Stereoselective Reductive Rearrangement of α-Hydroxy Epoxides: A New Method for Synthesis of 1,3-Diols[1]

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A novel and short synthetic method for the stereoselective synthesis of 1,3-diols has been developed by an unusual reductive rearrangement of a series of α-hydroxy epoxides with aluminum isopropoxide. The reaction process was also investigated with deuterium-labeled aluminum isopropoxide, which revealed a site-specific 1,2-carbon-to-carbon migration and successive stereoselective hydride shift. The main synthetically valuable feature is that up to three contiguous carbon centers, the C-1, C-2, and C-3, were stereoselectively controlled with C-2 being quaternary. This reaction is of particular importance to the synthesis of newly developed powerful asymmetric hydrogenation catalysts containing the chiral ligands of spirocyclic diols.

Introduction

Since the chiral synthesis of α-hydroxy epoxides was carried out by Sharpless asymmetric epoxidation,[2] the subject of their reactions and utilization has attracted the research interests of organic chemists.[3,4] Although rearrangements of epoxides promoted by Lewis acid are well-known, few, for example, the $TiCl_4$-induced semipinacol rearrangements of epoxy silyl ether, can control up to two carbon centers.[3] The aluminum isopropoxide (AIP) mediated stereoselective rearrangement has seldom been reported.[3b] Recently, our independent research has brought about the discovery of a novel reductive rearrangement of α-hydroxy epoxides effected by AIP, which completes two transformations in one step, the semipinacol rearrangement[3a] and the Meerwein−Pondorf−Verley type reduction,[5] and leads to the formation of 1,3-diol products. The value of this reaction involves the stereoselective derivation of three carbon centers with one being quaternary. The stereoselective construction of a quaternary center is of particular importance because it is one of the more difficult structure classes to access. One of the practical applications is toward the synthesis of chiral 1,3-diols,[6] to be used as ligands especially for catalytic hydrogenation.[7] This method is short, simple, and effective for preparing chiral diols, and two approaches could bring about the chiral synthesis. One would involve the synthesis of a racemic 1,3-diol and then resolution. Alternatively, the chiral 1,3-diols could be synthesized by this rearrangement directly from chiral hydroxy epoxides (e.g., available by alkylation of a chiral allylic epoxy ketone derived by oxidation of the Sharpless epoxidation products or directly from some natural source).

Results and Discussion

In consideration of the previously reported work on acyclic systems,[3] cyclic substrates, including α-hydroxycyclohexene oxides and several α-hydroxycyclopentene oxides, were chosen for our investigation. Thus, as indicated in Scheme 1, the racemic starting α-hydroxy epoxides (prepared from cycloalkenyl chlorides and appropriate ketones,[8] excluding **2a** and **3a**), when treated with AIP under the standard condition (2 equiv of AIP, refluxing temperature of 2-propanol or THF, 4−8 h), underwent a reductive rearrangement to produce 1,3-diols in good yields. All the experimental results are tabulated in Table 1, in which only few examples gave rise to allylic diol products resulting from the typical Lewis acid rearrangement (e.g., entries 1, 2, and 4)[9] or the simple nucleophilic addition−opening products (e.g., entries 3 and 11). Of all the Lewis acids examined,[10] only AIP proved to be effective for this reductive rearrange-

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(3) For Lewis acid-catalyzed rearrangements of epoxides, see: (a) for general review, Rickborn, B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 3, pp 733−755. (b)-Morgans, D. J.; Sharpless K. B. *J. Am. Chem. Soc.* **1981**, *103*, 462−464. (c) Maruoka, K.; Hasegawa, M.; Yamamoto, H.; Suzuki, K.; Shimazaki, M.; Tsuchihashi, G.-i. *J. Am. Chem. Soc.* **1986**, *108*, 3827−3830. (d) Maruoka, K; Sato, J.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5449−5450. (e) Marson, C. M.; Walker, A. J.; Pickering, J.; Hobson, A. D.; Wrigglesworth, R.; Edge, S. J. *J. Org. Chem.* **1993**, *58*, 5944−5951.

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(5) Haslam, J. H. U.S. Patent 2719863, 1957. (b) *Chem. Abstr.* **1956**, *50*, 4217.

(6) Blaser, H.-U. *Chem. Rev.* **1992**, *92*, 935−952. (b) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799−1800.

(7) For synthesis of chiral spirocyclic diols and their application to asymmetric organic reaction, see: (a) Chan, A. S. C.; Hu, W.; Pai, C.-C.; Lau, C.-P.; Jiang, Y.; Mi, A.; Yan, M.; Sun, J.; Lou, R.; Deng, J. *J. Am. Chem. Soc.* **1997**, *119*, 9570−9571. (b) Chan, A. S. C.; Lin, C.-C.; Sun, J.; Hu, W.; Li, Z.; Pan, W.; Mi, A.; Jiang, Y.; Huang, T.-M.; Yang, T.-K.; Chen, J.-H.; Wang, Y.; Lee, G.-H. *Tetrahedron: Asymmetry* **1995**, *6*, 2953−2959. (c) Brünner, R.; Gerlach, H. *Tetrahedron: Asymmetry* **1994**, *5*, 1613−1620. (d) Suemune, H.; Maeda, K.; Kato, K.; Sakai, K. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3441−3447. (e) Nieman, J. A.; Parvez, M.; Keay, B. A. *Tetrahedron: Asymmetry* **1993**, *4*, 1973−1976. (f) Carruthers, W.; Orridge, A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 2411−2416.

(8) Braude, E. A.; Coles, J. A. *J. Chem. Soc.* **1950**, 2014−2019.

(9) Eschinasi, E. H. *J. Org. Chem.* **1970**, *35*, 1598−1600.

