Analysis of the Conformational Nature, Resolvability, and Thermal Racemization of Hetero 2,3-Dispiro Cyclohexanones. The Weighting of Carbonyl/C-X Stabilization Relative to the Electronic Interaction between the Vicinal Electronegative Substituents

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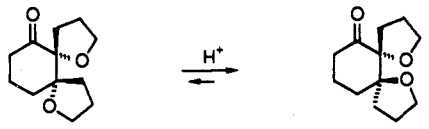
Received August 4, 1993. Revised Manuscript Received November 22, 1993®

Abstract: A series of hetero 2,3-dispiro cyclohexanones has been prepared. The conformations of the syn and anti isomers were assessed in the solid state, in solution, and in the gas phase (the latter by molecular mechanics calculations). The results are discussed in the light of steric, dipole, and gauche interactions; steric contributions give evidence of controlling ΔG_{eq}. On a different front, the syn/anti pairs were found to interconvert when heated in the presence of a catalytic amount of acid. Three representative examples of these chiral molecules were resolved and complete racemization was observed to result under the conditions of equilibration. A push-pull fragmentation of the cyclohexanone ring is proposed to account for these observations, with the tethered oniom ion–enol pair reclosing to reconstitute the original, although stereochemically scrambled, structure. The intervention of the thionium ion intermediates is less thermodynamically favorable than that of oxonium ions, as expected.

Recent development of the oxonium ion-initiated pinacol rearrangement[3] as a tool for the directed synthesis of polyspirocyclic tetrahydrofurans[4] has resulted in the discovery of a concise synthetic entry to the hetero 2,3-dispiro cyclohexanes **1** and **2**.

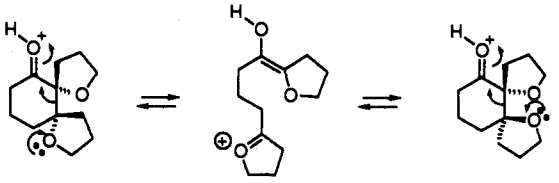


1 **2**

When heated in chloroform solution containing a catalytic quantity of *p*-toluenesulfonic acid, **1** and **2** undergo mutual equilibration, ultimately favoring **2** at equilibrium (K_{eq} = syn/anti = 0.56).[5] This reversible chemical transformation constitutes an epimerization that operates within a framework constructed of two vicinal quaternary carbon centers.

One possible way to rationalize this isomerization on mechanistic grounds is to invoke a push-pull fragmentation involving electron flow from the β-oxido atom to the protonated carbonyl as in **3**. The tethered oxonium ion–enol pair **4** results (Scheme 1). Rotation of either terminus of the chain relative to the other prior to intramolecular recyclization provides the enabling means for losing stereochemical "memory".

Scheme 1



3 **4** **5**

Several facets of this pathway invite systematic investigation. For example, since both **1** and **2** are chiral while **4** is not, optically enriched samples of either ketone should experience racemization under the conditions of equilibration. The issue of heteroatom dependence also surfaces. Are both oxygens necessary? What observable kinetic consequences would accompany systematic replacement by sulfur? Another concern is whether the electron flow depicted in **3** and **5** is more favorable when the C–O or (see below) C–S bond is projected axially or equatorially.

We now report an extended study of several congeners of **1** and **2** that defines their conformational properties in the solid (by crystallographic analysis), liquid (by NMR methods), and gaseous states (by molecular mechanics calculations). Several of these dispiro cyclohexanones have been resolved and subsequently isomerized to determine if racemization operates concurrently. Finally, consideration is given to a pair of electronic interactions that necessarily operate in these molecules. The first is the interaction that occurs between the carbonyl group and the immediately neighboring hetero atom. Also relevant are the lone-pair interactions between the electronegative substituents themselves, a dihedral angle dependence which has previously been recognized.[6] These effects may operate cooperatively or be inimical to each other. When the latter condition prevails, it becomes possible to gain an appreciation of which interaction is overriding.

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® Abstract published in *Advance ACS Abstracts*, January 1, 1994.

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(3) Paquette, L. A.; Lawhorn, D. E.; Teleha, C. A. *Heterocycles* **1990**, *30*, 765.

(4) (a) Negri, J. T.; Rogers, R. D.; Paquette, L. A. *J. Am. Chem. Soc.* **1991**, *113*, 5073. (b) Paquette, L. A.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3947.

(5) Paquette, L. A.; Andrews, J. F. P.; Vanucci, C.; Lawhorn, D. E.; Negri, J. T.; Rogers, R. D. *J. Org. Chem.* **1992**, *57*, 3956.

(6) Reviews: (a) Wolfe, S. *Acc. Chem. Res.* **1972**, *5*, 102. (b) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 3193.

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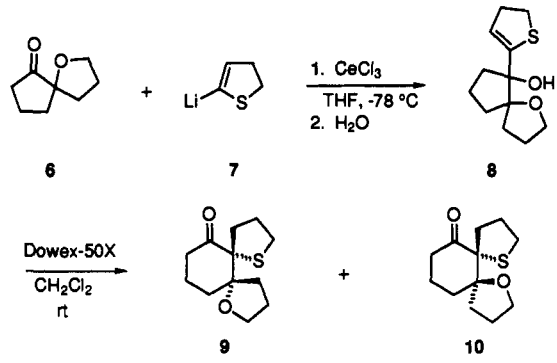
Scheme 2



6 7 8 9 10

Results

Synthetic Considerations. The preparation of monospirocyclic ketone **6** has been described previously.[4b] The conversion of this intermediate to **9** and **10** demanded that 2,3-dihydrothiophene be capable of C-5 metalation as in **7** and that carbinol **8** be amenable to conversion to its thionium ion as a prelude to Wagner–Meerwein 1,2-shift (Scheme 2). The method developed by Sosnovsky for the synthesis of 2,3-dihydrothiophene was adopted.[7] Our expectation that the deprotonation of this unstable heterocycle to give **7** would be uncomplicated was founded on the ease with which acyclic vinyl sulfides undergo α-proton abstraction with alkyllithium reagents.[8] Indeed, the conversion to **7** with *tert*-butyllithium in THF at −78 °C proceeded as readily as that with 2,3-dihydrofuran.[9] Conversion to the vinyl cerate was implemented so as to curb nonproductive enolization.[10]

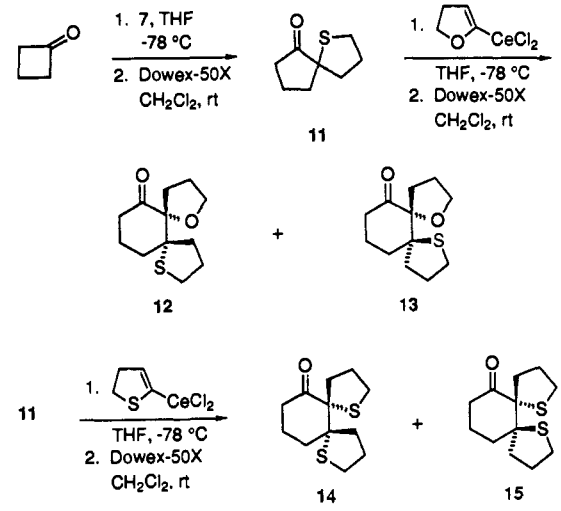
Thionium ions are known to play a useful role in electrophilic aromatic substitution reactions and are considered to be less stabilized and more electrophilic than oxonium ions.[11,12] Notwithstanding, when **8** was stirred with Dowex 50X resin in CH_2Cl_2 at room temperature for 24 h, isomerization to a 1:4.4 mixture of **9** and **10** occurred. The less polar anti isomer was readily separated from its syn counterpart by silica gel chromatography. As will be discussed, the stereochemical assignments to these ketones follow from definitive spectroscopic and crystallographic evidence.

In approaching a synthesis of the regioreversed isomers **12** and **13**, we focused again upon sequential introduction of the hetero spirocyclic rings, with initial acquisition of **11**. This ketone is readily obtained by exposure of commercially available cyclobutanone to **7** and subsequent acid-catalyzed rearrangement as before (Scheme 3). The second-stage ring expansion proceeded with high efficiency (96% combined yield) to deliver a more equitable distribution of the syn and anti stereoisomers (1:1.24).

