Hz), 4.05 (dd, 1, J = 2.69, 10.01 Hz), 3.45–3.20 (m, 3), 3.00–2.80 (m, 2), 2.50–2.30 (m, 2); ^{2}H NMR ($CHCl_3$) δ 2.33 (s, NC^2H_3); exact mass calcd for $C_{18}{}^2H_3{}^1H_{17}N_2$ (M^+) 267.1813, found 267.1806.

Acknowledgment. We thank Dr. R. M. Koenig (Organon) for a generous gift of **5a**. We gratefully acknowledge the technical assistance of L. Todisco (NEN) and R. Nugent (NEN) in the conversion of **5b** to **5c** and the help of Dr. P. Srinivasan (NEN) and L. Thomas (NEN) in obtaining the ^{3}H NMR for **5c** and the ^{2}H NMR spectrum for **5d**. We also thank Professor S. H. Snyder (Johns Hopkins) for performing receptor binding experiments on **5c** and Professor H.-R. Schulten (University of Bonn) for obtaining the field-desorption mass spectrum of **5c**. Finally we also gratefully acknowledge the technical assistance of M. Tutunjian (NEN) and R. Wellman (NEN) in performing the HPLC experiments on **5a**, **5c**, and **5d**.

Registry No. (±)-**5a**, 76612-54-9; (±)-**5b**, 77862-25-0; (±)-**5c**, 77862-26-1; (±)-**5d**, 77862-27-2.

1,4-Dihydroxy-2,5-dioxopiperazines from Activated *N*-Hydroxy Amino Acids

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With the characterization[1] of the mold metabolite aspergillic acid as a cyclic hydroxamic acid and the demonstration[2] of the in vivo N-hydroxylation of amides, interest in oxidized peptide bonds [C(O)N(OH)] continues to grow. It is now recognized that such hydroxamic acids occur frequently in nature, serving as growth factors, antibiotics, and microbial pigments.[3] In addition, they may play a role in the biosynthesis of microbial metabolites.[4] Such considerations led us to undertake the synthesis of 1,4-dihydroxy-2,5-dioxopiperazines (**9**) in our study of the biosynthesis of gliotoxin.[5]

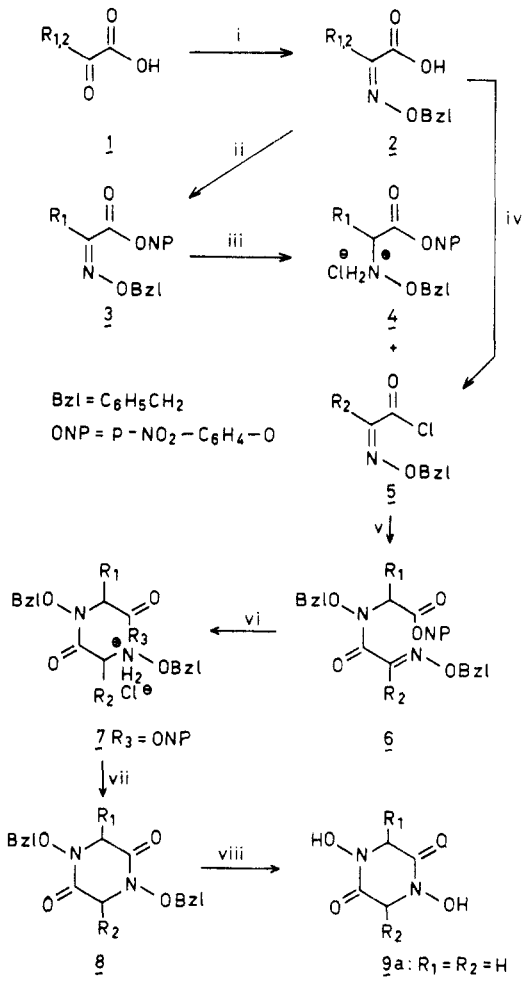
Since the only synthesis of *N,N'*-dihydroxydioxopiperazines (**9**) reported to date[6] is rather inefficient, we first set out to devise an efficient, generally applicable scheme for these compounds. Conventionally, dioxopiperazines are prepared by ring closure of the corresponding dipeptide alkyl esters. This approach fails, however, in the synthesis of the title compounds as the ethyl esters of *N,N'*-bis(benzyloxy)dipeptides **7** (R_3 = OC_2H_5) resisted all attempts to produce **8** by ring closure. This failure can be rationalized by assuming that the N(H) benzyloxy group in **7** (R_3 = OC_2H_5) causes increased steric hindrance and decreased nucleophilicity compared to the corresponding amine. The conversion **7** → **8** thus seemed to require an activated carboxylic acid derivative of **7**. Indeed, we found that ring closure could be achieved by neutralizing a solution of the *p*-nitrophenyl ester **7** with pyridine, giving **8** in fair to good yields (see Table I).

