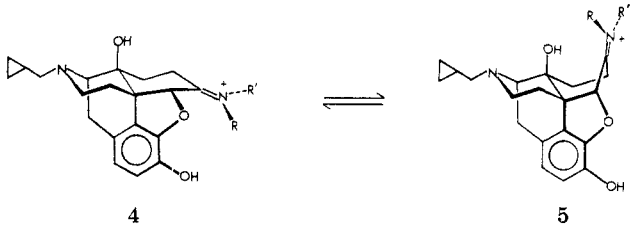
dominantly via β attack on a preferred chair conformation **4b**.



4 5

a: R = R' = $CH_2C_6H_5$
b: R = R' = H
c: R,R' = OB< and B<

In view of these results, we investigated a more direct synthetic procedure using pseudoallylic strain as the stereochemical determinant in the borane reduction of oxime **3** to the 6β isomer **1b**. We expected epimer **1b** to predominate in this reaction because, as a Lewis acid, the boron atom of borane should coordinate with the oxime nitrogen lone pair, thereby forming an intermediate (**5c**) analogous to a disubstituted iminium species (e.g., **5a**). Consistent with this expectation, we found that the epimeric products (**1a**:**1b**) of the reduction were in a ratio of about 1:9.

We conclude from these results that the steric course of reductive amination is determined by the substitution on the imine nitrogen when it is vicinal to a substutuent in a six-membered ring. Moreover, the facility with which an oxime can be prepared from a ketone gives this procedure a decided advantage over the generation of the more difficultly accessible iminium intermediate.

Experimental Section

General Procedure. Melting points were determined with a Thomas Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by MHW Laboratories, Phoenix, AZ. IR spectra were obtained on a Perkin-Elmer 281 infrared spectrometer. NMR spectra were taken at ambient temperature with Me_4Si as internal standard on a Nicolet 300-MHz spectrometer. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. Mass spectra were obtained on an AEI MS-30 instrument. All TLC data were determined with Analtech silica gel chromatographic plates (EtOAc–MeOH–NH_4OH, 5:1:0.2). All reagents were reagent grade and were used without subsequent purification.

Naltrexone Oxime (3). A solution prepared from naltrexone[8] (6.8 g, 20 mmol), 2 g of NH_2OH·HCl (29 mmol), sodium acetate (4 g) dissolved in water (5 mL), and ethanol (100 mL) was refluxed for 3 h. The ethanol was removed in vacuo, rendered sufficiently acidic with HCl to dissolve all solid material, and made alkaline with aqueous sodium carbonate. The precipitate that formed was collected by filtration and washed with water, the mother liquor and washings were extracted with chloroform (3 × 100 mL), and the solvent was removed in vacuo. The combined crops (6.6 g, 93%) were crystallized from aqueous ethanol. Oxime **3**: mp 239–240 °C (lit.[5] mp 235–236 °C).

Borane Reduction of Naltrexone Oxime (3). A borane–tetrahydrofuran (THF) solution (400 mL, 1 M) was cooled to −5 °C and added with stirring to **3** under N_2. The mixture was heated under reflux for 48 h and cooled (25 °C), and the excess borane was destroyed by cautious addition of water (10 mL). The borane complex was hydrolyzed by gradual addition of aqueous KOH (10%, 150 mL) and heating under reflux for 3 h. The resultant mixture was rendered acidic (pH 2–3) with HCl and heated under reflux for an additional 2 h. The THF was removed in vacuo, and the aqueous solution was rendered alkaline (Na_2CO_3). After extraction with chloroform (3 × 200 mL) and drying (Na_2SO_4), the solvent was removed in vacuo to afford the crude product (3 g, 88%). Medium-pressure chromatography (175 g of silica gel 200–245 mesh, 25:5:1 MeCN–MeOH–NH_4OH) gave four fractions. The first (280 mg, 10%) displayed no aromatic proton or C_5-H absorptions in its NMR spectrum. The second fraction appeared to be boron-complexed oxime **3** (570 mg, 20%). The more polar fractions were identified as follows. **1b**: 1.75 g (58%); mp 229–230 °C; R_f 0.23; [α] 25D −156° (*c* 1, MeOH); NMR δ 4.50 (1 H, d, J = 7.5 Hz C_5-H). **1a**: 0.200 g (7%); mp 179–180 °C; R_f 0.18; [α] 25D −184° (*c* 0.5, MeOH); NMR δ 4.72 (1 H, d, J = 3.7 Hz, C_5-H). The identity of **1b** was confirmed by conversion of authentic **1b**·2HCl[1,2] to the free base, mp 231–233 °C, with an identical R_f and NMR spectrum.

