Synthesis of (±)-Rosaprostol

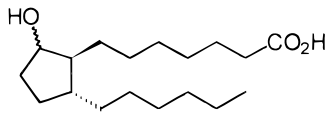
Marian Mikołajczyk* and Remigiusz Żurawiński

Centre of Molecular and Macromolecular Studies, Polish Academy of Sciences, 90-363 Łódź, Sienkiewicza 112, Poland

Received June 11, 1998

A total synthesis of racemic rosaprostol, an untiulcer drug, has been achieved in seven synthetic steps and in 42% overall yield starting from dimethyl methanephosphonate. The key steps include intramolecular carbenoid cyclization of dimethyl 1-diazo-2-oxoundecanephosphonate **4** leading to 2-dimethoxyphosphoryl-3-hexylcyclopentanone **5** and the Horner−Wittig reaction of the latter with methyl 5-formylpentanecarboxylate **6** employed for the introduction of the methoxycarbonylhexyl moiety at C(2) of the cyclopentanone ring.

Our laboratory has been engaged in a program directed toward the invention and development of general methods for the synthesis of functionalized cyclopentanones and cyclopentenones using organic phosphorus and sulfur reagents.[1] These endeavors have culminated in the elaboration of new and efficient routes to dihydrojasmone,[2] *cis*-jasmone,[3] methylenomycin B,[2,4] and recently both enantiomeric forms of isoterrein[5] and sarkomycin.[6] In the synthesis of the latter cyclopentanoid antibiotic the key steps included (a) intramolecular carbenoid cyclization for the construction of the cyclopentanone skeleton and (b) the Horner−Wittig reaction for the introduction of the exocyclic methylene moiety.



(±)-Rosaprostol **1**

To further demonstrate the effectiveness of this strategy for the synthesis of functionalized cyclopentanones, we selected rosaprostol **1,** a trade name for 7-(2-hexyl-5-hydroxycyclopentane)heptanoic acid. The sodium salt of **1** [a mixture of (1*RS*,2*SR*,5*RS*) and (1*RS*,2*SR*,5*SR*) isomers] has been launched in Italy under the name Rosal for the treatment of gastric and duodenal ulcers.[7] It shows gastric antisecretory activity and also cytoprotective action common to naturally occurring prostaglandins; however, it is devoid of their undesirable side effects including diarrhea, hypotension, and uterine stimulation.[8]

The synthetic approaches to rosaprostol **1** are few in number and of low efficiency. To date, four independent syntheses of rosaprostol have been reported. The first patented synthesis of **1** starting from ricinoleic acid involved, in a key step, the base-catalyzed cyclization of 9,12-dioxaoctadecanoic acid to the corresponding cyclopentenone that was elaborated to the final product.[9] In the second, improved (12% overall yield) preparation of **1** a key intermediate was 2-(6-carboxyhexyl)cyclopent-2-enone obtained also in a classical way by intramolecular cyclization of the proper 1,4-keto aldehyde.[10,11] Recently, Shono et al.[14] have reported a more efficient (20% overall yield) approach to **1** where the electroreductive intramolecular coupling of 8-cyano ketone was a crucial step. Another Japanese group[15] obtained rosaprostol **1** in 4% yield from methyl 2-oxobicyclo[3.1.0]hexane-1-carboxylate. Herein, we disclose a conceptually different approach to the synthesis of rosaprostol **1** which enabled the preparation of this drug in a much higher yield using easily available reagents and a simple sequence of reactions.

Results and Discussion

In our synthesis of rosaprostol **1** performed as shown in Scheme 1, readily available dimethyl methanephosphonate **2** was used as a substrate. The α-phosphonate carbanion was treated with a half molar amount of

* Phone: (48-42)681-58-32. Fax: (48-42)684-71-26. E-mail: marmikol@bilbo.cbmm.lodz.pl.

