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TANDEM RADICAL CYCLISATION - INTRAMOLECULAR MUKAIYAMA ALDOLISATION APPROACH TO FORSKOLIN

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Summary: The trans-decalin lactone(11), an advanced intermediate towards forskolin(1), has been elaborated in five steps from the bromo-acetal(4) using a novel stereoselective intramolecular radical mediated cyclisation reaction, viz (4)→(5), in tandem with an intramolecular Mukaiyama aldolisation, viz (10)→(11).

Forskolin(1) is the major pharmacologically active deterpene isolated from the roots of the Indian plant Coleus forskohlii.[1] Extracts of the roots from C.forskohlii have been used locally as a medicine for centuries. Forskolin is a potent positive inotropic agent, as well as being a potent bronchodilator and hypotensive agent. In addition, the molecule has been shown to inhibit platelet aggregation in vivo and in vitro, as well as the metastasis of tumors. The pharmacological activities of forskolin are related to its ability to activate adenylate cyclase, a membrane bound enzyme.[2]

Forskolin is one of the most oxygenated secondary metabolites yet isolated. In addition, its decalin based molecular framework accommodates eight asymmetric centres, seven of which are contiguous. These structural features, together with its wide pharmacological profile have combined to make forskolin a challenging target for synthesis. Previous synthetic approaches towards forskolin have been based on intramolecular cycloaddition, with the ubiquitous intramolecular Diels-Alder reaction predominant.[3] In this Letter, we describe a conceptually new approach to the decalin carbon framework in forskolin, which is based on a novel stereoselective intramolecular radical mediated cyclisation reaction viz (4)→(5), in tandem with an intramolecular Mukaiyama aldolisation, viz (10→(11) (cf. Scheme).

Thus, the known and readily available hydroxy β-ionone(2)[4] was first converted to the γ,δ-unsaturated ketone (3a; Bu_3SnH; 95%), and then into the corresponding vinyl ether (3b; $EtOCH{:}CH_2$, $Hg(OAc)_2$; 57%).[5] Treatment of the

vinyl ether(3b) with N-bromosuccinimide in methanol at -20°C led to a mixture of diastereoisomers of the bromo-acetal(4), which then underwent smooth stereoselective 5-exo-trig radical cyclisation in the presence of catalytic vitamin B_{12} (MeOH, $LiClO_4$, -1.8v, 24h)[6] to produce the cycloadduct(5) in 70% yield; n.m.r. data showed that the adduct(5) contained less than 5% of the corresponding isomer(6). Interestingly, cyclisation of the bromo-acetal(4) in the presence of tri-n-butyltin hydride (AIBN,C_6H_6, reflux,2h) led to predominantly the equatorial isomer (6 ; ratio 3:1; combined yield 95%). Treatment of the axial isomer(5) with Jones' reagent resulted in simultaneous hydrolysis and oxidation leading to the oily lactone(7) whose stereochemistry followed conclusively from n.O.e experiments. Furthermore, similar treatment of the isomeric acetal(6) produced the crystalline lactone (8 ; 85%) m.p. 81-81.5°C whose structure and stereochemistry were confirmed by X-ray crystallographic analysis.[7]

After conversion of the keto-lactone(7) to the corresponding dioxolan(9 ; 85%), treatment with lithium hexamethyldisilylazide followed by t-butyldimethylsilyl chloride (-70°C, then 0°C) provided the silyl ether (10 ; 95%). Addition of (10) to a cold solution of titanium tetrachloride in methylene dichloride (-78°C) resulted in smooth intramolecular Mukaiyama aldolisation leading to a mixture of diastereoisomers of the substituted decalin (11) in a combined yield of 62%. The geometry assigned to the epimer(11), which was separated by chromatography, followed conclusively from n.O.e experiments.

In a similar series of experiments to those used to produce the decalin(11) from (7), the isomeric keto-lactone(8) was converted into a mixture of diastereoisomers of the corresponding (cis-ring fused) substituted decalin(12)[8] in an overall yield of 85%. Thus, in five simple steps, starting from the bromo-acetal(4), we have been able to access the advanced precursors (11) and (12) to forskolin and its isomers, using the stereoselective tandem radical cyclisation-intramolecular Mukaiyama aldolisation approach [viz (4)→(5), then (10)→(11) and (4)→(6)→(12)]. Treatment of either of the substituted glycols (11) and (12) with potassium hydroxide in aqueous methanol resulted in facile β-elimination leading to the corresponding unsaturated 'trans' and 'cis'-decalin lactones (13) and (14) respectively.[8] Studies are now in progress to elaborate the ring C (pyranone) portion of forskolin, and thence forskolin itself, from (13) and intermediates, viz (15) and (16), derived therefrom.

