(m, 2 H, 2CHCO), 6.83–7.37 (m, 5 H, phenyl); ^{31}P NMR δ 111.0. Anal. Calcd for $C_{22}H_{27}BrNO_2PS$: C, 55.00; H, 5.67; Br, 16.63; P, 6.45. Found: C, 55.00; H, 5.70; Br, 16.67; P, 6.56.

Irradiation of the 7-Phosphanorbornenes. All the irradiations were conducted by using a 125-W medium-pressure mercury lamp and a water-cooled quartz immersion well. The irradiations were performed on 0.05 mol of the phosphanorbornene in 100 mL of THF and 100 mL of MeOH. After reaction, the solvents were removed under water-jet vacuum and the residue chromatographed through a deoxygenated silica gel column, with CH_2Cl_2, under argon. Irradiation times and yields are given in Table I. *O*-Methyl phenylphosphinothioate (**2**): ^{1}H NMR δ 3.70 (d, $^3J_{PH}$ = 12.5 Hz, 3 H, CH_3O), 7.45–8.15 (m, 5 H, phenyl), 8.26 (d, $^1J_{PH}$ = 540 Hz 1 H, PH). The spectrum is identical with that published by Tomioka and al.

O-Methyl Butylphosphinothioate (**28**, R = Bu) and Di-*O*-methyl Butylphosphonothioate (**29**, R = Bu). Irradiation of **7** gave the pure phosphinothioate: ^{1}H NMR δ 0.9–2.05 (m, 9 H, butyl), 3.48 (d, $^3J_{PH}$ = 13.5 Hz, 3 H, CH_3O), 7.3 (dq, $^1J_{PH}$ = 512 Hz, 1 H, PH); ^{31}P NMR δ 77.5; IR (neat) ν(PH) 2320; mass spectrum (70 eV, 70 °C), *m/e* (relative intensity) 152 (65, M).

Irradiation of compounds **5** and **9** gave a mixture of **28** and **29** (R = Bu), as indicated in Table I. The percentages have been estimated by integration of the methyl signals respectively at 3.23 and 3.35 ppm (d, $^3J_{PH}$ = 13.5 Hz) in C_6D_6 solution.

O-Methyl (4-bromobutyl)phosphinothioate (**18**): ^{1}H NMR δ 1.60–2.17 (m, 6 H, $(CH_2)_3P$), 3.38 (t, 2 H, CH_2Br), 3.60 (d, $^3J_{PH}$ = 14.2, 3 H, CH_3O), 7.51 (dm, $^1J_{PH}$ = 496 Hz, 1 H, PH); ^{31}P NMR δ 75.7; IR (neat) ν(PH) 2320.

O-Methyl (5-bromopentyl)phosphinothioate (**19**): ^{1}H NMR δ 1.40–2.15 (m, 8 H, $(CH_2)_4P$), 3.35 (t, 2 H, CH_2Br), 3.55 (d, $^3J_{PH}$ = 14.3, 3 H, CH_3O), 7.40 (dm, $^1J_{PH}$ = 492 Hz, 1 H, PH); ^{31}P NMR δ 76.5.

O-Methyl (6-bromohexyl)phosphinothioate (**20**): ^{1}H NMR δ 1.25–2.15 (m, 10 H, $(CH_2)_5P$), 3.33 (t, 2 H, CH_2Br) 3.60 (d, $^3J_{PH}$ = 14 Hz, 3 H, CH_3O), 7.40 (dm, $^1J_{PH}$ = 492 Hz, 1 H, PH).

O-Ethyl (4-bromobutyl)phosphinothioate (**25**): prepared under the same conditions as the O-methylated compound, but in ethyl alcohol: ^{1}H NMR δ 1.27 (t, 3 H, CH_3), 1.66–2.20 (m, 6 H, $(CH_2)_3P$), 3.28 (t, 2 H, CH_2Br), 3.70–4.20 (m, 2 H, CH_2O), 7.40 (dm, $^1J_{PH}$ = 514 Hz, 1 H, PH); ^{31}P NMR δ 71.4.

Cyclization of the Phosphinothioates 15–17. To a suspension of 1.2 g (0.05 mol) of NaH in 80 mL of THF at 50 °C was added dropwise a solution of 0.005 mol of ω-bromoalkyl phosphinothioate in 20 mL of THF. The mixture was stirred for 0.5 h at 50 °C, cooled at −10 °C and hydrolyzed with a saturated NH_4Cl aqueous solution. The organic layer was separated and the solvent removed. The residue was then worked up as usual with ether. After solvent removal, the oily residue was chromatographed through a silica gel column and then vacuum distilled (Kugelrohr).

1-Methoxyphospholane sulfide (**21**): bp 160 °C (3 mm); yield 65%; ^{1}H NMR δ 1.5–2.4 (m, 8 H, $(CH_2)_4$), 3.52 (d, $^3J_{PH}$ = 13.5 Hz, 3 H, CH_3O); ^{31}P NMR δ 119.7; IR (neat) ν(PC) 1110, ν(POC) 1025, ν(PS) 730 and 610; mass spectrum (70 eV, 70 °C), *m/e* (relative intensity) 150 (100, M), 122 (35, M − $(CH_2)_2$), 120 (77, M − OCH_2). Anal. Calcd for $C_5H_{11}OPS$: C, 39.99; H, 7.38. Found: C, 39.67; H, 7.41.

1-Ethoxyphospholane sulfide (**26**): bp 90 °C (0.3 mm); yield 67%; ^{1}H NMR δ 1.27 (t, $^3J_{HH}$ = 6, 8 Hz, 3 H, CH_3), 1.7–2.23 (m, 8 H, $(CH_2)_4P$), 3.7–4.2 (dq, $^3J_{HH}$ = 6.8 Hz, $^3J_{PH}$ = 9.6 Hz, 2 H, CH_2P); ^{31}P NMR δ 116.5.

