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Stereoselective synthesis of 3-mono- and 1,3-disubstituted 4-phenyl-1,2,3,4-tetrahydroisoquinolines

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Abstract

(1*S*,2*S*)-(+)-Thiomicamine was transformed in high yield and with high diastereoselectivity into (3*R*,4*R*)-4-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid and enantiomerically pure (3*R*,4*R*)-3-hydroxymethyl-4-phenyl- and (1*R*,3*R*,4*R*)-3-hydroxymethyl-1-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline derivatives. © 2000 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enantiomerically pure tetrahydroisoquinolines substituted at C-3 and/or C-4 are of considerable interest due to their biological activity and as constituents of many natural products and drugs. Among them, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Tic)[1] and 4-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (4-phenyl Tic)[2] have been used as conformationally restrained amino acids for peptide modification.[1,2] Many other 4-phenyl substituted tetrahydroisoquinolines have been found to show diverse biological properties.[3,4]

Recently, some of the reduced derivatives of Tic have found application in stereoselective synthesis, e.g. as ligands in enantioselective reduction of ketoacids[5] and ketones,[6] as chiral lithium amide bases for enantioselective deprotonation[7] as well as chiral oxidizing agents.[8]

In this paper we describe a simple procedure for transformation of readily available (1*S*,2*S*)-(+)-thiomicamine **1a** into enantiomerically pure (3*R*,4*R*)-4-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **7** and to enantiomerically pure tetrahydroisoquinolines **4a**,**b** and **10**, with a 1,2-aminoalcohol functionality, a system useful for inducing stereoselectivity in many types of asymmetric transformations.[9]

2. Results and discussion

The synthesis presented in Scheme 1 began with (1*S*,2*S*)-(+)-thiomicamine **1a**, which was converted into *N*-benzyl derivative **3a** in either of the two steps: i.e. condensation with benzaldehyde to

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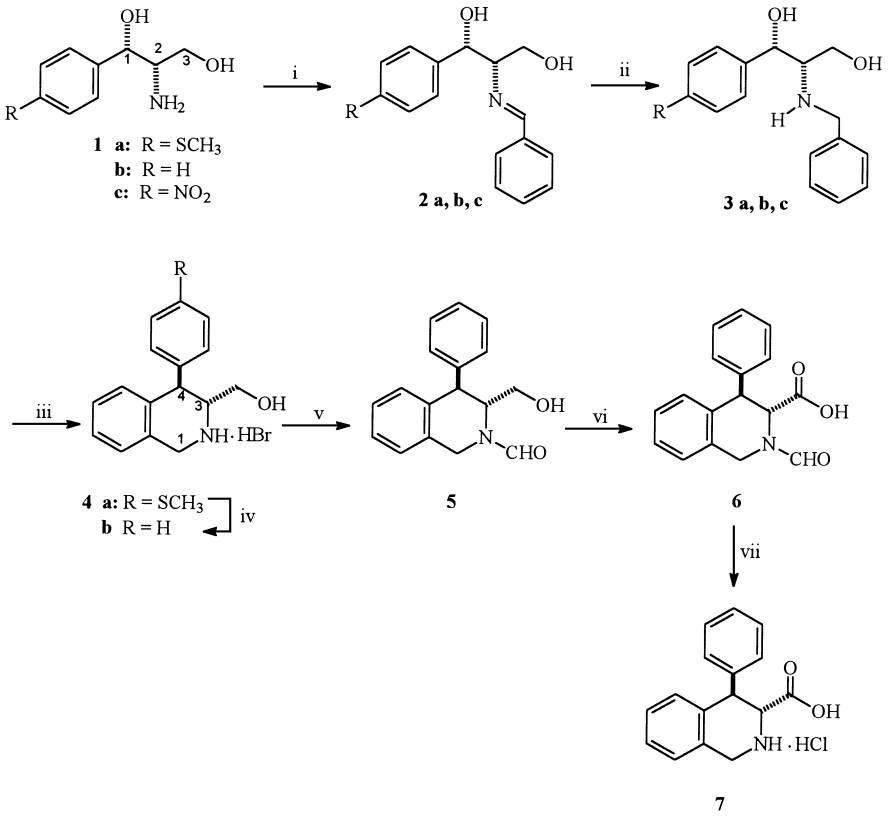
afford crystalline imine **2a**, followed by sodium borohydride reduction, or as a one-pot synthesis. The same procedure was applied to the synthesis of *N*-benzyl derivatives **3b**,**c** obtained from the corresponding (1*S*,2*S*)-2-amino-1-phenyl-1,3-propanediol **1b** and (1*R*,2*R*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol *ent-1c*, respectively. The ^{1}H NMR spectra of imines **2** were not reliable for characterization because of multiplicity of signals, as equilibrium occurs in solution between the imine and oxazolines, formed as minor components. The equilibrium was also responsible for changes in specific rotation during measurements.



