Total Synthesis of 6a-Carbaprostaglandin I_2 and Related Isomers

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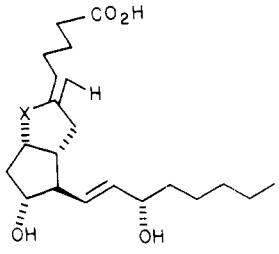
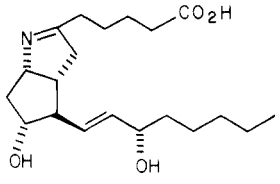
The total synthesis of 6a-carbaprostaglandin I_2 (**4**), an isosteric analogue of naturally occurring prostacyclin (PGI_2, **1**), is described. The synthetic sequence begins with the optically active, tricyclic ketone **5** and proceeds by way of the ring-expanded ketones **8** and **14**. The sequence also affords the three isomeric carbocyclic analogues **36**, **45**, and **46**, each of which exhibits lower biological activity than **4** in several test systems.

Prostacyclin (PGI_2, **1**), a recently discovered metabolite





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1, X = O (PGI_2)
2, X = S
4, X = CH_2

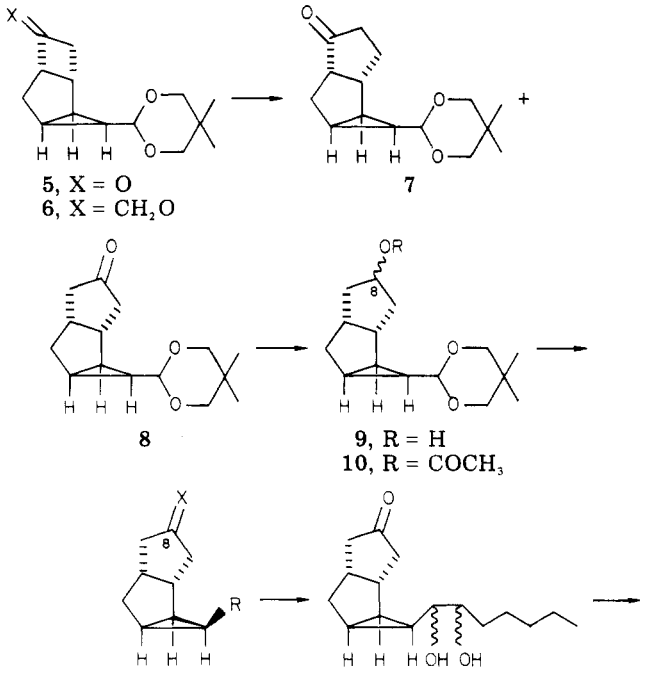
of arachidonic acid, has been shown to be a potent inhibitor of human platelet aggregation and a relaxer of certain vascular tissues.[1,2] Prostacyclin itself, however, has an extremely short biological and chemical half-life due to the enol ether function, and it rapidly decomposes to 6-oxoprostaglandin $F_1\alpha$ in neutral or acidic aqueous media.[3,4] It is therefore desirable to synthesize PGI_2 mimics which would be chemically stable yet retain the biological activities of naturally occurring prostacyclin. To this end, several stable analogues of **1** have been synthesized, as exemplified by (5*Z*)-9-deoxy-6,9α-epithio-Δ^5-PGF_1 (**2**)[5,6] and 9-deoxy-9α,6-nitrilo-PGF_1 (**3**)[7], both of which display varying degrees of prostacyclin-like activities.

Our approach to overcoming the inherent instability problem of **1** was to replace the enol ether oxygen atom with a methylene group as in 6a-carba-PGI_2 (**4**), a molecule which is isosteric with prostacyclin itself and one which is expected to be substantially more chemically stable than **1**.

Results and Discussion

The initial steps in the synthetic approach to the carbocyclic analogue **4** are outlined in Scheme I. Reaction of optically resolved cyclobutanone **5**[8] with dimethylsulfonium methylide by the method of Corey and Chaykovsky[9] gave the isomeric spiro epoxides **6** in 92% yield. It is assumed that an isomeric mixture of epoxides was formed in this reaction even though separation could not be achieved chromatographically. The epoxides were

Scheme I



5, X = O
6, X = CH_2O

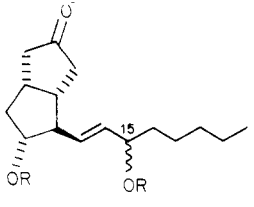
7

8

9, R = H
10, R = $COCH_3$

11, R = CHO, X = H, $OCOCH_3$
12, R = $CH{=}CHC_5H_{11}$, X = H, $OCOCH_3$
13, R = $CH{=}CHC_5H_{11}$, X = H, OH
14, R = $CH{=}CHC_5H_{11}$, X = O

15



16, R = H (15*S*)
17, R = H (15*R*)
18, R = *t*-$BuMe_2Si$ (15*S*)
19, R = *t*-$BuMe_2Si$ (15*R*)

then ring expanded by the method of Leriverend and Leriverend,[10] using anhydrous lithium iodide in tetrahydrofuran to give the isomeric cyclopentanones **7** and **8** (97% crude yield; ratio of **7**:**8** ca. 1:9 by TLC). Direct crystallization (acetone–*n*-hexane) of the major isomer from the crude product gave the pure 8-oxo isomer **8** in 60% yield from **6**. The structural assignments for ketones **7** and **8** are supported by standard spectral methods (see Experimental Section). In particular, ^{13}C NMR spectroscopy proved especially valuable for distinguishing **7**

(1) Moncada, S.; Herman, A. G.; Higgs, E. A.; Vane, J. R. *Thromb. Res.* **1977**, *11*, 323 and references cited therein.
(2) Armstrong, J. M.; Dusting, G. J.; Moncada, S.; Vane, J. R. *Circ. Res.* **1978**, *43*, 112 and references cited therein.
(3) Johnson, R. A.; Morton, D. R.; Kinner, J. H.; Gorman, R. R.; McGuire, J. C.; Sun, F. F.; Whittaker, N.; Bunting, S.; Salmon, J.; Moncada, S.; Vane, J. R. *Prostaglandins* **1976**, *12*, 915.
(4) Johnson, R. A.; Lincoln, F. H.; Thompson, J. L.; Nidy, E. G.; Mizsak, S. A.; Axen, U. *J. Am. Chem. Soc.* **1977**, *99*, 3887.
(5) Nicolaou, K. C.; Barnette, W. E.; Gasic, G. P.; Magolda, R. L. *J. Am. Chem. Soc.* **1977**, *99*, 7736.
(6) Shibasaki, M.; Ikegami, S. *Tetrahedron Lett.* **1978**, 559.
(7) Bundy, G. L.; Baldwin, J. M. *Tetrahedron Lett.* **1978**, 1371.
(8) Kelly, R.; VanRheenen, V. *Tetrahedron Lett.* **1973**, 1712.
(9) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 3782.
(10) Leriverend, M.-L.; Leriverend, P. *C. R. Hebd. Seances Acad. Sci., Ser. C* **1975**, *280*, 791. See also for a related example: Trost, B. M.; Latimer, L. H. *J. Org. Chem.* **1978**, *43*, 1031.

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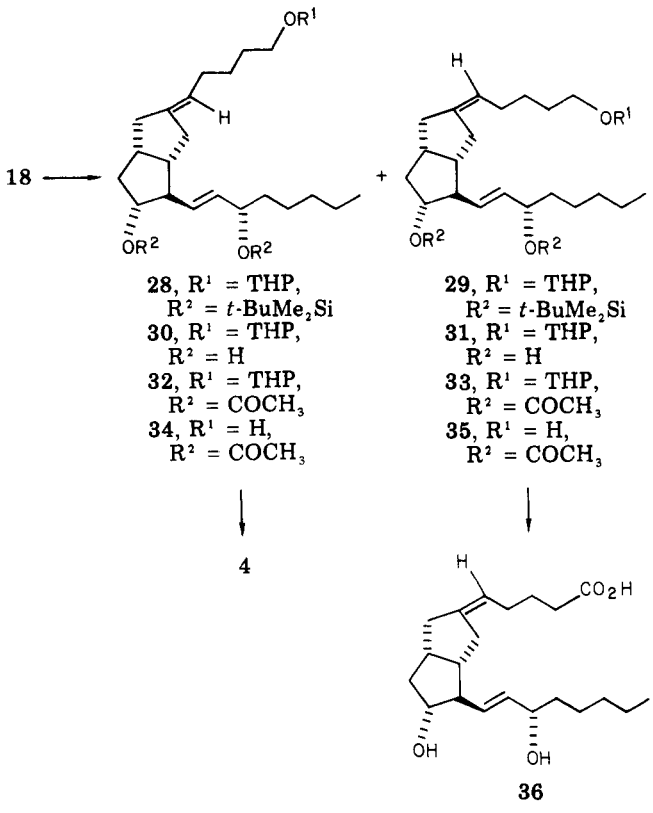
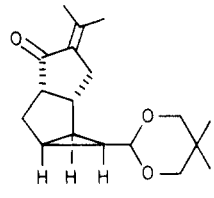
Scheme II



from 8. Ketone 8 exhibits two methylene resonances (for the carbon atoms α to the carbonyl group) at 45.0 and 44.4 ppm downfield from internal Me_4Si in $CDCl_3$. Both of these resonances become triplets with offset decoupling. Ketone 7 exhibits one α-methylene carbon at 38.6 ppm (triplet with offset decoupling) and one α-methine carbon at 42.3 ppm (doublet with offset decoupling). The structural assignments were further supported by the findings that condensation of 7 with acetone in the presence of aqueous base gave a single monoisopropylidene derivative (i.e., **20**) while a similar reaction carried out with 8 gave diisopropylidene **21**.



