Regio- and Stereo-controlled Total Synthesis of the Stemodane Nucleus; an Unusual Diterpene Skeleton

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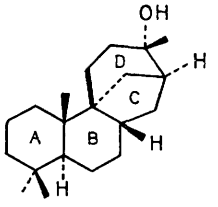
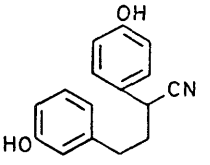
Summary Photocatalysed intramolecular oxidative phenol coupling and subsequent regiospecific intramolecular C–H insertion have been utilized as the key steps for a totally synthetic route to the unusual tetracyclic diterpene, deoxystemodin (**1**).

COMPOUND (**1**), which has an unusual carbon framework, and which is a recent addition to the diterpene skeletal variants, is encountered in stemodin and stemodinone.[1] An earlier synthetic approach[2] towards this skeleton envisaged the ABC + D → ABCD sequence for forming the ring system. The present communication describes an improved and stereospecific route (ABD + C → ABCD) towards (**1**) utilizing photocatalysed intramolecular oxidative phenol coupling[3] and regiospecific intramolecular C–H insertion (Bamford–Stevens reaction) as the key steps. This projected synthesis employs fewer steps as compared to the one reported[2] earlier and furnishes an overall yield of 34% from start to finish.



(1)



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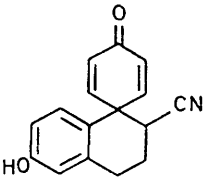
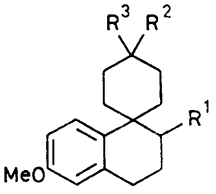
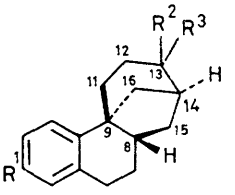


(3)

The known conversion[3] (**2** → **3**) *via* phenol coupling has been modified with an improved yield† by the use of trifluoroacetic acid (TFA) as the co-solvent. Treatment of (**2**) in TFA–ether (3 : 1) solution with $VOCl_3$ ($2{\cdot}5 \times 10^{-3}$ M solution) at −78 °C and under illumination (250 W tungsten lamp) for 3 h gave (**3**) which on catalytic hydrogenation over Pd–C (10%) and subsequent *O*-methylation by dimethyl sulphate and aqueous alkali afforded the known ketone (**4**). The carbonyl group in this ketone was protected *via* acetalization with ethylene glycol to obtain (**5**)‡ which on reduction[4] with di-isobutylaluminium hydride furnished the aldehyde (**6**), m.p. 47 °C. Deacetalization in the presence of aqueous acid gave (**7**), m.p. 59 °C. Attempts to effect the C-ring cyclization through internal aldol cyclization under various experimental conditions were not rewarding. The corresponding tosylhydrazone (**8**), m.p. 191 °C, was selectively formed according to the method of Farnum.[5] Thermal decomposition of (**8**) in acetamide solution in the presence of sodium at 140 °C for 3 h gave almost exclusively (87%) the known insertion product (**9**),[2a] found to be homogeneous by g.l.c. Molecular model examinations revealed that intramolecular C–H insertion at C-14 in the reactive conformation of the molecule would be easy from the β-face and this would lead to the desired relative stereochemistry at C-8, C-9, and C-14.





	R^1	R^2	R^3
(**4**);	CN	=O	
(**5**);	CN	–O–[CH_2]–O–	
(**6**);	CHO	–O–[CH_2]–O–	
(**7**);	CHO	=O	
(**8**);	CH : NNHTs	=O	

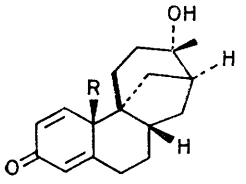
	R^1	R^2	R^3
(**9**);	OMe	=O	
(**10**);	OMe	α-Me	β-OH
(**11**);	OMe	β-Me	α-OH
(**12**);	OMe	β-Me	α-OAc
(**13**);	OH	β-Me	α-OH

Ts = $MeC_6H_4SO_2$-*p*

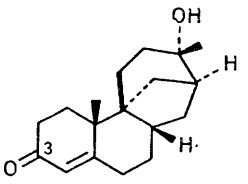
Addition of methylmagnesium iodide to (**9**) gave, as expected,[2b] a 40 : 60 mixture of the epimeric alcohols (**10**) and (**11**). Separation of the alcohol mixture was effectively done by converting them into their corresponding acetates and by subsequent chromatographic separation over neutral alumina; the desired acetate (**12**) had m.p. 111 °C. Demethylation[6] of (**12**) by boron tribromide and alkaline work-up afforded (**13**), m.p. 132·5 °C. When treated[7] with TFA and hexamethylphosphoric triamide, (**13**) gave the aldehyde (**14**), m.p. 91 °C, λ_{max} 246 nm. Steric influence due to the C-16 methylene bridge is expected to direct the introduction of the angular formyl group from the opposite β-face. Based on the significant difference in the electrophilicity of the cross-conjugated dienone and the aldehyde, preferential Wolff–Kishner reduction of (**14**) furnished (**15**), m.p. 75·5 °C. Controlled catalytic hydrogenation (1 mol of H_2) over Pd–C (10%) resulted in the

† The previously reported yield of this conversion was 49% which has been improved to 85% in this study.

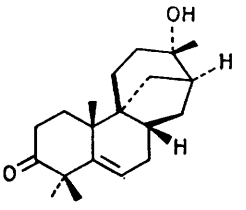
‡ Satisfactory C and H combustion analyses and spectral data (i.r., u.v., and n.m.r.) were obtained for all new compounds. Experimental details will be published elsewhere.



(14); R = CHO
(15); R = Me



(16)



(17)

selective reduction of the sterically more exposed[8] double bond to give (**16**), m.p. 79 °C. The C-13 hydroxy group was converted into the corresponding acetate. Methylation of this acetate employing methyl iodide and potassium t-butoxide afforded, after brief aqueous alkali treatment, the dimethyl derivative (**17**), 123 °C. Catalytic hydrogenation of (**17**) over Pd–C (5%) yielded the desired stemodane nucleus (**1**),[1] m.p. 144 °C, $\delta(CDCl_3)$ 0·90, 0·93, 0·97, and 1·13 (four 3H singlets due to the methyl protons), $\delta[(CD_3)_2SO]$ 3·23 (1H, s, –OH), ν_{max} 3590 and 3430 cm^{-1}. Hydrogenation is expected to have taken place from the less hindered α-face.

The derivative (**1**) as obtained from this synthesis was found to be completely identical with the deoxy natural derivatives of stemodine and stemodinone, thus corroborating the structures deduced for these unusual diterpene alcohols.

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