ketal, 54214-74-3; 5-acetoxy-4-oxoopentanal 4-(ethylene glycol ketal, 54214-75-4; *N*-*t*-BOC-glycine, 4530-20-5; benzyl *N*-*t*-BOC-glycinate, 54244-69-8; (±)-benzyl *N*-*t*-BOC-2-bromoglycinate, 142980-14-1; (±)-benzyl *N*-*t*-BOC-2-(diethoxyphosphoryl)-glycinate, 142980-15-2; (±)-benzyl 2-(diethoxyphosphoryl)-glycinate, 142980-16-3; phenylacetyl chloride, 103-80-0; (*R*)-methyl *p*-(benzyloxy)phenylglycinate hydrochloride, 88143-74-2; (*R*)-benzyl *p*-(benzyloxy)phenylglycinate hydrochloride, 67509-34-6; *N*-benzylamine, 100-46-9; ethyl thioformate, 29392-46-9; *N*-benzylthioformamide, 20278-32-4.

Supplementary Material Available: NMR spectra of 5, 6, 7, 11, 13, and 3 (6 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Studies Directed toward the Synthesis of Glycopeptide Antibiotic Teicoplanin: First Synthesis of the N-Terminal 14-Membered Ring[†]

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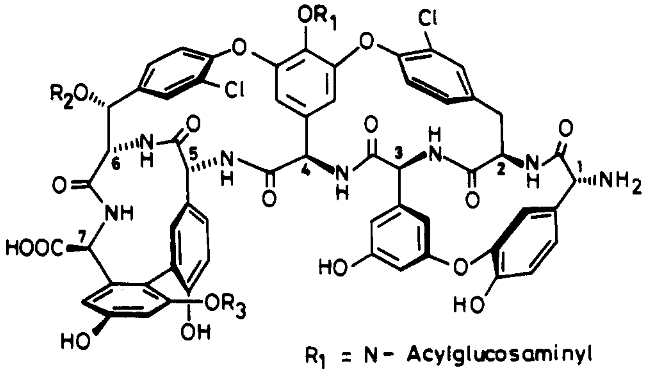
Received March 23, 1992

The N-terminal 14-membered ring formed by an ether linkage between the phenyl moieties of amino acids 1 and 3 of glycopeptide antibiotic teicoplanin 1 plays a crucial role in the binding of C-terminal D-Ala-D-Ala residues of the peptidoglycan precursor, thereby inhibiting bacterial cell wall biosynthesis. Herein, the first stereocontrolled synthesis of this very important cyclic peptide 2 is described. The two α-arylglycines present in this segment are constructed in optically pure form by diastereoselective Strecker synthesis using α-phenylglycinol as chiral auxiliary. Finally, the coupling between the acid function of amino acid 1 and the amino function of amino acid 2 leads to the desired macrocyclization. Optical purity of the synthetic product is determined by NMR studies.

Introduction

Recently, teicoplanin 1 has been introduced in therapeutic use for the parenteral treatment of severe infections caused by Gram-positive bacteria.[1] Teicoplanin, a complex of closely related antibiotics produced by *Actinoplanes teichomyceticus*,[2] belongs to the ristocetin family and is of particular interest because in vitro studies show it to be more active than vancomycin (minimum inhibitory concentrations are 2–8-fold less)[3] against many Gram-positive bacteria and in vivo studies show that effective doses for mice may be more than 1 order of magnitude lower than those of vancomycin. Moreover, teicoplanin is of low toxicity[2a] and exhibits substantially different pharmacokinetic behavior in vivo, having a half-life of 40 h in man.[4] Structurally, teicoplanin is very similar to vancomycin, except that in the former an extra cycle is present which is formed by an ether bond occurring between the phenyl moieties of amino acids 1 and 3.[5]



R1 = N- Acylglucosaminyl
R2 = N-Actyl-β-D-glucosaminyl
R3 = α- D-Mannosyl

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All these compounds express their antibiotic activity by inhibiting bacterial cell wall biosynthesis by selectively binding the C-terminal D-Ala-D-Ala residues of peptidoglycan precursor, muramyl pentapeptide.[6] Though many of these compounds have been known for over 30 years no total synthesis has, so far, been reported[7] due to their complex structures. As part of our recently initiated program on the syntheses of these glycopeptide antibiotics, several steps have been undertaken to overcome the major hurdles still associated in such syntheses. One of these is the presence of a large number of unnatural amino acids in these compounds, in particular α-phenylglycines which are amongst the most difficult amino acids to obtain in optically pure form. This has prompted us to develop an

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[†] IICT communication No. 3013.

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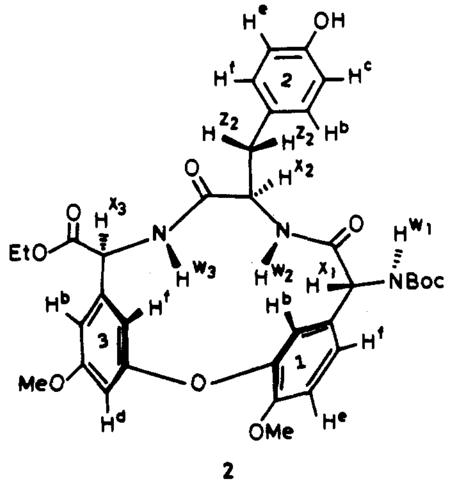
efficient method for the diastereoselective Strecker synthesis of optically pure α-amino acids using α-phenylglycinol as chiral auxiliary.[8] Available in both enantiomeric forms, this excellent chiral auxiliary is suitable for the synthesis of both L- as well as D-amino acids, the (*R*)-phenylglycinol being used for the former and vice versa. In addition, its facile removal by oxidative cleavage with lead tetraacetate under essentially neutral conditions makes it an ideal choice for the synthesis of α-arylglycines. This has been demonstrated by us[8] employing simple model compounds.

Herein, we report the application of this novel methodology in the first synthesis of N-terminal fourth ring 2 of teicoplanin.[9] This 14-membered cyclic tripeptide with phenolically coupled two α-arylglycine units plays a crucial role in the binding of C-terminal residues of peptidoglycan precursor inhibiting bacterial cell wall biosynthesis. In fact, it has been observed that when ristocetin A interacts with the peptide cell wall analogue di-*N*-acetyl-L-Lys-D-Ala-D-Ala, the aromatic ring of amino acid 1 of the antibiotic folds over the hydrogen-bond network formed between the carboxylate anion of the cell wall analogue and the amide bond of the antibiotic.[10] Though no such study has been done with teicoplanin as yet it is expected that teicoplanin which belongs to the ristocetin family should also behave in a similar fashion. The nonavailability of simpler models makes it difficult to carry out such studies. Our synthesis is aimed at overcoming this problem. It also highlights the novelty of using α-phenylglycinol as the chiral auxiliary for diastereoselective Strecker synthesis of α-amino acids.



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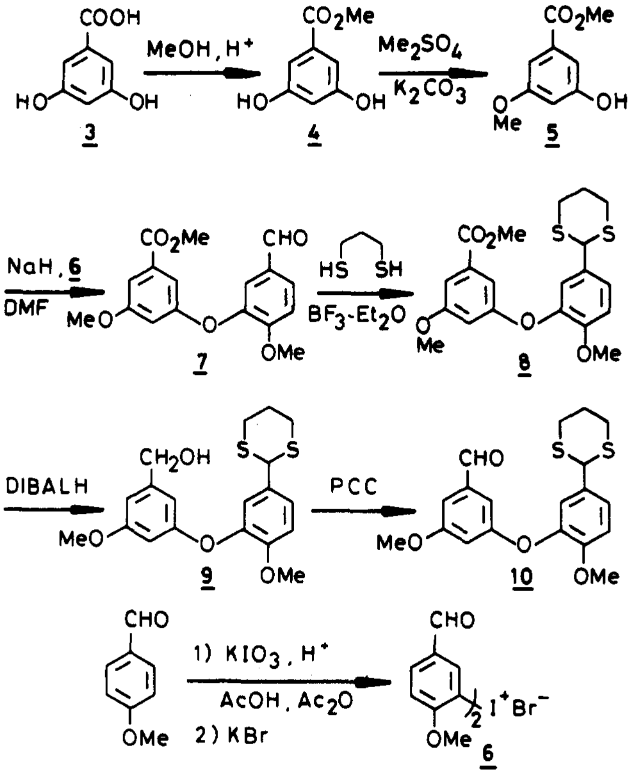
Results and Discussion

A thorough retrosynthetic analysis suggested that the most convenient way of constructing the ring would be to carry out cyclization between the acid function of amino acid 1 and the amino function of amino acid 2. This necessitated a priori synthesis of the diaryl ether moiety. The requisite key building block having the diaryl ether framework 7 was built up very conveniently following coupling between 3-methoxy-5-(methoxycarbonyl)phenoxide, prepared in two simple steps from 3,5-dihydroxybenzoic acid (3) and 5,5′-diformyl-2,2′-dimethoxydiphenyliodonium bromide (6)[11] (Scheme I). The aldehyde function on phenyl ring 1 was protected as 1,3-dithiane to be liberated later on at an appropriate stage for subsequent functionalization. With the conversion of methoxycarbonyl on phenyl ring 3 to aldehyde function the stage was now set to perform the first diastereoselective Strecker synthesis.

