A Concise, Stereocontrolled Thiazolium Ylide Approach to Kainic Acid

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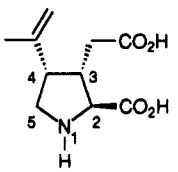
Racemic α-kainic acid (1) has been prepared from (1*SR*,2*SR*,5*RS*)-ethyl (*N*-(benzyloxycarbonyl)-3-aza-6-oxobicyclo[3.3.0]octane-2-carboxylate (11) in ca. 16% overall yield via a concise six-step synthetic sequence. Compound 11 is prepared on a large scale in 50% yield via the [3 + 2] cycloaddition of thiazolium ylide 9 and 2-cyclopentenone, which provides the requisite 2,3-*trans*, 3,4-*cis* stereochemical array about the trisubstituted pyrrolidine nucleus in 1. Chemoselective addition of the one-to-one adduct of MeLi and $TiCl_4$ to the ketone functionality in 11 followed by dehydration, oxidative ring opening, and nonbasic methylenation of the stereochemically labile C4 acetate moiety with CH_2I_2–Zn–$TiCl_4$ affords the fully protected penultimate intermediate 17 which is exhaustively hydrolyzed to provide 1. This represents a highly efficient and stereocontrolled preparation of (±)-α-kainic acid.

Introduction

The potent marine neurotoxin, α-kainic acid [(2*S*,3*S*,4*S*)-2-carboxy-4-isopropenylpyrrolidine-3-acetic acid (1)], is an extremely valuable tool in the study of excitatory amino acid receptors in the mammalian central nervous system.[1]



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The total synthesis of 1 has been reported by a number of laboratories.[2-7] Conceptually, approaches to the construction of the 2,3,4-trisubstituted pyrrolidine nucleus may be divided into two types: (a) via C3–C4 bond formation by intramolecular ene reaction,[2] cobalt-mediated free radical intramolecular cyclization,[3] intramolecular hetero Diels–Alder reaction,[4] intramolecular Pauson–Khand reaction,[5] or Michael reaction;[6] and (b) via simultaneous C2–C3 and C4–C5 bond formations utilizing an intramolecular azomethine ylide cycloaddition approach.[7] A potentially attractive, yet unrealized route to 1 involves the formation of the 2,3,4-trisubstituted pyrrolidine nucleus via intermolecular [3 + 2] cycloaddition of an azomethine ylide to a suitably substituted olefin. If successful, a cycloaddition of this type could furnish the desired three contiguous stereocenters present in 1 in the requisite C2,C3-*trans* and C3,C4-*cis* arrangement from relatively simple synthetic precursors; however, cycloaddition of the azomethine ylide formed by thermolysis of methyl *N*-benzylaziridine-2-carboxylate (2) with *Z*-olefin 3 has been reported[8] (Scheme 1) to afford only a 42% isolated yield of cycloadducts **4a–c**, with the majority (**4a** + **4b**, 80%) of the isolated product mixture bearing a C3,C4-*trans* relationship, presumably due to isomerization of 3 prior to cycloaddition.

One approach toward circumventing this problem (Scheme 2) involves the cycloaddition of an azomethine ylide of type 5 with 2-cyclopentenone, yielding a bicyclic adduct of type 6 in which the potentially labile C4 stereocenter (kainate numbering) is geometrically fixed in a *cis*-orientation with respect to C3 by virtue of the stereochemical requirements of the conformationally restricted 3-azabicyclo[3.3.0]octane nucleus.[9] Chemoselective addition of a methyl anion equivalent to the ketone functionality of 6 followed by dehydration should provide a trisubstituted olefin of the type 7 which may then be oxidatively cleaved and ultimately converted to 1. We now report a concise, stereocontrolled, and high yielding preparation of (±)-α-kainic acid through the successful application of this approach.

Results and Discussion

Kraus and Nagy were the first to report the successful tandem cycloaddition–cyclization of thiazolium ylide 9 (prepared in situ from thiazolium bromide 8 and triethyl-

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(1) Takemoto, T.; Shinozaki, H.; Watkins, J. C.; Cox, D. W. G.; Bradford, H. F.; Olney, J. W.; McGeer, P. L.; McGeer, E. G.; Hattori, T.; Coyle, J. T.; Schwarcz, R.; Fibiger, H. C.; Biziere, K.; Herndon, R. M.; de Gubareff, T.; Nadler, J. V.; Perry, B. W.; Cotman, C. W.; Price, M. T. In *Kainic Acid as a Tool in Neurobiology*; McGeer, E. G., Olney, J. W., McGeer, P. L., Eds.; Raven Press: New York, 1978; pp 1–263.

(2) (a) Oppolzer, W.; Andres, H. *Helv. Chim. Acta* **1979**, *62*, 2282–2284. (b) Oppolzer, W.; Thirring, K. *J. Am. Chem. Soc.* **1982**, *104*, 4979–4981.

(3) (a) Baldwin, J. E.; Li, C-S. *J. Chem. Soc., Chem. Commun.* **1987**, 166–168. (b) Baldwin, J. E.; Moloney, M. G.; Parsons, A. F. *Tetrahedron* **1990**, *46*, 7263–7282.

(4) Takano, S.; Sugihara, T.; Satoh, S.; Ogasawara, K. *J. Am. Chem. Soc.* **1988**, *110*, 6467–6471.

(5) (a) Takano, S.; Inomata, K.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1992**, 169–170. (b) Yoo, S-e; Lee, S-H; Jeong, N; Cho, I. *Tetrahedron Lett.* **1993**, *34*, 3435–3438.