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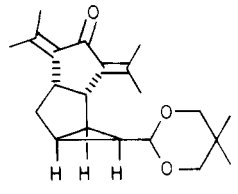

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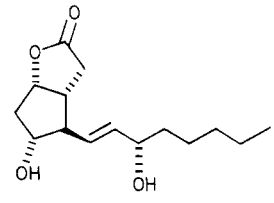
In the next step of Scheme I, ketone 8 was reduced with sodium borohydride in ethanol to give the epimeric alcohols **9**[11] which were then acetylated with acetic anhydride in pyridine to afford the epimeric acetates **10**[11] in essentially quantitative yield from 8. Hydrolysis of the acetal function in **10** with 88% formic acid (0–5 °C, 3 h) gave the endo aldehyde **11** in 86% yield (^1H NMR aldehyde peak at δ 9.42 (d, J = 6 Hz)). This substance was then condensed with *n*-hexylidenetriphenylphosphorane to give **12**, the acetate function at C-8 was hydrolyzed in aqueous base, and the resulting epimeric alcohols **13**[11] were oxidized with Jones' reagent at −20 °C to give the presolvolysis ketone **14** in 65% yield from **11**.

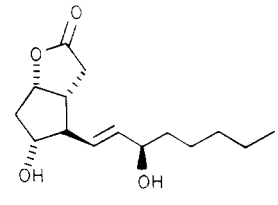
(11) Intermediates **9**–**13** are all epimeric at C-8. Since the desired presolvolysis intermediate **14** has sp^2 hybridization at this location, no attempt was made to separate the C-8 epimers at any stage of the synthesis.

The transformation of the vinylcyclopropane **14** into diols **16** and **17** was carried out by the ortho ester solvolysis method of Kelly and VanRheenen.[12] Thus, **14** was hydroxylated catalytically with osmium tetraoxide in the presence of *N*-methylmorpholine oxide dihydrate[13] to give the isomeric cis glycols **15** in essentially quantitative yield. Treatment of **15** with triethyl orthopropionate in the presence of pyridine hydrochloride afforded the corresponding isomeric cyclic orthopropionates which were solvolyzed in anhydrous formic acid (25 °C, 10 min), saponified with aqueous methanolic potassium carbonate, and treated with sodium metaperiodate[14] to give a 1:1 mixture of diols **16** and **17** in 44% combined yield from **15**.

The stereochemistries of the isomeric diols were initially determined by the respective affinities of the isomers for silica gel. Specifically, it was previously established that in certain solvent systems (e.g., 40% acetone in methylene chloride) the two lactone diols of known absolute configuration, **22** and **23**, were easily distinguished by TLC,



22



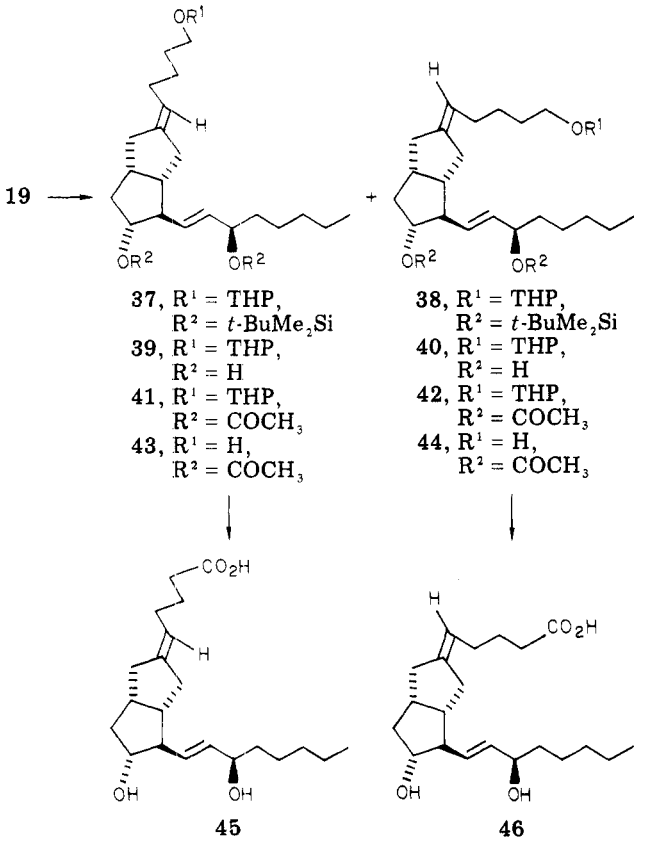
23

the 15*S* isomer **22** being more polar (R_f 0.45) than the 15*R* isomer **23** (R_f 0.52). For this reason, the more polar of the two carbocyclic diol intermediates (using 30% acetone in methylene chloride) was assigned as the 15*S* epimer **16** (R_f 0.16) and the less polar diol was assigned as the 15*R* epimer **17** (R_f 0.26). This initial assignment of stereochemistry was further supported by circular dichroism experiments[16] and the fact (vide infra) that the final carbocyclic analogues derived from **16** (i.e., **4** and **36**) are considerably more biologically active than the corresponding analogues derived from **17** (i.e., **45** and **46**). Each of the diols was then converted in standard fashion[17] and high yield to its bis(*tert*-butyldimethylsilyl ether) derivative (**18** from **16** and **19** from **17**).

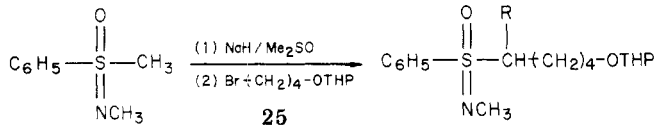
Initial attempts to attach the carboxylic acid side chain to ketone **18** relied on the Wittig condensation of **18** with the ylide derived from (4-carboxybutyl)triphenylphosphonium bromide.[18] Unfortunately, rapid enolization of **18** appeared to occur, since the inverse addition of the red ylide solution to **18** resulted in instantaneous decolorization of the ylide reagent and aqueous workup provided good yields of recovered **18** in addition to trace amounts of the desired acidic products. What was needed was a reagent which would be less basic and more nucleophilic than the above-mentioned Wittig reagent and, further, a reagent which would also regiospecifically introduce the desired carbon–carbon double bond in **4**. This objective was accomplished by employing the general method of Johnson and co-workers[19] using sulfoximine **26**. This

(12) Kelly, R. C.; VanRheenen, V. *Tetrahedron Lett.* **1976**, 1067.
(13) VanRheenen, V.; Kelly, R. C.; Cha, D. Y. *Tetrahedron Lett.* **1976**, 1973.
(14) Treatment of the crude sample of **16** and **17** with sodium metaperiodate selectively removes traces of unsolvolyzed **15** that are present and which are not easily removed by chromatography.
(15) Kelly, R. C., The Upjohn Company, unpublished results.
(16) Johnson, R. A.; Krueger, W. C., The Upjohn Company, manuscript in preparation.
(17) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(18) Corey, E. J.; Weinshenker, N. M.; Schaaf, T. K.; Huber, W. *J. Am. Chem. Soc.* **1969**, *91*, 5675.

Scheme III



reagent was synthesized in moderate yield from *N*-methylmethylphenylsulfoximine (**24**)[19] and 4-bromobutyl tetrahydropyranyl ether.



As outlined in Scheme II, treatment of **26** with methylmagnesium bromide (1.0 equiv) generated the corresponding sulfoximine α-carbanion **27**. To **27** was added ketone **18**, and the resulting adduct was treated with aluminum amalgam in tetrahydrofuran–water–acetic acid (3:1:1) to effect reductive elimination[19] to olefins **28** and **29** (48% yield from **18**). The mixture of **28** and **29** was treated with tetra-*n*-butylammonium fluoride[17,20] in tetrahydrofuran to give diols **30** and **31**, and these diols were, in turn, acetylated with acetic anhydride in pyridine to give diacetates **32** and **33**. Subsequent hydrolysis in aqueous acetic acid gave the isomeric alcohols **34** (34% from **28** and **29**) and **35** (39% from **28** and **29**), separable by high-pressure LC on neutral silica gel. Oxidation of the more polar alcohol (R_f 0.44 in 5% acetone in methylene chloride) with Jones' reagent followed by hydrolysis with aqueous base gave a single, crystalline acid diol, assigned as the 5*E* isomer **4** (56% from **34**; mp 62.4–63.3 °C). The identical sequence of reactions carried out on the less polar alcohol (R_f 0.49 in 5% acetone in methylene chloride) gave another crystalline acid diol, assigned as the 5*Z* isomer **36** (62% from **35**; mp 107.5–108.3 °C).

(19) Johnson, C. R.; Shanklin, J. R.; Kirchoff, R. A. *J. Am. Chem. Soc.* **1973**, *95*, 6462.
(20) Pless, J. *J. Org. Chem.* **1974**, *39*, 2644.

