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SYNTHESIS OF 12-O-METHYL-2a-METHOXYFERRUGINOL

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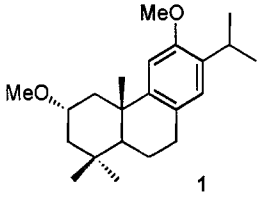
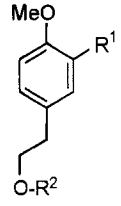
ABSTRACT. ---- A rapid synthesis of 12-O-methyl-2-methoxyferruginol (**1**) shows it not to be identical with the natural product ascribed this structure.

Recently, Pan and co-workers[1] reported an efficient and rapid method for the preparation of tricyclic aromatic diterpenes from a simple dimedone derivative and a substituted phenethyl iodide. However, the substitution pattern of the example they describe was un-natural (12-iso-propyl-13,14-dihydroxy) so it is difficult to assess the generality of this methodology. Ulubelen and Tuzlaci[2] have isolated a new diterpene from *Salvia pachystachys* Trautv. to which they assigned the structure 12-O-methyl-2a-methoxyferruginol 1 (AB ring junction trans).. Since some of



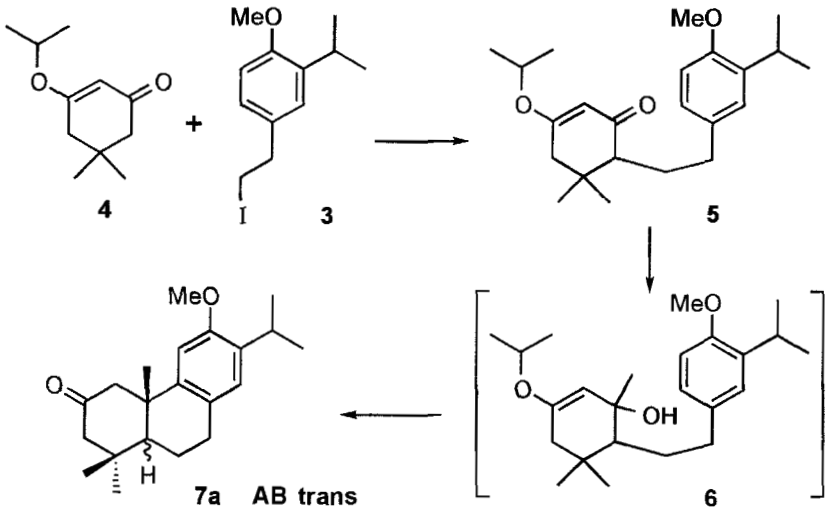
1



2a $R^1 = R^2 = H$
2b $R^1 = R^2 = CO\ CH_3$
2c $R^1 = C(CH_3)_2OH$ $R^2 = H$
2d $R^1 = C(=CH_2)CH_3$ $R^2 = CO\ CH_3$
2e $R^1 = CH(CH_3)_2$ $R^2 = CO\ CH_3$
2f $R^1 = CH(CH_3)_2$ $R^2 = H$

the ^1H nmr spectral data presented did not conform to the structure proposed, it called for an unambiguous synthesis of **1** which appeared to be an ideal target to prepare by the Pan approach.

The necessary aromatic moiety **3** was not readily available so we prepared it efficiently from 4-methoxyphenetol **2a** by : (i) Friedel/Crafts acetylation which afforded acetate **2b**, (ii) reaction with MeMgI which gave the diol **2c**, (iii) dehydration in glac, HOAc then furnished the acetate **2d** and finally, (iv) catalytic hydrogenation (**2e**), hydrolysis (**2f**) and substitution of the alcohol function gave the iodide **3**.



Under basic conditions, the easily prepared iso-propyl enol ether of dimedone **4** was alkylated by the iodide **3** following the Pan conditions but despite several attempts the yield of **5** remained a disappointing 16%. Since since our aim was primarily to confirm the structure of the natural product, we continued with the synthesis. Methyl lithium reacted smoothly with **5** but the product contained both the alcohol **6** and the enone resulting from the hydrolysis of the enol ether. As suggested[1], these were not separated before treating with phosphoric acid which resulted in a virtually inseparable 9 : 1 mixture of C-5 epimeric ketones **7a** and **7b**.

