4-(Acetylamino)-TEMPO (2, R = NHAc). Acetic anhydride (70.0 g, 0.686 mol) was added, dropwise, to a solution of 34.6 g (0.221 mol) of 4-amino-2,2,6,6-tetramethylpiperidine dissolved in 100 mL of anhydrous ether that had been cooled to 0 °C. After addition was complete (about 1 h), the solution was stirred for 30 min at room temperature. The precipitate was removed by filtration and washed with 20 mL of ether to give 55.6 g (98%) of 4-(acetylamino)-2,2,6,6-tetramethylpiperidinium acetate, mp 175 °C subl.

The acetate was dissolved in 400 mL of water and basified with 50.0 g of $K_2CO_3 \cdot 1.5\ H_2O$ (0.303 mol). To this solution was added 80 mL of 30% H_2O_2, 4.00 g of sodium tungstate, and 4.00 g of ethylenediaminetetracetic acid, tetrasodium salt. The mixture was stirred at room temperature for 72 h. The red precipitate was removed by filtration and washed with 20 mL of H_2O to give 38.6 g of product, which melted at 146–147 °C, lit.[22] mp 147.5 °C. The filtrate was saturated with solid K_2CO_3 and extracted with two 100-mL portions of CH_2Cl_2. The organic phase was washed with saturated aqueous sodium chloride, dried over Na_2SO_4, and evaporated to give 7.1 g more of product, mp 145–147 °C. The combined yield was 45.7 g (overall yield for the two steps, 97%).

General Procedure for Alcohol Oxidation. Method A. *p*-Toluenesulfonic acid monohydrate (4.00 g, 21 mmol) was suspended in 30 mL of CH_2Cl_2 containing 10 mmol of the alcohol to be oxidized and cooled to 0 °C. A solution of 4.47 g (21 mmol) of nitroxide **2**, R = NHAc, in 30 mL of CH_2Cl_2 was added dropwise over 30 min. This addition could be much slower if there were a problem with selectivity. The solution was stirred at 0 °C for 1 h and then at room temperature until it was almost completely decolorized. During the last of the reaction or sometimes after color was gone, a heavy white precipitate formed. The mixture was cooled in ice, and the precipitate was removed by filtration and washed with 10 mL of cold CH_2Cl_2 to give the salt **4** in essentially quantitative yield. The filtrate was washed with 50 mL of H_2O and 50 mL of saturated aqueous NaCl and dried over Na_2SO_4. After removal of the solvent, the product was purified by distillation or crystallization. The products were identified by MS, IR, and NMR spectroscopy, and in some cases by derivative formation (Table I).

General Procedure for Alcohol Oxidation. Method B. A solution of oxoammonium salt **3**, R = NHAc, was prepared by stirring a suspension of 4.00 g (21.0 mmol) of *p*-toluenesulfonic acid monohydrate with 4.47 g (21.0 mmol) of nitroxide **2**, R = NHAc, in 30 mL of CH_2Cl_2 for 20 min at 0 °C. An intense red color developed from the oxoammonium salt. This solution was added dropwise to 10 mmol of the alcohol to be oxidized in 30 mL of cold CH_2Cl_2 over 30 min. The orange solution was then stirred at room temperature until the color was essentially gone and a dense white precipitate formed. The reaction mixture was then processed as described in method A.

4-(Acetylamino)-2,2,6,6-tetramethyl-1-hydroxypiperidinium *p*-Toluenesulfonate (4). The salt, as recovered from the oxidation reactions, melted at 169–171 °C when the temperature was slowly raised. When the temperature was raised quickly, a second melting point at about 145 °C was observed, almost surely corresponding to a loss of water. The compound was recrystallized from water with no change in mp. Anal. Calcd for $C_{18}H_{30}N_2O_4S \cdot H_2O$: C, 53.44; H, 7.97; N, 6.97. Found: C, 53.72; H, 8.05; N, 6.89.

Recovery of Nitroxide 2, R = NHAc, from Salt 4, R = NHAc. A solution of 22.8 g (60 mmol) of **4** in 300 mL of H_2O was made basic with 19.8 g of $K_2CO_3 \cdot 1.5\ H_2O$ (120 mmol). Hydrogen peroxide, 20 mL of 30% (170 mmol), *or* 27.3 g of sodium perborate tetrahydrate (170 mmol) was added, and the solution was stirred at room temperature for 24 h to give an intense red solution. The solution was saturated with solid K_2CO_3, and a red precipitate formed. The precipitate was removed by filtration to give 11.99 g (98%) of **2**, R = NHAc, mp 146–147 °C. The purity was sufficient for use in further oxidations.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. We also acknowledge financial support from the University of Connecticut Research Foundation.

Direct Conversion of (1*S*,2*S*)-2-Amino-1-[(4-methylthio)phenyl]-1,3-propanediol into Its Enantiomer for Efficient Synthesis of Thiamphenicol and Florfenicol

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Received April 30, 1991

The usual synthesis of thiamphenicol and florfenicol involves the resolution of racemic *threo*-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol into its 1*S*,2*S* and 1*R*,2*R* isomers ((+)-**3** and (−)-**3**), of which only the latter is a useful precursor. An efficient conversion of the 1*S*,2*S* isomer into the 1*R*,2*R* enantiomer in high yield, is described.

