Asymmetric Synthesis of Darvon Alcohol

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Since the development of the titanium tartrate catalyzed asymmetric epoxidation by Katsuki and Sharpless[2] in 1980, many examples have appeared in the literature demonstrating the wide scope and utility of the reaction.[3] While many substitution patterns of allylic alcohol have been shown to give chiral epoxides with high enantiomeric excess and predictable absolute configuration, the tetrasubstituted case has not been correlated to date. This paper describes the preparation of Darvon alcohol **9** and establishes the absolute stereochemistry of the D-(−)-diethyl tartrate derived intermediate epoxide **6** as 2*R*,3*R*.[4]

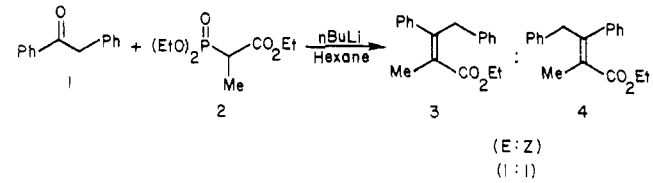
The tetrasubstituted epoxy alcohol **6** was prepared in three steps as shown in Scheme I. The Wittig–Horner reaction of deoxybenzoin (**1**) and ethyl 2-(diethoxyphosphinyl)propionate (**2**) produced a 1:1 mixture of *E*:*Z* isomers (**3** and **4**) separable by silica gel chromatography. Reduction of the *E* isomer[5] **3** with lithium aluminum hydride in ether gave the allylic alcohol **5** in 81% yield (note high regioselectivity). Asymmetric epoxidation with D-(−)-diethyl tartrate/TBHP gave the epoxy alcohol **6** in 90% chemical yield with 94% enantiomeric excess.[6]

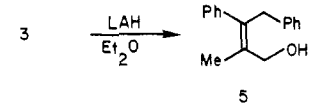
The correlation of epoxy alcohol **6** to Darvon alcohol hydrochloride (**9**) is shown in Scheme II. Epoxide ring opening with lithium aluminum hydride gave the 1,3-diol **7** in 94% yield. The primary alcohol was converted to the tosylate **8** (73%) which was displaced with dimethylamine in Me_2SO to afford Darvon alcohol hydrochloride (**9**) (79%) ($[\alpha]^{24}_D$ +8.2° (*c* 1.21, EtOH), authentic sample $[\alpha]^{24}_D$ +8.7° (*c* 1.20, EtOH)). The correlation demonstrates the 2*R*,3*R* absolute configuration of epoxy alcohol **6**, which is that predicted by the mechanism of asymmetric epoxidation using titanium–D-(−)-diethyl tartrate.[7]

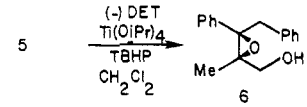
Experimental Section

Flash chromatography refers to the method of Still.[8] NMR data are reported in δ relative to Me_4Si. Anhydrous *tert*-butyl hydroperoxide (TBHP) in CH_2Cl_2 was prepared by the method of Sharpless and Verhoeven.[9]

