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A Simple Entry to Functionalised Seven-Membered Ring Systems *via* α-Hydroxycyclobutane Rearrangement followed by Retroaldol Cleavage

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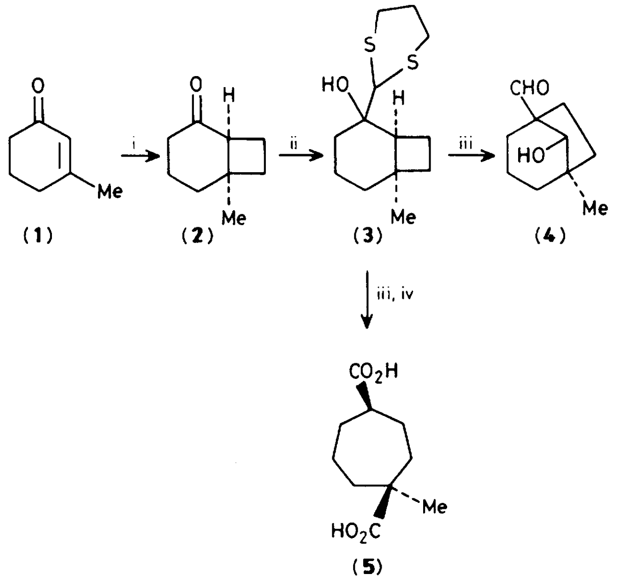
A novel three-step procedure for the synthesis of cycloheptane-1,4-dicarboxylic acid derivatives has been developed exploiting α-hydroxycyclobutane rearrangement and retroaldol cleavage.

The widespread occurrence of fused seven-membered ring systems in nature[1] has led to the development of new methods[2] for the construction of the cycloheptane unit. We report here a simple and efficient entry to a usefully functionalised seven-membered ring system starting from the easily accessible cyclohexenone.

The key reaction is the solvolytic rearrangement of a suitably substituted bicyclo[4.2.0]octane derivative in an aqueous acidic medium. Thus, 6-methylbicyclo[4.2.0]octan-2-one (**2**), obtained[3] in 60% yield by the photocycloaddition of 3-methylcyclohexenone (**1**) and ethene, when treated with the 2-lithio derivative of 1,3-dithiane[4] gave the corrresponding alcohol (**3**)† in 90% yield (Scheme 1). This alcohol (**3**), on reaction with HgO and HBF_4 in aqueous tetrahydrofuran (THF) produced a relatively unstable α-hydroxyaldehyde (**4**).‡ Compound (**4**) started decomposing to a mixture of unidentified products on standing even at 0 °C, so the alcohol (**3**), after being rearranged to (**4**) (monitored by t.l.c., *ca.* 2 h under the conditions mentioned above) was titrated with Jones reagent in the same operation to afford the crystalline dicarboxylic acid (**5**),§ [m.p. 113 °C, 70% yield, ν_{max} 1708 cm^{-1}; ^{1}H n.m.r. (100 MHz) δ($CDCl_3$) 1.24 (3H, s), 1.64—2.48 (10H, m), 2.88 (1H, t, J 8 Hz), 9.1 (2H, br.)]. The alcohol (**3**) undergoes a cyclobutyl cation rearrangement[5,6] and deprotection to give the hydroxyaldehyde (**4**) which then undergoes a retroaldol cleavage[7] and oxidation with Jones reagent to produce the dicarboxylic acid (**5**). The homogeneity of the dicarboxylic acid (**5**) was indicated by g.l.c., t.l.c., and ^{1}H n.m.r. (100 MHz) data of its methyl ester (CH_2N_2) (3 Me singlets at δ 1.20, 3.62, and 3.64). The relative stereochemistry of the two CO_2H groups was assigned as *cis* on the basis of the quantitative formation of an anhydride, ν_{max} 1810, 1740 cm^{-1}.

