3-(trimethylsilyl)prop-2-yn-1-ol, 5272-36-6; 1-(methylthio)but-2-yne, 118891-26-2; dimethyl but-2-yne-1,4-dioate, 762-42-5; di-*tert*-butoxyacetylene, 66478-63-5; *trans*-1-bromobut-2-ene, 29576-14-5; 3-bromo-1-butene, 22037-73-6; *cis*-crotyl chloride, 4628-21-1; *trans*-crotyl chloride, 4894-61-5; 3-chlorobut-1-ene, 563-52-0; 1-chloro-2-methylprop-2-ene, 563-47-3; 3-(methoxymethyl)-2,5-dimethylphenol, 118891-34-2; 1-bromo-3-methylbut-2-ene, 870-63-3.

Interannular Diastereoselectivity in the Hydroboration of Functionalized 1-Cyclohexylcyclohexenes

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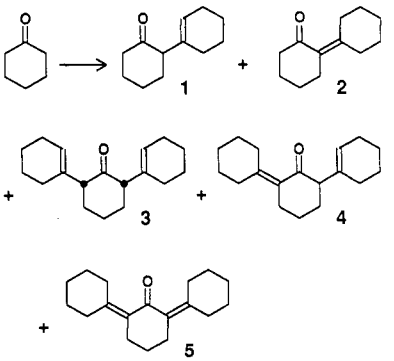
The reactions of thexylborane with 2-(1-cyclohexen-1-yl)cyclohexanone, *cis*-2,6-di(1-cyclohexen-1-yl)cyclohexanone, and related alcohols and ketals were investigated. All reactions are selective for products with erythro linkages between cyclohexyl rings, diastereoselectivities ranging from 66 to 97%. Greatest erythro selectivities were observed for equatorial homoallylic alcohols and ethylene ketals. The configurations of all products were unambiguously assigned by correlation with [1,1′-bicyclohexyl]-2,2′-diones and an erythro,erythro triketone (**25**), the configuration of which was determined by X-ray crystallography. The diastereoselectivities of these hydroborations and related examples from the literature can be qualitatively rationalized by the Houk transition structure model.

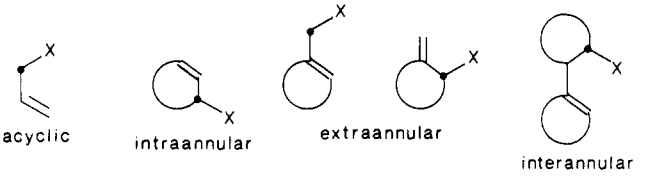
Hydroboration has proven to be extraordinarily useful in the stereoselective synthesis of complex organic molecules.[1] Good stereoselectivity may be achieved either by enantioselective reaction of optically active boranes with achiral alkenes[2] or by diastereoselective hydroboration of chiral alkenes.[3] In the latter case, stereoselection may be described as either "cyclic" or "acyclic", depending on whether the reactive double bond and the chiral center (stereogenic unit) are located within a ring. Cyclic diastereoselection is often high, presumably because the orientation of a polar functional group or a steric barrier is constrained relative to the diastereotopic faces of the double bond. Even in acyclic systems diastereoselective hydroboration may be controlled by allylic[4] or homoallylic[5] chiral centers.

The classification of diastereoselection as either cyclic or acyclic does not fully take into account the various possible conformational relationships between interacting centers in cyclic alkenes. Cyclic diastereoselectivity is more exactly described as "intraanular", since the reactive group and chiral center are in the same ring. Alternatively, two types of "extraannular" relationships may exist in which either the double bond or the chiral center is outside the ring (exocyclic), resulting in very different diastereoselectivities.[4e] Finally, when the carbon–carbon double bond

Scheme I



and chiral center are situated in separate rings "interannular" diastereoselectivity may result.[6]



Previous studies on bicyclohexyl systems revealed diastereoselective hydroboration of cyclohexenes in which boron or oxygen substituents are situated on the adjacent ring.[6] The large selectivities observed could not easily be rationalized by conventional mechanistic models. The current study was undertaken to further explore interannular diastereoselectivity in bicyclohexyls and 1,3-dicyclohexylcyclohexanes and to provide synthetic access to stereochemically defined polyalcohols and polyketones that might be of interest as ionophores. These new results, along with a configurational reassignment of [1,1′-bi-

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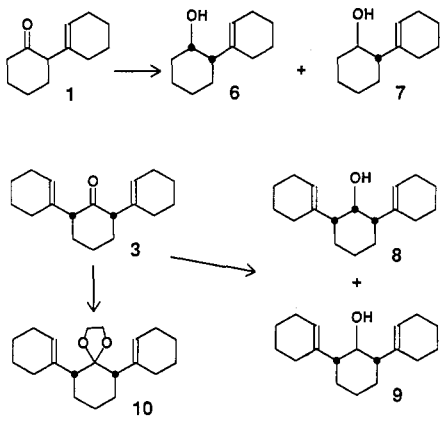
(2) See Brown, H. C.; Jadhav, P. K. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1983; Vol. 2, pp 1–43.
(3) (a) Klein, J.; Dunkelblum, E.; Avrahami, D. *J. Org. Chem.* **1967**, *32*, 935–939. (b) Pasto, D.; Klein, F. M. *Ibid.* **1968**, *33*, 1468–1476. (c) Gordon, M. H.; Robinson, M. J. T. *Tetrahedron Lett.* **1975**, 3867–3870. (d) Brener, L.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 2702–2704.
(4) (a) Still, W. C.; Barrish, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 2487–2489. (b) Heathcock, C. H.; Jarvi, E. T.; Rosen, T. *Tetrahedron Lett.* **1984**, *25*, 243–246. (c) Tsai, D. J.-S.; Midland, M. M. *J. Am. Chem. Soc.* **1985**, *107*, 3915–3918. (d) McGarvey, G. J.; Bajwa, J. S. *Tetrahedron Lett.* **1985**, *26*, 6297–6300. (e) Birtwistle, D. H.; Brown, J. M.; Foxton, M. W. *Tetrahedron Lett.* **1986**, *27*, 4367–4370.
(5) (a) Nicolaou, K. C.; Pavia, M. R.; Seitz, S. P. *J. Am. Chem. Soc.* **1982**, *104*, 2027–2029. (b) Evans, D. A.; Bartroli, J.; Godel, T. *Tetrahedron Lett.* **1982**, *23*, 4577–4580.
(6) (a) Bell, T. W. *Tetrahedron Lett.* **1980**, *21*, 3443–3446. (b) Bell, T. W. *J. Am. Chem. Soc.* **1981**, *103*, 1163–1171. (c) Jennings, P. W.; Gingerich, S. B. *J. Labelled Compd. Radiopharm.* **1983**, *20*, 591–603.

0022-3263/89/1954-1978$01.50/0

Scheme II



cyclohexyl]-2,2′-diones,[7] now enable a simple mechanistic explanation. Interannular diastereoselectivities are now qualitatively predictable, and these reactions provide conformationally constrained transition states for quantitatively testing theoretical models.

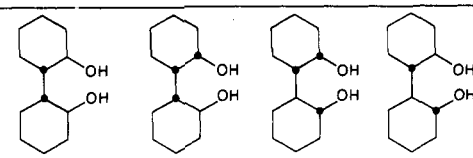
Results

Syntheses of Hydroboration Substrates. In order to test the interannular directing effects of stereochemically defined carbonyl and hydroxyl groups, a series of functionalized cyclohexylcyclohexenes (C_{12}) and 1,3-dicyclohexen-1-ylcyclohexanes (C_{18}) was required. The C_{12} and C_{18} manifolds were entered simultaneously by a one-pot aldol condensation/dehydration of cyclohexanone, according to the method of Plesek (Scheme I).[8] Distillation of the crude product gave as two main fractions a mixture of C_{12} enones (**1** and **2**, 14%) and a mixture of C_{18} dienones (**3–5**, 74%).

Pure samples of 2-cyclohexen-1-ylcyclohexanone (**1**) were required for diastereoselective hydroboration experiments. Although many studies have involved this homoconjugated enone,[8,9] these reports are apparently concerned with the 7:1 equilibrium mixture of **1** and the conjugated isomer (**2**), as indicated by UV data.[10] Although a selective synthesis of **1** could be devised, we sought a method to utilize the C_{12} distillation fraction obtained directly from condensation of cyclohexanone. The mixture of **1** and **2** was converted to the semicarbazone of **1** in 91% yield. Hydrolysis of the semicarbazones using aqueous oxalic acid[11] simply regenerated the equilibrium mixture of **1** and **2**. However, when pyruvic acid in acetic acid[12] was used under milder conditions, enone **1** was obtained free from the conjugated isomer ($\nu_{C=C}$ = 1626 cm^{-1} for **2**).[9a]

Isolation of *cis*-2,6-di(1-cyclohexen-1-yl)cyclohexanone (**3**) from the higher boiling distillation fraction was simplified by its crystallinity. Thus, dilution of the C_{18} fraction with methanol and cooling gave a 10% yield of **3** as a first crop. It was expected that additional **3** could be obtained by thermal equilibration of **3–5**, by analogy with equilibration of **1** and **2**.[10] Thus, the concentrated mother liquor was heated at 190 °C to obtain a second crop of dienone **3**. After two more iterations of this equilibration/crystallization process a total yield of 33% was obtained. It may be possible to approach the 74% yield of distilled C_{18} isomers by further iteration of this procedure.

Table I. Product Distributions for Reactions of C_{12} Alkenes with Thexylborane[a]



substrate	11	12	13	14
1	41 (33)	42 (36)	14 (11)	<2 (<3)
6		61	29	
7	93			<2

[a] Percent yields determined by GC; isolated yields in parentheses; see the Experimental Section.

Table II. Product Distributions for Reaction of C_{12} Enone 1 with 0.84 Molar Equiv of Thexylborane at Various Temperatures[a]

time, h	temp,[b] °C	1	6	7	11–14
3	−78	74	18	8	<0.5
21	−78	72	17	11	<0.5
31.5	−28	43	28	28	<0.5
48	−28	19	35	46	<0.5
76	+22	15	34	51	<1

[a] Percent composition of volatile products determined by GC; see the Experimental Section. [b] Current temperature attained by allowing reaction mixture to warm between previous and current "time" values.

