# Structural Analysis of *cis*-[*n*.3.1]Bicyclic Ketones by X-ray Crystallography. Impact of the Observed Conformational Crossover on π-Facially Diastereoselective Nucleophilic Additions to This Class of Ketones and on the Stereochemical Course of Electrophilic Reactions Involving Their Methylene Analogues

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X-ray crystallographic studies clearly show that *cis*-[*n*.3.1]bicyclic ketones **1** having *n* equal to 7 or less are conformationally predisposed such that the rigid chair cyclohexanone ring projects the polymethylene chain diaxially. In contrast, an increase in belt size to $n = 9$ is adequate to allow adoption of diequatorial geometry without evidence for dynamic chair–chair interconversion. These divergent ground-state characteristics are believed to persist in the methylene derivatives **2**. In order to evaluate the impact of this stereochemical crossover on the facial stereoselectivity of nucleophilic attack on **1** and electrophilic capture by **2**, the following reactions were examined: hydride and dissolving metal reduction, organometallic additions, condensation with dimethyloxosulfonium methylide, epoxidation, osmylation, oxymercuration, and cycloadditions involving chlorosulfonyl isocyanate and dichloroketene. The presence of an axially oriented loop strongly curtails otherwise favored axial approach by these reagents. With these systems, a strong preference for less hindered equatorial approach is observed. Although the $(CH_2)_9$ series is subject to near-identical inductive contributions from the polymethylene belt, the overwhelming diequatorial bias of this belt does not introduce a comparable steric bias and a general (although not exclusive) preference for axial attack is noted. These substitution effects are compared to those of the 4-*tert*-butylcyclohexyl analogues.

The ketone carbonyl is arguably the most important functional group in organic synthesis. Since its π bond makes available two faces with which to capture nucleophilic reagents, the control of diastereoselectivity in addition reactions to prochiral ketones holds considerable importance and has commanded a great deal of experimental[3] and theoretical attention.[4] Studies quantifying the extent of axial/equatorial approach of nucleophiles to cyclohexanones abound.[5] More recently, investigations of the stereochemistry of additions have been expanded to include adamantanones,[6] *trans*-decalones,[7] cyclopentanones,[8] 7-ketonorbornanes,[9] and related exocyclic olefins.[3d,10] The rigidity of the adamantane framework lends itself particularly well to the analysis of electronic contributions since the carbonyl π surfaces can be made virtually unbiased sterically with proper substitution. However, the means by which electronic information is transmitted remains controversial.[3,4,6-11]

Conformationally locked cyclohexanones are considered to suffer from two inherent limitations: (a) the steric nonequivalency of the two carbonyl faces such that nucleophilic attack is not geometrically equivalent and (b) the possibility that the very substituents employed to curtail chair–chair interconversion exert stereodirecting contributions. The relevance of steric factors to the first phenomenon is widely accepted, although quantitative information about the possible modulation of steric shielding is limited. Considerably less is known about b, concern for which has been raised only more recently.[11d,12]

Our abiding interest in π-facial diastereoselectivity has prompted investigation of the stereochemistry of addition reactions to ketones typified by **1** and their methylene analogues **2**. By means of X-ray crystallographic analysis, it has been possible for us to demonstrate that a fundamental conformational switchover occurs as one progresses from $n = 7$–9. The nonamethylene chain is consequently of sufficient length and flexibility to be accommodated diequatorially by the cyclohexanone ring. Any reduction

(1) National Institutes of Health Postdoctoral Fellow, 1990–1992.

(2) Author to whom inquiries regarding the X-ray crystallographic analyses should be addressed.

(3) For leading references, consult: (a) Wigfield, D. C. *Tetrahedron* **1979**, *35*, 449. (b) Fraser, R. R.; Stanciulescu, M. *J. Am. Chem. Soc.* **1987**, *109*, 1580. (c) Lodge, E. P.; Heathcock, C. H. *J. Am. Chem. Soc.* **1987**, *109*, 3353. (d) Cieplak, A. S.; Tait, B. D.; Johnson, C. R. *J. Am. Chem. Soc.* **1989**, *111*, 8447.

(4) For recent lead references, see: (a) Cieplak, A. S. *J. Am. Chem. Soc.* **1981**, *103*, 4540. (b) Mukherjee, D.; Wu, Y.-D.; Fronczek, F. R.; Houk, K. N. *J. Am. Chem. Soc.* **1988**, *110*, 3328. (c) Houk, K. N.; Wu, Y.-D. *Stereochemistry of Organic and Bioorganic Transformations*; Bartmann, W.; Sharpless, K. B., Eds.; VCH Publishers: New York, 1987; pp 247–260. (d) Wong, S. S.; Paddon-Row, M. N. *J. Chem. Soc., Chem. Commun.* **1990**, 456. (e) Kurita, Y.; Takayama, C. *Tetrahedron* **1990**, *46*, 3789. (f) Fang, J.-M.; Sun, S.-F.; Rei, M.-H. *J. Chem. Soc., Chem. Commun.* **1989**, 747. (g) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018.

(5) For example: (a) Dauben, W. G.; Fonken, G. J.; Noyce, D. S. *J. Am. Chem. Soc.* **1956**, *78*, 2579. (b) Calvet, A.; Levisalles, J. *Tetrahedron Lett.* **1972**, 2157. (c) Agami, C.; Kazakos, A.; Levisalles, J. *Tetrahedron Lett.* **1975**, 2035. (d) Moreau, G. *Bull. Soc. Chim. Fr.* **1972**, 2814. (e) Giddings, M. R.; Hudec, J. *Can. J. Chem.* **1981**, *59*, 459. (f) Kwart, H.; Takeshita, T. *J. Am. Chem. Soc.* **1962**, *84*, 2833. (g) Di Maio, G.; Li, W.; Vecchi, E. *Tetrahedron* **1985**, *41*, 4891. (h) Nagao, Y.; Goto, M.; Ochiai, M.; Shiro, M. *Chem. Lett.* **1990**, 1503. (i) Nagao, Y.; Goto, M.; Ochiai, M. *Chem. Lett.* **1990**, 1507. (j) Haubenstock, H. *Tetrahedron* **1990**, *46*, 6633.

(6) (a) Li, H.; le Noble, W. J. *Tetrahedron Lett.* **1990**, *31*, 4391 and earlier work by the le Noble group cited therein. (b) Adcock, W.; Trout, N. A. *J. Org. Chem.* **1991**, *56*, 3229.

(7) For example: Di Maio, G.; Migneco, L. M.; Vecchi, E. *Tetrahedron* **1990**, *46*, 6053.

(8) Halterman, R. L.; McEvoy, M. A. *J. Am. Chem. Soc.* **1990**, *112*, 6690.

(9) Leading references: (a) Okada, K.; Tomita, S.; Oda, M. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 459. (b) Li, H.; Mehta, G.; Padma, S.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2006. (c) Mehta, G.; Khan, F. A. *J. Am. Chem. Soc.* **1990**, *112*, 6140.

(10) (a) Paquette, L. A.; Hertel, L. W.; Gleiter, R.; Böhm, M. C.; Beno, M. A.; Christoph, G. G. *J. Am. Chem. Soc.* **1981**, *103*, 7106. (b) Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1987**, *109*, 5874. (c) Vedejs, E.; Dent, W. H., III. *J. Am. Chem. Soc.* **1989**, *111*, 6861. (d) Bodepuli, V. R.; le Noble, W. J. *J. Org. Chem.* **1991**, *56*, 2001 and relevant references cited in these papers.

(11) (a) Klein, J. *Tetrahedron Lett.* **1973**, 4307. (b) Anh, N. T.; Eisenstein, O.; Lefour, J.-M.; Trân Huu Dâu, M.-E. *J. Am. Chem. Soc.* **1973**, *95*, 6146. (c) Ashby, E. C.; Boone, J. R. J. *J. Org. Chem.* **1976**, *41*, 2890. (d) Cheung, C. K.; Tseng, L. T.; Lin, M.-H.; Srivastava, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1986**, *108*, 1598.

(12) Abraham, R. J.; Chadwick, D. J.; Sancassan, F. *Tetrahedron* **1982**, *38*, 1485.

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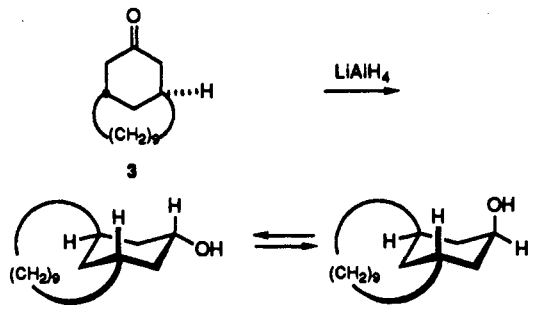
1 2

in the size of this belt induces sufficient ring strain that it can now be comfortably linked only in a diaxial manner. To what extent and in which direction will these structural changes impact on those reactions to which **1** and **2** are subjected? Will nucleophiles and electrophiles respond differently? Might uniparticulate and biparticulate electrophilic processes[13] involving **2** prove to be diastereoselectively distinctive as *n* is altered?

Of importance is the constancy of the alkyl inductive effects operating in **1** and **2** as *n* is systematically varied. Comprehensive study of the series was expected to clarify the importance to stereoinduction of those steric changes associated solely with the diaxial/diequatorial dichotomy.

## Results

**Synthesis of 1 and 2.** Ketones **1a** ($n = 3$)[14] and **1b** ($n = 5$)[15] were prepared as described elsewhere. The higher homologues **1c** ($n = 7$) and **1d** ($n = 9$)[16] were accessed by catalytic hydrogenation of the corresponding conjugated enones[16-18] below 0 °C. Lowering of the reaction temperature was found to increase the selectivity for cis ketone formation at the expense of the trans isomer. For example, hydrogenation of the enone precursor to **1d** at 25 °C produced a 9:1 mixture of cis and trans isomers.[19] At 0 °C, the ratio is greater than 25:1 in favor of **1d**. The stereochemical assignment to **1d** was confirmed by $LiAlH_4$ reduction to a pair of epimeric alcohols (see below). In contrast, only **4** was generated from trans-fused **3**. The $^{13}C$ NMR spectrum of **4** is characterized by broadened signals, suggesting that this alcohol is conformationally dynamic near 30 °C.[20]




The bicycloalkanones **1** were transformed into **2b–d** by conventional Wittig chemistry. Under these conditions, **1a** suffers enolization exclusively, **1b** and **1c** are enolized only to a small extent, and **1d** gives no indication of undergoing this side reaction.

(13) Paquette, L. A.; Allen, G. R., Jr.; Broadhurst, M. J. *J. Am. Chem. Soc.* **1971**, *93*, 4503.
(14) Moodie, W. T.; Parker, W.; Watt, I. *J. Chem. Soc., Perkin Trans. 2* **1979**, 664.
(15) Gioia, B.; Ballabio, M.; Beccalli, E. M.; Cecchi, R.; Marchesini, A. *J. Chem. Soc., Perkin Trans. 1* **1981**, 560.
(16) Marchesini, A.; Pagnoni, U. M.; Pinetti, A. *Tetrahedron Lett.* **1973**, 4299.
(17) Hirano, S.; Hiyama, T.; Fujita, S.; Kawaguti, T.; Hayashi, Y.; Nozaki, H. *Tetrahedron* **1974**, *30*, 2633.
(18) Paquette, L. A.; Wang, T.-Z.; Luo, J.; Cottrell, C. E.; Clough, A. E.; Anderson, L. B. *J. Am. Chem. Soc.* **1990**, *112*, 239.
(19) Still lower ratios were reported by earlier investigators.[16]
(20) Teleha, C. A. Unpublished results. Variable-temperature NMR studies were not performed in this instance.

