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INTRAMOLECULAR CYCLISATION OF α,β-EPOXY-ARTEMISIA KETONE

Elena Tsankova*, Valentin Enev and Svetlana Simova

Institute of Organic Chemistry and Centre of Phytochemistry

Bulgarian Academy of Sciences, 1113 Sofia, Bulgaria

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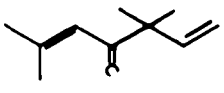
Abstract - α,β-epoxy-artemisia ketone, 2 undergoes intramolecular cyclisation by OM-DM yielding the tetrahydrofuran derivatives 3 - 6, while on treatment with BF_3-etherate 2 cyclises to the cyclopentanones 8 and 9. The structure of all products has been elucidated by spectral methods. The mechanism of the cyclisation reaction is discussed briefly.

Artemisia ketone, 1 is a long-known representative of the small group of monoterpenes whose carbon skeleton is not formed by simple head-to-tail linking of two isoprene units[1]. In this respect its biosynthesis has been the subject of much interest and speculation[2]. The synthesis of artemisia ketone has also been performed[3]. However, little is known[4] about its chemical behavior. Some preliminary studies of ours[5] showed that, in spite of the presence of the carbonyl function and the 1,5-diene system, artemisia ketone is quite unreactive. For that reason we directed our interest to the corresponding α,β-epoxide 2 which was prepared by epoxidation of natural artemisia ketone, isolated from the essential oil of Artemisia annua L.[6]



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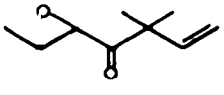


2

We now report some results of the intramolecular cyclisation of 2 by oxymercuration-demercuration (OM-DM) with mercury-II-acetate, and by treatment with BF_3-etherate.

Cyclisation of 2 by OM-DM

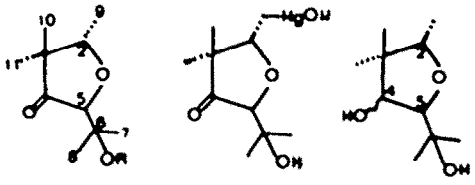
OM-DM of 2 according to Brown's general procedure[7] afforded the compounds 3, 4, 5 and 6 in the ratio of 22:5:1:1. The structure of the main product 3 follows from the spectral data which showed a molecular formula of $C_{10}H_{18}O_3$ (m/z 187, M^++1), the presence of a CO group in a 5-membered ring and a OH group (1743, 3460 cm^{-1}). The lack of other functional groups and the ^1H NMR signals (Table 1) for two protons on an O-bearing C-atom (3.87 and 4.14 ppm) showed that the remaining O-atom is part of a tetrahydrofuran ring. Further, the ^1H NMR signal at 1.23 ppm for two Me groups together with the base peak at m/z 128 due to an ion obtained by McLafferty rearrangement clearly showed that the OH group is located at C-6.

Table 1. ^{1}H NMR of 3, 4, 5, 6 and 7 (in $CDCl_3$, δ=ppm from TMS, J in Hz)

Protons	3	4	5	6	7
H-2	4.14 q (J=6.5)	4.35 t (J=8)	4.00 q (J=6.5)	3.64 q (J=6.5)	4.22 q (J=7)
H-4	-	-	3.84 dd (J=3.5,3)	3.88 d (J=7)	-
H-5	3.87 s	3.92s	3.72 d (J=3.5)	3.42 d (J=7)	3.98 s
H-7	1.23 s	1.31 s*	1.36 s*	1.25 s*	1.60 s
H-8		1.27 s*	1.32 s*	1.22 s*	
H-9	1.27 d (J=6.5)	2.11 d (J=8)	1.14 d (J=6.5)	1.13 d (J=6.5)	1.45 d (J=7)
H-10	1.00 s	1.05 s	1.03 s	0.96 s	1.08 s
H-11	0.98 s	1.01 s	0.86 s	0.88 s	0.98 s
OH/OAc	2.70 sbr	1.60 s	2.62 s	1.60 s	1.97 s
		2.55 sbr	4.61 d (J=3)	1.97 sbr	

*Assignment may be interchanged

Reduction of 3 with LAH yielded two diols which proved to be identical with the cyclisation products 5 and 6 (spectral data in Experimental). The considerable difference in their R_f-values and the presence of intramolecular hydrogen bonding only in 5 indicated that the two diols are epimers at C-4. This was substantiated by the coupling pattern of the H-4 signal in 5 and 6 - $J_{4,5}$=3.5 and 7 Hz, respectively (Table 1).

