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

Alejandro F. Barrero, Enrique J. Alvarez-Manzaneda and P. Linares Palomino

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 (+)-kalahana 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 (+)-kalahana ether (1b) have been reported. Armstrong et al.6 described an elegant synthesis, involving a BF3·OEt2 catalyzed cyclization of a laboriously prepared geranic acid epoxyallylsiliderivative. 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 (-)-kalahana 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 tetrahydrofuran derivative 9b, which was obtained from linalool; 9b was rendered impure by the difficult to remove 3-bromo-2,2,6-trimethyl-6-ethenyltetrahydropyrene.

RESULTS AND DISCUSSION

The authors have found that the chemical behavior 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. BF₃·OEt₂, SnCl₄ and BBr₃ were the most significant among the Lewis acids used.

The results obtained in the reaction of 3 with BF₃·OEt₂ were in agreement with those reported for other epoxysterpenes. 19 This acid is only an efficient cyclizing agent when it is used with epoxyallylsiliterpenes. 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 BF₃·OEt₂ in CH₂Cl₂ at -10°C were observed. The results obtained after 60 min. of reaction are shown in scheme 2 and table 1.

<table>
<thead>
<tr>
<th>Reaction of 3 with BF₃·OEt₂</th>
<th>Table 1</th>
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<tbody>
<tr>
<td>BF₃ / 3a</td>
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<tr>
<td></td>
<td>4ᵇ</td>
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<tr>
<td>0.28</td>
<td>20</td>
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<tr>
<td>0.48</td>
<td>21</td>
</tr>
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<td>0.57</td>
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a Molar proportion. b Chromatographic yields (%).
As can be seen, when the molar proportion BF₃/epoxide 3 was raised, yields in ketone 5 and diol 8 were increased and the proportion of fluorhydrine 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 BF₃.OEt₂ at room temperature for 2.5 h. yielded 5 (70%) and 7 (30%).

SnCl₄ was a most effective cyclizing agent. Taking into account the results previously obtained with this Lewis acid, a molar proportion of SnCl₄ / 3 of 0.24 was selected. Reactions were performed in CH₂Cl₂ at different temperatures (scheme 3 and table 2).

Some conclusions can be drawn from the above results. The acyclic compounds, which result from the opening of the epoxide ring were the major products at low temperature. As the reaction temperature became higher the proportion of cyclic derivatives increased. Chlorhydrine 6b was the main product when the reaction was performed at -65°C, with a large amount of starting material 3 being recovered. The tetrahydrofuran 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 SnCl₄ in CH₂Cl₂ at room temperature.
BBr₃ 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

<table>
<thead>
<tr>
<th>Reac[0.0001] of 3 with BBr₃</th>
<th>4ᵃ</th>
<th>5ᵇ</th>
<th>6ᵉᵇ</th>
<th>6ᶠᵇ</th>
<th>9ᵇᵇ</th>
<th>11ᵇ</th>
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<td>11</td>
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<tr>
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<td>---</td>
<td>---</td>
<td>---</td>
<td>85</td>
<td>3</td>
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</tr>
</tbody>
</table>

ᵃ Molar proportion. ᵇ Chromatographic yields (%).

As can be seen in table 3, bromhidrines 6ᵉ and 6ᶠ were the major products at low molar proportions of BBr₃ / 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 BBr₃. A possible mechanism for the formation of these furane derivatives, which is consistent with the experimental evidence, is shown in 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 karahane none (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 SnCl4 was the first step (85%).

In the first sequential synthesis (scheme 5), 4 was regioselectively open on treatment with BBr3, 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. The ratio of endo / exo isomers for compounds 10 and 14 in scheme 5 was 2:1.

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 BBr3.

Karahane none (2) can be prepared by a two-step sequence involving the efficient transformation of 6,7-epoxygeranyl acetate (3) into 9b, by using BBr3 in CH2Cl2 at -15°C, and the further treatment of this tetrahydropyrane derivative with hot collidine.

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 ($\delta$) 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-BuOH (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$_2$Cl$_2$ (210 ml), BF$_3$-OEt$_2$ in CH$_2$Cl$_2$ (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$_2$O (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) $\delta$ = 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) $\delta$ = 63.5 (CH$_2$-1'), 54.2 (KW-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) $\delta$ = 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, brt, 7.0, 1.5, H-2); $^{13}$C NMR (75 MHz) $\delta$ = 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), 171.1 (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) $\delta$ = 1.29 (6H, d, J$_{HF}=22.2$ Hz, Me-8 and 10), 1.67 (3H, bs, Me-9), 2.01 (3H, s, Me-CO$_2$-), 3.49 (1H, dt, J$_{6,H}=11$ Hz and J$_{6,s}=2$ Hz, H-6), 4.55 (2H, d, 7.0, H-1), 5.35 (1H, brt, 7.0, H-2); $^{13}$C NMR (75 MHz) $\delta$ = 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) $\delta$ = 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) $\delta$ = 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-epoxygerany! acetate (3) with SnCl₄