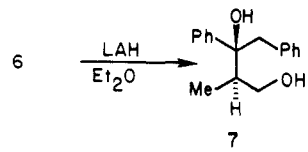
Scheme I

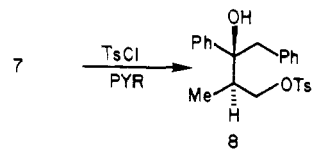


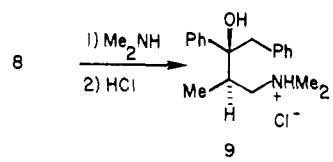




Scheme II







(*E*)-3,4-Diphenyl-2-methyl-2-butenoic Acid, Ethyl Ester (3). To a stirred solution of 1.6 M *n*-BuLi in hexane (5.0 mL, 8.0 mmol) at 0 °C was added ethyl 2-(diethoxyphosphinyl)-propionate (**2**) (1.72 mL, 8.0 mmol). The mixture was warmed to room temperature and stirred for 5 min followed by the addition of deoxybenzoin (**1**) (1.57 g, 8.0 mmol) in 10 mL of hexane over a period of 5 min. The solution was refluxed for 3 h, poured into H_2O (50 mL), and extracted with Et_2O (50 mL). The ether layer was washed with H_2O (3 × 25 mL) and saturated NaCl (1 × 25 mL), dried over $MgSO_4$, filtered, and evaporated, and the *E* (R_f 0.35) and *Z* (R_f 0.25) isomers were separated by flash chromatography on silica gel (bed size 4 cm × 12 cm), eluting with 5% EtOAc in hexane. Fractions containing the *E* isomer by thin layer chromatography were pooled and evaporated to afford 352 mg of **3** (16%) as a colorless oil: ^1H NMR (60 MHz, CCl_4) δ 1.3 (3 H, t), 1.7 (3 H, s), 3.9 (2 H, s), 4.2 (2 H, q), 6.8–7.3 (10 H, m); IR (neat) 3060, 3020, 2980, 2920, 2860, 1710, 1625, 1600, 1490, 1440, 1360, 1310, 1250 cm^{-1}.

(*E*)-3,4-Diphenyl-2-methyl-2-buten-1-ol (5). To a stirred suspension of LAH (135 mg, 3.55 mmol) in Et_2O (10 mL) at 0 °C was added ester **3** (630 mg, 2.25 mmol) dropwise. The mixture was warmed to room temperature and stirred for 3 h and then quenched by the addition of H_2O (140 μL), 20% (w/v) aqueous NaOH (100 μL), and H_2O (500 μL) to give a white granular precipitate. The mixture was filtered and the filtrate was dried over $MgSO_4$, filtered, evaporated and purified by flash chroma-

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(5) The *E* isomer for the allylic alcohol **5** was confirmed by ^1H NMR (250 MHz, benzene-d_6) analysis using increasing amounts of Eu(fod)$_3$ shift reagent from 0–3.5% (w/w) while measuring the change in the chemical shift of the benzylic protons at ca. 3.6 ppm.

(6) The enantiomeric excess was determined by ^1H NMR (250 MHz, benzene-d_6) analysis using Eu(hfbc)$_3$ chiral shift reagent. Increasing amounts of a stock solution of Eu(hfbc)$_3$ in benzene-d_6 were added to a benene-d_6 solution of a known racemic mixture of epoxy alcohol **6** (prepared by $VO(acac)_2$/TBHP epoxidation of allylic alcohol **5**) until a base-line separation of the 1:1 mixture of diastereomers was achieved. Equal addition of the Eu(hfbc)$_3$ stock solution to the chiral epoxy alcohol **6** and integration of the two diastereomeric peaks was used to calculate the enantiomeric excess.

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tography to afford 434 mg of **5** (81%) as a colorless oil: ^{1}H NMR (60 MHz, CCl_4) δ 1.7 (3 H, s), 3.1 (1 H, br s), 3.75 (2 H, br s), 4.3 (2 H, br s), 6.8–7.3 (10 H, m); IR (neat) 3300 (br), 3050, 3020, 2910, 2850, 1600, 1490, 1450, 1440, 1370, 1240 cm^{-1}.

