**(±)-19,20-Dihydro-24-*O*-methylchlorothricolide, Methyl Ester, Ethyl Carbonate (34A).** To a rapidly stirred solution of 9 mg (15 μmol) of the aldehyde A in 0.15 mL of dimethylformamide at room temperature was added 46 mg (0.12 mmol) of pyridinium dichromate. After 36 h, the mixture was poured into 10 mL of 10% HCl, the aqueous layer was extracted with ether (3 × 30 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was treated with excess ethereal diazomethane and chromatographed on silica gel (2 g) with ethyl acetate–petroleum ether (15:85). In this manner, there was obtained 7 mg (76%) of the methyl ester **34A** as a colorless oil: IR ($CHCl_3$) 2950, 1760, 1730, 1680, 1510, 1430 $cm^{-1}$; 400-MHz $^1H$ NMR ($CDCl_3$) δ 1.20 (d, 3 H, $J$ = 7.5 Hz, $CHCH_3$), 1.30 (s, 3 H, $CCH_3$), 1.30 (t, 3 H, $J$ = 7.5 Hz, $OCH_2CH_3$), 3.69 (s, 3 H, $OCH_3$), 3.97 (s, 3 H, $OCH_3$), 4.18 (q, 2 H, $J$ = 7.5 Hz, $OCH_2CH_3$), 4.37 (ddd, 1 H, $J$ = 10, 10, 4.5 Hz, C-7 H), 5.21 (dd, 1 H, $J$ = 16, 7.5 Hz, C-17 H), 5.37 (ddd, 1 H, $J$ = 16, 6, 6 Hz, C-16 H), 5.56 (d, 1 H, $J$ = 10 Hz, C-9 or C-10 H), 5.62 (ddd, 1 H, $J$ = 10, 5, 2 Hz, C-9 or C-10 H).

Anal. Calcd for $C_{34}H_{46}O_{10}$: $(M + H)^+$, 615.3169. Found: $(M + H)^+$, 615.3177.

**(±)-19,20-Dihydro-24-*O*-methylchlorothricolide, Methyl Ester, Ethyl Carbonate (34B).** By the procedure described for the methyl ester **34A**, 11.5 mg (19 μmol) of the aldehyde B, 59 mg (0.16 mmol) of pyridinium dichromate, and 0.2 mL of dimethylformamide afforded, after chromatography on silica gel (2 g) with ethyl acetate–petroleum ether (15:85), 8.5 mg (70%) of the methyl ester **34B** as a colorless oil: IR ($CHCl_3$) 2940, 1780, 1750, 1690, 1520, 1480, 1430, 1350 $cm^{-1}$; 400-MHz $^1H$ NMR ($CDCl_3$) δ 1.21 (s, 3 H, $CCH_3$), 1.22 (d, 3 H, $J$ = 7.5 Hz, $CHCH_3$), 1.29 (t, 3 H, $J$ = 7 Hz, $OCH_2CH_3$), 2.27 (dd, 1 H, $J$ = 14, 6 Hz), 2.35 (ddd, 1 H, $J$ = 13, 9, 4 Hz), 3.69 (s, 3 H, $OCH_3$), 4.06 (s, 3 H, $OCH_3$), 4.17 (q, 2 H, $J$ = 7 H, $OCH_2CH_3$), 4.36 (ddd, 1 H, $J$ = 10.5, 10.5, 4.5 Hz, C-7 H), 5.19 (ddd, 1 H, $J$ = 15, 5.5, 5.5 Hz, C-16 H), 5.26 (dd, 1 H, $J$ = 15, 9 Hz, C-17 H), 5.58 (br s, 2 H, C-9 and C-10 H).

Anal. Calcd for $C_{34}H_{46}O_{10}$: $(M + H)^+$, 615.3169. Found: $(M + H)^+$, 615.3157.

**24-*O*-Methylchlorothricolide, Methyl Ester, Ethyl Carbonate (1d).** To a rapidly stirred solution of 40 mg (73 μmol) of *O*-methyl chlorothricolide, methyl ester[6b] **1c** in 0.5 mL of pyridine at room temperature was added 28 μL (0.29 mmol) of ethyl chloroformate. After 30 min, an additional 28 μL of ethyl chloroformate was added and the reaction was stirred for an additional 30 min. The reaction mixture was poured into 20 mL of 5% HCl and extracted with ether (3 × 60 mL), and the combined organic extracts were dried ($MgSO_4$).

After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (10 g) with ethyl acetate–petroleum ether (1:3). In this manner, there was obtained 43 mg (96%) of the carbonate protected chlorothricolide **1d** as a colorless glass: IR ($CHCl_3$) 2950, 1765, 1710, 1680, 1350 $cm^{-1}$; 400-MHz $^1H$ NMR ($CDCl_3$) δ 1.27 (t, 3 H, $J$ = 7.5 Hz, $OCH_2CH_3$), 1.31 (d, 3 H, $J$ = 7 Hz, $CHCH_3$), 1.32 (s, 3 H, $CCH_3$), 2.28 (dd, 1 H, $J$ = 15, 7 Hz), 2.94 (br ddd, 1 H, $J$ = 11, 7, 7 Hz, C-21 H), 3.22 (br d, 1 H, $J$ = 8.5 Hz, C-18 H), 3.73 (s, 3 H, $OCH_3$), 4.00 (s, 3 H, $OCH_3$), 4.18 (q, 2 H, $J$ = 7.5 Hz, $OCH_2CH_3$), 4.38 (ddd, 1 H, $J$ = 10, 10, 4.5 Hz, C-7 H), 5.14 (dd, 1 H, $J$ = 15.5, 8.5 Hz, C-17 H), 5.42 (ddd, 1 H, $J$ = 15.5, 8.5, 4 Hz, C-16 H), 5.55 (d, 1 H, $J$ = 10 Hz, C-9 or C-10 H), 5.61 (ddd, 1 H, $J$ = 10, 5, 2 Hz, C-9 or C-10 H), 6.71 (br s, 1 H, C-19 H).

Anal. Calcd for $C_{34}H_{44}O_{10}$: $(M + H)^+$, 613.3013. Found: $(M + H)^+$, 613.3018.

**Generation of 24-*O*-Methylchlorothricolide, Methyl Ester (1c) from 24-*O*-Methylchlorothricolide, Methyl Ester, Ethyl Carbonate (1d).** A solution containing 14 mg (23 μmol) of the carbonate **1d** and 0.05 mL of concentrated $H_2SO_4$ in 0.5 mL of dry methanol was heated at 72 °C. After 24 h, the mixture was poured into 20 mL of water and the aqueous layer was extracted with ether (3 × 30 mL), and the combined organic extracts were dried ($MgSO_4$). After removal of the solvent at reduced pressure, the crude residue was chromatographed on silica gel (2 g) with ethyl acetate–petroleum ether (35:65). In this manner, there was obtained 9.6 mg (78%) of the deprotected material as a colorless oil. The spectra of this material was identical with that reported by Keller-Schierlein.[4]

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# Synthesis and Utilization of the Chiral Synthon Methyl 3-*O*-Benzyl-2,4,6-trideoxy-6-iodo-α-D-*erythro*-hexopyranoside in the Synthesis of a Potent HMG-CoA Reductase Inhibitor

John D. Prugh,* C. Stanley Rooney, Albert A. Deana, and Harri G. Ramjit

*Department of Medicinal Chemistry, Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania 19486*

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Synthesis of the potent HMG-CoA reductase inhibitor **1a** has been achieved by utilizing the chiral synthon **2**, which was prepared from methyl α-D-glucopyranoside in 12 steps (6 new). A key step in this sequence, which should have general applicability for the synthesis of 4-deoxy sugars, is the reductive scission of the 4-tosylate substituent of **9** with $NaBH_4$ in hot $(CH_3)_2SO$. Coupling of the aryl substituent to the synthon was accomplished via the anion of arylmethyl phenyl sulfoxide **13** followed by thermal elimination of benzenesulfinic acid to give cleanly the *all-trans* ene intermediate **16a**. Selective removal of the benzyl ether blocking group was achieved without effect on the olefin by a novel palladium-mediated oxidative procedure utilizing 20% $Pd(OH)_2/C$, Pd black, or 10% Pd/C in refluxing ethanol (or methanol). Anomeric hydrolysis conducted in 80% aqueous acetic acid followed by oxidation of the lactols **18** with *N*-iodosuccinimide and tetrabutylammonium iodide provided the target **1a** which was shown to be identical with the biologically active dextrorotatory isomer of **1a** prepared by resolution of the racemate. On the basis of model studies, the limitations of the palladium-catalyzed debenzylation procedure along with insights into the reaction mechanism provided by isolation of benzaldehyde and benzoic acid derivative byproducts are discussed.

The fungal-derived natural products compactin (**1c**)[1] and mevinolin (**1d**)[2] have been shown to be specific inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMG-CoA reductase), the rate-limiting enzyme

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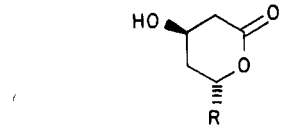
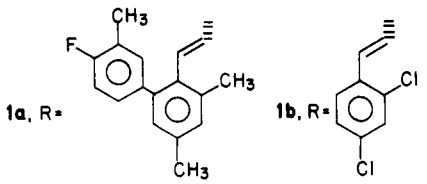
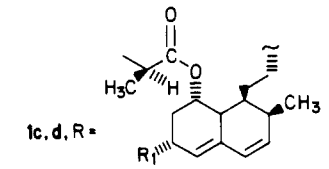
and natural point of cholesterogenesis regulation in mammals.[3] When given to man, these compounds characteristically cause an efficacious 30% drop in serum cholesterol and are thus thought to be useful in combating atherosclerosis.[4] Numerous partially[5] and totally synthetic analogues[6] have appeared, including the potent biphenyl analogue **1a**.[7] A common structural feature of these



**1**



**1a**, R = **1b**, R =

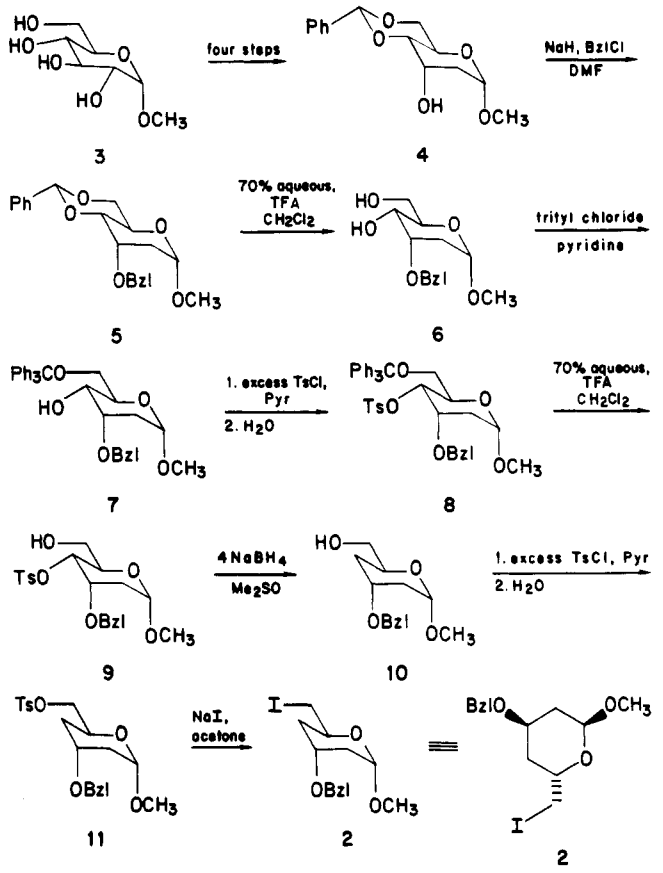


**1c**, **d**, R =

c, $R_1$ = H; d, $R_1$ = $CH_3$

compounds is the lactone moiety **1**. The absolute configuration of the lactone moiety in the two natural products is as written and the synthetic compound **1a**, by analogy to an X-ray crystallographic study of a similar compound, is presumed to be the same.[7] It occurred to us that **1a** and other synthetic analogues might be prepared by utilizing the chiral synthon **2** for the lactone top piece and, further, that this synthon could be prepared from D-glucose. Such a chiral synthesis of **1a** offered the possibility of being more efficient than the resolution of the racemic product[7] initially used. In addition, the absolute configuration of the lactone substituents could be established by relating them unambiguously to D-glucose. Preliminary accounts of the synthesis of **2**[8] and its utilization to prepare analogues[8,9] have been published. Subsequently other synthon approaches have appeared.[10] We now give a full account of our work which culminated in the chiral synthesis of **1a**.

