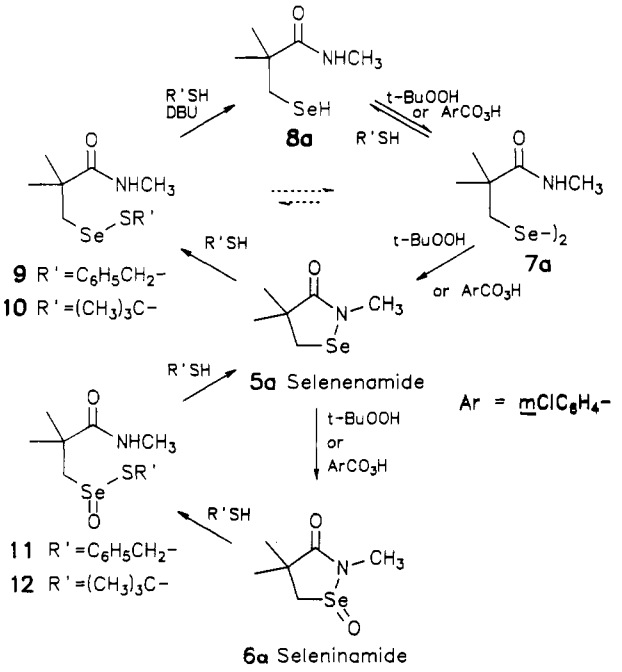
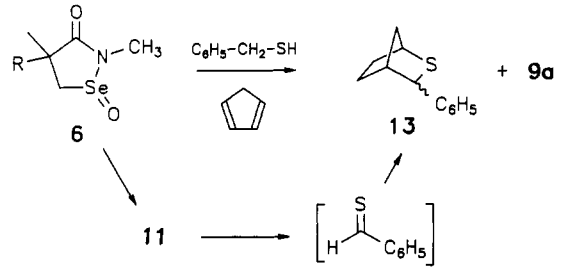
Scheme II. Redox Chemistry of **5a**



No benzyl thiolseleninate **11** was detected in the reaction of α-toluenethiol with **6a** under basic conditions. The transient



appearance of blue color, however, and the formation of selenosulfide **9** and adduct **13**[11] in high yield when cyclopentadiene was present demonstrated that thiobenzaldehyde was formed, probably by a syn elimination of the thiolseleninate **11**.[12] No selenenamide **5a** was observed, but this was expected since benzyl thiol reacted faster with **5a** than with **6a** under these conditions.

The diselenide **7a** and selenosulfide **9** did not react with α-toluenethiol under neutral conditions but with excess DBU each gave the selenolate **8a** and disulfide. ^{1}H NMR analysis of such mixtures was complicated by the rapid equilibration of selenolate **8a**$^-$ with diselenide **7a** such that only a single set of resonances was observed for the selenium-containing fragment. The selenolate was quantitatively trapped in situ by benzyl bromide to give the benzyl selenide or by a rapid quench with trifluoroacetic acid, giving selenol **8a** in yields as high as 85% when a tenfold excess of thiol was used.

Scheme II summarizes the redox results. Inspection of the scheme reveals that most of the features of the proposed glutathione peroxidase mechanism have been reproduced, with the selenenamide **5a** replacing the selenenic acid. The principle exception is that oxidation of selenol did not lead to **5a** but rather to the diselenide **7a**.

Acknowledgment. We thank the National Institutes of Health-NIADDK and the Wisconsin Alumni Research Foundation for support of this work.

(11) Vedejs, E.; Eberlein, T. H.; Mazur, D. J.; McClure, C. K.; Perry, D. A.; Ruggeri, R.; Schwartz, E.; Stults, J. S.; Varie, D. L.; Wilde, R. G.; Wittenberger, S. *J. Org. Chem.* **1986**, *51*, 1556.

(12) Syn eliminations of a selenolseleninate[15] and thiolsulfinates (Block, E.; O'Connor, J. *J. Am. Chem. Soc.* **1974**, *96*, 3929. Baldwin, J. E.; Lopez, R. C. G. *Tetrahedron* **1983**, *39*, 1487) have been observed.

