Anal. Calcd for $C_{20}H_{23}O_4 \cdot 0.75H_2O$: C, 67.69; H, 6.95; N, 4.10. Found: C, 67.64; H, 6.79; N, 4.02; H_2O (Karl Fisher), 3.74.

***N*-(2-Hydroxyethyl)norcodeine (5c).** A mixture of 13.8 g (48 mmol) of norcodeine,[13] 5.8 g (69 mmol) of $NaHCO_3$, 145 mL of absolute alcohol, and 6.16 g (49 mmol) of 2-bromoethanol was allowed to reflux with stirring under N_2 for 27 h. The solution was filtered hot, giving a mixture of product and inorganic material weighing 7.6 g, mp 189–195 °C. The filtrate was concentrated to 100 mL under vacuum and cooled to give an additional 7.2 g of product, mp 185–195 °C. Recrystallization of 3 g of the crude product from 35 mL of ethanol gave 1.1 g of near colorless crystals: mp 190–192 °C; NMR ($CDCl_3$ + Me_2SO-d_6) δ 6.5 (dd, 2 H), 5.6 (d, 1 H), 5.22 (d, 1 H), 4.75 (d, 1 H), 4.2 (br, 1 H), 3.78 (s, 3 H), 3.7–3.2 (m, 8 H), 2.9–2.4 (m, 4 H); mass spectrum, *m/e* 329 (M^+).

Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 14.01. Found: C, 69.11; H, 7.19; N, 4.20.

Codeine-6-(2-phenyltetrazole) Ether (5d). A solution of 1 g (3.3 mmol) of codeine in 50 mL of dry THF (distilled from CaH_2) was added to a suspension of 0.34 g (6.9 mmol) of NaH (50% dispersion in mineral oil, previously washed with 2 × 15 mL of dry THF). After being stirred for 1 h at room temperature under N_2, the mixture was treated with a solution of 1.2 g (6.7 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole (Aldrich) in 50 mL of dry THF. The mixture was stirred for 15 min at room temperature and quenched with 20 mL of 1 N alcoholic $NaOC_2H_5$. The solution was diluted with 50 mL of H_2O and evaporated to remove solvents. The aqueous solution was extracted with $CHCl_3$, and the combined extracts were washed with H_2O, dried (Na_2SO_4), and evaporated to give a crude solid which was recrystallized from 25 mL of CH_3CN, yielding 0.78 g (53%) of **5d** as colorless crystals: mp 207–208 °C; NMR ($CDCl_3$) δ 8.0–7.8 (m, 2 H), 7.65–7.4 (m, 3 H), 6.65 (d, 2 H), 5.95–5.4 (m, 4 H), 3.75 (s, 3 H), 3.5–3.2 (m, 2 H), 3.0–2.75 (m, 2 H), 2.5 (s, 3 H), 2.5–1.9 (m, 4 H); IR ($CHCl_3$) 2900, 1600, 1500, 1450 cm^{-1}; mass spectrum, *m/e* 443 (M^+).

Anal. Calcd for $C_{25}H_{25}N_5O_3$: C, 67.71; H, 5.68; N, 15.79. Found: C, 67.73; H, 5.72; N, 15.84.

Norcodeine-6-(2-phenyltetrazole) Ether (5e). A solution of 2.65 g (9.7 mmol) of norcodeine[10] (**5b**) in a mixture of 50 mL of dry THF and 7 mL of dry hexamethylphosphoramide (HMPA) was added to a suspension of 0.50 g (10.4 mmol) of NaH. (50% dispersion in mineral oil, washed with 2 × 20 mL of dry THF). After being stirred for 1.5 h at room temperature under N_2, the mixture was added to a solution of 1.84 g (10.2 mmol) of 5-chloro-1-phenyl-1*H*-tetrazole in 50 mL of dry THF and 2 mL of dry HMPA. The cloudy solution was stirred for 15 min at room temperature and quenched with 35 mL of 1 N alcoholic $NaOC_2H_5$. The solution was diluted with 50 mL of H_2O and evaporated under vacuum to remove THF. The aqueous solution was diluted to 100 mL with H_2O and extracted with 5 × 50 mL of $CHCl_3$. The extract was washed with 3 × 50 mL of H_2O, dried, filtered, and evaporated to give an oily residue, from which a light yellow solid precipitated after cooling for 17 h. The product was filtered, washed with H_2O to remove all solvents, and dried to give 2.7 g (64%), mp 186–188 °C. A 500-mg sample of the product recrystallized from 5 mL of CH_3CN in long light yellow needles to give 250 mg of **5e**, mp 191–192 °C. Mixture melting point with norcodeine was depressed (157–172 °C): NMR ($CDCl_3$) δ 7.95–7.8 (m, 2 H), 7.6–7.4 (m, 3 H), 6.65 (s, 2 H), 5.95–5.3 (m, 4, H), 3.75 (s, 3 H), 3.1–2.6 (m, 5 H), 2.2–2.7 (m, 3 H); IR (KBr) 2875, 1580, 1490, 1440 cm^{-1}; mass spectrum, *m/e* 429 (M^+).

Anal. Calcd for $C_{24}H_{23}N_5O_3$: C, 67.12; H, 5.39; N, 16.31. Found: C, 67.24; H, 5.50; N, 16.22.

