Total Synthesis of Racemic 12-Methylprostaglandins

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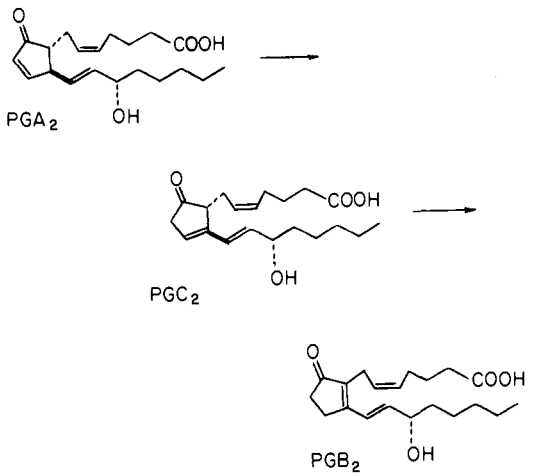
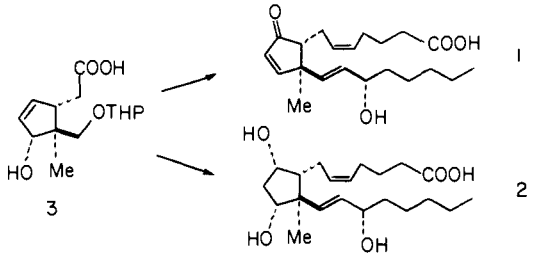
Abstract: A total synthesis of 12-methylprostaglandin A_2 (**1**) and 12-methylprostaglandin $F_{2\alpha}$ (**2**) starting from norbornadiene is reported. The preparation of the synthetic intermediate *anti*-7-methyl-2-bromo-5,5-ethylenedioxybicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (**7**) is described in detail as well as its conversion to sesquifenchene (**20**) which confirms the α orientation of the methyl group in the 12-methylprostaglandins.

Prostaglandins represent an intriguing class of highly active mammalian[3] hormones which may well be responsible for mediation of many physiological responses.[4] One of the problems with the natural prostaglandins is that they are rapidly metabolized (deactivated) in man. Some time ago Samuelsson[5] demonstrated that oxidation of the allylic C-15 alcohol followed by reduction of the $\Delta^{13,14}$ double bond constituted a rapid mode of deactivation. This problem has been dealt with by the Upjohn group through introduction of a methyl group at C-15.[6] In addition to oxidation at C-15, β-oxidation of the carboxyl side chain and ω-oxidation of the alkyl side chain represent further metabolic pathways.[5,7]

In the prostaglandin A series, an important mode of deactivation is the rapid transformation of prostaglandin A_2 to the more stable biologically inactive prostaglandin B_2 via prostaglandin C_2.[8] This rapid conversion of prostaglandin A_2 to



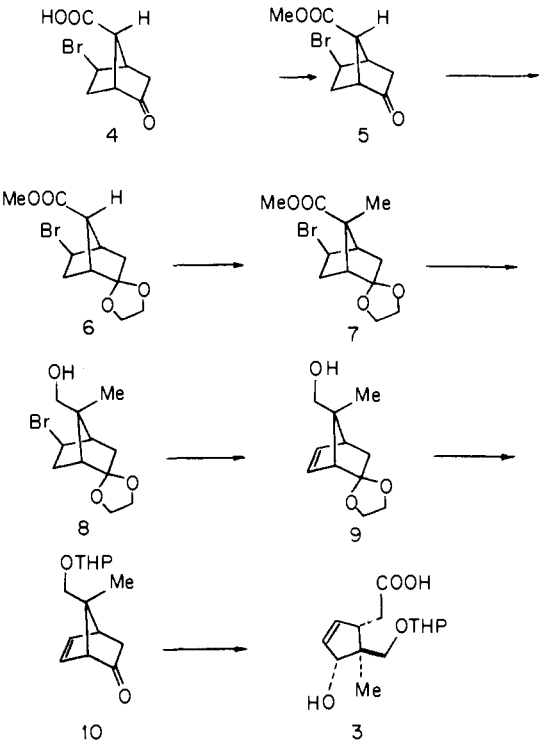
prostaglandin B_2 constitutes a well-known phenomenon for equilibration of cyclopentenone systems.[9] The introduction of a substituent (e.g., methyl group) at either C-8[10] or C-12 would inhibit this cyclopentenone rearrangement. Our attempts to block this mode of deactivation involved the introduction of a methyl group at C-12.[11] Over the past 2 years, extensive work has been carried out on 12-methylprostaglandins[11-13] as well as other C-12 substituted prostaglandins.[14-16] In addition to detailing below the total synthesis of 12-methylprostaglandin A_2 (**1**) we also report the synthesis of 12-methylprostaglandin



$F_{2\alpha}$ (**2**), which we set out to prepare in order to determine whether prostaglandins which bear a methyl group at C-12 possess significant biological activity while at the same time possessing fewer undesirable effects.

The development of the synthetic plan centered around the key intermediate hydroxy acid **3.** Compound **3** is similar to the intermediate employed by Corey et al. in their total synthesis of 12-methylprostaglandin A_2.[12] The synthesis of intermediate **3** which serves as the precursor to the C-12 methylprostaglandins in the A and F series is illustrated in Scheme I starting from the known bromo ketone **4.**[17]

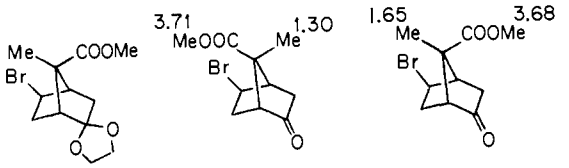
Scheme I



Esterification of keto acid **4** gave crystalline ester **5,** mp 92 °C. Ketalization of ester **5** employing 2-methyl-2-ethyl-1,3-dioxolane in benzene containing *p*-toluenesulfonic acid gave a 90% yield of crystalline bromoketal **6,** mp 74–75 °C. The intermediate ketal ester **6** represents a potentially useful intermediate for the preparation of a wide variety of C-12 substituted prostaglandins (e.g., 12-methylprostaglandin $F_{2\alpha}$,[11b] 12-fluoroprostaglandin $F_{2\alpha}$,[14] 12-hydroxymethylprostaglandin $F_{2\alpha}$,[16] and 12-hydroxyprostaglandin $F_{2\alpha}$[20]). A priori it was not obvious what stereoselectivity if any would accompany the methylation of the enolate derived from compound **6.** To our surprise alkylation of the ester **6** with methyl iodide (lithium

diisopropylamide/THF, −78 °C (1 h) → −40 °C (ca. 3 h)) resulted in a 78% yield after chromatography on silica gel of the bicyclo[2.2.1]heptane derivative **7,** mp 77–78 °C. We have observed under the reaction conditions formation of the corresponding methylated ester **11** in yields ranging from just a few percent to as high as 10%.

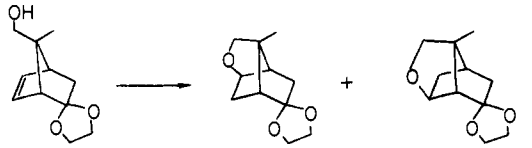
The initial assignment of stereochemistry was based on the following NMR data. The NMR spectrum of **7** in carbon tetrachloride exhibited methyl resonances at δ 1.48 and 3.62. The isomeric compound **11** included methyl resonances in the



11 12 13

NMR spectrum at δ 1.58 and 3.58. Deketalization of **7** afforded bromo ketone **12** whose C-7 methyl resonance moved upfield to δ 1.30 owing to shielding by the carbonyl. The bromo ketone **13** derived from **11** exhibited its C-7 methyl resonance at δ 1.65.

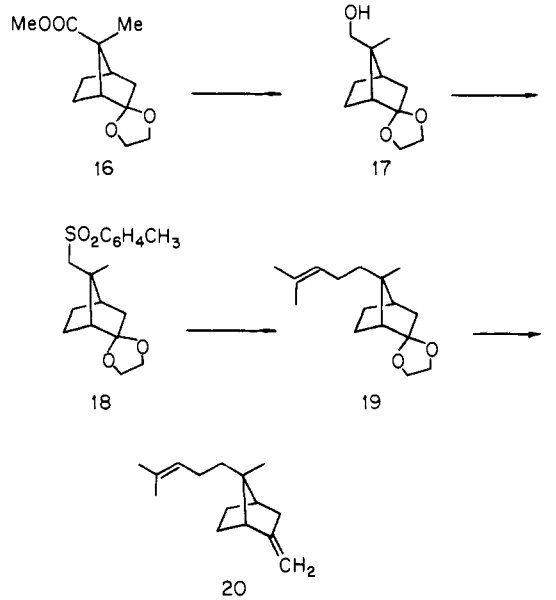
Additional evidence for our initial assignment was obtained by oxymercuration–demercuration[21] of hydroxy olefin **9** (vide infra). Treatment of compound **9** with mercuric acetate (1 equiv) in water/tetrahydrofuran (2:1) at 25 °C followed by sodium borohydride gave a 3:1 mixture of ethers **14** and **15.**



9 14 15

Confirmation of the structure assigned to compound **7** was eventually resolved by conversion of **7** to sesquifenchene (**20**) via the sequence of reactions outlined in Scheme II.[22] Treat-