Table I. Biological Activities for the Carbocyclic Prostacyclin Analogues

compd	relative potencies SM[a]	BP[b]	platelet[c]
PGE_1[d]	100	100	1
4	100-320	100	1
36	1-3.2	1-3.2	0.032
45	<0.1	10-32	0.032
46	<0.1	0.1-0.32	0.0032

[a] Stimulation of the isolated gerbil colon by the method of Weeks et al.[24] [b] Depression of rat blood pressure by the method of Weeks et al.[24] [c] Inhibition of ADP-induced human platelet aggregation by the method of Nishizawa et al.[25] [d] Standard of reference in all three biological test systems.

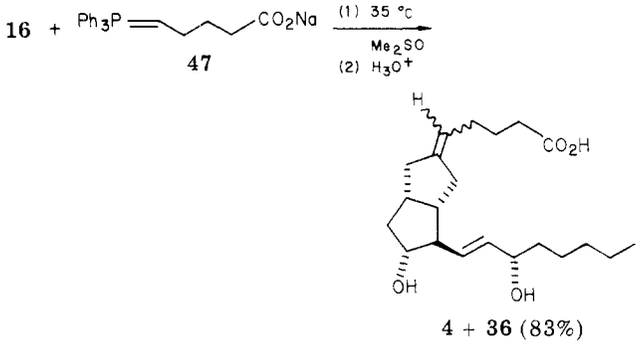
As outlined in Scheme III, the diprotected 15*R* ketone **19** was transformed by identical procedures (by way of intermediates **37** and **38**, **39** and **40**, and **41** and **42**) to two isomeric alcohols, **43** and **44**. The more polar alcohol (R_f 0.50 in 50% ethyl acetate in Skellysolve B) was converted by the methods described above for alcohols **34** and **35** to a single acid diol, assigned as the 5*E*,15*R* isomer **45**. The identical sequence of reactions carried out on the less polar alcohol (R_f 0.54 in 50% ethyl acetate in Skellysolve B) gave another acid diol, assigned as the 5*Z*,15*R* isomer **46**.

Owing to close structural similarity, the configurational assignments at C-5 for the final carbocyclic analogues **4**, **36**, **45**, and **46** have not, as yet, been determined unambiguously by a physical or chemical method. However, examination of the biological data summarized in Table I[24,25] lends strong assurance to the above assignments of configuration at C-5 and of stereochemistry at C-15. For example, isomer **4** is the most potent isomer in all three biological test systems, being essentially equipotent to the standard of reference, PGE_1. It is reasonable, therefore, to assign the 5*E*,15*S* stereochemistry to this isomer since this is the stereochemistry which is isosteric with prostacyclin (**1**). Isomer **36** is therefore assigned as the 5*Z*,15*S* isomer since it is considerably less active than **4** in all three test systems. Similar arguments can also be made for the assignments of **45** and **46**. Precedent for the effect of this difference in C-5 configuration on biological activities in the prostacyclin area is available.[21,22] In particular, (5*E*)-PGI_2 was found to be only 20% as active as (5*Z*)-PGI_2 (**1**, prostacyclin) as an inhibitor of human platelet aggregation.[22] Finally, reference to Table I further supports the stereochemical assignments at C-15. In particular, comparison of both 5*E* isomers, **4** and **45**, reveals that **4** is considerably more active than **45** in all three test systems. It is well established in the prostaglandin area[23] that the natural (15*S*) configuration is necessary for optimal agonist activity, and therefore, it is logical to assign the 5*E*,15*S* stereochemistry to **4** and the 5*E*,15*R* stereochemistry to **45**. The same argument applies to **36** and **46**.

After the completion of the total synthesis described above, a reinvestigation was made of the Wittig reaction as a means of attaching the carboxylic acid side chain. It has now been found that if an excess of ylide (6 equiv) is condensed with the unprotected ketone **16**, a good yield

(21) Corey, E. J.; Szekely, I.; Shiner, C. S. *Tetrahedron Lett.* **1977**, 3529.
(22) Johnson, R. A.; Lincoln, F. H.; Nidy, E. G.; Schneider, W. P.; Thompson, J. L.; Axen, U. *J. Am. Chem. Soc.* **1978**, *100*, 7690.
(23) Anderson, N. H.; Ramwell, P. W. *Arch. Intern. Med.* **1974**, *133*, 30.
(24) Weeks, J. R.; DuCharme, D. W.; Magee, W. E.; Miller, W. L. *J. Pharm. Exp. Ther.* **1973**, *186*, 67.
(25) Nishizawa, E. E.; Wynalda, D. J.; Snydam, D. E.; Molony, B. A. *Thromb. Res.* **1973**, *3*, 577.

of a mixture of 5*E* and 5*Z* isomers **4** + **36** is obtained. This result is in agreement with the recently published reports of Kojima and Sakai[26] and Nicolaou and co-workers.[27,28]



4 + **36** (83%)

Experimental Section

General Procedures. All melting points and boiling points are uncorrected. All analytical data were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (crystalline samples). Mass spectra were recorded at high (HRMS) or low resolution (MS) for derivatized (Me_3Si) or underivatized compounds at 70 eV. The ^1H NMR spectra were obtained on a Varian A-60D spectrometer operating at 60 MHz or a Varian HFT-80 spectrometer operating at 80 MHz on chloroform-*d* solutions. Chemical shifts are reported in δ (parts per million) relative to internal tetramethylsilane. The ^{13}C NMR spectra were recorded on a Varian CFT-20 spectrometer equipped with Fourier accessories. The spectrometer was operated at 20 MHz and was internally locked to the ^2H frequency of the solvent. Chemical shifts are reported in δ (parts per million) relative to tetramethylsilane. Thin-layer chromatography (TLC) was conducted with Analtech (Uniplates) glass plates precoated with silica gel GF (250 μm). Where mixed solvents were used for chromatography, the composition is expressed as a percent by volume of the former in the latter. The solvent system A-IX[29] is the organic layer from an equilibrated mixture of 90 mL of ethyl acetate, 20 mL of acetic acid, 50 mL of 2,2,4-trimethylpentane, and 100 mL of water. The TLC plates were visualized first by UV light (Mineralight UVS-11) and then by spraying with 50% aqueous sulfuric acid, followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck), 70–230 mesh. Acid-washed silica gel was Mallinckrodt CC-4. Brine refers to a saturated aqueous solution of NaCl and bicarbonate refers to a saturated aqueous solution of sodium bicarbonate. All solvents were reagent grade or reagent grade distilled from glass (Burdick & Jackson). All reagents were used as purchased and were reagent grade where available.

(7*RS*)-7-(Spiroepoxymethano)tricyclo[4.2.0.0^{2,4}]octane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (6). The general method of Corey and Chaykovsky[9] was employed. Thus, a solution of 131 mmol of sodium methylsulfinylmethide (prepared from 5.5 g (131 mmol) of a 57% NaH dispersion and 200 mL of Me_2SO in the usual manner[30]) was diluted with 150 mL of THF, alternately degassed and flushed with nitrogen, and cooled to 0–5 °C (ice bath). The resulting solution was treated with a solution of 26.8 g (131 mmol) of trimethylsulfonium iodide in 135 mL of Me_2SO during 10 min and then stirred for an additional 10 min. A solution of 15.5 g (65.5 mmol) of 7-oxotricyclo[4.2.0.0^{2,4}]octane-3-*endo*-carboxaldehyde neopentyl glycol acetal (**5**)[8] in 70 mL of THF was added with stirring, and the resulting solution was stirred for an additional 60 min at 0–5 °C. The reaction mixture was diluted with brine and extracted with diethyl ether (3 × 300 mL). The combined extracts were washed with water (4 × 500 mL) and brine (500 mL) and dried over sodium sulfate. Concentration in vacuo gave 18.7 g of crude **6** as a yellow oil. A 48 mm × 48 in. column was slurry packed with 600 g of silica gel in 20% ethyl acetate in Skellysolve B. The sample was applied in 1:1 methylene chloride–Skellysolve B and eluted with 20% ethyl acetate in Skellysolve B. The first fraction was 1500 mL, and subsequent fractions were 50 mL each. On the basis of TLC homogeneity, fractions 11–50 were combined to give 15.1 g (92%) of pure **6** as an oil that solidified on standing: NMR δ 0.70 (s, 3 H), 1.22 (s, 3 H), 0.8–3.0 (m, 9 H), 2.67 and 2.70 (2 s, 2 H total), 3.2–3.82 (apparent q, 4 H), 3.92 (d, J = 8 Hz, 1 H); IR (mull) 3070, 3020, 3010, 1115, 1100, 1015, 990, 970, 945, 925, 865, 835, 790, 785 cm^{-1}; MS *m/e* 249, 235, 233, 232, 219, 194, 115; TLC R_f 0.33 in 25% ethyl acetate in Skellysolve B. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.19; H, 8.95.