As judged by the typical ^1H nmr signals for the methyl groups, the trans isomer **7a** was the major product so the carbonyl was reduced with sodium borohydride and the alcohol converted in the usual manner (NaH,

MeI) to the methyl ether. Chromatography easily separated the major product **1** from a mixture containing more **1** and the methyl ether arising from reduction and methylation of the AB cis ketone **7b**. The properties of the purified synthetic material **1** and those given for the natural product[2] were far from identical. It was the ^{1}H nmr that had originally aroused our suspicion and here significant differences were observed particularly for the methoxyl residues (3.80 and 3.40 δ synthetic, 3.77 and 3.74 δ natural), the C-2 proton (3.53 δ compared to 3.80 δ) and the methyl groups (1.04, 1.25 and 1.53 δ as opposed to 0.85, 0.87 and 0.97 δ in the natural product).

Unfortunately, the spectroscopic data published for the natural product[2] does not suggest an alternate structure.

In results not reported here, attempts were made to optimise the initial alkylation and later to favor the cyclisation with a methoxyl group placed para to the point of closure[3]. No significant improvements resulted. Despite the low yields, particularly when attaching the homo-benzylic halide to the dimedone derivative, for the purpose of confirming structures the Pan method could probably be the fastest reliable synthetic route to many diterpenes with functions in the A ring.

EXPERIMENTAL[4]

PREPARATION OF 4-METHOXY-3-isoPROPYLPHENETOL **2f** *3-Acetyl-4-methoxyphenylethyl acetate* [**2b**]. To $AlCl_3$ (8 g : 2 eq) in 1,2-dichloroethane (170 mL) at 0° was added CH_3COCl (6.3 mL : 3 eq) and then alcohol **2a** (4.51 g). The mixture was stirred overnight at room temp then poured into ice/10% HCl and extracted (EtOAc) to give **2b** (4.54 g): ir: 1730 and 1665 cm^{-1}; ^{1}H nmr δ 1.98 (s, 3H), 2.56 (s, 3H), 2.84 (t, 2H, J = 7 Hz),, 3.85 (s, 3H), 4.19 (t, 2H, J = 7 Hz), 6.87 (d, J = 8.5 Hz), 7.28 (dd, J = 8.5 and 2 Hz) and 7.55 (d, J = 2 Hz); eims *m/z* [M^+] 194(32), 179(100), 176(79) 163(32) and 161(97).

3-(1-Hydroxy-1-methylethyl)-4-methoxyphenylethanol [**2c**] To the Grignard reagent prepared from Mg (4 g) and CH_3I (1.2 mL) in ether (75 mL) was added **2b** (6.94 g) in ether (36 mL) at 5° and the mixture was refluxed for 1 h then poured into sat NH_4Cl soln and extracted to give **2c** (4.54 g): ^{1}H nmr δ 1.58 (s, 6H), 2.77 (t, 2H, J = 6.5 Hz), 3.77 (t, 2H, J = 6.5 Hz), 3.87 (s, 3H), 6.84 (d, J = 8 Hz), 7.07 (dd, J = 8 and 2 Hz) and 7.14 (d, J = 2 Hz).

3-(1-Methylethenyl)-4-methoxyphenylethyl acetate [**2d**] Diol **2c** (4.54 g) was refluxed in glac HOAc (35 mL) for 2 h. The cooled soln was diluted with water and extracted with ether to give **2d** (4.53 g) : ^{1}H nmr δ 2.03 (s, 3H), 2.10 (s, 3H, Me-C=C), 2.86 (t, 2H, J = 7 Hz), 3.81 (s, 3H), 4.24 (t, 2H, J = 7 Hz), 5.03 and 5.13 (2d, 2H, J = 1.5 Hz, -C=CH$_2$), 6.80 (d, J = 8 Hz), 7.03 (d, J = 2 Hz) and 7.07 (dd, J = 8 and 2 Hz).

3-isoPropyl-4-methoxyphenylethyl acetate [**2e**] Hydrogenation of **2d** (4.53 g) in ether (46 mL) over 10% Pd/C (310 mg) at 30 psi during 20 h (Parr apparatus) afforded **2e** (3.08 g): ^{1}H nmr δ 1.20 (d, 6H, J = 7 Hz), 2.04 (s, 3H), 2.87 (t, 2H, J = 7 Hz), 3.29 (quint, J = 7 Hz), 3.80 (s, 1h), 4.24 (t, 2H, J = 7 Hz), 6.77 (d, J = 8 Hz), 7.00 (dd, J = 8 and 2 Hz) and 7.03 (br.s).

