(m, 3 H), 1.26 (t, J = 7 Hz, 3 H), 2.23–2.50 (m, 2 H), 3.65 (s, 3 H), 4.13 (q, J = 7 Hz, 2 H); mass spectrum, m/e (relative intensity) 186 (2.5), 154 (40), 140 (45), 113 (50), 126 (20), 108 (75), 99 (100). Anal. Calcd for $C_9H_{14}O_4$: C, 58.05; H, 7.58. Found: C, 57.79; H, 7.83.

Methyl 5-carbomethoxy-2,5-heptadienoate (8): colorless liquid; IR (film) 1730, 1720, 1660, 1220, 1185 cm^{-1}; ^1H NMR (CCl_4) δ 1.83 (d, J = 7 Hz, 3 H), 3.20 (br d, J = 6 Hz, 2 H), 3.66 (s, 3 H), 3.71 (s, 3 H), 5.68 (dt, J = 16, 1.5 Hz, 1 H), 6.84 (dt, J = 16, 6 Hz, 1 H), 6.96 (q, J = 7 Hz, 1 H); mass spectrum, m/e (relative intensity) 198 (2), 166 (90), 138 (40), 107 (60), 79 (100). Anal. Calcd for $C_{10}H_{14}O_4$: C, 60.60; H, 7.12. Found: C, 60.82; H, 6.93.

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Registry No. **4**, 1117-71-1; **6c**, 86834-71-1; **6d**, 86834-73-3; **6e**, 86846-31-3; **6f**, 86846-32-4; **6g**, 86834-77-7; **6h**, 86834-79-9; **6i**, 86834-80-2; **7a**, 86834-69-7; **7b**, 86834-70-0; **7c**, 86834-72-2; **7d**, 86834-74-4; **7e**, 86834-75-5; **7f**, 86834-76-6; **7g**, 86834-78-8; **8**, 86834-81-3; dimethyl malonate, 108-59-8; dimethyl malonate anion lithium, 74826-01-0; 2,2,5-trimethyl-1,3-dioxane-4,6-dione anion lithium, 71016-33-6; methyl phenylacetate anion lithium, 86834-82-4; methyl 2-phenylpropanoate anion lithium, 86834-83-5; methyl 4-phenylbutyrate anion lithium, 86834-84-6; methyl 2-methyl-4-phenylbutyrate anion lithium, 86834-85-7; methyl 9,10-dihydro-9,10-ethanoanthracene-11-carboxylate anion lithium, 86834-86-8; ethyl 2-methylpropanoate anion lithium, 53807-80-0; ethyl acetate anion lithium, 56267-15-3; methyl 3-butenoate anion lithium, 86834-87-9.

Chiral Syntheses of Protected 3-Amino-4-(alkoxycarbonyl)-2-azetidinones from β-Hydroxyaspartic Acid[1]

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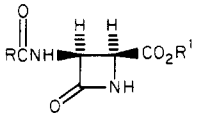
Analogues of the classical β-lactam antibiotics which contain modifications in the core bicyclic or monocyclic ring system are of considerable interest. Several such analogues with improved therapeutic value and resistance to the β-lactamases have recently been obtained from natural sources, by semisyntheses, and by total synthesis. Substituted 3-amino-4-(alkoxycarbonyl)-2-azetidinones **1**



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have been shown to be versatile intermediates for the synthesis of a number of biologically active nuclear analogues of β-lactam antibiotics.[3-5] Although the reported synthesis of **1** is efficient,[3] by design, it can only provide racemic material. Described here is the chiral synthesis of versatile forms of **1** (R = Boc, R^1 = CH_3, C_2H_5).

