(*R*)-1-Phenylethylamine as chiral auxiliary in the diastereoselective synthesis of tetrahydro-β-carboline derivatives

Aleksandra Siwicka, Krystyna Wojtasiewicz, Andrzej Leniewski, Jan K. Maurin, Anna Zawadzka, and Zbigniew Czarnocki

Abstract: Modified sodium borohydrides were used in the reduction of the imine moiety in compounds containing the (*R*)-1-arylethylamine motif as a chiral auxiliary. Diastereomeric products were formed with moderate to good stereoselectivity and were effectively separated by column chromatography.

Key words: asymmetric synthesis, indole alkaloids, hydrogen bond.

Résumé : On a utilisé des borohydrures de sodium modifiés pour effectuer la réduction de la portion imine de composés contenant un motif (*R*)-aryléthylamine comme auxiliaire chiral. Il y a formation de produits diastéréomères avec des stéréosélectivités allant de modérées à bonnes et il est possible de les séparer d'une façon efficace par chromatographie sur colonne.

Mots-clés : synthèse asymétrique, alcaloïdes de l'indole, liaison hydrogène.

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Introduction

Both enantiomers of 1-phenylethylamine (α-methylbenzylamine, α-PEA **3**) remain as attractive chirality sources in various asymmetric transformations. Their use as resolving agents, chiral ligands in catalytic processes, and synthetic chiral auxiliaries in stereodifferentiating reactions of prochiral substrates have been the subject of in-depth reviews (1, 2).

More recently, an interesting example of the use of α-PEA **3** in an asymmetric Strecker reaction leading to enantiomerically enriched 1-amino-*cis*-3-azabicyclo[4.4.0]decan-2,4-diones has been reported (3). In this process, which is called a second-generation asymmetric synthesis, trimethylsilyl cyanide was the reagent allowing a stereoselective cyanide-ion addition to the prochiral precursor derived from α-PEA and cyclohexanone derivative. In another application, **3** was used as the chiral auxiliary in the preparation of enantiopure conformationally constrained Gly-(*s-cis*)-Pro Turn Mimetic (4). The reaction of the prochiral imine moiety in α-PEA derivatives gave an access to a variety of chiral, nonracemic aliphatic amines (5). Conveniently, these processes can be performed as one-pot procedures. The use of α-PEA, even in the industrial scale, was proven possible, as illustrated by the development and the scale-up of the endothelin antagonists synthesis (6). The process involves the preparation of a racemic intermediate followed by an efficient dynamic resolution with a chiral amine.

In the field of the stereoselective synthesis of pharmacologically relevant compounds, we presented recently the application of α-PEA in the preparation of enantiomerically pure lortalamine analogues (7) and (*R*)-(–)-mianserin (8) compounds that are well-known antidepressants. The Bischler–Napieralski cyclization followed by diastereoselective reduction of the imine bond were the key steps in the enantiodivergent synthesis of both enantiomers of *N*-acetylcalycotomine (9) that was carried out in our laboratory (10). Encouraged by the positive results of using α-PEA in the stereoselective formation of isoquinoline alkaloids, we decided to extend this procedure to tetrahydro-β-carboline analogues.

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A. Siwicka, K. Wojtasiewicz, A. Leniewski, A. Zawadzka, and Z. Czarnocki.[1] Faculty of Chemistry, Warsaw University, Pasteura 1, 02-093 Warsaw, Poland.
J.K. Maurin. National Institute of Public Health, Chełmska 30/34, 00-750 Warsaw, Poland; Institute of Atomic Energy, 05-400 Otwock-Świerk, Poland.

[1]Corresponding author (email: czarnoz@chem.uw.edu.pl)

Results and discussion

The synthetic sequence started with the reaction of tryptamine **1** with diethyl oxalate followed by the treatment with (*R*)-1-phenylethylamine to afford the diamide **5** almost quantitatively (Scheme 1).

After careful optimization, we found that the subsequent Bischler–Napieralski cyclization gave best results when performed in refluxing dichloromethane with $POCl_3$.

Since all attempts to isolate and characterize the resulting imine **7** were unsuccessful because of its instability as a free base, we decided to subject its hydrochloride salt to a metal hydride reduction. Thus, upon treatment with sodium borohydride in EtOH, a pair of diastereomeric amines **9a** and **9b** was formed in 62:38 ratio, respectively, based upon

