Efficient and Highly Stereoselective Syntheses of Enantiomerically Enriched C(1)–C(7) Subunits of Erythronolides

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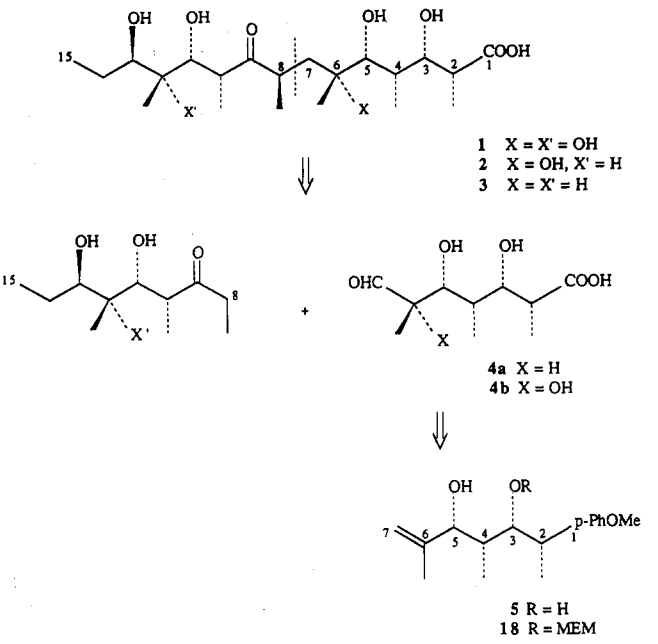
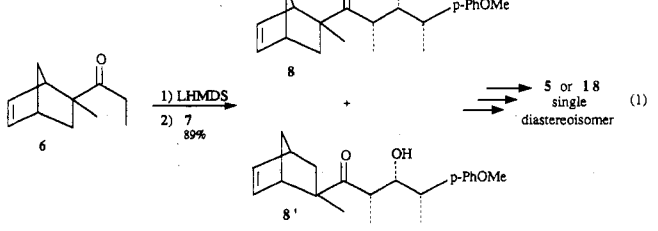
Stereocontrolled efficient syntheses of the C(1)–C(7) fragments of deoxyerythronolide and erythronolide seco acids are described. The key step of these syntheses involves a highly stereoselective aldol condensation between an enantiomerically enriched 2-arylpropanal and the lithium enolate of the racemic 2-methyl-5-norbornenyl ethyl ketone, which establishes in one operation the relative and absolute configurations of the three stereocenters C(2), C(3), and C(4). After syn-selective reductions of the carbonyl group, the configuration required at carbon C(6) was introduced by highly selective reactions carried out on the double bond regenerated by a thermal cycloreversion.

The erythromycins A and B, well-known members of the family of macrolide antibiotics, have been attractive synthetic targets because of their challenging complex molecular architecture. Several elegant approaches to their aglycon derivatives erythronolide A, erythronolide B, and 6-deoxyerythronolide B have been already reported[1,2] as well as interesting syntheses of a variety of fragments of their carbocyclic backbones.[3] Despite these numerous achievements, there remains the challenge of finding more methods to build the 10 asymmetric centers of the polyhydroxylated frameworks of these natural products in a stereoselective manner.

As a part of our research objectives directed at the control by a thermolabile group in stereoselective reactions, we have recently reported that a high degree of diastereoselectivity is achieved in the aldol condensations of the lithium enolate of *endo*-2-methylbicyclo[2.2.1]hept-5-enyl ethyl ketone **6** with a number of aldehydes.[4] Furthermore, we have also shown that a very high aldehyde diastereofacial selectivity was observed when enantiomerically enriched α-methyl aldehydes were used.[5] In this paper, we report efficient and highly stereoselective syntheses of the C(1)–C(7) sections of the seco-acids **1** (or **2**) and **3** of erythronolides A (or B) and deoxyerythronolide B (Scheme I). The key step of both syntheses involves the aldol condensation between the ketone **6** and enantiomerically enriched 2-(*p*-methoxyphenyl)propanal **7** which establishes in one operation (ds = 94%) the relative and absolute configurations of the three stereocenters C(2), C(3), and C(4). Subsequent manipulations including a retro Diels–Alder reaction lead in a few steps to potentially interesting polyfunctional synthons such as **5** or **18** which have been transformed to protected derivatives of fragments **4a** and **4b**. It must be noted that, due to poor enolate diastereofacial selectivity in the aldol condensation, a 1:1 mixture of two major diastereoisomers **8** and **8'** is obtained (eq 1).

Scheme I





Consequently all the bicyclic [2.2.1] compounds described here are mixtures of two diastereoisomers. However retrocycloadditions of these mixtures give rise to a single

(1) For a review covering efforts directed at macrolide syntheses through mid-1984 see: Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569.

(2) For recent efforts in the syntheses of erythronolides see: (a) Mulzer, J.; Mareski, P. A.; Buschmann, J.; Luger, P. *Synthesis* **1992**, 215 and references cited therein. (b) Sviridov, A. F.; Borodkin, V. S.; Ermolenko, M. S.; Yashunsky, D. V.; Kochetkov, N. K. *Tetrahedron* **1991**, *47*, 2291 and 2317.

(3) (a) Paterson, I.; Channon, J. A. *Tetrahedron Lett.* **1992**, *33*, 797. (b) Schlessinger, R. H.; Mjalli, A. M. M.; Adams, A. D.; Springer, J. P.; Hoogsteen, K. *J. Org. Chem.* **1992**, *57*, 2992. (c) Burke, S. D.; Lee, K. C.; Santafianos, D. *Tetrahedron Lett.* **1991**, *32*, 3957. (d) Totah, N. I.; Schreiber, S. L. *J. Org. Chem.* **1991**, *56*, 6255. (e) Born, M.; Tamm, C. *Synthesis* **1991**, 435. (f) Kim, Y. G.; Whang, K.; Cooke, R. J.; Cha, J. K. *Tetrahedron Lett.* **1990**, *31*, 3275. (g) Paterson, I.; Laffan, D. D. P.; Rawson, D. J. *Tetrahedron Lett.* **1988**, *29*, 1461. (h) Hoagland, S.; Morita, Y.; Bai, D. L.; Märki, H. P.; Kees, K.; Brown, L.; Heathcock, C. H. *J. Org. Chem.* **1988**, *53*, 4730. (i) Mulzer, J.; Autenrieth-Ansorge, L.; Kirstein, H.; Matsuoka, T.; Münch, W. *J. Org. Chem.* **1987**, *52*, 3784. (j) Burke, S. D.; Schoenen, F. J.; Nair, M. S. *Tetrahedron Lett.* **1987**, *28*, 4143 and references cited therein.

