Tetrahedron Vol 39, No 20, pp 3397 to 3403, 1983
Printed in Great Britain

0040-4020/83 $3.00 + .00
Pergamon Press Ltd.

TRANSANNULAR CYCLISATION OF ISOGERMACRONE-EPOXIDES

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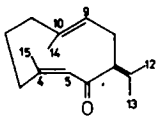
(*Received in UK 15 February* 1983)

Abstract—Isogermacrone-epoxide **2** undergoes acid- and base-induced transannular cyclisation yielding the eudesmane derivatives **8** and **12**, respectively, while on treatment with Lewis acid isogermacrone-diepoxide **3** is converted into **11**. The structure and stereochemistry of the cyclisation products have been elucidated by spectral methods and that of **8** has been determined by X-ray analysis. The mechanism of the cyclisation reactions is discussed briefly.

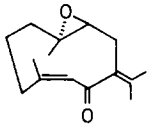
Recently we reported that the transannular cyclisation of isogermacrone by oxymercuration-demercuration proceeds highly regio-and stereoselectively leading to products with *trans*-eudesmane skeleton.[1] At that time we believed isogermacrone to be an *E,E*-germacradiene and our results was in accordance with the generalisation that *E,E* - 1,5 - germacradienes afford *trans*-decalin cyclisation products.[2-4] However, it was established by X-ray analysis[5] and ^1H and ^{13}C NMR studies[6] that isogermacrone possesses the germacra-4*Z*, 9*E*-diene system, as shown in **1**. Reconsidering our previous results,[1] the formation of *trans*-decalins can be rationalized in terms of $Hg(OAc)_2$ preferential attack at the *Z*-double bond. Although numerous studies on *Z,E* - germacradienes have demonstrated the formation of *cis*-decalins[7,8] as the electrophilic reagents attacks the *E*-bond, there are cases in which the cyclisation leads to guaiane and cadinane derivatives,[9] as well as to *trans*-decalins.[10] All this prompted us to extend our investigation to the transannular cyclisation of isogermacrone - 9,10 - epoxides as in this way an electrophilic attack at the *Z*-bond would be prevented. In the present paper we wish to describe some results of the acid- and base-induced cyclisation of the isogermacrone-epoxides **2** and **3**.

Epoxidation of **1** *and* **2**

Treatment of isogermacrone, **1** with *m*-Cl-perbensoic acid (*m*CPBA, 1 mole equiv.) in the presence of solid Na_2CO_3 afforded the epoxides **2** and **3** in the ratio of 9.8 : 0.1. The monoepoxide **2** crystallized directly from the oxidation mixture and was characterized by spectral methods after recrystallisation. MS, UV and IR data (Experimental), as well as the ^1H NMR data (Table 1) are in good agreement with structure **2**. Since the epoxidation with peracids is known to proceed stereospecifically,[11] a *trans*-configuration of the 9,10-oxirane is to be expected. This was confirmed by the stereochemistry of the cyclisation product **8**. Because of the low yield of the diepoxide **3** we failed to isolate it as a pure substance. An indication for the presence of **3** and its structure came from the nature of the cyclisation products of the crude oxidation mixture (see below) and from the spectral data of the latter. Alongside the signals due to **2**, the ^1H NMR exhibited two singlets at δ 1.25 and 1.30 each one for a Me group at C-atom bearing an O function, and a doublet of doublets (J = 10.5, 2) at δ 2.97 for H-9). Furthermore, a peak corresponded to the molecular ion of **3** (*m/z* 250) was clearly visible in the mass spectrum.



1



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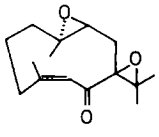


3

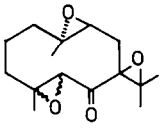
In order to obtain a larger amount of **3**, isogermacrone, **1** was subjected to epoxidation with 2 mole of *m*CPBA. However, the ratio of **2** and **3** in the resulting oxidation mixture turned out to be again 9.8 : 0.1. Then we tried to obtain **3** by epoxidation of **2** with H_2O_2 in alkaline medium. A complex mixture was obtained from which three crystalline compounds **A**, **B** and **C** were isolated in the ratio of 3 : 1 : 0.5 after repeated preparative TLC separation. On the basis of the spectral data $-C_{15}H_{22}O_4$ (*m/z* 266, M^+), IR (1717 cm^{-1}) and ^1H NMR (Table 1) the structure of the triepoxide **4** was assigned to the minor product **C**. The compounds **A** and **B** showed very similar chromatographic and spectral properties, in fact they differed mainly by their m.ps – 123–125° and 76–78°, respectively. From the IR, UV and ^1H NMR data (Table 1), and the identical MS ($C_{15}H_{22}O_3$, *m/z* 250, M^+) it was deduced that both **A** and **B** are isogermacrone - 4,5 - 9,10 - diepoxides. Since conformational change including the oxirane in the starting epoxide **2** is very unlikely due to the steric hinderance, **A** and **B** may be supposed to be the corresponding conformers **5** and **6**. NOE experiments

