Tetrahedron Letters 50 (2009) 3645–3647

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Unexpected cis selectivity in the Pictet–Spengler reaction

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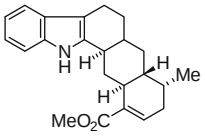
ARTICLE INFO

Article history:
Received 16 January 2009
Revised 5 March 2009
Accepted 16 March 2009
Available online 21 March 2009

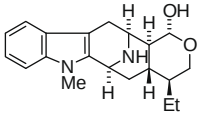
ABSTRACT

Whilst cis:trans selectivity of about 4:1 can be obtained from Pictet–Spengler reactions between tryptophan methyl esters and aldehydes using conditions of kinetic control, much higher cis selectivity (>95:5) can be obtained when both the tryptophan derivative and the aldehyde possess a suitable π-system; preliminary results on the scope and limitations of this exceptional stereocontrol are presented in this Letter.

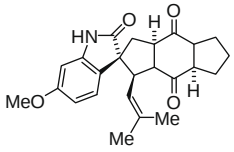
The Pictet–Spengler reaction is a key step in the total synthesis of a large number of indole alkaloids, as exemplified by syntheses of ajmalicine (**1**),[1] raumacline (**2**),[2] spirotryprostatin A (**3**)[3] and ajmaline (**4**).[4]



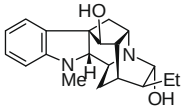
ajmalicine (**1**)



raumacline (**2**)



spirotryprostatin A (**3**)

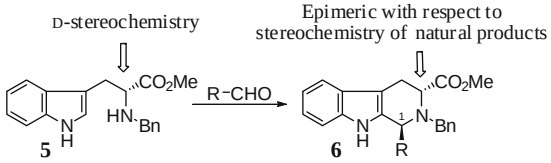


ajmaline (**4**)

The indolic Pictet–Spengler reaction involves the formation of an imine between a tryptamine derivative and an aldehyde, which can then undergo acid-catalysed cyclisation to generate a new piperidine ring.[5]

If the tryptamine derivative contains an α-substituent (e.g., tryptophan esters), then diastereoisomers can be generated. In the case of *N*-benzyl tryptophan derivatives, Cook ascertained that the trans isomer is the sole product;[6] his group have used this in their synthesis of bridged indole alkaloids such as ajmaline,[4] although this necessitates starting from non-DNA-encoded D-tryptophan, and epimerisation of the α-centre during the formation of the bridged ring system (Scheme 1).

It is worth noting that the tetrahydro-β-carboline moiety is the commonest sub-structure amongst indole alkaloids and, if derived from L-tryptophan, the 1-substituent is always required to be cis relative to the carboxylic acid derivative of the tryptophan.



Scheme 1. Trans control with *N*-benzyl derivatives.

For many indole alkaloids, the carboxylic group is absent in the final natural product (e.g., ajmalicine **1**), although tryptophan is the biosynthetic building block, and can be used in total syntheses if the carboxy group is removed after the Pictet–Spengler reaction.[7] For bridged indole alkaloids such as ajmaline, the α-carboxy group can be incorporated into the target molecule. In either case, cis-selective Pictet–Spengler reactions are required if L-tryptophan is to be used as the starting material.

We have studied the mechanism of the Pictet–Spengler reaction, and used this to develop a cis-selective procedure that involved kinetically controlled conditions (Scheme 2);[8] in contrast, the original[5] or improved[9] procedures used until the 1980s gave poor stereocontrol (mainly trans, and with problems of racemisation).

Using our conditions of kinetic control, we recently completed a total synthesis of the alkaloid (−)-raumacline.[2a] Notable in our approach was an early Pictet–Spengler reaction in which complete cis-stereocontrol was observed (Scheme 3); as far as we are aware, only one other cis-specific Pictet–Spengler reaction had been reported.[10]

However, in 2004, we reported that tryptophan allyl esters could be reacted with benzaldehyde, to give >95:5 cis:trans selectivity; this unexpected result turned out to be quite general, such that aryl aldehydes can be reacted with tryptophan allyl ester to give the cis-1,3-disubstituted tetrahydro-β-carbolines (Scheme 4).[11]

