Stereoselective Acetalization of 1,3-Alkanediols Controlled by Intramolecular van der Waals Attractive Interactions and Its Application to an Enantiodifferentiating Transformation of σ-Symmetric 1,3,5-Pentanetriols

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Abstract: Acetalization reactions of racemic bis(trimethylsilyl) ethers ($R^1R^2CHCH(OTMS)CH(R^3)CH_2OTMS$) with racemic menthone, under thermodynamically controlled conditions, stereoselectively give spiroacetal **2** (in which the substituent R^1R^2CH– is attached to the carbon adjacent to the axial oxygen atom with respect to the menthane ring) in preference to the diastereomeric spiroacetal **3** (in which the substituent is attached to the carbon adjacent to the equatorial oxygen atom). Correlation between the stereoselectivities and the structures of the spiroacetals as well as the higher stereoselectivities observed in the related acetalization with 7,7,7-trimethylmenthone indicates that the preferential formation of spiroacetal **2** of a folded structure is a result of intramolecular attractive interactions between the menthane moiety and the substituent attached to the 1,3-dioxane ring. Molecular mechanics (MM2) calculations give satisfactory agreement with experiments and provide support for the operation of the van der Waals attractive interaction as the most important factor determining the stereoselectivities. The stereoselective acetalization with *l*-menthone is successfully applied to a novel enantiodifferentiating transformation of σ-symmetric 1,3,5-pentanetriols ($HOCH_2CHRCH(OH)CHRCH_2OH$; R = Me or H). The reaction provides an efficient and straightforward route to chiral menthonide derivatives **13a-c**, which can be utilized as versatile chiral building blocks.

Introduction

Nonbonded interactions between substrates and reagents play an important role in determining the stereochemical course of reactions. Of these interactions, the van der Waals repulsive interaction, so-called steric hindrance, is often a major factor governing the stereoselectivity of reactions.[1] The effect of van der Waals interactions depends upon the distance between two atoms or molecules. While being repulsive at short distances, they become attractive at relatively long distances. Such attractive interactions are sometimes referred to as hydrophobic bonding in biochemical literature and examples involving large molecules are well documented.[2] In comparison with the well-recognized nature of the repulsive interactions, little attention has been focused on the attractive interactions in the organic chemistry of small molecules.

Nevertheless, there have been several examples reported which demonstrate that van der Waals attractive interactions are important in determining equilibrium conformations of relatively small molecules.[3-6] Carter and co-workers demonstrated that, in the 1,3,5-trineopentylbenzene system, the rotamer with all three neopentyl groups on the same side of the benzene ring is favored over the 2-proximal, 1-distal rotamer.[3] More recently, a similar conformational preference was reported in dialkyl derivatives of five- and six-membered heterocyclic systems.[4] Van der Waals attractions have also been claimed to be responsible for the position of the equilibrium between the valence-bond isomers 1,4- and 1,6-di-*tert*-butylcyclooctatetraene.[5]

To our knowledge, no attention has been directed to a possible role of the van der Waals attractions as a determinant of stereoselectivity in organic reactions. In kinetically controlled reactions, such interactions may stabilize one of the possible transition states leading to a stereoselective product formation. A stereoselective reaction is also expected under thermodynamic conditions where one of the possible diastereomeric products is preferentially stabilized by intramolecular van der Waals attractions.

We report here a stereoselective acetalization of 1,3-alkanediols with menthone which is controlled by the intramolecular van der Waals attractive interactions under thermodynamic conditions. We also describe an application of the stereoselective acetalization to a novel enantiodifferentiating transformation of σ-symmetric 1,3,5-pentanetriols.[7] The present study provides the first example of stereocontrol by van der Waals attractive interactions.

Results and Discussion

Stereoselective Acetalization of Racemic 1,3-Alkanediols with Racemic Menthone. We recently reported that acetalization of racemic 1,3-alkanediols with *l*-menthone proceeds in a highly stereocontrolled manner at the resulting dioxy carbon to afford spiroacetals **2** and **3** without the formation of other possible diastereomers **4** and **5** (Scheme I).[8] Because spiroacetals **2** and **3** are derived respectively from each enantiomer of the starting racemic diol derivatives, the acetalization with *l*-menthone gives rise to a 1:1 mixture of **2** and **3**. In contrast to this, we found that

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(2) (a) Galbler, R. *Electrical Interactions in Molecular Biophysics*; Academic Press: New York, 1978. (b) Tanford, C. *The Hydrophobic Effect: Formation of Micelles and Biological Membranes*; Wiley-Interscience: New York, 1973.
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(6) (a) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102. (b) Hirota, M.; Sekiya, T.; Abe, K.; Tashiro, H.; Karatsu, M.; Nishio, M.; Osawa, E. *Tetrahedron* **1983**, *39*, 3091.
(7) For a preliminary report, see: Harada, T.; Wada, I.; Uchimura, J.; Inoue, A.; Tanaka, S.; Oku, A. *Tetrahedron Lett.* **1991**, *32*, 1219.
(8) Harada, T.; Kurokawa, H.; Kagamihara, Y.; Tanaka, S.; Inoue, A.; Oku, A. *J. Org. Chem.* **1992**, *57*, 1412.

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Scheme I

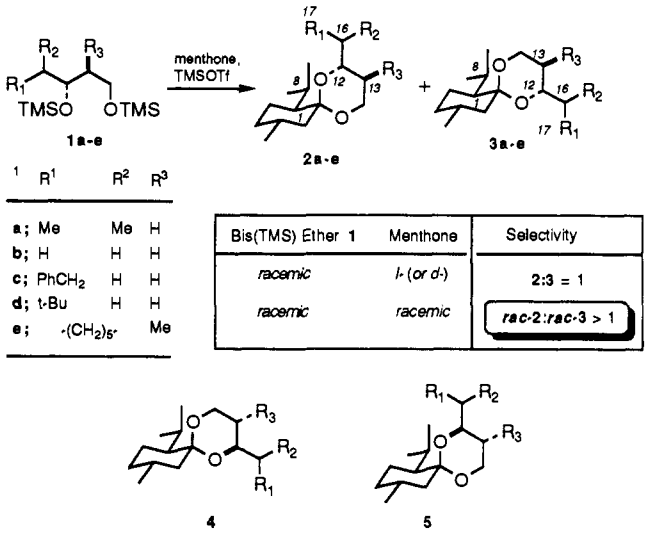


Table I. Acetalization of Bis(trimethylsilyl) Ethers **1a–e** with *dl*-Menthone

entry	substrate	conditions[a]	temp (°C)	solvent	products	yield (%)	ratio[b] (2:3)
1	1a	A	0	CH_2Cl_2	**2a, 3a**	85	2.7:1
2		A	–40	CH_2Cl_2		92	3.5:1
3		A	–80	CH_2Cl_2		94	4.0:1
4		B	–40	$CHCl_3$		78	4.1:1
5		A	–40	toluene		92	2.3:1
6		A	–40	THF		80	1.0:1
7		A[c]	–40	THF		*d*	1.2:1
8	**1b**	A	–40	CH_2Cl_2	**2b, 3b**	80	1.2:1[e]
9	**1c**	A	–40	CH_2Cl_2	**2c, 3c**	92	2.5:1
10		C	–40	$CHCl_3$		98	3.7:1
11	**1d**	B	–40	CH_2Cl_2	**2d, 3d**	88	3.5:1
12		C	–40	$CHCl_3$		77	5.4:1
13	**1e**	D	–40	CH_2Cl_2	**2e, 3e**	99	5.4:1
14		C[f]	–40	$CHCl_3$		90	7.8:1

[a] A: **1** (3 equiv), menthone (1 equiv, 0.33 M), and TMSOTf (0.3 equiv) for 16–18 h. B: **1** (1 equiv, 0.33 M), menthone (1.5 equiv), and TMSOTf (0.3 equiv) for 40 h. C: **1** (1 equiv, 0.33 M), menthone (1.5 equiv), and TfOH (0.3 equiv) for 40 h. D: **1** (1 equiv, 0.33 M), menthone (2.0 equiv), TMSOTf (0.3 equiv) for 18 h. [b] Unless otherwise noted, ratios were determined by capillary GC analysis. [c] Reaction was performed for 33 h. [d] Yield was not determined. [e] Determined by ^{13}C NMR. [f] Reaction was performed for 70 h.

spiroacetal **2** is a major product when the acetalization was performed by using *racemic menthone*. (Table I).[9]

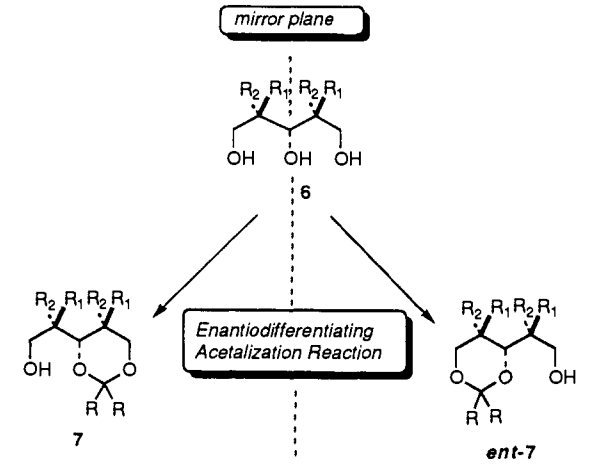
Acetalization of bis(trimethylsilyl) ether **1a** with *dl*-menthone in the presence of a catalytic amount of TMSOTf (30 mol %)[10] in CH_2Cl_2 at –40 °C for 16 h gave a 3.5:1 mixture of spiroacetals **2a** and **3a** in 85% yield (entry 1). Treatment of the major spiroacetal **2a** with **1a** (1.0 equiv) in the presence of TMSOTf (30 mol %) in CH_2Cl_2 at –40 °C for 39 h led to the formation of a 3.4:1 mixture of **2a** and **3a** (82% yield). Under similar reaction conditions, minor spiroacetal **3a** isomerized to a 3.2:1 mixture of **2a** and **3a** (82% yield). These results indicate that, in the present acetalization, spiroacetals **2a** and **3a** are in equilibrium, and hence, the observed selectivity is a result of thermodynamic control.

The lower the reaction temperature, the higher the selectivity of **2a** (entries 1–3). Reactions in $CHCl_3$ and toluene also afforded **2a** as a major diastereomer (entries 4 and 5). In THF, the isomerization between **2a** and **3a** was too slow to attain an equilibrium (entries 6 and 7).

Bis(trimethylsilyl) ethers **1b–e** also underwent stereoselective acetalization with racemic menthone to give spiroacetals **2b–e** as major products (entries 8–14). While the reaction of 1,3-butanediol derivative **1b** (R^1, R^2, R^3 = H) was less selective, the stereoselectivities were increased with an increase in the size of the substituents R^1 and R^2, being 5.4:1 and 7.8:1 in the reaction of **1d** (R^1 = *t*-Bu; R^2, R^3 = H) and **1e** (R^1, R^2 = $-(CH_2)_5-$; R^3 = Me), respectively. The selectivities were slightly, but constantly, higher in $CHCl_3$ than in CH_2Cl_2.

(9) In principle, acetalization of racemic **1** with racemic menthone can give rise to a mixture of **2** and **3** in an arbitrary ratio.

Scheme II



Enantiodifferentiating Transformation of σ-Symmetric 1,3,5-Pentanetriols. In recent years, considerable attention has been paid to enantiotopic group differentiating reactions of σ-symmetric compounds.[11] This sort of asymmetric induction serves as a powerful method in the asymmetric synthesis of natural products[11a] because multiple stereogenic centers can be introduced in a single step of the reaction. While being unprecedented, enantiodifferentiating protection of σ-symmetric 1,3,5-pentanetriols **6** should provide an efficient and straightforward route to chiral acetals **7**, whose acetonide derivatives (R = Me) have been frequently utilized as versatile chiral building blocks (Scheme II).[12,13]

The use of racemic menthone is indispensable for the stereoselective acetalization of racemic 1,3-alkanediols. Therefore, the reaction results in the formation of racemic products. However, one may expect enantioselective product formation in acetalization of σ-symmetric triols **6** with optically pure menthone because such prochiral diols can act either as (*R*)- or as (*S*)-1,3-alkanediols in an arbitrary ratio.

meso-1,3,5-Triol derivatives **9a,b** were prepared diastereoselectively by double hydroboration of dialkenyl carbinol derivative **8** with 9-BBN and BH_3–THF, respectively (eq 1).[14] After treatment of **9a–c** in 10% aqueous HCl/THF at room temperature, the resulting triols were directly subjected to a silylation reaction to furnish tris(trimethylsilyl) ethers **11a–c** in 70–100% yields (Scheme III).

