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USE OF DIMETHYLDIOXIRANE IN THE PREPARATION OF EPOXY DERIVATIVES RELATED TO INSECT JUVENILE HORMONES

Angel Messeguer [a*], Francisco Sánchez-Baeza [a], Josefina Casas [a,b] and Bruce D Hammock [b],

[a] Dpt. of Biological Organic Chemistry, CID (CSIC), J. Girona, 18 08034 Barcelona, Spain.

[b] Dpts. of Entomology and Environmental Toxicology Univ. of California Davis, CA 95616 USA

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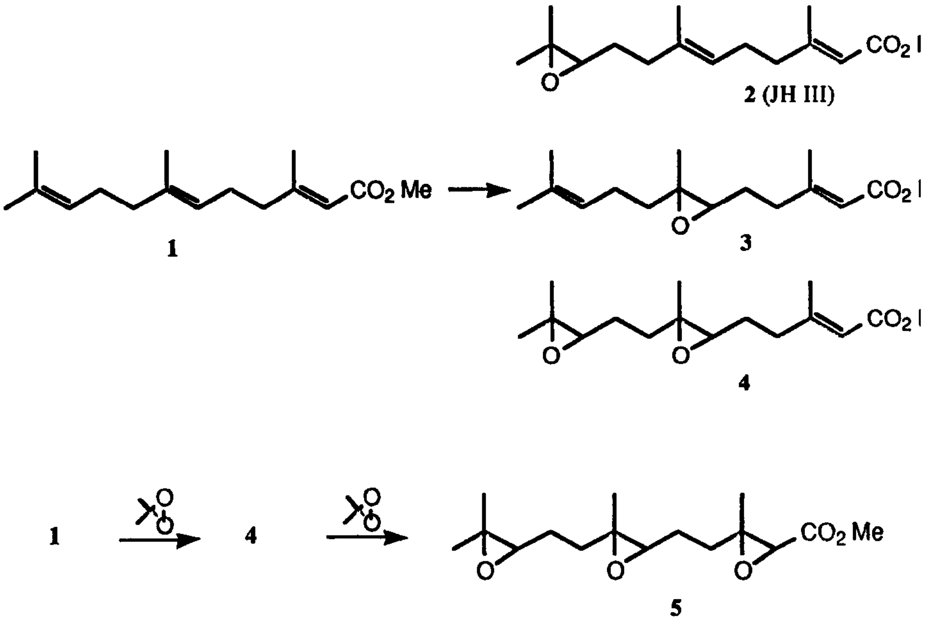
Summary: A study on the epoxidation of methyl farnesoate using the title reagent has been carried out In addition, dimethyldioxirane has shown to be a convenient reagent for the synthesis of putative metabolites of juvenile hormone III, such as diepoxide **4**, triepoxide **5** and epoxy diol **7**. This reagent has also shown to be an excellent tool for performing the preparation of tritium labelled derivatives **4** and **7** Finally, molecular mechanics and NMR studies for the characterisation of *cis* and *trans* tetrahydrofuran derivatives **8a** and **8b**, compounds resulting from the acid or enzymatic hydrolysis of epoxy diol **7**, are also reported.

Although initially considered as a catabolic intermediate of insect juvenile hormone III (JH III, **2**) (see Scheme I), recent investigations carried out by Richard et al [1] have shown that diepoxide **4** is produced by larval ring gland tissues of *Drosophila melanogaster* incubated with radiolabelled precursors It also appears that compound **4** is predominant in adults of this insect species and it exhibits low juvenile hormone activity These results prompted some of us to undertake a comparative study of the metabolism of JH III and its diepoxide in different biological matrices, such as *D. melanogaster* cell fractions and mammalian cytosolic epoxy hydrolase, to ascertain the role of epoxide metabolizing enzymes on these insect growth regulators [2]. With that aim, availability of putative metabolites, such as epoxides **3, 4** and **7**, and related derivatives (i e. the tetrahydrofurans **8** and the tetrol **9**), was required. In the course of the above study, preparation of tritiated compounds **4** and **7** was also needed

In this context, we anticipated that dioxiranes could constitute convenient reagents for the above purpose. It has been shown that dimethyldioxirane in acetone solution [3] is an efficient oxygen transfer agent which reacts with a variety of organic moieties under mild neutral conditions [4] In particular, this reagent has found important applications for the preparation of unstable epoxides such as those derived from aflatoxin B_1, silyl enol and precocenes [5-7]. Likewise, the successful epoxidation of deactivated double bond as those of α,β-unsaturated ketones has also been reported [8].

