to give three components. The fastest moving band gave 9-oxotylocrebrine (**30**) (3 mg, 4.3%) as a pale yellow powder: mp 207 °C dec; ^{1}H NMR (100 MHz) δ 3.85 (s, 3 H), 4.02 (s, 3 H), 4.04 (s, 3 H), 4.06 (s, 3 H), no other signals were clearly assigned because of insufficiency of the sample in quantity; mass spectrum, *m/e* (relative intensity) 407 (M^+, 100), 392 (20), 338 ($M^+ - C_4H_7N$, 17), 310 (13), 295 (11), 248 (15), 221 (12), 295 (13), 168 (49), 165 (52), 164 (28), 151 (50).

The second component obtained from the middle band was recrystallized from chloroform–hexane to give 9-oxoisotylocrebrine (**29**) (17 mg, 24%) as colorless crystals: mp 237–238 °C dec; IR ($CHCl_3$) 1620 cm^{-1}; ^{1}H NMR (100 MHz) δ ~1.5–2.4 (unresolved, 4 H), 2.81 (dd, 1 H, *J* = 16, 13 Hz), 3.52 (dd, 1 H, *J* = 16, 4 Hz), ~3.7–4.1 (m, 3 H) with s (3 H) at δ 3.77, s (6 H) at δ 3.96, and s (3 H) at δ 3.98), 7.71 (d, 1 H, *J* = 10 Hz), 7.74 (d, 1 H, *J* = 10 Hz), 8.78 (s, 1 H), 9.12 (s, 1 H); mass spectrum, *m/e* (relative intensity) 407 (M^+, 100), 392 (17), 338 ($M^+ - C_4H_7N$, 20), 310 (20), 166 (44).

Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.42; H, 6.23; N, 3.43.

The slowest moving band gave 9-oxotylophorine (**28**) (38 mg, 55%) as colorless crystals (from chloroform–hexane): mp 280–281 °C dec; IR ($CHCl_3$) 1615 cm^{-1}; ^{1}H NMR (90 MHz) δ ~1.6–2.5 (unresolved, 4 H), 2.82 (dd, 1 H, *J* = 15, 13 Hz), 3.50 (dd, 1 H, *J* = 15, 5 Hz), ~3.7–4.2 (m, (3 H) with s (3 H) at δ 4.00, s (3 H) at δ 4.06, and s (6 H) at δ 4.08), 7.21 (s, 1 H), 7.69 (s, 1 H), 7.70 (s, 1 H), 9.02 (s, 1 H); mass spectrum, *m/e* (relative intensity) 407 (M^+, 100), 338 ($M^+ - C_4H_7N$, 37), 310 (26).

Anal. Calcd for $C_{24}H_{25}NO_5$: C, 70.75; H, 6.18; N, 3.44. Found: C, 70.70; H, 6.18; N, 3.42.

(±)-Septicine (6). To a stirred, cooled (0 °C) mixture of $AlCl_3$ (133 mg, 1.00 mmol) and $LiAlH_4$ (114 mg, 3.00 mmol) in ether (20 mL) was added a solution of **27** (200 mg, 0.49 mmol) in a 1:1 (v/v) solution of THF–ether mixture (50 mL). The mixture was stirred at ambient temperature for 1 h, decomposed by addition of water under ice cooling, and then basified (pH 11) with 30% KOH. The organic phase was dried and evaporated. Purification of the resulting residue by column chromatography (silica gel, chloroform) followed by recrystallization from ether afforded (±)-septicine (**6**) (170 mg, 88%) as colorless needles: mp 137–138 °C (lit.[14b] mp 135–136 °C); ^{1}H NMR (90 MHz) δ ~1.4–4.0 (unresolved (11 H) with s (3 H) at δ 3.57, s (3 H) at δ 3.60, and s (6 H) at δ 3.80), 6.55 (s, 2 H) 6.68 (s, 4 H); mass spectrum, *m/e* (relative intensity) 395 (M^+, 70), 326 ($M^+ - C_4H_7N$, 75), 295 (100), 264 (45). The synthetic alkaloids did not depress the melting point of an authentic specimen of (±)-septicine, and IR, ^{1}H NMR, and mass spectra were identical.

(±)-Tylophorine (5). A solution of (±)-septicine (**6**) (65 mg, 0.16 mmol) in dichloromethane (80 mL) containing iodine (5 mg) was irradiated in a Pyrex vessel with a high-pressure Hg lamp. After 21 h, the solution was washed with 5% KOH, dried, and evaporated. The residual mixture was separated by HPLC (silica gel, chloroform–ethanol, 50:1 v/v, 3 mL/min flow rate). The first fraction afforded (±)-tylophorine (**5**) (28 mg, 43%) as light tan crystals (from chloroform–hexane): IR ($CHCl_3$) 1620, 1600, 1520, 1470, 1260, 1250, 910 cm^{-1}; ^{1}H NMR (100 MHz) δ ~1.4–4.2 (?) (unresolved (10 H) with s (6 H) at δ 4.03 and s (6 H) at δ 4.10), 4.60 (d, 1 H, *J* = 15 Hz), 7.11 (s, 1 H), 7.26 (s, 2 H), 7.78 (s, 1 H); mass spectrum, *m/e* (relative intensity) 393 (M^+, 47), 324 ($M^+ - C_4H_7N$, 100). The synthetic sample was identical in TLC behavior and in IR, ^{1}H NMR, and mass spectra with natural tylophorine.

The second fraction contained a light tan solid (8 mg, 12%) indicating two chracteristically fluorescent spots on TLC which is considered to be a mixture of tylocrebrine (**32**) and isotylocrebrine (**33**). The final fraction contained the starting material (7 mg, 11%).

Acknowledgment. We are indebted to Dr. J. A. Lamberton, CSIRO, for generously providing us with spectra of natural julandine and a sample of synthetic julandine and also to Professor E. Gellert, The University of Wollongong, for a sample of natural cryptopleurine. We are also grateful to Professor R. B. Herbert, The University of Leeds, for generous donation of a sample of synthetic septicine and a copy of its ^{1}H NMR spectrum and to Dr. T. R. Govindachari, Amurtanjan Ltd., for a sample of natural tylophorine.

Registry No. (±)-**4**, 23365-52-8; (±)-**5**, 25908-92-3; (±)-**6**, 26503-67-3; (±)-**7**, 23365-39-1; **9**, 34418-91-2; **10**, 6380-23-0; (±)-**11a**, 90171-73-6; (±)-**11b**, 90171-72-5; (±)-**12a**, 90243-11-1; (±)-**15**, 90171-74-7; (±)-**16**, 90171-75-8; (±)-**17**, 23367-75-1; (±)-**18**, 23367-76-2; (±)-**19**, 23365-51-7; (±)-**20**, 79228-21-0; **21**, 24423-88-9; (±)-**22a**, 86980-84-9; (±)-**22a**·picrate, 90194-63-1; (±)-**22b**, 86980-85-0; (±)-**22b**·picrate, 90245-06-0; (±)-**23a**, 86980-86-1; **24**, 90171-76-9; (±)-**26**, 76787-77-4; (±)-**27**, 76787-76-3; (±)-**28**, 86980-92-9; (±)-**29**, 86980-93-0; (±)-**30**, 86980-94-1; (±)-**32**, 30061-35-9; (±)-**33**, 90243-12-2; $(Ph)_3P{=}CHBr$, 39598-55-5; *p*-methoxyphenylacetyl chloride, 4693-91-8; 3,4-dimethoxybenzaldehyde, 120-14-9; 3,4-dimethoxyphenylacetyl chloride, 10313-60-7.