(2*R*,3*R*)-3,4-Diphenyl-2-methyl-2,3-epoxy-1-butanol (6). To a stirred solution of Ti(O-*i*-Pr)$_4$ (698 mg, 2.45 mmol) in CH_2Cl_2 (20 mL) at −20 °C was added D-(−)-diethyl tartrate (633 mg, 3.07 mmol). The pale yellow solution was stirred at −20 °C for 5 min followed by the addition of allylic alcohol **5** (487 mg, 2.04 mmol) and 6.54 M TBHP (0.63 mL, 4.08 mmol) in CH_2Cl_2. The solution was stirred at −20 °C for 5 h and the reaction was stopped by the addition of saturated Na_2SO_4 (0.5 mL) and Et_2O (1.5 mL). The mixture was warmed to room temperature and stirred for 3 h, filtered through Celite, dried over $MgSO_4$, filtered, and evaporated to give a colorless oil. This residue was dissolved in Et_2O (20 mL) and stirred vigorously with a 10% solution of NaOH in saturated NaCl (10 mL) at room temperature for 30 min. The layers were separated and the organic phase was washed with saturated NaCl (2 × 10 mL), dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography to afford 469 mg of **6** (90%) as a colorless oil: ^{1}H NMR (250 MHz, benzene-d_6) δ 1.00 (3 H, s), 1.67 (1 H, s, D_2O exchange), 3.14 (2 H, AB q), 3.71 (2 H, br s), 6.87–7.15 (10 H, m); IR (neat) 3420 (br), 3080, 3060, 3030, 2960, 2920, 1600, 1580, 1490, 1450, 1445, 1375, 1265 cm^{-1}.

(1*S*,2*R*)-2-Methyl-1-phenyl-1-(phenylmethyl)-1,3-propanediol (7). To a stirred suspension of LAH (120 mg, 3.71 mmol) in Et_2O (10 mL) at room temperature was added epoxy alcohol **6** (315 mg, 1.24 mmol) in Et_2O (5 mL) dropwise. The mixture was stirred at room temperature for 3.5 h and quenched by adding H_2O (125 μL), 20% (w/v) aqueous NaOH (95 μL), and H_2O (450 μL) to give a white granular precipitate. The mixture was filtered, and the filtrate was dried over Na_2SO_4, filtered, and evaporated to give the 1,3-diol **7** (94%) as a colorless oil: ^{1}H NMR (60 MHz, CCl_4) δ 0.75 (3 H, d), 2.0 (1 H, m), 3.1 (2 H, s), 3.0–3.9 (4 H, m), 6.7–7.3 (10 H, m).

(2*S*,3*R*)-1,2-Diphenyl-3-methyl-4-tosyl-2-butanol (8). To a stirred solution of 1,3-diol **7** (300 mg, 1.17 mmol) in pyridine (10 mL) at 0 °C was added tosyl chloride (260 mg, 1.36 mmol) in one portion. Thin layer chromatography (30% EtOAc/Hexane) after 18 h showed about a 1:1 mixture of tosylate and starting 1,3-diol so an additional portion of tosyl chloride (260 mg, 1.36 mmol) was added. The mixture was stirred an additional 4 h, poured onto ice and extracted with Et_2O (50 mL). The Et_2O phase was washed with 1 N HCl (4 × 25 mL) and saturated NaCl (2 × 25 mL), dried over $MgSO_4$, filtered, evaporated, and purified by flash chromatography to afford 350 mg of tosylate **8** (73%) as a colorless oil which crystallized on standing: ^{1}H NMR (60 MHz, CCl_4) δ 0.75 (3 H, d), 1.9 (1 H, s, D_2O exchange), 2.0–2.3 (3 H, s and 1 H, m), 3.05 (2 H, s), 3.5–4.1 (2 H, d of AB q), 6.4–7.7 (14 H, m); IR (neat) 3550 (br), 3060, 3020, 2970, 2920, 1600, 1490, 1440, 1350, 1185, 1170 cm^{-1}.

