

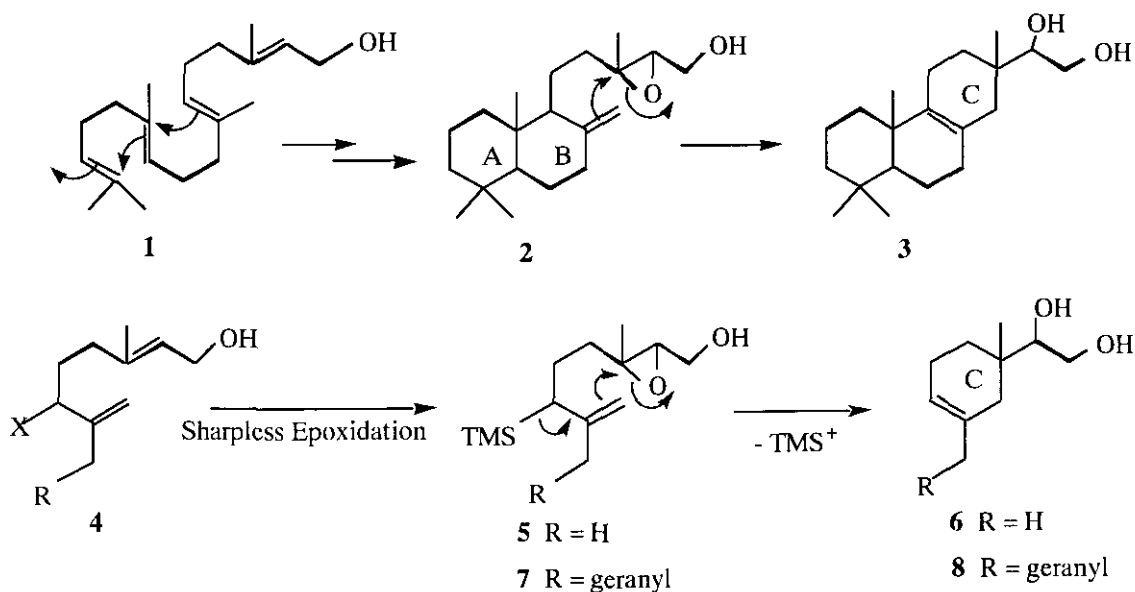
MODEL STUDY FOR THE CONSTRUCTION OF C RING OF PIMARA TYPE DITERPENES¹

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Abstract—As the model experiment to explore the construction route of our synthetic intermediat (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 $\text{Ti}(\text{O}^i\text{Pr})_4$ 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**,³ 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.⁴ The examination of the feasibility of TMS as a leaving group is the main purpose for this model experiment.⁵

Geraniol (**9**, R = H) was converted to allyl chloride (**10**, R = H)⁶ in 60% yield by treatment with SO_2Cl_2 in the presence of Na_2CO_3 . When the allyl chloride was submitted to the reaction with TMSLi in HMPA,⁷ 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 = 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 $\text{VO}(\text{acac})_2$ 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.

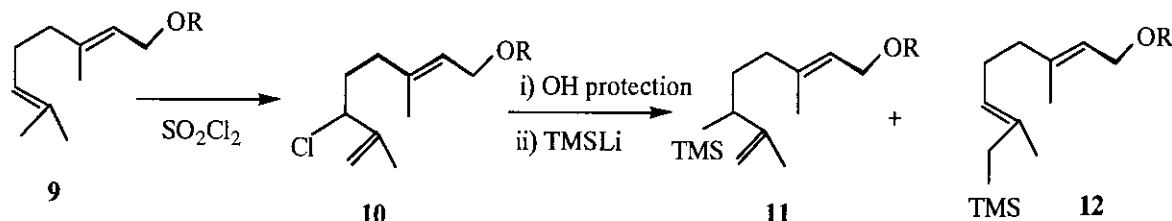


Table 1. Substitution Reaction of **10** with TMSLi ^a

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

a; The reaction with TMSLi was carried out at -75°C .

b; The ratio was determined by the integration of olefinic protons at δ 4.48 and 4.68 (1H each) of **11** and δ 4.89 (1H) of **12**.

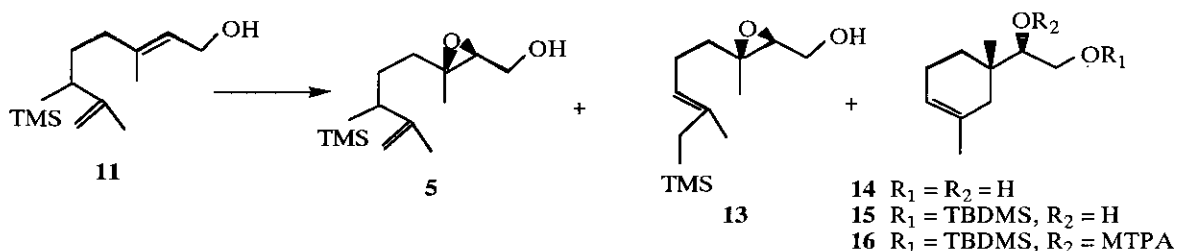
c; Recovered material (**10**) was isolated in 50% yield.