In the present paper, a study on the epoxidation of methyl farnesoat dimethyldioxirane and use of this reagent for efficient preparations of epoxides **4**, **5** is described. In addition, synthesis of compounds **8** and **9**, which constitute the metabolites of diepoxide **4** [2] is also reported. Finally, results on molecular mechani NMR studies to assign the structures of tetrahydrofuran isomers **8a** and **8b** are prese

SCHEME I



RESULTS AND DISCUSSION

Epoxidation of methyl farnesoate. Availability of an efficient procedure regioselective epoxidation of ester **1** at the terminal double bond is still a pending q Thus, conventional epoxidation procedures using peroxyacids or a two step r involving halohydrin intermediates give mixtures of the monoepoxides **2** and **3** w concomitant formation of diepoxide **4** depending upon the reagent excess utilized (Scheme I) [9]. In general, mixtures of compounds **2**:**3** from 2:1 to 6:1 isomeric ratios, respectively, are formed when equimolecular amounts of peroxyacid are used within the 40 to -20 °C temperature range, being the reaction at the terminal double bond favoured at low temperatures. In all cases, however, higher amounts of diepoxide **4** in comparison with monoepoxide **3** were detected in the crude reaction mixture [10] In any case, neither the peroxyacid oxidation nor the halohydrin procedure can be efficiently carried out below -20 °C due to solubility problems. In this context, dimethyldioxirane appeared as an interesting option since reactions can be carried out within a wider temperature range under homogeneous conditions