7-Oxotricyclo[4.3.0.0^{2,4}]nonane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (7) and 8-Oxotricyclo[4.3.0.0^{2,4}]-nonane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (8). A solution of 11.12 g (45 mmol) of epoxides **6** in 150 mL of THF was treated with 2 g of anhydrous lithium iodide. The resulting solution was stirred at room temperature for 45–60 min, diluted with 300 mL of brine, and extracted with ethyl acetate (2 × 150 mL). The combined extracts were washed with brine (200 mL), dried over sodium sulfate, and concentrated in vacuo to give 10.79 g (97%) of a crude mixture of **7** and **8** as a white solid. Recrystallization from acetone–*n*-hexane gave 6.74 g (60%) of pure **8** as colorless platelets: mp 98.0–99.1 °C; NMR δ 0.71 (s, 3 H), 1.22 (s, 3 H), 0.9–3.0 (m, 11 H), 3.32–3.77 (m, 4 H), 4.31 (d, J = 7 Hz, 1 H); IR (mull) 3040, 1755, 1730, 1165, 1120, 1110, 1015, 990, 970, 930 cm^{-1}; $[\alpha]_D$ +74° (*c* 0.8870, $CHCl_3$); MS *m/e* 250, 222, 163, 146, 115, 69; TLC R_f 0.33 in 10% acetonitrile in methylene chloride. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.02; H, 8.92.

The mother liquors from the above experiment were concentrated to give 4.05 g of a mixture of **7** and **8** as a beige solid. Chromatography (high pressure LC) of this sample over two prepacked Lobar columns (EM reagents, size B) connected in series, eluting with 5% acetonitrile in methylene chloride, afforded a pure sample of **7** as a colorless solid. Recrystallization from Skellysolve B at −20 °C gave pure **7** as colorless needles: mp 78.0–79.9 °C; NMR δ 0.72 (s, 3 H), 1.22 (s, 3 H), 0.9–3.1 (m, 11 H), 3.30–3.75 (m, 4 H), 4.11 (d, J = 7 Hz, 1 H); IR (mull) 3030, 1730, 1130, 1110, 1015, 985 cm^{-1}; $[\alpha]_D$ +62° (*c* 0.8285, $CHCl_3$); MS *m/e* 250, 222, 164, 146, 115, 69; TLC R_f 0.43 in 10% acetonitrile in methylene chloride. Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.26; H, 9.05.

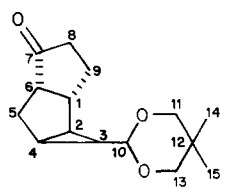
The data obtained from ^{13}C NMR experiments with **7** and **8** are summarized in Table II.

8-Isopropylidene-7-oxotricyclo[4.3.0.0^{2,4}]nonane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (20). A solution of 0.25 g (1.0 mmol) of ketone **7** in 12.5 mL of acetone was treated with 2.5 mL of 1 N aqueous NaOH. The reaction mixture was stirred at gentle reflux (70 °C oil bath) for 72 h, cooled, diluted with brine and 1 M aqueous $KHSO_4$, and extracted with ethyl acetate. The ethyl acetate extract was washed with bicarbonate and brine and dried over sodium sulfate. Concentration in vacuo gave 0.57 g of crude **20** as an oil. This material was chromatographed over 114 g of silica gel, eluting with 15% ethyl acetate in Skellysolve B, to afford 0.14 g (48%) of pure **20** as a colorless solid. Recrystallization from methanol–water gave pure **20** as colorless needles: mp 93–94 °C; NMR δ 0.71 (s, 3 H), 1.23 (s, 3 H), 1.0–3.0 (m, 9 H), 1.83 (bd s, 3 H), 2.23 (m, 3 H), 3.20–3.80 (m, 4 H), 4.14 (d, J = 7 Hz, 1 H); IR (mull) 1695, 1620, 1115, 1105, 1020, 990 cm^{-1}; MS *m/e* 290, 262, 115, 79, 77, 69, 68, 67, 45, 41, 39, 27; TLC R_f 0.38 in 25% ethyl acetate in Skellysolve B. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.68; H, 9.24.

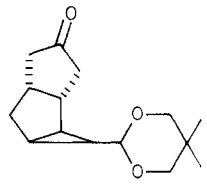
7,9-Diisopropylidene-8-oxotricyclo[4.3.0.0^{2,4}]nonane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (21). A solution of 0.50 g (2 mmol) of ketone **8** in 25 mL of acetone was treated with 5 mL of 1 N aqueous NaOH. The reaction mixture was heated with stirring at gentle reflux (70 °C oil bath) for 21 h. Then 2.0 mL of 6.0 N aqueous NaOH was added, and heating at 70 °C was continued for an additional 24 h. The reaction

(26) Kojima, K.; Sakai, K. *Tetrahedron Lett.* **1978**, 3743.
(27) Nicolaou, K. C.; Sipio, W. J.; Magolda, R. L.; Seitz, S.; Barnette, W. E. *J. Chem. Soc., Chem. Commun.* **1978**, 1067.
(28) Although it is not explicitly stated in either of the publications cited in ref 26 and 27, these authors undoubtedly synthesized the racemic forms of the analogues described in this article. In both instances, a symmetrical intermediate was formed at some point in their respective syntheses.
(29) Hamberg, M.; Samuelsson, B. *J. Biol. Chem.* **1966**, *241*, 275.
(30) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1962**, *84*, 866. *Ibid.* **1965**, *87*, 1345.

Table II. ^{13}C NMR Data for 7 and 8



7



8

compd	chemical shift (δ) for indicated carbon atom[a] 1	6	7	8	9	10	11, 13	other peaks
7	52.9 (d)	42.3 (d)	219.5 (s)	38.6 (t)		100.6 (d)	77.3 (t)	29.9, 28.9, 28.5, 27.8, 24.8, 23.0, 21.8, 21.6
8	39.9 (d) or 40.1 (d)	39.9 (d) or 40.1 (d)	45.0 (t) or 44.4 (t)	218.3 (s)	45.0 (t) or 44.4 (t)	100.8 (d)	77.3 (t)	33.3, 29.9, 27.7, 25.5, 23.0, 22.4, 21.8

[a] Letters in parentheses denote multiplicities of peaks upon offset decoupling.

mixture was cooled, diluted with brine and 1 N aqueous $KHSO_4$, and extracted with ethyl acetate. The ethyl acetate extract was washed with bicarbonate and brine and dried over sodium sulfate. Concentration in vacuo gave 0.88 g of crude **11** as an oil. This material was chromatographed over 50 g of silica gel, eluting with 5–7.5% ethyl acetate in Skellysolve B, to afford 0.20 g (30%) of **21** as a yellow solid. Recrystallization from methanol–water gave pure **21** as yellow needles: mp 125–126 °C; NMR δ 0.75 (s, 3 H), 1.26 (s, 3 H), 0.9–2.6 (m, 5 H), 1.84, 1.98, 2.28, 2.31 (4 s, 12 H), 2.9–3.28 (m, 2 H), 3.28–3.92 (m, 4 H), 4.15 (d, J = 7 Hz, 1 H); IR (mull) 3040, 1680, 1615, 1200, 1120, 1100, 1015 cm^{-1}; MS m/e 330, 244, 243, 200, 175, 162, 115, 69, 45, 41; TLC R_f 0.50 in 25% ethyl acetate in Skellysolve B. Anal. Calcd for $C_{21}H_{30}O_3$: C, 76.32; H, 9.15. Found: C, 76.21; H, 9.16.

(8*RS*)-8-Acetoxytricyclo[4.3.0.0^{2,4}]nonane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (10). A solution of 1.86 g (49 mmol) of $NaBH_4$ in 200 mL of 95% ethanol was purged with nitrogen and treated with a solution of 12.15 g (49 mmol) of ketone **8** in 75 mL of 95% ethanol. The reaction mixture was stirred at room temperature for 60 min, diluted with brine, and extracted with ethyl acetate (2 × 200 mL). The combined extracts were washed with 300 mL of brine, dried over sodium sulfate, and concentrated in vacuo to give 11.86 g (96%) of (8*RS*)-8-hydroxytricyclo[4.3.0.0^{2,4}]nonane-3-*endo*-carboxaldehyde neopentyl glycol acetal (**9**) as a white solid. Recrystallization of a small sample from acetone–*n*-hexane gave pure **9** as colorless platelets, mp 100.0–102.4 °C. Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.65; H, 9.83.

The above crude sample of **9** was dissolved in 200 mL of pyridine, cooled to 0–5 °C, and reacted with 20 mL of acetic anhydride and 0.2 g of 4-(*N*,*N*-dimethylamino)pyridine. The reaction mixture was stirred at room temperature for 60 min, diluted with brine, and extracted with ethyl acetate (2 × 300 mL). The combined extracts were washed with cold 1 N aqueous HCl (3 × 300 mL), bicarbonate (2 × 300 mL), and brine (300 mL) and dried over sodium sulfate. Concentration in vacuo gave 14.2 g (ca. 100%) of essentially pure **10** as a pale yellow oil: NMR δ 0.72 (s, 3 H), 1.20 (s, 3 H), 0.9–2.7 (m, 11 H), 1.98 (s, 3 H), 3.23–3.8 (apparent q, 4 H), 4.06 (d, J = 9 Hz, 1 H), 5.03 (quintet, J = 5 Hz, 1 H); IR (film) 3020, 1735, 1250, 1110, 1040, 1020 cm^{-1}; MS m/e 294, 234, 148, 130, 115; TLC R_f 0.61 in 50% ethyl acetate in Skellysolve B. Anal. Calcd for $C_{17}H_{26}O_4$: C, 69.36; H, 8.90. Found: C, 69.50; H, 9.06.

