1-Amino-2-oxo-3-oxabicyclo[3.1.0]hexane (2,3-Methanohomoserine Lactone), a Conformationally Constrained Amino Acid

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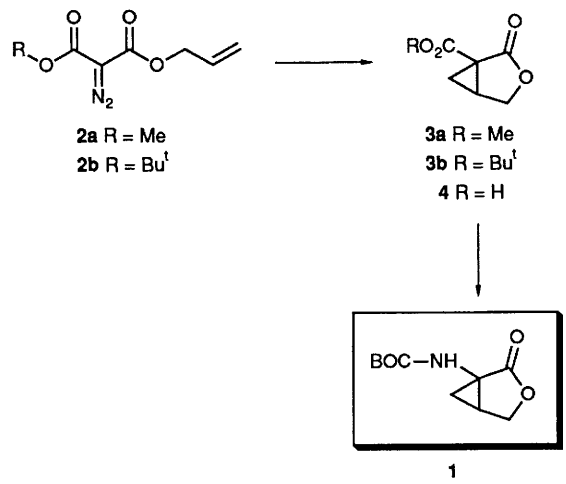
A rapid high yielding synthesis of *N*-t-butoxycarbonyl-1-amino-2-oxo-3-oxabicyclo[3.1.0]hexane is described; the synthesis relies on an intramolecular carbenoid reaction of an appropriate malonate derivative followed by Curtius degradation to give the unprotected amino group.

Conformationally constrained peptide analogues have recently become of importance in the study of bioactive peptides.[1] Cyclopropane analogues of amino acids exhibit particularly favourable characteristics in this respect.[2] Some congeners are also of natural origin,[3] and other applications for receptor binding studies[4] and elucidation of ethylene biosynthesis[5] have been reported. In connection with our investigations into the mode of action of certain neuromodulator peptides, we needed 1-amino-2-oxo-3-oxabicyclo-[3.1.0]hexane (2,3-methanohomoserine lactone) in a form



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suitable for use in peptide synthesis, *i.e.* as the corresponding t-butoxycarbonyl (BOC) derivative **1**. In this communication, we describe a rapid high yielding entry to this compound.

The synthesis was based on an intramolecular carbenoid reaction of allyl malonate precursors, followed by Curtius degradation. The distinction of the two carboxy groups would be effected at the hydrolysis stage of the ester *vs.* lactone moieties. Previous literature examples on the aminolysis of 2-substituted cyclopropane-1,1-dicarboxylates suggest that the less hindered ester function would be hydrolysed preferentially over the lactone group.[2d]

Methyl allyl diazomalonate **2a**[6] was refluxed with 5 mol% copper(I) iodide in toluene overnight to provide the cyclopropane derivative **3a** in 79% yield after chromatography.† Attempted hydrolysis with 100 mol% of LiOH in different solvent systems did not cleave the methyl ester, but returned, after acidic work-up, the starting material. When 500 mol% of LiOH was employed, however, the ester hydrolysis proceeded cleanly in tetrahydrofuran (THF) : water (1 : 1) to furnish the acid **4** in only 55% isolated yield.

Better overall yields were obtained with t-butyl allyl diazomalonate **2b**.[6] Cyclopropanation as for the methyl ester gave **3b** in 86% yield. Cleavage of the t-butyl ester was effected by acidolysis [trifluoroacetic acid (TFA) : CH_2Cl_2 (1 : 3)] to give the acid **4** in quantitative yield. Finally, treatment of the acid **4** with 100 mol% diphenylphosphoryl azide and triethylamine in t-butyl alcohol at reflux overnight gave, after chromatography, the desired aminocyclopropane carboxylic acid **1**‡ in 85% yield.

In summary, we have developed an efficient four-step synthesis of the protected 2,3-methanohomoserine lactone, which proceeds in 70% overall yield from t-butyl allyl malonate.

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† All new compounds gave satisfactory analytical and spectral data.

‡ *Spectroscopic data* for **1**: ^{1}H NMR ([$^2H_5$]pyridine) δ 1.15 (t, 1H, H-6, *J* 5.1 Hz), 1.47 (s, 9H, 3 Me), 1.61 (dd, 1H, H-6, *J* 5.4, 8.2 Hz), 2.38 (m, 1H, H-5), 4.05 (d, 1H, H-4, *J* 9.2 Hz), 4.50 (dd, 1H, H-4, *J* 9.2, 4.9 Hz); ^{13}C NMR ([$^2H_5$]pyridine) δ 17.48 (C-6), 23.79 (C-5), 27.91 (3 Me), 38.31 (C-1), 67.73 (C-4), 79.16 (q, Bu^t), 156.68 (ester), 174.90 (C-2, lactone).