Scheme I



To get the required (*S*)-configuration of amino acid 3 of teicoplanin, it was necessary to use the (*R*)-stereoisomer of α-phenylglycinol as chiral auxiliary. Consequently, treatment of 10 with (*R*)-phenylglycinol in chloroform gave the (*E*)-imine (Scheme II). Sequential addition of methanol (to prevent the formation of O-silylated product) and trimethylsilyl cyanide (TMSCN) gave a mixture of diastereomers. The ratio of (*S*)- and (*R*)-products, 12:13, was 73:27 as determined by ^{1}H NMR spectroscopy. The newly created chiral center with (*S*)-configuration gave a signal at δ 4.43 whereas the signal for its (*R*) counterpart was at δ 4.54. The two isomers were separated by silica gel column chromatography. The major product 12 was dissolved in dry ethanol and treated with ethereal HCl to convert the nitrile to the ethyl ester. Evaporation of the reaction mixture gave the hydrochloride salt which was neutralized carefully using phosphate buffer of pH 7 to avoid any possible epimerization of the highly base-sensitive newly created optically active center. The chiral auxiliary appendage was removed by oxidative cleavage using lead tetraacetate. The resulting aldimine 15 was hydrolyzed with dilute hydrochloric acid. Careful neutralization of the evaporated reaction mixture once again with phosphate buffer of pH 7 gave the free amine which was coupled with D-*N*-Cbz-tyrosine in the presence of dicyclohexylcarbodiimide (DCC) and 1-hydroxybenzotriazole (HOBT) in dimethylformamide (DMF) to get the dipeptide 17. Removal of the dithiane protection regenerated the aldehyde function on ring 1. The next task was, now, to carry out the second Strecker synthesis, diastereoselectively.

This time, it was the (*S*)-isomer of the chiral auxiliary which was employed to build up the requisite α-amino acid

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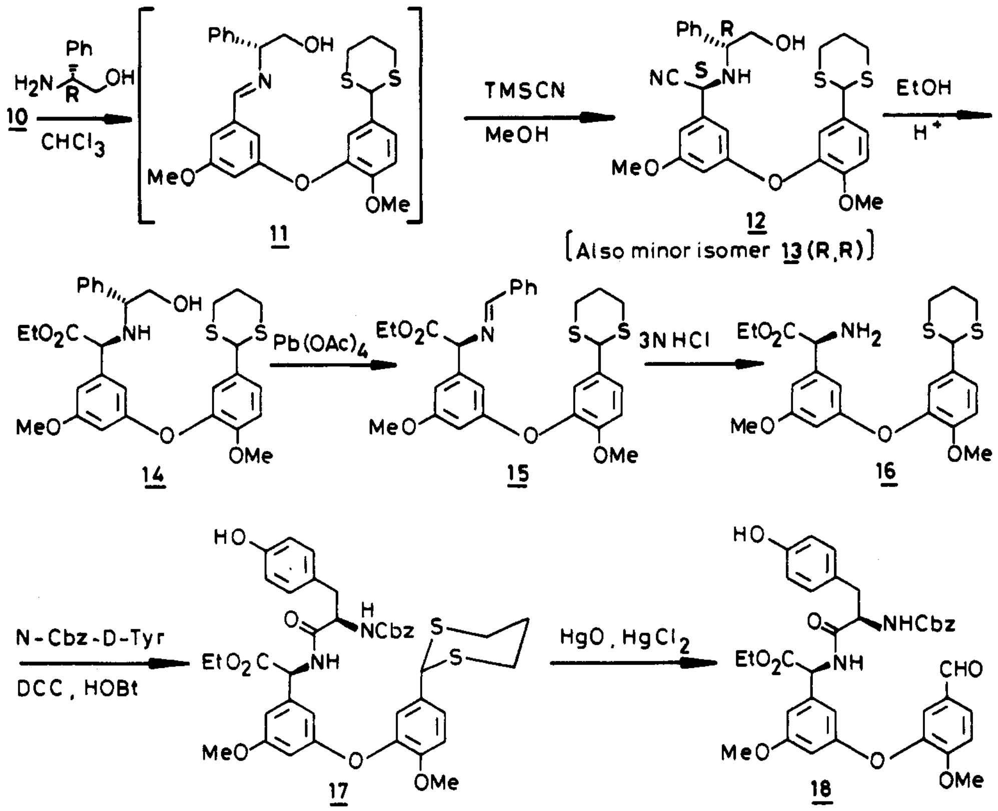
[8] Chakraborty, T. K.; Reddy, G. V.; Hussain, K. A. *Tetrahedron Lett.* **1991**, *32*, 7597.

[9] Proton numberings are the same as reported earlier for teicoplanin (see refs 2f and 2g).

[10] Waltho, J. P.; Williams, D. H. *J. Am. Chem. Soc.* **1989**, *111*, 2475.

[11] (a) Crimmin, M. J.; Brown, A. G. *Tetrahedron Lett.* **1990**, *31*, 2017. (b) Beringer, F. M.; Falk, R. A.; Karniol, M.; Lillien, I.; Masuello, G.; Mausner, M.; Sommer, E. *J. Am. Chem. Soc.* **1959**, *81*, 342.

Scheme II



on ring 1. The resulting (*E*)-imine **19** (Scheme III) was treated, in situ, with TMSCN in CHCl$_3$ to get a mixture of diastereomers, the ratio (1*R*,2*R*,3*S*)-**20**:(1*S*,2*R*,3*S*)-**21** being 89:11 (determined by ^{1}H NMR spectroscopy). The chloroform solution of the mixture was treated sequentially with an excess of trimethylsilyl ethanol (5–7 equiv) and dry ethereal HCl to give the corresponding (trimethylsilyl)ethyl esters which were separated by silica gel column chromatography to give (1*R*,2*R*,3*S*)-**22** as the major diastereomer. Removal of chiral auxiliary followed by Boc-protection of the resulting amine gave the advanced intermediate **25**.

Treatment of **25** with tetra-*n*-butylammonium fluoride gave the acid **26** (Scheme IV) which on coupling with pentafluorophenol using DCC gave the active ester **27**. Hydrogenation in the presence of hydrochloric acid gave the hydrochloride salt of amino acid **28**. Finally, a dioxane solution of **28** was added slowly under macrocyclization conditions to 1,4-dioxane (0.0003 M) having an excess of triethylamine at an elevated temperature.[12] The free amine reacted immediately with the active ester intramolecularly leading to the formation of the target 14-membered cyclic peptide **2**. The optical purity of **2** was confirmed unequivocally by ^{1}H NOE difference spectroscopy. The resultant interactions between hydrogen atoms through space are shown in Table I.

These results suggested the possible conformation of **2** as depicted in Figure 1. The configuration of amino acid 2, i.e., D-tyrosine unit, which is less likely to undergo any kind of epimerization was taken as reference in order to assign the absolute stereochemistries of amino acids 1 and 3.

Table I[a]

proton irradiated	resonance reduced (%)
1b	3f (6), X1 (7)
W2	1b (10), 3f (2), X1 (16)
X1	1b (7), W2 (4)
X3	3b (8), 3f (2)
W3	3f (9), X3 (3), X2 (11)
X2	W3 (7)

[a] ^{1}H NOE difference spectroscopic studies were done with a 10 mM solution of **2** in DMSO-d_6 (400 MHz).

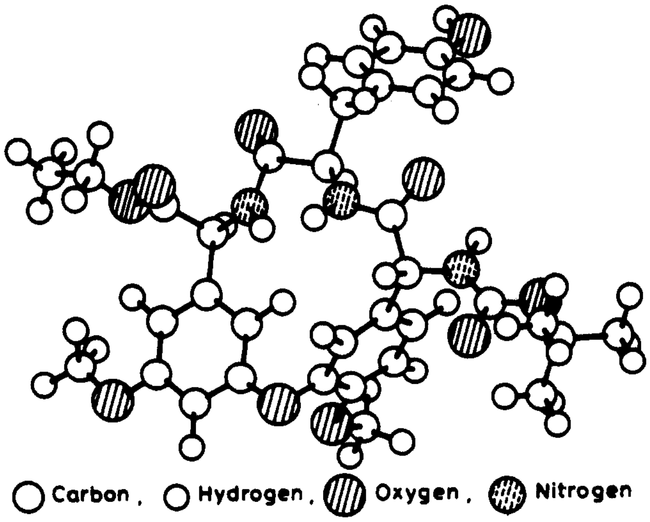


Figure 1. Ball and stick representation of **2**.