(10) We have examined $Ti(O\text{-}i\text{-}Pr)_4$, $Al(OEt)_3$, $Al(O\text{-}t\text{-}Bu)_3$, and $Ti(O\text{-}i\text{-}Pr)_4$ and found them not to be effective toward this reductive rearrangement. The reaction system can be refluxed for 2 days, using the Lewis acids $Al(OEt)_3$ and $Al(O\text{-}t\text{-}Bu)_3$, affording only a complicated mixture.

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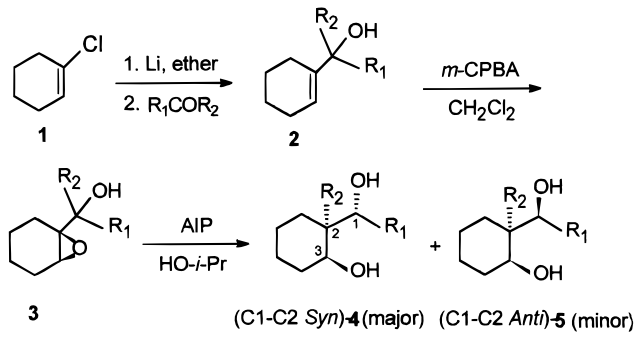
Scheme 1. Reaction of α-Hydroxy Epoxides with AIP



ment. In comparison with those promoted by other Lewis acids, such as $TiCl_4$ and $SnCl_4$,[3a,c,e] this rearrangement exhibited some similar characteristics. For example, two stereoselective carbon centers, C-2 and C-3, were successfully controlled with the C-2 being quaternary. In addition, epoxides containing aryl and methyl or isopropyl at C-1 (entries 6, 11, and 16) revealed the higher migratory aptitude of aryl than methyl and proton, which was consistent with the typical Pinacol rearrangement. Furthermore, the 1,1-disubstituted hydroxy epoxides were more effective toward this rearrangement than the 1-monosubstituted compounds (entry 11), for in several tested examples of monosubstituted substrates only the 1-α-furyl substrate **11a** was effective. Again, the carbon-to-carbon migration appeared to be in the *anti* form related to the broken C_2-O bond. For entries 7 and 8, the ^1H NMR interpretation of **7b** and **8b** indicated that an unexpected *syn* migration had taken place. Although this uncommon stereocontrolling process was unclear, the reverse stereoselectivity for both examples was quite good. It was also found that this carbon-to-carbon migration was highly stereoselective with respect to the steric situation of the epoxy moiety but not to the relative configuration of C-1. For example, substrate **2a** with a C_4-CH_3 and epoxy ring being at different faces of the cyclohexane ring, gave the right 1,3-diol **2b**, while **3a** with the C_4-CH_3 and epoxy ring at the same face, formed no corresponding 1,3-diol but a simple neucleophilic addition−opening product **3c**. This was probably due to the steric repulsion of the *syn* C_4-Me which prevented AIP from coordination with the epoxy oxygen.

It was interesting to note that this reductive rearrangement exhibited some surprising properties. For example, epoxides **7a**−**9a** containing ethyl or isopropyl and aryl at C-1 showed an unusual migration order, i.e., isopropyl and ethyl vs aryls, and also gave rise to high yields of 1,3-diols **7b**−**9b**. It is possible that these uncommon migrations incorporated formation of a carbocation intermediate of C-1, and the conjugated π-system of aryl group R_1 would be favorable to it (see Scheme 2). Because other examples mentioned above showed the ordinary migration order, we thought that the migration aptitude of R_1 and R_2 in our investigation scope was isopropyl and ethyl vs phenyl vs methyl. In addition, the stereochemistry of the secondary C_1-OH of the 1,3-diols was found to be independent of that of the α-hydroxy epoxide substrates. For example, **10a** and **14a,** both containing one diastereoisomer, formed the 1,3-diols **10b** and **14b** with two C_1-diastereoisomers, respectively, while **16a,** containing a pair of C_1-epimers, gave only one. The latter information would be of synthetic importance, because a mixture of certain hydroxy epoxides with a chiral epoxy moiety but epimeric at C-1 could be transformed to an optically active 1,3-diol with three contiguous chiral centers. It is also particularly important that the preparation of spirocyclic 1,3-diols, such as **12b** through a cycloenlargement of **12a**, was of high yield and stereoselectivity,[11] which implied powerful practical utilities of this reaction for the synthesis of chiral spirocyclic diol ligands.