**Scheme I**[a]




[a] Bzl = benzyl.

## Results and Discussion

The synthetic sequence developed for the elaboration of chiral synthon **2** from D-glucose is outlined in Scheme I. The known compound **4**,[11] readily available in four steps[11,12] from methyl α-D-glucopyranoside, has the required axial hydroxyl group at C3 and the equatorial hydroxymethyl group at C5 with the proper absolute configuration required for the preparation of **2**. What remained was to protect the C3 hydroxyl group, to remove the C4 hydroxyl group, and to convert the C5 hydroxymethyl group to iodomethyl. Accordingly, the hydroxyl group was converted to the benzyl ether **5**[13] with benzyl chloride and sodium hydride in DMF. Reported methods[13] for hydrolyzing the benzylidene group in **5** to give **6** gave

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(11) (a) Prins, D. A. *J. Am. Chem. Soc.* **1948**, *70*, 3955. (b) Richardson, A. C. *Carbohydr. Res.* **1967**, *4*, 422.

(12) (a) Freudenberg, K.; Toepffer, H.; Andersen, C. *Chem. Ber.* **1928**, *61*, 1750. (b) Ohle, H.; Spencker, K. *Ibid.* **1928**, *61*, 2387. (c) Richtmyer, N. K.; Hudson, C. S. *J. Am. Chem. Soc.* **1941**, 1727.

(13) (a) Brimacombe, J. S.; Mengech, A. S.; Tucker, L. C. N. *J. Chem. Soc., Perkin Trans. 1* **1977**, 643. (b) Ohrui, H.; Emoto, S. *Agric. Biol. Chem.* **1977**, *41*, 1773. (c) The product of our careful hydrolysis is in closer agreement with Ohrui and Emoto. The compound prepared by Brimacombe must have been impure.

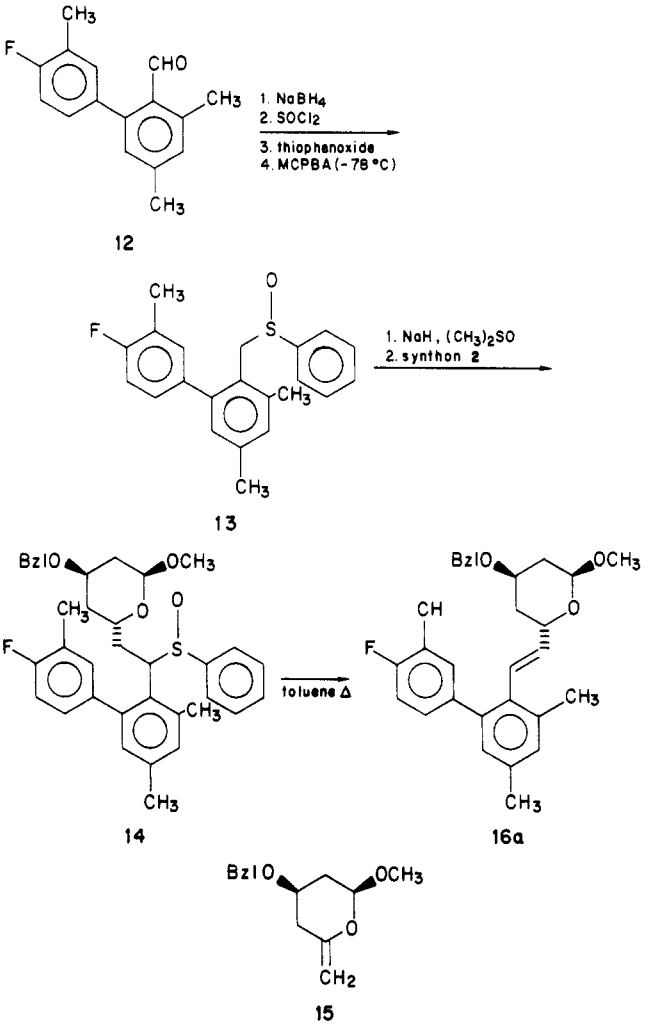
poor results in our hands. Subsequently, we found that treatment of **5** with 70% aqueous trifluoroacetic acid (TFA) in methylene chloride at ambient temperature for 10 min followed by quench and workup with aqueous sodium carbonate solution resulted in clean hydrolysis of the benzylidene group without disturbing the anomeric substituent to give **6**.

At first it seemed most expeditious to remove the C4 hydroxyl group via a Barton procedure[14] employing tributyltin radical reduction of the cyclic 4,6-*O*-thiocarbonate. However, all attempts with this methodology failed. We then thought that an intramolecular reduction of the 4-tosylate via an aluminum hydride ester formed at the vacant hydroxyl at the 6-position would accomplish reductive detosylation via intramolecular hydride transfer. The intermediate needed for such an intramolecular reduction is **9**, which was prepared from **6** in three steps involving the selective *O*-alkylation of the primary carbinol with trityl chloride[15] followed by treatment of the product with *p*-toluenesulfonyl chloride in pyridine to afford tosylate **8**. These two steps can be combined in a single pot. Detritylation of **8** using 70% aqueous TFA in methylene chloride then provided crystalline tosylate **9**. Although attempted intramolecular aluminum hydride reduction of **9** afforded some desired product, it gave primarily reduction of the tosylate to the mercaptan.

It is known that $NaBH_4$ is an effective reagent for the reduction of tosyl groups to alkanes.[16] Accordingly, reductive detosylation of **9** using 4 equiv of sodium borohydride[17] in $(CH_3)_2SO$ at 80 °C for 4 days under $N_2$ was found to afford the 2,4-dideoxy derivative **10** in 81% yield. This appears to be a new method for preparing 4-deoxy sugars and should have general synthetic applicability. The tosylate **11** was formed and converted to the corresponding iodide with a Finkelstein reaction, giving the desired chiral synthon **2**. All new steps in this sequence were accomplished in >77% yield.

The synthesis of the bottom piece **13** and its coupling to the synthon **2** to give the critical intermediate **16a** are outlined in Scheme II. Thus, the biphenyl aldehyde **12**[7a] was treated sequentially and without purification of intermediates with sodium borohydride to prepare the alcohol, thionyl chloride to prepare the chloromethyl derivative, thiophenoxide to prepare the sulfide, and *m*-chloroperbenzoic acid at −78 °C to prepare the sulfoxide **13** in 90% overall yield. The bottom piece was coupled to the synthon **2** by allowing an excess of the sodium salt of **13** to react with the synthon in $Me_2SO$ to give, after chromatography, a 38% yield of a mixture of the isomers of **14**. The isomer mixture, without separation, was heated in toluene to thermally eliminate sulfinic acid,[18] giving cleanly the trans isomer as evidenced by the 16.5-Hz coupling constant. This clean generation of the trans isomer, presumably because of steric reasons, is in sharp contrast to other approaches in these laboratories which have given cis–trans mixtures. The low yield in the coupling reaction to generate **14** is attributable to base-catalyzed elimination of HI from **2** as suggested by the chromatographic isolation of what appears to be exocyclic ene

**Scheme II**[a]




[a] Bzl = benzyl.

**15**.[19] A similar elimination product has been reported.[10e] We have not been able to improve on the yield of the coupling reaction.

It was more practical to study the deblocking of **16a** with the more easily accessible racemic **16b**. Accordingly, the readily available racemic lactone **1b**[7] was reduced to the lactols **26b** with diisobutylaluminum hydride,[20] which in turn was converted with TFA in methanol to an anomeric mixture of methyl glycosides. The mixture was readily separated by chromatography into $\alpha$, **28b**, and $\beta$, **27b**, anomers which were *O*-alkylated separately with benzyl chloride via their lithium salts to give the model compound **16b** and its anomer **17b**. The $\alpha$ anomeric configuration was assigned to **17b** on the basis of the larger axial–axial coupling constant of 9 Hz displayed by its anomeric hydrogen compared to the equatorial–axial coupling constant of 4.5 Hz displayed by the anomeric hydrogen of the $\beta$ anomer **16b**.

After a number of unsuccessful attempts with standard reagents (e.g., trimethylsilyl iodide, boron tribromide, boron trifluoroacetate) to cleave selectively the benzyl and methoxyl groups of **16b** without affecting the double bond, it was decided to investigate transfer hydrogenation conditions.[21] While double bonds are subject to transfer

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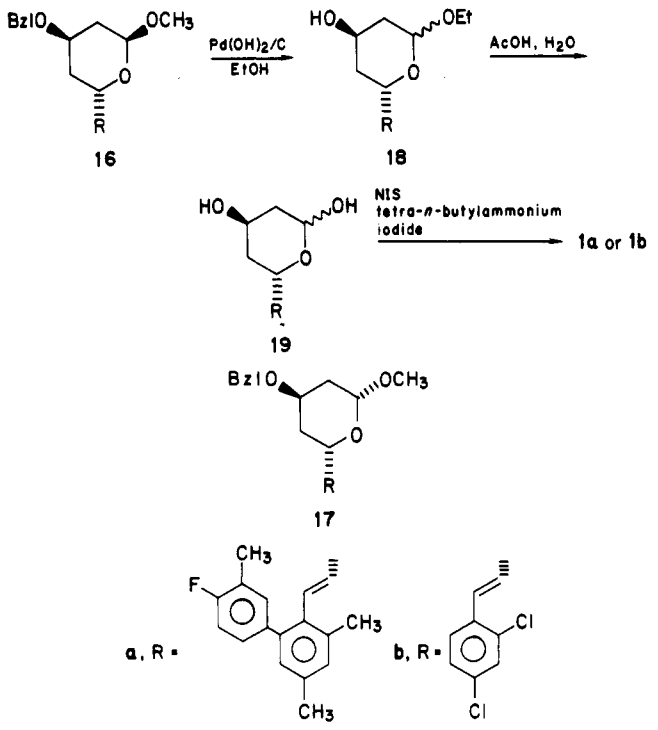
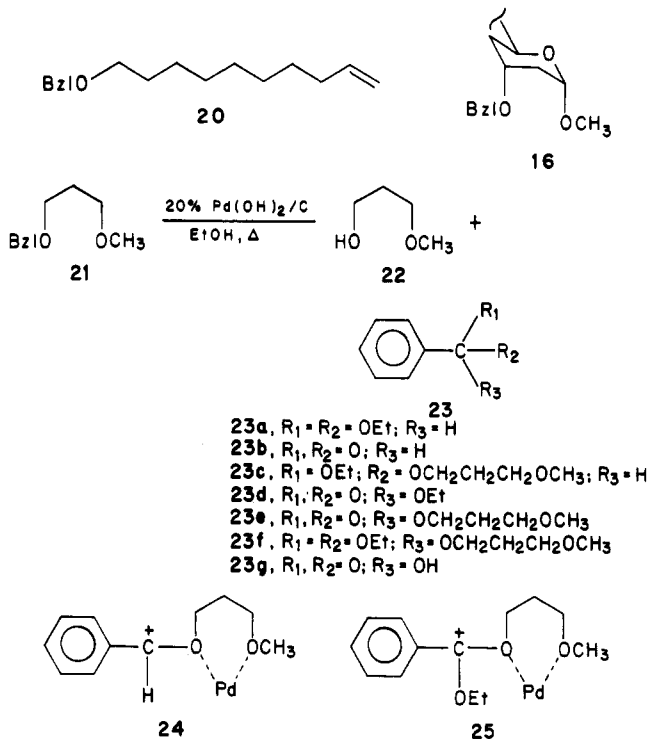
(17) One equivalent is consumed by the OH group. A 20% increase in yield was observed when 4 mol of $NaBH_4$ rather than 3 were used; also see: Krishnamurthy, S.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 849 and ref 12 therein.
(18) Trost, B. M.; Bridges, A. J. *J. Org. Chem.* **1975**, *40*, 2014.
(19) $^1H$ NMR ($CDCl_3$) (360 MHz) $\delta$ 1.74 (1 H, m), 2.25–2.34 (2 H, m), 2.63 (1 H, m), 3.51 (3 H, s), 3.64 (1 H, m, $H_{3a}$), 4.23 (1 H, d, vinyl, $J$ = 2 Hz), 4.50 (1 H, d, vinyl, $J$ = 2 Hz), 4.55–4.58 (3 H, m, $H_{1a}$, benzyl $CH_2$), 7.25–7.35 (5 H, m, Ar).
(20) Schmidlin, J.; Wettstein, A. *Helv. Chim. Acta* **1963**, *46*, 2799.

