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Synthesis of (±)-Karahana Ether and Karahanaenone by Selective Cyclization of 6,7-Epoxygeranyl Acetate

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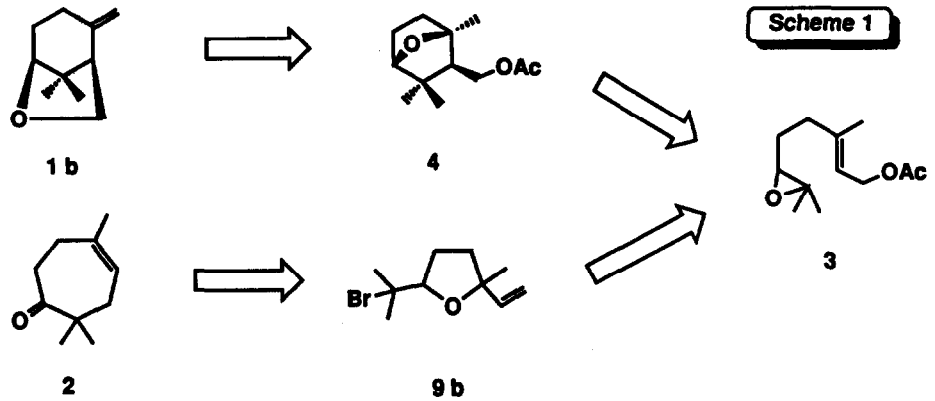
Abstract: Efficient methods for preparing (±)-karahana ether (**1b**) and karahanaenone (**2**) from 6,7-epoxygeranyl acetate(**3**), by Lewis-acid-catalyzed electrophilic cyclization, are described.

INTRODUCTION

Following the authors' synthesis work on fragrant compounds,[1-4] (±)-karahana ether (**1b**) and karahanaenone (**2**), interestingly odored monoterpenes isolated from the Japanese hop "Shinshu-wase"[2] were prepared by selective electrophilic cyclization of 6,7-epoxygeranyl acetate (**3**) (scheme 1).



A variety of syntheses of (±)-karahana ether (**1b**) have been reported. Armstrong et al [6] described an elegant synthesis, involving a $BF_3.OEt_2$ catalyzed cyclization of a laboriously prepared geranic acid epoxyallylsililderivative. Coates et al [7] used the radical cyclization of geranyl acetate; the main drawback of this method being the low yields and the difficult purification of the resulting products. Mori et al [8] synthesized (-)-karahana ether starting from 5,5-dimethyl-1,3-cyclohexanedione.

A number of synthetic methods for preparing karahanaenone (2), including cationic rearrangements, [9,10] cyclizations, [11,12] Diels-Alder cycloadditions, [13,14] as well as Cope, [15,16] and Claisen rearrangements, [17] have also been reported. Demole et al [18] prepared 2, starting from the tetrahydrofurane derivative 9b, which was obtained from linalool; 9b was rendered impure by the difficult to remove 3-bromo-2,2,6-trimethyl-6-ethenyltetrahydropyrane.

RESULTS AND DISCUSSION

The authors have found that the chemical behaviour of 6,7-epoxygeranyl acetate (3) toward the Lewis acids depends strongly on their nature and the experimental conditions. The choice of the suitable cyclizing agent and reaction conditions allowed the direction of the chemical process toward the increased formation of the major product, thus making the cyclization synthetically useful. $BF_3.OEt_2$, $SnCl_4$ and BBr_3 were the most significant among the Lewis acids used.

The results obtained in the reaction of 3 with $BF_3.OEt_2$ were in agreement with those reported for other epoxyterpenes. [19] This acid is only an efficient cyclizing agent when it is used with epoxyallylsililterpenes. [6,20] As described in the literature, the reaction temperature is not very critical; so, Lewis acid concentration effects on the reaction of 3 with $BF_3.OEt_2$ in CH_2Cl_2 at -10°C were observed. The results obtained after 60 min. of reaction are shown in scheme 2 and table 1.

Scheme 2

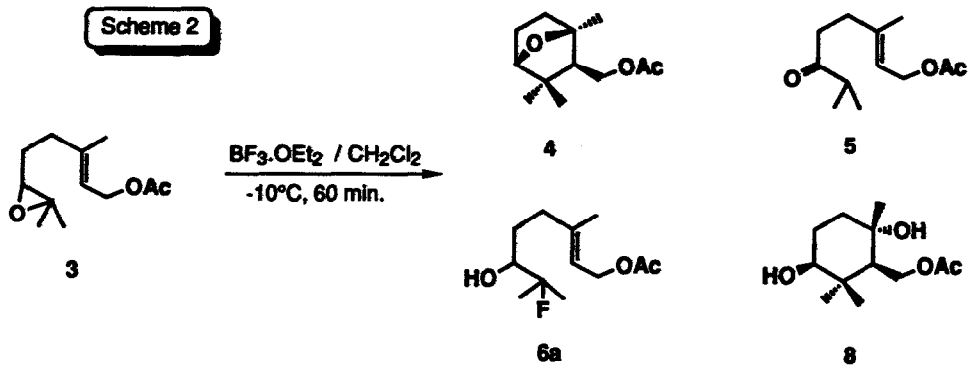


Table 1

Reaction of 3 with $BF_3.OEt_2$

BF_3 / 3[a]	4[b]	5[b]	6a[b]	8[b]
0.28	20	10	38	8
0.48	21	15	32	12
0.57	22	37	28	18

[a] Molar proportion. [b] Chromatographic yields (%).

As can be seen, when the molar proportion BF_3/epoxyde **3** was raised, yields in ketone **5** and diol **8** were increased and the proportion of fluorhidrine **6a** decreased. These results suggested that **6a** could be transformed into **5** in the reaction medium, as was confirmed experimentally. Thus, treatment of **6a** with $BF_3.OEt_2$ at room temperature for 2.5 h. yielded **5** (70%) and **7** (30%).

$SnCl_4$ was a most effective cyclizing agent.[21-23] Taking into account the results previously obtained with this Lewis acid, a molar proportion of $SnCl_4$ / **3** of 0.24 was selected. Reactions were performed in CH_2Cl_2 at different temperatures (scheme 3 and table 2).