Constituents of Microbial Iron Chelators. Alternate Syntheses of δ-*N*-Hydroxy-L-ornithine Derivatives and Applications to the Synthesis of Rhodotorulic Acid

Byung Hyun Lee, Gary J. Gerfen,[1a] and Marvin J. Miller*[1b]

Department of Chemistry, University of Notre Dame, Notre Dame, Indiana 46556

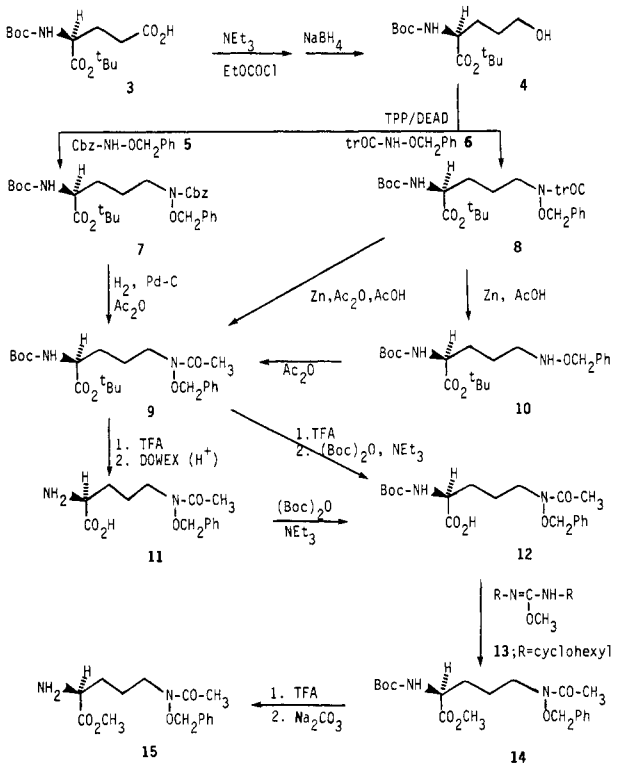
Received December 28, 1983

δ-*N*-Hydroxy-L-ornithine derivatives, the key constituents of several microbial iron chelators, have been prepared from protected forms of L-glutamic acid. Reduction of α-*tert*-butyl *N*-Boc-glutamate (**3**) provided α-*tert*-butyl L-*N*-Boc-δ-hydroxynorvaline (**4**). Direct treatment of **4** with Cbz-*O*-benzylhydroxylamine (**5**) or trOC-*O*-benzylhydroxylamine (**6**) gave the protected δ-*N*-hydroxyornithine derivatives **7** and **8**, respectively. δ-N-Deprotection followed by acetylation provided α-*tert*-butyl-L-*N*-Boc-δ-*N*-acetyl-δ-*N*-benzyloxyornithine (**9**). Appropriate α-amino and α-carboxyl deprotections of **8** and **9** provided derivatives of δ-*N*-hydroxy-L-ornithine suitable for the synthesis of rhodotorulic acid (**24**) by two routes. The first route employed conventional peptide synthetic methods. The second synthesis of rhodotorulic acid involved the direct dimerization of Leuch's anhydrides **25** and **26** derived from the δ-*N*-acetyl- and δ-*N*-trOC-δ-*N*-benzyloxyornithines **11** and **16**.

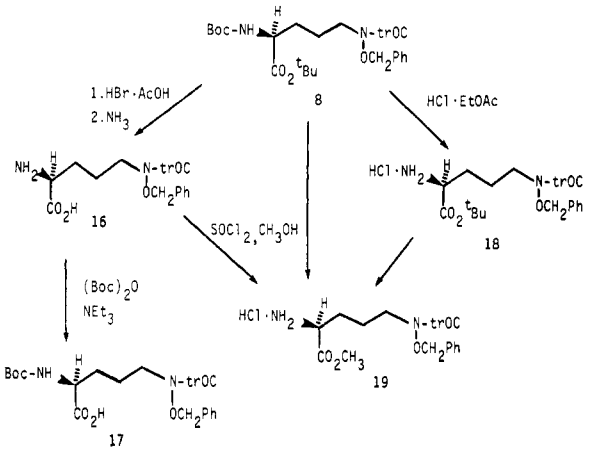
Several microorganisms synthesize low molecular weight chelating agents (siderophores) to sequester and solubilize biologically essential ferric ion from their environment. Study of these siderophores has provided insight into the

0022-3263/84/1949-2418$01.50/0

Scheme I



Scheme II



basic processes involved in iron metabolism. Structural analogues of these natural products are also anticipiated to facilitate the treatment of iron overload in patients with Cooley's anemia and other diseases requiring frequent blood transfusions. Thorough investigation of the structure–activity relationships of various classes of siderophores requires the availability of their basic building blocks. The natural siderophores use hydroxamate, thiohydroxamate, or catechol derivatives to chelate the iron in an octahedral high-spin complex. The hydroxamate containing siderophores are usually derived from 1-amino-ω-(hydroxyamino)alkanes **1a,b** or ω-*N*-hydroxy-L-α-amino acids **2a,b**.[2-7]

$H_2N(CH_2)_nNHOH$

1a, $n = 3$
1b, $n = 5$

$H_2NCH(CH_2)_nNHOH$
CO_2H

2a, $n = 3$
2b, $n = 4$

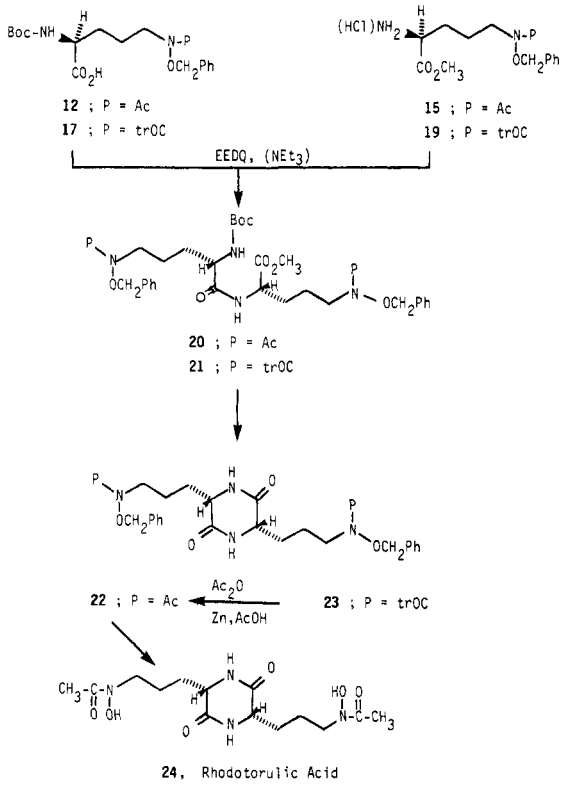
We have previously reported the synthesis of derivatives of the 1-amino-ω-(hydroxyamino)alkanes **1a,b** and their incorporation in the syntheses of schizokinen, schizokinen A, and arthrobactin.[8] The previous synthesis of derivatives of δ-*N*-hydroxy-L-ornithine (**2a**)[9] and ε-*N*-hydroxy-L-lysine (**2b**)[10,11] are of limited utility. This paper describes versatile approaches to the synthesis of δ-*N*-hydroxy-L-ornithine derivatives. L-Glutamic acid was chosen as the precursor to the δ-*N*-hydroxy-L-ornithine derivatives because it is an inexpensive, chiral starting material with the correct number of carbon atoms. Thus, reaction of α-*tert*-butyl *N*-Boc-glutamate (**3**) (Scheme I) with ethyl chloroformate and NEt_3 followed by reduction with $NaBH_4$[12] gave the alcohol **4** in 75–80% yield. Conversion of the alcohol **4** to the desired hydroxamates was accomplished by either of two methods. The first involved conversion of the alcohol **4** to a halide followed by alkylation with protected hydroxamates.[8-11] But, as before,[8-11] this type of alkylation gave a mixture of N- and O-alkylated products. The second approach employed direct reactions of protected hydroxylamines with the alcohol under the Mitsunobu conditions (DEAD/PPh_3).[13]

