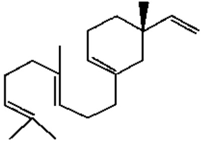
SYNTHESIS OF 6-EPOXYGERANYLGERANIOL AND ITS APPLICATION TO THE CONSTRUCTION OF A/B ACYCLIC PIMARANE TYPE DITERPENE*[1]

Yoshinobu Kashibuchi, Takashi Fukumoto, Minoru Oguchi, Toshifumi Hirukawa, and Tadahiro Kato*

Department of Chemistry, Faculty of Science, Science University of Tokyo,
Kagurazaka 1-3, Shinjuku-ku, Tokyo 162-8601, Japan

Abstract--Synthesis of A/B acyclic pimarane type diterpenes (**1** and **2**) was achieved through the TMS assisted cyclization of epoxy alcohol (**5**), which was prepared by Sharpless asymmetric epoxidation of allyl alcohol (**6**). The convenient preparation of the allyl alcohol (**6**) was explored starting from β-hydroxygeranylgeranioic acid (**7**) through bromo etherification to **8** followed by base treatment to give a mixture of conjugated epoxy esters (**9a** and **b**). The *Z* isomer (**9b**) was transformed to the *E* isomer (**9a**) by the action of ^{t}BuOK.

In the course of our study on pimarane type diterpenes, we needed the preparation of analogous compounds such as **1** and **2**, biogenetically regarded as A/B acyclic precursor of pimarane skeleton (**3**).[2] The pimarane skeleton is known to be biosynthesized by C ring formation from A/B cyclic precursor (**4**). Based on the biogenetical consideration, we set up the epoxy alcohol (**5**) as the direct candidate for our objective. The epoxy alcohol (**5**) may be easily derivable from the corresponding allyl alcohol (**6**) by application of asymmetric Sharpless epoxidation.[3] Assisted by allylic TMS group,[4] the ring formation of **5** under acidic conditions would give rise to the A/B acyclic diol (**2**), from which the hydrocarbon (**1**) may be derived. After completion of the model experiment,[5] we have achieved the preparation of **1** and **2**, the result being described in this paper.



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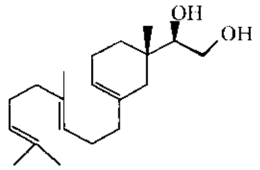

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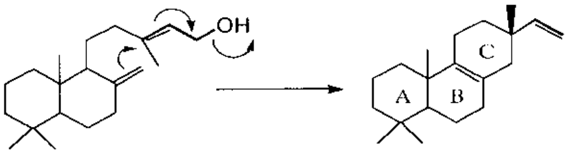

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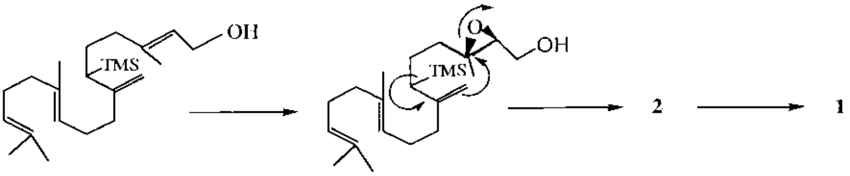

