stirred solution of the glycol (3.61 g) in MeOH (40 mL) was added $NaIO_4$ (2.25 g, 10.5 mmol) in water (20 mL) dropwise (20 min) at 0 °C, and the mixture was kept stirring for 2 h at the same temperature. The mixture was extracted thoroughly with ether, and the ethereal layers were evaporated in vacuo below 25 °C to give the crude aldehyde **16** (3.27 g), which was immediately used for the next conversion.

To a stirred solution of crude **16** (3.27 g) in 2-propanol (70 mL) was added Meldrum's acid (1.62 g, 11.2 mmol) followed by ethylenediammonium diacetate (120 mg, 0.67 mmol) at 0 °C, and the mixture was kept stirring at room temperature for 16 h. After the residue was diluted with ether and 5% $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to leave an unstable oil containing the tricyclic adduct **20** (4.24 g), which was immediately used for the next conversion.

The crude **20** (4.24 g) was dissolved in aqueous dioxane (75 mL of dioxane–H_2O, 2:1 v/v), and the mixture was refluxed for 15 h. After the mixture was diluted with ether and 5% $NaHCO_3$, the organic layer was separated and the aqueous layer was extracted with ether. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to leave a yellow oil, which was chromatographed on a silica gel column (AcOEt–hexane, 1:4 v/v) to give **22** (2.27 g, 59% overall from **14**) as a colorless oil: $[\alpha]^{28}_D$ −24.6° (*c* 0.15, $CHCl_3$); IR (film) 1720, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.33 (s, 3 H), 1.42 (s, 3 H), 1.90–4.10 (m, 9 H), 4.47 (br s, 2 H), 5.12 (s, 2 H), 7.51 (s, 5 H), 7.55 (s, 5 H); MS, *m/e* 423 (M^+), 91 (100); calcd for $C_{25}H_{29}NO_5$ 423.2045, found 423.2065.

(2*S*,3*S*,4*R*)-[1-(Benzyloxycarbonyl)-2-(hydroxymethyl)-4-(1-hydroxy-1-methylethyl)]-3-pyrrolidineacetic Acid Lactone (23). (a) To a stirred solution of **22** (317 mg, 0.75 mmol) in CH_2Cl_2 (6 mL) was added BBr_3 in CH_2Cl_2 (1 M, 0.82 mL, 0.82 mmol) dropwise at −40 °C, and the temperature was raised gradually to 0 °C (1 h) and kept at the same temperature for 30 min. After the reaction was quenched by addition of 5% $NaHCO_3$, the mixture was extracted with CH_2Cl_2. The extract was washed (brine), dried ($MgSO_4$), and evaporated in vacuo to leave the crude product, which was purified by a silica gel plate (AcOEt–hexane, 2:1 v/v) followed by recrystallization to give the unchanged **22** (141 mg, 44%) and **23** (102 mg, 41%; 74% based on consumed **22**) as colorless needles: mp 129–130 °C; $[\alpha]^{30}_D$ −9.84° (*c* 0.75, $CHCl_3$); IR (film) 3440, 1720, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.36 (s, 3 H), 1.45 (s, 3 H), 1.98–3.93 (m, 10 H, 1 H exchangeable), 5.12 (s, 2 H), 7.35 (s, 5 H); MS, *m/e* 333 (M^+), 91 (100). Anal. Calcd for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.70; H, 6.88; N, 4.35.

(b) **22** (300 mg, 0.71 mmol) was hydrogenated over 10% palladized charcoal (30.4 mg) in MeOH (12 mL) containing concentrated HCl (20 drops) under atmospheric pressure at room temperature for 13 h. After the solvent was removed, the resulting amino alcohol (214 mg) in CH_2Cl_2 (5 mL) was treated with carbobenzoxy chloride (90%, 0.19 mL, 1.22 mmol) and triethylamine (0.78 mL, 5.60 mmol) at 0 °C, and the mixture was stirred for 2.5 h at room temperature. After evaporation of the low volatiles under vacuum, the residue was chromatographed on a silica gel column (AcOEt–hexane, 2:1 v/v) to give **23** (224 mg, 94%).

