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BIOGENETICALLY PATTERNED SYNTHESIS OF CADAMBINE

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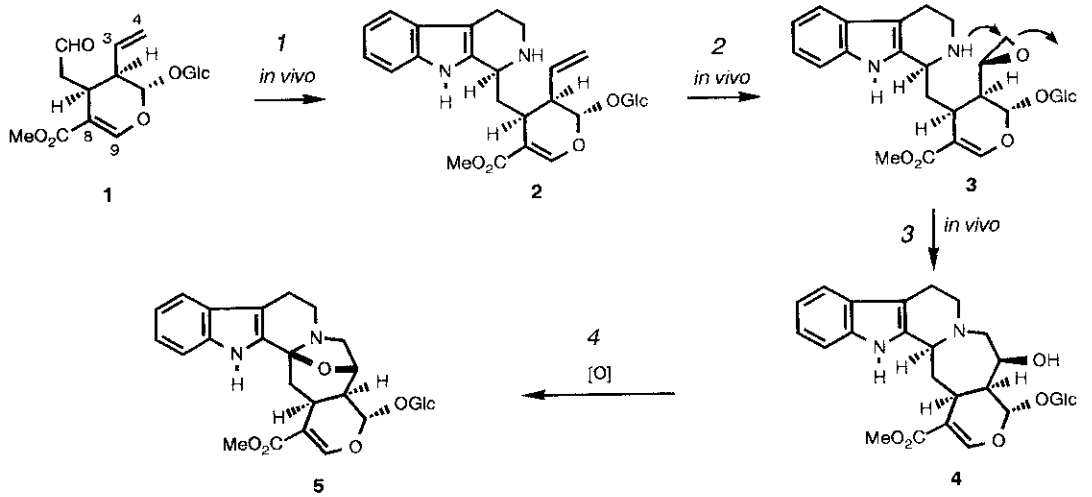
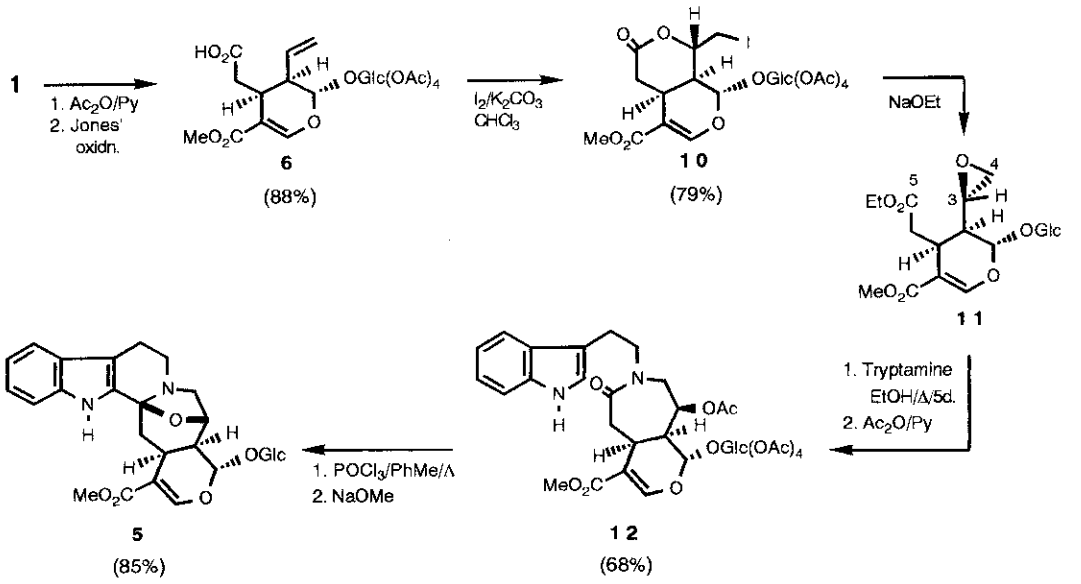
Summary: *We report the synthesis of the glucosidic indole alkaloid cadambine (**5**) in 48% yield from its biological precursor secologanin (**1**) in an intermolecular variant of the* in vivo *process where chemoselective and regioselective attack by tryptamine on a 3S-epoxide **11** yields the seven-membered azepine ring.*

The glucosidic indole alkaloid cadambine **5** isolated from *Anthocephalus cadamba*[1] is considered to be biosynthesized from secologanin **1** *via* the universal precursor strictosidine **2**. Stereospecific epoxidation to give the 18,19*S*-epoxystrictosidine **3** and regioselective intramolecular attack by $N_{(b)}$ on the epoxide yields 3α-dihydrocadambine **4** with the formation of a seven-membered azepine ring[1,2]. Oxidation of C-3 and cyclization of the alcohol leads to cadambine **5**. We now report the synthesis of cadambine from its biological precursor secologanin **1** in an intermolecular variant of the *in vivo* process where chemoselective and regioselective attack by tryptamine on a 3*S*-epoxide **11** yields the seven-membered azepine ring. Essentially we have interchanged the condensation step *1* and oxidation step *4* of the natural sequence.

