Chemistry of Oxaziridines. 15.[1] Asymmetric Oxidations Using 3-Substituted 1,2-Benzisothiazole 1,1-Dioxide Oxides

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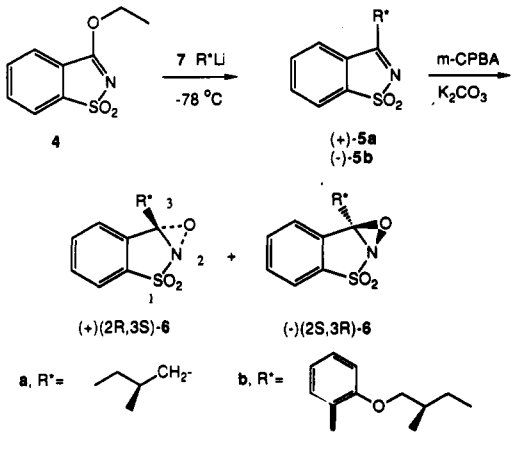
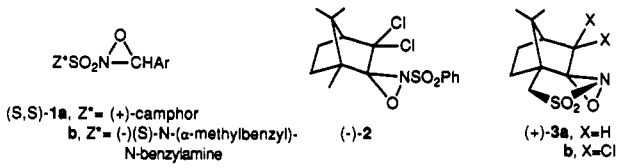
The synthesis and asymmetric oxidations of chiral nonracemic 3-substituted 1,2-benzisothiazole 1,1-dioxide oxides (**6**) are described. These new *N*-sulfonyloxaziridines are prepared by oxidation of the corresponding enantiomerically pure sulfonimines **5**. These reagents oxidize sulfides to sulfoxides (11–52% ee), epoxidize nonfunctionalized alkenes (17–61% ee), and oxidize enolates to α-hydroxy carbonyl compounds (11–81% ee). Epoxidation of (-)-(*S*)-limonene with (+)-(2*R*,3*S*)-**6a**, a double asymmetric synthesis, affords a 93:7 cis/trans mixture of limonene oxides. Evaluation of possible transition-state structures suggests that the molecular recognition is primarily determined by steric factors. These reagents are less effective than *N*-sulfonyloxaziridines **1–3** in their asymmetric oxidations because they lack well-defined regions that are topologically dissimilar near the active site.

The rational design and synthesis of new asymmetric oxidizing reagents that afford high enantioselectivities with predictable stereochemistry is an important goal.[2] Such "reagent-controlled" asymmetric oxidations can, in principal, avoid the problems inherent in resolution procedures and in the use of chiral auxiliaries for the preparation of enantiomerically pure materials.[3] Examples of such reagents are the *N*-sulfonyloxaziridines **1–3**, developed in our laboratory.[2] Because of their different active-site microenvironments these compounds exhibit dissimilar stereoselectivities in their asymmetric oxidations. For example, oxaziridines of type **1** epoxidize nonfunctionalized alkenes with stereoselectivities up to 80% ee.[4] Oxaziridines **2** and **3** are less reactive and do not epoxidize alkenes even on heating.[5,6] (-)-3,3-Dichlorocamphorsulfonyloxaziridine (**2**) [3,3-dichloro-1,7,7-trimethyl-2′-(phenylsulfonyl)spiro[bicyclo[2.2.1]heptane-2,3′-oxaziridine]] affords superior enantioselectivities for the asymmetric oxidation of sulfides (selenides) to sulfoxides (selenoxides), with ee's of 90–95%.[6] On the other hand, (+)-(camphorylsulfonyl)oxaziridine (**3a**) [tetrahydro-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxide] and (+)-[(8,8-dichlorocamphoryl)sulfonyl]oxaziridine (**3b**) [8,8-dichlorotetrahydro-9,9-dimethyl-4*H*-4a,7-methanooxazirino[3,2-*i*][2,1]benzisothiazole 3,3-dioxide] are better than either type **1** or **2** for the asymmetric oxidation of enolates affording α-hydroxy carbonyl compounds, with high stereoinduction (90–95% ee).[7] Studies of the structure–reactivity trends for asymmetric oxidations by **1–3** have provided useful information regarding

Scheme I



the topologies of both the active site and the transition states. It was concluded from these studies that the stereoinduction for oxidations by these reagents was primarily controlled by steric forces.[1,5-8]



In this paper the synthesis and enantioselective oxidations of chiral nonracemic 3-substituted 1,2-benzisothiazole 1,1-dioxide oxides **6**, a new type of *N*-sulfonyloxaziridine oxidizing reagent, are described. These studies are part of our continuing efforts to understand the origins of stereoinduction (molecular recognition) in asymmetric oxidations mediated by these compounds, with the goal of designing more efficient reagents.

Results and Discussion

The methodology employed for the preparation of chiral nonracemic 3-substituted 1,2-benzisothiazole 1,1-dioxide oxides **6** follows that previously developed for the synthesis of racemic **6** and is illustrated in Scheme I.[9] The requisite,

(1) Part 14. Davis, F. A.; Sheppard, A. C.; Chen, B. C.; Haque, M. S. *J. Am. Chem. Soc.* **1990**, *112*, 6679.

(2) For a review on the chemistry of *N*-sulfonyloxaziridines, see: Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *45*, 5703.

(3) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(4) (a) Davis, F. A.; Chattopadhyay, S. *Tetrahedron Lett.* **1986**, 5079. (b) Davis, F. A.; Przeslawski, R. M.; Chattopadhyay, S., unpublished results.

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(6) Davis, F. A.; ThimmaReddy, R.; Weismiller, M. C. *J. Am. Chem. Soc.* **1989**, *111*, 5964.

(7) (a) Davis, F. A.; Haque, M. S.; Ulatowski, T. G.; Towson, J. C. *J. Org. Chem.* **1986**, *51*, 2402. (b) Davis, F. A.; Haque, M. S. *J. Org. Chem.* **1986**, *51*, 4083. (c) Davis, F. A.; Ulatowski, T. G.; Haque, M. S. *J. Org. Chem.* **1987**, *52*, 5288. (d) Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021. (e) Davis, F. A.; Weismiller, M. C.; Lal, G. S.; Chen, B. C.; Przeslawski, R. M. *Tetrahedron Lett.* **1989**, 1613. (f) Davis, F. A.; Weismiller, M. C. *J. Org. Chem.* **1990**, *55*, 3715.

