4,4-Diethoxy-1-phenyl-2-butyn-1-one (12). Method A. The crude product was chromatographed with 5:100 (v/v) ether/hexane to give 158 mg (68%) of **12** as a light yellow liquid: bp 91 °C (0.07 mm); IR (CCl_4) 1640, 2210 cm^{-1}; NMR (CCl_4) δ 1.26 (t, 6, J = 7.5 Hz, OCH_2Me), 3.72 (complex m, 4, OCH_2Me), 5.34 (s, 1, $CH(OEt)_2$), 7.35–7.70 (m, 3, Ph), 8.06–8.24 (m, 2, Ph); mass spectrum, m/e (relative intensity) 232 (0.16), 231 (0.98), 203 (1.12), 188 (23.25), 187 (100), 160 (11.97), 159 (98.55), 157 (1.30), 155 (0.23), 131 (12.41), 129 (5.63), 127 (0.30), 105 (25.06), 103 (14.16), 89 (4.63), 81 (17.45), 77 (21.99), 59 (17.27), 53 (23.93), 51 (14.93), 45 (16.45).

Anal. Calcd for $C_{14}H_{16}O_3$: C, 72.41; H, 6.90. Found: C, 72.23; H, 7.22.

1-(Trimethylsilyl)-4-methyl-1-pentyn-3-one (13). Method A. The crude product was chromatographed with 1:100 (v/v) ether/hexane to give 120 mg (71%) of **13** as a colorless liquid: bp 23 °C (0.19 mm) [lit.[9] bp 78.2–81.80 °C (17 mm)]; IR and NMR spectra are identical with those previously reported.[9]

1-Phenyl-3-(trimethylsilyl)-2-propyn-1-one (14). Method A. The crude product was chromatographed with 2:100 (v/v) ether/hexane to give 128.9 mg (64%) of **14** as a pale yellow liquid: bp 64 °C (0.12 mm) [lit.[9] bp 98–99 °C (1 mm)]; IR and NMR spectra are identical with those previously reported.[9]

1-(*p*-Nitrophenyl)-3-(trimethylsilyl)-2-propyn-1-one (15). Method A. The crude product was chromatographed with 5:100 (v/v) ether/hexane to give 127 mg (51%) of **15** as a colorless solid: mp 132.2–132.7 °C (lit.[11b] mp 134–135 °C); IR ($CHCl_3$) 1667, 2128 cm^{-1}; NMR ($CDCl_3$) δ 0.36 (s, 9, $SiMe_3$), 8.32 (s, 4, p-O_2NPh).

5-[(*tert*-Butyldimethylsilyl)oxy]-3-pentyn-2-one (16). Method A. The crude product was chromatographed with 4:100 (v/v) ether/hexane to give 101 mg (48%) of **16** as a pale yellow liquid: bp 39 °C (0.08 mm); IR (CCl_4) 1683, 2192 cm^{-1}; NMR (CCl_4) δ 0.06 (s, 6, $SiMe_2$), 0.82 (s, 9, t-Bu), 2.19 (s, 3, COMe), 4.34 (s, 2, OCH_2); mass spectrum, m/e (relative intensity) 212 (0.29), 211 (0.49), 197 (1.69), 166 (0.41), 155 (39.23), 145 (7.66), 132 (2.79), 124 (38.24), 117 (8.67), 99 (2.58), 93 (3.84), 85 (2.34), 83 (11.83), 75 (100), 69 (1.72), 57 (6.27), 44 (29.31), 43 (21.72).

Anal. Calcd for $C_{11}H_{20}O_2Si$: C, 62.26; H, 9.43; Si, 13.21. Found: C, 61.96; H, 9.56; Si, 13.22.

6-[(*tert*-Butyldimethylsilyl)oxy]-2-methyl-4-hexyn-3-one (17). Method A. The crude product was chromatographed with 5:100 (v/v) ether/hexane to give 145 mg (60%) of **17** as a pale yellow liquid: bp 61 °C (0.15 mm); IR (CCl_4) 1670, 2195 cm^{-1}; NMR (CCl_4) δ 0.03 (s, 6, $SiMe_2$), 0.82 (s, 9, t-Bu), 1.08 (d, 6, J = 7.5 Hz, $CHMe_2$), 2.52 (septet, 1, J = 7.5 Hz, $CHMe_2$), 4.34 (s, 2, OCH_2); mass spectrum, m/e (relative intensity) 240 (0.01), 225 (0.34), 197 (0.93), 183 (9.73), 153 (5.68), 141 (5.15), 132 (0.22), 125 (2.60), 113 (5.85), 109 (12.79), 97 (1.93), 95 (1.09), 83 (10.42), 75 (100), 73 (23.17), 72 (1.96), 66 (3.14), 58 (24.75), 57 (5.54), 43 (89.55), 41 (13.48), 29 (7.71).

Anal. Calcd for $C_{13}H_{24}OSi$: C, 65.00; H, 10.00; Si, 11.67. Found: C, 64.71; H, 10.12; Si, 11.77.

4-[(*tert*-Butyldimethylsilyl)oxy]-1-phenyl-2-butyn-1-one (18). Method A. The crude product was chromatographed with 5:100 (v/v) ether/hexane to give 182 mg (66%) of **18** as a pale yellow liquid: bp 83.5 °C (0.08 mm); IR (CCl_4) 1661, 2225 cm^{-1}; NMR (CCl_4) δ 0.19 (s, 6, $SiMe_2$), 0.97 (s, 9, t-Bu), 4.64 (s, 2, OCH_2), 7.36–7.76 (m, 3, Ph), 8.06–8.26 (m, 2, Ph); mass spectrum, m/e (relative intensity) 274 (0.07), 231 (0.06), 217 (2.72), 187 (0.94), 169 (0.05), 153 (2.40), 145 (0.53), 132 (0.61), 131 (0.67), 105 (1.03), 93 (2.94), 75 (61.86), 58 (33.35), 43 (100).

Anal. Calcd for $C_{16}H_{22}O_2Si$: C, 70.07; H, 8.03; Si, 10.22. Found: C, 69.44; H, 8.11; Si, 10.47.

Methyl 5-Methyl-4-oxo-2-hexynoate (19). Method A. The crude product was chromatographed with 1:10 (v/v) ether/hexane to give 103 mg (67%) of **19** as a colorless liquid: bp 49.5 °C (0.68 mm); IR (CCl_4) 1675, 1705 cm^{-1}; NMR (CCl_4) δ 1.21 (d, 6, J = 7.5 Hz, $CHMe_2$), 2.67 (septet, 1, J = 7.5 Hz, $CHMe_2$), 3.83 (s, 3, CO_2Me); mass spectrum, m/e (relative intensity) 155 (0.77), 154 (0.78), 123 (28.78), 122 (36.01), 112 (56.60), 111 (31.30), 97 (21.14), 95 (23.89), 94 (29.28), 85 (16.01), 83 (6.56), 82 (34.24), 71 (25.40), 59 (19.80), 53 (33.84), 43 (100), 41 (57.58), 39 (36.41), 31 (76.85).

Anal. Calcd for $C_8H_{10}O_3$: C, 62.34; H, 6.49. Found: C, 61.96; H, 6.70.

Subjection of 9 to Reaction Conditions. (A) Treatment of **9** according to method A with the omission of the acyl chloride resulted in a 21% recovery of **9**.

(B) Treatment of **9** according to method A with the omission of both the acyl chloride and the stannane resulted in an 86% recovery of **9**.

Acknowledgment. We thank the American Cancer Society (Grant No. CH-72) for financial support.

Registry No. 5a, 3757-88-8; **5b**, 81535-78-6; **5c**, 81353-38-0; **5d**, 81535-79-7; **5e**, 81535-80-0; **6**, 5923-10-4; **7**, 7338-94-5; **8**, 3672-66-0; **9**, 1817-57-8; **9** hydrazone, 1474-94-8; **10**, 81535-81-1; **11**, 55402-04-5; **12**, 53366-80-6; **13**, 53210-05-2; **14**, 13829-77-1; **15**, 17950-66-2; **16**, 81535-82-2; **17**, 81535-83-3; **18**, 81535-84-4; **19**, 81553-85-7; **20**, 10160-87-9; **21**, 76782-82-6; chlorotributylstannane, 1461-22-9; phenylacetylene, 536-74-3; methoxytributylstannane, 1067-52-3; (trimethylsilyl)acetylene, 1066-54-2; methyl propiolate, 922-67-8; p-nitrobenzoyl chloride, 122-04-3; acetyl chloride, 75-36-5; isobutyryl chloride, 79-30-1; benzoyl chloride, 98-88-4.

The Total Synthesis of Prostaglandins by the Tropolone Route

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A general synthesis from α-tropolone methyl ether of natural and modified prostaglandins is detailed. A key intermediate in the synthesis, 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one, has been secured from α-tropolone methyl ether in improved yield and converted to an array of natural and modified prostaglandins through the use of a number of regio- and stereoselective reactions. In several instances, proof of structure and stereochemistry has been obtained through conversion of PGA_2 from the marine coral *Plexaura homomalla* to the synthetically derived products.

Introduction

The prostaglandins (PG), found naturally in mammals and some marine corals, exhibit a remarkably broad range of biological properties largely determined by the nature and stereochemistry of the functional groups located on the five-membered ring and on the two alkyl side chains.[2] In spite of the synthetic difficulties presented by these

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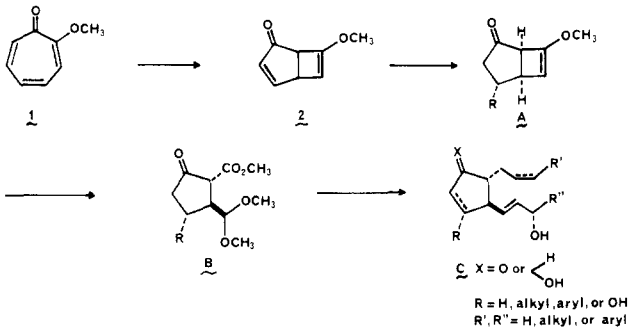
0022-3263/82/1947-2553$01.25/0

Chart I. Prostanoids C from α-Tropolone Methyl Ether (1)



molecules, a great many natural as well as modified PG have been prepared in order to evaluate their biological effects. Thus, numerous novel, conceptually different approaches have been developed to gain access to diverse prostanoids.[3]

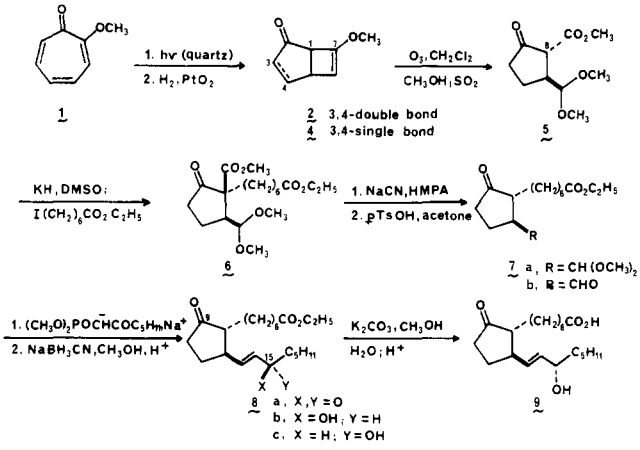
Despite the number of syntheses that had already been effected at the inception of our work, it was felt that an additional approach would be justified if it could be short and flexible enough to provide access to both natural prostaglandins and certain modified prostaglandins that otherwise would be difficult to obtain. Our work on such a synthesis is detailed in this paper.[4]

Results and Discussion

The synthetic route that was developed is summarized in general terms in Chart I. α-Tropolone methyl ether (1) is converted photochemically to the bicyclic intermediate 2. Through appropriate modification at C-4, the cyclopentanones A are obtained. Cleavage of the cyclobutene ring then affords the β-keto esters B, which are transformed to the corresponding prostanoids C.

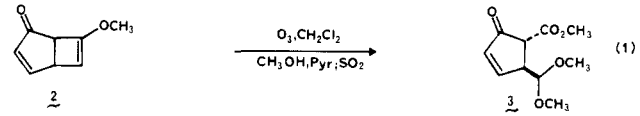
The first step in the approach is based on work by Dauben et al.,[5] who reported that irradiation of α-tropolone methyl ether (1)[6] furnished in 55% yield 7-methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2) via the 1-methoxy isomer.[5,7] A brief investigation of this photochemical conversion of α-tropolone methyl ether (1) provided con-

Scheme I. Synthesis of 11-Deoxy-PGE$_1$ (9)



ditions that permitted a substantial amelioration of the process (relatively concentrated anhydrous methanol solution at room temperature with a Hanau TQ 150 high-pressure mercury arc lamp). Under these conditions and by careful monitoring by VPC of the conversion of the intermediate 1-methoxy isomer to 2, isolated yields of over 80% of the bicyclic cyclopentenone 2 could be consistently achieved. It should be pointed out that α-tropolone, thanks to recent improvements in its synthesis,[6d] is now an inexpensive, readily available substance.

The bicyclic photoproduct 2 constitutes an excellent intermediate for PG synthesis in that it not only contains a cyclopentenone for use in securing ring functionality and a cyclobutene that can be cleaved to provide the means for constructing the prostaglandin side chains at C-8 and C-12 but also, and perhaps most importantly, has a folded geometry that affords an element of stereochemical control (vide infra). The usefulness of the bicyclic intermediate 2 is further enhanced by the chemoselectivity displayed by the double bonds. Thus, for example, ozonolysis of compound 2 in a mixture of methylene chloride, methanol, and pyridine followed by treatment of the resultant ozonide with sulfur dioxide[8] affords selectively the trans[9]-disubstituted cyclopentenone 3 (eq 1). This cyclo-



(1)

pentenone with differently functionalized appendages could presumably be transformed to PG by known methodology. This possibility was not pursued, however, because of the success of another approach, first demonstrated by the synthesis of 11-deoxy-PGE$_1$, described below.

Synthesis of 11-Deoxy-PGE$_1$. Catalytic hydrogenation of the substituted cyclopentenone 2 was also highly selective and afforded in 68% yield after purification the corresponding cyclopentanone 4 (Scheme I). Approximately 8% of the tetrahydro derivative[5] was also formed in this reduction. Ozonolysis as above of enol ether 4 then provided directly in 80% yield the relatively stable trans[9] β-keto ester acetal 5. This in situ acetal formation is particularly useful in cases such as the present in which

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(3) See: Bindra, J. S.; Bindra, R. "Prostaglandin Synthesis"; Academic Press, New York, 1977. Mitra, A. "The Synthesis of Prostaglandins"; Wiley-Interscience: New York, 1977. Crabbé, P., Ed.; "Prostaglandin Research", Academic Press: New York, 1977.

