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π-CYCLIZATION: THE SYNTHESIS OF (±)-SOLAVETIVONE AND (±)-HINESOL[1]

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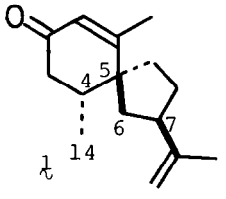
Summary: A general efficient approach leading to the total synthsis of (±)-solavetivone, (±)-hinesol, and related spirovetivanes, is described. The process involves stereoselective formation of the asymmetric center at C-7 by π-cyclization as a key step.

Naturally occurring spirovetivanes are divided into two classes based on the relative configuration between the C-4-C-14 and C-5-C-6 bonds:[2] one class consists of a number of sesquiterpenes, represented by solavetivone and oxylubimin isolated as phytoalexins from diseased potato tubers, possesses the trans configuration concerning the relevant bonds, while the other, including hinesol, β-vetivone, and others isolated from vetiver oil, takes the cis configuration. While considerable attention has been directed towards syntheses[3] of these sesquiterpenes owing to the characteristic skeleton, most of the works have been limited to the preparation of spirovetivanes belonging to the latter class. Only recently Yamada and co-workers[4] reported the synthesis of (±)-solavetivone through a lengthy route. We have also searched for a general and efficient process leading to the preparation of both classes with due regard to stereoselective formation of the asymmetric center at C-7 by π-cyclization[5] and succeeded in the synthesis of (±)-solavetivone[4] (±-1), (±)-hinesol[6] (±-2), (±)-β-vetivone[7] (±-3), and its close analogs. The approach is described in this paper.



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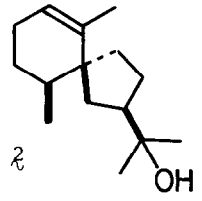

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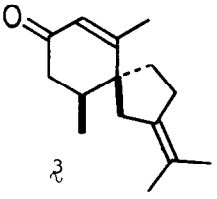

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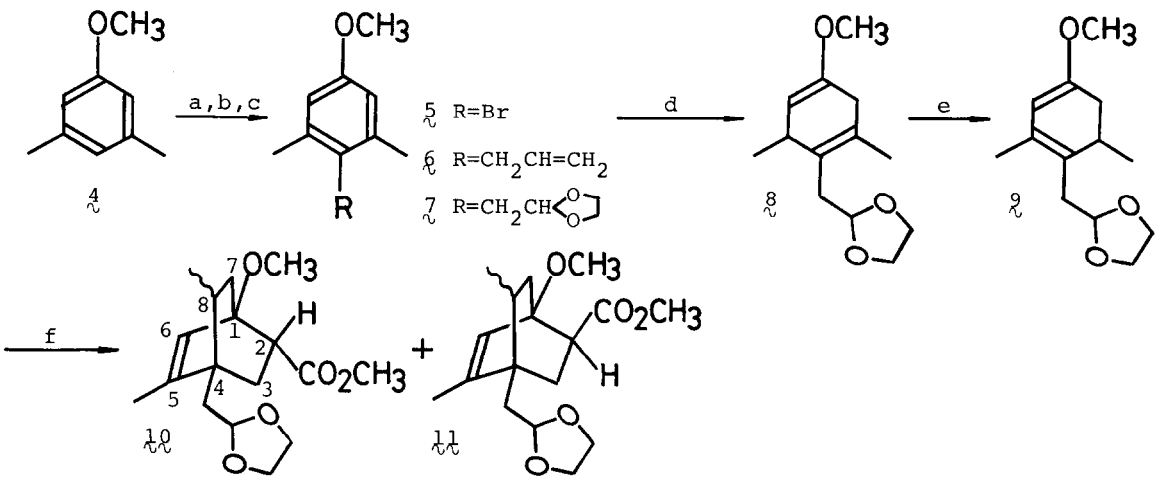
3,5-Dimethylanisole (4) was transformed, via several compounds[8] (5 ∼ 8) (Scheme 1), into the corresponding conjugate diene (9) in a 40% overall yield; 9, λ_{max} 277 nm (ε 5000); ν_{max} 1670, 1613, and 1130 cm^{-1}; δ 0.92 (3H, d J = 7), 1.76 (3H, s), and 4.77 (each 1H, t J = 1). Diels-Alder reactions of the diene (9) and methyl acrylate produced, depending on the conditions, a variety of ratios of mixtures of four bicyclo[2.2.2]octenes (10) and (11), which differed in the configuration of the 2-methoxycarbonyl group (endo and exo) and that of the 8-methyl group (syn and anti to the C-2-C-3 bond). The cycloaddition,

