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Diastereoselective Synthesis of 1-Benzyltetrahydroisoquinoline Derivatives from Amino Acids via 1,4 Chirality Transfer. Part 1

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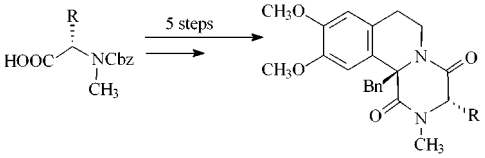
ABSTRACT



L-(−)-Phenylalanine, L-(+)-valine, and L-(−)-proline were used in the diastereoselective synthesis of benzyltetrahydroisoquinoline derivatives.

The search for methods for the asymmetric synthesis of chiral compounds has been an area of intense study over the past two decades.[1] The need for the preparation of chiral compounds in enantiomerically pure form has increased lately as a result of several factors, mainly connected with a stereodiscrimination of chiral compounds by most biological systems and therefore the pressure on the pharmaceutical industry to develop nonracemic drugs. Tetrahydroisoquinolines still attract considerable interest in the modern chemistry of biologically active compounds, and consequently several new effective approaches for their stereocontrolled synthesis have recently been developed.[2] Special attention has been devoted to the asymmetric synthesis using enantiospecific processes proceeding from the chiral pool to gain access to this broad class of compounds.[3] Of all the members of chiral pool, amino acids, because of their versatility, have been the most extensively used for the synthesis of chiral, enantiomerically pure heterocycles.[4]

In the case of biosynthesis of alkaloidal systems, the schemes for their bioformation have often included amino acids as primary precursors. In this report we wish to describe our preliminary results in the use of amino acids in diastereoselective synthesis of isoquinoline derivatives, being precursors of so-called mammalian alkaloids, compounds of considerable importance in modern neurochemistry.[5]

The basis of this work derives from that of Lawton,[6] where the interaction and participation of reactive groups along a peptide chain in the biosynthesis of indole and isoquinoline

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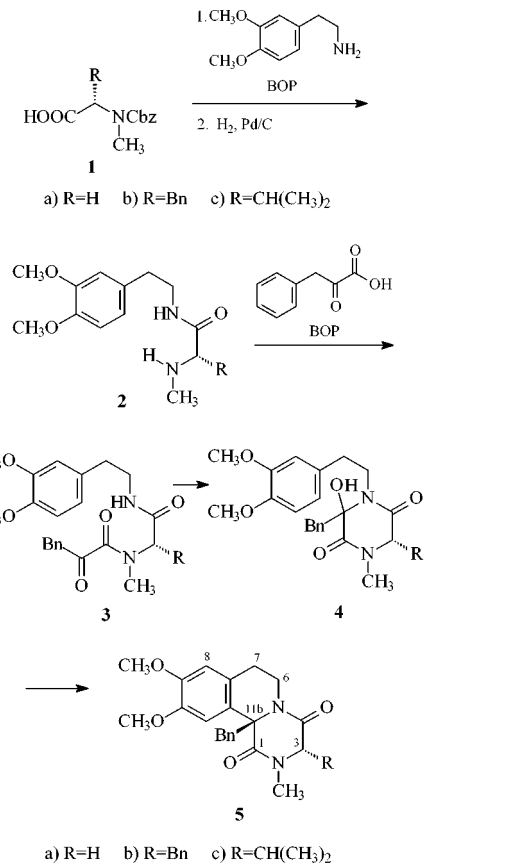
alkaloids was postulated. Also, recently presented efficient chirality transfer[7] with the use of 2,5-diketopiperazine units stimulated our attempts considerably.

Thus, reinvestigating an earlier "achiral" approach[6] we found that amide **2a** (Scheme 1) can be efficiently prepared

Scheme 1



from 2-(3,4-dimethoxylphenyl)ethylamine when blocked sarcosine **1a** was used as a starting compound in a BOP-mediated coupling.[8]

Treatment of **2a** with 1 equiv of 2-oxo-3-phenylpropanoic acid in the presence of BOP reagent[8] gave directly hydroxylactam derivative **4a**[9] in 70% yield. Despite prolonged efforts we were unable to isolate a ketoamide **3a** in this sequence.