Table I. *N,N'*-Dibenzyloxydioxopiperazines **8**[a]

8	% yield from 4	mp, °C (CH_2Cl_2/hexane)	formula
a, R_1 = H, R_2 = H	61	217-218	$C_{18}H_{18}N_2O_4$
b, R_1 = H, R_2 = CH_3	60	137-138	$C_{19}H_{20}N_2O_4$
c, R_1 = CH_3, R_2 = H	35		
d, R_1 = CH_3, R_2 = CH_3	44	170-171	$C_{20}H_{22}N_2O_4$
e, R_1 = *i*-C_3H_7, R_2 = H	21	114-115	$C_{21}H_{24}N_2O_4$
f, R_1 = *i*-C_3H_7, R_2 = CH_3	29	141-142	$C_{22}H_{26}N_2O_4$

[a] Satisfactory analyses (±0.3 for C, H, N) were reported for all compounds in the table.

Scheme I[a]



[a] i, $C_6H_5CH_2ONH_2$·HCl; ii, *p*-$NO_2C_6H_4OH$, DCC, AcOEt; iii, $(CH_3)_3N{\cdot}BH_3$, HCl, Et_2O; iv, $SOCl_2$, toluene; v, pyridine, CH_2Cl_2; vi, $(CH_3)_3N{\cdot}BH_3$, HCl, dioxane; vii, pyridine, CH_2Cl_2; viii, Pd/C, H_2, dioxane.

The precursor, active ester **7**, could easily be prepared since we found that our conditions[7] for the reduction of the α-oximino carboxylic acid derivatives **3** and **6** are, fortunately, compatible with the presence of a *p*-nitrophenyl ester. Thus, on reduction of **3** with $(CH_3)_3N{\cdot}BH_3$ in anhydrous ether, saturated with HCl, compound **4** precipitated from the reaction mixture as a crystalline solid

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0022-3263/81/1946-3346$01.25/0

(66–87% yield). The free amine of **4**, obtained simply by washing a CH_2Cl_2 solution of **4** with water, showed no tendency to dioxopiperazine formation. However, reaction with the α-oximino acid chloride **5**, prepared[8] from **1** via **2** as outlined in Scheme I, proceeded smoothly to give **6**, which on a second, selective $(CH_3)_3N{\cdot}BH_3$ reduction afforded **7**.

The ^1H NMR spectra of **8d** and **8f** showed the presence of two diastereomers in a 2:3 ratio (see Experimental Section). This indicates that reductions of **6d** and **6f** proceed with some chiral induction. At this time, we have made no attempt to determine the stereochemistry.

Finally, the O-protecting benzyl groups in **8** could easily be removed with H_2–Pd/C[9] to give the *N,N'*-dihydroxydioxopiperazines **9**. To illustrate this, compound **8a** was converted into **9a**, which gave the red color with $FeCl_3$ typical of hydroxamic acids and an insoluble copper complex with a methanolic cupric acetate solution.

