Preparative TLC (petroleum ether/Et_2O 3:2) of the crude product (0.27 g) from the reaction of **1b** gave pure ***cis*-4-[(benzyloxy)methyl]-1-cyclohexanol (11b)**: a liquid; IR, see Table III; ^1H NMR δ 7.36–7.26 (m, 5 H), 4.51 (s, 2 H), 3.32 (d, 2 H, J = 6.5 Hz), and the data in Table III; ^{13}C NMR δ 139.0, 129.0, 128.2, 128.1, 75.7, 73.7, 67.7, 37.4, 32.6, 24.6. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.51; H, 9.24.

$LiAlH_4$ Reduction of Epoxides 2b,c. The reduction of epoxides **2b,c** in the manner described above afforded crude products, which were analyzed by GC (Table II).

Preparative TLC (petroleum ether/Et_2O 3:2) of the crude product (0.29 g) from the reaction of **2b** gave pure ***trans*-3-[(benzyloxy)methyl]-1-cyclohexanol (14b)**: a liquid; IR, see Table III; ^1H NMR δ 7.36–7.26 (m, 5 H), 4.50 (s, 2 H), 3.30 (d, 2 H, J = 6.3 Hz). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.32; H, 9.15. Found: C, 76.54; H, 8.97.

$LiAlH_4$ Reduction of Epoxides 1b,c and 2b,c in the Presence of 12-Crown-4. The reduction of epoxides **1b,c** and **2b,c** in the manner described previously[1] afforded crude products, which were analyzed by GC. The results are shown in Tables I and II, respectively.

Acknowledgment. We gratefully acknowledge partial financial support of this work by the Consiglio Nazionale delle Ricerche, the Ministero dell'Università e della Ricerca Scientifica e Tecnologica (Roma, Italy), NATO Collaborative Science Grant RG 86/0147, and NSF Grant INT-8816449.

Registry No. **1b**, 137946-34-0; **1c**, 91108-45-1; **1d**, 1630-02-0; **1e**, 76704-24-0; **2b**, 138124-71-7; **2c**, 91108-46-2; **2d**, 1630-01-9; **2e**, 76704-23-9; **3b**, 137946-36-2; **3b**-OTMS, 137946-45-3; **3c**, 137946-38-4; **3d**, 94904-76-4; **4b**, 137946-37-3; **4b**-OTMS, 137946-44-2; **4c**, 137946-39-5; **4d**, 94904-78-6; **5c**, 138008-20-5; **5e**, 138008-19-2; **6b**, 138258-88-5; **6b**-OTMS, 138008-16-9; **6c**, 138008-10-3; **6d**, 94904-77-5; **6e**, 76644-34-3; **7b**, 138124-72-8; **7c**, 138230-39-4; **7d**, 138124-73-9; **7e**, 138008-22-7; **8b**, 138008-11-4; **8c**, 138008-13-6; **8d**, 138008-14-7; **8e**, 138008-21-6; **10b**, 138008-12-5; **10c**, 138124-74-0; **10d**, 138008-15-8; **11b**, 137946-40-8; **12b**, 137946-41-9; **13b**, 137946-42-0; **14b**, 137946-43-1; **15**, 1679-51-2; **16**, 137946-35-1; **17**, 19914-91-1; **18**, 138008-17-0; **19**, 138008-18-1; **26**, 132452-43-8; **27**, 108743-93-7; **28**, 76886-31-2; **29**, 137946-46-4; **30**, 137946-47-5.

Supplementary Material Available: Synthesis of and spectroscopic and analytical data for compounds **4c**, **6–8c**, **10c**, **7e**, **8e**, **12b**, **13b**, **26–28**, and **30** (6 pages). Ordering information is given on any current masthead page.

Stereoselective Acetalization of 1,3-Alkanediols by *l*-Menthone: Application to the Resolution of Racemic 1,3-Alkanediols and to the Determination of the Absolute Configuration of Enantiomeric 1,3-Alkanediols

Toshiro Harada,* Hideaki Kurokawa, Yasuhiro Kagamihara, Sachi Tanaka, Atsushi Inoue, and Akira Oku*

Department of Chemistry, Kyoto Institute of Technology, Matsugasaki, Sakyo-ku, Kyoto 606, Japan

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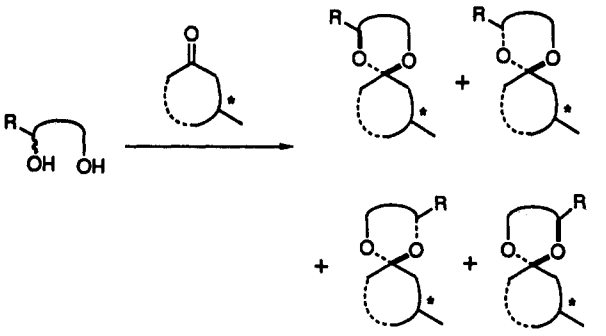
A general and reliable method for the resolution of racemic 1,3-alkanediols, which involves their conversion into diastereomeric spiroacetals derived from *l*-menthone, is described. Thus, the reaction of the *bis*-*O*-trimethylsilyl derivatives of racemic 1,3-alkanediols with *l*-menthone in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate affords the diastereomeric spiroacetals **3** and **4**. The two can be readily separated by silica gel column chromatography. Hydrolysis of each diastereomer under acidic conditions liberates the corresponding enantiomerically pure diol. An empirically derived correlation of configuration and ^1H NMR chemical shifts for spiroacetals **3** and **4** has been developed which is rationalized based on long-range effects due to the magnetic anisotropy inherent to the menthane ring in a rigid spiroacetal conformation. The method described here should be widely applicable to the determination of the absolute configuration of various 1,3-alkanediols.

Introduction

Enantiomerically pure 1,2- and 1,3-alkanediols and derivatives thereof are useful chiral building blocks.[1] Because many 1,2- and 1,3-diols are readily available only as racemic mixtures, a reliable general method for the resolution of such mixtures would be extremely valuable. One of the most promising approaches to the resolution of racemic 1,2- and 1,3-alkanediols involves their conversion into diastereomeric acetals by reaction with a chiral ketone.[2] As Scheme I shows, such acetalization generates a new asymmetric center from what was the carbonyl carbon atom of the ketone and thus produces four diastereomeric spiroacetals. Therefore, in this approach, it is indispensable to use a proper ketone which undergoes a stereoselective acetalization at the dioxy carbon to afford a pair of diastereomeric acetals.[3]

Scheme I



We found that the acetalization of racemic 1,3-alkanediols (*rac*-**1**) by *l*-menthone proceeds with high stereoselectivity to afford, of four possible diastereomers, only the

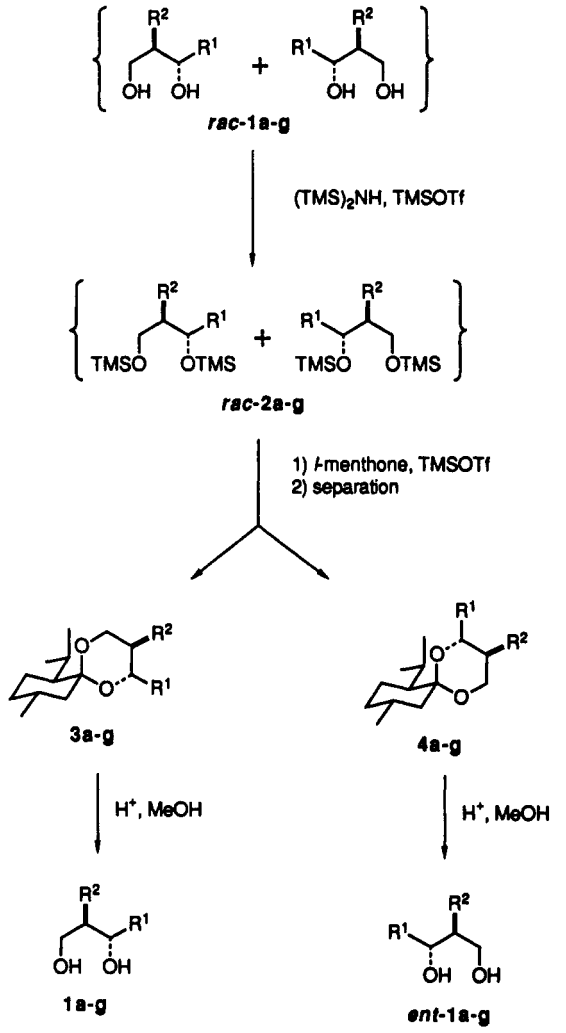
(1) Scott, J. W. In *Asymmetric Synthesis*; Morrison, J. D., Scott, J. W., Eds.; Academic Press: New York, 1984; Vol. 4, Chapter 1.

(2) (a) Eliel, E. L.; Ko, K.-Y. *Tetrahedron Lett.* **1983**, *24*, 3547. (b) Ellis, M. K.; Golding, B. T.; Watson, W. P. *J. Chem. Soc., Chem. Commun.* 1984, 1600.

(3) Meyers, A. I.; White, S. K.; Fuentes, L. M. *Tetrahedron Lett.* **1983**, *24*, 3551.

0022-3263/92/1957-1412$03.00/0

Scheme II



	R^1	R^2
a;	$PhCH_2CH_2$	H
b;	$n\text{-}C_6H_{17}$	H
c;	CH_3	H
d;	*iso*-Pr	H
e;	$CH_2{=}C(CH_3)$	H
f;	$(CH_3)_3CCH_2$	H
g;	*cyclo*-Hex	CH_3

spiroacetals **3** and **4**. Because **3** and **4** can be readily separated by flash chromatography on silica gel, what is in effect a resolution of racemic 1,3-alkanediols is achieved (Scheme II).[4]

Here, we describe in detail the optical resolution of racemic, 1,3-alkanediols via the spiroacetals derived from *l*-menthone. In addition, we describe how this stereoselective acetalization can be applied to the determination of the absolute configurations of enantiomeric 1,3-alkanediols.

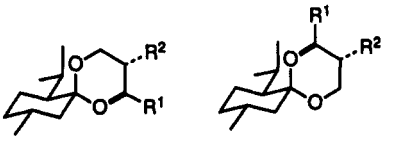
Results and Discussion

Stereoselective Acetalization of Racemic 1,3-Alkanediols by *l*-Menthone. Various racemic 1,3-alkanediols (*rac*-**1a–g**) were converted into the corresponding bis(trimethylsilyl) ethers (*rac*-**2a–g**) in high yield by reaction with hexamethyldisilazane (HMDS). Treatment of *rac*-**2** with *l*-menthone (1.2 equiv) in CH_2Cl_2 at −40 °C in the presence of trimethylsilyl trifluoromethanesulfonate (TMSOTf) (12 mol %)[5] gave a ca. 1:1 mixture of spiroacetals **3** and **4** in high total yield (Table I). It should be noted that the presence of the two other possible diastereomers (**5** and **6**) was not detected in any of the reaction mixtures.

Table I. Preparation of Spiroacetals 3 and 4[a]

		results of the bis-silylation of 1		results of the acetalization of 2	
entry	diol	product	yield (%)	products	yield (%)
1	**1a**	**2a**	91	**3a,4a**	98
2	**1b**	**2b**	91	**3b, 4b**	94
3	**1c**	**2c**	83	**3c,4c**	77
4	**1d**	**2d**	98	**3d, 4d**	70
5[b]	**1e**	**2e**	81	**3e, 4e**	85
6[b]	**1f**	**2f**	95	**3f, 4f**	83
7[b]	**1g**	**2g**	92	**3g, 4g**	75

[a] Unless otherwise noted pure *l*-menthone was employed for the acetalization. [b] An 11:1 mixture of *l*-menthone and isomenthone was employed for the acetalization.



