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An Expedient Route to the Preparation of Key Intermediates for the Total Synthesis of Aphidacolin, Stemodin and Oryzalexin S[1]

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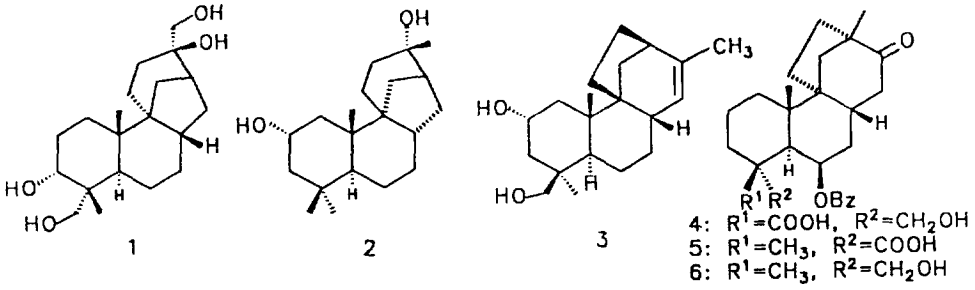
Abstract: A strategy for the construction of tricyclo[6.3.1.0^{1,6}]dodecane and tricyclo[7.2.1.0^{1,6}]dodecane carbon skeleton present in several complex diterpenes is described.

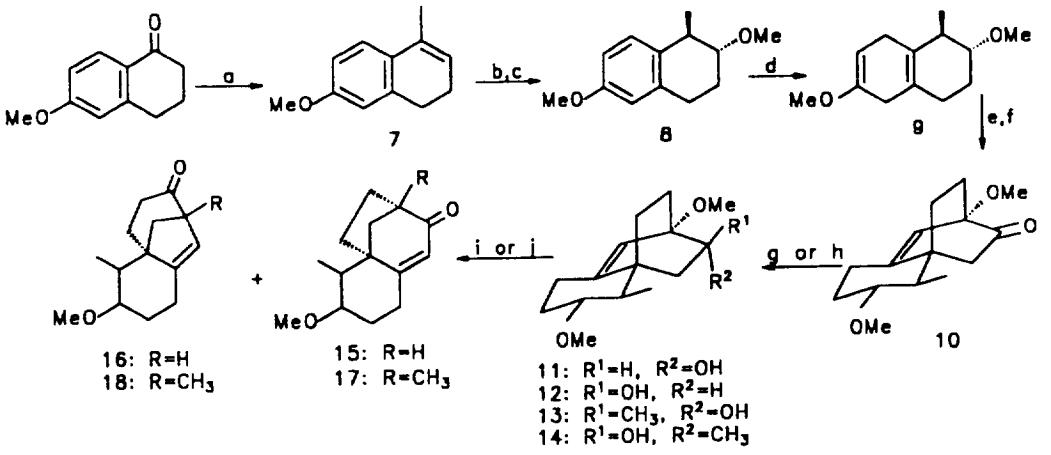
A number of tetracyclic diterpenes e.g., aphidacolin **1**[2], stemodin **2**[3], oryzalexin S **3**[4], scopadulcic acid A **4**, B **5**, and scopadulciol **6**[5] possess the spirofused bicyclo[3.2.1]octane moiety either with a bridgehead methyl or hydrogen as the structural subunit. Among these diterpenes, aphidacolin **1** isolated from the fungus *Cephalosporium aphidacola* Petch, has attracted considerable interest owing to its high potentiality as an anticancer and antiherpes agent. The presence of a unique tricyclo[6.3.1.0^{1,6}]dodecane or tricyclo[7.2.1.0^{1,6}]dodecane carbon skeleton in conjunction with a number of quaternary and stereogenic centres makes these diterpenes synthetically challenging and attractive.



We have earlier reported[6,7] the total synthesis of tricyclic sesquiterpenes which involved a novel skeletal rearrangement of 1-methoxybicyclo[2.2.2]octenols to bicyclo[3.2.1]octenones. This methodology is now extended to construct the tricyclo[6.3.1.0^{1,6}]dodecane and tricyclo[7.2.1.0^{1,6}]dodecane framework present in the above diterpenes. We now report a short and expedient route to the preparation of the key intermediates required for the synthesis of the diterpenes **1-6**.

