Synthesis and Ring-Opening Reactions of Functionalized Sultines. A New Approach to Sparsomycin

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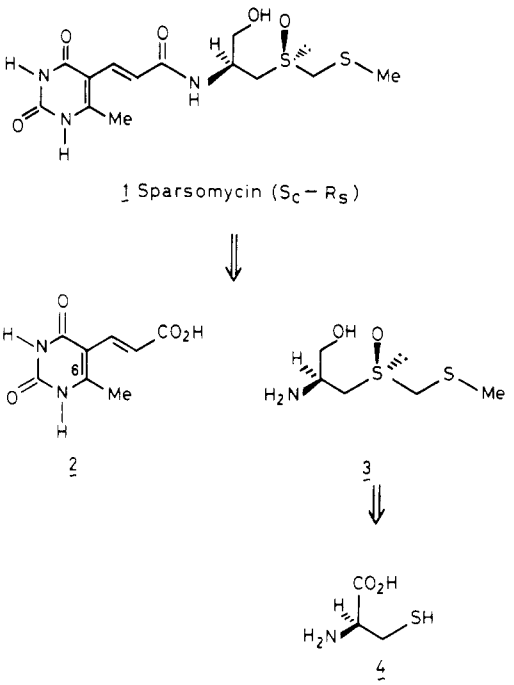
An efficient route leading to the functionalized five-membered cyclic sulfinate esters (γ-sultines) **14a,b** and **21a,b** is described on the basis of the reaction of the N-protected cystinol derivatives **11** and **20**, respectively, with *N*-chlorosuccinimide (NCS) and AcOH. Ring-opening reactions of the sultines can be performed in two ways. Treatment of **14** with Cl_2 or NCS/HCl gives the sulfonyl chloride **15** by cleavage of the C–O bond. Selective cleavage of the S–OR bond occurs when **14** or **21** is treated with $MeSCH_2Li$, *n*-BuLi, or $C_6H_5C(Li)(H)CN$ to yield the hydroxyalkyl sulfoxides **22–26**. These nucleophilic ring-opening reactions are stereospecific and proceed with inversion at the sulfoxide sulfur atom. The synthesis of **23a** constitutes a new approach to the antibiotic sparsomycin (**1**). Circular dichroism measurements can be employed in the assignment of absolute configurations to the sulfoxide sulfur atom of the sultines **14a,b** and **21a,b** (patents pending).

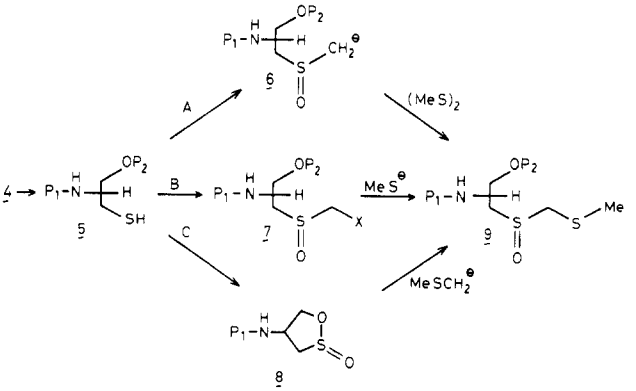
The antibiotic sparsomycin (**1**)[1] may be considered as an amide derived from the acid component **2** and the amine component **3** (Scheme I). The latter can be viewed as a derivative of D-cysteine (**4**), having its CO_2H function reduced and its SH function alkylated and oxidized. Recently, in the course of total syntheses of **1**, two approaches were developed to prepare protected derivatives of **3**, as represented by formula **9** (Scheme II). Helquist[2] applied successfully the sulfenylation of the α-sulfinyl carbanion **6**, prepared, in turn, from D-cysteine **4** (route A), while we[3,4] employed the reaction of the cysteinol α-halo sulfoxide derivative **7** with sodium methylmercaptide (route B).

An attractive alternative to these routes might feature the nucleophilic ring opening of a cyclic sulfinate ester or γ-sultine, **8** (approach C). Such an intermediate has a sulfur atom activated toward nucleophilic attack and simultaneously provides protection for the alcohol function. We report the viability of this approach: we have synthesized sultines of type **8** and have studied their ring-opening reactions with nucleophiles. In the course of our synthetic work on sulfur-containing natural products we have become interested in sultines for several reasons. In contrast to their lactone counterparts they are inherently chiral, so that in reactions with racemic nucleophiles (e.g., $R_1R_2R_3Cl^-$) ring opening will be a diastereoselective process. As will be shown below, these ring-opening reactions may proceed by cleavage of either the S–O bond or the C–O bond. Oxidation of sultines gives sultones which have a utility of their own in synthetic organic chemistry.[5]

Scheme I



Scheme II



Synthesis of γ-Sultines 8

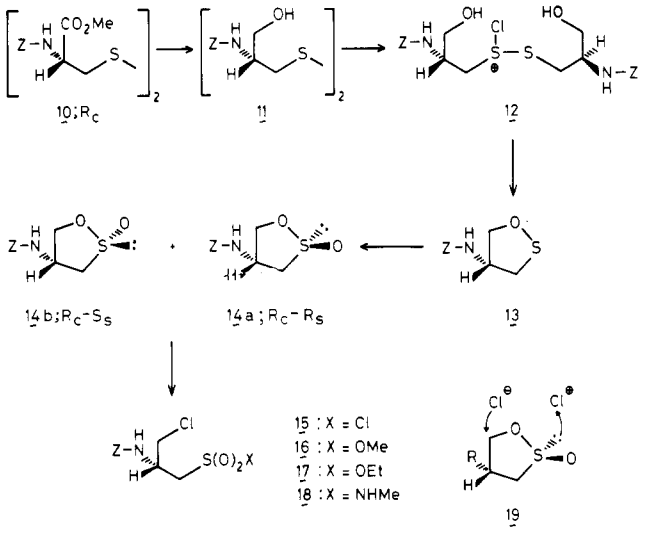
In contrast to the extensive literature which exists on the preparation of sulfinate esters[6] only a limited number of sultines have been described.[7] To our knowledge, no synthesis of *functionalized* sultines, e.g., **8**, have yet been reported.