(8*RS*)-8-Acetoxytricyclo[4.3.0.0^{2,4}]nonane-3-*endo*-carboxaldehyde (11). A solution of 14.5 g (49 mmol) of acetal **10** and 200 mL of 88% formic acid was stirred at 0–5 °C under nitrogen for 3 h. The reaction mixture was diluted with 500 mL of brine and extracted with ethyl acetate (3 × 150 mL). The combined extracts were washed with water (4 × 500 mL), bicarbonate (2 × 500 mL), and brine (500 mL) and dried over sodium sulfate. Concentration in vacuo gave 13.8 g of crude **11** as a yellow oil. A 48 mm × 36 in. column was slurry packed with 300 g of silica gel in 20% ethyl acetate in Skellysolve B. The sample was applied in 1:1 methylene chloride–Skellysolve B and eluted with 20% ethyl acetate in Skellysolve B. Fractions were 50 mL each, and, on the basis of TLC homogeneity, fractions 18–44 were combined to give 8.80 g (86%) of pure **11** as a colorless oil: NMR δ 1.97 (s, 3 H), 0.9–3.1 (m, 11 H), 5.1 (quintet, J = 5 Hz, 1 H), 9.42 (d, J = 6 Hz, 1 H); IR (film) 3300, 3020, 1735, 1710, 1370, 1240, 1115, 1040, 1020, 960, 910 cm^{-1}; MS $C_{12}H_{16}O_3$ (M^+) m/e(calcd) 208.1099, m/e(found) 208.1093; TLC R_f 0.28 in 25% ethyl acetate in Skellysolve B.

(8*RS*)-8-Hydroxy-3-*endo*-(*cis*-1′-heptenyl)tricyclo[4.3.0.0^{2,4}]nonane (13). A suspension of 34.55 g (81 mmol) of *n*-hexyltriphenylphosphonium bromide in 400 mL of toluene was alternately degassed and flushed with nitrogen (3 times), cooled to 0–5 °C, and treated with stirring with 1.4 M *n*-butyllithium in *n*-hexane until a permanent yellow color was produced. *n*-Butyllithium (1.4 M in *n*-hexane, 58 mL, 81 mmol) was then added and the resulting red-orange mixture was stirred at 0–25 °C during 60 min. The flask containing *n*-hexylidenetriphenylphosphorane was cooled to 0–5 °C and treated dropwise with stirring with a solution of 8.80 g (42 mmol) of aldehyde **11** in 50 mL of toluene. The reaction mixture was stirred at 0–5 °C for 60 min, treated with 20 mL of acetone, stirred for 20 min, diluted with brine, and extracted with ethyl acetate (3 × 200 mL). The combined extracts were washed with bicarbonate (2 × 500 mL) and brine (500 mL) and dried over sodium sulfate. Concentration in vacuo gave crude **12** as a pale yellow solid (contains triphenylphosphine oxide).

The above crude Wittig product was reacted with 60 mL of 10% aqueous KOH in 200 mL of methanol at room temperature for 60 min. The reaction mixture was acidified to pH 5 with galacial acetic acid, diluted with brine, and extracted with ethyl acetate (2 × 200 mL). The combined extracts were washed with bicarbonate (2 × 500 mL) and brine (500 mL) and dried over sodium sulfate. Concentration in vacuo gave crude **13** as a pale yellow solid. A 48 mm × 36 in. column was slurry packed with 200 g of silica gel in 25% ethyl acetate in Skellysolve B. The sample of crude **13** was applied in methylene chloride and eluted with 25% ethyl acetate in Skellysolve B. Fractions were 50 mL each, and, on the basis of TLC homogeneity, fractions 6–24 were combined to give 8.57 g (86% from **11**) of pure **13** as a colorless oil: NMR δ 0.88 (t, J = 5 Hz, 3 H), 0.8–2.5 (m, 19 H), 2.72 (s, 1 H), 3.8–4.4 (m, 1 H), 4.80–5.28 (m, 1 H), 5.28–5.85 (d of t, J = 7, 11 Hz, 1 H); IR (film) 3340, 3020, 1645, 1460, 1115, 1070, 1050, 1025, 965 cm^{-1}; MS for $C_{19}H_{34}SiO$ (M^+ of Me_3Si derivative) m/e(calcd) 306.2379, m/e(found) 306.2378; TLC R_f 0.28 in 25% ethyl acetate in Skellysolve B. On the same plate, **12** exhibits R_f 0.70.

8-Oxo-3-*endo*-(*cis*-1′-heptenyl)tricyclo[4.3.0.0^{2,4}]nonane (14). A solution of 8.57 g (36 mmol) of **13** in 300 mL of acetone was cooled to −20 °C under nitrogen and treated dropwise with stirring with 27.4 mL of 2.67 M Jones' reagent[31] during 15 min. The reaction mixture was stirred at −20 °C for 10 min, treated

(31) Fieser, L. F.; Fieser, M. "Reagents for Organic Synthesis"; Wiley: New York, 1967; Vol. 1, pp 142–144; and references cited therein.

with 30 mL of 2-propanol, and stirred at −20 °C for 30 min. It was then diluted with 1000 mL of brine and extracted with diethyl ether (3 × 300 mL). The combined extracts were washed with bicarbonate (1000 mL) and brine (100 mL) and dried over sodium sulfate. Concentration in vacuo gave 8.06 g of crude **14** as a yellow oil. A 48 mm × 36 in. column was slurry packed with 300 g of silica gel in 25% ethyl acetate in Skellysolve B. The sample of crude **14** was applied in Skellysolve B and eluted with 25% ethyl acetate in Skellysolve B. Fractions were 50 mL each, and, on the basis of TLC homogeneity, fractions 6–12 were combined to give 6.46 g (76%) of pure **14** as a pale yellow oil: NMR δ 0.89 (t, J = 5 Hz, 3 H), 0.7–2.9 (m, 19 H), 5.05–5.4 (m, 1 H), 5.4–5.85 (d of t, J = 6, 10 Hz, 1 H);[32] IR (film) 3020, 1740, 1640, 1155 cm^{-1}; MS for $C_{16}H_{24}O$ (M^+) m/e(calcd) 232.1827, m/e(found) 232.1811 (other ions at m/e 217, 214, 204, 203, 189, 175); TLC R_f 0.60 in 25% ethyl acetate in Skellysolve B.

(1′*RS*,2′*RS*)-8-Oxo-3-*endo*-(1′,2′-dihydroxyheptyl)tricyclo[4.3.0.0^{2,4}]nonane (15). A solution of 5.93 g (25.52 mmol) of ketone **14**, 75 mL of acetone, 5 mL of water, 3.12 mL of a solution of osmium tetraoxide in *tert*-butyl alcohol (30 mg/mL), and 3.98 g (25.98 mmol) of *N*-methylmorpholine oxide dihydrate was stirred at room temperature for 2 h. A solution of 4.0 g of sodium bisulfite in 25 mL of water was added, and the reaction mixture was stirred for 30 min. It was then diluted with brine and extracted with ethyl acetate. The extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 7.15 g of crude **15** as an oil. A 48 mm × 36 in. column was slurry packed with 300 g of silica gel in 20% acetone in methylene chloride. The sample of **15** was applied in methylene chloride and eluted with 20% acetone in methylene chloride. Fractions were 50 mL each, and, on the basis of TLC homogeneity, fractions 18–72 were combined to give 6.71 g (99%) of pure **15** as a very viscous, colorless oil: NMR δ 0.90 (t, J = 5 Hz, 3 H), 1.12–2.92 (m, 19 H), 2.72 (s, 2 H), 3.35–3.92 (m, 2 H); IR (film) 3400, 1750, 1470, 1165, 1040, 935 cm^{-1}; TLC R_f 0.24 and 0.31 in 25% ethyl acetate in Skellysolve B (two spots for threo and erythro glycols).

(3′*S*)-3α-Hydroxy-7-oxo-2β-(3′-hydroxy-*trans*-1′-octenyl)bicyclo[3.3.0]octane (16) and (3′*R*)-3α-Hydroxy-7-oxo-2β-(3′-hydroxy-*trans*-1′-octenyl)bicyclo[3.3.0]octane (17). A solution of 6.71 g (25.2 mmol) of glycols **15** in 100 mL of toluene was reacted at room temperature with 18.17 g (100 mmol) of triethyl orthopropionate and 30 mg of pyridine hydrochloride for 4 h. The solvent was evaporated in vacuo, and the remaining oil was dissolved in 50 mL of anhydrous formic acid[32] and stirred at room temperature for 10 min. The reaction mixture was diluted with 500 mL of brine and extracted with ethyl acetate. The ethyl acetate extract was washed with water (4 times), bicarbonate, and brine and dried over sodium sulfate. Concentration in vacuo gave 8.78 g of a yellow oil. This material was reacted with 7.0 g of potassium carbonate, 10 mL of water, and 100 mL of methanol at room temperature for 16 h, and the reaction mixture was diluted with brine and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 7.35 g of crude **16** and **17** containing traces of glycols **15**.

