The *cis*-Specific Pictet–Spengler Reaction

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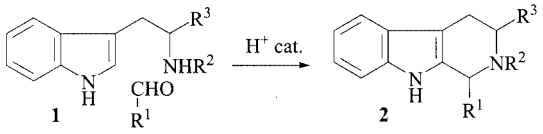
Keywords: Cyclization / Heterocycles / Alkaloids / Diastereoselectivity

The Pictet–Spengler reaction of tryptophan allyl ester with aryl aldehydes generates *cis*-tetrahydro-β-carbolines with complete stereo-control and with complete retention of optical integrity, when the reaction is carried out under kinetically controlled conditions.

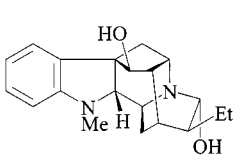
Introduction

The Pictet–Spengler reaction (e.g. Scheme 1) is a powerful way of accessing tetrahydro-β-carbolines, by the condensation of tryptamine derivatives with virtually any aldehyde.[1–3]

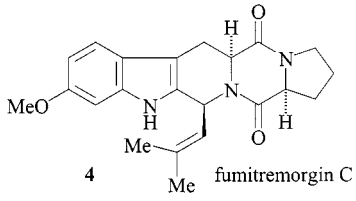


Scheme 1. The Pictet–Spengler route to tetrahydro-β-carbolines

Until the 1980's, biomimetic aqueous conditions were usually employed, with virtually no control of stereochemistry. In 1979, Cook's group introduced the use of refluxing benzene or toluene to effect cyclization, which made the Pictet–Spengler reaction much faster and higher yielding,[4] and an even faster microwave method has recently been reported.[5] Although poor stereo-control and racemization[6–8] were observed with tryptophan methyl ester, Cook's group were able to achieve excellent *trans* stereocontrol by using *N*-benzyl derivatives of tryptophan.[9] They used this *trans*-specific Pictet–Spengler reaction as a route to bridged indole alkaloids such as ajmaline (**3**) from *N*-benzyl tryptophan methyl ester[10] by using an epimerization pathway that traps out the desired *cis*-stereoisomer;[11] starting from D- or L-tryptophan, their procedure generates optically pure products, although the synthesis of bridged indole alkaloids requires D-tryptophan as the chiral source.



3 ajmaline



4 fumitremorgin C

However, if *cis*-selective Pictet–Spengler reactions could be achieved, this would provide access to bridged indole alkaloids from cheaper L-tryptophan. Moreover, there are important 1,3-disubstituted tetrahydro-β-carbolines that are not bridged, and these also possess the *cis*-1,3-relationship in almost all cases; in particular, the fumitremorgins (e.g. **4**)[12] have been found to possess potent anti-tumor properties against MDR cancer cell lines,[13,14] prompting several recent syntheses of fumitremorgins and related tryprostatins.[15–18]

In the early 1990's, we studied the mechanism of the Pictet–Spengler reactions of tryptamines,[19] and concluded that a *spiro*-intermediate was reversibly involved,[20] but that the formation of the six-membered ring was rate determining (Scheme 2). Consequently, provided the Pictet–Spengler reaction was conducted under conditions of kinetic control, we reasoned that the *cis*-diequatorial product should predominate. Our "kinetic" conditions led to a diastereo-control of typically 4:1 in favour of the *cis*-isomer, and we were pleased to discover that the reactions proceeded with complete retention of optical integrity when L-tryptophan derivatives were employed.[8,19,21]

In this paper, however, we report the fortuitous discovery that certain combinations of ester and aldehyde undergo the kinetically controlled Pictet–Spengler reaction with virtually 100 % *cis*-stereoselectivity.

