Synthesis of (−)-Acorenone B

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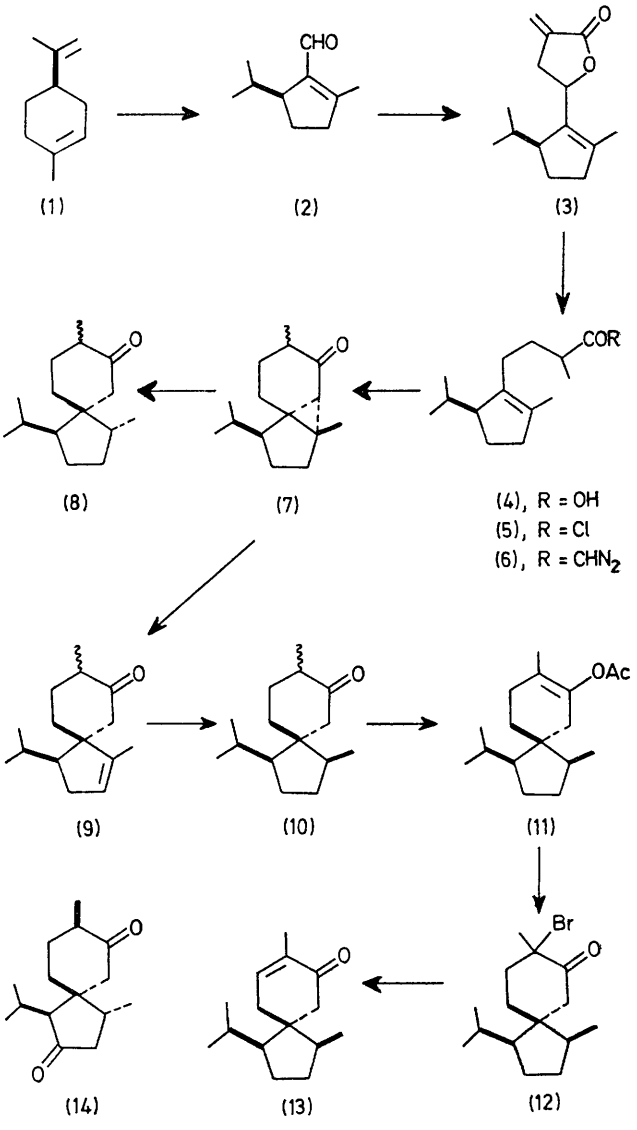
Summary A stereoselective synthesis of the natural sesquiterpene (−)-acorenone B is accomplished starting from (*R*)-(+)-limonene and proceeding *via* the key tricyclic intermediate (**7**).

THE foregoing communication described a method for synthesis of spiro carbocyclic systems based upon the intramolecular cycloaddition of a diazoketone, followed by reductive ($Li–NH_3$) scission of the peripheral bond in the resulting cyclopropane.[1] This method was used[2] in a total synthesis of (±)-α-chamigrene, which was stereochemically undemanding, however. We have now used this approach in a synthesis of natural (−)-acorenone B (**13**),[3] in which development of the appropriate configurations at the three contiguous, chiral centres of the sesquiterpene takes place in a fully stereocontrolled manner.[4]

By a sequence previously outlined in the enantiomeric series,[5] (*R*)-(+)-limonene (**1**) was transformed to the aldehyde (**2**). The latter underwent condensation with ethyl 2-bromomethylacrylate upon passage of the mixture in tetrahydrofuran through a heated column of granular zinc[6] to give the α-methylene-γ-lactone (**3**) [1775 and 1670 cm^{-1}; δ 5·2 (1H), 5·6 (1H), and 6·3 (1H)].[7] Hydrogenation of (**3**) in ethanol, first over Adams' catalyst (reduction of *exo*-methylene) and then over $Pd–CaCO_3$ (hydrogenolysis), afforded the carboxylic acid (**4**) [1710 cm^{-1}; δ 1·60 (vinyl Me) and 10·6 (CO_2H)] in 50% yield based on (**2**). Conversion of (**4**) into the diazoketone (**6**) (2110 cm^{-1}) *via* the acyl chloride (**5**) (1790 cm^{-1}) was effected as previously described, and decomposition of (**6**) (Cu powder, cyclohexane at reflux) gave the tricyclic ketone (**7**) (1680 cm^{-1}) as an oil in 38% yield (from **4**) after chromatography on alumina. G.l.c. and subsequent transformations of (**7**) showed it to be an epimeric mixture with respect only to the methyl group α to the carbonyl group, and indicated that carbenoid addition, following decomposition of (**6**), occurred with complete stereoselectivity at the face of the cyclopentene double bond opposite the isopropyl group.

Reduction of (**7**) with lithium in liquid ammonia produced (**8**) (49%), with a configuration at the cyclopentane ring corresponding to the acorone (**14**)[8] rather than the acorenone series. Protonation of the lithio intermediate from (**7**) thus occurs predominantly with inversion at the methyl-bearing cyclopropane carbon atom, a result in agreement with the findings of Piers and Worster in a related system.[9] Treatment of (**7**) with hydrogen chloride in chloroform, on the other hand, led cleanly to (**9**), which was hydrogenated (Rh–C) to give (**10**) (60% from **7**) (1710 cm^{-1}). Introduction of the enone function was effected in 34% overall yield *via* the enol acetate (**11**) and the α-bromoketone (**12**) to give (−)-acorenone B ($[\alpha]_D^{20}$ −19°), the identity of which was confirmed by comparison with an authentic sample of (±)-acorenone B.



The utility of a tricyclic intermediate such as (**7**) for stereocontrolled spiroannelation is thus demonstrated.

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