The DEAD/PPh_3 mediated alkylation of *O*-benzyl-*N*-Cbz-hydroxylamine (**5**) with alcohol **4** gave the desired N-alkylated product **7** in 60–65% yield with no competitive O-alkylation. Catalytic hydrogenation of **7** with Pd-C (5%) in the presence of acetic anhydride provided the desired acetylated compound **9** in 55% yield.[8] The disadvantage of this conversion is that, as in our previous work,[9] the free benzyl substituted hydroxylamine **10** could not be isolated. Therefore, the more complex acylations needed for the syntheses of other siderophores or their analogues might be difficult. Consequently, a different hydroxamate protecting group was studied. The alkylation of *N*-((trichloroethoxy)carbonyl)-*O*-benzylhydroxylamine (**6**) with alcohol **4** in the presence of DEAD/PPh_3 provided the desired N-alkylated products in 75–80% yield. Reductive cleavage of the trOC group with Zn and acetic acid[14] provided the isolable free *O*-benzyl substituted hydroxylamine **10**. Subsequent acetylation of **10** with acetic anhydride gave **9** in 85% yield. The reaction of **8** with Zn and acetic acid in the presence of acetic anhydride gave **9** directly. Trifluoroacetic acid catalyzed deprotection of **9** followed by ion exchange chromatography provided δ-*N*-acetyl-δ-*N*-benzyloxy-L-ornithine (**11**) in 56% yield.

In anticipation of needing versatile protected forms of δ-*N*-hydroxyornithine for the synthesis of peptide siderophores, we next prepared various derivatives of the δ-*N*-hydroxy-L-ornithine. Thus, treatment of **11** with di-*tert*-butyl pyrocarbonate [$(Boc)_2O$] gave the α-Boc derivative **12** which can also be prepared from **10** without isolation of **11**. Reaction of **12** with *O*-methyl-*N,N'*-dicyclohexylisourea (**13**)[15] gave the methyl ester **14** in 81% yield.

(1) (a) Kalamazoo College Work Study Program Interim, March–June, 1983. (b) Alfred P. Sloan Fellow, 1981–1985. Recipient of NIH Research Career Development Award, 1983–1988.
(2) Neilands, J. B. *Struct. Bonding (Berlin)* **1966**, *1*, 59.
(3) Neilands, J. B. *Science (Washington, D.C.)* **1967**, *156*, 1443.
(4) Neilands, J. B. In "Inorganic Biochemistry"; Eichorn, G., Ed.; Elsevier Publishing Co.: Amsterdam, 1972; Vol. 1, p 167.
(5) Emery, T. F. *Adv. Emzymol.* **1971**, *35*, 135.
(6) "Development or Iron Chelators for Clinical Use"; Martell, A. E., Anderson, W. F., Badman, D. G., Eds.; Elsevier: North Holland, NY, 1981.
(7) Neilands, J. B.; Peterson, T.; Leong, S. A. In "Inorganic Chemistry in Biology and Medicine"; Martell, A. E., Ed.; American Chemical Society: Washington, D.C., 1980; Chapter 16.
(8) Lee, B. H.; Miller, M. J. *J. Org. Chem. 1983, 48*, 24.
(9) Lee, B. H.; Miller, M. J. *Tetrahedron Lett.* **1984**, *25*, 927.
(10) Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1982**, *104*, 3096.
(11) Maurer, P. J.; Miller, M. J. *J. Am. Chem. Soc.* **1983**, *105*, 240.
(12) Ramasamy, K.; Olsen, R. K.; Emery, T. *Synthesis* **1982**, 42.
(13) Mitsunobu, O. *Synthesis* **1981**, 1.
(14) Windholz, T. B.; Johnston, D. B. R. *Tetrahedron Lett.* **1967**, 2555.

Scheme III



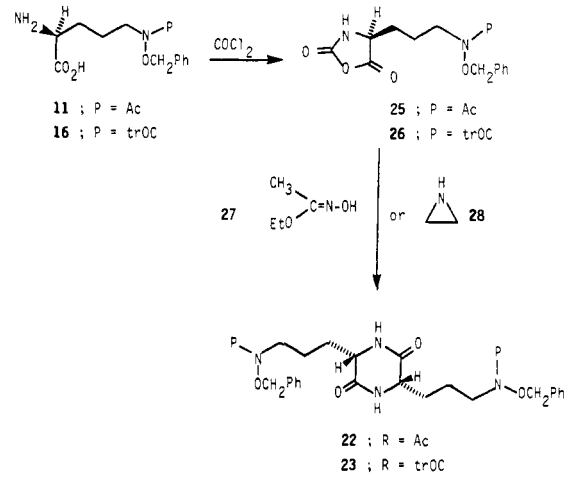
Deprotection of the α-amino group with TFA gave the amine **15**.

Alternatively (Scheme II), treatment of the δ-trOC protected derivative **8** with HBr and acetic acid gave the amino acid **16** with retention of the δ-*N*-trOC protecting group. As expected, this compound could be selectively protected at either the α-amino or the α-carboxyl positions to provide **17** or **19**. Interestingly, treatment of **8** with HCl in ethyl acetate resulted in rapid precipitation of the amine hydrochloride **18** with retention of the *tert*-butyl ester.

The variously protected δ-*N*-hydroxyornithine derivatives **12**, **15**, **17** and **19** can be utilized directly for the synthesis of rhodotoulic acid **24**.[16-18] This microbial iron chelator is a diketopipeazine derived from two residues of δ-*N*-hydroxyornithine. The required diketopiperazine was formed by a conventional stepwise peptide synthesis and by direct dimerization of a preformed Leuch's anhydride. In the first approach (Scheme III), the 2-ethoxy-*N*-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ) mediated coupling reaction of the acids **12** and **17** with amines **15** and **19** provided the dipeptides **20** and **21**, respectively, in 67–70% yields. Compound **20** was deprotected with TFA followed by a base workup to give the free amine of the dipeptide. Subsequent cyclization in methanol gave diketopiperazine **22**.