6-(2-Hydroxyethyl)norapocodeine (6c). A solution of 1 g (3 mmol) of **5c** in 5 mL of methanesulfonic acid was heated at 95 °C for 45 min. The solution was cooled to about 50 °C and poured slowly into a solution of 14 g of $KHCO_3$ in 75 mL of H_2O with stirring. After 1 h the mixture was filtered and the near colorless solid washed with H_2O and dried, giving 0.79 g (84%) of **6c**. A 200-mg sample of the product was purified by preparative-plate chromatography with 5% MeOH in EtOAc, recovering a band at R_f 0.35–0.60. The yield of pure product as a hydrate was 100 mg (42%): mp 68–72 °C; NMR ($CDCl_3$) δ 8.3 (dd, 1 H, J = 7.0 and 0.75 Hz), 7.2 (q, 1 H), 7.0 (dd, 1 H), 6.75 (s, 2 H), 3.82 (s, 3 H), 3.7–2.2 (m, 11 H); mass spectrum, *m/e* 311 (M^+); UV_{max} (EtOH) 274 nm (log ϵ 3.62); $[\alpha]^{23}_{Hg546}$ -55.5°.

Anal. Calcd for $C_{19}H_{21}NO_3 \cdot {}^1/_3H_2O$: C, 71.90; H, 6.87; N, 4.41; H_2O, 1.89. Found: C, 71.66; H, 7.03; N, 4.36, H_2O (Karl Fisher) 1.22.

6-(2-Chloroethyl)norapocodeine (6d). A mixture of 3 g (9.63 mmol) of 6-(2-hydroxyethyl)norapocodeine (**6c**), 100 mL of dry CH_3CN, and 2.5 mL of $SOCl_2$ was stirred at room temperature for 3 h. The solution was evaporated to dryness, and the residue was stirred for 72 h with a mixture of Et_2O (75 mL) and saturated aqueous $KHCO_3$ (30 mL). The mixture was then filtered, and the Et_2O layer was separated, dried (Na_2SO_4), and evaporated to give 739 mg (23%) of **6d**, mp 79–83 °C. No further purification of this material was required: ^1H NMR ($CDCl_3$, 60 MHZ) δ 8.2 (dd, 1 H, J = 7.0 and 0.75 Hz), 7.1 (q, 1 H), 7.0 (dd, 1 H), 6.8 (s, 2 H), 3.95 (s, 3 H), 3.7–2.5 (m, 11 H); IR ($CHCl_3$) 3450, 3000, 2900 cm^{-1}; UV (EtOH) 274 nm (log ϵ 3.99).

Anal. Calcd for $C_{19}H_{20}ClNO_2$: C, 69.19; H, 6.11; Cl, 10.75; N, 4.25. Found: C, 68.96; H, 6.34; Cl, 10.53; N, 4.13.

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Registry No. **1a**, 115-37-7; **1b**, 2579-67-1; **1c**, 73378-04-8; **4a**, 73378-05-9; **4b**, 70521-87-8; **4c**, 73384-20-0; **5a**, 76-57-3; **5b**, 467-15-2; **5c**, 73378-06-0; **5d**, 73378-07-1; **5e**, 73378-08-2; **6a**, 641-36-1; **6a**·HCl, 6377-14-6; **6b**·HCl, 73378-09-3; **6c**, 73378-10-6; **6d**, 73378-11-7; 2-bromoethanol, 540-51-2; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4.

Prostaglandins and Congeners. 27.[1] Synthesis of Biologically Active 16-Halomethyl Derivatives of 15-Deoxy-16-hydroxyprostaglandin E_2

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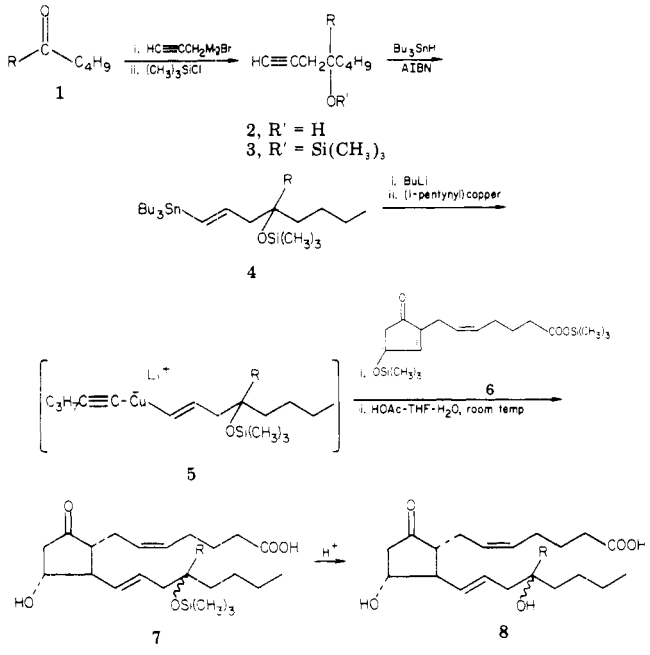
The 16-CF_3, -CHF_2, -CH_2F, and -CH_2Cl derivatives of DL-15-deoxy-16-hydroxyprostaglandin E_2 (**8a**, **8b**, **8c**, and **8d**, respectively) were prepared by conjugate addition of the lithiocuprates derived from the appropriately functionalized vinylstannanes **4** to cyclopentenone **6**. Hydrolysis of the rather stable O–Si linkage at C-16 of the prostaglandin is discussed. The ^{13}C NMR chemical shifts of the prostaglandin analogues and intermediates are noted.

