Article

J. Mex. Chem. Soc. **2006**, *50(4)*, 149-156

ISSN 1870-249X

Regio- and Enantioselective Functionalization of Acyclic Polyprenoids[†]

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Recibido el 2 de febrero del 2006; aceptado el 29 de septiembre del 2006.

Abstract: In this paper we present the results obtained in the positional selective functionalization of the double bond located at the terminal isopropylidene unit of acyclic polyprenoids. Studies to introduce the hydroxyl group or related oxygenated functions has been tested using oxidation with SeO_2 or catalytic procedures employing Pd(II) catalysts. This functionalization is usually found in many natural or synthetic acyclic terpenes and would permit to carry out epoxydations regio- and stereoselectives. Furthermore, asymmetric dihydroxilation procedure has been optimized in different polyprenoids in order to generalize this methodology as the key step for the enantioselective synthesis of epoxides.
Keywords: acyclic polyprenes, allylic functionalization, selenium dioxide, palladium, asymmetric dihydroxylation, terpenes.

Resumen: En este trabajo presentamos los resultados obtenidos en la funcionalización posicional selectiva del doble enlace situado en el extremo terminal de la cadena en poliprenoides acíclicos. Los estudios para introducir un grupo hidroxilo o funciones oxigenadas relacionadas han sido realizados empleando SeO_2 o un procedimiento catalítico en Pd(II). Esta funcionalización es frecuentemente encontrada en diferentes terpenos acíclicos naturales o sintéticos, y permite llevar a cabo epoxidaciones regio- y estereoselectivas. Por otro lado, se ha optimizado el protocolo de dihidroxilación asimétrica aplicado sobre diferentes poliprenoides con el propósito de generalizar esta metodología como paso clave en la síntesis enantioselectiva de epóxidos.
Palabras clave: poliprenos acíclicos, funcionalización alílica, dióxido de selenio, paladio, dihidroxilación asimétrica, terpenos.

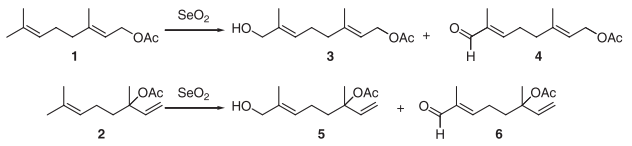
Terpenes are the most abundant family of Natural Products, including more than 25000 different compounds, which exhibit a great variety of skeletons and functionalizations [1]. Many of these molecules shows interesting properties of interest in the industry, and have been used as drugs, perfumes, insecticides, herbicides, phytohormones, antimicrobials, etc. Continuing our studies on the synthesis of bioactive terpenoids, we have been recently working on the development and optimization of new strategies of biomimetic synthesis using as key step radical tandem cyclizations [2]. These reaction are triggered by Ti(III)-mediated homolytic opening of epoxypolyprenes. A wide range of structures possessing different functionalities or ring size can be obtained using this synthetic method. The applicability of this process depends mainly on the availability of the epoxypolyprene used as starting material in the cyclization.

In this work, we present the results obtained in the selective functionalization of the double bond located at the opposed extreme to that where the functionalization present in many natural or synthetic acyclic terpenes used as synthetic starting materials is usually found. This achievement would permit to carry out regio- and stereoselective epoxydations [3]. Furthermore, the products obtained after cyclization of these epoxides would possess functionalized one of the methyl groups on the A ring, and thus, opens an easy access to numerous natural products presenting these characteristics. On the other hand, terpenes presenting a double allylic functionalization are importantant building blocks, of special relevance in the industries of drugs, perfumes and food [4].

The pursued appropriate introduction of the hydroxyl group has been tested using different protocols, namely, the asymmetric dihydroxylation [5], oxidation with SeO_2 or a catalytic procedure using Pd(II).

Selenium dioxide is a widely known oxidant for activated and saturated positions [6]. Its use in minor quantities employing *tert*-butyl hydroperoxide as reoxidant has proved to lead to allylic alcohols with synthetically useful yields [7, 8]. When geranyl acetate (**1**) or linalyl acetate (**2**) were exposed to the initial conditions (Table 1, entry 1), no satisfactory results were obtained (Scheme 1).

With the aim of improving these results, we turned then our efforts to optimize the experimental conditions reported for this transformation. Thus, when 0.7 equiv. of SeO_2 were used and the reaction were let to proceed at 0º C in DCM until



Scheme 1

Table 1

entry[a]	substrate	SeO_2 (equiv.)	time (hours)	product[b] (yield %)	by-product (yield %)
1	**1**	1.0	7	**3** (53%)	**4** (25%)
2	**1**	0.7	6	**3** (59%)	**4** (23%)
3	**1**	0.5	3	**3** (75%)	**4** (11%)
4	**2**	1.0	8	**5** (67%)	**6** (22%)
5	**2**	0.7	6	**5** (70%)	**6** (21%)
6	**2**	0.5	3	**5** (81%)	**6** (8%)
7	**7**	0.5	2.5	**8** (88%)	
8	**9**	0.5	1.5	**10** (24%)	
9	**9**	0.5	4	**10** (21%)	

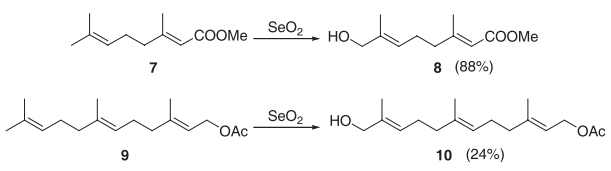
[a] The reactions were carried out at 0º C, employing 2 equiv. of *t*BuOOH and 10 mL of DCM/equiv. of starting material. [b] Based on recovered starting material.

disappearance of starting material, again poor yields of the desired product were obtained (Table 1, entry 2). The corresponding aldehyde derivative was the main by-product. To circumvent this sobreoxidation, different tests with products **1** and **2** were performed varying the quantity of SeO_2 and the reaction time (Table 1, entries 3, 5-6).

