26. The Chemistry of Thujone

Part XIV[1])

Synthesis of Biologically Active Aryl Terpenoid Analogues

by **Chris Carvalho, William R. Cullen, Michael D. Fryzuk, Helen Jacobs, Brian R. James, James P. Kutney*, Krystyna Piotrowska,** and **Vinod K. Singh**

Department of Chemistry, University of British Columbia, 2036 Main Mall, University Campus, Vancouver, B.C. V6T 1Y6, Canada

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Employing thujone-derived intermediates, a series of achiral (**9a–d**; *Scheme 1*) and chiral (**11b** and **11d**; *Scheme 2*) terpene analogues related to the biologically active 'terpenoid' hybrids have been prepared. The stereochemistry of the key epoxidation reaction was established by correlation of the product **11b** with the previously reported alcohol (*R*)-**20** of known absolute configuration *(Scheme 3)*.

Introduction. – In continuing our studies with thujone as a starting material for the syntheses of various natural products and related biologically active compounds, we have considered the syntheses of terpene analogues closely related to the family of active aromatic 'terpenoid hybrids' studied by *Bowers* [2] and others. *Bowers* [2] had shown earlier that epoxidation increases the biological activity of several farnesyl derivatives. Subsequently, he showed that activity was significantly increased when the terpenoid chain was shortened by one isoprene unit. Based on previously established chemistry of thujone [3], it was appropriate to extend our studies toward the synthesis of thujone-derived terpenoid analogues with structural features similar to the above mentioned family of compounds.

Results and Discussion. – The unsaturated acid **4** readily available from thujone (**1**) *via* **2** and **3** [1] [3] was reduced to the alcohol **5** with $LiAlH_4$. The latter, upon reaction with PBr_3 afforded the allylic bromide **6**. In more recent studies, the conversion to this bromide could be more conveniently accomplished by the use of hexamethylphosphorus triamide (HMPT) and carbon tetrabromide [4].

The aryl ether functionality, shown by *Bowers* to be important in potentiating biological activity, could now be introduced by nucleophilic displacement of the bromide function in **6** by appropriately substituted phenoxide ions. Thus, **6** was treated with phenoxide ions derived from 4-ethylphenol, 4-propylphenol, and benzo[*d*][1,3]dioxol-5-ol to provide the ethers **7a–c**. The anion of 4-ethylbenzyl alcohol, prepared from the alcohol and NaH, could be employed to afford **7d**.

As noted above, *Bowers'* observations that epoxidation increased biological activity within a structurally similar series of compounds stimulated our investigation directed

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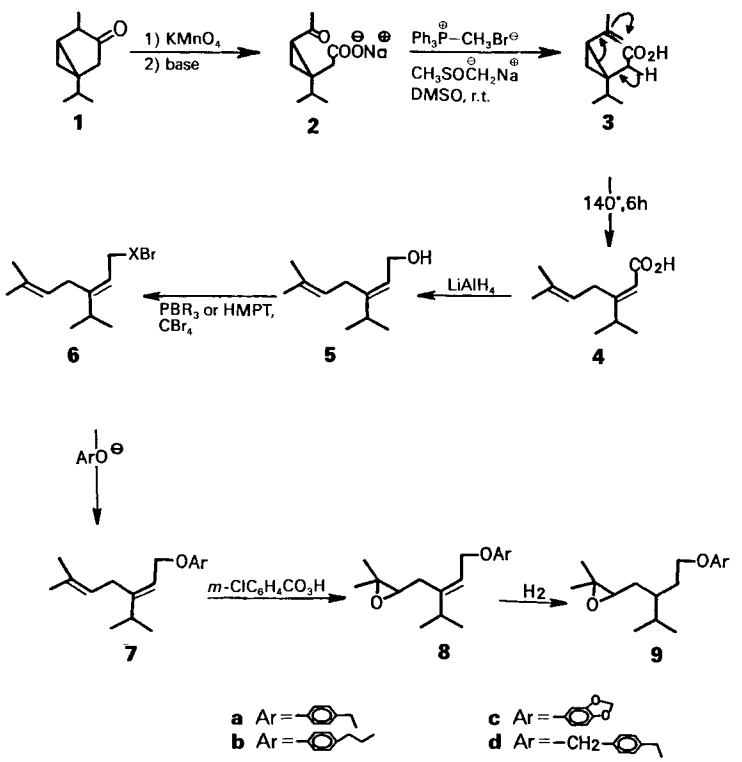
Scheme 1

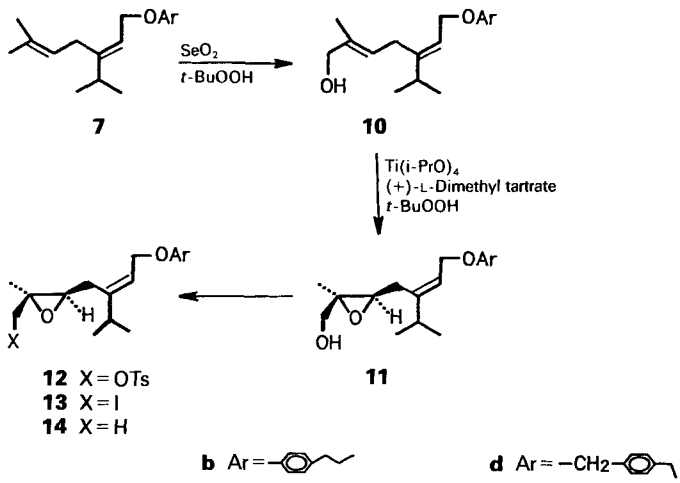


toward selective epoxidation of the terminal double bond in the isoprenoid aryl ethers **7a–d**. Epoxidation with *m*-chloroperbenzoic acid at 0° afforded the desired epoxides **8a–d** which were hydrogenated to the dihydroepoxides **9a–d**.