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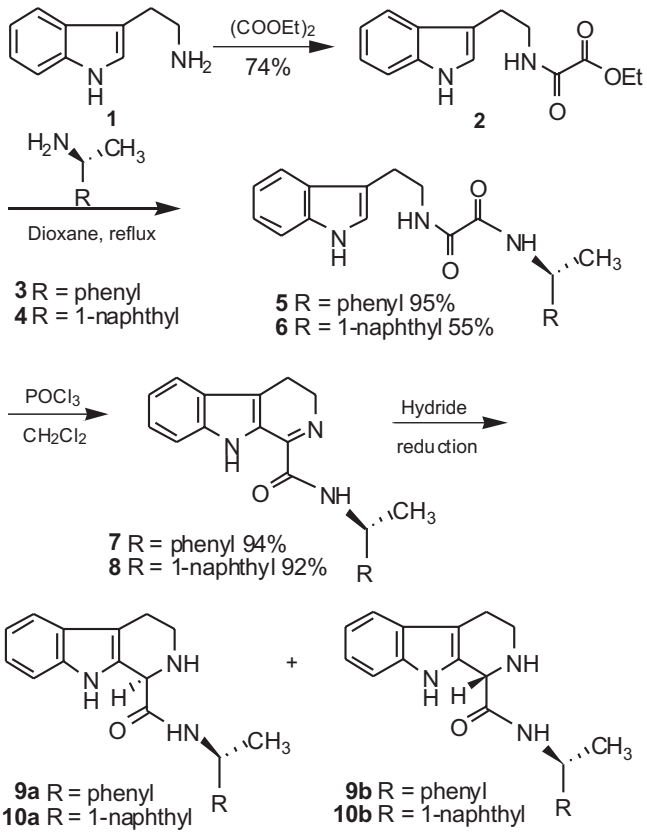
Table 1. Diastereomeric output for the reduction of **7** with various borohydrides.

Entry	Reducing reagent	Yield of **9**[a]	Ratio of **9a**:**9b**[b]
1	$NaBH_4$	81	62:38
2	$NaBH(CH_3COO)_3$	88	75:25
3	$NaBH[(CH_3)_2CHCOO]_3$	84	66:34
4	$NaBH[(CH_3)_3CCOO]_3$	89	78:22

[a]Isolated yield (%) of both **9a** and **9b**.
[b]Estimated from ^{1}H NMR on the crude reaction mixture.

Scheme 1. Reaction sequence leading to diastereoselective synthesis of tetrahydro-β-carboline derivatives (**9a**, **9b**, **10a**, and **10b**).



^{1}H NMR spectrum of the crude reaction mixture. The ratio of **9a** and **9b** was not affected neither by a prolonged contact with strongly basic solution of the reducing agent nor by solvent variations; these observations ruled out the possibility of an asymmetric transformation caused by a base-catalyzed epimerization at C-1 atom.

Therefore, it seemed reasonable to assume that both diastereomers **9a** and **9b** were formed in unequal amounts because of the chiral induction during a kinetically governed hydride approach to the substrate **7**. The prochiral imine moiety can be regarded as a planar structure resembling a carbonyl group, and the reduction process can be rationalized using the Cram or Felkin stereochemical models (11). Accordingly, the increase of steric demands in the nucleophile and (or) the imine molecules might have a positive effect on the chirality transfer.

Since it is well-known that sodium borohydride, modified with controlled amounts of simple carboxylic acids, forms reducing agents of enhanced selectivity (12), we applied such combined reagents to C=N bond reduction in **7**. Disappointingly, the diastereoselectivity was not improved significantly when hydrides such as $NaBH(AcO)_3$, $NaBH(i\text{-}PrCOO)_3$, and $NaBH(t\text{-}BuCOO)_3$ were applied.

Fortunately, the mixture of isomers could be effectively separated by column chromatography, affording pure and stable compounds **9a** and **9b**. The configuration at C-1 stereogenic centre in compound **9a** was assigned as (*R*) by the chemical transformation of **9a** into (*1R*)-1-(hydroxymethyl)-2-acetyl-1,2,3,4-tetrahydro-β-carboline of known absolute configuration by the method developed earlier in our laboratory (13). Full details for this procedure will be published in due course.

Seeking further improvement in the stereoselectivity, we decided to apply the same synthetic sequence using (*R*)-(+)-1-(1-naphthyl)ethylamine (**4**), another well-known and effective chiral inductor (7), as a chiral auxiliary. Thus, compound **8** was prepared in a good yield from tryptamine **1** and was consecutively subjected to a series of reactions affording easily separable diastereomers **10a** and **10b**. The results were summarized in Tables 1 and 2.