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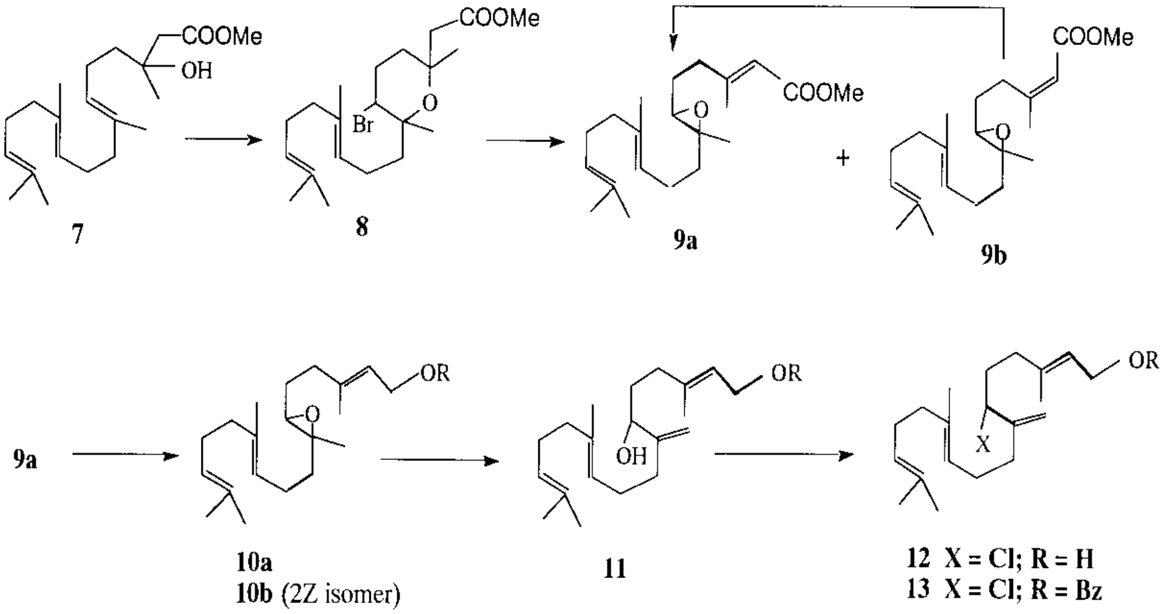
* Dedicated to Professor Bernhard Witkop.

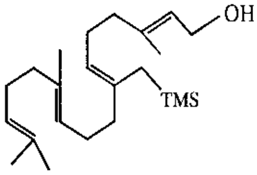
The requisite allyl alcohol (**6**) was synthesized by the sequential reactions depicted in Scheme 1 starting from methyl 3-hydroxy-3,7,11,15-tetramethylhexadeca-6,10,14-trienoate (**7**), which was prepared by the application of Reformatsky reaction to farnesyl acetone. Bromo etherification[6] of hydroxy ester (**7**) with 2,4,4,6-tetrabromocyclohexadienone in MeCN proceeded smoothly, affording a diastereomeric mixture of bromo ether (**8**) in 64% yield. After replacement of bromine with iodine by the action of Bu_4NI in THF, the resulting iodo ether was treated with 2 eq of ^{t}BuOK in THF at -40°C to furnish a 2:1 mixture of *E* and *Z* enoates (**9a**) and (**9b**) in 59% yield. The ratio was estimated by converting the mixture to the corresponding allyl alcohols (**10a**) and (**10b**), easily separated by usual silica gel column chromatography. The selective isomerization of *Z* enoate (**9b**) to *E* isomer (**9a**) was elaborated by revealing that *Z* isomer (**9b**) was effectively converted to the *E* isomer when the 2:1 mixture of *E*/*Z* isomers was treated with 0.1 eq of ^{t}BuOK in THF at room temperature for 1 h. Application of these conditions to the *E*/*Z* mixture provided the *E* allyl alcohol (**10a**, R = H) in 79% yield after reduction of **9a** with DIBALH at -60°C.



Scheme 1 Preparation of allyl chloride (**13**)

After protection of the hydroxyl group of **10a** as its TBDMS ether, the selective opening of the epoxide ring was achieved by treatment with LDA at 0°C, affording allyl alcohol (**11**, R = TBS) in 87% yield. The allyl alcohol (**11**, R = TBS) was converted to allyl chloride (**12**) in 85% yield by successive reactions of replacement of the hydroxyl group with chlorine by NCS and PPh_3 followed by deprotection of TBS group with TBAF in THF. The hydroxyl group of **12** was protected as its benzoate to give the benzoate (**13**), which was treated with TMSLi (6 eq) in the presence of HMPA[7] to provide an unseparable 2:1 mixture of **6** and **14**. Sharpless asymmetric epoxidation[5] of the mixture with $Ti(OiPr)_4$ and TBHP in the presence of (+)-DET afforded a 2:1 mixture of epoxy alcohols (**5** and **15**) in high yield. Without separation, the mixture was submitted to the reaction with Et_2AlCl (3 eq) at -78°C and the objective cyclization product (**2**) was isolated in 38% yield.[8]

The major byproducts of this cyclization consisted of a mixture of **16** and **17** (total 42% yield).
The diol (**2**) was converted to the corresponding thiocarbamate by the action of Im$_2$CS in rerfluxing toluene[9] in 90% yield. The hydrocarbon (**1**) possessing $[\alpha]_D$ +7.8°(c 0.1, MeOH) was obtained from the thiocarbamate by treatment with (MeO)$_3$P in 90% yield. Although enantiomeric excess (%) of **2** and **1** remains undetermined yet, more than 90% ee was suggested from our model experiment.[5]