This stereostructure is slightly different from those reported for N-terminal rings of teicoplanin and ristocetin A.[10] Unlike the phenyl ring 3 which has the same orientation in both **2** and ristocetin A with a large NOE between X3 and 3b, the phenyl ring 1 in **2** has different orientation than that in ristocetin A. Whereas in the former the NOE is present only between X1 and 1b, the latter shows very small, albeit similar, NOEs between X1 ↔ 1b and X1 ↔ 1f. Further studies on the conformation of **2** in the

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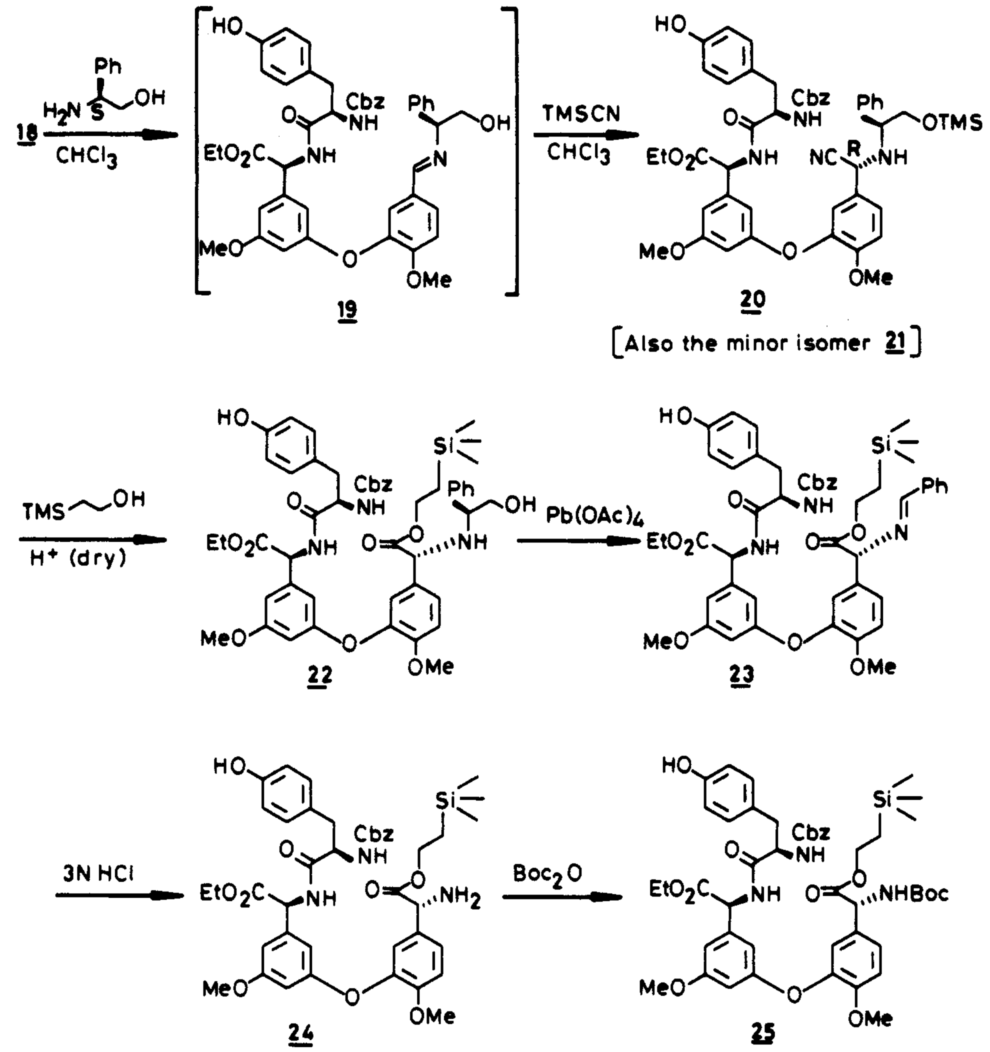
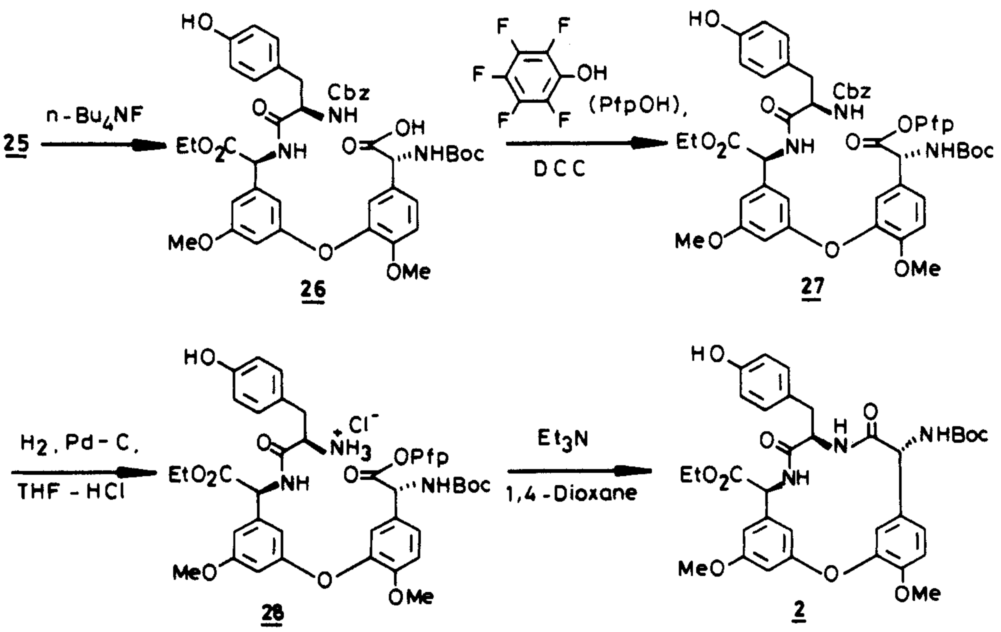
[12] Evans, D. A.; Ellman, J. A. *J. Am. Chem. Soc.* **1989**, *111*, 1063.

Scheme III



Scheme IV



presence of peptide analogues is presently underway.

Conclusion

The first stereocontrolled synthesis of the C-terminal 14-membered ring of glycopeptide antibiotic teicoplanin is described in this paper. The mild and simple procedure described here for the construction of α-arylglycines from α-aryl aldehydes will provide a means for the synthesis of optically pure phenylglycines in multifunctional molecules. The entire scheme presented here is devoid of any possible base-catalyzed epimerization and maintains optical purity throughout the synthesis. Finally, the conformation of the synthetic product is in conformity with the stereostructure of the parent teicoplanin as determined by NMR. The total synthesis of the parent antibiotic is now under progress.

Experimental Section

General Procedures. NMR spectra were recorded on Varian Gemini 200 and Varian Unity 400 instruments. IR spectra were recorded on Shimadzu IR-470 and Perkin-Elmer 283 B instruments. MS and HRMS were recorded on a Finnigan Mat 1210 spectrometer under electron impact (EI) or chemical ionization (CI) conditions. Elemental analyses were performed by IDPL, Hyderabad. Melting points were determined on a Fisher-Jons melting point apparatus and are uncorrected. Optical rotations were measured on a JASCO DIP-360 instrument.

All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25-mm E. Merck silica gel plates (60F-254) with UV light, I_2, and 7% methanolic phosphomolybdic acid–heat as developing agents. Acme, India, silica gel (finer than 200 mesh) was used for flash column chromatography.

All reactions were carried out under nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.

In the NMR signal assignments the teicoplanin numberings[9] were used.

3,5-Dihydroxybenzoic Acid Methyl Ester (4). A solution of **3** (5.0 g, 32.46 mmol) in methanol (40 mL) was treated with concentrated H_2SO_4 (0.5 mL) and refluxed for 5 h. After the methanol was removed in vacuo the residue was dissolved in ethyl acetate (100 mL). The ethyl acetate solution was washed successively with saturated $NaHCO_3$ solution (50 mL), water (50 mL), and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo to afford **4** (5.2 g, 96%) as a white solid, mp 168–170 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.09 (d, J = 2.2 Hz, 2 H, C2-*H* and C6-*H*), 6.57 (t, J = 2.2 Hz, 1 H, C4-*H*), 3.89 (s, 3 H, OCH_3). IR (KBr): ν_{max} 3560, 3050, 2910, 1710, 1590, 1320, 1280 cm^{-1}; MS (EI): *m/e* 168 (M^+). EIHRMS: *m/e* 168.0414 ($C_8H_8O_4$ requires 168.0422).

