loss of the yellow color and filtered while hot to remove the catalyst. Evaporation of the toluene left an oil, which solidified upon cooling. The solid was recrystallized from ethanol to give 50 mg (28%) of 2-ethylanthracene, mp 148–150 °C (lit.[13] mp 148–150 °C). A mixed melting point with authentic 2-ethylanthracene was not depressed.

Diels–Alder Reactions of Anthra[2,3-*b*]thiophene. 5,10-Dihydro-12,13-dicyano-5,10-ethenoanthra[2,3-*b*]thiophene (11). Among several attempts to prepare dicyanoacetylene by published methods, the one reported by Byrd and co-workers[14] was the most efficient. A solution of anthra[2,3-*b*]thiophene (0.40 g, 1.71 mmol) and dicyanoacetylene (0.39 g, 5.12 mmol) in toluene (35 mL) was heated under reflux for 2 h. Evaporation of the solvent following decolorization with Norit gave a yellow-white solid, which was recrystallized from benzene–toluene as white crystals: mp 234–235 °C; 0.43 g (82%); IR (Nujol) 2220 cm^{-1}; NMR (acetone-d_6) δ 7.2–8.2 (m, 8 H, aromatic CH), 6.0 (s, 2 H, $C_{4,10}$-H).

Anal. Calcd for $C_{20}H_{10}N_2S$: C, 77.40; H, 3.25; N, 9.03; S, 10.33. Found: C, 77.38; H, 3.38; N, 9.09; S, 10.34.

5,10-Dihydro-12,13-bis(methoxycarbonyl)-5,10-ethenoanthra[2,3-*b*]thiophene (12). A solution of 0.40 g (1.71 mmol) of anthra[2,3-*b*]thiophene and 0.73 g (5.1 mmol, 3 equiv) of dimethyl acetylenedicarboxylate in 30 mL of xylene was heated at reflux for 40 h, treated with decolorizing carbon, heated at reflux for 10 min, and then filtered while hot. Evaporation of the solvent left a reddish oil, which was crystallized from aqueous methanol. The resulting solid was sublimed at 150 °C (0.005 mm) and was recrystallized from benzene/hexane to give 0.30 g (47%) of **12** in nearly colorless clusters: mp 194–195 °C; IR (Nujol) 1735 and 1745 (ester C=O), 1225 and 1275 cm^{-1} (ester CO); NMR ($CDCl_3$, 80 MHz) δ 7.80 (s, 1 H, aromatic CH), 7.74 (s, 1 H, aromatic CH), 6.93–7.41 (m, 6 H, aromatic CH), 5.49 (s, 2 H, $C_{5,10}$-H), 3.76 (s, 6 H, CO_2CH_3); UV max (95% C_2H_5OH) 233 nm (log ϵ 4.62).

Anal. Calcd for $C_{22}H_{16}O_4S$: C, 70.20; H, 4.28; S, 8.52. Found: C, 70.30; H, 4.28; S, 8.70.

5,10-Dihydro-5,10-ethanoanthra[2,3-*b*]thiophene-12,13-dicarboxylic Anhydride (13). A mixture of 0.084 g (0.85 mmol) of recrystallized maleic anhydride and 0.20 g (0.85 mmol) of anthra[2,3-*b*]thiophene in 10 mL of dry xylene was heated at reflux for 48 h. The solution was cooled slightly, treated with decolorizing carbon, heated at reflux for 5 min, filtered, and allowed to cool. The resulting white solid was filtered and recrystallized from benzene/hexane to afford 0.21 g (75%) of **13** as a white solid, mp 282 °C. An analytical sample was prepared by a second recrystallization from benzene/hexane: mp 282 °C; IR (Nujol) 1870 and 1860 cm^{-1} (anhydride C=O); NMR ($CDCl_3$, 80 MHz) δ 7.71–7.81 (m, 2 H, aromatic CH), 7.09–7.44 (m, 6 H, aromatic CH), 4.85 (s, 2 H, $C_{5,11}$-H), 3.53 (s, 2 H, $C_{12,13}$-H); mass spectrum (70 eV), *m/e* 332 (calcd *m/e* 332.38); UV max (95% C_2H_5OH) 237 nm (log ϵ 4.95), 266 (log ϵ 4.36), 271 (log ϵ 4.37).

