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SYNTHESIS OF (±)-ASCOCHLORIN, AN ANTIVIRAL ANTIBIOTIC

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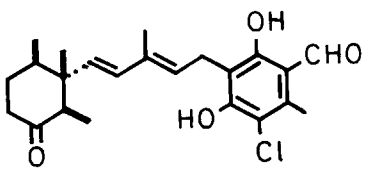
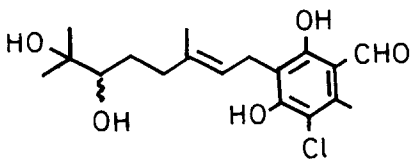
Summary : (±)-Ascochlorin, 5-chloro-2,4-dihydroxy-6-methyl-3-[(2E,4E)-5-(1,2,6-trimethyl-3-oxocyclohexyl)-3-methyl-3,4-pentadienyl]benzaldehyde, was synthesized in 14 steps from (±)-3,4-dimethyl-2-cyclohexenone.

Ascochlorin is an antiviral antibiotic isolated from the mycelium of Ascochyta viciae LIBERT by G. Tamura et al.[2)] Its structure including absolute stereochemistry was determined by X-ray analysis as depicted in 1.[3)] The unique feature of the structure 1 is the combination of a substituted benzene ring with a sesquiterpene side-chain. Mainly because of its structural novelty coupled with potentially useful bioactivity and partly because it was discovered in our Department, we started our synthetic work on 1 and its relatives. The early phase of our work was focused on the construction of the hexasubstituted benzene ring under mild conditions and culminated in the synthesis of (±)-colletochlorin A 2.[4)] We have now completed the first synthesis of (±)-ascochlorin 1.[5)]

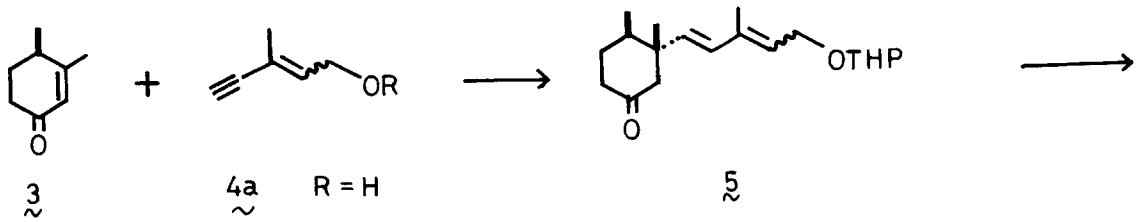
The synthesis of the sesquiterpene portion of (±)-1 started from (±)-3,4-dimethyl-2-cyclohexenone 3[6)] and 3-methyl-2-penten-4-yn-1-ol 4a.[7)] Hydrostannation (n-Bu_3SnH, AIBN)[8)] of 4b was followed by metal exchange with n-BuLi (THF, -78°) to give a lithiated diene.[8,9)] A mixed cuprate derived from the lithiodiene and n-PrC≡CCu in ether-$(Me_2N)_3P$[8-11)] was reacted with (±)-3 to give (±)-5 in 81% yield after quenching with NH_4Cl aq.[12,13)] Introduction of a Me group at C-2 of the cyclohexane ring of (±)-5 was effected after blocking the C-6 methylene group by formylation of (±)-5 with HCO_2Et-NaH in C_6H_6 at 10° to give (±)-6. This was converted to a dianion by treatment with 2 eq of LDA in