(2*S*,3*S*,4*R*)-[1-(Benzyloxycarbonyl)-2-carboxy-4-(1-hydroxy-1-methylethyl)]-3-pyrrolidineacetic Acid Lactone (24). To a solution of **23** (102 mg, 0.31 mmol) in acetone (3 mL) was added 8 N Jones reagent (0.18 mL, 1.44 mmol) at 0 °C, and the mixture was stirred at the same temperature for 3 h and at room temperature for 10 h. After the remaining oxidant was decomposed by addition of 2-propanol (0.5 mL), the mixture was diluted with ether and water. The organic layer was separated, and the aqueous layer was extracted with ether. The combined organic layers were washed (brine), dried ($MgSO_4$), and evaporated to leave **24** (90.0 mg, 84%) as a colorless amorphous foam: $[\alpha]^{30}_D$ +0.19 (*c* 1.06, $CHCl_3$); IR (film) 2950, 1700, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.68 (s, 3 H), 1.75 (s, 3 H), 1.80–4.12 (m, 6 H), 4.22 (br d, *J* = 5 Hz, 1 H), 5.18 (br s, 2 H), 7.38 (s, 5 H); MS, *m/e* 347 (M^+), 91 (100); calcd for $C_{18}H_{21}NO_6$ 347.1369, found 347.1371.

Kainic Acid Lactone (25). **24** (90.0 mg, 0.26 mmol) in methanol (3.7 mL) was hydrogenolized over 10% palladized charcoal (9.9 mg) under atmospheric pressure at room temperature for 2 h and an additional 10 h with addition of water (1.0 mL) at the same temperature. After removal of the catalyst by using Celite, the filtrate was evaporated in vacuo to leave a crystalline mass, which was recrystallized from aqueous methanol to give **25** (42.8 mg, 77%) as colorless needles: mp 264 °C dec (lit.[13] mp 276 °C dec); $[\alpha]^{27}_D$ −13.7° (*c* 0.1, H_2O) [lit.[13] $[\alpha]^{17}_D$ −10.0 (±1.0) (*c* 0.5, H_2O)]; IR (Nujol) 3550, 3430, 1690, 1600 cm^{-1}; ^1H NMR (D_2O) δ 1.33 (s, 3 H), 1.42 (s, 3 H), 2.55–2.61 (m, 1 H), 2.82 (dt, *J* = 12, 8 Hz, 1 H), 3.14–3.30 (m, 3 H), 3.76 (dd, *J* = 12, 9 Hz, 1 H), 3.99 (d, *J* = 3.5 Hz, 1 H); MS, *m/e* 213 (M^+), 168 (100).

Kainic Acid Lactone Methyl Ester (26). To a solution of **24** (108 mg, 0.31 mmol) in MeOH (2 mL) was added an excess of ethereal diazomethane at 0 °C. After the excess diazomethane was blown off by bubbling nitrogen, the reaction mixture was evaporated in vacuo to leave the ester carbamate (90 mg) as a colorless oil, which was immediately hydrogenolized over 10% palladized charcoal (9.0 mg) in MeOH (1.5 mL) under atmospheric pressure at room temperature for 70 min. After filtration through Celite, the filtrate was evaporated in vacuo to leave a faint yellow oil, which was chromatographed on a silica gel column (MeOH–Et_3N–CH_2Cl_2, 5:0.5:95 v/v) to give **26** (54.1 mg, 76%): $[\alpha]^{22}_D$ +15.3° (*c* 0.63, $CHCl_3$); IR (film) 3350, 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.39 (s, 3 H), 1.48 (s, 3 H), 2.18 (br s, 1 H, exchangeable), 2.40 (ddd, *J* = 8.8, 8.4, 8.4 Hz, 1 H), 2.56 (dd, *J* = 20, 8.3 Hz), 2.80–2.86 (m, 1 H), 2.82–2.90 (m, 1 H), 2.89 (dd, *J* = 11.3, 8.8 Hz, 1 H), 3.32 (dd, *J* = 11.3, 8.4 Hz, 1 H), 3.51 (d, *J* = 4.0 Hz, 1 H), 3.78 (s, 3 H); MS, *m/e* 228 (M^+ + 1), 168 (100); calcd for $C_{11}H_{17}NO_4$ 227.1157, found 227.1162.