Table 1. 400 MHz ^{1}H NMR[a] of 2, 4, 5, 7, 8, 11 and 12

Protons	2	4	5	7	8	11	12
H-3	0.98 ddd (J=13,13,4)	-	0.87 ddd (J=14,14,3.5)	-	5.53 m	5.60 m	-
H-5	6.14 sbr	4.15 s	3.63 s	3.72 s	2.77 sbr[b]	2.79 sbr[b]	-
H-8	2.86 dbr (J=16)	2.08 d (J=14.5)	2.93 dd (J=16,4)	2.93 dd (J=15,2)	2.84 dd (J=15,4.5)	2.04 d (J=13)	2.91 dd (J=15,6)
H-8'	2.17 ddbr (J=16,11)	2.18 dd (J=14.5,11)	2.24 dd (J=16,11)	2.09 ddbr (J=15,11)	2.47 ddbr (J=15,9.5)	2.62 dd (J=13,6)	2.37 dd (J=15,11)
H-9	2.81 d (J=11)	2.96 d (J=11)	2.80 dd (J=11,4)	2.67 dd (J=11,2)	3.94 dd (J=9.5,4.5)	3.83 d (J=6)	3.72 dd (J=11,6)
H-12	1.69 sbr	1.30 s	1.80 s	1.77 s	1.63 s	1.25 s	1.80 s
H-13	1.71 sbr	1.41 s	1.92 s	1.84 sbr	1.94 sbr	1.35 s	2.08 sbr
H-14	1.19 s	1.15 s	1.18 s	1.14 s	0.94 s	1.11 s	0.98 s
H-15	1.88 sbr	1.45 s	1.46 s	1.44 s	1.78 s	1.89 s	1.90 s

[a] In $CDCl_3$, δ = ppm from TMS, J in Hz

[b] double resonance showed homoallylic coupling between H-5 and H-3



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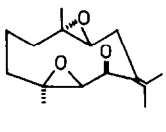

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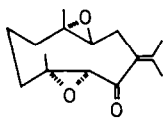

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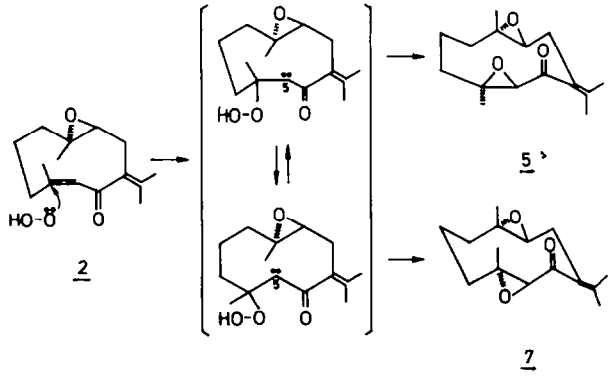
confirmed that **B** has the stereochemistry of both oxiranes as shown in **5**. This configuration was further supported by the ^{1}H NMR signal at δ 0.87 due to H-3. The molecular models show that when a *Z*-oxirane or double bond is present one of the C-3 methylene protons would be strongly shielded. Similarly the H-3 signal in **2** appears at δ 0.98. However, such a high field signal was not observed in the ^{1}H NMR of **A**. Furthermore, the NOE between H-5 and H-9 provided evidence about the *E*-configuration of the 4,5 - oxirane and *syn*-relationship of C-4 and C-10 Me groups, as shown in **7**. It is known [12,13] that the base-catalyzed epoxidation of α,β-unsaturated ketones proceeds in a non-stereospecific manner, although a high stereoselectivity is observed in several cases due to the stabilisation of the intermediate hydroperoxycarbanion by orbital overlap and charge delocalisation.[14,15] Hence, on epoxidation of **2** the carbanion obtained by inversion at C-5 (Scheme 1) is more stable and this explains the formation of **7** as the main product. Obviously the flexibility of the 10-membered ring facilitated such an inversion which leads to the more favourable isomeric epoxide. A similar case was recently reported to occure by alkaline epoxidation of the sesquiterpene ketone zerumbone.[16]

