distilled (70 °C (5 torr)), affording 108 mg (75%) of two products: 4,8-dimethyl-2,7-nonadienenitrile (**10a**), and 4,8-dimethyl-3,7-nonadienenitrile (**10b**), at a 10:1 ratio: MS, *m/e* (relative intensity) M^+ (163 (7), 148 (15), 121 (22), 94 (26), 81 (23), 80 (11), 70 (29), 69 (100), 55 (78), 53 (22); IR 2500, 2200, 1620, 1450, 1370, 980, 820; NMR of **10a** 6.63 (dd, J = 16.4, 6.9 Hz, 1 H), 5.28 (dd, J = 16.4, 1.5 Hz, 1 H), 5.04 (br t, J = 7.0 Hz, 1 H), 2.32 (m [(seven lines], 1 H), 2.03 (m, 2 H), 1.69 (s, 3 H), 1.59 (s, 3 H), 1.38 (m, 2 H), 1.05 (d, J = 6.7 Hz, 3 H). The minor isomer (**10b**), was identified by its NMR absorptions[23] at 5.2 (m, 2 H) and 3.03 (d, J = 7.7 Hz, 2 H). The isomeric ratio (10:1) was determined by integration of the 270-MHz NMR spectral peaks at 6.63 and 3.03.

Reduction of 5. PMHS (126 mg, 2.1 mequiv) was added to a THF (5 mL) solution containing **5** (190 mg, 1.02 mmol), $Pd(PPh_3)_4$ (49 mg, 4 mol %), and PPh_3 (40 mg, 0.15 mmol), and the mixture was stirred for 4 days. Yield was determined by GLC, using allylbenzene as an internal reference. A purified sample was obtained by preparative GLC using an SE-30 column. **7-Methyl-2-octene (11a)**: NMR 5.00 (m, 2 H), 2.00 (m, 2 H), 1.63 (dd, J = 3.6, 1 Hz, 3 H), 1.26 (m, 5 H), 0.85 (d, J = 6.85 Hz, 6 H). **7-Methyl-3-octene (11b)**: NMR 5.00 (m, 2 H) 2.00 (m, 4 H), 1.26 (m, 3 H), 0.95 (t, J = 7.5 Hz, 3 H), 0.9 (d, J = 6.85 Hz, 6 H) (the isomeric ratio (**11a**:**11b** = 2:1) was determined by integration of the 270-MHz NMR spectral peaks at δ 1.63 (vinylic methyl) and 0.95 (allylic methyl)); MS, *m/e* (relative intensity) 126 (M^+) (27), 111 (10), 98 (8), 83 (17), 65 (70), 56 (100).

Reduction of 6. PHMS (163 mg, 2.6 mequiv) was added to a THF solution of **6** (140 mg, 0.62 mmol) and $Pd(PPh_3)_4$ (5 mol %). After 1 h, no starting material could be detected by GLC. The solution was treated as described in the General Procedure, affording 2-dodecene[24] (**12**), which was Kugelrohr distilled (120 °C (100 torr)): 82 mg, 79% yield; NMR, 5.4 (m, 2 H), 1.9 (m, 2 H), 1.6 (m, 3 H), 1.2 (br s, 14 H), 0.9 (br t, 3 H).

Reduction of 13. PMHS (132 mg, 2.2 mequiv) was added to a THF (5 mL) solution containing **13** (173 mg, 0.5 mmol) and $Pd(PPh_3)_4$ (4.4 mg, 4 mol %). After 24 h, the solution was filtered through a silica gel column with CH_2Cl_2, solvent was removed under reduced pressure, and the products were Kugelrohr distilled (120 °C (100 torr)) to give 93 mg (79% yield) of 1-phenyl-1-butene[25a] and 1-phenyl-2-butene[25b] in a 6:1 ratio. The isomeric ratio was determined by integration of the 80-MHz NMR spectral peaks at δ 6.3 and 5.5.

