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

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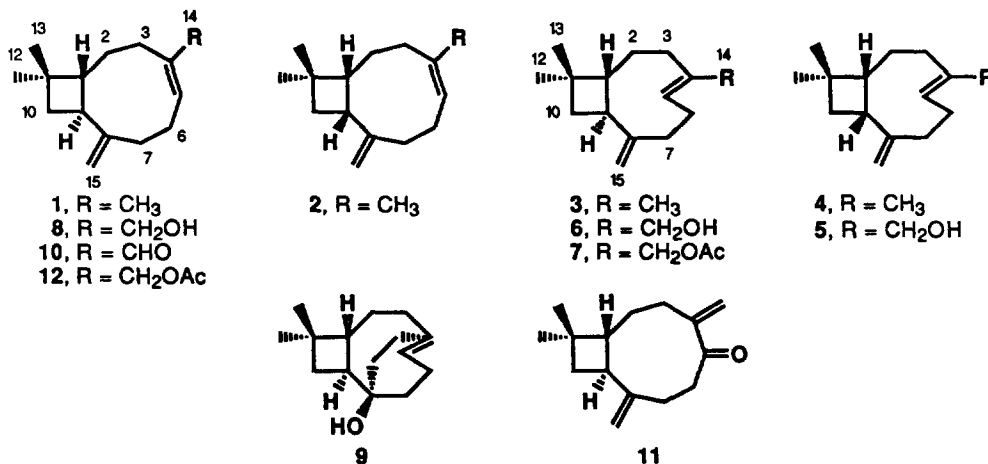
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Abstract: The isomerization of β -caryophyllene (3), under treatment with SeO_2 , is described. Chemical correlations, between 3 and 14-hydroxy- β -caryophyllene (6) from *Juniperus oxycedrus*, are established. High resolution ^1H NMR spectra and analysis by molecular mechanics of 3, 6 and 14-acetoxy- β -caryophyllene (7) indicate the existence of two conformational isomers, $\beta\alpha$ and $\beta\beta$, in each compound. At 25°C , the $\beta\alpha$ conformer predominates in 3 and 7 but the $\beta\beta$ conformer predominates in 6. The higher percentage of $\beta\beta$ 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-epoxy-derivatives. The oxepides 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 Zdero² isolated the strained 9-*epi*- β -caryophyllene (4) from *Euryops brevipapposus*. However, the structural analysis of the caryophyllenes



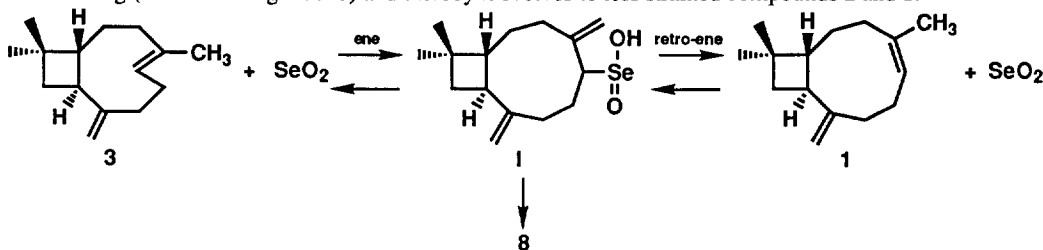
does not end with the determination of their configuration, since their stereochemistry is complicated by serious conformational aspects. In 1973, on the basis of observations made during a series of chemical transformations, Warnhoff and Srinivasan³ proposed the existence of two conformational isomers of β -caryophyllene (**3**) at room temperature. Later, Shirahama *et al.*⁴ extended the conformational analysis of **3** using ¹³C NMR and the pioneer molecular mechanics programme MM1. They found two predominant conformers, named $\beta\alpha$ and $\beta\beta$ 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 oxygenated 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 4Z geometry) and their spectra were not superimposable with those of the 14-hydroxy-derivative obtained by oxydation of β -caryophyllene with SeO₂, it was assigned the structure 14-hydroxy-9-*epi*- β -caryophyllene (**5**).⁶ Nevertheless, later observations proved to the authors that the assigned 9R 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 SeO₂, 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 ¹³C NMR signals of substances **3**, **6** and **7** are assigned to the corresponding atoms of the conformers $\beta\alpha$ and $\beta\beta$ of each compound. Furthermore, products **3**, **6** and **7** are treated with *m*-CPBA and stereoselectivity of reactions are studied by means of spectroscopically characterization of the two diastereomeric epoxides obtained from each.

