m/e (relative intensity) 470 (0.6), 468 (1), 466 (0.6), 265 (88), 263 (85), 223 (22), 221 (21), 206 (22), 205 (32), 204 (22), 203 (32), 141 (21), 125 (58), 124 (32), 123 (69), 109 (32), 95 (30), 43 (100).

Acknowledgment. High-resolution mass spectra were provided by the mass spectrometry facility at Massachusetts Institute of Technology, supported by a grant (Principal Investigator Professor K. Biemann) from the Biotechnology Research Branch, Division of Research Resources. The 360-MHz NMR data were obtained from the Stanford Magnetic Resonance Laboratory supported by NSF Grant GR 23633 and NIH Grant RR 00711. We acknowledge with thanks grants from NSF (GP 38410) and the Phillips Petroleum Company, Bartlesville, Ok, which aided in the purchase of NMR spectrometers.

Registry No. 4, 72926-49-9; 5, 72926-50-2; 6, 72926-51-3.

Circular Dichroism of Prostaglandin Benzoates. Assignment of Configuration at C-15

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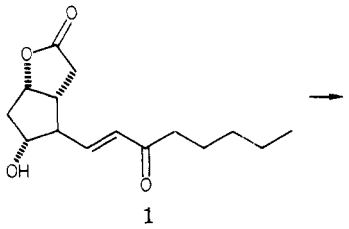
The synthesis of prostaglandin analogues frequently proceeds through intermediates such as **1** and **2** with the



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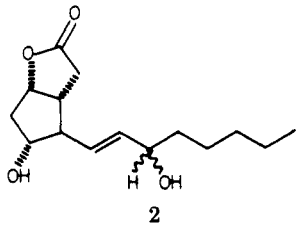


2

result that a mixture of epimers at C-15 (prostaglandin numbering) is produced.[1] This mixture is either separated and each epimer carried on to the final prostaglandin analogue or is carried on as the mixture and the epimers separated at the stage of the final analogue. The assignment of configuration at C-15 has often been made on the basis of the relative thin-layer chromatographic (TLC) mobilities of the epimers. The slightly more polar nature of the 15*S* epimer at the intermediate stage of **2** or in the final products has been consistent with the expectation that the 15*S* epimer of the final analogue will have greater biological activity than the 15*R* epimer.

Only in two cases have the configurations at C-15 been determined in an absolute sense. The absolute configuration of the naturally occurring prostaglandins was determined in two steps. First the relative configuration was determined by X-ray crystallography,[2] and then the absolute configuration was determined by correlation of the ozonolysis product L-2-hydroxyheptanoic acid with authentic material of known configuration.[3] The absolute configuration of the 15-methylprostaglandins has been determined by X-ray crystallography.[4]

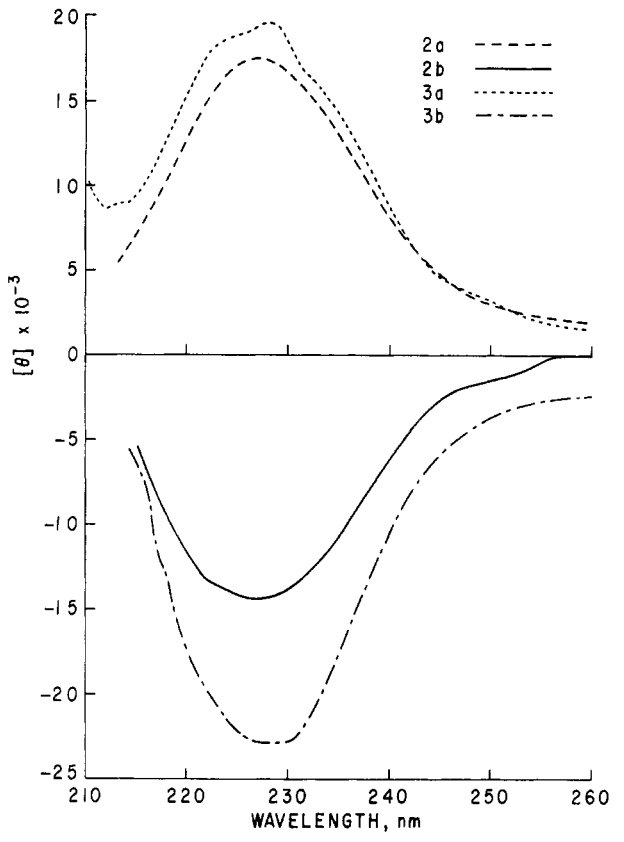


Figure 1. CD curves of 15-monobenzoates **2a**, **2b**, **3a**, and **3b** in MeOH.

In this report, we present circular dichroism (CD) data for the 15-benzoate derivatives of several synthetic intermediate and final prostaglandins. From these data, we have found an empirical correlation between CD spectra and the configuration at C-15 of the benzoate derivatives. That correlation is the subject of this note.

