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TOTAL SYNTHESIS OF 2,4-METHANOPROLINE

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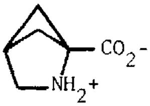
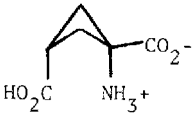
Abstract: The total synthesis of 2,4-methanoproline is achieved utilizing as the key step an intramolecular [2 + 2] photocycloaddition.

A common defense used by legume species against predatory insects is the incorporation of non-protein, potentially toxic amino acids into their seeds. Over 100 predators ignore the seeds of the Costa Rican tree Ateleia herbert smithii Pittier, and the search for the substances responsible led to the isolation[1] of 2,4-methanoproline (1) and 2,4-methanoglutamic acid (2). In this communication we report the total synthesis of 1 by an interesting, brief route involving an intramolecular [2 + 2] photocycloaddition.[2,3]



1



2

The 2-azabicyclo[2.1.1]hexane ring system found in 1 would seem to be available by [2 + 2] cycloaddition of an appropriate vinyl allyl amine. In fact, such a cycloaddition has been reported by Tamura to yield 3.[4] Furthermore, the intramolecular cycloaddition would be required to occur in this case on an unsaturated ester. Examples of [2 + 2] reactions of unsaturated esters are also known.[5] With these precedents in mind, the plan was executed as described below.[6]

3

N-acetyl-N-allyl-dehydroalanine ethyl ester (4) is produced by the condensation of ethyl pyruvate with allylamine and acetyl chloride in 22% yield.[7] On irradiation in acetone (300 nm in Rayonet reactor, 10^{-2} M), 4 undergoes a slow isomerization to 5[7], isolated in 55% yield after a combination of column and preparative gas chromatography. On the other hand, irradiation in ether leads to 5 plus an isomeric material which comprises 17% of the photoproduct. Its spectral data[7] lead us to tentatively propose structure 6, in which intramolecular Paterno-Buchi reaction has occurred. To our knowledge, this result is unprecedented!

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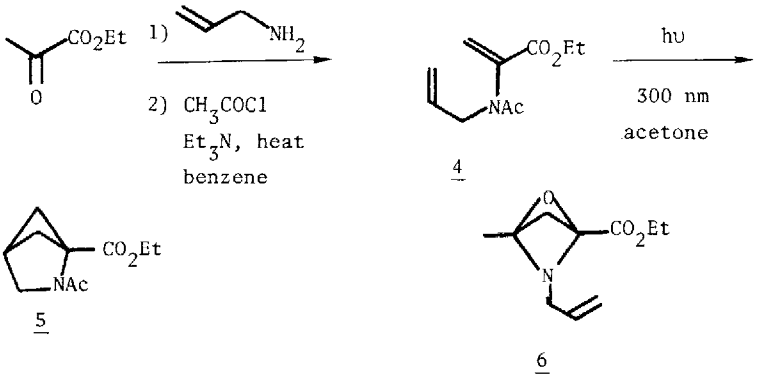
The conversion of 5 to 2,4-methanoproline is easily accomplished in refluxing aqueous KOH in 72% yield. The material obtained possesses spectral and chromatographic properties identical to those described in Ref. 1[8]. Though the yields in this synthesis are not optimum, the route is direct and is conceptually applicable to 2 as well.



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References and Notes

1. E. Bell, M. Qureshi, R. Pryce, D. Janzen, P. Lemke, and J. Clardy, J. Am. Chem. Soc., 102, 1409 (1980).

2. We recently applied such a cycloaddition to the total synthesis of isocomene: Ibid., 101, 7130 (1979).

3. A very similar route to this class of molecules has been applied to the total synthesis of 1: J. Clardy, private communication.

4. Y. Tamura, H. Ishibashi, M. Hirai, Y. Kita, and M. Ikeda, J. Org. Chem., 40, 2702 (1975).

5. H. Kosugi, S. Sekiguchi, R. Sekita, and H. Uda, Bull. Chem. Soc. Jap., 49, 520 (1976). M. Brown, J. Org. Chem., 33, 162 (1968).

6. Experimental details may be found in: M. Pirrung, Ph. D. Thesis, University of California, Berkeley, 1980.

7. 4: ^{1}H NMR ($CDCl_3$): δ1.30 (3H, t, J=7), 1.97 (3H, s), 4.00 (2H, br d, J=6), 4.10 (2H, q, J=7), 5.00 (2H, m), 5.60 (2H, m), 6.33 (1H, m). IR (thin film): 1720, 1665, 1625 cm^{-1}. UV (Et_2O) λ_{max}<200 nm, long tail, log ε_{200}=4.22, log ε_{300}=1.83. 5: ^{1}H NMR ($CDCl_3$): δ1.32 (3H, t, J=7), 1.70(2H, dd, J=2,5), 2.00 (3H, s), 2.05 (2H, m), 2.77 (1H, br t, J=2), 3.46 (2H, br s), 4.17 (2H, q, J=7). IR (thin film): 1740, 1660 cm^{-1}. 6: ^{1}H NMR ($CDCl_3$): δ1.32 (3H, t, J=7), 1.60 (3H, s), 2.76 (1H, d, J=14), 3.18 (1H, d, J=14), 3.90 (2H, overlapping dd's, J= 7, 13), 4.20 (2H, q, J=7), 5.20 (2H, m), 5.80 (1H, m). IR (CCl_4): 1755, 1740 cm^{-1}.

8. An error appeared in the spectral data originally published for 1. The resonance reported as δ1.17 should be δ1.71. Comparison spectra confirm this error.

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