mixture was poured onto ice and extracted with ether in the usual way, to yield a noncrystalline solid: $[\alpha]_D$ +6.7° (c 1.3, $CHCl_3$); Details of the ^1H and ^{13}C NMR spectra are given in Tables I and II; IR ν_{max}^{KBr} 1730, 1450, 1370, 1020, 950 and 910 cm^{-1}; MS, $C_{24}H_{36}Br_2O_4$, M^+ - 18 at m/e 490, 488, 486, further important peaks are found at m/e 423, 421, 381, 379, 337, 335, 241.

3-Bromo-7-hydroxy-15,16-epoxyisopimar-9(11)-ene (9). The diacetate 6 was dissolved in methanol–acetone and an excess of potassium carbonate was added. The suspension was stirred at room temperature for 2 h, and the reaction mixture was poured onto ice, neutralized with (5% HCl), and extracted with ether in the usual manner. The solid residue obtained by elimination of the solvent crystallized from n-hexane/methylene chloride: mp 166–167 °C; $[\alpha]_D$ -24° (c 0.64 $CHCl_3$); the ^1H and ^{13}C NMR spectra are described in Tables I and II; IR ν_{max}^{KBr} 3500, 1460, 1370, 1285, 1070, 920 and 875 cm^{-1}; MS, $C_{20}H_{31}BrO_2$, M^+ at m/e 384, 382, further important peaks are found at m/e 366, 364, 335, 333, 267, 253, 251. Anal. Calcd for $C_{20}H_{31}BrO_2$: C, 62.66; H, 8.09; Br, 20.89. Found: C, 62.70; H, 9.03; Br, 21.

3-Bromo-7-keto-15,16-epoxyisopimar-9(11)-ene (10). Pyridinium chlorochromate (431 mg, 2 mmol) was added with stirring to a solution of the epoxy alcohol 9 (386 mg, 1.0 mmol) dissolved in dry methylene chloride (15 mL). After 2 h dry ether (100 mL) was added and the supernatant was decanted from the blackish, gummy residue obtained. The ether-insoluble residue was washed three consecutive times with ether portions (10-mL each). The combined ether extracts were concentrated and chromatographed on a short column of silica gel with a mixture of n-hexane–ether (2:1) as eluent. A crystalline residue (294 mg) was obtained, which was homogeneous in TLC and crystallized from n-hexane: mp 158–160 °C; IR ν_{max}^{KBr} 3080, 1710, 1600, 1480, 1220, 1020, 860, 840 and 810 cm^{-1}; ^1H NMR (60 MHz) δ 0.93 (3 H, s), 0.98 (3 H, s), 1.03 (3 H, s), 1.05 (3 H, s), 2.60 (3 H, m), 3.98 (1 H, dd, J = 11.4 Hz), 5.40 (1 H, bs); MS, $C_{20}H_{29}BrO_2$, M^+ at m/e 382, 380, further important peaks are found at m/e 506, 504, 502, 446, 444, 442, 407, 405, 365, 363, 347, 345.

3-Bromo-7,11-diketo-15,16-epoxyisopimar-8-ene (11). Compound 10 (386 mg, 1.0 mmol) in acetone (35 mL) was treated at room temperature with Jones reagent (0.23 mol). After 15 min, the solution was poured into crushed ice and the product was extracted with ether. The ether solution was washed with water, aqueous solution of sodium bicarbonate, and water and dried over sodium sulfate, and the solvent was evaporated to give a bright yellow residue that was chromatographed on silica gel (0.05–0.2 mm). Elution with n-hexane afforded a yellow, noncrystalline solid that proved homogeneous on TLC (210 mg): UV λ_{max}^{EtOH} 271 nm (ε 18 200); IR ν_{max}^{KBr} 3040, 1670, 1600, 1250, 1220, 860, 830, 805 cm^{-1}; ^1H NMR (60 MHz) δ 0.95 (6 H, s), 1.08 (3 H, s), 1.10 (3 H, s), 2.60 (2 H, m), 3.94 (1 H, dd, J = 11.5 Hz); MS, $C_{20}H_{27}BrO_3$, M^+ at m/e 396, 394, other significant fragments appear at m/e 316, 314, 263, 249.

3-Bromo-7-hydroxyisopimar-9(11),5-diene (12). Powdered zinc (120 mg) and glacial acetic acid (10 mL) were added to compound 5 (80 mg) dissolved in tetrahydrofuran (25 mL). The mixture was stirred at room temperature for 6 h and later heated under reflux for half an hour under a stream of argon. The reaction mixture was poured onto ice and the product extracted in ether. The residue (53 mg) was filtered off in a short column of silica gel (0.05–0.2 mm) and the compound was eluted in n-hexane–ether (2:1). The compound was crystallized from n-hexane–methylene chloride: mp 110–112 °C; IR ν_{max}^{KBr} 3500, 3080, 1640, 1240, 1210, 920, 890, 860 cm^{-1}; ^1H NMR (90 MHz) 0.98 (3 H, s), 1.01 (3 H, s), 1.07 (6 H, s), 3.92 (1 H, dd, J = 12.8 Hz), 4.88 (1 H, d, J = 18 Hz), 4.88 (1 H, d, J = 13 Hz), 5.28 (1 H, t, J = 4 Hz), 5.84 (1 H, dd, J = 18.13 Hz); MS, $C_{20}H_{31}Br_2O$, M^+ at m/e 368, 366, other important fragments are found at m/e 350, 348, 300, 298, 288, 252, 198.

3,15-Dibromo-7,12,16-triacetoxyisopimar-9(11)-ene (7). The triol was obtained by elution from the general chromatography of the petroleum ether/AcEt (1:1). The combined fractions (2.48 g) were dissolved in pyridine (10 mL) and acetic anhydride (10 mL) was added, leaving the solution with shaking at room temperature overnight. The mixture was poured into ice and the soluble residue extracted in organic solvents in the usual way. The residue obtained (2.33 g) was submitted to further chromatography on silica gel (0.05–0.2 mm), using mixtures of n-hexane–ether as eluents. The triacetate 8 was separated from the n-hexane–ether (2:1) fractions as a crystalline solid. Recrystallization from n-hexane gave 8: mp 166–168 °C; $[\alpha]_D$ -159.5° (c 0.68, $CHCl_3$); IR ν_{max}^{KBr} 3040, 1735, 1730, 1620, 1250, 1230, 980, 860 cm^{-1}; details of the ^1H NMR and ^{13}C NMR spectra are given in Tables I and II; MS, $C_{26}H_{38}Br_2O_6$, M^+ at m/e 608, 606, 604, other important fragments at m/e 506, 504, 502, 446, 444, 442, 407, 405, 365, 363, 347, 345.

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Registry No. 1, 95387-43-2; 2, 64854-29-1; 3, 64854-30-4; 4, 95387-44-3; 5, 95387-45-4; 6, 95387-46-5; 7, 95387-47-6; 8, 95387-48-7; 9, 95387-49-8; 10, 95387-50-1; 11, 95387-51-2; 12, 95387-52-3.

Total Synthesis of (+)-Sparsomycin. Approaches Using Cysteine and Serine Inversion[1]

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The antitumor antibiotic (+)-sparsomycin and its epimeric sulfoxide isomer have been synthesized in optically active form starting with either L-cysteine or L-serine. The former route involves a racemization and resolution sequence whereas the latter approach, which proceeds in much higher overall yield, involves a formal "inversion" of configuration of L-serine by selective manipulation of the functional groups surrounding the central asymmetric carbon atom.

Introduction

Sparsomycin 1, a metabolite of *Streptomyces sparsogenes*[3] and *S. cuspidosporus*,[4] has been the subject of intensive biomedical investigations due to its activity against several tumor systems[5,6] bacteria,[4,6] fungi,[7] and viruses.[8]

(1) (a) Taken from the Ph.D. Dissertations of M. S. Shekhani, State University of New York at Stony Brook, 1979, and D.-R. Hwang, State University of New York at Stony Brook, 1982. (b) For a preliminary account of a portion of this work see: Helquist, P.; Shekhani, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 1057.

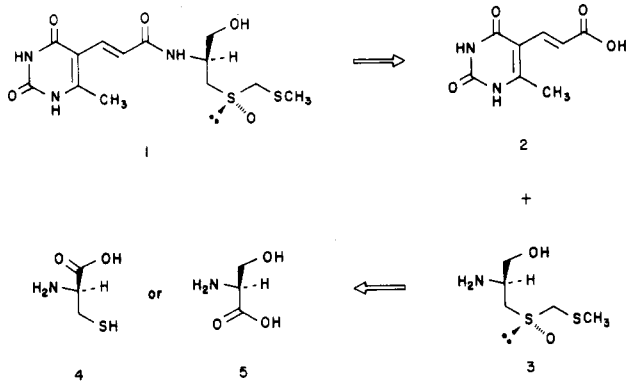
(2) Address correspondence to this author at the Department of Chemistry, University of Notre Dame, Notre Dame, IN 46556.

