observed ($|F_0| \geq 3\sigma(F_0)$). A multisolution sign-determining procedure revealed all of the non-hydrogen atoms uneventfully.[30] All hydrogens were located in a subsequent difference electron density synthesis. Block-diagonal least-square refinements with anisotropic non-hydrogen atoms and isotropic hydrogens have converged to a conventional R of 0.059 for the observed reflections. Additional crystallographic details are available and are described in the paragraph at the end of this paper on Supplementary Material.

Acknowledgment. We thank the Bristol-Myers Company and the Sterling-Winthrop Research Institute for support of this work.

Registry No. **3**, 6948-61-4; **4**, 92670-41-2; **5**, 94-41-7; **6**, 92670-42-3; **7**, 104-55-2; **8**, 92670-43-4; **9**, 92670-44-5; **10**, 92670-45-6; **11**, 35811-93-9; **12**, 92670-47-8; **13**, 92670-48-9; **15**, 92670-49-0; **16**, 92670-50-3; **17**, 122-57-6; **18**, 495-41-0; **19**, 538-44-3; **20**, 768-03-6; **21**, 4452-11-3; **22**, 769-60-8; **23** (n = 2), 92670-52-5; **25**, 92760-85-5; **26**, 92670-46-7; **27**, 92670-51-4; **28**, 50460-02-1; $C_6H_5COCH_2SH$, 2462-02-4; propiophenone, 93-55-0; thiophene-3-carboxaldehyde, 498-62-4; sodium polysulfide, 1344-08-7.

Supplementary Material Available: Tables of fractional coordinates, thermal parameters, bond distances, and bond angles for compound 1 (6 pages). Ordering information is given on any current masthead page.

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dl-Isoserine and Related Compounds

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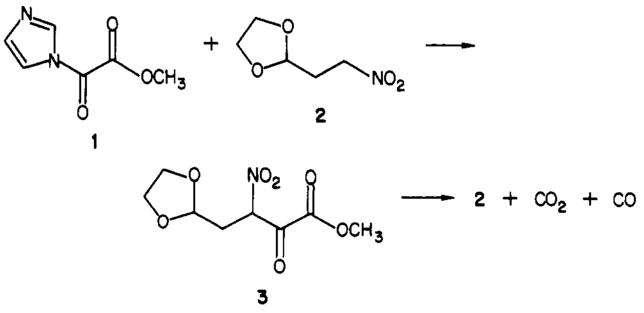
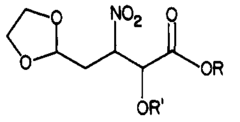
Received June 4, 1984

Syntheses of *dl*-isoserine (3-amino-2-hydroxypropanoic acid, 7) and further functionalized derivatives are described. Reaction of glyoxylic acid with nitromethane gives the known 2-hydroxy-3-nitropropanoic acid (8), which upon hydrogenolysis affords *dl*-isoserine in high yield. The comparable nitro-aldol reaction of 3-nitropropanal ethylene acetal (2) with glyoxylic acid produces 2-hydroxy-3-nitro-5-oxopentanoic acid ethylene acetal (4a) as a mixture of erythro and threo isomers. The methyl esters of hydroxy acid **4a** are chromatographically separable as the *tert*-butyldimethylsilyl ethers. Catalytic reduction (Pd/C) of these nitro compounds gives the corresponding methyl 3-amino-2-hydroxy-5-oxopentanoate ethylene acetals **9**. Ethyl 2-hydroxy-3-phthalimidopropanoate (**22**) and ethyl 2-oxo-3-phthalimidopropanoate (**23**) were also prepared along with several other N-protected β-amino-α-oxy esters related to isoserine.

Nitrocarbonyl compounds are useful intermediates in the synthesis of polyfunctional compounds.[1] An α-nitro ketone with protected aldehyde and carboxylic acid functions having structure 3 was synthesized[2] as a possible intermediate in a projected convergent synthesis of tetrodotoxin.[3,4] However, the esters of this tetrafunctionalized compound could not be converted to the free acid nor would they undergo transesterification reactions; acid or base catalysis resulted in regeneration of 3-nitropropanal ethylene acetal (2) with concommitant gas evolution (presumably carbon dioxide and carbon monoxide).



A key feature of structure **3** is the double activation of position 3 to aldol-type condensations by virtue of the carbonyl adjacent to the nitro group. Presumably this double activation accounts for its great sensitivity and requires modification. Obvious alternatives were to retain the 3-nitro group as represented by **4** or the 2-oxo group as represented by **5**.



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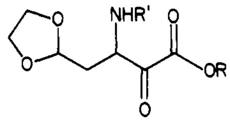

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This paper deals with the results from studies directed at the syntheses of **4** and **5**, which diverged somewhat from the original goals, becoming interrelated with previous work on the synthesis of the amino acid isoserine and related compounds.

L-Isoserine (3-amino-2-hydroxypropanoic acid, **7**) is a biologically active β-amino acid[5] and a constituent of the pentapeptide antibiotic edeine.[6] Chemically modified butirosin, in which isoserine replaces 4-amino-2-hydroxybutanoic acid, exhibits enhanced antibiotic activity.[7]

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[1] (a) Fischer, R. H.; Weitz, H. M. *Synthesis* **1980**, 261. (b) Dampawan, P.; Zajac, W. W. *J. Org. Chem.* **1982**, *47*, 1176.

[2] Crumbie, R. L.; Nimitz, J. S.; Mosher, H. S. *J. Org. Chem.* **1982**, *47*, 4040.

[3] Nimitz, J. S. Ph.D. Thesis, Stanford University, 1980.

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[5] Liebman, K. C.; Fellner, S. K. *J. Org. Chem.* **1962**, *27*, 438.

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[7] (a) Woo, P. W. K.; Dion, H. W.; Bartz, Q. R. *Tetrahedron Lett.* **1971**, 2617, 2621, 2625. (b) Plesosas, N.; Watson, D.; Westland, R. D. *Carbohydr. Res.* **1973**, *28*, 263.

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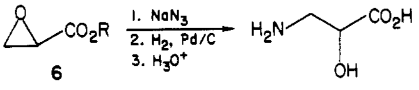
Several methods have been reported for converting isoserine to the corresponding β-lactam.[8]

Asymmetric syntheses of L-isoserine[9] and D-isoserine[10] have been reported, in addition to chemical resolution of the racemate.[11] The most successful preparations of racemic isoserine proceed through glycidic acid or ester **6**.[12] None of the reported syntheses to date, however, are especially suited for large-scale production.



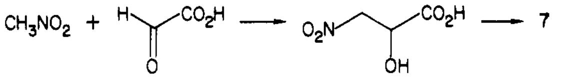
6 **7**

Of special interest to us was an early report[13] of the Sn/HCl reduction of 2-hydroxy-3-nitropropanoic acid to isoserine (**7**) in unspecified yield. This nitro compound was at that time rare but is in fact readily available via a nitro-aldol condensation,[14] thus providing an attractive entry to isoserine. This basic approach is potentially a general method for the synthesis of β-amino-α-hydroxy acids.

The requisite starting α-hydroxy-β-nitro acids or esters are readily available by base-catalyzed addition of nitroalkanes[15] to α-oxo acids or esters. This is a specialized case of the more general nitro-aldol (Henry) reaction[16] which generates β-nitro alcohols. The use of the Henry reaction for C–C bond formation has received a great deal of attention in the carbohydrate field.[17] With respect to the present case, several α-hydroxy-β-nitro acids have been synthesized via the Henry reaction and studied as isosteric and isoelectric analogues of malic, citric, and isocitric acids.[18] α-Hydroxy-β-nitro carbonyl compounds are also intermediates in a synthesis of α-diketones.[19]

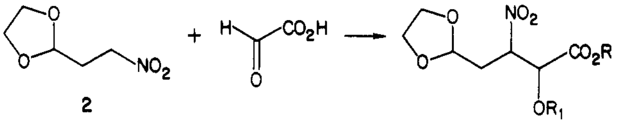
Results

The Nitro-Aldol Reaction and the Synthesis of Isoserine and Related Compounds. Nitromethane reacted with glyoxylic acid hydrate in the presence of base to yield *dl*-2-hydroxy-3-nitropropanoic acid (**8**) as described by Schecter and Conrad[14] (NaOH, H_2O, pH 9, 78%). Catalytic reduction of the nitro group (10% Pd/C, H_2, 85%) gave pure, powdery *dl*-isoserine (**7**). Other methods of reduction were not as successful; Pt/H_2 completely failed to reduce the nitro group under neutral or acidic conditions, and Raney nickel reduction led to the isolation of a bright green powder, which may be an isoserine–nickel complex.



