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STEREOSPECIFIC FORMATION OF A SUBSTITUTED *trans*-DECALINE AS AN INTERMEDIATE FOR THE SYNTHESIS OF CLERODANE INSECT ANTIFEEDANTS

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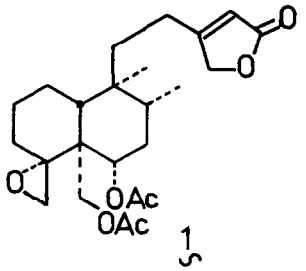
Summary: The stereospecific synthesis of *trans*-decaline 3† is described. This compound is an important intermediate in the total synthesis of Clerodane insect antifeedants, as exemplified by ajugarin-I.

A number of clerodane diterpenes, as represented by ajugarin-I[1], 1, possess insect antifeedant activity. During the last few years several papers on the synthetic approach towards these compounds have appeared[2-6]. Recently we published the synthesis of octalone 2[7] as an intermediate for a general synthesis of clerodanes. Starting with 2 we now want to report on the preparation of compound 3, which can serve as an important intermediate in the total synthesis of ajugarin-I. The stereospecific introduction of an equatorial methyl group at C-2 and the oxidation of C-4 are key transformations in this approach.



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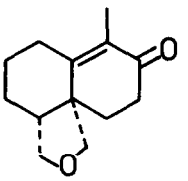

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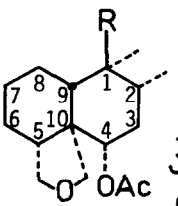
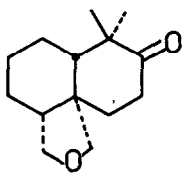


3 R=$(CH_2)_3$OAc
9 R=CH_3

Reductive alkylation of 2 using methyl iodide as alkylating agent gave decalone 4[7]. This compound was chosen as a model compound for the following series of reactions. Bromination and dehydrobromination (with LiBr and Li_2CO_3 in boiling DMF) of 4 gave 5 in an overall yield of 78%. Addition of methyllithium to 5 at -78°C gave the allylic alcohol 6 in 96% yield. This compound was then oxidized by pyridinium chlorochromate[8] to the α,β-unsaturated ketone 7 (yield 87%).



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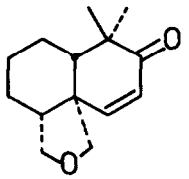

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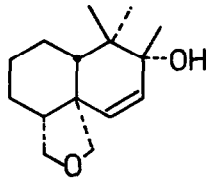

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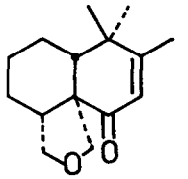

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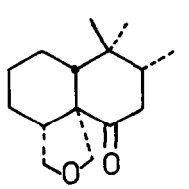
Reduction of the olefinic moiety in 7 by lithium in ammonia produced a 1:1 mixture of the C-2 epimers, as indicated by ^{1}H nmr. Catalytic hydrogenation (in methanol-triethylamine 5:1 with 10% Pd-C) of 7, however, afforded only one isomer in 96% yield. The ^{1}H nmr spectrum of this compound displays a triplet of doublets at 2.65 ppm with coupling constants of 13 and 13 Hz and a double doublet at 2.13 ppm with coupling constants of 13 and 4 Hz. These values are in good agreement with those found in the keto-ester derivative of teucvin[9], a norclerodane, with the same array of substituents at ring B, and indicate an equatorial position for the C-2 methyl. Hence catalytic hydrogenation of 7 produces exclusively the desired ketone 8. [^{13}C nmr of 8: δ = 212.5 (s), 72.7 (t), 69.0 (t), 60.6 (s), 54.1 (d), 45.4 (d), 43.7 (t), 40.3 (d), 37.1 (s), 28.6 (t), 27.3 (q), 25.7 (t), 22.2 (t), 16.6 (q), 15.3 (q)].
Reduction of 8 with $NaBH_4$ gave a 9:1 mixture of the equatorial and axial C-4 hydroxyl groups respectively, which were converted into their corresponding acetates and separated by column chromatography. Acetate 9 was thus obtained in 82% yield. [^{1}H nmr of 9: δ ($CDCl_3$) 0.53 (s,3H), 0.84 (d,J=7Hz,3H), 0.88 (s,3H), 1.2-1.9 (m,11H), 2.06 (s,3H), 3.35 (d, J=9Hz,1H), 3.82 (dd, J=9+5Hz,1H), 3.84 (d,J=9Hz,1H), 3.94 (d,J=9Hz,1H), 4.80 (dd, J=13+ 4Hz,1H)].
For an approach towards compounds like ajugarin-I, a substituent at C-1 had to be found from which the six carbon side chain can be constructed. The introduction of an allyl group was chosen for this purpose. Thus, reductive alkylation of 2 with allyl bromide gave 10[10]. As selective α-bromination of ketone 10 was unsuccessful we devised a different route for the introduction of the double bond in ring B. Generation of the enolate of 10 and reaction with diphenyldiselenide gave 11. Oxidation of 11 followed by subsequent elimination[11] afforded the α,β-unsaturated ketone 12 (30%).