Kainic Acid Lactone Methyl Ester (26) from Natural Kainic Acid (1). A solution of natural kainic acid (95 mg, 0.45 mmol) in concentrated H_2SO_4 (0.3 mL) was stirred at room temperature for 2.5 h, and to this stirred mixture was added MeOH (4 mL) in one portion and the mixture was stirred at the same temperature for 20 h. After being neutralized by addition of 5% $NaHCO_3$, the mixture was diluted with CH_2Cl_2 and water. The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were washed (brine), dried ($MgSO_4$), and evaporated in vacuo to leave a yellow oil, which was chromatographed on a silica gel column (MeOH–Et_3N–CH_2Cl_2, 5:0.5:95 v/v) to give **26** (31.8 mg, 31%) as a colorless oil: $[\alpha]^{22}_D$ +15.1° (*c* 0.64, $CHCl_3$). Spectral data were in all respects identical with those of the synthetic material.

(2*R*,3*RS*)-1-(Benzyloxy)-3,4-(isopropylidenedioxy)-2-(*N*-methyl-*N*-prenylamino)butane (15). To a stirred solution of **14** (540 mg, 1.19 mmol) in THF (10 mL) was added $LiAlH_4$ (100 mg, 2.63 mmol) portionwise at 0 °C, and the mixture was kept stirring at room temperature for 16 h. After decomposition of the remaining hydride by addition of 28% NH_4OH, the mixture was filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated in vacuo to leave a yellow oil, which was chromatographed on a silica gel column (AcOEt–hexane, 1:15 v/v) to give **15** (360 mg, 91%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 1.38 (s, 3 H), 1.60 (s, 3 H), 1.71 (d, *J* = 1 Hz, 3 H), 2.29 (s, 3 H), 2.62–3.01 (m, 1 H), 3.18 (br d, *J* = 6.8 Hz, 2 H), 3.63–4.28 (m, 5 H), 4.52 (s, 2 H), 5.0–5.34 (m, 1 H), 7.33 (s, 5 H); MS, *m/e* 333 (M^+), 91 (100); calcd for $C_{20}H_{31}NO_3$ 333.2302, found 333.2330.

(2*S*,3*S*,4*R*)-[1-(Benzyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]ethyl]-4-(1-hydroxy-1-methylethyl)]-3-pyrrolidineacetic Acid Lactone (30). To a stirred solution of **23** (95 mg, 0.29 mmol) in CH_2Cl_2 (2 mL) were added sequentially Et_3N (0.06 mL, 0.43 mmol), 4-(*N*,*N*-dimethylamino)pyridine (3.7 mg, 0.03 mmol), and *tert*-butyldimethylchlorosilane (52.6 mg, 0.35 mmol) at 0 °C, and the mixture was kept stirring at room temperature for 25 h. After low volatiles were removed under vacuum, the residue was chromatographed on a silica gel column (AcOEt–hexane, 1:8 v/v) to give **30** (107 mg, 83%) as a colorless oil: $[\alpha]^{29}_D$ −15.6° (*c* 1.01, $CHCl_3$); IR (film) 1725, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ −0.16 to 0.17 (m, 6 H), 0.86 (s, 9 H), 1.35 (s, 3 H), 1.45 (s, 3 H), 1.88–2.48 (m, 1 H), 2.48–3.06 (m, 3 H), 3.06–3.87 (m, 5 H), 5.03–5.32 (m, 2 H), 7.35 (s, 5 H); MS, *m/e* 448 (M^+ + 1), 447 (M^+), 91 (100); calcd for $C_{24}H_{28}NO_5Si$ (M^+ + 1) 448.2520, found 448.2541.