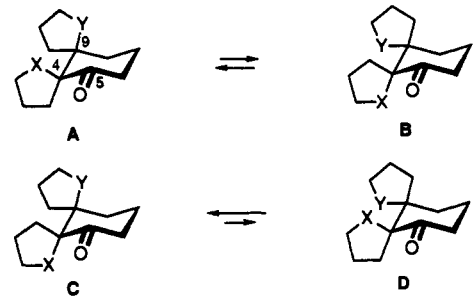
When **11** was reacted instead with the dihydrothiophene cerium reagent[13] and the resulting carbinol exposed to Dowex-50X resin, **14** and **15** were produced without complication (68%, ratio 1:1.2).

Solid-State Structural Studies. The X-ray-derived three-dimensional features of **1** have been reported earlier.[4b] This

Scheme 3



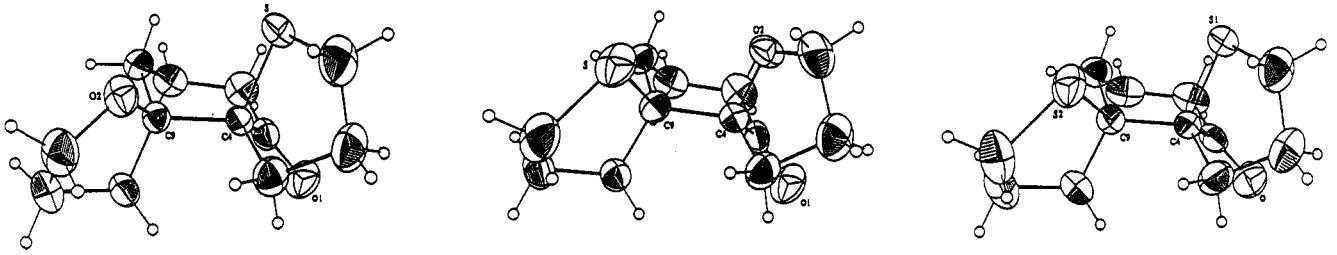
analysis established that its cyclohexanone core adopts a well-defined chairlike arrangement. However, in contrast to expectations based upon the minimization of electrostatic interactions between the carbonyl group and the flanking polar C—O bond,[14,15] the α-electronegative substituent was disposed equatorially. Adoption of this arrangement demands, of course, that the β C—O linkage be projected axially as in **A** (X = Y = O).[16] Diastereomer **2** could not be induced to crystallize.



All six ketones prepared in the course of this investigation proved to be highly crystalline solids well suited to X-ray crystallographic analysis. Several intriguing structural features have been made evident as a result. As seen in Figure 1, the syn isomers **9**, **12**, and **14** do *not* share with **1** a common preference for conformation **A**. Rather, all three ketones feature an axial α-hetero substituent as in **B**, irrespective of whether X represents oxygen or sulfur. One consequence of this behavior is the mandatory equatorial disposition of Y. The relevant X–C–C–Y dihedral angles adopted across the syn series (see Table 1) are informative in connection with the gauche effect,[6] as discussed subsequently. Inspection of the crystallographic data indicates further that when X is axially oriented, the bond linking the carbonyl group to C-4 is approximately the same length as that seen in the lone equatorial example **1** (Table 1). In line with precedent, the interconnective carbon–carbon bonds in the X–C–C–Y units become longer as the progressive change from oxygen to sulfur is made.

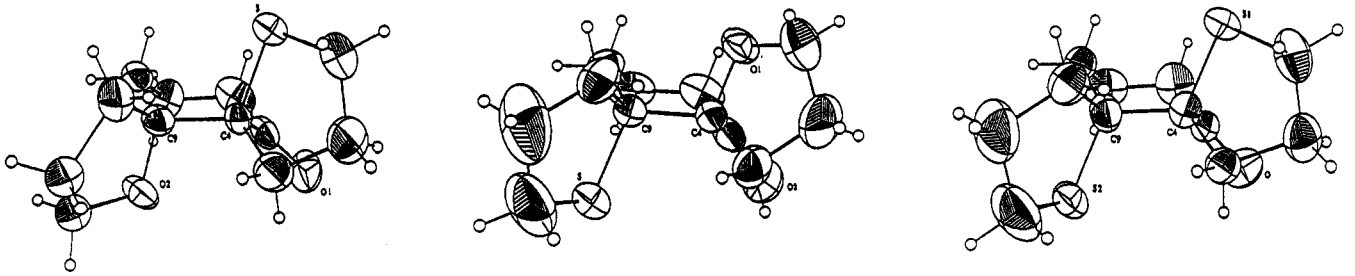
(7) Sosnovsky, G. *Tetrahedron* **1962**, *18*, 15, 903.
(8) (a) Oshima, K.; Shimozi, K.; Takahashi, H.; Yamamoto, H.; Nozaki, H. *J. Am. Chem. Soc.* **1973**, *95*, 2694. (b) Cookson, R. C.; Parsons, P. J. *J. Chem. Soc., Chem. Commun.* **1976**, 990. (c) Vlattas, I.; Della Vecchia, L.; Lee, A. O. *J. Am. Chem. Soc.* **1976**, *98*, 2008. (d) Harirchian, B.; Magnus, P. *J. Chem. Soc., Chem. Commun.* **1977**, 522. (e) Schmidt, R. R.; Schmid, B. *Tetrahedron Lett.* **1977**, 3583.
(9) Boeckman, R. K.; Bruza, K. J. *Tetrahedron Lett.* **1977**, 4187.
(10) (a) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392. (b) Paquette, L. A.; He, W.; Rogers, R. D. *J. Org. Chem.* **1989**, *54*, 2291 and relevant references cited therein.
(11) (a) Trost, B. M.; Mikhail, G. K. *J. Am. Chem. Soc.* **1987**, *109*, 4124. (b) Trost, B. M.; Sato, T. *J. Am. Chem. Soc.* **1985**, *107*, 719. (c) Trost, M. B.; Murayama, E. *Tetrahedron Lett.* **1982**, *23*, 1047.
(12) Paquette, L. A.; Dullweber, U.; Branan, B. M. *Heterocycles*, in press.
(13) The cerates are depicted as dichloro derivatives in order to reflect the approximate stoichiometry associated with their preparation. For a discussion of the probable structure of organocerium reagents, see: Denmark, S. E.; Edwards, J. P.; Nicaise, O. *J. Org. Chem.* **1993**, *58*, 569.
(14) (a) Eliel, E. L.; Allinger, N. L.; Angyal, S. Y.; Morrison, C. A. *Conformational Analysis*; Interscience: New York, 1965; pp 460–469. (b) Lambert, J. B. In *The Conformational Analysis of Cyclohexenes, Cyclohexadienes, and Related Hydroaromatic Compounds*; Rabideau, P., Ed.; VCH: Weinheim, Germany, 1989; Chapter 2.
(15) Denmark, S. E.; Dappen, M. S.; Sear, N. L.; Jacobs, R. T. *J. Am. Chem. Soc.* **1990**, *112*, 3466 and relevant references cited therein.
(16) This projection is drawn enantiomerically to those illustrated two-dimensionally in the schemes in order to facilitate viewing of the molecules. The crystallographic studies were performed on the racemic compounds; the ORTEP diagrams also depict the enantiomeric structural formulas. The numbering scheme is arbitrary but consistent throughout the entire series of dispiro ketones.

A. Syn series:



9 12 14

B. Anti series:



10 13 15

Figure 1. Computer-generated perspective drawings of the hetero 2,3-dispiro cyclohexanones as determined by X-ray crystallography.

Table 1. Relevant Crystallographic Details[a]

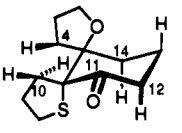
	X–C–C–Y dihedral angle, deg	bond lengths, Å			
		C(4)–C(5)	C(4)–C(9)	X–C(4)	Y–C(9)
		Syn Series			
1	57.3	1.536(3)	1.526(3)	1.423(3)	1.453(3)
9	–60.4	1.525(9)	1.557(3)	1.858(3)	1.426(2)
12	–58.0	1.539(5)	1.545(5)	1.444(4)	1.848(3)
14	–56.9	1.535(4)	1.554(3)	1.859(3)	1.848(3)
		Anti Series			
10[b]	–176.4	1.54(2)	1.55(1)	1.84(1)	1.45(1)
13	–178.1	1.536(7)	1.545(6)	1.457(5)	1.844(4)
15[b]	–176.1	1.540(7)	1.541(7)	1.804(4)	1.811(4)

[a] See representation A for atomic numbering. [b] Significant disorder observed.