Scheme II

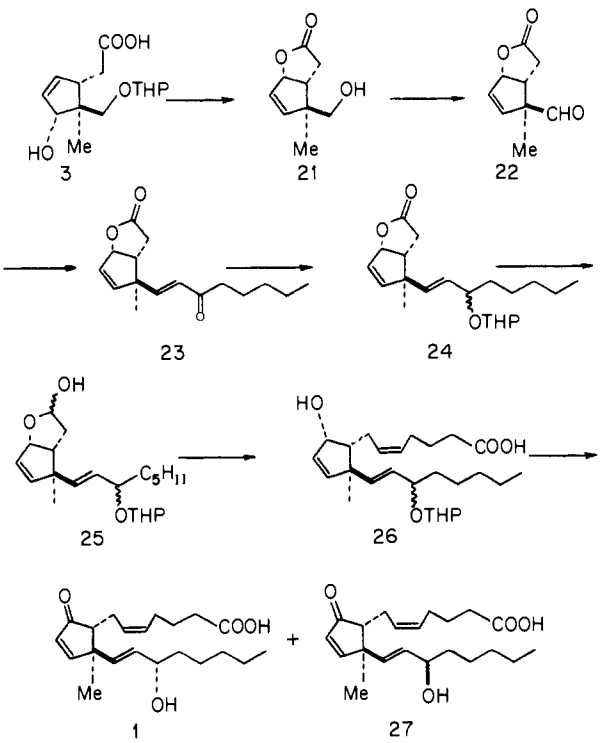


ment of **7** with tributyltin hydride[23] (1.5 equiv) in benzene containing azobisisobutyronitrile at 50–55 °C for 1.5 h resulted in a 94% isolated yield of pure ester **16** which was reduced ($LiAlH_4$/ether, 4.5 h) to alcohol **17.** Tosylation (*p*-toluenesulfonyl chloride (1 equiv)/pyridine, 0 °C) of alcohol **17** and exchange with iodide (sodium iodide (3 equiv)/acetone, reflux) produced a 78% overall yield of iodide which underwent sulfone formation in 77% yield upon treatment with 2 equiv of sodium *p*-toluenesulfinate in anhydrous DMF at 135–140 °C (15 h). Metalation of sulfone **18**[24] at −20 °C with *n*-butyllithium (1.3 equiv) in THF followed by cooling to −78 °C, addition of 1-bromo-3-methyl-2-butene (1.6 equiv), and gradual warming to 0 ° over 1.5 h resulted in formation of a new sulfone in near quantitative yield. NMR analysis of the coupled sulfone revealed lack of any new aliphatic methyl resonance, a consequence of coupling at the γ position, and no terminal vinyl resonance. The new sulfone was reduced ($Li/EtNH_2$, −78 °C, 30 min) and the product chromatographed (hexane/ether, 10:1) on silica gel to yield pure ketal **19** in 82% overall yield from sulfone **18.** Deketalization (acetic acid/water (3:7), 85 °C, 1.5 h) produced the desired ketone, which was methylenated with methylenetriphenylphosphorane in Me_2SO[25] affording sesquifenchene identical by NMR, IR, GLC, and TLC with a synthetic sample kindly provided by Professor Bessière-Chrétiene and Dr. C. Grison.[26]

Having established the stereochemical requirements about carbon atom C-7 in intermediate **7** we focused our attention on the transformation of the bicyclo[2.2.1]heptane derivative **7** to the key hydroxy carboxylic acid **3,** the common precursor to 12-methylprostaglandin A_2 (Scheme III) and 12-methylprostaglandin $F_{2\alpha}$ (Scheme IV). Reduction of ester **7** with lithium aluminum hydride gave bromide **8,** mp 93–94 °C, in near quantitative yield. Dehydrobromination with 1,5-diazabicyclo[5.4.0]undec-5-ene in refluxing benzene afforded **9** in 95% yield. Conversion of **9** to the ketone **10** was carried out via deketalization (30% glacial acetic acid, 90 °C, 2.5 h) and tetrahydropyranylation (dihydropyran/CH_2Cl_2/TsOH). Baeyer–Villiger oxidation of **10** employing hydrogen peroxide and sodium hydroxide in aqueous methanol under conditions reported by Weinshenker and Stephenson[27] gave the sensitive hydroxy acid **3** in 80% overall yield from **9.**

The conversion of hydroxy acid **3** to the required aldehyde **22** (Scheme III) was achieved by γ-lactone formation in the

Scheme III

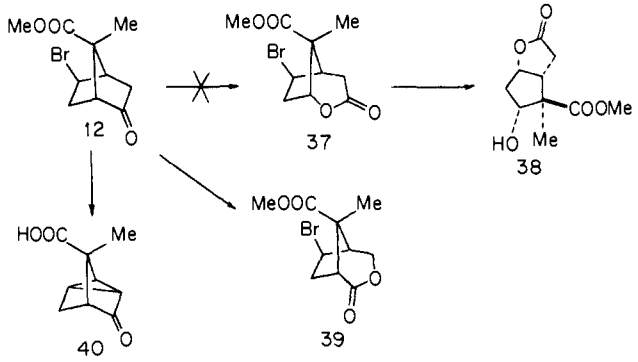


presence of a Lewis acid followed by acid-catalyzed cleavage of the tetrahydropyranyl ether in methanol. The overall yield for the conversion of **3** to **21** was 72%. Collins oxidation[28] of **21** gave the desired aldehyde **22** in 87% yield. Aldehyde **22** has

recently been prepared by an alternate route and converted to 12-methylprostaglandin A_2.[12] Treatment of aldehyde **22** with the sodio derivative of dimethyl (2-oxoheptyl)phosphonate[29] at elevated temperature provided enone **23** in 54% yield after chromatography.

Reduction of **23** under standard conditions (sodium borohydride, ethanol, −20 °C) gave in good yield a mixture of epimeric alcohols which was directly tetrahydropyranylated giving intermediate **24** as a diastereomeric mixture. Utilizing procedures outlined previously[30] compound **24** (epimeric mixture at C-15) was converted to a mixture of 12-methylprostaglandin A_2 (**1**) and 15-epi-12-methylprostaglandin A_2 (**27**), which were readily separated into chromatographically pure racemates (Scheme III) by preparative layer chromatography on silica gel plates (see Experimental Section). By analogy to the TLC behavior of natural and 15-epiprostaglandins reported by Anderson,[31] the more polar isomer has been assigned the natural 15*S* configuration.

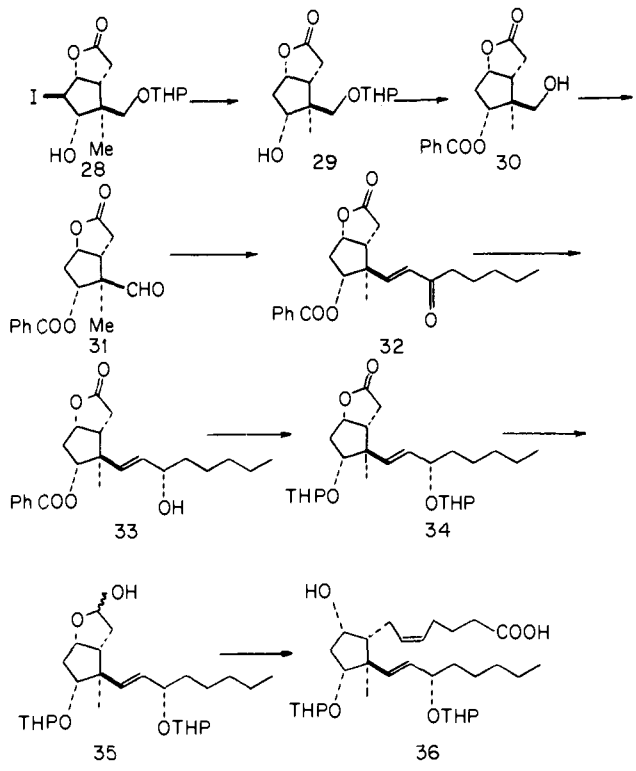
Although 12-methylprostaglandin $F_{2\alpha}$ (**2**) was prepared (vide infra) from hydroxy carboxylic acid **3** as shown in Schemes I and IV, our initial plan was to utilize the bicyclo[2.2.1]heptanone derivative **12** obtained from deketalization of compound **7**. It was anticipated that Baeyer–Villiger oxidation of ketone **12** would afford lactone **37** thus establishing the C-11 oxygen functionality. Hydrolysis of the lactone followed by displacement of the bromide by the carboxylate anion would establish the remaining center on the five-membered ring nucleus (cf. **37** → **38**). All attempts at



Baeyer–Villiger oxidation employing peracids resulted in very little, if any, of the derived lactone **37**. The product was the undesired lactone **39** which arises from migration of the "wrong" carbon atom. This result is in keeping with endo attack on the carbonyl by the peracid followed by migration of the wrong carbon atom via a chairlike transition state.[32] There is ample precedent that the relative ease of migration is not governed exclusively by the electronic distribution of the migrating group (cf. camphor).[33] Treatment of **12** with basic hydrogen peroxide led to cyclopropyl keto acid **40** (95%) with no lactone formation. The desired cleavage was achieved utilizing the bicyclo[2.2.1]heptenone **10** (vide supra). Under the conditions of basic hydrogen peroxide, cyclopropyl ketone formation is blocked and apparently the increased electronic preference for the desired cleavage predominates. Attempts with peracids on compound **10** were unsuccessful.