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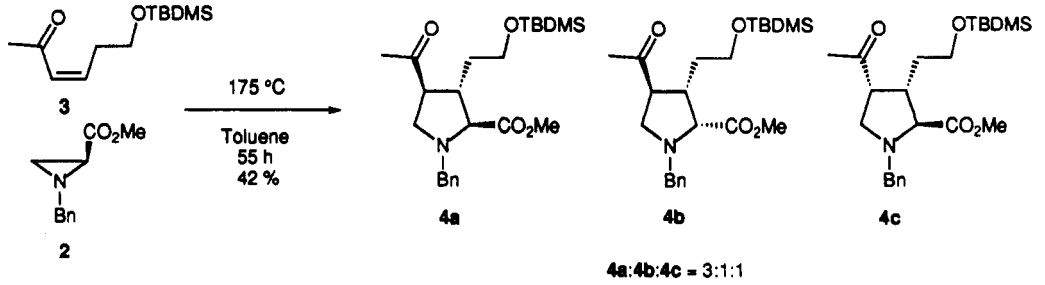
(7) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 1204–1206.

(8) DeShong, P.; Kell, D. A. *Tetrahedron Lett.* **1986**, *27*, 3979–3982.

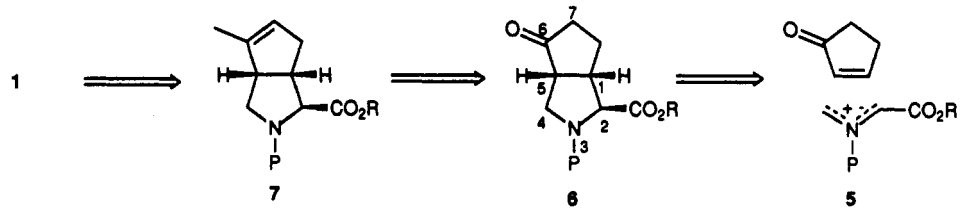
(9) This approach has been previously proposed; however, successful cycloaddition to 2-cyclopentenone was not achieved by these investigators: Husinec, S.; Porter, A. E. A.; Roberts, J. S.; Strachan, C. H. *J. Chem. Soc., Perkin Trans. 1* **1984**, 2517–2522.

0022-3263/94/1959-2773$04.50/0

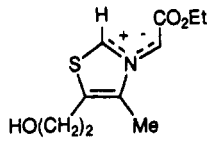
Scheme 1



Scheme 2



amine) with 2-cyclopentenone, yielding the tetracycle **10**, although no experimental details or physical data for this particular cycloadduct were provided.[10] Utilizing this



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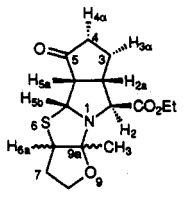
procedure, we have successfully prepared a separable mixture of tetracycles **10a** and **10b** (6.8:1) on a large scale (up to 1.5 mol) in excellent (70–80%) isolated yields (Scheme 3).[11,12] Since the 3-thiotetrahydrofuranyl portions of **10a** and **10b** are excised from the remainder of the molecule in the subsequent sequence of reactions, separation of diastereomers **10a** and **10b** was not routinely performed. Reductive cleavage of the thiazoline C–S bond with tri-*n*-butyltin hydride[10] followed by in situ hydrolysis of the resulting hemiaminal and protection of nitrogen as its benzyl carbamate afforded **11** in 64% overall yield from **10**. The relative stereochemistry of the C1, C2, and C5 centers in **11** was firmly established by single-crystal X-ray analysis (included in supplementary material).[12b] Chemoselective addition of the one-to-one adduct of MeLi and $TiCl_4$[13] to the ketone moiety in **11** furnished an 87% yield of the tertiary carbinol **12** which upon dehydration afforded a single trisubstituted olefin **13** (93%). Oxidative ring opening of **13** with RuO_4 under Sharpless conditions[14] (Scheme 4) and protection of the resulting carboxylic acid as its methyl ester yielded, after purification, the fully protected keto kainate derivative **14** (51% from **13**). Alternatively, catalytic osmylation of **13** afforded an inseparable mixture of diols **15** (98%) which was subjected to periodate cleavage yielding keto aldehyde **16** (97%). Buffered permanganate oxidation of **16**[15] and esterification furnished **14** (35% from **13**).

The C4 stereocenter of **14** was found to be extremely labile, with even silica gel effecting a significant degree of epimerization during purification of this ketone (see Experimental Section). Thus, it was not surprising that Wittig methylenation of **14** produced an approximately 1:2 mixture of α-kainate:α-*allo*-kainate diastereomers **17** and **18** in 85% yield.[16] All attempts to separate the isomers on a preparative scale were unsuccessful. Therefore, we

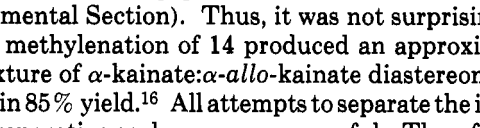
(10) Kraus, G. A.; Nagy, J. O. *Tetrahedron* **1985**, *41*, 3537–3545.