Scheme 1. Reagents and conditions: (i) PhCHO/MeOH/$CuSO_4$; (ii) $NaBH_4$/MeOH; (iii) 40% HBr/Δ; (iv) Raney nickel; (v) HCOOH/toluene; (vi) NaOCl/TEMPO; (vii) 15% HCl

The cyclization of *N*-benzylamines **3a**,**b** was performed in refluxing 40% hydrobromic acid[10] and proceeded with good yields and high diastereoselectivity, giving *trans*-3,4-disubstituted tetrahydroisoquinolines **4a**,**b** as the only isolated diastereomers.

The relative configuration of the C-3 and C-4 stereogenic centers in **4a**,**b** could be deduced from the value of the coupling constants (J = 11.3 and 10.2 Hz, respectively) between the H-3 and H-4 protons in ^{1}H NMR spectra of both compounds. This indicates *axial–pseudoaxial* orientation of these protons, thus permitting assignment of the absolute configuration as 3*R*,4*R*. It also shows that the cyclization step proceeded with retention of configuration at the 1*S* stereogenic center of the starting aminodiols **1a**,**b** leading to **4a**,**b** with 4*R* stereochemistry (*R* notation due to change in the priority of ligands). A similar steric course was observed in acid-catalyzed cyclization of (–)-pseudoephedrine to the corresponding tetrahydroisoquinoline.[11] To understand the stereochemistry

of this reaction an S_N1 mechanism rather than S_N2 should be postulated, because: (a) the same diastereomers, **4a**,**b**, were formed when polyphosphoric acid was used instead of HBr for the cyclization, excluding two successive S_N2 processes via intermediate bromo-derivative; (b) the aminodiol **3c**, having a nitro deactivating group at the *para* position of the benzyl substituent, failed to undergo cyclization in the reaction conditions applied. The high stereoselectivity of the cyclization step, leading to one diastereomer exclusively, could be explained by assuming that the more stable carbocation **A** is the intermediate in this transformation (Fig. 1).

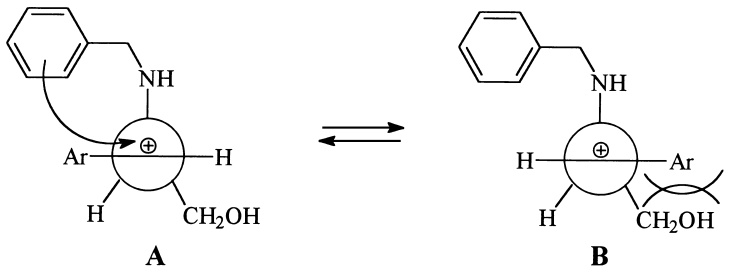
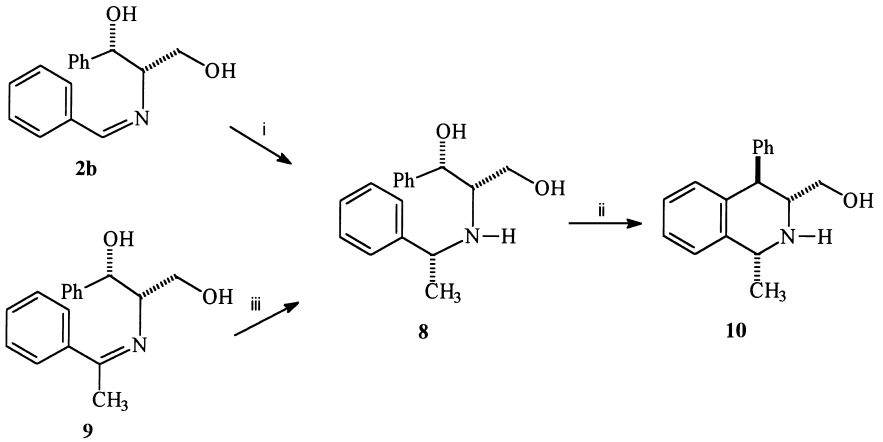