When the trOC protected dipeptide **21** was treated with HBr in acetic acid followed by treatment with NH_3 in CH_3OH, the diketopiperazine **23** was obtained in 60–65% yield.[19] Treatment of **23** with Zn and acetic acid in the presence of acetic anhydride provided dibenzylrhodotorulic acid **22** in 80% yield. This diketopiperazine **22** was hydrogenated with Pd-C (5%) to provide rhodotorulic acid **24**.

Scheme IV



Alternatively, the amino acids **11** and **16** (Scheme IV) were treated with phosgene in THF to provide the Leuch's anhydrides **25** and **26**. Subsequent treatment with ethyl *N*-hydroxyacetimidate (**27**)[20] or aziridine (**28**)[21] provided the diketopiperazines **22** and **23** in 20–50% yield. Compound **23** is not very soluble in organic solvents and purification was unsuccessful. However, impure **23** was treated with Zn and acetic acid in the presence of acetic anhydride to provide the acetylated compound **22** in 40–50% yield.

In conclusion we have demonstrated the utility of natural inexpensive amino acids for the synthesis of *N*-hydroxy-L-ornithine derivatives, which can be utilized directly for the synthesis of rhodotorulic acid. The incorporation of these amino acids in the synthesis of other siderophores and analogues with potential therapeutic use is in progress.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 727B spectrophotometer. Proton NMR spectra were obtained on Varian A-60A, EM-390, or Nicolet NB-300 spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane (δ units). Mass spectra were recorded on an AEI Scientific Apparatus MS 902 or Du Pont DP 102 spectrometer. Optical rotations were measured with an Autopol III, Automatic Polarimeter from Rudolph Research. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN.

L-*N*-Boc-δ-hydroxynorvaline *tert*-Butyl Ester (4). A solution of ethyl chloroformate (1.45 g, 13.4 mmol) in THF (35 mL) was added to a solution of N-Boc-L-glutamic acid 1-*tert*-butyl ester[23] (**3**, 3.93 g, 13 mmol) and NEt_3 (1.9 mL, 13.5 mmol) at −5 °C and the mixture was allowed to stir for 1 h at −5 °C. NEt_3·HCl was removed by filtration and the filtrate was treated with $NaBH_4$ (0.99 g, 26.8 mmol) in H_2O (10 mL) at 0 °C. The mixture was allowed to warm to room temperature and to stir for 4 h. The mixture was acidified with 3 N HCl to pH 3 and extracted with three portions of ethyl acetate (300 mL). The ethyl acetate layer

(15) Mathias, L. J. *Synthesis* **1979**, 561.
(16) Atkin, C. L.; Neilands, J. B. *Biochemistry* **1968**, *7*, 3734.
(17) Atkin, C. L.; Neilands, J. B.; Phaff, H. J. *J. Bacteriol.* **1970**, *103*, 722.
(18) Carrano, C. J.; Raymond, K. N. *J. Am. Chem. Soc.* **1978**, *100*, 5371.
(19) Similar procedures have reaction reported. (a) Isowa, Y.; Takashima, T.; Ohmori, M.; Kurita, H.; Sato, M.; Mori, K. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 1467. (b) Widmer, J.; Keller-Schierlein, W. *Helv. Chim. Acta* **1974**, *57*, 1904. (c) Fugil, T.; Hantanaka, Y. *Tetrahedron* **1973**, *29*, 3825.
(20) For a related reaction see: Buyle, R. *Helv. Chim. Acta* **1966**, *49*, 1425.
(21) Rosenmund, P.; Kaiser, K. *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 162.
(22) Allen, C. F. H.; Spangler, F. W.; Webster, E. R. "Organic Syntheses"; Wiley: New York; Collect. Vol. IV, 1963; p 433.
(23) This compound is commercially available or can be prepared from γ-benzyl glutamate.

was washed twice with 0.5 N NaOH, once with H_2O and brine. After the mixture was dried (Na_2SO_4) and the solvent evaporated, the desired compound **4** was isolated as an oil: 3.25 g (86.7%); $[\alpha]^{25}_D$ −26.5° ± 0.3° (*c* 6.7, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.43 (2 s, 18 H), 1.5–1.9 (m, 4 H), 3.63 (t, 2 H), 4.0–4.3 (m, 1 H), 5.20 (br d, 1 H, NH), 2.60 (s, 1 H, OH); IR (neat) 3400, 1700–1740 cm^{-1}.

***O*-Benzyl-*N*-((trichloroethoxy)carbonyl)hydroxylamine (6).** *O*-Benzylhydroxylamine hydrochloride (6.38 g, 0.04 mol) was suspended in dry acetonitrile (100 mL) and treated with pyridine (6.46 mL, 0.08 mol). Trichloroethyl chloroformate (5.51 mL, 0.04 mol) dissolved in acetonitrile (30 mL) was added dropwise with stirring for 30 min at room temperature. After the addition was completed, the reaction mixture was allowed to stir 1 h. Volatile components were evaporated, and the residue was taken into ethyl acetate. This was washed twice with 0.5 M citric acid, once with H_2O, once with 0.6 M $NaHCO_3$, and once again with H_2O. After the mixture was dried (Na_2SO_4) and the solvent was evaporated, compound **6** was obtained as a colorless oil in 80% (9.6 g) yield: ^1H NMR ($CDCl_3$) δ 4.74 (s, 2 H), 4.82 (s, 2 H), 7.40 (s, 5 H), 8.1 (br, 1 H, NH); IR (neat) 1640 cm^{-1}.

L-*N*(2)-Boc-*N*(5)-Cbz-*N*(5)-benzyloxyornithine *tert*-Butyl Ester (7). Compound **4** (0.58 g, 2 mmol) was dissolved in THF (30 mL) and treated with *O*-benzyl-*N*-Cbz-hydroxylamine (**5**, 0.514 g, 2 mmol) and TPP (0.68 g, 2.6 mmol). To this solution, DEAD (0.5 mL, 2.5 mmol) was added dropwise over 20 min with stirring at room temperature. After the addition was completed, the reaction was allowed to stir for an additional 5 h at room temperature. Volatile components were evaporated and the residue was chromatographed on a silica plate (2 mm, Chromatotron, Harrison Research, Palo Alto, CA), eluting with ether/hexane (1:2). Compound **7** was obtained as a colorless oil: 0.7 g (66%); $[\alpha]^{25}_D$ −8.4° (*c* 1.75, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.44 (s, 18 H), 3.50 (t, 2 H), 4.83 (s, 2 H), 4.93 (br s, 1 H, NH), 5.2 (s, 2 H), 7.40 (2 s, 10 H); IR (neat) 1700–1740 cm^{-1}.