(3) Argoudelis, A. D.; Herr, R. R. *Antimicrob. Agents Chemother.* **1962**, 780.

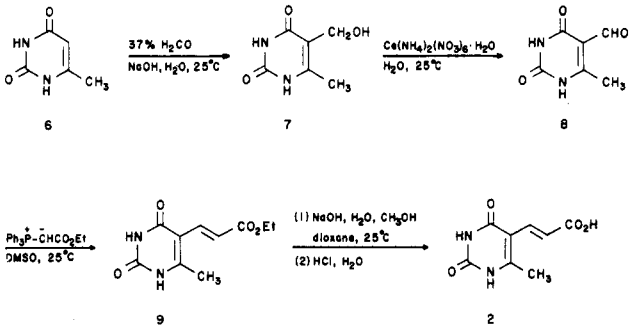
(4) Higashide, E.; Hasegawa, T.; Shibata, M.; Mizuno, K.; Akaike, H. *Takeda Kenkyusho Nempo* **1966**, *25*, 1; *Chem. Abstr.* **1967**, *66*, 54238.

0022-3263/85/1950-1264$01.50/0

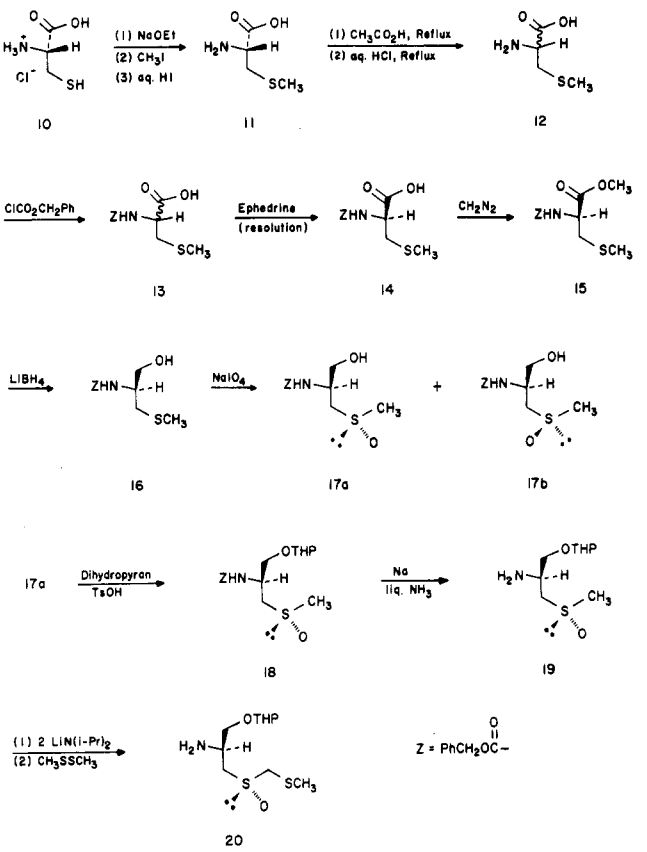
Scheme I



Scheme II



Scheme III



It has also proven to be very useful in the study of various aspects of protein biosynthesis,[9] a process which is inhibited by sparsomycin-induced blocking of the peptide elongation steps.[10] Although sparsomycin has been known for over 20 years, detailed studies of its activity and that of analogues are still being pursued.[11,12]

The bulk of the structural work on sparsomycin was first reported by Wiley and MacKellar in 1970,[13] but the full stereochemical details of the structure were not reported until 1981. The latter work, which we pursued jointly with Professor Ottenheijm, employed a combination of circular dichroism, X-ray diffraction, and synthesis to establish that sparsomycin possesses the S_C,R_S configuration.[14] Total syntheses of sparsomycin were investigated concurrently by Professor Ottenheijm and by our research group and first resulted in the development of routes to the enantiomer of the natural material.[1b,15] In this paper we wish to report the full details of our total synthesis of sparsomycin having the same absolute configuration as the naturally occurring compound.[16,17]

Results and Discussion

A. General Strategy. An obvious basic strategy for the synthesis of sparsomycin would be first to prepare the carboxylic acid **2** and the amine **3**, perhaps in protected form, and then to couple these two components by means of amide formation. The acid **2** had been prepared previously as part of the original structure elucidation studies of sparsomycin,[13] but **3** posed a challenge as a previously unknown system having a rather unusual array of reactive functional groups clustered around one chiral center. This amine bears a structural relationship to D-cysteine (**4**) or less obviously to L-serine (Scheme I). Indeed, we have accomplished syntheses of sparsomycin based upon the use of either of these simple amino acids.

B. Synthesis of the Acid Component 2. Ample opportunity existed for improving upon the originally reported preparation of **2**.[13] Our modified synthesis, as outlined in Scheme II, involves hydroxymethylation of commercially available 6-methyluracil (**6**) to give the alcohol **7**[18] (80–85%; in order to obtain these yields, rather specific conditions as described in the Experimental Section needed to be developed) oxidation with ceric ammonium nitrate[19] to produce the aldehyde **8** (60–67%), Wittig

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(15) Ottenheijm, H. C. J.; Liskamp, R. M. J.; Tijhuis, M. W. *Tetrahedron Lett.* **1979**, 387.
(16) For more recent, detailed accounts of the synthetic accounts of Professor Ottenheijm's synthetic work see: (a) 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. (b) Liskamp, R. M. J.; Zeegers, H. J. M.; Ottenheijm, H. C. J. *J. Org. Chem.* **1981**, *46*, 5408. (c) Ottenheijm, H. C. J.; Liskamp, R. M. J. Eur. Patent Appl. EP 48532, 1982; *Chem. Abstr.* **1982**, *97*, 55586.
(17) For another recent study directed toward the synthesis of sparsomycin, see: Rhee, K. H. *Hanguk Saenghwal Kwahak Yonguwon Nonchong* **1981**, *27*, 191; *Chem. Abstr.* **1982**, *96*, 143282.
(18) Kircher, W. *Justus Liebigs Ann. Chem.* **1911**, *385*, 293.

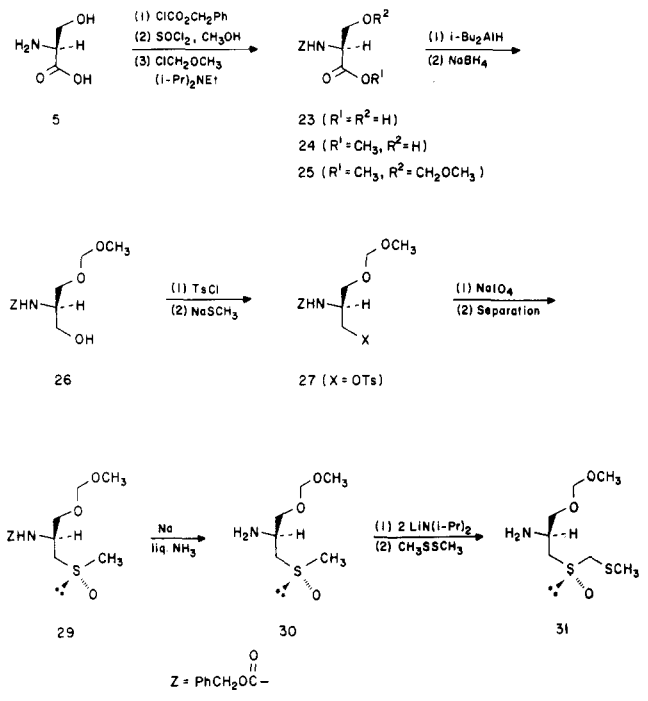
condensation with [(ethoxycarbonyl)methylene]-phosphorane to afford the unsaturated ester **9** (71–76%), and basic hydrolysis to give the desired **2**[13] (90–96%). The overall yield of **2** is typically 30–35%.

C. Synthesis of the Amine Component 3. Our first studies[1b] employed L-cysteine rather than the D isomer as the starting material and resulted in the synthesis of the enantiomer of naturally occurring sparsomycin. This approach was taken in order to use the more readily available L-cysteine during the initial stages of developing the basic methodology required for the synthesis of sparsomycin. There is no need to describe our work with L-cysteine in detail here because the same chemistry was ultimately applied to derivatives of the D series.