Anal. Calcd for $C_{20}H_{12}O_3S$: C, 72.27; H, 3.64; S, 9.65. Found: C, 72.50; H, 3.75; S, 9.49.

Acknowledgment. Computer time for the X-ray diffraction data analysis was provided by the West Virginia Network for Education Telecomputing.

Registry No. **6**, 22108-55-0; **7**, 80090-33-1; **8**, 87434-26-2; **9**, 87434-27-3; **10**, 52251-71-5; **11**, 87434-28-4; **12**, 87434-29-5; **13**, 87434-30-8; NCC≡CCN, 1071-98-3; $CH_3O_2CC{\equiv}CCO_2CH_3$, 762-42-5; 3-bromothiophene, 872-31-1; naphthalene-2,3-dicarboxylic anhydride, 716-39-2; maleic anhydride, 108-31-6.

Supplementary Material Available: Description of structural analysis and tables of crystal data, positional and temperature factors, interatomic distances, and bond angles for nonhydrogen atoms, and observed and calculated structure factors (17 pages). Ordering information is given on any current masthead page.

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Conversion of β-Hydroxyglutarohydroxamates to Carbapenem Precursors

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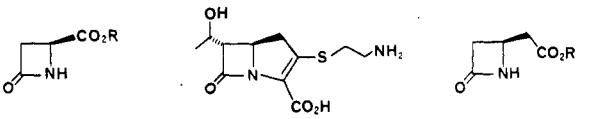
Isolation of the potent antibiotic thienamycin (1) and several similar antibiotics has stimulated an enormous effort aimed at the syntheses of these carbapenems.[1,2] Two very attractive intermediates for the synthesis of carbapenems are illustrated by structures **2** and **3**. We and others have previously described versatile approaches to the synthesis of chiral representatives of **2**.[3,4] The synthesis and utility of **3** has also been elegantly demonstrated by several groups.[4-10] Early in the development of our hydroxamate mediated approach to β-lactam synthesis, we recognized its potential for the preparation of chiral derivatives **3**.



2 1 3

A primary requirement for the initiation of the hydroxamate-mediated β-lactam synthesis is the availability of a suitably substituted β-hydroxy carboxylic acid.[11] Thus, the anticipated precursor to **3** was a monoester of β-hydroxyglutaric acid **5** (Scheme I). This precursor was especially attractive since the desired optical isomer [(R)-**5**] is readily available by chymotrypsin hydrolysis of the diester **4** (R=CH_3).[12]

In order to explore the feasibility of the synthesis proposed in Scheme I, we first tested the route with racemic materials. Thus, the racemic mono esters **5a,5b** were prepared from acetonedicarboxylic acid by straightforward processes. Coupling of these monoesters with O-substituted hydroxylamines in aqueous THF with a water-soluble carbodiimide gave the racemic O-substituted β-hydroxyglutaromonohydroxamic acids **6** in 50–80% yields. Treatment of **6a,6b** with the usual combination of diethyl azodicarboxylate and triphenylphosphine (DEAD/TPP)[11] under varying conditions gave multicomponent mixtures. After extractive workup and extensive chromatography, spectroscopic analyses indicated that mixtures of starting materials **6**, olefin (elimination products like **9**), desired β-lactam **7**, and the expected $Ph_3P{=}O$ and $EtO_2CNHNHCO_2Et$ were all obtained. In one of the cleaner cases, reaction of **6c** with DEAD/TPP for 10 min at room tempoerature gave a 78% yield of the olefins **9** and only a 22% yield of β-lactam **7c**. Several other cyclizations of hydroxamates **6** were tried with use of TPP/CCl_4/Et_3N,[11] TPP·Br_2, TPP·Cl_2, and TPP·(OTf). Prior conversion of **6** to the mesylate **8** (X = OMs) and subsequent treatment with base was also attempted. In all cases, mixtures were obtained with olefinic products usually being the major product. Details of these studies are provided in a dissertation.[13]