As we anticipated, the acetalization reaction of **11a–c** with optically pure *l*-menthone proceeded enantioselectively to afford spiroacetals **12a–c** as major products (Table II). Thus, for

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(12) For review, see: Hoffmann, R. W. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 489.

(13) (a) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873. (b) Patel, D. V.; VanMiddlesworth, F.; Donaubauer, J.; Gannet, P.; Sih, C. J. *J. Am. Chem. Soc.* **1986**, *108*, 4603.

(14) Harada, T.; Wada, I.; Matsuda, Y.; Uchimura, J.; Oku, A. *J. Chem. Soc., Chem. Commun.* **1990**, 21.

Scheme III

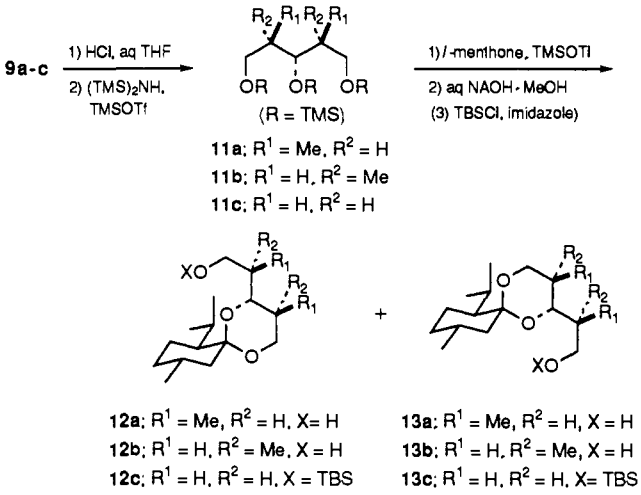
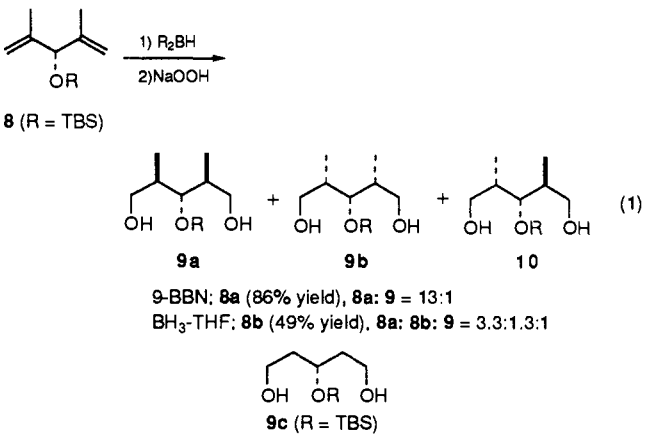


Table II. Enantiodifferentiating Acetalization of σ-Symmetric Tris(trimethylsilyl) Ethers **11a–c** with *l*-Menthone[a]

entry	substrate	temp (°C)	solvent	time (h)	products	yield (%)	ratio[b] (12:13)
1	**11a**	–40	CH_2Cl_2	16	**12a, 13a**	99	4.0:1
2		–40	$CHCl_3$	70		80	4.1:1
3[c]		–85	CH_2Cl_2	24		90	4.9:1
4[c]		–65	$CHCl_3$	24		99	4.9:1
5	**11b**	–40	CH_2Cl_2	15	**12b, 13b**	82	4.6:1
6	**11c**	–40	CH_2Cl_2	13	**12c, 13c**	89	3.0:1
7		–85	CH_2Cl_2	48		83	3.5:1

[a] Unless otherwise noted, reactions were performed by using 1.2 equiv of *l*-menthone and 0.3 equiv of TMSOTf. [b] Ratios were determined after isolation by flash chromatography. [c] Reaction was performed by using TfOH (0.3 equiv) as the acid catalyst first at –40 °C for 16 h and then at the temperature indicated.



example, treatment of **11a** in CH_2Cl_2 at –40 °C in the presence of TMSOTf (20 mol %) and desilylation of the resulting trimethylsiloxy spiroacetals gave rise to a 99% yield of **12a** and **13a** in a 4.0:1 ratio (entry 1). The selectivity of **12a** was improved to 4.9:1 when the reaction was performed at lower temperatures (entries 2 and 4). A slightly lower level of stereoselectivity was observed in the reactions of **11c** (entries 7 and 8), which affords spiroacetals of the less sterically demanding substituent (TMS-OCH_2CH_2–) on the 1,3-dioxane rings. In these reactions, products were isolated as TBS ethers **12c** and **13c**.

Spiroacetals **12a–c** and **13a–c** are readily separable by silica gel flash chromatography. The absolute configurations of **12a–c** were determined unambiguously by converting them to compounds of know absolute configuration (*vide infra*). The ready access to the starting triol derivatives in a stereoselective manner as well as the ease of the purification of **12a–c** makes the present

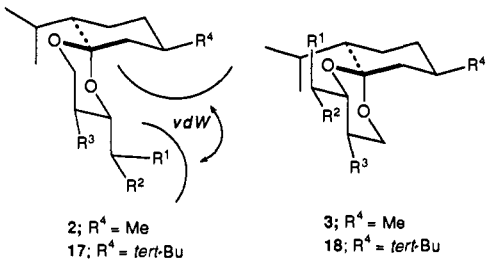
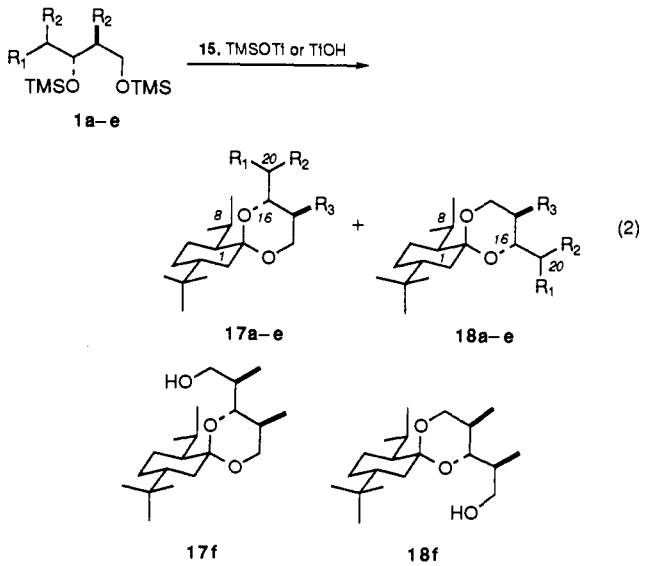


Figure 1.

enantiodifferentiating acetalization an efficient method for the preparation of these potential chiral building blocks.[15]

Acetalization of Racemic 1,3-Alkanediols with 7,7,7-Trimethylmenthone (15). Why are spiroacetals **2** and **12** more stable than **3** and **13**, respectively? Judging from their ^{1}H NMR spectra, the spiroacetals adopt rigid double-chair conformations (Figure 1).[8] Molecular model analysis showed that the steric environments nearby the R^1R^2CH– substituents are similar in both **2** and **3**. No unfavorable repulsive interaction is conceivable in spiroacetal **3**. However, the spatial orientation of the substituent with respect to the menthane moiety is different between spiroacetal **2**, of a folded structure, and spiroacetal **3**, of an extended structure. In other words, in **2**, but not in **3**, a part of the substituent (R^1 in Figure 1) resides over the menthane ring at a distance favorable for a van der Waals attractive interaction, and this may stabilize **2** relative to **3**. The observation that the selectivity of **2** increases with an increase in the size of the substituent supports the above hypothesis since the trend in van der Waals attraction energy parallels the total number of interactions between the two groups.

If such an attractive interaction is responsible for the observed stereoselectivity, higher selectivity is anticipated in the acetalization of 1,3-alkanediols with a homologue of menthone which possess an additional site for the van der Waals attractive interactions in the resulting acetals. Substitution of the methyl group (R^4) on the methane moiety with a *tert*-butyl group will increase the total number of attractive interactions in spiroacetal **17** (Figure 1). In order to probe the proposed intramolecular van der Waals attractive interaction as a determinant of the stereoselective reaction, we examined the acetalization of 1,3-alkanediols with 7,7,7-trimethylmenthone (**15**) (eq 2).



Trimethylmenthone **15** was prepared through the reaction sequence shown in Scheme IV. Reaction of *tert*-butylcyclohex-

(15) For an application to the enantiomerically pure C3/C7 fragment of pristinamycin PIIA, see: Adjé, N.; Breuiles, P.; Uguen, D. *Tetrahedron Lett.* **1992**, *33*, 2151.

Table III. Acetalization of Bis(trimethylsilyl) Ethers **1a–e** and **11a** with Trimethylmenthone **15**[a]

entry	substrate	acid cat. (equiv)	solvent	products	yield (%)	ratio[b] (**17**:**18**)	$\Delta\Delta G^c$ (kcal/mol)
1	**1a**	TfOH (0.3)	CH_2Cl_2	**17a, 18a**	96	3.8:1	0.04
2		TfOH (0.3)	$CHCl_3$		97	4.6:1	0.05
3	**1b**	TMSOTf (0.3)	CH_2Cl_2	**17b, 18b**	49	1.0:1	–0.08
4	**1c**	TfOH (0.3)	CH_2Cl_2	**17c, 18c**	85	3.2:1	0.11
5		TfOH (0.3)	$CHCl_3$		97	3.3:1	–0.05
6	**1d**	TMSOTf (0.3)	CH_2Cl_2	**17d, 18d**	72	6.8:1	0.31
7[d]		TfOH (0.3)	$CHCl_3$		90	8.2:1	0.19
8[d]	**1e**	TfOH (0.1)	CH_2Cl_2	**17e, 18e**	96	9.0:1	0.24
9[d]		TfOH (0.3)	$CHCl_3$		97	12:1	0.18
10	**11a**	TfOH (0.3)	CH_2Cl_2	**17f, 18f**	80	4.5:1	0.05
11		TfOH (0.3)	$CHCl_3$		81	4.8:1	0.07

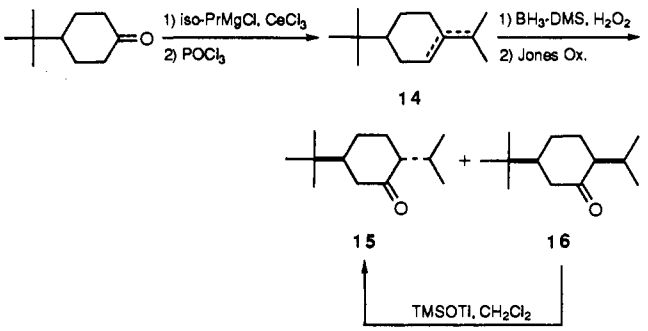
[a] Unless otherwise noted, reactions were performed at –40 °C for 40 h by using 1.5 equiv of **15**. [b] Ratios were determined by capillary GC analysis. [c] $\Delta\Delta G = \Delta G(\mathbf{17}–\mathbf{18}) - \Delta G(\mathbf{2}–\mathbf{3})$. [d] Reaction was performed for 70 h.