Work is in progress to convert **9** into sulfur-bridged dioxopiperazines, by synthetic as well as microbial methods. Now that *p*-nitrophenyl esters of *N*-benzyloxy amino acids **4** are easily accessible, and since the oxime reduction conditions appeared to be compatible with peptide bonds, it is very likely that peptides having one or more *N*-hydroxy amide linkages in their sequence can now be prepared.[10] In addition, as we have described previously, such *N*-hydroxy amino acid derivatives can easily be converted into α-functionalized[11] and α,β-dehydro amino acid derivatives.[12] Thus, we think compounds such as **4** deserve special attention as intermediates in the synthesis of natural products bearing the above structures.

Experimental Section

Infrared spectra were measured with a Perkin-Elmer spectrophotometer, Model 397. Proton magnetic resonance spectra were measured on a Varian Associates Model T-60 or a Bruker WH-90 spectrometer. Chemical shifts are reported as δ values (parts per million, relative to tetramethylsilane as an internal standard); deuteriochloroform was used as solvent unless stated otherwise. Mass spectra were obtained with a double-focusing Varian Associates SMI-B spectrometer. Melting points were taken on a Köfler hot stage (Leitz-Wetzlar) and are uncorrected. Thin-layer chromatography (TLC) was carried out by using Merck precoated silica gel F-254 plates (thickness 0.25 mm). Spots were visualized with a UV hand lamp or iodine vapor. For high-pressure LC the Miniprep LC (Jobin Yvon) was used.

α-Benzyloximino Carboxylic Acids 2. The α-keto acid **1** (or its hydrate, 100 mmol) was added at room temperature to a stirred solution of benzylhydroxylamine hydrochloride (16.75 g, 105 mmol) in 1 L of H_2O. Within a few minutes a crystalline mass or an oil separated. Stirring was continued for 2 h; then CH_2Cl_2 (200 mL) was added. The organic layer was separated and dried (Na_2SO_4), and the solvent was evaporated to give pure **2** in quantitative yield.

2 (R_1 = H): mp 78–80 °C (CCl_4/hexane); ^1H NMR δ 9.51 (s, 1 H, OH), 7.48 (s, 1 H, HC=), 7.35 (s, 5 H, C_6H_5), 5.28 (s, 2 H, CH_2).

2 (R_1 = CH_3): mp 83–85 °C (CCl_4/hexane); ^1H NMR δ 9.23 (s, 1 H, OH), 7.40 (s, 5 H, C_6H_5), 5.28 (s, 2 H, CH_2), 2.08 (s, 3 H, CH_3).

2 (R_1 = *i*-C_3H_7): oil; mixture of syn and anti; ^1H NMR δ 9.32 (s, 1 H, OH), 7.36 (s, 5 H, C_6H_5), 5.26 (s, 2 H, CH_2), 3.41 and 2.63 (2 m, 1 H, CH), 1.22 and 1.16 [2 d, 6 H, $(CH_3)_2$].

α-Benzyloximino *p*-Nitrophenyl Esters 3. Dicyclohexylcarbodiimide (11 g, 53 mmol) was added to an ice-cooled, stirred solution of **2** (50 mmol) and *p*-nitrophenol (8.3 g, 60 mmol) in 100 mL of ethyl acetate. Stirring was continued for 45 min at 0 °C and then 30 min at room temperature. The precipitated dicyclohexylurea was removed by filtration and the ethyl acetate was evaporated. Crystallization from 2-propanol gave pure **3**. Only one syn or anti isomer (not determined) formed in each of the following cases.

3 (R_1 = H): 80% yield; mp 87–88 °C; ^1H NMR δ 8.26 and 7.27 (AB, 4 H, C_6H_4), 7.72 (s, 1 H, HC=), 7.41 (s, 5 H, C_6H_5), 5.39 (s, 2 H, CH_2).