Highly Enantioselective Borane Reduction of Ketones Catalyzed by Chiral Oxazaborolidines. Mechanism and Synthetic Implications

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In recent years there has been a flood of papers describing research on the enantioselective reduction of ketones by a wide variety of reagents made by mixing aluminum or boron hydrides and various chiral diols or amino alcohols.[1] Although a number of systems have been described which provide useful enantioselectivity, our knowledge of reagent structure, scope, and mode of reduction has remained at a primitive level, limiting both application and further development. Among the most interesting enantioselective ketone reductions have been those reported by Itsuno and his group which employ mixtures of borane (2–3 molar equiv) in tetrahydrofuran (THF) and a chiral vicinal amino alcohol (1 equiv), (*S*)-2-amino-3-methyl-1,1,-diphenylbutan-1-ol (**1**) and the corresponding derivative from (*S*)-leucine thus far being the most effective (ca. 95% ee of (*R*)-1-phenylethanol from acetophenone).[2] Typically a 2.5:1 mixture of borane and the amino alcohol in THF is allowed to react at 0 °C for several hours (hydrogen evolution) giving a reducing mixture to which the ketone is added for reduction at 0–30 °C. Reduction of ketones with this reagent is faster than that with borane in THF at the same temperature.

We have found that a fast reaction occurs between amino alcohol **1** and 2 equiv of borane in THF at 35 °C to give 2 equiv of hydrogen gas and the oxazaborolidine **2**. Removal of excess borane and solvent in vacuo and two sublimations of the solid residue at 105–130 °C and 0.05 Torr afforded colorless crystals of **2**, mp 105–110 °C, electron impact mass spectrum (EIMS), M^+ 265.16365 (calcd. 265.16379).

The ^{1}H NMR spectrum of **2** (250 MHz in C_6D_6, δ) showed the expected peaks due to ligand [6.93–7.70 (m, 10 H, phenyl), 3.98 (dd, J = 2.9 Hz, ca. 1.5 Hz, 1 H, C–CH–N), 3.24 (br s, 1 H, NH), 1.66 (m, 1 H, $CHMe_2$), 0.535 (d, J = 6.9 Hz, 3 H, CH_3), and 0.42 (d, J = 6.5 Hz, 3 H, CH_3)], and the ^{11}B NMR spectrum (in THF) showed a single broadened peak at +28.1 ppm (downfield) from BF_3·Et_2O (internal capillary), clearly due to B–H since it narrowed upon broad band ^{1}H decoupling.[3] Although the B–H proton in **2** was not apparent in the ^{1}H NMR spectrum due to broadening,[4] the infrared spectrum (in THF) showed a characteristic B–H stretching band at 2563 cm^{-1} as well as N–H stretching at 3400 cm.$^{-1}$ ^{11}B NMR spectral studies as a function of concentration revealed that **2** is monomeric in 0.05–0.2 M solution. Solutions of **2** alone in THF did not reduce ketones, e.g., acetophenone, even after several hours at 23 °C. However, mixtures of **2** and BH_3·THF (0.6–2.0 mol equiv) effect complete reduction of acetophenone in less than 1 min at 23 °C with rates comparable to the Itsuno mixtures. Under the same conditions

(1) For reviews, see: (a) ApSimon, J. W.; Collier, T. L. *Tetrahedron* **1986**, *42*, 5157–5254. (b) Haubenstock, H. *Topics Stereochem.* **1983**, *14*, 231–300. (c) Mukaiyama, T.; Asami, M. In *Topics in Current Chemistry, No. 127, Organic Chemistry*; Springer-Verlag: Berlin, 1985; pp 133–167.

(2) See: (a) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469–470. (b) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555–557. (c) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Perkin Trans 1* **1985**, 2039–2044. (d) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2615–2619. (e) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395–396.

(3) The observed ^{11}B NMR chemical shift is consistent with structure **2**, see: (a) Eaton, G. R.; Lipscomb, W. N., *NMR Studies of Boron Hydrides and Related Compounds*; W. A. Benjamin: New York, 1969. (b) Nöth, H.; Wrackmeyer, B. *Nuclear Magnetic Resonance Spectroscopy of Boron Compounds*; Springer-Verlag: Berlin, 1978.

(4) See: Leach, J. B.; Ungermann, C. B.; Onak, T. P. *J. Magn. Reson.* **1972**, *6*, 74–83.

