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SYNTHESIS OF (±)-SILPHINENE USING ELECTROCHEMICAL METHOD AS A KEY STEP

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Summary: (±)-Silphinene has been synthesized from 2,6,6-trimethyl-9-methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-dione which has been produced efficiently by means of electrochemical method.

In connection with our synthetic work on bioactive substances using electrochemical methods, we describe herein a synthesis of (±)-silphinene, a constituent of the roots of Silphium perfoliatum,[1] which has attracted the considerable attention of synthetic chemists.[2,3] In addition, the present synthetic strategy may be used for other triquinane sesquiterpenes. In the previous paper,[4] the known phenol (**1**) was subjected to anodic oxidation [CCE: 58 mA (+920 - 1700 mV vs. SCE); ca. 2 F/mol] to afford 2,6,6-trimethyl-9-methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-dione (**2**) in 54% yield. This tricyclic compound (**2**) was selectively reduced with DIBAL-H (1.1 equiv.) and then subjected to acetylation followed by hydrolysis with oxalic acid to give an α-acetoxy ketone (**3**)[5] in good yield. On Grignard reaction using MeMgBr (8 equiv.), the CO group at C_9-position in **3** was selectively attacked by the reagent to afford a diol (**4**),[4] which was further reduced with $LiAlH_4$ to give rise to a triol (**5**).[5]

In the next step, **5** was oxidized with $Pb(OAc)_4$ in MeOH and then $NaClO_2$ to afford a bicyclic compound (**6**),[5] in almost quantitative yield, which was then subjected to esterification with methoxymethyl chloride - K_2CO_3 followed by PDC oxidation to give a mixture of two ketones (**7** and **8**)[5] in 70% yield (relative ratio: **7**/**8** = ca. 1). The former (**7**) was treated with 1N HCl and then NaOEt to afford a desired tricyclic α,β-unsaturated ketone (**9**)[5] in almost quantitative yield. On methylation using $Me_2Cu(CN)Li_2$, finally, **9** was readily converted into the known ketone (**10**),[6] in 92% yield, from which (±)-silphinene (**11**) had been already synthesized.[3] The triketone (**8**) was also converted into a triquinane-type compound (**12**), as seen in Scheme 1. Further synthetic study on other triquinane sesquiterpenes is in progress.

