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A CONVENIENT SYNTHESIS OF GEIPARVARIN

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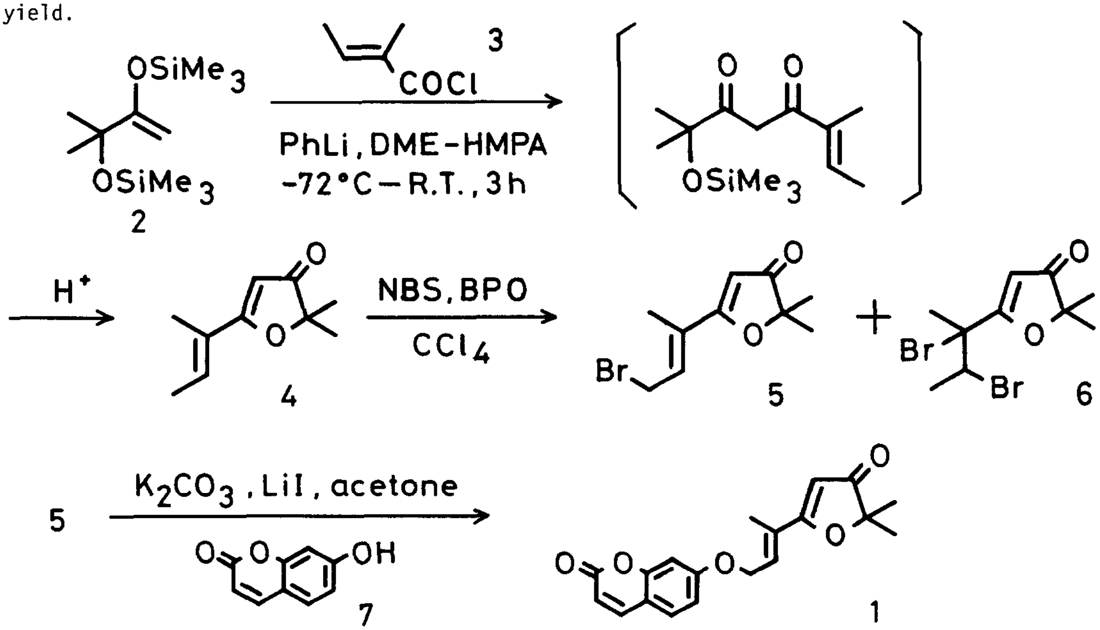
Abstract: Acylation of 3-methyl-2,3-bis(trimethylsiloxy)-1-butene (PhLi) with (E)-2-methyl-2-butenoyl chloride gives the corresponding 3(2H)-furanone derivative, which can be readily converted to the naturally occurring antitumor agent Geiparvarin by two steps.

Recently, considerable attention has been attracted to the synthesis of Geiparvarin (1),[1a-d] a constituent of *Geijera parviflora* Lindl,[2a-c] because of its unique structure jointing 3(2H)-furanone and cumarin skeletons as well as biological activity against *in vitro* human carcinoma of the nasopharynx.[1a,3] The synthetic methods of 1 reported so far[1a-d] involve a multitude of steps before the construction of 3(2H)-furanone skeleton. Moreover, two of the methods[1a,d] suffer from the formation of E/Z olefinic mixture. We report here a novel and more simplified (three steps) synthetic route to 1 by application of one-pot construction of 2,2-dimethyl-5-(1-methyl-1-propenyl)-3(2H)-furanone (4) from readily available starting materials such as 3-methyl-2,3-bis(trimethylsiloxy)-1-butene (2)[4] and (E)-2-methyl-2-butenoyl chloride (3). Selective bromination of 4 and the combination with 7-hydroxycumarin (7) successfully led to 1 in good yield.



To a cooled (-72°C) solution of the silyl enol-ether (2)[4] (4.21 g, 15 mmol) in DME (40 ml)-HMPA (2.5 ml) was added 16 ml of 1.2 M ether solution of phenyllithium[5] (19.2 mmol). After being stirred for 1 h, the acyl chloride (3) (1.43 g, 12.1 mmol) was added dropwise at -72°C. The cooling bath was removed and then the mixture was stirred for 3 h allowing to warm to room temperature gradually. The resulting mixture was acidified with 10% HCl and stirring was continued for additional 1 h. Workup in a usual manner gave oily product, which was purified by column chromatography on silica gel (hexane-ether 15:1) to give the 3(2H)-furanone (4)[6,7] (mp. 47-48°C, hexane) in 63% yield.

Treatment of 4 with N-bromosuccinimide (1.3 equiv.) and benzoyl peroxide (0.039 equiv.) in CCl_4 under reflux temperature afforded the desired bromide (5)[8] (76% yield) as a principal product together with dibrominated product (6)[9] (18% yield). Each compound was isolated by column chromatography (hexane-ether 12:1). Other product which was brominated at C-1 methyl group in the olefinic side chain was not detected despite careful separation.

Finally, the bromide (5) was allowed to react with 7 (2.6 equiv.) in the presence of K_2CO_3 (1.46 equiv.) and LiI (0.75 equiv.) in acetone under reflux for 16 h to give 1 in 70% yield after one purification by TLC (CH_2Cl_2-ether 4:1). The yield was increased up to 80% by using KI and 18-crown-6 (0.06 equiv.). Recrystallization from methanol afforded pure sample of 1 (mp. 159-160°C, lit.[1a] 160-161°C), whose IR and ^1H NMR spectral data are identical with those reported in the literature.[1a]

References and Notes

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6. E/Z olefinic mixture of 4: see reference 1a.
7. The $TiCl_4$ catalyzed reaction of 2 with 3 in CH_2Cl_2 (0°C, 1 h) also gave 4 in 34% yield, while the similar reaction of 2 with (E)-2-methyl-2-butenoic anhydride afforded 4 in 50% yield.
8. Mp. 74-75°C (hexane-ether 10:1); IR (KBr) 1694 and 1631 cm^{-1}; ^1H NMR (CCl_4) δ 1.35 (s, 6H), 1.99 (d, 3 H, J=1 Hz), 4.04 (d, 2 H, J=8 Hz), 5.50 (s, 1 H), 6.69 (dt, 1 H, J=8 and 1 Hz).
9. Mp. 76.5-78°C (hexane); IR (KBr) 1703 and 1587 cm^{-1}; ^1H NMR (CCl_4) δ 1.39 (s, 6 H), 1.96 (d, 3 H, J=7 Hz), 2.07 (s, 3 H), 4.81 (q, 1 H, J=7 Hz), 5.56 (s, 1 H).

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