positions of the hydrogen atoms were calculated geometrically and considered isotropically in all refinements.

Epoxide **6** crystallizes triclinically in the space group $P\bar{1}$ (No. 2) with a = 996.2 (3) pm, b = 1533.1 (6) pm, c = 920.5 (4) pm, α = 94.04 (3)°, β = 102.40 (3)°, and γ = 108.50°. The unit cell contains Z = 2 formula units, and the density was calculated to be 1.556 g·cm^{-3}. For details see supplementary material paragraph at the end of this section.

Photo-CIDNP Experiment of Divinyl Ether 1a. A sample of 10.0 mg (0.0267 mmol) of divinyl ether **1a** was dissolved in 1 mL of CD_3CN. ^1H NMR spectra (30 scans) were taken before, during, and after irradiation. (cf., Figure 1). The vertical gain for the spectrum during irradiation is increased by a factor of 2 in comparison to the spectra before and after irradiation.

Cyclic Voltammetry of Divinyl Ether 1a. A sample of 15.0 mg (0.0401 mmol) of divinyl ether **1a** and 200 mg (0.607 mmol) of tetrabutylammonium tetrafluoroborate were dissolved in 20 mL of absolute acetonitrile. The solution was purged with nitrogen, and the cyclic voltammogram was taken at a scan speed of 200 mV/s, employing a Pt electrode and a Ag/AgCl reference counter electrode. A reversible oxidation of divinyl ether **1a** was observed at +1.22 V (vs. SCE). A second oxidation was detected at ca. +1.51 V (vs. SCE).

Acknowledgment. Financial support from the Fonds der Chemischen Industrie and from the Deutsche Forschungsgemeinschaft is gratefully acknowledged. We thank Dr. W. Klotzbücher, Max-Planck-Institut für Strahlenchemie, Mülheim, FRG, for the UV matrix spectra of 1,1,4,4-tetraphenyl-3,4-epoxy-1-butene (**7**).

Registry No. **1a**, 93620-51-0; **1b**, 98760-54-4; **1c**, 98760-55-5; **3a**, 23219-07-0; **3b**, 98760-56-6; **5**, 98760-57-7; **6**, 98760-58-8; **7**, 98760-59-9; **9**, 98760-60-2; **10**, 98760-61-3; **11**, 98760-62-4; **13**, 41326-74-3; **15**, 2491-41-0; (*E*,*E*)-Ph(CH=CH)$_2$Ph, 538-81-8; $Cl_3CCH_2OCON{=}NCO_2CH_2CCl_3$, 38857-88-4; $Ph_2C{=}C{=}C{=}CPh_2$, 1450-63-1; $Ph_2C^-CHONa^+$, 55795-21-6; $PhCO(CH_2)_2COOEt$, 6270-17-3; 4-MeC_6H_4Li, 2417-95-0; PhLi, 591-51-5; **4**, 98760-63-5; $PH_2C{=}CH_2$, 530-48-3; $PH_2C{=}CHCHPh_2$, 4960-55-8; Ph_2CHCHO, 947-91-1; Ph_2CH_2, 101-81-5; $Ph_2CHCHPh_2$, 632-50-8; $Ph_2C{=}CCHO$, 1210-39-5; $Ph_2CHOCH(CH_3)_2$, 5670-79-1.

Supplementary Material Available: Tables of atomic coordinates and isotropic thermal parameters (Table III), bond lengths (Table IV), bond angles (Table V), and anisotropic thermal parameters (Table VI) for the epoxide **6** (4 pages). Ordering information is given on any current masthead page.

Organic Chemistry of L-Tyrosine. 1. General Synthesis of Chiral Piperazines from Amino Acids

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A new method for the conversion of optically active diketopiperazines (*cyclo*-dipeptides) into optically pure piperazines is described. Due to poor solubility of certain *cyclo*-dityrosine derivatives, the usual method using lithium aluminum hydride reaction was problematic, giving racemization under forcing conditions. However, the use of borane/tetrahydrofuran for this diketopiperazine to piperazine reduction proceeded well, affording high yields of optically pure materials. In this manner several mixed *cyclo*-dityrosine derivatives **9a–d** were transformed into the piperazines **10a–d**, potentially useful intermediates for the synthesis of the antibiotic alkaloids, piperazinomycin (**1**) and herquline (**2**). Finally, the naturally occuring alkaloid isolated from *Zanthoxylum arborescens*, **7b**, was prepared by this route.

The use of optically pure starting materials to control absolute stereochemistry is a well-established strategy in organic synthesis. Chiral α-amino acids are particularly valuable in this regard due to their great diversity of side chain structures and (often) ready availability.

In planning the total synthesis of the antifungal agent piperazinomycin[3] (**1**) and the platelet-aggregation inhibitor herquline[4] (**2**), alkaloids presumed to arise biosynthetically from two molecules of tyrosine[5] (**5**), we conceived of a common strategy utilizing substituted L-tyrosine-derived (2*S*,5*S*)-bis[(*p*-hydroxyphenyl)methyl]piperazines (**3**) as key intermediates. If one could successfully prepare compounds such as **3** in optically pure form in high overall yield from simple tyrosine derivatives, then several potential routes to piperazinomycin (**1**) and herquline (**2**) could be tested. For example, an intramolecular Ullmann coupling to give diaryl ethers applied to **3** (R = Me, X = I or Br, R′ = X′ = H) would produce the methyl ether of **1**. Similarly a carbon–carbon bond formation between a reduced derivative of **3** (X = X′ = Br or I) would give an intermediate for the synthesis of herquline **2**. Thus it appeared important for the synthesis of **1** and **2** to test methods for the preparation of **3** in high optical purity.

There are several general methods in the literature[6–9] for preparing the corresponding sterically pure pipera-

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(2) University of California Fellowship, 1983–4.

