in small portions to this mixture with stirring over a period of 3 h. The reaction mixture was filtered to remove insoluble salts. The organic layer was separated, dried ($MgSO_4$), and concentrated under reduced pressure. Distillation of the residue afforded 7.25 g of **5** (70% yield):[6] bp, 98–100 °C (0.6 mm); IR 3333 (OH), 1639, 900 cm^{-1}; NMR ($CDCl_3$) δ 0.95 (d, 3, J = 8.0 Hz, CH_3CH), 2.15 (s, 1, OH), 3.55 (d of t, 1, J = 11 Hz, J' = 3 Hz, $CHOH$), 4.1 (s, 2, CH_2Cl) 5.1 and 5.3 (2 singlets, 2, H_2C=C—).

Anal. Calcd for $C_{10}H_{17}ClO$: C, 63.83; H, 9.04; Cl, 18.62. Found: C, 63.71; H, 9.22; Cl, 18.74.

Oxidation of 5 with Jones Reagent. To a solution of 3.446 g (18.3 mmol) of **5** in 20 mL of acetone was added 12.8 mmol of Jones reagent (prepared by dissolving 1.28 g of chromium trioxide in 9.1 mL of water and cautiously adding 1.1 mL of concentrated H_2SO_4 at 0 °C) dropwise with stirring over a period of 1.5 h. The usual workup gave 3.18 g of 10-chloroisopulegone (**6**) as a yellow oil: IR 1709 and 909 cm^{-1}; NMR ($CDCl_3$) δ 1.05 (d, 3, J = 6 Hz, H_3CCH), 1.5–2.2 (m, 7), 4.1 (s, 2, CH_2Cl), 4.95, 5.3 ppm (H_2C=C—).

Menthofuran (1) from 10-Chloroisopulegone (6). A solution of 2.75 g (14.8 mmol) of **6** in 15 mL of *dry* triethylamine was refluxed for 36 h. The reaction mixture was cooled to room temperature and diluted with water, and the solution was extracted with ether. The ether extract, after washing with aqueous HCl, aqueous $NaHCO_3$, and water, was dried ($MgSO_4$), and the solvent was evaporated under reduced pressure. Distillation of the residue yielded 1.51 g of menthofuran (**1**) (68% yield). When the reaction was worked up after 8 h, distillation gave 0.96 g of menthofuran, bp 48 °C (2.8 mm), and 0.84 g of 10-chloropulegone (**7**) as a mixture of *E* and *Z* isomers; bp 76 °C (0.25 mm); IR 1681 cm^{-1}; NMR ($CDCl_3$) δ 1.0 (d, 3, J = 7 Hz), 1.95 (s, 3, CH_3C=C), 4.0 (2 singlets, 2, -CH_2Cl from E + Z isomers).

Alternatively, distillation of 3.169 of 10-chloroisopulegone (**6**) at 4–5 mm employing a bath temperature of 85–90 °C gave a slightly colored liquid which on distillation afforded 1.53 g of colorless **1**: bp 62 °C (4.5 mm), $[\alpha]^{25}_D$ +65.4°.[7]

3-Chloro-2-methyl-1-penten-4-one (8). The reaction of 5.9 g (60 mmol) of mesityl oxide with HOCl as described earlier gave 6.72 g of crude product which appeared to decompose on distillation at atmospheric pressure. Evaporative distillation at 0.5 mm and ambient temperature gave 5.62 g (71%) of **8**: IR 1724, 1653, 909 cm^{-1}; NMR ($CDCl_3$) δ 1.78 (s, 3, CH_3C=C), 2.23 (s, 3, CH_3CO), 4.85 (s, 1, CHCl), 5.15 and 5.22 (2 s, 2, >C=CH_2); mass spectrum, m/e (relative intensity) 134 (7), 132 (26), 119 (10), 117 (34), 93 (71), 92 (46), 90 (46), 89 (34), 59 (64), 55 (66), 54 (50), 53 (79), 52 (55), 51 (60), 50 (59), 44 (61), 43 (100), 42 (60), 41 (72).

A 2.3-g sample of crude **8** in 10 mL of triethylamine was refluxed for 72 h. Distillation gave 1.54 g of 3-chloro-2-methyl-2-penten-4-one (**9**): IR 1680 and 1612 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (s, 3), 2.10 (s, 3), 2.36 ppm (s, 3).

3-Chloro-2,6-dimethyl-1,5-heptadien-4-one (10). The reaction of 6.9 g (50 mmol) of freshly distilled[8] phorone with HOCl as described earlier gave a crude product which was plug-filtered through silica gel to remove the 10–15% of chlorohydrin[9] present. Distillation affords 6.4 g (74%) of chloro ketone **10** as a pale yellow liquid: bp 66–68 °C (0.5 mm); IR 1695 and 1639 cm^{-1}; NMR ($CDCl_3$) δ 1.8 (s, 3 H, CH_3CCCl), 1.97 and 2.22 (s, s, 6, $(CH_3)_2C$=CCO), 4.83 (s, 1, CHCl), 5.1 and 5.27 (2 s, 2, =CH_2), 6.3 (s, 1, =CHC=O); mass spectrum, m/e (relative intensity) 174 (1), 172 (2), 157 (7.5), 138 (33), 137 (15), 124 (23), 123 (67), 84 (48), 83 (100), 82 (33), 55 (66), 54 (37), 53 (60), 51 (48), 43 (54), 41 (54).