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(5) Dauben, W. G.; Koch, K.; Smith, S. L.; Chapman, O. L. *J. Am. Chem. Soc.* **1963**, *85*, 2616.

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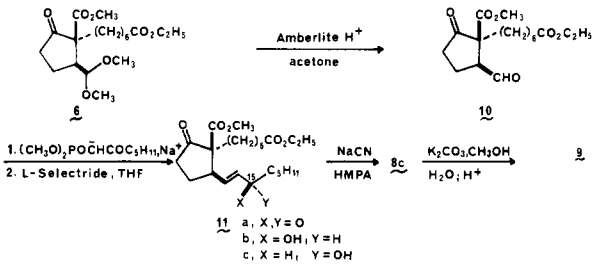
(7) Chapman, O. L.; Pasto, D. J. *J. Am. Chem. Soc.* **1960**, *82*, 3642. Chapman, O. L.; Fitton, P. *Ibid.* **1963**, *85*, 41. Chapman, O. L.; Smith, H. G.; King, R. W. *Ibid.* **1963**, *85*, 803. DePuy, C. H.; Chapman, O. L. "Molecular Reactions and Photochemistry"; Chapter 5, Prentice-Hall, Inc.: Englewood Cliffs, NJ, 1972; Chapter 5.

(8) DeMaster, R. D. Ph.D. Dissertation, University of Minnesota, *Diss. Abstr. Int. B.* **1971**, *31*, 5871. See also: Noland, W. E.; DeMaster, R. D. *Org. Synth.* **1972**, *52*, 135.

(9) See: Baret, P.; Barreiro, E.; Greene, A. E.; Luche, J. L.; Teixeira, M. A.; Crabbé, P. *Tetrahedron* **1979**, *35*, 2931 and references cited therein.

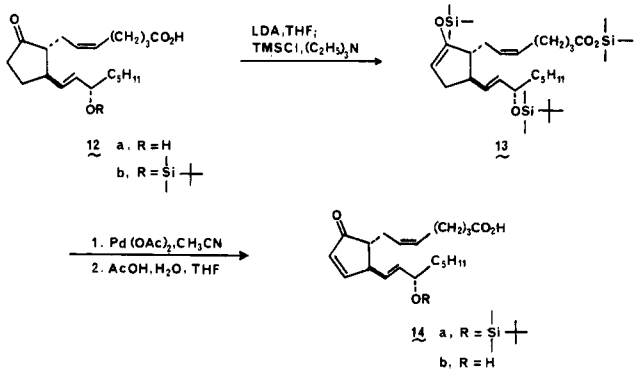
Scheme II. Alternative Synthesis of 11-Deoxy PGE_1 (9)



the free aldehyde would be very unstable. Alkylation of β-keto ester **5** at C-8[10] was achieved in 54% yield by reaction with potassium hydride in dimethyl sulfoxide[11] followed by treatment with ethyl 7-iodoheptanoate.[12] This produced a single keto diester to which structure **6** was assigned on the basis that alkylation most probably occurs from the side opposite to that of the bulky dimethoxymethyl group.

In our initial approach,[4a,b] compound **6** was decarbomethoxylated by warming with sodium cyanide in hexamethylphosphoric triamide,[13] which afforded the keto ester **7a** in 89% yield. The dimethyl acetal was unaffected under the particularly mild conditions of this useful reaction. Treatment of keto ester **7a** with ethanolic potassium acetate under known equilibration conditions[14] led to unchanged material, thus establishing the thermodynamically more stable trans configuration for the substituents on the cyclopentanone. Cleavage of the acetal protecting group in intermediate **7a** with *p*-toluenesulfonic acid in acetone liberated the aldehyde **7b**, which was subjected to an Emmons–Horner reaction[15] with the sodium salt of dimethyl 2-oxoheptylphosphonate to provide in 64% overall yield the expected[16] enedione **8a**. After a systematic study of various reducing agents,[4b] it was found that **8a** could be most effectively reduced, albeit to partial conversion, with sodium cyanoborohydride in acidic methanol,[17] which yielded regioselectively a 1:1 mixture of epimeric alcohols **8b** and **8c** together with diol and starting material. After thin-layer chromatographic separation of these products and recovery of the remaining starting material, the undesired β-isomer **8b** as well as any C-9,15-diol could be oxidized[18] to enedione **8a** and thus recycled. Alcohol **8c** could also be obtained from **8a**, but less satisfactorily, through selective protection of the C-9 ketone as the dioxolan, C-15 reduction, and then deprotection.[4a] Hydrolysis of the more polar[19] α-isomer **8c** in aqueous methanolic potassium carbonate then completed the synthesis affording crystalline 11-deoxy-PGE_1 (**9**),[20] identified through comparison with an authentic sample,

Scheme III. Conversion of 11-Deoxy-PGE_2 (12a) to PGA_2 (14b)



thus confirming the relative stereochemistry at the three asymmetric centers and the trans geometry of the double bond.

Subsequent to the completion of this synthesis, it was discovered that the C-15 ketone reduction could be markedly improved by inverting some of the steps (Scheme II). Namely, instead of effecting decarbomethoxylation of intermediate **6**, the elimination of the carbomethoxyl group is postponed until *after* the introduction of the lower chain and the reduction of the carbonyl group at C-15. This serves not only to provide complete regioselectivity in the reduction but also to allow now total conversion to the allylic alcohols without any appreciable diol formation. Specifically, treatment of compound **6** with Amberlite H^+ IR 120 in acetone afforded the expected aldehyde **10**. The diketone **11a** was then obtained by the Emmons–Horner reaction[15,16] in 77% overall yield from acetal **6**. Reduction of this diketone with L-Selectride[21] now occurred, even at total conversion, only at the C-15 carbonyl thanks to the anticipated shielding effect of the carbomethoxyl group on the C-9 carbonyl, and produced in excellent yield a ca. 1:1 mixture of 15α- and 15β-alcohols, which could be separated by chromatography on silica gel. The desired 15α-epimer **11c** was then decarbomethoxylated[13] to provide much more effectively the earlier prepared monoester **8c**, hydrolysis of which gave in high yield 11-deoxy-PGE_1 (**9**). The undesired 15β-epimer **11b** obtained from the reduction could be oxidized quantitatively to diketone **11a** with manganese dioxide in methylene chloride,[22] thus allowing it to be recycled. This new approach affords the prostanoid **9** in a rather respectable 10–15% overall yield from α-tropolone methyl ether (**1**).

Conversion of 11-Deoxy-PGE_2 to PGA_2. The 11-deoxy-PG are of interest not only due to their intrinsic biological properties (such as antagonists of the PG belonging to the E and F series[2]) but also as they can engender PG of the A family[23] and hence PG of the E and F families.[3,24] Because of the importance of the 11-deoxy-PGE to PGA transformation to the value of our approach, an effort was made,[25] with moderate success, to

(10) Prostanoid numbering.
(11) Pond, D. M.; Cargill, R. L. *J. Org. Chem.* **1967**, *32*, 4064. Brown, C. A. *Ibid.* **1974**, *39*, 3913.
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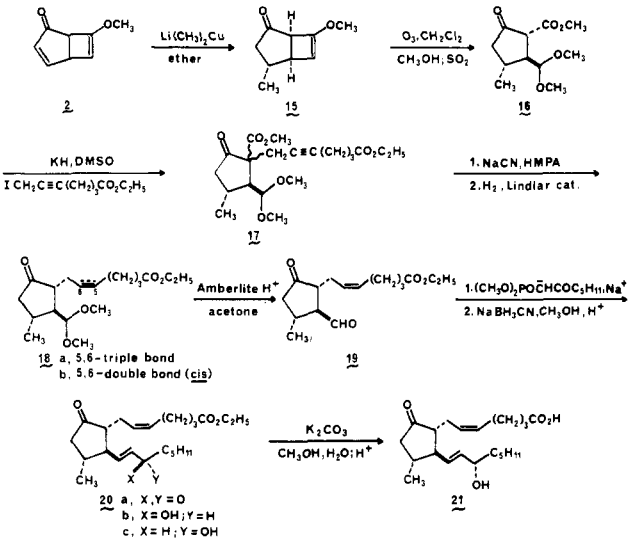
(18) Brown, H. C.; Garg, C. P. *J. Am. Chem. Soc.* **1961**, *83*, 2952. Brown, H. C.; Garg, C. P.; Liu, K. T. *J. Org. Chem.* **1971**, *36*, 387.
(19) Andersen, N. H. *J. Lipid Res.* **1969**, *10*, 316.
(20) Bagli, J.; Bogri, T. *Tetrahedron Lett.* **1972**, 3815; *J. Org. Chem.* **1972**, *37*, 2132. Alvarez, F. S.; Wren, D.; Prince, A. *J. Am. Chem. Soc.* **1972**, *94*, 7823.
(21) Brown, H. C.; Krishnamurthy, S. *J. Am. Chem. Soc.* **1972**, *94*, 7159. L-Selectride is the registered trademark of the Aldrich Chemical Co.
(22) Sondheimer, F.; Amendolla, C.; Rosenkranz, G. *J. Am. Chem. Soc.* **1953**, *75*, 5930.
(23) Stork, G.; Raucher, S. *J. Am. Chem. Soc.* **1976**, *98*, 1583.
(24) See: (a) Bundy, G. L.; Schneider, W. P.; Lincoln, F. H.; Pike, J. E. *J. Am. Chem. Soc.* **1972**, *94*, 2123. (b) Corey, E. J.; Ensley, H. E. *J. Org. Chem.* **1973**, *38*, 3187. (c) Schneider, W. P.; Bundy, G. L.; Lincoln, F. H.; Daniels, E. G.; Pike, J. E. *J. Am. Chem. Soc.* **1977**, *99*, 1222.
(25) For a preliminary communication, see: Teixeira, M. A.; Crabbé, P. *Rev. Latinoamer. Quim.* **1980**, *11*, 118.

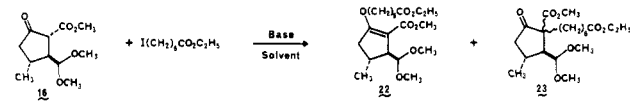
Scheme IV. Synthesis of 11α-Methyl-11-deoxy-PGE$_2$ (21)



improve upon the earlier work of Stork and Raucher.[23] These workers reported the conversion of an 11-deoxy-PGE$_2$ derivative to PGA$_2$ (**14b**) via the selenoxide elimination technique (46% overall yield). We found that palladium(II) oxidation of the trimethylsilyl enol ether of an 11-deoxy-PGE$_2$ derivative also could be used to effect the conversion to the corresponding PGA$_2$ derivative (Scheme III). More specifically, protection of 11-deoxy-PGE$_2$ (**12a**) as the C-15 *tert*-butyldimethylsilyl ether **12b** followed by treatment with lithium diisopropylamide and trapping of the resultant enolate with chlorotrimethylsilane in the presence of triethylamine[26] produced the trimethylsilyl enol ether **13**. Oxidation of **13** with palladium(II) acetate in dry acetonitrile[27] furnished the PGA$_2$ ether **14a** in 51% yield (65% based on nonrecovered starting material). Mild acid hydrolysis of the PGA$_2$ ether **14a** then cleanly afforded PGA$_2$ (**14b**), shown to be identical with an authentic sample secured from the marine coral *Plexaura homomalla*.

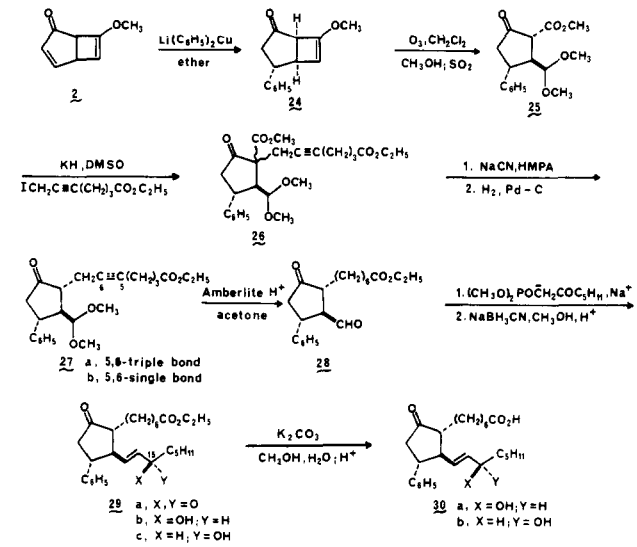
Synthesis of C-11 Substituted Prostanoids. Parallel to these efforts to construct the prostanoid skeleton and to gain access to natural PG, work was carried out on the synthesis of natural PG modified at the C-11 position. This objective could be realized because of the facility and selectivity in which bicycloheptadienone **2** enters into conjugate addition reactions with various cuprate reagents.[28] In the synthesis of 11α-methyl-11-deoxy-PGE$_2$ (**21**), the reaction of lithium dimethylcopper with enone **2** produced stereoselectively in 72% yield the 11α-methyl isomer **15**, with the formation of less than 16% of the separable 11β-methyl isomer (Scheme IV). The exo addition of the alkyl group had been anticipated from the bent geometry of the bicyclic intermediate **2**. Ozonolysis of the 11α-methyl isomer **15**, followed by decomposition of the ozonide with sulfur dioxide in methanol,[8] then gave in 54% yield the keto ester acetal **16**. The reaction time with sulfur dioxide was critical in that exposure for too long a period resulted in the formation of appreciable amounts of the corresponding ester diacetal.