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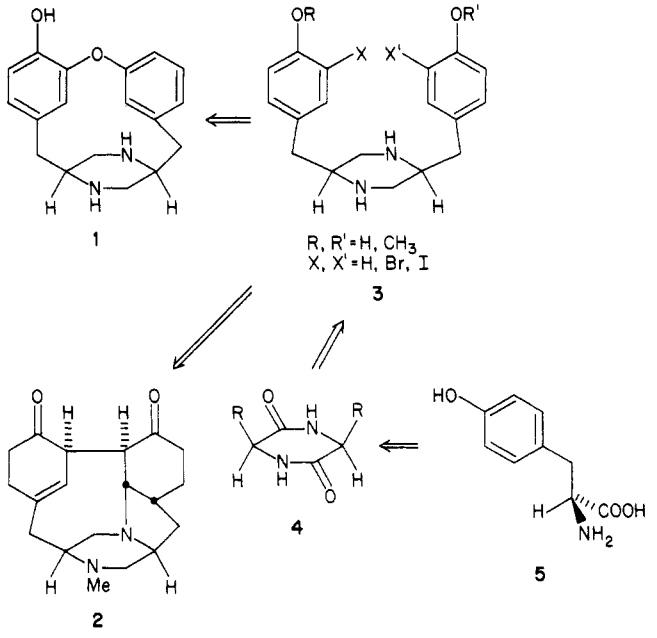
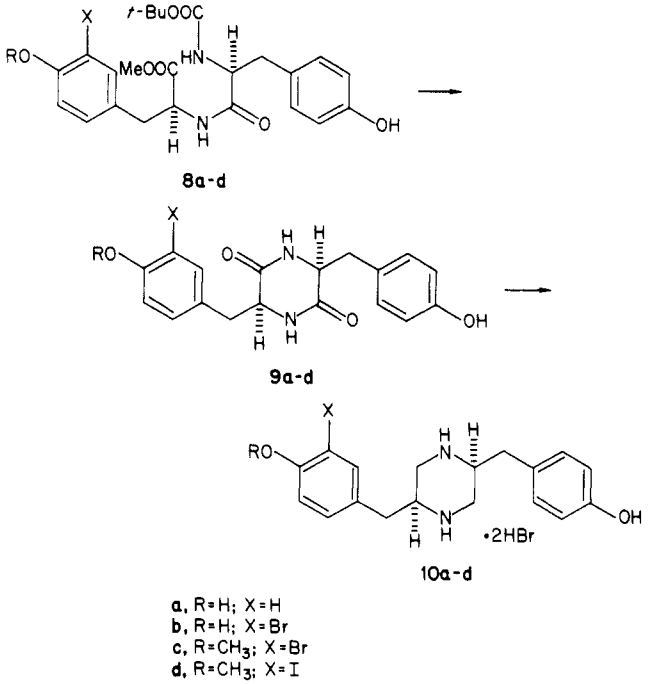


zine-2,5-diones (i.e., *cyclo*-dipeptides) **4** from amino acids. The subsequent reduction of *cyclo*-dipeptides was also precedented. Beck had reported[10] that *cyclo*-L-Phe-L-Phe (**6a**) is reduced without epimerization to (2*S*,5*S*)-dibenzylpiperazine **7a** using lithium aluminum hydride (LAH) in ether, in 66% yield. Stermitz[11] reduced the related *cyclo*-*N*-Me-L-Phe-*N*-Me-L-Phe (**6b**), also with LAH, giving (2*S*,5*S*)-1,4-dimethyl-2,5-dibenzylpiperazine (**7b**), a naturally occuring alkaloid isolated from *Zanthoxylum arborescens*.[12]

The novel mixed *cyclo*-dityrosines **9b–d**, as well as the previously reported[13] **9a** (Table I), were synthesized by cyclization of the appropriate *N*-*tert*-butoxycarbonyl dipeptide methyl ester **8a–d** (98% formic acid 25 °C; 2-butanol reflux) by the two-step procedure of Nitecki.[7] Dipeptide derivatives **8a–d** were prepared by standard DCC coupling of the appropriate protected amino acids (see Experimental Section). Unfortunately, the LAH reduction of phenolic *cyclo*-dityrosine derivatives **9a–d** was complicated by the very poor solubility of their conjugate bases in ethereal solvents. Under forcing conditions with LAH, racemization occurred.

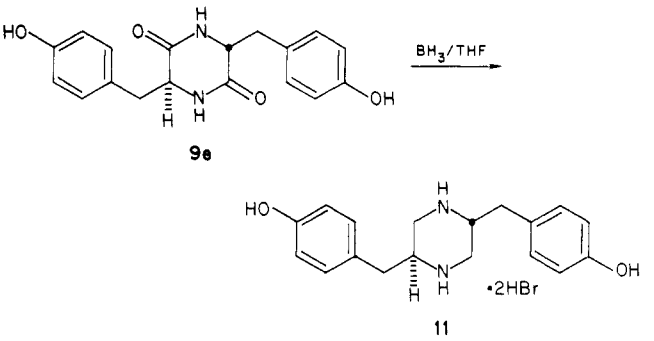
Borane/tetrahydrofuran (BH_3/THF) is a potent, yet selective,[14] reducing agent for polar functional groups like amides[15] and imides.[16] We report here that the *cyclo*-dipeptides **9a–d** are cleanly reduced by an excess (6–16 equiv) of this reagent in refluxing THF. The suspended solids slowly pass into solution, and the chiral piperazines **10a–d** are isolated as crystalline dihydrobromides (Table II) in 72–89% yields.

This procedure was shown to be stereospecific by reduction of achiral *cyclo*-D-Tyr-L-Tyr[13] (**9e**), giving piperazine **11** in 78% yield. This material was clearly distinct from its diastereomer **10a** by ^1H and ^{13}C NMR spectra.

