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STEREOCONTROLLED PREPARATION OF PRECURSORS TO ALL PRIMARY PROSTAGLANDINS FROM BUTADIENE†

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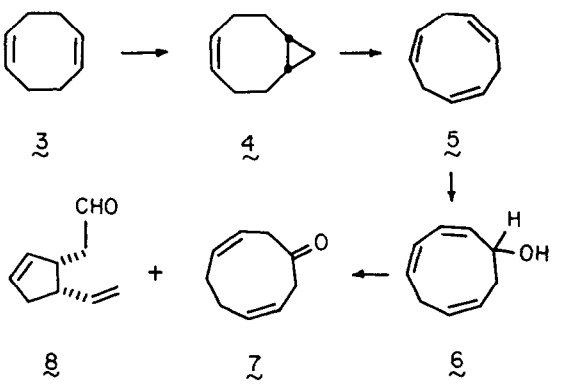
Abstract—Four key precursors to the primary prostaglandins have been prepared in efficient fashion from butadiene. In addition to its simplicity, the new approach capitalizes on the pivotal role of a single precursor molecule, allows for early resolution, and results in placement of four contiguous chiral centers about a cyclopentane ring without initial benefit of a stereodirecting group. Butadiene is cyclodimerized to *cis*^{2}-1,5-cyclooctadiene which is transformed in four steps to *cis*^{3}-1,4,7-cyclononatriene. Monoepoxidation and base-promoted ring opening of this medium ring hydrocarbon gives *cis*^{3}-2,4,7-cyclononatrien-1-ol which isomerizes exclusively to aldehyde **8** in the presence of potassium hydride at room temperature. The derived carboxylic acid is easily resolved and iodolactonized to **2**, the key intermediate from which **1**, **19**, **21**, and **22** are readily obtainable in few laboratory steps.

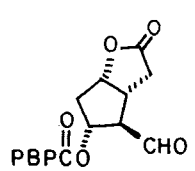
The important biological role of many prostanoids and the high interest in their medicinal potential are underscored by the voluminous literature on prostaglandin synthesis.[1] Of the several synthons which have evolved as suited to the stereoselective construction of this class of compounds, the aldehydo lactone **1** first prepared independently by the Corey[2] and Sutherland groups[3] has been accorded special attention. This intermediate can be functionalized with requisite sidechains by conventional Wittig chemistry and converted to the so-called primary prostaglandins with relative ease. We describe herein a new synthetic approach to this same group of compounds which is based upon the successful construction of iodolactone **2** from butadiene.[4] The scheme enjoys the economic advantage of being based on an inexpensive raw material and depends in its key step on the overriding of thermally favored [1,5] hydrogen sigmatropy by kinetically accelerated anionic [3,3] carbon sigmatropy. Further, the stereochemical requirement that four contiguous chiral centers be developed about the cyclopentane nucleus of this new synthon is achieved simply without the benefit of a stereodirecting group. The early stage at which optical resolution is accomplished is also noteworthy.

The cyclodimerization of butadiene to *cis*^{2}-1,5-cyclooctadiene (**3**) is performed today on commercial scale[5,6] and requires no comment here. The heating of **3** with sodium trichloroacetate in dimethoxyethane followed by dechlorination with lithium in t-butyl alcohol-tetrahydrofuran affords *cis*-bicyclo-[6.1.0]non-4-ene (**4**). The conversion of **4** to *cis*^{3}-1,4,7-cyclononatriene (**5**) was readily accomplished in 60% overall yield by appropriate modification of Detty's procedure[7] (see Experimental). Selective monoepoxidation of **5** and lithium diisopropylamide-promoted ring opening led efficiently to *cis*^{3}-2,4,7-cyclononatrien-1-ol (**6**).[8,9]



When heated with benzene solvent in sealed vessels at 160°, **6** underwent chemical change in accord with conventional first-order kinetics. However, the desired aldehyde **8** comprised only 20% of the reaction mixture, the major component (80%) being dienone **7**. The assignment of a structure to **7** is based chiefly upon its IR and NMR spectral properties. In particular, the substance exhibits a carbonyl stretching frequency at 1700 cm^{-1}, a combination of four olefinic (δ 6.0–5.35), four α-carbonyl (3.08), and four methylene protons (2.34–2.1), and a symmetry simplified ^{13}C spectrum (five lines). The isomeric trans,trans dienone **9** has recently been prepared via organometallic intermediates by Baker and Copeland.[10] When subjected to thermal activation at temperatures above 160°, **7** was smoothly transformed into *cis*-3,4-divinylcyclopentanone (**10**).

The complication of kinetically favored [1,5] hydrogen migration within **6** was resolved by making recourse to an anionic process. In agreement with earlier precedent,[11,12] treatment of **6** with 1.2 equiv of oil-free potassium hydride in anhydrous ether or



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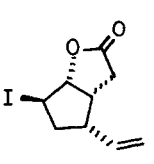

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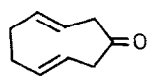
†Dedicated in fond memory of Prof. Robert B. Woodward.