Homoallylic alcohols were prepared by reduction of ketones **1** and **3** (Scheme II). Treatment of 2-(1-cyclohexen-1-yl)cyclohexanone (**1**) with sodium borohydride quantitatively gave 2-(1-cyclohexen-1-yl)cyclohexanols **6** and **7** in 59:41 ratio (axial:equatorial). Similar reduction of **3**[13] afforded the corresponding axial and equatorial alcohols (**8** and **9**) in a 2:1 ratio, respectively. In the case of dienone **3** other reducing agents were also examined. Reduction of **3** with diisobutylaluminum hydride (DIBAH) at −72 °C in hexanes/THF gave a 1:1 mixture of the alcohols. Remarkably, reaction of **3** with DIBAH in hydrocarbon solvents alone (−72 °C) favored axial alcohol **8** over equatorial alcohol **9** by an 11:2 ratio. This result may be interpreted as a consequence of increased DIBAH aggregation, disfavoring approach along the axial trajectory.

Ethylene ketal **10** was prepared as an additional hydroboration substrate by heating a mixture of dienones **3**, **4**, and **5** with ethylene glycol and *p*-toluenesulfonic acid in toluene under reflux for 3 days. Conjugated and homoconjugated enones apparently equilibrate under these conditions with the result that **10** could be obtained from the mixture in 50% yield.

Hydroboration Reactions. Hydroboration stereoselectivities were studied with thexylborane[14] because it is easily prepared and reacts readily with hindered alkylcyclohexenes. This reagent has an interpretive advantage over borane–THF or borane–dimethyl sulfide since its monohydroboration products are too hindered to undergo further reaction readily.

The reaction of C_{12} enone **1** with 2.1 molar equiv of thexylborane (−30 to 22 °C) followed by oxidation with alkaline hydrogen peroxide produced a mixture of four isomeric diols (**11–14**), as indicated in Table I. A control

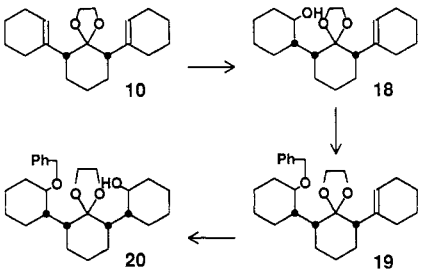
(7) Denmark, S. E.; Cramer, C. J.; Sternberg, J. A. *Tetrahedron Lett.* **1986**, *27*, 3693–3696.
(8) Plesek, J. *Chemicke Listy* **1956**, *50*, 252–257.
(9) (a) Roginskaia, T. N.; Svetozarskii, S. V.; Finkel'shtein, A. I.; Zil'berman, E. N. *J. Gen. Chem. USSR (Engl. Transl.)* **1958**, *28*, 2266–2269. (b) *Sadtler Standard IR Spectra (Prism)*; Sadtler Research Laboratories: Philadelphia, PA, 1963; no. 25040.
(10) Wenkert, E.; Bhattacharya, S. K.; Wilson, E. M. *J. Chem. Soc.* **1964**, 5617–5622.
(11) Kon, G. A. R.; Nutland, J. H. *J. Chem. Soc.* **1926**, 3101–3111.
(12) Hershberg, E. B. *J. Org. Chem.* **1948**, *13*, 542–546.
(13) Giannangeli, M.; Baiocchi, L. *Tetrahedron* **1980**, *36*, 1381–1384.
(14) Brown, H. C. *Organic Syntheses via Boranes*; Wiley: New York, 1975.

Table III. Product Distributions for Reactions of Selected C_{18} Alkenes with Thexylborane[a]

substrate	15	16	17
3	(60)	NI[b]	NI[b]
8	49		38
9		76 (74)	

[a] Percent yields determined by GC; isolated yields in parentheses; see the Experimental Section. [b] Not isolated.

Scheme III



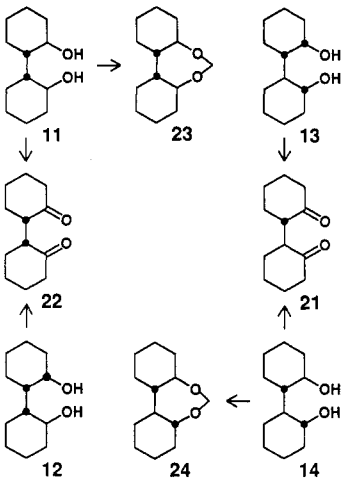
experiment was also performed to determine the sequence of events in this reaction, and the results are shown in Table II. In this control a reaction mixture containing enone 1 and 0.84 molar equiv of thexylborane was stirred at a series of temperatures between −78 and 22 °C. Monitoring was performed by gas chromatography of oxidized aliquots. As seen from Table II, homoallylic alcohols 6 and 7 gradually appeared before there was any sign of diol products.

To determine the interannular directive abilities of axial and equatorial hydroxyl groups, enols 6 and 7 were also hydroborated with thexylborane. The mixture of these two alcohols obtained by borohydride reduction of 1 was used without prior separation because axial enol 6 could only produce diols 12 and 13, whereas 7 could only form 11 and 14. The results of hydroboration at −30 to 22 °C are shown in Table I. It is noteworthy that both reactions selectively produce diols having an erythro linkage between the rings (11 and 12) and that the equatorial hydroxyl group in 7 exerts a stronger directive influence than the axial hydroxyl in 6.

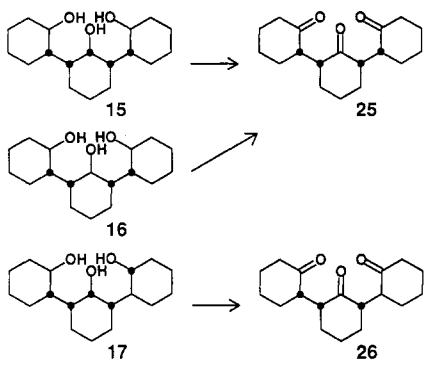
Similar hydroborations of C_{18} dienes were carried out with 3.1–3.5 molar equiv of thexylborane (Table III). Remarkably, hydroboration of dienone 3 at −21 to 22 °C and oxidative workup gave a single triol diastereomer (15) in 60% yield after recrystallization. Under similar conditions, axial dienol 8 gave erythro,erythro triol 15 and erythro,threo triol 17 in a 49:38 ratio. In parallel with the C_{12} series, hydroboration of equatorial dienol 9 more selectively affords the corresponding erythro,erythro triol 16. Although minor side products were detected by gas chromatography, triol 16 was the only product isolated and identified.

Reaction of ketal 10 with 2.1 molar equiv of thexylborane at 0–22 °C was particularly interesting in that only one of the cyclohexenyl substituents readily reacted, producing monoalochol 18 in 93% yield (Scheme III). When 18 was treated again with thexylborane under the same conditions, only starting material was recovered, confirming the low reactivity of this system. When 18 was benzylated by using the method of Rothenberger[15] and then treated with borane–THF, erythro,erythro product 20 was obtained (91%). In both steps the ethylene ketal group leads to remarkably high erythro diastereoselectivity.

Scheme IV



Scheme V



Product Configurations. The relative configurations of diols 11–14 were previously assigned by correlation with *d,l*- and *meso*-[1,1′-bicyclohexyl]-2,2′-diones (21 and 22, Scheme IV).[16] While the current work was in progress Denmark et al. reported a reassignment of the configurations of these key diketones based on crystallographic data.[7] This revision pertains then not only to the C_{12} diols produced in this work but also to the hydroboration stereoselectivities of unsubstituted bi-1-cyclohexen-1-yls and to the configurations of crown ethers derived from these 1,4-diols.[6a,b]

To confirm the stereochemical reassignment, a sample of *d,l*-diol 14 was prepared in 58% yield (GC) by treating bi-1-cyclohexen-1-yl with excess borane–THF, equilibrating organoborane intermediates at reflux temperature overnight, and then oxidizing with alkaline hydrogen peroxide.[17] This procedure complements the "kinetic" hydroboration of bi-1-cyclohexen-1-yl, which selectively affords *meso*-diol 11.[6a,b] Diols 11 and 14 were converted to their corresponding cyclic formaldehyde acetals (23 and 24, Scheme IV) by *N*-bromosuccinimide (NBS) in DMSO.[18] The ^1H NMR spectrum of 24 displayed the enantiotopic acetal protons as a singlet, whereas the dia-

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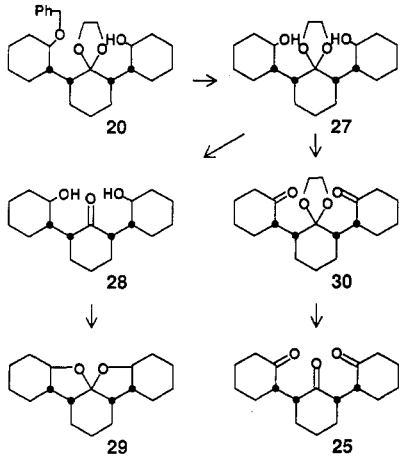
(16) Plenat, F.; Pietrasanta, F.; Darvich, M. R.; Christol, H. *Bull. Soc. Chim. Fr.* **1975**, 361–365.
(17) Bell, T. W., unpublished results, University of California at Los Angeles.
(18) Hanessian, S.; Yang-Chung, G.; Lavallee, P.; Pernet, A. G. *J. Am. Chem. Soc.* **1972**, *94*, 8929–8931.

Scheme VI



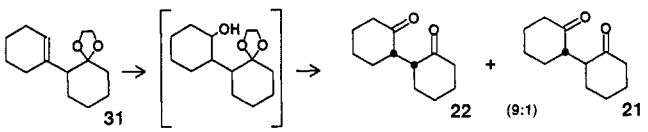
stereotopic acetal protons of **23** were observed as an AB system in the ^1H NMR spectrum, which was also complicated by the presence of an inseparable impurity. All four diols (**11**–**14**) were oxidized to 1,4-diketones **21** or **22** by PCC,[19] correlating symmetrical with unsymmetrical diols.

In the C_{18} series all configurational assignments were made by correlation or comparison with triketone **25**, prepared in 90% yield by oxidation of triol **15** with ruthenium tetroxide[20] (Scheme V). Single-crystal X-ray diffraction established the configuration of **25** as cis-erythro,erythro, as shown.[21] This correlation allows assignment of all stereogenic centers of **15**, except the central α-hydroxyl carbons. The outer ring α-hydroxyl carbon configurations are determined by the cis-addition hydroboration mechanism, as in the other cases. The central hydroxyl of **15** is readily assigned as axial by ^1H NMR spectroscopy, since the α-hydrogen appears as a sharp signal 0.37 ppm downfield from the doublet of triplets arising from the outer-ring α-hydroxyl methines.

