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SYNTHESIS OF AROMATIC DITERPENES
SYNTHESIS OF 12-HYDROXY-ABIETA-8,11,13-TRIEN-3,7-DIONE

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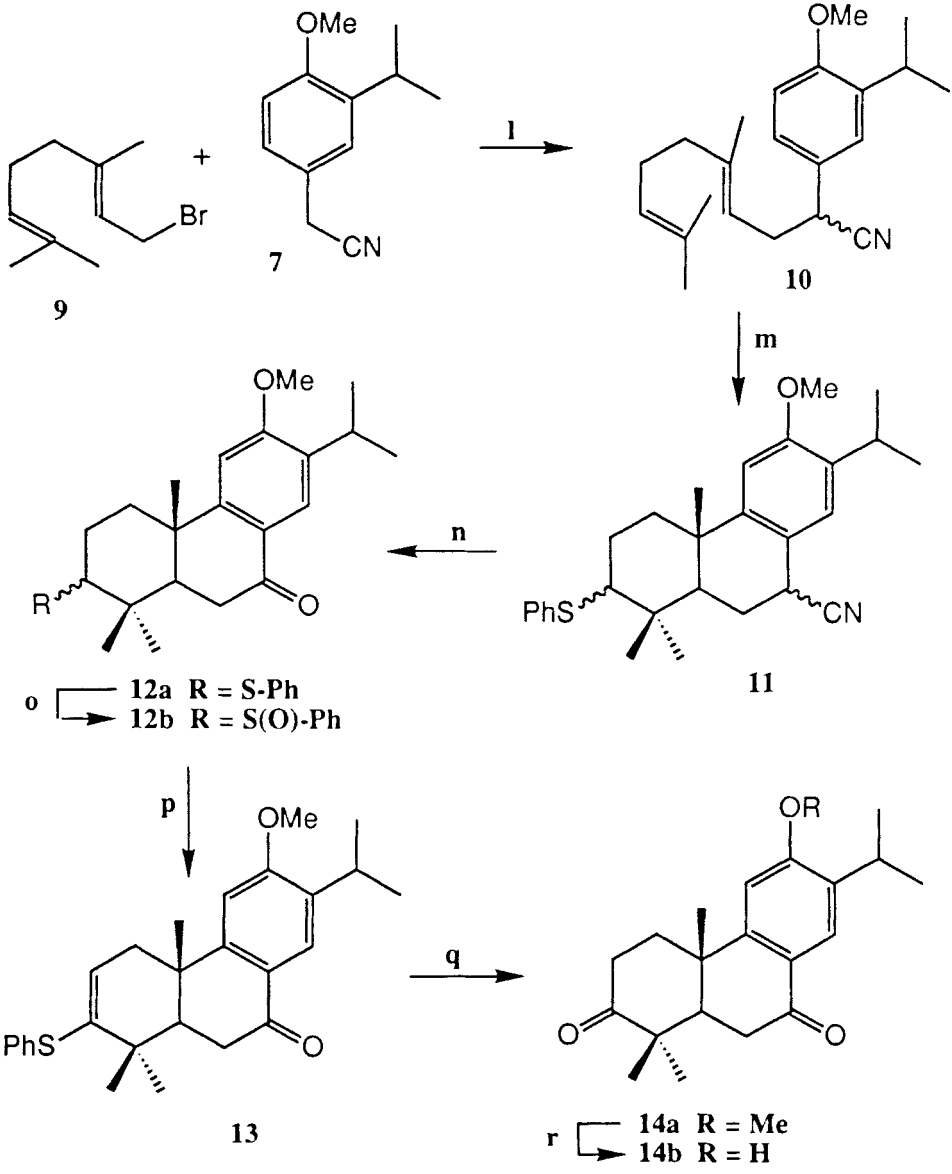
Abstract: Model studies involving cationic cyclisation of suitable dienes have provided a synthesis of the title compound. Preparation of the dienes from available aromatic starting materials and the modification of the cyclised products are described.

