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Lewis Acid Catalysed Rearrangement of 7,11-Epoxyisogermacrone. Formation of a New Carbon Skeleton.

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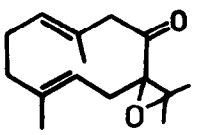
Abstract: *The fluorohydrin* 8 *has been found to be the main product of the reaction of 7,11-epoxyisogermacrone* 3 *with* $BF_3.Et_2O$. *When* TMS-OTf *is employed,* 3 *undergoes an unusual rearrangement leading to the product* 10 *with a new bicyclic carbon skeleton. The mechanism of the reaction is discussed.*

We have recently shown that the boron trifluoride catalysed rearrangement of 7,11-epoxygermacrone 1 provides the humulenone 2 in high yield[1]. This result encouraged us to apply the same reaction on 7,11-epoxyisogermacrone 3 in order to obtain the corresponding humulenone 4 which we need for further biomimetic transformations[2].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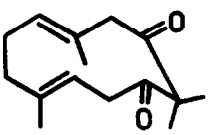
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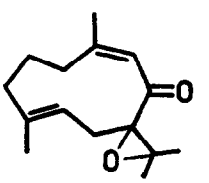
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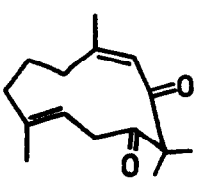
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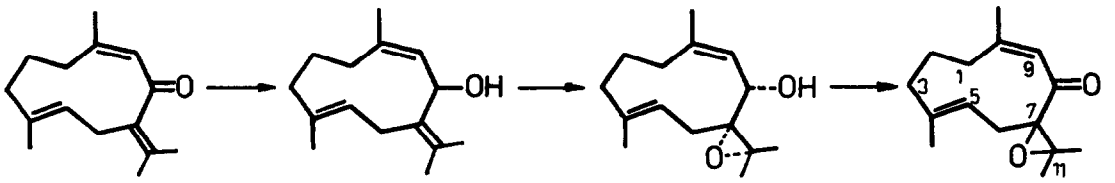
However, we observed the formation of the fluorohydrin 8 as the main product of the reaction of 3 with $BF_3.Et_2O$ When trimethylsilyltriflate (TMS-OTf) was used as a Lewis acid, the rearrangement of 3 followed an entirely different pathway leading to bicyclic products which possess a new carbon skeleton.

RESULTS AND DISCUSSION

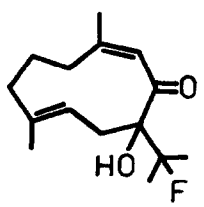
The initial epoxide 3 was prepared from isogermacrone 5[3], as outlined in Scheme 1, as the direct isomerisation of 1 in alkali medium was unsuccessful[4]. Accordingly, LAH reduction of 5 followed by Sharpless epoxidation[6] gave the 7,11-epoxy alcohol 7*. Subsequent oxidation with PDC-DMF[6] afforded the 7,11-epoxy ketone 3 in 76% overall yield. Its structure followed from the spectroscopic data, especially from the PMR spectrum (Table 1).



5 6 7 3

Scheme 1

Treatment of 3 with equimolar amounts of $BF_3.Et_2O$ at room temperature for 36 hours gave after chromatographic separation the humulenone 4 and the fluorohydrin 8 in a ratio of 1:4. The structure of the crystalline diketone 4, again followed from the characteristic PMR and CMR spectra (Table 1 and 3).



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The fluorohydrin 8 displayed a molecular formula $C_{15}H_{23}O_2F$ (m/z 254, M^+) and its IR spectrum showed the presence of an enone system (1660, 1620 cm^{-1}) and a hydroxyl group (3420 cm^{-1}). The location of the latter at C-7 followed from the lack of signal for a carbinol proton in the PMR spectrum (Table 1). The MS fragment at m/z 234 (M^+ - HF) and the PMR signals (Table 1) for the two tertiary Me groups at δ 1.21 and 1.46 (each d, J= 21 5 Hz) indicated that the fluorine atom is attached to C-11.

