A Controlled Synthesis of Isocarbacyclin[1]

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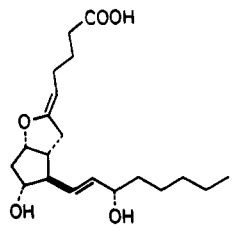
An efficient synthesis of isocarbacyclin (**2**), one of the most potent and stable prostacyclin analogues, has been achieved. The 5,6-dehydro-PGE_2 derivative **8** is converted to the α-silylated alcohol **12** via the four sequential reactions: (1) methylenation of the 9-keto group using a zinc–dibromomethane–titanium(IV) chloride mixed reagent, (2) stereoselective hydroboration by 9-borabicyclo[3.3.1]nonane and oxidative workup, (3) oxidation of the primary alcohol with pyridinium dichromate, (4) silylation of the aldehyde with the dilithium cyano-bis(dimethylphenylsilyl)cuprate. The *m*-(trifluoromethyl)benzoate **13** undergoes photochemical radical cyclization in aqueous THF containing *N*-methylcarbazole and magnesium perchlorate to lead to the allylsilane **15**. The same allylsilane is also accessible by reaction of the xanthate **14** with tributyltin hydride in the presence of di-*tert*-butyl peroxide. Deblocking of the 11- and 15-hydroxyls of **15**, regiospecific protodesilylation of the allylsilane, and alkaline hydrolysis of the ester group complete the synthesis of **2**. In a like manner, **24** is accessible from **18**.

Prostacyclin (**1**) possesses remarkable antihypertensive and platelet aggregation-inhibiting properties,[2] but for being a clinically useful agent, it must overcome the sensitivity of the 2-alkylidenetetrahydrofuran structure to hydrolytic destruction.[3] Isocarbacyclin (**2**),[4] among the various carbocyclic analogues so far prepared,[5] has deserved particular attention as a promising therapeutic agent for cardiovascular and circulatory diseases because of its potent physiological activities and satisfactory chemical stability. Efficient synthesis of **2** requires a



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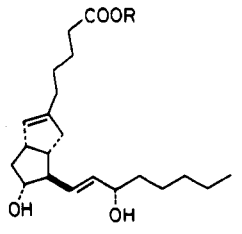
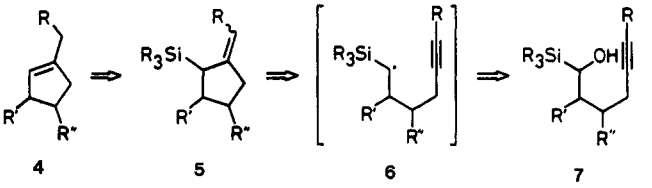


2, R = H
3, R = CH_3

controlled construction of the bicyclo[3.3.0]octene framework. Our basic strategy for the regiodefined introduction of the double bond to the fused five-membered ring is outlined in Scheme I. The 5-exo-dig addition of α-silylated radical **6** into the internal acetylenic bond,[6] followed by protodesilylation of the allylsilane **5**[7] is expected to allow

Scheme I



4 **5** **6** **7**

the selective formation of the desired cyclopentene skeleton **4**. Here the well-known Barton deoxygenation of alcohols[8] or the new Matsuura photochemical procedure[9] would provide a powerful tool for the generation of free radicals from **7**. These strategies and methodologies coupled with the recently developed three-component coupling prostaglandin (PG) synthesis[10,11] have opened a new, efficient way to **2**.[12]

The starting optically pure 5,6-dehydro-PGE_2 derivative **8** was obtained by the convergent one-pot linking of the appropriate cyclopentenone and the two side-chain units.[10] The 9-keto group (PG numbering) was methylenated by a zinc–dibromomethane–titanium(IV) mixed reagent[13] in dichloromethane to give **9** in 97% yield. Stereoselective hydroboration of **9** with 5 equiv of 9-borabicyclo[3.3.1]-nonane in THF containing 1 equiv of methyl acetate followed by workup with alkaline hydrogen peroxide gave the hydroxymethyl derivative **10** in 84% yield. Oxidation of the primary alcohol with 2.5 equiv of pyridinium dichromate in dichloromethane giving the labile aldehyde **11** (85%) was followed by immediate silylation with a

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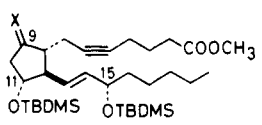
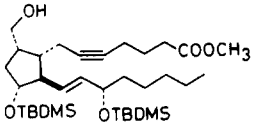
dilithium cyanobis(dimethylphenylsilyl)cuprate[7b,14] to afford the requisite α-silylated alcohol **12** in 85% yield as a 1:1 mixture of diastereomers. The key cyclization to the bicyclo[3.3.0]octane framework was cleanly effected by a photosensitized procedure.[9] Thus condensation of **12** and *m*-(trifluoromethyl)benzoyl chloride with added 4-(dimethylamino)pyridine in acetonitrile gave the benzoate **13** (90%), which in turn was exposed to a 500-W mercury lamp at room temperature in a 10:1 THF–water mixture containing *N*-methylcarbazole and magnesium perchlorate to produce the expected allylsilane **15** (5*Z*/5*E* = 1:1, 75%).



8, X = O
9, X = CH_2



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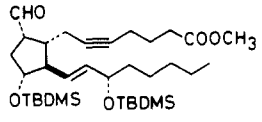

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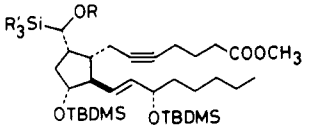
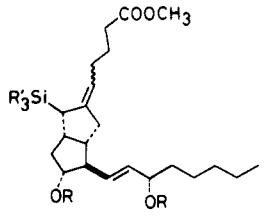


12, R = H
13, R = COC_6H_4-*m*-CF_3
14, R = C(S)SCH_3

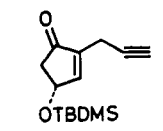


15, R = TBDMS
16, R = H

TBDMS = $Si(CH_3)_2$-*t*-C_4H_9 SiR'_3 = $Si(CH_3)_2C_6H_5$

Alternatively, the acetylenic alcohol **12** could also be converted to **15** by organotin chemistry.[8] Sequential treatment of **12** with (1) 1 equiv of lithium diisopropylamide in THF, (2) excess carbon disulfide and HMPA, and (3) methyl iodide formed the xanthate **14** in 68% yield. Subsequent reaction of **14** with a large excess of tributyltin hydride in the presence of di-*tert*-butyl peroxide in refluxing benzene led to the allylsilane **15** (5*Z*/5*E* = 1:1, 86%). Deblocking of the 11- and 15-hydroxyls of **15** with 1 N perchloric acid in a 50:1 methanol–ether mixture and subsequent protodesilylation[7,12a] of **16** with trifluoroacetic acid at −78 to −20 °C completed the synthesis of **3** in 94% yield. The methylenecyclopentane–cyclopentene transformation proceeded in a regiospecific manner, and no double bond isomers of **3** were detected by the 500-MHz ^1H NMR and HPLC assay. Alkaline hydrolysis of **3** gave **2**.[4]

This synthetic sequence finds a wide flexibility. The acetylenic compound **18** was obtainable by the organocopper conjugate addition of the ω side-chain unit[10,15] to the commercially available optically active enone **17**. This compound was converted in a like manner via **19**–**23** to the bicyclic allylsilane **24**, a useful intermediate for the modification of the α side chain of **2**.