The conversion of hydroxy acid **3** to 12-methylprostaglandin $F_{2\alpha}$ is outlined in Scheme IV. Treatment of **3** with aqueous sodium hydroxide at 0 °C followed by neutralization with carbon dioxide and treatment with aqueous potassium triiodide solution produced the iodo lactone **28** (carbonyl absorption ($CHCl_3$) at 5.61 μ) in 82% yield. Deiodination using tributyltin hydride in benzene at 50 °C (initiation with azobisisobutyronitrile) produced the hydroxytetrahydropyranyl derivative **29** (95%) which was benzoylated using benzoyl chloride in pyridine and hydrolyzed (methanol/*p*-toluenesulfonic acid) in quantitative yield to alcohol **30**.

Scheme IV



Oxidation of **30** using Collins reagent in methylene chloride at 0 °C produced the stable aldehyde **31** in >90% yield. Condensation of aldehyde **31** with the sodio derivative of dimethyl 2-oxoheptylphosphonate in dimethoxyethane at 45 °C for 16 h afforded stereospecifically the trans enone lactone **32**. Treatment of the enone **32** with sodium borohydride in ethanol at −20 °C gave in near quantitative yield of mixture of the 15α-hydroxy lactone **33** and the 15β epimer (ratio ca. 1:1). The epimers were cleanly separated by preparative thin layer chromatography on 0.25 mm silica gel plates (two elutions with 15% methyl ethyl ketone in benzene) or by column chromatography. By analogy with the TLC behavior of similar natural prostaglandin intermediates (where *p*-phenylbenzoate in place of benzoate was used)[30,34] the less polar isomer has been tentatively assigned the natural 15*S* configuration. (±)-12-Methylprostaglandin $F_{2\alpha}$ (**2**) was obtained from intermediate **33** employing procedures outlined previously by Corey[30] (see Experimental Section).

Experimental Section

Melting points were determined on a Fisher-Johns hot stage melting point apparatus. All melting points and boiling points are uncorrected. Infrared (IR) spectra were determined on a Perkin-Elmer 247 grating infrared spectrometer and nuclear magnetic resonance (NMR) spectra were recorded at either 60 MHz (Varian A-60A or T-60 spectrometer) or at 250 MHz as indicated. Chemical shifts are reported in parts per million (δ) relative to Me_4Si (δ_{Me_4Si} 0.0 ppm) as an internal standard. Low-resolution mass spectra were recorded on an LKB-9000 spectrometer. High-resolution spectra were recorded on a Varian MAT CH-5DF instrument. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn.

Reactions were run under an atmosphere of nitrogen. "Dry" solvents were dried immediately before use. Tetrahydrofuran and dimethoxyethane were distilled from lithium aluminum hydride; dimethylformamide (DMF), hexamethylphosphoramide (HMPA), dimethyl sulfoxide (Me_2SO), and pyridine were distilled from calcium hydride. Diethyl ether and dioxane were distilled from sodium. Methylene chloride was passed through a column of alumina prior to use.

Thin layer chromatography (TLC) was conducted on Analtech (Uniplate) glass plates precoated with silica gel GF (250 μ). Prepar-

ative layer chromatography was carried out on Analtech silica gel GF (2 mm) glass plates.

Nortricyclan-3-one-*anti*-5-carboxylic Acid (iv). A mixture of 40.0 g (0.436 mol) of norbornadiene and 13.2 g (0.440 mol) of paraformaldehyde in 480 mL of formic acid (88%) was treated with 20 drops of concentrated sulfuric acid. After ca. 20 h at room temperature, the reaction was quenched by the addition of 200 mL of water. The reaction mixture was carefully neutralized with sodium carbonate. The product was isolated by extraction with ether. The combined ether extracts were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo, affording 79.9 g (93%) of crude diformate iii which was used directly in the next reaction.

A solution of the above crude diformate (55.3 g, 0.280 mol) in 900 mL of acetone was placed in a 2-L three-neck round-bottom flask equipped with a mechanical stirrer and addition funnel. The contents of the flask were cooled to 0 °C and treated dropwise over 1.5 h with 553 mL of standard Jones reagent. After addition was complete the reaction mixture was warmed to room temperature where stirring was continued for an additional 20 h. The reaction was quenched with 2-propanol to consume the excess Jones reagent. The acetone solution was decanted and evaporated leaving an oily residue which was dissolved in ethyl acetate. The chromium salts were dissolved in 50% brine solution and extracted exhaustively with ethyl acetate. The combined ethyl acetate phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure, affording 40.1 g of crude crystalline keto acid.

The crude crystalline material was washed with benzene providing 27.2 g (64%) of crystalline keto acid iv, mp 143–144 °C (lit.[16] 144–145 °C). An analytically pure sample, mp 144–145 °C, was obtained by recrystallization from benzene.

Anal. ($C_8H_8O_3$) C, H.

5-Oxo-*exo*-2-bromobicyclo[2.2.1]heptane-*syn*-7-carboxylic Acid Methyl Ester (5). A solution of 21.5 g (0.141 mmol) of keto acid iv in 225 mL of glacial acetic acid was treated at reflux for 3 h with 225 mL of 48% hydrobromic acid. Air was passed through the reaction mixture prior to evaporation of the solvent under reduced pressure. The residue was dissolved in ethyl acetate. The resulting solution was washed with brine, dried over magnesium sulfate, and concentrated in vacuo, leaving 28.1 g of crude bromo acid **4** which was directly esterified with an ether (500 mL) solution of diazomethane, prepared from 25 g of nitrosomethylurea. There was obtained 29.0 g (88% overall) of crystalline methyl ester **5**: mp 89–90 °C; IR ($CHCl_3$) 3010, 2950, 2910, 2845, 1755, 1730, 1445, 1435, 1406, 1368, 1312, 1290, 1268, 1241, 1208, 1180, 1160, 1141, 1125, 1118, 1042, 1025, 978, 950, 920, 900, 880, 820 cm^{-1}; NMR (CCl_4) δ 2.0–3.4 (m, 7 H), 3.66 (s, 3 H), 4.05 (m, 1 H). Recrystallization from ethanol gave analytically pure **5**, mp 92 °C.

Anal. ($C_9H_{11}BrO_3$) C, H.

***exo*-2-Bromo-5,5-ethylenedioxybicyclo[2.2.1]heptane-*syn*-7-carboxylic Acid Methyl Ester (6).** A solution of 16.1 g (6.5 mmol) of bromo keto ester **5** and 35.8 g (0.30 mol) of 2-methyl-2-ethyl-1,3-dioxolane in 150 mL of benzene containing 2.75 g of *p*-toluenesulfonic acid was stirred at room temperature for 20 h. The reaction mixture was washed with saturated sodium bicarbonate solution and brine, and dried over anhydrous sodium sulfate. Evaporation of the solvent under reduced pressure gave 19 g of crude crystalline material. Recrystallization from ethanol gave 17.0 g of pure ketal **6**: mp 74–75 °C; IR ($CHCl_3$) 3000, 2955, 2890, 1729, 1435, 1370, 1329, 1310, 1251, 1231, 1210, 1190, 1155, 1105, 1070, 1040, 1021, 995, 950, 910, 898, 842 cm^{-1}; NMR ($CDCl_3$) δ 1.52 (d, 1 H, J = 14 Hz), 2.01 (dd, 1 H, J = 14, 5.5 Hz), 2.48 (m, 3 H), 2.92 (m, 2 H), 3.70 (s, 3 H), 3.90 (m, 5 H).

Anal. ($C_{11}H_{15}BrO_4$) C, H.

***anti*-7-Methyl-*exo*-2-bromo-5,5-ethylenedioxybicyclo[2.2.1]heptane-7-carboxylic Acid Methyl Ester (7).** To a solution of lithium diisopropylamide, prepared from 600 mg (6.0 mmol) of diisopropylamine in 12 mL of freshly distilled THF and 3.85 ml of *n*-butyllithium (1.56 M in hexane) at −78 °C, was added a solution of 1.53 g (5.2 mmol) of the bromo ketal **6** in 12 mL of THF over 2 h. After an additional 30 min at −78 °C, 1.5 mL (24 mmol) of methyl iodide was added. The reaction mixture was stirred at −78 °C for 1 h, warmed to −40 °C over 1 h, and stirred at −40 °C for an additional 2 h. The reaction was quenched at −40 °C with 1 mL of water and warmed to room temperature, and the solvent was removed under reduced pressure. The oily residue was taken up with 20 mL of water and was extracted with 3 × 25 mL of ether. The combined ethereal extracts were washed with 25 mL of brine and dried over anhydrous magnesium sulfate. Filtration and evaporation of the solvent afforded 1.55 g (98%) of crude **7**. Purification on 80 g of silica gel (hexane/ether, 4:1) afforded 1.24 g (78%) of the desired bicyclo[2.2.1]heptane derivative **7** which was homogeneous on TLC (hexane/ether, 1:1; R_f 0.59). Recrystallization (ethanol) afforded an analytical sample: mp 77–78 °C; IR ($CHCl_3$) 2980, 2950, 2880, 2830, 1728, 1472, 1455, 1440, 1382, 1330, 1319, 1290, 1251, 1250, 1160, 1130, 1100, 1078, 1060, 1020, 998, 950, 910, 891, 860, 840 cm^{-1}; NMR (CCl_4) δ 1.48 (s, 3 H), 1.63 (d, 1 H, J = 14 Hz), 2.2–2.7 (m, 5 H), 3.62 (s, 3 H), 3.82 (m, 4 H), 4.02 (m, 1 H).