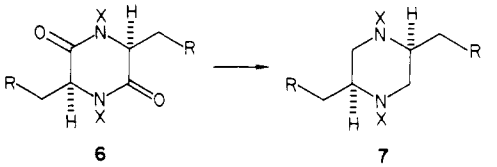


a, R = H; X = H
b, R = H; X = Br
c, R = CH_3; X = Br
d, R = CH_3; X = I

Thus both the cis and trans isomers **9a** and **9e** are stereospecifically reduced to **10a** and **11**, respectively, with none of the opposite isomer being produced in either case.



The more lipophilic dipeptides *cyclo*-L-Ala-L-Ala (**6c**) and *cyclo*-L-Phe-L-Phe (**6a**) were also readily reduced by



a, R = C_6H_5; X = H
b, R = C_6H_5; X = CH_3
c, R = H; X = H

BH_3/THF, although yields were lower in these cases (35–60%), due to incomplete precipitation by the standard HBr/HOAc workup.

Eschweiler–Clarke methylation of the piperazine dihydrobromide **7a** (37% aqueous formaldehyde, formic acid, 70 °C, 30 min, 90%) gave the aforementioned natural piperazine[15] **7b** from *Z. arborescens*, mp 122–4 °C, $[\alpha]^{23}$ +108° (*c* 0.054, EtOH) (lit.[11] mp 123–4.5 °C, $[\alpha]^{23}$ +118°).

The alanine-derived piperazine **7c** gave a crystalline bis(benzamide) derivative (benzoyl chloride, pyridine, 80 °C, 1 h, 50%) which had been previously prepared by an independent route by Tsuboyama[17] [mp 156–9 °C, $[\alpha]_D^{23}$ +189° (*c* 1, EtOH) (lit.[17] mp 160–1 °C, $[\alpha]_D^{23}$ +216°)].

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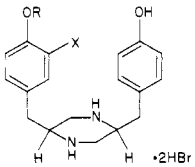
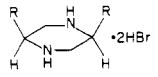
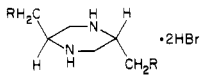
Table I. Physical Data for *cyclo*-Dipeptides

peptide	yield, %[a]	mp,[b] °C	$[\alpha]^{23}$, deg[c]	
9a, *c*-L-Tyr-L-Tyr	96	277–9	−126	(*c* 1, Me_2SO)
9b, *c*-3-Br-L-Tyr-L-Tyr	86	256–8	−110	(*c* 0.4)
9c, *c*-*O*-Me-3-Br-L-Tyr-L-Tyr	76	268–9	−156	(*c* 0.2)
9d, *c*-*O*-Me-3-I-L-Tyr-L-Tyr	68	255–6	−121	(*c* 0.2)
6c, *c*-L-Ala-L-Ala	*d*	283–6	−21.4	(*c* 0.4)
6a, *c*-L-Phe-L-Phe	*d*	319–20	−98	(*c* 0.2)
9e, *c*-D-Tyr-L-Tyr	*e*	292–3	*f*	

[a] Yield **8**→**9**, unless otherwise noted. [b] Uncorrected, all with decomposition. [c] In glacial acetic acid, except as noted. [d] Bachem Chemicals, Torrance, CA. [e] By pyrolysis of L-TyrOMe; see ref 13. [f] Trans isomer.

Table II. Physical Data for Piperazine Dihydrobromides

compd[a]	yield, %[b]	$[\alpha]^{23}_D$, deg[c]	anal, % C calcd	C found	H calcd	H found
						
10a, R = X = H	76	−15.1	46.98	47.01	5.26	5.35
10b, R = H; X = Br	89	−18.7	40.10	39.98	4.30	4.26
10c, R = CH_3; X = Br	72	−20.5	41.26	41.13	4.56	4.44
10d, R = CH_3; X = I	79	−12.1	38.03	37.96	4.20	4.29
						
7c, R = CH_3	60	+4.0	26.11	26.23	5.84	5.91
7a, R = $CH_2C_6H_5$	35	−12.9	50.49	50.43	5.65	5.60
						
11, R = C_6H_5	78	0.0	46.98	47.16	5.26	5.35

[a] Although crystalline, these compounds darken and decompose without sharp melting points. [b] By BH_3/THF reduction. [c] All are *c* 2 in H_2O.

The availability of *cyclo*-dipeptides bearing the full range of side chains, in conjugation with the known chemoselectivities of BH_3/THF, makes this a versatile method for the synthesis of chiral piperazines. Even though this procedure would not work for certain amino acids—e.g., Asn, Gln, Asp, and Glu—it is likely to be successful for nearly all the others and thus to be a truly general method. Elaboration of **10a–d** to piperazinomycin **1** and herquline **2** is being actively pursued.

Experimental Section

General. Melting points were determined on a Buchi melting-point apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a Bruker WP-200 spectrometer at 200.11 and 50.32 MHz, respectively, using tetramethylsilane or sodium 3-(trimethylsilyl)propionate as an internal standard. IR spectra were taken on a Perkin-Elmer 710B spectrometer and optical rotations were measured on a Perkin-Elmer 241 MC polarimeter. TLC was done on Merck Silica Gel 60 F_{254} sheets. Elemental analyses were performed by Spang Microanalytical Laboratory. Tetrahydrofuran (THF) and diethyl ether were distilled from sodium benzophenone ketyl. 98% Formic acid was prepared by drying 88% formic acid over boric anhydride, followed by distillation.[18] Technical grade thionyl chloride was redistilled until colorless. Anhydrous methanol, acetonitrile, bromine, and dimethylformamide (DMF) from Mallinckrodt were used as received. All reactions were performed in flame-dried glassware, under a atmosphere of dry argon.