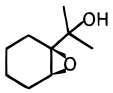
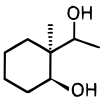
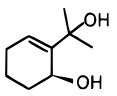
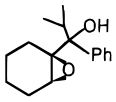
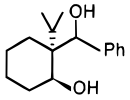
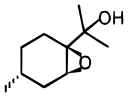
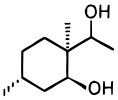
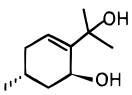
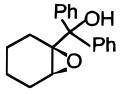
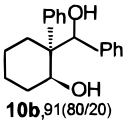
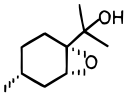
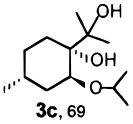
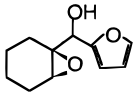
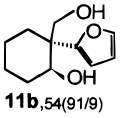
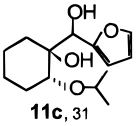
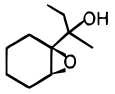
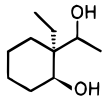
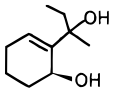
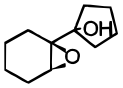
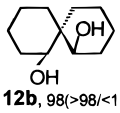
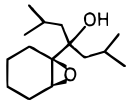
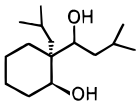
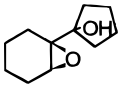
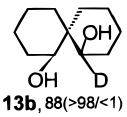
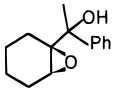
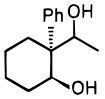
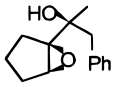
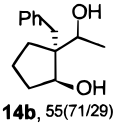
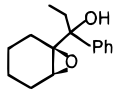
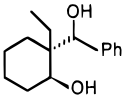
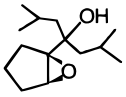
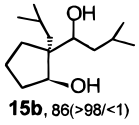
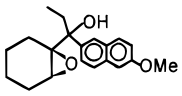
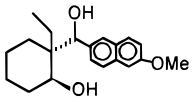
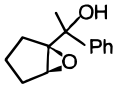
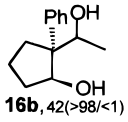
To assist with the stereochemistry assignments, we first investigated the 1,3-diol products possessing cyclohexanol moieties (entries 1, 2, 4, 6, 9, 10, 12, and 13), whose ^1H NMR for H-3 showed a singlet or a narrow doublet with the coupling constant $J < 2$ Hz. This fact suggested that the C_3-OH attached to the cyclohexane rings would be in the axial direction and the migration group R_2 would be in the *trans*-form related to this hydroxyl, due to the fact that the bulkier C-1-bearing moiety attached to C-2 preferred to be in the equatorial direction. In comparison with a literature result,[3e] the *anti*-migration products also exhibited similar ^1H NMR singlets for H-3. On the basis of this consideration, we thought this rearrangement, except for entries 7 and 8, could mainly include the *anti*-form of carbon-to-carbon migration.

To assign successively the relative stereochemistry of C-1 and C-2, three 1,3-diols **2b**, **10b**, and **12b**, as examples, were chosen for investigation by first preparing their acetonides (rt, excess acetone/*p*-TsOH, overnight). It was found that the ^1H NMR of both **12b** and its acetonide showed very similar doublets of doublets for H-1 at δ 3.56 (J = 11, 4.4 Hz) and 3.39 (J = 11, 4.2 Hz) and singlets for H-3 at δ 3.59 and 3.45, respectively. A molecular model examination suggested that the relative configuration for both compounds would be C_1-C_2 *syn* and C_2-C_3 *anti* (as indicated in Scheme 1). In addition, an investigation of the acetonide mixture (80/20) of **10b** with ^1H,^1H-NOESY technique indicated that the major isomer was of the C_1-C_2 *syn* configuration and the minor one was of the $C1-C_2$ *anti* configuration. Again a further investigation of the acetonide of **2b** with the ^1H,^1H-NOESY technique also showed the presence of C_1-C_2 *syn* configuration. On the basis of the above results, we presumed that the main stereochemistry for this reaction would be C_1-C_2 *syn* and C_2-C_3 *anti*. Further aspects of the sterochemistry of this rearrangement are currently under investigation.

For further examination of the reaction process and thus support for the stereochemistry assignments above, deuterium AIP (prepared from $AlEt_3$ and 2-propanol-d_8, see Experimental Section) were used to conduct this reaction. The α-hydroxy epoxide **12a**, when treated with deuterium AIP under the typical conditions, gave the spirocyclic diol **13b**, whose NMR and MS analyses suggested that the deuterium was located at C-1. On the basis of this fact and some information described above, a possible reaction mechanism thus was suggested (as showed in Scheme 2), in which aluminum complex **6** coordinated first with epoxy oxygen, facilitating a bond cleavage between this oxygen and the crowded quaternary C-2 and forming C_1-carbocation intermediate **7**. Then a hydride shift from the methine carbon of the

(11) In some examples, a larger scale of experiment (e.g., with >1 g of **12a**) gave a little lower stereoslectivity of the C-1 center (ca. 5% of 1-epimer of **12b** was formed).

Table 1. Rearrangement of α-Hydroxy Epoxides with AIP[a,b]

Entry	Substrates *syn/anti*	Products yields(%)(**4**/**5**)	by-Products yields(%)	Entry	Substrates *syn/anti*	Products yields(%)(**4**/**5**)	by-Products yields(%)
1	 **1a**	 **1b**, 26(>98/<1)	 **1c**, 36	9	 **9a**, 87/13	 **9b**, 95(73/27)	
2	 **2a**	 **2b**, 25(>98/<1)	 **2c**, 45	10	 **10a**	 **10b**, 91(80/20)	
3	 **3a**		 **3c**, 69	11[c]	 **11a**, 80/20	 **11b**, 54(91/9)	 **11c**, 31
4	 **4a**, 70/30	 **4b**, 43(91/9)	 **4c**, 32	12	 **12a**	 **12b**, 98(>98/<1)	
5	 **5a**	 **5b**, 53(>98/<1)		13	 **12a**	 **13b**, 88(>98/<1)	
6	 **6a**, 70/30	 **6b** 85(80/20)		14	 **14a**	 **14b**, 55(71/29)	
7	 **7a**, 61/39	 **7b** 98(72/28)		15	 **15a**	 **15b**, 86(>98/<1)	
8	 **8a**, 75/25	 **8b**, 73(65/35)		16	 **16a**, 80/20	 **16b**, 42(>98/<1)	