It should be noted that the formation of 8 was unexpected, as no fluorine product was detected when subjecting 1 to the BF_3-catalysed rearrangement. The different courses of the reaction of 1 and 3 may be attributed to the enone system in 3 which seemingly prevent the molecule to meet the stereoelectronic requirements for the acyl migration. Although the unusual migratory aptitude of the carbonyl group towards electron- deficient centre is well studied[7], the conversion of 3 into 4 is, in fact, the first example of a 1,2-shift of a conjugated CO group

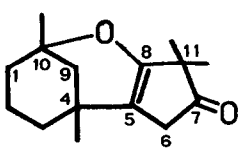
In order to avoid the participation of the Lewis acid which resulted in the fluorohydrin formation, we changed the boron trifluoride-etherate for TMS-OTf. When 3 was treated with equimolar

*It is worth noting that the reaction proceeds highly regioselectively as no 9,10-epoxy alcohol has been detected

amounts of TMS–OTf in CH_2Cl_2 at -10°C for 30 min, the compound **9** was formed as the major product (90%) together with traces of the bicyclic ketone **10** (1.7%).

The structure of **9** followed from the spectral data which showed the molecular formula $C_{15}H_{22}O_2$ (m/z 234, M^+), a result reinforced by the CMR spectrum (Table 3); the presence of a 5-membered CO group (1750 cm^{-1}, δ 218.6) and a tetrasubstituted vinyl ether moiety (1695 cm^{-1}, δ 75.9, 104.4 and 156.1). Further, the PMR spectrum (Table 2) exhibited signals for four tertiary methyl groups and the methylene protons at C-9* and C-6, the latter appearing as a typical AB-quartet (J = 22 Hz). Reduction of **9** with $NaBH_4$ afforded a mixture (as evidenced by PMR) of the diastereoisomeric alcohols **11**, which could not be separated.

The structure of the minor product **10** was also elucidated mainly on the basis of spectral data. The MS spectrum showed molecular formula $C_{15}H_{22}O_2$ (m/z 234, M^+) and a base peak at m/z 109 (C_8H_{13}), due to the splitting of the C-4/C-5 carbon bond. The presence of the α-disubstituted β-diketo-moiety in the 5-membered ring was further indicated by the IR (1730 cm^{-1}) and CMR data (δ 217.9 and 218.3, Table 3). In order to determine unambiguously the location of the double bond (as the H-9 signal appeared as a broad singlet) **10** was readily epoxidised to give a 1:1 mixture of the isomeric epoxides **12a** and **12b** Their PMR spectra (Table 2) contained sharp singlets for H-9 at δ 3.26 and 3.02, respectively, thus confirming the structure of **10**. Furthermore, each of the epoxides was quantitatively converted into the 9-hydroxy-derivatives of **9** by treatment with $BF_3.Et_2O$. The PMR data of the resulting products **13a** and **13b** (Table 2) were very similar to those of **9** except for the signal of H-9. This cyclisation confirmed not only the structure of themajor product **9**, but also revealed the close chemical relationship between **9** and **10**. Their formation from 7,11-epoxyisogermacrone **3** upon treatment with TMS–OTf can be rationalized as shown in Scheme 2



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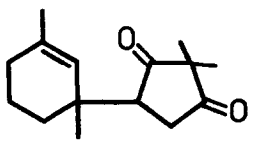

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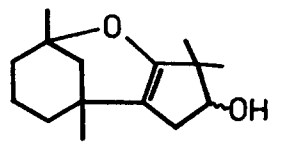

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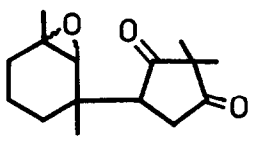

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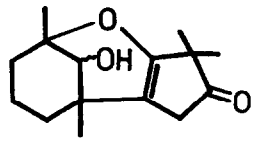

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* *the numbering of **3** is preserved in the products **9–13**.*