Because of the high cost of D-cysteine, we chose to investigate an approach which begins with the L isomer but which involves a racemization and resolution a short distance into the synthesis (Scheme III). L-Cysteine hydrochloride **10** is methylated by a modification of an earlier procedure[20] to give the *S*-methyl derivative **11** in greatly improved yield (88% vs the earlier 50%). Thioether **11** is then racemized according to the procedure reported for methionine[21] by first heating at reflux in acetic acid followed by hydrolysis of the acetyl derivative with 2.5 N hydrochloric acid. The racemate **12** (87% yield) is converted into its benzyloxycarbonyl derivative **13** (81%) which is then resolved through use of ephedrine[22] to produce the protected D-cysteine derivative **14** (60–65% of the theoretical maximum of 50% based upon the racemate). Reaction with diazomethane[23] generates the methyl ester **15** (98%), and reduction with lithium borohydride[16a] affords the alcohol **16** (51%). Sodium metaperiodate oxidation[24] then gives a 2:3 mixture of the epimeric sulfoxides **17a** and **17b** (90% combined yield) which may be separated chromatographically. The use of other oxidizing agents such as hydrogen perioxide did not significantly alter this ratio. Our previous structural studies had demonstrated that **17a** possesses the configuration corresponding to natural sparsomycin,[14] and therefore this sulfoxide isomer was processed further. The hydroxyl group is protected[25] by formation of the tetrahydropyranyl ether **18** (97%), and the amine protecting group is removed under dissolving metal conditions[26] to give **19** (72%). The latter operation is effected before subsequent sulfenylation (vide infra) because of the difficulty of removing the benzyloxycarbonyl group in the presence of the labile dithioacetal mono-*S*-oxide group.[16a,27]

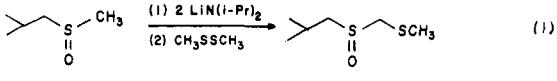
As a means of exploring a possible method for the desired sulfenylation, a model study was performed with methyl isobutyl sulfoxide **21** whereby treatment of this compound with 2 equiv[28] of lithium diisopropylamide (LDA) and then dimethyl disulfide gives the dithioacetal mono-*S*-oxide **22** (65%, eq 1). A similar reaction of allylic

Scheme IV



5 23 ($R^1 = R^2 = H$) 24 ($R^1 = CH_3$, $R^2 = H$) 25 ($R^1 = CH_3$, $R^2 = CH_2OCH_3$) 26 27 (X = OTs) 29 30 31

sulfoxides has been mentioned briefly by Trost.[29] On the basis of these results, **19** undergoes conversion to the key intermediate **20**, which is a protected form of **3** mentioned earlier (see Scheme I).



(1)

21 22

An unattractive feature of the above route to the amine **20** is the inefficient, low-yielding racemization/resolution approach for accomplishing the inversion of the L-cysteine system. As indicated in Scheme I, a structural relationship exists not only between **3** (or **20**) and D-cysteine (**4**) but also between **3** and L-serine (**5**), the latter being a much more suitable starting material with respect to availability. By operating separately upon the carboxy and hydroxy groups of L-serine, a formal "inversion" can in effect be accomplished, thus permitting entry into the D-cysteine system without actually operating upon the chiral center itself. Subsequent to our work,[1] similar strategies were reported by Hajdu[30] and by Rapoport.[31]

Our approach using L-serine (**5**) (Scheme IV) requires the reduction of the carboxy group of this amino acid, but because of difficulties that we have encountered in attempting direct reduction of the free carboxy group of various serine derivatives, we instead chose to work with a methyl ester. First, the amino group of **5** is protected (**23**, 90%), then the carboxy group is esterified (**24**, 95% from use of diazomethane, 81–85% from use of methyl iodide/sodium bicarbonate/DMF, or 74–81% from use of thionyl chloride/methanol), and thirdly, the hydroxy group is protected as the methoxymethyl (MOM) ether[32] to give **25** (91%). At this point in our studies we found that a method of reduction which proved to be more efficient and selective than the use of lithium borohydride (Scheme III) is a two-step sequence using diisobutylaluminum hydride[33]

(19) Trahanovsky, W. S.; Young, L. B.; Brown, G. L. *J. Org. Chem.* **1967**, *32*, 3865. At higher reaction temperatures, none of the desired aldehyde **8** is obtained, apparently due to further oxidation to the acid which is too water soluble to be isolated easily from this experiment.
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(28) The use of an extra equivalent of the base takes into account the competitive deprotonation of the sulfenylation product.
(29) Trost, B. M.; Stanton, J. L. *J. Am. Chem. Soc.* **1975**, *97*, 4018.
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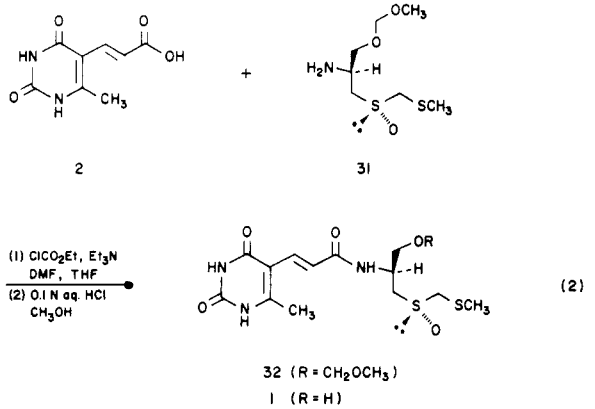
(32) Stork, G.; Takahashi, T. *J. Am. Chem. Soc.* **1977**, *99*, 1275.

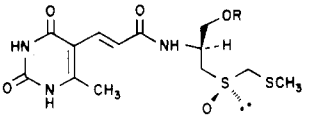
and then sodium borohydride[34] to produce the alcohol **26** (71–81%). The tosylate **27** (98%) formed from this alcohol reacts with sodium methyl mercaptide to furnish the sulfide **28** (91%) which is oxidized with sodium metaperiodate[24] to provide a 1:1 mixture of diastereomeric sulfoxides (92%) which are separable by fractional crystallization. The isomer **29** may be treated with dilute hydrochloric acid to give a hydroxy sulfoxide **17a** identical with the material obtained earler (Scheme III). On the other hand, removal of the amine protecting group[26] of **29** gives the amino sulfoxide **30** (45–71%; see Experimental Section) which may then be subjected to our earlier sulfenylation procedure to give the dithioacetal mono-*S*-oxide **31** (40%) which is synthetically equivalent to compound **21** in Scheme III. The sulfenylation step in Scheme IV was difficult to reproduce starting with greater than 0.15-g quantities of **30**, but the overall yield of **31** from L-serine was 5.9% compared to less than 1% of **21** from L-cysteine in the earlier route (Scheme III).

D. Completion of the Synthesis of (+)-Sparsomycin. The coupling of the acid **2** and the THP-containing amine **21** had been studied earlier by Professor Ottenheijm's group[15,16a] and by us through use of the 1-hydroxybenzotriazole/dicyclohexylcarbodiimide[35] and mixed anhydride[36] methods. However, we have now optimized the coupling using the methoxymethyl-containing amine **31**. The main difficulty that we faced was the limited solubility of **3** in most organic solvents. The best results are obtained through use of the mixed anhydride method[36] with a solvent system consisting of a mixture of THF and DMF to give the protected sparsomycin derivative **32** (71%, eq 2). Finally, hydrolytic removal of the hydroxy protecting group affords (+)-sparsomycin (**1**, 65%) having an optical rotation of $[\alpha]^{25}$ +71° (*c* 0.015, H_2O) in good agreement with the values of +69° and +75° reported previously.[3,16a] The synthetic material and an authentic



sample are also identical according to ^1H NMR spectra recorded on the same instrument except that the synthetic material is seen to contain a small amount of unidentified impurity which could not be removed by chromatography or recrystallization.

E. Synthesis of *S*-Episparsomycin. As mentioned earlier (Scheme IV), the oxidation of sulfide **28** produces a mixture of diastereomeric sulfoxides, of which the isomer **29** was employed to complete the synthesis described above. However, we have carried the diastereomer of **29** having the opposite configuration at sulfur through the remainder of the synthesis as well. Through use of the same steps as described for (+)-sparsomycin itself, *S*-episparsomycin (**33**) is obtained with yields for each of the steps being quite comparable to those for **1**. The optical rotation of $[\alpha]^{25}$ +45° (*c* 0.007, H_2O) and ^1H NMR spectrum of **33** are significantly different from those of **1**.



33

Conclusion

We have developed a reasonably efficient route to the antitumor antibiotic (+)-sparsomycin which proceeds via a formal inversion of the L-serine system. This route is capable of providing practical quantities of sparsomycin and analogues for clinical testing.