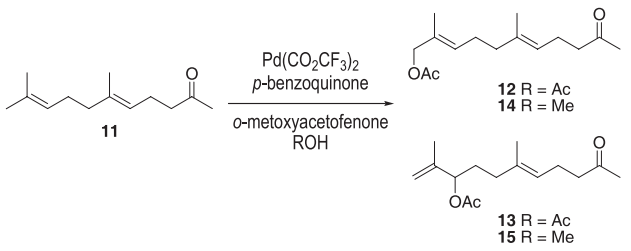
From these data, it can be deduced that prolonged reaction times (until disappearance of starting material) did not lead to satisfactory yield of the desired product, while the most efficient transformation took place when 0.5 equiv. of oxidant were employed and the reaction was let to proceed for no more than 3 h (entries 3 and 6).

Good results were obtained with methyl geraniate (**7**) (Table 1, entry 7) whereas farnesyl acetate (**9**), a terpene possessing three different double bonds, yielded 24% of the desired alcohol (Table 1, entry 8) after being subjected to these optimized conditions (Scheme 2).

A second methodology employed to achieve the pursued allylic functionalization is based on the use of Pd(II) complexes [9]. These reagents have proved to catalyze the regio- and stereoselective allylic oxidation of olefins to give alcohols, esters and ethers [10]. Although the application of this catalytic procedure to terpenic substrates would facilitate the access to oxygenated derivatives of high added value in pharmaceutical, perfume and flavour industries, its use with this kind of compounds has been limited. We started the study with the selective oxidation of the terminal methyl group of geranylacetone (**11**) by its treatment with a catalytic amount of palla-



Scheme 2



Scheme 3

dium bis(trifluoroacetate), benzoquinone as oxidant and *o*-methoxyacetophenone as auxiliary ligand (Scheme 3, Table 2) [11,12].

Under these conditions, the reaction proceeded slowly and inefficiently. Thus, after stirring **11** at room temperature for 72 h, (at this time, disappearance of starting material was confirmed via TLC control) only poor yields of **12** and **13** were obtained (Table 2, entry 1). Nevertheless, under these parameters, a good selectivity for the formation of the primary acetoxy derivative was noticed. Then we carried out an optimization of experimental procedure and greater yields of the desired compounds were obtained by increasing the quantity of catalyst, although this improvement was accompanied by a decrease of the selectivity of the reaction. The best result was achieved when 0.25 equivs of $Pd(CO_2CF_3)_2$ were used and the reaction was maintained at 45 ºC for 27 h (Table 2, entry 6). Under these conditions, compounds **12** and **13** were obtained in 45% yield and 2.5:1 ratio favoring the primary acetate **12**.

When this transformation was attempted with **11** using MeOH instead of AcOH as nucleophile, the reaction proceeded similarly and mixtures of the corresponding allyl ethers were obtained (Table 3). From these data, it can be inferred an increase in the quantity of Pd(II) that leads to more efficient but less selective processes (Table 3, entries 3 and 6).

When **1** was used as starting material for catalytic Pd(II) oxidation, allyl ethers **16** and **17** were obtained (Scheme 4, Table 4). Using this substrate, the best result was reached using 0.05 equiv. of catalyst and at room temperature (Table 4,

Table 2

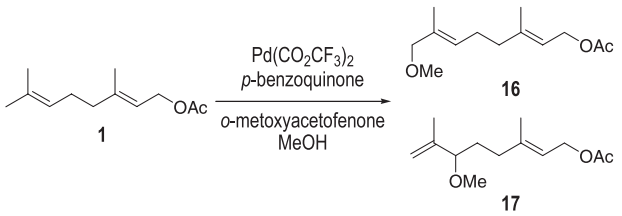
entry[a]	substrate	$Pd(CO_2CF_3)_2$ (equiv.)	temperature (ºC)	time (hours)	yield (%)	ratio **12**:**13**
1	**11**	0.05	25	73	10	7.5:1
2	**11**	0.10	25	48	28	3.0:1
3	**11**	0.25	25	48	33	3.0:1
4	**11**	0.05	45	16	32	2.5:1
5	**11**	0.10	45	25	40	2.0:1
6	**11**	0.25	45	27	45	2.5:1

[a] The reactions were carried out employing 0.2 equiv. of *o*-methoxyacetophenone, 1.0 equiv. of benzoquinone and 8 mL of AcOH.

Table 3

entry[a]	substrate	$Pd(COCF_3)_2$ (equiv.)	temperature (ºC)	time (hours)	yield (%)	ratio **14**:**15**
1	**11**	0.05	25	50	44	3.5:1
2	**11**	0.10	25	48	53	2.5:1
3	**11**	0.25	25	48	59	1.5:1
4	**11**	0.10	45	20	29	2.5:1
5	**11**	0.10	45	30	44	1.5:1
6	**11**	0.25	45	20	55	1.0:1

[a] The reactions were carried out employing 0.2 equiv. of *o*-methoxyacetophenone, 1.0 equiv. of benzoquinone and 8 mL of MeOH.



Scheme 4

Table 4

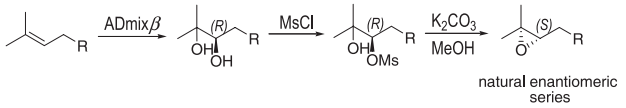
entry[a]	substrate	$Pd(COCF_3)_2$ (equiv.)		temperature (ºC)	time (hours)	yield (%)	ratio **16**:**17**
1	**1**	0.05	1	25	96	30	3.5:1
2	**1**	0.05	1	45	96	37	2.5:1
3	**1**	0.05	5	25	96	41	2.0:1
4	**1**	0.05	5	45	80	29	1.5:1
5	**1**	0.10	5	45	80	34	1.5:1
6	**1**	0.25	5	45	80	30	1.0:1
7	**1**	0.25	5	25	84	33	2.0:1

[a] The reactions were carried out employing 0.2 equiv. of *o*-methoxyacetophenone, 1.0 equiv. of benzoquinone and 8 mL of MeOH.