Recent reports from these laboratories and elsewhere have described the 15-deoxy-16-hydroxy-16-methyl-prostaglandins (**8e**) as potent bronchodilators[2] and gastric antisecretory agents.[3] It is well-known that introduction

0022-3263/80/1945-2278$01.00/0

Scheme I

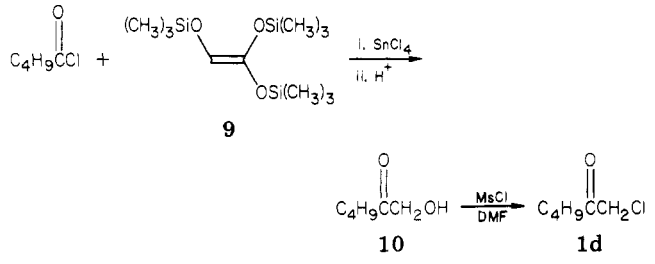


a, R = CF_3; b, R = CHF_2; c, R = CH_2F; d, R = CH_2Cl; e, R = CH_3

of a fluorine atom into a biologically active molecule frequently results in an enhancement of activity, since the subtle perturbation brought by fluorine to the molecule may induce important biological effects.[4] In a continuing effort to discover a selective prostaglandin derivative suitable for therapeutic use, we have undertaken the synthesis of the 16-mono- and poly(fluoromethyl) as well as the 16-chloromethyl derivatives of 15-deoxy-16-hydroxyprostaglandin E_2 (**8a–d**).

The key step in our synthetic approach is a conjugate addition to bis(trimethylsilyloxy) cyclopentenone **6** of an appropriately substituted lithiocuprate **5** derived from the corresponding vinylstannane **4** as shown in Scheme I. 1,1,1-Trifluoro-2-hexanone (**1a**)[5] was condensed with propargylmagnesium bromide to give 4-(trifluoromethyl)-4-hydroxy-1-octyne (**2a**) which was protected as the trimethylsilyl ether **3a**. Treatment of **3a** with tributylstannane[6,7] in the presence of azobis(isobutyronitrile) (AIBN) furnished (*E*)-1-(tributylstannyl)-4-(trifluoromethyl)-4-((trimethylsilyl)oxy)-1-octene (**4a**). Lithiation of vinylstannane **4a** with 1 equiv of *n*-BuLi followed by addition of 1-pentynyl copper,[8] solubilized in tributylphosphine and ether, and treatment of the resulting lithiocuprate **5** with cyclopentenone **6**[9] provided, after deblocking (HOAc–THF–H_2O, room temperature) and dry column chromatography, DL-15-deoxy-16-(trifluoromethyl)-16-(trimethylsilyloxy)-PGE_2 (**7a**) in 45% yield.

Scheme II



Acid hydrolysis of the 16-$OSiMe_3$ group in **7a** was extremely slow; less than 30% desilylation was observed after 8 h of exposure to HOAc–THF–H_2O (4:2:1) at 55 °C and this was accompanied by simultaneous formation of the corresponding PGA_2 derivative. However, **7a** could be effectively hydrolyzed to **8a** by HOAc–THF–H_2O (4:2:1) at 40 °C (3 h) in the presence of one drop of 4 N HCl. Under these conditions, the formation of the PGA_2 derivative was negligible. On the other hand, **7a** also could be desilylated to **8a** quantitatively by a suspension of potassium fluoride in DMF at room temperature without affecting the sensitive β-ketol system.[10]

For the difluoromethyl series (**b** series), the requisite 1,1-difluoro-2-hexanone (**1b**) was prepared in 50% yield by slow addition of 2 equiv of BuLi to difluoroacetic acid (inverse addition) at −78 °C during 3 h. Regular addition or reaction at higher temperature resulted in very low yields.[11,12] For the fluoromethyl series (**c** series), fluoromethyl ketone (**1c**) was prepared according to the literature procedure.[13]

For the chloromethyl series (**d** series), reaction of valeryl chloride with tris((trimethylsilyl)oxy)ethylene (**9**)[14] catalyzed by stannic chloride and followed by acid hydrolysis provided the hydroxymethyl ketone **10** which was converted to the chloromethyl ketone **1d** by treatment with mesyl chloride[15] in DMF at 85 °C (Scheme II). In our hands this process is superior to that previously reported[16] in terms of yield and absence of byproducts. Ketones **1b–d** were transformed via the intermediate octynes **2** and **3** to the corresponding vinylstannanes **4b–d**, as described above for the trifluoromethyl series **1a**. Conjugate addition to enone **6** provided the corresponding prostaglandin E_2 derivatives **8b–d**. The stability of the O–Si linkage in **7b–d** toward acid-catalyzed hydrolysis diminished as the electronegativity of the C-16 substitution (R) decreased, so that