1-Methoxyphosphorinane sulfide (**22**): bp 100 °C (0.4 mm); yield 70%; ^{1}H NMR δ 1.55–2.25 (m, 10 H, $(CH_2)_5$), 3.52 (d, $^3J_{PH}$ = 13.0 Hz, 3 H, CH_3O); ^{31}P NMR 91.5; IR (neat) ν(PC) 1120, ν(POC) 1020, ν(PS) 730 and 610; mass spectrum (70 eV, 80 °C), *m/e* (relative intensity) 164 (100, M), 136 (26, M − $(CH_2)_2$), 134 (62, M − OCH_2), 122 (37, M − $(CH_2)_3$). Anal. Calcd for $C_6H_{13}OPS$: C, 43.89; H, 7.98; P, 19.52. Found: C, 43.93; H, 8.05; P, 19.33.

1-Methoxyphosphepane sulfide (**23**): bp 150 °C (0.5 mm); yield 60%; ^{1}H NMR δ 1.45–2.30 (m, 12 H, $(CH_2)_6$), 3.49 (d, $^3J_{PH}$ = 13.0 Hz, 3 H, CH_3O); ^{31}P NMR δ 105.9; IR (neat) ν(PC) 1095, ν(POC) 1033, ν(PS) 690 and 590; mass spectrum (70 eV, 80 °C), *m/e* (relative intensity) 178 (50, M), 136 (22, M − $(CH_2)_3$), 122 (10, M − $(CH_2)_4$), 86 (100, C_6H_{14}), 84 (100, C_6H_{12}). Anal. Calcd for $C_7H_{15}OPS$: C, 47.17; H, 8.48. Found: C, 47.30; H, 8.52.

Registry No. **2**, 26855-55-0; **4**, 62241-64-9; **5**, 78870-58-3; **6**, 78961-93-0; **7**, 78870-59-4; **8**, 78870-60-7; **9**, 78870-61-8; **10**, 30540-37-5; **11**, 30540-40-0; **12**, 78870-62-9; **13**, 78870-63-0; **14**, 78939-72-7; **15**, 78870-64-1; **16**, 78870-65-2; **17**, 78870-66-3; **18**, 78870-67-4; **19**, 78870-68-5; **20**, 78870-69-6; **21**, 78870-70-9; **22**, 78870-71-0; **23**, 78870-72-1; **24**, 78870-73-2; **25**, 78870-74-3; **26**, 78870-75-4; **28** (R = Bu), 78870-76-5; **29** (R = Bu), 78870-77-6; 1-phenyl-3,4-dimethylphosphole, 30540-36-4; 1,4-dibromobutane, 110-52-1; 1,5-dibromopentane, 111-24-0; 1,6-dibromohexane, 629-03-8; maleic anhydride, 108-31-6; *N*-phenylmaleimide, 941-69-5.

A Highly Convergent and Efficient Total Synthesis of Prostaglandins (±)-PGA and (±)-PGB[1]

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Received February 20, 1981

The mixed cyanocuprate derived from *trans*-1-iodo-3-[(*tert*-butyldimethylsilyl)oxy]oct-1-ene was added regioselectively (1,4:1,2 = 15:1) to cyclopentadiene monoepoxide. The trans-1,4-adduct **4** was stereospecifically converted to epoxy alcohol **6** and then to the corresponding epoxy ketone **7** (97%). After the enol phosphate **8** was regiospecifically formed, a second 1,4-conjugate addition of the cyanocuprate derived from 1-lithio-7-[(trimethylsilyl)oxy]heptane was used to introduce the top chain of the prostaglandin nucleus. The resulting hydroxy enol phosphate **9** could be selectively transformed into either PGA or PGB under basic conditions. This new synthetic approach to prostaglandins provides a general route to new prostaglandin analogues in very few steps.

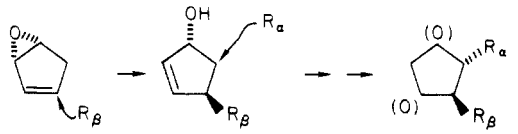
The total syntheses of various naturally occurring prostaglandins have been achieved with considerable success and creativity over the past decade.[2] Notwithstanding the elegant syntheses of the PG series using organocopper reagents,[3] there previously was absent an ap-

(1) A preliminary report on this synthetic strategy to prostaglandins was made at the 3rd IUPAC Meeting on Organic Synthesis, June 15–20, 1980, Madison, WI, and at the 2nd Chemical Congress of the North American Continent, August 25–29, 1980, Las Vegas, NV.

(2) For two comprehensive reviews on the syntheses of prostaglandins, see: Mitra, A., "The Synthesis of Prostaglandins"; Wiley: New York, 1977. Newton, R. F.; Roberts, S. M. *Tetrahedron* **1980**, *36*, 2163.

0022-3263/81/1946-4389$01.25/0

proach to the prostaglandins that involved the regiospecific introduction of both side chains onto cyclopentadiene monoepoxide, as generalized by the following:

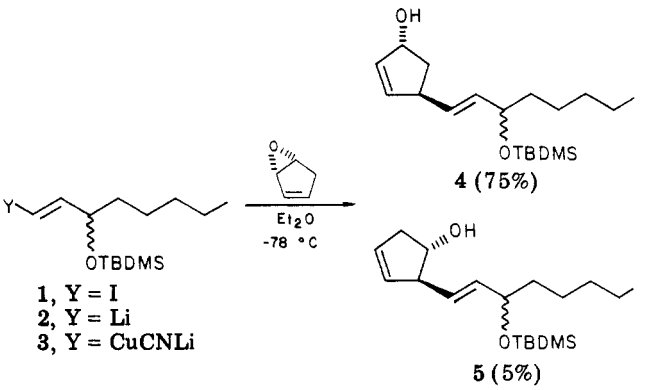


While a number of successful syntheses have employed an initial 1,2 opening of cyclopentadiene monoepoxide with organometallic reagents,[4] the regiospecific 1,4 opening of this simple starting material has eluded synthetic chemists. Our recent success with the regiospecific additions of mixed cyanoalkylcuprates to 1,3-cyclohexadiene monoepoxide and allylic epoxides in general[5] prompted the application of this methodology to the prostaglandin system. We report a highly convergent total synthesis of PGA and PGB from cyclopentadiene monoepoxide that promises to serve as a prototype for the synthesis of other prostaglandins and their derivatives.