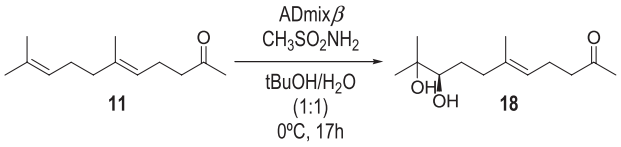
entry 3). It was also proved that the quantity of benzoquinone employed is not a determinant factor in the reaction outcome.

After these experiments, it can be concluded that, in general terms, this Pd-based method for the selective oxygenation of polyprenes gives only moderate results, mainly due to the lack of regioselectivity observed for the attack of the corresponding nucleophile to the p-allylpalladium intermediate. In any case, this should not be considered as a major inconvenient, since these compounds have been reported to interconvert via allylic isomerization.

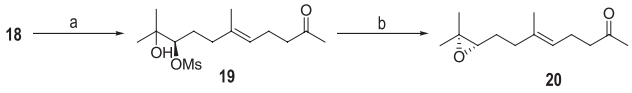
An alternative approach for achieving the desired selective functionalization of polyprenes was pursued using Sharpless asymmetric dihydroxylation protocol [5], which is based on the use of osmium tetroxide in the presence of chiral



Scheme 5



Scheme 6



a. MsCl, pyiridine, DMAP, 0º C, 50 min. b. K_2CO_3, MeOH, 25º C, 30 min.

Scheme 7

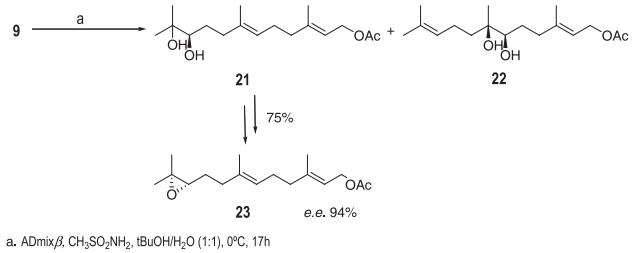
ligands. Some precedents reporting the use of this method to selectively functionalize polyprenes can be found in literature [13]. Our intention is to explore this protocol by widening the range of polyprenes studied with the aim of generalizing this methodology. The success in this transformation could open an expedite route to enantioenriched epoxides via a three-step sequence: dihydroxylation, selective mesylation of the secondary hydroxyl group and closing of the oxirane ring after basic treatment of the mesylate (Scheme 5).

An additional advantage of this protocol is that the dihydroxylation can be not only regio- but also stereoselectively controlled only by using the commercial premixed catalyst ADmixβ or ADmixα. It is known that the use of ADmixβ originates the *S* epoxides, which after cyclization should lead to terpenes of the normal enantiomeric series. We started this study by choosing geranylacetone (**11**) as starting material. Then this substrate is treated with ADmixβ for 17 at 5º C, a 67% yield of diol **18** is obtained (Scheme 6).

Diol **18** was then transformed in the corresponding mesylate by reaction with methanesulfonyl chloride in pyridine at 0º C in the presence of catalytic DMAP. The monomesylate derivative thus obtained (**19**), without purification with K_2CO_3 in MeOH at room temperature for 30 min to yield the (9*S*)-epoxide (**20**) with a global 74% yield (Scheme 7).

When this procedure was applied to farnesyl acetate (**9**), together with the expected diol (**21**), it was noticed the formation of 6,7-dihydroxyderivative (**22**) (Scheme 8).

Best conditions for the synthesis of **21** were found after making react **9** with ADmixβ for 7 h at 0 ºC. After this time, a 50% yield of starting material still remained without alteration, and the desired diol (**21**) can be obtained in 57% yield (based



Scheme 8

Table 5

entry[a]	substrate	time (h)	product	yield (%)[b]
1	**1**	3	**27**	76[c]
2	**2**	5	**28**	99[c]
3	**7**	2.7	**29**	81[c]
4	**9**	7	**21**	57
5	**11**	17	**18**	67
6	**24**	5	**30**	27
7	**25**	10	**31**	35[d]
8	**26**	11	**32**	26

[a] For 1.0 equiv. of substrate were employed 1.0 equiv. of methanesulphonamide, 1.4 g of ADmixβ and 32 mL of *t*BuOH:H_2O (1:1). [b] Yields based on recovered starting material. [c] Yield based on disappearance of starting material. [d] It was obtained 15% of desired product and 20% of stereoisomers mixture because of commercial staring material was a stereoisomers mixture.

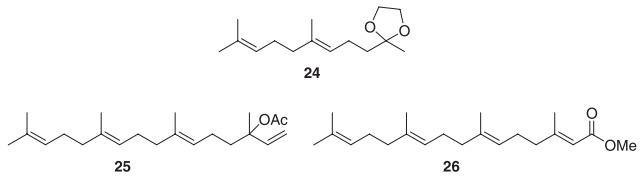


Figure 1

on 50% conversion). Mesylation of **21** and subsequent basic treatment led to obtain the corresponding 10(*S*)-epoxide (**23**), with a 75% yield. An enantiomeric excess of 94% was calculated for this compound after measuring its optical rotation value.

With the rest of tested terpenes (Table 5), it was followed the same procedure: the reaction was let to proceed just until apparition of diols corresponding to additions to interne double bonds (TLC and NMR control), thus permitting the recycling of the starting material.

