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A Short Synthesis of the Aromatic Monoterpene Espintanol

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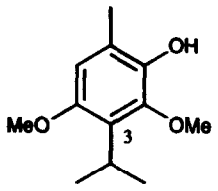
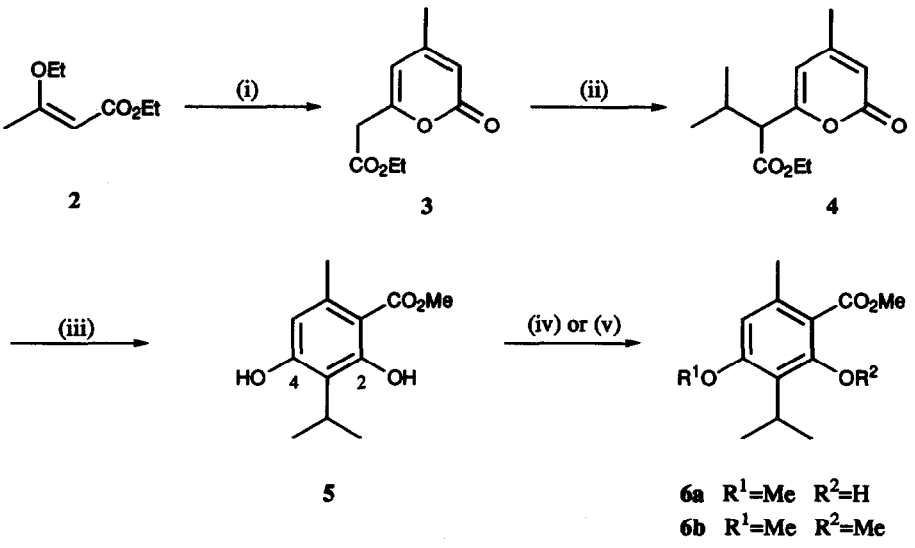
Abstract: *A flexible and expedient synthesis of the leishmanicidal and trypanocidal monoterpene espintanol* ***1****, first isolated in 1991 from the spruce Oxandra espintana, was achieved in seven steps and with an overall yield of 11%. Key steps were the direct conversion of the methyl ester* ***6b*** *to the methyl ketone* ***7*** *upon treatment with methyl lithium and the acid-catalyzed benzylic hydroperoxide rearrangement reaction of the secondary alcohol* ***11*** *to afford* ***1****.*

In 1991 a paper appeared describing the leishmanicidal and trypanosomal *in vitro* activities of the petroleum ether extract of the spruce *Oxandra espintana*[2]. Purification procedures led to the active principle, characterized as the aromatic monoterpene **1**, which was named espintanol. The same authors also reported a nine step synthesis of espintanol in which the final step involved an unselective demethylation of the trimethylated derivative, affording espintanol in *ca.* 2% yield. In order to obtain sufficient quantities of this substance for biological profiling, a totally new synthetic sequence was designed which would lead to multigram quantities of **1**, whilst allowing for the structural modification of the molecule in order to probe structure-activity relationships.



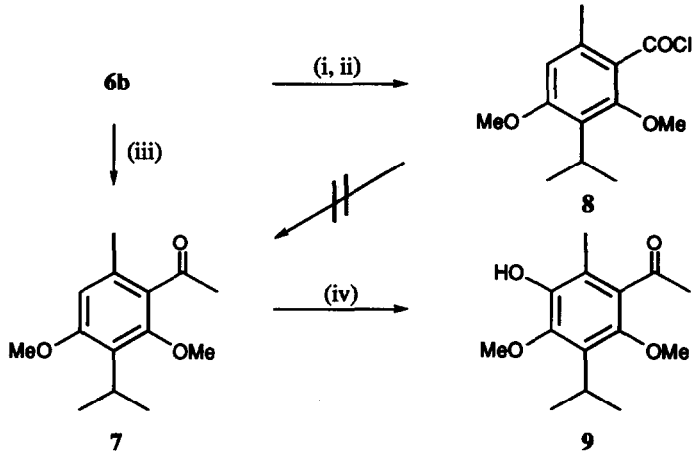
espintanol **1**

To allow the easy introduction of a variety of substituents at C-3, a strategy was devised in which the group at this position could be introduced *via* a facile manipulation of a non-benzenoid substrate. Thus, the known aromatic ester **5**[3] was synthesized in three steps from commercially-available ethyl 3-ethoxy-but-2-enoate (**2**), with the isopropyl group originating from a simple α-alkylation reaction on the intermediate 2*H*-pyran-2-one ester **3**, affording **4**[4,5]. Subsequently, it proved possible to either selectively mono-methylate **5** in the 4-position yielding **6a** or to dialkylate to afford the desired compound **6b** (Scheme 1).