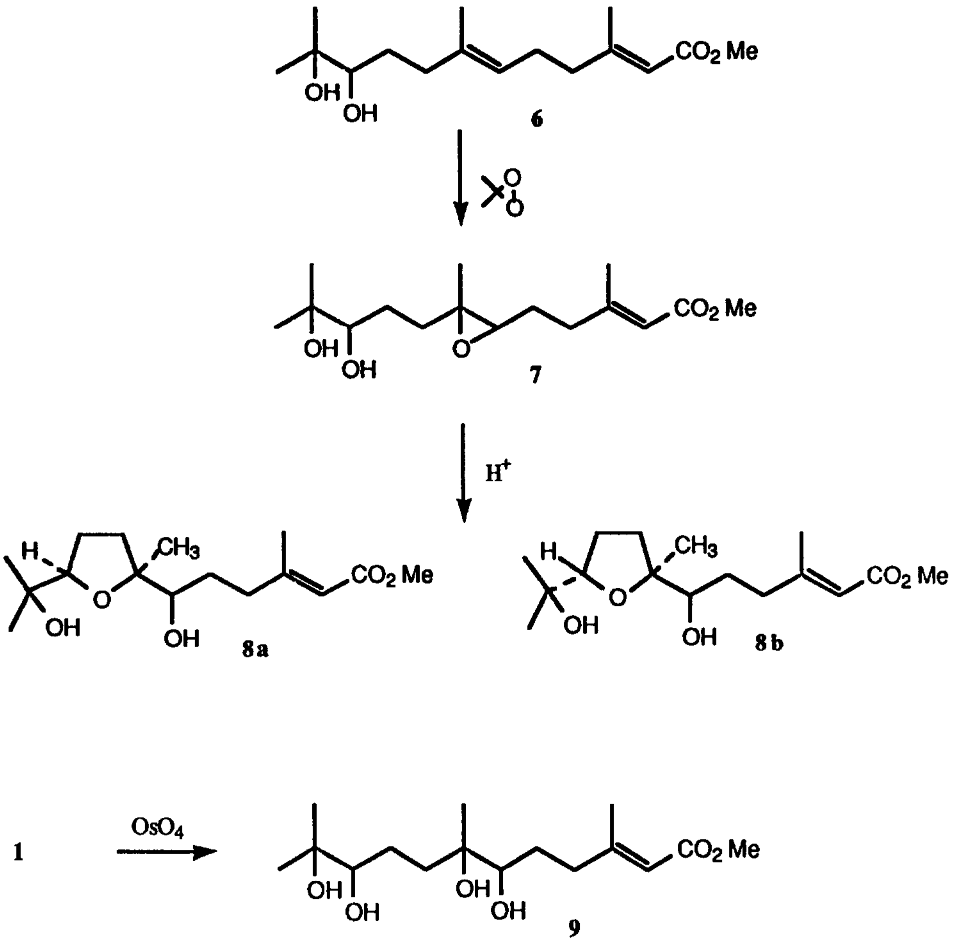
However, when acetonitrile solutions of ester **1** were treated with a slight equimolecular excess of dimethyldioxirane at different temperatures within 20 and -50 °C, HPLC monitoring of the crude reaction mixtures showed similar ratios of compounds **2**.**3** **4** to those obtained using the peroxyacid procedure. Thus, a **1**:**2**·**3**:**4** / 16:52·13 22 mixture of products was obtained at 20 °C, whereas at -50 °C the relative ratios only shifted to 5·55 9·28, respectively. Therefore, relative ratios between monoepoxides **2**:**3** were comprised within 4:1 and 6 1:1, respectively, and in both cases formation of diepoxide **4** was considerably high even in the presence of important amounts of unreacted methyl farnesoate This fact was more evident in an experiment carried out at -15 °C and using a slight equimolecular defect of dimethyldioxirane. In this case, relative ratios obtained for compounds **1**:**2** **3**·**4** were 37·42·13:7, respectively, which suggests that the diepoxide is preferentially formed from the epoxidation of compound **3** [11].

Synthesis of JH III related compounds. Dimethyldioxirane showed to be an excellent reagent for the preparation of epoxides **4**, **5** and **7** (Schemes I and II) Thus, when a slight excess of the corresponding molecular equivalents of the title reagent was added to ester **1** or to JH III (**2**), a rapid reaction took place (5 min at 0 °C) with a quantitative conversion of starting material into the diepoxide **4** Compound **4**, which had been previously prepared by both the bromohydrin [12] and the peroxyacid procedures [1], was isolated as a diastereomeric mixture and identified by comparison of its NMR spectrum with those of monoepoxides **2** and **3** Working under the above conditions, epoxidation of the conjugated double bond was not observed. Actually, as it has been recently shown by Adam et al [8] for the case of α,β-unsaturated ketones, epoxidation of the double bond of α,β-unsaturated esters with dimethyldioxirane required longer reaction times In our case, formation of triepoxide **5** was achieved after prolonging the treatment of **4** with dimethyldioxirane for 3 days at 0 °C, with daily addition of fresh oxidation reagent. Under these conditions, conversion of starting compound was complete and triepoxide **5** was isolated as a mixture of diastereomers and identified by spectral means (i.e a shift of the carbonyl absorption in the IR to 1756 cm^{-1}, presence of a singlet at δ 3.29 in the ^1H NMR spectrum, absence of C=C absorptions in the ^{13}C NMR spectrum together with the increment of peaks in the region of 60 ppm, and presence of the expected molecular peak in the MS spectrum).