(2*S*,3*S*,4*R*)-1-(Benzyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-3-(2-hydroxyethyl)-4-(1-hydroxy-1-methylethyl)pyrrolidine (31). A mixture of **30** (107 mg, 0.24 mmol) and $NaBH_4$ (20 mg, 0.53 mmol) in 2-propanol (2 mL) was refluxed for 40 min. After the excess hydride was decomposed by addition of 10% HCl, the mixture was made basic with 5% $NaHCO_3$ and extracted with ether and methylene chloride. The combined extracts were dried ($MgSO_4$) and evaporated in vacuo to leave a colorless oil, which was chromatographed on a silica gel column (AcOEt–hexane, 2:5 v/v) to give **31** (105 mg, 97%) as a colorless oil: $[\alpha]^{30}_D$ −35.4° (*c* 1.00, $CHCl_3$); IR (film) 3450, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.03 (s, 3 H), 0.07 (s, 3 H), 0.86 (s, 6 H), 0.89 (s, 3 H), 1.26 (s, 3 H), 1.35 (s, 3 H), 1.85–3.09 (m, 6 H, 2 H exchangeable), 3.09–4.03 (m, 7 H), 5.14 (br s, 2 H), 7.36 (br s, 5 H); MS, *m/e* 451 (M^+), 91 (100), 394 (M^+ − 57); calcd for $C_{20}H_{32}NO_5S$ (M^+ − 57) 394.2050, found 394.2009.

(2*S*,3*S*,4*S*)-3-(2-Acetoxyethyl)-1-(benzyloxycarbonyl)-2-[[(*tert*-butyldimethylsilyl)oxy]methyl]-4-isopropenylpyrrolidine (32). A solution of

31 (9.0 mg, 0.02 mmol) in acetic anhydride (5 mL) in a sealed tube was heated at 270 °C (bath temperature) for 2 h. After removal of low volatiles under vacuum, the residue was chromatographed on a silica gel column (AcOEt-hexane, 1:8 v/v) to give **32** (8.0 mg, 85%): $[\alpha]^{30}_D$ -36.1° (*c* 0.72, $CHCl_3$); IR (film) 1720, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) δ -0.10 to 0.15 (m, 6 H), 0.84 (s, 3 H), 0.86 (s, 3 H), 0.88 (s, 3 H), 1.02-1.83 (m, 5 H), 2.02 (s, 3 H), 2.08-2.68 (m, 1 H), 2.70-4.40 (m, 8 H), 4.54-4.75 (m, 1 H), 4.85-5.03 (m, 1 H), 5.03-5.24 (m, 2 H), 7.35 (s, 5 H); MS, *m/e* 475 (M^+), 91 (100). Anal. Calcd for $C_{26}H_{41}NO_5Si$: C, 65.65; H, 8.69; N, 2.94. Found: C, 65.68; H, 8.74; N, 3.03.

(2*S*,3*S*,4*S*)-1-(Benzyloxycarbonyl)-3-(2-hydroxyethyl)-2-(hydroxymethyl)-4-isopropenylpyrrolidine (34). A mixture of **32** (55 mg, 0.12 mmol) and K_2CO_3 (32 mg, 0.23 mmol) in methanol (1.5 mL) was stirred at room temperature for 1 h. After the mixture was diluted with CH_2Cl_2 and water, the organic layer was separated and the aqueous layer was further extracted with CH_2Cl_2. The combined organic layers were washed (brine), dried ($MgSO_4$), and evaporated in vacuo to leave crude **33** (51 mg), which was used immediately.