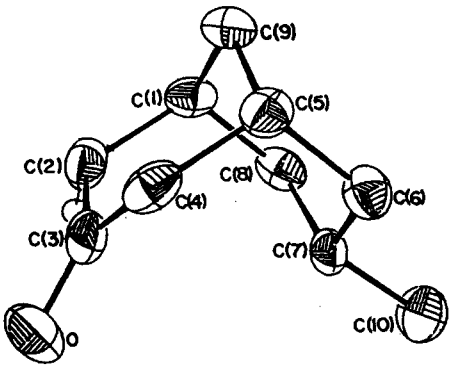



**Figure 1.** ORTEP drawing of *exo*-7-methylbicyclo[3.3.1]nonan-3-one.[21]

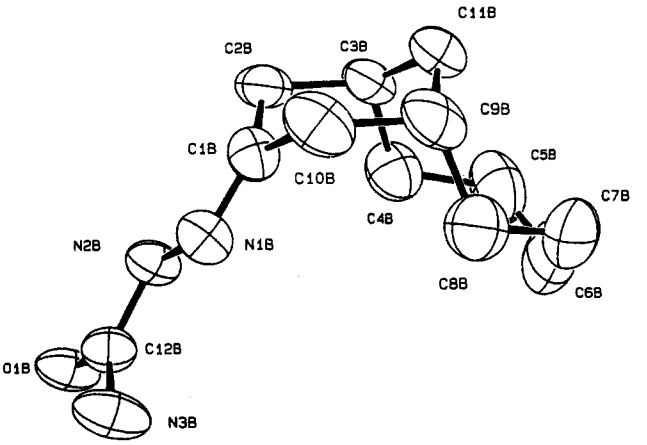



**Figure 2.** ORTEP drawing of the semicarbazone of **1b** (with hydrogens omitted for clarity).

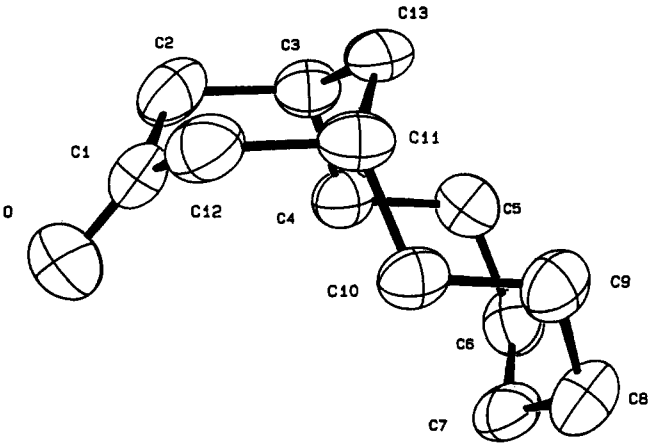



**Figure 3.** ORTEP drawing of **1c** (with hydrogens omitted for clarity).

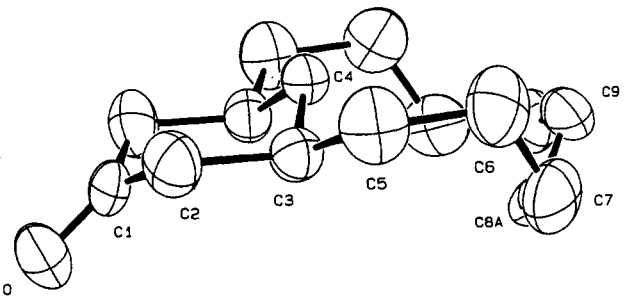



**Figure 4.** ORTEP drawing of **1d** (with hydrogens omitted for clarity). Only one of the positions for the disordered atom C8 is shown.

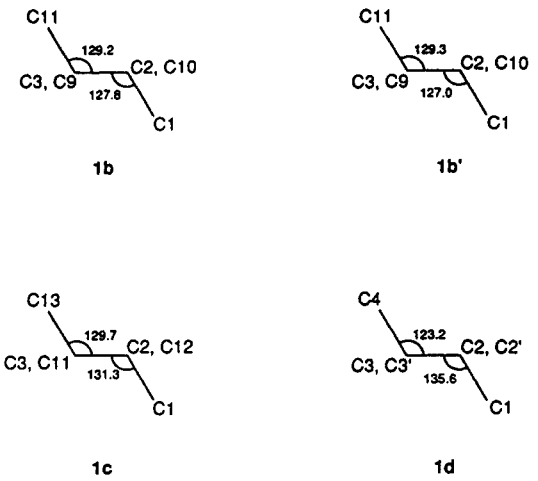



**Figure 5.** Dihedral angles associated with the back and legs of the cyclohexanone ring in **1b** (both molecules in the asymmetric unit), **1c**, and **1d**.

**X-ray Crystallographic Analyses and Conformational Criteria.** The X-ray crystal structure of *exo*-7-methylbicyclo[3.3.1]nonan-3-one, reproduced in Figure 1, has been reported previously by Richardson and Sorensen.[21] We assume with a high level of confidence that **1a** has an entirely similar ground-state conformation. Oily **1b** was converted to its semicarbazone derivative for the purpose of crystallographic analysis (Figure 2). Ketones **1c** and **1d** proved sufficiently crystalline for direct examination by X-ray diffraction methods (Figures 3 and 4).

Clearly revealed by these ORTEP diagrams is the fact that the polymethylene chains in **1a–c** are conjoined to the cyclohexane subunit in an axial–axial manner. In **1d**, on the other hand, the substitution on the six-membered ring is equatorial–equatorial. The torsion angle patterns for the cyclooctane and cyclodecane subunits in **1b** and **1c**, respectively, indicate that a bisecting pseudo-mirror plane exists in each instance, since symmetry-related torsion angles are comparable in magnitude but opposite in sign.[22] In **1b**, this plane contains atoms C6 and C11 and the cyclooctane conformation is the boat–chair form. In **1c**, the pseudo-mirror plane passes through C7 and C13, and a boat–chair–boat topography is adopted by the 10-membered ring. Because of the disorder exhibited by atom C8 in the 12-membered ring in **1d**, no bisecting mirror plane exists. Crystallographic mirror symmetry is obeyed for the portion of this ring containing atoms C3, C4, C5, C6, C7, and C9 before disappearing at C8.

A second interesting feature of the medium rings resides in the transannular distances separating those atoms related either by a pseudo-mirror or a crystallographic mirror plane. In **1b**, the C4---C8 distances are 3.182 (6) and 3.195 (6) Å for molecules A and B in the asymmetric unit. In **1c**, the corresponding distances are slightly larger: 3.280 (5) Å for C4---C10 and 3.294 (6) Å for C5---C9. A strikingly dramatic increase is seen for **1d**: 5.047 (9) Å for C5---C5′, 5.057 (9) Å for C6---C6′, and 4.56 (1) Å for C7---C7′. This phenomenon can be traced to the diequatorial orientation adopted in the latter ketone.

As in **1a**, the cyclohexanone rings in **1b–d** uniformly adopt the chair conformation. The dihedral angles, displayed in Figure 5 to provide a measure of existing distortion in these chairs, are defined in terms of the least-squares plane for the four atoms in the seat of the chair and the three-atom planes which constitute the back and the legs of the chair. In progressing from **1b** to **1d**, increased flattening at the C1 end is seen that amounts to approximately 8°. At the opposite end of the six-membered ring, the angles for **1b** and **1c** are essentially equivalent at 129.2–129.7°. The increased puckering shown by **1d** (123.2°) at C4 is likely the result of the crossover to an equatorial–equatorial substitution pattern at the flanking carbon atoms.

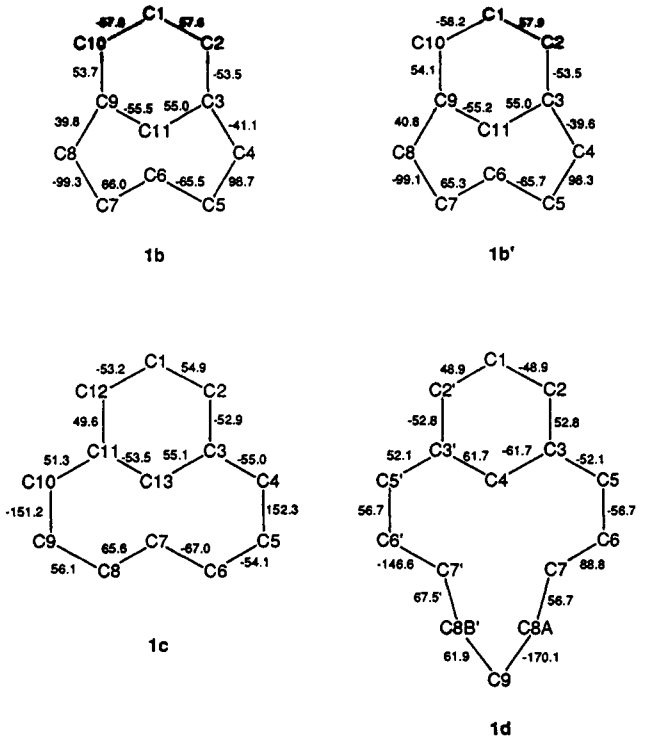



**Figure 6.** Selected torsion angles. The torsion angles for the six-membered rings listed here are endocyclic for these rings. For example, the 55.0° listed for the C3–C11 bond for **1b** is the C2–C3–C11–C9 torsion angle value. The remaining torstion angles are endocyclic for the second ring of each structure. For example, the −41.1° value listed for the C3–C4 bond for **1b** is the C11–C3–C4–C5 torsion angle. The esd's are within the following ranges: for **1b** and **1b′**, 0.4–0.9°; for **1c**, 0.4–0.6°; and for **1d**, 0.4–0.9°.

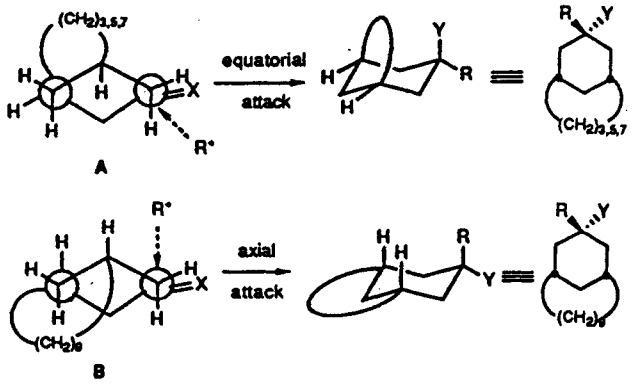
Further inspection of the torsion angles for the cyclohexanone rings (Figure 6) reveals slight differences in their conformations. A pseudo-mirror plane passes through atoms C1 and C11 in both molecules of **1b**. For **1c**, the best pseudo-symmetry element present is a 2-fold axis that bisects the C2–C3 and C11–C12 bonds and is orthogonal to a low quality mirror plane through C1 and C13. This reflects a slight twisting of the ring.[23] The crystallographically imposed mirror plane through atoms C1 and C4 in **1d**, which is orthogonal to a poor pseudo-2-fold axis that bisects the C2–C3 and C2′–C3′ bonds, is further indication of ring flattening at one end with puckering at the other.

Olefins **2b–d** are presumed to adopt conformations similar to those of their ketonic counterparts. This is evidenced by the striking correspondence of their $^1$H NMR spectra (see Experimental Section). Especially noteworthy are several indications that both **1** and **2** are essentially static cyclohexyl compounds. The onset of dynamic "ring flipping" within the six-membered cycle would average geminally related protons and reduce the magnitude of

(21) Richardson, J. F.; Sorenson, T. S. *Can. J. Chem.* **1985**, *63*, 1166.
(22) (a) Hendrickson, J. B. *J. Am. Chem. Soc.* **1964**, *86*, 4854. (b) Bucourt, R. In *Topics in Stereochemistry*; Eliel, E. L.; Allinger, N. L., Eds.; Wiley-Interscience: New York, 1974; Vol. 8.
(23) Duax, W. L.; Weeks, C. M.; Rohrer, D. C. In *Topics in Stereochemistry*; Eliel, E. L.; Allinger, N. L., Eds.; Wiley-Interscience: New York, 1976; Vol. 9.

vicinal coupling. Even in the case of **1d**, where ring flipping should be most facile, the $^1$H NMR spectrum is consistent with a static structure. The inhibition to ring inversion is directly linked to the need of forcing the methano bridge through the interior of a methylene loop, all of which are too short to make ready steric allowance.

Consequently, Newman projection A can be considered to correspond generically to those structural features prevailing in **1a–c**, **2b**, and **2c**, whereas projection B relates uniquely to **1d** and **2d**. Note that equatorial attack on




A gives rise to a product possessing relative stereochemistry (viz., R trans to the alicyclic bracket) similar to that resulting from axial attack on B. Nonetheless, the two series remain conformationally distinctive because of the very specific spatial orientation adopted by the polymethylene belts. This dichotomy is intrinsic to all of the two-dimensional formulas depicted herein.

