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THE SYNTHESIS OF (±)*CIS*-TRIKENTRIN A

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Abstract- *The synthesis of a novel sponge metabolite is described, utilising an aryl radical cyclisation to form the substituted indane system.*

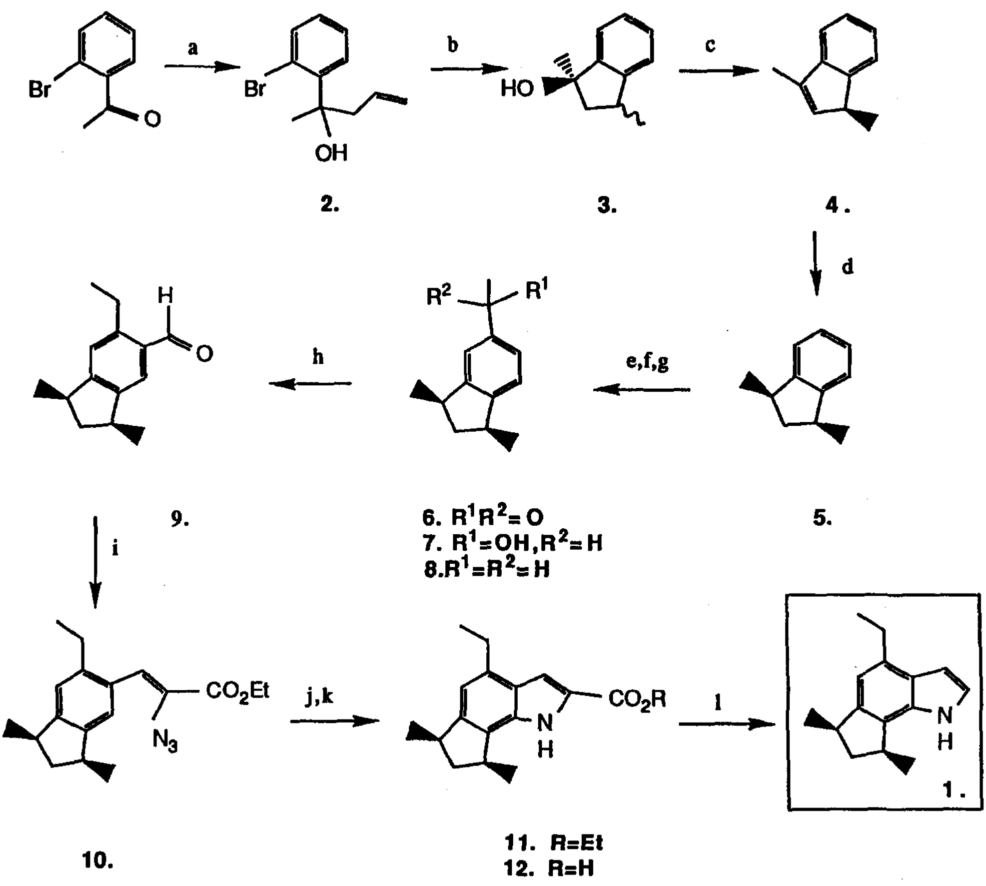
The trikentrins are a group of novel, biologically active indoles recently isolated from the marine sponge *Trikentrion flabelliforme.*[1] They all contain a dimethylcyclopentene moiety fused to an indole ring, as typified by *cis*- trikentrin A (1). The indane system present in 1 appeared an ideal candidate for the application of an aryl radical cyclisation to synthesis. While such cyclisations have been the subject of considerable mechanistic study[2,3], only examples giving heterocyclic rings have been used in the synthesis of natural products.

The radical precursor 2[4] was readily obtained (75%) by action of allylmagnesium bromide on *o*-bromoacetophenone. Treatment of 2 with tributyltin hydride led to a mixture of *cis*- and *trans*- indanols 3 after potassium fluoride work up. These could be separated by column chromatography but this was accompanied by the ready elimination of water. Conversion of the diastereomeric mixture to dimethylindene 4, and subsequent hydrogenation, provided an efficient route to the epimeric dimethylindanes [88% from 2] with the *cis*- isomer 5 predominating (9:1 *cis:trans*).

Acetylation of the mixture of dimethylindanes using CH_3COCl / $AlCl_3$ yielded the desired 5-substituted indane [shown as the major *cis*- compound 6] (85%) with no trace of the 4-substituted product, presumably due to steric effects. After reduction in two steps to the ethyl compound 8 (79%), regiospecific formylation was achieved using CH_2ClOMe /$TiCl_4$ to give 9 (74%).

The indole ring was then elaborated via condensation of 9 with ethyl azidoacetate and thermolysis of the resulting unsaturated azide 10 (95%)[5]. Removal of the minor amount of the *trans*- isomer could be accomplished by column chromatography at this stage. The ester 11 obtained was hydrolysed to the acid 12 (74%) with KOH in dioxan/water. Problems previously encountered in the decarboxylation of indole 2-carboxylic acids[6] were avoided by the use of flash vacuum pyrolysis to remove the acid function (89%), producing (±) *cis*- trikentrin A(1), identical in all respects except optical activity with the natural product[7].

Adaptations of this route directed to the synthesis of the other trikentrins is in progress.



a) CH_2CHCH_2MgBr,Et_2O b) $Bu_3SnH,AIBN,C_6H_6$ c) $H^+,CHCl_3$ d) $H_2,PdC,CHCl_3$ e) $AcCl,AlCl_3,CH_2Cl_2$ f) $NaBH_4,MeOH$ g) $H_2,PdC,CHCl_3$ h) $Cl_2HCOCH_3,TiCl_4,CH_2Cl_2$ i) $EtO_2CCH_2N_3,NaOEt,EtOH$ j) C_7H_8 k) KOH,H_2O,dioxan l) F.V.P.,600°C,0.003mmHg.

1) R. J. Capon and J. K. MacLeod, *Tetrahedron,* 1986, **42**, 6545.

2) B. Giese, "Radicals in Organic Syntheses", Pergamon, Oxford, 1986.

3) A. N. Abeywickrema and A. L. J. Beckwith, *J.Chem.Soc., Chem.Commun.,* 1986, 464.

4) All new compounds gave satisfactory elemental analyses or accurate mass measurements and ^1H & ^{13}C n.m.r. spectra consistent with the assigned structures.

5) C. J. Moody, *J.Chem.Soc., Perkin Trans.1,* 1984, 1333.

6) *See Ref.5 and E.Piers and R.K.Brown, Can.J.Chem,* 1962, **40**, 559.

7) δ_H 8.1(b,1H),7.15(dd,1H).6.83(s,1H),6.59(dd,1H),3.4(m,1H),3.2(m,1H),2.93(q,2H), 2.60(m,1H),1.49(d,3H),1.38(d,3H),1.37(t,3H),1.3(m,1H). (cf.Ref.1.)

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