3-Hydroxy-5-methoxybenzoic Acid Methyl Ester (5). To a solution of **4** (5.00 g, 29.76 mmol) in dry acetone (40 mL) were added potassium carbonate (8.20 g, 59.42 mmol) and tetrabutylammonium iodide (1.10 g, 2.97 mmol) followed by the addition of dimethyl sulfate (3.80 g, 29.69 mmol). The reaction mixture was refluxed for 3 h, cooled to room temperature, and filtered. The filtrate was concentrated in vacuo. Column chromatography (SiO_2, 2–15% EtOAc in petroleum ether eluant) afforded **5** (3.50 g, 65%) as a white solid, mp 93–95 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.18 (brs, 1 H, aromatic), 7.16 (d, J = 2.2 Hz, 1 H, aromatic), 6.63 (t, J = 2.2 Hz, 1 H, C4-*H*), 3.9 (s, 3 H, OCH_3), 3.81 (s, 3 H, OCH_3); IR (KBr): ν_{max} 3555, 3050, 2910, 2890, 1712, 1570, 1320, 1290, 1280 cm^{-1}; MS (EI): *m/e* 182 (M^+). EIHRMS: *m/e* 182.0581 ($C_9H_{10}O_4$ requires 182.0578).

5,5′-Diformyl-2,2′-dimethoxydiphenyliodonium Bromide (6). An ice cold solution of concd H_2SO_4 (40 mL) and glacial acetic acid (60 mL) was added dropwise to a well-stirred mixture of potassium iodate (40 g, 186.91 mmol), anisaldehyde (76 g, 0.56 mmol), glacial acetic acid (180 mL), and acetic anhydride (90 mL), keeping the temperature of the reaction mixture below 3 °C. Stirring was continued for 3 h at the same temperature and then overnight at room temperature. The reaction mixture was then filtered, and the residue was washed with acetic acid (50 mL). The filtrate was diluted with water (3 L) and washed with ether (2 × 1 L). To the aqueous layer was then added a solution of potassium bromide (26.00 g, 187.00 mmol) in water (50 mL). The precipitate was filtered and washed successfully with methanol (4 × 200 mL) and acetone (2 × 200 mL) and dried in a vacuum desiccator to give **6** (70.0 g, 53%), mp 205 °C. ^1H NMR[11b] (DMSO-d_6, 200 MHz): δ 9.9 (s, 1 H, C*H*O), 8.71 (d, J = 1.9 Hz, 1 H, C6-*H*), 8.11 (dd, J = 8.6, 1.9 Hz, 1 H, C4-*H*), 7.41 (d, J = 8.6 Hz, 1 H, C3-*H*), 4.00 (s, 3 H, OMe). IR (Nujol): ν_{max} 2725, 1683, 1584, 1455, 1373, 1300, 1270, 1025, 1002 cm^{-1}.

3-(5-Formyl-2-methoxyphenoxy)-5-methoxybenzoic Acid Methyl Ester (7). A solution of **5** (10.00 g, 54.94 mmol) in dry DMF (200 mL) was added dropwise to a suspension of sodium hydride (1.45 g, 60.43 mmol) in dry DMF (100 mL) under nitrogen atmosphere. The mixture was stirred for 0.5 h at room temperature. Compound **6** (28.82 g, 60.43 mmol) was added to the reaction mixture and stirred for 3 h at 90 °C. After being cooled to room temperature, the reaction mixture was poured into water (500 mL) and extracted with ethyl acetate (3 × 400 mL). The combined ethyl acetate extracts were washed with water (2 × 400 mL) and saturated aqueous NaCl (1 × 200 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 50% petroleum ether in C_6H_6 to pure C_6H_6 to 3% EtOAc in C_6H_6 eluant) afforded **7** (8.50 g, 50%) as a syrupy liquid. Unreacted starting material (2.00 g, 20%) was also recovered. ^1H NMR ($CDCl_3$, 200 MHz): δ 9.81 (s, 1 H, C*H*O), 7.67 (dd, J = 8.4, 2.0 Hz, 1 H, 1f), 7.46 (d, J = 2.0 Hz, 1 H, 1b), 7.28 (brs, 1 H, 3f), 7.13 (brs, 1 H, 3b), 7.08 (d, J = 8.5 Hz, 1 H, 1e), 6.69 (t, J = 2.2 Hz, 1 H, 3d), 3.89 (s, 3 H, $COOCH_3$), 3.84 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3). IR ($CHCl_3$): ν_{max} 2910, 2850, 2745, 1720, 1692, 1600, 1585, 1425, 1270–1185, 1120, 1110, 1005, 880, 865, 660 cm^{-1}. MS (EI): *m/e* 316 (M^+). EIHRMS: *m/e* 316.0948 ($C_{17}H_{16}O_6$ requires 316.0948).

3-[5-(1,3-Dithian-2-yl)-2-methoxyphenoxy]-5-methoxybenzoic Acid Methyl Ester (8). To a solution of **7** (5.00 g, 15.82 mmol) in dry methylene dichloride (75 mL) was added at room temperature propane-1,3-dithiol (2.18 g, 20.57 mmol) under nitrogen atmosphere followed by the addition of boron trifluoride etherate (0.35 g, 2.45 mmol), and the reaction mixture was stirred for 0.5 h. Solid sodium bicarbonate (0.412 g, 4.90 mmol) was added to the reaction mixture, the clear solution was decanted, and the solvent was evaporated in vacuo. Column chromatography of the crude product (SiO_2, 5–20% EtOAc in petroleum ether eluant) afforded **8** (6.00 g, 95%) as a white solid, mp 147–149 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.30 (dd, J = 8.5, 2.2 Hz, 1 H, 1f) 7.28 (brs, 1 H, 3f), 7.2 (brs, 1 H, 3b), 7.15 (d, J = 2.2 Hz, 1 H, 1b), 6.98 (d, J = 8.5 Hz, 1 H, 1e), 6.70 (t, J = 2.4 Hz, 1 H, 3d), 5.09 (s, 1 H, SC*H*S), 3.89 (s, 3 H, $COOCH_3$), 3.82 (s, 6 H, OCH_3), 3.12–2.83 (m, 4 H, SCH_2), 2.14–1.75 (m, CH_2). IR ($CHCl_3$) ν_{max} 3050, 2910, 1720, 1570, 1320, 1285, 1140, 1018, 942, 810, 750 cm^{-1}. MS (EI): *m/e* 406 (M^+). EIHRMS: *m/e* 406.0908 ($C_{20}H_{22}O_5S_2$ requires 406.0908).

3-[5-(1,3-Dithian-2-yl)-2-methoxyphenoxy]-5-methoxybenzenemethanol (9). To a stirred solution of **8** (5.00 g, 12.31 mmol) in dry methylene chloride (70 mL) at −78 °C was slowly added DIBALH (1.4 M, 36 mL, 25.86 mmol) under nitrogen atmosphere. After 0.5 h the reaction mixture was brought to −20 °C, and methanol (3 mL) was added. It was then treated with 1 N HCl (60 mL) at 0 °C and stirred for 0.5 h. The organic layer was separated, and the aqueous layer was extracted with methylene chloride (2 × 60 mL). The combined organic extracts were washed with water (1 × 50 mL) and saturated aqueous NaCl (1 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to give **9** (4.20 g, 91%) as a white solid, mp 107 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 7.23 (dd, J = 8.5, 2.4 Hz, 1 H, 1f), 7.11 (d, J = 2.2 Hz, 1 H, 1b), 6.93 (d, J = 8.5 Hz, 1 H, 1e), 6.62 (brs, 1 H, 3f), 6.49 (brs, 1 H, 3b), 6.42 (t, J = 2.3 Hz, 1 H, 3d), 5.04 (s, 1 H, S-C*H*-S), 4.58 (d, J = 5.1 Hz, 2 H, CH_2OH), 3.81 (s, 3 H, OCH_3), 3.75 (s, 3 H, OCH_3), 3.07–2.80 (m, 4 H, SCH_2), 2.15–1.76 (m, 2 H, CH_2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 166.43, 160.57, 158.84, 151.35, 143.98, 132.15, 124.62, 121.02, 112.94, 110.51, 108.69, 107.94, 55.88, 55.60, 52.13, 50.31, 31.93, 24.91. IR (KBr): ν_{max} 3350, 2920, 2890, 2840, 1610, 1590, 1575, 1515, 1455, 1415, 1312, 1275, 1228, 1140, 1050, 1018, 982, 942, 823, 810, 750 cm^{-1}. MS (EI): *m/e* 378 (M^+). EIHRMS: *m/e* 378.0961 ($C_{19}H_{22}O_4S_2$ requires 378.0959).