Table IV. MM2 Calculated Energies (kcal/mol) for the Stable Conformers of **2e** and **3e**

2e	ω_1[a]	ω_2[b]	E_{total}[c]	**3e**	ω_1[a]	ω_2[b]	E_{total}[c]	ΔE_{total}[d]	ΔE_{vdw}[e]	ΔE_{group}[f]
2E(1)	–83	58	0.00	**3E**(1)	–80	–64	0.71	0.71	0.74	0.89
2E(2)	–59	63	0.21							
2E(3)	73	61	0.35	**3E**(3)	78	–57	1.07	0.72	0.58	0.56
2E(4)	–149	63	1.17	**3E**(4)	–145	–60	1.47	0.30	0.12	0.27
2E(5)	168	63	1.21	**3E**(5)	170	–60	1.77	0.56	0.46	0.56

[a] $\omega_{H-C(1)-C(8)-H}$ in degrees. [b] $\omega_{H-C(12)-C(16)-H}$ in degrees. [c] Steric energies relative to the lowest energy conformer **2E**(1). [d] $E_{total}(\mathbf{3E}(n)) - E_{total}(\mathbf{2E}(n))$. [e] Contribution of the van der Waals energy term to ΔE_{total}. [f] Contribution of the van der Waals interaction energy between groups i and ii to ΔE_{vdw}.

Scheme IV



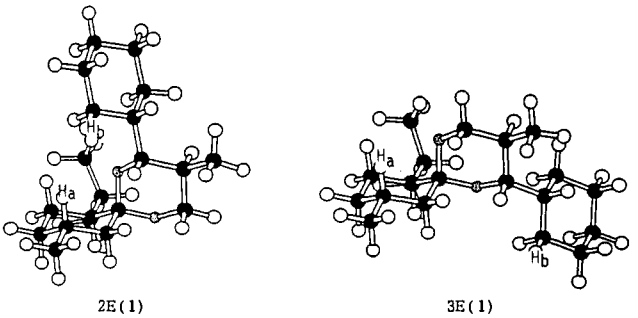


Figure 2.

anone with *i*-PrMgCl in the presence of $CeCl_3$[16] and dehydration of the resulting alcohol with $POCl_3$ in pyridine yielded alkene **14** as a mixture of regioisomers (*endo* olefin:*exo* olefin = 4:1) in 66% overall yield. Hydroboration of **14** with BH_3–DMS and subsequent oxidation of the resulting alcohols gave a 1.4:1 mixture of *trans*-**15** and *cis*-**16** in 62% overall yield, from which pure *trans*-**15** was isolated by silica gel flash chromatography. Acid-catalyzed isomerization of *cis*-**16** gave a 1.5:1 *trans/cis* mixture from which *trans*-**15** was isolated in 54% yield.

The results of acetalization are summarized in Table III. Trimethylmenthone **15** underwent acetalization somewhat slower than menthone, and a longer reaction time (40–70 h) and/or use of triflic acid as a catalyst were necessary to obtain an equilibrium mixture of spiroacetals **17** and **18**. The thermodynamic nature of the product distributions was verified by equilibriation experiments. Thus, treatment of **17a** with **15** (0.5 equiv) in the presence of TMSOTf (0.3 equiv) in CH_2Cl_2 at –40 °C for 40 h gave a 3.5:1 mixture of **17a** and **18a**. Under similar conditions, **18a** isomerized to a 3.8:1 mixture of **17a** and **18a**.

Formation of spiroacetal **17** predominated over that of **18** except for the nonselective reaction of 1,3-butanediol derivative **1b** (entry 3). Here again, slightly higher selectivities were observed in $CHCl_3$ than in CH_2Cl_2. As we anticipated, trimethylmenthone **15** exhibited higher stereoselectivities in acetalization than menthone. Enhancement of the selectivities was remarkable especially when the resulting spiroacetals bear bulky substituents on the 1,3-dioxane ring as in the reactions of **1d,e** (entries 6–9). Differences in free energy changes between diastereomeric spiroacetals at –40 °C ($\Delta\Delta G$ = (ΔG of **18** relative to **17**) – (ΔG of **3** relative to **2**)) increase in the order of the bulkiness of the substituent (Table III). These results provide strong support for the intramolecular van der Waals attractive interaction as a determinant for the observed stereoselectivity.

The acetalization reaction of tris(trimethylsilyl) ether **11a** was also examined by employing trimethylmenthone (entries 10 and 11). While the observed stereoselectivity of **17f** was higher than that of the reaction with *l*-menthone, the level of the improvement was not satisfactory for us to investigate further the possible enantiodifferentiating transformation by using optically pure trimethylmenthone.

Molecular Mechanics Calculations. The established examples in which molecular structure is governed by intramolecular van der Waals attraction were successfully treated by molecular mechanics calculations.[3,4,5b] Spiroacetals derived from menthone and trimethylmenthone are ideally suited for such treatment because force field parameters required in the calculations are well established for these compounds.[17] In order to have further support for our rationalization of the observed selectivities, molecular mechanics calculations were performed by using a MM2 force field.[18]

(16) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

(17) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, DC, 1982.

(18) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) We have used the version of this force field implemented on a MacroModel V3.0: 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.

Table V. MM2 Calculated Energies (kcal/mol) for the Stable Conformers of **2d** and **3d**

2d	ω_1[a]	ω_2[b]	E_{total}[c]	**3d**	ω_1[a]	ω_2[b]	E_{total}[c]	ΔE_{total}[d]	ΔE_{vdw}[e]	ΔE_{group}[f]
2D(1)	−79	−171	0.00	**3D**(1)	−80	−179	0.94	0.94	1.01	0.85
2D(2)	72	−171	0.74	**3D**(2)	71	166	1.18	0.44	0.67	0.55
2D(3)	171	−172	1.52	**3D**(3)	171	178	1.82	0.30	0.35	0.22
2D(4)	−148	−171	1.58	**3D**(4)	−152	163	1.87	0.29	0.54	0.30

[a] $\omega_{H-C(1)-C(8)-H}$ in degrees. [b] $\omega_{C(13)-C(12)-C(16)-C(17)}$ in degrees. [c] Steric energies relative to the lowest energy conformer **2D**(1). [d] E_{total}(**3D**(n)) − E_{total}(**2D**(n)). [e] Contribution of the van der Waals energy term to ΔE_{total}. [f] Contribution of the van der Waals interaction energy between groups i and ii to ΔE_{vdw}.

Table VI. MM2 Calculated Energies (kcal/mol) for the Stable Conformers of **2a** and **3a**

2a	ω_1[a]	ω_2[b]	E_{total}[c]	**3a**	ω_1[a]	ω_2[b]	E_{total}[c]	ΔE_{total}[d]	ΔE_{vdw}[e]	ΔE_{group}[f]
2A(1)	−79	−179	0.00	**3A**(1)	−80	178	0.72	0.72	0.66	0.84
2A(2)	−82	61	0.51	**3A**(2)	−79	−68	0.95	0.44	0.47	0.66
2A(3)	−59	68	0.61							
2A(4)	73	−179	0.63	**3A**(4)	72	178	1.02	0.39	0.31	0.46
2A(5)	72	67	0.80	**3A**(5)	78	−59	1.56	0.76	0.59	0.56
2A(6)	−149	−178	1.32	**3A**(6)	−150	177	1.57	0.25	0.19	0.29
2A(7)	−83	−63	1.41	**3A**(7)	−80	57	1.52	0.11	0.14	0.28
2A(8)	169	−178	1.49	**3A**(8)	170	179	1.69	0.20	0.20	0.23
2A(9)	−149	68	1.53	**3A**(9)	−145	−63	1.90	0.37	0.16	0.31
2A(10)	167	68	1.56	**3A**(10)	171	−67	2.10	0.54	0.41	0.49
2A(11)	−59	−55	1.63							
2A(12)	73	−58	1.80	**3A**(12)	78	64	2.18	0.38	0.28	0.24

[a] $\omega_{H-C(1)-C(8)-H}$ in degrees. [b] $\omega_{H-C(12)-C(16)-H}$ in degrees. [c] Steric energies relative to the lowest energy conformer **2A**(1). [d] E_{total}(**3A**(n)) − E_{total}(**2A**(n)). [e] Contribution of the van der Waals energy term to ΔE_{total}. [f] Contribution of the van der Waals interaction energy between groups i and ii to ΔE_{vdw}.

Table VII. MM2 Calculated Energies (kcal/mol) for the Stable Conformers of **17e** and **18e**

17e	ω_1[a]	ω_2[b]	E_{total}[c]	**18e**	ω_1[a]	ω_2[b]	E_{total}[c]	ΔE_{total}[d]	ΔE_{vdw}[e]	ΔE_{group}[f]
17E(1)	−82	59	0.00	**18E**(1)	−79	−64	1.06	1.06	1.12	1.37
17E(2)	−59	63	0.14							
17E(3)	73	62	0.29	**18E**(3)	78	−58	1.38	1.09	0.96	0.92
17E(4)	−150	63	1.09	**18E**(4)	−146	−60	1.77	0.68	0.49	0.62
17E(5)	169	64	1.15	**18E**(5)	170	−60	2.07	0.92	0.81	0.91
17E(6)	−71	147	2.43	**18E**(6)	−79	−143	3.45	1.02	1.09	1.31

[a] $\omega_{H-C(1)-C(8)-H}$ in degrees. [b] $\omega_{H-C(15)-C(19)-H}$ in degrees. [c] Steric energies relative to the lowest energy conformer **17E**(1). [d] E_{total}(**18E**(n)) − E_{total}(**17E**(n)). [e] Contribution of the van der Waals energy term to ΔE_{total}. [f] Contribution of the van der Waals interaction energy between groups i and ii to ΔE_{vdw}.

Table VIII. Differences in Calculated Steric Energy Contributions (kcal/mol) between the Stable Conformers of **2e** and **3e**

conformers	ΔE_{total}[a]	ΔE_{vdw}[a]	ΔE_{str}[b]	ΔE_{bnd}[c]	ΔE_{tor}[d]	ΔE_{dpl}[e]
2E,3E(1)	0.71	0.74	−0.01	0.07	−0.08	0.01
2E,3E(3)	0.72	0.58	0.03	−0.20	0.11	0.00
2E,3E(4)	0.30	0.12	−0.02	0.03	0.13	0.02
2E,3E(5)	0.56	0.46	0.06	0.05	−0.07	0.02

[a] See footnotes *c* and *d* in Table IV. [b] Contribution of the stretching energy term to ΔE_{total}. [c] Contribution of the bending energy term to ΔE_{total}. [d] Contribution of the torsional strain energy term to ΔE_{total}. [e] Contribution of the dipole–dipole interaction energy term to ΔE_{total}.

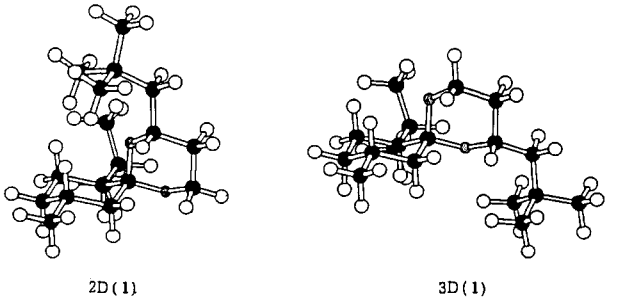


Figure 3.

Conformational searching by using a torsion-angle tree-search method[19] revealed that spiroacetals **2e** and **3e** have five and four stable conformers (**2E**(n) and **3E**(n))[20] within 2.0 kcal/mol of the corresponding lowest energy conformers **2E**(1) and **3E**(1), respectively (Figure 2 and Table IV). In these conformers, the cyclohexyl group adopts a similar local conformation with respect to the 1,3-dioxane ring. Thus, the dihedral angles $\omega_{H-C(12)-C(16)-H}$ for **2E**(n) and **3E**(n) are +58 to +63° and −64 to −57°, respectively. Rotations of the cyclohexyl groups are restricted by the adjacent equatorial methyl groups. The stable conformers **2E**(n) and **3E**(n) are rotamers of the isopropyl group on the menthane ring. The conformation of the isopropyl group (i.e., the value of dihedral angle $\omega_{H-C(1)-C(8)-H}$) is similar between pairs of conformers **2E**(n) and **3E**(n) (n = 1, 3, 4, and 5). The counterpart of **2E**(2) is not an energy minimum. The calculated ratio of **2e**:**3e** based on a Boltzman distribution of these stable conformers at −40 °C is 6.0:1, being in good agreement with the observed ratio.