3-Chloro-2,6-dimethyl-2,5-heptadien-4-one (11). A solution of 2.0 g of chloro ketone **10** in 10 mL of triethylamine was kept at ambient temperature for 20 h. distillation gave 1.8 g of **11**: bp 68–70 °C (0.5 mm); IR 1680, 1613, 840, 775 cm^{-1}; NMR ($CDCl_3$) δ 1.96 (s, 6), 2.02 (s, 3), 2.18 (s, 3), 6.43 (s, 1, CH=C); mass spectrum, m/e (relative intensity) 172 (2), 159 (18), 157 (66), 137 (11), 122 (12), 93 (12), 83 (100), 67 (11), 55 (64), 53 (51), 43 (11), 41 (15).

3,6-Dimethyl-2,6-cycloheptadienone (12) and 3,6-Dimethyl-3,5-cycloheptadienone (13). A solution of 1.35 g of **10** in 5 mL of triethylamine was refluxed for 4 days. The mixture was poured into 20% HCl and extracted with ether. The ether solution was dried ($MgSO_4$) and evaporated to leave 1.0 g of an oil. Flash chromatography on silica gel using 75% hexane–25% ethyl acetate as an eluant gave 0.1 g of cycloheptadienone **13** (R_F 0.60) and 0.3 g of cycloheptadienone **12** (R_F 0.25).

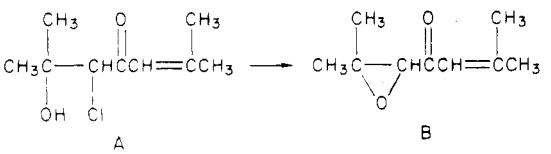
Ketone **13**:[10] bp 45 °C (0.5 mm); IR 1724, 1618 cm^{-1}; UV λ_{max} hexane 229 nm (ϵ 10 000), 282 nm (ϵ 200); NMR ($CDCl_3$) δ 1.90 (s, 6, CH_3C=C), 3.04 (s, 4, O=CCH_2C=C), 5.98 (s, 2, CH=C); mass spectrum, m/e (relative intensity) 136 (44), 108 (42), 93 (100), 91 (51), 79 (14), 77 (40),65 (13), 41 (22).

Ketone **12**: bp 70 °C (0.5 mm); UV λ_{max} hexane 232 nm (ϵ 22 000); IR 1666, 1618, 895 cm^{-1}; NMR ($CDCl_3$) δ 1.98 (s, 6, CH_3C=C), 2.42 (s, 4, —CH_2CH_2—) and 5.98 (s, 2, CH=C); mass spectrum, m/e (relative intensity) 136 (11), 121 (9), 108 (59), 93 (100), 91 (45), 77 (35), 53 (21), 41 (19).

(7) The low specific rotation of the menthofuran is a consequence of the original use of isopulegol of low (60%) optical purity in this sequence.

(8) Older samples of phorone react sluggishly with HOCl and require the addition of 1.5–2.5 equiv of HOCl before the conversion to monochloride is complete. Phorone, on standing, apparently forms a byproduct which catalyzes the decomposition of hypochlorous acid.

(9) The chlorohydrin A must be removed at this stage since in subsequent treatment with triethylamine it is converted to epoxide B which cannot be separated from 3,6-dimethyl-3,5-cycloheptadienone (**13**) by distillation or by column or gas chromatography.



A B

(10) When subjected to GC–mass spectral analysis a distilled sample of **13** showed the presence of ca. 1% ketone **12** and 1–2% of two other components showing molecular ions of m/e 136. These two components are most likely 3,6-dimethyl-2,4-cycloheptadienone and 3,6-dimethyl-2,5-cycloheptadienone. A 1,5-hydride shift occurs between 60–100 °C for 3,5-cycloheptadienone[11] to afford a thermal equilibrium with 2,4-cycloheptadienone. The thermal equilibrium in the case of the 3,6-dimethyl analogues must lie well on the side of the ketone **13**.

(11) ter Borg, A. P.; Kloosterziel, H. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1189. Hine, K. E.; Childs, R. F. *J. Am. Chem. Soc.* **1973**, *95*, 3289.

Syntheses of (*S*)-(-)-3-Piperidinol from L-Glutamic Acid and (*S*)-Malic Acid

Richard K. Olsen,* Krishna L. Bhat, and Robert B. Wardle

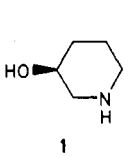
Department of Chemistry and Biochemistry, Utah State University, Logan, Utah 84322

William J. Hennen and Ganesh D. Kini

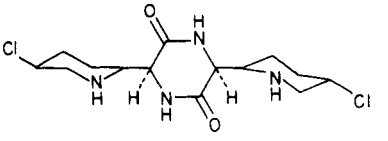
Department of Chemistry, Brigham Young University, Provo, Utah 84602

Received August 13, 1984

(*S*)-(-)-3-Piperidinol (**1**) has been prepared in chiral form from a carbohydrate precursor.[1] In connection with our



