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ASYMMETRIC SYNTHESES OF (5R,6R)-AEGINETOLIDE AND (5R)-DIHYDROACTINIDIOLIDE FROM (R)-2-HYDROXY-2-METHYLCYCLOHEXANONE

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 C_{11} -Cyclic terpenes, (5R, 6R) - (-)-aeginetolide and (5R) - (-)dihydroactinidiolide have been synthesized stereoselectively starting from (R)-2-hydroxy-2-methylcyclohexanone in short steps.

Dihydroactinidiolide (1) is a C_{11} -cyclic terpene isolated from an essential oil in the leaves of Actinidia polygama, 1) and is also a volatile constituent contained in the leaves of various tea²⁾ and tobaccoes.³⁾ The biological activities show the effects toward Felidae animals¹⁾ and recovery action of respiratory depression⁴⁾ and the growth inhibitor of seed germination.⁵⁾ A cyclic terpene, aeginetolide (2) with an analogous structure to ${f l}$ has been isolated from Aeginetia indica Linn.⁶⁾ Its biological effect has not been reported. Many reports have been concerned with the preparation of dihydroactinidiolide (1) in racemic form⁽⁾ because of its useful biological effects. Only a few papers have been reported on the synthesis of optically active one by the oxidation of carotenoids^{8a,b} and by the asymmetric synthesis starting from (R)-2,2,6-trimethyl-1,4-cyclohexanedione in rather long steps.^{8c)} We now wish to describe asymmetric total syntheses of (5R)-(-)-dihydroactinidiolide (1) and (5R,6R)-(-)-aeginetolide (2) in short steps from (R)-2-hydroxy-2-methylcyclohexanone (4); $[\alpha]_{2}^{2^{2}}$ +100.5° (c 1.34, CHCl₃), which is easily obtained in a high optical purity of 95% ee by the asymmetric synthesis of α-hydroxycycloalkanones from 2-((S)-2-methoxymethylpyrrolidino)-2cyclohexen-1-one (3) and methylmagnesium bromide developed recently in our laboratory.⁹⁾

The introduction of two methyl groups at α -position of carbonyl function in 4 was accomplished after protection of the free hydroxy function with trimethylsilyl group. Although the general method of silylation with trimethylsilylchloride under basic conditions gave poor results, treatment of 4 with 2-trimethylsilyloxy-2-penten-4-one, the silylating reagent under neutral conditions developed by Mitscher et al.,¹⁰⁾ at room temperature overnight gave the corresponding α -silyloxy ketone (5) in 86% yield after distillation, bp50 80 °C (bath temperature), $[\alpha]_{2}^{2}$ -21.9° (c 0.725, CHCl₃). The dimethylation¹¹⁾ of 5 was achieved by adding a mixture



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of 5, methyl iodide and a catalytic amount of 4 in THF into a suspension of potassium hydride in THF at room temperature, followed by stirring for 10 min. The crude 6 was deprotected with citric acid in methanol at room temperature to afford (R)-2-hydroxy-2,6,6-trimethylcyclohexanone (7) in 44% yield from 5: $[\alpha]_{\beta}^{2^2}$ +16.7° (c 0.719, CHCl₃).

The conversion of 7 to 2 and 1 was achieved by the reported procedure $^{7b)}$ in the synthesis of racemic 1. Treatment of 7 with acetic anhydride in the presence of a catalytic amount of N,N-dimethylaminopyridine using triethylamine as a solvent gave the corresponding α -acetoxyketone (8) in 81% yield; bp₁₃ 100 °C (bath temperature), $[\alpha]_{B}^{2}$ +32.9° (c 0.584, CHCl₃). The cyclization of 8 with lithium diisopropylamide at -78 °C gave the γ -lactone, (5R,6R)-(-)-aeginetolide (2) in 70% yield, $[\alpha]_{D}^{22}$ -69.5° (c 0.210, CHCl₃), mp 162 - 164 °C; ¹H-NMR (CDCl₃) δ 0.98 (S, 3H), 1.04 (S, 3H), 1.49 (broad S, 9H), 2.31 (broad S, 1H), 2.33 (d, 1H, J = 18 Hz), 2.95 (d, 1H, J = 18 Hz). The treatment of 2 with thionyl chloride and pyridine at room temperature gave the unsaturated lactone 1 in 95% yield, $[\alpha]_{1}^{2}$ -100.7° (c 0.366, CHCl₃) [lit^{8c)} [α]_D -119.9° (c l%, CHCl₃), lit^{8a)} [α]_D -86.3° (CHCl₃)], mp 54 - 57 °C (lit^{8c)} mp 69 - 71 °C); ¹H-NMR (CDCl₃) δ l.12 (S, 3H), 1.26 (S, 3H), 1.33 - 2.43 (m. 9H), 5.60 (S, 1H). Recrystallization from ether-hexane (1 : 4) afforded optically pure 1; $[\alpha]_{\beta}^{2}$ -119.7° (c 0.142, CHCl₃), mp 68 - 69 °C.

Thus total asymmetric syntheses of (5R)-dihydroactinidiolide and (5R,6R)aeginetolide with high optical purity were achieved in short steps from (R)-2hydroxy-2-methylcyclohexanone obtained easily from optically active 1,2-cyclohexanedione enamine and methylmagnesium bromide.¹²⁾

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