As is customary, exo shall refer to that isomer in which the original carbonyl oxygen or the exocyclic methylene carbon becomes oriented cis to the methano bridge. Conversely, the endo designation is reserved for denoting a trans relationship between Y and the same apical $CH_2$ group.

**Hydride Reduction of the Ketones.** The reductions with $LiAlH_4$, L-Selectride (Aldrich), and $LiAlH(O\text{-}t\text{-}Bu)_3$ were carried out in ether at room temperature. For solubility reasons, the reactions involving $NaBH_4$ were performed in methanol. Lastly, the conversion of **1a–d** to their cyclohexanols by dissolving metal reduction was effected with sodium in refluxing ammonia.

Product distributions were determined by capillary gas chromatography or by integration of uniquely characteristic signals in the $^1$H NMR spectra of unpurified reaction mixtures. The secondary alcohols were separated by column chromatography and the purified endo and exo epimers were individually characterized. The stereochemical assignments are convincingly based on several criteria. Moodie, Parker, and Watt had previously distinguished **5a** and **6a**.[14] In the other cases, those epimers


**5** **6**

**a**, $n$ = 3; **b**, $n$ = 5; **c**, $n$ = 7; **d**, $n$ = 9

that eluted more slowly on silica gel were assigned to have equatorial hydroxyl groups.[24] Added confirmation was

(24) (a) Doyle, M. P.; West, C. T. *J. Org. Chem.* **1975**, *40*, 3821. (b) Doyle, M. P.; McOsker, C. C.; Ball, N.; West, C. T. *J. Org. Chem.* **1977**, *42*, 1922. (c) Cherest, M. *Tetrahedron* **1980**, *36*, 1593. (d) Johnson, C. R.; Tait, B. D.; Cieplak, A. S. *J. Am. Chem. Soc.* **1987**, *109*, 5875. (e) Fort, Y.; Feghouli, A.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* **1990**, *55*, 5911.

**Table I. Endo/Exo Alcohol Ratios (5:6) Resulting from Reduction of 1a–d**

| | ketone | | | |
|---|---|---|---|---|
| reducing agent | **1a**[a] | **1b**[b] | **1c**[b] | **1d**[c] |
| $LiAlH_4$ | 90:10 | 93:7 | 91:9 | 85:15 |
| $LiAlH(O\text{-}t\text{-}Bu)_3$ | 89:11 | 90:10 | 91:9 | 91:9 |
| L-Selectride | 96:4 | 99:1 | >99:1 | 30:70 |
| $NaBH_4$ | 95:5 | 98:2 | 99:1 | 85:15 |
| Na, $NH_3$ | 23:77 | 5:95 | 5:95 | 75:25 |

[a] Ratios determined by capillary GC analysis of the acetates. [b] Ratios determined by capillary GC analysis of the carbinols. [c] Ratios determined by $^1$H NMR.

**Table II. Endo/Exo Alcohol Ratios (7:9 and 8:10) for Organometallic Additions to 1b–d**

| | ketone | | |
|---|---|---|---|
| reagent | **1b** | **1c** | **1d** |
| *n*-BuMgBr | >95:5 | >95:5 | 21:79 |
| *n*-BuLi | >95:5 | >95:5 | 31:61 |
| PhMgBr | >95:5 | >95:5 | 56:44 |
| PhLi | >95:5 | >95:5 | 57:43 |

derived from examination of the chemical shifts and coupling constants of the carbinol protons. In agreement with past experience, axially oriented protons inevitably appear upfield of their equatorial counterparts.[24e,25] Further, the axial hydrogens are seen as broadened triplets of triplets while the equatorial proton multiplicities are narrowly spaced triplets, a direct consequence of larger axial–axial $J$ values.

The results compiled in Table I show that hydride reduction of **1a–c** occurs primarily by *equatorial attack* (as depicted in A) to give endo alcohols predominantly. Dissolving metal reduction occurs in the opposite sense, giving chiefly the exo alcohols as a result of kinetic protonation of the anionic intermediate from an axial trajectory. In contrast, the reductions of **1d** occur with a strong penchant for axial attack (as depicted in B), except for L-Selectride. This pattern of behavior parallels that exhibited by 4-*tert*-butylcyclohexanone.[27]

**Organometallic Additions to the Ketones.** The four annulated ketones were allowed to react with *n*-BuMgBr, *n*-BuLi, PhMgBr, and PhLi in ether at room temperature. In every instance, **1a** underwent enolization exclusively; consequently, stereochemical data are not available for the $n$ = 3 example. The product distribution of the other condensation reactions have been compiled in Table II. The alcohols **7–10** obtained in these reactions were isolated in isomerically pure form by column chromatography. The exo/endo ratios are based on the quantities of epimers actually isolated.


**7**, R = *n*-Bu
**8**, R = Ph

**9**, R = *n*-Bu
**10**, R = Ph

As before, the diastereomers were initially assigned configuration on the strength of their order of elution from

(25) (a) Lemieux, R. U.; Kullnig, R. K.; Bernstein, H. J.; Schneider, W. G. *J. Am. Chem. Soc.* **1958**, *80*, 6098. (b) McElvain, S. M.; Clampitt, R. B. *J. Am. Chem. Soc.* **1959**, *81*, 5590. (c) Eliel, E. L.; Gianni, M. H.; Williams, Th. H.; Stothers, J. B. *Tetrahedron Lett.* **1962**, 741. (d) Raban, M.; Lauderback, S. K.; Kost, D. *J. Am. Chem. Soc.* **1975**, *97*, 5178.

(26) Bothner-By, A. A. *Adv. Magn. Reson.* **1965**, *1*, 195.

(27) Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part B*, 3rd ed.; Plenum Press: New York, 1990; p 242.

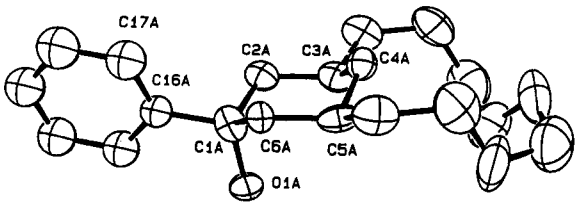
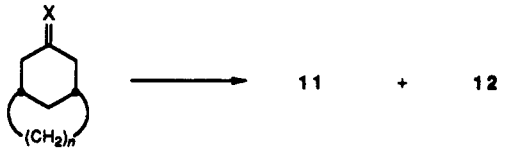



**Figure 7.** ORTEP drawing of **10d** (with hydrogens omitted for clarity). Only one of the disordered positions for atoms C10 and C12 is shown.

**Table III. Endo/Exo Ratios Associated with Epoxide Formation (11:12)**




| n | X | reaction condns[a] | % composition 11 | 12 |
|---|---|---|---|---|
| 5 | $CH_2$ | A | 3 | 97 |
| | O | B | >98 | <2 |
| | $CH_2$ | C | <1 | >99 |
| 7 | $CH_2$ | A | 9 | 91 |
| | O | B | >98 | <2 |
| | $CH_2$ | C | <1 | >99 |
| 9 | $CH_2$ | A | 35 | 65 |
| | O | B | <5 | >95 |
| | $CH_2$ | C | 70 | 30 |

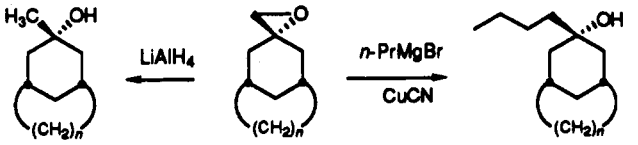
[a] A = peracetic acid oxidation; B = condensation with $CH_2{=}S(O)(CH_3)_2$; C = osmylation followed by monotosylation and $K_2CO_3$-promoted cyclization.

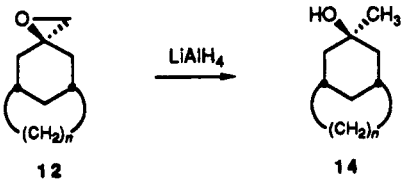
silica gel. Added corroboration was provided in the *n*-butyl series by ring opening of the stereoisomeric epoxides with *n*-propylcuprate as discussed in the subsequent section. In the phenyl series, the highly crystalline *endo*-**10b** was subjected to crystallographic analysis. As seen in Figure 7, the hydroxyl group in this less polar carbinol is projected in a pronounced way to the axial direction.

Therefore, the addition of Grignard and lithium reagents to **1b** and **1c** occurs in the same sense as the hydride reductions, with equatorial attack predominating heavily to generate endo alcohols **7** and **8** almost exclusively. By comparison, ketone **1d** undergoes these same reactions with only modest regard for stereoselectivity (Table II).

**Epoxide Formation Studies.** The direct epoxidation of **2b–d** was effected in $CH_2Cl_2$ at 0 °C with 35% peracetic acid buffered with sodium acetate. Product distributions were determined by integration of the characteristically different $-CH_2O-$ signals of **11** and **12** in the $^1H$ NMR spectra of the crude reaction products. The axially disposed methylene groups proved always to be the more deshielded. The data compiled in Table III under method A make evident the heavily favored formation of endo oxiranes **12b** and **12c**, a consequence of the heightened susceptibility of **2b** and **2c** to kinetically controlled epoxidation from their exo face (equatorial approach). Similar treatment of **2d** gave rise to a 1:2 mixture of **11d** and **12d**. Axial attack is consequently marginally favored when $n = 9$.

In order to produce the stereoisomeric epoxides, **1b–d** were exposed to $CH_2{=}S(O)(CH_3)_2$ according to the Corey–Chaykovsky procedure.[28] This process (method B, Table III) proved to be highly stereoselective even where **1d** is concerned. All of the stereoisomeric epoxides could be isolated analytically pure except for **11d**, which was inseparable from its endo epimer.

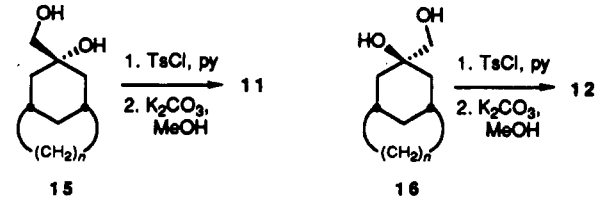



Reduction of each epoxide with $LiAlH_4$ gave the corresponding methyl carbinol (**13** or **14**). The availability of these alcohols provided for convenient cross-checking of stereochemical assignments on the strength of two criteria: (1) the more polar epimers on silica gel are those with equatorial hydroxyl groups and (2) the epimers showing a heightened tendency to lose water in the mass spectrometer carry axial hydroxyls.[24d,29] Thus, the stereochemistries of **11** and **12** were directly correlated to those of **13** and **14**, respectively.

Additionally, CuCN-catalyzed condensation[30] of the exo epoxides **11** with *n*-propylmagnesium bromide in THF at −20 °C gave the *exo*-*n*-butylcarbinols **7** identical to those isolated from addition of *n*-BuMgBr to the ketones. No reaction was observed when endo epoxides **12b** and **12c** were subjected to analogous cross-coupling conditions. Evidently, the rigid bicyclic topography of these oxiranes effectively wards off backside attack at the secondary site of the heterocyclic ring. This restriction does not apply to **12d**, which underwent the cleavage reaction as rapidly as **11d**.

**Stoichiometric Osmylation of the Alkenes.** The dihydroxylation reactions were carried out at room temperature in acetone solution containing a molar equivalent of $OsO_4$ (0.1 N in *tert*-butyl alcohol). The product distributions (Table III) were established by quantitative integration at 300 MHz of the $-CH_2O-$ signals clearly evident in the unpurified product mixtures. Stereochemical assignment to the diols thus obtained (**15** and **16**) was made possible by their conversion to the corresponding epoxides of known structure by standard procedures.[31]




For **2b** and **2c**, the trajectory of osmylation mimics that of peracid oxidation, i.e., equatorial approach, to afford endo diols **16b** and **16c**, respectively. As concerns **2d**, osmylation occurs in the sense opposite to peracid oxidation. In this example, the formation of **15d** (equatorial

(28) Corey, E. J.; Chaykovsky, M. *Organic Syntheses*; Wiley: New York, 1973; *Coll. Vol. V*, p 755.