(4) (a) Bloch, R.; Gilbert, L. *Tetrahedron Lett.* **1986**, *27*, 3511. (b) Bloch, R.; Gilbert, L. *Tetrahedron* **1988**, *44*, 2523.

(5) Ahmar, M.; Bloch, R.; Mandville, G.; Romain, I. *Tetrahedron Lett.* **1992**, *33*, 2501.

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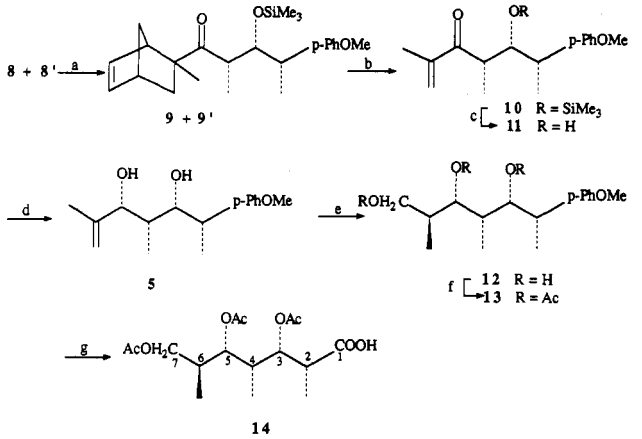
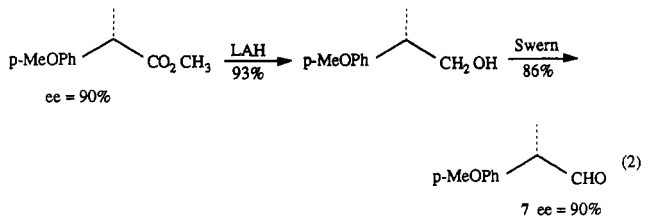
Scheme II[a]



[a] Reagents and conditions: (a) $SiMe_3Cl$, NEt_3, ether (95%); (b) 500 °C (90%); (c) HCl (1 N), THF (91%); (d) $NaBH_4$, Et_3B, THF/MeOH (4/1) (79%); (e) 9-BBN, THF then H_2O_2, NaOH (68%); (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (85%); (g) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$ (2/2/3) (73%).

enantiomer. For clarity, only one diastereoisomer of the bicyclic compounds will be represented in the synthetic schemes.

Synthesis of the C(1)–C(7) Fragment of Deoxyerythronolide B. (*S*)-2-(*p*-Methoxyphenyl)propanal (7) (ee = 90%) is prepared in two steps (eq 2) from the corresponding methyl propionate (ee = 90%) obtained by kinetic enzymatic resolution of the racemic ester catalyzed by horse liver esterase.[6]



The enantiomeric purity of the aldehyde 7 has been determined, after LAH reduction to the corresponding alcohol, by ^1H NMR in the presence of the chiral shift reagent Eu(hfc)$_3$. No racemization is observed in the Swern oxydation provided that a hindered base such as diisopropylethylamine is used.[7] Aldol condensation of the lithium enolate of ketone 6 with aldehyde 7 gives, after elimination of traces (~3%) of other stereoisomers by flash chromatography, 89% of a 1:1 mixture of all syn diastereoisomers 8 + 8′. In order to avoid a retro aldol reaction, the hydroxy group is protected as a trimethylsilyl ether, and then the double bond is regenerated by flash thermolysis (500 °C, contact time ~50 ms) to afford, after cleavage of the (trimethylsilyl)oxy group, the polyfunctionalized aldol 11 as a pure stereoisomer (77% for the three steps) (Scheme II).

The syn,syn diol 5 is prepared from 11 (80% ds) by $NaBH_4$ reduction of the diethylboron chelate using Narasaka methodology.[8] Hydroboration of the terminal double bond of the major diastereoisomer 5, purified by silica gel chromatography, is then achieved in the anti sense using 9-BBN.[9] In these conditions the required syn,syn,anti triol 12 is formed as a single diastereoisomer (ds > 98%) as shown by ^1H NMR of the crude product. Finally, the C(1)–C(7) fragment 14 of deoxyerythronolide B is obtained by $NaIO_4/RuCl_3$ oxidation of the aromatic ring after protection of the three hydroxy group as acetates.[10]

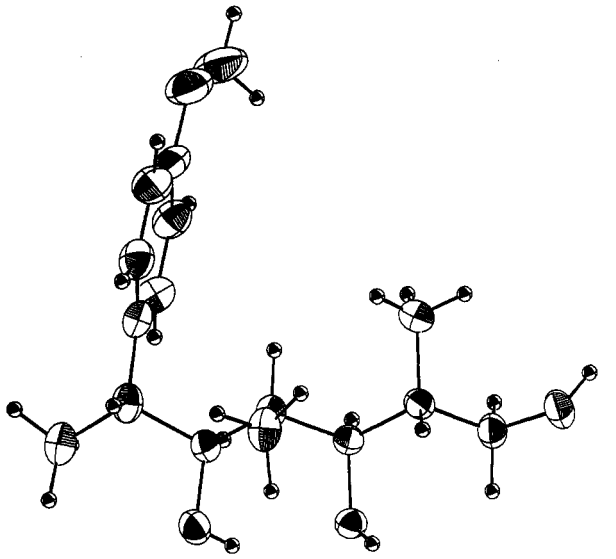
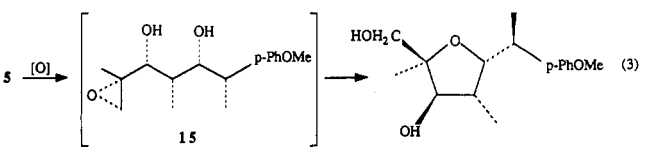


Figure 1. ORTEP representation of the racemic triol 12.