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Table I. Borane Reduction of Ketones Catalyzed by (*S*)-**3**

$$2R_1R_2CO + BH_3 \xrightarrow[1\ min,\ 25\ °C]{3,\ THF} (R_1R_2CH\text{-}O)_2BH \rightarrow R_1R_2CHOH$$

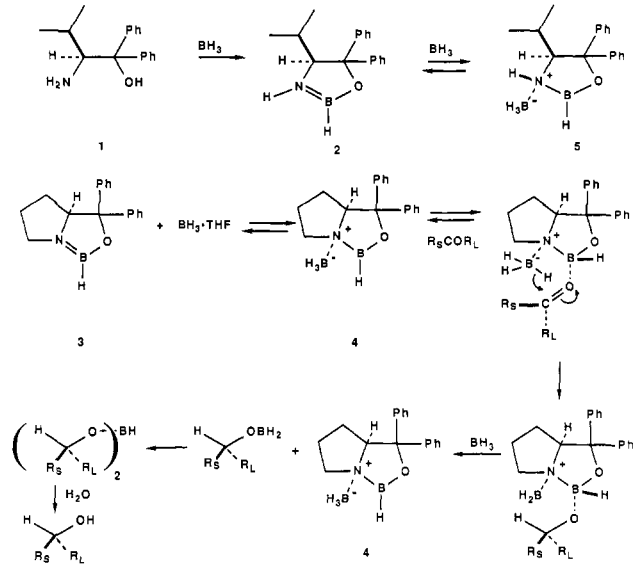
ketone	equiv BH_3	equiv **3**	config of prod.[a] (% ee)[b]
$C_6H_5COCH_3$	2	1	*R* (97)
$C_6H_5COCH_3$	1	0.1	*R* (97)[d]
$C_6H_5COCH_3$	1.2	0.025	*R* (95)
$C_6H_5COCH_3$	1.2	0.005	*R* (80)
$C_6H_5COC_2H_5$	1.2	0.05	*R* (86)
$C_6H_5COC_2H_5$	1	0.05	*R* (88)
$C_6H_5COC_2H_5$	0.6	0.05	*R* (90)[d]
t-$BuCOCH_3$	1.0	0.05	*R* (81)
t-$BuCOCH_3$	0.6	0.05	*R* (88)
t-$BuCOCH_3$	0.6	0.1	*R* (92)[c,d]
α-tetralone	0.6	0.05	*R* (89)[d]
$C_6H_5COCH_2Cl$	0.6	0.05	*S* (97)[d]

[a] For each entry conversion of ketone to alcohol was >99.7% as determined by gas chromatography. [b] Absolute configuration determined by isolation and measurement of rotation; ee determined by gas chromatographic analysis.[5] [c] Borane added over 5 min to a mixture of ketone and **3** at −10 °C. [d] Entries refer to optimal conditions for that substrate.

but in the absence of **2** there is little reduction of acetophenone by BH_3·THF. Using 1 equiv of **2** (derived from (*S*)-ligand **1**) and 1.2 equiv of BH_3·THF reduction of acetophenone occurs quantitatively (23 °C, 1 min) to form (*R*)-1-phenylethanol with 94.7% ee.[5] A catalytic amount of **2**, either 0.1 equiv or 0.025 equiv, under these conditions leads to equally good results (94.7% ee, 99.9% yield). However, a further reduction in the amount of **2** to 0.005 equiv gave (*R*)-1-phenylethanol of only 59% ee, probably as a consequence of competing noncatalyzed reduction by BH_3·THF.

An even better catalyst for the reduction of ketones is the oxazaborolidine **3**. The synthesis of **3** was carried out from (*S*)-(−)-2-(diphenylhydroxymethyl)pyrrolidine ((*S*)-diphenylprolinol)[6] by heating at reflux with 3 equiv of BH_3·THF in THF solution under a closed Ar–BH_3 atmosphere (total pressure 1.7 bar), removal of solvent, sublimation at 150–160 °C (0.1 Torr), and resublimation at 145–160 °C (0.05 Torr). The crystals so obtained had mp 107–124 °C, EIMS, M^+ 263.14826 (calcd. 263.14814). The ^{11}B NMR spectrum of **3** in 0.17 M solution in THF at 23 °C reveals a mixture of monomer and dimer with ^{11}B peaks at +28.3 ppm (broad s[7a] due to monomer) and +7.6 ppm (d, J_{BH} = 130 Hz[7b] due to dimer).[8] ^{11}B NMR analysis shows that the proportion of dimer increases with decreasing temperature, as expected, and also that in 0.4 M solution in C_6D_6 the dimer

Chart I



dominates. The infrared spectrum of **3** as a 0.1 M solution in THF shows B–H stretching bands at 2568 cm^{-1} (monomer) and 2413 cm^{-1} (dimer).[8] The ^1H NMR spectrum of **3** displays the peaks expected for the diphenylprolinol ligand.[9] The formation of **3** from (*S*)-diphenylprolinol is much slower than the corresponding conversion of **1** to **2** (vide supra), most likely because of angle strain in **3** due to the B=N multiple bond at the 5,5-ring fusion.

