Stereocontrolled Transformations of Cyclohexenediols Obtained from Nucleophilic Ring Opening of 7-Oxanorbornene Derivatives

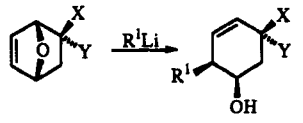
Odón Arjona,* Angel Martín-Domenech, and Joaquín Plumet*

Departamento de Química Orgánica I, Facultad de Química, Universidad Complutense, 28040 Madrid, Spain

Received July 9, 1993

7-Oxabicyclo[2.2.1]heptene derivatives are versatile building block for the synthesis of many compounds of current interest,[1] such as sugars,[2] pseudosugars,[3] cyclitols,[4] nucleosides,[5] and other.[6] For this reason, the ring opening of the oxygen bridge constitutes a key procedure.[7] The regio- and stereoselective ring opening of nonsymmetrical 7-oxabicyclo[2.2.1]heptenols by organolithium reagents to give cyclohexenediol derivatives 1 was reported by our group in 1989[8] (Scheme I), and the procedure constitutes an interesting methodology since 1 can be obtained optically pure.[9] Transformations of compounds of type 1 could be a source of interesting molecules if strict regio- and stereochemical control of the transformations could be achieved. For instance, epoxidation of compounds 1 could give compounds related to cyclitol epoxides, naturally ocurring compounds that are probably shikimate metabolites; some of these epoxides have interesting biological properties.[10] Ring opening of the epoxides may constitute a tool for the synthesis of branched pseudosugars. Pseudosugars have sparked a great deal of synthetic activity in recent years[11] because of their activity as enzyme inhibitors,[12] artificial sweeteners,[13] and their presence in aminocyclitol antibiotics.[14] In addition to epoxidation, ozonolysis of compounds like 1 could also be an important transformation if both ends of the double bond could be differentiated in the process. The compounds obtained

Scheme I

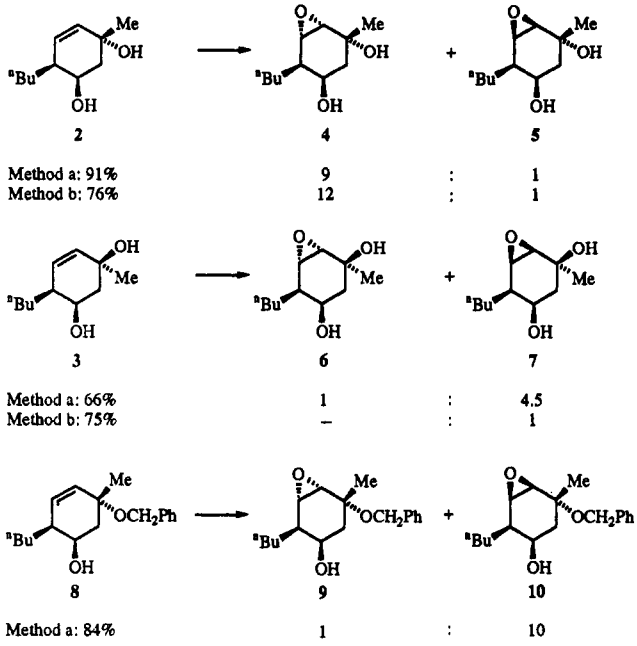


1

X = R, Y = OH; X = OH, Y = R

R = alkyl, vinyl, aryl; R^1 = H, alkyl, vinyl, aryl

Scheme II



2	4		5
Method a: 91%	9	:	1
Method b: 76%	12	:	1
3	6		7
Method a: 66%	1	:	4.5
Method b: 75%	–	:	1
8	9		10
Method a: 84%	1	:	10

in this way can be considered as functionalized building blocks for the synthesis of polypropionate fragments and related systems.[15] In this paper, we wish to report our results in these areas which make our previously reported ring opening of 7-oxanorbornene derivatives a powerful and simple synthetic tool.