8

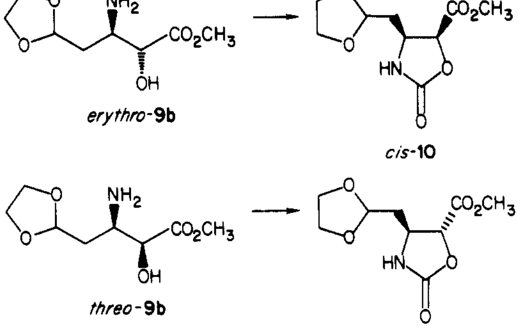
We extended this reaction to complex nitroalkanes by the addition of 3-nitropropanal ethylene acetal (**2**) to glyoxylic acid (2 N NaOH, EtOH, 1 h, 100%) to yield α-hydroxy-β-nitro acid **4a**. Esterification with diazomethane gave the methyl ester **4b** accompanied by a large amount of **2**, the product of a retro-nitro-aldol reaction most probably catalyzed by amines in the ethereal diazomethane solution. The use of distilled diazomethane completely suppressed the fragmentation reaction, and the methyl ester was isolated in 77% yield after column chromatography. More conveniently, the methyl ester could be made directly by treating **2** with methyl glyoxylate[20] (CH_3ONa, CH_3OH, 78%).



2

4a, R=R$_1$=H
4b, R=CH$_3$; R$_1$=H
4c, R=CH$_3$; R$_1$=Si-*t*-BuMe$_2$

As expected, **4a** and **4b** exist as a 1:1 mixture of erythro/threo isomers. The isomeric ratio is easily determined by integration of the well-resolved H-2 doublets in the proton NMR spectrum. Converting **4a** to the *tert*-butyldimethylsilyl ether[21] **4c** (*t*BDMSCl, DMF, imidazole, 67%) resulted in a chromatographically separable erythro/threo pair. Seebach et al.[22] reported that simple *O*-silylated nitro-aldol adducts were obtained with modest diastereoselectivity (>80%) by quenching the corresponding lithium nitronates with acetic acid at low temperature. Application of this procedure to the lithium nitronate of **4c** (1 equiv of LDA, THF, −78 °C) changed the erythro/threo composition of **4c** from 44:56 (vide infra) to 66:33 (95% recovery). The predominance of one isomer in the kinetic protonation experiment led to its tentative assignment as the erythro isomer, in analogy to the erythro selectivity observed by Seebach in related cases.[22] This assignment was confirmed by chemical means. Reduction of a 1:1 erythro/threo mixture of α-hydroxy-β-nitro esters **4b** gave β-amino-α-hydroxy esters **9b** (W-4 RaNi, CH_3OH, 96%), which were converted to a 1:1 mixture of *cis*- and *trans*-oxazolidones **10** (carbonyldiimidazole, THF, 55%).



erythro-**9b** *cis*-**10**

threo-**9b** *trans*-**10**

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(8) (a) Isenring, H. P.; Hofheinz, W. *Synthesis* **1981**, 385. (b) Birkofer, L.; Schramm, J. *Liebigs, Ann. Chem.* **1975**, 2195.

(9) (a) Miyazawa, T.; Akita, E.; Ito, T. *Agric. Biol. Chem.* **1976**, *40*, 1651. (b) Iriuchijima, S.; Ogawa, M. *Synthesis* **1982**, 41. (c) Ogawa, Y.; Inoue, S.; Niida, T. *Jpn. Kakai Tokkyo Koho* **1975**, *75*, 13322, (1975); *Chem. Abstr.* **1975**, *83*, P59267j. Miyazawa, T.; Akita, E. *Jpn. Kokai Tokkyo Koho* **1975**, *75*, 37723; *Chem. Abstr.* **1975**, *83*, P193732k.

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(16) Henry, *L. C. Hebd. Seances Akad. Sci.* **1895**, *120*, 1265.

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(18) (a) Schloss, J. V.; Porter, D. J. T.; Bright, H. J.; Cleland, W. W. *Biochemistry 1980*, *19*, 2358. (b) Porter, D. J. T.; Bright, H. J. *J. Biol. Chem.* **1980**, *225*, 4772.

(19) Petrakis, K. S.; Batu, G.; Fried, J. *Tetrahedron Lett.* **1983**, *24*, 3063.

(20) Kelly, T. R.; Schmidt, T. E.; Haggerty, G. *Synthesis* **1972**, 544.

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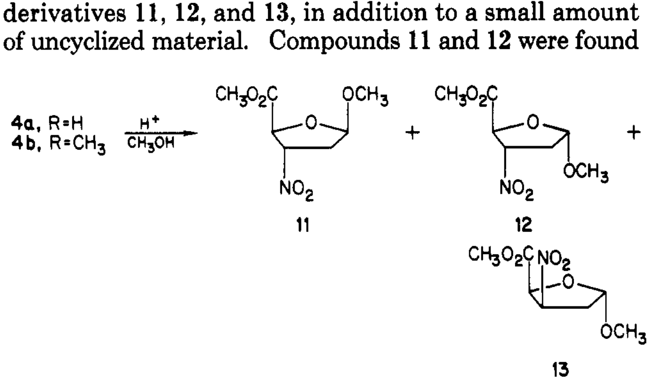
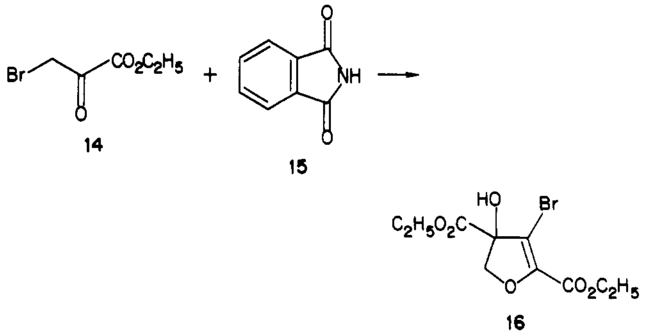
The larger $J_{4,5}$ coupling constant (8.8 Hz) was assigned to the cis isomer and the smaller (5.9 Hz) to the trans isomer, since it is known that 2-oxazolidones derived from α-amino-β-hydroxy esters exhibit larger $J_{4,5}$ coupling constants for the cis isomers (9.0–10.0 Hz) than for the trans isomers (4.0–6.0 Hz).[23] The erythro and threo derivatives **4c** were separated by column chromatography and separately converted to the corresponding β-amino-α-hydroxy esters **9b** by reduction (RaNi, CH_3OH, 69%) and desilylation (Bu_4NF, THF, 83%).[24,25] Transformation to the oxazolidones confirmed the initial stereochemical assignments. The erythro isomer **9b** produced *cis*-oxazolidone **10** ($J_{4,5}$ = 8.8 Hz), and *threo*-**9b** gave *trans*-oxazolidone **10** ($J_{4,5}$ = 5.9 Hz).