(11) The structural assignments for cycloadducts **10a** and **10b** were made on the basis of the following NOE results (arbitrary numbering system as shown). Thus, for **10a**, irradiation of the 9a-CH_3 (δ 1.56 ppm) shows NOEs at H_{5b} (δ 5.37 ppm) and H_{6a} (δ 3.82 ppm), requiring that they all be situated on the same face of the molecule. NOEs are observed to H_{2a} (δ 3.21 ppm) and H_{5b} when H_{5a} (δ 3.26 ppm) is irradiated, indicating that they too are on the same face of the molecule. There is only a very weak or no NOE to H_2 (δ 4.01 ppm) when H_{2a} is irradiated, allowing a *trans* relationship to be assigned between these protons. This assignment is strengthened by the observation of an NOE to H_2 from $H_{3\alpha}$ (δ 2.17 ppm) and $H_{4\alpha}$ (δ 2.67 ppm). Thus, for **10a**, the 9a-CH_3 and each of the ring juncture protons (H_{2a}, H_{5a}, H_{5b}, and H_{6a}) are aligned on the β-face of the molecule, and H_2 is situated on the α-face. For **10b**, irradiation of the 9a-CH_3 (δ 1.55 ppm) results in NOEs at H_2 (δ 3.72 ppm) and H_{6a} (δ 3.83 ppm), establishing that, unlike **10a**, the 9a-CH_3, H_2, and H_{6a} all reside on the same face of the molecule. Irradiation of H_{5a} (δ 3.41 ppm) evokes NOEs from H_{2a} (δ 3.22 ppm) and H_{5b} (δ 5.61 ppm) as seen in **10a**, and no NOE is seen between H_2 and H_{2a}. Finally, there is observed an NOE to H_2 from $H_{3\alpha}$ (δ 2.09 ppm) and $H_{4\alpha}$ (δ 2.59 ppm). These data indicate that for **10b**, H_{6a} and 9a-CH_3 are situated on the α-face of the molecule, with the remainder of **10b** existing in the same stereochemical configuration as in **10a**.



10a: 9a-$CH_3(\beta)$, $H_{6a}(\beta)$
10b: 9a-$CH_3(\alpha)$, $H_{6a}(\alpha)$

(12) (a) The observed stereochemical outcome for this cycloaddition is presumably due to reaction of the thiazolium ylide **9** in a conformation as represented by **9a**. The alternative conformation, **9b**, is expected to be less favored due to $A_{1,3}$ strain arising from interaction of the ethyl ester with the adjacent methyl substituent



9a **9b**

(b) The author has deposited atomic coordinates for this strucure with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

(13) Reetz, M. T.; Kyung, S. H.; Hullmann, M. *Tetrahedron*, **1986**, *42*, 2931–2935.

(14) Carlsen, H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.*, **1981**, *46*, 3936–3938.

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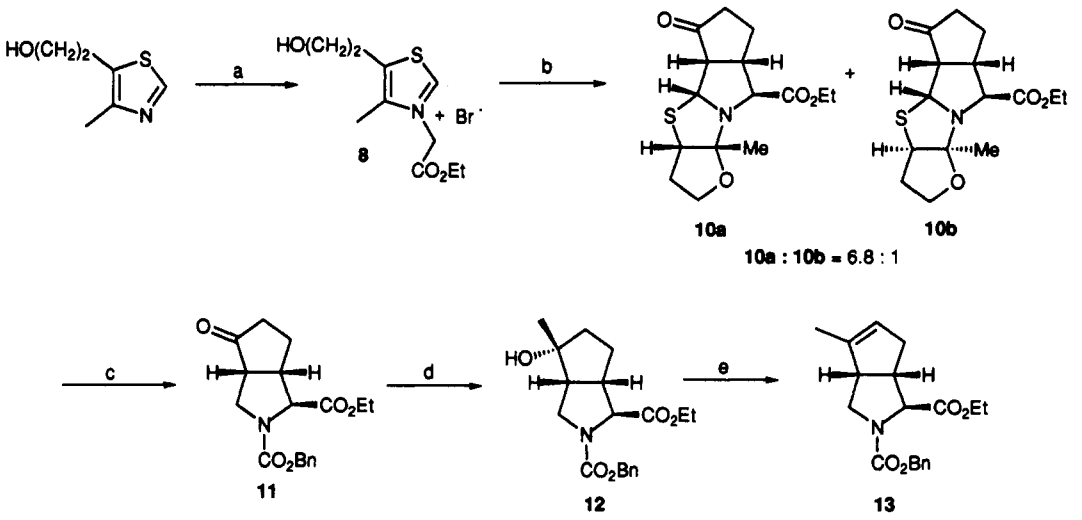
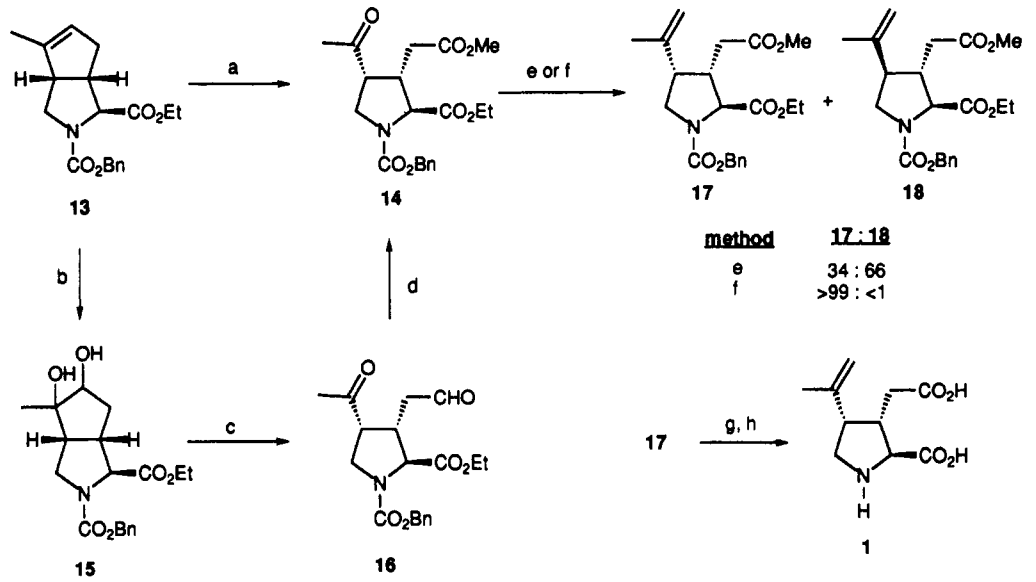
Scheme 3