The results obtained with **3** as catalyst for the reduction of acetophenone and a range of other ketones by borane in THF are summarized in Table I. Under optimum conditions (usually 0.6 equiv of BH_3, 0.05 equiv of (*S*)-**3** as catalyst, THF solution, 25 °C; starred entries in Table I) excellent yields and enantioselectivities are obtained for a variety of ketones. The reactions are very fast (over within 1 min after mixing of reactants), and the diphenylprolinol ligand is easily recovered upon workup, making the method especially attractive for large-scale synthesis. In addition, catalyst **3** can be prepared as described above and used directly without sublimation. It should be noted that the enantioselectivity of these reductions often decreases somewhat with increasing amount of BH_3·THF above 0.6 equiv or with decreasing temperature (e.g., 0–20 °C).[10]

It is possible to derive a reasonable mechanism for these enantioselective reductions based on the above results and on observations of the ^{11}B NMR spectra of mixtures of **3** and BH_3·THF which clearly indicate the formation of 1:1 complex **4**. The ^{11}B NMR spectrum (25 °C) of a mixture of **3** (0.55 M in THF) and 2 equiv of BH_3·THF shows only a slight absorption centered at +29 ppm (uncomplexed **3**) and the following major peaks: doublet at +4.04 and +2.38 ppm (due to O–BH–N of **4**; collapsed to a singlet at 3.21 ppm upon broadband ^1H irradiation), a quartet centered at −1.5 ppm (due to free BH_3·THF; collapsed to a singlet at −1.5 ppm upon ^1H irradiation), and an upfield broadened quartet centered at −19.37 ppm (due to N–BH_3; collapsed to a singlet upon ^1H irradiation). Although the formation of an analogous complex **5** can be observed in the ^{11}B NMR spectrum of a mixture of **2** and BH_3·THF under the same conditions, the proportion of **5** relative to free **2** is relatively small. Complex **4** is ideally structured to serve as an effective reagent for carbonyl reduction which we propose occurs by coordination of the elec-

(5) Determination of ee values was made by capillary gas chromatographic analysis of the (−)-menthyloxycarbonyl derivatives of the various alcohols obtained by reduction according to Westley and Halpern (Westley, J. W.; Halpern, B. *J. Org. Chem.* **1968**, *33*, 3978–3980). Using an OV-1 (or DB-1) silicone column (170 °C) the derivatives of (*R*)- and (*S*)-1-phenylethanol, for example, had retention times of 7.32 and 6.91 min, respectively.

(6) (*S*)-Diphenylprolinol was synthesized directly by reaction of *N*-(benzyloxycarbonyl)-(*S*)-proline methyl ester with phenylmagnesium chloride (8 equiv) in THF initially at 0 °C and then at 23 °C for 16 h; for a previous preparation, see: Kapfhammer, J.; Matthes, A. *Hoppe-Seylers Zeit. Physiol. Chem.* **1933**, *223*, 43–52. The (*S*)-diphenylprolinol obtained in this way, mp 74.0–74.8 °C, $[\alpha]_D^{22}$ −68.1° (*c* 3.17 in $CHCl_3$), had 99.0% ee as shown by conversion to the corresponding MTPA amide ((*S*)-(+)-MTPA acid chloride–methylene chloride aqueous sodium hydroxide at 0 °C, see: Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.) and HPLC analysis on a DuPont Zorbax silica column using 95:5 hexane–THF for elution, the minor diastereomer being the less polar. The ee values cited above are corrected by adding 1% to the experimentally observed values to correspond to values for optically pure catalyst **3**.

(7) (a) Narrowed by ^1H broadband irradiation. (b) Collapsed to a singlet by ^1H decoupling.