Reduction of Geranyl Acetate (14). PMHS (105 mg, 1.75 mequiv) was added to a THF (5 mL) solution containing **14** (161 mg, 0.83 mmol), $Pd(PPh_3)_4$ (62 mg, 6 mol %), and PPh_3 (45 mg, 0.17 mmol), and the mixture was stirred for 5 days. The yield (100%) was determined by GC analysis usng a $^1/_8$ in. × 6 ft column packed with OV-1 at 80 °C and with *n*-octane as an internal reference. The products were isolated by preparative GC using a column packed with 20% SE-30 on Chromosorb W. **3,7-Dimethyl-1,6-octadiene**:[26] NMR 5.70 (ddd, J = 13.2, 9.4, 7.1 Hz, 1 H), 5.11 (m, 1 H), 4.95 (d, J = 13.2 Hz, 1 H), 4.92 (d, J = 7.1 Hz, 1 H), 2.44 (m [seven lines], 1 H), 2.14 (br q, J = 7 Hz, 2 H), 1.68 (s, 3 H), 1.59 (s, 3 H), 1.31 (m, 2 H), 0.99 (d, J = 7 Hz, 3 H). **3,7-Dimethyl-2,6-octadiene**:[27] NMR 5.16 (br q, J = 6.0 Hz, 1 H), 5.06 (m, 1 H), 2.02 (m, 4 H), 1.68 (s, 3 H), 1.60 (s, 1 H), 1.59 (d, J = 6.0 Hz, 3 H). The isomeric ratio (48:52) was determined by GC.

Competition Experiments. A. Reduction of Allylic Acetate in the Presence of α,β-Unsaturated Aldehyde. PMHS (165 mg, 2.6 mequiv) was added to a THF solution containing cinnamyl acetate (**15**) (215 mg, 1.2 mmol), cinnamaldehyde (192 mg, 1.45 mmol), and $Pd(PPh_3)_4$ (53 mg, 4 mol %), and the solution was stirred under nitrogen for 24 h, after which no change was observed in cinnamaldehyde concentration (by GC analysis, 10% Carbowax column, 110 °C). No cinnamyl acetate could be detected. β-Methylstyrene and allylbenzene were present in a 2:1 ratio in 73% total yield (by GC analysis using acetophenone as an internal reference).

B. Reduction of α,β-Unsaturated Aldehyde in the Presence of Allylic Acetate. Bu_3SnH (0.40 mL, 1.6 mmol) was added over a period of 20 min to a THF solution containing cinnamaldehyde (149 mg, 1.13 mmol), 4-acetoxy-7-methyl-2-octene (**5**) (97 mg, 0.53 mmol), triphenylphosphine (16 mg, 0.06 mmol), $Pd(PPh_3)_4$ (81 mg, 6 mol %), and acetic acid (56 mg, 0.93 mmol). GC analysis revealed no change in the allylic acetate concentration. Cinnamaldehyde, however, was quantitatively converted into dihydrocinnamaldehyde (by GC analysis).

C. Reduction of Allylic Acetate in the Presence of Acyl Halide. PMHS (120 mg, 2 mequiv) was added to a THF (5 mL) solution containing cinnamyl acetate (150 mg, 0.85 mmol) and $Pd(PPh_3)_4$ (60 mg, 6 mol %). Slow formation of allylbenzene and β-methylstyrene was observed by GC analysis. After 30 min, cinnamoyl chloride (100 mg, 0.6 mmol) was added. No additional reduction of the cinnamyl acetate could be observed by GC within the next 5 h. Upon addition of Bu_3SnH (0.25 mL, 1 mmol), immediate formation of cinnamaldehyde and dihydrocinnamaldehyde was observed together with continuing reduction of cinnamyl acetate into β-methylstyrene and allylbenzene.

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Registry No. **1**, 81981-13-7; **2**, 79265-03-5; **3**, 86668-24-8; (*E*)-**4**, 86668-25-9; (*Z*)-**4**, 86668-26-0; **5**, 86668-27-1; **6**, 86668-28-2; **7**, 81981-14-8; **8**, 16170-45-9; **9a**, 86668-29-3; **9b**, 86668-30-6; **10a**, 86668-31-7; **10b**, 6250-73-3; **11a**, 86668-32-8; **11b**, 86668-33-9; **12**, 1652-96-6; **13**, 86668-34-0; **14**, 105-87-3; **15**, 103-54-8; PMHS, 9004-73-3; $Pd(PPh_3)_4$, 14221-01-3; cinnamaldehyde, 104-55-2.