Our first objective was the study of the epoxidation of compounds 1. The stereochemistry of the epoxidation of compounds 1 can be controlled by the substituents attached to the quaternary center.[16] Thus, reactions of model compounds 2 and 3 with *m*-CPBA (method a) afforded the epoxides 4-7 (Scheme II). The relatively low stereoselectivity obtained for compound 7 was improved by the use of *t*ert-butyl hydroperoxide under the conditions described by Sharpless *et al.*[16] (method b). Epoxide 10, which is related to 5, could be obtained with good stereoselectivity from benzyl derivative 8[9] by epoxidation with *m*-CPBA (Scheme II).

(1) (a) Vogel, P. *Bull. Soc. Chim. Belg.* **1990**, *99*, 395–439. (b) Vogel, P.; Fattori, D.; Gasparini, F.; Le Drian, C. *Synlett* **1990**, 173–185. See also Lipshutz, B. H. *Chem. Rev.* **1986**, *86*, 795–819.

(2) For some selected references see: (a) Wagner, J.; Vogel, P. *Carbohydr. Res.* **1991**, *222*, 151–61. (b) Jenganathan, S.; Vogel, P. *J. Org. Chem.* **1991**, *56*, 1133–42. (c) Neff, D. P.; Chen, Y. W.; Vogel, P. *Helv. Chim. Acta* **1991**, *74*, 508–16. (d) Wagner, J.; Vogel, P. *Tetrahedron* **1991**, *47*, 9641–58. (e) Takahashi, T.; Kotsubo, H.; Koizumi, T. *J. Chem. Soc. Perkin Trans. I* **1991**, 1667–71. (f) Bimwala, R. B.; Vogel, P. *Tetrahedron Lett.* **1991**, *32*, 1429–32. (g) Bimwala, R. B.; Vogel, P. *J. Org. Chem.* **1992**, *57*, 2076–83. (h) de Guchteneere, E.; Fattori, D.; Vogel, P. *Tetrahedron* **1992**, *48*, 10603–20. (i) Jeanneret, V.; Gasparini, F.; Péchi, P.; Vogel, P. *Tetrahedron* **1992**, *42*, 10637–44. (j) Durgnat, J.; Warm, A.; Vogel, P. *Synt. Comm.* **1992**, *22*, 1883–93.

(3) For recent selected references, see: (a) Ogawa, S.; Tsunoda, H. *Liebigs Ann. Chem.* **1992**, 637–41. (b) Aceña, J. L.; Arjona, O.; Fernández de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1992**, *57*, 1945–6.

(4) See Arjona, O.; de Dios, A.; Fernández de la Pradilla, R.; Plumet, J. *Tetrahedron Lett.* **1991**, *32*, 7309–12 and refs therein.

(5) For some selected references, see: (a) Sera, A.; Itoh K.; Yamaguchi, H. *Tetrahedron Lett.* **1990**, *31*, 6547–48. (b) Cox, P. J.; Simpkins, N. S. *Synlett* **1991**, 321–3.

(6) See, for instance: (a) Chen, Y.; Vogel, P. *Tetrahedron Lett.* **1992**, *33*, 4917–20. (b) Ashton, P. R.; Brown, G. R.; Isaacs, N. S.; Gruffida, D.; Kohnke, F. H.; Mathias, J. P.; Slawin, A. M. Z.; Smith, D. R.; Stoddardt, J. F.; Williams, D. J. *J. Am. Chem. Soc.* **1992**, *114*, 6330–53.

(7) Lautens, M. *Synlett.* **1993**, *3*, 177–85.

(8) Arjona, O.; Fernández de la Pradilla, R.; García, E.; Martín-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437–40.

(9) Arjona, O.; Fernández de la Pradilla, R.; Martín-Domenech, A.; Plumet, J. *Tetrahedron* **1990**, *46*, 8187–98.

(10) Thebtaranonth, C.; Thebtaranonth, Y. *Acc. Chem. Res.* **1986**, *19*, 84–90.

(11) Suami, T.; Ogawa, S. *Adv. Carbohydr. Chem. Biochem.* **1990**, *48*, 21–90.