(8) For previous studies on such monomer–dimer equilibria in related systems, see: (a) Bonnet, J.-P.; Laurent, J.-P. *J. Inorg. Nucl. Chem.* **1970**, *12*, 1449–1451. (b) Mikhailov, B. M.; Bochbareva, M. N.; Bogdanov, V. S.; Boldyreva, O. G.; Dorokhov, V. A. *J. Gen. Chem. USSR* **1971**, *41*, 1550–1554. (c) Pretsch, E.; Seibl, J.; Simon, W.; Clerc, T. *Spectral Data for Structure Determination of Organic Compounds*; Springer-Verlag: Berlin, 1983; p I 260.

(9) ^1H NMR data for **3** in 0.4 M C_6D_6 (δ): 6.9–7.70 (m, 10 H, phenyl), 4.42 (dd, *J* = 6.0, *J* = 4.6 Hz, 1 H, N–CH(C)–C), 3.02–3.16 (m, 2 H, N–CH_2–C), 1.61–1.70 (m, 2 H, N–C(C)–CH_2–C), 1.17–1.30 (m, 1 H, N–CH_2–CH_2–C), 0.54–0.59 (m, 1 H, N–CH_2–CH_2–C).

(10) After our studies had been carried out a paper appeared[2e] in which it was reported that a "white powder" of unknown composition could be obtained from the reaction of (*S*)-2-amino-3-methyl-1,1-diphenylbutan-1-ol with borane which accelerated the enantioselective reduction by borane of acetophenone *O*-methyloxime to 1-phenylethylamine.

trophilic ring boron with ketonic oxygen (*anti* to the larger carbonyl appendage) and hydrogen transfer from the NBH_3^- unit to the carbonyl carbon via a six-membered cyclic transition state, following the path formulated in Chart I. This mechanistic picture accords with all the facts available. It unambiguously explains the observed absolute stereochemistry of the reductions. In addition the observed differences between **3** and **2** are readily understood, including (1) the slower formation of **3** from BH_3·THF relative to **2** from **1** (excess strain of the B=N π-bond at the 5,5-ring fusion of **3**), (2) the stronger coordination of **3** with BH_3·THF to form **4**, and (3) the higher enantioselectivities observed with **3**.

We believe that the mechanistic understanding gained in this work will stimulate further exciting advances in this important area of chemistry. Many applications of this new catalytic methodology in synthesis can be foreseen.[11]

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Isolation and Characterization of a Stable Simple Enol

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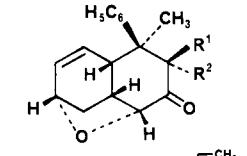
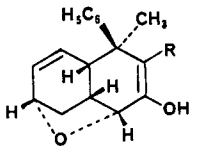
Enols lacking functionality which confers special stability have been called "simple enols" and are generally unstable relative to their carbonyl tautomers.[1] Certain simple enols exhibit unexpected stability, but the underlying reasons are clouded by the paucity of detailed structural data.[1,2] We have isolated simple enol **2** and find it to possess unusual stability. Reported herein are the X-ray structures of ketone **1** and enol **2** which suggest that the stability of enol **2** results from factors which destabilize its ketone tautomer **1**.



1 R^1 = H; R^2 =

3 R^1 = R^2 = H

4 R^1 = H; R^2 = H



2 R =

The synthesis of tricyclic ketone **1** has been reported.[3] The epimeric ketone **3** was of interest as an intermediate in a synthesis project. Surprisingly, treatment of ketone **1** in 5:1 CH_3OH/THF with 10 equiv of $NaOCH_3$ (25 °C, 2 h, Ar) followed by quenching with water afforded (instead of **3**) enol **2** in essentially quantitative yield. In solid or solution phase, enol **2** did not revert to ketones **1** or **3**. The structures of ketone **1** (Figure 1) and enol **2** (Figure 2) were confirmed by X-ray analysis. The relative energies of ketones **1** and **3** and enol **2** were determined by equilibration with 10 mol % $NaOCH_3$ in CD_3OD (sealed tube, 500 MHz PMR analysis), which required in excess of 20 h at 70 °C. The equilibrium ratio of **1**:**2**:**3** was found to be roughly 5:2:3,[4,5] which