Results and Discussion

We have utilized the kinetically controlled Pictet–Spengler reaction in a number of alkaloid synth-

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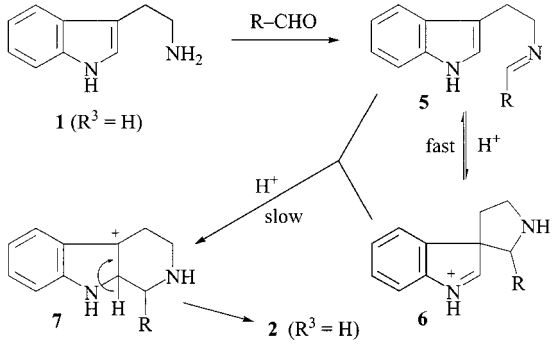


Scheme 2. Proposed mechanism for the Pictet−Spengler reaction

eses,[17,22] and it was during work towards ajmaline alkaloids (e.g. **3**) that we carried out a model reaction between benzaldehyde and the allyl ester of tryptophan, so that we could subsequently remove the ester using neutral Pd^0 catalysis. To our amazement, this reaction (**8** → **9a** in Scheme 3) yielded only the *cis*-tetrahydro-β-carboline, with none of the *trans*-isomer observable within our detection limits.

We therefore repeated the procedure using a variety of aryl and alkyl aldehydes (see Table 1), and observed *cis*-specific cyclization reactions in every case where the allyl ester was reacted with an aryl aldehyde (Entries 1−12).

There are a number of important observations. Firstly, we found that only allyl esters led to specificity in the reaction; using the propyl ester gave a typical *cis*/*trans* mixture of diastereoisomers (ca. 4:1), in line with our previous work with methyl and isopropyl esters (see Scheme 3).[8,21] Secondly, only aryl aldehydes condensed stereospecifically; alkyl aldehydes gave typical *cis*/*trans* mixtures, even if there was an aromatic ring elsewhere in the aldehyde (Entries 13−15). Thirdly, the reaction proceeded with a diverse range of aryl aldehydes, indicating the generality of the procedure. It should be noted that the reaction was very clean, and that we report here the results from a standard reaction procedure (see Exp. Sect.); optimization of reaction conditions for specific aldehydes led to excellent yields of the *cis*-isomers, as exemplified by the benzaldehyde product (Entries 1−3). We confirmed that the reaction was enantiospecific for this product using 1-anthryl-2,2,2-trifluoroethanol as an NMR chiral shift reagent.[23]

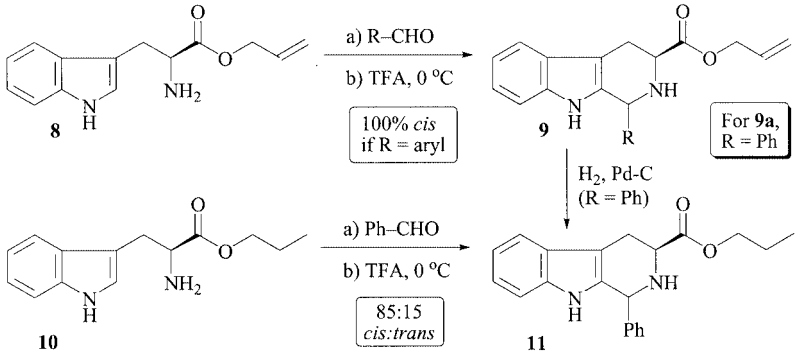
Table 1. Results of the Pictet−Spengler reaction of tryptophan allyl ester with various aldehydes (see Scheme 3, **8** → **9**); see Exp. Sect. for conditions; cyclization times were 8 h except for Entries 1 and 3

Entry	R	Yield (%)[a]	$[\alpha]_D^{26}$ (CH_2Cl_2)[b]	*cis*/*trans*[c]
1	Ph (6 h)	43		> 95:5
2	Ph (8 h)	57		> 95:5
3	Ph (11 h)	94	−13 (1.1)	> 95:5
4	2-Me-C_6H_4	75	−26 (1.1)	> 95:5
5	3-Me-C_6H_4	67	−6.3 (0.24)	> 95:5
6	4-Me-C_6H_4	78	−7.2 (0.26)	> 95:5
7	3-Cl-C_6H_4	67	−3.9 (0.25)	> 95:5
8	4-Cl-C_6H_4	54	−27 (0.57)	> 95:5
9	3-NO_2-C_6H_4	64	−17 (1.1)	> 95:5
10	4-NO_2-C_6H_4	67	+5.5 (0.51)	> 95:5
11	4-MeO-C_6H_4	62	−11.7 (0.29)	> 95:5
12	3-MeO-C_6H_4	64	−15 (0.47)	> 95:5
13	*cyclo*-C_6H_{11}	39		75:25
14	$CH_2CH_2CH_3$	67		78:22
15	$CH_2CH_2C_6H_5$	52		67:33