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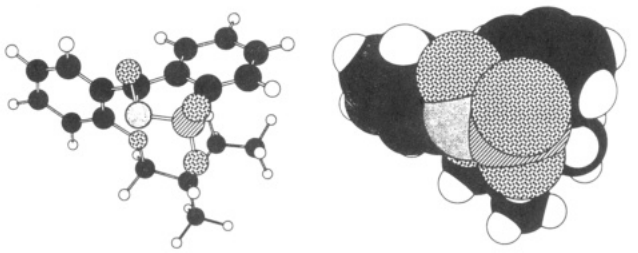
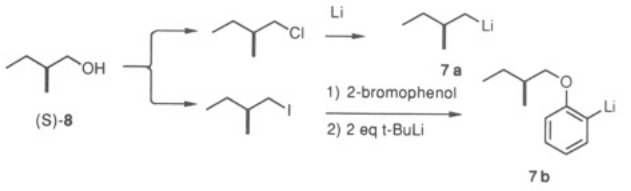


Figure 1. Computer-generated X-ray structure of (+)-(2*R*,3*S*)-**6b**.

enantiomerically pure, 3-alkyl- and -aryl-1,2-benzisothiazole 1,1-dioxides **5** were prepared by reaction of pseudosaccharin ethyl ether (**4**) with 1.1 equiv of an in situ generated chiral lithium reagent **7**. Thus, treatment of **4** with **7a** or **7b** (R*Li) at −78 °C in THF gave sulfonimines (−)-**5a** and (+)-**5b** in 54 and 70% yields, respectively.

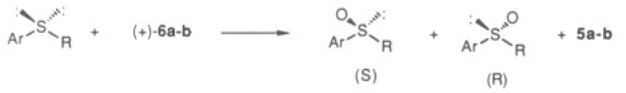
(*S*)-1-Lithio-2-methylbutane (**7a**) was generated by refluxing (*S*)-1-chloro-2-methylbutane[10a] with lithium wire in *n*-hexane for 18 h. The chloride rather than the bromide was used in these studies because it was found that the former gives higher yields of metalation vs Wurtz coupling.[11] (+)-(*S*)-1-Chloro-2-methylbutane was prepared from commercially available (*S*)-2-methyl-1-butanol (**8**) in 85% yield by using thionyl chloride.[10a]



Attempts to prepare [2-[(*S*)-2-methylbutoxy]phenyl]-lithium (**7b**) by ortho lithiation of the corresponding ether **7b** (Li = H), in analogy to the ortho lithiation of anisole by *n*-butyllithium,[12] failed. Starting material was recovered unchanged, although some phenol (ca. 10–15%) resulting from cleavage of the ether was obtained.[13] The desired product was prepared from the corresponding bromide (**7b**, Li = Br) by treatment with 2 equiv of *tert*-butyllithium in *n*-hexane at −78 °C. While *n*-butyllithium or *sec*-butyllithium also effects this lithiation, the excess reagent, necessary to drive the reaction to completion, adds to **4**, giving **5** (R* = *n*-butyl, *sec*-butyl), complicating workup and resulting in low yields. Although excess *tert*-butyllithium is also required to prepare **7b**, the excess of this reagent is destroyed prior to reaction with **4** by *cautious* warming to room temperature. The bromide was prepared in 69% yield by reaction of (+)-(*S*)-2-methyl-1-iodobutane[10] with 2-bromophenol in the presence of sodium hydroxide.

Both sulfonimines **5** gave satisfactory elemental analyses and exhibited infrared absorption at 1590–1605 cm^{-1} for the C–N double bond. The absorption at δ 175 ppm for the imino carbon in the ^{13}C NMR spectra of **5** is particularly characteristic of the structure of these compounds.[8]

Table I. Asymmetric Oxidation of Sulfides to Sulfoxides by (+)-6a and (+)-6b at 25 °C



			sulfoxide % ee (confign)	
entry	oxaziridine	solvent	*p*-Tol–S(O)–*n*-Bu	9-anthryl–S(O)–Me
1	(+)-**6a**	$CHCl_3$	19 (*S*)	52 (*S*)
2		CCl_4	14 (*S*)	50 (*S*)
3	(+)-**6b**	$CHCl_3$	11 (*S*)	13 (*S*)
4		CCl_4	14 (*S*)	30 (*S*)
5	(*S,S*)-**1b**[a]	$CHCl_3$	31 (*S*)	50 (*S*)
6	(−)-**2**[b]	CH_2Cl_2	61 (*S*)	95 (*S*)
7		CCl_4	84 (*S*)	95 (*S*)
8	(+)-**3a**[c]	$CHCl_3$	3 (*S*)	73 (*S*)
9	(+)-**3b**[d]	CH_2Cl_2	54 (*S*)	42 (*S*)
10		CCl_4	74 (*S*)	69 (*S*)

[a] Reference 8. [b] Reference 6. [c] Reference 5. [d] Reference 15.

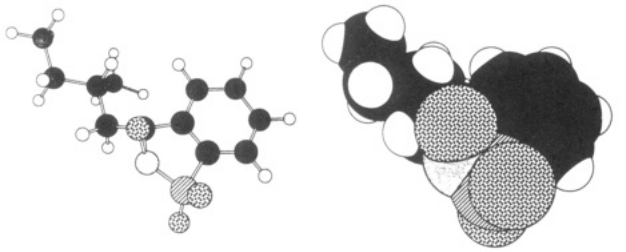


Figure 2. MMX-generated structure of (+)-(2*R*,3*S*)-**6a**.

Biphasic oxidation of (+)-**5a** and (−)-**5b** using 1.5 equiv of 95% *m*-chloroperbenzoic acid (*m*-CPBA) saturated with aqueous K_2CO_3 (CH_2Cl_2) gave oxaziridines **6a** and **6b** in 75 and 86% yields, respectively, as diastereomeric mixtures. The diastereomeric ratio, determined by NMR of (+)-**6a**/(−)-**6a**, is 85:15, whereas the ratio of (+)-**6b**/(−)-**6b** is 45:55. Several crystallizations from ethanol gave diastereomerically pure (+)-**6a** (34%) and (+)-**6b** (18%). Oxaziridines (+)-**6a,b** are stable white crystalline solids melting without decomposition. The oxaziridine carbon atom appears at δ 85 ppm in the ^{13}C NMR spectra of these compounds.

The absolute configuration of the oxaziridine three-membered ring in (+)-**6b** was determined to be 2*R*,3*S* by X-ray crystallographic analysis (Figure 1). The bond lengths and bond angles of the oxaziridine three-membered ring in (+)-**6b** is similar to those of oxaziridines of types **1**–**3**.[5,8] Note that the 3-aryl substituent in (+)-**6b** is situated such that the (*S*)-2-methylbutyl ether group is tucked underneath the benzisothiazole ring, away from the active site.

For asymmetric oxidations using oxaziridines **1**–**3a**, previous studies have shown that the configuration of the oxaziridine three-membered ring controls the product stereochemistry.[1,5,8] Therefore, on the basis of the structure–reactivity trends (Tables I–III), the absolute configuration of the oxaziridine three-membered ring in (+)-**6a** is 2*R*,3*S*. The MMX (PCMODEL) generated structure of (+)-**6a** is shown in Figure 2 and suggests that the conformation of the (*S*)-2-methylbutyl group is directed away from the active-site oxygen.[22] It is worth noting that PCMODEL faithfully reproduced the X-ray structure of (+)-**6b**.

