Application of Chiral Sulfoxides in Asymmetric Synthesis: The Enantiospecific Synthesis of the Chroman Ring of α-Tocopherol (Vitamin E)

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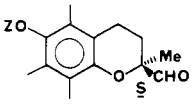
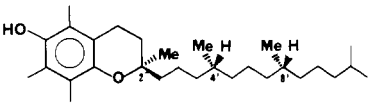
As part of a program aimed at exploring the use of chiral sulfoxides in asymmetric synthesis, we now report the enantiospecific synthesis of the (*S*)-chroman-2-carboxaldehyde **1a**, as its



1a Z = H
1b Z = CH_2Ph



2, 2R 4'R 8'R

benzyl ether **1b**, a key intermediate in the total synthesis of naturally occurring (2*R*,4′*R*,8′*R*)-α-tocopherol (**2**).

The optically active target molecule **1** was until now mainly prepared through optical resolution of the corresponding carboxylic acid[1,2] or synthetized from an optically active precursor.[3-5] Only one report[6] mentioned an attempt of asymmetric synthesis with a poor ee.

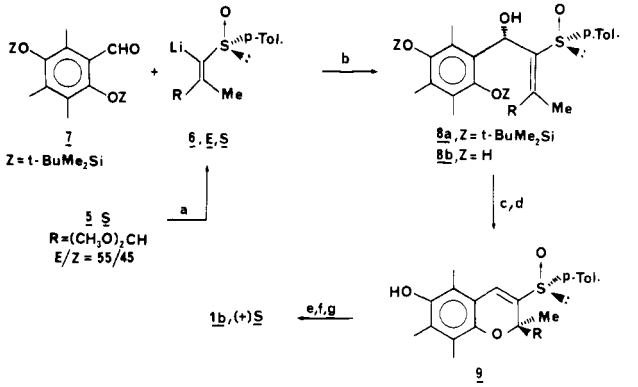
In the synthetic strategy we developed (Scheme I), the crucial steps were first the addition of the stereomerically pure and optically active lithio reagent **6**, as obtained from vinylic sulfoxide **5**, to the aldehyde **7** derived from trimethylhydroquinone and then the cyclization of the adduct **8a**, after deprotection, to chromane **9**. Both reactions indeed were shown to be stereospecific.

(+)-Menthyl (+)-(*R*)-*p*-toluenesulfinate (**3**) ($[\alpha]^{20}_D$ +200°, acetone, *c* 2.1), readily prepared (Scheme II) in 70% overall yield from (+)-menthol, followed by epimerization of the (*S*)-sulfinate to the *R*,[7] was treated with 2 mol of [(dimethylphosphoryl)-methyl]lithium at -70 °C in THF to give the sulfoxide (−)-(*R*)-**4** ($[\alpha]^{20}_D$ −141°, acetone, *c* 2.4) in about 50% yield.[8] Wittig–Horner reaction[9] of the lithio derivative of **4** with the dimethyl ketal of pyruvaldehyde afforded the optically active vinylic sulfoxide **5** in 98% yield as a mixture of isomers[10] (*E*/*Z* = 55/45).

The *E*,*Z* mixture of sulfoxide **5** was readily isomerized with LDA in THF (Scheme I) to the *E* isomer of the metalated species **6**. This result is fully consistent with that of Okamura:[11] the exclusive formation of the *E* isomer may be due to a substantial lowering of the inversion barrier of the vinylic anions,[12] the driving force for the isomerization being the chelation of lithium with the two oxygen atoms of the ketal.[13]

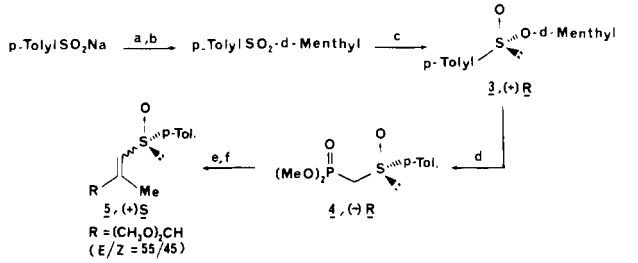
Addition of the lithio reagent **6** to the aldehyde **7**[1] at -78 °C provided the allylic alcohol **8a** in 75% yield as a sole diastereoisomer.[14] Removal of the silyl protecting group was smoothly

Scheme I[a]



[a] (a) LDA, THF, −100 °C, 3 min, (b) 2 h at −78 °C, (c) $(n\text{-Bu})_4$-NF, THF, room temperature 2 h; (d) MeONa, MeOH, reflux 3 h; (e) Raney Ni, benzene, reflux 3 h; (f) $C_6H_5CH_2Br$, CO_3K_2, DMF, room temperature 2 days; (g) $CHCl_3$, CF_3CO_2H/H_2O 1/1, 40 °C, 1 h.