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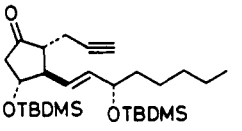

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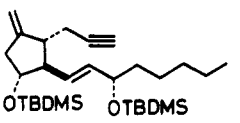

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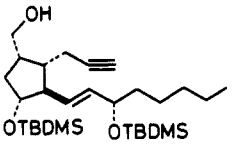

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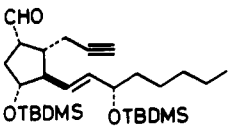

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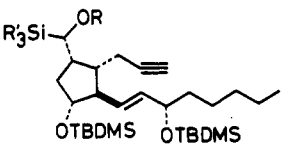
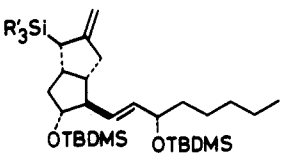


22, R = COC_6H_4-*m*-CF_3
23, R = C(S)SCH_3



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TBDMS = $Si(CH_3)_2$-*t*-C_4H_9 SiR'_3 = $Si(CH_3)_2C_6H_5$

Experimental Section

General Remarks. (a) Analyses. IR spectra were recorded on a JASCO IRA-1 spectrometer. Proton and carbon nuclear magnetic resonance (^1H and ^{13}C NMR) spectra were determined on a JEOL FX-90Q (90 MHz), GX-270 (270 MHz), or GX-500 (500 MHz) spectrometer. Chemical shifts of ^1H NMR are expressed in parts per million relative to internal tetramethylsilane (δ = 0) or chloroform (δ = 7.26) and of ^{13}C NMR relative to internal tetramethylsilane (δ = 0) or chloroform-*d* (δ = 77.1). Mass spectra (MS) and high-resolution mass spectra (HRMS) were recorded with a JEOL TMS-DX 300 spectrometer. Optical rotations were recorded on a JASCO DIP-181 digital polarimeter. The high-performance liquid chromatography (HPLC) analyses were carried out on a Waters 6000A apparatus with a Waters differential refractometer R401 RI detector using Zorbax Sil column (4.6 mm × 25 cm): solvent, 1:40 ethanol/hexane; flow rate, 1.4 mL/min; pressure, 140 kg/cm^2.

(b) Chromatography. R_f values on TLC were recorded on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. The plates were sprayed with a solution of 2% *p*-anisaldehyde in 5% ethanolic sulfuric acid and then heated until the spots became clearly visible. Column chromatography was conducted by using silica gel (E. Merck, 7734, 70–230 mesh; Fuji Devison, BW-80, 80–200 mesh; or Katayama K230, 230–400 mesh).

(c) Solvents. Ether, THF, and benzene were distilled over sodium–benzophenone ketyl under argon atmosphere. CH_2Cl_2 was distilled over P_2O_5. CH_3CN and hexamethylphosphoric triamide (HMPA) were distilled over CaH_2.

(d) Substrates and Reagents. 5,6-Dehydro-PGE_2 derivative **8**, $[\alpha]^{17}_D$ −8.9° (*c* 1.01, CH_3OH), was synthesized by our standard procedure.[10] The optically active enone **17**, $[\alpha]^{22}_D$ + 18.4° (*c* 1.23, CH_3OH), and (*S*,*E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-1-octene, $[\alpha]^{23}_D$ −37.5° (*c* 0.97, CH_3OH), were supplied from Teijin Co. The Zn–CH_2Br_2–$TiCl_4$ mixed methylenation reagent was prepared according to the procedure by Lombardo.[13a] The THF solution of $C_6H_5(CH_3)_2SiLi$ and $[C_6H_5(CH_3)_2Si]_2Cu(CN)Li_2$ were prepared by the method of Fleming.[7b,14] Copper(I) iodide (Nakarai) was continuously extracted with THF using a Soxhlet extractor and then dried in vacuo. Commercial hexane solution of *n*-C_4H_9Li (Mitsuwa or Nakarai) and pentane solution of *t*-C_4H_9Li (Aldrich) were stored at 4 °C and used directly from the bottles. Molarity

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of these alkyllithiums were determined by titration.[16] Tributylphosphine (Nakarai) was distilled before use. Carbon disulfide, methyl iodide, methyl acetate, and trifluoroacetic acid were used after distillation over P_2O_5. Dimethyl sulfoxide (DMSO) was dried over molecular sieves (4A). *N*-methylcarbazole was synthesized by the addition of methyl iodide (1.2 equiv) to the lithiated carbazole generated by mixing carbazole and *n*-C_4H_9Li (1.2 equiv) in ether at 0 °C in the presence of HMPA (1.0 equiv) followed by the stirring at 20 °C for 3 h. A solution of diisopropylamide (LDA) in THF was prepared by mixing equimolar amounts of diisopropylamine and *n*-C_4H_9Li in THF at 0 °C for 2 h, yielding a solution of LDA in THF. Reactions with organometallic reagents were conducted under argon atmosphere. The apparatus (ampule, test tube, and flask) for such reactions was evacuated by heating with a heat gun under high vaccum and then filled with argon.

(11α,13*E*,15*S*)-Methyl 11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-methyleneprost-13-en-5-yn-1-oate (9). In a 200-mL round-bottomed flask were placed a solution of the ketone **8** (961.8 mg, 1.62 mmol) in CH_2Cl_2 (60 mL) and the Zn–CH_2Br_2–$TiCl_4$ mixed methylenation reagent (slurry, 20 mL) at 0 °C. After being stirred for 1 h at 0 °C, the mixture was diluted with hexane (50 mL) and then poured into the cold saturated $NaHCO_3$ aqueous solution (100 mL). The mixture was extracted with ether (25 mL × 3). The combined extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (50 g) using a 20:1 mixture of hexane/ethyl acetate as eluant to give **9** (920.1 mg, 97%) as a colorless oil: TLC R_f 0.55 (5:1 hexane/ethyl acetate); $[\alpha]^{28}_D$ −7.1° (*c* 1.89, CH_3OH); IR ($CHCl_3$) 1740, 1660, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.02, 0.04 (s each, 12, 4 $OSiCH_3$), 0.87, 0.88, 0.89 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.6 (m, 8, 4 CH_2), 1.79 (tt, 2, *J* = 7.2, 7.2 Hz, $CH_2CH_2C(O)$), 2.1–2.4 (m, 7, 3 CH_2 and CH), 2.43 (t, 2, *J* = 7.2 Hz, $CH_2C(O)$), 2.65 (dd, 1, *J* = 6.9, 16.2 Hz, allylic CH), 3.67 (s, 3, OCH_3), 3.87 (dd, 1, *J* = 8.1, 15.0 Hz, CHO), 4.06 (dt, 1, *J* = 5.7, 5.7 Hz, allylic CHO), 4.95, 5.00 (br s each, 2, methylene), 5.41 (dd, 2, *J* = 7.6, 16.2 Hz, vinyl), 5.54 (dd, 2, *J* = 5.3, 15.2 Hz, vinyl); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −4.5, −4.4, −4.1, 13.9, 18.1, 18.3, 18.5, 22.3, 22.7, 24.6, 25.1, 26.0, 32.0, 33.0, 38.8, 42.6, 46.9, 51.2, 55.5, 73.3, 77.0, 79.6, 79.9, 107.1, 130.4, 135.6, 150.5, 173.4; MS, *m/z* 590 (M^+); HRMS, *m/z* calcd for $C_{34}H_{62}O_4Si_2$ 590.4186, found 590.4202.