In the same context, use of dimethyldioxirane was particularly valuable for the preparation of epoxy diol **7**. This compound, which had been postulated as the primary metabolite formed by the action of epoxy hydrolases on diepoxide **4**, was found to be highly reactive since it undergoes a rapid cyclisation to give the mixture of tetrahydrofurans **8** (Scheme II). The reaction is catalyzed by acids, but it can also occur in a buffered neutra incubation medium [2]. For that reason, attempted preparations of **7** by peroxyacid epoxidation of JH III diol **6** led to the concomitant formation of compounds **8a** and **8b** as major components of the crude reaction mixture. Conversely, use of dry dimethyldioxirane solution resulted in a rapid and quantitative conversion of diol **6** into the expected epoxy diol **7**, which was isolated as a mixture of diastereomers and identified by its spectra features. In particular, the triplets at δ 2.70 and 2.73 (J = 6 Hz) corresponding to the oxyranic proton of both diastereomeric pairs and the concomitant shift of a methy absorption to the 1.1-1.2 ppm region in the ^1H NMR spectrum, together with the peaks a 61.4 and 63.1 ppm (61.5 and 63.6 for the other diastereomeric pair, respectively) in the ^{13}C NMR spectrum, confirmed the presence of the epoxide moiety On the other hand, the GC/MS analysis of the TMS derivative using chemical ionization with CH_4 gave the (M^+ 15) peak and a fragmentation pattern in agreement with the presence of two TMS groups.

It is worth noting that the simplicity of experimental conditions involved with epoxidations using dimethyldioxirane makes their application to radiochemical synthese very attractive. Since tritium labelled JH III (**2**) is commercially available, we undertook the preparation of tritiated diepoxide **4**, the required substrate for the metabolic studies and of epoxy diol **7**, which was also needed for studying the biotransformation pathway o bispoxide **4** to give the tetrahydrofurans **8** [2]. In both cases, a one pot-reaction with an eas manipulation procedure led to the complete conversion of starting materials (labelled JH II or JH III diol derivative **6**) into the corresponding final products, **4** or **7**, respectively. In the latter case however, reactivity of the epoxy diol caused its partial conversion into the mixture of tetrahydrofurans **8**, so that a final TLC purification step was required to isolate **7** with high chemical and radiochemical purity

SCHEME II



Finally, preparation of the standard metabolites 8 and 9 was accomplished by conventional procedures In the first case, treatment of diepoxide 4 in acid medium led to the conversion of the compound into a 2 3 mixture of tetrahydrofurans 8a and 8b as predominate products [13]. These compounds could be separated by preparative TLC and characterised by spectral means (see below). Likewise, a bis dihydroxylation of ester 1 with OsO_4 following the general procedure reported by VanRheenen et al. [14] afforded the tetrol **9** (Scheme II) as a mixture of diastereomers in moderate yield (Scheme II) The compound was identified by comparison of its chromatographic and spectral features with those of epoxy diol **7** and tetrahydrofurans **8**.

MMP2 and NMR studies on tetrahydrofurans 8a and 8b During the incubations carried out with substrates **4** and **7** two tetrahydrofuran isomers **8** were obtained in different ratios, depending upon the biological matrix and the conditions used [2] Therefore a more detailed study to assign the their configuration was contemplated. The sole bibliographic precedent related to this problem was the work of one of us, in which a *cis* and *trans* configuration was assigned to the high and low R_f (TLC) stereoisomers, respectively, arising from the cyclisation of the diepoxide of *p*-ethylphenyl geranyl ether, a juvenile hormone mimic, in acid conditions [15] The assignation was essentially made by chromatographic criteria In our case, the polarity difference between compounds **8a** and **8b** was high enough to permit their neat separation by TLC procedures, thus suggesting a similar stereochemical assignation to that indicated above. However, these assignments must be regarded as tentative Unfortunately, all attempts to obtain good crystals from one of the isomers for X-ray analysis were unsuccessful.

Therefore, we decided to carry out a molecular mechanics study using the MMP2 method developed by N L Allinger [16,17] and Figure 1 shows the preferred conformations obtained for both stereoisomers. In fact, two conformations were possible for the *cis* isomer **8a**, but a 10 KJ/mol difference in relative energy values indicated that the one shown in the figure should be the preferred Conversely, in the case of the *trans* isomer **8b** the depicted conformation was a minimum with an energy value far below from those of all other possible conformations.