Scheme II[a]



[a] (a) $SOCl_2$, 0 °C; (b) Menthol-*d*, Et_2O, pyridine, 0 °C; (c) sulfur epimerization in acetone, HCl; (d) $(MeO)_2P(O)CH_3$, *n*-BuLi, THF, −78 °C; (e) *n*-BuLi, THF, −78 °C, (f) $(CH_3O)_2CHCOCH_3$, −78 °C.

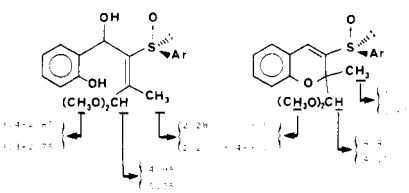
achieved with tetrabutylammonium fluoride in THF at room temperature to give the air-sensitive hydroquinone **8b** in 60% yield. The cyclization was achieved in refluxing methanol[15] in the presence of a 3-fold excess of sodium methoxide, leading to the stereospecific formation of chromene **9** in 96% yield[14] ($[\alpha]^{20}_D$ +31.1°, $CHCl_3$, c 0.85).

The last synthetic steps were straight forward: reductive desulfurization of **9** with Raney nickel (76% yield), benzylation of the phenol (87% yield), acidic cleavage of the ketal (98% yield) leading to optically pure (+)-(*S*)-formylchroman **10** ($[\alpha]^{20}_D$ +12.5°, $CHCl_3$, *c* 2.8; lit.[1,3] $[\alpha]_D$ +11.89° $CHCl_3$, *c* 5.2).

The absolute configurations of compounds **8** and **9** were not established. However, from the models generally used to explain the asymmetric induction of chiral sulfoxides,[16,17] it is possible

(1) Mayer, H.; Schudel, P.; Rüegg, R.; Isler, O. *Helv. Chim. Acta* **1963**, *46*, 650.
(2) (a) Scott, J. W.; Bizarro, F. T.; Parrish, D. R.; Saucy, G. *Helv. Chim. Acta*, **1976**, *59*, 290. (b) Cohen, N.; Lopresti, R. J.; Neukom, C. *J. Org. Chem.* **1981**, *46*, 2445.
(3) Cohen, N.; Lopresti R. J.; Saucy, G. *J. Am. Chem. Soc.* **1979**, *101*, 6710.
(4) Barner, R.; Schmid, M. *Helv. Chim. Acta* **1979**, *62*, 2384.
(5) Fuganti, C.; Grasselli, P. *J. Chem. Soc., Chem. Commun.* **1982**, 205.
(6) Akkerman, J. M.; De Koning, H.; Huisman H. O. *Heterocycles* **1981**, *15*, 797.
(7) Solladie, G. *Synthesis* **1981**, 185.
(8) Mikolajczyk, M.; Midura, W.; Grzejszczak, S.; Zatorski, A.; Chefczyuska, A. *J. Org. Chem.* **1978**, *43*, 473.
(9) Mikolajczyk, M.; Grejszczak, S.; Zatorski, A. *J. Org. Chem.* **1975**, *40*, 1979.
(10) These isomers are easily identified by ^1H NMR from the chemical shift of the vinylic proton: 6.35 ppm for the *E* isomer and 6.1 ppm for the *Z* isomer.
(11) Okamura, H.; Mitsuhira, Y.; Miura, M.; Takei, H. *Chem. Lett.* **1978**, 517.
(12) Houk, K. N.; Caramella, P. *Tetrahedron Lett.* **1981**, *22*, 819.
(13) The equilibration, in the same exptl. conditions, of vinylic sulfoxides **5** (R = phytyl) did not allow the preparation, of the corresponding pure *E* isomer but only a 1/1 mixture of the two isomers.

(14) ^1H and ^{13}C NMR of compounds **8b** and **9** did not show any splitting of signals that could correspond to the other diastereoisomer. For example,



8b showed only one s at 5.9 ppm for C*H*OH, one s at 4.32 for C*H*$(OMe)_2$, and two s at 3.25 and 2.67 ppm for the methoxy. **9** showed only one s at 4.4 for C*H*$(OMe)_2$, one s at 3.5 for the two methoxy groups, and one s at 0.95 for CH_3 on C(2). To confirm this conclusion we allowed reagent **6** to react with salicylaldehyde. In this case we observed a 28/72 mixture of the two diastereoisomeric allylic alcohols easily recognized by ^1H NMR. Each of these diastereoisomers was stereospecifically cyclized and the two corresponding chromenes also showed different NMR spectra.
(15) Cyclization does not occur in the absence of the sulfoxide group.
(16) (a) Mioskowski, C.; Solladie, G. *Tetrahedron* **1980**, *36*, 227. (b) Annunziata, R.; Cinquini, M.; Cozzi, F.; Montanari, F.; Restelli, A. *J. Chem. Soc., Chem. Commun.* **1983**, 1138. (c) Colombo, L.; Gennari, C.; Scolastico, C.; Guanti, G.; Narisano, E. *J. Chem. Soc.* **1981**, 1278.