3 (R_1 = CH_3): 81% yield; mp 100–101 °C; ^1H NMR δ 8.24 and 7.27 (AB, 4 H, C_6H_4), 7.40 (s, 5 H, C_6H_5), 5.37 (s, 2 H, CH_2), 2.23 (s, 3 H, CH_3).

3 (R_1 = *i*-C_3H_7): 54% yield; mp 71–72 °C; ^1H NMR δ 8.28 and 7.24 (AB, 4 H, C_6H_4), 7.40 (s, 5 H, C_6H_5), 5.32 (s, 2 H, CH_2), 3.54 (m, 1 H, CH), 1.25 [d, 6 H, $(CH_3)_2$].

***N*-Benzyloxy α-Amino Acid *p*-Nitrophenyl Ester Hydrochlorides 4.** Trimethylamine–borane (1.46 g, 20 mmol) was added at room temperature to a stirred solution of **3** (10 mmol) in 100 mL of anhydrous ether, saturated with dry HCl. Stirring was continued for 1 h, during which time a white crystalline precipitate formed. Then, another portion of $(CH_3)_3N{\cdot}BH_3$ (1.46 g, 20 mmol) was added and stirring was continued until completion of the reaction as monitored by TLC (CH_2Cl_2). The precipitate was collected and washed with dry ether to give **4** contaminated by traces of $(CH_3)_3N{\cdot}HCl$. Recrystallization afforded material homogeneous by ^1H NMR.

4 (R_1 = H): 66% yield, mp 85–87 °C (2-propanol); ^1H NMR ($CDCl_3/CD_3OD$) δ 8.28 and 7.39 (AB, 4 H, C_6H_4), 7.41 (s, 5 H, C_6H_5), 5.20 (s, 2 H, $CH_2C_6H_5$), 4.35 (s, 2 H, CH_2).

4 (R_1 = CH_3): 80% yield, mp 118–119 °C (*t*-BuOH); ^1H NMR ($CDCl_3/CD_3OD$) δ 8.28 and 7.39 (AB, 4 H, C_6H_4), 7.41 (s, 5 H, C_6H_5), 5.26 (s, 2 H, CH_2), 4.44 (q, 1 H, $CHCH_3$), 1.79 (d, 3 H, CH_3).

4 (R_1 = *i*-C_3H_7): 87% yield; mp 111–113 °C (*t*-BuOH); ^1H NMR ($CDCl_3/CD_3OD$) δ 8.27 and 7.35 (AB, 4 H, C_6H_4), 7.39 (s, 5 H, C_6H_5), 5.22 (AB, 2 H, $CH_2C_6H_5$), 4.11 (d, 1 H, CHN), 2.52 (m, 1 H, $CH(CH_3)_2$), 1.24 and 1.17 (2 d, 6 H, $2CH_3$).

α-Benzyloximino Acid Chlorides 5. These compounds were prepared by a slight modfication of the procedure of Waters and Hartung.[8]

A solution of $SOCl_2$ (9.0 g, 75 mmol) in 20 mL of dry toluene was added at room temperature to a stirred solution of **2** (25 mmol) and dimethylformamide (several drops) in 25 mL of dry toluene. Stirring was continued for 2 h at 80 °C after which time the solvent and excess $SOCl_2$ were evaporated. To remove residual $SOCl_2$ and liberated SO_2, 50 mL of toluene was added and evaporated; this was repeated twice. Distillation of the residue under reduced pressure afforded the pure acid chlorides **5**.

5 (R_2 = H): 94% yield; bp 82 °C (0.5 mmHg); ^1H NMR δ 7.49 (s, 1 H, CH), 7.32 (s, 5 H, C_6H_5), 5.33 (s, 2 H, CH_2); IR ($CHCl_3$) 1750 (C=O), 1580 cm^{-1} (C=N).

5 (R_2 = CH_3): 87% yield; bp 84 °C (0.3 mmHg); ^1H NMR δ 7.34 (s, 5 H, C_6H_5), 5.32 (s, 2 H, CH_2), 2.13 (s, 3 H, CH_3); IR ($CHCl_3$) 1745 (C=O), 1600 cm^{-1} (C=N).

