of water was slowly added with cooling and air was bubbled rapidly through the solution for 30 min to remove HCl. The aqueous phase was extracted with ether (200 and 75 mL) and the combined extracts were washed with 10% $NaHCO_3$ and saturated NaCl. After drying ($MgSO_4$), the organic phase was filtered and the solvent was removed under reduced pressure to afford 11.7 g (87%) of **4a,b**. The mixture was then chromatographed on a multigram HPLC system[14] using benzene–ether (15:1) on silica gel. The effluent was monitored at 280 nm.

The first major fraction to be eluted was (*R,R*)-**4a** (5.9 g). Recrystallization from hexane afforded a white solid: mp 104–105 °C; NMR (CCl_4) δ 1.6 (d, 3 H), 2.0 (m, 2 H), 2.3 (d, 1 H), 2.2–2.4 (m, 2 H), 3.50 (s, 3 H), 5.1–5.7 (m, 3 H), 7.2–8.1 (m, 7 H); IR ($CHCl_3$) 3450, 3320, 3020, 2130, 1730, 1510, 1250, 1175, 1065 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 339 (M^+, 14), 214 (00), 182 (25), 170 (57), 156 (23), 155 (88), 154 (23), 153 (22), 129 (46), 127 (24), 125 (29), 97 (26). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.92; H, 6.19; N, 3.94.

The second major fraction to be eluted was (*S,R*)-**4b** (5.8 g). Crystallization from hexane afforded a white solid: mp 78.5–80.5 °C; NMR (CCl_4) δ 1.6 (d, 3 H), 2.0 (broad, 2 H), 2.24 (d, 1 H), 2.15–2.6 (broad, 2 H), 3.57 (s, 3 H), 4.9–5.7 (m, 3 H), 7.2–8.1 (m, 7 H); IR ($CHCl_3$) 3460, 3320, 3020, 2130, 1740, 1510, 1250, 1175, 1065 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 339 (M^+, 9), 214 (98), 197(21), 182 (52), 170 (63), 156 (43), 155 (100), 154 (36), 153 (41), 129 (71), 128 (33), 127 (44), 125 (28), 97 (26). Anal. Calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.66; H, 6.04; N, 4.37.

(*R*)-(−)-Methyl 4,5-Tetradecadienoate [(*R*)-(−)-5]. This compound was prepared from the reaction of lithium di-*n*-octylcuprate with **4b** by two procedures.

Normal Addition. Carbamate **4b** (1.20 g, 3.5 mmol) in diethyl ether (25 mL) was added dropwise over a 10-min period to a stirred solution of lithium di-*n*-octylcuprate[15] (3.85 mmol) in diethyl ether (40 mL) cooled to −78 °C. After stirring the solution for an additional 7 h at −78 °C, the cooling bath was removed and the reaction mixture was allowed to come to 0 °C. Saturated NH_4Cl (10 mL) was then added and the mixture was stirred for 15 min to allow the copper salts to precipitate. The resulting slurry was filtered and the organic layer was separated, washed with 1 N HCl (10 mL) and saturated $NaHCO_3$ (15 mL), dried ($MgSO_4$), filtered, and concentrated at reduced pressure. Vacuum distillation of the residue afforded 0.52 g (62%) of (*R*)-(−)-**5**, $[\alpha]_D$ −45.0° (2.9, hexane): NMR (CCl_4) δ 0.87 (t, 3 H), 1.25 (broad s, 12 H), 1.9 (m, 2 H), 2.27 (m, 4 H), 3.54 (s, 3 H), 5.0 (m, 2 H); IR ($CHCl_3$) 2940, 1965, 1740 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 238 (M^+, 21), 140 (92), 98 (37), 85 (40), 83 (85), 81 (61), 80 (100), 79 (40), 71 (61), 67 (33).

Inverse Addition. Lithium di-*n*-octylcuprate (3.85 mmol) in diethyl ether (25 mL) cooled to −78 °C was added portionwise over 5 min to a cold (−78 °C) stirred solution of **4b** (1.20 g, 3.5 mmol) in diethyl ether (40 mL). The reaction mixture was stirred for 7 h at −78 °C and worked up as described above to afford 0.54 g (64%) of (*R*)-(−)-**5**, $[\alpha]_D$ −30.5° (7.5, hexane).

(*S*)-(+)-Methyl 4,5-Tetradecadienoate [(*S*)-(+)-5]. This compound was prepared from the reaction of lithium di-*n*-octylcuprate with **4a** by the procedures described for the preparation of (*R*)-(−)-**5**.

Use of inverse addition afforded (*S*)-(+)-**5** (65%), $[\alpha]_D$ +43.5° (5.1, hexane). Use of normal addition afforded (*S*)-(+)-**5** (61%), $[\alpha]_D$ +26.7° (4.6, hexane).

(*R*)-(−)-Methyl (*E*)-2,4,5-Tetradecatrienoate [(*R*)-(−)-1]. This compound was prepared from (*R*)-(−)-**5**, $[\alpha]_D$ −45.0°, by the method of Kocienski.[6] Allene (*R*)-(−)-1 was isolated (83%) as a light yellow oil, $[\alpha]_D$ −98.3° (3.8, hexane): NMR (CCl_4) δ 0.87 (t, 3 H), 1.3 (broad s, 12 H), 2.03 (m, 2 H), 3.65 (s, 3 H), 5.3 (m, 1 H), 5.6–5.9 (m, 1 H), 5.72 (d, 1 H), 7.1 (dd, 1 H); IR ($CHCl_3$) 2950, 2880, 1950, 1730, 1635, 1440, 985 cm^{-1}; MS (70 eV) *m/e* (rel intensity) 236 (M^+, 2),138 (67), 137 (21), 107 (21), 82 (28), 79 (100), 78 (39), 67 (21).

(*S*)-(+)-Methyl (*E*)-2,4,5-Tetradecatrienoate [(*S*)-(+)-1]. This compound was prepared from (*S*)-(+)-**5**, $[\alpha]_D$ +43.5°, by the method of Kocienski.[6] Allene (*S*)-(+)-1 was isolated as a light yellow oil, $[\alpha]_D$ +94.9° (3.3, hexane).

Acknowledgment. This work has been partially funded by grants from the National Science Foundation and the National Institutes of Health.

Registry No.—(*R*)-(−)-**1**, 28066-21-9; (*S*)-(+)-**1**, 65451-10-7; **2**, 65414-51-9; **3a**, 65414-52-0; **3b**, 65414-53-1; **4a**, 65414-54-2; **4b**, 65414-55-3; (*R*)-(−)-**5**, 65451-09-4; (*S*)-(+)-**5**, 65494-90-8; β-cyanopropionaldehyde, 3515-93-3; β-cyanopropionaldehyde dimethyl acetal, 14618-78-1; ethynyl bromide, 593-61-3; *R*-(−)-(1-naphthyl)ethyl isocyanate, 42340-98-7; lithium di-*n*-octylcuprate, 38317-57-6.

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Total Synthesis of 3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenylene Prostaglandins. 1. Photochemical Approach

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Received December 2, 1977

The total syntheses of optically active 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenylene prostaglandins **3**, **28**, **29**, and **30** are described. The synthetic route to these novel and biologically active prostaglandin analogues involved the photochemical cycloaddition of *m*-acetoxybenzaldehyde (**16**) and optically active acetal **5** to give the tricyclic oxetane **17** as the key step. The structure and optical purity of oxetane **17** were supported by model studies and NMR chiral shift reagent studies as well as subsequent transformations to the desired end products.

During the past several years, a number of prostaglandin analogues have been synthesized which have incorporated an aromatic ring at some location in the basic prostaglandin structure. Two such examples are the 17-phenyl-18,19,20-trinor- and the 16-phenoxy-17,18,19,20-tetranor-substituted prostaglandins represented by **1** and **2**, respectively. These

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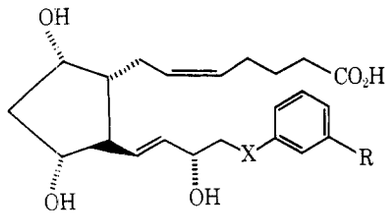
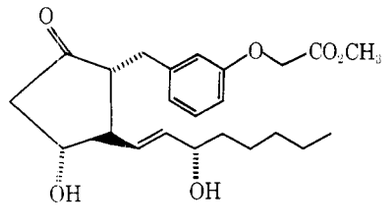


1, X = CH_2; R = H
2, X = O; R = CF_3

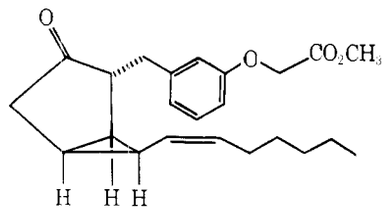


3

compounds belong to analogue families which have displayed not only structural diversity but also significant biological activity.[1] Although these examples involve modification of the lower, aliphatic side chain, other prostaglandin analogues have been synthesized which have incorporated an aromatic ring in the upper, carboxylic acid side chain. A specific example of this type of modification is illustrated by 3-oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin E_1 methyl ester (**3**),[2] the racemate of which has been demonstrated to be a potent inhibitor of ADP-induced human platelet aggregation in vitro.[3] Because of continued interest in the biological properties of *dl*-**3**, a method for the synthesis of the pure enantiomeric form of **3** of natural prostaglandin configuration was sought.