Cyclisation of **2** *and* **3**

When treated with $BF_3.Et_2O$ (1 mole equiv) the epoxide **2** was readily converted into the compounds **8** and **9** with 80.5 and 8.2% yield, respectively. The structure of the lactone **9** and the most probable mechanism of its formation have been described by us recently.[17] The structure of the ketol **8** followed from the spectral data which showed the molecular formula $C_{15}H_{22}O_2$ (*m/z* 234,



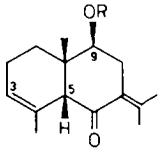
Scheme 1.

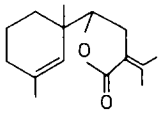
Table 2. ^{13}C NMR OF **8** and **11**

Carbon number	8	11
1	34.4 t	35.4 t
2	22.2 t	21.2 t
3	123.0 d	123.9 d
4	129.2 s*	129.4 s
5	60.6 d	56.5 d
6	204.8 s	195.0 s
7	129.9 s*	84.4 s
8	30.1 t	24.4 t
9	70.4 d	80.7 d
10	39.2 s	43.9 s
11	142.8 s	75.9 s
12	22.8 q*	26.2 q*
13	22.7 q*	27.9 q*
14	20.0 q	21.5 q
15	21.9 q	22.2 q

*Assignment may be interchanged.

M^+), a result reinforced by ^{13}C NMR (Table 2); the presence of the enone moiety (1680, 1620 cm^{-1}) and a OH group (3480 cm^{-1}) easily acetylated with Ac_2O/Py to give **10** (1750, 1250 cm^{-1}). The equatorial configuration of the C-9 O-function followed from the coupling constants of the H-9 signal of **8** and **10** (J = 9.5, 4.5). Further, the ^1H NMR (Table 1) revealed one tertiary and three olefinic Me groups (δ 0.94, 1.63, 1.78, 1.94). Since only





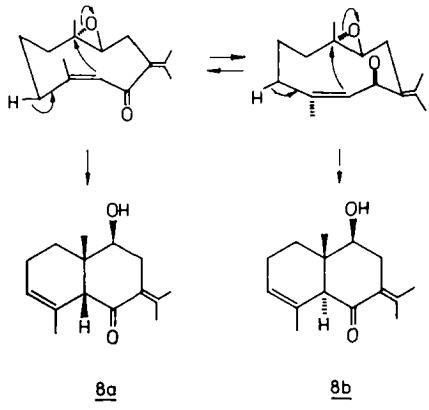
8 R=H

10 R=Ac

9

the signal at δ 1.63 showed a positive solvent induced shift of 0.21 ppm on passing from $CDCl_3$ to C_6D_6 it must correspond to the C-12 Me group. The ketol **8** is optically unactive. As the starting epoxide **2** is a racemic mixture, one may suppose the product **8** to be a racemic mixture too. However, when the possibility that both conformers of **2** may undergo an intramolecular cyclisation is taken into account, a mixture of the corresponding diastereomeric ketols **8a** and **8b** is to be expected (Scheme 2). Hence, the problem was to establish the stereochemistry of the ring junction. As ^1H and ^{13}C NMR data were not very helpful, this problem was solved by single crystal X-ray crystallography.

Details of the analysis are given in the Experimental. Tables 3–6 list fractional coordinates, bond lengths and angles, and torsion angles.[18] Figure 1 depicts a general view of the molecular structure of **8**. The compound is a *cis*-decalin with an equatorial OH group which is (–) synclinal with respect to the C-10 Me group [O(2)–C(9)–C(10)–C(14) = –58.9°]. The cyclohexene ring has a half-chair configuration with C-1 and C-10 lying 0.34 and –0.40 Å out of the plane of the other four atoms. The



8a **8b**

Scheme 2.

