# Transformations of Hydroxy Cyclic Sulfates: Stereospecific Conversion into 2,3,5-Trisubstituted Tetrahydrofurans

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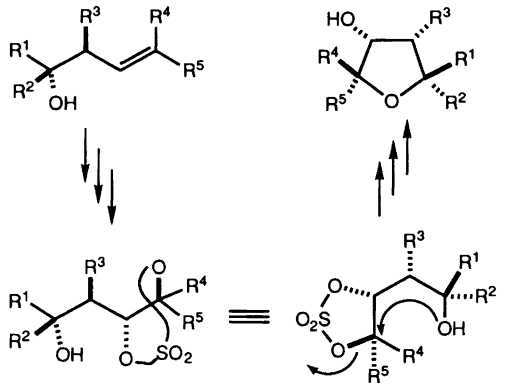
Kalantar, T. H. and Sharpless, K. B., 1993. Transformations of Hydroxy Cyclic Sulfates: Stereospecific Conversion into 2,3,5-Trisubstituted Tetrahydrofurans. – Acta Chem. Scand. 47: 307–313.

1,2-Cyclic sulfates have been prepared from *O*-protected ricinoleate and ricinelaidate esters. Upon deprotection of the 12-hydroxy moiety, the resulting 12-hydroxy-9,10-cyclic sulfates underwent stereospecific cyclization to the corresponding 2,3,5-trisubstituted tetrahydrofurans. The cyclization occurs by backside attack of the hydroxy oxygen on the distal carbon of the 1,2-cyclic sulfate, with inversion at that center.

Dedicated to Professor Salo Gronowitz on the occasion of his 65th birthday.

Substituted tetrahydrofurans are found in a wide variety of natural products, and their stereoselective preparation is therefore of intense interest.[1] Although bis-homoallylic alcohols often serve as synthetic precursors to tetrahydrofurans and tetrahydropyrans,[1] relatively few preparative methods based on the activation and subsequent cyclization of readily available substituted homoallylic alcohols to substituted tetrahydrofurans have been developed,[2] largely due to the expected unfavorable energetics of 5-*endo* ring closures.[3] Such closures appear to be quite facile, however, with the proper choice of olefin activating group.[2]

Recent work focusing on the Lewis-acid catalyzed closure of the epoxides derived from homoallylic alcohols[2e] indicates that while the epoxides derived from *trans*-substituted olefins will close with excellent stereoselectivity in high yield, those derived from the analogous *cis*-olefins close in only poor yield, and exhibit stereoselectivity resulting from initial solvent opening of the epoxide, followed by displacement of the solvent by the pendant hydroxy group, to give closure with net retention.

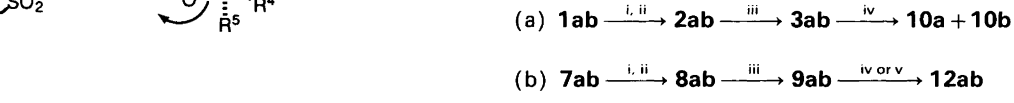


*Scheme 1.*

Inspired by the above problems, and as part of our ongoing efforts to develop the chemistry and demonstrate the utility of the highly reactive cyclic sulfate moiety, so analogous to the epoxide,[4] we sought to attempt the closure of hydroxy cyclic sulfates, derived from suitably protected homoallylic alcohols, to tetrahydrofurans (Scheme 1).

## Results and discussion

We chose as our homoallylic alcohol substrates esters of (+)-ricinelaidic and (+)-ricinoleic acids.[2e] Starting with ethyl (+)-ricinoleate, the two diastereomeric 12-*O*-benzyl ether 9,10-diols **1a** and **1b** (mixture), Fig. 1, Scheme 2, were prepared by benzylation of the 12-hydroxy moiety followed by $OsO_4$-catalyzed dihydroxylation of the olefin.[5] The corresponding mixture of cyclic sulfates was readily prepared[4] (90%); it is noteworthy that the benzyl ether moiety is quite stable, during this short reaction time, to the $RuO_4$ produced *in situ*.[6] The hydroxy group at C-12 was easily unmasked by hydrogenolysis.[7] The resulting oil, **3ab**, cyclized on standing for four days to yield a separable mixture of *only* tetrahydrofurans **10a** and **10b** (together, 82%), exhibiting inversion at C-9 and formed in the same isomer ratio as the mixture of the parent diols **1a** and **1b**. These tetrahydrofurans and their derived acetates exhibit expected $^1H$ and $^{13}C$ NMR spectra and optical rotations.[2a,c]



*Scheme 2.* (i) $SOCl_2$; (ii) catalytic $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $CCl_4$–$CH_3CN$–$H_2O$; (iii) $H_2$, Pd–C; (iv) neat, three days, then 20% aq. $H_2SO_4$–ether; (v) $NaOCH_2CH_3$–ethanol.

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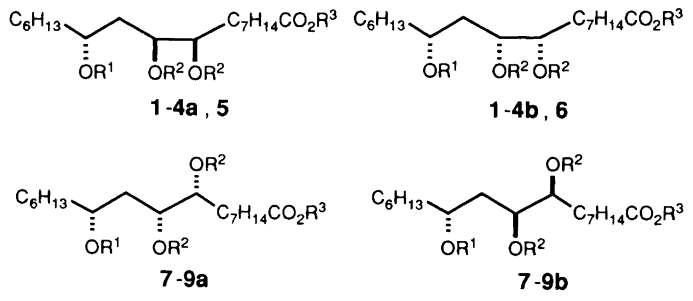



**1a ,b**; **7a ,b**: $R^1$ = Bn; $R^2$ = H; $R^3$ = $CH_2CH_3$
**2a ,b**; **8a ,b**: $R^1$ = Bn; $R^2$ = cyclic -$SO_2$-; $R^3$ = $CH_2CH_3$
**3a ,b**; **9a ,b**: $R^1$ = H; $R^2$ = cyclic -$SO_2$-; $R^3$ = $CH_2CH_3$
**4a ,b**: $R^1$ = Ac; $R^2$ = H; $R^3$ = $CH_3$
**5a ,b**: $R^1$ = Ac; $R^2$ = cyclic -$SO_2$-; $R^3$ = $CH_3$
**6**: $R^1$ = $R^2$ = H; $R^3$ = $CH_3$

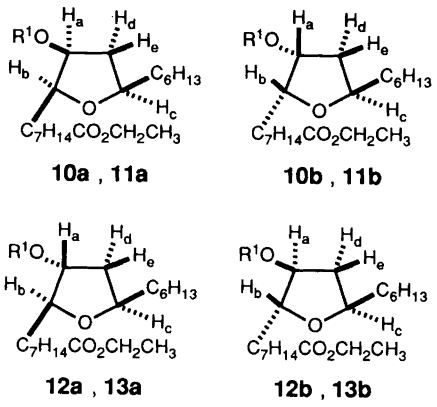
*Fig. 1.* The diols and cyclic sulfates derived from the ricinoleate and ricinelaidate esters.