Spiroacetals **2d** and **3d** were each found to have four stable conformers **2D**(n) and **3D**(n) (n = 1–4) within 2.0 kcal/mol of the lowest energy conformers **2D**(1) and **3D**(1) (Figure 3 and Table V). They possess a similar local conformation with respect to the neopentyl group and are rotamers of the isopropyl group on the menthane ring. Other possible conformations with respect to the neopentyl group are unfavorable due to repulsive interactions between the *tert*-butyl group and the 1,3-dioxane ring. The local conformation of the isopropyl group (i.e., $\omega_{H-C(1)-C(8)-H}$) is similar between pairs of conformers **2D**(n) and **3D**(n) (n = 1–4). Within an energy window of 2.0 kcal/mol, 12 and 10 conformers are responsible for spiroacetals **2a** and **3a**, respectively, those which correspond to the rotamers with respect to the two isopropyl groups on the menthane and the 1,3-dioxane ring (Table VI). The local conformations of the isopropyl groups in **2A**(n) closely resemble those of the counterpart **3A**(n). The counterparts of **2A**(3) and **2A**(11) are not energy minima. Calculated ratios of **2d**:**3d** and **2a**:**3a** at −40 °C are 5.2:1 and 3.8:1, respectively, being in good agreement with the experiments.

Results of the conformational analysis of spiroacetals **17e** and **18e** are similar to those for **2e** and **3e** (Table VII). The calculated ratio of **17e**:**18e** at −40 °C is 13:1. The calculation reproduces

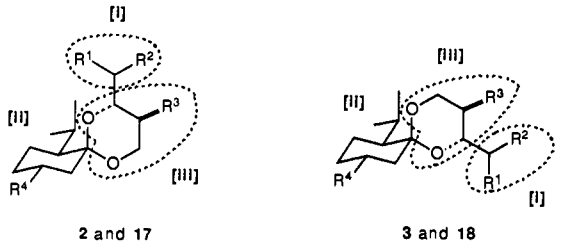


Figure 4.

well the improved selectivity observed in the acetalization with trimethylmenthone. Similar results were also obtained for **17a,d** and **18a,d**.[21]

The conformations of both the menthane and the 1,3-dioxane moieties bear a close resemblance between each pair of conformers **2**(*n*) and **3**(*n*). Thus, for example, least-squares superimposition of the menthane moiety of **2E**(*n*) and that of **3E**(*n*) gave rms deviations of 0.047 (*n* = 1), 0.082 (*n* = 3), and 0.051 Å/atom (*n* = 4), respectively. Similar treatment of the 1,3-dioxane moiety of **2E**(*n*) and that of the enantiomer of **3E**(*n*) gave deviations of 0.093 (*n* = 1), 0.062 (*n* = 3), and 0.049 Å/atom (*n* = 4), respectively.

Differences between diastereomeric spiroacetals lie in their global structures, that is, the spatial orientation of the substituent R^1R^2CH– with respect to the menthane ring. Calculated internuclear distances between the axial hydrogen (H_a) attached to the C(7) of the menthane ring and the equatorial hydrogen (H_b) of the cyclohexyl group in **2E**(*n*) (cf. Figure 2) are 2.94 (*n* = 1), 2.73 (*n* = 2), and 2.73 Å (*n* = 4), respectively, being close to the van der Waals minimum. On the other hand, distances between the corresponding hydrogen atoms in **3E**(*n*) are 6.36 (*n* = 1), 6.33 (*n* = 3), and 6.34 Å (*n* = 4), respectively. The energy for two interacting hydrogen atoms at the van der Waals minimum is –0.06 kcal/mol in the MM2 force field. While being smaller in amount, there are many possible stabilizing interactions between the cyclohexyl and menthane moieties in **2e**.

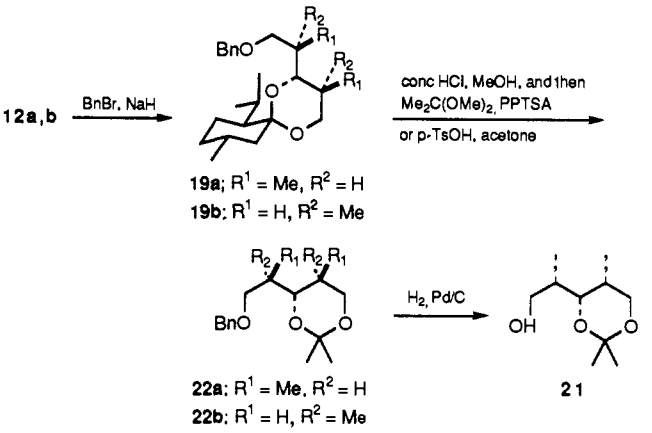
In MM2 calculations, the steric energy of a molecule is represented as a sum of independent energy terms such as stretching, bending, torsional, dipole–dipole interaction, and van der Waals interaction energy. As shown in Table VIII, differences in these components between pairs of conformers **2E**(*n*) and **3E**(*n*) are very small except for those of the van der Waals interaction energy (ΔE_{vdw}). Differences in total steric energy between these pairs (ΔE_{total}) are therefore considerably close to ΔE_{vdw}. Similar trends are also shown in the calculations of other spiroacetals (Tables V–VII). In view of the close resemblance of their local conformations, it is not surprising that the energy terms other than those for van der Waals interactions are nearly identical between the pairs of conformers. These results indicate that the van der Waals interaction energy, which is influenced by their global structures, is a major contributor to the stability of spiroacetal **2** (**17**) relative to **3** (**18**).

In order to analyze the origin of the van der Waals stabilization in spiroacetals **2** and **17** in more detail, further dissection of the van der Waals energy term was attempted.[22] When the whole molecules of spiroacetals **2e** and **3e** (or **17e** and **18e**) are divided into groups i, ii, and iii, as shown in Figure 4, the van der Waals interaction energy term is represented as a sum of the interaction energies between pairs of the groups and within the groups. As shown in Tables IX, the relative van der Waals interaction energy between groups i and ii is close to ΔE_{vdw} in each pair of conformers

(19) Lipton, M.; Still, W. C. *J. Comput. Chem.* **1988**, *9*, 343.

(20) Throughout the paper, capital letters are used for conformers. Conformers of spiroacetal **2** are numbered such that **2**(*n*) is the *n*th stable conformer of **2**. Each stable conformer of **3** has a counterpart in conformers **2**(*n*) which has similar local conformations with respect to the isopropyl group on the menthane ring and the substituent (R^1R^2CH–) on the 1,3-dioxane ring. Conformers of **3** are numbered such that the local conformations are similar between **2**(*n*) and **3**(*n*).

Scheme V



2E(*n*) and **3E**(*n*). Similar trends are also shown in the calculations of other spiroacetals (Tables V–VII). These results suggest strongly that the attractive interaction between these two groups is a dominant contributor to the stability of spiroacetals **2** and **17**.

As described above, the observed stereoselectivities were reproduced satisfactorily by the molecular mechanics calculations. The level of agreement with the experimental values is relatively high in comparison with previously studied systems.[3-5] This might be the result of the higher reliability of the force field parameters required for the calculations of these spiroacetals.

Determination of Stereochemistry. The structures of spiroacetals **2a–g**, **3a–g**, **12c**, and **13c** were determined previously on the basis of chemical correlations.[8] The absolute configurations of **12a,b** were established by converting them into the known acetonide derivatives **20a**[13a] and **21**[13b] (Scheme V). Thus, after protection of the hydroxy group of **12a** as a benzyl ether, removal of the menthonide moiety followed by treatment with 2,2-dimethoxypropane in the presence of pyridinium *p*-toluenesulfonate (PTSA) afforded (2*S*,3*R*,4*R*)-**20a** ($[\alpha]_D^{25}$ +20.5° (*c* 2.34, $CHCl_3$)). Treatment of benzyl ether **19b**, prepared from spiroacetal **12b**, in acetone in the presence of *p*-toluenesulfonic acid (TsOH) gave acetonide **20b**. Hydrogenolysis of **20b** afforded acetonide alcohol (2*S*,3*R*,4*R*)-**21** ($[\alpha]_D^{25}$ +7.6° (*c* 1.01, $CHCl_3$)).

The structures of spiroacetals **17a–f** and **18a–f** were determined on the basis of their ^1H NMR chemical shifts. We recently developed an empirically derived correlation of the structures and ^1H NMR chemical shifts for diastereomeric spiroacetals derived from menthones such as **2a–e** and **3a–e**.[8] The empirical trends are summarized as follows (Figure 5): (1) H_a of spiroacetal **3** constantly resonates at a lower field than does H_a of **2**. (2) The signals due to H_d and H_e of **3** are both centered at higher field than the signals due to the corresponding protons of **2**. (3) The values of $\Delta\delta_H$ ($\Delta\delta_H$ = δ_H of **3** – δ_H of **2**) calculated from the chemical shifts of H_a, H_d, and H_e all fall into relatively narrow ranges. (4) The absolute values of $\Delta\delta_{H_a}$ and $\Delta\delta_{H_d}$ are nearly identical. (5) When R^b = H, the respective chemical shifts of H_d and H_e are nearly identical among the members of the same family of spiroacetals. Since these empirical trends are rationalized on the basis of a long-range effect due to the magnetic anisotropy inherent to the menthane ring in these spiroacetals,[8,23] they should be equally applicable to the stereochemical determinations of **17** and **18**, whose structures closely resemble those of **2** and **3**, respectively. As shown in Tables X–XII, all the trends mentioned above are also observed in spiroacetals **17** and **18**. The validity of the stereochemical assignment was supported by the fact that the chemical shifts of H_a, H_b, and H_c are nearly identical between pairs of spiroacetals derived from menthone and trimethylmenthone. Slight but consistent increases in $\Delta\delta_{H_a}$

(21) Calculated ratios of **17a**:**18a** and **17d**:**18d** at –40 °C are 6.9:1 and 11:1, respectively. For additional data, see the supplementary material.

Table IX. Differences in Group van der Waals Energy (kcal/mol) between the Stable Conformers of **2e** and **3e**

2,3e	ΔE_{vdw}	[i–i]	[i–ii]	[i–iii]	[ii–ii]	[ii–iii]	[iii–iii]
2E,3E(1)	0.74	0.01	0.89	0.08	–0.14	–0.05	–0.03
2E,3E(3)	0.58	–0.02	0.40	0.27	0.02	–0.04	–0.04
2E,3E(4)	0.12	0.00	0.11	0.14	0.06	–0.16	–0.03
2E,3E(5)	0.46	0.06	0.43	–0.13	0.07	0.01	0.01

Table X. Chemical Shifts and Other ^{1}H NMR Data for H_a of Spiroacetals **17** and **18** in $CDCl_3$[a]

Acetal **18**	δ_{H_a}	J_{H_a,H_b}; J_{H_a,H_c}[a]	acetal **17**	δ_{H_a}	J_{H_a,H_b}; J_{H_a,H_c}[a]	$\Delta\delta_{H_a}$[b]
18a	3.69	11.7;2.7	**17a**	3.35	11.4;2.4	0.34
18b	4.14	12.0;2.7	**17b**	3.81	m;2.7	0.33
18c	3.97	m; m	**17c**	3.73	m; m	0.24
18d	4.12	11.4;2.7	**17d**	3.94	11.4; 2.4	0.18
18e	3.43	10.2	**17e**	3.23	10.2	0.20
18f	3.69	10.8	**17f**	3.44	10.5	0.25

[a] Vicinal coupling constant, in Hz. "m" indicates that J could not be determined due to interfering signals. [b] $\Delta\delta_{H_a} = \delta_{H_a}$ of **18** – δ_{H_a} of **17**.