Thiamphenicol, *threo*-(1*R*,2*R*)-2-(dichloroacetamido)-1-[(4-methylsulfonyl)phenyl]-1,3-propanediol (**1**),[1] and florfenicol (**2**),[2] the 3-fluoro derivative of **1**, are broad-spectrum antibiotics (Figure 1).

Current manufacturing processes for **1** and **2** involve an optical resolution at some stage of the synthesis. In most cases, entrainment resolution[3] is performed on racemic *threo*-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol[4] to afford the 1*R*,2*R* isomer (−)-**3** (the precursor of **1** and

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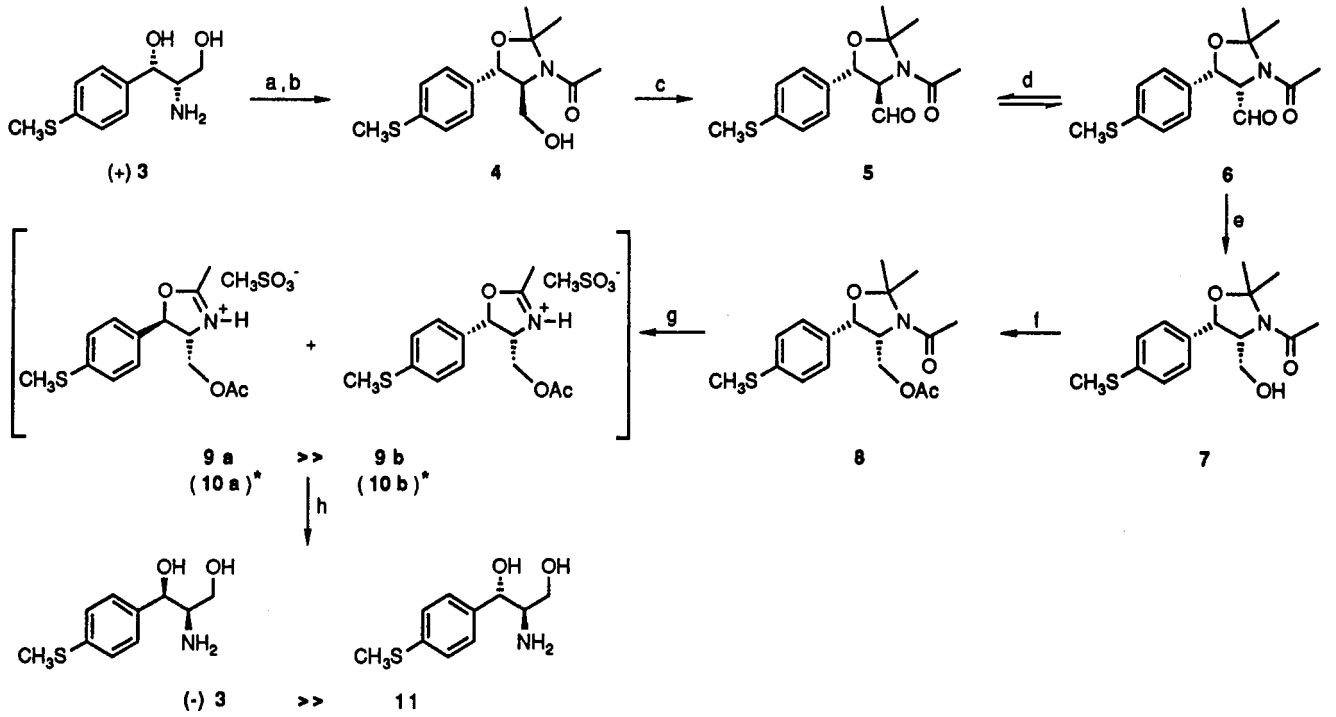
(4) Entrainment resolution of (±)-**3**: Long, L. M. U.S. Pat. 2,767,213, 1956; *Chem. Abstr.* **1957**, *51*, 7414b.

0022-3263/91/1956-6114$02.50/0

Scheme I[a]



[a] Key: (a) acetone, toluene, Δ; (b) CH_2Cl_2, CH_3COCl, Et_3N, K_2CO_3, MeOH; (c) CH_2Cl_2, $(COCl)_2$, DMSO, Et_3N; (d) DABCO, toluene, or neat. (e) THF, EtOH, $CaCl_2$, $NaBH_4$; (f) CH_3COCl, Et_3N, CH_2Cl_2; (g) $CHCl_3$, Ac_2O, CH_3SO_3H; (h) H_2O, NaOH, Δ. * indicates that in the text as well as in the experimental part **10a** and **10b** refer to oxazolines **9a** and **9b** as free bases, respectively.

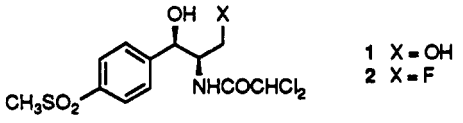


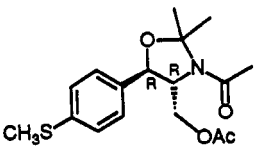
Figure 1.

2), and its 1*S*,2*S* enantiomer (+)-**3** with equal chemical and enantiomeric purities. Parallel processing of this latter material as a source of the desired 1*R*,2*R* isomer offers an opportunity to develop a practical route for the synthesis of **1** and **2** by maximizing utilization of the raw material and minimizing waste disposal.