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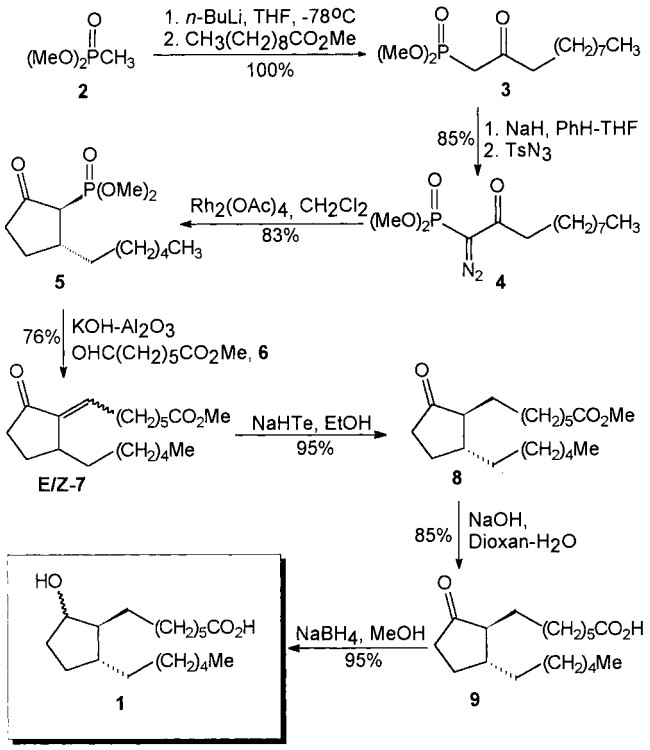
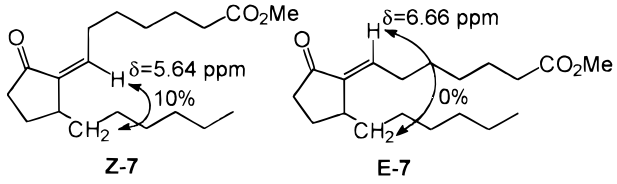
10.1021/jo981120g CCC: $15.00
Published on Web 10/30/1998

Scheme 1



methyl decanoate to produce the corresponding β-keto phosphonate **3**. In the next step **3** was converted under typical diazo-transfer reaction conditions into α-diazo-β-keto phosphonate **4**. This intermediate in the presence of rhodium(II) acetate afforded the desired *trans*-2-dimethoxyphosphoryl-3-hexylcyclopentan-1-one **5** in 83% yield. Both the coupling constant value between protons at C(2) and C(3) equal to $^3J_{H-H} = 8.4$ Hz and the lack of changes in the ^{1}H and ^{31}P NMR spectra of **5** upon heating in the presence of triethylamine are in corroboration of this assignment.

According to our strategy for the synthesis of **1**, the introduction of a proper substituent at the carbon atom C(2) would be accomplished via the Horner−Wittig reaction of **5** with methyl 5-formylpentanecarboxylate **6**.[16] Unexpectedly, our attempt to carry out this reaction under standard conditions (n-BuLi, THF, − 78 °C) led to recovery of the starting phosphonate **5**. Similarly, the use of other base systems like basic Al_2O_3, Al_2O_3/KF,[19] DBU/LiCl/MeCN,[20] DIPEA/LiCl/MeCN,[20] and K_2CO_3/18-crown-6/C_6H_6 failed to give the olefination product. However, we were pleased to find that when a mixture of Al_2O_3 and KOH (obtained by evaporation of Al_2O_3 and saturated water solution of KOH) was used as a base, the desired olefination product **7** was formed in a high yield (76%) as a 1.3:1 *E:Z* mixture. The olefinic methine proton appeared in the spectrum at $\delta = 6.66$ ppm as a double triplet ($^3J_{H-H} = 7.6$ and 1.9 Hz) for one isomer of **7** while the same shape resonance signal at $\delta = 5.64$ ppm ($^3J_{H-H} = 7.6$ and 2.3 Hz) of lower intensity was observed for the other. For characterization and configurational assignment purposes they have been separated by column chromatography. The assignment of *E/Z* geometry to **7** was resting upon NOE experiments. Since irradiation of the α-methylene protons at C(3) induced an enhancement in absorption intensity of the olefinic methine proton resonance signal at $\delta = 5.64$ ppm and the signal of the methine proton $\delta = 6.66$ ppm in the other isomer was not affected, the *Z* geometry was attributed to the first of them.