Anal. ($C_{14}H_{17}BrO_4$) C, H.

Continued elution with hexane/ether (4:1) provided 32 mg (2%) of the isomeric methylated ester (**11**): IR ($CHCl_3$) 2980, 2951, 2890, 1729, 1470, 1460, 1440, 1381, 1332, 1312, 1289, 1260, 1200, 1168, 1118, 1095, 1080, 1058, 1018, 980, 950, 922, 900, 860, 840 cm^{-1}; NMR (CCl_4) δ 1.39 (d, 1 H, J = 14 Hz), 1.58 (s, 3 H), 2.0–2.8 (m, 5 H), 3.58 (s, 3 H), 3.72 (m, 4 H), 3.90 (m, 1 H).

***syn*-7-Hydroxymethyl-*exo*-2-bromo-5,5-ethylenedioxy-7-methylbicyclo[2.2.1]heptane (8).** To a suspension of 249 mg (6.56 mmol) of lithium aluminum hydride in 16 mL of anhydrous ether was added a solution of 1.00 g (3.28 mmol) of ester **7** in 25 mL of anhydrous ether. The reaction mixture was heated to ca. 50 °C for 4 h after which time it was cooled and quenched with reagent grade ether. Evaporation of the solvent, after filtration to remove suspended matter, afforded 865 mg (95%) of the desired alcohol (IR (film) 3400 cm^{-1}; NMR (CCl_4) δ 1.30 (s, 3 H), 1.3–2.8 (m, 7 H), 3.5–4.2 (m, 7 H)) which was homogeneous on TLC (benzene/ether, 3:1; R_f 0.76) and used without further purification. Crystallization (hexane/ether) afforded an analytical sample, mp 93–94 °C.

Anal. ($C_{11}H_{17}BrO_3$) C, H.

***syn*-7-Methyl-2,2-ethylenedioxy-7-hydroxymethylbicyclo[2.2.1]-hept-5-ene (9).** A solution of 5.00 g (18.1 mmol) of bromide **8** and 26.2 g (172 mmol) of 1,5-diazabicyclo[5.4.0]undec-5-ene in 100 mL of benzene was refluxed (bath temperature, 105 °C) for 116 h. The reaction mixture was cooled and chromatographed on silica gel (benzene/ether, 3:1) to afford 3.00 g (84%) of olefin **9** which was homogeneous on TLC (benzene/ether, 1:1; R_f starting material 0.56, R_f product 0.36): IR (film) 3425, 3080, 2975, 2900, 1650, 1480, 1468, 1450, 1390, 1330, 1312, 1298, 1259, 1240, 1212, 1099, 1052, 1035, 958, 900, 865, 725 cm^{-1}; NMR (CCl_4) δ 1.20 (s, 3 H), 1.38 (d, 1 H, J = 12 Hz), 1.58 (s, 1 H, OH), 1.95–2.29 (m, 2 H), 2.40 (m, 1 H), 3.41 (s, 2 H), 3.75 (m, 4 H), 5.92 (m, 2 H).

Anal. ($C_{11}H_{16}O_3$) C, H.

***syn*-7-Methyl-7-tetrahydropyranyloxymethylbicyclo[2.2.1]hept-5-en-2-one (10).** To 3.61 g (18.4 mmol) of ketal **9** was added 188 mL of aqueous acetic acid (prepared from glacial acetic acid/water, 3:7 (v/v)). The reaction mixture was heated at 95 °C for 3 h after which time it was cooled to room temperature and neutralized with a cold solution of sodium hydroxide (32.8 g) in water (132 mL) followed by the addition of solid sodium carbonate. The product was isolated by ethyl acetate extraction (6 × 100 mL). The combined organic extracts were dried over anhydrous magnesium sulfate, filtered, and evaporated in vacuo, leaving 2.82 g (100%) (homogeneous on TLC (benzene/ethyl acetate, 1:1)) of keto alcohol (IR ($CHCl_3$) 3640, 3460, 1740 cm^{-1}; NMR (CCl_4) δ 1.14 (s, 3 H), 1.75 (d, 1 H, J = 16 Hz), 2.18 (dd, 1 H, J = 16, 3.5 Hz), 2.66 (m, 3 H), 3.60 (AB q, 2 H, J = 10 Hz), 5.85 (m, 1 H), 6.41 (m, 1 H)) which was used directly in the next reaction.

A solution of the above keto alcohol (2.80 g, 18.4 mmol) in 50 mL of dry methylene chloride containing *p*-toluenesulfonic acid (107 mg) was cooled to 0 °C and treated with 2.32 g of dihydropyran. After a total of 3 h at 0 °C, the reaction mixture was quenched with 2 mL of saturated sodium bicarbonate solution, diluted with 150 mL of ether, and washed with 50-mL portions of saturated sodium bicarbonate and brine. The organic phase was dried over anhydrous magnesium sulfate and filtered, and solvent was removed under reduced pressure to afford 5.06 g of crude **10**. Chromatography on 300 g of silica gel (benzene/ether, 12:1) afforded 4.20 g (97%) of the desired tetrahydropyranyl ether **10**, bp 65 °C (1.5 mm), which was homogeneous on TLC (benzene/ether, 4:1 two developments; R_f 0.72): IR ($CHCl_3$) 2935, 2862, 2848, 1739, 1465, 1450, 1440, 1420, 1380, 1360, 1351, 1340, 1320, 1311, 1300, 1280, 1270, 1260, 1200, 1180, 1171, 1155, 1131, 112, 1118, 1072, 1057, 1024, 995, 980, 930, 905, 880, 862, 840, 809 cm^{-1}; NMR (CCl_4) δ 1.20 (s, 3 H), 1.3–1.9 (m, 7 H), 2.18 (dd, 1 H, J = 16, 3 Hz), 2.75 (m, 2 H), 3.2–3.9 (m, 4 H), 4.43 (bs, 1 H), 5.99

(m, 1 H), 6.48 (m, 1 H).

Anal. ($C_{14}H_{20}O_3$) C, H.

Baeyer–Villiger Oxidation of Ketone 10. A solution of 588 mg (2.49 mmol) of ketone **10** in methanol (14 mL) containing water (12 mL) was cooled to 0 °C and treated with 3 mL of a 10% aqueous sodium hydroxide solution followed by 2.1 mL of 30% hydrogen peroxide. After ca. 30 h at 0–5 °C the reaction mixture was extracted with 2 × 20 mL of ether and acidified to pH 5.5 with concentrated hydrochloric acid, and the excess hydrogen peroxide was destroyed by the addition of solid sodium sulfite (2.0 g). After the pH was readjusted to ca. 5.5, the aqueous portion was extracted with 15 × 50 mL of ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was removed under reduced pressure to afford 599 mg (89%) of the desired hydroxy acid **3** which was used without further purification: IR (film) 3400–2300, 3050, 2940, 2870, 1720, 1375, 1260, 1200, 1130, 1120, 1030, 904, 865, 805 cm^{-1}; NMR ($CDCl_3$) δ 0.99 (s, 3 H), 4.57 (bs, 2 H), 5.80 (bs, 2 H); high-resolution mass spectrum *m/e* 270.1463 (calcd for $C_{14}H_{22}O_5$, *m/e* 270.1467).

5α-Hydroxy-2α-methyl-2β-(hydroxymethyl)cyclopent-3-ene-1α-acetic Acid γ-Lactone (21). A solution of 2.61 g (9.67 mmol) of hydroxyl carboxylic acid **3** in 120 mL of methylene chloride cooled to 0 °C was treated with 0.4 mL of boron trifluoride etherate. After 2 h at 0 °C, TLC analysis showed the absence of any of the hydroxy acid **3**. The reaction mixture was diluted with 80 mL of methylene chloride and washed with saturated brine solution. The methylene chloride fraction was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, giving 2.32 g of a mixture of the desired lactone **21** and 5α-hydroxy-2α-methyl-2β-(tetrahydropyranyloxymethyl)cyclopent-3-ene-1α-acetic acid γ-lactone which were used directly in the next reaction.