1



2

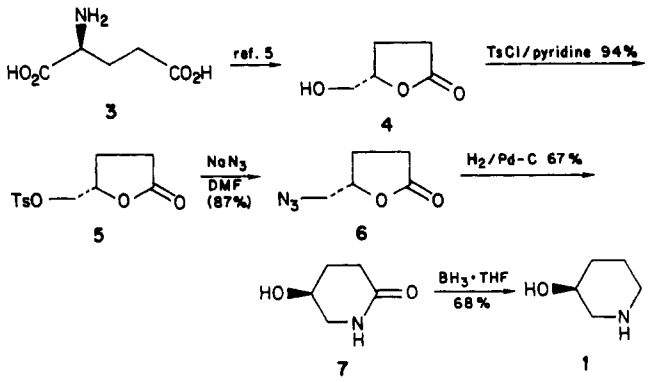
studies toward the synthesis of the piperazinedione antibiotic 593A (**2**) (NSC-135758),[2] which contains a 3-

(1) Deane, C. C.; Inch, T. D. *Chem. Commun.* **1969**, 813.

(2) Structure: Arison, G. H.; Beck, J. L. *Tetrahedron* **1973**, *29*, 2743. Pettit, G. R.; Von Dreele, R. B.; Herald, D. L.; Edgar, M. T.; Wood, H. B., Jr. *J. Am. Chem. Soc.* **1976**, *98*, 6742. Synthesis: Fukuyama, T.; Frank, R. K.; Jewel, C. F., Jr. *J. Am. Chem. Soc.* **1980**, *102*, 2122.

0022-3263/85/1950-0896$01.50/0

Scheme I

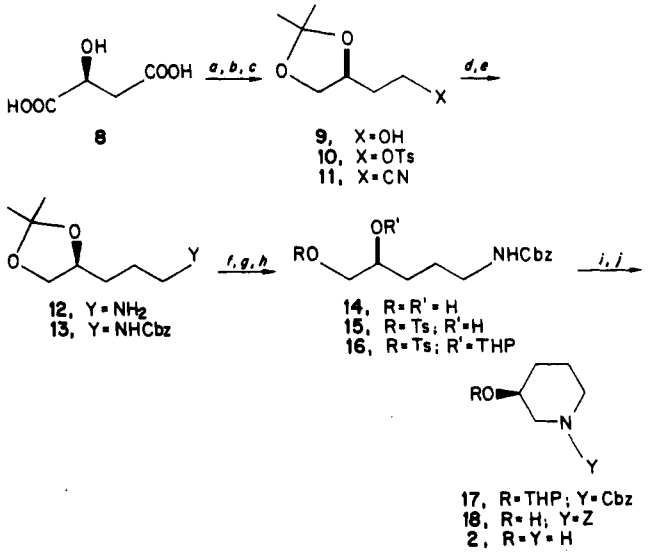


chloropiperidine unit of *S* configuration, we were interested in synthetic routes to the chiral piperidinol 1 that could serve as a model for approaches to the piperidine moiety of the antibiotic. We have studied two routes to 1 that originated from L-glutamic acid and from (*S*)-(−)-malic acid, two well-known substrates from the chiral pool.

L-(+)-Glutamic acid (3) was converted into the known[3] (*S*)-(+)-5-hydroxy-4-pentanolide (4) and the primary hydroxyl function was activated as its 4-methylbenzenesulfonate ester 5[4] in 94% yield. Displacement of the sulfonate group with sodium azide in *N,N*-dimethylformamide gave 5-azido-4-pentanolide (6) (87%). The transformation of 6 into (*S*)-(−)-piperidinol (2) in two steps had been reported.[1] This report, however, contained no experimental details or yields. We therefore sought to repeat the final two steps to establish their actual synthetic utility. The first step, the catalytic reduction of the azido function and concomitant formation of the hydroxy lactam (*S*)-5-hydroxy-2-piperidinone (7), was found to work well (67%). The second step, the reduction of the lactam function in 7 with lithium aluminum hydride in refluxing 1,4-dioxane, failed in our hands. The reduction of 7 was successfully carried out under much milder conditions with borane in tetrahydrofuran[5] to give (*S*)-(−)-3-piperidinol (1) in 68% yield from lactam 7 (Scheme I). The overall yield of 1 from the pentanolide 4, which involved only four steps, was 37%.

A second, but less satisfactory, route to (*S*)-(−)-3-piperidinol from (*S*)-(−)-malic acid (8) was investigated. Acid 8 was transformed to the known[6] acetonide triol 9, which was converted, as shown in Scheme II, to the crystalline amino diol 14. Selective activation[7] and protection of the primary and secondary alcohol functions gave 16 as an apparent mixture of diastereomers. Results to effect cyclization of 16 to the protected 3-piperidinol 17 proved to be erratic. Two initial attempts provided 17 in yields of 62% and 37%, respectively, along with recovered reactant 16. In subsequent studies, the diastereomers of 16 were separated, and it was observed that only the isomer isolated in lower yield (19%) underwent cyclization to 17, while the major isomer underwent no reaction. Efforts to resolve this ambiguity or to make application of a different protecting group have not been undertaken. Deprotection of 17 furnished 2; the overall yield from acetonide diol 9, proceeding in 10 steps, was 10%.