Substitution of trialkyl phosphites for triphenylphosphine during the use of the Mitsunobu reaction for the formation of β-lactams has been reported.[14] Thus, we attempted the cyclization of benzyl O-pivaloyl-β-

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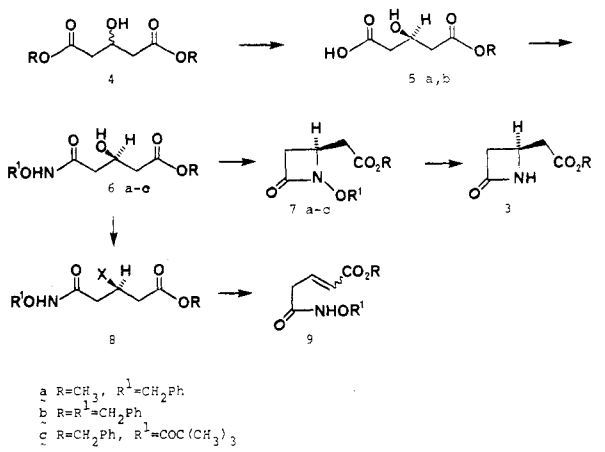
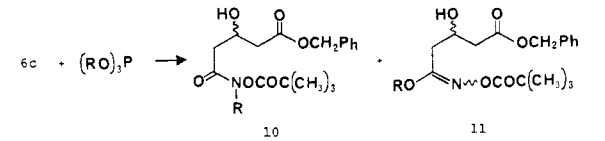
Scheme I



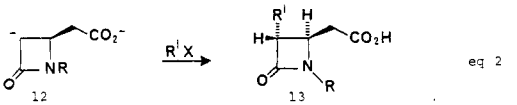
hydroxyglutarohydroxamate (**6c**) with phosphites and DEAD. Surprisingly, the reaction of trimethyl or triisopropyl phosphite and DEAD gave a mixture of N- and O-alkylated hydroxamates **10** and **11** (eq 1). No cyclization or elimination products were detected.



eq 1

Finally, the reaction was repeated with triphenyl phosphite, DEAD, and **6c** since direct alkylations at the benzene ring seemed unlikely. Although extremely slow (several days at room temperature), this reaction proceeded to give only the β-lactam **7c** and none of the olefin **9**. Reaction times could be shortened to 12 h by addition of excess $(PhO)_3P$ and heating to 60–70 °C. Some olefin (<5%) was detected upon prolonged heating of the reaction. The desired β-lactam was isolated in 50–70% yield after chromatography. Substitution of $(PhO)_2PPh$ or $(PhO)PPh_2$ for TPP in the cyclization of **6c** to **7c** with DEAD also decreased the reaction times and still avoided olefin formation.

After the cyclization of β-hydroxyglutarohydroxamic acids to *N*-alkoxy- or *N*-(acyloxy)-4-(methoxycarbonyl)-2-azetidinones **7** had been achieved, it was desirable to convert the products to a known compound and relate it to the synthesis of the carbapenem antibiotics. 4-[[(Benzyloxy)carbonyl]methyl]-2-azetidinone (**3**, R = CH_2Ph) was chosen as the correlation target since it had already been synthesized in racemic form by reaction of 4-acetoxy-2-azetidinone with the enolate of benzyl acetate.[8c] In addition, the corresponding chiral acid **3** (R = H) has recently been converted to the dianion **12** and subsequently alkylated to give the 3-substituted derivatives **13** useful for elaboration to the natural carbapenems **9** (eq 2).[9] Conceptually, **3** could be prepared by depivalation of **7c** followed by NO reduction.



eq 2

Thus, the *N*-(pivaloyloxy)-2-azetidinone **7c** was treated with various nucleophiles in order to remove the pivaloyl group. Use of relatively basic reagents resulted in elimination of the hydroxamic acid to form the olefin **9**, whereas several other nucleophilic reagents opened the ring by attacking the β-lactam carbonyl. For example, NaOH and LiOH gave olefin and ring-opened products, benzylamine gave the ring-opened benzylamide, and sodium sulfide[15] gave the olefin, some desired N-hydroxy β-lactam, and ester cleavage products. Depivalation was finally accomplished by treatment of **7c** with ammonium acetate in aqueous THF to give the *N*-hydroxy compound **7** (R^1 = H) in 60% yield. Subsequent $TiCl_3$ reduction[16] provided the desired N-unsubstituted β-lactam **3** (R = CH_2Ph).