(9α,11α,13*E*,15*S*)-Methyl 11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-(hydroxymethyl)prost-13-en-5-yn-1-oate (10). In a 30-mL round-bottomed flask was placed a solution of **9** (97.6 mg, 0.165 mmol) and methyl acetate (0.02 mL, 0.252 mmol) in THF (6 mL). To this was added a solution of 9-borabicyclo[3.3.1]nonane (0.5 M, 1.65 mL, 0.825 mmol) in THF at 0 °C, and the mixture was stirred for 2.5 h at 0 °C. To this were successively added 3 N NaOH aqueous solution (0.50 mL) and 30% H_2O_2 aqueous solution (0.50 mL) at 0 °C. After being stirred for 30 min at 0 °C, the mixture was poured into water (10 mL) and extracted with ether (5 mL × 3). The combined ethereal extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (6 g) using a 10:1 mixture of hexane/ethyl acetate as eluant to give **10** (84.7 mg, 84%) as a colorless oil: TLC R_f 0.46 (2:1 hexane/ethyl acetate); $[\alpha]^{26}_D$ +2.6° (*c* 1.50, CH_3OH); IR ($CHCl_3$) 3400, 1740, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.02, 0.03, 0.04 (s each, 12, 4 $OSiCH_3$), 0.87, 0.88, 0.89 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.6 (m, 10, 5 CH_2), 1.79 (tt, 2, *J* = 7.1, 7.1 Hz, $CH_2CH_2C(O)$), 2.0–2.3 (m, 7, 2 CH_2 and 3 CH), 2.42 (t, 2, *J* = 7.4 Hz, $CH_2C(O)$), 3.0–3.1 (m, 1, OH), 3.67 (s, 3, OCH_3), 3.7–3.9 (m, 2, CH_2OH), 3.97 (dd, 1, *J* = 3.6, 7.6 Hz, CHO), 4.04 (dt, 1, *J* = 6.1, 6.1 Hz, allylic CHO), 5.35 (dd, 2, *J* = 7.9, 15.5 Hz, vinyl), 5.45 (dd, 2, *J* = 5.3, 15.5 Hz, vinyl); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −4.7, −4.6, −4.3, 13.9, 17.8, 18.2, 18.4, 22.5, 24.3, 24.9, 25.8, 31.5, 31.8, 32.8, 38.6, 39.1, 41.7, 46.2, 51.2, 56.9, 63.4, 73.0, 78.8, 79.4, 80.5, 130.8, 135.1, 173.3; MS, *m/z* 608 (M^+); HRMS, *m/z* calcd for $C_{30}H_{55}O_5Si_2$ (M^+ − C_4H_9) 551.3588, found 551.3605.

(9α,11α,13*E*,15*S*)-Methyl 11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-formylprost-13-en-5-yn-1-oate (11). To a solution of **10** (46.0 mg, 7.6 × 10^{-2} mmol) in CH_2Cl_2 (10 mL) was added pyridinium dichromate (70.0 mg, 0.19 mmol) at 20 °C. The mixture was stirred for 11 h at 20 °C. The insoluble material was removed by filtration, and the filtrate was evaporated. The residual material was subjected to column chromatography on silica gel (5 g) using a 10:1 mixture of hexane/ethyl acetae as eluant to give **11** (39.0 mg, 85%) as a colorless oil; TLC R_f 0.59 (2:1 hexane/ethyl acetate); IR ($CHCl_3$) 1740, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.01, 0.02, 0.03, 0.04 (s each, 12, 4 $OSiCH_3$), 0.86, 0.89 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.7 (m, 8, 4 CH_2), 1.79 (tt, 2, *J* = 7.3, 7.3 Hz, $CH_2CH_2C(O)$), 1.9–2.3 (m, 8, 3 CH_2 and 2 CH), 2.41 (t, 2, *J* = 7.5 Hz, $CH_2C(O)$), 2.89 (ddd, 1, *J* = 3.8, 8.4, 17.3 Hz, CHC(O)H), 3.67 (s, 3, OCH_3), 3.92 (dd, 1, *J* = 7.1, 14.1 Hz, CHO), 4.06 (dt, 1, *J* = 5.5, 5.5 Hz, allylic CHO), 5.36 (dd, 1, *J* = 7.9, 15.9 Hz, vinyl), 5.53 (dd, 1, *J* = 5.1, 15.4 Hz, vinyl), 9.95 (d, 1, *J* = 2.9 Hz, C(O)H); MS, *m/z* 606 (M^+); HRMS, *m/z* calcd for $C_{34}H_{62}O_5Si_2$ 606.4136, found 606.4128.

(9α,11α,13*E*,15*S*)-Methyl 11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-[(dimethylphenylsilyl)hydroxymethyl]prost-13-en-5-yn-1-oate (12). To a solution of the aldehyde **11** (159.0 mg, 0.262 mmol) in THF (15.0 mL) was added a solution of $[C_6H_5(CH_3)_2Si]_2Cu(CN)Li_2$ (0.27 M, 1.20 mL, 0.314 mmol) in THF at −78 °C. The mixture was stirred at −78 °C for 30 min and then quenched with saturated NH_4Cl aqueous solution (10 mL) at the same temperature with vigorous shaking. The mixture was extracted with ether (10 mL × 3). The combined ethereal extracts were washed with saturated NaCl aqueous solution (25 mL), dried over Na_2SO_4, and evaporated. The residual material was subjected to column chromatography on silica gel (6 g) using a 15:1 mixture of hexane/ethyl acetate as eluant to give **12** (165.0 mg, 85%) as a colorless oil: TLC R_f 0.31 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 3400, 1740, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ −0.02, 0.01, 0.03 (s each, 12, 4 $OSiCH_3$), 0.36, 0.37 (s each, 6, 2 $SiCH_3$), 0.85, 0.87 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.7 (m, 10, 5 CH_2), 1.73 (tt, 2, *J* = 7.3, 7.3 Hz, $CH_2CH_2C(O)$), 1.93 (dt, 1, *J* = 7.1, 7.3 Hz, CH), 2.0–2.3 (m, 6, 2 CH_2 and 2 CH), 2.38 (t, 2, *J* = 7.4 Hz, $CH_2C(O)$), 3.09 (d, 1, *J* = 9.2 Hz, OH), 3.66 (s, 3, OCH_3), 3.9–4.1 (m, 3, 3 CHO), 5.29 (dd, 1, *J* = 8.4, 15.7 Hz, vinyl), 5.40 (dd, 1, *J* = 5.4, 15.3 Hz, vinyl), 7.3–7.6 (m, 5, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −4.6, −4.5, −4.1, −4.0, 13.9, 18.1, 18.3, 18.4, 22.6, 24.5, 25.0, 26.0, 32.0, 33.1, 37.5, 38.8, 42.0, 48.7, 51.2, 57.4, 64.6, 73.2, 79.4, 79.5, 80.7, 127.9, 129.1, 131.2, 134.1, 135.2, 138.1, 173.4; MS, *m/z* 685 (M^+ − C_4H_9); HRMS, *m/z* calcd for $C_{38}H_{65}O_5Si_3$ (M^+ − C_4H_9) 685.4140, found 685.4125.