Scheme II



[a] Reference 8. [b] TsCl, pyridine, 92%. [c] NaCN, DMF, 82%. [d] $LiAlH_4$, Et_2O, 70%. [e] CbzCl, MgO, H_2O, 93%. [f] 90% TFA, 60%. [g] TsCl, pyridine, 80%. [h] DHP, TsOH, Et_2O, 100%. [i] NaH, THF, 37–62%. [j] AcOH/H_2O/THF, 70%; H_2, Pd-C, 100%.

Experimental Section

General Methods. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Proton magnetic resonance spectra were obtained for all compounds by using Varian EM360 and JEOL FX90 spectrometers. Optical rotations were recorded on a Perkin-Elmer Model 241 polarimeter. Mass spectra were obtained on Hitachi Perkin-Elmer RMU-6E at an ionizing voltage of 70 eV. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. Tetrahydrofuran was distilled prior to use from sodium benzophenone ketyl or from lithium aluminum hydride. Methylene chloride was distilled from phosphorus pentoxide and stored over Linde 3A molecular sieves. Dimethylformamide was stored over 3A molecular sieves. Purified products were shown to be homogeneous by thin-layer chromatography on silica gel plates (1 in. × 3 in.) with visualization by iodine vapor. Column chromatography was performed by using medium-pressure liquid chromatography (MPLC) with glass columns packed with silica gel (0.040–0.063 mm).

(*S*)-5-*O*-[(4-Methylphenyl)sulfonyl]-4-pentanolide (5).[3] Compound 5 was prepared from lactone 6 by modification of the reported procedure,[4] in which addition of 0.1 equiv of *N,N*-dimethylaminopyridine provided 5 in a yield of 94% (literature yield, 48%).

(*S*)-5-Azido-4-pentanolide (6). To a stirred solution of 3.60 g (13.3 mmol) of (*S*)-5-*O*-[(4-methylphenyl)sulfonyl]-4-pentanolide (5) was added 5.2 g (80 mmol) of sodium azide, and the mixture was refluxed for 1 h. After cooling, the solvent was removed in vacuo, the residue triturated with chloroform (60 mL) and filtered through a Celite pad, and the pad washed with chloroform. The filtrate and washings were concentrated to give a crude oil that was purified by MPLC using hexane/acetone (80:20) as the eluant. The yield of pure 6 was 1.64 g (87%): $[\alpha]^{25}_D$ +92.93 (c 2.15, $CHCl_3$); IR (cm^{-1}) 2120 (N_3 stretching); ^1H NMR δ 1.52–2.90 (4 H, m), 3.12–3.86 (2 H, m), 4.55–4.93 (1 H, m). Anal. Calcd for $C_5H_7O_2N_3$: C, 42.29; H, 5.16; N, 29.61. Found: C, 42.55; H, 5.00; N, 29.77.

(*S*)-5-Hydroxy-2-piperidinone (7). To a solution of 4.23 g (30 mmol) of 5-azido-4-pentanolide 6 in 200 mL of dry methanol was added 0.96 g of 5% palladium on carbon and the mixture was shaken overnight under 50 psi of hydrogen. The mixture was filtered, and the filtrate was evaporated to dryness in vacuo. The residue was purified by chromatography using chloroform/

(3) Taniguchi, M.; Koga, K.; Yamada, S. *Tetrahedron* **1974**, *30*, 3547.
(4) Mori, K. *Tetrahedron* **1975**, *31*, 3011.
(5) Brown, H. C.; Heim, P. *J. Org. Chem.* **1973**, 38, 912.
(6) Corey, E. J.; Harak, N.; Knolle, J. *J. Am. Chem. Soc.* **1978**, *100*, 1942. Meyers, A. I.; Lawson, J. P. *Tetrahedron Lett.* **1982**, *23*, 4883.
(7) Corey, E. J.; Shirahama, H.; Yamamoto, H.; Terashima, S.; Venkateswarlu, A.; Schaaf, T. R. *J. Am. Chem. Soc.* **1971**, *93*, 1490. This paper reports the selective tosylation of a 1,2-diol derived from (*S*)-(−)-malic acid.

methanol (9:1) as elutant to yield, after evaporation, 2.31 g (67%) of **7**, which was recrystallized from methanol/ether to give product with melting point 123–124 °C (lit.[1] 124–125 °C).

(*S*)-1,2-*O*-Isopropylidene-4-*O*-[(4-methylphenyl)-sulfonyl]-1,2,4-butanetriol (10). To an ice-cold solution of 28.6 g (150 mmol) of 4-methylbenzenesulfonyl chloride and 183 mg (1.5 mmol) of 4-(dimethylamino)pyridine in 15 mL of dry pyridine was added 21.9 g (150 mmol) of (*S*)-1,2-*O*-isopropylidine-1,2,4-butanetriol (**9**).[6] After 1 h, the mixture was stored at 8 °C for 16 h then at room temperature for 1.5 h. The resulting dense oil was removed, and the aqueous solution was extracted with three 75-mL portions of ether. The initial oil and the combined ether extracts were diluted to 250 mL with ether. The ether solution was washed once with 100 mL of 5% aqueous sodium carbonate, repeatedly with half-saturated aqueous cupric sulfate until no intensification of color was observed, twice with water, and once with brine. The solution was cooled, dried over potassium carbonate, and evaporated in vacuo to yield 41.3 g (92%) of **10** as a red-orange oil. The oil obtained, which was homogeneous on TLC, was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.35 (3 H, s), 1.7–2.2 (2 H, m), 2.5 (3 H, s), 3.5–4.4 (5 H, m), 7.47 (2 H, d), 7.93 (2 H, d); TLC (Et_2O) R_f 0.65, (EtOAc) 0.59.

