

A Short Synthesis of the 6-Epi-arteannuin B Skeleton¹

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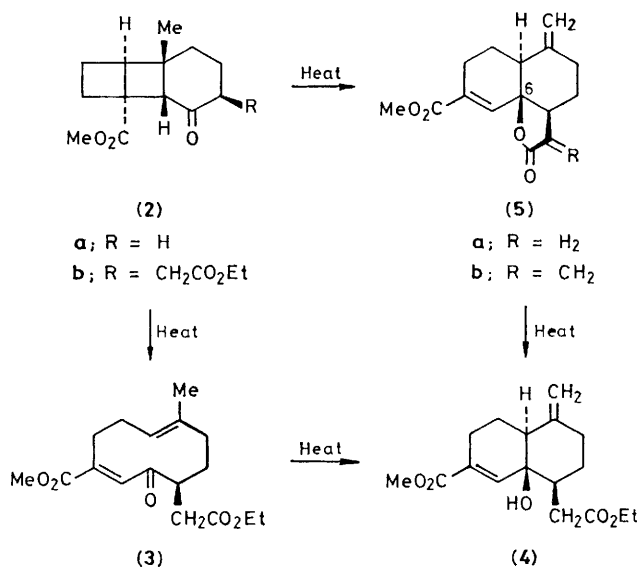
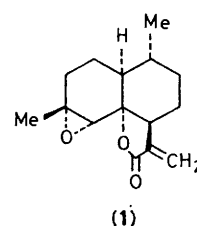
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Thermolysis of the readily available photoadduct (**2b**) affords, *via* a transannular ene reaction, the norcadinane sesquiterpene lactone (**5a**), the exocyclic methylene derivative (**5b**) of which has the 6-epi-arteannuin B skeleton.

(-)-Arteannuin B (**1**) is a cadinane sesquiterpene lactone isolated from *Artemisia anna* L.² It contains a *cis*-decalin ring system with the oxygen of a *trans*-lactone ring attached to a ring-junction carbon atom. Recently three stereoisomers of (**1**) containing a *cis*-lactone and *cis*- and *trans*-decalin ring systems have been synthesised.³ In view of our recent biomimetic synthesis of *trans*-decalins incorporating ring-junction oxygen-containing substituents,⁴ the arteannuin B skeleton with a *trans*-decalin presented a suitable synthetic target molecule.

The synthesis of *trans*-decalin systems containing a bridgehead hydroxy-group has been the topic of considerable recent interest.^{4,5} This system is easily derived from readily available precursors by a photochemical olefin metathesis sequence followed by a transannular ene reaction. Since the hydroxy-group can lead to lactone formation, by starting with the appropriately substituted photoadduct one can readily prepare the norcadinane sesquiterpene lactone skeleton (**5a**), which is epimeric at C-6 with that found in (-)-arteannuin B (**1**).

The photoadduct (**2b**) was synthesised in two ways. First, photocycloaddition of methyl cyclobutene-1-carboxylate with 3-methylcyclohex-2-enone afforded the photoadduct (**2a**)[†] which upon alkylation with ethyl bromoacetate gave (**2b**) (56% yield), and this was identical with (**2b**) obtained by photocycloaddition of the cyclobutene ester with 6-ethoxycarbonylmethyl-3-methylcyclohex-2-enone (74% yield). Since this photocycloaddition is known to occur regio- and stereo-



[†] To CH₂Cl₂ (5 ml) was added 3-methylcyclohex-2-enone (5.0 g) and methyl cyclobutene-1-carboxylate (5.1 g). The solution was photolysed with a 450 W Hanovia lamp at 0 °C in an all-quartz apparatus for 15 h. The product was isolated by chromatography on silica gel (63% yield).

selectively, the ring junction methyl and ethyl ester groups are *cis* to each other as in (2b), and this was confirmed by the appearance of 6-H as a singlet at δ 3.09^{4,5} in the ¹H n.m.r. spectrum of (2b).

Thermolysis of (2b) in refluxing decane (174 °C) for 18 h afforded the lactone (5a), m.p. 100–101 °C, in 58% yield [ν_{\max} (KBr) 1750, 1710, and 1640 cm^{-1} ; ¹H n.m.r. (CDCl_3) δ 6.82 (s, 1H), 4.97 (s, 1H), 4.84 (s, 1H), and 3.78 (s, 3H); ¹³C n.m.r. δ 35.19 (C-1), 19.9 (C-2), 24.5 (C-3), 135.0 (C-4), 134.4 (C-5), 83.5 (C-6), 37.5 (C-7), 29.9 (C-8 or C-9), 28.5 (C-9 or C-8), 143.0 (C-10), 42.0 (C-11), 175.2 (C-12), 109.6 (C-14), 166.8 (C-15), and 51.8 (CO_2CH_3) p.p.m.; mass spectrum (70 eV) m/z 262 (100%, M^+), 231 (14%, $M-\text{OCH}_3$), 203 (34%, $M-\text{CO}_2\text{CH}_3$), and 202 (51%)], together with the uncyclised hydroxy-ester (4), in 15% yield [ν_{\max} (film) 3500, 1725, and 1670 cm^{-1} ; ¹H n.m.r. (CDCl_3) δ 6.80 (s, 1H), 4.70 (s, 1H), 4.14 (q, 2H), 3.75 (s, 3H), and 1.27 (t, 3H)]. The spectral data for (4) and (5) are in close agreement with those observed for similar structures.⁴ Mechanistically, thermolysis of (2b), would be expected to give the 1(10)-*trans*-4-*cis*-cyclodecadienone (3) via a concerted cycloreversion process or an orbital-overlap-controlled fragmentation of a diyl intermediate.^{4,5} Under these high-temperature conditions, 1(10)-*trans*-4-*cis*-cyclodecadienones such as (3) are known to undergo transannular ene reactions yielding the *trans*-decalin (4) containing a ring-junction hydroxy-group.⁴ Intramolecular attack of the hydroxyl-group in (4) on the *cis*-ethyl ester afforded the *cis*-lactone (5a).

Methylenation of (5a) using Stiles reagent⁶ and a Mannich reaction⁷ afforded the α -methylene lactone (5b) in 56% overall yield, ν_{\max} (CHCl_3) 1760 and 1730 cm^{-1} ; ¹H n.m.r. (CDCl_3)

δ 6.63 (br. s, 1H), 6.37 (d, 1H, J 2 Hz), 5.74 (d, 1H, J 2 Hz), 4.97 (br. s, 1H), 4.90 (br. s, 1H), and 3.76 (s, 3H); mass spectrum (70 eV) m/z 274 (16%, M^+), 243 (3%, $M-\text{OCH}_3$), 242 (5%), 215 (3%, $M-\text{CO}_2\text{CH}_3$), 214 (5%), and 59 (100%).

Arteannuin B is the only member of the cadinanolide class of sesquiterpenes most probably derived from a germacranolide precursor.⁸ One could expect cadinanolide sesquiterpenes with the 6-*epi*-arteannuin B skeleton to be formed from a similar precursor, and derivatives of this new class will probably be isolated in the future.

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