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Stereochemistry of 14-Hydroxy-β-caryophyllene and Related Compounds

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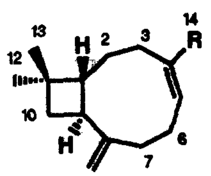
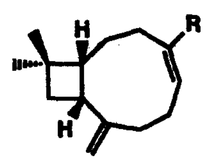
Abstract: The isomerization of β-caryophyllene (3), under treatment with SeO_2, is described. Chemical correlations, between 3 and 14-hydroxy-β-caryophyllene (6) from *Juniperus oxycedrus*, are established. High resolution ^1H NMR spectra and analysis by molecular mechanics of 3, 6 and 14-acetoxy-β-caryophyllene (7) indicate the existence of two conformational isomers, βα and ββ, in each compound. At 25°C, the βα conformer predominates in 3 and 7 but the ββ conformer predominates in 6. The higher percentage of 6ββ possibly derives from an intramolecular hydrogen bond. The treatment of 3, 6 and 7 with *m*-CPBA generates, in each case, two diastereomeric 4,5-epoxi-derivatives. The epoxides obtained from 6 have been isolated and analysed separately.

INTRODUCTION

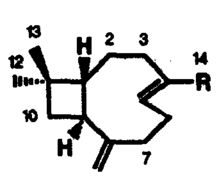
The stereochemistry of derivatives with the caryophyllene skeleton (4,11,11-trimethyl-8-methylen bicyclo [7,2] undec-4-ene) have presented a challenge to organic chemists for years. In 1964 Corey *et al.*[1] synthesized three (1-3) of the four isomeric hydrocarbons and, later, Bohlmann and Zdero[2] isolated the strained 9-*epi*-β-caryophyllene (4) from *Euryops brevipapposus*. However, the structural analysis of the caryophyllenes



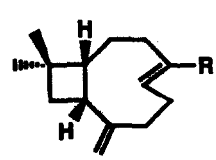
1, R = CH_3
8, R = CH_2OH
10, R = CHO
12, R = CH_2OAc



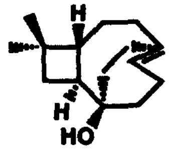
2, R = CH_3



3, R = CH_3
6, R = CH_2OH
7, R = CH_2OAc



4, R = CH_3
5, R = CH_2OH



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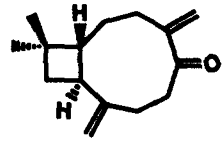

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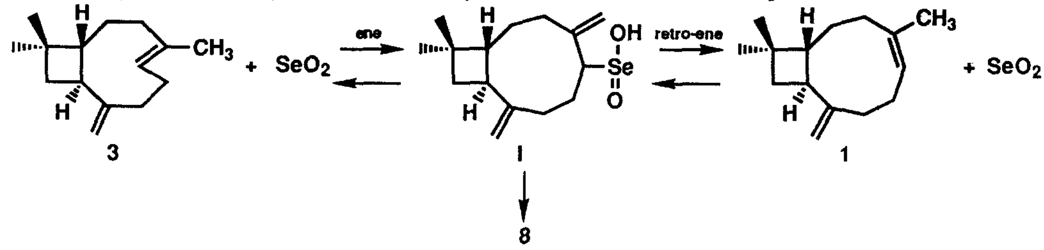
does not end with the determination of their configuration, since their stereochemistry is complicated by serious conformational aspects. In 1973, on the basis of observations made dring a series of chemical transformations, Warnhoff and Srinivasan[3] proposed the existence of two conformational isomers of β-caryophyllene (**3**) at room temperature. Later, Shirahama *et al.*[4] extended the conformational analysis of **3** using ^{13}C NMR and the pioneer molecular mechanics programme MM1. They found two predominant conformers, named βα and ββ following the directions of exomethylene and allylic methyl groups, at 76 and 24 per cent respectively.

At the end of the 1980's, the chemical analysis of the essential oil from the wood of *Juniperus oxycedrus* was initiated in the current authors' laboratory.[5] From the oxigenated sesquiterpene fraction, a 14-hydroxyderivative with the caryophyllene skeleton was isolated. This caryophyllenol behaved like a mixture of two conformational isomers in similar proportions. Since there was no nOe between H-5 and H-14 (indicative of 4*Z* geometry) and their spectra were not superimposable with those of the 14-hydroxy-derivative obtained by oxydation of β-caryophyllene with SeO_2, it was assigned the structure 14-hydroxy-9-*epi*-β-caryophyllene (**5**).[6] Nevertheless, later observations proved to the authors that the assigned 9*R* configuration was incorrect and, consequently, that the true structure of the natural caryophyllenol was 14-hydroxy-β-caryophyllene (**6**).[7] Now, the differences in the proportions of the conformers of **6** and **3**, two substances with identical carbon skeletons and configurations, were remarkable. For this reason the decision was made to complete the conformational analysis of **6** and to compare the results with those obtained with **3** and with the acetyl derivative **7**.

