

AN ANELATION PROCEDURE FOR THE SYNTHESIS
OF POLYSUBSTITUTED TERPENOID INTERMEDIATES

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The well known Robinson annelation¹ has been used repeatedly in the synthesis of steroids and terpenoids.

The method is, however, highly efficient only in cases where the desired product carries the typical steroid like substitution with an oxygen in the 3-position. In connection with our studies on diterpene alkaloid synthesis² we have developed an alternative relatively simple annelation procedure which is capable of producing the substitution pattern portrayed in formula 1. Intermediates of this type are potentially useful in the synthesis of a variety of polysubstituted terpenoids.

As an example of this process we wish to describe the synthesis starting with 7-methoxy-2-teralone³. This compound was methylated by the Stork method to give 96% of the methyl derivative 2a*⁴. Compound 2a was treated with a small excess of sodium hydride and benzyl chloromethyl ether⁵ in benzene and the mixture was stirred at room temperature for 14 hours.

Chromatography on silica gel gave a 60% yield of the pure oily product 2b.

Ketalization of 2b with ethylene glycol and p-toluenesulphonic acid in benzene yielded 90% of the crystalline ketal 3a (m.p. 66-67°C). Hydrogenation of this material with palladium on

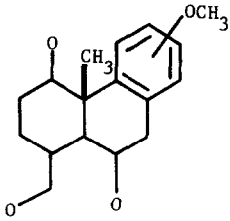
* All compounds gave correct molecular ions in mass spectrometry and all crystalline compounds correct elemental analyses. Infrared and N.M.R. data were in all cases in agreement with the structures assigned and will be mentioned only where specially relevant.

calcium carbonate in alcohol gave 92% of the oily alcohol 3b. Oxidation of 3b with chromium trioxide in pyridine gave a quantitative yield of the aldehyde 3c (N.M.R. singlet (1H) $\tau = 0.3$ p.p.m.) which was homogeneous in T.L.C. and immediately used in the synthesis.

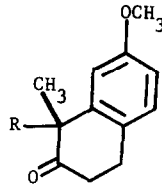
Treatment of the aldehyde 3c with an excess of the Grignard reagent prepared from 5-bromopentene-1 in tetrahydrofuran gave the alcohols 4a and 4b in a yield of 90% and a ratio 6:1. [Oxidation of the alcoholic group followed by reduction with lithium aluminum hydride may be used to invert this ratio].⁸ The alcohols were methylated with sodium hydride and methyl iodide in dioxane and the corresponding oily methoxy derivatives 5a and 5b which were obtained in a 96% yield were separated on silica gel. Hydroxylation of the double bond in these compounds with osmic acid-sodium chlorate, cleavage of the corresponding diols accompanied by deketalization by aqueous periodic acid and treatment of the resulting crude ketoaldehydes with aqueous methanolic bicarbonate at 50°C yielded the two crystalline aldehydes 6a (m.p. 95°C) and 6b (m.p. 89°C) respectively in an overall yield of 50%. Compound 6a; I.R.: 1675 cm^{-1} , N.M.R.: singlet (1H) $\tau = -0.25$ p.p.m. (aldehyde), N.M.R.: singlets (3H) $\tau = 6.20, 6.94, 8.55$ p.p.m. (2(OCH₃) and C-CH₃).

For compound 6b most of the spectral data were very similar as for compound 6a and the identity of the mass spectra of 6a and 6b demonstrated clearly that they were epimers. There are, however, two important differences in the N.M.R. spectrum of 6b which clearly define the configuration of the ring A methoxyl. The aliphatic methoxyl of 6b is shifted downfield to $\tau = 6.58$ p.p.m. by the deshielding influence of the benzene ring and conversely one of the aromatic hydrogens of the anisole ring is shifted downfield to $\tau = 2.42$ p.p.m. by the deshielding action of the ring A methoxyl. [All the aromatic hydrogens of 6a are above 2.60 p.p.m.]. Acetalization of 6a in refluxing benzene with p-toluenesulphonic acid and ethylene glycol yielded the oily acetal 7 [N.M.R.: doublet (1H) $\tau = 4.90$ p.p.m. (acetal hydrogen), quadruplet (1H) $\tau = 4.05$ p.p.m. (vinylic hydrogen)], which was used to introduce a variety of oxygen functions at the position indicated by the arrow. This work as well as synthetic studies in two similar series will be reported in full papers at a later date^{6, 7}.

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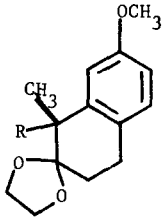


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2a (R=H)

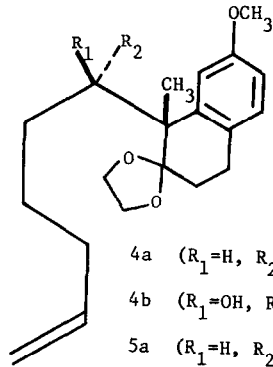
2b (R=-CH₂-O-CH₂-C₆H₅)



3a (R=-CH₂-O-CH₂-C₆H₅)

3b (R=-CH₂-OH)

3c (R=-C(=O)H)

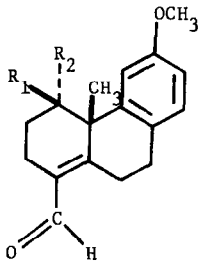


4a (R₁=H, R₂=OH)

4b (R₁=OH, R₂=H)

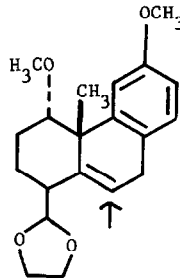
5a (R₁=H, R₂=OCH₃)

5b (R₁=OCH₃, R₂=H)



6a (R₁=H, R₂=OCH₃)

6b (R₁=OCH₃, R₂=H)



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7. Unpublished work by R. C. Jain, M. Sunagawa and R. Vlahov; see also M. Sunagawa, Ph.D. Thesis, University of New Brunswick, spring, 1972.
8. For a disucssion of the relatively high stereoselectivity in reactions of this type see reference 2.