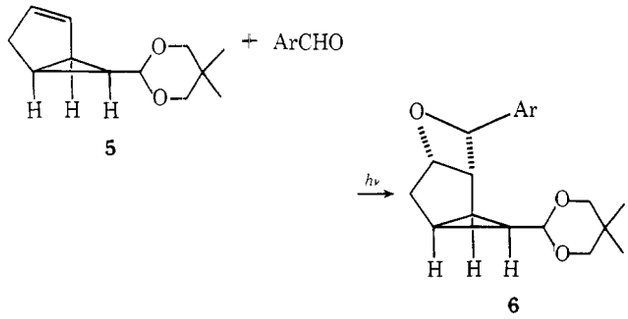
Results and Discussion

Strategy. The original synthesis of *dl*-**3** involved the preparation of the racemic bicyclo[3.1.0]hexanone intermediate *dl*-**4b** which was subsequently transformed into *dl*-**3** by



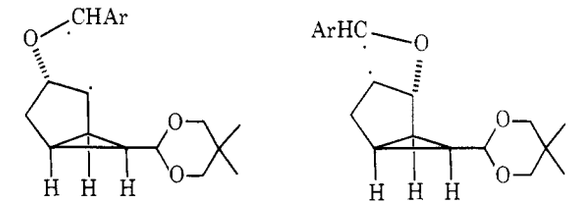
4b

way of a solvolytic ring opening reaction.[3] A successful synthesis of enantiomerically pure **3** would therefore be formally achieved by the synthesis of enantiomerically pure **4b.** To this end, use was made of *l*-bicyclo[3.1.0]hex-2-ene-6-*endo*-carboxaldehyde neopentyl glycol acetal **5,** which had been previously demonstrated to be the enantiomer which would lead to prostaglandins of natural configuration.[4] It was envisaged that a suitable aromatic aldehyde could be photochemically cycloadded to **5** to afford an oxetane **6** possessing the indicated



5 **6**

orientation and configuration. That **6** would be preferentially formed over other isomeric oxetanes was predicted on the following grounds: (1) the endo orientation of the neopentyl glycol acetal group of **5** essentially excludes approach to the β face of the molecule and thereby assures predominant cycloaddition from the α face; (2) extensive literature precedent for the photochemical formation of oxetanes from aromatic aldehydes or ketones with olefins[5] suggests that the reaction usually occurs by way of the most stable biradical intermediate. For the case in point, intermediate **7** should therefore

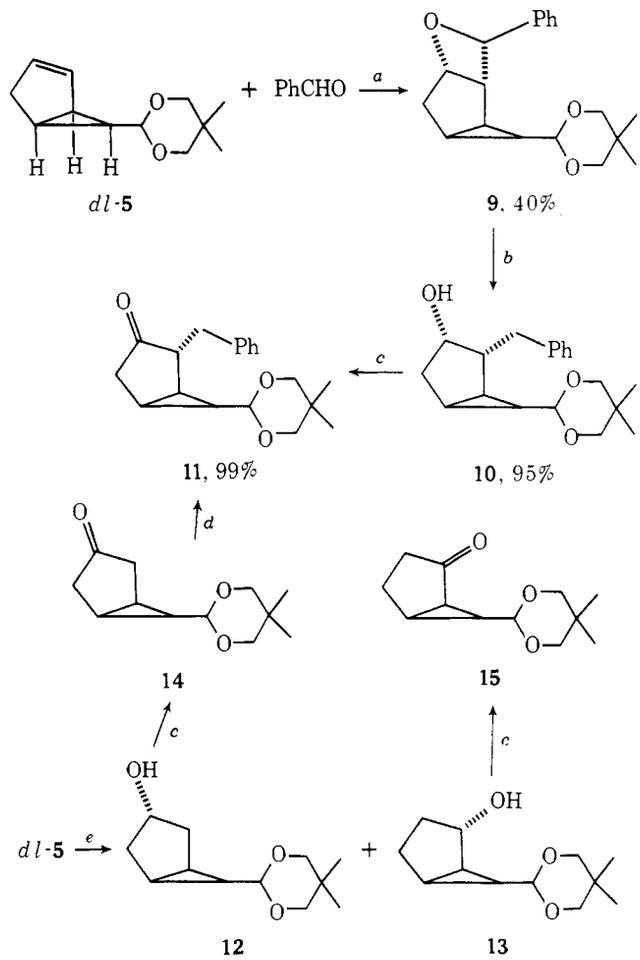


7 **8**

be favored over **8** since the former is stabilized by a cyclopropyl carbinyl interaction with the radical center on the ring.

Model Studies. To test the correctness of the above reasoning, the model series of reactions illustrated in Scheme I were carried out with *dl*-**5.** Irradiation of a solution of *dl*-**5** and benzaldehyde (molar ratio 3:1) in benzene afforded oxetane *dl*-**9** as the major product in addition to more polar impurities. Dissolving metal reductive cleavage of the benzylic carbon–

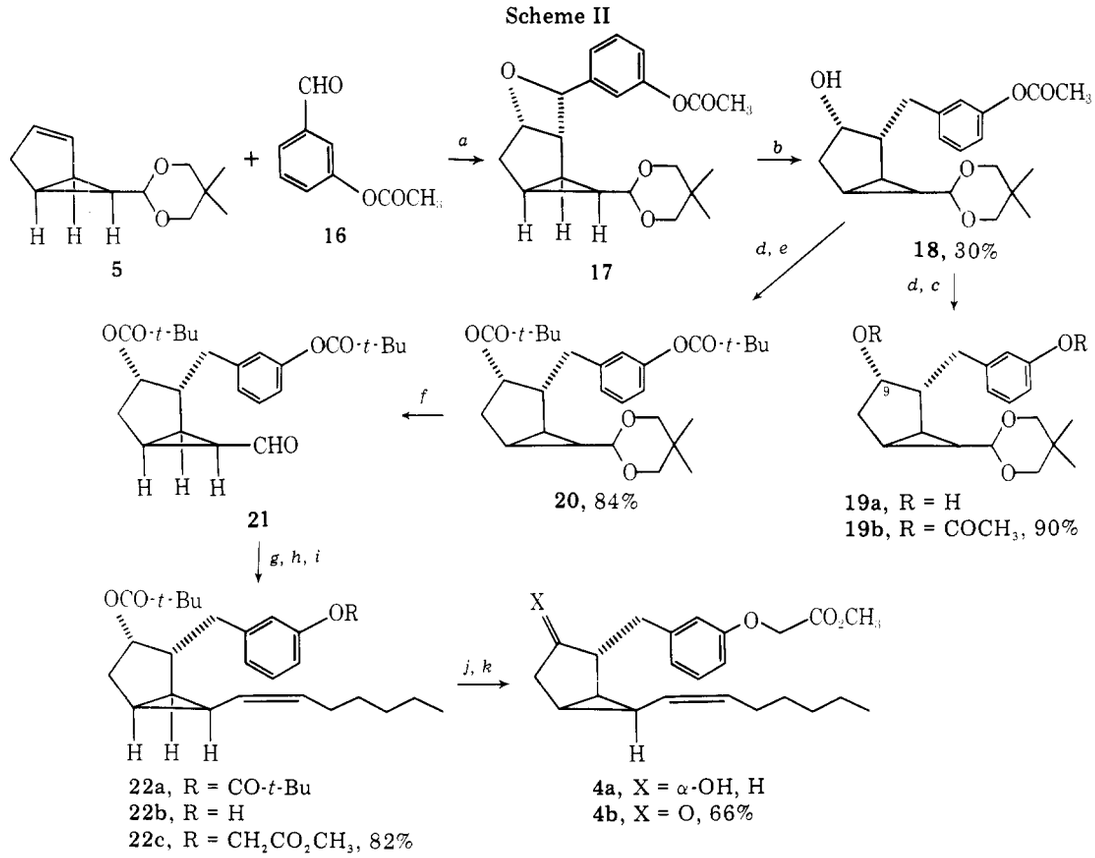
Scheme I



dl-**5** **9**, 40% **11**, 99% **10**, 95% **14** **15** **12** **13**

[a] *hν*, 350 nm, C_6H_6, N_2. [b] Na, *n*-BuOH, $C_6H_5CH_3$, reflux. [c] $CrO_3 \cdot 2pyr$, CH_2Cl_2, 25 °C. [d] *t*-BuOK, THF; $PhCH_2Br$, 25 °C. [e] BH_3, THF, 0 °C; H_2O_2, NaOH.

Scheme II

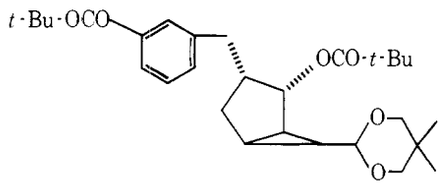


[a] *hν*, 350 nm, C_6H_6, 25 °C, N_2. [b] H_2, 10% Pd-C, EtOH, 25 °C. [c] Ac_2O, pyridine. [d] K_2CO_3, CH_3OH, H_2O, 25 °C. [e] *t*-BuCOCl, pyridine. [f] 88% HCO_2H, 0 °C, 4 h. [g] $Ph_3P{=}CH(CH_2)_4CH_3$, C_6H_6. [h] K_2CO_3, CH_3OH, H_2O. [i] NaH, $BrCH_2CO_2CH_3$, CH_3O–CH_2CH_2–OCH_3, 25 °C. [j] $NaOCH_3$, CH_3OH. [k] $CrO_3 \cdot 2$ pyr, CH_2Cl_2, 25 °C.

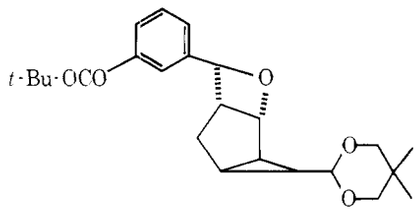
oxygen bond afforded alcohol *dl*-**10**, and subsequent oxidation of this material gave ketone *dl*-**11** in 94% overall yield from **9**. To confirm the structure assigned to *dl*-**11**, its synthesis was carried out by an independent route. Thus, hydroboration of *dl*-**5** gave secondary alcohols *dl*-**12** and *dl*-**13** (ratio ca. 3:1 by TLC) which were separated with some difficulty by chromatography. Oxidation of each alcohol separately gave the ketones *dl*-**14** (from *dl*-**12**) and *dl*-**15** (from *dl*-**13**). These isomers were distinguished by their respective infrared and ultraviolet spectra. Thus, the cyclopropyl conjugated ketone *dl*-**15** exhibited absorptions at ν_{max} (mull) 1710 cm^{-1} in the infrared and $\lambda_{max}^{n\rightarrow\pi^*}$ 278 nm (ϵ 41) in ethanol in the ultraviolet regions, while the nonconjugated isomer *dl*-**14** exhibited corresponding absorptions at ν_{max} (mull) 1740 cm^{-1} and $\lambda_{max}^{n\rightarrow\pi^*}$ 270 nm (ϵ 28) in ethanol. Finally, alkylation of *dl*-**14** with benzyl bromide gave *dl*-**11**, identical in all respects with the specimen of *dl*-**11** derived from oxetane *dl*-**9**.