In this paper, the isomerization process undergone by the endocyclic double bond of β-caryophyllene, under treatment with SeO_2, is described. Chemical correlations between **3** and **6**, which indicate the correct configuration of the caryophyllenol from *J. oxycedrus*, are established. Conformational analysis of the compounds **3**, **6** and **7** is carried out using high resolution ^1H NMR and molecular mechanics. The ^1H and ^{13}C NMR signals of substances **3**, **6** and **7** are assigned to the corresponding atoms of the conformers βα and ββ of each compound. Furthermore, products **3**, **6** and **7** are treated with *m*-CPBA and stereoselectivity of reactions are studied by means of spectroscopically caracterization of the two diastereomeric epoxides obtained from each.

RESULTS AND DISCUSSION

In contrast to that described in reference 8, the treatment of β-caryophyllene (**3**) with SeO_2 generated 14-hydroxy-isocaryophyllene (**8**). The true 4*E* configuration of **8** was established by the nOe observed between H-5 and H-14 and by its ^{13}C NMR spectrum. In this spectrum C-14 resonates at 67.3 ppm while, in the ^{13}C NMR spectrum of **6**, C-14 appears at 60.2 ppm in one conformer and at 62.0 ppm in the other in agreement with the 4*Z* geometry assigned to this natural caryophyllenol.[6] During the reaction of **3** with SeO_2, isocaryophyllene (**1**) was also produced. Its formation can be explained by the retro-ene reaction in Scheme 1. The ene reaction between **3** and SeO_2 generates the selenyl derivative **I**, which presents conformational mobility in the nine members ring (C-4 - C-5 single bond) and thereby it evolves to less strained compounds **1** and **8**.



Scheme 1

At first, the product **8** and the natural caryophyllenol from *J. oxycedrus* were thought to have the same 4Z configuration. Since their spectra did not coincide, *cis* geometry was assigned to the interannular junction of the natural caryophyllenol.[6] Once the 4*E* configuration of **8** became known it was necessary to revise the geometry assigned to the natural caryophyllenol. With the aim of establishing a chemical correlation between one of the two hydrocarbons, **3** or **4**, and the natural caryophyllenol, a series of chemical transformations of the latter were carried out. Its reaction with PBr_3 and $LiAlH_4$ generated the tricyclic alcohol **9**[9] and small amount of β-caryophyllene. Its oxidation with pyridinium dichromate (PDC) also produced a mixture of substances with a *trans* interannular junction: the aldehyde **10**[10] and the ketone **11**.[11] Lastly, ozonolysis reactions of the acetates **7** (derived from the natural caryophyllenol) and **12** (derived from **8**) arrived at the same seco-derivative **13** (Scheme 2), establishing definitively the structure 14-hydroxy-β-caryophyllene (**6**; 1*R*, 9*S*) for the natural caryophyllenol from *J. oxycedrus*.

During the writing of this paper, Hinkley *et al.*[12] described another chemical correlation between **3** and **6**.

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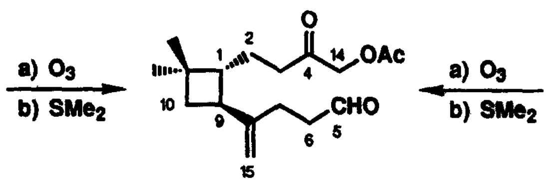
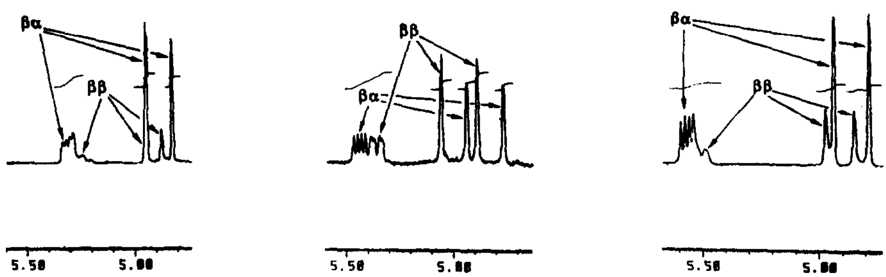