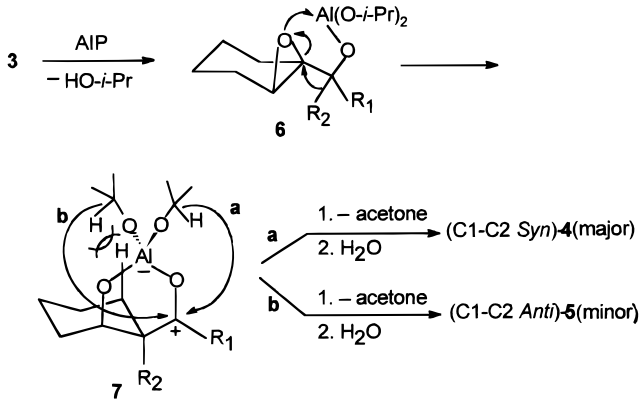
[a] The structures of all compounds were determined on the basis of NMR and mass spectroscopy, and ratios were established by ^{1}H NMR and/or GC-MS analysis. [b] For some examples with lower total yields (e.g., entries **16**, **14**, and **5**), the byproducts were complicated mixtures with very low polarity on TLC and not identified. [c] The 91:9 for **11b** represents a ratio of C_2-C_3 *anti* isomer to the *syn*.

isopropoxy group to the C_1-carbocation center in **7** followed by elimination of an acetone molecule and a final hydrolysis or alcoholization thus led to the formation of 1,3-diols **4** and/or **5**. Here two possible pathways exist for the hydride shift, **a** and **b,** which bring about two corresponding 1,3-diols, the C_1-C_2 *syn* **4** and the C_1-C_2 *anti* **5**, respectively. The shift in pathway **b** at the back of the six-membered ring consists of an Al atom interacting with an axial proton above the cyclohexane ring, and that in pathway **a** does not. Thus the C_1-C_2 *syn* product **4** was more abundant than the C_1-C_2 *anti* **5**. In fact, some examples, such as entries 1, 2, 4, 5, 12, 15, and 16, gave the exclusive C_1-C_2 *syn* isomers **4**. After all, we thought preliminarily that the stereoselectivity of C-1 for the 1,3-diols was mainly dependent on the migration ability of R_2, the contribution of R_1 to the stability of the C_1-carbocation, and the steric situiation of hydride shift.

The reductive rearrangement reported above is indeed a new approach for stereoselective synthesis of 1,3-diols and demonstrates a versatile and practical asymmetric organic reaction.[12] By using asymmetric hydroxy epoxides available by the Sharpless procedure or from natural sources, this method enabled a new and stereocontrolled

(12) As with the application scope and limitation of this method, we felt this reductive rearrangement could be generally applied to the substrates with 1,1-substituents varying from alkyl to aromatic groups, but not to the 1-monosubstituted substrate. In addition, the C_1-alkyl (especially Me) substituted subtrates in some cases gave a low yield of 1,3-diol products though the stereoselectivity of the C-1 center was good, and C_1-aromactic substituted substrates generally gave products with lower selectivity of C-1 though the reaction yield was generally high.

Scheme 2. A Suggested Reaction Process of α-Hydroxy Epoxides with AIP



approach to asymmetric synthesis. Thus, as an example, the chiral hydroxy epoxide **2a**, prepared from the natural (*R*)(+)-Pulegone in three steps (see Experimental Section),[9] was converted by this procedure smoothly to the chiral 1,3-diol ($[\alpha]^{20}_D = +25°$(*c* 2.35, $CHCl_3$)) with four asymmetric centers, though the yield was merely 25%.

Experimental Section

General Method. The ^{1}H NMR, ^{13}C NMR, and DEPT data and ^{1}H,^{1}H-NOESY spectra were obtained in $CDCl_3$ with TMS or $CDCl_3$ as internal standards. GC-MS, MS, and HRMS data were measured with EI (70 eV) or FAB techniques. Column chromatographies were performed generally on silica gel (200−300 mesh) eluting with petroleum ether/EtOAc (20:1 → 10:2) and TLC inspections on silica gel F_{254} plates with petroleum ether/EtOAc (10:2.5) unless otherwise noted. All starting α-hydroxy epoxides, except for **2a** and **3a**, were prepared by literature procedures[8] as in Scheme 1 and characterized by NMR and mass spectroscopy.

2-(1-Hydroxyethyl)-2-methylcyclohexanol (1b) and 2-(1-Hydroxy-1-methylethyl)-2-cyclohexen-1-ol (1c). The procedure described is a general method for all reductive rearrangement experiments unless otherwise noted. A mixture of α-hydroxy epoxide **1a** (0.5 g, 3.2 mmol), aluminum isopropoxide (1.3 g, 6.4 mmol), and 2-propanol (10 mL) was refluxed with stirring under Ar for 8 h. After TLC examination indicated the disappearance of the starting material, the solvent was removed in vacuo and the obtained gel residue was partitioned with ether and a 10% NaOH solution. The aqueous layer was separated and re-extracted with ether. The combined ether solution was washed with water and brine, dried (Na_2SO_4), concentrated in vacuo, and chromatographed on silica gel to give a mixture of **1b** and **1c** (0.31 g). The ratio was determined to be 43:57 on the basis of the ^{1}H NMR data and the yields were about 26% and 36%, respectively. The partially separated samples could be purified by careful chromatography. Compound **1b**: ^{1}H NMR δ 0.80 (s, 3H), 1.11 (d, J = 6.3 Hz, 3H), 1.18−1.82 (m, 8H), 3.67 (s, 1H), 3.81 (q, J = 6.3 Hz, 1H); ^{13}C NMR δ 17.2, 2 × 19.5, 20.7, 23.6, 30.0, 39.7, 75.7, 76.0; GC-MS *m*/*z* (%) 140 (M^+ − 18, 5), 125 (6), 96 (100); HRMS 140.1188, cacld for $C_9H_{16}O$ 140.1197. Compound **1c**: ^{1}H NMR δ 1.38, 1.41 (2 s, 2 × 3H), 1.25−2.13 (m, 6H), 4.49 (t, J = 4 Hz, 1H), 5.78 (t, J = 4 Hz, 1H); ^{13}C NMR δ 16.7, 25.2, 29.3, 29.7, 31.4, 64.3, 73.5, 123.6, 143.1; GC-MS *m*/*z* (%) 138 (M^+ − 8, 20), 123 (47), 82 (26), 43 (100); HRMS 138.1008, calcd for $C_9H_{14}O$ 138.1041.