Table XI. Chemical Shifts and Other ^{1}H NMR Data for H_d of Spiroacetals **17** and **18** in $CDCl_3$[a]

acetal **18**	δ_{H_d}	J_{H_d,H_b}; J_{H_d,H_c}[a]	acetal **17**	δ_{H_d}	J_{H_d,H_b}; J_{H_d,H_c}[a]	$\Delta\delta_{H_d}$[b]
18a	3.78	m; m	**17a**	4.10	11.4; 2.7	–0.32
18b	3.81	11.7; 2.7	**17b**	4.11	12.0; 3.0	–0.30
18c	*ca.* 3.8	m; m	**17c**	4.10	12.3; 3.0	*ca.* –0.3
18d	3.83	12.3; 2.4	**17d**	4.15	12.6; 2.4	–0.32
18e	3.32	11.4	**17e**	3.63	11.1	–0.31
18f	3.34	11.4	**17f**	3.63	11.4	–0.29

[a] Vicinal coupling constant, in Hz. "m" indicates that J could not be determined due to interfering signals. [b] $\Delta\delta_{H_d} = \delta_{H_d}$ of **18** – δ_{H_d} of **17**.

Table XII. Chemical Shifts and Other ^{1}H NMR Data for H_e of Spiroacetals **17** and **18** in $CDCl_3$[a]

acetal **18**	δ_{H_e}	J_{H_e,H_b}; J_{H_e,H_c}[a]	acetal **17**	δ_{H_e}	J_{H_e,H_b}; J_{H_e,H_c}[a]	$\Delta\delta_{H_e}$[b]
18a	3.78	m; m	**17a**	3.84	5.4; 1.5	–0.06
18b	3.74	6.3; 1.8	**17b**	3.80	5.1; 1.8	–0.06
18c	*ca.* 3.8	m; m	**17c**	3.81	5.4; 1.5	*ca.* 0.0
18d	3.74	5.4; 1.5	**17d**	3.80	6.6: 1.2	–0.06
18e	3.60	5.1	**17e**	3.68	5.7	–0.08
18f	3.64	5.1	**17f**	3.71	5.5	–0.07

[a] Vicinal coupling constant, in Hz. "m" indicates that J could not be determined due to interfering signals. [b] $\Delta\delta_{H_e} = \delta_{H_e}$ of **18** – δ_{H_e} of **17**.

and $\Delta\delta_{H_d}$ in spiroacetals derived from trimethylmenthone may be the result of an enhanced magnetic anisotropy of the trimethyl-substituted menthane ring.

In addition, confirmation of the structure **17e** was made by a single-crystal X-ray diffraction analysis (Figure 6). The conformation of **17e** in the crystal was similar to that predicted for the lowest energy conformation **17E**(1) by molecular mechanistic calculations.

Conclusions

We have shown that, under thermodynamic conditions, acetalization of various 1,3-alkanediols with menthone affords spiroacetal **2**, of a folded structure, in preference to the diastereomer **3**, of an extended structure. The correlation between the selectivities and the structures of spiroacetals as well as the enhanced selectivities observed in the acetalization with trimethylmenthone indicates that the preferential formation of the folded spiroacetal is due to the intramolecular attractive interactions between the substituents attached on the 1,3-dioxane ring and the menthane (or trimethylmenthane) moiety. Molecular mechanics calculations give satisfactory agreement with experiments and provide a strong support for the operation of the van der Waals attractive interaction as the most important factor

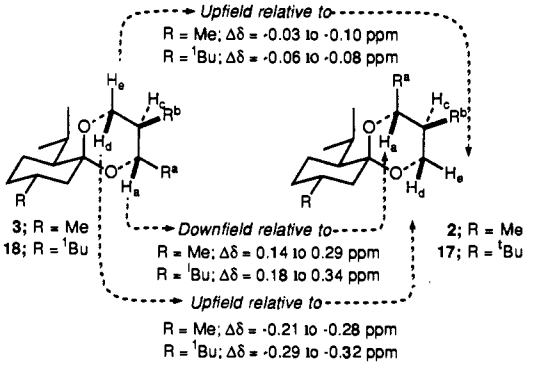


Figure 5.

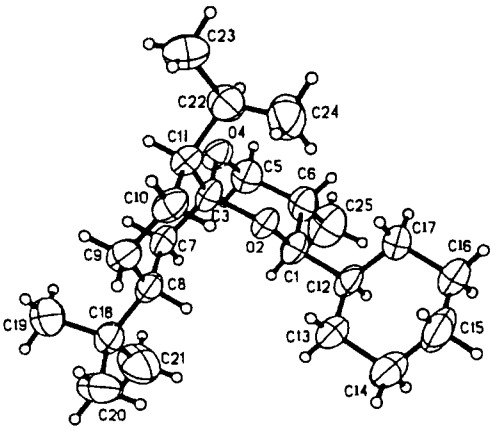


Figure 6.

determining the stereoselectivity of the reaction. As demonstrated by the application to a novel enantiodifferentiating transformation of σ-symmetric 1,3,5-pentanetriols, the intramolecular van der Waals attractive interactions should serve as a potential controlling factor in the development of stereoselective reactions.

Experimental Section

Unless otherwise noted, ^{1}H NMR spectra of $CDCl_3$ solutions were recorded at 300 MHz. 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 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, DMF, and pyridine were distilled from CaH_2. Bis(trimethylsilyl) ethers **1a–e** and **11c** were prepared as described previously.[8]

General Procedure for the Acetalization of Racemic Bis(trimethylsilyl) Ethers 1a–e with *dl*-Menthone. To an ampule fitted with a septum rubber were added successively **1** (1 mmol), *dl*-menthone[24] (0.33 mmol), and the solvent (1.0 mL) via a syringe under an argon atmosphere. To the resulting solution at –78 °C was added a catalytic amount of TMSOTf (or TfOH) and the ampule was sealed. The mixture was allowed to stand under the reaction conditions shown in Table I. The reaction was quenched by adding pyridine (0.2 mL). The mixture was diluted with hexane and was washed with aqueous $NaHCO_3$. The organic layer was dried and concentrated. The residue was then treated with 1 N NaOH in MeOH (2 mL) at 25 °C for 15 min. Water was then added and the mixture was extracted twice with hexane. The extracts were dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc) to

(22) A detailed analysis of partitioning of the conformational energies may reflect the force field properties and, therefore, should be handled with care. However, in the present case, there are good grounds for such analysis. In MM2 calculations, parameters for the van der Waals energy term were assigned independently to other energy terms which are influenced by local conformations of a molecule.[17] The close resemblance of the local structures between pairs of conformers of diastereomeric spiroacetals and the resulting equality of the energy terms other than van der Waals energy may justify the validity of such analysis.

give, in order of elution, **3**[8] and **2**.[8] The ratio of the products was determined by capillary GC analysis of the crude reaction mixture.

Isomerization Experiment. The isomerization reaction of **3a** is representative. To an ampule fitted with a septum rubber were added successively spiroacetal **3a** (36.9 mg, 0.145 mmol), **1a** (0.145 mmol), and CH_2Cl_2 (0.30 mL) via a syringe under an argon atmosphere. To the resulting solution at -78 °C was added TMSOTf (5 μL). The ampule was sealed and the mixture was allowed to stand at –40 °C for 39 h. The reaction was quenched by adding pyridine (0.1 mL). A workup procedure similar to that described in the acetalization of **1** gave a crude mixture of **2a** and **3a**, whose ratio was determined to be 3.4:1 by capillary GC analysis. Purification by flash chromatography (hexane/EtOAc, 98:2) gave 26.4 mg (72%) of a mixture of **2a** and **3a**.

3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-1,4-pentadiene (8). To a solution of 2,4-dimethyl-1,4-pentadiene-3-ol (6.19 g, 55.2 mmol) in DMF (55 mL) at room temperature were added successively imidazole (5.64 g, 82.8 mmol) and *t*-$BuMe_2SiCl$ (9.98 g, 66.2 mmol). The mixture was stirred for 15 h at room temperature. The mixture was diluted with hexane (300 mL) and washed twice with water. The organic layer was dried and concentrated. The residue was purified by flash chromatography (hexane) to give 12.0 g (96%) of **8**: bp (Kugelrohr) 100 °C (10 mmHg); ^{1}H NMR δ 0.03 (6H, s), 0.90 (9H, s), 1.58 (6H, br s), 4.39 (1H, br s), 4.84 (2H, m), 5.01 (2H, m); IR (liquid film) 1250 (s), 1090 (s), 830 (s), 775 (s) cm^{-1}; MS (CI), *m/z* (relative intensity) 277 (MH^+, 27), 211 (13), 185 (5), 169 (100); HRMS (CI), for $C_{13}H_{27}OSi$ (MH), calcd *m/z* 227.1832, found *m/z* 227.1830. Anal. Calcd for $C_{13}H_{26}OSi$: C, 68.96; H, 11.57. Found: C, 68.68; H, 11.76.

(2*R*,3*S*,4*S*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-1,5-pentanediol (9a). To a solution of BH_3/THF (1.6 mL of a 1 N solution in THF, 1.6 mmol) in THF was added a THF (1.6 mL) solution of 1,5-cyclooctadiene (0.19 mL, 1.6 mmol) at 0 °C. The mixture was refluxed for 1 h and then cooled to –85 °C. To the resulting suspension of 9-BBN in THF was added a THF (0.4 mL) solution of TBS ether **8** (121 mg, 0.533 mmol). The mixture was stirred for 16 h during which time it was allowed to warm to room temperature. The mixture was cooled to –10 °C and 6 N aqueous NaOH (0.32 mL) and 30% aqueous H_2O_2 were successively added. The cooling bath was removed and the mixture was stirred for 2 h. Brine was added and the mixture was extracted twice with EtOAc. The combined extracts were dried and concentrated *in vacuo* to give an oil. This was purified by flash chromatography (hexane/EtOAc, gradient elution from 75:25 to 65:35) to give 129.8 mg (93%) of **9a** which contained 7.1% of the diastereomer **10**. In the preparative scale experiment starting from 7.27 g (32.1 mol) of **8**, 5.85 g (69%) of pure **9a** was obtained. **9a**: ^{1}H NMR (200 MHz) δ 0.12 (6H, s), 0.91 (9H, s), 0.98 (6H, d, *J* = 7.1), 1.94 (2H, m), 2.24 (2H, br s), 3.63 (4H, m), 3.69 (1H, t, *J* = 4.9); IR (liquid film) 2950 (br), 2950 (s), 1250 (s), 1030 (s) cm^{-1}; MS (CI), *m/z* (relative intensity) 263 (MH^+, 14), 203 (12), 187 (11), 113 (100); HRMS (CI), for $C_{13}H_{31}O_3Si$ (MH), calcd *m/z* 263.2043, found *m/z* 263.2039. Anal. Calcd for $C_{13}H_{30}O_3Si$: C, 59.49; H, 11.52. Found: C, 59.23; H, 11.78. (2*R**,4*R**)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-1,5-pentanediol (**10**): ^{1}H NMR δ 0.08 (3H, s), 0.10 (3H, s), 0.90 (9H, s), 1.82–2.00 (2H, m), 2.01–2.42 (2H, br s); MS (CI), *m/z* (relative intensity) 263 (MH^+, 13), 203 (13), 187 (16), 113 (100); HRMS (CI), for $C_{13}H_{31}O_3Si$ (MH), calcd *m/z* 263.2043, found *m/z* 263.2080. Anal. Calcd for $C_{13}H_{30}O_3Si$: C, 11.55; H, 59.49. Found: C, 11.78; H, 59.21.

(2*S*,3*R*,4*R*)-3-(*tert*-Butyldimethylsiloxy)-2,4-dimethyl-1,5-pentanediol (9b). To a solution of **8** (1.99 g, 8.79 mmol) in THF (9 mL) at –85 °C was added a solution of BH_3–THF (17.6 mL of a 1 N solution in THF, 17.6 mmol). The mixture was stirred for 15 h during which time it was allowed to warm to room temperature. The mixture was cooled to –10 °C and 6 N aqueous NaOH (10.5 mL) and 30% H_2O_2 (21 mL) were successively added. The mixture was stirred for 2 h during which time it was allowed to warm to room temperature. Brine was then added and the mixture was extracted twice with EtOAc. The extracts were dried and concentrated *in vacuo* to give an oil. This was purified by flash chromatography (hexane/EtOAc, gradient elution from 75:25 to 67:33) to give, in order of elution, 336.5 mg (15%) of **9a**, 758.2 mg (33%) of a mixture of **10** and **9b**, and 873.1 mg (38%) of **9b**. The mixture of **10** and **9b** was separated further by flash chromatography to give 265 mg (11%) of pure **9b**. **9b**: ^{1}H NMR (200 MHz) δ 0.07 (6H, s), 0.88 (6H, d, *J* = 7.0), 0.89 (9H, s), 1.85–1.96 (2H, m), 2.39 (2H, br s), 3.47 (1H, dd, *J* = 10.6, 5.8), 3.58 (1H, dd, *J* = 10.6, 7.9), 3.89 (1H, t, *J* = 3.6); IR (liquid film) 3325 (br), 2950 (s), 1225 (s), 1030 (s) cm^{-1}.