Experimental Section

General Data. Melting points were recorded on a Thomas-Hoover Unimelt melting point apparatus or on a Fisher-Johns melting point block and are corrected. Infrared spectra were determined in chloroform solution, unless otherwise stated. All ^1H NMR and ^{13}C NMR spectra were obtained in chloroform-*d* or in dimethyl-d_6 sulfoxide, with tetramethylsilane (Me_4Si) as an internal standard, or in deuterium oxide with tert-butanol as an internal standard (CH_3 singlet at δ 1.20 relative to Me_4Si. E. Merck silica gel 60 (230-400 mesh ASTM) was used for flash chromatography,[37] and E. Merck precoated TLC sheets (silica gel 60 F-254) were used for all thin-layer chromatography (TLC). All materials were used as obtained commercially unless otherwise mentioned. Anhydrous dimethyl sulfoxide, anhydrous *N,N*-dimethylformamide, anhydrous diisopropylamine, and anhydrous acetonitrile were purified by distillation from calcium hydride under nitrogen. Anhydrous tetrahydrofuran and anhydrous diethyl ether were purified by distillation from dark blue or purple solutions of sodium benzophenone radical anion or dianion under nitrogen. These solutions were obtained by heating a mixture of 1000 mL of solvent, 10 g of sodium, and 30 g of benzophenone at reflux. *n*-Butyllithium was stored at 0 °C under nitrogen and was titrated prior to use by the method of Kofrom and Baclawski.[38] Anhydrous liquids were transfered by using a syringe and a needle. A double-manifold system in which one of the manifolds was connected to a source of dry nitrogen, and the other was connected to a vacuum pump was used for inert atmosphere and low pressure work. The standard isolation procedure that is mentioned for the individual experiments involved drying the solution of the crude product over solid, anhydrous magnesium sulfate or sodium sulfate and then removing the solvent by rotary evaporation in vacuo.

5-(Hydroxymethyl)-6-methyluracil (7). 6-Methyluracil (6.30 g, 0.05 mmol) was dissolved in 1.25 N aqueous sodium hydroxide (60 mL) at 25 °C. To this solution was added 37% aqueous formaldehyde (12.2 mL, 0.15 mmol), and the mixture was allowed to stir at 25 °C for 40 h. The resulting crystals were collected by filtration and then dissolved in boiling water (100 mL). The solution was acidified with concentrated hydrochloric acid to pH 5, and the resulting turbidity was removed by filtration. The solution was then concentrated in vacuo to a volume of 90 mL and was allowed to stand at 0 °C for 12 h. Collection of the resulting white crystals by filtration gave **7** (6.0 g, 77%): mp 302–308 °C dec (lit.[18] 305–310 °C dec); IR (KBr) 3500, 3100, 1800-1600, 1441, 1340, 1210, 1100 cm^{-1}; ^1H NMR (D_2O) δ 4.36 (s, 2 H), 2.24 (s, 3 H).

5-Formyl-6-methyluracil (8). To a suspension of **7** (4.03 g, 25 mmol) in water (50 mL) was added 1 N aqueous ceric am-

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monium nitrate (55 mL) at 25 °C. When the orange color had disappeared, the solution was subjected to several freeze–thaw cycles over a 2-day period. The resulting crystals were collected by filtration and dried to give 8 (2.6 g, 60%): mp 202–206 °C dec (lit.[13b] 200 °C dec); IR (KBr) 3560, 3440, 3200, 3000, 2880, 1730, 1680, 1540, 1420, 1120 cm^{-1}; ^{1}H NMR (D_2O) δ 9.85 (s, 1 H), 2.54 (s, 3 H).

Ethyl (*E*)-3-(6-Methyl-5-uracilyl)-2-propenoate (9). (Carbethoxymethylene)triphenylphosphorane (8.9 g, 26 mmol) and 5-formyl-6-methyluracil (8) (2.6 g, 17 mmol) were placed in a flask under nitrogen. Anhydrous dimethyl sulfoxide (100 mL) was added, and the mixture was allowed to stir for 50 h at 25 °C. The solvent was distilled under vacuum, and the residue was crystallized from ethanol giving 9 (2.6 g, 75%) as white crystals: IR (KBr) 3000, 1740, 1670, 1310, 1200, 1000 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.36 (d, J = 17 Hz, 1 H), 6.86 (d, J = 17 Hz, 1 H), 3.7 (q, J = 7 Hz, 2 H), 2.5 (br s, 2 H), 2.28 (s, 3 H), 1.22 (t, J = 7 Hz, 3 H).[13b]

(*E*)-3-(6-Methyl-5-uracilyl)-2-propenoic Acid (2). To a solution of 9 (1.0 g, 4.5 mmol) in methanol (15 mL), and dioxane (15 mL) was added 3 N aqueous sodium hydroxide (15 mL). After being stirred for 24 h at 25 °C, the mixture was concentrated in vacuo, and the residue was dissolved in water (15 mL). The solution was acidified (pH 2) with concentrated hydrochloric acid and then allowed to stand at 0 °C for 12 h. The resulting white solid was collected by filtration, washed with ice-cold water, and dried in air to afford 2 (0.78 g, 90%): mp 261–263 °C dec (lit.[13b] 265 °C dec); IR (KBr) 3020, 1700, 1620, 1420, 1320, 1290, 1200, 1000 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 7.31 (d, J = 15 Hz, 1 H), 6.81 (d, J = 15 Hz, 1 H), 2.27 (s, 3 H).

***S*-Methyl-L-cysteine (11).** L-Cysteine hydrochloride hydrate 10 (21.08 g, 0.12 mol) was suspended in absolute alcohol (350 mL), and freshly cut pieces of sodium (11 g, 0.48 mol) were then added (in a 15-min interval) to the above solution. After all the sodium had dissolved, methyl iodide (8.3 mL, 0.13 mol) was added, and the mixture was stirred at room temperature for 15 min. Large quantities of white solid were formed. Water was then added to dissolve all the solid, and the solution was a[illegible]dified by adding 48% aqueous hydroiodic acid, and some whi[illegible]lid was formed. Diethyl ether was added to make the mixture [illegible]d. The solution was cooled in a refrigerator (8 h), and the [illegible] crystals were collected by filtration, washed with cold abso[illegible]hanol and then with diethyl ether, and dried, giving *S*-m[illegible]-cysteine (11) (14.05 g, 88%): mp 245–251 °C dec (lit.[20] [illegible]5–250 °C dec) [α]$^{25}_D$ −32.5° (*c* 0.8, H_2O) (lit.[20] [α]$^{25}_D$ −32.[illegible] 1.0, H_2O)); IR (KBr) 3500, 1640, 1500 1430, 1360, 1300, 1[illegible] cm^{-1}; ^{1}H NMR (D_2O) δ 3.9 (dd, 1 H), 3.0 (m, 2 H), 2.12 (s, [illegible] H).

***S*-Methyl-DL-cysteine (12).** *S*-Methyl-L-cysteine (11) (13.01 g, 96 mmole was transferred into a 100-mL round-bottom flask, glacial acetic acid (45 mL) was added, and the mixture was heated at reflux under nitrogen for 3 h. Most of the acetic acid was removed in vacuo. To the residue (brown solid) was added 20% HCl solution (50 mL), and the mixture was heated at reflux under nitrogen for another 2 h. The solution became colored. Most of the solvent was removed in vacuo, and the solution was decolorized with Norit. The pH of the solution was adjusted to 4 by adding 1 N ammonium hydroxide solution, and a large amount of crystals formed. The mixture was cooled in a refrigerator (8 h) and was filtered. The solid was washed with cold ethanol and air dried. The mother liquid was made cloudy by adding more cold ethanol and cooled in the refrigerator for 5 h. The crystals were collected by filtration and washed with cold ethanol and air dried. The combined crops gave 11.03 g of 12 (87%). Its ^{1}H NMR and IR spectra were the same as those of 11.

***N*-(Benzyloxycarbonyl)-*S*-methyl-DL-cysteine (13).**[22] To a solution of 12 (1.35 g, 10 mmol) in 20 mL of 2 N aqueous sodium hydroxide solution at 0 °C was added benzyl chloroformate (1.5 mL, 10.5 mmol). The resulting mixture was vigorously stirred at 25 °C for 2 h, and the pH of the mixture was maintained at 10. The mixture was basified (pH 14) by addition of 2 N aqueous sodium hydroxide. It was then extracted with ethyl acetate. The organic extracts were washed with brine solution, and the standard isolation procedure gave 13 as an oil (2.5 g, 81%): IR ($CHCl_3$) 3480, 3000, 1740, 1520, 1080 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4 (s, 5 H), 5.8 (br d, 1 H), 5.15 (s, 2 H), 4.7 (m, 1 H), 2.9 (m, 2 H), 2.1 (s, 3 H). This compound may be further purified on a silica gel column eluted with ethyl acetate and methylene chloride (v/v = 5:95), containing 3 mL of trifluoroacetic acid per liter of solution), but it is sufficiently pure for the resolution experiment.