3-Bromo-4-*O*-methyl-L-tyrosine. A solution of 4-*O*-methyl-L-tyrosine[19] (50.0 g, 0.260 mol) in 98% formic acid (220 mL) was cooled to 5–7 °C (internal) in an ice/*p*-dioxane slush bath. With rapid mechanical stirring, bromine (13.10 mL, 0.260 mol) was introduced dropwise over 2.5 h from a calibrated buret. After stirring 6 h more the colorless paste was dissolved with 3 N HCl (250 mL), boiled for 1 h, and evaporated to dryness in vacuo. The off-white residue was dissolved in boiling water (200 mL), hot filtered, and slowly neutralized (pH 7) with 6 N NH_4OH (ca. 60 mL) causing the product to precipitate. After cooling overnight the thick slurry was filtered and the cake was washed with water (100 mL) and dried (80 °C, 0.1 mm, 12 h), leaving shiny flakes: 62.5 g, 88% yield; mp 224–5 °C dec; $[\alpha]^{23}_D$ −1.1° (*c* 2, HCl); IR (KBr) 3000, 1570 cm^{-1}; ^1H NMR (5% D_2SO_4 in D_2O) δ 7.50 (1 H, d, *J* = 3 Hz), 7.29 (1 H, dd, *J* = 3, 9 Hz), 7.04 (1 H, d, *J* = 9 Hz), 4.39 (1 H, t, *J* = 7 Hz), 3.89 (3 H, s), 3.25 (2 H, t, *J* = 7 Hz); ^{13}C NMR (5% D_2SO_4 in D_2O) δ 174.2, 158.0, 136.9, 133.1, 130.8, 116.2, 114.1, 59.3, 56.9, 37.3. Anal. Calcd for $C_{10}H_{12}NO_3Br$: C, 43.82; H, 4.41. Found: C, 43.90; H, 4.41.

L-Tyrosine Methyl Ester Hydrochloride. Distilled thionyl chloride (11.2 mL, 0.154 mol) was added dropwise (ca. 30 min) to rapidly stirred, dry methanol (100 mL) which was cooled to below −5 °C (internal) with an ice/$CaCl_2$ slush bath during the entire addition period.[20] L-Tyrosine (25.4 g, 0.140 mol) was then added, and on warming a brown solution resulted. After 3 h at reflux the solution was cooled and slowly diluted with dry diethyl ether (300 mL). The product precipitated as shiny needles and was collected by filtration. After washing with ether and drying in vacuo, the yellowish crude product, 31.9 g, mp 188–9 °C dec, $[\alpha]^{23}_D$ −5.2° (*c* 2.4, H_2O) was recrystallized from absolute ethanol (80 mL) to give colorless needles: 26.7 g, 82% yield; mp 189–90 °C dec; $[\alpha]^{23}_D$ −5.2°.[23] ^1H NMR and IR spectra were in accord with published spectra.[22]

3-Bromo-L-tyrosine Methyl Ester Hydrochloride. 3-Bromo-L-tyrosine[23] was esterified as described for L-tyrosine. The crude product was recrystallized from absolute ethanol (5 parts) as needles: 79% yield; mp 184–5 °C dec; $[\alpha]^{23}_D$ +0.8° (*c* 2, H_2O); IR (KBr) 2850, 1745 cm^{-1}; ^1H NMR (D_2O) δ 7.44 (1 H, d, *J* = 2 Hz), 7.13 (1 H, dd, *J* = 2, 8 Hz), 6.99 (1 H, d, *J* = 8 Hz), 4.38 (1 H, t, *J* = 6 Hz), 3.85 (3 H, s), δ 3.20 (2 H, t, *J* = 7 Hz); ^{13}C NMR (D_2O) δ 172.8, 155.0, 136.6, 132.7, 129.9, 119.7, 112.5, 56.9, 56.4, 37.3. Anal. Calcd for $C_{10}H_{13}NO_3ClBr$: C, 38.67; H, 4.22. Found: C, 38.74; H, 4.16.

3-Bromo-4-*O*-methyl-L-tyrosine Methyl Ester Hydrochloride. 3-Bromo-4-*O*-methyl-L-tyrosine was esterified as described for L-tyrosine, except that twice the volume of methanol was used. The ether-precipitated product was crystalline: 92% yield; mp 209–10 °C dec; $[\alpha]^{23}_D$ +2.5° (*c* 2, H_2O); IR (KBr) 2820, 1745 cm^{-1}; ^1H NMR (D_2O) δ 7.46 (1 H, d, *J* = 2 Hz), 7.21 (1 H, dd, *J* = 2, 9 Hz), 7.05 (1 H, d, *J* = 9 Hz), 4.36 (1 H, t, *J* = 7 Hz), 3.89 (3 H, s), 3.85 (3 H, s), 3.20 (2 H, t, *J* = 7 Hz); ^{13}C NMR (D_2O) δ 172.9, 157.7, 136.6, 132.8, 130.6, 116.0, 113.9, 59.2, 56.9, 56.4, 37.4. Anal. Calcd for $C_{11}H_{15}NO_3ClBr$: C, 40.71; H, 4.66. Found: C, 40.76; H, 4.55.

3-Iodo-4-*O*-methyl-L-tyrosine Methyl Ester Hydrochloride. 3-Iodo-4-*O*-methyl-L-tyrosine hemihydrate[24] was esterified as described for L-tyrosine. Recrystallization from absolute ethanol (9 parts) gave fine needles: 81% yield; mp 199–200 °C dec; $[\alpha]^{23}_D$ +3.5° (*c* 2, H_2O); IR (KBr) 2800, 1745 cm^{-1}; ^1H NMR (D_2O) δ 7.68 (1 H, d, *J* = 8 Hz), 7.26 (1 H, dd, *J* = 2, 8 Hz), 6.97 (1 H, d, *J* = 8 Hz), 4.36 (1 H, t, *J* = 7 Hz), 3.87 (3 H, s), 3.85 (3 H, s), 3.19 (2 H, dd, *J* = 3, 7 Hz); ^{13}C NMR (D_2O) δ 173.3, 160.5, 143.0, 134.0, 131.3, 115.1, 88.5, 59.4, 57.0, 56.5, 37.3. Anal. Calcd for $C_{11}H_{15}NO_3ClI$: C, 35.56; H, 4.07. Found: C, 35.61; H, 4.03.