To evaluate the efficiencies of this new type of chiral nonracemic *N*-sulfonyloxaziridine, the asymmetric oxidation of sulfides to sulfoxides and the epoxidation of alkenes

(9) Davis, F. A.; Towson, J. C.; Vashi, D. B.; ThimmaReddy, R.; McCauley, J. P., Jr.; Harakal, M. E.; Gosciniak, D. *J. Org. Chem.* **1990**, *55*, 1254.

(10) (a) Whitmore, F. C.; Olewine, J. H. *J. Am. Chem. Soc.* **1938**, *60*, 2570. (b) Bestmann, J. J.; Attygalle, A. B. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 784.

(11) Gilman, H.; Zoellner, E. A.; Dickey, J. B.; Selby, W. M. *J. Am. Chem. Soc.* **1935**, *57*, 1061.

(12) (a) Finnegan, R. A.; Altschuld, J. W. *J. Organomet. Chem.* **1967**, *9*, 193. (b) Shirley, D. A.; Johnson, J. R., Jr.; Hendrix, J. P. *J. Organomet. Chem.* **1968**, *11*, 209. (c) Ellison, R. A.; Kotsonis, F. N. *J. Org. Chem.* **1973**, *38*, 4192.

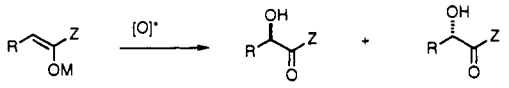
(13) For examples of the cleavage of ethers by alkali organometallic compounds, see: Maercker, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 972.

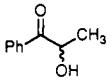
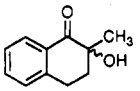
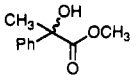
Table II. Epoxidation of Alkenes Using (+)-(2*R*,3*S*)-6b at 60 °C

entry	alkene	solvent	time, days	% yield	products: % ee (confign)	products: cis/trans
1	*trans*-β-methylstyrene	$CHCl_3$	6	20	44 [53.0][a] (1*R*,2*R*)	
2		CCl_4	6	20	51 (1*R*,2*R*)	
3	*cis*-β-methylstyrene	$CHCl_3$	9	20	61 (1*S*,2*R*)	
4		CCl_4	18	20	61 (1*S*,2*R*)	
5	1-methylcyclohexene	$CHCl_3$	6	90	17 [19.4][a,b] (1*S*,2*R*)	
6	(+)-(*R*)-limonene	$CHCl_3$	2	90		55:45
7	(−)-(*S*)-limonene	$CHCl_3$	2	90		93:7

[a] Epoxidation using (*R*,*R*)-1b (Ar = C_6F_5) at 60 °C, ref 4a. [b] Epoxidation using (*R*,*R*)-1b (Ar = C_6F_5) at 25 °C, ref 4b.

Table III. Asymmetric Oxidation of Enolates in THF with (+)-6a and (+)-6b at 0 °C



entry	product	conditns: base	*N*-sulfonyloxaziridine: % ee (confign)[b] [% isolated yield]: (+)-3a[a]	(+)-3b[b]	(+)-6a	(+)-6b
1		NHMDS	62 (*S*) [77][c]	95 (*S*) [61]	11 (*R*) [40]	68 (*R*) [55]
2		LDA	40.3 (*S*) [45]	95 (*S*) [74]	60 (*R*) [40]	81 (*R*) [45]
3		NHMDS	16 (*R*) [90]	95 (*R*) [66]	10 (*S*) [21]	6 (*S*) [35]
4		LDA	30 (*R*) [90]	95 (*R*) [60]	4 (*S*) [21]	39 (*S*) [61]
5		LDA	41 (*R*) [61][c]		15 (*R*) [60]	10 (*R*) [55]

[a] See ref 1, 7a, and 7c. [b] See ref 7f. [c] The % ee determined by the chiral shift reagent Eu(hfc)$_3$. Oxidation at −78 °C.

and hydroxylation of enolates to α-hydroxy carbonyl compounds by (+)-**6a,b** were explored.

Asymmetric Oxidation of Sulfides to Sulfoxides. Methyl 9-anthryl and *p*-tolyl *n*-butyl sulfides (ArSR) were oxidized by (+)-(2*R*,3*S*)-**6a,b** to the corresponding sulfoxides in $CHCl_3$ and CCl_4. The rates of oxidation, which were complete and quantitative within 2–3 h (20 °C), are slower than the rates observed for oxaziridine types 1 and 3 (1–5 min), but comparable to that of oxaziridine 2.[5,6,8] The enantiomeric excesses (% ee) were determined by using the Pirkle chiral HPLC column and the absolute configurations determined by comparison of the optical rotations to literature values.[5,6,8] These results are summarized in Table I.

Oxidation of sulfides to sulfoxides by *N*-sulfonyloxaziridines is considered to involve an S_N2 type reaction mechanism with a transition state where the lone pairs of the sulfide approach the active-site oxygen in the plane of the oxaziridine three-membered ring.[8] It was suggested that this arrangement is favored over spiro geometry, where the lone pairs bisect the oxaziridine three-membered ring, because there were fewer nonbonded interactions. However, recent calculations by Bach et al. suggest that there is no stereoelectronic preference for either transition-state geometry and that the enantioselection is determined by the substituents attached to the oxaziridine three-membered ring.[14]

The results summarized in Table I suggest that the enantioselection for the oxidation of sulfides to sulfoxides by (+)-(2*R*,3*S*)-**6a,b**, as observed for oxaziridine types 1–3, is determined by steric forces. The lack of solvent effects in these oxidations is in accord with the minor, if any, role played by stereoelectronic forces, i.e., dipole–dipole association, van der Waals attractions, π-stacking, etc. For the oxidation of sulfides to sulfoxides by (+)-(2*R*,3*S*)-**6a,b**, transition-state structures I–IV are analyzed (Dreiding models) for their nonbonding interactions (Figure 3).

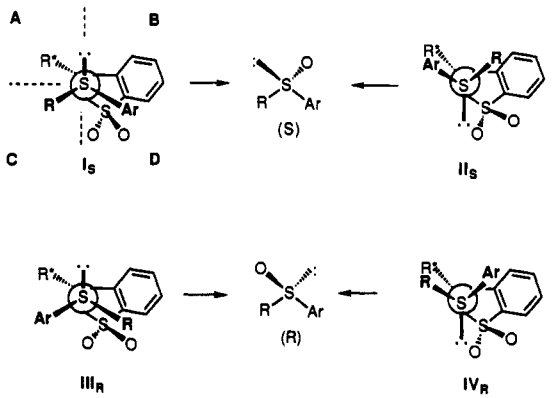


Figure 3. Planar transition states for the oxidation of sulfides to sulfoxides by (2*R*,3*S*)-**6**.