3-[5-(1,3-Dithian-2-yl)-2-methoxyphenoxy]-5-methoxybenzaldehyde (10). To a solution of **9** (4.00 g, 10.58 mmol) in methylene chloride (100 mL) at 0 °C was added pyridinium chlorochromate (2.28 g, 10.58 mmol), and the solution was stirred for 1 h. The reaction mixture was filtered through a short pad of Celite, and the filtrate was concentrated in vacuo. Column chromatography (SiO_2, 1–10% EtOAc in petroleum ether eluant) afforded **10** (3.42 g, 86%) as a white solid, mp 123 °C. ^1H NMR ($CDCl_3$, 200 MHz): δ 9.87 (s, 1 H, C*H*O), 7.29 (dd, J = 8.4, 2.2 Hz, 1 H, 1f), 7.19 (d, J = 2.2 Hz, 1 H, 1b), 7.10 (d, J = 2.2 Hz, 1 H, 3f), 6.98 (d, J = 8.4 Hz, 1 H, 1e), 6.97 (d, J = 2.2 Hz, 1 H, 3b), 6.76 (t, J = 2.2 Hz, 1 H, 3d), 5.09 (s, 1 H, SC*H*S), 3.83 (s, 3

H, OCH_3), 3.81 (s, 3 H, OCH_3), 3.11–2.82 (m, 4 H, SCH_2), 2.19–1.85 (m, 2 H, CH_2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 191.20, 160.93, 159.37, 151.16, 143.14, 138.10, 132.02, 124.85, 121.12, 112.69, 110.29, 108.90, 107.20, 55.68, 55.39, 49.94, 31.66, 24.62. IR ($CHCl_3$): ν_{max} 2925, 2880, 2760, 1700, 1600, 1580, 1500, 1460, 1438, 1420, 1338, 1295, 1260–1190, 1145, 1000, 930, 840, 660 cm^{-1}. MS (EI): *m/e* 376 (M^+). EIHRMS: *m/e* 376.0801 ($C_{19}H_{20}O_4S_2$ requires 376.0803).

***N*-[(*R*)-2-Hydroxy-1-phenylethyl]-(*S*)-*α*-amino-3-[5-(1,3-dithian-2-yl)-2-methoxyphenoxy]-5-methoxybenzeneacetonitrile (12).** To a solution of 10 (3.40 g, 9.04 mmol) in dry chloroform (90 mL) was added (*R*)-phenylglycinol (1.36 g, 9.95 mmol) under nitrogen atmosphere, and the solution was stirred for 5 h at room temperature. To the resulting intermediate imine was added methanol (3 mL) followed by trimethylsilyl cyanide (1.16 g, 11.75 mmol), and the mixture was stirred for 3 h. Concentration of the reaction mixture in vacuo followed by column chromatography (SiO_2, 1–12% EtOAc in petroleum ether eluant) afforded the required isomer 12 (3.16 g, 67%) and its isomer 13 (1.13 g, 24%) as syrupy liquids. ^{1}H NMR of 12 ($CDCl_3$, 200 MHz): δ 7.41–7.34 (m, 5 H, Ph), 7.30 (dd, J = 8.4, 2.2 Hz, 1 H, 1f), 7.17 (d, J = 2.2 Hz, 1 H, 1b), 6.97 (d, J = 8.2 Hz, 1 H, 1e), 6.78 (brs, 1 H, 3f), 6.73 (brs, 1 H, 3b), 6.48 (t, J = 2.3 Hz, 1 H, 3d), 5.10 (s, 1 H, SC*H*S), 4.43 (s, 1 H, ×3), 4.23 (dd, J = 9.0, 4.1 Hz, 1 H, PhC*H*(NH)CH_2OH), 3.83 (s, 3 H, OCH_3), 3.81–3.65 (m, 2 H, CH_2OH), 3.77 (s, 3 H, OCH_3), 3.11–2.84 (m, 4 H, SCH_2), 2.17–1.85 (m, 2 H, CH_2). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 131.91, 128.66, 127.47, 124.37, 120.65, 118.27, 112.63, 108.02, 106.94, 102.75, 66.83, 62.94, 55.75, 55.27, 53.34, 51.45, 50.04, 31.70, 24.66. IR ($CHCl_3$): ν_{max} 3550–3280, 2930, 2880, 2255, 1600, 1580, 1520, 1455, 1420, 1270–1190, 1140, 1105, 910, 660 cm^{-1}.

***N*-[(*R*)-2-Hydroxy-1-phenylethyl]-(*S*)-*α*-amino-3-[5-(1,3-dithian-2-yl)-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (14).** To a solution of 12 (3.10 g, 5.94 mmol) in ethanol (50 mL) was added dry ethereal HCl (15 mL), and the solution was stirred for 5 h at room temperature under nitrogen atmosphere. Ethanol was removed in vacuo, and the residue was neutralized with an excess of phosphate buffer (0.2 M, pH 7) and extracted with chloroform (2 × 50 mL). The organic layer was washed with water (1 × 50 mL) and saturated aqueous NaCl (1 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 5–12% EtOAc in petroleum ether eluant) afforded 14 (3.00 g, 90%) as a white solid, mp 45 °C. $[\alpha]^{22}{}_D$: +11.85° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.28 (s, 5 H, Ph), 7.22 (dd, J = 8.5, 2.2 Hz, 1 H, 1f), 7.10 (d, J = 2.2 Hz, 1 H, 1b), 6.92 (d, J = 8.5 Hz, 1 H, 1e), 6.55 (brs, 2 H, 3b and 3f), 6.38 (t, J = 2.2 Hz, 1 H, 3d), 5.04 (s, 1 H, SC*H*S), 4.23–4.09 (m, 4 H, OCH_2, X3 and PhC*H*(NH)CH_2OH), 3.80 (s, 3 H, OCH_3), 3.77–3.56 (m, 2 H, CH_2OH), 3.7 (s, 3 H, OCH_3), 3.07–2.78 (m, 4 H, SCH_2), 2.36 (brs, 2 H, N*H*, O*H*), 2.16–1.81 (m, 2 H, SCH_2), 1.17 (t, J = 7.3 Hz, 3 H, CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 172.94, 160.69, 158.71, 151.11, 144.21, 140.52, 139.69, 131.80, 128.44, 128.01, 127.38, 124.08, 120.48, 112.62, 108.56, 107.05, 102.43, 66.97, 62.98, 62.42, 61.09, 55.84, 55.21, 50.26, 31.83, 24.77, 13.98. IR (KBr): ν_{max} 3500–3250, 2950, 2920, 1710, 1600, 1580, 1505, 1455, 1265, 1182, 1138, 1010, 830, 760, 700 cm^{-1}. MS (EI): *m/e* 538 (fragment ion, $M^+ - CH_2OH$). EIHRMS: *m/e* 538.1708 ($C_{30}H_{35}NO_6S_2 - CH_2OH$ requires 538.1722).

(*S*)-*α*-Amino-3-[5-(1,3-dithian-2-yl)-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (16). Lead tetraacetate (2.80 g, 6.33 mmol) was added to a solution of 14 (3.00 g, 5.27 mmol) in methylene chloride–methanol (2:1, 55 mL) at 0 °C, and the reaction mixture was stirred for 5 min at the same temperature. To this reaction mixture was added phosphate buffer (0.2 m, 50 mL, pH 7), and the mixture was stirred for 0.5 h at room temperature. The reaction mixture was then filtered through Celite, and the organic layer was separated. The aqueous layer was extracted with methylene chloride (2 × 50 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo to afford the crude imine 15 which was dissolved in ether (50 mL) and treated with 3 N HCl (50 mL). The reaction mixture was stirred for 15 min at room temperature. The aqueous layer was separated and washed with ether (2 × 50 mL). Water was removed in vacuo to give the hydrochloride salt of 16 which was neutralized with phosphate buffer (0.2 M, pH 7) and extracted with ethyl acetate (2 × 50 mL). The combined organic extracts were washed with water (1 × 50 mL) and saturated aqueous NaCl (1 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo to get 16 (1.77 g, 75%) as a syrupy liquid which was subjected to the following reaction without further purification.