***N*-(Benzyloxycarbonyl)-*S*-methyl-D-cysteine (14).**[22] To a solution of 13 (1.9 g, 7.1 mmol) in anhydrous diethyl ether (5 mL) was added *l*-ephedrine (0.58 g, 3.5 mmol). Ethyl acetate was added dropwise until the solution became clear. The solution was allowed to stand at 25 °C for 15 h without disturbing and then was stored in a freezer for another 2 h. The crystals were collected by filtration and were dissolved in a minimum amount of ethyl acetate, and hexane was added to make the solution slightly cloudy. The solution was allowed to stand at 0 °C for 24 h. The resulting crystals were collected by filtration, washed with cold diethyl ether, and dried in air to afford the desired salt (0.91 g, 60%): mp 109–111 °C dec; [α]$^{25}_D$ −17.5° (*c* 0.2, EtOH).

The above salt (0.24 g, 0.56 mmol) was dissolved in water (10 mL), and to this solution was added an aqueous solution of hydrochloric acid (2 N, 0.3 mL). As soon as the acid was added, an oil separated. The mixture was extracted with ethyl acetate. The organic extracts were washed with brine solution and subjected to the standard isolation procedure to give 14 (0.14 g, 95%): [α]$^{25}_D$ +7.0° (*c* 0.2, CH_2Cl_2). The ^{1}H NMR and IR were the same as those of 13.

***N*-(Benzyloxycarbonyl)-*S*-methyl-D-cysteine Methyl Ester (15).** To a solution of 14 (0.27 g, 1.0 mmol) in anhydrous diethyl ether (15 mL) was added a solution of diazomethane, generated by the action of alcoholic potassium hydroxide on Diazald (*N*,4-dimethyl-*N*-nitrosobenzenesulfonamid),[23] in diethyl ether and alcohol. When a light green color persisted in the reaction mixture, the addition of diazomethane was stopped and the stirring was continued for another 1 h. After filtration, the reaction mixture was concentrated in vacuo to afford an oil (0.28 g, 98%): IR ($CHCl_3$) 3400, 1720, 1220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (s, 5 H), 6.3 (br d, 1 H), 5.1 (s, 2 H), 4.5 (m, 1 H), 3.7 (s, 3 H), 2.8 (br d, 2 H), 2.1 (s, 3 H).

***N*-(Benzyloxycarbonyl)-*S*-methyl-D-cysteinol (16).**[16a] To a solution of methyl ester 15 (0.14 g, 0.5 mmol) in 20 mL of anhydrous dimethoxyethane (DME) was added sodium borohydride (57 mg, 1.5 mmol) and lithium iodide (200 mg, 1.5 mmol) at 0 °C. The mixture was stirred at 25 °C for 3 h, and then an aqueous solution of hydrochloric acid (3 N, 10 mL) was added slowly. The mixture was stirred for 1 h at 25 °C. After DME was removed in vacuo, the aqueous portion was extracted with chloroform. The standard isolation procedure afforded the desired alcohol 16 as an oil (51% yield): IR ($CHCl_3$) 3480, 1730, 1530, 1100 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.4 (s, 5 H), 5.6 (m, 1 H), 5.1 (s, 2 H), 4.0–3.4 (m, 4 H), 2.1 (s, 3 H).

***N*-(Benzyloxycarbonyl)-*S*-methyl-D-cysteinol *S*-Oxide (17a and 17b).** To a solution of *N*-(benzyloxycarbonyl)-*S*-methylcysteinol (16) (0.39 g, 1.53 mmol) in acetonitrile (10 mL) was added a solution of sodium metaperiodate (0.35 g, 1.65 mmol) in water (10 mL) at 0 °C. The resulting homogeneous solution was stirred in a cold room for 12 h and concentrated in vacuo to afford a white solid which was partitioned between water and methylene chloride. The aqueous portion was extracted with methylene chloride. The standard isolation afforded solid 17a and 17b as indicated by its ^{1}H NMR spectrum. The methyl signals of the sulfoxides appeared at δ 2.57 and 2.61 as two singlets. HPLC analysis of this mixture suggested that the ratio of the two diastereoisomers was 2:3 in favor of the undesired sulfoxide 17b. A fractional recrystallization of the mixture (carbon tetrachloride and hexanes) gave the desired sulfoxide 17a (0.11 g, 24%) as a white crystalline solid. The mother liquor was concentrated in vacuo to give a white solid (0.18 g) which was enriched in the undesired sulfoxide 17b.

Compound 17a: IR ($CHCl_3$) 3500, 1730, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$ δ 7.33 (s, 5 H), 5.9 (br d, 1 H), 5.09 (s, 2 H), 4.0 (m, 1 H), 3.7 (m, 2 H), 3.0 (br d, 2 H), 2.57 (s, 3 H).

Compound 17b (enriched): IR ($CHCl_3$) 3500, 1740, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5 H), 5.9 (br d, 1 H), 5.09 (s, 2 H), 4.0 (m, 1 H), 3.7 (m, 2 H), 3.0 (m, 2 H), 2.61 (s, 3 H).

***N*-(Benzyloxycarbonyl)-*O*-(tetrahydropyranyl)-*S*-methyl-D-cysteinol *S*-Oxide (18).**[25] To a solution of the desired sulfoxide 17a (0.11 g, 0.41 mmol) in anhydrous THF (5 mL) was added a solution of dihydropyran (0.34 g, 4 mmol) and *p*-toluenesulfonic acid (20 mg) in anhydrous THF (5 mL) at 0 °C.

The resulting solution was stirred in a cold room for 12 h and at room temperature for 1 h and then was concentrated in vacuo to afford a yellow solid which was dissolved in ethyl acetate and washed with 5% aqueous sodium bicarbonate. The standard isolation afforded **18** (0.14 g, 97%) as a white crystalline solid: IR ($CHCl_3$) 3460, 1720, 1520, 1270, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.33 (s, 5 H), 6.0 (br d, 1 H), 5.1 (s, 2 H), 4.53 (m, 1 H), 3.5 (m, 5 H), 2.93 (m, 2 H), 2.54 (s, 3 H), 1.56 (m, 6 H).

***O*-(Tetrahydropyranyl)-*S*-methyl-D-cysteinol *S*-Oxide (19).** *N*-(Benzyloxycarbonyl)-*O*-(tetrahydropyranyl)-*S*-methyl-D-cysteinol *S*-oxide (**18**) (0.20 g, 0.56 mmol) was placed in a three-necked flask which was equipped with a filter funnel and a condenser. The entire apparatus was evacuated, flame-dried, and filled with nitrogen. A mixture of dry ice and acetone was placed in the condenser, and the bottom flask was chilled in a dry ice–acetone bath. Then ammonia gas was introduced and condensed in the flask. When enough liquid ammonia was condensed (about 20 mL), the stream of ammonia into the flask was stopped, and sodium (32 mg, 1.4 mmol) was placed on the plate of the funnel. Then the ammonia was allowed to reflux by placing the flask in a methanol bath. The condensed ammonia dripped into the funnel and dissolved the sodium. As the dark blue solution of sodium in ammonia dripped into the flask, it was immediately decolorized. Once the blue color persisted in the solution for several minutes, the refluxing of ammonia was stopped by placing the flask in a dry ice–acetone bath, and the reaction was quenched by adding ammonium chloride (0.5 g). The liquid ammonia was allowed to evaporate, and the residue was extracted with methylene chloride. The standard isolation gave an oil which was chromatographed on a silica gel column. Elution with methanol and methylene chloride (v/v = 1:5, containing 2 mL of aqueous ammonium hydroxide per liter of solution) gave the desired amine **19** (90 mg, 72%) as an oil: ^1H NMR ($CDCl_3$) δ 4.6 (br m, 1 H), 4.0–3.35 (m, 5 H), 2.9 (m, 2 H), 2.67 (s, 3 H), 1.60 (m, 6 H).