12

13

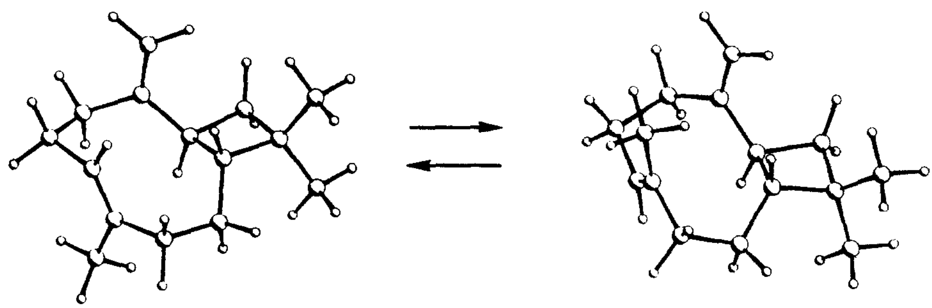
Scheme 2

The relative proportions of the two conformers of **6**[6] (determined by ^1H NMR) contrasted with that of the two conformers of **3**[4] (determined by ^{13}C NMR). With the intention of comparing results obtained by the same technique, the high resolution ^1H NMR spectra of **3**, **6** and **7** were performed. In the olefinic regions of this spectra (Figure 1) the signals of the two conformers of each compound can be distinguished. The protons of the exocyclic methylene are more shielded in the βα than in the ββ conformers while H-5 is more deshielded in the βα (where this hydrogen resonates as a double doublet) than in the ββ conformers (where it resonates as a broad doublet in **3**ββ and **7**ββ and as a double double doublet in **6**ββ). The ^1H NMR signals were assigned to the βα or to the ββ conformers of **3**, **6** and **7** on the basis of the similarity found between the relative intensity of each signal and the relative proportion of each conformer determined by molecular mechanics (Figure 2). The ^{13}C NMR signals (Experimental, Table 2) were also assigned without major difficulty. In the ^{13}C NMR

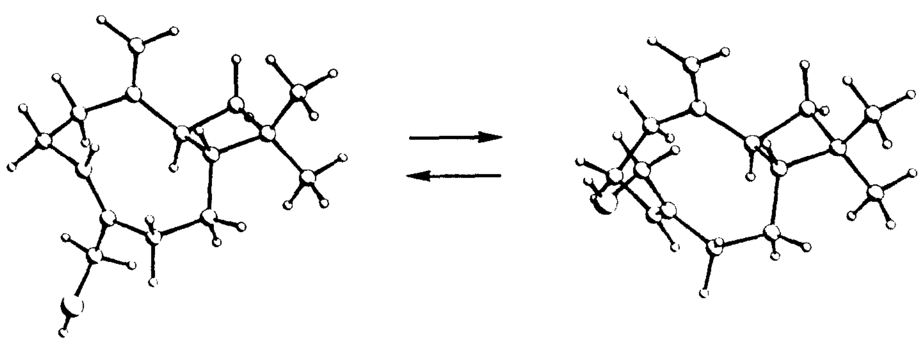


3 **6** **7**

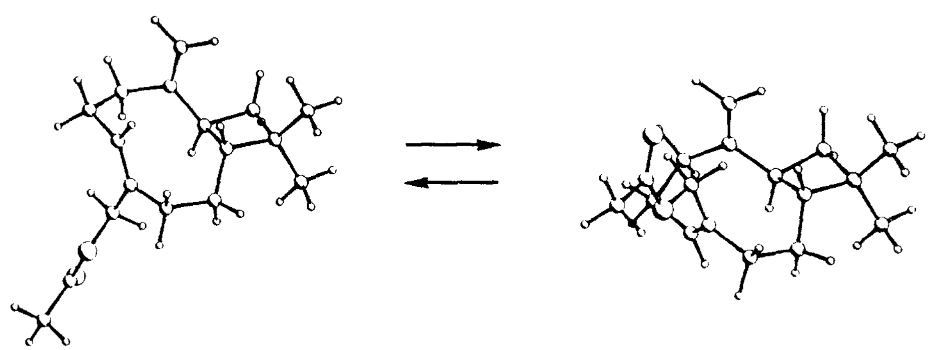
Figure 1. Olefinic regions from the ^1H NMR spectra of **3**, **6** and **7**.



	3βα	3ββ
SYBYL (population levels, energy)	59.59, 44.65 Kcal/mol	40.41, 44.88 Kcal/mol
^{1}H NMR (conformers percentages)	82	18



	6βα	6ββ
SYBYL	41.63, 45.15 Kcal/mol	58.37, 44.95 Kcal/mol
^{1}H NMR	42	58



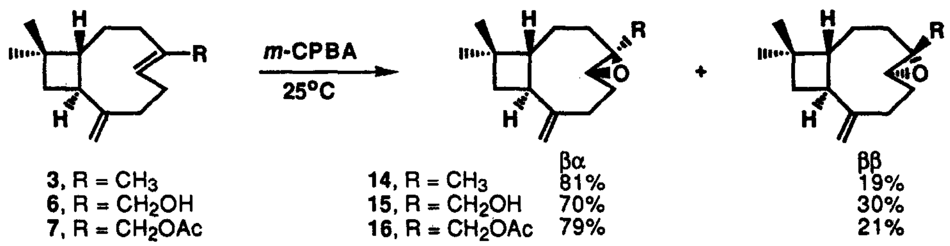
	7βα	7ββ
SYBYL	55.47, 46.50 Kcal/mol	44.53, 46.63 Kcal/mol
^{1}H NMR	68	32

Figure 2. Conformational analysis of **3**, **6** and **7** using molecular modelling and ^{1}H NMR.

spectra of **3** and **7**, the signals corresponding to the βα conformers were notably more intense. In the case of **6**, all showed a similar intensity and were assigned by comparison with those of **3** and **7**.