A wide variety of aromatic diterpenes is known in which oxygen functions are found in the A ring including more complex examples such as candelabrone[1] and ceasalpin F[2] or the simpler naturally occuring but unnamed 12-hydroxy-abieta-8,11,13-trien-3,7-dione **14b**. In the past, and in current projects, we have been trying to find rewarding syntheses of members of this group of natural products starting from the inexpensive, chiral podocarpic and dehydroabietic acids[3]. At the same time, however, we hoped to establish the three rings fundamental to these structures by the cyclisation of suitably unsaturated intermediates and this study describes some of our results in this area[4]. This approach to **14b** is inspired by the methodology of Harring and Livinghouse[5]. The products are all racemic.

For our purposes the starting materials were geranyl bromide **9** which is commercially available and 4-methoxy-3-iso-propylphenylacetonitrile **7** which is not. We first prepared the latter from p-methoxyphenylethanol **1** by introducing the iso-propyl passing via the C-acetyl derivative **2** , the tertiary alcohol **3** (Grignard addition) and hydrogenation of the dehydration product **4**. The resulting alcohol **5** was oxidised to the aldehyde, the oxime



For reaction conditions and yields - reference 4

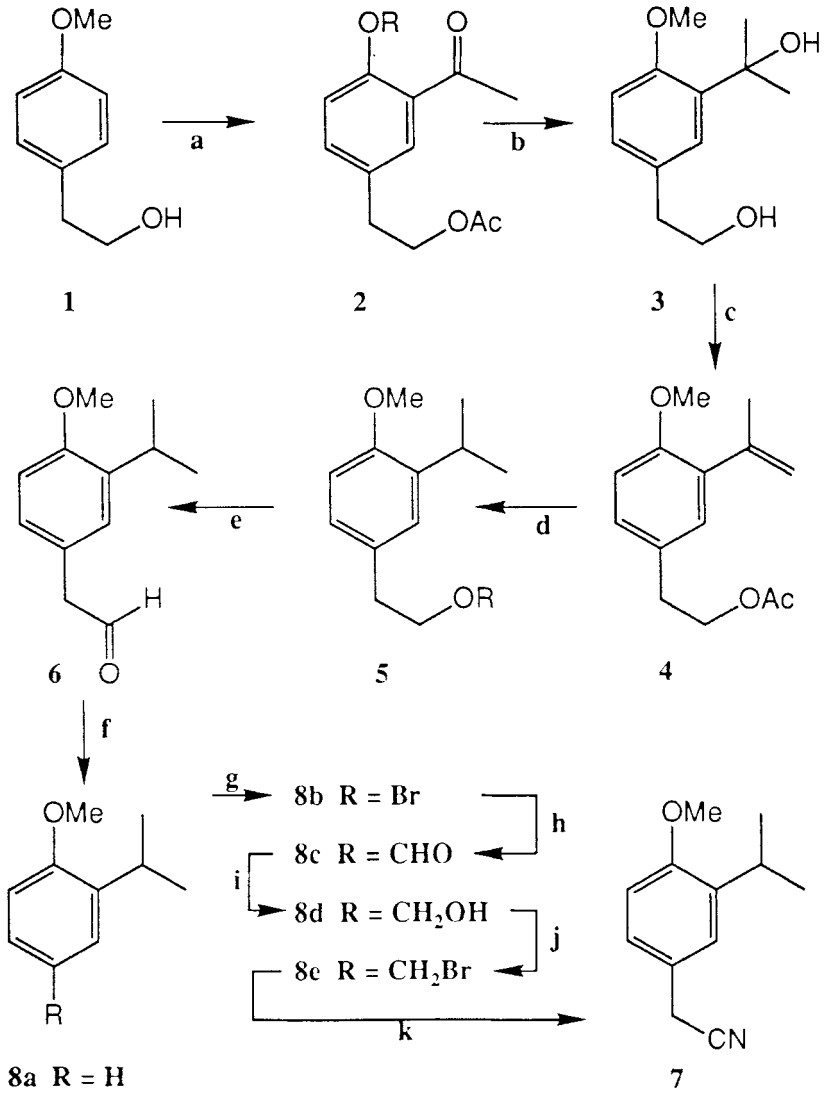
of which was dehydrated to the required nitrile **7**. This last step proved to be difficult in that the reaction mixture darkened alarmingly and the yields were variable and this prompted us to try an alternate preparation. In a parrallel project[6] involving the corresponding phenylpropanol we did not encounter the difficulties of this phenylethanol sequence.

