MODEL STUDY FOR THE CONSTRUCTION OF C RING OF PIMARA TYPE DITERPENES

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Abstract—As the model experiment to explore the construction route of our synthetic intermediate (8), the epoxy alcohol (5) was prepared by Sharpless epoxidation including asymmetric introduction of the epoxide ring. The cyclization of 5 to the diol (6) proceeded in 40% yield by the action of Ti(Oi-Pr)$_4$ at room temperature. The diol (6) having more than 90% enantiomeric excess was obtained from the asymmetric epoxide (5).

From biogenetical viewpoints, the C ring of pimarane type diterpenes as exemplified by the structure (3)$^2$ is constructed through the labdane type intermediate (2), the A/B ring system of which is formed by cyclization of geranylgeraniol (1) as depicted in the scheme. In the course of our synthetic study of the cyclic diterpenes, we have been interested in the construction of the intermediate (8) which is regarded as an alternative precursor possessing the preformed C ring. For the construction of 8, epoxy alcohol (7) was targeted as a useful substrate, which corresponds to the biogenetic precursor (2).
As the model experiments to explore the construction route of 8, the allyl alcohol (4, \( R = H \)) was chosen as a starting material which is expected to give the epoxy alcohol (5) by Sharpless epoxidation including asymmetric introduction of the epoxide ring. The examination of the feasibility of TMS as a leaving group is the main purpose for this model experiment.

Geraniol (9, \( R = H \)) was converted to allyl chloride (10, \( R = H \)) in 60% yield by treatment with \( \text{SO}_2\text{Cl}_2 \) in the presence of \( \text{Na}_2\text{CO}_3 \). When the allyl chloride was submitted to the reaction with TMSLi in HMPA, the substitution of Cl with TMS occurred easily to give TMS-alcohols (11 and 12, \( R = H \)), in which the rearranged product (12) predominated in the ratio of 11:12 = 1:2. It was soon found that the ratio of 11 and 12 depended largely on the protection group (R) of the substrate (10). The result for the product ratio is summarized in Table 1. From the result, we adopted the benzoate (10, \( R = \text{Bz} \)) as the substrate, obtainable directly from geranyl benzoate in 90% yield. The benzoate afforded the replacement product (11, \( R = H \)) with concomitant removal of the protecting benzoate group.

Since purification of 11 (\( R = H \)) was not easy by usual methods and also rearrangement of 11 (\( R = H \)) to 12 (\( R = H \)) was observed under acidic conditions, a 6:1 mixture of allyl alcohols (11 and 12, \( R = H \)) was used for the next reactions without purification. The allyl alcohol (11 plus 12, \( R = H \)) was treated with tert-butyl hydroperoxide (TBHP) in the presence of \( \text{VO(acac)}_2 \), at room temperature to give the corresponding epoxides in 60% yield with the ratio of 5:13 = 1:2. The epoxidation apparently accompanied the simultaneous 1,3-TMS shift.

![Chemical structure diagrams]

Table 1. Substitution Reaction of 10 with TMSLi

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate (10)</th>
<th>products and their ratio ( R ) ( 11 + 12 )</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Li</td>
<td>1:2 H</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>K</td>
<td>2:1 H</td>
<td>40(^c)</td>
</tr>
<tr>
<td>3</td>
<td>TMS</td>
<td>3:1 H</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>TES</td>
<td>3:1 TES</td>
<td>60</td>
</tr>
<tr>
<td>5</td>
<td>TBDMS</td>
<td>5:1 TBDMS</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>THP</td>
<td>2:1 THP</td>
<td>75</td>
</tr>
<tr>
<td>7</td>
<td>PMB</td>
<td>4:1 PMB</td>
<td>60</td>
</tr>
<tr>
<td>8</td>
<td>Bz</td>
<td>6:1 H</td>
<td>60(^d)</td>
</tr>
</tbody>
</table>

\(^a\) The reaction with TMSLi was carried out at -75°C.
\(^b\) The ratio was determined by the integration of olefinic protons at \( \delta \) 4.48 and 4.68 (1H each) of 11 and \( \delta \) 4.89 (1H) of 12.
\(^c\) Recovered material (10) was isolated in 50% yield.
\(^d\) When the reaction was carried out at -40°C, a 1:1 mixture of 11 and 12 was obtained in 95% yield.
When the Sharpless epoxidation was carried out with Ti(OPr)$_4$ at -40°C, a 5:1 mixture of 5 and 13 was obtained in 65% yield in addition to the cyclization product (14 = 6) in 8% yield. The cyclization of 5 to 14 proceeded in 40% yield by the action of Ti(OPr)$_4$ at room temperature. Addition of tetrabutylammonium fluoride (TBAF) resulted in the formation of no cyclization product. Improvement of the cyclization conditions has not yet been achieved. Although direct evidence is lacking at present, the epoxide (5) may be formed as a diastereomeric mixture. The low yield of 14 may be due to the concerted cyclization mechanism through the epoxide ring opening with concomitant removal of TMS cation from one diastereomer of 5.

