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Asymmetric Pictet-Spengler Reactions Employing Amino Acid Esters as Mediators of Selectivity

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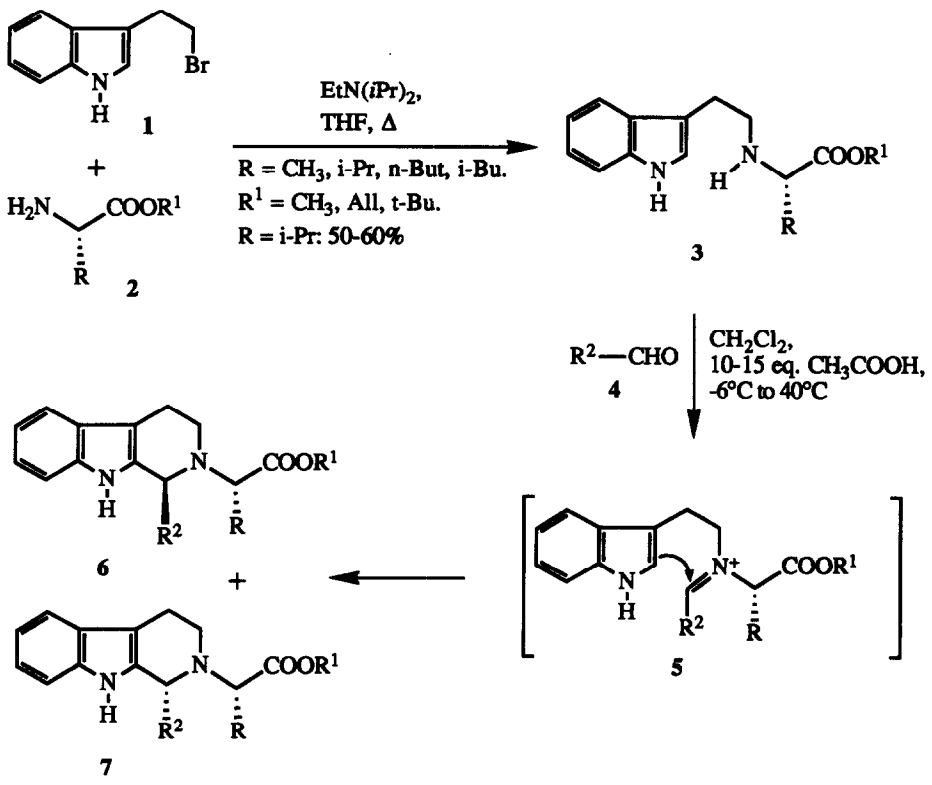
Abstract: The Pictet-Spengler cyclization of iminium salts generated *in situ* from N-(ß-3-indolyl)ethyl substituted amino acid esters and differently substituted aldehydes proceeds with high stereoselectivity to deliver chiral tetrahydro-ß-carbolines with diastereomer ratios up to 98.5:1.5.

The Pictet-Spengler reaction belongs to the most important and powerful methods of alkaloid chemistry. It has been applied in numerous cases for the construction of tetrahydroisoquinoline and -ß-carboline alkaloids as well as more complex classes of natural products derived from these heterocyclic systems. Consequently, the development of methods which allow to carry out this transformation in an asymmetric manner is of great interest to organic synthesis. Diastereoselective Pictet-Spengler reactions in the sense of „ex-chiral-pool" syntheses making use of tryptophan esters[1] or chiral aldehydes[2] have been studied in detail. However, only in two isolated cases[3] has this important transformation of alkaloid chemistry been carried out asymmetrically by employing a removable chiral auxiliary group. In addition, the use of the enzyme strictosidine synthase for this purpose has been investigated,[4] but the biocatalyst displays a rather narrow substrate tolerance. Thus, a generally applicable methodology for the execution of asymmetric Pictet-Spengler reactions is currently not available. The purpose of this paper is to report that highly stereoselective Pictet-Spengler cyclizations can be carried out if amino acid esters are used as mediators of selectivity.[5,6]