[a] Reagents and conditions: (a) $BrCH_2CO_2Et$, EtOH, reflux, 73%; (b) 2-cyclopentenone, Et_3N, CH_3CN, rt, 78%; (c) (i) tri-*n*-butyltin hydride, AIBN, toluene, reflux; (ii) HCl, H_2O, rt; (iii) benzyl chloroformate, NaOH, 5 °C, 64%; (d) MeLi, $TiCl_4$, CH_2Cl_2, Et_2O, −50–0 °C, 87%; (e) BF_3–Et_2O, CH_2Cl_2, reflux, 93%.

Scheme 4



[a] Reagents and conditions: (a) (i) RuO_2, $NaIO_4$, CCl_4, CH_3CN, H_2O, rt; (ii) MeI, K_2CO_3, DMF, rt, 51%; (b) OsO_4, *N*-methylmorpholine *N*-oxide, Me_2CO, H_2O, rt, 98%; (c) $NaIO_4$, THF, H_2O, rt, 97%; (d) (i) $KMnO_4$, NaH_2PO_3, *tert*-butyl alcohol, H_2O; (ii) MeI, K_2CO_3, DMF, rt, 37%; (e) Ph_3PCH_3Br, $KN(SiMe_3)_2$, toluene, 5 °C, 85%; (f) CH_2I_2, Zn, $TiCl_4$, Et_2O, 41%; (g) NaOH, H_2O, reflux; (h) ion exchange chromatography (Dowex 50X8–100 cation exchange resin, 5% aqueous pyridine eluent, 97%).

sought a method for conversion of **14** to **17** without accompanying epimerization. The nonbasic reagents CH_2X_2–Zn–$TiCl_4$ (X = I or Br)[17] have been reported to be useful in methylenation of readily enolizable ketones. We were pleased to find that reaction of **14** with CH_2I_2–Zn–$TiCl_4$ in THF at room temperature afforded a 41% yield of **17** without evidence of contamination of the *allo*-kainate isomer **18**.[16] Alkaline hydrolysis of **17** followed by cation-exchange chromatography (97%) then completed the preparation of **1**, which was identified by comparison to authentic α-kainic acid.

The synthesis described herein represents an extremely short, highly efficient method for the preparation of α-kainic acid in ca. 8% overall yield from 2-cyclopentenone. Of particular importance in the present synthesis is the creation of the appropriate stereochemical relationships between the three contiguous stereocenters (C2,C3-*trans*; C3,C4-*cis*) of the trisubstituted pyrrolidine in a single, facile cycloaddition reaction between thiazolium ylide **9** and 2-cyclopentenone. The four-step, two-pot sequence from 2-cyclopentenone to the fully protected azabicyclooctanone **11** has been performed on a large scale in ca.

(16) The ratio of diasteriomers **17** and **18** was quantitatively assigned based on peak ratios in the analytical SiO_2 HPLC chromatogram (eluent, hexane:$CHCl_3$ 95:5 to hexane:$CHCl_3$ 50:50; 10-min linear gradient, and then an additional 10 min with hexane:$CHCl_3$ 50:50). Structural assignments were made based on comparison of the ^1H NMR spectra of authentic kainic acid (Sigma Chemical Co.) with the hydrolysis products derived from the mixture of **17** and **18** (from Wittig methylenation) and from the single isomer **17** (from CH_2I_2–Zn–$TiCl_4$ methylenation).

(17) (a) Takai, K.; Hotta, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1978**, 2417–2420. (b) Imagawa, T.; Sonobe, T.; Ishiwari, H.; Akiyama, T.; Kawanisi, M. *J. Org. Chem.* **1980**, *45*, 2005–2006. (c) Lombardo, L. *Tetrahedron Lett.* **1982**, *23*, 4293–4296. (c) Hibino, J-i; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.*, **1985**, *26*, 5579–5580.

50% yield. Transformation of 11 to 1 was accomplished in a straightforward manner wherein the effective maintenance of the epimerization-prone C4 stereocenter in 14 was achieved via application of a nonbasic methylenating reagent (CH_2I_2–Zn–$TiCl_4$).

Experimental Section

General Procedures. Melting points were obtained using a Thomas-Hoover capilliary melting point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained at 300.15 and 75.48 MHz, respectively, with TMS as an internal standard. Field desorption mass spectroscopy (FDMS) was performed using either a VG 70SE or Varian MAT 731 instrument. Analytical silica gel HPLC was performed on a Rainin HPLC instrument utilizing a 4.6 × 250 mm steel column (Microsorb, 5-μm SiO_2 (100 Å pore size)). Eluent systems are provided for the individual examples. Preparative HPLC was performed with the Waters Prep LC/500 apparatus using dual silica gel prep-pack cartridges. Gradient solvent systems were employed as listed in the particular example. Analytical reverse-phase liquid chromatography was performed utilizing a Waters HPLC system employing a Waters Nova-Pak C18 column (8 × 100 mm, 6-μm spherical particles). Preparative reverse-phase HPLC was performed with a Waters Delta Prep 3000 instrument employing a Waters Nova-Pak C18 column (300 mm × 40 mm, 6-μm spherical particles). Preparative centrifugal thin-layer chromatography (PC-TLC) was performed on a Harrison Model 7924A Chromatotron using Analtech silica gel GF rotors. The plate thickness and solvent system employed are indicated in the particular example. Thin-layer chromatography (TLC) was performed using silica gel-coated glass plates (EM Science, 5 × 10 cm, 0.25 mm layer thickness) employing the solvent system indicated in the particular example.