Scheme 3

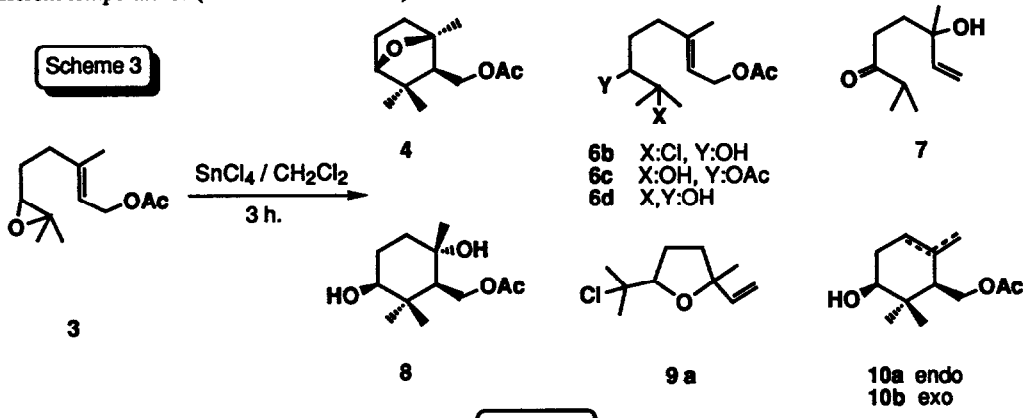


Table 2

Reaction of 3 with $SnCl_4$

Temperature	3[a]	4[a]	6b[a]	6c[a]	6d[a]	7[a]	8[a]	9a[a]	10a-b[a]
-65°C	50.7	---	24.4	---	2.6	---	1.8	---	---
-10°C	---	48.0	5.0	0.5	---	0.4	2.0	17.0	4.4
0°C	---	85.0	2.0	---	---	---	1.0	3.0	1.0

[a] Chromatographic yields (%).

Some conclusions can be drawn from the above results. The acyclic compounds, which result from the opening of the epoxyde ring were the major products at low temperature. As the reaction temperature became higher the proportion of cyclic derivatives increased. Chlorhidrine **6b** was the main product when the reaction was performed at -65°C, with a large amount of starting material **3** being recovered. The tetrahydrofurane derivative **9a**, together with the major product **4**, was obtained working at -10°C. The reaction carried out at 0°C yielded almost entirely compound **4**. Another deduction from these results is the transformation of **6b** into **9a** during the course of the reaction, which was subsequently confirmed. **6b** afforded **9a** in very high yield on treatment with $SnCl_4$ in CH_2Cl_2 at room temperature.

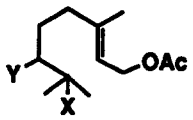
BBr_3 exhibited a considerably different behaviour toward **3** when compared with the previously mentioned Lewis acids. After trying different experimental conditions, -15°C was selected as the optimal reaction temperature. Table 3 shows the results obtained when different molar proportions were used.

Table 3

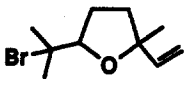
Reaction of 3 with BBr_3

BBr_3 / 3[a]	4[a]	5[b]	6e[b]	6f[b]	9b[b]	11[b]	12[b]
0.26	3	4	31	35	2	4	11
0.69	---	---	10	---	50	18	---
1.08	---	---	---	---	85	3	---

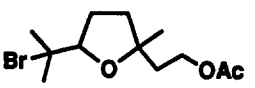
[a] Molar proportion. [b] Chromatographic yields (%).



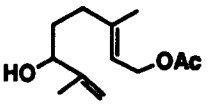
6e X:Br, Y:OH
6f X:OH, Y:Br



9 b



11



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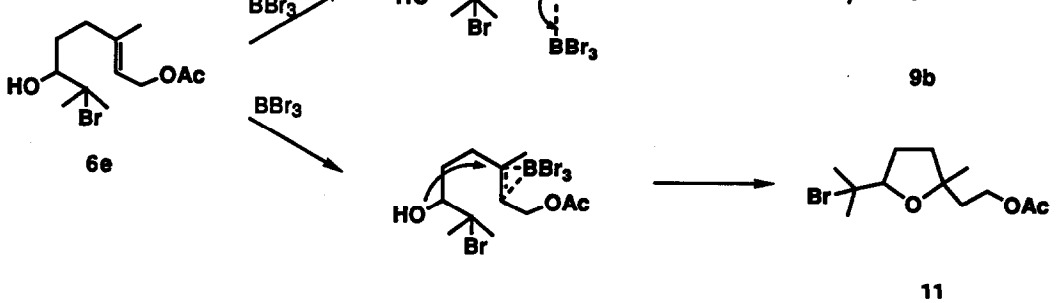
As can be seen in table 3, bromhidrines **6e** and **6f** were the major products at low molar proportions of BBr_3 / **3**. The yields of furane derivatives **9b** and **11** increased, and those of compounds **6e-f** decreased, when the Lewis acid concentration was raised. The ratio **9b**:**11** also increased with the proportion of BBr_3. A possible mechanism for the formation of these furane derivatives, which is consistent with the experimental evidence, is shown in scheme 4.