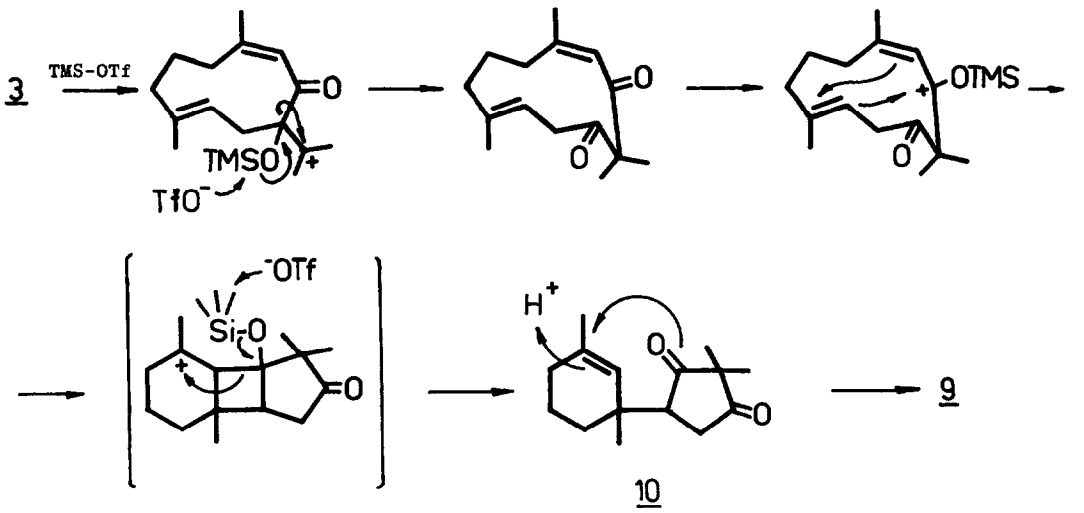
Table 1. PMR of compounds 3, 4 and 8 ($CDCl_3$, ppm, J in Hz)

	3	4	8
H-5	5 30 dbr (11)	5.28 t (8)	4.92 dd (12, 14)
H-6	2.80–3.00	3.17 dd (15, 8)	2.80 dd (14, 12)
H-6'		3.02 dd (15, 8)	2.68 d (14)
H-9	6.37 sbr	6.15 s	6.33 sbr
H-12	1.36 s	1.12 s	1.21 d (21.5)
H-13	1.21 s	1.40 s	1.46 d (21.5)
H-14	1.85 sbr	1.86 s	1.87 sbr
H-15	1.56 s	1.50 s	1.49 s

Table 2. PMR of compounds 9, 10, 12-13 ($CDCl_3$, ppm, J in Hz)

	9	10	12a	12b	13a	13b
H-5	-	2.85 dd (13, 10)	3.27 t (11)	2.97 t (10)	-	-
H-6	2.80 ABq (22)	2.80 dd (10, 23)	2.77 dd (18, 11)	2.76 dd (18, 10)	2.80 s	2.83 s
H-6'		2.62 dd (13, 23)	2.63 dd (18, 11)	2.56 dd (18, 10)		
H-9	1.82 ddd (2, 2, 12)	5.28 sbr	3.26 s	3.02 s	3.49 s	3.59 s
H-9'	1.44 d (12)	-	-	-	-	-
H-12	1.08 s	1 12 s	1.11 s	1.08 s	1.09 s	1.10 s
H-13	1.12 s	1.16 s	1.16 s	1.12 s	1.15 s	1.12 s
H-14	1.24 s	1.64 s	1.36 s	1.32 s	1.33 s	1.34 s
H-15	1.03 s	1.08 s	1.05 s	0.93 s	1.07 s	1.04 s

The assumption that the rearrangement of the germacrane skeleton of 3 involves two steps has been proved by the following experiments. When 3 was treated with TMS-OTf at -90°C and the reaction was quenched after 10 min, the reaction mixture was shown to consist of the humulenone 4 and the product 10 in a ratio of 10:1. The amount of 10 increased with the prolongation of the reaction time at the same temperature



Scheme 2

and after 90 mın the ratio of the products 4 and 10 reached 1:1. Hence, the first step of the reaction involves rıng expansıon to 4, whıch in the second step undergoes further rearrangement to 10. To test thıs point, 4 was smoothly converted to 10 in 90% yield by treatment with $ZnCl_2$ It is ınteresting to note that no formation of compound 9 has been detected ın the reactions described above. However, a short treatment of 10 with catalytıc amounts of 10% HCl in ether gave 9 in quantitative yield. This result suggest that 9 is most probably an artifact arising from 10, as depicted in Scheme 2. The role of the cyclisation agent ıs seemingly played by the trıfluoromethansulfonic acid whose presence in the reaction mıxture is due to partial hydrolysis of the used TMS–OTf. To confırm thıs statement, the ınıtial 7,11-epoxyisogermacrone 3 was treated with fresh TMS–OTf at -10°C for 30 mın to give 10 as the only product ın 92% yield.

Finally, ıt ıs important to stress that the compound 10 possesses a new bıcyclic carbon skeleton.

