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A TOTAL SYNTHESIS OF (±)-allo-KAINIC ACID

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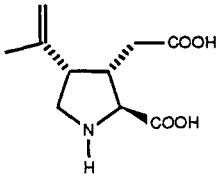
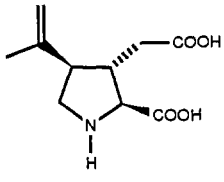
ABSTRACT A total synthesis of (±)-allo-kainic acid is outlined. The strategy incorporates a [3+2] dipolar cycloaddition of an azomethine ylid to establish the requisite pyrrolidine stereochemistry.

The neuroexcitory amino acids kainic acid (KA, 1) and allo-kainic acid (a-KA, 2) were isolated from the Japanese alga Diginea simplex Ag.[2] KA and a-KA have been shown to selectively block neuronal processes and are valuable tools in the study of neurofunctioning.[3] KA also possesses potent anthelminthic and insecticidal activities.[2] The unique biological activities associated with these natural products have led to the development of several strategies for their total synthesis.[4,5]



1



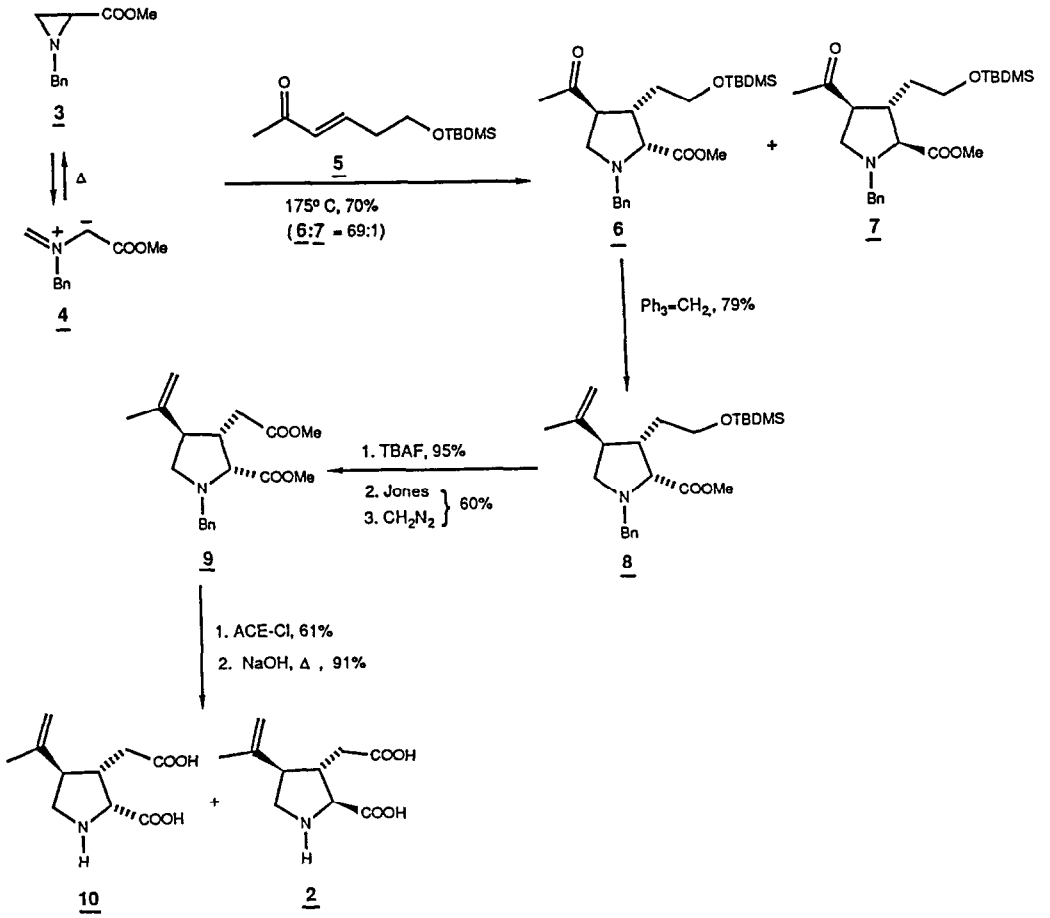
2

We had previously reported a regio- and stereoselective strategy for the preparation of highly functionalized pyrrolidines employing a [3+2] dipolar cycloaddition of azomethine ylids and electron-deficient alkenes.[6] This strategy appeared to be ideally suited for application to the total synthesis of KA (1) and a-KA (2). In this paper, we report the synthesis of pyrrolidine 9 by an intermolecular azomethine ylid cycloaddition and the elaboration of 9 into (±)-allo-kainic acid (2).

