hexane (or, in the case of **4c**, distillation under reduced pressure) afforded material of analytical purity. Using this protocol, we prepared and characterized butyrolactones **4a–e**, displaying the following analytical data.

***trans*-4,5-Dihydro-3-phenyl-4,5,5-trimethyl-2(3*H*)-furanone (4a)**: mp 90–92 °C (lit.[7] mp 92 °C); IR (KBr) 1765 (lit.[7] 1765), 1413, 1241, 1153, 988, 708 cm^{-1}; NMR ($CDCl_3$) 7.33 (s, 5 H, Ar *H*), 3.5 (d, J = 12 Hz, 1 H, C*H*C=O), 2.72–2.08 (m, 1 H, CH_3CH), 1.55 (s, 3 H, CH_3CO), 1.38 (s, 3 H, CH_3CO), 1.06 (d, 3 H, CH_3CH); TLC (CH_2Cl_2) R_f 0.55.

***trans*-4,5-Dihydro-3-phenoxy-4,5,5-trimethyl-2(3*H*)-furanone (4b)**: mp 74–75 °C (lit.[7] mp 74–75 °C); IR (KBr) 2975, 2865, 1772 (lit.[7] 1765), 1284, 1140 cm^{-1}; NMR ($CDCl_3$) 7.32–6.91 (m, 5 H, Ar *H*), 4.60 (d, J = 11 Hz, 1 H, C*H*C=O), 2.91–2.08 (br m, 1 H, CH_3CH), 1.52 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3), 1.11 (d, 3 H, $CHCH_3$); TLC (CH_2Cl_2) R_f 0.64.

***trans*-4,5-Dihydro-3-(phenylthio)-4,5,5-trimethyl-2-(3*H*)-furanone (4c)**: bp 125–130 °C (0.05 mm) [lit.[7] bp 150–160 °C (0.1 mm)]; IR (neat) 2978, 1767 (lit.[7] 1765), 1377, 1268, 1246, 1133, 1122 cm^{-1}; NMR ($CDCl_3$) 7.56–6.95 (m, 5 H, Ar *H*), 3.41 (d, J = 11 Hz, 1 H, C*H*C=O), 2.90–1.56 (br m, 1 H, CH_3CH), 1.40 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3), 1.10 (d, 3 H, $CHCH_3$); TLC (CH_2Cl_2) R_f 0.71.

***trans*-4,5-Dihydro-3-(2-thienyl)-4,5,5-trimethyl-2(3*H*)-furanone (4d)**: mp 92–92.5 °C; IR (KBr) 1766, 1397, 1383, 1378, 1241, 1129 cm^{-1}; NMR ($CDCl_3$) 7.29 (d, 2 H, =C*H*S), 7.00 (m, 2 H, other Ar *H*), 3.81 (d, J = 12 Hz, 1 H, C*H*O=O), 1.55 (s, 3 H, CH_3CO), 1.38 (s, 3 H), CH_3CO), 1.14 (d, 4 H, CH_3CH); TLC (ethyl acetate) R_f 0.77. Anal. Calcd for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71. Found: C, 63.18; H, 6.99.

***trans*-4,5-Dihydro-3-(1-naphthyl)-4,5,5-trimethyl-2-(3*H*)-furanone (4e)**: mp 164–165 °C; IR (KBr) 1760, 1396, 1260, 1132, 1075, 961 cm^{-1}; NMR ($CDCl_3$) 8.10–7.20 (m, 7 H, Ar *H*), 4.23 (d, J = 10 Hz, 1 H, C*H*C=O), 1.60 (s, 3 H, CH_3CO), 1.44 (s, 3 H, CH_3CO), 1.04 (d, 4 H, CH_3CH); TLC (ethyl acetate) R_f 0.75. Anal. Calcd for $C_{17}H_{18}O_2$: C, 80.29; H, 7.13. Found: C, 79.98; H, 7.18.

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Registry No. **1a**, 103-82-2; **1b**, 122-59-8; **1c**, 103-04-8; **1d**, 1918-77-0; **1e**, 86-87-3; *threo*-**2a**, 34296-63-4; *erythro*-**2a**, 33398-52-6; *threo*-**2b**, 114059-23-3; *erythro*-**2b**, 70982-80-8; *threo*-**2c**, 114094-14-3; *erythro*-**2c**, 114094-15-4; *threo*-**2d**, 75245-44-2; *erythro*-**2d**, 75245-45-3; *threo*-**2e**, 114059-24-4; *erythro*-**2e**, 114059-25-5; **3a**, 69974-12-5; **3b**, 70982-91-1; **3c**, 114059-26-6; **3d**, 114059-27-7; **3e**, 114059-28-8; **4a**, 71647-85-3; **4b**, 71647-89-7; **4c**, 71647-88-6; **4d**, 114059-29-9; **4e**, 114059-30-2; $(Me)_3CCHO$, 630-19-3; $(Me)_3CCOCH(Ph)CO_2CH(Me)_2$, 114059-31-3.

Improved Procedure for Preparation of Optically Active 3-Hydroxyglutarate Monoesters and 3-Hydroxy-5-oxoalkanoic Acids

Peter D. Theisen and Clayton H. Heathcock*

Department of Chemistry, University of California, Berkeley, California 94720

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We have recently reported the reaction of 1-phenylethanol with the prochiral anhydride **1**, leading to acids **2** and **3** in ratios of up to 15:1.[1] The chiral glutarate monoester **2** is useful for conversion into the Wadsworth–Emmons reagents **6** and **7**, useful synthons for the synthesis of mevinic acid analogues (Scheme I).