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***N*-(*tert*-Butoxycarbonyl)-L-tyrosyl-L-tyrosine Methyl Ester (8a).** A solution of L-tyrosine methyl ester hydrochloride (3.48 g, 15 mmol) and *N*-(*tert*-butoxycarbonyl)-L-tyrosine[25] (4.22 g, 15 mmol) in DMF (30 mL) and acetonitrile (120 mL) was cooled in ice. With stirring, triethylamine (2.10 mL, 15 mmol) was added followed by dicyclohexylcarbodiimide (DCC) (3.09 g, 15 mmol). After 2 h of continued stirring at 0 °C the mixture was placed in the freezer overnight. The dicyclohexylurea was filtered off and washed with ethyl acetate. The combined filtrate was evaporated in vacuo (0.1 mm, 50 °C) leaving a gummy residue which was taken up in ethyl acetate (250 mL) and water (150 mL). The organic layer was washed successively with 150-mL portions of 0.5 N HCl, H_2O, 0.5 N $NaHCO_3$, and brine. Drying over Na_2SO_4 and evaporation left 7.1 g yellow solid. Purification by flash chromatography[26] (R_f 0.40, 70% ethyl acetate/petroleum ether) gave a colorless foam: 5.11 g; 74% yield; mp 87–90 °C; $[\alpha]^{23}_D$ +38.8° (*c* 2, $CHCl_3$); IR (KBr) 3300, 1740, 1660, 1510, 1220, 1160 cm^{-1}; ^1H NMR δ 7.80 (2 H, br s), 6.90 (2 H, d, *J* = 8 Hz), 6.80 (2 H, d, *J* = 8 Hz), 6.67 (4 H, d, *J* = 8 Hz), 6.6 (1 H, buried amide NH), 5.31 (1 H, br s), 4.71 (1 H, m), 4.29 (1 H, m), 3.60 (3 H, s), 2.98–2.83 (4 H, 4 overlapping m), 1.37 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 171.6, 171.6, 155.8, 155.31, 155.30, 130.4, 130.3, 127.6, 126.9, 115.7, 115.7, 80.6, 56.1, 53.6, 52.4, 37.6, 37.1, 28.1. Anal. Calcd for $C_{24}H_{30}N_2O_7$: C, 62.87; H, 6.60. Found: C, 62.79; H, 6.64.

***N*-(*tert*-Butoxycarbonyl)-L-tyrosyl-3-bromo-L-tyrosine Methyl Ester (8b).** 3-Bromo-L-tyrosine methyl ester hydrochloride was coupled with *t*-BOC-L-Tyr by using DCC as described above. Yield 89% of **8b** as a colorless foam (R_f 0.38, 70% ethyl acetate/petroleum ether); mp 88–91 °C; $[\alpha]^{23}_D$ +39.6° (*c* 2, $CHCl_3$); IR (KBr) 3300, 1740, 1660, 1510, 1240, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.12 (1 H, d, *J* = 1 Hz), 6.99 (2 H, d, *J* = 8 Hz), 6.70 (2 H, d, *J* = 8 Hz), 6.88–6.70 (2 H, buried), 6.39 (1 H, br d, amide NH, *J* = 7 Hz), 6.20 (1 H, br s, OH), 6.13 (1 H, br s, OH), 5.04 (1 H, br s, carbamate NH), 4.72 (1 H, m), 4.28 (1 H, m), 3.69 (3 H, s), 3.05–2.86 (4 H, 4 overlapping m), 1.42 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 171.6, 171.4, 155.7 155.5, 151.9, 133.0, 130.4, 129.9, 129.0, 127.6, 116.4, 115.8, 110.25, 80.6, 56.2, 53.5, 52.5, 37.6, 36.8, 28.3. Anal. Calcd for $C_{24}H_{29}N_2O_7Br$: C, 53.64; H, 5.44. Found: C, 53.67; H, 5.50.

***N*-(*tert*-Butoxycarbonyl)-L-tyrosyl-3-bromo-4-*O*-methyl-L-tyrosine Methyl Ester (8c).** 3-Bromo-4-*O*-methyl-L-tyrosine methyl ester hydrochloride was coupled with *t*-BOC-L-Tyr by using DCC as described above. Yield 87% of **8c** as a colorless foam (R_f 0.30, 60% ethyl acetate/petroleum ether); mp 138–9 °C; $[\alpha]^{23}_D$ +35.0° (*c* 2, $CHCl_3$); IR (KBr) 3300, 1740, 1660, 1510, 1260, 1170 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.19 (1 H, d, *J* = 2 Hz), 6.98 (2 H, d, *J* = 8 Hz), 6.92 (1 H, dd, *J* = 2, 8 Hz), 6.76 (1 H, d, *J* = 8 Hz), 6.72 (2 H, d, *J* = 8 Hz), 6.41 (1 H, br d, amide NH, *J* = 7 Hz), 7.4–6.3 (1 H, v br s, OH), 5.04 (1 H, br s, carbamate NH), 4.71 (1 H, m) 4.24 (1 H, m), 3.84 (3 H, s), 3.67 (3 H, s), 2.93 (4 H, 4 overlapping m), 1.41 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 171.7, 171.3, 155.6, 155.6, 155.0, 134.0, 130.3, 129.3, 129.2, 127.4, 115.7, 112.0, 111.5, 80.6, 56.2, 56.1, 53.4, 52.4, 37.5, 36.7, 28.2. Anal. Calcd for $C_{25}H_{31}N_2O_7Br$: C, 54.45; H, 5.67. Found: C, 54.30; H, 5.67.