(12) See for instance: (a) Miwa, I.; Hara, H.; Okuda, J.; Suami, T.; Ogawa, S. *Biochem. Int.* **1985**, *11*, 809–16. (b) Wilcox, C. S.; Gaudino, J. J. *J. Am. Chem. Soc.* **1986**, *108*, 3102–4. (c) Shibata, Y.; Kosuge, Y.; Mizukoshi, T.; Ogawa, S. *Carb. Res.* **1992**, *228*, 377–98. (d) Moutchamp, J. L.; Piehler, L. T.; Frost, J. W. *J. Am. Chem. Soc.* **1992**, *114*, 4453–9. (e) Ogawa, S.; Uchida, C.; Shibata, Y. *Carbohydr. Res.* **1992**, *223*, 279–86. (f) Cai, S.; Stroud, M. R.; Hakowari, S.; Toyokumi, T. *J. Org. Chem.* **1992**, *57*, 6693–6. (g) Ogawa, S. Nakamura, Y. *Carbohydr. Res.* **1992**, *226*, 79–89.

(13) Ogawa, S.; Uematsu, Y.; Yoshida, S.; Sasaki, N.; Suami, T. *J. Carbohydr. Chem.* **1987**, *6*, 471–8.

(14) (a) Truscheit, E.; Frommer, W.; Junge, B.; Müller, L.; Schmidt, D. D.; Wingender, W. *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 744–61. (b) Junge, B.; Heiker, F. R.; Kurtz, J.; Mueller, L.; Schmidt, D. D. *Carbohydr. Res.* **1984**, *128*, 235–68.

(15) (a) Paterson, I.; Mansuri, M. M. *Tetrahedron* **1985**, *41*, 3569–3624. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309–62.

(16) (a) Henbest H. B.; Wilson, R. A. L. *J. Chem. Soc.* **1957**, 1958–65. (b) Sharpless, K. B.; Verhoeven, T. R. *Aldrichim. Acta* **1979**, *12*, 63–74.

0022-3263/93/1958-7929$04.00/0

Scheme III

4 11 (R = H); 12 (R = Ac)

The enantioselective version of the epoxidation process was achieved with enantiomerically pure (+)-2[9] to give, by means of method b, enantiomerically pure (+)-4 (81%, ee ≥ 99%). The stereochemical assignments of these epoxides were derived from their spectral features, particularly the ^{1}H NMR coupling constants between H-5 and H-6 ($J_{cis} > J_{trans}$) and DNOE measurements (for instance, in 4, the methyl group showed a 3.3% enhancement upon irradiation of H-4).

Our second goal was the use of the ring openings of such epoxides to achieve the totally regio- and stereoselective synthesis of deoxycyclitols. Thus, ring opening of 4 with MeOH–DDQ[17] gave 11 (85%), which was fully characterized as diacetate 12 (Ac_2O/pyr, 95%). In the same way, enantiomerically pure (+)-4 gave (+)-11 (85%, ee ≥ 99%) (Scheme III). The regio- and stereoselectivity of the oxirane opening were confirmed from irradiation experiments for the assignments of all the ^{1}H NMR signals and from the values of the H-6/H-1 and H-6/H-5 coupling constants ($J_{6,1}$ = 8.5 Hz, $J_{6,5}$ = 3.9 Hz for 11 and $J_{6,1}$ = 10.0 Hz, $J_{6,5}$ = 4.9 Hz for 12).