3-isoPropyl-4-methoxyphenetol [**2f**] Hydrolysis of ester **2e** (3.08 g) in MeOH (51 mL) and 5% aq NaOH (43 mL) gave the alcohol **2f** (2.50 g): ^{1}H nmr δ 1.22 (d, 6H, J = 7 Hz), 2.81 (t, 2H, J = 6.5 Hz), 3.29 (quint, 1H, J = 7 Hz), 3.81 (s, 3H), 6.79 (d, J = 8 Hz), 7.03 (dd, J = 8 and 2 Hz) and 7.03 (d, J = 2 Hz).

3-isoPropyl-4-methoxyphenylethyl iodide [**3**] Following the Corey procedure[5], iodine (4.19 g) was slowly added to a soln of alcohol **2f** (2.3 g), triphenylphosphine (4.13 g), imidazole (1.11 g) and CH_3CN (9.8 mL) in ether (16.4 mL) at 0°. After adding more ether the soln was washed with sat aq $Na_2S_2O_3$, sat aq $CuSO_4$ then water, dried, evaporated and chromatographed (silica gel, pet. ether) to give iodide **3** (pale yellow oil, 3.23 g: 90%), : ^{1}H nmr δ 1.26 (d, 6H, J = 7 Hz, CHMe$_2$), 3.16 (t, 2H, J = 8 Hz, 7-CH$_2$), 3.35 (m, 1H, CHMe$_2$), 3.35 (t, 2H, J = 8 Hz, CH$_2$I), 3.85 (s, 3H, OMe) and arom H at 6.82 (d, 1H, J = 8 Hz), 7.02 (d, 1H, J = 8 Hz) and 7.07 (br.s, 1H); ^{13}C nmr δ 6.45, 22.64, 26.63, 39.98 55.34, 110.30, 126.05, 126.12, 132.67, 137.07 and 155.59; eims *m/z* [M$^+$] 304(7), 178(13), 177(100), 163(19), 135(34).

ALKYLATION OF DIMEDONE isoPROPYL ETHER. The isopropyl enol ether **4** was prepared in refluxing benzene in a Dean-Stark apparatus from dimedone, isopropanol and p-TsOH (catalytic quant). Ether **4** (0.098 g) in THF (1 mL) was added to a soln of LDA (1.5 M in cyclohexane 0.79 mL) in THF (1 mL) at -78° and stirring continued for 40 min before slowly introducing iodide **3** (0.20 g) in ether (2.2 mL). After 1 h at -78° the soln was allowed to warm to room temp and stirred overnight. Sat aq NH_4Cl was added and the product extracted into ether. Flash chromatography (pet.ether/30% ether) gave some unreacted **4**, 4-methoxy-3-isopropylstyrene arising from HI elimination from **3** and then ketone **5** (0.030 g : 16%, colorless oil) : ir(film)

1645, 1600 and 1490 cm^{-1}; ^1H nmr δ (numbered as for a cyclised diterpene) 0.95 and 1.03 (2s, ring gem diMe), 1.19 (d, 6H, J = 7 Hz, $\underline{Me}_2$CH-Ar), 1.28 (d, 6H, J = 6 Hz, $\underline{Me}_2$CH-O), 1.98 (dd, 1H, J = 8 and 5 Hz, H-C.5), 2.12 (d,1H, J_{gem} = 17,5 Hz, H-C.3), 2.26 (d, 1H, J = 17.5 Hz, H-C.3), 3.28 (quint, 1H, J = 7 Hz, H-C.15), 3.79 (s, 3H, OMe), 4.42 (quint, 1H, J = 6 Hz, OC$\underline{H}$Me$_2$), 5.27 (s, 1H, H-C.1), 6.75 (d, 1H, J = 8 Hz, H-C.11), 6.99 (dd, 1H, J = 8 and 2 Hz, H-C.9) and 7.03 (d, J = 2 Hz, H-C.14), ^{13}C nmr δ 21.39 (ring gem diMe), 22.62 ($\underline{Me}_2$CH-Ar), 26.59 (C.15), 28.45 (OCH$\underline{Me}_2$), 34.23 (C.6), 34.96 (C.4), 42.12 (C.3 and C.7), 55.34 (OMe), 56.20 (C.5), 70.57 (O$\underline{C}$HMe$_2$), 100.86 (C.1), 110.11 (C.11), 126.14 (C.9 and C.14), 134.25 (C.13), 136.65 (C.8), 154.80 (C.12), 173.06 (C.2) and 202.44 (C.10); eims *m/z* [M^+] 358(0.3), 182(46), 176(43), 167(61) and 125(100).