It has been established in various areas of biologically active compounds that only one enantiomer is responsible for the biological action, and it was, therefore, of interest to determine whether appropriate modifications in the synthetic route outlined in *Scheme 1* could be developed so as to provide the corresponding chiral epoxides. The most attractive route involved application of the *Sharpless* epoxidation. For this purpose, allylic hydroxylation of one of the terminal Me groups of **7** was required. The reaction of **7b** and **7d** with selenium dioxide/*tert*-butyl hydroperoxide according to the *Sharpless* procedure [6] afforded the desired alcohols **10b** and **10d**, respectively. Epoxidation of **10b** and **10d** with titanium tetraisopropoxide (+)-L-dimethyl tartrate/*tert*-butyl hydroperoxide yielded the chiral epoxyalcohols **11b** and **11d**, respectively. Chromatographic separation on a *Pirkle* column suggested an enantiomeric excess of 87% for **11b**. Subsequent transformations *via* **12b,d** and **13b,d** yielded **14b** and **14d**, the enantiomers of racemic **8b** and **8d**, respectively.

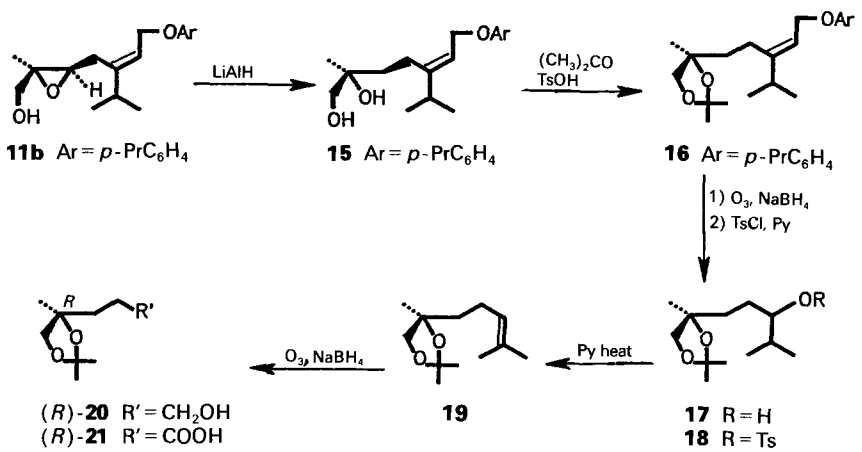
The absolute configuration of **11b** and, in turn, **11d** was established by correlating **11b** with an alcohol **20** of established configuration [7]. Thus, **11b** was reduced with $LiAlH_4$

Scheme 2



and the resulting diol **15** converted to the acetonide **16**. Ozonolysis of the olefinic linkage provided the expected ketone, which, without isolation, was directly reduced to the alcohol **17**. Conversion of the latter to the olefin **19** was achieved *via* the intermediate tosylate **18** which spontaneously underwent elimination on heating (110°, 4 h). The final step was achieved by ozonolysis under reductive conditions (O_3, $NaBH_4$). The resulting alcohol was then compared with the data provided by *Mori* [7] for both the (*R*) and (*S*) stereoisomers **20**[2]). These data ($[\alpha]_D$, IR, NMR) established the identity of our product as (*R*)-**20**.

Scheme 3



[2]) We are grateful to Professor *K. Mori*, University of Tokyo, for having kindly provided us with the data of (*R*)- and (*S*)-**20**.

Further confirmation of the chirality in (*R*)-**20** was obtained, when an authentic sample of (*S*)-**20** could be prepared from the chiral acid (*R*)-**21**[3]) [8] by $LiAlH_4$ reduction. The spectral data of (*S*)-**20** thus obtained indicated complete identity with (*R*)-**20**, except for optical rotation.

With both the chiral and achiral series in hand, extensive biological evaluation will be initiated. The biological data will be presented elsewhere.

Financial aid from the *Natural Sciences and Engineering Research Council of Canada* is gratefully acknowledged. We also wish to thank *Ciba-Geigy*, Agrochemicals Division, Basel, Switzerland, for their cooperation in performing the biological screening.

Experimental Part

General. All reagents and solvents were recrystallized or distilled prior to use. Column chromatography: *Merck* silica gel *60* (70–230 mesh and 230–400 mesh); FC = flash chromatography. Prep. and anal. TLC: *Merck* silica gel GF_{254}. B.p.: uncorrected. $[\alpha]_D$: *Perkin-Elmer-141* polarimeter, path length 10 cm. UV spectra (λ_{max} (ε or log ε) in nm): *Cary-15* spectrophotometer. IR spectra (cm^{-1}): *Perkin-Elmer-710* or *457* spectrophotometer, samples as neat film. ^{1}H-NMR spectra (δ in ppm, J in Hz): *Bruker WH-400, Bruker WP-80, Varian XL-100,* or *Nicolet-Oxford H-270* instruments; in $CDCl_3$ with TMS as internal standard. MS (*m/z* (% rel. int.)): low-resolution MS on *AEI-MS-902* or *Atlas-CH-4B* spectrometer; high-resolution MS on *AEI-MS-50* spectrometer. Microanalysis were performed by Mr. *P. Borda,* Microanalytical Laboratory, University of British Columbia.

3-Isopropyl-6-methylhepta-2,5-dien-1-ol (**5**). To a stirred slurry of $LiACH_4$ (0.6 g, 16.5 mmol) in dry Et_2O (30 ml), a soln. of **4** (3.0 g, 16.5 mmol) in Et_2O (25 ml) was added at such a rate that the Et_2O started refluxing. The mixture was further stirred for 2 h, then quenched with wet Et_2O, acidified with 10% HCl soln., and filtered through *Celite*. The org. layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated to give **5** as an oil (2.7 g, 98%) which was distilled at 70–75°/0.4 Torr. IR: 3600, 3430, 1655. ^{1}H-NMR: 1.00 (*d*, J = 6, 6 H); 1.15 (br. *s*, 1 H, exchangeable with D_2O); 1.68 (br. *s*, 6 H); 2.26 (*m*, 1 H); 2.76 (*d*, J = 7, 2 H); 4.15 (*d*, J = 7, 2 H); 4.99 (*t*, J = 7, 1 H); 5.42 (*t*, J = 7, 1 H). MS: 168 (M^+), 150, 135, 112, 107, 41. Anal. calc. for $C_{11}H_{20}O$: C 78.51, H 11.98; found: C 78.26, H 11.90.