The above sample of crude **16** and **17** was dissolved in 175 mL of methanol and reacted with a solution of 1.75 g of sodium metaperiodate in 75 mL of water. The reaction mixture was stirred at room temperature for 20 min, diluted with brine, and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 6.71 g of a crude mixture of **16** and **17** as a yellow oil. A 48 mm × 36 in. column was slurry packed with 400 g of silica gel in 40% acetone in methylene chloride. The sample of **16** and **17** was applied in methylene chloride and eluted with 40% acetone in methylene chloride. The first fraction was 350 mL, and subsequent fractions were 50 mL each. On the basis of TLC homogeneity, fractions 15–32 were combined to give 2.89 g of a mixture of **16** and **17** and fractions 33–48 were combined to give 0.31 g of pure **16**. The mixture of **16** and **17** was rechromatographed (high-pressure LC) over 241 g of silica gel 60 (E. Merck, 230–400 mesh), eluting with 20% acetone in methylene chloride (1 in. × 43 in. column, 14 mL/min, 37 psi). Fractions were 50 mL each, and on the basis of TLC homogeneity, fractions 20–46 were combined to give 1.83 g (27%) of pure **17** as a colorless oil and fractions 49–91 were combined to give 0.86 g of pure **16** as a colorless oil (1.17 g total, 17%). For **16**: NMR δ 0.88 (t, J = 5 Hz, 3 H), 0.75–2.88 (m, 17 H), 3.67 (bd s, 2 H), 3.6–4.23 (m, 2 H), 5.4–5.65 (m, 2 H); IR (film) 3400, 1740, 1165, 1130, 1095, 1075, 1025, 970 cm^{-1}; MS for $C_{22}H_{42}Si_2O_3$ (M^+ of bis(trimethylsilyl) derivative) m/e(calcd) 410.2659, m/e(found) 410.2672 (other ions at m/e 395, 392, 339, 320, 283, 249, 223, 173); TLC R_f 0.16 in 30% acetone in methylene chloride. For **17**: NMR δ 0.88 (t, J = 5 Hz, 3 H), 0.67–2.8 (m, 17 H), 3.48 (bd s, 2 H), 3.58–4.22 (m, 2 H), 5.42–5.73 (m, 2 H); IR (film) 3400, 1735, 1165, 1135, 1090, 1070, 1025, 970 cm^{-1}; MS for $C_{22}H_{42}Si_2O_3$ (M^+ of bis(trimethylsilyl) derivative) m/e(calcd) 410.2659, m/e(found) 410.2672 (the fragmentation pattern was identical with that for **16**); TLC R_f 0.26 in 30% acetone in methylene chloride.

(3′*S*)-3α-Hydroxy-7-oxo-2β-(3′-[(*tert*-butyldimethylsilyl)oxy]-*trans*-1′-octenyl)bicyclo[3.3.0]octane 3-(*tert*-Butyldimethylsilyl Ether) (18). Ketone diol **16** (1.17 g, 4.39 mmol) was reacted with 1.50 g (27.03 mmol) of imidazole and 1.99 g (13.18 mmol) of *tert*-butyldimethylsilyl chloride in 22 mL of DMF at 0 °C for 2 h. The reaction mixture was diluted with brine and extracted with ethyl acetate. The ethyl acetate extract was washed with cold 1 N aqueous HCl, bicarbonate, and brine and dried over sodium sulfate. Concentration in vacuo gave 2.35 g of crude **18** as an oil. A 19 mm × 24 in. column was slurry packed with 60 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample of **18** was applied in Skellysolve B and eluted with 5% ethyl acetate in Skellysolve B. Fractions were 20 mL each, and, on the basis of TLC homogeneity, fractions 12–20 were combined to give 1.95 g (90%) of pure **18** as a colorless oil: NMR δ 0.03 (s, 12 H), 0.88 (s, 18 H), 0.8–2.83 (m, 20 H), 3.95–4.22 (m, 2 H), 5.42–5.60 (m, 2 H); IR (film) 1745, 1255, 1120, 1080, 835, 775 cm^{-1}; MS for $C_{27}H_{51}Si_2O_3$ ($M^+ - CH_3$) m/e(calcd) 479.3376, m/e(found) 479.3376 (other ions at m/e 494, 437, 423, 363, 347, 305, 291, 251); TLC R_f 0.44 in 10% ethyl acetate in Skellysolve B.

(3′*R*)-3α-Hydroxy-7-oxo-2β-(3′-[(*tert*-butyldimethylsilyl)oxy]-*trans*-1′-octenyl)bicyclo[3.3.0]octane 3-(*tert*-Butyldimethylsilyl Ether) (19). In the same manner as detailed above for the preparation of **18**, 1.49 g (5.60 mmol) of **17** was converted to 2.46 g (89%) of pure **19** as a colorless oil: NMR δ 0.03 (s, 12 H), 0.90 (s, 18 H), 0.80–2.83 (m, 20 H), 3.75–4.27 (m, 2 H), 5.40–5.58 (m, 2 H); IR (film) 1745, 1255, 1120, 1080, 835, 775, 735 cm^{-1}; MS for $C_{27}H_{51}Si_2O_3$ ($M^+ - CH_3$) m/e(calcd) 479.3376, m/e(found) 479.3352 (other ions at m/e 494, 437, 423, 363, 347, 305, 291, 251); TLC R_f 0.48 in 10% ethyl acetate in Skellysolve B.

***N*-Methylphenyl-(5-hydroxypentyl)sulfoximine Tetrahydropyranyl Ether (26).** A solution of 20 mmol of sodium methylsulfinylmethide (prepared from 0.84 g (20 mmol) of a 57% NaH dispersion and 10 mL of Me_2SO in the usual manner[30]) was treated with a solution of 3.38 g (20 mmol) of methylphenyl-*N*-methylsulfoximine (**24**)[19] in 5 mL of Me_2SO. The reaction mixture was stirred at room temperature for 2 h and then treated with 7.12 g (30 mmol) of 4-bromobutyl 1-tetrahydropyranyl ether.[33] After 2.5 h of stirring at 15–25 °C, the reaction mixture was diluted with brine and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 10.09 g of crude **26** as an orange oil. A 48 mm × 36 in. column was slurry packed with 400 g of silica gel in 75% ethyl acetate in Skellysolve B. The sample of crude **26** was applied in methylene chloride and eluted with 1000 mL each of 75, 85, 90, 95, and 100% ethyl acetate in Skellysolve B. The first fraction was 2000 mL and subsequent fractions were 50 mL each. On the basis of TLC homogeneity, fractions 19–54 were combined to give 4.12 g (63%) of pure **26** as a pale orange oil which solidified to a waxy solid on standing: NMR δ 1.13–2.13 (m, 12 H), 2.63, (s, 3 H), 3.0–4.0 (m, 6 H), 4.50 (t, J = 2 Hz, 1 H), 7.45–8.05 (m, 5 H); IR (film) 3060, 2940, 2870, 1445, 1240, 1140, 1115, 1075, 1033, 1020, 865, 748, 735, 690 cm^{-1}; MS for $C_{12}H_{18}NO_2$ ($M^+ - C_5H_9O$) m/e(calcd) 240.1058, m/e(found) 240.1043 (other ions at m/e 325, 296, 224, 210, 182, 125, 85, 77); TLC R_f 0.19 in 50% ethyl acetate in Skellysolve B.

(32) Kelly, R. C.; VanRheenen, V.; Schletter, I.; Pillai, M. D. *J. Am. Chem. Soc.* **1973**, *95*, 2746.

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(5*E*)-2-Decarboxy-2-hydroxymethyl-6a-carbaprostaglandin I_2 1-(Tetrahydropyranyl Ether) 11,15-Bis(*tert*-butyldimethylsilyl Ether) (28) and (5*Z*)-2-Decarboxy-2-hydroxymethyl-6a-carbaprostaglandin I_2 1-(Tetrahydropyranyl Ether) 11,15-Bis(*tert*-butyldimethylsilyl Ether) (29). A solution of 2.05 g (6.30 mmol) of sulfoximine **26** in 15 mL of THF was alternately degassed and flushed with nitrogen (2 times), cooled to 0 °C and, treated with 2.2 mL of 2.7 M methylmagnesium bromide in ether (5.94 mmol). The resulting solution was stirred at 0 °C for 30 min, cooled to −20 °C, and treated dropwise with stirring with a solution of 1.95 g (3.94 mmol) of ketone **18** in 5 mL of THF. The reaction mixture was stirred at −20 °C for 30 min, quenched by the addition of 6 mL of saturated aqueous NH_4Cl, diluted with brine, and extracted with ethyl acetate. The extract was dried over sodium sulfate and concentrated in vacuo to give 4.08 g of a yellow oil. This material was dissolved in 30 mL of THF. Aluminum amalgam was prepared as follows: 1.59 g (59 mg-atoms) of aluminum metal (20 mesh) was washed successively with 5 mL of methanol (2 times), 5 mL of diethyl ether, 15 mL of 2% aqueous mercuric chloride, 5 mL of methanol, and 5 mL of diethyl ether. The above THF solution (at 15–20 °C) was treated with the aluminum amalgam followed by 20 mL of 50% aqueous acetic acid. The reaction mixture was stirred at 20 °C for 2 h and then filtered through Celite, washing well with ethyl acetate. The filtrate was washed with bicarbonate and brine, dried over sodium sulfate, and concentrated in vacuo to give 3.0 g of crude **28** and **29** as a pale yellow oil. A 19 mm × 24 in. column was slurry packed with 60 g of silica gel in 3% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 300 mL of 3% ethyl acetate in Skellysolve B and 500 mL of 5% ethyl acetate in Skellysolve B. Fractions were 20 mL each, and, on the basis of TLC homogeneity, fractions 10–15 were combined to give 2.08 g (48%) of a mixture of **28** and **29** as a pale yellow oil: NMR δ 0.05 (s, 12 H), 0.88 (s, 18 H), 0.75–2.38 (m, 32 H), 3.12–4.20 (m, 6 H), 4.57 (t, J = 4 Hz, 1 H), 5.07–5.63 (m, 3 H); IR (film) 2940, 2860, 1460, 1250, 1115, 1075, 1030, 970, 835, 775 cm^{-1}; TLC R_f 0.30 in 3% ethyl acetate in Skellysolve B (the 5*E* and 5*Z* isomers were not separable at this stage).

