Cupric oxide (0.007 g, 0.08 mmol) and anhydrous potassium carbonate (0.094 g, 0.68 mmol) were added. The tube was flushed with argon, and diiodomethane (82 μL, 1.02 mmol) was added. The tube was sealed and heated to 80–90 °C (oil bath temperature) for 24 h. After the mixture had been cooled to room temperature, aqueous HCl (4 mL of 1 N HCl in 20 mL of H_2O) was added and the solution extracted with ethyl acetate (5 × 20 mL). The combined extracts were washed with water (1 × 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure, to give a brown solid. Radial chromatography with 10% ethyl acetate/hexanes as eluent yielded (±)-pterocarpin (**3**) (35 mg, 35%), anhydropisatin (**15**, 1.5 mg, 2%), and a mixture of **3** and **15** (14.6 mg, 11% and 4%, respectively, by ^{1}H NMR). Flash column chromatography using silver nitrate impregnated silica gel (prepared by swirling SiO_2 in 4% $AgNO_3/CH_3CN$ and then evaporating the solvent under reduced pressure) gave pure (±)-pterocarpin (**3**) and anhydropisatin (**15**). Recrystallization of **3** from ethyl acetate/hexanes gave cylindrical colorless crystals: mp 190–192 °C (lit. mp 168–169 °C[24a] and 185–186 °C[24b]). Physical data for **3**: R_f (30% EtOAc/hexanes) 0.52; R_f [10% Et_2O/hexanes on $AgNO_3$ impregnated silica gel plate (made by dipping in 4% $AgNO_3/CH_3CN$ solution)] 0.14; ^{1}H NMR[8b,f] (300 MHz) 3.44–3.53 (m, 1 H), 3.66 (t, 1 H, J = 11), 3.79 (s, 3 H), 4.23 (dd, 1 H, J = 11, 4.4), 5.49 (d, 1 H, J = 6.7), 5.90 (2 overlapping d, 2 H), 6.43 (s, 1 H), 6.47 (d, 1 H, J = 2.6), 6.64 (dd, 1 H, J = 8.0, 2.5), 6.72 (s, 1 H), 7.40 (d, 1 H, J = 8.0). Physical data for **15**:[14] R_f [10% Et_2O/hexanes on $AgNO_3$ impregnated silica gel plate (made by dipping in 4% $AgNO_3/CH_3CN$ solution and then drying] 0.18; ^{1}H NMR (300 MHz) 3.80 (s, 3 H), 5.52 (s, 2 H), 5.99 (s, 2 H), 6.53 (d, J = 2.2, 1 H), 6.56 (dd, J = 2.2, 8, 1 H), 6.73 (s, 1 H), 7.02 (s, 1 H), 7.37 (d, J = 8, 1 H); EIMS m/z (relative intensity) 296 (100), 147 (12), 139 (13), 69 (12).

Acknowledgment. We thank Michael Kaufman for technical assistance. This work was supported financially by the National Institutes of Health, the Research Corporation, the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the University of Kansas General Research Fund and Biomedical Sciences Support Grant. T.A.E. gratefully acknowledges a granteeship from Eli Lilly and Company.

Supplementary Material Available: Experimental details for the preparation of **7a–d** and **8a–f** and IR, UV (if relevant), and low-resolution electron-impact mass spectral data for **7**, **8**, **12**, **13**, and **4** (6 pages). Ordering information is given on any current masthead page.

Chemistry of Oxaziridines. 13.[1] Synthesis, Reactions, and Properties of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxide Oxides

Franklin A. Davis,* James C. Towson, Dhiru B. Vashi, R. ThimmaReddy, John P. McCauley, Jr., Mark E. Harakal, and Donald J. Gosciniak

Department of Chemistry, Drexel University, Philadelphia, Pennsylvania 19104

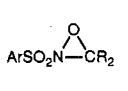
Received August 4, 1989

The synthesis, properties, and reactions of 3-substituted 1,2-benzisothiazole 1,1-dioxide oxides **8**, highly stable examples of 3,3-disubstituted *N*-sulfonyloxaziridines **3**, are described. These new *N*-sulfonyloxaziridines are prepared in high yield by oxidation of the corresponding sulfonimines **7**. The bicyclic sulfonimines were prepared by treatment of saccharin (**5**) or preferably pseudosaccharin ethyl ether **6** with organolithium reagents. Kinetic studies of the oxidation of sulfoxides to sulfones and the epoxidation of limonene reveal that these new oxidizing reagents exhibit reduced reactivity, but greater selectivity, compared to oxaziridines of type **1**, in their oxygen-transfer reactions due to greater steric hindrance of the active-site oxygen. This is reflected in lower rates of oxidation and in improved cis/trans selectivity for the epoxidation of (+)-limonene.

The *N*-sulfonyloxaziridines **1** and **2** are an important class of highly selective, neutral aprotic oxidizing reagents that are finding increased utility in organic synthesis.[2] Enantiomerically pure examples of these compounds are useful asymmetric oxidizing reagents affording high stereoselectivities for the asymmetric oxidation of sulfides (selenides) to sulfoxides (selenoxides) (66 to ≥95% ee),[3] for the epoxidation of alkenes (up to 65% ee),[4] and for the asymmetric oxidation of enolates to optically active α-hydroxy carbonyl compounds (55–95% ee).[5]

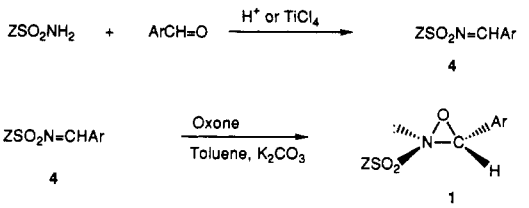
1a, Z= Alkyl, Aryl
b, Z= (-)(S)-N-(α-methylbenzyl)-N-benzylamine

(+)-**2**



3

Scheme I



For the past several years our studies have focused on the oxygen-transfer reactions of *N*-sulfonyloxaziridines **1a** and *N*-sulfamyloxaziridines **1b**.[6] More recently studies have been concerned with the properties of (camphorylsulfonyl)oxaziridines **2** because they are conveniently prepared, enantiomerically pure, without the need for diastereomer separation as is required for oxaziridines of

(1) Chemistry of Oxaziridines. 12: Davis, F. A.; Chen, B.-C. *J. Org. Chem.* **1990**, *55*, 360.
(2) For a review of the chemistry of N-sulfonyloxaziridines, see: Davis, F. A.; Sheppard, A. C. *Tetrahedron* **1989**, *54*, 5703.
(3) Davis, F. A.; Reddy, T. R.; Weismiller, M. W. *J. Am. Chem. Soc.* **1989**, *111*, 5964.
(4) Davis, F. A.; Chattopadhyay, S. *Tetrahedron Lett.* **1986**, 5079.
(5) 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) Boschelli, D., Smith, A. B. III; Stringer, O. D.; Jenkins, R. H., Jr.; Davis, F. A. *Tetrahedron Lett.* **1981**, 4385. (d) Davis, F. A.; Ulatowski, T. G.; Haque, M. S. *J. Org. Chem.* **1987**, *52*, 5288. (c) Davis, F. A.; Sheppard, A. C.; Lal, G. S. *Tetrahedron Lett.* **1989**, 779. (f) Davis, F. A.; Haque, M. S.; Przeslawski, R. M. *J. Org. Chem.* **1989**, *54*, 2021.
(6) Davis, F. A.; McCauley, J. P.; Chattopadhyay, S.; Harakal, M. E., Towson, J. C.; Watson, W. H.; Tavanaiepour, I. J. *J. Am. Chem. Soc.* **1987**, *109*, 3370.