For the preparation of **8** we examined first the method used[8,9] for the conversion of 1-mercaptopropan-3-ols into

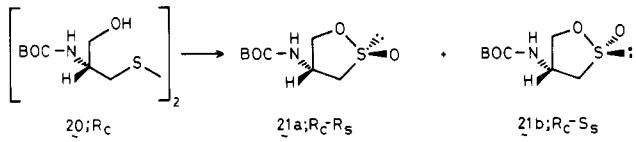
(1) Argoudelis, A. D.; Herr, R. R. *Antimicrob. Agents Chemother.* **1962**, 505. Higashide, E.; Hasegawa, T.; Shibita, M.; Mizuno, K.; Akaike, H. *Takeda Kenkyusho Nempo* **1966**, *25*, 1; *Chem. Abstr.* **1967**, *66*, 54238.
(2) Helquist, P.; Shekani, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 1057.
(3) Ottenheijm, H. C. J.; Liskamp, R. M. J.; Tijhuis, M. W. *Tetrahedron Lett.* **1979**, 387.
(4) Ottenheijm, H. C. J.; Liskamp, R. M. J.; van Nispen, S. P. J. M.; Boots, H. A.; Tijhuis, M. W. *J. Org. Chem.* **1981**, *46*, 3273.
(5) Hanefeld, W.; Kluck, D. *Synthesis* **1981**, 229. Smith, M. B.; Wolinsky, J.; *J. Org. Chem.* **1981**, *46*, 101. Fraser-Reid, B.; Sun, K. M.; Tsang, R. Y.-K.; Sinaij, P. Pietraszkiewicz, M. *Can. J. Chem.* **1981**, *59*, 260. Kondo, K.; Aoi, H.; Takemoto, K. *Synth. Commun.* **1980**, *10*, 267.
(6) Nudelman, A. *Phosphorus Sulfur* **1980**, *9*, 1.
(7) Sharma, N. K.; De Reinach-Hirtzbach, F.; Durst, T. *Can. J. Chem.* **1976**, *54*, 3012 and reference cited therein.
(8) Givens, E. N.; Hamilton, L. A. *J. Org. Chem.* **1967**, *32*, 2857.

0022-3263/81/1946-5408$01.25/0

Scheme III



Scheme IV



γ-sultines as it allowed us to use cysteinol as the starting material. Thus, the N-protected L-cystinol derivative **11**, prepared from **10** by $LiBH_4$ reduction followed by I_2 oxidation, was treated with 3 equiv of Cl_2 and an excess of AcOH (Scheme III). However, instead of the expected compound **14** the sulfonyl chloride **15** was formed (78% yield). The structure of **15** was secured by spectroscopic data and the formation of the derivatives **16–18**. We then reexamined the reaction conditions. When the reaction, which was monitored by TLC, was stopped just as **15** began to appear, in addition to starting material **11**, the sultines **14a** and **14b** could be isolated, albeit in low yields (7% and 28%, respectively). The molecular structures of **14a** and **14b** were assigned by spectroscopy and the preparation of derivatives; the absolute configuration of the sulfoxide sulfur atoms[10] was assigned by X-ray analysis of a homologue (vide infra). The two diastereomers showed a surprisingly large difference in R_f value on chromatography and were readily separated by silica gel chromatography, compound **14a** being the more polar component.[11]

Treatment of the isolated sultines with Cl_2 resulted in quantitative formation of **15**. The formation of **14** and **15** from **11** can be rationalized by the following sequence. Chlorine oxidation of **11** produces first the sulfonium ion **12**, which, by subsequent intramolecular displacements by the hydroxyl functions, leads to 2 mol of the sultene **13**.[12] This, on oxidation with Cl_2/AcOH, gives the sultines **14a** and **14b**. Finally, **15** is formed by cleavage of the C–O bond, a reaction known to proceed with sulfinate esters[13] and with some sultines[7] in the presence of halogens. This ring-opening reaction might be rationalized as depicted in **19**.

Apparently, ring opening of **14** to **15** and the oxidation steps that lead to **14** are competing reactions with similar rates in the Cl_2/AcOH procedure. We reasoned that the use of another oxidizing agent, generating Cl^+ and having a less nucleophilic counterion, might prevent the ring opening. Consequently, we studied, in turn, SO_2Cl_2 and *N*-chlorosuccinimide (NCS).[14] Reaction of **11** with 3 equiv of SO_2Cl_2 gave an intractable reaction mixture. Oxidation with NCS, however, was more successful; treatment of **11** with AcOH and 3 equiv of NCS gave **14a** and **14b** (1:1 ratio) in 90% yield. Thus it appears that under these reaction conditions no Cl_2 is being formed. With an excess (10 equiv) of NCS, compound **15** was again isolated as the sole product. The sultines were found to be unreactive toward NCS alone. Thus the production of **15** must be caused by reaction of the sultines with Cl^-/NCS or Cl_2. Reaction of **11** with 3 equiv as well as with an excess (10 equiv) or *N*-bromosuccinimide (NBS) gave the sultines **14a** and **14b** (1:1 ratio) in 86% yield. Here the use of an excess of NBS gave no detectable amounts of the ring-opened product.[15]

Earlier we had shown[4] in the synthesis of sparsomycin (**1**) that the *tert*-butoxycarbonyl (Boc) group was preferred for the N-protection of **9**. Therefore, we also prepared the sultines **21a** and **21b** (88% yield, 1:1 ratio) by treatment of **20** with 3 equiv of NCS, an excess of AcOH, and, to avoid removal of the acid-labile Boc group, 3 equiv of pyridine (Scheme IV). Structures **21a** and **21b** were assigned to the more polar and less polar diastereomeric products, respectively, by means of spectroscopy and an X-ray crystallographic analysis of **21a**.[17] These structures were also supported by conversion of the products into derivatives (vide infra).

The ^1H NMR spectra of **14a,b** and **21a,b** deserve some comment. Previous studies have shown that protons in a 1,3-syn-diaxial relationship to a sulfinyl oxygen atom experience deshielding, which has been referred to as the syn-axial effect.[18] This effect has been discussed for four-,[19] five-,[7] and six-membered[18,20] ring systems and caused a $\Delta\delta$ of 0.6–1.1 ppm. This effect was not observed in **14a,b** and **21a,b**; the ^1H NMR spectra showed nearly the same δ value for the C(4) proton in either a syn relationship with the sulfinyl oxygen (**21a**, δ 4.79) or an anti position (**21b**, δ 4.85). This indicates that the syn-axial effect may not be applicable to substituted γ-sultines, where substituents assume pseudoaxial and pseudoequatorial positions.[21]

(9) Dodson, R. M.; Hammen, P. D.; Davis, R. A. *J. Chem. Soc., Chem. Commun.* **1968**, 9.

(10) The *R/S* nomenclature as adopted for sulfinate esters (Mislow, K.; Green, M. M.; Laur, P.; Melillo, J. T.; Simmons, T.; Ternay, A. L. *J. Am. Chem. Soc.* 1965, *87*, 1958) has been followed here, in that the S–O "double" bond has a lower priority than the S–OR bond.

(11) The conformations of **14a** and **14b** are being studied by NMR and may provide some explanation for the large difference in polarity.