RESULTS AND DISCUSSION

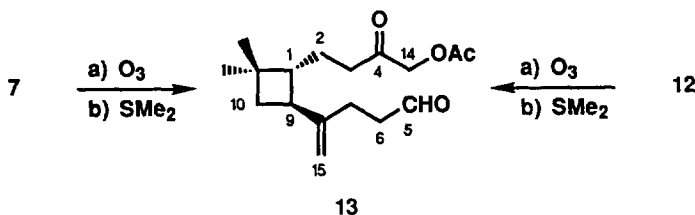
In contrast to that described in reference 8, the treatment of β -caryophyllene (**3**) with SeO₂ generated 14-hydroxy-isocaryophyllene (**8**). The true 4E configuration of **8** was established by the nOe observed between H-5 and H-14 and by its ¹³C NMR spectrum. In this spectrum C-14 resonates at 67.3 ppm while, in the ¹³C 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 4Z geometry assigned to this natural caryophyllenol.⁶ During the reaction of **3** with SeO₂, isocaryophyllene (**1**) was also produced. Its formation can be explained by the retro-ene reaction in Scheme 1. The ene reaction between **3** and SeO₂ 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 *4E* 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**; *1R*, *9S*) 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**.



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 $\beta\alpha$ than in the $\beta\beta$ conformers while H-5 is more deshielded in the $\beta\alpha$ (where this hydrogen resonates as a double doublet) than in the $\beta\beta$ conformers (where it resonates as a broad doublet in $3\beta\beta$ and $7\beta\beta$ and as a double double doublet in $6\beta\beta$). The ^1H NMR signals were assigned to the $\beta\alpha$ or to the $\beta\beta$ 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

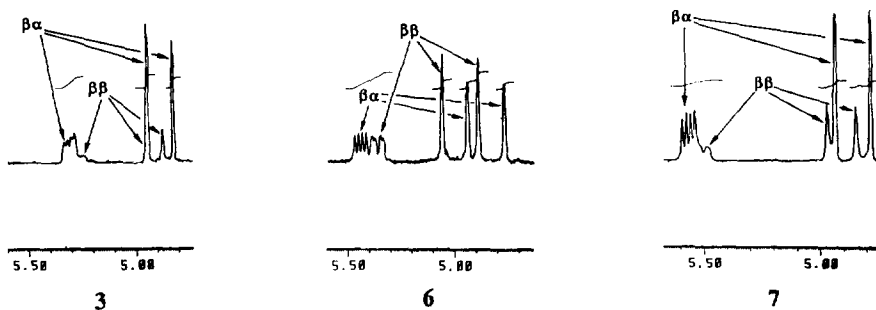


Figure 1. Olefinic regions from the ^1H NMR spectra of **3**, **6** and **7**.