In contrast to previous results, the increase of steric parameters neither in the reducing agent molecule nor in the imine-containing target derivative **8** did not give a significant improvement of the stereochemical outcome. In a search for a feasible explanation of the previous observations, we investigated the problem using quantum chemical methods. Despite considerable efforts, it was impossible to obtain good quality monocrystals of imine **7**, and therefore we performed a molecular modelling to find its optimal geometry. The procedure consisted of consecutive molecular- mechanic search through a conformational space and ab initio calculations used for conformers to optimize their geometries and to find the corresponding energies (14).[2] The two low-energy conformers **7a** and **7b** are shown in Fig. 1, where **7a** has the lowest total electron energy. Noticeably, in both conformers **7a** and **7b**, a strong hydrogen bond between the amide carbonyl group and the indole NH define the shape of the reacting part of the molecule. As a consequence, the chiral fragment derived from the 1-phenylethylamine was di-

[2]We used a Spartan'04 for Windows software for both tasks; a conformational search using MMFF94 force field and a Monte Carlo algorithm was performed. Two different low-energy conformers were selected for further ab initio optimization. A restricted Hartree–Fock method with the standard 6-31G** basis set was then applied. These calculations showed that the conformational energy ΔE between **7a** and **7b** was 2.383 kcal/mol.

Table 2. Diastereomeric output for the reduction of **8** with various borohydrides.

Entry	Reducing reagent	Yield of **10**[a]	Ratio of **10a**:**10b**[b]
1	$NaBH_4$	91	66:34
2	$NaBH(CH_3COO)_3$	86	76:24
3	$NaBH[(CH_3)_2CHCOO]_3$	93	64:36
4	$NaBH[(CH_3)_3CCOO]_3$	86	83:17

[a]Isolated yield (%) of both **10a** and **10b**.
[b]Estimated from ^{1}H NMR on the crude reaction mixture.

Fig. 1. The structure of conformers **7a** and **7b**.

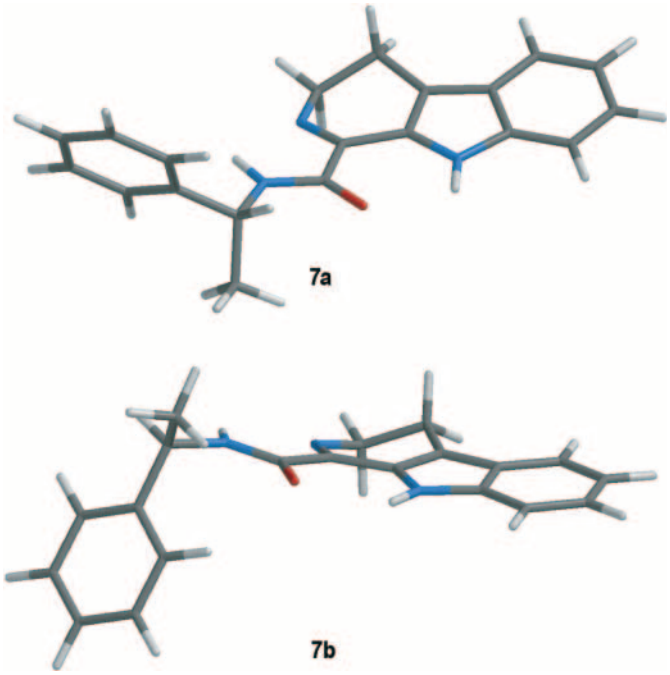
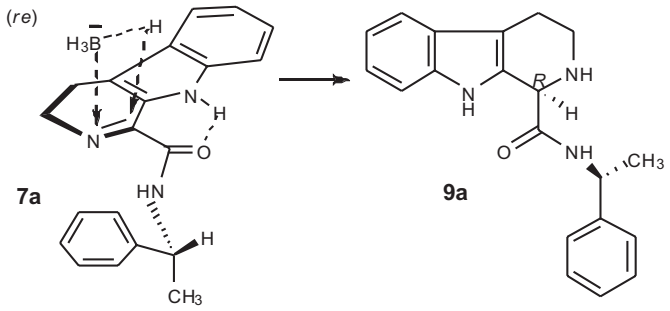


Fig. 2. Stereochemical model for the reduction of **7a**.



rected apart from the imine area (consult also Fig. 2), thus lowering its ability to the chirality induction. Apparently, such a disfavored interaction was not present in the isoquinoline analogue of imine **7**, thus allowing us to observe much better diastereoselectivity (10).

When a Felkin–Evans trajectory (15) for an early transition state was applied to conformer **7a** (Fig. 2), two major conclusions can be drawn from this consideration. First, the model correctly predicts diastereomer **9a** as the major product of the reduction process. Second, the bulkiest substituent of the chiral auxiliary (phenyl or naphthyl ring) is located in the most-remote part of the molecule and is guided in the opposite direction to the incoming nucleophile. This model accounts convincingly for both the relatively low level of diastereodifferentiation during the addition step and for only a small improvement after the replacement of the phenyl in compound **7** by the naphthyl moiety in compound **8**.

Conclusion

In the presented approach, we demonstrated the possibility to extend our earlier findings concerning the diastereoselective preparation of tetrahydroisoquinoline derivatives using enantiopure (*R*)-1-arylethylamines onto β-carboline analogues.