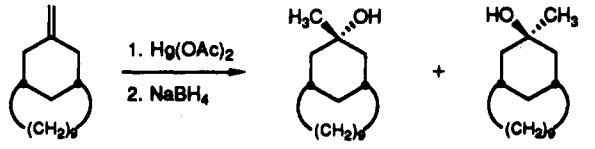
(29) (a) Senda, Y.; Ishiyama, J.; Imaizumi, S. *Tetrahedron* **1975**, *31*, 1601. (b) Wilson, N. K.; Stothers, J. B. *Top. Stereochem.* **1973**, *8*, 1.

(30) Manna, S.; Viala, J.; Yadagiri, P.; Falck, J. R. *Tetrahedron Lett.* **1986**, *27*, 2679.

(31) Corey, E. J.; Marfat, A.; Goto, G.; Brion, F. *J. Am. Chem. Soc.* **1980**, *102*, 7984.

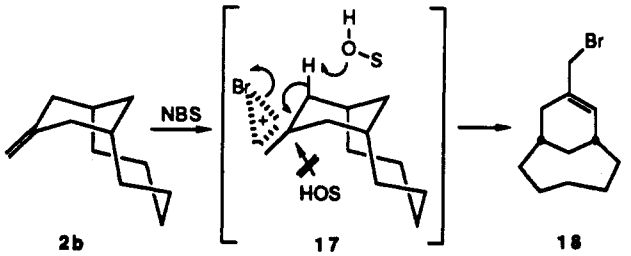
attack) is favored by a factor of 7:3 over epimer **16d** (axial attack).

**The Consequences of Oxymercuration.** Unexpectedly, our attempts to oxymercurate **2b** and **2c** proved problematic.[32,33] No reaction was observed when either alkene was exposed to mercuric acetate in aqueous THF. Prolongation of the reaction time led to complex mixtures, which after demercuration gave neither **13** nor **14**. In contrast, **2d** underwent smooth conversion under these conditions to a 24:76 mixture of **13d** and **14d**. The kinetically favored reaction pathway therefore involves transient formation of the equatorial mercurinium ion.




**2d** **13d** **14d**

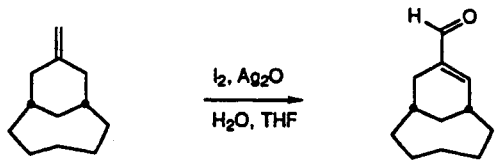
The inertness of **2b** to oxymercuration led us to investigate the reactivity of the exocyclic olefin toward several halogenating agents. An attempt to convert **2b** to the corresponding bromohydrin by treatment with *N*-bromosuccinimide in moist DMSO[34] resulted in the formation of allyl bromide **18**. This transformation was very clean. Although this somewhat sensitive compound was not purified, its identity was deduced by $^1$H NMR, $^{13}$C NMR, and mass spectral analysis of the directly isolated material.




**2b** **17** **18**

Evidently, nucleophilic opening of intermediate bromonium ion **17** by solvent is relatively slow due to the presence of the diaxial pentamethylene bridge that blocks the trajectory necessary for backside displacement at the tertiary center. As a consequence, proton abstraction by bromide ion or solvent becomes the favored process.

A similar event was observed in the attempted epoxidation of **2b** with $I_2/Ag_2O/H_2O$.[35] This reagent combination produced complex reaction mixtures from which enal **19** could be isolated in approximately 50% yield. This result is construed to be an indication that proton abstraction from the intermediate iodonium ion competes with iodohydrin formation. The resulting allylic iodide is presumably unstable to the reaction conditions, its hydrolysis, and subsequent oxidation leading to **19**.




**2b** **19**

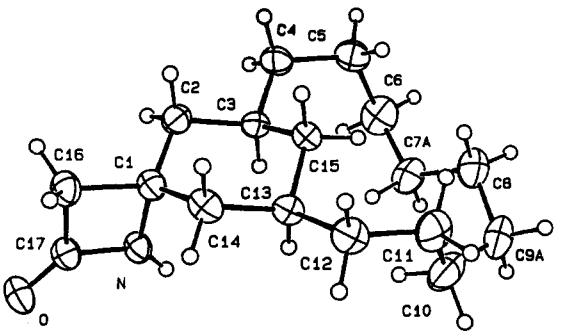



**Figure 8.** ORTEP drawing of **20d**. The non-hydrogen atoms are represented by 30% probability thermal ellipsoids. The hydrogen atoms are drawn with an artificial radius. Only one of the disordered positions for atoms C7 and C9 is shown.

**Table IV. Uniparticulate Electrophilic Additions to 2b and 2d**

| compd | reagent | product distribution (%) | |
|---|---|---|---|
| **2b** | CSI | **20b** (>99) | **21b** (<1) |
| **2d** | CSI | **20d** (72) | **21d** (28) |
| **2b** | DCK | **22b** (79) | **23b** (21) |
| **2d** | DCK | **22d** (86) | **23d** (14) |

The outcome of these experiments provides reasonable insight into the inertness of **2b** to the oxymercuration conditions.

**Cycloadditions Involving Chlorosulfonyl Isocyanate and Dichloroketene.** Condensation of **2b** with chlorosulfonyl isocyanate (CSI) and reductive hydrolysis of the cycloadduct with $NaHSO_3$[36] afforded β-lactam **20b** exclusively. Its formulation as the endo product rests entirely on analogy with the course of dichloroketene addition (vide infra). Olefin **2d**, by comparison, afforded the pair of epimeric β-lactams **20d** and **21d** in a 72:28 ratio. The product distribution was deduced by integration of the pairs of $-CH_2C(O)-$ and NH absorptions in the 300-MHz $^1$H NMR spectra of unpurified mixtures. Appropriate stereochemical distinction was made by X-ray crystallographic analysis of the major, less polar isomer **20d**, which was obtained free of **21d** by column chromatography (Figure 8).


**20** **21**


**22** **23**

Cycloaddition of dichloroketene (DCK) to **2b** and **2d** yielded the spirocyclobutanones **22** and **23** (Table IV). In these experiments, the $Cl_2C{=}C{=}O$ was generated by re-

(32) Larock, R. C. *Solvomercuration/Demercuration in Organic Synthesis*; Springer-Verlag: New York, 1986.
(33) For anomalous oxymercuration reactions, consult: Coxon, J. M.; Hartshorn, M. P.; Lewis, A. J. *Tetrahedron* **1970**, *26*, 3755.
(34) Dalton, D. R.; Dutta, V. P.; Jones, D. C. *J. Am. Chem. Soc.* **1968**, *90*, 5498.
(35) Parrilli, M.; Barone, G.; Adinolfi, M.; Mangoni, L. *Tetrahedron Lett.* **1976**, 207.
(36) Reviews: (a) Graf, R. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 172. (b) Rasmussen, J. K.; Hassner, A. *Chem. Rev.* **1976**, *76*, 389. (c) Szabo, W. A. *Aldrichimica Acta* **1977**, *10*, 23.

Table V. Percent Axial Attack on 1b–d, 2b–d, and 24 by Various Reagents

| reagent | 24 | 1a | 1b | 1c | 1d | 2b | 2c | 2d |
|---|---|---|---|---|---|---|---|---|
| $LiAlH_4$ | 92 | 10 | 7 | 9 | 85 | | | |
| $LiAlH(O\text{-}t\text{-}Bu)_3$ | 91 | 11 | 10 | 9 | 91 | | | |
| L-Selectride | 7 | 4 | 1 | 1 | 30 | | | |
| $NaBH_4$ | 80 | 5 | 2 | 1 | 85 | | | |
| Na, $NH_3$, *t*-BuOH | 95 | 77 | 95 | 95 | 75 | | | |
| *n*-BuMgBr | 56 | | <5 | <5 | 21 | | | |
| *n*-BuLi | | | <5 | <5 | 31 | | | |
| PhMgBr | 55 | | <5 | <5 | 56 | | | |
| PhLi | 58 | | <5 | <5 | 57 | | | |
| $CH_3CO_3H$ | 69[a] | | | | | 3 | 9 | 65 |
| $CH_2{=}S(O)(CH_3)_2$ | <1 | | <2 | <2 | <5 | | | |
| $OsO_4$ | 14[a] | | | | | <1 | <1 | 30 |
| $Hg(OAc)_2$ | 29[a] | | | | | | | 24 |
| CSI | >90[a] | | | | | <1 | | 72 |
| DCK | 80[a] | | | | | 21 | | 86 |

[a] 4-(*tert*-Butylmethylene)cyclohexane as substrate. Other relevant references not included in the text are: (a) Meaking, G. D.; Percy, R. K.; Richards, E. E.; Young, R. N. *J. Chem. Soc. C* **1968**, 1106. (b) Sevin, A., Censi, J.-M. *Bull. Soc. Chim. Fr.* **1974**, 96. (c) Jasserand, D.; Girard, J. P.; Rossi, J. C.; Granger, R. *Tetrahedron* **1976**, *32*, 1535. (d) Senda, Y.; Kamiyama, S.; Imaizumi, S. *J. Chem. Soc., Perkin Trans. 1* **1978**, 530. (e) Huffman, J. W.; Charles, J. T. J. *Am. Chem. Soc.* **1968**, *90*, 6486.

action of trichloroacetyl chloride with zinc–copper couple.[37] The pentamethylene-bridged diastereomers **22b** and **23b** could be distinguished on the basis of their $-CH_2CO-$ NMR absorptions. In related systems such as epoxides **11b/12b** and alcohols **13b/14b**, the axial oxiranyl methylene ($\delta$ 2.65) and methyl signals ($\delta$ 1.34) are appreciably more deshielded than their equatorial counterparts ($\delta$ 2.34 and 1.17, respectively). The same trend is reflected in the spectra of **22b** (axial $-CH_2CO-$ at $\delta$ 3.34) and **23b** (equatorial $-CH_2CO-$ at $\delta$ 3.13).

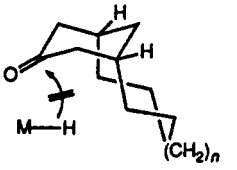
This effect is seemingly due in large part to steric deshielding since it is appreciably larger for 3,5-diaxially bridged systems than for those that have 3,5-diequatorial belts. The generalization impacts on **22d** and **23d** where a correlation between stereodisposition and chemical shift is no longer evident. For this reason, the stereochemistry of major adduct **22d** is assigned by correlation to **20d**, the preferred product of CSI capture. The exo/endo ratios for both pairs of addition reactions are compiled in Table IV.

## Discussion

The stereochemical course of cyclohexanone reductions is thought to be regulated either by steric factors operating in the immediate environment of the carbonyl group[4c,5a,38] or by electronic contributions that serve as the determinant of $\pi$-facial selectivity.[4a,d,11] Steric demands within the cyclohexanone are construed to be best served by hydride attack from the axial direction, since nearly perfect staggering is achieved between the C–H bonds originally $\alpha$ to the carbonyl and those evolving into the carbinol group at the transition state.[38d,e] The bulk of the nucleophilic hydride source cannot, however, be neglected.[39] With increasing size, a point is reached where steric approach control becomes overriding such that equatorial attack is kinetically preferred.[11c] The "effective size" of any reagent may in turn be dependent on a number of little understood factors such as solvation, self-association, metal ion–oxygen coordination, angle of attack, and the like.

The stereoselectivity preferences earlier observed in the reduction of 4-*tert*-butylcyclohexanone (**24**) can now be compared directly to those of **1a–d** (Table V). The diastereomeric product distributions observed for **1d** and **24** over the entire range of hydride reagents examined are strikingly similar. A decided preference for axial attack is seen, except when L-Selectride is involved. In this specific instance, the medium-ring bicyclic ketone is somewhat more tolerant of axial attack (30%) than is **24** (7%). This may be the result of existing conformational differences in the two ketones.

The opposite stereoselection observed with **1b** and **1c** is noteworthy (Table V). There can be little doubt that steric factors gain overriding importance in these systems. As seen in **25**, the rigid conformation adopted by either of these ketones so blockades steric accessibility to the carbonyl from the axial direction that equatorial attack proceeds more rapidly. Understandably, this stereochemical preference persists for **1b** and **1c** during the addition of organometallic reagents.