(2*S*,3*R*)-4-(Dimethylamino)-1,2-diphenyl-3-methyl-2-butanol Hydrochloride (9). To a stirred solution of tosylate **8** (350 mg, 0.853 mmol) in Me_2SO (5 mL) was added dimethylamine (2 mL, 30 mmol). The flask was stoppered and stirred at room temperature for 48 h, diluted with Et_2O (100 mL), and washed with H_2O (3 × 50 mL) and saturated NaCl (2 × 50 mL), dried over $MgSO_4$, filtered, and evaporated to a volume of 15 mL, and anhydrous HCl gas was bubbled through the solution which produced a white precipitate. The mixture was cooled to 0 °C, and the precipitate was filtered from solution and washed with cold Et_2O to afford 216 mg of **9** (79%) as a white solid: mp 242–243 °C (recrystallized from MeOH/EtOAc/Et_2O); ^{1}H NMR (250 MHz, D_2O) δ 0.77 (3 H, d), 2.21 (1 H, m), 2.45 (1 H, d of d), 2.57 (6 H, s), 2.85 (1 H, d of d), 3.14 (2 H, AB q), 6.9–7.35 (10 H, m); $[\alpha]^{24}_D$ +8.2° (*c* 1.21, EtOH). Authentic Darvon alcohol hydrochloride showed $[\alpha]^{24}_D$ +8.7° (*c* 1.20, EtOH) and gave an NMR, melting point (247–248 °C), and mixed melting point (243–244 °C) which proved its identity with our synthetic material. Anal. Calcd for $C_{19}H_{26}NOCl$: C, 71.34; H, 8.19; N, 4.38; Cl, 11.08. Found: C, 71.08; H, 8.14; N, 4.13; Cl, 11.35.

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Registry No. **1**, 451-40-1; **2**, 3699-66-9; **3**, 100191-02-4; **4**, 100191-03-5; **5**, 100191-04-6; **6**, 100191-05-7; **7**, 63463-58-1; **8**, 70650-46-3; **9**, 63526-63-6; dimethylamine, 124-40-3; (−)-diethyl tartrate, 13811-71-7.

New Synthesis of Jasmine Lactone and Related δ-Lactones from 1,2-Cyclohexanedione. Preparation and Dye-Sensitized Photooxygenation of 3-(2-Alkenyl)- and 3-(2-Alkynyl)-1,2-cyclohexanediones

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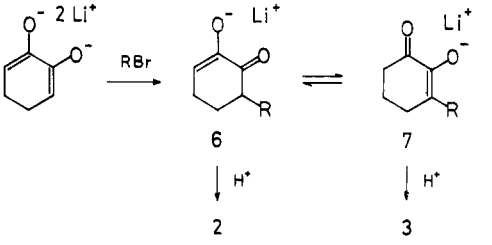
Jasmine lactone (**1c**), a fragrant component of jasmine oil (*Jasminum grandiflorum L.*),[1] was first synthesized in 1962 using cyclopentanone as the starting material.[2] The method has been modified and extended mainly to carry out the oxidative lactonization of the cyclopentanone ring effectively in the presence of a labile unsaturated side chain,[3] although alternative methods using a straight-chain sulfone acetal,[4] glutaraldehyde,[5] or acrolein dimer[5] have also appeared. In this paper, we describe full details of a new synthesis of jasmine lactone and related δ-lactones,[6] which involves monoalkylation of 1,2-cyclohexanedione and dye-sensitized photooxygenation of the resulting 3-substituted 1,2-cyclohexanediones as key steps (Scheme I).

Results and Discussion

α-Monoalkylation of 1,2-Cyclohexanedione. The monoalkylation was carried out via the dianion of 1,2-cyclohexanedione generated by lithium diisopropylamide in THF in a similar manner as reported by Kende and Eilerman in 1973.[7] Although the reaction gave no O-alkylated or polyalkylated products as noted by them, the C-alkylated product was found not to be 3-alkyl-2-hydroxy-2-cyclohexen-1-one (**3**) but to be 6-alkyl-2-hydroxy-2-cyclohexen-1-one (**2**), an enol tautomer of **3**, in spite of the fact that **3** is thermodynamically more stable than **2**. This result indicates that the alkylated lithium enolate anion **6** is hardly in equilibrium with the isomeric anion **7** under the reaction conditions used. Since **2** was



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