In principle, two strategies exist for converting the 1*S*,2*S* isomer (+)-**3** into its 1*R*,2*R* isomer (−)-**3**. One involves a racemization,[5,6] which ultimately again necessitates a resolution. A more attractive strategy invokes the direct conversion of one enantiomer into the other without racemization. For both strategies, the juxtaposition of the functionalities complicates the problems of chemoselectivity. Additionally, an industrial process requires a limited number of steps, high yields, and commercially available reagents.

Here we report an efficient conversion of (1*S*,2*S*)-(+)-**3** into (1*R*,2*R*)-(−)-**3** by a sequential inversion of configurations at C_2 and C_1, in which each stereogenic center controls the other and maintains its stereochemical integrity (Scheme I). The heterocycle **4** provides the proper structural framework to impart the necessary thermodynamic, kinetic, and physical properties for the first epimerization, as well as the trigger for the second one.

Enantiomerically pure aminodiol (+)-**3** was condensed with acetone in toluene with azeotropic removal of water.

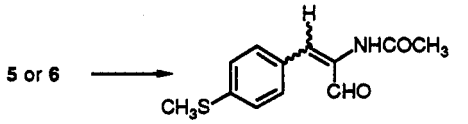


12

Figure 2.

N-Acetylation of the product derivatized both the amino and benzylic hydroxy groups to give *trans*-*N*-acetyl-1,3-oxazolidine **4** (65%). Chemoselective Swern oxidation[7] of **4** to the corresponding aldehyde **5**[8] occurred smoothly in quantitative yield.

The chemoselectivity of equilibration of **5** with **6**[9] re-



(1)

quires a basic catalyst that can effect epimerization without elimination; DABCO balances the desired properties. Although the equilibration of **5** with **6** with DABCO established a 45:55 ratio in toluene at 60 °C, a "second-order asymmetric transformation"[10] provided a stereoconver-

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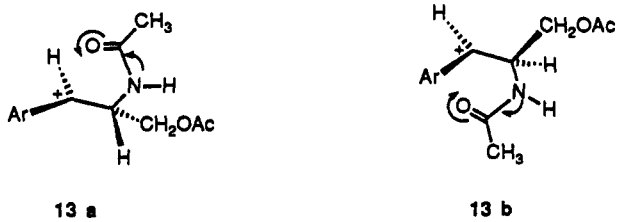
(8) ^1H NMR spectra of **5** and **6** show two rotamers due to restricted rotation of the nitrogen–carbon bond of the amido group. The rotamers are in ratios of 56:44 and 86:14 for **5** and **6**, respectively. For a similar example of restricted rotation in *N*-(carboxyalkyl)-1,3-oxazolidines see: Garner, P.; Park, J. M. *J. Org. Chem.* **1987**, *52*, 2361.

(9) Another example of base-promoted equilibrium of epimeric *N*-(carboxyalkyl)-5-formyl-1,3-oxazolidines is reported in: Thaisrivongs, S.; Pals, D. T.; Kroll, L. T.; Turner, S. R.; Han, F. *J. Med. Chem.* **1987**, *30*, 976.

(10) Morrison, J. D.; Mosher, H. S. *Asymmetric Organic Reactions*; American Chemical Society: Washington, 1976; p 23: "The interconversion of epimers in solution has been termed "first-order asymmetric transformation". When equilibration is accompanied by the separation of a crystalline phase from solution, the terms 'second-order asymmetric transformation' or 'optical activation' have been applied".



13 a 13 b

Figure 3.

gence into the single diastereomer **6**. Thus, heating neat **5** at 35 °C with a catalytic amount of DABCO caused equilibration with **6**, while the equilibrium was continuously displaced by crystallization of **6** from the medium, so that **5** was converted almost completely into **6**. After removal of the catalyst and recrystallization, pure *cis*-**6**[8] was obtained in 76% yield. Clean reduction of **6** with $NaBH_4$ and $CaCl_2$ in EtOH/THF provided (4*R*,5*S*)-*cis*-oxazolidine alcohol **7** in 97% yield.

A simple protocol accomplished the second epimerization. *O*-Acetylation of crude **7**[11] gave ester **8**, which was treated with CH_3SO_3H and Ac_2O in $CHCl_3$ at 35 °C for 2 h, producing acetone and a 95:5 diastereomeric mixture of oxazoline methanesulfonates **9a,b** (95%, Scheme I). The sequence was completed by hydrolysis with aqueous NaOH to give a 95:5 mixture of epimeric 2-aminopropanediols (1*R*,2*R*)-(−)-**3** and (1*S*,2*R*)-**11**. Crystallization produced analytically pure (−)-**3** in 86% yield based on **6**. The new process has been developed up to an industrial scale.

Mechanistic insight into the second epimerization was provided by a time-dependence study and examination of the behavior of the epimeric *O*-acetyl-(4*R*,5*R*)-*trans*-oxazolidine **12**. At 60% conversion of **8**, the ratio **9a:9b** was 97:3. At 100% conversion of **8**, the ratio was 95:5, and after prolonged exposure it became 90:10 (95% yield), which is the equilibrium composition (Figure 2).[12]

Similarly, **12** was converted into **9a** and **9b** in a ratio of 97:3 (93%), which eventually became the equilibrium ratio 90:10. There is no evidence that **12** is an intermediate in the conversion of **8** into **9a,b**. The ratio **9a:9b** is independent of the stereochemistry of the starting materials and appears to be kinetically controlled. A likely common intermediate that accounts for these observations is carbonium ion **13**, shown in two reactive forms (Figure 3). It is likely that the transition states reflect the relative stabilities of **9a** and **9b** in view of the similar values of the kinetic and thermodynamic ratios of **9a:9b**.