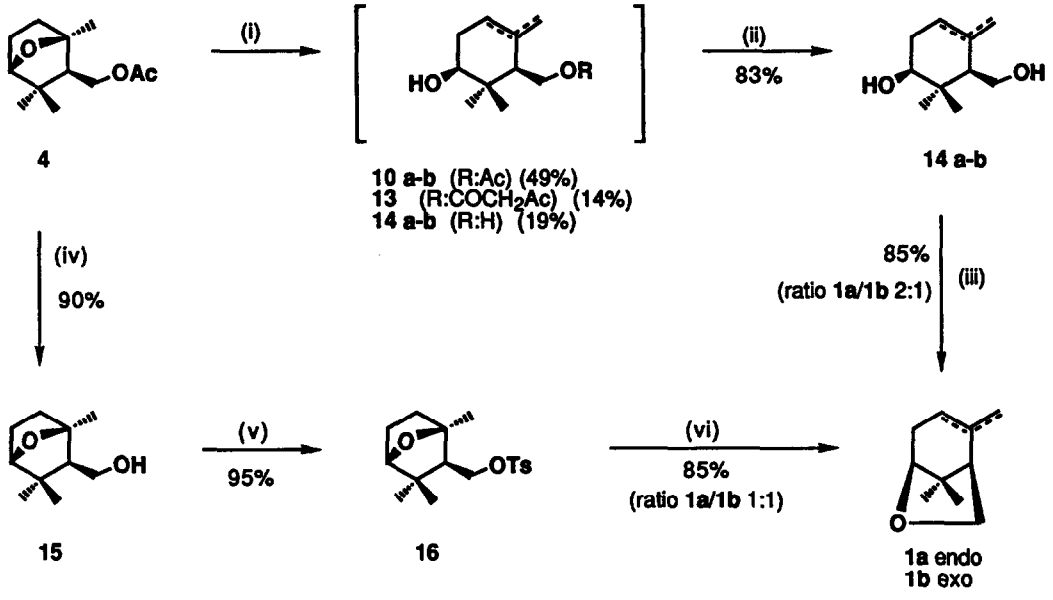
Scheme 4



The high selectivity achieved in some of the above cyclizations allowed the development of efficient method of syntheses of the fragrant terpenes (±)-karahana ether (**1b**) and karahanaenone (**2**). Two routes for preparing **1b** from 6,7-epoxygeranyl acetate (**3**) are shown in scheme 5. In each, cyclization of **3** to bicyclic ether **4** by $SnCl_4$ was the first step (85%).

In the first sequential synthesis (scheme 5), **4** was regioselectively open on treatment with BBr_3, yielding after saponification, a mixture of the alcohols **14a-b**, in good yields. **14a-b** were transformed into (±)-karahana ether (**1b**) and its easily separated isomer **1a** with TsCl and pyridine.[7] The ratio of endo / exo isomers for compounds **10** and **14** in scheme 5 was 2:1.

Scheme 5



(i) BBr_3, CH_2Cl_2, r.t., 10 min.; collidine, CH_2Cl_2. (ii) KOH, EtOH, reflux, 4 h. (iii) TsCl, Py, r.t., 5 h. (iv) KOH, EtOH, reflux, 4 h. (v) TsCl, Py, -15°C, 3.5 h., Ar. (vi) BBr_3, CH_2Cl_2, r.t., 15 min., N_2; collidine, reflux, 6 h.

A most favourable alternative route to **1b**, where **1b** and **1a** were obtained in a ratio of 1:1, involves the treatment of the tosyl derivative **16** with BBr_3.

Karahanaenone (**2**) can be prepared by a two-step sequence involving the efficient transformation of 6,7-epoxygeranyl acetate (**3**) into **9b**, by using BBr_3 in CH_2Cl_2 at -15°C, and the further treatment of this tetrahydrofurane derivative with hot collidine.[18]

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer Model 983 G spectrometer with samples between sodium

chloride plates (film) or as potassium bromide pellets. ^{1}H NMR (80 and 300 MHz) and ^{13}C NMR (75 MHz) spectra were performed on a Bruker WP 80 SY and 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. All mass spectra were registered on a Hewlett-Packard 5988A mass spectrometer using an ionizing voltage of 70 eV. Analytical TLC was performed on 0.25 mm-thick layers of silica gel 60 G (Merck 7331) and conventional and flash column chromatographies were carried out on silica gel pads (Merck 7729), using hexane-Bu^{t}OMe (H-E) mixtures of increasing polarity.

Reaction of 6,7-epoxygeranyl acetate (3) with $BF_3.OEt_2$.

To a stirred solution of 3 (1 g, 4.71 mmol) in dry CH_2Cl_2 (210 ml), $BF_3.OEt_2$ in CH_2Cl_2 (30 ml) was slowly added at -10° C under nitrogen. After stirring for 1 h, the reaction was quenched by addition of ice-water, diluted with $CHCl_3$ and the organic layer washed with aq. $NaHCO_3$ solution (3 x 30 ml) and H_2O (3 x 30 ml), dried and evaporated. Flash chromatography of the crude gave **4**, **5**, **6a** and **8**.

(2',5'-epoxy-2',6',6'-trimethyl) cyclohexylmethyl acetate (**4**)

^{1}H NMR (300 MHz) δ =1.01 (3H, *s*, Me-7'),1.07 (3H, *s*, Me-8'), 1.33 (3H, *s*, Me-9'), 2.02 (3H, *s*, Me-CO_2-), 3.76 (1H, *d*, 4.5 , H-5'), 3.97 (1H, *dd*, 11.5, 7.5 , H-1), 4.11 (1H, *dd*, 11.5, 7.5 , H-1); ^{13}C NMR (75 MHz) δ = 63.5 (CH_2-1), 54.2 (CH-1'), 85.8 (C-2'), 38.4 (CH_2-3'), 25.9 (CH_2-4'), 86.0 (CH_2-5'), 44.9 (C-6'), 18.3 (CH_3-7'), 23.2 (CH_3-8'), 25.8 (CH_3-9'), 171.1 (C-1''), 21.1 (CH_3-2''); IR (film) : 1076 and 972 cm^{-1} (pentacyclic ether); MS: *m/z* (%) = 212 (2), 197 (3), 152 (8), 43 (100).

3,7-dimethyl-6-oxo-2-octenyl acetate (**5**)

^{1}H NMR (300 MHz) δ = 1.08 (6H, *d*, 7.0 , Me-8 and 9), 1.70 (3H, *bs*, Me-10), 2.04 (3H, *s*, Me-CO_2-), 2.29 (2H, *t*, 7.5 , H-4), 2.56 (2H, *t*, 7.5 , H-5), 2.59 (1H, *h*, 7.0 , H-7), 4.56 (2H, *d*, 7.0 , H-1), 5.32 (1H, *bt*, 7.0, 1.5 , H-2); ^{13}C NMR (75 MHz) δ = 61.2 (CH_2-1), 118.7 (CH-2), 141.4 (C-3), 38.4 (CH_2-4), 33.2 (CH_2-5), 217.9 (C-6), 41.0 (CH-7), 18.3 (CH_3-8), 18.3 (CH_3-9), 16.7 (CH_3-10), 171.2 (C-1'), 21.1 (CH_3-2'); IR (film) : 1709 cm^{-1}(C=O, ketone), 1671 cm^{-1} (C=CH); MS: *m/z* (%) = 153 (4), 99 (2), 71 (100), 43 (87).