0022-3263/90/1955-1254$02.50/0

Table I. Synthesis of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxides (7) at −78 °C

entry	R	% isolated yield method A (from 5)	method B (from 6)	^{13}C NMR (δ) of imine C
1	methyl (**7a**)	77 (60)[a]	82[b]	164.4
2	*n*-butyl (**7b**)	67 (75)[a]	90	176.5
3	*sec*-butyl (**7c**)	46	60 (40)[c]	180.1
4	*tert*-butyl (**7d**)	64	85	181.5
5	*n*-pentyl (**7e**)	67	-	176.4
6	phenyl (**7f**)	80 (63)[a]	96	171.0
7	2-methoxyphenyl (**7g**)	79	-	172.2
8	2,6-dimethoxyphenyl (**7h**)	45	-	169.6
9	2-(trifluoromethyl)phenyl (**7i**)	67	67	170.7
10	4-(trifluoromethyl)phenyl (**7j**)	66	66	170.0
11	pentafluorophenyl (**7k**)	66	45	161.8

[a] Reference 11. [b] Warmed to 25 °C for 3 h. [c] Recovered 6.

type 1.[7] Oxaziridines of both types are prepared in excellent yield (90–95%) by biphasic oxidation of the corresponding sulfonimine **4** using buffered Oxone (Scheme I).[8] The sulfonimines **4** are prepared by condensation of a sulfonamide (RSO_2NH_2) or sulfamide ($R_2NSO_2NH_2$) with an aromatic aldehyde using an acid catalyst or $TiCl_4$.[8,9]

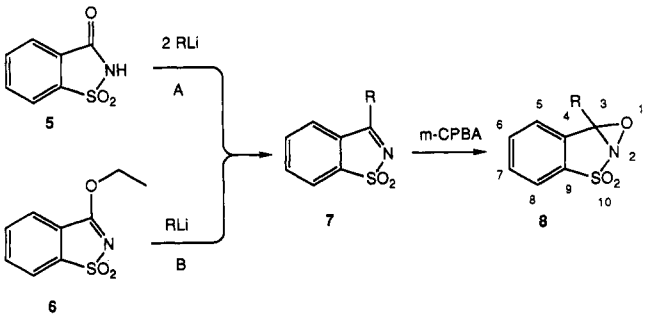
The synthesis of 3,3-disubstituted *N*-sulfonyloxaziridines **3** by this methodology, Scheme I, is problematic for several reasons. First, ketone-derived sulfonimines (ZSO_2N=CRAr) are generally unstable under the reaction conditions due, in part, to facile sulfonimine–enesulfonamide tautomerism.[9,10] However, Jennings and co-workers recently described an important method for preparing sulfonimines of ketones via reaction of sulfinyl chlorides (RS(O)Cl) with oximes.[11]

Another problem in the synthesis of **3** is that hydrolysis of ketone sulfonimines (ZSO_2N=CRAr) competes with oxidation to the oxaziridine when at least one group attached to the imine carbon is not aromatic, resulting in low yields.[10] Furthermore, Jennings et al. also reported that oxidation of ketone-derived sulfonimines gives cis–trans mixtures of the 3,3-disubstituted oxaziridines **3** where the barrier to pyramidal nitrogen inversion is in the range of 19–20 kcal mol^{-1}.[12] Notable exceptions are oxaziridines of type **2** which are configurationally stable and readily prepared (>90%) because the corresponding sulfonimine is resistant to hydrolysis due to its cyclic nature.[7]

The difficulty in preparing 3,3-disubstituted *N*-sulfonyloxaziridines **3** has hindered structure reactivity studies of their oxygen-transfer reactions. Such studies are particularly important for enantiomerically pure examples of these reagents where subtle changes in structure have a marked influence on the stereoselectivity of their oxidations.[2,13]

In this paper the synthesis, reactions, and properties of a new class of *N*-sulfonyloxaziridines, the 3-alkyl- and 3-aryl-1,2-benzisothiazole 1,1-dioxide oxides **8**, will be described. With these oxaziridines it was possible to systematically vary both the nature and size of the substituent attached to the oxaziridine carbon.

Scheme II



a, R = Me
b, R = *n*-butyl
c, R = *sec*-butyl
d, R = *tert*-butyl
e, R = *n*-pentyl
f, R = phenyl
g, R = 2-methoxyphenyl
h, R = 2,6-dimethoxyphenyl
i, R = 2-(trifluoromethyl)phenyl
j, R = 4-(trifluoromethyl)phenyl
k, R = pentafluorophenyl

Results and Discussion

Synthesis of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxides Oxides 8. Our general synthetic procedure for the synthesis of 3-substituted 1,2-benzisothiazole 1,1-dioxide oxides **8** is given in Scheme II. Two methods can be employed to prepare the bicyclic sulfonimines **7**. In the first method, method A, an organolithium reagent (RLi) is added to saccharin (**5**) using methodology developed by Abramovitch et al.[14] However, this procedure requires 2 equiv of RLi and sometimes gives low yields. An alternative procedure, which avoids the use of excess RLi, is treatment of pseudosaccharin ethyl ether **6** with 1.1 equiv of the organolithium reagent. Not only does this procedure generally give higher yields of **7** than method A, but the product was easier to purify (Table I). Interestingly, while *n*-BuLi, *t*-BuLi, PhLi, and the arylfluorolithium reagents generally gave good yields of **7b,-d,f,i–k** at −78 °C, goods yields of **7a** are obtained only after warming to room temperature for several hours. With *sec*-BuLi the reaction is incomplete at −78 °C, and decomposition occurs at room temperature (Table I).

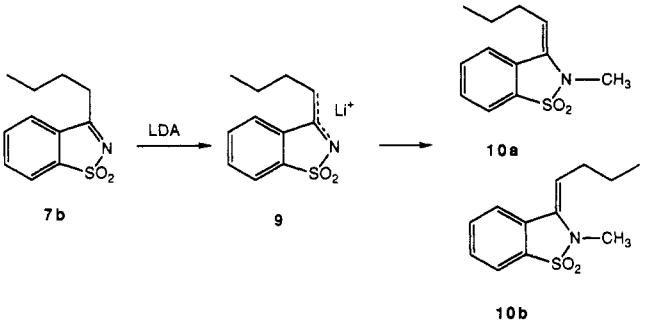
All new sulfonimines **7** give satisfactory elemental analysis and exhibit infrared absorption in the region 1590–1605 cm[11] (C=N). The imino carbon absorption at δ 162–182 ppm in the ^{13}C NMR spectrum is particularly diagnostic for the structure of **7**. These results are summarized in Table I.

A potentially more versatile route to substituted 1,2-benzisothiazole 1,1-dioxides **7** would be the reaction of

(7) Davis, F. A.; Towson, J. C.; Weismiller, M. C.; Lal, S.; Carroll, P. J. *J. Am. Chem. Soc.* **1988**, *110*, 8477.
(8) (a) Davis, F. A.; Chattopadhyay, S.; Towson, J. C.; Lal, S.; Reddy, T. *J. Org. Chem.* **1988**, *53*, 2087. (b) Vishwakarma, L. C.; Stringer, O. D.; Davis, F. A. *Org. Synth.* **1987**, *66*, 203.
(9) Jennings, W. B.; Lovely, C. J. *Tetrahedron Lett.* **1988**, 3725.
(10) Davis, F. A.; Lamendola, J. F., Jr.; Nadir, U.; Kluger, E. W.; Sdergran, T. C.; Panunto, T. W.; Billmers, R. Jenkins, R. H., Jr.; Turchi, I. J.; Watson, W. H.; Chen, J. S.; Kimura, M. *J. Am. Chem. Soc.* **1980**, *102*, 2000.
(11) Jennings, W. B.; Watson, S. P.; Boyd, D. R. *J. Chem. Soc., Chem. Commun.* **1988**, 931.
(12) Jennings, W. B.; Watson, S. P.; Tolley, M. S. *J. Am. Chem. Soc.* **1987**, *109*, 8099.
(13) For a review on chiral *N*-sulfonyloxaziridines, see: Davis, F. A.; Jenkins, R. H., Jr. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 4, pp 313–353.
(14) Abramovitch, R. A.; Smith, E. M.; Humber, M.; Purtschert, B.; Srinivasan, P. C.; Singer, G. M. *J. Chem. Soc., Perkin Trans. 1* **1974**, 2589.

azaenolate **9** with various electrophiles. However, reaction of **9**, prepared by treatment of **7b** with lithium diisopropyl amide (LDA), followed by iodomethane affords a single *N*-methyl derivative **10** in greater than 65% yield. Consistent with the proposed structure is the lack of IR absorption at 1560–1600 cm^{-1}, the appearance of a sharp singlet at δ 3.3 ppm (*N*-methyl), and absorptions characteristic of the vinyl protons at δ 5.4–5.6 ppm. While the available information cannot distinguish between the two possible *N*-alkylenamides, **10a** and **10b**, steric factors should favor **10b**.