Experimental Section

General. ^1H NMR measurements were performed on a spectrometer operating at 300 MHz. Chemical shifts are expressed in ppm (δ) relative to tetramethylsilane. Coupling constants are expressed in Hz. Chromatographic separations were accomplished by flash column chromatography on silica gel (230–400 mesh). Melting points were measured on a Kofler apparatus and are not corrected. Chemical ionization mass spectra were recorded at 110 eV with isobutane as ionizing agent. IR spectra: positions of interesting absorptions are quoted to ±2.5 cm^{-1}. HPLC analyses: column Merck 50329 Lichrospher (5 μm; 250 mm × 4.0 mm); eluent CH_3CN/pH 3 buffered solution of KH_2PO_4 (0.02 M).

Removal of solvents under reduced pressure involved evaporation at ca. 20 mmHg on a rotary evaporator. All reactions were run under nitrogen.

All products gave satisfactory microanalyses: C ±0.3%, H ±0.3%, N ±0.3%, S ±0.5%.

Enantiomerically Pure (+)-(1*S*,2*S*)-2-Amino-1-[4-(methylthio)phenyl]-1,3-propanediol ((+)-3 and (−)-3)). A solution of (±)-**3**[13] (21.3 g; 100 mmol) and (+)-**3**[14] (2.13 g; 10 mmol) in water (143 mL) and 1 N hydrochloric acid (70 mL) was heated under slow stirring at 75 °C until a clear solution was obtained. The solution was cooled to 45 °C in 30 min, seeded with (+)-**3** (0.2 g), and allowed to cool to 27 °C over 2 h. The solution was kept at 27 °C for 1 h. The insoluble material was collected by filtration, washed with warm (27 °C) water (15 mL), and dried under vacuum at 60 °C to give (+)-**3** (3.4 g), $[\alpha]_D^{20}$ 31° (*c* 2, 0.1 N HCl), mp 146–149 °C. Crystallization of crude (+)-**3** from 2-propanol (50 mL) provided (+)-**3** (3.0 g) in chemically and enantiomerically pure form, $[\alpha]_D^{20}$ 32.8° (*c* 2, 0.1 N HCl), mp 149–152 °C.

The filtrate and washings were combined with (±)-**3** (3.4 g; 16 mmol), and the mixture was heated at 75 °C until a clear solution was obtained. Following the above procedure, after crystallization from 2-propanol (50 mL), enantiomerically pure (−)-**3** (3.1 g) was obtained, $[\alpha]_D^{20}$ −33.0° (*c* 2, 0.1 N HCl), mp 149–151 °C.

Both (−)-**3** and (+)-**3** were obtained as single enantiomers by repeating the above procedure several times, each time lowering by 1 °C the filtration temperature with respect to the previous preparation.

(4*S*,5*S*)-3-Acetyl-2,2-dimethyl-4-(hydroxymethyl)-5-[4-(methylthio)phenyl]-1,3-oxazolidine (4). A stirred mixture of enantiomerically pure (+)-(1*S*,2*S*)-2-amino-1-[(4-methylthio)phenyl]-1,3-propanediol (100 g; 0.469 mol), toluene (920 mL), and acetone (100 mL) was heated at reflux for 18 h with a Dean Stark trap. A mixture of toluene, water, and acetone (≈11 g) was collected. The solvent (≈200 mL) was distilled at ambient pressure and then under vacuum (internal temperature 80 °C) to give a residue (118.6 g). Acetyl chloride (38.3 g; 0.49 mol) was added over 2 h at 15 °C to a stirred solution of the residue and Et_3N (70.6 g; 0.7 mol) in CH_2Cl_2 (1170 mL). The reaction mixture was stirred for 3 h at 15 °C and was poured into a 10% aqueous NH_4Cl solution (400 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (300 mL). The combined organic extracts were washed with water (100 mL), dried over sodium sulfate, and concentrated under vacuum. Potassium carbonate (24.8 g; 0.18 mol) was added to a solution of the residue in methanol (300 mL), and the mixture was stirred at 25 °C. After 1 h, the solvent was evaporated under vacuum and the residue was dissolved in CH_2Cl_2 (300 mL). The organic solvent was washed with water (50 mL), dried over sodium sulfate, and evaporated to dryness. Crystallization of the residue from methanol (180 mL) gave pure **4** (90 g; 65% yield): ^1H NMR (DMSO-d_6) δ 1.47 (s, 3 H), 1.50 (s, 3 H), 2.06 (s, 3 H), 2.47 (s, 3 H), 3.55 (dd, J = 5.7, 11.5, 4.0 Hz, 1 H), 3.61 (ddd, J = 5.7, 11.5, 6.8 Hz, 1 H), 4.06 (ddd, J = 3.8, 4.0, 6.8 Hz, 1 H), 5.07 (d, J = 3.8 Hz, 1 H), 5.24 (t, J = 5.7 Hz, 1 H), 7.27–7.41 (AA'BB' system, 4 H); $[\alpha]_D^{20}$ 16.9° (*c* 1.0, $CHCl_3$); IR (KBr) 3280, 1630 cm^{-1}; mp 142–145 °C; MS *m/z* (relative intensity) 296 (M^+ + 1; 100), 280 (11), 238 (39).