Our synthetic approach begins with the low-temperature (−80 °C) reaction of cyclopentadiene monoepoxide with the mixed cyanocuprate **3**. Reaction of the known[6] *trans*-vinylic iodide **1** with 2 equiv of *tert*-butyllithium in diethyl ether at −80 °C generates the vinyllithium reagent **2** in greater than 90% yield. Addition of the latter to an ethereal suspension of cuprous cyanide at −40 °C quantitatively affords the corresponding mixed cuprate **3** after 2 h. The reaction of **3** with freshly distilled cyclopentadiene oxide at −80 °C gave a 4:1 mixture of the trans 1,4 and trans 1,2 adducts (**4** and **5**, respectively) in 80% yield.[7]

Interestingly, an ethereal solution of the vinylic iodide **1** underwent complete halogen–metal exchange with *n*-butyllithium at −80 °C in 75 min. The above exchange with *tert*-butyllithium afforded 1 full molar equiv of lithium iodide, while the latter, being salt free, generated *n*-butyl iodide, which does not participate in the reaction. Formation of the cuprate **3** under the *salt-free* conditions and reaction with the epoxide again gave the expected trans 1,4 and trans 1,2 regioisomers in 80% yield. However, the ratio had now altered dramatically to favor the required trans 1,4 adduct by approximately 15:1. The regioisomers **4** and **5** were easily separated by column chromatography or with a Waters Prep 500 system on a preparative scale (i.e., typically, 20 g of pure 1,4 regioisomer could be obtained).

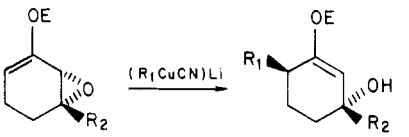
Once again,[5] the dramatic effect of the cyano ligand on the regiochemistry was demonstrated by the predominance (15:1) of the trans-1,4-opening process. When analogous reactions of cyclopentadiene monoepoxide with the homocuprate derived from **2**, the mixed cuprate containing a phenylthio ligand, or with a copper-catalyzed Grignard reagent (Y = MgI) were carried out, lower yields of a complex mixture of products were obtained. In these cases, the 1,4 adduct, **4**, and the 1,2 adduct, **5**, were formed in equal amounts.



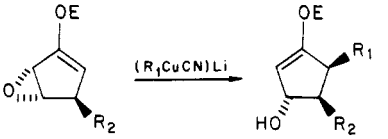
1, Y = I
2, Y = Li
3, Y = CuCNLi

Hydroxyl directed cis epoxidation[8] of the 1,4-adduct **4** with *tert*-butyl hydroperoxide and $VO(acac)_2$ and subsequent oxidation of the epoxy alcohol **6** with Collins reagent[9] afforded the novel keto epoxide **7** in 97% yield after chromatography. The introduction of the top chain of the prostaglandins via the alkylation of the enolate derived from the keto epoxide **7** should provide both known and novel PG analogues. While the formation of the enolate with LDA at −80 °C (THF, 1 h) was straightforward, it was, however, not surprising to find that no reaction occurred with 7-(trimethylsiloxy)heptyl iodide or any other primary iodide. When the temperature of the alkylation reaction was raised above −40 °C, then complete self-destruction of the enolate of **7** resulted.[10]

As shown in Scheme I, an alternative strategy for the introduction of the top chain was developed by using a second 1,4 addition of the appropriately substituted cyanocuprate reagent. In previous work,[1,5b] we showed for the first time that enol ethers of α,β-epoxy ketones can serve as valuable synthons for the regiospecific and stereospecific addition of mixed cyanocuprates, the products being exclusively derived from a trans 1,4 opening of the epoxide.



There was, however, no previous example of this reaction on substituted epoxycyclopentanones, such that the incoming group would be placed cis and in a 1,2 relationship with the bulky bottom chain. In this particular case, the regiochemical control, and indeed the stereochemical control, would certainly be put to the test.



Formation of the enolate of **7** with LDA (THF, −80 °C, 1 h) and its subsequent trapping with diethyl chloro-

(3) (a) Sih, C. J.; Price, P.; Sood, R.; Solomon, R. G.; Peruzzotti, G.; Casey, M. *J. Am. Chem. Soc.* **1972**, *94*, 3643. (b) Sih, C. J.; Price, P.; Sood, R.; Solomon, R. G.; Peruzzotti, G.; Casey, M. *Tetrahedron Lett.* **1973**, 2313. (c) Sih, C. J.; Solomon, R. G.; Price, P.; Sood, R.; Peruzzotti, G. *J. Am. Chem. Soc.* **1975**, *97*, 857. (d) Kluge, A. F.; Untch, K. G.; Fried, J. H. *Ibid.* **1972**, *94*, 9256. (e) Floyd, M. B. *Synth. Commun.* **1974**, *4*, 317. (f) Patterson, J. W., Jr.; Fried, J. H. *J. Org. Chem.* **1974**, *39*, 2406. (g) Corey, E. J.; Mann, J. *J. Am. Chem. Soc.* **1973**, *95*, 6832.

(4) (a) Stork, G.; Kowalski, C.; Garcia, G. *J. Am. Chem. Soc.* **1975**, *97*, 3258. (b) Stork, G.; Isobe, M. *Ibid.* **1975**, *97*, 6260.

(5) (a) Marino, J. P.; Floyd, D. M. *Tetrahedron Lett.* **1979**, 675. (b) Marino, J. P.; Hatanaka, N. *J. Org. Chem.* **1979**, *44*, 4467. (c) Marino, J. P.; Abe, H. *Synthesis* **1980**, *11*, 872. (d) Marino, J. P.; Abe, H. *J. Am. Chem. Soc.* **1981**, *103*, 2907.