**25** ($n$ = 1, 3)

The capture by **1d** of *n*-BuMgBr and *n*-BuLi is characterized by a significant dropoff in axial stereoselectivity (only 21–31%) relative to hydride reduction. Still more striking is the finding that PhMgBr and PhLi undergo addition to this ketone with essentially no preference for either carbonyl face. This lack of discrimination cannot originate from appreciable changes in staggering along those bonds adjacent to the carbonyl. Rather, the low stereoselectivity, particularly when the phenylating reagents are involved, is a consequence of the greater bulk of phenyl relative to *n*-butyl. The associated spatial requirements lead in turn to an increased bias for approach along an equatorial trajectory.[40] A further increase in the effective size of the nucleophile as in $CH_2{=}S(O)(CH_3)_2$ results in virtually complete kinetic preference for equatorial attack on **1d** (Table V). The analogous reaction involving **24** proceeds as well with stereospecific epoxide formation from the equatorial direction.[41]

Epoxidation of the exocyclic methylene compounds **2b** and **2c** occurs with an abnormal preference for attack of the peracid from the equatorial face. When the belt is fastened diequatorially as in **2d**, 65% of the oxidation occurs from the axial direction. This level of axial selectivity is normal for sterically unbiased methylenecyclohexanes.[3d,10c,24d,42] The stereochemical crossover exhibited by **2b** and **2c** can, as before, be related directly to steric inaccessibility from that direction syn to the polymethylene chain.

The general trend for osmylation is to proceed by late transition states[43] that find it easier to develop along

(37) Review: Brady, W. T. *Synthesis* **1971**, 415.

(38) (a) Cram, D. J.; Abd Elhafez, F. A. *J. Am. Chem. Soc.* **1952**, *74*, 5828. (b) Leitereg, T. J.; Cram, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 4011, 4019. (c) Karabatsos, G. J. *J. Am. Chem. Soc.* **1967**, *89*, 1367. (d) Chêrest, M.; Felkin, H.; Prudent, N. *Tetrahedron Lett.* **1968**, 2199. (e) Chêrest, M.; Felkin, H. *Tetrahedron Lett.* **1968**, 2205. (f) Brown, H. C.; Deck, H. R. *J. Am. Chem. Soc.* **1965**, *87*, 5620.

(39) Barton, D. H. R. *J. Chem. Soc.* **1953**, 1027; *Experientia* **1950**, *6*, 316.

(40) Ketone **2d** is more sensitive to the difference in relative size than is **24** (*n*-BuMgBr, 56% axial; PhLi, 58% axial): Ashby, E. C.; Noding, S. A. *J. Org. Chem.* **1979**, *44*, 4371.

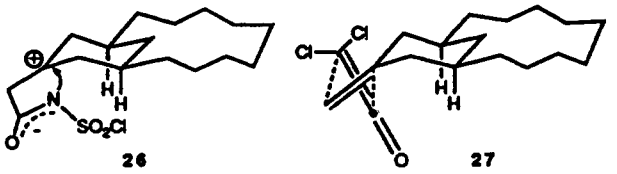
(41) Corey, E. J.; Chaykovsky, M. *J. Am. Chem. Soc.* **1965**, *87*, 1353.

(42) Carlson, R. G.; Behn, N. S. *J. Org. Chem.* **1967**, *32*, 1363.

(43) Cha, J. K.; Christ, W. J.; Kishi, Y. *Tetrahedron* **1984**, *40*, 2247.

equatorial planes as long as heteroatomic influences are absent.[10c] For **2b** and **2c**, the combined consequence of this mechanistic feature and strong axial shielding by the belt is stereospecific dihydroxylation. Similar oxidation of **2d** eventuates in a less equatorially selective reaction (70%), not unlike the favored pathway for 4-(*tert*-butylmethylene)cyclohexane (86% equatorial).[10c]

Kinetically preferred axial approach to **2d** returns during condensation with CSI and DCK. This stereoselectivity, which parallels that previously observed in simpler conformationally locked analogues,[44] suggests that the steric volume required to accommodate the developing zwitterionic intermediate **26** or the orthogonal arrangement **27**




**26** **27**

demanded of $\pi_{2a} + \pi_{2s}$ processes[45] is significantly less than that associated with osmylation. Notwithstanding, the structural constraints inherent to **2b** remain adequate to completely discourage axially directed ring closure as in **26** to form the $\beta$-lactam moiety. The result is stereospecific conversion to **20b**. Surprisingly, **2b** displays an ability to undergo a significant level (21%) of axial attack by DCK. Therefore, the steric environment local to the axial surface of its exocyclic double bond is not recognized during this cycloaddition as being greatly dissimilar from the far less sterically encumbered equatorial alternative when the ketene is oriented orthogonally as needed for incipient bond formation (see **27**). This particular example holds fascination because it represents the global maximum for axial attack on those belted systems having *n* equal to 7 or less (Table V).

In summary, we have shown that ketones **1** are constituted of conformationally rigid chair cyclohexane units, but with divergent spatial orientation of the polymethylene belt depending upon its length. The same constitutional features apply to the corresponding exo olefins **2**. The distinctively different geometries adopted by these otherwise related substrates offer a unique opportunity to assess stereoselectivity patterns. The results indicate that diaxial projection of the alicyclic chain so effectively blockades axially directed access to the carbonyl group or exocyclic double bond that equatorial trajectories for bond formation are generally kinetically preferred. The major exception is seen during cycloaddition of dichloroketene to **2b**, where a record-high level of 21% axial attack is observed. The transition state steric demands of $\pi_{2s} + \pi_{2a}$ reactions appear, therefore, to be less than those of the many other processes examined.

The product distribution patterns for **1d** and **2d** are more varied and reflect a greater dependency on the nature of the reagent involved. High axial selectivity is observed for $LiAlH_4$, $LiAlH(O\text{-}t\text{-}Bu)_3$, and $NaBH_4$ reduction of the ketone and for condensation of the alkene with CSI and DCK. The remaining examples show a progressive dropoff in axial attack, to the point where the equatorial preference can approach 80% (*n*-BuMgBr addition to **1d**; $Hg(OAc)_2$ on **2d**). This crossover is not totally unexpected, however, since a somewhat comparable general trend is followed by the corresponding 4-*tert*-butylcyclohexyl derivatives. In our view, the present findings provide strong positive reinforcement to the claim earlier made by Xie and leNoble that "...the [4-]*tert*-butyl group [in cyclohexyl systems] is indeed innocent of any directive effect...".[46] Substituents used for conformational locking, when disposed equatorially at C3/5 or C4 of a six-membered ring, seemingly exert distortions in the chair arrangement that impact in turn only marginally on product distribution. Markedly different is the situation surrounding rigid diaxial belting at C3/5 of the cyclohexane ring. This arrangement is one where the substituents do exert a very powerful influence on stereoselectivity. Any intrinsic differences in face selectivity vanish in deference to the substantial steric control exerted under these particular circumstances.

## Experimental Section

Melting points are uncorrected. Infrared spectra were recorded on a Perkin-Elmer Model 1320 spectrometer. $^1H$ NMR spectra were recorded at 300 MHz and $^{13}C$ NMR spectra at 75 MHz on a Bruker AC-300 instrument. Mass spectra were recorded on a Kratos MS-30 instrument at The Ohio State University Chemical Instrument Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All separations were carried out under flash chromatography conditions on Fluka silica gel H. Preparative GC purifications were accomplished on a 1 m × 6 mm column packed with 5% SE-30 on Chromosorb W. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried prior to use.

**General Procedure for Hydrogenation of Bicyclic Enones.** A solution of the enone (270 mg) in ethyl acetate (20 mL) was cooled to 0 °C prior to the addition of 10% palladium on carbon (60 mg). The system was purged with hydrogen and the reaction mixture was stirred under a balloon of hydrogen for 4–48 h (reaction progress monitored by TLC). The catalyst was removed by filtration and the filtrate evaporated. The product ketone was purified by distillation and/or column chromatography and/or recrystallization.

For **1b**: IR (neat, $cm^{-1}$) 1705; $^1H$ NMR ($CDCl_3$) $\delta$ 2.55 (dd, $J$ = 13.5, 6.4 Hz, 2 H), 2.3–2.0 (m, 5 H), 1.80–1.65 (m, 6 H), 1.40–1.15 (m, 2 H), 1.15–0.95 (m, 3 H); $^{13}C$ NMR ($CDCl_3$) ppm 212.2, 48.4, 35.6, 32.4, 30.9, 26.5, 25.0.

For **1b** semicarbazone: mp 205–210 °C dec (from ethanol); MS $m/z$ ($M^+$) calcd 223.1685, obsd 223.1716.

Anal. Calcd for $C_{12}H_{21}N_3O$: C, 64.54; H, 9.48. Found: C, 64.40; H, 9.53.

For **1c**: mp 87–88 °C (from hexane); IR (KBr, $cm^{-1}$) 1695; $^1H$ NMR ($CDCl_3$) $\delta$ 2.72 (dd, $J$ = 13.0, 7.0 Hz, 2 H), 2.35–2.22 (m, 3 H), 2.17 (d, $J$ = 13.0 Hz, 2 H), 1.77 (dt, $J$ = 15.5, 4.5 Hz, 1 H), 1.65–1.20 (series of m, 14 H); $^{13}C$ NMR ($CDCl_3$) ppm 211.9, 49.3, 36.7, 29.4, 26.6, 25.8, 23.4, 19.5; MS $m/z$ ($M^+$) calcd 194.1671, obsd 194.1709.

Anal. Calcd for $C_{13}H_{22}O$: C, 80.35; H, 11.41. Found: C, 80.50; H, 11.50.

For **1d**: mp 79–81 °C (from ethyl acetate–petroleum ether); IR (KBr, $cm^{-1}$) 1700; $^1H$ NMR ($CDCl_3$) $\delta$ 2.37 (dt, $J$ = 11.9, 2.0 Hz, 2 H), 2.16 (dt, $J$ = 13.5, 2.3 Hz, 1 H), 2.00 (t, $J$ = 9.0 Hz, 2 H), 1.82 (m, 2 H), 1.62–1.16 (series of m, 18 H), 0.78 (dt, $J$ = 13.5, 10.5, 1 H); $^{13}C$ NMR ($CDCl_3$) ppm 211.4, 49.6, 36.9, 34.5, 32.5, 25.5, 24.4, 23.4, 22.0; MS $m/z$ ($M^+$) calcd 222.1983, obsd 222.1980.

Anal. Calcd for $C_{15}H_{26}O$: C, 81.01; H, 11.79. Found: C, 80.93; H, 11.77.

For the more polar *trans*-bicyclo[9.3.1]pentadecan-12-one: IR (KBr, $cm^{-1}$) 1702; $^1H$ NMR ($CDCl_3$) $\delta$ 2.38 (br d, $J$ = 8.7 Hz, 2 H), 2.08 (m, 4 H), 1.70 (br s, 2 H), 1.37–1.24 (m, 18 H); $^{13}C$ NMR ($CDCl_3$) ppm 212.0, 49.6, 32.5, 31.8, 31.2, 24.6, 24.4, 22.5, 21.7; MS $m/z$ ($M^+$) calcd 222.1983, obsd 222.1980.

**General Procedures for Hydride Reduction of the Ketones. A. Reductions with $LiAlH_4$.** To a slurry of $LiAlH_4$ (20 mg) in anhydrous ether (2 mL) was added a solution of the ketone (10 mg) in the same solvent (4 mL). Reaction progress was monitored by TLC and generally required less than 1 h to achieve

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completeness. Standard quench and workup gave alcohol products that were analyzed as described in the text.

**B. Reductions with LiAlH(O-*t*-Bu)$_3$.** The reactions were carried out as above, quenched with 10% NaOH solution, and extracted into ether. The ether layer was washed with brine, dried, and evaporated to provide the alcohols.

**C. Reduction with NaBH$_4$.** To a solution of the ketone (10 mg) in methanol (2 mL) was added sodium borohydride (100 mg). The reaction mixture was stirred for 30 min, quenched with 10% sodium hydroxide solution, and extracted with ether. Workup and product analysis were achieved as before.

**D. Reductions with L-Selectride.** To a solution of the ketone (10 mg) in anhydrous ether (2 mL) was added L-Selectride in tetrahydrofuran (0.2 mL of 1 M). The reaction mixture was ultimately quenched with 10% NaOH solution and several drops of 30% $H_2O_2$. Workup and product analysis were accomplished in the predescribed manner.