Table 3. Fractional atomic coordinates with E.S.D.S. in brackets

Atom	X/A	Y/B	Z/C
O(1)	0.1665(2)	0.0982(4)	-0.2373(2)
O(2)	0.3083(2)	0.4140(4)	0.1429(2)
C(1)	0.4533(3)	0.1844(7)	0.1021(3)
C(2)	0.4402(4)	0.0411(8)	0.1688(3)
C(3)	0.3711(4)	-0.0857(6)	0.0977(4)
C(4)	0.3094(3)	-0.0651(5)	-0.0053(3)
C(5)	0.3034(3)	0.0952(4)	-0.0629(3)
C(6)	0.1903(3)	0.1270(4)	-0.1399(3)
C(7)	0.1115(3)	0.1951(4)	-0.0936(3)
C(8)	0.1568(3)	0.3213(4)	-0.0076(3)
C(9)	0.2668(3)	0.2809(5)	0.0721(3)
C(10)	0.3475(3)	0.2371(5)	0.0162(3)
C(11)	0.0093(3)	0.1462(5)	-0.1271(3)
C(12)	-0.0711(3)	0.2187(7)	-0.0841(4)
C(13)	-0.0368(3)	0.0166(6)	-0.2114(4)
C(14)	0.3679(3)	0.3783(5)	-0.0493(4)
C(15)	0.2492(4)	-0.2003(6)	-0.0740(5)
H(1)	0.482(4)	0.283(7)	0.147(4)
H(2)	0.502(4)	0.148(7)	0.062(4)
H(3)	0.511(4)	-0.003(7)	0.210(4)
H(4)	0.406(4)	0.082(7)	0.225(4)
H(5)	0.369(4)	-0.195(7)	0.131(4)
H(6)	0.345(3)	0.082(5)	-0.111(3)
H(7)	0.157(3)	0.424(6)	-0.043(4)
H(8)	0.106(4)	0.343(6)	0.037(4)
H(9)	0.255(3)	0.182(6)	0.114(3)
H(10)	-0.105(4)	0.146(6)	-0.056(4)
H(11)	-0.046(4)	0.277(7)	-0.015(4)
H(12)	-0.129(4)	0.252(7)	-0.148(4)
H(13)	-0.081(4)	0.061(7)	-0.280(4)
H(14)	-0.073(4)	-0.057(7)	-0.169(5)
H(15)	0.020(5)	-0.047(7)	-0.227(5)
H(16)	0.296(4)	0.401(6)	-0.117(4)
H(17)	0.390(4)	0.467(6)	-0.003(4)
H(18)	0.424(4)	0.347(6)	-0.080(4)
H(19)	0.160(4)	-0.178(7)	-0.103(4)
H(20)	0.270(4)	-0.214(7)	-0.135(4)
H(21)	0.263(4)	-0.295(7)	-0.028(4)
H(22)	0.268(4)	0.412(6)	0.189(4)

Table 4. Bond distances (Å) with E.S.D.S. in brackets

O(1)–C(6)	1.221(5)	C(5)–C(10)	1.549(5)
O(2)–C(9)	1.430(5)	C(6)–C(7)	1.488(4)
C(1)–C(2)	1.522(8)	C(7)–C(8)	1.507(6)
C(1)–C(10)	1.535(7)	C(7)–C(11)	1.343(6)
C(2)–C(3)	1.499(8)	C(8)–C(9)	1.518(6)
C(3)–C(4)	1.324(8)	C(9)–C(10)	1.531(4)
C(4)–C(5)	1.523(5)	C(10)–C(14)	1.532(6)
C(4)–C(15)	1.494(7)	C(11)–C(12)	1.494(5)
C(5)–C(6)	1.522(6)	C(11)–C(13)	1.515(7)

Table 5. Valence angeles (°) with E.S.D.S. in brackets

C(2)–C(1)–C(10)	112.7(4)	C(8)–C(7)–C(11)	124.1(3)
C(1)–C(2)–C(3)	111.7(4)	C(7)–C(8)–C(9)	113.7(3)
C(2)–C(3)–C(4)	124.9(5)	O(2)–C(9)–C(8)	109.9(3)
C(3)–C(4)–C(5)	121.5(4)	O(2)–C(9)–C(10)	108.1(3)
C(3)–C(4)–C(15)	122.0(4)	C(8)–C(9)–C(10)	113.5(3)
C(5)–C(4)–C(15)	116.2(4)	C(1)–C(10)–C(5)	108.2(3)
C(4)–C(5)–C(6)	110.6(3)	C(1)–C(10)–C(9)	110.0(3)
C(4)–C(5)–C(10)	113.7(3)	C(5)–C(10)–C(9)	109.2(3)
C(6)–C(5)–C(10)	111.8(3)	C(1)–C(10)–C(14)	109.5(4)
O(1)–C(6)–C(5)	120.0(3)	C(5)–C(10)–C(14)	108.6(3)
O(1)–C(6)–C(7)	121.6(4)	C(9)–C(10)–C(14)	111.4(3)
C(5)–C(6)–C(7)	118.4(3)	C(7)–C(11)–C(12)	122.0(4)
C(6)–C(7)–C(8)	114.1(3)	C(7)–C(11)–C(13)	124.8(3)
C(6)–C(7)–C(11)	121.8(3)	C(12)–C(11)–C(13)	113.2(4)