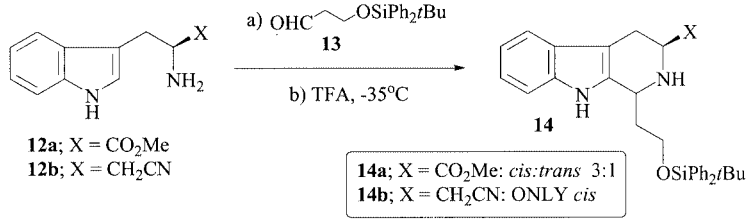
[a] The only products observed were the tetrahydro-β-carboline(s) and unchanged imine. [b] Concentrations are given in brackets. [c] For reactions in which the selectivity is quoted as > 95:5, none of the *trans* isomer was observed by NMR spectroscopy or isolated after chromatography; we estimate that the detection limits for by-products in the crude NMR spectra was 5 %.

We confirmed that the *cis*-stereoisomer of **9a** had been formed in two ways. Firstly, we hydrogenated the allyl group in **9a**, thereby converting it to the propyl ester **11**; we separately prepared the propyl esters as indicated in Scheme 4, in a 85:15 ratio of *cis*/*trans* isomers, and assigning the stereochemistry of these by comparison of the C(1) and C(3) ^{13}C chemical shifts in their NMR spectra.[24] The stereochemistry was also confirmed by a single-crystal X-ray structure of **9a** (see Figure 1), in which the 1- and 3-substituents occupy pseudo-equatorial positions in the half-chair conformer (see Exp. Sect. for additional X-ray data).

As far as we are aware, there are only two other examples claimed in the literature of tetrahydro-β-carbolines being formed in *cis*-specific Pictet−Spengler reactions. In the first example, Massiot and Mulamba reported that tryptophanamide reacts with $OHC(CH_2)_2C(SPh)_2CO_2Et$ to gen-



Scheme 3. The *cis*-specific Pictet−Spengler reaction (**8** → **9**, R = Ar)



Scheme 4. Stereoselectivity in the Pictet−Spengler reaction

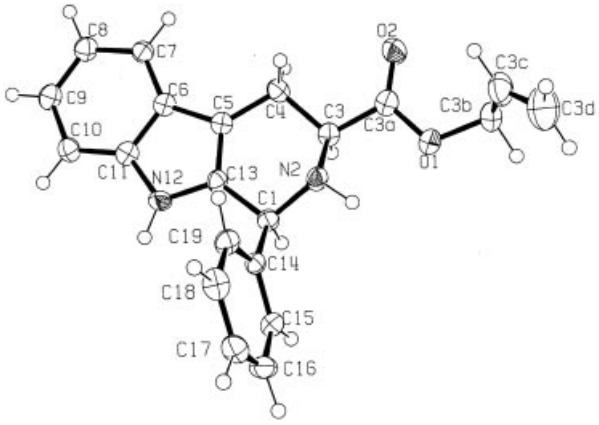


Figure 1. X-ray crystal structure of **9a** (R = Ph)

erate the *cis*-adduct exclusively.[25] In the other example, we had observed *cis*-specificity in the condensation of the amino-nitrile **12b** with the aldehyde **13**; this reaction only yielded the *cis*-tetrahydro-β-carboline **14b**, whereas the related reaction with tryptophan methyl ester **12a** only yielded a 3:1 *cis*/*trans* selectivity (Scheme 4).[26] The reason for the *cis*-specificity using allyl esters/aryl aldehydes is not yet clear, but it is possible that π-stacking between the allyl/aryl groups allows the cyclization to proceed through a diaxial intermediate. It is noteworthy that two X-ray crystal structures of N(2)-benzyl *cis*-1,3-disubstituted tetrahydro-β-carbolines show the 1,3-substituents to be both axial, although the methyl ester analogue of **9a** has a di-equatorial crystal structure.[19] This suggests that there is only a small energetic difference between the axial and equatorial positions in such compounds, so that modest stabilization through π-stacking might be sufficient to confer the *cis*-control that we observe. We are carrying out further experiments to test this hypothesis, and to try to rationalize the selectivity as fully as possible.

