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Enhancing the Yield and Diastereoselectivity of the Pictet-Spengler Reaction: A Highly Efficient Route to *Cis*-1,3-Disubstituted Tetrahydro-β-Carbolines

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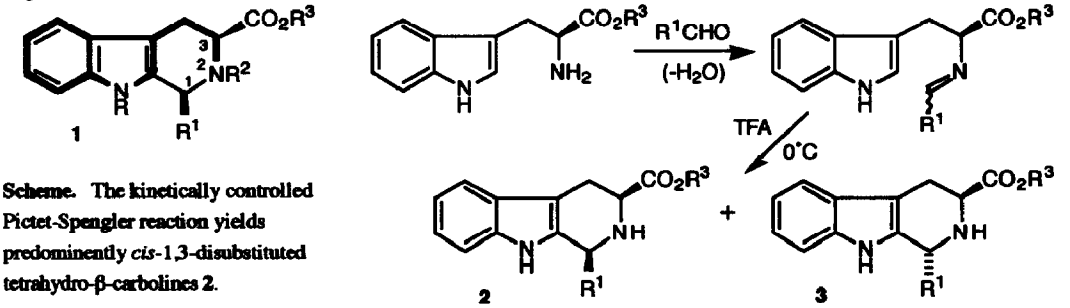
Abstract: Under conditions of kinetic control, the *cis*-diastereoselectivity of the Pictet-Spengler reaction between tryptophan esters and aldehydes can be controlled by varying the size of the ester group; the reaction proceeds in essentially quantitative yield with most aldehydes when conducted in chloroform in the presence of molecular sieves.

The Pictet-Spengler reaction is one of the most direct methods of accessing the tetrahydro-β-carboline ring system that is present in many indole alkaloids. More specifically, many indole alkaloids contain the *cis*-1,3-disubstituted sub-structure **1**, in which the skeleton of (L)-tryptophan can be discerned. By using conditions of kinetic control,[1] the Pictet-Spengler reaction between an (L)-tryptophan ester and an aldehyde can be controlled to give this desired relative and absolute stereochemistry (Scheme).



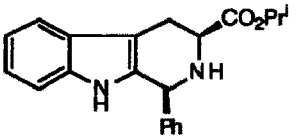
Scheme. The kinetically controlled Pictet-Spengler reaction yields predominently *cis*-1,3-disubstituted tetrahydro-β-carbolines **2**.

When *N*(2)-benzyl tryptophan methyl ester is employed in Pictet-Spengler reactions, high *trans*-diastereoselectivity is observed,[2] and this selectivity is further enhanced by using tryptophan isopropyl ester.[3] We wondered whether a corresponding enhancement of *cis*-diastereoselectivity might be observed when tryptophan esters were reacted under our conditions of kinetic control.

Table. Diastereoselectivity in the Pictet-Spengler reaction between aldehydes R^1CHO and (L)-TrpOR^3

R^1	R^3 = Me 2 : 3	Yield (%)[5a]	R^3 = Pr^i 2 : 3	Yield (%)[5b]
Ph	4.6:1	74	7.3:1	>95
cy-C_6H_{11}	2.5:1	71	3.5:1	>95
Et	3.5:1	75	2.7:1	88
Pr	4.0:1	72	2.7:1	>95
$(CH_2)_2Ph$	4.9:1	75	2.7:1	>95
Pr^i	4.9:1	82	3.5:1	>95

Switching from Trp-OMe to Trp-OPr^i had only a modest effect on the diastereoselectivity, with no clear trend becoming apparent. However, significant advantage could always be gained by using one or other of the esters - this could prove particularly valuable if the minor product has to be removed. We had supposed that the bulky isopropyl ester would prefer to lie in an equatorial position, as supported by the X-ray crystal structure of **2** (R^3=Pr^i, R^1=Ph) (Figure).[4] But based on our tabulated results, we conclude that the methyl ester already possesses a strong equatorial preference in the transition state, and that the *cis* : *trans* ratio is subtly governed by 1,3-diaxial versus $A_{1,2}$ interactions.[1] Moreover, when an *N*(2)-benzyl group is present, equatorial crowding should further disfavour an equatorial 1-substituent when bulky esters are used, as reported elsewhere.[3]



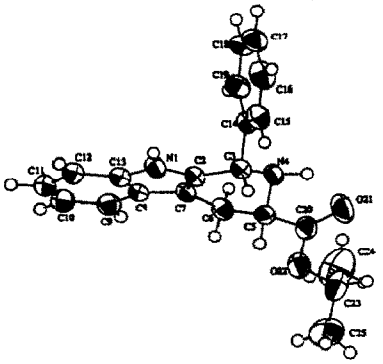


Figure X-Ray crystal structure of the *cis*-tetrahydro-β-carboline **2** (R^3=Pr^i, R^1=Ph); the crystallographic numbering is shown.[4]

Finally, but importantly, TLC and ^{13}C NMR on the crude products indicated quantitative conversion when the reaction was conducted in ethanol-free chloroform over molecular sieves.[5] Isolated yields were also essentially quantitative when the beads were crushed during work-up. With judicious choice of appropriate tryptophan esters, it seems that excellent yields and high *cis*- or *trans*- selectivity (≥ 3.5:1) can be assured in the Pictet-Spengler reaction.

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References and Notes

1. Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K. M.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc., Perkin Trans. 1* **1993**, 431.
2. Ungemach, F.; DiPierro, M.; Weber, R.; Cook, J. M. *J. Org. Chem.* **1981**, *46*, 164. By exploiting a reversible epimerisation at C(3), it is possible to trap the *cis*-1,3-disubstituted tetrahydro-β-carbolines, thereby gaining access to bridged indole alkaloids (eg. Fu, X.; Cook, J. M. *J. Org. Chem.* **1993**, *58*, 661)- but this necessitates the use of (D)-tryptophan in order to obtain the same absolute stereochemistry as the naturally occurring alkaloids.
3. a) Deng, L.; Czerwinski, K.; Cook, J. M. *Tetrahedron Lett.* **1991**, *32*, 175; b) Hermkens, P. H. H.; van Maarseveen, J. H.; Cobben, P. L. H. M.; Ottenheijm, H. C. J.; Kruse, C. G.; Scheeren, H. W. *Tetrahedron* **1990**, *46*, 833.
4. X-Ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.
5. a) Using our standard conditions (Bailey, P. D.; Hollinshead, S. P.; McLay, N. R. *Tetrahedron Lett.* **1987**, *28*, 5177 - Note 4, method A), isolated yields were *ca* 75%. The new method is as follows:
b) (L)-Tryptophan isopropyl ester (1 mmol) is dissolved in ethanol-free dry $CHCl_3$ (15 ml) and 4Å molecular sieves (activated at 350°C for 72 h) are added. The solution is cooled to 0°C, and the required aldehyde (1.2 mmol) and catalytic TFA (1 µl, *ca* 1 mol%) are added. After 48 h at 0°C, when imine formation is complete, excess TFA (2 mmol) is added. The cyclisation is monitored by TLC (*ca* 4-5 h reaction times are typical), and basic work-up includes crushing the molecular sieves in order to ensure complete extraction of the product. Isolated yields are >95% for all aldehydes reported herein (e.g. PhCHO, *cyclo*-$C_6H_{11}CHO$, PrCHO, $PhCH_2CH_2CHO$, Me_2CHO), except for (volatile) propanal (88%). The change of solvent had no effect on the diastereoselectivity.

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