(9α,11α,13*E*,15*S*)-Methyl 11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-[(dimethylphenylsilyl)((*m*-(trifluoromethyl)benzoyl)oxy)methyl]prost-13-en-5-yn-1-oate (13). To a solution of **12** (62.3 mg, 8.40 × 10^{-2} mmol) in CH_3CN (3.0 mL) were successively added 4-(dimethylamino)pyridine (25.0 mg, 0.21 mmol) and *m*-(trifluoromethyl)benzoyl chloride (0.03 mL, 0.18 mmol) at 18 °C. The mixture was stirred for 15 h at the same temperature and then poured into saturated NH_4Cl aqueous solution (3 mL). The resulting mixture was extracted with ether (3 mL × 3). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (5 g) using a 20:1 mixture of hexane/ethyl acetate as eluant to give **13** (69.3 mg, 90%) as a colorless solid: TLC R_f 0.33 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 1710, 1610, 1320, 1250, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ −0.04, −0.03, 0.00, (s each, 12, 4 $OSiCH_3$), 0.40, 0.41 (s each, 6, 2 $SiCH_3$), 0.85, 0.86 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.6 (m, 10, 5 CH_2), 1.74 (tt, 2, *J* = 7.3, 7.3 Hz, $CH_2CHC(O)$), 1.8–2.3 (m, 7, 2 CH_2 and 3 CH), 2.40 (t, 2, *J* = 7.6 Hz, $CH_2C(O)$), 2.4–2.5 (m, 1, allylic CH), 3.69 (s, 3, OCH_3), 3.76 (dd, 1, *J* = 7.3, 15.5 Hz, CHO), 3.9–4.0 (m, 1, allylic CHO), 5.20 (s, 1, vinyl), 5.22 (d, 1, *J* = 2.0 Hz, vinyl), 5.65 (d, 1, *J* = 2.3 Hz, CH(Si)O), 7.3–8.4 (m, 9, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −4.6, −4.4, −4.1, −3.9, −3.7, 13.9, 18.1, 18.3, 18.5, 18.6, 22.6, 24.5, 25.0, 26.0, 32.0, 33.1, 36.9, 38.7, 39.5, 46.2, 51.2, 55.7, 70.7, 73.1, 78.2, 79.8, 80.0, 126.6 (q, J_{C-F} = 4.1 Hz, CF_3), 127.9, 128.3, 129.0, 129.5, 129.9, 130.6, 132.0, 132.8, 134.2, 135.8, 136.2, 164.9, 173.5; MS, *m/z* 857 (M^+ − C_4H_9); HRMS, *m/z* calcd for $C_{46}H_{68}O_6Si_3F_3$ (M^+ − C_4H_9) 857.4276, found 857.4293.

(9α,11α,13*E*,15*S*)-Methyl 11,15-Bis[[(1,1-dimethylethyl)dimethylsilyl]oxy]-9-[(dimethylphenylsilyl)(((methylthio)(thiocarbonyl))oxy)methyl]prost-13-en-5-yn-1-oate (14).

(16) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

To a solution of **12** (40.5 mg, 5.45 x 10^{-2} mmol) in THF (8.0 mL) was added a solution of LDA (0.4 M, 0.14 mL, 5.6 × 10^{-2} mmol) in THF at −78 °C, and the mixture was stirred for 3 h. To this were successively added HMPA (0.24 mL, 1.32 mmol) and CS_2 (0.05 mL, 0.83 mmol), and the mixture was stirred for 1 h at 0 °C. To this was added CH_3I (0.06 mL, 0.96 mmol) at the same temperature. After 30 min, this mixture was poured into saturated NH_4Cl aqueous solution (10 mL). The mixture was extracted with ether (5 mL × 3). The combined ethereal extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (3 g) using a 20:1 mixture of hexane/ethyl acetate as eluant to give **14** (31.0 mg, 68%) as a yellow oil: TLC R_f 0.43 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 1740, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ −0.08, −0.06, −0.01, 0.02 (s each, 12, 4 $OSiCH_3$), 0.40, 0.43 (s each, 6, 2 $SiCH_3$), 0.80, 0.87 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.7 (m, 10, 5 CH_2), 1.73 (tt, 2, J = 7.3, 7.3 Hz, $CH_2CHC(O)$), 1.8–2.6 (m, 7, 2 CH_2 and 3 CH), 2.40 (t, 2, J = 7.4 Hz, $CH_2C(O)$), 2.50 (s, 3, SCH_3), 3.68 (s, 3, OCH_3), 3.72 (dd, 1, J = 7.9, 15.0 Hz, CHO), 4.00 (dt, 1, J = 5.3, 5.3 Hz, allylic CHO), 5.20 (dd, 1, J = 15.5, 7.7 Hz, vinyl), 5.37 (dd, 1, J = 5.6, 15.5 Hz, vinyl), 6.38 (d, 1, J = 2.3 Hz, CH(Si)O), 7.3–7.6 (m, 5, aromatic); ^{13}C NMR ($CDCl_3$, 67.5 MHz) δ −4.7, −4.6, −4.4, −4.2, −3.6, −3.4, 14.0, 17.9, 18.2, 18.4, 18.8, 22.6, 24.3, 25.0, 25.9, 31.8, 32.9, 36.7, 38.6, 39.9, 45.6, 51.4, 55.4, 73.0, 77.9, 79.5, 79.9, 80.6, 127.9, 129.6, 130.3, 134.1, 134.4, 135.9, 173.6, 213.4; MS, m/z 775 ($M^+ - C_4H_9$); HRMS, m/z calcd for $C_{40}H_{67}O_5Si_3S_2$ ($M^+ - C_4H_9$) 775.3738, found 775.3743.