Synthesis. The application of the above methods to the synthesis of optically pure **4b** is illustrated in Scheme II. Irradiation of a solution of *l*-**5** and *m*-acetoxybenzaldehyde[6] (**16**) (molar ratio 3:1) in benzene for 24 h afforded oxetane **17** which was subsequently converted to alcohol **18** in ca. 30% overall yield based on 28% of recovered **16**. Extended photolysis times did not significantly increase the yield of oxetane **17**, and the maximum conversion obtainable was ca. 70%. The structure proof of **17** rested primarily on its NMR spectrum. In particular, the oxetane proton pattern (δ 4.97–5.52) was essentially superimposable on that for *dl*-**9**. Further evidence for the assigned structure was gained by its eventual conversion to optically active **3** and **4b** and comparison with authentic racemic materials (vide infra). Accepting that the structure of the oxetane is correct as shown, the optical purity of **17** became of prime importance. Clearly, for the synthetic route to optically pure **4b** to be viable, the high level of optical purity of *l*-**5** must be maintained in **17**. Two experiments have shown that **17** is of high optical purity. First, reisolation of unconsumed olefin *l*-**5** and measurement of its specific rotation confirmed that racemization had not occurred to any extent during photolysis (e.g., by hydrogen atom abstraction to afford a symmetrical allylic radical intermediate). Secondly, the optical purity of diacetate **19b** (derived from monoacetate **18**) was determined by NMR spectroscopy using the chiral shift reagent tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III).[7] For this experiment, a sample of *dl*-**19b** was prepared in analogous fashion from *dl*-**5**. Successive addition of the shift reagent to a deuteriochloroform solution of *dl*-**19b** (ca. 0.3 M) eventually produced an NMR spectrum in which the C-9 acetate methyl group (prostaglandin numbering[2]) was shifted downfield by 3.8 ppm and split into two singlets, $\Delta\nu$ = 5 Hz. For *d*-**19b** (prepared from *l*-**5**), the addition of an amount of shift reagent necessary to produce the same 3.8 ppm downfield shift of the C-9 acetate methyl group failed to split the acetate singlet. This result confirmed that the sample of *d*-**19b** and therefore **18** was of high optical purity (≥90%).

Continuing with the synthetic sequence in Scheme II, the monoacetate **18** is a crystalline solid which may be upgraded at this stage by recrystallization or carried on in crude form. Hydrolysis of the phenolic acetate and esterification of the resulting diol with pivaloyl chloride afforded dipivalate **20** as a solid after silica gel chromatography. At this stage, the NMR spectrum of **20** (homogeneous by TLC in several solvent systems) suggested the presence of an impurity to the extent of 10–20%. Multiple recrystallizations eventually afforded a pure specimen of **20**. The impurity was then crystallized from the combined mother liquors of **20** and was shown to be isomeric with **20**. The structure of this impurity was tentatively assigned as **23**: a structure which would be derived from oxetane

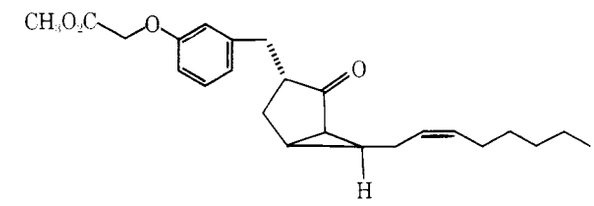


23



24

regioisomer **24** and one which will receive further support (vide infra). Dipivalate **20** may either be upgraded by recrystallization, or the mixture of **20** and **23** may be employed for the hydrolysis to **21** with concentrated (88%) formic acid. *endo*-Aldehyde **21** exhibited a doublet at 9.68 δ (J = 3 Hz). If the hydrolysis was allowed to proceed for longer reaction times (≥8 h at 0 °C) or at elevated temperatures (≥25 °C), significant quantities of the corresponding exo aldehyde (doublet at δ 9.05; J = 4 Hz) were formed. The aldehyde **21** was then condensed with *n*-hexylidenetriphenylphosphorane (to give **22a**), the phenolic ester of the Wittig product was then selectively hydrolyzed (to give **22b**), and the resulting phenol was finally alkylated with methyl bromoacetate to afford diester **22c** in 82% overall yield from aldehyde **21.** When a mixture of **20** and **23** was employed for the syntheses of **21** and **22c,** the isomer corresponding to **23** was carried through all steps. At no point was the isomeric impurity separated from the desired forms (i.e., **21** and **22a–c**) by TLC in several solvent systems. Finally, diester **22c** was treated with dry sodium methoxide to liberate the latent C-9 hydroxyl group which was then oxidized to afford ketone **4b.** At this stage, the isomeric impurity was chromatographically separable for the first time in the entire synthetic sequence. For **4b,** this impurity was tentatively assigned as **25.** That **4b** and **25** were isomeric was confirmed by high resolution mass spectrometry. Additionally, the infrared spectrum of **4b** exhibited carbonyl absorptions at 1765 and 1740 cm^{-1} while that for **25** exhibited absorptions at 1765, 1740 and 1720 cm^{-1} (the ester function in this type



25

of compound appears to exhibit two carbonyl stretches at 1765 and 1740 cm^{-1}). In the case of **4b,** the ketone carbonyl is coincident with the 1740-cm^{-1} ester band while in the case of **25** the ketone carbonyl absorbs at 1720 cm^{-1} due to conjugation with the cyclopropane ring.[8] These results implied that oxetane regioisomer **24** was formed as a by-product along with oxetane **17** in the photochemical cycloaddition reaction (ratio **17:24** ca. 9:1) for *l*-**5** and **16,** and literature precedent[9] for simple vinylcyclopropane systems supports this conclusion.

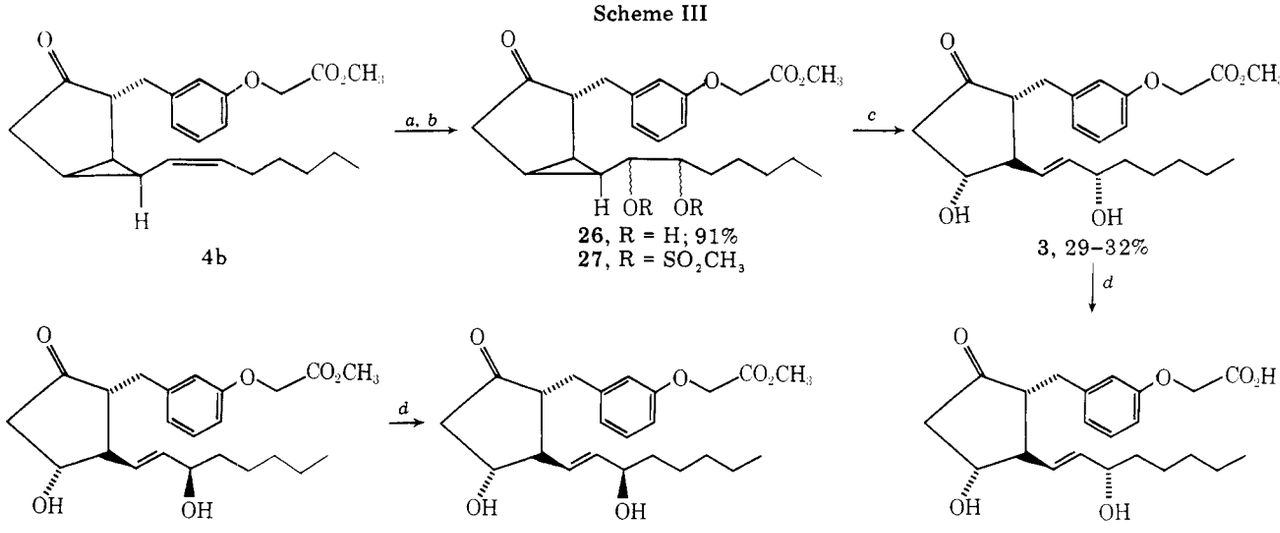
The transformations of **4b** into 3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (**29**) and (15*R*) -3-oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (**30**) are illustrated in Scheme III. *endo*-Olefin **4b** was hydroxylated catalytically with osmium tetroxide[10] to afford a mixture of *cis*-glycols **26.** This mixture was then esterified with methanesulfonyl chloride to give bismesylates **27,** which were then solvolyzed in aqueous acetone to give the epimeric esters **3** and **28** in 30–40% combined yield from **4b.** These isomers were separated by chromatography on silica gel, and the sample of **3** ([α]$_D$ −48 ° in ethanol) produced was identical by NMR and infrared spectroscopy and TLC (several systems) with an authentic sample of *dl*-**3.**[3] Methyl esters **3** and **28** were finally converted to their free acid forms **29** (mp 128.7–130.0 °C) and **30,** respectively, by enzymatic hydrolysis with the acetone-insoluble fraction from the sea whip, *Plexaura homomalla.*[11]

The biological evaluation of these novel prostaglandin analogues is in progress and will be reported elsewhere. However, it is interesting to note that free acid **29** is 30 times more potent than PGE_1 as an inhibitor of ADP-induced human platelet aggregation in vitro.[12]

Experimental Section

General. All melting points are corrected. All analytical data were obtained by the Physical and Analytical Chemistry Research Department of The Upjohn Co., with IR spectra being obtained either on neat samples (oils) or on Nujol mulls (crystalline samples). Mass spectra were recorded at high or low resolution for derivatized (Me_3Si)

Scheme III



[a] OsO_4, *N*-methylmorpholine oxide, acetone, H_2O, 25 °C. [b] CH_3SO_2Cl, pyridine, 0 °C. [c] Acetone–water (2:1), 25 °C. [d] *Plexaura homomalla* enzyme, H_2O.

or underivatized compounds at 70 eV. The NMR spectra were obtained on a Varian A-60D or T-60 spectrometer operating at 60 MHz on chloroform-*d* solutions containing internal tetramethylsilane. Thin-layer chromatography (TLC) was conducted using Analtech (Uniplate) glass plates precoated with silica gel GF (250 μm). Where mixed solvents were used for chromatography, the composition is expressed as a percent by volume of the former in the latter. The solvent system A-IX[13] is the organic layer from an equilibrated mixture of 90 mL of ethyl acetate, 20 mL of acetic acid, 50 mL of 2,2,4-trimethylpentane, and 100 mL of water. The TLC plates were visualized first by UV light (Mineralight UVS-11), then by spraying with a vanillin–phosphoric acid solution or 50% aqueous sulfuric acid, followed by heating. Unless otherwise noted, column chromatography utilized neutral silica gel (E. Merck), 70–230 mesh. Acid washed silica gel was Mallinckrodt CC-4. All solvents were reagent grade or reagent grade distilled from glass (Burdick and Jackson). All reagents were used as purchased and were reagent grade where available.