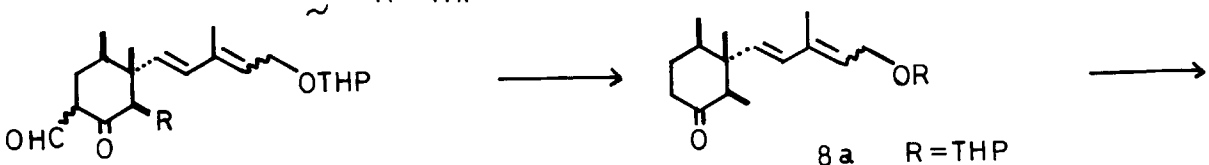
Ascochlorin 1



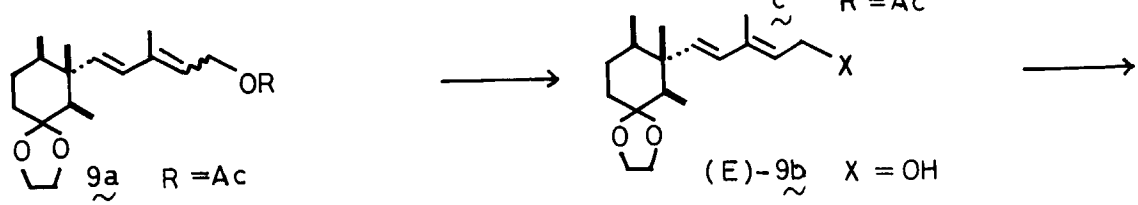
Colletochlorin A 2



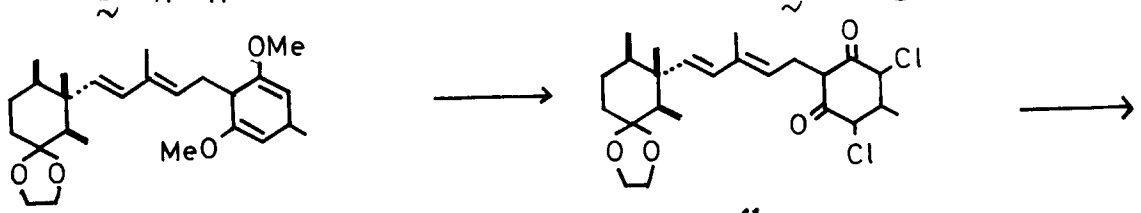
3 4a R = H b R = THP 5



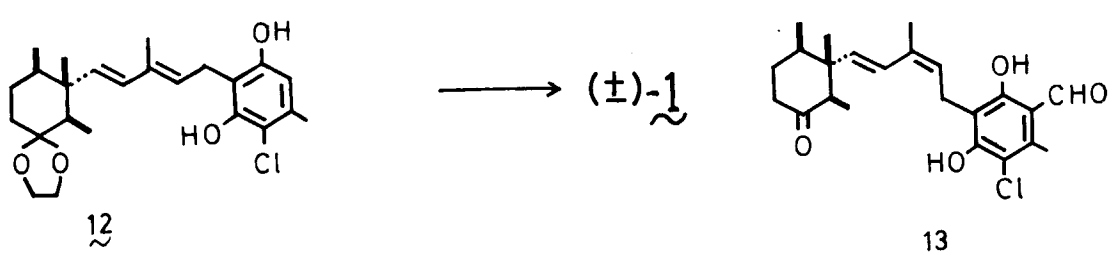
6 R = H 7 R = Me 8a R = THP b R = H c R = Ac



9a R = Ac b R = H (E)-9b X = OH c X = Br



10 11



12 (±)-1 13

THF (-20°), which was alkylated with 1.1 eq of MeI in THF-HMPA to give (±)-7. Hydrolysis of (±)-7 with 2% NaOH aq yielded (±)-8a after chromatographic purification (SiO_2) in 55% yield from (±)-5. Treatment of (±)-8a with AcOH-THF aq gave (±)-8b, whose acetylation (Ac_2O-C_5H_5N) afforded (±)-8c in 86.5% yield from (±)-8a. An acetal (±)-9a was obtained from (±)-8c by treatment with $MeOCH(O_2C_2H_4)$ and TsOH in 86% yield. This was hydrolyzed (K_2CO_3-MeOH aq) to give (±)-9b in 96% yield. Separation of the desired (2E)-isomer of (±)-9b from the undesired (2Z)-isomer was executed at this stage by chromatography (Merck Lobar column, Li Chroprep Si 60, 63 ∿ 125 μm). Elution with n-hexane-ether (2 : 1) first yielded (±)-(2Z)-9b followed by (±)-(2E)-9b in a ratio of 1 : 2. In their ^{1}H-NMR spectra (±)-(2E)-9b showed a 3H-signal [C=C(CH_3)-] at δ 1.71, while (±)-(2Z)-9b showed it at δ 1.80. Conversion of (±)-(2E)-9b to (±)-9c was effected by the method of Stork et al. using i) n-BuLi ii) TsCl and iii) LiBr.[14] This completed the synthesis of the sesquiterpene moiety of (±)-ascochlorin 1.

