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TETRAHEDRON: *ASYMMETRY*

Diastereoselective synthesis of some β-carboline derivatives from L-amino acids

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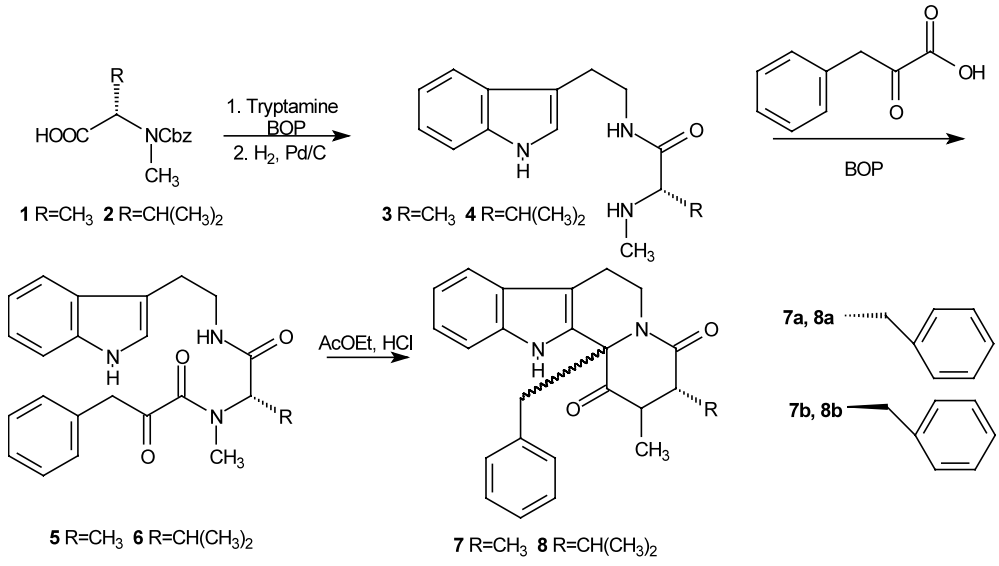
Abstract—L-Ala and L-Val were used as chiral inductors in a series of reactions in which a Pictet–Spengler cyclization, completed under mild conditions was the key step. Diketopiperazines **7a** and **8a** having *R* configuration at the newly created stereogenic center were obtained with good diastereoselectivity due to 1,4-chirality transfer. Surprisingly, L-Pro promoted the formation of the product with *S* configuration in the predominant diastereomers **9a** and **10a**. © 2002 Published by Elsevier Science Ltd.

1. Introduction

Alkaloids, especially those based on isoquinoline or indole systems, are among the most important groups of naturally occurring compounds as a result of their biological activity and possible pharmaceutical applications. Several approaches devoted specifically to the stereocontrolled transformations of such compounds have been developed[1] and have proved successful when compounds from the chiral pool were applied as starting materials.[2] Of the other possible starting materials, amino acids seemed to be of fundamental importance



Scheme 1.

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due to their versatility and widespread use in chemical synthesis. We would like to present herein our preliminary results on the stereoselective construction of indole derivatives using amino acids as chiral inductors. The idea for this work derives from a hypothesis, according to which the peptide chain has an influence on the stereochemistry in the biosynthesis of isoquinoline and indole alkaloids.[3]

2. Results and discussion

Recently, we have found that L-alanine, L-valine L-phenylalanine and L-proline could be used in the Pictet–Spengler condensation reaction for the diastereoselective construction of tetrahydroisoquinoline derivatives under mild conditions.[4] The work presented herein examines the possibility of using L-Ala, L-Pro and L-Val as chirality sources to allow the efficient and stereoselective construction of the β-carboline skeleton.

The first step, as shown in Scheme 1, involved preparation of the amides **3** and **4**,[5] respectively, from *N*-blocked-*N*-methyl-L-amino acids in the presence of BOP as a coupling mediator[6] and subsequent deblocking of the nitrogen atom under hydrogenolytic conditions. Further BOP-mediated coupling of amides **3**[7] and **4**[8] with phenylpyruvic acid gave ketoamides **5**[9] and **6**,[10] respectively, which were easily isolated from the reaction mixture. Initial attempts to apply the Pictet–Spengler-type condensation with methanolic hydrogen chloride solution resulted in low diastereoselectivities, probably due to unfavorable hydrogen bonding situations. We decided, therefore, to change the solvent for an aprotic one. Accordingly, we found that the best diastereoselectivity was obtained when ethyl acetate was applied as a solvent and the reaction was completed at room temperature.