Isobutyl Methyl Sulfide. Into ice-bath-chilled methanol (100 mL) was carefully added sodium metal (12 g, 0.52 mol). When all of the sodium disappeared, to this solution was added 2-methyl-1-propanethiol (50 mL, 0.46 mol) at 0 °C. The mixture was stirred at 0 °C for 1 h, and then methyl iodide (30 mL, 0.48 mol) was added slowly. The resulting solution was stirred at 0 °C for 0.5 h and at room temperature for 3 h. After the reaction time a saturated solution of ammonium chloride (50 mL) was added. The solution was extracted with petroleum ether. The petroleum ether extracts were combined, dried over magnesium sulfate, and distilled. The desired sulfide (bp 105–110 °C) (lit.[39] bp 110–112 °C) was collected as a colorless liquid (37.77 g, 79%): IR (neat) 2960, 1460, 1390, 1250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.38 (d, J = 6.3 Hz, 2 H), 2.2–1.4 (a singlet at δ 2.08 overlaps with a multiplet, 4 H), 0.98 (d, J = 6.3 Hz, 6 H).

Isobutyl Methyl Sulfoxide (21). To an ice bath chilled solution of isobutyl methyl sulfide (10.27 g, 98.7 mmol) in acetonitrile (100 mL) was added a 30% solution of hydrogen peroxide (11.7 mL). The resulting mixture was stirred at 0 °C for 12 h, and a saturated solution of sodium bisulfite (10 mL) was added to destroy excess hydrogen peroxide. The mixture was concentrated in vacuo, and the remaining aqueous solution was extracted with ethyl acetate. The organic extracts were dried over magnesium sulfate and distilled. After all solvents were removed, the remaining liquid was distilled under vacuum (0.05 mmHg). The desired sulfoxide (bp 48–55 °C (lit.[40] bp 45–46 °C (0.2 torr))) was collected as a colorless liquid (11.07 g, 93%): IR (neat) 2960, 1460, 1380, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.02–1.87 (a singlet at δ 2.56 overlaps with a multiplet, 6 H), 1.07 (m, 6 H).

Isobutyl (Methylthio)methyl Sulfoxide (22). To a solution of diisopropylamine (5.9 mL, 42 mmol) in anhydrous THF (40 mL) was added *n*-butyllithium (1.25 M, 34 mL, 42 mmol) at −78 °C. The resulting solution was stirred at 0 °C for 20 min and then cooled to −78 °C. To this solution was added a solution of isobutyl methyl sulfoxide (**21**) (2.31 g, 19 mmol) in anhydrous THF (10 mL), and the resulting mixture was stirred at −78 °C for 1 h. Then methyl disulfide (1.7 mL, 19 mmol) was added dropwise at −78 °C, and the resulting mixture was stirred at −78 °C for 1 h and then at 0 °C for 3 h. A saturated solution of ammonium chloride (20 mL) was then added, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate. The standard isolation gave a dark red oil. Column chromatography (silica gel, ethyl acetate/hexanes = 4:1)gave the desired product as a white solid which was dissolved in a minimum amount of hot petroleum ether with several drops of diethyl ether. Upon cooling in a dry ice–acetone bath white needlelike crystals were formed. Most of the solvent was removed by decantation, and the residue was dried under vacuum. White needlelike crystals (2.01 g, 65%) were obtained: mp 39–40° C; IR (KBr) 2960, 1460, 1385, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.65 (s, 2 H), 2.67 (m, 2 H), 1.8–2.6 (a strong singlet overlaps with a multiplet, 4 H), 1.14 (two overlapping doublets, 6 H).

***O*-(Tetrahydropyranyl)-*S*-((methylthio)methyl)-D-cysteinol *S*-Oxide (20).** To a solution of diisopropylamine (0.033 mL, 0.23 mmol) in anhydrous THF at 0 °C was added a solution of *n*-butyllithium (2.28 M, 0.1 mL, 0.23 mmol) under nitrogen, and the mixture was stirred at this temperature for 20 min. After the solution was cooled to −78 °C, compound **19** (25.3 mg, 0.12 mmole in anhydrous THF (5 mL) was added slowly. After the mixture was stirred at −78° C for 1 h, dimethyl disulfide (0.010 mL, 0.11 mmol) was added to the mixture. The mixture was then stirred at 0 °C for 12 h. The reaction was quenched by adding a saturated aqueous solution of ammonium chloride adjusted to pH 8 by adding aqueous ammonium hydroxide. This solution was extracted with methylene chloride. The standard isolation gave a yellow oil. Column chromatography on silica gel with methylene chloride and methanol (v/v = 9:1, containing 2 mL of aqueous ammonium hydroxide per liter of solvent) afforded **20** (12 mg, 40%) as an oil: IR ($CHCl_3$) 3440, 3000, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.62 (m, 1 H), 4–3.3 (overlapping m, 7 H), 2.9 (m, 2 H), 2.34 (s, 3 H), 1.63 (m, 8 H).

***N*-(Benzyloxycarbonyl)-L-serine (23).** To a solution of L-serine (**5**) (21.15 g, 0.20 mol) and sodium bicarbonate (42 g, 0.5 mol) in 500 mL of water was added benzyl chloroformate (34 mL, 0.24 mol) at 25 °C, and the mixture was stirred for 4 h. After extraction with ether, the aqueous phase was cooled in ice bath and acidified (pH 3) with concentrated hydrochloric acid. The resulting milky solution was extracted with ethyl acetate. The combined organic layers were washed with brine solution and dried over anhydrous sodium sulfate. Evaporation of the solvent in vacuo gave 43.35 g (88%) of the desired compound as a white solid: mp 115–116 °C (lit.[41] 115–116 °C); $[\alpha]^{25}_D$ +2.45° (*c* 0.42, MeOH) (lit.[41] $[\alpha]^{25}_D$ +3° (*c* 2.7, MeOH)); IR (KBr) 3320, 1740, 1690, 1540, 1300, 1250 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 7.35 (s, 5 H), 5.04 (s, 2 H), 4.06 (m, 1 H), 3.69 (d, J = 6 Hz, 2 H).

Methyl *N*-(Benzyloxycarbonyl)-L-serinate (24). Method A. To a solution of *N*-(benzyloxycarbonyl)-L-serine (36.18 g, 0.15 mol) in anhydrous methanol (300 mL) was added dropwise thionyl chloride (17 mL, 0.23 mol) at 0 °C, and the resulting solution was stirred at 25 °C for 24 h. Concentration of the mixture in vacuo gave a yellow oil, to which was added 300 mL of diethyl ether. The insoluble solid was removed by filtration, and the filtrate was washed with saturated sodium carbonate solution, dried over anhydrous sodium sulfate, and concentrated in vacuo. The residue was triturated with cold petroleum ether and then stored under 100 mL of petroleum ether in a refrigerator for 24 h. The petroleum ether was removed by decantation, and the remaining solid was recrystallized in anhydrous diethyl ether and pentane to give a white solid (31.4 g, 82%): mp 32–33 °C (lit.[42] 33–35 °C); $[\alpha]^{25}_D$ −14.5° (*c* 0.12, MeOH) (lit.[42] $[\alpha]^{25}_D$ −13° (*c* 1.0, MeOH)); IR (KBr) 3510, 3280, 1740, 1690, 1550, 1330, 1240 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.32 (s, 5 H), 5.8 (br d, 1 H), 5.1 (s, 2 H), 4.6–4.2 (m, 1 H), 4.0 –3.4 (m, 5 H), 2.8 (m, 1 H).

Method B. To a solution of *N*-(benzyloxycarbonyl)-L-serine (8.56 g, 35.8 mmol) and sodium bicarbonate (6.32 g, 75 mmol) in *N*,*N*-dimethylformamide (50 mL) was added methyl iodide (11.2 mL, 0.18 mol) under nitrogen. The mixture was stirred at room temperature for 30 h. The reaction mixture was then mixed with distilled water (50 mL) and extracted with methylene chloride.

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The methylene chloride extracts were combined and washed with water and brine. The standard isolation afforded a red oil which was purified on a silica gel column (eluted with ethyl acetate/hexanes = 1:1). The desired methyl ester was obtained as a colorless oil (6.71 g, 81%) which upon cooling in the refrigerator became solid. The solid had the same ^{1}H NMR and IR spectra as that obtained from method A.

Method C. *N*-(Benzyloxycarbonyl)-L-serine (1 g, 4.18 mmol) was suspended in anhydrous ethyl ether (10 mL). To this mixture was added a solution of diazomethane in anhydrous diethyl ether, prepared from Diazald and alcoholic potassium hydroxide,[23] in small portions. When the yellow-green color of diazomethane persisted in the reaction solution, the addition of diazomethane was stopped, but the stirring was continued for another 3 h. Then the reaction mixture was filtered and concentrated in vacuo to give an oil (0.99 g, 94%) which had the same ^{1}H NMR and IR spectra as those obtained from methods A and B.