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[1,2] Anionic Rearrangements of Substituted *N*-Hydroxy-2-azetidinones and Applications to the Synthesis of Bicyclic β-Lactams

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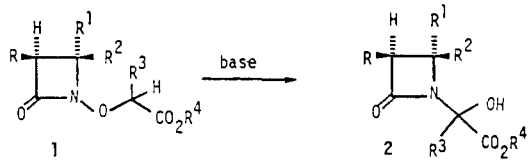
The Wittig ($R_2C^-OR^1\ M^+ \rightarrow R_2R^1CO^-M^+$) and related rearrangements have been thoroughly studied and frequently utilized synthetically.[1] However, only recently have analogous [1,2] anionic $NOC^- \rightarrow NCO^-$ rearrangements been reported.[2,3] Herein we describe a [1,2] anionic rearrangement of substituted *N*-hydroxy-2-azetidinones (eq 1) and demonstrate its utility for the synthesis of novel bicyclic β-lactams.



(1)

The first requirement was the synthesis of appropriate *N*-hydroxy β-lactam precursors. As usual, synthesis of β-lactams by our hydroxamate approach required preparation of the appropriate β-hydroxy acid precursor. Thus, treatment of the dianion of methyl acetoacetate[4] (**3**) with benzyl chloromethyl ether (**4**) gave the β-keto ester **5** in 60% yield (Scheme I). Reduction of **5** to the racemic[5] alcohol **6** with $NaBH_4$ (0 °C, CH_3OH, 30 min) proceeded in 90% yield. Saponification (1 N NaOH, THF/H_2O, room temperature, 1 h), of **6** provided the desired β-hydroxy acid **7** in 92% yield. Coupling of **7** and *O*-benzylhydroxylamine by the usual procedure[6] gave the hydroxamate **8** in 64% yield. Cyclization of **8** with diethyl azodicarboxylate/triphenylphosphine (DEAD/TPP)[6,7] provided the *N*-benzyloxy-substituted β-lactam **9** in 75–85% yields. Selective hydrogenation of **9** with a poisoned catalyst (5% Pd–C, 1 atm of H_2, 1 h, in ethanol containing quinoline) gave the desired *N*-hydroxy β-lactam **10** in 93% yield. Hydrogenation of **9** in the absence of quinoline resulted in formation of **11** by removal of both benzyl protecting groups. The structures of these β-lactams were