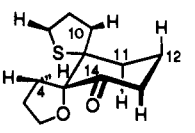
It is noteworthy that the structural results involving anti isomers **10**, **13**, and **15** constitute a cohesive conformational profile in which a well-defined cyclohexanone chair uniformly has both electronegative atoms oriented axially as in **C**. Although crystal packing forces must be considered, the uniformity of solid-state conformation suggests that steric and electronic factors combine to render **C** more thermodynamically stable than **D**.

Both C–S bond lengths in **15** are considerably shorter than they are in **14** and the other sulfur-containing congeners (Table 1). This may be a reflection of the significant disorder encountered in **10** and **15**.

Solution Conformational Studies.[17] Although the ^{1}H NMR spectra of the ketone pair **9**/**10** in both $CDCl_3$ and C_6D_6 at 300 MHz exhibit considerable overlap, each revealed vicinal coupling patterns indicative for adoption of a unique chair-like cyclohexanone conformation, i.e., clearly distinguished axial (diaxial ^3J = 12–14 Hz) and equatorial (all ^3J = 2–5 Hz) protons. Chair-like conformations are further supported by diagnostic W-couplings between the equatorial cyclohexanone α- and γ-protons in both compounds (12-H_{eq}/14-H_{eq}, $^4J_{H,H}$ = 1.5–2 Hz). Additionally, the deshielding experienced by the axial six-membered ring protons relative to their geminal equatorial partners provided key information about the disposition of the heteroatoms. In both compounds, significant deshielding of the axial protons α to the carbonyl is observed (For **9**: 12-H_{ax}/δ 2.98, 12-H_{eq}/δ 2.24. For **10**: 12-H_{ax}/δ 2.86, 12-H_{eq}/δ 2.28). This phenomenon is construed to be a clear indication of their 1,3-diaxial relationship to the sulfur atom. A similar deshielding operates on the axial β-proton in **10** (13-H_{ax}/δ 1.90, 13-H_{eq}/δ 1.34) as a consequence of its 1,3-diaxial relationship to the ether oxygen (see **E**). The corresponding effect is absent in **9** (13-H_{ax}/δ 1.42, 13-H_{eq}/δ 1.84).



E



F

In line with these assignments, both compounds show a very large chemical shift anisotropy of the geminal pair of protons in the γ-position of the tetrahydrothiophene ring (For **9**: 10-H_{exo}/δ 2.46, 10-H_{endo}/δ 1.64. For **10**: 10-H_{exo}/δ 2.82, 10-H_{endo}/δ 1.26). This effect results from placement of the respective exo proton on the equatorially oriented C-10 methylene group directly in the deshielding core of the carbonyl group.

Although the remaining protons of **9** and **10** could be located by DQF-COSY and HETCOR methods, signal overlap precluded detailed investigation of NOE interactions involving most of the stereochemically relevant protons. Nevertheless, two diagnostic enhancements were observed for **10** that confirm the two heterocyclic rings to be fixed anti as depicted in **E**: H-10_{endo}-{H-4_{endo}} = 1.5% and H-4_{endo}{H-10_{endo}} = 1%. Ketone **9** lacked the corresponding enhancements.

(17) The numbering schemes used in this section follow the systematic nomenclature (see Experimental Section) and are indicated in the representative structures **E** and **F**, respectively.

The fairly crowded ^{1}H NMR spectra of **14** and **15** could be fully assigned from 400-MHz DQF-COSY and HMQC spectra in C_6D_6 solution. As before, unique chair-like conformations of their cyclohexanone cores were obvious from distinctive vicinal coupling patterns and significant W-coupling (12-H_{eq}/14-H_{eq}, $^4J_{H,H}$ = 2 Hz). For both compounds, significant deshielding of the axial cyclohexanone α- and γ-protons (For **14**: 12-H_{ax}/δ 2.96, 12-H_{eq}/δ 2.12; 14-H_{ax}/δ 2.26, 14-H_{eq}/δ 1.84. For **15**: 12-H_{ax}/δ 2.89, 12-H_{eq}/δ 2.26; 14-H_{ax}/δ 1.88, 14-H_{eq}/δ 1.65) and the large shift anisotropy of those tetrahydrothiophene γ-protons proximal to the carbonyl (For **14**: 10-H_{exo}/δ 2.66, 10-H_{endo}/δ 1.97. For **15**: 10-H_{exo}/δ 3.08, 10-H_{endo}/δ 1.43) serve to define axial orientation of the sulfur atom α to the carbonyl.

In line with these assignments, deshielding by a 1,3-diaxial relationship to sulfur is also observed for the axial cyclohexanone β-proton in **15** (13-H_{ax}/δ 1.90, 13-H_{eq}/δ 1.44). This effect is absent in **14** (13-H_{ax}/δ 1.21, 13-H_{eq}/δ 1.28), where the respective heteroatom is oriented equatorially, as is further confirmed by a diagnostic W-coupling (14-H_{ax}/δ 2.26, 14-H_{endo}/δ 1.29; $^4J_{H,H}$ = 1 Hz) that requires axial attachment of the C-4 methylene group. Supporting NOE studies were not feasible for **14** and **15**, since all of the more relevant protons are located in highly crowded regions of their ^{1}H NMR spectra.

The 300-MHz ^{1}H NMR spectrum of **12** in C_6D_6 solution was sufficiently well resolved to permit detailed conformational analysis following its complete assignment based on DQF-COSY, RCT-COSY, and HETCOR methods. Again, characteristic vicinal coupling patterns and well-defined W-coupling (11-H_{eq}/13-H_{eq}, $^4J_{H,H}$ = 2 Hz) served to define a unique chair-like cyclohexanone conformation. As before, a further W-coupling ($^4J_{H,H}$ = 1.5 Hz) involving 11-H_{ax} (δ 2.46) and 10-H_{endo} (δ 1.13) is considered diagnostic for axial attachment of the associated methylene group and thus for equatorial orientation of the sulfur atom.

In further confirmation of the **F** geometry, axial protons 13-H_{ax} (δ 2.90) and 11-H_{ax} (δ 2.46) are strongly deshielded relative to 13-H_{eq} (δ 2.03) and 11-H_{eq} (δ 1.66), as a result of the close proximity of the first pair to oxygen. The chemical shift of 4-H_{exo} (δ 2.56) relative to 4-H_{endo} (δ 1.84) requires it to be experiencing strong carbonyl anisotropy. Finally, the observation of the transannular NOE interactions H-4$_{exo}${H-10$_{endo}$}, H-4$_{endo}${H-10$_{endo}$}, H-10$_{endo}${H-4$_{endo}$}, and H-8$_{endo}${H-4$_{endo}$} (all at approximately 2%) is in complete agreement with the chemical shift and scalar coupling arguments given above.

In all of the above examples where a strong preference for conformations **B** and **C** is obvious, the structures adopted in solution appear essentially identical to those present in the solid state.

In contrast, the dioxygen compounds **1** and **2** clearly do not adopt unique chair-like conformations in solution. For both compounds, the observed vicinal coupling patterns reflect the time averaging of the axial and equatorial positions in the cyclohexanone core (For **1**: 12-H, δ 2.69, J = 9.5, 6.5 Hz; 12′-H, δ 2.06, J = 6.5, 6.5 Hz; 13-H, δ 1.71, J = 6.5, 6.5, 6.5, 5 Hz; 13′-H, δ 1.14, J = 10, 9.5, 5.5, 4.5 Hz; 14-H, δ 2.05, J = 10, 5 Hz; 14′-H, δ 1.32, J = 6.5, 4.5 Hz. For **2**: 12-H, δ 2.47, J = 8, 5.5 Hz; 12′-H, δ 2.12, J = 8, 5.5 Hz; 14-H, δ 1.70, J = 8, 4 Hz). Furthermore, several broad resonances in the ^{1}H NMR spectrum of **1** at 25 °C (400 MHz/C_6D_6) that sharpen upon warming to 60 °C provide direct evidence for a dynamical exchange process. Evaluation of the coupling information available for **1** permits attribution of greater axial character to H-12, H-13′, and H-14. The downfield shifts of H-12 (vs H-12′) and H-14 (vs H-14′) and the contrasting upfield position of H-13′ (vs H-13) combine to indicate a preference of **1** in solution for conformation **B** with an axially oriented α-heteroatom. The alternative option **A** is preferred in the solid state.