(4*R*,5*S*)-3-Acetyl-2,2-dimethyl-4-formyl-5-[4-(methylthio)phenyl]-1,3-oxazolidine (5). A solution of DMSO (40.3 g; 0.51 mol) in CH_2Cl_2 (100 mL) was added to a stirred solution of oxalyl chloride (26.2 g; 0.21 mol) in CH_2Cl_2 (100 mL) over 30 min at −60 °C under nitrogen, and the solution was stirred at −60 °C for 30 min. A solution of **4** (50.9 g; 0.17 mol) in CH_2Cl_2 (600 mL) was added dropwise over 30 min at −60 °C. The reaction mixture was stirred at −60 °C for 15 min and then warmed to −50 °C. Et_3N (91.0 g; 0.96 mol) was added to the solution at −50 °C with stirring over 20 min. The reaction mixture was allowed to warm to 0 °C over 2 h and then was poured into a 10% aqueous NH_4Cl solution (300 mL). The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (200 mL). The combined organic extracts were washed with water (200 mL) and dried over sodium sulfate, and the solvent was evaporated under vacuum to give **5** as an oily crude product (51.5 g) (HPLC assay >95% determined as **4** after reduction with sodium borohydride, yield ≥95%),[15] which consisted on the basis of ^1H NMR data, of

(11) (1*S*,2*R*)-2-Amino-4-(methylthiophenyl)-1,3-propanediol (**11**) was prepared in 83% yield from **7** by basic hydrolysis (see Experimental Section).

(12) The **9a,b** equilibrium composition (90:10) was also obtained starting either from pure **10a** or **10b** (see Experimental Section).

(13) Portelli, M.; Renzi, G. *Ann. Chim.* **1969**, *59*, 306; *Chem. Abstr.* **1969**, *71*, 50487a.

(14) Portelli, M.; Renzi, G.; Soranzo, B. *Ann. Chim.* **1970**, *160*; *Chem. Abstr.* **1970**, *73*, 3636e.

two rotamers in a ratio of 56:44.[8] **Major rotamer**: ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 3 H), 1.70 (s, 3 H), 2.16 (s, 3 H), 2.42 (s, 3 H), 4.35 (dd, J = 8.79, 2.91 Hz, 1 H), 4.91 (d, J = 8.79 Hz, 1 H), 7.19–7.24 (AA'BB' system, 4 H), 9.50 (d, J = 2.91 Hz, 1 H). **Minor rotamer**: ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3 H), 1.88 (s, 3 H), 2.16 (s, 3 H), 2.43 (s, 3 H), 4.28 (dd, J = 6.83, 2.93 Hz, 1 H), 5.06 (d, J = 6.83 Hz, 1 H), 7.27–7.30 (AA'BB' system, 4 H), 9.61 (d, J = 2.93 Hz, 1 H); MS m/z (relative intensity) 294 (M^+ + 1; 78), 236 (100); IR (CCl_4) 2980, 1742, 1732, 1673 cm^{-1}.

DABCO-Catalyzed Equilibration of 5 and 6 in Toluene. A solution of **5** (2.95 g; 10.04 mmol) and DABCO (44.9 mg; 0.4 mmol) in toluene (29.5 mL) was stirred at 60 °C for 24 h. ^{1}H NMR analysis of the solution (4-(methylthio)benzaldehyde (380 mg; 2.5 mmol) as internal standard) showed the presence of **5** and **6** in a ratio of 45:55 ((5 + 6) accounts for 94% of the starting **5**). The same result was obtained starting from **6**.

(4*S*,5*S*)-3-Acetyl-2,2-dimethyl-4-formyl-5-[4-(methylthio)phenyl]-1,3-oxazolidine (6). A homogeneous mixture of DABCO (1.44 g; 12.8 mmol) and of crude **5** (51.5 g) was stirred at 40 °C. The mixture, which became heterogeneous, was cooled to 35 °C and then stirred for 2 h at 35 °C. The semisolid mixture was kept at 25 °C for 3 h (**5**:**6** = 5 : 95 as determined by ^{1}H NMR in $CDCl_3$ on the basis of integration of the aldehydic protons after acidic removal of DABCO (see below).[7] The reaction mixture was poured into a vigorously stirred mixture of CH_2Cl_2 (150 mL) and a solution prepared by diluting 0.5 N hydrochloric acid (26 mL) to 100 mL with water. The aqueous phase was extracted with CH_2Cl_2 (150 mL). The combined organic extracts were dried over sodium sulfate and evaporated under vacuum. The residue (51 g) consisting of a mixture of **5** and **6** in a ratio of 5:95 was crystallized from 4-*tert*-butyltoluene (100 mL) to afford pure **6** (38.5 g; 76% yield based upon (4)). **Major rotamer** (86%): ^{1}H NMR ($CDCl_3$) δ 1.73 (s, 3 H), 1.85 (s, 3 H), 1.93 (s, 3 H), 2.48 (s, 3 H), 4.49 (dd, J = 2.8, 6.4 Hz, 1 H), 5.46 (d, J = 6.4 Hz, 1 H), 7.23–7.31 (AA'BB' system, 4 H), 9.17 (d, J = 2.8 Hz, 1 H). **Minor rotamer** (14%): ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 3 H), 1.89 (s, 3 H), 2.23 (s, 3 H), 2.47 (s, 3 H), 5.00 (dd, J = 7.0 Hz, 1 H), 5.36 (d, J = 7.0 Hz, 1 H), 7.23–7.31 (AA'BB' system, 4 H), 9.06 (s, 1 H); IR (KBr) 1735, 1660, 1645 cm^{-1}; mp 97–102 °C; $[\alpha]_D^{20}$ 124.3° (*c* 1, $CHCl_3$); MS m/z (relative intensity) 294 (M^+ + 1; 100); 236 (35); 153 (20).