To test the general applicability of this reaction, it was applied in the construction of a bicyclo[5.3.0]decane system, the basic skeleton of a large number of natural products. 3-Methylcyclohexenone (**1**) and cyclopentene were irradiated according to Corey's procedure[6] to give a tricyclo-[6.3.0.0^{2,7}]undecane derivative in 92% yield as a 2 : 1 mixture (g.l.c. and ^{1}H n.m.r.) of two stereoisomers (**6a**) (*cis-transoid-cis*) and (**6b**) (*cis-cisoid-cis*) respectively. The major isomer (**6a**) was predicted to be *cis-transoid-cis* by analogy with the photocycloadditions of cyclohexenes and cyclopentenes which yield predominantly *transoid* adducts.[6,8] The tricycloundecane mixture (**6**), being inseparable by conventional tech-



Scheme 1. *Reagents and conditions*: i, $CH_2{=}CH_2$, $h\nu$, CH_2Cl_2, −30 °C, 5 h, 60%; ii, 1,3-dithiane, Bu^{n}Li, THF, −10 °C, 90%; iii, HgO (red), HBF_4 (48%), aq. THF (15%), room temp., 2 h; iv, Jones reagent, 0 °C, 70%.

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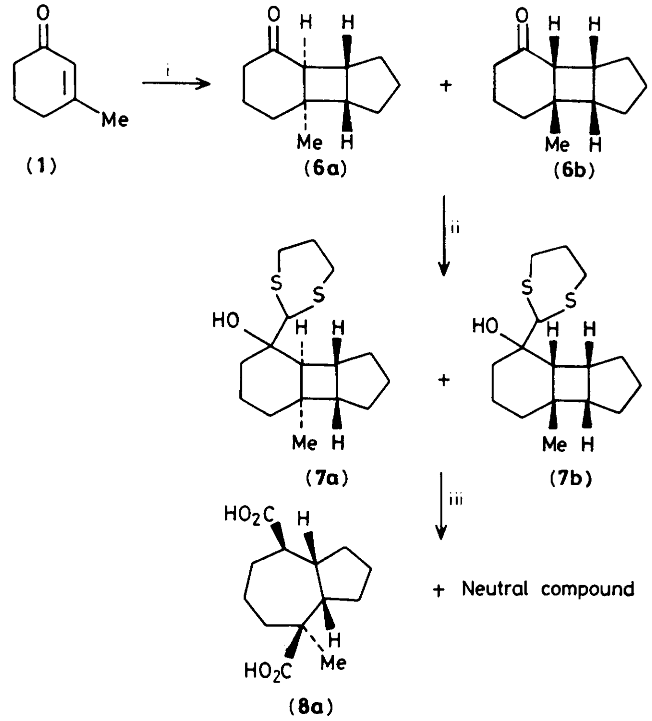
† Satisfactory spectroscopic and microanalytical data were obtained for compounds (**3**), (**6**), and (**7**).

‡ Compound (**4**), though not very stable, was characterized by its i.r. and ^{1}H n.m.r. data, recorded immediately after isolation.

§ Satisfactory microanalytical data were obtained for the dicarboxylic acids (**5**) and (**8a**).



Scheme 2. *Reagents and conditions*: i, cyclopentene, *hν*, cyclohexane, −10 °C, 5 h, 92%; ii, 1,3-dithiane, Bu^nLi, THF, −10 °C, 87%; iii, HgO (red), HBF_4 (48%), aq. THF (15%), room temp., 2 h, Jones reagent, 0 °C, 48%.

niques, was then converted to the corresponding alcohols (**7**) in 87% yield (Scheme 2). This mixture of alcohols (**7a**) and (**7b**) (2 : 1) in an one-pot operation as above (HgO, HBF_4, aq. THF, Jones reagent) afforded a dicarboxylic acid (**8a**)¶ in 48% yield {m.p. 184 °C; ν_{max} 1705 cm^{-1}; ^1H n.m.r. (100 MHz) δ [$(CD_3)_2SO$] 0.88 (3H, s), 1.36—3.00 (15H, m), 12.0 (2H, br.)} and a neutral compound (22%).

This procedure thus leads to the construction of a usefully functionalised derivative of a seven-membered ring system in three steps and in good overall yield from readily available cyclohexenone. We believe that extension of this approach to appropriately substituted cyclohexenones and alkenes will provide substrates suitable for elaboration into a wide variety of naturally occurring cycloheptanoids

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¶ The homogeneity of (**8a**) as a single isomer was confirmed by g.l.c. and ^1H n.m.r. of its methyl ester and the stereochemistry was assigned by analogy with (**5**).

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