The analogous acetate diols **4a** and **4b** were prepared by dihydroxylation of acetate-protected methyl (+)-ricinoleate and determined by comparison with authentic materials and spectra[2] to have the stereochemistry shown.[8] The cyclic sulfate of **4a**, **5a**,[9] was treated with base (anhydrous $NaOC_2H_5$–ethanol) to yield only the tetrahydrofuran **10a** (64%, Scheme 3), the product of backside attack of the 12-hydroxy group at C-9, with inversion at C-9. It can thus be concluded by a process of elimination that tetrahydrofuran isomer **10b** is derived only from the diol **1b**.

(a) **4a** $\xrightarrow{\text{i or ii}}$ **5a** $\xrightarrow{\text{iv}}$ **10a**

(b) **4b** $\xrightarrow{\text{v}}$ **6**

*Scheme 3.* (i) $SOCl_2$; (ii) $SOCl_2$, triethylamine in diethyl ether (iii) catalytic $RuCl_3 \cdot 3H_2O$, $NaIO_4$, $CCl_4$–$CH_3CN$–$H_2O$; (iv) $NaOCH_2CH_3$–ethanol; (v) 5% $H_2SO_4$–methanol.

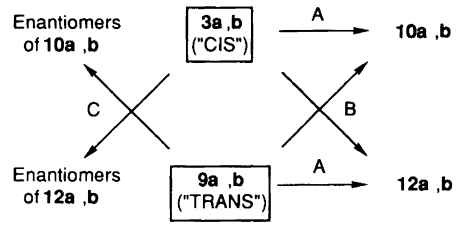



**10a** , **10b** , **12a** , **12b**: $R^1$ = H
**11a** , **11b** , **13a** , **13b**: $R^1$ = Ac

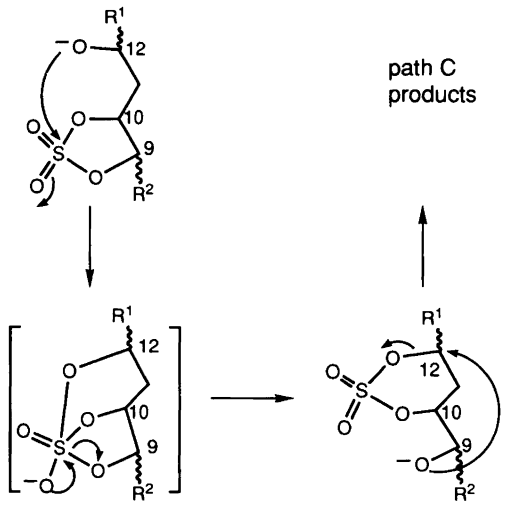
*Fig. 2.* The diastereomeric 2,3,5-trisubstituted tetrahydrofurans.

Similar results were obtained with the cyclic sulfate mixture **8ab** (Scheme 2) derived from ethyl (+)-ricinelaidate. After hydrogenolysis of the benzyl ether, the discrete, and surprisingly stable[10] hydroxy cyclic sulfate intermediate was cyclized, either neat (70% yield) or by treatment with anhydrous ethoxide (80% yield, in greater purity than from neat cyclization, above) to only tetrahydrofurans **12a** and **12b** (inseparable mixture); **12a** and **12b** were formed, again, in the same ratio as that of their parent diols, **7a** and **7b**.

The clear stereochemical outcome of this series of closures leads directly to an understanding of the mechanism of the closure of hydroxy cyclic sulfates derived from both the *cis*-(ricinoleate) and *trans*-(ricinelaidate) olefins to tetrahydrofurans. Ionization[11] of the cyclic sulfate at C-9, followed by trapping of an intermediate carbocation by the C-12 hydroxy group would result in the formation of all four diastereomeric tetrahydrofurans from each pair of diol cyclic sulfates (paths A *and* B, Scheme 4). Solvent-assisted opening with initial inversion at C-9 followed by solvent displacement with inversion by the 12-hydroxy group would result in net retention at C-9, and the formation of path B products only. Intramolecular isomerization to a less strained 1,3-cyclic sulfate[12] (Scheme 5) followed by closure would result in path C products. Only backside attack of the 12-hydroxy group on C-9 (path A) will lead to the observed products. Thus, **10a** and **10b** (**12a** and **12b**) are derived from cyclic sulfates **3a** and **3b** (**9a** and **9b**), respectively.




*Scheme 4.*




*Scheme 5.*

It is clear from an examination of molecular models of the hydroxy cyclic sulfate closure that the attacking oxygen, carbon and leaving oxygen can be essentially collinear, allowing this 5-*endo* cyclization to proceed smoothly. An examination of these models and those for the *cis* and *trans* epoxide closures shows that the closures of the cyclic sulfates should be more facile than closures of the epoxides. A model of the *cis* epoxide closure suggests that collinearity requires such severe distortion of the ground state structure that backside attack should be severely restricted, and, in fact, such closure is not observed in this system.[2c]

The nucleophilic attack of a benzyl ether oxygen on electrophilic carbon has been extensively exploited to prepare substituted tetrahydrofurans.[13] As well, in the presence of $Ti(OiPr)_4$, epoxides will undergo nucleophilic attack by benzyl ether oxygens.[14] The highly reactive cyclic sulfate is not, however, opened by a benzyl ether oxygen. The benzyl ether cyclic sulfates studied here are stable, both neat and in solution (they are shown by NMR spectroscopy to be stable over a period of more than two weeks). $^1H$ NMR and IR spectroscopy show that the cyclic sulfate moiety is not displaced with closure to the tetrahydrofuran until *after* deprotection of the C-12 oxygen. Surprisingly, the hydroxy cyclic sulfate intermediate is sufficiently stable to allow isolation and characterization.[7]

## Conclusion

Hydroxy cyclic sulfates, easily prepared from readily available homoallylic alcohols, can be stereospecifically converted, via backside attack of the hydroxy oxygen on the distal carbon bearing the cyclic sulfate leaving group, into substituted tetrahydrofurans in good yield. A wider range of substitution patterns than that examined here should be accessible.[2f] In addition, enantiopure cyclic sulfates available from enantiopure diols prepared by asymmetric dihydroxylation[15] of suitably protected homoallylic alcohols will allow stereospecific access to a wide range of enantiomerically pure substituted tetrahydrofurans.