3-Isopropyl-6-methylhepta-2,5-dien-1-yl Bromide (**6**). *a)* A cooled (0°) soln. of **5** (2.2 g, 13.1 mmol) and pyridine (3.3 g, 43.2 mmol) in dry Et_2O (30 ml) was treated with PBr_3 (3.9 g, 14.4 mmol) in Et_2O (10 ml). The mixture was stirred at 0° for 1 h, poured into ice/H_2O and extracted with Et_2O. The Et_2O phase was washed with H_2O and brine, dried ($MgSO_4$), and evaporated: oily **6** (2.3 g, 76%) that distilled at *ca.* 50°/4 Torr. IR: 1651. ^{1}H-NMR: 1.03 (*d*, J = 7, 6 H); 1.70 (*s*, 6 H); 2.30 (*sept.*, J = 7, 1 H); 2.84 (*d*, J = 7, 2 H); 4.08 (*d*, J = 8.5, 2 H); 5.10 (*t*, J = 7, 1 H); 5.56 (*t*, J = 8.5, 1 H). MS: 232, 231 (M^+), 152, 151, 69. Anal. calc. for $C_{11}H_{19}Br$: C 57.15, H 8.28; found: C 57.30, H 8.30.

b) To a soln. of **5** (100 mg, 0.60 mmol) and CBr_4 (335 mg, 1.01 mmol) in anh. THF (10 ml) was added dropwise a soln. of HMPT (200 mg, 1.23 mmol) in anh. THF while maintaining the temp. at 5°. The turbid mixture was stirred at 5° for 1 additional h. This mixture was then diluted with H_2O and extracted with Et_2O. The Et_2O layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The crude mixture was purified through a short silica-gel column (hexane): pure **6** (104 mg, 76%).

1-[(4-Ethylphenyl)oxy]-3-isopropyl-6-methylhepta-2,5-diene (**7a**). Bromide **6** (360 mg, 1.56 mmol) was added to a slurry of finely ground KOH (90 mg, 1.60 mmol) and 4-ethylphenol (190 mg, 1.56 mmol) in dry THF (25 ml). The turbid mixture was stirred at r.t. for 18 h. Then, most of the THF was distilled off, the residue diluted with H_2O and extracted with Et_2O, the combined org. phase washed with H_2O and brine, dried ($MgSO_4$), and evaporated, and the oily residue purified by FC (hexane/AcOEt 95:5): pure **7a** (366 mg, 87%). B.p. 100°/5 Torr. IR: 1660, 1615, 1515. ^{1}H-NMR: 1.05 (*d*, J = 7, 6 H); 1.22 (*t*, J = 8, 3 H); 1.67 (*s*, 3 H); 1.70 (*s*, 3 H); 2.31 (*sept.*, J = 7, 1 H); 2.60 (*q*, J = 8, 2 H); 2.82 (*d*, J = 7.5, 2 H); 4.55 (*d*, J = 6, 2 H); 5.04 (*t*, J = 7.5, 1 H); 5.55 (*t*, J = 6, 1 H); 6.83 (*d*, J = 9, 2 H); 7.09 (*d*, J = 9, 2 H). MS: 272 (M^+), 151, 122, 69. Anal. calc. for $C_{17}H_{28}O$: C 83.77, H 10.36; found: C 83.58, H 10.29.

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[3]) We thank Dr. *N. Cohen, F. Hoffmann-La Roche & Co. Ltd.,* for having kindly provided us with an authentic sample of (*R*)-**21**.

3-Isopropyl-6-methyl-1-[(4-propylphenyl)oxy]hepta-2,5-diene (**7b**). As for **7a**, with **6** (2.31 g, 10 mmol), KOH (600 mg, 10.17 mmol), and 4-propylphenol (1.5 g, 11.02 mmol) in dry THF (50 ml): pure **7b** (2.53 g, 89%) as a colorless oil. B.p. 120°/4 Torr. IR: 1665, 1610, 1510, 1462, 1233. ^{1}H-NMR: 0.94 (*t*, *J* = 7.5, 3 H); 1.04 (*d*, *J* = 7, 6 H); 1.51 (*m*, 2 H); 1.66 (*s*, 3 H); 1.68 (*s*, 3 H); 2.30 (*sept.*, *J* = 7, 1 H); 2.51 (*t*, *J* = 7.5, 2 H); 2.80 (*d*, *J* = 7, 2 H); 4.51 (*d*, *J* = 6, 2 H); 4.99 (*t*, *J* = 7, 1 H); 5.47 (*t*, *J* = 6, 1 H); 6.81 (*d*, *J* = 9, 2 H); 7.06 (*d*, *J* = 9, 2 H). MS: 286 (M^+), 151, 136, 107, 69. Anal. calc. for $C_{20}H_{30}O$: C 83.86, H 10.56; found: C 84.00, H 10.60.

1-[(Benzo[d][1,3]dioxol-5-yl)oxy]-3-isopropyl-6-methylhepta-2,5-diene (**7c**). As for **7a**, with **6** (1.16 g, 5.02 mmol), benzo[*d*][1,3]dioxol-5-ol (690 mg, 5.02 mmol), and KOH (281 mg, 5.02 mmol) in anh. dimethoxyethane (50 ml): **7c** (1.15 g, 80%) as a colorless oil. B.p. 135°/4 Torr. IR: 1631, 1506, 1489, 1186. ^{1}H-NMR: 1.00 (*d*, *J* = 7, 6 H); 1.6 (*s*, 6 H); 2.2 (*sept.*, *J* = 7, 1 H); 2.78 (*d*, *J* = 7, 2 H); 4.45 (*d*, *J* = 7.5, 2 H); 5.0 (*t*, *J* = 7, 1 H); 5.46 (*t*, *J* = 7.5, 1 H); 5.94 (*s*, 2 H); 6.32 (*dd*, *J* = 8.5, 2.5, 1 H); 6.51 (*d*, *J* = 2.5, 1 H); 6.71 (*d*, *J* = 8.5, 1 H). MS: 288 (M^+), 151, 138. Anal. calc. for $C_{18}H_{24}O_3$: C 74.97, H 8.39; found: C 75.31, H 8.38.