5 **6**

The spiroacetals derived from *l*-menthone and 1,3-diols are conformationally rigid. The 1,3-dioxane ring preferentially assumes the less crowded of two chair conformations (**7** = **8**, rather than **9**).[6] When *rac*-**2** reacts with *l*-menthone, the formation of **5** (= **12**) or **6** (= **13**) is highly unlikely due to the 1,3-diaxial interaction between the substituent R^1 and the menthane ring. Therefore, the enantiomeric diols **1** and *ent*-**1** are converted only into spiroacetals **3** (= **10**) and **4** (= **11**), respectively.

l-Menthone, whether commercially available or prepared in the laboratory by the oxidation of *l*-menthol, is usually contaminated by a small amount of isomenthone (**14**), its C-4 epimer.[7] An 11:1 mixture of *l*- and isomenthone was employed successfully in the acetalization described here (entries 5–7). Spiroacetals derived from isomenthone were not detected in any of the reaction mixtures.

It is highly probable that *l*- and isomenthone are in equilibrium under the reaction conditions described here. However, it is *l*-menthone that undergoes acetalization predominantly (Scheme III). Thus, even when pure *l*-menthone (1.2 equiv) was used, capillary GC analysis of the reaction mixtures still showed isomenthone to be present (eg., *l*-menthone:isomenthone = 13:1 in entry 1).[8] Spiroacetals derived from isomenthone may therefore be in equilibrium with **3** and **4** under the reaction conditions described here.[9] The results of MM2 calculations[10,11]

(4) For a preliminary report, see: Harada, T.; Kurokawa, H.; Oku, A. *Tetrahedron Lett.* **1987**, *27*, 4847.

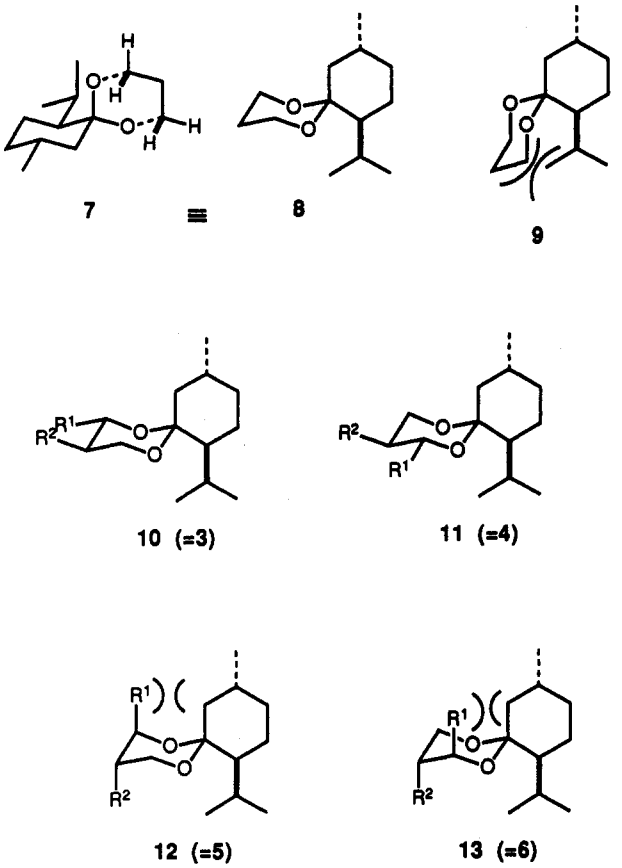
(5) Tsunoda, T.; Suzuki, M.; Noyori, R. *Tetrahedron Lett.* **1980**, *21*, 1357.

(6) (a) Harada, T.; Ikemura, Y.; Nakajima, H.; Ohnishi, T.; Oku, A. *Chem. Lett.* **1990**, 1441. (b) Harada, T.; Wada, I.; Oku, A. *J. Org. Chem.* **1989**, *54*, 2599. (c) Harada, T.; Sakamoto, K.; Ikemura, Y.; Oku, A. *Tetrahedron Lett.* **1988**, *29*, 3097. (d) Harada, T.; Wada, I.; Oku, A. *Ibid.* **1987**, *28*, 4181. (e) Harada, T.; Hayashiya, T.; Wada, I.; Iwa-ake, N. *J. Am. Chem. Soc.* **1987**, *109*, 527.

(7) Thomas, A. F. In *The Total Syntheses of Natural Products*; ApSimon, J., Ed.; John Wiley & Sons: New York, 1973; Vol. 2, p 124.

(8) There is no evidence that points to the isomerization of *l*-menthone during the early stages of the reaction. However, isomerization may become significant later, when the rate of acetalization is slow because the concentrations of the reactants are lower.

(9) Harada, T.; Wada, I.; Uchimura, J.; Inoue, A.; Tanaka, S.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1219.



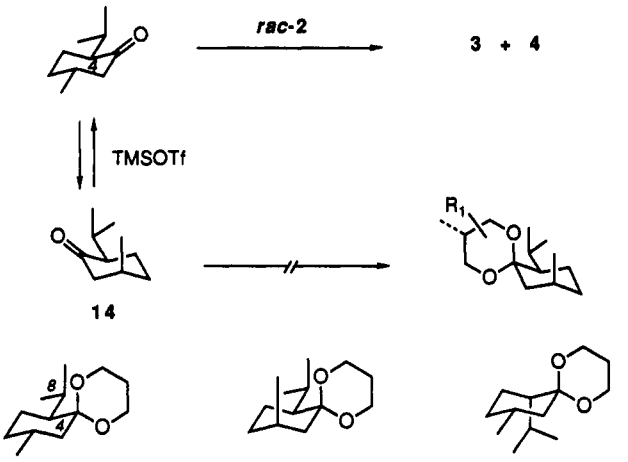
(summarized in Figure 1) performed in order to estimate the relative stabilities of the model compounds **15** and **16** suggest that acetalization by isomenthone would be, thermodynamically, a highly unfavorable process.

Resolution of Racemic 1,3-Alkanediols. The diastereomeric spiroacetals **3** and **4** obtained from a given racemate exhibited considerably different mobilities during silica gel TLC analysis (Table II), so the separation of the two was easily achieved by flash chromatography. Moreover, spiroacetal **3** always eluted faster than **4**. This behavior permits the prediction of the absolute configurations of the parent diols.

The enantiomerically pure diol **1** was obtained simply by treating a methanolic solution of spiroacetal **3** at room temperature with a catalytic amount of either concentrated HCl or *p*-toluenesulfonic acid (Scheme II). Similarly, hydrolysis of spiroacetal **4** gave *ent*-**1**. A mixture of *l*-menthone and isomenthone was recovered in yields of 70–80%. The recovered material contained 10–20% isomenthone. The results summarized in Table II show that the method described here can be used to resolve a variety of racemic 1,3-alkanediols. The absolute configurations of the diols, except that of **1f**, were unambiguously established by measuring their specific rotations ($[\alpha]_D$)[12-14] or by converting them to compounds of known absolute configuration (vide infra).

(10) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *88*, 8127.
(11) The calculations were made with the aid of the program MACROMODEL. See: Still, W. C.; Mohamadi, F.; Richards, N. G. J.; Guida, W. C.; Lipton, M.; Liskamp, R.; Chang, G.; Hendrickson, T.; DeGunst, F.; Hasel, W. *MacroModel V3.0*, Department of Chemistry, Columbia University, New York, NY 10027.
(12) MacNeil, P. A.; Roberts, N. K.; Bosnich, B. *J. Am. Chem. Soc.* **1981**, *103*, 2273.
(13) Buchi, G.; Crombie, L.; Godir, P. J.; Kaltenbram, J. S.; Siddalingaiah, K. S.; Whiting, D. A. *J. Chem. Soc.* **1961**, 2843.
(14) Rouch, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

Scheme III



15a; 0.00 (-80)	**16a**; 2.15 (-81)	**16d**; 2.54 (166)
15b; 0.70 (73)	**16b**; 3.13 (70)	**16e**; 4.21 (50)
15c; 1.13 (-149)	**16c**; 3.56 (-148)	**16f**; 4.24(-82)

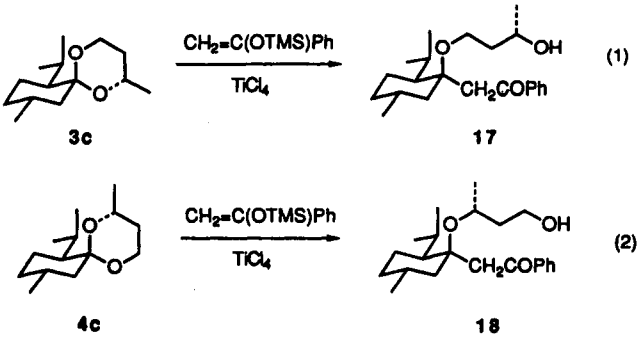
Figure 1. Relative steric energies (kcal/mol) calculated with the aid of MACROMODEL. The magnitude (in deg) of the H–C(4)–C(8)–H dihedral angles are shown in parentheses.

As noted above, of a given pair of spiroacetals, **3** was always eluted faster than **4** during silica gel column chromatography. Similar behavior was observed during column chromatography of the diastereomeric spiroacetals **3h–j** and **4h–j** obtained by the enantiodifferentiating

3h; R^1, R^2 = H, X = TBS	**4h**; R^1, R^2 = H, X = TBS
3i; R^1 = CH_3, R^2 = H, X = H	**4i**; R^1 = CH_3, R^2 = H, X = H
3j; R^1 = H, R^2 = CH_3, X = H	**4j**; R^1 = H, R^2 = CH_3, X = H

acetalization of prochiral 1,3,5-pentanetriols by *l*-menthone.[9] This relationship between structure and R_f implies that, of a given pair, spiroacetal **4** displays a stronger affinity for the acidic surface of silica gel.

We recently reported[6] that Lewis acid-promoted ring-opening of spiroacetals derived from prochiral diols and *l*-menthone occurred exclusively by way of cleavage of the equatorial C–O bond. The ring-opening of spiroacetals **3c** and **4c** occurs in a similar manner. Thus, treatment of **3c** and **4c** with acetophenone enol trimethylsilyl ether in the presence of titanium tetrachloride gave exclusively the products of the cleavage of the equatorial C–O bond, **17** and **18**, respectively (eqs 1 and 2).[15]



(15) Harada, T.; Kurokawa, H.; Oku, A. *Tetrahedron Lett.* **1987**, *27*, 4850.

Table II. Products of the Hydrolysis of Spiroacetals 3 and 4 and Some of Their Physical Properties

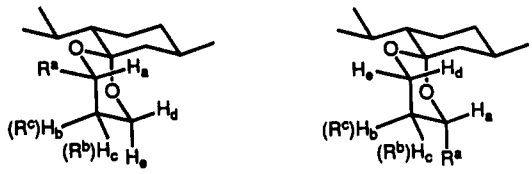
entry	spiroacetal	retardation factor (R_f) solvent system A[a]	retardation factor (R_f) solvent system B[b]	product of hydrolysis (% yield)	ee[c] (%)	$[\alpha]_D$ (deg)
1	**3a**	0.50	0.55	**1a** (92)	>95	+18.6 (*c* 0.474, $CHCl_3$)[d]
2	**4a**	0.31	0.46	*ent*-**1a** (97)	>95	−18.9 (*c* 1.05, $CHCl_3$)[d]
3	**3b**	0.63	0.63	**1b** (100)	92	+14 (*c* 0.66, $CHCl_3$)[d]
4	**4b**	0.44	0.49	*ent*-**1b** (100)	94	
5	**3c**	0.48	0.53	**1c** (68)	97	+28.9 (*c* 0.969, MeOH)
6	**4c**	0.40	0.46	*ent*-**1c** (53)	92	−31 (*c* 1.2, MeOH)[e]
7	**3d**	0.57	0.58	**1d** (83)	>95	+12.0 (*c* 2.43, $CHCl_3$)[f]
8	**4d**	0.48	0.37	*ent*-**1d** (88)	98	−11.3 (*c* 2.00, $CHCl_3$)
9	**3e**	0.78	0.87			
10	**4e**	0.57	0.67	*ent*-**1e** (99)		−19.8 (*c* 4.70, $CHCl_3$)
11	**3f**	0.87	0.98	**1f** (94)		−16.3 (*c* 1.03, $CHCl_3$)
12	**4f**	0.60	0.71			
13	**3g**	0.89	0.89			
14	**4g**	0.67	0.76	*ent*-**1g** (85)		24.3 (*c* 0.939, $CHCl_3$)[g]

[a] Petroleum ether/Et_2O/benzene (90:5:5). [b] Petroleum ether/Et_2O (90:10). [c] Determined by capillary GC analysis (30-m OV-1) of the corresponding (+)-MTPA diesters. [d] Specific rotations of the corresponding bisacetates. [e] Lit.[12] $[\alpha]_D^{23.3}$ −30.8° (neat). [f] Lit.[13] $[\alpha]_D^{27}$ −6.9° (*c* 2.84, $CHCl_3$). [g] Lit.[14] $[\alpha]_D^{25}$ +14.8° (*c* 0.79, $CHCl_3$).