The previous synthesis had two disadvantages. First, the prochiral recognition in the reaction of 1-phenylethanol with **1**, although good, still gives a 94:6 mixture of **2** and **3**, at best. In order to remove the minor isomer, it is necessary to convert the mixture of **2** and **3** into methyl esters **4** and **5**, which are separable by preparative HPLC. The second problem comes in the protocol for conversion of **2** into the phosphonates **6** and **7**. For example, the conversion of **4** to reagent **7** involves reaction with dimethyl (lithiomethyl)phosphonate. Although the methyl ester reacts faster than the phenethyl ester, this reaction is accompanied by much β elimination of the (*tert*-butyldimethylsilyl)oxy group. Consequently, it is necessary to desilylate **4**, carry out the (lithiomethyl)phosphonate reaction, and then reinstall the silyl protecting group. Similar problems are encountered in the preparation of **6**. In this Note, we report a modification of our original synthesis that solves these two problems.

The solution arrived at involves replacement of the 1-phenylethanol used in our original work with 1-(1′-naphthyl)ethanol. The racemic 1-(1′-naphthyl)ethanol (**8**) is obtained in 95% yield on a 0.5 M scale by treatment of commercially available 1-naphthaldehyde with methyllithium in ether.[2] The alcohol is separated into its two enantiomers by an enzyme-mediated transesterification procedure developed by Klibanov and co-workers (Scheme II).[3] The racemic alcohol, 2,2,2-trichloroethyl butyrate, a crude preparation of porcine pancreatic lipase (Sigma, E.C. 3.1.1.3), and heptane are stirred at 60 °C. On a large scale the reaction takes several days. Because the enzyme gradually loses its activity with time, the procedure we have developed calls for the periodic addition of fresh enzyme. A total of 100 g of crude enzyme resolves 60 g of alcohol in 14 days. After the enzyme is filtered from the reaction mixture, the resulting liquid is fractionally distilled to remove the excess 2,2,2-trichloroethyl butyrate and the 2,2,2-trichloroethanol byproduct from the reaction mixture. The (*S*)-**8** and (*R*)-**9** remaining in the reaction mixture can also be separated by distillation (bp 125 and 145 °C, respectively), though in practice it has proven easier to distill the two as a mixture and then separate by chromatography. The process converts 95–98% of the *R* isomer present in the mixture. Further reaction time does not increase the percentage of conversion. The *R* alcohol is isolated as its butyrate ester. Saponification of the ester affords optically pure *R* alcohol in 91% yield from the racemic mixture. The *S* alcohol isolated from the reaction mixture contains 2–5% of the *R* isomer. Optically pure (>99.5% ee) material is obtained in 90–95% yield (from the racemic mixture) after two recrystallizations.

Anhydride **1** is obtained from commerially available diethyl 3-hydroxypentanedioate by a slight modification of the previously reported procedure.[1,4] Silylation of the alcohol with *tert*-butyldimethylchlorosilane and imidazole, saponification of the diester to the diacid by NaOH in ethanol, and finally, closure of the anhydride utilizing acetic anhydride in benzene afford anhydride **1** in 80% yield for the three-step sequence. The only purification required is a recrystallization of the final product.

The protocol developed for utilization of the *R* alcohol is shown in Scheme III. Reaction of anhydride **1** with (*R*)-1-(1′-naphthyl)ethanol in the presence of (dimethylamino)pyridine (DMAP) with CH_2Cl_2 as solvent gives acid

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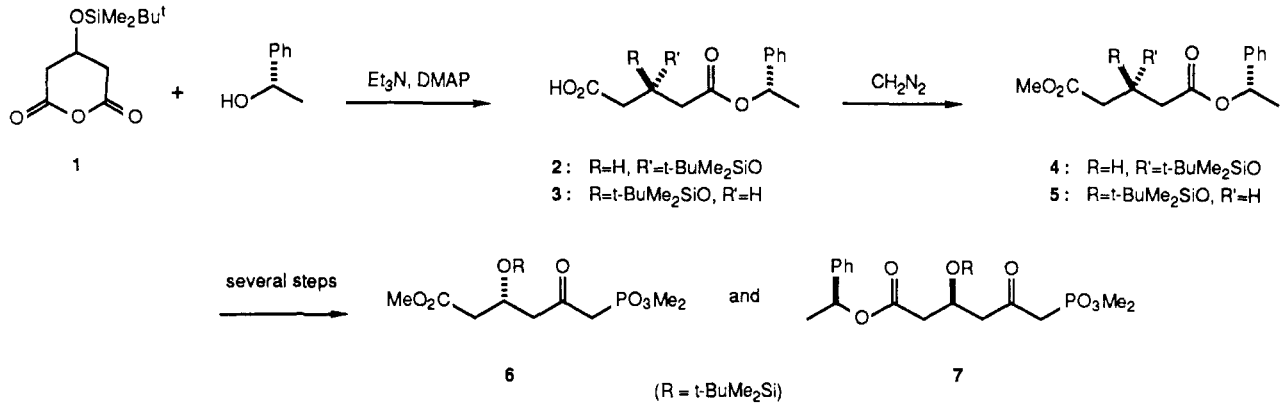
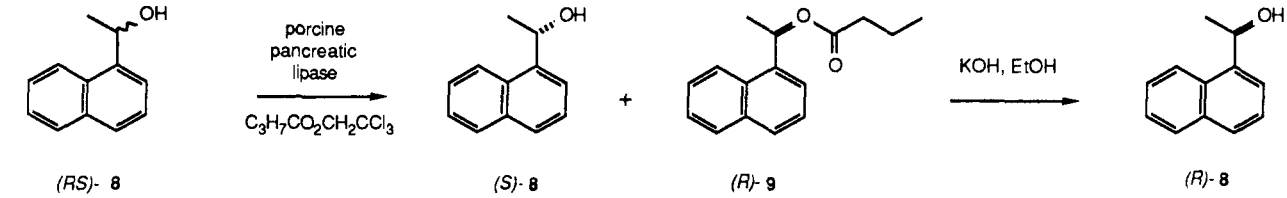
0022-3263/88/1953-2374$01.50/0