Preparation of Thiazolium Bromide 8.[10] A solution of 4-methyl-5-thiazoleethanol (306 g, 2.09 mol) and ethyl bromoacetate (356.2 g, 2.09 mol) in ethanol (1 L) was warmed under reflux for 2 h. The ethanol was removed by distillation and 2-propanol (1.5 L) was added. Cooling at 0 °C for 3 h effected crystallization of 476 g of **5** (73%): mp 96–98 °C; FDMS (230, M^+ – Br). Anal. Calcd for $C_{10}H_{16}BrNO_3S$: C, 38.72; H, 5.20; N, 4.52. Found: C, 38.64; H, 5.04; N, 4.47.

Cycloaddition of Thiazolium Ylide 9 with 2-Cyclopentenone. Preparation of Tetracycles 10a and 10b. A suspension of the thiazolium salt 8 (20 g, 64.5 mmol) and 2-cyclopentenone (25.0 g, 304.5 mmol) in acetonitrile (30 mL) was treated with triethylamine (7.17 g, 70.9 mmol). The resulting mixture was allowed to stir at rt under N_2 for 24 h. The reaction mixture was partitioned between ether (200 mL) and brine (200 mL), the layers were separated, and the aqueous phase was extracted with ether (3 × 200 mL). The combined organic layers were washed with brine (200 mL), dried (K_2CO_3), and concentrated to a dark-colored oil (17.98 g). Preparative HPLC (gradient elution, hexane:ethyl acetate 4:1 to hexane:ethyl acetate 1:1) afforded 13.6 g of **10a** and 1.98 g of **10b**[11] (combined yield: 78%). **10a**: mp 70–74 °C; ^1H NMR (pyridine-d_5) δ 1.21 (t, J = 7.08 Hz, 3H), 1.56 (s, 3H), 1.72–1.79 (m, 1H), 1.90–2.00 (m, 1H), 2.01–2.10 (m, 1H), 2.13–2.20 (m, 1H), 2.27–2.34 (m, 1H), 2.63–2.71 (m, 1H), 3.18–3.28 (m, 2H), 3.82 (dd, J = 2.75 and 7.32 Hz, 1H), 3.93 (ddd, J = 5.80, 9.16 and 9.16 Hz, 1H), 4.01 (d, J = 7.93 Hz, 1H), 4.09 (ddd, J = 5.80, 9.16 and 9.16 Hz, 1H), 4.20–4.30 (m, 2H), 5.37 (d, J = 7.93 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.27, 23.30, 27.07, 33.35, 38.10, 47.09, 53.36, 59.56, 60.92, 65.37, 70.13, 72.72, 107.33, 172.73, 216.02; FDMS (311, M^+). Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.63; H, 6.87; N, 4.29. **10b**: mp 126–128 °C; ^1H NMR (pyridine-d_5) δ 1.20 (t, J = 7.10 Hz, 3H), 1.55 (s, 3H), 1.95–2.15 (m, 2H), 2.17–2.26 (m, 1H), 2.27–2.37 (m, 2H), 2.55–2.63 (m, 1H), 3.17–3.26 (m, 1H), 3.41 (dd, J = 7.63 and 9.16 Hz, 1H), 3.72 (d, J = 7.02 Hz, 1H), 3.83 (d, J = 5.49 Hz, 1H), 3.81–3.89 (m, 1H), 4.01–4.07 (m, 1H), 4.20–4.30 (m, 2H), 5.61 (d, J = 7.63 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.20, 22.88, 25.77, 34.44, 39.30, 47.70, 53.37, 55.28, 61.37, 66.75, 69.05, 74.28, 109.13, 172.86, 215.53; FDMS (311, M^+). Anal. Calcd for $C_{15}H_{21}NO_4S$: C, 57.86; H, 6.80; N, 4.50. Found: C, 57.56; H, 6.86, N, 4.33.

(1*SR*,2*SR*,5*RS*)-Ethyl *N*-(Benzyloxycarbonyl)-3-aza-6-oxobicyclo[3.3.0]octane-2-carboxylate (11). A solution of the mixture **10a** and **10b** (311 g, 1.0 mol), AIBN (24.6 g, 150 mmol), and tributyltin hydride (360 mL, 1.3 mol) in toluene (1.6 L) under N_2 was warmed under reflux for 6 h, at which time TLC analysis (hexane:ethyl acetate 1:1) indicated complete consumption of starting material. The volatiles were removed by distillation, and the oil which remained was treated with ether (1 L) and 1 N HCl (1.1 L, 1.1 mol). Vigorous stirring of the biphasic mixture was maintained for 14 h at rt. The ether layer was siphoned from the mixture, and the aqueous phase was similarly washed with ether (10 × 1 L). The aqueous phase was then cooled to 5 °C and treated sequentially with ethyl acetate (1 L), benzyl chloroformate (190 g, 1.06 mol), and, dropwise with vigorous stirring, 50% NaOH (170 mL, 2.1 mol). On complete addition of the NaOH, stirring was continued as the system was allowed to warm slowly to rt and remain there for 1 h. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (4 × 1 L). The combined organic extracts were washed with H_2O (1 L), dried ($MgSO_4$), and concentrated *in vacuo* to a red oil (318 g). Purification by preparative HPLC (gradient elution: hexane:ethyl acetate 4:1 to hexane:ethyl acetate 1:1) gave 212 g of **11** as a white solid (64%): mp 66–68 °C; ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.12 and 1.25 (t, J = 7 Hz, 3H), 1.85–2.03 (m, 1H), 2.20–2.41 (m, 3H), 2.75–2.85 (m, 1H), 3.00–3.12 (m, 1H), 3.75–3.88 (m, 2H), 4.00–4.15 (m, 1H), 4.18–4.30 (m, 2H), 4.95–5.20 (m, 2H), 7.21–7.40 (m, 5H). FDMS (331, M^+). Anal. Calcd for $C_{18}H_{21}NO_5$: C, 65.24; H, 6.39; N, 4.23. Found: C, 64.95; H, 6.39; N, 4.27.