As shown, the preferred conformations for tetrahydrofurans **8a** and **8b** mainly differ in the orientation of the (1-hydroxy-1-methyl)ethyl substituent Thus, while in the *cis* isomer this substituent is oriented in a direction near to the plane defined by the tetrahydrofuran ring, in the *trans* isomer it is situated almost perpendicular to this ring As consequence, the relative orientations of the CH and the two CH_2 groups of the furan ring are also different in both isomers, which would allow the prediction of the respective ^1H NMR coupling pattern

A detailed analysis of the respective models shows that in **8a** the CH forms diedral angles of approximately 20° and 160° with the C-H bonds of its contiguous CH_2 group, which would result in similar ^3J values in the ^1H NMR Likewise, in **8b** the diedral angles are both of approximate 60°, which would also give rise close ^3J values. Conversely, relative orientations of the two CH_2 groups are more meaningful. Thus, in **8a** they are in an almost eclipsed conformation, which would lead to similar J values for all couplings. However, in **8b** there are C-H bonds of the contiguous CH_2 groups with diedral angles of approximately 90°, which would give rise to a more complex spectrum pattern than that expected for **8a** due to the diversity in J values.

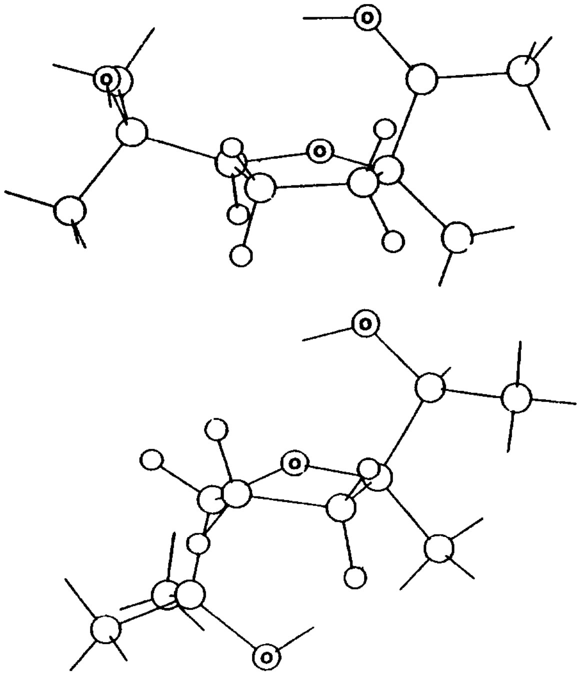


Figure 1. Preferred conformations adopted by the *cis* and *trans* tetrahydrofuran derivatives 8a (above) and 8b (below), respectively, according to the MMP2 calculations.

The above predictions on the relative orientations of the tetrahydrofuran substituents in the *cis* and *trans* isomers were consistent with the data obtained from the complementary NMR study carried out. Thus, use of appropriate 2D techniques permitted the unequivocal assignation of the chemical shifts for all atoms of both isomers in both ^1H and the ^{13}C NMR spectra, although the patterns obtained were not simple enougl measuring all the coupling constants between the hydrogen atoms of the tetrahydrof ring. In any case, as expected, the coupling pattern observed for the CH_2 region in the NMR of isomer **8a** was much simpler than that of the isomer **8b**; therefore, the stereochemistry was assigned to **8a**, in agreement with the theoretical prediction. Fin this assignation was also in concordance with the differences observed between the cher shifts of the respective ring carbon atoms directly linked to the furan oxygen

EXPERIMENTAL SECTION

Dimethyldioxirane solutions in acetone (within the 70-90 mM range) were prepared titrated as reported by Murray and Jeyaraman [3a]. In some cases, a GC titration with m citronellate and its epoxide in the presence of tetradecane as internal standard was also (unpublished results from this laboratory). Methyl farnesoate (**1**) and juvenile horn III (**2**) were prepared by previously reported methods [9]. All other compounds and reag were commercially available Tritiated juvenile hormone III [10-^{3}H H(N)]-JH III (Ci/mmol specific activity) was from New England Nuclear.