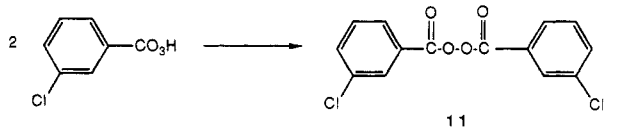
The formation of *N*-alkylenamide **10** rather than the desired sulfonimine is apparently the result of negative charge in the azaenolate **9** being concentrated on the nitrogen atom due to the powerful electron-attracting sulfonyl group. We have observed similar results for the



alkylation of the azaenolates derived from (–)-(camphorsulfonyl)imine, the sulfonimine corresponding to **2**.[15] Similarly Barton et al. observed the formation of *N*-alkylenamides on alkylation of 1-(acetylamino)cyclohexane with alkyl halides.[16]

Molecular models suggest that the C–N double bond in **7** is more hindered than in sulfonimines of type **4**. This observation is consistent with the fact that while sulfonimines **3** and **4** are readily hydrolyzed, **7** can be stored at room temperature without any special precautions to exclude moisture. Furthermore, **7** is stable to chromatography (silica gel) whereas **4** is rapidly hydrolyzed to the sulfonamide and aldehyde under similar conditions.[8a]

Attempts to oxidize **7** to **8** using the Oxone procedure failed,[8a] although in some cases small amounts of **8** could be detected after several days, i.e. **7a** and **7b**. Biphasic oxidation using 85% *m*-chloroperbenzoic acid–$NaHCO_3$ and benzyltriethylammonium chloride (BTEAC) in $CHCl_3$ gave better, but variable, results. For example, oxidation of **7a** and **7i–k** to **8a** and **8i–k** were complete within 2-24 h whereas the other sulfonimines required up to 5 days. Under these conditions less than 5–10% of oxaziridines **8g–h** were formed. An additional problem was that the oxaziridines generated during these long oxidation times proved difficult to purify, requiring flash chromatography. The reason for this is that oxidative decomposition of the phase-transfer catalysts occurs as well as dimerization of *m*-CPBA to give ca. 5–15% of bis(*m*-chlorobenzoyl) peroxide (**11**).[17]



11

Table II. Synthesis of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxide Oxides (8)

entry	oxaziridine (R)	% isolated yield	^{13}C NMR of oxaziridine carbon (δ)
1	**8a** (methyl)	90	83.9
2	**8b** (*n*-butyl)	85	86.4
3	**8c** (*sec*-butyl)	87	89.2
4	**8d** (*tert*-butyl)	84	90.4
5	**8e** (*n*-pentyl)	82	86.2
6	**8f** (phenyl)	74	85.4
7	**8g** (2-methoxyphenyl)	70	84.6
8	**8h** (2,6-dimethoxyphenyl)	78	84.4
9	**8i** (2-(trifluoromethyl)phenyl)	54	86.1
10	**8j** (4-(trifluoromethyl)phenyl)	55	84.4
11	**8k** (pentafluorophenyl)	60	79.6

The best condition for the oxidation of **7** to **8** is biphasic oxidation using 3 equiv of >95% *m*-CPBA buffered with K_2CO_3 in CH_2Cl_2. Oxidation was complete within 1–2 h, affording good to excellent yields of the 3-substituted 1,2-benzisothiazole 1,1-dioxide oxides **8**. Significantly, the phase-transfer catalyst was not necessary for good yields. These results are summarized in Table II.

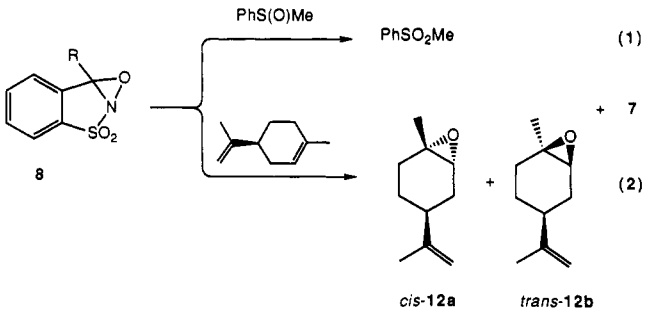
The 3-alkyl- and 3-aryl-1,2-benzisothiazole 1,1-dioxides oxides (**8a–k**) are stable, white crystalline solids melting without decomposition. Treatment of **8** with aqueous potassium iodide in acetic acid gives I_2, a characteristic reaction of oxaziridines.[2] The methyl and *tert*-butyl groups in **8a** and **8d** are shifted upfield by 0.28 and 0.31 ppm, respectively, compared to **7a** and **7d**. The oxaziridine 3-carbon in **8** appears at δ 80–90 ppm in the ^{13}C NMR spectra (Table II). In contrast to oxaziridines of type **1** the 1,2-benzisothiazole 1,1-dioxide oxides **8** are stable to chromatography.

Oxidations Using 3-Substituted 1,2-Benzisothiazole 1,1-Dioxide Oxides. Previous studies have established that *N*-sulfonyloxaziridines **1–2** transfer oxygen to sulfides and alkenes by an S_N2-type mechanism that involves displacement of a substituted sulfonimine **4** from the oxaziridine by the lone pair on the sulfur atom or the π-bond of the alkene.[18] While the reaction rates are subject to both steric and electronic factors the former predominates. For example, the product stereochemistry for the asymmetric oxidation of sulfides to sulfoxides and for the asymmetric epoxidation of alkenes by enantiomerically pure examples of **1** and **2** is controlled by the configuration of the oxaziridine three-membered ring.[2-4] Steric factors are responsible for the chiral recognition with the favored transition state being the one where the substrate approaches the active-site oxygen from the least hindered direction.

In order to evaluate the oxidizing potential of our new oxaziridines a kinetic study of the oxidation of methyl phenyl sulfoxide to methyl phenyl sulfone and a study of the stereoselective epoxidation of limonene to *cis*- and *trans*-limonene oxides (**12**) by **8** were undertaken. For comparison, results from oxidation of these substrates using 2-(phenylsulfonyl)-3-(*p*-nitrophenyl)- and 3-(pentafluorophenyl)oxaziridines **1** (Z = Ph, Ar = *p*-Ph, C_6F_5) are also included.

The oxidation of methyl phenyl sulfoxide (PhS(O)Me) to methyl phenyl sulfone ($PhSO_2Me$) was carried out by treating the sulfoxide with 1 equiv of oxaziridines **1** or **8** at 25 °C in $CHCl_3$ as previously described (eq 1).[18] Li-

(15) Davis, F. A., Weismiller, M. C.; Lal, G. S.; Chen, B. C.; Przeslawski, R. M. *Tetrahedron Lett.* **1989**, 1613.
(16) Boar, R. B.; McGhie, J. F.; Robinson, M.; Barton, D. H. R.; Horwell, D. C. Stick, R. V. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1237.
(17) Brown, J. C.; Cross, B. E.; Hanson, J. R. *Tetrahedron* **1967**, *23*, 4095. Hortmann, A. G.; Aron, A. J.; Bhattacharya, A. K. *J. Org. Chem.* **1978**, *43*, 3374.
(18) Davis, F. A.; Billmers, J. M.; Gosciniak, D. J.; Towson, J. C.; Bach, R. D. *J. Org. Chem.* **1986**, *51*, 4240.



monene was epoxidized in a similar fashion by heating equivalent amounts of the oxaziridine and the alkene at 60 °C in $CHCl_3$ (eq 2). The rate of oxidation was followed by gas chromatography using the internal standard method. The ratios of *cis*- and *trans*-limonene 1,2-oxides (**12**) were determined using a 12-m Carbowax capillary column. As reported by Royals and Leffingwell, *cis*-limonene 1,2-oxide (**12a**) eluted first.[19] These results are summarized in Tables III and IV.

Steric factors can best explain the small rate differences observed for the oxidation of methyl phenyl sulfoxide to methyl phenyl sulfone by substituted **8** (eq 1). As the bulk of R in **8** increases the rate decreases and is approximately 3 times slower for R = *tert*-butyl, **8d**, than for R = methyl, **8a** (Table III, compare entries 1 and 4). A similar trend is seen for substituents on phenyl where **8f** is slightly faster than **8g** and **8h** is unreactive (Table III, entires 5–7). Based on previous observations, stereoelectronic contributions to these rates are expected to be minimal.[18] Indeed the relative rate differences between **8a** and **8j** and **1a** (Z = Ph, Ar = $PhNO_2$-*p* and C_6F_5) are only 2.35, 2.84, and 8.7, respectively (Table III, compare entries 1 with 9, 11, and 12). Furthermore, it is important to note that part of this rate difference probably reflects easier steric approach of the substrate to the active-site oxygen in oxaziridines of type **1**.

Surprisingly, oxaziridines **8i** and **8k**, bearing electron-attracting fluoro substituents, were unreactive, failing to oxidize methyl phenyl sulfoxide even after 51 h. However, these oxaziridines were reactive enough to oxidize methyl phenyl sulfide (PhSMe) to methyl phenyl sulfoxide (PhS(O)Me), but the rate of oxidation is slow. For example **8i** and **8k** afforded 40:60 and 0:100 mixtures of sulfide and sulfoxide within 2 h. The reason for the low reactivity of these oxaziridines is not readily apparent, but is likely related to increased steric hindrance of the active-site oxygen caused by the *o*-aryl substituents. Note however, that **8g** does oxidize the sulfoxide to the sulfone (Table III, entry 6). Perhaps the *o*-O-CH_3 group is less hindered than the *o*-CF_3 group because the oxygen atom moves the methyl group further from the active site.

As previously reported and consistent with the S_N2-type displacement mechanism, steric effects are more pronounced for epoxidations than for the sulfoxide to sulfone oxidations by **1**.[18] A similar trend is observed for the epoxidation of (+)-limonene using **8** (eq 2). The rate of epoxidation falls off rapidly in going from R = Me to R = *sec*-butyl (Table IV, entries 1–3). In contrast to the sulfoxide oxidations, no epoxidation was observed for R bulkier than *sec*-butyl; i.e. **8d** and **8f–i** (*tert*-butyl, aryl) even after heating at 60 °C for 61 h. The exception is **8j** where the 3-aryl substituent includes the powerful electron-attracting 4-trifluoromethyl group (Table IV, entry 9). Note that in (+)-limonene only the more nucleophilic alkene is epoxidized.