1-[(4-Ethylbenzyl)oxy]-3-isopropyl-6-methylhepta-2,5-diene (**7d**). To NaH (50% dispersion (790 mg, 16.46 mmol) washed repeatedly with dry pentane) was added 4-ethylbenzyl alcohol (530 mg, 3.90 mmol) in THF (20 ml) followed by a soln. of **6** (905 mg, 3.91 mmol) in THF (15 ml). The suspension was stirred at r.t. for 5 h. Usual workup followed by FC as above afforded **7d** (770 mg, 68%). B.p. 110°/4 Torr. IR: 1665, 1610, 1512, 1460, 1085. ^{1}H-NMR: 1.02 (*d*, *J* = 7, 6 H); 1.23 (*t*, *J* = 7, 3 H); 1.61 (*s*, 3 H); 1.67 (*s*, 3 H); 2.26 (*sept.*, *J* = 7, 1 H); 2.64 (*q*, *J* = 7, 2 H); 2.73 (*d*, *J* = 7, 2 H); 3.93 (*d*, *J* = 6.5, 2 H); 4.47 (*s*, 2 H); 4.96 (*t*, *J* = 7, 1 H); 5.39 (*t*, *J* = 6.5, 1 H); 7.18 (*d*, *J* = 8, 2 H); 7.26 (*d*, *J* = 8, 2 H). MS: 286 (M^+), 150, 136, 119, 107. Anal. calc. for $C_{20}H_{30}O$: C 83.86, H 10.56; found: C 84.00, H 10.57.

5,6-Epoxy-1-[(4-ethylphenyl)oxy]-3-isopropyl-6-methylhept-2-ene (**8a**). At 0°, **7a** (366 mg, 1.35 mmol) and *m*-$ClC_6H_4CO_3H$ (290 mg, 1.68 mmol) were stirred in CH_2Cl_2 for 1 h. The mixture was washed with 5% aq. $NaHCO_3$ soln. and brine, dried ($MgSO_4$), and evaporated. The mixture was chromatographed (petroleum ether/AcOEt 97:3): **8a** (331 mg, 85%) as a colorless oil. B.p. 133°/10 Torr. IR: 1657, 1612, 1513, 1226, 897. ^{1}H-NMR: 1.05 (*d*, *J* = 7, 6 H); 1.21 (*t*, *J* = 7, 3 H); 1.31 (*s*, 3 H); 1.34 (*s*, 3 H); 2.31 (*dd*, *J* = 16, 6, 1 H); 2.44 (*dd*, *J* = 16, 6, 1 H); 2.39 (*sept.*, *J* = 7, 1 H); 2.60 (*q*, *J* = 7, 2 H); 2.74 (*dd*, *J* = 6, 6, 1 H); 4.57 (*m*, 2 H); 5.67 (*t*, *J* = 6, 1 H); 6.84 (*d*, *J* = 8, 2 H); 7.10 (*d*, *J* = 8, 2 H). MS: 288 (M^+), 167, 122, 71. Anal. calc. for $C_{19}H_{28}O_2$: C 79.12, H 9.79; found: C 78.95, H 9.66.

5,6-Epoxy-3-isopropyl-6-methyl-1-[(4-propylphenyl)oxy]hept-2-ene (**8b**). As for **8a**, with **7b** (634 mg, 2.22 mmol), *m*-$ClC_6H_4CO_3H$ (479 mg, 2.78 mmol), and CH_2Cl_2 (30 ml): **8b** (620 mg, 92%) which distilled at 123°/4 Torr. IR: 1661, 1618, 1516, 1469, 1241. ^{1}H-NMR: 0.93 (*t*, *J* = 8, 3 H); 1.09 (*d*, *J* = 7, 6 H); 1.24 (*s*, 3 H); 1.26 (*s*, 3 H); 1.61 (*sext.*, *J* = 8, 2 H); 2.30 (*dd*, *J* = 14, 6, 1 H); 2.36 (*sept.*, *J* = 7, 1 H); 2.42 (*dd*, *J* = 14, 6, 1 H); 2.52 (*t*, *J* = 8, 2 H); 2.72 (*dd*, *J* = 6, 6, 1 H); 4.55 (*m*, 2 H); 5.64 (*t*, *J* = 6, 1 H); 6.82 (*d*, *J* = 9, 2 H); 7.06 (*d*, *J* = 9, 2 H). MS: 302 (M^+), 167, 136, 107, 43. Anal. calc. for $C_{20}H_{30}O_2$: C 79.42, H 10.00; found: C 79.60, H 9.90.

1-[(Benzo[d][1,3]dioxol-5-yl)oxy]-5,6-epoxy-3-isopropyl-6-methylhept-2-ene (**8c**). As for **8a**, with **7c** (319 mg, 1.11 mmol) and *m*-$ClC_6H_4CO_3H$ (239 mg, 1.39 mmol) in CH_2Cl_2. The pure **8c** (286 mg, 85%) was distilled at 180°/4 Torr. IR: 1630, 1505, 1181. ^{1}H-NMR: 1.07 (*d*, *J* = 7, 6 H); 1.29 (*s*, 3 H); 1.32 (*s*, 3 H); 2.28 (*dd*, *J* = 14, 9, 1 H); 2.40 (*m*, 2 H); 2.70 (*dd*, *J* = 6, 6, 1 H); 4.49 (*m*, 2 H); 5.60 (*t*, *J* = 7, 1 H); 5.90 (*s*, 2 H); 6.33 (*dd*, *J* = 9, 3, 1 H); 6.50 (*d*, *J* = 3, 1 H); 6.68 (*d*, *J* = 9, 1 H). MS: 304 (M^+), 167, 138, 71, 43. Anal. calc. for $C_{18}H_{24}O_4$: C 71.02, H 7.95; found: C 70.23, H 8.13.