In summary, we have found that the Pictet−Spengler reaction of tryptophan allyl ester with aryl aldehydes generates *cis*-tetrahydro-β-carbolines with complete stereo-control, when the reaction is carried out under kinetically controlled conditions, and with complete retention of optical integrity. This reaction (and selectivity) tolerates all substituted phenyl derivatives that we tried for the aldehyde (electron-withdrawing and electron-donating groups, and substituents in the *o-, m-,* or *p*-positions), which means that this should be adaptable to a wide range of targets of medicinal or synthetic interest; for example, as we can prepare methoxyphenyl derivatives, this should provide access to yohimbine alkaloids through Birch reduction and further elaboration. We are carrying out further studies to establish the explanation for this stereo-control, and we hope that the chemistry will be of use in the synthesis of a wide range of indole alkaloids.

Experimental Section

General: All reactions were carried out under argon using dry solvents. Optical rotations were measured at 23 °C using a Thorn Automation Type 243 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX 400 or 300 MHz spectrometers using $CDCl_3$ as the solvent. Mass spectrometric analyses were carried out using positive ion electrospray ionisation combined with orthogonal TOF-MS (Micromass LCT). IR spectra were recorded on a Perkin−Elmer 783 spectrometer.

L-Tryptophan allyl ester is commercially available (Neosystem, as the HCl salt), although we could readily prepare it as follows. Acetyl chloride (12.9 mL) was slowly added to a suspension of L-tryptophan (15 g, 73.4 mmol) in allyl alcohol (150 mL). The reaction mixture was then heated at reflux for 4−5 hours, cooled to room temperature, and a 10 % aqueous solution of NH_3 (300 mL) was added. The aqueous layer was extracted with dichloromethane (3 × 200 mL) and the combined organic extracts were washed with brine (300 mL), dried over $MgSO_4$, filtered and the solvents evaporated. The product was purified by column chromatography to give yellow crystals.

Standard Procedure for the Synthesis of Tetrahydro-β-carbolines: L-tryptophan allyl ester (150 mg, 0.613 mmol) was dissolved in CH_2Cl_2 (5 mL) with 3 Å molecular sieves (15 mg/mmol of ester) under argon. The solution was cooled to 0 °C, and the appropriate aldehyde (1 mmol) added. After 30 min, the solution was allowed to warm to room temperature and stirred overnight. A small aliquot was then removed, the solvents were evaporated off and the remaining solid analyzed by NMR spectroscopy confirming complete formation of the imine. The solution was then cooled to 0 °C, TFA (2 equiv.) was added, and the reaction stirred at this temperature for 8 hours. The reaction was quenched with saturated aqueous $NaHCO_3$ (12 mL) and warmed to room temperature. The phases were separated and the combined organic solutions were washed with brine, dried over $MgSO_4$, and the solvent removed on a rotary evaporator. The products were purified by column chromatography (230−400 mesh silica), leading to isolation of the tetrahydro-β-carbolines **9**, and unchanged imine (ca. 20 %). Quoted

yields (Table 1) are corrected for recovered imine, but the reactions are readily optimized for specific aldehydes.