During the course of these investigations, α-hydroxy-β-nitro acid **4a** changed on standing at room temperature either as a neat oil or in solution. Based on the proton NMR spectrum, it was deduced that an internal acetal exchange was taking place with the formation of a furanose ring. When treated with acid in methanol, a 1:1 erythro/threo mixture of either **4a** or **4b** produced furanose derivatives **11**, **12**, and **13**, in addition to a small amount of uncyclized material. Compounds **11** and **12** were found to have ^1H NMR spectra identical with samples of the optically active forms of **11** and **12**, obtained by an independent synthesis from D-xylose in connection with an alternate approach to these compounds.[26] The furanose derivatives **11–13** are alternately protected forms of the acyclic analogues **4a–c**. These compounds are now available for study in aldol-type condensations, and the feasibility of reduction to the amino derivatives has been established. A diastereo- and enantioselective route to these compounds, however, would be preferred, and for these reasons we have undertaken a parallel study for the synthesis of optically active compounds **11** and **12** from carbohydrate precursors,[26] which will be described in a separate report.

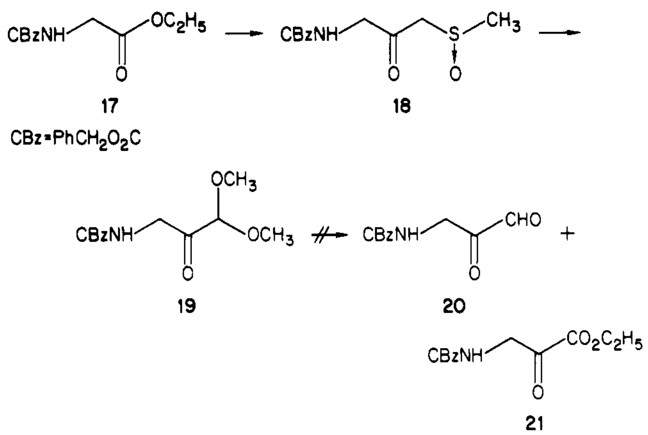


Synthesis of N-Protected β-Aminopyruvic Acids. We sought to prepare N-protected β-aminopyruvic acid derivatives which might be further alkylated in the β-position to give compounds of general structure **5**. Several routes are described below.

Reactions of Ethyl 3-Bromopyruvate. Treatment of ethyl 3-bromopyruvate (**14**) with phthalimide (**15**) and a catalytic amount of its potassium salt did not produce the desired Gabriel product but instead led to self-condensation of the bromopyruvate to give the known[27] dihydrofuran **16** (86%). Although considerable effort was expended in studying this reaction, we were unable to find conditions which directly produced the desired β-phthalimidopyruvate.



Pummerer Rearrangement of β-Sulfinyl Amides. The Pummerer rearrangement of β-keto sulfoxides is known to give α-keto aldehydes[28] and α-hydroxy esters.[29] To expand this method to the synthesis of isoserine esters and related compounds, β-sulfinyl amide **18** was prepared from ethyl *N*-(benzyloxycarbonyl)glycinate, **17**, (NaH, Me_2SO, 85%). Pummerer rearrangement of **18** (I_2, CH_3OH, reflux, 100%)[28d] led to the desired α-keto aldehyde, isolated as a mixture of the dimethyl acetal **19** and the dimethyl ketal of **19**. Hydrolysis of **19** to the free α-keto aldehyde **20**,[29,30] or oxidation[31] to the carboxylic ester **21** gave only degradation products.



Addition of Nitrogen Nucleophiles to β-Substituted α-Hydroxy Esters. Azide anion adds to ethyl glycidate (**6**) regiospecifically at the β-carbon, and subsequent hydrogenolysis yields isoserine.[12d] In a parallel reaction we found that phthalimide (**15**) adds to ethyl glycidate in the presence of a catalytic amount of base to yield exclusively the β-addition product **22** (96%). Confirmation of the β-amino-α-hydroxy structure for **22** came from the downfield shift of the methine triplet from 4.45 to 5.29 ppm upon acetylation. The oxidation of α-hydroxy ester **22** to α-keto ester **23** met with limited success. Pyridinium chlorochromate (PCC)[32a] effected oxidation in reasonable

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[23] Futagawa, S.; Inui, T.; Shiba, T. *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3308.

[24] The crude product was difficult to separate from Bu_4NF, and the actual yield is thus somewhat lower.

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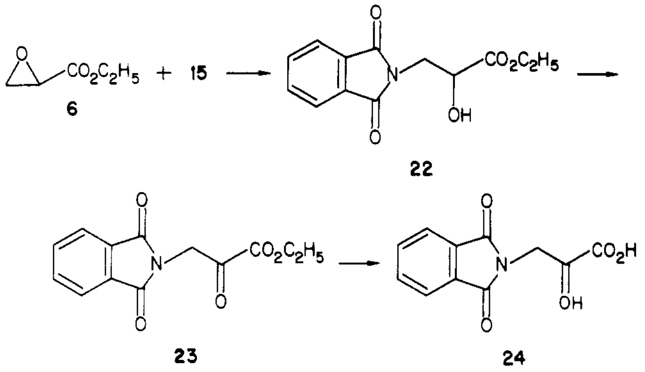
[28] (a) Russell, G. A.; Janzen, E. G.; Becker, H.-D.; Smentowski, F. J. *J. Am. Chem. Soc.* **1962**, *84*, 2652. (b) Russell, G. A.; Janzen, E. G.; Strom, E. T. *J. Am. Chem. Soc.* **1962**, *84*, 4155. (c) Moore, T. L. *J. Org. Chem.* **1967**, *32*, 2786. (d) Jung, F.; Durst, T. *J. Chem. Soc., Chem. Commun.* **1973**, 4. (e) Iriuchijima, S.; Maniwa, K.; Tsuchihashi, G. *J. Am. Chem. Soc.* **1975**, *97*, 596.

[29] Iriuchijima, S.; Ogawa, M. *Synthesis* **1982**, 41.

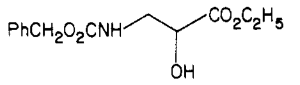
[30] (a) Huet, F.; Lechevallier, A.; Pellet, M.; Conia, J. M. *Synthesis* **1978**, 63. (b) Grieco, P. A.; Nishizawa, M.; Oguri, T.; Bourke, S. D.; Marinovic, N. *J. Am. Chem. Soc.* **1977**, *99*, 5473. (c) Ellison, R. A.; Luckenbach, E. R.; Chiu, C.-W. *Tetrahedron Lett.* **1975**, 499.

[31] (a) Hanessian, S. *Carbohydr. Res.* **1966**, *2*, 86. (b) Wright, J. B. *J. Am. Chem. Soc.* **1955**, *77*, 4883. (c) Deslongchamps, P.; Atlani, P.; Frehel, D.; Malaval, A.; Moreau, C. *Can. J. Chem.* **1974**, *52*, 3651.



yield (PCC, NaOAc, CH_2Cl_2, 66%), but only on a small (1 mmol) scale. Oxidation with potassium permanganate and copper sulfate in benzene[32b] proved capricious, with yields of **23** ranging from 0 to 80%. Swern oxidation[32c] gave low yields and incomplete conversion. Several other methods[32d–o] were unsuccessful. The α-keto ester **23** could be hydrolyzed to the acid (dilute HCl, 89%). However, further studies on the synthesis and reactions of ethyl β-phthalimidopyruvate (**23**) and acid **24** were discontinued when attempts to alkylate the lithium enolate of **23** were uniformly unsuccessul.

Several N-protected ethyl esters of isoserine, compounds **25–29**, were synthesized, but numerous attempts to oxidize these compounds[31,32] to the corresponding α-keto esters failed under a wide variety of conditions, including those which were successful for the oxidation of the phthalimido derivative **22** to **23**.