5,6-Epoxy-1-[(4-ethylbenzyl)oxy]-3-isopropyl-6-methylhept-2-ene (**8d**). As for **8a**, with **7d** (500 mg, 1.75 mmol), *m*-$ClC_6H_4CO_3H$ (378 mg, 2.19 mmol), and CH_2Cl_2 (20 ml): **8d** (378 mg, 71%). B.p. 115°/4 Torr. IR: 1655, 1508, 1460, 1105. ^{1}H-NMR: 1.06 (*d*, *J* = 7, 6 H); 1.22 (*t*, *J* = 7, 3 H); 1.25 (*s*, 3 H); 1.26 (*s*, 3 H); 2.22 (*dd*, *J* = 14, 6, 1 H); 2.30 (*sept.*, *J* = 7, 1 H); 2.33 (*dd*, *J* = 14, 6, 1 H); 2.77 (*q*, *J* = 7, 2 H); 2.80 (*t*, *J* = 6, 1 H); 4.04 (*m*, 2 H); 4.47 (*s*, 2 H); 5.52 (*t*, *J* = 6.5, 1 H); 7.15 (*d*, *J* = 8, 2 H); 7.24 (*d*, *J* = 8, 2 H). MS: 302 (M^+), 167, 135, 119. Anal. calc. for $C_{20}H_{30}O_2$: C 79.42, H 10.00; found: C 79.53, H 9.95.

5,6-Epoxy-1-[(4-ethylphenyl)oxy]-3-isopropyl-6-methylheptane (**9a**). A soln. of **8a** (100 mg) in AcOEt (4 ml) was stirred at r.t. with *Adam*'s catalyst (3.0 mg) under H_2 at 1 atm for 1 h. The suspension was filtered and the solvent evaporated: **9a** (100%). B.p. *ca.* 140°/4 Torr. IR: 1610, 1510, 1460, 1225. ^{1}H-NMR: 0.91 (*d*, *J* = 6, 6 H); 1.21 (*t*, *J* = 7.5, 3 H); 1.53 (*s*, 3 H); 1.56 (*s*, 3 H); 1.74 (*m*, 6 H); 2.59 (*q*, *J* = 7.5, 2 H); 2.72 (*t*, *J* = 6, 1 H); 4.00 (*t*, *J* = 6, 2 H); 6.81 (*d*, *J* = 8.5, 2 H); 7.11 (*d*, *J* = 8.5, 2 H). MS: 290 (M^+), 169, 122, 107, 71, 55, 43. HR-MS: 290.2250 ($C_{19}H_{30}O_2$, calc. 290.2238).

5,6-Epoxy-3-isopropyl-6-methyl-1-[(4-propylphenyl)oxy]heptane (**9b**). Hydrogenation of **8b** (170 mg) in AcOEt (5 ml) in presence of *Adam*'s catalyst (4 mg) gave **9b** (164 mg, 96%). B.p. 128°/4 Torr. IR: 1612, 1510, 1465, 1230. ^{1}H-NMR: 0.89 (*d*, *J* = 7, 6 H); 0.92 (*t*, *J* = 7, 3 H); 1.27 (*s*, 3 H); 1.31 (*s*, 3 H); 1.76 (*m*, 8 H); 2.53 (*t*, *J* = 7,

2 H); 2.77 (*t*, *J* = 6, 1 H); 4.00 (*t*, *J* = 6, 2 H); 6.82 (*d*, *J* = 9, 2 H); 7.10 (*d*, *J* = 9, 2 H). MS: 304 (M^+), 169, 136, 107, 71, 69, 55, 43. Anal. calc. for $C_{20}H_{32}O_2$: C 78.90, H 10.59; found: C 79.00, H 10.60.

*1-[(Benzo[*d*][1,3]dioxol-5-yl)oxy]-5,6-epoxy-3-isopropyl-6-methylheptane* (**9c**). Hydrogenation of **8c** (100 mg) as described above gave **9c** (100%). B.p. 170°/4 Torr. IR: 1627, 1500, 1484, 1184. ^{1}H-NMR: 0.90 (*d*, *J* = 8, 6 H); 1.26 (*s*, 3 H); 1.30 (*s*, 3 H); 1.68 (*m*, 6 H); 2.75 (*t*, *J* = 6, 1 H); 3.93 (*t*, *J* = 6, 2 H); 5.90 (*s*, 2 H); 6.30 (*dd*, *J* = 9, 3, 1 H); 6.50 (*d*, *J* = 3, 1 H); 6.70 (*d*, *J* = 9, 1 H). MS: 306 (M^+), 169, 138. HR-MS: 306.1832 ($C_{18}H_{26}O_4$, calc. 306.1824).

5,6-Epoxy-1-[(4-ethylbenzyl)oxy]-3-isopropyl-6-methylheptane (**9d**). Hydrogenation of **9c** (50 mg) over *Adam*'s catalyst (92 mg) in AcOEt gave **9d** (100%). B.p. 130°/4 Torr. IR: 1512, 1462, 1092. ^{1}H-NMR: 0.97 (*d*, *J* = 7, 6 H); 1.24 (*t*, *J* = 8, 3 H); 1.24 (*s*, 3 H); 1.29 (*s*, 3 H); 1.67 (*m*, 6 H); 2.66 (*q*, *J* = 8, 2 H); 2.74 (*m*, 1 H); 3.52 (*t*, *J* = 6, 2 H); 4.48 (*s*, 2 H); 7.15 (*d*, *J* = 8, 2 H); 7.29 (*d*, *J* = 8, 2 H). MS: 304 (M^+), 169, 135, 127, 119. Anal. calc. for $C_{20}H_{32}O_2$: C 78.90, H 10.59; found: C 78.76, H 10.60.

