Chemical shifts are reported in ppm. Low-resolution electron-impact (EI) mass spectra were obtained with a Du Pont (CEC) 21-471 double-focusing mass spectrometer operating at 70 eV. Exact mass measurements were obtained on a Du Pont (CEC) 21-110 instrument. In cases where fragmentation precluded observation of a parent molecular ion using EI, chemical-ionization (CI) techniques were used instead. These spectra were recorded on a Finnigan-MAT TSQ-70 spectrometer at 70 eV with methane gas. High-pressure liquid chromatography was performed on a Waters 6000A instrument with two linked 2 ft × $^1/_4$ in. columns packed with LC Porasil (type A) silica gel. Combustion analyses (Atlantic Microlabs, Atlanta, GA) were obtained on samples that had been further purified by bulb-to-bulb distillation (Kugelrohr).

Skelly B was stirred over sulfuric acid for 24 h and over sodium carbonate for 12 h, filtered, and distilled. All other reagents and solvents were obtained from commercial sources and purified by standard methods.

General Procedure. A mixture of β-keto ester (5 mmol), allylic alcohol (5 mmol), and 4-(*N*,*N*-dimethylamino)pyridine (5 mmol) was dissolved in sufficient toluene (ca. 200 mL) to ensure wetting of the 25 g of oven-dried molecular sieves (4 Å) that was subsequently added to the vessel. The mixture was then heated at reflux until no starting material was detectable by ^{1}H NMR spectroscopy; this typically required 12–36 h. After being cooled to room temperature, the solution was washed with saturated ammonium chloride (2 × 25 mL) and dried ($\mathrm{MgSO_4}$). The toluene was removed by rotary evaporation, and the products were isolated by HPLC (1.5% EtOAc–98.5% Skelly B). Yields are reported in Table I. Spectral data are as follows.

2-Propenyl 3-oxobutanoate (1): ^{1}H NMR (300 MHz) δ 5.78 (m, 1 H), 5.14 (m, 2 H), 4.50 (d, 2 H), 3.35 (s, 2 H), 2.13 (s, 3 H); ^{13}C NMR (300 MHz) δ 199.8, 166.4, 131.4, 118.2, 65.4, 49.5, 29.6; IR 3050 (m), 2995 (m), 2930 (m), 1765 (s), 1740 (s), 1670 (s) cm^{-1}; LRMS (EI), *m/e* 85 (0.14), 84 (0.12), 58 (0.28), 57 (0.20), 43 (1.00), 41 (0.49), 39 (0.29); LRMS (CI), *m/e* 143 (M + 1, 0.44), 85 (1.00).

(*E*)-2-Butenyl 3-oxobutanoate (3): ^{1}H NMR (300 MHz) δ 5.65 (m, 2 H), 4.51 (d, 2 H), 3.40 (s, 2 H), 2.21 (s, 3 H), 1.67 (d, 3 H); ^{13}C NMR (300 MHz) δ 200.0, 167.0, 131.9, 124.6, 65.9, 50.0, 29.9, 17.5; IR 2980 (m), 2910 (m), 1760 (s), 1735 (s), 1670 (s) cm^{-1}; LRMS (EI), *m/e* 156 (M$^+$, 0.01), 85 (0.32), 71 (0.81), 69 (0.32), 58 (0.40), 57 (0.37), 55 (0.83), 54 (0.35), 43 (1.00), 42 (0.36), 41 (0.30), 39 (0.47); HRMS for $\mathrm{C_8H_{12}O_3}$ calcd 156.07864, found 156.07902.