(6) Corey, E. J.; Beams, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

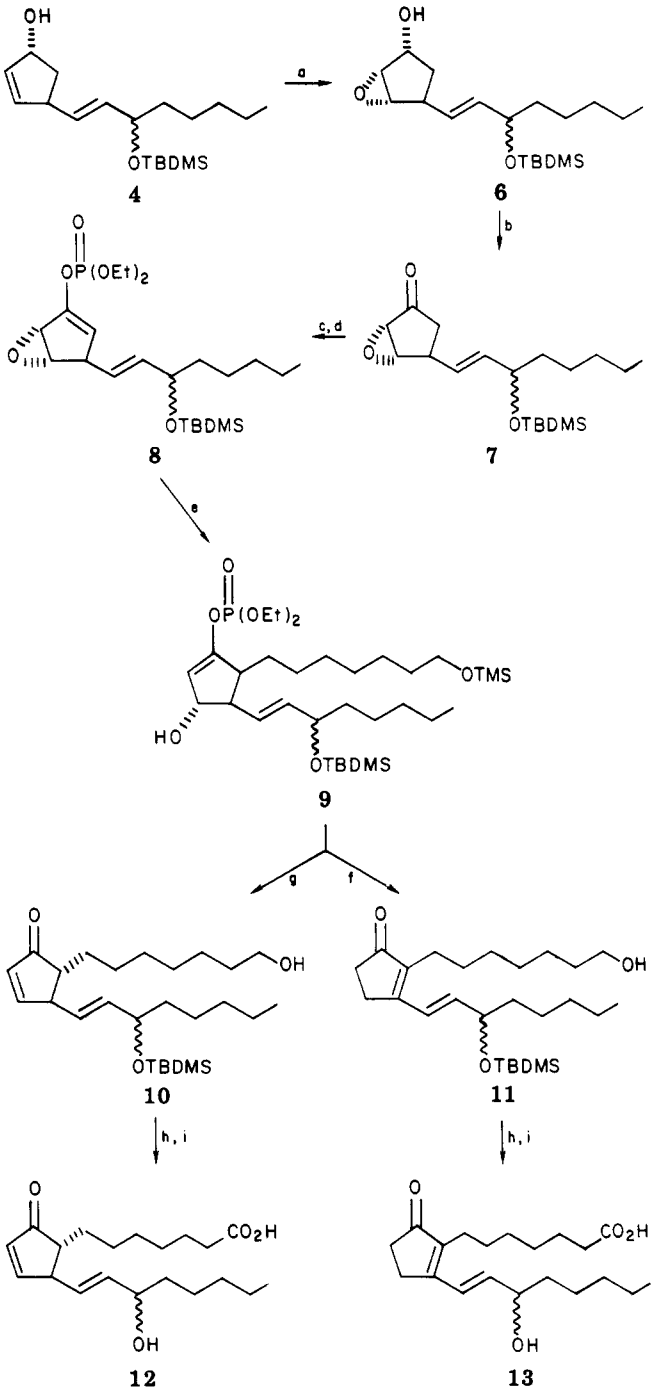
(7) GLC analyses were conducted on a Varian 1400 instrument equipped with a TCD, using a 1.5% OV-101 on Chromosorb GHP with a He carrier (24 mL/min^{-1}). Chromatograms were generally run from 100 to 250 °C at 15 °C min^{-1}, and this gave retention temperatures for **4** and **5** of 212 and 206 °C, respectively.

(8) Itoh, T.; Jitsukawa, K.; Kaneda, K.; Teranishi, S. *J. Am. Chem. Soc.* **1979**, *101*, 159.

(9) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.

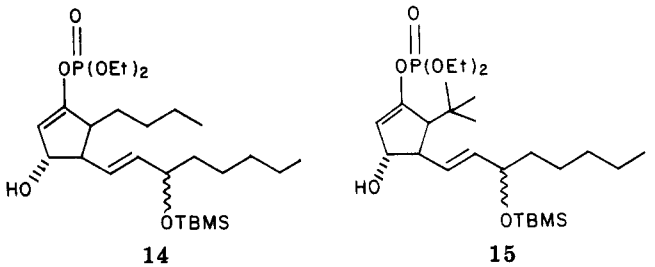
(10) It should be pointed out, however, that preliminary reactions of the enolate of **7** with more reactive allylic halides and aldehydes (aldol reactions) occur in good to excellent yields and will be the subject of future communications.

Scheme I



a, $VO(acac)_2$, *tert*-butyl hydroperoxide, C_6H_8; b, CrO_3Py_2, 10 equiv, CH_2Cl_2; c, LDA, THF, −78 °C, 1 h; d, $(EtO)_2P(O)Cl$, THF; e, $CNCuLi(CH_2)_7OTMS$, Et_2O, −78 → −40 °C, 2 h; f, NaOMe, MeOH, 48 h; g, NaH, $C_6H_5CH_2Br$, 48 h; Jones reagent; i, aqueous HF, CH_3CN

phosphate produced the epoxy enol phosphate 8 in over 80% yield contaminated with a small amount of 7 (10%). Without purification, the enol phosphate 8 was added to an ethereal suspension of the mixed cyanocuprate derived from 1-lithio-7-[(trimethylsilyl)oxy]heptane,[11] at −80 °C. After 2 h at between −80 and −40 °C, the reaction mixture was quenched with a saturated ammonium chloride solution and subjected to a normal extraction workup. After simple column chromatography, only the 1,4-regioisomer 9 was isolated in ~60% yield. None of the 1,2 regioisomer could be detected by either chromatographic or spectral analysis. Based on previous work in our laboratory,[12] we expect that the stereochemistry of the side chains is initially cis and that the 1,4 opening proceeded in a trans fashion.[13] In a similar manner, mixed cyano-*n*-butylcuprate and *tert*-butylcuprate added regiospecifically and presumably stereospecifically to yield the trans 1,4 adducts, 14 and 15.