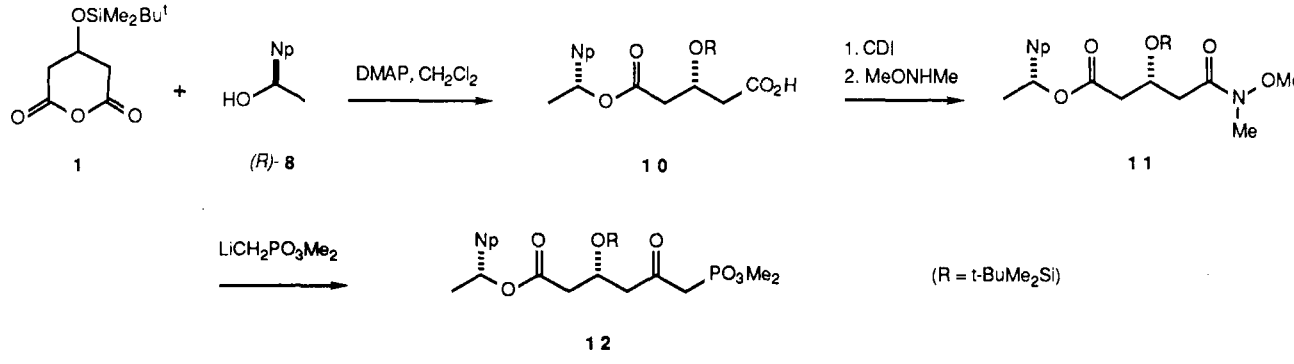
Scheme I



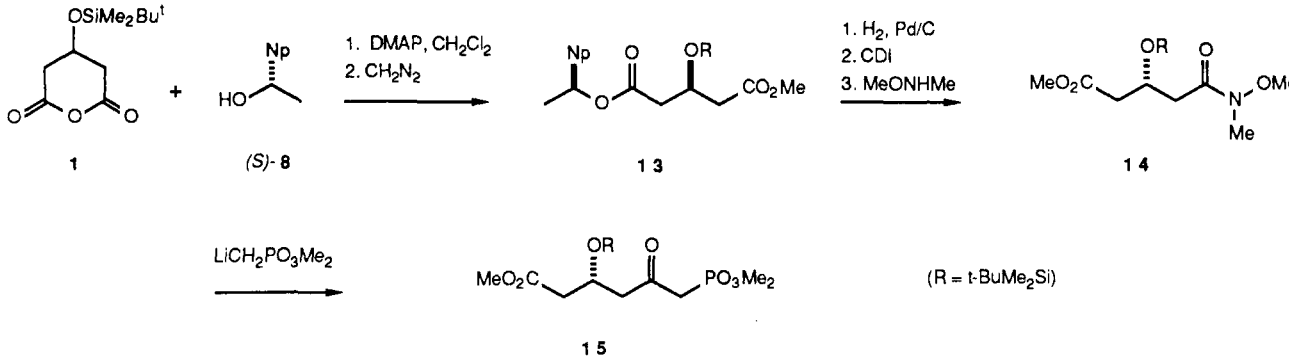
Scheme II



Scheme III



Scheme IV



10 in 92% yield. The reaction proceeds with a high degree of asymmetric induction; acid **10** and its C-3 diastereomer are obtained in a (40–50):1 ratio (40:1, −40 °C, 2 days; 50:1, −75 °C, 9 days). Conversion of acid **10** to the Weinreb amide **11**[5] is accomplished quantitatively by treatment with *N,N'*-carbonylbis[imidazole] in CH_2Cl_2,[6] followed by the addition of *N,O*-dimethylhydroxylamine hydrochloride. Condensation of amide **11** with dimethyl (lithiomethyl)-phosphonate (120 mol %, 20 min, −110 °C) affords keto phosphonate **12** (66% yield, 88% based on recovered starting material). Amide **11** is a versatile chiral synthon with three differentiated functional groups. The foregoing process for its production is mild, requiring no chromatographic purification of intermediates, and extremely efficient, amenable to the production of multigram quantities.

By an analogous route, the (*S*)-(−)-1-(1'-naphthyl)ethanol produced in the enzymatic resolution is utilized in the production of keto phosphonate **15**, as shown in Scheme IV. Treatment of anhydride **1** with (*S*)-**8** and subsequent esterification with diazomethane furnish optically active diester **13** in 93% yield. Hydrogenolysis of the naphthylethyl ester and amide formation utilizing *N,N'*-

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carbonylbis[imidazole][6] and *N,O*-dimethylhydroxylamine hydrochloride afford amide **14** in 95% yield for the two-step sequence. Condensation with dimethyl (lithiomethyl)phosphonate affords keto phosphonate **15** in 62% yield (82% based on recovered starting material).

The condensation reaction of amides **11** and **14** with the phosphonate anion is extremely sensitive to the reaction conditions; competing pathways are retro-aldol reaction and β elimination of the silyloxy group. Increasing the amount of phosphonate anion in the reaction mixture decreases the amount of starting material recovered without a concurrent increase in product yield. The decrease in yield is due to decomposition, most likely through retro-aldol pathways. At −78 °C, attack of the anion occurs exclusively at the amide, although a minor amount of a mixture of products resulting from silyloxy elimination is obtained. At −110 °C no products resulting from silyloxy elimination are recovered; although a small amount of naphthylethyl alcohol can be isolated from the product mixture, no material resulting from attack of the anion at the ester is recoverable.