The compounds prepared and their ultraviolet and CD spectral properties are outlined in Table I. The absorption maxima in the ultraviolet spectra are typical of the benzoate chromophore. The intense band at 229 nm is due to a charge-transfer transition and the weaker maxima between 265 and 280 nm to the B_{2u} transition. The intensities of the extinction coefficients are consistent with the number of benzoate groups present in each compound, i.e., $\epsilon_{229} \simeq 13\,000$ per benzoate group.

Listed first in Table I are two epimeric pairs of 15-benzoates, **2a** and **2b** and **3a** and **3b**. All have strong CD bands at about 230 nm, but these bands have opposite signs of rotation depending on the configuration at C-15 (see Figure 1). The two 15(*S*)-benzoates (**2a** and **3a**) have a positive sign of rotation while the two 15(*R*)-benzoates (**2b** and **3b**) have a negative sign of rotation. The CD of

(1) Cf. (a) Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press: New York, 1977. (b) Mitra, A. "The Synthesis of Prostaglandins"; Wiley-Interscience: New York, 1977.

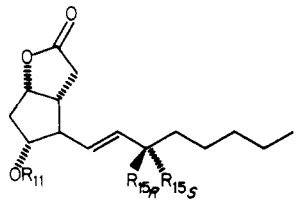
(2) Abrahamsson, S. *Acta Crystallogr.* **1963**, *16*, 409.

(3) Nugteren, D. H.; vanDorp, D. A.; Bergstrom, S.; Hamberg, M.; Samuelsson, B. *Nature (London)* **1966**, *212*, 38.

(4) Chidester, C. G.; Duchamp, D. J. Abstracts of the American Crystallographic Association, Winter Meeting, 1974, Vol. 2, Series 2, p 34.

0022-3263/80/1945-1528$01.00/0

Table I. Ultraviolet and Circular Dichroism Data for Prostaglandin Benzoate Esters



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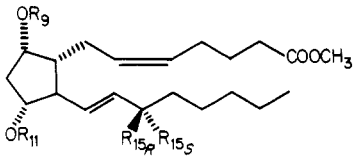

3

compd	R_9	R_{11}	R_{15R}	R_{15S}	UV max, nm (ϵ)	CD, nm (θ)
2a		H	H	$OCOC_6H_5$	228 (13900) 266[a] (870) 273 (935) 279 (757)	226 (17600)
2b		H	$OCOC_6H_5$	H	228 (13800) 266[a] (780) 273 (890) 280 (715)	227 (−14300)
3a	H	H	H	$OCOC_6H_5$	228 (13650) 266[a] (766) 273 (865) 279 (690)	228 (19900)
3b	H	H	$OCOC_6H_5$	H	229 (13600) 267[a] (784) 272 (888) 279 (718)	229 (−23000)
2c		COC_6H_5	H	$OCOC_6H_5$	229 (24750) 268[a] (1550) 273 (1700) 281 (1400)	235 (−23400) 257 (1500) 271 (800)
2d		COC_6H_5	$OCOC_6H_5$	H	229 (25200) 267[a] (1500) 273[a] (1700) 280 (1400)	221 (−26500) 271 (−1180) 279 (−840)
2e		COC_6H_5	CH_3	$OCOC_6H_5$	229 (26800) 266[a] (1630) 273 (1840) 280 (1440)	233 (−33000) 255 (2400)
2f		COC_6H_5	$OCOC_6H_5$	CH_3	229 (27600) 266[a] (1700) 273 (1900) 280 (1500)	228 (−20000) 262 (−2400)
3c	H	COC_6H_5	H	$OCOC_6H_5$	229 (26850) 266[a] (1550) 272 (1800) 279 (1400)	235 (−32300) 258 (1380)
3d	COC_6H_5	H	H	OH	229 (12350) 267[a] (766) 273 (879) 280 (718)	231 (15000)
3e	H	COC_6H_5	H	OH	228 (12950) 267[a] (766) 273 (840) 280 (794)	231 (−18000)
3f	COC_6H_5	COC_6H_5	H	OH	228 (27050) 267[a] (1650) 273 (1900) 280 (1550)	236 (−45000) 221 (11000)
3g	COC_6H_5	COC_6H_5	H	$OCOC_6H_5$	229 (38600) 273 (2680) 280 (2190)	258 (960) 236 (−64000) 220 (3400)
4	9β-$OCOC_6H_5$	11β-$OCOC_6H_5$	H	OH	229 (25850) 267[a] (1550) 274 (1800) 280 (1500)	236 (−24650) 221 (7050)

[a] Shoulder.

the B_{2u} transition was too weak for sign determination for these molecules.