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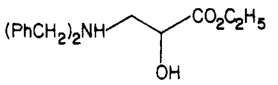

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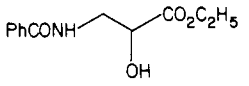

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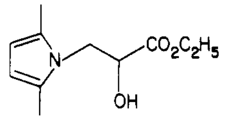

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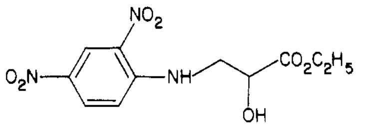

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Experimental Section

Melting points are uncorrected and were determined either in capillary on a "Meltemp" aluminum block or on a thin glass cover plate on a microscope hot stage. IR spectra were determined on a Perkin-Elmer 237 B grating instrument and major signals were recorded in cm^{-1}. Proton NMR spectra were determined on a Varian XL-100 or Nicolet 300 MHz instrument in the FT mode. NMR spectra were taken in $CDCl_3$ solvent and recorded in parts per million (ppm, δ) downfield from internal tetramethylsilane (Me_4Si) unless otherwise noted. Coupling constants are in hertz (Hz) and splitting pattern abbreviations are s, singlet; d, doublet; t, triplet, q, quartet; m, unresolved multiplet; dd, doublet of doublets; ddd, doublet of double doublets (8 signals); dq, doublet of quartets (8 signals); br, broad. Mass spectra were done on a Finnegan Model MAT-44 at 70 eV. Reactions were followed routinely by using silica gel GF thin-layer chromatography (TLC) plates (250 μ, Analtech). Preparative TLC separations were accomplished on silica gel GF plates (1000 μm, Analtech). Column chromatography refers to flash chromatography as described by Still, Kahn, and Mitra[33] and was performed on silica gel G (0.032–0.063 mm, ICN Nutritional Biochemicals).

***dl*-2-Hydroxy-3-nitropropanoic Acid (8).** The procedure of Schecter and Conrad[14] was followed using phenolphthalein in situ to maintain a slight excess of base. From 1.0 g of glyoxylic acid hydrate (11 mmol) and 5.0 mL of nitromethane (92 mmol) there was obtained 1.56 g of a light yellow oil (98% crude yield) which crystallized on standing. Recrystallization (5:2, benzene–ether) gave 1.15 g (73% purified yield) of off-white cubic crystals: mp 73–74 °C (lit.[14] mp 75–76 °C); ^1H NMR ($CDCl_3$, 300 MHz) δ 4.84 (2 H, d, *J* = 4.4 Hz), 4.75 (1 H, t, *J* = 4.4 Hz); IR (Nujol) 3400 (br), 1740, 1550, 1370 cm^{-1}.

***dl*-3-Amino-2-hydroxypropanoic Acid (Isoserine, 7).** 2-Hydroxy-3-nitropropanoic acid (**8**, 100 mg, 0.74 mmol) in methanol (40 mL) and 10% Pd/C (40 mg) were shaken together under hydrogen (2.7 atm); after 15 h, the catalyst and a fine white precipitate were removed by filtration through Celite. The methanol filtrate was discarded, and the Celite filter cake washed thoroughly with distilled, deionized water. Vacuum evaporation of the aqueous extracts left isoserine (**7**) as a powdery, white solid: 63.0 mg, 85%; mp 239–240 °C, closed capillary; decomposes with gas evolution (lit.[12c] mp 242 °C); ^1H NMR (D_2O, 300 MHz) δ 4.28 (1 H, dd, *J* = 8.32, 4.03 Hz), 3.39 (1 H, dd, *J* = 13.06, 4.04 Hz), 3.16 (1 H, dd, *J* = 13.05, 8.34 Hz). Recrystallization of this material from 30% aqueous ethanol (30% recovery) raised the melting point only slightly (240–241 °C). A mixture melting point with an authentic sample (Sigma Chemical Company, mp 240.0–240.5 °C dec) was 240–241 °C.

2-Hydroxy-3-nitro-5-oxopentanoic Acid Ethylene Acetal (4a). 3-Nitropropanal, ethylene acetal[2] (**2**, 427 mg, 2.90 mmol) in 95% ethanol (1 mL) was added to aqueous NaOH (3.8 mL, 2 N, 7.4 mmol) at 20 °C. Glyoxylic acid hydrate (320 mg, 3.48 mmol, Aldrich Chemical Company) was added in one portion and the mixture vigorously stirred for 30 min. Cold, 6 N HCl was added to pH 1.8; the solution was saturated with NaCl and then extracted with ether (4 × 25 mL). These extracts were diluted with $CHCl_3$ and dried (Na_2SO_4), and the solvents were evaporated to leave the crude product **4a** as a pale yellow oil (640 mg, 100% yield). This was a 1:1 mixture of erythro/threo forms as shown by NMR ($CDCl_3$, 300 MHz) δ 5.08 (2 H, m), 4.82 (0.5 H, d, *J* = 3.32 Hz), 4.62 (0.5 H, d, *J* = 2.83 Hz), 3.95 (4 H, m), 2.79 (0.5 H, ddd, *J* = 15.2, 6.7, 3.4 Hz), 2.76 (0.5 H, ddd, *J* = 15.2, 8.5, 3.5 Hz), 2.45 (0.5 H, ddd, *J* = 15.2, 6.6, 4.4 Hz), 2.28 (0.5 H, dt, *J* = 15.2, 4.3 Hz); IR 3450 (br), 2990, 2910, 1740, 1550, 1380 cm^{-1}. Mixture **4a** is stable in EtOAc solution at 5 °C for several days but slowly cyclizes to furan derivatives. This process was studied more on the methyl ester **4b**, vide infra.

Methyl 2-Hydroxy-3-nitro-5-oxopentanoate Ethylene Acetal (4b) from the Acid. An ether solution of the crude nitro-aldol adduct **4a** (0.95 g, 4.3 mmol) was added to an excess of diazomethane (generated from "Diazald", Aldrich Chemical Company) in ether. Excess diazomethane was destroyed with glacial acetic acid. The solvent was removed in vacuo and the residue chromatographed (30 g silica gel, 3-cm o.d. column, 30% EtOAc/hexanes) to obtain the pure methyl ester **4b** (0.77 g, 77% from **2**) as an approximately 1:1 mixture of erythro/threo isomers: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.04 (2 H, m), 4.75 (0.5 H, dd, *J* = 5.1, 3.95 Hz), 4.55 (0.5 H, dd, *J* = 6.2, 2.81 Hz), 3.94 (7 H, m includes OCH_3, s at 3.87), 3.36 (0.5 H, d, *J* = 5.6 Hz, OH), 3.26

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(0.5 H, d, J = 6.3 Hz, OH), 2.77 (1 H, m), 2.35 (0.5 H, ddd, J = 15.1, 5.7, 4.7 Hz), 2.19 (0.5 H, dt, J = 15.1, 3.9 Hz); IR 3470 (br), 2970, 2905, 1745, 1550, 1380 cm^{-1}. Anal. Calcd for $C_8H_{13}NO_7$: C, 40.85; H, 5.57, N, 5.95. Found: C, 40.96; H, 5.54; N, 5.83.

From Methyl Glyoxylate. 3-Nitropropanal ethylene acetal[2] (**2**, 216 mg, 1.46 mmol) in methanol (2 mL) was added to a stirred solution of sodium methoxide (1.2 equiv) in methanol (12 mL). Methyl glyoxylate[20] (340 mg, 2.6 equiv) in methanol (2 mL) was introduced, and the reaction was stirred at 20 °C for 12 h. Water (2 mL) was added and the mixture was acidified to pH 2 with 2 N HCl. The clear solution was saturated (NaCl) and extracted (2 × 50 mL of ether); and the combined extracts were diluted (50 mL of $CHCl_3$) and dried (Na_2SO_4), and the solvents were removed under vacuum to give an orange oil (560 mg). This oil was subjected to flash column chromatography (20 g of silica gel, 1:3 EtOAc/hexane). The desired methyl ester **4b** (270 mg, 78% yield) was identical with that prepared from the acid with diazomethane (TLC, ^{1}H NMR, IR). Starting material **2** (19 mg, 9% recovery) was also isolated. When the above reaction was carried out in ethanol instead of methanol, the transesterified ethyl ester, ethyl 2-hydroxy-3-nitro-5-oxopentanoate ethylene acetal, was isolated.