Table I



base, solv	temp, °C	time, h	isolated yield, %	
KH, Me_2SO	18	20	47	11
KH, xylene	reflux	12.5	40	10
K_2CO_3, butanone	reflux	12.5	40	10
NaH, DME	reflux	0.5	45	13
$(C_6H_5)_3CLi$, ether	18	16	52	trace
$TlOC_2H_5$ neat (excess iodo ester)	70	18	50	13

Scheme V. Synthesis of 11α-Phenyl-11-deoxy-PGE$_1$ (30)

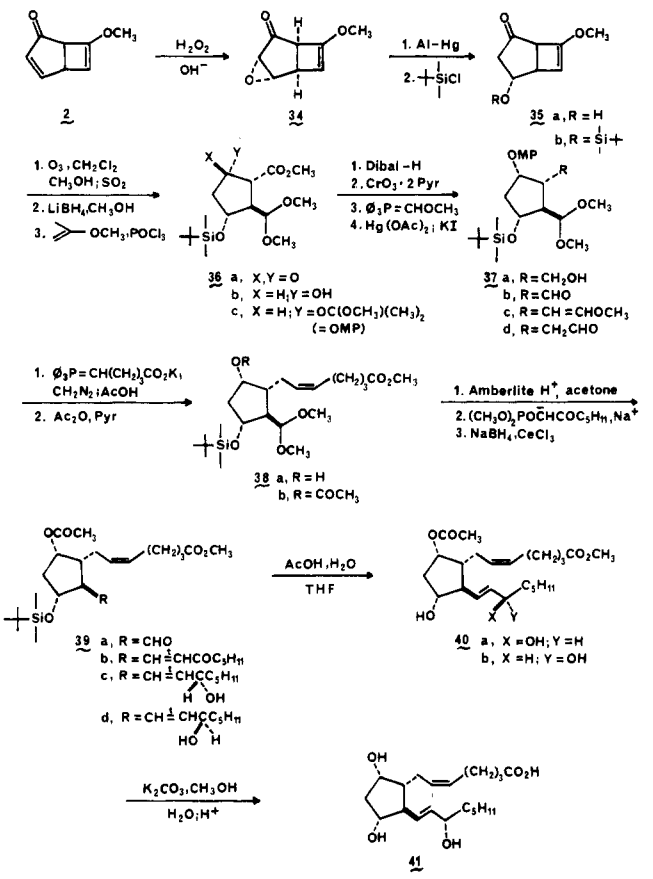


In contrast with the experience in the C-11 unsubstituted series, attempts under various conditions to alkylate the substituted β-keto ester **16** with ethyl 7-iodoheptanoate[12] provided mainly the O-alkylated product **22** and only small amounts of the desired C-alkylated material **23** (ca. 4–5:1, Table I).[29] Fortunately, however, it was found that this problem could be overcome by using ethyl 7-iodo-5-heptynoate.[30] Alkylation of the potassium enolate of **16**, generated with potassium hydride in Me_2SO, with ethyl 7-iodo-5-heptynoate gave exclusively in 73% yield the desired diester **17**, shown by NMR spectroscopy to be a ca. 1:1 isomeric mixture at C-8.[31] This changeover could simply be the result of the increased rigidity (or softness[32]) of the alkylating agent.

Decarbomethoxylation of diester **17** with sodium cyanide[13] afforded in 94% yield the equilibrated acetylenic monoester **18a**, which was partially reduced with the Lindlar catalyst[33] to provide the cis-olefin **18b** in 97% yield. Cleavage of the acetal with Amberlite then gener-

(26) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324.
(27) Ito, Y.; Hirao, T.; Saegusa, T. *J. Org. Chem.* **1978**, *43*, 1011.
(28) See: Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630. House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59. Posner, G. H. "An Introduction to Synthesis using Organocopper Reagents"; Wiley-Interscience: New York, 1980, and references cited therein.
(29) Attempted alkylation of **16** in the presence of alumina produced decarbomethoxylation. This was subsequently developed into a useful procedure for effecting decarbalkoxylation of β-keto esters. See: Greene, A. E.; Cruz, A.; Crabbé, P. *Tetrahedron Lett.* **1976**, 2707.
(30) Corey, E. J.; Sachdev, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 8483.
(31) Subsequent to the completion of this work,[4b] several other examples of this type of changeover have been noted. See: Torii, S.; Tanaka, H.; Mandai, T. *J. Org. Chem.* **1975**, *40*, 2221. Ide, J.; Sakai, K. *Tetrahedron Lett.* **1976**, 1367. Toru, T.; Kurozumi, S.; Tanaka, T.; Miura, S.; Kobayashi, M.; Ishimoto, S. *Ibid.* **1976**, 4087.
(32) Pearson, R. G. *J. Am. Chem. Soc.* **1963**, *85*, 3533. See also: Ho, T. L. *Chem. Rev.* **1975**, *75*, 1.
(33) Lindlar, H. *Helv. Chim. Acta* **1952**, *35*, 446. Lindlar, H.; Dubuis, R. *Org. Synth.* **1966**, *46*, 89.

Scheme VI. Synthesis of $PGF_{2\alpha}$ (41)



ated the corresponding aldehyde, which was converted[16] to diene dione **20a** in 52% overall yield after purification.

After a survey of several reagents, it was found that the reduction of **20a** could be effected regioselectively and in reasonable high conversion with sodium cyanoborohydride in acidic methanol,[17] which gave a ca. 1:1 mixture of the C-15 epimeric alcohols, separable by silica gel chromatography. The 15α-hydroxy isomer **20c** was hydrolyzed with aqueous methanolic potassium carbonate to afford crystalline 11α-methyl-11-deoxy-PGE_2 (**21**). This compound was identical in all respects but for chiroptical properties with a sample obtained from (15*S*)-PGA_2 from *Plexaura homomalla*[4c,34] through the use of lithium dimethylcopper,[4c] thereby confirming the assigned stereochemistry and demonstrating the easy adaptability of the route to the synthesis of 11-alkyl- and 2-series-PG.

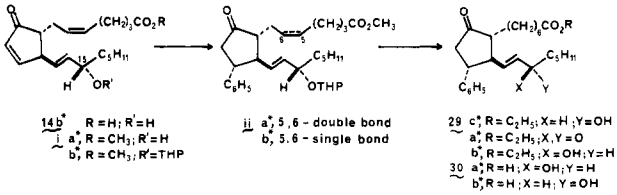
This flexibility is further illustrated by the synthesis of 11α-phenyl-11-deoxy-PGE_1. The reaction of lithium diphenylcopper with enone **2** was in this case totally stereoselective, providing the 11α-phenyl derivative **24** in 75% yield (Scheme V). Ozonolysis of **24**, followed by treatment with sulfur dioxide afforded essentially quantitatively the trisubstituted cyclopentanone **25**. Alkylation of **25** with ethyl 7-iodo-5-heptynoate[30] then furnished in 78% yield a C-alkylated epimeric mixture **26**. Decarbomethoxylation of the keto diesters **26** with sodium cyanide[13] gave in nearly quantitative yield keto ester **27a**, which was reduced catalytically to effect saturation of the acetylenic bond and provide keto ester **27b**. Treatment of this material with Amberlite H^+ IR 120 slowly liberated the corresponding aldehyde **28**, which was submitted to the usual Emmons–Horner reaction to give the enedione **29a** (80% overall yield from **26**), shown to be identical, except for rotation, with a sample prepared[35] from (15*S*)-PGA_2 from Cuban coral.[4c,34]

Sodium cyanoborohydride reduction of the totally synthetic enedione **29a** cleanly provided in 89% yield a mixture of C-15 alcohols **29b,c**, which proved to be inseparable by the usual techniques. The semicrystalline mixture of free acids **30a,b** from the alkaline hydrolysis of esters **29b,c** was also inseparable. However, the ratio of the 15α and 15β epimers in the mixture could be determined by making use of available PGA_2 with the 15*R* configuration from the Mexican coral *Plexaura homomalla* Esper and PGA_2 with the 15*S* stereochemistry from the Cuban soft coral.[4c,34] Comparison, particularly in the olefinic region, of the 250-MHz NMR spectrum of the ester mixture **29b,c** with the spectra of carefully prepared admixtures of of (15*S*)- and (15*R*)-11α-phenyl-11-deoxy-PGE_1 ethyl esters secured[35] from (15*S*)- and (15*R*)-PGA_2, respectively, indicated a 1.5–2:1 ratio of the 15α to 15β alcohols in **29b,c**.[36] Thus, in the reduction of enedione **29a** with sodium cyanoborohydride, the 11α-phenyl substituent has a pronounced effect not only on the relative reactivity of the C-9 carbonyl but on the stereoselectivity at C-15 as well (vide supra).

Other substituents have similarly been introduced at the C-11[10] position in formula A (Chart I). These include the 11α-cyano, through the conjugate addition reaction of enone **2** with acetone cyanohydrin,[37] and the 11α-*n*-butyl, through the reaction of enone **2** with lithium di-*n*-butylcopper. In addition, the 11β-butyl-11α-methyl derivative **33**, an 11,11-disubstituted PG precursor, was prepared. This was accomplished by 1,3-cycloaddition of diazomethane[38] to enone **2** to afford the crystalline tricyclic pyrazoline **31**, which was pyrolyzed in xylene to provide the known[5,38a] β-methyl enone **32** in 70% overall yield (eq 2). The reaction of this enone with lithium di-*n*-butylcopper then produced in 80% yield the 11,11-disubstituted cyclopentanone.[10] The NMR spectrum indicated a 4:1

(34) See: Greene, A. E.; Padilla, A.; Crabbé, P. *J. Org. Chem.* **1978**, *43*, 4377.

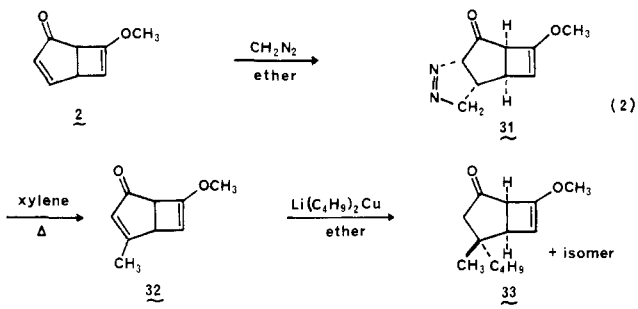
(35) The comparison sample of enedione **29a*** (* signifies that the absolute stereochemistry is indicated) was prepared from (15*S*)-PGA_2 (**14b***) as follows: esterification with diazomethane (→**ia***, 100%), protection of the C-15 hydroxyl as the tetrahydropyranyl (THP) ether (→**ib***, 78%), conjugate addition of lithium diphenylcopper (→**iia***, 73%), selective catalytic hydrogenation of the Δ^5 double bond (→**iib***, 100%), transesterification and acid cleavage of the THP ether (→**29c***, 54%), and finally manganese dioxide oxidation[22] of the resultant allylic alcohol (→**29a***, 85%). Reduction of enedione **29a*** with sodium cyanoborohydride[17] yielded the mixture of allylic alcohols **29b*,c*** (83% based on nonrecovered **29a***), hydrolysis of which provided the mixture of acids **30a*,b*** (99%, $[\alpha]_D$ −80.9°). The pure acid **30b*** (mp 89–90 °C; $[\alpha]_D$ −75.9°) was secured from **iib*** by acid hydrolysis of the THP ether followed by saponification (60%). The preparation of pure (15*R*)-11α-phenyl-11-deoxy-PGE_1 ethyl ester (**29b***) and the corresponding free acid **30a*** (mp 98–99 °C; $[\alpha]_D$ −88.6°) from (15*R*)-PGA_2 (C-15 epimer of **14b***) was effected exactly as described above for the syntheses of **29c*** and **30b*** from (15S)-PGA_2 (**14b***).



(36) Computation of the ratio from the optical rotation of the optically active mixture of acids **30a*,b***, obtained[35] by reduction of the optically active enedione **29a*** with sodium cyanoborohydride followed by ester hydrolysis (exactly as for **29a** → **30a,b**), and the optical rotations of the individual, optically pure acids **30a*** and **30b***[35] confirms this result.

(37) Ercoli, A.; De Ruggieri, P. *J. Am. Chem. Soc.* **1953**, *75*, 650.

(38) See: (a) Uyera, T.; Miyakoshi, S.; Kitahara, Y. *Synth. Commun.* **1973**, *3*, 365. (b) Vogel, P.; Crabbé, P. *Helv. Chim. Acta* **1973**, *56*, 557. (c) Guzman, A.; Vera, M.; Crabbé, P. *Prostaglandins* **1974**, *8*, 85.



mixture of isomers in which compound **33**, in keeping with the stereochemical results obtained above, is preponderant. Although it has not been demonstrated, these C-11 substituted derivatives could, in principle, be converted to C-11 substituted PG by the methodology outlined above.

Synthesis of $PGF_{2\alpha}$. To culminate our work on the tropolone approach to PG and to further demonstrate its flexible nature, we sought a direct, stereocontrolled route to the C-11 hydroxylated PG, PGF and PGE. It appeared, given the high degree of stereoselectivity observed in the above conjugate addition reactions with enone **2**, that it might be possible to introduce a hydroxyl group stereoselectively at C-11 and that this intermediate, in turn, might be convertible to PGF and PGE.

It was gratifying that treatment of enone **2** with alkaline hydrogen peroxide[24b,c,38c] gave with total stereoselectivity in 89% yield the epoxy ketone **34**, by exclusive exo attack of the hydroperoxide anion (Scheme VI). Cleavage of the epoxide **34** with aluminum amalgam[24b,c,38c] furnished the β-ketol **35a** nearly quantitatively. The 11α-hydroxyl group[10] was initially protected as its THP ether; however, ozonolysis of this intermediate afforded the corresponding β-keto ester in only rather poor yield. However, the corresponding *tert*-butyldimethylsilyl ether **35b** formed[39] quantitatively, and on ozonolysis in methylene chloride–methanol under essentially the conditions described above afforded the desired β-keto ester **36a** in good yield. This intermediate was then converted stereorationally to $PGF_{2\alpha}$ by using a sequence of reactions, described below, differing somewhat from the aforementioned.

The 9-keto group of **36a** was reduced with lithium borohydride in methanol at −78 °C, conditions known to produce selectively the 9α-hydroxyl in similar compounds,[9] to give exclusive formation of the desired alcohol **36b**. The α-configuration of the hydroxyl group, resulting from the attack of hydride from the less hindered β side, was evidenced by the correspondence of the 250-MHz NMR spectrum with that of the C-11 unsubstituted analogue of known[9] stereochemistry, by the very narrow IR band at 3450 cm^{-1}, indicative of hydrogen bonding, and by the observed anisotropic shielding effect of the acetoxyl group on the methyl of the carbomethoxyl group in the corresponding C-9 acetate derivative, also indicative[9,40] of a cis relationship between the substituents at C-8 and C-9.[10]

The encumbering substitution surrounding the C-9 hydroxyl group in **36b** prevented the formation of significant amounts of the corresponding *tert*-butyldimethylsilyl ether under the usual[39] reaction conditions (even after 72 h). However, treatment of alcohol **36b** with 2-methoxypropene[41a] in methylene chloride in the presence of a catalytic amount of phosphorus oxychloride[41b] furnished quantitatively the corresponding acetal **36c**. Reduction of intermediate **36c** with diisobutylaluminum hydride in toluene at −70 °C afforded the corresponding alcohol **37a**, which was readily oxidized to aldehyde **37b** by using Collins reagent in methylene chloride.[42] The Wittig reaction of (methoxymethylene)triphenylphosphorane with aldehyde **37b**, initially problematic, was eventually carried out in high yield by using lithium diisopropylamide to generate the ylide (5 equiv) and by carrying out the reaction in THF–toluene at −10 °C. The resultant enol ether **37c** was then selectively hydrolyzed through treatment with mercuric acetate followed by aqueous potassium iodide[43] to give the required homologated aldehyde **37d**.