(2*R*,3*S*,4*S*)-2,4-Dimethyl-1,3,5-tris(trimethylsiloxy)pentane (11a). To a solution of diol **9a** (2.29 g, 8.74 mmol) in THF (10 mL) at room temperature was added 10% aqueous HCl (5.0 mL). The mixture was stirred for 2 h at room temperature and then it was concentrated *in vacuo*. Residual water was removed by by azeotropic distillation with benzene (250 mL). To a THF (10 mL) solution of the residue (i.e., the crude triol) were added hexamethyldisilazane (5.5 mL, 26.2 mmol) and TMSOTf (17 μL, 0.09 mmol). The mixture was stirred for 1 h at 25 °C. It was diluted with hexane and washed successively with water and aqueous $NaHCO_3$. The extract was dried and concentrated. The residue was purified by flash chromatography (hexane/EtOAc, 99.5:0.5) to give 2.33 g (70%) of **12a**: bp (Kugelrohr) 135 °C (10 mmHg); ^{1}H NMR δ 0.09 (18H, s), 0.10 (9H, s), 0.94 (1H, d, *J* = 6.9), 1.82 (2H, m), 3.38 (2H, dd, *J* = 9.6, 7.5), 3.46 (1H, t, *J* = 5.7), 3.67 (2H, dd, *J* = 9.6, 4.2); IR (liquid film) 1245 (s), 1090 (s), 880 (s), 835 (s), 745 (s) cm^{-1}; MS (CI), *m/z* (relative intensity) 365 (MH^+, 3), 275 (8), 259 (4), 103 (100). Anal. Calcd for $C_{16}H_{40}O_3Si_3$: C, 52.69; H, 11.05. Found: C, 52.59; H, 11.20.

(2*S*,3*R*,4*R*)-2,4-Dimethyl-1,3,5-tris(trimethylsiloxy)pentane (11b). **11b** was prepared in 100% yield from diol **8b** by a procedure similar to that described above **11b**: bp (Kugelrohr) 135 °C (10 mmHg); ^{1}H NMR δ 0.09 (18H, s), 0.10 (9H, s), 0.96 (1H, d, *J* = 6.9), 1.74 (2H, m), 3.32 (2H, dd, *J* = 9.9, 6.9), 3.47 (2H, dd, *J* = 9.9, 6.0), 3.67 (1H, t, *J* = 5.1); IR (liquid film) 1240 (s), 1080 (s), 830 (s), 740 (s) cm^{-1}; MS (CI), *m/z* (relative intensity) 365 (MH^+, 0.5), 233 (45), 185 (43), 103 (100). Anal. Calcd for $C_{16}H_{40}O_3Si_3$: C, 52.69; H, 11.05. Found: C, 52.88; H, 11.31.

General Procedure for Acetalization of 11a–c with *l*-Menthone. To a solution of **11a–c** (5 mmol), *l*-menthone (5.5 mmol), and CH_2Cl_2 (6 mL) was added TMSOTf (1 mmol) at –40 or –85 °C. The mixture was stirred for 16 h. The reaction was quenched by adding pyridine (1 mL) and 1% methanolic NaOH (9 mL), and the mixture was stirred for an additional 7 h at room temperature. The mixture was concentrated *in vacuo* and then partitioned between EtOAc and aqueous $NaHCO_3$. In the reactions of **11a,b**, the dried and concentrated organic layer was purified by flash chromatography (hexane/EtOAc, gradient elution from 95:5 to 70:30) to give, in order of elution, **13a,b** and **12a,b**. In the reaction of **11c**, the crude mixture was treated under the usual silylation conditions (TBSCl, imidazole, DMF, room temperature, 15 h). Purification by flash chromatography (2% EtOAc in hexane) of the crude mixture gave in the order of elution **13c** and **12c**.

Spiroacetal 12a: R_f 0.31 (hexane/EtOAc, 80:20); ^{1}H NMR (200 MHz) δ 0.67 (1H, t, *J* = 13.0), 0.74 (3H, d, *J* = 6.6), 0.83 (3H, d, *J* = 7.0), 0.91 (6H, d, *J* = 7.2), 1.08 (3H, d, *J* = 7.1), 1.32–2.36 (10H, m), 2.68 (1H, ddd, *J* = 13.6, 3.3, 1.8), 3.48 (1H, dd, *J* = 10.4, 2.7), 3.60 (1H, t, *J* = 11.0), 3.66 (2 H, m), 3.75 (1H, dd, *J* = 11.2, 4.0); IR (liquid film) 3375 (br), 2900 (s), 1115 (s) cm^{-1}; MS, *m/z* (relative intensity) 284 (M^+, 30), 269 (13), 227 (24), 199 (26), 139 (24), 112 (41), 95 (68), 69 (67), 55 (88), 41 (100); HRMS, for $C_{17}H_{32}O_3$, calcd *m/z* 284.2353, found *m/z* 284.2344.

Spiroacetal 13a: R_f 0.35 (hexane/EtOAc, 80:20); ^{1}H NMR (200 MHz) δ 0.64 (1H, t, *J* = 13.0), 0.71 (3H, d, *J* = 6.7), 0.86 (6H, d, *J* = 7.0), 0.88 (3H, d, *J* = 6.6), 1.09 (3H, d, *J* = 7.2), 1.15–2.04 (9H, m), 2.23 (1H, sept d, *J* = 7.0, 1.6), 2.64 (1H, ddd, *J* = 13.7, 3.8, 1.6), 3.39 (1H, t, *J* = 11.0), 3.47–3.72 (3H, m), 3.92 (1H, br d, *J* = 10.8); IR (liquid film) 3375 (br), 2950 (s), 1115 (s) cm^{-1}; MS, *m/z* (relative intensity) 284 (M^+, 24), 269 (12), 227 (22), 199 (29), 139 (28), 95 (66), 69 (66), 41 (100); HRMS, for $C_{17}H_{32}O_3$, calcd *m/z* 284.2353, found *m/z* 284.2359.

Spiroacetal 12b: R_f 0.23 (hexane/EtOAc, 80:20); ^{1}H NMR (200 MHz) δ 0.63 (1H, t, *J* = 12.9), 0.88 (6H, d, *J* = 7.0), 0.91 (3H, d, *J* = 7.0), 1.04 (3H, d, *J* = 6.6), 1.10 (3H, d, *J* = 6.8), 1.15–1.82 (9H, m), 2.49 (1H, sept d, *J* = 6.9, 1.2), 2.72 (1H, ddd, *J* = 13.6, 3.2, 2.0), 3.48 (1H, dd, *J* = 15.2, 4.5), 3.55 (1H, dd, *J* = 11.4, 1.2), 3.61 (1H, m), 3.68 (1H, dd, *J* = 9.6, 2.4), 4.23 (1H, dd, *J* = 11.2, 2.6); IR (liquid film) 3425 (br), 2950 (s), 1110 (s) cm^{-1}; MS, *m/z* (relative intensity) 284 (M^+, 46), 269 (22), 227 (41), 139 (42), 112 (62), 69 (66), 55 (87), 41 (100); HRMS, for $C_{17}H_{32}O_3$, calcd *m/z* 284.2353, found *m/z* 284.2349.

Spiroacetal 13b: R_f 0.30 (hexane/EtOAc, 80:20); ^{1}H NMR (200 MHz) δ 0.58 (1H, t, *J* = 12.8), 0.87 (3H, d, *J* = 6.6), 0.89 (3H, *J* = 7.2),

(23) (a) Jackman, L. M.; Sternhell, S. *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: Oxford, U.K., 1969; p 238. (b) Gaudemer, A. In *Stereochemistry*; Kagan, H. B., Ed.; Thieme: Stuttgart, Germany, 1977; Vol. 1, p 99.

(24) Commercially available menthone was found to be not exactly a 1:1 mixture of *d* and *l* isomers. Equimolar amounts of optically pure *d*- and *l*-menthone were mixed and used.

0.89 (3H, d, J = 7.1), 0.90 (3H, d, J = 7.2), 1.09 (3H, d, J = 7.2), 1.17–1.84 (9H, m), 2.48 (1H, sept d, J = 7.1, 1.8), 2.74 (1H, ddd, J = 13.9, 3.7, 2.1), 3.43–3.57 (2H, m), 3.64 (1H, dd, J = 10.6, 4.5), 3.91 (1H, dd, J = 9.1, 2.6), 4.00 (1H, dd, J = 11.2, 2.7); IR (liquid film) 3375 (br), 2950 (s), 1120 (s) cm^{-1}; MS, m/z (relative intensity) 284 (M^+, 40), 269 (20), 227 (36), 139 (39), 112 (58), 69 (66), 55 (87), 41 (100); HRMS, for $C_{17}H_{32}O_3$, calcd m/z 284.2353, found m/z 284.2358.

Spiroacetal 12c: R_f 0.24 (petroleum ether/Et_2O, 98:2); ^1H NMR (200 MHz) δ 0.03 (6H, s), 0.66 (1H, t, J = 12.5), 0.87 (9H, d, J = 6.9), 0.88 (9H, s), 1.00–1.80 (9H, m), 2.39 (1H, sept d, J = 7.0, 1.6), 2.70 (1H, ddd, J = 13.4, 3.0, 1.8), 3.60–3.86 (3H, m), 3.95 (1H, m), 4.09 (1H, td, J = 12.2, 2.8); IR (liquid film) 2960 (s), 1110 (s), 1095 (s), 840 (s) cm^{-1}; MS, m/z (relative intensity) 370 (M^+, 13), 355 (8), 313 (16), 89 (100); HRMS, for $C_{21}H_{42}O_3Si$, calcd m/z 370.2905, found m/z 370.2899.

Spiroacetal 13c: R_f 0.34 (petroleum ether/Et_2O, 98:2); ^1H NMR (200 MHz) δ 0.04 (6H, s), 0.66 (1H, dd, J = 13.6, 12.6), 0.86 (3H, d, J = 6.9), 0.87 (3H, d, J = 6.5), 0.88 (3H, d, J = 7.1), 0.88 (9H, s), 1.08–1.77 (9H, m), 2.35 (1H, sept d, J = 7.0, 2.6), 2.68 (1H, ddd, J = 13.2, 3.5, 1.9), 3.64–3.78 (3H, m), 3.85 (1H, td, J = 12.0, 2.9), 4.10 (1H, m); IR (liquid film) 2960 (s), 1120 (s), 1100 (s), 840 (s) cm^{-1}; MS, m/z (relative intensity) 370 (M^+, 14), 355 (8), 313 (16), 89 (100); HRMS, for $C_{21}H_{42}O_3Si$, calcd m/z 370.2905, found m/z 370.2901.