5-Isopropyl-2-methyl-7-[(4-propylphenyl)oxy]hepta-2,5-dien-1-ol (**10b**). A suspension of SeO_2 (390 mg, 3.51 mmol), **7b** (1.0 g, 3.50 mmol), and 3M anh. *t*-BuOOH/toluene (2.3 ml, 7.0 mmol) in dry CH_2Cl_2 (20 ml) was stirred for 1 h (N_2). The mixture was diluted with Et_2O and washed 3× with H_2O. The org. phase was then stirred with $NaBH_4$ (1.0 g, dissolved in 5.0 ml of MeOH) for ½ h and then poured into H_2O. The org. layer was washed with brine, dried ($MgSO_4$), and evaporated. The yellow oil was purified by FC (petroleum ether/AcOEt 9:1): **10b** (460 mg, 62% based on recovered **7b**) as a viscous liquid. IR: 3260. ^{1}H-NMR: 0.92 (*t*, *J* = 8, 3 H); 1.04 (*d*, *J* = 8, 6 H); 1.25 (*s*, 1 H, exchangeable with D_2O); 1.60 (*m*, 2 H); 1.71 (*s*, 3 H); 2.30 (*sept.*, *J* = 8, 1 H); 2.51 (*t*, *J* = 8, 2 H); 2.86 (*d*, *J* = 7, 2 H); 3.97 (*s*, 2 H); 4.49 (*d*, *J* = 6, 2 H); 5.29 (*t*, *J* = 7, 1 H); 5.51 (*t*, *J* = 6, 1 H); 6.81 (*d*, *J* = 9, 2 H); 7.06 (*d*, *J* = 9, 2 H). MS: 302 (M^+), 166, 136, 135, 107. HR-MS: 302.2248 ($C_{20}H_{30}O_2$, calc. 302.2246). Anal. calc. for $C_{20}H_{30}O_2$: C 79.40, H 10.00; found: C 79.40, H 9.90.

7-[(4-Ethylbenzyl)oxy]-5-isopropyl-2-methylhepta-2,5-dien-1-ol (**10d**). As for **10b**, with SeO_2 (776 mg, 7.0 mmol), **7d** (2.0 g, 7.0 mmol), and anh. *t*-BuOOH in CH_2Cl_2: **10d** (912 mg, 51%) as a viscous liquid. IR: 3400. ^{1}H-NMR: 1.02 (*d*, *J* = 6.84, 6 H); 1.23 (*t*, *J* = 7.6, 3 H); 1.66 (*s*, 3 H); 2.26 (*sept.*, *J* = 6.8, 1 H); 2.64 (*q*, *J* = 7.61, 2 H); 2.78 (*d*, *J* = 6.85, 2 H); 3.96 (*s*, 2 H); 4.02 (*d*, *J* = 6.53, 2 H); 4.47 (*s*, 2 H); 5.25 (*m*, 1 H); 5.43 (*t*, *J* = 6.5, 1 H); 7.17 (*d*, *J* = 8.14, 1 H); 7.25 (*d*, *J* = 8.1, 1 H). MS: 302 (M^+), 230, 187, 166, 135, 119, 91. Anal. calc. for $C_{20}H_{30}O_2$: C 79.41, H 10.00; found: C 78.94, H 9.70.

(2S,3R)-2,3-Epoxy-5-isopropyl-2-methyl-7-[(4-propylphenyl)oxy]hept-5-en-1-ol (**11b**). A soln. of titanium tetraisopropoxide (3.2 ml, 0.37 mmol) and (+)-L-dimethyl tartrate (73 mg, 0.41 mmol) in CH_2Cl_2 (10 ml) was cooled to −20° and stirred for 15 min. Then, **10b** (113 mg, 0.37 mmol) followed by 3M anh. *t*-BuOOH (0.25 ml, 0.75 mmol) were added. The resulting homogeneous soln. was stored overnight (*ca.* 18 h) in a freezer at *ca.* 20°. The mixture was quenched with H_2O and the emulsion filtered through a pad of *Celite*. The filtrate was diluted with Et_2O washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The oil was purified by chromatography (hexane/AcOEt 9:1): pure **11b** (86 mg, 72%) as a viscous liquid. HPLC (*Pirkle* column, 2% i-PrOH in hexane): 87% e.e. $[\alpha]_D = -10.0$ ($CHCl_3$, *c* = 1.655). UV: 202 (15300), 224.4 (9600), 277 (1300), 284 (1100). IR: 3450, 1620. ^{1}H-NMR: 0.92 (*t*, *J* = 8, 3 H); 1.10 (*d*, *J* = 6, 6 H); 1.35 (*s*, 3 H); 1.61 (*m*, 2 H); 2.34 (*dd*, *J* = 14, 6, 1 H); 2.39 (*sept.*, *J* = 6, 1 H); 2.48 (*dd*, *J* = 14, 5, 1 H); 2.52 (*t*, *J* = 7, 2 H); 3.05 (*m*, 1 H); 3.57 (*q*, *J* = 14, 1 H); 3.66 (*q*, *J* = 14, 1 H); 4.55 (*m*, 2 H); 5.66 (*t*, *J* = 7, 1 H); 6.83 (*d*, *J* = 8, 2 H); 7.07 (*d*, *J* = 8, 2 H). MS: 318 (M^+), 136, 107. HR-MS: 318.2200 ($C_{20}H_{30}O_3$, calc. 318.2195). Anal. calc. for $C_{20}H_{30}O_3$: C 75.40, H 9.50; found: C 75.30, H 9.70.