Table 2. MM2-Derived Strain Energies and Total Energies for the Two Chair Conformations on the Hetero 2,3-Dispiro Cyclohexanones

compd	conformer	ΔE_{strain}, kcal/mol	ΔE_{total}, kcal/mol
		Syn Series	
1	**A**	14.7	31.6
	B	12.5	29.4
9	**A**	17.3	28.8
	B	13.4	24.8
12	**A**	15.0	26.5
	B	12.8	24.3
14	**A**	15.7	22.7
	B	12.6	19.7
		Anti Series	
2	**C**	11.7	28.6
	D	15.4	32.3
10	**C**	12.4	23.9
	D	17.3	28.8
13	**C**	11.8	23.3
	D	15.3	26.8
15	**C**	11.3	18.3
	D	16.9	24.0

A considerably lower activation barrier for conformational exchange must be operative for **2** where all ^{1}H resonances are already fully time-averaged (sharp) at 25 °C (400 MHz/C_6D_6). Furthermore, the virtually identical vicinal splitting patterns observed for the geminal 12-H/12′-H pair indicate the two interconverting conformers of **2** to be roughly equivalent energetically. As a noteworthy, more subtle manifestation of dynamic exchange between two chair-like conformers, W-coupling is observed for both 12-H ($^4J_{H,H}$ = 1 Hz; to 14-H) and 12′-H ($^4J_{H,H}$ = 1 Hz; to 14′-H, δ 1.52). In this context, it is interesting to recall that **2** is the only compound in the entire series that could not be induced to crystallize.

Assessment of the Relative Stabilities by Molecular Mechanics Calculations. MM2 calculations[18] were also performed on each of the eight structures. Geometries preminimized on MODEL version KS 2.99[19a] were individually subjected to a multiconformer run that encompassed all three rings. Over 55 conformations were generated and minimized in each instance in order to ensure proper identification of the global minimum-energy conformer. The MMX program (version 90.000) was then utilized to optimize the lowest energy chair conformations of the two possible chair arrangements. The calculated energies have been compiled in Table 2.[19b]

The effect of the α-heteroatom in the syn series is seen to exert a strong preference for adoption by the cyclohexanone ring of chair conformation **B**. The extent to which **B** is favored over **A** ranges from 2 to 4 kcal/mol and appears to be only modestly dependent on the specific nature of X (O or S). We therefore conclude that the chair conformation with X axial and Y equatorial is energetically optimal and that the adoption by **1** of conformation **A** in the solid state is a likely consequence of energetic overriding by an unaccounted electronic effect, since crystal packing forces are unlikely to contribute a discrepancy as large as 2.6 kcal/mol. In this regard, it is relevant that the calculated difference in kcal/mol between **1A** and **1B** in the gas phase is on the more modest end of the scale.

The data gathered for the anti isomers shown in Table 2 reveal a dominance of conformer **C** over **D** to a level that exceeds 5.5

(18) (a) Allinger, N. L. *J. Am. Chem. Soc.* **1977**, *99*, 8127. (b) Burkert, U.; Allinger, N. L. *Molecular Mechanics*; American Chemical Society: Washington, D.C., 1982; Monograph 177.

(19) (a) We thank Professor K. Steliou for making this program available to us. (b) The MMX minimized energies in Table 2 were obtained utilizing a Coulombic interaction potential instead of bond dipole–bond dipole interactions. MMX energies using dipole–dipole interactions were also performed (available on request from the authors), and the resultant energies reflect the same trends. The difference between these calculations has been documented [Gajewski, J. J.; Gilbert, K. E.; McKelvey, J. In *Advances in Molecular Modeling*; Liotta, E., Ed.; JAI Press, Inc.: Greenwich, CT, 1990; Vol. 2, p 69].

Table 3. Acid-Promoted Equilibration of the Syn and Anti Isomers

starting ketone	reaction time, h	syn/anti ratio	total percent recovery	$\Delta G°_{334}$, kcal/mol
1	31	1:1.8	- - - -	0.39
2	21	1:1.9	83	0.43
9	96	1:2.3	96	0.55
10	97	1:3.25	83	0.78
12	456	2.22:1	49	*a*
13	456	1:8.63	43	*a*
14	183	1.86:1	52	*a*
15	183	1.2:1	60	*a*

[a] Incomplete equilibration with concurrent decomposition of the substrates.

kcal/mol in the case of the disulfur system **15**. Thus, the energetic rewards of positioning both X and Y as axial substituents can be substantial and certainly adequate to make **C** the only observable structure for **10**, **13**, and **15** on the NMR time scale and in adopted crystalline forms.

As a lead-in to the equilibration experiments, it is appropriate to point out the calculated energetic relationships between each syn/anti isomer pair. In the absence of solvation effects, we see that the anticipated arrangement of heteroatoms provides for a greater level of intrinsic stabilization. For **1B**/**2C**, the difference in ΔE_{total} amounts to only 0.8 kcal/mol, while for **14B**/**15C**, this disparity climbs to 1.3 kcal/mol.

Acid-Catalyzed Syn/Anti Equilibration Studies. The standard conditions adopted for the equilibration experiments involved refluxing a chloroform solution of the isomerically pure ketone in the presence of a catalytic quantity of *p*-toluenesulfonic acid for extended periods of time. The resulting two components in the isomeric mixture were separated chromatographically and accurately weighed to assess their distribution. Exposure of **1** to the standard conditions for 31 h has previously been shown to produce a 1:1.8 mixture of **1** and **2**. When beginning with **2** (21 h reaction time), a comparable syn/anti ratio (1:1.9) was realized (Table 3). Accordingly, the anti isomer is clearly favored thermodynamically, with $\Delta G°_{334}$ residing within the limits of 0.39–0.43 kcal/mol.

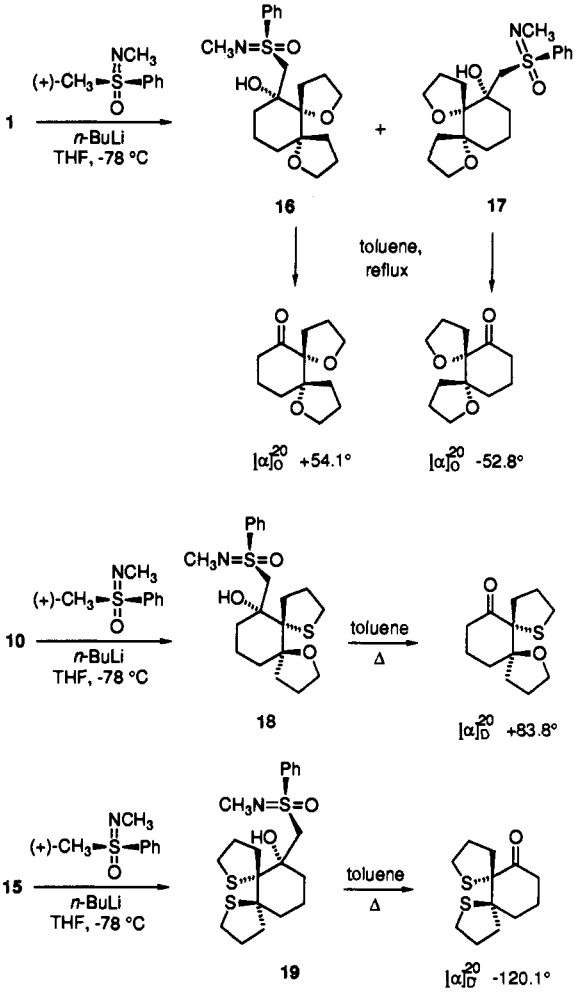
Analogous processing of **9** and **10** revealed their equilibration to proceed more slowly, such that heating for 96 h did not result in arrival at the true equilibrium position. However, recovery of the ketones remained high. As a consequence, it is possible to surmise that the anti isomer is again the thermodynamic sink and by a factor somewhat larger than that governing the dioxygen example (0.55–0.78 kcal/mol, see Table 3).

