DIASTEREOSELECTIVE CYCLIZATION OF α-FORMYLATED ALLYLSILANES INTO BICYCLIC α-METHYLENE-γ-BUTYROLACTONES; A FACILE SYNTHESIS OF p-MENTHANOLIDES

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Abstract: Intramolecular cyclization of α-formylated allylsilanes, ethyl (Z)- and (E)-2-(trimethylsilyl)methyl-6(R)-methyl-7-formyl-hept-2-enoates (5a and 5b), was effected by BF₃-etherate, giving cis (1S,2S,5R)- and trans (1R,2S,5R)-hydroxy esters (6 and 7) in complete diastereoselectivities. Treatment of the allylsilanes (5a and 5b) with TiCl₄ predominantly gave the cis (1S,2S,5R)-isomer in excellent yields. These hydroxy esters (6 and 7) were easily converted into α-methylene-γ-butyrolactones, cis- and trans-p-menthanolides (II and III).

The moiety of α-methylene-γ-butyrolactone is an important partial structure of many naturally occurring terpenoid lactones. The α-methylene-γ-butyrolactones fused to six-membered carbocyclic rings were found in eudesmanolide sesquiterpenoids and monoterprenoid lactones such as paeonilactone-B (I) isolated from paeony root (Paeonia albiflora PALLAS trichocarpa BUNGE) by Hayashi et al. We have reported a facile synthesis of α-methylene-γ-butyrolactones fused to five or six membered carbocyclic rings employing the intramolecular Hosomi reaction of α-formylated β-alkoxycarbonylallylsilanes (eq. 1). This method will be very useful to synthesize these terpenoid lactones. For this purpose, this cyclization reaction needs a proper and high diastereoselectivity. The target molecules in this synthetic application are cis- and trans-p-menthanolides (II and III), which have been prepared from isopulegol. In this communication, we report a more facile synthesis of II and III, having a bicyclic α-methylene-γ-lactone function, by a highly diastereoselective intramolecular cyclization reaction of optically active formylated allylsilanes (5a and 5b) derived from (+)-citronellol.
A synthesis of the optically active allylsilanes (5a and 5b) starting from (+)-citronellol was as follows. Tetrahydropyranyl ether of (+)-citronellol (1) was treated with ozone followed by methyl sulfide to give an aldehyde (2) in good yield. The Honer-Emmons variant of the Wittig reaction of the aldehyde (2) with (EtO)_2P(0)CH_2SiMe_3COOEt afforded a mixture of (E)- and (Z)-α,β-unsaturated esters (4a and 4b) in 37% yield. Removal of the protecting group followed by the Swern oxidation of the mixture yielded a mixture of aldehydes, which can be separated into (Z)- and (E)-α,β-unsaturated esters (5a and 5b) by hplc in 69 and 25% yields, respectively. The geometry of the double bond of the α,β-unsaturated esters was elucidated by 1H-nmr spectroscopy. The (Z)-unsaturated ester (5a) was also selectively synthesized from the aldehyde (2) and ethyl β-trimethylsilylpropionate via several steps in good yield as shown in Scheme 1.

Intramolecular Hosomi reaction of the formylated allylsilanes (5a and 5b) was effected by TiCl_4 or BF_3-etherate in CH_2Cl_2 at a low temperature to give cyclohexanol derivatives in excellent yields. The results are summarized in Table 1. In these reactions, we obtained only two isomers ([1S,2S,5R] (6) and [1R,2S,5R] (7)) of four possible stereoisomers (6,7,8 and 9). And also, we selectively obtained cis-hydroxy ester (6) by treatment of the (Z)-isomer (5a) with BF_3-etherate, or the (E)-isomer with TiCl_4. On the other hand, the trans- isomer (7) was selectively obtained from the (E)-ester (5b) by the use of BF_3-etherate. The cis- and trans- hydroxy esters were quantitatively converted into cis- and trans-fused lactones (II and III), respectively. The spectral data were coincident with those of p-menthanolides (II and III).
TABLE I. Cyclization Reaction of 5a and 5b

<table>
<thead>
<tr>
<th>Run</th>
<th>Aldehyde</th>
<th>Acid</th>
<th>Reaction conditions</th>
<th>Product Yield (%)</th>
<th>Conversion Yield (%)</th>
<th>Ratio</th>
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<td></td>
<td></td>
<td></td>
<td>Temp.(°C)</td>
<td>Time(h)</td>
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<td>7</td>
</tr>
<tr>
<td>1</td>
<td>5a</td>
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<tr>
<td>3</td>
<td>5b</td>
<td>BF₃Et₂O</td>
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<tr>
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<td>35</td>
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</table>

a) All reactions were carried out in CH₂Cl₂ with 1.1 equiv. of the Lewis acid at 0.01 M concentration of the substrate.

