



Use of Azalactones in a "Pictet-Spengler-Like" Reaction. Stereoselective Synthesis of 1,3,4-Substituted Tetrahydro- β - Carbolines

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Abstract: A "Pictet-Spengler-like" reaction between azalactones **1** and conformationally constrained tryptamines **4** in refluxing 1N HCl over 72 h. gave the corresponding tetrahydro- β -carbolines **3** in moderate to good yields. The observed equatorial orientation of the C-1 substituent in the THBC's results from a combination of the thermal reaction conditions and conformational constraints imposed by the starting tryptamines. Copyright © 1996 Elsevier Science Ltd

The Pictet-Spengler reaction (P-S) is a classical and straightforward method for the synthesis of tetrahydro- β -carbolines (THBC's).^{1,9} Traditionally this reaction has been performed by condensation of tryptamines with carbonyl compounds such as aldehydes and reactive ketones. Other electrophilic reagents like α -ketoacids² or enamines³ have been used successfully, broadening the scope of the reaction. Recently, Audia and co-workers⁴ have shown that azalactones (**1**, Figure 1) are "arylacetaldehyde equivalents", undergoing P-S condensation with tryptamine under hydrolytic conditions.

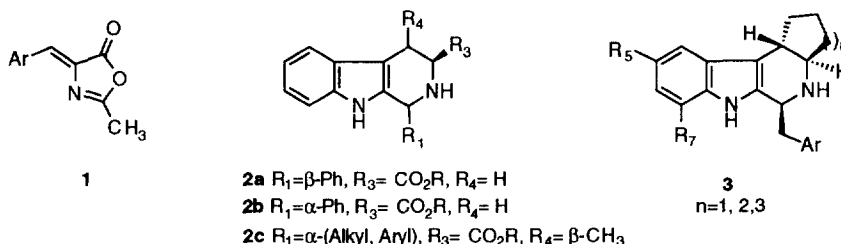


Figure 1

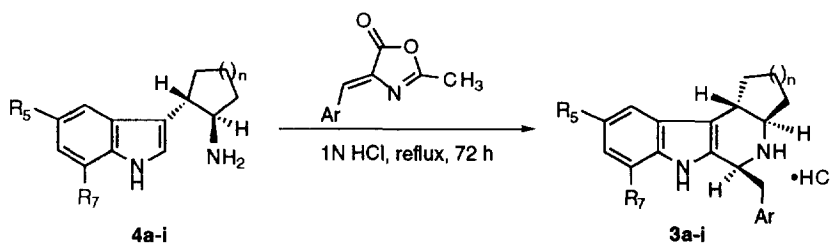
Stereoselective P-S reactions have been achieved using chiral substrates such as aldehydes,⁵ iminium salts⁶ or acetylenic sulfoxides.⁷ Alternatively, the P-S reaction between (L)-tryptophan esters and aldehydes can be controlled under kinetic conditions⁸ to give the desired relative and absolute stereochemistry, and this methodology has been applied to the synthesis of a wide variety of natural products.⁹ For example, the *cis* relationship between R₁ and R₃ in **2a** (Figure 1) can be obtained under kinetic control reaction conditions, while the *trans* isomers **2b** are the thermodynamically favoured products.⁸ This stereochemical control also

applies to β -methyltryptophan, and the carboline **2c**¹⁰ has been prepared in a stereospecific manner under thermodynamic reaction conditions.

In this paper we report a "Pictet-Spengler-like" reaction using azalactones **1** as "arylacetaldehyde equivalents" with different *trans*-(2-aminocycloalkyl)indoles¹¹ under hydrolytic and thermal conditions, giving rise to the THBC's **3**.