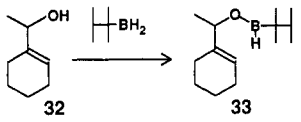
The configurations of *cis*-2,6-di(1-cyclohexen-1-yl)-cyclohexanone (**3**) and related dienols **8** and **9** were previously assigned.[13] Hydroboration of axial dienol **8** was observed to give triol **15**, in agreement with the NMR assignment, along with triol **17**, which was unsymmetrical by ^1H and ^{13}C NMR spectroscopy. Triol **17** has the only possible unsymmetrical configuration obtainable by hydroboration of **8**. The inseparable mixture of triols **15** and **17** was oxidized to triketones **25** and **26**, which were separated by chromatography. Symmetrical triol **16**, obtained by hydroboration of equatorial dienol **9**, was also correlated with erythro,erythro trione **25** by oxidation (Scheme V).

The hydroborations of all C_{18} ketal derivatives were determined to be erythro selective by correlation of products with erythro,erythro triketone **25** (Scheme VI). Benzyl ether **20** was hydrogenolized[22] to diol **27**, which was symmetrical according to its 12-signal ^{13}C NMR spectrum. Deketalization in 80% acetic acid[23] gave symmetrical keto diol **28**, which rapidly dehydrated to form spiroketal **29** upon standing in $CDCl_3$. This problem was avoided by prior oxidation of **27** with Dess–Martin periodinane[24] in acetonitrile, affording ketal dione **30** in 98% yield.

Scheme VII



Scheme VIII



Deketalization with acidic silica gel in CH_2Cl_2[25] then provided pure triketone **25** (76%), completing the configurational assignment of all hydroboration products.

Discussion

The reassigned configurations of [1,1′-bicyclohexyl]-2,2′-diones **21** and **22**[7] apply also to the hydroboration products of bi-1-cyclohexen-1-yl.[6a,b,16] Partial resolution of *meso*-[1,1′-bicyclohexyl]-2,2′-diol (**11**) has been erroneously reported;[6b] it is now clear that the small observed rotation must have been due to the presence of an optically active impurity. The symmetry properties of formaldehyde acetals **23** and **24** provide simple confirmation of the reassignments made by Denmark et al.[7]

An additional report of interannular diastereoselectivity in hydroboration[6c] also contains a clue to the cause of Criegee and Reinhardt's misassignment,[26] as deduced by Denmark et al.[7] (Scheme VII).[27] Jennings and Gingerich reported that borane addition to **31** (the ethylene ketal of **1**) followed by Jones oxidation of the crude alcohol gave a 9:1 mixture of diketones **22** and **21** (51%).[6c,27] Like the hydroborations of ketals **10** and **19**, this reaction is strongly erythro selective. The diketone mixture then isomerized upon standing, affording crystalline *d,l*-dione **21**, as presumably occurred during Criegee and Reinhardt's correlation. Although our assignments of C_{18} hydroboration products rest on similar correlations with triketone **25** (Schemes V and VI), no epimerization was observed during oxidation of these triols.

To interpret the diastereoselective hydroborations of olefinic ketones **1** and **3**, the order of ketone reduction and alkene addition reactions must be known. Table II clearly shows that in the C_{12} series (i.e. **1**) thexylborane reacts with the carbonyl group before the carbon–carbon double bond. Moreover, the resulting borinate ester does not significantly undergo intermolecular hydroboration or cyclic hydroboration at room temperature. The carbonyl group of C_{18} dienone **3** is considerably more hindered, and the two types of functional groups may compete for reaction with the first equivalent of thexylborane, as suggested by control experiments.

In the hydroborations of olefinic alcohols there is also a question of which functional group reacts first. Still and Barrish reported that a trisubstituted alkene reacts with BH_3–THF more slowly than a secondary, allylic hydroxyl group located in the same molecule.[4a] A more relevant case is provided by Birtwistle et al.,[4e] who found that thexylborane reacts with allylic alcohol **32** to form borinate ester **33** prior to olefin hydroboration (Scheme VIII). These results suggest that monosubstituted cyclohexanols **6** and

(19) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647–2650.
(20) Nakata, H. *Tetrahedron* **1963**, *19*, 1959–1963.
(21) Crystallographic data are included as supplementary material.
(22) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746–1757.
(23) Babler, J. H.; Malek, N. C.; Coghlan, M. J. *J. Org. Chem.* **1978**, *43*, 1821–1823.
(24) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
(25) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63–65.
(26) Criegee, R.; Reinhardt, H. G. *Chem. Ber.* **1968**, *101*, 102–112.
(27) Structural formulas corrected for reassigned configurations.

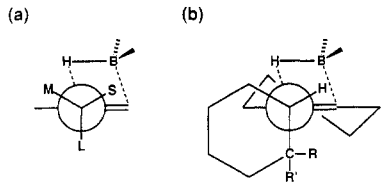


Figure 1. Hydroboration transition structures according to the Houk steric model (ref 1). (a) General transition structure showing preferred positions of large (L), medium (M), and small (S) allylic substituents. (b) Application of Houk model to functionalized 1-cyclohexylcyclohexenes.

7 react primarily at the hydroxyl group. In agreement with this, reaction of equatorial alcohol **7** produces as little threo diol **14** as does hydroboration of ketone **1**, which was shown to proceed via the borinate ester. On the other hand, the erythro selectivity of axial alcohol **6** (**12:13** $\simeq$ 2) is lower than that of ketone **1** (**12:13** $\simeq$ 3), indicating that prior hydroboration of the olefinic center is a significant competing pathway (cf. Table I). The hydroxyl groups of C_{18} alcohols **8** and **9** are considerably more hindered, and olefin addition is expected to assume greater precedence. As shown in Table III, hydroboration of axial alcohol **8** gives a lower yield of triol **15** than does direct reaction of ketone **3**, indicating that these reactions do not proceed entirely via a common borinate ester intermediate.

Houk et al. have reported the most detailed theoretical analysis of stereoselective hydroboration reactions.[1] Their steric model for the preferred transition structure is shown in Figure 1. On the basis of ab initio calculations on borane addition to 1-butene, a large carbon substituent (L) prefers the position anti to the forming C–H bond, whereas medium and small substituents are located in the "outside" and "inside" positions, respectively (cf. Figure 1a). According to this model, the major transition structure in hydroboration of functionalized 1-cyclohexylcyclohexenes would be as shown in Figure 1b. Homoallylic functional groups (CRR′ = C=O or CHOR) occupy the anti position, and the other β-carbon of the pendant cyclohexane ring is "outside" the transient 4-membered ring. This model predicts all of the hydroboration reactions in this study to be erythro selective, as observed.

Hydroborations of related 1-cyclohexylcyclohexenes **34–38** have been reported,[6a,b] and the selectivities of these reactions are compared with the results of the current study in Table IV. In this table the column "% erythro selective" compares stereoselectivities on a per reaction basis, correcting for double hydroborations and expressing unidentified products as error ranges. Prior to the stereochemical reassignment of Denmark et al.[7] the hydroboration of bi-1-cyclohexen-1-yl (**34**) appeared anomalously threo selective, but it is now observed that all of the tabulated reactions are erythro selective. For the bi-1-cyclohexen-1-yl series (**34–36**) cyclization of the monohydroboration intermediate was precluded by control experiments,[6a,b] so the transition structures may also be represented as in Figure 1b. Qualitatively, the diastereoselectivities of these reactions are independent of the electronic nature of the symmetry-breaking substituent (e.g. CRR′ = CHOH, CHOBHR, C=O, $C(OR)_2$, CHOR, or $CHBH_2$). These results provide strong support for the steric hydroboration model proposed by Houk et al.[1]

All hydroborations presented in Table IV show high erythro selectivity (>80%) except reactions of axial alcohols **6** and **8** and tetramethyl diene **35**. The stereochemical difference between transition structures for reactions of axial alcohols and various equatorial alcohols and ethers (**7**, **9**, **37**, and **38**) is illustrated in Figure 2 by using the

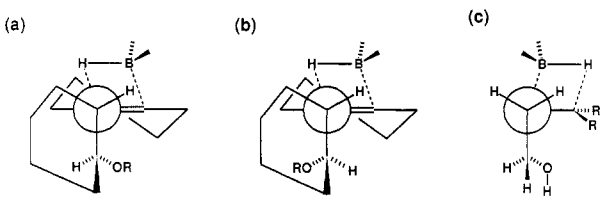
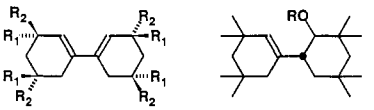


Figure 2. Orientations of homoallylic oxygen substituents in hydroboration transition structures. (a) Equatorial ($\angle$CCCO = 60°), producing stabilized erythro transition structure. (b) Axial ($\angle$CCCO = −60 °C). (c) Regioisomeric transition structure with stabilizing hydroxyl interaction ($\angle$CCCO = 60°) (ref 1).

Table IV. Erythro Selectivities of Hydroborations of Functionalized 1-Cyclohexylcyclohexenes



34 $R_1 = R_2 = H$ **37** R = H

35 R_1 = Me; R_2 = H **38** R = $PhCH_2$

36 $R_1 = R_2$ = Me

substrate	methods[a]	% yield erythro	% yield threo	% erythro-selective[b]
1	A, B	83	14	86 ± 2
6	A, B	61	30	66 ± 5
7	A, B	92	0	96 ± 4
8	A, C	68[c]	19[c]	75 ± 7
9	A, C	76	–[d]	87 ± 11
10	A, D	93	–[e]	97 ± 4
19	E	80	3	89 ± 9
34[f]	E	96	0	98 ± 2
35[f]	E	52	22	65 ± 13
36[f]	E	78	0	89 ± 11
37[f]	E	91	0	96 ± 5
38[f]	E	68	0	84 ± 16

[a] Method A, thexylborane; method B, GC yield with internal standard; method C, GC yield; method D, yield determined by ^{1}H NMR; method E, borane–THF, isolated yield. [b] Range shown accounts for unidentified and undetected products. [c] Includes half of the yield of erythro,threo triol **17**. [d] An unknown, possibly diastereomeric product was detected (22%). [e] An unknown, possibly diastereomeric product was detected (6%). [f] Reference 6.

Houk model. Equatorial oxygen substituents lie in close proximity to the reacting double bond with a dihedral angle ($\angle$CCCO) of +60° (Figure 2a). Axial hydroxyl or borinate ester groups are more distant ($\angle$CCCO = −60°, Figure 2b). Houk et al. have reported the results of calculations on the regioisomeric mode of borane addition to a homoallylic alcohol indicating a 1.1 kcal/mol preference for the former hydroxyl group orientation ($\angle$CCCO = +60°, Figure 2c).[1] Both regioisomeric, electron-deficient transition structures should be stabilized by through-space donation of electron density or by electrostatic interaction. In agreement with our experimental results, the Houk model predicts greater erythro selectivity for hydroborations of alkenes with equatorial oxygen substituents.