Figure 1.

The (+)-thiomicamine-derived tetrahydroisoquinoline **4a** was readily transformed into the analog **4b** by desulfurization with Raney nickel in THF at room temperature. The so obtained desulfurization product, **4b**, was identical with the sample prepared from the more expensive aminodiol **1b**, according to the above-mentioned procedure.

Continuing the synthesis of amino acid **7**, amine **4a** was *N*-formylated with formic acid in toluene to give formamide **5** in high yield, before the oxidation of hydroxymethyl substituent was attempted. In order to avoid the formation of *N*,*O*-diformyl derivative, a formate salt of **4a** was first precipitated, and then heated in toluene with a water-trap. The oxidation of **5** in a CH_2Cl_2–H_2O system with sodium hypochlorite and 2,2,6,6-tetramethyl-1-piperidinoxy radical (TEMPO) as catalyst[12] gave selectively *N*-formyl acid **6** in excellent yield. Both *N*-formyl derivatives, **5** and **6**, exist in solution as mixture of rotamers as judged from the ^1H NMR spectra, in which most of the absorption bands were doubled at the ratios 6.5:1 and 7.5:1, respectively. Another feature of the spectra was that the H-3 and H-4 protons' absorption appeared as singlets, whereas in the case of the parent amine **4b** it gave rise to doublets with $J = 10.2$ Hz. A change of conformation of the nitrogen-containing ring was apparently forced by an intramolecular hydrogen bonding formed between hydroxyl proton and formyl oxygen. Hydrolysis of *N*-formyl derivative **6** in refluxing 15% hydrochloric acid afforded pure amino acid **7**, isolated as crystalline hydrochloride, with 52% overall yield from **1a**. This compound was first prepared from *D*-3,3-diphenylalanine by a Pictet–Spengler condensation with formaldehyde as a 2.8:1 separable mixture of diastereomers.[2] The specific rotation of our sample, $[\alpha]_D = -59.0$, was in accordance with that given in the literature,[2] $[\alpha]_D = -59.2$, and so were the spectral characteristics.

In another series of experiments, 3-hydroxymethyl-1-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **10** was synthesized, as illustrated in Scheme 2. The key intermediate, amine **8**, was obtained in two ways: by methyllithium addition to imine **2b**, and by sodium borohydride reduction of imine **9**, prepared by condensation of aminodiol **1b** with acetophenone.



Scheme 2. Reagents and conditions: (i) CH_3Li/THF/0°C; (ii) 40% HBr/Δ; (iii) $NaBH_4$/MeOH

The addition of methyllithium to imine **9** proceeded with a high degree of stereoselectivity affording (1*S*,2*S*,α*R*)-diastereomer **8**[13] with 80% d.e., while the reduction resulted in ca. 1:1 mixture of diastereomers. Cyclization of **8** (80% d.e.) in refluxing 40% hydrobromic acid afforded (1*R*,3*R*,4*R*)-2-hydroxymethyl-1-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **10** in high yield, isolated as a single isomer, after one crystallization from diethyl ether. The all *equatorial*/*pseudoequatorial* orientation of substituents, and thus the (1*R*,3*R*,4*R*)-absolute configuration of **10** was confirmed by ^{1}H NMR spectroscopy, both, by the value of the H-3 and H-4 coupling constant, J = 10.7 Hz, and on the basis of NOE experiment, which showed through a space interaction between H-1 and H-3 protons and a weak interaction between H-4 and CH_3 group protons.