The results imply that the equatorial oxygens of the spiroacetals are more basic than the sterically hindered axial oxygens. It is reasonable to assume that it is the intensity of the interaction between the less-hindered equatorial oxygen and the acidic surface of silica gel that governs the order of elution of spiroacetals **3** and **4**. It may be that **3** is eluted faster than **4** because the basicity of the equatorial oxygen of **3** is reduced as a result of steric hindrance by the neighboring substituent on the 1,3-dioxane ring.

Except for the pair **3c** and **4c**, the various pairs of diastereomeric spiroacetals were base-line separated upon capillary GC analysis (OV-1 and/or PEG). Of a given pair, **3** always eluted faster than **4**. Thus, the order of elution was the same as in silica gel column chromatography. Therefore, acetalization by *l*-menthone can also be utilized to determine the enantiomeric composition of 1,3-alkanediols. In connection with our ongoing project on the utilization of *l*-menthone as a chiral template for diols, we found it necessary to determine the stereochemical stability of the asymmetric carbon of the bis(trimethylsilyl) ether **2e** in the presence of TMSOTf. Thus, enantiomerically pure *ent*-**2e** was treated with 1.0 equiv of TMSOTf in CH_2Cl_2 at 0 °C for 16 h. The enantiomeric composition of the recovered bis(trimethylsilyl) ether was determined by capillary GC analysis of the products formed by acetalization by *l*-menthone. That only spiroacetal **4e** was present clearly showed that the bis(trimethylsilyl) ether was not racemized at all under the conditions employed.

Determination of the Absolute Configuration of 1,3-Alkanediols. The consistent and predictable differences in the NMR spectra of diastereomeric derivatives are widely used to determine the enantiomeric purity of the chiral compounds from which they were derived.[16-18] In a few limited cases, such differences can be further utilized to determine the absolute configurations of the chiral compounds.[17d,e] Mosher and Dale[18] have described an empirically derived correlation between configuration and ^1H NMR chemical shift for diastereomeric α-methoxy-α-(trifluoromethyl)phenylacetates (MTPA esters). This method has been utilized to determine the absolute configurations of various secondary alcohols.[19]



3 **4**

Figure 2.

Table III. Chemical Shifts and Other ^1H NMR Data for H_a of Spiroacetals 3 and 4[a]

acetal 3	δH_a	$J_{Ha,Hb}$; $J_{Ha,Hc}$[b]	acetal 4	δH_a	$J_{Ha,Hb}$; $J_{Ha,Hc}$[b]	$\Delta\delta H_a$[c]
3a	3.95	11.2; 2.4	**4a**	3.78	m; m	0.17
3b	3.92	m; m	**4b**	3.68	m; m	0.24
3c	4.10	11.4; 3.0	**4c**	3.88	12.4; 3.2	0.22
3d	3.66	11.6; 2.6	**4d**	3.37	10.7; 2.8	0.29
3e	4.34	11.6; 2.8	**4e**	4.12	11.8; –	0.22
3f	4.01	11.2; 2.6	**4f**	3.87	12.0; 3.7	0.14
3g	3.33	10.3; –	**4g**	3.18	10.2; –	0.14
3g[d]	3.39	9.8; –	**4g**[d]	3.21	9.8; –	0.18
3h	4.10	m; m	**4h**	3.95	m; m	0.15
3i	3.69	10.4; –	**4i**	3.48	10.6; –	0.21
3i[d]	3.43	10.8; –	**4i**[d]	3.24	10.6; –	0.19
3j	3.91	–; 2.4	**4j**	3.67	–; 2.4	0.24
3k	4.04	11.4; 3.3	**4k**	3.90	11.7; 2.7	0.14
3l[d]	4.17	10.5; –	**4l**[d]	3.99	10.3; –	0.18

[a] Unless otherwise noted, the ^1H NMR spectra are of $CDCl_3$ solutions. [b] Vicinal coupling constant, in Hz. "m" indicates that *J* could not be determined due to interfering signals. [c] $\Delta\delta H_a = \delta H_a$ of **3** − δH_a of **4**. [d] Spectrum is that of a C_6D_6 solution.

As Scheme IV shows, enantiomerically pure diol **1** and its enantiomer *ent*-**1** would be converted into the spiroacetals **3** and **4**, respectively, upon the acetalization by *l*-menthone. Acetalization by *d*-menthone would afford the spiroacetals *ent*-**4** and *ent*-**3**, respectively. Therefore, if the two diasteromeric spiroacetals (**3** and **4** or *ent*-**3** and *ent*-**4**) could be differentiated spectroscopically, then it would be possible to determine the absolute configuration of a 1,3-alkanediol of unknown absolute configuration.

The signals due to the protons H_a, H_d, and H_e in the ^1H NMR spectra of the spiroacetals **3** and **4** were unequivo-

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Scheme IV

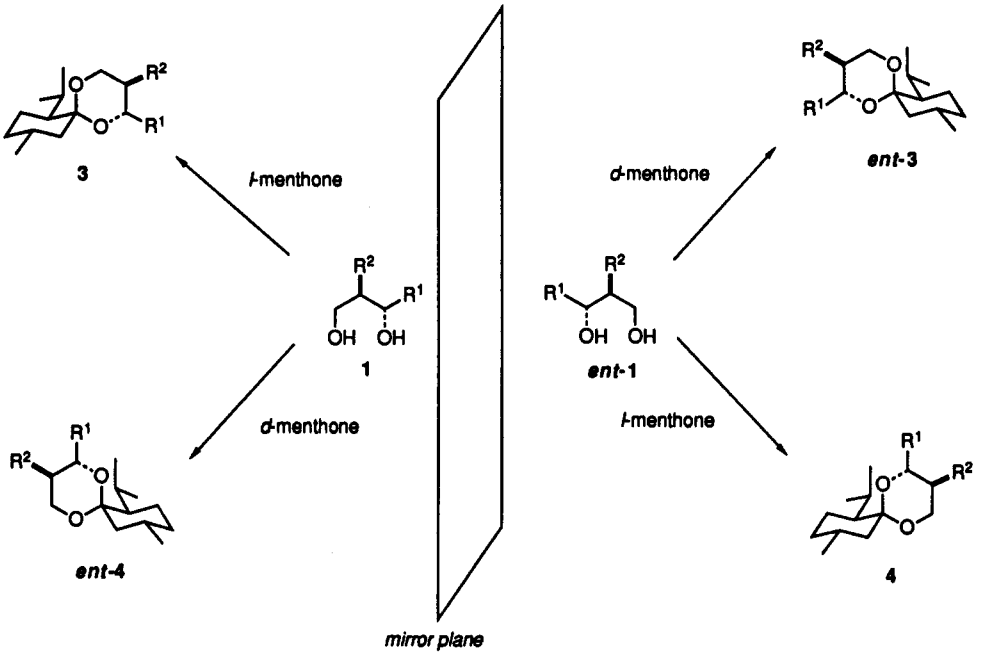


Table IV. Chemical Shifts and Other ^{1}H NMR Data for H_d of Spiroacetals 3 and 4[a]

acetal 3	δH_d	$J_{Hd,Hb}$; $J_{Hd,Hc}$[b]	acetal 4	δH_d	$J_{Hd,Hb}$; $J_{Hd,Hc}$[b]	$\Delta\delta H_d$[c]
3a	3.84	11.7; 3.5	**4a**	4.08	11.6; 3.2	−0.24
3b	3.83	11.8; 3.0	**4b**	4.07	11.5; 3.1	−0.24
3c	3.84	11.5; 3.0	**4c**	4.06	12.0; 3.2	−0.22
3d	3.83	11.8; 2.6	**4d**	4.06	12.3; 2.6	−0.23
3e	3.84	12.0; 2.7	**4e**	4.06	12.3; 2.6	−0.22
3f	3.80	11.2; 2.6	**4f**	4.02	12.0; 3.7	−0.22
3g	3.28	m; –	**4g**	3.52	m; –	−0.24
3g[d]	3.29	11.1; –	**4g**[d]	3.53	11.1; –	−0.24
3h	3.85	11.4; 3.0	**4h**	4.10	11.4; 2.8	−0.25
3i	3.39	11.2; –	**4i**	3.60	11.3; –	−0.21
3i[d]	3.12	11.2; –	**4i**[d]	3.38	11.2; –	−0.26
3j	4.00	–; 2.4	**4j**	4.22	–; 2.6	−0.22
3k	3.81	12; 0; 2.7	**4k**	4.05	12.3; 2.7	−0.24
3l[d]	3.24	11.2; –	**4l**[d]	3.52	11.2; –	−0.28

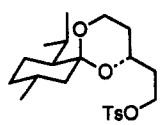
[a] Unless otherwise noted, the ^{1}H NMR spectra are of $CDCl_3$ solutions. [b] Vicinal coupling constant, in Hz. "m" indicates that J could not be determined due to interfering signals. [c] $\Delta\delta H_d = \delta H_d$ of 3 − δH_d of 4. [d] Spectrum is that of a C_6D_6 solution.

Table V. Chemical Shifts and Other ^{1}H NMR Data for H_e of Spiroacetals 3 and 4[a]

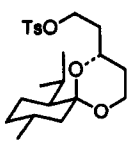
acetal 3	δH_e	$J_{He,Hb}$; $J_{He,Hc}$[b]	acetal 4	δH_e	$J_{He,Hb}$; $J_{He,Hc}$[b]	$\Delta\delta H_e$[c]
3c	3.73	5.6; 1.8	**4c**	3.78	5.1; 1.4	−0.05
3a	3.75	6.3; 1.8	**4a**	3.80	5.6; 1.6	−0.05
3b	3.74	5.8; 1.6	**4b**	3.78	5.1; 1.6	−0.04
3d	3.79	5.8; 1.8	**4d**	3.82	5.2; 1.8	−0.03
3e	3.72	5.6; 1.8	**4e**	3.78	5.4; 1.6	−0.06
3f	3.65	5.9; 1.6	**4f**	3.70	5.4; 1.6	−0.05
3h	3.74	5.8; 1.6	**4h**	3.79	5.3; 1.6	−0.05
3k	3.72	5.7; 1.5	**4k**	3.77	5.1; 1.2	−0.05
3g	3.50	4.9; –	**4g**	3.59	5.1; –	−0.09
3g[d]	3.56	4.7; –	**4g**[d]	3.65	5.2; –	−0.09
3i	3.65	5.2; –	**4i**	3.75	4.8; –	−0.10
3i[d]	3.42	m; –	**4i**[d]	3.52	4.9; –	−0.10
3j	3.50	–; 1.4	**4j**	3.57	–; 2.0	−0.07
3l[d]	3.50	5.0; –	**4l**[d]	3.60	5.6; –	−0.10

[a] Unless otherwise noted, the ^{1}H NMR spectra are of $CDCl_3$ solutions. [b] Vicinal coupling constant, in Hz. "m" indicates that J could not be determined due to interfering signals. [c] $\Delta\delta H_e = \delta H_e$ of 3 − δH_e of 4. [d] Spectrum is that of a C_6D_6 solution.