Methyl 2-[(*tert*-Butyldimethylsilyl)oxy]-3-nitro-5-oxopentanoate Ethylene Acetal (4c). Ethyl ester **4b** (173 mg, 0.736 mmol) was treated with *tert*-butyldimethylsilyl chloride[21] (250 mg, 1.65 mmol) and imidazole (120 mg, 1.76 mmol) in DMF (8 mL) (50 °C, 14 h, N_2 atmosphere). Water was added (8 mL) and the mixture was extracted (4 × 40 mL of ether); the extracts were washed (saturated NaCl, 5 mL) and dried ($MgSO_4$), and the ether was evaporated to give a clear viscous oil consisting of a 44:56 mixture of erythro/threo isomers as measured by ^{1}H NMR. Flash chromatography (12 g of silica gel, 15% EtOAc in hexane) effected clean separation of the two diastereomers. The erythro isomer eluted first: R_f 0.27; 75.6 mg, 29%; IR (neat) 2960, 2940, 2900, 2870, 1765 (1740 sh), 1560, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, benzene internal reference) δ 4.98 (2 H, m), 4.90 (1 H, d, J = 2.93 Hz), 3.90 (4 H, m), 3.78 (3 H, s), 2.79 (1 H, ddd, J = 15.60, 9.60, 3.72 Hz), 2.02 (1 H, ddd, J = 15.60, 5.16, 3.00 Hz), 0.88 (9 H, s), 0.05 (3 H, s), 0.01 (3 H, s). The threo isomer eluted second: R_f 0.20; 98.2 mg, 38%; IR (neat) 2960, 2940, 2900, 2870, 1765 (1740 sh), 1560, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.01 (2 H, m), 4.56 (1 H, d, J = 6.00 Hz), 3.92 (4 H, m), 3.81 (3 H, s), 2.65 (1 H, ddd, J = 15.40, 9.00, 3.40 Hz), 2.06 (1 H, dt, J = 15.40, 4.10 Hz), 0.88 (9 H, s), 0.08 (3 H, s), 0.06 (3 H, s). Anal. Calcd for $C_{14}H_{27}SiO_7N$: C, 48.13; H, 7.73; N, 4.01. Found: C, 48.24; H, 7.61; N, 3.94.

Low-Temperature Deprotonation/Protonation Sequence.[22] Lithium diisopropylamide, LDA, 0.40 molar solution in THF–hexane, was prepared and titrated.[34] A portion (0.40 mL, 0.160 mmol) was transferred to a flask containing THF (1 mL). This was cooled to −78 °C, and the 44:56 erythro/threo mixture of methyl 2-*tert*-butyldimethylsilyl)oxy]-3-nitro-5-oxopentanoate, ethylene ketals (38.2 mg, 0.109 mmol in 2 mL of THF) was added slowly. The pale yellow solution was stirred at −78 °C for 35 min and then cooled to −100 °C. Acetic acid in THF (0.25 mL of 1:1 mixture) was added, the yellow color disappeared, and the reaction was warmed to −85 °C over a period of 30 min. The reaction mixture was quenched with ether–water and worked up to give a yellow oil (36.1 mg, 94.5% recovery), which was found to be a 66:33 erythro/threo mixture by integration of the doublet at δ 4.56 (threo isomer) and at δ 4.90 (erythro isomer). Assignments are made by analogy to the results of Seebach et al., who found that the erythro isomer was favored by this procedure.

Methyl 3-Amino-2-hydroxy-5-oxopentanoate Ethylene Acetal (9b). Nitro alcohol **4b** (78.7 mg, 0.33 mmol) was shaken with hydrogen and W-4 Raney nickel catalyst in methanol (2.7 atm, 15 h, 20 °C). Filtration and removal of the solvent gave a yellow oil (**9b**) as a mixture of erythro/threo isomers (66 mg, 96%): IR (neat) 3660–2275 (br), 2930, 1730 (s), 1600, 1415, 1270, 1210, 1125, 1025 cm^{-1}; isolation of the individual isomers in a later experiment (vide infra) permitted deconvolution of the ^{1}H NMR ($CDCl_3$, 300 MHz) erythro δ 5.01 (1 H, t, J = 4.6 Hz), 4.20 (1 H, d, J = 3.6 Hz), 3.99 (2 H, m), 3.87 (2 H, m), 3.80 (3 H, s), 3.40 (1 H, m), 1.90 (3 H, br s), 1.80 (2 H, m), threo δ 5.02 (1 H, t, J = 4.6 Hz), 4.14 (1 H, d, J = 2.4 Hz), 3.99 (2 H, m), 3.87 (2 H, m), 3.82 (3 H, s), 3.42 (1 H, m), 1.82 (5 H, m overlapping br s).

***cis*- and *trans*-4-Carbomethoxy-5-(dioxol-2-ylmethyl)-2-oxazolidone (10).** Carbonyl diimidazole in dry THF (0.47 mL of a 0.30 M solution, 0.14 mmol) was added dropwise to the erythro/threo mixture of amino alcohol ester **9b** (28.3 mg, 0.14 mmol) in dry THF (3 mL), and the mixture was stirred (20 °C, 24 h, under argon) until TLC analysis indicated complete reaction (EtOAc elutant, less polar product R_f 0.68; starting material R_f 0.10). Removal of solvent and flash chromatography (4 g of silica gel, 10-mm o.d. column, 12:7:1 hexanes:ethyl acetate:methanol) of the residue gave a single fraction of the diastereomeric oxazolidones as a 1:1 cis/trans mixture of a clear, colorless oil (17.6 mg, 55%): IR (neat) 3340 (br), 2960, 2900, 1760 (s), 1440, 1380 cm^{-1}; later isolation of the individual isomers permitted the following assignments: ^{1}H NMR ($CDCl_3$, 300 MHz) cis isomer δ 5.83 (1 H, br s, NH), 5.04 (1 H, d, J = 8.8 Hz), 4.99 (1 H, dd, J = 5.1, 3.0 Hz), 4.34 (1 H, ddd, J = 11.0, 8.8, 1.8 Hz), 4.01 (2 H, m), 3.89 (2 H, m), 3.83 (3 H, s), 2.04 (1 H, ddd, J = 14.4, 3.0, 1.8 Hz), 1.72 (1 H, ddd, J = 14.4, 11.0, 5.1 Hz), trans isomer δ 5.76 (1 H, br s, NH), 4.98 (1 H, dd, J = 4.7, 2.2 Hz), 4.67 (1 H, d, J = 5.9 Hz), 4.13 (1 H, ddd, J = 9.1, 5.2, 3.6 Hz), 4.00 (2 H, m), 3.88 (2 H, m), 3.85 (3 H, s), 2.22 (1 H, dt, J = 14.4, 3.6 Hz), 2.02 (1 H, ddd, J = 14.4, 9.1, 2.2 Hz). Anal. Calcd for $C_9H_{13}NO_6$: C, 46.75; H, 5.62; N, 6.06. Found: C, 46.75; H, 5.63; N, 5.93.