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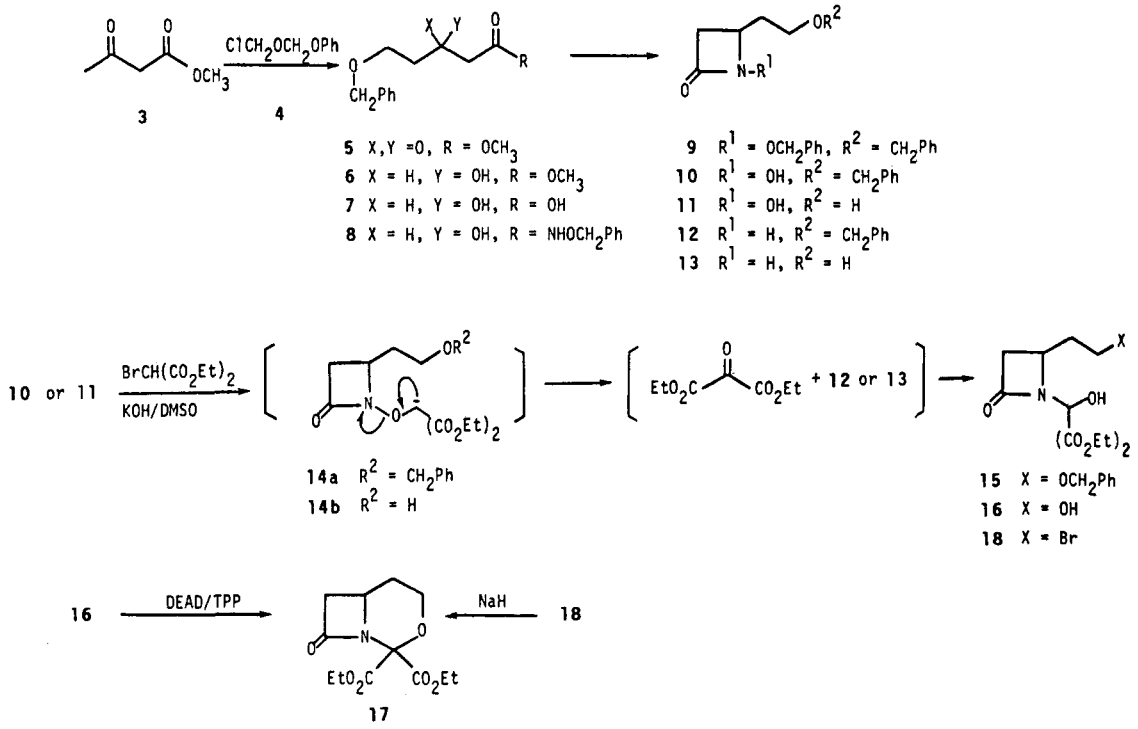
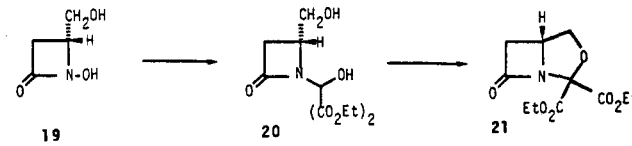
Scheme I



reconfirmed by treatment of **10** with $TiCl_3$[8] to give the N-unsubstituted β-lactam **12** that, upon catalytic hydrogenation, provided the known β-lactam **13**.[9]

Our previous synthesis of the oxamazins (**1**, R^3 = H) utilized an alkylation of *N*-hydroxy β-lactams with α-halo acetates as the key step.[10] However, the relative stability of the oxamazins suggested that, for the present study, R^3 of **1** should be changed to promote the ionization required to initiate the rearrangement of **1** to **2**. Thus, we anticipated that alkylation of **10** or **11** with bromomalonates should provide our desired substrates **14a** or **14b**. Several combinations of solvent and base (NaH, DBU, DBN, K_2CO_3, etc.) were used in attempts to effect the alkylations. All failed, and starting β-lactam was recovered. Surprisingly, however, separate reaction of **10** and **11** with diethyl bromomalonate and either KOH or K_2CO_3 in Me_2SO at room temperature for 5 h provided the [1,2] anionic rearrangement products, carbinolamines **15** and **16**, directly in 35–55% yields! The carbinolamine hydrolysis products **12** and **13** were also obtained in 25–35% yields, indicating

Scheme II



that the [1,2] anionic rearrangement had been more complete than indicated by the isolated yields of **15** and **16**. The structure of the carbinolamine **15** was verified by its independent preparation in 35% yield from **12** and diethyl ketomalonate.[9]

The utility of carbinolamines like **15** for the synthesis of several classical antibiotics and carbapenems has been clearly demonstrated.[11] However, we also noted the potential for carbinolamines **16** and **20** to serve as direct precursors of 3-oxacephams and isooxapenams, which have been of considerable recent interest themselves,[12] and as versatile precursors of carbapenems.[13] Thus, the direct treatment of diol **16** under the Mitsunobu conditions[7] (DEAD/TPP) provided the disubstituted 3-oxacepham **17** directly in 65% yield. Alternatively, **16** was first converted to the bromide **18** (CBr_4/TPP). Subsequent treatment with NaH (DMF/CH_2Cl_2, 2:1) provided the same oxacepham **17** in 56% overall yield from **16**.