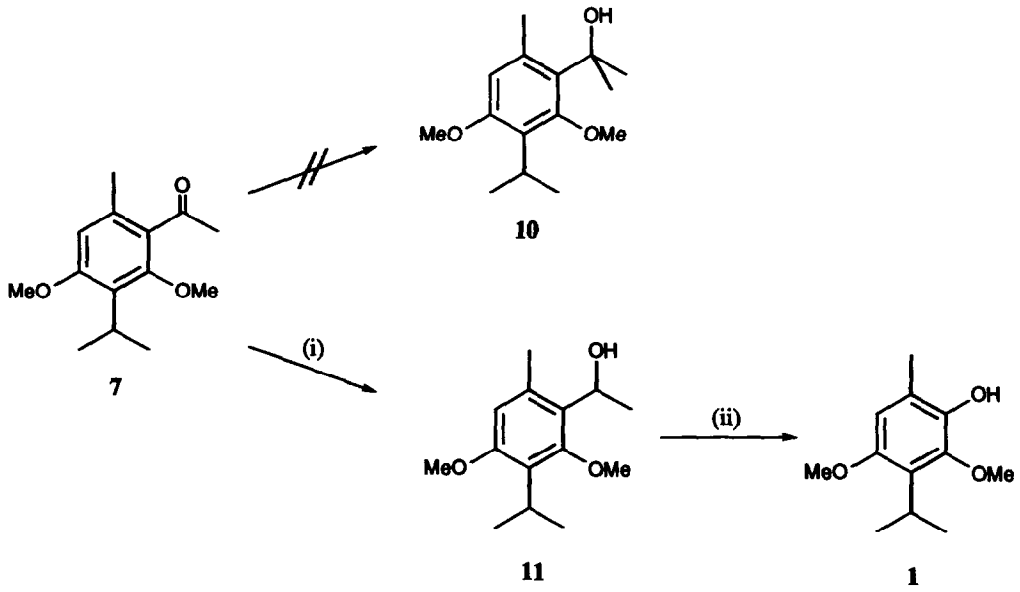
Scheme 1; (i) BF_3.AcOH, 42%. (ii) 1. EtONa, DMF; 2. *i*-PrBr, 65%. (iii) MeONa, MeOH, 70%. (iv) for **6a**; Na_2CO_3, $(MeO)_2SO_2$, Me_2CO, 99%.(v) for **6b**; NaH, $(MeO)_2SO_2$, DMF, 94%.

It was originally intended to convert methyl ester **6b** to the natural product *via* a Baeyer-Villiger rearrangement of the methyl ketone **7**. Reaction of the acid chloride **8** with a variety of organometallic reagents failed to provide sufficient quantities of **7** for further studies. However, **7** could be prepared in 99% yield on treatment of ester **6** with an excess of methyl lithium at low temperature. Upon reaction of **7** with *m*-CPBA in refluxing 1,2-dichloroethane the only product that could be isolated was the phenol **9** which was the result of a ring oxidation process (Scheme 2).



Scheme 2; (i) NaOH, H_2O, 92%. (ii) $SOCl_2$, 78%. (iii) MeLi, Et_2O, 99%. (iv) *m*-CPBA, $ClCH_2CH_2Cl$, 34%.

Highly substituted compounds, even those bearing several electron-donating groups such as **7**, have been shown to be problematic substrates in the Baeyer-Villiger rearrangement[6]. In such cases a procedure involving an acid-catalyzed benzylic hydroperoxide rearrangement of either a secondary or, even better, a tertiary alcohol, has been shown to be an excellent alternative[7]. As conversion of the methyl ketone **7** to the tertiary alcohol **10** proved difficult, it was decided to proceed *via* the less reactive secondary alcohol **11**. Reduction of **7** with lithium aluminium hydride afforded alcohol **11** in 90% yield and subsequent treatment of **11** with hydrogen peroxide in the presence of a catalytic amount of either *p*-toluene sulphonic acid hydrate or boron trifluoride etherate afforded espintanol **1** in good yield (Scheme 3).