(12) While sultenes have been proposed before as reactive intermediates, only recently has the first stable sultene been prepared; see: Astrology, G. W.; Martin, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 4390 and references cited therein.

(13) Douglass, I. B. *J. Org. Chem.* **1965**, *30*, 633; **1974**, *39*, 563.

(14) Both reagents have been used for the conversion of *tert*-butyl hydroxyalkyl sulfoxides into sultines (see ref 7).

(15) This interesting difference in reactivity of the sultines **14** toward NBS and NCS might be explained by a polarization difference between their N–halogen bonds; the N–Br bond is less polarized than the N–Cl bond,[16] so that NBS may not be reactive enough to cause ring opening of **14**. We noticed that during the NBS reaction Br_2 was formed. From this it may follow that the sultines **14** are stable toward Br_2 but reactive toward Cl_2.

(16) Lumbroso, H.; Gasco, L.; Malên, C. *Bull. Chem. Soc. Fr.* **1951**, *15*, 823.

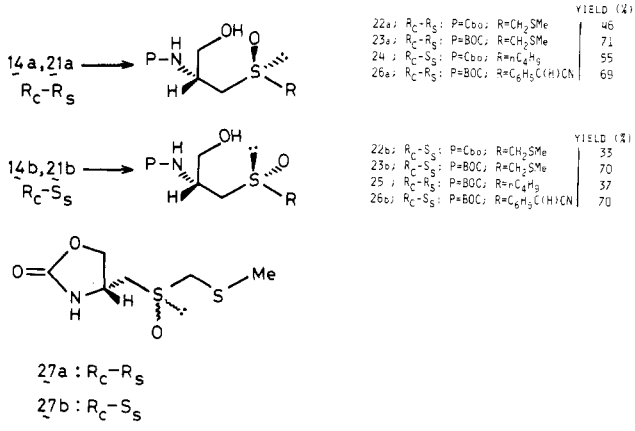
(17) A detailed discussion of the X-ray crystallographic analysis of **21a** and a conformational analysis of **21a** and **21b** based on NMR spectroscopy will be the subject of a future report.

(18) Harpp, D. N.; Gleason, J. G. *J. Org. Chem.* **1971**, *36*, 1314 and references cited therein.

(19) Johnson, C. R.; Siegl, W. O. *Tetrahedron Lett.* **1969**, 1879.

(20) Buchanan, G. W.; Sharma, N. K.; De Reinach-Hirtzbach, F.; Durst, T. *Can. J. Chem.* **1977**, *55*, 44.

Scheme V



Nucleophilic Ring-Opening Reactions of Sultines

The most widely used procedure for the synthesis of sulfoxides of high optical purity involves the reaction of an optically active sulfinate ester with a Grignard reagent, the Andersen synthesis.[22] Recently, this method has been used by Colombo et al.[23] for the synthesis of optically active thioacetal monosulfoxides by reaction of an optically active sulfinate ester with (alkylthio)methyllithium. These reactions are stereospecific and proceed with inversion at sulfur.[24] Nucleophilic ring opening of sultines has been reported only twice. Grignard reagents[25] as well as organocopper–lithium reagents[26] gave the corresponding sulfoxide alcohols. Although the stereochemistry of these ring-opening reactions has not been rigorously established, it has been discussed and assumed[25] by analogy to open-chain sulfinates to proceed also with inversion at sulfur.

We found that Colombo's approach[23] was also applicable for the conversion of **8** into **9**. Thus, reaction of **14** and **21** at −78 °C with 3 equiv of (methylthio)methyllithium, prepared according to Peterson,[27] gave the desired dithioacetal monoxides **22** and **23** (Scheme V; the yields for **22** have not been optimized). The known[4] compounds **27a** and **27b** were found as side products (19% and 11% yields, respectively) when the reaction mixtures of **14** → **22** were not acidified rapidly after completion.

The formation of **22** and **23** was found to be stereospecific; no trace of the corresponding diastereomers was found. Since the absolute configuration of sultine **21a**[17] as well as of the ring-opened products **22** and **23**[28] has been rigorously established, we can now conclude that in analogy to open-chain sultinates, *sultines undergo nucleophilic ring-opening reactions with inversion at sulfur.*[29]

The reactivity of **14** and **21** toward other nucleophiles was also studied. Reaction of **14a** and **21b** with *n*-butyllithium gave the sulfoxides **24** and **25**, respectively. In an attempt to prepare other α-functionalized sulfoxides in addition to **22** and **23**, compounds **21a** and **21b** were treated with lithium benzylcyanide[30] to give the α-cyano sulfoxides **26a** and **26b**, respectively. In each case diastereomers having different configurations at the C(H)(CN) carbon atom were formed in unequal amounts: for **26a** the ratio was 1/2; for **26b** the ratio was 9/11 (the stereochemistry is undetermined). This shows that asymmetric induction by the chiral sulfur atom is at work. So far, optically active α-cyano sulfoxides have been virtually unexplored.[31]

Treatment of **21b** with 2 equiv of NaOMe in MeOH gave a mixture of the starting material and **21a** in a 1:1 ratio. This epimerization can be explained by a transesterification reaction of the ring-opened R_C–R_S methyl sulfinate ester;[32] ring closure of the latter gives **21a**. None of the ring-opened methyl sulfinate esters could be isolated.

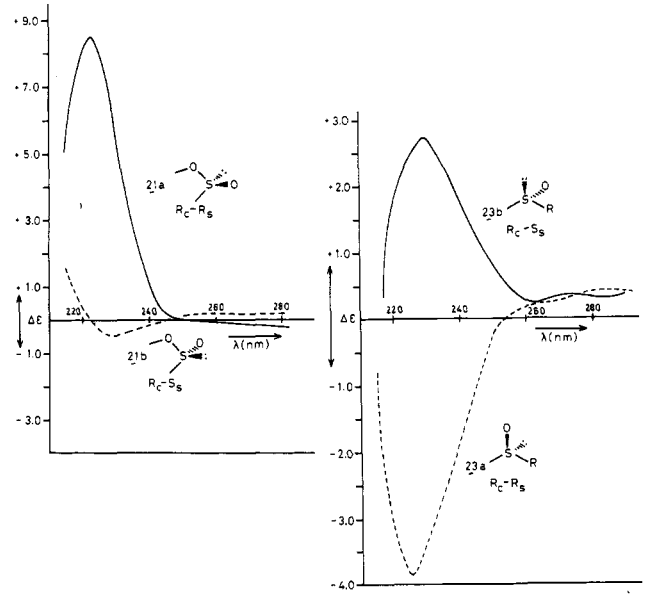


Figure 1. CD spectra of **21a,b** and **23a,b** in acetonitrile.