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(24) Hevesi, L.; Nagy, J. B.; Krief, A.; Derouane, E. G. *Org. Magn. Reson.* **1977**, *10*, 14.
(25) (a) Underwood, G. M.; Chan, A. K.; Green, T.; Watts, C. T.; Kingsbury, C. A. *J. Org. Chem.* **1973**, *38*, 2735. (b) Identical with an authentic commercial sample (Aldrich).
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Resolution of Chiral Alcohols with Mandelic Acid

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Our continued interest in the area of asymmetric induction has led us to explore new and convenient methods for the resolution of chiral alcohols. Current methods concentrate on the formation of salts between chiral amines and the monophthalate esters and of diastereomeric esters through reaction with chiral acids.[1] The former method is limited by the rather large spatial separation of the chirality in the amine and alcohol moieties. Available acids that are generally effective for the latter technique are represented by camphanic acid[2] and α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's reagent)[3] although use of these as well as other acids is hampered by inaccessibility and/or high cost. It occurred to us that mandelic acid[4] might well serve this purpose, notwithstanding the potential during esterification for racemization and self-condensation of this acid to form the

(1) Jacques, J.; Collet, A.; Wilen, S. H. "Racemates, Enantiomers, and Resolutions"; Wiley: New York, 1981.
(2) Gerlach, H.; Zagalak, B. *J. Chem. Soc., Chem. Commun.* **1973**, 274.
(3) Dale, J. A.; Dull, D. L.; Mosher, J. S. *J. Org. Chem.* **1969**, *34*, 2543.
(4) Mandelate esters of racemic alcohols have been prepared previously (in unspecified yields), and the diastereomers were shown to the be easily separable by gas chromatography (Cross, J. M.; Putney, B. F.; Bernstein, J. *J. Chromatogr. Sci.* **1970**, *8*, 679). However, a preparative separation followed by hydrolysis afforded alcohol with only moderate optical purity. No evidence was presented regarding the possibility of epimerization either during the esterification or the GC analysis, which in either case would have led to crossover of the alcohols.

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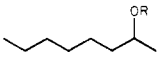
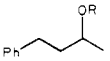
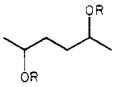
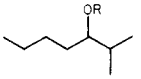
Table I

ester[a]	method of prepn (% yield)	HPLC[c] α[b]	diastereomeric spectral differences[d] ^{1}H	diastereomeric spectral differences[d] ^{13}C	crystalline diastereomer mp, °C (% yield)
	A (97)	0.90	1.25, 1.02	25.3, 24.8	45 (59)
	A (97)	0.94	1.22, 1.00	20.1, 19.6	53-54 (23)
	B (61)	0.92	1.20, 1.04	31.6, 31.3[e]	85-86 (52)
	B (70)	0.96	1.52, 1.40	22.1, 21.7[g]	62-64 (34)
	A (85)	0.90*	5.22, 5.02[f]	19.8, 19.5	125-127 (35)
	A (50)	0.92			35 (6)
	A (76)		2.3, 2.2	39.3, 39.1[h]	74-76 (40)

[a] Method A, R = PhCH(OH)CO-; method B, R = PhCH(OAc)CO-. [b] μ-Porasil with 10:1 hexane/ethyl acetate, except for the asterisked value (μ-C_{18} with CH_3OH/H_2O). [c] Selectivity factor. [d] Unless noted, α-methyl group of alcohol moiety. [e] Benzylic CH_2. [f] *CH*-OH. [g] OAc. [h] α bridgehead.

known dimer.[5] That neither of these processes intervene was demonstrated by the separate reactions of (+)- and (−)-mandelic acid with (−)-menthol.[6] Esterification was effected with 5 mol % of toluenesulfonic acid in benzene at reflux and with azeotropic removal of water. The absorptions of the isopropyl methyl groups of the resulting diastereomeric esters (each produced in 93% yield) were well separated in the proton NMR spectra, and no cross contamination could be detected in either of these reactions (limit of detection ~2%). It is also important to note that while the esterification of menthol was the slowest amoung the alcohols that we examined (24 h), the rate of formation of the diastereomeric esters was qualitatively identical. Thus, formation of the mandelate esters provides a ready method for the assessment of the enantiomeric purity of either mandelic acid or of menthol and, as can be seen from the table, a variety of secondary alcohols (Table I). In most cases, differences between the diastereomeric esters were observed in both the ^{1}H and ^{13}C spectra and along with chromatographic analysis this data could be used to assess the ratio of diastereomers present.