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(10) Corey has reported that tetra-*n*-butylammonium fluoride in THF was incompatible with the integrity of the prostaglandin β-ketol systems; E. J. Corey and A. Venkateswarlu, *J. Am. Chem. Soc.*, **94**, 6190 (1972). After completion of this manuscript, Newton et al. reported that aqueous HF in acetonitrile is a useful desilylation reagent for the regeneration of the β-ketol system in prostaglandin E compounds; R. F. Newton, D. P. Reynolds, M. A. W. Finch, D. R. Kelly, and S. M. Roberts, *Tetrahedron Lett.*, 3981 (1979).
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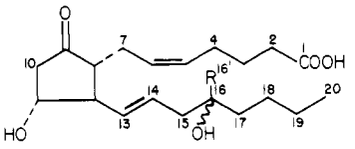
Table I. ^{13}C NMR Chemical Shifts (Parts per Million) of Prostaglandin Analogues 8a-e[a,b]



R (compd)	CH_3 (8e)	CH_2Cl (8d)	CH_2F (8c)	CHF_2 (8b)	CF_3 (8a)
C1	177.8	178.4	178.2	178.4	178.8
C2	33.3	33.4	33.4	33.4	33.3
C3	24.5	24.6	24.6	24.5	24.5
C4	26.5	26.2	26.6	26.6	26.5
C5	130.8	130.9	130.9	130.9	131.0
C6	126.7	126.7	126.7	126.7	126.6
C7	25.0	25.2	25.1	25.1	25.2
C8	54.7	54.7	54.7	54.7	54.6
C9	215.0	215.1	215.0	215.2	214.8
C10	46.5	46.5	46.5	46.4	46.3
C11	72.0	72.1	72.0	72.1	72.2
C12	53.7	53.7	53.6	53.5	53.6
C13	133.6	134.4	134.2	134.7	135.1
C14	129.4	128.2	128.1 (128.0)	127.4 (127.3)	126.6
C15	44.8	40.4 (40.2)	39.5 (dd)	37.2 (36.8)	37.2 (36.9)
C16	75.13 (75.06)	74.2	73.9 (73.6) (d, J_{CCF} = 17.3, 17.6 Hz)	74.1 (t, J_{CCF} = 20 Hz)	75.2 (75.0) (q, J_{CCF} = 26.5 Hz)
C17	42.1 (41.3)	37.1 (36.7)	36 (dd)	34.0	34.0
C18	26.1	25.6 (25.3)	~25.0	24.8	24.9
C19	23.2	23.2	23.3	23.3	23.1
C20	14.1	14.1	14.0	14.0	13.9
C16′	26.7 (26.2)	51.4 (50.8)	87.3 (87.5) (d, J_{CF} = 170 Hz)	117.4 (t, J_{CF} = 247 Hz)	126.5 (125.5) (q, J_{CF} = 286 Hz)

[a] The chemical shifts in parentheses represent chemical shifts of the corresponding 16 epimer. The two peaks for any one carbon of those carbons are approximately of equal height. [b] d = doublet, t = triplet, q = quartet, dd = an ill-resolved pair of doublets.

7c and **7d** can be desilylated to **8c** and **8d** by HOAc–THF–H_2O at 40 °C without HCl catalysis, while catalytic HCl at 40 °C was necessary for the conversion of **7b** to **8b**.

The paired peaks for certain carbons, notably carbons 14–17 and/or C-16′, in the ^{13}C NMR spectra (Table I) of **8a–d** indicated approximately 50/50 mixtures of two diastereomers at C-16. The chemical shift of C-16′ of **8a–e** (Table I) is consistent with the trend observed for the reactivity of the O–Si linkage toward acid hydrolysis. The chemical-shift constancy of all carbons, except carbons 13–17 of **8a–e** indicated that substitution of fluorine(s) or chlorine on the C-16 methyl did not affect the conformation of the parent molecule. These substitutions, however, substantially change the electronic nature of the β chain in the vicinity of the homoallylic active site, although not in a linearly additive manner. The large upfield shifts of carbons 15 and 17 as compared with that observed for the nonhalogenated parent compound reflect a combination of the long range γ effect[17] and the inductive effect exerted by the 16′ halogens.

When an excess of tributylstannane was employed, the vinylstannanes **4** usually were obtained as a trans/cis mixture in a ratio of ca. 85:15 as evidenced by the ^{13}C NMR spectra (Table II). However, in the fluoromethyl and chloromethyl series, a dehalogenated vinylstannane (**4e**) contaminates the desired vinylstannane if too large an excess of tributylstannane is used.[18] Thus, the byproducts isolated along with the 16-fluoromethyl and 16-(chloromethyl)prostaglandins **8c** and **8d** were the corresponding 13-cis analogues and the 16-methyl analogue **8e**. The less polar[6] 13-cis analogues and the 16-methyl analogue **8e**, which is more polar than the 16-halomethyl derivatives, are readily separated from the desired products by dry-column chromatography.

Preliminary testing in guinea pigs bronchconstricted by histamine, serotonin, or acetylcholine (Konzett–Rossler assay)[19] indicated that **8a–d** all are nearly as potent as the nonhalogenated compound **8e**[2] as bronchodilators. Further interesting details of their biological activities will be reported elsewhere.