The planned syntheses (Scheme I) relied heavily on the previously described hydroxamate-mediated ring closure.[6,7] However, the utility of this approach depended on two requirements: (a) the availability of the L-*erythro*-β-hydroxyaspartic acid monoester **4** and (b) the avoidance of the formation of the succinimide derivative **7** observed in related systems.[8,9]

DL-*erythro*-β-Hydroxyaspartic acid has been prepared by conversion of fumaric acid to β-chloromalic acid and subsequent treatment with ammonia.[10] The L isomer was then obtained by resolution.[11] L-*erythro*-β-Hydroxyaspartic acid has also been prepared enzymatically from dihydroxyfumarate.[12] On a more practical scale, the chiral (−)-*trans*-epoxysuccinic acid (**2**) has been treated with ammonia to give L-**3** directly.[13] The epoxide **2** is available from a fermentation broth of *Aspergillus fumigatus* in a yield of over 20 g/L.[14] However, since the fermentation route to **2** was not available to us, the chiral epoxide was prepared from L-tartaric acid by the recently described procedure of Mori and Iwasawa.[15] Thus, diethyl *L*-tartarate was converted to diethyl epoxysuccinate, saponified to the free acid **2**, and subsequently treated with concentrated ammonium hydroxide to give pure crystalline L-*erythro*-β-hydroxyaspartic acid (**3**, Scheme I).

The monomethyl ester **4a** (R^1 = CH_3) was prepared nearly quantitatively by simple, but selective, acid-catalyzed esterification.[16] Reaction with *tert*-butyl pyrocarbonate gave the Boc derivative **5a** which upon coupling with *O*-benzylhydroxylamine gave the desired hydroxamate **6a**. As in the case of hydroxamate methyl esters of malic acid, **6a** was very susceptible to formation of imide **7**.[8] Attempts to purify **6a** by several chromatographic methods resulted in further conversion to imide. Consequently, the crude hydroxamate **6a** was used directly in the azodicarboxylate/triphenylphosphine-mediated cyclization step to provide β-lactam **8a**.

Alternatively, subjection of **4b**, the monoethyl ester of βhydroxyaspartic acid, to the same reaction sequence proceeded without difficulty. During the coupling reaction of the ethyl (*tert*-butoxycarbonyl)-β-hydroxyaspartate **5b** with *O*-benzylhydroxylamine, the hydroxyamate product **6b** precipitated cleanly from the aqueous reaction mixture. No imide was formed even during recrystallization to obtain the analytical sample. Cyclization gave the β-lactam as expected.

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(2) Fellow of the Alfred P. Sloan Foundation, 1981–1985. NIH Research Career Development awardee, 1983–1988.

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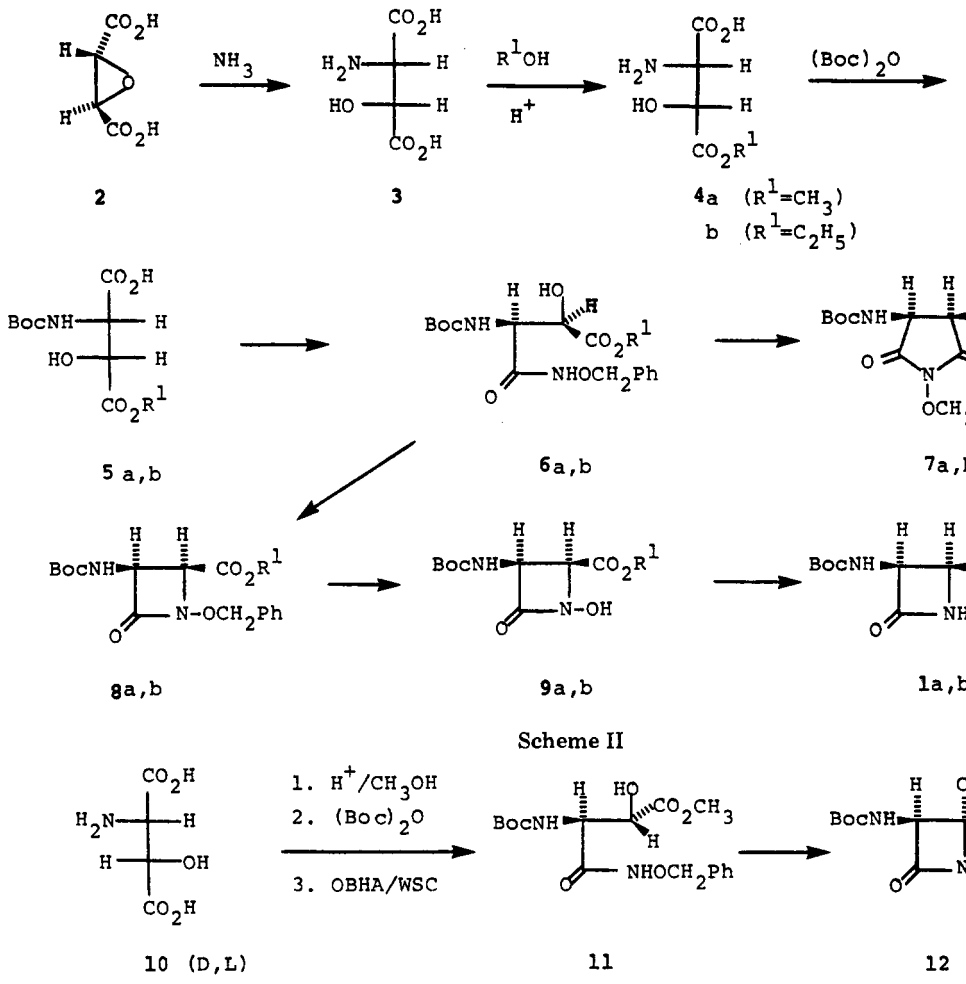
Scheme I