The use of this technique for the resolution of alcohols is illustrated by the separation of racemic 2,5-hexanediol. Formation of the diastereomeric mixture of diesters of this diol (containing approximately 20% of the meso isomer) was carried out as above but with 2 equiv of mandelic acid. Conversion was essentially complete after 3 h, and a simple aqueous workup afforded the crude diastereomeric mixture in 95% yield. Two recrystallizations of this material from ethyl acetate afforded one of the diastereomers that was stereochemically homogeneous by ^{13}C analysis.

Hydrolysis of the diester with aqueous potassium hydroxide returned the diol in 95% yield and with an optical purity of 98%. However, use of these conditions led to partial racemization of the mandelic acid, thus preventing its reuse. Examination of a variety of hydrolysis conditions led to the discovery that potassium carbonate in methanol–water effected hydrolysis with minimum racemization as evidenced by the recovery of 71% of mandelic acid with an optical purity greater than 99%.

With certain alcohols, for example, α-phenethanol, it was not possible to use the strongly acidic conditions described above for esterification. An alternate procedure was devised where the alcohol was first esterified with *O*-acetylmandelic acid under essentially neutral conditions with dicyclohexylcarbodiimide and the acetyl group then removed by selective thiolysis.

Experimental Section

Materials. All solvents were reagent grade and used without purification. Mandelic acid was obtained from Norse Laboratories, Newbury Park, CA.

Procedures. Reactions were routinely effected under a dry nitrogen atmosphere with magnetic stirring. Nuclear magnetic resonance sectra were obtained by using a Varian HA-100 or EM-390 for ^{1}H NMR and a Varian FT-80A spectrometer for ^{13}C NMR. High-resolution mass spectra (HRMS) were obtained using a Du Pont 21-110B instrument. Optical rotations were obtained by using a Perkin-Elmer 141 polarimeter and a 10-cm, 1-mL cell at 25 °C. Analytical chromatography was performed with Merck silica gel plates (TLC) or with a Waters ALC-100 system with μ-porasil columns (HPLC). Preparative chromatography (preparative HPLC) was effected with a Waters Prep 500 system with two silica columns by using the indicated ratio of hexane to ethyl acetate. Elemental analysis was performed by Galbraith Laboratories, Inc., Knoxville, TN.

Esterification. Method A. To a 500-mL flask equiped with a Dean–Stark trap and condensor were added 5.00 g (42.5 mmol) of 2,5-hexanediol (3:1 *d,l*/meso),[7] 12.95 g (85.1 mmol) of (−)-mandelic acid, 0.83 g (4.4 mmol) of $TsOH\cdot H_2O$, and 200 mL of benzene. The stirred solution was heated at reflux, and the progress of the reaction was monitored by TLC. After 4 h the crude reaction mixture was washed with a 200-mL portion of 2 N Na_2CO_3. The aqueous layer was extracted with three 100-mL portions of diethyl ether, and then the combined organic layers

(5) Toniolo, C.; Perciaccante, V.; Falcetta, J.; Rupp, R.; Goodman, M. *J. Org. Chem.* **1970**, *35*, 6.

(6) All possible diasteromers of menthyl mandelate are known. For a leading reference see: Jamison, M. J.; Turner, E. E. *J. Chem. Soc.* **1942**, 611.

(7) Commercially available 2,5-hexanediol (Aldrich) usually contains large amounts of (at least 50%) the meso isomer. Substantial amounts of this impurity were removed by treatment in $CHCl_3$ with anhydrous, powdered $CaCl_2$, leaving the solution enriched in the *d,l* isomer.

were washed with one 300-mL portion of brine. The organic layer was filtered through cotton, dried over $MgSO_4$, and concentrated. The crude product was purified by preparative HPLC (7.5:1), ultimately affording 13.9 g (35.9 mmol; 85%) of a diastereomeric mixture of 2,5-hexanediol dimandelates.