Data for 9a: Brown oil, 94 % yield (11 h reaction time); R_f = 0.22 (2 % Et_2O/DCM). $\tilde{\nu}$ = 3652, 3052, 2990, 2307, 1732, 1266 cm^{-1}. $[\alpha]_D^{23}$ −13 (c = 1.09, CH_2Cl_2). δ_H ($CDCl_3$, 400 MHz) = 2.28 (br. s, 1 H, N*H*), 2.93 (ddd, J = 15.0, 11.4, 2.5 Hz, 1 H, ArC*H*H), 3.15 (ddd, J = 15.0, 4.2, 1.8 Hz, 1 H, ArCH*H*), 3.87 (dd, J = 11.1, 7.7 Hz, 1 H, $ArCH_2CH$), 4.55−4.66 (m, 2 H, $OCH_2CH{=}CH_2$), 5.10 (s, 1 H, ArC*H*NH), 5.19 (dd, J = 10.4, 1.4 Hz, 1 H, $OCH_2CH{=}CHH$), 5.28 (dd, J = 17.2, 1.4 Hz, 1 H, $OCH_2CH{=}CHH$), 5.81−5.86 (m, 1 H, $OCH_2CH{=}CH_2$), 7.05−7.45 (10 H, Ar*H* and indole N*H*) ppm. δ_C ($CDCl_3$, 100 MHz) = 26.2, 57.3, 59.1, 66.2, 109.2, 111.4, 118.6, 119.3, 120.0, 122.3, 127.5, 128.7, 128.9, 129.0, 129.1, 129.6, 132.2, 135.1, 136.6, 141.2, 172.4 ppm. HRMS (ES+): calcd. for $C_{21}H_{21}N_2O_2$ $[M + H]^+$ 333.1604, found 333.1617 (100 %), 334.1642 (10 %). All compounds reported in this paper were fully characterized by ^1H and ^{13}C NMR spectroscopy, IR, $[\alpha]_D$, MS and HRMS; supplementary information is available on request.

X-ray Analysis of 9a: Data were collected on a crystal of dimensions 0.20 × 0.20 × 0.05 mm (obtained by slow evaporation of a solution of **9a** in CH_2Cl_2), monoclinic, space group $P2_1$, a = 9.0452(5) Å, b = 5.4434(3) Å, c = 17.5863(12) Å, α = 90°, β = 102.668(3)°, γ = 90°, V = 844.81(9) $Å^3$, Z = 2, $\rho_{calcd.}$ = 1.307 Mg/m^3, θ_{max} = 27.53°,Mo-K_α, λ = 0.71073 Å, scan mode CCD rotation images (thick slices), T = 150(2) K, 5632 measured reflections, of which 3239 were independent [R_{int} = 0.0462], 3239 reflections were included in the refinement [2234 $I > 2\sigma(I)$], Lorentzian and polarization corrections were performed, absorption correction semi-empirical from equivalents (μ = 0.085 mm^{-1}, max./min. transmission 0.9958/0.9832). Absolute stereochemistry was not determined. The structure was solved by direct methods using SHELXS-97 (G.M. Sheldrick, *SHELXS-97. Program for crystal structure solution*, **1997**, University of Göttingen, Germany), refinement method full-matrix least-squares on F^2 using SHELXL-97 (G.M. Sheldrick, *SHELXL-97. Program for crystal structure refinement*, **1997**, University of Göttingen, Germany), no. of parameters = 306, H atoms were subjected to isotopic refinement, final residuals refined against $|F^2|$ were wR_2 = 0.1171 (all data) R_1 = 0.0558 [$I > 2\sigma(I)$], max. and min. residual electron density 0.195 and −0.252 e $Å^{-3}$. CCDC-228672 contains the supplementary crystallographic data for this paper. These data can be obtained online free of charge [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

We thank Dr. Ian Fleet for mass spectra, the EPSRC for financial support, and the use of the EPSRC's Chemical Database Service at Daresbury.