Experimental Section

All reactions were performed under an atmosphere of argon or nitrogen. Solvents were removed under reduced pressure by using a Büchi rotavapor followed by vacuum pumping. Boiling points are uncorrected. Dry-column chromatography[20] was carried out with Woelm silica gel (equilibrated with 10% of the eluting solvent for several hours).

Infrared (IR) spectra were recorded with neat samples on a Perkin-Elmer Model 21 spectrophotometer or Nicolet 7199 FT-IR instrument. Proton magnetic resonance (^1H NMR) spectra were recorded in $CDCl_3$ solutions on an HA-100D spectrometer. Carbon-13 magnetic resonance (^{13}C NMR) spectra were taken in $CDCl_3$ solutions on a Varian CFT-20 spectrometer. Chemical shifts of ^1H and ^{13}C NMR spectra are given in parts per million downfield from an internal tetramethylsilane standard; coupling constants are given in hertz. Mass spectra were recorded on an AEI MS-9 instrument at 70 eV.

The experimental procedures for the preparation of **2–4**, **7**, and **8** (**a–d**) were exemplified in the **b** series. Only pertinent physical and spectroscopic data of the **a**, **c**, and **d** series were presented.

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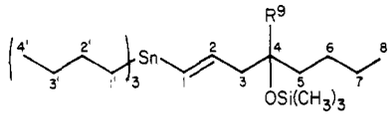
Table II. ^{13}C NMR Chemical Shifts (Parts per Million) of Vinylstannanes 4a-e[a,b]



R (compd)	CH_3 (4e)	CH_2Cl (4d)	CH_2F (4c)	CHF_2 (4b)	CF_3 (4a)
C1	130.5 (129.8)	132.6 (131.5)	132.1 (131.2)	132.9 (131.8)	133.1 (131.7)
C2	146.1 (145.6)	144.0 (143.8)	144.1 (143.7)	143.0 (142.6)	142.2 (142.0)
C3	51.2 (49.7)	46.4 (45.1)	45.1 (d, J = 4.2 Hz)	43.3 (t, J = 2.4 Hz)	43.1 (41.6)
C4	76.0	77.9	77.0 (d, J = 20 Hz)	77.6 (t, J = 20.4 Hz)	78.4 (q, J = 28 Hz)
C5	42.2 (42.6)	37.6 (37.9)	36.1 (d, J = 4.1 Hz)	34.2 (t, J = 2.1 Hz)	34.4 (34.7)
C6	26.2	25.6	25.4	24.9	25.1
C7	23.3	23.2	23.2	23.3	23.2
C8	14.2	14.1	14.1	14.0	13.9
C9	27.5	50.9	87.4 (d, J = 176 Hz)	117.6 (t, J = 249 Hz)	126.5 (q, J = 288 Hz)
C1′	9.52 (10.3)	9.58 (10.3)	9.53 (10.2)	9.55 (10.2)	9.51 (10.1)
C2′	27.3	27.4	27.3	27.4	27.4
C3′	29.2	29.3	29.2	29.3	29.2
C4′	13.7	13.8	13.7	13.7	13.7

[a] The numbers in parentheses represent the chemical shifts of the corresponding cis isomer which constitutes ca. 10–15% of the reported vinylstannane. [b] d = doublet, t = triplet, q = quartet.

1,1-Difluoro-2-hexanone (1b). To a vigorously stirred mixture of 1 mol of *n*-BuLi (2.2 M solution in hexane) and 1350 mL of ether cooled in a dry ice–acetone bath was added 39.87 g (0.41 mol) of difluoroacetic acid in 200 mL of ether through a dropping funnel very slowly during 3 h. After addition, the jellied mixture was stirred at the same temperature for 1 h and divided into three portions which were quenched separately by pouring into 450 mL of cold 4 N HCl and 400 mL of ice water. The organic layers were separated, combined, washed with water and brine, and dried (Na_2SO_4). The solution was distilled through a very long fractionating column to give, after a large forerun was collected, 26.8 g (yield 48%) of product: bp 105–115 °C; IR 1750 cm^{-1}; ^1H NMR δ 5.68 (t, J = 54, CHF_2), 2.68 (t, J = 7, O=CCH_2).

4-Hydroxy-4-(difluoromethyl)-1-octyne (2b). To a stirred suspension of 1.1 g of magnesium and 10 mg of mercuric chloride in 11 mL of ether was added 0.5 mL of propargyl bromide (80% solution in toluene), and the mixture was stirred vigorously for several minutes to initiate the reaction. Then a solution of 5.0 g (36.8 mmol) of 1,1-difluoro-2-hexanone (**1b**) and 3.7 mL of propargyl bromide in 11 mL of ether was added dropwise at such a rate so as to maintain a gentle reflux. After addition, the mixture was stirred at ambient temperature for 20 min and cooled to 5 °C, 15 mL of saturated ammonium chloride solution was added dropwise, and the mixture was filtered through Celite. The filtrate was concentrated in vacuo followed by vacuum distillation to give 3.3 g (yield 51%) of a colorless liquid: bp 72 °C (12 mm); IR 3448 (OH), 3330 (HC≡C), 2130 (C≡C) cm^{-1}; ^1H NMR δ 5.77 (t, J = 55, CHF_2), 2.55 (d, J = 2, C-3 H), 2.10 (t, J = 2, C-1 H). Anal. Calcd for $C_9H_{14}F_2O$: C, 61.34; H, 8.00. Found: C, 61.49; H, 8.17.