3-Methyl-2-butenyl 3-oxobutanoate (4): ^{1}H NMR (300 MHz) δ 5.21 (t, 1 H), 4.49 (d, 2 H), 3.31 (s, 2 H), 2.11 (s, 3 H), 1.62 (s, 3 H), 1.58 (s, 3 H); ^{13}C NMR (300 MHz) δ 200.0, 166.8, 139.2, 118.0, 61.8, 49.7, 29.6, 25.3, 17.6; IR 2995 (m), 2940 (m), 1760 (s), 1740 (s), 1670 (s) cm^{-1}; LRMS (EI), *m/e* 170 (M$^+$, 0.03), 103 (0.51), 86 (0.47), 85 (1.00), 71 (0.48), 69 (0.92), 68 (0.68), 67 (0.60), 58 (0.43), 57 (0.30), 53 (0.52), 43 (0.84), 42 (0.71), 41 (0.70), 40 (0.33), 30 (0.52); HRMS for $\mathrm{C_9H_{14}O_3}$ calcd 170.09429, found 170.09487. Anal. Calcd: C, 63.51; H, 8.29. Found: C, 63.58; H, 8.30.

1-Methyl-2-propenyl 3-oxobutanoate (5): ^{1}H NMR (300 MHz) δ 5.78 (m, 1 H), 5.18 (m, 3 H), 3.38 (s, 2 H), 2.20 (s, 3 H), 1.28 (d, 3 H); ^{13}C NMR (300 MHz) δ 200.0, 166.2, 137.1, 116.2, 72.0, 50.2, 29.8, 19.7; IR 3060 (w), 2980 (m), 2940 (m), 1765 (s), 1740 (s), 1670 (m) cm^{-1}; LRMS (EI), *m/e* 85 (0.31), 71 (0.66), 58 (0.20), 57 (0.33), 55 (0.84), 43 (1.00), 39 (0.30); LRMS (CI), *m/e* 157 (M + 1, 0.03), 103 (1.00), 85 (0.85).

2-Propenyl 2-methyl-3-oxobutanoate (6): ^{1}H NMR (300 MHz) δ 5.82 (m, 1 H), 5.25 (m, 2 H), 4.52 (d, 2 H), 3.38 (q, 1 H), 2.21 (t, 3 H), 1.22 (d, 3 H); ^{13}C NMR (300 MHz) δ 202.7, 170.0, 131.5, 118.0, 65.3, 49.5, 29.4, 13.8; IR 3050 (m), 2985 (m), 2930 (m), 1755 (s), 1735 (s), 1670 (s) cm^{-1}; LRMS (EI), *m/e* 85 (0.85), 72 (0.35), 69 (0.89), 68 (0.55), 43 (1.00), 41 (0.62); LRMS (CI), *m/e* 157 (M + 1, 0.43), 99 (1.00).

(*E*)-2-Butenyl 2-methyl-3-oxobutanoate (7): ^{1}H NMR (360 MHz) δ 5.65 (m, 2 H), 4.50 (d, 2 H), 3.47 (q, 1 H), 2.19 (s, 3 H), 1.68 (d, 3 H), 1.29 (d, 3 H); ^{13}C NMR (300 MHz) δ 203.0, 170.1, 131.6, 124.5, 65.7, 53.4, 28.1, 17.4, 12.4; IR 2960 (m), 2920 (w), 1760 (s), 1730 (s), 1680 (m) cm^{-1}; LRMS (EI), *m/e* 170 (M$^+$, 0.04), 142 (0.37), 117 (0.34), 99 (0.59), 86 (0.64), 84 (0.71), 74 (0.66), 72 (0.84), 71 (0.50), 57 (0.51), 56 (0.81), 55 (1.00), 43 (0.90), 39 (0.52); HRMS for $\mathrm{C_9H_{14}O_3}$ calcd 170.09429, found 170.09504. Anal. Calcd: C, 63.51; H, 8.29. Found: C, 63.54; H, 8.25.

3-Methyl-2-butenyl 2-methyl-3-oxobutanoate (8): ^{1}H NMR (360 MHz) δ 5.21 (t, 1 H), 4.50 (d, 2 H), 3.39 (q, 1 H), 2.09 (s, 3 H), 1.64 (s, 3 H), 1.58 (s, 3 H), 1.19 (d, 3 H); ^{13}C NMR (360 MHz) δ 203.1, 170.3, 139.5, 118.0, 62.0, 53.5, 28.1, 25.5, 17.8, 12.5; IR 2995 (m), 2960 (m), 1760 (s), 1735 (s), 1670 (w) cm^{-1}; LRMS (EI), *m/e* 85 (0.36), 72 (0.21), 69 (0.65), 68 (0.28), 67 (0.20), 57 (0.13), 43 (1.00), 41 (0.66), 39 (0.17); LRMS (CI), *m/e* 185 (M + 1, 0.01), 99 (0.08), 69 (1.00). Anal. Calcd: C, 65.19; H, 8.75. Found: C, 65.31; H, 8.76.