**Scheme III**[a]




[a] Bzl = benzyl.

**Scheme IV**[a]




[a] Bzl = benzyl.

hydrogenation, it was hoped that hydrogenolysis of the benzyl group might proceed at a faster rate than saturation of the hindered olefin. When a mixture of **16b**, 20% palladium hydroxide on carbon (Pearlman's catalyst), cyclohexene, and ethanol was heated at reflux for 40 min, it was observed that both benzyl ether cleavage and saturation of the double bond took place concurrently (Scheme III). Unexpectedly, however, the product mixture was found by TLC and $^1$H NMR to consist of an $\alpha$ and $\beta$ mixture of ethoxy rather than methoxy anomers. Since anomeric exchange with the solvent ethanol had not been reported in literature examples of carbohydrate benzyl ether cleavage under transfer hydrogenation conditions,[21a] we elected to look at this aspect of the reaction in greater detail. In an effort to determine if anomeric exchange and scrambling would occur in the absence of transfer hydrogenation, the reaction was repeated, but with the omission of cyclohexene. Disappearance of starting material was much slower in this second experiment; however, when the product was isolated it was found to be composed of a pair of ethoxy anomers (ratio 1.6:1; $\alpha$:$\beta$) from which *the benzyl group had been removed without affecting the double bond.* Some insights into the mechanism and limitations of this novel debenzylation are described in the next section. Hydrolysis of the anomeric ethoxy substituent of **18b** was carried out with 80% aqueous acetic acid at 90 °C for 30 min to give an inseparable mixture of anomeric lactols **19b**. Oxidation of the lactol mixture with *N*-iodosuccinimide and tetrabutylammonium iodide[21] proceeded smoothly to give the racemic lactone **1b**.

The procedures worked out for the model system were applied then to the completion of the synthesis of **1a**. Accordingly, debenzylation of **16a** was carried out with Pearlman's catalyst in refluxing ethanol to give the anomeric mixture **18a**. In a separate experiment the component anomers were separated by chromatography for characterization by high-resolution $^1$H NMR and MS as reported in the Experimental Section. In a probe run it was found that when hydrolysis of the ethoxy group of **18a** was carried out in hot 80% aqueous acetic acid for 35 min, significant epimerization of the allylic 6-position of the pyran ring occurred, resulting in a (4- and 6-position) cis–trans mixture of lactols. Subsequently, milder room temperature hydrolysis overnight was found to avoid 6-position epimerization. After chromatography the hydrolysis product **19a** was obtained as a mixture of lactol anomers (47% yield over two steps). The mixture of lactols was oxidized with *N*-iodosuccinimide and tetrabutylammonium iodide to give the target chiral lactone **1a** accompanied by a small amount of 6-position epimer,[22] necessitating separation of the unwanted cis isomer by chromatography. This product (isolated in 57% yield) was identical in all respects with a sample of the biologically active crystalline dextrorotatory isomer prepared by a different route and resolved from a racemic product.[7a]

## Mechanism and Scope of the Oxidative Benzyl Ether Cleavage

Investigation of the mechanism and generality of the novel palladium-mediated debenzylation reaction quickly showed that unadorned benzyl ethers such as **20** do not undergo this debenzylation under these conditions. We reasoned that **16** was an effective substrate for the reaction because of the binding assistance to palladium supplied by a second ligand; namely, the axial methoxyl group three carbons away from the axial benzyloxy group as depicted in **16**. If this is so, then **21**, which has a similarly disposed methoxy group, should also undergo debenzylation under

(21) (a) Hanessian, S.; Wong, D. H.; Therien, M. *Synthesis* **1981**, 394. (b) Rao, V. S.; Perlin, A. S. *J. Org. Chem.* **1982**, *47*, 367.

(22) This epimerization is attributed to acid impurity in NIS, for the longer the reaction goes the more cis product appears. This finding was made when the reaction was scaled up and the reaction time extended in an effort to maximize conversion. Interestingly this epimerization did not occur with the model **19b** with a 2,4-dichloroethylidene substituent which would not form an allylic carbonium ion as easily as the biphenyl counterpart.

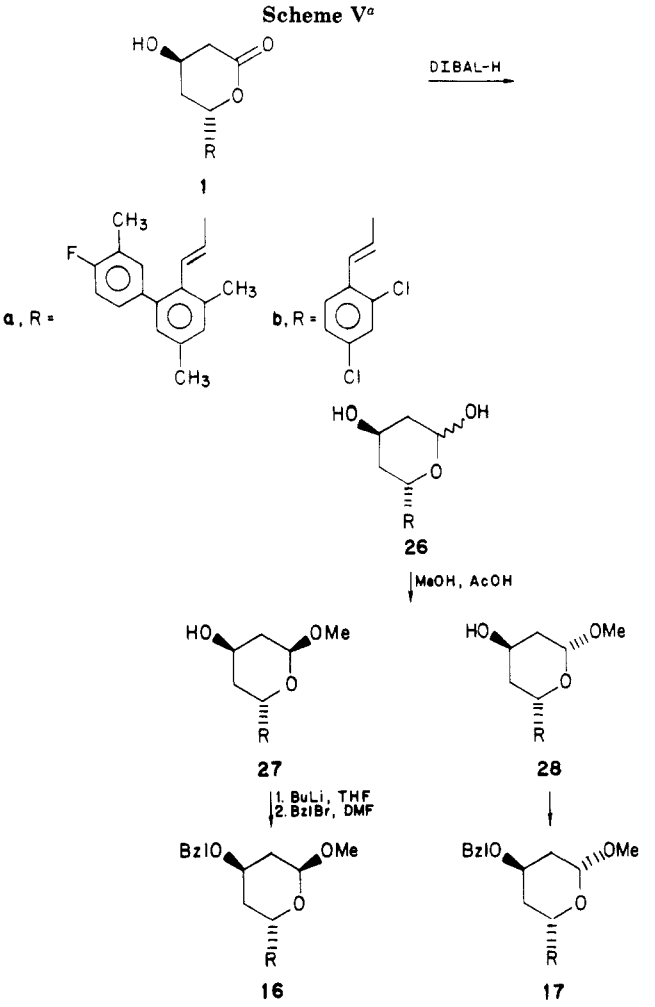
the same conditions, as indeed it does (Scheme IV). We then used **21** as a model to study in detail the fate of the benzyl group. As indicated by $^1$H NMR of the mixture and GC–mass spectral evidence in three modes (see supplementary data) the benzyl group of **21** is converted to **23a** (51%), **23b** (28.6%), **23c** (1.5%), **23d** (13.6%), **23e** (4.2%), **23f** (<0.3%), **23g** (0.6%), and <2% toluene indicating an oxidative cleavage of the benzyl group. The observed oxidation products can be formally derived from the reaction of ethanol or water (from moist Pearlman's catalyst) with the palladium-bound carbonium ions **24** and **25** which, in turn, are formally derived from successive hydride ion transfers to catalyst from **21** and an intermediate acetal. The exact composition of the mixture of oxidation products is probably variable and dependent on the time of reflux and the amount of water in the catalyst. The ultimate fate of the "hydride" ion is not known. Pearlman's catalyst from two different sources as well as palladium black catalyzed oxidative debenzylation accompanied by anomeric exchange with solvent and scrambling. The acidity of these two catalysts is believed responsible for the observed anomeric solvent exchange and scrambling. Late in the investigation of the debenzylation of **16a**, it was found that 10% palladium on carbon (Engelhard Lot 28597, pH of aqueous slurry ~10) reproducibly accomplished selective oxidative cleavage of the benzyl group without anomeric scrambling or exchange with solvent.[23] The availability of a catalyst which did not modify the anomeric configuration of **16a** afforded the opportunity to test our hypothesis that the 1,3-diaxial relationship of the benzyloxy and methoxy groups in **16a** was crucial in providing anchimeric binding with palladium. Thus it was predicted that the corresponding $\alpha$ anomer, **17a**, in which the anomeric methoxy group is equatorial, and therefore not positioned to play a ligand role, would be a poor substrate for the reaction. Accordingly compound **17a** was synthesized starting from chiral **1a**[7c] (prepared by resolution of the racemate) by a sequence of reactions similar to those employed for **17b** (Scheme V). The synthetic sequence also gave rise to $\beta$-methoxy derivatives **27a** and **16a** which were shown to be identical with the same products prepared by the synthon route. Under conditions identical with those used to debenzylate **16a** with the effective Engelhard Pd/C catalyst, only ca. 6% debenzylation of **17a** occurred (HPLC) after 3 days of reflux. Upon isolation $^1$H NMR showed **17a** to be unchanged. Thus, the importance of the 1,3-diaxial configuration of benzyloxy and methoxy groups is demonstrated. It seems reasonable that a properly placed second ligand other than methoxy would also work. In our view the scope of this oxidative debenzylation may be limited to compounds with a strategically placed second ligand capable of binding to palladium. However, the reaction should be useful in the selective deprotection of selected polyhydroxylated compounds.

## Experimental Section

**General Methods.** Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. $^1$H NMR spectra are reported in ppm ($\delta$) using tetramethylsilane as the internal standard. Analtech silica gel GF prescored TLC plates were used throughout. Preparative TLC separations were accomplished on

(23) A second lot of Engelhard 10% Pd/C catalyst (pH of aqueous slurry = 7.3) caused debenzylation accompanied by anomeric scrambling with solvent ethanol, while a lot of Aldrich 10% Pd/C (pH of aqueous slurry = 9.8) was without any effect. Interestingly, a combination of these two lots of catalyst resulted in benzyl ether cleavage without affecting the anomeric methoxy group.

**Scheme V**[a]




[a] Bzl = benzyl.

Analtech silica gel GF 20 × 20 cm × 2000 $\mu$m thickness plates.

**Methyl 3-*O*-Benzyl-2-deoxy-$\alpha$-D-*ribo*-hexopyranoside (6).** Methyl 3-*O*-benzyl-4,6-*O*-benzylidene-2-deoxy-$\alpha$-D-*ribo*-hexopyranoside (5) (14.4 g, 40 mmol) was dissolved in $CH_2Cl_2$ (200 mL). Trifluoroacetic acid (70% TFA in water, 9.6 mL) was added with vigorous stirring. The reaction was stirred vigorously for 10 min and immediately quenched by adding 40 mL of saturated aqueous $Na_2CO_3$ with vigorous stirring. The $CH_2Cl_2$ layer was separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried ($K_2CO_3$, anhydrous), filtered, and evaporated in vacuo to give the crude product and benzaldehyde. The mixture was chromatographed on 250 g of silica gel (EM Reagents, 70–230 mesh), eluting with 15% acetone in $CH_2Cl_2$ for 1 L, then with 20% acetone in $CH_2Cl_2$ thereafter (~2.5 L). The fractions containing the product (visualized on silica gel TLC plate with 7% phosphomolybdic acid in ethanol followed by heat) were collected and the solvent was evaporated in vacuo to leave 9.1 g (88%) of product as a glassy oil; $[\alpha]^{25}_D$ +170.58° (*c* 0.2, $CHCl_3$)[13c] [reported $[\alpha]^{21}_D$ +161.9° (*c* 0.1, $CHCl_3$);[13b] $[\alpha]_D$ +101° (*c* 1, $CHCl_3$)[13a]]. Anal. Calcd for $C_{14}H_{20}O_5 \cdot {}^1/_2H_2O$: C, 60.70; H, 7.63. Found: C, 60.78; H, 7.38.