The relative configuration of the five asymmetric carbon centers C(2) to C(6) has been confirmed by single-crystal X-ray analysis of the racemic triol 12;[18] an ORTEP representation is shown in Figure 1. The absolute configurations of all compounds follow from the (*S*)-configuration of the 2-(*p*-methoxyphenyl)propanal (7) used in the aldol condensation. The enantiomeric purity of aldol 11 has been determined by ^1H NMR in the presence of Eu(hfc)$_3$ and evaluated to be 90% showing that no loss of enantiomeric purity occurs during the aldol condensation.

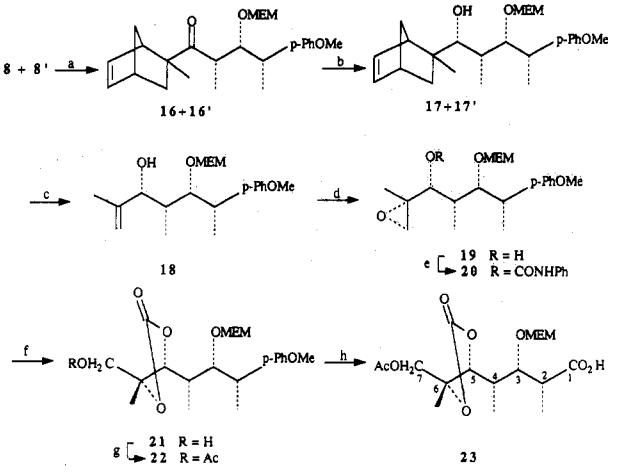
Synthesis of the C(1)-C(7) Fragment of Erythronolides. Our first attempts starting from the diol 5 were unsuccessfull due to the great tendency of the epoxide 15 to spontaneously cyclize into a tetrahydrofuran under weakly acidic conditions (eq 3).



It was then necessary to protect the hydroxy functionality involved in this cyclization by a group stable in acidic medium. The (methoxyethoxy)methyl (MEM) group was chosen since its chelating ability could favor the syn reduction of the carbonyl moiety. The starting material of our synthesis is the mixture of enantiomerically enriched aldols 8 + 8′ described above (Scheme III). After protection of the hydroxy group as a MEM ether,[11] the mixture of the two syn,syn diastereoisomers 16 + 16′ is

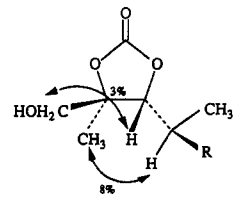
(6) Ahmar, M.; Girard, C.; Bloch, R. *Tetrahedron Lett.* **1989**, *30*, 7053.
(7) Walba, D. M.; Thurmes, W. N.; Haltiwanger, R. C. *J. Org. Chem.* **1988**, *53*, 1046.
(8) Narasaka, K.; Pai, F. C. *Tetrahedron* **1984**, *40*, 2233.
(9) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487.
(10) (a) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936. (b) Nunez, M. T.; Martin, V. S. *J. Org. Chem.* **1990**, *55*, 1928.
(11) Corey, E. J.; Gras, J. L.; Ulrich, P. *Tetrahedron Lett.* **1976**, 809.

Scheme III[a]



[a] Reagents and conditions: (a) MEMCl, iPr_2NEt, CH_2Cl_2 (90%); (b) LAH–LiI–Et_2O, −90 °C (96%); (c) 500 °C (95%); (d) t-BuOOH, VO(acac)$_2$, CH_2Cl_2 (93%); (e) PhNCO, Et_3N, DMAP, CH_2Cl_2 (79%); (f) $BF_3{\cdot}Et_2O$, 0 °C then H_3O^+ (83%); (g) Ac_2O, Et_3N, DMAP, CH_2Cl_2 (92%); (h) $NaIO_4$, $RuCl_3$, $CCl_4/CH_3CN/H_2O$ (2/2/3) (94%).

reduced following the methodology reported by Suzuki[12] to afford the all syn diastereoisomers **17** + **17'** with very high selectivity (ds = 92%). A single diastereoisomer **18** is then obtained by heating **17** + **17'** in flash thermolysis conditions (500 °C, contact time 50 ms). The enantiomeric purity (ee = 90%) of the olefin **18** as well as the relative configuration of the C(5) stereogenic center have been determined by chemical correlation with the diol **5**. The double bond of **18** is stereoselectively epoxidized by *tert*-butyl hydroperoxide[13] in the presence of a vanadium catalyst to give the stable epoxide **19**. After several experiments we found that the best conditions for the elaboration of C(6) involves the Lewis acid induced intramolecular ring opening of the epoxide with assistance of the proximate urethane group of **20** easily prepared from the alcohol **19**.[14] Under these conditions, a remarkable regio- and stereocontrol of the ring cleavage gives rise to the protected polyol **21**.[15] Finally, protection of the primary alcohol as an acetate and oxidation of the *p*-methoxyphenyl group by $NaIO_4/RuCl_3$ lead to the fully protected C(1)–C(7) fragment **23** of erythronolide A or B. The relative configuration of the C(6) stereocenter has been checked by NOE difference experiments effected with the compound **21**.



In conclusion, the syntheses of the enantiomerically enriched (ee = 90%) C(1)–C(7) fragments **14** of deoxyerythronolide B and **23** of erythronolides have been achieved, respectively, in eight and nine steps from the aldehyde **7** with overall yields of 24% and 39%. The overall diastereoselectivity (ds ~85%) obtained for the elaboration of the five asymmetric carbon centers of **23** is one of the best ever reported. The synthesis of the C(8)–C(15) segment of the erythronolides is currently under investigation following a similar strategy.