When a sulfur atom is resident β to the ketone carbonyl as in **12**–**15**, the rates of isomerization are further depressed. Thermal degradation of the substrates was seen to be kinetically competitive, and recovery levels in the 40–60% range became the norm. Despite the fact that complete equilibration could not be realized because of these complications, it is still apparent that mutual isomerization does operate.

The predominance of **14** in the product mixtures resulting from the heating of either **14** or **15** in an acidic environment must be viewed with caution. It is possible and even likely that **15** degrades more rapidly under these experimental conditions than does **14**. Such behavior would obviously skew the final results improperly.

Resolution of 1, 10, and 15. Racemization under Acidic Conditions. All three ketones were resolved through application of Johnson's sulfoximine method[20] (Scheme 4). Addition of the optically pure carbanion derived from the (*S*)-(+)-enantiomer to **1** afforded four diastereomers after chromatographic separation in isolated yields of 37%, 24%, and 10% (the last is a mixture of the opposite facial isomers). Since knowledge of the absolute configurations was unimportant, definitive stereochemical assignments to the adducts and to the ketones recovered from the thermal degradation of **16** and **17** were not pursued. Heating the

Scheme 4



pure major sulfoximine adduct, $[\alpha]^{20}_D$ +44.8°, in toluene furnished optically pure dextrorotatory **1**, $[\alpha]^{20}_D$ +54.1°. Similar processing of the second most prevalent diastereomer arbitrarily labeled as **17** afforded **1** having the opposite configuration, $[\alpha]^{20}_D$ −52.8°.

In related experiments, **10** was transformed via **18**, $[\alpha]^{20}_D$ +38.2°, into its dextrorotatory enantiomer, $[\alpha]^{20}_D$ +83.8°. Lastly, the disulfur series was represented by the acquisition of (−)-**15**, $[\alpha]^{20}_D$ −121.8°.

When the antipodal samples of **1** were heated in $CHCl_3$ containing catalytic amounts of *p*-toluenesulfonic acid for 19 h, *complete racemization was observed in both cases.* Neither the syn nor the anti isomer recovered from these reactions exhibited any vestige of residual rotatory power.

That (+)-**10** was equally subject to ready racemization was apparent after its exposure to *p*-toluenesulfonic acid in hot chloroform for 24 h. Ensuing chromatographic separation and purification by crystallization returned an anti stereoisomer that exhibited an $[\alpha]_D$ of 0! When the dithia analogue (−)-**15** was comparably treated for a similar period of time, the rotation of recovered **15** had dropped to −33.0°. As expected, the syn isomer **14** produced under these conditions was substantially less optically active, $[\alpha]^{20}_D$ +3.6°. Clearly, the disulfur compounds racemize more slowly.

Discussion

2-Heteroatom Ketone Effect. The issue of conformational preferences for 2-substituted cyclohexanones has provoked considerable interest and attention. As early as 1955,[21] it was recognized that an increase in the steric size of a 2-alkyl substituent

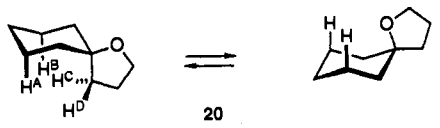
(20) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021.

(21) Robins, P. A.; Walker, J. *J. Chem. Soc.* **1955**, 1789.

was met with an enhancement in the level of the axial conformer. The 2-alkyl ketone effect, as this phenomenon is now known,[22,23] is attributable to the allylic 1,3 strain that develops between the carbonyl oxygen and R group.[14] While the consequences of R = methyl are rather negligible, progression to ethyl and isopropyl has been shown via equilibration experiments to destabilize the equatorial conformer by 0.7 and 1.7 kcal/mol, respectively.[24]

A change in the nature of R to a polar substituent superimposes the added factor of dipole–dipole interaction. First studied in 2-halocyclohexanones,[14] the consequence of enhanced electrostatic repulsion is also to destabilize the more polar equatorial conformer, as long as the solvent polarity is not especially elevated. For heptane solutions of 2-bromo-, 2-chloro, and 2-fluorocyclohexanone, the axial conformer dominates to the extent of 85%, 76%, and 48%, respectively.[25] Under comparable conditions, the axial conformers of 2-methoxy- and 2-(methylthio)cyclohexanone are favored to the extent of 63%[14b] and 70%, respectively.[26] This preference is dictated by the minimization of steric and dipole–dipole interactions, as well as hyperconjugative effects of the type $\sigma_{C-X} \rightarrow \pi^*_{C=O}$ and $n_O \rightarrow \pi^*_{C=O}$[27] in conformance with the generalized anomeric effect.[28] Similar considerations have been invoked to explain conformational interactions in 2-heterosubstituted methylenecyclohexanes.[29,30]

When spiro heterocyclic rings are involved, consideration must also be accorded to the counterbalancing of diaxial nonbonded steric compression. Thus, quantitation of the conformational behavior of **20** in CS_2 solution at 35 °C has shown the O-axial



20

isomer to predominate (~68%).[31] This preference, which corresponds to $\Delta G°_{308}$ of 0.46 kcal/mol, has been logically rationalized in terms of the relief in syn-axial compression that materializes between H^A/H^D and H^B/H^C when the oxygen atom is projected axially. No deformation of the cyclohexane chair was detected following X-ray crystallographic analysis of derivatives of **20**. Since the *A* values for ethyl and methoxy are 2.1 and 0.6 kcal/mol, respectively, the preference for the O-axial isomer is seen to be less than additive. This arises presumably because of bending within the five-membered ring of either O or CH_2 away from H_A and H_B, with the larger CH_2 deriving the larger benefit. A doubling of the number of resident spirocyclic rings, as in the present series of compounds, introduces added nonbonded steric ramifications that must be similarly addressed. Relevantly, our X-ray diffraction results confirm that no deformation of the cyclohexanone chair materializes.

Gauche Effect of Vicinal Polar Bonds on Six-Membered Rings. Originally discovered in connection with studies aimed at establishing the conformational preference of substituted ethanes,[32] the pronounced tendency of highly electronegative substituents to adopt a gauche relationship has been subjected to detailed quantum-mechanical analysis.[33] Zefirov and his co-workers have been predominantly responsible for extending this field into the realm of trans 1,2-disubstituted cyclohexanes.[34] For the usual repulsive dipole–dipole reasons, this class of compounds should prefer to position both X and Y axially. However, this spatial arrangement lacks all vestiges of the gauche effect, which can only materialize when the diequatorial conformer is reached.

Through adaptation of the Hill equation for subtracting out steric effects,[35] the Russian workers have shown that while strongly electronegative oxygen substituents exert added electrostatic attraction (the gauche effect), atoms of the second period such as sulfur actually experience heightened repulsion. The consequence of placing two trans-related ether oxygens on a cyclohexane ring is to favor the gauche relationship present uniquely in the diequatorial conformer. The tendency for the equivalent structure substituted with two sulfur atoms is to project the heteroatoms as distal as possible. The O/S interaction is also slightly repulsive in nature.[14a]

Counterbalancing of Electronic and Steric Interactions in Hetero 2,3-Dispiro Cyclohexanones. Since the subclass most relevant to the preceding discussion involves the anti isomers **10**, **13**, and **15**, their uniform preference for adoption of conformation **C** is analyzed first. A minimum of two salient factors needs to be considered in evaluating the strong bias disfavoring the diequatorial arrangement **D**. The first involves the minimization of nonbonded steric interactions. From the dynamic conformational behavior of the simple spirocycle **20**, it has been determined that the magnitude of the multiply-directed 1,3-diaxial interaction to the ring methylene group is 0.46 kcal/mol. On this basis, the intuitive expectation is that **D** would be sterically destabilized relative to **C** by roughly 0.7 kcal/mol because of the additive contributions of three approximately equivalent interactions. This value is considerably smaller than the steric energies derived by MM2 methods (Table 2) and may therefore be an underestimate because other nonbonded interactions stemming from the proximal five-membered rings have not been factored in.