## Experimental

NMR spectra were obtained for $CDCl_3$ solutions at concentrations of 3 to 50 mg $ml^{-1}$, at either 250, 270 (Bruker), or 300 (Varian Gemini) MHz. Infrared spectra were obtained as solutions, films, or KBr pellets on a Perkin-Elmer FT-IR spectrometer. High resolution electron impact and low resolution chemical ionization mass spectra were obtained at the Mass Spectrometry Laboratory, University of Alberta. Elemental Analyses were performed by Robertson Laboratories, Madison, NJ. Thin layer chromatography (TLC) was performed on Merck precoated glass plates (Silica Gel 60, F-254, 0.25 mm thick). The plates were developed with phosphomolybdic acid. Preparative chromatography[16] was performed using Silica Gel 60, 230–400 mesh. Gradient elution was preferred. Medium-pressure liquid chromatography was performed using a Lobar prepacked LiChroPrep Si 60 column. Air- and water-sensitive reactions were conducted under an atmosphere of argon in oven- (140°C) or flame-dried flasks. Diethyl ether was dried by distillation from sodium–benzophenone ketyl; ethanol and methanol were dried by distillation from $Mg/I_2$; $CH_2Cl_2$ was dried over activated 3 Å molecular sieves[17] or by being refluxed over $CaH_2$; $CCl_4$, $CH_3CN$ and *N,N*-dimethylformamide were dried over activated 3 Å sieves for 24 to 48 h.

*(9S*,10R*,12R)-Ethyl 9,10-dihydroxy-12-benzyloxyoctadecanoate*, **1ab**. NaH (144 mg, 4.8 mmol, 80% w/w in oil, washed with pentane) was suspended in DMF (40 ml) at 0°C. (+)-Ethyl ricinoleate was added (1.500 g, 4.6 mmol). After the mixture had been stirred for 15 min, benzyl bromide (0.546 ml, 4.6 mmol) was added over 5 min. The reaction mixture was stirred overnight then quenched with $H_2O$ (100 ml) and ethyl acetate (150 ml) and stirred vigorously for 5 min. The organic phase was washed with $H_2O$ (3 × 75 ml) and the aqueous layers were backwashed with ethyl acetate (40 ml); the combined organics were washed with $H_2O$ (10 ml), dried ($MgSO_4$), and evaporated to yield a colorless oil (1.916 g, 100%). $^1H$ NMR: δ 7.32 (m, 5 H), 4.56 (d, *AB*, $J_{AB}$ = 10.1 Hz, 1 H), 4.47 (d, *AB*, $J_{AB}$ = 10.1 Hz, 1 H), 4.10 (2 q, $J$ = 7.6 Hz, 4 H), 2.26 (2 t, $J$ = 7.5 Hz, 4 H), 1.60 (m), 1.29 (m, 32 H), 1.23 (2 t, $J$ = 7.2 Hz, 6 H), 0.86 (2 t, $J$ = 6.1 Hz, 6 H).

The benzyl ether (1.91 g, 4.6 mmol) from above was directly dihydroxylated with $OsO_4$ (57.1 mg, 0.22 mmol), and *N*-methylmorpholine *N*-oxide (1.10 g, 9.4 mmol) in 4:1 $CH_3CN$–$H_2O$ (25 ml) at room temperature for 18 h, quenched and worked up (see the preparation of **4a**, **4b** below) to yield the crude diol (2.208 g) which was chromatographed (ether–hexane) to yield solid **1ab** (634 mg, 31% over two steps) as a 1:1.2 mixture (based

on the integration of the benzylic proton signals in the $^1H$ NMR spectrum) of diastereomers. $^1H$ NMR: δ 7.3 (2 m, 10 H), 4.64 (d, A*B*, $J_{AB}$ = 11.1 Hz, 1 H), 4.41 (d, *A*B, $J$ = 11.1 Hz, 1 H), 4.55 (d, A*B'*, $J_{AB'}$ = 11.4 Hz, 1 H), 4.51 (d, *A*B', $J_{AB'}$ = 11.4 Hz, 1 H), 4.10 (2 q, $J$ = 7.1 Hz, 4 H), 3.99 (s, 1 H), 3.85, 3.83 (m, 1 H), 3.67–3.75 (m, 3 H), 3.52–3.60 (m, 2 H), 3.26 (d, $J$ = 3.0 Hz, 1 H), 2.25 (2 t, $J$ = 7.6 Hz, 4 H + 1 H overlapping), 2.07 (d, $J$ = 3.7 Hz, 1 H), 1.84 (ddd, $J$ = 3.4, 10.7, 14.5 Hz, 1 H), 1.75–1.45 (m, 15 H), 1.40–1.25 (m, 32 H), 1.23 (2 t, $J$ = 7.5 Hz, 6 H), 0.86 (2 t, $J \sim 3.4$ Hz, 6 H); $^{13}C$ NMR: δ 174.1, 138.3, 138.8, 128.8, 128.7, 128.1, 127.9, 80.2, 74.8, 74.6, 74.4, 71.4, 70.7, 60.0, 34.8, 34.3, 33.5, 33.3, 33.1, 31.9, 31.6, 29.3, 29.2, 29.0, 25.8, 25.4, 24.8, 24.4, 22.4, 14.0, 13.7; IR (neat): 3436, 2933, 2861, 1733, 1467, 1456, 1374, 1349, 1303, 1251, 1185, 1092, 1067, 733, 697 $cm^{-1}$; MS (CI): *m/z* 451 ($MH^+$), 468 ($MNH_4^+$); HRMS (EI): *m/z* calculated for $[M - C_2H_5O - H_2O]^+$ 387.2899, found 387.2885.