Listed next in Table I are two pairs of 11,15-dibenzoates of structure **2** in which the C-15 configurations are epimeric. Again, all compounds have strong bands in the region of 220–235 nm, but now they all have negative signs of

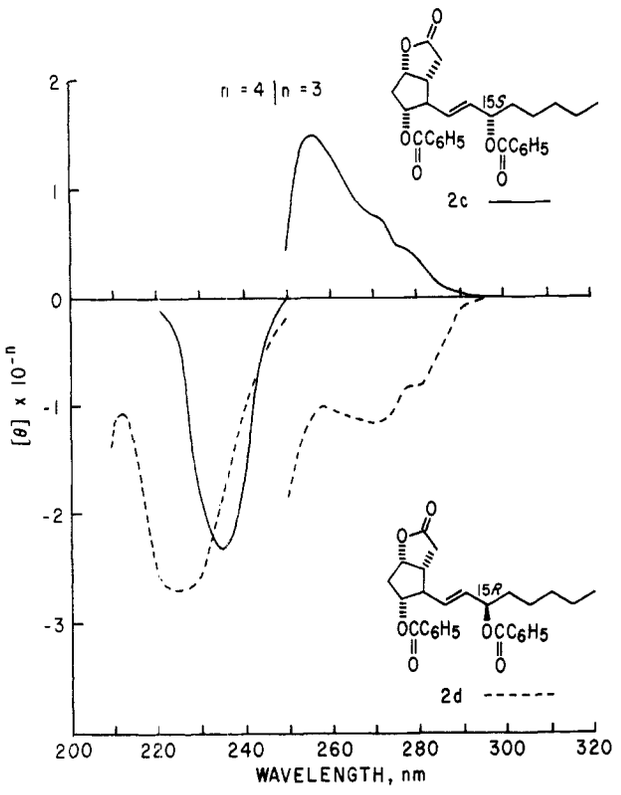

Figure 2. CD curves of 2c and 2d in MeOH.

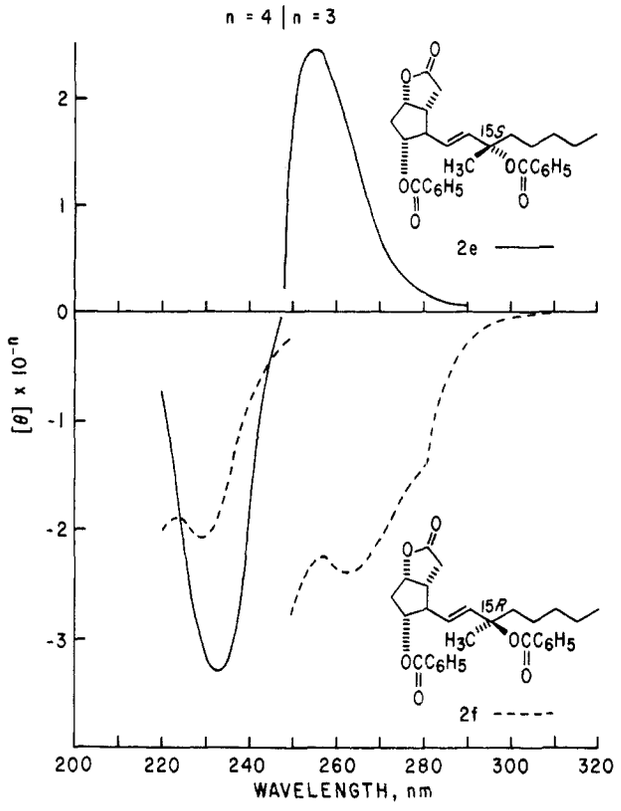

Figure 3. CD curves of 2e and 2f in MeOH.

rotation. Only at the higher wavelength of 255–270 nm in the region of the B_{2u} transition are differences seen that correlate with configuration at C-15. Here the 15(*S*)-benzoates (**2c** and **2e**) exhibit a positive sign of rotation and the 15(*R*)-benzoates (**2d** and **2f**) a negative rotation. The differences in these CD curves are more apparent from the illustrations shown in Figures 2 and 3. A similar positive rotation at 258 mμ is also found for the 11,15-dibenzoate derivative of $PGF_{2\alpha}$ methyl ester (**3c**). We suggest that these differences in the CD spectra of 15-monobenzoates and 11,15-dibenzoates may be used as an empirical method of assigning configuration at the C-15 position of prostaglandin intermediates and final compounds. An example is included in a forthcoming paper.[5]

Also included in Table I are UV and CD data for several other benzoate derivatives of prostaglandins, including the 9- and 11-monobenzoates (**3d** and **3e**), the 9,11-dibenzoate (**3f**), and the 9,11,15-tribenzoate (**3g**) of $PGF_{2\alpha}$ methyl ester and the 9,11-dibenzoate of 11-*epi*-$PGF_{2\beta}$ methyl ester (**4**). We initially were curious as to whether any of these molecules would exhibit spectral interactions typical of the dibenzoates studied by Harada and Nakanishi,[6] but this has not proven to be the case.

Experimental Section

General Procedures. The ^1H NMR spectra were obtained with a Varian A-60D spectrometer as solutions in deuteriochloroform with tetramethylsilane as an internal standard. High-resolution mass spectra were obtained with a CEC 21-110B spectrometer. Ultraviolet spectra were obtained with a Cary 15 spectrophotometer. Circular dichroism spectra were obtained with a Cary 60 ORD-CD instrument.