3. Conclusion

(+)-Thiomicamine **1a**, a cheap industrial waste product, has been converted in a five-step simple synthesis into enantiomerically pure (3*R*,4*R*)-4-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **7**, an α-amino acid, useful in the synthesis of modified peptides of biological interest.[1,2]

The obtained enantiomerically pure tetrahydroisoquinolines **4a**,**b** and **10**, substituted at C-3 with hydroxymethyl group, which represent 1,2-aminoalcohols in a sterically rigid conformation, have been devised and are being tested as potential chiral ligands for addition of organometallic reagents to prochiral imines.[14]

4. Experimental

4.1. General

Melting points: determined on a Koffler block and are not corrected. IR spectra: Perkin–Elmer 180 in KBr pellets. NMR spectra: Varian Gemini 300, with TMS as internal standard. Mass spectra (EI): Joel D-100, 75 eV and FAB with NBA (*m*-nitrobenzylalkohol) as the matrix.

Specific rotation: Perkin–Elmer polarimeter 243B at 20°C. Merck DC-Alufolien Kieselgel 60_{254} were used for TLC. Optically active 2-amino-1-aryl-1,3-propanediols **1a–c** were purchased from the Aldrich Chemical Co. and used as received; Raney nickel 'ready for use' from Fluka Co.

*4.2. Synthesis of imines **2**. General procedure*

2-Amino-1-aryl-1,3-propanediol **1** (20 mmol), benzaldehyde (2.23 g, 21 mmol) in methanol (20 ml) and catalytic amount of anhydrous $CuSO_4$ were heated at reflux for 5 h. After cooling, pure imine **2**, which crystallized out of the solution in pure form, was filtered off and air-dried.

*4.2.1. (1S,2S)-2-Benzylideneamino-1-(4-methylthiophenyl)-1,3-propanediol **2a***

Colorless crystals (yield 89%), m.p. 109–112.5°C, $[\alpha]_D = +177.8$ (*c* 1.0, acetone), +126.6 after 20 h; IR (KBr) cm^{-1}: 3411, 1641. EI MS *m/z* (%): 301 (M^+) (0.7), 153 (35), 149 (100), 131 (40), 91 (37). HR MS calcd for $C_{17}H_{19}NO_2S$ (M+1): 302. 1215; found: 302.1216.

*4.2.2. (1S,2S)-2-Benzylideneamino-1-phenyl-1,3-propanediol **2b***

Colorless crystals (yield 88%), m.p. 153–154°C (lit.[15] 151°C), $[\alpha]_D = +144.3$ (*c* 1.1, acetone) +114.2 after 20 h; IR (KBr) cm^{-1}: 3418, 1642. EI MS *m/z* (%): 255 (M^+) (0.5), 224 (5), 148 (88), 131 (33), 118 (50), 91 (100). HR MS calcd for $C_{16}H_{17}NO_2$ (M+1): 256.1338; found: 256.1326.

4.2.3. (1R,2R)-2-Benzylideneamino-1-(4-nitrophenyl)-1,3-propanediol ent-***2c***

Creamy crystals (yield 85%), m.p. 146.5–148°C (lit.[15] **2c**: 148-149°C), $[\alpha]_D = -151.0$ (*c* 1, acetone), –128.3 after 20 h; IR (KBr) cm^{-1}: 3426, 1639. EI MS *m/z* (%): 300 (M^+) (0.6), 269 (21), 149 (45), 148 (100), 131 (21), 118 (29) 104 (20), 91 (62). HR MS calcd for $C_{16}H_{16}N_2O_4$ (M+1): 301.1188; found: 301.1187.

