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MECHANISM DRIVEN *TRANS* STEREOSPECIFICITY IN THE PICTET-SPENGLER REACTION. STEREOSPECIFIC FORMATION OF *TRANS*-1,2,3-TRISUBSTITUTED-TETRAHYDRO β-CARBOLINES BY CONDENSATION OF N_b-DIPHENYLMETHYL TRYPTOPHAN ISOPROPYL ESTERS WITH ALDEHYDES

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***Summary**: Stereoelectronic control in the Pictet-Spengler condensation of N_b-alkylsubstituted tryptophan alkyl esters has been employed to promote 100% stereoselectivity in this process. The reaction of N_b-diphenylmethyl tryptophan isopropyl ester **8** with acetaldehyde in benzene at reflux yielded the trans-diastereomer **10d** to the complete exclusion of the corresponding cis isomer. This trans stereospecificity was also observed for butyraldehyde and cyclohexylcarboxaldehyde.*

The Pictet-Spengler condensation has served as an important ring forming reaction in the synthesis of indole alkaloids for many years.[1,2] More recently it has been employed to prepare alkaloids of important pharmacological significance including β-carboline-3-alkyl esters,[3] canthin-6-ones,[4] eudistomins,[5] and fumertrimorgens,[6] as well as permitting entry into new ring systems.[7] In keeping with our interest in controlling the chirality in the Pictet-Spengler reaction for the enantiospecific synthesis of indole alkaloids,[8] new results were recently reported which indicated that attack on intermediate **1**

Figure 1

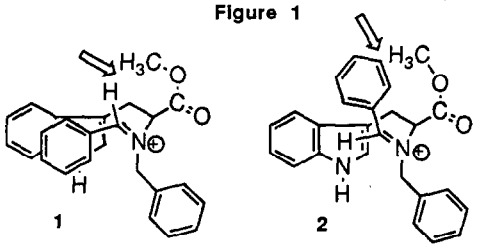
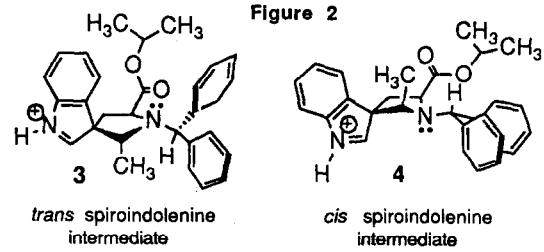


Figure 2



trans spiroindolenine intermediate

cis spiroindolenine intermediate

(Figure 1) was favored over attack *via* **2**. This resulted in *trans* stereospecificity in the condensation when benzaldehyde was employed and was shown to increase in the case of butyraldehyde when the methyl ester function in **1** was replaced with an isopropyl ester group.[9] Presumably, the steric interactions between the imine substituent in **1** and the ester functions not only favors the intermediacy of the E isomer (**1**) over the Z isomer (**2**, not favored) during the cyclization but facilitate attack from the face opposite the ester group.[9] This is also consonant with the *trans* stereospecificity observed in the cyclization of **1** rather than conversion of **2** into the *cis* diastereomer; the latter is not favored in the case of N_b-benzyl tryptophan alkyl esters.[10]

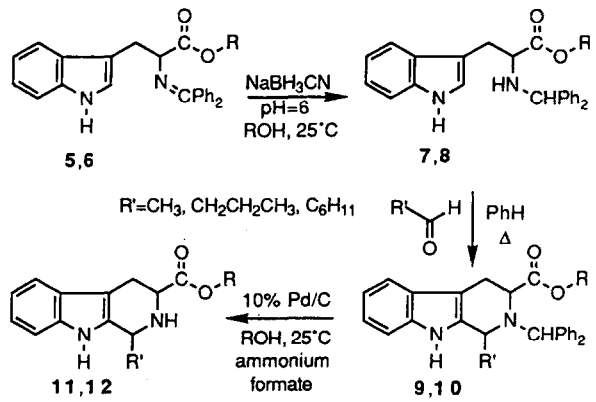
It is clear that the size of the ester substituent in the tryptophan alkyl ester and of the aldehyde influences the *trans* stereospecificity when N_b-benzyl tryptophans are involved in the cyclization;[9] however, until now the Pictet-Spengler reaction had never provided the 1,3-disubstituted tetrahydro-β-carboline with 100% stereoselectivity when acetaldehyde was employed as the substrate. Examination