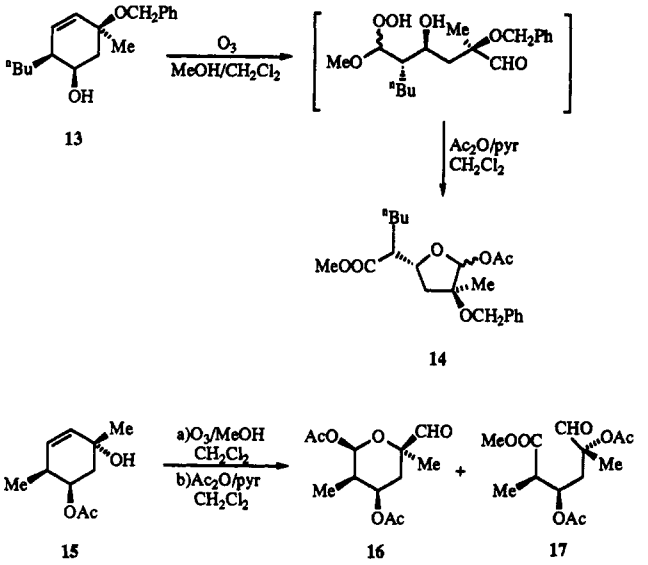
The third objective was the study of the ozonolysis reactions of these cyclohexene derivatives. We observed that the ozonolysis is also dependent on the stereochemistry and nature of the substituents on the quaternary center. Thus, unsymmetrical ozonolysis of 13,[9] according to the method described by Schreiber and co-workers,[18] gave acetal ester 14 (65% yield). However, the same unsymmetrical ozonolysis of acetate 15[9] afforded a 2.4:1 mixture (85% yield) of acetal aldehyde 16, product of normal ozonolysis, and open-chain derivative 17, analogous to 14 (Scheme IV).

In summary, in this report we describe some synthetically useful transformations of model cyclohexenediols obtained from 7-oxanorbornene derivatives. Application of this methodology to the preparations of valuable compounds will be the subject of further research.

Experimental Section

General Methods. All reactions were carried out under a positive pressure of dry argon with freshly distilled solvents under anhydrous conditions unless otherwise stated. Reagents and solvents were handled by means of standard syringe techniques. Benzene was distilled from calcium hydride; methylene chloride, hexane, and ethyl acetate were distilled from phosphorus pentoxide. Analytical TLC was carried out on 0.20-mm E. Merck precoated silica gel plates (60F-254) with detection by UV light or acidic vanillin solution. Column chromatography was performed with SDS or E. Merck 230–400-mesh silica gel. Infrared spectra were recorded on a Perkin-Elmer 681 spectrophotometer. ^{1}H NMR spectra were recorded on a Brüker AM-200 or a Varian VXR-300 instrument with $CDCl_3$ as the solvent. ^{13}C NMR spectra were measured on a Brüker AM-200, with $CDCl_3$ as the solvent, and were completely decoupled. In both ^{1}H and ^{13}C NMR, chemical shifts are reported in δ units downfield from tetramethylsilane. The following abbreviations are used to describe peak patterns when appropriate: br, broad; s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Optical rotations were measured in $CHCl_3$ at 20 °C with the sodium lamp of a Perkin-Elmer 241 polarimeter. Ozonolysis reactions were performed in a Fisher Ozone 500 apparatus.

Scheme IV



Starting materials. Compounds 2, 3, 8, 13, and 15 were prepared by previously described methods. See ref 9.

General Procedures for Epoxidation of Cyclohexene Derivatives. Method a: To a solution of the cyclohexenediol derivative in CH_2Cl_2 at 0 °C was added a solution of 1.3 equiv of *m*-CPBA (Merck) in CH_2Cl_2. The reaction mixture was then diluted with ethyl acetate and washed with 10% Na_2SO_3 and $NaHCO_3$ solutions. The aqueous layer was extracted with ethyl acetate. The combined organic extracts were washed with water and brine and dried over $MgSO_4$. Removal of the drying agent and evaporation of the solvent under reduced pressure led to the crude product, which was purified by column chromatography on silica gel (AcOEt/hexane or AcOEt/Et_2O as eluents). **Method b:** To a solution of the cyclohexenediol derivative in C_6H_6 at rt were added $VO(acac)_2$ (Aldrich) and a solution of 1.3 equiv of *t*-BuOOH (30% in H_2O, Merck) in C_6H_6. The reaction mixture was then diluted with ethyl acetate and 10% Na_2SO_3 solution; the organic layer was washed with brine and dried ($MgSO_4$). Removal of the drying agent and evaporation of the solvent under reduced pressure led to the crude product, which was purified by column chromatography on silica gel (AcOEt/hexane or AcOEt/Et_2O as eluents).