L-*N*(2)-Boc-*N*(5)-acetyl-*N*(5)-benzyloxyornithine *tert*-Butyl Ester (9). Compound **7** (0.528 g, 1 mmol) was dissolved in ethyl acetate (50 mL) and acetic anhydride (0.27 g, 1.35 mmol) was added. The mixture was treated with Pd on carbon (5%, 100 mg) under 1 atm of H_2 for 1.5 h at 0 °C and warmed to room temperature for an additional 2.5 h with stirring. After the mixture was filtered and evaporated, the residue was chromatographed on a silica plate (2 mm, Chromatotron), eluting with ethyl acetate/hexane (2:3). The desired compound **9** was obtained as a colorless oil: 240 mg (55%); $[\alpha]^{25}_D$ −16.0° ± 1.0° (*c* 2.7, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.43 (s, 18 H), 1.5–1.85 (m, 4 H), 2.07 (s, 3 H), 3.65 (t, 2 H), 4.0–4.3 (br s, 1 H), 4.8 (s, 2 H), 5.13 (br d, 1 H, NH), 7.40 (s, 5 H); IR (neat) 1700–1740, 1650 cm^{-1}.

L-*N*(2)-Boc-*N*(5)-trOC-*N*(5)-benzyloxyornithine *tert*-Butyl Ester (8). Compound **4** (0.6 g, 2.1 mmol), TPP (0.73 g, 2.73 mmol), and *O*-benzyl-*N*-((trichloroethoxy)carbonyl]-hydroxylamine (**6**, 0.638 g, 2.1 mmol) were dissolved in THF (25 mL) and treated dropwise with DEAD (0.46 mL, 2.3 mmol) in THF (10 mL) over 20 min. After the addition was completed, the mixture was allowed to stir for 16 h at room temperature. Volatile components were evaporated and the residue was chromatographed on a column of silica gel (2 × 50 cm), eluting with ethyl acetate/hexane (20:80). The desired product **8** was obtained as a colorless oil: 0.967 g (80%); $[\alpha]^{25}_D$ −8.6° ± 0.2° (*c* 2.55, CH_3OH); ^1H NMR ($CDCl_3$) δ 1.43 (s, 18 H), 1.5–1.8 (m, 4 H), 3.53 (t, 2 H), 4.0–4.3 (m, 1 H), 4.80 (s, 2 H), 4.90 (s, 2 H), 5.0 (d, 1 H, NH), 7.40 (m, 5 H); IR (neat) 1720 cm^{-1}; mass spectrum (EI), *m/e* 456, 458, 460, 462 [for $HO_2CNHCH(CO_2H)(CH_2)_3N(trOC)$-$OCH_2Ph$], 412, 414, 416, 418, [for $NH_2CH(CO_2H)(CH_2)_3N$-$(OCH_2Ph)trOC$].

Compound 9 from 8. Compound **8** (162 mg, 0.28 mmol) was dissolved in acetic acid (2 mL) and treated with Zn dust (150 mg). This mixture was allowed to stir for 1 h at room temperature. It was taken into ethyl acetate and filtered (gravity). This solution was washed three times with saturated Na_2CO_3 and once with H_2O and brine. After the mixture was dried (Na_2SO_4) and the solvent was evaporated, compound **10** was obtained as a colorless oil: ^1H NMR ($CDCl_3$) δ 1.3–1.9 (m, 4 H), 1.45 (s, 18 H), 2.90 (t, 2 H), 4.0–4.3 (m, 1 H), 4.68 (s, 2 H), 4.9–5.1 (br, 1 H, NH), 7.45 (s, 5 H).

Compound **10** was dissolved in acetonitrile (10 mL) and treated with acetic anhydride (2 equiv). The mixture was allowed to stir for 2 h at room temperature. After the solvent was evaporated, compound **9** was isolated as a colorless oil: 101 mg (81% from **8**). This product had identical spectral, TLC, and optical rotation properties when compared with those for the previous preparation of **9**.

When compound **8** (162 mg, 0.28 mmol) in acetic acid (2 mL) was treated with Zn dust (150 mg) in the presence of acetic anhydride (2 equiv) at room temperature for 1 h with stirring, the desired N-acetylated product **9** was obtained in 85% yield. This product had properties identical with those described before.

L-*N*(5)-Acetyl-*N*(5)-benzyloxyornithine (11). Compound **9** (437 mg, 1 mmol) was treated with CF_3CO_2H (3 mL) for 1 h at room temperature. After excess CF_3CO_2H was removed, the residue was dissolved in CH_3OH/H_2O (1:1, 3 mL) and passed through a column packed with DOWEX 50 X-8[(H^+), 20 mL bed], eluting with H_2O (200 mL) and 1% ammonia (aqueous solution, 500 mL). The ammonia solution was evaporated to provide the desired product **11** as a solid: 160 mg (57%); mp 159–161 °C (lit.[19c] mp 161–163 °C); $[\alpha]^{25}_D$ +13.7° (*c* 1, 1 N HCl) [lit.[19c] $[\alpha]^{25}_D$ +13.9° (*c* 1, 1 N HCl)]; ^1H NMR (Me_2SO-d_6) δ 1.6 (m, 4 H), 2.0 (s, 3 H), 3.2–3.8 (m, 5 H), 4.85 (s, 2 H), 7.40 (m, 5 H); IR (KBr) 1650 cm^{-1}.

Compound 12 from 9. Compound **9** (1.28 g, 2.93 mmol) was stirred with TFA (5 mL) for 1 h at room temperature. Excess TFA was removed by vacuum distillation. The residue was dissolved in THF/H_2O (2:1, 30 mL) and treated with di-*tert*-butyl dicarbonate (0.67 g, 3.07 mmol) and NEt_3 (0.84 mL, 6 mmol) in THF (10 mL). The mixture was allowed to stir at room temperature for 16 h. Volatile components were evaporated and the residue was taken into 1 N NaOH (20 mL). This solution was washed with ethyl acetate (20 mL) and the aqueous solution was acidified to pH 2.5 with solid citric acid. The mixture was extracted with three portions of ethyl acetate (100 mL). After the organic layer was dried (Na_2SO_4) and the solvent was evaporated, compound **12** was obtained as a colorless oil: 0.83 g (75%); $[\alpha]^{25}_D$ +6.0° (*c* 1.3, ethanol) [lit.[19c] $[\alpha]^{25}_D$ +5.0° (*c* 1.88, *l* = 1, ethanol)]; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 2.5–1.8 (m, 4 H), 2.07 (s, 3 H), 3.65 (t, 2 H), 4.0–4.3 (br s, 1 H), 4.80 (s, 2 H), 5.15 (d, 1 H, NH), 7.40 (s, 5 H); IR (neat) 1710, 1650 cm^{-1}.

Compound **12** can also be prepared from **11** with a similar procedure (85% yield).

Compound 14 from 12. Compound **12** (0.35 g, 0.92 mmol) was dissolved in CCl_4 (30 mL) and treated with *O*-methyl-*N,N'*-dicyclohexylisourea (**13**, 0.23 g, 0.965 mmol). The mixture was refluxed for 2 h. After the mixture was filtered and evaporated, the residue was chromatographed on a silica plate (2 mm, Chromatotron), eluting with ethyl ethyl acetate/hexane (1:1). The desired compound **14** was isolated as a colorless oil: 0.32 g (81%); $[\alpha]^{25}_D$ −9.3° (*c* 1.25, CH_3OH) [lit.[19c] $[\alpha]^{27}_D$ −9.0° (*c* 1.00, CH_3OH)]; ^1H NMR ($CDCl_3$) δ 1.43 (s, 9 H), 1.5–1.9 (s, 2 H), 2.07 (s, 3 H), 3.67 (t, 2 H), 3.70 (s, 3 H), 4.80 (s, 2 H), 5.32 (d, 1 H, NH), 7.40 (s, 5 H); IR (neat) 1700–1740, 1650 cm^{-1}.