Next, the epoxidation was carried out in the presence of (+)-diethyl tartrate at room temperature to give the diol (14) ([α]$_D$ = -14.1°) in 20% and a 2:1 mixture of epoxides (5 and 13) in 23% yield. The epoxide mixture was converted to the diol (14) by treatment with Lewis acids such as Ti(OPr)$_4$ or Et$_2$AlCl in 38% and 43% yields, respectively. (±)-Diol (14) was converted to MTPA ester (16) by the sequential reactions of etherification of 14 with TBDMS chloride to 15, followed by esterification with (−)-α-methoxy-α-trifluoromethylethylenecarbamic acid (MTPA) and DCC. $^1$H NMR showed the 1:1 signals at 3.49 and 3.59 due to OMe group while the latter signal was minute in the MTPA ester (16) prepared from (−)-14. More than 90% enantiomeric excess of (−)-14 was estimated by the integration of the two signals.

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**EXPERIMENTALS**

All the materials obtained in the present study were oily. Unless otherwise noted, $^1$H NMR and $^{13}$C NMR spectra were recorded on solutions in CDCl$_3$ with SiMe$_4$ as internal standard with JEOL FX 90Q (90 MHz) spectrometer. Chemical shifts are reported in δ-units with δ$_H$ ($^1$H NMR) and δ$_C$ ($^{13}$C NMR), and J-values are in Hz. The MS spectra were measured with Hitachi M-80 and M-80A spectrometers. The IR spectra were measured with Hitachi 270-30 spectrophotometer in solution, showing the reasonable absorption bands for all the compounds. The usual work-up involved dilution of the reaction mixture with water, extraction with ether, washing of the organic extracts with water and brine, followed by drying over Na$_2$SO$_4$, and evaporation at aspirator pressure. Column chromatographic purification was carried out on Kiesel gel 60, Art 7734 (70-230 mesh), the elution solvents being indicated.

**Allyl Chloride (10, R = Bz).** To a suspended mixture of Na$_2$CO$_3$ (41.0 g, 387 mmol) and geranyl benzoate (9, R = Bz) (20 g, 77.4 mmol) in CH$_2$Cl$_2$ (300 mL) was dropped a CH$_2$Cl$_2$ (50 mL) solution of SO$_2$Cl$_2$ (6.5 mL, 81 mmol) at 0°C and the mixture was stirred for 40 min under the same conditions and treated by usual work up. Silica gel column chromatography with hexane-AcOEt 25:1 afforded the chloride (10, R = Bz) (20 g, 90%). δ$_H$ 1.77 (3H, s), 1.80 (3H, s), 4.35 (1H, t, J=6.7 Hz), 4.82 (2H, d, J=7.7 Hz), 4.84...
MTPA Ester of Asymmetric Epoxidation. When saturated NaHCO₃ solution. The usual bath was removed and the mixture was stirred for 20 h at -40°C. The reaction was quenched by adding aq saturated NaHCO₃ solution. The usual mixture was stirred at rt. The reaction was quenched by adding aq saturated NH₄Cl solution. The usual workup and column chromatography with hex-AcOEt 10:1 afforded a 6:1 mixture of TMS-alcohols (11 and 12, R = H). δ H 0.00 (9H, s), 1.63 (6H, s), 4.12 (2H, d, J=7.2 Hz), 4.48 (s) and 4.68 (s) (total 1.8 H), 4.89 (br. s), and 5.38 (1H, t, J=7.2 Hz). EIMS Found: m/z 226. Calcd for C₁₅H₂₀O₄Si: M, 226.