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 727b spectrometer. NMR spectra were obtained in chloroform-*d* with tetramethylsilane as a reference on Varian A60, Varian EM 390, and Nicolet NB300 300-MHz instruments. Mass spectra were recorded on an AEI Scientific Apparatus 902 or a DuPont DP 102 spectrometer. HPLC analyses were performed with a Beckman-Altex model 332 apparatus. Gravity and medium-pressure chromatography were performed on Merck silica gel unless otherwise noted. Elemental analyses were performed by Midwest Microlabs, Indianapolis, IN, or MHW Laboratories, Phoenix, AZ.

Monomethyl 3-Hydroxypentanedioic Acid (5a). Monomethyl acetonedicarboxylate (0.16 mol, prepared by methanolysis of glutaconic anhydride[17,18]) was dissolved in 250 mL of methanol in a three-necked 1-L flask fitted with a Teflon stirbar, condenser, and thermometer. The solution was cooled to 5 °C in an ice bath, and then sodium borohydride (6.4 g, 0.17 mol, 110 mol %) was added portionwise over 30 min. The pH was maintained between 4 and 7 by the addition of 6 N HCl, keeping the temperature below 10 °C. After stirring for an additional hour at 0 °C, the mixture was acidified to pH 3 with the slow addition of 6 N HCl. It was then extracted with ethyl acetate (600 mL in five portions). The extracts were combined and washed with brine and dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo to yield the crude product as a light yellow oil suitable for use in the next reaction (18.8 g, 0.116 mol, 73%): ^1H NMR ($CDCl_3$) δ 2.6 (4 H, 2 d superimposed), 3.72 (s, 3 H), 4.5 (q, 1 H, *J* = 6–7 Hz), 6.97 (br s, 2 H).

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Monobenzyl 3-hydroxypentanedioic acid (5b) was prepared in 54% yield from monobenzyl acetone dicarboxylate by the procedure described above: mp 68–68.5 °C (recrystallized from EtAc–hexanes); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.49, (d, J = 6 Hz), 2.53 (d, J = 6 Hz) together 4 H, 4.47 (quintet, 1 H), 5.11 (s, 2 H), 6.56 (br s, 2 H), 7.33 (s, 5 H); IR ($CHCl_3$) 3500 (br), 1720 cm^{-1}. Anal. Calcd for $C_{12}H_{14}O_5$: C, 60.5; H, 5.92. Found: C, 60.28; H, 6.02.

Hydroxamates of 3-hydroxyglutaric acids (6) were prepared by the carbodiimide-mediated coupling of the acid and hydroxylamine described previously.[11]

Methyl *O*-benzyl-β-hydroxyglutaromonohydroxamate (6a) was obtained in 62.8% yield: mp 78–79 °C NMR ($CDCl_3$, 90 MHz) δ 2.29 (2 H, br d, J = 6 Hz), 2.48 (2 H, d, J = 6 Hz), 3.69 (3 H, s), 4.36 (2 H, quintet superimposed on a br s), 4.87 (2 H, s), 7.4 (5 H, s), 9.39 (1 H, br s); IR (KBr) 1720, 1680 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.42; H, 6.41; N, 5.38. Found: C, 58.32; H, 5.98; N, 5.24.

Benzyl *O*-benzyl-β-hydroxyglutaromonohydroxamic acid (6b) was prepared in 76% yield: mp 94.5–96 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.27 (2 H, br d), 2.5 (2 H, d, J = 6 Hz), 3.87 (1 H, br s), 4.37 (1 H, quintet, J = 6 Hz), 4.84 (2 H, br s), 5.1 (2 H, s), 7.38 (10 H, s), 9.29 (1 H, br s); IR (KBr) 3500 (br), 3150, 3000, 1715, 1660 cm^{-1}. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.17; N, 4.08. Found: C, 66.55; H, 6.19; N, 3.88.