CD Spectra of 21 and 23

Previously we showed that for sparsomycin[4] as well as for several α-functionalized sulfoxides used as synthetic intermediates [28] that CD can be employed in the assignment of the configuration of the sulfoxide sulfur atom; a negative sign of the Cotton effect centered at the S(O) absorption band in the 220–230-nm region correlates with an *R* configuration (as in **22a** and **23a**) and a positive sign with an *S* configuration (as in **22b** and **23b**). Examples in which CD spectra have been applied to sulfinates or sultines are so few[25] as to allow no generalizations. The CD spectra of the sultines **21a** and **21b** were measured and compared with those of **23a** and **23b** (Figure 1).

For **21a** and **21b** a striking difference is observed in the magnitude of rotational strength, whereas the bands for the sulfoxides **23a** and **23b** have nearly the same amplitude. This may be rationalized as follows. In the region of 220–240 nm each spectrum consists of a composite

(21) This syn-axial effect was applied incorrectly by Sharma et al.,[7] who assigned erroneous structures to γ-sultines having a phenyl substituent at C(4).

(22) Andersen, K. K. *Tetrahedron Lett.* **1962**, 93. Andersen, K. K.; Foley, J.; Perkins, R.; Gaffield, W.; Papanikalaou, N. *J. Am. Chem. Soc.* **1964**, *86*, 5637. Andersen, K. K. *Int. J. Sulfur Chem. Part B*, **1971**, *6*, 69.

(23) Colombo, L.; Gennare, C.; Narisano, E. *Tetrahedron Lett.* **1978**, 3861.

(24) Axelrod, M.; Bickart, P.; Jacobus, H.; Green, M. M.; Mislow, K. *J. Am. Chem. Soc.* **1968**, *90*, 4835.

(25) Pirkle, W. H.; Hoekstra, M. S. *J. Am. Chem. Soc.* **1976**, *98*, 1832.

(26) Harpp, D. N.; Vines, S. M.; Montillier, J. P.; Chan, T. H. *J. Org. Chem.* **1976**, *41*, 3987.

(27) Peterson, D. J. *J. Org. Chem.* **1967**, *32*, 1717.

(28) Ottenheijm, H. C. J.; Liskamp, R. M. J.; Helquist, P.; Lauher, J. W.; Shekhani, M. *J. Am. Chem. Soc.* **1981**, *103*, 1720.

(29) Whereas the ring-opening reactions of **14** and **21** proceeded with inversion, the *R*/*S* nomenclature does not change in those cases where there is a reversal in the priority assignments for the sulfur substituents, e.g., in going from **14** to **22**, or **21** to **23**, and **26**. See also ref 10.

(30) Kaiser, E. M.; Hauser, C. R. *J. Am. Chem. Soc.* **1966**, *88*, 2348.

(31) After completion of our study on the reaction of sultines with a prochiral nitrile, the preparation of α-cyano sulfoxides from sulfinate esters was reported: Annunziato, R.; Cinquini, M.; Colonna, S.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 614.

(32) For the methanolysis of sulfinate esters, see: Darwish, D.; Noreyko, J. *Can. J. Chem.* **1965**, *43*, 1366.

chromophore, which includes an inherently symmetric but chirally perturbed amide band as well as an inherently chiral sulfoxide band. With the sulfoxides **23a** and **23b** and other sulfoxides we have studied before,[4] the contribution due to the chiral carbon atom is small, so that their CD curves are nearly mirror images. This behavior contrasts with that of the sultines **21a** and **21b**, where the contribution of the chiral carbon is evidently considerably larger and on the same order of magnitude as that of the sulfoxide atom. As yet we have no explanation for this increase of rotational strength of the amide chromophore. Nevertheless, the CD curves of **21a** and **21b** allow the conclusion that the sign of the band which is due to the sulfoxide chromophore is positive and negative, respectively. From this it follows that the correlation between the sign of the Cotton effect and the absolute configuration of the sulfoxide sulfur atom in unsubstituted sultines is identical with that mentioned above for α-functionalized sulfoxides: *compounds that have a geometrical arrangement as depicted in **21a** and **23b** have a positive sign of the Cotton effect, and their stereomers **21b** and **23a** a negative one.*[29] This implies that the nucleophilic ring-opening reactions of sultines **14** and **21** that lead to α-functionalized sulfoxides are accompanied by a change in the sign of the Cotton effect.[33] In addition, it can be concluded that at least for γ-sultines, CD can be employed in the assignment of the absolute configuration of the sulfoxide sulfur atom. Whereas this method is as direct and reliable as the method of ^{1}H NMR using chiral fluoro alcohols,[25] we have to urge caution when sultines having an additional chiral center are studied; the strong effect of coupling of both chromophores could lead to an alteration in the sign of the 220–240-nm band; i.e., both sulfoxide diastereomers could have cotton effects of the same sign.

In summary, we have shown that sultines can undergo ring-opening reactions either by cleavage of the C–O bond or by cleavage of the S–OR bond. Previously, we have shown[4] that **23a** is easily converted into (R_C)-**3** and can be subsequently coupled with **2** to give (R_C)-sparsomycin. Thus, the sequence of reactions **20** → **21a** → **23a** constitutes a new approach to sparsomycin (**1**).

Work is in progress on determining the inductive power of the chiral sulfur atom of the sultines in ring-opening reactions with racemic nucleophiles. Also, the general appplicability of the CD rule for sultines as delineated in this paper will be studied.

Experimental Section

^{1}H NMR spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer with Me_4Si or *t*-BuOH as an internal standard. $CDCl_3$ was used as the solvent unless stated otherwise. ^{13}C NMR spectra were measured on a Bruker WP-60 spectrometer. IR spectra were measured with a Perkin-Elmer spectrophotometer, Model 997, and UV spectra on a Perkin-Elmer spectrophotometer, Model 555. Circular dichroism spectra were measured with a Dichrograph II apparatus (Roussel-Jouan).

Mass spectra were obtained with a double-focusing Varian Associates SMI-B spectrometer. Melting points were taken on a Köfler hot stage (Leitz-Wetzlar) and are uncorrected. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness 0.25 mm), with the following solvent systems: (A) MeOH/CH_2Cl_2, 1/9 v/v; (B) MeOH/CH_2Cl_2, 6/94 v/v; (C) MeOH/CH_2Cl_2, 4/96 v/v; (D) MeOH/CH_2Cl_2, 3/97 v/v. Spots were visualized with an UV lamp, iodine vapor, ninhydrin, or Cl_2–TDM.[34] For column chromatography Merck silica gel H (type 60) was used. The Miniprep LC (Jobin Yvon) was used for preparative HPLC.