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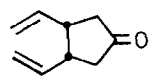


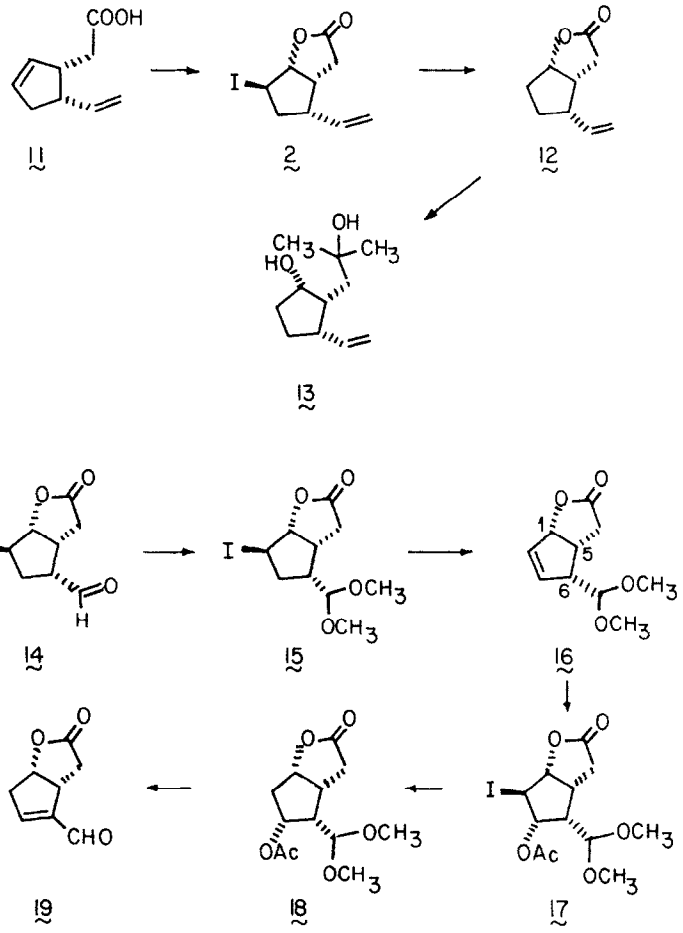
10

tetrahydrofuran at room temperature was adequate to promote quantitative conversion to **8**, homogeneous by tlc and vpc analysis. As a result of the boat conformation of the oxy-Cope transition state within $6^- - K^+$, the sidechains in **8** must be cis. Consequently, the chiral center attached to the vinyl group must later be epimerized. That such a transformation can indeed be accomplished (see below) is considered confirmatory of the indicated stereochemistry.

The clean conversion of the potassium alkoxide of **6** to **8** is especially noteworthy because it represents the first example where the process kinetically favored under thermolysis conditions does not continue to be preferred following a substituent change from –OH to $-O^{\ominus}K^{\oplus}$. Detailed kinetic studies have now shown[4] that the general effect of alkoxide anion substitution on neighboring C–H and C–C bond reactivity is substantially accelerative, although appreciably less so for [1,5] ~ H (10^5–10^6) than for [3,3] ~ C sigmatropy (10^{10}–10^{11}). In view of this large rate differential, the neutral [1,5] ~ H shift is certain to be overridden under oxy anionic conditions, precisely as required by our strategy.

When oxidized with silver oxide in alkaline solution,[13] **8** was transformed into the oily carboxylic acid **11** whose resolution was efficiently achieved with *endo*-bornylamine.[14] Several recrystallizations of the diastereomeric salt from acetone gave colorless crystals having $[\alpha]_D^{23} + 120°$. The free acid recovered from this material exhibited $[\alpha]_D^{23} + 157°$. For the purpose of determining the level of enantiomeric enrichment, **11*** was cyclized to **2***, $[\alpha]_D^{23} - 21.8°$, using standard iodolactonization methodology[15,16] and subsequently reduced with tri-n-butytlin hydride. The regiospecific formation of **2** stems chiefly from the kinetic advantages of γ- vs δ-lactone ring formation. Reaction of lactone **12***, $[\alpha]_D^{23} - 3.2°$, with excess methyllithium provided diol **13*** which was directly subjected to $Eu(tfc)_3$ analysis ($CDCl_3$ soln).[17] Whereas racemic **13** shows four cleanly separated singlets attributable to the presence of two diastereotopic methyl groups in each enantiomer, the optically active diol exhibited only two singlets in that region of the spectrum. Resolution was therefore considered to be $\geq 98\%$ complete. That the desired antipode of **11*** was in hand is to be demonstrated subsequently.

The ozonolysis of **2** at $-78°$ in dichloromethane solution containing 5 equiv of methanol, followed by reductive workup with dimethyl sulfide, provided aldehyde **14**. Despite the hindered environment of its carboxaldehyde group, this molecule exhibited some



11 2 12 13 14 15 16 17 18 19

resistance to epimerization (see below). Consequently, the ketalization of **14** with trimethyl orthoformate and *p*-toluenesulfonic acid was examined. The nicely crystalline product (**15**) was smoothly dehydroiodinated with diazobicycloundecene (DBU) in refluxing tetrahydrofuran to give double bond isomer **16** as the only characterizable product (91%). The ^1H NMR spectrum of **16** (in $CDCl_3$) is characterized by a pseudosinglet olefinic absorption of area 2 at δ 5.98, a multiplet centered at 5.4 for H_1, and a doublet ($J \approx 7$ Hz) at 4.2 for the acetal proton. The signal due to H_6 coincides with that of another proton and appears as a complex multiplet in the region 3.3–3.0. The extensive coupling with H_6 contrasts with that observed in the epimeric series (see **22**) and presumably arises as a consequence of its dihedral angle relationship to H_5 and long range coupling to H_1 and *exo*-H_4 (near W-plan arrangements). Although **16** did not respond well to the usual Prevost conditions or to various selenium reagents, success was realized with IOAc in acetic acid under anhydrous conditions.[18] When the workup was also performed with the exclusion of water, a crystalline iodo acetate was isolated in 65% yield. In view of the endo orientation of the acetal substituent and the V-shaped geometry of the bicyclic lactone nucleus, iodonium ion formation on the exo face was considered a certainty. Less well resolved was the question concerning the regioselectivity of the ring opening, rearside approach to C_7 and C_8 appearing almost equally congested. Nonetheless, the only product which could be detected was assigned structure **17** on spectral grounds and particularly the strength of the ensuing conclusive chemical evidence.