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to predict the chirality *S* for the created hydroxylic center. In such a case the observed *S* chirality of the chromancarboxaldehyde **1b** would support a syn S_Ni2 mechanism for the stereospecific cyclization of molecule **8b**.

Further applications of this methodology to the asymmetric synthesis of other natural products are in progress.

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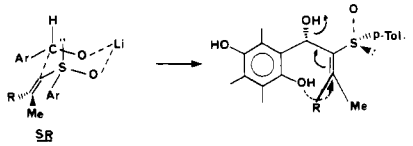
Registry No. 1b, 69400-39-1; **1b**, 91712-49-1; **3**, 91796-57-5; **4**, 61187-71-1; (*Z*)-**5**, 91712-50-4; (*E*)-**5**, 91712-51-5; **6**, 91712-52-6; **7**, 91712-53-7; **8a**, 91712-54-8; **8b**, 91741-62-7; **9**, 91712-55-9; pyruvic aldehyde dimethyl ketal, 6342-56-9.

(17) See reaction below:



On the Mechanism of Metal-Catalyzed Epoxidation: A Model for the Bonding in Peroxo–Metal Complexes

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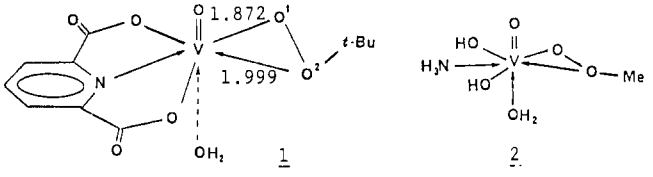
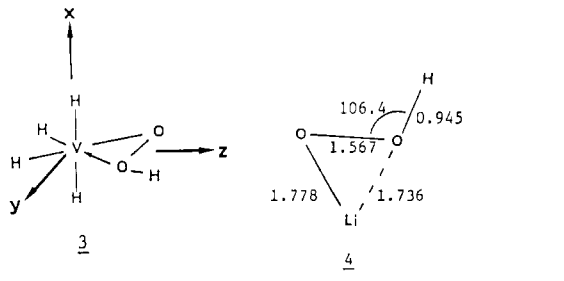
The transfer of oxygen from alkyl hydroperoxides may be effectively catalyzed by high-valent d^0 transition-metal complexes (e.g., Mo^{VI}, V^V, Ti^{IV}). This epoxidation reaction is used extensively in the commercial production of propylene oxide[1] and in many aspects of organic synthesis.[2,3] Although controversy still surrounds the mechanism of these reactions,[4] considerable insight into the subtleties of this catalytic process has resulted from a variety of physical organic data.[3] The X-ray crystal structure of (dipic)VO(OO-*t*-Bu)H_2O (**1**) is a deformed pentagonal bipyramide with the peroxo oxygens in the equatorial plane.[5] The most striking aspect of this complex is that the proximal oxygen–metal bond is only slightly longer than that of the coordinated distal oxygen–metal bond. While hydrogen peroxide is not sufficiently reactive to epoxidize a nonconjugated carbon–carbon double bond, its "electrophilicity" may be markedly enhanced by placing it in conjugation with a multiple bond (e.g., C=O, C=NH).[6] The alkaline-earth anions of H_2O_2 or ROOH will epoxidize conjugated alkenes by a mechanism involving a Michael-type addition.[7] We attribute the fact that ROO^- does not react with simple alkenes to the "super nucelophilicity" of this anion as a consequence of the α-effect.[8] How then can d^0 metal complexes of ROO^- exhibit "electrophilic" behavior toward simple alkenes? We now provide a general theoretical model that describes the metal–peroxide bonding in such complexes and an explanation for why these metal-bound "peroxy anions" can readily transfer oxygen to nucleophilic alkenes.