Z-L-Cystinol (11). To a stirred, cooled (−78 °C) solution of sodium borohydride (6.81 g, 180 mmol) and lithium iodide (24.09 g, 180 mmol) in 600 mL of dry dimethoxy ethane (DME) was added methyl ester **10**, prepared according to the procedure of Gustus,[35] in one portion. The reaction mixture was allowed to warm to room temperature and then stirred until the reaction was complete, as monitored by TLC (system A). The solution was neutralized to pH 7 with an aqueous solution of 1 N HCl with ice cooling. Stirring was continued for 1 h at room temperature, after which time the volume was reduced to half its volume. A methanolic solution 0.1 M in iodine and 0.2 M in pyridine was added until a faint yellow color of iodine persisted. The excess of iodine was destroyed by adding a few crystals of $Na_2S_2O_5$. After evaporation of DME and methanol in vacuo, water and dichloromethane were added. The aqueous layer was extracted three times with dichloromethane and twice with ethyl acetate. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated in vacuo. After recrystallization of the residue from ethyl acetate, 12.53 g (87% yield) of **11** was obtained. This material was homogenous on TLC (R_f 0.17, solvent system B): NMR (CD_3OD) δ 2.67–3.13 (m, 2 H, CH_2S), 3.63 (br d, 2 H, CH_2O), 3.80–4.10 (m, 1 H, $CHCH_2$), 5.07 (s, 2 H, $C_6H_5CH_2$), 7.32 (s, 5 H, C_6H_5); IR (KBr) 3300, 1695, 1680, 1535 cm^{-1}. Anal. Calcd for $C_{22}H_{28}N_2O_6S_2$: C, 54.98; H, 5.87; N, 5.83. Found: C, 55.27; H, 5.84; N, 5.65.

4-[(Benzyloxycarbonyl)amino]-1,2-oxathiolane 2-Oxide (14a,b). To a stirred solution of Z-cystinol (**11**; 4.80 g, 10 mmol) in 100 mL of glacial acetic acid was added a solution of *N*-chlorosuccinimide (4.01 g, 30 mmol) in 150 mL of glacial acetic acid dropwise at room temperature. The reaction mixture was stirred overnight. After completion of the reaction as monitored by TLC (solvent system B) the acetic acid was evaporated in vacuo at room temperature. The residue was dissolved in 400 mL of dichloromethane and 15 mL of water. The organic layer was separated and dried, and the solvent evaporated in vacuo. The residue was dried and then chromatographed over silica (eluant MeOH/CH_2Cl_2, 0.5/99.5 v/v) to yield **14a** (45%) and **14b** (45%). The synthesis of **14a** and **14b** with *N*-bromosuccinimide (3 equiv or more) was carried out as described above. After evaporation of acetic acid, residual bromine was removed by dissolving the residue in methanol and evaporation of the solvent in vacuo; this was repeated twice. Column chromatography of the residue gave **14a** (43% yield) and **14b** (43% yield).

14a: mp 87 °C (AcOEt–hexane) R_f 0.43 (solvent system B); NMR δ 3.34 and 3.07 (AB part of ABX spectrum, 8 lines, J_{AB} = 13.9 Hz, J_{AX} = 6.2 Hz, J_{BX} = 2.4 Hz, 2 H, $CH_2S(O)$), 4.38–4.52 and 4.62–4.88 (m, 3 H, $CHCH_2O$), 5.09 (s, 2 H, $C_6H_5CH_2$), 5.45 (br d, 1 H, NH), 7.33 (s, 5 H, C_6H_5); IR (KBr) 3310, 1720, 1530, 1110 cm^{-1}; exact mass calcd for $C_{11}H_{13}NO_4S$ 255.147, found 255.149. Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.89; H, 5.11; N, 5.35.

14b: R_f 0.64 (solvent system B); NMR δ 2.91 and 3.20 (AB part of ABX spectrum, 8 lines, J_{AB} = 13.9 Hz, J_{AX} = 6.2 Hz, J_{BX} = 2.4 Hz, 2 H, $CH_2S(O)$), 4.58 and 4.75 (AB part of ABX spectrum, 8 lines, J_{AB} = 9.6 Hz, J_{AX} = 5.7 Hz, J_{BX} = 1.9 Hz, 2 H, CH_2O), 4.98 (m, 1 H, $CHCH_2O$), 5.10 (s, 2 H, $C_6H_5CH_2$), 6.36 (br d, 1 H, NH), 7.33 (s, 5 H, C_6H_5); IR (KBr) 3320, 1690, 1545, 1108 cm^{-1}; exact mass calcd for $C_{11}H_{13}NO_4S$ 255.147, found 255.147. Anal. Calcd for $C_{11}H_{13}NO_4S$: C, 51.75; H, 5.13; N, 5.49. Found: C, 51.42; H, 5.20; N, 5.35.

3-Chloro-2-[(benzyloxycarbonyl)amino]-1-propanesulfonyl Chloride (15). To a stirred solution of Z-cystinol (**11**; 1.44 g, 3 mmol) in 40 mL of glacial acetic acid was added a solution of chlorine (1.59 g, 22 mmol) in 15 mL of dry, ethanol-free dichloromethane in small portions at room temperature. After the addition was complete, the reaction mixture was stirred for 2 h at room temperature, after which time the excess of chlorine was removed by a stream of argon. Evaporation of the solvent at room temperature in vacuo gave **15**: 78% yield; R_f 0.25 (solvent system

(33) We anticipate that ring-opening reactions that lead to alkyl sulfoxides will proceed with conservation of the sign of the Cotton effect. This prediction is based upon our observation[28] that the sign of the Cotton effect of alkyl sulfoxides (RS(O)R_1, is opposite that of the corresponding α-functionalized derivatives (RS(O)CH(X)(R_2).

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B); NMR δ 3.67–4.00 (m, 2 H, CH_2SO_2Cl), 4.00–4.10 (br d, 2 H, CH_2Cl), 4.44–4.82 (m, 1 H, $CHCH_2Cl$), 5.13 (s, 2 H, $C_6H_5CH_2$), 5.59 (br d, 1 H, NH), 7.35 (s, 5 H, C_6H_5); IR (Nujol) 3340, 1695, 1380, 1360, 1350, 1175 cm^{-1}; mass spectrum, *m/e* 325, 327, 329 (M^+).

Methyl 3-Chloro-2-[(benzyloxycarbonyl)amino]-1-propanesulfonate (16). The sulfonyl chloride **15** was converted in 43% yield to **16** by chromatography over silica gel with solvent system C: R_f 0.82 (solvent system C); NMR δ 3.45–3.52 (AB part of ABX spectrum, 2 H, $CH_2S(O_2)$), 3.75 and 3.92 (AB part of ABX spectrum, J_{AX} = 4.2 Hz, J_{BX} = 5.4 Hz, J_{AB} = 11.4 Hz, CH_2Cl), 3.90 (s, 3 H, OCH_3), 4.41 (m, 1 H, $CHCH_2Cl$), 5.12 (s, 2 H, $C_6H_5CH_2$), 5.69 (br d, 1 H, NH), 7.35 (s, 5 H, C_6H_5); IR (Nujol) 3320, 1695, 1545, 1350, 1330, 1180 cm^{-1}; exact mass calcd for $C_{12}H_{16}ClNO_5S$ 321.252, found 321.251. Anal. Calcd for $C_{12}H_{16}ClNO_5S$: C, 44.79; H, 5.01; N, 4.35. Found: C, 44.55; H, 4.80; N, 4.11.