*(9S*, 10R*, 12R)-Ethyl 12-benzyloxyoctadecanoate 9,10-cyclic sulfate*, **2ab**. **1ab** (0.625 g, 1.39 mmol) was dissolved in $CCl_4$ (4 ml). $SOCl_2$ (150 μl, 2.1 mmol) was then added by syringe. The reaction mixture was stirred for 1.5 h at room temperature then heated gently until the starting material had been consumed, then cooled to 0°C, and $CH_3CN$ (4 ml), $RuCl_3 \cdot 3H_2O$ (4.0 mg, 0.015 mmol), $NaIO_4$ (0.600 g, 2.80 mmol) and $H_2O$ (6 ml) were added to the flask. The reaction mixture was stirred vigorously for 15 min at 0°C then worked up (see the preparation of **5a** below) to yield a pale yellow oil, **2ab** (0.639 g, 90%), a 1:1 mixture of two diastereomers (by $^1H$ NMR). $^1H$ NMR: δ 7.3 (m, 10 H), 5.15 (ddd, ABM*X*, $J_{MX}$ = 5.3 Hz, $J$ = 3.2, 10.5 Hz, 1 H), 5.04 (apparent ddd, ABM*X'*, $J_{MX'}$ = 5.2 Hz, $J$ = 8.6, 3.5 Hz, 1 H), 4.87 (ddd, AB*M*X, $J_{MX}$ = 5.3 Hz, $J$ = 2.9, 10.4 Hz, 1 H), 4.67 (ddd, AB*M*X', $J_{MX'}$ = 5.2 Hz, $J$ = 3.1, 10.8 Hz, 1 H), 4.61 (d, A*B*, $J_{AB}$ = 11.1 Hz, 1 H), 4.37 (d, *A*B, $J_{AB}$ = 11.1 Hz, 1 H), 4.54 (d, *A*B', $J_{AB'}$ = 11.8 Hz, 1 H), 4.41 (d, A*B'*, $J_{AB'}$ = 11.8 Hz, 1 H), 4.10 (2 q, $J$ = 7.1 Hz, 4 H), 3.64 (ddt, ABN*Y*, $J_{NY} \sim 6.9$ Hz, $J_{AY}$ = 4.5 Hz, $J_{BY}$ = 2.6 Hz, 1 H), 3.50 (apparent quintet, $J \sim 5.9$ Hz, 1 H), 2.26 (2 t, $J$ = 7.5 Hz, 4 H), 2.16 (ddd, *AB*MX', $J_{AB'}$ = 14.4 Hz, $J_{AX'}$ = 5.2 Hz, $J$ = 8.7 Hz, 1 H), 2.02 (ddd, *AB*MX, $J_{AB}$ = 16.8 Hz, $J$ = 10.7, 2.4 Hz, 1 H), 1.8 (m, 4 H), 1.6 (m, 12 H), 1.3 (m, 30 H), 1.23 (2 t, $J$ = 7.1 Hz, 6 H), 0.85 (2 t, $J \sim 4.7$ Hz, 6 H); $^{13}C$ NMR: δ 174.1, 128.7, 128.2, 86.6, 86.5, 83.7, 83.0, 74.9, 74.7, 71.9, 71.1, 60.1, 34.1, 33.6, 33.5, 33.1, 32.1, 31.6, 29.3, 29.1, 28.8, 28.6, 28.4, 28.1, 25.1, 24.9, 24.7, 24.4, 22.4, 14.1, 13.8; IR (neat) 2928, 2964, 1732, 1460, 1380, 1209, 1092, 1070, 1028, 969, 962, 830, 739, 697 $cm^{-1}$; HRMS (EI): *m/z* calculated for $[M - H_2SO_4 - C_7H_7]^+$ 323.2586, found 323.2578.

*Cyclization to (9S, 10S, 12R)-ethyl 10-hydroxy-9,12-epoxyoctadecanoate*, **10a**, *and (9R, 10R, 12R)-ethyl 10-hydroxy-9,12-epoxyoctadecanoate*, **10b**. **2ab** (0.620 g, 1.2 mmol), *tert*-butyl alcohol (2 ml) and 10% Pd–C (0.5 g) were taken up in ethyl acetate (100 ml). The mixture was hydrogenated at 50 psi (Parr shaker) for 2 h, then filtered, and evaporated to yield a colorless oil (0.452 g, 89%). After four days *in vacuo*, it was hydrolyzed in ether (50 ml) and 20% aqueous $H_2SO_4$ (5 ml) and stirred for 8 h. The organic layer was washed with saturated aqueous $NaHCO_3$ (25 ml), and concentrated to yield a pale reddish oil (331 mg, 82%) containing two diastereomeric tetrahydrofurans. The isomers were separated by chromatography (ether–hexane). The less polar isomer, **10a**, 118 mg, was obtained pure; the more polar isomer, **10b**, 109 mg, was obtained as a 5:1 mixture of the more and less polar components, respectively.[2c]

**10a**: $^1H$ NMR: δ 4.13 (m, $H_a$, 1 H), 4.09 (q, $J$ = 7.3 Hz, 2 H), 3.72 (apparent quintet, $H_c$, $J \sim 6.5$ Hz, 1 H), 3.47 (apparent dt, $H_b$, $J \sim 3.5$, 6.7 Hz, 1 H), 2.35 (ddd, A*M*X, $H_d$, $J$ = 6.9, 7.2, 13.9 Hz, 1 H), 2.26 (t, $J$ = 7.4 Hz, 2 H), 1.48 (ddd, *A*MX, $H_e$, $J$ = 1.7, 6.7, 13.9 Hz, 1 H), 1.23 (t, $J$ = 7.3 Hz, 3 H), 1.6 and 1.7 (m, 22 H), 0.88 (t, $J$ = 6.8 Hz, 3 H); $^{13}C$ NMR: δ 174.1, 83.1, 77.6, 72.9, 60.0, 41.8, 36.6, 43.2, 31.6, 29.4, 29.1, 28.9, 28.5, 26.0, 25.9, 24.7, 22.3, 14.0, 13.7; IR (neat): 3448, 2926, 2862, 1737, 1465, 1457, 1375, 1186, 1090, 1038 $cm^{-1}$; $[\alpha]_D^{23} = +16.3°$ ($c$ = 0.49, $CCl_4$); HRMS (EI): *m/z* calculated for $[M - H_2O]^+$ 324.2664, found 324.2667.

**10b**: $^1H$ NMR: δ 4.13 (m, $H_a$, $H_c$, 2 H), 4.08 (q, $J$ = 7.3 Hz, 2 H), 3.72 (apparent dt, $H_b$, $J \sim 2.9$, 6.9 Hz, 1 H), 2.24 (t, $J$ = 7.5 Hz, 2 H), 2.04 (apparent dd, $H_d$, $J \sim 6.7$ Hz, $J_{de}$ = 13.6 Hz, 1 H), 1.66 (ddd, $H_e$, $J$ = 8.9, 9.1 Hz, $J_{de}$ = 13.6 Hz, 1 H), 1.55 (m, 6 H), 1.3 (m, 16 H), 1.21 (t, $J$ = 7.3 Hz, 3 H), 0.84 (t, $J$ = 6.8 Hz, 3 H); $^{13}C$ NMR: δ 174.4, 82.0, 77.2, 76.6, 73.7, 60.3, 42.0, 36.5, 34.5, 31.9, 29.7, 29.4, 29.2, 26.4, 26.3, 26.1, 25.1, 22.7, 14.3, 14.0; IR (neat): 3437, 2929, 2855, 1734, 1467, 1459, 1374, 1181, 1107, 1083, 1033 $cm^{-1}$; $[\alpha]_D^{23} = -4.3°$ ($c$ = 0.47, $CCl_4$; after correction for the presence of 17 mol% **10a**: $[\alpha]_D^{23} = -9.4°$); HRMS (EI): *m/z* calculated for $[M - H_2O]^+$ 324.2664, found 324.2663.

