Synthesis of Tetrahydrodicranenone B

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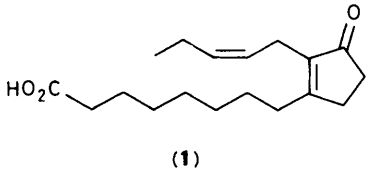
The naturally occurring cyclopentenone, tetrahydrodicranenone B (**1**), has been synthesised from 6-methoxyindanone by a route which involves reductive alkylation and ozonolysis to the key cyclopentenone (**3**), followed by elongation of the lower side chain to give the alcohol (**7**), and functional group manipulation.

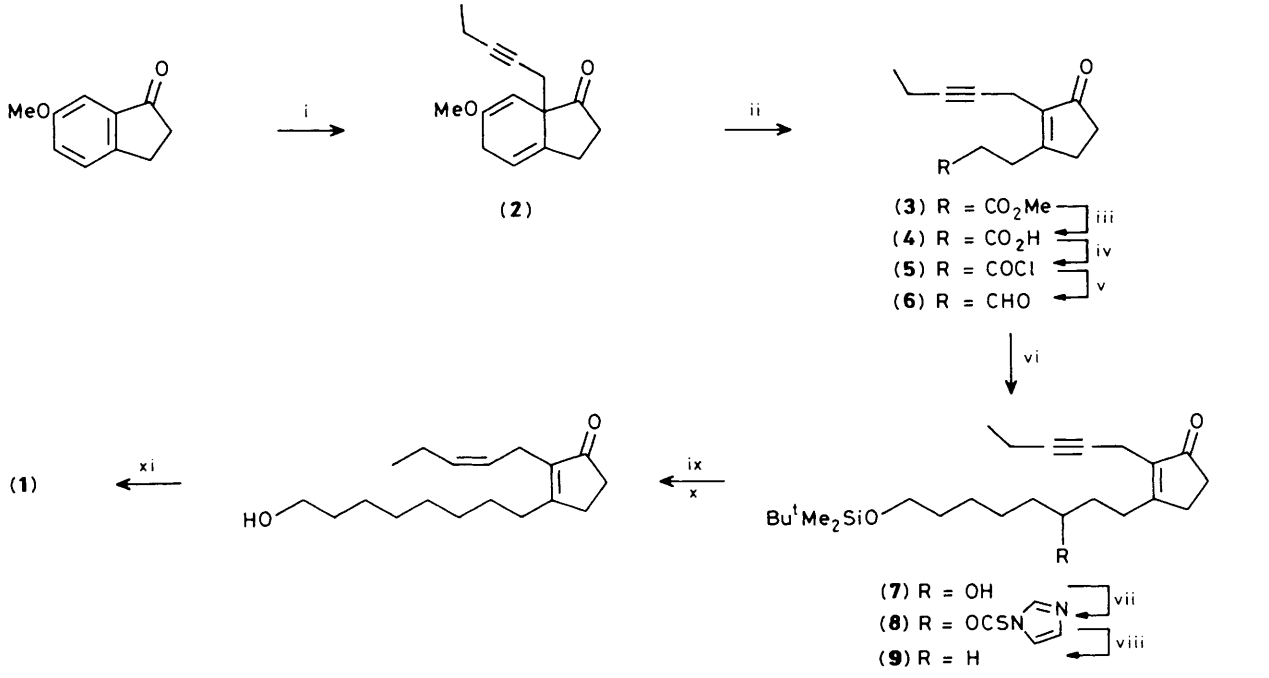
The structural diversity and biological importance of cyclopentanoid natural products have made them attractive targets for synthesis, and in recent years considerable effort has been devoted to the development of new methods for the construction of five-membered rings.[1] We now report a fundamentally new approach to 2,3-disubstituted cyclopent-2-en-1-ones, illustrated by its application to the first synthesis of tetrahydrodicranenone B (**1**), one of a group of naturally occurring, antimicrobial fatty acids isolated from Japanese mosses.[2–4]

Our approach is centred on the reductive alkylation of indan-1-ones, a reaction which we have previously used as a key step in the synthesis of novel [10]-annulene derivatives.[5,6] 6-Methoxyindanone[7] was subjected to the normal Birch reduction/alkylation conditions[5] quenching with 1-iodopent-2-yne to give the dihydroindanone (**2**). The vinyl ether double bond in (**2**) underwent selective ozonolysis, and the intermediate aldehyde obtained upon reductive work up with zinc and acetic acid was immediately oxidised further using Jones' reagent. The resulting carboxylic acid spontaneously decarboxylated with the double bond moving into conjugation with the carbonyl to give the cyclopentenone (**3**). Thus the key 2,3-disubstituted cyclopent-2-en-1-one (**3**) is available in just two operations (reduction/alkylation and ozonolysis/oxidation) from 6-methoxyindanone in an overall yield of 29%. The direct, selective reduction of the cyclopentenone ester (**3**) to the cyclopentenone aldehyde (**6**) proved difficult and therefore this was achieved indirectly by hydrolysis to the acid (**4**), conversion into the acid chloride (**5**) using preformed dimethylformiminium chloride, and then selective reduction using lithium (tri-t-butoxy)aluminium hydride (38% overall). The lower side chain was then elongated by selective addition of the Grignard reagent derived from the t-butyl(dimethyl)-silyl ether of 5-bromopentan-1-ol to the aldehyde to give the alcohol (**7**) (67%) (Scheme 1).

The synthesis was completed by radical deoxygenation[8] of the alcohol (**7**) *via* the thiocarbonylimidazolide (**8**) to give the cyclopentenone (**9**) (Scheme 1). Finally, reduction of the acetylene (100%), and deprotection and oxidation[9] (54%) gave tetrahydrodicraneone B (**1**), the spectra (i.r., n.m.r., mass) of which were identical to those of the natural product.



(**1**)



Scheme 1. *Reagents:* i, K, NH_3, Bu^tOH, −78 °C; LiBr, $EtC{\equiv}CCH_2I$; ii, O_3, MeOH then Zn, AcOH; Jones' reagent; iii, KOH, MeOH, H_2O; iv, dimethylformiminium chloride, C_6H_6; v, $LiAlH(OBu^t)_3$; vi, $Bu^tMe_2SiO(CH_2)_5MgBr$; vii, 1,1'-thiocarbonyldi-imidazole; viii, Bu^n_3SnH, azoisobutyronitrile (AIBN), toluene; ix, Pd–$BaSO_4$, pyridine; x, AcOH, H_2O, tetrahydrofuran (THF); xi, Pt, O_2, acetone, H_2O.

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