9,9,9-Trimethylmenthone (15). A reaction flask containing $CeCl_3 \cdot 7H_2O$ (65 g, 174 mmol) was heated at 140 °C for 4 h *in vacuo*. To this was added THF (450 mL) at 0 °C. The resulting suspension was stirred for 18 h at room temperature. To the suspension at 0 °C were added successively *i*-PrMgBr (136 mL of a 1.43 M solution in THF) and a THF (100 mL) solution of 4-*tert*-butylcyclohexanone (23.1 g, 150 mmol). The mixture was stirred for 1 h at 0 °C. A solution of AcOH (30 mL) in water (750 mL) was added and the mixture was extracted three times with ether. The combined extracts were washed with brine and aqueous $NaHCO_3$, dried, and concentrated *in vacuo*. To a solution of the residue (i.e., the crude alcohol) in pyridine (200 mL) at room temperature was added $POCl_3$ (25 mL, 270 mmol). The mixture was heated at 90 °C for 1.5 h and then allowed to cool to room temperature. The mixture was poured onto ice–water (1 L) and extracted twice with ether. The extracts were washed successively with 10% aqueous HCl, 10% aqueous K_2CO_3, and brine. Then this was dried and concentrated *in vacuo*. Vacuum distillation (108 °C, 20 mmHg) of the residue gave 22.7 g (126 mmol, 66% yield) of a *ca.* 3:1 mixture of 4-*tert*-butyl-1-isopropylcyclohexene (**14**) and 4-*tert*-butyl-1-isopropylidenecyclohexane. **14**: ^1H NMR δ 0.86 (9H, s), 0.98 (3H, d, J = 6.9), 0.98 (3H, d, J = 6.9), 1.00–2.10 (7H, m), 2.16 (1H, sept, J = 6.9), 5.40 (1H, m).

To a solution of crude **14** (3.35 g, 16.9 mmol) in THF (40 mL) at 0 °C was slowly added BH_3–DMS (8.45 mL of a 2 M solution in THF, 17.0 mmol). The mixture was stirred for 1 h during which time it was allowed to warm to room temperature. The mixture was cooled to −10 °C and 6 N aqueous NaOH (2.8 mL) and 30% aqueous H_2O_2 (5.6 mL) were added successively. The mixture was then refluxed for 1 h. Brine was added at room temperature and the mixture was extracted twice with EtOAc. The combined extracts were dried and concentrated *in vacuo* to give the crude alcohol (2.93 g). To a solution of the crude alcohol in 30 mL of acetone at 0 °C was added Jones reagent (5 N) until the orange color of the reagent persisted. Stirring was continued for 1 h at room temperature. Then, the excess reagent was destroyed by adding *i*-PrOH. The mixture was concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and the organic layer was washed with brine, dried, and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc, 98:2) to give, in order of elution, *trans*-**15** (1.05 g, 32%), a mixture of *trans*-**15** and *cis*-**16** (0.303 g, 9%), and *cis*-**16** (0.722 g, 22%). **15**: bp (Kugelrohr) 130 °C (10 mmHg); ^1H NMR δ 0.86 (3H, d, J = 6.6), 0.89 (9H, s), 0.93 (3H, d, J = 6.6), 1.26–1.56 (3H, m), 1.94–2.20 (5H, m), 2.42 (1H, ddd, J = 12.6, 3.6, 2.4); IR (liquid film) 2940 (s), 2850 (s), 1700 (s), 1357 (s) cm^{-1}; MS, m/z (relative intensity) 196 (M^+, 15), 181 (22), 154 (22), 41 (100); HRMS, for $C_{13}H_{24}O$, calcd m/z 196.1828, found m/z 196.1829. Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.26; H, 12.44. **16**: bp 130 °C (10 mmHg); ^1H NMR δ 0.82 (3H, d, J = 6.2), 0.87 (9H, s), 0.94 (3H, d, J = 6.0), 1.40–1.70 (4H, m), 1.85–2.20 (4H, m), 2.29 (1H, m); IR (liquid film) 2940 (s), 2890 (s), 2850 (s), 1700 (s), 1357 (s) cm^{-1}; MS, m/z (relative intensity) 196 (M^+, 10), 181 (16), 154 (39), 69 (100); HRMS, for $C_{13}H_{24}O$, calcd m/z 196.1828, found m/z 196.1832. Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.53; H, 12.32.

Acetalization of Bis(trimethylsilyl) Ethers 1a–e and Tris(trimethylsilyl) Ethers with Trimethylmenthone 15: The reaction was performed in a sealed ampule in a manner similar to that described in the acetalization with *dl*-menthone.

Spiroacetal 17a: bp 130 °C (0.05 mmHg); ^1H NMR δ 0.63 (1H, J = 12.6), 0.86 (9H, s), 0.97 (3H, d, J = 5.9), 0.89 (6H, d, J = 6.9), 0.94 (3H, d, J = 6.6), 0.95 (1H, m), 1.05–1.65 (7H, m), 1.78 (1H, d quint, J = 7.2, 2.1), 2.38 (1H, sept d, J = 7.0, 1.9), 2.80 (1H, dt, J = 13.2, 2.7), 3.35 (1H, ddd, J = 11.2, 6.9, 2.4), 3.84 (1H, ddd, J = 11.4, 5.1, 1.5), 4.10 (1H, td, J = 11.4, 2.7); IR (liquid film) 2940 (s), 1140 (s), 1105 (s) cm^{-1}; MS, m/z (relative intensity) 296 (M^+, 3), 239 (12), 197 (11), 83 (100); HRMS, for $C_{19}H_{36}O_2$, calcd m/z 296.2717, found m/z 296.2713. Anal. Calcd for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24. Found: C, 77.02; H, 12.32.

Spiroacetal 18a: bp (Kugelrohr) 130 °C (0.05 mmHg); ^1H NMR δ 0.67 (1H, t, J = 12.9), 0.87 (9H, s), 0.87 (3H, d, J = 6.6), 0.88 (3H, d, J = 6.8), 0.90 (6H, d, J = 6.9), 0.91 (1H, m), 1.05–1.72 (7H, m), 1.78 (1H, d quint, J = 12.3, 3.0), 2.38 (1H, sept d, J = 7.0, 2.4), 2.79 (1H, dt, J = 13.2, 2.7), 3.69 (1H, ddd, J = 11.7, 6.0, 2.7), 3.76–3.80 (2H, m); IR (liquid film) 2940 (s), 1150 (s), 1140 (m), 1105 (s) cm^{-1}; MS, m/z (relative intensity) 296 (M^+, 4), 239 (14), 197 (13), 83 (100); HRMS, for $C_{19}H_{36}O_2$, calcd m/z 296.2717, found m/z 296.2720. Anal. Calcd for $C_{19}H_{36}O_2$: C, 76.97; H, 12.24. Found: C, 76.73; H, 12.32.

Spiroacetal 17b: ^1H NMR δ 0.70 (1H, t, J = 12.9), 0.86 (9H, s), 0.89 (3H, d, J = 7.1), 0.90 (3H, d, J = 6.9), 0.90 (1H, m), 1.05–1.65 (6H, m, including d (3H, J = 6.0) at 1.13), 1.78 (1H, d quint, J = 12.6, 3.0), 2.39 (1H, sept d, J = 7.2, 1.8), 2.80 (1H, dt, J = 13.2, 2.4), 3.80 (1H, ddd, J = 11.7, 5.1, 1.8), 3.75–3.88 (1H, m), 4.11 (1H, td, J = 12.0, 3.0); IR (liquid film) 2940 (s), 1160 (s), 1140 (s), 1110 (s) cm^{-1}; MS, m/z (relative intensity) 268 (M^+, 8), 253 (18), 211 (67), 55 (100); HRMS, for $C_{17}H_{32}O_2$, calcd m/z 268.2404, found m/z 268.2406. Anal. Calcd for $C_{17}H_{32}O_2$: C, 76.06; H, 12.02. Found: C, 76.08; H, 12.19.

Spiroacetal 18b: ^1H NMR δ 0.73 (1H, t, J = 13.2), 0.86 (9H, s), 0.88 (6H, d, J = 6.9), 0.91 (3H, d, J = 6.9), 1.19–1.62 (6H, m, including d (3H, J = 6.0) at 1.15), 1.78 (1H, d quint, J = 12.3, 3.0), 2.37 (1H, sept d, J = 6.9, 2.4), 2.80 (1H, dt, J = 13.5, 2.4), 3.74 (1H, ddd, J = 11.7, 6.3, 1.8), 3.81 (1H, td, J = 11.7, 2.7), 4.14 (1H, dqd, J = 12.0, 6.0, 2.7); IR (liquid film) 2950 (s), 1160 (s), 1140 (s), 1110 (s) cm^{-1}; MS, m/z (relative intensity) 268 (M^+, 4), 253 (13), 211(51), 55 (100); HRMS, for $C_{17}H_{32}O_2$, calcd m/z 268.2404, found m/z 268.2393.

Spiroacetal 17c: ^1H NMR δ 0.71 (1H, t, J = 13.0), 0.83 (9H, s), 0.91 (3H, d, J = 7.1), 0.93 (3H, d, J = 7.0), 0.94 (1H, m), 1.11 (1H, dt, J = 12.2, 3.0), 1.15–1.85 (8H, m), 2.42 (1H, sept d, J = 7.2, 1.7), 2.55–2.91 (3H, m), 3.73 (1H, m), 3.81 (1H, ddd, J = 11.7, 5.3, 1.4), 4.10 (1H, td, J = 12.1, 2.6), 7.14–7.32 (5H, m); IR (liquid film) 3030 (m), 2950 (s), 1150 (s), 1135 (s), 1100 (s), 735 (s), 700 (s) cm^{-1}; MS, m/z (relative intensity) 358 (M^+, 12), 343 (6), 301(29), 91 (100); HRMS, for $C_{24}H_{38}O_2$, calcd m/z 358.2873, found m/z 358.2862. Anal. Calcd for $C_{24}H_{38}O_2$: C, 80.39; H, 10.68. Found: C, 80.49; H, 10.83.

Spiroacetal 18c: ^1H NMR δ 0.73 (1H, t, J = 13.0), 0.86 (9H, s), 0.89 (3H, d, J = 7.0), 0.93 (3H, d, J = 7.0), 0.94 (1H, m), 1.12 (1H, dt, J = 12.4, 2.8), 1.16–1.88 (8H, m), 2.39 (1H, sept d, J = 7.0, 2.6), 2.61–2.80 (3H, m), 3.73–3.85 (2H, m), 3.97 (1H, m), 7.15–7.32 (5H, m); IR (liquid film) 3030 (m), 2950 (s), 1150 (s), 1125 (s), 1110 (s), 750 (s), 700 (s) cm^{-1}; MS, m/z (relative intensity) 358 (M^+, 11), 343 (6), 301 (28), 91 (100); HRMS, for $C_{24}H_{38}O_2$, calcd m/z 358.2873, found m/z 358.2872.

Spiroacetal 17d: ^1H NMR δ 0.73 (1H, t, J = 12.9), 0.80–1.02 (26H, m, including s (9H) at 0.88 and s (9H) at 0.96), 1.08–1.67 (7H, m), 1.79 (1H, d quint, J = 12.2, 1.8), 2.40 (1H, sept d, J = 7.0, 1.7), 2.86 (1H, dt, J = 13.2, 2.4), 3.79 (1H, ddd, J = 9.9, 5.4, 1.5), 3.93 (1H, ddt, J = 11.3, 8.7, 2.1), 4.14 (1H, ddd, J = 14.4, 11.3, 2.7); IR (liquid film) 2930 (s), 1135 (s), 1120 (s), 1085 (s) cm^{-1}; MS, m/z (relative intensity) 324 (M^+, 7), 309 (3), 267 (21), 69 (100); HRMS, for $C_{21}H_{40}O_2$, calcd m/z 324.3030, found m/z 324.3020. Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.42. Found: C, 77.68; H, 12.39.

Spiroacetal 18d: bp (Kugelrohr) 135 °C (0.08 mmHg); ^1H NMR δ 0.69 (1H, t, J = 12.9), 0.80–1.02 (26H, m, including s (9H) at 0.87 and s (9H) at 0.93), 1.04–1.63 (7H, m), 1.78 (1H, d quint, J = 12.2, 2.8), 2.37 (1H, sept d, J = 7.2, 2.7), 2.84 (1H, dt, J = 13.2, 2.4), 3.74 (1H, ddd, J = 11.4, 5.7, 1.5), 3.85 (1H, td, J = 12.3, 2.7), 4.12 (1H, ddt, J = 11.4, 4.2, 2.7); IR (liquid film) 2930 (s), 1135 (s), 1115 (s), 1090 (s) cm^{-1}; MS, m/z (relative intensity) 324 (M^+, 7), 309 (4), 267 (21), 69 (100); HRMS, for $C_{21}H_{40}O_2$, calcd m/z 324.3030, found m/z 324.3022. Anal. Calcd for $C_{21}H_{40}O_2$: C, 77.72; H, 12.48. Found: C, 77.55; H, 12.37.