*(9S, 10S, 12R)-Ethyl 10-acetoxy-9,2-epoxyoctadecanoate*, **11a**, *and (9R, 10R, 12R)-ethyl 10-acetoxy-9,12-epoxyoctadecanoate*, **11b**. 10 mg of each of **10a** and **10b** were dissolved in 2:1 pyridine–acetic anhydride (2 ml) and stirred for 24 h before being evaporated to yield the respective tetrahydrofuranyl acetates, **11a** and **11b**.[2c]

**11a**: $^1H$ NMR: δ 5.18 (m, $H_a$, 1 H), 4.10 (q, $J$ = 7.1 Hz, 2 H), 3.74 (apparent quintet, $H_c$, $J \sim 6.9$ Hz, 1 H), 3.60 (ddd, $H_b$, $J$ = 4.2, 5.2, 7.7 Hz, 1 H), 2.43 (apparent quintet, $H_d$, $J \sim 7.2$ Hz, 1 H), 2.26 (t, $J$ = 7.4 Hz, 2 H), 2.04 (s, 3 H), 1.6 (m, 6 H), 1.49 (ddd, $H_e$, $J$ = 2.1, 7.3, 14.2 Hz, 1 H), 1.3 (m, 16 H), 1.23 (t, $J$ = 7.1 Hz, 3 H), 0.86 (t, $J$ = 6.6 Hz, 3 H); HRMS (EI): *m/z* calculated for $[M - C_2H_5O]^+$ 339.2535, found 339.2535.

**11b**: $^1H$ NMR: δ 5.26 (m, $H_a$, 1 H), 4.09 (quartet overlapping a multiplet, $J$ = 7.1 Hz, 3 H, 3 H), 3.80 (ddd, $H_b$, $J$ = 3.3, 5.5, 7.3 Hz, 1 H), 2.25 (t, $J$ = 7.5 Hz, 2 H), 2.05 (s, 3 H), 2.06 (apparent dd, overlapped by acetate methyl, $H_d$, 1 H), 1.78 (ddd, $H_e$, $J \sim 4.9$, 9.1, 13.9 Hz,

1 H), 1.6 (m, 6 H), 1.3 (m, 16 H), 1.26 (t, $J = 7.1$ Hz, 3 H), 0.86 (t, $J = 6.6$ Hz, 3 H); HRMS (EI): *m/z* calculated for $[M - C_2H_5O]^+$ 339.2535, found 339.2535.

*(12R)-Ethyl 12-benzyloxyricinelaidate.* NaH (192 mg, 6.4 mmol, 80% in oil, washed with pentane) and (+)-ethyl ricinelaidate (2.00 g, 6.1 mmol) were combined in DMF (50 ml) at 0°C. After the mixture had been stirred for 15 min, benzyl bromide (0.73 ml, 6.1 mmol) was added and the mixture was stirred and warmed to room temperature over 12 h. $H_2O$ (100 ml) was added to quench and the mixture was washed with hexane (3 × 50 ml). The organic phase was washed with $H_2O$ (3 × 20 ml), dried ($MgSO_4$), filtered and concentrated to yield a colorless oil (2.25 g, 88%). The material was sufficiently pure to use directly in the next reaction. $^1$H NMR: δ 7.3 (m, 5 H), 5.42 (m, 2 H), 4.53 (d, A*B*, $J_{AB}$ = 11.6 Hz, 1 H), 4.46 (d, *A*B, $J_{AB}$ = 11.6 Hz, 1 H), 4.10 (q, $J = 7.1$ Hz, 2 H), 3.36 (apparent quintet, $J \sim 4.4$ Hz, 1 H), 2.26 (t, $J = 7.6$ Hz, 2 H), 2.23 (m, 2 H), 1.97 (m, 2 H), 1.5 (m, 4 H), 1.3 (m, 16 H), 1.23 (t, $J = 7.0$ Hz, 3 H), 0.85 (t, $J = 6.4$ Hz, 3 H); IR (neat): 2932, 2857, 1738, 1465, 1462, 1374, 1246, 1182, 1097, 1072, 1027, 968, 734, 699 cm$^{-1}$; HRMS (EI): *m/z* calculated for $C_{27}H_{44}O_3$ 416.3290, found 416.3298.

*(9R*, 10R*, 12R)-Ethyl 9,10-dihydroxy-12-benzyloxyoctadecanoate*, **7ab**. The benzyl ether (2.08 g, 5.0 mmol) from above, *N*-methylmorpholine *N*-oxide (0.732 g, 6.3 mmol), and $OsO_4$ (48.9 mg, 0.19 mmol) were taken up in 75 ml acetone–water (55/10, v/v) and stirred for 18 h then quenched and worked up (see the preparation of **4a**, **4b** below) to yield a crude oil (2.23 g, 99%) which was chromatographed (ether–hexane) to yield a 1:1.1 ratio (based on integration of the benzylic proton signals in the $^1$H NMR spectrum) of the two diastereomers (1.053 g, 47%).[9b] $^1$H NMR: δ 7.3 (m, 10 H), 4.63 (d, A*B*, $J_{AB}$ = 11.1 Hz, 1 H), 4.56 (d, A*B'*, $J_{AB'}$ = 11.4 Hz, 1 H), 4.48 (d, *A*B', $J_{AB'}$ = 11.4 Hz, 1 H), 4.09 (2 q, $J = 7.2$ Hz, 4 H), 3.84 (d, $J = 1.7$ Hz, 1 H), 3.70 (m, 3 H), 3.61 (m, 1 H), 3.32 (m, 2 H), 3.10 (d, $J = 4.1$ Hz, 1 H), 2.31 (d, $J \sim 1.5$ Hz, 1 H), 2.29 (d, $J = 2.8$ Hz, 1 H), 2.25 (2 t, $J = 7.5$ Hz, 4 H), 1.77 (m, 4 H), 1.6 (m, 8 H), 1.45 (m, 4 H), 1.28 (m, 32 H), 1.22 (2 t, $J = 7.1$ Hz, 6 H), 0.86 (2 t, $J = 5.8$ Hz, 6 H); $^{13}$C NMR: δ 174.2, 138.4, 138.1, 128.8, 128.7, 128.1, 128.0, 79.9, 74.6, 74.5, 74.1, 71.3, 71.2, 70.5, 60.1, 37.2, 36.1, 34.2, 33.4, 33.3, 33.2, 31.6, 29.3, 29.0, 28.9, 25.5, 25.4, 25.2, 24.7, 24.3, 22.4, 14.0, 13.8; IR (neat): 3436, 2926, 2861, 1736, 1454, 1373, 1302, 1248, 1183, 1096, 1063, 738, 700 cm$^{-1}$; MS (CI): *m/z* 451 ($MH^+$), 468 ($MNH_4^+$); HRMS (EI): *m/z* calculated for $[M - C_2H_5O - H_2O - C_6H_5CH_2OH]^+$ 279.2323, found 279.2430.