***N*-[*N*-[(Phenylmethoxy)carbonyl]-D-tyrosyl]-(*S*)-*α*-amino-3-[5-(1,3-dithian-2-yl)-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (17).** To a solution of *N*-Cbz-D-tyrosine (1.49 g, 4.73 mmol) in dry DMF (10 mL) was added 1-hydroxybenzotriazole hydrate (1.06 g, 7.88 mmol) under nitrogen atmosphere. The reaction mixture was cooled to 0 °C followed by the addition of 1,3-dicyclohexylcarbodiimide (1.22 g, 5.91 mmol). After the mixture was stirred for 30 min a solution of crude 16 (1.77 g, 3.94 mmol) in DMF (25 mL) was added at 0 °C and stirring was continued for 1.5 h at room temperature. The reaction mixture was then poured into water (80 mL) and extracted with ethyl acetate (4 × 100 mL). The ethyl acetate extracts were washed with water (2 × 100 mL) and saturated aqueous NaCl (1 × 100 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 1–10% EtOAc in $CHCl_3$ eluant) afforded 17 (2.2 g, 75%) as a white solid, mp 70 °C. $[\alpha]^{22}{}_D$: +26.46° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.34 (s, 5 H, Ph), 7.25 (dd, J = 8.3, 2.2 Hz, 1 H, 1f), 7.11 (d, J = 2.2 Hz, 1 H, 1b), 6.99 (d, J = 8.5 Hz, 1 H, 1e), 6.85 (d, J = 8.3 Hz, 2 H, 2b and 2f), 6.62 (d, J = 8.5 Hz, 2 H, 2c and 2e), 6.54 (brs, 1 H, 3f), 6.39 (t, J = 2.2 Hz, 1 H, 3d), 6.28 (brs, 1 H, 3b), 6.33 (brs, 1 H, phenolic O*H*), 6.17 (brs, 1 H, N*H*Cbz), 5.57 (d, J = 7.4 Hz, 1 H, CON*H*), 5.4 (d, J = 7.4 Hz, 1 H, X3), 5.11 (s, 2 H, CH_2Ph), 5.05 (s, 1 H, SC*H*S), 4.39–4.30 (m, 1 H, ×2), 4.26–4.08 (m, 2 H, CH_3CH_2), 3.89 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.08–2.80 (m, 6 H, SCH_2, Z2, Z2′), 2.72–1.82 (m, 2 H, –CH_2–), 1.21 (t, J = 7.2 Hz, –CH_2CH_3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 170.41, 169.98, 160.82, 158.78, 155.81, 155.15, 150.88, 144.14, 138.05, 136.02, 132.17, 130.13, 128.34, 127.83, 127.32, 123.08, 124.26, 120.37, 115.62, 112.79, 108.52, 107.67, 102.97, 66.91, 61.96, 55.11, 55.91, 55.29, 50.24, 37.93, 31.84, 24.76, 14.04, 13.83. IR (KBr): ν_{max} 3500–3150, 2900, 1730, 1715, 1700, 1680, 1670, 1610, 1600, 1510, 1460, 1260, 1210, 1200, 1140, 1055, 1020, 830, 760, 692 cm^{-1}.

Anal. Calcd for $C_{39}H_{42}N_2O_9S_2$: C, 62.72; H, 5.67; N, 3.75. Found: C, 62.61; H, 5.62; N, 3.72.

***N*-[*N*-[(Phenylmethoxy)carbonyl]-D-tyrosyl]-(*S*)-*α*-amino-3-[5-formyl-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (18).** Mercuric oxide (0.216 g, 2.00 mmol) and mercuric chloride (0.569 g, 2.10 mmol) were added to a solution of 17 (0.746 g, 1.00 mmol) in acetonitrile–water (85:15, 40 mL) and stirred for 2 h at room temperature. The reaction mixture was filtered through Celite. The filtrate was concentrated in vacuo. The residue was taken in chloroform (50 mL) and washed with water (40 mL). The aqueous layer was extracted once again with $CHCl_3$ (30 mL). The combined organic extracts were washed with saturated aqueous NaCl (1 × 50 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 5–10% EtOAc in $CHCl_3$ eluant) afforded 18 (0.557 g, 85%) as a white solid, mp 63 °C. $[\alpha]^{22}{}_D$: +32.51° (*c* 1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 9.81 (s, 1 H, C*H*O), 7.67 (dd, J = 8.5, 2.0 Hz, 1 H, 1f), 7.46 (d, J = 2.0 Hz, 1 H, 1b), 7.35 (s, 5 H, Ph), 7.14 (d, J = 8.5 Hz, 1 H, 1e), 6.86 (d, J = 8.3 Hz, 2 H, 2b and 2f), 6.62 (d, J = 8.6 Hz, 2 H, 2c and 2e), 6.58 (d, J = 1.9 Hz, 1 H, 3f), 6.47 (t, J = 2.1 Hz, 1 H, 3d), 6.31 (brs, 2 H, 3b and C_6H_4O*H*), 6.17–6.14 (brs, 1 H, N*H*Cbz), 5.5 (d, J = 7.2 Hz, 1 H, W3), 5.37 (d, J = 7.2 Hz, 1 H, X3), 5.11 (s, 2 H, PhCH_2), 4.40–4.31 (m, 1 H, X2), 4.24–4.11 (m, 2 H, C$H_2$$CH_3$), 3.99 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.09–3.02 (dd, J = 14.0, 7.9 Hz, 1 H, Z2), 2.85–2.81 (dd, J = 14.0, 9.1 Hz, 1 H, Z2′), 1.19 (t, J = 7.2, 3 H, CH_2CH_3); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 190.73, 170.36, 170.04, 161.06, 157.97, 156.17, 155.86, 155.15, 145.78, 138.46, 136.08, 130.21, 129.00, 128.47, 128.10, 127.93, 127.23, 119.17, 115.68, 112.15, 109.18, 108.47, 104.22, 67.02, 62.13, 56.27, 56.17, 55.48, 38.14, 13.89. IR (KBr): ν_{max} 3500–3200, 2950, 2880, 2760, 1738, 1720, 1695, 1690, 1675, 1600, 1510, 1460, 1435, 1275, 1220, 1180, 1160, 1110, 1035, 1020, 815, 740, 695, 660 cm^{-1}. MS (EI): *m/e* 548 (fragment ion, $M^+ - PhCH_2OH$).

Anal. Calcd for $C_{36}H_{36}N_2O_{10}$: C, 65.84; H, 5.53; N, 4.27. Found: C, 65.69; H, 5.50; N, 4.26.

***N*-[*N*-[(Phenylmethoxy)carbonyl]-D-tyrosyl]-(*S*)-*α*-amino-3-methoxy-5-[2-methoxy-5-[*N*-[(*S*)-1-phenyl-2-[(trimethylsilyl)oxy]ethyl]-(*R*)-*α*-amino-*α*-cyanomethyl]phen-**

oxy]benzeneacetic Acid Ethyl Ester (20). To a solution of **18** (1.00 g, 1.52 mmol) in dry chloroform (15 mL) under nitrogen atmosphere was added (*S*)-phenylglycinol (0.230 g, 1.67 mmol), and the reaction was stirred for 24 h at room temperature. To the resulting imine (**19**) was added trimethylsilyl cyanide (0.226 g, 2.29 mmol), and the solution was stirred for 24 h at room temperature. The reaction mixture was concentrated in vacuo to afford crude **20** and **21** (1.3 g). The diastereomeric mixture (89:11 of **20**:**21** as determined by ^{1}H NMR of the crude mixture) was used as such for the next step.