The Amino Acid 16 from 8. Compound **8** (0.568 g, 1 mmol) was dissolved in $HBr{\cdot}CH_3CO_2H$ (35%, 4 mL). The mixture was allowed to stir for 15 min at room temperature. After excess acetic acid was removed by freeze-drying, the residue was suspended in H_2O (50 mL) and treated with NH_3 (aqueous solution, 5%) until the pH of the solution was at 9. The precipitate was collected and washed with H_2O (20 mL) and dried in a vacuum desiccator. Compound **16** was isolated as a powder: 275 mg (67%); mp 170–172 °C; ^1H NMR (Me_2SO-d_6) δ 1.6–1.8 (m, 4 H), 3.0–4.4 (m, 5 H), 4.9 (s, 4 H), 7.40 (s, 5 H); IR (KBr) 3425, 1720 (shoulder) 1700, 1680 (shoulder), 1620 cm^{-1}. This product is not very soluble in organic solvents.

Compound 18 from 8. Compound **8** (0.568 g, 1 mmol) was dissolved in $HCl{\cdot}CH_3CO_2Et$ (saturated, 20 mL). The mixture was allowed to stir at room temperature for 24 h. The ppt was collected and recrystallized from methanol/ether to yield **18** as white crystals: 405 mg (80%); mp 140–141 °C; ^1H NMR (CD_3OD) δ 1.43 (s, 9 H), 1.6–2.1 (m, 4 H), 3.65 (t, 2 H), 3.90 (t, 1 H), 4.90 (s, overlapped with CD_3OD and exchangeable protons), 4.97 (s, 2 H), 7.2–7.6 (m, 5 H); IR (KBr) 1700–1740 cm^{-1}. Anal. Calcd for $C_{19}H_{28}N_2O_5Cl_4$: C, 45.08; H, 5.57; N, 5.53. Found: C, 45.07; H, 5.86; N, 5.54. $[\alpha]^{25}_D$ +11.9° ± 0.2° (*c* 1.15, *l* = 1, CH_3OH).

Compound 19. Method 1. Compound **18** (0.1 g, 0.2 mmol) in methanol (10 mL) was added to a solution of methanolic $SOCl_2$ [This solution was prepared by the addition of $SOCl_2$ (1 mL) to

methanol (20 mL) at 0 °C]. The mixture was refluxed for 2 h. After the solvent was evaporated, the residue was crystallized from methanol/ether to yield **19** as white crystals: mp 127–129 °C; ^{1}H NMR (CD_3OD) δ 1.5–2.1 (m, 4 H), 3.63 (t, 2 H), 3.80 (s, 3 H), 4.10 (t, 1 H), 4.90 (s, 2 H), 4.97 (s, 2 H), 7.3–7.65 (m, 5 H); IR (KBr) 1700–1740 cm^{-1}; $[\alpha]^{25}_D$ +13.0° (*c* 1.00, *l* = 1, CH_3OH). Anal. Calcd for $C_{16}H_{22}N_2O_5Cl_4$: C, 41.40; H, 4.78; N, 6.03. Found: C, 41.55; H, 4.84; N, 6.24; 80–85% yield.

Method 2. Compound **8** (1.64 g, 2.88 mmol) was dissolved in $CH_3OH/SOCl_2$ (40:1, 41 mL) and refluxed for 2 h. After the solvent was evaporated, the residue was crystallized from methanol/ether to yield **19** as white crystals, 0.87 g (65%).

Method 3. Compound **16** (0.412 g, 1 mmol) was dissolved in $CH_3OH/SOCl_2$ (40:1, 20 mL) and refluxed for 2 h. After the solvent was evaporated, the residue was crstallized from methanol/ether to yield **19** as white crystals: 278 mg (60%).

All three preparations provided **19** with the same melting point and ^{1}H NMR spectrum.

Compound 17 from 16. The amino acid **16** (261 mg, 0.633 mmol) was dissolved in THF/H_2O (2:1, 30 mL) and treated with NEt_3 (0.09 mL, 0.65 mmol). To this solution di-*tert*-butyl dicarbonate (138 mg, 0.633 mmol) in THF (5 mL) was added. The mixture was allowed to stir at room temperature for 2 days. The mixture was taken into ethyl acetate (100 mL) and washed twice with 0.5 M citric acid and once with H_2O and brine. After the mixture was dried ($MgSO_4$) and the solvent evaporated, the desired compound **17** was obtained as a colorless oil: 310 mg (96%); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.5–1.9 (m, 4 H), 3.55 (t, 2 H), 4.0–4.5 (m, 1 H), 4.81 (s, 2 H), 4.89 (s, 2 H), 7.40 (s, 5 H), 7.9 (br s, 1 H); IR (neat) 3450, 1715, 1690 (shoulder) cm^{-1}; $[\alpha]^{25}_D$ +1.3° (*c* 4.1, CH_3OH); mass spectrum (EI), *m/e* 512 (M^+).

The Dipeptide 20 from 14. Compound **14** (295 mg, 0.75 mmol) was stirred with TFA (3 mL) for 30 min at room temperature. After excess TFA was removed, the residue was partitioned between ethyl acetate (50 mL) and 10% Na_2CO_3. The organic layer was dried (K_2CO_3) and evaporated. The residue containing the amine **15** was dissolved in acetonitrile (20 mL) and treated with EEDQ (203 mg, 0.82 mmol) and the acid **12** (284 mg, 0.75 mmol) in acetonitrile (5 mL). The mixture was allowed to stir at room temperature for 16 h. After the solvent was evaporated, the residue was chromatographed on a silica plate (2 mm, Chromatotron), eluting with ethyl acetate/hexane (2:1). The dipeptide **20** was obtained as a colorless oil: 0.33 g (67%); $[\alpha]^{25}_D$ −12.0° ± 0.2° (*c* 1.75, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.42 (s, 9 H), 1.5–1.9 (m, 8 H), 2.07 (2 s, 6 H), 3.67 (m, 7 H), 4.4 (br, 2 H), 4.80 (s, 4 H), 5.30 (d, 1 H), 7.43 (s, 10 H); IR (neat) 1700–1740, 1650–1680 cm^{-1}.

Diketopiperazine 22 from 20. The dipeptide **20** (135 mg, 2.05 mmol) was stirred with CF_3CO_2H (2 mL) at room temperature for 30 min. Excess TFA was removed by rotary evaporation. The residue was partitioned between ethyl acetate (30 mL) and 10% Na_2CO_3. The organic layer was dried (K_2CO_3) and evaporated. The residue was dissolved in CH_3OH (10 mL). It was allowed to stir at room temperature for 4 days. After the solvent was evaporated, the residue was crystallized from chloroform/ether to yield the diketopiperazine **22** as white crystals: 45 mg (42%); mp 127–129 °C; $[\alpha]^{25}_D$ −16.5° (*c* 0.67, CH_3OH) [lit.[19c] mp 129–131 °C and also reported to sometimes be 104–105 °C; lit.[19a] mp 97–99 °C]; $[\alpha]^{25}_D$ −16.4° (*c* 1.00, CH_3OH]; ^{1}H NMR ($CDCl_3$) δ 1.65–1.96 (m, 8 H), 2.10 (s, 6 H), 3.67 (t, 4 H), 4.0 (m, 2 H), 4.82 (s, 4 H), 6.50 (s, 2 H, NH), 7.42 (s, 10 H); IR ($CHCl_3$) 1640 cm^{-1}.