Preparation of Benzoates. In general, benzoates were prepared by addition of slight excesses of benzoyl chloride to a pyridine solution of the appropriate prostaglandin alcohol. The reactions were checked for completion by quenching an aliquot in water–ether and examining the ether layer by thin-layer chromatography. If the reaction was judged incomplete and if no further change occurred with time or with warming, additional benzoyl chloride was added. The reactions were worked up by stirring the reaction with water to ensure hydrolysis of excess benzoyl chloride. The aqueous mixture was then saturated with sodium chloride and extracted with ether, and the ether layer was dried over $MgSO_4$. Crude products were generally purified by chromatography on silica gel columns.

3α,5α-Dihydroxy-2β-(3′-oxo-*trans*-1′-octenyl)cyclopentane-1α-acetic Acid γ-Lactone 3-*tert*-Butyldimethylsilyl Ether. A solution of 3α,5α-dihydroxy-2β-(3′-oxo-*trans*-1′-octenyl)cyclopentane-1-acetic acid γ-lactone[7] (2.66 g, 0.010 mol) in dimethylformamide (10 mL) was cooled in an ice bath and stirred under N_2. The procedure of Corey and Venkateswarlu[8] was followed: *tert*-butyldimethylsilyl chloride (1.50 g, 0.010 mol) and imidazole (1.36 g, 0.020 mol) were added to the solution. The solution was stirred at room temperature for 2 h, additional silyl chloride (0.150 g) and imidazole (0.136 g) were added, and stirring was continued for 1.5 h. The reaction now was complete (TLC) and was worked up by addition of ice–water (50 mL) and extraction with ether (2 × 25 mL). The ether extracts were washed with water and brine and then were dried over $MgSO_4$. The crude product (3.55 g) was used without purification in the following reaction.

(3′*S*)- and (3′*R*)-3α,5α-Dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic Acid γ-Lactone 3-*tert*-Butyldimethylsilyl Ether. The crude product from the above reaction was dissolved in THF/water (30 mL, 5:1). The solution was stirred at room temperature. Sodium borohydride (0.125 g) was added in portions. After 2 h, the reaction was worked up by adding brine (100 mL) and extracting with ether (3 × 35 mL). The combined ether extracts were washed with water and brine and then dried over $MgSO_4$. The crude product (3.23 g) was chromatographed on two Merck size C Lobar silica gel columns by using 40% ethyl acetate in hexane as the solvent. Eluted first was (3′*S*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)-cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether (1.22 g): ^1H NMR ($CDCl_3$) δ 5.50 (m, 2 H, –CH=CH–), 4.90

(5) Nidy, E. G.; Johnson, R. A. *J. Org. Chem.*, **1980**, *45*, 1121.
(6) Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257.
(7) Corey, E. J.; Arnold, Z.; Hutton, J. *Tetrahedron Lett.* **1970**, 307.
(8) Corey, E. J.; Venkateswarla, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

(1 H, m, >CHOCO–), 4.00 (m, 2 H, CHO–), 0.84 (m, 12 H, *t*-Bu). Eluted second was a compound (0.680 g) assumed to be the 13,14-dihydro derivative of either the preceding (3′*S*) epimer or the following (3′*R*) epimer, since it lacked the signal for olefinic protons in its NMR spectrum. Eluted last was (3′*R*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether (0.570 g): ^{1}H NMR ($CDCl_3$) δ 5.55 (m, 2 H, CH=CH), 4.95 (m, 1 H, >CHOCO–), 4.10 (m, 2 H, >CH-O–), 0.89 (m, 12 H, *t*-Bu).

A small sample (20 mg) of the above first-eluted product (the 3′*S* epimer) was hydrolyzed in 1 mL of a solution made up of acetic acid/THF/H_2O/HCl, 30 mL:10 mL:10 mL:24 drops. The reaction was complete in 3 h. The product was identical with an authentic sample of (3′*S*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone.[9] Likewise, a small sample of the last-eluted product above was hydrolyzed and was different by TLC from the 3′*S* epimer. In 60% acetone–hexane, the TLC polarity of the hydrolyzed products was such that the 3′*S* epimer was the more polar.

(3′*S*)-3α,5α-Dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)-cyclopentane-1α-acetic Acid γ-Lactone 3′-Benzoate (2a). Benzoyl chloride (0.210 g, 0.0015 mol) was added to a solution of (3′*S*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether (0.382 g, 0.0010 mol) in pyridine (3 mL). Reaction was complete within 1 h. Water (20 mL) was added and the mixture stirred 1 h and then extracted with ether (3 × 10 mL). The combined ether extracts were washed with ice/1 N HCl (1:1) until the wash solution remained acidic and 5% $NaHCO_3$ solution and then dried over $MgSO_4$. The NMR spectrum of the crude product (0.44 g) was consistent with the structure.