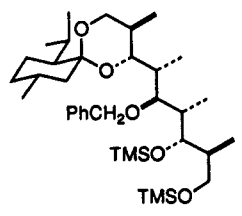
cally identified from the value of the respective coupling constants (Figure 2). The chemical shifts of these protons and the corresponding vicinal coupling constants are shown in Tables III–V for **3a–j** and **4a–j** and the related spiroacetals **3k,l** and **4k,l**.[20]



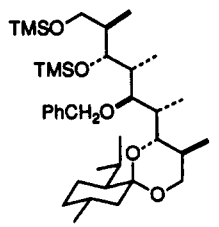
3k



4k



3l



4l

Inspection of the data in Tables III–V reveals several trends: (1) For a given pair of spiroacetals 3 and 4, H_a of 3 consistently resonates at a lower field than does H_a of 4, regardless of the natures of the substituents R^a, R^b, and R^c. (2) For a given pair of spiroacetals 3 and 4, the signals due to H_d and H_e of 3 are both centered at higher field than are the signals due to the corresponding protons of 4. (3) The values of $\Delta\delta_H$ ($\Delta\delta_H = \Delta\delta_H$ of 3 − $\Delta\delta_H$ of 4) calculated from the chemical shifts of H_a, H_d, and H_e all fall into relatively narrow ranges. Thus, $\Delta\delta_{Ha}$ = +0.14 to +0.29 ppm, $\Delta\delta_{Hd}$ = −0.21 to −0.28 ppm, and $\Delta\delta_{He}$ = −0.03 to −0.10 ppm. (4) The absolute values of $\Delta\delta_{Ha}$ and $\Delta\delta_{Hd}$ are nearly identical. (5) When $R^b = R^c$ = H, the respective chemical shifts of H_d and H_e are nearly identical among the members of the same family of spiroacetals.[21] Thus,

(20) The structures of 3l and 4l were established by correlation studies. Harada, T.; Kagamihara, Y.; Sakamoto, K.; Oku, A. Unpublished results.

(21) The ^{1}H NMR data in Tables IV and V show that, when the equatorial substituent R^b is methyl, the vicinal axial proton H_d is deshielded by *ca.* 0.5 ppm, whereas the equatorial proton H_e is shielded by *ca.* 0.2 ppm. The chemical shifts of these protons have similar values in the spectra of **3(4)g**, **3(4)i**, and **3(4)l**.

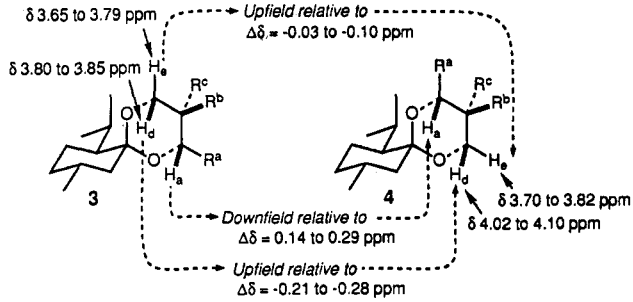


Figure 3.

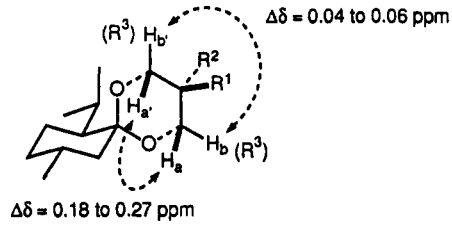


Figure 4.

in the spectrum of spiroacetals, **3**, the chemical shift of H_d is between 3.80 and 3.85 ppm, whereas that of H_c is between 3.65 and 3.79 ppm. In the spectrum of spiroacetal **4**, the respective ranges are 4.02 to 4.10 ppm and 3.70 to 3.82 ppm. (6) The values of $\Delta\delta_{Ha}$, $\Delta\delta_{Hd}$, and $\Delta\delta_{He}$ are not solvent-dependent; they are not affected by changing the solvent from $CDCl_3$ to C_6D_6. These trends are recapitulated in Figure 3.

It should be emphasized that the trends described above were observed when the spectra of the members of each pair of spiroacetals **3** and **4** described here were compared. Because the structure of a give spiroacetal can be correlated with the chemical shifts of the protons H_a, H_d, and H_e, ^1H NMR spectroscopy can be utilized to establish the absolute configuration of the parent 1,3-alkanediols. Thus, a 1,3-alkanediol of unknown absolute configuration can be converted, by reactions with *l*- and *d*-menthone, into two diastereomeric spiroacetals, the structures of which can be inferred by interpreting their ^1H NMR spectra in the light of the trends described above. If such a diol reacted with *l*-menthone to give **3** and with *d*-menthone to give *ent*-**4** then the absolute configuration of the diol must be **1** (the left half of Scheme IV). If, on the other hand, **4** is produced by reaction with *l*-menthone and *ent*-**3** is obtained by reaction with *d*-menthone then the diol must be *ent*-**1** (the right half of Scheme IV).

When the spectra of spiroacetals **3** and **4** are compared, it becomes evident that the values of $\Delta\delta_{Ha}$, $\Delta\delta_{Hd}$, and $\Delta\delta_{He}$ all fall into relatively narrow ranges. Similar phenomena are seen when the chemical shifts of the appropriate protons of the spiroacetal **19a–l** are compared (Table VI and Figure 4).[6c,e] It is not clear which axial proton signal in the spectra of these compounds can be assigned to H_a and which to $H_{a'}$. It is equally difficult to properly assign the two equatorial proton (H_b and $H_{b'}$) signals. However, the absolute values of $\delta_{Ha}-\delta_{Ha'}$ fall into a narrow range ($\Delta\delta_{Ha,a'}$ = 0.18–0.27 ppm) and, furthermore, are very close to the absolute values of $\Delta\delta_{Ha}$ and $\Delta\delta_{Hd}$ derived from the spectra of the various pairs of diastereomeric spiroacetals **3** and **4**. The absolute values of $\delta_{Hb} - \delta_{Hb'}$ derived from the spectra of spiroacetals **19a–f** are also nearly identical ($\Delta\delta_{Hb,b'}$ = 0.04–0.06 ppm) and are very close to the absolute values of $\Delta\delta_{He}$.

It is well-documented that, in the absence of such complicating factors as the rapid interconversion of the conformers and the presence of certain substituents which are capable of exerting pronounced long-range diamagnetic anisotropic effects, the equatorial protons of cyclohexanes resonate downfield from their axial counterparts.[22] The chemical shift of a given proton of a functional group that is attached to a cyclohexane ring also depends on whether the functional group occupies an equatorial or axial position.[22] That the chemical shifts of equatorial and axial protons (and those of otherwise equivalent protons of equatorial and axial substituents) differ is believed to be a result of the long-range effects due to the magnetic anisotropy of the carbon–carbon single bonds of the cyclohexane ring.[22]

Table VI. Intramolecular Chemical Shift Differences for the Protons of Spiroacetal 19[a]

acetal	R^1	R^2	R^3	$\Delta\delta H_{a,a'}$[b]	$\Delta\delta H_{b,b'}$
19a	Me	H	H	0.21	0.06
19b	H	Me	H	0.22	0.04
19c	Ph	H	H	0.19	m
19d	H	Ph	H	0.21	0.05
19e	Ph	Me	H	0.23	0.06
19f	Me	Ph	H	0.27	m
19g	H	H	Me	0.23	
19h	H	H	n-C_6H_{13}	0.25	
19i	H	H	$CH_2{=}CHCH_2$	0.26	
19j	H	H	$BnOCH_2$	0.18	
19k	H	H	$BnO(CH_2)_2$	0.19	
19l	H	H	$PhS(CH_2)_3$	0.24	

[a] The ^1H NMR spectra are of $CDCl_3$ solutions. "m" indicates that the signals could not be unequivocally identified due to interfering signals. [b] $\Delta\delta H_{a,a'} = \delta H_a - \delta H_{a'}$; $\Delta\delta H_{b,b'} = \delta H_b - \delta H_{b'}$.

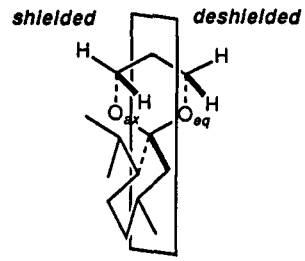


Figure 5.

The spiroacetals derived from *l*-menthone and 1,3-diols assume rigid double-chair conformations in which the two oxygen atoms occupy equatorial and axial positions relative to the menthane ring. In spiroacetal **19**, the environments of H_a and $H_{a'}$ are quite similar with respect to the 1,3-dioxane ring but not with respect to the menthane ring. Thus, the long-range diamagnetic anisotropic effects of the menthane ring, which could shield H_a and deshield $H_{a'}$, may be what are responsible for the chemical shifts of H_a and $H_{a'}$ being different (Figure 5). That the chemical shifts of the two equatorial protons (H_b and $H_{b'}$) of **19** also differ from each other, but not to as great on extent, can also be explained in terms of similar effects, which are felt less intensely because H_b and $H_{b'}$ are located farther from the menthane ring than are the axial protons H_a and $H_{a'}$.

That the values of $\Delta\delta_H$ calculated from the respective chemical shifts of the various seemingly equivalent (but located in *different* molecules) protons of the diastereomeric spiroacetals **3** and **4** are very close to the corresponding values of $\Delta\delta_H$ calculated from the respective chemical shifts of the seemingly equivalent (and located in the *same* molecule) protons of the spiroacetals **19** suggests that the argument used above can also be used to

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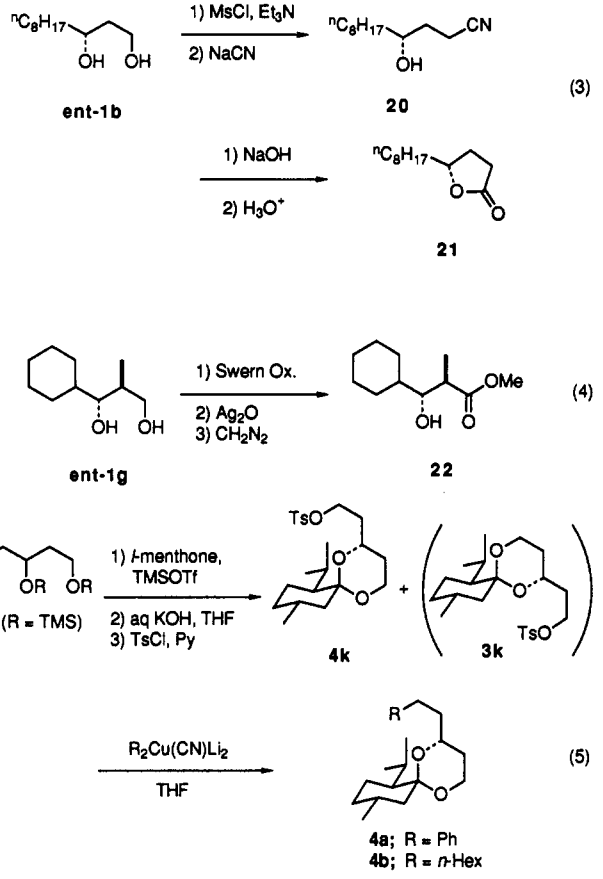
explain why the seemingly equivalent protons of **3** and **4** are, in fact, nonequivalent. Thus, H_a of **3** should be deshielded to about the same degree as H_a of **19**, whereas H_a of **4** should be shielded to about the same degree as $H_{a'}$ of **19**. That the chemical shifts of H_d of **3** and H_d of **4** differ must also be a result of the same long-range diamagnetic anisotropic effects, which are felt more intensely by one axial proton than by the other. Similarly, it is likely that the absolute values of $\Delta\delta_{He}$ are smaller than those of $\Delta\delta_{Hd}$ because the equatorial protons H_e are located farther from the menthane ring than are the axial protons and, consequently, do not feel the long-range diamagnetic effect of the menthane ring as intensely.