[(2S,3R)-2,3-Epoxy-7-[(4-ethylbenzyl)oxy]-5-isopropyl-2-methylhept-5-en-1-ol (**11d**). As for **11b**, with titanium tetraisopropoxide (937 mg, 3.31 mmol), (+)-L-dimethyl tartrate (587 mg, 3.31 mmol), CH_2Cl_2 (25 ml), **10d** (1.0 g, 3.31 mmol), and anh. *t*-BuOOH (1 h at −20°): pure **11d** (470 mg, 45%) as a colorless viscous liquid. B.p. > 200°/1 Torr (dec.). $[\alpha]_D = -9.20$ ($CHCl_3$, *c* = 0.10). IR: 3400, 1505, 1455, 1080. ^{1}H-NMR: 1.06 (*dd*, *J* = 6.8, 1.4, 6 H); 1.23 (*t*, *J* = 7.6, 3 H); 1.28 (*s*, 3 H); 2.25 (*dd*, *J* = 14.66, 6.4, 1 H); 2.32 (*m*, 1 H); 2.37 (*dd*, *J* = 14.6, 4.6, 1 H); 2.63 (*q*, *J* = 7.6, 2 H); 2.97 (*t*, *J* = 5, 1 H); 3.52 (*d*, *J* = 12, 1 H); 3.62 (*d*, *J* = 12, 1 H); 4.06 (*m*, 2 H); 4.48 (*s*, 2 H); 5.56 (*t*, *J* = 6.6, 1 H); 7.17 (*d*, *J* = 8, 1 H); 7.25 (*d*, *J* = 8.0, 1 H). MS: 300 ($M^+ - H_2O$), 257, 230, 216, 135, 119, 91. Anal. calc. for $C_{20}H_{30}O_3$: C 75.40, H 9.50; found: C 75.16, H 9.36.

(5R)-5,6-Epoxy-3-isopropyl-6-methyl-1-[(4-propylphenyl)oxy]hept-2-ene (**14b**). To a mixture of **11b** (350 mg, 1.10 mmol) and anh. pyridine (0.5 ml) in dry CH_2Cl_2 (1.0 ml), freshly crystallized TsCl (420 mg, 2.09 mmol) was added. The flask was stoppered and kept in a freezer (−4°) for 16 h. The mixture was diluted with brine and extracted with Et_2O. The Et_2O layer was washed with $CuSO_4$ soln. and brine, dried ($MgSO_4$), and evaporated: **12b** (506 mg). The crude **12b** was refluxed with NaI (450 mg) in dry acetone (20 ml) for 2 h. Acetone was evaporated and the residue diluted with H_2O and extracted with Et_2O. The Et_2O layer was washed with sodium thiosulfate soln., H_2O, and brine, dried ($MgSO_4$), and evaporated: 420 mg of crude **13b**. To the crude **13b** (420 mg) in THF/HMPA 4:1 (15 ml), 600 mg of $NaBH_3CN$ were added under N_2. The mixture was stirred at 60° for 3 h, diluted with H_2O,

and extracted with Et_2O. The Et_2O layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. Column chromatography (hexane/CH_2Cl_2 92:8) gave pure **14b** (150 mg, 45% based on **11b**). B.p. *ca.* 90° (oil bath)/1 Torr. $[\alpha]_D = +2.67$ ($CHCl_3$, $c = 0.06$). IR: 3006, 1651, 1612, 1513, 1464, 1246, 1012. ^{1}H-NMR: 0.93 (*t*, *J* = 7.3, 3 H); 1.08 (*d*, *J* = 6.8, 6 H); 1.30 (*s*, 3 H); 1.33 (*s*, 3 H); 1.61 (*sext.*, *J* = 7.5, 2 H); 2.30 (*dd*, *J* = 14.6, 6, 1 H); 2.38 (*m*, 1 H); 2.42 (*dd*, *J* = 14.6, 5, 1 H); 2.53 (*t*, *J* = 8, 2 H); 2.73 (*dd*, *J* = 6, 5, 1 H); 4.56 (*m*, 2 H); 5.65 (*t*, *J* = 6.3, 1 H); 6.83 (*d*, *J* = 8.6, 2 H); 7.08 (*d*, *J* = 8.6, 2 H). MS: 302 (M^+), 259, 167, 136, 107, 71, 55.

(5R)-5,6-Epoxy-1-[(4-ethylbenzyl)oxy]-3-isopropyl-6-methylhept-2-ene (**14d**). As for **14b**, with **11d** (150 mg): **14d** (73 mg, 52%) with similar 400-MHz ^{1}H-NMR, IR, and MS as racemic **8d** (see above). $[\alpha]_D = +3.0$ ($CHCl_3$, $c = 0.05$). IR: 3047, 1649, 1506, 1460, 1095. ^{1}H-NMR: 1.07 (*d*, *J* = 7, 6 H); 1.23 (*t*, *J* = 7, 3 H); 1.27 (*s*, 3 H); 1.28 (*s*, 3 H); 2.23 (*dd*, *J* = 14, 6, 1 H); 2.31 (*m*, 1 H); 2.33 (*dd*, *J* = 14, 6, 1 H); 2.65 (*q*, *J* = 7, 2 H); 2.67 (*t*, *J* = 6, 1 H); 4.05 (*m*, 2 H); 4.48 (*s*, 2 H); 5.53 (*t*, *J* = 6.5, 1 H); 7.14 (*d*, *J* = 8, 2 H); 7.26 (*d*, *J* = 8, 2 H). MS: 302 (M^+), 187, 167, 135, 119 (100), 107, 91.

(2R)-5-Isopropyl-2-methyl-7-[(4-propylphenyl)oxy]hept-5-ene-1,2-diol (**15**). A soln. of **11b** (200 mg, 0.63 mmol) in anh. Et_2O (5 ml) was added to a stirred suspension of $LiAlH_4$ (24 mg, 0.63 mmol) in anh. Et_2O (5 ml). The mixture was stirred for an additional 20 min at r.t., then carefully quenched with cold dil. HCl soln. and extracted with Et_2O. The Et_2O layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated: **15** as an oil (173 mg, 86%). B.p. 230°/0.5 Torr. UV: 202 (4.29), 224.8 (4.12), 279.9 (3.45), 285.4 (3.40). IR: 3300, 1200. ^{1}H-NMR: 0.94 (*t*, *J* = 8, 3 H); 1.07 (*d*, *J* = 7, 6 H); 1.20 (*s*, 3 H); 1.54–1.67 (*m*, 4 H); 2.06 (br. *s*, 2 H, exchangeable with D_2O); 2.14–2.23 (*m*, 2 H); 2.33 (*sept.*, *J* = 7, 1 H); 2.54 (*t*, *J* = 8, 2 H); 3.42, 3.47 (*AB*, 1 H each); 4.54 (*d*, *J* = 6, 2 H); 5.52 (*t*, *J* = 6, 1 H); 6.84 (*d*, *J* = 9, 2 H); 7.08 (*d*, *J* = 9, 2 H). MS: 320 (M^+), 185, 153, 136, 107. HR-MS: 320.2349 ($C_{20}H_{32}O_3$, calc. 320.2351). Anal. calc. for $C_{20}H_{32}O_3$: C 75.00, H 10.10; found: C 75.00, H 10.10.