Table 3. CMR of compound 4, 9 and 10 ($CDCl_3$, ppm)

	4	9	10		4	9	10
C-1	31.3 t#	35 2 t	31.6 t	C-9	115.4 d	45 4 t	128.5 d
C-2	20.3 t	20.4 t	19.1 t	C-10	157.0 s	75.9 s	132.4 s
C-3	41.0 t	38.5 t	38.4 t	C-11	61.9 s	48.8 s	53.6 s
C-4	142 6 s	30.9 s	33.9 s	C-12	22.3 q*	22.8 q*	23.8 q*
C-5	122.1 d	104.4 s	55.8 d	C-13	21.3 q*	25.6 q*	21.3 q*
C-6	41.9 t	39.2 t	38.4 t	C-14	23.9 q	28.7 q	22.3q*
C-7	206.7 s	218 6 s	218.3 s	C-15	14.6q	21.4 q	19.4 q
C-8	198.7 s	156 1 s	217.9 s				

#multiplicity confirmed by DEPT measurement, assignment may be interchanged*

EXPERIMENTAL

M. ps are uncorrected; UV: in EtOH; IR: film or KBr pellets; PMR: in $CDCl_3$ at 250 MHz; chemical shifts in δ from TMS, J values in Hz; CMR in $CDCl_3$ at 69.2 MHz; Flash chromatography: on Merck Kieselgel 60 ,(No 9385); PTLC: on Merck Kieselgel 60 PF_{254}; TLC: on Merck Alufolien 60 F_{254}; "work-up in the usual way" implies dilution with H_2O, extraction with ether, washing, drying (Na_2SO_4) and removal of the solvent under reduced pressure.

Reduction of 5. Treatment of 5 (660 mg 3 mmol) with LAH (500 mg) in dry ether (5 ml) for 30 min at room temperature gave a crude product (650 mg) which after Flash-chromatography (SiO_2 90 g, PE:EE 12:1) yielded:

6 (550 mg), oil, IR: 3540, 1640 cm^{-1}; MS-EI: 218 (M^+,8), 201 (60), 200 (25); PMR (60 MHz): 1.53 (3H, s, H-12), 1.68 (3H, s, H-13), 1 70 (3H, s, H-14), 2.00 (3H,s, H-15), 4 83 (2H, brd, J=10 Hz, H-5 and H-8), 5.46 (1H, d, J=10 Hz, H-9).

Epoxidation of 6 To a soln of 6 (660 mg, 3 mmol) in dry benzene (3 ml) was added $VOSO_4$ (15 mg) and the suspension was stirred at room temperature. Then 80% soln of TBHP (0.4 ml, 4 mmol) in benzene (2 ml) was added dropwise over 30 min and stirring was continued for a further 30 min Work-up in the usual way gave:

7 (700 mg), oil, IR. 3500, 1640 cm^{-1}; MS-EI: 236 (M^+, 40), 219 (100), 191 (30), 161 (70); PMR. 1.42 (3H, s, H-12), 1.59 (3H, s, H-13), 1.68 (3H, sbr, H-14), 1.75 (3H, s, H-15), 4 50 (1H, d, J=10Hz H-8), 4.85 (1H, d, J = 12 Hz, H-5), 5.22 (1H, d, J=10 Hz, H-9).

Oxidation of 7. To a soln of PDC (2.3 g) in DMF (4 ml) was added a soln of 7 (700 mg, 3 mmol) in DMF (1 ml) and the mixture was left at room temperature for 24 h. Work-up in the usual way gave a crude product (690 mg) which after recrystallisation from hexane gave:

3 (660 mg), m.p. 44-46° C, UV: 234 nm; IR: 1680, 1620cm^{-1}, MS-EI:234 (M, 20), 219 (12),

PMR in Table 1.

Reaction of 3 with $BF_3.Et_2O$. To a soln of 3 (230 mg, 1 mmol) in dry ether (3 ml) was added a freshly distilled $BF_3.Et_2O$ (0 5 ml) and the soln was kept at room temperature for 36 h. Work-up in the usual way gave a crude product (210 mg) which after Flash-chromatography (SiO_2 90 g, PE:EE 10:1) separation afforded.

4 (40 mg), m.p 54-56°C (Hexane); UV:234 nm; IR:1703, 1676, 1622 cm^{-1} MS-EI: 234 (M^+, 10), 206 (3), 108 (50), 95 (100),

PMR in Table 1 CMR in Table 3.