[3a*S*-[2*E*,3aα,4α(1*E*,3*R),5β,6aα]]-Methyl 5-[Hexahydro-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-octenyl]-1-(dimethylphenylsilyl)-2(1*H*)-pentalenylidene]pentanoate and Its 2*Z* Isomer (15).** In a 10-mL test tube was placed a solution of **13** (14.0 mg, 1.53 × 10^{-2} mmol), $Mg(ClO_4)_2$ (3.4 mg, 1.53 × 10^{-2} mmol), and *N*-methylcarbazole (3.0 mg, 1.66 × 10^{-2} mmol) in a 10:1 mixture of THF and water (8.0 mL). This solution was irradiated by using a 500-W high-pressure mercury lamp at 18 °C for 16 h. The solution was poured into saturated $NaHCO_3$ aqueous solution (5 mL), and the mixture was extracted with ether (3 mL × 3). After evaporation of the solvent, the residual material was subjected to column chromatography on silica gel (1.5 g) using a 100:1 mixture of hexane/ethyl acetate as eluant to give **15** (8.3 mg, 75%) as a colorless oil: TLC R_f 0.46 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 1740, 1360, 1250, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.00, 0.02, 0.03 (s each, 12, 4 $OSiCH_3$), 0.24, 0.25, 0.26, 0.28 (s each, 6, 2 $SiCH_3$), 0.7–1.0 (m, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.0–1.7 (m, 12, 6 CH_2), 1.7–2.0 (m, 5, 3 CH and CH_2), 2.0–2.3 (m, 5, allylic 2 CH_2 and allylic CH), 3.5–3.7 (m, 1, CHO), 3.66, 3.67 (s each, 3, OCH_3), 4.02 (br, 1, CHO), 4.92, 5.09 (br each, 1, vinyl) 5.3–5.5 (m, 2, vinyl), 7.3–7.5 (m, 5, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −4.6, −4.5, −4.4, −4.1, −3.9, −3.4, 14.1, 18.1, 18.3, 22.6, 25.1, 25.4, 26.0, 29.2, 31.8, 33.6, 33.9, 38.7, 39.4, 39.7, 43.5, 43.7, 44.5, 45.0, 46.0, 51.4, 56.1, 73.3, 78.2, 119.2, 119.7, 127.7, 128.9, 129.0, 130.9, 133.8, 134.0, 134.3, 134.4, 138.3, 138.4, 143.1, 144.3, 174.1; MS, m/z 726 (M^+); HRMS, m/z calcd for $C_{42}H_{74}O_4Si_3$ 726.4895, found 726.4906.

[3a*S*-[2*E*,3aα,4α(1*E*,3*R),5β,6aα]]-Methyl 5-[Hexahydro-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-4-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-octenyl]-1-(dimethylphenylsilyl)-2(1*H*)-pentalenylidene]pentanoate and Its 2*Z* Isomer (15).** In a 20-mL test tube was placed a solution of the xanthate **14** (1.3 mg, 1.6 × 10^{-3} mmol) and tributyltin hydride (0.05 mL, 0.19 mmol) in benzene (1.0 mL). To this was added di-*tert*-butyl peroxide (2.5 mg, 1.71 × 10^{-2} mmol), and the mixture was stirred for 4 h at 65 °C. The reaction mixture was evaporated, and the residual material was subjected to column chromatography on silica gel (0.5 g) using a 200:1 mixture of hexane/ethyl acetate as eluant to give **15** (1.0 mg, 86%) as a colorless oil. TLC R_f value and spectral data of this compound were identical with those of the product derived from the *m*-(trifluoromethyl)benzoate **13** by the photochemical method described above.

[3a*S*-[2*E*,3aα,4α(1*E*,3*R),5β,6aα]]-Methyl 5-[Hexahydro-5-hydroxy-4-(3-hydroxy-1-octenyl)-1-(dimethylphenylsilyl)-2(1*H*)-pentalenylidene]pentanoate and Its 2*Z* Isomer (16).** To a solution of the allylsilane **15** (27.9 mg, 3.8 × 10^{-2} mmol) in a 1:50 mixture of ether and methanol (4.0 mL) was added a 1 M perchloric acid aqueous solution (0.6 mL, 0.6 mmol) at 18 °C. After the mixture was stirred for 30 min, to it was added saturated $NaHCO_3$ aqueous solution (3 mL). The mixture was extracted with ether (2 mL × 3). The combined ethereal extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (3 g) using a 1:1 mixture of hexane/ethyl acetate as eluant to give **16** (18.7 mg, 98%) as a colorless oil: TLC R_f 0.14 (1:1 hexane/ethyl acetate); IR ($CHCl_3$) 3600, 3400, 1730, 1100 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.25, 0.26, 0.28 (s each, 6, 2 $SiCH_3$), 0.88 (t, 3, J = 6.7 Hz, CH_3), 1.0–2.3 (m, 24, 9 CH_2, 4 CH, and 2 OH), 3.5–3.7 (m, 1, CHO), 3.66, 3.67 (s each, 3, OCH_3), 4.04 (dt, 1, J = 6.4, 6.4 Hz, allylic CHO), 4.97, 5.12 (t each, 1, J = 7.0 and 6.7 Hz, respectively, vinyl), 5.4–5.6 (m, 2, vinyl in chain), 7.3–7.5 (m, 5, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −4.4, −4.1, −3.8, −3.4, 14.1, 14.2, 22.6, 25.2, 25.5, 29.2, 31.8, 33.7, 33.8, 37.4, 39.6, 39.9, 40.0, 43.6, 43.7, 44.1, 44.8, 46.8, 51.5, 57.2, 60.4, 73.0, 76.3, 119.6, 120.0, 127.7, 129.0, 132.5, 132.8, 133.9, 135.3, 135.5, 138.2, 138.3, 143.1, 144.0, 174.1; MS, m/z 480 ($M^+ - H_2O$), 462 ($M^+ - 2\ H_2O$); HRMS, m/z calcd for $C_{30}H_{44}O_3Si$ ($M^+ - H_2O$) 480.3059, found 480.3052.

[3a*S*-[3aα,5β,6α(1*E*,3*R),6aα]]-Methyl 1,3a,4,5,6,6a-Hexahydro-5-hydroxy-6-(3-hydroxy-1-octenyl)-2-pentalenepentanoate (Isocarbacyclin Methyl Ester) (3).** To a solution of the allylsilane **16** (4.0 mg, 8.0 × 10^{-3} mmol) in CH_2Cl_2 (1.0 mL) was added a solution of trifluoroacetic acid in CH_2Cl_2 (1%, 1.0 mL, 0.13 mmol) at −78 °C. The mixture was stirred at −78 °C for 5.5 h and at −20 °C for 9 h and then poured into saturated $NaHCO_3$ aqueous solution (2 mL). The mixture was extracted with ether (2 mL × 3). The combined ethereal extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (0.5 g) using a 1:1 mixture of hexane/ethyl acetate to give **3** (2.8 mg, 96%) as a colorless oil: TLC R_f 0.14 (1:1 hexane/ethyl acetate); IR ($CHCl_3$) 3600, 3400, 1730 cm^{-1}; $[\alpha]^{19}_D$ +10.6° (*c* 0.26, CH_3OH); ^1H NMR ($CDCl_3$, 500 MHz) δ 0.89 (t, 3, J = 6.9 Hz, CH_3), 1.2–1.8 (m, 15, 6 CH_2, CH, and 2 OH), 1.8–2.1 (m, 4, $CH_2CH_2C(O)$ and allylic CH_2 in chain), 2.3–2.4 (m, 2, allylic CH_2 in ring), 2.32 (t, 2, J = 7.2 Hz, $CH_2C(O)$), 2.41 (dd, 1, J = 16.3, 8.7 Hz, allylic CH), 3.00 (dd, 1, J = 1.8, 7.0 Hz, allylic CH), 3.67 (s, 3, OCH_3), 3.78 (dd, 1, J = 2.4, 9.5 Hz, CHO), 4.09 (dt, 1 J = 6.3, 6.3 Hz, allylic CHO), 5.29 (d, 1, J = 1.2 Hz, vinyl in ring), 5.5–5.6 (m, 2, vinyl in chain); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ 14.0, 22.6, 24.6, 25.1, 27.1, 29.6, 30.5, 31.7, 33.8, 37.0, 39.4, 44.1, 45.4, 51.4, 58.1, 73.2, 76.9, 128.2, 133.7, 135.5, 141.1, 174.1; MS, m/z 346 ($M^+ - H_2O$), 328 ($M^+ - 2\ H_2O$); HRMS, m/z calcd for $C_{22}H_{34}O_3$ ($M^+ - H_2O$) 346.2508, found 346.2500. Homogeneity of **3** was confirmed as follows: HPLC (for conditions, see General Remarks) indicated a single peak at t_R 20.5 min. Carbacyclin methyl ester and its 5*Z* isomer gave t_R 24.2 and 22.1 min, respectively under the same conditions. Absence of the Δ^6-isomer was also confirmed after alkaline hydrolysis to isocarbacyclin (**2**). The 500-MHz ^1H NMR spectrum of synthetic **2** showed a signal due to the C-9α proton at δ 5.29[4,12g,h] but not at δ 5.35 where the signal of C-7 proton of the Δ^6-isomer should occur. For detailed ^1H NMR data of the latter isomer, see ref 17.