Experimental Section[16]

(2*S*,3*R*,4*S*)-3-Hydroxy-4-(*p*-methoxyphenyl)-2-pentyl *endo*-2-Methylbicyclo[2.2.1]-5-hepten-2-yl Ketones (8 + 8'). To a solution of 1,1,1,3,3,3-hexamethyldisilazane (2.38 mL, 11.2 mmol) in 30 mL of tetrahydrofuran at −20 °C was added a 1.29 M solution of n-BuLi in hexanes (7.70 mL, 10 mmol). The reaction mixture was stirred for 10 min at −20 °C and then cooled at −50 °C. Ketone **6** (2.02 g, 12 mmol) in 10 mL of tetrahydrofuran was added at −50 °C, and the reaction mixture was stirred for 3 h at this temperature. After the solution was cooled at −78 °C, aldehyde **7** (1.81 g, 11.7 mmol) in 10 mL of tetrahydrofuran was added and 30 min later the reaction was quenched with saturated NH_4Cl solution (40 mL), diluted with water (40 mL), and extracted with ether (3 × 40 mL). The combined extracts were dried over $MgSO_4$ and concentrated to give a clear liquid. Flash chromatography of this material on silica gel (hexane/ether = 7/3) gave a 1:1 mixture of aldols 8 + 8' (3.24 g, 89%) as a colorless liquid. IR (neat): 3500, 1680, 1640 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.5–0.6 (m, 1H); 0.84 and 0.87 (2s, 3H); 1.04–1.13 (m, 1H); 1.07 and 1.09 (2d, J = 7 Hz, 3H); 1.32–1.40 (m, 1H); 1.36 (d, J = 7 Hz, 3H); 2.20–2.35 (m, 1H); 2.65–2.85 (m, 4H); 3.6 (2dd, J = 9.0, 1.0 Hz, 1H); 3.81 (s, 3H); 5.97 (m, 1H); 6.2 (m, 1H); 6.85 (d, J = 8.6 Hz, 2H); 7.15 (d, J = 8.6 Hz, 2H). CIMS (NH_3) m/z (rel intensity): 346 (MNH_4^+, 10), 329 (MH^+, 23), 263 (100). Anal. Calcd for $C_{21}H_{28}O_3$: C, 76.88; H, 8.59. Found: C, 77.01; H, 8.74.

(2*S*,3*R*,4*S*)-4-(*p*-Methoxyphenyl)-3-(trimethylsiloxy)-2-pentyl *endo*-2-Methylbicyclo[2.2.1]-5-hepten-2-yl Ketones (9 + 9'). To a stirred solution of aldols 8 + 8' (770 mg, 2.35 mmol) in 20 mL of diethyl ether was added successively, at room temperature, triethylamine (490 μL, 3.5 mmol), trimethylsilyl chloride (530 μL, 4.23 mmol), dimethyl sulfoxide (20 μL, 0.23 mmol), and DMAP (5 mg). The mixture was stirred at room temperature for 4 h and poured into water. The organic phase was washed three times with a saturated NaCl solution, dried over $MgSO_4$, and concentrated under reduced pressure. The residue (967 mg) was chromatographed on silica gel (elution with 10% Et_2O–hexane) to yield 891 mg (95%) of a mixture of ethers 9 + 9' as a colorless oil. IR (neat): 1690, 1610, 1510, 1250 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: −0.05 (s, 9H); (0.51m, 1H); 0.97 and 1.0 (2s, 3H); 1.11 and 1.13 (2d, J = 7 Hz, 3H); 1.26 and 1.27 (2d, J = 7 Hz, 3H); 1.2–1.45 (m, 2H); 2.4 (m, 1H); 2.65 (m, 1H); 2.78 and 2.94 (2bs, 2H); 3.13 (m, 1H); 3.79 and 3.8 (2s, 3H); 4.0 (m, 1H); 6.04 (m, 1H); 6.22 (m, 1H); 6.85 (d, J = 8.6 Hz, 2H); 7.10 (d, J = 8.6 Hz, 2H). CIMS (NH_3) m/z (rel intensity): 401 (MH^+, 24), 335 (80), 245 (100), 135 (41). Anal. Calcd for $C_{24}H_{36}O_3Si$: C, 71.95; H, 9.06. Found: C, 72.13; H, 9.08.

(4*S*,5*R*,6*S*)-2,4-Dimethyl-6-(*p*-methoxyphenyl)-5-(trimethylsiloxy)-1-hepten-3-one (10). Ethers 9 + 9' (850 mg, 2.12 mmol) were evaporated through an horizontal mullite tube (500 °C, 10^{-3} Torr), and the thermolysate was collected in a trap cooled to liquid nitrogen temperature. After being warmed to room temperature, the content of the trap was dissolved in ether and the resulting solution was dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, hexane/ether = 92/8) to provide 640 mg (90%) of the ethylenic ketone **10** as a colorless oil, $[\alpha]^{20}_D$ = +20.1 ($CHCl_3$, c 0.75). IR (neat): 1675, 1610, 1510, 1250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: −0.02 (s, 9H); 1.08 (d, J = 6.8 Hz, 3H); 1.24 (d, J = 7.2 Hz, 3H); 1.84 (s, 3H); 2.75 (qd, J = 6.6, 7.2 Hz, 1H); 3.26 (qd, J = 5.0, 6.8 Hz, 1H); 3.8 (s, 3H); 4.04 (dd, J = 5.0, 6.6 Hz, 1H); 5.5 (bs, 1H); 5.67 (bs, 1H); 6.85 (d, J = 8.7 Hz, 2H); 7.10 (d, J = 8.7 Hz, 2H). CIMS (NH_3) m/z (rel intensity): 335 (MH^+,

(12) Mori, Y.; Kuhara, M.; Takeuchi, A.; Suzuki, M. *Tetrahedron Lett.* **1988**, *29*, 5419.
(13) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, 4733.
(14) Roush, W. R.; Brown, R. J.; Dimare, M. *J. Org. Chem.* **1983**, *48*, 5083.
(15) The only other product formed is a small amount of the tetrahydrofuran arising from the cleavage of the MEM group and cyclisation.
(16) For a general description of experimental parameters see: Bloch, R.; Bortolussi, M.; Girard, C.; Seck, M. *Tetrahedron* **1992**, *48*, 453.

24), 245 (100), 135 (24). Anal. Calcd for $C_{19}H_{30}O_3Si$: C, 68.22; H, 9.04. Found: C, 68.41; H, 8.90.

