EurJOC European Journal of Organic Chemistry

FULL PAPER

DOI: 10.1002/ejoc.201403218

Synthesis of (+)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid, a Diastereoselective Approach

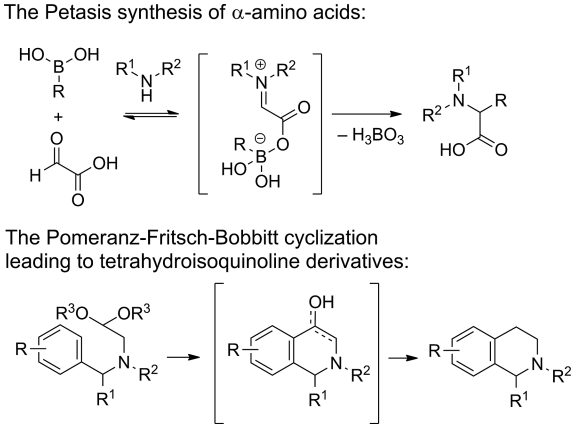
Ilona Bułyszko,[a] Maria Chrzanowska,[a] Agnieszka Grajewska,[a] and Maria D. Rozwadowska*[a]

Keywords: Total synthesis / Asymmetric synthesis / Multicomponent reactions / Diastereoselectivity / Cyclization / Nitrogen heterocycles

The diastereoselective synthesis of (+)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (90 % *ee*) was accomplished by employing a combination of two synthetic methods, that is, the Petasis synthesis of amino acids and the Pomeranz–Fritsch–Bobbitt synthesis of tetrahydroisoquinoline derivatives. The stereochemical outcome of the synthesis was controlled by chiral aminoacetaldehyde acetals, which were used as the amine component of the Petasis step to yield the Pomeranz–Fritsch–Bobbitt substrate for the tetrahydroisoquinoline ring formation in one simple operation.

Introduction

We have recently reported[1,2] a new and practical method for the synthesis of tetrahydroisoquinoline derivatives that are functionalized at C-1 by using a combination of two synthetic methods, that is, a multicomponent Petasis reaction and a Pomeranz–Fritsch–Bobbitt cyclization. In Scheme 1, the three-component Petasis reaction, which involves boronic acid, a carbonyl derivative, and an amine,[3] for the preparation of an amino acid and the Pomeranz–Fritsch–Bobbitt cyclization of amino acetals[4] are shown.



Scheme 1.

Our method[1,2] involves a substantial modification to the Petasis reaction. We used aminoacetaldehyde acetals as the amine component and thus prepared the key intermediate for the Pomeranz–Fritch–Bobbitt cyclization in one step. By employing this approach, we have performed the racemic syntheses of several tetrahydroisoquinoline-1-carboxylic acids[1] and simple isoquinoline alkaloids[2] in satisfactory overall yields. To further develop this procedure, we have undertaken experiments to adapt our approach to asymmetric synthesis. Herein, we present the diastereoselective synthesis of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1**), which is related to simple isoquinoline alkaloids[4] and important arylglycine derivatives[5] and was selected to demonstrate the effectiveness of our approach.

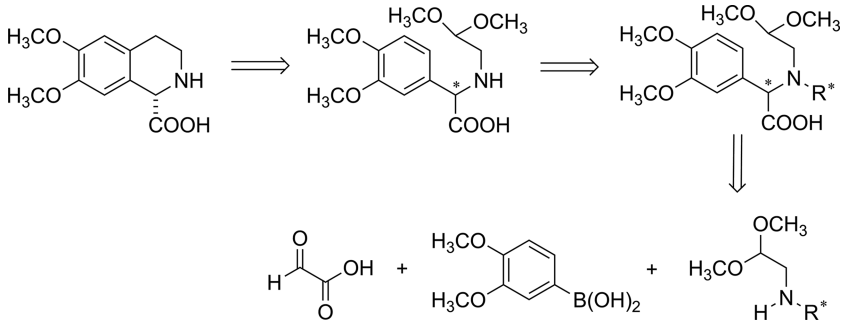
In 2008 Fülöp and co-workers[6] reported the first preparation of both enantiomers of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid [(–)-**1** and (+)-**1**] in high yield and high enantiomeric purity. Their method was based on the chemoenzymatic kinetic resolution of the racemic ethyl ester of **1** by using CAL-B (*Candida antarctica* lipase B) to prepare (–)-**1** and alcalase for (+)-**1**. The retrosynthetic analysis of the total diastereoselective synthesis of (+)-**1** as reported herein is shown in Scheme 2.