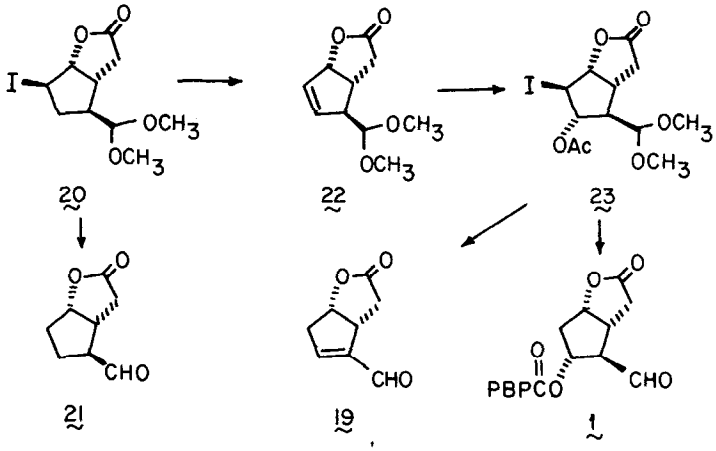
Reductive deiodination of **17** with tri-n-butyltin hydride in toluene at 80°[10] proceeded efficiently to give **18**. When treated at room temperature with concentrated hydrochloric acid in 2% isopropyl alcohol-chloroform solution, **18** underwent not only hydrolysis of its ketal, but particularly facile (antiplanar) β-elimination of acetic acid as well. Since the well known aldehyde **19**[20,21] was produced, the acetate group in **17** and **18** is required to be bonded to C_7.

Initial attempts to epimerize **14** under acidic (*p*-TsOH; 1 N HCl) or mildly alkaline conditions (K_2CO_3/MeOH; $NaHCO_3$) led to no reaction or to modest conversions that proceeded entirely too slowly. Stronger bases such as sodium methoxide expectedly attacked the lactone ring as well. The two-phase acidic conditions originally devised by Brown *et al.*[19] proved moderately satisfactory, but were abandoned when discovered to be capricious with regard to the extent of equilibration and the production of an unknown by-product (up to 20%). Optimum results were achieved with *p*-chloroaniline in a mixed solvent system consisting of isopropyl alcohol and acetic acid (*ca* 7:1). Subsequent direct ketalization routinely afforded **20** in 85–90% overall yield.

The important aldehyde **21** was obtained by tri-n-butyltin hydride reduction of **15** or **20** and subsequent hydrolysis as above under two-phase conditions. A shorter alternative route to **21** consisted of reductive dehalogenation of **2** and ozonolysis of **12** followed by acidic epimerization.

When treated with DBU, **20** was more rapidly (8 hr, 20°) converted to **22** than was **15** to **16** (5 hr, 66°), this rate difference reflecting the diminished steric shielding surrounding *endo*-H_7 in the epimerized acetal. Further, **22** could be transformed into **23** through application of predescribed conditions. In contrast to the stable crystalline **17**, **23** was obtained as a heat- and light-sensitive oil which proved difficult to purify. Reductive deiodination of this intermediate furnished a *trans*-locked β-acetoxy acetal which was efficiently converted to **19**. Usefully, the same deiodination product was easily transformed to **1** in three well-precedented laboratory manipulations.

That the appropriate enantiomer of **11*** had been earlier obtained was established by conversion of a sample of the enantiomerically pure acid to **19***. The optical rotation observed for our material (248°) proved to be in excellent agreement with the $[\alpha]_D$ of an authentic pure sample.[22] In light of the prior elaboration of several 11-desoxy prostaglandins from **21**,[23,24] a formal total synthesis of these substances is achieved. Also, the ready availability of **22** opens a direct access route to the A prostaglandins.[25] Since **19** is an established precursor of the C prostaglandins[20] and thromboxane B_2,[21] and the successful elaboration of F prostaglandins from **1** has been described previously,[26,27] the present scheme provides a



preparatively useful route to a wide selection of prostanoid hormones from the simplest of achiral conjugated dienes.

EXPERIMENTAL

PMR spectra were obtained with a Varian EM-360 spectrometer; apparent splittings are given in all cases. ^{13}C NMR spectra were recorded on a Bruker WP-80 spectrometer and infrared spectra were determined on a Perkin–Elmer Model 467 instrument. Mass spectra were recorded on an AEI-MS9 spectrometer at an ionization potential of 70 eV. Elemental analyses were performed by the Scandinavian Microanalytical Laboratory, Herlev, Denmark.

cis-9,9-*Dichlorobicyclo*[6.1.0]*non*-4-*ene*. A mixture of 325 g (2.98 mol) *cis*,*cis*-1,5-cyclooctadiene, 111 g (0.599 mol) sodium trichloroacetate and 175 ml 1,2-dimethoxyethane was slowly heated with stirring to 100° in a thermostated oil bath. During the first 2 hr, considerable CO_2 was evolved and a dark brown color developed. After 20 hr, the cooled mixture was filtered through a pad of diatomaceous earth. The residue was washed with 500 ml ether and the combined filtrates were distilled through a 20 cm Vigreux column. The pressure within the distillation apparatus was gradually reduced to 10 mm and the product was collected at 95–110°. There was obtained 82 g (71%) colorless liquid of sufficient purity for use in the next step.

cis-*Bicyclo*[6.1.0]*non*-4-*ene* (**4**). Li wire (16% g, 2.33 g-at) was cut into small pieces, washed free of oil with pentane, and added to 500 ml dry THF. A soln containing 67.9 g (0.354 mol) *cis*-9,9-dichlorobicyclo[6.1.0]non-4-ene, 65.7 g (0.89 mol) t-BuOH, and 400 ml THF was slowly added dropwise with intermittent cooling from an ice-bath to maintain a gentle reflux rate. Upon completion of the addition, the mixture was heated at reflux for 2 hr, cooled, and filtered through a glass wool plug. To the filtrate was added 2 l of pentane and this soln was washed with water (4 × 500 ml) and saturated brine (300 ml) prior to drying over $MgSO_4$. The solvents were removed by distillation through a 20 cm Vigreux column at atmospheric pressure. The residue was distilled under reduced pressure to yield 40 g (93%) hydrocarbon as a colorless liquid, b.p. 78–81° (25 mm); ^1H NMR (δ, $CDCl_3$) 5.58 (m, 2 H), 2.16 (m, 6 H), 0.53 (m, 5 H), and −0.10 (m, 1 H).[7]

cis,*cis*-1,4,7-*Cyclononatriene* (**5**). A soln of 30.9 g (0.253 mol) of **4** in 250 ml CCl_4 was stirred magnetically at 0° (ice-bath cooling) while a 25% (v/v) soln of Br_2 in CCl_4 was added dropwise until the red color just persisted. The mixture was concentrated on a rotary evaporator to give a pale yellow oil which partially crystallized upon standing.

