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A STEREOCONTROLLED TOTAL SYNTHESIS OF OPTICALLY ACTIVE (R,R)-PHYTOL

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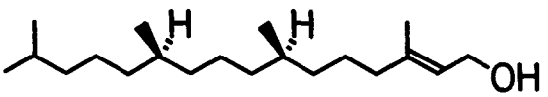
Summary: *A stereospecific synthesis of (R,R)-phytol with highly stereochemical purity in both absolute and geometrical configurations was achieved by utilizing the S_N2 type ring-opening reaction of (R)-β-methyl-β-propiolactone, and the S_N2' type ring-opening reaction of isopropenyl oxirane, from (R)-pulegone as a starting material.*

Phytol (1) occurs abundantly in plants as an alcohol part of the ester side-chain of chlorophyl, and is a useful material for the syntheses of α-tocopherol (vitamin E)[1] and phylloquinone (vitamin K_1).[2] Natural phytol is an acyclic diterpene alcohol possesing an R-configuration at two asymmetric carbons (C_7 and C_{11}) and an E-configuration of the double bond.[3]

In spite of the enormourous literatures on the synthesis of racemic phytol,[4] a few reports have been published on that of optically active phytol.[3,5] We wish to describe here a method for the stereocontrolled synthesis of (R,R)-phytol (1) with highly optical purity *via* (3R,7R)-3,7,11-trimethyldodecanoic acid (2); one asymmetric center at the C_{11} carbon of 1 was derived from easily available (R)-(+) pulegone (4) and the other one at the C_7 carbon was constructed by the S_N2 type ring-opening reaction of (R)-(+)-β-methyl-β-propiolactone (10) with a Grignard reagent in the presence of a copper(I) salt, which proceeds with almost complete inversion.[6] In addition, the geometrical configuration at the prenyl alcohol moiety was controlled by the S_N2' type reaction of isopropenyl oxirane (15) with a Grignard reagent in the presence of a copper(I) salt.[7]

The acyclic isoprenoid synthons of C_{15} unit possessing two chiral centers, such as 2 and 3, are important intermediates for the synthesis of 1. Recently, in connection with the synthesis of α-tocopherol many efforts have been devoted



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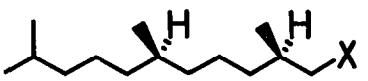


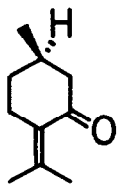
2 X = CO_2H 3 X = CH_2OH

to the synthesis of 2 or 3 from several chiral synthons, prepared by microbiological procedures,[8] classical optical resolution of racemic mixtures,[9] or from naturally occurring chiral compounds.[10] In the present synthesis, one of the key intermediates of C_{11} unit, (R)-4,8-dimethylnonyl bromide (9), easily prepared from 4, was converted to the Grignard reagent (11) which was coupled with the lactone 10 of C_4 unit to afford the C_{15} acid 2 *(vide infra)*.

According to the procedure by Overberger et al.,[10] 4 was converted into optically pure (R)-(+)-citronellic acid (5) in 98% yield; $[\alpha]_D^{23}$ +9.08° (C 3.17, MeOH), lit.[11] $[\alpha]_D$ +9.05° (C 3.2, MeOH). Platinum-catalyzed hydrogenation of 5 and subsequent reduction with lithium aluminum hydride gave (R)-(+)-3,7-dimethyloctanol (6) in 99% yield. Treatment of 6 with hydrogen bromide at 115 °C afforded (R)-(-)-3,7-dimethyloctyl bromide (7) in 99% yield; bp 68∿70 °C/1.5 mmHg; $[\alpha]_D^{23}$ -6.56° (neat). Cyanation of 7[12] and subsequent alkaline hydrolysis furnished (R)-(-)-4,8-dimethylnonanoic acid (8) in 82% yield; bp 120 °C/2 mmHg; $[\alpha]_D^{23}$ -0.59° (neat). Reduction of 8 with lithium aluminum hydride followed by bromination with hydrogen bromide gave (R)-(-)-4,8-dimethylnonanoyl bromide (9) in 92% yield; bp 75∿80 °C/1 mmHg; $[\alpha]_D^{23}$ -2.55° (neat). Thus, the chiral synthon of C_{11} unit, which possesses one asymmetric carbon corresponding to the C_{11} carbon of 1, was obtained in an overall yield of 72% from 4.

The chiral C_4 unit (R)-lactone 10, which involves the C_7 asymmetric carbon of 1, was easily obtained from optically pure (S)-(+)-3-bromobutyric acid ($[M]_{546}^{24}$ +116.2° (0.168 M, 2M $HClO_4$), lit.[13] $[M]_{546}^{25}$ +116.5° (0.163 M, 2M $HClO_4$)), in a yield of 71%; $[\alpha]_D^{24}$ +26.8° (C 5.0, $CHCl_3$).[6,14]

Synthesis of the key intermediate 2 was easily achieved by the S_N2 type ring-opening reaction of the lactone 10 with the Grignard reagent 11, prepared from 9 in 95% yield, in the presence of a copper(I) salt. Thus, when 11 was added to a mixture of 10 and copper(I) iodide (2 mol%) in THF-Me_2S (20:1) at -20 °C and the reaction mixture was allowed to warm to room temperature for 2.5 h, 2 was



