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Convergent Stereocontrolled Construction of 5-7-6 Tricyclic Aza Analogues of Phorbol and Aconite Alkaloids

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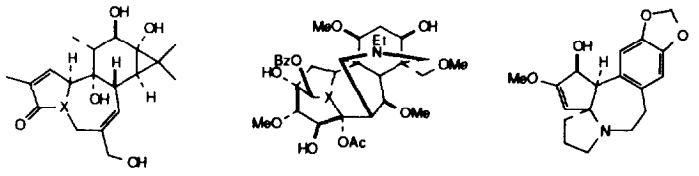
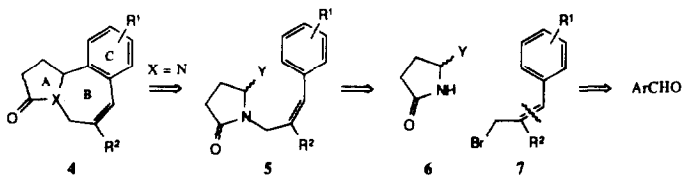
Abstract: An acyliminium cyclization is used to construct the central seven-membered ring of 5-7-6 tricyclic aza-analogues of diterpenoids.

The stereocontrolled construction of 5-7-6 tricyclic systems[1] of angular fusion is a problem of increasing importance that requires a general solution, in view of the number of classes of biologically active compounds incorporating that skeleton. Thus, the tumour-promoter phorbol (**1**) is representative of diterpenes of the tigliane skeleton,[2] whereas the related 5-7-6 daphnane skeleton is found in gnidicin which exhibits significant activity against P388 leukaemia.[3] Aconitine (**2**) (X = CH) incorporating a 5-7-6 substructure is representative of another set of complex carbocyclic systems, the aconite alkaloids,[4] notable for their cardiotonic and sedative properties. The antileukaemic activity of the *Cephalotaxus* alkaloids,[5] such as cephalotaxine (**3**) suggested that a general route to 5-7-6 systems that are either carbocyclic, or incorporate one nitrogen atom in the ring system would be of notable



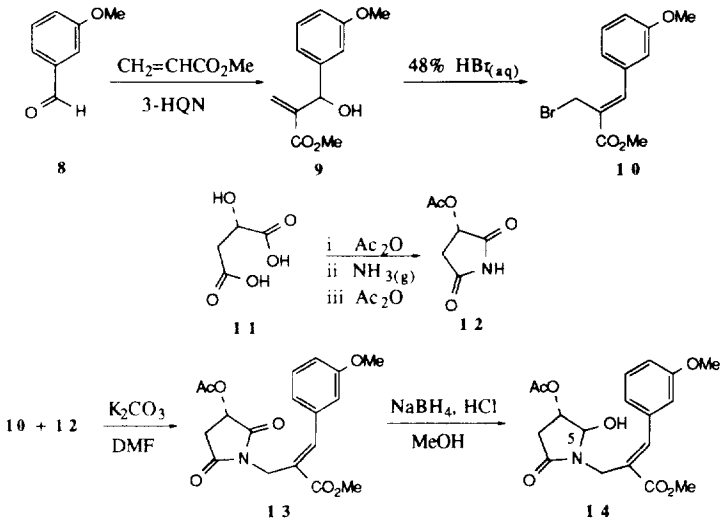
Phorbol (**1**) X = C(β-OH) Aconitine (**2**) X = CH Cephalotaxine (**3**)



4 **5** **6** **7**

value. It could also provide access to the hithero unknown aza-analogues of diterpenoids related to phorbol and the aconite alkaloids, (X = N in **1** and **2**).

