Oxidation of Silyl Enol Ethers Using 2-Sulfonyloxaziridines. Synthesis of α-Siloxy Epoxides and α-Hydroxy Carbonyl Compounds

Summary: The first isolation and detection of α-siloxy epoxides **2** in the oxidation of silyl enol ethers **1** to α-hydroxy carbonyl compounds **4** (Rubottom reaction) by 2-sulfonyloxaziridine **5** is described. Asymmetric oxidation of silyl enol ethers by (+)-(*R*,*R*)-**6** affords optically active α-hydroxy carbonyl compounds.

Sir: The Rubottom reaction, the peracid oxidation of silyl enol ethers **1**, is a widely used method for the synthesis of α-hydroxy carbonyl compounds **4** (Scheme I).[1] The initially isolated α-trimethylsiloxy carbonyl compounds **3** are thought to be formed via an acid-catalyzed rearrangement of an intermediate siloxy epoxide, **2** (Scheme I). However, all attempts to isolate or even detect α-siloxy epoxides **2** have been unsuccessful to date.[1,2]

In connection with our interest in the synthesis of α-hydroxy carbonyl compounds,[4] we have explored the oxidation of silyl enol ethers **1** using 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)oxaziridine (**5**), an aprotic and neutral oxidizing reagent.[5] In this communication we describe the first detection and isolation of α-siloxy epoxides **2** as well as general methodology for the synthesis of α-hydroxy carbonyl compounds **4** under mild conditions.

Silyl enol ethers[6] (typically 0.6 mmol) dissolved in 5 mL of acid free chloroform[9] were oxidized with 1 equiv of oxaziridine **5** dissolved in 10 mL of $CHCl_3$ in an inert atmosphere. When the oxidation was complete, as determined by the disappearance of the oxaziridine proton at δ 5.6, the solvent was removed and the residue extracted with 5 × 5 mL portions of *n*-pentane. After filtration and removal of the solvent the reaction mixture was hydrolyzed by treatment with HF/MeCN,[10] Bu4NF/THF, or 5% HCl/THF, and **4** was isolated by preparative TLC eluting with *n*-pentane/ether or ether/dichloromethane. Products were identified by comparison with authentic samples. These results are summarized in the Table I.

In the course of monitoring the oxidation of **1c** by NMR in acid-free $CDCl_3$,[9] we noted the quantitative formation of a new species identified as the elusive α-siloxy epoxide **2c**. That this new species is indeed **2c** is based on the fact that its ^1H spectrum is nearly identical with 1-phenyl-2-methylpropene oxide (**7c**)[11-13] (Table II). The IR and ^{13}C

Scheme I

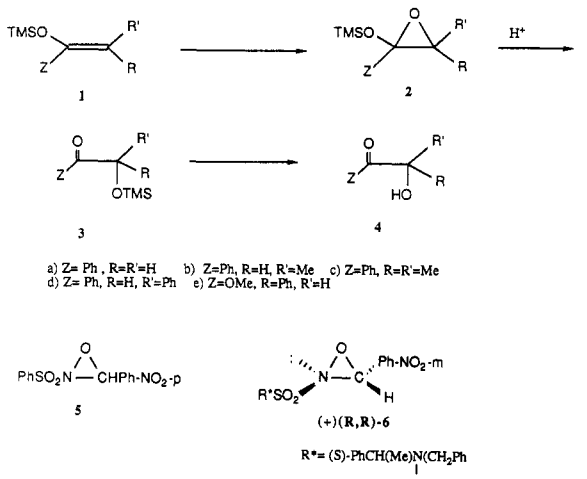
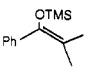
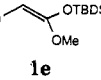
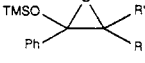
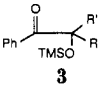
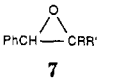