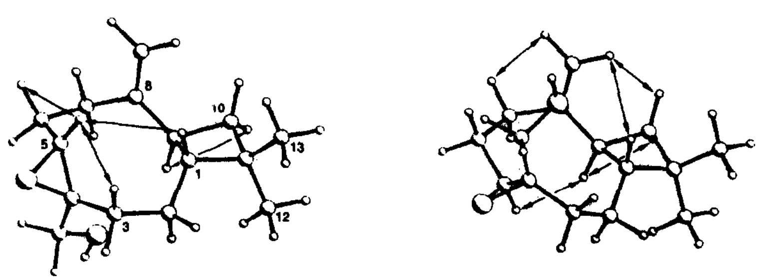
In the past, the Allinger MM1 molecular modelling programme gave theoretical conclusions in agreement with the experimental data obtained from β-caryophyllene.[4] Not possessing MM1, the authors used a more recent programme, the SYBYL system,[13] which had given good results with other cyclic molecules in earlier works. This theoretical analysis of **3**, **6** and **7** also indicated the existence of two conformers, βα and ββ, in close relative proportions to those determined experimentally (Figure 2). In **3**, as in **7**, the predominant conformer is βα. However, the ratio is inverted in **6**, where the ββ conformer predominates slightly. The increased percentage of **6**ββ could derive from an intramolecular hydrogen bond between the hydroxyl group and the double bond $\Delta^{8(15)}$. This hydrogen bond could also be responsible for the chemical shift of C-8 in **6**ββ (159.0 ppm), which is substantially less shielded than in **7**ββ (C-8 at 154.7 ppm). This carbon resonates more closely in the βα conformers: 154.0 ppm in **6**βα and 152.9 ppm in **7**βα. Intramolecular hydrogen bonds between hydroxyl groups and double bonds have been previously reported.[14]

The preparation of 4,5-epoxiderivatives generated valuable information at the first stage of the conformational analysis of β-caryophyllene.[3] In the authors' laboratory, the treatment of **3**, **6** and **7** with *m*-CPBA yielded a mixture of two diastereomeric epoxides in each case (Scheme 3). The diastereomers **15**βα and



Scheme 3

15ββ were isolated by column chromatography and each isomer was analysed separately by spectroscopic techniques. The connectivities of their hydrocarbon skeletons were confirmed using 2D NMR techniques[15] and their configurations determined by NOESY experiments (Figure 3). The diastereomers of **14** and **16** could not be separated by chromatography over silica gel. Their ^{1}H (Table 3) and ^{13}C NMR (Table 4) signals were analysed on the spectra of the mixtures and were assigned by comparison with those of **15**βα and **15**ββ. Their relative proportions were measured on the integral of the ^{1}H NMR spectra.



15βα **15**ββ

Figure 3. Observed nOes by means of NOESY experiences on the diastereomers **15**βα and **15**ββ.

The existence of two conformers in **3**, **6** and **7** allows the exposure of both sides of the endocyclic double bond to the *m*-CPBA attack. Thus, the oxidation of the βα conformers generates the βα epoxides and that of the ββ conformers yields the ββ epoxides. The **14βα/14ββ** and **16βα/16ββ** ratios are directly proportional to those of the starting conformers (**3βα/3ββ** and **7βα/7ββ**). However, the **15βα/15ββ** ratio (>1) notably differs from the **6βα/6ββ** ratio (< 1) pointing towards a higher reactivity of **6βα**. This fact might be additional evidence for the existence of an intramolecular hydrogen bond. In the **6βα** conformer, the allylic OH is free to coordinate with the peroxyacid,[16] thus accelerating the epoxidation of the neighbouring endocyclic double bond. In contrast, the hydroxyl group of **6ββ** is employed in the intramolecular hydrogen bond.

EXPERIMENTAL

Optical rotations were determined on a Perkin-Elmer Model 141 polarimeter, using $CHCl_3$ as solvent. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were performed on a Bruker AM 300 spectrometer using TMS as internal standard and $CDCl_3$ as solvent. Chemical shifts (δ) are expressed in parts per million (ppm) and coupling constants (*J*) in hertz. NOEDIF and NOESY experiments were performed on the Bruker AM 300 spectrometer. IR spectra were recorded on a Perkin-Elmer Model 983 G spectrometer with samples between sodium chloride plates (film). All mass spectra were registered on a Hewlett-Packard 5988A mass spectrometer using an ionizing voltage of 70 eV (EIMS) or by chemical ionization (methane, CIMS). Gas Chromatography (GC) analysis was run on a Hewlett-Packard 5890A gas chromatograph. Chromatographic separations were carried out by conventional column on Merk silica gel 60 (70-230 mesh) using hexane-Et_2O (H-E) mixtures of increasing polarity or by flash chromatography on Merk silica gel 60 (230-400 mesh).

Computational aspects. The SYBYL force field[13] was used implemented as in the program Spartan 3.0.[17]

β-Caryophyllene (3)

A sample of **3** (DGF company, Granada, Spain) was purified on a 20% $AgNO_3$ silica gel column to 98% purity (GC). Oil ; $[\alpha]_D$ -12.9° (*c* 1.07). At 25°C the compound exists as a mixture of two conformational isomers: **3βα** and **3ββ** at 82 and 18% respectively, as deduced from the ^1H NMR integral. ^1H and ^{13}C NMR spectra are in tables 1 and 2.