_N_-[_N_-[(Phenylmethoxy)carbonyl]-D-tyrosyl]-(_S_)-α-amino-3-[5-[_N_-[(_S_)-2-hydroxy-1-phenylethyl]-(_R_)-α-amino-α-[[[(trimethylsilyl)ethyl]oxy]carbonyl]methyl]-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (22). To a solution of a diastereomeric mixture of **20** and **21** (0.665 g, 0.76 mmol) in chloroform (3 mL) under nitrogen atmosphere was added sequentially (trimethylsilyl)ethanol (0.630 mg, 5.30 mmol) and saturated ethereal HCl (3 mL). The reaction mixture was stirred for 3 h at room temperature. Chloroform was removed in vacuo, and ether (10 mL) was added, stirred, and decanted to remove excess (trimethylsilyl)ethanol. The resulting hydrochloride salt was neutralized with an excess of phosphate buffer (0.2 M, pH 7) and extracted with chloroform (2 × 25 mL). The combined chloroform extracts were washed with water (1 × 25 mL) and saturated aqueous NaCl (1 × 25 mL), dried (Na_2SO_4), and concentrated in vacuo. Column chromatography (SiO_2, 10–20% EtOAc in $CHCl_3$ eluant) afforded **22** (0.365 g, 52%) as a white solid in diastereomerically pure form, mp 58 °C. The other minor diastereomer was also isolated (0.049 g, 6.4%), mp 57 °C. Data for **22**. $[\alpha]^{22}{}_{D}$: +25.19° (*c* 1.3, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 9.17 (s, 1 H, C_6H_4OH), 8.9 (d, *J* = 7.5 Hz, 1 H, W3), 7.43 (d, *J* = 8.8 Hz, 1 H, N*H*Cbz), 7.32–7.22 (m, 10 H, 2 Ph), 7.1 (s, 3 H, 2b, 2f and 1b), 7.04 (s, 1 H, 1f), 6.98 (s, 1 H, 1e), 6.64 (s, 2 H, 2c and 2e), 6.60 (s, 1 H, 3f), 6.45 (s, 1 H, 3b), 6.29 (t, *J* = 2.2 Hz, 1 H, 3d), 5.34 (d, *J* = 7.4 Hz, 1 H, X3), 5.03 (t, *J* = 5.2 Hz, 1 H, PhC*H*(NH)CH_2OH), 4.93 (s, 2 H, PhCH_2O-), 4.34 (ddd, *J* = 14.3, 8.8, 3.5 Hz, 1 H, X2), 4.19–3.96 (m, 5 H, CH_2CH_2TMS, CH_2CH_3, X1), 3.69 (s, 6 H, 2-OCH_3), 3.39 (m, 2 H, –CH_2OH), 3.11 (d, *J* = 11 Hz, 1 H, N*H*CH(Ph)CH_2OH), 2.79 (dd, *J* = 14.3, 3.5 Hz, Z2), 2.59 (dd, *J* = 14.3, 12.5 Hz, 1 H, Z2′), 1.08 (t, *J* = 7.1, 3 H, –CH_3), 0.86 (t, *J* = 8.3 Hz, 2 H, CH_2TMS). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 175.23, 171.88, 171.66, 162.56, 160.40, 157.39, 156.81, 152.53, 145.90, 141.11, 139.80, 137.80, 132.98, 131.83, 130.23, 130.05, 129.52, 129.15, 128.78, 125.93, 121.27, 117.35, 114.47, 110.12, 108.99, 104.86, 68.59, 65.43, 64.77, 64.50, 63.64, 63.39, 57.82, 57.64, 57.00, 39.97, 31.25, 18.81, 15.51, –0.01. IR (KBr): ν_{max} 3450–3200, 2920, 1720, 1718, 1670, 1660, 1505, 1450, 1265, 1140, 1058, 1020, 835, 760, 700 cm^{-1}.

Anal. Calcd for $C_{50}H_{59}N_3O_{12}Si$: C, 65.12; H, 6.45; N, 4.56. Found: C, 65.01; H, 6.47; N, 4.57.

_N_-[_N_-[(Phenylmethoxy)carbonyl]-D-tyrosyl]-(_S_)-α-amino-3-[5-[(_R_)-amino[[[(trimethylsilyl)ethyl]oxy]carbonyl]methyl]-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (24). Lead tetraacetate (0.208 g, 0.469 mmol) was added to an ice-cold solution of **22** (0.360 g, 0.39 mmol) in methylene chloride and methanol (2:1, 4 mL), and the reaction mixture was stirred for 5 min at the same temperature. To the reaction mixture was added aqueous phosphate buffer (0.2 M, 4 mL, pH 7), and the mixture was stirred for 0.5 h at room temperature. The reaction mixture was filtered through Celite, and the organic layer was separated. The aqueous layer was extracted with methylene chloride (2 × 10 mL). The combined organic extracts were concentrated in vacuo to give the crude imine **23** which was subjected to hydrolysis as such.

To a solution of **23** in ether (5 mL) was added 3 N HCl (4 mL), and the reaction mixture was stirred for 15 min at room temperature. The aqueous layer was separated and washed with ether (2 × 10 mL). Water was removed in vacuo to afford a hydrochloride salt, which was neutralized with an excess of aqueous phosphate buffer (0.2 M, pH 7) and extracted with ethyl acetate (2 × 20 mL) and saturated aqueous NaCl (1 × 20 mL), dried (Na_2SO_4), and concentrated in vacuo to get further reaction without purification.

_N_-[_N_-[(Phenylmethoxy)carbonyl]-D-tyrosyl]-(_S_)-α-amino-3-[5-[(_R_)-_N_-[(1,1-dimethylethoxy)carbonyl]amino[[[(trimethylsilyl)ethyl]oxy]carbonyl]methyl]-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (25). To a solution of **24** (0.205 g, 0.256 mmol) in methylene chloride (5 mL) was added di-*tert*-butyl dicarbonate (0.067 g, 0.307 mmol), and the reaction mixture was stirred for 3 h at room temperature. Methylene chloride was removed in vacuo. Column chromatography (SiO_2, $CHCl_3$) afforded **25** (0.185 g, 80%) as a white solid, mp 69 °C. $[\alpha]^{27}{}_{D}$: +2.76° (*c* 0.65, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 200 MHz): δ 9.17 (s, 1 H, C_6H_4OH), 8.90 (d, *J* = 7.3 Hz, 1 H, W3), 7.71 (d, *J* = 8.0 Hz, 1 H, W1), 7.44 (d, *J* = 9.2 Hz, 1 H, W2), 7.32–7.05 (m, 10 H, Ph, 2b, 2f, 1b, 1e, and 1f), 6.65 (s, 2 H, 2c and 2e), 6.61 (s, 1 H, 3f), 6.49 (s, 1 H, 3b), 6.29 (s, 1 H, 3d), 5.34 (d, *J* = 7.3 Hz, 1 H, X3), 5.09 (d, *J* = 8.0 Hz, 1 H, X1), 4.94 (s, 2 H, PhCH_2), 4.36 (m, 1 H, X2), 4.14–4.06 (m, 4 H, –OCH_2CH_3, –OCH_2CH_2TMS), 3.70 (s, 3 H, –OCH_3), 3.69 (s, 3 H, OCH_3), 2.80 (dd, *J* = 10.5, 3.5 Hz, 1 H, Z2), 2.60 (dd, *J* = 12.0, 10.5 Hz, 1 H, Z2′), 1.37 (s, 9 H, Boc), 1.11 (t, *J* = 7 Hz, 3 H, –CH_2CH_3), 0.84 (t, *J* = 8.2 Hz, –CH_2TMS), –0.05 (s, 9 H, TMS). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 176.87, 176.08, 175.14, 165.55, 164.10, 160.89, 160.27, 156.29, 147.55, 143.86, 142.16, 135.32, 134.45, 133.36, 132.99, 132.72, 132.43, 130.71, 126.71, 119.88, 112.64, 111.71, 106.66, 83.60, 70.23, 68.07, 66.19, 62.08, 61.23, 61.04, 60.86, 60.40, 42.06, 33.25, 21.74, 18.99, 3.54. IR (KBr): ν_{max}, 3552–3250, 2960, 1740, 1720, 1700, 1685, 1675, 1600, 1510, 1370, 1340, 1265, 1250, 1155, 1055, 1005, 858, 838, 695 cm^{-1}.

Anal. Calcd for $C_{47}H_{59}N_3O_{13}Si$: C, 62.58; H, 6.59; N, 4.66. Found: C, 62.41; H, 6.54; N, 4.64.

_N_-[_N_-[(Phenylmethoxy)carbonyl]-D-tyrosyl]-(_S_)-α-amino-3-[5-[(_R_)-_N_-[(1,1-dimethylethoxy)carbonyl]aminocarboxymethyl]-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (26). To a solution of **25** (0.185 g, 205 mmol) in THF (10 mL) was added tetra-*n*-butylammonium fluoride (1.0 M soln in THF, 0.246 mL), and the solution was stirred at room temperature for 0.5 h. The reaction mixture was poured into aqueous HCl (10%, 5 mL) and extracted with ethyl acetate (3 × 10 mL). The combined extracts were washed with saturated aqueous NaCl (10 mL), dried (Na_2SO_4), and concentrated in vacuo. Short silica gel column chromatography (3% MeOH in $CHCl_3$ eluant) afforded **26** (0.148 g, 90%) which was subjected to esterification without characterization.

_N_-[_N_-[(Phenylmethoxy)carbonyl]-D-tyrosyl]-(_S_)-α-amino-3-[5-[(_R_)-_N_-[(1,1-dimethylethoxy)carbonyl]amino[(pentafluorophenoxy)carbonyl]methyl]-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester (27). To an ice-cooled solution of **26** (0.150 g, 0.187 mmol) and pentafluorophenol (0.069 g, 0.374 mmol) in dry methylene chloride (7 mL) was added 1,3-dicyclohexylcarbodiimide (0.058 g, 0.280 mmol), and the reaction mixture was stirred for 1 h at room temperature. Methylene chloride was removed in vacuo. Short column chromatography (SiO_2, $CHCl_3$) afforded **27** (0.145 g, 80%) as a white solid which without characterization was used in the next step.