Method B.[8] **I. Formation of *O*-Acetylmandelate Esters.** To a solution of 2.87 g (14.71 mmol) of D-(−)-*O*-acetylmandelic acid,[9] 2.30 g (14.71 mmol) of 1-menthol, and 0.17 g (1.47 mmol) of 4-(dimethylamino)pyridine in 35 mL of CH_2Cl_2 at 0 °C was added dropwise over 8 min with stirring 3.04 g (14.76 mmol) of dicyclohexylcarbodiimide in 12 mL of CH_2Cl_2. A white precipitate of dicyclohexylurea was observed in the reaction medium before the addition was complete. The reaction was then allowed to procede at 25 °C for an additional 22 h. The urea was removed by filtration, and the resulting solution was washed successively with 100-mL portions of 0.5 N HCl, 2 N Na_2CO_3, and brine. The organic layer was dried over $MgSO_4$, concentrated, and then purified by preparative HPLC (6:1), affording 4.42 g (13.25 mmol, 90%) of ester.[10]

II. Thyolysis. To 866 mg (2.6 mmol) of stereochemically pure menthyl *O*-acetylmandelate[11] in 50 mL of CH_3OH was added 35 mL of a solution prepared by acidification of a NaSH solution (0.62 mmol/mL, pH 11.2) in a 3/2 CH_3OH/H_2O solvent system to pH 8.0 with 2 N HCl.[11] Addition of the slightly alkaline reagent to the stirred ester solution was accompanied by cloudiness. An additional 10 mL of CH_3OH was added to restore homogeniety. The yellow solution was heated to 45 °C for 8 h. The crude reaction mixture was diluted with 100 mL of H_2O and extracted with three 100-mL portions of diethyl ether. The aqueous layer was saturated with NaCl and reextracted with two 100-mL portions of diethyl ether. The combined extracts were concentrated, affording a yellow-white crystalline solid. The solid was dissolved in 150 mL of diethyl ether. This solution was washed with five 100-mL portions of H_2O and then with 100 mL of brine. The organic phase was filtered through cotton, dried over $MgSO_4$, and concentrated to give 751 mg (99%) of a white solid. The NMR (^1H and ^{13}C) and HPLC data for the hydroxy ester agreed in all respects with those obtained from a chemically and stereochemically pure sample prepared by method A.

Resolution. Fractional Crystallization. Upon being allowed to stand, a chemically pure sample of 2,5-hexanediol dimandelate (10.5 g) changed from a viscous oil to a slushy and gelatinous mass. Small aliquots of 2.1 hexane/EtOAc were added gradually with swirling until a free-flowing solution was obtained. The resulting white precipitate was filtered, the mother liquor concentrated, and the process repeated. The combined solid material was recrystallized twice from 2:1 hexane/EtOAc to afford 1.84 g (35%) of diester (mp 125–127 °C), stereochemically homogeneous by HPLC analysis.

HPLC. The mixture of diastereomers of 2-octyl mandelate (985 mg) prepared by method A from 2-octanol and (−)-mandelic acid was partially separated into its components by preparative HPLC (7.5:1) with a single pass. The respective fractions were concentrated and subsequently dried in vacuo. The first fraction eventually solidified whereas the second did not. Recrystallization of the more mobil diastereomer from hexane afforded 290 mg of product (59% based on one diastereomer).

2-Octyl Mandelate (1). Method A: yield 97%; chemically pure by ^{13}C NMR; ^1H NMR (one isomer) δ 0.89 (t, J = 3.0 Hz, 3 H), 1.05 (d, J = 7.0, 3 H), 0.6–1.9 (m, 5 H), 4.49 (s, 1 H), 4.78–5.13 (m, 1 H), 5.15 (s, 1 H), 7.23–7.62 (m, 5 H); ^{13}C NMR δ 173.4, 138.7, 129.8, 128.5, 128.3, 126.5, 73.5, 73.1, 35.8, 31.8, 25.3, 22.6, 19.5, 14.0.

2-Pentyl Mandelate (2). Method A was used except that 2 equiv of alcohol was used: yield 97% (after simple workup); NMR δ 0.09–1.79 (m, 7 H), 0.99, 1.18 (d, J = 6.0, 3 H), 3.58 (br s, 1 H), 4.78–5.06 (m, 1 H), 5.12 (s, 1 H), 7.22–7.53 (m, 5 H); ^{13}C NMR δ 173.6, 173.5; 139.1, 139.0; 128.6, 128.4; 126.8, 126.7; 73.3, 73.2; 73.15; 38.1; 38.0; 20.1, 19.6; 18.8, 18.3; 14.0, 13.8; HRMS, calcd for $C_{13}H_{18}O_3$ m/e 222.1256, found m/e 222.1263. Anal. Calcd for $C_{13}H_{18}O_3$: C, 72.69; H, 9.15. Found: C, 72.54; H, 9.15.

