Total Synthesis of (±)-15-Norsolavetivone

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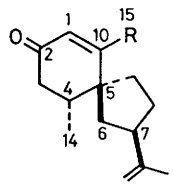
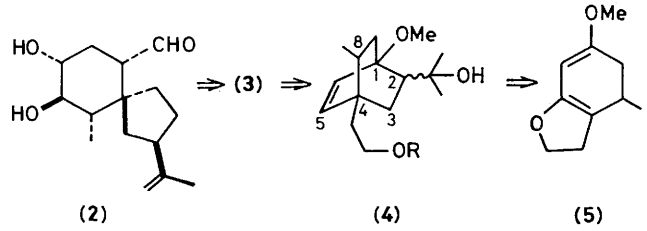
The total synthesis of (±)-15-norsolavetivone, a key intermediate in the synthesis of oxygenated spirovetivane stress metabolites, is described.

The genus Solanum produces a group of sesquiterpenes of the spirovetivane type, which respond to microbial infection as disease-resistant elements.[1,2] Most of these sesquiterpenes, *e.g.* solavetivone[3] (**1**) and oxylubimin[4] (**2**), described as phytoalexins (stress metabolites), are characterized structurally by the *trans*-configuration between the C(4)–C(14) and C(5)–C(6) bonds. However, of these spirovetivanes, only (±)-(**1**), the least oxygenated, has been synthesized recently by a few groups.[5–7] We describe herein a total synthesis of the title compound, (±)-15-norsolavetivone, (±)-(**3**), a key intermediate in the synthesis of the more oxygenated spirovetivane phytoalexins.



(**1**) R = Me
(**3**) R = H

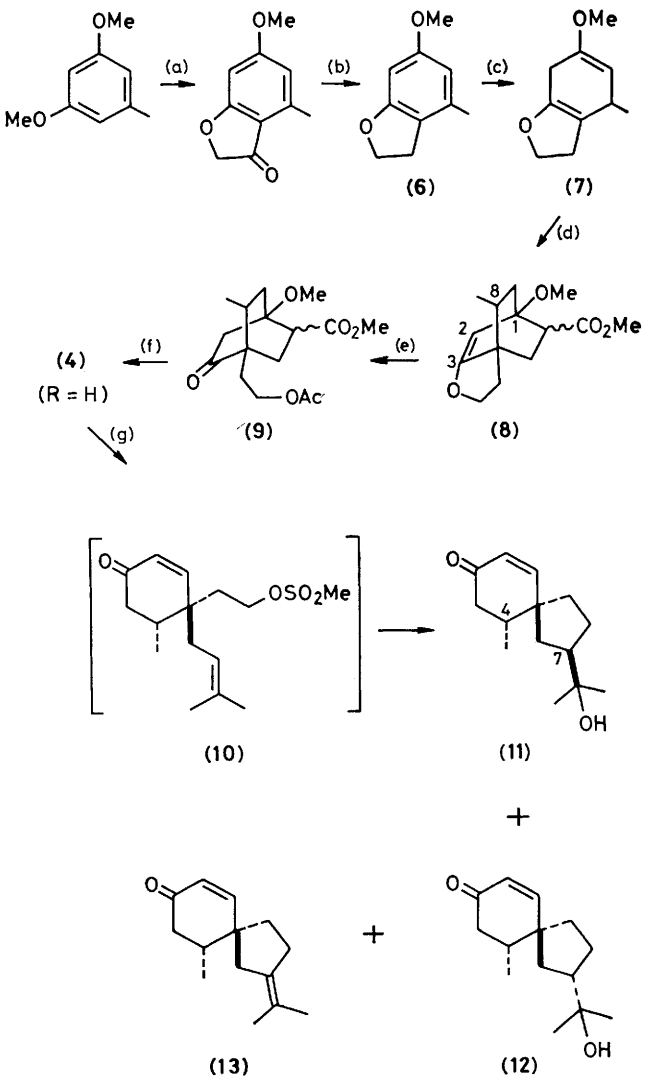


Scheme 1

Our synthetic strategy (Scheme 1) involves the stereoselective synthesis of *anti*-8-methylbicyclo[2.2.2]octenes (**4**) from 6-methoxy-4-methyl-2,3,4,5-tetrahydrobenzofuran (**5**), which is based on our previous study[8] of cycloadditions of 4-substituted 3,5-dimethyl-5,6-dihydroanisoles with methyl acrylate. Thus the synthesis of (**3**) (Scheme 2) started with orcinol dimethyl ether, which was converted *via* 6-methoxy-4-methyl-2,3-dihydrobenzofuran (**6**)† into the tetrahydro derivative (**7**), equivalent to (**5**) (69%). The cycloaddition of (**7**) with methyl acrylate proceeded as expected, giving a mixture of *syn*-8-methylbicyclo[2.2.2]octene adducts (**8**) (70%) [*endo*- and *exo*-CO_2Me epimers, δ 0.83 and 0.86 (1.8 and 1.2H, each d, *J* 6 Hz, 8-CH_3)], which afforded (**4**; R = H) (50%) *via* the keto-acetates (**9**). Compound (**4**; R = $MeSO_2$) was smoothly transformed by treatment with acid in water–methyl isobutyl ketone (1 : 5, heterogeneous)‡ *via* the prenyl-