Inspection of the X-ray structure of (+)-(2*R*,3*S*)-**6b** and the computer-generated structure of (+)-(2*R*,3*S*)-**6a** suggests that there are no dominant steric control elements near the active-site oxygen with the exception of the sulfonyl oxygen (Figures 1 and 2). Earlier studies have, however, suggested that the relative bulk of this oxygen is small in sulfide[5] and enolate[1] oxidations by (+)-**3a**. This means that quadrants A, B, and D (Figure 3) are of similar size, in accord with the low to moderate enantioselectivities (11–52% ee) exhibited by these reagents (Table I; entries 1–4). The fact that (+)-(2*R*,3*S*)-**6a** and (+)-(2*R*,3*S*)-**6b** give predominantly the (*S*)-sulfoxides implies that structures I_S and II_S are energetically more favored than III_R or IV_R, with II_S being lowest in energy (Figure 3). The highest energy structure appears to be IV_R, perhaps because of an unfavorable repulsive interaction between the π-system of **6** and the π-aryl system of the sulfide. The somewhat lower ee's exhibited by (+)-**6b** compared to (+)-**6a** for the

(14) Bach, R. D.; Coddens, B. A.; McDouall, J. J. W.; Schlegel, H. B.; Davis, F. A. *J. Org. Chem.* **1990**, *55*, 3325.
(15) Weismiller, M. C., unpublished results from these laboratories.

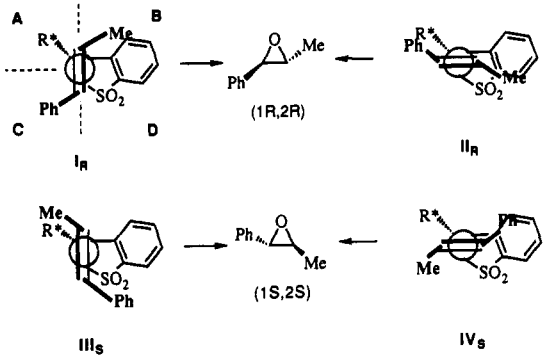
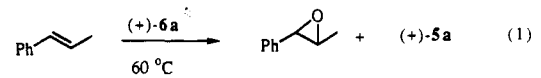


Figure 4. Transition states for the epoxidation of *trans*-β-methylstyrene.

oxidation of methyl 9-anthryl sulfide, where substrate group size difference is large, are in agreement with the greater bulk of the aryl group (R*), which increases the size of quadrant A for **6b** and raises the energy of II_S.

As is evident from the results listed in Table I, oxaziridines **6** are less efficient for the enantioselective oxidation of sulfides to sulfoxide than either of types **1**, **2**, or **3b** (Table I, entries 5–7 and 9–10). We attribute the higher selectivity of these latter reagents to the presence of well-defined regions or quadrants near the active-site oxygen that are more topologically different than those found in **6**.

Asymmetric Epoxidation of Alkenes. The epoxidation of *trans*- and *cis*-β-methylstyrene and 1-methylcyclohexene was accomplished by heating with (+)-(2*R*,3*S*)-**6a** at 60 °C for several days (eq 1). Even at



60 °C the rates of epoxidation are very slow for the less reactive arylalkenes. For example, while epoxidation of 1-methylcyclohexene was complete in 2 days, less than a 20% yield of *trans*- and *cis*-β-methylstyrene oxides was obtained after 6 and 18 days, respectively. Epoxidation rates for when (+)-**6b** was used were even slower, and studies with this reagent were not pursued further. The ee's were determined by separation of the enantiomeric epoxides on a chiral capillary column, and the absolute configurations were determined by comparison with known samples.[4,16,17] The enantioselectivities exhibited by (+)-(2*R*,3*S*)-**6a** for these alkenes are comparable to the values obtained when (*S*,*S*)-**1b** (Ar = C_6F_5) was used, i.e., 53 and 19% ee, respectively.[4] These results are summarized in Table II.

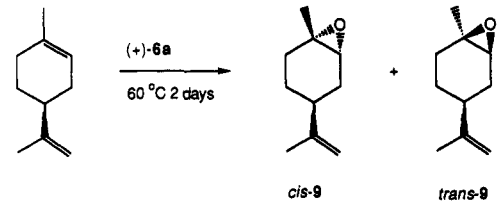
Epoxidation of *trans*-β-methylstyrene to (1*R*,2*R*)-*trans*-β-methylstyrene oxide by (+)-(2*R*,3*S*)-**6a** is consistent with the transition-state model developed for the asymmetric oxidation of sulfides to sulfoxides (Figure 3). It was argued on the basis of the structure-reactivity trends that unfavorable nonbonded interactions between the substrate and the aromatic π-system/sulfonyl oxygen in **6** were responsible for controlling the stereochemistry (i.e., quadrants B and D are somewhat larger than quadrant A, Figure 3). For the epoxidation of alkenes (Figure 4), structure I_R is favored because the phenyl group is located in vacant quadrant C. Structure II_R is also favored because Ph is directed away from the benzisothiazole ring in quadrant B and the SO_2 group in quadrant D, respectively.

(16) Schurig, V.; Weber, R. *J. Chromatogr.* **1981**, *217*, 51.
(17) Prezleswski, R. M., unpublished results. Details of the preparation and application of this column for the analysis of chiral epoxides will be described elsewhere.

Similar arguments can be made for the epoxidation of *cis*-β-methylstyrene to (1*S*,2*R*)-*cis*-β-methylstyrene oxide (Table II, entries 3 and 4).

Earlier studies have shown that racemic **6** (R* = *n*-butyl, *sec*-butyl, etc.) gave better cis/trans selectivities, 75:25, for the epoxidation of (*R*)-(+)-limonene (**8**) than did **1** (R = Z* = Ph, Ar = *p*-NO_2Ph), 65:35, or perbenzoic acid, 1:1.[8,9]

In principal, it is possible to improve the cis/trans epoxidation selectivity by employing double asymmetric synthesis, i.e., epoxidizing chiral limonene with an enantiomerically pure reagent such as (+)-**6**. In double asymmetric syntheses the inherent diastereofacial preferences of the two chiral reactants may reinforce or oppose one another.[3] Heating (*R*)-(+)-limonene with (+)-**6a** for 2 days at 60 °C resulted in a 90% yield of a 55:45 cis/trans mixture of limonene oxides (**9**). The cis/trans selectivity improved to 93:7 when (*S*)-(−)-limonene was epoxidized by (+)-**6a** (Table II, entries 6 and 7). Double asymmetric synthesis is apparently operating in these epoxidations because (*S*)-(−)-limonene and (+)-**6**, the matched pair, give a high 93:7 cis/trans ratio whereas (*R*)-(+)-limonene and (+)-**6**, the mismatched pair, give a 55:45 cis/trans ratio (Table II, entries 6 and 7).