To a stirred solution of **33** (51 mg) in THF (1.5 mL) was added 1 N *n*-Bu_4NF-THF solution (0.22 mL, 0.22 mmol) at 0 °C, and the mixture was stirred at room temperature for 40 min. After the mixture was diluted with ether and water, the organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and evaporated in vacuo to leave a colorless oil, which was chromatographed on a silica gel column (AcOEt-hexane, 2:1 v/v) to give **34** (35.8 mg, 92%): $[\alpha]^{30}_D$ -43.3° (*c* 0.56, $CHCl_3$); IR (film) 3400, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95-1.74 (m, 2 H), 1.64 (br s, 3 H), 1.94-2.42 (m, 1 H), 2.64 (br s, 2 H, exchangeable), 2.61-2.96 (m, 1 H), 3.24-3.95 (m, 7 H), 4.58 (br s, 1 H), 4.82 (br s, 1 H), 5.07 (s, 2 H), 7.28 (s, 5 H); MS, *m/e* 319 (M^+), 91 (100); calcd for $C_{18}H_{25}NO_4$ 319.1783, found 319.1769.

1-(Benzyloxycarbonyl)kainic Acid (35). To a stirred solution of **34** (32 mg, 0.1 mmol) in acetone (1 mL) was added 8 N Jones reagent (0.125 mL, 1.00 mmol) at 0 °C, and the stirring was continued at the same temperature for 5 min. The mixture was then raised to room temperature (10 min) and, after the addition of water (five drops), stirred for 90 min at the same temperature. The excess oxidant was quenched by addition of 2-propanol (0.5 mL), and the mixture was diluted with ether and water. The organic layer was separated, and the aqueous layer was further extracted with ether. The combined organic layers were washed (brine), dried ($MgSO_4$), and evaporated in vacuo to leave the diacid **35** (34 mg): IR (film) 3100, 2950, 1700, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.71 (br s, 3 H), 1.94-2.58 (m, 2 H), 2.67-4.00 (m, 4 H), 4.18-4.56 (m, 1 H), 4.56-4.82 (m, 1 H), 4.96 (br s, 1 H), 5.05-5.27 (m, 2 H), 7.14-7.50 (m, 5 H), 7.50-8.07 (br s, 2 H, exchangeable); MS, *m/e* 347 (M^+), 91 (100); calcd $C_{18}H_{21}NO_6$ 347.1369, found 347.1362.

1-(Benzyloxycarbonyl)kainic Acid Dimethyl Ester (36). A solution of **35** (34 mg) in methanol (1 mL) was treated with an excess of ethereal diazomethane. After the excess diazomethane was blown off, the reaction mixture was evaporated to leave an oily residue, which was chromatographed on a silica gel column (AcOEt-hexane, 1:4 v/v) to give **36** (23 mg, 61% overall) as a colorless oil: $[\alpha]^{30}_D$ -25.2° (*c* 1.03, $CHCl_3$); IR (film) 1740, 1700 cm^{-1}; ^1H NMR ($CDCl_3$) 1.16-1.92 (m, 1 H), 1.69 (s, 3 H), 2.25 (d, *J* = 3.4 Hz, 1 H), 2.32 (s, 1 H), 2.56-3.23 (m, 2 H), 3.23-4.03 (m, 7 H), 4.16-4.34 (m, 1 H), 4.57-4.82 (m, 1 H), 4.82-5.00 (m, 1 H), 5.00-5.32 (m, 2 H), 7.18-7.52 (m, 5 H); MS, *m/e* 375 (M^+), 91 (100); calcd for $C_{20}H_{25}NO_6$ 375.1682, found 375.1697.