The amino acid esters **3** which were used as the starting materials in the asymmetric syntheses are readily available via alkylation of the amines **1** with ß-(3-indolyl)ethyl bromide[7] **2** (Scheme 1). If the secondary amines **3** are treated with the aldehydes **4** at -6°C to 40°C in CH_2Cl_2 as solvent and in the presence of 10-15 equiv. of acetic acid, the iminium intermediates **5** are formed *in situ*. They cyclize spontaneously by intramolecular attack of the indole nucleus on the iminium functionality to deliver the tetrahydro-ß-carbolines **6** and **7** in satisfactory yields and with high to very high diastereomer ratios (up to 98.5:1.5; Table 1). The predominantly formed stereoisomers **6** can be isolated in a straightforward way by simple flash chromatography and recrystallization from ether/petroleum ether. Their absolute configuration was unambiguously proven by an X-ray analyses for **6b** (R = i-Pr, R^1 = Me, R^2 = 4-NO_2-Ph).[8] The diastereomer ratios **6**:**7** were determined from the crude reaction mixtures by HPLC or by means of 400 MHz-^{1}H nmr spectroscopy (see Table 1). The diastereoselectivity of the Pictet-Spengler reactions is particularly influenced by the size of the amino acid side chain „R". Thus, out of the amino acid esters investigated the derivatives of valine and isoleucine induce the highest diastereomer ratios, the use of the sterically less demanding leucine or alanine esters gives inferior results (Table 1, entries 1 and 10).



Scheme 1

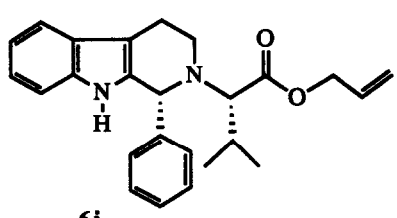
Table 1. Results of the asymmetric Pictet-Spengler reactions employing the amino acid derivatives **3**.

entry	**6**	R^2	amino acid ester	T [°C]	$[\alpha]_D^{25}$ [°] (c=1,CHCl3)	mp [°C]	δ [ppm] of 1-H [a]	yield [a] [%]	*ds* [a,b] **6**:**7**
1	**a**	Ph	Val-OMe	25	-240.0	123	4.88	72	90:10
2	**a**	Ph	Val-OMe	6	-	-	-	51	93:7
3	**b**	4-NO_2-Ph	Val-OMe	25	-240.9	208	4.99	67	80:20
4	**c**	2-NO_2-Ph	Val-OMe	25	-76.5	184	5.34	59	98.5:1.5
5	**d**	2,4-di-Cl-Ph	Val-OMe	25	-205.3	Öl	5.50	78	93.5:6.5
6	**e**	4-MeO-Ph	Val-OMe	25	-219.4	132	4.78	25	96:4
7	**f**	4-EtO-Ph	Val-OMe	40	-199.2	121	4.80	85	93:7
8	**g**	4-Me-Ph	Val-OMe	25	-245.3	141	4.84	48	91.5:8.5
9	**h**	Ph-CH=CH_2	Ile-OMe	25	-213.6	174	4.52	53	86:14
10	**i**	Ph	Leu-OAll	25	-171.0	110	5.07	69	72:28

[a] All tetrahydro-ß-carbolines **6** were characterizd by means of their 200-MHz-^{1}H und 50.3-MHz-^{13}C-NMR spectra (in CDCl3). The elemental analyses are in accord with the calculated values [b] Determined from the crude reaction mixtures by HPLC or by integration of the respective signals found for 1-H of the diastereomers **6** and **7**.

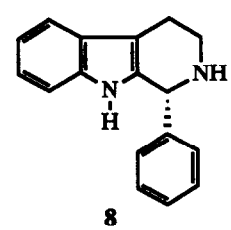
The size of the ester group has only a subordinate influence on the stereoselectivity, i. e. valine ethyl, allyl and tert-butyl ester do not induce higher de values than the respective methyl ester. However, the isomer ratios are significantly enhanced at lower reaction temperatures (Table 1, entries 1 and 2 as well as 6 and 7). In addition, *ortho*-substituted aromatic aldehydes (Table 1, entries 4 and 5) deliver the Pictet-Spengler adducts with higher diastereoselectivity than *para*- or unsubstituted carbonyl compounds (Table 1, entries 1 and 3). Also, for iminium intermediates **5** carrying electron donating substituents (Table 1, entries 6-8) a better stereodiscrimination is recorded than for the corresponding electrophiles embodying -M-substituents or no further functional group at all (Table 1, entries 1 and 3). The tetrahydrocarboline **6h** which is derived from cinnamic aldehyde and the benzaldehyde derivative **6a** are obtained with comparable isomer ratios, i. e. the introduction of a double bond between the aromatic nucleus and the heteroanalogous carbonyl group influences the stereoselectivity only to a minor extent. However, if aliphatic aldehydes are used in the reaction sequence outlined in Scheme 1, the desired heterocycles are produced only with low diastereomer discrimination. For instance, if the Pictet-Spengler cyclization is carried out with chloral hydrate, the isomeric tetrahydro-ß-carbolines are formed in a ratio of 70:30. In addition, for aliphatic aldehydes the yields are generally below 20%. This is probably due to competing self-aldolization of these C-H-acidic carbonyl compounds under the conditions of the relatively slow conversion of **3** to **6** and **7**. In addition, the aliphatic Pictet-Spengler adducts **6** and **7** turned out to be only moderately stable.