Dipolar cycloaddition of a toluene solution of aziridine 3 and enone 5 proceeded in a sealed tube at 175°C to give pyrrolidines 6 and 7 (6:7=69:1) in 70% yield (Scheme 1).[6,7] Wittig olefination of 6 (79%) introduced the C-4 isopropenyl moiety (8[7]), and the oxidation state of the C-3 substituent was adjusted by removal of the silyl protecting group with fluoride (95%) followed by oxidation of the primary alcohol with Jones reagent and reaction with diazomethane (60%) to produce pyrrolidine diester 9.[8] Removal of the N-benzyl substituent was accomplished by treatment of 9 with α-chloroethyl chloroformate (ACE-Cl) according to the method of Olofson.[9]

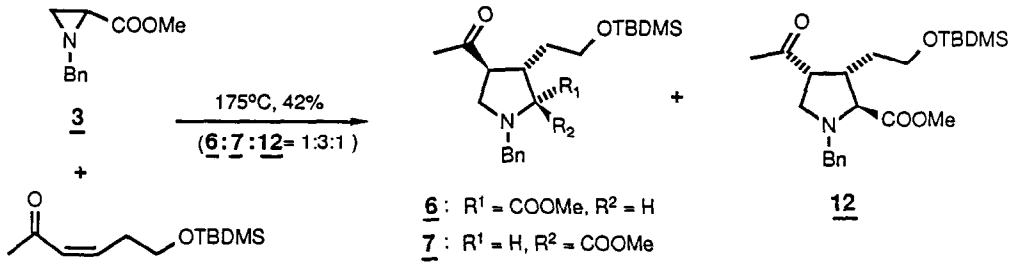
Kraus had previously reported that the C-2 configuration of pyrrolidine derivatives such as 9 could be epimerized under basic conditions to give the a-KA relative configuration.[4c] When these conditions were applied to hydrolysis of the N-ACE dimethyl ester, a 1:1 mixture of allo-kainic acid (2)[10] and 2-epi-allo-kainic acid (10)[11] was obtained (Scheme 1).

Scheme 1



We have also investigated the application of the azomethine ylid technology to the total synthesis of kainic acid (1), and the results are outlined in Scheme 2. This strategy had particular appeal since subsitution of Z-enone 11 for E-enone 5 as the dipolarophilic component in the cycloaddition was expected to result in formation of a pyrrolidine having the requisite C-3,C-4 syn-stereochemistry of KA (1). After extensive experimentation, however, we found that cycloaddition of aziridine 3 and Z-enone 11 in toluene solution in a sealed tube at 175°C for 55 h gave only a 42% combined yield of adducts 6, 7, and 12 (6:7:12=1:3:1). The presence of pyrrolidines 6 and 7 which bear the anti-3,4-relationship of substituents suggested that enone 11 had undergone isomerization of alkene geometry prior to cycloaddition. Subsequent experiments confirmed that isomerization of Z-enone 11 occurred at a rate which was competitive with the rate of cycloaddition. Therefore, the approach to the synthesis of kainic acid (1) was abandoned.

Scheme 2



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References and Notes

1. Current address: Department of Chemistry and Biochemistry, The University of Maryland, College Park, MD 20742.

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5. Analogs of KA and allo-KA have also been prepared: Allan, R. D. Tetrahedron Lett. 1978, 2199. Goldberg, O.; Luini, A.; Teichberg, V. I. ibid. 1980, 21, 2355. Muruyama, K.; Morimura, S.; Nakamura, Y.; Sunagawa, G. J. Pharm. Soc. Jpn. 1965, 85, 757. Kennewell, P. D.; Mathura, S. S.; Taylor, J. B.; Sammes, P. G. J. Chem. Soc., Perkin I. 1980, 2542.

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7. All reported compounds gave IR, ^{1}H NMR, and MS data consistent with the proposed structure.

8. Spectral data for pyrrolidine 9: IR (CCl_4): 1740 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ 7.25 (m, 5H), 4.78 (s, 1H), 4.76 (s, 1H), 3.82 (d, J=13.1 Hz, 1H); 3.62 (s, 3H), 3.60 (s, 3H), 3.58 (d, J=3.1 Hz, 1H), 3.30 (d, J=7.9 Hz, 1H), 2.84 (m, 2H), 2.60 (t, J=7.8 Hz, 1H), 2.41 (m, 3H), 1.74 (s, 3H). MS calcd. for $C_{19}H_{25}NO_4$: 331.1783, Found: 331.1790.

9. Olofson, R. A.; Martz, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, T. J. Org. Chem. 1984, 49, 2081.

10. Racemic allo-KA was identical chromatographically and spectroscopically (200 MHz ^{1}H NMR) with natural allo-KA furnished by Professor Ohfune.

11. Spectral data for 2-epi-allo-kainic acid (10): ^{1}H NMR (D_2O): δ 4.44 (t, 1H, J=1.5 Hz), 4.40 (br s, 1H), 3.63 (d, 1H, J=10.1 Hz), 3.15 (dd, 1H, J=7.0, 11.6 Hz), 2.57 (dd, 1H, J=9.8, 11.6 Hz), 2.13 (m, 2H), 1.96 (m, 2H), 1.88 (m, 2H), 1.16 (s, 3H).

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