**E. Dissolving Metal Reductions.** Sodium metal (95 mg) was added to 50 mL of $NH_3$, stirring was maintained for 15 min, and the ketone (20 mg) as a solution with *tert*-butyl alcohol (65 mg) in 2 mL of ether was introduced. After 2–3 h, the reaction mixture was quenched with methanol (1 mL) and the ammonia was evaporated. Aqueous workup as described in B gave the product alcohols.

For **5b**: mp 90.5–92 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 4.17 (m, 1 H), 2.15 (d, $J$ = 14.3 Hz, 1 H), 2.15–1.90 (m, 2 H), 1.85–1.65 (m, 12 H), 1.45–1.30 (m, 4 H); $^{13}$C NMR ($CDCl_3$) ppm 68.3, 37.8, 32.8, 32.1, 30.9, 27.5, 25.5; MS $m/z$ ($M^+ - 1$) calcd 167.1436, obsd 167.1430.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.29; H, 12.02.

For **6b**: mp 66–69 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 3.96 (m, 1 H), 2.00–1.65 (m, 10 H), 1.50–1.00 (m, 9 H); $^{13}$C NMR ($CDCl_3$) ppm 63.4, 40.9, 32.8, 32.4, 32.3, 27.2, 25.3; MS $m/z$ ($M^+$) calcd 168.1514, obsd 168.1492.

Anal. Calcd for $C_{11}H_{20}O$: C, 78.51; H, 11.98. Found: C, 78.64; H, 12.02.

For **5c**: mp 90.5–91.5 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 4.19 (dt, $J$ = 6.4, 3.3 Hz, 1 H), 2.45–2.25 (m, 3 H), 1.95–1.80 (m, 2 H), 1.80–1.65 (m, 4 H), 1.60–1.25 (m, 14 H); $^{13}$C NMR ($CDCl_3$) ppm 68.2, 39.4, 31.2, 30.0, 27.0, 25.9, 24.4, 19.8; MS $m/z$ ($M^+ - 1$) calcd 195.1749, obsd 195.1680.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.69; H, 12.42.

For **6c**: mp 112–113 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 4.02 (dt, $J$ = 11.6, 4.2 Hz, 1 H), 2.07 (br d, $J$ = 14.9 Hz, 1 H), 1.95–1.20 (series of m, 22 H); $^{13}$C NMR ($CDCl_3$) ppm 63.7, 42.9, 34.2, 29.0, 26.5, 26.0, 23.8, 19.6; MS $m/z$ ($M^+ - 1$) calcd 195.1749, obsd 195.1743.

Anal. Calcd for $C_{13}H_{24}O$: C, 79.53; H, 12.32. Found: C, 79.73; H, 12.34.

For **5d**: mp 116.5–117 °C (from petroleum ether–ether); $^1$H NMR ($CDCl_3$) $\delta$ 3.72 (m, 1 H), 1.92 (br s, 4 H), 1.63–1.33 (m, 18 H), 1.14 (m, 2 H), 0.94 (dt, $J$ = 11.3, 11.3 Hz, 2 H), 0.14 (dt, $J$ = 11.3, 11.3 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 71.3, 43.8, 35.0 (2 C), 34.3, 26.0, 24.5, 23.8, 22.3; MS $m/z$ ($M^+$) calcd 224.2140, obsd 224.2117.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.28; H, 12.59. Found: C, 80.00; H, 12.48.

For **6d**: mp 92.5–93 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.14 (t, $J$ = 3.4 Hz, 1 H), 1.90 (d, $J$ = 14.8 Hz, 1 H), 1.84 (d, $J$ = 10.3 Hz, 1 H), 1.80–1.28 (m, 22 H), 1.13 (m, 2 H), 0.40 (m, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 67.6, 41.7, 34.5, 33.4, 31.4, 25.7, 24.7, 23.5, 22.1.

**General Procedure for Grignard and Organolithium Additions to 1.** To a solution of the ketone (50 mg) in anhydrous ether (5 mL) was added a 2 molar excess of organometallic reagent. The mixture was stirred at room temperature for 2 h, diluted with ether, washed with $NH_4Cl$, $NaHCO_3$, and NaCl solutions, then dried. After filtration and solvent evaporation, the alcohol products were separated from recovered ketone by column chromatography.

For **7b**: mp 58–59.5 °C (from hexane at −20 °C); $^1$H NMR ($CDCl_3$) $\delta$ 2.20–2.05 (m, 3 H), 1.85–1.65 (m, 7 H), 1.58 (m, 4 H), 1.40–1.20 (m, 10 H), 0.97 (br s, 1 H), 0.89 (br t, $J$ = 6.9 Hz, 3 H); $^{13}$C NMR ($CDCl_3$) ppm 73.0, 47.6, 41.8, 32.3, 31.8, 31.7, 27.7, 25.6, 25.0, 23.2, 14.1; MS $m/z$ ($M^+ - H_2O$) calcd 206.2034, obsd 206.2022.

Anal. Calcd for $C_{15}H_{28}O$: C, 80.29; H, 12.58. Found: C, 80.47; H, 12.64.

For **7c**: mp 62–63 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 2.50–2.34 (m, 2 H), 2.28 (dt, $J$ = 14.8, 2.0 Hz, 1 H), 1.80–1.40 (series of m, 16 H), 1.35–1.15 (m, 9 H), 1.00 (br s, 1 H), 0.89 (br t, $J$ = 6.8 Hz, 3 H); $^{13}$C NMR ($CDCl_3$) ppm 72.9, 46.9, 43.6, 33.2, 29.2, 27.3, 25.9, 25.1, 24.5, 23.3, 19.8, 14.1; MS $m/z$ ($M^+ - H_2O$) calcd 234.2947, obsd 234.2994.

Anal. Calcd for $C_{17}H_{32}O$: C, 80.88; H, 12.78. Found: C, 81.06; H, 12.88.

For **7d**: oil; $^1$H NMR ($CDCl_3$) $\delta$ 1.97 (br d, $J$ = 12.9 Hz, 1 H), 1.70 (d, $J$ = 12.5 Hz, 2 H), 1.65–1.25 (series of m, 25 H), 1.15–1.00 (m, 4 H), 0.93 (br t, $J$ = 6.8 Hz, 3 H), 0.22 (dt, $J$ = 14.7, 14.7 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 73.7, 46.8, 38.6, 35.5, 34.5, 34.2, 25.9, 25.2, 24.8, 23.8, 23.3, 22.5, 14.2; MS $m/z$ ($M^+$) calcd 280.2766, obsd 280.2754.

For **8b**: mp 85–86.5 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (d, $J$ = 7.2 Hz, 2 H), 7.31 (t, $J$ = 7.2 Hz, 2 H), 7.20 (t, $J$ = 7.2 Hz, 1 H), 2.35–2.20 (m, 3 H), 2.11 (dd, $J$ = 14.6, 5.7 Hz, 2 H), 2.00–1.85 (m, 2 H), 1.85–1.70 (m, 7 H), 1.45–1.25 (m, 5 H); $^{13}$C NMR ($CDCl_3$) ppm 151.5, 127.9, 126.3, 124.3, 75.4, 43.6, 32.2, 32.0, 31.7, 27.3, 25.5; MS $m/z$ ($M^+ - OH$) calcd 222.1800, obsd 222.1779.

Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90. Found: C, 83.30; H, 9.93.

For **8c**: mp 100–101 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.49 (dd, $J$ = 8.1, 1.4 Hz, 2 H), 7.32 (t, $J$ = 8.1 Hz, 2 H), 7.20 (tt, $J$ = 8.1, 1.4 Hz, 1 H), 2.58 (m, 2 H), 2.40 (dt, $J$ = 14.8, 2.2 Hz, 1 H), 2.17 (dd, $J$ = 14.4, 6.3 Hz, 2 H), 2.00–1.80 (m, 2 H), 1.80–1.70 (m, 3 H), 1.65–1.25 (m, 13 H); $^{13}$C NMR ($CDCl_3$) ppm 151.3, 128.1, 126.4, 124.4, 75.4, 45.4, 33.7, 29.3, 27.0, 25.6, 24.6, 19.7; MS $m/z$ ($M^+$) calcd 272.2140, obsd 272.2113.

Anal. Calcd for $C_{19}H_{28}O$: C, 83.77; H, 10.36. Found: C, 83.69; H, 10.42.

For **8d**: mp 110–111 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.54 (d, $J$ = 7.3 Hz, 2 H), 7.38 (t, $J$ = 7.3 Hz, 2 H), 7.28 (t, $J$ = 7.3 Hz, 1 H), 2.40 (br d, $J$ = 10.2 Hz, 2 H), 1.98 (br d, $J$ = 12.6 Hz, 1 H), 1.80 (br s, 1 H), 1.65–1.10 (m, 22 H), 0.43 (dt, $J$ = 10.8, 10.8 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 146.0, 128.4, 127.3, 126.2, 74.7, 46.7, 35.2, 34.4, 34.3, 25.8, 24.8, 23.7, 22.5; MS $m/z$ ($M^+$) calcd 300.2453, obsd 300.2465.

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.75; H, 10.95.

For **9d**: mp 80–81 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 1.98 (dt, $J$ = 12.7, 2.0 Hz, 1 H), 1.85–1.45 (m, 9 H), 1.45–1.15 (m, 18 H), 1.10–0.9 (m, 4 H), 0.88 (t, $J$ = 6.8 Hz, 3 H), 0.08 (dt, $J$ = 12.6, 12.6 H, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 73.2, 45.5, 44.4, 34.7, 34.3, 32.0, 25.9, 25.3, 24.3, 23.7, 23.2, 22.0, 13.9; MS $m/z$ ($M^+$) calcd 280.2766, obsd 280.2761.

Anal. Calcd for $C_{19}H_{36}O$: C, 81.36; H, 12.94. Found: C, 81.54; H, 12.98.

For **10d**: mp 107–109 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 7.50 (d, $J$ = 7.4 Hz, 2 H), 7.34 (t, $J$ = 7.4 Hz, 2 H), 7.26 (t, $J$ = 7.4 Hz, 1 H), 2.13 (dt, $J$ = 12.9, 2.2 Hz, 1 H), 2.10–1.90 (m, 2 H), 1.75 (d, $J$ = 13.1 Hz, 2 H), 1.70–1.30 (m, 19 H), 1.25–1.05 (m, 2 H), 0.24 (dt, $J$ = 12.5, 12.5 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 149.6, 128.1, 126.6, 124.4, 75.3, 47.5, 34.6, 34.3, 32.6, 26.1, 24.5, 23.9, 22.1; MS $m/z$ ($M^+$) calcd 300.2453, obsd 300.2435.

Anal. Calcd for $C_{21}H_{32}O$: C, 83.94; H, 10.73. Found: C, 83.77; H, 10.72.

**General Procedure for Wittig Olefination of 1.** To a cold (0 °C), magnetically stirred slurry of methyltriphenylphosphonium bromide (1.07 g) in dry THF (20 mL) was added *n*-butyllithium (1.85 mL of 1.5 M). The reaction mixture was stirred at rt for 4 h, treated with a solution of **1d** (470 mg) in THF (10 mL), and agitated overnight. Petroleum ether was added, the precipitate was removed by filtration, and the filter cake was washed with petroleum ether. The filtrate was evaporated and the residue was chromatographed to give 430 mg (93%) of **2d**.

For **2b** (purified by preparative GC at 115 °C): $^1$H NMR ($CDCl_3$) $\delta$ 4.70 (t, $J$ = 1.6 Hz, 2 H), 2.30 (dd, $J$ = 13.2, 5.5 Hz, 2 H), 2.05–1.90 (m, 3 H), 1.90–1.55 (m, 7 H), 1.41 (dt, $J$ = 14.5, 4.5 Hz, 1 H), 1.35–1.10 (m, 5 H); $^{13}$C NMR ($CDCl_3$) ppm 144.6, 111.0, 41.2, 33.5, 31.9, 31.2, 27.5, 25.2; MS $m/z$ ($M^+$) calcd 164.1565, obsd 164.1545.

Anal. Calcd for $C_{12}H_{20}$: C, 87.73; H, 12.27. Found: C, 88.02; H, 12.26.