3,7-dimethyl-7-fluoro-6-hydroxy-2-octenyl acetate (**6a**).

^{1}H NMR (300 MHz) δ = 1.29 (6H, *d*, $J_{H,F}$=22.2 Hz, Me-8 and 10), 1.67 (3H, *bs*, Me-9), 2.01 (3H, *s*, Me-CO_2-), 3.49 (1H, *dt*, $J_{6,F}$= 11 Hz and $J_{6,5}$=2 Hz, H-6), 4.55 (2H, *d*, 7.0 , H-1), 5.35 (1H, *bt*, 7.0 , H-2); ^{13}C NMR (75 MHz) δ = 61.3 (CH_2-1), 118.8 (CH-2), 141.8 (C-3), 36.1 (CH_2-4), 29.1 (CH_2-5), 76.2 (CH-6), 97.9 (C-7), 23.5 (CH_3-8), 16.4 (CH_3-9), 21.3 (CH_3-10), 171.,2 (C-1'), 21.2 (CH_3-2'); IR (film) : 3370 cm^{-1} (OH), 1691 cm^{-1} (C=CH); MS: *m/z* (%) = 172 (2), 157 (9), 126 (3), 61 (40), 43 (100).

(2',5'-dihydroxy-2',6',6'-trimethyl) cyclohexylmethyl acetate (**8**)

^{1}H NMR (300 MHz) δ = 0.82 (3H, *s*, Me-7'), 1.08 (3H, *s*, Me-8'), 1.2 (3H, *s*, Me-9'), 2.04 (3H, *s*, Me-CO_2-), 3.33 (2H, *dd*, 11.0, 4.0 , H-5), 4.30 (1H, *dd*, 11.8, 5.5 , H-1), 4.35 (1H, *dd*; 11.8, 5.5, H-1); ^{13}C NMR (75 MHz) δ = 63.1 (CH_2-1), 52.2 (CH-1'), 72.1 (C-2'), 39.9 (CH_2-3'), 28.5 (CH_2-4'), 77.6 (CH-5'), 39.1(C-6'), 15.1 (CH_3-7'), 24.0 (CH_3-8'), 28.0 (CH_3-9'), 171.1 (C-1''), 21.3 (CH_3-2''); IR (film) : 3426 cm^{-1} (OH); MS: *m/z* (%) = 159 (1), 137 (6), 101 (100), 72 (6), 43 (92).

Reaction of 6,7-epoxygeranyl acetate (3) with $SnCl_4$

To a stirred solution of **3** (4 g, 18.86 mmol) in dry CH_2Cl_2 (250 ml), a solution of $SnCl_4$ (0.49 ml) in CH_2Cl_2 (25 ml) was slowly added at low temperature under nitrogen. After stirring for 3 h, the mixture was diluted with $CHCl_3$ (150 ml) and washed with 0.5 M Na_2CO_3 solution (3 x 30 ml), 2 N HCl (3 x 30ml) and brine. The organic phase was dried over anh. Na_2SO_4 and the solvent evaporated to afford a crude reaction that by flash chromatography gave **4**, **6b**, **6c**, **6d**, **7**, **8**, **9a** and **10a-b**. Compounds **10a** and **10b** were further separated by $AgNO_3$-SiO_2 1:5 column chromatography.

7-chloro-3,7-dimethyl-6-hydroxy-2-octenyl acetate (**6b**)

^1H NMR (300 MHz) δ = 1.53 (3H, *s*, Me-8), 1.57 (3H, *s*, Me-9), 1.69 (3H, *s*, Me-10), 2.03 (3H, *s*, Me-CO_2-), 3.46 (1H, *dd*, 11.0, 2.0 , H-6), 4.57 (2H, *d*, 7.0 , H-1), 5.37 (1H, *bt*, 7.0, H-2); ^{13}C NMR (75 MHz) δ = 61.4 (CH_2-1), 118.9 (CH-2), 141.7 (C-3), 36.4 (CH-4), 29.5 (CH_2-5), 78.4 (CH-6), 76.1(C-7), 27.2 (CH_3-8), 29.2 (CH_3-9), 16.5 (CH_3-10), 171.2 (C-1'), 21.1 (CH_3-2'); IR (film) : 3470 cm^{-1} (OH), 1671 cm^{-1}(C=CH); MS: *m/z* (%) = 241 (5), 213(4), 191(4), 177 (6), 135 (32), 43 (100).

6-acetoxy- 3,7-dimethyl-7-hydroxy-2-octenyl acetate (**6c**)

^1H NMR (300 MHz) δ = 1.17 (3H, *s*, Me-8), 1.18 (3H, *s*, Me-9), 1.68 (3H, *d*, 0.8, Me-10), 2.03 (3H, *s*, Me-CO_2-), 2.08 (3H, *s*, Me-CO_2-), 4.55 (2H, *d*, 7.0 , H-1), 4.77 (1H, *dd*, 10.0, 3.0 , H-6), 5.32 (1H, *dt*, 7.0, 1.3 , H-2); ^{13}C NMR (75 MHz) δ = 61.3 (CH_2-1), 118.9 (CH-2), 143.3 (C-3), 36.0 (CH_2-4), 29.7 (CH_2-5), 79.5 (CH-6), 72.5(C-7), 26.6 (CH_3-8), 25.0 (CH_3-9), 16.5 (CH_3-10), 171.2 (C-1', C-1"), 21.0 (CH_3-2', CH_3- 2"); IR (film) : 3468 cm^{-1} (OH), 1680 cm^{-1}(C=CH), 1736, 1733 and 1240 cm^{-1} (CH_3CO_2-).