(4*R*,5*S*)-3-Acetyl-2,2-dimethyl-4-(hydroxymethyl)-5-[4-(methylthio)phenyl]-1,3-oxazolidine (7). Sodium borohydride (4.9 g; 0.13 mol) was added at 5 °C to a stirred mixture of $CaCl_2$ (14.3 g; 0.13 mol), a solution of **6** (53.7 g; 0.18 mol), and THF (220 mL) in EtOH (570 mL). The mixture was stirred for 2 h at 5 °C and then poured into a mixture of pH 7.0 aqueous buffer solution (300 mL, 0.05 M K_2HPO_4 adjusted to pH 7.0 with H_3PO_4), and CH_2Cl_2 (400 mL). The aqueous phase was extracted with CH_2Cl_2 (300 mL), the combined organic extracts were dried over sodium sulfate, and the solvent was evaporated under vacuum to give crude **7** (54.7 g; HPLC assay 96%, yield 97%). Analytically pure **7** was obtained by crystallization of the crude material from toluene: ^{1}H NMR (DMSO-d_6) δ 1.58 (s, 3 H), 1.62 (s, 3 H), 2.10 (s, 3 H), 2.46 (s, 3 H), 3.03 (ddd, J = 11.2, 5.1, 5.3 Hz, 1 H), 3.18 (dd, J = 11.2, 8.0, 5.3 Hz, 1 H), 4.25 (ddd, J = 5.0, 8.0, 5.1 Hz, 1 H), 4.65 (t, J = 5.3 Hz, 1 H), 5.25 (d, J = 5.0 Hz, 1 H), 7.22–7.32 (AA'BB' system, 4 H). $[\alpha]_D^{20}$ 80.8° (*c* 1.0, $CHCl_3$); IR (KBr) 3320, 1630 cm^{-1}; mp 131–134 °C; MS m/z (relative intensity) 296.1 (M^+ + 1; 100), 238.1 (60), 220 (11).

(4*R*,5*S*)-4-(Acetoxymethyl)-3-acetyl-2,2-dimethyl-5-[4-(methylthio)phenyl]-1,3-oxazolidine (8). Acetyl chloride (32 g; 0.41 mol) was added with stirring at 15 °C to a solution of crude **7** (100 g; 0.34 mol) and Et_3N (42 g; 0.42 mol) in CH_2Cl_2 (600 mL). After being stirred for 1 h at 15 °C, the reaction mixture was poured into a mixture of water (500 mL) and CH_2Cl_2 (200 mL). The organic phase was washed with a 10% aqueous NH_4Cl solution (100 mL) and then with water (300 mL). The organic layer was evaporated under vacuum to give crude **8** (113.5 g). An analytically pure sample of **8** was obtained by crystallization from diisopropyl ether: ^{1}H NMR (DMSO-d_6) δ 1.60 (s, 3 H), 1.63 (s, 3 H), 1.73 (s, 3 H), 2.10 (s, 3 H), 2.47 (s, 3 H), 3.71 (dd, J = 11.6, 5.7 Hz, 1 H), 3.78 (dd, J = 11.6, 6.6 Hz, 1 H), 4.53 (ddd, J = 4.9, 6.6, 5.7 Hz, 1 H), 5.35 (d, J = 4.9 Hz, 1 H), 7.25–7.35 (4 H, aromatics); IR (CCl_4) 1748, 1660, 1390, 1228 cm^{-1}; MS m/z (relative intensity) 338 (M^+ + 1; 100), 280 (65), 220 (38); mp 91–93 °C.

(−)-(1*R*,2*R*)-2-Amino-1-[4-(methylthio)phenyl]-1,3-propanediol ((−)-3) from 8. Compound **8** (11 g; 32.6 mmol) was added under nitrogen at 25 °C to a stirred solution of CH_3SO_3H (8.2 g; 85.9 mmol) and Ac_2O (3.3 g; 33 mmol) in $CHCl_3$ (EtOH free, 21 mL). The solution (solution A) was heated at 35 °C for 2 h.[16] The solution was poured at 15 °C into a stirred solution of sodium hydroxide (10.5 g; 0.26 mol) in water (100 mL). The reaction mixture was heated to reflux and kept at 95 °C for 4 h (during the first hour a mixture of water and $CHCl_3$ (70 mL) was distilled off). The reaction mixture, containing (−)-**3** and **11** in a ratio of 95.6:4.4,[17] was then cooled to 15 °C in 2 h. The mixture was filtered, and the insoluble material was washed with water (2 × 10 mL) and dried under vacuum at 60 °C to give pure (−)-**3** (6.0 g; 28.1 mmol, 86% overall yield from **6**: $[\alpha]_D^{20}$ −33° (*c* 2; HCl 0.1 N); ee 99.5%;[18] mp 149–151 °C.