Oxidation of β-caryophyllene (3) with SeO_2

A solution of SeO_2 (1.1 g, 9.9 mmol) in EtOH (10 ml) was added to a solution of **3** (2.0 g, 9.8 mmol) in EtOH and the mixture was stirred for 3 h. at room temperature. H_2O (70 ml) was added and the mixture was extracted with Et_2O. The resulting organic layers were washed with sat. $NaHCO_3$ aq. solution and H_2O, dried over anh. Na_2SO_4 and the solvent removed. The flash chromatography of the residue (75:25 H-E) yielded 1.3 g of isocaryophyllene (**1**) and 0.9 g of 14-hydroxy-isocaryophyllene (**8**). **1**: colorless oil; $[\alpha]_D$ -16.06° (*c* 1.03); IR (neat): υ 3069 (H-C=), 1628 (C=C), 1377, 1365 (CH_3-C-CH_3), 884 (C=CH_2); ^1H NMR: δ 0.98 (3H, *s*, H-12), 1.00 (3H, *s*, H-13), 1.41-1.52 (2H, *m*, H-2), 1.54 (1H, *dd*, *J*=10.5, *J*=9.6, H-10), 1.66 (3H, *br s*, H-14), 1.72 (1H, *dd*, *J*=10.8, *J*=8.6, H-10'), 1.85 (1H, *ddd*, *J*=11.5, *J*=9.2, *J*=4.7, H-1), 2.00 (1H, *ddd*, J=13.1, *J*=6.7, *J*=3.9, H-3), 2.13 (1H, *ddd*, *J*=13.7, *J*=9.8, *J*=4.2, H-3'), 2.14-2.26 (4H, *m*, H-6, H-6', H-7, H-7'), 2.52 (1H, *q*, *J*=9.1, H-9), 4.76 (1H, *d*, *J*=1.8, H-15), 4.84 (1H, *d*, *J*=2.0, H-15'), 5.26 (1H, *brt*, *J*=7.5, H-5); ^{13}C NMR: δ 23.13 (C-12), 23.32 (C-14), 25.67 (C-2), 28.51 (C-6), 28.79 (C-3), 30.04 (C-13), 33.18 (C-11), 35.59 (C-7), 40.17 (C-9), 40.54 (C-10), 51.95 (C-1), 110.40 (C-15), 124.98 (C-5), 136.28 (C-4), 156.70 (C-8). **8**: yellow oil; $[\alpha]_D$ -10.4° (*c* 1.07); IR (neat): υ 3336 (OH), 1377,1364 (CH_3-C-CH_3), 1010 (C-O), 884 (C=CH_2); ^{1}H NMR: δ 0.96 (3H, *s*, H-13), 0.98 (3H, *s*, H-12), 1.55 (1H, *dd*, $J_{10\beta,10\alpha}$=10.7, $J_{10\beta,9}$=9.3, H-10β), 1.70 (1H, *dd*, $J_{10\alpha,10\beta}$=10.9, $J_{10\alpha,9}$=8.8, H-10α), 1.80 (1H, *ddd*, $J_{1,2}$=11.4, $J_{1,9}$=9.2, $J_{1,2}$=4.1, H-1), 2.49 (1H, *q*, *J*=9.1, H-9), 4.01 (2H, *br s*, H-14), 4.74 (1H, *d*, *J*=1.9, H-15), 4.82 (1H, *d*, *J*=1.9, H-15'), 5.50 (1H, *br t* , *J*=7.9, H-5), NOEDIF: Irradiation at δ 4.01 (H-14) generated nOe in H-5 and irradiation at 5.50 ppm (H-5) caused reciprocal nOe in H-14; ^{13}C NMR: δ 22.9 (C-12), 25.3 (C-2), 26.7 (C-3), 27.3 (C-6), 30.1 (C-13), 33.3 (C-11), 35.1 (C-7), 40.1 (C-10), 40.7 (C-9), 52.1 (C-1), 67.3 (C-14), 110.6 (C-15), 126.7 (C-5), 139.7 (C-4), 155.5 (C-8).

14-hydroxy-β-caryophyllene (6)

The alcohol **6** at 91% (GC) purity was isolated from *Juniperus oxycedrus*, as previously described.[5,6] At room temperature it presents two major conformers: **6βα** (42%) and **6ββ** (58%) on the basis of their ^{1}H NMR spectrum. ^{1}H and ^{13}C NMR spectra are in tables 1 and 2.

Reaction of 6 with PBr_3 and $LiAlH_4$

Br_3P (0.106, 2 mmol) in anhydrous Et_2O (3 ml) was slowly added to a stirred solution of **6** (0.186 g, 2 mmol) in Et_2O (5 ml) at -10°C, under an inert atmosphere. After stirring for 7 min. the cooling bath was removed and $LiAlH_4$ (0.062 g) in Et_2O (3 ml) was added. The mixture was stirred for 1 h., diluted with moist Et_2O, dried on anh. Na_2SO_4 and evaporated to dryness. The analysis of the residue by GC-MS, with an authentic sample as standard, showed a small proportion of β-caryophyllene (**3**). Lastly, the residue was run on a silica gel chromatography column (95:5, H-E) yielding **9**[9] (33 mg), **6** (66 mg) and **3** (3 mg).