Table 6. Torsion angels (°) with E.S.D.S. in brackets

Cyclohexene ring		Cyclohexanone ring	
C(5)–C(10)–C(1)–C(2)	−60.3(5)	C(8)–C(9)–C(10)–C(5)	−56.7(4)
C(10)–C(1)–C(2)–C(3)	44.8(6)	C(9)–C(10)–C(5)–C(6)	51.3(4)
C(1)–C(2)–C(3)–C(4)	−14.2(8)	C(10)–C(5)–C(6)–C(7)	−45.0(4)
C(2)–C(3)–C(4)–C(5)	0.3(8)	C(5)–C(6)–C(7)–C(8)	39.6(4)
C(3)–C(4)–C(5)–C(10)	−16.6(6)	C(6)–C(7)–C(8)–C(9)	−41.9(4)
C(4)–C(5)–C(10)–C(1)	44.8(4)	C(7)–C(8)–C(9)–C(10)	52.5(4)
Other selected torsion angles			
C(1)–C(10)–C(5)–C(6)	171.0(3)	C(8)–C(7)–C(11)–C(12)	2.3(6)
C(14)–C(10)–C(5)–C(4)	163.6(3)	C(8)–C(7)–C(11)–C(13)	−178.4(4)
C(14)–C(10)–C(5)–C(6)	−70.3(4)	C(6)–C(7)–C(11)–C(12)	−177.5(4)
C(9)–C(10)–C(5)–C(4)	−74.8(4)	C(6)–C(7)–C(11)–C(13)	1.7(6)
O(2)–C(9)–C(10)–C(14)	−58.9(3)	O(1)–C(6)–C(7)–C(11)	40.3(5)

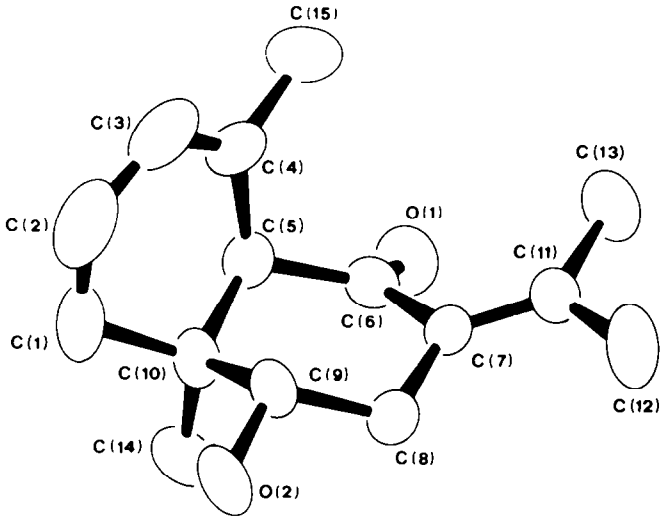
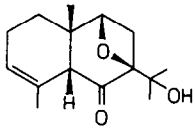


Fig. 1.

cyclohexanone ring has a chair configuration with remarkable deviation of the ring torsion angles from the theoretical values.[19] The flattering occurs along the sequence C(5)–C(6)–C(7)–C(8). Torsion angles C(6)–C(7)–C(11)–C(13) = 1.7° and C(8)–C(7)–C(11)–C(12) = 2.3° indicate the presence of two strictly planar fragments in this part of the molecule. A similar geometrical feature was observed in the crystal structure of cuahtemone.[20] The enone system is not planar, as indicated by the endocyclic and exocyclic torsion angles of Table 6. This is in good agreement with the intensity of the UV absorption ($\epsilon = 7640$). Furthermore, the space group of the crystal is centrosymmetric which means that both enantiomers are present. The formation of the racemic ketol **8a** as the single product of the transannular cyclisation leads to the conclusion that the reaction proceeds stereospecifically. On the other hand, the absence of cyclisation products positionally isomeric of **8a** at the endocyclic double bond provided evidence about the suggestion that the transannular C–C formation occurs synchronously with the elimination of a C-3 H-atom, as shown in Scheme 2.