The reactions of enol phosphates and derivatives have been thoroughly examined in recent years.[14,15a] Borowitz and co-workers[14] have shown that the reaction with alkyllithium reagents (or Grignard reagents) cleanly affords the corresponding enolates in high yields. In our case, the conversion of the hydroxy enol phosphate 9 into the PGA and PGB systems was effected by two different sets of basic reaction conditions. Treatment of 9 with 2 equiv of sodium methoxide in methanol (room temperature, 48 h) produced an 86% yield of 1-hydroxy-15-(*tert*-butyldimethylsiloxy)-PGB, 11. The reaction product 11 clearly proceeded through the intermediacy of the PGA enone and absolutely confirmed that the addition of the second cuprate reagent to the epoxy enol ether 8 was the result of a 1,4 addition to the epoxide. The ease with which the enone of PGA can isomerize to the more stable PGB has been well recognized in the chemistry of five-membered-ring systems in general.[16] A further set of reaction conditions was therefore required in which the hydrolysis of the enol phosphate 9 could be halted at the PGA stage, and to this end, alkylation with benzyl bromide and sodium hydride (THF, room temperature, 48 h) yielded the required 1-hydroxy-15-(*tert*-butyldimethylsiloxy)-PGA, 10, in 84% yield after chromatography. The absence of any PGB enone was primarily due to the insoluble nature of the base used for the alkylation. Intermediates 10 and 11 were easily converted to (±)-PGA and (±)-PGB by known transformations,[15a-c] and their structures were reconfirmed by comparison of literature NMR data (^1H and ^{13}C).[17] We expect that epimerization at C_8 of the enol phosphate 9 to yield the desired trans stereochemistry at carbons 8 and

(11) Prepared in the following manner: (1) *tert*-butyl acetate, LDA, THF, −80 °C; HMPA, 1,5-dibromopentane (1:1, 64% yield); cf. Kieczykowski, G. R.; Pogonowski, C. S.; Richman, J. E.; Schlessinger, R. H. *J. Org. Chem.* **1977**, *42*, 175. (2) NaI, acetone, reflux, 12 h (99% yield). (3) $LiAlH_4$, THF, 15 °C, 15 min (92% yield). (4) Hexamethyldisilazene (1.2 equiv), chlorotrimethylsilane (1 drop), diethyl ether (99%). (5) *sec*-butyllithium, THF, −80 °C, 5 min (99% yield).

(12) Reference 5b and unpublished work of M. G. Kelly on cyclopentadiene oxide.

(13) The enol phosphate 9 was present as a pair of diastereomers, and for that reason the 360-MHz ^1H NMR could not be used to definitely assign the stereochemistry between the two chains at C_8 and C_{12}.

(14) Borowitz, I. J.; Casper, E. W. R.; Crouch, R. K.; Yee, K. C. *J. Org. Chem.* **1972**, *37*, 3872.

(15) (a) Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 4745. (b) Newton, R. F.; Reynolds, D. P., Finch, M. A. W.; Kelly, D. R.; Roberts, S. M. *Tetrahedron Lett.* **1979**, 3989. (c) Bowden, K.; Heilbron, I. M.; Jones, E. R. H.; Weedon, B. C. L. *J. Chem. Soc.* **1946**, 39.

(16) (a) Jones, R. L. *J. Lipid Res.* **1972**, *13*, 511. (b) Jones, R. L.; Cammock, S. *Adv. Biosci.* **1973**, *9*, 61. (c) Ellison, R. A. *Synthesis* **1973**, 397.

(17) (a) Lukacs, G.; Piriou, E.; Gero, S. D.; Van Dorp, D. A. *Tetrahedron Lett.* **1973**, 515. (b) Pike, J. E.; Lincoln, F. H.; Schneider, W. P. *J. Org. Chem.* **1969**, *34*, 3552. (c) Klok, R.; Pabon, H. J. J.; Van Dorp, D. A. *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 813.

12 occurred during the formation of enone **10**. A number of additional attempts were made in order to effect a milder hydrolysis of the enol phosphate with retention of the 11-α-hydroxy group. Work is continuing in order to find proper conditions for the conversion of **9** into the PGE and PGF series.

Experimental Section

Infrared spectra were obtained on a Perkin-Elmer 727B or 457 grating spectrophotometer. ^{1}H NMR spectra were obtained on a Varian T60A, a JEOL-FX90Q, or a 360-MHz Bruker spectrometer with tetramethylsilane as the standard. ^{13}C NMR spectra were obtained on a JEOL-FX90Q spectrometer with deuteriochloroform as the standard ($CDCl_3$, ppm 77.00). Mass spectra were obtained on a Finnigan automated GC/MS-EICI system mass spectrometer at 70 eV. Elemental analyses were performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. Gas chromatographic separations were accomplished on a Varian 1400 instrument with a thermal conductivity detector. Column chromatography was carried out on EM Reagent silica gel 60 (230–400 mesh ASTM) or Fisher Scientific Co. Florisil (100–200 mesh). Preparative thin-layer chromatography was carried out on EM Reagent silica gel 60 F-254 precoated (2 mm) PLC plates. All chromatography solvents were distilled before use. Diethyl ether was freshly distilled from LAH (under N_2) and methylene chloride from P_2O_5. Technical grade cuprous cyanide was purchased from J. T. Baker. All reactions were carried out in flame-dried glassware under an inert atmosphere of dry nitrogen.

Preparation of 4 and 5. Under an argon atmosphere, an ethereal solution of the vinylic iodide **1**[6a] (40.5 g, 0.11 mol, in 300 mL) was treated with *tert*-butyllithium (1.84 M in pentane, 119.6 mL, 0.22 mol) at −78 °C (dry ice–*i*-PrOH), and the resulting solution was stirred at this temperature for 2 h. The vinyllithium reagent (**2**) was then transferred (under argon) to an ethereal suspension of cuprous cyanide (26.8 g, 0.3 mol, in 200 mL) at −40 °C. After being stirred for 1 h at this temperature, the bright red organocuprate reagent (**3**) was ready for use.