Sharpless Epoxidation of TMS-alcohol (11, R = H). After Ti(O'Pr)₄ (0.11 mL, 0.40 mmol) was added to a CH₂Cl₂ (2 mL) solution of TMS-alcohols (100 mg, 0.44 mmol) (a ca. 6:1 mixture of 11 and 12, R = H) at -40°C and then stirred for 5 min at the same temperature, anhydrous butyl hydroperoxide (TBHP) in 2M solution of dichloroethane (0.66 mL, 1.32 mmol) was gradually added and the mixture was kept for 24 h at -40°C. The reaction was quenched by adding aq saturated NaHCO₃ solution. The usual workup and chromatography with hexane-AcOEt 5:1 afforded a 5:1 mixture of epoxyalcohols (5 and 13) (64 mg, 60%) and a cyclized dl-diol (14) (6 mg, 8%). When the reaction was carried out using 500 mg of TMS-alcohols, 0.55 mL of Ti(O'Pr)₄ (0.98 eq) and 3.30 mL of 2M of TBHP in dichloroethane (3 eq) and the reaction mixture was stirred at rt for 20 h, the cyclized diol (14) was obtained in 20% yield (73 mg) accompanied with epoxy alcohols (5 and 13) (123 mg, 23%). Epoxy alcohols (5:1 mixture of 5 and 13) δ H -0.04 (9H, TMS-H), 1.25 (3H, s), 1.63 (3H, s), 2.96 (1H, dd, J=6.4 and 6.1 Hz), 3.50-4.00 (2H, br), 4.47 (s) and 4.68 (s) (total 1.8 H), and 4.91 (0.2 H, t, J=6.3 Hz). Cyclized dl-diol (14) δ H 0.88 (3H, s), 1.64 (3H, br. s), 3.50 (2H, m), 3.74 (1H, t, J=7.9 Hz) and 5.38 (1H, br. s). δ C 131.7 (s), 120.1 (d), 78.8 (d), 62.9 (t), 39.1 (t), 35.4 (s), 29.6 (t), 24.0 (t), 22.1 (q), and 19.3 (q). HRMS of 14 Found: m/z 170.1330. Calcd for C₁₀H₁₈O₂: M, 170.1307.

Asymmetric Epoxidation. To a CH₂Cl₂ (20 mL) solution of TMS-alcohols (500 mg, 2.20 mmol) (a ca. 5:1 mixture of 11 and 12, R = H) were added Ti(O'Pr)₄ (0.55 mL, 2.00 mmol) and then (+)-diethyl tartrate (0.38 mL, 2.20 mmol) at -40°C and the mixture stirred for 5 min at the same temperature. A 2M solution of butyl hydroperoxide (TBHP) in dichloroethane (3.30 mL, 6.60 mmol) was gradually added. The cooling bath was removed and the mixture was stirred for 20 h at rt. The reaction was quenched by adding aq saturated NaHCO₃ solution. The usual workup afforded the cyclized diol (14) (84 mg, 23%) [α]D₉ -14.1° (c 0.1, MeOH) and a mixture of epoxy alcohols (5 and 13) (107 mg, 20%).

Cyclization of Epoxy alcohol (5). After a mixture of epoxy alcohols (5:1 mixture of 5 and 13) (50 mg, 0.2 mmol) and Ti(O'Pr)₄ (83 μL, 0.28 mmol) was stirred at rt overnight, the reaction mixture was quenched with aq saturated NaHCO₃. The usual workup gave the cyclized product (14) (15 mg, 43%).

When Et₂AlCl was applied at -80°C in CH₂Cl₂, the cyclized product (14) was isolated in 38% yield.

**MTPA Ester of MonoTBDMS Ether of Diol (14).** A mixture of diol (14) (50 mg, 0.30 mmol),
imidazole (33 mg, 0.48 mmol), and butyldimethylsilyl chloride (TBDMSCI) (64 mg, 0.42 mmol) in DMF (5 mL) was stirred for 15 min. Usual workup afforded monoTBDMS ether (15) (78 mg, 92 %) \( \delta_H \) 0.00 (6H, s), 0.91 (9H, s), 0.88 (3H, s), 1.64 (3H, br s), 3.50 (2H, m), 3.74 (1H, br s), and 5.38 (1H, br s).

A mixture of monoTBDMS ether (15) (70 mg, 0.24 mmol), (-)-MTPA (\( \alpha \)-methoxy-\( \alpha \)-trifluoromethylphenylacetic acid) (46.6 \( \mu \)L, 0.26 mmol), DCC (83 mg, 0.40 mmol) and DMAP (9 mg, 0.07 mmol) in toluene (5 mL) was stirred for 5 h. After addition of aq saturated NH\(_4\)Cl solution, the mixture was treated as usual to give MTPA ester (16) (105 mg, 86 %). MTPA ester (16) from \( \pm \) diol (14) \( \delta_H \) (270 MHz) 0.00 (6H, s), 0.79 (3H, s), 0.81 (9H, s), 1.55 (3H, br s), 3.49 (1.5 H, s), 3.59 (1.5 H, s), 3.75 (2H, m), 5.29 (1H, br s), and 7.29-7.69 (5H). MTPA ester (16) from (-) diol (14). \( \delta_H \) (270 MHz) The above signals excepting 3.49 (3H, s) and 3.59 (minute).

REFERENCES
1. This constitutes Part 55 of the series, Cyclization of Polyenes. For Part 54, Scientia Iranica, in press. For Part 53, see Heterocycles, 1996, 43, 601.
3. The synthesis of 7 and 8 will be reported elsewhere. In the cyclization of 7 to 8, non-cyclized product possessing 3-enyl-1,2-diol moiety derived from opening of the epoxide ring was isolated in addition to the cyclization product (8).

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