***N*-(*tert*-Butoxycarbonyl)-L-tyrosyl-3-iodo-4-*O*-methyl-L-tyrosine Methyl Ester (8d).** 3-Iodo-4-*O*-methyl-L-tyrosine methyl ester hydrochloride was coupled with *t*-BOC-L-Tyr by using DCC as described above. Yield 72% of **8d**, as a slightly yellow solid (R_f 0.33, 60% ethyl acetate/petroleum ether); mp 152–5 °C; $[\alpha]^{23}_D$ +35.3° (*c* 2, $CHCl_3$); IR (KBr) 3280, 1730, 1660, 1490, 1260, 1160 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.61 (1 H, br s, OH), 7.44 (1 H, d, *J* = 1 Hz), 7.01–6.62 (6 H, m), 6.6 (1 H, amide NH), 5.16 (1 H, br s, carbonyl NH), 4.72 (1 H, m), 4.30 (1 H, m), 3.80 (3 H, s), 3.66 (3 H, s), 2.93–2.82 (4 H, 4 overlapping m), 1.40 (9 H, s); ^{13}C NMR ($CDCl_3$) δ 171.4, 171.3, 157.3, 155.6, 155.5, 140.1, 130.4, 130.3, 129.8, 127.6, 115.7, 110.9, 85.9, 80.6, 56.6, 56.3, 53.4, 52.4, 37.6, 36.5, 28.3. Anal. Calcd for $C_{25}H_{31}N_2O_7I$: C, 50.18; H, 5.22. Found: C, 50.03; H, 5.13.

Preparation of *cyclo*-Dipeptides 9a–d. Cyclization of *N*-*t*-BOC-dityrosine methyl esters **8a–d** was accomplished using Nitecki's two-step procedure,[7] which was readily scaled-up to 10–50 mmol quantities. The precipitated products from 2-butanol were collected by filtration, washed with methanol and dried in vacuo (0.1 mm, 50 °C). No further purification was necessary. Physical constants are listed in Table I and spectral data is given below.

***cyclo*-L-Tyrosyl-L-tyrosine (9a).** IR (KBr) 3150, 1675, 1510, 1460, 1220 cm^{-1}; ^1H NMR[13b] (CF_3CO_2H) δ 8.18 (2 H, br s, NH), 7.11 (4 H, d, *J* = 9 Hz), 7.03 (4 H, d, *J* = 9 Hz), 4.57 (2 H, m), 3.09 (2 H, dd, *J* = 4, 14 Hz), 2.40 (2 H, dd, *J* = 8, 14 Hz); ^{13}C NMR (Me_2SO-d_6) δ 166.3, 156.1, 130.6, 126.7, 115.1, 55.8, 38.8. High-resolution mass spectroscopy, *m/e* 326.1265, calcd for $C_{18}H_{18}N_2O_4$ 326.1267.

***cyclo*-3-Bromo-L-tyrosyl-L-tyrosine (9b).** IR (KBr) 3210, 1670, 1515, 1470, 1240 cm^{-1}; ^1H NMR (CF_3CO_2H) δ 8.18 (1 H, br d, NH, *J* = 7 Hz), 8.15 (1 H, br s, NH′), 7.29–7.02 (7 H, m), 4.56 (2 H, 2 overlapping m), 3.14–2.99 (2 H, overlap), 2.50 (1 H, dd, *J* = 7, 14 Hz), 2.30 (1 H, dd, *J* = 7, 15 Hz); ^{13}C NMR (Me_2SO-d_6) δ 166.2, 156.1, 152.8, 133.8, 130.7, 130.0, 128.8, 126.5, 116.2, 115.1, 109.1, 55.8, 55.6, 40.0, 39.7; high-resolution mass spectroscopy, *m/e* 404.0371/406.0328, calcd for $C_{18}H_{17}N_2O_4Br$ 404.0371/406.0351.

***cyclo*-3-Bromo-4-*O*-methyl-L-tyrosyl-L-tyrosine (9c).** IR (KBr) 3180, 1670, 1500, 1470, 1270 cm^{-1}; ^1H NMR (CF_3CO_2H) δ 8.21 (2 H, br s, NH), 7.34 (1 H, d, *J* = 2 Hz), 7.16–7.04 (6 H, overlap), 4.58 (2 H, overlap m), 3.98 (3 H, s) 3.12 (1 H, dd, *J* = 4, 14 Hz), 3.05 (1 H, obscured), 2.54 (1 H, dd, *J* = 7, 14 Hz), 2.27 (1 H, dd, *J* = 7, 14 Hz); ^{13}C NMR (Me_2SO-d_6) δ 171.2, 171.0, 157.3, 157.1, 135.9, 133.0, 131.8, 129.8, 127.9, 117.6, 114.3, 113.3, 57.6, 57.4, 57.1, 40.1, 39.7; high-resolution mass spectroscopy, *m/e* 418.0552/420.0525, calcd for $C_{19}H_{19}N_2O_4Br$ 418.0528/420.0508.

***cyclo*-3-Iodo-4-*O*-methyl-L-tyrosyl-L-tyrosine (9d).** IR (KBr) 3290, 1670, 1495, 1455, 1250 cm^{-1}; ^1H NMR (CF_3CO_2H) δ 8.20 (2 H, br d, *J* = 10 Hz, NH), 7.57 (1 H, d, *J* = 2 Hz), 7.19–6.98 (6 H, overlap), 4.58 (2 H, overlap m), 3.93 (3 H, s), 3.10 (1 H, dd, *J* = 4, 14 Hz), 3.05 (1 H, dd, *J* = 4, 14 Hz), 2.47–2.29 (2 H, overlap dd); ^{13}C NMR (Me_2SO-d_6) δ 171.3, 171.1, 159.8, 157.6, 142.5, 133.0, 133.0, 130.4, 128.0, 117.7, 113.2, 87.3, 57.7, 57.5, 57.2, 39.5, 40.1; high-resolution mass spectroscopy, *m/e* 466.0378, calcd for $C_{19}H_{19}N_2O_4I$ 466.0389.