Reaction of 6-methoxy-1-tetralone with MeLi followed by acidic work up afforded the olefin **7**. Hydroboration of **7** followed by oxidation gave the *trans* alcohol whose methyl ether **8** was reduced with Li/EtOH/NH_3 to afford the diene **9**. Cycloaddition reaction of the diene **9** with α-chloroacrylonitrile gave an adduct which was hydrolysed to the ketone **10**.

Sodium borohydride reduction of the ketone **10** furnished a mixture of the *endo* and *exo* alcohols **11** & **12** (2:1) in good yield. This mixture was treated with $BF_3.Et_2O$ or methanesulfonyl chloride in triethylamine affording a separable mixture of the enones **15** and **16**[8]. The enones **15** & **16** possess the BCD ring skeleton of oryzalexin S, aphidacolin and stemodin with all the functional groups and stereogenic centres at appropriate places which could be further elaborated.



Reagents & Conditions: *a) MeLi, Ether, 0°C, 2h, then H_3O^+, 90% b) BH_3 in THF, 6h, NaOH, H_2O_2, 85% c) NaH, MeI, THF, $(nBu)_4N^+I^-$, R.T., 24 h, 95% d) Li, Liq. NH_3, EtOH, Ether, -33°C, 2h, 90% e) CH_2:C(Cl)CN, benzene, reflux, 36h, 80% on the basis of 40% recovery of starting material(aromatised) f) $Na_2S.9H_2O$, EtOH, H_2O, 24h, 80% g) $NaBH_4$, EtOH, 1h, 90% h) MeLi, Ether, 0°C, 2h, 90% i) $BF_3.Et_2O$, benzene, reflux, 12h, 72% j)MsCl, Et_3N, 0°C, 2h, then H_3O^+, 75%*

Reaction of the ketone **10** with methyl lithium yielded a mixture of the *endo* and *exo* alcohols **13** & **14** which was readily separated by chromatography. The *endo* alcohol **13** on treatment with $BF_3.Et_2O$ gave a separable mixture of enones **17** & **18**(1:9). Similar treatment of the *exo* alcohol **14** resulted in the same proportion of the enones **17** & **18**[8]. The unsaturated ketone **17**, with its structural features, formed the BCD ring system of scopadulcanes. The acid catalysed[7] conversion of **18** into **17** is being examined to improve the selectivity in the rearrangement. The conversion of **15**, **16** and **17** into the natural products is under progress.

In conclusion, we report an expedient route to the preparation of key intermediates for the total syntheses of aphidacolin, stemodin and oryzalexin S.

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References and notes:

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8. All the new compounds exhibited satisfactory spectral and analytical data. Selected spectral data for **15**: IR (neat): ν_{max} 2930, 1670 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 5.69 (1H, bs), 3.37 (3H, s), 3.39 (3H, s), 1.1-3.1 (13H, m), 1.1 & 0.96 (3H, d J=7Hz). For **16**: IR (neat): ν_{max} 2930, 1720 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 5.55 (1H, bs), 3.38 (3H, s), 3.33 (3H, s), 3.31 (1H, m), 1.2-2.6 (12H, m) 1.03 & 0.93 (3H, d J=7.1Hz). For **17**: IR (neat): ν_{max} 2925, 1670 cm^{-1}. ^1H NMR (90 MHz, $CDCl_3$): δ 5.7 (1H, bs), 3.4 (3H, s), 3.36 (3H, s), 2.98 (1H, dt J=9 & 5.4 Hz), 1.1-2.6 (11H, m), 1.21 (3H, s), 1.04 & 0.91 (3H, d J=7Hz). For **18**:IR (neat): ν_{max} 2925, 1720 cm^{-1}. ^1H NMR (90MHz, $CDCl_3$): δ 5.22 (1H, s), 3.36 (3H, s), 3.3 (3H, s) 2.96 (1H, dt J=9 & 3.6 Hz) 1.3-2.7 (11H, m), 1.1 (3H, s), 1.0 & 0.91 (3H, s).

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