The IR spectra were recorded with a Perkin Elmer 399 B spectrometer The ^1H and NMR spectra were recorded with a Varian Unity 300 spectrometer. Unless other stated, all NMR spectra were performed in carefully neutralized $CDCl_3$ solutions chemical shifts are given in ppm downfield from tetramethylsilane. When diastereon

Epoxidation of methyl (2*E*,6*E*)-3,7,11-trimethyl-2,6-dodecadienoate (1) Assays were carried out by adding 160 μL of a 70 mM solution of dimethyldioxirane to a solution of ester 1 (10 μmol) in CH_3CN (0.5 mL) at the desired temperature. The HPLC analyses for monitoring the epoxidation course were carried out with a Waters modular system provided with two model 510 pumps, an automated gradient controller and a 481 UV detector set at 235 nm. The injector used was a 480 Model (Applied Biosystems). Analyses were carried out with a 10 x 0.4 cm column packed with ODS-2 (5μ). Elution conditions were set as follows: 65:35 $CH_3CN.H_2O$ (1 mL/min) for 4 min. From min 4 to 5 a gradient from 65:35 to 75:25 (1 mL/min) was programmed and these conditions were maintained up to min 12. Then the system was set at the initial eluent mixture. Under these conditions, retention times for compounds **1**, **2**, **3** and **4** were 13.3, 4.7, 5.1 and 2.2 min, respectively.

Methyl (2*E*)-6,7,10,11-diepoxy-3,7,11-trimethyldodec-2-enoate (4). An approximate 200% molecular excess of dimethyldioxirane solution in acetone was added to a solution of ester 1 (0.025 g, 0.1 mmol) in dry CH_2Cl_2 (1 mL). The mixture was allowed to stand at room temperature until reaction was completed (TLC, GC monitoring, 5 minutes). Then, reagent excess and solvents were carefully removed under N_2 and the residue was redissolved in pentane and dried (Na_2SO_4). Evaporation of solvent afforded the expected diepoxide as a pure compound in near quantitative yield. This compound was obtained as a diastereomeric mixture and it was identified by comparison of the spectral data with those reported by Ichinose et al. [12] (see also ref 1). ^{13}C NMR 16.4 (16.7), 18.6 (18.6), 18.7, 24.5 (24.7), 24.8, 26.7, 35.1 (35.5), 37.6, 50.8, 58.3 (58.4), 60.4 (60.5), 62.3 (62.8), 63.7 (63.9), 115.7 (115.8), 158.7 (158.8), 167.0. MS (C.I., isobutane). m/z, 283 (M^++1), 266, 251, 233.

Synthesis of tritiated diepoxide 4 A solution of JH III (2 mg) and [10-^{3}H H(N)]-JH III (70 μCi) in CH_2Cl_2 (1 mL) was treated with the dimethyldioxirane solution (0.3 ml). The crude reaction mixture was allowed to stand at room temperature for 5 minutes and concentrated under N_2. The residue was redissolved in pentane and dried (Na_2SO_4). Decantation of supernatant and evaporation of solvent under N_2 yielded the expected tritiated diepoxide 4 in over 96% chemical (TLC) and radiochemical purities (radioscanner analysis).

Methyl 2,3,6,7,10,11-triepoxy-3,7,11-trimethyldodecanoate (5) This compound was obtained from JH III (0.026 g, 0.1 mmol) as described above, although total conversion took place in 3 days with daily addition of fresh solution of dimethyldioxirane to the reaction crude. Triepoxide **5** was isolated from preparative TLC as a mixture of four diastereomers in near quantitative yield. IR (neat): ν, 2960, 2930, 1756, 1457, 1440,1386, 1205, cm^{-1} ^{1}H NMR: ∂, 1 23, (s, 3H), 1 28 (s, 6H), 1.32 (s, 3H), 1.4-1 8 (8H), 2.71 (t, 1H, J = 6 Hz), 2.76 (t, 1H, J = 6 Hz), 3 38 (s, 1H), 3.79 (s, 3H). ^{13}C NMR: 16 1 (16 3), 16.4 (16.7), 18.6 (18.7), 24.1 (24.4), 24.5 (24 7), 24 8, 34 4 (34.6), 35.1 (35.5), 52.3, 58.2 (58 2, 58.6, 58 6), 58.4, 60 4 (60 5, 60 6, 60.6), 62.1 (62.2), 62.1 (62.3, 62.7, 62.8), 63.8 (63.9), 168 8. MS (C I., isobutane): m/z, 299 (M^{+}+1), 281, 263, 213.