To a soln of this dibromide in 300 ml DMF was added 116.3 g (1.74 mol) anhyd Li_2CO_3, 43.0 g (1.66 mol) anhyd LiF, and some powdered soft glass. With magnetic stirring, this mixture was heated at 100° for 12 hr in a thermostated oil bath, then cooled and poured into 2 l of ice and water. The product was extracted into hexane (5 × 400 ml), washed with water (4 × 300 ml) and brine, dried, and concentrated at atmospheric pressure by distillation of solvent through a 20 cm Vigreux column. The resulting oil was heated at its reflux temp (170°) for 0.5 hr and crystallized from MeOH to give 18.4 g (60%) of **5**, m.p. 50–51°.[28–30]

cis,*cis*-1,4,7-*Cyclononatriene oxide*. A stirred soln of **5** (1.5 g, 12.5 mmol) in 30 ml ether was cooled to 0° while monoperphthalic acid (20.5 ml of 0.62 N) in ether was added dropwise from an addition funnel. The soln was stored overnight in a refrigerator, washed with $NaHCO_3$aq, dried, and evaporated to leave 1.4 g (90%) of a crystalline residue, m.p. 40–42°, consisting of an 18:1:1 mixture of monoepoxide, diepoxide, and unreacted **5**. Recrystallization from pentane gave colorless crystalline monoepoxide, m.p. 50.5–51.5°, but this procedure was not necessary and the unpurified product could be used directly.

2,4,7-*Cyclononatrien*-1-*ol* (**6**). Diisopropylamine (27.8 g, 0.276 mol) was added dropwise to a cold (0°) soln of n-BuLi (185 ml of 1.5 N in hexane, 0.276 mol) in 100 ml of anhyd THF under N_2 during 30 min. After an additional 0.5 hr, a soln of the monoepoxide (25 g unpurified, 0.184 mol) in 50 ml of the same solvent was introduced dropwise over 1 hr. After 4 hr, 100 ml of 10% NH_4Claq was added to the dark brown mixture which was diluted with ether (300 ml) and extracted successively with three 100 ml portions NH_4Cl aq and once with brine (100 ml) prior to drying and solvent evaporation. Distillation of the residue gave **6** as a clear liquid, b.p. 55–60° (0.07 mm), which solidified on standing: 20 g (80%), homogeneous by tlc (1:1 hexane–ether). The ^1H NMR and IR spectra of this alcohol were identical to those reported earlier.[8,9]

Pyrolysis of **6**. A base-washed glass ampoule was charged with 100 mg (0.73 mmol) of **6** and 250 mg benzene. The soln was degassed, sealed *in vacuo*, and heated at 170° in a furnace for 2 hr. The products were isolated by preparative VPC (0.25 in. × 5 ft 10% SE-30, 105°) and identified as **7** (70%), **8** (20%), and **10** (10%, time-dependent; increases at the expense of **7** at longer reaction times).

For **7**. IR (neat, cm^{-1}) 3020, 2940, 2860, 1700, and 1640; ^1H NMR (δ, $CDCl_3$) 6.0–5.35 (m, 4 H), 3.08 (d, J = 7.5 Hz, 4 H), and 2.34–2.1 (m, 4 H); ^{13}C NMR (ppm, $CDCl_3$) 210.50, 133.24, 124.56, 26.37, and 26.07; *m/e* calc. 136.0888, obs 136.0892. (Found: C, 79.35; H, 8.92. Calc. for $C_9H_{12}O$: C, 79.42; H, 8.83%).

For **10**. IR (neat, cm^{-1}) 3080, 1745, 1635, 990, and 910; ^1H NMR (δ, $CDCl_3$) 6.15–5.55 (series of m, 4 H), 5.3–4.75 (m, 2 H), 3.3–2.75 (m, 2 H), and 2.5–2.1 (m, 2 H); ^{13}C NMR (ppm, $CDCl_3$) 217.2, 137.4, 116.1, 44.0, 42.7. (Found: C, 79.24; H, 8.86. Calc. for $C_9H_{12}O$: C, 79.42; H, 8.83%).

Pyrolysis of **7**. A soln of **7** (50 mg, 0.36 mmol) in 200 mg benzene contained in a base-washed glass ampoule was degassed. The vessel was sealed *in vacuo* and heated in a furnace at 210° for 4 hr. The sole product (47 mg, 94%), which was isolated by medium pressure liquid chromatography on silica gel (elution with 2% EtOAc in hexane), exhibited spectra identical to that of **10** described above.