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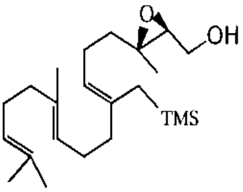

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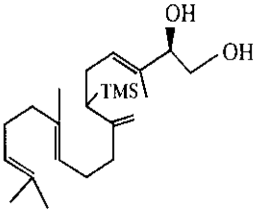

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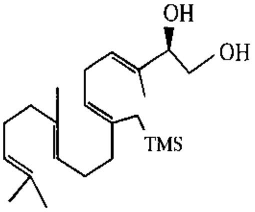

17

EXPERIMENTALS

General. Starting materials and reagents were purchased from commercial suppliers and used without further purification except the followings. The farnesylacetone was kindly provided by Kurarey Co. Ltd., to whom we appreciate. THF and Et$_2$O were distilled over sodium and benzophenone under N$_2$. CH$_2$Cl$_2$ and MeCN were distilled from CaH$_2$ under N$_2$. All oxygen- or moisture-sensitive reactions were carried out under N$_2$ or Ar in oven-dried glassware. Air- or moisture-sensitive liquids were transferred by syringe or cannula and introduced into the reaction flasks through rubber septa. Unless otherwise stated, reactions were stirred with a Teflon-covered stirrer bar and carried out at rt. 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$_4$. Concentration refers to the removal of solvent using rotatory evaporator at 40-100 Torr followed by use of a vacuum pump at approximately 1 Torr. Silica gel column chromatography was performed using Merck brand silica gel 60 A(230-400 Mesh). The term"brine" refers to saturated NaCl. Proton and carbon nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were measured at 90 MHz on a JEOL FX-90A instrument or at 400 MHz on a FX-400 instrument. Chemical shifts are reported in ppm downfield from tetramethylsilane. MS spectral analyses were performed by Hitachi M-80 and M-80A spectrometers at 70 eV.

Reformatsky Reaction of Farnesylacetone. Zn powder was activated as follows. To 100 g of Zn powder (Merck Art. 8789 Zink Pulver <60 m> 95 %) was added 2% aq HCl (300 mL), shaken for 1 min and then filtered by suction. The Zn powder was successively washed with 2% aq HCl (300 mL), water (100 mL x 3), EtOH (200 mL x 2), and then ether (200 mL). The powder was dried under reduced pressure and then warmed at 130°C overnight. To a stirred mixture of pulverized Zn powder (6.5 g, 99.4 mmol), farnesylacetone (20.0 g, 76.2 mmol), B(OMe)$_3$ (200 mL) in dry THF (150 mL) was dropped methyl bromoacetate (9.4 mL, 99.3 mmol) under argon atmosphere at such a rate that the temperature of the reaction mixture was kept below 50°C. After the reaction mixture was kept stirring for 5 h at rt, aq 10% NH$_4$OH was added. The usual work up and SiO$_2$ chromatography with hexane:AcOEt 7:1 afforded an oily hydroxy ester (**7**) (23.6 g, 92%). δ_C 172.7 (s), 135.2 (s), 134.8 (s), 130.8 (s), 124.5 (d), 124.2 (d) x 2, 70.8 (s), 51.1 (q), 45.1 (t), 42.0 (t), 39.7 (t) x 2, 26.8 (t) x 2, 26.8 (q), 25.4 (q), 22.6 (t), 17.5 (q), 15.9 (q) x 2. HRMS (CI) Found: m/z 336.2632. Calcd for $C_{21}H_{36}O_3$ 336.2664.

Bromo etherification of Hydroxy Ester (7). To MeCN (7.5 mL) solution of hydroxy ester (**7**) (300 mg, 0.891 mmol) was added 2,4,4,6-tetrabromocyclohexa-2,5-dienone (390 mg, 0.95 mmol) at 0°C and the mixture was kept for 2 h. After evaporation of MeCN, the residue was passed through an alumina column with hexane:ether 5:1 to remove the resultant tribromophenol. The eluant was chromatographed on SiO_2 column with hexane:AcOEt 15:1 to obtain an oily bromo ether (**8**) (238 mg, 64.3%). δ_H 5.10 (2H, m), 4.01 (1H, m), 3.61 (3H, s), 1.65 (3H, s), 1.59 (6H, s), and 1.2-1.4 (6H).