(*S*)-4,5-*O*-Isopropylidene-4,5-dihydroxypentanenitrile (11). Anhydrous sodium cyanide (4.4 g, 88.5 mmol) was dissolved in 150 mL of hot (95–100 °C), dry *N*,*N*-dimethylformamide (DMF). To this solution was added 17.8 g (59 mmol) of **10** in 20 mL of dry DMF. The solution was stirred at 85 °C for 3.5 h and the solvent was evaported in vacuo. The residue was dissolved in dichloromethane, washed with saturated aqueous sodium chloride (2 × 80 mL), and dried over potassium carbonate. Kugelrohr distillation yielded 7.54 g (82%) of **11** as a clear oil, bp 80–82 °C (0.7 mm): ^{1}H NMR ($CDCl_3$) δ 1.33 (3 H, s), 1.4 (3 H, s), 1.67–2.23 (2 H, m), 2.55 (2 H, t), 3.5–3.8 (1 H, m), 4.0–4.4 (2 H, m); TLC ($CHCl_3$) R_f 0.29, (CH_2Cl_2) 0.39. Anal. Calcd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03. Found: C, 62.16; H, 8.23; N, 8.94.

(*S*)-1,2-*O*-Isopropylidene-5-amino-1,2-pentanediol (12). A solution of 7.89 g (51 mmol) of nitrile **11** in 30 mL of anhydrous ether was added dropwise to a stirred mixture of 2.05 g (51 mmol) of lithium aluminum hydride and 85 mL of anhydrous ether such that a gentle reflux was maintained. The reaction mixture was refluxed for 5 h, cooled, and quenched sequentially with 2.0 mL of water, 2.0 mL of 15% aqueous sodium hydroxide, and 6.0 mL of water. The solution was filtered and the salts were reslurried and filtered from two 50-mL portions of dichloromethane. The combined organic solutions were dried over potassium carbonate. Kugelrohr distillation (receiving bulb cooled to −20 °C) of the residue gave 5.72 g (70%) of **12** as a clear oil (75 °C at 2.4 mm): ^{1}H NMR ($CDCl_3$) δ 1.35 (3 H, s), 1.4 (3 H, s), 1.3–1.9 (6 H, m), 2.6–2.95 (2 H, t), 3.4–3.8 (1 H, m), 3.9–4.4 (2 H, m); $[\alpha]^{20}_D$ +19.15° (*c* 1, $CHCl_3$); TLC ($CHCl_3$/MeOH, 80:20) R_f 0.72.

(*S*)-*N*-[(Benzyloxy)carbonyl]-1,2-*O*-isopropylidene-5-amino-1,2-pentanediol (13). To a stirred, ice-cold mixture of 5.72 g (36 mmol) of (*S*)-1,2-*O*-isopropylidene-5-amino-1,2-pentanediol (**12**), 2.87 g (63 mmol) of magnesium oxide, and 200 mL of water was added 7.2 mL (48 mmol) of carbobenzoxy chloride. After 3 h at 0 °C, the reaction mixture was stirred overnight at room temperature. The solution was filtered, and the solids were washed with 3 × 70 mL of dichloromethane. The combined organic layers were dried over potassium carbonate, filtered, and evaported in vacuo. The clear oily residue was purified by MPLC on silica gel with elution by hexane/acetone (9:1) to give 9.85 g (93%) of **13**: ^{1}H NMR ($CDCl_3$) δ 1.32 (3 H, s), 1.38 (3 H, s), 1.3–1.8 (4 H, m), 2.9–3.85 (3 H, m), 3.85–4.3 (2 H, m), 5.13 (2 H, s), 5.2–5.6 (1 H, br s), 7.4 (5 H, s); $[\alpha]^{23}_D$ −27.15° (*c* 1, CH_2Cl_2); TLC (hexane/acetone 80:20) R_f 0.34, ($CHCl_3$/MeOH 9:1) 0.73. Two attempts to obtain correct elemental analysis from chromatographically purified samples of **13** failed to give results within 0.4% of theoretical values.