Next step in the synthesis of rosaprostol **1** required reduction of the enone moiety in **7** to saturated alcohol. It was found, however, that the use of sodium borohydride in pyridine, although effecting ketone and olefin reduction in one step, produced the methyl ester of rosaprostol **1** as a mixture of four diastereomers. Therefore, we decided to separate reduction of the olefin and keto moiety. Treatment of a mixture of **E**- and **Z-7** with sodium hydrogen telluride[21] permitted selective reduction of the olefinic bond and gave the corresponding *trans*-cyclopentanone **8** in 95% yield. Alkaline hydrolysis of the latter to the keto acid **9** and subsequent reduction of the keto group with sodium borohydride allowed us to complete the synthesis of rosaprostol **1** in 42% overall yield. It was obtained as a 1:1 mixture of *trans*−*trans* and *trans*−*cis* stereoisomers, the spectral data of which were essentially consistent with those reported in the literature.

Experimental Section

General Procedures. Tetrahydrofuran was distilled over potassium/benzophenone, and benzene was distilled over Na wire, both immediately prior use. Methylene chloride was distilled over P_2O_5 and stored over anhydrous Na_2CO_3. Oil-free NaH was prepared by a washing mineral oil dispersion twice with hexane. NMR spectra were recorded at 200 MHz for ^{1}H, 81 MHz for ^{31}P, and 50 MHz for ^{13}C with C_6D_6 as solvent, unless noted otherwise. High-resolution mass spectra were recorded using chemical ionization. Column chromatography was done on Merck 60F_{254} silica gel (70−230 mesh), and flash column chromatography was carried out on Merck 60F_{254} silica gel (230−400 mesh). Reaction mixtures were analyzed by TLC using Merck 60F_{254} TLC plates.

Dimethyl 2-Oxoundecanephosphonate (3). To a magnetically stirred solution of dimethyl methanephosphonate **2** (40.0 g, 0.322 mol) in dry THF (650 mL) under nitrogen at −78 °C was added dropwise n-BuLi (128.8 mL, 0.322 mol) in hexane. After 15 min a solution of methyl decanoate (30 g, 0.161 mol) in 100 mL of dry THF was added. The mixture was stirred at −78 °C for an additional 30 min, and then the reaction mixture was allowed to warm to 0 °C. The reaction mixture was quenched by addition of 5% aqueous HCl and

(16) The aldehyde **6** was prepared from the monomethylester of pimelic acid via the acid chloride which was reduced to aldehyde. Since the modified Resenmund reduction of the acid chloride was reported[17] to give the aldehyde **6** in 63% yield, we used bis(triphenylphosphine)-tetrahydroboratocopper (I)[18] as a reducing agent and obtained **6** in 90% yield (see Experimental Section).

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extracted with $CHCl_3$ (3 × 50 mL). The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated under vacuum. An excess of dimethyl methanephosphonate **2** was removed under vacuum using a Kugelrohr apparatus (75 °C/0.01 mmHg). The remaining crude dimethyl 2-oxoundecanephosphonate **3** (44.8 g, 100%, calculated with respect to carboxylic ester) was used without purification for the next reaction. An analytically pure sample was obtained by distillation under reduced pressure: bp 140−2 °C/0.01 mmHg; R_f = 0.17 (hexane/AcOEt 1:1); $n^{20}{}_D$ = 1.4481; ^{31}P NMR δ 23.10; ^{1}H NMR δ 3.37 (d, J = 11.1, 6H), 2.71 (d, J = 22.6, 2H), 2.36 (t, J = 7.2, 2H), 1.64−1.45 (m, 2H), 1.38−1.10 (m, 12H), 0.91 (t, J = 6.5, 3H); ^{13}C NMR δ 202.12, 53.14 (d, J = 5.6), 44.55, 42.03 (d, J = 126.3), 32.88, 30.49, 30.46, 30.32, 29.97, 24.32, 23.65, 14.90; MS (15 eV) *m/e* (%) 278 (M^+, 3), 166 (100); HRMS (CI) $(M + H)^+$ calcd for $C_{13}H_{28}O_4P$ 279.1725, obsd 279.1720.