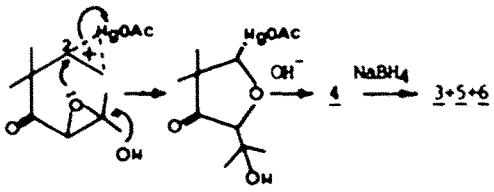


3 R=H
7 R=Ac

4

5 4β-OH
6 4α-OH

The stereochemistry at C-2 and C-5 in the cyclisation products was established on the basis of NOE difference spectroscopy. The NOE between the Me group at 1.08 ppm and H-2, and the Me group at 0.98 ppm and H-5 in 7 (^{1}H NMR in Table 1) revealed the trans-relationship of H-2 and H-5. Furthermore, NOE was observed between the Me group at 0.86 ppm H-4 and H-5 in 5, and the Me group at 0.96 ppm H-2 and H-4 in 6. Hence, the cyclisation of 2 via OM-DM leads to the trans-2,5-disubstituted tetrahydrofuran derivative 3. The formation of only one diastereomeric product shows that the reaction proceeds stereoselectively, most probably due to steric reasons. As can be seen in Scheme 1 the Markovnikov intranucleophilic attack at C-2 should be preferred from the opposite side of the mercury σ-complex. Similar stereocontrol has been observed in the



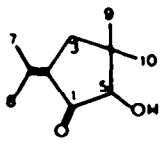
Scheme 1

cyclisation of linalool by OM-DM[8].

Since it is well known[9] that the organomercurial acetate and hydroxide are reduced by $NaBH_4$ rapidly and smoothly, the isolation of 4 (spectral data in Experimental, ^1H NMR in Table 1) is quite unusual. In view of eliminating the eventual insufficiency of the metal hydride, the demercuration was carried out with 2 moles $NaBH_4$. However, an increase of the amount of 5 and 6 (12% each) at the expense of 3 (52%) was observed in this case, and 4 was isolated again in 13% yield.

Cyclisation of 2 with BF_3-etherate

Treatment of 2 with $BF_3.Et_2O$ (1 mole equiv) afforded two compounds in the ratio of 1:1. On the basis of the mass spectra showing equal molecular formulae - $C_{10}H_{16}O_2$ (m/z 168, M^+) and the very similar UV and IR spectra (Experimental) which reveal the presence of a conjugated CO group and a OH group, the structures 8 and 9 were assigned to the cyclisation products. The ^1H NMR spectra of 8 and 9 (Table 2) are also very similar, in fact they differ mainly in the shape of the signals due to the protons geminal to the OH group and the C-3 methylene protons. The structures 8 and 9 were further confirmed by reduction with LAH. While 8 afforded the cis- and trans-1,2-diols 10 and 11 in the ratio of 3:1, 9 yielded the cis- and trans-1,3-diols in the ratio of 1:1. The considerable stereoselectivity in the reduction of 8



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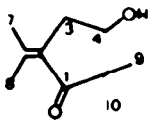

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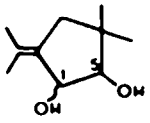
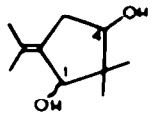


10 1β-OH

11 1α-OH



12 1β-OH

13 1α-OH

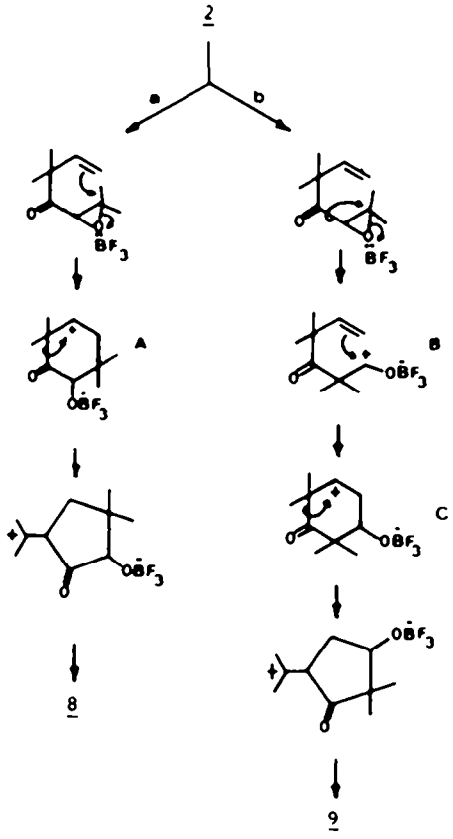
Table 2. ^1H NMR of 8, 9, 10, 11, 12 and 13 (in $CDCl_3$, δ=ppm from TMS, J in Hz)