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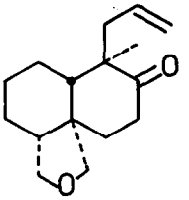

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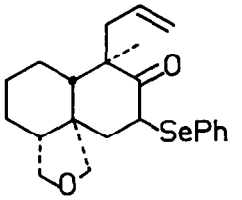

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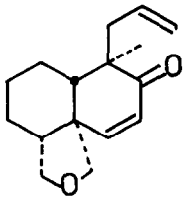

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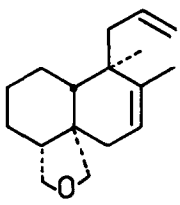
Because of the low yield of 12 and expected difficulties in the selective functionalization of the allylic side chain we chose for an alternative approach and investigated the direct oxidation of C-4 in 15. This compound was obtained by reaction of 13[10] with 9-BBN, followed by oxidation with hydrogen peroxide to 14 and acylation with pyridine-Ac_2O (overall yield 92%). Allylic oxidation of 15 with CrO_3 in acetic acid[12] gave the α,β-unsaturated ketone 16 in 55% yield. Catalytic hydrogenation of 16 under the same conditions as in the case of 6, proceeded stereoselectively and produced 17 (97%).
[^{1}H nmr of 17: δ ($CDCl_3$) 0.80 (s,3H), 0.87 (d,J=7Hz,3H), 1.1-1.8 (m,13H), 2.03 (s,3H), 2.12 (dd,J=13+ 4Hz,1H), 2.70 (dd,J=13+13Hz,1H), 3.35 (d,J=9Hz,1H), 3.80 (dd,J=9+4Hz,1H), 4.00 (d,J=9Hz,1H), 4.03 (t,br,2H), 4.04 (d,J=9Hz,1H)].



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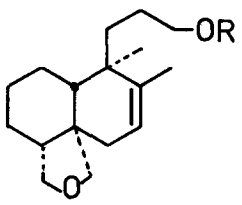
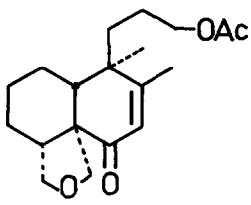


14, R=H
15, R=OAc



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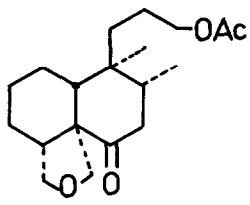

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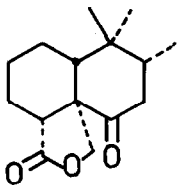
Reduction of ketone 17 with $NaBH_4$ was less stereospecific than in the case of 8 ; the equatorial and axial C-4 hydroxyl groups were formed in a ratio of 4:1 respectively. The mixture of the two isomers was reacted with Ac_2O-pyridine-4-N,N-dimethylaminopyridine to give the corresponding acetates.
Separation by column chromatography gave 3 in 69% yield. [^{1}H nmr of 3: δ ($CDCl_3$) 0.53 (s,3H), 0.80 (d,J=7Hz,3H), 1.1-1.8 (m,15H), 2.04 (s,6H), 3.35 (d,J=9Hz,1H), 3.83 (dd,J=9+5Hz,1H), 3.85 (d,J=9Hz,1H), 3.95 (d,J=9Hz,1H), 4.02 (t,br,2H), 4.76 (dd,J=13+ 4Hz,1H)].
Further investigations concerned the transformation of the cyclic ether moiety into more accessible groups for the construction of functionalities as in the ajugarins.
RuO_4 oxidation[7] of 8 gave the isomeric lactones 18 and 19 in a ratio of 1:1. The same oxidation of acetate 9 proceeded regiospecifically and afforded lactone 20 in 95% yield. Compound 3 could also be oxidized in the same manner and gave 21 (95%).
[^{1}H nmr of 21: δ ($CDCl_3$) 0.60 (s,3H), 0.86 (d,J=7Hz,3H), 1.1-2.0 (m,15H), 2.03 (s,6H), 4.00 (t,br,2H), 4.32 (d,J=9Hz,1H), 4.42 (d,J=9Hz,1H), 4.68 (dd,J=13+ 4Hz,1H)].
On refluxing 9 in acetic anhydride in the presence of pyridine hydrochloride[13], an ether cleavage reaction occurred producing the diacetate 22. [^{1}H nmr of 22: δ ($CDCl_3$) 0.66 (s,3H), 0.83 (d,J=7Hz,3H), 0.88 (s,3H), 1.2-2.0 (m,11H), 2.00 (s,3H), 2.04 (s,3H), 3.47 (dd, J=11+9Hz, 1H), 3.96 (dd,J=11+3.5Hz,1H), 4.20 (d,J=13Hz,1H), 4.73 (d,J=13Hz,1H), 4.75 (dd,J=12+ 4Hz,1H)].
The yield of 22 was 80%.



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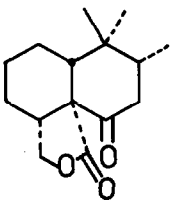

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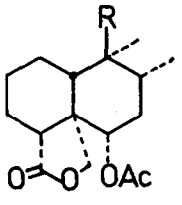
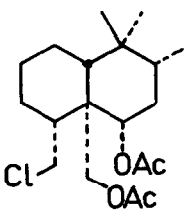


20. R=CH_3
21. R=$(CH_2)_3OAc$



22

Further studies towards the total synthesis of ajugarin-I and derivatives with possible insect antifeedant activity are in progress.

†This and subsequent compounds are pairs of enantiomers. In each case the isomer is drawn which corresponds to the absolute configuration of ajugarin-I[1b]. All intermediates had mass, nmr and ir spectra in accord with their expected structures. Some were characterized further by carbon and hydrogen analyses.

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