After the mixture cooled to −78 °C, 1 equiv of freshly distilled cyclopentadiene oxide (9 g, 0.11 mol) was added, and the mixture was stirred for 6 h prior to warming to room temperature. The reaction mixture was quenched with a saturated ammonium chloride solution (100 mL), and the resulting inorganic salts were removed by filtration through Celite. The organic phase was separated, washed with brine (100 mL), and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo gave 40.0 g of a light brown oil. The products were isolated by column chromatography (silica gel 60, 70–230 mesh, 5:1, petroleum ether/ether) and preferably HPLC (Waters Prep 500; 6:1 hexane/ethyl acetate), and afforded 27.8 g of **4** (75% yield) and 1.7 g of **5** (5% yield), both as light yellow oils.

4: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.84–5.79 (2 H, m, ring olefin), 5.42–5.36 (1 H, H_{13} PG number, dd, J_{13-14} = 15.4 Hz, J_{13-12} = 6.1 Hz), 5.35–5.29 (1 H, H_{14} PG number, dd, J_{13-14} = 15.4 Hz, J_{14-15} = 7.1 Hz), 4.86–4.83 (1 H, m, allylic α to OH), 3.99–3.94 (1 H, dt, allylic α to $OSiR_3$), 3.50–3.44 (1 H, m, ring CH), 1.99–1.83 (2 H, m, ring CH_2), 1.28–1.23 (8 H, m, $(CH_2)_4$), 0.86–0.82 (12 H, s and t, CH_3 and $SiC(CH_3)_3$), 0.0 (6 H, 2 s, $Si(CH_3)_2$); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 138.9, 134.3, 134.0, 133.3, 77.5, 74.2, 47.4, 41.6, 39.0, 32.5, 28.0, 26.6, 25.7, 23.3, 14.7, −3.5, −4.0; IR (liquid film) 3350, 3050–2860, 1470, 1405, 1360, 1260, 1080, 970, 840, 770 cm^{-1}. Anal. Calcd C, 70.31; H, 11.18. Found: C, 70.21; H, 11.15.

5: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.73–5.69 (1 H, m, ring olefin), 5.61–5.56 (1 H, m, ring olefin), 5.44–5.41 (2 H, m, olefin), 4.13–4.09 (1 H, dt, allylic α to $OSiR_3$), 4.02–3.99 (1 H, m, homoallylic α to OH), 3.17–3.10 (1 H, m, doubly allylic), 2.69–2.60 (1 H, m, CH of ring), 2.27–2.20 (1 H, m, CH of ring), 1.31–1.23 (8 H, m, $(CH_2)_4$), 0.86–0.82 (12 H, s and t, CH_3 and $SiC(CH_3)_3$), 0.0 (6 H, 2 s, $Si(CH_3)_2$); IR (liquid film) 3350, 3050–2860, 1470, 1405, 1360, 1260, 1080, 970, 840, 770 cm^{-1}.

Preparation of Keto Epoxide 7. The epoxy alcohol **6** (17.75 mmol) was added at 0 °C to a preformed solution of CrO_3·Pyr_2 (10 equiv), 17.75 g of CrO_3, and 28.04 g of pyridine in CH_2Cl_2 (1600 mL), and stirring was continued at room temperature for 2 h. The organic phase was separated by decantation and the solvent was removed in vacuo. The resulting product was taken up in diethyl ether (400 mL), washed with saturated sodium bicarbonate (3 × 100 mL), and brine (100 mL), and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo gave a viscous brown oil, which was purified by chromatography (silica gel 60, 70–230 mesh, 40:60 ether/light petroleum). Compound **7** was obtained as a light yellow oil (5.8 g, 97% overall yield from **5**).

7: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.62–5.54 (1 H, ddd, H_{14} PG number, J_{14-12} = 0.9 Hz, J_{14-15} = 6.1 Hz, J_{14-13} = 15.6 Hz), 5.44–5.37 (1 H, dd, H_{13} PG number, J_{13-12} = 8.1 Hz), 4.05–4.02 (1 H, dt, allylic α to $OSiR_3$), 3.73–3.72 (1 H, d, J = 2.0 Hz, epoxide H), 3.32–3.31 (1 H, d, J = 2.0 Hz, epoxide H), 3.23–3.19 (1 H, overlapping ddd, allylic α to epoxide, $J_{12-7\beta}$ = 8.0 Hz), 2.59–2.52 (1 H, dd, ring CH cis to epoxide, $H_{7\beta}$ PG number, $J_{12-7\beta}$ = 8.0 Hz), 2.59–2.52 (1 H, dd, ring CH cis to epoxide, $H_{7\beta}$ PG number, $J_{12-7\beta}$ = 8.0 Hz), 2.59–2.52 (1 H, dd, ring CH cis to epoxide, H_7 MG number, J_{12-7} = 8.0 Hz, $J_{7-7'}$ = 18.1 Hz), 1.88–1.81 (1 H, D, $J_{7'-7}$ = 18.1 Hz, ring CH trans to epoxide), 1.43–1.17 (8 H, m, $(CH_2)_4$), 0.89–0.83 (12 H, s and t, CH_3 and $SiC(CH_3)_3$, 0.0 (6 H, 2 s, $Si(CH_3)_2$); IR (liquid film) 3060–2860, 1755, 1465, 1410, 1370, 1255, 1170, 1065, 975, 835, 770 cm^{-1}. Anal. Calcd C, 67.41; H, 10.12. Found: C, 67.53; H, 10.12.

8: ^{1}H NMR (CCl_4) δ 5.55–5.3 (2 H, m, olefinic), 5.25–5.1 (1 H, br m, ring olefin), 4.4–3.8 (5 H, m, OCH_2 and allylic α to $OSiR_3$), 3.7–3.6 (1 H, br m, epoxide H), 3.6–3.5 (1 H, br d, epoxide H), 3.3–3.15 (1 H, br m, doubly allylic), 1.5–1.05 (14 H, m, 2 OEt, $(CH_2)_4$), 0.9–0.8 (12 H, s and t, CH_3 and $Si(CH_3)_3$), 0.0 (6 H, s, $Si(CH_3)_2$); IR (liquid film) 3050–2850, 1635, 1460, 1370, 1285, 1260, 1190, 1040, 970, 840, 780 cm^{-1}.