1-Methyl-2-propenyl 2-methyl-3-oxobutanoate (9): ^{1}H NMR (300 MHz) δ 5.66 (m, 1 H), 5.03 (m, 3 H), 3.44 (q, 1 H), 2.00 (s, 3 H), 1.19 (d, 3 H), 1.11 (d, 3 H); ^{13}C NMR (300 MHz) δ 202.9, 169.5, 136.9, 115.8, 71.6, 53.4, 29.3, 19.3, 13.6; IR 3050 (w), 2990 (m), 2960 (m), 1760 (s), 1740 (s), 1670 (m) cm^{-1}; LRMS (EI), *m/e* 99 (0.21), 74 (0.27), 72 (0.37), 57 (0.36), 55 (0.88), 43 (1.00); LRMS (CI), *m/e* 171 (M + 1, 0.05), 117 (1.00), 99 (0.72).

Acknowledgment. We thank the Robert A. Welch Foundation for its financial support. Funds for the purchase of the Finnigan-MAT TSQ-70 mass spectrometer were kindly provided by the National Institutes of Health.

Registry No. **1**, 1118-84-9; (*E*)-**3**, 82259-92-5; **4**, 21597-32-0; **5**, 25456-01-3; **6**, 111903-66-3; (*E*)-**7**, 111903-67-4; **8**, 111903-68-5; **9**, 111903-69-6; 4-DMAP, 1122-58-3; $\mathrm{MeCOCH_2CO_2Et}$, 141-97-9; $\mathrm{MeCOCH(Me)CO_2Et}$, 609-14-3; $\mathrm{HOCH_2CH{=}CH_2}$, 107-18-6; $\mathrm{HOCH(Me)CH{=}CH_2}$, 598-32-3; (*E*)-$\mathrm{HOCH_2CH{=}CHMe}$, 504-61-0; $\mathrm{HOCH_2CH{=}CMe_2}$, 556-82-1; $\mathrm{MeCOCH_2CO_2Me}$, 105-45-3.

An Efficient Synthesis of (3*R*,4*R*)-3-(1(*R*)-Hydroxyethyl)-4-(benzoyloxy)-2-azetidinone from L-Threonine. Use of Phenylalkoxymethyl as a Novel N-Protecting Group

Samuel Chackalamannil,* Naomi Fett, Michael Kirkup,
Adriano Afonso, and Ashit K. Ganguly

*Schering Corporation, 60 Orange Street, Bloomfield,
New Jersey 07003*

Received August 12, 1987

The optically active azetidinone 1 is a valuable intermediate in the synthesis of penem[1] (15) and carbapenem[2] (14) antibiotics. While degradation of 6-aminopenicillanic acid[3] has been the traditional method of preparing 1, the

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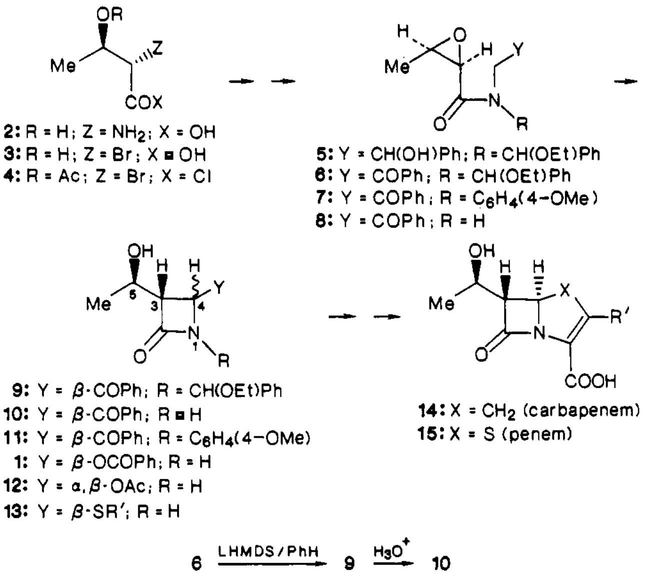
0022-3263/88/1953-0450$01.50/0