***N*-(Benzyloxycarbonyl)-*O*-(methoxymethyl)-L-serine Methyl Ester (25).** To a solution of methyl *N*-(benzyloxycarbonyl)-L-serinate (6.0 g, 23.7 mmol) in anhydrous methylene chloride (200 mL) was added *N,N*-diisopropylethylamine (6.2 mL, 35.6 mmol) and chloromethyl methyl ether (2.7 mL, 35.6 mmol)[32] under nitrogen. The mixture was heated at reflux for 14 h and then concentrated in vacuo to give a dark red residue. To the residue was added water (100 mL) and diethyl ether (400 mL). The mixture was well shaken, and the aqueous portion was separated. The ether layer was washed with water and brine solution. The standard isolation gave a pale yellow oil (6.2 g, 88%): $[\alpha]^{25}_D$ +3.0° (*c* 0.23, CH_2Cl_2); IR (neat) 3400, 1720, 1530, 1220, 1060 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (s, 5 H), 5.7 (br d, 1 H), 5.1 (s, 2 H), 4.5 (m, 3 H), 3.7 (m, 5 H), 3.3 (s, 3 H).

Anal. Calcd for $C_{14}H_{19}NO_6$: C, 56.55; H, 6.44. Found: C, 56.46; H, 6.59.

***N*-(Benzyloxycarbonyl)-*O*-(methoxymethyl)-L-serinol (26).**[33,34] To a solution of *N*-(benzyloxycarbonyl)-*O*-(methoxymethyl)-L-serine methyl ester (25) (6.51 g, 22 mmol) in anhydrous THF (150 mL) was added dropwise a solution of diisobutylaluminum hydride in hexane (1 M, 26 mL, 26 mmol) at −70 °C under nitrogen. The mixture was stirred at −70 °C for 14 h, and the excess hydride was destroyed by adding anhydrous ethanol (10 mL). The solution was allowed to warm up to room temperature and concentrated in vacuo. The residue was dissolved in anhydrous ethanol (200 mL), and then sodium borohydride (5.01 g, 131 mmol) was added in small protions at 0 °C. The resulting mixture was stirred at 0 °C for 1 h and at 25 °C for 6 h and then concentrated in vacuo. To the residue was added cold water (100 mL), and then concentrated hydrochloric acid was added slowly until most of the solid had dissolved. The acidified solution (pH 2) was stirred for 15 min and then was extracted with ethyl acetate. The standard isolation gave an oil which was chromatographed on a silica gel column. Elution with ethyl acetate and hexanes (v/v = 4/1) gave the desired alcohol as an oil (4.37 g, 74%) which became a solid upon cooling in a refrigerator: mp 33–35 °C; $[\alpha]^{25}_D$ −1.2° (*c* 0.22, CH_2Cl_2); IR (KBr) 3320, 1690, 1540, 1280 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5 H), 5.35 (m, 1 H), 5.1 (s, 2 H), 4.6 (s, 22 H), 3.7 (m, 5 H), 3.35 (s, 3 H), 2.5 (br s, 1 H).

Anal. Calcd for $C_{13}H_{19}NO_5$: C, 57.98; H, 7.11. Found: C, 57.67; H, 7.26.

Tosylate 27 of *N*-(Benzyloxycarbonyl)-*O*-(methoxymethyl)-L-serinol. To a solution of *N*-(benzyloxycarbonyl)-*O*-(methoxymethyl)-L-serinol (26) (4.71 g, 17.5 mmol) in 20 mL of anhydrous pyridine was added a solution of tosyl chloride (7.3 g, 38.3 mmol) in 10 mL of anhydrous pyridine at 0 °C. The resulting solution was stirred at 0 °C for 24 h and then extracted with diethyl ether. The etheral solutions were washed with cold 6 N HCl solution (40 mL) to remove pyridine and then with water, dried over anhydrous potassium carbonate, and concentrated in vacuo at 25 °C to afford a pale yellow oil which was stored under 100 mL of petroleum ether in a refrigerator for 10 h, and the crystallized tosyolate was collected by suction-filtration. After the mixture was washed with cold petroleum ether, 7.41 g of tosylate 27 (98%) was obtained: mp 55–56 °C; $[\alpha]^{25}_D$ −10.7° (*c* 0.35, CH_2Cl_2); IR (KBr) 3420, 1680, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.7 (d, *J* = 8 Hz, 2 H), 7.33 (a singlet overlaps with a doublet, 7 H), 5.2 (m, 1 H), 5.1 (s, 2 H), 4.5 (s, 2 H), 4.05 (br s, 3 H), 3.5 (m, 2 H), 3.25 (s, 3 H), 2.4 (s, 3 H).

Anal. Calcd for $C_{20}H_{25}NO_7S$: C, 56.72; H, 5.95. Found: C, 56.84; H, 6.11.

***N*-(Benzyloxycarbonyl)-*O*-(methoxymethyl)-*S*-methyl-D-cysteinol (28).** To a solution of tosylate 27 (2.35 g, 5.56 mmol) in ethanol (100 mL) was added a 2 M solution of sodium methylmercaptide (5 mL, 10 mmol) in methanol. The resulting solution was stirred at 40 °C for 3 h, and a saturated solution of ammonium chloride (10 mL) was added. The solution was concentrated in vacuo, and the remaining aqueous solution was extracted with methylene chloride. The organic extracts were dried over anhydrous sodium sulfate and concentrated in vacuo. The desired sulfide was obtained as a pale yellow oil (1.60 g, 95%) which upon cooling at 0 °C became a solid: mp 25–26 °C; $[\alpha]^{25}_D$ +20.6° (*c* 0.13, CH_2Cl_2); IR (KBr) 3370, 1690, 1520, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.33 (s, 5 H), 5.2 (br s, 1 H), 5.10 (s, 2 H), 4.60 (s, 2 H), 3.7 (m, 3 H), 3.33 (s, 3 H), 2.70 (d, *J* = 6.4 Hz, 2 H), 2.12 (s, 3 H).

Anal. Calcd for $C_{14}H_{21}NO_4S$: C 56.16, H 7.06. Found: C 55.96, H 7.10.

***N*-(Benzyloxycarbonyl)-*O*-(methoxymethyl)-*S*-methyl-D-cysteinol *S*-Oxide (29 and 29a).** Compounds 29 and 29a were prepared from compound 28 (0.72 g, 2.41 mmol) as described in the synthesis of 17a and 17b. The sulfoxide was obtained as a white solid (0.71 g, 93%) which was a mixture of two diastereoisomers with a ratio of 1:1. One of the diastereoisomers, compound 29, could be separated by fraction recrystallization (0.22 g, 31%) in methylene chloride and hexanes from the other diastereoisomer 29a. However, the diastereoisomer 29a could not be completely separated from compound 29.

The first diastereoisomer 29 formed needlelike crystals: mp 112–113 °C; $[\alpha]^{25}_D$ +75.56° (*c* 0.16, CH_2Cl_2); IR (KBr) 3330, 1690, 1540, 1270, 1040, 1020 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5 H), 5.7 (br s, 1 H), 5.1 (s, 2 H), 4.63 (s, 2 H), 4.3 (m, 1 H), 3.75 (m, 2 H), 3.35 (s, 3 H), 3.0 (br d, *J* = 6 Hz, 2 H), 2.62 (s, 3 H).

Anal. Calcd for $C_{14}H_{21}NO_5S$: C, 53.31; H, 6.71. Found: C, 53.53; H, 6.91.

A mixture enriched in diastereoisomer 29a was obtained by concentration of the mother liquid after the fractional recrystallization: ^{1}H NMR ($CDCl_3$) δ 7.34 (s, 5 H), 5.7 (br s, 1 H), 5.10 (s, 2 H), 4.63 (s, 2 H), 4.3 (m, 1 H), 3.75 (m, 2 H), 3.35 (s, 3 H), 3.0 (m, 2 H), 2.58 (s, 3 H).

***O*-(Methoxymethyl)-*S*-methyl-D-cysteinol *S*-Oxide (30).** Following the preparation procedure of amine 19, the N-protected sulfoxide 29 (0.57 g, 1.81 mmol) was allowed to react with sodium (0.1 g, 4.3 mmol) in liquid ammonia to give the desired amine sulfoxide 30 as an oil (0.26 g, 81%): $[\alpha]^{25}_D$ +113° (*c* 0.23, CH_2Cl_2); IR (neat) 3400, 2900, 1600, 1040 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.64 (s, 2 H), 3.56 (m, 2 H), 3.37 (s, 3 H), 2.86 (m, 2 H), 2.63 (s, 3 H), 1.86 (s, 2 H).

