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AN ENANTIOSELECTIVE ENTRY INTO THE *STRYCHNOS* ALKALOID SKELETON

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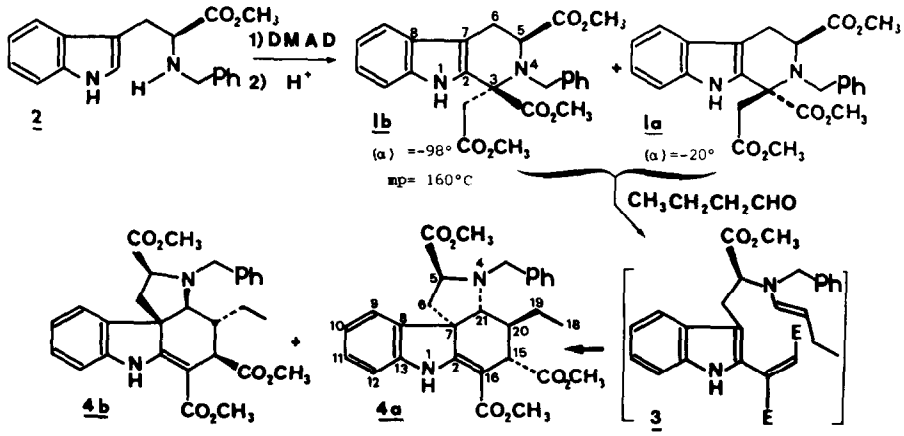
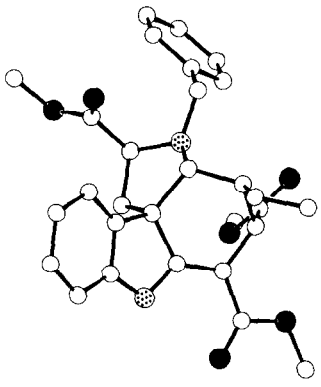
Summary : A tryptophan derivative is used for the first time as a chiral precursor of *Strychnos* alkaloid skeleta. Removal of the extra carbon is presented and discussed.

The accompanying paper[1] dealt with a short synthetic entry into the *Strychnos* alkaloid skeleton[2]. We wish now to describe herein extension of this approach to the obtention of the corresponding optically active series.



SCHEME 1

Use of N(4)-benzyl-(S)-tryptophan methyl ester 2 instead of tryptamine[1] allows the preparation of tetrahydro-β-carbolines 1a,b according to our method[3] (see footnote). Reaction of 1a+1b with butyraldehyde is more sluggish than in the preceeding case[1] and after 72 hours in refluxing toluene (a large excess of acetic acid and of butyraldehyde), a 68% yield of a mixture of two β-anilinoacrylates 4a,b is obtained (4a:4b = 85:15). Reactions with the separated β-carbolines 1a or 1b give the same ratio of these two compounds (however, the faster moving 1a reacts ca 10 times more rapidly than 1b) which again proves the intermediacy of an open fumarate 3 as mentioned before[1] (see scheme 1). Compounds 4a[6] and 4b are separated by crystallization (4a, m.p.= 190°C, $[\alpha]_D$(C=1,$CHCl_3$) = +303°) followed by chromatography of the mother liquors (4b, $[\alpha]_D$(C=1,$CHCl_3$) = -190°). To ascertain the absolute configuration of the four newly created asymmetric centers, a crystal of 4a was submitted to X-ray analysis which revealed the structure shown below:

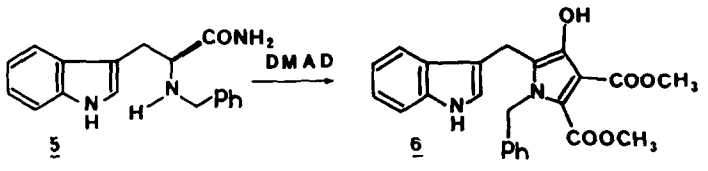


4a

The crystal structure was studied with a monocrystalline fragment of about .5x.4x.4 mm3. From 2563 unique reflexions, collected by a 4-circle graphite monochromated automatic diffractometer, 2494 were used in the calculations ($I > 3\sigma(I)$). The cell is monoclinic, $P2_1$, Z=2, with a= 11.411(6), b= 14.007(8), c= 8.906(5) Å, and β = 108.6(4)°. Direct methods[7] were used for the solution of the structure and the large blocs least-squares method[8] for the parameters refinement. Anisotropic thermal parameters were used for C,N,O, atoms, and H atoms were calculated at their theoretical (C-H=1.08 Å) positions. The final R-factors are R= 0.096 and Rw= 0.068[9].