Preparation of 9. Under an argon atmosphere, a solution of 1-lithio-7-(trimethylsiloxy)heptane[11] (3 mmol in 10 mL of Et_2O) was added to an ethereal suspension of cuprous cyanide (448 mg, 5 mmol in 15 mL) at −40 °C, and after the mixture was stirred at this temperature for 1 h, the reagent was ready for use.

After cooling to −78 °C, a solution of the epoxy enol phosphate (**8**) (560 mg, 1.18 mmol) in diethyl ether (10 mL) was added dropwise, and stirring was continued at this temperature for 1 h and at −50 to −40 °C for another hour. The reaction was quenched with saturated ammonium chloride (10 mL), and the inorganic salts were removed by filtration through Celite. The organic phase was separated, washed with brine (15 mL), and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo gave 840 mg of a brown oil.

TLC and spectral analysis showed no starting material and the only product was isolated by column chromatography as a light brown oil, 380 mg, 60% yield (silica gel 60, 70–230 mesh, diethyl ether).

9: ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.59–5.47 (2 H, m, olefinic), 5.40 (1 H, br s, ring olefin), 4.52–4.48 (1 H, m, allylic α to OH), 4.22–4.14 (4 H, m, 2 OCH_2), 4.13–4.06 (1 H, m, allylic α to $OSiR_3$), 3.62–3.52 (2 H, t, J = 6.6 Hz, CH_2 α to SiR_3), 2.85 (1 H, br m, allylic ring proton), 2.72–2.69 (1 H, br m, allylic ring proton), 1.60–1.17 (26 H, t and m, 2 OEt, $(CH_2)_4$ and $(CH_2)_6$, 0.93–0.84 (12 H, s and t, CH_3 and $OSiC(CH_3)_3$), 0.09 (9 H, s, $Si(CH_3)_3$), 0.00 (6 H, 2 s, $Si(CH_3)_2$); ^{13}C NMR (2.25 MHz, $CDCl_3$) δ 155.2, 136.5, 127.1, 111.4, 78.4, 73.1, 64.5, 62.1, 53.5, 46.4, 38.6, 32.7, 31.8, 29.5, 29.2, 28.2, 27.3, 25.8, 24.7, 22.4, 18.1, 16.0, 14.1, −4.3, −4.5; IR (liquid film) 3420, 3050–2860, 1660, 1470, 1260, 1100, 1040, 970, 840, 780 cm^{-1}.

Preparation of Enone 10. A stirred suspension of sodium hydride (30 mg, 1.25 mmol) and the enol phosphate **9** (310 mg, 0.47 mmol) in THF (2 mL) was treated with benzyl bromide (1.25 mmol, 214 mg) after 1 h. after the mixture was stirred for 2 days, the organic phase was washed with saturated ammonium chloride (3 mL) and brine (3 mL) and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo gave 200 mg of crude enone and excess benzyl bromide. Column chromatography afforded 166 mg (84%) of 1-hydroxy-15-[(*tert*-butyldimethylsilyl)oxy]-PGA, **10**: ^{1}H NMR (CCl_4) δ 7.4–7.2 (1 H, dd, J = 6 Hz), 6.0–5.9 (1 H, dd, J = 6 Hz, J = 2 Hz), 5.5–5.35 (2 H, m, olefinic), 4.1–3.9 (1 H, m, allylic α to $OSiR_3$), 3.6–3.4 (3 H, t, J = 6 Hz, CH_2 α to OH, and m, doubly allylic); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 210.5, 164.5, 135.4, 134.3, 1280, 1040, 970, 840, 775 cm^{-1}.

Preparation of 11. Sodium methoxide (54 mg, 1 mmol) was added at room temperature to a methanolic solution of the enol phosphate (330 mg, 0.5 mmol, in 3 mL), and after the mixture

was stirred for 48 h, the reaction was determined complete (TLC analysis). The solvent was removed in vacuo and the product added to diethyl ether (10 mL). The organic phase was washed with saturated ammonium chloride (5 mL) and brine (5 mL) and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo gave 198 mg of a light oil. Chromatography afforded 181 mg (86%) of 1-hydroxy-15-(*tert*-butyldimethylsiloxy)-PGB, 11: ^{1}H NMR (CCl_4) δ 6.6 (1 H, d, J = 15 Hz, olefinic, H_{13}), 5.9 (1 H, dd, J_{13-14} = 15 Hz, J_{14-15} = 5 Hz, olefinic, H_{14}), 4.3–4.05 (1 H, dt, allylic α to $OSiR_3$, H_{15}), 3.7–3.5 (2 H, t, J = 6 Hz, CH_2 α to OH), 2.5–1.8 (6 H, m, 3 CH_2), 1.6–1.1 (18 H, m, $(CH_2)_4$, $(CH_2)_5$, 0.9–0.75 (12 H, s and t, CH_3 and $SiC(CH_3)_3$), 0.0 (6 H, 2 s, $Si(CH_3)_2$); ^{13}C NMR (22.5 MHz, $CDCl_3$) δ 209.6, 163.2, 141.4, 140.3, 123.8, 75.6, 72.3; IR (liquid film) 3400, 3050–2860, 1700, 1665, 1600, 1470, 1390, 1360, 1260, 1100, 1040, 970, 840, 775 cm^{-1}.