(*S*)-*N*-[(Benzyloxy)carbonyl]-5-amino-1,2-pentanediol (14). A solution of 90% aqueous trifluoroacetic acid (10 mL) and 1.83 g (6.24 mmol) of **13** were stirred for 5 min at room temperature. The solution was evaporated in vacuo to give an oil, which was dissolved in chloroform and dried over potassium carbonate. Evaporation of the chloroform gave an oily residue, which was crystallized from ether (0 °C, overnight) to give 0.73 g of a white solid (mp 63–65 °C). Recrystallization from ethyl acetate gave 0.56 g (35%) of **14**, mp 69–70 °C. Additional product was obtained by the evaporation of the mother liquors, treating the residue with triethylamine in methanol at room temperature for 24 h, followed by evaporation, and recrystallization from ether, followed by a second recrystallization from ethyl acetate. The total yield of **14** was 1.02 g (60%), mp 69–70 °C: ^{1}H NMR ($CDCl_3$) δ 1.2–1.7 (4 H, m), 2.95–4.0 (7 H, m), 5.1 (2 H, s); 5.4 (1 H, br s), 7.37 (5 H, s); TLC (hexane/acetone 60:40) R_f 0.11, ($CHCl_3$/EtOH) 0.25. Anal. Calcd for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56; N, 5.53. Found: C, 61.50; H, 7.56; N, 5.58; $[\alpha]^{25}_D$ −9.7° (*c* 0.89, CH_3OH).

(*S*)-*N*-[(Benzyloxy)carbonyl]-1-*O*-[(4-methylphenyl)-sulfonyl]-5-amino-1,2-pentanediol (15). One hundred milligrams (0.4 mmol) of (*S*)-*N*-[(benzyloxy)carbonyl]-5-amino-1,2-pentanediol (**14**) was added to an ice-cold solution of 78.5 mg (0.4 mmol) of 4-methylbenzenesulfonyl chloride in 5 mL of dry pyridine. After 1 h at 0 °C, the reaction mixture was stored at 8 °C for 40 h. The reaction mixture was poured into 20 mL of ice-cold 3 N hydrochloric acid and extracted with two 20-mL portions of ether. The ether extracts were washed with 5 mL of 3 N hydrochloric acid and dried over magnesium sulfate. Evaporation in vacuo gave 130 mg (80%) of chromatographically pure oil. The yields for this reaction typically varied from 65% to 80%: ^{1}H NMR ($CDCl_3$) δ 1.2–1.8 (4 H, m), 2.46 (3 H, s), 2.7–3.45 (3 H, m), 3.7–4.15 (3 H, m), 4.9–5.2 (2 H, s at 5.13 with a broad underlying absorption, 1 H), 7.25–7.6 (5 H, s at 7.43 and 2 H, d), 7.87–8.07 (2 H, d); TLC (EtOAc) R_f 0.53, (hexane/acetone 90:10) 0.66.

(*S*)-*N*-[(Benzyloxy)carbonyl]-1-*O*-[(4-methylphenyl)-sulfonyl]-2-*O*-(2-tetrahydropyranyl)-5-amino-1,2-pentanediol (16). To a solution of 0.24 mg of 4-methylbenzenesulfonic acid and 240 mg (0.59 mmol) **15** in 12 mL of anhydrous ether in a darkened flask was added 110 μL (1.2 mmol) of dihydropyran, and the solution was stirred overnight at room temperature. The reaction was quenched with 5 mL of water and the water backwashed with 5 mL of ether. The combined ether solutions were dried over magnesium sulfate and evaporated in vacuo to yield 290 mg (100%) of **16** as an oil, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 1.4–2.0 (10 H, m), 2.5 (3 H, s), 3.0–4.2 (7 H, m), 4.65 (1 H, d), 5.2 (2 H, s), 7.3–7.5 (5 H, s, plus 2 H, d), 7.9 (2 H, d).

(*S*)-*N*-[(Benzyloxy)carbonyl]-3-*O*-(2-tetrahydropyranyl)-3-piperidinol (17). To 50 mg (2 mmol) of 50% sodium hydride in mineral oil, prewashed with hexane and suspended in 15 mL of dry tetrahydrofuran, was added dropwise a solution of 250 mg (0.51 mmol) of **16** in 5 mL of tetrahydrofuran and the reaction was stirred overnight at room temperature. The reaction was quenched with 0.5 mL of water, and the solvent was evaporated in vacuo. The residue was taken up in dichloromethane, washed successively with 5% aqueous sodium bicarbonate and brine, and dried over potassium carbonate. The mixture of **16** and **17** present was separated by preparative TLC on silica gel with chloroform as the liquid phase. The yield of **17** was 100 mg (62%) with 90 mg of **16** being recovered: ^{1}H NMR ($CDCl_3$) δ 1.5–2.0 (8 H, m), 2.5–3.5 (9 H, m), 4.0–4.4 (1 H, m), 5.2 (2 H, s), 7.45 (5 H, s); $[\alpha]^{25}_D$ +4.23° (*c* 1, $CHCl_3$); TLC (hexane/acetone 70:30) R_f 0.6. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.71; H, 7.84; N, 4.39. Found: C, 67.95; H, 8.06; N, 4.67.

Compound **16** was separated into two components by MPLC on a column of silica gel by elution with hexane/acetone (90:10 ratio, then 85:15): major component, R_f 0.32, 60% yield, $[\alpha]^{25}_D$ −29.2° (*c* 1.26, $CHCl_3$); minor component, R_f 0.21, 19% yield, $[\alpha]^{25}_D$ −7.1° (*c* 1.29, $CHCl_3$). The ^{1}H NMRs of these compounds were similar and appeared to be consistent for isomers epimeric at the tetrahydropyranyl group. Several attempts to effect cyclization of the major isomer, R_f 0.32, of **16** under the same or similar conditions as described above for preparation of **17** resulted in isolation of recovered reactant. The minor isomer, R_f 0.21, was transformed to **17** but, in the one experiment attempted, in only 50% yield.