(1*R*,2*S*,4*R*)-4-Methyl-1-(1-hydroxy-1-methylethyl)-1,2-epoxycyclohexane (2a) and (1*S*,2*R*,4*R*)-4-Methyl-1-(1-hydroxy-1-methylethyl)-1,2-epoxycyclohexane (3a). To an ice-water cooling solution of (4*R*)-1-(1-hydroxy-1-methylethyl)-4-methylcyclohexene (9 g, 58.4 mmol, prepared by a literature procedure[9]) in CH_2Cl_2 (200 mL) was added in portions 65% *m*-CPBA (18.6 g, ca. 70 mmol) with stirring. After completing addition, stirring was continued for 2 h, and TLC inspection (petroleum ether/EtOAc 10:1) showed the disappearance of starting material. The reaction system was washed with a saturated $NaHCO_3$ solution, dried (Na_2SO_4), concentrated, and chromatographed to yield a mixture of **2a/3a** (7.3 g, 73%) in a ratio of 75:25, determined by GC-MS. Pure **2a** was available by HPLC resolution. Compound **2a**: ^{1}H NMR δ 0.82 (d, J = 6.6 Hz, 3H), 1.18 (s, 6H), 1.22−2.16 (m, 7H), 3.34 (s, 1H); ^{13}C NMR δ 21.3, 24.2, 24.5, 25.2, 25.3, 30.0, 33.7, 56.3, 64.8, 69.9; GC-MS *m*/*z* (%) 155 (M^+ − 5, 4), 112 (13), 97 (34), 70 (100); HRMS 155. 1055, calcd for $C_9H_{15}O_2$ 155. 1068. Compound **3a**: ^{1}H NMR δ 0.84 (d, J = 6.4 Hz, 3H), 1.16, 1.20 (2 s, 2 × 3H), 1.22−2.16 (m, 7H), 3.29 (d, J = 5.5 Hz, 1H); ^{13}C NMR δ 21.7, 24.3, 24.5, 26.0, 27.6, 27.9, 32.7, 55.5, 65.1, 69.7; GC-MS *m*/*z* (%) 155 (M^+ − 15, 4), 97 (28), 84 (13), 71 (13), 70 (100).

(1*S*,2*R*,5*R*)-2-(1-Hydroxyethyl)-2,5-dimethylcyclohexanol (2b) and (3*S*,5*R*)-2-(1-Hydroxy-1-methylethyl)-5-methylcyclohexen-1-ol (2c). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **2a** (2 g, 11.8 mmol) gave a mixture of **2b**/**2c** (1.4 g) in 25% and 45% yields. The partially separated samples could be purified by careful chromatography. Compound **2b**: ^{1}H NMR δ 0.37 (s, 3H), 0.85 (d, J = 6.4 Hz, 3H), 1.08 (d, J = 6.4 Hz, 3H), 0.96−1.83 (m, 7H), 3.32 (s, OH), 3.66 (s, 1H), 3.79 (q, J = 6.4 Hz, 1H); ^{13}C NMR δ 17.3, 19.6, 22.2, 23.8, 25.8, 29.6, 38.9, 39.4, 75.7, 76.7; GC-MS *m*/*z* (%) 154 (M^+ − 18, 2), 139 (154 − 15, 7), 110 (77), 95 (100), 81 (33); HRMS 139.1105, calcd for $C_9H_{15}O$ 139.1119. Compound **2c**: ^{1}H NMR δ 0.93 (d, J = 6.4 Hz, 3H), 1.32, 1.38 (2 s, 6H), 1.45−2.19 (m, 5H), 3.03 (s, OH), 4.45 (d, J = 1.3 Hz, 1H), 5.73 (dd, J = 5.4, 2.4 Hz, 1H); ^{13}C NMR δ 21.5, 22.6, 29.7, 30.1, 34.1, 39.6, 64.4, 73.7, 124.3, 142.9; GC-MS *m*/*z* (%) 152 (M^+ − 18, 7), 137 (22), 109 (14), 95 (18), 43 (100); HRMS 152.1177, calcd for $C_{10}H_{16}O$ 152.1197.

(1*S*,2*S*,4*R*)-1-(1-Hydroxy-1-methylethyl)-2-isopropoxy-4-methylcyclohexanol (3c). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the mixture of **3a/2a** (3 g, 17.6 mmol, 25/75) gave the products **3c** (0.69 g, 69%) and the mixture of **2b/2c** (1.4 g) in a ratio of 35:65. Compound **3c**: ^{1}H NMR δ 0.85 (d, J = 6.4 Hz, 3H), 1.14 (d, J = 6 Hz, 6H), 1.17, 1.28 (2 s, 6H), 1.24−2.14 (m, 7H), 3.76 (m, 1H), 4.01 (s, 1H); ^{13}C NMR δ 21.3, 22.0, 23.8, 24.0, 25.0, 25.1, 26.4, 29.7, 33.0, 67.8, 73.7, 75.3, 76.1; GC-MS *m*/*z* (%) 212 (M^+ − 18, 1), 171 (M^+ − 59, 6), 129 (34), 112 (100), 97 (62); HRMS 171.1375, calcd for $C_{10}H_{19}O_2$ 171.1380.