The erythro selectivities observed by hydroborations of **10**, **19** (and **31**) are also consistent with the Houk model. Bulky ethylene ketal substituents should strongly prefer the less crowded anti position and olefin reactivity would be enhanced by proximity with the equatorial oxygen atom. This model can also be used to rationalize the pronounced difference in reactivity of the two cyclohexenyl groups in C_{18} ketal **10** (Scheme III). Reaction of **10** or alcohol **18** with thexylborane places an RR′BH or ROBHR′ group in close proximity to the activating equatorial oxygen

atom. Formation of a Lewis acid–base complex between boron and this equatorial ketal oxygen might be expected to reduce the activation of the double bond toward electrophilic attack.

The poor erythro selectivity observed in hydroboration of chiral tetramethyl diene **35** appears to be a consequence of competing interannular and intraannular effects. Monohydroboration of **35** can produce two possible intermediates, **39** or **40**, which can lead to only three possible diols, **41**, **42**, or **43** (Scheme IX). Erythro diol **42** is the major product (52%), threo diol **41** is the minor product (22%), and the alternate threo diol (**43**) was not observed. These results are most easily rationalized by assuming an intraannular effect favoring borane addition trans to the 3-methyl substituent (**39** > **40**). The minor intermediate (**40**) selectively affords **42** due to a constructive combination of intra- and interannular effects. The major intermediate (**39**) produces both **41** and **42** because of a destructive interplay between intra- and interannular effects. The approach of 9-BBN in hydroboration of 1,3-dimethylcyclohexene is indeed trans to the 3-position substituent,[3d] but the opposite intraannular directive effect is observed for borane addition to trans 1,5-dimethyl-3-isopropylcyclohexene.[3c,28] Hydroboration of a 1-alkyl-3,5-dimethylcyclohexene would provide a better model for intraannular diastereoselectivity in **35**, but results of this type have not been reported.

In conclusion, homoallylic oxygen substituents produce moderate to high interannular diastereoselectivity in hydroboration of 1-cyclohexylcyclohexenes. Erythro selectivity is always observed, as predicted by the Houk steric model. Equatorial oxygen substituents lead to higher erythro selectivity than do axial oxygen substituents. This stereochemical effect may be qualitatively rationalized by the Houk model. Further calculations will be required to quantitatively model stereoselective hydroboration of these conformationally restricted alkenes.

Experimental Section

General Procedure. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl immediately prior to use. Anhydrous methylene chloride was obtained either by distillation from CaH_2 or by filtration through super activity I Woelm neutral alumina. Anhydrous, acid-free deuterochloroform ($CDCl_3$) and benzyl bromide were obtained by the latter method. Dimethyl sulfoxide (DMSO) was distilled from CaH_2 under reduced pressure. Anhydrous benzene was obtained by distillation from CaH_2 under reduced pressure. Anhydrous methanol was obtained by distillation from $Mg(OCH_3)_2$.[29] Brine refers to saturated aqueous NaCl. ^1H NMR spectra were recorded at 300 MHz on a Nicolet NT-300 or a GE QE-300 spectrometer. All chemical shifts were measured relative to residual solvent resonances (δ ($CHCl_3$) = 7.26, δ (DMSO) = 2.49, δ (benzene) = 7.15) or relative to TMS (δ = 0.00) when the residual solvent resonances were obscured. Coupling constants were reported in hertz. All ^{13}C NMR spectra were obtained in $CDCl_3$ on one of the above two high-field instruments at ~75 MHz. Chemical shifts were measured relative to the solvent resonance (δ ($CDCl_3$) = 77.00). Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. Low-resolution mass spectra were obtained on a Hewlett-Packard 5980A spectrometer at 70 eV. High-resolution mass spectra (HRMS) were recorded on either a Kratos MS-30 or a MS-890 spectrometer at 70 eV. Infrared (IR) spectra were obtained with Perkin-Elmer Model 727 or 1430 spectrometers, employing polystyrene film for calibration. Gas–liquid chromatography (GC) was performed on a Hewlett-Packard Model 5830A gas chromatograph (with flame ionization detection, carrier flow 20 mL/min) using the following $^1/_8$ in. o.d. columns: column A, 6 ft 3% NPGS on 80–100 mesh WHP, 170–190 °C at 0.5°/min; column B, 6 ft 1.5% OV-17 on 100–120 mesh Gas Chrom Q, 150–245 °C at 8°/min; column C, 4 ft 1.5% OV-17 on 100–120 mesh Gas Chrom Q, 150–225 °C at 10°/min; column D, 10 ft 2.7% OV-17 on 80–100 mesh Gas Chrom Q, conditions as noted. Analytical thin-layer chromatography (TLC) was performed by using Machery–Nagel 0.2 mm silica coated plastic sheets. Flash chromatography[30] employed Merck silica gel 60 (230–400 mesh). Filtration column chromatography utilized ICN silica TSC (activity III). All reactions were carried out under an atmosphere of dry nitrogen and stirred magnetically unless otherwise indicated. Thexylborane[14] was prepared by adding 2,3-dimethyl-2-butene to a −10 to −15 °C solution of borane–tetrahydrofuran complex (BH_3–THF) in THF dropwise by syringe, and then the reaction mixture was stirred for 1 h at 0 °C.

2(*R),6(*S**)-Di(1-cyclohexen-1-yl)cyclohexanone (3).** To a flask equipped with a Dean–Stark trap and a reflux condenser were added cyclohexanone (500 g, 5.09 mol), toluene (200 mL), and KOH (7.5 g). The flask was heated in a thermostated oil bath at 190 °C. After 6.5 h, 58 mL of water (theoretical quantity: 61 mL) had been azeotropically removed. Toluene was removed by distillation under aspirator vacuum, and the residual liquid was distilled at reduced pressure. A small forerun was collected, followed by a fraction containing C_{12} ketones **1** and **2** (62.0 g, 14%), bp 108–135 °C (0.7–0.8 mm) (lit.[8] bp 113 °C (2 mm)). A second fraction was collected consisting of a mixture of dienones **3**, **4**, and **5** (322.8 g, 74%), bp 148–175 °C (0.7–0.8 mm) (lit.[8] bp 172 °C (2 mm)). The latter oil was diluted with methanol (686 mL), seeded with a crystal of pure **3**, and stored at −3 °C overnight. The product was collected by vacuum filtration (45.1 g), mp 77.2–77.8 °C. The supernatant liquid was concentrated and reheated to 190 °C. After 3 h the oil was diluted and cooled as above to yield an additional 41.0 g of white crystals, mp 77.2–77.8 °C. This process was repeated, and the combined crops were recrystallized from methanol to yield 81.8 g of white crystals, mp 78.8–79.1 °C (lit.[8] mp 79 °C). By repetition of the isomerization/crystallization procedure twice more, a further 62.6 g of **3** was obtained (total 144.4 g, 33% yield): ^1H NMR ($CDCl_3$) δ 5.40 (s, 2 H, olefin), 2.92 (d of d, 2 H, J = 5.1, 12.0, CHC=O), 2.2–1.5 (m, 22 H, CH_2); ^{13}C NMR δ 210.5, 135.8, 123.3, 59.1, 32.7, 27.3, 25.4, 24.1, 22.7, 22.3; IR (film) 2930 (s), 2860 (s), 2838 (s), 1699 (s), 1668 (w), 1440 (w), 1127 (w), 1040 (w), 907 (w) cm^{-1}. Anal. Calcd for $C_{18}H_{26}O$: C, 83.67; H, 10.14. Found: C, 83.48; H, 10.11.

Purification of 2-(1-Cyclohexen-1-yl)cyclohexanone (1). The lower boiling distillation fraction from the preceding procedure was treated with semicarbazide hydrochloride.[11] A white solid was obtained by crystallization from the reaction mixture (91%), mp 182.5–184.4 °C (lit.[11] mp 179–181 °C). The product is a mixture of isomers (55:45), as indicated by ^1H NMR ($CDCl_3$) δ 8.36 (s, 1 H, NNHCO, minor), 7.75 (s, 1 H, NNHCO, major), 6.3–4.6 (broad m, 2 H, $CONH_2$), 5.42 (m, 1 H, C=CH, minor), 5.37 (m, 1 H, C=CH, major), 3.15 (narrow m, 1 H, C=CCHC=N, major), 2.78 (narrow m, 1 H, C=CHC=N, minor), 2.5–1.4 (m, 16 H, CH_2). The hydrolysis method was modeled after the procedure of Hershberg.[12] A solution of sodium pyruvate (15.3 mmol in 20 mL of water) was added to a mixture of the semicarbazone (1.78 g, 7.6 mmol) in glacial acetic acid (40 mL) and stirred overnight. The solution was extracted with hexanes, and the combined extracts were washed with 5% $NaHCO_3$ and water, dried ($MgSO_4$), and concentrated in vacuo to yield a clear, colorless oil (1.07 g, 82%). The IR spectrum demonstrated the absence of conjugated enone **2** ($\nu_{C=C}$ = 1626 cm^{-1}),[9a] whereas literature methods apparently give product containing ~12% of **2**.[10] ^1H NMR ($CDCl_3$) δ 5.42 (br s, 1 H, C=CH), 2.88 (d of d, 1 H, J = 5.2, 11.0, −CHC=O), 2.45–2.22 (m, 2 H, $-CH_2C$=O), 2.15–1.50 (m, 14 H, aliphatic); ^{13}C NMR δ 211.3, 135.7, 123.5, 58.6, 42.0, 31.7, 27.5, 27.2, 25.2, 24.7, 22.7, 22.3; IR (film) 2940 (s), 2850 (s), 1703 (s), 1448 (s), 1122 (s) cm^{-1}.

***cis*- and *trans*-2-(1-Cyclohexen-1-yl)cyclohexanol (6 and 7).** To a stirred solution of enone **1** (173 mg, 0.97 mmol) in anhydrous methanol (5 mL) was added sodium borohydride (73

(28) Ground-state molecular mechanics calculations have been used to rationalize this result: White, D. N. J.; Bovill, M. J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 225–229.