of the stereochemistry of the spiroindolenine intermediate[11] which is generated in the Pictet-Spengler reaction (Figure 2) has now permitted execution of this process with 100% stereoselectivity and forms the subject of this letter.

The key to complete stereospecificity in this condensation stems from stereoelectronic control[9b] during attack on the favored E iminium ion (as in **1**) illustrated for the spiroindolenine intermediate **3** (attack at C-3 of the indole unit[11]) generated from reaction of N_b-diphenylmethyl tryptophan isopropyl ester with acetaldehyde. Attack on the E isomer from the face opposite the ester function would provide the more stable spiroindolenine intermediate **3** rather than the all eclipsed intermediate **4**.[12] These two structures, depicted in Figure 2, represent the intermediates derived from attack on the iminium ion with stereoelectronic control before nitrogen inversion is permitted to occur at N-2. In fact, calculations (MacroModel version 2.5-MM2 force field) in the analogous methyl ester case reveals that the *trans* isomer **3** is 2.1kcal/mole more stable than the *cis* isomer **4**.

Scheme 1

[5,7,9,11:R=CH_3 **6,8,10,12:**R=iPr]

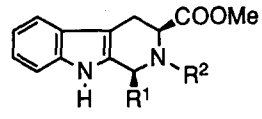


Fischer esterification of tryptophan with methanol and 2-propanol followed by transimination of the two esters, individually, with diphenylimine, according to the procedure of O'Donnell and Polt,[13] provided imines **5** and **6**. They were reduced to the corresponding N_b-diphenylmethyl alkyl esters **7** and **8** with $NaCNBH_3$ at pH 6 in good yields.[14] The N_b-diphenylmethyl esters were then heated with the aldehydes illustrated in Scheme 1 in benzene at reflux for three days to provide the 1,2,3-trisubstituted-1,2,3,4-tetrahydro-β-carbolines **9** and **10**. In the case of acetaldehyde the condensation was carried out in a sealed tube to prevent the loss of aldehyde. Moreover, in cases where the Pictet-Spengler condensation did not occur in benzene at reflux due to the steric bulk of the aldehyde, TFA was added to the reaction to facilitate the condensation. The stereochemistry of the N_b-diphenylmethyl β-carbolines was assigned by conversion into their 1,3-disubstituted counterparts[11] by CTH,[15] followed by analysis of the carbon-13 NMR spectrum of the latter materials *via* the method of Sandrin *et al.*[16]

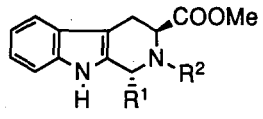
The *cis* and *trans* ratios of the 1,2,3-trisubstituted-1,2,3,4-tetrahydro-β-carbolines prepared in this study are illustrated in Tables I and II. In the methyl ester series (Table I) the reaction of N_b-benzyl tryptophan methyl ester with acetaldehyde in benzene at reflux provided the *cis* and *trans* diastereomers **9a** in a ratio of 26:74; however in the N_b-diphenylmethyl series (**9d**) the ratio was improved significantly to favor the *trans* diastereomer [10(*cis*):90(*trans*)]. The increase in stereoselectivity in favor of the *trans* diastereomer was even more pronounced when butyraldehyde was employed as the substrate. When the N_b-benzyl group in the tryptophan methyl ester case was replaced by the N_b-diphenylmethyl substituent the ratio of *cis* to *trans* isomers was altered from 23:77 (**9b**) to 0:100 (**9e**). It was known from previous work that the bulky cyclohexanecarboxaldehyde provided only the *trans* diastereomer in the N_b-benzyl series, consequently it was not surprising that TFA had to be added to the reaction medium to effect

cyclization in the latter case (see **9f**, Table I). It is important to note that the reaction in benzene at reflux provided the ratios from a kinetic trapping experiment, while the results in TFA provide a thermodynamic ratio. It is also apparent that the *trans* diastereomer is favored thermodynamically as well as kinetically in the N_b-alkyl series in keeping with previous reports.[10]