cis-(4-*Vinyl*-3-*cyclopentenyl*)*acetaldehyde* (**8**). KH (15.0 g of a 23.6% suspension, 88 mmol) was placed in a 250 ml 3-necked round bottom flask, blanketed with N_2, and washed free of oil with anhyd ether (2 × 50 ml). Additional dry ether (75 ml) was added and the slurry was stirred at 0° while **6** (10.0 g, 73.5 mmol) dissolved in 75 ml of the same solvent was introduced dropwise. After completion of the addition, the soln was allowed to warm to room temp and stirred for 4 hr. The reddish-brown mixture was rapidly poured into a stirred mixture of 10% NH_4Claq (100 ml) and ice (50 g). The organic phase was separated, washed with sat $NaHCO_3$aq (50 ml) and brine (50 ml), dried, and concentrated. The light brown oil (9.9 g), homogeneous by tlc and vpc, was extensively decomposed on attempted distillation and therefore was oxidized directly. An analytical sample was isolated by preparative vpc (5 ft × 0.25 in. 5% SE-30, 100°); IR (neat, cm^{-1}) 1720 and 1620; ^1H NMR (δ, $CDCl_3$) 9.78 (t, J = 1 Hz, 1 H), 6.0–5.35 (m, 3 H), 5.2–4.75 (m, 2 H), and 3.5–2.0 (series of m, 6 H); ^{13}C NMR (ppm, $CDCl_3$) 202.14, 139.21, 133.39, 130.60, 115.73, 45.33, 45.09, 43.03, and 37.26; *m/e* calc. 136.0888, obs 136.0892. (Found: C, 79.54; H, 8.96. Calc. for $C_9H_{12}O$: C, 79.42; H, 8.83%).

cis-(4-*Vinyl*-3-*cyclopentenyl*)*acetic acid* (**11**). Ag_2O (8.52 g, 36.8 mmol, prepared *in situ* by the method of Campaigne,[13] was stirred with 30 ml water in a cooled 100 ml flask. To this suspension was added a soln of **8** (2.00 g, 14.7 mmol) in 2 ml of ether. The cooled reaction mixture was rapidly stirred for 30 min and the brown-black solid was removed by filtration and washed with several portions hot water. The cooled filtrate was sequentially extracted with ether, acidified, and reextracted with CH_2Cl_2 (3 × 30 ml). The latter solns were combined, dried, and evaporated to give 1.5 g (70%) of **11** as a pale yellow oil which could be purified by Kugelrohr distillation at 100° and 0.1 torr; IR (neat, cm^{-1}) 3100, 1710,

1630, 1430, 940, and 910; ^{1}H NMR (δ, $CDCl_3$) 14.3 (s, 1 H), 6.0–5.7 (m, 3 H), 5.10 (dd, J = 7 and 1 Hz, 1 H), 4.96 (s, 1 H), 3.2–2.9 (m, 2 H), and 2.7–2.0 (m, 4 H).

A sample of **11** was hydrogenated over Pd-C and treated with diazomethane to give the perhydro methyl ester. This substance was purified by preparative vpc for analysis; *m/e* calc. 170.1307, obs 170.1312. (Found: C, 70.38; H, 10.55. Calc. for $C_{10}H_{18}O_2$: C, 70.54; H, 10.66%).

Resolution of **11**. The carboxylic acid was dissolved in acetone and treated with an equivalent amount of *endo*-bornylamine. The ppt was recrystallized seven times from acetone to give crystals, m.p. 108–109°, exhibiting $[\alpha]_D^{23}$ + 120° (*c* 1.66, C_2H_5OH). Acidification of this salt gave **11*** as a colorless oil, $[\alpha]_D^{23}$ + 157° (*c* 3.52, C_2H_5OH).

Iodolactonization of **11**. To a stirred soln of **11** (1.0 g, 6.58 mmol) in 53 ml 0.5 N $NaHCO_3$ was slowly added a soln containing I_2 (1.67 g, 6.6 mmol) and KI (4.02 g, 24.2 mmol) in water (50 ml) until the reddish color persisted. After 2 hr, the mixture was extracted with CH_2Cl_2 (4 × 50 ml) and the combined organic phases were washed with 5% $Na_2S_2O_3$aq (2 × 30 ml), water (50 ml), and brine (30 ml) prior to drying. Removal of solvent left a yellowish liquid which was filtered through a small column of silica gel (CH_2Cl_2 elution) and recrystallized from hexane-EtOAc (9:1): There was obtained 1.5 g (85%) of **2** as a colorless crystalline solid, m.p. 71–71.5°; IR (nujol, cm^{-1}) 3030, 2990, 1790, 1640, 1185, and 1005; ^{1}H NMR (δ, $CDCl_3$), 5.9–5.4 (m, 1 H), 5.2–4.8 (m, 3 H), 3.9–3.6 (m, 1 H), 3.4–2.8 (m, 2 H), 2.4–2.1 (m, 2 H), and 2.0–1.6 (m, 2 H); *m/e* calc. 277.9806, obs 277.9813. (Found: C, 38.94; H, 4.01. Calc. for $C_9H_{11}IO_2$: C, 38.87; H, 3.99%).

Analogous treatment of **11***, $[\alpha]_D^{23}$ + 157°, gave **2***, m.p. 80–81°, $[\alpha]_D^{23}$ − 21.8° (*c* 1.82, C_2H_5OH).

endo-6-*Vinyl*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**12**). A soln of **2** (300 mg, 1.08 mmol) and tri-n-butyltin hydride (350 mg, 1.21 mmol) in 10 ml dry toluene was heated at 80° under N_2 with stirring for 20 hr, cooled, and concentrated on a rotary evaporator. The residue was taken up in EtOAc (25 ml) and stirred for 4 hr with a soln of KF (0.25 g) in water (25 ml). The ppt was removed by filtration and the organic phase was separated, dried, and evaporated. Preparative tlc purification of the resulting oil on silica gel (elution with pentane–EtOAc 2:1) gave **12** as a colorless oil, 100 mg (62%), which was purified for analysis by preparative vpc (5 ft × 0.25 in. 5% SE-30, 130°C); IR (neat, cm^{-1}) 3080, 1775, 1640, 1180, 995, and 910; ^{1}H NMR (δ, $CDCl_3$) 5.95–5.6 (m, 1 H), 5.16–4.95 (m, 3 H), 3.15–2.38 (series of m, 4 H), and 2.2–1.5 (series of m, 4 H); *m/e* 152.0838, obs. 152.0841. (Found: C, 70.99; H, 7.92. Calc. for $C_9H_{12}O_2$: C, 71.07; H, 7.89%).