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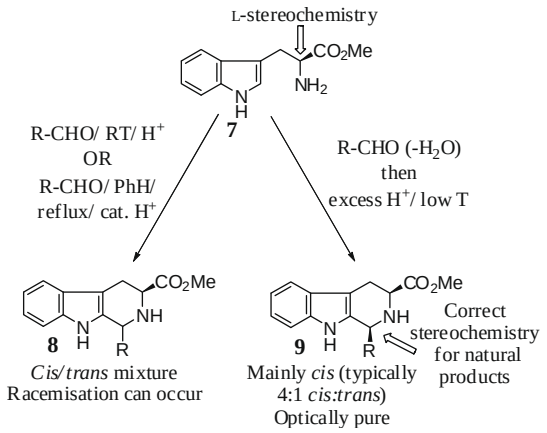
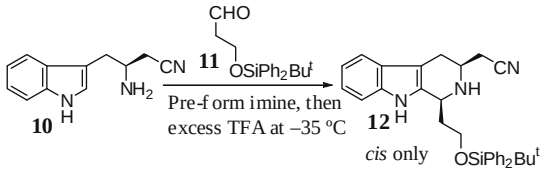
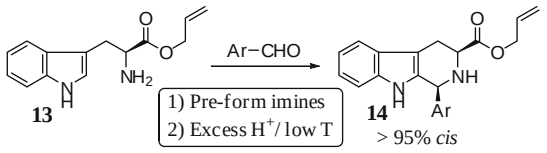
doi:10.1016/j.tetlet.2009.03.121



Scheme 2. Stereocontrol in the Pictet–Spengler reaction.



Scheme 3. Cis selectivity with homologous nitrile **14**.



Scheme 4. Cis selectivity with tryptophan allyl esters.

At that time, no other types of aldehyde or tryptophan derivatives were found to give high cis selectivity. However, we report in this Letter a much wider range of other tryptophan derivative/aldehyde combinations that also give outstanding cis selectivity of >95:5. Although we are not yet able to provide either a definitive explanation, or a definitive 'rule' for this stereocontrol, our results provide strong guidelines for those wishing to access *cis*-tetrahydro-β-carbolines using the Pictet–Spengler reaction.

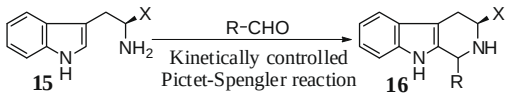
Firstly, we report the use of benzyl esters in place of allyl esters, for which we hoped that the aryl group would have the same effect as the ethylene moiety. Tryptophan benzyl ester is surprisingly difficult to be prepared,[12] but did provide some improvement in cis selectivity with benzaldehyde, although all other aldehydes showed only modest selectivity (see Table 1, entries 13–16). The use of benzyl esters can be useful for aldehydes with sensitive side chains because (unlike allyl) the benzyl group can be removed under mild hydrogenation conditions.

Secondly, these results with the benzyl ester allowed us to complete a useful matrix of results using four tryptophan esters and four archetypical aldehydes (Scheme 5), as summarised in Table 1, which also provides a reminder that the use of isopropyl esters (in ethanol-free chloroform) ensures the highest yield of the Pictet–Spengler product[13] (but with varying stereocontrol).

From Table 1, it is clear that both the ester and the aldehyde must contain an appropriate π-moiety (in addition to the C=O π-bond) in order for high cis selectivity to be observed. However, the addition of 10 equiv of toluene, anisole or nitrobenzene to these reactions (entry 9) did not reduce the cis selectivity, despite the fact that one might have expected the π-additives to interfere with any π-stacking interactions.

Table 1
Results from the kinetically controlled Pictet–Spengler reaction using a range of tryptophan esters[14]

Entry	X in **15**	R in aldehyde	Yield (%)	Cis:trans ratio
1[8]	$-CO_2Me$	–Ph	74	4.6:1
2[8]	$-CO_2Me$	–Cyclohexyl	71	2.5:1
3[8]	$-CO_2Me$	$-(CH_2)_2Ph$	72	4.0:1
4[8]	$-CO_2Me$	$-(CH_2)_2CH_3$	75	4.9:1
5[13]	$-CO_2{}^iPr$	–Ph	>95	7.3:1
6[13]	$-CO_2{}^iPr$	–Cyclohexyl	>95	3.5:1
7[13]	$-CO_2{}^iPr$	$-(CH_2)_2Ph$	>95	2.7:1
8[13]	$-CO_2{}^iPr$	$-(CH_2)_2CH_3$	>95	2.7:1
9[11]	$-CO_2Allyl$	–Ph	57	>20:1
10[11]	$-CO_2Allyl$	–Cyclohexyl	39	3.0:1
11[11]	$-CO_2Allyl$	$-(CH_2)_2Ph$	52	2.0:1
12[11]	$-CO_2Allyl$	$-(CH_2)_2CH_3$	67	3.5:1
13	$-CO_2Bn$	–Ph	74	4.7:1
14	$-CO_2Bn$	–Cyclohexyl	81	3.3:1
15	$-CO_2Bn$	$-(CH_2)_2Ph$	72	2.3:1
16	$-CO_2Bn$	$-(CH_2)_3CH_3$	77	3.1:1



Scheme 5. Scope of selectivity (Tables 1 and 2).