Oxidation of 6 with PDC

A mixture of **6** (0.03 g, 0.14 mmol), CH_2Cl_2 (2 ml) and pyridinium dichromate (PDC, 0.095 g, 0.25 mmol), was stirred for 6 h. at room temperature. Et_2O (50 ml) was added and the suspension was filtered through silica gel (Et_2O). The solvent was removed and a 3:7 (GC analysis) mixture (0.024 g) of **10**[10] and **11**[11] was obtained.

14-Acetoxy-β-caryophyllene (7)

Overnight treatment of **3** (0.1 g) in pyridine (1 ml) with Ac_2O (1 ml), yielded the acetyl derivative **7**: oil; $[\alpha]_D$ -14.0° (*c* 1.02); IR (neat): υ 1741 (C=O), 891 (C=CH_2); EIMS *m/z* (rel. int.): 206 (M^+-Me_2C=CH_2, 1), 202 (M^+-AcOH, 5), 187 (M^+-AcOH-Me, 7), 159 (15),149 (14), 146 (M^+-AcOH-Me_2C=CH_2, 13), 145 (14), 105 (27), 91 (45), 78 (79), 63 (100). This compound exists, at room temperature as a 32:68 (^{1}H NMR integral) mixture of the conformational isomers **7βα** and **7ββ**. ^{1}H and ^{13}C NMR spectra are in tables 1 and 2.

Ozonolysis reactions of 14-acetoxy-β-caryophyllene (7) and 14-acetoxy-isocaryophyllene (12)

An O_2/O_3 stream (0.75 mmol O_3/h) was bubbled through a solution of **7** (269 mg, 1.03 mmol) in CH_2Cl_2 (26 ml) at -78°C for 3 h. Then, Me_2S (2.6 ml) was added and the mixture was stirred at room temperature for 12 h. The solvent was removed, the residue was filtered on silica gel (Et_2O as eluent) and the Et_2O was again removed . The flash chromatography (4:6 H-E) yielded 26 mg of **13**: oil; $[\alpha]_D$+60.8° (*c* 1.03); IR (neat): υ 2721 (OC-H), 1751 (C=O), 1728 (C=O), 890 (C=CH_2); ^{1}H NMR: δ 1.02 (3H, *s*, H-13), 1.03 (3H, *s*, H-12), 1.43 (1H, *t*, *J*=10.3, H-10β), 1.66 (2H, *q*, *J*=7.4, H-2), 1.80 (1H, *dd*, $J_{10\alpha,10\beta}$=8.5, H-10α), 1.89 (1H, *dt*, $J_{1,9}$=9.6, $J_{1,2}$=7.6, H-1), 2.14 (3H, *s*, CH_3CO_2), 2.28 (2H, *br t*, *J*=7.6, H-7), 2.32 (2H, *t*, *J*=7.4, H-3), 2.37 (1H, *br q*, *J*=10.0, H-9), 2.55 (2H, *dt*, $J_{6,7}$=7.6, $J_{6,5}$=1.8, H-6), 4.60 (2H, *s*, H-14), 4.66 (1H, *br s*, H-15), 4.77 (1H, *br s*, H-15'), 9.75 (1H, *t*, *J*=1.8, H-5); ^{13}C NMR: δ 22.3 (C-12), 23.9 (C-2), 26.5 (C-7), 31.0 (C-13), 33.6 (C-11), 37.0 (C-3), 39.7 (C-10), 41.8 (C-6), 47.6 (C-9), 51.6 (C-1), 67.9 (C-14), 107.7 (C-15), 150.5 (C-8), 202.1 (C-5), 203.6 (C-4); EIMS *m/z* (rel. int.): 252 (M^+-C_2H_2O, 1), 196 (M^+-C_2H_2O-C_4H_8, 2), 184 (M^+-$C_7H_{10}O$, 2), 142 (M^+-C_2H_{10}-C_7H_{10}, 2), 124 (16), 111 (14), 110 (M^+-$C_{10}H_{16}$, 3), 109 (23), 106 (29), 93 (16), 79 (17), 43 (100).

Acetylation of **8**, by the usual procedure, yielded the acetyl derivative **12**. Ozonolysis of **12** (187 mg), according to the described procedure generated 32 mg of a substance whose spectroscopic features were identical to those of **13**.

Epoxidation reactions of 6, 3 and 7

3-Chloroperoxybenzoic acid (0.208 g, 1.21 mmol) in CH_2Cl_2 (3 ml) was added to a solution of **6** (O.205 g, 0.93 mmol) in CH_2Cl_2 (4 ml), under an inert atmosphere, and the mixture was stirred for 2 h. Then, 10% aq. Na_2SO_3 was added. The mixture was extracted with H_2O. The solvent was removed and the residue was run on a silica gel chromatography column, giving 67 mg of **15ββ** (86:14, H-E) and 120 mg of **15βα** (85:15, H-E). **15ββ**: oil; $[\alpha]_D$ +26.5° (*c* 0.63); IR (neat): υ 3330 (OH), 1237, 1017 (C-O), 875 (C=CH_2), 815; ^1H and ^{13}C NMR data in tables 3 and 4 respectively; CIMS *m/z* (rel. int.): 237 (MH^+, 15), 219 (MH^+-H_2O, 75), 201 (MH^+-2H_2O, 100), 189 (MH^+-H_2O-CH_2OH, 13), 145 (MH^+-2H_2O-C_4H_8, 10). **15βα**: oil; $[\alpha]_D$ -14.6° (*c* 1.01); IR (neat): υ 3329 (OH), 1233, 1017 (C-O), 873 (C=CH_2), 849. ^1H and ^{13}C NMR data in tables 3 and 4.