(19) Royals, E. E.; Leffingwell, J. C. *J. Org. Chem.* **1966**, *31*, 1937.

The diastereoselective epoxidation of alkenes by peracids has been review by Berti[20] and studied by Rebek.[21] In general the epoxidation of alkenes by peracids is not very sensitive to steric effects. For example the epoxidation of limonene by perbenzoic acid (PBA) affords a 1:1 cis/trans mixture of limonene 1,2-epoxides (**12a**/**12b**), respectively (Table IV, entry 12).[22] In *N*-sulfonyloxaziridines the active-site oxygen is one bond removed from the C and N atoms of the oxaziridine three-membered ring. For this reason epoxidations using these reagents should be more sensitive to steric effects than peracids and the substituents attached to the oxaziridine C and N atoms. Indeed the higher cis/trans ratios for the epoxidation of limonene by **1** and **8** compared to PBA confirms this hypothesis (Table IV, compare entry 12 with entries 1–3 and 9–11). The best cis/trans selectivity, 74/26, was observed for oxaziridines **8b–c** (R = *n*-butyl and *sec*-butyl) and can be predicted assuming approach of the oxaziridine from the least hindered face of the alkene.

In summary 3-substituted 1,2-benzisothiazole-1,1-dioxide oxides **8**, stable examples of 3,3-disubstituted *N*-sulfonyloxaziridines **3**, are readily prepared by oxidation of the corresponding sulfonimines **7**. In general these new oxidizing reagents exhibit reduced reactivity but greater selectivity in their oxygen-transfer reactions due to greater steric hindrance of the active-site oxygen as reflected in improved selectivity for the epoxidations of chiral alkenes. These compounds are also more stable than oxaziridines of type **1** or **3**, melting without decomposition and stable to chromatography.

Experimental Section

IR spectra were recorded on a Perkin-Elmer 467 grating spectrometer using sodium chloride plates for liquids and potassium bromide disks for solids. NMR spectra were recorded on a JEOL FX90Q (90 MHz) or on a Bruker 250 (250 MHz) instrument. Proton and carbon chemical shifts are reported relative to tetramethylsilane (TMS). Gas chromatographic analyses were run on a Hewlett-Packard 5890 GC equipped with a 12 m × 0.25 mm Carbowax-20 fused silica capillary column using a flame ionization detector. Melting points were recorded on a Mel-Temp apparatus and were uncorrected. Organic reagents were purchased primarily from Aldrich Chemical Co. and used as obtained unless stated otherwise. THF and ether were distilled from sodium and benzophenone prior to use. Elemental analyses were performed by Micro-Analysis, Inc., Wilmington, DE.

General Procedure for the Synthesis of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxides (7). Method A. In a dry 500-mL three-necked, round-bottomed flask equipped with magnetic stir bar, argon, and syringe inlets was placed 5.49 g (0.030 mol) of saccharin (**5**) in 250 mL of freshly distilled THF. The flask was cooled to −78 °C in a dry ice–acetone bath, and 2 equiv (0.060 moles) of the appropriate lithium reagent were carefully added by syringe or cannula. The reaction was stirred at −78 °C for an additional 4 h, 100 mL of H_2O was added, and the reaction mixture was warmed to room temperature. The solution was transferred to a 1-L separatory funnel where 200 mL of ether was added and the aqueous layer was separated. The organic layer was washed successively with 10% HCl (2 × 100 mL), 10% $NaHCO_3$ (2 × 125 mL), and 100 mL of H_2O and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave a white solid, which was crystallized from absolute ethanol to give sulfonimine **7**. See Table I for yields.

(20) Berti, G. *Top. Stereochem.* **1973**, *7*, 93.

(21) Rebek, J., Jr. *Heterocycles* **1981**, *15*, 517. Rebek, J., Jr.; Marshall, L.; McManis, J.; Wolak, R. *J. Org. Chem.* **1986**, *51*, 1649.

(22) Newhall, W. F. *J. Org. Chem.* **1964**, *29*, 185.

Method B. In a dry 50-mL two-necked round-bottom flask equipped with a magnetic stirring bar, argon, and syringe inlets was placed 0.21 g (1.0 mmol) of 3-ethoxy-1,2-benzisothiazole 1,1-dioxide (**6**) in 20 mL of dry THF. After the reaction mixture was cooled to −78 °C in a dry ice–acetone bath, 1.1–1.3 equiv of the appropriate organolithium reagent were added via syringe. The reaction mixture was stirred for 4 h at this temperature, warmed to room temperature in the case of **7a** and **7c**, and quenched at −78 °C by addition of 2.0 mL of saturated NH_4Cl solution. After the reaction mixture was warmed to room temperature, 30 mL of ethyl ether was added, and the organic solution was washed with saturated NaCl solution (2 × 20 mL) and dried over anhydrous $MgSO_4$. Removal of the solvent under vacuum gave **7**. See Table I for yields.

3-Ethoxy-1,2-benzisothiazole 1,1-Dioxide (6). In a dry 500-mL single-neck, round-bottomed flask equipped with magnetic stir bar and air condenser were placed 5.49 g (0.030 mol) of saccharin (**5**) and 8.0 g (0.039 mol, 1.3 equiv) of PCl_5. The contents were gently heated until the reaction had subsided, at which time the temperature was raised to 175 °C for an additional 1.5 h. The $POCl_3$ was removed by suction to give crude 3-chloro-1,2-benzisothiazole 1,1-dioxide, which was treated with 400 mL of absolute ethanol. After the reaction mixture was refluxed for 1 h, the solution was filtered, the filtrate was cooled in an ice bath, and the resulting solid was collected by filtration to give 3.7 g (60%): mp 212 °C; IR (KBr) 1610 (C=N), 1350 and 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.53 (t, 3 H, CH_3, J = 7.3 Hz), 4.68 (q, 2 H, CH_2, J = 7.3 Hz), 7.73–7.86 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 14.1, 68.2, 121.8, 123.5, 127.0, 133.2, 133.9, 143.4, 168.9 (C=N). Anal. Calcd for $C_9H_9NO_3S$: C, 51.17; H, 4.29. Found: C, 51.30; H, 4.40.

3-Methyl-1,2-benzisothiazole 1,1-dioxide (7a): yield 4.9 g (77%); mp 215–216 °C (lit.[14] mp 217 °C); ^{13}C NMR ($CDCl_3$) δ 27.3, 120.2, 123.8, 133.3, 133.5, 164.4 (C=N).

3-*n*-Butyl-1,2-benzisothiazole 1,1-dioxide (7b): yield 4.49 g (67%); mp 91–92 °C (lit.[14] mp 94 °C); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.2, 27.4, 30.7, 122.2, 124.1, 131.2, 133.6, 134.0, 139.5, 176.5 (C=N).

3-*sec*-Butyl-1,2-benzisothiazole 1,1-dioxide (7c): yield 3.08 g (46%); mp 52–55 °C; IR (KBr) 1605 (C=N), 1335 and 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.0 (t, 3 H, CH_3, J = 14.3 Hz), (d, 3 H, CH_3, J = 6.8 Hz), 1.61–1.99 (m, 2 H, CH_2), 3.00–3.24 (m, 1 H, CH), 7.73–7.88 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 11.2, 17.0, 27.1, 36.5, 121.9, 124.6, 130.5, 133.6, 133.9, 139.6, 180.1 (C=N). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.86. Found: C, 58.91; H, 5.84.

3-*tert*-Butyl-1,2-benzisothiazole 1,1-dioxide (7d): yield 4.29 g (64%); mp 119–122 °C; IR (KBr) 1605 (C=N), 1330 and 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.03 (s, 9 H, 3 CH_3), 7.70–8.00 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 28.0, 53.4, 122.3, 126.5, 129.5, 132.7, 133.4, 140.6, 181.5 (C=N). Anal. Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87. Found: C, 58.97; H, 5.70.

3-*n*-Pentyl-1,2-benzisothiazole 1,1-dioxide (7e): yield 87%; mp 75–77 °C; IR (KBr) 1605 (C=N), 1335 and 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85–1.0 (t, 3 H, CH_3, J = 6.0 Hz), 1.29–1.57 (m, 4 H, CH_2), 1.71–2.1 (m, 2 H, CH_2), 2.89–3.06 (t, CH_2, J = 7.1 Hz), 7.72–7.93 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 13.57, 22.0, 24.78, 30.78, 30.93, 121.9, 124.0, 130.9, 133.3, 133.9, 139.2, 176.4 (C=N). Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37. Found: C, 60.98; H, 6.37.

3-Phenyl-1,2-benzisothiazole 1,1-dioxide (7f): yield 5.84 g (80%); mp 165–166 °C (lit.[14] mp 168 °C); ^1H NMR ($CDCl_3$) δ 7.77–8.08 (m, 9 H, Ar); ^{13}C NMR ($CDCl_3$) δ 122.9, 126.6, 129.3, 129.4, 130.4, 133.4, 133.7, 141.0, 171.0 (C=N).