2-Ethyl-2-(1-hydroxyethyl)cyclohexanol (4b) and 2-(1-Hydroxy-1-methylpropyl)-2-cyclohexen-1-ol (4c). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **4a** (0.74 g, 44 mmol) gave the product of **4b/4c** (0.56 g) in a ratio of 57:43. The partially separated samples could be purified by careful chromatography. Major isomer of **4b**: ^{1}H NMR δ 0.68 (t, J = 7.4 Hz, 3H), 1.02 (d, J = 6.4 Hz, 3H), 0.77−1.85 (m, 10H), 3.91 (s, 1H), 3.95 (q, J = 6.4 Hz, 1H), 4.29 (s, OH); ^{13}C NMR δ 6.9, 17.0, 19.3, 20.3, 23.1, 25.4, 29.3, 40.6, 2 × 72.9; GC-MS *m*/*z* (%) 154 (M^+ − 18, 2), 136 (M^+ − 36, 6), 110 (88), 82 (23), 81 (100); HRMS 136.1240, calcd for $C_{10}H_{16}$ 136.1248. Minor isomer of **4b**: no NMR data could be collected because of its poor resolution with background; GC-MS *m*/*z* (%) 154 (M^+ − 18, 1), 136 (5), 96 (100), 95 (20), 81 (96). Compound **4c**: ^{1}H NMR δ 0.70 (t, J = 7.4 Hz, 3H), 0.77−2.03 (m, 8H), 1.25 (s, 3H), 4.31 (t, J = 4 Hz, 1H), 5.65 (t, J = 4 Hz, 1H), 4.29 (s, OH); ^{13}C NMR δ 9.1, 17.3, 25.4, 26.2, 31.4, 34.5, 64.6, 76.7, 125.7, 141.2; GC-MS *m*/*z* (%) 152 (M^+ − 18, 7), 141 (30), 123 (100), 81 (15), 79 (19); HRMS 152.1203, calcd for $C_{10}H_{16}O$ 152.1197.

2-(1-Hydroxy-3-methylbutyl)-2-(2-methylpropyl)cyclohexanol (5b). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **5a** (0.3 g, 1.2 mmol) gave the product **5b** (0.16 g, 53%): ^{1}H NMR δ 0.78−0.85 (m, 12H), 0.90−1.90 (m, 14H), 4.09−4.16 (m, 2H), 4.34 (s, OH); ^{13}C NMR δ 17.7, 19.6, 20.3, 21.4, 21.9, 24.0, 24.1, 25.0, 25.1, 29.6, 41.6, 42.2, 49.8, 73.2, 73.6; GC-MS *m*/*z* (%) 224 (M^+ − 18, 4), 123 (39), 97 (39), 96 (100), 84 (45); HRMS 224.2140, calcd for $C_{15}H_{28}O$ 224.2133.

2-(1-Hydroxyethyl)-2-phenylcyclohexanol (6b). Following the typical procedure (above, 2 equiv of AIP, refluxing

temperature, 8 h), the epoxide **6a** (1.0 g, 4.6 mmol) gave a mixture of two isomers of **6b** (0.85 g, 85%) in a ratio of 80:20. Major isomer: ^{1}H NMR δ 0.70 (d, J = 6.4 Hz, 3H), 1.25−2.16 (m, 8H), 4.08 (q, J = 6.4 Hz, 1H), 4.66 (s, 1H), 7.18−7.38 (m, 5H); ^{13}C NMR δ 17.7, 19.1, 19.6, 21.0, 29.6, 48.4, 74.7, 76.3, 126.0−128.3, 141.8; GC-MS *m/z* (%) 202 (M^+ − 18, 5), 158 (100), 143 (30), 130 (33), 129 (33); HRMS 202.1345, calcd for $C_{14}H_{18}O$ 202.1353. Minor isomer: ^{1}H NMR δ 0.87 (d, J = 6.4 Hz, 3H), 1.25−2.16 (m, 8H), 3.90 (q, J = 6.4 Hz, 1H), 4.81 (s, 1H), 7.18−7.38 (m, 5H); ^{13}C NMR δ 17.7, 19.6, 21.4, 27.0, 29.2, 49.1, 69.5, 73.9, 126.0−128.3, 141.0; GC-MS *m/z* (%) 202 (M^+ − 18, 6), 158 (100), 143 (28), 130 (30), 129 (28).

2-Ethyl-2-(1-hydroxy-1-phenylmethyl)cyclohexanol (7b). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **7a** (0.2 g, 0.86 mmol) gave a mixture of two isomers of **7b** (0.19 g, 95%) in a ratio of 72:28. Major isomer: ^{1}H NMR δ 0.68−0.82 (m, 3H), 0.77−2.18 (m, 10H), 3.66 (dd, J = 8.8, 1.7 Hz, 1H), 4.17(s, OH), 4.56 (s, 1H), 7.09−7.29 (m, 5H); ^{13}C NMR δ 11.0, 10.9, 20.5, 21.0, 23.9, 29.6, 48.5, 74.7, 82.1, 125.8−129.8, 141.8; GC-MS *m/z* (%) 216 (M^+ − 18, 3), 158 (100), 143 (24), 130 (28), 129 (24); HRMS 216.1500, calcd for $C_{15}H_{20}O$ 216.1509. Minor isomer: ^{1}H NMR δ 0.68−0.82 (m, 3 H), 0.77−2.18 (m, 10 H), 3.43 (dd, J = 9.0, 1.5 Hz, 1 H), 4.17 (s, OH), 4.72 (s, 1H), 7.09−7.29 (m, 5H); ^{13}C NMR δ 11.2,19.9, 21.4, 24.2, 27.0, 29.1, 49.0, 69.6, 80.3, 125.8−129.8, 141.4; GC-MS *m/z* (%) 216 (M^+ − 18, 3), 158 (100), 143 (26), 131 (10), 130 (28).