In the case of monoterpenes **1**, **2** and **7** (Table 5, entries 1-3), good yields were obtained, whilst for geranylgeranyl acetate (**25**) and methylgeranylgeraniate (**26**), the obtained yield of the desired alcohols diminished noticeably (Table 5, entries 7 and 8). However, considering the number of double bonds present in **25** and **26**, the latter results should not be underestimated. In the case, of the ketal derivative **24** of geranylacetone (**11**), the low yield found must be due to the instability of the ketal in the reaction medium (Table 5, entry 6).

From the present study on the selective functionalization of acyclic and polyolefinic terpenoids, the following conclusion can be inferred. Firstly, the allylic oxidation of different acyclic monoterpenes with SeO_2 in the presence of *t*BuOOH in DCM at 0º C leads to the corresponding 10-hydroxyderivatives with yields close to 70%, based on recovered staring material. When sesqui- or diterpenes are used as substrates, the efficiency of the process decreases considerably, and complex mixtures are formed. On the other hand, the treatment of terpenes as geranyl acetate (**1**) or geranylacetone (**11**) with $Pd(CO_2CF_3)_2$ in the presence of *p*-benzoquinone and *o*-metoxyacetofenone, permits to functionalize selectively the double bond at the extreme of the chain in moderate yields. Using this protocol, mixtures of acetoxy- o metoxyallyl isomers where obtained when AcOH or MeOH are used as solvents. The employment of MeOH permits to increase the yields up to 60%. Finally, the selective functionalization of terpenes using Sharpless asymmetric dihydroxylation protocol permits the enantioselective access to epoxides of the natural series, with yields varying from good to moderate. Enantiomeric excesses of 95% were calculated for the thus-obtained products, on the basis of their $[\alpha]_D$ values.

Experimental

General: All air- and water-sensitive reactions were performed in flasks flame-dried under a positive flow of argon and conducted under an argon atmosphere. Reagents were purchased at the higher commercial quality and used without further purification, unless otherwise stated. Silica gel SDS 60 (35-70 mm) was used for flash column chromatography. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and a solution of phosphomolybdic acid in ethanol and heat as developing agent. HPLC with UV detection was used. Semi-preparative HPLC separations were carried out on a column of Spherisorb (5 mm Silica, 10 × 250 mm) in an Agilent Serie 1100 instrument. Flow rate of 2.0 mL/min. IR spectra were recorded with a Mattson model Satellite FTIR instrument as NaCl plates (films). NMR studies were performed with a Bruker ARX 400 (^{1}H 400 MHz/^{13}C 100 MHz) spectrometer. The accurate mass determination was carried out with an AutoSpec-Q mass spectrometer arranged in an EBE geometry (Micromass Instruments, Manchester, UK) and equipped with a FAB (LSIMS) source. The instrument was operated at 8 KV of accelerating voltage and Cs^+ were used as primary ions. The low resolution mass spectra were carried out in an quadrupolar mass spectrometer Platform II (Micromass Instruments,

Manchester UK) equipped with a solid probe for the sample introduction.

General procedure for Oxidation with SeO_2 reaction: Standard Protocol. A mixture of SeO_2 (55 mg, 0.50 mmol), *tert*-butyl hydroperoxide 5.0-6.0 M in decane (0.18 mL, 1.00 mmol) and DCM (11 mL) was stirred at 0º C for 20 min. Then, the corresponding starting material was added (1.00 mmol). The mixture was stirred for 3 h, diluted with 25 mL of DCM, washed with water for three times and brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

Compounds 3 and 4. After subjecting **1** (326 mg, 1.66 mmol) to the SeO_2 oxidation general procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 21 mg (0.10 mmol, 6%, 11% based on recovered starting material) of **4** and 142 mg (0.67 mmol, 41%, 75% based on recovered starting material) of **3**.

8-Hidroxy-geranyl acetate (3). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.37 (1H, bt), 5.30 (1H, bt), 4.56 (2H, d, *J* = 7.0 Hz), 3.94 (2H, s), 2.12 (2H, bt, *J* = 7.1 Hz), 2.04 (2H, bt, *J* = 7.2 Hz), 1.98 (3H, s), 1.66 (3H, s), 1.61 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 141.8, 135.3, 125.1, 118.6, 68.7, 61.4, 39.1, 25.7, 21.0, 16.4, 13.7 ppm.

8-Acetoxy-2,6-dimethylocta-2,6-dienal (4). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.35 (1H, s), 6.42 (1H, dt, *J* = 7.2 Hz, *J* = 1.1 Hz), 5.37 (1H, bt), 4.56 (2H, d, *J* = 7.0 Hz), 2.46 (2H, q, *J* = 7.5 Hz), 2.20 (2H, t, *J* = 7.5 Hz), 2.02 (3H, s), 1.71 (3H, s), 1.70 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.1, 171.0, 153.3, 140.4, 139.7, 119.6, 61.1, 37.7, 27.0, 21.0, 16.4, 9.2 ppm.

Compounds 5 and 6. After subjecting **2** (264 mg, 1.34 mmol) to the SeO_2 oxidation general procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 11 mg (0.05 mmol, 4%, 8% based on recovered starting material) of **5** and 140 mg (0.66 mmol, 40%, 81% based on recovered starting material) of **6**.

8-Hidroxylinalyl acetate (5). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.90 (1H, dd, *J* = 17.5 Hz, *J* = 11.0 Hz), 5.32 (1H, td, *J* = 7.1 Hz, *J* = 1.2 Hz), 5.08 (1H, d, *J* = 11.0 Hz), 5.14 (1H, d, *J* = 17.5 Hz), 3.97 (2H, s), 2.01 (3H, s), 2.10-1.60 (4H, m), 1.63 (3H, s), 1.52 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.2, 141.7, 135.2, 125.5, 113.3, 82.9, 68.9, 39.4, 23.7, 22.2, 22.0, 13.6 ppm.