3-(2-Methoxyphenyl)-1,2-benzisothiazole 1,1-Dioxide (7g). In a dry 500-mL, three-necked, round-bottomed flask equipped with magnetic stir bar, 125-mL dropping funnel, reflux condenser, argon, and syringe inlets was placed 12.0 g (12 mL, 0.1110 moles) of freshly distilled anisole in 125 mL of dry ether. The ether was heated to a gentle reflux, 73 mL of a 1.37 M *n*-butyllithium solution in ether was added dropwise over 30 min, and the reaction mixture was refluxed overnight.[23] Titration of the resulting solution with diphenylacetic acid[24] indicated a 0.48 M solution. The entire reaction was transferred to a dry 250-mL graduated cylinder equipped with a syringe inlet by cannula. In a new, dry 500-mL, three-necked round-bottomed flask equipped with magnetic stir bar, argon, and syringe inlets was placed 5.49 g (0.030 moles) of saccharin (**5**) in 150 mL of dry THF, the solution was cooled to −78 °C, and 120 mL (0.060 mol) of the solution prepared above was added by cannula. The reaction mixture was stirred for 4 h at −78 °C, 100 mL of H_2O was cautiously added dropwise, and the mixture was warmed to room temperature. After the solution was transferred to a 1-L separatory funnel, 300 mL of ether was added, and the solution was washed successively with 100 mL 10% HCl and saturated aqueous $NaHCO_3$ (3 × 125 mL). If needed, additional THF is added to dissolve any solids that appeared after the $NaHCO_3$ wash. The organic solvent was dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo to give a yellow solid. Crystallization from absolute ethanol gave 6.50 g (79%) of a white solid; mp 167–8 °C; IR (KBr) 1600 (C=N), 1370 and 1130 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.83 (s, 3 H, OCH_3), 7.05–7.92 (m, 8 H, Ar); ^{13}C NMR ($CDCl_3$) δ 55.9, 111.9, 120.3, 121.6, 122.5, 127.4, 131.2, 132.0, 133.3, 133.6, 134.2, 140.2, 158.2, 172.2 (C=N). Anal. Calcd for $C_{14}H_{11}NO_3S$: C, 61.53; H, 4.06. Found: C, 61.34; H, 4.30.

3-(2,6-Dimethoxyphenyl)-1,2-benzisothiazole 1,1-Dioxide (7h). In a dry 100-mL two-necked, round-bottomed flask equipped with a magnetic stir bar, argon, and syringe inlets was placed 2.76 g (0.020 mol) of 1,3-dimethoxybenzene in 50 mL of freshly distilled hexane. The reaction was cooled to 0 °C, and 24 mL of a 1.7 M *tert*-butyllithium solution in pentane was added dropwise over 20 min by syringe. The reaction was stirred at room temperature for 45 min, during which time a white salt precipitated, and enough dry ether (ca. 30 mL) was added to dissolved the salt. In a separate 250-mL three-necked round-bottomed flask equipped with magnetic stir bar, argon, and syringe inlets was placed 3.3 g (0.0016 mol) of **6** in 100 mL of dry THF. The contents were cooled to −78 °C, and the lithiated dimethoxybenzene prepared previously was added via cannula. The reaction was stirred for 4 h at −78 °C, quenched by addition of 20 mL of H_2O, warmed to room temperature, and transferred to a 250-mL separatory funnel. The organic layer was separated, washed with saturated aqueous NaCl, and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave a solid which was purified by flash chromatography (1:1 CH_2Cl_2–*n*-hexane) to give 2.1 g (45%) of **7h**: mp 184–185 °C; IR (KBr) 1600 (C=N), 1170 and 1130 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.75 (s, 6 H, OCH_3), 6.66–7.91 (m, 7 H, Ar); ^{13}C NMR ($CDCl_3$) δ 56.0, 104.0, 122.0, 125.7, 132.3, 132.6, 132.8, 133.2, 139.1, 158.3, 169.6 (C=N). Anal. Calcd for $C_{15}H_{13}NO_4S$: C, 59.40; H, 4.32. Found: C, 59.12; H, 4.36.

3-(2-(Trifluoromethyl)phenyl)-1,2-benzisothiazole 1,1-Dioxide (7i). In a dry 250-mL three-necked round-bottom flask equipped with a magnetic stir bar, nitrogen, and syringe inlets was placed 7.88 g (0.035 mol) of 2-bromobenzotrifluoride (Aldrich) in 50 mL of dry THF. The reaction mixture was cooled to −78 °C in a dry ice–acetone bath, 16 mL of 2 M *n*-butyllithium in pentane was added slowly over a period of 10 min, and the reaction mixture was stirred at −78 °C for 15 min. In a separate 500-mL three-necked round-bottomed flask, equipped with a magnetic stirring bar, nitrogen, and syringe inlets, was placed 5.3 g (0.025 mol) of **6** in 200 mL of dry THF. The contents of the flask were cooled to −78 °C, and the solution of lithiated benzotrifluoride previously prepared was added via cannula. After the mixture was stirred at this temperature for 4 h the solution was warmed to 0 °C, 50 mL of water was added dropwise, and the solution was allowed to warmed to room temperature. The reaction mixture was transferred to a separatory funnel and extracted with ethyl ether (3 × 75 mL), and the organic solution was washed with 50 mL of saturated aqueous NaCl solution. The ether layer was dried over anhydrous $MgSO_4$, and the solvent was removed in vacuo to give a yellowish oil which upon titration with *n*-pentane solidified. Crystallization from ethyl alcohol gave 5.2 g (67%) of **7i**: mp 147–150 °C; ^1H NMR ($CDCl_3$) δ 7.25–8.05 (m, 8 H, Ar); ^{13}C NMR ($CDCl_3$) δ 122.26, 125.46, 126.93, 126.99, 128.65, 130.99, 131.74, 133.45, 133.62, 139.0, 170.73 (C=N); MS (70 eV) m/z

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

(24) (a) Gilman, H.; Swiss, J. *J. Am. Chem. Soc.* **1940**, *63*, 1847. (b) Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

Table III. Second-Order Rate Constants for the Oxidation of Methyl Phenyl Sulfoxide by 3-Substituted 1,2-Benzisothiazole 1,1-Dioxide Oxides (8) at 25 °C in $CHCl_3$

entry	oxaziridine (R)	10^5k, L/mol^{-1} s^{-1}	correlation coefficient, r	relative rate
1	**8a** (methyl)	14.72 ± 0.51	0.996	1.0
2	**8b** (*n*-butyl)	14.39 ± 0.43	0.997	0.98
3	**8c** (*sec*-butyl)	8.89 ± 0.34	0.995	0.60
4	**8d** (*tert*-butyl)	3.97 ± 0.15	0.994	0.27
5	**8f** (phenyl)	5.53 ± 0.17	0.994	0.38
6	**8g** (2-methoxyphenyl)	4.23 ± 0.10	0.995	0.29
7	**8h** (2,6-dimethoxyphenyl)	*a*		
8	**8i** (2-(trifluoromethyl)phenyl)	*a*		
9	**8j** (4-(trifluoromethyl)phenyl)	34.65 ± 1.78	0.988	2.35
10	**8k** (pentafluorophenyl)	*a*		
11	$PhSO_2\overline{N-O-CHPh-NO_2-p}$	41.76 ± 1.65	0.994	2.84
12	$PhSO_2\overline{N-O-CHC_6F_5}$	128.4 ± 6.98	0.993	8.72

[a] No measurable reaction was observed up to 51 h.

Table IV. Second-Order Rate Constants for the Oxidation of (*R*)-(+)-Limonene by 3-Substituted 1,2-Benzisothiazole 1,1-Dioxide Oxides (8) at 60 °C in $CHCl_3$

entry	oxiziridine (R)	10^5k, L/mol^{-1} s^{-1}	corr coeff, r	*cis*-/*trans*-**12**	rel rate
1	**8a** (methyl)	17.6 ± 2.18	0.977	68/32	1.0
2	**8b** (*n*-butyl)	16.4 ± 0.26	0.999	73/27	0.93
3	**8c** (*sec*-butyl)	5.2 ± 0.44	0.992	74/26	0.30
4	**8d** (*tert*-butyl)	*a*			
5	**8f** (phenyl)	*a*			
6	**8g** (2-methoxyphenyl)	*a*			
7	**8h** (2,6-dimethoxyphenyl)	*a*			
8	**8i** (2-(trifluoromethyl)phenyl)	*a*			
9	**8j** (4-(trifluoromethyl)phenyl)	19.13 ± 0.63	0.997	71/29	1.1
10	$PhSO_2\overline{N-O-CHPh-NO_2-p}$	364.5 ± 34.5	0.981	65/35	20.7
11	$PhSO_2\overline{N-O-CHC_6F_5}$	845.9 ± 56.4	0.98	59/41	48.1
12	PBA[b]			50/50	

[a] No measurable reaction was observed up to 62 h. [b] See ref 22.