Scheme I

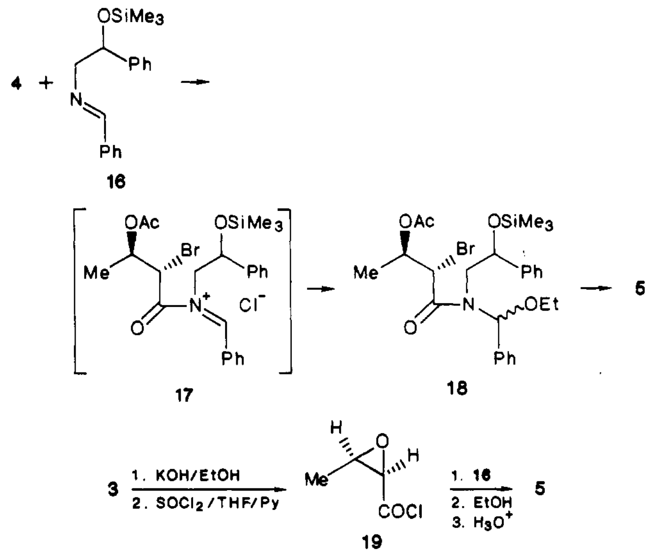


latest efforts have been directed toward the conversion of L-threonine (2) to 1.[4-7] The low cost of L-threonine and its potential for a stereospecific conversion to 1 in fewer steps render it particularly attractive.

The general strategy involved in the conversion of L-threonine to azetidinone 1 involves intramolecular cyclization of an N-protected epoxy amide[6,7] (e.g., 7 → 11). This reaction generates the stereogenic centers at C-3 and C-5 in 11 in the required absolute configuration (3*S*,5*R*). Since the C-4 nucleophilic substitution occurs in an anti manner with respect to the C-3 hydroxyethyl side chain (e.g., 12 → 13), the overall construct is stereospecific. This protocol has been used by the Sankyo group[5,6] in the synthesis of thienamycin intermediates and by Hanessian[7] in penem synthesis. The presence of a bulky N-protecting group, usually aryl, is mandatory for the efficient cyclization of 7 and, in the methodology presently available, its removal at a later stage constitutes a major disadvantage. The N-deprotection[8] of azetidinone 11, for example, requires stoichiometric amounts of ceric ammonium nitrate,[9] an expensive reagent. Alternative aryl or benzyl protecting groups offer little advantage in that their deprotection poses similar problems.

Prompted by our own interest in the penem antibiotics,[1a,d,h] we have been exploring routes for an efficient synthesis of 1 from L-threonine. The success of this plan depended a great deal on the utilization of an N-protecting group that could be readily introduced and subsequently removed under mild hydrolytic conditions. As an α-alkoxymethyl substituent would meet this condition, we chose to explore its applicability in detail. The present paper delineates the successful outcome of these efforts.

Scheme II



Direct introduction of an α-alkoxymethyl group by N-alkylation or N-hydroxymethylation of 8 followed by O-alkylation was unsuccessful. Preparation of *N*-alkoxy amides by trapping acyliminium intermediates with alcohols have been reported.[10] This methodology was applied in the present case to generate the (phenylethoxymethyl)-substituted amide 5 as described below.