Thirdly, we have carried out further Pictet–Spengler reactions with the homologous nitrile **10**, and have extended the range of aldehydes that react with high cis selectivity. Our starting point was the reaction of **10** with $Ph_2Bu^tSiO-(CH_2)_2-CHO$ (**11**), which forms >95% of the cis adduct (Scheme 3);[2a] when repeated using tryptophan methyl ester (Table 2, entry 2), this reaction gave a 3:1 cis:trans ratio of products, confirming the need for a π-group in the ester. Demonstration that the aldehyde must also possess a π-group came from the use of the TBDMS-protected aldehyde (entry 3), which reverted to the normal selectivity in the Pictet–Spengler reaction. However, most intriguingly, we found that the high cis selectivity was retained when **10** was reacted with alkyl aldehydes possessing phenyl group(s) at a range of positions, substantially increasing the scope of this highly cis-selective reaction.

In summary, Table 1 demonstrates the yield and modest cis selectivity that can be obtained using a range of tryptophan esters in the kinetically controlled Pictet–Spengler reaction; the excellent cis control using tryptophan allyl ester with aryl aldehydes is also highlighted. However, the excellent cis control possible using the homologous nitrile **10** with a wide range of aldehydes possessing a phenyl group in the side chain is extraordinary; we are still prob-

Table 2
Pictet–Spengler reactions with nitrile **10**[15]

Entry	X in **15**	R in aldehyde	Yield %	Cis:trans ratio
1	$-CH_2CN$	$-(CH_2)_2OSiBu^tPh_2$	59	>20:1
2	$-CO_2Me$	$-(CH_2)_2OSiBu^tPh_2$	82	3.0:1
3	$-CH_2CN$	$-(CH_2)_2OSiBu^tMe_2$	51	3.6:1
4	$-CO_2allyl$	$-(CH_2)_2OSiBu^tPh_2$	58	2.5:1
5	$-CH_2CN$	$-CH_2OSiBu^tPh_2$	70	>20:1
6	$-CH_2CN$	$-(CH_2)_3OSiBu^tPh_2$	58	>20:1
7	$-CH_2CN$	$-(CH_2)_6OSiBu^tPh_2$	53	>20:1
8	$-CH_2CN$	$-(CH_2)_7OSiBu^tPh_2$	56	>20:1
9	$-CH_2CN$	$-(CH_2)_2Ph$	41	>20:1
10	$-CH_2CN$	$-(CH_2)_2OBn$	64	>20:1

ing the reasons for this. Furthermore, this chemistry is being exploited in the total synthesis of indole alkaloids.

Acknowledgement

We thank the EPSRC for funding.

