Acid-catalysed rearrangement of caryophyllene oxide

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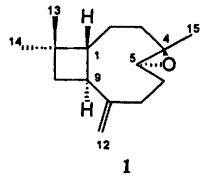
One of the major products 2 from the reaction of caryophyllene oxide in sulfuric acid is shown to arise from rearrangement of the exocyclic double bond and 1,2-epoxide of the starting material to an endocyclic double bond and 1,4-epoxide system. A hydrated 1,5-epoxide was isolated as a minor component of the reaction.

The acid-catalysed hydration of caryophyllene oxide **1** was first studied in 1953,[1] as part of an effort to establish the structure of caryophyllene. In the original study, clovanediol **4** was reported as the only product obtained in moderate yield (40%) through hydration and rearrangement of the starting material in sulfuric acid. The rearrangement of caryophyllene oxide in superacidic media has been the subject of more recent studies, which also reported only **4** and related clovenes.[2]



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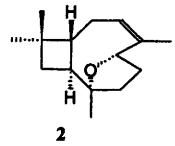

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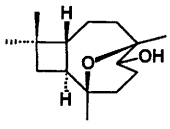

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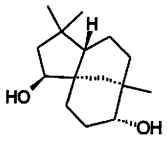

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Having recently isolated a natural product with NMR spectra closely matching those of clovanediol,[3] but with an apparently opposite optical rotation to that reported in the literature, we decided to repeat the original reaction with sulfuric acid in order to obtain an authentic sample of **4**. In our hands, the reaction of caryophyllene oxide with acid did indeed produce the expected hydration product **4**, but also yielded a rearranged epoxide not previously reported, as one of the major products.

Owing to the conformational flexibility of the nine-membered ring in caryophyllene oxide, there has been some discrepancy in the way in which **1** (1*R*,4*R*,5*R*,9*S*) is represented in the literature. Some authors have chosen to emphasize the *trans* nature of the caryophyllene precursor to **1** (which is predominantly epoxidized from the upper-face)[4] by drawing **1** with both the epoxide bonds to oxygen as β.[4,5] Others have been more concerned with an accurate representation of the likely conformation of **1** (see Scheme 1), depicting the C–O bond at the 5-position as α, and refer to **1** as caryophyllene 4β,5α-oxide.[2,3,6] We have chosen to adopt the latter convention since it more clearly illustrates the reactions undergone by **1** in acidic media.

Results and discussion

Reflux of caryophyllene 4β,5α-oxide in sulfuric acid [1] yielded a complex mixture of products by TLC. One of the major products, **4**, was simply purified by column chromatography, whilst **2** and **3** required purification by column chromatography followed by HPLC. Compound **4** was characterized from its NMR spectra and gave excellent agreement with published data for clovanediol (1*S*,2*S*,5*S*,8*R*,9*R*).[2,3]

The other major product of the reaction was **2**, of similar polarity to **1** and shown by accurate mass spectroscopy to have the same molecular formula as **1**. Analysis of ^{13}C–DEPT spectra showed that the double bond was now endocyclic (δ_C 140.1 C and 122.7 CH) and that the oxygenated carbon resonances had undergone a significant downfield shift (δ_C 85.2 C and 80.5 CH) when compared with the 1,2-epoxide of the starting material (δ_C 63.4 CH and 59.5 C). This would suggest that the strain associated with the three-membered epoxide ring in the starting material had been relieved in the product **2** as a result of ring expansion. Compound **2** was fully characterized by two-dimensional NMR spectroscopy. Thus, having identified all carbon atoms and protons connected by a single bond from PFG-HSQC† spectra, it was then possible to utilize 2 and 3 bond proton–carbon correlations observed in PFG-HMBC‡ spectra and proton couplings observed in ^1H–^1H COSY spectra to locate the endocyclic bond at the 3,4-position and the epoxide linkage between carbons 5 and 8 of the caryophyllane skeleton and assign all ^{13}C and ^1H resonances in **2** (Table 1). The full knowledge of ^1H assignments for **2** was then particularly useful in establishing relative stereochemistry through NOEs observed in NOESY spectra. Thus, observation of a correlation between the 12-methyl and 9-H showed that the methyl group was on the lower face of the molecule, whilst one of the 7-H protons (δ_H 2.18) showed a strong correlation with 1-H, demonstrating that the carbon backbone of the new tetrahydrofuran ring was on the upper face of **2**. Further analysis of NOESY correlations (Table 1) confirmed the α-stereochemistry shown for the epoxide linkage.

