Pergamon

Tetrahedron Letters, Vol. 37, No. 16, pp. 2877-2880, 1996

0040-4039/96 $15.00 + 0.00

S0040-4039(96)00411-X

Further Rearrangements of Diepoxycyclohexanes: Formation of Acetyldihydroxycyclopentane Derivatives

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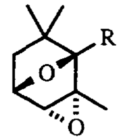
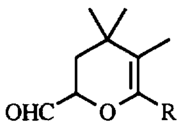
Abstract: 3,8-Dioxatricyclo[3.2.1.$0^{2,4}$]octane derivatives are readily prepared by the Diels Alder reaction of furan followed by epoxidation. The oxygen atoms are *cis* to each other and when treated with Lewis acids such as BF_3 rearrange stereospecifically to give derivatives of acetyldihydroxycyclopentane with all five ring atoms chiral. Evidence for an enol ether intermediate has been provided from the adduct using dimethyl acetylenedicarboxylate. Copyright © 1996 Elsevier Science Ltd

We have reported[1] that the diepoxycyclohexane **1** with the oxygen atoms *trans* to each other rearranges in the presence of $BF_3–Et_2O$ to the dihydropyrancarbaldehyde **2**. In order to study the general utility of this rearrangement further related compounds were prepared and reacted with $BF_3–Et_2O$ and other Lewis acids. So long as the epoxide was trisubstituted these compounds rearranged stereospecifically to give heavily substituted cyclopentane derivatives.

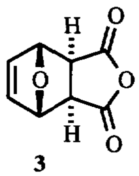


1



2

The diepoxycyclohexane ring system is readily available via a Diels-Alder reaction[2] between furan and a dienophile followed by epoxidation of the resultant double bond. Using furan and maleic anhydride the adduct **3** was converted[3] into the diester **4** with the epoxy oxygen atoms *cis* to each other. Only starting material was recovered when the diester **4** was treated with $BF_3–Et_2O$. All attempts at preparing the isomer of **4** with *trans* epoxy oxygen atoms failed. However the probable cause of its lack of reactivity is the absence of a third substituent on the epoxide ring as found in **1**. It is of note that when activated by a benzene ring a related diepoxycompound readily undergoes an acid catalysed rearrangement.[4-6]



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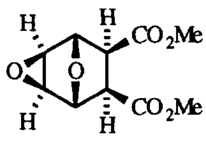

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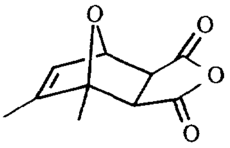
The Diels Alder reaction between 2,3-dimethylfuran[7] and maleic anhydride gave the adduct **5** (90%)[8] which was converted (*m*-CPBA followed by hydrolysis) into the diacid **6** (5%). When treated with BF_3–Et_2O (20 °C, 60 sec) this diacid gave the lactone **7** (77%). With acidic methanol either **6** or **7** gave the ester **8**. Reduction of the anhydride **5** followed by epoxidation gave the diol **9** (86%) which in the presence of acid rearranged to the ether **10**. These rearrangements are analogous to those observed before[1] but with the intermediate carbocation trapped by the adjacent carboxyl or alcohol group giving a lactone or ether repectively (**Scheme 1**).



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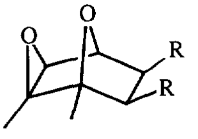
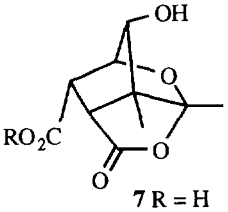
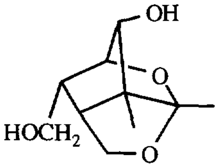


6 R = CO_2H
9 R = CH_2OH
15 R = Me



7 R = H
8 R = Me



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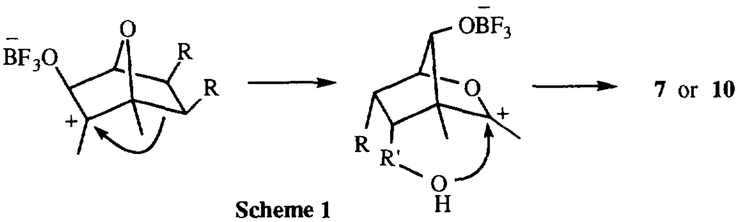
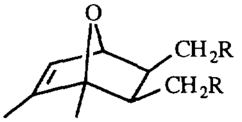
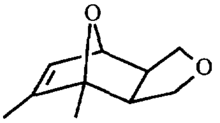


Scheme 1

To prevent lactone or ether formation the diol **11** was treated with tosyl chloride to give a mixture of the ditosylate **12** (52%) and tricyclic ether **13** (28%). $LiAlH_4$ reduction of **12** gave the tetramethyl derivative **14** (52%). Epoxidation of **14** gave the *cis* diepoxy compound **15** (81%) which with BF_3–Et_2O (0 °C, 15 min) gave the dihydroxyketone **16**‡ (52%). The relative stereochemistry shown was deduced from nOe experiments. Only a *cis* diol was isolated from this reaction. Epoxidation (40%) of the tricyclic **13** followed by treatment with BF_3–Et_2O (0 °C, 45 min) gave the bicyclic ketone **17**‡ (23%). The stereochemistry of **17** was shown by X-ray crystallography.[9] The stereochemistry of these diols (**16** and **17**) may be explained by **scheme 1** followed by **scheme 2** with the formation of the unstable enol ether **18** which is hydrolysed on work up.