The second effect that adds to the preferred stabilization of **C** is the minimization of the carbonyl–α-heteroatom dipole–dipole interaction. We estimate the magnitude of the favorable energetic interaction arising from adoption of this geometry to be 0.3 kcal/mol. That is, the full extent of the axial preference seen in 2-methoxycyclohexanone is taken as operational in **13**. Since the experimental data for 2-(methylthio)cyclohexanone are comparable, the energy values for **10** and **15** should be entirely similar. *The gauche effect contributes too little to override the steric and dipole contributions.*[36]

The trends evident in the syn series suggest that the energetic differences between conformers **A** and **B** are more closely balanced. Ketones **1** and **12** are particularly noteworthy in this regard. While the adoption of conformation **B** might well decrease the energy content because of the onset of the 2-heteroatom effect, the facility with which **1** adopts conformation **A** is most readily rationalized by invoking an additional effect involving the

(22) Malhotra, S. K.; Johnson, F. *J. Am. Chem. Soc.* **1965**, *87*, 5493.
(23) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
(24) Rickborn, B. *J. Am. Chem. Soc.* **1962**, *84*, 2414.
(25) Bingham, R. C. *J. Am. Chem. Soc.* **1976**, *98*, 535.
(26) Wladislaw, B.; Viertler, H.; Olivato, P. R.; Calegao, I. C. C.; Pardini, V. L.; Rittner, R. *J. Chem. Soc., Perkin Trans. 2* **1980**, 453.
(27) (a) Eisenstein, O.; Anh, N. T.; Jean, Y.; Devaquet, A.; Cantacuzene, J.; Salem, L. *Tetrahedron* **1974**, *30*, 1717. (b) Consult footnote 20 in ref 15.
(28) (a) Szarek, W. A., Horton, D., Eds. *Anomeric Effect: Origin and Consequences*; ACS Symposium Series No. 87; American Chemical Society: Washington, D.C., 1979. (b) Kirby, A. J. *The Anomeric Effect and Related Stereoelectronic Effects at Oxygen*; Springer-Verlag: Berlin, 1983. (c) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983. (d) Juaristi, E.; Cuevas, G. *Tetrahedron* **1992**, *48*, 5019.
(29) (a) Ouédrango, A.; Phan Viet, M. T.; Saunders, J. K.; Lessard, J. *Can. J. Chem.* **1987**, *65*, 1761. (b) Lessard, J.; Saunders, J. K.; Phan Viet, M. T. *Tetrahedron Lett.* **1982**, *23*, 2059. (c) Phan Viet, M. T.; Lessard, J.; Saunders, J. K. *Tetrahedron Lett.* **1979**, 317. (d) Lessard, J.; Phan Viet, M. T.; Martino, R.; Saunders, J. K. *Can. J. Chem.* **1977**, *55*, 1015.
(30) Zefirov, N. S.; Baranenkov, I. V. *Tetrahedron* **1983**, *39*, 1769.
(31) (a) Picard, P.; Moulines, J. *Tetrahedron* **1978**, *34*, 671. (b) Picard, P.; Moulines, J. *Tetrahedron Lett.* **1970**, 5133.
(32) Eliel, E. L. *Acc. Chem. Res.* **1970**, *3*, 1.
(33) (a) Whangbo, M.-H.; Wolfe, S. *Can. J. Chem.* **1976**, *54*, 949. (b) Van-Catledge, F. A. *J. Am. Chem. Soc.* **1974**, *96*, 5693. (c) Wolfe, S.; Tel, L. M.; Haines, W. J.; Robb, M. A.; Csizmadia, I. G. *J. Am. Chem. Soc.* **1973**, *95*, 4863. (d) Wolfe, S.; Tel, L. M.; Csizmadia, I. G. *Can. J. Chem.* **1973**, *51*, 2423. (e) Philips, L.; Wray, V. *J. Chem. Soc., Chem. Commun.* **1973**, 90. (f) Wolfe, S.; Rauk, A.; Tel, L. M.; Csizmadia, I. G. *J. Chem. Soc. B* **1971**, 136.
(34) (a) Zefirov, N. S.; Gurvich, L. G.; Shashkov, A. S.; Krimer, M. Z.; Vorob'eva, E. A. *Tetrahedron* **1976**, *32*, 1211. (b) Zefirov, N. S.; Samoshin, V. V.; Subbotin, O. A.; Baranenkov, V. I.; Wolfe, S. *Tetrahedron* **1978**, *34*, 2953. (c) Zefirov, N. S.; Samoshin, V. V.; Palyulin, V. A. *Zh. Org. Khim.* **1983**, *19*, 1888.
(35) Hill, T. L. *J. Chem. Phys.* **1948**, *16*, 399.
(36) Burkert, U. *Tetrahedron* **1979**, *35*, 1945.

β-heteroatom. Does the equatorial orientation of Y in **B** introduce an interaction that is especially unfavorable when X and Y are strongly negative oxygen atoms? Since **9** and **12** do not share with **1** any detectable tendency to exist as conformer **A**, it may well be that atoms mismatched in their electronegativity do not give rise to an equivalently significant effect.

Heteroatom Control of Racemization at Two Vicinal Quaternary Carbons. Turning finally to the acid-catalyzed stereoinversions experienced by these ketones, we wish to draw attention to the rate retardations that accompany the introduction of sulfur at X, Y, or X/Y in tandem. Protonation of the carbonyl oxygen is recognized to be met with the buildup of positive charge at carbon without significant change in the sp^2-hybridization at that center. The two issues of interest focus on Y and center about (a) a possible orientational dependence to the relative ease of responding electronically at the electron-deficient center (as indicated by the electron flow in **G** and **H**) and (b) a detectable inherent

G H

difference in the ability of oxygen and sulfur to proceed to open-chain oxonium and thionium ion intermediates, respectively (see Scheme 1). The experimental data that has been gathered (Table 3) suggest that the kinetic requirement for suitable stereoelectronic alignment can be met in both the syn and anti isomers without significant buildup of steric strain.

Heteroatom effects are quite a different matter. C=S$^+$ p–d overlap is well-known to be much less favorable than C=O$^+$,[11] as evidenced by the ease of acid hydrolysis of acetals relative to mono- and dithioacetals. As a consequence, ketones **1** and **2**, those substrates substituted by two tetrahydrofuran rings, lose stereochemical "memory" most rapidly. Replacement of the α-oxygen by sulfur has demonstrable rate-retarding ramifications. Formation of a thionium ion is yet more difficult to accomplish in **13–15**.

Experimental Section

Melting points are uncorrected. ^{1}H NMR spectra and ^{13}C spectra were recorded at the indicated field strengths. High-resolution mass spectra were recorded at The Ohio State University Chemical Instrumentation Center. Elemental analyses were performed at the Scandinavian Microanalytical Laboratory, Herlev, Denmark. All reactions were carried out under a nitrogen atmosphere, and the ensuing separations were effected under flash chromatography conditions on Merck silica gel HG_{254}. The organic extracts were dried over anhydrous magnesium sulfate. Solvents were reagent grade and in many cases dried before use.

(±)-(5*R,6*S**)-1-Oxa-7-thiadispiro[4.0.4.4]tetradecan-11-one and (±)-(5*R**,6*R**)-1-Oxa-7-thiadispiro[4.0.4.4]tetradecan-11-one (9 and 10).** A solution of 2,3-dihydrothiophene (4.31 g, 50 mmol) in cold (–78 °C), dry THF (200 mL) was treated with *tert*-butyllithium (32.4 mL of 1.7 M in pentane) and stirred at this temperature for 1 h prior to the addition of **6** (6.75 g, 48.2 mmol) dissolved in THF (10 mL). After being stirred for an additional 3 h at –78 °C, the reaction mixture was quenched with saturated $NaHCO_3$ solution, poured onto a larger volume of $NaHCO_3$ solution, and extracted with ether. The combined extracts were washed with brine and dried prior to solvent evaporation. The residual oil was stirred with Dowex-50X resin (4.0 g) in CH_2Cl_2 (2000 mL) for 24 h, filtered, and concentrated. Chromatography on silica gel (elution with 20% ether in hexane) gave first **10** (5.06 g, 46%) and subsequently **9** (1.16 g, 11%).