Amides **11** and **14** are valuable chiral synthons that can be made in large quantities by the foregoing procedures. Phosphonates **12** and **15** are suitable synthons for the lactone moiety of HMG CoA reductase inhibitors. Presented here is a short, efficient route that is useful for the production of multigram quantities of **12** and **15** in high optical purity (96–97% ee).

Experimental Section

General. Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone immediately prior to use. Methylene chloride was distilled from phosphorus pentoxide. Hexane was distilled at atmospheric pressure. All reactions were conducted under a nitrogen atmosphere unless otherwise indicated. Boiling points and melting points (Pyrex capillary) are uncorrected. All ^{1}H NMR spectra were recorded with $CDCl_3$ as solvent unless otherwise noted. Chemical shifts are expressed in ppm downfield from internal tetramethylsilane. Significant ^{1}H NMR data are tabulated in the order multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constant(s) in hertz. ^{13}C NMR spectra were measured at 62.89, 75.47, or 125 MHz. Minor diastereomers are indicated in parentheses. ^{19}F NMR spectra were measured at 235 MHz. Mass spectral data are tabulated as m/z (intensity expressed as percent of total ion current). Elemental analyses were performed by the Microanalytical Laboratory of the College of Chemistry, University of California, Berkeley, CA.

(*RS*)-1-(1′-Naphthyl)ethanol (8). Under an argon atmosphere, into a 1-L round-bottomed flask equipped with a magnetic stirring bar and pressure-equalized dropping funnel fitted with a rubber septum was placed 330 mL (0.53 mol) of a 1.6 M solution of MeLi in ether. The system was cooled to −78 °C and a solution of 80.50 g (0.50 mol, Aldrich, 97%) of 1-naphthaldehyde in 100 mL of ether was added dropwise by the addition funnel. The reaction mixture was stirred for 1 h after the addition was completed, warmed to room temperature, and stirred for an additional 1 h. The system was cooled to 0 °C and 250 mL of saturated aqueous K_2CO_3 was carefully added. The layers were separated and the aqueous layer was further extracted with ether. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure with a rotary evaporator to obtain 90 g of a clumpy yellow solid. This material was recrystallized from hexanes to afford 81.92 g (95%) of a fluffy white solid, mp 65–66 °C (lit.[7] mp 66–67 °C). IR ($CHCl_3$): 3620, 3015, 3000, 1115 cm^{-1}. ^{1}H NMR: δ 1.83 (d, 3, J = 6.4), 1.92 (d, 1, J = 3.5), 5.69 (dq, 1, J = 3.5, 6.4), 7.51 (m, 3), 7.74 (m, 1), 7.79 (m, 1), 7.89 (m, 1), 8.13 (m, 1). ^{13}C NMR: δ 24.29, 66.97, 121.90, 123.07, 125.43, 125.44, 125.92, 127.80, 128.76, 130.15, 133.68, 141.26. Anal. Calcd for $C_{12}H_{12}O$: C, 83.68; H, 7.02. Found: C, 83.70; H, 6.98.

Resolution of 1-(1′-Naphthyl)ethanol. (*S*)-1-(1′-Naphthyl)ethanol (8) and (*R*)-1-(1′-Naphthyl)ethyl Butyrate (9). Under argon into an oven-dried 500-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum were placed 60.00 g (0.348 mol) of *rac*-1-(1′-naphthyl)ethanol (**8**), 91.66 g (0.418 mol) of 2,2,2-trichloroethyl butyrate,[8] 20 g of porcine pancreatic lipase (Sigma, E.C. 3.1.1.3), and 120 mL of heptane. The mixture was heated to 60 °C with stirring and held there during the course of the reaction. Fresh enzyme (10 g) was added each day until a total of 100 g had been added to the reaction mixture. The mixture was stirred at 60 °C for 14 days and then cooled to room temperature. The enzyme was filtered off and rinsed well with hexane. The organic fractions were combined and concentrated under reduced pressure with a rotary evaporator. The 2,2,2-trichloroethanol and 2,2,2-trichloroethyl butyrate were removed by fractional distillation under reduced pressure to obtain 72 g of a 1:1 mixture of (*S*)-**8** and (*R*)-**9** as a clear oil (bp 125–144 °C, 0.5 mmHg). The alcohol was separated from the ester by radial preparative layer chromatography (4-mm plate of silica gel, eluted first with hexanes and then with EtOAc, 5 g per run) to obtain 31.20 g of (*S*)-**8** as a white solid and 40.51 g (96% yield) of (*R*)-**9** as a clear oil. Two recrystallizations of the solid from hexanes afforded 28.40 g of optically pure material (99.5% ee, ^{1}H NMR analysis of the Mosher ester[9]) (94% yield from the racemic mixture) as white needles, mp 43.5–45 °C (lit.[7] mp 43–44 °C). Butyrate **9**: $[\alpha]^{25}_D$ +41.9° (*c* 1.0, ether). IR (thin film): 3020, 2990, 1745, 1195, 780 cm^{-1}. ^{1}H NMR: δ 0.94 (t, 3, J = 7.4), 1.68 (m, 2), 1.70 (d, 3, J = 6.6), 2.36 (t, 2, J = 7.2), 6.67 (q, 1, J = 6.6), 7.46 (m, 3), 7.61 (m, 1), 7.81 (m, 1), 7.88 (m, 1), 8.08 (m, 1). ^{13}C NMR: δ 13.31, 18.16, 21.36, 36.09, 68.71, 122.76, 122.79, 124.96, 125.25, 125.87, 128.01, 128.52, 129.95, 133.49, 137.24, 172.25. Anal. Calcd for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.50; H, 7.39.