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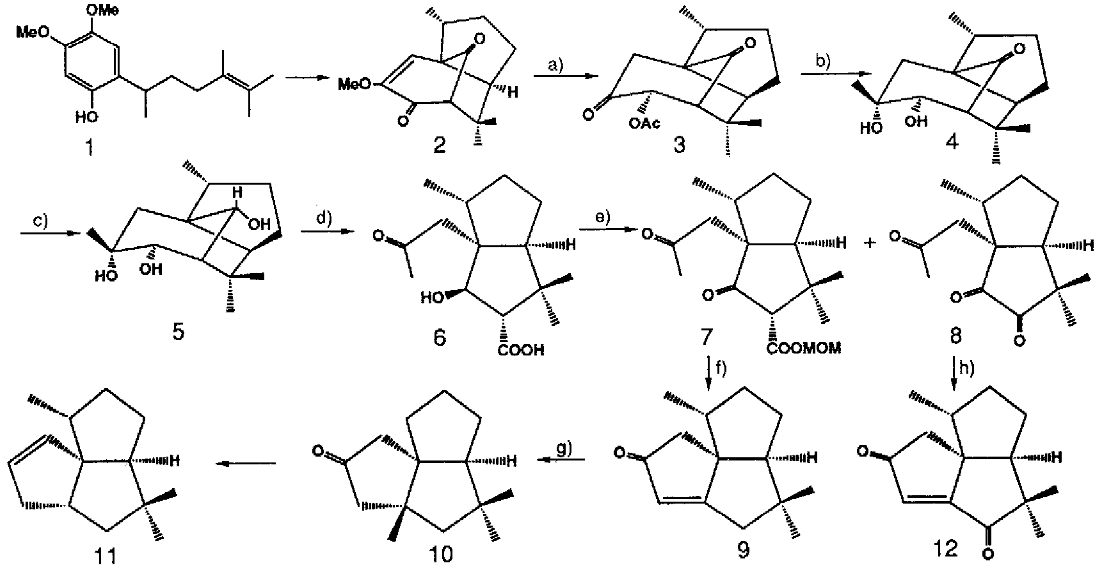
5. The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: **3**: mp 86 - 88 °C; $C_{16}H_{22}O_4$ [m/z 278.1524(M^+)]; IR (film) 1760 - 1740br. cm^{-1}; δ ($CDCl_3$) 0.88(3H, s), 0.89(3H, d, J = 7.3 Hz), 1.21(3H, s), 2.19(3H, s), 2.52(1H, d, J = 15.1 Hz), 2.55(1H, d, J = 4.4 Hz), 2.58(1H, d, J = 15.1 Hz), 5.45(1H,d, J = 4.4 Hz). **4**: mp 140 °C; $C_{15}H_{24}O_3$ [m/z 252.1720(M^+)]; IR (film) 3400, 1720 cm^{-1}; δ ($CDCl_3$) 3.83(1H, d, J = 4.4 Hz). **5**: mp 175 - 180 °C; $C_{15}H_{26}O_3$ [m/z 254.1873(M^+)]; IR (Nujol) 3400 cm^{-1}; δ ($CDCl_3$) 2.20(1H, d, J = 4.1 Hz), 3.29(1H, s), 3.70(1H, d, J = 4.1 Hz). **6**: mp 163 - 165 °C; $C_{15}H_{24}O_4$ [m/z 268.1685(M^+)]; IR (Nujol) 3500, 1730sh., 1700 cm^{-1}; δ ($CDCl_3$) 2.20(3H, s), 2.38(1H, d, J = 19.1 Hz), 2.64(1H, d, J = 11.2 Hz), 3.02(1H, d, J = 19.1 Hz), 4.45(1H, d, J = 11.2 Hz). **7**: $C_{17}H_{20}O_5$ [m/z 310.1761(M^+)]; IR (film) 1760, 1720, 1650, 1610 cm^{-1}. **8**: $C_{14}H_{20}O_3$ [m/z 236.1427(M^+)]; IR (film) 1750sh., 1740, 1710 cm^{-1}. **9**: $C_{14}H_{20}O$ [m/z 204.1504(M^+)]; IR (film) 1710, 1630 cm^{-1}; δ ($CDCl_3$) 1.95(1H, d, J = 17.3 Hz), 2.24(1H, d, J = 14.0 Hz), 2.52(1H, dd, J = 1.5 Hz, 14.0 Hz), 2.64(1H, d, J = 17.3 Hz), 5.87(1H, d, J = 1.5 Hz). **12**: $C_{14}H_{18}O_2$ [m/z 218.1287(M^+)]; IR (film) 1720, 1690sh. cm^{-1}; δ ($CDCl_3$) 0.79(3H, d, J = 6.1 Hz), 1.10(3H, s), 1.18(3H, s), 1.4 - 2.4(6H, complex), 2.14(1H, d, J = 17.6 Hz), 2.73(1H, d, J = 17.6 Hz), 6.46(1H, s).
6. The synthetic sample (**10**) as racemic form has the following spectral data: $C_{15}H_{24}O$ [m/z 220.1830(M^+)]; IR (film) 1740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 0.96(3H, d, J = 6.4 Hz), 0.98(3H, s), 1.04(3H, s), 1.11(3H, s), 1.27(1H, m), 1.55 - 1.70(2H, complex), 1.76(1H, d, J = 15.0 Hz), 1.80(1H, d, J = 15.0 Hz), 1.92 - 2.18(3H, complex), 2.02(1H, d, J = 18.1 Hz), 2.15(1H, d, J = 18.1 Hz), 2.42(1H, d, J = 18.1 Hz), 2.44(1H, d, J = 18.1 Hz). The ^1H NMR spectral data of **10** are compatible with the data cited in ref. 3.



a) 1. DIBAL-H (1.1 equiv)/THF under Ar (-78 °C) 2. Ac_2O/DMAP/pyridine (room temp) (82% in 2 steps) 3. sat.aq. $(COOH)_2$/MeOH (60 °C, 4 h) (76%); b) MeMgBr (8 equiv)/THF under Ar (0 °C, 2 h) (72%); c) $LiAlH_4$/THF (-78 - 0 °C) (98%); d) 1. $Pb(OAc)_4$ (10 equiv)/MeOH (room temp., 10 min) (100%) 2. $NaClO_2$/20% aq. acetone (room temp., 18 h) (99%); e) 1. MOMCl/K_2CO_3/DMF (room temp., 4 h) (97%) 2. PDC (10 equiv)/4 Å MS/CH_2Cl_2 (room temp., 4 h); f) 1. 1N HCl (cat.)/dioxane (refluxing temp., 20 h) (96%) 2. excess NaOEt/EtOH (refluxing temp., 3 h) (100%); g) $Me_2Cu(CN)Li_2$ (10 equiv)/Et_2O under Ar (-30 °C, 30 min) (92%); h) 10% KOH/benzene (refluxing temp., 3 h) (79%).

Scheme 1. Synthesis of (±)-silphinene

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