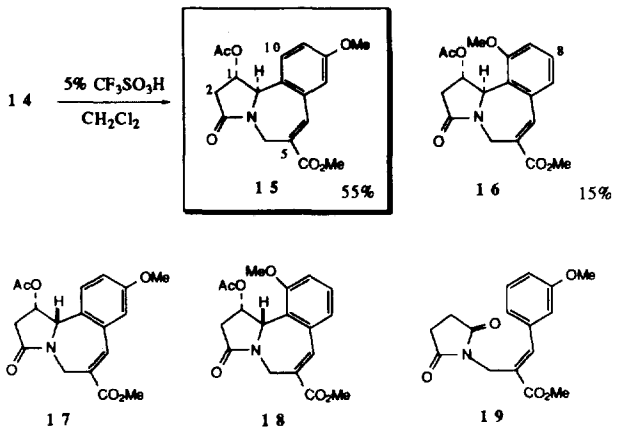
The strategy envisaged was guided by three features: (a) a convergent synthesis, (b) the desirability of a direct and intramolecular formation of the central seven-membered ring, and (c) location of the nitrogen atom at a position that would facilitate the synthesis, stereocontrol and potential pharmacological activity of the resulting 5-7-6 prototypes. Stipulation of X = N in **4** enables advantage to be taken of an acyliminium cationic cyclization[6] of **5** possessing a substituted benzene ring which would act as the π-nucleophile. Construction of **5** would depend upon an efficient *N*-alkylation of a lactam **6** by an allylic electrophile **7**. The *cisoid* configuration of **5**, a key requirement for direct cyclization to **4**, would require the development of new methodology that would deliver the configuration depicted for **7**. The configuration was envisaged as being controllable by rendering R^2 in **7** electron-deficient, in which R^2 would be in the favoured *trans*-relation to the conjugated aromatic ring.



A Baylis-Hillman reaction[7] of 3-methoxybenzaldehyde **8** with methyl acrylate using 3-hydroxyquinuclidine (3-HQN) as the catalyst afforded alcohol **9** (91%).[8] It was anticipated that S_N2' attack upon the allylic alcohol **9** could proceed *via* a conjugatively stabilized cationoid species that would lead to an unsaturated ester of the desired configuration. This was realized by treatment of **9** with 48% aqueous HBr (16 h, 20 °C), affording **10** (80%) as an oil.[8] In a model study, reaction of **10** with succinimide (K_2CO_3, DMF, 16 h, 20 °C) furnished imide **19** (80%), but the latter could not be cleanly reduced with sodium borohydride in methanol.

(3S)-3-Acetoxysuccinimide **12** was selected as a suitable precursor of the γ-lactam ring, since, following *N*-alkylation[9] and subsequent regioselective reduction,[9,10,11] advantage

could be taken of a stereoselective cyclization controlled by the absolute configuration of the acyloxy carbon atom.[11a] The succinimide **12** was prepared[11] by successive treatment of *(S)*-malic acid with acetyl chloride, ammonia and acetyl chloride (overall yield 50%). The succinimide **12** and the bromide **10** (1.0 eq.) were stirred with K_2CO_3 (1.0 eq.) in DMF[12] for 2.5 h at 20 °C, which after aqueous work-up, and column chromatography (silica; 7:3 ethyl acetate: 40-60 °C petroleum) afforded the imide **13** (62%).



Reduction[10,11] of imide **13** (1.38 mmol) with sodium borohydride (6.92 mmol) in methanol at -8 °C for 20 min) gave a 1:2.5 mixture[13] of epimers **14** (0.44 g, 87%). This material (without recrystallization) was treated with 5% CF_3SO_3H[14] in dichloromethane (75 min, 20 °C), then quenched with saturated aqueous sodium hydrogen carbonate to give a mixture[15] of tricyclic lactams **15-18**. Column chromatography (silica; 4:1 ethyl acetate: 40-60 °C petroleum ether) afforded a 3.7:1 mixture (70%) of **15:16** (R_F 0.5), and a 4:1 mixture (10%) of **17:18** (R_F 0.1). The major isomer is assigned as **15**, the α-H at the 10b-position resulting from the anticipated approach of the aromatic ring towards the less hindered face of the acyliminium moiety (*i.e.* opposite to the 1-acetoxy group).[11a] Recrystallization (twice from ethyl acetate) of the 3.7:1 mixture of **15:16** afforded the single isomer[16] **15**, m.p. 180-182 °C, of the absolute configuration depicted, $[\alpha]_D$ +144° ($CHCl_3$).

Suitable modification of **15** can be envisaged including (a) elimination of acetic acid across the 1,2-positions, (b) electrophilic substitution of the aromatic ring and (c) manipulation of the C-5 ester group to give compounds of potential pharmacological interest.[17] Although cyclizations involving acyliminium species that result in six-membered rings[6] are abundant, the present example provides one of the few known acyliminium cyclizations resulting in a seven-membered ring.[18] The succinct enantioselective synthesis of the key lactam intermediate **15** establishes a convergent strategy for the synthesis of highly functionalized aza-analogues of natural products that incorporate an angularly fused 5-7-6 tricyclic system, including aza-analogues (X = N) of phorbol (**1**) and aconitine (**2**).

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