4.3. Synthesis of N*-benzylamines **3**. General procedure*

To a solution of imine **2** (14.5 mmol) in methanol:THF (2:1) (75 ml) $NaBH_4$ (1.65 g, 43.5 mmol) was added portionwise with stirring at ice-water bath temperature, and then the mixture was refluxed for 2 h. It was cooled to rt and 5% hydrochloric acid was added and the whole was stirred for 1 h at rt. The solvents were evaporated, and the crystalline residue was basified with 20% sodium hydroxide and extracted with diethyl ether. After the standard work-up, the crude reaction product was recrystallized from diethyl ether–hexane.

*4.3.1. (1S,2S)-2-Benzylamino-1-(4-methylthiophenyl)-1,3-propanediol **3a***

Colorless crystals (yield 92%), m.p. 74–74.5°C; $[\alpha]_D = +74.0$ (*c* 1.07, acetone); ^1H NMR ($CDCl_3$) δ: 2.48 (s, 3H, SCH_3), 2.5 (bs, 2H, exchanges with D_2O, OH), 2.78 (m, 1H, H-2), 3.36 (dd, J = 3.1, 11.1 Hz, 1H, H-3), 3.65 (dd, J = 3.8, 11.0 Hz, 1H, H-3′), 3.67 and 3.80 (2d, J = 13.2 Hz, 1H each, CH_2Ph), 4.61 (d, J = 7.1 Hz, 1H, H-1), 7.20–7.34 (m, 9H, Ar-H). EI MS *m/z* (%): 304 $(M+1)^+$ (2), 150 (100), 91 (73). HR MS calcd for $C_{17}H_{21}NO_2S$ (M+1): 304.1371; found: 304.1353.

*4.3.2. (1S,2S)-2-Benzylamino-1-phenyl-1,3-propanediol **3b***

Colorless crystals (yield 80%), m.p., specific rotation and spectral properties were identical with literature values.[16]

*4.3.3. (1*R*,2*R*)-2-Benzylamino-1-(4-nitrophenyl)-1,3-propanediol hydrochloride* ent-***3c·HCl***

Creamy crystals (yield 90%), m.p. 212°C (dec.), subl. from ca. 190°C, $[\alpha]_D = -26.8$ (*c* 0.6, methanol); ^{1}H NMR (d_6-DMSO) δ: 3.21 (m, 1H, H-2), 3.34 (dd, J = 4.7, 12.4 Hz, 1H, H-3), 3.64 (dd, J = 3.3, 12.4 Hz, 1H, H-3′), 4.31 (s, 2H, CH_2Ph), 5.06 (d, J = 8.5 Hz, 1H, H-1), 5.58 and 6.76 (2bs, 1H each, exchange with D_2O, OH), 7.41–7.67 (m, 7H, Ar-H), 8.23 (d, J = 8.8 Hz, 2H, Ar-H), 9.03 and 9.41 (2bs, 1H each, exchange with D_2O, H_2N^+). EI MS *m*/*z* (%): 303 $(M+1)^+$ (0.5), 150 (75), 91 (100). HR MS calcd for $C_{16}H_{18}N_2O_4$ (M+1): 303.1345; found: 303.1361.

4.4. Cyclization of N*-benzylamines* ***3*** *to tetrahydroisoquinolines* ***4****. General procedure*

A mixture of *N*-benzylamine **3** (12 mmol) in 40% hydrobromic acid (30 ml) was heated at reflux with stirring for 1.5 h, then left at rt for 17 h. The precipitated crystals were filtered off, washed with cold water and air-dried to give tetrahydroisoquinoline hydrobromide **4·HBr** as crystalline solid.