***dl*-7-Oxa-8-phenyltricyclo[4.2.0.0^{2,4}]octane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (9).** A Pyrex photolysis vessel, equipped with an immersible, water-cooled cold-finger and fritted gas inlet, was charged with a solution of 5.82 g (30 mmol) of *dl*-**5** and 1.06 g (10 mmol) of benzaldehyde in 25 mL of benzene. Dry nitrogen was bubbled through the solution for 15 min to remove dissolved oxygen, and the reaction mixture was then irradiated at 350 nm with a Rayonet Type RS preparative photochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with six RUL 3500-Å lamps for 48 h. The photolysate was concentrated in vacuo to give 7.31 g of a pale yellow oil which was chromatographed as follows: a 28 mm × 48 in. column was slurry-packed with 300 g of silica gel in Skellysolve B. The sample was applied in Skellysolve B and eluted with 250 mL of Skellysolve B, 1500 mL of 10% ethyl acetate in Skellysolve B, 1000 mL of 20% ethyl acetate in Skellysolve B, and 500 mL of ethyl acetate. Fractions 1 and 2 were 500 mL each (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 12–25 were combined to give 4.20 g of recovered *dl*-**5**. Fractions 83–113 were combined to give 1.19 g (47% based on recovered **5**) of pure oxetane **9** as a pale tan oil which crystallized on standing at −19 °C. A small portion of this material was recrystallized from ethyl acetate–Skellysolve B (3×) to give colorless microcrystals: mp 103.0–105.0 °C. The IR showed bands at 3030, 1600, 1580, 1490, 1110, 1020, 1005, 750, and 700 cm^{-1}. The NMR showed absorptions at δ 0.68 (s, 3 H), 1.18 (s, 3 H), 0.9–2.7 (m, 5 H), 3.00 (t, J = 4 Hz, 1 H), 3.1–3.8 (m, 4 H), 3.50 (d, J = 8 Hz, 1 H), 5.13 (t, J = 4 Hz, 1 H), 5.40 (d, J = 4 Hz, 1 H), 7.33 (bd s, 5 H). The mass spectrum exhibited peaks at m/e 300 (M$^+$; very weak), 299, 115, 108, 107, 80, 79, 77, 70, 69, 45, and 41. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.31.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.67; H, 8.21.

***dl*-2-*exo*-Benzyl-3-*exo*-hydroxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (10).** A 50-mL round-bottom flask, equipped with magnetic stirring bar and reflux condenser, was charged with 10 mL of toluene and 0.07 g (3.03 mg-atoms) of sodium metal. After heating the mixture to reflux, a solution of 0.25 g (0.83 mmol) of oxetane **9** and 0.16 mL (ca. 1.8 mmol) of *n*-butyl alcohol in 1.0 mL of toluene was added dropwise with stirring from the top of the reflux condenser. The addition funnel was rinsed with toluene (2 × 0.5 mL) and the reaction mixture was refluxed for 2.5 h. Methanol (0.5 mL) was then added to destroy the unreacted sodium. The reaction mixture was cooled to room temperature, diluted with brine, and extracted with ethyl acetate (2×). After washing the combined extracts with brine (3×) and drying over magnesium sulfate, concentration in vacuo gave 0.277 g of crude product which was chromatographed as follows: a 19 mm × 24 in. column was slurry packed with 60 g of silica gel in 20% ethyl acetate in Skellysolve B. The sample was applied and eluted with 300 mL of 20% ethyl acetate in Skellysolve B and 500 mL of 50% ethyl acetate in Skellysolve B. The first fraction was 200 mL (discarded). Subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 13–23 were combined to give 0.213 g (85%) of pure **10** as a white crystalline solid. Recrystallization of this material from ethyl acetate–Skellysolve B gave a white powder: mp 119.8–122.8 °C. The IR showed bands at 3290, 3020, 1600, 1585, 1495, 1115, 1085, 1070, 1020, 995, 985, 735, and 700 cm^{-1}. The NMR showed absorptions at δ 0.67 (s, 3 H), 1.18 (s, 3 H), 0.55–3.19 (m, 8 H), 2.23 (bd s, 1 H), 3.19–3.85 (m, 4 H), 4.10 (d, J = 7 Hz, 1 H), 3.85–4.37 (m, 1 H), 7.22 (bd s, 5 H). The mass spectrum exhibited peaks at m/e 115, 107, 105, 91, 79, 69, 55, 45, 43, and 41. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.08.

Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.54; H, 8.89.

***dl*-3-*exo*-Hydroxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (12) and *dl*-2-*exo*-Hydroxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (13).** A 500-mL three-neck, round-bottom flask, equipped with magnetic stirring bar, nitrogen inlet, and serum stopper, was charged with 5.82 g (30 mmol) of acetal *dl*-**5** and 100 mL of tetrahydrofuran. The resulting solution was stirred, alternately degassed and flushed with nitrogen several times, and then cooled to 0 °C. A solution of 25 mL of 1.0 M borane in tetrahydrofuran (25 mmol) was added, and the reaction mixture was then warmed to room temperature with stirring for 1 h. After cooling back down to 0 °C, excess borane was quenched by the cautious addition of 3 mL of water. The reaction mixture was then treated with 6.6 mL of 3 N aqueous sodium hydroxide followed by the dropwise addition of 6.6 mL of 30% hydrogen peroxide, and then allowed to stir at room temperature overnight. After dilution with brine, the product was extracted with chloroform (3×). The combined organic fractions were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 7.17 g of crude product which was chromatographed as follows: a 28 mm × 48 in. column was slurry packed with 300 g of silica gel in 5% acetone in methylene chloride. The sample was applied in methylene chloride and eluted with 250 mL of 5% acetone in methylene chloride, 500 mL of 10% acetone in methylene chloride, 1000 mL of 20% acetone in methylene chloride, and 500 mL of 30% acetone in methylene chloride. The first fraction was 1000 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 28–38 were combined to give 2.44 g (38%) of alcohol **12** as colorless crystals: mp 97–102 °C. Recrystallization from ethyl acetate–Skellysolve B gave pure **12** as colorless needles: mp 105.3–106.8 °C. The IR showed bands at 3480, 3050, 3030, 1110, 1105, 1070, 1020, 1000, and 975 cm^{-1}. The NMR showed absorptions at δ 0.70 (s, 3 H), 1.20 (s, 3 H), 0.6–2.4 (m, 7 H), 2.92 (bd s, 1 H), 3.20–3.81 (m, 4 H), 3.92 (d, J = 7.5 Hz, 1 H), 3.8–4.46 (m, 1 H). The mass spectrum exhibited peaks at m/e 212 (M$^+$; very weak), 115, 96, 69, 55, 45, and 41. TLC using 30% ethyl acetate in Skellysolve B showed one spot, R_f 0.48.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.81; H, 9.70.

Fractions 39–56 were combined to give 2.36 g (37%) of a mixture of **12** and **13**. Fractions 57–66 were combined to give 0.55 g (9%) of slightly impure acetal **13** as a colorless solid. Recrystallization of this material from ethyl acetate–Skellysolve B (2×) gave pure **13** as colorless needles: mp 117.8–119.5 °C. The IR showed bands at 3420, 3040, 3020, 1115, 1095, 1015, 1005, 990, and 980 cm^{-1}. The NMR spectrum showed absorptions at δ 0.70 (s, 3 H), 1.20 (s, 3 H), 0.5–2.6 (m, 7 H), 3.17 (bd s, 1 H), 3.17–3.80 (m, 4 H), 4.12 (d, J = 7 Hz, 1 H), 4.17–4.43 (m, 1 H). The mass spectrum exhibited peaks at m/e 212 (M$^+$; very weak), 115, 109, 96, 79, 55, 45, and 41. TLC using 30% ethyl acetate in Skellysolve B showed one spot, R_f 0.41.

Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.81, 67.50; H, 9.03, 9.38.

***dl*-2-Oxobicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (15).** A 250-mL flask, equipped with magnetic stirring bar and calcium sulfate drying tube, was flushed with dry nitrogen and charged with 40 mL of methylene chloride and 2.24 g (28.26 mmol) of pyridine followed by 1.41 g (14.13 mmol) of chromium trioxide. After stirring at room temperature for 30 min, the burgundy-colored reaction mixture was treated all at once with a solution of 0.50 g (2.36 mmol) of alcohol **13** in a minimal volume of methylene chloride. The reaction mixture was then stirred at room temperature for 30 min, diluted with 130 mL of ether, and washed with 5% aqueous sodium hydroxide (3 × 75 mL), water, saturated aqueous cupric sulfate (2 × 75 mL), and brine, and dried over magnesium sulfate. Concentration in vacuo gave 0.50 g (ca. 100%) of slightly impure product as an oily solid. Recrystallization of this material from ether–hexane (2×) gave pure **15** as colorless needles: mp 99.8–101.0 °C. The IR showed bands at 3060, 1710, 1185, 1110, 1095, 1015, 995, and 930 cm^{-1}. The NMR spectrum showed absorptions at δ 0.70 (s, 3 H), 1.20 (s, 3 H), 1.5–2.5 (m, 7 H), 3.1–3.8 (m, 4 H), 4.30 (d, J = 6 Hz, 1 H). The mass spectrum exhibited peaks at m/e 209 (M$^+$ − 1; very weak), 125, 115, 95, 69, 56, 55, 45, 41, 30, and 29. The ultraviolet spectrum showed $\lambda_{max}^{n\to\pi^*}$ 278 nm (ε 41) in ethanol. TLC using 50% ethyl acetate in Skellysolve B showed one spot, R_f 0.42.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.83; H, 8.89.

***dl*-3-Oxobicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (14).** In the same manner that **13** was oxidized to **15**, alcohol **12** (2.38 g, 11.21 mmol) was oxidized to ketone **14** using 175 mL of methylene chloride, 10.93 g (138.12 mmol) of pyridine, and 6.90 g (69.06 mmol) of chromium trioxide. Identical workup as before gave 2.54 g of crude **14** which was chromatographed as follows: a 19

mm × 24 in. column was slurry-packed with 60 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 350 mL of 5% ethyl acetate in Skellysolve B, 250 mL of 10% ethyl acetate in Skellysolve B, and 500 mL of 25% ethyl acetate in Skellysolve B. The first fraction was 300 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 21–34 were combined to give 2.28 g (97%) of pure **14** as a waxy solid. Recrystallization from Skellysolve B at −19 °C gave colorless microprisms: mp 54.0–55.3 °C. The IR showed bands at 3050, 3030, 2750, 2650, 1740, 1150, 1115, 1015, 995, and 980 cm^{-1}. The NMR spectrum showed absorptions at δ 0.68 (s, 3 H), 1.20 (s, 3 H), 0.9–3.0 (m, 7 H), 3.15–3.82 (m, 4 H), 4.07 (d, J = 7 Hz, 1 H). The mass spectrum exhibited peaks at m/e 210 (M^+; very weak), 209 ($M^+ - 1$; very weak), 125, 115, 95, 69, 67, 56, 55, 45, 43, and 41. The ultraviolet spectrum showed $\lambda_{max}^{n\rightarrow\pi^*}$ 270 nm (ε 28) in ethanol. TLC using 50% ethyl acetate in Skellysolve B showed one spot, R_f 0.50.

Anal. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.02, 68.67; H, 8.92, 8.96.