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 $\text{Ti}(\text{O}^i\text{Pr})_4$ 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 $\text{Ti}(\text{O}^i\text{Pr})_4$ at room temperature.⁸ 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**.³

Next, the epoxidation was carried out in the presence of (+)-diethyl tartrate at room temperature to give the diol (**14**) ($[\alpha]_D^{25} -14.1^\circ$) 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 $\text{Ti}(\text{O}^i\text{Pr})_4$ or Et_2AlCl 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 -trifluoromethylphenylacetic acid (MTPA) and DCC. ^1H 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.



EXPERIMENTALS

All the materials obtained in the present study were oily. Unless otherwise noted, ^1H 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} (^1H 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_2SO_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_2CO_3 (41.0 g, 387 mmol) and geranyl benzoate (**9**, R = Bz) (20 g, 77.4 mmol) in CH_2Cl_2 (300 mL) was dropped a CH_2Cl_2 (50 mL) solution of SO_2Cl_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

(1H, s), 5.01 (1H, s), 5.52 (1H, t, $J=7.7$ Hz), and 7.30-8.16 (5H, m). δ_c 16.1 (q), 17.1 (q), 34.5 (t), 36.6 (t), 61.7 (t), 66.1 (d), 114.3 (t), 119.6 (d), 140.6 (s), 144.2 (s) and signals due to benzoate at 128.3 (d), 129.6 (d), 132.8 x 2 (s and d), and 166.5 (s). EIMS Found: m/z 292. Calcd for $C_{17}H_{21}O_2Cl$: M, 292.

Reaction of Allyl Chloride (10, R = Bz) with TMSLi. To an ether solution of TMSLi-HMPA, freshly prepared by adding MeLi (61.2 mmol) in ether (1.4 M, 40.8 mL) to a mixture of hexamethyldisilane (12.48 mL, 61.2 mmol) and hexamethylphosphoramide (HMPA) (40 mL) at -75°C under nitrogen atmosphere and then diluted with ether (100 mL), was gradually dropped an ether solution (30 mL) of allyl chloride (10, R = Bz) (3.0 g, 10.2 mmol) at -75°C under nitrogen atmosphere and the mixture was stirred under the same conditions for 15 min. The reaction mixture was quenched by adding aq saturated NH_4Cl 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, 0.2H) and 5.38 (1H, t, $J=7.2$ Hz). EIMS Found: m/z 226. Calcd for $C_{13}H_{26}OSi$: M, 226.

Sharpless Epoxidation of TMS-alcohol (11, R = H). After $\text{Ti}(\text{O}^i\text{Pr})_4$ (0.11 mL, 0.40 mmol) was added to a CH_2Cl_2 (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 t -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 NaHCO_3 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 $\text{Ti}(\text{O}^i\text{Pr})_4$ (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 $C_{10}H_{18}O_2$: M, 170.1307.

Asymmetric Epoxidation. To a CH_2Cl_2 (20 mL) solution of TMS-alcohols (500 mg, 2.20 mmol) (a ca. 5:1 mixture of 11 and 12, R = H) were added $\text{Ti}(\text{O}^i\text{Pr})_4$ (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 t -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 NaHCO_3 solution. The usual workup afforded the cyclized diol (14) (84 mg, 23%) [α] $_D^{25}$ -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 $\text{Ti}(\text{O}^i\text{Pr})_4$ (83 μL , 0.28 mmol) was stirred at rt overnight, the reaction mixture was quenched with aq saturated NaHCO_3 . The usual workup gave the cyclized product (14) (15 mg, 43 %).

When Et_2AlCl was applied at -80°C in CH_2Cl_2 , 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 *t*-butyldimethylsilyl chloride (TBDMSCl) (64 mg, 0.42 mmol) in DMF (5 mL) was stirred for 15 min. Usual workup afforded monoTBDMMS ether (**15**) (78 mg, 92 %) δ_{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, t, $J=7.9$ Hz), and 5.38 (1H, br). A mixture of monoTBDMMS ether (**15**) (70 mg, 0.24 mmol), (-)-MTPA (α -methoxy- α -trifluoromethylphenylacetic acid) (46.6 μ 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_4Cl solution, the mixture was treated as usual to give MTPA ester (**16**) (105 mg, 86 %). MTPA ester (**16**) from (\pm) diol (**14**) δ_{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**). δ_{H} (270 MHz) The above signals excepting 3.49 (3H, s) and 3.59 (minute).

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