Acid chloride[5] 4 was generated from acid 3, readily available from L-threonine, by sequential O-acetylation and oxalyl chloride treatment (91%). A solution of 4 in dichloromethane was added to a solution of the imine 16 at 0 °C (Scheme II). Cooling was discontinued, and after 25 min, excess triethylamine was added, followed by anhydrous ethanol, to give 18 as a mixture of diastereomers. Treatment of a solution of 18 in methanol with potassium carbonate yielded the epoxy alcohol 5, which, without purification, was oxidized with pyridinium chlorochromate (PCC) to yield the cyclization precursor 6 in an overall yield of 69%. Alternatively, 6 could be generated from the acid chloride 19 in a similar manner, albeit in a lower yield (Scheme II). Cyclization of 6 was carried out in benzene[11] at 8–12 °C with lithium hexamethyldisilazide (LHMDS) in 71% yield[12] (Scheme I). As in the reported case,[7] only the trans disubstituted azetidinone 9 (as a mixture of two diastereomers due to the presence of the phenylalkoxymethyl group) could be detected. Deprotection of 9 was achieved in THF by treatment with 1 N H_2SO_4 to give 10 (74%): mp 134–135 °C; $[\alpha]_D$ − 77.5° ($CHCl_3$, *c* 0.52). Baeyer–Villiger oxidation of 10 led to the previously reported azetidinone[7] 1: mp 145–147 °C; $[\alpha]_D$ +96.8° (*c* 0.58, MeOH) [reported, mp 146–147 °C; $[\alpha]_D$ +97.2°, MeOH].

In summary, the above synthesis constitutes an efficient stereospecific conversion of L-threonine to azetidinone 1 by employing phenylalkoxymethyl as an N-protecting group. The versatility of this process is underscored by the facile generation of the phenylalkoxymethyl epoxy amide 5 by acyliminium ion trapping and the mild hydrolytic deprotection of the azetidinone 9.

Experimental Section

General Procedures. NMR spectra were recorded on a Varian XL-200 or XL-400 spectrometer with TMS as internal standard.

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[11] Use of polar solvents gave considerable amounts of side products.

[12] Yields are not optimized.

IR spectra were recorded on a Perkin-Elmer 727B spectrophotometer. Optical rotations were measured on a JASCO DIP-140 digital polarimeter. Melting points were measured on a Reichert hot stage melting point apparatus. Fast atom bombardment (FAB) mass spectra were obtained on a Finnigan MAT 312 double-focusing mass spectrometer in glycerol-thioglycerol matrix with xenon atom bombardment. High-resolution mass spectra were obtained under similar conditions by peak matching against albuterol.

Preparation of (2*S*,3*R*)-2-Bromo-3-acetoxybutyroyl Chloride (4). Acetyl chloride (6.8 g, 86.9 mmol) was added dropwise to the acid **3** (neat, 15.2 g, 83.1 mmol) with stirring. The reaction mixture was cooled in a bath at 5 °C as exotherm began. After completion of addition, the cooling bath was removed. After 45 min, the mixture was heated at 45–50 °C for 1.5 h. Heating was discontinued, and 10 mL of toluene was added. The mixture was cooled in an ice bath, and oxalyl chloride (11.5 g, 90.4 mmol) was added dropwise. After completion of addition, the mixture was allowed to warm to room temperature, followed by heating at reflux for 30 min. Toluene and excess of reagents were removed by fractonal distillation. The residue was subjected to bulb-to-bulb distillation at 80–90 °C under high vacuum (1 mmHg) to yield 18.4 g (91%) of acid chloride **4**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.44 (d, J = 6.0 Hz, 3 H), 2.11 (s, 3 H), 4.67 (d, J = 6.0 Hz, 1 H), 5.41 (m, 1 H); IR (neat) 1810, 1790, 1740 cm^{-1}.

(2*R*,3*R*)-*N*-[Phenylethoxymethyl]-*N*-(2-oxo-2-phenylethyl)-2,3-epoxybutyramide (6). Generation of 2-Phenyl-2-(trimethylsiloxy)ethylamine. To a solution of 2-amino-1-phenylethanol (Aldrich) (5.1 g, 37.2 mmol) in 25 mL of dichloromethane was added bis(trimethylsilyl)acetamide (6.1 g, 31.1 mmol). The reaction mixture was stirred at room temperature for 3 h. The mixture was diluted with dichloromethane (150 mL) and washed with water (2 × 100 mL). The organic phase was dried over magnesium sulfate and concentrated in vacuo. The crude product thus obtained was directly used for the next step.