Reduction of *cyclo*-Dipeptides to Piperazine Dihydrobromides. To a well stirred suspension of *cyclo*-dipeptide (10 mmol) in THF (50 mL) was added 1 M BH_3/THF (60–80 mL) by syringe. After 1 h stirring at 20 °C the mixture was heated to reflux (under an efficient condenser) until all the solid passed into solution (**9a**, **b**, 96–144 h, 16 equiv BH_3 in two portions; **9c**, **d**, 24–48 h, 8 equiv BH_3; **6a**, **c**, 4 h, 6 equiv BH_3). The solution was filtered, cooled in ice, and slowly treated with 12% HBr/HOAc (50 mL). After the mixture was stirred 1 or 2 h the crude products precipitated as dihydrobromides (often with a mole of THF of crystallization) and were collected by filtration. In cases where precipitation was incomplete (**7a**, **11**) the filtrate was diluted with a volume of dry *n*-hexane and left to stand in the freezer overnight to give a second crop. Recrystallization from water (**10a–d**, **11**) or methanol/ether (**7a**, **c**) gave the pure compounds, which were dried in vacuo (0.1 mm, 50 °C, 24 h). Physical constants for the products are given in Table II and spectral data is listed below.

(2*S*,5*S*)-2,5-Bis[(*p*-hydroxyphenyl)methyl]piperazine Dihydrobromide (10a). IR (KBr) 3300–3000, 1545, 1510, 1210 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.41 (2 H, br s, OH), 9.27 (4 H, br s, NH), 7.18 (4 H, d, *J* = 8 Hz), 6.77 (4 H, d, *J* = 8 Hz), 3.76 (2 H, overlap m), 3.38–3.08 (8 H, overlap m); ^{13}C NMR (Me_2SO-d_6) δ 156.8, 130.6, 125.2, 115.7, 52.0, ca. 40.2 (solvent obscured), 32.7.

(2*S*,5*S*)-2-[(*o*-Bromo-*p*-hydroxyphenyl)methyl]-5-[(*p*-hydroxyphenyl)methyl]piperazine Dihydrobromide (10b). IR (KBr) 3300–2900, 1570, 1415, 1190 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.42 (6 H, br s, NH, OH), 7.58 (1 H, d, *J* = 1 Hz), 7.24 (1 H, dd, *J* = 9,1 Hz), 7.20 (2 H, d, *J* = 8 Hz), 6.98 (1 H, d, *J* = 9 Hz), 6.78 (2 H, d, *J* = 8 Hz), 3.83 (2 H, overlap m), 3.30–3.15 (8 H, overlap m); ^{13}C NMR (Me_2SO-d_6) δ 156.7, 153.4, 133.7, 130.5, 129.9, 127.2, 125.1, 116.7, 115.7, 109.5, 52.0, 51.7, 2 x ca. 40.2 (solvent obscured), 32.8, 32.1.

(2*S*,5*S*)-2-[(*o*-Bromo-*p*-methoxyphenyl)methyl]-5-[(*p*-hydroxyphenyl)methyl]piperazine Dihydrobromide (10c). IR (KBr) 3300–2900, 1580, 1520, 1270 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.45 (5 H, br s, NH, OH), 7.69 (1 H, d, *J* = 2 Hz), 7.44 (1 H,

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dd, J = 2, 9 Hz), 7.21 (2 H, d, J = 9 Hz), 7.14 (1 H, d, J = 9 Hz), 6.78 (2 H, d, J = 9 Hz), 3.85 (2 H, obscured m), 3.85 (3 H, s), 3.30–3.15 (8 H, overlap m); ^{13}C NMR (Me_2SO-d_6) δ 156.8, 154.9, 133.8, 130.5, 130.3, 128.9, 125.1, 115.7, 113.1, 110.9, 56.3, 52.1, 51.6, 2 X ca. 40.1 (solvent obscured), 32.9, 32.1.

(2*S*,5*S*)-2-[(*o*-Iodo-*p*-methoxyphenyl)methyl]-5-[(*p*-hydroxyphenyl)methyl]piperazine Dihydrobromide (10d). IR (KBr) 3250–2800, 1510, 1250 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 9.33 (5 H, br s, NH, OH), 7.84 (1 H, d, J = 2 Hz), 7.42 (1 H, dd, J = 2, 8 Hz), 7.18 (2 H, d, J = 8 Hz), 7.03 (1 H, d, J = 8 Hz), 6.77 (2 H, d, J = 8 Hz), 3.83 (2 H, obscured m), 3.83 (3 H, S), 3.30–3.12 (8 H, overlap m); ^{13}C NMR (Me_2SO-d_6) δ 157.2, 156.8, 139.8, 130.8, 130.5, 129.5, 125.2, 115.8, 111.7, 86.7, 56.6, 52.1, 51.9, 2 x ca. 40.1 (solvent obscured), 32.9, 31.9.

(2*S*,5*S*)-2,5-Bis(phenylmethyl)piperazine Dihydrobromide (7a). IR (KBr) 3300–2700, 1455, 1070, 970, 740 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 9.43 (4 H, br s, NH), 7.42–7.32 (10 H, m), 3.89 (2 H, m), 3.43–3.18 (8 H, overlap m); ^{13}C NMR (Me_2SO-d_6) δ 135.4, 129.6, 129.0, 127.5, 51.7, ca. 40.1 (solvent obscured), 33.7.