***dl*-2-*exo*-Benzyl-3-oxobicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (11).** A 250-mL flask, equipped with magnetic stirring bar, was charged with 125 mL of tetrahydrofuran (Burdick and Jackson) and 2.66 g (12.65 mmol) of ketone **14**. After purging the reaction vessel with nitrogen for several minutes, solid potassium *tert*-butoxide (1.55 g; 13.81 mmol) was added, and the reaction mixture was stirred at room temperature for 5 min. The enolate containing solution was then treated dropwise with benzyl bromide (2.18 g; 12.74 mmol), stirred for 1 h, and quenched with 35 mL of water. The reaction mixture was concentrated in vacuo, diluted with brine, and extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over magnesium sulfate, and concentrated in vacuo to give 4.60 g of crude product as an oil which was chromatographed as follows: a 19 mm × 24 in. column was slurry-packed with 60 g of silica gel in 2% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 350 mL of Skellysolve B, 250 mL of 5% ethyl acetate in Skellysolve B, 250 mL of 10% ethyl acetate in Skellysolve B, and 500 mL of 20% ethyl acetate in Skellysolve B. The first fraction was 500 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 6–17 were combined to give 0.65 g (13%) of dialkylated material. Fractions 18–25 were combined to give 1.07 g (28%) of pure **11** as a white crystalline solid. Recrystallization of this material from benzene–hexane (2×) and then acetone–ether gave pure **11** as colorless prisms: mp 130.3–132.8 °C. The IR showed bands at 3060, 1735, 1600, 1500, 1470, 1115, 1100, 1015, 990, 790, 765, and 710 cm^{-1}. The NMR spectrum showed absorptions at δ 0.64 (s, 3 H), 1.17 (s, 3 H), 1.03–1.83 (m, 3 H), 2.10–3.17 (m, 5 H), 3.17–3.77 (m, 4 H), 4.06 (d, J = 6.5 Hz, 1 H), 7.20 (s, 5 H). The mass spectrum exhibited peaks at m/e 300 (M^+), 219, 170, 128, 123, 115, 104, 91, 81, 69, 45, and 41. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.39. TLC using 10% acetone in benzene showed one spot, R_f 0.49.

Anal. Calcd for $C_{19}H_{24}O_3$: C, 75.97; H, 8.05. Found: C, 75.72; H, 8.11.

***dl*-2-*exo*-Benzyl-3-oxobicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (11).** A 50-mL round-bottom flask, equipped with magnetic stirring bar and calcium sulfate drying tube, was flushed with dry nitrogen and charged with 10 mL of methylene chloride and 0.278 g (3.5 mmol) of pyridine. Solid chromium trioxide (0.176 g, 1.76 mmol) was then added in one portion and the resulting mixture stirred at room temperature for 30 min. To this burgundy-colored solution was added a solution of 0.0884 g (0.293 mmol) of alcohol **10** in a minimal volume of methylene chloride. After stirring at room temperature for 45 min, the reaction mixture was transferred to a separatory funnel containing 100 mL of 5% aqueous sodium hydroxide and 100 mL of ether. The remaining chromium salts were washed with a little ether which was combined with the organic phase. After thorough mixing, the layers were separated and the organic phase was washed with 5% aqueous sodium hydroxide (2 × 100 mL), water, saturated aqueous cupric sulfate, water, and brine, and dried over $MgSO_4$. Concentration in vacuo gave 0.0872 g (99%) of crude product **11** as a white solid. The NMR and infrared spectra of this material were identical with those of an independently synthesized sample of **11**, as were its R_f values in three different solvent systems. Recrystallization of the crude oxidation product from benzene–hexane (2×) and then from acetone–ether gave colorless prisms: mp 128.5–131 °C, undepressed on admixture with authentic *dl*-**11**.

***m*-Acetoxybenzaldehyde (16).** The method of Bender and Nakamura[6] was employed. Thus, a 250-mL flask, equipped with a magnetic stirring bar and calcium sulfate drying tube, was charged with 25.0 g (0.205 mol) of *m*-hydroxybenzaldehyde and 100 mL of pyridine followed by 25.0 mL of acetic anhydride. After stirring at room temperature for 40 min, the reaction mixture was diluted with brine and ice and extracted with ethyl acetate (2×). The combined extracts were washed with 1.2 N aqueous hydrochloric acid (2×), saturated aqueous sodium bicarbonate (2×), and brine, and dried over magnesium sulfate. Concentration in vacuo gave 32.52 g of a red-orange oil which was distilled at reduced pressure to give 24.95 g (74%) of pure **16**: bp 100 °C (1.0 mm). The NMR spectrum showed absorptions at δ 2.25 (s, 3 H), 7.1–7.8 (m, 4 H), 9.78 (s, 1 H).

***d*-8-(*m*-Acetoxyphenyl)-7-oxatricyclo[4.2.0.0^{2,4}]octane-3-*endo*-carboxaldehyde Neopentyl Glycol Acetal (17).** A Pyrex photolysis vessel, equipped with an immersible, water-cooled cold-finger and fritted gas inlet, was charged with a solution of 5.82 g (30 mmol) of *l*-bicyclo[3.1.0]-hex-2-ene-6-*endo*-carboxaldehyde neopentyl glycol acetal **5**[4] ($[\alpha]_D$ − 227 ° in methanol) and 1.64 g (10 mmol) of *m*-acetoxybenzaldehyde in 25 mL of benzene. Dry nitrogen was bubbled through the solution for 15 min to remove dissolved oxygen, and the reaction mixture was then irradiated at 350 nm with a Rayonet Type RS preparative photochemical reactor (The Southern New England Ultraviolet Co., Middletown, Conn.) equipped with six RUL 3500-Å lamps for 24 h. Extended irradiation times did not significantly increase the yield of product. The photolysate was concentrated in vacuo to give 10 g of a pale yellow oil which was chromatographed as follows: a 28 mm × 48 in. column was slurry-packed with 300 g of silica gel in 10% ethyl acetate in Skellysolve B. The sample was applied and eluted with 700 mL of 15% ethyl acetate in Skellysolve B, 1000 mL of 25% ethyl acetate in Skellysolve B, 1000 mL of 35% ethyl acetate in Skellysolve B, 1000 mL of 50% ethyl acetate in Skellysolve B, and 1000 mL of 70% ethyl acetate in Skellysolve B. The first fraction was 500 mL (discarded), and subsequent fractions were 50 mL each. Based on TLC homogeneity, fractions 9–16 were combined to give 4.17 g of recovered olefinic acetal **5** as a white crystalline solid: mp 53–55 °C ($[\alpha]_D$ − 227 ° in methanol). The rotation of this material was identical with that of pure starting material which confirmed that racemization of *l*-**5** had not occurred during photolysis. Fractions 26–32 were combined to give 0.46 g (28%) of recovered *m*-acetoxybenzaldehyde. Fractions 33–58 were combined to give 1.50 g of impure **17** which was submitted to HPLC purification as follows: an LC-1-43 column (Chromatronix, Inc., Berkeley, Calif.) containing 241 g of "sized" Silica Gel H (mean particle diameter ca. 40 μm) was equilibrated with 30% ethyl acetate in Skellysolve B. The sample was diluted to 6 mL with methylene chloride, injected onto the column, and eluted with 30% ethyl acetate in Skellysolve B at 10.5 mL/min and 25 psi with a Milton Roy Co. pump (Model DC-1-60R Simplex Milroyal Pump, Milton Roy Co., Philadelphia, Pa.). The first fraction was 800 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 24–45 were combined to give 0.86 g (33% based on recovered **16**) of pure *d*-**17** as a pale yellow oil; $[\alpha]_D$ + 55 ° (*c* 0.7505, 95% ethanol). The IR showed bands at 3040, 2950, 2860, 2840, 1765, 1610, 1590, 1485, 1470, 1370, 1205, 1115, 1020, 1005, 990, 790, and 700 cm^{-1}. The NMR spectrum showed absorptions at δ 0.68 (s, 3 H), 1.20 (s, 3 H), 0.8–2.5 (m, 5 H), 2.28 (s, 3 H), 2.99 (t, J = 4 Hz, 1 H), 3.12–3.88 (m, 4 H), 3.48 (d, J = 8 Hz, 1 H), 4.97–5.52 (m, 2 H), 6.78–7.60 (m, 4 H). The mass spectrum exhibited peaks at m/e 358 M^+; very weak), 116, 115, 108, 107, 79, 70, 69, 45, 43, and 41. TLC using 25% ethyl acetate in Skellysolve B showed a single spot, R_f 0.18.

***d*-2-*exo*-(*m*-Acetoxybenzyl)-3-*exo*-hydroxybicyclo[3.1.0]-hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (18).** A glass Parr hydrogenation bottle (ca. 500 mL) was charged with 5.66 g of partially purified *d*-8-(*m*-acetoxyphenyl)-7-oxatricyclo[4.2.0.0^{2,4}]octane-6-*endo*-carboxaldehyde neopentyl glycol acetal **17**, 100 mL of absolute ethanol, and 0.30 g of 10% palladium on carbon. The resulting mixture was then hydrogenated on a Parr apparatus at 20 psi overnight (ca. 16–18 h). The mixture absorbed ca. 15 mmol of hydrogen, and longer reduction times resulted in no further absorption. The resulting mixture was filtered through Celite to remove the catalyst, and the filtrate was concentrated in vacuo to give 5.66 g of crude **18**. A 48 mm × 36 in. column was slurry-packed with 500 g of silica gel in 25% ethyl acetate in Skellysolve B. The sample of **18** was applied in methylene chloride and eluted with 1 L each of 30, 30, 40, 50, 60, 70, and 80% ethyl acetate in Skellysolve B. Fractions were 50 mL each. Based on TLC homogeneity fractions 72–89 were combined to give 3.65 g of **18** as a solid (30% yield overall from *l*-**5** based on recovered *l*-**5**). In a separate experiment, a sample of chromatographically pure **18** was recrystallized from ethyl acetate–*n*-hexane (2×) to give colorless needles: mp 122.2–125.9 °C; $[\alpha]_D$ + 31 ° (*c* 0.9188, ethanol). The IR showed bands at 3220, 1775, 1610, 1590, 1490, 1200, 1185, 1150, 1115, 1110, 1080, 1015, and 695 cm^{-1}. The NMR spectrum showed absorptions at δ 0.73 (s, 3 H), 1.25 (s, 3 H), 0.5–3.22 (m, 9 H), 2.30 (s, 3 H), 3.22–3.86 (m, 4 H), 4.00–4.37 (m, 2 H), 6.72–7.50 (m, 4 H). The mass spectrum exhibited peaks at m/e

360 (M^+; weak), 359, 342, 331, 317, 316, 304, 301, 300, 256, 214, 211, 125, 115, 107, and 69. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.32.

Anal. Calcd for $C_{21}H_{28}O_5$: C, 69.97; H, 7.83. Found: C, 69.98; H, 7.94.