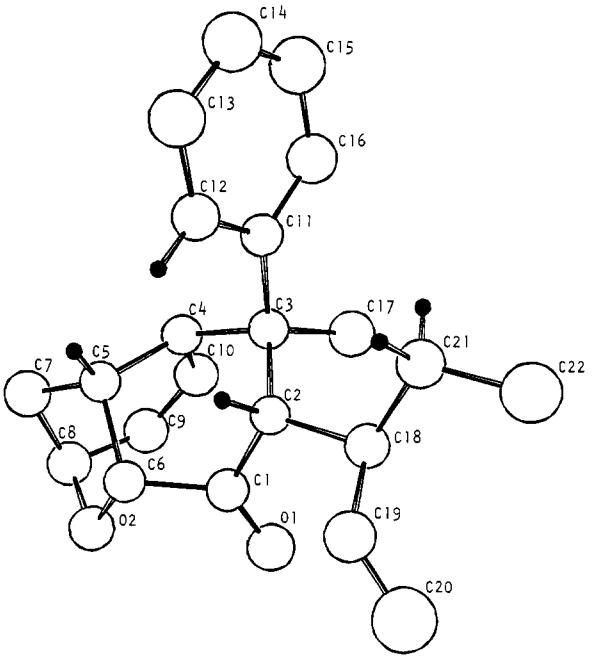


Figure 1. X-ray structure of ketone **1**. Most hydrogens omitted for clarity.

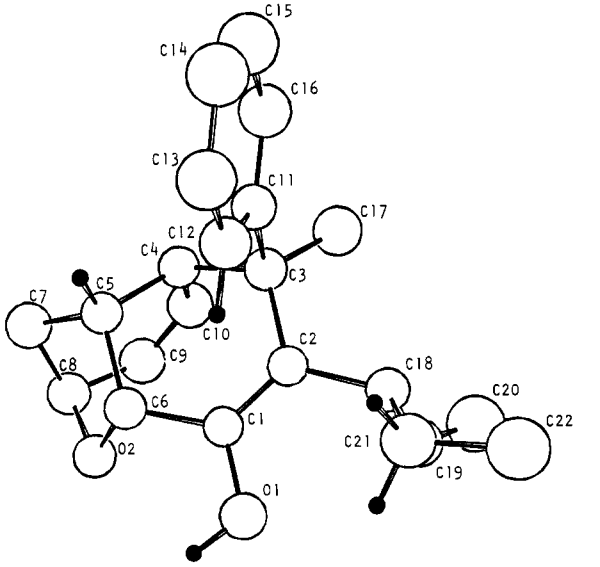


Figure 2. X-ray structure of enol **2**. Most hydrogens omitted for clarity.

corresponds to a free energy difference between enol **2** and ketones **1** and **3** of, respectively, 0.6 and 0.3 kcal/mol.

The X-ray structures of **1** and **2** suggest that the relative thermodynamic stability of enol **2** has its origin in steric and dipolar destabilization of ketones **1** and (presumably) **3** which is relieved on enolization.[1,2,6] Remarkable in the structure of ketone **1** is the sp^3 bond angle C3–C2–C18 of 119.0° which results from van der Waals contact of methylene C21 with C11 of the phenyl ring (see Table I). This contact is relieved on enolization. Additionally, C2 of **1** is strained by contacts of phenyl-bound hydrogen H(C12) with H(C2) and H(C5). Enolization eliminates the H(C2)–H(C12) contact and permits torsional reorganization of the phenyl substituent to relieve the H(C5)–H(C12) contact.

Ketone **1** is further destabilized by dipole–dipole interaction of the carbonyl with the nearly eclipsed ether bridge. Not only does the enol functional group have a lower dipole moment,[7] but the torsional angle with the adjacent C–O bond increases in **2**.

(1) Hart, H. *Chem. Rev.* **1979**, *79*, 515. Hart, H.; Sasaoka, J. *J. Chem. Ed.* **1981**, *57*, 685.
(2) For well-characterized enols of the type first isolated by Fuson, see: (a) Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1007. (b) Kaftory, M.; Biali, S. E.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 1701. (c) Nugiel, D. A.; Rappoport, Z. *J. Am. Chem. Soc.* **1985**, *107*, 3669.
(3) Pratt, D. V.; Hopkins, P. B. *Tetrahedron Lett.* **1987**, *28*, 3065.
(4) All compounds were characterized by IR, ^1H NMR (500 MHz), and MS.
(5) The same ratio was obtained starting with **1**, **2**, or **3**.
(6) Miller, A. R. *J. Org. Chem.* **1976**, *41*, 3599.
(7) Saito, S. *Chem. Phys. Lett.* **1976**, *42*, 399.

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