It is instructive to first examine the frontier MOs (FMO) of the anti periplanar conformer of H_2O_2. The HOMO (ψ_9) lies in the plane of the four atoms and is comprised of a combination of a σ O–O bond and an orbital of "π^* symmetry". The LUMO (ψ_{10}) is the σ^*_{O-O} with a contribution from an in-plane orbital of π-symmetry (Figure 1).[9] It is a σ O–O bond that must be broken during an oxygen transfer from a peroxo complex. Employing LiOOH (**4**) as a model that can be adequately treated theoretically with ab initio calculations,[10] we found that a bridged structure existed at an energy minimum.[11] The HOMO of LiOOH is the π^*_{O-O} orbital ($\psi_{10'}$) that is orthogonal to the molecular plane. The in-plane orbitals, which are involved in the oxygen transfer, give rise to three MOs that are reminiscent of the Walsh orbitals of ethylene oxide.[12a] The next HOMO

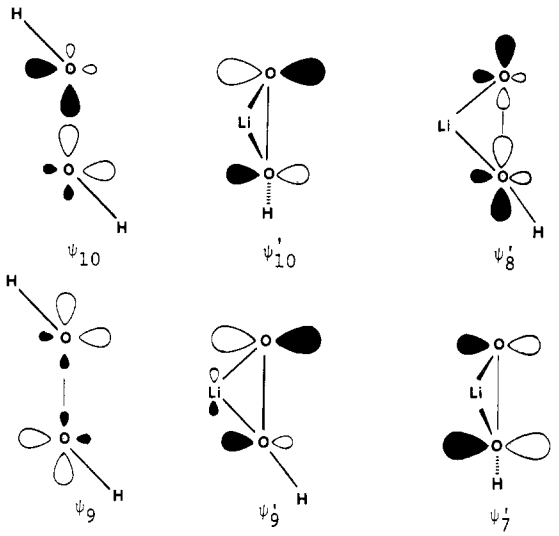


Figure 1. Frontier molecular orbitals of H_2O_2 and LiOOH (STO-3G).

(1) (a) Landau, R.; Sullivan, G. A.; Brown, D. *ChemTech* **1979**, 602. (b) Shell Oil, Brit. Pat. 1 249 079, 1971. Shell Oil, U. S. Pat. 3 923 843, 1975.

(2) (a) Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63. Behrens, C. H.; Sharpless, K. B. *Ibid.*, **1983**, *16*, 67. (b) Sharpless, K. B.; Behrens, C. H.; Katsuki, T.; Lee, A. W. M.; Martin, V. S.; Takatani, M.; Walker, F. J.; Woodard, S. S.; Viti, S. M. *Pure Appl. Chem.* **1983**, *55*, 589.

(3) Sharpless, K. B.; Woodard, S. S.; Finn, M. G. *Pure Appl. Chem.* **1983**, *55*, 1823.

(4) For an alternate viewpoint of the mechanism involving a peroxometallocyclic intermediate, see: (a) Mimoun, H. *J. Mol. Catal.* **1980**, *7*, 1. (b) Chaumette, P.; Mimoun, H.; Saussine, L.; Fischer, J.; Mitschler, A. *J. Organomet. Chem.* **1983**, *250*, 291.

(5) Mimoun, H.; Chaumette, P.; Mignard, M.; Saussine, L. *Nouv. J. Chim.* **1983**, *7*, 467.

(6) For a discussion with previous references, see: Arias, L. A.; Adkins, S.; Nagel, C. J.; Bach, R. D. *J. Org. Chem.* **1983**, *48*, 888.

(7) Apeloig, Y.; Karni, M.; Rapport, Z. *J. Am. Chem. Soc.* **1983**, *105*, 2784.

(8) Hoz, S. *J. Org. Chem.* **1982**, *47*, 3545.

(9) The lower lying occupied π (ψ_7) and π^* (ψ_8) orbitals of the O–O bond are orthogonal to the molecular plane of the H_2O_2 molecule.

(10) The calculations were performed with the GAUSSIAN 80 series of programs with standard MO theory. Both minimal STO-3G and split valence 4-31G basis sets were used: Binkley, J. F.; Whiteside, R. A.; Krishnan, R.; Seeger, R.; DeFrees, D. J.; Schlegel, H. B.; Topiol, S.; Kahn, L. R.; Pople, J. A. *QCPE* **1981**, *13*, 406.

(11) The structure of LiOOH is basis set dependent since the molecule is essentially linear (O–O–Li = 176°) with an STO-3G basis set. Minimizing the geometry by 4-31G, with the OOLi bond angle constrained to the STO-3G minimum of 176°, results in an increase in energy of 18.8 kcal/mol relative to the cyclic 4-31G minimized structure.

(12) (a) Bach, R. D.; Wolber, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 1401. (b) Bach, R. D.; Wolber, J. G. *J. Am. Chem. Soc.* **1984**, *106*, 1410.

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