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The same sequence was used for the synthesis of the isooxapenam **21** (Scheme II). Treatment of **19**[6b] with diethyl bromomalonate (KOH/Me_2SO, room temperature, 5 h) provided carbinolamine **20** in 55% yield. Direct cyclization of **20** with DIAD (diisopropyl azodicarboxylate)/TPP (110 mol %, THF, room temperature, 1 h) followed by chromatographic purification gave the 3,3-disubstituted isoxapenam **21**[14] in 80% yield. Further studies on the synthetic utility of the [1,2] anionic rearrangements of substituted *N*-hydroxy β-lactams and related substrates are in progress.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer 727b spectrometer. NMR spectra were obtained in chloroform-*d* with tetramethylsilane as a reference on Varian EM-390 and Nicolet NB-300 300-MHz instruments. Mass spectra were recorded on an AEI Scientific Apparatus 902 except for FD spectra, which were obtained by Dr. John Occolowitz at Eli Lilly and Co. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN, and M-H-W Laboratories, Phoenix, AZ. Liquid chromatography was performed using a Harrison Research Chromatotron, Model 7924, with 1-, 2 or 4-mm plates.

3-Hydroxy-5-(benzyloxy)pentanoic Acid (7). In a 250-mL flask, fitted with a septum and flushed with N_2, NaH (4.22 g, 84 mmol of a 54% oil dispersion) was washed with three portions of hexane and THF (130 mL) was then added. To this solution was added methyl acetoacetate (**3**; 8.62 mL, 80 mmol) dropwise by a cannula at 0 °C from a separate cooled flask. After the addition was complete, the mixture was stirred 10 min more at 0 °C and *n*-BuLi (44 mL, 2 M, 88 mmol) was added dropwise with a cannula from another precooled flask at 0 °C. After 10 min, benzyl chloromethyl ether (**4**; 11.2 mL, 80 mmol, neat) was added dropwise. After the addition was complete, the mixture was warmed to room temperature and stirred for 40 min more. The reaction was quenched with 6 N HCl to give an apparent pH of 5 for the reaction mixture. The mixture was extracted with ethyl acetate, and the organic layer was dried (Na_2SO_4) and evaporated to provide crude **5** as an oil: ^1H NMR ($CDCl_3$) δ 2.79 (t, 2 H), 3.47 (s, 2 H), 3.70 (t, 2 H), 3.73 (s, 3 H), 4.48 (s, 2 H), 7.34 (s, 5 H); IR (neat) 1720 , 1745 cm^{-1}. Crude **5** was dissolved in MeOH (100 mL) and treated with $NaBH_4$ (2.5 g, 80 mmol) at 0 °C. The reaction mixture was allowed to stir at 0 °C for 30 min then quenched with 100 mol % of 1 N HCl and extracted with ethyl acetate. The organic layer was washed with brine and dried (Na_2SO_4). After the solvent was evaporated, the crude methyl ester was obtained as an oil: ^1H NMR ($CDCl_3$) δ 1.77 (q, 2 H), 2.44 (d, 2 H), 3.43 (br, 1 H, OH), 3.61 (t, 2 H), 3.66 (s, 3 H), 4.0–4.31 (m, 1 H), 4.47 (s, 2 H), 7.34 (s, 5 H); IR (neat) 1740 cm^{-1}; mass spectrum (EI), *m/e* 238 (M^+).