Results and Discussion

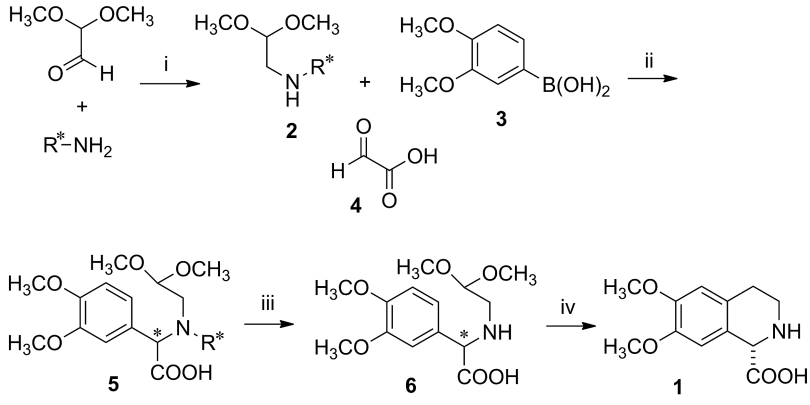
The diastereoselectivity of our synthesis was accomplished by using chiral aminoacetaldehyde acetals **2a**–**2d** as the amine components of the Petasis reaction to yield the diastereomeric amino acetals for the Pomeranz–Fritsch–Bobbitt cyclization (see Scheme 3). Acetals **2a**–**2d** were prepared in high yield by heating at reflux a benzene solution (Dean–Stark apparatus) of dimethoxyacetaldehyde with readily cleavable chiral amines such as (*S*)-(–)-α-phenyleth-

[a] Faculty of Chemistry, A. Mickiewicz University, ul. Umultowska 89b, 61-614 Poznań, Poland
E-mail: mdroz@amu.edu.pl
http://www.chemia.amu.edu.pl

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201403218.



Scheme 2. Retrosynthetic presentation of the synthesis of (+)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid.



	R*	Y (%)	*dr*[a]
5a	Ph, Me	90	70:30
5b	$C_{10}H_7$, Me	83	79:21
5c		quant.	56:44
5d		quant.	13:87

i: *1.* PhH, Δ, 4 h, *2.* $NaBH_4$, CH_3OH

ii: DCM, r.t., 72 h

iii: H_2, $Pd(OH)_2$, CH_3OH, 24 h

iv *1.* 20% HCl, r.t., Ar, 72 h *2.* H_2, Pd/C, 24 h

[a] HPLC after derivatization with diazomethane

Scheme 3. The synthesis of acid **1** from acetal **2**, boronic acid **3**, and glyoxylic acid (**4**) and through addition product **5** and the cyclization of *N*-dealkylated compound **6** (DCM = dichloromethane).

ylamine, (*S*)-(–)-α-naphthylethylamine, (*S*)-(+)-tetrahydronaphthyl-1-amine, and (*R*)-(–)-1-indanamine, respectively, followed by a $NaBH_4$ reduction and a bulb-to-bulb distillation. Because of the low value of the specific rotation of acetal **2c** {$[a]_D^{20}$ = +2.97 (*c* = 1.16, $CHCl_3$)}, enantiomer *ent*-**2c** {$[a]_D^{20}$ = –2.26 (*c* = 1.23, $CHCl_3$)} was prepared to compare the HPLC analyses and prove the enantiomeric purity of **2c**.

In the first series of experiments, amino acetal **2a**, which contained (*S*)-(–)-α-phenylethylamine as the auxiliary and building block, was chosen as the amine component because of its well-recognized utility of both enantiomers in the synthesis of enantioenriched compounds.[7] Chiral α-phenylethylamines have also been tested in a few Petasis reactions[8] to afford products in fair to good yields with various degrees of diastereoselectivity (0–99%*de*), which depended on the type of boronic acid and amine that were employed. α-(1-Naphthyl)ethylamine also found application in the reaction.[9]

When we performed the Petasis reaction between amino acetal **2a**, 3,4-dimethoxyphenylboronic acid (**3**), and glyoxylic acid (**4**) in dichloromethane at room temp. for 72 h, amino acid **5a** was formed in approximately a 70:30 diastereomeric ratio (see Scheme 3). After trituration of the crude product with hexane, **5a** was isolated as a sticky solid in 90% yield, which was pure enough to be used in the next step. Attempts to isolate **5a** as a pure compound by crystallization or chromatographic separation were unsuccessful. In the latter case, substantial decomposition of the compound was observed during chromatography. Such a

situation was also observed during the syntheses of amino acids **5b**–**5d**.