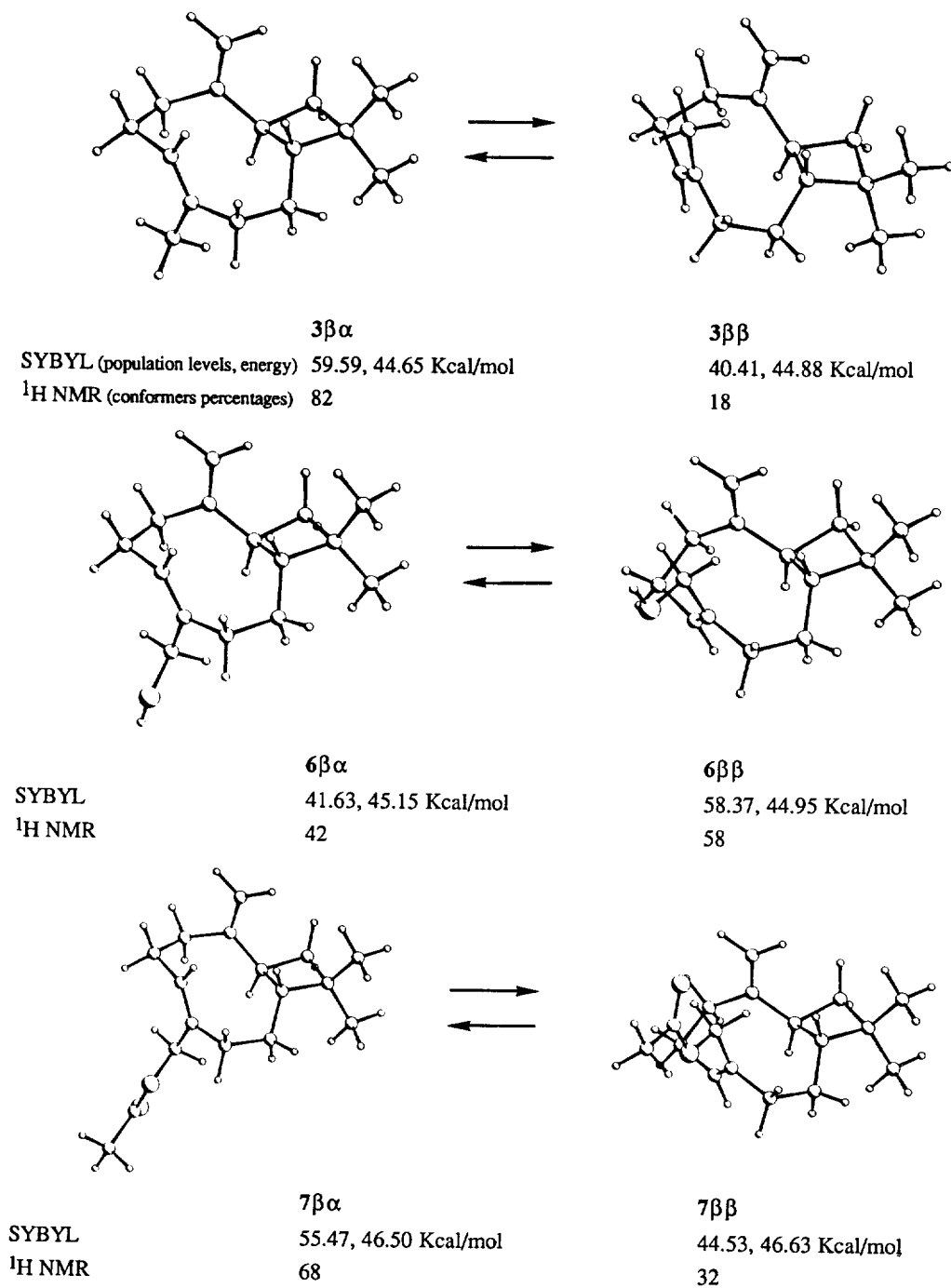
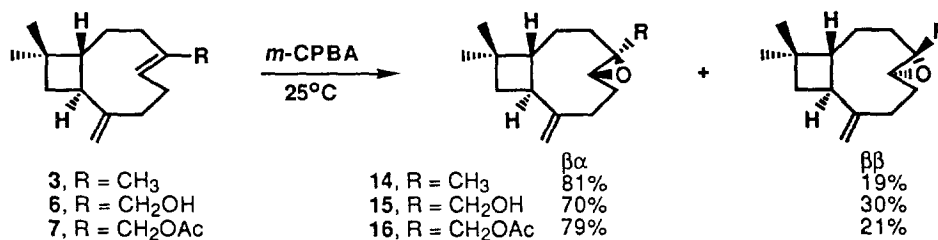