(1*SR*,2*SR*,5*RS*,6*RS*)-Ethyl *N*-(Benzyloxycarbonyl)-3-aza-6-hydroxy-6-methylbicyclo[3.3.0]octane-2-carboxylate (12). A solution of ether (100 mL) and CH_2Cl_2 (100 mL) at −78 °C under N_2 was treated sequentially with $TiCl_4$ (45.3 mL of a 1 M solution in CH_2Cl_2, 45.3 mmol) and MeLi (32.3 mL of a 1.4 M solution in ether, 45.3 mmol).[13] The resulting dark solution was allowed to stir at −78 °C for 30 min and then allowed to warm slowly to −50 °C. A solution of **11** (10.0 g, 30.2 mmol) in CH_2Cl_2 (50 mL) was then added dropwise. Upon complete addition, the reaction mixture was allowed to warm slowly to 0 °C and remain there for 2 h, at which time TLC analysis (hexane:ethyl acetate 2:1) revealed complete consumption of **11**. The reaction mixture was poured into ether (300 mL) and H_2O (300 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 100 mL). The combined organic phases were washed with H_2O (200 mL) and brine (200 mL) and then dried ($MgSO_4$) and concentrated *in vacuo* to a pale yellow oil (10.44 g). Purification by preparative HPLC (gradient elution hexane:ethyl acetate 7:1 to hexane:ethyl acetate 1:1) gave 9.12 g of **12** as a colorless oil (87%): ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.15 and 1.25 (t, J = 7 Hz, 3H), 1.30 (s, 3H), 1.61 (br s, 1H), 1.60–1.92 (m, 3H), 2.00–2.19 (m, 1H), 2.38–2.50 (m, 1H), 2.70–2.85 (m, 1H), 3.55–3.65 (m, 1H), 3.78–3.92 (m, 1H), 3.98–4.10 (m, 1H), 4.14–4.26 (m, 2H), 4.97–5.21 (m, 2H), 7.20–7.40 (m, 5H); FDMS (347, M^+). Anal. Calcd for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25; N, 4.03. Found: C, 65.78; H, 7.33; N, 4.08.

(1*SR*,2*SR*,5*SR*)-Ethyl *N*-(Benzyloxycarbonyl)-3-aza-6-methylbicyclo[3.3.0]oct-6-ene-2-carboxylate (13). To a solution of **12** (8.40 g, 24.2 mmol) in CH_2Cl_2 (75 mL) was added $BF_3{\cdot}Et_2O$ (5.0 mL, 40.7 mmol), and the resulting solution was refluxed for 16 h. After cooling to rt, the reaction mixture was poured into ether (200 mL) and H_2O (200 mL), the layers were separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic layers were washed with H_2O until the pH was neutral, dried ($MgSO_4$), and concentrated *in vacuo* to afford 7.45 g of **13** as a pale yellow oil (93%): ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.15 and 1.25 (t, J = 7 Hz, 3H), 1.68 and 1.72 (s, 3H), 2.30–2.43 (m, 1H), 2.59–2.75 (m, 1H), 2.84–2.96 (m, 1H), 3.08–3.17 (m, 1H), 3.58–3.82 (m, 2H), 3.98–4.25 (m, 3H), 4.95–5.20 (m, 2H), 5.15 (s, 1H), 7.00–7.41 (m, 5H); FDMS (329, M^+). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 69.51; H, 6.99; N, 4.15.

(2*SR*,3*SR*,4*SR*)-Methyl *N*-(Benzyloxycarbonyl)-2-(ethoxycarbonyl)-4-acetylpyrrolidine-3-acetate (14). A mixture consisting of $RuO_2{\cdot}H_2O$ (0.45 g, 3.4 mmol, 0.20 equiv) and $NaIO_4$ (14.9 g, 70.0 mmol, 4.1 equiv) in CH_3CN (30 mL), CCl_4 (30 mL) and H_2O (45 mL) was vigorously stirred at rt for 15 min.[14] To

