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Total Synthesis of (\pm) - β -Bulnesene, (\pm) -Cryptofauronol, (\pm) -Fauronyl Acetate, and (\pm) -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 communication¹ we have described the preparation of epoxy-bridged perhydroazulenes, of the type (1), by the intramolecular cycloaddition of isolated olefinic bonds to 3oxidopyrylium 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 (\pm) - β -bulnesene (2),³ (\pm) cryptofauronol (3)⁴ and its acetate (4),⁴ and (\pm) -valeranone (5).⁵

In the route to (\pm) - 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 acetonitrile¹ (sealed tube) gave the perhydroazulene cycloadducts (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}



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 CrO_3 -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 (\pm) - β -bulnesene (2) and its 4-epimer (16), respectively. As expected^{3d} the major isomer (\pm) -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 (\pm) - β -bulnesene (2) these signals occurred

[†] All new compounds gave satisfactory microanalytical and spectroscopic data; yields have not been optimised.



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 $\delta 0.88$ (J 7 Hz) and $\delta 14.9$ 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 (\pm) -cryptofauronol (3) and its subsequent conversion into (\pm) -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, $SnCl_4$; ii, H_2O . E = electrophile.



Scheme 3. i, Mg then 2-furaldehyde; ii, ${}^{1}O_{2}$ -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%) [ν_{max} (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 (\pm)-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

[‡] We thank Professor Hikino for providing a sample of natural cryptofauronol.

a modification of Hikino's method⁴ 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).

We thank the S.E.R.C. and Shell Research Ltd. (Sittingbourne, Kent), for a C.A.S.E. Studentship (to L. J. S.).

Received, 21st March 1983; Com. 363

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