† All new compounds were fully characterized by spectroscopic means (i.r., n.m.r., and mass spectrometry) and gave satisfactory elemental analyses or precise mass measurement.

‡ Treatment of (**4**) (R = $MeSO_2$) with oxalic acid in aqueous acetone gave (**12**) as the major product (38%), with (**11**) and (**13**) as minor products (each 16%) in contrast with the stereoselective formation of (4*SR*, 7*SR*)-solavetivane (63%) under the same conditions; *cf.*, ref. 7(a).

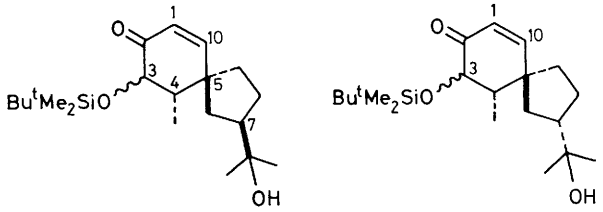


Scheme 2. Reagents: (a) $ClCH_2COCl$–$AlCl_3$ in CS_2, reflux, 7 h. (b) $NaBH_4$ in THF–MeOH, 0 °C, 1.5 h; H_2–Pd in THF–EtOH, room temp., 12 h. (c) Li in liquid NH_3–EtOH. (d) CH_2=$CHCO_2Me$ and DCMA, 150 °C, 5 days. (e) $(CO_2H)_2$ in aqueous MeOH, room temp., 2 h; Ac_2O–pyridine, room temp., 23 h. (f) *p*-$MeC_6H_4SO_2NHNH_2$ in acidic THF, reflux, 20 h; MeLi (excess) in THF, 35—40 °C, 15 h. (g) $MeSO_2Cl$ in CH_2Cl_2, −78 °C, 15 min; $(CO_2H)_2$ (10 mol. equiv.) in H_2O–$MeCOBu^t$ (1 : 5), 130 °C, 8 h.

cyclohexenone§ (**10**) into a mixture of three 15-norsolavetivanes. The 15-norsolavetivone derivative (**11**) with a (4*SR*, 7*SR*)-isopropyl moiety was isolated as the major product (35%) together with its (4*SR*, 7*RS*)-epimer (**12**) (25%) and the 7-isopropylidene derivative (**13**) (30%), by preparative h.p.l.c. (μ-Porasil, hexane–ether, 1 : 1). The spirovetivane (**11**), when treated with pyridine-modified alumina,[9] underwent smooth dehydration to give (±)-(**3**) (68%) in an overall yield of 5.7% from the orcinol.

The configuration at C(7) in (**11**) and (**12**) was assigned tentatively on the basis of the following facts. Treatment of (**11**)

§ Treatment of (**4**) (R = $MeSO_2$) with formic acid led to isolation of (**10**) (98%).



(**14a**) 3 α H (**15a**) 3 α H

(**14b**) 3 β H (**15b**) 3 β H

with lithium di-isopropylamide in tetrahydrofuran (THF) and hexamethylphosphoramide (−65 °C) and then with t-butyldimethylsilyl chloride in THF (room temp.), followed by oxidation with perbenzoic acid in hexane (room temp.),[10] gave the 3,4-diequatorial-3-silyl ether (**14a**) [δ 3.89 (1H, d, *J* 11 Hz, 3-H) and 6.80 (1H, d, *J* 10 Hz, 10-H)] and its 3-epimer (**14b**) in 51 and 25% yields, respectively. The same treatment for (**12**) afforded the corresponding 3,4-diequatorial-3-silyl ether (**15a**) [δ 3.90 (1H, d, *J* 11 Hz) and 6.67 (1H, *J* 10 Hz)] and its 3-epimer (**15b**) in 50 and 26% yields. The observed difference (Δδ 0.13) between the chemical shifts of the C(10) protons in (**14a**) and (**15a**) was rationalized by assuming that the hydroxy-group in the C(7) isopropyl moiety would be situated near the hydrogen atom at C(10) only in (**14a**) and hence would deshield the proton in question. A definite assignment was provided by transformation of (**11**) and (**14a**) into natural spirovetivanes.[11]

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