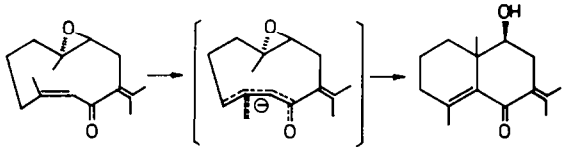
When the crude reaction mixture obtained after epoxidation of **1** was treated with $BF_3.Et_2O$ a new crystalline compound (2% yield) was isolated together with **8** and **9**. As judged from the MS ($C_{15}H_{22}O_3$, m/z 250, M^+) and ^{13}C NMR spectra (Table 2) three O-atoms are present in the molecule of this compound. An OH and a CO-group (3400, 1720 cm^{-1}) account for two of them. Since ^1H NMR (Table 1) exhibited only one signal characteristic for a proton on an oxirane (δ 3.83), the remaining O-atom must be part of a ring attached to a secondary and a tertiary C-atom. Based on this evidence, this compound was concluded to possess structure **11** and to be a cyclisation product of the diepoxide **3**. Structure **11** is in good agreement with the other spectral data. The ^1H NMR signals for two Me groups on an O-bearing C-atom (δ 1.25, 1.35) together with the base peak at m/z 192 due to an ion obtained by McLafferty rearrangement, clearly showed that the OH group is located at C-11. Further, the ^1H NMR displayed the signals for the C-8 methylene protons at δ 2.04 and 2.62 as doublet and doublet of doublets with $J_{gem} = 13$ and $(J_{8',9}) = 6$, a coupling which requires a dihedral angle H-9/H-8 of approx. 90°. The



11

latter was found to be present in the Dreiding model of **11**. A comparison of the ^1H NMR of **8** and **11** showed that the chemical shifts of H-5 in both compounds are quite identical but the C-10 Me signal of **11** is paramagnetic shifted with 0.17 ppm with respect to this of **8**. This indicated a syn-relationship betwen the O-ring and C-10 Me group which is in agreement with the configuration of the 9,10-oxirane in the initial epoxide **3**. The next problem was the stereochemistry of the ring junction. Based on the very close ^{13}C NMR correlation between **8** and **11** we tentatively prefer a *cis*-decalin system for **11**. The available small quantities of **3** and **11** respectively do not allow any additional chemical transformations in order to establish the stereochemistry of the decalin skeleton unambiguously.

We further examined the base-induced cyclisation of **2** using basic alumina, as follows. The epoxide **2** was directly absorbed on basic alumina for 72 hr and then eluted with ether to give the ketol **12** in 60% yield. The spectral data-UV (280 nm), IR (3450, 1655, 1625, 1615 cm^{-1}) and ^1H NMR (Table 1) are consistant with structure **12**. The latter was further confirmed by the following base-catalyzed isomerisation of **8**. On treatment with NaOEt in EtOH **8** was easily converted into the fully conjugated ketone **12**. The formation of the cyclisation product **12** proceeds most probably via an enolate anion intermediate, as shown in Scheme 3.



2 12

Scheme 3.

EXPERIMENTAL

M.ps are uncorrected. UV: in EtOH; IR: film or KBr pellets; ^{1}H NMR: in $CDCl_3$ (unless indicated otherwise) at 250 and 400 MHz, chemical shifts in δ downfield from TMS, J values in Hz; ^{13}C NMR: in $CDCl_3$ at 63 MHz; low resolution MS at 70 eV; preparative TLC (PTLC): on Kieselgel 60 PF_{254} (Merck). "Work-up in the usual way" implies dilution with water, extraction with ether, washing, drying (Na_2SO_4) and removal of the solvent under reduced pressure.

Epoxidation of isogermacrone **1**. To a soln of **1** (1.09 g, 5 mmole) in $CHCl_3$ (10 ml) was added solid Na_2CO_3 (2 g) and the suspension was stirred vigorously at room temp. Then 70% *m*CPBA (1.23 g, 5 mmol) in $CHCl_3$ (25 ml) was added dropwise over 15 min and stirring was continued for a further 30 min. Work-up in the usual way gave a semicrystalline product (1.45 g). Crystallisation from hexane-ether (7 : 1) gave **2** (1.07 g): m.p. 68–70°; λ_{max} 251 nm (ϵ = 7640); IR (KBr): 1680, 1630, 1140, 1090 cm^{-1}; MS: m/z = 234 (80, M$^+$), 219 (40), 191 (50); ^{1}H NMR: in Table 1.