Figure 2. Conformational analysis of 3, 6 and 7 using molecular modelling and ^1H NMR.

spectra of **3** and **7**, the signals corresponding to the $\beta\alpha$ 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, $\beta\alpha$ and $\beta\beta$, in close relative proportions to those determined experimentally (Figure 2). In **3**, as in **7**, the predominant conformer is $\beta\alpha$. However, the ratio is inverted in **6**, where the $\beta\beta$ conformer predominates slightly. The increased percentage of $\beta\beta$ 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 $\beta\beta$ (159.0 ppm), which is substantially less shielded than in $\beta\alpha$ (C-8 at 154.7 ppm). This carbon resonates more closely in the $\beta\alpha$ conformers: 154.0 ppm in $\beta\alpha$ and 152.9 ppm in $\beta\alpha$. Intramolecular hydrogen bonds between hydroxyl groups and double bonds have been previously reported.¹⁴

The preparation of 4,5-epoxid derivatives 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** $\beta\alpha$ and



Scheme 3

15 $\beta\beta$ 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 techniques¹⁵ 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 ¹H (Table 3) and ¹³C NMR (Table 4) signals were analysed on the spectra of the mixtures and were assigned by comparison with those of **15** $\beta\alpha$ and **15** $\beta\beta$. Their relative proportions were measured on the integral of the ¹H NMR spectra.

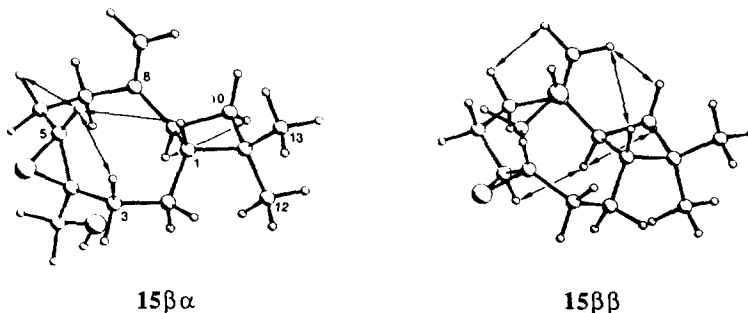


Figure 3. Observed nOes by means of NOESY experiences on the diastereomers **15** $\beta\alpha$ and **15** $\beta\beta$.

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 $\beta\alpha$ conformers generates the $\beta\alpha$ epoxides and that of the $\beta\beta$ conformers yields the $\beta\beta$ epoxides. The $14\beta\alpha/14\beta\beta$ and $16\beta\alpha/16\beta\beta$ ratios are directly proportional to those of the starting conformers ($3\beta\alpha/3\beta\beta$ and $7\beta\alpha/7\beta\beta$). However, the $15\beta\alpha/15\beta\beta$ ratio (>1) notably differs from the $6\beta\alpha/6\beta\beta$ ratio (<1) pointing towards a higher reactivity of $6\beta\alpha$. This fact might be additional evidence for the existence of an intramolecular hydrogen bond. In the $6\beta\alpha$ 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 $6\beta\beta$ 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-Et₂O (H-E) mixtures of increasing polarity or by flash chromatography on Merk silica gel 60 (230-400 mesh).

Computational aspects. The SYBYL force field¹³ 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; $[\alpha]_D -12.9^\circ$ (*c* 1.07). At 25°C the compound exists as a mixture of two conformational isomers: $3\beta\alpha$ and $3\beta\beta$ 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 Et₂O. The resulting organic layers were washed with sat. NaHCO_3 aq. solution and H_2O , dried over anhydrous 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; $[\alpha]_D -16.06^\circ$ (*c* 1.03); IR (neat): ν 3069 (H-C=), 1628 (C=C), 1377, 1365 ($\text{CH}_3\text{-C-CH}_3$), 884 (C=CH₂); ^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; $[\alpha]_D -10.4^\circ$ (*c* 1.07); IR (neat): ν 3336 (OH), 1377, 1364 (CH₃-C-CH₃), 1010 (C-O), 884 (C=CH₂); ¹H 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-10 β), 1.70 (1H, *dd*, $J_{10\alpha,10\beta}=10.9$, $J_{10\alpha,9}=8.8$, H-10 α), 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; ¹³C 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: **6** $\beta\alpha$ (42%) and **6** $\beta\beta$ (58%) on the basis of their ¹H NMR spectrum. ¹H and ¹³C NMR spectra are in tables 1 and 2.