The diastereomeric mixture of L-alanine derivatives **7a**[11] and **7b** had diastereomeric ratio (dr) of 91:9 while those derived from L-valine **8a**[12] and **8b** had dr of 93:7 (in both cases the dr was established on the basis of ^{1}H NMR of the crude reaction mixture). X-Ray analysis of the predominant diketopiperazine **8a**[13] confirmed our expectations of the stereochemistry at the C-1 stereogenic centre (Fig. 1).

Following our previous findings in the synthesis of isoquinolines,[4] we expected a better stereochemical outcome along with an opposite diastereomeric preference when L-proline was used as the chirality source. Indeed, we were able to obtain diketopiperazine **9**[16] as a result of the Pictet–Spengler condensation performed under mild conditions (HCl in ethyl acetate at room temperature). Unfortunately, despite exhaustive efforts, we were unable to obtain a single crystal of **9a** suitable for X-ray crystallographic analysis. In the search for another derivative, potentially more prone to form crystals suit-

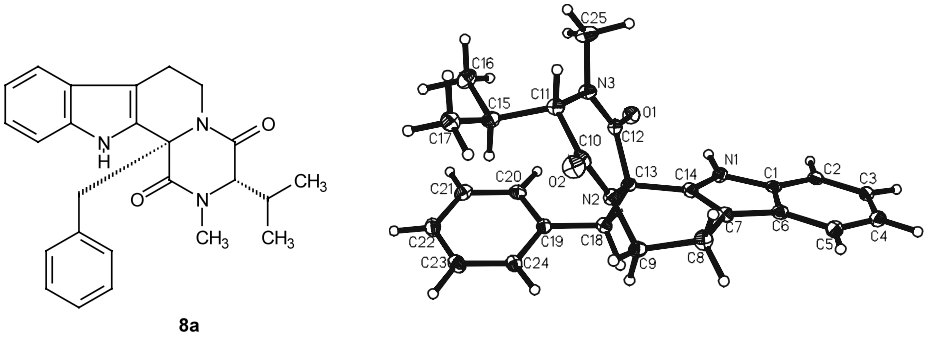

Figure 1. The structure and ORTEP diagram for compound **8a**.

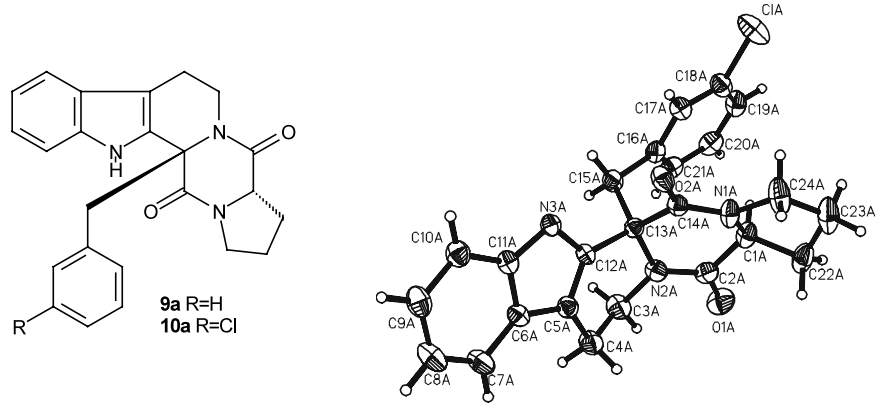

Figure 2. The structure and ORTEP diagram for compound **10a**.

able for X-ray diffraction analysis, we decided to apply *m*-chlorophenylpyruvic acid as a starting material. The required diketopiperazine **10a**[17] was finally obtained with dr of 99:1. Subsequent X-ray analysis[18] did indeed reveal that the C-1 stereogenic centre had *S* configuration (Fig. 2).

Interestingly, it therefore seems that the stereochemical outcome of the Pictet–Spengler reaction is directly dependent on the structure of the L-amino acid used. Moreover, the results presented are relatively uncommon examples of constructing the β-carboline skeleton with the Pictet–Spengler condensation from tryptamine under the 1,4-chiral influence of amino acids. In summary, the satisfactory chemical yields together with the high stereoselectivity of the method presented suggest that this approach might be an attractive starting point for the synthesis of indole alkaloids.