[2*R*-[2α,3β(1*E*,3*S),4α]]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-octenyl]-2-(2-propynyl)cyclopentanone (18).** In a 500-mL ampule equipped with a spiral tube was placed a solution of (*S*,*E*)-3-(*tert*-butyldimethylsiloxy)-1-iodo-1-octene (2.64 g, 7.16 mmol) in ether (42 mL) and cooled to −78 °C. To this solution was added a solution of *tert*-butyllithium in pentane (1.77 M, 8.10 mL, 14.3 mmol), and the mixture was stirred for 3 h at this temperature. In a 30-mL round-bottomed flask were placed copper(I) iodide (1.36 g, 7.16 mmol) and THF (22 mL). To this suspension was added tributylphosphine (4.64 mL, 18.62 mmol) at room temperature under stirring. The mixture was stirred until a clear solution was obtained (ca. 20 min). To the alkyllithium solution prepared above was added the solution of the copper–phosphine complex, and then the mixture was stirred for 10 min at −78 °C. To the resulting suspension was slowly added a solution of the enone **17** (1.00 g, 3.99 mmol), in THF (50 mL), over a period of 2 h. The reaction mixture was stirred for 2.5 h at −78 °C and

(17) (a) Shibasaki, M.; Iseki, K.; Ikegami, S. *Tetrahedron Lett.* **1980**, *21*, 169. (b) Iseki, K.; Mase, T.; Okazaki, T.; Shibasaki, M.; Ikegami, S. *Chem. Pharm. Bull.* **1983**, *31*, 4448.

poured into a saturated NH_4Cl aqueous solution (100 mL). The mixture was extracted with ether (40 mL × 3). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (50 g) using a 10:1 mixture of hexane/ethyl acetate as eluant to give the crude product (7.5 g). This was dissolved in CH_2Cl_2 (50 mL) followed by the addition of 30% hydrogen peroxide aqueous solution (5 mL, 410 mmol) at 0 °C. The resulting mixture was stirred for 80 min at 0 °C and poured into water (30 mL) and extracted with CH_2Cl_2 (40 mL × 3). The combined organic extracts were washed with 5% sodium bisulfite aqueous solution (200 mL), dried over Na_2SO_4, and evaporated. The residual material was subjected to column chromatography on silica gel (80 g) using a 30:1 mixture of hexane/ethyl acetate as eluant to give **18** (1.68 g, 85%) as a colorless oil: TLC R_f 0.73 (2:1 hexane/ethyl acetate); $[\alpha]^{24}_D$ −35.2° (*c* 2.24, CH_3OH); IR ($CHCl_3$) 3300, 2120, 1750 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.01, 0.05, 0.06, 0.07 (s each, 12, 4 $OSiCH_3$), 0.88, 0.89 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.2–1.6 (m, 8, 4 CH_2), 1.96 (t, 1, J = 2.6 Hz, acetylenic), 2.0–2.4 (m, 3, $C(O)CHCH_2$ and allylic CH), 2.6–2.9 (m, 3, $C(O)CH_2$ and C(O)CH), 4.0–4.2 (m, 2, 2 CHO), 5.52 (dd, 1, J = 7.9, 15.2 Hz, vinyl), 5.68 (dd, 1, J = 5.3, 15.5 Hz, vinyl); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −4.9, −4.5, −4.1, 13.9, 16.8, 18.0, 18.2, 22.6, 24.9, 25.8, 25.9, 31.9, 38.5, 47.5, 52.1, 52.5, 70.1, 72.7, 73.2, 80.9, 128.1, 137.0, 212.7; MS, m/z 492 (M^+); HRMS, m/z calcd for $C_{24}H_{43}O_3Si_2$ ($M^+ - C_4H_9$) 435.2750, found 435.2738.

[1*R*-[1α(1*E*,3*R),2β,5β]]-(1,1-Dimethylethyl)[[1-[2-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-3-methylene-2-(2-propynyl)cyclopentyl]ethenyl]hexyl]oxy]dimethylsilane (19).** In a 100-mL round-bottomed flask were placed a solution of the ketone **18** (412.5 mg, 0.84 mmol) in CH_2Cl_2 (20 mL) and the $Zn–CH_2Br_2–TiCl_4$ mixed methylenation reagent[13a] (slurry, 10 mL) at 0 °C. The mixture was stirred at 0 °C for 1 h and was poured into a cold saturated $NaHCO_3$ aqueous solution (20 mL). The mixture was extracted with ether (10 × 3 mL). The combined ethereal extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (45 g) using a 30:1 mixture of hexane/ethyl acetate as eluant to give **19** (308.7 mg, 78%) as a colorless oil: TLC R_f 0.71 (5:1 hexane/ethyl acetate); $[\alpha]^{24}_D$ −20.3° (*c* 1.77, CH_3OH); IR ($CHCl_3$) 3300, 2120 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.02, 0.04 (s each, 12, 4 $OSiCH_3$), 0.87, 0.89 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.6 (m, 8, 4 CH_2), 1.93 (t, 1, J = 2.6 Hz, acetylenic), 2.2–2.8 (m, 6, 2 CH_2 and 2 CH), 3.88 (dd, 1, J = 7.9, 14.8 Hz, CHO), 4.07 (dt, 1, J = 5.6, 11.2 Hz, allylic CHO), 4.98, 5.02 (br s each, 2, methylene), 5.42 (dd, 1, J = 7.9, 15,3 Hz, vinyl), 5.57 (dd, 1, J = 5.1, 15.3 Hz, vinyl); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −4.6, −4.4, −4.1, 14.1, 18.1, 18.3, 21.4, 22.7, 25.1, 26.0, 31.9, 38.7, 42.3, 45.9, 55.2, 69.1, 73.0, 76.6, 82.7, 107.3, 129.8, 136.0, 149.8; MS, m/z 490 (M^+); HRMS, m/z calcd for $C_{29}H_{54}O_2Si_2$ 490.3662, found 490.3658.