Scheme II

Reduction to the N-unsubstituted β-lactam 1 was accomplished by the two-step procedure described previously.[17] Thus, **8a** was treated with H_2 and Pd/C to provide the *N*-hydroxy compound **9a**, which could be isolated or used directly in the $TiCl_3$-mediated N–O reduction[18] to provide the desired optically active β-lactam **1a**.

In order to test the compatability of this approach for the preparation of the trans-substituted β-lactams, we repeated the sequence with commercially available DL-*threo*-β-hydroxyaspartic acid (Scheme II). Interestingly, in this sequence, use of the methyl esters of the β-hydroxy apartic acid did not lead to formation of the imide like **7**, at any stage.

Since all four of the optical isomers of β-hydroxyaspartic acid have been described,[16,19] all four of the optical isomers of the versatile β-lactam **1** should now be accessible. Consequently, the synthesis of a number of chiral β-lactams of biological interest should be greatly facilitated.

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 a Du Pont DP102 spectrometer or on an FD instrument at Eli Lilly and Co. HPLC analysis was performed on a Beckman-Altex Model 332 apparatus. The Chromatotron used was obtained from Harrison Research. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN, or MHW Laboratories, Phoenix, AZ.

(–)-*trans*-Epoxysuccinic Acid (2). Diethyl (–)-*trans*-epoxysuccinate[15] (2 g, 10.6 mmol) was added to 100 mL of an ice cold solution of KOH (1.38 g, 21.2 mmol) in ethanol and stirred for 3 h at room temperature. After evaporation to dryness, the residue was dissolved in 10 mL of water, and the pH was adjusted to 3.0 with 6 N HCl. When the mixture was cooled, the precipitated product was filtered and dried to give 1.28 g (9.8 mmol, 93%) of (–)-*trans*-epoxysuccinic acid (**2**) hydrate: mp >230 °C dec [lit.[20] mp (DL, after recrystallization from water) 233 °C]; $[\alpha]^{22}_D$ –81.5° (*c* 1.8, H_2O). The literature melting points and optical rotations of (+)- and (–)-*trans*-epoxysuccinic acid vary considerably depending on the recrystallization solvent.[14,20–22] This is probably due to varying degrees of hydration of the compound; ^1H NMR (D_2O) δ 3.7 (s).

L-*erythro*-β-Hydroxyaspartic Acid (3). The acid **2** (1.03 g, 6.87 mmol) was dissolved in concentrated ammonium hydroxide (50 mL) and heated in a 250-mL capacity pressure bottle (Sargent) at 110 °C for 30 h. After cooling, the aqueous solution was concentrated to 10 mL, and the pH was adjusted to 3.0 with 6 N HCl. On addition of EtOH the crude tan product precipitated (0.7 g, 4.7 mmol, 68%). Recrystallization from the minimum amount of boiling water (with a few drops of EtOH after cooling) gave pure **3**: 0.425 g (2.9 mmol, 42%); mp >220 dec; $[\alpha]_D$ 49–

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53°;[13,22] ^{1}H NMR (D_2O) δ 4.2 (1 H, d, J = 3 Hz), 4.65 (1 H, d, J = 3 Hz).