Analogous treatment of **2*** afforded **12***, $[\alpha]_D^{23}$ − 3.2° (*c* 1.91, C_2H_5OH).

Reaction of **12** *with methyllithium*. To a cold (−78°) magnetically stirred soln of **12** (100 mg, 0.72 mmol) in 10 ml anhyd ether was added dropwise 2 ml 1.4 N MeLi in ether (2.8 mmol). The mixture was stirred at −78° for 1 hr, treated slowly with water (2 ml), and warmed to room temp. The organic phase was separated, washed with brine (10 ml), dried, and evaporated. The resulting clear liquid which crystallized on standing (82 mg, 68%) was recrystallized from petroleum ether–ether (4:1) to give **13** as colorless needles, m.p. 75–76°; IR (nujol, cm^{-1}) 3300, 1635, 1145, 1065, 995, and 920; ^{1}H NMR (δ, $CDCl_3$) 6.12–5.82 (m, 1 H), 4.95 (s, 1 H), 4.83 (dd, J = 6 and 3 Hz, 1 H), 4.32 (m, 1 H), 3.9–2.9 (br mound, 2 H), 2.7–2.4 (br m, 1 H), 2.2–1.4 (series of m, 7 H), 1.3 (s, 3 H), and 1.26 (s, 3 H). (Found: C, 71.71; H, 11.15. Calc. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94%).

Comparable treatment of **12*** afforded **13***, m.p. 84–85°, $[\alpha]_D^{23}$ + 40° (*c* 1.21, EtOH).

Europium shift experiments with **13**. Generally, a 10 mg sample of the diol in 200 μl $CDCl_3$ was treated with 13-20 mg (27–40 mol-eq) tris(trifluoromethylcamphorato)europium and the ^{1}H NMR spectra of these solns were recorded (60 MHz) at 250 Hz sweep width. With the racemic sample, four Me signals emerged from the original two and appeared at δ 4.0, 3.8, 2.7, and 2.5, sufficiently well separated for accurate integration (1:1:1:1 ratio). The optically active diol showed only the two signals at 4.0 and 2.7 (1:1 ratio).

endo-5-(*Dimethoxymethyl*)-exo-8-*iodo*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**15**). O_3 was bubbled through a cold (−78°) soln of **2** (5.0 g, 17.9 mmol) in 50 ml CH_2Cl_2 and 10 ml MeOH until a blue color appeared. The excess O_3 was purged with O_2 for 30 min and Me_2S (1.5 g, 24.2 mmol) together with *p*-toluenesulfonic acid (100 mg, 0.6 mmol) were added. This mixture was stirred at 0° for 20 hr, at which point trimethyl orthoformate (17.0 g, 0.16 mol) was introduced. After being stirred for an additional 20 hr at room temp, the mixture was shaken with sat $NaHCO_3$aq (2 × 25 ml), dried, and evaporated. There was obtained 4.6 g (79%) of **15** as a pale yellow crystalline solid. Recrystallization of this material from EtOAc-hexane gave colorless needles, m.p. 72–73°; IR (nujol, cm^{-1}) 1790; ^{1}H NMR (δ, $CDCl_3$) 5.2 (d, J = 6 Hz, 1 H), 4.6–4.3 (m, 2 H), 3.35 (s, 3 H), 3.3–2.5 (series of m, 4 H), and 2.2–1.9 (m, 2 H); *m/e* calc. 326.0015, obs 326.0020. (Found: C, 36.73; H, 4.63. Calc. for $C_{10}H_{15}IO_4$: C, 36.84; H, 4.60%).

Comparable treatment of **2*** (40% ee) gave **15***, m.p. 91.5–94°, $[\alpha]_D^{23}$ − 16.5° (*c*, 1.38, C_2H_5OH).

endo-5-(*Dimethoxymethyl*)-3-*oxo*-2-*oxabicyclo*[3.3.0]*oct*-7-*ene* (**16**). A magnetically stirred soln of **15** (3.24 g, 10 mmol) and DBU (1.9 g, 12.5 mmol) in 50 ml of anhyd THF was heated at 60° for 5 hr. After cooling, CH_2Cl_2 (100 ml) was added and the soln was washed with 5% NH_4Claq (2 × 50 ml) and brine prior to drying and concentration. Chromatography on Florisil (CH_2Cl_2 elution) provided 1.8 g (91%) of **16** as a clear oil; IR (neat, cm^{-1}) 1785 and 1620; ^{1}H NMR (δ, $CDCl_3$) 5.98 (pseudosinglet, 2 H), 5.4 (m, 1 H), 4.2 (d, J = 7 Hz, 1 H), 3.4 (s, 3 H), 3.36 (s, 3 H), 3.3–2.85 (m, 2 H), and 2.7–2.4 (m, 2 H). (Found: C, 60.46; H, 7.06. Calc. for $C_{10}H_{14}O_4$: C, 60.63; H, 7.07%).

endo-5-(*Dimethoxymethyl*)-endo-6-*acetoxy*-exo-7-*iodo*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**17**). Unsaturated **16** (500 mg, 2.5 mmol) dissolved in 1 ml AcOH was added via syringe to a soln of I_2 (641 mg, 2.52 mmol) and AqOAc (460 mg, 2.75 mmol) in AcOH (15 ml) and the suspension was stirred under a N_2 for 20 hr. The ppt was separated by filtration and the filtrate was evaporated to leave a yellow semi-solid which was recrystallized from EtOAc–hexane. Purified **17** was obtained as a yellowish solid (610 mg, 63%), m.p. 106° dec; IR (nujol, cm^{-1}) 1785 and 1750; ^{1}H NMR (δ, $CDCl_3$) 5.52 (t, J = 5 Hz, 1 H), 4.80 (t, J = 3 Hz, 1 H), 4.42 (d, J = 3 Hz, 1 H), 4.22 (dd, J = 5 and 3 Hz, 1 H), 3.40 (2, 3 H), 3.36 (s, 3 H), 3.3–2.2 (series of m, 4 H), and 2.22 (s, 3 H).