***d*-2-*exo*-[*m*-(Pivaloyloxy)benzyl]-3-*exo*-(pivaloyloxy)bicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (20) and *l*-2-*exo*-(Pivaloyloxy)-2-*exo*-[*m*-(pivaloyloxy)benzyl]bicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (23).** A 500-mL flask, equipped with a magnetic stirring bar, was charged with 16.40 g (45.50 mmol) of chromatographically pure acetate **18** and 200 mL of methanol. The resulting solution was then treated with a solution of 6.0 g of potassium carbonate in 65 mL of water. The reaction mixture was stirred for 16 h at room temperature, diluted with 500 mL of ice-cold water, acidified to pH 5 with 1 M aqueous potassium bisulfate, and saturated with sodium chloride. The resulting aqueous mixture was extracted with chloroform (4 × 150 mL). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 16.57 g of crude 2-*exo*-(*m*-hydroxybenzyl)-3-*exo*-hydroxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde neopentyl glycol acetal (**19a**) as a pale yellow oil.

The above sample of diol **19a** was dissolved in 150 mL of pyridine and treated with 17.75 mL of pivaloyl chloride. The reaction mixture was stirred at room temperature for 2 days. Excess acid chloride was decomposed by the dropwise addition of 20 mL of water. The reaction mixture was diluted with 1000 mL of brine and extracted with ethyl acetate (2 × 200 mL). The combined extracts were washed with brine, water, saturated aqueous cupric sulfate (until all pyridine was removed), saturated aqueous sodium bicarbonate, and brine, and dried over sodium sulfate. Concentration in vacuo gave crude **20** which was chromatographed as follows: a 48 mm × 36 in. column was slurry-packed with 500 g of silica gel in 3% ethyl acetate in Skellysolve B. The sample was applied with Skellysolve B and eluted with 10% ethyl acetate in Skellysolve B. Fractions were 100 mL each. Based on TLC homogeneity, fractions 12–36 were combined to give 18.56 g (84%) of **20** as an oil which crystallized on standing at room temperature. This material was dissolved in 100 mL of methanol, heated to 40–45 °C on a steam bath, diluted with water to the point of incipient cloudiness, cooled, seeded, and allowed to crystallize overnight at 4 °C to give 8.81 g of essentially pure **20** as colorless needles: mp 106–112 °C. Subsequent recrystallizations from *n*-hexane (6×) gave analytically pure **20:** mp 112.4–115.1 °C; $[\alpha]_D$ +23° (*c* 0.8270, ethanol). The IR showed bands at 3040, 1755, 1725, 1610, 1590, 1285, 1235, 1160, 1150, 1120, 1100, 1020, and 990 cm^{-1}. The NMR showed absorptions at δ 0.72 (s, 3 H), 1.22 (s, 12 H), 1.36 (s, 9 H), 0.5–3.12 (m, 8 H), 3.25–3.83 (m, 4 H), 4.18 (d, J = 6.5 Hz, 1 H), 4.77–5.19 (m, 1 H), 6.70–7.37 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 486 (M^+; weak), 384, 298, 214, 196, 193, 115, 107, 85, 69, 57, 45, and 41. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.50. GLPC using 6 ft × ⅛ in. 1% OV-17 on 80/100 Gas Chrom Q at 225 °C (60 mL/min), t_R = 8.4 min.

Anal. Calcd for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.47; H, 8.84.

The mother liquors from the above crystallization were combined. Recrystallization from methanol–water (2×) gave 1.0 g of isomeric dipivalate **23** as colorless microcrystals; mp 135.1–136.6 °C; $[\alpha]_D$ −25 ° (*c* 0.9000, ethanol). The IR showed bands at 3040, 1755, 1720, 1610, 1585, 1285, 1170, 1140, 1120, 1110, and 975 cm^{-1}. The NMR spectrum showed absorptions at δ 0.70 (s, 3 H), 1.20 (s, 3 H), 1.22 (s, 9 H), 1.33 (s, 9 H), 0.5–3.13 (m, 8 H), 3.15–3.82 (m, 4 H), 4.23 (d, J = 6 Hz, 1 H), 5.15–5.42 (m, 1 H), 6.71–7.54 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 486 (M^+; weak), 384, 298, 214, 196, 193, 171, 115, 107, 85, 69, and 57. TLC using 25% ethyl acetate in Skellysolve B showed a single spot, R_f 0.50. GLPC using 6 ft × ⅛ in. 1% OV-17 on 80/100 Gas Chrom Q at 225 °C (60 ml/min), t_R = 7.4 min.

Anal. Calcd for $C_{29}H_{42}O_6$: C, 71.57; H, 8.70. Found: C, 71.32; H, 8.94.

***d*-2-*exo*-(*m*-Acetoxybenzyl)-3-*exo*-acetoxybicyclo[3.1.0]-hexane-6-*endo*-carboxaldehyde Neopentyl Glycol Acetal (19b).** A sample of 1.01 g (ca. 3.17 mmol, prepared as previously described) of crude diol **19a** was dissolved in 25 mL of pyridine and treated with 5 mL of acetic anhydride. After stirring for 15.5 h at room temperature, the reaction mixture was diluted with 200 mL of brine and extracted with ethyl acetate (2 × 100 mL). The combined extracts were washed with saturated aqueous sodium bicarbonate (2 × 100 mL), water, saturated aqueous cupric sulfate (2 × 100 mL), water, and brine, and dried over sodium sulfate. Concentration in vacuo gave 0.75 g (90%) of nearly pure diacetate, which was further purified by passage through a 1-in. plug of silica gel to give pure *d*-**19b** as an oil; $[\alpha]_D$ +7° (*c* 0.7060, ethanol). The IR showed bands at 3030, 2950, 2860, 1765, 1735, 1610, 1590, 1490, 1470, 1450, 1395, 1370, 1240, 1205, 1145, 1115, 1100, 1065, 1040, 1015, 985, 960, 930, 790, and 695 cm^{-1}. The NMR showed absorptions at δ 0.72 (s, 3 H), 1.22 (s, 3 H), 1.98 (s, 3 H), 2.27 (s, 3 H), 0.8–3.0 (m, 8 H), 3.28–3.85 (m, 4 H), 4.17 (d, J = 6.5 Hz, 1 H), 4.75–5.22 (m, 1 H), 6.80–7.47 (m, 4 H). The mass spectrum exhibited peaks at *m/e* 402 (M^+; very weak), 401, 115, 107, 73, 69, 45, 44, 43, 42, 41, and 30. TLC using 50% ethyl acetate in Skellysolve B showed one spot, R_f 0.66.

Optical Purity Studies on *d*-19b and *dl*-19b. A sample of ca. 60 mg of *dl*-**19b** (prepared in the same manner as *d*-**19b,** except that *dl*-**5** was used in the preparation of *dl*-**17**) was dissolved in 0.5 mL of deuteriochloroform (Stohler Isotope Chemicals) and transferred to an NMR tube (5 × 180 mm). An NMR spectrum was recorded. Incremental amounts of tris[3-(heptafluoropropylhydroxymethylene)-*d*-camphorato]europium(III) (Willow Brook Laboratories, Inc. Eu-OPTI-SHIFT II) were then added (as the solid) by "small spatula tips" and the NMR spectrum of the resulting solution was recorded. After the addition of 28 spatula tips of shift reagent, the C-9 acetate signal was shifted downfield by 3.8 ppm and was split into two singlet resonances of equal intensity (one each for the *d* and *l* enantiomeric forms) with $\Delta\nu$ = 5 Hz. Correspondingly, the phenolic acetate signal was shifted downfield by 1.35 ppm and was split into two singlets with $\Delta\nu$ = 2 Hz.

The same experiment was then repeated with a sample of *d*-**19b** (ca. 120 mg) dissolved in 1.0 mL of deuteriochloroform. The shift reagent was added in increments until the C-9 acetate signal was shifted downfield by ca. 3.8 ppm. At this point, only *one* singlet was detected (>90% *d*-enantiomer by NMR). Similar results were obtained by monitoring the phenolic acetate signal.

Optically Active 2-*exo*-[*m*-(Pivaloyloxy)benzyl]-3-*exo*-pivaloyloxybicyclo[3.1.0]hexane-6-*endo*-carboxaldehyde (21). A 50-mL flask, equipped with a magnetic stirring bar, was charged with 0.48 g (0.97 mmol) of *d*-acetal **20** and immersed in an ice bath. Stirring was initiated, and 25 mL of 88% formic acid (precooled to 0 °C) was added all at once. The reaction mixture was stirred at 0 °C for 4 h, diluted with 200 mL of brine, and extracted with 150 mL of ethyl acetate. The extract was then washed with brine, and saturated aqueous sodium bicarbonate (2×), and dried over magnesium sulfate. Concentration in vacuo gave 0.55 g of crude **21** as an oil which was chromatographed as follows: a 19 mm × 24 in. column was wet-packed with 60 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 300 mL of 5% ethyl acetate in Skellysolve B, 500 mL of 10% ethyl acetate in Skellysolve B, and 500 mL of 15% ethyl acetate in Skellysolve B. The first fraction was 350 mL (discarded), and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 19–35 were combined to give 0.37 g of pure, optically active **21** as an oil which partially solidified at −19 °C. The NMR spectrum showed absorptions at δ 1.20 (s, 9 H), 1.33 (s, 9 H), 0.6–3.2 (m, 8 H), 5.1–5.5 (m, 1 H), 6.6–7.5 (m, 4 H), 9.68 (d, J = 3 Hz, 1 H). TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.50.

Optically Active 2-*exo*-{*m*-[(Methoxycarbonyl)methoxy]-benzyl}-3-*exo*-(pivaloyloxy)-6-*endo*-(*cis*-1-heptenyl)bicyclo[3.1.0]hexane (22c). A 250-mL pointed flask, equipped with a magnetic stirring bar, was charged with 5.68 g (13.3 mmol) of *n*-hexyltriphenylphosphonium bromide and 75 mL of benzene. The system was stoppered with a serum cap and then alternately degassed and flushed with nitrogen (3×). *n*-Butyllithium (1.6 M in hexane) was added dropwise with stirring until a permanent yellow color was produced. An additional 8.24 mL (13.2 mmol) of *n*-butyllithium was then added. The reaction mixture was stirred at 25 °C for 45 min to generate the red ylide. The suspended lithium bromide was allowed to settle, and the supernatant was transferred to an oven-dry 500-mL three-neck flask via a cannula with positive nitrogen pressure. The lithium bromide was washed with 40 mL of benzene and allowed to settle, and the supernatant again transferred via cannula. The red benzene solution was cooled to 10 °C in a water bath, and a solution of 3.52 g (8.79 mmol) of aldehyde **21** in 10 mL of benzene was added all at once. Residual aldehyde was washed in with 2 × 3 mL of benzene, and the reaction mixture was stirred at 25 °C for 15 min. Acetone (5 mL) was added to react with excess Wittig reagent, and the reaction mixture was heated to 60 °C for 10 min, cooled to room temperature, and diluted with brine. The layers were mixed and separated. The aqueous phase was extracted with benzene (150 mL), and the combined extracts were dried over sodium sulfate. Concentration in vacuo gave 8.65 g of crude product. This material was suspended in Skellysolve B and filtered, washing well with Skellysolve B. The filtrate was concentrated in vacuo to give a brown oil which was filtered through 50 g of silica gel, eluting with 1000 mL of 10% ethyl acetate

in Skellysolve B. Fractions of 50 mL were collected. Based on TLC homogeneity, fractions 2 and 3 were combined to give 3.38 g (82%) of pure **22a** as an oil.