4.4.1. (3R,4R)-3-Hydroxymethyl-4-(4-methylthiophenyl)-1,2,3,4-tetrahydroisoquinoline hydrobromide ***4a·HBr***

Creamy crystals (yield 92%), m.p. 245–248°C (dec.), $[\alpha]_D = -77.5$ (*c* 1.0, methanol); ^{1}H NMR (d_6-DMSO) δ: 2.48 (s, 3H, CH_3), 3.42 (ddd, J = 11.8, 5.5, 5.2 Hz, 1H, CH_2OH), 3.60 (ddd, J = 11.8, 4.7, 3.0 Hz, 1H, CH_2OH), 3.69 (ddd, J = 11.3, 5.5, 3.0 Hz, 1H, H-3), 4.29 (d, J = 11.3Hz, 1H, H-4), 4.34 and 4.63 (2d, J = 15.7 Hz, 1H each, CH_2N^+), 5.56 (t, J = 4.7 Hz, 1H, exchanges with D_2O, $^+NH_2$), 6.68 (d, J = 7.4 Hz, 1H, Ar-H), 7.15–7.33 (m, 7H, Ar-H), 9.39 (bs, 2H exchange with D_2O, $^+NH_2$); EI MS *m*/*z* (%): 285 (M^+) (5), 254 (100), 179 (74), 130 (6). HR MS calcd for $C_{17}H_{19}NOS$: 285.1187; found: 285.1177.

*4.4.2. (3*R*,4*R*)-3-Hydroxymethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline hydrobromide* ***4b·HBr***

Creamy crystals (yield 89%), m.p. 239–245°C (dec.) subl. ca. 200°C, $[\alpha]_D = -34.8$ (*c* 1.0, methanol); ^{1}H NMR (d_6-DMSO) δ: 3.41 (m 1H, CH_2O), 3.60 (ddd, J = 11.8, 4.4, 3.0 Hz, 1H, CH_2O), 3.75 (ddd, J = 11.3, 5.8, 3.0 Hz, 1H, H-3), 4.31 (d, J = 10.4 Hz, 1H, H-4), 4.35 and 4.65 (2d, J = 15.7 Hz, 1H each, CH_2N^+), 5.57 (t, J = 4.7 Hz, 1H, exchanges with D_2O, OH), 6.66 (d, J = 7.7 Hz, 1H, Ar-H), 7.14–7.42 (m, 8H, Ar-H), 9.40 (bs, 2H, exchange with D_2O, $^+NH_2$); EI MS *m*/*z* (%): 239 (M^+) (0.5), 237 (18), 236 (100), 179 (12); HR MS calcd for $C_{16}H_{17}NO$: 239.1310; found: 239.1306.

4.5. Desulfurization of tetrahydroisoquinoline ***4a*** *with Raney nickel*

A suspension of isoquinoline hydrobromide **4a·HBr** (1.84 g, 5 mmol) in THF (100 ml) was neutralized with 1% HCl until a clear solution was formed, then treated with wet Raney nickel (ca. 3 ml) and kept at rt under vigorous stirring until no more starting material was present according to TLC (ca. 5 h). It was then filtered through a pad of Celite, the inorganic residue was washed with THF (3×30 ml). The solvent was removed from the filtrate under reduced pressure to give crude isoquinoline **4b** in quantitative yield. It was then treated with 10% hydrobromic acid in methanol to deposit pure hydrobromide salt **4b·HBr** (79%), m.p. 239–244°C and $[\alpha]_D = -34.8$ (*c* 1.0, methanol), identical with a sample prepared from **2b** as described above.

4.6. (3R,4R)-2-Formyl-3-hydroxymethyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **5**