α-Methyl L-*erythro*-β-Hydroxyaspartate Hydrochloride (4a). L-*erythro*-β-Hydroxyaspartic acid (**3**; 1 g, 6.7 mmol) was dissolved in methanol (15 mL) containing concentrated HCl (1.1 mL) and heated at reflux for 3 h. When the mixture cooled, the solvent was evaporated to dryness and the residue vacuum desiccated. The solid was titurated with ether and filtered to give **4a**: 1.32 g (6.66 mmol, 99%); mp 182–183 °C [lit.[16] mp (DL) 205 °C].

α-Ethyl L-*erythro*-β-Hydroxyaspartate Hydrochloride (4b). L-*erythro*-β-Hydroxyaspartic acid (**3**; 407 mg, 2.73 mmol) was suspended in 10 mL of absolute ethanol containing 0.5 mL (0.6 mmol) of concentrated HCl. The suspension was refluxed for 7 h, cooled to room temperature, and filtered to remove 28.7 mg (0.2 mmol, 7%) of the starting diacid **3**. The filtrate was evaporated to give **4b** as a gum which was used directly in the next step.

Substitution of *p*-toluenesulfonic acid (200 mol %) for concentrated HCl appears to facilitate the esterification. In this case, refluxing for 6 h gave a homogeneous solution. Again, evaporation gave a gum which was used directly in the next step.

α-Methyl *N*-(*tert*-Butoxycarbonyl)-L-*erythro*-β-hydroxyaspartate (5a). Compound **4a** (600 mg, 3.0 mmol) was dissolved in THF/water (1:1, 15 mL) containing *tert*-butyl pyrocarbonate (660 mg, 3.0 mmol, Aldrich) and triethylamine (1.25 mL, 9.0 mmol). After 1.5 h the solution was extracted with 25 mL of ethyl acetate and then acidified to pH 2 with cold 6 N HCl. The aqueous solution was extracted again with three 25-mL portions of ethyl acetate. These latter extracts were combined, washed with brine (50 mL), dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yield compound **5a** (632 mg, 2.4 mmol, 80%). This compound or its DCHA salt would not crystallize: ^{1}H NMR ($CDCl_3$) δ 1.46 (9 H, s), 3.8 (3 H, s), 4.53 (1 H, d), 4.8–4.9 (1 H, br d), 5.73–5.8 (1 H, br d), 6.9–7.1 (2 H, br s). The ethyl ester **5b**, prepared in the same manner, was also not crystalline: ^{1}H NMR ($CDCl_3$) δ 1.27 (3 H, t), 1.45 (9 H, s), 4.28 (2 H, q), 4.53 (1 H, d), 4.85 (1 H, br d), 5.8 (1 H, br d, NH), 7.4–8.3 (2 H, br s, CO_2H, OH).

Methyl *O*-Benzyl N^{α}-(*tert*-Butoxycarbonyl)-L-*erythro*-β-hydroxyaspartyl-α-hydroxamate (6a). The protected amino acid **5a** (0.83 g, 3.18 mmol) and *O*-benzylhydroxylamine hydrochloride (OBHA, 0.56 g, 3.5 mmol, Aldrich) were dissolved in 40 mL of water and adjusted to pH 4 with 1 N NaOH. The water-soluble carbodiimide, 1-ethyl-3-[3-(dimethylamino)-propyl]carbodiimide hydrochloride (WSC, 1.2 g, 6.36 mmol) in 20 mL of H_2O was added all at once. The pH was maintained at 4–5 by manual addition of 1.0 N HCl. The resulting suspension was stirred for 30 min and then filtered. The crude product was air dried to give **6a**: 345 mg (30%) mp 130–133 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (9 H, s), 3.77 (3 H, s), 4.14–4.7 (2 H, br m), 4.87 (2 H, s), 5.5–5.7 (1 H, br d), 7.4 (5 H, s), 9.1–9.3 (1 H, br s for hydroxamate NH). The aqueous filtrate was extracted with four 50-mL portions of ethyl acetate. The combined extracts were washed with 25 mL of brine, dried over $MgSO_4$, filtered, and evaporated to give 205 mg (0.6 mmol, 19%) more of **6a** contaminated with a trace of the succinimide **7**. Attempted chromatography or recrystallization of **6a** resulted in further conversion to **7** which also was not obtained in pure form at this stage. However, see the experiment for **8a**.