A Wittig reaction of **37d** with the ylide[16] generated from (4-carboxybutyl)triphenylphosphonium bromide by using dimsylpotassium in Me_2SO afforded, after esterification with diazomethane and brief contact with weak acid, the hydroxy ester **38a** in greater than 30% overall yield from alcohol **36b**. Clearly, from this key, functionally differentiated intermediate **38a**, which is obtained highly stereoselectively from α-tropolone methyl ether (**1**), all PG belonging to the E and F families can be synthesized.[44]

The completion of the synthesis of $PGF_{2\alpha}$ was achieved essentially by the methodology described above. Thus, cleavage of the acetal in the presence of the silyl ether, found to be more selective on the acetate derivative **38b** than on the free alcohol **38a**, was carried out with Amberlite in acetone to afford cleanly the desired aldehyde **39a**. The Emmons–Horner reaction[15,16] then gave the conjugated ketone **39b**, which was reduced with sodium borohydride in methanol in the presence of cerium trichloride[45] to furnish a mixture of C-15 epimeric alcohols. Separation of the epimers could be more readily achieved after mild acid hydrolysis of the silyl ether protecting group, which produced the isomeric allylic alcohols **40a** and **40b**. The less polar[19] 15β-isomer **40a** could be easily recycled through manganese dioxide oxidation[22] to the corresponding enone. The more polar[19] 15α-isomer **40b** upon basic hydrolysis engendered racemic $PGF_{2\alpha}$ (**41**), indistinguishable from an authentic sample.

Conclusion

The feature of the tropolone route to prostaglandins that should be underscored is its flexibility. In addition to affording the primary PG and the 11-substituted prostanoids reported above, the methodology has been used for the simple preparation of a large number of novel prostaglandins modified in the upper and lower side chains.[9,46] This versatility and the attendant high degree of stereoselectivity distinguish the tropolone route from many of the other approaches to prostaglandins.

Experimental Section

Solvents were generally redistilled prior to use. Tetrahydrofuran, dioxane, dimethoxyethane, and ether were distilled from lithium aluminum hydride, hexamethylphosphoric triamide, dimethyl sulfoxide, methylene chloride, pyridine, pentane, and hexane were distilled from calcium hydride, and acetonitrile and dimethylformamide were distilled from phosphorus pentoxide. Reactions were generally stirred under a nitrogen or argon atmosphere. Reaction products were isolated by addition of water

(39) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.
(40) Artenius, M.; Danneels, D. *Org. Magn. Reson.* **1979**, *7*, 345.
(41) (a) Newman, M. S.; Vander Zwan, M. C. *J. Org. Chem.* **1973**, *38*, 2910. (b) Kluge, A. F.; Untch, K. G.; Fried, J. H. *J. Am. Chem. Soc.* **1972**, *94*, 7827.
(42) Ratcliffe, R.; Rodehorst, R. *J. Org. Chem.* **1970**, *35*, 4000.
(43) Corey, E. J.; Narasaka, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1976**, *98*, 6417.
(44) For possible alternative procedures for effecting the conversion of β-keto ester **36a** to hydroxy ester **38a**, see: Kondo, K.; Umemoto, T.; Yako, K.; Tunemoto, D. *Tetrahedron Lett.* **1978**, 3927. Stork, G.; Isobe, M. *J. Am. Chem. Soc.* **1975**, *97*, 6260. Lin, C. H.; Stein, S. J. *Synth. Commun.* **1976**, *6*, 503.
(45) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226.
(46) Krief, A.; Dumont, W.; Deprés, J. P.; Greene, A. E.; Crabbé, P., unpublished work.

followed by extraction with the solvent indicated and drying over anhydrous sodium sulfate, magnesium sulfate, or potassium carbonate.

Thin-layer chromatography was performed on Merck $60F_{254}$ (0.25 mm) sheets, which were visualized with molybdatophosphoric acid in ethanol. Merck 70–230 or 230–400 mesh silica gel 60, Mallinckrodt silicic acid silicar CC-4 or CC-7, or Fluka Florisil was employed for column chromatography. A Beckman Acculab 4 spectrophotometer was used to record the IR spectra, and a Beckman DBT spectrophotometer was used for the UV spectra. A JEOL PMX-60 spectrometer was employed for the ^1H NMR spectra (Me_4Si as the internal reference), and a WP Bruker spectrometer was used for the ^{13}C NMR spectra. Mass spectra were obtained on a MS-30 AEI mass spectrometer (70 eV, direct insertion probe) or on a VG Micromass 70 70F instrument. Optical rotations were determined on a Perkin-Elmer 141 polarimeter. Melting points were obtained by using a Büchi–Tottoli apparatus and are not corrected. Microanalyses were performed by the Central Service of the CNRS, Lyon.

7-Methoxybicyclo[3.2.0]hepta-3,6-dien-2-one (2).[5,7] The irradiation of 5.39 g (39.1 mmol) of α-tropolone methyl ether (1)[6,47] was carried out at room temperature under argon in three equal portions, each in 260 mL of dry methanol, with the use of an Hanau TQ 150 high-pressure mercury arc lamp (quartz filter), and was followed by TLC and GLC.[5,7] After completion of the irradiations (each ca. 7 h), the solutions were combined and freed from solvent under reduced pressure, and the resulting oil was evaporatively distilled under high vacuum to afford 4.47 g (83%) of oily bicyclic dienone 2:[5,7] bp 70–71 °C (bath) (0.2 torr); ^1H NMR ($CDCl_3$) δ 7.70 (dd, J = 2, 7 Hz, 1 H), 5.97 (d, J = 7 Hz, 1 H), 5.03 (s, 1 H), 3.63 (s, 5 H); IR (film) 1700, 1630, 1570 cm^{-1}; UV (C_2H_5OH) 225 nm (ε 6800) [lit.[5] UV (C_2H_5OH) 225 nm (ε 6000)]; mass spectrum, m/e 136 (M^+).

Methyl (1*R,2*S**)-2-(Dimethoxymethyl)-5-oxo-3-cyclopentenecarboxylate (3).** A solution of 200 mg (1.47 mmol) of dienone 2 in 5 mL of methylene chloride and 1 mL of methanol was cooled to −78 °C, and 80 μL of pyridine was added.[48] A stream of ozone-oxygen was passed through the solution until TLC indicated only a small amount of starting material remained. Distilled sulfur dioxide (0.35 mL) was then added, and the resulting solution was left at −20 °C for 16 h. Following partial concentration under reduced pressure, the solution was diluted with ether, washed with cold 5% aqueous potassium carbonate, dried over sodium sulfate, filtered, and then concentrated under reduced pressure to afford 227 mg (ca. 72%) of sensitive keto ester 3: ^1H NMR ($CDCl_3$) δ 7.51 (dd, J = 3,6 Hz, 1 H), 6.01 (dd, J = 2,6 Hz, 1 H), 4.21 (d, J = 6 Hz, 1 H), 3.62 (s, 3 H), 3.19 (s, 3 H), 3.15 (s, 3 H); IR (film) 1735, 1705, 1640 cm^{-1}; mass spectrum, m/e 214 (M^+).

7-Methoxybicyclo[3.2.0]hept-6-en-2-one (4). A mixture of 4.03 g (29.6 mmol) of dienone 2 and platinum (from 420 mg of platinum oxide) in 350 mL of ethyl acetate was stirred rapidly under hydrogen. Following examination of an aliquot of the reaction mixture by GLC that indicated completion of the reaction (ca. 1 h), the hydrogen was removed, the mixture was filtered, and the filtrate was concentrated under reduced pressure. Purification of the resultant oil by silica gel chromatography using 10% ethyl acetate in hexane afforded 2.80 g (68%) of the dihydro derivative 4: ^1H NMR ($CDCl_3$) δ 4.65 (s, 1 H), 3.46 (s, 3 H), 3.26–2.80 (m, 3 H), 2.40–1.63 (m, 3 H); IR (film) 3070, 1740, 1635 cm^{-1}; mass spectrum, m/e 138 (M^+). Further elution yielded 332 mg (8%) of the corresponding tetrahydro derivative:[5] ^1H NMR ($CDCl_3$) δ 3.83 (m, 1 H), 3.20 (s, 3 H); IR (film) 1740, 1130 cm^{-1}; mass spectrum m/e 140 (M^+).

Methyl (1*R,2*S**)-2-(Dimethoxymethyl)-5-oxocyclopentanecarboxylate (5).** A 2.30-g (16.7 mmol) sample of enol ether 4 in 40 mL of methylene chloride and 5 mL of methanol at −78 °C was treated with a stream of ozone-oxygen until the solution turned slightly blue. After removal of the excess ozone with argon, 20 mL of sulfur dioxide was distilled into the solution. The resulting solution was then left for 2 h at −25 °C. After being partially concentrated under reduced pressure, the solution was diluted with ether, washed successively with cold aqueous potassium carbonate, water, and brine, dried, filtered, and then concentrated under reduced pressure to afford 2.89 g (80%) of oily keto ester 5. An analytical sample was obtained by preparative TLC: ^1H NMR (250 MHz, $CDCl_3$) δ 4.25 (d, J = 6 Hz, 1 H), 3.70 (s, 3 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 3.17 (d, J = 10.5 Hz, 1 H), 2.5–1.5 (m, 5 H); IR (film) 1745, 1730, 1120, 1070 cm^{-1}; mass spectrum, m/e 216 (M^+).

Anal. Calcd for $C_{10}H_{16}O_5$: C, 55.54; H, 7.46. Found: C, 55.94; H, 7.45.

This material was unaltered on prolonged treatment with potassium acetate in ethanol[14] or with basic alumina in chloroform.[9]

Ethyl 7-[(1*R,2*R**)-1-Carbomethoxy-2-(dimethoxymethyl)-5-oxocyclopentyl]heptanoate (6).** A 4.17 g (19.3 mmol) sample of keto ester 5 in 47 mL of dry Me_2SO was treated with 4.1 g of a dispersion of potassium hydride[11] in mineral oil (22.5%, 23.1 mmol) dropwise over 3 min under argon. After being stirred for 15 min, 11.0 g (38.8 mmol) of ethyl 7-iodoheptanoate[12,30] was added rapidly, and stirring was continued overnight. The crude product was isolated with hexane in the usual manner and was purified by dry silica gel chromatography using chloroform as the eluent to give 3.88 g (54%) of keto diester 6: ^1H NMR ($CDCl_3$) δ 4.25 (d, J = 6 Hz, 1 H), 4.05 (q, J = 7 Hz, 2 H), 3.60 (s, 3 H), 3.35 (s, 6 H), 1.20 (t, J = 7 Hz, 3 H); IR (film) 1750, 1730, 1120, 1070, 1050 cm^{-1}; mass spectrum, m/e 341 ($M^+ - OCH_3$).

Anal. Calcd for $C_{19}H_{32}O_7$: C, 61.27; H, 8.66. Found: C, 61.60; H, 8.64.

Ethyl 7-[(1*R,2*S**)-2-(Dimethoxymethyl)-5-oxocyclopentyl]heptanoate (7a).** A solution of 2.96 g (7.96 mmol) of keto diester 6 and 800 mg (16.3 mmol) of sodium cyanide in 80 mL of hexamethylphosphoric triamide[13] was stirred for 1.5 h at 75–80 °C (bath temperature) and then overnight at room temperature. The reaction mixture was poured into hexane–10% aqueous hydrochloric acid (hood!) and the product was isolated with hexane in the usual manner to afford 2.23 g (89%) of oily keto ester 7a. An analytical sample was obtained by preparative TLC: ^1H NMR ($CDCl_3$) δ 4.20 (d, J = 5 Hz, 1 H), 4.05 (q, J = 7 Hz, 2 H), 3.35 (s, 6 H), 1.20 (t, J = 7 Hz, 3 H); IR (film) 1730, 1180, 1120, 1070 cm^{-1}; mass spectrum, m/e 283 ($M^+ - OCH_3$).

Anal. Calcd for $C_{17}H_{30}O_5$: C, 64.94; H, 9.62. Found: C, 65.22; H, 9.41.

A 60-mg sample of the keto ester 7a was stirred for 140 h with 1.3 g of potassium acetate in 30 mL of 95% ethanol.[14] Conventional workup provided material that was indistinguishable from the starting material by IR, NMR, and TLC comparison.

(±)-15-Dehydro-11-deoxy-PGE$_1$, Ethyl Ester (8a). A 2.49-g (7.93 mmol) sample of acetal 7a and 195 mg of *p*-toluenesulfonic acid in 195 mL of acetone were stirred under argon for 67 h. Solid sodium bicarbonate was then added, and the resulting mixture was partitioned between ether and water. The product was isolated with ether in the usual manner to yield 2.16 g of crude aldehyde 7b:[20] ^1H NMR ($CDCl_3$) δ 9.75 (d, J = 2 Hz, 1 H), 4.05 (q, J = 7 Hz, 2 H), 1.20 (t, J = 7 Hz, 3 H); IR (film) 2720, 1730 cm^{-1}.

The above crude aldehyde in 35 mL of dry dimethoxyethane (DME) was added rapidly to a stirred mixture at −25 °C of phosphonate salt[15,16] in DME [from the addition of 1.92 g (8.65 mmol) of dimethyl (2-oxoheptyl)phosphonate in 60 mL of DME to 350 mg of sodium hydride dispersion (55–60%, ca. 8.4 mmol) in 50 mL of DME, under argon at room temperature, with subsequent stirring for 1 h]. After 2 h at −25 °C, 0.5 h at 0 °C, and 1.5 h at room temperature, the mixture was treated with 0.2 mL of acetic acid. The solution was then concentrated, and the product was isolated by dry silica gel chromatography using methylene chloride to afford 1.86 g (64%) of the oily enedione 8a: ^1H NMR ($CDCl_3$) δ 6.68 (dd, J = 7.5, 15 Hz, 1 H), 6.02 (d, J = 15 Hz, 1 H), 4.02 (q, J = 7 Hz, 2 H), 1.23 (t, J = 7 Hz, 3 H), 0.88 (t, J = 7 Hz, 3 H); IR (film) 1735, 1695, 1670, 1625, 1180 cm^{-1}.