A second compound **3**, with polarity intermediate between **2** and **4** was isolated in smaller amounts and shown to be a hydration product by accurate MS (molecular formula $C_{15}H_{26}O_2$). Inspection of the ^{13}C–DEPT spectra showed the absence of a double bond and the presence of three oxygenated carbons and four methyl groups. Relatively downfield chemical shift values for the oxygenated carbons (δ_C 76.7 C, 75.3 CH and 72.7 C) again suggested that the strained 1,2-epoxide of the starting material was no longer present. Analysis of two-dimensional correlations, as previously, located the three oxygenated carbons at C-4, -5 and -8 of the caryophyllane skeleton and allowed the assignment of all ^{13}C and ^1H resonances (Table 2). Given that **3** is not a 1,2-epoxide, it must either contain an epoxide linkage between positions 4 and 8 (hydroxy group at C-5) or an epoxide between positions 5 and 8 (hydroxy at C-4). Conversion of the -OH group to an -OD group (by D_2O shake of the $CDCl_3$ solution) resulted in a

† PFG-HSQC stands for pulsed field gradient-heteronuclear single quantum correlation.

‡ PFG-HMBC stands for pulsed field gradient-heteronuclear multiple bond correlation.

Table 1 NMR data for compound **2**

Assignment	δ_C	Mult. (DEPT)	δ_H	HMBC correlation from ^1H to ^{13}C	^1H–^1H COSY correlation	NOESY correlation from ^1H to ^1H
1	45.6	CH	1.68	122.7, 85.2, 49.3, 34.2, 29.6, 21.1	5.37, 2.04	5.37, 2.18, 1.98, 0.99
2	29.6	CH_2	2.04	122.7, 45.6	5.37, 1.98, 1.68	5.37
			1.98	140.1, 122.7, 49.3, 45.6, 34.2	5.37, 2.04	5.37, 1.68, 1.58
3	122.7	CH	5.37	80.5, 45.6, 26.2	2.04, 1.98, 1.68	2.04, 1.98, 1.68
4	140.1	C				
5	80.5	CH	4.50	140.1, 122.7, 85.2, 34.6, 26.2	2.45, 1.95	2.45, 1.95, 1.65
6	34.6	CH_2	2.45	140.1, 85.2, 31.3	4.50, 2.18, 1.95, 1.58	4.50, 2.18, 1.58
			1.95	140.1, 80.5	4.50, 2.45, 2.18	4.50, 2.18
7	31.3	CH_2	2.18	80.5, 49.3, 34.6, 26.5	2.45, 1.95, 1.58	2.45, 1.95, 1.68, 1.22
			1.58	85.2, 49.3, 34.6, 26.5	2.45, 2.18	2.45, 1.98
8	85.2	C				
9	49.3	CH	2.10	85.2, 45.6, 36.2, 31.3, 29.6, 26.5	1.58, 1.22	1.58, 1.18, 1.00
10	36.2	CH_2	1.58	85.2, 49.3, 45.6, 29.9, 21.1	2.10, 1.22	2.10, 1.98
			1.22	85.2, 49.3, 34.2, 29.9, 21.1	2.10, 1.58	2.18, 0.99
11	34.2	C				
12	26.5	CH_3	1.18	85.2, 49.3, 31.3		2.10
13	29.9	CH_3	0.99	45.6, 36.2, 34.2, 21.1		1.68, 1.22
14	21.1	CH_3	1.00	36.2, 34.2, 29.9		2.10
15	26.2	CH_3	1.65	140.1, 122.7, 80.5		4.50