(4*R*,5*R*)- and (4*R*,5*S*)-4-(Acetoxymethyl)-5-[4-(methylthio)phenyl]-2-methyl-1,3-oxazoline (10a and 10b) from 8. Solution A (see previous preparation) was heated for 20 min at 35 °C and then poured into a stirred solution of Et_2O (500 mL) and Et_3N (10.1 g; 0.1 mol). Water (300 mL) was added to the mixture, and the organic phase was washed with a 10% aqueous NH_4Cl solution (100 mL) and with water (100 mL). The organic extract was dried over sodium sulfate and evaporated under vacuum to give a residue (9.2 g), consisting of a mixture of **10a**, **10b**, and **8** (**10a** + **10b** 60% yield based on consumed **8**; **10a**/**10b** = 97/3; unreacted **8**, 35%).[19] In a parallel experiment solution A was kept at 35 °C for 16 h. The reaction mixture was worked up as described above to give a **10a,b** mixture (8.5 g; 94% yield; **10a**/**10b** = 90/10).[19] Crystallization of the **10a,b** mixture from diisopropyl ether (15 mL) afforded pure **10a** (6.5 g; 72% yield). The mother liquors were concentrated under vacuum to give a residue, which was purified by flash chromatography (eluent Et_2O/Et_3N = 97/3) affording pure **10b** (0.61 g; 6% yield).

10a: $[\alpha]_D^{20}$ 153.5° (*c* 1, $CHCl_3$); mp 64–66 °C; ^{1}H NMR ($CDCl_3$) δ 2.09 (s, 3 H), 2.11 (d, J = 1.1 Hz, 3 H); 2.49 (s, 3 H), 4.18 (m, 1 H), 4.25 (m, 2 H), 5.13 (d, J = 6.8 Hz, 1 H), 7.19–7.28 (4 H, aromatics); IR (CCl_4) 1750, 1675, 1230 cm^{-1}; MS m/z (relative intensity) 280 (M^+ + 1; 41), 220 (47), 173 (11), 65 (100).

10b: $[\alpha]_D^{20}$ 132.2° (*c* 1, $CHCl_3$); mp 71–73 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (s, 3 H), 2.13 (d, J = 1.4 Hz, 3 H), 2.48 (s, 3 H), 3.62 (dd, J = 6.1, 16.7 Hz, 1 H), 3.81 (dd, J = 5.6, 16.7 Hz, 1 H), 4.52 (m, 1 H), 5.60 (d, J = 10.2 Hz, 1 H), 7.10–7.30 (4 H, aromatics); IR (CCl_4) 1745, 1670, 1235 cm^{-1}; MS m/z (relative intensity) 280 (M^+ + 1; 7.22), 220 (18), 173 (5.5), 65 (100).

Equilibration of 9a and 9b. Compound **10a** (3.57 mmol) was added under nitrogen at 15 °C to a stirred solution of CH_3SO_3H (0.9 g; 9.37 mmol) and Ac_2O (0.36 g; 3.53 mmol) in $CHCl_3$ (2.3 mL). The solution was heated at 35 °C. After 1 h the reaction mixture was worked up with Et_3N and Et_2O, as described in the preparation of **10a,b**, to provide a **10a,b** mixture (**10a**/**10b** = 97/3, 95% yield).[19] In a parallel experiment, after 16 h, the solution was worked up to provide a **10a,b** mixture (**10a**/**10b** = 90/10; 95% yield).[19]

When using **10b** instead of **10a**, ratios **10a**/**10b** = 15/85 and 90/10 were obtained after 1 and 14 h, respectively (>96% yield).[19]

(4*R*,5*R*)-4-(Acetoxymethyl)-3-acetyl-2,2-dimethyl-5-[4-(methylthio)phenyl]-1,3-oxazolidine (12). Compound **12** was

(15) An analytical sample was prepared by adding sodium borohydride (5 mg) to a solution of **5** (20 mg) in THF (2 mL). A mixture of CH_3CN/H_2O = 30/70 was used as eluent for the HPLC analysis.

(16) A sample, worked up and analyzed as described in the preparation of **10a** and **10b** from **8**, showed a ratio **10a**/**10b** = 95/5.

(17) The (−)-**3**:**11** ratio was determined by HPLC analysis (the analytical conditions are reported in the General section).

(18) The ee was determined by HPLC analysis on the *N*-acetyl derivative. The liquid chromatograph was equipped with supelcosyl LC-(*S*)-phenylurea (5 μm; 250 mm × 4.6 mm) column (supplied by SUPELCO) and a mixture of hexane/methylene chloride/methanol = 92/6/2 was used as eluent. The analytical sample was prepared as follows: acetic anhydride (10 μL) was added to a solution of **3** (10 mg) and triethylamine (12 μL) in methylene chloride (2 mL) kept at 25 °C with stirring. After 20 min the mixture was diluted with methanol (10 mL), methylene chloride (6 mL), and hexane (3 mL).

(19) The relative amounts of **10a**, **10b**, and **8** were determined by ^{1}H NMR (solvent $CDCl_3$) on the basis of integrals of the benzylic protons, whose resonances are at 5.13, 5.60, and 5.30 ppm, respectively.

prepared from ent-4 following the O-acetylation procedure described for the preparation of 8. Pure 12 was obtained as a colorless oil after purification of the crude product by flash chromatography (eluent Et_2O) in 92% yield: ^1H NMR (DMSO-d_6) δ 1.48 (s, 3 H), 1.51 (s, 3 H), 2.04 (s, 3 H), 2.10 (s, 3 H), 2.48 (s, 3 H), 4.26 (m, $\Delta\nu$ = 8.0, 2 H), 4.38 (m, $\Delta\nu$ = 13.9 Hz, 1 H), 5.05 (d, J = 4.0 Hz, 1 H), 7.26–7.41 (4 H, aromatics); IR (CCl_4) 1748, 1670, 1380, 1220 cm^{-1}; MS m/z (relative intensity) 338 (M^+ + 1; 53), 280 (100), 238 (22), 220 (35).