Anal. Calcd for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.22; H, 9.97.

(±)-8-Carbomethoxy-15-dehydro-11-deoxy-PGE$_1$, Ethyl Ester (11a). A 2.25-g (6.0 mmol) sample of acetal 6 and 4.4 g of Amberlite H^+ IR-120 in 300 mL of acetone were stirred under argon for 48 h. After filtration of the mixture, solvent evaporation under reduced pressure afforded 2.01 g of crude aldehyde 10: ^1H

(47) Doering, W. von E.; Knox, L. H. *J. Am. Chem. Soc.* **1951**, *73*, 828.
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NMR ($CDCl_3$) δ 9.60 (d, J = 2 Hz, 1 H), 4.05 (q, J = 6.5 Hz, 2 H), 3.55 (s, 3 H), 2.4–2.2 (m, 4 H), 1.20 (t, J = 6.5 Hz, 3 H); IR (film) 2760, 1740, 1730 cm^{-1}.

The above crude aldehyde in 23 mL of dry DME was added rapidly to a stirred mixture at −78 °C of phosphonate salt[15,16] in DME [from the addition of 1.76 g (7.92 mmol) of dimethyl (2-oxoheptyl)phosphonate in 55 mL of DME to 0.330 g of sodium hydride dispersion (55–60%, ca. 7.6 mmol) in 35 mL of DME under argon at room temperature, with subsequent stirring for 1 h]. The mixture was stirred overnight at −25 °C, 1 h at 0 °C, and 1.5 h at room temperature, then 0.2 mL of acetic acid was added at −10 °C, and the resulting solution was stirred for 1 h. The solution was concentrated, and the product was isolated by dry silica gel chromatography using 5% ethyl acetate in methylene chloride to afford 1.97 g (77%) of oily diketone **11a**: ^1H NMR ($CDCl_3$) δ 6.82 (dd, J = 7, 16 Hz, 1 H), 6.28 (d, J = 16 Hz, 1 H), 4.22 (q, J = 7 Hz, 2 H), 3.68 (s, 3 H), 1.18 (t, J = 7 Hz, 3 H), 0.95 (t, J = 7 Hz, 3 H); IR (film) 1745–1730, 1695, 1690, 1650, 1625 cm^{-1}; UV (C_2H_5OH) 224 nm (ε 12 100); mass spectrum, m/e 422 (M^+).

Anal. Calcd for $C_{24}H_{38}O_6$: C, 68.22; H, 9.07. Found: C, 67.81; H, 9.31.

(±)-8-Carbomethoxy-11-deoxy-PGE$_1$, Ethyl Ester (11c). To a stirred solution of 420 mg (1.0 mmol) of diketone **11a** in 6 mL of THF at −78 °C under argon was added 2.01 mL (1.0 mmol) of a 0.5 M solution of L-Selectride[21] in THF. Following completion of the reaction (carefully monitored by TLC), 0.70 mL of 15% aqueous hydrogen peroxide and 0.73 mL of 1.58 M aqueous sodium hydroxide were simultaneously added dropwise. After being stirred for 2 h at room temperature, the reaction mixture was diluted with ether, and the organic phase was washed successively with 10% aqueous potassium carbonate, saturated aqueous sodium sulfite, and brine. After being dried over sodium sulfate, the solution was filtered and concentrated to give 415 mg of a mixture of allylic alcohols **11b** and **11c**. Separation of the mixture by silica gel chromatography using ethyl acetate–hexane gave, in order of elution,[19] 170 mg (40%) of 15β-isomer **11b**, 65 mg (15%) of a mixture of 15α and 15β isomers, and 165 mg (39%) of 15α-isomer **11c**: ^1H NMR ($CDCl_3$) δ 5.68–5.25 (m, 2 H), 4.12 (br q, J = 7 Hz, 3 H), 3.63 (s, 3 H), 1.22 (t, J = 7 Hz, 3 H), 0.95 (t, J = 6 Hz, 3 H); IR (film) 3450, 1745, 1735 cm^{-1}; mass spectrum, m/e 425 (M^+ + 1).

Anal. Calcd for $C_{24}H_{40}O_6$: C, 67.89; H, 9.50. Found: C, 67.63; H, 9.60.

The 15β-isomer **11b** could be quantitatively oxidized to diketone **11a** by using manganese dioxide in methylene chloride at room temperature.

(±)-11-Deoxy-PGE$_1$ (9) via (±)-11-Deoxy-PGE$_1$, Ethyl Ester (8c): From Enedione 8a. To a solution of 746 mg (2.05 mmol) of enedione **8a** in 20 mL of methanol containing a trace of bromophenol as indicator at −25 °C under argon was added 85 mg (1.35 mmol) of sodium cyanoborohydride.[17] Over the next 44 h, a total of 0.80 mL of 10% aqueous hydrochloric acid was added so as to maintain a yellow solution. The solution was then partitioned between ether and water. The organic phase was separated and washed with aqueous sodium bicarbonate, dried over potassium carbonate, filtered, and concentrated under reduced pressure to afford 744 mg of a crude mixture of alcohols **8b** and **8c**. The more polar[19] isomer, 11-deoxy-PGE$_1$, ethyl ester (**8c**), was separated by preparative TLC: ^1H NMR ($CDCl_3$) δ 5.7–5.4 (m, 2 H), 4.10 (br q, J = 7 Hz, 3 H), 1.22 (t, J = 7 Hz, 3 H), 0.92 (t, J = 6 Hz, 3 H); IR (film) 3430, 1735, 1175 cm^{-1}.

From Allylic Alcohol 11c. A solution of 140 mg (0.33 mmol) of alcohol **11c** and 35 mg (0.71 mmol) of sodium cyanide in 3.3 mL of dry hexamethylphosphoric triamide[13] was stirred for 1.5 h at 75–80 °C (bath temperature) and then overnight at room temperature. The reaction mixture was poured into hexane–10% aqueous hydrochloric acid (hood!), and the product was isolated with hexane in the usual manner to provide 105 mg (87%) of 11-deoxy-PGE$_1$, ethyl ester (**8c**), identical with that prepared above.

A 30-mg (0.08 mmol) sample of 11-deoxy PGE$_1$, ethyl ester (**8c**) and 200 mg of potassium carbonate were stirred overnight in 20 mL of 40% aqueous methanol. The usual product isolation yielded 26 mg (94%) of crystalline 11-deoxy-PGE$_1$ (**9**): mp 81–83 °C (ether–pentane) (lit.[20] mp 82.5–85 °C, 85–86 °C); ^1H NMR ($CDCl_3$) δ 6.40 (br s, 2 H), 5.65 (m, 2 H), 4.3–4.0 (br m, 1 H), 0.90 (t, J = 5 Hz, 3 H); IR (KBr) 3380, 1725, 1190, 1020, 980 cm^{-1}. This material was identical in all respects with an independently prepared sample kindly provided by Dr. W. Bartmann (Hoechst A. G.).

Anal. Calcd for $C_{20}H_{34}O_4$: C, 70.97; H, 10.13. Found: C, 71.22; H, 9.90.

PGA$_2$ (14b). To 0.66 mL (0.4 mmol) of a recently prepared 0.61 M LDA–THF solution at −78 °C under nitrogen was added dropwise a solution of 72 mg (0.16 mmol) of 11-deoxy-PGE$_2$ 15-*tert*-butyldimethylsilyl ether (**12b**), prepared conventionally,[39] in 3 mL of THF.[23] The reaction mixture was stirred at −78 °C for 15 min and then treated with 0.25 mL of a chlorotrimethylsilane (3 mL)–triethylamine (2 mL)–tetrahydrofuran (7 mL) solution.[26] After being stirred for 15 min, the reaction mixture was poured into pentane, and the product was isolated with pentane in the usual manner to furnish 90 mg of crude oily trimethylsilyl enol ether **13**, used directly in the following reaction; ^1H NMR ($CDCl_3$) δ 5.50 (m, 4 H), 4.50 (s, 1 H), 4.11 (br m, 1 H), 1.00 (s, 9 H), 0.37 (s), 0.15 (s); IR (film) 1720, 1640, 835, 780 cm^{-1}.

A 90-mg (ca. 0.15 mmol) sample of crude enol ether **13** partially dissolved in 3 mL of a 2:1 mixture of acetonitrile and hexane was treated with 37 mg (0.16 mmol) of palladium acetate in 2 mL of dry acetonitrile.[27] The reaction mixture was stirred for 30 min at −10 °C and then for 1 h at room temperature. After filtration of the mixture through a small pad of silicic acid, the solvents were removed in vacuo to afford 60 mg of an oil. Purification of this material over silica gel, using 20% ethyl acetate in hexane, provided 15 mg of **12b** and 37 mg (51% from **12b**) of pure PGA$_2$ 15-*tert*-butyldimethylsilyl ether **14a**, identical with an authentic sample prepared[39] from PGA$_2$ (**14b**) ^1H NMR ($CDCl_3$) δ 9.93 (br s, 1 H, exchanged with D_2O), 7.50 (dd, J = 2, 6 Hz, 1 H), 6.23 (dd, J = 2, 6 Hz, 1 H), 5.50 (m, 4 H), 4.11 (br m, 1 H), 3.30 (br m, 1 H), 1.00 (s, 9 H), 0.15 (s, 6 H); IR (film) 3600–2400, 1740, 1710, 1590, 835, 780 cm^{-1}; mass spectrum, m/e 448 (M^+).

A solution of 37 mg (0.08 mmol) of ether **14a** in 1 mL of AcOH–H_2O–THF (3:1:1) was kept at room temperature for 30 h. Isolation of the product afforded PGA$_2$ (**14b**), identical with an authentic sample from *Plexaura homomalla*.[24c,34]

(1*R,4*R**,5*R**)-7-Methoxy-4-methylbicyclo[3.2.0]hept-6-en-2-one (15).** A 2 M solution of methyllithium in ether (12 mL, 24 mmol) was added dropwise to a stirred suspension of 2.27 g (12 mmol) of finely divided cuprous iodide in 10 mL of dry ether at −10 °C under nitrogen. A 1.55-g (11.4 mmol) sample of enone **2** in 4 mL of ether was added to the resultant clear solution, and stirring was continued for 20 min. The reaction mixture was then poured into a saturated aqueous solution of ammonium chloride and stirred for 1 h, after which the reaction product was isolated with ether to afford 1.63 g of a mixture. Purification of the mixture by chromatography on Florisil with methylene chloride as the eluent gave 270 mg (16%) of the *endo*-methyl isomer and 1.25 g (72%) of the *exo*-methyl isomer **15**: ^1H NMR ($CDCl_3$) δ 4.79 (s, 1 H), 3.58 (s, 3 H), 1.17 (d, J = 6 Hz, 3 H); IR (film) 1735, 1630 cm^{-1}; mass spectrum, m/e 152 (M^+).

Methyl (1*R,2*S**,3*R**)-2-(Dimethoxymethyl)-3-methyl-5-oxocyclopentanecarboxylate (16).** A solution of 750 mg (4.9 mmol) of enol ether **15** in 12 mL of methylene chloride and 2.4 mL of methanol at −78 °C was treated with a stream of ozone-oxygen until the solution turned faintly blue. After elimination of the excess of ozone with argon, 0.84 mL of sulfur dioxide was distilled into the solution.[8] After 20 h at −30 °C, the solution was poured into a cold aqueous solution of potassium carbonate, and the reaction product was isolated with methylene chloride in the usual manner to give a mixture. Purification of the mixture by column chromatography on Florisil with ether–hexane gave 609 mg (54%) of the keto ester acetal **16**: ^1H NMR ($CDCl_3$) δ 4.35 (d, J = 5 Hz, 1 H), 3.73 (s, 3 H), 3.39 (s, 3 H), 3.36 (s, 3 H), 3.26 (d, J = 5 Hz, 1 H), 1.21 (d, J = 6 Hz, 3 H); IR (film) 1760, 1730, 1130, 1070 cm^{-1}; mass spectrum, m/e 230 (M^+). The corresponding diacetal (122 mg, 9%) was also isolated: ^1H NMR ($CDCl_3$) δ 4.46 (d, J = 7.5 Hz, 1 H), 3.70 (s, 3 H), 3.39 (s, 3 H), 3.27 (s, 9 H), 1.07 (d, J = 6 Hz, 3 H); IR (film) 1735, 1140, 1120, 1070, 1050 cm^{-1}.

Anal. Calcd for $C_{13}H_{24}O_6$: C, 56.50; H, 8.76. Found: C, 56.39; H, 8.42.

Alkylation of β-Keto Ester 16: With Ethyl 7-Iodo-5-heptynoate. A stirred solution of 590 mg (2.57 mmol) of keto ester

16 in 6 mL of dry Me_2SO was treated with 458 mg of a potassium hydride[11] dispersion in mineral oil (22.5%, 2.58 mmol) dropwise over 3 min under nitrogen. After 15 min, 2.16 g (7.74 mmol) of ethyl 7-iodo-5-heptynoate[30] was added rapidly, and the mixture was stirred overnight. The reaction mixture was then poured into water, and the product was isolated with ether in the usual manner and was purified by chromatography over Florisil with 70% ether in hexane to give 718 mg (73%) of a ca. 1:1 mixture of diesters **17**: ^1H NMR ($CDCl_3$) δ 4.75 and 4.45 (2d, J = 7.5 Hz and 5 Hz, 1 H), 4.13 (q, J = 7.5 Hz, 2 H), 3.70 and 3.65 (2s, 3 H), 3.38 and 3.33 (2s, 6 H), 2.80 (m, 2 H), 1.25 (t, J = 7.5 Hz, 3 H), 1.20 (d, J = 6 Hz, 3 H); IR (film) 1755, 1730, 1130, 1110, 1050 cm^{-1}; mass spectrum, m/e 382 (M^+).

Anal. Calcd for $C_{20}H_{30}O_7$: C, 62.81; H, 7.91. Found: C, 62.84; H, 7.90.