To a stirred solution of 3 (4 g, 18.86 mmol) in dry CH₂Cl₂ (250 ml), a solution of SnCl₄ (0.49 m) in CH₂Cl₂ (25 ml) was slowly added at low temperature under nitrogen. After stirring for 3 h, the mixture was diluted with CHCl₃ (150 ml) and washed with 0.5 M Na₂CO₃ solution (3 x 30 ml), 2 N HCl (3 x 30ml) and brine. The organic phase was dried over anh. Na₂SO₄ 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 AgNO₃-SiO₂ 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- CO₂-), 3.46 (1H, dd, 11.0, 2.0 , H-6), 4.57 (2H, d, 7.0 , H-1), 5.37 (1H, br, 7.0, H-2); 13C NMR (75 MHz) δ = 61.4 (CH₂-1), 118.9 (CH-2), 141.7 (C-3), 36.4 (CH₄), 29.5 (CH₂-5), 784 (CH-6), 76.1(C-7), 27.2 (CH₃-8), 29.2 (CH₃-9), 16.5 (CH₃-10), 171.2 (C-1'), 21.1 (CH₃-2'); 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-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- CO₂-), 2.08 (3H, s, Me- CO₂-), 4.53 (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); 13C NMR (75 MHz) δ = 61.3 (CH₂-1), 118.9 (CH-2), 143.3 (C-3), 36.0 (CH₂-4), 29.7 (CH₂-5), 79.5 (CH₆), 72.5(C-7), 26.6 (CH₃-8), 25.0 (CH₃-9), 16.5 (CH₃-10), 171.2 (C-1', C-1''), 21.0 (CH₃-2', CH₃- 2''); IR (film) : 3468 cm⁻¹ (OH), 1680 cm⁻¹(C=CH), 1736, 1733 and 1240 cm⁻¹ (CH₃CO₂-).

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- CO₂-), 3.28 (1H, dd, 10.4, 2.0 , H-6). 4.55 (2H, d, 7.0 , H-1). 5.34 (1H, br, 7.0, H-2); 13C NMR (75 MHz) δ = 61.4 (CH₂-1), 118.7 (CH-2), 142.1 (C-3), 36.6 (CH₂-4), 29.5 (CH₂-5), 78.0 (CH-6), 73.1 (C-7), 26.4 (CH₃-8), 23.2 (CH₃-9), 16.6 (CH₃-10), 171.3 (C-1'), 21.0 (CH₃-2', CH₃- 2''); IR (film) : 3458 cm⁻¹ (OH), 1668 cm⁻¹(C=CH), 1736, 1733 and 1240 cm⁻¹ (CH₃CO₂-).

6.7-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(C=CH₂), 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''); 13C NMR (75 MHz) (trans, cis) δ = 85.6-83.7 (C-2), 36.9-37.6 (CH₂-3), 27.6-27.8 (CH₂-4), 83.9-85.5 (CH₅), 71.1-71.2 (C-1'), (CH-6), 27.6-27.8 (CH₃-2'), 143.4-143.7 (CH-1''), 111.5-111.4 (CH₂-2''), 26.6-26.2 (CH₃-C-2), 25.6-25.7 (CH₃-2); IR (film) : 3006 and 1640 cm⁻¹(C=CH₂), 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 = 153 (6), 137 (26), 119 (34), 107 (51), 81 (50), 57 (16), 43 (100).

(5'-hydroxy-6',6'-dimethyl-2'-methylene) cyclohexenylmethyl acetate (10b)

$^1$H NMR (300 MHz) δ = 3.42 (3H, s, Me-7'), 1.05 (3H, s, Me-8'), 1.95 (3H, s, Me-9'), 2.38 (1H, t, 6.7, H-5'), 3.39 (1H, dd, 10.3, 1.9, H-6), 4.58 (2H, d, 7.0, H-1), 5.38 (1H, bs, 1.8, H-3'); $^{13}$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$_3$-5), 79.07 (CH-6), 75.20 (C-7), 28.86 (CH$_3$-8), 16.57 (CH$_3$-9), 31.15 (CH$_3$-10), 171.3 (C-1'), 21.1 (CH$_3$-2'); IR (film): 3462 cm$^{-1}$ (OH), 1670 cm$^{-1}$ (C=CH), 1738 and 1240 cm$^{-1}$ (CH$_3$CO$_2$-); MS: m/z (%) = 153 (2), 137 (7), 123 (10), 119 (31), 107 (18), 93 (23), 53 (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$_2$Cl$_2$ (80 ml), a solution of BBr$_3$ in CH$_2$Cl$_2$ (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 CH$_3$Cl (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$_2$SO$_4$ and the solvent evaporated 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, MeCO$_2$-), 3.39 (1H, dd, 10.3, 1.9, H-6), 4.58 (2H, d, 7.0, H-1), 5.38 (1H, bs, 1.8, 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$_3$-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$_3$CO$_2$-); 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, MeCO$_2$-). 3.85 (1H, dd, 11.4, 1.9, H-6), 4.51 (2H, d, 7.0, H-1), 5.33 (1H, br, 7.1, H-2); $^{13}$C NMR (75 MHz) δ = 61.16 (CH$_2$-1), 119.79 (CH-2), 140.33 (C-3), 38.02 (CH$_2$-4), 31.60 (CH$_3$-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$_3$CO$_2$-), 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-
Reaction of 3,7-dimethyl-7-fluoro-6-hydroxy-2-octenyl acetate (6a) with BF₃.OEt₂.