Rhodotorulic Acid (24). Compound **22** (35 mg, 0.07 mmol) was dissolved in methanol (30 mL) and treated with Pd on carbon (5%, 50 mg) under 1 atm of H_2 for 3 h at room temperature. After the mixture was filtered and evaporated, the residue was crystallized from ethanol/H_2O (9:1) to yield rhodotorulic acid (**24**) as white crystals: 16 mg (70%); mp 217–218 °C (lit.[19c] 216–218 °C). The 300-MHz ^{1}H NMR (Me_2SO-d_6) spectra were in good agreement with that reported.[16] In butanol/H_2O/acetic acid (4:1:1) the same R_f value was obtained as that reported for natural substance (0.63).[16]

The Dipeptide 21. Compounds **17** (1.242 g, 2.68 mmol) and **19** (1.37 g, 2.68 mmol) and EEDQ (0.73 g, 2.94 mmol) were suspended in acetonitrile (25 mL). The mixture was allowed to stir at room temperature for 16 h. After the solvent was evaporated, the mixture was taken into ethyl acetate and washed once with H_2O, twice with 0.5 N HCl, once again with H_2O, once with saturated Na_2CO_3, and once with H_2O and brine. After the mixture was dried (Na_2SO_4) and the solvent was evaporated, the residue was chromatographed on silica gel (2 × 50 cm), eluting with ether/hexane (1:1). Compound **21** was isolated as a colorless oil: 1.737 g (70%); $[\alpha]^{25}_D$ −4.5° (*c* 3.35, CH_3OH); ^{1}H NMR ($CDCl_3$) δ 1.40 (s, 9 H), 1.5–1.9 (m, 8 H), 3.50 (t, 4 H), 3.65 (s, 3 H), 4.83 (s, 4 H), 4.92 (s, 4 H), 5.23 (d, 1 H, NH), 6.8 (d, 1 H, NH), 7.2–7.6 (m, 10 H); IR (neat) 3370, 1740, 1720, 1680 cm^{-1}.

The Diketopiperazine 23. Compound **21** (1.6 g, 1.72 mmol) was dissolved in $HBr{\cdot}CH_3CO_2H$ (33%, 5 mL). The mixture was allowed to stir for 20 min at room temperature. After acetic acid was removed by freeze-drying, the residue was treated with $NH_3{\cdot}CH_3OH$ (saturated, 5 mL). The mixture was allowed to stir at room temperature for 1 day. The precipitate was collected (250 mg, mp 137–139 °C) and the filtrate was retreated with $NH_3{\cdot}CH_3OH$ (saturated, 2 mL). The mixture was allowed to stir at room temperature 1 day. The precipitate was collected (200 mg, mp 169–170 °C) and the filtrate was again retreated with ammonia in methanol (saturated, 2 mL). The mixture was allowed to stir for 1 more day at room temperature. The precipitate was collected (140 mg, mp 169–170 °C). All three crops have the same ^{1}H NMR and IR. Attempted recrystallization failed because of low solubility in organic solvents. The total yield of **23** was 0.59 g (70%): ^{1}H NMR ($CDCl_3$) δ 1.5–2.1 (m, 8 H), 3.53 (t, 4 H), 3.9–4.2 (m, 2 H), 4.83 (s, 4 H), 4.93 (s, 4 H), 6.57 (s, 2 H, NH), 7.40 (s, 10 H); IR ($CHCl_3$) 3400, 1715, 1675 cm^{-1}.

When compound **21** was treated with HBr in acetic acid followed by freeze-drying and the residue was treated with NEt_3 (1 equiv) in methanol, the desired compound **23** was obtained as a powder in 40% yield. This product had spectral properties identical with those above and mp 169–170 °C.

Compound 22 from 23. Compound **23** (60 mg, 0.08 mmol) was suspended in acetic acid (1.5 mL) and treated with Zn dust (50 mg) in the presence of acetic anhydride (50 mg). The mixture was allowed to stir at room temperature for 1 h. The mixture was taken into ethyl acetate (50 mL) and filtered. The filtrate was washed three times with saturated Na_2CO_3 and once with H_2O and brine. After the mixture was dried (Na_2SO_4) and the solvent evaporated, the residue was crystallized from $CHCl_3$/hexane to yield **22** as white crystals: 32 mg (80%). This product had spectral properties identical with those in the previous preparation, but the melting point was 102–103 °C (see discrepancies in the literature melting points mentioned earlier).

Leuch's Anhydride 26 from 16. Compound **16** (371 mg, 0.9 mmol) was suspended in THF (20 mL) and treated with phosgene. The mixture was allowed to stir for 1 h more after the suspension was completely dissolved in THF (15 mL). N_2 was flushed through the system and then the solvent was evaporated. The residue was crystallized from $CHCl_3$/hexane to give **26** as white crystals: 360 mg (92%); mp 75–79 °C; ^{1}H NMR ($CDCl_3$) δ 1.5–2.1 (m, 4 H), 3.53 (t, 2 H), 4.0–4.4 (m, 1 H), 4.81 (s, 2 H), 4.90 (s, 2 H), 6.95 (m, 1 H, NH), 7.40 (s, 5 H); IR ($CHCl_3$) 1860, 1790, 1720 (shoulder), 1710, 1690 (shoulder) cm^{-1}.

Diketopiperazine 23 from 26. Compound **26** (100 mg, 0.23 mmol) was dissolved in THF (3 mL) and treated with aziridine (**28**)[22] (0.3 mL). The mixture was allowed to stir for 30 min at room temperature. After the solvent was evaporated, the residue was crystallized from $CHCl_3$/hexane to provide **23** as white crystals in 45–55% yield, mp 146–148 °C (when prepared in CH_3OH, the melting point of **23** was 137–139 °C). This product has the same ^{1}H NMR and IR spectra when compared with those in the previous preparation. However we cannot explain the discrepancy in the melting points which we and others[19a,c] have observed in related diketopiperazines (like **22**).

When crude compound **23** was treated with Zn dust in the presence of acetic anhydride in acetic acid, the desired N-acetylated diketopiperazine **22** was obtained in 40–50% yield.

Diketopiperazine 22 from 11. The amino acid **11** (75 mg, 0.268 mmol) was suspended in THF (20 mL) and treated with phosgene for 1.5 h at room temperature. After the phosgene flow was stopped the mixture was allowed to stir for an additional 1.5 h at room temperature. The mixture was flushed with N_2 for 2 h. After the solvent was evaporated, Leuch's anhydride **25** was obtained as an oil: 50 mg (71%); ^{1}H NMR ($CDCl_3$) δ 1.6–1.9 (m, 4 H), 2.10 (s, 3 H), 3.67 (t, 2 H), 4.2–4.45 (m, 1 H), 7.42 (s, 5 H);

IR (neat) 1860, 1790, 1640 cm^{-1}.