The $[\alpha]_D^{23}$ of **17*** of 40% ee was determined to be −90.7° (*c* 1.09, $CHCl_3$).

endo-5-(*Dimethoxymethyl*)-endo-6-*acetoxy*-2-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**18**). A magnetically stirred soln containing 620 mg (1.61 mmol) of **17** and 500 mg (1.72 mmol) tri-n-butyltin hydride in 10 ml toluene was heated at 80° under N_2 for 20 hr. Following the evaporation of solvent, the residue was taken up in EtOAc (25 ml) and stirred overnight with a soln of KF (1 g) in water (25 ml). The ppt was separated by filtration and the organic phase was removed and dried. Evaporation of solvent gave 370 mg (89%) of **18** after preparative tlc on silica gel (EtOAc elution); IR (neat, cm^{-1}) 1785, 1740, 1150, 1130, and 1060; ^{1}H NMR (δ, $CDCl_3$) 5.35 (dd, J = 14 and 8 Hz, 1 H), 4.98 (t of d, J = 7 and 2 Hz, 1 H), 4.42 (d, J = 6 Hz, 1 H), 3.4 (s, 3 H), 3.36 (s, 3 H), 3.2–2.9 (m, 1 H), 2.8–1.8 (series of m, 5 H), and 2.02 (s, 3 H); *m/e* calc. 258.1103, obs 258.1108.

Hydrolysis-elimination of **18**. A sample of **18** (117 mg, 0.45 mmol) was dissolved in 5 ml $CHCl_3$ containing 10 drops i-PrOH. Conc HCl (2 ml) was added and the soln was stirred vigorously for 1 hr prior to the addition of brine (10 ml). The organic phase was separated, washed with sat $NaHCO_3$aq (10 ml) and NaCl aq (10 ml), dried, and evaporated. There was obtained 48 mg (70%) of **19**, m.p. 69–72° after sublimation. The ^{1}H spectrum was superimposable upon that of an authentic sample.[20,21]

Similar treatment of the acetate derived from optically active **11***, $[\alpha]_D^{23}$ + 114°, furnished **19***, m.p. 73–74°, $[\alpha]_D^{23}$ + 236 (c 1.06, C_2H_5OH).

exo-5-(*Dimethoxymethyl*)-exo-7-*iodo*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**20**). A soln of **2** (3.2 g, 11.4 mmol) in CH_2Cl_2 (25 ml) and MeOH (5 ml) was ozonized in the predescribed manner and subsequently treated with Me_2S (100 mg, 14.4 mmol) at 0° for 24 hr. The mixture was washed with water (2 × 20 ml) and brine (20 ml), dried, and concentrated to leave a glassy syrup. The epi-aldehyde was taken up in i-PrOH (30 ml) and AcOH (5 ml) and this soln was stirred under N_2 while *p*-chloroaniline (1.75 g, 13.7 mmol) was added in one portion. After 24 hr, the brownish liquid was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (30 ml) and stirred with 30 ml of 2 N HCl for 30 min. The layers were separated and the aqueous phase was extracted with CH_2Cl_2 (30 ml). The combined organic layers were washed with 2 N HCl (25 ml) and brine (25 ml) before drying. Trimethyl orthoformate (10 g, 94 mmol) and *p*-toluenesulfonic acid (100 mg) were added to the stirred soln. After 6 hr, the mixture was washed with 10% $NaHCO_3$aq (30 ml), dried, and concentrated to give 3.3 g (88%) of **20**. The analytical sample was prepared by medium-pressure liquid chromatography on silica gel (elution with hexane-EtOAc, 3:1); IR (neat, cm^{-1}) 2940, 2830, 1782, 1150, 1060, 955, and 885; ^1H NMR (δ, $CDCl_3$) 5.1 (dd, J = 6 and 3 Hz, 1 H), 4.42 (d, J = 6 Hz, 1 H), 4.15 (d or t, J = 7 and 3 Hz, 1 H), 3.38 (s, 3H), 3.33 (s, 3 H), and 3.1–2.0. (Found: C, 37.18; H, 4.81. Calc. for $C_{10}H_{15}IO_4$: C, 36.84; H, 4.63%).

exo-3-*Oxo*-2-*oxabicyclo*[3.3.0]*octylcarboxaldehyde* (**21**)

A. From **12**. A soln of **12** (800 mg, 5.2 mmol) in 30 ml CH_2Cl_2–MeOH (4:1) was ozonized at −78°. Me_2S (500 mg, 8 mmol) was added and the soln was stirred at 0° for 24 hr. Solvent evaporation left a residue which was taken up in 20 ml $CHCl_3$ containing 2% i-PrOH. Conc HCl was added and the soln was stirred for 1 hr at room temp before brine (20 ml) was added and the phases were separated. The organic layer was washed again with brine (20 ml), dried, and concentrated to furnish 670 mg (83%) of **21**. The spectra of this product were superimposable upon those of authentic material.[23]

B. From **15**. A soln of **15** (500 mg, 1.23 mmol) and tri-n-butyltin hydride (400 mg, 1.37 mmol) in 15 ml dry toluene was heated at 80° for 18 hr and worked up in the manner described to yield 200 mg (83%) acetal; IR (neat, cm^{-1}) 2840, 1780, 1060, and 170; ^1H NMR (δ, $CDCl_3$) 5.0 (t, J = 3 Hz, 1 H), 4.3 (d, J = 4 Hz, 1 H), 3.35 (s, 6 H), 3.0 (m, 1 H), and 2.8–1.4 series of m, 7 H); *m/e* calcd 200.1048, obs 200.1053.