(2*S*,5*S*)-2,5-Dimethylpiperazine Dihydrobromide (7c). IR 3450, 2900, 2550, 1440, 1400, 1360 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 9.50 (4 H, br s, NH), 3.76 (2 H, m), 3.47 (2 H, dd, J = 4, 14 Hz), 3.24 (2 H, dd, J = 7, 14 Hz), 1.45 (6 H, d, J = 7 Hz); ^{13}C NMR (Me_2SO-d_6) δ 46.4, 42.0, 14.2.

***trans*-2,5-Bis[(*p*-hydroxyphenyl)methyl]piperazine Dihydrobromide (11).** IR (KBr) 3300–2900, 1560, 1210 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 8.05 (4 H, br s, NH), 7.27 (4 H, d, J = 8 Hz), 6.85 (4 H, d, J = 8 Hz), 3.90–2.65 (10 H, overlap m); ^{13}C NMR (Me_2SO-d_6) 156.4, 130.3, 126.5, 115.5, 60.9, 59.7, 54.0, 34.0.

(2*S*,5*S*)-1,4-Dibenzoyl-2,5-dimethylpiperazine. (2*S*,5*S*)-2,5-Dimethylpiperazine dihydrobromide (**7c**) (110 mg, 0.4 mmol) was dissolved in dry pyridine (2 mL) at 80 °C and treated with benzoyl chloride (220 mg, 1.6 mmol). After 2 h of stirring the cooled mixture was partitioned between ethyl acetate (10 mL) and 1 N HCl (20 mL). The organic layer was dried with Na_2SO_4 and evaporated to leave an orange residue. Flash chromatography (R_f 0.35, 70% ethyl acetate/petroleum ether) gave 66 mg colorless solid, 50% yield; IR (KBr) 1640, 1605, 1420 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42 (10 H, br s); 4.43 (2 H, m); 3.88 (2 H, dd, J = 4, 15 Hz), 2.98 (2 H, dd, J = 11, 15 Hz), 1.16 (6 H, d, J = 6 Hz). Anal. Calcd for $C_{20}H_{22}N_2O_2$: C, 74.51; H, 6.87. Found: C, 74.51; H, 6.72.

(2*S*,5*S*)-1,4-Dimethyl-2,5-bis(phenylmethyl)piperazine (7b). A suspension of (2*S*,5*S*)-bis[(*p*-hydroxyphenyl)methyl]-piperazine dihydrobromide (**7a**; 128 mg, 0.3 mmol) in 98% formic acid (700 mg) and 37% formaldehyde (800 mg) was heated at 70 °C for $^1/_2$ h. The cooled reaction mixture was partitioned between ethyl acetate (10 mL) and saturated aqueous $NaHCO_3$ (35 mL). The organic layer was dried over Na_2SO_4 and evaporated in vacuo to leave 91 mg of off-white solid. Flash chromatography (R_f 0.3, ethyl acetate) gave a colorless crystalline solid: 81 mg, 90% yield; IR, ^{1}H and ^{13}C NMR, and mass spectra were in accord with values reported.[11]

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Registry No. **1**, 83858-82-6; **2**, 71812-08-3; **6a**, 2862-51-3; **6c**, 5845-61-4; **7a**·2HBr, 98778-70-2; **7b**, 81536-08-5; **7c**·2HBr, 98778-71-3; **8a**, 27513-48-0; **8b**, 98778-72-4; **8c**, 98778-73-5; **8d**, 98778-74-6; **9a**, 10125-11-8; **9b**, 98778-75-7; **9c**, 98778-76-8; **9d**, 98778-77-9; **9e**, 10125-12-9; **10a**, 98778-78-0; **10b**, 98778-79-1; **10c**, 98778-80-4; **10d**, 98778-81-5; **11**, 98854-94-5; 4-*O*-methyl-L-tyrosine, 6230-11-1; 3-bromo-4-*O*-methyl-L-tyrosine, 98778-82-6; L-tyrosine methyl ester hydrochloride, 3417-91-2; 3-bromo-L-tyrosine, 38739-13-8; 3-bromo-L-tyrosine methyl ester hydrochloride, 98778-83-7; 3-bromo-4-*O*-methyl-L-tyrosine methyl ester hydrochloride, 98778-84-8; 3-iodo-4-*O*-methyl-L-tyrosine, 98778-85-9; 3-iodo-4-*O*-methyl-L-tyrosine methyl ester hydrochloride, 98778-86-0; *N*-(*tert*-butoxycarbonyl)-L-tyrosine, 3978-80-1; L-tyrosine, 60-18-4; (2*S*,5*S*)-1,4-dibenzoyl-2,5-dimethylpiperazine, 59525-66-5; benzoyl chloride, 98-88-4; borane, 13283-31-3.

Synthesis of 2′-*C*-Fluoro-β-daunomycin. An Example of Configurational Retention in Fluorodehydroxylation with Diethylaminosulfur Trifluoride

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Fluorodehydroxylation of benzyl 3-azido-3-deoxy-4,6-*O*-benzylidene-α-D-altropyranoside in the presence of diethylaminosulfur trifluoride proceeded with configurational retention at C-2. On the basis of this reaction a new synthesis of benzyl 3-amino-2,3,6-trideoxy-2-fluoro-β-L-galactopyranoside, a C-2 fluoro analogue of daunosamine was accomplished. From the latter and daunomycinone, 2′-*C*-fluoro-β-daunomycin was stereospecifically prepared and its antitumor activity evaluated.

The antibiotic daunomycin (**1**) is a clinically useful antineoplastic agent.[1] As part of a program directed toward the synthesis of analogues of **1** modified in the amino–sugar moiety,[2,3] we now report the synthesis of 2′-*C*-fluoro-β-daunomycin (**2**). The synthesis of **2** was undertaken in the hope that strengthening of the glycosidic linkage of daunomycin would result in an improvement of its ther-

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