From the heterocycles **6** the mediator of selectivity can be removed by means of standard operations in an efficient manner. A representative example is given in Scheme 2. After deprotection of the amino acid ester,[9] the liberated acid is converted into the corresponding amide which is then dehydrated to the α-amino nitrile by treatment with trifluoroacetic anhydride.[10] Finally, on heating in HCl/methanol the desired secondary amine **8** is liberated. Its enantiomeric homogeneity was ascertained by conversion into the amide of (S)-α-methoxy-α-(trifluoromethyl)phenylacetic acid (Mosher's acid) and subsequent nmr spectroscopic investigation. All individual steps involved in the conversion of the amino acid derivatice **6i** to the tetrahydro-ß-carboline **8** proceed with high yields and are operationally simple.



6i

1) $(PPh_3)_4Pd$, THF, morpholine, 92%
2) DEAC, HoBt, NH_3, DMF, quant.
3) $(CF_3CO)_2O$, NEt_3, CH_2Cl_2, 79%
4) HCl/CH_3OH, Δ, 77%



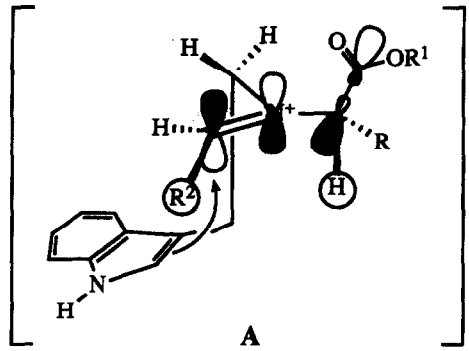
8

Scheme 2

HoBt = N-hydroxybenzotriazole
DEAC = N-ethyl-N´-diethylamino-ethylcarbodiimide hydrochloride

$[\alpha]_D^{25} = 4.5°$ (c = 1, $CHCl_3$)

To rationalize the steric course of the Pictet-Spengler reactions we assume that the imimium salts **5** preferably adopt the conformation **A** in which - by analogy to the Felkin-Anh model for nucleophilic attack on carbonyl groups[11] - the π*-orbital of the C=N-bond and the σ*-orbital of the αC-$COOR^1$-bond are oriented parallel to each other[6b,c]. In addition, **A** is favoured because in this orientation the voluminous substituent R^2 and the small αH of the amino acid ester (as compared to the sterically more demanding „R" in the anti Felkin-Anh orientation) are in a 1,3-realationship. Furthermore, the small iminium-H (in contrast to the larger „R^2") lies above the indole nucleus and in the vicinity of the N-CH_2 group of the indolylethyl moiety.[1,12]



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References and Notes

Dedicated to Prof. Dr. Wolfgang Steglich on the occasion of his 60th anniversary.

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6) While we carried out the studies described in this paper G. Bringmann et al., Universität Würzburg, investigated the use of (S)-phenylethyl amine as mediator of selectivity in asymmetric Pictet-Spengler reactions (G. Bringmann, personal communication). We are grateful to Prof. Dr. G. Bringman for the communication of these informations in advance.
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8) Crystal data: $C_{23}H_{25}N_3O_4$ crystallizes orthorhombic, space group $P2_12_12_1$ (Nr. 19), with a = 10.204(5) Å, b = 11.4678(6) Å, c = 18.48(1) Å, Z = 4, μ = 0.51 cm^{-1}. 3746 reflexes were measured, 2717 thereof independent with $I>2\sigma(I)$. The structure determination was carried out by means of direct methods (SHELX-76 und SHELXS-86 [G.M.Sheldrick, SHELX-76, Program for Crystal Structure Determination, University of Cambridge, 1976. G.M.Sheldrick, SHELXS-86, Göttingen 1986.]), R = 0.0425, R_w = 0.048, $w = 1 / \sigma^2(F) + 0.0001 * F^2$. All C, N, und O atoms were refined anisotropically. The H atoms are in the calculated locations with equal isotropic temperature factors for CH, CH_2, CH_3 and phenyl H. Further details of the X-ray analysis are available from the Fachinformationszentrum Karlsruhe, Gesellschaft für wissenschaftlich-technische Information mbH, W-76344 Eggenstein-Leopoldshafen 2, by referring to the registration number CSD-57243, the authors and this paper.
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