Synthesis of (1*S,3*S**,4*R**,5*R**,6*S**)-6-*n*-Butyl-4,5-epoxy-3-methylcyclohexane-1,3-diol (4) and (1*S**,3*S**,4*S**,5*S**,6*S**)-6-*n*-Butyl-4,5-epoxy-3-methylcyclohexane-1,3-diol (5). Method a:** From 150 mg of 2 (0.82 mmol) and 216 mg of *m*-CPBA (1.07 mmol) in anhyd CH_2Cl_2 was obtained a 9:1 mixture of epoxides 4 and 5. After column chromatography (AcOEt/Et_2O, 1:1), 133 mg of 4 (81%) and 5 (10%) were obtained both as pale yellow oil. **Method b:** From 92 mg of 2 (0.50 mmol), 0.09 mL of *t*-BuOOH (0.65 mmol, 30% H_2O), and a catalytic amount of $VO(acac)_2$ in C_6H_6 was obtained a 12:1 mixture of epoxides 4 and 5. After column chromatography (AcOEt/Et_2O, 1:1), 70 mg of 4 (70%) and 6 mg of 5 (6%) were isolated. The same procedure was used for optically pure (+)-2. Data for 4: R_f 0.31 (AcOEt/Et_2O, 1:1). $[\alpha]_D$ +120° (*c*, 6.00 $CHCl_3$); IR (film) ν_{max} 3400, 2950, 2920, 1370, 1140, 1100, 1040, 850 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, *J* = 6.8 Hz), 1.20–1.75 (m, 7H), 1.42 (s, 3H), 1.56 (dd, 1H, *J* = 13.8, 3.5 Hz), 1.68 (dd, 1H, *J* = 13.8, 8.5 Hz), 2.06 (m, 1H), 2.47 (br, 1H), 3.04 (d, 1H, *J* = 3.8 Hz), 3.29 (dd, 1H, *J* = 3.8, 1.6 Hz), 3.97 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 13.9, 22.9, 26.2, 27.6, 39.1, 41.4, 58.9, 60.1, 65.4, 68.6 ppm. Anal. Calcd for $C_{11}H_{20}O_3$: C, 71.69; H, 10.94. Found: C, 71.60; H, 11.00. Data for 5: R_f 0.23 (AcOEt/Et_2O, 1:1); IR ($CHCl_3$) ν_{max} 3400, 2950, 2920, 1370, 1100,

(17) Iranpoor N.; Bartork, I. M. *Tetrahedron Lett.* **1990**, *31*, 735–8.
(18) (a) Schreiber, S. L.; Claus, R. E.; Reagan, J. *Tetrahedron Lett.* **1982**, *23*, 3867–3870. (b) Hayes, R.; Wallace, T. W. *Tetrahedron Lett.* **1990**, *31*, 3355–3356.

1040, 940 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (t, 3H, J = 7.0 Hz), 1.18–1.60 (m, 6H), 1.47 (s, 3H), 1.52 (dd, 1H, J = 13.8, 2.8 Hz), 1.60–1.78 (m, 2H), 1.95–2.05 (m, 1H), 2.04 (ddd, 1H, J = 13.8, 6.8, 0.8 Hz), 3.08 (d, 1H, J = 3.8 Hz), 3.33 (tap, 1H), 3.88 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 13.9, 22.8, 27.0, 29.0, 29.1, 37.5, 42.6, 57.8, 60.1, 66.3, 68.9 ppm. Anal. Calcd for $C_{11}H_{20}O_3$: C, 71.69; H, 10.94. Found: C, 71.75; H, 10.80.

