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A SIMPLE TOTAL SYNTHESIS OF (±)-ASCOFURANONE

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Abstract: A simple, efficient total synthesis of (±)-ascofuranone is described.

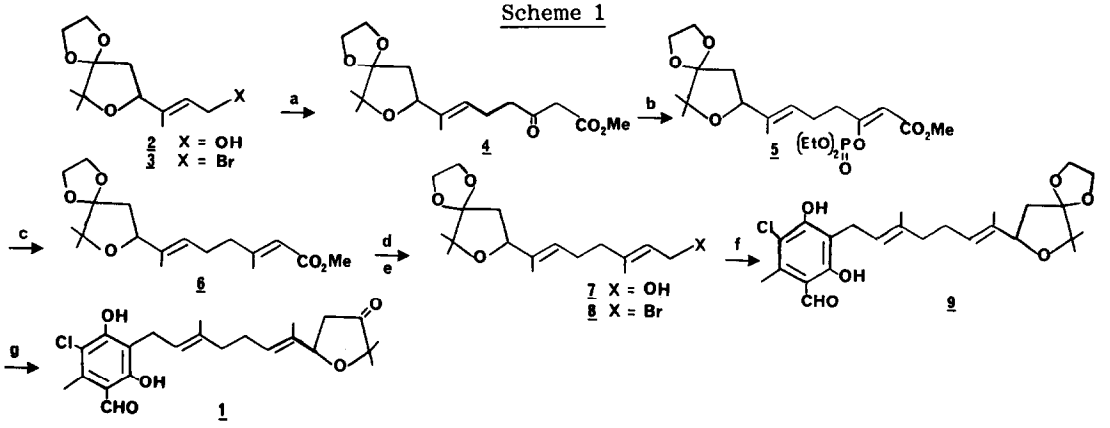
The fungal metabolite ascofuranone (1) was first isolated from the culture filtrate of the pathogenic fungus Ascochyta viciae Libert.[1,2] Compound 1 is an important hypolipidemic agent[2] that is reported to be superior to clofibrate, a widely used hypolipidemic agent. Clofibrate causes atrophy of the spleen and heart while 1 does not produce these symptoms. The acute toxicity of 1 compares very favorably with that of clofibrate.[3] Ascofuranone reduces both serum lipid and also hepatic and cardiac cholesterol content.

The structure of 1 has been confirmed by X-ray analysis[4] and its synthesis has been reported recently.[5]

Our continued interest in fungal metabolites and functionalized furanones led us to devise a simple, efficient route to 1 from an allylic alcohol (2) previously prepared by us in connection with the synthesis of the antitumor agent geiparvarin.[6] Introduction of the second double bond with E geometry was accomplished by a method developed by Weiler.[7,8] A strategy that eliminates protection and deprotection protocols was used in the synthesis of Colletochlorin D.[9] The same methodology was employed to attach the prenylated chain to the 5-chloroorsellinaldehyde.

Allylic alcohol 2 was treated with carbon tetrabromide and triphenylphosphine to afford bromide 3 in quantitative yield. Reaction of 3 with the dianion of methyl acetoacetate[7] gave keto ester 4[10] in 86% yield. The β-keto ester (4) was then converted into the corresponding enol phosphate 5 (90% yield) by treatment with sodium hydride in THF, followed by addition of diethyl chlorophosphate. Subsequent reaction of 5 with lithium dimethylcuprate in ether afforded diene 6[11] with the desired E geometry in 85% yield and > 95% stereoselectivity. Reduction of the ester group of 6 with DIBAL at -78°C gave the corresponding alcohol (7) in 96% yield. Treatment of this alcohol with carbon tetrabromide and triphenylphosphine at -78°C afforded the prenylated bromide (8) in 94% yield. Coupling of 8 with 5-chloroorsellinaldehyde using potassium hydroxide in dilute solution at 0°C gave the protected ascofuranone (9)[12] which was subsequently deprotected with aqueous acetic acid to yield (±)-ascofuranone.[13] The synthetic product was identical with the natural product in all respects (TLC, IR, NMR, MS).

Scheme 1



a: methyl acetoacetate, NaH, n-BuLi, 0°C; b: NaH, $(EtO)_2POCl$; c: $LiCuMe_2$, -78°C to -47°C; d: DIBAL, CH_2Cl_2, -78°C; e: CBr_4, PPh_3, -78°C; f: 5-chloroorsellinaldehyde, KOH, H_2O, 0°C; g: HOAc, H_2O.

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10. 4, IR (neat) 1760, 1730, 1665, 1645, ^1H NMR δ 1.21, 1.23 (2s, 6H), 1.62 (s, 3H), 2.03 (m, 2H), 2.31 (m, 2H), 2.58 (m, 2H), 3.44 (s, 2H), 3.73 (s, 3H), 3.94 (m, 4H), 4.36 (dd, 1H), 5.45 (t, 1H, J=7.1); MS (HR) M^+ Calcd. 326.1780, Found 326.1722.
11. 6, IR (neat) 2990, 2972, 2890, 1720, 1650, 1432, 1380, 1360, 1220, 1150, 1110, 1090, 1060, 1030; ^1H NMR δ 1.21, 1.23 (2s, 6H), 1.62 (s, 3H), 2.04 (m, 2H), 2.16 (d, 3H, J=1.1), 2.18 (m, 4H), 3.68 (s, 3H), 3.95 (m, 4H), 4.37 (t, 1H), 5.45 (m, 1H), 5.66 (s, 1H); MS (HR) M^+ Calcd. 324.1937, Found 324.1931.
12. 9, IR ($CHCl_3$) 3503, 2995, 2925, 2880, 1630, 1460, 1420, 1370, 1280, 1250, 1140, 1105, 1020, 905; ^1H NMR δ 1.21, 1.20 (2s, 6H), 1.58 (s, 3H), 1.77 (s, 3H), 2.00 (m, 2H), 2.15 (m, 4H), 2.6 (s, 3H), 3.38 (d, 2H, J=7), 3.94 (m, 4H), 4.34 (t, 1H), 5.2 (t, 1H), 5.4 (t, 1H), 6.53 (s, 1H), 10.13 (s, 1H), 12.68 (s, 1H).
13. 1, IR ($CHCl_3$) 3505, 2998, 2960, 2916, 2850, 1750, 1630, 1450, 1410, 1365, 1280, 1240, 1165, 1100; ^1H NMR δ 1.22, 1.28 (2s, 6H), 1.628 (s, 3H), 1.786 (s, 3H), 2.01-2.09 (m, 2H), 2.2-2.1 (m, 2H), 2.34 (dd, 1H, J=9.5, J=18.15), 2.43 (dd, 1H, J=6.8, J=18.15) 2.6 (s, 3H), 3.38 (d, 2H, J=7.1), 4.54 (dd, 1H, J=6.8, J=9.5), 5.2 (t, 1H, J=7.2), 5.5 (t, 1H, J=6.9), 6.44 (s, 1H), 10.14 (s, 1H), 12.7 (s, 1H); MS (HR) M^+ Calcd. 420.1703, Found 420.1707, M^+: M^++2=2.85:1.

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