Asymmetric Oxidation of Enolates. The lithium and sodium enolates of 1-phenyl-1-propanone, 2-methyl-1-tetralone, and methyl 2-phenylpropionate were oxidized by addition of (+)-(2*R*,3*S*)-**6a** or (+)-(2*R*,3*S*)-**6b** to the preformed enolate anions as previously described.[1,7] Oxidation of these enolates was incomplete at −78 °C, and warming to 0 °C for several hours was required. By contrast the sodium and the lithium enolates of 1-phenyl-1-propanone and methyl 2-phenylpropionate, respectively, were completely oxidized within a few minutes at −78 °C by (+)-**3a,b**.[1,7f] The enantiomeric purity of the α-hydroxy carbonyl compounds was determined by using the chiral shift reagent Eu(hfc)$_3$, and the absolute configurations were assigned by comparison of the optical rotations with literature values.[1] These results are summarized in Table III.

Several trends are evident from the results summarized in Table III for the asymmetric oxidation of enolates. Oxaziridines (+)-(2*R*,3*S*)-**6a** and (+)-(2*R*,3*S*)-**6b** give α-hydroxy carbonyl compounds having configurations opposite to those realized with (+)-**3a,b**. For example, (*S*)-2-hydroxy-1-phenylpropanone was obtained by using (+)-**3a,b**, while the *R* configuration was obtained by using (+)-**6a,b** (Table III, entries 1 and 2). A similar reversal in configuration is observed for 2-hydroxy-2-methyl-1-tetralone with these reagents (entries 3 and 4). It is worth mentioning that for the asymmetric oxidation of sulfides to sulfoxides both (+)-**3a,b** and (+)-**6a,b** gave the (*S*)-sulfoxides (Table I). For the oxidation of the lithium enolate of 1-phenylpropanone the ee's exhibited by **6a,b** are better than for oxaziridine (+)-**3a**, 60–80% vs 40% ee, but inferior to (+)-**3b** (Table II, entry 2).

Studies of the enantioselective oxidation of ketone enolate anions by **3a** identified (i) the enolate geometry, (ii) the enolate substitution pattern, and (iii) the enolate solution structure as responsible for the stereoinduction.[1] A mechanistic rationale involving an S_N2 type substitution

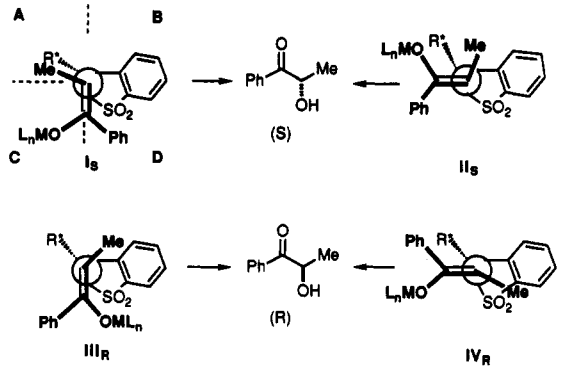


Figure 5. Proposed transition-state structure for the asymmetric oxidation of the propiophenone enolate anion by (+)-6.

of the enolate aggregate on (+)-**3a**, via an "open" transition state, was formulated. As observed for the oxidation of sulfides to sulfoxides and for the epoxidation of alkenes by the reagents, steric factors are primarily responsible for the stereoinduction. While the origins of the very high enantioselectivities observed with (+)-**3b** for enolate oxidations are less clear, similar steric arguments are useful in predicting the product stereochemistry.[7f]

Figure 5 shows the transition-state structures I–IV for the oxidation of the 1-phenylpropanone enolate anion by (+)-6 with are evaluated for their nonbonded interactions. Given the reasonable assumption that the aggregated metal enolate is sterically the most demanding region in the vicinity of the enolate C–C bond, then the lowest energy structure appears to be IV_R. This is in accord with the fact that these reagents give predominantly (*R*)-2-hydroxy-1-phenylpropanone (Table III, entries 1 and 2). However, this analysis suggests that I_S should also have a favorable geometry. As argued for the oxidation of sulfides to sulfoxides and the epoxidation of alkenes, an adverse interaction between the phenyl group of the enolate and oxaziridine and/or the sulfonyl oxygen may increase the energy of this structure. The higher ee's associated with (+)-**6b** vs (+)-**6a**, 68–81% vs 11–60%, may be related to the increase in size of quadrant A, which raises the energies of structures I_S and II_S compared to IV_R. Possible chelation of the enolate aggregate with one of the sulfonyl oxygens and/or the oxaziridine nitrogen may also favor structures III_R and IV_R over I_S and II_S, respectively.[1]

While similar structures can be drawn and arguments made to explain the stereoinduction for oxidation of the other enolates listed in Table III, the energy differences are too small for such interpretations to have any real significance.

Summary and Conclusions. For the asymmetric oxidation of sulfides to sulfoxides and the hydroxylation of enolates to α-hydroxy carbonyl compounds, the stereoselectivities exhibited by (+)-(2*R*,3*S*)-**6a,b** are clearly inferior to those of the camphor-based oxaziridines of types **2** and **3**. Furthermore, these reagents are more difficult to obtain in enantiomerically pure form because diastereomer separation, not required for **2** and **3**, is necessary. The asymmetric epoxidation of alkenes with (+)-**6a** does however show promise. The stereoselectivities obtained with this reagent, 51–61% ee, are similar to those of oxaziridines of type **1** and afford some of the highest enantioselectivities reported for the asymmetric epoxidation of nonfuctionalized alkenes.[18] The double asymmetric epoxidation of (−)-(*S*)-limonene with (+)-(2*R*,3*S*)-**6a** to afford a 93:7 mixture of cis/trans limonene oxide is potentially quite useful.

Chiral nonracemic 3-substituted 1,2-benzisothiazole 1,1-dioxides (**6**) are the only oxaziridines reactive enough to epoxidize alkenes, oxidize sulfides to sulfoxides, and hydroxylate enolates to α-hydroxy carbonyl compounds. Thus the opportunity for analyzing the origins of the enantioinduction (molecular recognition) for the asymmetric oxidation of a diverse group of substrates is possible. Furthermore, mechanistic rationales developed by using *N*-sulfonyloxaziridines are likely to be more reliable than those developed with other systems because these reagents have rigid, well-defined active sites.

The steric approach model, wherein the chiral recognition is primarily determined by evaluating the nonbonded interactions in the transition state, provides a useful rationale for the product stereochemistry (Figures 3–5). For (+)-(2*R*,3*S*)-**6a,b** the dominant transition-state control element appears to be an unfavorable interaction between the π-system of the benzisothiazole ring system (quadrant B) and the substrate. We believe that the low to moderate stereoselectivities (10–80% ee) exhibited by these reagents are a reflection of the fact that quadrants A, B, and D offer similar steric environments to the substrate. Thus the much better enantioselectivities exhibited by reagents **1–3** are likely related to the presence of well-defined regions or quadrants that topologically differ from one another near the active-site oxygen. Thus topological dissymmetry near the active-site oxygen in the *N*-sulfonyloxaziridines appears to be a fundamental requirement for achieving high stereoinduction with these reagents.