(relative intensity) 313 (M + 2, 3.1), 312 (M + 1, 8.5), 311 (M^+, 49.8), 263 (34.3), 247 (80.6), 246 (14.0), 227 (17.9), 226 (15.2), 208 (10.2), 197 (16.9), 178 (12.2), 145 (15.7), 95 (12.6), 76 (100), 75 (30.4), 50 (72.9). Anal. Calcd for $C_{14}H_8F_3NSO_2$: C, 54.02; H, 2.59; N, 4.50. Found: C, 53.64; H, 2.26; N, 4.42.

3-(4-(Trifluoromethyl)phenyl)-1,2-benzisothiazole 1,1-dioxide (7j) was prepared as described above from 4-bromobenzotrifluoride: yield 65.5% (*n*-pentane–CH_2Cl_2); mp 187–190 °C; ^1H NMR ($CDCl_3$) δ 7.7–8.18 (m, 8 H, Ar); ^{13}C NMR ($CDCl_3$) δ 123.37, 126.20, 129.81, 133.82, 133.9, 140.91, 169.9 (C=N); MS-FAB *m*/*z* (relative intensity) 312.9 (M + 1, 20.1), 311.9 (M^+, 100), 190.9 (24.5), 175.1 (11.7), 163.2 (7.9). Anal. Calcd for $C_{14}H_8F_3NSO_2$: C, 54.02; H, 2.59; N, 4.50. Found: C, 53.69; H, 2.39; N, 4.34.

3-(Pentafluorophenyl)-1,2-benzisothiazole 1,1-dioxide (7k) was prepared as described above from bromopentafluorobenzene (Aldrich): yield 45%; mp 165–167 °C (*n*-pentane–CH_2Cl_2); ^1H NMR ($CDCl_3$) δ 7.4–8.15 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 123.32, 125.54, 129.79, 134.27, 134.52, 139.56, 139.83, 161.78 (C=N); MS-FAB *m*/*z* (relative intensity) 334 (M + 1, 100), 154 (56.6), 138 (34.3), 137 (89.3), 136 (87.7), 107 (36.9). Anal. Calcd for $C_{13}H_4F_5NSO_2$: C, 46.85; H, 1.21; N, 4.20. Found: C, 46.71; H, 1.05; N, 4.04.

General Procedure for the Synthesis of 3-Substituted 1,2-Benzisothiazole 1,1-Dioxide Oxides. In a 100-mL three-necked Morton flask equipped with mechanical stirrer and 50-mL addition funnel was placed 2.0 mmol of the appropriate 3-substituted 1,2-benzisothiazole 1,1-dioxide **7** in 30 mL of CH_2Cl_2 and 30 mL of saturated K_2CO_3 solution. The reaction mixture was stirred vigorously while a solution of 0.56 g (3.0 mmol) of 95% *m*-CPBA in 20 mL of CH_2Cl_2 was added dropwise over 10 min. In the case of the hindered imines, **8g** and **8h**, 6.0 mmol of 95% *m*-CPBA was used. The progress of the reaction was monitored by TLC using CH_2Cl_2. In all cases the R_f of the oxaziridine was greater than the imine. When the reaction was complete the organic phases were separated from the aqueous phase, and washed successively with aqueous Na_2SO_3, $NaHCO_3$, and saturated NaCl (2 × 50 mL), and dried over anhydrous $MgSO_4$. Removal of the solvent in vacuo gave the crude oxaziridines as white solids and after crystallization from absolute ethanol afforded pure **8**. See Table II for yields.

3-Methyl-1,2-benzisothiazole 1,1-dioxide oxide (8a): mp 90–91 °C (lit.[10] mp 91–92 °C); ^{13}C NMR ($CDCl_3$) δ 15.6, 83.9 (oxaziridine C), 123.8, 125.7, 132.6, 133.4, 134.1, 135.1.

3-*n*-Butyl-1,2-benzisothiazole 1,1-dioxide oxide (8b): mp 76–78 °C; IR (KBr) 1370 and 1180 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.91–0.98 (m, 3 H, CH_3), 1.42–1.54 (m, 4 H, CH_2CH_2), 2.20–2.70 (m, 2 H, CH_2), 7.70–7.80 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.2, 25.6, 28.1, 86.4 (noxaziridine C), 123.7, 125.9, 132.7, 133.5, 134.1, 134.6. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48. Found: C, 55.46; H, 5.68.

3-*sec*-Butyl-1,2-benzisothiazole 1,1-dioxide oxide (8c): mp 66–67 °C; IR (KBr) 1360 and 1160 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.80–2.00 (m, 6 H, 2 CH_3), 2.40–2.87 (m, 2 H, CH_2), 3.16–3.39 (m, 1 H, CH), 7.74 (s, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 12.4, 16.1, 24.9, 34.1, 89.3 (oxaziridine C), 124.4, 126.8, 133.7, 134.7, 135.5. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48. Found: C, 55.21; H, 5.52.

3-*tert*-Butyl-1,2-benzisothiazole 1,1-dioxide oxide (8d): mp 131–132 °C; IR (KBr) 1335 and 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.34 (s, 9 H, 3 CH_3), 7.62–8.13 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 26.3, 34.1, 90.5 (oxaziridine C), 124.2, 127.6, 132.0, 133.5. Anal. Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48. Found: C, 55.08; H, 5.31.

3-*n*-Pentyl-1,2-benzisothiazole 1,1-dioxide oxide (8e): oil; IR (thin film) 2950 (CH), 1160, and 1320 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.94–2.72 (m, 11 H, pentyl H's), 7.69–7.79 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 13.51, 21.96, 22.99, 28.97, 30.90, 86.21 (oxaziridine C), 123.43, 125.81, 132.42, 133.45, 133.94, 134.48. Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.98. Found: C, 57.00; H, 5.80.

3-Phenyl-1,2-benzisothiazole 1,1-dioxide oxide (8f): mp 105–106 °C; IR (KBr) 1350 and 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.56 (s, 5 H, Ar), 7.58–7.94 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 85.4 (oxaziridine C), 124.1, 128.1, 129.1, 129.2, 131.5, 133.0, 134.1, 134.4, 134.5. Anal. Calcd for $C_{13}H_9NO_3S$: C, 60.22; H, 3.50. Found: C, 59.93; H, 3.65.

3-(2-Methoxyphenyl)-1,2-benzisothiazole 1,1-dioxide oxide

(**8g**): mp 105 °C; IR (KBr) 1330 and 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.77 (s, 3 H, CH_3), 6.99–7.82 (m, 8 H, Ar); ^{13}C NMR ($CDCl_3$) δ 55.6, 84.6 (oxaziridine C), 111.3, 117.6, 120.8, 123.6, 126.6, 128.6, 132.1, 132.5, 132.8, 133.7, 136.6, 157.9. Anal. Calcd for $C_{14}H_{11}NO_4S$: C, 58.12; H, 3.83. Found: C, 58.12; H, 3.87.

3-(2,6-Dimethoxyphenyl)-1,2-benzisothiazole 1,1-dioxide oxide (8h): mp 134–136 °C; IR (KBr) 1330 and 1170 (SO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.76 (s, 3 H, OCH_3), 3.90 (s, 3 H, OCH_3), 6.66–7.80 (m, 7 H, Ar); ^{13}C NMR ($CDCl_3$) δ 56.2, 84.4 (oxaziridine C), 104.1, 108.1, 126.8, 131.9, 132.0, 132.3, 135.5, 136.5, 138.9, 139.9, 158.5, 159.2. Anal. Calcd for $C_{15}H_{13}NO_5S$: C, 56.42; H, 4.10. Found: C, 56.19; H, 3.78.

General Procedure for the Preparation of 3-Aryl-1,2-benzisothiazole 1,1-Dioxide Oxide (8i–k) Using a PTC. In a 1-L three-necked Morton flask equipped with a mechanical stirrer and dropping funnel were placed 16 mmol of **7i–k** in 150 mL of $CHCl_3$, 100 mL of water, and 1.5 g (10 mmol) of K_2CO_3. After the reaction mixture was cooled to 5 °C in an ice bath, a solution of 4.3 g (20 mmol) of 85% *m*-chloroperbenzoic acid (*m*-CPBA) and 650 mg (20 mol %) of benzyltriethylammonium chloride (BTEAC) in 100 mL of $CHCl_3$ was added dropwise to the rapidly stirring reaction mixture over a period of 30 min. Completion of the oxidation was determined by TLC (1:1 CH_2Cl_2–hexane). The reaction mixture was transferred to a 1-L separatory funnel, the phases were separated, and the organic solution was washed with 2 × 150 mL each of saturated solutions of Na_2SO_3, $NaHCO_3$, NaCl, and finally 100 mL of water. After drying over anhydrous K_2CO_3, the solvent was removed on rotary evaporator to afford the crude oxaziridines, which were triturated with *n*-pentane until solid.