The above mixture was dissolved in 118 mL of methanol containing 1.0 g of *p*-toluenesulfonic acid cooled to 0 °C. After 5 h at 0 °C, TLC analysis (ether) indicated that the reaction had gone to completion. The reaction mixture was quenched by the addition of 7 mL of saturated sodium bicarbonate solution and concentrated under reduced pressure. The residue was dissolved in ethyl acetate and washed with water and saturated brine solution. The combined aqueous washes were backwashed with ethyl acetate. The combined ethyl acetate extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, affording 1.47 g of crude **21**. Chromatography on 90 g of silica gel (ether/hexanes, 9:1) afforded 1.47 g (72%) of the desired hydroxy lactone **21** which was homogeneous on TLC (ether; R_f 0.33). Distillation afforded an analytical sample: bp 95 °C (0.4 mm); IR ($CHCl_3$) 3625, 3500, 3002, 2960, 2925, 2875, 1765, 1602, 1465, 1360, 1335, 1172, 1042, 1020 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (s, 3 H), 2.4–2.7 (m, 2 H), 2.7–3.25 (m, 2 H), 3.4 (s, 2 H), 5.63 (d, 1 H), 5.86 (m, 2 H).

Anal. ($C_9H_{12}O_3$) C, H.

5α-Hydroxy-2α-methyl-2β-formylcyclopent-3-ene-1α-acetic Acid γ-Lactone (22). To a solution of dry pyridine (3.0 mL) and dry methylene chloride (34 mL) cooled to 0 °C was carefully added 1.88 g of chromium trioxide. After a total of 2 h at room temperature the Collins reagent was cooled to 0 °C and 526 mg (3.14 mmol) of 5α-hydroxy-2α-methyl-2β-(hydroxymethyl)cyclopent-3-ene-1α-acetic acid γ-lactone (**21**) in 4.6 mL of methylene chloride was added in one portion. After ca. 10 min the reaction mixture was quenched with 35 mL of dry benzene and filtered through Celite, followed by washing the filter pad with 4 × 100 mL of benzene. The filtrate was refiltered through Celite followed by removal of the solvent under reduced pressure. There was obtained 502 mg (96%) of the desired aldehyde **22** which was homogeneous by TLC analysis (ether, R_f 0.75) and used immediately in the next reaction.

5α-Hydroxy-2α-methyl-2β-(3-oxo-*trans*-1-octenyl)cyclopent-3-ene-1α-acetic Acid γ-Lactone (23). To a stirred suspension of 118 mg (2.44 mmol) of 50% sodium hydride dispersion (washed with hexane prior to use) in 21 mL of dimethoxyethane (freshly distilled from lithium aluminum hydride) cooled to 0 °C under nitrogen was added dropwise a solution of 516 mg (2.32 mmol) of dimethyl (2-oxoheptyl)phosphonate in 10 mL of dry dimethoxyethane. After addition was complete, the reaction mixture was warmed to 25 °C (1 h). The phosphonate anion was cooled to 0 °C and treated with a solution of 386 mg (2.32 mmol) of aldehyde **22** in 11 mL of dry dimethoxyethane. The resulting mixture was then warmed to 55 °C and stirred for 14 h. The reaction was quenched by the addition of water and the solvent was removed under reduced pressure leaving an oily residue which was dissolved in ethyl acetate. The organic phase was extracted with brine. The combined aqueous layers were backwashed with ethyl acetate. The combined organic washings were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude enone (557 mg) was chromatographed on 35 g of silica gel. Elution with ether/hexane (2:3) gave 326 mg (54%) of pure enone **23**. Distillation afforded an analytical sample: bp 87 °C (0.05 mm); IR ($CHCl_3$) 3000, 2955, 2925, 2875, 1772, 1695, 1670, 1622, 1460, 1360, 1210, 1172, 1030 cm^{-1}; NMR (CCl_4) δ 0.90 (bt, 3 H), 1.21 (s, 3 H), 1.05–1.80 (m, 6 H), 2.3–2.6 (m, 4 H), 2.8–3.1 (m, 1 H), 5.39 (d, 1 H), 5.88 (m, 2 H), 6.26 (AB q, 2 H, J, 16 Hz, $\Delta\nu$ = 43.1 Hz).

Anal. ($C_{16}H_{22}O_3$) C, H.

5α-Hydroxy-2α-methyl-2β-[(3*RS*)-3-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopent-3-ene-1α-acetic Acid γ-Lactone (24). To a suspension of 48 mg (1.27 mmol) of sodium borohydride in 5 mL of 95% ethanol cooled to −20 °C was added a solution of 296 mg (1.13 mmol) of 5α-hydroxy-2α-methyl-2β-(3-oxo-*trans*-1-octenyl)cyclopent-3-ene-1α-acetic acid γ-lactone (**23**) in 16 mL of 95% ethanol. After 3 h the reaction was quenched by the addition of 12 drops of glacial acetic acid and the solvent was removed under reduced pressure. The residue was diluted with 20 mL of water and extracted with 5 × 30 mL of ether. The combined ether extracts were dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo leaving 307 mg of alcohol which was used in the next reaction.

To a solution of the above alcohol in 12 mL of methylene chloride cooled to 0 °C were added 142 mg (1.69 mmol) of dihydropyran and 10 mg of *p*-toluenesulfonic acid. After 1.5 h at 0 °C, the reaction was quenched by the addition of pyridine (4 drops). The reaction mixture was diluted with 75 mL of ether and washed with 50 mL of saturated brine solution. The organic layer was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, providing 501 mg of crude product. Chromatography on 35 g of silica gel (elution with hexanes/ether, 3:1) afforded 357 mg (91%) of **24**: bp 70 °C (0.15 mm); IR ($CHCl_3$) 3000, 2930, 2870, 2850, 1765, 1465, 1358, 1335, 1170, 1125, 1109, 1073, 1020, 975 cm^{-1}; NMR ($CDCl_3$) δ 4.4–4.7 (m, 1 H), 5.3–5.6 (m, 2 H), 5.7–6.0 (m, 2 H).

Anal. ($C_{21}H_{32}O_4$) C, H.

12-Methylprostaglandin A_2 (1). To a solution of 168 mg (0.483 mmol) of lactone **24**, in 4.1 mL of dry toluene cooled to −60 °C under nitrogen was added dropwise 0.26 mL (1.45 mmol) of diisobutylaluminum hydride. After 1 h, the reaction was cautiously quenched at −60 °C with methanol until evolution of gas ceased. The reaction mixture was diluted with 50 mL of ether and warmed to room temperature followed by washing with 25 mL of saturated brine solution. Several drops of 2 M sodium bisulfate were necessary to break up the gelatinous precipitate. The aqueous phase was exhaustively extracted with ether. The combined ether fractions were washed with saturated brine solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo, leaving 178 mg (100%) of hemiacetal **25** which was homogeneous by TLC analysis (ether/hexane, 3:1).

A 1.85-mL (3.67 mmol) aliquot of sodio methylsulfinylmethide prepared from 480 mg of sodium hydride (50% oil dispersion, washed with hexane to remove mineral oil) in 5 mL of dimethyl sulfoxide which had been heated for 1.25 h at 75 °C was added to 913 mg (1.93 mmol) of 5-triphenylphosphoniopentanoic acid, which had been dried at ca. 75–80 °C (<0.1 mm) for 1.5 h. After 5 min, a solution of 175 mg (0.5 mmol) of hemiacetal **25** in 1 mL of dimethyl sulfoxide was added and allowed to stir at room temperature for 18 h. The reaction mixture was quenched with ice, acidified with 2 N sodium bisulfate, and diluted to 25 mL with water. The aqueous portion was extracted with 5 × 20 mL of ether. The combined ethereal extracts were further extracted with 3 × 10 mL of 1 N sodium hydroxide solution. After acidification of the hydroxide washes with 2 N sodium bisulfate, the aqueous portion was extracted with 5 × 35 mL of ether, which were combined and washed with 50 mL of brine. The ethereal phase was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo affording 638 mg of crude **26**. Purification on 40 g of silica gel (methylene chloride/methanol, 30:1) afforded 186 mg of the desired hydroxy carboxylic acid **26** in 89% overall yield from lactone **26**: IR ($CHCl_3$) 3610, 3000, 3500–2400 (br), 2925, 2865, 2850, 1707, 1453, 1440, 1380, 1206, 1130, 1110, 1076, 1035, 1022, 980, 866, cm^{-1}.

To a solution of 0.95 mL (11.76 mmol) of dry pyridine in 15 mL of dry methylene chloride at 0 °C was added 588 mg (5.88 mmol) of dry chromium trioxide. After 15 min at 0 °C and 45 min at room temperature, the solution of chromium trioxide/pyridine complex was

transferred to a 100-mL two-neck flask containing 3 g of Celite (dried at ca. 125 °C (<0.1 mm) for 2 h). The reaction mixture was cooled to −23 °C and a solution of 164 mg (0.378 mmol) of hydroxy carboxylic acid **26** in 2 mL of methylene chloride was added. After 20 min at −23 °C, the reaction was quenched with 3.03 g (22 mmol) of finely crushed sodium bisulfate. The reaction mixture was allowed to warm to room temperature over 5 min and filtered through anhydrous magnesium sulfate. The filter pad was washed with an additional 250 mL of methylene chloride. The combined organic washings were evaporated under reduced pressure to afford 116 mg (71%) of a cyclopentenone which was homogeneous on TLC (methylene chloride/methanol, 19:1, R_f 0.53) and used without further purification: IR ($CHCl_3$) 3400–2400 (br), 3000, 2925, 2850, 1703, 1595, 1440, 1208, 1130, 1055, 1020, 980 cm^{-1}.