The azalactones (**1**) were prepared by condensation of *N*-acetylglycine and the corresponding aryl aldehyde in Ac₂O, using NaOAc as base.¹² The *trans*-(2-aminocycloalkyl)indoles (**4a-i**) were prepared stereoselectively by *N*-Boc aziridine ring opening with the corresponding indolylmagnesium bromides in the presence of CuBr as we have recently described.¹¹ The Pictet-Spengler condensation was conducted in refluxing 1N HCl solution over 72h., yielding the corresponding THBC's which were isolated as hydrochloride salts¹³ (Table 1).

Table 1



Entry	Compound	n	R ₅	R ₇	Ar	Yield (%)
1	3a	1	CH ₃	H	3,4-di-CH ₃ OC ₆ H ₃	88
2	3b	2	CH ₃	H	3,4-di-CH ₃ OC ₆ H ₃	65
3	3c	1	CH ₃	H	1-Naphthyl	75
4	3d	2	CH ₃	H	1-Naphthyl	76
5	3e	1	CH ₃	CH ₃	3,4-di-CH ₃ OC ₆ H ₃	30
6	3f	2	CH ₃	CH ₃	3,4-di-CH ₃ OC ₆ H ₃	42
7	3g	1	CH ₃	CH ₃	1-Naphthyl	65
8	3h	2	CH ₃	CH ₃	1-Naphthyl	44
9	3i	3	CH ₃	H	3,4-di-CH ₃ OC ₆ H ₃	40

The THBC's were obtained in good (5-methyltryptamines, **4a-d**) or moderate (5,7-dimethyl counterpart) yields.

The THBC's were isolated as single diastereoisomers¹⁴ and the relative stereochemistry at the C-1 centre determined using NMR methods. Full ¹H and ¹³C assignments were obtained using DQF-COSY and HMQC experiments. The large (*c.* 10Hz) H-1 to NH-2_{ax} and H-3 to NH-2_{ax} couplings provides indirect evidence for a *trans* relationship between these pairs of protons. This conclusion was corroborated by 1D nOe difference experiments (Figure 2) where the strong/medium enhancements observed from H-1 to H-2_{eq} and to H-3 confirms a *cis* relationship of the C-1 and C-3 substituents. In order to rule out any possible influence that the C-4 substituent could exercise over the newly created C-1 stereogenic centre, the THBC **5** was prepared (40% isolated yield) from the corresponding *cis* tryptamine¹⁵ in a P-S reaction with the

azalactone **1** (Ar= 3,4-di-CH₃OC₆H₃) under the same reaction conditions. NMR results confirmed the product had an all *cis* relative stereochemistry (Figure 2) with the C-1 substituent in an equatorial position.

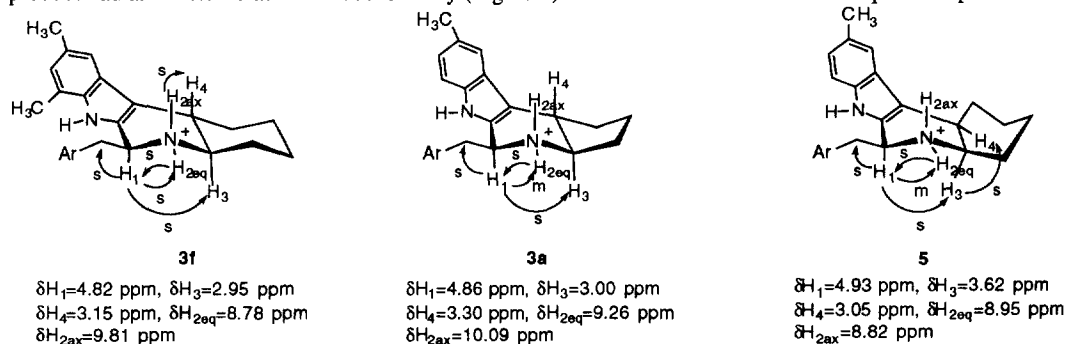
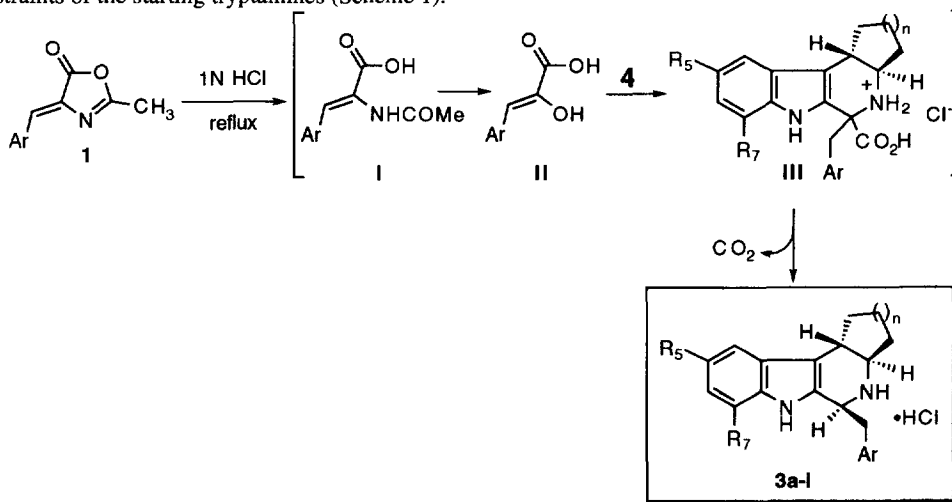