6,7-dihydroxy-3,7-dimethyl-2-octenyl acetate (**6d**)

^1H NMR (300 MHz) δ = 1.11 (3H, *s*, Me-8), 1.15 (3H, *s*, Me-9), 1.67 (3H, *s*, Me-10), 2.00 (3H, *s*, Me-CO_2-), 3.28 (1H, *dd*, 10.4, 2.0 , H-6), 4.55 (2H, *bd*, 7.0 , H-1), 5.34 (1H, *bt*, 7.0, H-2); ^{13}C NMR (75 MHz) δ = 61.4 (CH_2-1), 118.7 (CH-2), 142.1 (C-3), 36.6 (CH_2-4), 29.5 (CH_2-5), 78.0 (CH-6), 73.1 (C-7), 26.4 (CH_3-8), 23.2 (CH_3-9), 16.6 (CH_3-10), 171.3 (C-1'), 21.0 (CH_3-2'); IR (film) : 3451 cm^{-1} (OH), 1668 cm^{-1}(C=CH); MS: *m/z* (%) = 170 (1), 141(1), 81 (25), 68 (62), 59 (100), 43 (99).

2,6-dimethyl-6-hydroxy-7-octen-3-one (**7**)

^1H NMR (80 MHz) δ = 1.06 (6H, *d*, 6.0, Me-1 and Me-9), 1.23 (3H, *s*, Me-10), 2.54 (2H, *t*, 7.5, H-4), 2.63 (1H, *h*, 7.0 , H-2), 5.05 (1H, *dd*, 10.0, 2.0 , H-2), 5.27 (1H, *dd*, 16.0, 1.0 , H-8), 5.85 (1H, *dd*, 17.0, 10.0 , H-7); IR (film) : 3485 cm^{-1} (OH), (C=O) 1709 cm^{-1}, 3010 and 1608 cm^{-1}($CH=CH_2$), 1366 and 1380 cm^{-1} (gem-dimethyl); MS: *m/z* (%) = 170 (1), 141(1), 81 (25), 68 (62), 59 (100), 43 (99).

5-(1'-chloro-1'-methyl) ethyl-2-methyl-2-vinyltetrahydrofurane (**9a**)

^1H NMR (300 MHz) (trans) δ =1.30 (3H, *s*, Me-C-2), 1.51 (3H, *s*, Me-C-1'), 1.52 (3H, *s*, Me-2'), 3.94 (1H, *t*, 6.7, H-5), 4.96 (1H, *dd*, 10.6, 1.5, H-2"), 5.15 (1H, *dd*, 17.2, 1.6, H-2"), 5.81 (1H, *dd*, 17.2, 10.6, H-1") (cis) δ =1.26 (3H, *s*, Me-C-2), 1.50 (3H, *s*, Me-C-1'), 1.53 (3H, *s*, Me-2'), 4.00 (1H, *t*, 6.7, H-5), 4.95 (1H, *dd*, 10.7, 1.6 , H-2"), 5.18 (1H, *dd*, 17.4, 1.6, H-2"), 5.94 (1H, *dd*, 17.2, 10.6, H-1"); ^{13}C NMR (75 MHz)(trans, cis) δ = 85.6-83.7 (C-2), 36.9-37.6 (CH_2-3), 27.6-27.8 (CH_2-4), 83.9-85.5 (CH-5), 71.1-71.2 (C-1'), (CH-6), 27.6-27.8 (CH_3-2'), 143.4-143.7 (CH-1"), 111.5-111.4 (CH_2-2"), 26.6-26.2 (CH_3-C-2), 25.6-25.7 (CH_3-C-1'); IR (film) : 3006 and 1640 cm^{-1}($CH=CH_2$), 1232 and 1200 cm^{-1} (gem-dimethyl), 1096 and 920 cm^{-1} (pentacyclic ether), 805 cm^{-1} (C-Cl); MS: *m/z* (%) = 175 (7), 173 (123), 155 (1), 111 (100), 93 (73), 67 (32).

(5'-hydroxy-2',6',6'-trimethyl) 2'-cyclohexenylmethyl acetate (**10a**)

^{1}H NMR (300 MHz) δ = 0.95 (3H, *s*, Me-7'), 1.00 (3H, *s*, Me-8'), 1.70 (3H, *bs*, Me-9'), 2.04 (3H, *s*, $MeCO_2$-), 3.43 (1H, *t*, 5.4, H-5'), 4.14 (1H, *dd*, 11.8, 4.2, H-1), 1.44 (1H, *dd*, 11.8, 4.2, H-1), 5.38 (1H, *bs*, 1.8, H-3'); ^{13}C NMR (75 MHz) δ = 61.3 (CH_2-1), 48.4 (CH-1'), 136.6 (C-2'), 120.7 (CH-3'), 29.7 (CH_2-4'), 73.5 (CH-5'), 37.2 (C-6'), 22.4 (CH_3-7'), 26.8 (CH_3-8'), 19.4 (CH_3-9'), 170.7 (C-1'), 21.2 (CH_3-2'); IR (film) : 3474 cm^{-1} (OH), 1670 cm^{-1} (C=CH), 1738 and 1240 cm^{-1} (CH_3-CO_2-); MS: *m/z* 29.7(CH_3-2'); IR (film) : 3474 cm^{-1} (R-OH), 1670 cm^{-1} (C=CH), 1738 and 1240 cm^{-1} (CH_3-CO_2-); MS: *m/z* (%) = 153 (6), 137 (26), 119(34), 107(51), 81 (50), 57(16), 43(100).

(5'-hydroxy-6',6'-dimethyl-2'-methylen) cyclohexylmethyl acetate (**10b**)

^{1}H NMR (300 MHz) δ = 0.82 (3H, *s*, Me-7'), 1.04 (3H, *s*, Me-8'), 1.99 (3H, *s*, $MeCO_2$-), 2.38 (1H, *m*, H-1'), 3.43 (1H, *dd*, 8.5, 4.0, H-5'), 4.30 (1H, *dd*, 11.6, 4.7, H-1), 4.38 (1H, *d*, 11.6, H-1), 4.6 (1H, *bs*, H-9'), 4.86 (1H, *bs*, H-9'); ^{13}C NMR (75 MHz) δ = 62.6 (CH_2-1), 50.7 (CH-1'), 145.6 (C-2'), 31.1 (CH_2-3'), 31.4 (CH_2-4'), 76.6 (CH-5'), 39.3 (C-6'), 17.4 (CH_3-7'), 20.1 (CH_3-8'), 109.9 (CH_2-9'), 171.3 (C-1"), 21.1 (CH_3-2'); IR (film) : 3462 cm^{-1} (OH), 1646 cm^{-1}($C=CH_2$), 1736 and 1236 cm^{-1} (CH_3-CO_2-); MS: *m/z* (%) = 153 (2), 137 (7), 123 (10), 119 (31), 107 (18), 93 (23), 57(6), 43(100).