(4*S*,5*R*,6*S*)-2,4-Dimethyl-5-hydroxy-6-(*p*-methoxyphenyl)-1-hepten-3-one (11). To a solution of the trimethylsiloxy ether **10** (630 mg, 1.88 mmol) in 5 mL of tetrahydrofuran was added HCl (1 N, 90 μL, 0.094 mmol, 5%), and the mixture was stirred at room temperature for 45 min. The solution was diluted with water (10 mL) and extracted with Et_2O (4 × 10 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/Et_2O = 50/50) to yield 450 mg (91%) of the ketone **11** as a white solid, mp 65 °C, $[\alpha]^{20}_D$ = −6.0 ($CHCl_3$, *c* 0.71). IR ($CHCl_3$): 3500, 1660, 1610, 1510, 1250 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 1.1 (d, *J* = 7.2 Hz, 3H); 1.37 (d, *J* = 6.8 Hz, 3H); 1.83 (s, 3H); 2.1 (bs, 1H); 2.78 (qd, *J* = 6.8, 9.4 Hz, 1H); 3.06 (qd, *J* = 2.2, 7.2 Hz, 1H); 3.82 (s, 3H); 3.9 (dd, *J* = 2.2, 9.4 Hz, 1H); 5.54 (s, 1H); 5.7 (s, 1H); 6.9 (d, *J* = 8.6 Hz, 2H); 7.0 (d, *J* = 8.6 Hz, 2H). CIMS (NH_3) *m/z* (rel intensity): 263 (MH^+, 12), 245 (13), 182 (79), 164 (12), 135 (100), 116 (19). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.23; H, 8.58.

(3*R*,4*S*,5*R*,6*S*)-2,4-Dimethyl-6-(*p*-methoxyphenyl)-1-heptene-3,5-diol (5). To a stirred solution of methanol (3.5 mL) in 15 mL of tetrahydrofuran was added 1.76 mL (1.76 mmol) of 1 M triethylborane in THF. The solution was stirred for 1.5 h at room temperature and cooled at −70 °C, and 420 mg (1.6 mmol) of aldol **11** was added. After 2 h of additional stirring at −70 °C, sodium borohydride (64 mg, 1.76 mmol) was added. The mixture was stirred for 3 h at −70 °C, allowed to warm to room temperature, poured into saturated aqueous NH_4Cl (30 mL), and extracted with ethyl acetate (3 × 20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was dissolved in MeOH (5 mL), and the solution was heated at 60 °C for 30 min. The solvent was evaporated under atmospheric pressure and the residue purified by chromatography (silica gel, hexane/ether = 80/20) to give 326 mg (79%) of the diol **5** as a colorless solid, mp 137 °C; $[\alpha]^{20}_D$ = −47 ($CHCl_3$, *c* 0.81). IR ($CHCl_3$): 3600, 3500, 1610, 1515 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.82 (d, *J* = 7.1 Hz, 3H); 1.34 (d, *J* = 7 Hz, 3H); 1.42 (s, 3H); 1.48 (m, 1H); 2.20 (bs, 2H); 2.8 (qd, *J* = 9.8, 7 Hz, 1H); 3.81 (s, 3H); 3.88 (dd, *J* = 9.8, 1.7 Hz, 1H); 4.13 (d, *J* = 3 Hz, 1H); 4.87 (s, 1H); 4.96 (s, 1H); 6.82 (d, *J* = 8.8 Hz, 2H); 7.15 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (62.8 MHz, $CDCl_3$): 4.42, 19.11, 19.36, 35.53, 43.02, 55.16, 79.92, 81.1, 110.23, 113.90, 128.16, 136.63, 145.70, 157.92. CIMS (NH_3) *m/z* (rel intensity): 282 (MNH_4^+, 20), 265 (MH^+, 6), 264 (M^+, 21), 247 (32), 229 (43), 183 (34), 136 (100), 135 (76). Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.80; H, 9.25.

(2*S*,3*S*,4*S*,5*R*,6*S*)-2,4-Dimethyl-6-(*p*-methoxyphenyl)-1,3,5-heptanetriol (12). To a solution of the diol **5** (212 mg, 0.8 mmol) in 6 mL of tetrahydrofuran was added at 0 °C 6.4 mL (3.2 mmol) of 0.5 M 9-BBN in tetrahydrofuran. The solution was allowed to warm to room temperature and stirred for 15 h. Then 1 mL of EtOH, 2.2 mL of 2 N NaOH, and 1.4 mL of 30% H_2O_2 were added successively, and the mixture was stirred for 10 h at room temperature. The solution was poured into 10 mL of 1 N NaOH and extracted with diethyl ether (3 × 20 mL) and methylene chloride (2 × 20 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (elution with 60% EtOAc–hexane) to yield 144 mg (68%) of triol **12** as a white solid, mp 94 °C, $[\alpha]^{20}_D$ = +17.7 ($CHCl_3$, *c* 0.3). IR ($CHCl_3$): 3640, 3500, 1610, 1515, 1250 cm^{-1}. ^1H NMR (250 MHz, C_6D_6) δ: 0.15 (d, *J* = 6.7 Hz, 3H); 0.5 (bs, 3H); 1.0 (d, *J* = 7.3 Hz, 3H); 1.2–1.7 (m, 2H); 1.44 (d, *J* = 6.7 Hz, 3H); 2.82 (qd, *J* = 6.7, 9.9 Hz, 1H); 3.17–3.38 (m, 2H); 3.28 (s, 3H); 3.5 (dd, *J* = 1.4, 9.2 Hz, 1H); 3.83 (dd, *J* = 1.0, 9.9 Hz, 1H); 6.27 (d, *J* = 8.9 Hz, 2H); 7.04 (d, *J* = 8.9 Hz, 2H). CIMS (NH_3) *m/z* (rel intensity): 283 (MH^+, 14), 265 (100), 135 (24), 111 (11). Anal. Calcd for $C_{16}H_{26}O_4$: C, 68.06; H, 9.28. Found: C, 67.81; H, 9.45.