Methyl 3-Amino-2-[(*tert*-butyldimethylsilyl)oxy]-5-oxopentanoate Ethylene Acetal (9c). The separated erythro and threo isomers of **4c** were each subjected to reduction with Raney nickel (W-4) in methanol (10 mL) under H_2 (1 atm). After 18 h of stirring at room temperature, the catalyst was removed by filtration through Celite; the methanol was evaporated, and the residue was taken up in $CHCl_3$ and dried ($MgSO_4$). Filtration and evaporation of solvent gave the 3-amino-2-(*tert*-butyldimethylsilyl) ether as an oil. For the erythro isomer, 22 mg of **4c** was converted to 12 mg of *erythro*-**9c** (60%); for the threo isomer, 35 mg of **4c** was converted to 22 mg of *threo*-**9c** (69%): IR 3380, 2940, 1760, 1410, 1140 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) erythro δ 5.02 (1 H, br t, J = 4.8 Hz), 4.14 (1 H, d, J = 4.4 Hz), 3.98 (2 H, m), 3.86 (2 H, m), 3.73 (3 H, s), 3.28 (1 H, ddd, J = 9.7, 3.5, 3.2 Hz)8 1.87 (1 H, ddd, J = 14.2, 4.9, 3.2 Hz), 1.68 (1 H, ddd, J = 14.2, 9.7, 4.7 Hz), 1.60 (2 H, br s), 0.91 (9 H, s), 0.08 (3 H, s), 0.07 (3 H, s), threo δ 5.03 (1 H, t, J = 4.4 Hz), 4.17 (1 H, d, J = 3.0 Hz), 3.98 (2 H, m), 3.86 (2 H, m), 3.74 (3 H, s), 3.32 (1 H, m), 1.80 (2 H, m), 1.40 (2 H, br s), 0.94 (9 H, s), 0.10 (3 H, s), 0.07 (3 H, s).

Methyl 3-Amino-2-hydroxy-5-oxopentanoate Ethylene Acetal (9b) from the Silyl Ether. The individual erythro and threo isomers of **9c** were separately stirred with tetra-*n*-butylammonium fluoride (TBAF, 2 equiv) in dry THF (1 mL) for 18 h. The reaction was diluted with water (1 mL) and extracted with ethyl acetate (8 × 5 mL). The combined dried ($MgSO_4$), filtered extracts were evaporated to give **9b** as an oil. For the erythro isomer, 12 mg of starting material gave 5 mg of crude *erythro*-**9b** (65%) and, for the threo isomer, 15 mg was converted to 8 mg of crude *threo*-**9b** (83%). The spectral properties of **9b** thus obtained were identical with those of **9b** reported earlier. The crude amino alcohols **9b** were each converted to the corresponding 2-oxazolidones **10** as described earlier.

Methyl (Methyl 2,3-dideoxy-3-nitro-β-DL-ribofuranosid)uronate (11), Methyl (Methyl 2,3-dideoxy-3-nitro-α-DL-ribofuranosid)uronate (12), and Methyl (Methyl 2,3-dideoxy-3-nitro-α-DL-xylofuranosid)uronate (13). Crude hydroxy acid **4a** (0.812 g, 3.71 mmol) was stirred in anhydrous HCl/CH_3OH (100 mL, 0.4 N) at room temperature for 24 h. Methanol was removed in vacuo; benzene (2 × 100 mL) was added to the residue and the benzene removed under reduced pressure. Ether was added (200 mL) and the solution was extracted with water (50 mL) until the aqueous phase tested neutral. The ether layer was dried ($MgSO_4$), filtered, and reduced in vacuo to a pale yellow oil. Column chromatography (25% acetone in hexane, 30 g of silica gel, 3-cm o.d. column) gave methyl furanoside **12** (R_f 0.34) (166 mg, 22%), methyl furanosides **11** and **13** eluting as a single band (R_f 0.26) (268 mg, 35%). **12**: IR 2940, 1730, 1550 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 5.59 (1 H, ddd, J = 8.3, 6.3, 3.4 Hz), 5.27 (1 H, dd, J = 5.0, 1.0 Hz), 5.16 (1 H, d, J = 3.4 Hz), 3.83 (3 H, s), 3.40 (3 H, s), 2.75 (1 H, ddd, J = 14.0, 6.2, 5.2 Hz), 2.56 (1 H, ddd, J = 14.1, 8.3, 1.1 Hz). Anal. Calcd for $C_7H_{11}NO_6$: C,

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40.97; H, 5.36; N, 6.82. Found: C, 40.94; H, 5.29; N, 6.52. Components **11** (less mobile) and **13** (more mobile) were separated by HPLC (Whatman Partisil M-9 10/25, 30% ethyl acetate in hexanes). **13**: IR 2960, 1760, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 5.43 (2 H, m), 4.86 (1 H, d, J = 5.9 Hz), 3.82 (3 H, s), 3.43 (3 H, s), 2.87 (1 H, ddd, J = 14.4, 5.4, 4.0 Hz), 2.47 (1 H, ddd, J = 14.4, 7.8, 2.4 Hz). **11**: IR 2960, 1760, 1560 cm^{-1}; ^{1}H NMR ($CDCl_3$, 100 MHz) δ 5.45 (1 H, d, J = 3.3 Hz), 5.25 (1 H, br d, J = 4.5 Hz), 5.05 (1 H, ddd, J = 8.7, 3.3, 2.1 Hz), 3.85 (3 H, s), 3.36 (3 H, s), 2.88 (1 H, ddd, J = 14.7, 2.1, 0.7 Hz), 2.48 (1 H, ddd, J = 14.7, 8.8, 4.7 Hz).

3-[(Benzyloxycarbonyl)amino]-1-(methylsulfinyl)-2-propanone (18). Sodium hydride (630 mg, 50% dispersion, 3.1 equiv, washed with hexane) was stirred in Me_2SO (6 mL) at 75 °C under nitrogen for 30 min. It was then cooled, THF (6 mL) was added, and the solution was cooled further to 0 °C. Ethyl benzyloxycarbonyl glycinate[28e] **17** (1 g) in 4 mL of THF was then added, keeping the reaction temperature at ca. 5 °C. After 5 min aqueous NH_4Cl solution was added and the product extracted into CH_2Cl_2. The extracts were washed (brine) and dried ($MgSO_4$), and the solvent was removed to give a crude product wich was crystallized from dichloromethane/ether: white prisms, 0.96 g (85%), mp 100 °C; ^{1}H NMR ($CDCl_3$) δ 2.69 (s), 3.95, 3.57 (AB q, J_{AB} = 13.1 Hz), 4.22, 4.13 (2 × AB q, J_{AB} = 19.8 Hz), 5.13 (s, 2 H), 5.62 (bt, NH, J = 5.5 Hz), 7.3 (5 Ar H); IR (Nujol) 3300, 1725, 1690, 1030 cm^{-1}. Anal. Calcd for $C_{12}H_{15}NO_4S$: C, 53.5; H, 5.6; N, 5.2; S, 11.9. Found: C, 53.4; H, 5.7; N, 5.1; S, 11.8.

Reaction with Methanolic Iodine.[28c] Sulfoxide **18** (200 mg) was treated with iodine (120 mg, 0.63 equiv) in methanol (4 mL) under reflux for 2 h. The solvent was then removed, and the dark residue was taken up in chloroform and washed with sodium thiosulfate solution and brine and dried ($MgSO_4$), and the solvent was removed. Careful TLC of the resulting oil (2:3 ether/hexane) gave two isolable products as colorless oils: 3-[(benzyloxycarbonyl)amino]-1,1,2,2-tetramethoxypropane (28 mg, 12%); ^{1}H NMR ($CDCl_3$) δ 3.28 (s, 6 H), 3.43 (m, 2 H), 3.51 (s, 6 H), 4.26 (s, 1 H), 5.10 (s, 2 H), 5.7–5.4 (bs, NH), 7.34 (s, 5 H); IR (liquid film) 3380, 1725 cm^{-1}. Anal. Calcd for $C_{15}H_{23}NO_6$: C, 57.5; H, 7.3; N, 4.5. Found: C, 57.3; H, 7.4; N, 4.6. The second and major product was 3-[(benzyloxycarbonyl)amino]-1,1-dimethoxy-2-propanone (**19**) (177 mg, 76%): ^{1}H NMR ($CDCl_3$) δ 3.42 (s, 6 H), 4.28 (d, 2 H, J = 5.0 Hz), 4.58 (s, 1 H), 5.12 (s, 2 H), 5.60–5.20 (bs, NH), 7.35 (s, 5 H); IR (Nujol) 3400, 1760, 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{17}NO_5$: C, 58.4; H, 6.4. Found: C, 58.2; H, 6.6. NMR studies in CD_3OD at 45–50 °C revealed that acetalization was complete in 50 min before ketalization could be detected.