Epoxidation of epoxide **2**. To a soln of **2** (350 mg) in MeOH (5 ml) was added by stirring and cooling to 15° successively 30% H_2O_2 (0.5 ml) and 4% NaOH aq (0.15 ml). The stirring was continued for 3 hr and the temp. was raised to 22°. The mixture was worked-up in the usual way and the crude product (350 mg) was separated by PTLC to give **4** (15 mg): m.p. 88–90° (petrol ether/ether 5 : 1); MS: m/z = 266 (13, M$^+$), 251(22), 233(40); **5** (30 mg): m.p. 76–78° (petrol ether/ether 5 : 1); λ_{max} 254 nm (ϵ = 4150); IR (KBr): 1707, 1650 cm^{-1}; MS: m/z = 250 (8, M$^+$), 235(10), 222(16) and **7** (90 mg): m.p. 123–125° (petrol ether/ether 7 : 1); λ_{max} 252 nm (ϵ = 4075); IR (KBr): 1694, 1657 cm^{-1}; MS: identical to that of **5**. ^{1}H NMR of **4**, **5** and **7**: in Table 1.

Cyclisation of **2** *and* **3**

(a) To a soln of **2** (220 mg, 1 mmole) in dry ether (5 ml) was added freshly destilled $BF_3.Et_2O$ (0.5 ml, 1 mmole) at 0° and the mixture was kept at this temp for 45 min. Work-up in the usual way and separation on PTLC gave **9** (17 mg) and **8** (177 mg): m.p. 99–101° (hexane/ether 10 : 1); IR and UV: in the text; MS: m/z = 234 (75, M$^+$), 219(13), 201(10); ^{1}H and ^{13}C NMR: in Tables 1 and 2.

(*b*) Treatment of the crude product after epoxidation of **1** (500 mg) with BF_3Et_2O (1 ml) under the same conditions as above and subsequent separation of PTLC gave **9** (35 mg), **8** (350 mg) and **11** (10 mg): m.p. 107–109° (hexane/ether 7 : 1); MS: m/z = 250 (8, M$^+$), 192(100), 177(57); ^{1}H and ^{13}C NMR: in Tables 1 and 2.

(c) A soln of **2** (150 mg) in petrol ether–ether (1:2) was absorbed on basic Al_2O_3 (50 g) and kept at room temp for 72 hr. Elution with the same solvent gave unreacted **2** (20 mg). Further elution with ether gave **12** (90 mg): viscous liquid, λ_{max} 280 nm (ϵ = 9190); MS: m/z = 234 (55, M$^+$), 219 (20), 201 (7); ^{1}H NMR: in Table 1.

Acetylation of **8**. To a soln of **8** (100 mg) in dry pyridine (3 ml) was added Ac_2O (2 ml) and the mixture was kept at room temp overnight. Work-up in the usual way and purification on PTLC gave **10** (90 mg): viscous liquid. λ_{max} 254 nm (ϵ = 7700); IR (film): 1750, 1690, 1630, 1250 cm^{-1}; MS: m/z = 276 (10, M$^+$), 216(75), 201(20); ^{1}H NMR (250 MHz): 1.00 (3H, s, H-14), 1.74 (3H, s, H-15), 1.67 (3H, sbr, H-12), 1.95 (3H, sbr, H-13), 2.50 (1H, dd, J = 14, 4.5, H-8), 2.90 (1H, dd, J = 14, 8, H-8'), 5.10 (1H, dd, J = 8, 4.5, H-9), 2.77 (1H, s, H-5), 5.53 (1H, m, H-3), 2.07 (3H, s, OCH_3).

Isomerisation of **8**. To a soln of Na (100 mg) in EtOH (5 ml) was added **8** (60 mg) and the mixture was kept at room temp for 2 hr. Work-up in the usual way and purification of PTLC gave **12** (40 mg).