o-iso-Propylanisole **8a** is cleanly brominated by m-CPBA and KBr in the presence of 18-crown-6 . The bromo substituant in the product **8b** was replaced by an aldehyde residue (Grignard, DMF) and after reduction to the benzylic alcohol **8d** and conversion to the primary bromide **8d**, the nitrile **7** was obtained by reaction with KCN and 18-crown-6 in almost quantitative yield. Although the overall yields were similar, this second route was easier, cleaner and faster

Conditions for the alkylation of the 4-methoxy-isopropyl substrate **2** by the geranyl bromide **9** were optimised using unsubstituted phenylacetonitrile itself and each subsequent step was first mastered in this cheaper model series but in this communication only the methoxy-isopropyl compounds will be described.

The allylic (geranyl) bromide **9** readily alkylates the nitrile **2** (LDA, THF: 85%) to afford the non-conjugated dienyl compound **10**. Cyclisation attempts gave very poor results with N-phenylselenosuccinimide[7] and with the mercury(II) triflate N,N-dimethylaniline complex[8] but using methyl benzenesulfenate with BF_3 in nitromethane[9] gave the phenylthio ether **11** in good yield. The relative stereochemistry as ascertained by ^1H nmr discloses a *trans* ring junction, predominantly the β-isomer at C.3 and both epimers at the nitrile bearing C.7. The data is best interpreted if the A ring is in the boat (or twisted boat) conformation.

In the presence of LDA the benzylic proton α to the nitrile is removed and the intermediate reacts readily with oxygen and the ensuing work-up provokes the elimination of the nitrile to afford the ketone **12a**. Introducing the carbonyl at C.3 was more demanding. The thio ether was first oxidised to the sulfoxide **12b** (m-CPBA, CH_2Cl_2 : 92%). The latter, on treatment with trifluoroacetic anhydride and pyridine was transformed to the vinyl thio ether **13** which after complexing with titanium tetrachloride in acetic acid and then refluxing in water, afforded the 3,7-diketone **14a** in excellent yield (93%). Overall, from the coupling of the two starting products, the yield is 18% (as compared to 20% in the model sequence).



For reaction conditions and yields - reference 4

Demethylation with BBr_3 gave the phenol **14b** which was identical in all respects with the natural product obtained from *Chamaecyparis formosensis* by Yu-Shia Cheng[10] except , of course, that our product was racemic. The 200 MHz ^1H nmr spectrum promptly provided by Professor Yu-Shia Cheng and that of our product were identical. We hope that essentially the same methodology will afford syntheses of more complex diterpenes.