Now, we can easily synthesize cis- and trans-p-menthanolides from (+)-citronellol in fairly good yield and selectivity. The selectivity of the cyclization reaction was assumed as shown in Figure 1. The six-membered cyclic intermediate, chelating with the Lewis acids, expected to have an equatorial conformation of the ester and the methyl functions, giving trans relationship between these two groups. The cis and trans selectivities of the cyclization reaction have not been clear yet. However, it may be explained that the transition states (5aC and 5bT) of the cyclization reaction (using BF₃-etherate) of the (Z)- and (E)-esters (5a and 5b) are preferable to the transition states (5aT and 5bC) owing to a steric or electronic repulsion. The cis selectivity of the cyclization reaction of both (Z)- and (E)-esters using TiCl₄ may partly suggest a transition state (B). The details of the mechanisms are now being investigated.

Fig. 1

ACKNOWLEDGEMENTS
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REFERENCES AND NOTES


   b) T. J. Brocksom and J. T. B. Ferreira, *ibid.*, 1981, 11, 105


7. Spectral data; Sa, ir, 1730, 1710, 1640, 850 cm<sup>-1</sup>, l<sup>~</sup>-nmr 6; 6.49(1H, t, J=7 Hz, olefinic H), 10.72(1H, t, J=2 Hz, CHO);
   Sb, ir; 1730, 1710, 1640, 850 cm<sup>-1</sup>, l<sup>~</sup>-nmr 6; 5.58(1H, t, J=7 Hz, olefinic H), 10.74(1H, t, J=2 Hz, CHO).

8. A procedure for the cyclization reaction; CH<sub>2</sub>Cl<sub>2</sub> (30ml) solution of the aldehyde (5a or 5b) (0.3 mmol) was stirred with a Lewis acid (0.33 mmol) at a low temperature monitoring by tlc. The reaction mixture was poured in aqueous IN NaOH solution, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. The crude material was subjected to hplc with 10% EtOAc-hexane. The stereochemistry of the resulting hydroxy esters (6 and 7) was determined from the l<sup>~</sup>-nmr data, especially the splitting patterns of the C-1,2 and 5 methine proton signals, as described below.

Spectral data: 6, ir (neat); 3450, 1710, 1630 cm<sup>-1</sup>, H-nmr δ; 6.49(1H, t, J=7 Hz, olefinic H), 10.72(1H, t, J=2 Hz, CHO); 5b, ir; 1730, 1710, 1640, 850 cm<sup>-1</sup>, H-nmr δ; 5.58(1H, t, J=7 Hz, olefinic H), 10.74(1H, t, J=2 Hz, CHO).

Oxidation of the hydroxy esters (6 and 7) gave the same cyclohexanone derivatives (10). 10, ir (neat); 1710, 1630 cm<sup>-1</sup>, H-nmr(500 MHz, CDCl<sub>3</sub>); δ 3.51(1H, dd, J=5.5, 13.5 Hz, 2-H), 5.54, 6.34 (each 1H, s, olefinic H).

9. Spectral data; II (oil), [α]<sub>D</sub> 139.3° (CHCl<sub>3</sub>, c=0.28), ir (neat); 1770, 1665, 1260, 1190, 1125, 1005, 950, 880, 815 cm<sup>-1</sup>, H-nmr(500 MHz, CDCl<sub>3</sub>); δ 0.94(3H, d, J=7 Hz, 5-Me), 2.84(1H, ddd, J=4, 5, 11 Hz, 2-H), 4.51(1H, dt, J=4, 4 Hz, 1-H), 5.52, 6.10(each 1H, d, J=1 Hz, olefinic H). III (colorless needles, mp 37-39°C), [α]<sub>D</sub> +54.4° (CHCl<sub>3</sub>, c=0.26), ir (KBr); 1780, 1690, 1270, 1250, 1005, 950, 850, 830 cm<sup>-1</sup>, H-nmr(500 MHz, CDCl<sub>3</sub>); δ 1.05(3H, d, J=7 Hz, 5-Me), 2.36(1H, ddt, J=3, 7, 12 Hz, 2-H), 3.74(1H, dt, J=3, 12 Hz, 1-H), 5.39, 6.01(each 1H, d, J=3 Hz, olefinic H).


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