Table I. Oxidation of Silyl Enol Ethers to α-Hydroxy Carbonyl Compounds Using 2-Sulfonyloxaziridines in Chloroform

entry	silyl enol ether (1)	temp, °C (time, h)	hydrolysis method	% yield (4)[a]
1		60 (3)	5% HCl/THF	65[b,c]
		60 (0.5)	5% HCl/THF	51
2	 **1a**	60 (3)	5% HCl/THF	65[c,d]
3	**1a**	60 (3)	HF/MeCN	55
4	 **1b**	25 (17)	5% HCl/THF	80[e]
5	**1b**	60 (1)	5% HCl/THF	81
6	**1b**	60 (1)	Bu_4NF/THF	41
7	 **1c**	25 (4.5)	Bu_4NF/THF	79[f]
8	**1c**	60 (1)	Bu_4NF/THF	75
9	 **1d**	60 (7.5)	HF/MeCN	98
10	**1d**	60 (7.5)	Bu_4NF/THF[g]	
11	 **1e**	25 (0.1)	5% HCl/THF	54[i]

[a] Isolated yield of pure material (>98%). [b] Reference 1a. [c] GLC yield using a 6 ft × 1/4 in., Ov-17 on 90/100 mesh Sulpelcoport column. [d] Reference 1a. [e] Reference 20. [f] Reference 1a. [g] Over-oxidation to benzoin observed. [h] Reference 1h. [i] Reference 4b.

Table II. Comparison of Proton Chemical (δ) Shifts of Siloxy Epoxides 2, α-Siloxy Carbonyls 3, and Epoxides 7 ($CDCl_3$)

(R′, R)	 **2**	 **3**	 **7**
b (R = H, R′ = Me)	1.44 (d), 2.96 (q)	1.49 (d), 5.04 (q)	1.44 (d), 3.02 (m)
c (R = R′ = Me)	1.0 (s), 1.50 (s)	1.58 (s)	1.08 (s), 1.49 (s)
d (R = H, R′ = Ph)	3.83 (s)	5.84 (s)	3.85 (s)

(1) (a) Rubottom, G. M., Vazquez, M. A., Pelegrina, D. R., *Tetrahedron Lett.* **1974**, 4319. (b) Brook, A. G., MaCrae, O. M. *J. Organomet. Chem.* **1974**, *77*, C19. (c) Hassner, A.; Reuss, R. H.; Pinnick, H. W., *J. Org. Chem.* **1975**, *40*, 3427. (d) Rubottom, G. M., Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599. (e) Hanzlik, R. P.; Hilbert, J. M. *J. Org. Chem.* **1978**, *43*, 610. (f) Boeckman, R. K., Jr., Ramaiah, M. *J. Org. Chem.* **1977**, *42*, 1581. (g) Rubottom, G. M.; Gruber, J. M.; Boeckman, R. K., Jr., Ramaiah, M.; Medwid, J. B. *Tetrahedron Lett.* **1978**, 4603. (h) Rubottom, G. M.; Marrero, R. *J. Org. Chem.* **1975**, *40*, 378. (i) McCormick, J. P.; Tomasik, W.; Johnson, M. W. *Tetrahedron Lett.* **1981**, *22*, 607.

(2) Brook reported the detection of a heterocyclic α-siloxy epoxide, but gave no details.[1b] Addition of siloxycarbenes to carbonyl compounds is reported to give an unstable heterocyclic α-siloxy epoxides.[3]

(3) Brook, A. G.; Pearce, R.; Pierce, J. B. *Can. J. Chem.* **1971**, *49*, 1622.

(4) (a) Davis, F. A.; Vishwakarma, L. C. *Tetrahedron Lett.* **1985**, *26*, 3539. (b) Davis, F. A.; Vishwakarma, L. C. *J. Org. Chem.* **1984**, *49*, 3241. (c) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402. (d) Davis, F. A.; Hague, M. S. *J. Org. Chem.* **1986**, *51*, 4083.

(5) Davis, F. A.; Stringer, O. D. *J. Org. Chem.* **1982**, *47*, 1774.

(6) Silyl enol ethers **1a-d**[7] were prepared as previously described. Silyl ketene acetal **1e** was obtained by using a modification of the procedure reported by Ireland et. al.[8] THF was used in place of HMPA to dissolve the *t*-$BuMe_2SiCl$. The *Z*/*E* ratio obtained for **1e** was 21/79, which differs from that reported previously, 71/29, obtained under Ireland's conditions.[8]

(7) Cazeau, P.; Moulines, F.; Laporte, O.; Duboudin, F. *J. Organomet. Chem.* **1980**, *201*, C9-C13.