Figure 2

The diastereoselectivity of the classical P-S reaction has been studied extensively with L-tryptophane esters.⁸ Thus, *cis*-1,3-disubstituted THBC's can be obtained with good diastereoselectivity by using kinetically controlled reaction conditions under acidic medium. On the other hand, higher temperatures (thermodynamic control) lead to a poor diastereoselectivity and risk of epimerization.

An explanation for the stereochemical outcome observed in the Pictet-Spengler-like reaction with azalactones **1** and tryptamines **4** has to take into account the reaction conditions and the conformational constraints of the starting tryptamines (Scheme 1).



Scheme 1

Strong acidic conditions (1N HCl/reflux) are required to transform the azalactone **1** into the reactive arylpyruvic acid **II** which undergoes P-S reaction with tryptamines **4**, giving rise to the THBC acid **III**. Under acidic thermal conditions **III** decarboxylates to the THBC **3**, delivering the C-1 substituent in an equatorial position (see Figure 2). The stereochemical result at the C-1 substituent is opposite to that expected in the classical thermodynamically controlled P-S reaction for 1,3-disubstituted THBC's. Thus, the β -orientation of the substituent in **3** must be influenced by steric constraints introduced by the cycloalkyl ring of the tryptamines **4**. The final THBC has all the substituents locked in the energetically favoured equatorial

orientation. The same result was also observed in the THBC **5** where the cyclohexyl appendage has a *cis* fusion. In this case the all-*cis* substitution is also the lowest energy conformation, as the 1 α -isomer contains an unfavoured 1,3-diaxial interaction. Finally, a 3:1 mixture of 1,3-disubstituted carbolines (60% isolated yield) was obtained when this modified P-S reaction was applied to α -methyltryptamine with the azalactone **1** (Ar= 1-naphthyl).

We, therefore, conclude that the observed stereochemistry at C-1 is due to the conformational constraints induced by the cycloalkyl ring of the tryptamine.

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- General Procedure for the synthesis of tetrahydro- β -carboline hydrochlorides 3:** A suspension of the tryptamines hydrochloride **4** (1 mmol) and the corresponding 4-alkylidene-2-methyloxazolin-5-one (1.2 mmol) was refluxed under Ar atmosphere for 72 h. After this time the reaction mixture was allowed to reach room temperature and tetrahydro- β -carboline hydrochlorides isolated by filtration. Finally, the crude solid was purified by flash chromatography using dichloromethane/methanol (9:1) as eluent.
- The C-1 *trans* THBC was not detected in the reaction mother liquor after isolation of the *cis* products.
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