**Methyl 3-*O*-Benzyl-6-*O*-trityl-2-deoxy-$\alpha$-D-*ribo*-hexopyranoside (7).** To a solution of compound **6** (4.6 g, 17.9 mmol) in dry pyridine (50 mL) was added triphenylmethyl chloride (5.24 g, 18.8 mmol). The resulting solution was stirred under nitrogen for 6 days.[14] A saturated solution of $NaHCO_3$ (50 mL) and water (~300 mL) were added and water/pyridine was removed by azeotropic distillation in vacuo at low bath temperature. The product was extracted with ether, dried ($K_2CO_3$, anhydrous), filtered, and evaporated. The crude product was chromatographed on 500 g of silica gel (EM Reagents, 70–230 mesh), eluting with $CH_2Cl_2$ (1.5 L) followed by 5% acetone in $CH_2Cl_2$ (2.5 L). Fractions containing the product were collected and the solvent was evaporated in vacuo to leave 7.9 g (86%) of product as a gum; $[\alpha]^{25}_D$ +87.23° (*c* 0.35, $CHCl_3$); $^1$H NMR ($CDCl_3$) (60 MHz) $\delta$ 1.75

(1 H, m, $J_{gem}$ = 15 Hz), 2.16 (H, m, $J_{gem}$ = 15 Hz), 3.23–4.20 (5 H, m), 3.42 (3 H, s), 4.42 (1 H, d, $J$ = 12 Hz), 4.78 (1 H, d, $J$ = 12 Hz), 4.78 (1 H, d, $J$ = 4 Hz), 7.1–7.65 (20 H, m). Anal. Calcd for $C_{33}H_{34}O_5$: C, 77.62; H, 6.71. Found: C, 77.38; H, 6.76.

**Methyl 3-*O*-Benzyl-4-*O*-tosyl-6-*O*-trityl-2-deoxy-α-D-*ribo*-hexopyranoside (8).** Compound 7 (13.3 g, 26.05 mmol) was dissolved in dry pyridine (41 mL) and cooled in an ice bath under $N_2$. *p*-Toluenesulfonyl chloride (9.93 g, 52.09 mmol) was added all at once, and the resulting reaction mixture was stirred at room temperature under $N_2$ overnight. The reaction mixture was partitioned between ether and water. The ether layer was extracted 4 times with water, dried ($K_2CO_3$ anhydrous), filtered, and evaporated in vacuo. The crude product (19.1 g) was chromatographed on silica gel (1 kg, EM Reagents, 70–230 mesh), eluting with $CH_2Cl_2$ until excess *p*-toluenesulfonyl chloride had been eluted from the column. Elution was continued with 2% acetone in $CH_2Cl_2$. The fractions containing the product were collected, and the solvent was evaporated in vacuo to leave 15.5 g (89.5%) of product as a glassy gum; $[\alpha]^{25}_D$ +66.24° (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$) (60 MHz) δ 1.82–2.20 (2 H, m), 2.33 (3 H, s), 2.80–3.38 (2 H, m), 3.40 (3 H, s), 4.00 (1 H, m), 4.18–4.80 (5 H, m), 7.02–7.50 (20 H, m). Anal. Calcd for $C_{40}H_{40}O_7S$: C, 72.27; H, 6.06. Found: C, 71.94; H, 6.32.

**Methyl 3-*O*-Benzyl-4-*O*-tosyl-2-deoxy-α-D-*ribo*-hexopyranoside (9).** Compound 8 (15.3 g, 23.01 mmol) was dissolved in $CH_2Cl_2$ (200 mL). Trifluoroacetic acid (70% TFA in water, 9.6 mL) was added with vigorous stirring at room temperature. The vigorous stirring was continued for 5 min, as the reaction turned yellow. The reaction was then quenched by the addition of saturated aqueous $Na_2CO_3$ solution (40 mL) with vigorous stirring. The reaction was now colorless. The $CH_2Cl_2$ layer was separated and the aqueous layer extracted with $CH_2Cl_2$. The combined $CH_2Cl_2$ extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give the crude product. This product was chromatographed on 650 g of silica gel (EM Reagents, 70–230 mesh), eluting with 3 L of $CH_2Cl_2$ to remove triphenylcarbinol followed by elution with 10% acetone in $CH_2Cl_2$. Fraction collection was begun when the faintly visible opaque band of product neared the bottom of the column. The fractions containing the product were combined and the solvent was evaporated in vacuo to leave 8.1 g (83.5%) of product: mp 100–101 °C; $[\alpha]^{25}_D$ +115.07° (*c* 0.48, $CHCl_3$); $^1H$ NMR ($CDCl_3$) (60 MHz) δ 1.78 (1 H, m, $J_{gem}$ = 15 Hz), 2.20 (1 H, m, $J_{gem}$ = 15 Hz), 2.40 (1 H, s), 3.30 (3 H, s), 3.55–3.93 (3 H, m), 4.20 (1 H, m), 4.44–4.84 (4 H, m), 7.08–7.40 (7 H, m), 7.70 (2 H, d). Anal. Calcd for $C_{21}H_{26}O_7S$: C, 59.70; H, 6.20. Found: C, 60.09; H, 6.37.

**Methyl 3-*O*-Benzyl-2,4-dideoxy-α-D-*erythro*-hexopyranoside (10).** Compound 9 (6.55 g, 15.50 mmol) was dissolved in dry $Me_2SO$ (50 mL). Sodium borohydride (2.35 g, 62.01 mmol) was added, and the reaction mixture was stirred under $N_2$ in an oil heating bath at 80 °C for 4 days. The resulting mixture was cooled to room temperature, diluted with ether, and extracted once with water. The aqueous extract was then extracted 4 times with ether. The combined ether extracts were dried ($MgSO_4$), filtered, and evaporated in vacuo to give the crude product. This material was chromatographed on a 60 mm × 150 mm flash chromatography silica gel column, eluting with 15% acetone in $CH_2Cl_2$. A small portion (0.9 g) containing an impurity was rechromatographed on a 30 mm × 130 mm flash chromatography column, eluting with the same solvent to give a combined total of 3.18 g (81.3%) of product as a gum; $[\alpha]^{24}_D$ +94.00° (*c* 0.55, $CHCl_3$); $^1H$ NMR ($CDCl_3$) (90 MHz) δ 1.40–2.25 (4 H, m), 3.40 (3 H, s), 3.60 (2 H, m), 3.80 (1 H, m), 4.25 (1 H, m), 4.52 (1 H, d, $J_{gem}$ = 12 Hz), 4.65 (1 H, d, $J_{gem}$ = 12 Hz), 4.80 (1 H, d, $J$ = 4.5 Hz), 7.20–7.48 (5 H, m). Anal. Calcd for $C_{14}H_{20}O_4$: C, 66.65; H, 7.97. Found: C, 66.66; H, 8.06.

**Methyl 3-*O*-Benzyl-6-*O*-tosyl-2,4-dideoxy-α-D-*erythro*-hexopyranoside (11).** Alcohol 10 (2.5 g, 9.91 mmol) was dissolved in dry pyridine (20 mL) under $N_2$. *p*-Toluenesulfonyl chloride (3.78 g, 19.8 mmol) was added all at once, and the reaction solution was stirred at room temperature for 4 h. Water (5 mL) was added dropwise with stirring. A slight exotherm occurred, and stirring was continued for 1 h at ambient temperature. Ether was added to the reaction mixture. The organic phase was extracted with water 3 times, then 2 times with dilute aqueous hydrochloric acid (washings acidic), followed by 1 extraction with water and extraction with aqueous $NaHCO_3$. The ether extract was dried ($MgSO_4$), filtered, and evaporated in vacuo to leave 3.0 g of product. Purification on a 60 mm × 150 mm flash chromatography silica gel column, eluting with 2% acetone in $CH_2Cl_2$, gave 3.0 g (77.5%) of product as a gum: $[\alpha]^{25}_D$ +22.80° (*c* 1.2, $CHCl_3$); $^1H$ NMR ($CDCl_3$) 60 MHz) δ 1.42–2.30 (4 H, m), 2.42 (3 H, s), 3.28 (3 H, s), 3.60–4.60 (6 H, m), 4.70 (1 H, d, $J$ = 4 Hz), 7.10–7.40 (7 H, m), 7.75 (2 H, d). Anal. Calcd for $C_{21}H_{26}O_5S{\cdot}H_2O$: C, 61.74; H, 6.91. Found: C, 61.50; H, 6.55.

**Methyl 3-*O*-Benzyl-6-iodo-2,4,6-trideoxy-α-D-*erythro*-hexopyranoside (2).** A solution of compound 11 (3.0 g, 7.34 mmol) and NaI (13 g, 86.7 mmol) in acetone (130 mL) was refluxed under $N_2$ with stirring for 24 h, while protected from the light. When TLC showed the reaction to be complete, the acetone was evaporated in vacuo and the residue was partitioned between ether and water. The ether layer was washed with dilute aqueous sodium thiosulfate and then twice with water, dried ($MgSO_4$), filtered, and evaporated in vacuo to give crude product which was homogeneous on TLC but colored slightly yellow. It was purified by flash chromatography on silica gel (60 mm × 130 mm), eluting with methylene chloride to give 2.28 g (86%) of product as a mobile oil. In order to insure a dry product, dry toluene (50 mL) was added and removed in vacuo 4 times: $[\alpha]^{24}_D$ +53.45° (*c* 0.66, $CHCl_3$); $^1H$ NMR ($CDCl_3$) (360 MHz)[24] δ 1.55 (1 H, ddd, $H_{4a}$, $J_{gem}$ = 13.5 Hz, $J_{4a-5}$ = 12 Hz, $J_{4a-3}$ = 3 Hz), 1.76 (1 H, dt, $H_{2a}$, $J_{gem}$ = 15 Hz, $J_{2a-1}$ = 4.5 Hz, $J_{2a-3}$ = 4.5 Hz), 1.95 (1 H, br d, $H_{4e}$, $J_{gem}$ = 13.5 Hz), 2.04 (1 H, br d, $H_{2e}$, $J_{gem}$ = 15 Hz), 3.17 (1 H, dd, $H_6$, $J_{gem}$ = 10.5 Hz, $J_{6-5}$ = 7.5 Hz), 3.27 (1 H, dd, $H_{6'}$, $J_{gem}$ = 10.5 Hz, $J_{6'-5}$ = 4 Hz), 3.46 (3 H, s, $OCH_3$), 3.78 (1 H, p, $H_3$, $J$ = 4.5 Hz), 4.09 (1 H, ddd, $H_5$, $J_{5-6}$ = 7.5 Hz, $J_{5-6'}$ = 4 Hz, $J_{4a-5}$ = 12 Hz), 4.51 (1 H, d, benzyl, $J_{gem}$ = 12 Hz), 4.64 (1 H, d, benzyl, $J_{gem}$ = 12 Hz), 4.82 (1 H, d, $H_1$, $J_{2a-1}$ = 4.5 Hz), 7.25–7.40 (5 H, m, Ar). Anal. Calcd for $C_{14}H_{19}IO_3$: C, 46.43; H, 5.29. Found: C, 46.75; H, 5.44.

**4′-Fluoro-2-(hydroxymethyl)-3,3′,5-trimethyl-1,1′-biphenyl.** 4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-carboxaldehyde (12) (5.0 g, 20.6 mmol) was suspended in ethanol (40 mL) and cooled in an ice–water bath. $NaBH_4$ (0.75 g, 20 mmol) was added with stirring. After 5 min, the cooling bath was removed and stirring was continued at ambient temperature for 1 h. The clear solution was cooled in an ice–water bath and excess $NH_4Cl$ (4 g) was added. The reaction mixture was partitioned between water and ether. The aqueous layer was extracted twice with ether. The combined ether extracts were extracted with saturated NaCl solution, dried ($MgSO_4$), filtered, and evaporated in vacuo to leave 4.9 g (97.4%) of product: mp 99–102 °C. This material was used in the next step without further purification. A small sample was vacuum sublimed for analysis: mp 102–103 °C; $^1H$ NMR ($CDCl_3$) (90 MHz) δ 2.25 (6 H, s), 2.45 (3 H, s), 4.48 (2 H, s), 6.75–7.25 (5 H, m). Anal. Calcd for $C_{16}H_{17}FO$: C, 78.66; H, 7.01. Found: C, 79.00; H, 7.33.

**2-(Chloromethyl)-4′-fluoro-3,3′,5-trimethyl-1,1′-biphenyl.** 4′-Fluoro-2-(hydroxymethyl)-3,3′,5-trimethyl-1,1′-biphenyl (4.9 g, 20.6 mmol) was added in divided portions over 10 min to $SOCl_2$ (20 mL) with stirring. The reaction mixture was stirred at reflux for 1 h while protected with a drying tube. The reaction mixture was cooled to room temperature, 50 mL of dry toluene was added, and the excess $SOCl_2$ and toluene were removed in vacuo. Dry toluene (50 mL) was added again, and the mixture was evaporated to dryness in vacuo to leave 6.2 g (100%—some toluene present) of yellow oil. This material was used without purification in the next step: $R_f$ (silica gel) 0.84 (40% methylene chloride in hexane); $^1H$ NMR ($CDCl_3$) (60 MHz) δ 2.36 (6 H, s), 2.50 (3 H, s), 4.50 (2 H, s), 6.9–7.44 (5 H, m).