8 (160 mg), m.p. 50-52° C (Hexane); UV: 235 nm; IR: 420, 1660, 1620, 1080cm^{-1};MS-EI: 254 (M^+, 30) ,234 (30), 109 (60), 95 (100);

PMR in Table 1

Reaction of 3 with TMS-OTf.

a/ To a cooled to -10°C soln of 3 (230 mg, 1 mmol) in dry CH_2Cl_2 was added TMS-OTf (0.03 ml, 1 mmol) under N_2 and the mixture was kept at the same temperature for 30 min. After working up in the usual way, the crude product (200 mg) was separated by Flash chromatography (SiO_2 90 g, PE:EE-6:1) to give:

9 (190 mg), m.p. 64-66° C (Hexane), IR: 1750, 1670, 1150, 1080cm^{-1}; MS-EI: 234 (M^+, 45), 219 (30), 206 (15), 191 (100).

PMR in Table 2. CMR in Table 3.

10 (4 mg), oil, IR 1761, 1720 cm^{-1}, MS-EI: 234 (M^+, 4) 109 (100)

PMR in Table 2. CMR in Table 3.

b/. Similar treatment of 3 (230 mg, 1 mmol) at -90°C for 10 min gave 4 (180 mg) and 10 (15 mg).

c/. The reaction of 3 (230 mg) with TMS-OTf carrying out at -90°C for 90 min yielded 4 (100 mg) and 10 (90 mg).

d/. Repetition of the same conditions of the reaction of 3 (230 mg,) as described in a/, but using fresh TMS-OTf afforded 10 (210 mg).

Conversion of 4 to 10. To a soln of $ZnCl_2$ (2 mg) in dry ether (1 ml) was added a soln of 4 (16 mg) in ether (0.5 ml) and the mixture was left for 12 h. Work-up in the usual way gave 10 (12 mg)

Conversion of 10 to 9 . To a soln of 10 (10 mg) in ether (1 ml) was added two drops of 10% HCl. The mixture was kept at room temperature for 10 min and then was worked up in the usual way to give 9 (10 mg)

Reduction of 9. Treatment of 9 (10 mg) with $NaBH_4$ (1 mg) in MeOH (1 ml) for 10 min at room temperature gave:

11 (9 mg), oil, IR: 3500, 1670 cm^{-1}; MS-CI: 237 (M^++1); PMR: 0.97 (3H, s, H-15a), 0.99 (6H, s, H-15b and H-12b), 1.00 (3H, s, H-12a), 1 04 (6H, s, H-13a and b), 1.21 (6H, s, H-14a and b), 1.34 (1H, d, J=13 Hz, H-9a), 1.78 (1H, dd, J=13, 2 Hz, H-9'a) 1.82 (1H, dd, J=12,2 Hz, H-9'b), 1.87 (1H, dd, J=14, 7 Hz, H-6a), 1.99 (1H, dd, J=15, 4 Hz, H-6b), 2.46 (1H, dd, J=15,4 Hz, H-6'b), 2.48 (1H, dd, J=14, 7 Hz, H-6'a).

Epoxidation of 10. To a stirred soln of mCPBA (30 mg, 0.1 mmol) in $CHCl_3$ (1 ml) was added at room temperature a soln of 10 (30 mg, 0.1 mmol) in $CHCl_3$ (0.5 ml) and stirring continued for 1 h. Work-up in the usual way gave a crude product (28 mg) which was separated by PTLC (PE:EE - 4:1) to give:

12a (10 mg), oil, IR: 1750, 1720 cm^{-1}; MS-EI: 250 (M^+, 60), 233 (40), 222 (40), 126 (100).

PMR in Table 2

12b (12 mg), oil,IR. 1750, 1718 cm^{-1}; MS-EI: 250 (M^+,5) 232 (20), 208 (10), 191 (15), 125 (60)

PMR in Table 2

Preparation of 13a. To a soln of 12a (10 mg) in dry ether (1 ml) a catalytic amounts of BF_3Et_2O was added The mixture was left for 1 h and then was worked up in the usual way. The crude product obtained (10 mg) was purified by PTLC (PE:EE-3 1) to give

13a (8 mg), oil, IR: 3500, 1750, 1670, 1160, 1080 cm^{-1}; MS-CI: 251 (M^++1).

PMR in Table 2

Preparation of 13b. Treatment of 12b (10 mg) with BF_3Et_2O under the same condition as above gave:
13b (7 mg), oil, IR: 3450, 1750, 1670, 1080 cm^{-1} ; MS-CI:251 (M +1).
PMR in Table 2.

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