(*R*)-1-(1′-Naphthyl)ethanol (8). Into a 500-mL round-bottomed flask equipped with a magnetic stirring bar were placed 40.50 g (0.107 mol) of butyrate **9** and 312 mL of a 1 M solution of KOH in absolute ethanol [20.57 g of KOH (85%, Mallinckrodt), 0.312 mol]. The mixture was stirred at room temperature for 3 h. The ethanol was removed under reduced pressure with a rotary evaporator. The last traces of solvent were removed under high vacuum (3 h, 1.0 mmHg) to obtain 70 g of an off-white solid. The crude material was partially dissolved in 100 mL of H_2O and extracted (2 × 250 mL) with ether. The ether fractions were combined, dried over $MgSO_4$, and concentrated under reduced pressure with a rotary evaporator to obtain 28 g of an off-white solid. The material was recrystallized from hexanes to afford 27.32 g (95%, 91% from the racemic mixture) of optically pure material [$[\alpha]^{25}_D$ +82.1° (*c* 1.0, ether); lit.[7] $[\alpha]^{25}_D$ +78.9° (*c* 1, $CHCl_3$); optical purity confirmed by ^{1}H NMR analysis of the Mosher ester[9]] as a white crystalline solid, mp 66–67 °C (lit.[7] mp 66–67 °C).

3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioic Anhydride (1). Under a nitrogen atmosphere into an oven-dried 500-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum were placed 25 g (Aldrich, 95%, 0.116 mol) of diethyl 3-hydroxyglutarate and 200 mL of CH_2Cl_2. To this stirring solution were added 26.29 g (0.174 mol) of *tert*-butylchlorodimethylsilane and 15.83 g (0.233 mol) of imidazole. The resulting suspension was stirred at room temperature overnight, diluted with ether (300 mL), and washed successively with H_2O (2 × 100 mL) and brine (1 × 100 mL). The combined aqueous washings were extracted with 100 mL of ether, the combined organic fractions were dried over $MgSO_4$, and the solvent was removed under reduced pressure with a rotary evaporator to obtain 45.00 g of crude material as a clear oil.

Under a nitrogen atmosphere into an oven-dried 500-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed the crude silyl ether. To the stirring liquid, at 0 °C, were added 13.92 g (0.348 mol) of NaOH pellets and 150 mL of MeOH. The cold bath was removed, and the resulting suspension was stirred overnight at room temperature. The solvent was removed with a rotary evaporator, and the residual MeOH was removed under high vacuum (12 h, 1.0 mmHg)

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to obtain 45 g of an off-white solid. The crude dicarboxylate, 200 mL of benzene, and 150 mL of acetic anhydride were placed in a 1-L round-bottomed flask equipped with a magnetic stirring bar and a reflux condenser fitted with a rubber septum under a nitrogen atmosphere. The mixture was heated at reflux for 1.5 h, diluted with 500 mL of $CHCl_3$, and washed with several portions of saturated aqueous $NaHCO_3$ and brine. The organic solution was dried over $MgSO_4$, and the solvent was removed with a rotary evaporator. The resulting brown liquid was heated under high vacuum (4 h, 50–60 °C, 1.0 mmHg). Upon cooling to room temperature, the material solidified to afford 28 g of a brown solid. The material was recrystallized from hexanes to obtain 22.48 g (79% from diethyl 3 hydroxyglutarate) of an off-white crystalline solid. The IR and ^1H NMR spectral data are in agreement with those previously reported for this compound.[4] ^{13}C NMR: δ −5.03, −5.02, 17.78, 25.43, 39.07, 61.88, 165.16.

Hydrogen (3*R*,1′*R*)-1-(1′-Naphthyl)ethyl 3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (10). Under an argon atmosphere into an oven-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum were placed 14.00 g (0.081 mol) of (*R*)-**8**, 5.50 g (0.045 mol) of DMAP, and 25 mL of CH_2Cl_2. The flask was cooled to −75 °C (Cryocool), and 11.00 g (0.045 mol) of anhydride **1** was added. The mixture was stirred at −75 °C for 9 days, diluted with 500 mL of ether, and washed with 100 mL of 1 M aqueous H_3PO_4 and 50 mL of saturated aqueous $NaHCO_3$. The combined aqueous washings were extracted with 50 mL of ether. The combined organic fractions were dried over $MgSO_4$ and concentrated under reduced pressure with a rotary evaporator to afford 27.01 g of an orange oil. The crude material was taken up in 200 mL of ether and extracted with 450 mL of 0.1 N NaOH. The layers were separated and the aqueous portion was acidified with 50 mL of 1 N HCl. The ether portion was concentrated under reduced pressure with a rotary evaporator and chromatographed (radial preparative layer chromatography, 4-mm plate of silica gel, 9:1 hexanes/EtOAc as eluant) to afford 6.20 g of recovered (*R*)-**9**. The acidified aqueous portion was extracted (3 × 150 mL) with ether. The combined ether extracts were dried over $MgSO_4$ and concentrated under reduced pressure with a rotary evaporator to afford 17.27 g (92%) of a clear oil as a 50:1 mixture of **4** and its C-3 epimer. [The diastereomeric ratio was determined by conversion of the acid to the methyl ester with CH_2N_2, followed by ^1H NMR analysis of the methyl ester peaks (**4**: δ 3.67; C-3 diastereomer: δ 3.65)]. IR ($CHCl_3$): 3500–3100 (br), 3010, 2970, 1730, 1720, 1095 cm^{-1}. ^1H NMR: δ 0.00 (s, 3), 0.07 (s, 3), 0.80 (s, 9), 1.68 (d, 3, J = 6.5), 2.66 (m, 4), 4.56 (m, 1), 6.65 (q, 1, J = 6.5), 7.52 (m, 4), 7.82 (m, 1), 7.92 (m, 1), 8.12 (m, 1). ^{13}C NMR: δ −5.00, −4.85, 17.86, 21.89, 25.61, 41.90, 42.38, 65.99, 69.91, 123.05, 123.31, 125.33, 125.62, 126.28, 128.43, 128.87, 130.08, 133.77, 137.19, 170.03, 175.68 Anal. Calcd for $C_{23}H_{32}O_5Si$: C, 66.31; H, 7.74. Found: C, 66.53; H, 7.66.