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(30) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.

mg, 1.9 mmol). The reaction mixture was stirred for 2 h with monitoring by TLC (CH_2Cl_2), poured into water (10 mL), and extracted with ether (3 × 10 mL). The combined ethereal extracts were washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated in vacuo to yield a clear, colorless oil (175 mg, 100%). GC analysis (column D, 150–170 °C at 1°/min) showed a 3:2 ratio of cis to trans isomers. A portion was flash chromatographed (1:1 hexanes/ethyl acetate) to give pure samples of **6** and **7** whose ^1H NMR spectra agreed with literature data.[16]

Preparation of 2(*R),6(*S**)-Di(1-cyclohexen-1-yl)cyclohexen-1(*r**)-ol (8) and 2(*R**),6(*S**)-Di(1-cyclohexen-1-yl)-cyclohexan-1(*s**)-ol (9).** A mixture of axial alcohol **8** and equatorial alcohol **9** was obtained in a 1.8:1 ratio by the literature method.[13] The following procedure gives an 11:2 ratio of alcohols **8** and **9**. A suspension of dienone **3** (2.56 g, 10.0 mmol) in pentane (50 mL) was stirred with dry ice cooling, and a solution of diisobutylaluminum hydride (1.0 M in hexanes, 30 mL, 30.0 mmol) was added dropwise, maintaining the internal temperature below −72 °C (2.3 h). After 3.5 h, TLC (9:1 hexanes/ethyl acetate) indicated that no starting material remained, and the solution was warmed to 0 °C. A 2 N aqueous solution of HCl (15 mL) was added dropwise while the temperature was maintained below 10 °C. A voluminous white gel formed, which was dissolved by addition of sufficient 6 N aqueous HCl (10 mL). The layers were separated, and the aqueous portion was extracted with ether (3 × 15 mL). The combined organic solutions were extracted with 1.5 N HCl (25 mL) and brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to yield a clear, colorless oil (2.57 g, 99%). The products were separated by flash chromatography (27:2 hexanes/ethyl acetate). After prolonged standing at −7 °C each isomer crystallized. Axial alcohol **8**: 1.96 g (75%); mp 39–42 °C; ^1H NMR (DMSO-d_6) δ 5.33 (br s, 2 H, C=CH), 3.80 (br s, 1 H, CH(OH)), 3.46 (d, 1 H, J = 5.1, OH), 2.1–1.2 (m, 24 H, aliphatic); ^{13}C NMR δ 139.5, 121.5, 67.8, 49.4, 28.2, 25.9, 25.3, 23.4, 23.1, 22.6; IR (film) 3555 (m), 3480 (m, sh), 2950 (s), 2850 (s), 1655 (w), 1440 (m), 1105 (m), 970 (m) cm^{-1} (lit.[13] ν_{max} 3560 cm^{-1}). Equatorial alcohol **9**: 36 mg (1%); mp 30.5–32.5 °C; ^1H NMR (DMSO-d_6) δ 5.37 (br s, 2 H, C=CH), 5.34 (d, 2 H, J = 5.8, OH), 3.22 (m, 1 H, CH(OH)), 2.0–1.2 (m, 24 H, aliphatic); ^{13}C NMR δ 139.0, 123.4, 71.1, 53.9, 30.5, 29.7, 25.8, 25.2, 23.0, 22.7; IR (film) 3535 (m), 3475 (m, sh), 2920 (s), 2850 (s), 1659 (w), 1445 (m), 1270 (m), 1102 (m), 1041 (m), 919 (m) cm^{-1} (lit.[13] ν_{max} 3555 cm^{-1}).

6(*R),10(*S**)-Di(1-cyclohexen-1-yl)-1,4-dioxaspiro[4.5]-decane (10).** To a flask equipped with a reflux condenser and a Dean–Stark trap was added the mixture of dienones **3**, **4**, and **5** (15.35 g, 59.4 mmol), toluene (375 mL), ethylene glycol (25 mL, 404 mmol), and a catalytic amount of *p*-toluenesulfonic acid (294 mg). The solution was heated under reflux for 1 day, 19 mL of a water/ethylene glycol mixture was removed, and the flask was recharged with additional ethylene glycol (21 mL, 340 mmol). Reflux, water removal, and ethylene glycol addition were repeated each day for a total of 3 days. The solution was cooled and quenched with 5% $NaHCO_3$ (50 mL), and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were washed with water (1 × 35 mL) and brine (1 × 35 mL), dried ($MgSO_4$), and concentrated in vacuo to give a brown solid. Two recrystallizations from 95% ethanol afforded 8.22 g of pale yellow crystals: mp 88.5–89 °C (total 9.07 g, 50%); ^1H NMR ($CDCl_3$) δ 5.53 (m, 2 H, C=CH), 3.83 (s, 4 H, OCH_2CH_2O), 2.2–1.2 (m, 24 H, aliphatic); ^{13}C NMR δ 137.8, 124.2, 113.5, 66.4, 65.4, 54.3, 29.6, 29.5, 26.0, 25.8, 23.8, 22.6; IR (film) 2924 (s), 2880 (s), 2846 (s), 2830 (s), 1657 (w), 1437 (m), 1190 (m), 1131 (m), 1081 (m), 1021 (m), 952 (m), 919 (m) cm^{-1}; M^+ m/z 302. Anal. Calcd for $C_{20}H_{30}O_2$: C, 79.42; H, 10.00. Found: C, 79.51; H, 9.98.

Reaction of 2-(1-Cyclohexen-1-yl)cyclohexanone (1) with Excess Thexylborane. A solution of thexylborane (4.94 mmol) was cooled to −30 °C, and enone **1** (403 mg, 2.26 mmol) was added dropwise by syringe. The reaction flask was slowly warmed to −9 °C over 1 h, packed in ice, and allowed to warm to room temperature overnight. The reaction mixture was recooled to 0 °C, and ethanol (1.7 mL), 3 N NaOH (1.7 mL), and 30% H_2O_2 (4.1 g, 36 mmol) were added carefully, maintaining the temperature below 40 °C. The flask was heated at 45–50 °C in a thermostated oil bath overnight and then cooled to room temperature. The aqueous layer was saturated with K_2CO_3 (5.8 g) and extracted with ether (2 × 10 mL) and $CHCl_3$ (5 mL). The combined organic extracts were dried (K_2CO_3). The internal standard, 2-methoxynaphthalene (89.3 mg), was added, and the resulting solution was analyzed by GC using column A (cf. Table I). The products were separated by flash chromatography (2:1 chloroform/ethyl acetate, with a few drops of triethylamine used in packing). The eluent was pooled into five fractions, which were analyzed by TLC and GC (column A) in comparison with authentic samples.[25] Fraction 1: R_f = 0.33 (2:1 $CHCl_3$/ethyl acetate, v/v), 205 mg, 4:1 mixture of erythro diol **12** to threo diol **13**. Fraction 2: R_f = 0.19 and 0.33, 27 mg, 3:1 mixture of *meso*-diol **11** to threo diol **13**. Fraction 3: R_f = 0.19, 129 mg, *meso*-diol **11**. Fraction 4: R_f = 0.12 and 0.19, 4 mg. Fraction 5: R_f = 0.12 and 0.19, 7 mg, 13:1 mixture of *d,l*-diol **14** to *meso*-diol **11**. The total isolated yield of diols was 83%.

Reaction of 2-(1-Cyclohexen-1-yl)cyclohexanols (6 and 7) with Excess Thexylborane. Hydroboration of a 3:2 mixture of **6** and **7**, respectively, was effected as described above for hydroboration of **1**. GC analysis (column A) was performed after addition of 2-methoxynaphthalene (91 mg). The results are summarized in Table I.

Reaction of 2-(1-Cyclohexen-1-yl)cyclohexanone (1) with 0.84 Equiv of Thexylborane. The reaction was run as described above, but enone **1** (188 mg, 1.05 mmol) was added to 0.84 equiv (0.89 mmol) of thexylborane at −78 °C. The reaction temperatures and times are listed in Table I. Aliquots were analyzed by GC (column D, 50–190 °C at 15°/min). Quenching of 250-μL aliquots of reaction solution was effected by addition to 1 mL of 1:1 THF/ethanol (v/v) with cooling by means of an ice–salt bath. Addition of 3 N NaOH (135 μL) and 30% H_2O_2 (46 mg) followed by heating at 50 °C for 70 min prepared each sample for GC analysis. The results are given in Table II.

3(*R)-(2(*R**)-Hydroxycyclohex-1(*S**)-yl)-[1(*S**),1′(*R**)-bicyclohexyl]-2(*r**),2′(*S**)-diol (15).** To a solution of thexylborane (420 mmol) cooled to −21 °C was added dienone **3** (34.84 g, 134.8 mmol). The solution was warmed to 0 °C over 1 h, and then the reaction flask was packed in ice and allowed to warm to room temperature overnight. The reaction mixture was recooled to 0 °C, and ethanol (140 mL), 3 N NaOH (140 mL), and 30% H_2O_2 (81.1 g, 759 mmol) were added carefully, maintaining the internal temperature below 40 °C. The flask was heated at 45–50 °C in a thermostated oil bath for 80 min and then cooled to room temperature. The aqueous layer was saturated with K_2CO_3 (240 g) and extracted with ether (3 × 200 mL). The combined organic solutions were washed with saturated aqueous K_2CO_3 (1 × 240 mL), dried (K_2CO_3), and concentrated in vacuo at 80 °C to give 40 g of white solid. Recrystallization from CH_3CN gave 23.9 g (60%) of white needles, mp 193.7–194.5 °C. An analytical sample was prepared by a second recrystallization: mp 194.3–195.3 °C; ^1H NMR ($CDCl_3$) δ 4.4 (br s, 3 H, OH), 3.66 (s, 1 H, internal CH(OH)), 3.29 (d of t, 2 H, $J \simeq$ 9.5, 4.0, external CH(OH)), 2.0–1.0 (m, 26 H, aliphatic); ^{13}C NMR δ 74.3, 69.7, 50.6, 49.0, 35.9, 33.2, 27.2, 26.0, 24.7, 20.7; IR (4% in $CDCl_3$) 3144 (m), 2931 (s), 2860 (s), 1447 (m), 1375 (w), 1342 (w), 1158 (w), 1102 (w), 1084 (w), 1064 (m), 1044 (m), 1016 (w), 980 (w), 861 (w) cm^{-1}; M^+ m/z 296. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 73.04; H, 10.69.

