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Formation Of The Oxatricyclo[3.2.1.0^{3,6}]octane Ring System *Via* An Intramolecular Bromoetherification.

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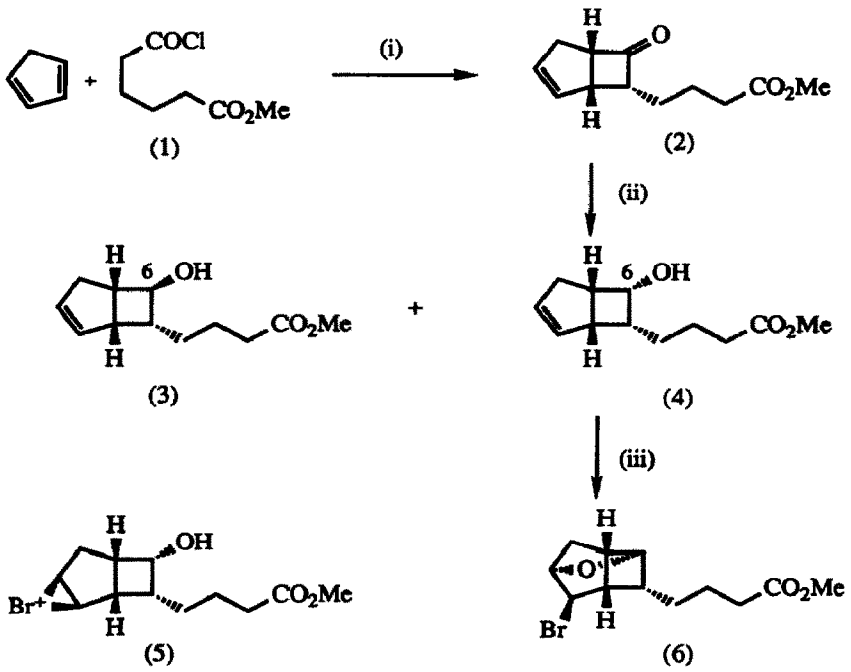
Abstract: The formation of a substituted bicyclo [3.2.0] hept-2-ene-6-one (2), and its subsequent reduction and cyclisation to (6), *via* an intramolecular bromoetherification, is described.

The bicyclo [3.2.0] hept-2-en-6-one ring system has been shown to be of great value in the synthesis of prostaglandins[1], prostaglandin analogues[2], leukotrienes[3] and other natural products[4], allowing a remarkable degree of regiochemical and stereochemical control to be excercised[1]. As part of our ongoing programme for the development of innovative strategies towards the design of novel therapeutic agents, we were interested in applying the elegant chemistry of the bicyclo [3.2.0] hept-2-en-6-one system to a series of peptidomimetics[5,6]. The bicyclo [3.2.0] hept-2-en-6-one ring system itself represents a small, rigid template, capable of orientating suitably appended peptide side-chains in such a manner as to mimic the proposed bioactive conformations of a number of peptides. During the course of our studies in this area we have observed an unusual and interesting cyclisation which results in the formation of a rigid functionalised tricyclic ring system[7].

Thus, the 7-substituted bicyclo [3.2.0] hept-2-en-6-one (2), (Scheme), was obtained in 75% yield as the *endo* adduct[8], *via* a [2+2] cycloaddition between cyclopentadiene and the ketene derived from acid chloride (1), readily prepared from adipic acid monomethyl ester. Sodium borohyride reduction of the 6-keto group[9] led to an epimeric mixture of the alcohols (3) and (4), in a 1:7 mixture respectively[10]. Treatment of (4) with N-bromosuccinimide in aqueous acetone furnished (6) in 81% yield[11]. Cyclisation of (4) to (6) occurs rapidly and in a regio- and stereochemically controlled manner, by attack of the 6-*endo* hydroxy group upon the *exo* 2,3-bromonium ion (5).

Molecular modelling of (6) indicates that the tetrahydropyran ring assumes a rigid distorted chair conformation, with the alkyl substituent at C-7 orientated axially, and the bromine atom at C-2 orientated equatorially. Compound (6) possesses functionality suitable for further elaboration to produce a number of potential peptidomimetics. Further investigation of the bicyclo [3.2.0] hept-2-ene-6-one ring system, and its application as a template scaffold for a series of peptidomimetics is currently being carried out and will be reported elsewhere.



Scheme. *Reagents and Conditions:* (i) NEt_3, 45°C (ii) $NaBH_4$, MeOH, RT (iii) NBS, Me_2CO, H_2O, RT.

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10. Compound (3) ^{1}H NMR; H-C6$_{endo}$ δ=3.53ppm. Compound (4) ^{1}H NMR; H-C6$_{exo}$ δ=4.31ppm.
11. The structure of (6) was confirmed using 2D ^{1}H COSY NMR, and by correlation with Ref. 7.

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