Epoxy Ester (9a, b). After a mixture of bromo ether (**8**) (600 mg, 1.45 mmol) and tetrabutylammonium iodide (640 mg, 1.74 mmol) in dry THF (25 mL) was stirred at rt overnight, ^{t}BuOK (325 mg, 2.89 mmol) was added at -40°C and the mixture was kept for 24 h at the same temperature. Aq 10% NH_4Cl was added and the mixture was treated by usual workup. An oily 2:1 mixture of epoxy esters (**9a** and **b**) (284 mg, 59%) was obtained after SiO_2 column chromatography with hexane:AcOEt 15:1. δ_H 5.73 (1H, br s), 5.11 (2H, br t), 3.71 (3H, s), 2.72 (1H, t, J = 7.0 Hz), 2.20 (3H, s), 1.69 (3H, s), 1.62 (6H, s), and 1.29 (3H, s). HRMS Found: m/z 334.2497. Calcd for $C_{21}H_{34}O_3$ 334.2508.

Epoxy Alcohols (10a and b). 1.0 M Toluene solution of DIBALH (11.6 mL, 11.3 mmol) was gradually dropped to the mixture of epoxy esters (**9a** and **b**) (1.8 g, 5.4 mmol) in toluene (20 mL) at -60°C. After the mixture was kept stirring for an h, water was added and the mixture was stirred for 30 min. The usual work up and SiO_2 chromatography with hexane:AcOEt 10:1 afforded *Z*-epoxy alcohol (**10b**) (430 mg, 26%) (less polar oil) and *E*-epoxy alcohol (**10a**) (890 mg, 54%, oil), respectively. *E*-Epoxy alcohol (**10a**) δ_H 5.43 (1H, t, J = 7.7 Hz), 5.07 (2H, br t), 4.12 (2H, d, J = 7.7 Hz), 2.68 (1H, t, J = 5.4 Hz), 1.65 (6H, s), 1.59 (6H, s), and 1.23 (3H, s). δ_C 136.7 (s), 134.9 (s), 130.6 (s), 124.3 (d), 123.9 (d), 123.1 (d), 60.3 (d), 58.3 (t), 39.3 (t), 38.3 (t), 35.9 (t), 26.6 (t), 26.2 (t), 23.3 (t), 25.3 (q), 17.3 (q), 16.1 (q), 15.8 (q), and 15.5 (q). *Z*-Epoxy alcohol (**10b**) δ_H 5.43 (1H, t, J = 7.7 Hz), 5.07 (2H, br t), 4.12 (2H, d, J = 7.7 Hz), 2.68 (1H, t, J = 5.4 Hz), 1.65 (6H, s), 1.59 (6H, s), and 1.23 (3H, s). δ_C 137.2 (s), 135.0 (s), 130.7 (s), 125.4 (d), 123.9 (d), 123.1 (d), 62.7 (d), 58.0 (t), 39.3 (t), 38.3 (t), 28.2 (t), 26.7 (t), 26.3 (t), 23.3 (t), 25.4 (q), 22.9 (q), 17.3 (q), 16.3 (q), and 15.6 (q). HRMS Found: **10a** m/z 318.2545; **10b** m/z 318.2529. Calcd for $C_{20}H_{34}O_2$ 318.2559.

Isomerization and Reduction of Epoxy Esters (9a and b). After a 2:1 mixture of **9a** and **b** (12.0 g, 35.9 mmol) and ^{t}BuOK (400 mg, 3.56 mmol) in dry THF (150 mL) was stirred for 1 h, aq 10% NH_4Cl was added and the mixture was extracted with ether. The ether solution was treated by usual work up and the residue (mainly **9a**) was dissolved in dry toluene (150 mL). 1 M Toluene solution of DIBALH (120 mL, 120 mmol) was gradually added to the crude epoxy ester (**9a**) in the stirred toluene solution (300 mL) at -60°C and the stirring was kept for 1 h. The usual work up and SiO_2 chromatography afforded an oily *E*-epoxy alcohol (**10a**) (8.67 g, 79%).