With Ethyl 7-Iodoheptanoate. A stirred solution of 330 mg (1.4 mmol) of keto ester **16** in 4 mL of Me_2SO was treated with 328 mg of a potassium hydride[11] dispersion in mineral oil (22.5% 1.8 mmol) dropwise over 3 min under argon. After 15 min, 800 mg (2.8 mmol) of ethyl 7-iodoheptanoate[12] was added rapidly and the mixture was stirred overnight. The reaction mixture was then poured into water, and the products were isolated with ether in the usual manner and were purified by chromatography on silica gel to give 60 mg (11%) of diester **23**: ^1H NMR ($CDCl_3$) δ 4.30 (d, J = 5 Hz, 1 H), 4.15 (q, J = 7.5 Hz, 2 H), 3.75 (s, 3 H), 3.38 (s, 3 H), 3.30 (s, 3 H), 1.27 (t, J = 7.5 Hz, 3 H), 1.20 (d, J = 6 Hz, 3 H); IR (film) 1755, 1730, 1130, 1110, 1050 cm^{-1}. Later fractions yielded 258 mg (47%) of enol ether **22**: ^1H NMR ($CDCl_3$) δ 4.33 (d, J = 4.5 Hz, 1 H), 4.11 (q, J = 7.5 Hz, 2 H), 3.69 (s, 3 H), 3.43 (s, 3 H), 3.34 (s, 3 H), 1.25 (t, J = 7.5 Hz, 3 H), 1.04 (d, J = 6.5 Hz, 3 H); IR (film) 1730, 1680, 1625, 1120, 1070, 1050 cm^{-1}; UV (CH_3OH) 256 nm (ϵ 8810).

Anal. Calcd for $C_{20}H_{34}O_7$: C, 62.15; H, 8.87. Found: C, 62.42; H, 8.51.

Ethyl 7-[(1*R,2*S**,3*R**)-2-(Dimethoxymethyl)-3-methyl-5-oxocyclopentyl]-5-heptynoate (18a).** A solution of 550 mg (1.4 mmol) of the diester **17** and 140 mg (2.9 mmol) of sodium cyanide in 14 mL of hexamethylphosphoric triamide[13] was stirred for 1.5 h at 75–80 °C (bath temperature) and then overnight at room temperature. The reaction mixture was poured into hexane–10% aqueous hydrochloric acid (hood!), and the product was isolated with hexane in the usual manner to provide 440 mg (94%) of oily monoester **18a**. An analytical sample was obtained by preparative TLC: ^1H NMR ($CDCl_3$) δ 4.4 (d, J = 5 Hz, 1 H), 4.13 (q, J = 7.5 Hz, 2 H), 3.43 (s, 6 H), 1.24 (t, J = 7.5 Hz, 3 H), 1.17 (d, J = 6 Hz, 3 H); IR (film) 1735, 1130, 1070, 1050 cm^{-1}; mass spectrum, m/e 324 (M^+).

Anal. Calcd for $C_{18}H_{28}O_5$: C, 66.64; H, 8.70. Found: C, 66.98; H, 8.54.

Ethyl (5*Z*)-7-[(1*R,2*S**,3*R**)-2-(dimethoxymethyl)-3-methyl-5-oxocyclopentyl]-5-heptenoate (18b).** A mixture of 300 mg (0.93 mmol) of acetylenic compound **18a** and 350 mg of Lindlar catalyst in 5 mL of acetone was stirred rapidly under hydrogen for 6 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure to give 292 mg (97%) of cis-olefin **18b**: ^1H NMR ($CDCl_3$) δ 5.66–5.0 (m, 2 H), 4.30 (d, J = 3 Hz, 1 H), 4.08 (q, J = 7.5 Hz, 2 H), 3.80 (s, 3 H), 3.41 (s, 3 H), 1.23 (t, J = 7.5 Hz, 3 H), 1.13 (d, J = 6 Hz, 3 H); IR (film) 1735, 1070 cm^{-1}; mass spectrum, m/e 326 (M^+).

(±)-11α-Methyl-15-dehydro-11-deoxy-PGE$_2$, Ethyl Ester (20a). A mixture of 292 mg (0.90 mmol) of olefin **18b** and 600 mg of Amberlite H^+ IR-120 (28–35 mesh) in 40 mL of anhydrous acetone was stirred under nitrogen at room temperature for 36 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure to afford 231 mg of crude aldehyde **19**: ^1H NMR ($CDCl_3$) δ 9.63 (s, 1 H), 5.56–5.0 (m, 2 H), 4.04 (q, J = 7.5 Hz, 2 H), 1.26 (t, J = 7.5 Hz, 3 H), 1.17 (d, J = 6 Hz, 3 H); IR (film) 2730, 1735 cm^{-1}.

A 156-mg sample of the above crude aldehyde in 25 mL of DME was added to a stirred mixture at −78 °C of phosphonate salt[15,16] in DME [from the addition of 134 mg (0.60 mmol) of dimethyl (2-oxoheptyl)phosphonate in 9.5 mL of DME to 26 mg of sodium hydride dispersion (55–60%, ca. 0.60 mmol) in 8 mL of DME under argon at room temperature, with subsequent stirring for 1 h]. The mixture was stirred for 2 h at −25 °C, 0.5 h at 0 °C, and 1.5 h at room temperature, and then 10 μL of acetic acid was added. The solution was concentrated, and the product was isolated by dry silica gel chromatography with methylene chloride to give 118 mg (52%) of oily diene dione **20a**: ^1H NMR ($CDCl_3$) δ 6.66 (dd, J = 8, 14 Hz, 1 H), 6.10 (d, J = 14 Hz, 1 H), 5.66–5.0 (m, 2 H), 4.08 (q, J = 7.5 Hz, 2 H), 1.22 (t, J = 7.5 Hz, 3 H), 1.21 (d, J = 6 Hz, 3 H), 0.88 (br t, 3 H); IR (film) 1740, 1700, 1675, 1630 cm^{-1}; UV (CH_3OH) 228 nm (ϵ 13 800); mass spectrum, m/e 376 (M^+).

(±)-11α-Methyl-11-deoxy-PGE$_2$, Ethyl Ester (20c). To a solution of 89 mg (0.23 mmol) of diene dione **20a** in 2 mL of methanol containing a trace of bromophenol as indicator at −25 °C was added 13 mg (0.21 mmol) of sodium cyanoborohydride.[17] During the next 36 h, the pH was maintained between 3–4.6 (yellow) by the addition of small amounts of 10% aqueous hydrochloric acid. At the end of this period, the solution was partitioned between water and ether. The organic phase was separated and washed with aqueous sodium bicarbonate and water, dried over sodium sulfate, filtered, and concentrated to give a mixture of products. Purification of the mixture by silica gel chromatography with ethyl acetate in hexane gave 39 mg (44%) of starting diene dione **20a**, 21 mg (23%) of alcohol **20b**, and finally 23 mg (26%) of alcohol **20c**: ^1H NMR ($CDCl_3$) δ 5.66–5.16 (m, 4 H), 4.10 (q, J = 7.5 Hz, 2 H), 1.24 (t, J = 7.5 Hz, 3 H), 1.18 (d, J = 6 Hz, 3 H), 0.88 (br t, 3 H); IR (film) 3460, 1735 cm^{-1}; mass spectrum, m/e 378 (M^+).

The alcohol **20b** could be converted to starting material **20a**: a 10-mg sample of alcohol **20b** and 200 mg of manganese dioxide in 3 mL of methylene chloride were stirred for 24 h. Filtration of the mixture and concentration of the filtrate under reduced pressure yielded 8 mg (80%) of diene dione **20a**, identical with that prepared above.

(±)-11α-Methyl-11-deoxy-PGE$_2$ (21). A 30-mg (0.08 mmol) sample of alcohol **20c** and 160 mg of potassium carbonate in 10 mL of 35% aqueous methanol were stirred for 22 h. The usual product isolation then afforded, after recrystallization, 25 mg (90%) of 11α-methyl-11-deoxy-PGE$_2$ (**21**): mp 59–61 °C (ether–pentane); ^1H NMR ($CDCl_3$) δ 5.83–5.33 (m, 4 H), 5.03 (m, 2 H), 4.23 (br m, 1 H), 1.13 (d, J = 6 Hz, 3 H), 0.95 (br t, 3 H), IR (Nujol) 3340, 1730 cm^{-1}. This material was identical in all respects, except for rotation and melting point, with a sample obtained from PGA_2 from *Plexaura homomalla*.[4c,34]

(1*R,4*R**,5*R**)-7-Methoxy-4-phenylbicyclo[3.2.0]hept-6-en-2-one (24).** A 2 M solution of phenyllithium in 7:3 benzene–ether (6.84 mL, 13.7 mmol) was added dropwise to a stirred suspension of 1.3 g (6.83 mmol) of finely divided cuprous iodide in 4 mL of dry ether at −10 °C under nitrogen. After the mixture was stirred for 15 min, 850 mg (6.3 mmol) of enone **2** was added in 3 mL of ether, and the mixture was then stirred for an additional 20 min. The mixture was poured into a saturated aqueous solution of ammonium chloride and stirred for 1 h, and the reaction product was isolated with ether in the usual manner and purified by chromatography on Florisil with 50% methylene chloride in hexane to afford 998 mg (75%) of the *exo*-phenyl isomer **24**: ^1H NMR ($CDCl_3$) δ 7.50–6.59 (m, 5 H), 3.90 (s, 1 H), 3.61 (s, 3 H); IR (film) 2840, 1730, 1630, 1600 cm^{-1}; mass spectrum, m/e 214 (M^+).

Methyl (1*R,2*S**,3*R**)-2-(Dimethoxymethyl)-3-phenyl-5-oxocyclopentanecarboxylate (25).** A solution of 800 mg (3.7 mmol) of enol ether **24** in 10 mL of methylene chloride and 1.75 mL of methanol at −78 °C was treated with a stream of ozone-oxygen until the solution turned slightly blue. After elimination of the excess ozone with argon, 0.66 mL of sulfur dioxide was distilled into the solution.[8] After 20 h at −20 °C, the solution was poured into a cold aqueous solution of potassium carbonate, and the product was isolated with methylene chloride in the usual manner to give 1.07 g (98%) of keto ester **25**: ^1H NMR ($CDCl_3$) δ 7.56–7.06 (m, 5 H), 4.13 (d, J = 4 Hz, 1 H), 3.76 (s, 3 H), 3.39 (s, 3 H), 3.17 (s, 3 H); IR (film) 2840, 1755, 1725, 1600, 1130, 1065 cm^{-1}; mass spectrum, m/e 261 ($M^+ - OCH_3$).

Ethyl 7-[(1*R,*S**,2*S**,3*R**)-1-Carbomethoxy-2-(dimethoxymethyl)-5-oxo-3-phenylcyclopentyl)-5-heptynoate (26).** A stirred solution of 1.00 g (3.4 mmol) of keto ester **25** in 10 mL of Me_2SO was treated dropwise under nitrogen with 600 mg of a potassium hydride[11] dispersion in mineral oil (22.5%, 3.4 mmol). After 15 min, 1.15 g (4.1 mmol) of ethyl 7-iodo-5-heptynoate[30] was added rapidly, and the mixture was stirred for 16 h. The

reaction mixture was then poured into water, and the product was isolated with ether in the usual manner and purified by chromatography over neutral alumina with 20% ether in hexane to provide 1.18 g (78%) of a mixture of diesters **26**. An analytical sample was obtained by preparative TLC: ^{1}H NMR ($CDCl_3$) δ 7.5–7.17 (m, 5 H), 4.40 and 4.25 (2d, J = 6 Hz and 4 Hz, 1 H), 4.13 (q, J = 7.5 Hz, 2 H), 3.70 (s, 3 H), 3.25, 3.20, 2.84, 2.77 (4s, 6 H), 1.23 (t, J = 7.5 Hz, 3 H); IR (film) 2840, 1760, 1735, 1600, 1110, 1080 cm^{-1}.

Anal. Calcd for $C_{25}H_{32}O_7$: C, 67.55; H, 7.26. Found: C, 67.45; H, 7.32.

Ethyl 7-[(1*R,2*S**,3*R**)-2-(Dimethoxymethyl)-5-oxo-3-phenylcyclopentyl]-5-heptynoate (27a).** A solution of 550 mg (1.24 mmol) of the diester **26** and 176 mg (3.6 mmol) of sodium cyanide in 18 mL of hexamethylphosphoric triamide[13] was stirred for 6 h at 75–80 °C (bath temperature) and then overnight at room temperature. The reaction mixture was poured into hexane–10% aqueous hydrochloric acid, and the product was isolated with hexane in the usual manner to afford 472 mg (99%) of oily monoester **27a**. An analytical sample was obtained by preparative TLC: ^{1}H NMR ($CDCl_3$) δ 7.50–7.17 (m, 5 H), 4.23 (d, J = 4 Hz, 1 H), 4.13 (q, J = 7.5 Hz, 2 H), 3.43 (s, 3 H), 3.21 (s, 3 H), 2.83–2.52 (m, 2 H), 1.23 (t, J = 7.5 Hz, 3 H); IR (film) 2840, 1730, 1600, 1130, 1065 cm^{-1}.

Anal. Calcd for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.52; H, 7.88.

Ethyl 7-[(1*R,2*S**,3*R**)-2-(Dimethoxymethyl)-5-oxo-3-phenylcyclopentyl]heptanoate (27b).** A mixture of 472 mg (1.22 mmol) of acetylenic compound **27a** and 100 mg of 10% palladium on carbon in 5 mL of ethyl acetate was stirred under hydrogen for 16 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure to give 470 mg (99%) of keto ester **27b**: ^{1}H NMR ($CDCl_3$) δ 7.50–7.17 (m, 5 H), 4.23 (d, J = 4 Hz, 1 H), 4.13 (q, J = 7.5 Hz, 2 H), 3.43 (s, 3 H), 3.21 (s, 3 H), 1.23 (t, J = 7.5 Hz, 3 H); IR (film) 2840, 1735, 1600, 1130, 1075 cm^{-1}; mass spectrum, m/e 390 (M^+).

(±)-11α-Phenyl-15-dehydro-11-deoxy-PGE$_1$, Ethyl Ester (29a). A mixture of 450 mg (1.15 mmol) of keto ester **27b** and 3.6 g of Amberlite H^+ IR 120 (28–35 mesh) in 230 mL of dry acetone was stirred under nitrogen at room temperature for 80 h. The mixture was then filtered, and the filtrate was concentrated under reduced pressure to afford 377 mg of crude aldehyde **28**: ^{1}H NMR ($CDCl_3$) δ 9.75 (d, J = 3 Hz, 1 H), 7.50–7.17 (m, 5 H), 4.13 (q, J = 7.5 Hz, 2 H), 1.23 (t, J = 7.5 Hz, 3 H); IR 2720, 1730, 1600 cm^{-1}.