4-((Trimethylsilyl)oxy)-4-(difluoromethyl)-1-octyne (3b). To a 5 °C solution of 11.5 g of 4-hydroxy-4-(difluoromethyl)-1-octyne (**2b**) and 11.3 g of imidazole in 45 mL of DMF was added 10.3 mL of chlorotrimethylsilane during 15 min. After addition, the mixture was stirred at the same temperature for 1 h and then at ambient temperature for 18 h. The solution was poured into a cold mixture of hexane and saturated $NaHCO_3$ solution. The hexane layer was separated, washed with brine, and dried (Na_2SO_4). The solvent was carefully evaporated to dryness to give 16.2 g (quantitative yield) of a colorless liquid: IR no OH, 3330 (HC≡C), 2130 (C≡C) cm^{-1}; ^1H NMR δ 5.68 (t, J = 55, CHF_2), 2.44 (d, J = 2, C-3 H), 1.98 (t, J = 2, C-1 H), 0.13 (s, $OSiMe_3$). Anal. Calcd for $C_{12}H_{22}F_2OSi$: C, 58.02; H, 8.93. Found: C, 58.38; H, 8.96.

(*E*)-1-(Tributylstannyl)-4-(difluoromethyl)-4-((trimethylsilyl)oxy)-1-octene (4b). To a stirred mixture of 13.0 g (52.4 mmol) of 4-(difluoromethyl)-4-(trimethylsilyloxy)-1-octyne (**3b**) and 70 mg of azobis(isobutyronitrile) was added 17.3 mL (65 mmol) of tributylstannane with a syringe under a nitrogen atmosphere. The mixture was heated at 130 °C and stirred for 2 h and then cooled to ambient temperature. The mixture was vacuum distilled to give, after a forerun, 25.6 g (yield 91%) of pure product: bp 140 °C (0.25 mm); ^1H NMR δ 6.0 (m, olefin), 5.54 (t, J = 56, CHF_2); ^{13}C NMR see Table II. Anal. Calcd for $C_{24}H_{50}F_2OSiSn$: C, 53.43; H, 9.34. Found: C, 53.21; H, 9.22.

DL-15-Deoxy-16-((trimethylsilyl)oxy)-16-(difluoromethyl)-PGE$_2$ (7b) and DL-15-Deoxy-16-hydroxy-16-(difluoromethyl)-PGE$_2$ (8b). To a stirred solution of 5.33 g (9.89 mmol) of difluoromethyl vinylstannane **4b** in 5 mL of THF cooled in a dry ice–acetone bath was added 5.5 mL (9.89 mmol) of *n*-BuLi (1.8 M in hexane) during 20 min. After being stirred at −70 °C for 15 min and then at −35 °C for 1.5 h, the mixture was recooled to −78 °C and a solution of 1.29 g (9.89 mmol) of (1-pentynyl)-copper[21] and 4.9 mL of tributylphosphine in 10 mL of ether was added during 15 min. After the solution was stirred at −78 °C for 1.5 h, a solution of 3.0 g (8.3 mmol) of bis((trimethylsilyl)oxy) cyclopentenone **6**[9] in 5 mL of ether was added during 20 min to the resulting yellowish mixed cuprate **5b**. After being stirred at the same temperature for 10 min and then at −35 °C for 1.5 h, the mixture was recooled to −70 °C and quenched by pouring into a cold mixture of 200 mL of saturated ammonium chloride, 150 mL of ether, and 3 mL of acetic acid and stirring vigorously for 20 min. The aqueous phase was separated and extracted with ethyl acetate. The combined organic solution was washed with cold dilute HCl, H_2O, and brine and concentrated in vacuo at 30 °C. The residual liquid was stirred with 50 mL of acetic acid, 25 mL of THF, and 12.5 mL of water at room temperature for 1 h. The mixture was diluted with toluene and concentrated in vacuo at 30 °C to dryness. The residue was applied to 25 g of silica gel (silicAR CC-7) and washed with 200 mL of hexane followed by 200 mL of ethyl acetate. The ethyl acetate solution was concentrated in vacuo (30 °C) to give 4.78 g of brown oil. The oil was purified by a silica gel dry-column chromatography, eluting with 40% ethyl acetate–0.5% acetic acid in hexane. From the column segments was isolated 1.3 g (yield 33%) of DL-15-deoxy-16-((trimethylsilyl)oxy)-16-(difluoromethyl)-PGE$_2$ (**7b**): ^1H NMR δ 5.5 (m, olefin), 4.10 (q, J = 7, 11β-H), 2.86 (dd, J = 18

(21) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *J. Org. Chem.*, **31**, 4071 (1966).