4-Phenyl-2-butyl *O*-Acetylmandelate (3). Method B: yield 61% (after preparative HPLC (10:1)); ^1H NMR δ 1.07 (d, J = 6 Hz, 3 H), 1.82 (m, 2 H), 2.61 (t, J = 6.0 Hz, 2 H), 4.98 (sextet, J = 6.0, 1 H), 5.92 (s, 1 H), 7.17 (m, 5 H), 7.46 (m, 5 H); ^{13}C NMR δ 170.0, 168.4, 141.4, 134.1, 129.2, 129.0, 128.9, 128.8, 127.9, 126.1, 74.9, 72.1, 31.9, 20.9, 19.9. Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.59; H, 6.79. Found: C, 73.47; H, 6.84.

α-Phenylethyl *O*-Acetylmandelate (4). Method B: 71% yield after preparative HPLC (12:1); ^1H NMR δ 1.41 (d, J = 6.0 Hz, 3 H), 2.17 (s, 3 H), 5.91 (q, J = 6.0, 1 H), 5.98 (s, 1 H), 6.8–7.7 (m, 10 H); ^{13}C NMR δ 170.4, 168.3, 141.0, 134.3, 129.4, 129.0, 128.8, 128.5, 128.3, 127.9, 126.2, 74.9, 74.0, 21.9, 20.9. Anal. Calcd for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.31; H, 6.31.

2,5-Hexanediol Dimandelate (5). Method A: yield after simple workup, 85%; ^1H NMR (mixture of isomers) δ 0.67–1.70 (m, 10 H), 3.92 (m, 2 H), 4.35 (m, 2 H), 5.03, 5.09, 5.12 (s, 1 H), 7.32 (m, 10 H); ^{13}C NMR (one isomer) δ 173.3, 138.9, 129.5, 128.4, 126.6, 73.0, 72.2, 30.7, 19.8. Anal. Calcd for $C_{22}H_{26}O_6$: C, 68.38; H, 6.78. Found: C, 68.57; H, 6.88.

2-Methyl-3-heptyl Mandelate (6). Method A: yield 50% (after preparative HPLC (6:1)); ^1H NMR δ 0.51 (d, J = 6.0 Hz, 1 H), 0.59 (d, J = 3.0, 3 H), 0.89 (d, J = 6.0 Hz, 3 H), 1.06–1.88 (m, 7 H), 1.06–1.88 (m, 7 H), 3.61 (d, J = 6.0, 1 H), 4.79 (q, J = 4.5 Hz, 1 H), 5.12 (d, J = 6.0 Hz, 1 H), 7.38 (m, 5 H); ^{13}C NMR δ 173.8, 139.0, 128.4, 126.7, 81.0, 78.8, 77.2, 73.1, 31.3, 30.9, 27.8, 22.6, 18.2, 16.7, 14.0. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.63; H, 8.96.

***exo*-Norbornyl Mandelate (7). Method A**: yield 76% (after preparative HPLC (6:1)); ^1H NMR δ 0.67–1.86 (m, 7 H), 2.09 (m, 1 H), 2.23 (m, 1 H), 5.08 (m, 1 H), 3.60 (m, 1 H), 4.65 (m, 1 H), 5.09 (m, 1 H), 7.38 (m, 5 H); ^{13}C NMR δ 173.6, 138.9, 128.7, 128.5, 127.7, 128.5, 126.7, 79.8, 73.14, 41.5, 39.4, 35.6, 35.3, 28.3, 24.2. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.147; H, 7.37. Found C, 72.98; H, 7.37.