2,6-Dimethyl-6-acetoxy octa-2,7-dienal (6). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.34 (1H, s), 6.42 (1H, td, *J* = 7.3 Hz, *J* = 1.1 Hz), 5.90 (1H, dd, *J* = 17.5 Hz, *J* = 11.0 Hz), 5.13 (2H, dd, *J* = 17.5 Hz, *J* = 11.0 Hz), 2.31 (2H, q, *J* = 8.0 Hz), 2.09-1.98 (1H, m), 1.97 (3H, s), 1.90-1.80 (1H, m), 1.68 (3H, s), 1.53 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 195.2, 169.9, 153.9, 143.7, 141.3, 113.8, 82.4, 38.3, 23.8, 23.4, 22.1, 9.2 ppm.

Compound 8. After subjecting **7** (500 mg, 2.75 mmol) to the SeO_2 oxidation general procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1) on silica gel to afford 263 mg (1.33 mmol, 48%, 88% based on recovered starting material) of **8**.

Methyl 8-hydroxygeraniate (8). IR (film): ν_{max} 3422, 2949, 2924, 2861, 1719, 1649, 1436, 1226, 1149, 1061, 1015, 862 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.63 (1H, bs), 5.33 (1H, bt), 3.95 (2H, bs), 3.64 (3H, s), 2.23-2.14 (4H, m), 2.12 (3H, s), 1.93 (1H, bs), 1.61 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.2, 159.6, 135.9, 124.2, 115.4, 68.6, 50.8, 40.5, 25.5, 18.8, 13.7 ppm; HRFABMS calcd. for $C_{11}H_{18}O_3Na$ $[M+Na]^+$ 221.1154, found: 221.1151. (public ToxicolA).

Compound 10. After subjecting **9** (415 mg, 1.57 mmol) to the SeO_2 oxidation general procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:2) on silica gel to afford 62 mg (0.21 mmol, 24%, 13% based on recovered starting material) of **10**.

12-Hydroxyfarnesyl acetate (10). IR (film): ν_{max} 3425, 2973, 2920, 2859, 1737, 1646, 1449, 1370, 1250, 1018, 923, 842 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.38 (1H, t, *J* = 7.0 Hz), 5.34 (1H, t, *J* = 7.1 Hz), 5.10 (1H, t, *J* = 6.7 Hz), 4.60 (2H, d, *J* = 7.1 Hz), 3.99 (2H, bs), 2.05 (3H, s), 2.25-1.95 (9H, m), 1.70 (3H, s), 1.66 (3H, s), 1.60 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 141.9, 134.9, 134.7, 125.4, 123.7, 118.2, 68.4, 61.2, 39.3, 39.1, 26.1, 26.0, 20.8, 16.2, 15.8, 13.4 ppm; HRFABMS calcd. for $C_{17}H_{28}O_3Na$ $[M+Na]^+$ 303.1936, found 303.1903.

General procedure for Oxidation with $Pd(CO_2CF_3)_2$ reaction: Standard Protocol. To a mixture of starting material (1.00 mmol), ROH (3.0 mL)* and *o*-metoxyacetophenone (30 mg, 0.20 mmol) stirred for 15 min at 25º C under Ar, were added *p*-benzoquinone (108 mg, 1.00 mmol) and $Pd(CO_2CF_3)_2$ (80 mg, 0.25 mmol). After 48 h the mixture was diluted with hexane (20 mL) and filtered through silica gel. The organic layer was washed with water, 10% aqueous $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated under reduced pressure.

Compounds 12 and 13. After subjecting **11** (415 mg, 2.12 mmol) to the $Pd(CO_2CF_3)_2$ oxidation general procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 6:1) on silica gel to afford 42 mg (0.17 mmol, 8%) of **13** and 127 mg (0.50 mmol, 24%) of **12.**

11-Acetoxygeranylacetone (12). IR (film): ν_{max} 2964, 2920, 2862, 1739, 1718, 1443, 1360, 1234, 1023, 833, 732 cm^{-1}; ^{1}H

* ROH = AcOH or MeOH.

NMR ($CDCl_3$, 400 MHz) δ 5.41 (1H, ta, *J* = 6.8 Hz), 5.02 (1H, t, *J* = 7.0 Hz), 4.40 (2H, s), 2.40 (2H, m), 2.20 (2H, m), 2.07 (3H, s), 2.02 (3H, s), 2.10-1.90 (4H, m), 1.65 (3H, s), 1.59 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.7, 171.0, 135.9, 129.1, 123.8, 112.8, 70.2, 43.9, 31.3, 30.0, 26.2, 23.3, 22.5, 21.0, 13.9 ppm; HRFABMS calcd. for $C_{15}H_{24}O_3Na$ $[M+Na]^+$ 275.1623, found: 275.1627.

10-Methylen-9-hydroxygeranylacetone (13). IR (film): ν_{max} 3435, 2924, 2855, 1714, 1447, 1362, 1233, 1161, 1062, 1019, 898 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.08 (1H, t, *J* = 12,2 Hz), 4.99 (1H, s), 4.93 (1H, m), 4.03 (1H, t, *J* = 6.4 Hz), 2.39 (2H, m), 2.20 (2H, m), 2.07 (3H, s), 2.10-1.90 (4H, m), 1.70 (3H, s), 1.62 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.9, 136.2, 125.6, 123.0, 111.1, 75.7, 43.7, 35.7, 33.2, 30.0, 22.5, 17.7, 16.1 ppm; HRFABMS calcd. for $C_{13}H_{22}O_2Na$ $[M+Na]^+$ 233.1517, found: 233.1519.