The above sample of **22a** was dissolved in 100 mL of methanol. A solution of 1.3 g of potassium carbonate in 15 mL of water was added, and the reaction mixture was stirred at 25 °C for 2 h. The major portion of methanol was removed in vacuo, and the residue was diluted with 300 mL of brine. The pH of this mixture was adjusted to 5–6 with 1 N aqueous hydrochloric acid, and the mixture was then extracted with diethyl ether (3×). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. Concentration in vacuo gave 3.00 g (~100%) of crude phenol **22b.**

The above sample of phenol **22b** was dissolved in 40 mL of 1,2-dimethoxyethane and 1.80 g (11.77 mmol) of methyl bromoacetate. The solution was alternately degassed and flushed witn nitrogen (2×), cooled to 0 °C, and treated in portions with 0.38 g of 57% sodium hydride dispersion (~9.03 mmol). The mixture was then stirred at 25 °C overnight (16 h). Excess hydride was destroyed by the dropwise addition of 2 mL of glacial acetic acid. The reaction mixture was diluted with 300 mL of brine and extracted with ethyl acetate (150 mL). The organic fraction was washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. Concentration in vacuo gave a yellow oil which was purified as follows: a 19 mm × 24 in. column was slurry-packed with 60 g of silica gel in 5% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 375 mL of 5% ethyl acetate in Skellysolve B and 500 mL of 10% ethyl acetate in Skellysolve B. Fractions were 20 mL each. Based on TLC homogeneity, fractions 12–25 were combined to give 3.29 g of diester **22c** as an oil (82% from **21**). The IR showed bands at 1775, 1750, 1735, 1620, 1590, 1480, 1450, 1439, 1281, 1208, and 1159 cm^{-1}. The NMR spectrum showed absorptions at δ 0.89 (t, J = 5 Hz, 3 H), 1.20 (s, 9 H), 0.6–3.0 (m, 16 H), 3.82 (s, 3 H), 4.65 (s, 2 H), 4.73–5.95 (m, 3 H), 6.62–7.43 (m, 4 H). TLC using 10% ethyl acetate in Skellysolve B showed on spot, R_f 0.27.

***l*-2-*exo*-{*m*-[(Methoxycarbonyl)methoxy]benzyl}-6-*endo*-(*cis*-1-heptenyl)bicyclo[3.1.0]hexan-3-one (4b).** A 100-mL flask, equipped with a magnetic stirring bar and reflux condenser, was charged with 2.83 g (6.20 mmol) of diester **22c** and 40 mL of absolute methanol. The resulting solution was alternately degassed and flushed with nitrogen (3×), treated with 10 mL of 25% sodium methoxide in methanol, and heated with stirring at 70 °C for 20 h. The reaction mixture was cooled to room temperature, acidified with 10 mL of glacial acetic acid, diluted with brine, and extracted with ethyl acetate (2×). The combined extracts were washed with saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. Concentration in vacuo gave 1.50 g of crude **4a.** The aqueous fraction from above was acidified with 1 M aqueous potassium bisulfate and extracted with chloroform (2×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 0.87 g of the free acid of **4a** as an oil. This material was esterified with diazomethane and combined with the previous sample of **4a** and purified as follows: a 28 mm × 36 in. column was slurry-packed with 200 g of silica gel in 10% ethyl acetate in Skellysolve B. The sample was applied in methylene chloride and eluted with 450 mL of 10% ethyl acetate in Skellysolve B, 1000 mL of 20% ethyl acetate in Skellysolve B, 1000 mL of 30% ethyl acetate in Skellysolve B, and 500 mL of 40% ethyl acetate in Skellysolve B. The first fraction was 500 mL and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 65–93 were combined to give 1.97g (85%) of alcohol **4a** as an oil.

A 250-mL flask, equipped with a magnetic stirring bar, was charged with 80 mL of methylene chloride and 5.02 g (63.46 mmol) of pyridine. Chromium trioxide (3.17 g, 31.7 mmol) was then added with stirring, and the burgundy-colored mixture was stirred at 25 °C under nitrogen for 30 min. A solution of 1.97 g (5.29 mmol) of the above alcohol in 5 mL of methylene chloride was added all at once. Residual alcohol was washed in with methylene chloride, and the resulting reaction mixture was stirred at 25 °C for 45 min. The mixture was then transferred to a separatory funnel, and the chromium salts were washed with diethyl ether (3 × 75 mL). The combined organic fractions were diluted with 50 mL of diethyl ether, washed with 1 N aqueous sodium hydroxide (3 × 100 mL), 1 N aqueous hydrochloric acid and brine, and dried over sodium sulfate. Concentration in vacuo gave 1.87 g of crude **4b** as an oil which was purified as follows: a 28 mm × 36 in. column was slurry-packed with 187 g of silica gel in 10% ethyl acetate in Skellysolve B. The sample was applied in Skellysolve B and eluted with 550 mL of 10% ethyl acetate in Skellysolve B, 530 mL of 15% ethyl acetate in Skellysolve B, and 1000 mL of 20% ethyl acetate in Skellysolve B. Fractions were 20 mL each. Based on TLC homogeneity, fractions 48–62 were combined to give 1.52 g of pure **4b** as an oil (66% overall from **22c**); $[\alpha]_D$ −39° (c 0.8380, ethanol). The IR showed bands at 3020, 2920, 2850, 1765, 1740, 1605, 1585, 1510, 1450, 1440, 1285, 1255, 1210, 1160, 1090, 780, and 695 cm^{-1}. The NMR spectrum showed absorptions at δ 0.87 (t, J = 5 Hz, 3 H), 0.6–3.3 (m, 16 H), 3.77 (s, 3 H), 4.60 (s, 2 H), 4.5–5.1 (m, 1 H), 5.37–5.95 (m, 1 H), 6.58–7.40 (m, 4 H). The mass spectrum exhibited peaks at m/e 370.2170 (M^+; calcd for $C_{23}H_{30}O_4$: 370.2144), 352, 342, 339, 311, 205, 204, 191, and 179. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.33.

Fractions 63–74 were combined to give 0.14 g of 3-*exo*-{*m*-[(methoxycarbonyl)methoxy]benzyl}-6-*endo*-(*cis*-1-heptenyl)bicyclo-[3.1.0]hexan-2-one (**25**) as an oil; $[\alpha]_C$ −37° (c 0.7915, ethanol). The IR showed bands at 3020, 3000, 2920, 2860, 1765, 1740, 1720, 1615, 1605, 1585, 1490, 1455, 1440, 1295, 1240, 1210, 1160, 1090, and 690 cm^{-1}. The NMR spectrum showed absorptions at δ 0.89 (t, J = 5 Hz, 3 H), 0.6–3.45 (m, 16 H), 3.82 (s, 3 H), 4.64 (s, 2 H), 4.95–6.00 (m, 2 H), 6.58–7.45 (m, 4 H). The mass spectrum exhibited peaks at m/e 370.2148 (M^+; calcd for $C_{23}H_{30}O_4$: 370.2144), 352, 339, 313, 299, 260, 220, 191, 179, and 150. TLC using 25% ethyl acetate in Skellysolve B showed one spot, R_f 0.27.

***l*-3-Oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin E_1 Methyl Ester (3) and *l*-(15*R*)-3-Oxa-4,5,6-trinor-3,7-*inter*-*m*-phenyleneprostaglandin E_1 Methyl Ester (28).** A 500-mL flask, equipped with a magnetic stirring bar, was charged with 8.07 g (21.78 mmol) of ketone **4b,** 100 mL of acetone, and 6.4 mL of water. The resulting solution was then treated with 2.6 mL of osmium tetroxide in *tert*-butyl alcohol (concentration, 30 mg/mL). *N*-Methylmorpholine oxide dihydrate (33.3 g, 22 mmol) was added, and the reaction mixture was stirred under nitrogen at 25 °C for 2 h. A solution of 5.0 g of sodium bisulfite in 25 mL of water was added and stirring was continued for 30 min. The reaction mixture was concentrated in vacuo, diluted with brine, and extracted with ethyl acetate (2×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 9.08 g of crude **26** which was purified as follows: a 48 mm × 36 in. column was slurry-packed with 454 g of silica gel in 20% ethyl acetate in Skellysolve B. The sample was applied in CH_2Cl_2 and eluted with 1 L each of 35, 45, 55, 70, and 80% ethyl acetate in Skellysolve B. The first fraction was 500 mL and subsequent fractions were 50 mL each. Based on TLC homogeneity, fractions 50–77 were combined to give 8.06 g (91%) of pure **26** as 1:1 mixture of isomers. TLC using 50% ethyl acetate in Skellysolve B showed two equally intense spots, R_f = 0.20 and 0.15.

A 250-mL three-neck flask, equipped with a magnetic stirring bar, thermometer, addition funnel, and a nitrogen inlet, was charged with 8.06 g (19.93 mmol) of glycols **26** and 100 mL of pyridine. The resulting solution was alternately degassed and flushed with nitrogen (2×), cooled to 6 °C, and treated with 7.72 mL (ca. 100 mmol) of methanesulfonyl chloride. The addition was carried out with vigorous stirring and at a rate that allowed the internal temperature to be maintained at 3–8 °C. After 2.5 h, the reaction mixture was diluted with 500 mL of methylene chloride. The total organic phase was washed with brine, 1 N aqueous hydrochloric acid (ice-cold; 5×), saturated aqueous sodium bicarbonate and brine, and dried over sodium sulfate. Concentration in vacuo gave 13.09 g of crude bismesylates **27** as a viscous oil.