Ethyl 3-Chloro-2-[(benzyloxycarbonyl)amino]-1-propanesulfonate (17). The sulfonyl chloride **15** (1.52 g, 4.7 mmol) was dissolved in 200 mL of chloroform containing ethanol and solid sodium carbonate. The reaction mixture was stirred overnight. Subsequently the precipitate was removed and the solvent evaporated in vacuo. The residue was recrystallized from chloroform/hexane to give the ethyl sulfonate **17**: 40% yield; mp 133–134 °C; NMR δ 1.40 (t, 3 H, $SO_3CH_2CH_3$), 3.44–3.51 (AB part of ABX spectrum, 2 H, CH_2SO_2), 3.75 and 3.92 (AB part of ABX spectrum, J_{AX} = 4.3 Hz, J_{BX} = 5.5 Hz, J_{AB} = 11.4 Hz, 2 H, CH_2Cl), 4.32 (q, 2 H, CH_2CH_3), 4.46 (m, 1 H, $CHCH_2Cl$), 5.12 (s, 2 H, $C_6H_5CH_2$), 5.65 (br d, 1 H, NH), 7.35 (s, 5 H, C_6H_5); IR (Nujol) 3315, 1690, 1545, 1345, 1330, 1180, 1170 cm^{-1}; mass spectrum, *m/e* 335, 337 (M^+). Anal. Calcd for $C_{13}H_{18}ClNO_5S$: C, 46.50; H, 5.40; N, 4.17. Found: C, 46.11; H, 5.26; N, 4.35.

***N*-Methyl-3-chloro-2-[(benzyloxycarbonyl)amino]-1-propanesulfonamide (18).** To a stirred and chilled (0 °C) solution of the sulfonyl chloride **15** (200 mg, 0.61 mmol) in dry, ethanol-free chloroform was added a solution of methylamine in benzene (1.22 mmol). The solution was stirred at room temperature overnight, the salt was removed by filtration, and the solvent was evaporated in vacuo. The crude product was next purified by column chromatography (solvent system D) to give the sulfonamide **18**: 62% yield; R_f 0.61 (solvent system B); NMR δ 2.74 (d, 3 H, $NHCH_3$), 3.34 (d, 2 H, CH_2SO_2), 3.71 and 3.87 (AB part of ABX spectrum, J_{AX} = 4.0 Hz, J_{BX} = 5.0 Hz, J_{AB} = 11.3 Hz, 2 H, CH_2Cl), 4.41 (m, 1 H, $CHCH_2Cl$), 4.71 (br, 1 H, $NHCH_3$), 5.12 (s, 2 H, $C_6H_5CH_2$), 5.51 (br d, 1 H, NH), 7.36 (s, 5 H, C_6H_5); IR (KBr) 3320, 1690, 1535, 1330, 1155 cm^{-1}; exact mass calcd for $C_{12}H_{17}ClN_2O_4S$ 320.2675, found 320.266. Anal. Calcd for $C_{12}H_{17}ClN_2O_4S$: C, 44.93; H, 5.34; N, 8.73. Found: C, 44.83; H, 5.21; N, 8.46.

***N*-(*tert*-Butoxycarbonyl)-L-cystinol (20).** *N*-(*tert*-butoxycarbonyl)-L-cystine methyl ester (7.03 g, 15 mmol), prepared as described earlier,[4] was reduced with lithium borohydrate [sodium borohydride (3.41 g, 90 mmol) and lithium iodide (12.05 g, 90 mmol) in 200 mL of dry DME] as described for the preparation of **11**. The workup, however, was modified due to the acid lability of the N-protecting group: the pH was adjusted to 5 by addition of aqueous 1 N $KHSO_4$ to the stirred and cooled (0 °C) solution. Sometimes a sticky mass precipitated before neutralization was complete. In that case the solvent was evaporated in vacuo, the residue dissolved in methanol/water (1/1 v/v), and the neutralization then completed. The oxidation with iodine was carried out as described for the preparation of **11**. Subsequently, the methanol was evaporated in vacuo, and water and ethyl acetate were added. The aqueous phase was extracted five times with ethyl acetate. The collected organic layers were washed with brine and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was recrystallized from methanol/water to give **20**: 87% yield: mp 124–125 °C; R_f 0.23 (solvent system A); NMR (CD_3OD) δ 1.41 (s, 9 H, *t*-Bu), 2.85 (d, 2 H, CH_2S), 3.46–4.05 (m, 3 H, $CHCH_2O$); IR (KBr) 3360, 3600–3100, 1685, 1525 cm^{-1}. Anal. Calcd for $C_{16}H_{32}N_2O_6S_2$: C, 46.58; H, 7.82; N, 6.79. Found: C, 46.78; H, 7.92; N, 6.87.

4-[(*tert*-Butoxycarbonyl)amino]-1,2-oxathialane 2-Oxide (21a,b). A solution of *N*-chlorosuccinimide (4.01 g 30 mmol) in 150 mL of glacial acetic acid was added dropwise to a solution of *N*-(*tert*-butoxycarbonyl)-L-cystinol (**20**; 4.12 g, 10 mmol) and pyridine (2.4 g, 30 mmol) in 100 mL of glacial acetic acid. By use of the procedure as described for **14a** and **14b**, **21a** and **21b** were isolated in a 1/1 ratio (86% yield).

21a: mp 127 °C (CH_2Cl_2–CCl_4); R_f 0.43 (solvent system B); ^1H NMR δ 1.44 (s, 9 H, *t*-Bu), 3.14 and 3.45 (AB part of ABX spectrum, J_{AX} = 2.9 Hz, J_{BX} = 6.0 Hz, J_{AB} = 13.9 Hz, 2 H, CH_2S), 4.33–4.98 (m, 2 H, CH_2O), 4.79 [m, 1 H (covered by CH_2O), $CHCH_2O$], 5.05 (br, 1 H, NH); IR (KBr) 3325, 1683, 1530, 1102 cm^{-1}; ^{13}C NMR (CD_2Cl_2) δ 28.4 ($(CH_3)_3C$), C–N covered by CD_2Cl_2 signals, 67.4 (CS), 80.7 ($(CH_3)_3C$), 77.6 (COS(O)), 155.2 (C(O)N); exact mass calcd for $C_7H_{12}NO_4S$ (M^+ - CH_3) 206.139, found 206.139. Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.42; H, 6.83; N, 6.33. Found: C, 43.46; H, 6.90; N, 6.13.