[1*S*-[1α,2α,3β(1*E*,3*R),4α]]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy-1-octenyl]-2-(2-propynyl)cyclopentanemethanol (20).** In a 30-mL round-bottomed flask was placed a solution of **19** (494.0 mg, 1.01 mmol) in THF (5 mL). To this solution was added a solution of 9-borabicyclo[3.3.1]nonane in THF (0.5 M, 4.5 mL, 2.3 mmol) at 0 °C, and the mixture was stirred at 0 °C for 30 min. After warming to 18 °C, the mixture was stirred for 2.5 h at this temperature. Then 3 N NaOH aqueous solution (0.6 mL) and 30% H_2O_2 aqueous solution (0.6 mL) were successively added at 0 °C, and the mixture was stirred for 15 min. The reaction mixture was poured into water (5 mL), and the mixture was extracted with ether (3 mL × 3). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (50 g) using a 7:1 mixture of hexane/ethyl acetate as eluant to give **20** (194.7 mg, 38%) as a colorless oil: TLC R_f 0.22 (5:1 hexane/ethyl acetate); $[\alpha]^{21}_D$ +1.1° (*c* 1.08, CH_3OH); IR ($CHCl_3$) 3400, 3300, 2320 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.0–0.1 (m, 12, 4 $OSiCH_3$), 0.8–1.0 (m, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.9 (m, 11, 5 CH_2 and OH), 1.95 (t, 1, J = 2.6 Hz, acetylenic), 2.0–2.3 (m, 5, CH_2 and 3 CH), 3.7–3.9 (m, 2, CH_2O), 3.9–4.1 (m, 2, 2 CHO), 5.3–5.5 (m, 2, vinyl); ^{13}C NMR (C_6D_6, 22.5 MHz) δ −4.6, −4.4, −4.1, 14.1, 18.0, 18.2, 18.3, 22.9, 25.4, 26.0, 32.1, 39.0, 41.2, 45.6, 57.1, 63.2, 69.1, 73.1, 78.8, 84.0, 131.0, 135.7; MS, m/z 508 (M^+); HRMS, m/z calcd for $C_{29}H_{56}O_3Si_2$ 508.3768, found 508.3780.

[1*S*-[1α,2α,3β(1*E*,3*R),4α]]-4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-octenyl]-2-(2-propynyl)cyclopentanecarboxaldehyde (21).** To a solution of oxalyl chloride (0.03 mL, 0.34 mmol) in CH_2Cl_2 (2.0 mL) was added DMSO (0.05 mL, 0.70 mmol) slowly under stirring at −50 °C. After 5 min, to this was added a solution of **20** (132 mg, 0.26 mmol) in CH_2Cl_2 (1.0 mL), and the mixture was stirred for 5 min at −50 °C. Triethylamine (0.2 mL, 1.4 mmol) was added to the mixture at −50 °C and stirred for 10 min at the same temperature. After warming to 17 °C, the mixture was stirred for 1 h and then poured into water (5 mL). The mixture was extracted with CH_2Cl_2 (3 mL × 3). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (10 g) using a 15:1 mixture of hexane/ethyl acetate as eluant to give **21** (124.7 mg, 95%) as a colorless oil: TLC R_f 0.44 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 3300, 2320, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ 0.02, 0.03, 0.04, 0.05 (s each, 12, 4 $OSiCH_3$), 0.87, 0.89 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.0–1.6 (m, 9, 4 CH_2 and CH), 1.9–2.2 (m, 3, acetylenic and CH_2 in ring), 2.2–2.5 (m, 3, allylic CH and CH_2), 2.8–3.0 (m, 1, C(O)CH), 3.95 (dd, 1, J = 6.8, 13.7 Hz, CHO), 4.07 (dt, 1, J = 5.5, 5.5 Hz, allylic CHO), 5.36 (dd, 1, J = 8.4, 16.5 Hz, vinyl), 5.56 (dd, 1, J = 5.1, 15.4 Hz, vinyl), 9.97 (d, 1, J = 2.9 Hz, C(O)H); MS, m/z 449 ($M^+ - C_4H_9$); HRMS, m/z calcd for $C_{25}H_{45}O_3Si_2$ ($M^+ - C_4H_9$) 449.2907, found 449.2926.

[1*S*-[1α,2α,3β(1*E*,3*R),4α]]-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-octenyl]-2-(2-propynyl)cyclopentyl](dimethylphenysilyl)methyl *m*-(Trifluoromethyl)benzoate (22).** To a solution of the aldehyde **21** (123.8 mg, 0.24 mmol) in THF (8.0 mL) was added a solution of $C_6H_5(CH_3)_2SiLi$ (0.62 M, 0.48 mL, 0.30 mmol) in THF at −78 °C and stirred for 5 min at this temperature. To this mixture were successively added HMPA (0.4 mL, 2.4 mmol) and *m*-(trifluoromethyl)benzoyl chloride (0.11 mL, 0.74 mmol) at −78 °C. The mixture was warmed to 0 °C, stirred for 60 min, and then poured into a saturated NH_4Cl aqueous solution (6 mL). The mixture was extracted with ether (6 mL × 3), and the combined ethereal extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (6 g) using a 70:1 mixture of hexane/ethyl acetate as eluant to give **22** (132.5 mg, 67%) as a colorless oil: TLC R_f 0.60 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 3300, 2120, 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ −0.05, −0.04, −0.01 (s each, 12, 4 $OSiCH_3$), 0.39 (s, 6, 2 $SiCH_3$), 0.82, 0.84, 0.85 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–1.4 (m, 8, 4 CH_2), 1.4–2.6 (m, 7, 2 CH_2 and 3 CH), 1.84 (t, 1, J = 2.6 Hz, acetylenic), 3.78 (dd, 1, J = 7.3, 15.8 Hz, CHO in ring), 3.9–4.0 (m, 1, allylic CHO), 5.1–5.3 (m, 2, vinyl), 5.64 (d, 1, J = 2.3 Hz, CH(Si)O), 7.3–8.3 (m, 9, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ −5.0, −4.7, −4.5, −4.2, −4.1, 14.0, 17.8, 18.2, 22.6, 25.1, 25.9, 31.9, 36.5, 38.7, 39.1, 45.5, 55.7, 69.1, 70.4, 72.9, 78.1, 83.3, 126.5, 126.7, 127.7, 127.9, 129.1, 129.2, 129.6, 130.1, 131.7, 132.8, 133.1, 134.2, 136.2, 164.9; MS, m/z 757 ($M^+ - C_4H_9$); HRMS, m/z calcd for $C_{41}H_{60}O_4Si_3F_3$ ($M^+ - C_4H_9$) 757.3751, found 757.3737.