Epoxidation of **3** (0.502 g, 2.46 mmol) by a similar procedure, followed by flash chromatography (95:5, H-E) of the final residue yielded a mixture (429 mg) of **14βα** (81%) and **14ββ** (19%). ^1H and ^{13}C NMR data are in tables 3 and 4.

Starting from **7** (0.064 g, 0.27 mmol) a mixture (26 mg) of the epoxides (flash chromatography, 85:15 H:E) **16βα** (79%) and **16ββ** (21%) was obtained. ^1H and ^{13}C NMR data are in tables 3 and 4.

Table 1. Relevant ^1H NMR data* of the compounds **3**, **6** and **7**.

H	3		6		7	
	βα	ββ	βα	ββ	βα	ββ
5	5.30, *dd*	5.26, *br d*	5.44, *dd*	5.36, *ddd*	5.60, *dd*	5.51, *br d*
	J=10.3, 4.5	*J*=12	*J*=11.0, 5.7	*J*=11.7, 4.5, 2.2	*J*=10.9, 5.5	*J*=12
7	1.91, *dt*	—	—	—	1.85, *dt*	—
	J=11.9, 5.3	—	—	—	*J*=12.5, 5.3	—
10β	—	—	—	—	1.56, *t*	—
	—	—	—	—	*J*=10.4	—
12	1.00, *s*	0.97, *s*	1.00, *s*	1.00, *s*	0.97, *s*	0.95, *s*
13	0.97, *s*	0.96, *s*	0.99, *s*	0.98, *s*	0.95, *s*	0.93, *s*
14	1.61, *d*	1.58, *s*	3.92, *d*	3.67, *d*	4.44, *d*	4.32, *d*
	J=1.1	—	*J*=12.2	*J*=11.8	*J*=12.0	*J*=11.9
14'	—	—	4.16, *d*	4.12, *d*	4.68, *d*	4.68, *d*
	—	—	*J*=12.2	*J*=11.8	*J*=12.0	*J*=11.9
15	4.82, *d*	4.87, *br s*	4.76, *d*	4.89, *br s*	4.81, *br s*	4.87, *br s*
	J=1.7	—	*J*=1.8	—	—	—
15'	4.94, *d*	4.94, *br s*	4.94, *br s*	5.06, *br s*	4.96, *br s*	4.99, *br s*
	J=1.7					
CH_3CO_2	—	—	—	—	2.03, *s*	2.01, *s*

* The data mean δ in ppm, multiplicity and coupling constants (Hz) respectively

Table 2. ^{13}C NMR data* of the compounds 3, 6 and 7.

C	3		6		7	
	βα	ββ	βα	ββ	βα	ββ
1	53.7	56.0	50.4	56.9	51.2	55.8
2	28.4	29.8	29.3	30.6	28.8	29.6
3	40.1	34.9	33.8	29.3	34.0	29.3
4	135.6	135.1	138.0	137.8	133.3	133.3
5	124.4	124.6	128.9	129.5	131.2	131.1
6	29.5	31.5	30.0	30.6	29.3	30.3
7	34.9	39.9	34.9	40.4	34.9	39.9
8	154.8	155.2	154.0	159.0	152.9	154.7
9	48.6	49.5	49.8	49.1	49.3	49.1
10	40.4	42.7	40.7	42.6	40.3	42.6
11	33.1	33.1	33.0	33.0	32.8	32.8
12	22.7	22.0	22.2	21.9	22.3	21.9
13	30.2	29.9	30.1	29.8	30.0	29.9
14	16.4	16.4	60.2	62.0	61.4	65.4
15	111.7	110.9	113.1	110.2	113.5	111.5
$\underline{C}H_3CO_2$	—	—	—	—	21.1	21.1
$CH_3\underline{C}O_2$	—	—	—	—	171.2	171.2

*Chemical shifts in ppm

Table 3. ^1H NMR data* of the epoxides 14-16.