21b: mp 135–136 °C (CH_2Cl_2) R_f 0.64 (solvent system B); ^1H NMR δ 1.43 (s, 9 H, *t*-Bu), 2.94 and 3.22 (AB part of ABX spectrum, J_{AX} = 1.3 Hz, J_{BX} = 6.6 Hz, J_{AB} = 9.7 Hz, 2 H, CH_2S), 4.59 and 4.76 (AB part of ABX spectrum, J_{AX} = 1.9 Hz, J_{BX} = 5.5 Hz, J_{AB} = 9.7 Hz, 2 H, CH_2O), 4.85 (m, 1 H, $CHCH_2O$), 6.06 (br, 1 H, NH); ^{13}C NMR (CD_2Cl_2) δ 28.5 ($(CH_3)_3C$), 50.9 (C-N), 62.8 (CS), 80.2 ($(CH_3)_3C$), 83.0 (COS(O)), 155.2 (C(O)N); IR (KBr) 3325, 1725, 1525, 1115 cm^{-1}; exact mass calcd for $C_7H_{12}NO_4S$ (M^+ - CH_3) 206.139, found 206.139. Anal. Calcd for $C_8H_{15}NO_4S$: C, 43.42; H, 6.83; N, 6.33. Found: C, 43.56; H, 6.85; N, 6.29.

***N*-(Benzyloxycarbonyl)-*S*-oxo-*S*-[(methylthio)methyl]-L-cysteinol (22a,b) and *N*-(*tert*-Butoxycarbonyl)-*S*-oxo-*S*-[(methylthio)methyl]-L-cysteinol (23a,b).** The anion of dimethyl sulfide was prepared in a manner analogous to the method described by Peterson et al.:[27] TMEDA (0.70 g, 0.91 mL, 6.0 mmol), freshly distilled dimethyl sulfide (0.37 g, 0.44 mL, 6.0 mmol), and 2 mL of freshly distilled THF, respectively, were brought via a syringe into a 50-mL, cooled (0 °C), round-bottomed flast (equipped with a septum) containing 3.75 mL of a 1.6 M solution of *n*-butyllithium in hexane (6 mmol). The resulting solution was stirred at room temperature for 4 h, cooled to −30 °C, and added dropwise to a cooled (−78 °C) solution of the sultine **14a,b** (510 mg, 2.0 mmol) in 6 mL of freshly distilled THF. Subsequently, the reaction mixture was stirred at −70 °C for 30 min and at room temperature for 30 min, and then rapidly quenched at 0 °C with 5 mL of a saturated aqueous solution of $KHSO_4$. Immediately thereafter the pH of the mixture was adjusted to 6–8 by addition of solid sodium carbonate. Ethyl acetate was added, and then the aqueous layer was extracted four times with ethyl acetate. The combined organic layers were dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue was chromatographed under slightly elevated pressure (10 mmHg; eluant MeOH/CH_2Cl_2, 5/95 v/v) to give **22a** (46% yield) and **22b** (33% yield), respectively. Compounds **23a** and **23b** were obtained in 71% and 70% yields, respectively, after preparative HPLC (solvent system C) and were identical in every aspect with the corresponding compounds obtained earlier.[4]

22a: mp 93 °C (CH_2Cl_2–hexane); R_f 0.35 (solvent system A); NMR (CD_2Cl_2) δ 2.27 (s, 3 H, SCH_3), 2.96 and 3.33 (AB part of ABX spectrum, J_{AX} = 4.9 Hz, J_{BX} = 5.8 Hz, J_{AB} = 13.4 Hz), 3.60–3.95 (m, 2 H, CH_2OH), 3.71 and 3.84 (AB spectrum covered by CH_2OH, 2 H, J_{AB} = 13.5 Hz, $S(O)CH_2S$), 4.26 (m, 1 H, $CHCH_2O$), 5.09 (s, 2 H, $C_6H_5CH_2$), 5.94 (br d, 1 H, NH), 7.34 (s, 5 H, C_6H_5); IR (KBr) 3335, 1680, 1530, 1006 cm^{-1}; exact mass calcd for $C_{13}H_{19}NO_4S_2$ 317.256, found 317.256. Anal. Calcd for $C_{13}H_{19}NO_4S_2$: C, 49.19; H, 6.03; N, 4.41. Found: C, 49.15; H, 6.03; N, 4.34.

22b: mp 162 °C (CH_2Cl_2–hexane); R_f 0.32 (solvent system A); NMR (CD_2Cl_2) δ 2.29 (s, 3 H, SCH_3), 2.97 and 3.21 (AB part of ABX spectrum, J_{AX} = 7.0 Hz, J_{BX} = 6.4 Hz, J_{AB} = 13.2 Hz, 2 H, $CHCH_2S(O)$), 3.73–4.00 (m, 4 H, $CHCH_2O$ and $S(O)CH_2S$), 4.16 (m, 1 H, $CHCH_2O$), 5.09 (s, 2 H, $C_6H_5CH_2$), 5.70 (br, 1 H, NH), 7.35 (s, 5 H, C_6H_5); IR (KBr) 3330, 1695, 1538, 1025, 1015 cm^{-1}; exact mass calcd for $C_{13}H_{19}NO_4S_2$ 317.256, found 317.257. Anal. Calcd for $C_{13}H_{19}NO_4S_2$: C, 49.19; H, 6.03; N, 4.41. Found: C, 49.16; H, 5.95; N, 4.16.

2-Oxo-4-[[[(methylthio)methyl]sulfoxo]methylene]oxazolidine (27a,b). The ring-opening reaction of the sultine **14a** or **14b** was carried out as described above for the preparation of **22a** and **22b** with a slightly different workup. Instead of being quenched with a saturated aqueous solution of $KHSO_4$, the reaction mixture was stirred overnight with solid $KHSO_4$. Methanol was then added and the mixture stirred for another 2 h at room temperature. After removal of the salts by filtration, the filtrate

was concentrated to dryness, and the residue chromatographed on silica (eluant MeOH/CH_2Cl_2, 5/95 v/v) to give **27a** (19%) and **27b** (11%), respectively.

27a: R_f 0.24 (solvent system A); NMR (CD_2Cl_2) δ 2.31 (s, 3 H, SCH_3), 2.89–3.29 (br d, 2 H, $CHCH_2S$), 3.77 and 3.90 (AB spectrum, J_{AB} = 13.8 Hz, 2 H, $S(O)CH_2S$), 4.10 and 4.69 (s, 3 H, $CHCH_2O$), 6.40 (br s, 1 H, NH); IR (Nujol) 3250, 1745, 1710, 1040 cm^{-1}; mass spectrum m/e 209 (M^+).