Spiroacetal 17e: mp 82–83 °C (recrystallized from hexane); ^1H NMR δ 0.67 (1H, t, J = 12.8), 0.68 (3H, d, J = 6.8), 0.85 (9H, s), 0.89 (3H,

d, J = 7.1), 0.91 (3H, d, J = 6.9), 0.92 (1H, m), 1.03–1.95 (17H, m), 2.35 (1H, sept d, J = 7.2, 1.8), 2.80 (1H, dt, J = 13.2, 2.4), 3.23 (1H, br d, J = 10.2), 3.63 (1H, t, J = 11.2), 3.68 (1H, dd, J = 11.2, 5.8); IR (liquid film) 2930 (s), 1150 (s), 1135 (s), 1090 (s), 1070 (s) cm^{-1}; MS, m/z (relative intensity) 350 (M^+, 13), 293 (12), 251 (8), 81 (100); HRMS, for $C_{23}H_{42}O_2$, calcd m/z 350.3187, found m/z 350.3183. Anal. Calcd for $C_{23}H_{42}O_2$: C, 78.80; H, 12.07. Found: C, 78.67; H, 12.34.

Spiroacetal 18e: ^1H NMR δ 0.60 (1H, t, J = 12.9), 0.68 (3H, d, J = 6.9), 0.85 (9H, s), 0.86 (3H, d, J = 7.0), 0.90 (3H, d, J = 6.9), 1.04–1.92 (17H, m), 2.37 (1H, sept d, J = 6.9, 2.4), 2.70 (1H, dt, J = 13.2, 2.7), 3.32 (1H, t, J = 11.4), 3.43 (1H, br d, J = 10.2), 3.60 (1H, dd, J = 11.4, 5.1); IR (liquid film) 2960 (s), 1150 (s), 1130 (s), 1095 (s) cm^{-1}; MS, m/z (relative intensity) 350 (M^+, 6), 293 (13), 251 (7), 81 (100); HRMS, for $C_{23}H_{42}O_2$, calcd m/z 350.3187, found m/z 350.3185.

Spiroacetal 17f: bp 140 °C (0.08 mmHg); ^1H NMR δ 0.71 (1H, t, J = 12.9), 0.75 (3H, d, J = 6.6), 0.85 (3H, d, J = 7.0), 0.86 (9H, s), 0.93 (3H, d, J = 7.2), 0.95 (1H, m), 1.08 (1H, m), 1.11 (3H, t, J = 7.2), 1.16–1.35 (2H, m), 1.64 (1H, m), 1.78 (1H, d quint, J = 12.3, 2.7), 1.85–2.05 (2H, m), 2.15–2.28 (2H, m), 2.79 (1H, dt, J = 13.5, 2.4), 3.44 (1H, dd, J = 10.5, 2.4), 3.60–3.67 (4H, m, including at t (1H, J = 11.4) at 3.63 and dd (1H, J = 11.4, 4.2) at 3.71); IR (liquid film) 3400 (br), 2950 (s), 1145 (s), 1115 (s) cm^{-1}; MS, m/z (relative intensity) 326 (M^+, 24), 311 (12), 269 (37), 95 (100); HRMS, for $C_{20}H_{38}O_3$, calcd m/z 326.2822, found m/z 326.2826. Anal. Calcd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Found: C, 73.35; H, 11.88.

Spiroacetal 18f: ^1H NMR δ 0.64 (1H, t, J = 13.2), 0.72 (3H, d, J = 6.6), 0.78–0.95 (16H, m, including s (9H) at 0.84), 0.97–1.40 (6H, m, including d (3H, J = 7.2) at 1.10), 1.56 (1H, m), 1.77 (1H, d quint, J = 12.0, 2.4), 1.83–2.00 (2H, m), 2.21 (1H, br sept, J = 6.9), 2.70–2.76 (2H, m), 3.34 (1H, t, J = 11.4), 3.64 (1H, m), 3.65 (1H, dd, J = 11.4, 5.1), 3.69 (1H, dd, J = 10.8, 5.1), 3.91 (1H, br d, J = 10.8); IR (liquid film) 3400 (br), 2950 (s), 1145 (s), 1110 (s) cm^{-1}; MS, m/z (relative intensity) 326 (M^+, 18), 311 (9), 269 (32), 95 (100); HRMS, for $C_{20}H_{38}O_3$, calcd m/z 326.2822, found m/z 326.2828.

(2*S*,3*R*,4*R*)-5-(Benzyloxy)-2,4-dimethyl-1,3-pentanediol Acetonide (20a). To a stirred suspension of KH (35% in mineral oil, 380 mg, 3.33 mmol) in THF (2 mL) was added 631 mg (2.22 mmol) of spiroacetal **12a** at room temperature. After 10 min, benzyl bromide (0.47 mL, 3.99 mmol) was added and the mixture was stirred further for 3.5 h at room temperature. The mixture was poured into H_2O and extracted twice with EtOAc. Combined extracts were dried and concentrated *in vacuo*. The residue was purified by flash chromatography (hexane/EtOAc, 98:2) to give 698 mg (84%) of the benzyl ether **19a**: ^1H NMR (200 MHz) δ 0.68 (1H, t, J = 13.3), 0.74 (3H, d, J = 6.7), 0.83 (3H, d, J = 7.0), 0.88 (3H, d, J = 6.0), 0.88 (3H, d, J = 7.2), 1.05 (3H, d, 7.0), 1.12 (9H, m), 2.35 (1H, sept, d, J = 7.2, 2.2), 2.69 (1H, ddd, J = 14.1, 3.5, 1.6), 3.30 (1H, dd, J = 9.7, 7.8), 3.40 (1H, dd, J = 10.8, 2.8), 3.58 (1H, t, J = 10.8), 3.65 (1H, t, J = 6.3), 3.68 (1H, dd, J = 9.6, 5.8), 4.48 (2H, m), 7.24–7.43 (5H, m); IR (liquid film) 2950 (s), 1120 (s), 1095 (s) cm^{-1}; MS, m/z (relative intensity) 374 (M^+, 9), 243 (6), 219 (4), 160 (5), 139 (4), 105 (27), 91 (100); HRMS, for $C_{24}H_{38}O_3$, calcd m/z 374.2822, found m/z 374.2820.

To a solution of **19a** (668 mg, 1.78 mmol) in methanol (3 mL) was added one drop of concentrated aqueous HCl and the mixture was stirred at room temperature for 22 h. The mixture was poured into H_2O and extracted twice with Et_2O. Combined extracts were dried and concentrated *in vacuo*. Kugelrohr distillation of the residue under reduced pressure (105–120 °C (26 mmHg)) gave 162 mg (59%) of *l*-menthone. The residue was was purified by flash chromatography (EtOAc/hexane, 60:40) to give 297 mg (70%) of 5-(benzyloxy)-2,4-dimethyl-1,3-pentanediol.

To a solution of the benzyloxy diol (276 mg, 1.16 mmol) and pyridinium *p*-toluenesulfonate (30 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) at room temperature was added $Me_2C(OMe)_2$ (0.71 mL, 5.8 mmol). The mixture was stirred for 2.5 h at room temperature and then poured into H_2O. The mixture was extracted twice with EtOAc. The combined extracts were washed with aqueous Na_2CO_3, dried, and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexane/EtOAc, 90:10) gave 285 mg (98%) of **20a**:[13a] $[\alpha]_D^{25}$ +20.5° (c 2.34, $CHCl_3$) (lit[13a] $[\alpha]_D^{25}$ −22.0° for (*2R,3S,4S*)-**20a**); ^1H NMR (200 MHz) δ 0.52 (3H, d, J = 6.6), 1.12 (3H, d, J = 7.0), 1.28 (3H, s), 1.49 (3H, s), 1.85–2.24 (2H, m), 3.26 (1H, t, J = 11.4), 3.31 (1H, dd, J = 10.2, 2.4), 3.35 (1H, dd, J = 9.2, 6.0), 4.35 (2H, s), 7.06–7.39 (5H, m); IR (liquid film) 2950 (s), 1095 (s) cm^{-1}.

(2*R*,3*R*,4*S*)-5-(Benzyloxy)-2,4-dimethyl-1,3-pentanediol Acetonide (20b). By a procedure similar to that described above, benzyl ether **19b** (371 mg, 89%) was obtained by starting from spiroacetal **12b** (318 mg, 1.12 mmol). **19b**: ^1H NMR (200 MHz) δ 0.62 (1H, t, J = 13.0), 0.88 (3H, d, J = 7.2), 0.90 (3H, d, J = 6.6), 1.04 (3H, d, J = 6.7), 1.06 (3H, d, J = 6.8), 1.13–1.95 (9H, m), 2.49 (1H, sept d, J = 6.9, 1.2), 2.74 (1H, ddd, J = 14.2, 3.0, 1.9), 3.28 (1H, dd, J = 9.2, 5.5), 3.36 (1H, dd, J = 19.5, 5.0), 3.53 (1H, dd, J = 11.4, 1.5), 3.65 (1H, dd, J = 9.6, 2.4), 4.20 (1H, dd, J = 11.3, 2.6), 4.47 (2H, m), 7.22–7.42 (5H, m); IR (liquid film) 2950, 1115(s), 1095 (s) cm^{-1}; MS, m/z (relative intensity) 374 (M^+, 23), 317 (3), 139 (4), 112 (11), 91 (100); HRMS, for $C_{24}H_{38}O_3$, calcd m/z 374.2822, found m/z 374.2825.

To a solution of **19b** (352 mg, 0.94 mmol) in acetone (3 mL) was added *p*-toluenesulfonic acid (18 mg, 0.094 mmol) and the mixture was stirred for 15 h at room temperature. The mixture was then poured into aqueous $NaHCO_3$ and was extracted twice with Et_2O. Combined extracts were dried and concentrated *in vacuo*. Purification of the residue by flash chromatography (hexane/Et_2O, 90:10) gave 78.9 mg (54%) of *l*-menthone and 185 mg (71%) of diol **20b**: ^1H NMR (200 MHz) δ 1.02 (3H, d, J = 6.6), 1.05 (3H, d, J = 5.8), 1.38 (3H, s), 1.40 (3H, s), 1.70–1.90 (2H, m), 3.34 (2H, ddd, J = 12.8, 10.2, 4.9), 3.54 (1H, dd, J = 11.4, 2.5), 3.72 (1H, dd, J = 9.8, 2.5), 4.05 (1H, dd, J = 11.5, 2.8), 4.44 (1H, d, J = 11.8), 4.50 (1H, d, J = 11.8), 7.23–7.40 (5H, m); IR (liquid film) 2850(s), 1110 (s) cm^{-1}.

(2*S*,3*R*,4*R*)-2,4-Dimethyl-1,3,5-pentanetriol 3,5-Acetonide (21). A mixture of **20b** (167 mg (0.598 mmol) and Pd/C (10%, 600 mg) in ethanol (6 mL) was stirred under H_2 (1 atm) for 17 h at room temperature. 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 105 mg (84%) of **21**[13b]: $[\alpha]_D^{25}$ +7.6° (c 1.01, $CHCl_3$) (lit[13b] $[\alpha]_D^{25}$ +7.73°); ^1H NMR (200 MHz) δ 0.99 (3H, d, J = 6.7), 1.07 (3H, d, J = 6.8), 1.37 (3H, s), 1.39 (3H, s), 1.50–1.07 (3H, m), 3.54 (2H, d, J = 13.0), 3.56 (1H, dd, J = 12.0, 2.0), 3.61 (1H, dd, J = 9.7, 2.7), 4.07 (1H, dd, J = 12.1, 3.2); IR (liquid film) 3425 (br), 2925 (s), 1100 (s) cm^{-1}.

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Supplementary Material Available: Listings of results of the MM2 calculations for **17a,c** and **18a,c**, X-ray crystallographic data for compound **17e**, atomic coordinates, isotropic and anisotropic displacement coefficients, and bond lengths and angles (10 pages). Ordering information is given on any current masthead page.