Epoxide Ring Opening of 10a. A mixture of *E*-epoxy alcohol (**10a**) (13 g, 42.4 mmol), imidazol (4.33 g, 63 mmol) and TBDMSCl (7.67 g, 50.9 mmol) in dry DMF (100 mL) was stirred for 1 h at rt. The usual work up and SiO_2 column chromatography with hexane:AcOEt 30:1 afforded an oily TBDMS ether (**10a**, R = TBDMS) (17.8 g, 99%). The TBDMS ether (1.9 g, 4.47 mmol) in dry benzene (4 mL) was added to LDA solution, freshly prepared by adding ^{n}BuLi (1.6 M hexane solution, 8.4 mL, 13.4 mmol) to ^{i}Pr$_2$NH (3.23 mL, 22.4

mmol) in dry benzene (20 mL) at 0°C. The reaction mixture was stirred for 3 h under nitrogen atmosphere. Aq 10% NH_4Cl was added and usual work up, followed by SiO_2 chromatography with hexane : AcOEt 10 : 1 afforded an oily hydroxy TMS ether (**11**) (1.65 g, 87%). δ_H 5.32 (1H, t, J = 6.7 Hz), 5.12 (2H, br m), 5.02 (1H, s), 4.86 (1H, s), 4.16 (2H, d, J = 6.7 Hz), 4.03 (1H, t, J = 6.1 Hz), 1.66 (3H, s), 1.58 (9H, s), 0.89 (9H, s), and 0.04 (6H, s). HRMS Found: m/z 410.2620. Calcd for $C_{26}H_{38}O_2Si$ 410.2641.

Allyl Chloride (12). After a mixture of allyl alcohol (**11**, R = TBDMS,1 g, 2.38 mmol) and PPh_3 (1.89 g, 7.2 mmol) in dry CH_2Cl_2 (50 mL) was stirred for 5 min at rt, NCS (960 mg, 7.18 mmol) was added to the mixture and the mixture was stirred for 30 min. After usual work up, the residue was taken into THF (100 mL) containing TBAF (4.0 mL, 4.0 mmol) and the mixture was kept for 5 h at rt. Usual work up followed by SiO_2 column chromatography with hexane:AcOEt 10:1 gave an oily allyl chloride (**12**) (652 mg, 85%). δ_H 5.45 (1H, t, J = 6.9 Hz), 5.13 (3H, br s), 4.97 (1H, s), 4.35 (1H, t, J = 6.7 Hz), 4.16 (2H, d, J = 6.9 Hz), 1.69 (6H, s), and 1.62 (6H, s). δ_C 148.2 (s), 137.0 (s), 135.3 (s), 130.7 (s), 124.7 (d), 124.2 (d), 123.6 (d), 112.5 (t), 65.3 (d), 58.8 (t), 39.5 (t), 36.4 (t), 34.9 (t) x 2, 31.1 (t), 26.6 (t), 25.3 (q), 17.4 (q), 16.0 (q), and 15.9 (q).

Replacement of Allyl Chloride (12, R = H) with TMS Group. A mixture of allyl chloride (**12**, R = H, 300 mg, 0.923 mmol), pyridine (0.1 mL, 1.24 mmol) and benzoyl chloride (0.14 mL, 1.21 mmol) in CH_2Cl_2 (5 mL) was stirred at rt for 5 h. The usual work up and SiO_2 column chromatography with hexane:AcOEt 30:1 afforded an oily benzoate (**13**) (350 mg, 88%). δ_H 7.3-8.1 (5H), 5.52 (1H, t, J = 6.9 Hz), 5.12 (3H, br s), 4.96 (1H, s), 4.85 (2H, d, J = 6.9 Hz), 4.35 (1H, t, J = 6.7 Hz), 1.78 (3H, s), 1.68 (3H, s), and 1.61 (6H, s). To the benzoate (**13**) (100 mg, 0.233 mmol) in dry ether (3 mL) was gradually added at -90°C a TMSLi solution freshly prepared by adding MeLi (1.4 M ether solution, 1.33 mL,1.86 mmol) to a mixture of hexamethyldisilane (0.38 mL, 1.86 mmol) and HMPA (1.10 mL, 6.32 mmol) at 0°C. After being stirred for 15 min at the same temperature, the reaction mixture was quenched with aq 10% NH_4Cl. The usual work up and SiO_2 column chromatography with hexane:AcOEt 10:1 afforded an oily 2:1 mixture of TMS alcohols (**6** and **14**) (55.5 mg, 66%). The mixture was submitted to the next reaction without separation. TMS alcohols (**6** and **14**) δ_H 5.39 (1H, t, J = 7.4 Hz), 5.12 (total 2.3 H, m), 4.76 and 4.56 (total 1.7 H, each s), 4.14 (2H, d, J = 7.4 Hz), 1.67 (6H, s), 1.60 (6H, s), 0.04 (3H, s), and 0.00 (6H, s).