(5*E*)-2-Decarboxy-2-hydroxymethyl-6a-carbaprostaglandin I_2 11,15-Diacetate (34) and (5*Z*)-2-Decarboxy-2-hydroxymethyl-6a-carbaprostaglandin I_2 11,15-Diacetate (35). A solution of 1.23 g (1.89 mmol) of **28** and **29** in 15 mL of THF was reacted under nitrogen for 16 h at 25 °C with 12.2 mL of tetra-*n*-butylammonium fluoride in THF (0.62 M, 7.56 mmol). The reaction mixture was diluted with brine and extracted with ethyl acetate. The ethyl acetate extract was washed with cold 0.5 M aqueous potassium bisulfate (2 times), bicarbonate, and brine and dried over sodium sulfate. Concentration in vacuo gave 1.13 g of crude **30** and **31** as an orange oil: TLC R_f 0.45 in 30% acetone in methylene chloride (the 5*E* and 5*Z* isomers were not separable at this stage).

The above sample of crude **30** and **31** was dissolved in 10 mL of pyridine and reacted with 1.5 mL of acetic anhydride and 10 mg of 4-(*N*,*N*-dimethylamino)pyridine. The reaction mixture was stirred for 30 min at 25 °C, diluted with brine, and extracted with ethyl acetate. The ethyl acetate extract was washed with cold 0.5 M aqueous potassium bisulfate (2 times), bicarbonate, and brine and dried over sodium sulfate. Concentration in vacuo gave 1.08 g of crude **32** and **33** as an orange oil: TLC R_f 0.66 in 10% acetone in methylene chloride (the 5*E* and 5*Z* isomers were not separable at this stage).

The above sample of crude **32** and **33** was dissolved in 25 mL of acetic acid–water–THF (20:10:3), and the reaction mixture was stirred at 40 °C for 24 h, diluted with brine, and extracted with ethyl acetate. The ethyl acetate extract was washed with bicarbonate (2 times) and brine, dried over sodium sulfate, and concentrated in vacuo to give 0.80 g of crude **34** and **35** as a yellow oil. This material was chromatographed (high-pressure LC) over two prepacked Lobar columns (EM reagents, size B) connected in series, eluting with 25% ethyl acetate in *n*-hexane. Fractions were 20 mL each, and, on the basis of TLC homogeneity, fractions 49–80 were combined to give 0.313 g (39% from **28** and **29**) of pure **35** as a pale yellow oil: NMR δ 0.88 (t, J = 5 Hz, 3 H), 0.73–2.72 (m, 23 H), 1.83 (br s, 1 H), 1.98 (s, 3 H), 2.03 (s, 3 H), 3.65 (t, J = 6 Hz, 2 H), 4.58–5.50 (m, 5 H); IR (film) 3460, 1740, 1440, 1365, 1235, 1060, 1010, 970 cm^{-1}; MS for $C_{26}H_{44}SiO_3$ (M^+ − HOAc for Me_3Si derivative) m/e(calcd) 432.3060, m/e(found) 432.3076 (other ions at m/e 417, 390, 372, 342, 300, 282); TLC R_f 0.49 in 5% acetone in methylene chloride. Fractions 101–132 were combined to give 0.269 g (34% from **28** and **29**) of pure **34** as a pale yellow oil: NMR δ 0.88 (t, J = 6 Hz, 3 H), 0.68–2.65 (m, 24 H), 1.98 (s, 3 H), 2.02 (s, 3 H), 3.63 (t, J = 6 Hz, 2 H), 4.56–5.67 (m, 5 H); IR (film) 3450, 1740, 1440, 1370, 1245, 1060, 1020, 970 cm^{-1}; MS for $C_{26}H_{44}SiO_3$ (M^+ − HOAc for Me_3Si derivative) m/e(calcd) 432.3060, m/e(found) 432.3063 (other ions at m/e 417, 390, 372, 342, 300, 282); TLC R_f 0.44 in 5% acetone in methylene chloride.

(5*E*)-6a-Carbaprostaglandin I_2 (4). Alcohol **34** (0.3233 g, 0.77 mmol) was dissolved in 30 mL of acetone, cooled to −40 °C, and treated with 1.2 mL of 2.67 M Jones' reagent[31] (3.20 mmol). The reaction mixture was stirred at −40 to −20 °C, treated with 1.0 mL of 2-propanol, diluted with brine, and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 0.355 g of an oil. This material was reacted with 13 mL of a 5% solution of KOH in 9:1 methanol–water. The reaction mixture was stirred under nitrogen at 25 °C for 2 h, acidified to pH 3 with 0.5 M aqueous potassium bisulfate, diluted with brine, and extracted with ethyl acetate. The ethyl acetate extract was washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 0.289 g of crude **4** as an orange oil. A 19 mm × 24 in. column was slurry packed with 25 g of acid-washed silica gel in 35% ethyl acetate in *n*-hexane. The sample of crude **4** was applied in methylene chloride and eluted with 35% ethyl acetate in *n*-hexane. Fractions were 20 mL each, and, on the basis of TLC homogeneity, fractions 28–84 were combined to give 0.152 g (56%) of pure **4** as an oil which solidified on standing. Recrystallization from diethyl ether–*n*-hexane (2 times) gave pure **4** as white rosettes: mp 62.4–63.3 °C; NMR δ 0.90 (t, J = 5 Hz, 3 H), 0.68–2.62 (m, 23 H), 3.52–4.27 (m, 2 H), 5.03–5.68 (m, 3 H), 5.65 (s, 3 H); IR (mull) 3480, 3340, 3140, 2720, 2640, 2560, 1725, 1675, 1265, 1250, 1090, 1075, 970 cm^{-1}; MS for $C_{29}H_{55}Si_3O_4$ (M^+ − CH_3 for the tris(trimethylsilyl) derivative) m/e(calcd) 551.3408, m/e(found) 551.3392 (other ions at m/e 566, 495, 476, 405, 386, 73); $[\alpha]_D$ +90° (c 0.810, CH_3OH); TLC R_f 0.40 in the A-IX solvent system.[29] Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 71.69; H, 9.77.

(5*Z*)-6a-Carbaprostaglandin I_2 (36). Alcohol **35** (0.3377 g, 0.80 mmol) was converted to 0.173 g (62%) of chromatographically pure **36** by the method described for the preparation of **4**. The product was initially an oil which solidified on standing. Recrystallization from acetone–*n*-hexane (2 times) gave pure **36** as a white microcrystalline material: mp 107.5–108.8 °C; NMR δ 0.90 (t, J = 5 Hz, 3 H), 0.68–2.63 (m, 23 H), 3.45–4.28 (m, 2 H), 4.93–5.63 (m, 3 H), 5.15 (s, 3 H); IR (mull) 3460, 3360, 3310, 2630, 1720, 1700, 1350, 1320, 1200, 1180, 1090, 1070, 1015, 995, 975 cm^{-1}; MS for $C_{29}H_{55}Si_3O_4$ (M^+ − CH_3 for the tris(trimethylsilyl) derivative) m/e(calcd) 551.3408, m/e(found) 551.3398 (other ions at m/e 566, 495, 476, 405, 386, 73); $[\alpha]_D$ +39° (c 0.866, CH_3OH); TLC R_f 0.41 in the A-IX solvent system.[29] Anal. Calcd for $C_{21}H_{34}O_4$: C, 71.96; H, 9.78. Found: C, 72.05; H, 9.96.

(5*E* and *Z*,15*R*)-2-Decarboxy-2-hydroxymethyl-6a-carbaprostaglandin I_2 1-Tetrahydropyran ethers) 37 and 38 were prepared in 66% combined yield from ketone **19** (2.40 g, 4.85 mmol) in the same manner used in the preparation of **28** and **29**: NMR δ 0.05 (s, 12 H), 0.88 (s, 18 H), 0.75–2.38 (m, 32 H), 3.12–4.20 (m, 6 H), 4.56 (t, J = 4 Hz, 1 H), 5.07–5.63 (m, 3 H); IR (film) 2940, 2860, 1460, 1250, 1115, 1075, 1030, 970, 835, 775 cm^{-1}; TLC R_f 0.32 in 3% ethyl acetate in Skellysolve B (the 5*E* and 5*Z* isomers were not separable at this stage).