Dimethyl 1-Diazo-2-oxoundecanephosphonate (4). To a magnetically stirred suspension of NaH (3.9 g; 0.162 mol) in THF (100 mL) and benzene (500 mL) under nitrogen at 0 °C was added dropwise dimethyl 2-oxoundecanephosphonate **3** (41.0 g, 0.147 mol) in benzene (150 mL). After 1.5 h of stirring, tosyl azide (32.0 g, 0.162 mol) in benzene (80 mL) was added and the reaction mixture was allowed to warm to room temperature. After 4 h, the mixture was filtered on a Celite pad, concentrated in vacuo, and chromatographed on silica gel (ethyl acetate−hexane gradient as an eluent) affording dimethyl 1-diazo-2-oxoundecanephosphonate **4** (38.2 g, 85%) as a light yellow liquid: $n^{22}{}_D$ = 1.4683; R_f = 0.35 (hexane/AcOEt 1:1); ^{31}P NMR ($CDCl_3$) δ 15.13; ^{1}H NMR ($CDCl_3$) δ 3.79 (d, J = 11.9, 6H), 2.48 (t, J = 7.4, 2H), 1.65−1.47 (m, 2H), 1.32−1.15 (m, 12H), 0.83 (t, J = 6.5, 3H); ^{13}C NMR ($CDCl_3$) δ 191.97 (d, J = 13.5), 62.23 (d, J = 220.5), 53.06 (d, J = 4.6), 38.92, 31.40, 28.95, 28.92, 28.80, 28.68, 23.82, 22.19, 13.59; MS (15 eV) *m/e* (%) 305 (M^+ + 1, 6), 151 (100); HRMS (CI) $(M + H)^+$ calcd for $C_{13}H_{26}N_2O_4P$ 305.1630, obsd 305.1624.

2-Dimethoxyphosphoryl-3-hexylcyclopentan-1-one (5). To a refluxing solution of the dirhodium (II) tetraacetate (0.19 g, 0.43 mmol) in 400 mL of CH_2Cl_2 was added slowly dimethyl 1-diazo-2-oxoundecanephosphonate **4** (12.5 g, 41 mmol) in 50 mL of CH_2Cl_2. Reflux was continued until disappearance of the substrate (about 2 h, monitored by TLC). After cooling, the resulted solution was washed with water (2 × 30 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (ethyl acetate/hexane gradient as an eluent) affording **5** (9.4 g, 83%) as a colorless liquid: $n^{21}{}_D$ = 1.4619; R_f = 0.20 (hexane/AcOEt 1:1); ^{31}P NMR δ 26.01; ^{1}H NMR δ 3.59 (d, J = 10.8, 3H), 3.40 (d, J = 11.0, 3H), 2.65−2.38 (m, 1H), 2.24 (dd, J = 25.8, J = 8.4, 1H), 2.15−1.75 (m, 3H), 1.70−1.50 (m, 1H), 1.38−0.85 (m, 10H), 0.90 (t, J = 6.6, 3H); ^{13}C NMR δ 211.37 (d, J = 3.4), 53.91 (d, J = 6.6), 53.72 (d, J = 134.8), 52.60 (d, J = 6.8), 39.49, 39.35 (d, J = 4.6), 36.19 (d, J = 5.3), 32.74, 30.21, 28.54 (d, J = 10.6), 27.75, 23.63, 14.93; MS (15 eV) *m/e* (%) 276 (M^+, 5), 191 (100); HRMS (CI) $(M + H)^+$ calcd for $C_{13}H_{26}O_4P$ 277.1568, obsd 277.1559.

Methyl 5-Formylpentanecarboxylate (6). To a stirred solution of bis(triphenylphosphine)tetrahydroboratocopper(I) [$(Ph_3P)_2CuBH_4$] (26.8 g, 0.044 mol) and triphenylphosphine (21.2 g, 0.081 mol) in acetone (130 mL) was added dropwise solution of methyl 5-(chloroformyl)pentanecarboxylate (7.0 g, 0.036 mol) in acetone (50 mL). After 2 h the mixture was filtered and concentrated in vacuo and 50 mL of ethyl ether added. The mixture was filtered once again and concentrated, and the residue was distilled under reduced pressure (bp 68−9 °C/0.1 mmHg) affording aldehyde **6** (5.2 g, 90%) as a colorless liquid: $n^{21}{}_D$ = 1.4341; R_f = 0.60 (hexane/AcOEt 1:1); ^{1}H NMR δ 9.28 (t, J = 1.5, 1H), 3.36 (s, 3H), 2.00 (t, J = 7.4, 2H), 1.75 (dt, J = 7.2, J = 1.4, 2H), 1.37 (qw, J = 7.5, 2H), 1.27−1.12 (m, 2H), 1.03−0.84 (m, 2H); ^{13}C NMR δ 202.0, 174.0, 51.7, 44.2, 34.4, 29.4, 25.5, 22.5; MS (15 eV) *m/e* (%) 159 (M^+ + 1, 2), 55 (100). Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.70; H, 8.87.