Compounds 14 and 15. After subjecting **11** (351 mg, 1.79 mmol) to the $Pd(CO_2CF_3)_2$ oxidation general procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 98 mg (0.43 mmol, 24%) of **15** and 148 mg (0.66 mmol, 35%) of **14.**

11-Metoxygeranylacetone (14). IR (film): ν_{max} 2953, 2924, 2854, 1717, 1454, 1374, 1158, 1094, 803 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.36 (1H, bs), 5.17 (1H, bs), 3.74 (2H, dd, *J* = 10.5 Hz, *J* = 2.0 Hz), 3.26 (3H, s), 2.42 (4H, m), 2.25 (2H, m), 2.09 (3H, s), 1.55-1.67 (1H, m), 1.48-1.53 (1H, m), 1.18 (3H, s), 1.13 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.8, 136.1, 132.2, 128.0, 122.9, 78.7, 57.4, 43.8, 39.3, 30.0, 26.2, 22.5, 16.0, 13.8 ppm; HRFABMS calcd. for $C_{14}H_{24}O_2Na$ $[M+Na]^+$ 247.1674, found: 247.1675.

10-Methylen-9-metoxygeranylacetone (15). IR (film): ν_{max} 2926, 2854, 2819, 1720, 1449, 1363, 1098, 967, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.08 (1H, t, *J* = 12.2 Hz), 4.90 (1H, quint, *J* = 1.6 Hz), 4.84 (1H, s), 3.42 (1H, t, *J* = 6.6 Hz), 3.16 (3H, s), 2.41 (2H, m), 2.25 (2H, m), 2.10 (3H, s), 2.10-1.90 (4H, m), 1.59 (3H, s), 1.55 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.7, 144.4, 128.4, 123.4, 113.6, 85.3, 55.5, 43.7, 35.6, 31.8, 29.9, 26.5, 22.5, 17.7 ppm; HRFABMS calcd. for $C_{14}H_{24}O_2Na$ $[M+Na]^+$ 247.1674, found: 247.1672.

Compounds 16 and 17. After subjecting **1** (308 mg, 1.57 mmol) to the $Pd(CO_2CF_3)_2$ oxidation general procedure conditions, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1) on silica gel to afford 50 mg (0.22 mmol, 14%) of **17** and 101 mg (0.48 mmol, 28%) of **16.**

8-Metoxygeranyl acetate (16). IR (film): ν_{max} 3420, 2978, 2925, 2854, 2818, 1740, 1647, 1449, 1366, 1233, 1092, 1023, 955 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.35 (1H, t, *J* = 7.7 Hz), 5.32 (1H, t, *J* = 7.6 Hz), 4.57 (2H, d, *J* = 7.1 Hz), 3.75 (2H, s), 3.26 (3H, s), 2.18 (2H, m), 2.10 (2H, m), 2.02 (3H, s), 1.72 (3H, s), 1.65 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 400 MHz) δ 171.2, 141.9, 132.6, 127.4, 118.6, 78.7, 61.4, 57.5, 39.2, 25.9, 21.1, 16.5, 13.9 ppm; HRFABMS calcd. for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1467, found: 249.1465.

7-Methylen-6-metoxygeranyl acetate (17). IR (film): ν_{max} 2925, 2854, 1741, 1449, 1368, 1233, 1101, 1024, 901 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.35 (1H, t, *J* = 7.0 Hz), 4.93 (1H, s), 4.86 (1H, s), 4.57 (2H, d, *J* = 7.1 Hz), 3.44 (1H, t, *J* = 6.6 Hz), 3.16 (3H, s), 2.10-1.90 (4H, m), 2.06 (3H, s), 1.70 (3H, s), 1.64 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.2, 144.3, 142.0, 118.5, 113.8, 85.2, 61.4, 56.1, 35.7, 31.6, 21.1, 16.5, 16.4 ppm; HRFABMS calcd. for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 249.1467, found: 249.1465.

General procedure for asymmetric dihydroxylation with ADmixβ: Standard Protocol. To a solution of ADmixβ (1400 mg) and methanesulfonamide (98 mg, 1.00 mmol) in *t*BuOH : H_2O (32 mL, 1:1) at 0º C and vigorously stirred, was added the starting material (1.00 mmol) in *t*BuOH (2 mL). After 3 h, $Na_2S_2O_3$ (1300 mg) was added and the mixture stirred for 30 min at room temperature. The *t*BuOH is evaporated and the aqueous solution was extracted with DCM and AcOEt. The organic layer was washed with NaOH 2N, brine, dried over Na_2SO_4 and concentrated under reduced pressure.

Compound 18. After subjecting **11** (600 mg, 3.06 mmol) to the dihydroxylation general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 1:1, then 1:3) on silica gel to afford 280 mg (1.23 mmol, 40%, 67% based on recovered starting material) of **18**.

9(*R*),10-Dihydroxygeranylacetone (18). $[\alpha]_D^{20}$ + 5.50º (*c* 1.35, $CHCl_3$); IR (film): ν_{max} 3424, 2970, 1709, 1376, 1163, 1078, 760 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.00 (1H, t, *J* = 7.0 Hz), 3.19 (1H, d, *J* = 8.3 Hz), 2.39 (2H, m), 2.17 (2H, m), 2.03 (3H, s), 1.98-1.82 (2H, m), 1.55 (3H, s), 1.50-1.40 (2H, m), 1.07 (3H, s), 1.01 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.6, 135.6, 123.6, 79.9, 68.4, 43.9, 34.0, 31.0, 27.5, 23.9, 22.5, 23.8, 18.4 ppm; HRFABMS calcd. for $C_{13}H_{24}O_3$ e$[M+H]^+$ 229.1804, found: 229.1811.

To a solution of **19** (150 mg, 0.66 mmol), Et_3N (0.17 mL, 0.99 mmol), DMAP (9 mg, 0.07 mmol) in DCM (23 mL) at -12º C under Ar, was added methanesulfonylchloride (0.6 mL, 6.66 mmol). After 50 min, aqueous $NaHCO_3$ was added and the mixture stirred for 15 min. The solution was extracted with Et_2O and dried over $MgSO_4$. The crude, without any purification, was diluted into MeOH (10 mL) and stirred at room temperature for 10 min, then K_2CO_3 (364 mg, 2.64 mmol) was added. After 30 min the MeOH was evaporated, water was added and the solution was extracted with Et_2O. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 1:1) on silica gel to afford 104 mg (0.49 mmol, 75%) of **20**.