For **2c** (purified by preparative GC at 120 °C): mp 34.5–35.5 °C; $^1$H NMR ($CDCl_3$) $\delta$ 4.69 (t, $J$ = 1.6 Hz, 2 H), 2.41–2.35 (m, 2 H), 2.11 (dt, $J$ = 14.8, 2.1 Hz, 1 H), 2.02 (dd, $J$ = 12.9, 0.8 Hz, 2 H), 1.85–1.25 (m, 15 H), 1.20–1.05 (m, 2 H); $^{13}$C NMR ($CDCl_3$) ppm 145.1, 110.2, 42.9, 34.5, 28.5, 27.2, 26.8, 23.6, 19.9; MS $m/z$ ($M^+$) calcd 192.1878, obsd 192.1890.

Anal. Calcd for $C_{14}H_{24}$: C, 87.42; H, 12.58. Found: C, 87.62; H, 12.50.

For **2d** (purified by preparative GC at 155 °C): $^1$H NMR ($CDCl_3$) $\delta$ 4.64 (s, 2 H), 2.25 (dt, $J$ = 12.4, 2.6 Hz, 2 H), 2.00 (dt, $J$ = 13.3, 2.0 Hz, 1 H), 1.74 (t, $J$ = 10.8 Hz, 2 H), 1.65–1.25 (m, 18 H), 1.25–1.10 (m, 2 H), 0.54 (dt, $J$ = 11.0, 10.2 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 149.4, 107.6, 43.2, 37.8, 34.4, 33.2, 25.6, 24.6, 23.5, 22.1; MS $m/z$ ($M^+$) calcd 220.2191, obsd 220.2182.

Anal. Calcd for $C_{16}H_{28}$: C, 87.19; H, 12.81. Found: C, 87.27; H, 12.58.

**General Procedure for Peracid Oxidation of 2.** To a solution of **2d** (45.6 mg) in $CH_2Cl_2$ (3 mL) was added NaOAc (7.6 mg). The mixture was cooled to 0 °C, treated with 0.15 mL of 35% peracetic acid in HOAc, stirred for 15 min, warmed at rt, and agitated for an additional 2 h. The mixture was diluted with ether, washed with $Na_2SO_3$, $K_2CO_3$ (2x), and NaCl solutions, dried, and evaporated. The residue was subjected to column chromatography and gave 46.5 mg (95%) of a 65:35 mixture of **12d** and **11d**.

**General Procedure for Condensation of 1 with $CH_2$=S(O)$(CH_3)_2$.** To a slurry of 60% sodium hydride (30 mg, washed with hexane) in dry DMSO (3 mL) was added $(CH_3)_3S(O)I$ (200 mg). After 30 min of stirring, a solution of **1d** (54 mg) in 10 mL of dry DMSO was introduced and warmed after 15 min to 60 °C for 0.5 h. The cooled reaction mixture was taken up in ether and washed with cold water. The aqueous phase was extracted with ether (2 × 25 mL), and the combined ethereal layers were washed with water and brine prior to drying and evaporation. Column chromatography of the residue gave 49 mg (85%) of **12d**.

For **11b**: oil; $^1$H NMR ($CDCl_3$) $\delta$ 2.34 (s, 2 H), 2.19 (m, 2 H), 2.15 (d, $J$ = 5.2 Hz, 1 H), 2.00–1.70 (m, 9 H), 1.40–1.30 (m, 4 H), 1.12 (dd, $J$ = 14.2, 1.9 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) ppm 55.8, 48.6, 38.3, 32.3, 31.9, 31.8, 26.8, 25.4; MS molecular ion too fleeting to be accurately mass measured.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: 79.99; H, 11.23.

For **11c**: mp 54–56 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 2.37 (s, 2 H), 2.30–2.10 (m, 6 H), 2.00–1.75 (m, 4 H), 1.70–1.15 (m, 10 H), 1.10 (dd, $J$ = 14.1, 2.0 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) ppm 56.3, 49.9, 39.8, 33.3, 29.1, 26.9, 26.1, 23.8, 19.8; MS $m/z$ ($M^+$) calcd 208.1827, obsd 208.1776.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.28; H, 11.69.

For **12b**: mp 39.5–41.0 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.65 (s, 2 H), 2.10–1.90 (m, 5 H), 1.85–1.75 (m, 5 H), 1.45–1.15 (m, 7 H), 1.09 (dd, $J$ = 12.6, 1.7 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 57.3, 55.0, 39.2, 33.5, 32.2, 31.9, 26.8, 25.1; MS $m/z$ ($M^+$) calcd 180.1514, obsd 180.1517.

Anal. Calcd for $C_{12}H_{20}O$: C, 79.94; H, 11.18. Found: C, 80.10; H, 11.21.

For **12c**: mp 89–90 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.70 (s, 2 H), 2.20–2.10 (m, 3 H), 2.02–1.76 (m, 4 H), 1.70–1.20 (series of m, 13 H), 1.11 (dd, $J$ = 12.8, 1.8 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) ppm 56.4, 55.4, 40.8, 34.6, 29.1, 26.3, 26.1, 23.5, 19.6; MS $m/z$ ($M^+$) calcd 208.1827, obsd 208.1840.

Anal. Calcd for $C_{14}H_{24}O$: C, 80.71; H, 11.61. Found: C, 80.85; H, 11.64.

For **12d**: mp 72–74 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.61 (s, 2 H), 2.07 (dt, $J$ = 13.1, 2.3 Hz, 1 H), 1.90–1.73 (m, 2 H), 1.75–1.25 (m, 18 H), 1.25–1.05 (m, 4 H), 0.29 (dt, $J$ = 13.1, 12.3 Hz, 1 H);[47] $^{13}$C NMR ($CDCl_3$) ppm 58.9, 53.6, 41.4, 34.6, 34.3, 33.1, 25.9, 24.3, 23.7, 21.9; MS $m/z$ ($M^+$) calcd 236.2140, obsd 236.2174.

Anal. Calcd for $C_{16}H_{28}O$: C, 81.29; H, 11.94. Found: C, 81.22; H, 11.87.

**General Procedure for Epoxide Reduction.** A solution of the 35:65 mixture of **11d** and **12d** (41.5 mg) in anhydrous ether (4 mL) was added to a suspension of $LiAlH_4$ (60.5 mg) in the same solvent (4 mL). After overnight stirring, standard workup and column chromatography gave 14.9 mg (35%) of **13d** and 27.9 mg (65%) of **14d**.

For **13b**: mp 36–38 °C; $^1$H NMR ($CDCl_3$) $\delta$ 2.20–2.00 (m, 3 H), 1.85–1.75 (m, 6 H), 1.65–1.60 (m, 3 H), 1.35–1.15 (m, 6 H), 1.17 (s, 3 H), 1.03 (br s, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 71.4, 43.2, 35.4, 32.2, 31.9, 31.4, 27.5, 25.5; MS $m/z$ ($M^+$) calcd 182.1671, obsd 182.1705.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 79.40; H, 12.25.

For **13c**: mp 72–74 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 2.50–2.35 (m, 2 H), 2.28 (dt, $J$ = 14.8, 2.0 Hz, 1 H), 1.85–1.20 (series of m, 19 H), 1.18 (s, 3 H), 1.03 (br s, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 71.3, 45.1, 34.8, 33.4, 28.9, 27.0, 25.8, 24.5, 19.7; MS $m/z$ ($M^+$) calcd 210.1984, obsd 210.2004.

Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 79.71; H, 12.47.

For **13d**: mp 86.5–88 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 1.98 (dt, $J$ = 13.2, 2.0 Hz, 1 H), 1.7–1.3 (m, 21 H), 1.27 (s, 3 H), 1.20–1.00 (m, 4 H), 0.10 (dt, $J$ = 13.2, 11.9 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 72.3, 48.9, 35.3, 34.6, 34.4, 27.8, 25.9, 24.7, 23.8, 22.4; MS $m/z$ ($M^+$) calcd 238.2297, obsd 238.2295.

Anal. Calcd for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.60; H, 12.62.

For **14b**: mp 61–62 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 1.96 (m, 2 H), 1.83 (d, $J$ = 14.4 Hz, 1 H), 1.78–1.50 (m, 10 H), 1.50–1.35 (m, 6 H), 1.34 (s, 3 H); $^{13}$C NMR ($CDCl_3$) ppm 70.4, 43.4, 33.8, 33.2, 30.9, 30.1, 26.2, 24.0; MS $m/z$ ($M^+$) calcd 182.1671, obsd 182.1694.

Anal. Calcd for $C_{12}H_{22}O$: C, 79.06; H, 12.16. Found: C, 78.30; H, 12.13.

For **14c**: mp 118–119 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 2.16 (br d, $J$ = 14.9 Hz, 1 H), 1.90–1.75 (m, 6 H), 1.68–1.40 (m, 14 H), 1.42 (s, 3 H), 1.35–1.22 (m, 2 H); $^{13}$C NMR ($CDCl_3$) ppm 70.2, 46.9, 34.2, 32.7, 29.3, 26.4, 25.0, 24.5, 19.9; MS $m/z$ ($M^+$) calcd 210.1984, obsd 210.2018.

Anal. Calcd for $C_{14}H_{26}O$: C, 79.94; H, 12.46. Found: C, 80.00; H, 12.45.

For **14d**: oil; $^1$H NMR ($CDCl_3$) $\delta$ 2.02 (dt, $J$ = 12.8, 2.2 Hz, 1 H), 1.80–1.25 (series of m, 21 H), 1.22 (s, 3 H), 1.10–0.97 (m, 4 H), 0.08 (dt, $J$ = 12.8, 11.8 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 71.5, 47.4, 34.5, 34.4, 32.4, 31.9, 26.1, 24.5, 23.9, 22.1; MS $m/z$ ($M^+$) calcd 238.2300, obsd 238.2281.

Anal. Calcd for $C_{16}H_{30}O$: C, 80.61; H, 12.68. Found: C, 80.47; H, 12.86.

**General Procedure for the CuCN-Catalyzed Cross-Coupling of Epoxides with *n*-PrMgBr.** To a mixture of **12d** (14.3 mg) and CuCN (9.8 mg) in 5 mL of anhydrous THF (5 mL) at −20 °C was added *n*-propylmagnesium bromide (0.25 mL of 2.0 M). The reaction mixture was gradually warmed to rt during 3 h, quenched with $NH_4Cl$, diluted with ether, and washed with water and $NaHCO_3$ and NaCl solutions. Drying, filtration, and solvent evaporation gave an oily residue, which upon purification by column chromatography gave 13.5 mg (80%) of **9d**.

**General Procedure for Osmylation/Cyclization.** To a solution of **2d** (42 mg) in acetone (1 mL) was added 3 mL of 0.1 N $OsO_4$ in *tert*-butyl alcohol. The reaction mixture was stirred overnight, diluted with water, treated with sodium dithionite, and filtered through a plug of Celite. The filtrate was diluted with ethyl acetate and washed with $Na_2SO_3$ solution. The aqueous phase was reextracted with ethyl acetate, and the combined organic solutions were washed with brine, dried, and evaporated. Column chromatography of the residue afforded 39.6 mg (82%) of **15** and **16** as a 7:3 mixture of diastereomers.

A solution of the above material in pyridine (2 mL) was cooled to 0 °C, treated with *p*-toluenesulfonyl chloride (32.9 mg), and placed in a refrigerator overnight. The reaction mixture was poured into ice-cold water and extracted with ether. The ethereal phase was washed with cold 1 N HCl until acidic and then with water and brine, dried, and evaporated. The residue (62.6 mg) was taken up in methanol (6 mL) containing $K_2CO_3$ (50.1 mg) and shaken. After 10 min, the product was extracted into ether, rinsed with water and brine, dried, and chromatographed. There was obtained a 7:3 mixture of **11d** and **12d** (18.3 mg, 59%).

**Osmylation of 2b.** A solution of **2b** (49.1 mg, 0.3 mmol) in acetone (2 mL) was treated with 3.4 mL of 0.1 N $OsO_4$ (in *t*-

(47) A peak characteristic of **11d** appears at $\delta$ 2.57.

BuOH), stirred for 20 h, and diluted with water (1 mL). Solid $Na_2S_2O_4$ was introduced, and after 1 h the mixture was filtered through Celite and extracted with ethyl acetate (2 × 20 mL). The combined organic layers were washed with brine, dried, and concentrated. Chromatography of the residue gave 44.4 mg (75%) of **16b**.