**(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)methyl Phenyl Sulfide.** Sodium hydride in mineral oil (50% dispersion, 1.36 g, 28.3 mmol) was suspended in dry DMF (20 mL). Thiophenol (3.2 mL, 3.43 g, 31.2 mmol) was added dropwise slowly with stirring. Then the mixture was heated at 50 °C bath temperature for 30 min, at which time the NaH was visibly consumed, and no more hydrogen was evolved. A solution of 2-(chloro-

(24) The numbering system used to describe the details of the 360-MHz $^1H$ NMR spectra begins with 1 at the anomeric carbon and proceeds clockwise around the D-pyranose ring drawn in the standard chair conformation with a for axial and e for equatorial hydrogens. The substituents appended to the 5-position are numbered 6 and 7.

methyl)-4′-fluoro-3,3′,5-trimethyl-1,1′-biphenyl (6.2 g, 23.6 mmol) in dry DMF (17 mL) was added dropwise at a rapid rate. The resulting mixture was heated at a bath temperature of 50 °C for 30 min. The reaction mixture was cooled and partitioned between ether and 200 mL of dilute NaOH solution. The ether layer was extracted again with dilute NaOH solution and then extracted 2 times with dilute NaCl solution, dried ($MgSO_4$), filtered, and evaporated in vacuo to leave 7.45 g (94.1%) of oil which slowly crystallized. This product was nearly homogeneous on TLC and was used in the next step without further purification. A small sample was purified by flash chromatography eluting with $CH_2Cl_2$/hexane (1:4): mp 72–74 °C; $^1H$ NMR ($CDCl_3$) (60 MHz) $\delta$ 2.22 (3 H, d, $J$ = 2 Hz), 2.30 (3 H, s), 2.48 (3 H, s), 4.00 (2 H, s), 6.70–7.34 (10 H, m). Anal. Calcd for $C_{22}H_{20}FS$: C, 78.77; H, 6.01. Found: C, 78.40; H, 6.39.

**(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)methyl Phenyl Sulfoxide (13).** A solution of (4′-fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)methyl phenyl sulfide (7.45 g, 22.2 mmol) in $CH_2Cl_2$ (67 mL) was cooled under nitrogen to −78 °C in a dry ice–acetone bath. *m*-Chloroperbenzoic acid (technical grade, 80–85%; 4.60 g, 26.6 mmol) was added in divided portions (as the solid) in about 10 min. The reaction mixture was stirred at −78 °C for 30 min and then allowed to warm to room temperature. TLC indicated only a trace of starting sulfide and some sulfone present. The reaction was filtered and the crystals of *m*-chlorobenzoic acid were washed with a small amount of $CH_2Cl_2$. The filtrate and $CH_2Cl_2$ washings were diluted with ether and washed twice with dilute aqueous NaOH. The organic layer was dried ($MgSO_4$), filtered, and evaporated in vacuo to give crude product which was purified by flash chromatography on an 80 mm × 150 mm column, eluting with 3.5% acetone in methylene chloride. The fractions containing the product were collected and evaporated in vacuo to leave 6.92 g (94.1%) of the product. In order to insure a dry product, 50 mL of dry toluene was added and the solvent evaporated in vacuo. This was repeated 3 times. Upon seeding, the oil crystallized: mp 78–86 °C; $^1H$ NMR ($CDCl_3$) (60 MHz) $\delta$ 2.20 (3 H, d, $J$ = 2 Hz), 2.28 (3 H, s), 2.35 (3 H, s), 4.00 (1 H, d, $J_{gem}$ = 12.5 Hz), 4.30 (1 H, d, $J_{gem}$ = 12.5 Hz), 6.60–7.50 (10 H, m). Anal. Calcd for $C_{22}H_{21}FSO$: C, 74.97; H, 6.01. Found: C, 75.01; H, 6.19.

**(2*S*,4*R*,6*S*)-1-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)-2-[4-(benzyloxy)-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran-6-yl]ethyl Phenyl Sulfoxide (14).** Sodium hydride (0.030 g, 0.63 mmol) was suspended in dry $Me_2SO$ (0.5 mL) under $N_2$ and heated at 60–70 °C for 1 h until hydrogen evolution ceased. After cooling to room temperature, a solution of compound **13** (0.211 g, 0.60 mmol) in dry $Me_2SO$ (0.6 mL) was added by syringe through a septum and stirring was continued for 10 min. A solution of compound **2** (0.109 g, 0.3 mmol) in dry $Me_2SO$ (0.6 mL) was added dropwise while the reaction mixture was stirred and cooled in an ice–water bath. After the addition was complete, the ice bath was removed and the reaction mixture was stirred at ambient temperature for 1 h. The reaction mixture was then partitioned between ether (50 mL) and water (25 mL). The aqueous layer was extracted with ether, and the combined ether extracts were washed with water (25 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to leave 0.3 g of crude product mixture. Flash chromatography was carried out on a 20 × 150 mm column, eluting with 2% acetone in $CH_2Cl_2$ (20 fractions of 10 mL each) and then 5% acetone in methylene chloride (30 fractions of 10 mL each). The fractions containing the desired isomers of the product ($R_f$ 0.29 and 0.37, 5% acetone/$CH_2Cl_2$; silica gel); were combined and evaporated in vacuo to leave 68.9 mg of product as an isomer mixture (38% based on the synthon). The isomer mixture was used in the next step without further separation.

**(2*S*,4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)ethenyl]-4-(benzyloxy)-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (16a).** A suspension of isomer mixture **14** (3.0 g, 5.11 mmol) and anhydrous potassium carbonate (5 g) in dry toluene (250 mL) was stirred and warmed in a heating bath at 90 °C for 3 h. The reaction mixture was cooled to room temperature and the solvent evaporated in vacuo. The residue was repeatedly (5 times) refluxed and triturated with a small amount of $CH_2Cl_2$ and then filtered through a tightly packed plug of glass wool. The solvent was then evaporated in vacuo. The crude product was purified by flash chromatography on a 60 × 180 mm column, eluting with $CH_2Cl_2$ (12 fractions, 100 mL each), followed by 2% acetone in methylene chloride (15 fractions, 100 mL each). The fractions containing the desired product ($R_f$ 0.25 (silica gel) eluting with methylene chloride) were collected and evaporated to leave 2.0 g of product as a gum (85%); $[\alpha]^{24}_D$ +62.72° ($c$ 0.59, $CHCl_3$): $^1H$ NMR ($CDCl_3$) (360 MHz)[24] $\delta$ 1.54 (1 H, ddd, $H_{4a}$, $J_{gem}$ = 13.5 Hz, $J_{4a-5}$ = 12 Hz, $J_{4a-3}$ = 3 Hz), 1.74 (1 H, br d, $H_{4e}$, $J_{gem}$ = 13.5 Hz), 1.82 (1 H, dt, $H_{2a}$, $J_{gem}$ = 15 Hz, $J_{2a-1}$ = 4.5 Hz, $J_{2a-3}$ = 4.5 Hz), 1.96 (1 H, br d, $H_{2e}$, $J_{gem}$ = 15 Hz), 2.28 (3 H, d, $CH_3$, $J$ = 2 Hz), 2.34 (3 H, s, $CH_3$), 2.37 (3 H, s, $CH_3$), 3.38 (3 H, s, $OCH_3$), 3.69 (1 H, p, $H_3$, J ~ 4 Hz), 4.52 (1 H, d, benzyl, $J_{gem}$ = 12 Hz), 4.61 (1 H, m, $H_5$), 4.63 (1 H, d, benzyl, $J_{gem}$ = 12 Hz), 4.67 (1 H, t, $H_1$, $J_{1-2a}$ = $J_{1-2e}$ = 4.5 Hz), 5.44 (1 H, dd, $H_6$, $J_{5-6}$ = 6 Hz, $J_{6-7}$ = 16.5 Hz), 6.43 (1 H, d, $H_7$, $J_{6-7}$ = 16.5 Hz), 6.90–7.42 (10 H, m, Ar); $^{19}F$ NMR ($CDCl_3$) (360 MHz) 121.497 (1 F, m). Anal. Calcd for $C_{30}H_{33}FO_3$: C, 78.23; H, 7.22. Found: C, 78.37; H, 7.40.

**(*E*)-6α-[2-(2,4-Dichlorophenyl)ethenyl]-2α- and -2β-hydroxy-4β-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (26b).** (*E*)-6α-[2-(2,4-Dichlorophenyl)ethenyl-4β-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (racemic **1b**)[7] (2.87 g, 10 mmol) was dissolved in anhydrous THF (175 mL) and cooled under $N_2$ to −78 °C in a dry ice–acetone bath. Diisobutyl aluminum hydride[20] (21.19 mL, 23.85% in toluene, $d$ = 0.8446, 4.27 g, 30 mmol) was added by syringe over a period of 10 min with stirring. Methanol (5.4 mL) was added carefully over a period of 5 min. The bath was taken away and water (21.4 mL) was added dropwise rapidly. The reaction was warmed to 0 °C and stirred for 10 min. Celite (21.4 g) was added and stirring was continued for 5 min. Then sodium sulfate (107.1 g) was added and the mixture was stirred for 20 min. The mixture was filtered and the solid was washed with ether (5 × 25 mL). The solvent was evaporated in vacuo to leave a wet gum. The gum was dissolved in ether (200 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo to leave 2.56 g (90%) of product mixture; $^1H$ NMR ($CDCl_3$ + $D_2O$) $\delta$ 1.5–2.2 (8 H, m), 4.2 (2 H, m), 4.8 (1 H, m), 5.07 (1 H, m), 5.4 (2 H, m), 6.15 (2 H, dd, $J$ = 6, 16.5 Hz), 6.6–7.4 (6 H, m).

**(*E*)-6α-[2-(2,4-Dichlorophenyl)ethenyl]-4β-hydroxy-2β-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (27b) and (*E*)-6α-[2-(2,4-Dichlorophenyl)ethenyl]-4β-hydroxy-2α-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (28b).** Trifluoroacetic acid (2 mL) was added to a solution of (*E*)-6α-[2-(2,4-dichlorophenyl)-ethenyl]-2α- and -2β-hydroxy-4β-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (2.2 g, 7.6 mmol) in methanol (40 mL), and the mixture was stirred at room temperature for 1 h. Aqueous saturated $Na_2CO_3$ (20 mL) was added and the mixture was stirred vigorously for 15 min. Ether (200 mL) was added. The separated ether phase was extracted with water (5 × 50 mL), dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo to leave a crude mixture of the two anomers. Flash chromatography (50 × 150 mm column), eluting with 10% acetone in $CH_2Cl_2$, gave as the first product to emerge the 2β-methoxy isomer **27b**, 0.57 g, $R_f$ 0.57 (silica gel, 10% acetone in methylene chloride): mp 90–93 °C; $^1H$ NMR ($CDCl_3$) (360 MHz)[24] $\delta$ 1.70 (1 H, ddd, $H_{4a}$, $J_{gem}$ = 13.5 Hz, $J_{4a-5}$ = 12 Hz, $J_{4a-3}$ = 3 Hz), 1.90 (1 H, dt, $H_{2a}$, $J_{gem}$ = 13.5 Hz, $J_{2a-1}$ = $J_{2a-3}$ = 3 Hz), 1.97 (2 H, br d, $H_{2e}$ + $H_{4e}$, $J_{gem}$ = 13.5 Hz), 3.4 (3 H, s, $OCH_3$), 4.13 (1 H, p, $J$ = 3 Hz), 4.72 (1 H, dd, $H_5$, $J_{5-4a}$ = 12 Hz, $J_{5-6}$ = 6 Hz), 4.96 (1 H, d, $H_1$, $J_{1-3a}$ = 3 Hz), 6.21 (1 H, dd, $H_6$, $J_{6-5}$ = 6 Hz, $J_{6-7}$ = 15 Hz), 6.97 (1 H, d, $H_7$, $J_{7-6}$ = 15 Hz), 7.20 (1 H, dd, $Ar_5$, $J$ = 7.5, 2 Hz), 7.37 (1 H, d, $Ar_3$, $J$ = 2 Hz), 7.48 (1 H, d, $Ar_6$, $J$ = 7.5 Hz). Anal. Calcd for $C_{14}H_{16}Cl_2O_3$: C, 55.46; H, 5.32. Found: C, 55.79; H, 5.49. The yield of 2α-methoxy isomer **28b**, was 0.63 g, $R_f$ 0.32 (silica gel, 10% acetone in methylene chloride): mp 87–89 °C; $^1H$ NMR ($CDCl_3$) (360 MHz) $\delta$ 1.60–1.75 (2 H, m, $H_{4a}$ + $H_{2a}$), 1.80 (1 H, br d, $H_{4e}$, $J_{gem}$ = 12 Hz), 1.94 (1 H, br d, $H_{2e}$, $J_{gem}$ = 12 Hz), 3.50 (3 H, s, $OCH_3$), 4.40 (1 H, p, $H_3$, $J$ ≃ 3 Hz), 4.62 (1 H, m, $H_5$), 4.85 (1 H, dd, $H_1$, $J_{1-2a}$ = 9 Hz, $J_{1-2e}$ = 2 Hz), 6.19 (1 H, dd, $H_6$, $J_{6-7}$ = 15 Hz, $J_{6-5}$ = 6 Hz), 6.96 (1 H, d, $H_7$, $J_{6-7}$ = 15 Hz), 7.20 (1 H, dd, $Ar_5$, $J$ = 8, 2 Hz), 7.37 (1 H, d, $Ar_3$, $J$ = 2 Hz), 7.47 (1 H, d, $Ar_6$, $J$ = 8 Hz). Anal. Calcd for $C_{14}H_{16}Cl_2O_3$: C, 55.46; H, 5.32. Found: 55.67; H, 5.50.