Synthesis of (1*S,3*R**,4*S**,5*S**,6*S**)-6-*n*-Butyl-4,5-epoxy-3-methylcyclohexane-1,3-diol (7) and (1*S**,3*R**,4*R**,5*R**,6*S**)-6-*n*-Butyl-4,5-epoxy-3-methylcyclohexane-1,3-diol (6). Method a:** From 150 mg of **3** (0.82 mmol) and 216 mg of *m*-CPBA (1.07 mmol) in anhyd CH_2Cl_2 was obtained a mixture of epoxides **7** and **6**. After column chromatography (hexane/AcOEt, 1:3), 90 mg of **7** (55%) and 18 mg of **6** (11%) were obtained, both as pale yellow oil. **Method b:** From 100 mg of **3** (0.55 mmol), 0.10 mL of *t*-BuOOH (0.70 mmol, 30% H_2O), and a catalytic amount of $VO(acac)_2$ in C_6H_6 was obtained only epoxide **7** (122 mg, 75%). The reaction time was 5 days. Data for **6**: R_f 0.44 (hexane/AcOEt, 1:3); IR ($CHCl_3$) ν_{max} 3360, 2960, 2925, 1375, 1140, 1035, 990, 920 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.0 Hz), 1.29–1.78 (m, 8H), 1.33 (s, 3H), 1.45 (dd, 1H, J = 14.6, 1.6 Hz), 1.72 (m, 1H), 1.84 (ddd, 1H, J = 14.6, 4.6, 1.6 Hz), 2.90 (dd, 1H, J = 3.8, 1.6 Hz), 3.06 (dd, 1H, J = 3.8, 1.3 Hz), 3.95 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.0, 22.7, 26.9, 29.3, 29.4, 37.4, 40.0, 55.3, 58.5, 67.8, 68.9 ppm. Anal. Calcd for $C_{11}H_{20}O_3$: C, 71.69; H, 10.94. Found: C, 71.50; H, 10.85. Data for **7**: R_f 0.17 (hexane/AcOEt, 1:3); IR ($CHCl_3$) ν_{max} 3400, 2980, 2925, 1380, 1160, 1105, 1060, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz), 1.30–1.50 (m, 4H), 1.38 (s, 3H), 1.42 (dd, 1H, J = 14.5, 2.3 Hz), 1.60–1.80 (m, 3H), 2.09 (ddd, 1H, J = 14.5, 4.9, 1.3 Hz), 2.62 (br, 1H), 2.82 (br, 1H), 3.22 (dd, 1H, J = 4.0, 1.4 Hz), 3.37 (ddd, 1H, J = 3.9, 1.3, 1.2 Hz), 3.89 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 13.8, 22.6, 28.1, 28.4, 28.9, 38.2, 42.8, 58.3, 59.9, 67.7, 67.8 ppm. Anal. Calcd for $C_{11}H_{20}O_3$: C, 71.69; H, 10.94. Found: C, 71.78; H, 10.80.

Synthesis of (1*S,2*R**,3*S**,4*S**,5*S**)-5-Benzyloxy-2-*n*-butyl-3,4-epoxy-5-methylcyclohexan-1-ol (10).** By means of method a, from 50 mg of **8** (0.18 mmol) and 48 mg of *m*-CPBA (0.23 mmol) in anhyd CH_2Cl_2 was obtained a 10:1 mixture of epoxides **10** and **9** (overall yield, 84%). From the crude reaction mixture was isolated compound **10** by column chromatography (hexane/AcOEt, 6:1). Data for **10**: R_f 0.31 (hexane/AcOEt, 6:1); IR ($CHCl_3$) ν_{max} 3440, 2960, 2925, 1375, 1160, 1105, 1060, 930 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.94 (t, 3H, J = 7.0 Hz), 1.20–2.06 (m, 7H), 1.53 (s, 3H), 1.78 (dd, 1H, J = 13.9, 3.3 Hz), 2.00 (ddd, 1H, J = 13.9, 6.3, 0.8 Hz), 2.28 (br, 1H), 3.23 (d, 1H, J = 3.8 Hz), 3.30 (ddd, 1H, J = 3.8, 2.3, 0.8 Hz), 3.92 (m, 1H), 4.54 (m, 2H), 7.26–7.36 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 24.8, 27.3, 29.3, 37.7, 39.0, 58.1, 59.4, 64.2, 66.4, 73.8, 127.4, 127.5, 128.4, 137.8 ppm. Anal. Calcd for $C_{18}H_{21}O_3$: C, 75.76; H, 7.42. Found: C, 75.80; H, 7.35.

