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STEREOSPECIFIC SYNTHESIS OF TRANS-1,3-DISUBSTITUTED-1,2,3,4-TETRAHYDRO β-CARBOLINES

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The stereospecific synthesis of trans-1,3-disubstituted-1,2,3,4-tetrahydro β-carbolines has been accomplished in good yield by a two step sequence which involves Pictet-Spengler condensation of N_b-benzyltryptophan methyl ester with aldehydes, followed by removal of the 2-benzyl moiety from the corresponding tetrahydro β-carboline via catalytic hydrogenation.

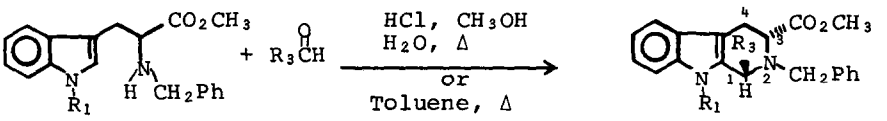
Interest in β-carboline alkaloids has been stimulated by their biological activity[1] and proposed role in disease states such as alcoholism and mental illness.[2] More recently 1,3-disubstituted-1,2,3,4-tetrahydro β-carbolines have come under close scrutiny because they have been shown to possess strong sedative, analgesic and antidepressive actions.[3] Alkaloids such as 5α-carboxystrictosidine[4] have been isolated; while several groups[4,5a,b,c,d] have investigated the cis/trans ratios for 1,3-disubstituted tetrahydro β-carbolines produced in the Pictet-Spengler reaction. In all of the reactions discussed in references 5a-d, mixtures of cis and trans isomers were reported with exception of the harman substitution pattern in which position-one is substituted with a small group. We now wish to report a simple, two step procedure for the stereospecific preparation of trans-1-substituted-3-methoxycarbonyl-1,2,3,4-tetrahydro β-carbolines.

In the course of the preparation of tetrahydro β-carbolines for CMR studies we found that N_b-benzyltryptophan methyl ester 1 reacted in a stereospecific fashion with aldehydes 3, 4 and 5 to provide the trans 1,3-disubstituted derivatives 6, 8, and 9, respectively (see Scheme I), while condensation of N_b-H tryptophan methyl ester with the same aldehydes gave both diastereomers. Aldehydes employed in this condensation have been cyclohexylcarboxaldehyde 3, salicyaldehyde 4, and propionaldehyde 5. None of the cis diastereomers were isolated, although efforts were not made to identify compounds present in less than 5% yield. The relative stereochemistries of the tetrahydro β-carbolines 6, 8 and 9 were determined by catalytic debenzylation followed by comparison of the properties of the N_b-H products 11, 13 and 15 with those of authentic samples.[5b,d] The stereochemistry of the authentic samples had been previously assigned on the basis of their carbon spectra[6,7] in addition to X-ray data on the trans-1-ethyl, 3-methoxycarbonyl tetrahydro β-carboline 15.[8] Furthermore, the analogous stereospecific reaction was observed when N_a-methyl, N_b-benzyltryptophan methyl ester 2 was heated with either cyclohexylcarboxaldehyde 3 or propionaldehyde 5; the trans

1-3-disubstituted bases 7 and 10, respectively, were isolated in good yield, and were converted (H_2, Pd/C) to the corresponding N_b-H derivatives 12 and 16 in over 90% yield (Table I).

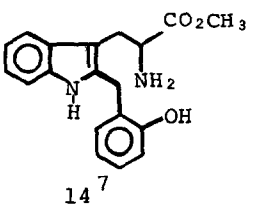
In the N_a-methyl cases, the trans isomers are formed in preference to the cis diastereomers for the $A^{1,2}$ strain[9] present in 12 and 16 far outweighs the destabilization due to the 1,3 interaction which occurs in these two compounds. In fact, examination of molecular models illustrates that 12 (R_3 = cyclohexyl) should exist entirely as the trans isomer.

Scheme I[a]

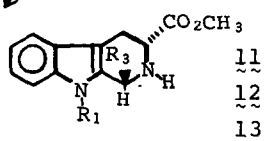


1, R_1=H — 3, R_3=cyclohexyl — 6, R_1=H, R_3=cyclohexyl
2, R_1=CH_3 — 3, R_3=cyclohexyl — 7, R_1=CH_3, R_3=cyclohexyl
1, R_1=H — 4, o-hydroxyphenyl — 8, R_1=H, R_3=o-hydroxyphenyl
1, R_1=H — 5, ethyl — 9, R_1=H, R_3=ethyl
2, R_1=CH_3 — 5, ethyl — 10, R_1=CH_3, R_3=ethyl

5% Pd/C, H_2, 10-25 psi



14[7]



11, R_1=H, R_3=cyclohexyl
12, R_1=CH_3, R_3=cyclohexyl
13, R_1=H, R_3=o-hydroxyphenyl
15, R_1=H, R_3=ethyl
16, R_1=CH_3, R_3=ethyl

Table I

	mp	% yield		mp	% yield
6	167-169°	87	11	147-149°	77
7	118-120°	85	12	145-147°	92
8	243-254°	97	13	168-169°	75
9	149-150°	46[b]	15	152-153°	97
10	105-106°	70	16	77-78°	95

[a] This work was carried out with *dl* ester. [b] See Ref. 10.

The propensity toward formation of the trans diastereomer in bases 6, 8, and 9 is obviously due to the effect of the N_b-benzyl group. Examination of molecular models does indicate that the 1,2,3-trisubstituted derivative (from attack of

the indole double bond on the iminium ion) which leads to the cis diastereomer is more congested sterically than the analogous intermediate which leads to the trans isomer. This steric crowding may have forced the 1-substituent in the cis case closer to the N_a- H function thereby increasing the $A^{1,2}$ strain already present in this stereoisomer. There is evidence that some Pictet-Spengler cyclizations undergo reaction at C-2 of indole[11] instead of C-3 (spiroindolenine),[12] consequently, the actual mechanism of cyclization must be determined before an accurate explanation for the stereospecificity we observed can be put forward.

In summary, if one begins with N_b-benzyltryptophan methyl ester 1 of known configuration, the method described here (coupled with the 1,3-transfer of chirality alluded to in other work by Yamada)[13] permits for the first time the stereospecific synthesis of 1-substituted-3-methoxycarbonyl-1,2,3,4-tetrahydro β-carbolines of known absolute stereochemistry. In addition, the methoxycarbonyl group at C-3 can be removed by standard reactions[13] to provide 1-substituted-1,2,3,4-tetrahydro β-carbolines also of known absolute configuration.[14]

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10. The other two products in this reaction which resulted in the poor yield were formed by reaction of excess propionaldehyde with 9 or by self-condensation of propionaldehyde, followed then by Pictet-Spengler condensation with 1. Careful examination of the reaction mixture provided none of the cis isomer of 9. Furthermore, the mass spectrum and NMR of the side products in this sequence, likewise, failed to support formation of products of cis stereochemistry. The yield of 9 can be much improved by careful addition of propionaldehyde over the course of the reaction.

11. Very reactive electrophiles sometimes attack position-2 of indole in preferto reaction at position-3 [see G. Casnati, A. Dossena, and A. Pochini, Tetrahedron Lett., 52, 5277 (1972)].

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14. The 1-substituted-3-methoxycarbony-1,2,3,4-tetrahydro β-carbolines of cis stereochemistry are available by epimerization (CH_3OH/HCl) of the substituent at carbon-1 of the corresponding trans isomer, followed by chromatography on silica(see citations 5b, 5d, and 7).

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