The crude ester **6** (60 mmol) was dissolved in THF (60 mL) and treated with 1 N NaOH (60 mL, 60 mmol). The mixture was allowed to stir at room temperature for 1 h. After the reaction was completed, more 1 N NaOH (100 mL) was added and the aqueous layer was washed with ether (3 × 150 mL). The aqueous layer was then acidified to pH 2.5 with 6 N HCl. The mixture was reextracted with ether (3 × 150 mL). The organic layer was dried (Na_2SO_4) and evaporated to provide **7** as an oil in 35–50% overall yield from **3**: ^1H NMR ($CDCl_3$) δ 1.75 (q, 2 H), 2.50 (d, 2 H), 3.60 (t, 2 H), 4.0–4.3 (m, 1 H), 4.48 (s, 2 H), 7.35 (s, 5 H), 6.9 (br, CO_2H/OH); mass spectrum (EI), *m/e* 224 (M^+).

***O*-Benzyl 3-Hydroxy-5-(benzyloxy)pentanohydroxamate (8).** Acid **7** (2.24 g, 10 mmol) and *O*-benzylhydroxylamine (free amine; 1.5 g, 15 mmol) were dissolved in THF/H_2O (5:2, 70 mL) and treated with 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (WSC; 3 g, 15.7 mmol; Sigma) while maintaining the solution at pH 4.5. The mixture was allowed to stir at room temperature for 1 h. After the mixture was taken up in ethyl acetate (100 mL), it was washed with 0.5 M citric acid, dried (Na_2SO_4), and evaporated. The residue was chromatographed on a silica plate (Chromatotron, 4 mm), eluting with ethyl acetate/hexane (1:2). Compound **8** was isolated as an oil (64% yield) and then crystallized from ethyl acetate/hexane: mp 77–79 °C; ^1H NMR ($CDCl_3$) δ 1.7 (q, 2 H), 2.2 (br, 2 H), 3.57 (t, 2 H), 3.9–4.25 (m, 1 H), 4.43 (s, 2 H), 4.80 (s, 2 H), 7.33 (s, 5 H), 7.37 (s, 5 H), 9.5 (br s, 1 H, NH). Anal. Calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.23. Found: C, 69.04; H, 7.02; 4.44.

4-[2-(Benzyloxy)ethyl]-*N*-(benzyloxy)-2-azetidinone (9). Hydroxamate **8** (1.57 g, 5.57 mmol) and Ph_3P (1.6 g, 6.11 mmol) were dissolved in THF (50 mL), and diethylazodicarboxylate (DEAD, 0.923 mL, 5.6 mmol) in THF (10 mL) was added over 20 min. After the addition was complete, the mixture was allowed to stir at room temperature for 16 h. Volatile components were evaporated, and the residue was chromatographed on a silica plate (Chromatotron, 4 mm), eluting with ethyl acetate/hexane (1:2). The desired **9** was isolated as a colorless oil (75–85% yield from several trials): ^1H NMR ($CDCl_3$) δ 1.6–2.2 (m, 2 H), 2.2–2.8 (m, 2 H), 3.48 (t, 2 H), 3.5–3.8 (m, 1 H), 4.47 (s, 2 H), 4.97 (s, 2 H), 7.37 (s, 5 H), 7.43 (s, 5 H); IR (neat) 1775 cm^{-1}; mass spectrum (FD), 311 (M^+), 312 ($M^+ + 1$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found C, 72.73, H, 6.87, N, 4.70.

4-[2-(Benzyloxy)ethyl]-*N*-hydroxy-2-azetidinone (10). β-Lactam **9** (297 mg, 1 mmol) was dissolved in ethanol containing quinoline (35 μL) and treated with Pd on carbon (5%, 200 mg) under 1 atm of H_2 for 1 h at room temperature. After the mixture was filtered and evaporated, it was taken up in ethyl acetate (100 mL). The solution was washed with in 1 N HCl and brine. After drying ($MgSO_4$) and evaporating, compound **10** was isolated as an oil: 93% yield; ^1H NMR ($CDCl_3$) δ 1.7–2.2 (m, 2 H), 2.3–2.9 (m, 2 H), 3.53 (t, 2 H), 3.7–4.0 (m, 1 H), 4.52 (s, 2 H), 7.38 (s, 5 H); IR (neat) 1770 cm^{-1}.

