Total Synthesis of (±)-β-Bulnesene, (±)-Cryptofauronol, (±)-Fauronyl Acetate, and (±)-Valeranone

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A versatile method for the preparation of perhydroazulenes and *cis*-fused 1-decalones is described and exemplified by the synthesis of the title compounds.

In a recent communication[1] we have described the preparation of epoxy-bridged perhydroazulenes, of the type (1), by the intramolecular cycloaddition of isolated olefinic bonds to 3-oxidopyrylium species, themselves generated under mild conditions from the corresponding pyranulose acetates.[2] In order to use cycloadducts of the type (1) for the synthesis of natural products, such as sesquiterpenes, methods for using the epoxy-bridge to introduce appropriate substituents are required. Herein we describe two methods exploiting the epoxy-bridge for the synthesis of (±)-β-bulnesene (2),[3] (±)-cryptofauronol (3)[4] and its acetate (4),[4] and (±)-valeranone (5).[5]

In the route to (±)-β-bulnesene (2) (Scheme 1), a reductive cleavage of the epoxy-bridge is utilised. The starting material for our synthesis was the substituted furfuryl alcohol (7),† itself prepared as a mixture of isomers (80%) [oil, ν_{max} (film) 3380, 1640 cm^{-1}] by a Grignard reaction between 2-furaldehyde and 3-methylpent-4-enyl bromide (6). Oxidation of the alcohol (7) with *m*-chloroperoxybenzoic acid in dichloromethane and acetylation of the product pyranulose (8) with acetic anhydride in pyridine afforded the acetate (9) as a mixture of stereoisomers, obtained in 55% overall yield from the alcohol (7). Heating the acetate (9) at 150 °C for 20 h in acetonitrile[1] (sealed tube) gave the perhydroazulene cyclo-adducts (10). From the 400 MHz ¹H n.m.r. spectrum the cycloadduct proved to be a 1:5 mixture of the two epimers (10a) and (10b), respectively. Previous work has shown that the cycloaddition proceeds regioselectively in an *exo*-manner. The formation of (10b) as the major product can be explained by considering steric interactions in the transition states leading to the isomeric adducts; that leading to (10a) is more cluttered than that leading to (10b). Oppolzer has noticed a similar relationship in his photochemical route to β-bulnesene.[3d]

(1) (2)

(3) (4) R = OAc

(5) R = H
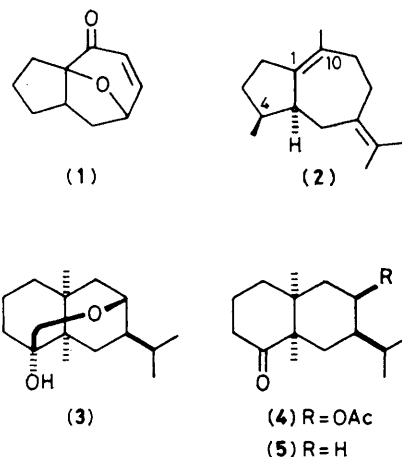
Although either isomer could be used, difficulty in separation made it convenient to process the isomeric mixture. Catalytic hydrogenation over 5% Pd–C in ethanol produced the saturated ketones (11) (73%) [ν_{max} (film) 1725 cm^{-1}], which reacted stereoselectively with methylmagnesium iodide to produce the alcohols (12) (77%). Further manipulations involved chlorination, using thionyl chloride and hexamethylphosphoric triamide (HMPA),[6] to give the chloride (13), followed by reduction by sodium in diethyl ether at room temperature to cleave the epoxy bridge and simultaneously introduce the 1(10)-olefinic bond. The resulting alcohols (14) (76%) were oxidised with CrO₃–pyridine to give the ketones (15) (70%) followed by Wittig condensation to introduce the isopropylidene group. The product (72%) was shown to be a 17:83 mixture of (±)-β-bulnesene (2) and its 4-epimer (16), respectively. As expected[3d] the major isomer (±)-4-*epi*-β-bulnesene (16) exhibited the C(4)-methyl group as a doublet at δ 1.05 (*J* 5 Hz), and a ¹³C signal at δ 18.7 p.p.m. (from Me₄Si), whilst, for (±)-β-bulnesene (2) these signals occurred
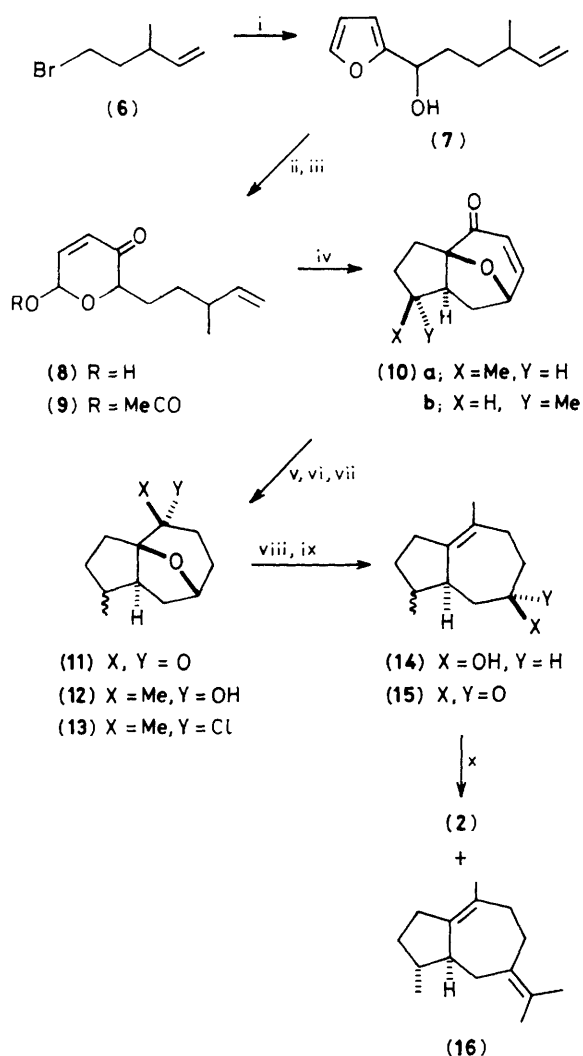