Protons	8	9	10	11	12	13
H-1	-	-	4.58 dbr (J=5)	4.42 d (J=7)	4.05 sbr	4.14 s
H-3	2.40 dbr (J=14)	2.91 ddbr (J=16,6)	2.33 dbr (J=16)	2.17 sbr	2.66 ddbr (J=17,7)	2.74 ddbr (J=17,7)
H-3'	2.29 dbr (J=14)	2.48 ddbr (J=16,7)	1.93 d (J=16)		2.43 dd (J=17,3.5)	2.11 dd (J=17,7)
H-4	-	3.96 dd (J=6,7)	-	-	3.75 dd (J=7,3.5)	4.10 t (J=7)
H-5	3.82 s	-	3.56 d (J=5)	3.60 d (J=7)	-	-
H-7	1.83 sbr	1.85 s	1.65 s	1.64 s	1.67 s	1.78 s
H-8	2.26 sbr	2.24 sbr	1.85 sbr	1.81 s	1.83 sbr	1.86 sbr
H-9	0.82 s*	1.03 s*	0.97 s*	0.86 s*	0.79 s*	0.81 s*
H-10	1.24 s*	1.05 s*	1.04 s*	1.08 s*	1.15 s*	1.08 s*

*Assignment may be interchanged.

is due to the presence of the OH group located in α-position to the CO group. The OH group coordinates with the metal atom to form a chelate ring and, as a result, the attack of the metal hydride ion from the less hindered side is favoured. The MS, IR (Experimental) and ^{1}H NMR data (Table 2) are consistent with the structure and stereochemistry of the diols 10 - 13.

The formation of the cyclisation products 8 and 9 can be rationalized as shown in Scheme 2. After the initial attack of the Lewis acid at the oxirane, the reaction proceeds along two different pathways. Path a includes a Markovnikov scission of the oxirane and cyclisation incorporating the double bond. The resulting cyclohexane intermediate A undergoes ring contraction due to acyl migration and following proton loss leads to product 8. Path b includes a rearrangement leading to the intermediate B. Subsequent cyclisation to C, ring contraction and proton loss result in product 9. The fact that 8 and 9 are obtained in a ratio of 1:1 shows that both pathways are equally favoured. The acid-induced rearrangement of α,β-epoxy-ketones, esters and thioesters in which the electronegative group migrates to a positive center (i.e. the formation of B in Scheme 2) is well-known[10]. The acyl migration occurring in the intermediates A and C can be regarded as a particular case of this rearrangement. The driving force in this case is probably the formation of the more stable tertiary carbocation intermediates.



Scheme 2

The results of this study demonstrate that OM-DM made available in reasonable yield trans-1,2-disubstituted tetrahydrofuran derivatives, while BF_3-etherate formed cyclopentanone compounds. Since the starting α,β-epoxy-artemisia ketone 2 has been recently found in nature[11], it is probable that many of this cyclisation products may, in time, be discovered as natural products.

EXPERIMENTAL

M.ps are uncorrected. UV: in EtOH; IR: in $CHCl_3$; low resolution MS: EI at 70 eV, CI with i-butane at 200°; ^{1}H NMR: in $CDCl_3$ at 250 MHz, chemical shift in δ downfield from TMS, J values in Hz, all data are summarized in Tables 1 and 2; NOE difference experiments: the samples were prepared by blowing Ar through the $CDCl_3$ soln for 15 min. All Me groups were irradiated (5 s) under homogated conditions (NS=600). One control experiment (offset 3000 Hz) was done as well. Subtraction of the FID's with and without irradiation followed by Fourier transformation of the difference gave spectra consisting only of the signals due to the NOE. "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. Preparative TLC (PTLC): on

Kieselgel 60 PF_{254} (Merck).