Despite moderate selectivity, the described method might be an attractive alternative to the existing procedures (16, 17, 18) because of the relatively high chemical yields and facile chromatographic separation of diastereomers, which then may be subjected to further transformations leading to the pure enantiomers of 1-substitued-tetrahydro-β-carboline derivatives. The work in this area is in progress.

Experimental

(1*R*)-*N*-[(1*R*)-1-phenylethyl]-2,3,4,9-tetrahydro-1*H*-β-carboline-1-carboxamide 9a and (1*S*)-*N*-[(1*R*)-1-phenylethyl]-2,3,4,9-tetrahydro-1*H*-β-carboline-1-carboxamide 9b

In a typical experiment (see Table 1, entry 4), a sample of compound **5** (335 mg, 1 mmol) was refluxed in methylene chloride (15 mL) with $POCl_3$ (0.5 mL, 5.5 mmol) for 2 h. After that time, the volatiles were evaporated, and dry MeOH (10 mL) was slowly introduced. The mixture was evaporated into dryness, and the procedure was repeated twice followed by the evaporation with a fresh portion of xylene (20 mL) to remove traces of methanol. The residue was then dissolved in dioxane (20 mL), and a freshly prepared modified borohydride solution was introduced at 10 °C. The borohydride was prepared by stirring $NaBH_4$ (180 mg, 4 mmol) with pivaloyl acid (1.11 g, 12 mmol) in dry THF (10 mL) for 3 h. The resultant solution was stirred for 1 h at 10 °C and was poured onto 5% aq. NaOH (50 mL). The mixture was then extracted with methylene chloride (3 × 20 mL). After drying and evaporation, the residue was subjected to column chromatography on silica gel

using ethyl formate as eluent to afford pure diastereomers **9a** and **9b** (R_f values are 0.45 and 0.49, respectively).

Selected data for compound **9a**: brown foam (194 mg, 61%). $[\alpha]_D^{23}$ +55.2 (*c* 0.5, $CHCl_3$). ^{1}H NMR δ_H: 8.85 (1H, br s, H-9), 7.96 (1H, br d, *J* = 7 Hz, $NHCHCH_3$), 7.47 (1H, d, *J* = 8 Hz, H-8), 7.38 (1H, br t, *J* = 2 Hz, H-2) 7.31 (1H, d, *J* = 8 Hz, H-5), 7.27–7.24 (3H, m, H_{arom}), 7.21–7.18 (2H, m, H_{arom}), 7.14 (1H, td, *J* = 7.5 Hz, *J* = 1 Hz, H-6), 7.07 (1H, m, H-7), 5.09 (1H, qt, *J* = 7.5 Hz, H-1′), 4.62 (1H, s, H-1), 3.26 (1H, dt, *J* = 13 Hz, *J* = 5 Hz, H-3), 2.97 (1H, m, H-3), 2.77 (1H, dt, *J* = 15.5 Hz, *J* = 5 Hz, H-4), 2.72–2.66 (1H, m, H-4), 1.54 (3H, d, *J* = 7 Hz, H-2′). ^{13}C NMR δ_C: 170.6, 143.0, 136.0, 129.6, 128.7, 127.2, 126.8, 125.8, 121.8, 119.2, 118.0, 111.2, 109.2, 54.7, 48.4, 42.0, 22.5, 22.2. ESI-MS *m*/*z* (%): 320 (100%, M + H^+). HR-MS (ES(+)): $[M + H]^+$ calcd. for $C_{20}H_{22}N_3O$: 320.1763; found: 320.1776.

Selected data for compound **9b**: (48 mg, 15%). ^{1}H NMR δ_H: 8.92 (1H, br s, H-9), 7.96 (1H, br d, *J* = 6.5 Hz, $NHCHCH_3$), 7.57 (1H, d, *J* = 8 Hz, H-8), 7.48 (1H, br t, *J* = 9 Hz, H-2), 7.38–7.33 (5H, m, H_{arom}), 7.20 (1H, m, H_{arom}), 7.16 (1H, m, H-6), 7.08 (1H, m, H-7), 5.06 (1H, qt, *J* = 7.5 Hz, H-1′), 4.56 (1H, s, H-1), 3.25 (1H, m, H-3), 3.05 (1H, m, H-3), 2.79 (1H, m, H-4), 2.71 (1H, m, H-4), 1.45 (3H, d, *J* = 6.5 Hz, H-2′). ^{13}C NMR δ_C: 170.5, 143.1, 136.0, 129.8, 128.7, 127.4, 126.8, 126.1, 121.8, 119.2, 118.0, 111.2, 109.1, 57.7, 48.6, 41.9, 22.4, 22.0. HR-MS (ES(+)): $[M + H]^+$ calcd. for $C_{20}H_{22}N_3O$: 320.1763; found: 320.1769.

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