Experimental Section

Details concerning the recording of spectra, the analytical instruments used, the determination of melting points, elemental analyses, and the purification of solvents have been previously described.[5] A 3% OV-17 column (6 ft × $^1/_8$ in. 80/100 Supelcoport) and an SPB-35 columns (60 m × 0.75 mm, 1-μm film thickness, borosilica glass) were used for GLC analysis. An SE-30 manganese(II) bis[3-(heptafluorobutyryl)-(1*R*)-camphorate][16] custom Supelco column (15 m × 0.75 mm, borosilicate glass) at a flow rate of 8 mL/min at 60 °C (isothermal) was used to separate the enantiomeric epoxides.[17]

Unless otherwise noted, organic reaction mixtures were washed with water (H_2O) and with saturated sodium chloride solution (NaCl) and dried over anhydrous $MgSO_4$. Solvents were removed under vacuum with a rotary evaporator. Air-sensitive materials were generally transferred via syringes into flame-dried reaction flasks equipped with rubber septa. All reactions were carried out under an atmosphere of dry nitrogen or argon. (*S*)-1-Chloro-2-methylbutane was prepared according to the method of Whitmore and Olewine.[10a] *m*-Chloroperbenzoic acid (*m*-CPBA) was purified by using monophosphate buffer of pH 7.5.[19] Lithium diisopropylamide (LDA) was freshly prepared, and sodium bis(trimethylsilyl)amide was purchased from Aldrich Chemical Co.

PCMODEL, Serena Software, Bloomington, IN. MMX version by K. E. Gilbert and J. J. Gajewski based on MM2 (Allinger, QCPE 395) and MMP1 Pi (Allinger, QPEC 318) modified by K. Steliou.

(+)-3-[(*S*)-2-Methylbutyl]-1,2-benzisothiazole 1,1-Dioxide (5a). (*S*)-1-Lithio-2-methylbutane (7a). To a suspension of 0.6 g of lithium wire (3.2-mm diameter, 1% Na, freshly cut into small pieces, under a stream of argon) in 100 mL of *n*-hexane, freshly distilled from CaH_2, was added 9.0 g (85 mmol) of (*S*)-1-chloro-2-methylbutane in one portion. The solution was warmed to 45 °C with an oil bath and kept at this temperature for 18 h. As the reaction progressed, a deep lavender color appeared and the lithium wire floating at the top of the reaction mixture sank

(18) For leading references to the asymmetric epoxidation of nonfunctionalized alkenes, see: Shang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801.

(19) Schwartz, N. N.; Blumberger, J. H. *J. Org. Chem.* **1964**, *29*, 1976.

to the bottom. After the reaction was complete, stirring was stopped and the solids were allowed to settle to the bottom of the flask.

In a separate 500-mL reaction flask was placed 8.7 g (41 mmol) of pseudosaccharin ethyl ether (4) in 300 mL of tetrahydrofuran (THF) cooled to −78 °C. The (S)-1-lithio-2-methylbutane (**7a**) solution, prepared above, was added dropwise to the cooled reaction flask containing 4 under argon pressure, via a flex-needle assembly (12 gauge, 36 in.), over a period of 45 min. After the red solution was stirred for 4 h at −78 °C, the reaction mixture was quenched by slow addition of 40 mL of H_2O, warmed to room temperature, and diluted with 200 mL of ether. After washing and drying, the resulting white solid was purified by flash chromatography (30:70 ether/*n*-pentane), affording 10.8 g (54%) of (+)-**5a**; mp 54–55 °C; $[\alpha]^{20}_D$ +24.2° (*c* 2.0, $CHCl_3$); IR (NaCl film) 1605 cm^{-1} (s, C=N), 1335 and 1170 cm^{-1} (m, SO_2); ^1H NMR ($CDCl_3$) δ 0.94 (t, 3 H, *J* = 7.2 Hz, Me), 1.02 (d, 3 H, *J* = 6.5 Hz, Me), 1.31–1.51 (m, 2 H, CH_2), 2.1–2.34 (m, 1 H, CH), 2.67–2.98 (m, 2 H, CH_2), 7.69–7.73 (m, 3 H, arom), 7.87–7.90 (m, 1 H, arom); ^{13}C NMR ($CDCl_3$) δ 7.70, 18.88, 29.07, 32.39, 37.26, 121.71, 124.20, 130.97, 133.27, 133.80, 138.97, 175.88 (C=N). Anal. Calcd for $C_{12}H_{15}O_2SN$: C, 60.74; H, 6.37. Found: C, 60.42; H, 6.37.

(+)-3-[*o*-(*S*)-(2-Methylbutoxy)phenyl]-1,2-benzisothiazole 1,1-Dioxide (5b). (*S*)-1-Iodo-2-methylbutane. To a precooled (0 °C) mixture of 4.4 g (50 mmol) of (−)-(*S*)-2-methylbutanol (Aldrich) and 15.5 g (50 mmol) of triphenyl phosphite in 100 mL of methylene chloride (CH_2Cl_2) was added 15.6 g (62 mmol) of iodine in 400 mL of CH_2Cl_2 over 1 h. After stirring for 2 h and 1 h at room temperature, the reaction mixture was washed with saturated sodium thiosulfate solution, washed with H_2O, and dried to give a viscous liquid, which was distilled at 48–55 °C (20 mmHg), affording 5.8 g (60%) of the iodide: ^1H NMR ($CDCl_3$) δ 0.80–1.48 (m, 9 H) 3.19–3.23 (m, 2 H, ICH_2CH).

***o*-(*S*)-(2-Methylbutoxy)phenyl Bromide.** A solution of 3.4 g (20 mmol) of 2-bromophenol in 20 mL of 95% ethanol (EtOH) and 0.9 g (24 mmol) of powdered NaOH pellets was refluxed for 20 min, at which time 4.9 g (25 mmol) of (*S*)-2-methylbutyl iodide in 10 mL of 95% EtOH was added dropwise. The reaction mixture was refluxed for 20 h, at which time the solvent was removed, H_2O added, and the mixture extracted with *n*-pentane. After washing with 10% NaOH solution and drying, the oil was distilled, bp 112–113 °C (0.1 mmHg), to give 2.8 g (64%) of *o*-(*S*)-(2-methylbutoxy)phenyl bromide: $[\alpha]^{20}_D$ +8.18 (5.0 neat); IR (neat) 3300, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.95 (t, 3 H, *J* = 7.2 Hz, CH_3CH), 1.05 (d, 3 H, *J* = 6.8 Hz, CH_3CH_2), 1.28–1.93 (m, 3 H), 3.74–3.87 (m, 2 H, OCH_2), 7.19–7.53 (m, 4 H, Ar); MS, *m/e* (relative intensity) 244 (M + 2, 27), 242 (M, 27), 173 (100), 171 (95).