(1′*R*,3*R*)-1-(1′-Naphthyl)ethyl 4-(*N*-Methyl-*N*-methoxycarbamoyl)-3-[(*tert*-butyldimethylsilyl)oxy]butanoate (11). Under an argon atmosphere into an oven-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum were placed 10.00 g (24.0 mmol) of acid **10** and 50 mL of CH_2Cl_2. To the system was carefully added 3.89 g (24.0 mmol) of *N*,*N*′-carbonylbis[imidazole]. The mixture was stirred at room temperature for 10 min, and 2.50 g (24.0 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride was added. The reaction mixture was stirred overnight at room temperature, diluted with ether, and washed successively with 0.25 N HCl (2 × 75 mL), saturated aqueous $NaHCO_3$ (2 × 75 mL), and brine (1 × 50 mL). The organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure with a rotary evaporator. The last traces of solvent were removed under high vacuum (4 h, 0.5 mmHg) to afford 11.00 g (quantitative yield) of amide **11** as a clear oil. IR (film): 3030, 2960, 2940, 1740, 1670, 1095, 845, 785 cm^{-1}. ^1H NMR: δ 0.04 (s, 3), 0.05 (s, 3), 0.81 (s, 9), 1.70 (d, 3, J = 6.6), 2.65 (m, 4), 3.15 (s, 3), 3.60 (s, 3), 4.66 (m, 1), 6.65 (q, 1, J = 6.6), 7.48 (m, 3), 7.62 (m, 1), 7.81 (m, 1), 7.88 (m, 1), 8.10 (m, 1). ^{13}C NMR: δ −4.97, −4.81, 17.91, 21.86, 25.70, 32.33, 39.39, 42.74, 61.18, 66.26, 69.50, 123.14, 123.27, 125.36, 125.55, 126.19, 128.27, 128.76, 130.12, 133.72, 137.38, 170.26, 193.08. Anal. Calcd for $C_{25}H_{37}NO_5Si$: C, 65.32; H, 8.12; N, 3.05. Found: C, 65.49; H, 7.94; N, 3.05.

(1′*R*)-1-(1′-Naphthyl)ethyl (3*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(dimethoxyphosphinyl)-5-oxohexanoate (12). Under an argon atmosphere into an oven-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed 8.0 mL (13.60 mmol) of a 1.7 M solution of *n*-butyllithium in hexanes. The system was cooled to −78 °C and 1.53 mL (1.75 g, 13.73 mmol) of dimethyl methylphosphonate was added dropwise by syringe. During the addition, a mixture of 2 mL of THF and 2 mL of Et_2O was added to aid in stirring. The reaction mixture was stirred at −78 °C for 15 min after completion of the addition and then cooled to −110 °C (ether/liquid N_2). To the system was added streamwise a solution of 4.95 g (10.77 mmol) of amide **11** in 2 mL of a 1:1 mixture of ether and THF. The syringe that delivered the amide was rinsed with 0.5 mL of THF. The mixture was stirred at −110 °C for 15 min, then allowed to warm to −80 °C over 15 min, and stirred for an additional 15 min. An ice-cold mixture of 20 mL of 1 M aqueous H_3PO_4 and 60 mL of Et_2O was added to the flask. The cooling bath was removed and the mixture allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc. The organic fractions were combined, dried over $MgSO_4$, and concentrated under reduced pressure with a rotary evaporator to obtain 5.40 g of a clear oil. The material was purified by radial preparative layer chromatography (4-mm plate of silica gel, 4:1 hexanes/EtOAc and then 100% EtOAc as eluant) to obtain 1.20 g of recovered amide **11** and 3.71 g (66%, 88% based on recovered starting material) of phosphonate **12** as a clear oil. IR ($CHCl_3$): 3010, 2960, 2940, 1740, 1730, 1380, 1260, 1070, 1050, 850 cm^{-1}. ^1H NMR: δ 0.03 (s, 3), 0.04 (s, 3), 0.80 (s, 9), 1.70 (d, 3, J = 6.6), 2.56 (dd, 1, J = 5.5, 15.2), 2.62 (dd, 1, J = 6.1, 15.2), 2.88 (d, 2, J = 5.9), 3.04 (d, 2, J = 22.6), 3.73 (s, 3), 3.78 (s, 3), 4.57 (m, 1), 6.64 (q, 1, J = 6.6), 7.52 (m, 4), 7.81 (m, 1), 7.89 (m, 1), 8.07 (m, 1). ^{13}C NMR: δ −5.06, −4.96, 17.78, 21.72, 25.60, 42.14, 42.21 (d, J = 128), 50.66, 52.84 (d, J = 1.6), 52.91 (d, J = 1.6), 65.22, 69.63, 123.02, 123.23, 125.26, 125.55, 126.19, 128.33, 128.79, 130.04, 133.68, 137.18, 170.01, 199.85 (d, J = 6.5). Anal. Calcd for $C_{26}H_{39}O_7PSi$: C, 59.75; H, 7.52; P, 5.93. Found: C, 59.97; H, 7.33; P, 5.72.