this mixture was added a solution of 13 (5.62 g, 17.1 mmol) in CH_3CN (5 mL) and CCl_4 (5 mL). The black-colored mixture was stirred at rt for 4 h, then partitioned between ether (100 mL) and H_2O (100 mL). The layers were separated, and the aqueous phase was extracted with ether (2 × 100 mL). The combined organic layers were washed with H_2O (2 × 100 mL), dried ($MgSO_4$), filtered through Celite, and concentrated *in vacuo*. The crude carboxylic acid was dissolved in DMF (50 mL) and treated sequentially with K_2CO_3 (3.6 g, 25.7 mmol) and MeI (4.85 g, 34.2 mmol). The reaction mixture was stirred at rt under N_2 for 3 h and then partitioned between ether (300 mL) and 1 N HCl (300 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 200 mL). The combined organic phases were washed with H_2O (500 mL), dried ($MgSO_4$), and concentrated to afford 5.75 g of crude 14. Analytical silica gel HPLC (hexane:5% ethanol in $CHCl_3$ [95:5 to 50:50; 10-min linear gradient and then 50:50 for an additional 10 min]) showed the presence of two components (ratio = 94.3:5.7) with retention times of 12.63 and 13.52 min, respectively. Attempted purification by preparative normal-phase HPLC (100% hexane to hexane:ethyl acetate 3:1; 2-h linear gradient) afforded, after concentration of the fractions containing product, 4.42 g of a colorless oil. Analytical silica gel HPLC (conditions as above) showed the continued presence of the components with retention times of 12.63 and 13.52 min, now in a ratio of 84.4:15.6. An essentially identical ratio was obtained by analytical reverse-phase chromatography (45% CH_3CN in H_2O, eluent), with the products appearing at 6.57 and 7.16 min (14.2:85.8 ratio).[18] Purification of 14 was achieved by preparative reverse-phase HPLC (45% CH_3CN in H_2O, eluent; 200 mg per chromatography). Fractions containing pure 14 were extracted with ether, dried ($MgSO_4$) and concentrated *in vacuo* affording 3.40 g of 14 as a waxy white solid (51%): mp 55–57 °C; ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.15 and 1.30 (t, J = 7 Hz, 3H), 2.20 and 2.22 (s, 3H), 2.43–2.65 (m, 2H), 2.82–3.01 (m, 1H), 3.46–3.79 (m, 1H), 3.68 and 3.70 (s, 3H), 3.71–3.83 (m, 2H), 4.00–4.10 (m, 1H), 4.20–4.30 (m, 2H), 4.95–5.20 (m, 2H), 7.22–7.39 (m, 5H); FDMS (391, M^+). Anal. Calcd for $C_{20}H_{25}NO_7$: C, 61.37; H, 6.44; N, 3.58. Found: C, 61.60; H, 6.68; N, 3.66.

Catalytic Osmylation of 13: Preparation of Diols 15. A vigorously stirred solution of 13 (4.25 g, 12.9 mmol) and *N*-methylmorpholine *N*-oxide (3.84 g, 28.4 mmol) in acetone (125 mL) and H_2O (35 mL) was treated at rt with OsO_4 (ca. 5–10 mg), and the resulting mixture was stirred at rt for 16 h. The reaction mixture was partitioned between ether (200 mL) and H_2O (200 mL). The layers were separated, and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phase was washed with H_2O (200 mL), dried ($MgSO_4$), and concentrated *in vacuo* affording a light-brown oil (5.11 g). Purification (PC-TLC, 4-mm silica gel, gradient elution hexane:ethyl acetate 9:1 to hexane:ethyl acetate 1:2) gave 4.61 g of the mixture of diols 15 (98%) as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.10–1.35 (m, 6H), 1.61–2.00 (m, 1H), 2.03–2.25 (m, 1H), 2.38–3.05 (m, 4H), 3.35–3.80 (m, 2H), 3.86–4.31 (m, 4H), 5.00–5.25 (m, 2H), 7.20–7.45 (m, 5H); FDMS (363, M^+). Anal. Calcd for $C_{19}H_{25}NO_6$: C, 62.80; H, 6.93; N, 3.85; Found: C, 62.68; H, 6.82; N, 3.55.

(2*SR*,3*SR*,4*SR*)-*N*-(Benzyloxycarbonyl)-2-(ethoxycarbonyl)-4-acetylpyrrolidine-3-acetaldehyde (16). To a stirred solution of 15 (4.60 g, 12.7 mmol) in THF (60 mL) was added a solution of $NaIO_4$ (4.10 g, 19.1 mmol) in H_2O (40 mL), and the resulting mixture was stirred vigorously at rt for 3 h. The mixture was partitioned between ether (100 mL) and H_2O (100 mL), the layers were separated and the aqueous phase was extracted with ether (3 × 100 mL). The combined organic phase was washed with H_2O (100 mL), then dried ($MgSO_4$), and concentrated to afford 4.47 g of 16 (97%) as a colorless oil: ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.13 and 1.30 (t, J = 7.0 Hz, 3H), 2.16 and 2.18 (s, 3H), 2.62–3.10 (m, 3H), 3.50–3.60 (m, 1H), 3.69–3.84 (m, 2H), 4.00–4.13 (m, 1H), 4.18–4.35 (m, 2H), 4.95–5.21 (m, 2H), 7.20–7.42 (m, 5H), 9.70 (s, 1H); FDMS (361, M^+). Anal. Calcd for $C_{19}H_{23}NO_6$: C, 63.15; H, 6.41; N, 3.88; Found: C, 63.10; H, 6.57; N, 3.87.

(18) Further evidence that epimerization of 14 occurs on SiO_2 was obtained when pure 14 (from preparative reverse-phase HPLC, see Experimental Section) was subjected to silica gel chromatography. HPLC analysis (normal and reverse phase) of the eluted product revealed the presence of the original two components in a ratio of 87:13.