(-)-Kainic acid (1). A mixture of **36** (141 mg, 0.38 mmol) and 38% NaOH (3.4 mL) in MeOH (2 mL) was refluxed for 14 h. After being cooled, the mixture was diluted with CH_2Cl_2 and water. The aqueous layer was separated and washed with CH_2Cl_2. The aqueous layer was then filtered through two separate columns of ion-exchange resin [Amberlite IRA-45 (OH^- form), H_2O then 1 N HCO_2H and Amberlite CG-120 (H^+ form), H_2O] to give a colorless solid, which was recrystallized from aqueous MeOH to give **1** (32.4 mg, 40%) as colorless needles: mp 243-244 °C dec (lit.[15] mp 250-252 °C dec); $[\alpha]^{27}_D$ -14.2° (*c* 0.23, H_2O) [lit.[15] $[\alpha]^{20}_D$ -14° (*c* 1, H_2O)]; IR (Nujol) 3500, 3130, 2600, 1680, 1600 cm^{-1}; ^1H NMR (D_2O δ 1.76 (s, 3 H), 2.20-2.57 (m, 2 H), 2.80-3.82 (m, 4 H), 4.11 (d, *J* = 3.6 Hz, 1 H).

1-(Benzyloxycarbonyl)kainic Acid Dimethyl Ester (36) from Natural Kainic Acid (1). To a stirred solution of natural **1** (103 mg, 0.48 mmol) in a mixture of 2 N NaOH (0.85 mL) and dioxane (0.36 mL) was added benzyl chlorocarbonate (90%, 0.09 mL, 0.57 mmol) at 0 °C, and the mixture was stirred for 10 min at the same temperature and for 5 h at room temperature. After the mixture was diluted with ether and water, the aqueous layer was separated. The aqueous layer was then made acidic by addition of concentrated HCl and extracted with CH_2Cl_2. The extract was washed (brine), dried ($MgSO_4$), and evaporated to give the crude carbamate **35** (157 mg) as an amorphous solid, which was used immediately.

A stirred solution of the crude **35** (157 mg) in MeOH (3 mL) was treated with an excess of ethereal diazomethane. After the excess diazomethane was blown off, the solution was evaporated in vacuo to leave a yellow oil, which was chromatographed on a silica gel column (AcOEt-hexane, 1:4 v/v) to give **36** (145 mg, 80%) as a colorless oil: $[\alpha]_D$ -26.0° (*c* 1.03, $CHCl_3$). Spectral data were in all respects identical with those of the synthetic material.

(2*S*,3*S*,4*S*)-1-(Benzyloxycarbonyl)-3-(2-hydroxyethyl)-2-(hydroxymethyl)-4-isopropenylpyrrolidine (34) from Natural Kainic Acid (1). To a stirred solution of **36** [238 mg, 0.63 mmol, obtained from natural kainic acid (**1**)] in THF (5 mL) was added $LiAlH_4$ (30 mg, 0.79 mmol) portionwise at 0 °C, and the mixture was stirred at the same temperature for 1 h. The mixture was treated with 28% NH_4OH at 0 °C to decompose the excess hydride and the mixture, after being stirred for 8 h, was filtered through Celite. The filtrate was dried ($MgSO_4$) and evaporated in vacuo to leave a pale yellow oil, which was chromatographed on a silica gel column (AcOEt-hexane, 2:1 v/v) to give **34** (152 mg, 75%) as a colorless oil: $[\alpha]^{29}_D$ -46.5° (*c* 0.56, $CHCl_3$). Spectral data were in all respects identical with those of the synthetic material.

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Synthesis of (±)-Fredericamycin A

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Abstract: The synthesis of (±)-fredericamycin A (**1**) and supporting studies are reported with full experimental detail. Model studies on the construction of the parent spiro system (**25**) from dimethyl phthalate and the anion of indene are described. Preparation of synthons for the upper (**59**) and lower (**82**) units of **1** and investigations into controlling the regiochemistry of their coupling are delineated. The regiospecific union of **59** and **82** and the elaboration of the resulting product (**86**) into **1** are presented.

In 1981 scientists at the Frederick Cancer Research Center in Frederick, Maryland, reported the isolation[1] of a red substance with promising activity[2] in a variety of in vitro anticancer screens. The structure of the substance, appropriately christened fre-

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