Pergamon

Tetrahedron Letters, Vol. 37, No. 32, pp. 5813-5816, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)01233-6

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

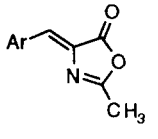
Jesús Ezquerra and Carlos Lamas*
Centro de Investigación Lilly, S. A. Paraje de la Cruz S/N, 28130 Valdeolmos, Madrid, Spain.

Alfredo Pastor, Pilar Alvarez and Juan José Vaquero
Departamento de Química Orgánica, Universidad de Alcalá, 28871 Alcalá de Henares, Madrid, Spain.

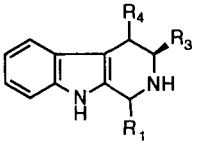
Will G. Prowse
Eli Lilly and Co. Ltd, Lilly Research Centre Ltd, Erl Wood Manor, Windlesham, Surrey, GU20 6PH, England.

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

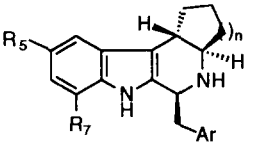
The Pictet-Spengler reaction (P-S) is a classical and straightforward method for the synthesis of tetrahydro-β-carbolines (THBC's).[1,9] Traditionally this reaction has been performed by condensation of tryptamines with carbonyl compounds such as aldehydes and reactive ketones. Other electrophilic reagents like α-ketoacids[2] or enamines[3] have been used successfully, broadening the scope of the reaction. Recently, Audia and co-workers[4] have shown that azalactones (**1**, Figure 1) are "arylacetaldehyde equivalents", undergoing P-S condensation with tryptamine under hydrolytic conditions.



1



2a R_1=β-Ph, R_3= CO_2R, R_4= H
2b R_1=α-Ph, R_3= CO_2R, R_4= H
2c R_1=α-(Alkyl, Aryl), R_3= CO_2R, R_4= β-CH_3



3
n=1, 2,3

Figure 1

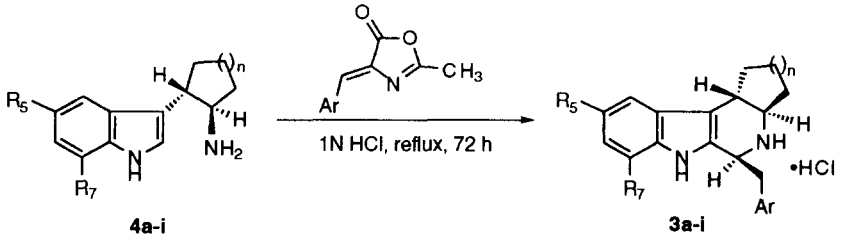
Stereoselective P-S reactions have been achieved using chiral substrates such as aldehydes,[5] iminium salts[6] or acetylenic sulfoxides.[7] Alternatively, the P-S reaction between (L)-tryptophan esters and aldehydes can be controlled under kinetic conditions[8] to give the desired relative and absolute stereochemistry, and this methodology has been applied to the synthesis of a wide variety of natural products.[9] For example, the *cis* relationship between R_1 and R_3 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)indoles[11] 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 Ac_2O, 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 salts[13] (Table 1).

Table 1



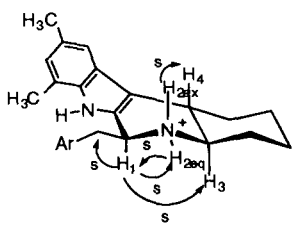
4a-i **3a-i**

Entry	Compound	n	R_5	R_7	Ar	Yield (%)
1	**3a**	1	CH_3	H	3,4-di-$CH_3OC_6H_3$	88
2	**3b**	2	CH_3	H	3,4-di-$CH_3OC_6H_3$	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-$CH_3OC_6H_3$	30
6	**3f**	2	CH_3	CH_3	3,4-di-$CH_3OC_6H_3$	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-$CH_3OC_6H_3$	40

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

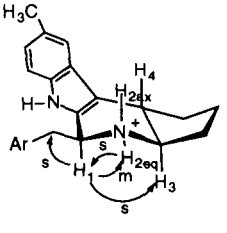
The THBC's were isolated as single diastereoisomers[14] and the relative stereochemistry at the C-1 centre determined using NMR methods. Full ^1H and ^{13}C assignments were obtained using DQF-COSY and HMQC experiments. The large (*c.* 10Hz) H-1 to NH-2_{ax} and H-3 to NH-2_{ax} couplings provides indirect 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* tryptamine[15] in a P-S reaction with the

azalactone **1** (Ar= 3,4-di-$CH_3OC_6H_3$) 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.



