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THE PREPARATION OF (±) 18,19-EPOXY-14,15,16-TRISNORCLERODAN-13-OIC ACID AS A KEY INTERMEDIATE IN THE TOTAL SYNTHESIS OF CLERODANE TYPE DITERPENES

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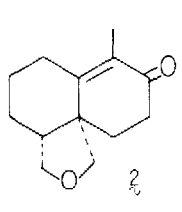
Summary: The stereospecific preparation of (±) 18,19-epoxy-14,15,16-trisnorclerodan-13-oic acid is described. This compound can serve as a key intermediate in the preparation of clerodane diterpenes as it possesses the right stereochemistry at all asymmetric centres.

In the course of our efforts directed towards the total synthesis of *trans*-clerodanes as illustrated by 1[1] we initially elected to undertake the synthesis of intermediate 7[+]. A major problem in the total synthesis of clerodanes is the stereoselective introduction of the substituents at C-8 and C-9. Several attempts to resolve this problem have been published[2-4]. Recently the first total synthesis of a clerodane was presented[5]. Although an elegant solution was found for the introduction of the substituents at C-9, the introduction of the methyl group at C-8 gave a 1 : 1 mixture of the two possible isomers.

We now present our solution to this problem following the route outlined below. Reductive alkylation of 2 with lithium in ammonia with allyl bromide as alkylating agent gave 3 in 70-85% yield. Analogous reductive alkylations are known to give the *trans*-decalin structure[2]. A 0.24 ppm upfield shift of the C-9 methyl in the nmr spectrum of 3 was observed on changing the solvent from $CDCl_3$ to hexadeuterobenzene. This value is in good agreement with an axial position of the C-9 methyl[6] as is required for the clerodane skeleton.

The next stage in the synthesis involved the introduction of a methyl group at C-8. Addition of methyllithium to 3 followed by hydrolysis gave the isomeric alcohols 4a and 4b.



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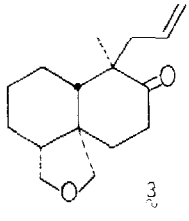

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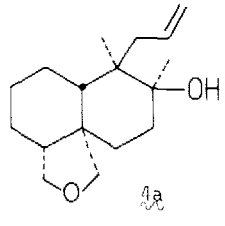
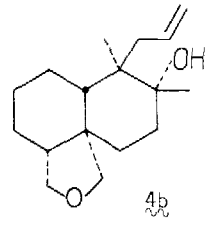


4a

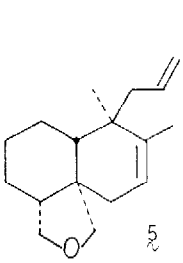


4b

Due to steric hindrance towards carbonyl addition, α deprotonation was a serious side reaction[7]; only 50% addition had taken place. By repeated addition of methyllithium to the hydrolysed products, a 95% conversion could be achieved. Dehydration of 4a and 4b by refluxing in benzene in the presence of boron-trifluoride etherate gave the diene 5 in quantitative yield. Hydroboration followed by Jones' oxidation of 5 afforded 6 in 56% yield.

An equilibration reaction with base was carried out in order to favour the energetically more stable equatoral position of the C-8 methyl. A Wolff-Kishner reduction of 6 gave the carboxylic acid 7 in 55% yield.

The nmr and ir data of 7 are in full agreement with those found by Payne and Jefferies for the same compound which was derived from a natural clerodane[8]. In one case only a short equilibration time of 6 was used. Gc-ms analysis of the methyl ester of the product after the reduction revealed then a 10% contamination by a second compound whose mass spectrum was fully identical with the mass spectrum of the methyl ester of 7. Probably this compound is the isomer with the C-8 methyl in axial position. We have shown that the cyclic ether is convertible into an unsaturated lactone[9]. Several ways are known for the termination of the side chain at C-9 which is now suitably functionalised[10].



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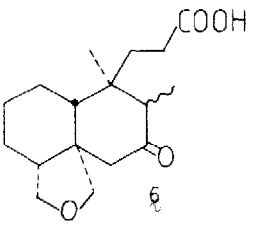

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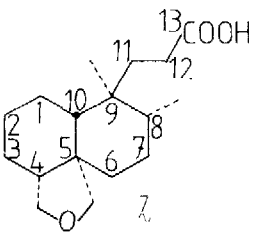

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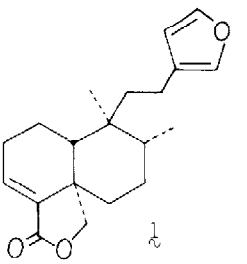

1

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†This and subsequent products are pairs of enantiomers. In each case the isomer is drawn which corresponds to 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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