4-(2-Hydroxyethyl)-*N*-hydroxy-2-azetidninone (11). Pure β-lactam **9** (297 mg, 1 mmol) was dissolved in methanol and treated with Pd on carbon (5%, 100 mg) under 1 atm of H_2 for 2 h at room temperature. After the mixture was filtered and evaporated, compound **11** was isolated as an oil: 90% yield; ^1H NMR (acetone-d_6) δ 1.7–2.1 (m, 2 H), 2.2–2.9 (m, 2 H), 3.0 (br, 2 OH), 3.75 (t, 2 H), 3.8–4.0 (m, 1 H); IR (neat) 1750–1770 cm^{-1}.

4-[2-(Benzyloxy)ethyl]-2-azetidinone (12). This compound was prepared by the usual $TiCl_3$ reduction procedure[6] from *N*-hydroxy β-lactam **11**. The N-unsubstituted β-lactam **12** was isolated as a colorless oil in 70–80% yield: ^1H NMR ($CDCl_3$) δ 1.87 (q, 2 H), 2.63 (ddd, 1 H), 3.07 (ddd, 1 H), 3.53 (t, 2 H), 3.67–3.85 (m, 1 H), 4.47 (s, 2 H), 6.53 (br, s, 1 H, NH) 7.33 (s, 5 H); IR (neat) 1760 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_2$: C, 69.54; H, 8.27: N, 6.76. Found: C, 69.29; H, 7.99; N, 6.92.

Compound **12** was also isolated as a hydrolysis product (25–35%) from the alkylation reaction of **11** with diethyl bromomalonate. In addition, treatment of **15** with 1 equiv of NaH provided **12** in 70% yield [DMF/CH_2Cl_2 (1:2), room temperature, 5 h].

4-(2-Hydroxyethyl)-2-azetidinone (13). The benzyl ether **12** (207 mg, 1 mmol) was dissolved in CH_3OH (50 mL) and treated with Pd on carbon (10%, 100 mg) under 1 atm of H_2 for 2 h at room temperature. After the mixture was filtered and evaporated, the residue was chromatographed on a silica plate (2 mm, Chromatotron), eluting with $CHCl_3$/MeOH (9:1). The desired compound **13** was isolated as an oil (72%). It slowly solidified; mp 48–50 °C (lit.[9] mp 50 °C). NMR and IR were identical with those reported.[9]

Alkylation Reaction of *N*-Hydroxy β-Lactams 10, 11, and 19 with Diethyl Bromomalonate. The *N*-hydroxy β-lactam as an approximate 0.1 M solution in Me_2SO (from the bottle, not predried) was treated with KOH (1 equiv) and diethyl bromomalonate (1 equiv). The mixture was allowed to stir for 5 h at room temperature and then taken up in ethyl acetate. The solution was washed twice with H_2O and brine. After the solvent was dried and evaporated, the residue was chromatographed on a silica plate.

Compound **15** was isolated as a colorless oil in 35–45% yield by chromatography, eluting with ethyl acetate/hexane (1:2): ^1H NMR (90 MHz, $CDCl_3$) δ 1.30 (t, 6 H), 1.8–2.5 (m, 2 H), 2.73 (dd, 1 H, J_{gem} = 15 Hz, J_{trans} = 3 Hz) 3.13 (dd, 1 H, J_{gem} = 15 Hz, J_{cis} = 6 Hz), 3.57 (t, 2 H), 4.2–4.45 (m, 5 H), 4.50 (s, 2 H), 5.17 (s, 1

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H, OH), 7.33 (s, 5 H); IR (neat) 1750, 1770 cm^{-1}; mass spectrum (FD), m/e 379 (M^+), 380 (M + 1), 306 (M - CO_2Et).