[1*S*-[1α,2α,3β(1*E*,3*R),4α]]-*O*-[4-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-3-[3-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-octenyl]-2-(2-propynyl)cyclopentyl](dimethylphenysilyl)methyl *S*-Methyl Carbonodithioate (23).** To a solution of the aldehyde **21** (21.2 mg, 4.2×10^{-2} mmol) in THF (1.5 mL) was added a solution of $C_6H_5(CH_3)_2SiLi$ (0.6 M, 0.2 mL, 0.13 mmol) in THF at −78 °C and stirred for 5 min at this temperature. To this mixture were successively added HMPA (0.4 mL, 2.2 mmol) and CS_2 (0.02 mL, 0.33 mmol) and warmed to 0 °C. After 60 min, to this was added CH_3I (0.02 mL, 0.33 mmol) and stirred for 30 min at 0 °C. The reaction mixture was poured into a saturated NH_4Cl aqueous solution (2 mL), and the mixture was extracted with ether (2 mL × 3). The combined ethereal extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (5 g) using a 20:1 mixture of hexane/ethyl acetate as eluant to give **23** (26.0 mg, 84%) as a yellow oil: TLC R_f 0.51 (5:1 hexane/ethyl acetate); IR ($CHCl_3$) 3310, 2120 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ −0.07, −0.06, −0.01, 0.02 (s each, 12, 4 $OSiCH_3$), 0.41, 0.43 (s each, 6, 2 $SiCH_3$), 0.7–1.0 (m, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1–2.6 (m, 15, 6 CH_2 and 3 CH), 1.18 (t, 1, J = 2.5 Hz, acetylenic),

2.52 (s, 3, SCH_3), 3.73 (dd, 1, J = 8.6, 15.0 Hz, CHO), 4.01 (dt, 1, J = 5.6, 5.6 Hz, allylic CHO), 5.23 (dd, 1, J = 7.3, 15.5 Hz, vinyl), 5.39 (dd, 1, J = 5.4, 15.3 Hz, vinyl), 6.39 (d, 1, J = 2.3 Hz, CH(Si)O), 7.2-7.6 (m, 5, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ -4.6, -4.4, -4.0, -3.7, -3.4, 14.1, 18.0, 18.3, 18.5, 18.7, 22.7, 25.1, 26.0, 32.0, 36.6, 38.7, 40.0, 45.5, 55.5, 69.0, 73.0, 78.0, 80.5, 83.4, 127.7, 127.9, 129.7, 130.2, 134.3, 136.1, 213.8; MS, m/z 732 (M^+); HRMS, m/z calcd for $C_{39}H_{68}O_3Si_3S_2$ 732.3917, found 732.3908.

[3a*R*-[3aα,4α(1*E*,3*R),5β,6aα]]-(1,1-Dimethylethyl)[[1-[2-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-(dimethylphenylsilyl)-2-methylene-4-octahydropentalenyl]ethenyl]hexyl]oxy]dimethylsilane (24).** The solution of **22** (20.0 mg, 2.45×10^{-2} mmol), $Mg(ClO_4)_2$ (5.5 mg, 2.46×10^{-2} mmol), and *N*-methylcarbazole (4.5 mg, 2.48×10^{-2} mmol) in a 10:1 mixture of THF and water (7.5 mL) was irradiated by using a 500-W high-pressure mercury lamp at 20 °C for 4 h. This solution was poured into a saturated $NaHCO_3$ aqueous solution (5 mL). The resulting mixture was extracted with ether (5 mL × 3). The combined organic extracts were dried over Na_2SO_4 and evaporated. The residual material was subjected to column chromatography on silica gel (2 g) using a 100:1 mixture of hexane/ethyl acetate as eluant to give **24** (7.7 mg, 50%) as a colorless oil: TLC R_f 0.77 (5:1 hexane/ethyl acetate); $[\alpha]^{24}_D$ -27.5° (c 1.04, hexane); IR ($CHCl_3$) 1640, 1460, 1360 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ -0.01, 0.02 (s each, 12, 4 $OSiCH_3$), 0.28, 0.29 (s each, 6, 2 $SiCH_3$), 0.85, 0.88 (s each, 21, 2 $OSiC(CH_3)_3$ and CH_3), 1.1-1.5 (m, 9, 4 CH_2 and CH), 1.8-2.4 (m, 7, 2 CH_2 and 3 CH), 3.67 (dd, 1, J = 9.2, 16.2 Hz, CHO), 3.9-4.1 (m, 1, allylic CHO), 4.55, 4.74 (br s each, 2, methylene), 5.3-5.6 (m, 2, vinyl), 7.2-7.6 (m, 5, aromatic); ^{13}C NMR ($CDCl_3$, 22.5 MHz) δ -4.6, -4.4, -4.2, -4.1, 14.0, 18.1, 18.3, 22.7, 25.1, 26.0, 31.9, 38.7, 39.3, 41.0, 43.9, 44.7, 46.1, 55.7, 73.3, 78.2, 104.8, 127.6, 128.9, 130.8, 134.0, 134.5, 138.2, 153.4; MS, m/z 626 (M^+); HRMS, m/z calcd for $C_{37}H_{66}O_2Si_3$ 626.4370, found 626.4387.

[3a*R*-[3aα,4aα(1*E*,3*R),5β,6aα]]-(1,1-Dimethylethyl)[[1-[2-[5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-1-(dimethylphenylsilyl)-2-methylene-4-octahydropentalenyl]ethenyl]hexyl]oxy]dimethylsilane (24).** In a 20-mL test tube was placed a solution of the xanthate **23** (17.5 mg, 2.4×10^{-2} mmol) in benzene (1.0 mL). Tributyltin hydride (0.01 mL, 3.7×10^{-2} mmol) and di-*tert*-butyl peroxide (2.5 mg, 1.71×10^{-2} mmol) were added at 75 °C, and the mixture was stirred for 36 h. The reaction mixture was evaporated, and the residual material was subjected to column chromatography on silica gel (3 g) using a 25:1 mixture of hexane/ethyl acetate as eluant to give **24** (11.9 mg, 79%) as a colorless oil. TLC R_f value and spectral data of this compound were identical with those of the product derived from the *m*-(trifluoromethyl)benzoate **22** by the photochemical method described above.

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A Stereoselective Synthesis of (+)-Prelog-Djerassi Lactone from Furanoid Intermediates

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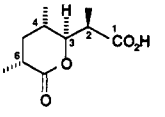
A facile and concise asymmetric synthesis of the methyl ester of Prelog-Djerassi lactonic acid **22** has been completed in nine chemical operations and 10% overall yield from furaldehyde (**4**) by employing a strategy that featured the use of homochiral furfuryl carbinols as latent hydropyranones. The stereocenters at C(2) and C(3) of **22** were established in an absolute sense by the diastereoselective aldol condensation of furaldehyde (**4**) with the boron enolate derived from the chiral imide **5** using the methodology developed by Evans. Removal of the chiral auxiliary followed by oxidation of the furan ring unmasked the hydropyranone ring system, and subsequent protection of the anomeric hydroxyl group led to the production of the glycoside derivative **13a** in good overall yield. Homologation of **13a** via conjugate addition of lithium dimethylcuprate followed by oxidation afforded the enone **17**, which was olefinated by a Wittig reaction to give the diene **18**. Sequential stereoselective, catalytic hydrogenation of **18** and Jones oxidation completed the asymmetric synthesis of the methyl ester of Prelog-Djerassi lactone **22**.

Introduction

The Prelog-Djerassi lactonic acid **1**, which was originally isolated as a degradation product of narbomycin, methymycin, picromycin, and neomethymycin,[2-4] has served as an important focal point for the design and application of new methods that allow the stereoselective elaboration of cyclic and acyclic carbon skeleta bearing a number of contiguous and/or alternating stereocenters. Since the stereochemical relationships present in **1** are found in other macrolide and ionophore antibiotics, the strategies and tactics that have been developed for its assemblage may be extended to the stereoselective syntheses of those more complex natural products. It is therefore not surprising that Prelog-Djerassi lactonic acid **1** has emerged as one of the standard benchmarks against which new methodology for effecting stereoselective carbon-carbon bond construction and functionalization of carbon frameworks is measured, and at this writing some 34 successes in this venture have been recorded.[5]



1

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