Preparation of (±)-PGA (12). A solution of enone **10** (97 g, 0.22 mmol) in 20 mL of acetone at −5 °C was treated with 0.16 mL of Jones reagent (2.5 equiv) over a period of 15 min. After being stirred for 30 min between −5 and 0 °C, the mixture was treated with 2-propanol (0.5 mL) and filtered through Celite. The filtrate was added to water (20 mL) and extracted with ethyl acetate (3 × 20 mL), and the combined organics were concentrated in vacuo. A solution of the crude acid in acetonitrile (5 mL) was treated with an aqueous hydrogen fluoride solution and the desilylated product was isolated after 1 h. Chromatography afforded (±)-PGA as an oil, 52 mg, 71% yield: ^{1}H NMR ($CDCl_3$) δ 7.4–7.5 (1 H, dd, J = 6 Hz), 6.1–6.0 (1 H, dd, J = 6 Hz, J = 2 Hz), 5.6–5.4 (2 H, m, olefins), 4.05 (1 H, m, allylic α to OH), 3.2 (1 H, m, doubly allylic); IR (liquid film) 3420, 3080–2740, 1715, 1700, 1590; λ_{max} (EtOH) 217 nm (ϵ 10 000).

Preparation of (±)-PGB (13). The enone **11** (132 mg, 0.3 mmol) was oxidized with 2.8 equiv of Jones reagent in acetone at −5 °C and desilylated exactly as reported above for (±)-PGA **12**. Short-path chromatography gave (±)-PGB **13** as an oil, 78 mg, 78% yield: ^{1}H NMR ($CDCl_3$) δ 6.75 (1 H, d, J = 15 Hz, H_{13}), 6.15 (1 H, dd, J_{13-14} = 15 Hz, $J_{14,15}$ = 5 Hz, H_{14}), 4.4–4.1 (1 H, dt, allylic α to OH, H_{15}), 2.9–2.0 (8 H, m, 4 CH_2), 1.9–1.1 (16 H, 8 CH_2), 1.1–0.75 (3 H, t, CH_3); IR (liquid film) 3440, 1730, 1695, 1650, 1660, 970 cm^{-1}; λ_{max} (EtOH) 279 nm (ϵ 26 500).

Preparation of 14. An ethereal solution of the mixed cyano-*n*-butylcuprate (3.55 mmol in 25 mL, prepared from *n*-butyllithium and cuprous cyanide as reported for **3** above), cooled to −78 °C, was treated with a solution of the enol phosphate **8** in diethyl ether (0.95 mmol in 5 mL). After being stirred at this temperature for 1 h, and a further hour at ca. −45 °C, the reaction mixture was quenched by the addition of a saturated ammonium chloride solution (10 mL). The inorganic salts were removed by filtration through Celite, and the resulting organic phase was washed with brine (15 mL) and dried over anhydrous magnesium sulfate. Filtration and concentration in vacuo gave 620 mg of a light brown oil. TLC and spectral analysis showed no starting material, and the only product was isolated by column chromatography as a light oil, 290 mg, 58% overall yield from **7** (silica gel 60, 70–230 mesh, diethyl ether; R_f 0.53): ^{1}H NMR (360 MHz, $CDCl_3$) δ 5.60–5.49 (2 H, m, olefinic), 5.41–5.40 (1 H, br s, ring olefin), 5.41–5.40 (1 H, br s, ring olefin), 4.52–4.47 (1 H, m, allylic α to OH), 4.21–4.13 (4 H, m, 2 OCH_2), 4.12–4.06 (1 H, m, allylic α to $OSiR_3$), 2.86–2.84 (1 H, m, allylic ring proton), 2.72–2.70 (1 H, m, allylic ring proton), 1.44–1.19 (20 H, t and m, 2 OEt, $(CH_2)_4$, $(CH_2)_3$), 0.92–0.83 (15 H, s and m, 2 CH_3, $SiC(CH_3)_3$), 0.0 (6 H, 2 s, $Si(CH_3)_2$); IR (liquid film) 3400, 3050–2860, 1655, 1470, 1260, 1180, 1040, 980, 880, 840, 780 cm^{-1}.

Preparation of 15. The *tert*-butyl adduct **15** was obtained as a light yellow oil following chromatography (silica gel 60, 230–400 mesh, diethyl ether; R_f 0.49; 58% overall yield from **7**), using the procedure reported above for the preparation of **14** (*tert*-butyllithium substituted for *n*-butyllithium): ^{1}H NMR (CCl_4) δ 5.60–5.35 (3 H, M, olefinic), 4.3–3.8 (6 H, m, allylic α to OH, allylic α to $OSiR_3$, 2 OCH_2CH_3), 2.8–2.55 (2 H, m, ring allylic), 1.60–1.1 (14 H, m, 2 OCH_2CH_3, $(CH_2)_4$), 0.95 (9 H, s, *tert*-butyl), 0.85 (12 H, s and m, *tert*-butyl, CH_3), 0.0 (6 H, 2 s, $Si(CH_3)_2$); IR (liquid film) 3420, 3050–2860, 1650, 1470, 1400, 1370, 1260, 1170, 1040, 960, 840 cm^{-1}.

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Useful Syntheses of *erythro*- and *threo*-*N*-Oleoyl-D-sphingosines (Ceramides) and Galactosylceramides (Cerebrosides) from L-Serine[1]

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The 4-(carbomethoxy)-2-phenyl-Δ^2-oxazoline formed from L-serine provides the basis for a useful synthesis of ceramides and cerebrosides. The natural erythro configuration and its threo epimer are formed in equal amounts but are readily separated chromatographically, so that both epimers are available for experiments in which the properties of erythro and threo configurations are to be compared. The method produces the final cerebroside product on a scale of 100 mg or more. The optical purity of the product was shown to be close to 100%. In addition to the threo epimer, other analogues of the natural cerebrosides with different chain lengths and stereochemistries should be readily available by using the route developed. Such molecules are of interest to us for ^{13}C NMR and related studies of membrane organization.

Cerebrosides (**1**, Figure 1) are a subclass of glycosphingolipids and are one of the main constituents of brain membranes.[2,3] They are the simplest type of glycosphingolipid and thus serve as a model for the hydrophobic and interfacial regions of more complex glycosphingolipids. Cerebroside and cerebroside sulfate have been shown to bind stereospecifically morphinelike compounds, a nec-

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