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5. All new compounds described here presented spectroscopic and elemental analysis to confirm their structures. Selected details are provided below.
6. Castro's reagent: Benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexaflurophosphate, see: Castro, B.; Evin, G.; Selve, C.; Seyer, R. *Tetrahedron Lett.* **1975**, 1219–1222.
7. Selected data for **3**: $[\alpha]_D^{23}$ −4.2 (*c* 1.0, $CHCl_3$), ^1H NMR ($CDCl_3$, 500 MHz) δ: 8.36 (1H, s, disappearing with D_2O), 7.7–7.0 (5H, m), 7.31–7.24 (1H, br.m, disappearing with D_2O), 3.7–3.52 (2H, br.m), 3.06–2.92 (2H, br.m), 3.06–2.92 (1H, br.m), 2.27 (1H, s), 1.44–1.28 (1H, br.s), 1.25–1.23 (3H, d, $J=7.0$ Hz); ^{13}C NMR ($CDCl_3$, 125 MHz): 174.8, 136.3, 127.3, 122.0, 121.9, 119.3, 118.7, 113.0, 111.2, 60.4, 39.14, 3.11, 25.4, 19.6.
8. Specific rotation for **4**: $[\alpha]_D^{23}$ −19.2 (*c* 1.0, $CHCl_3$).
9. Specific rotation for **5**: $[\alpha]_D^{23}$ −77.2 (*c* 1.0, $CHCl_3$).
10. Specific rotation for **6**: $[\alpha]_D^{23}$ −52.3 (*c* 1.0, $CHCl_3$).
11. Specific rotation for **7a**: $[\alpha]_D^{23}$ −24.6 (*c* 1.0, $CHCl_3$).
12. Selected data for **8a**: mp 220–227°C, $[\alpha]_D^{23}$ −53.2 (*c* 1.0, $CHCl_3$), ^1H NMR ($CDCl_3$, 500 MHz) δ: 9.27 (1H, s), 7.50–7.05 (9H, m), 4.95–4.85 (1H, dd, $J_1=13.0$ Hz, $J_2=5.0$ Hz), 3.81 and 3.85 (2H, ABq, $J=14.5$ Hz), 3.47, 3.25, 3.03, 2.73 (4H, m, -CH_2-CH_2-), 2.93 (3H, s), 1.16–1.02 (1H, m), 0.52–0.48 (3H, d, $J=6.5$ Hz), 0.82–0.78 (3H, d, $J=7.0$ Hz), ^{13}C NMR ($CDCl_3$, 125 MHz): 166.6, 165.3, 136.0, 135.3, 132.7, 130.6, 130.3, 128.8, 128.6, 126.5, 122.5, 119.8, 119.5, 118.6, 111.5, 109.5, 68.2, 68.2, 66.0, 45.5, 45.4, 36.0, 33.3, 20.6, 18.3.
13. All measurements for **8a** crystal were done at $T=100$ K on Kuma KM4CCD κ-axis diffractometer using graphite-monochromated Mo-Kα radiation ($\lambda=0.71073$ Å). 1204 frames were collected. The data were corrected for Lorentz and polarization effects. No absorption correction was applied. Data reduction and analysis were carried out with the Kuma Diffraction (Wrocław) programs. The structure was solved by direct methods[14] and refined using SHELXL.[15] The $F_o^2>2s(F_o^2)$ criterion was used only for calculating *R* factors and is not relevant to the choice of reflections for the refinement. $C_{25}H_{27}N_3O_2$, M=401.50, monoclinic space group $P2_1$; $a=14.083(3)$, $b=11.102(2)$, $c=14.415(3)$ Å, $\beta=113.75(3)°$, $V=2063.0(7)$ Å^3, $Z=4$ and $D_x=1.293$ Mg/m^3. Colorless crystal, μ(Mo-Kα)=0.083 mm^{-1}, $F(000)=856$, 5377 reflections collected. Least squares on F^2 (all reflections), $R=0.0514$, $wR_2=0.0757$ (observed).
14. Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467–473.
15. Sheldrick, G. M. SHELXL-93. Program for the Refinement of Crystal Structures, Univ. of Göttingen, Germany.
16. Specific rotation for **9a**: $[\alpha]_D^{23}$ +68.6 (*c* 1.0, $CHCl_3$).
17. Selected data for **10a**: mp 205–208°C, $[\alpha]_D^{23}$ +61.4 (*c* 1.0, $CHCl_3$).
18. X-Ray intensity data for **10a** were measured at $T=293$ K on a Kuma KM4 κ-axis diffractometer with Mo-Kα radiation ($\lambda=0.71073$ Å). 6278 unique reflections collected. The data were corrected for Lorentz and polarization effects. No absorption corrections were applied. The structures were solved by direct methods from SHELS[14] and refined using SHELXL software.[15] Crystal data for compound **10a**: $C_{24}H_{22}ClN_3O_2$, M=419.90, monoclinic space group $P2_1$; $a=9.0880(18)$, $b=14.099(3)$, $c=16.127(3)$ Å, $\beta=92.20(3)°$, $V=2064.9(7)$ Å^3, $Z=4$ and $D_x=1.347$ Mg/m^3. Colorless crystal, μ(Mo-Kα)=0.211 mm^{-1}, $F(000)=876$. Least squares on F^2 (all reflections), $R=0.0436$, $wR_2=0.1222$ (observed).