Scheme 1. i, Mg then 2-furaldehyde; ii, m-chloroperoxybenzoic acid; iii, Ac₂O, pyridine; iv, 150 °C, 20 h, MeCN; v, H₂, 5% Pd–C; vi, MeMgI; vii, SOCl₂, HMPA; viii, Na, diethyl ether; ix, CrO₃–pyridine; x, Me₂C=PPh₃.

at δ 0.88 (J 7 Hz) and δ 14.9 p.p.m.; the synthetic material also possessed the identical g.c. retention times of the natural material.

Cleavage of the epoxy-bridge can also be effected by a skeletal rearrangement to the decalin system. For example, compound (17)[7] with tin tetrachloride in dichloromethane affords, after work-up, the cis-decalone (19) (60%). The rearrangement presumably proceeds via the intermediate oxonium ion (18)(Scheme 2) involving a cis-fused decalin system. That the ketone (19) formed is initially cis-fused was shown by brief treatment with triethylamine which isomerised it to the corresponding trans-fused isomer (20).

The perhydroazulene to decalone rearrangement has been utilised in a 7-step synthesis of (±)-cryptofauronol (3) and its subsequent conversion into (±)-valeranone (5) (Scheme 3). Grignard reaction between 2-furaldehyde and the bromide (21) afforded the alcohol (22) (89%). Furan oxidation to the corresponding pyran-3-one by either m-chloroperoxybenzoic acid or bromine–methanol was thwarted by concurrent oxidation of the disubstituted olefinic bond. In order to overcome this side reaction a more selective oxidation procedure had to be used and singlet oxygen oxidation,[8] followed by reduction of the peroxide adduct with triphenylphosphine,
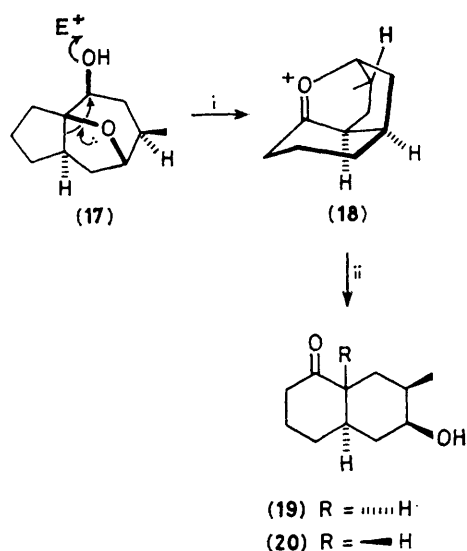
Scheme 2. i, SnCl₄; ii, H₂O. E = electrophile.
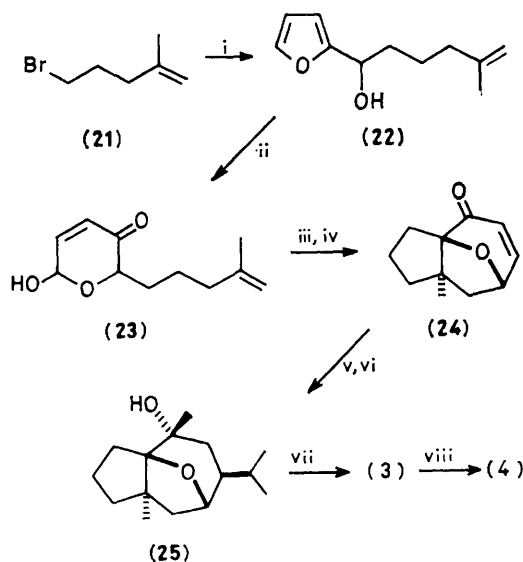
Scheme 3. i, Mg then 2-furaldehyde; ii, ¹O₂–MeOH then PPh₃; iii, Ac₂O, pyridine; iv, 150 °C, 24 h, MeCN; v, Me₂CHMgI, CuBr·Me₂S; vi, MeMgI; vii, TiCl₄; viii, Ac₂O, NaOAc, reflux.

proved effective. By this method the alcohol (22) was converted into the pyranulose (23) (74%), m.p. 55 °C, and, after acetylation and thermolysis in acetonitrile at 150 °C for 24 h, to the single cycloadduct (24) (62%) [νmax (film) 1696 cm⁻¹]. Reaction of the adduct with isopropylmagnesium iodide in the presence of Me₂S·CuBr, followed by reaction with methylmagnesium iodide afforded the alcohol (25) (84%) as a single isomer. By treatment with titanium tetrachloride at 0 °C the alcohol (25) was smoothly converted into (±)-cryptofauronol (3)‡ (83%) (24% overall yield from 2-furaldehyde), m.p. 107—109 °C. The synthetic material gave identical i.r. and ¹H n.m.r. spectra to the natural product.[4] Heating the alcohol with acetic anhydride in the presence of sodium acetate gave the racemate of the related natural product, fauronyl acetate (4).[4] By using

a modification of Hikino's method[4] the synthetic material was converted into ($\pm$)-valeranone (5) [18% yield from the alcohol (3)].

The above syntheses illustrate the usefulness of the highly functionalised and readily available perhydroazulene adducts of the type (1).

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