1,4-Dibenzyloxy-2,5-dioxopiperazines 8. The acid chloride **5** (4.5 mmol) was added at room temperature to a stirred solution of **4** (4 mmol) and pyridine (0.75 g, 9.5 mmol) in 25 mL of dry CH_2Cl_2. Stirring was continued at room temperature for 16 h. The reaction mixture was washed twice with 0.1 N aqueous HCl (100 mL) and the organic layer was separated and dried (Na_2SO_4). The residue, after evaporation of the solvent, was used in the next reaction without further purification. As a representative example, **6a** was recrystallized from 2-propanol.

6a: mp 87–88 °C; ^1H NMR δ 8.25 and 7.28 (AB, 4 H, C_6H_4), 7.98 (s, 1 H, CH), 7.38 (s, 5 H, C_6H_5), 7.35 (s, 5 H, C_6H_5), 5.27 (s, 2 H, CH_2), 4.96 (s, 2 H, CH_2), 4.58 (s, 2 H, CH_2); IR (KBr) 1775, 1595 cm^{-1} (C=N). Anal. Calcd for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57; N, 9.07. Found: C, 62.54; H, 4.55; N, 9.02.

Trimethylamine–borane was added at room temperature in two to four portions of 8 mmol (584 mg) each, 1 h apart, to a stirred solution of crude **6** (4 mmol) in 25 mL of dioxane, saturated with dry HCl. After completion of the reaction as monitored by TLC (CH_2Cl_2/CH_3OH, 99:1 v/v) the solvent was evaporated to give

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crude **7** which was used in the next reaction without further purification.

Excess pyridine (2.4 g, 30 mmol) was added to a stirred solution of crude **7** (4 mmol) in 25 mL of dry CH_2Cl_2. Stirring was continued for 24 h at room temperature. The solution was washed twice with 0.1 N aqueous HCl (50 mL) and the organic layer was separated and dried (Na_2SO_4). After evaporation of the solvent, the dioxopiperazines were isolated either by column chromatography (**8d** and **8f**) on silica gel (Merck, Kieselgel H, CH_2Cl_2/CH_3OH 98:2 v/v as eluent) or by precipitation. To the stirred residue were added 5 mL of methanol and some water just to the point of turbidity. The precipitate was collected and washed several times with a 5% aqueous $NaHCO_3$ solution and then with water to give the dioxopiperazines **8** which were homogeneous on TLC (CH_2Cl_2/CH_3OH, 96:4 v/v). Recrystallization was achieved by using CH_2Cl_2/hexane mixtures. One isomer only crystallized with **8d** and **8f** as determined by using ytterbium tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate as a ^1H NMR shift reagent. For the overall yields, melting points, and elemental analyses see Table I.

8a: ^1H NMR δ 7.39 (s, 10 H, 2 C_6H_5), 4.99 (s, 4 H, 2 $CH_2C_6H_5$), 3.98 (s, 4 H, 2 CH_2); IR (KBr) 1675 cm^{-1} (C=O); mass spectrum, *m/e* 326 $[M]^+\cdot$, 234 $[M - C_7H_8]^+\cdot$, 220 $[M - C_6H_5CHO]^+\cdot$, 181 $[C_{14}H_{13}]^+\cdot$, 91 $[C_7H_7]^+$.

8b,c: ^1H NMR δ 7.39 and 7.40 (2 s, 10 H, 2 C_6H_5), 4.99 (AB, 2 H, $CH_2C_6H_5$), 4.96 (s, 2 H, $CH_2C_6H_5$), 3.99 (q, 1 H, $CHCH_3$), 3.95 (s, 2 H, CH_2), 1.50 (d, 3 H, CH_3); IR (KBr) 1680 cm^{-1} (C=O); mass spectrum, *m/e* 340 $[M]^+\cdot$, 248 $[M - C_7H_8]^+\cdot$, 234 $[M - C_6H_5CHO]^+\cdot$, 181 $[C_{14}H_{13}]^+\cdot$, 91 $[C_7H_7]^+$.