Ethyl *O*-Benzyl N^{α}-(*tert*-Butoxycarbonyl)-L-*erythro*-β-hydroxyaspartyl-α-hydroxamate (6b). The protected amino acid ethyl ester **5b** (277 mg, 1 mmol) was coupled with OBHA by using the WSC as described for **6a**. The desired product precipitated and was removed by filtration to give 361 mg (94%) of product after air drying. Recrystallization from ethyl acetate–hexanes gave 290 mg of an analytically pure sample: mp 157–159 °C; TLC (silica, ethyl acetate) R_f 0.6; ^{1}H NMR ($CDCl_3$) δ 1.27 (3 H, t), 1.4 (9 H, s), 4.23 (2 H, q; 1 H, m, superimposed), 4.5 (1 H, m), 4.9 (2 H, s), 5.67 (1 H, br d, NH), 7.4 (5 H, s), 8–9.5 (br NH); mass spectrum (FD), m/e 382 (M^+), 383 (M + 1), 384 (M + 2), 91. $[\alpha]^{20}_D$ 17.8° (c 0.5, ETAc). Anal. Calcd for $C_{18}H_{26}N_2O_7$: C, 56.54; H, 6.85; N, 7.32. Found: C, 56.27; H, 6.96; N, 7.25.

The formation of the hydroxamate can also be accomplished without the use of the expensive water-soluble carbodiimide. Thus, **5b** (7 g) was dissolved in 200 mL of ethyl acetate, and a solution of *O*-benzylhydroxylamine (from 4.85 g of the HCl salt) in 100 mL of ethyl acetate was added. To this solution was added 5.2 g of dicyclohexylcarbodiimide, and the solution was stirred at room temperature for 3 h. The solution was then filtered to remove the precipitated urea, and the precipitate was washed with another 50-mL portion of ethyl acetate. The combined ethyl acetate solution was washed with 10% sodium bicarbonate solution and then with 1 N HCl. The organic solution was dried over $MgSO_4$, filtered, evaporated, and recrystallized from benzene–hexane to provide **6b** in 66% overall yield from the β-hydroxyaspartic acid.

Methyl *O*-Benzyl DL-*threo*-Hydroxamate 11. DL-threo-β-hydroxyaspartic acid (**10**; 1.0 g, 6.71 mmol; Chemolog, Fluka) was added to a solution of 30 mL of methanol containing 0.48 mL of $SOCl_2$ at room temperature. The solution was heated to reflux for 3 h and then cooled. The solvent was evaporated to leave a white semisolid residue. The ^{1}H NMR of the residue indicated a ~5:1 ratio of the desired mono β-ester and the diester. The crude mixture of esters (1.0 g) was dissolved in 30 mL of THF–H_2O (1:1). Di-*tert*-butyl dicarbonate [$(Boc)_2O$, 1.31 g, 6 mmol] was added followed by triethylamine (1.66 mL, ~12 mmol). The suspension was stirred at room temperature for 2 h after which a ninhydrin test on an aliquot was negative. The solution was poured into 25 mL of ethyl acetate in a separatory funnel also containing 20 mL of 5% $NaHCO_3$. The layers were separated, and the aqueous layer was extracted with two 20-mL portions of ethyl acetate. The aqueous layer was then acidified to pH 4 with solid citric acid and then to pH 2 with cold 6 N HCl and extracted with three 25-mL portions of ethyl acetate. These latter ethyl acetate portions were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated to give the Boc amino acid as an oil (solidified upon standing) in 83.5% overall yield from **10**: ^{1}H NMR ($CDCl_3$) δ 1.42 (9 H, s), 3.8 (3 H, s), 4.8 (2 H, m), 5.7 (NH, br), 7.3–7.8 (br, CO_2H); mass spectrum (CI with CH_4), m/e 264 (M + 1).