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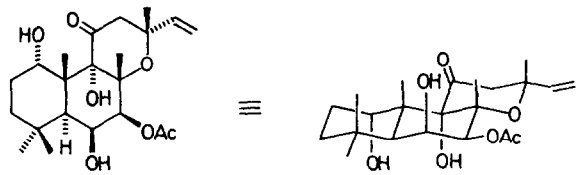
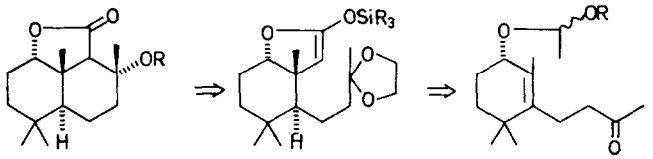
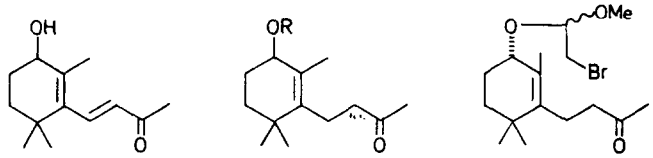


(1)

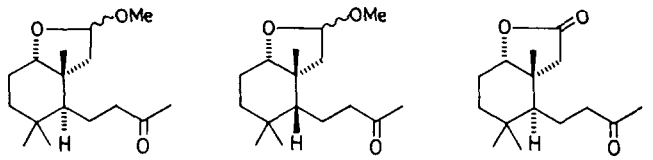


Scheme

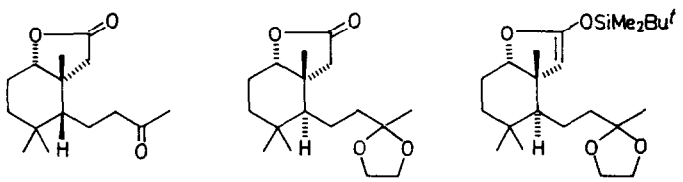


(2) (3) (4)

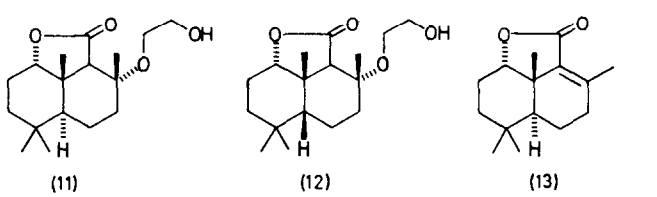
a R = H; *b* R = CH:CH_2



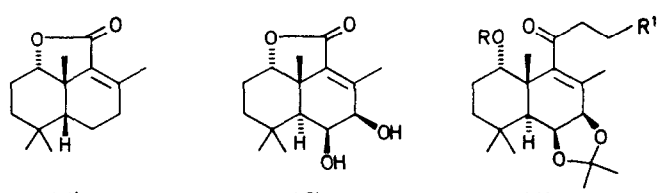
(5) (6) (7)



(8) (9) (10)



(11) (12) (13)



(14) (15) (16)

References

+ Present address: Glaxo Group Research, Greenford, Middlesex, UB6 OHE.

1. S.V. Bhat, B.S. Bajwa, H. Dornauer, N.J. de Souza and H.W. Fehlhaber, Tetrahedron Lett., 1977, 1669.

2. See: K.B. Seamon, Annu.Rept., Med.Chem., 1984, 19, 293.

3. P.G. Baraldi, A. Barco, S. Benetti, G.P. Pollini, E. Polo and D. Simoni, J.C.S.Chem.Commun., 1986, 757; F.E. Ziegler, B.H. Jaynes and M.T. Saindane, Tetrahedron Lett., 1985, 44, 3307; K.C. Nicolaou and W.S. Li, J.C.S., Chem.Commun., 1985, 421; P.R. Jenkins, K.A Menear, P. Barraclough and M.S. Nobbs, ibid, 1984, 1423.

4. H.B. Henbest, J.Chem.Soc., 1951, 1074.

5. Satisfactory spectroscopic data, together with microanalytical and/or mass spectroscopic data were obtained for all new compounds.

6. cf. R. Scheffold, G. Rytz and L. Walder, "Modern Synthetic Methods" 1983, Vol.3, 355, Ed., R.Scheffold.

7. We thank Dr. M.J. Begley of this department for this information.

8. The geometry assigned to the epimer(12), which was separated by chomatography, followed from the p.m.r. data: δ 0.97(Me), 1.11(Me), 1.36(Me), 1.45(Me), 2.33(1H), 4.28(1H, dd, J8 and 4.5Hz), together with n.O.e. experiments.

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