

## A VERSATILE APPROACH TO *TRANS*-1,3-DISUBSTITUTED TETRAHYDRO- $\beta$ -CARBOLINES USING OXAZINANES

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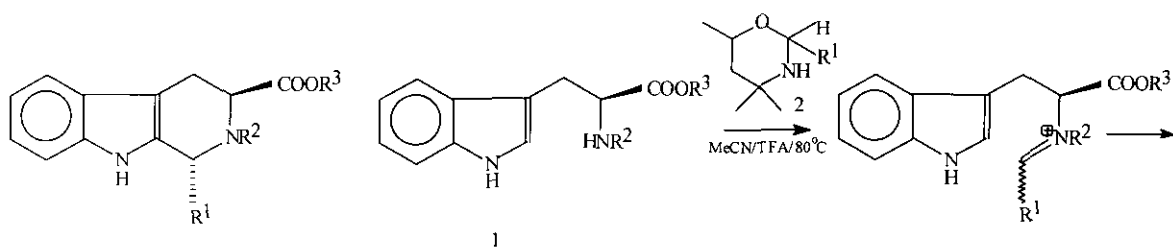
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**Abstract** - Under the conditions of thermodynamic control, the diastereoselectivity of the reaction between tryptophan esters and oxazinanes (carbonyl equivalents) can be controlled by incorporating *N*<sub>6</sub>-benzyl substituents; the reaction proceeds in essentially quantitative yield and with *trans*-diastereoselectivity.

The Pictet-Spengler reaction<sup>1</sup> has long been an important reaction for the synthesis of numerous naturally occurring alkaloids, embodying tetrahydro- $\beta$ -carbolines or tetrahydroisoquinoline framework, mediating pharmacologically useful effects.<sup>2</sup> Therefore, the synthesis of these systems in a synthetically useful manner is of widespread interest to both organic synthesis and medicinal chemistry. Conventional Pictet-Spengler reaction quite often lacks practicability owing to handling and non-availability of desired functionalized aldehydes. Perhydrooxazines (oxazinanes), which have been synthesized from a variety of reagents other than aldehydes,<sup>3</sup> have amply demonstrated synthetic superiority<sup>4</sup> over conventional carbonyl compounds owing to carbonyl character<sup>3</sup> of the C-2. However, a generally applicable methodology for the execution of title protocol is currently not available. We have seen, in accordance with the carbonyl compounds, by using conditions of thermodynamic control, the Pictet-Spengler reaction between (L)-tryptophan ester and appropriately substituted oxazinanes can be controlled to give the title compounds selectively.

The oxazinanes which were used as reagents in the diastereoselective synthesis are readily available from a variety of cheaply available combinations. If the secondary amines (1) are treated with oxazinanes (2) – existing mainly in tautomeric iminium form,<sup>5</sup> at 80°C in anhydrous acetonitrile as solvent in the

presence of 2 to 3 equivalents of trifluoroacetic acid, the iminium intermediate (Scheme) formed *in situ* cyclises spontaneously by intramolecular attack of C-2 of indole nucleus on iminium functionality to deliver 1,3-disubstituted tetrahydro- $\beta$ -carbolines (**3**) and (**4**) in excellent yields and with very high diastereomeric ratios (Table). The *trans*- $N_b$ -substituted diastereomers are thermodynamically more stable than their *cis*-congeners especially where the reactions are catalysed by TFA and conversion of *cis*-diastereomer into the more stable *trans*-diastereomers is believed to occur under acidic conditions by cleavage of the carbon (C-1)-nitrogen (N-2) bond with complete retention of configuration at C-3



**Scheme.** The thermodynamically controlled reaction yields predominantly *trans*-1,3-disubstituted tetrahydro- $\beta$ -carbolines (**3**).

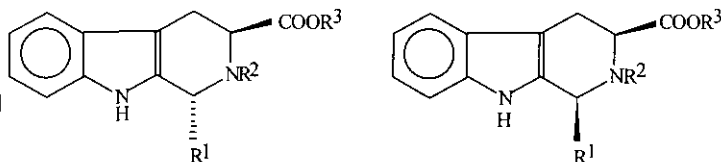


Table : Diastereoselectivity in the Pictet-Spengler<sup>3</sup> reaction between oxazinanones (**2**) and (L)-TrpOR<sup>3</sup>.