The protected amino acid (263 mg, 1 mmol) was dissolved in a solution containing 300 mg (1.88 mmol) of *O*-benzylhydroxylamine hydrochloride (OBHA) in 20 mL of water at pH 4.5 (adjusted with 1.0 N NaOH). A solution of 1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide (WSC, 500 mg, ~2.6 mmol) in 3 mL of water was added. A precipitate began forming immediately, and the pH drifted to 5.5. The pH was readjusted to 4.5 with 1.2 N HCl. After 20 min the white solid was removed by filtration and air-dried to give **11**, 347 mg (94% yield). Recrystallization from ethyl acetate hexanes gave **11**: 309 mg (84%); mp 132–133.5 °C; ^{1}H NMR δ 1.38 (9 H, s), 3.75 (3 H, s), 3.75 (br s, OH), 4.6 (2 H, m), 4.9 (2 H, s), 5.6 (d, NH), 7.4 (s, 5 H), 9.5 (br s, NH). Anal. Calcd for $C_{17}H_{24}N_2O_7$: C, 55.43; H, 6.57; N, 7.6. Found: C, 55.21; H, 6.67; N, 7.66.

***N*-(Benzyloxy)-*cis*-2-azetidinone (8a).** The hydroxamate **6a** (290 mg, 0.79 mmol) and triphenylphosphine (227 mg, 0.86 mmol) were dissolved in 20 mL of dry THF in an oven-dried, 50-mL, round-bottomed flask fitted with a drying tube. Diisopropyl azodicarboxylate (0.16 mL, 0.8 mmol, Aldrich) was added by syringe over 10 min. After 4 h the solution was evaporated and chromatographed (Chromatotron, 2-mm silica plate using CH_2Cl_2 with 1% of 2-propanol) to provide 160 mg (0.46 mmol, 58%) of **8a**. Recrystallization from ethyl acetate and hexanes gave a relatively pure solid: mp 57–60 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (OH, s), 3.7 (3 H, s), 4.3–4.37 (1 H, d, J = 5 Hz), 5.0–5.1 (4 H, m), 7.4 (5 H, s); $[\alpha]^{20}_D$ 51° (c 1.5, ethyl acetate). The imide contaminate **7** was also isolated at this stage by HPLC of the recrystallization mother liquor on a 250 × 4.6 mm 5-μm silica column by using 95:5 hexane/isopropyl alcohol. ^{1}H NMR of **7** ($CDCl_3$, 300 MHz) δ 1.399 (9 H, s), 4.13–4.36 (2 H, br m), 5.078 (2 H, br m), 7.395 (5 H, s).

The corresponding ethyl ester **8b** was prepared from 175 mg (0.46 mmol) of **6b** in a similar fashion except that diethyl azodicarboxylate (DEAD) was used along with TPP. After 1.5 h the solvent was evaporated, and the residue was chromatographed (Chromatotron, 1-mm silica plate, with CH_2Cl_2 containing 1% IPA). The product was collected and evaporated to give **8b** as an oil in quantitative yield. Recrystallization from CH_2Cl_2–hexanes (~1:10) was accomplished by slowly letting the solution evaporate to half the original volume (~15 mL) at room tem-

perature and then cooling it in an ice bath to give **8b**: 78% yield; mp 88–90 °C; ^{1}H NMR ($CDCl_3$) δ 1.25 (3 H, t), 1.4 (9 H, s), 4.25 (2 H, s), 4.35 (1 H, d, $J \approx 5$ Hz), 5.0–5.2 (4 H, m, overlapping NH, CH, CH_2Ph), 7.42 (5 H, s); IR (neat oil before recrystallization) 1790, 1745–1750, 1725 cm^{-1}; mass spectrum (FD), *m/e* 336 (M^+ – 28, loss of ethylene from the ethyl ester by McLafferty rearrangement), 308 (M^+ – 56, loss of isobutylene from the Boc group); $[\alpha]_D$ +46° (*c* 0.49, EtAc).

