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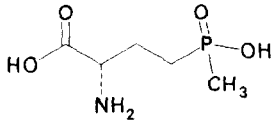
FACILE SYNTHESIS OF D,L-PHOSPHINOTHRICIN FROM METHYL 4-BROMO-2-PHTHALIMIDOBUTYRATE

E. W. Logusch

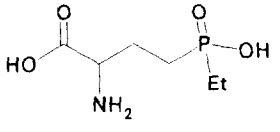
Monsanto Agricultural Company
800 North Lindbergh Boulevard
St. Louis, Missouri 63167

Summary: Synthetic versatility of the title bromide is illustrated by simple preparations of D,L-phosphinothricin, D,L-2-amino-4-phosphonobutyric acid, and aminocyclopropanecarboxylic acid.

Phosphinothricin, 1, is a naturally occurring phosphinic acid analog of L-glutamate possessing unique antibiotic[1] and herbicidal[2] properties. Its activity has been attributed to an ability to inactivate the enzyme glutamine synthetase (EC 6.3.1.2), thus blocking in vivo ammonia incorporation into amino acids and pyrimidines.[3] Phosphinothricin was first isolated from two different streptomycete species,[1,4] although the racemic P-ethyl analog 2 was prepared considerably earlier by Mastalerz and with remarkable prescience was shown to inhibit glutamine synthetase.[5]



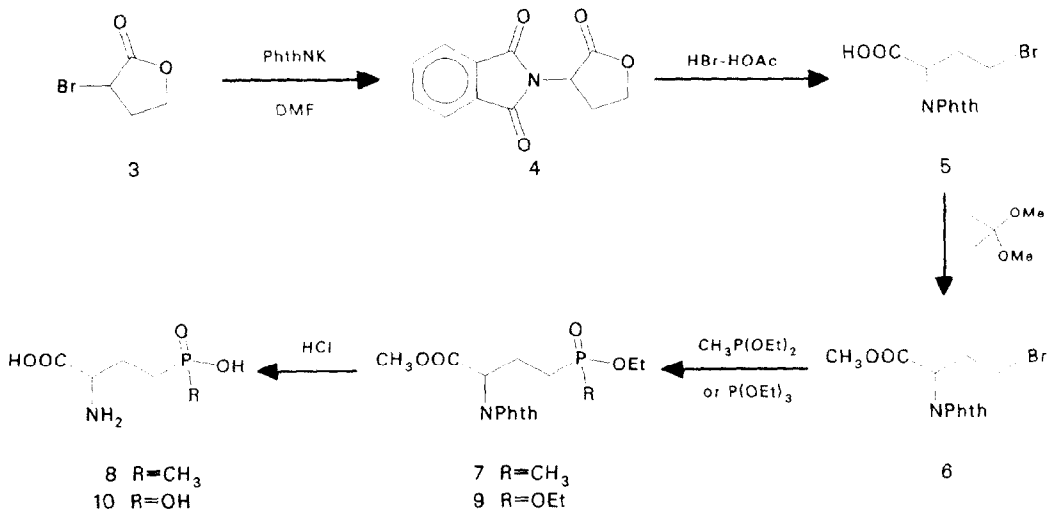
PHOSPHINOTHRICIN, 1



2

Most syntheses[6] of 1 or its racemate have employed a glycine enolate equivalent either for alkylation with 2-haloethylphosphinates or for conjugate addition to vinylphosphinates.[7] Dialkyl methylphosphonites have also been utilized for conjugate addition or Michaelis-Arbuzov reaction with unsaturated or halogenated carbonyl compounds, followed by conversion to the amino acid.[8] For our own purposes we required a protected 2-amino-4-bromobutyrate as a common precursor for the generalized synthesis of 4-heteroatom substituted 2-aminobutyrates such as 1, and we report herein that readily available methyl 4-bromo-2-phthalimidobutyrate is a convenient intermediate for the efficient synthesis of D,L-phosphinothricin and analogs.

SCHEME 1



3 4 5 6

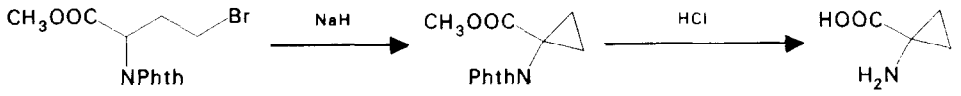
8 R=CH_3
10 R=OH

7 R=CH_3
9 R=OEt

Reaction of a slight excess of 2-bromo-4-butyrolactone 3 (Scheme 1) with potassium phthalimide in dimethylformamide at 100° gave lactone 4 almost quantitatively after precipitation from water,[9] containing some phthalimide but usable in the next step. Pure 4 could be obtained in 75% yield by two recrystallizations from water-acetone, m.p. 173-176°. This material was dissolved in HBr-acetic acid and allowed to stand for 24 hours, affording bromoacid 5 in 95% yield as large prisms, m.p. 121-123°, after evaporation of solvent, decolorization with neutral charcoal in ether-hexane and crystallization. Esterification of 5 with 2,2-dimethoxypropane in 10/1 methanol-acetyl chloride, followed by workup with aqueous bicarbonate, gave methyl 4-bromo-2-phthalimidobutyrate 6 as an orange oil sufficiently pure for subsequent reactions; decolorization with neutral charcoal in ether-hexane and crystallization afforded pure 6 in 80% yield as large prisms, m.p. 41-43°.

