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

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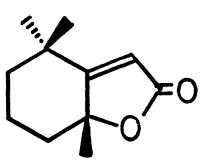
C_{11}-Cyclic terpenes, (5R,6R)-(-)-aeginetolide and (5R)-(-)-dihydroactinidiolide have been synthesized stereoselectively starting from (R)-2-hydroxy-2-methylcyclohexanone in short steps.

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 tea[2] and tobaccoes.[3] The biological activities show the effects toward Felidae animals[1] and recovery action of respiratory depression[4] and the growth inhibitor of seed germination.[5] A cyclic terpene, aeginetolide (2) with an analogous structure to 1 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[7] 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); $[\alpha]_D^{22}$ +100.5° (c 1.34, $CHCl_3$), which is easily obtained in a high optical purity of 95% ee by the asymmetric synthesis of α-hydroxycycloalkanones from 2-((S)-2-methoxymethylpyrrolidino)-2-cyclohexen-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, bp_{50} 80 °C (bath temperature), $[\alpha]_D^{22}$ -21.9° (c 0.725, $CHCl_3$). The dimethylation[11] of 5 was achieved by adding a mixture



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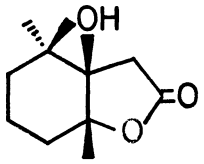

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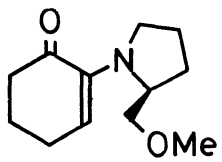

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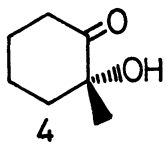

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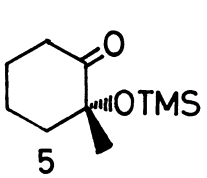

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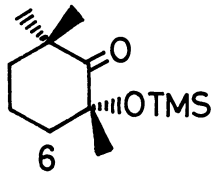

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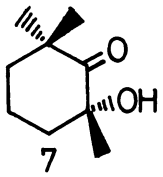

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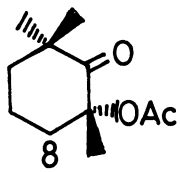

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of 5, methyl iodide and a catalytic amount of 4 in THF into a suspension of potassium hydride in THF at room temperature, followed by stirring for 10 min. The crude 6 was deprotected with citric acid in methanol at room temperature to afford (R)-2-hydroxy-2,6,6-trimethylcyclohexanone (7) in 44% yield from 5: $[\alpha]_D^{22}$ +16.7° (c 0.719, $CHCl_3$).

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; bp_{13} 100 °C (bath temperature), $[\alpha]_D^{22}$ +32.9° (c 0.584, $CHCl_3$). 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, $CHCl_3$), mp 162 - 164 °C; ^{1}H-NMR ($CDCl_3$) δ0.98 (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, $[\alpha]_D^{22}$ -100.7° (c 0.366, $CHCl_3$) [lit[8c] $[\alpha]_D$ -119.9° (c 1%, $CHCl_3$), lit[8a] $[\alpha]_D$ -86.3° ($CHCl_3$)], mp 54 - 57 °C (lit[8c] mp 69 - 71 °C); ^{1}H-NMR ($CDCl_3$) δ1.12 (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; $[\alpha]_D^{22}$ -119.7° (c 0.142, $CHCl_3$), 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)-2-hydroxy-2-methylcyclohexanone obtained easily from optically active 1,2-cyclohexanedione enamine and methylmagnesium bromide.[12]

References

1) T. Sakan, S. Isoe, and S. B. Hyeon, *Tetrahedron Lett.*, 1967, 1623.
2) M. Kawakami and T. Yamanishi, *Agric. Biol. Chem.*, 47, 2077 (1983).
3) H. Kaneko and K. Ijichi, *Agric. Biol. Chem.*, 32, 1337 (1968).
4) J. N. Schumacher, *U. S. Patent* , 3 576 008; *Chem Abstr.*, 75, 77083 (1971).
5) K. L. Stevens and G. B. Merrill, *Experientia*, 37, 1133 (1981).
6) S. S. Dighe and A. B. Kulkarni, *Indian J. Chem.*, 12, 413 (1974).
7) For recent example; a) T. K. Chakraborty and S. Chandrasekaran, *Tetrahedron Lett.*, 25, 2895 (1984); b) G. M. Rubottom and H. D. Juve, Jr., *J. Org. Chem.*, 48, 422 (1983), and references cited therein.
8) a) S. Isoe, S. B. Hyeon, S. Katsumura, and T. Sakan, *Tetrahedron lett.*, 1972, 2517; b) W. Eschenmoser, P. Uebelhart, and C. H. Eugster, *Helv. Chim. Acta*, 65, 353 (1982); c) F. Kienzle, H. Mayer, R. E. Minder, and H. Thommen, *ibid.*, 61, 2616 (1978).
9) T. Fujisawa, M. Watanabe, and T. Sato, *Chem. Lett.*, 1984, 2055.
10) T. Veysoglu and L. A. Mitscher, *Tetrahedron Lett.*, 22, 1303 (1981).
11) A. A. Millard and M. W. Rathke, *J. Org. Chem.*, 43, 1834 (1978).
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