3-(2-(Trifluoromethyl)phenyl)-1,2-benzisothiazole 1,1-dioxide oxide (8i): yield 54%; mp 114–116 °C (purified by flash chromatography, eluting with 80:20 *n*-pentane–ether); ^1H NMR ($CDCl_3$) δ 7.27–7.88 (m, Ar); ^{13}C NMR ($CDCl_3$) δ 86.0 (oxaziridine C), 124.9, 128.1, 128.2, 128.4, 128.44, 128.5, 131.2, 132.8, 133.9, 134.4, 135.6; MS-FAB *m/z* (relative intensity) 328.9 (M + 1, 13.9) 327.8 (M^+, 100, 312.9 (88.3), 311.9 (38.6), 172.9 (37.3), 169 (24.2), 137.12 (63.6), 136.1 (39.7), 107.2 (33.4). Anal. Calcd for $C_{14}H_8F_3NO_3S$: C, 51.38; H, 2.46; N, 4.28. Found: C, 51.25; H, 2.84; N, 4.15.

3-(4-(Trifluoromethyl)phenyl)-1,2-benzisothiazole 1,1-dioxide oxide (8j): yield 55% (CH_2Cl_2–*n*-hexane); mp 137–140 °C; ^1H NMR ($CDCl_3$) δ 7.59–7.9 (m, 8 H, Ar); ^{13}C NMR ($CDCl_3$) δ 84.429 (oxaziridine C), 124.37, 126.04, 126.09, 126.14, 126.18, 127.82, 128.69, 133.22, 133.68, 134.14, 134.47, 134.54; MS-FAB *m/z* (relative intensity) 329 (M + 2, 4.05), 328 (M + 1, 9.1), 327 (molecular ion, 54.7), 311 (31.7), 298 (15.9), 297 (100), 263 (13.0), 247 (38.2), 233 (35.1), 184 (46.5), 145 (57.4), 76 (34.6), 50 (24.7). Anal. Calcd for $C_{14}H_8F_3NO_3S$: C, 51.38; H, 2.46; N, 4.28. Found: C, 51.35; H, 2.35; N, 4.17.

3-(Pentafluorophenyl)-1,2-benzisothiazole 1,1-dioxide oxide (8k): yield 60% (CH_2Cl_2–*n*-hexane); mp 146–9 °C; ^1H NMR ($CDCl_3$) δ 7.58–7.92 (m, 8 H, Ar); ^{13}C NMR ($CDCl_3$) δ 79.59 (oxaziridine C), 124.74, 127.05, 133.33, 134.34, 134.91, 135.11, 135.39, 136.66, 140.02; MS-FAB *m/z* (relative intensity) 350.1 (M + 1, 18.5), 335.1 (29.9), 334.1 (100), 211.2 (84.6), 208.2 (26.5), 154.1 (54.3), 138.1 (31.7), 137.1 (76.1), 136.1 (80.2), 115.1 (26.1), 107.1 (37.5). Anal. Calcd for $C_{13}H_4F_5NO_3S$: C, 44.71; H, 1.15; N, 4.01. Found: C, 44.56; H, 1.23; N, 3.97.

***N*-(Pentafluorobenzylidene)benzenesulfonamide** was prepared as previously described[8b] from 15.7 g (0.1 mol) of benzenesulfonamide and 19.9 g (0.1014 mol) of pentafluorobenzaldehyde to give after crystallization from ethyl acetate–*n*-hexane 24.5 g (79%) of white crystals: mp 112–114 °C; ^1H NMR ($CDCl_3$) δ 7.55–8.02 (m, 5 H, Ar), 9.23 (s, 1 H, CH); ^{13}C NMR ($CDCl_3$) δ 128.38, 129.46, 134.32, 136.99, 159.31 (C=N); MS-FAB *m/z* (relative intensity) 336.1 (M + 1, 2.7), 335.1 (M^+, 15.3), 143 (10.9), 142 (16.7), 141 (100), 78.1 (26.3), 77.1 (99.2), 51.1 (76.3), 50.1 (16.0). Anal. Calcd for $C_{13}H_6F_5NO_2S$: C, 46.57; H, 1.80; F, 28.34; N, 4.18. Found: C, 46.74; H, 1.79; F, 28.32; N, 4.16.

2-(Phenylsulfonyl)-3-(pentafluorophenyl)oxaziridine. The oxaziridine was prepared as previously described from 25 g (0.075 mol) of the sulfonimine using buffered Oxone[8a] to give after crystallization from CH_2Cl_2–*n*-pentane white needles: 22.5 g (85%); mp 72–74 °C; ^1H NMR ($CDCl_3$) δ 5.8 (s, 1 H, CH), 7.44–8.08 (m, 5 H, Ar); ^{13}C NMR ($CDCl_3$) δ 69.57 (oxaziridine C), 129.55, 129.67, 129.81, 130.38, 133.09, 133.94, 134.58, 135.62. MS (70 eV) *m/z* (relative intensity) 336 (M + 1, 9.04), 335 (M^+, 5.6), 197 (11.2), 196 (21.3), 195 (25.0), 168 (10.2), 167 (16.3), 143 (11.7), 142 (17.7), 141 (97.8), 117 (16.2), 99 (10.2), 78 (27.5), 77 (100), 51 (65.1). Anal. Calcd for $C_{13}H_6F_5NO_3S$: C, 44.45; H, 1.72; N, 3.99; F, 27.05. Found: C, 44.43; H, 1.8; N, 4.03; F, 27.43.

3-Butylene-*N*-methyl-1,2-benzisothiazole 1,1-Dioxide (10). In a 50-mL round-bottom flask equipped with magnetic stir bar, 25-mL addition funnel, syringe, and argon inlets was placed 6.2 mL of a 0.36 M solution of freshly prepared lithium diisopropyl amide. 3-*n*-Butyl-1,2-benzisothiazole 1,1-dioxide (**7b**), 0.54 g (2.24 mmol), in 8 mL of dry THF was added dropwise over 0.5 h to the stirring LDA solution at −78 °C. After the reaction mixture was stirred for an additional 0.5 h, 0.42 mL (1.3 mmol) of iodomethane in 2.5 mL of THF was added to the reaction mixture via syringe. After stirring for an additional 2 h at −78 °C, the reaction was quenched by addition of 10 mL of H_2O and warmed to room temperature. The aqueous layer was extracted with ether (2 × 25 mL); the organic phases were combined and dried over anhydrous $MgSO_4$. Removal of the solvent gave a solid, which was purified by preparative TLC (silica gel) eluting with 1:1 ether–*n*-pentane (top band) to give 0.34 g (64%) of **10**: mp 93–4 °C; IR (KBr) 1665 and 915 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.9–1.6 (m, 5 H), 2.45 (q, 2 H, CH_2, J = 22.2 Hz), 3.32 (s, 3 H, CH_3), 5.4–5.6 (t, 1 H, CH, J = 15.2 Hz), 7.25–7.82 (m, 4 H, Ar); ^{13}C NMR ($CDCl_3$) δ 13.8, 23.6, 28.6, 31.1, 107.6 (CH=C), 120.4, 121.0, 129.2, 132.8. Anal. Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37. Found: C, 60.89; H, 6.36.

Kinetic Study of the Oxidation of Phenyl Methyl Sulfoxide to Phenyl Methyl Sulfone. In a 2.0-mL glass vial, typically 0.1 mmol of the appropriate oxaziridine and an equimolar amount of methyl phenyl sulfoxide were combined with an adequate amount of bibenzyl internal standard (typically 0.01 g) and diluted to 1.5 mL with anhydrous $CHCl_3$ (dried over anhydrous K_2CO_3). The vial was sealed and thermostated at 25 ± 1.0 °C. The course of the oxidation was determined by GLC by sampling 2 μL of the reaction mixture at the prescribed time interval. The amount of sulfoxide and sulfone were determined by using predetermined response factors.

The reactions were followed beyond 75% completion. All kinetic determinations were performed at least twice, and the results were averaged. The second order rate constants (k) were determined form the slope of the least-squares line obtained by plotting reciprocal concentration ($1/c$) versus time (t). Errors reported are standard deviations. These results are summarized in Table III.

Kinetic Study of the Oxidation of (*R*)-(+)-Limonene to (*R*)-(+)-Limonene Oxides (Mixture of Cis/Trans). In a 2.0-mL glass vial, typically 0.1 mmol of the appropriate oxaziridine and an equimolar amount of (*R*)-(+)-limonene were combined with an adequate amount of internal standard (naphthalene) and diluted to 1.5 mL with anhydrous $CHCl_3$. The vial was sealed and placed in a thermostatically controlled oil bath at 60 ± 1 °C. For kinetic studies the oxidation was folllowed by GLC analysis using the internal standard method as discussed above. The amount of unreacted limonene and amounts of *cis*- and *trans*-limonene oxides (**12**) were determined by comparison of the integrated peak areas.