A mixture of 116 mg (0.269 mmol) of the above enone and a solution of 1.7 mL of acetic acid/water (55:30) containing 0.3 mL of THF was heated at 39 °C for 8 h. The reaction was cooled to 0 °C and the volatile material was removed under reduced pressure (<0.1 mm) leaving 98 mg of crude material. Purification on 10 g of silica gel (methylene chloride/methanol, 60:1) afforded 66 mg (70%) of 12-methylprostaglandin A_2 as an epimeric mixture at C-15. The epimeric mixture was separated on two 20 × 20 cm silica gel plates (0.25 mm) (six developments with methylene chloride/ether/acetic acid (90:10:1)) providing 25 mg of the more polar 12-methylprostaglandin A_2 (**1**) and 25 mg of the corresponding 15-epi-12-methylprostaglandin A_2 (**27**). IR and NMR data of both compounds are identical: IR ($CHCl_3$) 3610, 3500–2500 (br), 3000, 2960, 2935, 2875, 2860, 1707, 1590, 1455, 1378, 1340, 1210, 1050, 975 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 0.86 (bt, 3 H, $-CH_2CH_3$), 1.12 (s, 3 H, $-CH_3$), 4.08 (m, 1 H, $-CHOH$), 5.23–5.92 (m, 4 H), 6.03 (d, 1 H, J = 6 Hz), 7.33 (d, 1 H, J = 6 Hz). Treatment of 12-methylprostaglandin A_2 with an ethereal solution of diazomethane gave 12-methylprostaglandin A_2 methyl ester, bp 90 °C (0.04 mm).

Anal. ($C_{22}H_{34}O_4$) C, H.

***syn*-7-Methyl-2,2-ethylenedioxybicyclo[2.2.1]heptane-7-carboxylic Acid Methyl Ester (16).** A solution of 300 mg (0.98 mmol) of bromo ester **7** in 5 mL of benzene was treated at room temperature with 450 mg (1.5 mmol) of tri-*n*-butyltin hydride in 2.5 mL of benzene containing 164 mg (1.0 mmol) of azobisisobutyronitrile. The mixture was heated at 50–55 °C for 1.5 h. The reaction mixture was diluted with ether and washed with 5% aqueous sodium hydroxide solution followed by water. The organic solution was dried over anhydrous magnesium sulfate, filtered, and concentrated under reduced pressure, leaving 806 mg of material. Purification of the crude residue on silica gel (elution with hexane/ether, 5:1) gave 209 mg (94%) of pure methyl ester **16**: IR ($CHCl_3$) 2950, 2870, 1718, 1462, 1450, 1429, 1375, 1328, 1295, 1280, 1249, 1200, 1152, 1099, 1070, 1051, 1015, 990, 975, 955, 945, 901, 885, 872, 855, 828 cm^{-1}; NMR (CCl_4) δ 1.38 (s, 3 H), 3.60 (s, 3 H), 3.75 (m, 4 H).

Anal. ($C_{12}H_{18}O_4$) C, H.

***syn*-7-Methyl-7-(hydroxymethyl)-2,2-ethylenedioxybicyclo[2.2.1]heptane (17).** To a suspension of 80 mg (2.1 mmol) of lithium aluminum hydride in 4.0 mL of anhydrous ether was added dropwise a solution of 240 mg (1.06 mmol) of *syn*-7-methyl-2,2-ethylenedioxybicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (**16**) in 4.0 mL of dry ether. After refluxing for 3.5 h, the reaction was quenched by the addition of ether followed by the careful dropwise addition of 0.5 mL of water at 0 °C. The mixture was diluted with ether and filtered. The filtrate was washed with saturated aqueous brine solution, dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo, leaving 222 mg of crude alcohol **17**. Purification of the crude product on silica gel (elution with hexane/ether, 10:3) gave 189 mg (90%) of pure alcohol: IR ($CHCl_3$) 3620, 3450 cm^{-1}; NMR (CCl_4) δ 1.21 (s, 3 H), 1.25–2.20 (m, 8 H), 2.69 (s, 1 H, OH), 3.40 (s, 2 H), 3.75 (m, 4 H).

Anal. ($C_{11}H_{18}O_3$) C, H.

***syn*-7-Methyl-7-(*p*-toluenesulfonylmethyl)-2,2-ethylenedioxybicyclo[2.2.1]heptane (18).** A solution of 160 mg (0.81 mmol) of alcohol **17** in 2.0 mL of dry pyridine was treated dropwise at 0 °C with a solution of 155 mg (0.81 mmol) of *p*-toluenesulfonyl chloride in 0.8 ml of pyridine. After 15 h at 0–5 °C, the reaction mixture was concentrated under high vacuum and the residue was dissolved in ether and washed with ice/water. Standard workup provided 250 mg of tosylate (NMR (CCl_4) δ 1.18 (s, 3 H), 2.41 (s, 3 H), 3.76 (m, 6 H), 7.42 (AB q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 23.7 Hz)) which was employed directly in the next reaction.

A mixture of the above tosylate (240 mg, 0.68 mmol) and sodium iodide (300 mg, 2.0 mmol) in reagent grade acetone was refluxed for 5 h at 70 °C. The solvent was removed under reduced pressure and the residue was dissolved in ether and washed with water. The ether solution of product was dried ($MgSO_4$), filtered, and concentrated in vacuo, giving 191 mg (91%) of essentially pure iodide (NMR (CCl_4) δ 1.31 (s, 3 H), 3.20 (s, 2 H), 3.78 (m, 4 H)) which was used directly in the next reaction.

A mixture of the above iodide (190 mg, 0.62 mmol) and sodium *p*-toluenesulfinate (220 mg, 1.24 mmol) in 4 mL of anhydrous dimethylformamide was stirred for 15 h at 135–140 °C (bath temperature). The reaction mixture was diluted with ether and washed with water. The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure, providing 206 mg of crude sulfone which crystallized from ether/hexane, 1:1. There was obtained 143 mg of crystalline sulfone **18**, mp 115–116 °C. The mother liquor was chromatographed on silica gel (elution with hexane/ether, 5:1) affording an additional 17 mg of pure sulfone. Analytically pure **18**, mp 117–118 °C, was obtained by recrystallization from ethanol. The IR spectrum ($CHCl_3$) exhibited peaks at 1592, 1310, and 1141 cm^{-1}. The NMR spectrum in CCl_4 exhibited peaks at δ 1.45 (s, 3 H), 2.46 (s, 3 H), 3.04 (s, 2 H), 3.81 (m, 4 H), 7.55 (AB q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 24.7 Hz).

Anal. ($C_{18}H_{24}O_4$) C, H.

***syn*-7-Methyl-7-(4-methylpent-3-enyl)-2,2-ethylenedioxybicyclo[2.2.1]heptane (19).** A solution of 110 mg (0.33 mmol) of sulfone **18** in 3 mL of anhydrous tetrahydrofuran cooled to −78 °C was treated dropwise with 0.37 mL of a 1.2 M solution of *n*-butyllithium in hexane. The solution was gradually warmed to −20 °C over a 1-h period followed by cooling to −78 °C and addition of 73 mg (0.44 mmol) of prenyl bromide in 0.3 mL of dry tetrahydrofuran. After addition was complete, the reaction mixture was gradually warmed to 0 °C over 1.5 h. The reaction mixture was diluted with ether and washed with water. Standard workup gave 133 mg of prenylated sulfone (NMR (CCl_4) δ 1.37 (s, 3 H), 1.42 (s, 6 H), 2.37 (s, 3 H), 3.72 (m, 4 H), 4.41 (bt, 1 H, J = 7 Hz), 7.27 (AB q, 4 H, J = 8 Hz, $\Delta\nu_{AB}$ = 22.6 Hz)) which was employed directly in the next reaction.

Lithium metal (100 mg) was dissolved in 10 mL of dry ethylamine over a 30-min period at 0 °C. The blue-colored solution was cooled to −78 °C and a solution of 133 mg (0.33 mmol) of prenylated sulfone in 0.8 mL of anhydrous tetrahydrofuran was added dropwise. After 30 min at −78 °C, the reaction was quenched by the addition of 1,3-butadiene followed by methanol. The reaction mixture was concentrated in vacuo and the residue dissolved in ether and washed with water. The ether layer was dried over magnesium sulfate, filtered, and concentrated under reduced pressure, leaving 81 mg of crude **19** (98%). Chromatography on silica gel (elution with hexane/ether, 10:1) gave 67 mg (82% overall) of pure ketal **19**: IR ($CHCl_3$) 2990, 2948, 2875, 1470, 1445, 1430, 1380, 1325, 1260, 1200, 1135, 1105, 1069, 1050, 1015, 981, 941, 882, 870, 820 cm^{-1}; NMR (CCl_4) δ 1.18 (s, 3 H), 1.61 (s, 3 H), 1.65 (s, 3 H), 3.72 (m, 4 H), 5.02 (bt, 1 H, J = 7 Hz).

Anal. ($C_{16}H_{26}O_2$) C, H.