The crude product (0.30 g) was hydrolyzed in 5 mL of a solution of HOAc/THF/H_2O/HCl (30 mL:10 mL:10 mL:24 drops). After 3 h, hydrolysis was complete and the product (0.21 g) was obtained by extraction. The crude product was purified by chromatography, on one Merck size B Lobar silica gel column. Elution was with 35% ethyl acetate in hexane. Pure **2a** (0.16 g) was obtained as a colorless, waxy solid: ^{1}H NMR ($CDCl_3$) δ 8.03, 7.49 (m, 5 H, aromatic), 5.62 (m, 2 H, –CH=CH), 5.50 (m, 1 H, >CHOCOPh), 4.87 (m, 1 H, >CHOCO–), 4.00 (q, 1 H, 11-CHO–), 0.88 (t, 3 H, J = 5.5 Hz, CH_3); mass spectrum (trimethylsilyl ether), *m/e* 444.2353 (calcd for $C_{25}H_{36}SiO_5$ 444.2332), 429, 426, 354, 339, 322, 307, 249, and 105. The UV and CD spectra are given in Table I.

(3′*R*)-3α,5α-Dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)-cyclopentane-1α-acetic Acid γ-Lactone 3′-Benzoate (2b). 2b was prepared in exactly the same way as described above for the preparation of **2a**. The chromatographically purified product (0.17 g) was obtained as a colorless, viscous oil: ^{1}H NMR ($CDCl_3$) δ 8.07, 7.52 (m, 5 H, aromatic), 5.62 (m, 2 H, –CH=CH–), 5.50 (m, 1 H, >CHOCOPh), 4.92 (m, 1 H, >CHOCO–), 4.01 (q, 1 H, *J* = 6.5 Hz, >CHO–), 0.88 (t, 3 H, *J* = 5.5 Hz, CH_3); mass spectrum (trimethylsilyl ether), *m/e* 444.2340 (calcd for $C_{25}H_{36}SiO_5$ 444.2332), other peaks similar to those for **2a**. The UV and CD spectra are given in Table I.

Prostaglandin $F_{2\alpha}$ 15-Benzoate Methyl Ester (3a). $PGF_{2\alpha}$ methyl ester (368 mg) was converted to the 9,11-*n*-butylboronate ester by a previously described method.[10] The crude product was then dissolved in pyridine (4 mL) and stirred for 3 h at room temperature with 0.15 mL of benzoyl chloride. Water (30 mL) was added and the mixture left overnight. The product was extracted with ether and the ether extract was washed with aqueous acid to remove pyridine, dried, and concentrated. The crude product was chromatographed on silica gel (Merck size B Lobar column) to give pure **3a** (320 mg) as a colorless, viscous oil: NMR ($CDCl_3$) δ 8.03 (m, 2 H, ortho aromatic protons), 7.47 (m, 3 H, other aromatic protons), 5.5 (m, 5H, –CH=CH–, >CHOCO), 4.15 (m, 1 H, >CHO–), 3.97 (m, 1 H, >CHO–), 3.63 (s, 3 H, $COOCH_3$), 0.88 (5, 3 H, *J* = 5 Hz, CH_3); mass spectrum (bis(trimethylsilyl) ether)] *m/e* 494, 479, 404, 378, 237, 217, and 105. Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 70.96; H, 8.48.

15-*epi*-Prostaglandin $F_{2\alpha}$ 15-Benzoate Methyl Ester (3b). 15-*epi*-$PGF_{2\alpha}$ methyl ester[11] (270 mg) was converted to the 9,11-*n*-butylboronate ester by a previously described method.[10] The crude product was dissolved in pyridine (5 mL) and stirred for 3 h at room temperature with benzoyl chloride (0.15 mL). Water (35 mL) was added and the mixture was left overnight at room temperature. The product was extracted with ether and the ether was washed with aqueous acid to remove pyridine and dried. The crude product was chromatographed on silica gel to give pure **3b** (70 mg) as a colorless, viscous oil: NMR ($CDCl_3$) δ 8.03 (m, 2 H, ortho aromatic protons), 7.47 (m, 3 H, other aromatic protons), 5.62 (m, 2 H, CH=CH), 5.37 (m, 3 H, CH=CH, >CHOCO–), 4.14 (m, 1 H, >CHO), 3.94 (m, 1 H, >CHO–), 3.64 (s, 3 H, $COOCH_3$), 0.88 (t, 3 H, *J* = 5 Hz, CH_3): high-resolution mass spectrum [bis(trimethylsilyl) ether] *m/e* 616.3592 (calcd for $C_{34}H_{56}Si_2O_6$ 616.3615), 494, 479, 404, 378, 314, 237, 217, and 105.

(3′*S*)-3α,5α-Dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)-cyclopentane-1α-acetic Acid γ-Lactone 3,3′-Dibenzoate (2c). A solution of (3′*S*)-3α,5α-dihydroxy-2β-(3′ hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone[9] (372 mg) in pyridine (5 mL) was stirred with benzoyl chloride (280 mg) for 4 h. Water was added and the mixture left overnight in the refrigerator and then worked up. The crude product was chromatographed on silica gel to give pure **2c** (300 mg) as a colorless, viscous oil: NMR ($CDCl_3$) δ 8.03 (m, 4 H, ortho aromatic protons), 7.48 (m, 7 H, other aromatic protons), 5.90–4.90 (m, 5 H, olefinic protons, >CHO–), 0.88 (t, 3 H, *J* = 5 Hz, CH_3); high-resolution mass spectrum, *m/e* 476, 371, 354.1824 [calcd for $M^+ - C_6H_5COOH$ ($C_{22}H_{26}O_4$) 354.1831], 283, 232, 105.