Isoquinoline formate, **4b·HCOOH**, (2.85 g, 10 mmol) was prepared by stirring of isoquinoline **4b** with stoichiometric amount of 85% formic acid in toluene (36 ml) at rt for 17 h. The precipitated salt was filtered off, suspended in toluene (36 ml) and heated at reflux until clear solution was obtained (ca. 1 h). It was then washed with 5% NaOH and 5% HCl, dried and the solvent was evaporated to give 2.01 g of pure *N*-formyl derivative **5** and 0.38 g of recovered starting isoquinoline **4b**; yield 90%, m.p. 133.0–134.5°C (from methanol/diisopropyl ether), $[\alpha]_D = -116.7$ (*c* 1.1, methanol). IR (KBr) cm^{-1}: 3499 sh, 3439 br, 1657; ^1H NMR ($CDCl_3$) δ: (major rotamer) 3.1 (bs, 1H, exchanges with D_2O, OH), 3.58–3.85 (m, 3H, H-3 and CH_2O), 4.15 (s, 1H, H-4), 4.29 and 5.25 (2d, J = 18.1 Hz, 1H each, CH_2N), 6.90–7.31 (m, 9H, Ar-H), 7.68 (s, 1H, HC=O). EI MS *m*/*z* (%): 267 (M^+) (32), 236 (100), 208 (50), 179 (24), 178 (20), 117 (11). HR MS calcd for $C_{17}H_{17}NO_2$: 267.1259; found: 267.1262.

4.7. (3R,4R)-2-Formyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **6**

A two-phase system composed of the organic part-isoquinoline **5** (1.6 g, 6 mmol), TEMPO (1 mol%) in methylene chloride (18 ml) and the aqueous part of sodium bicarbonate (12.5 ml), potassium bromide (60 mg) and tetrabutylammonium chloride (80 mg) was prepared. To this mixture, a solution of 1.1N sodium hypochlorite (16.5 ml) in saturated sodium bicarbonate (12 ml) and brine (24 ml) was added dropwise during 0.5 h at ice-water bath temperature under vigorous stirring. The stirring was continued for 1 h at this temperature, then for 1 h at rt. Phases were separated, the organic solution was treated with 10% sodium hydroxide (3×5 ml) and the combined aqueous extracts were acidified with 15% hydrochloric acid and reextracted with methylene chloride (3×50 ml). After work-up, 1.47 g (87.5%) of pure acid **6** was obtained; m.p. 182–183°C (from methanol/diisopropyl ether), $[\alpha]_D = -91.3$ (*c* 0.96, methanol). IR (KBr) cm^{-1}: 3436, 2798-2100 (br), 1725, 1615; ^1H NMR ($CDCl_3$) δ: 4.45 (d, J = 1.4 Hz, 1H, H-4), 4.50 (d, J = 17.9 Hz, 1H, H-1), 4.81 (s, 1H, H-3), 5.14 (d, J = 18.1 Hz, 1H, H-1′), 6.92–7.31 (m, 9H, Ar-H), 7.70 (s, 1H, HC=O), 9.60 (bs, 1H, exchanges with D_2O, OH). EI MS *m*/*z* (%): 281 (M^+) (100), 252 (43), 236 (53), 235 (29), 208 (52), 179 (39), 178 (39), 130 (25), 117 (17). HR MS calcd for $C_{17}H_{15}NO_3$ (M+1): 282.1130; found: 282.1116.

4.8. (3R,4R)-4-Phenyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride **7·HCl**

N-Formyl acid **6** (0.47 g, 1.67 mmol) in 15% hydrochloric acid (10 ml) was refluxed for 10 h. After cooling the precipitate was filtered off to give pure, crystalline hydrochloric salt, **7·HCl** (0.42 g, 87%); m.p. 236–239°C (dec.); subl. from ca. 190°C, $[\alpha]_D = -58.5$ (*c* 1.0, methanol) [lit.[2] m.p. 263–266°C (dec.), $[\alpha]_D = -59.2$ (*c* 1.0, methanol)], spectral properties were identical with literature values.[2]

4.9. (1S,2S)-2-(α-Methylbenzylideneamino)-1-phenyl-1,3-propanediol **9**

A mixture of aminodiol **1b** (0.3 g, 1.8 mmol), acetophenone (0.23 ml, 1.84 mmol) and two drops of trifluoroacetic acid in toluene (30 ml) was heated at reflux, for 2 h, with azeotropic removal of water. After cooling the solution was washed with $NaHCO_3$, dried and the solvent was evaporated to give imine **9**, as an oil (0.38 g, 78%), $[\alpha]_D$ +75.2 (*c* 1.4, acetone) +65.7 after 20 h. The imine was used in the next step of the synthesis without further purification.