**(*E*)-4β-(Benzyloxy)-6α-[2-(2,4-dichlorophenyl)ethenyl]-2β-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (16b).** 6α-[2-(2,4-Dichlorophenyl)ethenyl]-4β-hydroxy-2β-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (0.93 g, 3.07 mmol) was dissolved in dry THF

(10 mL) and the solution was cooled under $N_2$ to −78 °C. *n*-Butyllithium in hexane (1.05 M) (3.1 mL, 3.22 mmol) was added, followed by benzyl bromide (0.46 mL, 0.64 g, 3.68 mmol). DMF (3 mL) was added and the whole warmed to 50 °C in a stream of $N_2$ to blow off most of the THF. The reaction mixture was then heated at 50 °C for 2 h. After being cooled to room temperature, the mixture was partitioned between ether (100 mL) and water (50 mL). The ether was extracted with water (5 × 50 mL), dried ($MgSO_4$), and filtered and the solvent was evaporated in vacuo to leave the crude product as an oil. Flash chromatography (40 × 155 mm column), eluting with methylene chloride, gave 1.12 g of the desired product as a clear, colorless gum (92.6%): $R_f$ (silica gel, methylene chloride) 0.32; $^1$H NMR ($CDCl_3$) (360 MHz)[24] δ 1.69 (1 H, ddd, $H_{4a}$, $J_{gem}$ = 13.5 Hz, $J_{4a-5}$ = 12 Hz, $J_{4a-3}$ = 3 Hz), 1.83 (1 H, dt, $H_{2a}$, $J_{gem}$ = 15 Hz, $J_{2a-1}$ = $J_{2a-3}$ = 4.5 Hz), 1.93 (1 H, br d, $H_{4e}$, $J_{gem}$ = 13.5 Hz), 2.08 (1 H, br d, $H_{2e}$, $J_{gem}$ = 13.5 Hz), 3.44 (3 H, s, $OCH_3$), 3.82 (1 H, p, $H_3$, $J \simeq 4$ Hz), 4.54 (1 H, d, benzyl, $J_{gem}$ = 12 Hz), 4.68 (1 H, d, benzyl, $J_{gem}$ = 12 Hz), 4.82 (1 H, m, $H_5$), 4.84 (1 H, d, $H_1$, $J_{1-2a}$ = 4.5 Hz), 6.08 (1 H, dd, $H_6$, $J_{6-7}$ = 16 Hz, $J_{6-5}$ = 6 Hz), 6.94 (1 H, d, $H_7$, $J_{6-7}$ = 16 Hz), 7.16–7.48 (8 H, m, Ar). Anal. Calcd for $C_{21}H_{22}Cl_2O_3$: C, 64.13; H, 5.64. Found: C, 63.95; H, 5.70.

**(*E*)-4β-(Benzyloxy)-6α-[2-(2,4-dichlorophenyl)ethenyl]-2α-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (17b).** 6α-[2-(2,4-Dichlorophenyl)ethenyl]-4β-hydroxy-2α-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (3.0 g, 10 mmol) was carried through the same benzylation procedure as used for the corresponding 2β compound to give 3.5 g (89%) of the desired 2α product: $^1$H NMR ($CDCl_3$) (360 MHz)[24] δ 1.53–1.65 (2 H, m, $H_{2a}$ + $H_{4a}$), 1.97 (1 H, br d, $H_{4e}$, $J_{gem}$ = 14 Hz), 2.13 (1 H, br d, $H_{2e}$, $J_{gem}$ = 14 Hz), 3.54 (3 H, s, $OCH_3$), 4.00 (1 H, m, $H_3$), 4.52–4.67 (3 H, m, benzyl + $H_5$), 4.83 (1 H, d, $H_1$, $J_{1-2a}$ = 9 Hz), 6.23 (1 H, dd, $H_6$, $J_{6-7}$ = 16 Hz, $J_{6-5}$ = 6 Hz), 6.94 (1 H, d, $H_7$, $J_{6-7}$ = 16 Hz), 7.17–7.48 (8 H, m, Ar). Anal. Calcd for $C_{21}H_{22}Cl_2O_3$: C, 64.13; H, 5.64. Found: C, 64.14; H, 5.61.

**(*E*)-6α-[2-(2,4-Dichlorophenyl)ethenyl]-2α-ethoxy-4β-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran and (*E*)-6α-[2-(2,4-Dichlorophenyl)ethenyl]-2β-ethoxy-4β-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (18b).** To a solution of compound **16b** (0.041 g, 0.106 mmol) in EtOH (2.5 mL) was added 20% Pd-$(OH)_2$/C catalyst (0.012 g). The mixture was maintained at reflux under a $N_2$ atmosphere for 50 h, at which point TLC (silica gel, 5% acetone–$CH_2Cl_2$) indicated that reaction was nearly complete. Following filtration through Supercel and evaporation there was obtained 0.032 g of a crude oil. $^1$H NMR ($CDCl_3$) indicated that the product was a mixture of two ethoxy anomers with the α anomer predominating. Purification was carried out by preparative TLC (silica gel 2000 μm, 5% acetone–$MeCl_2$). Extraction of the band at $R_f$ 0.26 with EtOAc gave 0.010 g of α anomer, while extraction of the band at $R_f$ 0.56 afforded 0.004 g of β anomer.

α anomer: $^1$H NMR ($CDCl_3$) (360 MHz)[24] δ 1.25 (3 H, t, $OCH_2CH_3$, $J$ = 7 Hz), 1.65–1.75 (2 H, m, $H_{4a}$ + $H_{2a}$), 1.79 (1 H, br d, $H_{4e}$, $J_{gem}$ = 12 Hz), 1.94 (1 H, br d, $H_{2e}$, $J_{gem}$ = 12 Hz), 3.59 (1 H, dq, $OCHHCH_3$, $J_{gem}$ = 9 Hz, $J$ = 7 Hz), 4.01 (1 H, $OCHHCH_3$, $J_{gem}$ = 9 Hz, $J$ = 7 Hz), 4.41 (1 H, p, $H_3$, $J \approx 3$ Hz), 4.61 (1 H, m, $H_{5a}$), 4.91 (1 H, dd, $H_1$, $J_{1-2a}$ = 9 Hz, $J_{1-2e}$ = 2 Hz), 6.24 (1 H, dd, $H_6$, $J_{6-7}$ = 15 Hz, $J_{6-5}$ = 6 Hz), 6.95 (1 H, d, $H_7$, $J_{6-7}$ = 15 Hz), 7.20 (1 H, dd, $Ar_5$, $J$ = 8, 2 Hz), 7.37 (1 H, d, $Ar_3$, $J$ = 2 Hz), 7.47 (1 H, d, $Ar_6$, $J$ = 8 Hz); MS, $m/z$ 316 ($M^+$), 298, 263; exact mass $m/z$ calcd for $C_{15}H_{17}Cl_2O_3$ 316.0633, found 316.0592.

β anomer: $^1$H NMR ($CDCl_3$) (360 MHz)[24] δ 1.28 (3 H, t, $OCH_2CH_3$, $J$ = 7 Hz), 1.65–1.75 (1 H, m, $H_{4a}$), 1.90 (1 H, dt, $H_{2a}$, $J_{gem}$ = 13.5 Hz, $J_{2a-1}$ = $J_{2a-3}$ = 3 Hz), 1.97 (2 H, br d, $H_{2e}$ + $H_{4e}$, $J_{gem}$ = 13.5 Hz), 3.51 (1 H, dq, $OCHHCH_3$, $J$ = 7, 9 Hz), 3.85 (1 H, dq, $OCHHCH_3$, $J$ = 7, 9 Hz), 4.14 (1 H, m, $H_{3e}$), 4.75 (1 H, m, $H_{5a}$), 5.08 (1 H, d, $J_{1-2a}$ = 3 Hz), 6.21 (1 H, dd, $H_6$, $J_{6-5}$ = 6 Hz, $J_{6-7}$ = 15 Hz), 6.96 (1 H, d, $H_7$, $J_{7-6}$ = 15 Hz), 7.21 (1 H, dd, $Ar_5$, $J$ = 9, 2.5 Hz), 7.37 (1 H, d, $Ar_3$, $J$ = 2.5 Hz), 7.48 (1 H, d, $Ar_6$, $J$ = 9 Hz); MS, $m/z$ 316 ($M^+$), 298; exact mass calcd $m/z$ for $M^+ - H_2O$ 298.0527, found 298.0540.

**(*E*)-6α-[2-(2,4-Dichlorophenyl)ethenyl]-2,4β-dihydroxy-3,4,5,6-tetrahydro-2*H*-pyran (19b).** A mixture of 6α-[2-(2,4-dichlorophenyl)ethenyl]-4β-hydroxy-2α-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (0.010 g, 0.033 mmol), HOAc-$d_4$ (0.5 mL), and $D_2O$ (0.1 mL) was heated in an NMR tube at 90 °C for three periods of 10-min duration each. $^1$H NMR and TLC indicated that reaction was essentially complete after the third period of heating. The reaction mixture, after quenching in dilute NaOH solution, was extracted with $Et_2O$ and then EtOAc to yield 0.007 g of crude product. Preparative TLC (silica gel 2000 μm, 40% EtOAc–$CH_2Cl_2$) afforded 4 mg of product of $R_f$ 0.4. $^1$H NMR (360 MHz) showed the product to be a mixture of anomers and identical with the lactol product of the diisobutylaluminum hydride reduction of the racemic lactone **1b**. A similar experiment conducted with the α-ethoxy anomer but heated at 90 °C for 15 min gave similar results.

**(*E*)-6α-[2-(2,4-Dichlorophenyl)ethenyl]-4β-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (Racemic 1b).** A solution of the mixture of anomers **19b** (0.145 g, 0.5 mmol) in $CH_2Cl_2$ (5 mL) was added to a mixture of *N*-iodosuccinimide (0.57 g, 2.5 mmol) and tetra-*n*-butylammonium iodide (6.2 g, 0.5 mmol) in $CH_2Cl_2$ (10 mL). After being stirred at room temperature for 30 min, the reaction was complete as evidenced by TLC (20% acetone–$CH_2Cl_2$). The reaction mixture was treated with aqueous sodium thiosulfate and extracted with $CH_2Cl_2$. The $CH_2Cl_2$ solution was dried and concentrated to dryness in vacuo to give a viscous yellow oil. Purification by silica gel flash column chromatography (10% acetone/$CH_2Cl_2$) gave a white solid (0.1 g, 69% yield) which was identical with the known racemic lactone **1b**.[7]

**(4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)ethenyl]-2-ethoxy-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran (18a).** To a solution of **16a** (0.987 g, 2.14 mmol) in EtOH (50 mL) was added 20% $Pd(OH)_2$/C (Pearlman's catalyst,[26] 0.23 g). The mixture was heated at reflux under a nitrogen atmosphere for 100 h.[27] (An additional 80 mg of Pearlman's catalyst was added after 28 h.) Following filtration through Supercel and evaporation of solvent there was obtained 0.825 g of crude product as a mixture of *R* and *S* anomers. In a separate experiment utilizing 0.114 g of benzyl ether as starting material and a reaction time of 13 h, the crude mixture of anomers (0.097 g) was purified by preparative TLC (silica gel 2000 μm, 5% acetone–$CH_2Cl_2$) to give 0.033 g of oily *R* anomer, and (after a second preparative TLC purification) 0.016 g of oily *S* anomer.

