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A SYNTHESIS OF 3α-DIHYDROCADAMBINE

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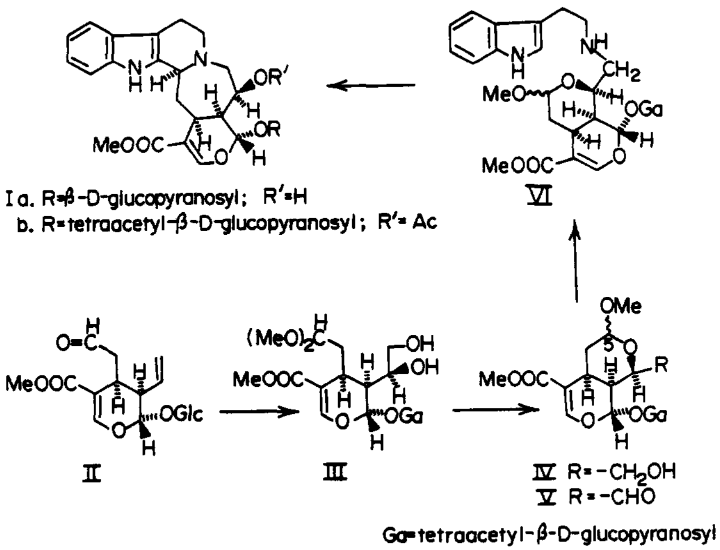
Summary: 3α-Dihydrocadambine has been synthesized from secologanin.

The structure and configuration Ia was assigned independently by Brown and Fraser[1] and by us[2] to 3α-dihydrocadambine, an alkaloid isolated from Anthocephalus cadamba[1] and Nauclea diderrichii.[2] It is probable that the alkaloid is formed biosynthetically from secologanin (II) by a condensation of the aldehyde with the tryptamine component, followed by an oxidative coupling of the vinyl side chain to close the seven-membered ring.

We have synthesized the alkaloid from the readily available secologanin, but, for several strategic reasons, we chose not to follow the presumed biosynthetic route. Instead we dihydroxylated the side chain of the dimethyl acetal of tetraacetyl-II; the major epimer formed (III) has the configuration at the secondary alcohol required for the alkaloid.[3] Treatment of III with Amberlite IR 120 resin in methanol converted it quantitatively to the cyclic acetals IV (C-5 epimers)[4], providing protection for both the aldehyde and the secondary alcohol functions. Oxidation of IV with PCC on Celite in dichloromethane with sodium acetate present[5] converted it in good yield to an aldehyde (V) that was immediately treated with tryptamine hydrochloride in the presence of sodium cyanoborohydride, to provide VI (a separable mixture of anomers; yield, 56% from IV).

Regeneration of the aldehyde from VI and catalysis of the Pictet-Spengler to form the desired skeleton both require acidic conditions, but the difficulty of hydrolyzing an acetal in the presence of a neighboring basic nitrogen is well known, and comment has been made[6] about the difficulty of forming a seven-membered ring by a Pictet-Spengler reaction; (there is precedent, however.[7]) Attempts to carry out the conversion under various acidic conditions confirmed that it is difficult to hydrolyze the acetal without causing irreversible damage to the rest of the molecule; however, when VI was heated in 90% formic acid to 95° for 18 h, and then deacylated (K_2CO_3 in MeOH), chromatography provided a material (yield 10%, not optimized) identical with natural 3α-dihydrocadambine; the product was further characterized as its pentaacetate, which was identical in every respect, including optical activity (CD, 350 - 205 nm), with a sample of Ib prepared from natural Ia.



Ia. R=β-D-glucopyranosyl; R'=H

b. R=tetraacetyl-β-D-glucopyranosyl; R'= Ac

II

III

IV R=-CH_2OH

V R=-CHO

VI

Ga=tetraacetyl-β-D-glucopyranosyl

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