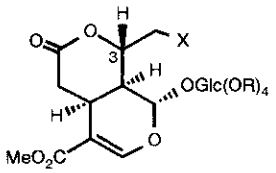


Our first step was a simple Jones' oxidation of secologanin tetra-acetate to give secoxyloganin tetra-acetate **6**. However, the subsequent epoxidation of the 3,4-vinyl group presented major problems both in competitive attack on the 8,9-enol ether and in controlling C-3 stereochemistry. These were eventually resolved by a highly chemoselective and stereoselective iodolactonisation of secoxyloganin tetra-acetate to afford the key intermediate **10**.



Halolactonization of **6** can give two other products **8** and **9** in addition to the desired 3(*S*) lactone **7**: using bromine, the glucoside (R = H) gave a quantitative yield of the undesired 9-lactone, whereas the tetra-acetate (R = Ac) gave a 2:1 ratio of 9- and 3-lactones[3], the latter being a 10:1 mixture of stereoisomers **7** and **8**, *i.e.* increasing the steric bulk of the sugar moiety reduced the rate of 8,9 *vis-à-vis* 3,4 attack. We then decided to replace bromine by iodine because its larger size could also decrease 8,9-selectivity, and indeed using iodine on the glucoside afforded a 50:50 mixture of 9- and 3-lactones. Combining the two steric effects by using the tetra-acetate with iodine as electrophile we obtained essentially one 3-lactone in good yield with none of the other stereoisomer.

			Product ratio (%)		
X	R	**Solvent**	**7**	**8**	**9**
Br	H	H_2O	-	-	100
Br	Ac	CH_2Cl_2	30	3	67
I	H	H_2O/KI_3	50	-	50
I	Ac	CH_2Cl_2	95	-	5



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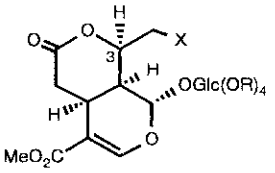

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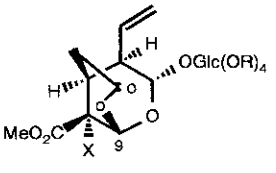

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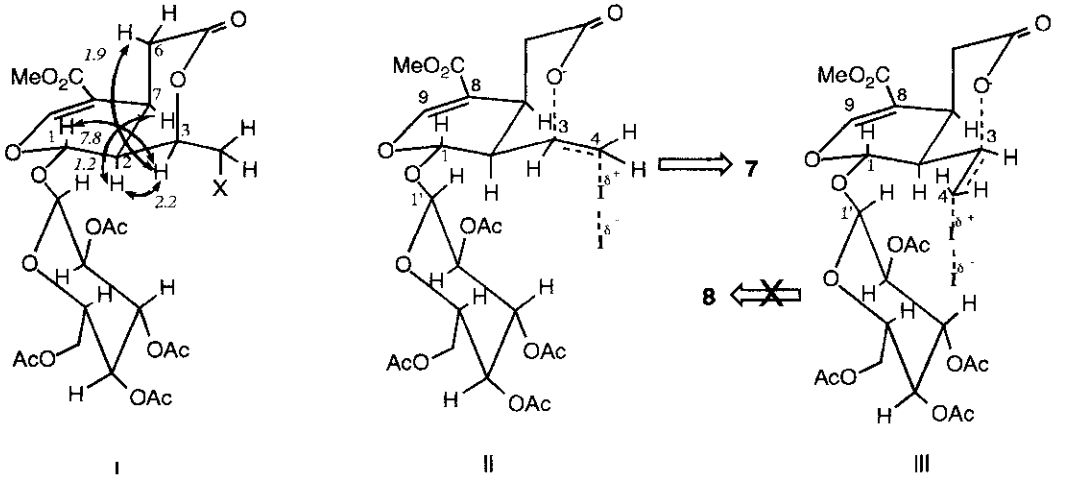
On the basis of stereochemical arguments given below we had anticipated that the major product would be the desired 3*S*-lactone **7**, but to confirm this n.O.e. experiments were required. These showed key through-space correlations for H-3 with H-1 and H-6_{ax} but not with H-7 or H-6_{eq} (Fig. I) only consistent with an equatorial 3*S* orientation. If H-3 had been axial, some interaction with H-7 and H-6_{eq} would have been expected and none with H-1.