X-Ray analysis of **8**. Single crystals of **8** were obtained by slow evaporation of cyclohexane–benzene (1 : 1). They were monoclinic, space group $P2_1/c$ (C_{2h}, No 14), with a = 13.298(7), b = 8.351(2), c = 13.014(8) Å, β = 109.81(4)°, V = 1360 Å^3, D_c = 1.144 gxcm^{-1}, Z = 4. The unit-cell parameters were determined on a four-circle diffractometer by least-squares refinement of the

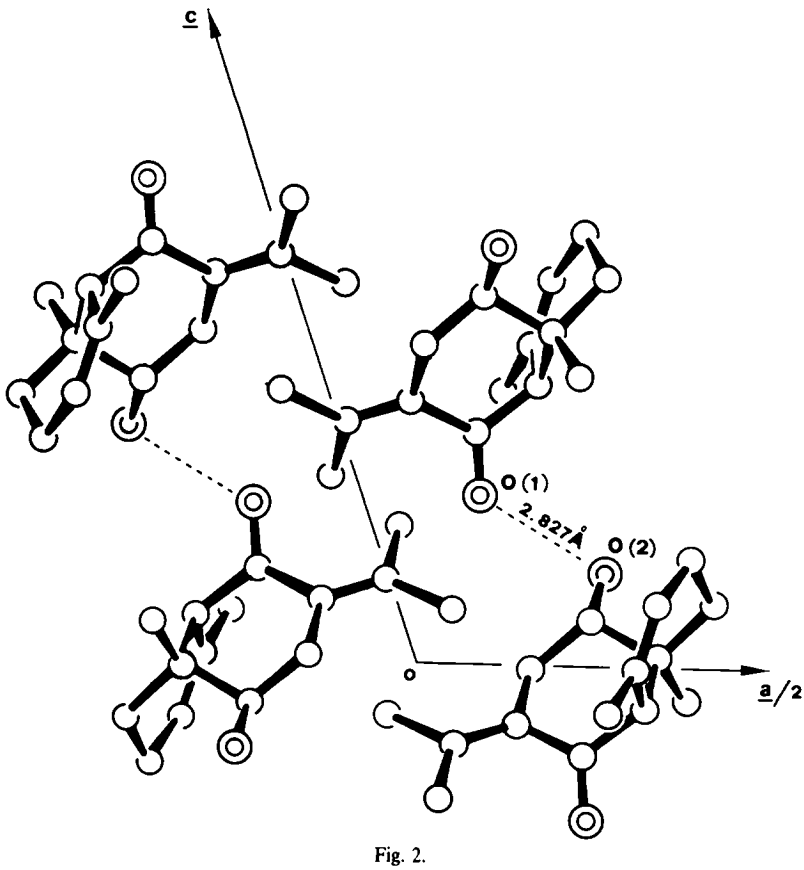


Fig. 2.

values of the setting angles of 15 selected reflections, using Mo–K_α radiation ($\lambda = 0.71059$ Å). The intensity data were collected on the diffractometer at room temp with $2\nu - \nu$ scanning mode up to $\sin \nu/\lambda = 0.63$ Å^{-1} using the crystal of $0.5 \times 1.0 \times 0.05$ mm. The intensities of three standard reflections were monitored after every 50 reflections. Their intensities were stable within $I \pm 1\%$ of their mean values; 2837 reflections were measured, of which 1566 unique reflections with $I \geq 2\sigma$ (I) were selected as observed structure amplitudes. The structure was solved by direct methods,[21] refinement by least-squares method and the other crystallographic calculations were done using the package of Cerrini *et al.*[22] At a late stage in the refinement, all the H-atoms were located in a difference Fourier map and were refined with fixed *B* values equal to that of carrier atoms. The final conventional *R* value at convergence was 0.058. The arrangement of the molecules in the crystal as viewed along *b* axis is shown in Fig. 2. The packing along *a* and *b* axes involves only normal Van der Waals interactions, while the molecules are connected side by side through hydrogen bonds between the carbonyl O(1) and the OH O(2) oxygens of molecules related by unit-cell translation along *c* axis. The geometrical parameters of the hydrogen bond are the following: O(1)...O(2) = 2.827 Å, O(2)–H = 0.930 Å, H...O(1) = 1.910 Å, O(2)(H...O(1) = 171° and C(9)–O(2)–H = 103°.

Acknowledgements—One of us (E.T.) wishes to thank Dr. J. Jakupovic, Institute of Organic Chemistry, Technical University, West Berlin for the ^{1}H NMR measurements at 400 MHz and the NOE experiments, and the UNDP (project BUL 77/009) for partial support of this work.

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