Reaction of 6,7-epoxygeranyl acetate (3) with BBr_3.

To a stirred solution of **3** (1.04 g, 4.88 mmol) in dry CH_2Cl_2 (80 ml), a solution of BBr_3 in CH_2Cl_2 (10 ml) was added dropwise at -15 °C under nitrogen. After stirring for 2 h, 0.4 ml of collidine were added. Then, the mixture was diluted with $CHCl_3$ (100 ml) and washed with 1N HCl solution (3 x 25 ml) and sat. $NaHCO_3$ (60 ml). The organic phase was dried over anh. Na_2SO_4 and the solvent evapored to afford a crude reaction, that by column chromatography yielded **4**, **5**, **6e**, **6f**, **9b**, **11** and **12**.

7-bromo-3,7-dimethyl-6-hydroxy-2-octenyl acetate (**6e**)

^{1}H NMR (300 MHz) δ = 1.71 (3H, *d*, 0.9, Me-9), 1.72 (3H, *s*, Me-8), 1.77 (3H, *s*, Me-10), 2.03 (3H, *s*, Me-CO_2-), 3.39 (1H, *dd*, 10.3, 1.9, H-6), 4.58 (2H, *d*, 7.0 , H-1), 5.38 (1H, *bt*, 7.1, 1.4, H-2); ^{13}C NMR (75 MHz) δ = 61.36 (CH_2-1), 119.04 (CH-2), 141.71 (C-3), 36.34 (CH_2-4), 29.92 (CH_2-5), 79.07 (CH-6), 75.20 (C-7), 28.86 (CH_3-8), 16.57 (CH_3-9), 31.15 (CH_3-10), 171.17 (C-1'), 21.12 (CH_3-2'); IR (film) : 3462 cm^{-1} (OH), 1680 cm^{-1}(C=CH),1736 and 1236 cm^{-1}(CH_3CO_2-); MS: *m/z* (%) = 293 (8), 215(47), 135 (100).

6-bromo-3,7-dimethyl-7-hydroxy-2-octenyl acetate (**6f**)

^{1}H NMR (300 MHz) δ = 1.27 (3H, *s*, Me-8), 1.28 (3H, *s*, Me-10), 1.63 (3H, *s*, Me-9), 1.97 (3H, *s*, Me-CO_2-), 3.85 (1H, *dd*, 11.4, 1.9 , H-6), 4.51 (2H, *d*, 7.0 , H-1), 5.33 (1H, *bt*, 7.0, H-2); ^{13}C NMR (75 MHz) δ = 61.16 (CH_2-1), 119.57 (CH-2), 140.33 (C-3), 38.02 (CH_2-4), 31.60 (CH_2-5), 61.68 (CH-6), 72.38 (C-7), 26.32 (CH_3-8), 16.34 (CH_3-9), 26.24 (CH_3-10), 171.03 (C-1'), 20.95 (CH_3-2'); IR (film) : 3466 cm^{-1} (OH), 1670 cm^{-1}(C=CH),1737 and 1235 cm^{-1}(CH_3CO_2-), 608 cm^{-1}(C-Br); MS: *m/z* (%) = 277 (6), 275(5), 235 (14), 233 (16),216 (4), 215 (21), 153 (57), 135 (100).

5-(1'-bromo-1'-methyl) ethyl-2-methyl-2-vinyltetrahydrofurane (**9b**)

^{1}H NMR (300 MHz) δ =1.32 (3H, *s*, Me-C-2), 1.72 (3H, *s*, Me-C-1'), 1.71 (3H, *s*, Me-2'), 4.03 (1H, *d*, 6.7, H-5), 4.97 (1H, *dd*, 9.5, 1.8, H-2"), 5.17 (1H, *dd*, 12.0, 2.0 , H-2"), 5.84 (1H, *dd*, 16.5, 10.0 , H-

1"); ^{13}C NMR (75 MHz) δ = 84.09 (C-2), 36.87 (CH_2-3), 28.57 (CH_2-4), 86.13 (CH-5), 68.53 (C-1'), 29.15 (CH_3-2'), 143.45 (CH-1"), 111.44 (CH_2-2"), 26.67 (CH_3-C-2), 31.27 (CH_3-C-1'); IR (film) : 3005 and 1654 cm^{-1}($CH=CH_2$), 1233, 1202 and 1367 cm^{-1} (gem-dimethyl), 1111 and 919 cm^{-1} (pentacyclic ether), 600 cm^{-1} (C-Br); MS: *m/z* (%) = 233 (17), 235(13), 217 (38), 215 (50), 153 (100), 137 (30).

5-(1'-bromo-1'-methyl) ethyl-2-methyl-2-(2"-acetoxy) ethyltetrahydrofurane (11)

^1H NMR (300 MHz) δ =1.25 (3H, *s*, Me-C-3), 1.67 (6H, *s*, Me-2', Me-C-1'), 2.02 (3H, *s*, Me-CO_2-), 3.83 (1H, *t*, 6.6, H-5), 4.19 (2H, *m*, H-2"); ^{13}C NMR (75 MHz) δ = 82.65 (C-2), 37.47 (CH_2-3), 28.94 (CH_2-4), 86.52 (CH-5), 68.12 (C-1'), 29.37 (CH_3-2'), 39.19 (CH_2-1"), 61.51 (CH_2-2"), 26.70 (CH_3-C-2), 31.66 (CH_3-C-1'), 171.15 (C=O), 21.13 (CH_3CO_2-); IR (film) : 1739 cm^{-1} (CH_3CO_2-), 1235 cm^{-1} (gem-dimethyl), 1071 cm^{-1} (pentacyclic ether), 600 cm^{-1} (C-Br); MS: *m/z* (%) = 293 (33), 275(7), 233 (20), 213 (100).

