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The structure of some *trans*-diketopiperazine derivatives of isoquinoline and β-carboline

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Abstract—The study on the absolute stereochemistry of *trans*-diketopiperazine **3a** was performed by a crystallographic method. This result supports our previous assignments concerning the diverse chiral induction in the Pictet–Spengler condensation from L-amino acids.

1. Introduction

As a part of our programme to stereoselectively create pharmacologically relevant heterocyclic systems from the chiral pool,[1] we recently proposed a new method that took advantage of the mild Pictet–Spengler reaction on suitably designed L-amino acid derivatives.[2] The final 2,5-diketopiperazine (DKP) based 1,2,3,4-tetrahydroisoquinolines and 1,2,3,4-tetrahydro-β-carbolines were formed with high diastereoselectivity. Interestingly, acyclic proteinogenic amino acids (L-Ala, L-Phe and L-Val) promoted the creation of *cis*-configured diketopiperazines such as **1a**, whereas L-Pro gave predominantly the *trans* derivatives such as **2a** (Fig. 1).

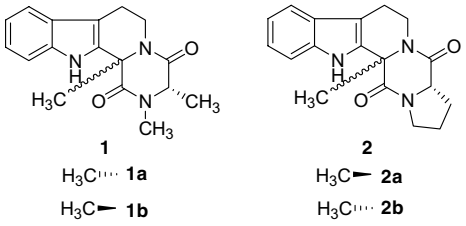

Figure 1. The chemical structures of **1a**, **1b**, **2a** and **2b**.

Such diastereodivergent-type behaviour is synthetically important since it allows the optional creation of an (*R*)- or (*S*)-configuration at the C-1 stereogenic centre in isoquinoline or β-carboline skeletons. This in turn is crucial to their bioactivity.[3]

The *cis*-fused diketopiperazines are thermodynamically more stable and constitute a predominant class of naturally occurring products,[4] which seems logical considering their biosynthetic origin, usually from two proteinogenic L-α-amino acids. However, there are only a few reports on trans-configured diketopiperazines derived from natural sources, such as metabolites isolated from the fungi *Aspergillus chevalieri*.[5] Interestingly, these are based mainly on D-proline skeleton.[6] Recently, Davies et al. demonstrated that they were in fact products of the non-enzymatic epimerization of the parent L-Pro-DKPs.[4] Indeed, there are strong literature indications that *cyclo*-L-Pro-L-XXX derivatives are extremely prone to the selective base-catalyzed epimerization resulting in the formation of *cyclo*-D-Pro-L-XXX systems.[7] The above findings are of particular importance in connection with our previous reports.[2] Even though the stereochemistries of the key intermediates and the final products were determined with the aid of X-ray crystallography, the assignments were done on the relative basis assuming the configurational stability of the parent amino acid fragment. Therefore, our claim for the unusual preference of L-Pro to create the *trans*-DKP framework obviously needed confirmation.

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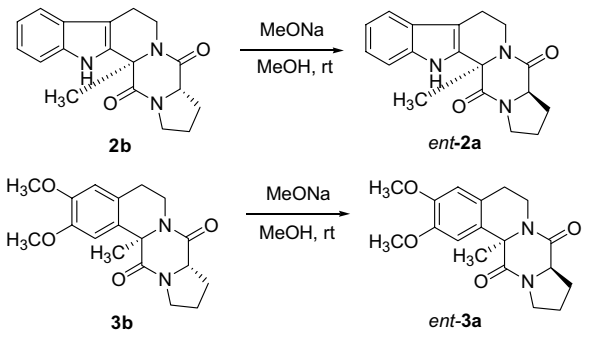
2. Results and discussion