To a precooled solution (−78 °C) of 4.8 g (20 mmol) of the phenolic bromide **7b** (Li = Br), prepared above, in 50 mL of *n*-hexane was slowly added *tert*-butyllithium (24.6 mL, 42 mmol, 1.7 molar solution in *n*-hexane) over 20 min. The reaction mixture was stirred for $^1/_2$ h at −78 °C and *carefully* warmed to room temperature for 10–20 min, during which time the contents of the flask rapidly warmed and a yellow solid precipitated, signifying that the excess *tert*-butyllithium had been destroyed. At this time the reaction mixture was rapidly cooled to −78 °C and the precipitated solids were allowed to settle. TLC analysis (*n*-hexane) of the clear supernatant layer indicated the absence of the bromide.

In a separate flask, 3.3 g (16 mmol) of **4** in 200 mL of THF was cooled to −78 °C, and lithium compound **7b**, prepared above, was added dropwise, under argon pressure, via a flex-needle assembly, over 45 min. The red solution was stirred for 4 h and the progress of the reaction monitored by TLC (CH_2Cl_2). On completion, the reaction mixture was quenched by slow addition of H_2O, warmed to room temperature, diluted with 150 mL of ethyl ether, washed, and dried to give a solid, which was washed with *n*-pentane. The solid was dissolved in 100 mL of ethyl ether and filtered and the solvent removed to give a gummy material, which solidified on washing with *n*-pentane. Crystallization from EtOH gave 0.48 g (70%) of **5b**: mp 70 °C; IR (KBr) 1605 (C=N), 1340 and 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.6–2.0 (m, 9 H, aliphatic protons), 3.75 (m, 2 H, OCH_2), 6.9–7.83 (m, 8 H arom); ^{13}C NMR ($CDCl_3$) δ 12.0, 17.2, 74.2, 115.1, 121.3, 123.6, 125.1, 127.5, 131.6, 133.6, 137.4, 138.6, 140.5, 157.6, and 174.5 (C=N); $[\alpha]^{20}_D$ −4.5° (*c* = 3.1, $CHCl_3$). Anal. Calcd for $C_{18}H_{19}O_3NS$: C, 65.66; H, 5.77. Found: C, 65.54; H, 5.71.

(+)-(2*R*,3*S*)-3-[(*S*)-2-Methylbutyl]-1,2-benzisothiazole 1,1-Dioxide Oxide (6a). In a 250-mL three-necked Morton flask equipped with a mechanical stirrer and a 250-mL addition funnel was placed 3.0 g (13 mmol) of sulfonimine **5a**, in 30 mL of CH_2Cl_2 and 40 mL of saturated K_2CO_3 solution. Purified *m*-CPBA (>95%), 3.3 g (20 mmol) in 30 mL of CH_2Cl_2, was added dropwise over a period of 20 min. Rapid stirring was continued until TLC (CH_2Cl_2) analysis indicated that the reaction was complete (approximately 30 min). The organic phase was washed with saturated Na_2SO_3, H_2O, saturated $NaHCO_3$, and saturated NaCl solution and dried to give white crystalline **6a**. ^1H NMR indicated the presence of an 85:15 ratio of (+)-**6a**/(−)-**6a**, determined by integration of the methylene doublets adjacent to the oxaziridine carbon appearing at δ 2.75 and 2.5 ppm. Repeated crystallization from EtOH afforded a single diastereomer identified as (+)-(2*R*,3*S*)-**6a**, 1.2 g (34%): mp 83 °C, $[\alpha]^{20}_D$ +104° (*c* 3.2, $CHCl_3$); IR (KBr) 1360 and 1170 cm^{-1} (m, SO_2); ^1H NMR ($CDCl_3$) δ 0.89–0.96 (m, 6 H, 2 Me), 1.31–1.39 (m, 2 H, CH_2), 1.70–1.81 (m, 2 H, CH_2), 2.75 and 2.78 (dd, 1 H, *J* = 12 Hz and *J* = 3.4 Hz, CH), 7.68–7.73 (m, 4 H, arom); ^{13}C NMR ($CDCl_3$) δ 10.69, 19.22, 29.24, 30.53, 34.78, 85.42 (oxaziridine C), 123.57, 125.95, 128.90, 132.34, 133.90, 133.99. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.92; H, 5.93. Found: C, 56.47; H, 5.96.

(+)-(2*R*,3*S*)-3-[*o*-(*S*)-(2-Methylbutoxy)phenyl]-1,2-benzisothiazole 1,1-Dioxide Oxide (6b). Oxidation of 3.2 g (10 mmol) of sulfonimine **5b** with 2.58 g (15 mmol) of 95% *m*-CPBA for 1.5 h gave **6b** as a 45:55 mixture of (+)-**6b**/(−)-**6b** determined by integration of the methyl protons appearing as doublets centered at δ 0.65 and 0.66 ppm. Repeated crystallization from EtOH gave 0.48 g (18%) of (+)-(2*R*,3*S*)-**6b**: mp 123–125 °C; $[\alpha]^{20}_D$ +101.3° (*c* = 3.1, $CHCl_3$); IR (KBr) 1350 and 1180 cm^{-1} (SO_2); ^1H NMR ($CDCl_3$) δ 0.6–1.5 (m, 9 H, aliphatic protons), 3.5–3.81 (m, 2 H, OCH_2CH), 7.04–7.83 (m, 8 H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.01, 15.82, 25.45, 34.25, 72.94 (OCH), 84.68 (oxaziridine C), 111.39, 117.15, 120.32, 123.15, 126.42, 128.31, 131.83, 132.35, 133.47, 136.64, 157.37. Anal. Calcd for $C_{18}H_{19}O_4NS$: C, 62.60; H, 5.50. Found: C, 62.60; H, 5.51.

General Procedure for Oxidation of Sulfides to Sulfoxides. Typically, 0.017 g (0.05 mmol) of (+)-**6a** or (+)-**6b** in 1 mL of CH_2Cl_2 was added to 1.1 equiv of the appropriate sulfide in 1 mL of CH_2Cl_2 as previously reported.[8] The mixture was stirred for 1 h and the sulfoxides were isolated by preparative TLC (silica gel G) eluting with ether.