Ethyl 2-Hydroxy-3-phthalimidopropanoate (22). Ethyl glycidate[35] (**6**, 200 mg) in DMF (2 mL) was added to a mixture of phthalimide (**15**, 220 mg) and potassium phthalimide (40 mg) in DMF (50 mL); the mixture was heated to 90 °C and stirred (12 h) until the epoxide was consumed as shown by TLC. The reaction mixture was diluted with water (500 mL) and extracted ($CHCl_3$, 3 × 150 mL); the extracts were washed with water (50 mL) and brine (50 mL) and dried ($MgSO_4$); and the solvent was removed under low pressure to give a yellow oil which crystallized: white needles on recrystallization from ether (435 mg, 96%); mp 82–83 °C; ^{1}H NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7.2 Hz), 2.90–3.40 (1 H, bs, OH), 3.99 (2 H, d, J = 6.3 Hz), 4.20 (2 H, q, J = 7.2 Hz), 4.45 (t), 7.63–7.83 (4 H, m, Ar H); IR (Nujol) 3450, 1770, 1730, 1720 cm^{-1}. Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.3; H, 4.9; N, 5.3. Found: C, 59.3; H, 5.0; N, 5.3.

Ethyl 2-Acetoxy-3-phthalimidopropanoate. Alcohol **22** (270 mg) was converted to the acetoxy derivative by treatment with acetyl chloride and pyridine in benzene solution (304 mg, 97%): mp 103 °C, white prisms from ether; ^{1}H NMR ($CDCl_3$) δ 1.27 (3 H, t, J = 7.2 Hz), 2.11 (3 H, s), 4.38–4.10 (4 H, m), 5.29 (1 H, t, J = 5.7 Hz), 7.69–7.92 (4 H, m); IR (Nujol) 1775, 1750, 1735, 1720 cm^{-1}. Anal. Calcd for $C_{15}H_{15}NO_6$: C, 59.0; H, 4.9; N, 4.6. Found: C, 59.0; H, 5.1; N, 4.6.

Ethyl 2-Oxo-3-phthalimidopropanoate (23). Alcohol **22** (150 mg) in CH_2Cl_2 (2 mL) was added to a stirred suspension of pyridinium chlorochromate[32a] (PCC, 322 mg, 1.5 equiv) and NaOAc (140 mg, 3 equiv) in CH_2Cl_2 (5 mL). After 16 h **22** was still present as shown by TLC, and more oxidant (322 mg) and NaOAc (140 mg) were added. After a further 4 h, 215 mg of PCC and 93 mg of NaOAc were added, and the mixture stirred for 14 h. The reaction mixture was diluted with ether and filtered twice through Florosil. The filtrate was evaporated to give a yellow oil (containing no unoxidized alcohol) which was purified by TLC (3:2 ether/hexane) and recrystallized from hexane to give white prisms (86 mg, 58%): mp 87 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (3 H, t, J = 7.1 Hz), 4.41 (2 H, q, J = 7.1 Hz), 4.99 (2 H, s), 7.27–7.92 (4 H, m); IR (Nujol) 1780, 1765, 1745, 1715 cm^{-1}. Anal. Calcd for $C_{13}H_{11}NO_5$: C, 59.8; H, 4.2; N, 5.4. Found: C, 59.9; H, 4.3; N, 5.3.

2-Hydroxy-3-phthalimidopropanoic Acid (24). Ester **23** (1 g) was stirred for 3 days at 60 °C with 1 N HCl. During this time the suspended solid dissolved. The mixture was extracted (ethyl acetate, 3 × 200 mL), the extracts were dried ($MgSO_4$), and the solvent was removed to afford white crystals which were recrystallized from methanol: 0.80 g, 89%, mp 202 °C; ^{1}H NMR (Me_2SO-d_6) δ 3.60–3.00 (bs, OH), 3.78 (2 H, d, J = 6 Hz), 4.29 (1 H, t, J = 6 Hz), 7.86 (4 H, s); IR (Nujol mull) 3450, 1775, 1755, 1700 cm^{-1}. Anal. Calcd for $C_{11}H_9NO_5$: C, 56.2; H, 3.8; N, 6.0. Found: C, 56.1; H, 4.0; N, 6.0.

Ethyl 2-Hydroxy-3-iodopropanoate. A mixture of ethyl 3-chloro-2-hydroxypropanoate[12c,36] (5 g) and NaI (9.8 g) in acetone (300 mL) was refluxed for 18 h. With due care not to lose the volatile iodo product, the usual workup gave a yellow oil which solidified and was crystallized from hexane to give white needles: 7.0 g, 88%; mp 54 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (3 H, t, J = 7.1 Hz), 3.25 (1 H, bs, OH), 3.50 (2 H, ABX, $\Delta\nu_{AB}$ = 12.3 Hz, J_{AB} = 10.6, J_{AX} = J_{BX} = 3.9 Hz), 4.22 (1 H, t, J = 3.9 Hz), 4.29 (2 H, m); mass spectrum, m/e 244 (M^+). Anal. Calcd for $C_5H_9O_3I$: C, 24.6; H, 3.7; I, 52.1. Found: C, 24.7; H, 3.7; I, 50.0.

Ethyl 3-Azido-2-hydroxypropanoate.[12d] Ethyl 2-hydroxy-3-iodopropanoate (4 g) and sodium azide (2 g) in water (1 L) were stirred at 85–88 °C for 36 h. The cooled solution was extracted with methylene chloride (4 × 200 mL), the extracts were washed with brine (1 × 100 mL) and dried ($MgSO_4$), and the solvent was removed to give a pale yellow liquid (2.11 g, 81%) which could be directly used in the synthetic sequence. A sample was obtained as a colorless liquid: bp 55 °C (65 mm); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.33 (3 H, t, J = 7.2 Hz), 3.31 (1 H, bs, OH), 3.50 (2 H, ABX, $\Delta\nu_{AB}$ = 42 Hz, J_{AB} = 12.8 Hz, J_{AX} = 3.3 Hz, J_{BX} = 4.3 Hz), 4.30 (2 H, q), 4.37 (1 H, br s); IR (liquid film) 3480, 2120, 1730 cm^{-1}; mass spectrum, m/e 160 (M + 1). Anal. Calcd for $C_5H_9N_3O_3$: C, 37.7; H, 5.7; N, 26.4. Found: C, 37.5; H, 5.8; N, 26.4.

Ethyl 3-[(Benzyloxycarbonyl)amino]-2-hydroxypropanoate (25). The azide (1.2 g) was hydrogenated over 10% Pd/C in ethanol. When the azide was completely reduced as shown by TLC (1:9 ether/benzene), the system was flushed with nitrogen and the reaction mixture was treated with benzyl chloroformate (1.28 g) and triethylamine (0.76 g). After being stirred for 12 h at room temperature, the solution was processed in the usual way to give a yellow oil. Chromatography (3:7 ether/hexane) gave the product as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.28 (3 H, t, J = 7.1 Hz), 3.30 (1 H, bs, OH), 3.58 (2 H, m), 4.24 (3 H, m), 5.10 (2 H, s), 5.15 (1 H, bt, NH), 7.35 (5 H, m); IR (liquid film) 3350, 1725. Acetylation with acetyl chloride and pyridine in benzene gave the *O*-acetyl derivative which was purified by preparative TLC (40% ether:60% hexane) to give a colorless oil (112 mg, 97%): ^{1}H NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7.1 Hz), 2.14 (3 H, s), 3.68 (2 H, t, J = 5.6 Hz), 4.20 (2 H, q, J = 7.1 Hz), 5.10 (4 H, m), 7.34 (5 H, m). Anal. Calcd for $C_{15}H_{19}NO_6$: C, 58.3; H, 6.1; N, 4.3. Found: C, 58.0; H, 6.4; N, 4.4.