Saponification. To 1.04 g (2.7 mmol) of crystalline, stereochemically pure (−)-2,5-hexanediol (−)-dimandelate in 25 mL of CH_3OH was added 1.61 g (11.6 mmol) of K_2CO_3 (anhydrous powder) with stirring followed by enough H_2O to effect nearly complete solution. After 12 h at ambient temperature the reaction mixture was acidified to pH 3.5 by the dropwise addition of 2 N aqueous HCl. The solution was then poured through a column of Amberlyst-25 (10 equiv) anion-exchange resin (hydroxide form) repeatedly until only the diol could be detected by TLC. The resulting basic diol solution was neutralized with 2 N HCl,[12] concentrated, and dried (ca. 2 mmHg, 30 min, 25 °C) to afford a fine white powder. The solid was transferred to the top of a short column of silica gel (slurry, ethyl acetate) and then eluted with 250 mL of ethyl acetate. The effluent was concentrated, leaving a viscous oil which solidified upon standing to afforded 264 mg of slightly yellow diol. This material was sublimed (1 mmHg, 45 °C), giving 251 mg (79%) of pure (2*R*,5*R*)-2,5-hexanediol: mp 52–53 °C; $[\alpha]_D$ −34.3° (*c* 10, $CHCl_3$); optical purity 97.7%.[12]

The mandelic acid was recovered in the following manner: The anion-exchange resin was washed successively with 250 mL of H_2O, 400 mL 2 N HCl, and 200 mL of H_2O. The last two washes were combined, concentrated, and dried in vacuo, affording a crude yellow solid. An ethyl acetate solution of the crude material was filtered through cotton (to remove insoluble impurities) and concentrated to afford ca. 60% of the crude acid. Hence the resin was rinsed with an additional 250 mL of 2 N HCl followed by 500

(8) Nieses, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522.

(9) A procedure for the preparation of *O*-acetylmandelic acid is described by: Breitholle, Edward G.; Stammer, Charles H. *J. Org. Chem.* **1974**, *39*, 1311.

(10) The ^{13}C NMR spectrum of the crude product mixture obtained when unacetylated mandelic acid was employed under the same conditions was consistent with unreacted menthol and a mandelic acid dimer (cyclic diester). The latter material probably was formed via an intramolecular esterification of mandelic acid anhydride.

(11) Menthyl *O*-acetylmandelate was prepared here in two steps by first forming menthyl mandelate according to esterification method A followed by acetylation of the hydroxy ester via the same procedure employed to form *O*-acetylmandelic acid.

(12) Serck-Hanssen, K.; Stellber-Stenhagen, S.; Stenhage, E. *Ark. Kemi* **1953**, *5*, 203. The value of $[\alpha]_D$ −35.6° reported on page 219 of this reference is apparently in error, as the value presented (α_D −2.93° (*c* 8.28)) corresponds to $[\alpha]_D$ −35.1°. The data reported on page 209 of $[M]_{5893}$ −41.3° and +41.5° correspond to $[\alpha]_D$ −34.9° and 35.1°. We have used the maximum value of 35.1° in our calculations of optical purity.

mL of H_2O. The mandelic acid was isolated again as above. The two portions of crude acid were combined and recrystallized from benzene to afford 585 mg (3.8 mmol, 71%) of (−)-mandelic acid; $[\alpha]_D$ −152.2° (*c* 0.0472, H_2O); optical purity 99.3%. An additional 126 mg (0.83 mmol) of acid was obtained by concentrating and cooling of the mother liquor. The optical purity of this material was 85.7% ($[\alpha]_D$ −130.5°).

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Registry No. 1 (isomer 1), 86748-47-2; 1 (isomer 2), 19939-69-6; 2 (isomer 1), 86748-48-3; 2 (isomer 2), 86748-49-4; 3 (isomer 1), 86748-50-7; 3 (isomer 2), 86748-51-8; 4 (isomer 1), 86748-52-9; 4 (isomer 2), 86766-02-1; 5 (isomer 1), 86748-53-0; 5 (isomer 2), 86783-90-6; 6 (isomer 1), 86748-54-1; 6 (isomer 2), 86748-55-2; 7 (isomer 1), 86748-56-3; 7 (isomer 2), 86748-57-4; NaSH, 16721-80-5; H_2S, 7783-06-4; *dl*-2,5-hexanediol, 38484-56-9; *meso*-2,5-hexanediol, 38484-55-8; (−)-mandelic acid, 611-71-2; D-(−)-*O*-acetylmandelic acid, 51019-43-3; *l*-menthol, 2216-51-5; 4-(dimethylamino)pyridine, 1122-58-3; dicyclohexylcarbodiimide, 538-75-0; *l*-menthyl D-(−)-*O*-acetylmandelate, 26171-76-6; *l*-menthyl D-(−)-mandelate, 25926-70-9; (±)-2-octanol, 4128-31-8; (2*R*,5*R*)-2,5-hexanediol, 17299-07-9.