Sesquifenchene (20). Ketal **19**, (76 mg, 0.30 mmol) was treated at 85 °C for 1.5 h with 6 mL of 30% acetic acid followed by neutralization with solid sodium bicarbonate. The product was isolated via standard procedures using ether. There was obtained 61 mg (97%) of *syn*-7-methyl-7-(4-methylpent-3-enyl)bicyclo[2.2.1]heptan-2-one: IR ($CHCl_3$) 1725 cm^{-1}; NMR (CCl_4) δ 1.02 (s, 3 H), 1.60 (s, 3 H), 1.67 (s, 3 H), 5.05 (bt, 1 H, J = 7 Hz).

A suspension of 26 mg (0.6 mmol) of 57% sodium hydride dispersion (washed with anhydrous benzene to remove mineral oil) in 1.0 mL of dry dimethyl sulfoxide was stirred at 75 °C for 45 min under an atmosphere of nitrogen. The resultant blue-green solution was cooled to room temperature and a solution of 214 mg (0.6 mmol) of methyltriphenylphosphonium bromide (dried at 75 °C in vacuo for 1.5 h) in 1.0 mL of dry dimethyl sulfoxide was added. After 10 min a solution of the above ketone (57 mg, 0.28 mmol) in 1.0 mL of dimethyl sulfoxide was added. The reaction mixture was heated at 60–65 °C for 18 h. The reaction was quenched by the addition of pentane followed by washing with water. The organic portion was dried over magnesium sulfate, filtered, and concentrated under reduced pressure, leaving 70 mg of material. Chromatography on silica gel (elution with hexane/ether, 10:1) gave in order of elution 17 mg of pure sesquifenchene and 22 mg of recovered starting ketone. The IR and NMR spectra and retention time on VPC of synthetic sesquifenchene (**20**)

were identical with those of a synthetic sample kindly provided by Professor Bessière-Chrétiene and Dr. C. Grison.[26]

Iodolactonization of Carboxylic Acid 3. The hydroxy acid **3** (698 mg, 2.58 mmol) was dissolved in 4.5 mL of water containing sodium hydroxide (112 mg, 2.80 mmol) at 0 °C. The cooled homogeneous solution was neutralized to pH ca. 7 with carbon dioxide and treated with 4.6 g (28.4 mmol) of potassium iodide and 2.3 g (9.1 mmol) of iodine in 4.5 mL of water. The resultant black solution was stirred for 30 h at 5 °C at which time methylene chloride was added followed by the addition of solid sodium sulfite to decolorize the solution. The product was isolated by extraction with methylene chloride. The combined organic extracts were dried over anhydrous magnesium sulfate and concentrated in vacuo to yield 834 mg (82%) of 3α,5α-dihydroxy-4β-iodo-2α-methyl-2β-(tetrahydropyranyloxymethyl) cyclopentane-1α-acetic acid γ-lactone (**28**) which was homogeneous on TLC (benzene/ether, 1:1): IR ($CHCl_3$) 3600, 3400, 1770 cm^{-1}; NMR ($CDCl_3$) δ 0.91 (s, 3 H), 4.20 (m, 2 H), 4.58 (m, 1 H), 5.1 (m, 1 H).

3α,5α-Dihydroxy-2α-methyl-2β-(tetrahydropyranyloxymethyl)cyclopentane-1α-acetic Acid γ-Lactone (29). To a solution of 950 mg (2.40 mmol) of 3α,5α-dihydroxy-4β-iodo-2α-methyl-2β-(tetrahydropyranyloxymethyl)cyclopentane-1α-acetic acid γ-lactone (**28**) in 40 mL of benzene containing 40 mg of azobisisobutyronitrile was added 1.2 g (4.1 mmol) of tri-*n*-butyltin hydride. After ca. 2 h at 55 °C, the benzene was removed in vacuo and the residue was allowed to stand on a column of silica gel (200 g) for 1 h prior to elution with benzene/ether (3:2). There was obtained 5.85 mg (91%) of pure lactone **29:** IR ($CHCl_3$) 3620, 3450, 1765 cm^{-1}; NMR (CCl_4) δ 0.99 (s, 3 H), 4.45 (bs, 1 H), 4.86 (m, 1 H).

Anal. ($C_{14}H_{22}O_5$) C, H.

3α,5α-Dihydroxy-2α-methyl-2β-(tetrahydropyranyloxymethyl)-cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate. To a stirred solution of 1.73 g (6.4 mmol) of lactone **29** in 8 mL of dry pyridine was added 100 mg (7.1 mmol) of benzoyl chloride. After 16 h at room temperature, the pyridine was removed under reduced pressure. The residue was dissolved in ethyl acetate. The organic solution was washed with saturated sodium bicarbonate solution and brine. The aqueous layers were backwashed with ethyl acetate. There was obtained 2.40 g (100%) of benzoate (IR ($CHCl_3$) 1769, 1718 cm^{-1}; NMR (CCl_4) δ 1.08 (s, 3 H), 4.50 (m, 1 H), 5.0 (bt, 1 H), 5.25 (m, 1 H), 7.40 (m, 3 H), 7.90 (m, 2 H)) which was used directly in the next reaction.

3α,5α-Dihydroxy-2α-methyl-2β-(hydroxymethyl)cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate (30). A solution of the above 3α,5α-dihydroxy-2α-methyl-2β-(tetrahydropyranyloxymethyl)-cyclopentane-1α-acetic acid γ-lactone 3-benzoate (2.40 g, 6.40 mmol) in 90 mL of methanol cooled to 0 °C was treated with 900 mg of *p*-toluenesulfonic acid. After 2 h at 0 °C, the temperature was raised to 25 °C where stirring was continued for an additional 1 h. The reaction was quenched by the addition of a saturated solution of sodium bicarbonate. The methanol was removed on a rotary evaporator and the residue was dissolved in ethyl acetate. The aqueous layer was extracted exhaustively with ethyl acetate. The combined organic phases were washed with brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo, providing 1.82 g (99%) of lactone **30:** bp 120 °C (0.15 mm); IR ($CHCl_3$) 3625, 3500, 1770, 1712 cm^{-1}; NMR ($CDCl_3$) δ 1.02 (s, 3 H), 3.40 (s, 2 H), 5.05 (m, 1 H), 5.41 (t, 1 H, J = 6 Hz), 7.45 (m, 3 H), 7.98 (m, 2 H).

Anal. ($C_{16}H_{18}O_5$) C, H.

3α,5α-Dihydroxy-2α-methyl-2β-formylcyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate (31). To a solution of 7.1 g (90 mmol) of dry pyridine in 70 mL of dry methylene chloride cooled to 0 °C was carefully added in small portions 4.5 g (45 mmol) of chromium trioxide. The reaction mixture was stirred at 0 °C for an additional 15 min followed by warming to room temperature. After 2 h the reaction mixture was cooled to 0 °C and a solution of 3α,5α-dihydroxy-2α-methyl-2β-(hydroxymethyl)cyclopentane-1α-acetic acid γ-lactone 3-benzoate (**30,** 1.10 g, 4.5 mmol) in 7 mL of dry methylene chloride was added in one portion. After 10 min at 0 °C the reaction mixture was quenched by the addition of benzene and filtered through Celite. The Celite was washed exhaustively with benzene. The combined organic solutions were filtered through a second pad of Celite to remove the last traces of chromium salts and concentrated under reduced pressure, leaving 1.08 g (99%) of crude crystalline aldehyde **31.** Three recrystallizations from carbon tetrachloride gave pure **31:** mp 111–112 °C; IR ($CHCl_3$) 3015, 2960, 2940, 2875, 2820, 2720, 1768, 1719, 1602, 1584, 1495, 1470, 1452, 1418, 1395, 1361, 1321, 1315, 1262, 1244, 1205, 1178, 1105, 1091, 1063, 1022, 1005, 971, 940, 911, 895, 870 cm^{-1}; NMR ($CDCl_3$) δ 1.26 (s, 3 H), 2.17–2.45 (m, 2 H), 2.68–2.86 (m, 2 H), 3.4 (m, 1 H), 5.12 (m, 1 H), 5.68 (t, 1 H), 5.54 (m, 3 H), 8.00 (m, 2 H), 9.56 (s, 1 H); high-resolution mass spectrum, 288.1012 (calcd for $C_{16}H_{16}O_5$, *m/e* 288.0998).

3α,5α-Dihydroxy-2α-methyl-2β-(3-oxo-*trans*-1-octenyl)cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate (32). To a stirred suspension of 164 mg (3.42 mmol) of 50% sodium hydride dispersion in 30 mL of dimethoxyethane (freshly distilled from lithium aluminum hydride) cooled to 0 °C under nitrogen was added dropwise a solution of 760 mg (3.42 mmol) of dimethyl (2-oxoheptyl)phosphonate in 15 mL of dry dimethoxyethane. After addition was complete, the reaction mixture was warmed to 25 °C. After 1 h at 25 °C the phosphonate anion was cooled to 0 °C and treated with a solution of 986 mg (3.42 mmol) of aldehyde **31** in 15 mL of dry dimethoxyethane. The resulting mixture was then warmed to 55 °C and stirred for 20 h. The reaction was quenched by the addition of water and the solvent was removed under reduced pressure leaving an oily residue which was dissolved in ethyl acetate. The organic phase was extracted with brine. The combined aqueous layers were backwashed with ethyl acetate. The combined organic washings were dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude enone was chromatographed on 150 g of silica gel. Elution with hexane/ether (1:1) gave 1.10 g (83%) of pure enone **32** as a colorless syrup: IR ($CHCl_3$) 1770, 1715, 1698, 1670, 1620, 1600, 1581 cm^{-1}; NMR ($CDCl_3$) δ 0.88 (t, 3 H), 1.25 (s, 3 H), 5.08 (m, 1 H), 5.38 (t, 1 H), 6.20 (d, 1 H, J = 16 Hz), 6.75 (d, 1 H, J = 16 Hz), 7.50 (m, 3 H), 8.0 (m, 2 H).