11 R = OH
12 R = OTs
14 R = H



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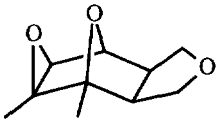

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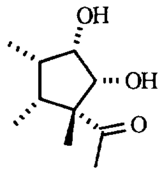
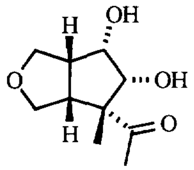


16



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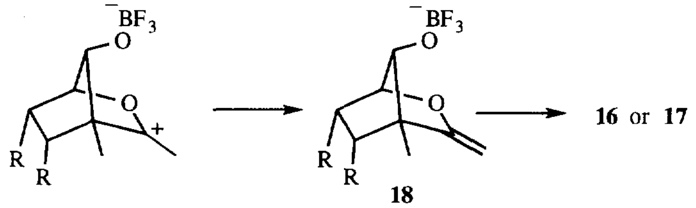
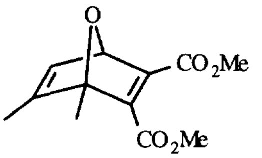


Scheme 2

An alternative possible intermediate is ring closure of the zwitterion (see **scheme 2**) to give an oxetane ring. This highly strained ketal would be expected to hydrolyse readily to give the dihydroxyketone **16** or **17**. Some support for the enol ether intermediate comes from reactions using dimethyl acetylenedicarboxylate. The adduct with 2,3-dimethylfuran, **19**, was converted into the epoxide **20**. Treatment with BF_3–Et_2O or lithium perchlorate gave a complex mixture of unstable products which could not be characterised. However treatment of **20** with magnesium bromide gave the enol ether **21**‡ (46%). This product was not very stable and the expected hydrolysis products could not be isolated.



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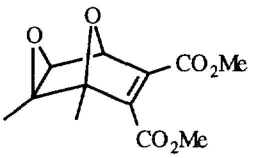

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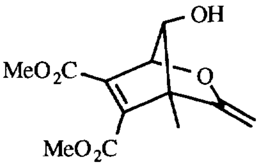

21

It must be concluded that the difference in the course of the rearrangement between the compounds with *trans* oxygen atoms and those with *cis* oxygen atoms is that carbocation trapping is preferred to rearrangement. However the *trans* co-planar relationship of the relevant oxygen to the carbocation may facilitate formation of the aldehyde **2**. This rearrangement offers a facile method for the stereospecific synthesis of highly functionalised cyclopentane ring systems.

We thank the Palm Oil Research Institute of Malaysia for a studentship (CKO), University of London Ukrainian Scholarship Programme (GVB) and M Motevalli for the X-ray study of **17**.

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9. Details to be published separately.

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‡ Spectroscopic data for (**16**) ^{1}H: δ 0.91 (d, J = 7.5 Hz, 4-Me), 0.97 (d, J = 7.5 Hz, 5-Me), 1.41 (s, 3-Me), 1.97 (dq, J = 9.5, 7.5 Hz, 4-H), 1.64 (b, OH), 2.20 (s, Ac), 2.43 (ddq, J = 6.3, 9.5, 7.5 Hz, 5-H), 3.65 (b, OH), 3.87 (d, J = 7.0 Hz, 2-H), 4.07 (dd, J = 6.3, 7.0 Hz, 1-H); ^{13}C: δ 9.7, 12.4 (4-Me and 5-Me), 24.6 (3-Me), 30.3 (Ac), 37.6, 45.6 (C4 and C5), 61.0 (C3), 74.2, 81.1 (C1 and C2), 218.0 (Ac).

Spectroscopic data for (**17**) ^{1}H: δ 1.18 (s 4-Me), 2.24 (s, Ac), 2.64 (ddd, J = 5, 8.5, 9 Hz, 3a-H), 2.90 (m, 6a-H), 3.44 (dd, J = 7, 9 Hz, 1-H), 3.70 (dd, J = 8.5, 10 Hz, 3-H), 3.82 (dd, J = 5, 10 Hz, 3-H), 3.98 (d, J = 4.5 Hz, 5-H), 4.14 (dd, J = 3.5, 9 Hz, 1-H), 4.46 (dd, J = 4.5, 9 Hz, 1-H); ^{13}C: δ 24.7 (4-Me), 27.8 (Ac), 44.5, 51.2 (C3a and C6a), 60.9 (C4), 67.9, 71.8, 72.0, 78.1 (C1, C3, C5 and C6), 211.6 (Ac).

Spectroscopic data for (**21**) ^{1}H: δ 1.67 (s, C-Me), 2.22 (d, J = 9 Hz, OH), 3.74 and 3.77 (s, O-Me), 4.29 (d, J = 9 Hz, 7-H), 4.96 (s, 1-H), 5.20 and 5.27 (d, J = 1 Hz, =CH_2); ^{13}C: δ 13.9 (4-Me), 52.4 (OMe), 72.7 (C7), 84.5 (C1), 89.5 (C4), 109.7 (=CH_2), 140.3 (C6), 148.6, 149.0 (C3, C5), 162.2, 163.4 (CO_2).

(*Received in UK* 7 *February* 1996; *revised* 28 *February* 1996; *accepted* 1 *March* 1996)