Methyl (2*E*)-6,7-epoxy-10,11-dihydroxy-3,7,11-trimethyldodec-2-enoate (7) This compound was obtained as a diastereomeric mixture from diol **6** (0.27 g, 0.1 mmol) following the procedure described for diepoxide **4**, although in this case the dimethyldioxirane solution was thoroughly dried over molecular sieves In addition, the instability of the compound led to low recovery yields after chromatography; therefore, the residue obtained after solvent evaporation (>95% purity, NMR) was used for the biochemical assays without further purification. ^{1}H NMR: ∂, 1.10 (s, 3H), 1 16 (s, 3H), 1.23 (s, 3H), 1.3-2.3 (6H), 2.1 (br, 1H), 2 12 (s, 3H), 2.15-2 3 (m, 2H), 2 6 (br, 1H), 2 70 (t, 1H, J = 6 Hz, one diastereomer), 2.73 (t, 1H , J = 6 Hz, one diastereomer), 3.28 (dd, 1H, J_1 = 30 Hz, J_2 = 10 Hz), 3 62 (s, 3H), 5.66 (s, 1H) ^{13}C NMR· ∂,16 4, 16.9, 19 0, 23 5 (23 6), 26.6 (26 8), 26.7, 35.3 (35 7), 37.8, 51 2, 61 4 (61 5), 63.1 (63.6), 73 2 (73 3), 78 0 (78.8), 116, 159.4 (159 6), 167 8 MS (C I., methane, bistrimethylsilyl ethers) m/z, 429 (M^{+}-15), 355 (M^{+}-OTMS), 265, 131

Synthesis of tritiated epoxy diol 7 A solution of JH III (0 3 mg) and [10-^{3}H H(N))-JH III (10 µCi,) in dimethoxyethane (0 1 mL) was stirred with 5% solution of $HClO_4$ (0 1 mL) at room temperature. When the reaction was completed (TLC monitoring, 30 min), solvents were partially removed under N_2 and the residue extracted with EtOAc (3 x 1 mL), centrifuged and joined organic fractions were dried (Na_2SO_4) The residue obtained after solvent removal under N_2, which contained the tritiated dihydroxy derivative **6**, was redissolved in dry CH_2Cl_2 (1 mL) and allowed to react with dimethyldioxirane solution (0 2 mL) in the presence of NaH_2PO_4 for 3 minutes at room temperature Then the crude reaction mixture was worked up as described above for tritiated compound **4** to give a final residue which contained epoxy diol **7** in approx. 80% radioactive purity (overall yield from starting JH III was 40%). A mixture of tetrahydrofurans **8a**:**8b** in a 1:1 isomer ratio accounted for most of the remaining radioactivity. Pure labeled compound **7** could be isolated, although with moderate recovery due to its instability, by TLC over silicagel eluting with a 1: 1 hexane.ethyl acetate mixture.