Initially, we performed the ab initio Hartree–Fock calculations with the standard 6-31G** basis set for two representative pairs of diastereomers: L-alanine derivatives **1a** and **1b** together with the β-carbolines derived from L-proline: **2a** and **2b**. We assumed that the mode of asymmetric induction was influenced by energetic factors, which, as a consequence, might affect the stability of the final compounds. The calculations indicated molecules **1a** and **2a** as thermodynamically more stable isomers (Fig. 1).[8] The same preference was found in the quantum chemical calculations performed on analogous diastereomeric pairs in the isoquinoline series.[2a] However, we soon ruled out the possibility of equilibration of the final diastereomeric mixture. We found that the Pictet–Spengler reaction was irreversible in our case and neither of the pure diastereomers could have been epimerized under acidic (even harsh) conditions.[2] This therefore means that the thermodynamic preference refers to the transition states of the Picted–Spengler cyclization, which are probably 'product-like'.[2] Very recently however, we noticed that bases had a profound effect on selected final diketopiperazines. Thus, treatment of compounds **2b** and **3b** with traces of sodium methoxide in methanol at room temperature brought about fast epimerization to compounds identical with all spectral properties with the previously described trans-DKP isomers, except for the specific rotation values[9,10] (Scheme 1).



Scheme 1.

The final proof for the absolute stereochemistry came from the X-ray analysis that included the anomalous scattering data performed for the previously reported[2b] diketopiperazine derivative **3a** (Fig. 2).[11]

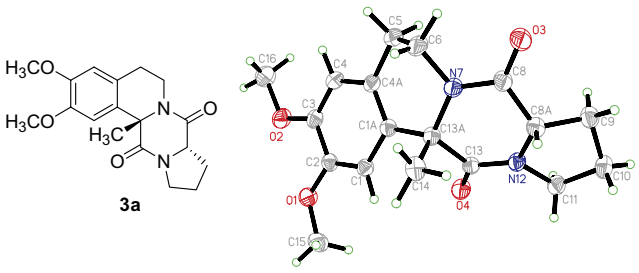


Figure 2. The absolute stereochemistry and the ORTEP diagram for compound **3a**.

3. Conclusion

All the above results suggest that the previous configuration assignments[2] in the 'proline' series were all correct and we can therefore regard the therein presented approach as 'diastereodivergent-like', because one can control its stereochemical outcome by varying the structure of the starting L-amino acid used as a chirality source.

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8. The calculated total energies for compounds **1a** and **1b**: −967.9791414 e.u. and −967.9773287 e.u., respectively ($\Delta E = -1.14$ kcal/mol); total energies for compounds **2a** and **2b**: −1005.8547056 e.u. and −1005.8504770 e.u., respectively ($\Delta E = -2.65$ kcal/mol)].
9. Compound *ent*-**2a**: colourless oil, $[\alpha]_D^{23} = -132.5$ (*c* 0.33, $CHCl_3$), compound **2a**: colourless oil, $[\alpha]_D^{23} = +147.2$ (*c* 0.97, $CHCl_3$).[2b]
10. Compound *ent*-**3a**: colourless oil, $[\alpha]_D^{23} = -130.3$ (*c* 0.99, $CHCl_3$), compound **3a**: oil, $[\alpha]_D^{23} = +106.9$ (*c* 1.06, $CHCl_3$),[2b] after rigorous purification: colourless oil, $[\alpha]_D^{23} = +124.5$ (*c* 1.03, $CHCl_3$).
11. Selected data for compound **3a**: mp 120–130 °C, all measurements for crystal were done at $T = 293$ K on Enraf Nonius Turbo CAD4 diffractometer using graphite-monochromated Cu Kα radiation ($\lambda = 1.54184$ Å). Friedel opposites were collected. The structure was solved by direct methods[12] and refined using SHELXL.[13] $C_{18}H_{22}N_2O_4$, $M = 330.38$, orthorhombic space group $P2_12_12_1$; $a = 7.6576(10)$, $b = 10.2670(8)$, $c = 21.345(2)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1678.2(3)$ Å^3, $Z = 4$ and $D_x = 1.308$ mg/m^3. Colourless crystal, $F(000) = 704$, 3906 reflections collected, 3364 independent ($R_{int} = 0.0192$), 2826 with $I > 2\sigma(I)$, $R = 0.0386$, $wR2 = 0.1024$ (observed). The absolute structure was verified basing on the Flack[14] parameter calcula-

tion. The value of 0.1(2)—close to zero—confirmed the correctness of the structure. CCDC 268807 contains the supplementary crystallographic data. These data can be obtained free of charge at www.ccdc.cam.ac.uk/const/retrieving.html [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].

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