Hydroboration of Axial Dienol 8 with Thexylborane. A solution of thexylborane (7.0 mmol) was stirred at −23 °C as a precooled (≤−10 °C) solution of dienol **8** (532 mg, 2.04 mmol) in THF (2 mL) was added by means of a cannula. Additional THF (2 × 1 mL) was used to assist the transfer. The reaction mixture was stirred overnight at 0 °C and then warmed to 10 °C for 2 h. The mixture was recooled to −10 °C, and ethanol (5.5 mL), 3 N NaOH (3 mL), and 30% H_2O_2 (758 mg, 22.2 mmol) were added carefully, maintaining the temperature below 40 °C. The reaction mixture was heated at 45–50 °C in a thermostated oil bath for 3 h and then cooled to room temperature. The aqueous layer was saturated with K_2CO_3 (5.5 g) and extracted with ether (3 × 5 mL). The combined organic layers were washed with saturated aqueous K_2CO_3 (1 × 5 mL) and dried (K_2CO_3). GC analysis (column C) indicated a 49:38 ratio of symmetrical triol **15** (12.3 min) and an unknown component (10.8 min). The solution was concentrated in vacuo at 80 °C to give 555 mg (92%) of white solid. Analysis by ^{13}C NMR suggested the unknown component to be unsymmetrical triol **17**: ($CDCl_3$) δ 72.5, 71.7, 69.6, 68.8, 50.4, 50.1, 49.6, 48.9, 48.5, 47.7, 36.1, 35.5, 32.1, 27.4, 27.0, 26.8, 24.5, 20.6. All

attempts to separate **17** from **15** by chromatography or crystallization failed. A sample enriched in triol **17** was obtained from the mother liquor of an attempted recrystallization (CH_3CN).

Hydroboration of Equatorial Dienol 9 with Thexylborane. The hydroboration was performed as described for **8** except that the dienol **9** (329 mg, 1.26 mmol) was added to the thexylborane solution at −10 °C, and the resulting mixture was allowed to warm to room temperature overnight. GC analysis (column C) indicated a 76:22 ratio of two components (9.7 min, 10.2 min). Flash chromatography (ethyl acetate) gave 229 mg of triol **16** as a white solid and 65 mg of a 7:3 mixture (GC) of **16** and unknown components (total yield of **16**, 74%). The pure sample was recrystallized twice from $CHCl_3$ to afford white crystals: mp 192.5–193 °C; ^1H NMR ($CDCl_3$) δ 3.75 (t, 1 H, J = 10.2, internal CH(OH)), 3.60 (m, 2 H, external CH(OH)), 3.14 (br s, 1 H, internal OH), 2.87 (br s, 2 H, external OH), 2.1–1.1 (m, 26 H, aliphatic); ^{13}C NMR δ 74.7, 72.6, 48.1, 46.1, 36.6, 28.8, 27.6, 26.3, 26.1, 25.0; IR (KBr) 3399 (s), 2924 (s), 2855 (s), 1449 (m), 1354 (w), 1300 (w), 1273 (m), 1199 (w), 1138 (m), 1120 (w), 1080 (w), 1056 (s), 1032 (s), 1017 (m), 949 (w), 872 (m), 828 (m) cm^{-1}; M^+ m/z 296. Anal. Calcd for $C_{18}H_{32}O_3$: C, 72.93; H, 10.88. Found: C, 73.01; H, 10.68.

6(*R)-(1-Cyclohexen-1-yl)-10(*S**)-(2(*S**)-hydroxycyclohex-1(*R**)-yl)-1,4-dioxaspiro[4.5]decane (18).** A solution of ketal **10** (302 mg, 1.0 mmol) in 500 μL of THF was added dropwise via syringe to a stirred solution of thexylborane (2.1 mmol in 2–3 mL of THF) at 0 °C. Additional THF (3 × 300 μL) was used to insure a quantitative transfer of **10** (total time 30 min). The reaction mixture was stirred for 1 h at 0 °C, warmed to room temperature, and stirred 5.8 h. The reaction flask was cooled in ice, and ethanol (2 mL), 3 N NaOH (0.7 mL), and 30% H_2O_2 (500 mg, 4.7 mmol) were added carefully, maintaining the temperature below 40 °C. The flask was heated at 45–50 °C in a thermostated oil bath for 75 min and then cooled. The aqueous layer was saturated with K_2CO_3 (1.3 g) and extracted with ether (3 × 2 mL). The combined organic layers were washed with saturated K_2CO_3 (1 × 2 mL), dried (K_2CO_3), and concentrated in vacuo at 70 °C to give **18** (310 mg, 97%) as a white solid. Analysis by ^1H NMR and ^{13}C NMR indicated this material to be ≥93% pure, contaminated by a small amount of starting material and possibly a diastereomeric product. An analytical sample was purified by flash chromatography (10:1 hexanes/ethyl acetate) followed by sublimation (110 °C, 0.1 mm); mp 105.5–106.5 °C; ^1H NMR ($CDCl_3$) δ 5.52 (s, 1 H, C=CH), 4.60 (br s, 1 H, OH), 3.96 (m, 4 H, OCH_2CH_2O), 3.14 (m, 1 H, CH(OH)), 2.15–1.0 (m, 25 H, aliphatic); ^{13}C NMR δ 137.8, 124.7, 113.4, 70.1, 66.7, 65.8, 54.2, 53.2, 42.4, 35.2, 33.1, 29.7, 29.5, 26.1, 25.8, 25.0, 24.4, 23.7, 22.3; IR (film) 3404 (m), 2908 (m), 2848 (m), 1484 (w), 1462 (w), 1446 (m), 1417 (w), 1343 (w), 1328 (w), 1195 (m), 1131 (w), 1119 (m), 1084 (m), 1073 (m), 1020 (w), 933 (w), 904 (w), 837 (w) cm^{-1}; M^+ m/z 320. Anal. Calcd for $C_{20}H_{32}O_3$: C, 74.96; H, 10.06. Found: C, 74.93; H, 10.24.

6(*R)-(1-Cyclohexen-1-yl)-10(*S**)-[2(*S**)-[(phenylmethyl)oxy]cyclohex-1(*R**)-yl]-1,4-dioxaspiro[4.5]decane (19).** A solution of ketal enol **18** (1.00 g, 3.12 mmol) and 1,10-phenanthroline (2 mg) in THF (5 mL) was stirred in a flask fitted with a reflux condenser. Four equivalents of HMPA (2.2 mL) were added, and the flask was cooled to 0 °C in an ice bath. Ethylmagnesium bromide (3.0 M in ether) was added dropwise until a wine-red color persisted. The reaction mixture was stirred for 45 min, and then excess anhydrous benzyl bromide (≥0.6 g, ≥1.2 equiv) was added, and the flask was heated at 80 °C in an oil bath. The color of the solution rapidly changed from deep purple to pale yellow. Analysis by TLC indicated that the reaction was complete within 2.5 h. The reaction mixture was cooled, diluted with ether (60 mL), washed with water (1 × 10 mL, 2 × 20 mL) and brine (1 × 10 mL), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil. Flash chromatography (22:1 petroleum ether/ethyl acetate) provided 1.16 g (91%) of **19** as a clear oil: ^1H NMR ($CDCl_3$) δ 7.75–7.28 (m, 5 H, aromatic), 5.58 (s, 1 H, C=CH), 4.59, 4.48 (AB q, 2 H, J = 11, CH_2Ph), 3.95 (m, 4 H, OCH_2CH_2O), 3.44 (m, 1 H, $CH(OCH_2Ph)$), 2.3–1.1 (m, 25 H, aliphatic); IR (film) 3050 (w), 2919 (s), 2846 (s), 1446 (m), 1187 (m), 1077 (m) cm^{-1}.

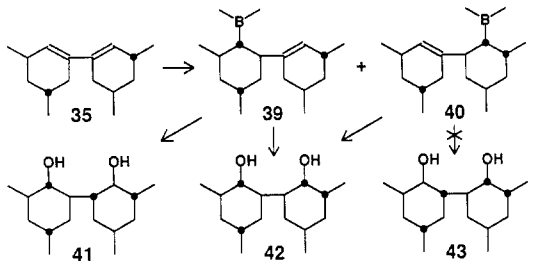
6(*R)-[2(*R**)-Hydroxycyclohex-1(*S**)-yl]-10(*S**)-[2-(*S**)-[(phenylmethyl)oxy]cyclohex-1(*R**)-yl]-1,4-dioxaspiro[4.5]decane (20).** A solution of BH_3–THF (1.0 M, 2.83 mL, 2.83 mmol) was added dropwise via syringe pump over 20 min to a stirred solution of **19** (1.16 g, 2.83 mmol) in THF (4 mL) at 0 °C. The resulting solution was allowed to warm to room temperature overnight. The reaction mixture was cooled in ice, and ethanol (4 mL), 3 N NaOH (1 mL), and 30% H_2O_2 (1.6 g) were added carefully, maintaining the temperature below 40 °C. The flask was heated at 45–50 °C in a thermostated oil bath for 3.3 h and then cooled. The aqueous layer was saturated with K_2CO_3 (2.6 g) and extracted with ether (2 × 3 mL). The combined organic solutions were washed with saturated K_2CO_3 (1 × 4 mL), dried (K_2CO_3), and concentrated in vacuo at 70 °C to give **20** (1.11 g, 91%) as a colorless oil. The ^1H NMR spectrum indicated that the product was nearly pure. Flash chromatography (3:1 hexanes/ethyl acetate) gave pure **20** (77%). Other unidentified material eluted from the column amounted to less than 5% of the theoretical yield. The alcohol slowly crystallized after standing for several weeks: mp 79–82 °C; ^1H NMR ($CDCl_3$) δ 7.47–7.20 (m, 5 H, aromatic), 4.95 (s, 1 H, OH), 4.60, 4.38 (AB q, 2 H, J = 11.3, CH_2Ph), 4.31–3.95 (m, 4 H, ketal), 3.26 (m, 1 H, CH(OR)), 3.18 (m, 1 H, CH(OR)), 2.25 (m, 1 H, aliphatic CH), 2.10 (m, 1 H, aliphatic CH), 2.00–1.10 (m, 24 H, aliphatic); ^{13}C NMR δ 139.3, 128.1, 127.5, 127.1, 113.7, 79.1, 70.3, 70.2, 66.7, 66.2, 55.1, 52.9, 42.9, 42.2, 35.4, 33.51, 33.46, 31.5, 26.9, 26.6, 26.3, 26.1, 25.4, 24.5, 24.2; IR (film) 3440 (s), 3062 (w), 3030 (w), 2930 (s), 2860 (s), 1495 (w), 1448 (s), 1748 (m), 1202 (s), 1095 (s), 960 (m), 948 (m), 900 (m), 840 (w), 738 (m), 700 (m) cm^{-1}; M^+ m/z 428. A sample was distilled in a Kugelrohr apparatus at 200–250 °C (0.3 mm) for analysis. Anal. Calcd for $C_{27}H_{40}O_4$: C, 75.66; H, 9.41. Found: C, 75.56; H, 9.50.