Because credible reasons for the nonequivalence of the various seemingly equivalent protons of spiroacetals **3** and **4** can be given and also because $\Delta\delta_H$ for a given pair of such protons tends to assume a constant value, what is described here appears to be a sound and reliable method for determining the absolute configurations of 1,3-alkanediols.

Determination of the Absolute Configuration of 1,3-Alkanediols 1. The absolute configuration of *ent*-**1b** was established by converting it into (+)-(*R*)-γ-dodecanolactone (**21**), a pheromone of the rove beetle[23] (eq 4).



Thus, the selective mesylation of *ent*-**1b** (obtained by the hydrolysis of **4b**) followed by reaction of the mesylate with NaCN/DMF gave the hydroxynitrile **20** in 67% yield. Hydrolysis of **20** and lactonization of the hydroxy acid so formed provided (+)-(*R*)-**21** ($[\alpha]_D$ +36.2° (*c* 0.801, MeOH)).[24]

The absolute configuration of the unsaturated diol *ent*-**1e** was established by catalytically hydrogenating it to yield *ent*-**1d**. The absolute configuration of *ent*-**1g** was established by converting it into methyl (2*R*,3*R*)-3-cyclohexyl-2-methyl-3-hydroxypropanoate (**22**) ($[\alpha]_D$ −6.6° (*c* 2.48, $CHCl_3$))[25] (eq 4). The absolute configuration of diol **1a** was established by the following correlation studies between spiroacetals **4a** and **4b** (eq 5). Thus, enantiodifferentiating acetalization of tris(trimethylsilyl) ether **23** with *l*-menthone[9] followed by tosylation of the resulting hydroxy spiroacetals gave a 2.8:1 mixture of tosylates **4k** and **3k** from which pure **4k** was isolated in 65% yield. Reactions of **4k** with $(Ph)_2Cu(CN)Li_2$ and $(n\text{-}C_6H_{13})_2Cu(CN)Li_2$ gave spiroacetals **4a** (89%) and **4b** (93%), respectively.[26]

Experimental Section

Unless otherwise noted, ^1H NMR spectra of $CDCl_3$ solutions were recorded at 200 MHz. *J* values are given in Hz. Microanalyses were performed by the Microanalysis Center of Kyoto University. GC analyses were performed with 20-m PEG-20M and 30-m OV-1 capillary columns. Glass plates coated with Merck silica gel 60 F254 were used for analytical TLC. Wakogel C-300 was used for flash chromatography. Unless otherwise specified, all organic extracts were dried over Na_2SO_4. *l*-Menthone was purchased from Norse Laboratories Inc.. THF was distilled from sodium benzophenone ketyl. CH_2Cl_2 and DMF were distilled from CaH_2.

The racemic diols *rac*-**1a**,[27] **-1b**,[28] **-1d**[29] **-1e**,[29] and **-1f** were prepared by the $LiAlH_4$ reduction of the hydroxy ester formed by the reaction of the lithium enolate of EtOAc with the appropriate aldehyde. The preparation of 5,5-dimethyl-1,3-hexanediol (*rac*-**1f**) is representative.

Thus, to a solution of $(i\text{-}Pr)_2NH$ (8.50 g, 84 mmol) in THF (120 mL) at 0 °C was added BuLi (52.5 mL of 1.6 M solution in hexane). The mixture was stirred for 30 min. The solution of lithium diisopropylamide that resulted was cooled to −80 °C, whereupon a THF (10 mL) solution of EtOAc (7.05 g, 80 mmol) was slowly added. After 30 min, 3,3-dimethylbutanal (3.50 g, 35 mmol) was added. The mixture was stirred for an additional 30 min before the reaction was quenched with water. After extraction with EtOAc, the organic layer was washed with brine, dried, and then concentrated in vacuo. To a solution of the crude hydroxy ester in THF (100 mL) at rt was added $LiAlH_4$ (1.51 g, 40 mmol). The mixture was refluxed for 2 h and then was cooled to 0 °C. Water was added to quench the reaction. The mixture was acidified with 1 N aqueous HCl and was extracted twice with EtOAc. The combined organic layers were dried and concentrated in vacuo. The residue was purified by Kugelrohr distillation (80 °C (0.03 mmHg)) to give 3.72 g (73%) of *rac*-**1f**: ^1H-NMR δ 0.97 (9 H, s), 1.37 (1 H, dd, *J* = 3.0, 14.7), 1.47 (1 H, dd, *J* = 7.8, 14.7), 1.69 (2 H, m), 2.10 (2 H, m), 3.80–3.93 (2 H, m), 4.04 (1 H, m); IR (liquid film) 3330 (br), 1050 cm^{-1} (s); MS (CI) *m*/*z* (relative intensity) 147 (M^+ + 1, 6), 129 (100). Anal. Calcd for $C_8H_{18}O_2$: C, 65.71; H, 12.41. Found: C, 65.41; H, 12.16.

(1*R,2*S**)-1-Cyclohexyl-2-methyl-1,3-propanediol (1g).** To a DMF (143 mL) solution of 1-cyclohexyl-2-methyl-2-propen-1-ol (22.0 g, 0.143 mol, which was prepared in 69% yield by the reaction of cyclohexanecarboxaldehyde with $(CH_2{=}C(CH_3))MgBr$) at 25 °C were added successively imidazole (15.4 g, 0.214 mol) and *t*-$BuMe_2SiCl$ (23.7 g, 0.157 mol). The mixture was stirred for 16 h at 25 °C, and then it was diluted with hexane (300 mL) and was washed twice with water. The organic layer was dried and then concentrated in vacuo. Distillation of the residue gave 35.5 g (91%) of 3-(*tert*-butyldimethylsiloxy)-3-cyclohexyl-2-methyl-1-propene: bp 72–75 °C (0.4 mmHg); ^1H NMR δ −0.02 (3 H, s), 0.03 (3 H, s), 0.89 (9 H, s) 1.05–1.49 (5 H, m), 1.57–1.79 (8 H, m, including t (3 H, *J* = 0.9) at 1.64), 1.94 (1 H, m), 3.63 (1 H, d, *J* = 7.5), 4.78 (2 H, m).

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To a THF (100 mL) suspension of 9-BBN (12.2 g, 100 mmol) at −80 °C was added a solution of the silyl ether (17.9 g, 66.7 mmol) in THF (100 mL). The mixture was stirred for 16 h during which time it was allowed to warm to rt. The mixture was cooled to −10 °C, and 6 N aqueous NaOH (24 mL) and 30% H_2O_2 (48 mL) were successively added. The mixture was stirred for 2 h during which time it was allowed to warm to 25 °C. Brine was then added, and the mixture was extracted twice with EtOAc. The combined extracts were dried and then concentrated in vacuo to give an oil. This was purified by flash chromatography (hexane/EtOAc, gradient elution from 95:5 to 70:30) to give 17.3 g (77%) of (2*S**,3*R**)-3-(*tert*-butyldimethylsiloxy)-3-cyclohexyl-2-methylpropanol: ^{1}H NMR δ 0.00 (3 H, s), 0.02 (3 H, s), 0.83 (9 H, s), 0.89 (3 H, d, *J* = 7.1), 1.00–2.80 (12 H, m), 3.33 (1 H, t, *J* = 4.8), 3.48 (1 H, dd, *J* = 5.6, 10.4), 3.61 (1 H, dd, *J* = 4.4, 10.4).

A mixture of the siloxy alcohol (2.47 g, 7.70 mmol) and $Bu_4N^+F^-$ (38.6 mL of a 1 M in THF) was stirred for 16 h at 25 °C. Brine was then added, and the mixture was extracted twice with EtOAc. The combined extracts were dried and concentrated. The residue was purified by flash chromatography (EtOAc/hexane (50:50)) to give 1.17 g (88%) of **1g**:[14] mp 59–60 °C (hexane).

General Procedure for the Preparation of the Bis(trimethylsilyl) Ethers 2a–g. To a solution of diol 1 (40 mmol), 1,1,1,3,3,3-hexamethyldisilazane (HMDS, 13.0 g, 81 mmol), and THF (40 mL) at 25 °C was added a few drops of TMSOTf. The mixture was stirred for 0.5–1 h. It was diluted with petroleum ether. The mixture was washed twice with ice-cold water, dried, and then concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/hexane) or by distillation.

5-Phenyl-1,3-bis(trimethylsiloxy)pentane (2a): ^{1}H NMR δ 0.11 (9 H, s), 0.13 (9 H, s), 1.67–1.81 (4 H, m), 2.54–2.76 (2 H, m), 3.47 (2 H, t, *J* = 6.7), 3.87 (1 H, quintet, *J* = 5.8), 7.15–7.20 (3 H, m), 7.26–7.28 (2 H, m); IR (liquid film) 1245 (s), 835 (s), 745 (s), 690 cm^{-1} (s).

1,3-Bis(trimethylsiloxy)undecane (2b): ^{1}H NMR δ 0.09 (9 H, s), 0.10 (9 H, s), 0.87 (3 H, br t, *J* = ca 7), 1.22–1.46 (14 H, m), 1.56–1.73 (2 H, m), 3.62 (2 H, t, *J* = 6.8), 3.76 (1 H, quintet, *J* = 6.4); IR (liquid film) 1250 (s), 840 (s), 750 cm^{-1} (s).

1,3-Bis(trimethylsiloxy)butane (2c): ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.101 (9 H, s), 0.108 (9 H, s), 1.148 (3 H, d, *J* = 6.2), 1.63 (2 H, m), 3.62 (2 H, m), 3.946 (1 H, m).

4-Methyl-1,3-bis(trimethylsiloxy)pentane (2d): bp 122 °C (24 mmHg); ^{1}H NMR 0.09 (18 H, s), 0.84 (3 H, d, *J* = 6.7), 0.86 (3 H, d, *J* = 6.9), 1.60 (3 H, m), 3.55 (3 H, m); IR (liquid film) 1255 (s), 1100 (s), 840 (s), 750 cm^{-1} (s).

2-Methyl-3,5-bis(trimethylsiloxy)pentene (2e): bp 47 °C (1.5 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.093 (9 H, s), 0.106 (9 H, s), 1.686 (3 H, t, *J* = 1.1), 1.71 (2 H, m), 3.60 (2 H, m), 4.188 (1 H, t, *J* = 6.4), 4.763 (1 H, m), 4.889 (1 H, m); IR (liquid film) 1255 (s), 1095 (s), 850 (s), 750 cm^{-1} (s).

5,5-Dimethyl-1,3-bis(trimethylsiloxy)hexane (2f): ^{1}H NMR δ 0.11 (9 H, s), 0.13 (9 H, s), 0.92 (9 H, s), 1.36 (1 H, dd, *J* = 4.8, 14.4), 1.44 (1 H, dd, *J* = 6.5, 14.4), 1.56 (2 H, s), 1.70 (2 H, m), 3.62 (2 H, t, *J* = 6.9), 3.94 (1 H, td, *J* = 5.8, 6.0); IR (liquid film) 1255 (s), 1090 (s), 845 cm^{-1} (s).

(1*R,2*S**)-1-Cyclohexyl-2-methyl-1,3-bis(trimethylsiloxy)propane (2g)**: bp 98–99 °C (0.4 mmHg); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.096 (9 H, s), 0.108 (9 H, s), 0.894 (3 H, d, *J* = 6.9), 0.98–1.85 (12 H, m), 3.283 (1 H, dd, *J* = 5.2, 6.0), 3.392 (1 H, dd, *J* = 7.5, 9.8), 3.675 (1 H, dd, *J* = 3.8, 9.8); IR (liquid film) 1250 (s), 1090 (s), 880 (s), 845 cm^{-1} (s).