Scheme 3; (i) $LiAlH_4$, Et_2O, 90%. (ii) H_2O_2, cat. $BF_3.OEt_2$ or $TsOH.H_2O$, THF, 50-68%.

The spectral and physical properties of the synthetic material were identical to those reported for the natural compound except that in the literature **1** was obtained as a yellow-brown oil[2] whereas synthetic material, after one low temperature recrystallization from hexane, was an off-white solid with a melting point of 42.3-43°C. The synthesis of espintanol was thus completed in seven steps with an overall yield of 11%[8]. This route allowed the preparation of multigram quantities of the natural product.

Experimental:

All solvents were purified and dried using standard procedures.

*2-Hydroxy-3-isopropyl-4-methoxy-6-methyl benzoic acid methyl ester (**6a**)*: Dimethyl sulphate (1.0 ml, 10.5 mmol) was added to a mixture of 2,4-dihydroxy-3-isopropyl-6-methyl benzoic acid methyl ester (**5**)[3] (0.50 g, 2.2 mmol) and sodium carbonate (1.33 g, 12.5 mmol) in dry acetone (50 ml) and the resulting mixture heated at reflux for 20 hours. The mixture was filtered and the filtrate concentrated. The residue was purified by column chromatography (eluant; hexane:ether, 9:1) affording **6a** as an oil (0.53 g, 99%); ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 1.21 (6H, d, J=7.5 Hz, $-CH(CH_3)_2$), 2.45 (3H, s, 6-CH_3), 3.52 (1H, sept., J=7.5 Hz, $-CH(CH_3)_2$), 3.77 (3H, s, 4-OCH_3), 3.84 (3H, s, $-CO_2CH_3$), 6.18 (1H, s, 5-H), 11.90 (1H, s, 2-OH). (Found: C, 65.66; H, 7.61%. $C_{13}H_{18}O_4$ requires C, 65.53; H, 7.61%).

*3-Isopropyl-2,4-dimethoxy-6-methyl benzoic acid methyl ester (**6b**)*: 2,4-Dihydroxy-3-isopropyl-6-methyl benzoic acid methyl ester (**5**) (0.50 g, 2.2 mmol) was dissolved in DMF (10 ml) and NaH (132 mg, 5.0 mmol)

was added portionwise. After one hour at room temperature, dimethyl sulphate (0.48 ml, 5.0 mmol) was added dropwise and stirring continued for 16 hours. The reaction mixture was poured into water (25 ml) and extracted with ether (3x50 ml). The organic layer was separated, washed with water (20 ml) and brine (20 ml), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (eluant; hexane:ether, 9:1) affording **6b** as a low melting solid (0.49 g, 94%); m.p. 39-42°C; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 1.23 (6H, d, J=7.5 Hz, -CH(CH_3)$_2$), 2.20 (3H, s, 6-CH_3), 3.35 (1H, sept., J=7.5 Hz, -CH(CH_3)$_2$), 3.66 (3H, s, 2-OCH_3), 3.73 (3H, s, 4-OCH_3), 3.85 (3H, s, -CO_2CH_3), 6.40 (1H, s, 5-H). (Found: C, 66.37; H, 8.00%. $C_{14}H_{20}O_4$ requires C, 66.65; H, 7.95%).

1-(3-Isopropyl-2,4-dimethoxy-6-methyl-phenyl)-ethanone (7): 3-Isopropyl-2,4-dimethoxy-6-methyl benzoic acid methyl ester (**6b**) (14.5 g, 57 mmol) was dissolved in ether (200 ml) and cooled to -50°C. Methyl lithium (75.4 ml of 1.5 M solution in ether, 119.7 mmol) was added dropwise and the solution stirred at -50°C for 30 minutes then allowed to warm to room temperature. Excess saturated aqueous ammonium chloride was added carefully and the mixture extracted with ether (3x200 ml). The organic layer was separated, washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$), filtered and concentrated to afford **7** as a white solid (13.5 g, 99%); m.p. 69-70°C; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 1.30 (6H, d, J=7.5 Hz, -CH(CH_3)$_2$), 2.25 (3H, s, 6-CH_3), 2.52 (3H, s, -$COCH_3$), 3.42 (1H, sept., J=7.5 Hz, -CH(CH_3)$_2$), 3.65 (3H, s, 2-OCH_3), 3.80 (3H, s, 4-OCH_3), 6.45 (1H, s, 5-H). (Found: C, 71.69; H, 8.56%. $C_{14}H_{20}O_3$ requires C, 71.16; H, 8.53%).