3,7-dimethyl-6-hydroxy-2,7-octadienyl acetate (12)

^1H NMR (300 MHz) δ = 1.68 (3H, *bs*, 1.1, Me-10), 1.69 (3H, *bs*, 1.2, Me-9), 2.02 (3H, *s*, Me-CO_2-), 4.01 (1H, *t*, 6.5 , H-6), 4.55 (2H, *bd*, 7.1, H-1), 4.81 (1H, *m*, 1.5 , H-8), 4.91 (1H, *m*, H-8), 5.34 (1H, *qt*, 7.1, 1.3, H-2); ^{13}C NMR (75 MHz) δ = 61.38 (CH_2-1), 118.58 (CH-2), 141.99 (C-3), 35.5 (CH_2-4), 32.81 (CH_2-5), 75.47 (CH-6), 147.39 (C-7), 111.20 (CH_2-8), 17.59 (CH_3-9), 16.52 (CH_3-10), 171.19 (C-1'), 21.09 (CH_3-2'); IR (film) : 3451 cm^{-1} (OH), 1669 cm^{-1}(C=CH), 1664 cm^{-1}(C=CH_2), 1737 and 1236 cm^{-1}(CH_3CO_2-).

Reaction of 3,7-dimethyl-7-fluoro-6-hydroxy-2-octenyl acetate (6a) with $BF_3.OEt_2$.

To a stirred solution of **6a** (0.15 g, 0.64 mmol) in dry CH_2Cl_2 (25 ml), cooled at 10°C, a solution of $BF_3.OEt_2$ (0.054 g, 0.38 mmol) in CH_2Cl_2 (5 ml) was added dropwise . The reaction mixture was stirred for 1 h. After working-up, as it was above described for the reaction with $BF_3.OEt_2$, a crude of 99 mg was obtained. Its ^1H-NMR spectrum showed the presence of **5** (70 %) and **7** (30 %).

Reaction of 7-chloro-3,7-dimethyl-6-hydroxy-2-octenyl acetate (6b) with $SnCl_4$.

To a stirred solution of **6b** (0.115 g, 0.46 mmol) in dry CH_2Cl_2 (25 ml) a solution of $SnCl_4$ (0.027 g, 0.106 mmol) in CH_2Cl_2 (5 ml) was slowly added at 0°C. The mixture was further stirred for 2 h under nitrogen. Following the same work-up used in the reaction with $SnCl_4$, **9a** (86 mg) was obtained.

Reaction of (2',5'-epoxy-2',6',6-trimethyl)cyclohexylmethyl acetate (4) with BBr_3.

To a stirred solution of **4** (0.85 g, 4.01 mmol) in dry CH_2Cl_2 (60 ml) a solution of BBr_3 (1.08 g, 4.31 mmol) in CH_2Cl_2 (15 ml) was added dropwise. After stirring at room temperature under nitrogen for 10 min, the mixture was added to a 1M solution of collidine in CH_2Cl_2 (10 ml) . The mixture was washed with 1M HCl (5 x 30 ml) and saturated $NaHCO_3$ (3 x 30 ml). Organic layers were dried over anh. Na_2SO_4 and

evaporated to yield a crude (708 mg), that by column chromatography yielded **10 a-b** (0.407 g, 49 %), **13** (0.126 g, 14 %) and **14 a-b** (0.155 g, 19 %).

(5'-hydroxy-2',6',6'-trimethyl) 2'-cyclohexenyl methyl acetyl acetate (13)

^{1}H NMR (300 MHz) δ = 0.91 (3H, *s*, Me-C-6'), 0.99 (3H, *s*, Me-C-6'), 1.68 (3H, *bs*, Me-9'), 2.24 (3H, *s*, MeCOCH$_2$CO$_2$), 3.42 (2H, *s*, MeCOCH$_2$CO$_2$), 3.42 (1H, *t*, 5.3, H-5'), 4.19 (1H, *dd*, 11.8, 4.4 , H-1), 4.51 (1H, *dd*, 11.8, 4.4 , H-1), 5.36 (1H, *m*, H-3'); ^{13}C NMR (75 MHz) δ = 64.6 (CH$_2$-1), 48.4 (CH-1'), 132.6 (C-2'), 120.5 (CH-3'), 31.7 (CH$_2$-4'), 73.6 (CH-5'), 37.1 (C-6'), 22.3 (CH$_3$-7'), 26.3 (CH$_3$-8'), 18.8 (CH$_3$-9'), 166.9 (C-1''), 50.2 (CH$_2$-2''), 200.3 (C-3''), 30.3 (CH$_3$-4''); IR (film) : 3479 cm^{-1} (OH), 1645 cm^{-1}(C=CH), 1741 cm^{-1}(-CH$_2$-CO$_2$-), 1709 cm^{-1} (CH$_3$COCH$_2$COO-); MS: *m/z* (%) = 153 (13), 137 (8), 134 (12), 119 (18), 85 (25), 43 (100).

(5'-hydroxy-2',6',6'-trimethyl) 2'-cyclohexenyl carbinol (14a)

^{1}H NMR (300 MHz) δ = 0.92 (3H, *s*, Me-C-6'), 1.08 (3H, *s*, Me-C-6'), 1.72 (3H, *bs*, Me-C-2'), 3.35 (1H, *d*, 4.5 , H-5'), 5.42 (1H, *bs*, H-3'); ^{13}C NMR (75 MHz) δ = 58.80 (CH$_2$-1), 51.14 (CH-1'), 131.59 (C-2'), 120.39 (CH-3'), 32.26 (CH$_2$-4'), 71.44 (CH-5'), 37.13 (C-6'), 24.25 (CH$_3$-C-6'), 28.56 (CH$_3$-C-6'), 22.52 (CH$_3$-C-2'); IR (film) : 3252 cm^{-1} (OH), 1673 cm^{-1}(C=CH).