*(9R*, 10R*, 12R)-Ethyl 12-benzyloxyoctadecanoate 9,10-cyclic sulfate*, **8ab**. **7ab** (0.500 g, 1.1 mmol) was dissolved in $CCl_4$ (5 ml). $SOCl_2$ (170 μl, 2.3 mmol) was added and the reaction mixture was stirred at room temperature for two hours, then refluxed for 5 min and cooled to 0°C. $CH_3CN$ (5 ml), $RuCl_3 \cdot 3H_2O$ (4.1 mg, 0.016 mmol), $NaIO_4$ (599 mg, 2.80 mmol) and $H_2O$ (8 ml) were then added, and the mixture was stirred and allowed to warm until the intermediate cyclic sulfite had been consumed. The reaction was worked up (see the preparation of **5a** below) to yield a pale yellow oil (0.560 g, 99%), a 1:1 mixture of diastereomers (by integration of cyclic sulfate α-protons). $^1$H NMR: δ 7.3 (m, 10 H), 4.78 (ddd, ABX*X'*, $J = 2.5$, 8.2, 10.4 Hz, 1 H), 4.67 (m, 2 H), 4.61 (d, A*B*, $J_{AB}$ = 11.2 Hz, 1 H), 4.52 (m, 3 H, including 1 benzylic proton), 4.40 (d, *A*B, $J_{AB}$ = 11.2 Hz, 1 H), 4.10 (2 q, $J = 7.0$ Hz, 4 H), 3.61 (m,2 H), 2.25 (2 t, $J = 7.5$ Hz, 4 H), 2.04 (m, 1 H), 1.95 (m, 2 H), 1.75 (ddd, *AB*MX, $J = 2.6$, 10.3 Hz, $J_{AB}$ = 12.9 Hz, 1 H), 1.60 (m, 12 H), 1.26 (m, 32 H), 1.23 (2 t, $J = 7.0$ Hz, 6 H), 0.86 (2 t, $J = 6.9$ Hz, 6 H); $^{13}$C NMR: δ 174.1, 138.3, 128.8, 128.1, 128.0, 87.8, 87.4, 84.7, 80.7, 77.2, 75.0, 74.7, 71.8, 71.0, 60.2, 37.4, 35.3, 34.1, 33.6, 33.1, 31.6, 31.4, 31.3, 29.2, 29.1, 28.7, 28.6, 24.9, 24.6, 24.3, 14.0, 13.8; IR (neat): 2933, 2858, 1739, 1733, 1462, 1387, 1210, 1094, 1073, 1028, 933, 827, 738, 699, 646 cm$^{-1}$; MS (CI): *m/z* 513 ($MH^+$), 530 ($MNH_4^+$); HRMS (EI): *m/z* calculated for $[M - H_2SO_4]^+$ 414.3134, found 414.3139.

*(9R*, 10R*, 12R)-Ethyl 12-hydroxyoctadecanoate 9,10-cyclic sulfate*, **9ab**. **8ab** from above (0.512 g, 1.0 mmol), *tert*-butyl alcohol (5 ml), and 10% Pd–C (0.5 g) were taken up in ethyl acetate (100 ml) and hydrogenated (50 psi, Parr shaker) for 3 h then filtered, dried ($Na_2SO_4$), and concentrated to a chromatographically pure pale yellow oil, **9ab** (401 mg, 95%). $^1$H NMR: δ 4.88 (ddd, ABM*X*, $J = 2.7$, 8.4, 10.8 Hz, 1 H), 4.79 (m, 1 H), 4.57 (apparent dt, AB*M*X, $J = 4.0$, 8.4 Hz, 1 H), 4.11 (2 q, $J = 7.1$ Hz, 4 H), 4.10 (m, 1 H), 3.84 (m, 2 H), 2.26 (2 t, $J = 7.0$ Hz, 6 H), 1.95 (m, 2 H), 1.74 (m, 2 H), 1.59 (m, 6 H), 1.46 (m, 6 H), 1.30 (m, 32 H), 1.23 (2 t, $J = 7.1$ Hz, 6 H), 0.86 (2 t, $J = 6.6$ Hz, 6 H); IR (neat): 3432, 2932, 2857, 1726, 1454, 1384, 1210, 1109, 1098, 1034, 933, 827, 725, 646 cm$^{-1}$.

*Closure to (9R*, 10S*, 12R)-ethyl 12-hydroxy-9,12-epoxyoctadecanoate*, **12ab**. (a) **9ab** was kept under vacuum for four days and was then hydrolyzed in ether (50 ml) and 20% aq. $H_2SO_4$ (5 ml) for 24 h. The organic phase was then washed with saturated aqueous $NaHCO_3$ (20 ml), $H_2O$ (20 ml), dried ($MgSO_4$), filtered, and evaporated to yield a pale yellow oil (262 mg, 81%) which was chromatographed (ether–hexane) to yield 168 mg of a mixture of the two diastereomeric tetrahydrofurans[2c] and an unidentified impurity.