Generation of [1-Phenyl-1-(trimethylsiloxy)ethyl]-2-benzaldimine (16). The crude product from above was mixed with benzaldehyde (4.4 g, 42 mmol). The reaction mixture was stirred for 2 min, and benzene (50 mL) was added. The water liberated was removed by addition of anhydrous magnesium sulfate. The mixture was filtered, and the residue was washed with benzene (2 × 10 mL). The solvent was removed under reduced pressure. The product was subjected to high vacuum for 2 h and used immediately for the next step.

Generation of 18. To a stirred solution of the above benzaldimine in 25 mL of dichloromthane, kept cooled in an ice bath, was added a solution of the acid chloride **4** (9.0 g, 37.1 mmol) in 25 mL of dichloromethane. After completion of addition, cooling was discontinued. The reaction mixture was stirred for 25 min, and triethylamine (5.4 g, 53.6 mmol) was added, followed, after 2 min, by anhydrous ethanol (6.9 g, 150.2 mmol). The reaction mixture was stirred at room temperature for 1.5 h. To this was added dichloromethane (25 mL) and water (50 mL). Layers were separated, and the aqueous phase was extracted with dichloromethane (3 × 30 mL). Combined organic phases were washed with water (150 mL), dried over magnesium sulfate, and concentrated in vacuo to give 17.8 g (87%) of crude **18**.

To a solution of 8.9 g (16.2 mmol) of the above crude product in 55 mL of methanol was added anhydrous potassium carbonate (2.2 g, 16.1 mmol). The reaction mixture was stirred at room temperature for 18 h. The suspensions were filtered, and the filtrate was concentrated in vacuo. The residue was dissolved in dichloromethane and washed with water (100 mL). The aqueous phase was extracted with dichloromethane (75 mL). Combined organic phases were washed with water (100 mL), dried over magnesium sulfate, and concentrated under reduced pressure to give the crude alcohol **5**.

To a solution of the above product in dichloromethane (25 mL) was added a powdered mixture of pyridinium chlorochromate (13.8 g, 64 mmol) and anhydrous sodium acetate (3 g, 37.6 mmol). The suspension was stirred at room temperature for 1.5 h. The reaction mixture was diluted with dichloromethane (50 mL) and filtered, and the filtrate was concentrated in vacuo. The residue was subjected to chromatography on silica gel with 35% ethyl acetate in hexanes as eluent to give 4.5 g (79% based on crude **18**) of epoxy amido ketone **6**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J = 7.0 Hz, 1 H), 1.2 (t, J = 7.0 Hz, 1.3 H), 1.28 (t, J = 7.0 Hz, 0.7 H), 1.38 (d, J = 6.0 Hz, 1.7 H), 1.55 (d, J = 6.0 Hz, 1.3 H), 4.17–5.92 (m, 6 H), 6.50 (s, 0.2 H), 6.58 (s, 0.2 H), 6.94 (s, 0.3 H), 7.0 (s, 0.3 H), 7.20–7.56 (m, 7 H), 7.71–7.83 (m, 3 H); IR (neat) 1665, 1700 cm^{-1}; MS (FAB), *m/e* 352 $(M - 1)^+$.

(3*S*,4*S*)-1-[Phenylethoxymethyl]-3-(1(*R*)-hydroxyethyl)-4-benzoyl-2-azetidinone (9). To a solution of epoxy ketone **6** (1.25 g, 3.5 mmol) in 10 mL of dry benzene, cooled in a bath at 8 °C, was added a solution of lithium hexamethyldisilazide in hexanes (Aldrich) (5.3 mL, 5.3 mmol). The reaction mixture was stirred at 8–12 °C for 1.5 h, and 8 mL of 20% aqueous solution of citric acid was added, followed by 20 mL of ethyl acetate. Layers were separated, and the aqueous phase was extracted with ethyl acetate (15 mL). The organic phases were combined, dried over magnesium sulfate, and concentrated under reduced pressure. The residue was subjected to chromatography on silica gel with 30% ethyl acetate in hexanes to give 890 mg (71%) of azetidinone **9**.