Compound **27** (27.6 mg, 0.134 mmol) was dissolved in THF (10 mL) and treated dropwise with compound **25** (50 mg, 0.10 mmol) in THF over 30 min. After the addition was completed, the mixture was allowed to stir for 16 h at room temperature. After the solvent was evaporated, the residue was crystallized from ether to provide **22** as white crystals, 14 mg (20%). This product had properties identical with those described before.

Acknowledgment. We gratefully acknowledge the support of the research by the NIH (Grant GM25845). The 300-MHz NMR spectrometer used was made available by grants from the NIH and the University of Notre Dame. Technical assistance was provided by Kathleen Peterson.

Registry No. **3**, 24277-39-2; **4**, 90194-99-3; **5**, 15255-86-4; **6**, 90195-00-9; **7**, 90219-04-8; **8**, 90195-01-0; **9**, 90195-02-1; **10**, 90195-03-2; **11**, 52816-28-1; **12**, 52816-29-2; **14**, 52816-30-5; **15**, 90195-04-3; **16**, 90195-05-4; **17**, 90195-06-5; **18**, 90195-07-6; **19**, 90195-08-7; **20**, 52816-32-7; **21**, 90195-09-8; **22**, 38532-33-1; **23**, 90195-10-1; **24**, 18928-00-2; **25**, 90195-11-2; **26**, 90195-12-3; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; trichloroethyl chloroformate, 17341-93-4; di-*tert*-butyl dicarbonate, 24424-99-5; glutamic acid, 56-86-0.

Synthesis and Binding Studies of Crown Ethers Bearing Pharmacophoric Groups: Epoxy Lariat Crown Ethers

Bruce B. Jarvis,* Vivekananda M. Vrudhula, Dennis M. Dishong, and George W. Gokel*

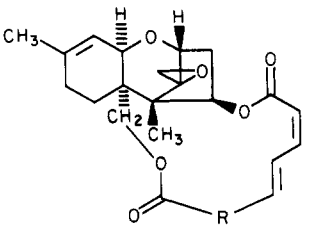
Department of Chemistry, University of Maryland, College Park, Maryland 20742

Received January 19, 1984

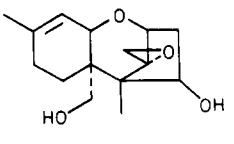
A series of lariat ethers (derivatives of 18-crown-6, 15-crown-5, and 12-crown-4) bearing pendant epoxy groups has been prepared and the homogeneous stability (binding) constants (K_s) with Na^+ and K^+ in MeOH have been measured. The epoxy groups appear to have only a marginal influence on complexation of K^+ in the larger ring compounds and do not enhance Na^+ binding. These epoxy lariat ethers exhibit no in vivo activity against P388 mouse leukemia at dose levels of 128 mg/kg and below.

Alkylating agents constitute an important class of compounds used in the treatment of cancer.[1] Many natural products with proven high antitumor activity are known to possess bioalkylating functionalities such as oxirane, α,β-unsaturated carbonyl, α-carbinol amide, and urethane groups.[2] During the past several years, a great deal of effort has been directed at establishing structure–activity relationships for natural products possessing anticancer activity.[3] One class that has been of interest to us is the trichothecenes,[4] which possess a 12,13-epoxide group. The epoxide appears to function as a bioalkylating center and is responsible for the potent biological activity associated with this series of fungal metabolites.

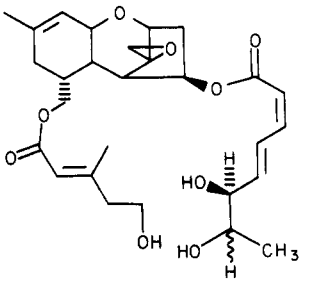
Our interests have been centered on the macrocyclic trichothecenes (e.g., **1**),[5a] which exhibit the highest cytotoxicity and cycostaticity of the trichothecenes. The role played by the macrocylic ring in the bioactivity of these compounds is not clear, although reduction of the diene system or loss of the macrolide chain by hydrolysis to give verrucarol (**2**) leads to trichothecenes of considerably lower activity.[5b,c] The nonmacrolide trichoverrins **3** and other related trichoverroids are about 2 orders of magnitude less cytotoxic than the macrocyclic trichothecenes, which



1



2



3

suggests that the macrolide ring in **1** plays an important role in potentiating the cytotoxicity of these compounds.[6]

Other macrocyclic antibiotics such as valinomycin, nonactin, gramicidin, antanamide, nystatin, and amphotericin B function as ionophores.[7] The macrolide antibiotic erythromycin requires potassium or ammonium ions in order to bind to the 50S subunit of bacterial ribosomes,[8,9] which suggests that perhaps cation complexation brings about

(1) Ross, W. C. J. "Biological Alkylating Agents"; Butterworths: London, 1962.

(2) Kupchan, S. M. *Intra-Sci. Chem. Rept.* **1974**, *8*, 57.

(3) Cassidy, J. M., Douros, J. D., Eds. "Anticancer Agents Based on Natural Product Models"; Academic Press: New York, 1980.

(4) (a) Ueno, Y. Ed. "Trichothecenes-Chemical, Biological, and Toxicological Aspects"; Halsted Press-Kodansha Scientific: New York and Tokyo, 1983. (b) Ong, C. W. *Heterocycles* **1982**, *19*, 1685. (c) Bamburg, J. R.; Strong, F. M. In "Microbial Toxins"; Kadis, S., Ceigler, A., Agl, S. J., Eds.; Academic Press: New York, 1971; Vol. 7, p 207. (d) Bamburg, J. R. In "Mycotoxins and Other Fungal Related Food Problems", J. V., Rodricks, Ed.; American Chemical Society, Washington, DC, 1976; ACS Symp. Ser. No. 149, p 144.

(5) (a) Jarvis, B. B.; Mazzola, E. P. *Acc. Chem. Res.* **1982**, *15*, 388. (b) Tamm, Ch. *Fortschr. Chem. Org. Naturst.* **1974**, *31*, 63. (c) Tamm, Ch., Breitenstein, W. In "The Biosynthesis of Mycotoxins, A Study in Secondary Metabolism"; Steyn, P. S., Ed.; Academic Press: New York, 1980; p 69.

(6) (a) Jarvis, B. B.; Stahly, G. P.; Pavanasasivam, G.; Midiwo, J. O.; DeSilva, T.; Holmlund, C. E.; Mazzola, E. P.; Geoghegan, R. F., Jr. *J. Org. Chem.* **1982**, *47*, 1117.

(7) Lehninger, A. L. "Biochemistry", 2nd ed.; Worth Publishers Inc.: New York, 1975; p 802.

(8) Vazquez, D. In "Antibiotics"; Corcoran, J. W., Han, F. E., Eds.; Springer-Verlag: New York, 1975; Vol. III, p 252.

(9) Taubman, S. B.; Jones, N. R.; Young, F. E.; Corcoran, J. W. *Biochem. Biophys. Acta.* **1966**, *123*, 483.

0022-3263/84/1949-2423$01.50/0