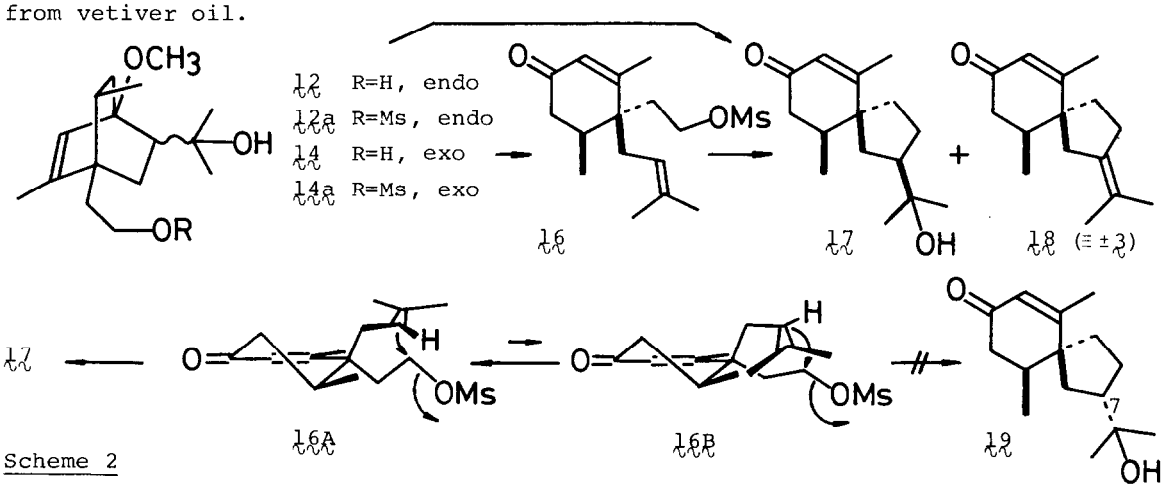


Scheme 1: a) Br_2, Fe(cat.) in CCl_4, -30 °C, 5 h, y 85%. b) Mg, CH_2=CH-CH_2Br in ether, reflux, 15 h, y 83%. c) OsO_4-$NaIO_4$; $(CH_2OH)_2$, PTS in Benzene, y 77%. d) Li in liq NH_3-THF (4:1), reflux, 2 h; EtOH, y 85%. e) 140 °C, 10 h, y 85%. f) CH_2=CH-CO_2CH_3

when carried out in ether at 20 °C (2 d, 15000 atm), afforded a 3.2:1 (by NMR) mixture of the syn-endo and anti-endo adducts (10) as the sole isolable products in a 65% yield. The endo adducts (10) were transformed by a three-step process [(i) 2M HCl and ether (2:1), 40 °C, 15 h, (ii) $NaBH_4$ in CH_3OH, 0 °C, 1 h, and (iii) CH_3Li in ether, room temp, 2 h] into the corresponding bicyclooctene diols, which were separated easily to give the syn-endo (12) and anti-endo diols (13) in 60 and 15% yields, respectively: 12, δ 1.06 (3H, d J = 7, 8-CH_3), 0.89 [6H, s, $C(CH_3)_2OH$], 1.81 (3H, s, 5-CH_3), and 5.89 (1H, br s, 6-H); 13, δ 0.74 (3H, d J = 6), 0.92 (6H, s), 1.77 (3H, s), and 5.91 (1H, br s). On the other hand, the cycloaddition at 190 °C (4 d, 1 atm) produced a mixture of the endo (10) and exo adducts (11), each being a 0.9:1 mixture of the syn and anti isomers, which were separated easily in 45 and 14% yields, and treated in the same manner as mentioned above, respectively. The syn-endo (12) and anti-endo diols (13) were isolated in 33 and 37% yields from 10, while the syn-exo (14) and anti-exo adducts (15) in 30 and 33% yields, respectively: 14, δ 0.97 (3H, d J = 7), 1.04 and 1.29 (each 3H, s), 1.81 (3H, s), and 6.02 (1H, br s); 15, δ 0.75 (3H, d J = 7), 1.02 and 1.24 (each 3H, s), 1.73 (3H, s), and 6.07 (1H, br s). Each of these bicyclooctene diols was converted [CH_3SO_2Cl and $(C_2H_5)_3N$ in CH_2Cl_2, -78 °C, 10 min] into the corresponding methanesulfonate (12a) ∿ (15a).