For **9**: colorless crystals, mp 59–62 °C (from hexanes); IR 2950, 2875, 1705, 1445, 1430, 1310, 1235, 1080, 1070, 1045, 940, 890; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98–3.91 (m, 1 H), 3.88–3.80 (m, 1 H), 3.04–2.90 (m, 1 H), 2.89–2.80 (m, 2 H), 2.48–2.41 (m, 1 H), 2.27–2.24 (m, 1 H), 2.19–2.09 (m, 1 H), 2.01–1.59 (series of m, 9 H), 1.50–1.36 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.6, 87.5, 75.9, 68.3, 36.8, 36.3, 33.8, 32.5, 30.8, 30.5, 26.9, 19.3; MS *m/z* (M$^+$) calcd 210.1078, obsd 210.1036.

For **10**: colorless crystals, mp 60–62 °C (from hexanes); IR (KBr, cm^{-1}) 1695; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90–3.83 (m, 1 H), 3.80–3.73 (m, 1 H), 2.95–2.77 (m, 3 H), 2.63 (ddd, *J* = 13.0, 5.9, 3.3 Hz, 1 H), 2.28–2.22 (m, 1 H), 2.18–2.06 (m, 2 H), 2.05–1.75 (m, 7 H), 1.74–1.65 (m, 1 H), 1.49 (ddd, *J* = 10.8, 12.9, 6.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.9, 90.7, 71.4, 69.0, 37.0, 36.0, 34.4, 34.3, 31.3, 30.9, 25.9, 20.3; MS *m/z* (M$^+$ – H) calcd 209.1000, obsd 209.0967. Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02. Found: C, 63.59; H, 7.95.

1-Thiaspiro[4.5]decan-6-one (11). A 1.73-g (20.1 mmol) sample of 2,3-dihydrothiophene dissolved in dry THF (80 mL) was metalated as described above with *tert*-butyllithium (12.4 mL of 1.7 M). Cyclobutanone (1.28 g, 18.3 mmol) was introduced via cannula, followed 3 h later by the same workup. The resulting unpurified carbinol was stirred with Dowex-50X resin (3.0 g) in CH_2Cl_2 (1000 mL) for 2 days; subsequent purification by silica gel chromatography (elution with 10% ethyl acetate in hexanes) gave 2.55 g (89%) of **11** as a colorless oil: IR (neat, cm^{-1}) 1745; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.00–2.94 (m, 2 H), 2.53–2.42 (m, 1 H), 2.41–2.31 (m, 1 H), 2.25–2.04 (m, 5 H), 2.02–1.92 (m, 1 H), 1.91–1.75 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 216.0, 63.5, 38.3, 36.8, 35.3, 33.2, 30.6, 19.8; MS *m/z* (M$^+$) calcd 156.0609, obsd 156.0610. Anal. Calcd for $C_8H_{12}OS$: C, 61.50; H, 7.74. Found: C, 61.58; H, 7.73.

(±)-(5*R,6*R**)-1-Oxa-7-thiadispiro[4.0.4.4]tetradecan-14-one and (±)-(5*R**,6*S**)-1-Oxa-7-thiadispiro[4.0.4.4]tetradecan-14-one (12 and 13).** Cerium trichloride heptahydrate (5.77 g, 15.5 mmol) was heated at 140 °C and 1 Torr overnight. After the reaction mixture was cooled, anhydrous THF (100 mL) was introduced and the slurry was stirred at room temperature for 3 h, cooled to –78 °C, and treated dropwise with *tert*-butyllithium until a pink color persisted. A solution of 5-lithio-2,3-dihydrofuran in dry THF (25 mL) [prepared from 987 mg (14.1 mmol) of 2,3-dihydrofuran and 9.11 mL of 1.7 M *tert*-butyllithium] was next introduced, and the reaction mixture was stirred at –78 °C for 2 h before the addition of **11** (2.003 g, 12.8 mmol) via cannula. After an additional 3 h in the cold, the mixture was allowed to warm to room temperature and worked up in the predescribed manner. The unpurified carbinol was dissolved in CH_2Cl_2 (1000 mL) and stirred with Dowex-50X resin (3.0 g) for 48 h. The products, isolated as before, were separated by chromatography on silica gel (elution with 10% ether in hexanes). The first to elute was **12** (1.536 g, 53%) to be followed by **13** (1.239 g, 43%).

For **12**: colorless crystals (from hexanes): mp 50–52 °C; IR (KBr, cm^{-1}) 1710; ^{1}H NMR (300 MHz, C_6D_6) δ 3.77 (dd, *J* = 14.7, 7.6 Hz, 1 H), 3.48 (dt, *J* = 5.1, 7.7 Hz, 1 H), 2.95–2.84 (m, 1 H), 2.61–2.35 (m, 4 H), 2.06–2.00 (m, 1 H), 1.89–1.80 (m, 1 H), 1.75–1.46 (m, 6 H), 1.45–1.22 (m, 2 H), 1.18–1.08 (m, 1 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 208.9, 94.3, 69.2, 68.9, 37.4, 36.9, 34.7, 32.4, 31.0, 26.9, 26.6, 23.6; MS *m/z* (M$^+$) calcd 226.1028, obsd 226.1027.

For **13**: colorless crystals; mp 63–65 °C; IR (KBr, cm^{-1}) 1705; ^{1}H NMR (300 MHz, C_6D_6) δ 3.72–3.65 (m, 1 H), 3.58–3.51 (m, 1 H), 2.60–2.42 (m, 4 H), 2.17–2.05 (m, 2 H), 1.92–1.78 (m, 2 H), 1.77–1.45 (m, 8 H); ^{13}C NMR (75 MHz, C_6D_6) ppm 207.3, 93.5, 69.4, 67.8, 38.31, 38.26, 37.6, 33.5, 30.9, 29.1, 26.6, 23.0; MS *m/z* (M$^+$) calcd 226.1028, obsd 226.1028. Anal. Calcd for $C_{12}H_{18}O_2S$: C, 63.68; H, 8.02. Found: C, 63.83; H, 8.12.

(±)-(5*R,6*R**)-1,7-Dithiadispiro[4.0.4.4]tetradecan-11-one and (±)-(5*R**,6*S**)-1,7-Dithiadispiro[4.0.4.4]tetradecan-11-one (14 and 15).** Cerium trichloride heptahydrate (7.357 g, 19.8 mmol) was heated at 140 °C and 1 Torr overnight. After cooling, dry THF (125 mL) was added and the slurry was stirred at room temperature for 3 h prior to cooling to –78 °C and dropwise titration with *tert*-butyllithium until a faint pink color persisted. At this point, a solution of 5-lithio-2,3-dihydrothiophene [from 1.547 g (17.9 mmol) of 2,3-dihydrothiophene and 11.62 mL of 1.7 M *tert*-butyllithium in dry THF (35 mL)] was introduced via cannula. The slurry was stirred for 2 h in the cold before **11** (2.55 g, 16.3 mmol) was added. This mixture was stirred at –78 °C for 3 h, then warmed to room temperature, and worked up as predescribed. The resulting oily carbinol was dissolved in CH_2Cl_2 (1000 mL), stirred with Dowex-50X (5.0 g) for 6 days, filtered, and evaporated. The residue was subjected to silica gel chromatography (elution with 5% ether in hexanes) to furnish initially **15** (1.476 g, 37%) and subsequently **14** (1.223 g, 31%).

For **14**: colorless crystals; mp 92.5–95 °C (from hexanes); IR (KBr, cm^{-1}) 1695; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.04 (td, *J* = 13.9, 7.1 Hz, 1 H), 2.96–2.71 (m, 4 H), 2.58 (dd, *J* = 11.6, 5.5 Hz, 1 H), 2.28–2.16 (m, 3 H), 2.14–1.99 (m, 4 H), 1.92–1.78 (m, 2 H), 1.76–1.56 (m, 3 H);

^{13}C NMR (75 MHz, $CDCl_3$) ppm 207.4, 75.2, 70.8, 41.2, 37.0, 35.5, 34.4, 32.4, 32.1, 32.0, 31.2, 22.2; MS *m/z* (M^+) calcd 242.0799, obsd 242.0802. Anal. Calcd for $C_{12}H_{18}OS_2$: C, 59.46; H, 7.48. Found: C, 59.44; H, 7.47.