A 344-mg sample of the above crude aldehyde in 7 mL of DME was added rapidly to a stirred mixture at −78 °C of phosphonate salt[15,16] in DME [from the addition of 222 mg (1.0 mmol) of dimethyl (2-oxoheptyl)phosphonate in 21 mL of DME to 40 mg of sodium hydride dispersion (55–60%, ca. 1.0 mmol) in 12 mL of DME under argon at room temperature, with subsequent stirring for 1 h]. The mixture was stirred for 16 h at −20 °C and 1.5 h at room temperature, and then 0.10 mL of acetic acid was added. The solution was concentrated, and the product was isolated by dry silica gel chromatography using methylene chloride as the eluent to give 375 mg (81%) of oily enedione **29a**: ^{1}H NMR ($CDCl_3$) δ 7.5–7.17 (m, 5 H), 6.58 (dd, J = 8, 16 Hz, 1 H), 5.92 (d, J = 16 Hz, 1 H), 4.14 (q, J = 7.5 Hz, 2 H), 1.23 (t, J = 7.5 Hz, 3 H), 0.86 (t, J = 7 Hz, 3 H); IR (film) 1730, 1690, 1675, 1630 cm^{-1}; UV (CH_3CN) 210 nm (ϵ 28 200), 228 (ϵ 22 100). This material was identical in all respects, except for rotation, with a sample prepared from PGA_2 from *Plexaura homomalla*.[4c,34,35]

Anal. Calcd for $C_{28}H_{40}O_4$: C, 76.32; H, 9.15. Found: C, 76.16; H, 9.15.

(±)-11α-Phenyl-11-deoxy-PGE$_1$, Ethyl Ester (29c) and C-15 Epimer 29b. To a solution of 332 mg (0.75 mmol) of enedione **29a** in 11 mL of methanol containing a trace of bromophenol as indicator at −40 °C was added 50 mg (0.79 mmol) of sodium cyanoborohydride.[17] During the next 48 h the temperature was maintained at −18 °C and the pH between 3–4.6 (yellow) by the addition of small amounts of 10% aqueous hydrochloric acid. At the end of this period, the solution was partitioned between water and ether. The organic phase was separated and washed with aqueous sodium bicarbonate and water, dried over sodium sulfate, filtered, and concentrated to give an oil. Purification of this oil by silica gel chromatography using ethyl acetate–hexane afforded 103 mg (31%) of starting enedione **29a**, followed by 172 mg (52%) of an inseparable ca. 1:2 mixture of C-15 alcohols **29b,c**, respectively (see text): ^{1}H NMR (CCl_4) δ 7.5–7.0 (m, 5 H), 5.66–5.26 (m, 2 H), 4.07 (br q, J = 7.5 Hz, 3 H), 1.22 (t, J = 7.5 Hz, 3 H), 0.86 (t, J = 7 Hz, 3 H); IR (film) 3440, 1735 cm^{-1}. This mixture was identical in all respects, except for rotation, with a mixture prepared from PGA_2 from *Plexaura homomalla*.[4c,34,35]

(±)-11α-Phenyl-11-deoxy-PGE$_1$ (30b) and C-15 Epimer 30a. An 85-mg (0.19 mmol) sample of alcohols **29b,c** and 480 mg of potassium carbonate in 10 mL of 35% aqueous methanol were stirred for 14 h at room temperature. The usual product isolation then afforded 71 mg (89%) of a semicrystalline ca. 1:2 mixture of hydroxy acids **30a,b**, respectively: ^{1}H NMR (CCl_4) δ 7.5–7.0 (m, 5 H), 5.66–5.06 (m, 2 H), 3.96 (m, 1 H), 0.83 (br t, 3 H); IR (Nujol) 3300, 1730, 1600 cm^{-1}.

(1*R,4*R***S**,5*R**)-4-Butyl-7-methoxy-4-methylbicyclo[3.2.0]hept-6-en-2-one (33).** A 1.5 M solution of *n*-butyllithium in hexane (1.61 mL, 2.42 mmol) was added dropwise to a stirred suspension of 229 mg (1.20 mmol) of finely divided cuprous iodide in 1.5 mL of dry ether at −35 °C under argon. The mixture was stirred for 15 min, and then 168 mg (1.12 mmol) of enone **32**, prepared in 70% yield from enone **2**,[38a] was added in 2 mL of ether. After being stirred for an additional 15 min, the mixture was allowed to warm to −10 °C and was then poured into a saturated aqueous solution of ammonium chloride and stirred for 0.5 h. The reaction product was isolated with ether in the usual manner and purified by preparative TLC to give 187 mg (80%) of ketone **33** as a ca. 4:1 mixture of isomers: ^{1}H NMR (CCl_4) δ 4.78 (s, 1 H), 3.59 (s, 3 H), 1.18 and 1.08 (2s, 3 H), 0.89 (t, J = 6 Hz, 3 H); IR (film) 1740, 1635 cm^{-1}.

Methyl (1*R,2*R**,3*R**,5*S**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-(dimethoxymethyl)-5-hydroxycyclopentanecarboxylate (36b).** Because of the relative instability of the intermediates, alcohol **36b** was best prepared with only a final purification. To a well-stirred solution of 1.35 g (9.92 mmol) of enone **2** in 77 mL of methanol at −25 °C was added 5.4 mL (53 mmol) of 30% hydrogen peroxide followed by dropwise addition of 0.73 mL (0.73 mmol) of 1 N aqueous potassium hydroxide.[24b,c,38c] After being stirred for 0.5 h, the reaction mixture was poured into 35 mL of saturated aqueous ammonium chloride. After partial elimination of methanol under reduced pressure, the product was isolated with methylene chloride in the usual manner to give 1.35 g (89%) of oily epoxy ketone **34**: ^{1}H NMR ($CDCl_3$) δ 4.74 (s, 1 H), 3.88 (m, 1 H), 3.63 (s, 3 H), 3.39 (m, 2 H), 3.20 (m, 1 H); IR (film) 1740, 1630, 840, cm^{-1}; mass spectrum, m/e 152 (M^+).

A solution of 1.35 g (8.88 mmol) of epoxy ketone **34** in 168 mL of EtOH–H_2O–THF–sat aq $NaHCO_3$ (87:48:30:3) at 0 °C was treated with aluminum amalgam. (The aluminum amalgam was prepared[24c] by addition of 15 g of aluminum (0.555 g atom, 25 mesh) to a solution of 15 g (55 mmol) of mercuric chloride in 300 mL of water. The mixture was heated at 40 °C until a violent generation of hydrogen occurred (ca. 15 s) and was then filtered and washed twice with 15 mL of methanol and twice with 15 mL of ether. The aluminum amalgam was kept under ether until used.) After 3 h, the reaction mixture was filtered, and the solid material was washed three times with 100 mL of ethyl acetate. After the addition of powdered NaCl to the filtrate, the product was isolated with ethyl acetate to provide 1.35 g (99%) of hydroxy ketone **35a**, used directly in the following reaction; ^{1}H NMR ($CDCl_3$) δ 4.74 (s, 1 H), 4.23 (d, J = 6 Hz, 1 H), 3.63 (s, 3 H), 3.28 (br m, 1 H), 3.15–2.82 (br m, 3 H), 2.07 (d, J = 16 Hz, 1 H); IR (film) 3440, 1740, 1630 cm^{-1}.

A solution of 1.6 g (10.6 mmol) of *tert*-butyldimethylsilyl chloride and 1.45 g (21.3 mmol) of imidazole in 11 mL of dimethylformamide was added to 1.35 g (8.77 mmol) of hydroxy ketone **35a** in 7 mL of dimethylformamide under nitrogen at room temperature.[39] The mixture was stirred for 0.5 h and then poured into a saturated aqueous solution of ammonium chloride–pentane at 0 °C. After being stirred for 5 min, the product was isolated with pentane to yield 2.3 g (98%) of silyl ether **35b**: ^{1}H NMR ($CDCl_3$) δ 4.74 (s, 1 H), 4.14 (d, J = 5 Hz, 1 H), 3.63 (s, 3 H), 3.25 (br m, 1 H), 3.04–2.74 (br m, 2 H), 1.96 (d, J = 16 Hz, 1 H), 0.99 (s, 9 H), 0.17 (s, 6 H); IR (film) 1740, 1630, 835, 780 cm^{-1}.

A stream of ozone in oxygen was passed through a solution of 2.30 g (8.58 mmol) of silyl ether **35b** in 120 mL of methylene chloride and 15 mL of methanol at −78 °C until the solution

became faintly blue (ca. 45 min). After elimination of excess ozone with nitrogen, 4 mL of sulfur dioxide[8] was distilled into the solution. After 2 h at −20 °C, the reaction mixture was poured into ether. The ethereal solution was washed with 5% aqueous sodium bicarbonate, and the product was isolated in the usual manner to give 2.33 g of crude keto ester **36a**, used as such for the next reaction: ^{1}H NMR ($CDCl_3$) δ 4.73–4.19 (m, 2 H), 3.79 (s, 3 H), 3.49 (s, 3 H), 3.42 (s, 3 H), 3.70–2.86 (br m), 2.59 (t, J = 9 Hz, 2 H), 0.99 (s, 9 H), 0.15 (s, 6 H); IR (film) 1760, 1735, 1665, 1625, 1250, 835, 780 cm^{-1}.

A 2.33-g (ca. 6.73 mmol) sample of keto ester **36a** in 75 mL of methanol at −78 °C under nitrogen was treated with 430 mg (19.5 mmol) of lithium borohydride. After being stirred for 15 min, the reaction mixture was treated with 24 mL of a 4 M NaH_2PO_4 solution followed by 48 mL of water. The product was then isolated with a 1:1 mixture of ether–pentane in the usual fashion and was purified by chromatography over silica gel with 20% ethyl acetate in hexane to provide 1.05 g (30% yield from **2**) of pure alcohol **36b**: ^{1}H NMR ($CDCl_3$) (250 MHz) δ 4.30 (br m, 2 H), 4.07 (d, J = 4 Hz, 1 H), 3.73 (s, 3 H), 3.36 (s, 6 H), 3.26–2.64 (m, 3 H), 1.87–1.77 (br m, 2 H), 0.99 (s, 9 H), 0.21 (s, 3 H), 0.15 (s, 3 H); IR (film) 3450, 1735, 1250, 835, 780 cm^{-1}; mass spectrum, m/e 285 (M^+ − MeOH − MeO).

Anal. Calcd for $C_{14}H_{25}O_4Si$: mol wt 285.1522. Found: mol wt (mass spectrum) 285.1532 (M^+ − MeOH − MeO).

A small sample of alcohol **36b** was acetylated with acetic anhydride in pyridine under the usual conditions to afford the corresponding acetate: ^{1}H NMR ($CDCl_3$) δ 5.17 (br m, 1 H), 4.20 (br s, 2 H), 3.65 (s, 3 H), 3.36 (s, 3 H), 3.33 (s, 3 H), 2.90 (br m, 2 H), 2.00 (br s, 5 H), 0.99 (s, 9 H), 0.21 (s, 3 H), 0.15 (s, 3 H); IR (film) 1735, 1300, 1230, 835, 780 cm^{-1}.

Anal. Calcd for $C_{14}H_{25}O_7Si$: mol wt 333.1369. Found: mol wt (mass spectrum) 333.1383 (M^+ − C_4H_9).

Methyl (5*Z*)-7-[(1*R,2*R**,3*R**,5*S**)-3-[(*tert*-Butyldimethylsilyl)oxy]-2-(dimethoxymethyl)-5-hydroxycyclopentyl]-5-heptenoate (38a).** A solution of 46 mg (0.13 mmol) of alcohol **36b** in 1 mL of dry methylene chloride at 0 °C was treated with 60 μL (0.63 mmol) of 2-methoxypropene and 3 μL of $POCl_3$.[41] The mixture was stirred for 15 min at 0 °C and then 3 mL of pentane containing 3 drops of triethylamine was added. The usual workup afforded 55 mg (99%) of acetal **36c**: ^{1}H NMR ($CDCl_3$) δ 4.26 (m, 3 H), 3.67 (s, 3 H), 3.41 (s, 3 H), 3.31 (s, 3 H), 3.19 (s, 3 H), 2.88 (m, 2 H), 2.07 (br m, 2 H), 1.39 (s, 3 H), 1.32 (s, 3 H), 0.99 (s, 9 H), 0.17 (s, 3 H), 0.12 (s, 3 H); IR (film) 1735, 1380, 1250, 835, 780 cm^{-1}.

To a solution of 55 mg (0.13 mmol) of acetal **36c** in 2 mL of toluene at −70 °C was added 0.35 mL (0.42 mmol) of a 1.2 M solution of diisobutylaluminum hydride in toluene. After being stirred for 30 min, the reaction mixture was treated with 0.2 mL of methanol. Ether (15 mL) was added and the reaction mixture was allowed to warm to room temperature after which a sodium and potassium tartrate solution (0.6 M, 0.2 mL) was added, and the resultant mixture was stirred for 30 min. Isolation of the product with ether furnished 50 mg (98%) of alcohol **37a**: ^{1}H NMR ($CDCl_3$) δ 4.26 (br d, 3 H), 3.97–3.60 (br m, 2 H), 3.44 (s, 3 H), 3.41 (s, 3 H), 3.23 (s, 3 H), 1.43 (s, 6 H), 0.99 (s, 9 H), 0.15 (s, 3 H); IR (film) 3500, 1380, 835, 780 cm^{-1}.

A solution of Collins reagent, prepared in situ[42] from 0.20 mL of dry pyridine, 3.6 mL of dry methylene chloride, and 124 mg of chromium trioxide, was added to a stirred solution of 50 mg (0.13 mmol) of alcohol **37a** in 1.4 mL of dry methylene chloride. After 30 min, the mixture was diluted with 15 mL of a 1:1 ether–pentane mixture and after an additional 30 min was filtered through cotton with the aid of additional ether–pentane. The filtrate was washed with 5% sodium hydroxide, water, and brine, dried, and then concentrated to provide 46 mg (92%) of aldehyde **37b**: ^{1}H NMR ($CDCl_3$) δ 9.59 (d, J = 3 Hz, 1 H), 4.63–3.63 (br m, 3 H), 3.33 (s, 3 H), 3.29 (s, 3 H), 3.16 (s, 3 H), 2.85 (br m, 1 H), 2.54–1.62 (m, 3 H), 1.37 (s, 6 H), 0.99 (s, 9 H), 0.15 (s, 3 H); IR (film) 2740, 1720, 1380, 835, 780 cm^{-1}.