(4*R*,5*R*)-4-(Acetoxymethyl)-5-[4-(methylthio)phenyl]-2-methyl-1,3-oxazoline (10a and 10b) from 12. Compound 12 (5 g; 14.8 mmol) was added under nitrogen at 25 °C to a stirred solution of CH_3SO_3H (3.7 g; 39.0 mmol) and Ac_2O (1.5 g; 15 mmol) in $CHCl_3$ (EtOH free, 10 mL). The solution (solution B) was heated at 35 °C for 20 min.

The solution was poured into a stirred solution of Et_2O (250 mL) and Et_3N (4.6 g; 45 mmol). Water (220 mL) was added to the mixture, and the organic phase was washed with 10% aqueous NH_4Cl solution (50 mL) and with water (50 mL). The organic extract was dried over sodium sulfate and evaporated under vacuum to give a **10a,b** mixture **10a/10b** = 97/3)[19] (3.96 g; 14.2 mmol; 96% yield). In a parallel experiment, solution B was kept at 35 °C for 16 h. After workup, a **10a,b** mixture **10a/10b** = 90/10) (3.92 g; 95% yield) was obtained.

Enantiomerically Pure (+)-(1*S*,2*R*)-2-Amino-3-[4-(methylthio)phenyl]-1,3-propanediol (11) from 7. Sodium hydroxide (1.76 g; 44 mmol) was added at room temperature to a suspension of crude 7 (10 g; 33.9 mmol) in water (17 mL); the suspension was heated at reflux with stirring for 8 h. Water (25 mL) was added to the solution and the mixture was cooled to 15 °C over 1 h. The mixture was filtered, and the insoluble material was washed with water (3 × 5 mL) and dried under vacuum to give crude 11 (6.65 g). Crystallization from toluene gave enantiomerically pure 11 (6.0 g; 83% yield): $[\alpha]_D^{20}$ −32.8° (*c* 2, HCl 0.1 N) (lit.[14] $[\alpha]_D^{20}$ −35°); mp 117–119 °C; ^1H NMR (DMSO-d_6) δ 2.45 (s, 3 H), 2.78 (ddd, J = 7.00, 6.23, 4.54 Hz, 1 H), 3.26 (dd, J = 10.44, 7.00 Hz, 1 H), 3.38 (dd, J = 10.44, 4.54 Hz, 1 H), 4.37 (d, J = 6.23 Hz, 1 H), 7.23–7.28 (4 H, aromatics).

Acknowledgment. We thank Mr. A. Gentile, Mr. D. Tentorio, and Mr. M. Paiocchi for technical assistance and Mr. P. Gironi for analyses.

Registry No. 1, 15318-45-3; 2, 73231-34-2; (+)-3, 16854-32-3; (−)-3, 23150-35-8; 4, 135204-34-1; 4 deacetyl derivative, 135204-38-5; *ent*-4, 135761-07-8; 5, 135761-08-9; 6, 135204-36-3; 7, 135761-09-0; 8, 135204-55-6; 9a, 13571-10-3; 9b, 135761-12-5; 10a, 96795-26-5; 10b, 135761-11-4; 11, 27348-48-7; 12, 135761-13-6.

Cycloaddition of (*N*-Alkyl-*N*-phenylamino)ketene with Imines

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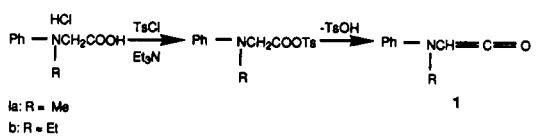
Received April 30, 1991

(*N*-Alkyl-*N*-phenylamino)ketenes were prepared in the presence of various imines, and a [2 + 2] cycloaddition reaction occurred to yield 3-(*N*-alkyl-*N*-phenylamino)-2-azetidinones. The size and electronic nature of the imine substituents were varied in order to probe those factors that influence the stereochemistry of the cycloaddition. The stereochemistry of the 2-azetidinone was determined by the substitution pattern of the imines. In general, the stereochemistry of the 2-azetidinone products are significantly influenced by the bulk of the N substituent on the imine. These results are discussed in terms of a two-step zwitterionic intermediate.

The 2-azetidinone (β-lactam) ring system is the center of reactivity of the penicillins and related antibiotics.[1-3] The first 2-azetidinone ring system was synthesized by Staudinger in 1907, but 2-azetidinones as a class of compounds became important only after it was established that penicillin contained a 2-azetidinone unit as the structural feature.[4,5]

The reaction of acid halides and imines serves as a general synthetic method to 2-azetidinones when the α-position of the acid halide contains an anion-stablizing group.[6-14] Examples of acid halides employed include

Scheme I



chloroacetyl chloride, azidoacetyl chloride, and phthaloylglycyl chloride. It is usually difficult to predict the stereochemistry of the products, as some reports describe the [2 + 2] cycloaddition to be stereospecific,[10,11,13] while others observe a mixture of *cis*- and *trans*-2-azetidinones.[7] Two different mechanisms have been proposed in the literature to explain the formation of the 2-azetidinones: (1) bonding of the imine nitrogen to the carbon atom of

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