***N*-(Benzyloxy)-DL-*trans*-2-azetidinone (12).** The hydroxamate **11** (250 mg, 0.679 mmol) was cyclized with DEAD/TPP in the usual manner. After 3 h, the solvent was evaporated, and the residue was chromatographed on silica gel with CH_2Cl_2–IPA (99.5:0.5). The solvent was evaporated from the β-lactam-containing fractions to provide 160 mg (67%) of **12**. Recrystallization from ethyl acetate–hexanes gave the analytical sample: mp 93.5–95 °C; ^{1}H NMR ($CDCl_3$) δ 1.4 (9 H, s), 3.75 (3 H, s), 4.23 (1 H, d, J = 2.5 Hz), 4.43 (1 H, br d), 5.05 (2 H, s), 5.65 (NH), 7.4 (m, 5 H); IR (neat oil before recrystallization) 1800, 1755, 1715 cm^{-1}. Anal. Calcd for $C_{17}H_{22}N_2O_6$: C, 58.28; H, 6.33; N, 8.00. Found: C, 58.11; H, 6.03; N, 7.87.

***N*-Hydroxy-2-azetidinone (9a).** Compound **8a** (62.7 mg, 0.18 mmol) was dissolved in 10 mL of CH_3OH and 13 mg of 5% Pd/C was added. H_2 gas was bubbled through the solution for 1 h. The catalyst was removed by filtration and the filtrate evaporated to give 46.5 mg (100% yield) of **9a**. Recrystallization from ethyl acetate–hexanes gave the analytical sample: mp 125–126 °C; ^{1}H NMR ($CDCl_3$) δ 1.43 (9 H, s), 4.13 (3 H, s), 4.63–4.73 (1 H, d, J = 4 Hz), 5.0–5.3 (2 H, br), 6.3–6.7 (1 H, br); IR (KBr) 3365 (NOH), 1785, 1730, 1705 cm^{-1}; $[\alpha]^{20}_D$ +46° (*c* 1.5, ethyl acetate). Anal. Calcd for $C_{10}H_{16}N_2O_6$: C, 46.15; H, 6.15; N, 10.78. Found: C, 46.18; H, 6.30; N, 10.60.

3-[(*tert*-Butoxycarbonyl)amino]-4-(methoxycarbonyl)-2-azetidinone (1a). The *N*-(benzyloxy)-2-azetidinone (**8a**; 67.6 mg, 0.19 mmol) was dissolved in 10 mL of absolute CH_3OH and hydrogenated over 5% Pd/C as above for 40 min. The catalyst was removed by filtration and washed with 5 mL more of CH_3OH. The combined methanolic solutions of the *N*-hydroxy β-lactam **9a** were added to a solution of $TiCl_3$ (MCB, 20% aqueous, 0.8 mL, 1 mmol) and $NaHCO_3$ (0.28 g, 3.4 mmol) in 10 mL of water adjusted to pH 6.5 with 10% aqueous Na_2CO_3. After being stirred for 1 h under argon, the solution was extracted with three 50-mL portions of ethyl acetate. The combined extracts were quickly washed with ice cold 10% Na_2CO_3 (20 mL), ice cold 0.1 N HCl (20 mL), and brine (25 mL). After the mixture was dried over $MgSO_4$, evaporation gave 46.5 mg of the crude product. TLC (silica; ethyl acetate–hexanes, 1:1) revealed two components with R_f 0.75 and 0.1, respectively. Chromatography (Chromatotron, 1-mm silica plate with ethyl acetate–hexanes, 1:1) separated the unidentified nonpolar (R_f 0.75) component [7.4 mg; ^{1}H NMR δ 1.5 (9 H, s), 3.7 (3 H, s), 4.7 (1 H, s), 5.23 (0.5 H, s) and 5.37 (0.5 H, s), 6.5–7.0 (2 H, br), 7.2–8.0 (4 H, br m); IR (CCl_4) 1750, 1710, 164 cm^{-1}] and the desired β-lactam **1a** (28.5 mg, 61%). Crystallization from ethyl acetate–hexanes gave the solid: mp 112–114.5 °C; ^{1}H NMR δ 1.43 (9 H, s), 3.8 (3 H, s), 4.40–4.47 (1 H, d, J = 5.5 Hz), 5.1–5.6 (2 H, br m), 6.5–6.6 (1 H, br); IR (KBr) 1780, 1730 (shoulder), 1720, 1705 (shoulder); mass spectrum (FD), *m/e* 244 (M^+), 245 (M + 1); $[\alpha]^{20}_D$ +86° ±10% (*c* 0.275, ethyl acetate).