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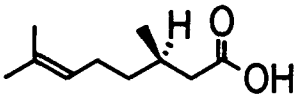

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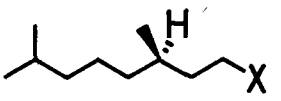
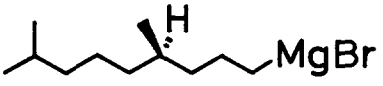


6 X = OH 8 X = CO_2H

7 X = Br 9 X = CH_2Br

10

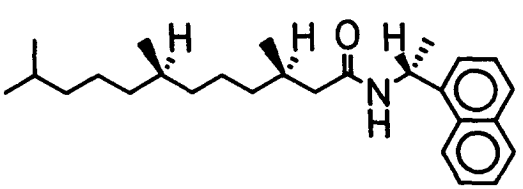


11

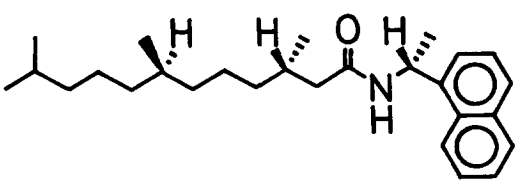
obtained in 90% yield; bp 180 °C (bath temp.)/1 mmHg; $[\alpha]_D^{24}$ +5.46° (C 5.0, $CHCl_3$), lit.[15] $[\alpha]_D$ +5.43° (C 5.0, $CHCl_3$). The specific rotation indicated high optical purity of 2, and the enantiomeric purity of the asymmetric C_3 carbon was determined by TLC analysis of the diastereomeric amide (12), prepared from the acyl chloride of 2 and (R)-(+)-α-(1-naphthyl)ethylamine. Separation of 12 by silica gel TLC (C_6H_6:AcOEt = 8:1) gave two components in a ratio of 96:4, corresponding to the (3R,7R)- and (3S,7R)-amides,respectively. Thus, the configuration of the β-carbon of (S)-3-bromobutyric acid was transformed into 2 with net retention of 96% through the two step inversion (cyclization to 10 and the ring-opening reaction of 10). Since the transformation of 4 to 2 seemed to proceed without racemization, the enantiomeric purity of the asymmetric C_3 and C_7 carbon of 2 could be determined to be 96% and 100% R, respectively.

Stereoselective introduction of a prenyl alcohol moiety with an E-configuration was readily achieved by a copper-catalyzed S_N2' type reaction of Grignard reagent with the oxirane 15.[7,16] The acid 2 upon reduction with lithium aluminum hydride gave the alcohol 3, followed by the treatment with hydrogen bromide to afford the corresponding bromide 13 in 87% yield; bp 132 °C/0.5 mmHg; $[\alpha]_D^{24}$ -4.44° (C 5.0, $CHCl_3$). The Grignard reagent (14), prepared from 13 and magnesium by refluxing in THF in 76% yield, was added to a solution of 15 and copper(I) iodide (5 mol%) in THF-Me_2S (20:1) at -20 °C. After the reaction mixture was allowed to warm to 0 °C for 2 h, phytol (1) was obtained in 95% yield in a ratio of E to Z as 97:3.[17]

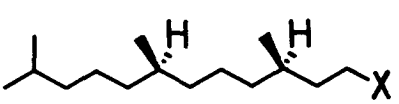
As mentioned above, the synthesis of (R,R)-phytol with highly stereochemical purity with regard to both absolute and geometrical configurations could be achieved by utilizing both copper(I) catalyzed Grignard reactions; the S_N2 type ring-opening reaction of (R)-β-methyl-β-propiolactone and the stereoselective S_N2' type one of isopropenyl oxirane.



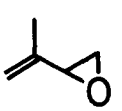
(3R,7R)-12



(3S,7R)-12



13 X = Br 14 X = MgBr



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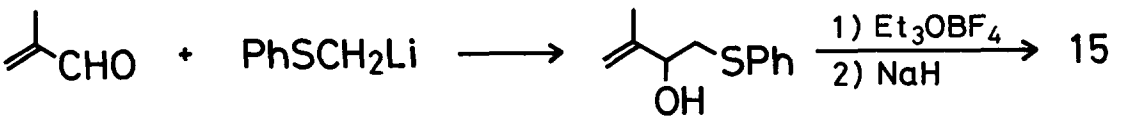
16. Although the oxirane 15 is a useful reagent, there are a few reports on the preparative method.[7,18] It was prepared by the modified procedure of Shanklin et al.[19] 3-Methyl-1-phenylthio-3-buten-2-ol, prepared from methacrylaldehyde and phenylthiomethyllithium, was treated with Et_3OBF_4 in CH_2Cl_2 at room



temperature for 12 h. The solvent was exchanged by diglyme, and then a solution of the sulfonium salt was added to a suspension of NaH in diglyme at 0 °C under vacuum (0.5~1 mmHg). The produced oxirane was collected in a trap cooled by liquid N_2, and distillation afforded pure 15 in 29% yield; bp 84 °C.
17. The ratio of E:Z was determined by capillary glpc analysis (F.F.A.P. 50 m) of phytyl acetate, prepared from 1 and acetic anhydride in pyridine.
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