(2*S*,3*S*,4*S*,5*R*,6*S*)-2,4-Dimethyl-6-(*p*-methoxyphenyl)-1,3,5-triacetoxyheptane (13). To a stirred solution of triol **12** (62 mg, 0.22 mmol) in 13 mL of CH_2Cl_2 were added triethylamine (140 μL, 0.99 mmol), acetic anhydride (95 μL, 0.99 mmol), and (dimethylamino)pyridine (1 mg). The reaction mixture was stirred for 15 h, poured into 5 mL of 2 N HCl, and extracted with ether (3 × 5 mL). The combined extracts were washed with a saturated solution of $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was purified by chromatography (silica gel, elution with hexane/ether = 50/50) to give 76.5 mg (85%) of the triacetate **13** as an oil, $[\alpha]^{20}_D$ = +14.4 ($CHCl_3$, *c* 0.43). IR (film): 1740, 1515, 1240 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.87 (d, *J* = 6.9 Hz, 6H); 1.21 (d, *J* = 7.1 Hz, 3H); 1.85 (qdd, *J* = 6.8, 3.8, 6.9 Hz, 1H); 2.02 (s, 3H); 2.04 (s, 3H); 2.10 (s, 3H); 2.2 (m, 1H); 3.05 (qd, *J* = 8.7, 7.1 Hz, 1H); 3.7–3.8 (m, 2H); 3.8 (s, 3H); 4.79 (dd, *J* = 5.9, 6.8 Hz, 1H); 5.11 (dd, *J* = 3.8, 8.7 Hz, 1H); 6.85 (d, *J* = 8.7 Hz, 2H); 7.1 (d, *J* = 8.7 Hz, 2H). CIMS (NH_3) *m/z* (rel intensity): 426 (MNH_4^+, 100), 349 (11), 135 (36). Anal. Calcd for $C_{22}H_{32}O_7$: C, 64.69; H, 7.90. Found: C, 65.07; H, 7.81.

(2*R*,3*S*,4*R*,5*S*,6*S*)-3,5,7-Triacetoxy-2,4,6-trimethylheptanoic Acid (14). To a biphasic solution of triacetate **13** (65 mg, 0.16 mmol) in 0.65 mL of carbon tetrachloride, 0.65 mL of acetonitrile, and 1 mL of water were added sodium periodate (496 mg, 2.3 mmol) and ruthenium trichloride (1 mg, 3.5×10^{-3} mmol). The mixture was stirred for 16 h at room temperature, poured into 10 mL of water, and extracted with methylene chloride (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure, and the residue was chromatographed on silica gel (methylene chloride/methanol = 90/10) to yield 40 mg (73%) of acid **14** as a viscous colorless oil, $[\alpha]^{20}_D$ = −6.4 ($CHCl_3$, *c* 0.28). IR ($CHCl_3$): 3500, 1735 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ: 0.94 (d, *J* = 7.3 Hz, 3H); 0.99 (d, *J* = 7 Hz, 3H); 1.19 (d, *J* = 7 Hz, 3H); 2.02–2.32 (m, 2H); 2.06 (s, 3H); 2.09 (s, 3H); 2.10 (s, 3H); 2.95 (qd, *J* = 6.0, 7.0 Hz, 1H); ABX system (δ_A 3.94, δ_B 4.04, J_{AB} = 11 Hz, J_{AX} = 6.3 Hz, J_{BX} = 4.5 Hz, 2H); 4.85 (dd, *J* = 7.2, 4.9 Hz, 1H); 5.25 (dd, *J* = 6.0, 6.0 Hz, 1H); 6.5 (bs, 1H). CIMS (NH_3) *m/z* (rel intensity): 364 (MNH_4^+, 100), 287 (15). Anal. Calcd for $C_{16}H_{26}O_8$: C, 55.78; H, 7.57. Found: C, 56.15; H, 7.61.

(2*S*,3*R*,4*S*)-3-[(2-Methoxyethoxy)methoxy]-4-(*p*-methoxyphenyl)-2-pentyl *endo*-2-Methylbicyclo[2.2.1]-5-hepten-2-yl Ketones (16 + 16′). To a solution of aldols **8** + **8′** (1.7 g, 5.17 mmol) in 30 mL of methylenechloride were added ethyldiisopropylamine (1.35 mL, 7.76 mmol), (2-methoxyethoxy)methyl chloride (0.89 mL, 7.76 mmol), and (dimethylamino)pyridine (10 mg) at 0 °C. The mixture was allowed to warm to room temperature, stirred for 30 h, and concentrated under reduced pressure. Diethyl ether (20 mL) was added, the solid salt was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, elution with 5% Et_2O/CH_2Cl_2) to give 1.94 g (90%) of MEM ethers **16** + **16′** as a colorless oil. IR (neat): 1700, 1610, 1250, 1030 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.61 (m, 1H); 0.93 and 0.94 (2s, 3H); 1.12 and 1.14 (2d, *J* = 7 Hz, 3H); 1.10–1.40 (m, 2H); 1.35 and 1.36 (2d, *J* = 7 Hz, 3H); 2.35 (m, 1H); 2.75 (m, 3H); 3.13 (qd, *J* = 7.0 and 6.5 Hz, 1H); 3.37 (s, 3H); 3.48 (m, 2H); 3.70 (m, 2H); 3.80 (s, 3H); 3.84 (m, 1H); 4.48–4.65 (2AB syst., $\Delta\nu_{AB}$ = 28.6 and 23.0 Hz; J_{AB} = 6.8 and 6.7 Hz, 2H); 6.03 (m, 1H); 6.22 (m, 1H); 6.86 (d, *J* = 8.7 Hz, 2H); 7.17 (d, *J* = 8.7 Hz, 3H). Anal. Calcd for $C_{25}H_{36}O_5$: C, 72.08; H, 8.71. Found: C, 71.78; H, 8.68.

5-*exo*-(1*R*,2*S*,3*R*,4*S*)-[1-Hydroxy-2-methyl-3-[(2-methoxyethoxy)methoxy]-4-(*p*-methoxyphenyl)-1-pentyl]-5-*endo*-methylbicyclo[2.2.1]hept-5-enes (17 + 17′). To a solution of ketones **16** + **16′** (1.66 g, 4 mmol) in 60 mL of diethyl ether was added anhydrous lithium iodide (0.535 g, 4 mmol), and the resulting mixture was stirred at −40 °C for 5 min and then cooled to −90 °C (toluene–liquid nitrogen). The solution was then treated with 4 mL (4 mmol) of a 1 M solution of $LiAlH_4$ in diethyl ether and stirred at −90 °C for 1 h. The solution was allowed to warm to room temperature and hydrolyzed with 1 mL of water. The solid salts were removed by filtration and washed twice with ether. The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/Et_2O = 70/30) to yield 1.61 g (96%) of alcohols **17** + **17′** as a clear oil. IR (neat): 3500, 1615, 1250, 1040 cm^{-1}. ^1H NMR (250 MHz, $CDCl_3$) δ: 0.25 and 0.72 (2m, 1H); 0.62 and 0.63 (2s, 3H); 0.94 and 0.95 (2d, *J* = 7 Hz, 3H); 1.28 (d, *J* = 6.8 Hz, 3H); 1.1–1.4 (m, 2H); 1.6–1.8 (m, 3H); 2.6–3.2 (m, 3H); 3.41 and 3.42 (2s, 3H); 3.45–3.80 (m, 5H); 3.82 (s, 3H); 4.05 (m, 1H); 4.95 (m, 2H); 5.85 and 6.05 (2m, 2H); 6.85 (m, 2H);

7.10 (m, 2H). Anal. Calcd for $C_{25}H_{38}O_5$: C, 71.74; H, 9.15. Found: C, 71.92; H, 9.26.