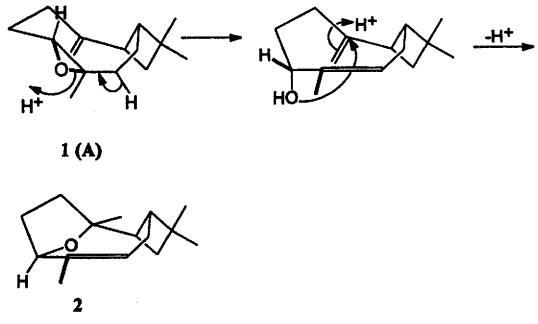
Table 2 NMR data for compound **3**

Assignment	δ_C	Mult. (DEPT)	δ_H	HMBC correlation from ^1H to ^{13}C	^1H–^1H COSY correlation	NOESY correlation from ^1H to ^1H
1	42.4	CH	2.08	72.7, 36.2, 34.4, 30.5, 21.3	2.52, 1.68, 1.43	1.02, 1.00
2	18.5	CH_2	1.68	42.4, 36.2	2.08, 1.43, 1.30	1.43, 1.30, 1.18
			1.43		2.08, 1.88, 1.68	1.68
3	29.2	CH_2	1.88	76.7, 42.4, 27.1, 18.5	1.43, 1.30	2.52, 1.30
			1.30	42.4, 27.1	1.88, 1.68	1.88, 1.68
4	76.7	C				
5	75.3	CH	3.44	76.7, 29.2, 27.1	1.95, 1.75	1.95, 1.75, 1.57, 1.18
6	25.3	CH_2	1.95	75.3, 36.1	3.44, 1.75, 1.62, 1.57	3.44, 2.52, 1.75, 1.57
			1.75	36.1	3.44, 1.95, 1.62, 1.57	3.44, 1.95
7	36.1	CH_2	1.62	75.3, 72.7, 25.3	1.95, 1.75, 1.57	1.02
			1.57		1.95, 1.75, 1.62	3.44, 1.95, 1.02
8	72.7	C				
9	36.2	CH	2.52	42.4, 26.0, 18.5	2.08, 1.42, 1.32	1.95, 1.88, 1.42, 0.99
10	35.1	CH_2	1.42	42.4, 36.2, 34.4, 21.3	2.52, 1.32	2.52, 1.32, 0.99
			1.32	72.7, 42.4, 36.2, 34.4, 30.5, 21.3	2.52, 1.42	1.42, 1.02, 1.00
11	34.4	C				
12	26.0	CH_3	1.02	72.7, 36.1		2.08, 1.62, 1.57, 1.32
13	30.5	CH_3	1.00	42.4, 35.1, 34.4, 21.3		2.08, 1.32
14	21.3	CH_3	0.99	34.4		2.52, 1.42
15	27.1	CH_3	1.18	76.7, 75.3, 29.2		3.44, 1.68

significant upfield shift at C-5 (δ_C 75.4 CH, Δ 0.153 ppm) indicating that **3** contained a hydroxy group at C-5 and was therefore a six-membered 4,8-epoxide. Since all proton assignments were known from the analysis of two-dimensional spectra, it was possible to use NOEs observed in NOESY spectra to determine stereochemistry at the 4- and 8-positions, although the stereochemistry at the 5-position remained unclear.

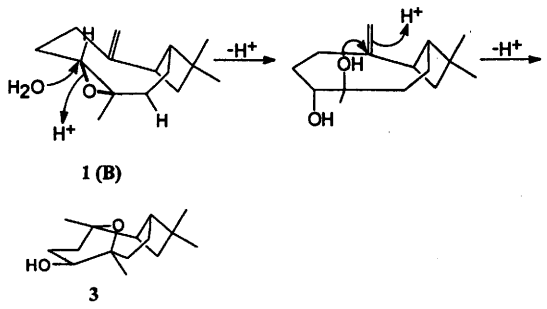
Formation of the major product **2** can most simply be rationalized if it is assumed that caryophyllene oxide adopts a conformation with the terminal double bond pointing down and the 1,2-epoxide facing outwards (as in conformation A, Scheme 1). This conformation has been proposed previously to account for the formation of **4**, since it allows nucleophilic attack of the terminal bond at the back face of the nascent carbocation ion at C-4 formed during opening of the epoxide ring in acid. Compound **2** can be produced from this same conformation if (instead of nucleophilic C-alkylation at C-4) proton loss occurs at C-3 to convert the nascent carbocation into a double bond. Intramolecular addition of the 5-hydroxy group to the terminal double bond then generates **2**.

Compound **3** may be the result of initial opening of the epoxide by water at C-5 followed by intramolecular addition of



Scheme 1 Rearrangement of **1** (conformer **A**) to **2**

the resulting 4-hydroxy group to the terminal double bond. The observed stereochemistry of this product would require that caryophyllene oxide adopts the more open conformation B (Scheme 2) with the terminal double bond projecting upwards. The possibility of more than one stable conformational state for the nine-membered caryophyllane system have been postulated by others.[2,7] Our own molecular modelling studies (using the MM2* force field of Macromodel[8]) seemed to confirm the



Scheme 2 Possible mechanism for hydration of **1** (conformer **B**) to **3**

Table 3 MM2* Energies (kJ mol^{-1}) for conformers **A** and **B** of **1**

Conformation	*In vacuo*	In water
A	228.3	192.5
B	224.8	195.6
Next lowest energy conformer	244.3	211.9

above hypothesis concerning the existence of two conformational preferences for **1**, since conformers **A** and **B** were indeed predicted to be the most stable states by computation and were both of significantly lower energy than the next most stable conformer for the nine-membered ring (Table 3).