***d,l*-[1,1′-Bicyclohexyl]-2,2′-diol (14).** A solution of bi-1-cyclohexen-1-yl (1.01 g, 6.22 mmol) in THF (10 mL) in a flask equipped with a reflux condenser was treated with BH_3–THF solution (1.0 M, 6.22 mmol), heated under reflux overnight, and then cooled to room temperature. Successive additions of ethanol (6 mL), 3 N NaOH (2.1 mL), and 30% H_2O_2 (1.91 g, 16.9 mmol) were made, maintaining the temperature below 40 °C. The reaction mixture was heated at 45–50 °C for 70 min. The aqueous layer was saturated by addition of K_2CO_3 (3.5 g) and extracted with ether (2 × 4 mL). The combined organic layers were washed with saturated aqueous K_2CO_3 (1 × 2 mL). GC analysis (column D, 50–190 °C at 15°/min, including coinjection) indicated that diol **15** comprised 58% of the product mixture. The solution was concentrated in vacuo to provide 1.13 g (92%) of crude diols. Recrystallization (ethyl acetate) provided 383 mg of **14** as white needles, mp 183.5–184.5 °C (lit.[16,6b] mp 184 °C). The ^1H NMR spectrum was in agreement with the literature data.[16]

1,2,3,4,4a,7a,8,9,10,11,11a,11b-Dodecahydrodibenzo[*d,f*]-[1,3]dioxepin (24). A solution of diol **14** (204 mg, 1.0 mmol) and *N*-bromosuccinimide in DMSO (10 mL) was heated overnight at 50 °C. The reaction mixture was cooled and then quenched by addition of 5% aqueous $NaHCO_3$ (ca. 20 mL) and extracted with ether (1 × 15, 2 × 10 mL). The combined extracts were washed with water (2 × 5 mL) and brine (4 mL), dried (Na_2SO_4), and concentrated in vacuo to give 170 mg of crude acetal **24** mixed with unreacted diol **14**. Purification of a portion by flash chromatography (9:1 hexanes/ethyl acetate) was accompanied by significant hydrolysis: ^1H NMR ($CDCl_3$) δ 4.77 (s, 2 H, OCH_2O), 3.45 (m, 2 H, CH(OR)), 2.05–0.80 (m, 18 H, aliphatic); ^{13}C NMR δ 92.5, 77.1, 50.3, 33.9, 30.6, 25.6, 25.3; HRMS M^+ m/z calcd for $C_{13}H_{22}O_2$ 210.1620 found 210.1618 (11.4%).

3(*R)-(2-Oxocyclohex-1(*S**)-yl)-[1(*S**),1′(*R**)-bicyclohexyl]-2,2′-dione (25).** Triol **15** (593 mg, 199 mmol) was dissolved in CCl_4 (100 mL), and RuO_2 (112 mg, 0.597 mmol) was suspended in the solution. An aqueous solution of $NaIO_4$ (2.00 g, 9.35 mmol, 30 mL) was added. The resulting mixture was stirred vigorously for 2 h in an open flask, whereupon TLC (ether) indicated a single spot (R_f = 0.29; for **15**, R_f = 0.21). Mechanical stirring was employed for larger scale reactions. The layers were separated, and the aqueous layer was extracted with CCl_4 (3 × 10 mL). The CCl_4 extracts were combined, and the excess oxidant was reduced by treatment with 2 mL of 2-propanol for 1 h. Addition of Celite, filtration through a Celite pad, and concentration of the filtrate in vacuo gave 522 mg (90%) of **25** as a white solid. One crystallization (hexanes) afforded white blades, mp 110–110.4 °C. A second crop gave larger crystals (identical by ^1H NMR), one of which was used to establish the structure of **25** by single-crystal

Scheme IX



X-ray diffraction: ^{1}H NMR ($CDCl_3$) δ 2.74 (m, 2 H, CHC=O), 2.56 (m, 2 H, CHC=O), 2.43 (m, 2 H, CHC=O), 2.27 (~d of t, 2 H, $J \simeq 5.1, 13.2$, CHC=O), 2.06–1.58 (m, 18 H, aliphatic); ^{13}C NMR δ 210.7, 208.7, 50.7, 50.1, 41.7, 29.3, 28.8, 26.2, 25.4, 25.0; IR (film) 2940 (s), 2870 (s), 1700 (s), 1447 (m), 1352 (w), 1310 (m), 1267 (w), 1124 (m), 1010 (w) cm^{-1}; M$^+$ m/z 290. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.49; H, 9.02. Found: C, 74.21; H, 8.97.

Crystal data for 25: $C_{18}H_{26}O$, M = 290.41, orthorhombic, space group P_{nma}, a = 12.871 (3) Å, b = 26.118 (8) Å, c = 4.844 (3) Å, V = 1628 (2) Å^3, D_{calcd} = 1.185, D_{obsd} = 1.167, Z = 1/2 (a mirror plane bisects with molecule). Intensity data were collected on an Enraf-Nonius CAD-4 diffractometer using Mo Kα radiation (λ = 0.710 73 Å) in the $w - 2\theta$ mode. The structure was solved by direct methods by using 547 of the 1736 observed reflections, $I > 3\sigma(I)$. The hydrogen atom positions were calculated using standard geometries. Refinement factors: R_{uw} = 0.052; R_w = 0.060. The final difference Fourier map showed no significant electron density (≤0.105 e^{-1}/Å^3). Bond angles and lengths, positional parameters, and general temperature factor expressions are given in the supplementary material.

Oxidation of Triol 16 with RuO_4. The oxidation of **16** (105 mg, 0.35 mmol) was performed as described for **15**. After 2 h, TLC (ethyl acetate) showed a single component, which had a higher R_f value than **16**. The workup was performed as before but included a filtration through activity III silica gel, which was rinsed with ether (2 × 3 mL) to afford 70 mg (68%) of white solid. A symmetrical diketo alcohol structure was deduced by spectroscopic analysis: ^{1}H NMR ($CDCl_3$) δ 3.36 (t, 1 H, J = 9.7, C*H*(OH)), 2.54–2.25 (m, 6 H, CHC=O), 2.1–1.2 (m, 20 H, aliphatic); ^{13}C NMR δ 214.3, 72.2, 53.0, 44.6, 42.2, 28.8, 28.6, 26.9, 26.2, 25.4; IR (film) 3450 (m), 2920 (s), 2855 (s), 1698 (s), 1448 (m), 1123 (m), 1048 (m), 936 (w) cm^{-1}. The oxidation of triol **16** (195 mg, 0.66 mmol) was repeated, but the reaction mixture was stirred overnight. After workup as above, **25** was obtained quantitatively as a white solid. Recrystallization from hexanes (2×) furnished a sample identical with authentic **25** by comparison with melting points, mixed melting points, ^{1}H NMR, ^{13}C NMR, and GC (Column B).

Oxidation of Triol Mixture 15 and 17. The oxidation of mixed triols **15** and **17** (225 mg, 0.76 mmol) was conducted as described for pure **15** to afford 157 mg (71%) of a mixture of triketones. Flash chromatography (2:1 hexanes/ethyl acetate) provided fractions as follows: pure unsymmetrical trione **26** (34 mg, crystallized after prolonged standing, mp 67–70 °C); a mixture of **25** and **26** (25 mg); and pure symmetrical triketone **25** (75 mg). For triketone **26**: ^{1}H NMR ($CDCl_3$) δ 3.00–2.80, 2.77–2.60 (m, 4 H, CHC=O), 2.40–2.27 (m, 4 H, CH_2C=O), 2.1–1.2 (m, 18 H, aliphatic); ^{13}C NMR δ 211.4, 211.0, 210.7, 50.7, 50.2, 49.4, 49.1, 42.2, 42.1, 30.7, 30.2, 29.8, 29.7, 27.8, 27.2, 25.3, 25.2, 24.9; IR (film) 2938 (s), 2868 (s), 1701 (s), 1449 (m), 1347 (w), 1311 (w), 1285 (w), 1127 (m), 919 (m) cm^{-1}; HRMS, M$^+$ m/z calcd for $C_{18}H_{26}O_3$ 290.1882, found 290.1879 (9.3%).

6(*R)-(2(*R**)-Hydroxycyclohex-1(*S**)-yl)-10(*S**)-(2-(*S**)-hydroxycyclohex-1(*R**)-yl)-1,4-dioxaspiro[4.5]decane (27).** A degassed mixture of benzyl ether **20** (284 mg, 0.69 mmol), 5% Pd/C (46 mg), and 2-propanol (4 mL) was stirred under a hydrogen atmosphere. After 9 h, the reaction was complete as indicated by TLC (1:1 hexanes/ethyl acetate). The catalyst was removed by filtration through Celite, which was rinsed with several portions of CH_2Cl_2. The filtrate was concentrated in vacuo to give 177 mg (76%) of **27** as a white solid: mp 185–187 °C; ^{1}H NMR ($CDCl_3$) δ 4.22 (m, 4 H, OCH_2CH_2O), 3.87 (br s, 2 H, OH), 3.23 (~d of t, 2 H, J = 4.1, 9.7, CH(OH)), 2.04–1.00 (m, 26 H, aliphatic); ^{13}C NMR δ 113.7, 70.6, 67.1, 66.9, 53.9, 43.2, 35.0, 33.2, 26.4, 26.2, 25.5, 24.4; IR (~4% in $CDCl_3$) 3454 (m), 2932 (s), 2860 (m), 1448 (m), 1347 (w), 1325 (w), 1300 (w), 1283 (w), 1204 (m), 1191 (m), 1123 (m), 1108 (m), 1078 (m), 1047 (m), 954 (w), 936 (m), 836 (w) cm^{-1}; M$^+$ m/z 338.