Preparation of Spiroacetals 3 and 4. The preparation of **3a** and **4a** is typical. To a solution of **2a** (6.37 mmol), *l*-menthone (7.01 mmol), and CH_2Cl_2 (13 mL) at −40 °C was added TMSOTf (0.7 mmol). The mixture was stirred for 18 h at −40 °C, and then the reaction was quenched by adding pyridine. The mixture was diluted with petroleum ether and was washed with aqueous $NaHCO_3$. The organic layer was dried and concentrated. The residue was purified by flash chromatography (petroleum ether/Et_2O (96:4)) to give, in order of elution, 971 mg (48%) of **3a** and 998 mg (50%) of **4a**. **3a**: ^{1}H NMR δ 0.70 (1 H, dd, *J* = 12.6, 13.4), 0.89 (6 H, d, *J* = 7.2), 0.93 (3 H, d, *J* = 7.4), 1.16–1.94 (10 H, m), 2.41 (1 H, d hept, *J* = 1.8, 7.2), 2.56–2.82 (3 H, m), 2.75 (1 H, ddd, *J* = 1.8, 6.3, 11.2), 3.84 (1 H, dt, *J* = 3.5, 11.7), 3.95 (1 H, dddd, *J* = 2.4, 5.0, 7.4, 11.2), 7.13–7.36 (5 H, m); IR (liquid film) 1160 (s), 1120 (s), 750 (s), 700 (s) cm^{-1}; MS *m*/*z* (relative intensity) 316 (M^+, 26), 231 (25), 91 (100); HRMS calcd for $C_{21}H_{32}O_2$ 316.2404, found 316.2398. **4a**: ^{1}H NMR δ 0.69 (1 H, dd, *J* = 12.4, 13.2), 0.89 (3 H, d, *J* = 6.6), 0.91 (3 H, d, *J* = 7.0), 0.94 (3 H, d, *J* = 6.7), 1.12–1.89 (10 H, m), 2.45 (1 H, d hept, *J* = 1.8, 7.0), 2.54–2.94 (3 H, m), 3.78 (1 H, m), 3.80 (1 H, ddd, *J* = 1.6, 5.6, 11.8), 4.08 (1 H, dt, *J* = 3.2, 11.6), 7.12–7.34 (5 H, m); IR (liquid film), 1160 (s), 1120 (s), 750 (s), 700 cm^{-1} (s); MS *m*/*z* (relative intensity) 316 (M^+, 18), 231 (21), 91 (100); HRMS calcd for $C_{21}H_{32}O_2$ 316.2404, found 316.2399. Anal. Calcd for $C_{21}H_{32}O_2$: C, 79.70; H, 10.19. Found: C, 79.70; H, 10.22.

Spiroacetal 3b: ^{1}H NMR δ 0.66 (1 H, t, *J* = 13.0), 0.88 (12 H, m), 1.1–1.6 (21 H, m), 1.68 (1 H, br d, *J* = ca. 12), 2.36 (1 H, d hept, *J* = 3.2, 7.0), 2.68 (1 H, ddd, *J* = 1.8, 3.1, 13.6), 3.74 (1 H, ddd, *J* = 1.6, 5.8, 11.2), 3.83 (1 H, dt, *J* = 3.0, 11.8), 3.92 (1 H, m); IR (liquid film) 2930 (s), 1120 (s), 1010 cm^{-1} (s); MS *m*/*z* (relative intensity) 324 (M^+, 18), 309 (12), 267 (25), 239 (34), 55 (100); HRMS calcd for $C_{21}H_{40}O_2$ 324.3030, found 324.3022.

Spiroacetal 4b: ^{1}H NMR δ 0.66 (1 H, t, *J* = 13.0), 0.89 (12 H, m), 1.1–1.6 (21 H, m), 1.69 (1 H, br d, *J* = 12.8), 2.38 (1 H, d hept, *J* = 1.4, 7.0), 2.69 (1 H, ddd, *J* = 1.8, 3.1, 13.4), 3.68 (1 H, m), 3.78 (1 H, ddd, *J* = 1.6, 5.1, 11.5), 4.07 (1 H, dt, *J* = 3.1, 11.5); IR (liquid film) 2940 (s), 1120 (s), 1010 (s) cm^{-1}; MS *m*/*z* (relative intensity) 324 (M^+, 20), 309 (13), 267 (22), 239 (33), 55 (100); HRMS calcd for $C_{21}H_{40}O_2$ 324.3030, found 324.3016. Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.58; H, 12.70.

Spiroacetal 3c: ^{1}H NMR δ 0.68 (1 H, dd, *J* = 12.4, 13.5), 0.87 (6 H, d, *J* = 7.0), 0.89 (3 H, d, *J* = 7.1), 1.13 (3 H, d, *J* = 6.1), 1.18–1.78 (8 H, m), 2.38 (1 H, d hept, *J* = 2.4, 7.0), 2.69 (1 H, ddd, *J* = 2.0, 3.2, 13.4), 3.73 (1 H, ddd, *J* = 1.8, 5.6, 11.6), 3.84 (1 H, dt, *J* = 3.0, 11.5), 4.10 (1 H, dqd, *J* = 3.0, 5.9, 11.4); IR (liquid film) 2970 (s), 1460 (s), 1165 (s), 1120 cm^{-1} (s); MS *m*/*z* (relative intensity) 226 (M^+, 21, 211 (40), 169 (80), 141 (100), 55 (77); HRMS calcd for $C_{14}H_{26}O_2$ 226.1933, found 226.1940.

Spiroacetal 4c: ^{1}H NMR δ 0.66 (1 H, t, *J* = 12.4), 0.87 (6 H, d, *J* = 7.0), 0.88 (3 H, d, *J* = 6.8), 1.11 (3 H, d, *J* = 6.0), 1.17–1.80 (8 H, m), 2.39 (1 H, d hept, *J* = 1.8, 7.0), 2.69 (1 H, ddd, *J* = 2.0, 3.2, 11.6), 3.78 (1 H, ddd, *J* = 1.4, 5.1, 13.1), 3.88 (1 H, dqd, *J* = 3.2, 6.0, 12.4), 4.06 (1 H, dt, *J* = 3.2, 12.0); IR (liquid film) 2970 (s), 1460 (s), 1165 (s), 1120 cm^{-1} (s); MS *m*/*z* (relative intensity) 226 (M^+, 37), 211 (42), 169 (83), 141 (100), 55 (61); HRMS calcd for $C_{14}H_{26}O_2$ 226.1933, found 226.1929.

Spiroacetal 3d: ^{1}H NMR δ 0.64 (1 H, t, *J* = 12.8), 0.80–0.98 (15 H, m), 1.10–1.77 (10 H, m), 2.39 (1 H, d hept, *J* = 2.4, 7.2), 2.68 (1 H, ddd, *J* = 2.9, 3.2, 13.4), 3.66 (1 H, ddd, *J* = 2.6, 6.1, 11.6), 3.79 (1 H, ddd, 1.8, 5.8, 11.8), 3.83 (1 H, dt, 2.6, 11.8); IR (liquid film) 2950 (s), 1455 (s), 1165 (s), 1115 cm^{-1} (s); MS *m*/*z* (relative intensity) 254 (M^+, 10), 211 (9), 169 (14), 83 (100), 55 (54); HRMS calcd for $C_{16}H_{30}O_2$ 254.2247, found 254.2254.

Spiroacetal 4d: ^{1}H NMR δ 0.66 (1 H, t, *J* = 12.8), 0.77–1.00 (15 H, m), 1.1–1.8 (10 H, m), 2.39 (1 H, d hept, *J* = 1.8, 7.0), 2.69 (1 H, ddd, *J* = 2.0, 3.2, 13.4), 3.37 (1 H, ddd, *J* = 2.8, 6.9, 10.7), 3.82 (1 H, ddd, *J* = 1.8, 5.2, 11.6), 4.06 (1 H, dt, *J* = 3.2, 11.6); IR (liquid film) 2950 (s), 1455 (s), 1165 (s), 1115 cm^{-1} (s); MS *m*/*z* (relative intensity) 254 (M^+, 8), 197 (7), 169 (11), 83 (100), 55 (54); HRMS calcd for $C_{16}H_{30}O_2$ 254.2247, found 254.2252.

Spiroacetal 3e: ^{1}H NMR δ 0.67 (1 H, t, *J* = 13.0), 0.81 (6 H, d, *J* = 6.6), 0.82 (3 H, d, *J* = 7.0), 1.15–1.78 (11 H, m, including br s at 1.67), 2.39 (1 H, d hept, *J* = 2.0, 7.1), 2.65 (1 H, ddd, *J* = 2.2, 3.2, 13.6), 3.72 (1 H, ddd, *J* = 1.8, 5.6, 12.2), 3.84 (1 H, dt, *J* = 2.7, 12.0), 4.34 (1 H, dd, *J* = 2.8, 11.6), 4.76 (1 H, m), 4.84 (1 H, m); IR (liquid film) 2960 (s), 1115 (s), 900 cm^{-1} (s); MS *m*/*z* (relative intensity) 252 (M^+, 8), 195 (4), 167 (9), 81 (100); HRMS calcd for $C_{16}H_{28}O_2$ 252.2090, found 252.2093.

Spiroacetal 4e: ^{1}H NMR δ 0.63 (1 H, t, *J* = 12.8), 0.81 (1 H, d, *J* = 6.8), 0.81 (1 H, d, *J* = 7.0), 0.82 (1 H, d, *J* = 6.7), 1.13 (1 H, ddd, *J* = 2.3, 6.8, 9.6), 1.28–2.15 (10 H, m, including brs at 1.66), 2.34 (1 H, d hept, *J* = 1.8, 6.8) 2.67 (1 H, brd, *J* = 13.4), 3.78 (1 H, ddd, *J* = 1.6, 5.4, 11.0), 4.06 (1 H, dt, *J* = 2.6, 12.3), 4.12 (1 H, brd, 11.8), 4.73 (1 H, m), 4.90 (1 H, m); IR (liquid film) 2960 (s), 1130 (s), 1100 (s), 900 cm^{-1} (s); MS *m*/*z* (relative intensity) 252 (M^+, 8), 195 (4), 167 (8), 81 (100); HRMS calcd for $C_{16}H_{28}O_2$ 252.2090, found 252.2080.

Spiroacetal 3f: ^{1}H NMR δ 0.59 (1 H, t, *J* = 13.0), 0.74–0.82 (9 H, m), 0.84 (9 H, s), 0.97–1.68 (10 H, m), 2.30 (1 H, d hept, *J* = 1.8, 7.0), 2.66 (1 H, ddd, *J* = 1.8, 3.4, 13.2), 3.65 (1 H, ddd, *J* = 1.6, 5.9, 11.2), 3.80 (1 H, dt, *J* = 2.6, 11.2), 4.01 (1 H, tdd, *J*

= 2.6, 8.2, 11.2); IR (liquid film) 2950 (s), 1125 (s), 1030 (s), 990 cm^{-1} (s); MS, m/z (relative intensity) 282 (M^+, 16), 267 (8), 197 (25), 111 (60) 69 (100); HRMS calcd for $C_{18}H_{34}O_2$ 282.2560, found 282.2556.

Spiroacetal 4f: ^1H NMR δ 0.61 (1 H, dd, J = 12.4, 13.2), 0.80 (3 H, d, J = 6.9), 0.81 (3 H, J = 6.9), 0.83 (3 H, d, J = 6.0), 0.86 (9 H, s), 1.05–1.70 (11 H, m), 2.32 (1 H, d hept, J = 1.8, 7.0), 3.70 (1 H, ddd, J = 1.6, 5.4, 12.0), 3.87 (1 H, tdd, J = 3.7, 12.0, 12.8), 4.02 (1 H, ddd, J = 3.7 12.0, 12.8); IR (liquid film) 2950 (s), 1155 (s), 1130 (s), 1095 (s), 975 cm^{-1} (s); MS m/z (relative intensity) 282 (M^+, 21), 267 (8), 197 (23), 111 (72), 69 (100); HRMS calcd for $C_{18}H_{34}O_2$ 282.2560, found 282.2565.