(5'-hydroxy-6',6'-dimethyl-2'-methylen) cyclohexylcarbinol (14b)

^{1}H NMR (300 MHz) δ = 0.93 (3H, s, Me-C-6'), 0.99 (3H, s, Me-C-6'), 3.45 (1H, dd, J = 5.9 and 3.4 Hz, H-5'), 3.70 (1H, dd, J= 10.9 Hz and 3.5 Hz, H-1), 3.92(1H,dd, J = 10.9 Hz and J=7.6 Hz, H-1),4.74 (1H, *bs*, H-C-2'), 4.93 (1H, *bs*, H-1); ^{13}C NMR (75 MHz) δ = 61.99 (CH$_2$-1), 55.13 (CH-1'), 147.52 (C-2'), 31.07 (CH$_2$-3'), 29.49 (CH$_2$-4'), 75.14 (CH-5'), 38.92 (C-6'), 20.46 (CH$_3$-C-6'), 27.46 (CH$_3$-C-6'), 110.57 (CH$_2$-C-2'); IR (film): 3286 cm^{-1} (OH), 1644 cm^{-1} (C=CH$_2$).

Saponification of esters 10a-b and 13 to give 14a-b.

A solution of a 3:1 mixture (0.502 g) of **10a-b** and **13** in 2N alc. KOH (7 ml) was refluxed for 4 h. After evaporation, the crude was diluted with H$_2$O (4 x 25 ml), dried over anh Na$_2$SO$_4$ and evaporated to afford a crude (0.397 g) that on chromatographic column yielded **14a-b** (0.334 g, 83 %).

(±)-Karahana ether (1b).

To a stirred solution of diols **14a-b** (in the ratio 2:1) (0.850 g, 5.0 mmol) in dry pyridine (7 ml) tosyl chloride (0.950 g, 5.0 mmol) was added dropwise at 0°C. After stirring for 5 h at room temperature, the mixture was diluted with OEt$_2$ (60 ml) and washed with 1 M HCl (2 x 30 ml), sat. NaHCO$_3$ (100 ml) and brine (150 ml). The organic layer was dried over Na$_2$SO$_4$ and evaporated to yield a crude (1.010 g), that by flash column chromatography afforded 0.612 g of a 2:1 mixture of bicyclic ethers **1a-b**. Their spectral data were in accordance with those previously reported [2,7].

Saponification of 4. (2', 5'-epoxy-2', 6', 6'-trimethyl) cyclohexylcarbinol (15).

To a stirred solution of **4** (1.250 g, 5.80 mmol) in MeOH (25 ml) a 2N alc. KOH solution (15 ml) was slowly added, and the mixture refluxed for 2 h. After working-up as done for diols **14a-b**, **15** (0.887 g, 90 %) was obtained. ^{1}H NMR (400 MHz) δ =1.06 (3H, *s*, Me-C-6'),1.12 (3H, *s*, Me-C-6'), 1.40 (3H, *s*, Me-C-2'), 3.60 (1H, *dd*, 7.2, 11.0, H-1), 3.66 (1H, *dd*, 11.5, 7.4 , H-1), 3.77 (1H, *d*, 5.3, H-5'); ^{13}C NMR (75 MHz) δ = 58.76 (CH_2-1), 55.51 (CH-1'), 84.18 (C-2'), 36.43 (CH_2-3'), 23.93 (CH_2-4'), 84.02 (CH_2-5'), 42.57 (C-6'), 16.28 (CH_3-C-6'), 24.08 (CH_3-C-6), 20.92 (CH_3-C-2').

Tosylation of 15. (2', 5'-epoxy-2', 6', 6'-trimethyl) cyclohexylmethyl tosylate (16).

To a stirred solution of **15** (0.825 g, 485 mmol) in dry pyridine (8 ml), cooled at -10°C, 1.4 g (7.34 mmol) of freshly prepared tosyl chloride was added to the solution under argon. The resulting suspension was stirred for 3.5 h at -5°C and then diluted with CH_2Cl_2 (30 ml). Organic layer was washed with brine (100 ml), $NaHSO_4$ aq. solution (3 x 25 ml) and brine (100 ml). The organic phase was dried over Na_2SO_4 and evaporated to yield a crude (1.606 g), that after being chromatographed on silica gel (75:25 H:E) afforded **16** (1.49 g, 95 %).^{1}H NMR (300 MHz) δ = 0.82 (3H, *s*, Me-C-6'), 0.94 (3H, *s*, Me-C-6'), 1.16 (3H, *s*, Me-C-2'), 2.34 (3H, *s*, Me-C-4"), 3.61 (1H, *d*, 5.1, H-5'), 3.89 (2H, *m*, H-1), 7.25 (2H, *d*, 8.0, H-3",H-5"), 7.67 (2H, *d*, 3.5 , H-2', H6"); ^{13}C NMR (75 MHz) δ = 69.03 (CH_2-1), 54.24 (CH-1'), 85.42 (C-2'), 37.94 (CH_2-3'), 25.67 (CH_2-4'), 85.63 (CH-5'), 44.74 (C-6'), 18.07 (CH_3-C-6'), 22.68 (CH_3-C-6'), 25.40 (CH_3-C-2'), 144.67 (C-1"), 129.71 (CH-2', C-6"), 127.67 (CH-3", C-5"), 21.40 (CH_3-C-4"); IR (film) : 1076 and 972 cm^{-1}(pentacyclic ether), 1364 and 1189 cm^{-1} (R-O-SO_2-R'), 1598 cm^{-1}(arom.), 817 and 784 cm^{-1} (p-di-sust. arom); MS: (%) = 325 (4), 324 (2), 289 (3), 229 (8), 153 (100).

Reaction of 16 with BBr_3. Preparation of 1a-b.

To a solution of **16** (1.050 g, 3.23 mmol) in dry CH_2Cl_2 (50 ml), 0.508 g (2.03 mmol) of BBr_3 in CH_2Cl_2 (9 ml) were slowly added, and the reaction mixture stirred for 15 min at room temperature under nitrogen. Then, collidine (16 ml) was added and the mixture refluxed for 6 h. After dilution with CH_2Cl_2 (40 ml), the organic phase was washed with $NaHSO_4$ aq. solution (75 ml), brine (100 ml) and dried over anh Na_2SO_4. The solvent was evaporated to afford a crude (0.482 g) that by column chromatography (9:1 H:E) yielded a 1:1 mixture of **1 a-b** (0.256 g, 52 %).

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