Sharpless Epoxidation of TMS Alcohols (6 and 14). To a dry CH_2Cl_2 (5 mL) solution of a 2:1 mixture of TMS alcohols (**6** and **14**) (50 mg, 0.14 mmol), $Ti(O^iPr)_4$ (0.04 mL, 0.14 mmol), and (+)-diethyl tartrate (0.024 mL, 0.14 mmol) was gradually dropped 2 M ^tBuOOH in 1,2-dichloroethane (0.90 mL, 1.8 mmol) at - 40°C under nitrogen atmosphere. After being stirred for 15 min at the same temperature, the reaction was quenched with saturated aq $NaHCO_3$ and then extracted with CH_2Cl_2. The usual work up and SiO_2 column chromatography with hexane:AcOEt 5:1 afforded an oily 2:1 mixture of epoxy alcohols (**5** and **15**) (48 mg, 92%). δ_H 5.12 (total 2.3 H, m), 4.76 and 4.56 (total 1.7 H, s), 3.6-3.9 (3 H, m, 1-H_2 and OH), 2.95 (1H, dd, J = 6.1, 6.4 Hz),1.65 (3H, s),1.58 (6H, s),1.26 (3H, s), 0.04 (3H, s), and 0.00 (6H, s).

Cyclization of Epoxy Alcohols (5 and 15). To a CH_2Cl_2 solution (5 mL) of a 2:1 mixture of epoxy alcohols (**5** and **15**) (50 mg, 0.13 mmol) was gradually dropped 0.97 M hexane solution of Et_2AlCl(0.40 mL, 0.39 mmol) at -80°C under nitrogen atmosphere. After being stirred for 15 min at the same temperature, the reaction was quenched by addition of saturated aq $NaHCO_3$ and then extracted with ether. The usual work up and SiO_2 column chromatography with hexane:AcOEt 5:1 afforded the oily cyclized diol (**2**) (17 mg, 38%) and a mixture of an oily allyl alcohols (**16** and **17**) (21 mg, 42%). Cyclized diol (**2**) δ_H 5.37 (1H, m), 5.09 (2H, m), 3.3-3.8 (3H, m), 1.67 (3H, s), 1.59 (6H, s), and 0.85 (3H, s). HRMS Found m/z 306.2550. Calcd for $C_{20}H_{34}O_2$ 306.2559.

Thiocarbamate of Cyclized Diol (2). After a mixture of diol (**2**) (10 mg, 0.033 mmol) and Im_2CS (11.0 mg, 0.065 mmol) in toluene (1.0 mL) was refluxed for 1 h, the mixture was treated by usual work up followed by SiO_2 chromatography with hexane:AcOEt10:1 to give thiocarbamate (10.2 mg , 90%). δ_H 5.44 (1H, m), 5.08 (2H, m), 4.45-4.90 (3H, m), 1.68 (3H, s), 1.60 (6H), 1.42 (2H, s), and 0.94 (3H, s). HRMS Found m/z 348.2100. Calcd for $C_{21}H_{32}O_2S$ 348.2123.

(4S)-2-Homogeranyl-4-methyl-4-vinyl cyclohexene (1). A mixture of thiocarbamate (10 mg, 0.029 mmol) and $P(OCH_3)_3$ (5 mL) was warmed for 4 days at 100°C. After addition of aq 2N KOH (10 mL), the mixture was stirred for 2 h at rt. The usual work up afforded hydrocarbon (**1**) (7 mg, 90%) after SiO_2 column chromatography with hexane. $[\alpha]_D^{24}$ + 7.8°(c 0.1, MeOH); δ_H 5.88 (1H, dd, J = 9.2 and 16.1 Hz), 5.41 (1H, m), 5.16 (2H, m), 5.0 (2H, m), 1.72 (3H, s), 1.63 (6H, s), 1.47 (2H, m), and 1.02 (3H, s). HRMS Found m/z 272.2501. Calcd for $C_{20}H_{32}$ 272.2504.

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Received, 23rd April, 1998