The later stages of the present synthesis followed our route previously employed in the synthesis of (±)-colletochlorin A.[4] Alkylation of 1,5-dimethoxy-3-methyl-1,4-cyclohexadiene with (±)-9c (t-BuLi/THF-HMPA, -78°) yielded (±)-10 in 40% yield. Treatment of (±)-10 with 2.2 eq of N-chloro-succinimide in DMF-H_2O (10 : 1) in the presence of $CaCO_3$ gave (±)-11 in 43% yield after acidification followed by chromatographic purification (SiO_2). Aromatization of (±)-11 to (±)-12 (M^+=420. 2068, $C_{24}H_{33}O_4Cl$ requires 420.2067) was achieved in 43% yield by heating (±)-11 with DBU in THF for 3 hr. Finally a formyl group was introduced to (±)-12 by treatment with EtMgBr in Et_2O followed by $HC(OEt)_3$ (100°).[15] The crude product was treated with 35% $HClO_4$-Et_2O (2 : 3) at 0° to give (±)-ascochlorin 1 (41 mg) as prisms, mp 142 ∿ 146°, Found : C, 67.90; H, 7.15. $C_{23}H_{29}O_4Cl$ requires : C, 68.22; H, 7.22%; ν_{max} (KBr) 3300 (m), 2980 (m), 1705 (m), 1615 (s), 1450 (m), 1420 (m), 1375 (m), 1325 (w), 1285 (m), 1250 (s), 1170 (m), 1110 (m), 1005 (w), 970 (m), 905 (w), 815 (w), 780 (w), 730 (w), 715 (w), 615 (w), 585 (w), 530 (w) cm^{-1}; δ (400 MHz, $CDCl_3$) 0.695 (3H, s), 0.812 (3H, d, J=6.59 Hz), 0.829 (3H, d, J=6.59 Hz), 1.60 (1H, m), 1.92 (3H, s), ∿ 1.95 (2H, m), 2.39 (3H, m), 2.603 (3H, s), 3.525 (2H, d, J=7.33 Hz), 5.39 (1H, d, J=16.12 Hz), 5.51 (1H, t, J=7.33Hz), 5.90 (1H, d, J=16.12Hz), 6.385 (1H, s), 10.14 (1H, s), 12.7 (1H, s). These spectral data coincided with those of the natural ascochlorin.[2,16] Starting from (±)-(2Z)-9b, the isomer (±)-13, mp 180 ∿ 184°, of (±)-ascochlorin was also synthesized.[17]

The present work confirmed the wide applicability of our general method[4] for the synthesis of prenylated phenols of microbial origin. Synthesis of (±)-ascofuranone is now in progress.

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12) All new compounds described in this paper gave satisfactory elemental and/or mass spectral analyses together with consistent spectral data.
13) Both (E)- and (Z)-4b gave the same (±)-5 with (2E)/(2Z)-ratio = 2 : 1. The (E, Z)-mixture of 4b was therefore used as the starting material. Trapping with MeI of the enolate anion generated by the conjugate addition of the cuprate reagent to (±)-3 gave poor results with low reproducibility.
14) G. Stork, P.A. Grieco and M. Gregson, Tetrahedron Letters, 1393 (1969).
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16) Coincidence of the IR spectrum (KBr) of (±)-1 with that of 1 indicates that (±)-1 is not a racemic compound but a racemic mixture.
17) ^{1}H-NMR data of (±)-13 (400 MHz, $CDCl_3$) : 0.82 (3H, s), 0.85 (3H, d, J=6.59 Hz), 0.877 (3H, d, J=6.59 Hz), 1.66 (1H, m), 1.81 (3H, s), ∿1.94 (2H, m), 2.45 (3H, m), 2.59 (3H, s), 3.55 (2H, d, J=7.33Hz), 5.485 (1H, t, J=7.33 Hz), 5.49 (1H, d, J=16.11Hz), 6.44 (1H, s), 6.69 (1H, d, J=16.11 Hz), 10.131 (1H, s), 12.7 (1H, s).

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