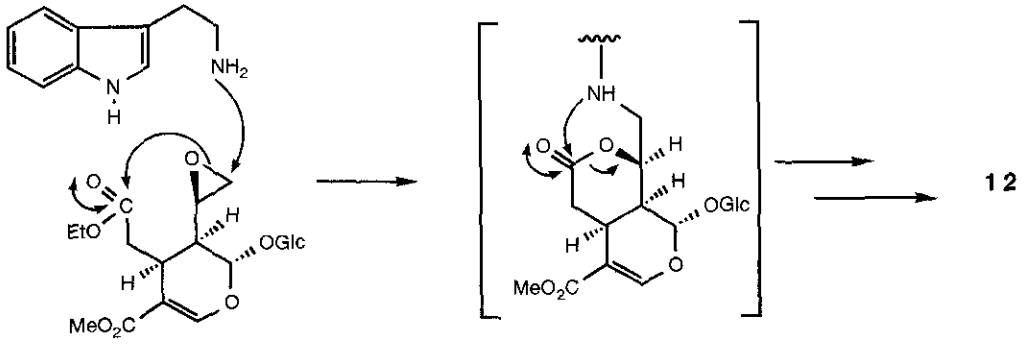
Formation of the 3*S*-iodolactone **7** rather than the 3*R* **8** is rationalised by the following argument. Attack by iodine and carboxylate on the 3,4-alkene must be in an antiperiplanar manner with a chair-like transition state for the δ-lactone ring. Both II and III satisfy these requirements, but by rotation about the C-1/O bond the acetylated sugar moiety sweeps through the region that would be occupied by C-4 and the iodine electrophile in III, but only by H-3 in II. Hence the latter with lesser steric crowding is preferred exclusively with iodine, although with the smaller bromine reaction does occur to some extent *via* the alternative pathway. Again, rotation about the C-1'/O linkage will sweep directly under the 8,9-alkene across the trajectory of the electrophile with a resulting steric retardation. This is particularly effective with the bulky iodine, diverting attack almost completely to the 3,4-alkene, but much less so with the smaller bromine electrophile.



I II III

Subsequent treatment with alkoxide afforded the desired 3*S*-epoxide with concomitant de-acetylation of the sugar. The next step required a chemoselective and regioselective reaction of tryptamine with C-4 of the epoxide in the presence of other sites that were susceptible to nucleophilic attack: the other carbon C-3 of the epoxide, the C-5 ester, the C-10 ester and the conjugated alkene at C-9. Of these possibilities the β-alkoxyacrylate ester system was known to react sluggishly, and under basic conditions C-3 was unlikely to compete with the less hindered C-4. The greatest danger lay with the C-5 ester, since, although we wished it to react subsequently with the amine to form the azepine ring, if it reacted first, an amide would be formed. This would not be nucleophilic enough to open the epoxide under these reaction conditions, and in any case would almost certainly lead to a six rather than seven-membered ring. Initially we used sodium methoxide to give the epoxide with a methyl C-5 ester, but the reaction with tryptamine in refluxing methanol yielded a mixture of products including amides. We considered that increasing the size of

the alkyl group at the C-5 ester might decrease its rate of reaction relative to the epoxide. An isopropyl group seemed suitable but potassium isopropoxide reacted too slowly with the lactone and Zemplen de-acetylation was incomplete. However the ethyl ester epoxide **11** could be obtained readily, using 1.7 equivalents of sodium ethoxide in ethanol, interestingly without any appreciable exchange of the C-10 methyl ester. In the event the ethyl group provided sufficient steric retardation to be effective. Thus heating **11** with tryptamine in ethanol under reflux for five days, and subsequent acetylation gave in the reasonable yield of 68% from **10** the desired azepine lactam **12** ($[\alpha]_D^{20}$ -85° ($CHCl_3$), ν_{max} 1757 (OAc), 1642 (NCO) cm^{-1}, δ 7.28 (*d*, *J*≈ 1.5, H-17), 5.18 (*d*, *J* = 7, H-21), 4.47 (*m*, H-19), 4.01 (*m*, H-5_a), 3.41 (*m*, H-5_b), 3.36 (*m*, 2H-$18_{a,b}$), 3.09 (*m*, H-6_a), 3.00 (*m*, H-15), 2.99 (*m*, 2H-$14_{a,b}$), 2.91 (*m*, H-6_b), 1.90 (*m*, H-20), M^+ 772.2680 Calc. for $C_{37}H_{44}N_2O_{16}$ 772.2690). Direct cyclisation to a seven-membered ring is much more difficult than a six or five, but we rationalised that it could in this case be obtained by initial formation of a δ-lactone **13** from the C-3 alcohol, and subsequent opening of the lactone by $N_{(b)}$ *via* a five-membered ring intermediate.



11 **13**

Finally, Bischler-Napieralski cyclization of **12** followed by Zemplen de-acetylation gave cadambine **5** (tetra-acetate: m.p. 149-151°C, $[\alpha]_D^{20}$ -124° ($CHCl_3$)[4]) identical with natural material in an overall yield of 48% from secologanin **1**. This synthesis corroborates the structure and absolute stereochemistry unambiguously determined for cadambine from n.m.r. and c.d. spectra and other data[1]. Cadambine and its immediate precursor can be selectively reduced[1] to either 3α- or 3β-dihydrocadambine, which have been obtained as a mixture in a previous synthesis[5].

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References

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2. G.I. Dimitrienko, D.G. Murray and S. McLean, *Tet. Letters*, 1961 (1974).
3. D. M. Duckworth, Ph.D. Thesis, Manchester University, 1978.
4. The rotation given in ref. 1 is incorrect.
5. R.G. Hamilton, G.N. Saunders and S. McLean, *Can. J. Chem.*, **61**, 284 (1983).

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