Methyl 6-hydroxy-3-methyl-6[tetrahydro-5(1-hydroxy-1-methyl ethyl)-2-methyl-2-furanyl]hex-2-enoate (8a, *cis* isomer) (8b, *trans* isomer). A solution of diepoxide **4** (0.054 g, 0.2 mmol) in THF (2 mL) was treated with a 2.5 % $HClO_4$ and the mixture was stirred at room temperature until reaction was completed (1 h, TLC monitoring). The crude reaction mixture was extracted with Et_2O and the organic extracts were washed with 5% $NaHCO_3$ solution, brine and dried (Na_2SO_4). The residue obtained after solvent removal was purified by preparative TLC (hexane ethyl acetate, from 3:1) to give the cyclic derivatives **8a** and **8b** as major components in a 2:3 isomer ratio. **8a** (higher Rf in TLC): ^{1}H NMR: ∂, 1.15 (s, 3H),1.16 (s, 3H), 1.27 (s, 3H), 1.4-1.7 (4H), 1.8-2.0 (m, 2H), 2.0-2.3 (m, 2H), 2.16 (s, 3H), 2.3-2.5 (2H, OH), 3.54 (dd, 1H, J_1 = 10 Hz, J_2 = 3 Hz), 3.68 (s, 3H), 3.82 (t, 1H, J = 7 Hz), 5.71 (s, 1H); ^{13}C NMR: ∂, 19.1, 23.9, 25.8, 27.2, 27.7, 30.1, 31.4, 38.0, 51.5, 72.5, 76.4, 84.7, 86.8, 116, 161, 168; MS (E I) for bistrimethylsilyl ethers: m/z, 429 (M$^+$-15), 215. **8b** (lower Rf in TLC): ^{1}H NMR: ∂, 1.17 (s, 6H), 1.21 (s, 3H), 1.35-1.65 (4H), 1.8-1.9 (m, 2H), 2.0-2.3 (m, 2H), 2.18 (s, 3H), 2.4-2.55 (2H, OH), 3.50 (dd, J_1 = 10 Hz, J_2 = 3 Hz), 3.68 (s, 3H), 3.77 (dd, 1H, J_1 = 9 Hz, J_2 = 7 Hz), 5.72 (s, 1H), ^{13}C NMR: ∂, 19.0, 23.9, 24.0, 26.4, 26.9, 29.5, 30.7, 37.8, 51.1, 71.0, 76.2, 86.2, 88.1, 116, 161, 168. MS (E I) for bistrimethylsilyl ethers: m/z, 429 (M$^+$-15), 215

Methyl (2*E*)-6,7,10,11-tetrahydroxy-3,7,11-trimethyldodec-2-enoate (9) Following the general oxidation procedure reported by VanRheenen et al [14], methyl farnesoate (**1**, 0.025 g, 0.1 mmol) was added to a mixture of *N*-methylmorpholine-*N*-oxide (36 mg, 0.2 mmol), H_2O (0.1 mL), acetone (0.04 mL) and OsO_4 (0.16 mg) in *t*-BuOH (0.02 mL). After being stirred for 20 hours at room temperature, the crude reaction mixture was treated for 15 minutes with a slurry of $Na_2S_2O_4$ (5 mg) and Celite (25 mg) in H_2O (1.5 mL), and filtered off. The filtrate was acidified to pH 2 with 1N H_2SO_4, saturated with NaCl and extracted with EtOAc (3 x 5 mL). The aqueous layer was concentrated under nitrogen and reextracted with EtOAc (2 x 5 mL). The joined organic fractions were dried (Na_2SO_4) and evaporated, yielding the expected tetrol as a mixture of two diastereomers (0.012 g, 38 % yield, one spot in TLC). ^{1}H NMR (CDCl$_3$ + D$_2$O)· ∂, 1.11 (s, 3H), 1.16 (s, 3H), 1.20 (s, 3H), 1.3-1.9 (6H), 2.16 (s, 3H), 2 23 (m, 1H, allylic), 2.44 (m, 1H, allylic), 3.3-3.5 (2H), 3.68 (s, 3H), 5.71 (s, 1H) ; ^{13}C NMR: ∂, 18.9 (18.9), 20.7 (21.3), 23 2, 25 0 (25.1), 26.6, 28 8 (29.1), 35 8 (36.1), 37.8, 50.9, 73.2 (73.2), 74.4 (74.6), 75.5 (77.2), 78.9 (79.1), 115.5, 159 9 (159 9), 167.2; MS (C.I , methane, tetraquistrimethylsilyl ethers): m/z, 591 (M$^+$-15), 517 (M$^+$-OTMS), 427, 337, 247, 131.

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