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SYNTHESIS OF (+)-Isoeremolactone.

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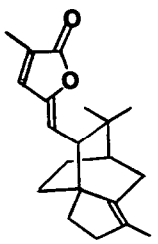
Abstract: The synthesis of (+)-isoeremolactone from tricyclovetivene has been achieved via a BF_3 catalysed epoxide rearrangement.

The biogenetically interesting diterpene, eremolactone was isolated by Jeffries[1] and Birch[2] from two species of the genus Eremophila. The structure of the more stable double bond isomer, isoeremolactone (1), was proven by X-ray analysis[3] which led to the deduction of the structure of eremolactone as (2). The absolute stereochemistry was not defined and the configuration of the C-2 methyl group is not certain, although on biogenetic grounds the β configuration would appear most likely.

There have been interesting synthetic routes[4] developed for the construction of the tricyclo[5.2.2.$0^{1,5}$] undecane skeleton but these lack the optimum fractionality for elaboration to (1), and, moreover, afford racemic products. Thus a chiral synthesis of isoeremolactone (1) poses considerable problems in construction of a suitably functionalised tricyclic skeleton having the correct relative and absolute stereochemistry for elaboration to the desired diterpene. It was considered that a valuable such intermediate to (1) would be the aldehyde (3) which could formally be combined with the known butenolide (6) to give isoeremolactone (1), although control of the stereochemistry of the exocyclic double bond would be expected to be difficult.

The most reasonable proposals[5] for the biogenesis of eremolactone (2) may be summarised as invoking cyclisation of (8) followed by oxidation and rearrangement to the hypothetical intermediate (10). Hydride transfer in (10) followed by skeletal rearrangement terminated by deprotonation would give isoeremolactone (1) or eremolactone (2). This sequence is in accord with the sesquiterpene biogenetic relationship between (-) β-acorenol[6] (9) and tricyclovetivene (11) and, indeed,Andersen[7] found that acid treatment of (11) afforded a hydrocarbon mixture containing the rearranged product (5) which is related to the proposed synthetic intermediate (3). It was therefore our intention to model a synthetic strategy to (3) from tricyclovetivene (11) which would have the advantage of chiral starting material, since (11) can be prepared readily from zizanoic acid (12) of known absolute configuration and already the subject of chiral



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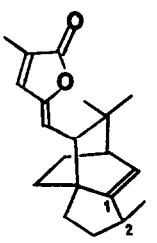

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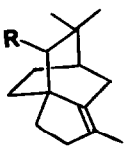
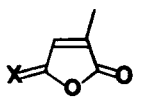
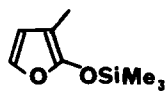


3 R=CHO
4 R=CH_2OH
5 R=Me



6 X=H_2
7 X=PPh_3



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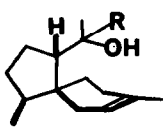
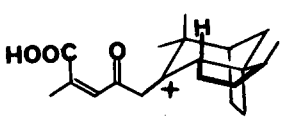


8 R=$CH_2CH_2CH=CMe_2$
9 R=Me



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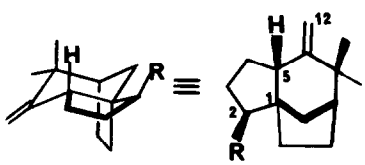
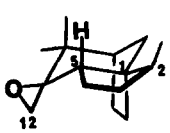


11 R=Me
12 R=COOH



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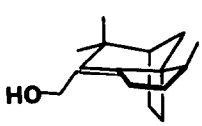

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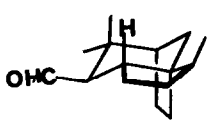

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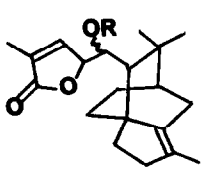
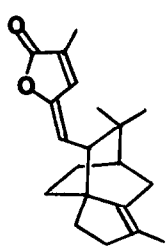


19 R=$SiMe_3$
20 R=H
21 R=SO_2Me



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synthesis.[8]

Tricyclovetivene (11) was treated with m.chloroperbenzoic acid to give 90% yield of a 4:1 mixture of epoxides in which the major epoxide was assigned the structure (13). It was envisaged that Lewis acid catalysed ring opening of the epoxide (13) with concomitant hydride transfer from C-5 would give the carbonium ion intermediate (14) which could suffer deprotonation to (15) or rearrangement to (4). Alternatively opening of the epoxide with hydride transfer from C-12 would produce the β-aldehyde (16). In the event treatment of (13) with $BF_3.Et_2O$ (1.5eq., Et_2O solvent, room temp., 16h) afforded a mixture of four non-hydrocarbon products from which the desired primary alcohol (4) was separated (30%) by chromatography on alumina. The other products were the mixture of ethers (17) and the aldehyde (16). The minor α-epoxide of (11) on similar $BF_3.Et_2O$ treatment gave a complex mixture of products including (4), in diminished yield, and both epimeric ethers (17) but no aldehyde (16) was found. Treatment of (4) with $BF_3.Et_2O$ did not give (17) and we propose that these ethers are formed by α-protonation of the allylic alcohol (15) followed by rearrangement and subsequent intramolecular trapping of a C-1 carbonium ion. There is a precedent[9] for the formation of tetrahydrofurans from rearrangement of epoxides derived from exo-methylene functions.

Oxidation of the alcohol (4) using pyridine chlorochromate in CH_2Cl_2 afforded by the aldehyde (3) in 80% yield after careful isolation by rapid chromatography on deactivated alumina (epimerisation of the CHO group ensued if activated alumina was used). Comparative NMR data showed that the aldehyde proton in the β-CHO epimer of (3) was shielded by the olefinic double bond relative to that for (3).

Comparison of the structures (1) and (3) initially suggested the final step in the synthesis to be a Wittig Reaction involving the phosphorane (7) which had previously been used in butenolide synthesis.[10] This reaction between (3) and (7) could not be achieved despite extensive experimentation and the solution to the problem came from the work of Asaoka[11] who reported the application of α-trimethylsilyloxyfurans to the synthesis of 4-ylidenebutenolides. Conversion of (6) to the moisture-sensitive furan (18) followed by reaction with the aldehyde (3) in CD_2Cl_2 at -78 °C in the presence of $SnCl_4$ gave (19) in almost quantitative yield. The trimethylsilyl ether required careful deprotection ($Bu_4\overset{+}{N}F^-$/HOAc in THF) to give the alcohol (20) which was converted to the mesylate (21) followed by treatment with Et_3N to give a product in 88% yield which represents the formal dehydration of (20). As noted earlier this conversion of (21) to the 4-ylidene-butenolide was expected to give a mixture of the desired Z-isomer (1) and the E-isomer (22) and, indeed, NMR showed the product to be a mixture of E and Z forms in the ratio 2:1 (E/Z). The geometric isomers were separated by careful chromatography over alumina and the E-isomer (22) was subjected to

X-ray analysis[12] which confirmed the structure in every respect. The synthetic Z-isomer (1) was shown to be identical with the authentic sample of isoeremolactone which was kindly supplied by Professor Jeffries. Since the absolute stereochemistry of zizanoic acid (12) is known[13] this synthesis defines the absolute configuration of isoeremolactone (1), however, the configuration of the C-2 methyl substituent of eremolactone (2) is still not established although biogenetic reasoning would suggest the β-configuration by analogy with tricyclovetivene (11).

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