27b: R_f 0.22 (solvent system A); NMR (CD_2Cl_2) δ 2.32 (s, 3 H, SCH_3), 2.94–3.29 (m, 2 H, $CHCH_2S$), 3.78 and 3.86 (AB spectrum, J_{AB} = 13.6 Hz, 2 H, $S(O)CH_2S$), 4.17–4.69 (m, 3 H, $CHCH_2O$), 6.84 (br s, 1 H, NH); IR (Nujol) 3240, 1760, 1710, 1045 cm^{-1}; mass spectrum, m/e 209 (M^+).

***N*-(Benzyloxycarbonyl)-*S*-oxo-*S*-*n*-butyl-L-cysteinol (24) and *N*-(*tert*-Butoxycarbonyl)-*S*-oxo-*S*-*n*-butyl-L-cysteinol (25).** A cooled (CO_2/2-propanol) solution of the *n*-butyllithium–TMEDA complex, prepared by adding TMEDA (523 mg, 0.68 mL, 4.5 mmol) to a solution of *n*-butyllithium in hexane (4.5 mmol), was added to a stirred, cooled (−78 °C) solution of the sultine **14a** (383 mg, 1.5 mmol) or **21b** (331 mg, 1.5 mmol) in 5 mL of freshly distilled, dry THF. The reaction mixture was stirred at −70 °C for 30 min and at room temperature for another 30 min. The workup was carried out as described to the preparation of **22** and **23**. Compounds **24** and **25** were obtained after HPLC (solvent system C) in yields of 55% and 37%, respectively.

24: R_f 0.33 (solvent system A); NMR δ 0.95 (t, 3 H, CH_2CH_3), 1.10–2.0 (m, 4 H, $S(O)CH_2CH_2CH_2CH_3$), 2.52–3.29 (m, 4 H, $CH_2S(O)CH_2$), 3.57–3.97 (m, 2 H, $CHCH_2O$), 3.97–4.40 (m, 1 H, $CHCH_2O$), 5.09 (s, 2 H, $C_6H_5CH_2$), 5.88 (br, 1 H, NH), 7.34 (s, 5 H, C_6H_5); IR (KBr) 3430, 3200, 1715, 1510, 1060 cm^{-1}; exact mass calcd for $C_{15}H_{23}NO_4S$ 313.225, found 313.226.

25: R_f 0.32 (MeOH/CH_2Cl_2, 9/91 v/v); NMR (CD_2Cl_2) δ 0.97 (t, 3 H, CH_2CH_3), 1.42 (s, 9 H, *t*-Bu), 1.22–1.93 (m, 4 H, $S(O)CH_2CH_2CH_2CH_3$), 2.62–3.21 (m, 4 H, $CH_2S(O)CH_2$), 3.78 (t, 2 H, CH_2OH), 3.87–4.27 (m, 1 H, $CHCH_2O$), 5.44 (br, 1 H, NH); IR (KBr) 3430, 1710, 1530, 1060 cm^{-1}; mass spectrum, m/e 222 (M^+ − *t*-Bu). Anal. Calcd for $C_{12}H_{25}NO_4S$: C, 51.59; H, 9.02; N, 5.01. Found: C, 51.53; H, 8.97; N, 4.99.

***N*-(*tert*-Butoxycarbonyl)-*S*-oxo-*S*-(cyanobenzyl)-L-cysteinol (26a,b).** The anion of benzyl cyanide[30] was prepared by addition of benzyl cyanide (0.72 mL, 703 mg, 6 mmol) to 3.75 mL of a cooled (0 °C) 1.6 M solution of *n*-butyllithium (6.0 mmol) in hexane; 15 mL of freshly distilled, chilled THF was then added to dissolve the anion. The resulting, yellow-colored solution was added dropwise to a stirred, cooled (−78 °C) solution of **21a** or **21b** (442 mg, 2 mmol) in 5 mL of freshly distilled THF. Subsequently, the reaction mixture was stirred for 30 min at −70 °C and for another 30 min at room temperature. The workup was carried out as described for **22** and **23**. Compounds **26a** and **26b** were obtained in yields of 69% and 70%, respectively, after HPLC (solvent system D).

26a: R_f 0.31 (solvent system A); NMR δ 1.39 and 1.48 (2 s, 9 H, *t*-Bu), 3.02–3.59 (m, 2 H, $CHCH_2S(O)$), 3.59–3.89 (m,2 H, $CHCH_2O$), 4.09 (m, 1 H, $CHCH_2O$), 5.22 and 5.37 (2 s, 1 H, S(O)CHCN), 5.4 (br d, 1 H, NH), 7.47 (s, 5 H, C_6H_5); IR (KBr) 3460, 2240, 1680, 1520, 1050 cm^{-1}; mass spectrum, m/e 281 ($M^+ - C_4H_9$). Anal. Calcd for $C_{16}H_{22}N_2O_4S$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.98; H, 6.62; N, 8.28.

26b: R_f 0.28 (solvent system A); NMR δ 1.40 and 1.44 (2 s, 9 H, *t*-Bu), 2.87–3.42 (m, 2 H, $CHCH_2S(O)$, 3.78 (br d, 2 H, $CHCH_2O$), 4.09 (m, 1 H, $CHCH_2O$), 4.96 and 5.17 (2 s, 1 H, S(O)CHCN), 5.3 (br, 1 H, NH), 7.44 (s, 5 H, C_6H_5); IR (KBr) 3450, 2240, 1685, 1525, 1050 cm^{-1}; mass spectrum, m/e 312 (M^+ − CN). Anal. Calcd for $C_{16}H_{22}N_2O_4S$: C, 56.79; H, 6.55; N, 8.28. Found: C, 56.82; H, 6.51; N, 8.23.

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Notes

A High-Yielding Synthesis of Monoalkylhydrazines

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In our effort to prepare 13,14-diazaprostanoic acids we required a facile synthesis of monoalkylhydrazines.[1] These compounds have been prepared by several methods which have been reviewed.[2-4] The most general and high-yielding syntheses reported to date involve the treatment of primary amines with chloroamine[5] (55–71% based on the chloroamine) or hydroxylamine-*O*-sulfonic acid (50–70%, based on hydroxylamine-*O*-sulfonic acid)[6] and the condensation of a carbonyl compound with ethyl carbazate followed by reduction and hydrolysis (75%).[7] In our hands, both of these latter procedures gave relatively poor yields of higher monoalkylhydrazines (*n*-hexylhydrazine 40%) and workup was found to be relatively tedious. Others have reported similar difficulty with the latter method.[8]

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