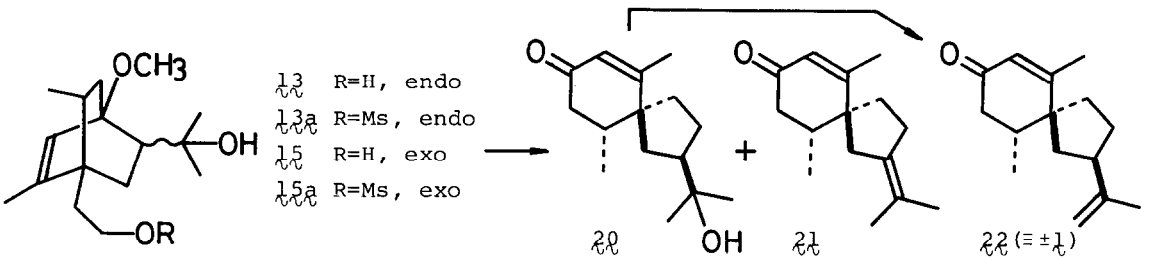
Cleavage of the C-1-C-2 bond of the syn-endo methoxyalcohol mesylate (12a) was achieved by treatment with formic acid (room temp, 30 min) to give prenylcyclohexenone (16) quantitatively; 16, ν_{max} 1670 and 1616 cm^{-1}; δ 1.06 (3H, d J = 6), 1.62 and 1.70 (each 3H, br s), 1.98 (3H, s), 4.06 (2H, t J = 8), and 5.89

(1H, s). Likewise, the syn-exo mesylate (14a) was transformed smoothly into the same prenyl compound (16). Treatment of the compound (16) with 0.4M oxalic acid (in 33% aq acetone, 85 °C, 4 h) effected formation of the skeleton in question, giving two spirovetivanes (17) and (18) with the relevant C-4-C-14 and C-5-C-6 bonds oriented cis each other in 58 and 35% yields, respectively: 17, mp 121-123 °C; ν_{max} 3640, 3475, 1665, and 1615 cm^{-1}; δ 1.01 (3H, d J = 7), 1.24 and 1.97 (6H and 3H, each s), and 5.75 (1H, br, s); 18, oil; δ 0.97 (3H, d J = 6 Hz), 1.14 and 1.87 (6H and 3H, each s), and 5.65 (1H, br s). The π-cyclization must have taken place by attack of the prenyl double bond towards the primary cationic carbon formed by removal of the mesyloxyl group. It is noted that no isomer (19) differing from (17) in the configuration at C-7 could be detected by careful IR, NMR, and GLC analyses. This high stereoselectivity for formation of the C-7 asymmetric center with the desired configuration (SR) could be rationalized in terms of the relative stability of two conformers (16A) and (16B) with maximum overlap between π-orbitals of the relevant primary cationic carbon and the prenyl double bond (Scheme 2); namely, severe steric repulsion between the ring methyl and prenyl methyl groups would destabilize the latter (16B). There seem not to be any precedents for such a stereoselective ring closure. The oxalic acid treatment of 12a and 14a (in aq acetone, 85 °C, 4 h) resulted successively in the bond cleavage and π-cyclization, affording 17 and 18 in 60 and 27% yields and in 58 and 29% yields, respectively. Compounds 17 and 18 were identified with authentic specimens of (±)-hinesolone and (±)-β-vetivone (±-3), respectively. The former could be easily transformed by procedures developed by Dauben and coworkers[2b] into (±)-hinesol (±-2) and (±)-β-vetispirene. The present result consitutes a new synthetic pathway to the spirovetivanes isolated from vetiver oil.



Scheme 2

Treatment of the anti-endo (13a) and anti-exo mesylates (15a) with oxalic acid under the same conditions produced only isomeric spirovetivanes (20) and (21) with the C-4-C-14 and C-5-C-6 bonds oriented trans each other in 63 and 23%



yields and in 69 and 26% yields, respectively: 20, oil; ν_{max} 3480, 1668, and 1615 cm^{-1}; δ 0.97 (3H, d J = 7), 1.18 and 1.95 (6H and 3H, each s), and 5.65 (1H, br s); 21, oil; ν_{max} 1681 and 1620 cm^{-1}; δ 0.98 (3H, d J = 6), 1.61, 1.62, and 1.89 (each 3H, s), and 5.66 (1H, br s). Dehydration of the former (20) proceeded smoothly by heating with pyridine-modified alumina (Woelm, neutral) at 220 °C for 8 min[9] to give an isopropenyl compound (22), oil, in a 60% yield: ν_{max} 3100, 1675, 1615, and 855 cm^{-1}; δ 1.00 (3H, d J = 7), 1.75 and 1.93 (each 3H, s), 4.74 (2H, s), and 5.74 (1H, s); its syn- and anti-DNP, mp 107.5 °C and 137-138 °C. The compound (22) was identified as (±)-solavetivone (±-1) by direct comparison with natural solavetivone and its DNP derivatives (MS, IR, NMR, and TLC). The present synthesis of (±)-solavetivone involves 12 steps and the overall yield amounts to 3.2%.

References and Footnotes

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6) For recent syntheses, see, refs 2b and 3.
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