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10. See reference 1; this neatly exploited both *cis* and *trans* selective Pictet-Spengler reactions to access both antipodes; the *cis*-tetrahydro-β-carboline [from tryptophanamide and $(PhS)_2C(CO_2Me)$-$(CH_2)_2CHO$] was diastereomerically pure within the NMR detection limits. Using chiral aldehydes (Z-protected α-aminoaldehydes) with Trp-OMe, *cis* specific reactions have been reported for matched substrates (Pulka, K.; Kulis, P.; Tymecka, D.; Lukasz, F., Wilczek, M.; Kozminski, W.; Misicka, A. *Tetrahedron* **2008**, *64*, 1506. Aqueous Pictet-Spengler reactions show typical *cis* selectivity of about 4:1, although a 9:1 *cis:trans* ratio was reported for Trp-OMe with 2-hydroxybenzaldehyde (Saha, B.; Sharma, S.; Sawant, D.; Kundu, B. *Tetrahedron Lett.* **2007**, *48*, 1379).
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14. General method for the entries given in Table 1. L-Tryptophan allyl ester (150 mg, 0.613 mmol) was dissolved in DCM (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) was added. After 30 min, the solution was allowed to warm to room temperature and was stirred overnight. A small aliquot was then removed, the solvents were evaporated off and the remaining solid was analysed 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 mixture was stirred at this temperature for 3–8 h. The reaction mixture was quenched with satd aq $NaHCO_3$ (12 mL) and was warmed to room temperature. The phases were separated and the combined organic solutions were washed with brine, dried over $MgSO_4$ and reduced in vacuo. The products were purified by column chromatography leading to isolation of the tetrahydro-β-carboline. Table 1, entry 9: 57% yield. R_f 0.22 (2% Et_2O/CH_2Cl_2). IR ν_{max} (neat) 3652, 3052, 2990, 2307, 1732, 1266 cm^{-1}. $[\alpha]_D^{23}$ − 13 (*c* 1.09, CH_2Cl_2). ^1H NMR ($CDCl_3$, 400 MHz) δ 2.28 (1H, br s, N*H*), 2.93 (1H, ddd, *J* = 15.0, 11.4, 2.5 Hz, ArC*H*H), 3.15 (1H, ddd, *J* = 15.0, 4.2, 1.8 Hz, ArCH*H*), 3.87 (1H, dd, *J* = 11.1, 7.7 Hz, $ArCH_2CH$), 4.55–4.66 (2H, m, $OCH_2CH = CH_2$), 5.10 (1H, s, ArC*H*NH), 5.19 (1H, dd, *J* = 10.4, 1.4 Hz, $OCH_2CH = CHH$), 5.28 (1H, dd, *J* = 17.2, 1.4 Hz, $OCH_2CH=CHH$), 5.81–5.86 (1H, m, $OCH_2CH=CH_2$), 7.05–7.45 (10H, m, Ar*H* and indole N*H*) ppm. ^{13}C NMR ($CDCl_3$, 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%).
15. General method for the entries given in Table 2. The amino-nitrile (150 mg, 0.684 mmol) was dissolved in CH_2Cl_2 (5 mL) with 3 Å molecular sieves (15 mg/mmol of amino-nitrile) under N_2. The solution was cooled to 0 °C, and the appropriate aldehyde (0.855 mmol) in CH_2Cl_2 (2.5 mL) was added. After 30 min, the solution was allowed to warm to room temperature and was stirred overnight. A small aliquot was then removed, the solvents were evaporated off and the remaining solid was analysed by NMR spectroscopy confirming complete formation of the imine. The mixture was then cooled to −78 °C before the addition of TFA (2 equiv). The reaction mixture was stirred at −78 °C for 3 h, 0 °C for 1 h and room temperature for 2 h (except entry 3, which was run at −35 °C until the reaction was complete by TLC). The resulting red mixture was filtered and the molecular sieves were washed thoroughly with CH_2Cl_2 (25 mL) before the addition of sat. aqueous $NaHCO_3$ (15 mL). The phases were separated and the combined organic solutions were washed with satd aq $NaHCO_3$ (15 mL) and brine (15 mL), dried over $MgSO_4$ and reduced in vacuo. The products were purified by column chromatography leading to isolation of the tetrahydro-β-carboline. Data for Table 2, entry 1: 59% yield. R_f 0.38 (10% Et_2O/CH_2Cl_2). IR ν_{max} (neat) 3362, 3071, 2930, 2250, 1428, 1112 cm^{-1}. ^1H NMR ($CDCl_3$, 500 MHz) δ 1.06 (9H, s, $C(CH_3)_3$), 1.46 (1H, br s, N*H*), 1.76 (1H, ddt, *J* = 14.8, 4.1, 3.7 Hz, C*H*HCH$_2$OSi), 2.07–2.13 (1H, m, CH*H*CH$_2$OSi), 2.43–2.47 (1H, m, ArC*H*H), 2.49 (2H, dd, *J* = 6.8, 2.5 Hz, C*H*HCN), 2.84 (1H, ddd, *J* = 15.0, 4.0, 1.9 Hz, ArCH*H*), 3.15–3.21 (1H, m, C*H*CH$_2$CN), 3.85–3.87 (2H, m, CH$_2$CH$_2$OSi), 4.19–4.22 (1H, m, ArC*H*), 6.98–7.04 (3H, m, Ar*H*), 7.26–7.38 (7H, m, Ar*H*), 7.57–7.61 (4H, m, Ar*H*), 8.86 (1H, br s, indole N*H*) ppm. ^{13}C NMR ($CDCl_3$, 125 MHz) δ 19.5, 25.0, 27.1, 28.5, 37.7, 51.3, 53.7, 62.9, 111.1, 117.9, 118.0, 119.4, 121.6, 123.6, 127.3, 128.0, 128.1, 130.1, 130.2, 135.5, 135.6 ppm. HRMS (ES^+): Calcd for $C_{31}H_{35}N_3OSi$ $[M+H]^+$: 494.6223. Found: 494.6217 (100%).