(2*SR*,3*SR*,4*SR*)-Methyl *N*-(Benzyloxycarbonyl)-2-(ethoxycarbonyl)-4-acetylpyrrolidine-3-acetate (14). A solution of 16 (4.46 g, 12.3 mmol) in *tert*-butyl alcohol (25 mL) was treated seqentially with 5% aqueous NaH_2PO_3 (25 mL) and 1 M $KMnO_4$ (13.5 mL).[15] The reaction mixture was stirred vigorously at rt for 3 h, partitioned between saturated aqueous Na_2SO_3 (100 mL) and ether, and acidified with 2 M $NaHSO_4$ to pH 2. The layers were separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic phase was washed with H_2O until the aqueous extracts were neutral, dried ($MgSO_4$), and concentrated *in vacuo* to a light-yellow oil. Without purification, the foregoing oil was dissolved in DMF (50 mL) and treated sequentially with K_2CO_3 (13.8 g, 100 mmol) and MeI (5.2 g, 37.0 mmol). The resulting mixture was allowed to stir under N_2 at rt for 30 h. The reaction mixture was partitioned between ether (200 mL) and 1 N HCl (200 mL). The layers were separated, and the aqueous layer was extracted with ether (3 × 100 mL). The combined organic phase was dried ($MgSO_4$) and concentrated *in vacuo* to 3.0 g of a yellow oil. Crude 14 was purified by preparative reverse-phase HPLC (as in the previous example) affording 1.78 g of 14 (37%).

(2*SR*,3*SR*,4*SR*)-Methyl *N*-(Benzyloxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenylpyrrolidine-3-acetate (17) by Wittig Methylenation. To a stirred suspension of methyltriphenylphosphonium bromide (7.45 g, 20.9 mmol) in toluene (100 mL) at 5 °C under N_2 was added a 0.5 M solution of potassium bis(trimethylsilyl)amide in toluene (36.6 mL, 18.3 mmol), and the reaction was allowed to continue at 5 °C for 1 h. To a stirred solution of 14 (3.25 g, 8.30 mmol) in toluene (50 mL) at 5 °C under N_2 was added (dropwise, via teflon cannula) the foregoing solution of methyltriphenylphosphonium ylide until the reaction was judged complete (TLC; hexane:ethyl acetate 2:1 eluent). The reaction mixture was partitioned between ether (500 mL), and H_2O (500 mL) and the layers were separated. The aqueous phase was extracted with ether (3 × 200 mL), and the combined organic phase was dried ($MgSO_4$), filtered, and evaporated *in vacuo* affording 6.5 g of a yellow oil. Chromatography (PC-TLC, 4-mm silica gel, hexane:ethyl acetate 9:1 eluent; three equal batches) furnished 2.75 g of 17 and 18 (85%, 17:18 = 1:2).[16]

(2*SR*,3*SR*,4*SR*)-Methyl *N*-(Benzyloxycarbonyl)-2-(ethoxycarbonyl)-4-isopropenylpyrrolidine-3-acetate (17) by Nonbasic Methylenation with CH_2I_2–Zn–$TiCl_4$. To a stirred suspension of zinc metal (3.00 g, 46.0 mmol) and CH_2I_2 (2.06 mL, 25.5 mmol) in THF (80 mL) was added $TiCl_4$ (5.6 mL of a 1.0 M solution in CH_2Cl_2, 5.6 mmol).[17] The resulting black mixture was stirred at rt under N_2 for 1 h and then was treated with a solution of 14 (2.00 g, 5.11 mmol) in CH_2Cl_2 (5 mL). The reaction was allowed to proceed at rt under N_2 for 16 h and then was partitioned between ether (200 mL) and 0.5 N HCl (200 mL). The layers were separated and the aqueous phase was extracted with ether (3 × 200 mL). The combined organic phase was washed with H_2O (200 mL) and brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to a yellow oil (2.11 g). Purification was effected by PC-TLC (4-mm silica gel, hexane:ethyl acetate 9:1 to hexane:ethyl acetate 4:1 gradient elution) affording 0.82 g of 17 as a colorless oil (41%)[16] and 0.27 g of recovered 14 (13.5%): ^1H NMR ($CDCl_3$, doubling due to amide rotamers) δ 1.13 and 1.24 (t, J = 7 Hz, 3H), 1.68 (s, 3H), 2.02–2.31 (m, 2H), 2.83–2.87 (m, 1H), 3.00–3.05 (m, 1H), 3.45–3.57 (m, 1H), 3.66 (s, 3H), 3.69–3.79 (m, 1H), 4.04–4.24 (m, 3H), 4.64–4.69 (m, 1H), 4.89–4.92 (m, 1H), 4.99–5.20 (m, 2H), 7.26–7.35 (m, 5H); FDMS (389, M^+). Anal. Calcd for $C_{21}H_{27}NO_6$: C, 64.77; H, 6.99; N, 3.60; Found: C, 64.99; H, 7.17; N, 3.50.

(2*SR*,3*SR*,4*SR*)-2-Carboxy-4-isopropenylpyrrolidine-3-acetic acid (1). A mixture of 17 (0.64 g, 1.64 mmol) in 2.5 N NaOH (10 mL) was refluxed for 4 days. The pH was adjusted to 2 by addition of 1 N HCl, and the precipitate was filtered. The filtrate was then subjected to cation-exchange chromatography (Dowex 50XB-100, 50–100 dry mesh resin) utilizing 10% aqueous pyridine as the eluent. Evaporation *in vacuo* afforded 0.33 g of 1 (97%) as a white solid: mp 243–245 °C dec; FDMS (213, M^+); ^1H NMR (D_2O + KOD) δ 1.66 (s, 3H), 2.05–2.15 (m, 2H), 2.49–2.60 (m, 1H), 2.65–2.80 (m, 2H), 3.06–3.15 (m, 1H), 3.19 (d, J = 5 Hz, 1H), 4.63 (s, 1H), 4.83 (s, 1H); ^{13}C NMR (D_2O + KOD) δ

22.5, 37.3, 44.2, 47.9, 48.1, 67.1, 112.1, 144.5, 181.6, 181.7. Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57; Found: C, 56.39; H, 7.34; N, 6.54.

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