(b) Alternatively, NaH (20 mg, 0.67 mmol, 80% in oil) was weighed into a cooled (0°C) flask. **9ab** (220 mg, 0.52 mmol) was dissolved in ethanol (10 ml), cooled to 0°C, added slowly to the NaH and the resultant mixture was allowed to stir overnight and warm to room temperature. The solvent was then removed and the residue hydrolyzed (10 ml ether–5 ml 20% aqueous $H_2SO_4$). After 10 h, the ether layer was removed, the aqueous layer

was washed with ether and the combined organic layers were neutralized ($K_2CO_3$), dried ($Na_2SO_4$), filtered and evaporated to yield a chromatographically pure colorless oil (122 mg, 70%), a 1:1 mixture of the expected diastereomers.[2c] $^1$H NMR: δ 4.10 (2 q, $J$ = 7.1 Hz, 4 H), 4.00, 3.94 (m, 6 H), 3.72 (m, 2 H), 3.63 (m, 1 H), 2.40 (m, 1 H), 2.26 (2 t, $J$ = 7.5 Hz, 4 H), 1.86 (ddd, *AB*MX, $J_{AB}$ = 13.2 Hz, $J$ = 2.1, 5.6 Hz, 1 H), 1.61 (m, 6 H), 1.45 (m, 6 H), 1.29 (m, 32 H), 1.26 (2 t, $J$ = 7.1 Hz, 6 H), 0.85 (2 t, $J$ = 6.6 Hz, 6 H); $^{13}$C NMR: δ 174.3, 86.7, 84.7, 78.5, 78.0, 60.1, 41.1, 40.7, 38.9, 36.5, 35.7, 34.2, 32.8, 32.5, 31.6, 29.2, 29.1, 28.8, 25.8, 25.6, 24.7, 22.4, 14.0, 13.8; IR (neat): 3442, 2932, 2857, 1737, 1466, 1375, 1248, 1179, 1099, 1035, 859, 726 cm$^{-1}$; HRMS (EI): *m/z* calculated for $[M-H_2O]^+$ 324.2664, found 324.2666.

*(9*R**, 10*S**, 12*R*)-Ethyl 10-acetoxy-9,12-epoxyoctadecanoate*, **13ab**. **12ab** (10 mg) was dissolved in 2:1 pyridine–acetic anhydride (2 ml) for 4 h. Volatiles were removed and the residue was dissolved in 10% ethyl acetate–hexane, filtered and evaporated to yield the inseparable tetrahydrofuranyl acetates.[2c] $^1$H NMR: δ 4.89 (apparent quintet, $H_{a,a'}$, $J \sim 3.5$ Hz, 2 H), 4.10 (2 q, $J$ = 7.1 Hz, 4 H), 3.90 (m, $H_{b,b',c,c'}$ with signal at δ 3.76, 3 H), 3.76 (apparent dt, $J \sim 2.8$, 6.2 Hz, 1 H), 2.38 (apparent dt, $H_{d'}$, $J$ = 7.2, 13.9 Hz, 1 H), 2.26 (2 t, $J$ = 7.5 Hz, 4 H), 2.03 (2 s, 6 H), 1.91 (ddd, $H_d$, A*B*MX, $J_{AB}$ = 13.5 Hz, $J$ = 1.2, 5.2 Hz, 1 H), 1.70 (ddd, $H_e$, *A*BMX, $J_{AB}$ = 13.7 Hz, $J$ = 6.4, 8.7 Hz, 1 H), 1.60 (m including $H_{e'}$, 6 H), 1.4 (m, 7 H), 1.29 (m, 32 H), 1.23 (2 t, $J$ = 7.1 Hz, 6 H), 0.86 (2 t, $J$ = 6.5 Hz, 6 H); HRMS (EI): *m/z* calculated for $[M-C_2H_5O]^+$ 339.2535, found 339.2539.

*(9*R**, 10*S**, 12*R*)-Methyl 9,10-dihydroxy-12-acetoxyoctadecanoate*, **4a** *and* **4b**. (+)-Methyl 12-*O*-acetylricinoleate[18] (1.180 g, 3.3 mmol), *N*-methylmorpholine *N*-oxide (0.787 g, 6.73 mmol) and $OsO_4$ (60 μl, 0.56 M in toluene, 0.034 mmol) were stirred in 9:1 acetone–water (10 ml) for 24 h, then quenched with $Na_2S_2O_5$, filtered, diluted with ether (100 ml), washed with 1 M HCl (2 × 75 ml), saturated aqueous $NaHCO_3$ (50 ml), and brine (50 ml), filtered and dried ($Na_2SO_4$) to yield a mixture of the diastereomeric acetate diols as a colorless oil (1.191 g, 91%). The diastereomers were separated by MPLC (40% ethyl acetate–hexane); the less polar fraction contained 0.647 g of a white solid, **4a** and the more polar fraction contained 0.378 g of **4b**, a 5:1 mixture of the more polar and less polar materials, respectively.

(9*R*, 10*S*, 12*R*)-Methyl 9,10-dihydroxy-12-acetoxyoctadecanoate, **4a**: $^1$H NMR: δ 5.05 (m, 1 H), 3.66 (s, 3 H), 3.65 (m, 1 H), 3.44 (m, 1 H), 3.29 (m, 1 H), 2.30 (t, $J$ = 7.5 Hz, 2 H), 2.10 (s, 3 H), 1.60 (m, 6 H); 1.29 (m, 16 H), 0.86 (t, $J$ = 6.6 Hz, 3 H); $^{13}$C NMR: δ 174.6, 172.9, 74.2, 71.9, 69.9, 51.3, 36.0, 34.8, 33.8, 31.6, 31.5, 29.2, 28.8, 25.7, 25.2, 24.6, 22.3, 20.9, 13.7; IR (neat): 3416, 2925, 2853, 1733, 1471, 1372, 1250, 1158, 1101, 1066, 1027 cm$^{-1}$; $[\alpha]_D^{23} = -11.5°$ ($c$ = 0.13, 95% ethanol); MS (CI): $m/z$ 389 ($MH^+$), 406 ($MNH_4^+$), HRMS (EI): $m/z$ calculated for $[M-CH_3O]^+$ 357.2641; found, 357.2626.

(9*S*, 10*R*, 12*R*)-Methyl 9,10-dihydroxy-12-acetoxyoctadecanoate, **4b**: $^1$H NMR: δ 4.97 (apparent quintet, $J \sim 6.6$ Hz, 1 H), 3.67 (s, 3 H), 3.62 (m, 1 H), 3.61 (m, 1 H), 2.31 (t, $J$ = 7.5 Hz, 2 H), 2.10 (s, from residual **4a**), 2.06 (s, 3 H, ratio of integrals **4b**/**4a** = 5), 1.74 (t, $J$ = 6.4 Hz, 2 H), 1.61 (m, 6 H), 1.42 (m, ~2 H), 1.29 (m, 16 H), 0.86 (t, $J$ = 6.6 Hz, 3 H); $^{13}$C NMR: δ 174.7, 171.7, 74.5, 73.4, 72.5, 72.4, 51.3, 35.9, 34.2, 33.9, 31.5, 29.2, 28.9, 28.8, 25.6, 25.0, 24.6, 22.3, 21.1, 13.8; IR (neat): 3602, 3464, 2929, 2856, 1730, 1462, 1438, 1422, 1268, 1195, 1171, 1025 cm$^{-1}$; $[\alpha]_D^{23} = +7.2°$ ($c$ = 0.46, 95% ethanol; after correction for the presence of 17 mol% **4a**: $[\alpha]_D^{23} = +11.0°$C); MS (CI): 389 ($MH^+$), 406 ($MNH_4^+$); HRMS (EI): $m/z$ calculated for $[M-OH]^+$ 371.2797, found 371.2802.