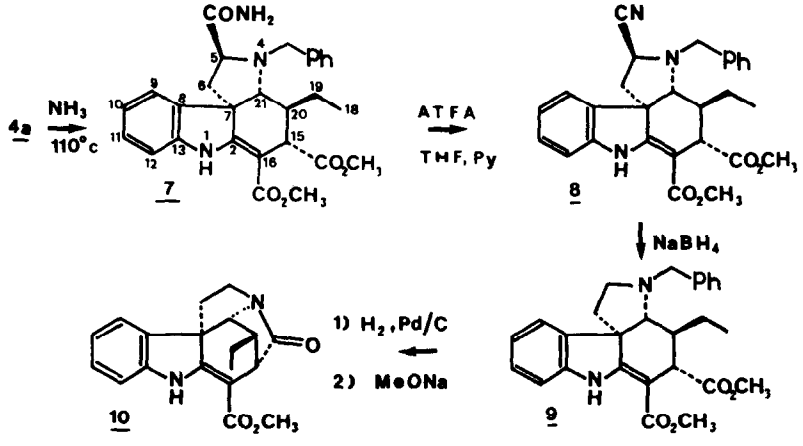
This method has been subsequently applied by Bailey[4,5] to prepare 1a,1b in 51% yield. In our hands, using MeOH instead of $CHCl_3$ in the preparation of the enamine, 1a,1b are obtained in quantitative yield as a 1 to 1 mixture of isomers.

In order to incorporate 4 into a synthetic scheme, its C-5 substituent has to be removed. By analogy with previous work from this laboratory[10,11], the reaction sequence has been first performed on a tryptophanamide derivative 5. This route had to be abandoned because of the main formation of hydroxypyrrole 6 at the enamine preparation step (see scheme 2).



SCHEME 2

However, it was found that the reaction of triester 4a with a large excess of NH_3 (sealed tube, 110°C, MeOH) was selective and led exclusively in 81% yield to the desired amide 7[6], $[\alpha]_D$(C=1,$CHCl_3$): = +272° (scheme 3).

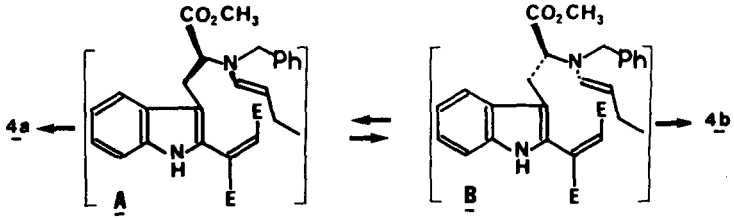


SCHEME 3

Amide 7 was uneventfully transformed into amine 9[6] $[\alpha]_D$(C=1,$CHCl_3$) = +258° via aminonitrile 8[6] $[\alpha]_D$(C=1,$CHCl_3$) = +264° in 80% overall yield. Debenzylation of 9 was followed by lactamization in 97% overall yield to pentacyclic amide 10[6] $[\alpha]_D$(C=1,$CHCl_3$) = +573°.

Compound 4b could not be crystallized and on the basis of ^1H NMR spectra it is assigned the structure shown above (scheme 1). The strong preference to produce 4a can be rationalized by inspection

of molecular models of the postulated transition state 3 (scheme 1). When the enamine reacts on the top face of the indole nucleus (A) the two esters are kept separate. On the other hand, when the enamine reacts on the bottom face of the indole (B) they come into proximity and this transition state is disfavoured:



This tentative explanation rests, of course, on the assumption that the mecanism is a concerted one, which has not been proved.

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9 - The atomic coordinates for this work are available on request from the Director of the Cambridge Crystallographic data centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 IEW. Any request should be accompanied by full literature citation for this communication.

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