*R* anomer: $^1$H NMR ($CDCl_3$) (360 MHz)[24] δ 1.02 (3 H, t, $OCH_2CH_3$, $J$ = 7 Hz), 1.17–1.45 (3 H, m, $H_{4a}$, $H_{4e}$, $H_{2a}$), 1.66 (1 H, br d, $H_{2e}$, $J$ = 13.5 Hz), 2.07 (3 H, d, $ArCH_3$, $J$ = 2 Hz), 2.12 (3 H, s, $ArCH_3$), 2.16 (3 H, s, $ArCH_3$), 3.54 (1 H, dq, $OCHHCH_3$, $J$ = 7, 9 Hz), 3.92 (1 H, dq, $OCHHCH_3$, $J$ = 7, 9 Hz), 4.30 (1 H, m, $H_{2e}$), 4.35 (1 H, m, $H_{5e}$), 4.85 (1 H, dd, $H_{1a}$, $J$ = 9, 3 Hz), 5.46 (1 H, dd, $H_6$, $J_{6-7}$ = 15.5 Hz, $J_{6-5}$ = 6 Hz), 6.42 (1 H, d, $H_7$, $J_{6-7}$ = 15.5 Hz), 6.92 (1 H, br s, ArH), 6.96 (1 H, d, ArH, $J$ = 9 Hz), 7.01 (1 H, br s, ArH), 7.05 (1 H, m, ArH), 7.10 (1 H, br d, ArH, $J$ = 7.5 Hz); MS, $m/z$ exact mass calcd for $C_{24}H_{29}FO_3$ 384.2101, found 384.2124.

*S* anomer: $^1$H NMR ($CDCl_3$) (360 MHz)[24] δ 1.22 (3 H, t, $OCH_2CH_3$, $J$ = 7 Hz), 1.46 (1 H, ddd, $H_{4a}$, $J$ = 3, 12, 12 Hz), 1.71 (1 H, br d, $H_{4e}$, $J$ = 12 Hz), 1.80 (1 H, dt, $H_{2a}$, $J$ = 14, 3 Hz), 1.91 (1 H, br d, $H_{2e}$, $J$ = 14 Hz), 2.28 (3 H, d, $ArCH_3$, $J$ = 2 Hz), 2.33 (3 H, s, $ArCH_3$), 2.37 (3 H, s, $ArCH_3$), 3.45 (1 H, dq, $OCHHCH_3$, $J$ = 7, 9 Hz), 3.72 (1 H, dq, $OCHHCH_3$, $J$ = 7, 9 Hz), 4.03 (1 H, m, $H_{3e}$), 4.49 (1 H, m, $H_{5a}$), 4.98 (1 H, d, $H_{1e}$, $J$ = 3 Hz), 5.44 (1 H, dd, $J_{6-7}$ = 16 Hz, $J_{6-5}$ = 6 Hz), 6.41 (1 H, d, $H_7$, $J_{6-7}$ = 16 Hz), 6.93 (1 H, br s, ArH), 6.96 (1 H, d, ArH, $J$ = 9 Hz), 7.06 (1 H, br s, ArH), 7.05 (1 H, m, ArH), 7.10 (1 H, br d, ArH, $J$ = 7.5 Hz); MS, $m/z$ 384 ($M^+$) 366, 338; exact mass calcd for $C_{24}H_{27}FO_2$ ($M^+ - H_2O$) 366.1995, found ($M^+ - H_2O$) 366.2061.

**(2*S*,4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)ethenyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran.** A mixture of **16a** (0.098 g, 0.212 mmol), 10% palladium on carbon (Engelhard Lot No. 28,597) and EtOH (6 mL) was heated at reflux for 51 h. Following filtration through Supercel and evaporation there was obtained 0.065 g of an oil which was purified by preparative TLC (silica gel 2000 μm, 4% acetone–$CH_2Cl_2$) to give 0.051 g of an oily product: $^1$H NMR ($CDCl_3$) (360 MHz)[24] δ 1.45 (1 H, ddd, $H_{4a}$, $J$ = 2.5, 11, 12 Hz), 1.70 (1 H, br d, $H_{4e}$, $J$ = 12 Hz), 1.81 (1 H, dt, $H_{2a}$, $J$ = 14, 3 Hz),

(25) Sprung, L.; Sprung, J. *J. Am. Chem. Soc.* **1943**, *65*, 1276.
(26) The Pearlman's catalyst was Benning No. 8443-19, Merck Sharp & Dohme Research Laboratories, Rahway, NJ.
(27) In other runs the time for complete disappearance of starting material as indicated by TLC varied from 13 h to several days.

1.91 (1 H, br d, $H_{2e}$, $J$ = 14 Hz), 2.27 (3 H, d, $ArCH_3$, $J$ = 2 Hz), 2.32 (3 H, s, $ArCH_3$), 2.37 (3 H, s, $ArCH_3$), 3.36 (3 H, s, $OCH_3$), 3.60 (1 H, d, OH, $J$ = 10 Hz), 4.04 (1 H, m, $H_{3e}$), 4.46 (1 H, m, $H_{5a}$), 4.86 (1 H, d, $H_1$, $J$ = 3 Hz), 5.45 (1 H, dd, $H_6$, $J_{6-7}$ = 16 Hz, $J_{6-5}$ = 6 Hz), 6.42 (1 H, d, $H_7$, $J_{6-7}$ = 16 Hz), 6.94 (1 H, br s, ArH), 6.97 (1 H, d, ArH, $J$ = 9 Hz), 7.01 (1 H, br s, ArH), 7.06 (1 H, m, ArH), 7.11 (1 H, br d, ArH); MS, $m/z$ 370 ($M^+$), 352, 338; exact mass calcd for $C_{23}H_{27}FO_3$ 370.1944, found 370.1964.

**(4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)ethenyl]-2,4-dihydroxy-3,4,5,6-tetrahydro-2*H*-pyran (19a).** To a solution of **18a** (0.826 g, 2.15 mmol) in glacial acetic acid (39 mL) was added water (12 mL). After standing at room temperature for 30 h, the mixture was poured into 800 mL of 1.56 N NaOH. Extraction with ether (1200 mL), followed by washing the ether extract with water and brine, drying ($MgSO_4$), and evaporation yielded 0.686 g of a glass. Flash chromatography on a 45-mm diameter column of 250–400-mesh silica gel, employing 4% acetone–$CH_2Cl_2$, gave 0.358 g of a mixture of $\alpha$ and $\beta$-hydroxy anomers. TLC (silica gel, 6% acetone–$MeCl_2$) exhibited an elongated spot, $R_f$ 0.2. In the $^1H$ NMR ($CDCl_3$) spectrum the anomeric proton of the major isomer (~3:1 ratio) appeared as a multiplet at $\delta$ 5.34; MS, $m/z$ 356 ($M^+$), 338, 320; exact mass $m/z$ calcd for $C_{22}H_{25}FO_3$ 356.1788, found 356.1653.

**(+)-(4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)ethenyl]-4-hydroxy-3,4,5,6-tetrahydro-2*H*-pyran-2-one (1a).** To a solution of *N*-iodosuccinimide (0.789 g, 3.5 mmol) in $CH_2Cl_2$ (85 mL) was added tetra-*n*-butylammonium iodide (0.260 g, 0.7 mmol). The mixture immediately became an iodine brown color. Compound **19a** (0.250 g, 0.7 mmol) in $CH_2Cl_2$ (15 mL) was added and the mixture was stirred for 2 h. At this point TLC (silica gel, 10% acetone–$CH_2Cl_2$) indicated that the starting material had disappeared. An excess of saturated sodium thiosulfate solution was added with stirring to decolorize the mixture. The mixture was extracted with $CH_2Cl_2$ and the $CH_2Cl_2$ extracts were washed well with water. After drying ($MgSO_4$), the $CH_2Cl_2$ solution was evaporated to dryness. The residue (0.53 g) was dissolved in ether and the ether was washed 3 times with water. After washing with saturated brine and drying ($MgSO_4$), the solvent was evaporated to give an oily residue (0.22 g). Purification was carried out by flash chromatography on a 30-mm column of 230–400-mesh silica gel, employing 7.5% acetone–$CH_2Cl_2$ as the developing solvent. There was obtained 0.141 g (56.7%) of fractions which by HPLC contained >95% of the desired lactone. An analytical sample crystallized from ether–hexane had mp 88–90 °C; $[\alpha]^{23}_D$ +39.9° (*c* 0.4, $CHCl_3$). A mixed melting point with resolved dextrorotatory lactone was undepressed. The IR, MS (low and high resolution), and 360-MHz $^1H$ NMR spectra were identical with those of the resolved dextrorotatory lactone.[7a] Anal. Calcd for $C_{22}H_{23}FO_3$: C, 74.56; H, 6.54. Found: C, 74.73; H, 6.75.

**1-(Benzyloxy)-9-decene (20).** To a suspension of 50% sodium hydride in mineral oil (0.24 g, 5 mmol) in dry DMF (5 mL) was added, by syringe, with stirring, 1-hydroxy-9-decene (0.781 g, 5 mmol) dissolved in dry DMF (5 mL). The mixture was warmed to 65–75 °C for 1 h and then cooled to room temperature. Benzyl bromide (0.59 mL, 0.86 g, 5 mmol) was added neat by syringe with stirring. After 30 min of stirring the reaction was worked up by partitioning between ether (200 mL) and water (100 mL). The ether layer was washed with water 3 times, dried ($MgSO_4$), and filtered, and the solvent was evaporated in vacuo to leave a crude product which was purified by flash chromatography on 50 × 150 mm column, eluting with 40% $CH_2Cl_2$ in hexane, to give 0.80 g (65%) of product: $^1H$ NMR ($CDCl_3$) (60 MHz) $\delta$ 1.2–2.2 (14 H, m, $CH_2$), 3.42 (2 H, t, $CH_2CH_2O$), 4.41 (2 H, s, benzyl), 4.80–5.15 (2 H, m, vinyl), 5.40–6.10 (1 H, m, vinyl), 7.25 (5 H, s, Ar). Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 83.06; H, 11.01.

**1-(Benzyloxy)-3-methoxypropane (21).** Sodium hydride (10.45 g of 50% in mineral oil, 0.218 mol) was separated from mineral oil by washing by decantation with hexane 3 times under $N_2$. Dry DMF (100 mL) was added followed by the slow addition of neat 3-methoxy-1-propanol[25] (17.84 g, 0.198 mol) with mechanical stirring. When evolution of hydrogen had stopped, the reaction was cooled in an ice bath and benzyl bromide (26.0 mL, 37.26 g, 0.218 mol) was added with vigorous mechanical stirring. The reaction was stirred at ambient temperature (cake broken up), followed by the addition of dry DMF (100 mL), and then stirred at room temperature overnight. The reaction was partitioned between ether and water (400 mL each). The water layer was separated and extracted with ether 2 times. The combined ether extracts were washed with water 5 times, dried ($MgSO_4$), and filtered and the solvent was evaporated in vacuo to give 33.65 g of crude product which was distilled; bp 95–95.5 °C at 1.5 mm; wt 18.12 g (51%) as a mobile oil; $^1H$ NMR ($CDCl_3$) (60 MHz) $\delta$ 1.86 (2 H, p, $J$ = 7 Hz, $CH_2CH_2CH_2$), 3.28 (3 H, s, $OCH_3$), 3.45 (2 H, t, $J$ = 7 Hz, $OCH_2$), 3.55 (2 H, t, $J$ = 7 Hz, $OCH_2$), 4.45 (2 H, s, benzyl), 7.27 (5 H, s, Ar); MS, $m/z$ exact mass calcd for $C_{11}H_{16}O_2$ 180.1150, found 180.1146.