and 7, one of 10-CH_2), 0.13 (s, $OSiMe_3$); mass spectrum, *m/e* 474 (M^+ calcd for $C_{24}H_{40}F_2O_5Si$ 474.2613, found 474.2596), 456, 441, 405, 347, 330, 247. The silyl ether **7b** was stirred with 30 mL of acetic acid, 15 mL of THF, 7.5 mL of water, and 3 drops of 4 N HCl at 40 °C for 2 h. The mixture was worked up by solvent extraction, washing with water and brine, and drying. The oily residue was purified by dry-column chromatography, eluting with 60% ethyl acetate–0.5% acetic acid in hexane. From the column segments was isolated 1.05 g (yield 32% from cyclopentenone **6**) of DL-15-deoxy-16-hydroxy-16-(difluoromethyl)-PGE_2 (**8b**) as two very closely overlapping spots on TLC (solvent 40% ethyl acetate–0.5% acetic acid in hexane): IR 3400 (OH), 1740, 1710, 975 (trans C=C) cm^{-1}; ^1H NMR δ 5.64 (t, J = 56, CHF_2), 5.50 (m, olefin), 4.10 (q, J = 7, 11β-H), 2.72 (dd, J = 18 and 7, one of 10-CH_2); ^{13}C NMR see Table I. Anal. Calcd for $C_{21}H_{32}F_2O_5$: C, 62.67; H, 8.02. Found: C, 62.61; H, 8.25.

4-(Trifluoromethyl)-4-hydroxy-1-octyne (2a): yield 81%; bp 65–70 °C (12 mm); ^1H NMR δ 2.63 (d, J = 3, C-3 H), 2.13 (t, J = 3, C-1 H). Anal. Calcd for $C_9H_{13}OF_3$: C, 55.66; H, 6.75; F, 29.35. Found: C, 55.27; H, 7.01; F, 28.74.

4-(Trifluoromethyl)-4-((trimethylsilyl)oxy)-1-octyne (3a): yield 89%; ^1H NMR δ 2.79 (d, J = 3, C-3 H), 2.22 (t, J = 3, C-1 H), 0.35 (s, $OSiMe_3$).

(*E*)-1-(Tributylstannyl)-4-(trifluoromethyl)-4-((trimethylsilyl)oxy)-1-octene (4a): yield 87%; bp 125–130 °C (0.07 mm); ^1H NMR δ 5.9 (m, olefin), 2.50 (br d, C-3 H); ^{13}C NMR see Table II. Anal. Calcd for $C_{24}H_{49}F_3OSiSn$: C, 51.71; H, 8.86; F, 10.23. Found: C, 51.89; H, 8.84; F, 10.22.

DL-**15-Deoxy-16-((trimethylsilyl)oxy)-16-(trifluoromethyl)-PGE_2 (7a)**: yield 45%; ^1H NMR δ 5.5 (m, olefin), 4.10 (q, J = 7, 11β-H), 0.17 (s, $OSiMe_3$); mass spectrum, *m/e* 492 (M^+), 474 (M – H_2O), 459, 348, 265, 247, 227.

DL-**15-Deoxy-16-hydroxy-16-(trifluoromethyl)-PGE_2 (8a)**: yield 95% from **7a**; IR 3400, 1740, 1710, 975 (trans C=C) cm^{-1}; ^1H NMR δ 5.50 (m, olefin), 4.06 (q, J = 7, 11β-H); ^{13}C NMR see Table I; mass spectrum, *m/e* 420 (M^+ calcd for $C_{21}H_{31}F_3O_5$ 420.2124, found 420.2110), 402, 384, 315, 276, 247, 121. Anal. Calcd for $C_{21}H_{31}F_3O_5$: C, 59.98; H, 7.43. Found: C, 59.74; H, 7.67.

4-(Fluoromethyl)-4-hydroxy-1-octyne (2c): yield 56%; bp 75–80 °C (12 mm); ^1H NMR δ 4.40 (d, J = 48, CH_2F), 2.5 (d, J = 2, C-3 H), 2.08 (t, J = 2, C-1 H).

4-(Fluoromethyl)-4-((trimethylsilyl)oxy)-1-octyne (3c): quantitative yield; IR no OH; ^1H NMR δ 4.38 (d, J = 48, CH_2F), 2.48 (d, J = 2, C-3 H), 2.0 (t, J = 2, C-1 H), 0.2 (s, $OSiMe_3$).

(*E*)-1-(Tributylstannyl)-4-(fluoromethyl)-4-((trimethylsilyl)oxy)-1-octene (4c): yield 82%; bp 120–130 °C (0.2 mm); ^1H NMR δ 5.92 (m, olefin), 4.18 (d, J = 48, CH_2F), 2.34 (m, C-3 H); ^{13}C NMR see Table II. Anal. Calcd for $C_{24}H_{51}FOSiSn$: C, 55.28; H, 9.86. Found: C, 54.98; H, 9.81.

DL-**15-Deoxy-16-((trimethylsilyl)oxy)-16-(fluoromethyl)-PGE_2 (7c)**: ^1H NMR δ 5.45 (m, olefin), 4.23 (d, J = 48, CH_2F), 0.13 (s, $OSiMe_3$); mass spectrum, *m/e* 438 (M – H_2O), 405 (438 – CH_2F), 381.