Compound **4a** undergoes a facile Pictet−Spengler-type condensation with methanolic hydrogen chloride, affording a diketopiperazine derivative **5a** almost quantitatively. In the chemistry of isoquinolines such an easy cyclization of nonphenolic derivatives is quite rare, thus providing further evidence for significant influence of the peptidelike moiety in this process.[10]

The above-mentioned preliminary results prompted us to investigate the possibility of stereocontrolled Pictet−Spengler-type condensation and chiral induction at C-11b in the formation of compound **5b**. Thus, the same reaction sequence was performed using protected *N*-methyl-L-phenylalanine **1b**.[11] Condensation with 2-(3,4-dimethoxylphenyl)ethylamine and subsequent deblocking of nitrogen atom under hydrogenation conditions afforded amide **2b** in 87% yield. The HPLC analysis of **2b** on chiral columns revealed that no detectable racemization could be observed.[12] Treatment of the amide **2b** with phenylpyruvic acid in the presence of BOP reagent[9] gave ketoamide **3b**, which is in contrast to the earlier findings for sarcosine. Despite these differences, we finally found that compound **3b** underwent efficient stereocontrolled Pictet−Spengler-type condensation with methanolic hydrogen chloride solution, giving two diastereoisomers of **5b** in 92% chemical yield.[9]

Their ratio of 89:11 was established on the basis of ^{1}H NMR of the crude reaction mixture.

Configuration assignment at C-11b in diastereomers **5b** was based upon analysis of substituent interactions at C-3, C-1″, and C-1′ carbon atoms seen in their ^{13}C NMR spectra. Chemical shifts[9] of 64.27, 41.06, and 37.58 ppm were assigned to the respective carbon atoms in (3*S*,11b*S*)-**5b** and 61.49, 36.93, and 36.51 ppm in (3*S*,11b*R*)-**5b**. In our opinion steric interactions between benzylic methylene groups in (3*S*,11b*S*)-**5b** were responsible for observed shielding effects. These considerations were further confirmed by an X-ray study.

Even better results were obtained when L-(+)-valine was used as a chiral inductor. Amide **2c**[13] could be isolated in 85% yield with no observable racemization.[12] Subsequent coupling with phenylpyruvic acid and Pictet−Spengler cyclization afforded final derivative **5c**[14] in 89% chemical yield as a sole diastereomer. In the analogous series starting from L-(−)-proline the amide **2d**[15] was formed in 78% yield. The final diketopiperazines (3*S*,11b*S*)-**5d**[16] (Figure 1) and (3*S*,11b*R*)-**5d** were formed in a 92:8 ratio, respectively.[17]

A single crystal of (3*S*,11b*S*)-**5d** was subjected to X-ray analysis, which indicated the (*S*) configuration at C-11b

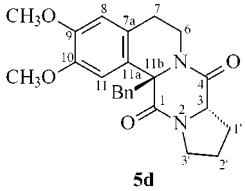


Figure 1. Structure of (3*S*,11b*S*)-**5d**.

(7) (a) Iyer, M. S.; Gigstad, K. M.; Namdev, N. D.; Lipton, M. *Amino Acids* **1996**, *11*, 259−268. (b) Le, T. X.; Bussolari, J. C.; Gauthier, D. et al. *Abstracts of Papers, Part 2*, 212th National Meeting of the American Chemical Society, Orlando, FL, Aug 25−29, 1996; American Chemical Society; Washington, DC, 1996; ORGN 414.

(8) Castro's reagent, benzotriazol-1-yl-oxy-tris(dimethylamino)phosphoniumhexafluorophosphate, see: Castro, B.; Evin G.; Selve, C.; Seyer, R. *Tetrahedron Lett.* **1975**, 1219.

(9) All new compounds described in the present paper gave spectroscopic data and elemental analyses completely in accord with their assigned structures. Details will be provided in a subsequent full paper.