**Benzyl Ether Cleavage of 1-(Benzyloxy)-3-methoxypropane (21).** To a solution of **21** (0.074 g, 0.41 mmol) in ethanol (1 mL) was added 0.041 g of $Pd(OH)_2/C$ (Pearlman's catalyst),[26] and the mixture was stirred and heated at reflux (bath temperature 90 °C) for 8 h. The cooled reaction mixture was filtered through a tight Celite and glass wool plug. The catalyst was washed with ethanol in sufficient amount so that the final volume of filtered solution of products was 2 mL. Half of this solution was used in the GC–MS study directly. The solvent was removed from the remaining 1-mL sample to leave 0.35 g of a mixture of products which had an odor of benzaldehyde. For each component of the mixture, the GC–MS field ionization mass and area percent are reported. High-resolution MS of $M^+$ or M – X and chemical ionization data for most of the components are given in the supplementary data. The $^1H$ NMR of the mixture is reported in standard format except for the relative intensities of the signals indicated in parentheses with the first signal at 1.25 arbitrarily taken as 6: $^1H$ NMR ($CDCl_3$) (360 MHz) (mixture) $\delta$ 1.25 (6 H, t, $J$ = 7 Hz, acetal $CH_3$ (6)), 1.40 (3 H, t, $J$ = 7 Hz, ester $CH_3$ (1)), 1.80 (2 H, p, $J$ = 6 Hz, acetal $CH_2CH_2CH_2$ (1.4)), 2.10 (2 H, p, $J$ = 6 Hz, ester $CH_2CH_2CH_2$ (0.6)), 3.30 (3 H, s, $OCH_3$ (0.5)), 3.35 (3 H, s, $OCH_3$ (2.5)), 3.45–3.70 (4 H, m, acetal $OCH_2$ (6.6)), 3.80 (2 H, t, $J$ = 6 Hz, $OCH_2$ (1)), 4.40 (2 H, q, $J$ = 7 Hz, ester $OCH_2CH_3$ (0.6)), 4.45 (2 H, t, $J$ = 7 Hz, ester $OCH_2CH_2$ (0.5)), 5.52 (1 H, s, acetal CH (1)), 7.20–7.70 (5 H, m, Ar (8.3)), 7.85 (2 H, d, $J$ = ~9 Hz, ortho H, benzaldehyde (0.4)), 8.10 (2 H, d, $J$ = ~9 Hz, ortho H, benzoate ester (1.1)), 10.4 (1 H, s, CHO (0.2)). FIMS compound, $M^+$ (area %): toluene, 92 (1.78); **22**, 90 (33.0); **23a**, 180 (33.7); **23b**, 106 (18.6); **23c**, 224 (1.1); **23d**, 150 (9.0); **23e**, 194 (2.8); **23f**, 268 (<0.2); **23g**, 122 (0.4).

**(2*R*- and 2*S*,4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl-[1,1′-biphenyl]-2-yl)ethyl]-2,4-dihydroxy-3,4,5,6-tetrahydro-2*H*-pyran (26a).** Using the method to prepare **26b**, chiral **1a**[10g] (1.77 g, 5 mmol) was converted to the mixture of lactols, **26a**, 1.26 g (71%); $^1H$ NMR ($CDCl_3$) (part) 2*S* isomer, $\delta$ 5.18 (1 H, dd, $H_{1a}$, $J$ = 3, 9 Hz); 2*R* isomer, $\delta$ 5.33 (1 H, d, $H_{1e}$, $J$ = 3 Hz), ratio of 2*R*:2*S* = 25:75.

**(2*S*,4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)ethenyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (27a) and (2*R*,4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)ethenyl]-4-hydroxy-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (28a).** Glacial acetic acid (10 mL) was added to a solution of **26a** (1.26 g, 3.54 mmol) in methanol (20 mL), and the solution was allowed to stand for 24 h. The reaction was then dissolved in ether (200 mL) and extracted with water 4 times and then a saturated solution of $NaHCO_3$, dried ($MgSO_4$), and filtered and the solvent was evaporated in vacuo to leave 1.20 g of clear gum which $^1H$ NMR indicated was a 50:50 mixture of the two methoxy anomers. Flash chromatography on a 50 × 150 mm silica gel column, eluting with 5% acetone in $CH_2Cl_2$, gave 0.57 g of the $\beta$ isomer (MeO axial) **27a**, $R_f$ 0.53 (5% acetone/$CH_2Cl_2$). This product was identical with the 10% Pd/C debenzylation product of **16a**. The second product to emerge from the column was 0.45 g of gum, the $\alpha$ isomer (MeO equatorial) **28a**, $R_f$ 0.31 (5% acetone/$CH_2Cl_2$): $^1H$ NMR ($CDCl_3$) (360 MHz) $\delta$ 1.37–1.63 (3 H, m, $H_{4a}$ + $H_{2a}$ + $H_{4e}$), 1.86 (1 H, br d, $H_{2e}$, $J$ = 13.2 Hz), 2.22 (3 H, d, $CH_3$, $J$ = 1.7 Hz), 2.33 (3 H, s, $CH_3$), 2.37 (3 H, s, $CH_3$), 3.48 (3 H, s, $OCH_3$), 4.29 (1 H, p, $H_3$, $J$ = 3 Hz), 4.36 (1 H, m, $H_5$), 4.75 (1 H, dd, H, $J$ = 2.2, 9.5 Hz), 5.46 (1 H, dd, $H_6$, $J$ = 6.1, 16.1 Hz), 6.43 (1 H, d, $H_7$, $J$ = 16.1 Hz), 6.92–7.26 (5 H, m, Ar); exact mass calcd for $C_{23}H_{27}FO_3$ 370.1944, found 370.1945.

**(2*S*,4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1′-biphenyl]-2-yl)ethenyl]-4-(benzyloxy)-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (16a).** Using the method substantially

the same as that for the preparation of **16b**, **27a** 0.57 g (1.54 mmol) was converted to **16a**, 0.53 g (75%); isolated by chromatography eluting with 1% acetone/$CH_2Cl_2$. This product was identical with the same product prepared from the synthon.

**(2*R*,4*R*,6*S*)-(*E*)-6-[2-(4′-Fluoro-3,3′,5-trimethyl[1,1-biphenyl]-2-yl)ethenyl]-4-(benzyloxy)-2-methoxy-3,4,5,6-tetrahydro-2*H*-pyran (17a).** Using the method substantially the same as that for the preparation of **16b**, 0.45 g (1.21 mmol) of **28a** was converted to **17a**, a clear gum, 0.44 g (80%), $R_f$ 0.41 (1% acetone/$CH_2Cl_2$): $[\alpha]^{24}_D$ −21.26 (*c* 0.6, $CHCl_3$); $^1H$ NMR ($CDCl_3$) (360 MHz) δ 1.33 (1 H, ddd, $H_{4a}$, *J* = 2.9, 11.2, 13.9 Hz), 1.51 (1 H, ddd, $H_{2a}$, *J* = 3.2, 9.8, 13.2 Hz), 1.69 (1 H, br d, $H_{4e}$, *J* = 13.4 Hz), 2.07 (1 H, br d, $H_{2e}$, *J* = 13.4 Hz), 2.28 (3 H, d, $CH_3$, *J* = 1.7 Hz), 2.33 (3 H, s, $CH_3$), 2.37 (3 H, s, $CH_3$), 3.48 (3 H, s, $OCH_3$), 3.91 (1 H, p, $H_3$, *J* = 3.2 Hz), 4.34 (1 H, m, $H_5$), 4.50 (1 H, d, benzyl, *J* = 12 Hz), 4.55 (1 H, d, benzyl, *J* = 12 Hz), 4.73 (1 H, dd, H, *J* = 3.2, 9.5 Hz), 5.46 (1 H, dd, $H_6$, *J* = 6.4, 16.4 Hz), 6.42 (1 H, d, $H_7$, *J* = 16.4 Hz), 6.93–7.40 (10 H, m, Ar); exact mass calcd for $C_{30}H_{33}FO_3$ 460.2402, found 460.2410. Anal. Calcd. for $C_{30}H_{33}FO_3$: C, 78.23; H, 7.22. Found: C, 78.39; H, 7.49.

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**Registry No.** **1a**, 85493-98-7; (±)-**1b**, 86097-37-2; **2**, 82300-44-5; **5**, 63592-79-0; **6**, 64951-98-0; **7**, 82300-39-8; **8**, 82300-40-1; **9**, 82300-41-2; **10**, 82300-42-3; **11**, 82300-43-4; **12**, 80617-38-5; **13**, 90691-40-0; **14** (isomer 1), 100295-44-1; **14** (isomer 2), 100295-45-2; **16a**, 90691-43-3; **16b**, 100189-68-2; **17a**, 100295-49-6; **17b**, 100295-46-3; α-**18a**, 90691-44-4; β-**18a**, 90761-94-7; α-**18b**, 100189-69-3; β-**18b**, 100295-47-4; α-**19a**, 90691-45-5; β-**19a**, 90761-26-5; α-**19b**, 93863-87-7; β-**19b**, 93922-60-2; **20**, 100189-71-7; **21**, 96516-91-5; **22**, 1589-49-7; **23a**, 774-48-1; **23b**, 100-52-7; **23c**, 100189-72-8; **23d**, 93-89-0; **23e**, 100189-73-9; **23f**, 100189-74-0; **23g**, 65-85-0; **27a**, 100189-70-6; **27b**, 93922-58-8; **28a**, 100295-48-5; **28b**, 93863-44-6; 4′-fluoro-2-(hydoroxymethyl)-3,3′,5-trimethyl-1,1′-biphenyl, 90691-37-5; 2-(chloromethyl)-4′-fluoro-3,3′,5-trimethyl-1,1′-biphenyl, 90691-38-6; (4′-fluoro-3,3′,5-trimethyl-[1,1′-biphenyl]-2-yl)methyl phenyl sulfide, 90691-39-7; 1-hydroxy-9-decene, 13019-22-2.

**Supplementary Material Available:** Detailed results of the GC/MS study of debenzylation products **23a–g** including high resolution, low resolution, chemical ionization, field ionization, capillary GC retention times, and percent area of each of the compounds (1 page). Ordering information is given on any current masthead page.

# Syntheses of Some Proposed Biosynthetic Precursors to the Isocyclic Ring in Chlorophyll *a*

Kevin M. Smith* and Dane A. Goff

*Department of Chemistry, University of California, Davis, California 95616*

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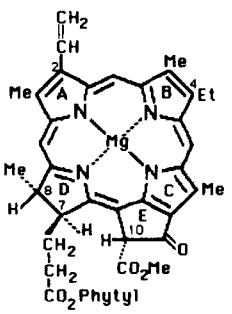
In connection with studies on the biosynthesis of the isocyclic ring E in chlorophyll *a* (**1**), the magnesium(II) 2,4-divinylporphyrin β-keto ester **8** and hydroxypropionate **6** have been synthesized. The key porphyrin intermediate **36** in these syntheses was obtained most efficiently by cyclization of a 1′-methyl-8′-unsubstituted a,c-biladiene dihydrobromide **31** in hot *o*-dichlorobenzene. An alternative route through copper(II)-promoted cyclization of a 1′,8′-dimethyl-a,c-biladiene hydrobromide, **29**, gave lower yields of porphyrin. The keto ester groups were added by way of the corresponding porphyrin imidazolides **20b** and **39** by using the magnesium(II) complex of methyl hydrogen malonate. Borohydride reduction of the magnesium(II) 2,4-divinylporphyrin β-keto ester **8** gave the corresponding hydroxypropionate porphyrin **6**, but attempts to dehydrate this to give the acrylate **12**, an intermediate also of possible biological significance, were unsuccessful.

The biosynthesis of isocyclic ring E of chlorophyll *a* (**1**) has long been a subject for speculation. In 1948 Granick proposed that the 6-propionic methyl ester side chain of a suitable porphyrin precursor can be oxidized to a β-keto ester as shown in Scheme I.[1] This β-keto ester then undergoes cyclization to form the cyclopentanone ring. In 1968 Ellsworth and Aronoff isolated the magnesium complexes of monovinyl (**2**) and divinyl (**3**) protoporphyrin IX monomethyl esters, mesoporphyrin IX monomethyl ester (**4**), monovinyl (**5**) and divinyl (**6**) 6-β-hydroxypropionate monomethyl esters, monovinyl (**7**) and divinyl (**8**) 6-β-keto methyl esters, and monovinyl (**9**) and divinyl (**10**) pheoporphyrin $a_5$ monomethyl esters from a mutant of the green algae *Chlorella* in which the synthesis of chlorophyll *a* was blocked.[2,3] The corresponding magnesium monovinyl (**11**) and divinyl (**12**) 6-acrylate monomethyl esters were not isolated, but their presence was inferred from mass spectrometry and oxidative degradation.




**1**

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