Spiroacetal 3g: ^1H NMR (300 MHz, C_6D_6) δ 0.400 (3 H, d, J = 6.7), 0.655 (1 H, t, J = 13.1), 0.891 (3 H, d, J = 6.6), 1.075 (3 H, d, J = 7.1), 1.1–1.9 (21 H, m, including d (3 H, J = 7.0) at 1.195), 2.640 (1 H, ddd, J = 1.7, 3.3, 13.4), 2.752 (1 H, d hept, J = 2.1, 7.0), 3.221 (1 H, t, J = 11.32), 3.329 (1 H, brd, J = 10.3), 3.498 (1 H, dd, J = 4.9, 11.2); IR (liquid film) 2930 (s), 1135 (s), 1125 cm^{-1} (s); MS m/z (relative intensity) 308 (M^+, 15), 251 (4), 223 (6), 137 (76), 81 (100); HRMS calcd for $C_{20}H_{36}O_2$: 308.2717, found 307.2713.

Spiroacetal 4g: ^1H NMR (300 MHz, C_6D_6) δ 0.384 (3 H, d, J = 6.7), 0.710 (1 H, dd, J = 12.6, 13.3), 0.903 (3 H, d, J = 6.6), 1.06–1.80 (24 H, m, including d (3 H, J = 7.1) at 1.096 and d (3 H, J = 7.0) at 1.188), 2.687 (1 H, ddd, J = 2.1, 3.3, 13.5), 2.803 (1 H, d hept, J = 2.1, 7.0), 3.149 (1 H, brd, J = 10.3), 3.471 (1 H, t, J = 11.2), 3.593 (1 H, dd, J = 5.1, 10.5); IR (liquid film) 2930 (s), 1135 (s), 995 cm^{-1} (s); MS m/z (relative intensity) 308 (18), 251 (5), 223 (10), 137 (78), 81 (100); HRMS calcd for $C_{20}H_{36}O_2$ 308.2727, found 308.2708.

General Procedure for the Hydrolysis of Spiroacetals 3 and 4. To a solution of **3** or **4** (1 mmol) in MeOH (2-4 mL) at rt was added few drops of concentrated aq HCl or solid *p*-toluenesulfonic acid (0.05 mmol). The mixture was stirred at rt for 10–20 h. Water was then added, and the MeOH was removed in vacuo. The residue was extracted three times with EtOAc. The combined extracts were dried and then concentrated in vacuo. The residue was purified by flash chromatography (EtOAc/petroleum ether) to give *l*-menthone (which contained 10–20% isomenthone) and the optically active diol **1** or *ent*-**1**. The specific rotations ($[\alpha]_D$) of **1a–g** or the corresponding bisacetates are shown in Table II.

Ring-Opening of Spiroacetals 3c and 4c. To a solution of **3c** (114.3 mg, 0.505 mmol), acetophenone enol trimethylsilyl ether (0.56 mmol), and CH_2Cl_2 (5 mL) at −85 °C was added $TiCl_4$ (0.56 mmol, 0.56 mL of a 1 M solution in CH_2Cl_2). The resulting yellow solution was stirred at −85 °C for 30 min. Then pyridine (0.2 mL) was added. The mixture was poured into brine and was extracted twice with petroleum ether/EtOAc. The combined extracts were washed with aqueous $NaHCO_3$, dried, and then concentrated in vacuo to give an oil, from which **17** (145.6 mg, 75%) was isolated by flash chromatography. **17**: ^1H NMR δ 0.70 (3 H, d, J = 6.8), 0.84 (3 H, d, J = 6.0), 0.86 (3 H, d, J = 6.8), 1.21 (3 H, d, J = 6.4), 1.24–2.00 (14 H, m), 3.16 (1 H, d, J = 15.8), 3.45 (1 H, d, J = 15.8), 3.5–3.68 (2 H, m), 4.02 (1 H, m), 7.40–7.64 (3 H, m), 7.88–7.95 (2 H, m); IR (liquid film) 3410 (br), 2950 (s), 1680 (s), 1455 (s), 1220 (s), 1140 (s), 755 (s), 695 cm^{-1} (s); MS m/z (relative intensity) 346 (M^+, 3), 273 (28), 227 (32), 189 (43), 153 (34), 141 (30), 105 (100); HRMS calcd for $C_{22}H_{34}O_3$ 346.2505, found 346.2509.

Similarly, **18** was obtained from **4c** in 67% yield. **18**: ^1H NMR δ 0.66 (3 H, d, J = 7.0), 0.81 (3 H, d, J = 6.2), 0.87 (3 H, d, J = 6.8), 1.20 (3 H, d, J = 6.2), 1.26–2.08 (14 H, m), 3.14 (1 H, d, J = 15.2), 3.60 (1 H, d, J = 15.2), 3.68–3.99 (2 H, m), 4.08 (1 H, m), 7.40–7.64 (3 H, m), 7.88–7.95 (2 H, m); IR (liquid film) 3410 (br), 2950 (s), 1680 (s), 1455 (s), 1220 (s), 1140 (s), 755 (s), 695 cm^{-1} (s); MS m/z (relative intensity) 346 (M^+, 3), 273 (45), 189 (59), 155 (59), 120 (47), 105 (100); HRMS calcd for $C_{22}H_{34}O_3$ 346.2505, found 346.2500.

The structures of **17** and **18** were inferred from the spectra of the corresponding acetates, which were obtained in yields of 85 and 90%, respectively. Acetate of **17**: ^1H NMR δ 0.70 (3 H, d, J = 7.0), 0.82 (3 H, d, J = 6.2), 0.87 (3 H, d, J = 6.8), 1.25 (3 H, d, J = 6.2), 1.26–2.00 (11 H, m), 2.01 (3 H, s), 3.13 (1 H, d, J = 14.4), 3.35–3.45 (3 H, m), 5.08 (1 H, m), 7.40–7.60 (3 H, m), 7.85–7.95 (2 H, m); IR (liquid film) 2930 (s), 1750 (s), 1690 (s), 1450 (s), 1380 (s), 1250 (s), 1150 (s), 755 (s), 695 cm^{-1} (s). Acetate of **18**: ^1H NMR δ 0.64 (3 H, d, J = 7.0), 0.82 (3 H, d, J = 6.4), 0.87 (3 H, d, J = 6.8), 1.19 (3 H, d, J = 6.4), 1.20–2.20 (14 H, m, including s (3 H) at 2.05), 3.045 (1 H, d, J = 15.2), 3.53 (1 H, d, J = 15.2), 3.95 (1 H, q, J = 8.0), 4.22 (2 H, t, J = 7.2), 7.40–7.60 (3 H, m), 7.89–8.00 (1 H, m).

(*R*)-γ-Dodecanolactone (21). To a solution of (*R*)-1,3-undecanediol (*ent*-**1b**) (339.4 mg, 1.81 mmol), Et_3N (0.26 mL, 1.90 mmol), and CH_2Cl_2 (4.5 mL) at 0 °C was added methanesulfonyl chloride (0.15 mL, 1.9 mmol). After it had been stirred for 15 min, the mixture was diluted with petroleum ether and was passed through a pad of Celite. The filtrate was concentrated in vacuo. To a DMF (5 mL) solution of the residue (i.e., the crude mesylate) at 25 °C were successively added NaCN (181 mg, 3.7 mmol) and NaI (74 mg, 0.49 mmol). The mixture was heated at 110 °C for 2 h, and then it was poured into water. The mixture was extracted twice with Et_2O. The combined extracts were dried and then concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc (90:10)) to give 240 mg (67%) of (*R*)-4-hydroxydodecanonitrile (**20**):[24] ^1H NMR δ 0.88 (3 H, t, J = 7.0), 1.22–1.61 (14 H, m), 1.69 (1 H, m), 1.84 (1 H, m), 2.50 (2 H, dd, J = 6.6, 7.9), 3.73 (1 H, m).

A solution of the hydroxynitrile **20** (113.5 mg, 0.576 mmol), EtOH (2.5 mL), water (1 mL), and KOH (0.67 g, 12 mmol) was refluxed for 48 h. The cooled mixture was diluted with water and was then acidified with concentrated HCl. The mixture was extracted with CH_2Cl_2. The extract was concentrated in vacuo. The residue was dissolved in benzene (5 mL) which contained a few drops of concentrated aqueous HCl. The solution was concentrated in vacuo. The residue was purified by flash chromatography (petroleum ether/EtOAc (90:10)) to give 104.4 mg (92%) of (*R*)-**21**:[24] $[\alpha]^{24}_D$ +36.2° (*c* 0.801, MeOH) (lit.[24b] $[\alpha]_D$ + 37.7° (*c* 0.71, MeOH)); ^1H NMR δ 0.870 (3 H, t, J = 7.0), 1.20–1.92 (15 H, m), 2.304 (1 H, qd, J = 6.8, 12.7), 2.514 (2 H, dd, J = 6.8, 9.2), 4.471 (1 H, m).

Hydrogenation of *ent*-1e. A mixture of *ent*-**1e** (56.0 mg, 0.482 mmol), 10% Pd/C (7 mg), and EtOH (0.5 mL) at rt was stirred under H_2 (1 atm) for 10 h. Removal of the catalyst by filtration, evaporation of the solvent from the filtrate, and purification of the residue by flash chromatography (EtOAc/hexane (50:50)) gave 45.7 mg (80%) of *ent*-**1d**: $[\alpha]^{23}_D$ −10.9° (*c* 1.32, $CHCl_3$).

Methyl (2*R*,3*R*)-3-Cyclohexyl-3-hydroxy-2-methylpropanoate (22). To a solution of oxalyl chloride (256 mg, 2.02 mmol) in CH_2Cl_2 (6 mL) at −85 °C was added a solution of DMSO (188 mg, 2.4 mmol) in CH_2Cl_2 (3 mL). The mixture was stirred for 10 min. Then diol *ent*-**1g** (289 mg, 1.68 mmol) was added. After 20 min, Et_3N (0.930 mL, 6.67 mmol) was added. The still cooled (−85 °C) mixture was stirred for an additional 30 min, and then it was allowed to warm to rt over 50 min. Aqueous NH_4Cl was then added, and the mixture was extracted with EtOAc. The extract was washed with aqueous $NaHCO_3$, dried, and then concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, gradient elution from 90:10 to 50:50) to give, in order of elution, 91.2 mg (32%) of (2*R*,3*R*)-3-cyclohexyl-3-hydroxy-2-methylpropanal and 75.4 mg (26%) of *ent*-**1g**. To a stirred solution of the hydroxyaldehyde (91.2 mg, 0.536 mmol) in EtOH (2.7 mL) at rt were successively added a solution of $AgNO_3$ (145 mg, 0.858 mmol) in water (1.8 mL) and a solution of NaOH (149 mg, 3.65 mmol). After 4 h, the mixture was filtered. The filtrate was extracted with Et_2O, and then it was acidified (pH 1) with 2 N aqueous HCl and again extracted with Et_2O. The combined extracts were dried and then concentrated in vacuo. The residue was dissolved in Et_2O (2 mL). The excess ethereal CH_2N_2 was added to the cold (0 °C) solution. Excess CH_2N_2 was then destroyed by adding HOAc. Saturated aqueous $NaHCO_3$ was added, and the mixture was extracted twice with Et_2O. The combined extracts were dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, gradient elution from 95:5 to 90:10) to give 49.5 mg (46%) of hydroxy ester **22**: $[\alpha]^{20}_D$ −6.6° (*c* 2.48, $CHCl_3$) (lit.[25] $[\alpha]^{23}_D$ −8.1° (*c* 1.05, $CHCl_3$); ^1H NMR δ 0.90–1.45 (8 H, m, including d (3 H, J = 7.2) at 1.213), 1.55–1.85 (6 H, m), 2.512 (1 H, d, J = 7.5), 2.695 (1 H, qd, J = 7.2, 6.0), 3.370 (1 H, dt, J = 7.5, 6.0), 3.705 (3 H, s); IR (liquid film) 3500 (br), 1730 (s), 1105 cm^{-1} (s).