Entry	$R^1$	$R^2$	$R^3$	Diastereomeric ratio		Yield (%) <sup>6</sup>
				<b>3</b>	<b>4</b>	
1.	Ph	benzyl	Me	99	1	88
2.	4-MeOC <sub>6</sub> H <sub>4</sub>	benzyl	Me	98	2	91
3.	3,4,5-tri-MeOC <sub>6</sub> H <sub>2</sub>	benzyl	Me	99	1	90
4.	Ph	4-MeO-benzyl	Pr <sup>1</sup>	97	3	86
5.	4-MeOC <sub>6</sub> H <sub>4</sub>	4-MeO-benzyl	Pr <sup>1</sup>	98	2	88
6.	3,4,5-tri-MeOC <sub>6</sub> H <sub>2</sub>	4-MeO-benzyl	Pr <sup>1</sup>	99	1	92

stereocentre.<sup>2</sup> However, like the conventional Pictet-Spengler reaction<sup>7</sup> the diastereoselectivity is not controlled by varying the size of the ester group where  $N_b$ -benzyl substituents<sup>8</sup> are present. The

predominantly formed stereoisomer can be isolated in a straightforward way using simple chromatography and recrystallisation. The diastereomers were identified by analysing 200 MHz-  $^1\text{H}$  NMR and 50.3 MHz-  $^{13}\text{C}$  NMR and the stereochemistry was unambiguously assigned by comparison with the literature NMR data.<sup>9</sup>

This method of preparation of the title compounds may be considered a variant of the classical Pictet-Spengler reaction in that the same iminium intermediate is deemed to be involved in the reaction. This approach will be preferred in those cases where the aldehydes required for a Pictet-Spengler reaction are unstable or difficult to access as the oxazinanes can be readily functionalized at C-2.<sup>3</sup> The utility of this approach using oxazinanes bearing aliphatic substituents (equivalents of aliphatic aldehydes) at C-2 to effect synthesis of some target alkaloids is in progress.

#### ACKNOWLEDGEMENTS

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#### REFERENCES AND NOTES

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6. Using our standard conditions of reflux at 80°C, the yields refer to that of isolated compounds.

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8. The (L)-tryptophan methyl or iso-propyl esters lacking *N*<sub>6</sub>-benzyl substituents yielded equilibrated mixtures of corresponding **3** and **4**.
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Spectroscopic data of selected **3**

Entry 1: IR (KBr) 3337 (s, NH), 1722 (s, ester)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  3.22 (d,  $J=4.5$  Hz, 2H,  $\text{CH}_2$ ), 3.62 (s, 3H,  $\text{OCH}_3$ ), 3.86 (d,  $J=2.3$  Hz, 2H,  $\text{CH}_2$ ), 3.92-3.96 (m, 1H, CH), 5.46 (s, 1H, CH), 7.07-7.52 (m, 15H, Ar-H & NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  24.36 ( $\text{CH}_2$ ), 51.31( $\text{OCH}_3$ )\*, 54.32 ( $\text{CH}_2\text{C}_6\text{H}_5$ ), 56.06 (C-3)\*, 60.84 (C-1)\*, 106.31, 110.83, 118.16, 119.24, 121.54, 127.05, 127.53, 128.00, 128.31, 128.55, 128.67, 128.89, 134.88, 136.50, 139.41, 142.17, 173.56 (CO).

Entry 4: IR ( $\text{CHCl}_3$ ) 3310 (s, NH), 1714 (s, ester)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.11 (d,  $J=6.3$  Hz, 3H,  $\text{CH}_3$ ), 1.21 (d,  $J=6.2$  Hz, 3H,  $\text{CH}_3$ ), 3.17 (d,  $J=4.2$  Hz, 2H,  $\text{CH}_2$ ), 3.79 (m, 3H,  $\text{OCH}_3$ , merged with multiplet of  $\text{CH}_2\text{Ph}$ ), 3.78-3.82 (m, 2H,  $\text{CH}_2\text{Ph}$ ), 3.86-3.91 (m, 1H, CH), 4.91-5.00 (heptet,  $J=6.2$  Hz, 1H, CH), 5.43 (s, 1H, C-1 H), 6.83-7.52 (m, 14H, Ar-H & NH).  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ )  $\delta$  21.78 ( $\text{CH}_3$ ), 21.90 ( $\text{CH}_3$ ), 24.35 ( $\text{CH}_2$ ), 53.72 (CH), 55.92 (C-3)\*, 60.95 (C-1)\*, 67.59 ( $\text{OCH}_3$ ), 106.40, 110.73, 113.72, 118.11, 119.22, 121.45, 127.12, 127.93, 128.65, 128.84, 129.77, 131.44, 134.94, 136.50, 142.42, 158.76, 172.69 (CO).

\* characteristic signals

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