Reaction of 6 with PBr₃ and LiAlH₄

Br₃P (0.106, 2 mmol) in anhydrous Et₂O (3 ml) was slowly added to a stirred solution of **6** (0.186 g, 2 mmol) in Et₂O (5 ml) at -10°C, under an inert atmosphere. After stirring for 7 min. the cooling bath was removed and LiAlH₄ (0.062 g) in Et₂O (3 ml) was added. The mixture was stirred for 1 h., diluted with moist Et₂O, dried on anh. Na₂SO₄ 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), CH₂Cl₂ (2 ml) and pyridinium dichromate (PDC, 0.095 g, 0.25 mmol), was stirred for 6 h. at room temperature. Et₂O (50 ml) was added and the suspension was filtered through silica gel (Et₂O). 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 Ac₂O (1 ml), yielded the acetyl derivative **7**: oil; $[\alpha]_D -14.0^\circ$ (*c* 1.02); IR (neat): ν 1741 (C=O), 891 (C=CH₂); EIMS *m/z* (rel. int.): 206 (M⁺-Me₂C=CH₂, 1), 202 (M⁺-AcOH, 5), 187 (M⁺-AcOH-Me, 7), 159 (15), 149 (14), 146 (M⁺-AcOH-Me₂C=CH₂, 13), 145 (14), 105 (27), 91 (45), 78 (79), 63 (100). This compound exists, at room temperature as a 32:68 (¹H NMR integral) mixture of the conformational isomers **7** $\beta\alpha$ and **7** $\beta\beta$. ¹H and ¹³C NMR spectra are in tables 1 and 2.

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

An O₂/O₃ stream (0.75 mmol O₃/h) was bubbled through a solution of **7** (269 mg, 1.03 mmol) in CH₂Cl₂ (26 ml) at -78°C for 3 h. Then, Me₂S (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 (Et₂O as eluent) and the Et₂O was again removed. The flash chromatography (4:6 H-E) yielded 26 mg of **13**: oil; $[\alpha]_D +60.8^\circ$ (*c* 1.03); IR (neat): ν 2721 (OC-H), 1751 (C=O), 1728 (C=O), 890 (C=CH₂); ¹H NMR: δ 1.02 (3H, *s*, H-13), 1.03 (3H, *s*, H-12), 1.43 (1H, *t*, $J=10.3$, H-10 β), 1.66 (2H, *q*, $J=7.4$, H-2), 1.80 (1H, *dd*, $J_{10\alpha,10\beta}=8.5$, H-10 α),