(1′*S*)-1-(1′-Naphthyl)ethyl Methyl (3*S*)-3-[(*tert*-Butyldimethylsilyl)oxy]pentanedioate (13). The enantiomer of acid **10** was prepared by reaction of anhydride **1** with (*S*)-**8** (vide supra). The resulting crude acid (26.32 g) was taken up in a minimal amount of ether (100 mL) and added to 300 mL of an ice-cold solution of 0.23 M CH_2N_2 in ether. The mixture was allowed to warm slowly to room temperature and was held at that temperature overnight. The solvent was removed with a rotary evaporator to afford 27.70 g of an orange oil. The material was purified by radial preparative layer chromatography (4-mm plate of silica gel, eluted first with hexanes and then with EtOAc, 4 g per run) to afford 18.00 g (93%) of diester **13** (50:1 mixture of **13** and its C-3 epimer) as a clear oil. Also recovered was 6.15 g of (*S*)-**8**. Diester **13**: IR ($CHCl_3$): 3010, 2960, 2940, 2860, 1740, 1260, 1100, 850 cm^{-1}. ^1H NMR: δ 0.01 (s, 3), 0.05 (s, 3), 0.80 (s, 9), 1.72 (d, 3, J = 6.6), 2.59 (m, 2), 2.64 (dd, 1, J = 5.9, 15.3), 2.66 (dd, 1, J = 6.1, 15.3), 3.67 (s, 3), 4.58 (m, 1), 6.66 (q, 1, J = 6.6), 7.52 (m, 3), 7.55 (m, 1), 7.82 (m, 1), 7.89 (m, 1), 8.11 (m, 1). ^{13}C NMR: δ −5.02, −4.85, 17.83, 21.88, 25.59, 42.19, 42.60, 51.51, 66.19, 69.71, 123.07, 123.27, 125.30, 125.58, 126.22, 128.36, 128.84, 130.09, 133.74, 137.26, 170.12, 171.40. Anal. Calcd for $C_{24}H_{34}O_5Si$: C, 66.94; H, 7.96. Found: C, 67.17; H, 7.75.

(3*R*)-Methyl 4-(*N*-Methyl-*N*-methoxycarbamoyl)-3-[(*tert*-butyldimethylsilyl)oxy]butanoate (14). Into an oven-dried 250-mL round-bottomed flask equipped with a magnetic stirring bar were placed 17.44 g (40.5 mmol) of diester **13** and 100 mL of EtOAc. To the system was added 500 mg of 10% Pd/C, and the flask was attached to an atmospheric hydrogenation apparatus. The reaction mixture was stirred at room temperature for 5 days, diluted with EtOAc, and filtered through a Celite pad. The Celite was rinsed well with EtOAc, and the combined organic fractions were concentrated under reduced pressure with a rotary evaporator to afford 18 g of a clear, pale yellow oil.

The crude acid prepared above was placed under an argon atmosphere into an oven-dried 250-mL round-bottomed flask equipped with a magnetic stirring bar and a rubber septum. To the system was added 100 mL of CH_2Cl_2, and 6.57 g (40.5 mmol) of *N*,*N*′-carbonylbis[imidazole] was carefully added. The mixture was stirred at room temperature for 15 min and 3.95 g (40.5 mmol) of *N*,*O*-dimethylhydroxylamine hydrochloride was added. The mixture was stirred at room temperature overnight, diluted with

ether, and washed successively with 0.25 N HCl (2 × 75 mL), saturated aqueous $NaHCO_3$ (2 × 75 mL), and brine (1 × 50 mL). The organic fraction was dried over $MgSO_4$ and concentrated under reduced pressure with a rotary evaporator to afford 18.5 g of a clear oil. The material was purified by column chromatography (150 g of silica gel, eluted first with hexanes and then with EtOAc) to afford 12.25 g (95%) of a clear oil. IR ($CHCl_3$): 3020, 2990, 2950, 2880, 1740, 1660, 1450, 1265, 1095, 845 cm^{-1}. ^1H NMR: δ 0.06 (s, 3), 0.08 (s, 3), 0.85 (s, 9), 2.60 (m, 4), 3.17 (s, 3), 3.67 (s, 3), 3.70 (s, 3), 4.63 (m, 1). ^{13}C NMR: δ -5.28, -4.95, 17.70, 25.50, 31.73, 39.46, 42.41, 51.22, 61.07, 66.20, 171.27, 194.57. Anal. Calcd for $C_{14}H_{29}NO_5Si$: C, 52.63; H, 9.15; N, 4.38. Found: C, 52.47; H, 9.12; N, 4.29.