Methyl 9-Oxo-19,20-bisnor-7-prostenoate (7). To a stirred solution of 2-dimethoxyphosphoryl-3-hexylcyclopentan-1-one **5** (2.5 g, 9.0 mmol) and aldehyde **6** (1.56 g, 9.9 mmol) in benzene (70 mL) at room temperature was added Al_2O_3−KOH [obtained by evaporation under reduced pressure of a mixture of Al_2O_3 (1.5 g) and saturated aqueous solution of KOH (0.5 g, 9.0 mmol)]. After stirring for 3 h, the mixture was filtered on a Celite pad, concentrated in vacuo, and chromatographed on silica gel using hexane/ethyl acetate (4:1) as eluent affording **7** (2.12 g, 76%) as a mixture of isomers (E/Z = 1.3:1). Pure isomers were separated and characterized.

Z-7: $n^{22}{}_D$ = 1.4770; R_f = 0.44 (hexane/AcOEt 4:1); ^{1}H NMR (C_6D_6, 300 MHz) δ 5.64 (dt, J = 7.6, J = 2.3, 1H), 3.34 (s, 3H), 2.90−2.78 (m, 2H), 2.35−2.23 (m, 1H), 2.08 (t, J = 7.4, 2H), 2.18−1.87 (m, 2H), 1.72−1.02 (m, 18H), 0.93 (t, J = 6.9, 3H); ^{13}C NMR δ 207.7, 173.9, 140.8, 139.8, 51.6, 43.0, 39.2, 35.5, 34.7, 32.9, 30.5, 30.2, 29.8, 28.4, 27.8, 27.3, 25.8, 23.8, 15.0; MS (15 eV) *m/e* (%) 309 (M^+ + 1, 4), 308(M^+, 19), 191 (100); HRMS (CI) $(M + H)^+$ calcd for $C_{19}H_{33}O_3$ 309.2430, odsd 309.2435.

E-7: $n^{25}{}_D$ = 1.4715; R_f = 0.34 (hexane/AcOEt 4:1); ^{1}H NMR (C_6D_6, 300 MHz) δ 6.66 (dt, J = 7.6, J = 1.9, 1H), 3.35 (s, 3H), 2.72−2.57 (m, 1H), 1.60−1.00 (m, 24H), 0.91 (t, J = 6.9, 3H); ^{13}C NMR δ 205.79, 173.83, 142.95, 135.90, 51.60, 39.34, 36.66, 35.66, 34.55, 32.88, 30.43, 29.98, 29.73, 29.36, 28.53, 25.81, 25.64, 23.73, 15.00; MS (15 eV) *m/e* (%) 309 (M^+ + 1, 5), 308 (M^+, 29), 191 (100); HRMS (CI) $(M + H)^+$ calcd for $C_{19}H_{33}O_3$ 309.2430, obsd 309.2430.

Methyl 2-Hexyl-5-oxocyclopentaneheptanoate (8). To a magnetically stirred tellurium powder (0.319 g, 2.5 mmol) in ethanol (10 mL) under a possitive pressure of an inert gas was added sodium borohydride (0.123 g, 3.3 mmol) in one portion. The reaction mixture was warmed to 40 °C, and when a clear, almost colorless solution was formed, the temperature was lowered to 0 °C and acetic acid (0.1 mL) was added. The solution of **7** (0.308 g, 1 mmol) in ethanol (1 mL) was added, and the reaction mixture was stirred for 5 h at room temperature and then filtered through Celite and concentrated. The residual liquid was purified by column chromatography (hexane/ethyl acetate 4:1) affording **8** (0.295 g, 95%) as a colorless liquid: $n^{21}{}_D$ = 1.4605; R_f = 0.40 (hexane/AcOEt 4:1); ^{1}H NMR δ 3.35 (s, 3H), 2.16−1.96 (m, 2H), 2.10 (t, J = 7.4, 2H), 1.82−0.85 (m, 24H), 0.93 (t, J = 6.9, 3H); ^{13}C NMR δ 218.97, 173.97, 55.50, 51.61, 42.43, 38.35, 35.73, 34.75, 32.92, 30.65, 30.61, 29.97, 29.09, 28.07, 27.84, 27.80, 25.92, 23.75, 15.03; MS (15 eV) *m/e* (%) 310 (M^+, 4), 83 (100); HRMS (CI) $(M + H)^+$ calcd for $C_{19}H_{35}O_3$ 311.2586, obsd 311.2595.