General Procedure for the Asymmetric Epoxidation of Alkenes by (+)-6. In a 2-mL glass vial were placed 8 mg (0.031 mmol) of (+)-(2*R*,3*S*)-**6a** and 1.2 equiv of the alkene in 1.0 mL of CCl_4 or $CDCl_3$. The solution was transferred to a 5-mm NMR tube and thermostated in an oil bath at 60 °C. The progress of the reaction was monitored by following the appearance of the absorption at δ 2.95 ppm for the protons attached to the carbon atom adjacent to the imine bond in (+)-**5a**. When the reaction was complete (3–18 days), the mixture was transferred to a 1-dram vial, the solvent evaporated nearly to dryness, 1.0 mL of *n*-pentane added, the solution cooled to −20 °C, and the solvent carefully decanted from the precipitated imine (+)-**5a**. Analysis of the reaction mixture was accomplished by using the chiral capillary column. (+)-(1*R*,2*R*)-*trans*-β-Methylstyrene oxide,[4] (−)-(1*S*,2*R*)-*cis*-β-methylstyrene oxide,[20] and (−)-(1*S*,2*R*)-1-methylcyclohexene oxide[4] were the first to be eluted as determined by comparison with authentic materials.[17]

General Procedure for the Epoxidation of Limonene. A 5-mL glass vial containing 0.037 g (0.146 mmol) of (+)-**6a** and 0.019 g (0.146 mmol) of (*R*)- or (*S*)-limonene in 3 mL of $CHCl_3$ was thermostated at 60 °C. The progress of the reaction was monitored by TLC (2% ether/pentane) until complete (typically 2–3 days). The cis/trans limonene oxides were determined by using capillary GLC as previously described.[9]

General Procedure for the Asymmetric Oxidation of Enolates. Enolates of the respective carbonyl compounds, typically 0.25 mmol in 3 mL of THF, were generated as previously described[1,7] and were oxidized by treatment with 1.2 equiv of

(20) Witkop, B.; Foltz, C. M. *J. Am. Chem. Soc.* **1957**, *79*, 197.

(+)-6a or (+)-6b in 2 mL of THF at −78 °C followed by warming to 0 °C for 1.5 h. After quenching with 0.5 mL of saturated NH_4I solution, washing, and drying, the α-hydroxy carbonyl compounds were isolated by preparative TLC (silica gel G) eluting with 1:1 *n*-pentane/ether for 2-hydroxy-1-phenylpropanone and methyl 2-hydroxy-2-phenylpropanoate and with $CHCl_3$ for 2-hydroxy-2-methyl-1-tetralone. Products were identified by comparison of their spectral properties with those of authentic samples and their ee's and configurations determined as previously described.[1,7]

X-ray Analysis of (+)-3-(2*R*,3*S*)-[*o*-(*S*)-(2-Methylbutoxy)phenyl]-1,2-benzisothiazole 1,1-Dioxide Oxide (6b). Data were collected on an Enraf-Nonius CAD4 diffractometer using a crystal of dimensions of 0.42 × 0.26 × 0.14 mm. Crystal data: $C_{18}H_{19}NO_4S$, M_r 345.4230, orthorhombic, $P2_12_12_1$, a = 8.489 (1) Å, b = 14.429 (1) Å, c = 14.570 (2) Å, V = 1784.7 Å^3, Z = 4, D_{calcd} = 1.286 g cm^{-3}, λ(Cu Kα) = 1.541 84 Å, μ = 17.5 cm^{-1}. Lattice parameters were determined from 25 reflections with 22° ≤ 2θ ≤ 62°; 2125 reflections were measured by the ω−2θ scan technique with 4° ≤ 2θ ≤ 150°. Intensities of three standard reflections (302, 211, 040) recorded every 3500 s of X-ray exposure showed no significant decay. A total of 1578 unique, observed reflections with $I > 3\sigma(I)$ were used during structure refinement. Data were corrected for Lorentz and polarization effects but not for absorption. The structure was solved by MULTAN 11/82.[21] Hydrogen atoms were found from subsequent difference Fourier syntheses. Refinement by full-matrix least squares to minimize $\sum w(|F_o| - |F_c|^2)$ led to R = 0.060 and R_w = 0.082 for 218 variables with $w = 1/\sigma^2$. The maximum least-squares shift to esd ratio was 0.01 in the final refinement cycle. The largest residual electron density in the final difference map was +.30 e Å^{-3}. All computer programs were from the Enraf-Nonius SDP Package.[22]

Acknowledgment. This work was supported by grants from the National Science Foundation (CHE 8502076) and the National Institutes of Health (Institute of General Medical Sciences) through Grant GM 34014.

Supplementary Material Available: X-ray data including tables of atomic positional parameters, thermal parameters, bond distances, and bond angles for (+)-(2*R*,3*S*)-**6b** as well as proton NMR spectra for **5b** and *o*-(*S*)-(2-methylbutoxy)phenyl bromide (7 pages). Ordering information is given on any current masthead page.

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(22) Frenz, B. A. In *Computing in Crystallography*; Schenk, H., Olthof-Hazekamp, R., van Konigsveld, H., Bassi, Eds.; Delft University Press: 1978; pp 64-71.

Total Syntheses of Galactosidase Inhibitors (+)-Galactostatin and (+)-1-Deoxygalactostatin[1]

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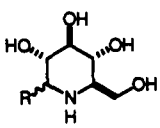
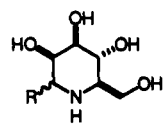
β-Galactosidase inhibitors, (+)-galactostatin and its 1-deoxy analogue (+)-deoxygalactostatin, have been synthesized by utilizing the allylic alcohol 7 as a common chiral building block.

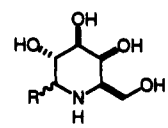
The antibiotics nojirimycin (**1**)[2-4] and 1-deoxynojirimycin (**2**),[4-6] the first representative naturally occurring azahexoses, are essentially D-glucose and its 1-deoxy analogue in which the ring oxygen is replaced by the NH group. Subsequently, the D-mannose analogues of **1** and **2**, mannojirimycin (**3**)[7] and 1-deoxymannojirimycin (**4**),[8,9] have been found in nature. These sugar analogues having



1, R = OH
2, R = H

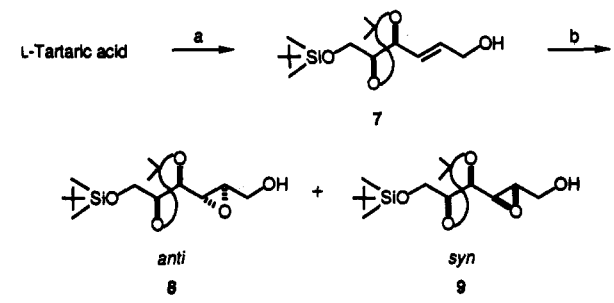


3, R = OH
4, R = H



5, R = OH
6, R = H

Scheme I[a]



[a] (a) Reference 15; (b) RCO_3H or t-BuO_2H, $VO(acac)_2$ (Table I).

nitrogen have been shown to be potent and specific inhibitors of the hydrolysis of the corresponding glycosides, D-glucosides and D-mannosides, by specific glycosidases. In an attempt to explore the potential of azapyranoses in studies of glycohydrolases, the basic analogues of D-galactose and its 1-deoxy derivative, i.e., **5** and **6**, respectively, have recently been synthesized from D-galactose[10] or D-glucose[11] and have been tentatively named *galacto-*

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