Methyl (*R*)-3-[(*tert*-Butyldimethylsilyl)oxy]-6-(dimethoxyphosphinyl)-5-oxohexanoate (15). Under an argon atmosphere into an oven-dried 100-mL round-bottomed flask equipped with a magnetic stirring bar and rubber septum was placed 11.05 mL of 1.7 M *n*-BuLi in hexanes. The system was cooled to -78 °C and 2.20 mL (2.52 g, 20.3 mmol) of dimethyl methylphosphonate was added dropwise by syringe. During the addition, a mixture of 2 mL of THF and 2 mL of ether was added to the system to aid in stirring. The reaction mixture was stirred for 15 min after the completion of the addition and cooled to -110 °C (ether/liquid N_2). To the system was added streamwise a solution of 5.00 g (15.65 mmol) of amide **14** in 2 mL of a 1:1 mixture of ether and THF. The syringe that delivered the amide was rinsed with 0.5 mL of THF. The mixture was stirred at -110 °C for 15 min, then allowed to warm to -80 °C over 15 min, and stirred for an additional 15 min. An ice-cold mixture of 20 mL of 1 M H_3PO_4 and 60 mL of ether was added to the flask. The cooling bath was removed and the mixture allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with EtOAc. The organic fractions were combined, dried over $MgSO_4$, and concentration under reduced pressure with a rotary evaporator to obtain 6.25 g of a clear oil. The material was purified by column chromatography (150 g of silica gel, 2:1 hexanes/EtOAc as eluant) to obtain 1.25 g of recovered amide **14** and 3.69 g (62%, 82% based on recovered starting material) of phosphonate **15** as a clear oil. The IR and ^1H NMR spectral data are in agreement with those previously reported for this compound.[1b] ^{13}C NMR: δ -5.12, -4.94, 17.75, 25.55, 42.00, 42.67 (d, J = 128.2), 50.93, 51.43, 52.86 (d, J = 1.6), 52.98 (d, J = 1.6), 65.26, 171.16, 199.78 (d, J = 6.4).

Registry No. 1, 91424-40-7; (±)-8, 57605-95-5; (*R*)-8, 42177-25-3; (*S*)-8, 15914-84-8; 9, 113794-42-6; (*R,R*)-10, 113794-43-7; (*S,S*)-10, 113794-49-3; 11, 113794-44-8; 12, 113794-45-9; 13, 113794-46-0; 14, 113794-47-1; 15, 96555-58-7; MeNHOMe, 6638-79-5; $H_3CCH_2CH_2CO_2CH_2CCl_3$, 57392-44-6; $EtOCOCH_2CH(OH)CH_2CO_2Et$, 32328-03-3; $MeP(O)(OEt)_2$, 756-79-6; *t*-BuSi(Me$_2$)Cl, 18162-48-6; 1-naphthaldehyde, 66-77-3; bis(dimethyl-*tert*-butylsilyl) ether, 91424-39-4; dimethyl 3-[(*tert*-butyldimethylsilyl)oxy]pentanedioate, 113794-48-2; 3-[(*tert*-butyldimethylsilyl)oxy]-5-(methoxycarbonyl)pentanoic acid, 109744-49-2.

Total Synthesis of Oxynitidine via Lithiated Toluamide-Imine Cycloaddition[1]

Robin D. Clark* and Jahangir[2]

Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

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We have demonstrated that *trans*-3-aryl-4-substituted-3,4-dihydro-1(2*H*)-isoquinolones are readily available from a one-pot procedure involving cycloaddition of lithiated *N,N*-diethyl-*o*-toluamides with benzaldimines followed by electrophilic trapping of the 4-lithio-3-aryl-3,4-dihydro-1-(2*H*)-isoquinolone that is generated under the basic reaction conditions.[3] We felt that this methodology would afford direct access to intermediates (e.g., **9**) for the synthesis of benzo[*c*]phenanthridine alkaloids.[4] We now report a total synthesis of the benzo[*c*]phenanthridine alkaloid oxynitidine (**13**)[5] that utilizes this annelation-trapping strategy to assemble all of the carbon atoms in a single step.

Preliminary Studies

In a model study, *N,N*-diethyl-*o*-toluamide (**1**) was deprotonated with LDA in THF at -70 °C and treated sequentially with 1 equiv of piperonal *N*-methylimine (**3**) and 1.5 equiv of bromoacetaldehyde dimethyl acetal to afford the *trans*-3,4-disubstituted 3,4-dihydroisoquinolone **4** in 54% yield (Scheme I). Numerous attempts were made to cyclize **4** to a tetracyclic compound under a variety of acidic conditions and with a number of Lewis acids.[6] However, these attempts were uniformly unsuccessful (<5% yield of cyclized products). On the basis of ^1H NMR spectroscopic evidence, the 3-aryl group and the 4-(2,2-dimethoxyethyl) side chain of **4** are pseudoaxially oriented[7] ($J_{3,4}$ = 0.0 Hz), which may account for the observed lack of intramolecular cyclization. The lack of propensity for cyclizations to occur in a related system was observed by Shamma and Tomlinson,[8] who were able to cyclodehydrate an acid of type **7** (specifically the 7,8-methylenedioxy analogue of **7**) only under specialized conditions (methanesulfonic acid, phosphorus pentoxide).[9] Accordingly, acetal **4** was hydrolyzed to the aldehyde **6**, which was oxidized with permanganate under phase-transfer conditions[10] to acid **7** (96% from **4**). Treatment of acid **7** with methanesulfonic acid-phosphorus pentoxide then gave the desired ketone **10** in 71% yield. Conversion to the benzo[*c*]phenanthridine **12** was then accomplished by utilizing Cushman and Cheng's protocol of sodium borohydride reduction followed by dehydration-dehydrogenation by heating in acetic acid with palladium on carbon.[11] Compound **12** was thus obtained in 47% yield along with a small amount (15%) of the hydrogenolysis product **14**.

Synthesis of Oxynitidine

For the preparation of oxynitidine (**13**), the readily available amide **2**[12] was condensed with **3** and treated with

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(2) Syntex Postdoctoral Fellow, 1987-1988.

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