METHYLATION AND CYCLISATION. MeLi (1.87 mL, 1.4 M in ether) was added to the enone **5** (0.172 g) in THF (4.3 mL) at room temp and stirring continued for 2 h. The mixture was poured into water and extracted with ether to give a mixture of products (tlc and nmr) which was heated under N_2 at 115° in 85% phosphoric acid for 6 h. Water was added and the product obtained by ether extraction and flash chromatography (pet.ether/15% ether) was a mixture of **7a** and **7b** (9:1 resp): ir 1710 cm^{-1}; ^1H nmr δ 0.60, 1.10 and 1.34 (methyls 'cis'), 1.02, 1.19, 1.23 (methyls 'trans'), 1.26 (d, 6H, J = 7 Hz, isoPr-Me), 2.34 (d, 1H, J = 15 Hz, H-C.3), 2.62 (d, 1H, J = 15 Hz, H-C.3), 3.00 (dd, 1H, J = 15 and 1 Hz, H-C.1), 3.22 (quint, 1H, J = 7 Hz, C$\underline{H}$Me$_2$), 3.80 (s, 3H, OMe), 6.72 (s, 1H, H-C.11) and 6.83 (s, 1H, H-C.14); eims *m/z* [M^+] 314(23), 216(19), 215(100), 201(39), 173(43) and 158(44); hrms *m/z* 314.2246 ($C_{21}H_{30}O_2$ requires 314.224).

REDUCTION AND METHYLATION. The ketone **7a** (containing ca 10% **7b**) (0.071 g) was reduced with $NaBH_4$ (0.0073 g) in MeOH (2.16 mL) and the product obtained by flash chromatography was taken up in THF (2.8 mL) and treated with NaH (11 mg, 95%) and then CH_3I (0.016 mL). Flash chromatography gave **1** (13 mg) as the main component : ir film 3020-2800(CH), 1610 and 1500(arom), 1455, 1240 and 1090 cm^{-1}; ^1H nmr δ 1.04 (s, 3H, Me(ax)-C.4), 1.19 and 1.20 (2d, 6H, J = 7 Hz, isoPr-Me)[6], 1.25 (s, 3H, Me(eq)-C.4), 1.53 (s, 3H, Me-C.10), 2.66 (dd, 2H, J = 10 and 4 Hz, H-C.7), 3.21 (quint, 1H, J = 7 Hz, C$\underline{H}$Me$_2$), 3.40 (s, 3H, MeO-C.2), 3.53 (ddd, 1H, J = 11 and 4 Hz, H-C.2), 3.80 (s, 3H, MeO-C.12), 6.77 (s, 1H, H-C.11) and 6.80 (s, 1H, H-C.14); ^{13}C nmr δ 22.55 and 22.67 (C16 and C17), 22.75 (C6), 26.33 (C15), 30.63 (C7), 31.82 (C20), 32.41

(C18), 32.63 (C19), 35.20 (C10), 40.22(C4), 41.42 and 42.67 (C1 and C3), 51.06 (C5), 55.42 and 55.51 (MeO at C2 and C12), 74.82 (C2), 109.10 (C11), 125.48 (C14), 127.83 (C8), 134.15 (C13), 145.49 (C9) and 155.10 (C12); hrms *m/z* 330.2560 ($C_{22}H_{34}O_2$ requires 330.2559).

The smaller amount of the minor product (**1** but with rings AB cis) showed ; ^{1}H nmr δ 0.39, 0.97 and 1.58 (3s, each 3H, Me_2C.4 and C.10), 1.18 (2d, 6H, isoPr Me)[6], 1.69 (dd, 1H, J = 12 and 3 Hz, H-C.5), 2.80 (dd, 2H, J = 11.5 and 3.5 Hz, H-C.7), 3.22 (quint, 1H, J = 7 Hz, H-C.15), 3.40 (s, 3H, MeO-C.2), 3.60 (dd, 1H, J = 8.5 and 4 Hz, H-C.2), 3.82 (s, 3H, MeO-C.12), 6.80 (s,1H, H-C.11) and 6.82 (s, 1H, H-C.14).

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