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SYNTHESIS OF (±)-COSTUNOLIDE, AN ANTITUMOR GERMACRANOLIDE, FROM E,E-FARNESOL BY USE OF A LOW-VALENT CHROMIUM REAGENT

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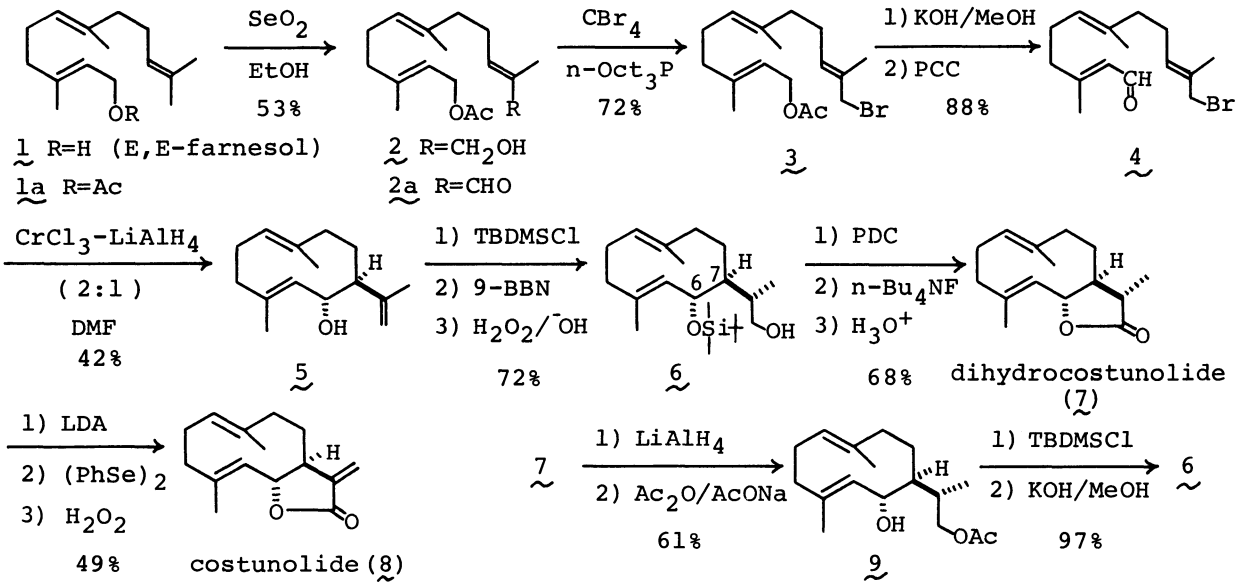
E,E-Farnesol was transformed into ω-bromo-farnesal, which cyclized to afford a racemic germacrane-type compound (5) with a low-valent chromium reagent. 5 was then converted to (±)-dihydrocostunolide and (±)-costunolide.

Costunolide (8)[1] has been known as an antitumor germacranolide and was an attractive target in several synthetic studies. Grieco and Nishizawa synthesized 8 from α-santonin,[2] which was also a starting material in the synthesis of dihydrocostunolide (7) accomplished by Corey and Hortmann.[3] As one of our chemical transformation studies starting with readily available terpenoids,[4] we have synthesized (±)-costunolide (8) from E,E-farnesol (1). In this synthesis, a low-valent chromium reagent[5] has been successfully employed in construction of the germacrane-skeleton from a linear precursor.[6]

Selenium dioxide (1 mol equiv.) treatment of E,E-farnesyl acetate (1a) in 95% ethanol, which was prepared by acetylation of E,E-farnesol (1), afforded ω-hydroxy-farnesyl acetate (2) in 53% yield with a 31% recovery of 1a. The E geometry of the ω-hydroxyl function was ascertained by consideration of the reaction mechanism of selenium dioxide oxidation[7] and furthermore by ^{1}H NMR analysis of an ω-aldehydic derivative (2a) ($\delta_{\underline{CH}O}$ 9.39[8]) prepared by manganese dioxide oxidation of 2. Treatment of ω-hydroxy-farnesyl acetate (2) with carbon tetrabromide and trioctyl phosphine in ether[9] provided ω-bromo-farnesyl acetate (3) in 72% yield. Alkaline hydrolysis (0.1% KOH-MeOH, 0 °C) of 3 followed by oxidation (PCC-AcONa in CH_2Cl_2) yielded ω-bromo-farnesal (4) in 88% yield.

Intramolecular C-C bond formation of ω-bromo-farnesal (4) by employing a low-valent chromium reagent[5] was examined under a variety of conditions and it was found that treatment of 4 with $CrCl_3$-$LiAlH_4$ (2:1)(4 mol equiv.) in N,N-dimethylformamide at room temperature provided the desired germacrane-type compound (5, racemic)[10] in 42% yield. Silylation of 5 (racemic) with *t*-butyldimethylsilyl chloride (TBDMSCl) and subsequent stereoselective hydroboration-oxidation with 9-borabicyclo[3.3.1]nonane (9-BBN) and alkaline hydrogen peroxide oxidation furnished a diol-monosilyl ether (6, racemic). The relative configurations at C-6, C-7, and C-11 of 6 were substantiated by the following conversion. Thus, dihydrocostunolide (7), which was prepared from costunolide (8) by the known proce-



dure,[1] was subjected to $LiAlH_4$ reduction and subsequent acetylation (Ac_2O-AcONa in tetrahydrofuran) to afford a diol-monoacetate (9). Silylation of 9 (TBDMSCl) followed by alkaline hydrolysis (1% KOH-MeOH, r.t.) furnished 6, $[\alpha]_D$ +73° ($CHCl_3$), which was found to be identical with above-mentioned 6 (racemic) in IR, ^1H NMR, and MS comparisons.

Pyridinium dichromate (PDC) oxidation of 6 (racemic) followed by desilylation (tetrabutylammonium fluoride) and subsequent lactonization (aq. HCl) provided (±)-dihydrocostunolide (7) in 68% yield. Finally, treatment of 7 (racemic) with lithium diisopropylamide (LDA) and diphenyl diselenide and subsequent treatment with hydrogen peroxide furnished (±)-costunolide (8), which was identified with authentic costunolide (8) in IR, GLC, and ^1H NMR comparisons.

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10) 5: colorless oil, m/z 220 (M^+). IR (CCl_4, cm^{-1}): 3650, 1640, 900. δ($CDCl_3$): 1.42, 1.68, 1.78 (3H each, all br s, CH_3 x 3), 4.10 (1H, t, J=10 Hz. 6-H), 4.5-5.0 (2H, m, 1-H, 5-H), 4.90 (2H, br s, 12-H_2).

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