9(*S*),10-epoxygeranylacetone (20). $[\alpha]_D^{20}$ - 4.42º (*c* 1.05, $CHCl_3$); IR (film): ν_{max} 2959, 1715, 1443, 1359, 1159 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.19 (1H, t, *J* = 7.0 Hz), 2.62 (1H, m), 2.39 (2H, m), 2.17 (2H, m), 2.03 (3H, s), 1.98-1.82 (2H, m), 1.67 (3H, s), 1.50-1.40 (2H, m), 1.28 (3H, s), 1.24 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 208.6, 135.6, 123.3, 64.1, 58.3, 43.7, 36.4, 30.0, 27.5, 24.9, 22.5, 18.8, 16.0 ppm; HRFABMS calcd. for $C_{13}H_{22}O_3Na$ $[M+Na]^+$ 233.1517, found: 233.1509.

Compounds 21 and 22. After subjecting **9** (500 mg, 1.89 mmol) to the dihydroxylation general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1, then 1:2) on silica gel to afford 11 mg (0.04 mmol, 2%, 4% based on recovered starting material) of **22** and 163 mg (0.55 mmol, 29%, 57% based on recovered starting material) of **21**.

10(*R*),11-dihydroxyfarnesylacetate (21). $[\alpha]_D^{20}$ + 13.1º (*c* 1.0, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) d 5.23 (1H, t, *J* = 7.0 Hz), 5.09 (1H, t, *J* = 6.6 Hz), 4.52 (2H, d, *J* = 7.0 Hz), 3.27 (1H, dd, *J* = 10.4 Hz, *J* = 1.6 Hz), 2.22-2.02 (6H, m), 1.99 (3H, s), 1.63 (3H, s), 1.55 (3H, s), 1.55-1.45 (2H, m), 1.13 (3H, s), 1.09 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.3, 142.0, 135.3, 124.2, 118.4, 78.0, 73.0, 61.5, 39.4, 36.7, 29.7, 26.4, 26.0, 23.2, 21.0, 16.4, 15.9 ppm.

6(*R*),7(*R*)-dihydroxyfarnesylacetate (22). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.35 (1H, t, *J* = 7.0 Hz), 5.08 (1H, t, *J* = 7.1 Hz), 4.55 (2H, d, *J* = 7.1 Hz), 3.36 (1H, d, *J* = 9.8 Hz), 2.35-2.00 (4H, m), 2.02 (3H, s), 1.68 (3H, s), 1.65 (3H, s), 1.59 (3H, s), 1.60-1.35 (4H, m), 1.09 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 177.1, 142.1, 132.1, 124.3, 118.8, 76.7, 75.0, 61.4, 38.8, 36.6, 29.4, 25.7, 22.1, 21.1, 21.0, 17.7, 16.6 ppm.

Compound 23. After subjecting **21** (150 mg, 0.50 mmol) to the mesylation and basic treatment procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1) on silica gel to afford 192 mg (0.68 mmol, 74%) of **23**.

10(*S*),11-Epoxyfarnesylacetate (23). $[\alpha]_D^{20}$ – 2.8º (*c* 1.0, $CHCl_3$); IR (film): ν_{max} 1720, 1365, 1230 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.31 (1H, td, *J* = 7.0 Hz, *J* = 1.2 Hz), 5.12 (1H, t, *J* = 6.2 Hz), 4.55 (2H, d, *J* = 7.1 Hz), 2.67 (1H, t, *J* = 6.2 Hz), 2.16-2.00 (6H, m), 2.02 (3H, s), 1.71-1.55 (2H, m), 1.67 (3H, s), 1.59 (3H, s), 1.27 (3H, s), 1.23 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 171.0, 142.0, 134.5, 124.2, 118.4, 64.1, 61.3, 58.2, 39.4, 36.3, 27.4, 26.1, 24.9, 21.0, 18.7, 16.4, 16.0 ppm.

Compound 27. After subjecting **1** (400 mg, 2.04 mmol) to the dihydroxylation general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1, then 1:2) on silica gel to afford 357 mg (1.55 mmol, 76%) of **27**.

6(*R*),7-dihydroxygeranylacetate (27). $[\alpha]_D^{20}$ + 18.8 (*c* 0.97, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ 5.33 (1H, t, *J* = 7.0 Hz), 4.53 (2H, d, *J* = 7.0 Hz), 3.27 (1H, dd, *J* = 10.5 Hz, *J* = 2.0 Hz), 2.27 (1H, m), 2.04 (1H, m), 2.00 (3H, s), 1.66 (3H, s), 1.55 (1H, m), 1.39 (1H, m), 1.15 (3H, s), 1.10 (3H, s) ppm; ^{13}C RMN ($CDCl_3$, 100 MHz) δ 171.2, 142.0, 118.5, 77.9, 72.9, 61.3, 36.5, 29.4, 26.3, 23.1, 20.9, 16.3 ppm; EI-MS *m/z* 231 (MH^+).

Compound 28. After subjecting **2** (400 mg, 2.04 mmol) to the dihydroxylation general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 2:1, then 1:2) on silica gel to afford 467 mg (2.03 mmol, 99%) of **28**.

6(*R*),7-Dihydroxy-(*R*)-linalylacetate (28). $[\alpha]_D^{20}$ – 2.9º (*c* 1.4, CH_2Cl_2); IR (film): ν_{max} 3432, 2975, 2937, 2875, 1735, 1644, 1371, 1254, 1171, 1075, 1021, 924 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.93 (1H, m), 5.15 (1H, t, *J* = 3.3 Hz), 5.12-5.06 (1H, m), 3.28 (1H, m), 2.85-2.60 (2H, bs), 1.99 (3H, s), 1.95-1.65 (2H, m), 1.51 (3H, s), 1.49-1.25 (2H, m), 1.17 (3H, s), 1.12 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.2, 141.8, 113.5, 83.2, 78.6, 73.1, 37.2, 26.5, 25.7, 23.9, 23.4, 22.2 ppm; HRFABMS calcd. for $C_{12}H_{22}O_4Na$ $[M+Na]^+$ 253.1412, found: 253.1410.