4.10. (1S,2S,αR)-2-(α-Methylbenzylamino)-1-phenyl-1,3-propanediol **8**

(a) From imine **2b**: To a solution of imine **2b** (0.51 g, 2 mmol) in THF (40 ml) methyl lithium (1.6 M solution in ether; 5.6 ml, 9 mmol) was added at 0°C under an argon atmosphere. The mixture was stirred at 0°C for 2 h, then quenched with 20% NH_4Cl at the low temperature. Phases were separated at rt and the aqueous one was extracted with ethyl ether. From the combined organic extracts basic products were taken into 5% HCl. The acidic aqueous solution was basified with 20% NaOH, reextracted into diethyl ether, dried and the solvent was evaporated to give 0.41 g (83%) of oily product **8**, as a mixture of diastereomers (9:1). $[\alpha]_D = +136.1$ (*c* 1.2, chloroform), *ent*-**8**[13] $[\alpha]_D = -137.7$ (*c* 1.0, chloroform). ^{1}H NMR (major isomer) ($CDCl_3$) δ: 1.37 (d, J = 6.6 Hz, 3H, CH_3), 2.54 (ddd, J = 7.4, 3.8, 2.5 Hz, 1H, H-2), 3.31 (dd, J = 11.3, 2.2 Hz, 1H, CH_2O), 3.68 (dd, J = 11.3, 3.8 Hz, 1H, CH_2O), 3.85 (q, J = 6.6 Hz, 1H, H-α), 4.64 (d, J = 7.4 Hz, 1H, H-1), 7.14–7.38 (m, 10H, Ar-H). EI MS *m*/*z* (%): 271 (M^+) (2), 240 (3), 164 (66), 105 (100). HR MS calcd for $C_{17}H_{21}NO_2$: (M+1) 272.1650; found: 272.1659.

(b) From imine **9**: To a solution of imine **9** (0.5 g, 2.08 mmol) in methanol (10 ml) $NaBH_4$ (0.12 g, 3.12 mmol) was added in portions at 0°C, with stirring. The mixture was stirred at rt for 1 h, then the solvent was evaporated at reduced pressure, and the residue partitioned between 5% NaOH and ethyl ether. Phases were separated, the aqueous one extracted with diethyl ether (2×20 ml) and the combined organic extracts were worked-up in the usual way. Amine **8** was obtained in quantitative yield as a mixture ca 1:1 of diastereomers.

4.11. (1R,3R,4R)-3-Hydroxymethyl-1-methyl-4-phenyl-1,2,3,4-tetrahydroisoquinoline **10**

A solution of amine **8** (0.31 g, 1.15 mmol) and 40% hydrobromic acid (3 ml) was heated at reflux for 1 h, then water was added at rt and the mixture was basified with 20% NaOH, and extracted with ethyl ether. After the usual work-up, 0.27 g (93%) of isoquinoline **10** was obtained as colorless crystals from diethyl ether, m.p. 118–120°C (dec.), $[\alpha]_D = -77.9$ (*c* 1.0, methanol). ^{1}H NMR ($CDCl_3$) δ: 1.55 (d, J = 6.6 Hz, 3H, CH_3), 3.17 (ddd, J = 10.7, 7.7, 3.0 Hz, 1H, H-3), 3.40 (dd, J = 10.7, 7.7 Hz, 1H, CH_2O), 3.58 (dd, J = 10.7, 3.0 Hz, 1H, CH_2O), 3.87 (d, J = 10.5 Hz, 1H, H-4), 4.30 (q, J = 6.6 Hz, 1H, H-1), 6.72 (d, J = 7.7 Hz, Ar-H), 7.01–7.32 (m, 8H, Ar-H). EI MS *m*/*z*: (%): 253 (M^+) (0.5), 238 (11), 222 (100), 179 (75), 144 (3), 130 (5). HR MS calcd for $C_{17}H_{19}NO$ (M+1): 254.1545; found: 254.1545.

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