Penicillin–Cephalosporin Conversion. 8.[1] Synthesis of 2,3′-Dithio-Substituted Cephalosporin via Electrolytic Chlorination of Thiazoline–Azetidinone

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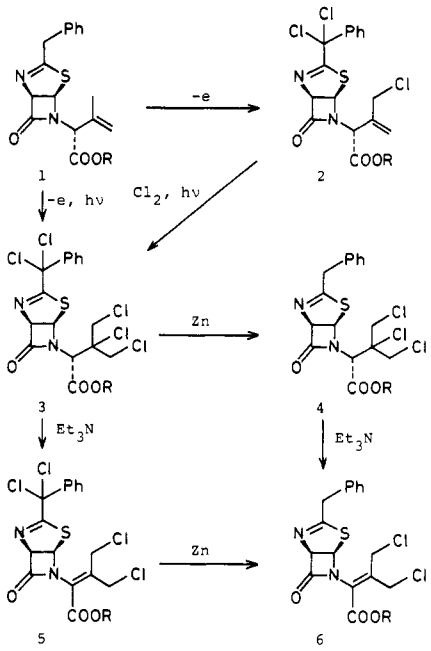
Recently, thiazoline–azetidinones **1**, derived from natural penicillin, have played an important role in penicillin–cephalosporin conversion chemistry.[2] In preceding papers, we disclosed an efficient ene-type chlorination of **1**, providing useful trichloride intermediates **2**[3] which leads directly to the corresponding 3′-thio-substituted cephalosporins.[4] As an extension of this work, we described here a straightforward route to 2,3′-dithio-substituted cephalosporins **9**[5] starting from compound **1** which undergoes electrolytic chlorination to give pentachloride **3** and subsequent intramolecular recyclization into **9** via dichloride **6** (Schemes I and II).

The electrochemical chlorination of **1** was carried out in a manner similar to that reported in the preceding paper.[3] As expected, the chlorination in an aqueous NaCl–H_2SO_4–$CHCl_3$ system gave trichloride **2** in 80% yield after passage of 15 F/mol of electricity. Without isolation, continued electrolysis under irradiation with a 750-W halogen lamp afforded pentachloride **3** in 50% overall yield after an additional 5 F/mol of electricity was passed. The successful conversion of **2** to **3** was achieved by treatment with chlorine in CH_2Cl_2 under illumination for 10 min (90% yield).

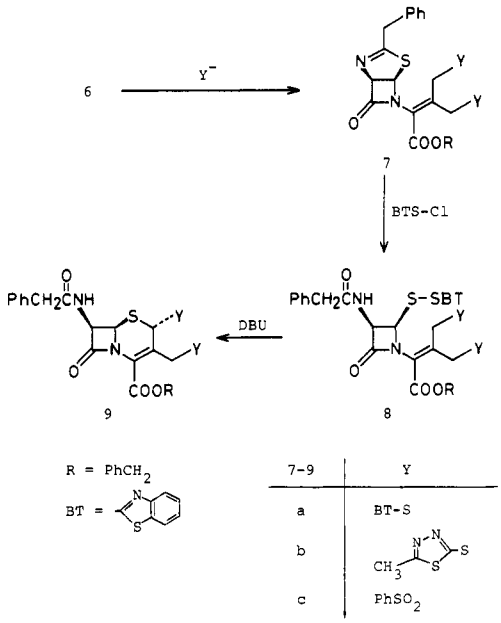
The conversion of **3** to the dichloride **6** was performed by the reduction of the geminal chlorine atoms with 2 equiv of zinc powder in acetic acid–CH_2Cl_2 solution, giving **4** (96%) and subsequent dehydrochlorination with triethylamine in CH_2Cl_2 (86%). The dichloride **6** was also obtained by the dehydrochlorination followed by the reduction of tetrachloride **5** (73% overall yield).

One direct route from **6** to the desired derivatives **9** would be hydrolytic ring opening of the thiazoline moiety followed by the intramolecular nucleophilic replacement of the allylic chlorine atom with the leaving thiol group, leading to 3′-chlorocephalosporin **9** (C(2) Y = H; C(3′) Y

Scheme I



Scheme II



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