Benzyl *O*-pivaloyl-β-hydroxyglutaromonohydroxamic acid (6c) was prepared in 50% yield: mp 72.5–73.5 °C; ^{1}H NMR ($CDCl_3$, 90 MHz) 1.32 (9 H, s), 2.5 (2 H, d, J = 6 Hz), 2.63 (2 H, d, J = 6 Hz), 4.17 (1 H, br s), 4.47 (1 H, quintet, J = 6 Hz), 4.17 (1 H, br s), 4.47 (1 H, quintet, J = 6 Hz), 5.13 (2 H, s), 7.39 (5 H, s), 8.39 (1 H, br s); IR (KBr) 3450, 3175, 2975, 1770, 1710, 1680 (s). Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.65; H, 6.74; N, 4.22.

Azodicarboxylate-Mediated Cyclizations: General Procedures. The hydroxamic acid and the phosphorous compound R_3P (R = Ph, PhO, or a combination thereof, CH_3O, *i*-PrO) were dissolved in tetrahydrofuran (0.03–0.05 M) in a round-bottomed flask fitted with a Teflon stirbar and nitrogen inlet and outlet. After the solution was brought to the reaction temperature, diethyl azodicarboxylate was added dropwise via syringe over 1–2 min. Reactions were monitored by TLC (silica, 1:1 ethyl acetate/Skellysolve B) and quenched with 500–1000 mol % of water if olefin formation was observed by TLC. The reaction mixture was concentrated under reduced pressure and either chromatographed directly (ether–hexanes, CH_2Cl_2–hexanes or CH_2Cl_2–ether on silica gel) or first subjected to a cold aqueous workup that included basic (0.1 N NaOH) and acidic (0.5 M citric acid) extractions, followed by treatment with CH_2Cl_2–hexanes to remove most of the diethyl hydrazidodicarboxylate, and then chromatography.

***N*-(Benzyloxy)-4-[(methoxycarbonyl)methyl]-2-azetidinone (7a)** was prepared as an oil in 49.6% yield by the reaction of **6a** with $(PhO)_3P$ (500 mol %)/DEAD (125 mol %) for 16 h at room temperature: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.27–3.00 (m, 4 H, CH_2 of ring and $CH_2CO_2CH_3$), 3.68 (s, 3 H), 3.94 (m, 1 H), 4.93 (s, 2 H), 7.47 (s, 5 H).

***N*-(Benzyloxy)-4-[[(benzyloxy)carbonyl]methyl]-2-azetidinone (7b)** was prepared as an oil in 35% yield by the reaction of **6b** with $(PhO)_2PPh$/DEAE: ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.27–2.97 (m, 4 H, CH_2 of the ring and CH_2CO_2R), 3.97 (m, 1 H), 4.90 (s, 2 H), 5.10 (s, 2 H), 7.37 and 7.41 (2 s, 10 H).

1-(Pivaloyloxy)-4-[[(benzyloxy)carbonyl]methyl]-2-azetidinone (7c) was prepared as an oil in 70% yield by the reaction of **6c** with $(PhO)_3P$/DEAD for 3–4 days at room temperature: ^{1}H NMR δ 1.30 (s, 9 H), 2.53–3.27 (m, CH_2CO_2R and CH_2 of the ring), 4.43 (dq, 1 H, J = 2 and 6 Hz), 5.2 (s, 2 H), 7.40 (s, 5 H); In the 300-MHz NMR, the multiplet between δ 2.53 and 3.27 is shown to be two sets of double doublets for the protons on C_3 and one doublet of quartets for the methylene protons of the C_4 substituent; IR ($CHCl_3$) 1805, 1765, 1735 cm^{-1}.