The reactions were followed beyond 75% completion. All kinetic determinations were performed at least twice and the results averaged. The second-order rate constants (k) were calculated from the slope of the line obtained by plotting the reciprocal of the concentration ($1/c$) vs the time (t) by using a least-squares program. Errors reported are standard deviations. These results are summarized in Table IV.

Acknowledgment. The financial support of the National Science Foundation is gratefully acknowledged. We thank Thomas W. Panunto for preliminary studies on **10**.

Registry No. **5**, 81-07-2; **6**, 18712-15-7; **7a**, 34989-82-7; **7b**, 55379-09-4; **7c**, 124401-00-9; **7d**, 65818-60-2; **7e**, 124401-01-0; **7f**, 53440-57-6; **7g**, 124401-02-1; **7h**, 124401-03-2; **7i**, 124401-04-3; **7j**, 124401-05-4; **7k**, 124401-06-5; **8a**, 73845-10-0; **8b**, 124401-07-6; **8c**, 124401-08-7; **8d**, 124401-09-8; **8e**, 124401-10-1; **8f**, 124401-11-2; **8g**, 124401-12-3; **8h**, 124401-13-4; **8i**, 124401-14-5; **8j**, 124401-15-6;

8k, 124401-16-7; 10, 124401-19-0; $H_3C(CH_2)_4Li$, 3525-31-3; PhLi, 591-51-5; MeOPh, 100-66-3; o-$BrC_6H_4CF_3$, 392-83-6; p-$BrC_6H_4CF_3$, 402-43-7; $PhSO_2NH_2$, 98-10-2; PhSOMe, 1193-82-4; 3-chloro-1,2-benzisothiazole 1,1-dioxide, 567-19-1; 1,3-dimethoxybenzene, 151-10-0; bromopentafluorobenzene, 344-04-7; N-(pentafluorobenzylidene)benzenesulfonamide, 124401-17-8; pentafluorobenzaldehyde, 653-37-2; 2-(phenylsulfonyl)-3-(pentafluorophenyl)oxaziridine, 124401-18-9; (R)-(+)-limonene, 5989-27-5.

Cephalotaxine Analogues: Stereospecific Synthesis of Spiro-Fused 3-Benzazepine and 1,3-Benzodiazepine Derivatives

John M. Gardiner and Martin R. Bryce*

Department of Chemistry, University of Durham, South Road, Durham, DH1 3LE, U.K.

Paul A. Bates and Michael B. Hursthouse

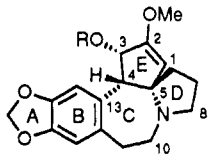
Department of Chemistry, Queen Mary College, Mile End Road, London, E1 4NS, U.K.

Received June 19, 1989

The previously reported spirolactam **3** was converted into aldehyde derivative **17** (55% yield) via alkylation of **3** with bromo-*tert*-butyl acetate followed by transesterification to methyl ester **16** and reduction of **16** with diisobutylaluminum hydride. Treatment of aldehyde **17** with hydrochloric acid afforded benzazepinol **21** (90%), which was readily dehydrated using boron trifluoride–etherate to yield derivative **22** (90%). An alternative approach to the fused benzazepine system **33** started from 3,4-dimethoxyphenylacetic acid (**23**), which was converted into nitrostyrene derivative **26**. Cycloaddition of butadiene (derived from butadiene sulphone) to **26** yielded **27** (70–75%), which underwent stereospecific reaction with methyl acrylate to yield nitro diester **28** (87%). Reduction of **28** with zinc–HCl gave lactam–ester **29** (90%), which cyclized in a stereospecific reaction with diisobutyl aluminum hydride to furnish benzazepinol **33** (91%), the structure of which was confirmed by single-crystal X-ray analysis. Analogous reactions starting from nitropiperonal afforded dinitro ester **37** (62% yield for three steps), which was reduced by zinc–HCl to yield amine–lactam **38** (55%), which, in turn, was cyclized with formaldehyde to give benzodiazepine derivative **40** (71%).

Introduction

Alkaloids produced by conifers of the *Cephalotaxus* genus are of considerable current interest. While the parent compound, cephalotaxine (**1**), is biologically inactive, a range of naturally occurring ester derivatives, e.g. harringtonine (**2**), display promising antitumour properties and they are presently in phase II clinical trials.[1-8] The

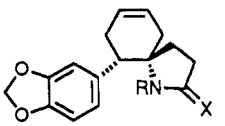


1: R = H (Cephalotaxine)

2: R = $-C(=O)-C(OH)(CH_2CO_2Me)-(CH_2)_2C(OH)Me_2$ (Harringtonine)

central synthetic challenges provided by the cephalotaxine skeleton have been identified[1] as (i) the formation of the C(4)–C(13) bond, (ii) the quaternary center at C(5), (iii) the enol ether moiety at C(1)–C(2), (iv) the stereochemistry at C(3) and C(4), and (v) the formation of the benzazepine ring. Five total syntheses of (±)-cephalotaxine (**1**) have been reported,[9-13] and other partial syntheses and model studies directed toward this skeleton have been described recently.[14-19]

We have reported the stereospecific synthesis of spirolactam derivative **3** in four steps starting from piperonal (54% overall yield).[16] The stereochemistry of structure **3**, which derives from a stereospecific Michael addition (cf. **27** → **28**) has been established unequivocally by single-crystal X-ray analysis of thiolactam **4**.[16] A conspicuous feature of structure **3** is that the relative stereochemistry



3: X = O; R = H
4: X = S; R = H
5: X = H_2; R = H
6: X = O; R = CH_2CO_2H
7: X = O; R = C(O)C(O)Cl
8: X = H_2; R = C(O)C(O)Cl
9: X = H_2; R = $C(O)CO_2H$
10: X = H_2; R = CH_2CO_2Et
11: X = H_2; R = $C(O)CH_2Cl$
12: X = H_2; R = $(CH_2)_2OH$
13: X = H_2; R = $(CH_2)_2Cl$
14: X = O; R = $(CH_2)_2Cl$
15: X = O; R = CH_2CO_2-*t*-Bu
16: X = O; R = CH_2CO_2Me
17: X = O; R = CH_2CHO

(1) Hudlicky, T.; Kwart, L. D.; Reed, J. W. *Alkaloids, Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; J. Wiley: New York, 1987; Vol. 5, Chapter 5.
(2) Huang, L.; Xue, Z. *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1984; Vol. 23, Chapter 3.
(3) Smith, C. R., Jr.; Mikolajczak, K. L.; Powell, R. G. *Antitumour Agents Based on Natural Product Models*; Academic Press: New York, 1980; Chapter 11.
(4) Ohnuma, T.; Holland, J. F. *J. Clin. Oncol.* **1985**, *3*, 604.
(5) Warrell, R. P.; Coonley, C. J.; Gee, T. S. *J. Clin. Oncol.* **1985**, *3*, 617.
(6) O'Dwyer, P. J.; King, S. A.; Hoth, D. F.; Suffness, M.; Leyland-Jones, B. *J. Clin. Oncol.* **1986**, *4*, 1563.
(7) Ajani, J. A.; Dimery, I.; Chawla, S. P.; Pinnamaneni, K.; Benjamin, R. S.; Legha, S. S.; Krokoff, I. H. *Cancer Treat. Rep.* **1986**, *70*, 375.
(8) Tan, C. T. C.; Luks, E.; Bacha, D. M.; Steinherz, P.; Steinherz, L.; Mondora, A. *Cancer Treat. Rep.* **1987**, *71*, 1245.
(9) Weinreb, S. M.; Auerbach, J. *J. Am. Chem. Soc.* **1975**, *97*, 2503.
(10) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. T.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507.
(11) Yasuda, S.; Yamada, T.; Hanaoka, M. *Tetrahedron Lett.* **1986**, *27*, 2023.
(12) Burkholder, T. P.; Fuchs, P. L. *J. Am. Chem. Soc.* **1988**, *110*, 2341.
(13) Kuehne, M. E.; Bormann, W. E.; Parsons, W. H.; Spitzer, T. D.; Blount, J. F.; Zubieta, J. *J. Org. Chem.* **1988**, *53*, 3439.
(14) Tinner-Harding, T.; Ullrich, J. W.; Chiv, F. T.; Chen, S. F.; Mariano, P. S. *J. Org. Chem.* **1982**, *47*, 3360.
(15) Raucher, S.; Jones, D. S.; Stenkamp, R. E. *J. Org. Chem.* **1985**, *50*, 4523.
(16) Bryce, M. R.; Gardiner, J. M.; Hursthouse, M. B.; Short, R. L. *Tetrahedron Lett.* **1987**, *28*, 577.
(17) Bryce, M. R.; Gardiner, J. M. *Tetrahedron* **1988**, *44*, 599.
(18) Hill, R. K.; Sawada, S.; Bock, M. G.; Greene, J. R. *Heterocycles* **1987**, *25*, 515.
(19) Kavash, R. W.; Mariano, P. S. *Tetrahedron Lett.* **1989**, *30*, 4185.

0022-3263/90/1955-1261$02.50/0