Experimental

Cyclisation of the diene **10**

Following the method described by Livinghouse[5] a solution of methylbenzenesulfenate (0.126 g : 0.875 mmole prepared from phenyl disulfide[11,12]) in nitromethane (12.0 mL) was cooled to -30°C and BF_3-CH_3NO_2 (1.34 mL of 1.24 M prepared by bubbling BF_3 into CH_3NO_2 at 0°C) was added. After 2.25 min. the diene **10** (0.207 g : 0.817 mmole) was introduced in CH_3NO_2 (2 mL) and stirring was continued at -30°C for 2 h. Sat. aq. $NaHCO_3$ (100 mL) was added and the mixture allowed to warm to room temp. The product was extracted into ether, washed with $NaHCO_3$, water and brine and after drying over $MgSO_4$, the solvent was evaporated. Flash chromatography (silica gel, pet. ether-ether(15%)) afforded the cyclised product **11** (0.224 g : 76%), *7-cyano-3-phenylthio-12-methoxyabieta-8,11,13-triene*, m.p. 194-195°C: ir (Mattson Sirius 100 FTIR, KBr): 3050, 2227, 1598 and 1503 cm^{-1}; ^1H nmr (Varian XL-200) δ: 1.02 (s, 3H, Me-C.4(α)), 1.18 and 1.19 (2d, 6H, J = 6.5 Hz, iso-Pr methyls), 1.23 (s, 3H, Me-C.4(β)), 1.40 (s, 3H, Me-C.10), 1.76 (dd, J = 11.92 and 1.16 Hz, H-C.5), 2.04 (m, 2H, H_2-C.6), 2.25 and 1.51 (2m, 2H, H_2-C.1), 2.25 and 2.04 (2m, 2H, H_2-C.2), 2.95 (dd, 1H, J = 7.98 and 7.47 Hz, H-C.3), 3.21 (sept, 1H, J = 6.88 Hz, H-C.15), 3.77 (s, 3H, MeO-C.12), 4.06 (d, 1H, J = 5.18 Hz, H-C.7), 6.65 (s, 1H, H-C.11), 7.01 (s, 1H, H-C.14), 7.15 to 7.35 (m, 3H) and 7.35 to 7.45 (m, 2H, Ph-S); mass m/z: 433 (M^+, 15.5), 309 (12), 308 (52), 255 (37), 254 (19), 241 (19), 240 (41), 229 (35), 228 (100), 226 (31), 226 (32), 185 (25), 110 (41) and 97 (23). Exact mass calcd for $C_{28}H_{35}NOS$: 433.2269; found (hrms): 433.2354.

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4 The conditions and yields for the lettered reactions in the drawings were: **(a)** CH_3COCl,$AlCl_3$, CH_2CL_2, r.t., 8 h : 78%. **(b)** CH_3MgI, ether, 5°C : 85%. **(c)** glac. HOAc, reflux, 2 h : 100%. **(d)** H_2, Pd/C, 40 psi, ether: 99%. **(e)** PCC, HOAc, Celite, Molecular sieve 4Å, CH_2Cl_2: 75% counting the recovered starting material. **(f)** The primary acetate was first hydrolysed with NaOH in MeOH/H_2O at r.t. for 2h (100%) then i) $NH_2OH.HCl$, NaOH, EtOH/H_2O, r.t., 4 h ii) Ac_2O, reflux, 4 h : 57%. **(g)** KBr, 18-cr-6, m-CPBA, CH_2Cl_2, 0°C, 30 min : 84%. **(h)** Mg, THF then DMF: 98%. **(i)** $NaBH_4$, MeOH, r.t., 12 min : 97%. **(j)** PBr_3, pyr, benzene, r.t., 3 h : 98%. **(k)** KCN, 18-cr-6, CH_3CN, 60°, 1 h : 80%. **(l)** LDA, THF, -78°C then add **9**, r.t., 3 h :85%. **(m)** See Experimental Section **(n)** i) LDA, THF, -78°C, bubble O_2, 1 h ii) 1M $SnCl_2$ in 2M HCl, 0°C : 55%. **(o)** m-CPBA, CH_2Cl_2, -78°C : 92%. **(p)** Trifluoroacetic anhydride, pyr, CH_2Cl_2, 0°C, 5 h : 72%. **(q)** glac. HOAc, $TiCl_4$, r.t., 20 min ii) H_2O, reflux, 1 h : 93%. **(r)** BBr_3, CH_2Cl_2, 0°C rising to r.t., overnight : 91%.

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