Anal. ($C_{23}H_{28}O_5$) C, H.

3α,5α-Dihydroxy-2α-methyl-2β-[(3*S*)-3-hydroxy-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone 3-Benzoate (33). To a suspension of 59 mg (1.55 mmol) of sodium borohydride in 10 mL of absolute ethanol cooled to −20 °C under nitrogen was added 1.10 g (2.92 mmol) of benzoate enone **32** in 30 mL of absolute ethanol. After 1.5 h, TLC (ether/benzene, 3:1) indicated the complete absence of starting benzoate enone **32.** The reaction was quenched with 4 drops of glacial acetic acid and the solvent was removed under reduced pressure. The oily residue was treated with ethyl acetate and water. The aqueous phase was extracted exhaustively with ethyl acetate. The combined organic solutions were washed with saturated brine solution, dried over anhydrous magnesium sulfate, and concentrated in vacuo, leaving 1.02 g of an oil. The crude product was chromatographed on 250 g of silica gel packed in benzene/ether/butanone (1:1:0.1). Taking 50-mL fractions, elution was with benzene/butanone (17:3). The following were combined: fractions 6–9, pure less polar (15*S*), 374 mg; fractions 10–14, mixture, 569 mg; fractions 15–20, pure more polar (15*R*), 182 mg. Chromatography of the 569 mg (mixture) on 250 g of silica gel gave an additional 234 mg of pure **33.** The NMR spectrum ($CDCl_3$) exhibited peaks at δ 1.20 (s, 3 H), 4.08 (m, 1 H), 5.11 (m, 1 H), 5.31 (t, 1 H), 5.60 (m, 2 H), 7.50 (m, 3 H), 8.00 (m, 2 H). The IR spectrum ($CHCl_3$) showed bands at 3610, 3500, 1768, 1715, 1600, 1581 cm^{-1}.

3α,5α-Dihydroxy-2α-methyl-2β-[(3*S*)-3-hydroxy-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone. To a suspension of finely powdered anhydrous potassium carbonate (332 mg, 2.40 mmol) in 6 mL of methanol was added 608 mg (1.58 mmol) of benzoate **35** in 1 mL of methanol. After 2 h, TLC (ether/hexane, 3:1) indicated the absence of starting benzoate. The reaction mixture was treated with 20 mL of ethyl acetate, filtered through Celite, and concentrated in vacuo. The crude oily residue was dissolved in ethyl acetate and washed with saturated brine solution. The organic solution was dried and concentrated under reduced pressure, leaving 452 mg of pure diol: bp 160 °C (0.01 mm); IR ($CHCl_3$) 3610, 3450, 1765 cm^{-1}; NMR ($CDCl_3$) δ 1.08 (s, 3 H), 4.90 (m, 1 H), 5.43 (m, 2 H).

Anal. ($C_{16}H_{26}O_4$) C, H.

3α,5α-Dihydroxy-2α-methyl-2β-[(3*S*)-tetrahydropyranyloxy-*trans*-1-octenyl]cyclopentane-1α-acetic Acid γ-Lactone 3-Tetrahydropyranyl Ether (34). A solution of 430 mg (1.52 mmol) of 3α,5α-dihydroxy-2α-methyl-2β-[(3*S*)-3-hydroxy-*trans*-1-octenyl]cyclopentane-1α-acetic acid γ-lactone in 20 mL of dry methylene chloride containing 430 mg (5.11 mmol) of dihydropyran and a catalytic amount (30 mg) of *p*-toluenesulfonic acid was stirred at 0 °C for 2 h. The reaction mixture was diluted with 50 mL of ether, washed with saturated brine solution, dried, and concentrated under reduced pressure, affording 994 mg of a crude pale-yellow oil. The crude product was chromatographed on 200 g of silica gel. Elution with hexane/ether (3:2) gave 640 mg of compound **34:** IR ($CHCl_3$) 3000,

2935, 2860, 2845, 1768, 1469, 1455, 1440, 1410, 1380, 1368, 1357, 1342, 1320, 1301, 1278, 1260, 1180, 1128, 1120, 1075, 1045, 1020, 985, 975, 909, 872, 810 cm^{-1}.

12-Methylprostaglandin $F_{2\alpha}$ 11,15-Bis(tetrahydropyranyl ether) (36). To a solution of 332 mg (0.738 mmol) of lactone **34** in 7.5 mL of toluene cooled to −60 °C under nitrogen was added dropwise 0.40 mL (2.20 mmol) of diisobutylaluminum hydride. After 1 h, the reaction was cautiously quenched at −60 °C with methanol. The reaction mixture was diluted with 60 mL of ether and warmed to room temperature followed by washing with water. Several drops of 2 M sodium bisulfate were necessary to break up the gelatinous precipitate. The aqueous phase was exhaustively extracted with ether. The combined ether fractions were washed with saturated brine solution, dried, and concentrated in vacuo, leaving 327 mg (98%) of hemiacetal **35** which was homogeneous by TLC analysis (ether/hexane, 3:1).

A suspension of 240 mg (10 mmol) of 50% sodium hydride dispersion in 5.0 mL of dry diemthyl sulfoxide was stirred at 75 °C for 1.25 h under nitrogen. To the above solution (2.88 mL) of dimsyl sodium cooled to room temperature was added (4-carboxybutyl)triphenylphosphonium bromide (1.4 g, 3.00 mmol, dried for 1.5 h at ca. 75 °C (0.1 mm) prior to use) in 2.6 mL of dry dimethyl sulfoxide. After 15 min, a solution of 327 mg of the above hemiacetal (**35**) in 7.8 mL of dry dimethyl sulfoxide was added to the dark ylide solution. After 18 h at room temperature, the reaction mixture was quenched with ice and acidified carefully with 2 M sodium bisulfate solution. The resulting mixture was extracted exhaustively with ether. The combined ether layers were extracted with 3 × 10 mL of 1 N sodium hydroxide solution. The combined basic extracts were acidified with 2 M sodium bisulfate solution followed by extraction (5 × 35 mL) with ether. The combined ether washings were dried and evaporated in vacuo, leaving 374 mg of crude 12-methylprostaglandin $F_{2\alpha}$ bis(tetrahydropyranyl ether) (**36**). Purification on 30 g of silica gel (elution with methylene chloride/methanol, 19:1) afforded 276 mg of pure **36** (IR ($CHCl_3$) 3620, 3520, 3375–2400, 1710 cm^{-1}) which was analyzed as its methyl ester.

Anal. ($C_{32}H_{54}O_7$) C, H.

12-Methylprostaglandin $F_{2\alpha}$ (2). A solution of 163 mg (0.325 mmol) of 12-methylprostaglandin $F_{2\alpha}$ bis(tetrahydropyranyl ether) (**36**) in tetrahydrofuran (0.42 mL) was treated with 4 ml of glacial acetic acid/water (65:35) and heated at 45 °C for 6 h. Removal of the solvent under reduced pressure (<0.1 mm) gave 153 mg of an oily residue which was directly chromatographed on 20 g of silica gel. Elution with benzene/dioxane/acetic acid (60:60:1) gave 40 mg of crystalline 12-methylprostaglandin $F_{2\alpha}$, mp 57–59 °C. 12-Methylprostaglandin $F_{2\alpha}$ was analyzed as its methyl ester: mp 51–53 °C; IR ($CHCl_3$) 3600, 3400, 3000, 2950, 2925, 2850, 1728, 1470, 1460, 1438, 1380, 1365, 1318, 1255, 1245, 1210, 1160, 1120, 1050, 1015, 980, 955, 920, 865, 836 cm^{-1}; NMR (250 MHz) ($CDCl_3$) δ 0.88 (t, 3 H), 1.01 (s, 3 H), 2.50 (m, 1 H), 3.63 (s, 3 H), 3.68 (m, 1 H), 3.97 (m, 1 H), 4.16 (m, 1 H), 5.34 (m, 4 H).

Anal. ($C_{22}H_{38}O_5$) C, H.

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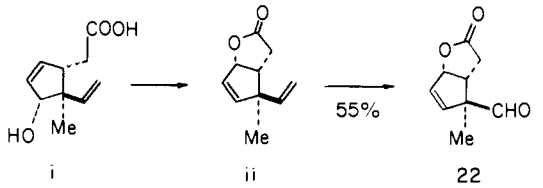

i ii 22

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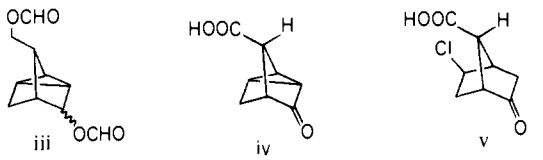

iii iv v

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