For **16b**: mp 71–72 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 3.48 (s, 2 H), 2.74 (s, 2 H), 2.05–1.90 (m, 2 H), 1.83 (d, $J$ = 14.4 Hz, 1 H), 1.75–1.15 (series of m, 15 H); $^{13}$C NMR ($CDCl_3$) ppm 72.7, 72.0, 37.8, 33.6, 30.1, 29.7, 26.5, 23.7; MS $m/z$ ($M^+ - H_2O$) calcd 180.1514, obsd 180.1525.

Anal. Calcd for $C_{12}H_{22}O_2$: C, 72.68; H, 11.18. Found: C, 72.60; H, 11.19.

For **16c**: mp 110–111 °C (from hexane); $^1$H NMR ($CDCl_3$) $\delta$ 3.65 (s, 2 H), 2.60 (s, 2 H), 2.18 (d, $J$ = 12.7 Hz, 1 H), 1.95–1.80 (m, 2 H), 1.78–1.63 (m, 6 H), 1.60–1.40 (m, 11 H), 1.38–1.25 (m, 2 H); $^{13}$C NMR ($CDCl_3$) ppm 72.4, 71.2, 41.2, 33.4, 29.7, 26.5, 24.9, 24.3, 19.9; MS $m/z$ ($M^+$) calcd 226.1933, obsd 226.1976.

Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.28; H, 11.63.

**Oxymercuration of 2d.** Mercuric acetate (70.1 mg) was added to water (0.2 mL) and THF (0.2 mL). After dissolution during 15 min, **2d** (52.1 mg) was introduced and rinsed in with 0.2 mL of THF. After 10 min, addition of 4 M NaOH (0.3 mL) was followed by addition of 20 mg of $NaBH_4$ dissolved in 0.5 mL of 4 M NaOH. The reaction mixture was stirred for 2 h, decanted from the mercury pool, diluted with ether, washed with brine, and dried. After filtration and solvent evaporation, column chromatography afforded 37.7 mg of **14d** and 12.0 mg of **13d** (88% combined yield).

**Allylic Bromination of 2b.** To a solution of **2b** (50 mg) in DMSO (1 mL) and water (13 $\mu$L) was added 107.5 mg of NBS. After 15 min, the reaction mixture was taken up in ether, washed with $NaHCO_3$ solution, water, and brine, then dried and evaporated. There was isolated 59.6 mg (82%) of **18** as a colorless oil; $^1$H NMR ($C_6D_6$) $\delta$ 5.52 (br s, 1 H), 3.65 (d, $J$ = 9.5 Hz, 1 H), 3.61 (d, $J$ = 9.5 Hz, 1 H), 2.20 (dt, $J$ = 17.2, 2.9 Hz, 1 H), 2.20–2.00 (m, 2 H), 1.75–1.00 (series of m, 13 H); $^{13}$C NMR ($C_6D_6$) ppm 132.9, 131.9, 40.2, 34.8, 33.1, 31.6, 30.9, 30.6, 30.4, 25.7, 24.8, 23.4; MS $m/z$ ($M^+$) calcd 242.0670, obsd 242.0622.

**Carboxaldehyde 19.** To a mixture of iodine (261.7 mg) in THF (4 mL) was added water (1 mL), silver(I) oxide (245.6 mg), and **2b** (49.8 mg). After 30 min, the reaction mixture was filtered, taken up in ether, washed with $Na_2SO_3$, water, and brine, then dried. Filtration, rotary evaporation, and chromatography afforded 26.5 mg (50%) of **19**. An analytical sample was secured by preparative GC at 115 °C: IR (neat, cm$^{-1}$) 1670; $^1$H NMR ($CDCl_3$) $\delta$ 9.45 (s, 1 H), 6.78 (d, $J$ = 4.6 Hz, 1 H), 2.58 (dt, $J$ = 13.0, 6.5 Hz, 1 H), 2.50–1.9 (m, 5 H), 1.80–1.30 (m, 9 H), 1.08 (dt, $J$ = 13.0, 8.0 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 195.1, 156.0, 138.5, 34.0, 32.3, 30.6, 30.2, 29.4, 27.8, 25.8, 24.6, 23.4.

Anal. Calcd for $C_{12}H_{18}O$: C, 80.85; H, 10.18. Found: C, 80.61; H, 10.15.

**Chlorosulfonyl Isocyanate Additions.** A solution of **2b** (51.9 mg, 0.31 mmol) in ether (2 mL) was treated with CSI (0.15 mL) and stirred for 20 h. Saturated $Na_2SO_3$ solution (4 mL) was added slowly along with several drops of 10% NaOH. The two-phase system was stirred vigorously for 15 min, the ether phase was separated, and the aqueous layer was extracted with ether. The combined organic solutions were washed with brine, dried, and evaporated. The residue was chromatographed to give 37.5 mg (58%) of **20b**, mp 132–133 °C (from hexane): IR (KBr, cm$^{-1}$) 3250–3050, 1750–1680; $^1$H NMR ($CDCl_3$) $\delta$ 5.93 (br s, 1 H), 2.86 (s, 2 H), 2.08 (br d, $J$ = 14.4 Hz, 1 H), 2.25–1.87 (m, 3 H), 1.87–1.70 (m, 8 H), 1.47–1.10 (m, 6 H); $^{13}$C NMR ($CDCl_3$) ppm 167.6, 52.6, 51.5, 41.8, 32.7, 31.8, 30.8, 26.6, 25.2; MS $m/z$ ($M^+$) calcd 207.1623, obsd 207.1637.

Anal. Calcd for $C_{13}H_{21}NO$: C, 75.32; H, 10.21. Found: C, 74.86; H, 10.07.

In a similar fashion, **2d** (46.3 mg, 0.21 mmol) was reacted with 0.1 mL of CSI to give 27.9 mg (50%) of **20d** and 10.5 mg (19%) of **21d**.

For **20d**: mp 154–156 °C (from hexane); IR (KBr, cm$^{-1}$) 3300–3000, 1675; $^1$H NMR ($CDCl_3$) $\delta$ 6.43 (br s, 1 H), 2.65 (d, $J$ = 1.5 Hz, 2 H), 2.05 (br d, $J$ = 14.5 Hz, 1 H), 1.75–1.30 (m, 22 H), 1.20–1.05 (m, 2 H), 0.27–0.17 (m, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 168.1, 56.0, 49.1, 44.4, 34.5, 34.0, 33.8, 25.8, 24.4, 23.6, 21.9; MS $m/z$ ($M^+$) calcd 263.2249, obsd 263.2232.

Anal. Calcd for $C_{17}H_{29}NO$: C, 77.51; H, 11.10. Found: C, 77.35; H, 11.14.

For **21d** (not obtained pure): $^1$H NMR ($CDCl_3$) characteristic signals at $\delta$ 5.93 and 2.63; $^{13}$C NMR ($CDCl_3$) ppm 168.2, 55.9, 49.4, 45.2, 44.6, 35.2, 34.1, 33.9, 25.9, 24.4, 22.1.

**Dichloroketene Cycloadditions.** A mixture of **2b** (52.0 mg, 0.31 mmol) and zinc–copper couple (40 mg) in anhydrous ether (5 mL) was gently refluxed while a solution of trichloroacetyl chloride (0.06 mL) in ether (5 mL) was introduced via a syringe pump during 30 min. After an additional 4 h of heating, the reaction mixture was cooled, filtered, and evaporated. The residue was taken up in hexane, washed with $NaHCO_3$ and brine solutions, dried, and again evaporated. Chromatographic purification gave 60.5 mg (79%) of **22b** and 16.1 mg (21%) of **23b**.

For **22b**: mp 124–127 °C (from hexane); IR (KBr, cm$^{-1}$) 1800; $^1$H NMR ($CDCl_3$) $\delta$ 3.34 (s, 2 H), 2.17 (br d, $J$ = 14.5 Hz, 1 H), 2.05–1.99 (m, 4 H), 1.83–1.73 (m, 7 H), 1.38–1.26 (m, 6 H); $^{13}$C NMR ($CDCl_3$) ppm 194.4, 96.5, 56.3, 42.7, 38.0, 32.4, 32.0, 31.4, 26.6, 25.3; MS molecular ion too fleeting to be accurately mass measured.

Anal. Calcd for $C_{14}H_{20}Cl_2O$: C, 61.10; H, 7.33. Found: C, 61.09; H, 7.37.

For **23b** (not obtained pure): $^1$H NMR ($CDCl_3$) characteristic signal at $\delta$ 3.13; $^{13}$C NMR ($CDCl_3$) ppm 193.5, 98.0, 55.4, 44.8, 36.5, 34.5, 29.7, 28.4, 25.8, 22.9.

In similar fashion, 50.0 mg (0.23 mmol) of **2d** was reacted with 52.5 mg of zinc–copper couple and 0.06 mL of trichloroacetyl chloride to give 64.7 mg (85%) of **22d** and 9.9 mg (13%) of **23d**.

For **22d**: mp 92–94 °C (from hexane); IR (KBr, cm$^{-1}$) 1795; $^1$H NMR ($CDCl_3$) $\delta$ 2.96 (s, 2 H), 2.20 (d, $J$ = 13.5 Hz, 2 H), 2.12 (dt, $J$ = 12.8, 2.2 Hz, 1 H), 1.85–1.70 (m, 2 H), 1.67–1.33 (m, 16 H), 1.26 (dd, $J$ = 13.5, 12.3 Hz, 2 H), 1.09 (br t, $J$ = 11.5 Hz, 2 H), 0.26 (dt, $J$ = 12.8, 11.5 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) ppm 194.3, 92.1, 55.2, 47.0, 43.2, 34.5, 34.1, 33.9, 25.9, 24.5, 23.7, 21.9.

Anal. Calcd for $C_{18}H_{28}Cl_2O$: C, 65.25; H, 8.52. Found: C, 65.26; H, 8.51.

For **23d** (not obtained pure): $^1$H NMR ($CDCl_3$) characteristic signal at $\delta$ 3.04; $^{13}$C NMR ($CDCl_3$) obvious peaks at ppm 98.5, 53.5, 46.8, 41.2, 34.2, 33.8, 21.9.

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**Registry No.** **1a**, 10036-09-6; **1b**, 77188-49-9; **1b** semicarbazone, 137495-54-6; **1c**, 137495-23-9; **1d**, 51388-41-1; **2a**, 19437-17-3; **2b**, 137515-56-1; **2c**, 137495-24-0; **2d**, 137495-25-1; **5a**, 10036-10-9; **5b**, 137495-26-2; **5c**, 137495-27-3; **5d**, 137495-28-4; **6a**, 10036-08-5; **6b**, 137495-29-5; **6c**, 137567-49-8; **6d**, 137567-50-1; **7b**, 137495-30-8; **7c**, 137495-31-9; **7d**, 137495-32-0; **8b**, 137495-33-1; **8c**, 137622-84-5; **8d**, 137495-34-2; **9b**, 137495-35-3; **9c**, 137567-51-2; **9d**, 137567-52-3; **10b**, 137495-36-4; **10c**, 137495-37-5; **10d**, 137567-53-4; **11b**, 137495-38-6; **11c**, 137495-39-7; **11d**, 137495-40-0; **12b**, 137567-54-5; **12c**, 137567-55-6; **12d**, 137567-56-7; **13b**, 137495-41-1; **13c**, 137495-42-2; **13d**, 137495-43-3; **14b**, 137495-44-4; **14c**, 137567-57-8; **14d**, 137567-58-9; **15d**, 137567-63-6; **16d**, 137495-45-5; **16c**, 137495-46-6; **16d**, 137495-47-7; **18**, 137495-48-8; **19**, 137495-49-9; **20b**, 137495-50-2; **20d**, 137495-51-3; **21b**, 137567-59-0; **21d**, 137567-60-3; **22b**, 137495-52-4; **22d**, 137495-53-5; **23b**, 137567-61-4; **23d**, 137567-62-5.

**Supplementary Material Available:** Crystallographic details, crystallographic experimental procedures, and tables of final positional and anisotropic positional parameters, bond lengths, and bond angles for **1b** semicarbazone, **1c**, **1d**, **10d**, and **20d** (46 pages). Ordering information is given on any current masthead page.