8d: ^1H NMR δ 7.39 (s, 10 H, 2 C_6H_5), 4.97 (AB, 4 H, 2 $CH_2C_6H_5$), 3.99 (q, 2 H, 2 $CHCH_3$), 1.55 (d, 6 H, 2 CH_3); IR (KBr) 1675 cm^{-1} (C=O); mass spectrum, *m/e* 354 $[M]^+\cdot$, 262 $[M - C_7H_8]^+\cdot$, 248 $[M - C_6H_5CHO]^+\cdot$, 181 $[C_{14}H_{13}]^+\cdot$, 91 $[C_7H_7]^+$. Second isomer: ^1H NMR δ 7.39 (s, 10 H, 2 C_6H_5), 4.97 (s, 4 H, 2 $CH_2C_6H_5$), 4.03 (q, 2 H, 2 $CHCH_3$), 1.53 (d, 6 H, 2 CH_3).

8e: ^1H NMR δ 7.39 and 7.40 (2 s, 10 H, 2 C_6H_5), 4.99 (s, 2 H, $CH_2C_6H_5$), 4.94 (AB, 2 H, $CH_2C_6H_5$), 4.01 (s, 2 H, CH_2), 3.85 (d, 1 H, CHN), 2.48 [m, 1 H, $CH(CH_3)_2$)], 1.01 and 0.94 (2 d, 6 H, 2 CH_3); IR (KBr) 1670 cm^{-1} (C=O); mass spectrum, *m/e* 368 $[M]^+\cdot$, 276 $[M - C_7H_8]^+\cdot$, 262 $[M - C_6H_5CHO]^+\cdot$, 181 $[C_{14}H_{13}]^+\cdot$, 91 $[C_7H_7]^+$.

8f: ^1H NMR δ 7.39 (s, 10 H, 2 C_6H_5), 4.96 (s, 2 H, $CH_2C_6H_5$), 4.95 (AB, 2 H, $CH_2C_6H_5$), 4.13 (q, 1 H, $CHCH_3$), 3.87 (d, 1 H, CHN), 2.55 [m, 1 H, $CH(CH_3)_2$], 1.59 (d, 3 H, CH_3), 1.03 and 0.95 (2 d, 6 H, 2 CH_3); IR (KBr) 1675 cm^{-1} (C=O); mass spectrum, *m/e* 382 $[M]^+\cdot$, 290 $[M - C_7H_8]^+\cdot$, 276 $[M - C_6H_5CHO]^+\cdot$, 181 $[C_{14}H_{13}]^+\cdot$, 91 $[C_7H_7]^+$. Second isomer: ^1H NMR δ 7.39 (s, 10 H, 2 C_6H_5), 5.02 (AB, 2 H, $CH_2C_6H_5$), 4.96 (s, 2 H, $CH_2C_6H_5$), 4.13 (q, 1 H, $CHCH_3$), 3.94 (d, 1 H, CHN), 2.55 [m, 1 H, $CH(CH_3)_2$], 1.57 (d, 3 H, CH_3), 1.06 and 0.99 (2 d, 6 H, 2 CH_3).