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Registry No. **1a**, 86832-64-6; **2**, 17015-08-6; **3**, 7298-98-8; **4a**, 20790-73-2; **4b**, 86767-40-0; **5a**, 86767-41-1; **5b**, 86767-42-2; **6a**, 86767-43-3; **6b**, 86767-44-4; **8a**, 86767-45-5; **8b**, 86767-46-6; **9a**, 86767-47-7; **10**, 4294-45-5; **10** monomethyl β-ester, 84035-03-0; **10** monomethyl β-ester/*N*-*tert*-butoxycarbonyl derivative, 86767-48-8; **11**, 86832-65-7; **12**, 86832-66-8; diethyl (–)-*trans*-epoxysuccinate, 74243-85-9; *O*-benzylhydroxylamine hydrochloride, 2687-43-6; *O*-benzylhydroxylamine, 622-33-3.

Influence of Steric Effects upon the Rate Constants for Competing $B_{AC}2$ and E1cB Ester Hydrolyses

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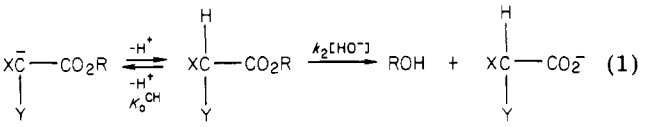
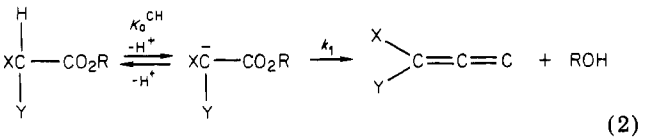
The rates of hydrolysis of carboxylic acid esters which possess an α-ionizable proton (pK_a^{CH}) are proportional to hydroxide concentration ($k_{obsd} = k'[HO^-]$) when pH ≪ pK_a^{CH} and independent of pH ($k_{obsd} = k_{pl}$) when pH ≫pK_a^{CH}. There are two mechanisms which account for this pH dependence. For the $B_{AC}2$ mechanism (eq 1) k'





= k_2 and $k_{pl} = k_2K_w/K_a^{CH}$ while for the E1cB mechanism (eq 2) $k' = k_1K_a^{CH}/K_w$ and $k_{pl} = k_1$.[1] Because the two mechanisms are kinetically equivalent they cannot be distinguished by use of their pH–rate profiles (but see footnote 2). Many criteria have been proposed to distinguish between the mechanisms of eq 1 and 2. These include the use of (i) dependence of log k' or log k_{pl} on proton basicity of the leaving group,[3] (ii) trapping of intermediate ketene,[3] (iii) deuterium isotope effects,[3,4] (iv) curvature in buffer plots,[5] and (v) steric effects.[6,7] As the departure of the leaving group from the carbon atom adjacent to the carbanion in the E1cB reaction is a dissociative process, one might expect that a sterically bulky group in the molecule would enhance the rate of the departure step.[8] However, it has been concluded that expulsion of the leaving group in E1cB alkene-forming reactions is "remarkably insensitive" to substituent effects.[9,10]

(1) (a) Holmquist, B.; Bruice, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 2993, 3003. (b) Another mechanism, nucleophilic attack of water on the ester moiety of the substrate carbanion, is also kinetically equivalent to the two mechanisms mentioned in the text. However, because of the strong electron-donating effects of the carbanion lone pair, nucleophilic attack of water on the ester moiety of the carbanion ($k_{anion}^{H_2O}$) must be much slower than nucleophilic attack of water on the ester moiety of the unionized ester ($k_o^{H_2O}$). Therefore, the possibility that $k_{pl} = k_{anion}^{H_2O}$ is ruled out, as discussed in ref 1 and 3.

(2) For the E1cB hydrolysis of *p*-nitrophenyl acetoacetate, for example, a pH–rate profile with two plateau regions was observed. This pH–rate profile cannot be explained by a $B_{AC}2$ mechanism but can be explained on the basis of an E1cB mechanism with a change from preequilibrium to irreversible in carbanion formation.[3]

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(8) For example: Bartlett, P. D.; Tidwell, T. T. *J. Am. Chem. Soc.* **1968**, *90*, 4421. Note, however, solvolytic substitution is a charge- (carbenium ion) forming reaction while E1cB ester hydrolysis is a charge-(carbanion) consuming reaction.
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