For **15**: colorless crystals; mp 107–110 °C; IR (KBr, cm^{-1}) 1690; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.97–2.75 (m, 6 H), 2.26–1.78 (m, 11 H), 1.68–1.57 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 206.2, 74.5, 68.8, 40.4, 39.8, 36.9, 35.1, 34.7, 32.7, 31.1, 30.1, 22.0; MS *m/z* (M^+) calcd 242.0799, obsd 242.0809.

Resolution of 1. A solution of (+)-(*S*)-*N*,*S*-Dimethyl-(*S*)-phenylsulfoximine (885 mg, 5.23 mmol) in dry THF (35 mL) was cooled to –78 °C, and *tert*-butyllithium (3.60 mL of 1.6 M) was introduced via syringe. After 30 min, a cold (–78 °C) solution of (±)-**1** (1.00 g, 4.76 mmol) in the same solvent (5 mL) was introduced via cannula. The reaction mixture was stirred under nitrogen for 1 h before being poured into saturated NH_4Cl solution. The products were extracted into ether, and the combined organic phases were dried and evaporated. The residual viscous gum was chromatographed on silica gel (elution with 60% ether in hexanes) to separate the two most prevalent diastereomeric adducts. The least polar isomer, referred to as **16** (642 mg, 36%) was isolated in a pure state. The more polar product **17** was resubjected to MPLC (silica gel, elution with 50% ether in hexanes) for further purification (196 mg, 11%). A third fraction composed of **17** and a third diastereomer (263 mg, 15%) was also obtained.

For **16**: colorless crystals; mp 167–169 °C (from hexanes); IR (KBr, cm^{-1}) 3500–3100, 1440, 1300, 1210, 1145, 1070, 1040, 880, 850, 740; ^{1}H NMR (250 MHz, C_6D_6, 350 K) δ 7.78–7.72 (m, 2 H), 7.23 (br s, 1 H), 7.04–6.96 (m, 3 H), 4.53–4.47 (br m, 1 H), 4.13–4.10 (br m, 1 H), 3.93–3.78 (m, 2 H), 3.62–3.48 (m, 2 H), 3.20–3.00 (br s, 1 H), 2.54 (s, 3 H), 2.54–2.45 (m, 1 H), 1.96–1.83 (m, 4 H), 1.72–1.34 (m, 8 H); ^{13}C NMR (50 MHz, C_6D_6) ppm 140.1, 132.4, 129.4, 129.1, 92.5, 89.0, 79.7, 71.1, 68.9, 59.0, 36.6, 36.4, 33.7, 30.9, 28.9, 27.4, 25.5, 19.8; MS *m/z* (M^+) calcd 379.1817, obsd 379.1814; $[\alpha]^{20}_D$ +44.8° (*c* 3.73, $CHCl_3$). Anal. Calcd for $C_{20}H_{29}NO_4S$: C, 63.30; H, 7.70. Found: C, 63.35; H, 7.77.

Thermal Activation of 16. The adduct **16** (642 mg, 1.69 mmol) was heated at reflux in toluene (25 mL) for 48 h, cooled, and introduced directly on a silica gel column. After removal of the toluene by hexane elution, recourse to ethyl acetate–hexane (1:1) eluted fractions containing pure (+)-**1**, which was recrystallized from hexane: $[\alpha]^{20}_D$ +54.1° (*c* 9.93, $CHCl_3$).

The second adduct **17** (196 mg, 0.52 mmol) was likewise heated in toluene (10 mL) for 20 h to give (–)-**1** quantitatively: $[\alpha]^{20}_D$ –52.8° (*c* 6.16, $CHCl_3$).

Resolution of 10. Condensation of the (*S*)-(+)-sulfoximine (635 mg, 3.75 mmol) with **10** (772 mg, 3.41 mmol) in the predescribed manner followed by silica gel chromatography (gradient elution 10–50% ethyl acetate in hexanes) returned 97 mg (13%) of unreacted **10** and permitted the isolation of three adducts: A (432 mg, 37%), **B** (283 mg, 24%), and C (121 mg, 10%).

For the major diastereomer (**18**): colorless solid; mp 159–161 °C; IR (KBr, cm^{-1}) 3400–3030, 1445, 1340, 1240, 1150, 1080, 1030, 995, 880; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88–7.85 (m, 2 H), 7.63–7.52 (m, 3 H), 7.26 (br s, 1 H), 3.75 (t, *J* = 6.6 Hz, 2 H), 3.0–1.3 (series of m, 21 H); ^{13}C NMR (62.5 MHz, C_6D_6) ppm 140.9, 132.6, 129.5, 129.1, 89.7, 79.6, 77.1, 67.8, 62.0, 36.5, 36.0, 35.1, 34.2, 34.0, 33.5, 28.7, 26.8, 19.8; MS *m/z* (M^+) calcd 395.1589, obsd 395.1600; $[\alpha]^{20}_D$ +38.2° (*c* 9.88, CH_2Cl_2). Anal. Calcd for $C_{20}H_{29}NO_3S_2$: C, 60.73; H, 7.39. Found: C, 60.58; H, 7.40.

A solution of this adduct (384 mg, 0.97 mmol) in toluene (20 mL) was refluxed for 40 h, evaporated, and directly chromatographed on silica gel (elution with 20% ethyl acetate in hexanes) to furnish (+)-**10** (213 mg, 97%); $[\alpha]^{20}_D$ +83.3° (*c* 6.25, CH_2Cl_2).

Resolution of 15. Analogous condensation of **15** (1.340 g, 5.53 mmol) with the (*S*)-(+)-sulfoximine (1.029 g, 6.08 mmol) and comparable workup afforded four diastereomeric adducts: A (114 mg, 5%), **B** (397 mg, 17%), C, (746 mg, 33%), and D (753 mg, 33%).

For diastereomer C (**19**): colorless solid; mp 167.5–170 °C (from ether–hexanes); IR (KBr, cm^{-1}) 3600–3000, 1455, 1440, 1425, 1345, 1300, 1230, 1145, 1070, 980, 760, 735, 690, 630; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87–7.84 (m, 2 H), 7.64–7.53 (m, 3 H), 3.90 (br d, *J* = 13.5 Hz, 1 H), 3.57 (br d, *J* = 13.2 Hz, 1 H), 2.83–2.79 (m, 2 H), 2.77–2.65 (m, 2 H), 2.60–2.54 (m, 1 H), 2.54 (s, 3 H), 2.49–2.31 (m, 1 H), 2.15–1.63 (series of m, 12 H), 1.47 (dm, *J* = 13.3 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) ppm 138.7, 133.2, 129.6, 128.7, 78.4, 67.8, 61.7, 41.61, 41.55, 39.6, 35.1, 33.9, 33.7, 33.6, 28.5, 26.3, 17.7 (1C not observed due to conformational exchange broadening); MS *m/z* (M^+ – PhSONMe) calcd 257.1034, obsd 257.0993; $[\alpha]^{20}_D$ +39.1° (*c* 7.68, CH_2Cl_2). Anal. Calcd for $C_{20}H_{29}NO_2S_3$: C, 58.36; H, 7.10. Found: C, 58.57; H, 7.32.

A solution of this adduct (237 mg, 0.575 mmol) in toluene (10 mL) was refluxed for 72 h, evaporated, and chromatographed on silica gel (elution with 20% ethyl acetate in hexanes) to give (–)-**15**: mp 107–110 °C; $[\alpha]^{20}_D$ –121.8° (*c* 3.33, CH_2Cl_2).

Acknowledgment. We thank the National Science Foundation and the Eli Lilly Company for financial support.

Supplementary Material Available: Crystallographic experimental section and tables of X-ray crystal data, bond lengths and angles, final fractional parameters, thermal parameters, and final computed atomic coordinates for **9**, **10**, and **12–15** (52 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.