(3′*R*)-3α,5α-Dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)-cyclopentane-1α-acetic Acid γ-Lactone 3,3′-Dibenzoate (2d). A solution of (3′*R*)-3α,5α-dihydroxy-2β(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone[9] (372 mg) and benzoyl chloride (280 mg) in pyridine (5 mL) was left at room temperature for 1 h and then worked up. After chromatography, pure **2d** (420 mg) was obtained as a colorless, viscous oil: NMR ($CDCl_3$) δ 8.06 (m, 4 H, ortho aromatic protons), 7.55 (m, 6 H, other aromatic protons), 5.88–4.92 (m, 5 H, olefinic protons, >CHO–), 0.85 (t, 3 H, *J* = 5 Hz, CH_3); high-resolution mass spectrum, *m/e* 371, 354.1827 ($M^+ - C_6H_5COOH$, calcd for $C_{22}H_{26}O_4$ 354.1831), 249, 232, 105. Anal. Calcd for $C_{29}H_{32}O_6$: C, 73.09; H, 6.77. Found: C, 72.71; H, 7.19.

During storage in the refrigerator, the oil crystallized. One recrystallization from ether at –30 °C gave colorless crystals, mp 60–63 °C.

(3′*S*)- (2e) and (3′*R*)-3α,5α-Dihydroxy-2β-(3′-hydroxy-3′-methyl-*trans*-1′-octenyl)cyclopentane-1α-acetic Acid γ-Lactone 3,3′-Dibenzoates (2f). These two compounds were gifts of E. W. Yankee and E. L. Cooper. **2e** was a crystalline material, mp 93.5–96.0 °C,[12a] and **2f** was a viscous oil.[12b]

Prostaglandin $F_{2\alpha}$ 11,15-Dibenzoate Methyl Ester (3c). $PGF_{2\alpha}$ methyl ester (286 mg) was stirred in pyridine (5 mL) with benzoyl chloride (0.22 mL) at room temperature for 1 h. TLC at this time showed complete consumption of starting material and the presence of two main products, the dibenzoate and the tribenzoate. After workup, the crude product was chromatographed on a column of silica gel to give pure **3c** (210 mg) as a colorless oil: NMR ($CDCl_3$) δ 8.01 (m, 4 H, ortho aromatic protons), 7.45 (m, 6 H, other aromatic protons), 5.74 (m, 2 H, CH=CH), 4.95–5.62 (m, 4 H, CH=CH, >CHOCO–), 4.28 (m, 1 H, >CHOH), 3.66 (s, 3 H, $COOCH_3$), 0.87 (t, 3 H, *J* = 5 Hz, CH_3); mass spectrum (trimethylsilyl derivative), *m/e* 648, 526 ($M^+ - C_6H_5COOH$), 511, 404 ($M^+ - 2C_6H_5COOH$), 314, and 105.

Prostaglandin $F_{2\alpha}$ 9-Benzoate Methyl Ester (3d). A solution of $PGF_{2\alpha}$ methyl ester 11,15-bis(ethoxyethyl) ether (0.256 g) in pyridine (5 mL) was stirred at room temperature for 3 h, after which the reaction was complete. The crude product following

(9) (a) Kelly, R. C.; VanRheenen, V.; Schletter, I.; Pillai, M. D. *J. Am. Chem. Soc.* **1973**, *95* 2746. (b) Corey, E. J.; Schaaf, T. K.; Huber, W.; Koelliker, V.; Weinshenker, N. M. *Ibid.* **1970**, *92*, 397.

(10) Johnson, R. A.; Nidy, E. G.; Baczynskyj, L.; Gorman, R. R. *J. Am. Chem. Soc.* **1977**, *99*, 7738.

(11) Bundy, G. L.; Schneider, W. P.; Lincoln, F. H.; Pike, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 2123.

(12) (a) Mass spectrum of **2e**: no M^+, *m/e* 368, 263, 247, 246, 203, 191, 190 and 189. Anal. Calcd for $C_{30}H_{34}O_6$: C, 73.45; H, 6.99. Found: C, 73.39; H, 7.02. (b) Mass spectrum of **2f**: no M^+, *m/e* 368, 247, 246, 203, 191, 190, and 189. We thank E. W. Yankee and E. L. Cooper for providing these analytical data for **2e** and **2f**.

workup was hydrolyzed with acetic acid/THF/water (20:10:3) at 40 °C for 4 h. The crude material was chromatographed on silica gel to give 0.210 g of **3d**: ultraviolet and CD spectra are given in Table I; ^{1}H NMR ($CDCl_3$) δ 8.03 (m, 2 H, ortho aromatic protons), 7.50 (m, 3 H, other aromatic protons), 5.72–5.12 (m, 5 H, olefinic protons, >CHOCO–), 4.30–3.70 (m, 2 H, C_{11} and C_{15} protons), 3.60 (s, 3 H, $COOCH_3$), 0.88 (t, 3 H, J = 5 Hz, CH_3); high-resolution mass spectrum (bis(trimethylsilyl) derivative), m/e 616.3592 (calcd for $C_{34}H_{56}Si_2O_6$ 616.3615), 601, 585, 545, 494, 455, 423, 404, 333, 263, and 173. Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 70.98; H, 8.91.