Table I. *Cis :Trans* Ratios of 1,2,3-Trisubstituted-β-carboline Methyl Esters



Cis

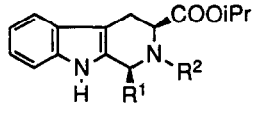


Trans

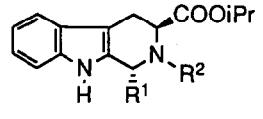
Compound	R^1	R^2	*cis:trans* aprotic	*cis:trans* in TFA
9a	CH_3	Bn	26:74	12:88
9b	$CH_2CH_2CH_3$	Bn	23:77	11:89
9c	C_6H_{11}	Bn	0:100	0:100
9d	CH_3	$CH(Ph)_2$	**10:90**	**0:100**
9e	$CH_2CH_2CH_3$	$CH(Ph)_2$	**0:100**	**0:100**
9f	C_6H_{11}	$CH(Ph)_2$	**N.R.**	**0:100**

Outlined in Table II are the results from the Pictet-Spengler cyclization of N_b-alkyl tryptophans in the isopropyl ester series. The size of the ester function had little or no effect on the ratio of *cis* to *trans* diastereomers in the case of acetaldehyde in the N_b-benzyl series (compare **9a** and **10a**, Tables I and II) for the ratio was about the same (23:77).

Table II. *Cis :Trans* Ratios of 1,2,3-Trisubstituted-β-carboline Isopropyl Esters



Cis



Trans

Compound	R^1	R^2	*cis:trans* aprotic	*cis:trans* in TFA
10a	CH_3	Bn	23:77	13:87
10b	$CH_2CH_2CH_3$	Bn	13:87	12:88
10c	C_6H_{11}	Bn	0:100	5:95
10d	CH_3	$CH(Ph)_2$	**0:100**	**0:100**
10e	$CH_2CH_2CH_3$	$CH(Ph)_2$	**N.R.**	**0:100**
10f	C_6H_{11}	$CH(Ph)_2$	**N.R.**	**0:100**

However, replacement of the N_b-benzyl function in the isopropyl ester series with the N_b-diphenylmethyl substituent (see **8**) provided the *trans* stereoisomer **10d** with acetaldehyde (0:100) in stereospecific fashion. This represents the first reported case of complete stereospecificty with acetaldehyde, to this authors knowledge, in the Pictet-Spengler reaction even though this reaction is eighty years old.[1] Moreover, since optically active (R)- and (S)- tryptophans are both available commercially, the N_b-diphenylmethyl, isopropyl series provides a potential means in which to generate 1,3-disubstituted β-carbolines with 100% enantiospecificity. Removal of the N_b-diphenylmethyl substituent *via* CTH proceeds smoothly and in high yield to provide the corresponding 1,3-disubstituted THβC *via* this 1,3-transfer of chirality. Here, in the reactions of **8** with both butyraldehyde and

cyclohexanecarboxaldehyde, respectively, the transition states which resemble spiroindolenine **3** were too high in energy to form in benzene at reflux; however, the cyclizations proceeded smoothly upon addition of TFA to provide the corresponding *trans* diastereomers **10e** and **10f**, respectively. No evidence for the presence of any of the *cis* diastereomer was observed in the latter three entries in Table II.[17] Whether the formation of **9f**, **10e** and **10f** has occurred *via* the spiroindolenine intermediate[11] or by direct attack at C-2 is not known at this time.[18]

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