Epoxidation of artemisia ketone 1. To a soln of 1 (1.0 g) in MeOH (8 ml) was added by stirring and cooling to 15° successively 30% H_2O_2 (1 ml) and 4% aq NaOH (0.75 ml). The stirring was continued for 1 hr and the temp was raised to 22°. Work-up in the usual way gave 2 (0.95 g): b.p. 75-76°/10 Torr; IR:1715, 1640, 1250, 995, 910, 810 cm^{-1}; MS and ^1H NMR: identical to those described in Ref.11.

OM-DM of 2. A soln of 2 (340 mg, 2 mM) in THF (3 ml) was added dropwise to a stirred yellow suspension of $Hg(OAc)_2$ (640 mg, 2 mM) in 50% THF-H_2O (15 ml). The yellow colour disappeared within 20 min. The mixture was stirred further 2 hr. Then NaOH soln (3M, 6 ml) and $NaBH_4$ soln (80 mg in 8 ml 3M NaOH) were added dropwise and the black suspension was stirred for 30 min. The mixture was worked-up in the usual way and the crude product (320 mg) was separated by PTLC to give 3 (208 mg): oil, EI-MS, m/z: 171 (2, M^+-Me), 128 (100), 113 (54) IR: 3460, 1743 cm^{-1}; 4 (48 mg): oil, EI-MS, m/z: 402 (2, M^+), 185 (100), 167(30) IR: 3500, 1740 cm^{-1}; 5 (10 mg): m.p.113-115°(hexane-ether 10:1)*; CI-MS, m/z: 189 (5, M^++1), 171 (100), 153 (3); IR (10^{-3}M soln): 3570, 3460 cm^{-1} and 6 (10 mg): m.p. 83-84°; CI-MS: identical to that of 5; IR (10^{-3}M soln): 3590 cm^{-1}.

Reduction of 3. Reduction of 3 (20 mg) with LAH (50 mg in 8 ml ether) and subsequent separation of the crude product (140 mg) on PTLC gave 5 (65 mg) and 6 (62 mg).

Acetylation of 3. To a soln of 3 (20 mg) in Ac_2O (0.6 ml) was added $ZnCl_2$ (cat amount). The mixture was stirred for 10 min, worked-up in the usual way and purified on PTLC to give 7 (15 mg): m.p. 48-50°; EI-MS, m/z: 168 (100, M^+-60), 153 (20); IR: 1750, 1742, 1250 cm^{-1}.

Cyclisation of 2 with $BF_3.Et_2O$. To a soln of 2 (200 mg) in dry ether (5 ml) was added freshly destilled $BF_3.Et_2O$ (0.6 ml) at 0° and the mixture was kept at this temp for 2 hr. Work-up in the usual way and separation on PTLC gave 8 (76 mg): m.p. 53-55°; EI-MS, m/z: 168 (80, M^+), 150 (35), 135 (100); UV: 253 nm; IR: 3450, 1706, 1625 cm^{-1} and 9 (70 mg): viscous oil, EI-MS, m/z: 168 (100, M^+), 150 (20), 135 (15); UV: 254 nm; IR: 3420, 1704, 1628 cm^{-1}.

Reduction of 8. Reduction of 8 (50 mg) with LAH (20 mg in 5 ml ether) and subsequent separation on PTLC gave 10 (25 mg): m.p. 48-50°; CI-MS, m/z: 171 (100, M^++1), 136 (10); IR (10^{-3}M soln): 3630, 3575 cm^{-1} and 11 (8 mg): m.p.118-120°; CI-MS: identical to that of 10; IR (10^{-3}M soln): 3620 cm^{-1}.

Reduction of 9. Reduction of 9 (50 mg) with LAH (20 mg in 5 ml ether) and subsequent separation on PTLC gave 12 (18 mg): oil, CI-MS, m/z: 171 (100, M^++1), 153 (20): IR (10^{-3}M soln): 3400 cm^{-1} and 13 (15 mg): oil, CI-MS: identical to that of 12; IR (10^{-3}M soln): 3630 cm^{-1}.

*all crystalline compounds are recrystallized in this solvent mixture.

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