Prostaglandin $F_{2\alpha}$ 11-Benzoate Methyl Ester (3e). A solution of $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester[10] (482 mg) in pyridine (5 mL) was stirred at room temperature with benzoyl chloride (0.12 mL) for 1 h. After workup, the crude reaction product was stirred with acetic acid/THF/water (3:1:1) in order to remove the protecting group from the C-15 hydroxyl. The crude hydrolyzed product was chromatographed on silica gel to give pure **3e** (280 mg) as a viscous oil: NMR ($CDCl_3$) δ 8.01 (m, 2 H, ortho aromatic protons), 7.43 (m, 3 H, other aromatic protons), 5.57 (m, 2 H, CH=CH), 5.40 (m, 2 H, CH=CH), 5.10 (m, 1 H, >CHOCO–), 4.15 (m, 2 H, >CHOH), 3.64 (s, 3 H, $COOCH_3$), 0.83 (t, 3 H, J = 5 Hz, CH_3); for ultraviolet and CD spectra, see Table I; high-resolution mass spectrum (bis(trimethylsilyl) derivative), m/e 616.3605 (calcd for $C_{34}H_{56}Si_2O_6$ 616.3615), 494, 423, 333, and 199. Anal. Calcd for $C_{28}H_{40}O_6$: C, 71.16; H, 8.53. Found: C, 70.88; H, 8.53. The ultraviolet spectrum of **3e** is consistent with the introduction of one benzoyl group into the molecule. The other spectral properties of the molecule clearly differentiate **3e** from the isomeric 9-benzoate (**3d**); therefore **3e** must be the 11-benzoate.

Prostaglandin $F_{2\alpha}$ 9,11-Dibenzoate Methyl Ester (3f). A solution of $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester[10] (144 mg, 0.3 mmol) in pyridine (2 mL) was stirred with benzoyl chloride (169 mg, 1.2 mmol) at room temperature for 2 h. After workup, the *tert*-butyldimethylsilyl protecting group was removed by stirring the dibenzoate in acetic acid/THF/water (3:1:1) at room temperature overnight. There was obtained after workup 149 mg of an oil which was chromatographed (high-performance LC) on 34 g of analytical grade silica gel by using 30% ethyl acetate in hexane as eluant. Pure **3f** (127 mg, 0.2 mmol, 66%) was obtained in fractions (10 mL each) 16–24 as a colorless oil: IR (neat) ν_{OH} 3500, $\nu_{C=O}$ 1715, $\nu_{C=C}$ 1600, 1585, 1490 cm^{-1}; NMR ($CDCl_3$) δ 7.72 (m, 10 H, aromatic), 5.73 (m, 2 H, CH=CH), 5.42 (m, 4 H, CH=CH, 2>CH–OCO–), 4.16 (m, 1 H, >CHOH), 3.65 (s, 3 H, $COOCH_3$), 0.88 (t, 3 H, J = 5 Hz, CH_3); UV and CD, see Table I; mass spectrum, m/e 648.3475 (calcd for trimethylsilyl ether, $C_{38}H_{52}SiO_7$, 648.3482), 633, 617, 605, 577, 527, 526, 455, 404, 333, 314, 105. Anal. Calcd for $C_{33}H_{44}O_7$: C, 72.89; H, 7.69; Found: C, 72.54; H, 7.88.

Prostaglandin $F_{2\alpha}$ Tribenzoate Methyl Ester (3g). A solution of $PGF_{2\alpha}$ methyl ester (0.119 g) in pyridine (5 mL) was stirred with benzoyl chloride (0.25 mL) for 3 h. TLC indicated that complete benzoylation was slow, one of the hydroxyl groups being more resistant to esterification. After workup, the crude product was chromatographed on a silica gel column. The pure tribenzoate[13] (**3g**, 0.075 g) was obtained as a viscous oil: NMR ($CDCl_3$) δ 7.98 (m, 6 H, ortho aromatic protons), 7.41 (m, 9 H, other aromatic protons), 5.80 (m, 2 H, –CH=CH–), 5.40 (m, 5 H, CH=CH, >CHOCO–), 3.60 (s, 3 H, $COOCH_3$), 0.87 (t, 3 H, J = 5 Hz, CH_3); mass spectrum, m/e 680.3317 (calcd for $C_{42}H_{48}O_8$ 680.3349).

