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PREPARATION AND REACTIONS OF *cis*-5,10-METHANOXYMETHANO-1-METHYL-$\Delta^{1,9}$-2-OCTALONE AS AN INTERMEDIATE IN THE TOTAL SYNTHESIS OF CLERODANE TYPE DITERPENES

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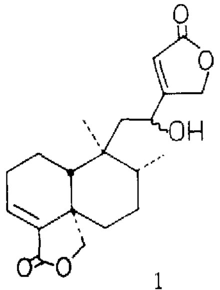
Summary: The synthesis of *cis*-5,10-methanoxymethano-1-methyl-$\Delta^{1,9}$-2-octalone (5) is described. Its value as an intermediate is demonstrated by a number of reactions that are essential in the planned total synthesis of clerodane diterpenes.

A considerable number of clerodane type diterpenes contain an unsaturated γ lactone at ring A, e.g. Olearin 1[1]. In search of a total synthesis of this type of clerodanes we wish to present 5 as a valuable intermediate. Initially the decalone 2[2+] was chosen as a starting compound for the planned total synthesis. However, reductive-alkylation of 2 in order to functionalise C-1[3], yielded complex mixtures of products. G.c.-m.s. analysis showed that the ester functionalities gave rise to unwanted side reactions. In order to circumvent these complications we searched for a way to transform the ester groups into other functionalities that are inert towards the planned chemical reactions at ring B and yet allow the construction of an unsaturated lactone at ring A.

Conversion of the diester 2 into a cyclic ether as in compound 5 seemed to fulful these requirements. The α,β-unsaturated ketone was therefore protected as its dienol ether 3 and reduced to the corresponding diol by $LiAlH_4$. Hydrolysis gave 4 which was dehydrated to 5 by refluxing in 4n hydrochloric acid [nmr of 5 : δ ($CDCl_3$) = 1.79 (s,3H), 3.69 (d, J=9Hz, C-10 CHa), 3.92 (d, J=9Hz, C-10 CHb), 3.69 (dd, J=9 + 4Hz, C-5 CHa), 4.10 (dd, J=9 + 6Hz, C-5 CHb]. The overall yield of these conversions was 84%.



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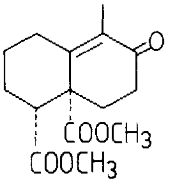

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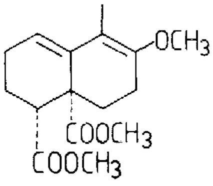

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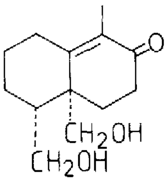

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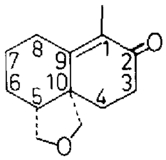

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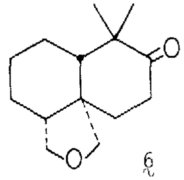
Reductive-alkylation of 5 with lithium in ammonia[7], using methyliodide as alkylating agent, gave 6 in 94% yield. The cyclic ether could quantitatively and regiospecifically be converted into lactone 7 by oxidation either with bromine at pH 5[4] or with RuO_4[5]. Before introducing the double bond the oxo group was protected as its ethylene ketal yielding 8.

Treatment of **8** with LDA at -78°C and subsequent addition of diphenyldiselenide[6] gave, after oxidation and elimination, the unsaturated lactone **9** in 74% yield. [nmr of **9** : δ (CDCl$_3$) = 0.81 (s,3H), 0.93 (s,3H), 4.00 (s,4H), 3.81 (dd, J= 7 + 3Hz,1H), 4.32 (d,J=7Hz,1H)].



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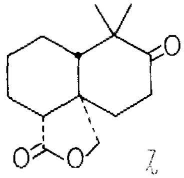

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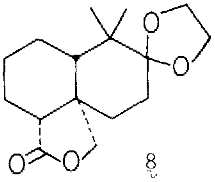

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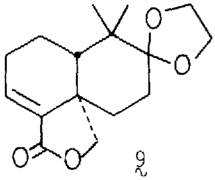

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From these experiments **5** is shown to be a suitable intermediate as in this compound the functionalities at ring B can be introduced as required for clerodanes. The cyclic ether is inert towards most reagents, e.g. reductive-alkylation and organometallic reagents[8], while its conversion into an α,β-unsaturated lactone can be effected at a strategical moment in the sequence of transformations in the synthesis under study.

[†] This and subsequent compounds are pairs of enantiomers. In each case the isomer is drawn which corresponds to the stereochemistry of the natural clerodanes. All intermediates had mass, nmr and ir spectra in accord with their expected structures. Some were further characterised by carbon and hydrogen analyses.

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