1,4-Dihydroxy-2,5-dioxopiperazine (9a). A solution of **8a** (652 mg, 2 mmol) in 50 mL of dioxane was treated at room temperature and atmospheric pressure with H_2 and 10% Pd/C (50 mg) until 90 mL of H_2 (4 mmol) had been consumed, which took about 2 h. During this procedure **9a** precipitated. This precipitate and the catalyst were collected and separated by thorough washing with water. The dioxane and water layers were combined and the solvents evaporated. The residue was crystallized from hot CH_3OH to give **9a** (257 mg, 1.76 mmol), which was homogeneous on TLC ($BuOH/AcOH/H_2O$ 4:1:1 v/v): mp 180 °C dec; ^1H NMR (D_2O) δ 4.44 (s); IR (KBr) 3050 and 2700 (OH), 1690 and 1655 cm^{-1} (C=O); mass spectrum, *m/e* 146 $[M]^+\cdot$, 118 $[M - CO]^+\cdot$. Anal. Calcd for $C_4H_6N_2O_4$: C, 32.88; H, 4.14; N, 19.17. Found: C, 33.19; H, 4.14; N, 19.23.

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Registry No. 1 (R_1 = H), 298-12-4; 1 (R_1 = CH_3), 127-17-3; 1 (R_1 = i-C_3H_7), 759-05-7; **2** (R_1 = H), 77845-97-7; **2** (R_1 = CH_3), 77845-98-8; (*E*)-**2** (R_1 = i-C_3H_7), 77845-99-9; (*Z*)-**2** (R_1 = i-C_3H_7), 77846-00-5; **3** (R_1 = H), 77846-01-6; **3** (R_1 = CH_3), 77846-02-7; **3** (R_1 = i-C_3H_7), 77846-03-8; **4** (R_1 = H), 77846-04-9; **4** (R_1 = CH_3), 77846-05-0; **4** (R_1 = i-C_3H_7), 77846-06-1; **5** (R_2 = H), 77846-07-2; **5** (R_2 = CH_3), 77846-08-3; **6a**, 77846-09-4; **6b**, 77846-10-7; **6c**, 77846-11-8; **6d**, 77846-12-9; **6e**, 77846-13-0; **6f**, 77846-14-1; **7a**, 77846-15-2; **7b**, 77846-16-3; **7c**, 77846-17-4; **7d**, 77846-18-5; **7e**, 77846-19-6; **7f**, 77846-20-9; **8a**, 77846-21-0; **8b/8c**, 77846-22-1; **8d** (isomer 1), 77846-23-2; **8d** (isomer 2), 77846-24-3; **8e**, 77846-25-4; **8f** (isomer 1), 77846-26-5; **8f** (isomer 2), 77846-27-6; **9a**, 77846-28-7; benzylhydroxylamine·HCl, 2687-43-6.

Improved Preparation of (+)-(*R*)-Methyloxirane

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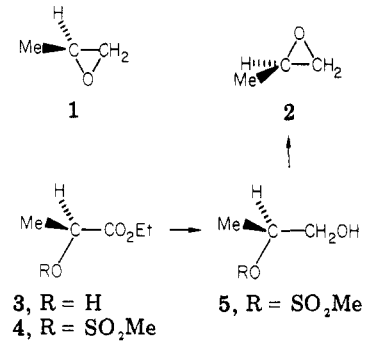
In the course of studies directed toward the synthesis of some macrocyclic dilactone antibiotics[1] we had need of optically active methyloxirane as a convenient chiral starting material.[2] Although preparations[3,4] for both (−)-(*S*)-methyloxirane (**1**) and (+)-(*R*)-methyloxirane (**2**)



3, R = H
4, R = SO_2Me
5, R = SO_2Me

have been reported, the methods reported for the latter are tedious and inefficient. Since the readily available ethyl (+)-(*S*)-lactate (**3**)[5] is a convenient precursor for (−)-(*S*)-methyloxirane, we investigated the possibility of also using this ester for the preparation of (+)-(*R*)-methyloxirane and herein report a rapid and efficient preparation for this useful chiral material in an overall yield of 71% from **3**.

Reaction of ethyl (+)-(*S*)-lactate (**3**) with methanesulfonyl chloride in toluene in the presence of triethylamine afforded the (−)-(*S*)-mesylate (**4**)[6] in 98% yield after distillation at reduced pressure. By this means, the chiral center was prepared for inversion during the epoxide-forming step. Selective reduction of the ethyl ester was

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