2-Ethyl-2-(1-hydroxy-1-(6-methoxy-2-naphthyl)methyl-)cyclohexanol (8b). Following the typical procedure (above, 2 of equiv AIP, refluxing temperature, 8 h), the epoxide **8a** (0.4 g, 1.28 mmol) gave a mixture of two isomers of **8b** (0.29 g, 73%) in a ratio of 65:35. Major isomer: ^{1}H NMR δ 0.68 (t, J = 7.3 Hz, 3H), 0.76−2.17 (m, 10H), 3.76 (dd, J = 10, 2 Hz, 1H), 3.84 (s, 3H), 4.70 (s, 1H), 7.03−7.65 (m, 6H); ^{13}C NMR δ 11.2, 19.3, 21.0, 21.4, 24.3, 29.8, 48.7, 55.4, 74.9, 83.0, 105.3−137.2, 157.7; GC-MS *m/z* (%) (mixture of 2 isomers) 296 (M^+ − 18, 3), 249 (3), 239 (19), 238 (100); HRMS 296.1780, calcd for $C_{20}H_{24}O_2$ 296.1770. Minor isomer: ^{1}H NMR δ 0.76−2.16 (m, 1H), 3.55 (dd, J = 10, 2 Hz, 1H), 3.83 (s, 3H), 4.75 (s, 1H), 7.03−7.65 (m, 6H); ^{13}C NMR δ 11.5, 20.2, 21.7, 24.5, 27.3, 29.4, 49.2, 55.4, 70.0, 80.5, 118.7−136.8, 157.7.

2-(1-Hydroxy-1-phenylmethyl)-2-isopropylcyclohexanol (9b). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **9a** (0.4 g, 1.6 mmol) gave a mixture of two isomers of **9b** (0.38 g, 95%) in a ratio of 73:27. Major isomer: ^{1}H NMR δ 0.72, 0.73 (2 d, J = 6.5 Hz, 2 × 3H), 1.24−2.26 (m, 9H), 3.51 (s, OH), 3.84 (d, J = 1 Hz, 1H), 4.63 (s, 1H), 7.21−7.40 (m, 5H); ^{13}C NMR δ 16.0, 18.8, 21.1, 21.2, 23.2, 28.7, 29.5, 49.4, 76.0, 84.4, 126.0−129.5, 141.9; GC-MS *m/z* (%) 230 (M^+ − 18, 4), 158 (100), 145 (14), 143 (26), 130 (28); HRMS 230.1651, calcd for $C_{16}H_{22}O$ 230.1665. Minor isomer: ^{1}H NMR δ 0.38, 0.82 (2 d, J = 6.5 Hz, 2 × 3H), 1.24−2.26 (m, 9H), 3.51 (s, OH), 3.56 (d, J = 1 Hz, 1H), 4.87 (s, 1H), 7.21−7.40 (m, 5H); ^{13}C NMR δ 15.8, 19.8, 21.4, 23.8, 27.3, 27.8, 29.0, 49.2, 70.0, 82.9, 126.0−129.5, 141.2; GC-MS *m/z* (%) 230 (M^+ − 18, 3), 158 (100), 143 (25), 130 (26), 91 (22).

2-(1-Hydroxy-1-phenylmethyl)-2-phenylcyclohexanol (10b). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **10a** (0.5 g, 1.8 mmol) gave a mixture of two isomers of **10b** (0.46 g, 91%) in a ratio of 80:20. ^{1}H NMR δ (2 isomers) 1.19−2.42 (m, 16H), 4.17, 4.74, 4.75, 4.94 (4 s, 4 H), 6.65−7.37 (m, 20 H). Major isomer: ^{13}C NMR δ 18.9, 19.9, 20.7, 29.4, 49.3, 74.0, 82.9, 125.9−128.5 (10CH), 140.0, 140.5; GC-MS *m/z* (%) 264 (M^+ − 18, 3), 158 (100), 143 (19), 130 (21), 129 (16); HRMS 264.1518, calcd for $C_{19}H_{20}O$ 264.1509. Minor isomer: ^{13}C NMR δ 19.6, 21.2, 26.7, 28.9, 49.5, 67.0, 81.4, 125.9−128.5, 139.8, 140.4; GC-MS *m/z* (%) 247 (M^+ − 18 − 17, 3), 158 (100), 143 (19), 130 (21), 129 (16).

2-(α-Furyl)-2-(hydroxymethyl)cyclohexanol (11b) and 1-((α-Furyl)hydroxymethyl)-2-isopopoxycyclohexanol (11c). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **11a** (0.9 g, 4.6 mmol) gave a mixture of **11b** (0.49 g, yielding 54%) in a ratio of 91:9 and **11c** (0.36 g, 31%). Major isomer of **11b**: ^{1}H NMR δ 0.77−1.94 (m, 8H), 3.23 (s, OH), 3.64, 3.84 (ABq, J = 11 Hz, 2 × 1H), 4.18 (dd, J = 6, 3 Hz, 1H), 6.13 (d, J = 3 Hz, 1H), 6.26 (dd, J = 3, 1.8 Hz, 1H), 7.28 (d, J = 1.8 Hz, 1H); ^{13}C NMR δ 21.2, 21.5, 28.3, 29.9, 45.6, 66.8, 71.9, 106.4, 110.0, 141.0, 157.8; GC-MS *m/z* (%) 196 (M^+, 1), 178 (M^+ − 18, 46), 135 (92), 134 (49), 108 (100); HRMS 178.0988, calcd for $C_{11}H_{14}O_2$ 178.0990. No NMR data for the minor isomer could be collected due to the low intensity and its poor resolution with background. **11c**: ^{1}H NMR δ 1.10 (d, J = 6 Hz, 6H), 0.96−1.84 (m, 8H), 2.97 (s, OH), 3.46 (dd, J = 7.5, 4 Hz, 1H), 3.68 (hept, J = 6 Hz, 1H), 4.74 (s, 1H), 6.26 (m, 2H), 7.30 (dd, J = 2, 1.8 Hz, 1H); ^{13}C NMR δ 21.2, 21.6, 21.9, 23.3, 27.5, 32.2, 70.0, 70.6, 74.0, 80.8, 108.2, 110.0, 141.7, 153.8; GC-MS *m/z* (%) 221 (M^+ − 15 − 18, 23), 178 (72), 148 (41), 135 (96), 108 (100); HRMS 221.1168, calcd for $C_{13}H_{17}O_3$ 221.1173.