1,3,5-Pentanetriol Tris(trimethylsilyl) Ether (23). 1,4-Pentadien-3-ol was converted to the corresponding *tert*-butyldimethylsilyl ether (83%) in a manner similar to that used to

prepare *rac*-**1g**. To a THF (29 mL) suspension of 9-BBN (3.51 g, 28.8 mmol) at −80 °C was added a solution of the silyl ether (1.88 g, 9.45 mmol) in THF (10 mL). The mixture was stirred for 14 h during which time it was allowed to warm to rt. The mixture was then cooled to −10 °C, and 6 N aqueous NaOH (6 mL) and 30% aqueous H_2O_2 (12 mL) were successively added. The mixture was stirred for 2 h, during which time it was allowed to warm to rt. Brine was added and the mixture was extracted three times with EtOAc. The combined extracts were dried and then concentrated in vacuo to give an oil. This was purified by flash chromatography (EtOAc/hexane (50:50)) to give 1.56 g (73%) of 3-(*tert*-butyldimethylsiloxy)-1,5-pentanediol: ^{1}H NMR (60 MHz, CCl_4) δ 0.00 (6 H, s), 0.87 (9 H, s), 4.52 (1 H, br t, J = 5), 4.85–5.30 (2 H, m), 5.78 (ddd, J = 5, 10, 17); IR (liquid film) 1255 (s), 840 (s), 774 cm^{-1} (s).

The siloxy diol (1.55 g, 6.88 mmol) was dissolved in THF (7 mL) which contained 10% aq HCl (3.5 mL). The mixture was stirred for 1.5 h at 25 °C, and then it was concentrated in vacuo. Residual water was removed by azeotropic distillation with benzene (250 mL). To a THF (13 mL) solution of the residue (i.e., the crude triol) was added HMDS (4.35 mL, 20.6 mmol) and TMSOTf (12 μL, 0.07 mmol). The mixture was stirred for 20 h at 25 °C. It was diluted with Et_2O, washed successively with water and aqueous $NaHCO_3$, dried, and then concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc (99.5:0.5)) to give 1.43 g (62%) of **23**: ^{1}H NMR δ 0.09 (18 H, s), 0.10 (9 H, s), 1.08 (2 H, m), 1.65 (2 H, m), 3.65 (5 H, m); IR (liquid film) 1260 (s), 845 cm^{-1} (s).

Spiroacetals 3k and 4k. To a solution of the tris(trimethylsilyl) ether **23** (0.700 g, 2.08 mmol), *l*-menthone (267 mg, 1.73 mmol), and CH_2Cl_2 (1.7 mL) at −40 °C was added TMSOTf (0.067 mL, 0.35 mmol). The mixture was stirred for 19 h at −40 °C, and then the residue was quenched by adding pyridine (0.06 mL). Aqueous $NaHCO_3$ was added, and the mixture was extracted twice with hexane. The combined extracts were dried and then concentrated in vacuo. The residue was dissolved in EtOH (7 mL) which contained a few drops of 50% aqueous NaOH. The solution was stirred for 22 h at 25 °C. Water was then added, and the mixture was extracted with EtOAc. The extract was dried and then concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, gradient elution from 90:10 to 85:15) to give 0.413 g (93%) of the hydroxy spiroacetal as a mixture of diastereomers.

To a solution of the hydroxyspiroacetal (413 mg, 1.61 mmol) in pyridine (1.8 mL) at 25 °C was added *p*-toluenesulfonyl chloride (399 mg, 2.09 mmol). The mixture was stirred for 4 h at 25 °C. It was diluted with Et_2O (100 mL) and was washed (aqueous $CuSO_4$, aqueous $NaHCO_3$, and brine), dried ($MgSO_4$), and then concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc, gradient elution from 96:4 to 80:20) to give, in order of elution, 165 mg (25%) of tosylate **3k** and 454 mg (69%) of tosylate **4k**. **3k**: ^{1}H NMR δ 0.654 (1 H, dd, J = 12.9, 13.2), 0.772 (3 H, d, J = 6.6), 0.851 (3 H, d, J = 6.9), 0.865 (3 H, d, J = 6.6), 1.09–1.91 (10 H, m), 2.332 (1 H, d hept, J = 1.2, 7.2), 2.454 (3 H, s), 2.627 (1 H, ddd, J = 1.8, 3.3, 13.5), 3.773 (1 H, ddd, J = 1.2, 5.1, 11.4), 3.895 (1 H, tdd, J = 2.7, 9.3, 11.7), 4.051 (1 H, dt, J = 2.7, 12.3), 4.10–4.24 (2 H, m), 7.35 (2 H, m), 7.79 (2 H, m); IR (liquid film) 1365 (s), 1180 (s), 1100 (s), 665 cm^{-1} (s); MS m/z (relative intensity) 410 M$^+$, 13), 395 (11), 325 (28), 67 (100); HRMS calcd for $C_{22}H_{34}O_5S$ 410.2128, found 410.2116. **4k**: ^{1}H NMR δ 0.469 (1 H, dd, J = 12.6, 13.2), 0.818 (6 H, d, J = 7.2), 0.876 (3 H, d, J = 6.6), 0.995 (1 H, ddd, J = 2.4, 3.9, 12.6), 1.22–1.54 (6 H, m), 1.63–1.88 (3 H, m), 2.220 (1 H, d hept, J = 2.7, 7.2), 2.454 (3 H, s), 2.564 (1 H, ddd, J = 1.8, 3.3, 13.5), 3.718 (1 H, ddd, J = 1.5, 5.7, 11.4), 3.805 (1 H, dt, J = 2.7, 12.0), 4.044 (1 H, tdd, J = 3.3, 8.1, 11.4), 4.08–4.20 (2 H, m), 7.345 (2 H, m), 7.799 (2 H, m); IR (liquid film) 1365 (s), 1180 (s), 1115 (s), 665 cm^{-1} (s); MS m/z (relative intensity) 410 (M$^+$, 12), 395 (10), 325 (28), 67 (100); HRMS calcd for $C_{22}H_{34}O_5S$: 410.2128, found 410.2133.

Preparation of Spiroacetals 4a,b from 4k. To a suspension of CuCN (109 mg, 1.22 mmol) in THF (1.2 mL) at −85 °C was added PhLi (2.45 mmol, 1.36 mL of a 1.8 M in cyclohexane and ether). The mixture was allowed to warm to −25 °C over 2.5 h, and then it was cooled to −85 °C. To the resulting brown solution was added a THF (0.5 mL) solution of **4k** (99.7 mg, 0.243 mmol). The mixture was allowed to slowly warm to 25 °C, and then it was stirred for an additional 20 h before the reaction was quenched by adding brine. The mixture was then diluted with Et_2O and was filtered through a pad of Celite. The filtrate was washed with brine, dried ($MgSO_4$), and then concentrated in vacuo. The residue was purified by flash chromatography (hexane/EtOAc (99:1)) to give 68.2 mg (89%) of a spiroacetal, the ^{1}H NMR spectrum of which was identical to that of **4a** prepared by the reaction of *rac*-**2a** with *l*-menthone.

The reaction of **4k** with $(n\text{-}C_6H_{13})_2Cu(CN)Li_2$ in a manner similar to that described above gave a spiroacetal (93%), the ^{1}H NMR spectrum of which was identical to that of **4b** prepared by the reaction of *rac*-**2b** with *l*-menthone.

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Registry No. *rac*-**1a**, 115404-97-2; **1a**, 115346-55-9; *ent*-**1a**, 115346-88-8; *rac*-**1b**, 114825-72-8; **1b**, 115458-75-8; *ent*-**1b**, 115404-96-1; *ent*-**1b** mesylate, 138490-50-3; *rac*-**1c**, 18826-95-4; **1c**, 24621-61-2; *ent*-**1c**, 6290-03-5; *rac*-**1d**, 115404-98-3; **1d**, 16451-48-2; *ent*-**1d**, 16451-50-6; *rac*-**1e**, 117708-76-6; *ent*-**1e**, 138602-98-9; *rac*-**1f**, 138490-32-1; **1f**, 138602-99-0; *rac*-**1g**, 138602-95-6; *rac*-**1g** TBDMS ether, 138490-39-8; *ent*-**1g**, 129170-75-8; *rac*-**2a**, 115346-89-9; *rac*-**2b**, 115346-90-2; *rac*-**2c**, 112434-94-3; *rac*-**2d**, 115346-91-3; *rac*-**2e**, 138490-33-2; *rac*-**2f**, 135067-17-3; *rac*-**2g**, 135067-18-4; **3a**, 115346-74-2; **3b**, 115346-75-3; **3c**, 115346-76-4; **3d**, 115346-54-8; **3e**, 138490-34-3; **3f**, 138490-35-4; **3g**, 138490-36-5; **3h**, 138490-40-1; **3i**, 135211-96-0; **3j**, 135211-97-1; **3k**, 138490-41-2; **3k** free hydroxy, 135211-98-2; **3l**, 138490-42-3; **4a**, 115404-93-8; **4b**, 115404-94-9; **4c**, 115404-95-0; **4d**, 115404-90-5; **4e**, 138602-96-7; **4f**, 138602-97-8; **4g**, 138604-11-2; **4h**, 138603-00-6; **4i**, 135067-27-5; **4j**, 135211-95-9; **4k**, 138603-01-7; **4k** free hydroxy, 135067-28-6; **4l**, 138603-02-8; **17**, 115346-81-1; **17** acetate, 138490-43-4; **18**, 115346-82-2; **18** acetate, 138490-44-5; **19a**, 105857-47-4; **19b**, 105928-22-1; **19c**, 105857-46-3; **19d**, 105928-21-0; **19e**, 105857-48-5; **19f**, 105928-23-2; **19h**, 138490-45-6; **19i**, 138490-46-7; **19j**, 138490-47-8; **19k**, 138490-48-9; **19l**, 138490-49-0; **20**, 69830-97-3; **21**, 69830-91-7; **22**, 78604-73-6; **22** free acid, 138603-03-9; **22** aldehyde, 138490-51-4; **23**, 74685-20-4; EtOAc, 79-20-9; $(CH_2{=}C(CH_3))Br$, 75-26-3; PhLi, 591-51-5; $(C_6H_{13})_2Cu(CN)Li_2$, 138516-49-1; 3,3-dimethylbutanal, 2987-16-8; (±)-1-cyclohexyl-2-methyl-2-propen-1-ol, 138490-37-6; cyclohexanecarboxaldehyde, 2043-61-0; (±)-3-(*tert*-butyldimethylsiloxy)-3-cyclohexyl-2-methyl-1-propene, 138490-38-7; *l*-menthone, 14073-97-3; acetophenone enol trimethylsilyl ether, 13735-81-4; 1,5-pentadien-3-ol, 922-65-6; 3-(*tert*-butyldimethylsiloxy)-1,4-pentadiene, 82865-59-6; 3-(*tert*-butyldimethylsiloxy)-1,5-pentanediol, 135067-24-2; 1,3,5-pentanetriol, 4328-94-3.

Supplementary Material Available: High-field ^{1}H NMR spectra of **2a–g**, **3a–g**, **4c–g**, **17**, **18**, **17-OAc**, **18-OAc**, **23**, **3k**, **and 4k** (26 pages). Ordering information is given on any current masthead page.