To a stirred solution of 6a (0.15 g, 0.64 mmol) in dry CH₂Cl₂ (25 ml), cooled at 10°C, a solution of BF₃.OEt₂ (0.054 g, 0.38 mmol) in CH₂Cl₂ (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 BF₃.OEt₂, 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 SnCl₄.

To a stirred solution of 6b (0.115 g, 0.46 mmol) in dry CH₂Cl₂ (25 ml) a solution of SnCl₄ (0.027 g, 0.106 mmol) in CH₂Cl₂ (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 SnCl₄, 9a (86 mg) was obtained.

Reaction of (2',5'-epoxy-2',6',6-trimethyl)cyclohexylmethyl acetate (4) with BBr₃.

To a stirred solution of 4 (0.85 g, 4.01 mmol) in dry CH₂Cl₂ (60 ml) a solution of BBr₃ (1.08 g, 4.31 mmol) in CH₂Cl₂ (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 CH₂Cl₂ (10 ml). The mixture was washed with 1M HCl (5 x 30 ml) and saturated NaHCO₃ (3 x 30 ml). Organic layers were dried over anh. Na₂SO₄ 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)

\( ^1H \) NMR (300 MHz) \( \delta = 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\( _2CO_2 \)), 3.42 (2H, s, MeCOCH\( _2CO_2 \)), 3.42 (1H, t, J = 5.3, H-5'), 4.19 (1H, dd, J = 11.8, 4.4 , H-1), 4.51 (1H, dd, J = 11.8, 4.4 , H-1), 5.36 (1H, m, H-3'); \( ^13C \) NMR (75 MHz) \( \delta = 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=CHCO\( _2 \)), 1709 cm\(^{-1}\) (CH=CO\( _2 \)), 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)

\( ^1H \) NMR (300 MHz) \( \delta = 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'); \( ^13C \) NMR (75 MHz) \( \delta = 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_{3-7'}), 28.56 (CH_{3-6'}), 22.52 (CH_{3-9'}); IR (film) : 3252 cm\(^{-1}\) (OH), 1673 cm\(^{-1}\) (C=CH).

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

\( ^1H \) NMR (300 MHz) \( \delta = 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); \( ^13C \) NMR (75 MHz) \( \delta = 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_{3-7'}), 27.46 (CH_{3-6'}), 110.57 (CH_{2-2'}); IR (film): 3286 cm\(^{-1}\) (OH), 1644 cm\(^{-1}\) (C=CH).

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.
Synthesis of (±)-karahana ether

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 aq. 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) \( \delta = 1.06 (3H, s, Me-C-6'), 1.12 (3H, s, Me-C-6'), 1.40 (3H, s, Me-C-2'), 3.60 (1H, dd, 7.2, 11.0, H-1), 3.66 (1H, dd, 11.5, 7.4, H-1)\); \(^1\)C NMR (75 MHz) \( \delta = 58.76 (CH2-1), 55.51 (CH-1), 84.18 (C-2'), 36.43 (CH2-3'), 23.93 (CH2-4'), 84.02 (CH2-5'), 42.57 (C-6'), 16.28 (CH3-C-6'), 24.08 (CH3-C-6), 20.92 (CH3-C-2').

Tosylation of 15. (2', 5'-epoxy-2', 6', 6'-trimethyl) cyclohexylmethy 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 CH2Cl2 (30 ml). Organic layer was washed with brine (100 ml), NaHSO4 aq. solution (3 x 25 ml) and brine (100 ml). The organic phase was dried over Na2SO4 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) \( \delta = 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''); \(^1\)C NMR (75 MHz) \( \delta = 69.03 (CH2-1), 54.24 (CH-1'), 85.42 (C-2'), 37.94 (CH2-3'), 25.67 (CH2-4'), 85.63 (CH-5'), 44.74 (C-6'), 18.07 (CH3-C-6'), 22.68 (CH3-C-6'), 25.40 (CH3-C-2'), 144.67 (C-1''), 129.71 (CH-2', C-6'), 127.67 (CH-3', C-5''), 21.40 (CH3-C-4''); IR (film) : 1076 and 972 cm\(^{-1}\) (penta cyclic 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 CH2Cl2 (50 ml), 0.508 g (2.03 mmol) of BBr\(_3\) in CH2Cl2 (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 CH2Cl2 (40 ml), the organic phase was washed with NaHSO4 aq. solution (75 ml), brine (100 ml) and dried over anh Na2SO4. 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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REFERENCES AND NOTES


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