(3*R*,4*S*,5*R*,6*S*)-2,4-Dimethyl-5-[(2-methoxyethoxy)-methoxy]-6-(*p*-methoxyphenyl)-1-hepten-3-ol (18). The thermolysis of the bicyclic compounds 17 + 17′ (1.50 g, 3.58 mmol) was performed in the conditions described for 9 + 9′ leading to 1.20 g (95%) of alcohol 18 as an oil after purification by flash chromatography (silica gel, CH_2Cl_2/Et_2O = 3/1), $[\alpha]^{20}_D$ = −19.2 ($CHCl_3$, *c* 0.50). IR (neat); 3465, 1615, 1580, 1245, 1030 cm^{-1}. ^{1}H NMR (250 MHz, C_6D_6) δ: 1.20 (d, *J* = 6.9 Hz, 3H); 1.27 (d, *J* = 6.9 Hz, 3H); 1.37 (s, 3H); 1.74 (m, 1H); 2.21 (bs, 1H); 2.92 (qd, *J* = 6.9, 8.7 Hz, 1H); 3.11 (s, 3H); 3.32 (s, 3H); 3.26–3.34 (m, 2H); 3.52 (m, 1H); 3.62 (dd, *J* = 8.7, 2.3 Hz, 1H); 3.70 (m, 1H); 4.12 (m, 1H); 4.72 (AB syst. $\Delta\nu_{AB}$ = 32.3 Hz, J_{AB} = 6.4 Hz, 2H); 4.88 (bs, 1H); 5.30 (bs, 1H); 6.75 (d, *J* = 8.7 Hz, 2H); 6.94 (d, *J* = 8.7 Hz, 2H). Anal. Calcd for $C_{20}H_{32}O_5$: C, 68.15; H, 9.15. Found: C, 68.10; H, 9.33.

(2*S*,3*R*,4*S*,5*R*,6*S*)-2,4-Dimethyl-1,2-epoxy-5-[(2-methoxyethoxy)methoxy]-6-(*p*-methoxyphenyl)-3-heptanol (19). To a stirred solution of alcohol 18 (810 mg, 2.3 mmol) in dichloromethane (30 mL) containing a catalytic amount of $VO(acac)_2$ (12.2 mg, 4.6 × 10^{-2} mmol) was added dropwise, at −5 °C, 1.02 mL (4.6 mmol) of a 4.5 M solution of t-BuOOH in dichloromethane.[17] The reaction mixture was stirred for 2 h at −5 °C, quenched with water (10 mL), and extracted with dichloromethane (2 × 15 mL). The combined extracts were dried over sodium sulfate and concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (CH_2Cl_2/Et_2O = 70/30) to give 788 mg (93%) of the epoxy alcohol 19 as a colorless oil, $[\alpha]^{20}_D$ = −6.4 ($CHCl_3$, *c* 0.55). IR (neat): 3460, 1610, 1580, 1250, 1035 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.90 (d, *J* = 6.9 Hz, 3H); 1.13 (s, 3H); 1.32 (d, *J* = 7.0 Hz, 3H); 1.85 (m, 1H); 2.28 (bs, 1H); 2.60 (d, *J* = 4.8 Hz, 1H); 2.95 (d, *J* = 4.8 Hz, 1H); 3.05 (qd, *J* = 6.9, 7.0 Hz, 1H); 3.37 (s, 3H); 3.48–3.78 (m, 6H); 3.80 (s, 3H); 4.54 (AB syst. $\Delta\nu_{AB}$ = 59 Hz, J_{AB} = 6.6 Hz, 2H); 6.83 (d, *J* = 8.6 Hz, 2H); 7.15 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (62.8 MHz, $CDCl_3$): 8.6, 16.1, 18.0, 36.9, 41.3, 50.4, 55.2, 58.2, 58.9, 67.8, 71.7, 72.9, 86.7, 97.5, 113.7, 128.6, 136.8, 158.0. Anal. Calcd for $C_{20}H_{32}O_6$: C, 65.14; H, 8.75. Found: C, 65.06; H, 8.80.

(2*S*,3*R*,4*S*,5*R*,6*S*)-1,2-Epoxy-2,4-dimethyl-5-[(2-methoxyethoxy)methoxy]-6-(*p*-methoxyphenyl)-3-[(*N*-phenylcarbamoyl)oxy]heptane (20). To a solution of alcohol 19 (737 mg, 2 mmol), triethylamine (560 μL, 4 mmol), and (dimethylamino)-pyridine (24 mg, 0.2 mmol) in 15 mL of anhydrous dichloromethane was added phenyl isocyanate (326 μL, 3 mmol). The solution was stirred at room temperature for 36 h, poured into water, and extracted with dichloromethane. The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed on silica gel (CH_2Cl_2/Et_2O = 3/1) to yield 771 mg (79%) of urethane 20 as a clear oil, $[\alpha]^{20}_D$ = −34.2 ($CHCl_3$, *c* 1.25). IR (neat): 3320, 3140, 1740, 1605, 1585, 1450, 1030 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.0 (d, *J* = 6.8 Hz, 3H); 1.02 (s, 3H); 1.35 (d, *J* = 6.7 Hz, 3H); 1.95 (m, 1H); 2.50 (d, *J* = 5.3 Hz, 1H); 2.82 (d, *J* = 5.3 Hz, 1H); 2.98 (m, 1H); 3.41 (s, 3H); 3.80 (s, 3H); 3.55–3.9 (m, 5H); 4.69 (d, *J* = 8.2 Hz, 1H); 4.72 (AB syst. $\Delta\nu_{AB}$ = 46 Hz, J_{AB} = 6.6 Hz, 2H); 6.67 (bs, 1H); 6.84 (d, *J* = 8.7 Hz, 2H); 7.07 (m, 1H); 7.15 (d, *J* = 8.7 Hz, 2H); 7.25–7.42 (m, 4H). CIMS (NH_3) *m/z* (rel intensity): 488 (MH^+, 98), 487 (M^+, 13), 412 (100), 135 (67), 119 (93). Anal. Calcd for $C_{27}H_{37}NO_7$: C, 66.45; H, 7.64; N, 2.87. Found: C, 66.08; H, 7.75; N, 2.73.