***O*-(Methoxymethyl)-*S*-((methylthio)methyl)-D-cysteinol *S*-Oxide (31).** Following the same procedure as in the preparation of compound 21, the sulfoxide 30 (0.11 g, 0.61 mmol) was allowed to react with lithium diisopropylamide, prepared from diisopropylamine (0.2 mL, 1.34 mmol) and *n*-butyllithium (0.95 mL of 1.41 M in *n*-hexane, 1.34 mmol), and dimethyl disulfide (0.055 mL, 0.61 mmol) to give the desired product 31 as an oil (56 mg, 41%): $[\alpha]^{25}_D$ +86.12° (*c* 0.03, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 4.6 (s, 2 H), 3.7 (m, 2 H), 3.5 (br s, 3 H), 2.8 (m, 2 H), 2.3 (s, 3 H), 1.7 (br s, 2 H).

***O*-(Methoxymethyl)sparsomycin (32).** To a solution of acid 2 (0.14 g, 0.73 mmol) in a mixture of *N,N*-dimethylformamide (DMF) and THF (1 : 1, 12 mL) was added triethylamine (0.11 mL, 0.79 mmol). The resulting solution was stirred at 0 °C for 5 min, and ethyl chloroformate (0.070 mL, 0.73 mmol) was added. The mixture was stirred at room temperature for 4 h, and a solution of amine 31 (0.15 g, 0.55 mmol) in 10 mL of a mixed solvent of DMF and THF (1:1) was added dropwise at room temperature. The resulting solution was stirred at room temperature for 36 h. The solution was then concentrated under vacuum at a bath temperature of 60 °C to afford a yellow solid. Column chromatography of this residue on silica gel (eluted with methanol/ethyl acetate = 1:1) gave the desired product 32 as a white solid (0.12 g, 45%): $[\alpha]^{25}_D$ +76.86° (*c* 0.01, MeOH); ^{1}H NMR (Me_2SO-d_6) δ 8.3 (br d, *J* = 8 Hz, 1 H), 7.6–6.9 (m, 4 H), 4.8–4.2 (a singlet overlaps with a multiplet, 3 H), 3.8 (AB spectrum, *J* = 14 Hz, 2 H), 3.5 (br d, *J* = 5 Hz, 2 H), 3.25 (s, 3 H), 3.0 (br d,

J = 8 Hz, 2 H), 2.25 (two overlapping singlets, 6 H). An analogous sequence of reactions was performed for the *O*-((β-ethoxyethoxy)methyl) series of derivatives. The yield in this coupling step was 71%.

(+)-Sparsomycin (1). Compound **32** (15 mg) was dissolved in 5 mL of methanol, and to this solution was added 1 N hydrochloric acid solution (5 mL). The resulting solution was heated at 50 °C for 5 h and then concentrated in vacuo to afford a white solid which was purified on a silica gel column (ethyl acetate/methanol v 1:1). The synthetic sparsomycin was obtained as a white solid (8.9 mg, 65%). However there were some minor impurities present and several attempts to further purify this material failed: $[\alpha]^{25}_D$ +71° (*c* 0.009, H_2O) (lit.[1] +69° (*c* 0.5, H_2O), lit.[16a] +75° (*c* 0.245, H_2O)); ^1H NMr (D_2O) δ 7.29 (d, J = 15.56 Hz, 1 H), 3.83 (d, J = 14.95 Hz, 1 H), 3.65 (m, 3 H), 3.06 (m, 1 H), 2.28 (s, 3 H), 2.17 (s, 3 H).

***O*-(Methoxymethyl)-*S*-episparsomycin.** Following the same procedure described in the synthesis of amine **19**, a mixture of two diastereoisomers **29** and **29a** (1.53 g, 4.9 mmol) was allowed to react with sodium (0.10 g, 4.3 mmol) in liquid ammonia to give the corresponding amine sulfoxides as an oil (0.7 g, 81%): ^1H NMR ($CDCl_3$) δ 4.64 (s, 2 H), 3.56 (m, 3 H), 3.37 (s, 3 H), 2.86 (m, 2 H), 2.63 (s, 3 H), 1.86 (br s, 2 H).

The amine sulfoxide (0.42 g, 2.32 mmol) was sulfenylated, according to the procedure described in the synthesis of compound **21**, to give a mixture of compounds. Upon column purification (methanol/methylene chloride = 1:10, containing 2 mL of aqueous ammonium hydroxide per liter of solvent) the diastereoisomer with the opposite configuration at the chiral sulfur center (compared to the amine sulfoxide **31**) could be obtained in 13% yield (68 mg): ^1H NMR ($CDCl_3$) δ 4.66 (s, 2 H), 3.93 (d, J = 13.5 Hz, 1 H), 3.71 (d, J = 13.5 Hz, 1 H), 3.58 (br s, 1 H), 3.38 (s, 3 H), 3.09 (dd, J = 13.2, 4.8 Hz, 1 H), 2.81 (dd, J = 13.2, 7.5 Hz), 2.33 (s, 3 H), 1.9 (br s, 2 H).

Following the procedure described in the synthesis of compound **32**, the O-protected *S*-episparsomycin was prepared in 62% yield: ^1H NMR (D_2O) δ 7.5 and 7.7 (AB quartet, J = 15.6 Hz, 2 H), 4.8 (m, 1 H), 4.36 and 4.50 (AB quartet, J = 13.8 Hz, 2 H), 4.18 (m, 2 H), 3.62 (d, 2 H), 2.80 (s, 3 H), 2.71 (s, 3 H).

***S*-Episparsomycin (33).** Following the procedure described in the synthesis of (+)-sparsomycin, *S*-episparsomycin (**33**) was obtained: $[\alpha]^{25}_D$ +45° (*c* 0.007, H_2O) (lit.[16a] +48° (*c* 0.175, H_2O)); ^1H NMR (D_2O) δ 7.27 (d, J = 15.56 Hz, 1 H), 6.91 (d, J = 15.56 Hz, 1 H), 4.374 (m, 1 H), 4.04 (d, J = 13.93 Hz, 1 H), 3.85 (d, J = 13.93 Hz, 1 H), 3.652 (m, 2 H), 3.28 (dd, J = 13.5, 5.26 Hz, 1 H), 3.03 (dd, J = 13.5, 8.4 Hz, 1 H), 2.27 (s, 3 H), 2.18 (s, 3 H).

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A Highly Efficient One-Flask Method for the Preparation of the Individual Diastereoisomers of Ribonucleoside 3′,5′-Cyclic N-Substituted Phosphoramidates via the Direct Appel Reaction. X-ray Structure of *trans*-5-Isopropyl-2′-deoxyuridine 3′,5′-Cyclic *N*-Benzylphosphoramidate

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A superior method for the preparation of 3′,5′-cyclic N-substituted phosphoramidates of purine and pyrimidine ribo- and deoxyribonucleosides is reported. An Appel-type reaction of various 3′,5′-cyclic nucleoside monophosphates using a Ph_3P/CCl_4 pretreatment followed by addition of the requisite amine gives the corresponding phosphoramidate as a mixture of diastereomers in 31–85% isolated yields. Separation of the individual diastereomers is accomplished by chromatography on SiO_2. Most notably the reactions proceed readily with 3′,5′-cyclic ribonucleoside monophosphates *without protection* of the 2′-OH or potentially reactive functionality on the nitrogen base. In most instances both diastereomers are formed in useful amounts. Amino groups used included $C_6H_5CH_2NH$, C_6H_5NH, and $(CH_2)_5N$. Nucleosides employed were adenosine, deoxyadenosine, uridine, 5-isopropyl-2′-deoxyuridine, and 5-iodo-2′-deoxyuridine. An X-ray crystallographic study of one diastereomer of the *N*-benzylphosphoramidate based on the 3′,5′-cyclic diester of adenosine established the trans relationship of the $PhCH_2NH$ and nitrogen base as well as the equatorial position of the $PhCH_2NH$ on the chair form of the 1,3,2-dioxaphosphorinane ring. The structural parameters observed for the five- and six-membered rings are consistent with those of other neutral cyclic nucleotide derivatives.

Nucleoside 3′,5′-cyclic phosphoramidates, neutral derivatives of nucleoside 3′,5′-cyclic monophosphates, have proved to be valuable for the determination of binding and activation requirements for the active sites of protein kinases and phosphodiesterases.[1] They and other neutral derivatives have been useful in the study of the chair-twist conformational equilibrium available to the phosphate ring of such compounds derived from thymidine.[2] Recently, the anilidates of protected cAMP and other nucleotide

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