1-(3-Isopropyl-2,4-dimethoxy-5-hydroxy-6-methyl-phenyl)-ethanone (9): 1-(3-Isopropyl-2,4-dimethoxy-6-methyl-phenyl)-ethanone (**7**) (0.5 g, 2.1 mmol) was dissolved in dichloroethane (50 ml) and 3-chloro perbenzoic acid (1.0 g, 5.8 mmol) was added in one portion. The mixture was heated to reflux for 48 hours and allowed to cool. The organic layer was washed with aqueous sodium bisulphate (25 ml), sodium bicarbonate (50 ml), water (20 ml) and brine (10 ml), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (eluant; hexane:ether, 5:1) to afford **9** as a yellow solid (0.18 g, 34%); m.p. 98-100°C; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 1.36 (6H, d, J=7.5 Hz, -CH(CH_3)$_2$), 2.10 (3H, s, 6-CH_3), 2.52 (3H, s, -$COCH_3$), 3.35 (1H, sept., J=7.5 Hz, -CH(CH_3)$_2$), 3.65 (3H, s, 2-OCH_3), 3.79 (3H, s, 4-OCH_3), 5.43 (1H, s, 5-OH). (Found: C, 66.09; H, 7.99%. $C_{14}H_{20}O_4$ requires C, 66.65; H, 7.99%).

1-(3-Isopropyl-2,4-dimethoxy-6-methyl-phenyl)-ethanol (11): 1-(3-Isopropyl-2,4-dimethoxy-6-methyl-phenyl)-ethanone (**7**) (13.5 g, 57 mmol) was dissolved in ether (200 ml) and cooled to 0°C. A 1.0 M solution of lithium aluminium hydride in ether (68 ml, 68.0 mmol) was added dropwise and stirring continued for 2 hours at room temperature. Water (2.7 ml), followed by 15% aqueous NaOH (2.7 ml) and water (8.1 ml) were added sequentially. The mixture was stirred for 1 hour, filtered and concentrated to afford **11** as a white solid (12.2 g, 90%); ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 1.30 (3H, d, J=7.5 Hz, -CH(CH_3)), 1.37 (3H, d, J=7.5 Hz, -CH(CH_3)), 2.35 (3H, s, 6-CH_3), 3.33 (1H, sept., J=7.5 Hz, -CH(CH_3)$_2$), 3.60 (1H, br.d, J=7.0 Hz, -CH(OH)), 3.78 (3H, s, 2-OCH_3), 3.80 (3H, s, 4-OCH_3), 5.15 (1H, br.q, J=7.0 Hz, -CH(OH)), 6.45 (1H, s, 5-H). (Found: C, 70.74; H, 9.25%. $C_{14}H_{22}O_3$ requires C, 70.56; H, 9.30%).

3-Isopropyl-2,4-dimethoxy-6-methyl-phenol (1): 1-(3-Isopropyl-2,4-dimethoxy-6-methyl-phenyl)-ethanol (**11**) (5.0 g, 24 mmol) was dissolved in THF (150 ml) and 30% H_2O_2 (150 ml) and TsOH.H_2O (0.40 g, 2.1 mmol) added sequentially. The resulting solution was heated to reflux for 10 minutes then allowed to cool. A saturated aqueous solution of sodium sulphite (300 ml) was added and the resulting mixture extracted with ether (4x100 ml). The organic extracts were combined, washed with water (50 ml) and brine (50 ml), dried ($MgSO_4$), filtered and concentrated. The residue was purified by column chromatography (eluant; hexane:ethyl acetate, 4:1), followed by one low temperature recrystallization from hexane, to afford **1** as an off-white, amorphous powder (3.42 g, 68%); m.p. 42.3-43°C; ^{1}H-n.m.r. (250 MHz, $CDCl_3$) δ 1.35 (6H, d, J=7.5 Hz, -CH(CH_3)$_2$), 2.25 (3H, s, 6-CH_3), 3.33 (1H, sept., J=7.5 Hz, -CH(CH_3)$_2$), 3.65 (6H, s, 2-OCH_3, 4-OCH_3), 5.30 (1H, s, OH), 6.45 (1H, s, 5-H). (Found: C, 68.49; H, 8.44%. $C_{12}H_{18}O_3$ requires C, 68.55; H, 8.63%).

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8. All new compounds gave satisfactory spectral and analytical data.

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