This product (200 mg, 0.10 mmol) in 5 ml dioxane was stirred with 5 ml 2 N HCl for 8 hr at 20°. CH_2Cl_2 (10 ml) was added and the organic phase was separated. The aqueous layer was reextracted with CH_2Cl_2 (10 ml) and the combined organic phase was washed with 10% $NAHCO_3$aq (10 ml) and brine (10 ml). Drying and solvent evaporation afforded 145 mg (95%) of **21**.

exo-5-(*Dimethoxymethyl*)-3-*oxo*-2-*oxabicyclo*[3.3.0]*oct*-7-*ene* (**22**). A soln of **20** (3.4 g, 10.5 mmol) and DBU (2.4 g, 15.6 mmol) in 30 ml anhyd THF was stirred vigorously at room temp for 8 hr, then concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (50 ml), 1 N HCl (25 ml) was added, and the soln was stirred for 30 min. The organic layer was separated and the aqueous phase was extracted with CH_2Cl_2 (30 ml). The combined CH_2Cl_2 layers were washed with 10% NaCl aq, dried, and concentrated. The resulting dark brown viscous liquid (2.0 g) was chromatographed on Florisil (elution with hexane–EtOAc, 4:1) to give 1.8 g (86%) of **22** as a colorless oil; IR (neat, cm^{-1}) 3060, 1785, 1620, 1150, and 1060; ^1H NMR (δ, $CDCl_3$) 6.0 (narrow m, 2 H), 5.65–5.35 (m, 1 H), 4.12 (d, J = 6 Hz, 1 H), 3.38 (t, J = 6 Hz, 1 H), 3.38 (s, 3 H), and 3.2–2.2 (series of m, 4 H). (Found: C, 60.58; H, 7.09. Calc. for $C_{10}H_{14}O_4$: C, 60.62; H, 7.07%).

exo-5-(*Dimethoxymethyl*)-endo-6-*acetoxy*-exo-7-*iodo*-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane* (**23**). Treatment of 1.0 g (5.0 mmol) with AqOAc (900 mg, 5.4 mmol) and I_2 (1.3 g, 5.1 mmol) in 25 ml AcOH in the predescribed manner gave a yellowish oil which was purified by Florisil chromatography (elution with hexane–ether, 4:1). There was obtained 1.65 g (86%) of **23** as a gummy solid, m.p. 80°; IR (neat, cm^{-1}) 2950, 2840, 1785, and 1750; ^1H NMR (δ, $CDCl_3$) 5.36 (t, J = 5 Hz, 1 H), 5.3–4.9 (m, 1 H), 4.52 (d, J = 6.5 Hz, 1 H), 4.45–4.2 (m, 1 H), 3.45 (s, 3 H), 3.38 (s, 3 H), 3.25–2.2 (series of m, 4 H), and 2.08 (s, 3 H). (Found: C, 37.30; H, 4.44. Calc. for $C_{12}H_{17}IO_6$: C, 37.53; H, 4.43%).

The optically active **23*** exhibited a m.p. of 90° dec.

3-*Oxo*-2-*oxabicyclo*[3.3.0]*oct*-6-*enyl*-6-*carboxaldehyde* (**19**). A soln of **23** (300 mg, 0.78 mmol) and tri-n-butyltin hydride (250 mg, 0.86 mmol) in 10 ml benzene was heated at reflux under N_2 for 12 hr. The solvent was evaporated and the resulting oil was dissolved in EtOAc (25 ml) and stirred vigorously with 25 ml of 5% KF. After 5 hr, the mixture was filtered and the separated organic phase was washed with brine and dried. Concentration left the acetate as a pale yellow oil which was purified by preparative layer chromatography on silica gel (elution with EtOAc-hexane, 1:1): 173 mg (86%); IR (neat, cm^{-1}) 1785 and 1760; ^1H NMR (δ, $CDCl_3$) 5.3–4.9 (m, 2 H), 4.27 (d, J = 5 Hz, 1 H), 3.42 (s, 3 H), 3.40 (s, 3 H), 3.1–2.1 (series of m, 6 H), and 2.0 (s, 3 H); *m/e* calc. 258.1103, obs 258.1107.

A soln of the acetate (175 mg, 0.68 mmol) in 5 ml of $CHCl_3$–2% i-PrOH and conc HCl was stirred vigorously for 4 hr prior to the addition of brine (10 ml) and CH_2Cl_2 (25 ml). The separated organic phase was washed with brine, dried, and evaporated to give a yellowish oil, sublimation of which at 60° and 1 torr furnished 75 mg (73%) of **19** as a colorless crystalline solid, m.p. 72°. The ^1H NMR spectrum of this material was superimposable upon that of an authentic sample[27] and the material isolated as above.

endo-7-(*p-Phenylbenzoyloxy*)-3-*oxo*-2-*oxabicyclo*[3.3.0]*octane*-exo-6-*carboxaldehyde* (**1**). To a soln of the preceding acetate (170 mg, 0.65 mmol) in 10 ml MeOH was added K_2CO_3 (91 mg, 0.66 mmol) and the mixture was stirred at room temp for 2 hr. AcOH (40 μl, 0.7 mmol) was introduced and the filtered soln was concentrated to yield a semisolid. This residue was taken up in pyridine (5 ml) and treated with *p*-phenylbenzoyl chloride (175 mg, 0.80 mmol) and 4-dimethylaminopyridine (20 mg, 0.16 mmol). After being stirred for 36 hr, the mixture was evaporated and the residue was purified by prep tlc on silica gel (elution with 90% EtOAc in hexane). There was obtained 160 mg (61%) of the ester acetal, whose ^1H NMR spectrum was superimposable upon that of an authentic sample.[19]

Hydrolysis of this product by the method of Brown *et al.*[19] afforded **1** in 80% yield.

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