Polar diastereomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.32 (d, J = 7.0 Hz, 3 H), 1.42 (t, J = 6.0 Hz, 3 H), 3.34–3.46 (m, 1 H), 3.65–3.82 (m, 1 H), 3.94–4.10 (m, 1 H), 4.28–4.50 (m, 1 H), 5.30 (d, J = 2.5 Hz, 1 H), 6.14 (s, 1 H), 7.10–7.28 (m, 3 H), 7.30–7.68 (m, 4 H), 7.72–7.84 (m, 3 H); IR (CH_2Cl_2) 1685, 1760 cm^{-1}; MS (FAB), *m/e* 352 $(M - 1)^+$.

Less polar diastereomer: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.16 (d, J = 7.0 Hz, 3 H), 1.18 (t, J = 6.0 Hz, 3 H), 3.33–3.46 (m, 1 H), 3.53–3.70 (m, 1 H), 3.88–4.03 (m, 1 H), 4.13–4.28 (m, 1 H), 4.80 (d, J = 2.0 Hz, 1 H), 6.03 (s, 1 H), 7.26–7.48 (m, 7 H), 7.48–7.86 (m, 3 H); IR (CH_2Cl_2) 3550–3650, 3200–3650, 1760, 1685 cm^{-1}; MS (FAB), *m/e* 352 $(M - 1)^+$.

(3*S*,4*S*)-3-(1(*R*)-Hydroxyethyl)-4-benzoyl-2-azetidinone (10). To a solution of azetidinone **9** (890 mg, 2.5 mmol) in 2 mL of tetrahydrofuran was added 1 mL of 1 N H_2SO_4. The reaction mixture was stirred at room temperature for 24 h. To this was added 10 mL of ethyl acetate and 10 mL of water. Solid sodium bicarbonate was added until the aqueous phase was neutral. Layers were separated, and the aqueous phase was extracted with ethyl acetate (10 mL). Combined organic phases were dried over magnesium sulfate and concentrated in vacuo. The residue was subjected to chromatography over silica gel with 60% ethyl acetate in hexanes to yield 408 mg (74%) of azetidinone **10**, which was crystallized from dichloromethane–ether: mp 134–135 °C; $[\alpha]_D$ −77.5° ($CHCl_3$, c 0.52); ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.37 (d, J = 6.3 Hz, 3 H), 2.15 (br s, 1 H), 3.25 (m, 1 H), 4.30–4.50 (m, 1 H), 5.07 (d, J = 2.4 Hz, 1 H), 6.38 (br s, 1 H), 7.46–7.70 (m, 3 H), 8.10–8.20 (m, 2 H); IR (CH_2Cl_2) 3550–3650, 3425, 1770, 1695 cm^{-1}; MS (FAB), *m/e* 220 $(M + 1)^+$; calcd for $C_{12}H_{14}NO_3$ (M + H) 220.0993, found 220.0974.

Acknowledgment. We thank Dr. B. Pramanik for providing mass spectral data.

Synthesis of *cis*-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene

Romesh C. Bansal, Clinton E. Browne, and
Edmund J. Eisenbraun*

*Department of Chemistry, Oklahoma State University,
Stillwater, Oklahoma 74078*

Jane S. Thomson

*National Institute for Petroleum and Energy Research,
Bartlesville, Oklahoma 74005*

Received May 4, 1987

cis-1,2,3,4,4a,9,10,10a-Octahydrophenanthrene (**3a**) was first synthesized in 1933 via the well-known Bogert[1a]–Cook[1b] acid-catalyzed cyclization of 1-phenethylcyclohexanol (**1**), shown in Scheme I. Hydrocarbon **3a** is of

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[1] (a) Bogert, M. T. *Science* (*Washington, D.C.*) **1933**, *77*, 289. (b) Cook, J. W.; Hewett, C. L.; Robinson, A. M. *J. Chem. Soc.* **1939**, 168. (c) Roberts, R. M.; Khalaf, A. A. *Friedel*–Crafts *Alkylation Chemistry*, Marcel Dekker: New York, 1984; pp 645–648.