1-Hydroxy-4-[[(benzyloxy)carbonyl]methyl]-2-azetidinone (7, R^1 = H). Compound **7c** (142 mg, 0.445 mmol) was dissolved in 10 mL of THF–H_2O (1:1) and treated with 250 mg (730 mol %) of ammonium acetate. Acetone was added until the solution became homogeneous. The solution was stirred at room temperature for 12 h and then concentrated to remove the THF. The aqueous residue was adjusted to pH 9 with an aqueous 5% Na_2CO_3 solution and extracted with three 10-mL portions of ethyl acetate to remove any starting material (**7c**) and pivalamide. The aqueous layer was then acidified to pH 2 with 1.2 N HCl, saturated by the addition of solid NaCl, and extracted with five portions of ethyl acetate. These latter extracts were combined, washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated to yield the *N*-hydroxy compound as an oil in 60% yield. This compound was used directly without further purification:[19] ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.30–3.10 (m, 4 H, CO_2CH_2Ph and CH_2 of the ring), 4.06 (dq, 1 H, J = 2 and 6 Hz, methine of the ring), 5.13 (s, 2 H), 7.38 (s, 5 H).

4-[[(Benzyloxy)carbonyl]methyl]-2-azetidinone (3). The *N*-hydroxy compound **7** (R^1 = H; 65 mg, 0.3 mmol) was dissolved in 5 mL of THF–H_2O (1:4). Nitrogen was bubbled through the solution and 3.0 mL of a 20% aqueous solution of $TiCl_3$ (Matheson Coleman and Bell) was added dropwise while maintaining the pH at 7 by automatic addition of 1 N NaOH with a pH stat. After stirring at room temperature for 1.5 h, the solution was purged with air and the resulting suspension was filtered through Celite. The Celite was washed with methanol. The filtrate and washings were combined, concentrated, and extracted with five 25-mL portions of ethyl acetate. The ethyl acetate layers were combined, washed with brine, dried over $MgSO_4$, filtered, and evaporated to yield 30 mg (50%) of **3** as an oil. Crystallization from ethyl acetate–hexanes gave 16 mg of **3** as white crystals: mp 92–92.5 °C (lit.[8c] mp 95 °C, from benzene); ^{1}H NMR ($CDCl_3$, 90 MHz) δ 2.50–2.80 and 3.0–3.3 (m, 4 H, CH_2 of ring and CH_2CO_2Bz), 3.97 (dq, 1 H, methine of ring), 5.13 (s, 2 H), 6.13 (br s, NH), 7.4 (s, 5 H).

Acknowledgment. We are grateful to the National Institutes of Health and Eli Lilly and Co. for their support. M.A.M. gratefully acknowledges the receipt of a Reilly Fellowship (1982). The instrumental assistance of Mr. Donald R. Schifferl and Mrs. Kathleen Peterson is appreciated. The 300-MHz NMR system used was made available by grants from the NIH and the University of Notre Dame.

Registry No. **3** (R = CH_2Ph), 81019-86-5; **5a**, 87118-53-4; **5b**, 87395-67-3; **6a**, 87395-68-4; **6b**, 87395-69-5; **6c**, 87395-70-8; **7a**, 87395-71-9; **7b**, 87395-72-0; **7c**, 87395-73-1; **7** (R = CH Ph; R^1 = H), 87395-74-2; (*E*)-**9c**, 87395-75-3; (*Z*)-**9c**, 87395-76-4; monomethyl acetonedicarboxylate, 78315-99-8; glutaconic anhydride, 5926-95-4; monobenzyl acetonedicarboxylate, 87395-77-5.

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Selective Hydrolysis–Decarboxylation of Ethyl 1,4-Dimethyl-3-(ethoxycarbonyl)-1*H*-pyrrole-2-acetate

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The conversion of title compound **1** to ethyl 1,4-dimethyl-1*H*-pyrrole-2-acetate (**5**) is an important transformation in the synthesis of 5-benzoyl-1,4-dimethyl-1*H*-pyrrole-2-acetic acid antiinflammatory agents.[1] Carson and Wong[1] described a three-step method in which diester **1** is hydrolyzed to diacid **4** with 25% NaOH, **4** is selectively reesterified to acid ester **2** with 0.5% HCl in ethanol, and

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0022-3263/83/1948-4423$01.50/0