*Confirmation of the stereochemistry of* **4a** *and* **4b**: *(9*S*, 10*R*, 12*R*)-Methyl 9,10,12-trihydroxyoctadecanoate*, **6**. **4b** (125 mg, 0.36 mmol) was refluxed for 3 h in dry methanol (10 ml) with conc. $H_2SO_4$ (0.05 ml) then cooled, diluted with ethyl acetate (100 ml) and washed with $H_2O$ (3 × 50 ml), and saturated aqueous $NaHCO_3$ (20 ml), dried ($Na_2SO_4$) and evaporated to yield white crystals (94 mg, 95%), identical by $^{13}$C NMR with an authentic[2c] sample of **6**. $^{13}$C NMR: δ 174.7, 75.3, 74.3, 72.4, 51.3, 38.1, 36.1, 33.8, 31.6, 29.2, 29.1, 28.9, 28.8, 25.7, 25.1, 24.6, 22.3, 13.7.

*(9*R*, 10*S*, 12*R*)-Methyl 9,10-dihydroxy-12-acetoxyoctadecanoate 9,10-cyclic sulfate*, **5a**. **4a** (0.606 g, 1.56 mmol) was dissolved in dry $CCl_4$ (6 ml) and $SOCl_2$ (0.200 ml, 2.74 mmol) was added. The reaction mixture was stirred (room temperature, 1 h), cooled to 0°C and $CH_3CN$ (6 ml), $RuCl_3 \cdot 3H_2O$ (4.1 mg, 0.0156 mmol), $NaIO_4$ (600 mg, 2.80 mmol) and $H_2O$ (9 ml) were added. The mixture was stirred at 0°C for 10 min, warmed to room temperature until the intermediate sulfite had been consumed, diluted with ether (100 ml), washed with $H_2O$ (2 × 50 ml), saturated aqueous $NaHCO_3$ (50 ml), filtered, dried ($MgSO_4$), and evaporated to yield pale yellow oil (0.777 g), which was chromatographed (ether–hexane) to yield a colorless viscous oil (294 mg, 42%[9]), **5a**. $^1$H NMR: δ 4.96, 4.91 (m, 3 H), 3.65 (s, 3 H), 2.28 (t, $J$ = 7.4 Hz, 2 H), 2.13 (ddd, *A*BX, $J$ = 3.3, 10.7 Hz, $J_{AB}$ = 14.8 Hz, 1 H), 2.03 (s, 3 H), 1.76 (ddd, A*B*X′, $J$ = 2.4, 9.1 Hz, $J_{AB'}$ = 14.7 Hz, 1 H), 1.6 (m, 6 H), 1.3, 1.25 (m, 14 H), 0.86 (t, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR: δ 174.6, 85.7, 82.7, 70.4, 51.4, 34.4, 33.8, 32.8, 31.5, 28.7, 28.4, 28.1, 25.1, 24.7, 24.5, 22.3, 22.2, 20.1, 17.5, 13.8; IR (neat): 2929, 2851, 1734, 1465, 1439, 1382, 1242, 1206, 1175, 1118, 1029, 973, 937, 864, 844, 818 cm$^{-1}$; $[\alpha]_D^{23} = -14.3°$ ($c$ = 0.91, 95% ethanol); MS (CI): 451 ($MH^+$), 468 ($MNH_4^+$); HRMS (EI): $m/z$ calculated $[M-CH_3O]^+$ 419.2103, found 419.2093.

*Cyclization to (9S, 10S, 12R)-ethyl 10-hydroxy-9,12-epoxyoctadecanoate*, **10a**. Dry ethanol (10 ml) was added via syringe to NaH (10 mg, 0.32 mmol, 80% in oil) and cooled to 0°C. **5a** (149 mg, 0.33 mmol) was added via syringe and the pale yellow solution was stirred for 24 h while being warmed to room temperature. The solvent was removed *in vacuo*, without exposure to moisture. Ether (7 ml) and 20% aqueous $H_2SO_4$ (2 ml) were added and the mixture was stirred for 12 h. The organic phase was removed, neutralized over solid $K_2CO_3$, dried ($MgSO_4$), and concentrated to yield an oil (122 mg, 97%) which was chromatographed (ether–hexane) to yield the desired tetrahydrofuran, **10a** (79.1 mg, 64%), as above.

*Alternative preparation of (9R*, 10S*, 12R)-methyl 9,10-dihydroxy-12-acetoxyoctadecanoate 9,10-cyclic sulfate*, **5b**. A 1.4:1 mixture of **4a**:**4b** (209 mg, 0.538 mmol, prepared by dihydroxylation of (12*R*)-methyl 12-acetoxyricinoleate, as above) and triethylamine (160 µl, 1.15 mmol) were dissolved in dry ether (10 ml), and cooled to 0°C. $SOCl_2$ (40 µl, 0.548 mmol) was added over 5 min. The intermediate cyclic 9,10-sulfite was isolated by diluting the reaction mixture with 30 ml ether, washing with $H_2O$ (2 × 10 ml), drying ($MgSO_4$), filtering, and evaporating. The resulting colorless oil was taken up in $CCl_4$–$CH_3CN$–$H_2O$ (5:5:7 ml) and $NaIO_4$ (249 mg, 1.16 mmol), and $RuCl_3 \cdot 3H_2O$ (4.4 mg, 0.017 mmol) were added. The mixture was stirred for 5 min at 0°C and worked up in the usual manner to give a 1.5:1 mixture of the desired cyclic sulfates **5ab** as a pale yellow oil (196 mg, 81%). $^1$H NMR: δ 5.05–4.90 (3 complex multiplets, 6 H), 3.68 (s, 6 H), 2.31 (t, $J$ = 7.5 Hz, 4 H), 2.15 (m, 1 H), 2.10 (s, 3 H), 2.07 (s, 3 H, ratio 2.10:2.07 = 1.5:1), 2.00–1.85 (m, 3 H), 1.60 (m, 12 H), 1.33 (m, 16 H), 1.29 (m, 16 H), 0.89 (t, $J$ = 6.5 Hz, 6 H).

*Acknowledgments.* We thank the National Institutes of Health (GM-28384) for financial support. We are extremely grateful to Dr. E. D. Mihelich (Eli Lilly Co.) for providing authentic samples and spectra in advance of publication. T. H. K. acknowledges the support of NSERC (Canada) and the Alberta Heritage Scholarship Fund.

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Received April 16, 1992.