(4'R)-3-Isopropyl-1-[(4-propylphenyl)oxy]-5-(2',2',4'-trimethyl-1',3'-dioxolan-4'-yl)pent-2-ene (**16**). TsOH (5 mg) was added to a soln. of **15** (173 mg, 0.054 mmol) in dry acetone (10 ml) at r.t. and left for 2.5 h. The mixture was stirred with solid K_2CO_3 (30 mg) for a few min, then diluted with H_2O and extracted with Et_2O. The org. layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The oil was purified by chromatography (AcOEt/hexane 2:8): pure **16** (180 mg, 92%). B.p. 205°/0.5 Torr. UV: 202.3 (4.02), 225.0 (3.84), 276.5 (2.98), 284.4 (2.89). IR: 2880, 1200. ^{1}H-NMR: 0.92 (*t*, *J* = 8, 3 H); 1.06 (*d*, *J* = 8, 6 H); 1.30 (*s*, 3 H); 1.38 (*s*, 3 H); 1.40 (*s*, 3 H); 1.61 (*m*, 2 H); 1.64 (*m*, 2 H); 2.19 (*m*, 2 H); 2.31 (*sept.*, *J* = 8, 1 H); 2.52 (*t*, *J* = 8, 2 H); 3.71, 3.78 (*AB*, *J* = 8, 1 H each); 4.53 (*d*, *J* = 6, 2 H); 5.49 (*t*, *J* = 6, 1 H); 6.82 (*d*, *J* = 8, 2 H); 7.06 (*d*, *J* = 8, 2 H). MS: 360 (M^+), 345, 167, 149, 136. HR-MS: 360.2669 ($C_{23}H_{36}O_3$, calc. 360.2664). Anal. calc. for $C_{23}H_{36}O_3$: C 76.60, H 10.10; found: C 76.70, H 10.20.

(4'R)-2-Methyl-5-(2',2',4'-trimethyl-1',3'-dioxolan-4'-yl)pent-2-ene (**19**) via **17**. A soln. of **16** (120 mg) in MeOH (50 ml) was treated, at −60°, with an excess of O_3 till the blue color persisted. The excess of O_3 was evaporated by passing N_2 through the soln. Then, $NaBH_4$ (150 mg) added and stirring continued for 2 h. Most of the MeOH was removed by distillation and the residue diluted with Et_2O. The Et_2O soln. was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The crude **17** (84 mg) was dissolved in AcOEt/hexane and passed through a small pad of silica gel. Without further purification, **17** (84 mg) was heated with TsCl (70 mg) in dry pyridine (2 ml) at 110° for 4 h. The mixture was cooled, poured into ice/H_2O, and extracted with Et_2O. The extract containing the tosylate **18** was washed with $CuSO_4$ soln. and brine, dried ($MgSO_4$), and evaporated. The residual oil was purified by column chromatography (hexane/AcOEt 95:5): pure **19** (50 mg) as a colorless liquid. IR: 1376, 1252, 1212, 1065. ^{1}H-NMR: 1.28 (*s*, 3 H); 1.39 (*d*, *J* = 6, 6 H); 1.56 (*m*, 2 H); 1.61 (*s*, 3 H); 1.68 (*s*, 3 H); 2.05 (*m*, 2 H); 3.70 (*d*, *J* = 8, 1 H); 3.80 (*d*, *J* = 8, 1 H); 5.1 (*m*, 1 H). MS: 183 ($M^+ - CH_3$), 140, 123, 115, 109, 97, 82, 67, 43. HR-MS: 198.1604 ($C_{12}H_{22}O_2$, calc. 198.1619).

(4R)-2,2,4-Trimethyl-1,3-dioxolane-4-propanol ((*R*)-**20**). Reaction of **19** (13 mg) with O_3 in MeOH and $NaBH_4$ and workup as above for **19** gave pure (*R*)-**20** (7 mg). IR and ^{1}H-NMR data identical to those of authentic material [7][2]). $[\alpha]_D = +0.50$ (MeOH, $c = 0.60$; [7]: $[\alpha]_D = +0.80$ (acetone, $c = 1.6$)). IR: 3401, 1450, 1377, 1060. ^{1}H-NMR: 1.30 (*s*, 3 H); 1.39 (*s*, 3 H); 1.40 (*s*, 3 H); 1.66 (*m*, 4 H); 3.74, 3.79 (*AB*, *J* = 8, 1 H each). MS: 159 ($M^+ - CH_3$), 115, 99 (100), 81, 72, 57.

Alcohol (S)-**20**. A soln. of **21**[3]) (100 mg) in anh. Et_2O (2 ml) was added to a $LiAlH_4$ (30 mg) suspension in anh. Et_2O (3 ml) and stirred at r.t. for 1 h. The mixture was decomposed with 5% aq. NaOH soln. and extracted with Et_2O. The Et_2O layer was washed with H_2O and brine, dried ($MgSO_4$), and evaporated. The crude alcohol was purified by FC (AcOEt/hexane 1:9): pure (*S*)-**20** (60 mg), identical to (*R*)-**20**, except for $[\alpha]_D = -0.66$ (MeOH, $c = 0.60$; [7]: $[\alpha]_D = -0.50$ (acetone, $c = 2.25$)). IR: 3437, 1445, 1370, 1052. ^{1}H-NMR: 1.30 (*s*, 3 H); 1.39 (*s*, 3 H); 1.40 (*s*, 3 H); 1.64 (*m*, 4 H); 3.66 (*m*, 2 H); 3.74, 3.80 (*AB*, *J* = 8.3, 1 H each).

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