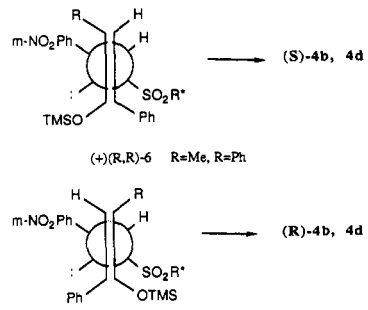
(8) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(9) Chloroform was filtered through basic alumina or treated with Na_2CO_3 prior to use.

(10) Jones, T. K.; Denmark, S. E. *J. Org. Chem.* **1985**, *50*, 4037.

0022-3263/87/1952-0954$01.50/0

Scheme II



NMR spectra of **2c** are also consistent with the proposed structure.[14] Furthermore, addition of a trace of *p*-toluenesulfonic acid to **2c** resulted in its immediate and quantitative rearrangement to α-siloxy ketone **3c**.[1a] At 60 °C, in the absence of acid, the rearrangement of **2c** to **3c** also appeared to be accelerated. α-Siloxy epoxide **2c** proved to be surprisingly stable when the oxidation was carried out in anhydrous THF (16 h, 25 °C) and was isolated in greater than 90% yield, as an oil, by extraction into *n*-pentane. α-Siloxy epoxides **2b** and **2d** were also observed by NMR, but were much less stable, rearranging within 1–8 h to α-siloxy ketones **3b** and **3d**, respectively (Table II).

Asymmetric oxidation of silyl enol ethers **1b** and **1d** at 60 °C by chiral sulfamyloxaziridine (+)-(*R,R*)-**6**[15] gave, after standard workup, optically active α-hydroxy ketones (−)-(*S*)-**4b** and (+)-(*S*)-**4d**, in 7.5% and 11.0% ee and 31% and 62% isolate yields, respectively.[16] In analogy with the epoxidation of alkenes by chiral 2-sulfonyloxaziridines, an open transition state having planar geometry is predicted for the reaction of silyl enol ethers with (+)-(*R,R*)-**6** (Scheme II).[19] The relatively low enantioselectivities obtained in these asymmetric oxidations are understandable considering that the steric difference for reaction of (+)-(*R,R*)-**6** at the re and si faces of the silyl enol ethers is minimal (Scheme II).

In summary, the first isolation and characterization of the elusive α-siloxy epoxides **2** in the Rubottom reaction (Scheme I) is described. We attributed our ability to isolate these labile species to the use of 2-sulfonyloxaziridine **5**, an aprotic and neutral oxidizing reagent. On hydrolysis α-siloxy epoxides **2** afford good to excellent yields of α-hydroxy ketones **4**. In the synthesis of complex polyfunctionalized molecules that require the Rubottom reaction the use of 2-sulfonyloxaziridine **5** is indicated.

(11) A sample of **7c**[12] was prepared in 87% isolated yeild by heating the alkene at 60 °C with oxaziridine **5** for 18 h as previously reported.[13]

(12) Puterbaugh, W. H.; Hauser, C. R. *J. Am. Chem., Soc.* **1964**, *86*, 1394.

(13) Davis, F. A.; Abdul-Malik, N. F.; Awad, S. B.; Harakal, M. E *Tetrahedron Lett.* **1981**, *22*, 917.

(14) ^{13}C NMR (C_6D_6) **2c**: δ 1.84 (TMS), 20.53 (Me_2), 65.93 (CMe_2), 89.12 (PhC[O]OTMS), 127.53–139.93 (Ph); IR (Nujol) 1250 cm^{-1} (COC). **3c**: δ 2.52 (TMS), 29.66 (Me_2), 81.44 (C(OTMS)Me_2), 123.62–136.29 (Ph), 203.10 (CO). **7c**: δ 26.17 (Me), 32.83 (Me), 68.59 (CMe_2), 72.54 (PhCH[O]), 134.52–145.68 (Ph); IR (neat)[12] 1250 and 910 cm^{-1}.

(15) (+)-(*R,R*)-**6** was prepared as previously described: Davis, F. A.; McCauley, J. P., Jr.; Harakal, M. E. *J. Org. Chem.* **1984**, *49*, 1465. Additional details will be published elsewhere.

(16) The optical purities of (−)-(*S*)-**4b**[17] and (+)-(*S*)-**4d**[18] were determined by comparision of the optical rotations with authentic samples.

(17) Konishi, J.; Ohta, H.; Tsuchihashi, G.-i., *Chem. Lett.* **1985**, 1111 and references cited therein.

