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SYNTHESIS OF 2,4-METHANOPROLINE

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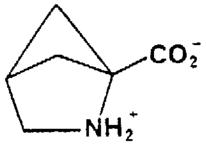
Abstract: An efficient synthesis of 2,4-methanoproline from serine is described. The cyclobutane is formed by a sensitized intramolecular [2+2] photoaddition.

We recently reported, in collaboration with other groups, the isolation and structural elucidation of two amino acids from the seeds of Atelia herbert smithii.[1] Interest in these compounds was originally stimulated by their possible role in protecting seeds from insect predation. Full biological testing was hampered by lack of material, consequently we wish to report an efficient synthesis of one of these amino acids, 2,4-methanoproline (1), by a photochemical route.



1

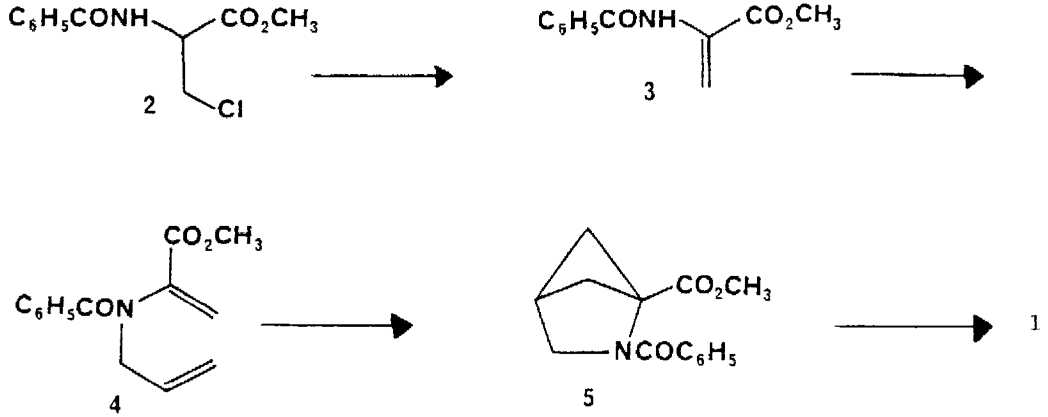
2,4-Methanoproline 1 is the only member of the 2-azabicyclo[2.1.1]hexane system and represents an interesting, achiral proline analog. We believed that formation of the 2-azabicyclo[2.1.1]hexane system in 1 might best be accomplished by sensitized intramolecular [2+2] photoaddition of an appropriate diene.[2]

Thus serine was converted by known procedures to methyl-2-benzamido-3-chloropropionate (2) in 83% yield.[3] Compound 2 was converted to the dehydroamino acid derivative (3)[4] by dehydrochlorination with potassium t-butoxide in THF at -78°C. This enoate was N-alkylated using potassium t-butoxide followed by 20 equivalents of allyl bromide and allowing the solution to warm to room temperature. A better overall yield of (4)[5] resulted if these operations were combined and 2 was added directly to a -78°C THF solution of 2.1 equivalents of potassium t-butoxide, followed by allyl bromide and warming to room temperature. In this fashion 94% isolated yields of diene 4 could be obtained.

A 2% benzene solution of diene 4 containing 0.2% acetophenone was photolysed for 10 hours using a 450W Hanovia medium pressure mercury lamp.[6] The reaction mixture was concentrated to an oil and chromatographed (silica, hexanes/ethyl acetate, 3/2) to give photoadduct (5)[7] in 87% yield from diene 4.

The protected amino acid 5 was refluxed in 6N HCl for four hours, concentrated and passed through Amberlite IR-45, OH form, to give 1 quantitatively from 5. The overall yield of this sequence is 68% from serine.

The synthetic material was identical with the natural 2,4-methanoproline by ^{1}H NMR, ^{13}C NMR, TLC (silica, n-BuOH/AcOH/H_2O, 3/1/1, R_f = 0.25) and had identical crystallographic lattice parameters.[8]



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References and Notes:

1. E.A. Bell, M.Y. Qureshi, R.J. Pryce, D.H. Jansen, P. Lemke and J. Clardy, J. Am. Chem. Soc., 1980, 102, 1409-1412.
2. For a review of bicyclo[n.1.1]alkanes see J. Meinwald and Y. Meinwald, "Advances in Alicyclic Chemistry", H. Hart and G.J. Karabatsos, Eds., Academic Press Inc., New York, New York, 1966, vol. 1, pp.1-51.
3. E.P. Painter, J. Am. Chem. Soc., 1947, 69, 229-232. 2: mp 114.5-115; 90 MHz NMR ($CDCl_3$) δ 3.85 (3H, s) 4.04 (2H, dd, J=6.0, 6.8 Hz), 5.2 (1H, m, J=6.0, 6.8, 15 Hz), 7.4-8.0 (5H, m), 6.93-7.20 (1H, br d, J=15Hz); MS m/z 241, 206, 182, 105 (base).
4. 3: IR (neat) 1739, 1695 cm^{-1}; 90 MHz NMR ($CDCl_3$) δ 3.87 (3H, s), 5.95 (1H, br s), 7.15 (1H, s), 7.4-8.0 (5H, m); HRMS gave the molecular ion as $C_{11}H_{11}NO_3$.
5. 4: IR (neat) 1773, 1669-1626 cm^{-1}; 90 MHz NMR δ 3.90 (3H, s), 4.26 (2H, d, J=12Hz, additional small splitting), 5.08 (1H, br s), 5.23 (1H, d, J=12 Hz, additional small splitting), 5.63 (1H, s), 6.02 (1H, s), 5.60-6.2 (1H, m), 7.23- 7.67 (5H, m); HRMS gave the molecular ion as $C_{14}H_{15}NO_3$.
6. R.H.S. Liu, Tetrahedron Lett., 1966, 2159-2165.
7. 5: IR (KBr) 1754, 1620 cm^{-1}; 90 MHz NMR δ 1.80 (2H, d, J=6Hz, additional small splitting), 2.10-2.30 (2H, br m), 2.73-2.87 (1H, br m), 3.57 (2H, br s), 3.82 (3H, s), 7.4-7.93 (5H, br m); HRMS gave the molecular ion as $C_{14}H_{15}NO_3$.
8. 1: mp 226-227 dec.; A typographical error occurred in the original report of the ^{1}H NMR (ref. 1). The chemical shift labeled δ 1.17 should be δ 1.71. The mass spectrum of our synthetic material was markedly different from that of the natural product samples originally submitted for mass spectral analysis. Synthetic material exhibited major peaks at m/z 127, 109, 82, 81, 80, 68, 54 and 41 and no signal (less than 2%) at m/z 146 and 87. We feel that m/z 146 and 87 may arise from an impurity in the natural samples. In our TLC system (see text) we were able to detect a minor ninhydrin positive contaminant at R_f=0.43. HRMS of our synthetic material gave the molecular ion as $C_6H_9NO_2$.

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