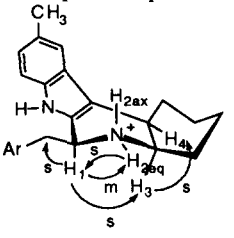
3f

δH_1=4.82 ppm, δH_3=2.95 ppm
δH_4=3.15 ppm, δH_{2eq}=8.78 ppm
δH_{2ax}=9.81 ppm



3a

δH_1=4.86 ppm, δH_3=3.00 ppm
δH_4=3.30 ppm, δH_{2eq}=9.26 ppm
δH_{2ax}=10.09 ppm



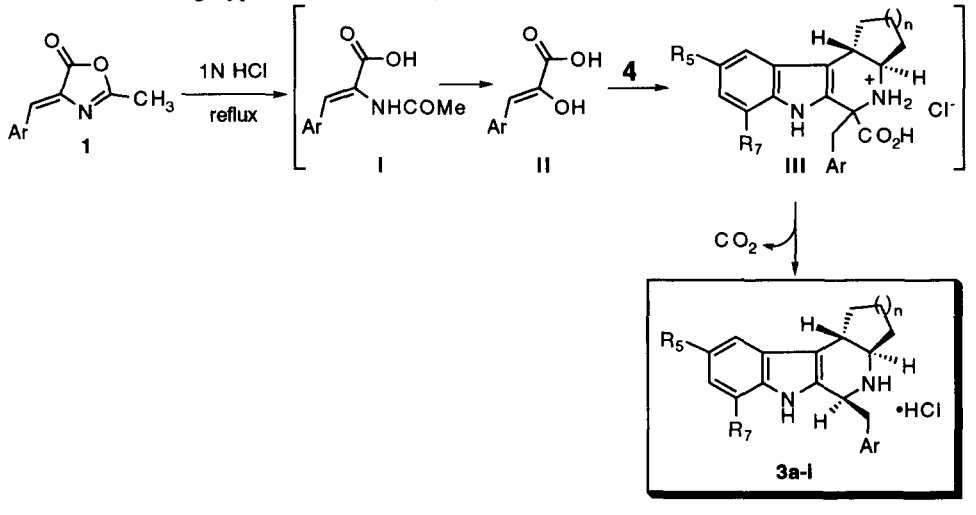
5

δH_1=4.93 ppm, δH_3=3.62 ppm
δH_4=3.05 ppm, δH_{2eq}=8.95 ppm
δH_{2ax}=8.82 ppm

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* fussion. In this case the all-*cis* substitution is also the lowest energy conformation, as the 1α-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.

Acknowledgements: This research was supported by the Spanish **FARMA III** programme (Ministerio de Industria y Ministerio de Sanidad). A. P. and P. A. are grateful to Lilly, S. A. for a fellowship. We are also grateful to Dr. James A. Audia (Lilly Research Laboratories, Indianapolis, IN) for helpful discussions and access to unpublished results.

References and Notes

1. Whaley, W. M.; Govindachari, T. R. *Org. React* **1951**, *6*, 151 and references cited therein.
2. Hudlicky, T.; Kutcham, T. M.; Shen, G.; Sutliff, V. E.; Coscia, C. J. *J. Org. Chem.* **1981**, *46*, 1738-1741.
3. Vohra, R.; MacLean, D. B. *Tetrahedron Lett.* **1993**, *34*, 7673-7676.
4. Audia, J. A.; Droste, J. J.; Nissen, J. S.; Murdoch, G. R.; Evard, D. A. *J. Org. Chem.* **1996**, (In press)
5. Melnyk, P.; Ducrot, P.; Thal, C. *Tetrahedron Lett.* **1993**, *49*, 8589-8596.
6. (a) Reddy, M. S.; Cook, J. M. *Tetrahedron Lett.* **1994**, *35*, 5413-5416. (b) Waldmann, H.; Schmidt, G.; Jansen, M.; Geb, J. *Tetrahedron Lett.* **1993**, *37*, 5867-5870.
7. Lee, A. W. M.; Chan, W. H.; Tao, C. Y.; Lee, Y. K. *J. Chem. Soc. Perkin Trans 1*, **1994**, 477-481.
8. (a) Bailey, P. D.; Moore, M. H.; Morgan, K. M.; Smith, D. I.; Vermon, J. M. *Tetrahedron Lett.* **1994**, *35*, 3587-3588. (b) Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Morgan, K.; Palmer, S. J.; Prince, S. N.; Reynolds, C. D.; Wood, S. D. *J. Chem. Soc. Perkin Trans 1*, **1993**, 431-439. (c) Bailey, P. D.; McLay, N. R. *J. Chem. Soc. Perkin Trans 1*, **1993**, 441-449.
9. Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797-1842.
10. Behforouz, M.; West, S. J.; Chakrabarty, C.; Rusk, D. A.; Zarrinmayeh, H. *Heterocycles* **1992**, *34*, 483-495.
11. Ezquerra, J.; Pedregal, C.; Lamas, C.; Pastor, A.; Alvarez, P.; Vaquero, J. J. *Tetrahedron Lett.* **1996**, *37*, 683-686.
12. Plöchl, J.; *Ber*, **1883**, *16*, 2815-2825
13. **General Procedure for the synthesis of tetrahydro-β-carboline hydrochlorides 3**: A suspension of the tryptamines hydrochloride **4** (1 mmol) and the correponding 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.
14. The C-1 *trans* THBC was not detected in the reaction mother liquor after isolation of the *cis* products.
15. Ghosh, A.; Wang, W.; Freeman, J. P.; Althaus, J. S.; VonVolgtlander, P. F.; Scahill, T. A.; Mizsak, S. A.; Szmuszkovicz, J. *Tetrahedron* **1991**, *47*, 8653-8662.

(*Received in UK* 23 *May* 1996; *revised* 18 *June* 1996; *accepted* 21 *June* 1996)