H	14βα	14ββ	15βα	15ββ	16βα	16ββ
1	1.74, *br t*	—	1.78, *br t*	1.75, *br dd*	1.79, *br t*	—
2α	—	—	1.46, *ddd*	1.41, *dddd*	—	—
2β	—	—	1.64, *ddd*	1.55, *br ddd*	—	—
3α	—	—	2.50, *ddd*	2.12, *ddd*	—	—
3β	—	—	0.80, *dddd*	1.67, *ddd*	—	—
5	2.86, *dd*	2.98, *dd*	3.04, *dd*	3.13, *dd*	3.00, *dd*	3.11, *dd*
6α	—	—	1.37, *m*	2.17, *dddd*	—	—
6β	—	—	2.26, *m*	1.48, *ddt*	—	—
7α	—	—	2.10, *m*	2.06, *ddd*	—	—
7β	—	2.50, *ddd*	2.26, *m*	2.53, *ddd*	—	2.52, *ddd*
9	2.58, *ddd*	—	2.63, *ddd*	2.34, *ddd*	2.67, *ddd*	—
10α	1.67, *dd*	1.84, *dd*	1.65, *dd*	1.85, *dd*	1.68, *dd*	—
10β	1.59, *t*	—	1.55, *t*	1.61, *dd*	1.58, *t*	—
12	1.00, *s*	1.00, *s*	1.00, *s*	1.00, *s*	1.00, *s*	1.00, *s*
13	0.98, *s*	0.96, *s*	0.98, *s*	0.96, *s*	0.98, *s*	0.96, *s*
14	1.20, *s*	1.26, *s*	3.81, *br d*	3.60, *br d*	4.55, *d*	4.36, *d*
14'	—	—	3.38, *dd*	3.51, *br d*	3.61, *dd*	3.75, *br d*
15	4.95, *d*	5.09, *s*	4.96, *d*	5.13, *s*	5.02, *br s*	5.13, *s*
15'	4.84, *d*	4.97, *s*	4.81, *d*	5.02, *s*	4.84, *br s*	5.02, *s*
CH_3CO_2	—	—	—	—	2.08, *s*	2.08, *s*

Coupling constants (*J*): Compound 14βα: 1,9= 1,2α= 9.7 Hz; 5,6α= 10.7 Hz; 5,6β= 4.2 Hz; 9,10β= 10α,10β= 10.6 Hz; 9,10α= 8.3 Hz; 15,15'= 1.6 Hz. Compound 14ββ: 5,6α= 11.4 Hz; 5,6β= 2.6 Hz; 7β,7α= 12.9 Hz; 7β,6β= 6.3 Hz; 7β,6α= 2.1 Hz; 10α,10β= 11.0 Hz; 10α,9= 8.0 Hz. Compound 15βα: 1,9= 1,2α= 9.9 Hz; 2α,3β= 13.4 Hz; 2α,2β= 10.4 Hz; 2α,3α= 4.3 Hz; 2β,3β= 5.5 Hz; 2β,3α= 3.0 Hz; 3α,3β= 13.0 Hz; 3β,14'= 1.1 Hz; 5,6α= 11.0 Hz; 5,6β= 4.1 Hz; 9,10β= 10α,10β= 10.6 Hz; 9,10α= 8.3 Hz; 14,14'= 12.2 Hz; 15,15'= 1.6 Hz. Compound 15ββ: 1,2α=10.3 Hz; 1,9= 9.5 Hz; 2α,2β= 14.5 Hz; 2α,3α= 12.4 Hz; 2α,3β= 5.4 Hz; 2β,3α= 5.7 Hz; 2β,3β= 2.6 Hz; 3α,3β= 15.1 Hz; 5,6β= 6β,7α= 11.6 Hz; 5,6α= 2.4 Hz; 6α,6β= 12 Hz; 6α,7α= 5.3 Hz; 6α,7β= 2.1 Hz; 6β,7β= 6.3 Hz; 7α,7β= 12.8 Hz; 9,10β= 10.0 Hz; 9,10α= 8.1 Hz; 10α,10β= 10.7 Hz; 14,14'= 11.7 Hz. Compound 16βα: 1,9= 1,2α= 10.0 Hz; 5,6α= 10.9 Hz; 5,6β= 3.9 Hz; 9,10β= 10α,10β= 10.5 Hz; 9,10α= 8.4 Hz; 14,14'= 12.2 Hz; 14',3β= 1.3 Hz. Compound 16ββ: 5,6β= 11.6 Hz; 5,6α= 2.7 Hz; 7β,7α= 12.9 Hz; 7β,6β= 6.2 Hz; 7β,6α= 2.0 Hz; 14,14'= 12.0 Hz.

* Chemical shifts in ppm.

Table 4. ^{13}C NMR data* of the epoxides **14-16**.

C	14βα	14ββ	15βα	15ββ	16βα	16ββ
1	50.8	54.0	49.3	54.9	49.6	54.2
2	27.3	27.8	26.5	27.5	26.5	27.4
3	39.3	36.4	33.5	31.3	33.6	30.8
4	59.9	61.0	62.9	63.1	60.1	60.8
5	63.8	61.1	65.1	61.9	63.8	61.0
6	30.3	30.3	30.3	29.1	30.4	29.6
7	29.9	36.7	28.7	36.8	29.0	36.5
8	151.9	152.8	151.5	155.1	151.2	152.8
9	48.8	47.2	49.1	47.3	49.0	47.3
10	39.9	42.4	39.9	42.4	39.9	42.5
11	34.1	33.1	34.5	33.2	34.5	33.2
12	21.7	21.7	21.5	21.7	21.5	21.6
13	30.0	30.0	30.0	29.8	30.0	30.0
14	17.1	22.7	62.1	65.2	64.1	68.1
15	112.9	112.3	113.4	111.9	113.7	112.6
<u>C</u>H_3CO_2	—	—	—	—	20.9	21.0
CH_3<u>C</u>O_2	—	—	—	—	171.3	171.3

*Chemical shifts in ppm

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