The above sample of **27** was dissolved in 250 mL of acetone and treated with 125 mL of water. The reaction mixture was stirred at room temperature (25 °C) for 10 h and 20 min. Solid sodium bicarbonate was then added to adjust the pH to 6–7. The reaction mixture was concentrated in vacuo (to remove the major portion of acetone), diluted with brine, and extracted with chloroform (3×). The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 8.58 g of crude solvolysis product. A 48 mm × 36 in. column was slurry-packed with 430 g of silica gel in 5% acetone in methylene chloride. The solvolysis product was applied in methylene chloride and eluted with 1 L each of 10, 20, 30, 40, 50, and 60% acetone in methylene chloride. Fractions were 50 mL each. Based on TLC homogeneity, fractions 25–38 were combined to give 3.17 g of an oil containing a monomesylate. TLC using 20% acetone in methylene chloride showed two major spots, R_f 0.64 and 0.57. Fractions 65–81 were combined to give 0.81 g of essentially pure (15*R*)-prostaglandin **28.** Fractions 81–100 were combined to give 1.90 g of pure (15*S*)-prostaglandin **3.**

The above monomesylate fraction (fractions 25–38) was recycled (mesylation followed by solvolysis and chromatography) to afford an additional 0.23 g of (15*R*)-prostaglandin **28** (total yield 1.04 g, 13% based on **26**) and 0.42 g of (15*S*)-prostaglandin **3** (total yield 2.32 g, 29% based on **26**). The (15*S*)-prostaglandin **3** was obtained as an oil which slowly solidified at −19 °C to a waxy mass. A portion of this sample was rechromatographed by HPLC (2% methanol in chloro-

form) to give 1.14 g of very pure **3** as an oil. This material was dissolved in 7 mL of diethyl ether, cooled to −14 °C, and treated with *n*-hexane to the point of incipient cloudiness. The solution was seeded with the above waxy solid and stored at 0 °C for 30 min, then at 4 °C for 3 h and finally at −19 °C overnight. The procedure afforded 0.296 g of **3** as a white, tacky solid: mp 45–53 °C; $[\alpha]_D$ −48° (*c* 0.8275, ethanol). The IR showed bands at 3380, 2960, 2920, 2860, 1765, 1740, 1725, 1615, 1605, 1585, 1490, 1460, 1375, 1285, 1210, 1165, 1085, 1005, 970, 880, 785, and 700 cm^{-1}. The NMR spectrum showed absorptions at δ 0.92 (t, J = 5 Hz, 3 H), 0.7–3.0 (m, 14 H), 3.78 (s, 3 H), 3.0–4.4 (m, 4 H), 4.60 (s, 2 H), 5.48 (m, 2 H), 6.52–7.42 (m, 4 H). The mass spectrum exhibited peaks at 548.2979 (M^+ of $(Me_3Si)_2$ derivative; calcd for $C_{29}H_{48}Si_2O_6$: 548.2989), 533, 477, 458, 387, 368, 361, 333, and 179. TLC using 30% acetone in methylene chloride showed one spot, R_f 0.32. TLC using 7.5% methanol in methylene chloride showed one spot, R_f 0.35.

Several combined samples of slightly impure (15*R*)-prostaglandin **28** were twice rechromatographed by HPLC (one chromatography using 5% methanol in chloroform and a second using 20% acetone in methylene chloride) to afford a pure specimen of **28** as an oil; $[\alpha]_D$ −44° (*c* 0.9325, ethanol). The IR showed bands at 3420, 1745, 1605, 1590, 1490, 1215, 1160, 1085, and 975 cm^{-1}. The NMR spectrum showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 0.6–3.5 (m, 16 H), 3.78 (s, 3 H), 3.5–4.3 (m, 2 H), 4.59 (s, 2 H), 5.53 (m, 2 H), 6.47–7.45 (m, 4 H). The mass spectrum exhibited peaks at 548.3022 (M^+ of $(Me_3Si)_2$ derivative; calcd for $C_{29}H_{48}Si_2O_6$: 548.2989), 533, 477, 458, 387, 361, 333, 279, 217, and 179. TLC using 30% acetone in methylene chloride showed one spot, R_f = 0.37. TLC using 7.5% methanol in methylene chloride showed one spot, R_f = 0.38.

***l*-3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (29).** A 500-mL flask, equipped with a magnetic stirring bar, was charged with 0.79 g (1.95 mmol) of methyl ester **3** and 30 mL of 95% ethanol. The resulting solution was then treated with 52 mL of water, followed by 7.90 g of purified coral enzyme powder[11] and 112 mL of water. The reaction mixture was stirred at 24 °C for 14.5 h, diluted with 500 mL of acetone, allowed to stand for 30 min, and finally filtered through Celite. The filtered material was washed with 1000 mL of acetone, and the total filtrate was concentrated in vacuo to remove the major portion of acetone. The resulting aqueous mixture was diluted with brine, equilibrated with 200 mL of ethyl acetate and acidified to pH ~ 3 with 1 M aqueous citric acid. The layers were mixed and separated and the aqueous phase was again extracted with ethyl acetate. The combined extracts were washed with brine, dried over sodium sulfate, and concentrated in vacuo to give 0.87 g of crude **29** as an oil. A 19 mm × 24 in. column was slurry-packed with 43 g of Silica Gel CC-4 (Mallinckrodt) in 50% ethyl acetate in *n*-hexane. The sample was applied in methylene chloride and eluted with 275 mL of 50% ethyl acetate in *n*-hexane, 500 mL of 60% ethyl acetate in *n*-hexane, and 500 mL of ethyl acetate. Fractions were 20 mL each. Based on TLC homogeneity, fractions 32–80 were combined to give 0.41 g (54%) of pure **29** as a white solid. This sample was recrystallized from ethyl acetate–*n*-hexane to give 0.2901 g of pure **29** as white microcrystals: mp 128.7–130.0 °C. (In a separate experiment, an apparent isomorphic form of **29** was obtained: mp 100.1–102.5 °C); $[\alpha]_D$ −61° (*c* 0.8155, ethanol.) The IR showed bands at 3540, 3360, 3000, 2740, 2680, 2600, 2540, 1760, 1740, 1605, 1585, 1490, 1300, 1200, 1175, 1165, 1100, 1065, 960, 730, and 690 cm^{-1}. The NMR spectrum showed absorptions at δ 0.90 (t, J = 5 Hz, 3 H), 0.6–3.52 (m, 14 H), 3.52–4.36 (m, 2 H), 4.62 (bd s, 2 H), 5.49 (m, 2 H), 6.08–7.42 (m, 7 H, aryl H + 2 OH + CO_2H). The mass spectrum exhibited peaks at *m/e* 606.3226 (M^+ of $(Me_3Si)_3$ derivative; calcd for $C_{31}H_{54}Si_3O_6$: 606.3228), 591, 589, 535, 516, 501, 445, 426, and 237. TLC using A-IX[13] showed one spot, R_f 0.13.

Anal. Calcd for $C_{22}H_{30}O_6$: C, 67.67; H, 7.74. Found: C, 67.64; H, 7.84.

Optically Active (15*R*)-3-Oxa-4,5,6-trinor-3,7-*inter-m*-phenyleneprostaglandin E_1 (30). A 500-mL flask equipped with a magnetic stirring bar was charged with 0.91 g (2.25 mmol) of slightly impure methyl ester **28** and 36 mL of 95% ethanol. The resulting solution was then treated with 60 mL of water, followed by 9.10 g of purified coral enzyme powder[11] and 129 mL of water. The reaction mixture was stirred at room temperature for 24 h and worked up as detailed in the previous experiment (for the preparation of **29**) to give 1.07 g of crude **30** as an oil. A 28 mm × 36 in. column was slurry-packed with 214 g of Silica Gel CC-4 (Mallinckrodt) in 30% ethyl acetate in *n*-hexane. The sample was applied in methylene chloride and eluted with 1 L each of 40, 45, and 55% ethyl acetate in *n*-hexane followed by 500 mL each of 70 and 85% ethyl acetate in *n*-hexane. The first fraction was 500 mL and subsequent fractions were 20 mL each. Based on TLC homogeneity, fractions 132–169 were combined to give 0.50 g (57%) of pure **30** as an oil; $[\alpha]_D$ −45° (*c* 0.8595, EtOH). The IR showed bands at 3420, 2620, 2560, 1740, 1605, 1585, 1490, 1240, 1160, 1080, and 975 cm^{-1}. The NMR spectrum showed absorptions at δ 0.88 (t, J = 5 Hz, 3 H), 0.6–3.35 (m, 14 H), 4.01 (m, 2 H), 4.60 (bd s, 2 H), 5.53 (m, 2 H), 6.28 (bd s, 3 H, 2 OH + CO_2H), 6.4–7.50 (m, 4H). The mass spectrum exhibited peaks at *m/e* 606.3202 (M^+ of $(Me_3Si)_3$ derivative; calcd for $C_{31}H_{54}Si_3O_6$: 606.3228), 591, 535, 516, 501, 445, 426, 419, 391, 313, 279, 237, and 199. TLC using A-IX[13] showed one spot, R_f 0.18.

Acknowledgment. The authors thank P. A. Meulman and R. J. Wnuk for IR and mass spectra. We especially acknowledge with gratitude Dr. H. A. Karnes and associates for the preparation of generous supplies of intermediates, and Dr. N. A. Nelson for helpful discussions and a sample of *dl*-**3**.

Registry No.—**3**, 59829-42-4; **4a**, 59751-50-7; **4a** acid, 59751-49-4; **4b**, 59751-51-8; *dl*-**5**, 39521-36-3; *l*-**5**, 59685-80-2; **9**, 65423-67-8; **10**, 65423-68-9; **11**, 65423-69-0; **12**, 65452-58-6; **13**, 65452-59-7; **14**, 65452-60-0; **15**, 65452-61-1; **16**, 34231-78-2; **17**, 59657-47-5; **18**, 59657-49-7; *d*-**19b**, 59657-50-0; *dl*-**19b**, 65494-92-0; **20**, 59657-48-6; **21**, 59751-47-2; **22a**, 59751-48-3; **22b**, 64313-68-4; **22c**, 64313-69-5; **23**, 65423-63-4; **25**, 65423-64-5; **26** isomer 1, 65451-53-8; **26** isomer 2, 65451-54-9; **27** isomer 1, 65451-55-0; **27** isomer 2, 65451-56-1; **28**, 65423-65-6; **29**, 65451-57-2; **29** $(Me_3Si)_3$ derivative, 65423-66-7; **30**, 65451-59-3; **30** $(Me_3Si)_3$ derivative, 65451-59-4; benzaldehyde, 100-52-7; benzyl bromide, 100-39-0; *m*-hydroxybenzaldehyde, 100-83-4; acetic anhydride, 108-24-7; pivaloyl chloride, 3282-30-2; *n*-hexyltriphenylphosphonium bromide, 4762-26-9; methyl bromoacetate, 96-32-2.

References and Notes

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