Compound 29. After subjecting **7** (530 mg, 2.91 mmol) to the dihydroxylation general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 3:1, then 1:2) on silica gel to afford 509 mg (2.36 mmol, 81%) of **29**.

Methyl 6(*R*),7-dihydroxygeraniate (29). $[\alpha]_D^{20}$ + 26.1º (*c* 1.4, MeOH); IR (film): ν_{max} 3434, 2973, 2952, 2878, 1703, 1649, 1437, 1385, 1227, 1152, 1077, 1028, 865 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.68 (1H, s), 3.65 (3H, s), 3.30 (1H, dd, *J* = 10.5 Hz, *J* = 2.0 Hz), 2.49-2.35 (2H, m), 2.14 (3H, s), 1.67-1.54 (1H, m), 1.53-1.37 (1H, m), 1.18 (3H, s), 1.13 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3, 160.0, 115.5, 77.7, 73.1, 50.9, 37.9, 29.3, 26.6, 23.3, 18.9 ppm; HRFABMS calcd. for $C_{11}H_{20}O_4Na$ $[M+Na]^+$ 239.1259, found: 239.1261.

Compound 30. After subjecting **24** (220 mg, 0.92 mmol) to the dihydroxylation general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:2, then 1:1) on silica gel to afford 40 mg (0.15 mmol, 16%, 27% based on recovered starting material) of **30**.

2,6-dimethyl-9-(2-methyl-1,3-dioxolan-2-yl)non-6-ene-2,3(*R*)-diol (30). IR (film): ν_{max} 3415, 2976, 2928, 2876, 1652, 1450, 1384, 1251, 1136, 1056, 947, 860 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.12 (1H, t, *J* = 6.9 Hz), 3.88 (4H, m), 3.28 (1H, d, *J* = 10.4 Hz), 2.36-1.93 (4H, m), 1.60-1.49 (4H, m), 1.53 (3H, s), 1.25 (3H, s), 1.14 (3H, s), 1.08 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 135.4, 125.2, 110.4, 78.5, 73.3, 65.0, 39.3, 37.1, 30.0, 26.8, 24.1, 23.7, 23.1, 16.2 ppm; HRFABMS calc. for $C_{15}H_{28}O_4Na$ $[M+Na]^+$ 295.1885, found: 295.1886.

Compound 31. After subjecting **25** (300 mg, 0.90 mmol) to the dihydroxylation general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 5:1, then 3:1, then 1:2) on silica gel to afford 64 mg (0.17 mmol, 18%, 35% based on recovered starting material) of **31**.

14(*R*),15-Dihydroxygeranyllinalyl acetate (31). IR (film): ν_{max} 3432, 2971, 2930, 2856, 1737, 1645, 1450, 1250, 1171, 1081, 1020, 925 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.95 (1H, dd, *J* = 17.5 Hz, *J* = 11.0 Hz), 5.20-5.05 (2H, m), 5.13 (1H, d, *J* = 17.5 Hz), 5.08 (1H, d, *J* = 11.0 Hz), 3.33 (1H, dd, *J* = 10.4 Hz, *J* = 1.8 Hz), 2.30-2.15 (1H, m), 2.12-1.90 (7H, m), 1.99 (3H, s), 1.66-1.30 (4H, m), 1.65 (3H, s), 1.61 (3H, s), 1.51 (3H, s), 1.18 (3H, s), 1.14 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 170.1, 141.9, 135.5, 135.1, 124.9, 124.7, 113.2, 83.1, 78.3, 73.1, 39.9, 36.9, 31.8, 29.8, 26.5, 26.4, 23.8, 23.4, 23.3, 22.3, 22.2, 16.0 ppm; HRFABMS calcd. for $C_{22}H_{38}O_4Na$ $[M+Na]^+$ 389.2674, found: 289.2671.

Compound 32. After subjecting **26** (420 mg, 1.32 mmol) to the dihydroxylation general procedure, the resulting crude was purified by column chromatography (hexane/*t*-BuOMe, 6:1, then 1:1) on silica gel to afford 66 mg (0.19 mmol, 14%, 26% based on recovered starting material) of **32**.

Methyl 14(*R*),15-dihydroxygeranyl-geranyl acetate (32). IR (film): ν_{max} 3432, 2973, 2948, 2855, 1720, 1649, 1436, 1224, 1148, 1078, 862 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 5.67 (1H, s), 5.18 (1H, t, *J* = 7.0 Hz), 5.08 (1H, m), 3.69 (3H, s), 3.33 (1H, dd, *J* = 10.4 Hz, *J* = 1.8 Hz), 2.30-1.95 (10H, m), 2.16 (3H, s), 1.62 (3H, s), 1.60 (3H, s), 1.45-1.32 (2H, m), 1.20 (3H, s), 1.16 (3H, s) ppm; ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.4, 160.3, 136.1, 135.1, 124.9, 123.1, 115.3, 78.4, 73.0, 50.9, 41.0, 39.6, 36.9, 29.8, 26.5, 25.9, 23.4, 18.9, 16.1, 16.0 ppm; HRFABMS calcd. for $C_{21}H_{36}O_4Na$ $[M+Na]^+$ 375.2508, found: 375.2502.

Acknowledgements:

We acknowledge the Spanish Ministry of Science and Technology, Project BQU 2002-03211, for partial support of this research. The authors thank the Spanish Ministry of Education and Science and the Regional Andalucian Government for grants to Jesús F. Arteaga and Elena M. Sánchez.

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