DL-**15-Deoxy-16-hydroxy-16-(fluoromethyl)-PGE_2 (8c)**: yield 30% from cyclopentenone **6**; IR 3400, 1740, 1710, 975 (trans C=C) cm^{-1}; ^1H NMR δ 5.45 (m, olefin), 4.18 (d, J = 48, CH_2F), 2.75 (dd, J = 18 and 7, one of 10-CH_2); ^{13}C NMR see Table I. Anal. Calcd for $C_{21}H_{33}FO_5$: C, 65.60; H, 8.65. Found: C, 65.24; H, 8.79.

1-Chloro-2-hexanone (1d). To a stirred solution of 11.5 g (99 mmol) of 1-hydroxy-2-hexanone (**10**) [bp 45–48 °C (4 mm), for preparation procedure see ref 14] in 110 mL of DMF was added 35 mL of mesyl chloride dropwise during 15 min. The mixture was stirred at 85 °C for 3 h and cooled to 5 °C. Water (50 mL) was slowly added and the mixture was extracted with ether. The combined ether extract was washed with water and brine and dried over Na_2SO_4. The solution was concentrated by simple distillation followed by vacuum distillation through a Vigreux column to give 11.0 g (yield 82%) of colorless liquid: bp 30–32 °C (4 mm); IR 1739, 1724 cm^{-1}; ^1H NMR δ 4.12 (s, CH_2Cl), 2.60 (t, J = 7, C-3 H). Anal. Calcd for $C_6H_{11}ClO$: C, 53.53; H, 8.24. Found: C, 53.30; H, 8.22.

4-(Chloromethyl)-4-hydroxy-1-octyne (2d): yield 50%; bp 60–61 °C (4 mm); IR 2128 (C≡C) cm^{-1}; ^1H NMR δ 3.73 and 3.57 (AB q, J = 10, CH_2Cl), 2.52 (d, J = 3, C-3 H), 2.06 (t, J = 3, C-1 H).

4-(Chloromethyl)-4-((trimethylsilyl)oxy)-1-octyne (3d): yield 95%; bp 50–55 °C (4 mm); IR no OH; ^1H NMR δ 3.58 (s, CH_2Cl), 2.50 (d, J = 3, C-3 H), 1.99 (t, J = 3, C-1 H).

(*E*)-1-(Tributylstannyl)-4-(chloromethyl)-4-((trimethylsilyl)oxy)-1-octene (4d): yield 97%; bp 130–155 °C (0.1–0.2 mm); ^1H NMR δ 5.98 (m, olefin), 3.40 (s, CH_2Cl), 2.40 (m, C-3 H); ^{13}C NMR see Table II. Anal. Calcd for $C_{24}H_{51}ClOSiSn$: C, 53.59; H, 9.56. Found: C, 53.28; H, 9.86.

DL-**15-Deoxy-16-((trimethylsilyl)oxy)-16-(chloromethyl)-PGE_2 (7d).** This material was not isolated as a pure intermediate product. The crude material from the conjugate addition was deblocked directly by acetic acid–THF–water (4:2:1) at 40 °C for 1 h to **8d**.

DL-**15-Deoxy-16-hydroxy-16-(chloromethyl)-PGE_2 (8d)**: yield 35% from cyclopentenone **6**; IR 3400, 1740, 1710, 975 (trans C=C) cm^{-1}; ^1H NMR δ 5.50 (m, olefin), 4.10 (q, J = 7, 11β-H), 3.53 (s, CH_2Cl); ^{13}C NMR see Table I. Anal. Calcd for $C_{21}H_{33}ClO_5$: C, 62.91; H, 8.30. Found: C, 62.85; H, 8.57.

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Registry No. 1a, 360-34-9; **1b**, 656-74-6; **1c**, 371-37-9; **1d**, 20261-68-1; **2a**, 73397-42-9; **2b**, 73397-43-0; **2c**, 73397-44-1; **2d**, 73397-45-2; **3a**, 73397-46-3; **3b**, 73397-47-4; **3c**, 73397-48-5; **3d**, 73397-49-6; (*E*)-**4a**, 73397-50-9; (*Z*)-**4a**, 73453-99-3; (*E*)-**4b**, 73397-51-0; (*Z*)-**4b**, 73397-52-1; (*E*)-**4c**, 73397-53-2; (*Z*)-**4c**, 73397-54-3; (*E*)-**4d**, 73397-55-4; (*Z*)-**4d**, 73397-56-5; (*E*)-**4e**, 66792-29-8; (*Z*)-**4e**, 66792-30-1; **5b**, 73453-93-7; **6**, 59013-08-0; **7a**, 73454-00-9; **7b**, 73397-57-6; **7c**, 73397-58-7; **7d**, 73397-59-8; **8a**, 16-epimer 1, 73397-60-1; **8a**, 16-epimer 2, 73397-61-2; **8b**, 16-epimer 1, 73397-62-3; **8b**, 16-epimer 2, 73397-63-4; **8c**, 16-epimer 1, 73397-64-5; **8c**, 16-epimer 2, 73397-65-6; **8d**, 16-epimer 1, 73397-66-7; **8d**, 16-epimer 2, 73397-67-8; **8e**, 16-epimer 1, 71709-03-0; **8e**, 16-epimer 2, 71069-42-6; **10**, 73397-68-9; propargyl bromide, 106-96-7; (1-pentynyl)copper, 19093-51-7.