11-*epi*-Prostaglandin $F_{2\beta}$ 9,11-Dibenzoate Methyl Ester (4). The procedure of Mitsunobu and Yanaba[14] was used. $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester (1.21 g, 2.5 mmol) was dissolved in THF (125 mL). With stirring at 20 °C, triphenylphosphine (2.62 g, 10 mmol), benzoic acid (1.21 g, 10 mmol), and, slowly, diethylazodicarboxylate (1.74 g, 10 mol) were added sequentially to the solution. The starting material was consumed within 30 min as determined by TLC. Excess THF was removed under reduced pressure. Hexane–20% ethyl acetate (100 mL) was added to the residue. Crystals formed and after several hours these were removed by filtration. The filtrate was concentrated and the residue (3.7 g) was chromatographed (high-performance LC) on a Merck size C Lobar silica gel column by using 5% acetone in hexane. Appropriate fractions were combined and rechromatographed under the same conditions. In this way the intermediate 11-*epi*-$PGF_{2\beta}$ 9,11-dibenzoate 15-*tert*-butyldimethylsilyl ether methyl ester (0.580 g) was obtained. The latter was hydrolyzed in 10 mL of a solution made up of acetic acid (27 mL), THF (9 mL), water (9 mL), and 1 N aqueous HCl (24 drops) for 4 h at room temperature. After workup, the crude product (0.420 g) was chromatographed on a Merck size B Lobar silica gel column by using 15% acetone–hexane. The pure dibenzoate **4** (0.350 g) was a viscous oil: NMR ($CDCl_3$) δ 8.00 (m, 4 H, ortho aromatic protons), 7.43 (m, 6 H, other aromatic protons), 5.68 (m, 2 H, CH=CH), 5.45, 5.25 (m, 4 H, CH=CH, >CHOCO–), 4.02 (m, 1 H, >CH–O–), 3.63 (s, 3 H, $COOCH_3$), 0.84 (t, 3 H, J = 5 Hz, CH_3); mass spectrum, m/e 648, 635, 577.2642 (calcd for $M^+ - C_5H_{11}$, $C_{33}H_{42}SiO_7$; 577.2621), 404, 333, 314, 199, and 105.

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Registry No. 2a, 73070-13-0; **2a** *tert*-butyldimethylsilyl ether, 73078-82-7; **2a** trimethylsilyl ether, 73070-14-1; **2b**, 73089-63-1; **2b** trimethylsilyl ether, 73135-94-1; **2c**, 73070-15-2; **2d**, 73089-64-2; **2e**, 73070-16-3; **2f**, 73089-65-3; **3a**, 73070-17-4; **3a** bis(trimethylsilyl) ether, 73070-18-5; **3b**, 73070-19-6; **3b** bis(trimethylsilyl) ether, 73070-20-9; **3c**, 73070-21-0; **3c** trimethylsilyl ether, 73070-22-1; **3d**, 64982-03-2; **3d** bis(trimethylsilyl) ether, 73070-23-2; **3e**, 73070-24-3; **3e** bis(trimethylsilyl) ether, 73070-05-0; **3f**, 73070-06-1; **3f** trimethylsilyl ether, 73070-07-2; **3g**, 59895-13-5; **4**, 73070-08-3; 3α,5α-dihydroxy-2β-(3′-oxo-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether, 64072-25-9; 3α,5α-dihydroxy-2β-(3′-oxo-*trans*-1′-octenyl)cyclopentane-1-acetic acid γ-lactone, 60623-67-8; (3′*S*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether, 64072-30-6; (3′*R*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone 3-*tert*-butyldimethylsilyl ether, 64091-16-3; $PGF_{2\alpha}$ methyl ester, 33854-16-9; $PGF_{2\alpha}$ methyl ester 9,11-*n*-butylboronate ester, 73070-09-4; 15-*epi*-$PGF_{2\alpha}$ methyl ester, 13228-05-2; 15-*epi*-$PGF_{2\alpha}$ methyl ester 9,11-*n*-butylboronate ester, 73070-10-7; (3′*S*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone, 26054-67-1; (3′*R*)-3α,5α-dihydroxy-2β-(3′-hydroxy-*trans*-1′-octenyl)cyclopentane-1α-acetic acid γ-lactone, 39182-59-7; $PGF_{2\alpha}$ methyl ester 11,15-bis(ethoxyethyl) ether, 73070-11-8; $PGF_{2\alpha}$ 15-*tert*-butyldimethylsilyl ether methyl ester, 65147-38-8; 11-*epi*-$PGF_{2\beta}$ 9,11-bisbenzoate 15-*tert*-butyldimethylsilyl ether methyl ester, 73070-12-9.

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Synthesis of Natural Isocoumarins, Artemidin and 3-Propylisocoumarin

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It has been demonstrated, principally by Castro and co-workers, that a variety of heterocyclic compounds may be obtained by the interaction of cuprous acetylides with aryl halides bearing ortho nucleophilic substituents.[1] The claim made in 1963 that cuprous phenylacetylide reacted with *o*-iodobenzoic acid (**1**) to yield 3-phenylisocoumarin (**2**)[1a,b] led to the suggestion, in a review of the chemistry

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