Synthesis of (1*R,2*S**,4*S**,5*S**,6*S**)-5-*n*-Butyl-6-methoxy-2-methylcyclohexane-1,2,4-triol (11).** To a solution of 80 mg of **4** (0.40 mmol) in anhyd methanol (1.5 mL) was added 20 mg (16 mmol % epoxide) of DDQ. The reaction mixture was refluxed for 2 h. Then the mixture was washed with ether and filtered, and the solvent was evaporated under reduced pressure to afford the crude product, which was purified by column chromatography on silica gel (AcOEt/Et_2O, 1:1). The pure product (59 mg, 85%) was obtained as a pale yellow oil. Data for **11**: R_f 0.17 (Et_2O/AcOEt, 1:1); IR ($CHCl_3$) ν_{max} 3400, 2910, 2860, 1650, 1350, 1310, 1120, 1070, 1000, 960, 850, 810 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90 (t, 3H, J = 7.0 Hz), 1.30 (s, 3H), 1.34–1.40 (m, 6H), 1.64 (dd, 1H, J = 13.5, 10.8 Hz), 1.85 (dd, 1H, J = 13.5, 4.2 Hz), 2.26 (br, 1H), 3.36 (dd, 1H, J = 8.5, 3.9 Hz), 3.39 (s, 3H), 3.43 (d, 1H, J = 8.5 Hz), 4.09 (m, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 14.0, 23.3, 27.7, 40.7, 57.1, 67.7, 70.8, 73.2, 82.3 ppm. Anal. Calcd for $C_{12}H_{24}O_4$: C, 62.03; H, 10.41. Found: C, 62.13; H, 10.30. In the same way, enantiomerically pure (+)-**11** was prepared from (+)-**4**; $[\alpha]_D$ +98° (*c*, 6.00, $CHCl_3$). The diacetate of **11** (**12**) was prepared as follows: To a solution of 60 mg of **11** (0.26 mmol) in 3 mL of Ac_2O (freshly distilled from $CaCl_2$) was added 0.12 mL (1.56 mmol) of anhyd pyridine. The reaction mixture was stirred for 5 h at rt. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel (AcOEt/Et_2O, 1:1). Irradiation experiments led to the assignments of all the ^{1}H NMR signals of **12**. Data for **12**: R_f 0.45 (AcOEt/Et_2O, 1:1); ^{1}H NMR ($CDCl_3$) δ 0.84 (t, 3H, J = 6.3 Hz), 1.13 (s, 3H), 1.24–1.33 (m, 7H), 1.68 (dd, 1H, J = 14.1, 10.5 Hz), 1.85 (dd, 1H, J = 14.1, 4.2 Hz), 1.99 (s, 3H), 2.10 (s, 3H), 2.45 (br, 1H), 3.27 (s, 3H), 3.51 (dd, 1H, J = 10.0, 4.9 Hz), 4.82 (d, 1H, J = 10.0 Hz), 5.13 (m, 1H) ppm.

General Procedure for the Ozonolysis Reactions. Ozone was bubbled into a stirred -78 °C solution of the cyclohexene derivative (**13** or **15**) in MeOH and CH_2Cl_2 containing $NaHCO_3$. When the solution acquired a pale blue coloration, the addition of ozone was stopped, and the excess ozone was removed by passing argon through the solution until it became colorless. The mixture was allowed to reach rt, diluted with C_6H_6, filtered, and evaporated under reduced pressure to a volume of ca. 1 mL. Then CH_2Cl_2 was added, and, with stirring under argon, the solution was cooled to 0 °C and treated with pyridine and acetic anhydride. After 2 h at rt, the reaction mixture was diluted with ether; washed successively with 0.1 M HCl, water, Na_2CO_3, and water, dried, and evaporated under reduced pressure. The crude product was purified by column chromatography over Florisil (AcOEt/hexane, 1:3).