Ethyl 3-(Benzoylamino)-2-hydroxypropanoate (26). By the same procedure used for making **25**, ethyl 3-azido-2-hydroxypropanoate (215 mg) was hydrogenated and the resulting amine treated with benzoic anhydride (0.43 g) and triethyl amine in ether (20 °C, 1 h) to give the benzamide **26** (380 mg, 85%) as a colorless oil. After purification by column chromatography (silica gel, 7:3 ether/hexane), a sample was distilled for analysis: bp 70 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 1.29 (3 H, t, J = 7.0 Hz), 3.84 (3 H, m), 4.21 (2 H, q, J = 7.0 Hz), 4.39 (1 H, t, J = 4.6 Hz), 6.75 (1 H, br s, NH), 7.45 (3 H, m), 7.75 (2 H, m). Anal. Calcd for

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$C_{12}H_{15}O_4N$: C, 60.74; H, 6.37; N, 5.91. Found: C, 60.6; H, 6.4; N, 5.9.

Ethyl 3-(Dibenzylamino)-2-hydroxypropanoate (27). By the same procedure used for making **25**, ethyl 3-azido-2-hydroxypropanoate (1 g) was hydrogenated and the resulting crude ethyl isoserinate treated with benzyl bromide (1.2 g, 1.1 equiv for monobenzylation). The product isolated after the usual workup was ethyl 3-(dibenzylamino)-2-hydroxypropanoate as a colorless oil (827 mg, 42%) instead of the monobenzyl derivative: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.21 (3 H, t, J = 7.1 Hz), 2.94 (2 H, ABX, $\Delta\nu_{AB}$ = 29.7 Hz, J_{AB} = 14.0 Hz, J_{AX} = 3.9 Hz, J_{BX} = 6.9 Hz), 3.2–3.4 (1 H, bs, OH), 3.63 (2 H, AB, $\Delta\nu_{AB}$ = 70.1 Hz, J_{AB} = 13.6 Hz), 4.12 (2 H, m), 5.19 (1 H, dd, J = 6.9, 3.9 Hz), 7.35 (10 H, m); IR (liquid film) 3500, 1730 cm^{-1}. Repetition with 2.1 equiv of benzyl bromide for 12 h gave the product in 76% yield. The *O*-acetyl derivative of **27** was obtained (82% yield) by treating with acetyl chloride and pyridine: oil, bp 90 °C (0.05 mm); ^{1}H NMR ($CDCl_3$) δ 1.18 (3 H, J = 7.1 Hz), 2.10 (3 H, s), 2.98, 2.90 (d AB q, 2 H, J_{AB} = 14.0, J_{AX} = 7.0 Hz, J_{BX} = 4.0 Hz), 3.76, 3.49 (AB q, 4 H, J_{AB} = 13.6 Hz), 4.15, 4.07 (q, AB q, 2 H, J_{AB} = 10.7 Hz)8, 5.19 (dd, 1 H), 7.32–7.19 (m, 10 H). Anal. Calcd for $C_{21}H_{25}NO_4$: C, 71.0; H, 7.0; N, 3.9. Found: C, 70.9; H, 7.0; N, 3.9.

Ethyl 3-(2,5-Dimethylpyrryl)-2-hydroxypropanoate (28). The azide (0.4 g) in ethanol was hydrogenated as before. The catalyst was removed by filtration and the solution of ethyl isoserinate diluted with toluene (200 mL). A few drops of glacial acetic acid were then added, and the volume was reduced to 10 mL at room temperature. Toluene (250 mL) was then added and hexane-2,5-dione (10.6 g) introduced.[37] Water was azeotroped from the refluxing mixture over a 2-h period. Workup in the standard manner gave an oil which was distilled: 0.4 g, 75%, bp 65 °C (0.1 mm). This material crystallized and was recrystallized from hexane: white needles, mp 58 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, J = 7.3 Hz), 2.24 (s, 6 H), 2.81 (d, J = 5.6 Hz, OH), 4.14, 3.96 (d, AB q, J_{AB} = 14.8 Hz, J_{AX} = 4.06 Hz, J_{BX} = 8.33 Hz), 4.29, 4.25 (q, AB q, J_{AB} = 10.9 Hz), 4.34 (ddd, 1 H), 5.79 (s, 2 H); IR (liquid film) 3450, 1725–1750 cm^{-1}. Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.6; H, 8.1; N, 6.6. Found: C, 62.5; H, 8.1; N, 6.6. This material rapidly deteriorates in solution and more slowly as the solid in air.

Ethyl 3-[(2,4-Dinitrophenyl)amino]-2-hydroxypropanoate (29). The azide (0.3 g) was converted to ethyl isoserinate as in the synthesis of **25**. This was treated with 2,4-dinitrofluorobenzene[38] (0.35 g) in ether. After the standard workup procedure, the crude product was purified by column chromatography (1:1 ether/hexane) and recrystallized from ether/hexane to give yellow prisms (0.46 g, 81%): mp 122 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (t, J = 7.1 Hz), 3.26 (d, OH, J = 4 Hz), 3.86, 3.80 (2 d, AB q, J_{AB} = 13.5 Hz), 4.30 (q), 4.51 (ddd, J_{AX} = 3.0 Hz, J_{BX} = 4.4 Hz), 7.09 (d, 1 H, J = 9.5 Hz), 8.29 (dd, 1 H, J = 2.6 Hz), 0.82 (bt, NH, J = 4.5 Hz), 9.13 (d); IR (Nujol mull) 3540, 3340, 1730 cm^{-1}. Anal. Calcd for $C_{11}H_{13}N_3O_7$: C, 44.1; H, 4.3. Found: C, 44.2; H, 4.3.

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Registry No. **2**, 82891-99-4; *erythro*-**4a**, 93715-55-0; *threo*-**4a**, 93715-56-1; *erythro*-**4b**, 93715-57-2; *threo*-**4b**, 93715-58-3; *erythro*-**4c**, 93715-59-4; *threo*-**4c**, 93715-60-7; **6** (R = C_2H_5), 4660-80-4; **7**, 632-12-2; **8**, 74612-09-2; *erythro*-**9b**, 93715-61-8; *threo*-**9b**, 93715-62-9; *erythro*-**9c**, 93715-63-0; *threo*-**9c**, 93715-64-1; *cis*-**10**, 93715-65-2; *trans*-**10**, 93715-66-3; **11**, 93715-67-4; **12**, 93715-68-5; **13**, 93715-69-6; **15**, 85-41-6; **17**, 1145-81-9; **18**, 82508-27-8; **19**, 93715-70-9; **22**, 93715-71-0; **23**, 90175-96-5; **24**, 4403-39-8; **25**, 93715-72-1; **25** *O*-acetyl deriv, 93715-73-2; **26**, 93715-74-3; **27**, 93715-75-4; **27** *O*-acetyl deriv, 93715-76-5; **28**, 93715-77-6; **29**, 93715-78-7; Me_2SO, 67-68-5; glyoxylic acid, 298-12-4; nitromethane, 75-52-5; methyl glyoxylate, 922-68-9; *tert*-butyldimethylsilyl chloride, 18162-48-6; carbonyl diimidazole, 530-62-1; 3-[*N*-(benzyloxycarbonyl)amino]-1,1,2,2-tetramethoxypropane, 93715-79-8; potassium phthalimide, 1074-82-4; ethyl 2-acetoxy-3-phthalimidopropanoate, 93715-80-1; ethyl 2-hydroxy-3-iodopropanoate, 93715-81-2; ethyl 3-chloro-2-hydroxypropanoate, 93715-82-3; ethyl 3-azido-2-hydroxypropanoate, 93715-83-4; benzyl chloroformate, 501-53-1; ethyl 3-amino-2-hydroxypropanoate, 93715-84-5; benzyl bromide, 100-39-0; acetyl chloride, 75-36-5; benzoic anhydride, 93-97-0; hexane-2,5-dione, 110-13-4; 2,4-dinitrofluorobenzene, 70-34-8.

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