2-Hexyl-5-oxocyclopentaneheptanoic Acid (9). A solution of methyl 2-hexyl-5-oxocyclopentaneheptanoate **8** (0.155 g, 0.5 mmol) in 95% ethanol (6 mL) was heated at 45 °C with 3 mL of aqueous 1 N NaOH. After 3 h the reaction mixture was concentrated under reduced pressure, acidified by addition of 5% aqueous HCl, and extracted with chloroform. The organic extracts were dried over Na_2SO_4 and concentrated, and the residue was purified by column chromatography (hexane/AcOEt 1:1) to yield acid **9** (0.127 g, 86%): $n^{22}{}_D$ = 1.4695; R_f = 0.27 (hexane/AcOEt 1:1); ^{1}H NMR δ 2.34 (t, J = 7.4, 2H), 2.26−196 (m, 2H), 1.89−1.15 (m, 24H), 0.89 (t, J = 6.7, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 221.73, 179.83, 54.90, 41.40, 37.74, 34.62, 33.90, 31.70, 29.40, 29.36, 28.72, 27.79, 26.93, 26.90, 26.50, 24.47, 22.50, 13.96; MS (15 eV) *m/e* (%) 296 (M^+, 3), 83 (100); HRMS (CI) $(M + H)^+$ calcd for $C_{18}H_{33}O_3$ 297.2430, obsd 297.2438.

2-Hexyl-5-hydroxycyclopentaneheptanoic Acid (1). To a stirred solution of 2-hexyl-5-oxocyclopentaneheptanoic acid **9** (0.080 g, 0.27 mmol) and sodium hydroxide (0.021 g, 0.54 mmol) in methanol (0.8 mL) at −10 °C was added sodium borohydride (0.011 g, 0.27 mmol). After 3 h at 0 °C, the solvent was evaporated in vacuo and the residue dissolved in 0.5 mL of water. The solution was acidified by addition of 5% aqueous HCl and extracted with chloroform. Organic extracts were dried over Na_2SO_4, concentrated under reduced pressure, and chromatographed on silica gel (ethyl acetate/hexane 1:1) affording **1** (0.076 g, 95%) as a mixture of *trans*−*trans* and *trans*−*cis* isomers: R_f = 0.18 and 0.23 (petroleum ether/Et_2O/AcOH 8:8:0.1); ^{1}H NMR δ 4.19−4.10 (m, 1H), 3.92−3.80 (m, 1H), 2.18 (t, J = 7.3, 4H), 2.10−1.96 (m, 1H), 1.82−0.85 (m, 51H), 0.93 (t, J = 6.6, 6H); ^{13}C NMR δ 180.13, 79.93, 75.13,

55.09, 52.71, 45.71, 43.02, 37.15, 36.33, 35.23, 34.95, 34.71, 34.61, 33.03, 30.86, 30.77, 30.69, 30.48, 30.12, 30.03, 29.53, 29.48, 29.21, 28.79, 28.67, 25.68, 23.81, 15.06; HRMS (CI) $(M + H - H_2O)^+$ calcd for $C_{18}H_{33}O_2$ 281.2480, obsd 281.2476.

Acknowledgment. Financial support of this work by the State Committee for Scientific Research (Grant 3 T09A 126 12) is gratefully acknowledged. One of us (M.M.) gratefully acknowledges an award from the Alexander von Humboldt Foundation that facilitated the preparation of the final form of this paper.

Supporting Information Available: ^1H and ^{13}C NMR spectra for compounds **1** and **3**−**9** and ^{31}P NMR spectra for compounds **3**−**5**. Experimental procedures for methylation of (±)-**1** and reduction of the keto ester **8** (22 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.

JO981120G