Deketalization of 27. A stirred solution of ketal **27** in 80% acetic acid (1.5 mL) was heated at 60–80 °C for 8 h. TLC (1:1 hexanes/ethyl acetate) showed two new spots (R_f = 0.60 and 0.25, for **27** R_f = 0.28). The reaction mixture was carefully added to a saturated $NaHCO_3$ solution (22.5 mL), with use of ether (15 mL) to assist the transfer. After the addition of brine (15 mL) the aqueous portion was extracted with ether (2 × 10 mL). The combined organic layers were washed with brine (7 mL), dried ($MgSO_4$), and concentrated in vacuo to give an oil. Trituration with hexanes afforded 16 mg of 2(*R**)-(2(*R**)-hydroxycyclohex-1(*S**)-yl)-6(*S**)-(2(*S**)-hydroxycyclohex-1(*R**)-yl)cyclohexanone (**28**) as cubic white crystals: mp 111–112 °C; ^{1}H NMR ($CDCl_3$) δ 3.37 (m, 2 H, CH(OH)), 2.7–1.0 (m, 26 H, aliphatic); ^{13}C NMR δ 210.9, 71.3, 54.6, 43.6, 36.8, 29.6, 29.5, 26.1, 26.0, 24.8; IR (film) 3393 (m), 2932 (s), 2860 (m), 1694 (m), 1448 (m), 1036 (m), 1018 (m), 936 (m), 909 (m) cm^{-1}. Concentration of the NMR sample left an oil consisting of a mixture of *both* new components, according to TLC analysis. Retrituration with hexanes afforded 4 mg of crystalline **28** (R_f = 0.25). The combined hexane solutions were subjected to flash chromatography (1:1 hexanes/ethyl acetate) to afford 19 mg of spiroketal **29** as a white crystalline solid (R_f = 0.60): mp 75–78 °C; ^{1}H NMR ($CDCl_3$) δ 3.57–3.42 (m, 2 H, CH(OR)), 2.20–1.00 (m, 26 H, aliphatic); ^{13}C NMR δ 114.3, 81.8, 81.2, 47.9, 47.6, 46.5, 46.3, 32.8, 31.7, 27.4, 25.7, 25.5, 24.9, 24.6, 24.3, 23.7, 23.3, 19.2; IR (film) 2924 (s), 2850 (s), 1445 (s), 1304 (m), 1144 (m), 1080 (m), 1032 (m), 937 (m), 915 (m), 870 (m), 864 (m) cm^{-1}.

6(*R)-[2-Oxocyclohex-1(*S**)-yl]-10(*S**)-[2-oxocyclohex-1(*R**)-yl]-1,4-dioxaspiro[4.5]decane (30).** A mixture of diol **27** (57 mg, 0.17 mmol), Dess–Martin periodinane[24] (281 mg, 0.66 mmol), and acetonitrile (2 mL) was stirred overnight at room temperature. Ether (5 mL) and 1.3 N NaOH (2 mL) were added, and the resulting mixture was vigorously stirred for 10 min. The organic layer was washed with 1.3 N NaOH (2 mL) and brine (2 mL), dried ($MgSO_4$), and concentrated in vacuo to give 55 mg (98%) of **30** as a white solid: mp 135–137 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (m, 4 H, OCH_2CH_2O), 2.47 (m, 2 H, CHC=O), 2.23 (m, 4 H, CHC=O), 2.14–1.07 (m, 20 H, aliphatic); ^{13}C NMR δ 213.1, 114.2, 66.2, 65.4, 50.8, 47.4, 42.0, 32.4, 27.74, 27.67, 25.8, 22.7; IR (~4% in $CDCl_3$) 2939 (s), 2894 (m), 2865 (m), 1700 (s), 1446 (w), 1335 (w), 1305 (w), 1218 (w), 1203 (w), 1180 (m), 1120 (w), 1090 (m), 1065 (w), 1048 (w), 950 (w) cm^{-1}; M$^+$ m/z 334.

Deketalization of 30. A mixture of 0.73 M H_2SO_4 (26 mg), silica gel 60 (60–200 mesh, 262 mg), and CH_2Cl_2 (2 mL) was stirred for ca. 10 min. Ketal **30** (18 mg, 0.054 mmol) was added, and the mixture was stirred overnight at room temperature. TLC analysis (silica, 10:1 CH_2Cl_2/ethyl acetate) indicated only one product, which had a higher R_f value than **30**. The mixture was filtered using a fritted-glass funnel, and the silica gel was washed with CH_2Cl_2 (5 × 2 mL). The filtrate was concentrated in vacuo to give 12 mg (76%) of a white crystalline solid. The sample proved to be identical with symmetrical triketone **25**, according to ^{1}H NMR and ^{13}C NMR spectra, including the ^{13}C NMR spectrum of a 1:1 mixture.

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Registry No. 1, 1502-22-3; 1 (semicarbazone deriv 1), 119245-41-9; 1 (semicarbazone deriv 2), 119245-42-0; **2**, 1011-12-7; **3**, 20780-25-0; **4**, 119245-27-1; **5**, 3293-32-1; **6**, 119245-28-2; **7**, 119245-29-3; **8**, 75835-27-7; **9**, 75879-77-5; **10**, 119245-30-6; **11**, 55529-18-5; **12**, 119324-10-6; **13**, 119324-11-7; **14**, 119324-12-8; **15**, 119245-31-7; **16**, 119324-13-9; **17**, 119324-14-0; **18**, 119245-32-8; **19**, 119245-33-9; **20**, 119245-34-0; **23**, 119245-35-1; **24**, 119324-15-1; **25**, 119245-36-2; **26**, 119324-16-2; **27**, 119245-37-3; **28**, 119245-38-4;

29, 119245-39-5; 30, 119245-40-8; cyclohexanone, 108-94-1; bi-1-cyclohexen-1-yl, 1128-65-0.

Supplementary Material Available: Tables of positional parameters, bond angles, bond lengths, and general temperature factor expressions (4 pages); observed and calculated reflections for 3(*R**)-(2-oxocyclohex-1(*S**)-yl)-[1(*S**),1′(*R**)-bicyclohexyl]-2,2′-dione (**25**) (3 pages). Ordering information is given on any current masthead page.

Notes

Iodine Oxidation of α-Tocopherol and Its Model Compound in Alkaline Methanol: Unexpected Isomerization of the Product Quinone Monoketals

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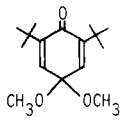
Iodine in alkaline methanol has been shown to bring about the oxidative coupling or oxidation of the alkyl substituent of alkylphenols.[1] The reagent has also been employed in the synthesis of bichalcones.[2] To extend the scope of this oxidation, the author initiated a study of 4-alkoxyphenols, including α-tocopherol (**3b**) and its model compound, 2,2,5,7,8-pentamethylchroman-6-ol (**3a**), whose chemical oxidation has been extensively investigated in connection with the biological antioxidant activity shown by the former.[3]

Dropwise addition of a methanolic solution of I_2 (1 mol equiv) to a solution of 2,6-di-*tert*-butyl-4-methoxyphenol in methanol containing excess KOH under N_2 at room temperature (ca. 10 °C), immediately afforded *p*-benzoquinone dimethyl ketal **1** in over 90% yield. Likewise, dimethyl ketal **2** was obtained from 2,3,5,6-tetramethyl-4-methoxyphenol in 54% yield. Model compound **3a**, a



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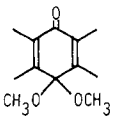

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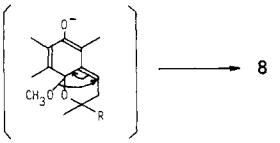
cyclic ether fused to a benzene ring, was subjected to similar iodine oxidation at room temperature. An oily product, isolated in 67% yield after extractive workup of the reaction mixture, is assigned 8a-methoxychroman-6-one **4a** based on its spectral data (see the Experimental Section). $NaBH_4$ reduction of the product to the parent phenol **3a** and acid hydrolysis to give *p*-benzoquinone **10a** are consistent with structure **4a**.[4] Chromanone **4a** was also obtained by treating **3a** with benzoyl peroxide in refluxing methanol[4] but in somewhat lower yield. Surprisingly, however, **4a** was no longer formed when the same iodine oxidation of **3a**, which is quite rapid even at 10 °C, was carried out at 50 °C. The crystalline major product (ca. 30%) obtained is isomeric with **4a**. Its structure, 4-methoxychroman-6-ol **8a**, is based on the following spectral observations. The IR spectrum suggests the presence of a hydroxyl group(s), and the UV spectrum exhibits a marked resemblance to that of the parent phenol **3a**. The ^1H NMR spectrum indicates that C-4 bears a methoxy group (δ 3.36) and a hydrogen (δ ca. 4.2). Treatment of **8a** with acid afforded 3,4-dehydrochroman-6-ol **9a**. It is notable that oxidation at C-4 has been quite rare in the chroman-6-ol series. The distinct products from reactions at the different temperatures are reconciled by the experiments which follow. Oxidation of **3a** with I_2 at room temperature followed by warming before the workup, gave rise to **8a** (48%), but no **4a** was detected. It is, therefore, assumed that **4a** isomerizes to **8a** (70%) in hot methanol in the presence of the alkali. The principal byproduct in this isomerization reaction is **9a** (15%), which is assumed not to derive from **8a** since prolonged heating neither increased the yield of **9a** appreciably nor decreased that of **8a**. Chromane **8a** remained virtually intact after being heated in alkaline methanol.

Iodine oxidation of (2*RS*,4′*R*,8′*R*)-**3b** at room temperature in the same manner afforded 8a-methoxy-α-tocopherone (**4b**) (68%) as an inseparable mixture of diastereomers. After exposure to alkaline methanol at 60 °C **4b** was converted into isomeric 4-methoxy-α-tocopherol (**8b**), isolated as a pair of diastereomers (72% in total) whose stereochemistry has not been determined. The rearrangement of **4b** was accompanied by formation of 3,4-dehydro-α-tocopherol (**9b**) (19%).

The benzoquinone monoketals from the 4-alkoxyphenols are probably formed by the solvolysis of the primary products, 4-alkoxy-4-iodocyclohexa-2,5-dien-1-ones. The apparently unprecedented dienone–phenol rearrangement of **4a** and **4b** is tentatively thought to proceed as shown in Scheme I. Protonation of enolate anion **6** and subsequent attack of methanol at the 4-position with simultaneous loss of the C-8a methoxy group would furnish 8.[5] If the proton attached to C-3 in enol **7** is removed, **9** is expected to form. Further investigation of the structural requirements for this isomerization is needed since ketal **2**, bearing no cyclic ether function, did not tend to isom-



6

(1) Omura, K. *J. Org. Chem.* **1984**, *49*, 3046.
(2) Ali, S. M.; Ilyas, M. *J. Org. Chem.* **1986**, *51*, 5415.
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(5) Unless **6** is protonated, the attack by the nucleophilic solvent would be unlikely since C-4 is nucleophilic. This protonation, however, may not necessarily be required if **8** is formed by migration of the C_4–C_{4a} double bond with concomitant intramolecular 1,3-shift of the 8a-methoxy group.

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