Synthesis of D,L-phosphinothricin was readily accomplished as follows. Reaction of 6 with an excess of diethyl methylphosphonite in dry toluene at 100° under an inert atmosphere was monitored by NMR until the disappearance of starting bromide; solvent was evaporated and the residue heated at 80° and 1 mm Hg to remove volatile phosphinates. MPLC chromatography of the crude product on silica gel using 4/1 ethyl acetate-isopropanol gave pure 7 as a colorless oil in 90% yield. Phosphinate 7 was heated at reflux for 12 hours in 10/1 6N hydrochloric acid-acetic acid; removal of precipitated phthalic acid, evaporation of solvents and treatment of the residue with 2 eq. propylene oxide in cold ethanol gave a precipitate which was collected, azeotroped with water and evacuated at elevated temperature to give pure D,L-phosphinothricin, 8, in 85% yield as a white foam.

SCHEME 2



6 11 ACC, 12

Use of neat triethyl phosphite in the Michaelis-Arbuzov reaction of 6 (Scheme 1) afforded the corresponding phosphonate 9, which was similarly hydrolyzed to give D,L-2-amino-4-phosphonobutyric acid 10[7,10] in 70% overall yield. The latter compound is a well known antagonist of glutamate-mediated neurotransmission;[11] it is only a weak competitive inhibitor of glutamine synthetase.[12]

A further application of bromide 6 is demonstrated by its facile conversion to aminocyclopropanecarboxylic acid (ACC),[13] biogenetic precursor of the ubiquitous plant hormone ethylene.[14] Exposure of 6 to an equivalent of sodium hydride in tetrahydrofuran for 12 hours (Scheme 2), followed by aqueous workup and crystallization from ether-hexane, furnished cyclopropane 11 as tiny needles in 87% yield, m.p. 139-141°. Treatment of 11 with refluxing 6N hydrochloric acid for 6 hours, followed by removal of precipitated phthalic acid, evaporation of solvent and recrystallization from water-acetone, afforded pure ACC hydrochloride as colorless prisms in 95% yield, m.p. 220-222°. Exposure of the latter to a suspension of slightly basic Dowex WGR-2 resin in water, followed by filtration, evaporation of solvent and recrystallization from water-ethanol, furnished pure ACC, 12, as small plates in 91% yield, m.p. 231-233°.[15]

References and Notes

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15. All compounds had spectral data consistent with assigned structures and gave satisfactory elemental analyses. ^{1}H NMR spectra (60 MHz) were recorded on a Varian EM 360 spectrometer. Shifts reported as ppm downfield from tetramethylsilane. ^{31}P NMR spectra (40 MHz) were recorded on a JEOL FX-100 fourier transform spectrometer using proton irradiation and external deuterium lock. Shifts reported as ppm downfield from 85% H_3PO_4. 6 ^{1}H ($CDCl_3$): 2.77 (2H,q,J=3.5), 3.32 (1H,m), 3.52 (1H, m), 3.72 (3H,s), 5.15 (1H,t,J=3.5), 7.78 (4H, m). 7 ^{1}H ($CDCl_3$): 1.30 (3H,t,J=3), 1.50 (3H,d,J=7), 1.65-2.80 (4H,m), 3.75 (3H,s), 4.10 (2H,quin,J=3), 4.95 (1H,t,J=3.5), 7.92 (4H,m). 7 ^{31}P ($CDCl_3$): 54.25. 9 ^{1}H ($CDCl_3$): 1.30 (6H,t,J=3), 1.35-2.87 (4H,m), 3.72 (3H,s), 4.08 (4H,quin,J=3), 4.87 (1H,t,J=3), 7.80 (4H,m). 9 ^{31}P ($CDCl_3$): 30.08. 11 ^{1}H ($CDCl_3$): 1.60 (4H,dd-dd,J=9/3,15/5), 3.60 (3H,s), 7.65 (4H,m). Analysis of 6 ($C_{13}H_{12}Br_1N_1O_4$): calculated, C 47.87, H 3.71, N 4.29; found, C 47.98, H 3.72, N 4.28. Analysis of 7 ($C_{16}H_{20}N_1O_6P_1$ + 1.2 H_2O): calculated, C 51.26, H 6.02, N 3.74; found, C 51.25, H 5.73, N 3.60. Analysis of 9 ($C_{17}H_{22}N_1O_7P_1$ + 0.6 H_2O): calculated, C 51.80, H 5.93, N 3.55; found, C 51.78, H 5.67, N 3.56. Analysis of 11 ($C_{13}H_{11}N_1O_4$): calculated, C 63.67, H 4.52, N 5.71; found, C 63.68, H 4.56, N 5.67.

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