Ozonolysis of 13. From 160 mg of **13** (0.6 mmol) in MeOH/CH_2Cl_2 (1:4, 4 mL) containing $NaHCO_3$ (277 mg, 3.3 mmol) were added CH_2Cl_2 (10 mL), pyridine (197 mg, 2.49 mmol), and acetic anhydride (118 mg, 3 mmol). Yield of **14**: 132 mg (65%). Data for **14**: R_f 0.25 (hexane/AcOEt, 3:1); IR ($CHCl_3$) ν_{max} 2960, 2920, 1700, 1450, 1380, 1240, 1220, 1180, 1100, 1010 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3H, J = 7.0 Hz), 1.23–1.39 (m, 5H), 1.41 (s, 3H), 1.52–1.60 (m, 1H), 1.70 (dd, 1H, J = 13.1, 9.5 Hz), 2.09 (s, 3H), 2.30 (dd, 1H, J = 13.1, 6.1 Hz), 2.47 (ddd, 1H, J = 10.8, 9.0, 3.9 Hz), 3.70 (s, 3H), 4.52 (s, 2H; m, 1H), 6.22 (s, 1H), 7.32 (m, 5H) ppm; ^{13}C NMR ($CDCl_3$) δ 13.8, 17.1, 21.4, 22.6, 28.2, 29.4, 39.7, 51.6, 52.8, 65.2, 81.2, 85.4, 99.1, 127.2, 27.5, 128.3, 138.3, 169.8, 174.2 ppm. Anal. Calcd for $C_{21}H_{29}O_5$: C, 69.78; H, 8.09. Found: C, 69.65; H, 8.00.

Ozonolysis of 15. From 100 mg of **15** (0.34 mmol) inMeOH/CH_2Cl_2 (1:4, 4 mL) containing $NaHCO_3$ (150 mg, 1.78 mmol) were added CH_2Cl_2 (10 mL) pyridine (91 mg, 1.16 mmol), and acetic anhydride (55 mg, 0.6 mmol). In this way, 120 mg of a mixture of **16** and **17** was obtained. Compound **16** was separated by column chromatogrphy on Florisil, giving 70 mg (60%) as a pale yellow oil. Spectroscopic data of **17** were read from the ^{1}H and ^{13}C NMR spectra of the reaction crude. Data for **16**: R_f 0.35 (hexane/AcOEt, 2:1); IR ($CHCl_3$) ν_{max} 2920, 1780, 1740, 1460, 1430, 1380, 1270, 1130, 1110, 1090, 1060, 1040, 990 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.04 (d, 3H, J = 7.2 Hz), 1.17 (s, 3H), 1.94 (dd, 1H, J = 15.5, 6.6 Hz), 2.05 (s, 3H), 2.10 (s, 3H), 2.19 (d, 1H, J = 15.5 Hz), 2.37 (m, 1H), 5.06 (d, 1H, J = 4.5 Hz), 5.12 (dt, 1H, J = 6.6, 1.5 Hz), 9.53 (d, 1H, J = 1.5 Hz) ppm; ^{13}C NMR ($CDCl_3$) δ 10.9, 20.5, 21.2, 23.4, 33.9, 34.8, 66.3, 95.7, 100.2, 167.9, 171.1, 205.1 ppm. Anal. Calcd for $C_{12}H_{17}O_4$: C, 63.98; H, 7.61. Found: C, 63.75; H, 7.52. Data for **17**: R_f 0.22 (hexane/AcOEt, 2:1); ^{1}H NMR ($CDCl_3$) δ 1.17 (d, 3H, J = 7.0 Hz), 1.60 (s, 3H), 2.02 (s, 3H), 2.08 (d, 1H, J = 5.8 Hz), 2.17 (s, 3H), 2.76 (dd, 1H, J = 5.8, 4.8 Hz), 2.91 (m, 1H), 3.70 (s, 3H), 5.48 (m, 1H), 9.50 (s, 1H) ppm; ^{13}C NMR ($CDCl_3$) δ 12.2, 14.2, 30.3, 42.1, 44.5, 51.9, 60.4, 68.9, 70.3, 170.0, 171.1, 173.4, 205.0 ppm.

Acknowledgment. This research was supported by the CICYT (Ministerio de Educación y Ciencia, Grant No. PB 90-0035) and Pharma Mar S. A.