(10) The presence of a *N*-acyliminium intermediate has been postulated in similar reactions: Wang, H. S.; Ganesan, A. *Org. Lett*. **1999**, *1*, 1647−1649.

(11) Coggins, J. R.; Benoiton, N. L. *Can. J. Chem*. **1971**, *49*, 1968−1971.

(12) (*S*):(*R*) = 99.5:0.5 on ChiraDex column (Merck).

carbon atom (Figure 2).[18] The same chirality sense can be found in a majority of naturally occurring isoquinolines, including benzyl derivatives and related compounds.[19]

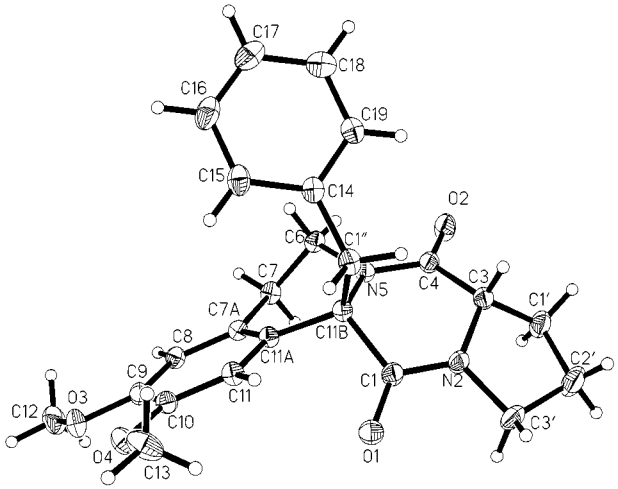


Figure 2. ORTEP diagram for compound (3*S*,11b*S*)-**5d**.

It appears, therefore, that the above-described approach allows the construction of tetrahydroisoquinolines in acceptable chemical yields and good stereoselectivity, thus creating an interesting alternative to the existing procedures.

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(13) Selected data for **2c**:[9] mp 52−54 °C, $[\alpha]^{23}_D$ +25.3 (*c* 1.0, $CHCl_3$).
(14) Selected data for **5c**:[9] $[\alpha]^{23}_D$ +64.5 (*c* 1.0, $CHCl_3$).
(15) Selected data for **2d**:[9] mp 65−66 °C, $[\alpha]^{23}_D$ −24.4 (*c* 1.0, $CHCl_3$).
(16) Selected data for (3*S*,11b*S*)-**5d**:[9] mp 117−120 °C, $[\alpha]^{23}_D$ +215.6 (*c* 1.0, $CHCl_3$).
(17) The ratio of approximately 92:8 was established on the basis of ^{1}H NMR and GC−MS techniques.
(18) X-ray data for (3*S*,11b*S*)-**5d**: $C_{24}H_{26}N_2O_4 \cdot H_2O$, M_r = 424.48, monoclinic $P2_1$, a = 9.858(2), b = 8.0360(16), c = 13.969(3) Å, β = 98.79(3)°, V = 1093.6(4) Å^3, Z = 2, ρ_x = 1.289 g·cm^{-3}, $F(000)$ = 452, μ(Mo Kα) = 0.091 mm^{-1}, T = 293 K. Data collection: Kuma KM4 κ-axis diffractometer, λ(Mo Kα) = 0.71073 Å, colorless crystal 0.7 × 0.5 × 0.25 mm^3, unit cell parameters by least squares for 25 reflections with 18.4 $<2\theta<$20.8°. Structure solution and refinement: direct methods (SHELXS97[a]), least squares on F^2 (SHELXL97[b]). Strong hydrogen bonds between water molecule and carbonyl oxygen atoms of molecules related by translation along *a*-direction. (a) Sheldrick G. M. *Acta Crystallogr.* **1990**, *A46*, 467−473. (b) Sheldrick G. M. *SHELXL-97 Program for X-ray Structure Refinement*; University of Göttingen: Germany, 1997.
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