When compound **11** was alkylated with diethyl bromomalonate by the general procedure, **16** was isolated as a colorless oil in 40% yield by chromatography, eluting with ethyl acetate/hexane (2:1): ^1H NMR ($CDCl_3$, 90 MHz) δ 1.28 (dt, 6 h), 1.9–2.2 (m, 2 H), 2.73 (dd, 1 H, J_{gem} = 15 Hz, J_{trans} = 3 Hz), 3.15 (dd, 1 H, J_{gem} = 15 Hz, J_{cis} = 6 Hz), 3.73 (t, 2 H), 4.1–4.5 (m, 5 H), 5.8 (br s, 1 OH); IR (neat) 1750, 1770 cm^{-1}.

When compound **19** was alkylated with diethyl bromomalonate by the general procedure, carbinolamine **20** was isolated in 55% yield by chromatography, eluting with ethyl acetate/hexane (4:1). The product was crystallized from ethyl acetate/hexane: mp 102–104 °C; ^1H NMR ($CDCl_3$, 90 MHz), δ 1.3 (dt, 6 H), 2.9 (m, 3 H), 3.5–4.0 (m, 3 H), 4.7 (m, 4 H), 5.6 (br s, 1 H, OH); IR ($CHCl_3$) 3500, 1780 cm^{-1}; mass spectrum (FD) m/e 276 (M + 1), 202 (M - CO_2Et). Anal. Calcd for $C_{11}H_{17}NO_7$: C, 47.99; H, 6.22; N, 5.09. Found: C, 47.62; H, 6.42; N, 5.14.

Condensation Reaction of Diethyl Ketomalonate with *N*-Unsubstituted β-Lactams 12 and 13. Compound **12** or **13** was dissolved in toluene (~0.1 M) and treated with diethyl ketomalonate (1.1 equiv). The solution was refluxed for 2 h with azeotropic distillation. After the solvent was evaporated, the residue was chromatographed on a silica plate. When compound **12** was condensed with diethyl ketomalonate, compound **15** was isolated in 35% yield by chromatography, eluting with ethyl acetate/hexane (2:1). Some of the starting material **12** was also recovered (30–40%).

When compound **13** was condensed with diethyl ketomalonate, carbinolamine **16** was isolated in 35% yield by chromatography.

Compounds 15 and **16**, prepared in this manner, had spectral and TLC properties identical with those of the compounds prepared by the reactions of **10** and **11** with diethyl bromomalonate.

Cyclization of the Adducts 16 and 20 by the Mitsunobu Reaction. The adduct **16** or **20**, as an approximate 0.1 M solution in dry THF, was treated with PPh_3 (1.3 equiv). To this solution was added DEAD or diisopropylazodicarboxylate (DIAD, 1.1 equiv in a small amount of dry THF) dropwise over 10 min with stirring at room temperture. The mixture was allowed to stir for 1 h at room temperature and then concentrated.

When carbinolamine **16** was cyclized by this procedure, 3-oxacepham (**17**) was isolated in 65% yield by chromatography, eluting with ethyl acetate/hexane (3:2). The product was crystallized from ethyl acetate/hexane: mp 53–54 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.30 (dt, 6 H), 1.77–2.05 (7, 2 H), 2.66 (dd, 1 H, J_{gem} = 15.3 Hz, J_{trans} = 1.8 Hz), 3.33 (dd, 1 H, J_{gem} = 15.3 Hz, J_{cis} = 3.9 Hz), 3.62 (m, 1 H), 3.93 (m, 1 H), 4.16 (m, 1 H), 4.26–4.41 (m, 4 H); IR ($CDCl_3$) 1750, 1785 cm^{-1}; mass spectrum (FD), m/e 271 (M^+), 272 (M + 1), 198 (M - CO_2Et). Anal. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16. Found: C, 52.90; H, 6.49; N, 5.27.

When carbinolamine **20** was cyclized by this procedure isooxapenam (**21**) was isolated in 80% yield by chromatography eluting with ethyl acetate/hexane (3:2). The product was isolated as a colorless oil: ^1H NMR ($CDCl_3$, 90 MHz), δ 1.30 (dt, 6 H), 2.87 (dd, 1 H, J_{gem} = 15 Hz, J_{trans} = 2.5 Hz), 3.43 (dd, 1 H, J_{gem} = 15 Hz, J_{cis} = 5 Hz), 4.0 (m, 1 H), 4.15–4.45 (m, 6 H); IR (neat) 1755, 1790 cm^{-1}; mass spectrum (FD), m/e 258 (M + 1), 184 (M - CO_2Et).