1.89 (1H, *dt*, $J_{1,9}=9.6$, $J_{1,2}=7.6$, H-1), 2.14 (3H, *s*, CH₃CO₂), 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); ¹³C 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⁺-C₂H₂O, 1), 196 (M⁺-C₂H₂O-C₄H₈, 2), 184 (M⁺-C₇H₁₀O, 2), 142 (M⁺-C₂H₁₀-C₇H₁₀, 2), 124 (16), 111 (14), 110 (M⁺-C₁₀H₁₆, 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 CH₂Cl₂ (3 ml) was added to a solution of **6** (0.205 g, 0.93 mmol) in CH₂Cl₂ (4 ml), under an inert atmosphere, and the mixture was stirred for 2 h. Then, 10% aq. Na₂SO₃ was added. The mixture was extracted with H₂O. The solvent was removed and the residue was run on a silica gel chromatography column, giving 67 mg of **15 $\beta\beta$** (86:14, H-E) and 120 mg of **15 $\beta\alpha$** (85:15, H-E). **15 $\beta\beta$** : oil; [α]_D +26.5° (*c* 0.63); IR (neat): ν 3330 (OH), 1237, 1017 (C-O), 875 (C=CH₂), 815; ¹H and ¹³C NMR data in tables 3 and 4 respectively; CIMS *m/z* (rel. int.): 237 (MH⁺, 15), 219 (MH⁺-H₂O, 75), 201 (MH⁺-2H₂O, 100), 189 (MH⁺-H₂O-CH₂OH, 13), 145 (MH⁺-2H₂O-C₄H₈, 10). **15 $\beta\alpha$** : oil; [α]_D -14.6° (*c* 1.01); IR (neat): ν 3329 (OH), 1233, 1017 (C-O), 873 (C=CH₂), 849. ¹H and ¹³C 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 **14 $\beta\alpha$** (81%) and **14 $\beta\beta$** (19%). ¹H and ¹³C 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) **16 $\beta\alpha$** (79%) and **16 $\beta\beta$** (21%) was obtained. ¹H and ¹³C 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	
	$\beta\alpha$	$\beta\beta$	$\beta\alpha$	$\beta\beta$	$\beta\alpha$	$\beta\beta$
5	5.30, <i>dd</i> $J=10.3, 4.5$	5.26, <i>br d</i> $J=12$	5.44, <i>dd</i> $J=11.0, 5.7$	5.36, <i>ddd</i> $J=11.7, 4.5, 2.2$	5.60, <i>dd</i> $J=10.9, 5.5$	5.51, <i>br d</i> $J=12$
7	1.91, <i>dt</i> $J=11.9, 5.3$	—	—	—	1.85, <i>dt</i> $J=12.5, 5.3$	—
10 β	—	—	—	—	1.56, <i>t</i> $J=10.4$	—
12	1.00, <i>s</i>	0.97, <i>s</i>	1.00, <i>s</i>	1.00, <i>s</i>	0.97, <i>s</i>	0.95, <i>s</i>
13	0.97, <i>s</i>	0.96, <i>s</i>	0.99, <i>s</i>	0.98, <i>s</i>	0.95, <i>s</i>	0.93, <i>s</i>
14	1.61, <i>d</i> $J=1.1$	1.58, <i>s</i>	3.92, <i>d</i> $J=12.2$	3.67, <i>d</i> $J=11.8$	4.44, <i>d</i> $J=12.0$	4.32, <i>d</i> $J=11.9$
14'	—	—	4.16, <i>d</i> $J=12.2$	4.12, <i>d</i> $J=11.8$	4.68, <i>d</i> $J=12.0$	4.68, <i>d</i> $J=11.9$
15	4.82, <i>d</i> $J=1.7$	4.87, <i>br s</i>	4.76, <i>d</i> $J=1.8$	4.89, <i>br s</i>	4.81, <i>br s</i>	4.87, <i>br s</i>
15'	4.94, <i>d</i> $J=1.7$	4.94, <i>br s</i>	4.94, <i>br s</i>	5.06, <i>br s</i>	4.96, <i>br s</i>	4.99, <i>br s</i>
CH ₃ CO ₂	—	—	—	—	2.03, <i>s</i>	2.01, <i>s</i>

* 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	
	$\beta\alpha$	$\beta\beta$	$\beta\alpha$	$\beta\beta$	$\beta\alpha$	$\beta\beta$
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
CH ₃ CO ₂	—	—	—	—	21.1	21.1
CH ₃ CO ₂	—	—	—	—	171.2	171.2

*Chemical shifts in ppm

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

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

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

* Chemical shifts in ppm.

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

C	14 β α	14 β β	15 β α	15 β β	16 β α	16 β β
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
CH ₃ CO ₂	—	—	—	—	20.9	21.0
CH ₃ CO ₂	—	—	—	—	171.3	171.3

*Chemical shifts in ppm

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