(*S*)-*N*-[(Benzyloxy)carbonyl]-3-piperidinol (18). To a solution of 50 mg of **17** in 2 mL of tetrahydrofuran was added a mixture of acetic acid (9 mL) and water (4.5 mL). After stirring for 1 h at room temperature, the solution was evaporated in vacuo. The residue was dissolved in ethyl acetate, washed with saturated aqueous sodium chloride, dried ($MgSO_4$), and evaporated to yield

25 mg (70%) of 18: ^{1}H NMR ($CDCl_3$) δ 1.32–1.95 (4 H, m), 2.00–2.50 (1 H, br d), 2.97–3.18 (2 H, m), 3.20–3.94 (3 H, m), 5.14 (2 H, s), 7.35 (5 H, s); IR (neat) (cm^{-1}) 3350, 3050, 2950, 1700, 1530. Anal. Calcd for $C_{13}H_{17}NO_3$: C, 66.38; H, 7.23; N, 5.96. Found: C, 66.13; H, 7.38; N, 5.85.

(*S*)-(−)-3-Piperidinol (1). Method A. To 15 mL of a 1 M solution of diborane in hexane was added 10 mL of dry tetrahydrofuran. The solution was cooled to 0 °C under argon, and a suspension of (*S*)-5-hydroxy-2-piperidinone (**7**) (0.50 g) in 15 mL of dry tetrahydrofuran was added slowly with stirring. The mixture was then heated to reflux under an argon atmosphere for 2 h. After cooling to room temperature, the reaction mixture was treated with 2.5 mL of cold 6 N hydrochloric acid and the volatile components were removed in vacuo. The residue was dissolved in 10 mL of water, and the aqueous solution was saturated with solid sodium hydroxide and extracted with ethyl acetate (3 × 50 mL). The organic extracts were dried (Na_2SO_4) and evaporated in vacuo. The residual oil was purified by chromatography using chloroform/methanol (7:3) as the elutant to yield 0.30 g (68%) of **1**. The ^{1}H NMR spectrum of **1** was identical with that of racemic 3-piperidinol (Aldrich Chemical); $[\alpha]^{22}_D$ −7.4° (*c* 0.4, CH_3OH) [lit.[1] −7.5° (*c* 2, CH_3OH)].

Method B. To a solution of 30 mg of (*S*)-*N*-[(benzyloxy)carbonyl]-3-piperidinol (**18**) dissolved in 10 mL of ethanol was added 3 mg of 10% palladium on carbon. The mixture was shaken overnight at 50 psi of hydrogen gas on a Parr hydrogenator. The reaction mixture was filtered through a Celite pad, and the pad was washed with ethanol. The filtrate and washings were evaporated in vacuo to yield 13 mg (100%) of **1**, which was identical in all respects with that reported[8] from the mass spectral data for this compound: mass spectrum, *m/e* 44 (base peak), 56, 57, 70, 100, 101, 102.

Acknowledgment. Support of this research by the National Institutes of Health (National Cancer Institute, Grant CA 22922) is gratefully acknowledged.

(8) Budzikiewicz, H.; Grotjahn, L. *Tetrahedron* **1972**, *28*, 1881.

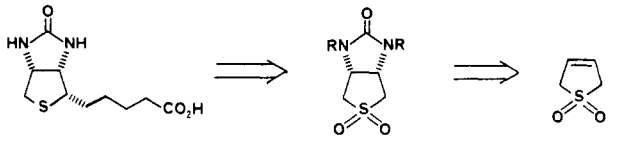
Preparation of (3aα,6aα)-1,3-Dibenzylhexahydro-1*H*-thieno[3,4-*d*]-imidazol-2(3*H*)-one: A Key Biotin Intermediate

Hans Aaron Bates,* Lloyd Smilowitz, and James Lin

Department of Chemistry, State University of New York at Stony Brook, Stony Brook, New York 11794-3400

Received June 25, 1984

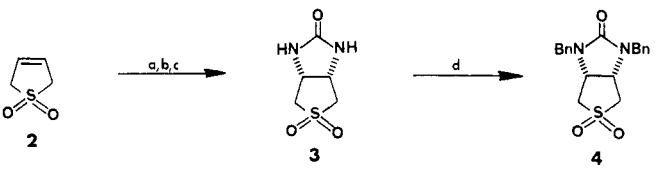
The vitamin biotin (**1**), which is prepared commercially by total synthesis,[1] has been the target of several ingenious