[1] W. M. Whaley, T. R. Govindachari, *Organic Reactions* **1951**, *6*, 151.
[2] R. A. Abramovitch, I. D. Spenser, *Adv. Heterocycl. Chem.* **1964**, *3*, 79.
[3] K. Stuart, R. Woo-Ming, *Heterocycles* **1975**, *3*, 223.
[4] D. Soerens, J. Sandrin, F. Ungemach, P. Mokey, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro, J. M. Cook, *J. Org. Chem.* **1979**, *44*, 535.
[5] N. Srinivasan, A. Ganesan, *Chem. Commun.* **2003**, 916.
[6] D. Harrison, R. B. Sharma, *Tetrahedron Lett.* **1986**, *27*, 521.
[7] M. Nakagawa, H. Fukushima, T. Kawate, M. Hongu, S. Kodato, T. Une, M. Taniguchi, T. Hino, *Tetrahedron Lett.* **1986**, *27*, 3235.
[8] P. D. Bailey, S. P. Hollinshead, N. R. McLay, *Tetrahedron Lett.* **1987**, *28*, 5177.
[9] F. Ungemach, M. DiPierro, R. Weber, J. M. Cook, *J. Org. Chem.* **1981**, *46*, 164.
[10] J. Li, T. Wang, P. Yu, A. Peterson, R. Weber, D. Soerens, D. Grubisha, D. Bennett, J. M. Cook, *J. Am. Chem. Soc.* **1999**, *121*, 6998.
[11] L. Zhang, J. M. Cook, *Heterocycles* **1988**, *27*, 2795.
[12] T. Hino, M. Nakagawa, *Heterocycles* **1997**, *46*, 673.
[13] S. K. Rabindran, H. He, M. Singh, E. Brown, K. I. Collins, T. Annable, L. M. Greenberger, *Cancer Research* **1998**, *58*, 5850.
[14] H. He, S. K. Rabindran, L. M. Greenberger, G. T. Carter, *Med. Chem. Res.* **1999**, *9*, 424.
[15] S. D. Edmondson, S. J. Danishefsky, L. Sepp-Lorenzino, N. Rosen, *J. Am. Chem. Soc.* **1999**, *121*, 2147.
[16] L. E. Overman, M. D. Rosen, *Angew. Chem. Int. Ed.* **2000**, *39*, 4596.
[17] P. D. Bailey, P. J. Cochrane, K. Lorenz, I. D. Collier, D. P. J. Pearson, G. M. Rosair, *Tetrahedron Lett.* **2001**, *42*, 113.
[18] C. Meyers, E. M. Carreira, *Angew. Chem. Int. Ed.* **2003**, *42*, 694.
[19] P. D. Bailey, S. P. Hollinshead, N. R. McLay, K. M. Morgan, S. J. Palmer, S. N. Prince, C. D. Reynolds, S. D. Wood, *J. Chem. Soc., Perkin Trans. 1* **1993**, 431.
[20] P. D. Bailey, *J. Chem. Res.* **1987**, 202.
[21] P. D. Bailey, M. H. Moore, K. M. Morgan, D. I. Smith, J. M. Vernon, *Tetrahedron Lett.* **1994**, *35*, 3587.
[22] [22a] P. D. Bailey, N. R. McLay, *J. Chem. Soc., Perkin Trans. 1* **1993**, 441. [22b] P. D. Bailey, S. P. Hollinshead, N. R. McLay, J. H. Everett, C. D. Reynolds, S. D. Wood, F. Giordano, *J. Chem. Soc., Perkin Trans. 1* **1993**, 451. [22c] P. D. Bailey, I. D. Collier, S. P. Hollinshead, M. H. Moore, K. M. Morgan, D. I. Smith, J. M. Vernon, *J. Chem. Soc., Perkin Trans. 1* **1997**, 1209. [22d] P. D. Bailey, K. M. Morgan, *J. Chem. Soc., Perkin Trans. 1* **2000**, 3578.
[23] The NMR signal from H-3 from **9a** (dd, δ = 4.0 ppm, 1 H) was shifted upfield upon the addition of 1-anthryl-2,2,2-trifluoroethanol; this was resolved into 2 × dd of equal intensity when DL-tryptophan allyl ester was used in the Pictet−Spengler reaction.
[24] P. D. Bailey, S. P. Hollinshead, *J. Chem. Soc., Chem. Commun.* **1985**, 1575.
[25] G. Massiot, T. Mulamba, *J. Chem. Soc., Chem. Commun.* **1983**, 1147.
[26] P. D. Bailey, P. D. Clingan, T. J. Mills, R. A. Price, R. G. Pritchard, *Chem. Commun.* **2003**, 2800.

Received January 12, 2004