1,7-Dihydroxyspiro[5.5]undecane (12b). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 4 h), the epoxide **12a** (0.5 g, 2.7 mmol) gave as the only product **12b** (0.49 g, 98%): ^{1}H NMR δ 0.66−2.10 (m, 16H), 3.56 (dd, J = 11, 4.4 Hz, 1H), 3.59 (s, 1H), 4.31 (s, OH); ^{13}C NMR δ 18.7, 19.6, 19.9, 20.2, 24.8, 29.0, 29.7, 30.3, 40.4, 78.5, 78.6; MS *m/z* (%) 166 (M^+ − 18, 11), 148 (100), 122 (63), 111 (33), 81 (93); HRMS 166.1344, calcd for $C_{11}H_{18}O$ 166.1353.

1,7-Dihydroxy-1-deuteriospiro[5.5]undecane (13b). To the solution of 1.1 mL of 2-propanol-d_8 (ca. 14 mmol) in dry THF (20 mL) was added 1.7 mL of a 2.6 M solution of $AlEt_3$ in THF. The mixture was refluxed under Ar for 1 h to give the deuterium AIP solution (ca. 4.4 mmol) which was used directly in the reaction for **12a** (0.4 g, 2.2 mmol) according to the typical procedure (above, refluxing temperature, 4 h) to give the product **13b** (0.36 g, 88%): ^{1}H NMR δ 1.11−2.06 (m, 16H), 3.54 (s, 1H), 4.55 (s, OH), 4.86 (s, OH); ^{13}C NMR δ 18.6, 19.5, 19.8, 20.0, 24.7, 28.8, 29.4, 30.2, 40.1, 77.9 (t, CD), 78.4; GC-MS *m/z* (%) 167 (M^+ − 18, 12), 149 (100), 122 (47), 95 (38), 81 (95); FAB-HRMS 186.1583, calcd for [$C_{11}H_{19}DO_2$ + H] 186.1599.

2-Benzyl-2-(1-hydroxyethyl)cyclopentanol (14b). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **14a** (0.5 g, 2.3 mmol) gave a mixture of two isomers of **14b** (0.28 g, 55%) in ae ratio of 71:29. Major isomer: ^{1}H NMR δ 1.18 (d, J = 6.5 Hz, 3H), 1.26−2.83 (m, 8H), 3.95 (q, J = 6.5 Hz, 1H), 4.17 (t, J = 6.7 Hz, 1H), 7.04−7.87 (m, 5H); ^{13}C NMR δ 18.5 (CH_3), 21.1, 30.5, 36.3, 43.4, 51.2, 70.1, 79.8, 124.7−138.6 (Ph); GC-MS *m/z* (%) 202 (M^+ − 18, 10), 158 (76), 143 (23), 129 (54), 91 (100); HRMS 202.1345 calcd for $C_{14}H_{18}O$ 202.1353. Minor isomer: ^{1}H NMR δ 1.17−2.83 (m, 11H), 3.92 (q, J = 6.4 Hz, 1H), 4.04 (t, J = 6.4 Hz, 1H), 7.04−7.87 (m, 5H); GC-MS *m/z* (%) 202 (M^+ − 18, 9), 158 (100), 129 (55), 117 (29), 91 (94).

2-(1-Hydroxy-3-methybutyl)-2-(2-methylpropyl)cyclopentanol (15b). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **14a** (0.45 g, 2.0 mmol) gave the product **15a** (0.39 g, 85%): ^{1}H NMR δ 0.95 (m, 12H), 1.10−2.10 (m, 12H), 4.05 (m, 2H); ^{13}C NMR δ 21.2, 21.3, 2 × 24.2, 24.4, 24.6, 25.4, 32.6, 37.5, 40.7, 47.6, 50.5, 71.6, 81.3; GC-MS *m/z* (%) 210 (M^+ − 18, 1), 153 (10), 124 (100), 123 (13), 97 (31); HRMS 192.1877, calcd for $C_{14}H_{24}$ 192.1872.

2-(1-Hydroxyethyl)-2-phenylcyclopentanol (16b). Following the typical procedure (above, 2 equiv of AIP, refluxing temperature, 8 h), the epoxide **16a** (0.57 g, 2.8 mmol) gave the product **16b** (0.24 g, 42%): ^{1}H NMR δ 0.84 (d, J = 6.6 Hz, 3H), 1.48−2.28 (m, 6H), 4.17 (q, J = 6.6 Hz, 1H), 4.60 (t, J = 5.4 Hz, 1H), 7.16−7.42 (m, 5H); ^{13}C NMR δ 19.5, 20.7, 31.8, 32.9, 58.5, 71.6, 80.6, 126.5, 4 × 128.0, 141.4S; MS *m/z* (%) 206 (M^+, 23), 188 (69), 144 (100), 129 (89) 105 (95); HRMS 206.1308, calcd for $C_{13}H_{18}O_2$ 206.1302.

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