Bromide 18. The alcohol **16** (60 mg, 0.3 mmol) and PPh_3 (87 mg, 0.33 mmol) were dissolved in dry acetonitrile (20 mL) and treated dropwise with CBr_4 (110 mg, 0.33 mmol) in acetonitrile (5 mL) such that the temperature did not rise above ambient. After the mixture was stirred at room temperture for 4 h, the solvent was evaporated, and the residue was chromatographed on a silica plate (1 mm, Chromatotron), eluting with ethyl acetate/hexane (1:1). Bromide **18** was isolated in 75% yield as a colorless oil: ^1H NMR ($CDCl_3$, 90 MHz) δ 1.30 (dt, 6 H), 2.0–2.7 (m, 2 H), 2.70 (dd, 1 H, J_{gem} = 15 Hz, J_{trans} = 3 Hz), 3.20 (dd, 1 H, J_{gem} = 15 Hz, J_{cis} = 6 Hz), 3.47 (dt, 2 H), 4.2–4.6 (m, 5 H), 4.97 (s, 1 H, OH); IR (neat) 1750, 1770 cm^{-1}; mass spectrum (FD), m/e 351, 353 (M^+ 1), 278, 280 (M - CO_2Et).

Cyclization of Bromide 18 to 3-Oxacepham (17). Bromide **18** (40 mg, 0.114 mmol) was dissolved in DMF/CH_2Cl_2 (2:1, 5 mL) and treated with NaH (50% oil, 5.5 mg, 0.114 mmol). The reaction mixture was allowed to stir at room temperature for 5 h and taken up in ethyl acetate (50 mL). The solution was washed several times with H_2O and brine. After the solvent was dried (Na_2SO_4) and evaporated, the residue was chromatographed on a silica plate, eluting with ethyl acetate/hexane (3:2). The desired compound **17** was isolated in 75% yield. This product had identical melting point, spectral, and TLC properties when compared with those of **17** previously prepared from **16**.

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Stereochemistry of the Dehydration of 1,2-Diphenylpropanols via Iodo Intermediates

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The reactivity and stereoselectivity of new dehydration reagents may be easily studied with the use of the secondary benzylic alcohol substrates, *threo*- and *erythro*-1,2-diphenylpropanol (**1** and **2**). These substrates provide the easily differentiated geometric alkene isomers (*Z*)- and (*E*)-1,2-diphenylpropene (**3** and **4**) depending upon the syn or anti mode of elimination (Scheme I). Cram and coworkers[2,3] and, more recently, Reeve and Doherty[4] have studied this system. However, there are unanswered questions important to such stereochemical studies. After a reagent effects dehydration, are the alkene products stable to reaction conditions, thus enabling direct product-mechanism analysis, or do the alkenes *rapidly* react to either return to starting material or to some adduct of different stereochemistry? Are these secondarily produced adducts unstable to reaction conditions (elimination to alkenes adds further complexity to a direct product-mechanism analysis)? Indeed, an acid-catalyzed dehydration of alcohol **1** or **2** illustrates these points, since under the same reaction conditions identical product mixtures enriched in the (*E*)-isomer **4** result. It has been proposed, however, that dehydrations of **1** and **2** induced by iodine or methyltriphenoxyphosphonium iodide (MTPI) both initially form iodo intermediates **5** and/or **6** which undergo an equilibration to predominately **5** (erythro). Subsequent E2 anti elimination affords the least stable (*Z*)-alkene **3** (Scheme II).[4] Iodine,[4] hydrobromic acid,[3a,5] and *p*-toluenesulfonic acid[2,4,6] further isomerize alkenes **3** and/or **4** to mixtures rich in the more thermodynamically stable

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