(18) (−)-(*S*)-2-Hydroxy-1-phenylpropanone (**4b**) was prepared optically pure by reaction of the 1,3-dioxlanone of (−)-(*S*)-lactic acid with phenyllithium at −78 °C: $[\alpha]_D$ −86.7 (*c* 2, $CHCl_3$).[4d]

(19) Davis, F. A.; Harakal, M. E.; Awad, S. B. *J. Am. Chem. Soc.* **1983**, *105*, 3123. Davis, F. A.; Chattopadhyay, S. *Tetrahedron Lett.* **1986**, *27*, 5079.

(20) Harada, K.; Shiono, S. *Bull. Chem. Soc. Jpn.* **1984**, *51*, 1040.

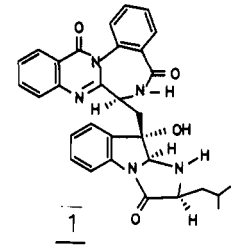
Acknowledgment. We thank Professors Scott Denmark (U. of Illinois) and Eric Block (SUNY Albany) for helpful discussions. This work was supported by the National Science Foundation (CHE 8502076).

Franklin A. Davis,* Aurelia C. Sheppard
Department of Chemistry
Drexel University
Philadelphia, Pennsylvania 19104
Received August 1, 1986

Crystallization-Induced Asymmetric Transformation: Stereospecific Synthesis of a Potent Peripheral CCK Antagonist

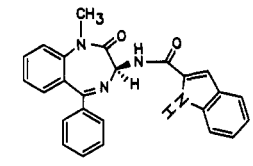
Summary: An efficient, catalytic method for the total conversion of a racemate into a single enantiomer is reported. The combined, in situ resolution–racemization was applied to 3(*RS*)-amino-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one to produce the optically pure *S* enantiomer in 91% yield. Acylation with indole-2-carboxylic acid produced L-364,718, an extremely potent nonpeptidal peripheral CCK antagonist.

Sir: The recent isolation of asperlicin (**1**)[1] and its identification as a selective antagonist of the gastrointestinal hormone cholecystokinin (CCK) has spawned great activity in this area.[2] Asperlicin's lack of oral bioavailability, modest potency, and poor water solubility make it unattractive as a potential therapeutic agent. Thus, a search for a better antagonist, either semisynthetic or synthetic, was undertaken.[3] The result was an extremely potent nonpeptidal CCK antagonist with high selectivity for peripheral tissue: L-364,718 (**2**).[3,4]



1

ASPERLICIN



2

L-364,718

The differences in potency[3] of (*S*)-**2** vs. racemic **2** made it desirable to use the optically pure antagonist as the drug candidate. Thus, a practical asymmetric synthesis was required to permit clinical trials. This paper describes the synthesis of 3(*S*)-amino-1,3-dihydro-1-methyl-5-phenyl-2*H*-1,4-benzodiazepin-2-one [(*S*)-**3**], the key intermediate for the preparation of L-364,718 (**2**), via an efficient, catalytic, one-pot resolution–racemization sequence which renders alternate methods of asymmetric synthesis moot (Scheme I).

(1) (a) Goetz, M. A.; Lopez, M.; Monaghan, R. L.; Chang, R. S. L.; Lotti, V. J.; Chen, T. B. *J. Antibiot.* **1985**, *38*, 1633. (b) Liesch, J. M.; Hensens, O. D.; Springer, J. P.; Chang, R. S. L.; Lotti, V. J. *J. Antibiot.* **1985**, *38*, 1638. (c) Chang, R. S. L.; Lotti, V. J.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Albers-Schonberg, G.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. *Science (Washington, D. C.)* **1985**, *230*, 177.

(2) Albers-Schonberg, G.; Chang, R. S. L.; Lotti, V. J.; Chen, T. B.; Monaghan, R. L.; Birnbaum, J.; Stapley, E. O.; Goetz, M. A.; Lopez, M.; Patchett, A. A.; Liesch, J. M.; Hensens, O. D.; Springer, J. P. In *Proceedings of the Ninth American Peptide Symposium* Deber, C. M., Hruby, V. J., Kopple, K. D., Eds.; Pierce Chemical Co.: Rockford, IL, 1985; pp 565–574.

(3) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whitter, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R. M. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 4918.

0022-3263/87/1952-0955$01.50/0