Both 4,8-epoxides and 5,8-epoxides of caryophyllane have been reported from base-catalysed intramolecular displacement reactions of caryophyllene oxide derivatives where the terminal double bond is replaced by a diol.[9] Several 4,8-epoxides of caryophyllene have recently been reported as natural products[10] although 5,8-epoxides appear not to be known in nature. Neither **2** nor **3** have been reported previously from natural or synthetic sources.

Experimental

IR spectra were recorded in CCl_4 on a Shimadzu FTIR-8201 PC instrument. All NMR experiments were run on Bruker DPX 300 or DRX 500 instruments. Spectra were taken for 5–10% (w/v) solutions in $CDCl_3$ with Me_4Si as internal reference and *J* values are given in Hz. Two dimensional spectra were recorded with 1024 data points in F_2 and 256 data points in F_1. MS were recorded in EI mode at 70 eV on a Finnigan-MAT 95 MS spectrometer. $[\alpha]_D$ values are given in 10^{-1} deg cm^2 g^{-1}. For column chromatography silica gel (Kieselgel 60) was employed. HPLC separations were performed using a PREPSIL 20 mm × 25 cm column, flow rate 8 ml min^{-1}

Reaction of caryophyllene oxide in sulfuric acid

4β,5α-Caryophyllene oxide **1** (1*R*,4*R*,5*R*,9*S*; $[\alpha]_D$ −57; purchased from Aldrich) (1 g) was refluxed in a mixture of acetone (4 ml), water (0.6 ml) and sulfuric acid (0.1 ml) for 2 h. Acetone was removed by rotary evaporation and the reaction worked up by neutralization and extraction into diethyl ether. Column chromatography in a solvent gradient (hexane to 50% EtOAc–hexane) yielded **2** (4% EtOAc–hexane, R_f 0.33), **3** (10% EtOAc–hexane, R_f 0.28) and **4** (50% EtOAc–hexane, R_f 0.12).

5α,8α-Epoxycaryophyll-3-ene 2. (277 mg) Colourless oil; $[\alpha]_D$ −5.40 (*c* 4.69, $CHCl_3$); *m/z* (EI) 220.1818 (Δ +0.9 mmu for $C_{15}H_{24}O$) (M^+, 18%), 219 (18), 203 (12), 202 (85), 164 (80), 162 (100), 147 (90), 146 (70); ν_{max}/cm^{-1} 2953, 2928, 2885, 1551, 1453, 1370, 1254, 1217, 1161; δ_H 5.37 (1 H, dd, *J* 7.2, 1.3), 4.50 (1 H, dd, *J* 9.5, 5.5), 2.44 (1 H, m), 1.65 (3 H, s), 1.18 (3 H, s), 1.00 (3 H, s), 0.99 (3 H, s).

4β,8β-Epoxycaryophyllan-5-ol 3. (44 mg) Colourless oil; $[\alpha]_D$ −26.00 (*c* 2.17, $CHCl_3$); *m/z* (EI) 238.1939 (Δ −0.6 mmu for $C_{15}H_{26}O_2$) (M^+, 14%); 195 (17), 194 (16), 177 (38), 138 (22), 126 (68), 108 (88), 95 (100); ν_{max}/cm^{-1} 3452, 2930, 2862, 1462, 1371, 1284, 1246, 1150; δ_H 3.44 (1 H, dd, *J* 11.5, 4.9), 2.52 (1 H, m), 1.18 (3 H, s), 1.02 (3 H, s), 1.00 (3 H, s), 0.99 (3 H, s).

Clovanediol 4. (205 mg) White solid; mp 150–153 °C; $[\alpha]_D$ +3.82 (*c* 4.5, $CHCl_3$); *m/z* (EI) 238.1930 (Δ 0.3 mmu for $C_{15}H_{26}O_2$) (M^+, 30%), 220 (100), 205 (35), 179 (60), 164 (85); ν_{max}/cm^{-1} 3450, 1209, 1150, 1090, 1030. NMR data as reported in the literature.[3]

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