To a suspension of 210 mg (0.61 mmol) of (methoxymethyl)triphenylphosphonium chloride (dried for 3 h at 60 °C at 1 torr) in 2.6 mL of dry THF at −10 °C was added dropwise 0.65 mL (0.57 mmol) of a 0.88 M solution of lithium diisopropylamide in 1:1 THF–hexane. After being stirred at −10 °C for 30 min, the resultant deep red reaction mixture was treated with a solution of 46 mg (0.12 mmol) of aldehyde **37b** in 1 mL of dry toluene–THF (1:3.4). After 45 min the nearly colorless mixture was poured onto 10 g of ice, 20 mL of pentane was added, and the resultant mixture was then stirred for 15 min. Isolation of the product with pentane in the usual manner afforded an oily residue, which was triturated with pentane to separate the product from most of the phosphorus containing material. Filtration and evaporation of the pentane produced 79 mg of crude enol ether **37c**, which was used directly below: ^{1}H NMR ($CDCl_3$) δ 6.18 (d, J = 12 Hz, 1 H), 4.73 (m, 1 H), 4.14 (br d, J = 5 Hz, 3 H), 3.49 (s, 3 H), 3.32 (s, 6 H), 3.19 (s, 3 H), 1.37 (s, 6 H), 0.99 (s, 9 H), 0.15 (s, 6 H); IR (film) 1650, 1380, 835, 780 cm^{-1}.

The crude enol ether **37c** (79 mg) in 8 mL of 9:1 tetrahydrofuran–water was stirred with 242 mg (0.76 mmol) of mercuric acetate at room temperature for 20 min, after which at 0 °C 5 mL (5 mmol) of aqueous potassium iodide was slowly added.[43] After being stirred at room temperature for 30 min, the reaction mixture was extracted with pentane, which was washed with a 1 M potassium iodide solution, water, and brine. Isolation of the product in the usual fashion gave 45 mg of crude aldehyde **37d**: ^{1}H NMR ($CDCl_3$) δ 9.59 (br s, 1 H), 4.35–3.82 (br m, 3 H), 3.33 (s, 3 H), 3.29 (s, 3 H), 3.16 (s, 3 H), 2.62 (br m, 2 H), 1.37 (s, 6 H), 0.99 (s, 9 H), 0.15 (s, 6 H); IR (film) 2740, 1720, 1380, 835, 780 cm^{-1}.

To a solution of dimsylpotassium in Me_2SO [prepared under nitrogen from 245 mg of a potassium hydride dispersion in oil (24.4%, 1.49 mmol) and 1 mL of Me_2SO at room temperature for 1 h] was added 350 mg (0.79 mmol) of (4-carboxybutyl)triphenylphosphonium bromide (dried in vacuo for 3 h). The resultant deep red solution was treated with 45 mg (0.11 mmol) of aldehyde **37d** in 0.7 mL of 3:2 Me_2SO–DME. After being stirred for 3 h, the reaction mixture was poured into 10 mL of cold water, to which 20 mL of ethyl acetate and 0.6 mL of aqueous sodium hydrogen sulfate (to pH 2–3) were then added. Isolation of the product with ethyl acetate by the usual procedure afforded a brown residue, which was treated with excess diazomethane in ether and then, after evaporation of the ether, with 10 mL of a mixture of MeOH–H_2O–AcOH (20:2:1) for 30 min. Solvent removal yielded a viscous oil, which was purified by chromatography over silica gel with ethyl acetate in hexane to yield 18 mg (32% overall from alcohol **36b**) of pure ester **38a**: ^{1}H NMR ($CDCl_3$, 100 MHz) δ 5.45 (m, 2 H), 4.33 (br m, 1 H exchanged in D_2O), 4.08 (br d, J = 5 Hz, 3 H), 3.67 (s, 3 H), 3.39 (s, 3 H), 3.37 (s, 3 H), 0.88 (s, 9 H), 0.09 (s, 3 H); IR (film) 3520, 1735, 835, 780 cm^{-1}; mass spectrum, m/e 399 (M^+ − OCH_3).

Anal. Calcd for $C_{21}H_{39}O_5Si$: mol wt 399.2554. Found: mol wt (mass spectrum) 399.2554 (M^+ − OCH_3).

$PGF_{2\alpha}$ (41). An 18-mg (0.04 mmol) sample of alcohol **38a** was dissolved in 0.25 mL (3.1 mmol) of dry pyridine and 0.25 mL (2.6 mmol) of acetic anhydride was added. At the completion of the reaction (TLC), 2 mL of water was added, and the product was isolated with ether to yield 19 mg (96%) of acetate **38b**: ^{1}H NMR ($CDCl_3$, 100 MHz) δ 5.35 (d t, 2 H), 5.00 (m, 1 H), 4.19 (br d, J = 5 Hz, 2 H), 3.63 (s, 3 H), 3.34 (s, 6 H), 2.00 (s, 3 H), 0.85 (s, 9 H), 0.09 (s, 3 H), 0.06 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 174.0, 170.8, 129.4, 129.2, 107.0, 78.3, 77.1, 76.2, 75.8, 73.0, 55.4, 55.1, 54.8, 51.4, 43.6, 41.6, 33.6, 26.7, 25.8, 24.9, 21.3, 17.9, −4.6, −4.9; IR (film) 1735, 1250, 835, 780 cm^{-1}.

A mixture of 46 mg (0.10 mmol) of acetate **38b** and 40 mg of Amberlite H^+ IR 120 in 3 mL of dry acetone was stirred at room temperature under nitrogen for 36 h. The mixture was then filtered through cotton, and the filtrate was concentrated under reduced pressure. The residue was taken up in pentane, which was filtered and then evaporated under reduced pressure to afford 33 mg (79%) of aldehyde **39a**, used immediately below; IR (film) 2740, 1735, 1250, 835, 780 cm^{-1}.

To a stirred suspension of 7.5 mg of a sodium hydride dispersion in oil (55–60%, ca. 0.17 mmol) in 2.75 mL of dry DME under nitrogen was added 36 μL (0.17 mmol) of dimethyl (2-oxoheptyl)phosphonate.[15,16] After being stirred for 1 h at room temperature, the mixture was cooled to −10 °C and 33 mg (0.08 mmol) of aldehyde **39a** in 0.5 mL of dry DME was added. The mixture was stirred at −20 °C for 2 h and at 0 °C for 1 h. A saturated solution of aqueous ammonium chloride (1 mL) was then added, and the product was isolated with ether in the usual manner to give the crude enone. Purification of this material by

chromatography over silica gel with 10% ethyl acetate in hexane afforded 15 mg (37%) of enone **39b**: ^{1}H NMR ($CDCl_3$) δ 6.82–5.92 (m, 2 H), 5.45–4.89 (br m, 3 H), 3.96 (br m, 1 H), 3.68 (s, 3 H), 2.09 (s, 3 H), 0.88 (s, 9 H), 0.09 (s, 6 H); IR (film) 1735, 1670, 1630, 1250, 870, 735 cm^{-1}.

A 49-mg (0.09 mmol) sample of enone **39b** in 1 mL of methanol containing 34 mg (0.10 mmol) of $CeCl_3 \cdot 6H_2O$ was treated at room temperature with 3.6 mg (0.10 mmol) of sodium borohydride.[45] The reaction mixture was stirred at room temperature for 20 min, after which 6 drops of a saturated aqueous solution of ammonium chloride was added. The products were isolated with ethyl acetate in the usual manner to provide 49 mg (100%) of the C-15 epimeric alcohols **39c** and **39d**: ^{1}H NMR ($CDCl_3$) δ 5.42 (m, 4 H), 5.02 (br m, 1 H), 4.09 (br m, 1 H), 3.69 (s, 3 H), 0.88 (s, 9 H), 0.09 (s, 6 H), IR (film) 3500, 1735, 1250, 870, 735 cm^{-1}.

Treatment of the above 49-mg (0.09 mmol) sample of allylic alcohols **39c** and **39d** with 1 mL of acetic acid–water–THF (3:1:1) for 24 h at room temperature yielded on solvent evaporation a mixture of epimeric alcohols **40a** and **40b**. Separation of the mixture on silica gel with 2% methanol in methylene chloride afforded 10 mg of the less polar[19] 15β-isomer **40a**, 12 mg of the more polar[19] 15α-isomer **40b**, and 5 mg of a mixture of the α and β isomers (71% yield). α-Isomer **40b**: ^{1}H NMR ($CDCl_3$) δ 5.51–4.84 (br m, 5 H), 3.90 (br m, 2 H), 3.57 (s, 3 H), 2.00 (s, 3 H), 0.91 (br t, 3 H); IR (film) 3450, 1735, 1250 cm^{-1}. Treatment of the β-isomer **40a** (10 mg, 0.02 mmol) with 36 mg (0.4 mmol) of manganese dioxide in 0.5 mL of methylene chloride for 14 h generated the corresponding enone (8.5 mg).

A 6-mg (0.01 mmol) sample of diester **40b** was stirred at room temperature in 2.0 mL of 35% aqueous methanol containing 32 mg (0.23 mmol) of potassium carbonate. After 36 h, water was added, and the methanol was evaporated under reduced pressure. The aqueous solution was then acidified to pH 2–3 with cold 10% hydrochloric acid, and the product was isolated with ether in the usual manner to furnish quantitatively (5 mg) $PGF_{2\alpha}$ (**41**). This material was indistinguishable from an authentic sample of racemic $PGF_{2\alpha}$ that was kindly provided to us by Dr. J. Pike (The Upjohn Co.). The corresponding methyl ester, obtained by treatment of $PGF_{2\alpha}$ with diazomethane in ether and purified by filtration over silicic acid, was also identical in all respects with an authentic sample; ^{1}H NMR ($CDCl_3$) δ 5.48 (m, 4 H), 4.39–3.85 (br m, 2 H), 3.67 (s, 3 H), 0.90 (br t, 3 H); IR (film) 3300, 1735 cm^{-1}; mass spectrum, m/e 350 ($M^+ - H_2O$).

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Registry No. **1**, 2161-40-2; **2**, 59807-39-5; **3**, 81424-02-4; **4**, 57337-65-2; **4** dihydroxy derivative, 81424-03-5; **5**, 74787-11-4; **6**, 57337-67-4; **7a**, 57337-68-5; **7b**, 57337-69-6; **8a**, 57337-70-9; **8b**, 61045-36-1; **8c**, 57378-32-2; **9**, 34603-80-0; **10**, 81424-04-6; **11a**, 81424-05-7; **11b**, 81424-06-8; **11c**, 81424-07-9; **12b**, 81424-08-0; **13**, 81424-09-1; **14a**, 75758-61-1; **14b**, 37517-79-6; **14b***, 13345-50-1; **15**, 81424-10-4; **15** (*endo*-methyl isomer), 81446-07-3; **16**, 81446-08-4; **16** diacetal derivative, 81424-11-5; **17** (isomer 1), 81424-12-6; **17** (isomer 2), 81446-09-5; **18a**, 81424-13-7; **18b**, 81424-14-8; **19**, 81424-15-9; **20a**, 81424-16-0; **20b**, 81424-17-1; **20c**, 81424-18-2; **21**, 62777-52-0; **22**, 81424-19-3; **23**, 81424-20-6; **24**, 81424-21-7; **25**, 81424-22-8; **26** (isomer 1), 81424-23-9; **26** (isomer 2), 81446-10-8; **27a**, 81424-24-0; **27b**, 81424-25-1; **28**, 81424-26-2; **29a**, 81424-27-3; **29a***, 81424-28-4; **29b**, 81424-29-5; **29b***, 81424-30-8; **29c**, 81424-31-9; **29c***, 78407-39-3; **30a**, 81424-32-0; **30a***, 81424-33-1; **30b**, 81424-34-2; **30b***, 81424-35-3; **32**, 81424-36-4; **33** (4α-butyl isomer), 81424-37-5; **33** (4β-butyl isomer), 81446-11-9; **34**, 81424-38-6; **35a**, 81424-39-7; **35b**, 81424-40-0; **36a**, 81424-41-1; **36b**, 81424-42-2; **36b** acetate, 81424-43-3; **36c**, 81424-44-4; **37a**, 81424-45-5; **37b**, 81424-46-6; **37c**, 81424-47-7; **37d**, 81424-48-8; **38a**, 81424-49-9; **38b**, 81424-50-2; **39a**, 81424-51-3; **39b**, 81424-52-4; **39c**, 81424-53-5; **39d**, 81424-54-6; **40e**, 81424-55-7; **40b**, 81424-56-8; **41**, 23518-25-4; **41** methyl ester, 57794-75-9; **ia***, 31753-19-2; **ib***, 36677-05-1; **iia***, 81424-57-9; **iib***, 81424-58-0; ethyl 7-iodoheptanoate, 51100-70-0; ethyl 7-iodo-5-heptynoate, 81424-59-1; 2-methoxypropene, 116-11-0; (methoxymethyl)triphenylphosphonium chloride, 4009-98-7; (4-carboxybutyl)triphenylphosphonium bromide, 17814-85-6; dimethyl (2-oxoheptyl)phosphonate, 36969-89-8.

Preparation of Ring-Substituted (Arylsulfonyl)cyclopropanes and (Arylsulfonyl)bicyclobutanes from γ,δ-Epoxy Sulfones

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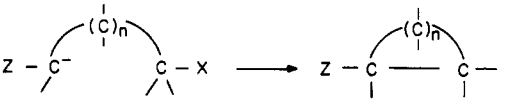
Treatment of γ,δ-epoxy sulfones **2** with *n*-butyllithium provides 1-(hydroxyalkyl)-2-(arylsulfonyl)cyclopropanes (**3**). Dehydration of the latter, when applicable, yields 1-alkenyl-2-(arylsulfonyl)cyclopropanes (**5**) which can be epoxidized and converted by a second base treatment into 2-(hydroxyalkyl)-1-(arylsulfonyl)bicyclo[1.1.0]butanes (**7**). An alternative route to bicyclobutanes consists of treating the epoxy sulfones **2** consecutively with *n*-butyllithium, methanesulfonyl chloride, and *n*-butyllithium. 1-(Arylsulfonyl)bicyclo[1.1.0]butanes (**9**), devoid of the hydroxyl groups in the side chain, are obtained in ca. 50% overall yield.

Intramolecular nucleophilic substitution at a remote center by a stabilized carbanion is a method that has been extensively utilized for carbocyclic ring formation. Halogens, sulfonate esters, and epoxidic oxygens have been most often used as the leaving group X (Scheme I), while the carbanion-stabilizing group Z could be a carbonyl, nitrile, ester, sulfone, or other electron-withdrawing group.[1,2]

Scheme I



When the leaving group X is an epoxidic oxygen, some ambiguity may result from the presence of two sites where displacement by the anion can occur.[2,3] The actual re-

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