_N_-D-Tyrosyl-(_S_)-α-amino-3-[5-[(_R_)-_N_-[(1,1-dimethylethoxy)carbonyl]amino[(pentafluorophenoxy)carbonyl]methyl]-2-methoxyphenoxy]-5-methoxybenzeneacetic Acid Ethyl Ester Hydrochloride (28). Palladium on activated charcoal (10%, 30 mg) was added to a solution of **27** (0.145 g, 0.150 mmol) in THF (6 mL). Aqueous HCl (10%, 245 μL, 0.30 mmol) was added, and the mixture was stirred for 3 h at room temperature under an atmosphere of hydrogen. The reaction mixture was filtered through Celite and washed with THF (10 mL). The filtrate was concentrated in vacuo, and the residue was dried thoroughly under vacuum. The crude amine hydrochloride salt **28**, without purification, was subjected to macrocyclization.

Cyclization of 28 to 2. The crude amine hydrochloride **28** (0.150 mmol) was dissolved in dry 1,4-dioxane (10 mL) and slowly added over 15 h using syringe pump to a preheated (90 °C) solution of triethylamine (0.104 mL, 0.750 mmol) in 1,4-dioxane (500 mL). The reaction mixture was stirred for an additional 1 h at 90 °C. The reaction mixture was concentrated in vacuo to a volume of 10 mL, poured over 10 mL of 10% aqueous HCl, and extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with saturated aqueous NaCl (20 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was purified by column chromatography (SiO_2, 0–20% EtOAc in $CHCl_3$) to give the desired **2** (0.048 g, 50%) as a white solid, mp 245 °C dec. $[\alpha]^{22}{}_{D}$: –3.7° (*c* 0.7, $CHCl_3$). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.16 (s, 1 H, C_6H_4OH), 9.01 (d, *J* = 7 Hz, 1 H, W3), 8.69 (d, *J* =

8.8 Hz, 1 H, W2), 7.31 (s, 1 H, 1b), 7.15 (d, J = 8.6 Hz, 1 H, 1f), 7.06 (d, J = 8.7 Hz, 1 H, 1e), 6.93 (d, J = 8.3 Hz, 2 H, 2b and 2f), 6.85 (d, J = 8.2 Hz, 1 H, W1), 6.70 (t, J = 2.1 Hz, 1 H, 3d), 6.61 (s, 1 H, 3b), 6.60 (d, J = 8.5 Hz, 2 H, 2c and 2e), 6.22 (s, 1 H, 3f), 5.31 (d, J = 7 Hz, 1 H, X3), 5.18 (d, J = 8.2 Hz, 1 H, X1), 4.63 (ddd, J = 10.0, 8.8, 5.2 Hz, 1 H, X2), 4.01 (m, 2 H, $-OCH_2CH_3$), 3.76 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 2.84 (dd, J = 13.6, 10.0 Hz, 1 H, Z2), 2.55 (dd, J = 13.6, 5.2 Hz, 1 H, Z2′), 1.37 (s, 9 H, Boc), 1.08 (t, J = 7.0 Hz, CH_2CH_3). ^{13}C NMR (DMSO-d_6, 50 MHz): δ 169.69, 169.51, 168.89, 160.60, 159.05, 155.72, 154.32, 149.90, 142.75, 140.84, 131.80, 129.90, 127.48, 121.31, 120.28, 114.97, 112.96, 108.56, 103.51, 102.69, 78.37, 61.31, 55.84, 55.72, 55.49, 53.44, 36.81, 28.13, 13.81. IR (KBr): ν_{max} 3500–3200, 3000, 1740, 1695, 1670, 1630, 1620, 1590, 1520, 1375, 1275, 1142, 1130, 1060, 1040, 870, 845, 690 cm^{-1}. MS (EI): m/e 549 (fragment ion, M^+ – Boc).

Anal. Calcd for $C_{34}H_{39}N_3O_{10}$: C, 62.85; H, 6.05; N, 6.47. Found: C, 62.80; H, 6.00; N, 6.49.

Acknowledgment. We thank Dr. Rama Rao for his keen interest and encouragement. We also thank Dr. J. A. R. P. Sharma for helping us to draw the ball and stick representation of 2.

Registry No. **1**, 61036-62-2; **2**, 143145-51-1; **3**, 99-10-5; **4**, 2150-44-9; **5**, 19520-74-2; **6**, 129866-90-6; **7**, 143145-52-2; **8**, 143145-53-3; **9**, 143145-54-4; **10**, 143145-55-5; **11**, 143145-56-6; **12**, 143145-57-7; **13**, 143145-58-8; **14**, 143145-58-8; **15**, 143145-60-2; **16**, 143145-61-3; **17**, 143145-62-4; **18**, 143145-63-5; **19**, 143145-64-6; **20**, 143145-65-7; **21**, 143234-79-1; **22**, 143145-66-8; **23**, 143145-67-9; **24**, 143145-68-0; **25**, 143171-01-1; **26**, 143145-69-1; **27**, 143145-70-4; **28**, 143171-02-2; Z-D-Tyr-OH, 20989-17-7; 4-$MeOC_6H_4CHO$, 123-11-5; $HS(CH_2)_3SH$, 109-80-8; $Me_3SiCH_2CH_2OH$, 2916-68-9; (R)-$H_2NCH(Ph)CH_2OH$, 56613-80-0; (S)-$H_2NCH(Ph)CH_2OH$, 64205-12-5.

Supplementary Material Available: ^1H NMR spectra of **4–9** and **12** and both ^1H and ^{13}C NMR spectra of **10**, **14**, **17**, **18**, **22**, **25**, and **2** (21 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

Aluminoxy Acetals from α-Amino Esters: Chirality Transfer via Sequential Addition of Hydride and C-Nucleophiles. 2-Amino Alcohols and Sphingosines[†]

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Received February 26, 1992 (Revised Manuscript Received July 6, 1992)

The reaction of α-imino esters (O'Donnell's Schiff bases) with aluminum hydrides to produce acetal-like intermediates and subsequent reaction with carbon nucleophiles has been studied. Treatment of optically pure imine-protected amino esters with iBu_2AlH or $iBu_2AlH{\cdot}Bu_3Al$, followed by RMgX or RLi provided *threo*-2-amino alcohols in high yield (73–85%) and excellent "*syn*" stereoselectivity (8:1 to >20:1, *threo* or *like* product preferred). Use of nonpolar solvents (CH_2Cl_2–hexane) provided the highest stereoselectivities. Use of the less-reactive $iBu_2AlH{\cdot}iBu_3Al$ complex lowered the amount of undesired primary alcohol products observed. Thermally labile aluminoxy acetal intermediates were observed by ^1H NMR and were trapped with N-(trimethylsilyl)imidazole to produce relatively stable monosilyl acetals (mixed acetals). Alanine-derived Schiff bases **2a–e** showed a correlation between the steric bulk of the ester and *threo* selectivity. The presence of THF reduced this correlation, suggesting the C-nucleophile addition involves a Lewis acid-assisted S_N2-like displacement of the aluminoxy acetal or displacement of a tight-ion pair. In addition to the synthesis of optically pure arylethanolamines **6a–d** from representative amino acids, *threo*-sphingosines **8a–d** were synthesized from L-serine-derived Schiff base **4b**, and 1-deoxy-*threo*-sphingosines **9a–d** were synthesized from L-alanine in a similar fashion. Experimental details are provided.

Introduction

As part of our program for the development of methods for the synthesis of complex carbohydrates, we became interested in the synthesis of sphingosines (Scheme I). Sphingosines[2] and their derivatives (cf. ceramides, cerebrosides, glycosphinolipids, gangliosides, and their *lyso* derivatives)[3] are known to play diverse roles in many biological systems. Glycosphingolipids influence cell metabolism in vertebrates, as well as in lower organisms (fungi).[7c] Galactosyl ceramide has recently been shown to be a receptor for HIV binding in cells lacking the CD4 receptor.[4e] Analogs of glycosphingolipids have been the subject of much interest as inhibitors of influenza-induced sialidase activity, as well as endoglycoceramidase inhib-

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[†] This paper is dedicated to Professor Gilbert J. Stork on the occasion of his 70th birthday.

[‡] University of Arizona Undergraduate Biology Research Program participant, funded in part by a grant from the Howard Hughes Medical Institute.

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