(5*E*,15*R*)-2-Decarboxy-2-hydroxymethyl-6a-carbaprostaglandin I_2 11,15-diacetate (43) and (5*Z*,15*R*)-2-decarboxy-2-hydroxymethyl-6a-carbaprostaglandin I_2 11,15-diacetate (44) were prepared from **37** and **38** (2.08 g, 3.20 mmol) by way of intermediates **39** and **40** and **41** and **42** in the same manner used in the preparation of **34** and **35**. The mixture of **43** and **44** was separated by repeated chromatography (high-pressure LC) over two prepacked Lobar columns (EM reagents, size B) connected in series, eluting with 25% ethyl acetate in Skellysolve B. Fractions were combined on the basis of TLC homogeneity to afford 0.63 g (47%) of pure **43** as a pale yellow oil: NMR δ 0.88 (t, J = 5 Hz, 3 H), 0.8–2.77 (m, 24 H), 1.98 (s, 3 H), 2.03 (s, 3 H), 3.64 (t, J = 6 Hz, 2 H), 4.53–5.65 (m, 5 H);

IR (film) 3457, 1736, 1436, 1374, 1246, 1060, 1047, 1022, 967 cm^{-1}; MS for $C_{26}H_{44}SiO_3$ (M^+ – HOAc for Me_3Si derivative) *m/e*(calcd) 432.3060, *m/e*(found) 432.3059 (other ions at *m/e* 417, 390, 372, 300, 282, 175, 133, 132, 131, 129, 117); TLC R_f 0.50 in 50% ethyl acetate in Skellysolve B. For **44** (0.39 g, 29%): NMR δ 0.90 (t, J = 5 Hz, 3 H), 0.8–2.83 (m, 24 H), 1.98 (s, 3 H), 2.04 (s, 3 H), 3.65 (t, J = 6 Hz, 2 H), 4.55–5.67 (m, 5 H); IR (film) 3456, 1736, 1456, 1436, 1372, 1242, 1066, 1025, 969 cm^{-1}; MS for $C_{26}H_{44}SiO_3$ (M^+ – HOAc for Me_3Si derivative) *m/e*(calcd) 432.3060, *m/e*(found) 432.3050 (other ions at *m/e* 417, 390, 372, 300, 282, 175, 133, 132, 131, 129, 117); TLC R_f 0.54 in 50% ethyl acetate in Skellysolve B.

(5*E*,15*R*)-6a-Carbaprostaglandin I_2 (45) was prepared in 49% yield from alcohol **43** (0.63 g, 1.50 mmol) in the same manner used in the preparation of **4**. The chromatographically pure sample of **45** was initially a colorless oil which partially solidified to a white semisolid on standing at −19 °C. Attempts to recrystallize this material were not successful: NMR δ 0.92 (t, J = 5 Hz, 3 H), 0.75–2.65 (m, 23 H), 3.52–4.32 (m, 2 H), 5.13–5.73 (m, 3 H), 5.23 (s, 3 H); IR (film) 3500, 3050, 2700, 1710, 1620, 1260, 1150, 1090, 1030, 980 cm^{-1}; MS for $C_{29}H_{55}Si_3O_4$ (M^+ – CH_3 for the tris(trimethylsilyl) derivative) *m/e*(calcd) 551.3408, *m/e*(found) 551.3387 (other ions at *m/e* 495, 476, 461, 405, 386, 379, 360, 173, 117); $[\alpha]_D$ +61° (*c* 0.8485, CH_3OH); TLC R_f 0.44 in the A-IX solvent system.[29]

(5*Z*,15*R*)-6a-Carbaprostaglandin I_2 (46) was prepared in 63% yield from alcohol **44** (0.39 g, 0.93 mmol) in the same manner used in the preparation of **4**. The chromatographically pure sample of **46** was a colorless oil: NMR δ 0.88 (t, J = 5 Hz, 3 H), 0.70–2.75 (m, 23 H), 3.52–4.28 (m, 2 H), 5.08–5.75 (m, 3 H), 5.46 (s, 3 H); IR (film) 3400, 1710, 1450, 1370, 1250, 1080, 1050, 970 cm^{-1}; MS for $C_{29}H_{55}Si_3O_4$ (M^+ – CH_3 for the tris(trimethylsilyl) derivative) *m/e*(calcd) 551.3408, *m/e*(found) 551.3420 (other ions at *m/e* 566, 495, 476, 461, 405, 386, 379, 360, 199, 173, 117); $[\alpha]_D$ +20° (*c* 0.675, CH_3OH); TLC R_f 0.45 in the A-IX solvent system.[29]

(5*E*)-6a-Carbaprostaglandin I_2 (4) and (5*Z*)-6a-Carbaprostaglandin I_2 (36). A solution of 75.83 mmol of sodium methylsulfinylmethide (prepared from 3.19 g (75.83 mmol) of a 57% NaH dispersion and 50 mL of Me_2SO in the usual manner[30]) was cooled to 10–15 °C and treated with stirring with 16.81 g (37.92 mmol) of (4-carboxybutyl)triphenylphosphonium bromide under nitrogen. The red solution containing ylide **47** was stirred at 25 °C for 15 min and then treated with a solution of 1.68 g (6.31 mmol) of ketone diol **16** in 25 mL of Me_2SO. The reaction mixture was stirred at 35 °C for 10 h, cooled to 15 °C, quenched with 15 mL of water, and diluted with 1 N aqueous NaOH. The aqueous solution was washed with diethyl ether (2 times), acidified to pH 3 with 0.5 M aqueous potassium bisulfate, and extracted with diethyl ether (2 times). The combined ethereal extracts were washed with brine (2 times), dried over sodium sulfate, and concentrated in vacuo to give 3.90 g of crude **4** and **36** as a yellow oil. This material was chromatographed over 350 g of silica gel, eluting with 30% acetone in methylene chloride. Fractions were combined based on TLC homogeneity to give 1.83 g (83%) of a mixture of **4** and **36**. The identities of **4** and **36** were established by TLC comparison with authentic samples of each pure isomer in several solvent systems.

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Registry No. 4, 69552-46-1; **4** tris(Me_3Si) derivative, 70398-64-0; **5**, 39521-44-3; **6** isomer A, 70398-67-3; **6** isomer B, 70428-02-3; **7**, 70398-65-1; **8**, 70398-66-2; **9** isomer A, 70398-62-8; **9** isomer B, 70428-01-2; **10** isomer A, 70398-63-9; **10** isomer B, 70469-90-8; **11** isomer A, 70398-68-4; **11** isomer B, 70428-03-4; **12** isomer A, 70398-69-5; **12** isomer B, 70428-04-5; **13** isomer A, 70398-70-8; **13** isomer B, 70428-05-6; **13** Me_3Si derivative isomer A, 70398-71-9; **13** Me_3Si derivative isomer B, 70428-06-7; **14**, 70398-72-0; **15**, 70398-73-1; **16**, 69552-54-1; **16** bis(Me_3Si) derivative, 70398-74-2; **17**, 70428-07-8; **17** bis(Me_3Si) derivative, 70428-08-9; **18**, 70398-75-3; **19**, 70428-09-0; **20**, 70398-76-4; **21**, 70398-77-5; **24**, 30004-67-2; **25**, 31608-22-7; **26**, 70398-78-6; **28**, 70470-13-2; **29**, 70470-14-3; **30**, 70398-79-7; **31**, 70428-10-3; **32**, 70398-80-0; **33**, 70428-11-4; **34**, 70398-81-1; **34** Me_3Si derivative, 70398-82-2; **35**, 70428-12-5; **35** Me_3Si derivative, 70428-13-6; **36**, 69609-77-4; **36** tris(Me_3Si) derivative, 70470-15-4; **37**, 70398-83-3; **38**, 70428-14-7; **39**, 70428-15-8; **40**, 70428-16-9; **41**, 70428-17-0; **42**, 70428-18-1; **43**, 70428-19-2; **43** Me_3Si derivative, 70428-20-5; **44**, 70428-21-6; **44** Me_3Si derivative, 70428-22-7; **45**, 69609-79-6; **45** tris(Me_3Si) derivative, 70428-23-8; **46**, 69609-80-9; **46** tris(Me_3Si) derivative, 70428-24-9; **47**, 41723-91-5; hexyltriphenylphosphonium bromide, 4762-26-9; sodium methylsulfinylmethide, 15590-23-5; methylmagnesium bromide, 75-16-1; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6.

Carbon-13 Nuclear Magnetic Resonance Study of Benzo[*b*]thiophenes and Benzo[*b*]thiophene *S*-Oxides and *S*,*S*-Dioxides

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The ^{13}C NMR spectra of benzo[*b*]thiophenes and a series of benzo[*b*]thiophene *S*-oxides and *S*,*S*-dioxides of well-defined structure were recorded. A comparison between benzothiophenes and the sulfoxide and sulfone derivatives permits the characterization of the effect of the sulfoxide and sulfone moieties on ^{13}C chemical shifts in this heteroaromatic system. A comparison of the ^{13}C resonances of benzothiophene *S*-oxides and *S*,*S*-dioxides with the corresponding derivatives of 2,3-dihydrobenzothiophene shows a decrease in aromaticity on going from the benzo[*b*]thiophene to the *S*-oxide and *S*,*S*-dioxide systems, the sulfoxide being more aromatic than the sulfone.

The chemical literature contains a number of reports on ^{13}C NMR studies of substituted thiophenes[1-9] and methylbenzothiophenes[10,11] but the corresponding sulfoxides and sulfones have largely been ignored.

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