(2*S*,3*R*,4*S*,5*R*,6*S*)-2,3-(Carbonyldioxy)-2,4-dimethyl-5-[(2-methoxyethoxy)methoxy]-6-(*p*-methoxyphenyl)-1-heptanol (21). To a solution of urethane 20 (640 mg, 1.31 mmol) in diethyl ether (35 mL) was added at 0 °C $BF_3{\cdot}Et_2O$ (178 μL, 1.44 mmol), and the mixture was stirred at 0 °C for 75 min. Then 25 mL of 1 N H_2SO_4 solution was added, and the two-phase system was stirred at room temperature for 3 h. The two layers were separated, the aqueous layer was extracted with CH_2Cl_2, and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by flash chromatography (silica gel, CH_2Cl_2/Et_2O = 4/1) to give 451 mg (83%) of alcohol 21 as an oil: $[\alpha]^{20}_D$ = −64.7 ($CHCl_3$, *c* 0.64). IR (neat): 3420, 1790, 1610, 1580, 1240, 1030 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.86 (s, 3H); 1.14 (d, *J* = 6.9 Hz, 3H); 1.32 (d, *J* = 6.9 Hz, 3H); 1.90 (m, 1H); 2.97 (m, 1H); 3.34 (d, *J* = 11 Hz, 1H); 3.40 (s, 3H); 3.43–3.78 (m, 5H); 3.82 (s, 3H); 3.90–4.10 (m, 2H); 4.68 (d, *J* = 10.4 Hz, 1H); 4.87 (AB syst. $\Delta\nu_{AB}$ = 15.2 Hz, J_{AB} = 7.4 Hz, 2H); 6.85 (d, *J* = 8.7 Hz, 2H); 7.08 (d, *J* = 8.7 Hz, 2H). Anal. Calcd for $C_{21}H_{32}O_8$: C, 61.15; H, 7.82. Found: C, 61.09; H, 8.05.

(2*R*,3*R*,4*S*,5*R*,6*S*)-1-Acetoxy-2,3-(carbonyldioxy)-2,4-dimethyl-5-[(2-methoxyethoxy)methoxy]-6-(*p*-methoxyphenyl)-heptane (22). To a solution of alcohol 21 (240 mg, 0.58 mmol), triethylamine (82 μL, 0.58 mmol), (dimethylamino)pyridine (7 mg, 0.06 mmol) in 10 mL of dichloromethane was added acetic anhydride (55 μL, 0.58 mmol). The reaction mixture was stirred at room temperature for 2 h and concentrated under reduced pressure. The residue was taken up in 10 mL of diethyl ether, the solid ammonium salt was removed by filtration, and the filtrate was concentrated under reduced pressure. The residue was chromatographed on silica gel (hexane/ether = 7/3) to yield 243 mg (92%) of the acetate 22 as a clear oil, $[\alpha]^{20}_D$ = −16.4 ($CHCl_3$, *c* 1.5). IR (neat): 1810, 1750, 1615, 1580, 1240 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 0.92 (s, 3H); 1.05 (d, *J* = 6.9 Hz, 3H); 1.31 (d, *J* = 7 Hz, 3H); 1.90 (m, 1H); 2.22 (s, 3H); 2.92 (m, 1H); 3.35 (s, 3H); 3.32–3.66 (m, 4H); 3.80 (s, 3H); 3.90 (m, 1H); 4.15 (AB syst. $\Delta\nu_{AB}$ = 18.1 Hz, J_{AB} = 12.3 Hz, 2H); 4.68 (d, *J* = 7.4 Hz, 1H); 4.80 (AB syst. $\Delta\nu_{AB}$ = 17.2 Hz, J_{AB} = 7.4 Hz, 2H); 6.84 (d, *J* = 8.7 Hz, 2H); 7.10 (d, *J* = 8.7 Hz, 2H). Anal. Calcd for $C_{23}H_{34}O_9$: C, 60.77; H, 7.54. Found: C, 60.60; H, 7.63.

(2*R*,3*S*,4*S*,5*R*,6*R*)-7-Acetoxy-5,6-(carbonyldioxy)-3-[(2-methoxyethoxy)methoxy]-2,4,6-trimethylheptanoic Acid (23). Oxidation of the acetate 22 (90 mg, 0.2 mmol) was performed in the conditions described for 13 with $NaIO_4$ (513 mg, 2.4 mmol) and $RuCl_3{\cdot}xH_2O$ (2 mg) to give after purification 73 mg (94%) of acid 23 as a viscous colorless oil, $[\alpha]^{20}_D$ = +3.5 ($CHCl_3$, *c* 0.52). IR (neat): 3300–2900, 1810, 1750, 1715, 1240 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ: 1.11 (d, *J* = 7 Hz, 3H); 1.27 (d, *J* = 7 Hz, 3H); 1.47 (s, 3H); 2.15 (s, 3H); 2.17 (m, 1H); 2.80 (m, 1H); 3.38 (s, 3H); 3.5–3.9 (m, 5H); 4.24 (s, 2H); 4.78 (m, 3H). CIMS (NH_3) *m/z* (rel intensity): 410 (MNH_4^+, 100). Anal. Calcd for $C_{17}H_{28}O_{10}$: C, 52.03; H, 7.19. Found: C, 51.97; H, 6.82.

(17) Hanson, R. M.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 1922.

(18) The author has deposited atomic coordinates for 12 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Center, 12 Union Road, Cambridge, CB2 1EZ, UK.