1, Biotin **2**

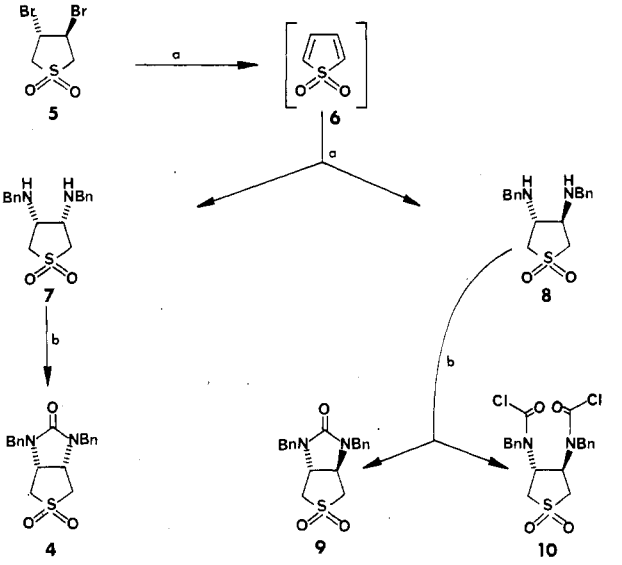
syntheses.[2] Our retrosynthetic analysis of biotin suggested that the abundantly available 2,5-dihydrothiophene 1,1-dioxide (**2**) might serve admirably as the ultimate starting material in a practical synthesis of biotin. Previous investigators with similar intentions have prepared (6aα,3aα)-hexahydro-1*H*-thieno[3,4-*d*]imidazol-2(3*H*)-one (**3**) from 2,5-dihydrothiophene 1,1-dioxide (**2**)[3,4] but have not reported further progress in conversion of **3** into biotin (**1**). When we prepared **3**,[4,5] we found that it was remarkably insoluble in organic solvents compatible with reduction of sulfone **3** to the corresponding sulfide.[6,7] In order to gain increased organic solubility, **3** was N-benzylated (Scheme I) with a large excess of benzyl bromide in aqueous sodium hydroxide to afford **4** in 95% yield.[8-10]

Scheme I[a]



[a] (a) EtO_2CNCl_2, $NaHSO_3$; (b) HBr; (c) KNCO; (d) $PhCH_2Br$, NaOH, H_2O.

Scheme II[a]



[a] (a) $PhNH_2$, CH_3OH; (b) $COCl_2$, Et_3N.

A shorter alternative synthesis of **4** was concurrently pursued. As shown in Scheme II, 2,5-dihydrothiophene 1,1-dioxide (**2**) may easily be brominated to afford dibromide **5**.[11] Dehydrobromination of **5** generated the unisolable thiophene 1,1-dioxide (**6**),[12,13] which reacted

(1) Goldberg, M. W.; Sternbach, L. H. *U. S. Pat.* 2489232 and 2489235, 1949; *Chem. Abstr.* **1951**, *45*, 184b, 186g.

(2) For recent syntheses and leading references, see: Volkmann, R. A.; Davis, J. T.; Metz, C. N. *J. Am. Chem. Soc.* **1983**, *105*, 5946. Baggiolini, E. G.; Lee, H. L.; Pizzolato, G.; Uskoković, M. R. *J. Am. Chem. Soc.* **1982**, *104*, 6460. Rossy, P.; Vogel, F. G. M.; Hoffmann, W.; Paust, J.; Nürrenbach, A. *Tetrahedron Lett.* **1981**, *22*, 3493. Whitney, R. A. *Can. J. Chem.* **1981**, *59*, 2650. Confalone, P. N.; Pizzolato, G.; Lollar Confalone, D.; Uskoković, M. R. *J. Am. Chem. Soc.* **1980**, *102*, 1954. Fliri, A.; Hohenlohe-Oehringen, K. *Chem. Ber.* **1980**, *113*, 607.

(3) Ellis, F.; Sammes, P. G. *J. Chem. Soc., Perkin Trans. 1* **1972**, 2866.

(4) Ohba, K.; Kitahara, T.; Mori, K.; Matsui, M. *Agric. Biol. Chem.* **1974**, *38*, 2431. Ger. Offen. 2534962; *Chem. Abstr.* **1976**, *85*, 33009t.

(5) Ohba, K.; Mori, K.; Kitahara, T.; Kitamura, S.; Matsui, M. *Agric. Biol. Chem.* **1974**, *38*, 1679.

(6) Takaya, T.; Yoshimoto, H.; Imoto, E. *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2636.

(7) Baker, B. R.; Querry, M. V.; Safir, S. R.; McEwen, W. L.; Bernstein, S. *J. Org. Chem.* **1947**, *12*, 174.

(8) Corfield, G. C.; Crawshaw, A.; Monks, H. H. *J. Macromol. Sci., Chem.* **1975**, *A9*, 1085.

(9) Reuschling, D.; Pietsch, H.; Linkies, A. *Tetrahedron Lett.* **1978**, 615.

(10) Curran, W. V.; Angier, R. B. *J. Org. Chem.* **1966**, *31*, 201.

(11) Bailey, W. J.; Cummins, E. W. *J. Am. Chem. Soc.* **1954**, *76*, 1932.

(12) Ellis, F.; Sammes, P. G.; Hursthouse, M. B.; Neidle, S. *J. Chem. Soc. Perkin Trans. 1* **1972**, 1560.

(13) Procházka, M.; Horák, V. *Collect. Czech. Chem. Commun.* **1959**, *24*, 2278.

0022-3263/85/1950-0899$01.50/0