The diastereomeric composition of amino acid **5a** was established by both ^{1}H NMR spectroscopic and chiral HPLC analysis of the crude product (after derivatization with diazomethane). Thus, the diastereomeric ratio of approximately 70:30 for compound **5a** could be deduced from the ^{1}H NMR spectroscopic data by comparing the integration values of the doublet resonances at δ = 1.47 and 1.58 ppm, which represent the methyl group protons of the nitrogen substituent. A similar diastereomeric composition (approximately 72:28) was also established by HPLC analysis. The latter method was used for the determination of the diastereomeric compositions of amino acids **5b**–**5d** (see Scheme 3).

To improve the diastereoselectivity of the Petasis step, we investigated the influence of several parameters on the degree of diastereoselectivity in the synthesis of **5a**. Of the solvents examined, only a moderate increase in *dr* (diastereomeric ratio, 77:23) was observed when the reaction was carried out in toluene. However, this reaction resulted in lower conversion value because of the poor solubility of amino acids in this solvent. In addition, the reaction did not progress in either ethanol or water at room temp. after 72 h, whereas a mixture of products, which consisted of polymeric substances, were formed at an elevated temperature (80 °C). An increase in the *dr* could not be achieved at a lower temperature (e.g., –20, –10, and 0 °C). In this case, the progress of the reaction was very slow, and when the reaction was conducted at either –20 or –10 °C, only approximately a 30% conversion was observed after 10 d. Thus, the typical Petasis reaction conditions, that is, DCM as the solvent at room temperature for 72 h of reaction time, were employed for the synthesis of amino acids **5b**–**5d**.

Next, we examined aminoacetaldehyde acetals **2b**–**2d**, which were derived from the chiral amines (*S*)-(–)-α-naphthylethylamine (for **2b**), (*S*)-(+)-tetrahydronaphthyl-1-amine (for **2c**), and (*R*)-(–)-1-indanamine (for **2d**), in the Petasis reaction. Amino acids **5b**–**5d** were prepared with high conversion but still only with a moderate diastereoselectivity (see Scheme 3). The highest asymmetric induction (87:13 *dr*), but the opposite configuration at C-1 for the major isomer, was achieved in the reaction with amino acetal **2d**. In the reaction with amino acetal **2c**, practically no induction was observed.

The final step of the synthesis, the construction of the tetrahydroisoquinoline ring system, employed the Pomeranz–Fritsch–Bobbitt cyclization/hydrogenolysis process.[10] The procedure for this step involved the treatment of the Pomeranz–Fritsch–Bobbitt amino acetal with 20% hydrochloric acid followed by a catalytic hydrogenation with a Pd/C catalyst. When this was applied to Petasis product **5a**, a sluggish reaction occurred, which led to a mixture of compounds.

Fortunately, the *N*-deprotected amino acid (+)-**6** which was easily prepared from compounds **5a** and **5b** by hydrogenolysis in methanol in the presence of Pearlman's catalyst, could be efficiently cyclized to give isoquinoline acid **1**. Moreover, compound **6** was a crystalline compound, which could be purified and enantiomerically enriched by crystallization of the crude products from 96% ethanol. When amino acid **5a** was used in this reaction, crystalline *N*-debenzylated product (+)-**6** was obtained in 85% yield with an *er* (enantiomeric ratio) of approximately 72:28. The crystallization of the crude product from 96% ethanol afforded an almost racemic first crop of crystals, which were isolated in 33% yield. The second crop of crystals supplied a sample of **6** in 48% yield with 80:20 *er*. Enantiomerically pure (+)-**6** {$[\alpha]_D^{20}$ = +85 (*c* = 1.15, MeOH); m.p. 141–142 °C} was prepared by a series of recrystallizations of the enriched fractions from 96% ethanol.

N-Dealkylated product (+)-**6** was then subjected to the Pomeranz–Fritsch–Bobbitt cyclization/hydrogenolysis procedure.[10] In the course of experiments, we noticed that the steric outcome of this step strongly depended on the reaction conditions and the workup procedure. The results were in accordance with the well-known configurational instability of aryl glycine derivatives,[11] which included tetrahydroisoquinoline-1-carboxylic acids.[12] After many control experiments, reproducible results were obtained when the cyclization step was carried out in 20% hydrochloric acid at room temperature for 72 h under argon in darkness. This mixture was then hydrogenated for 24 h in the presence of 10% Pd/C catalyst (20% w/w) by using hydrogen from a balloon. When a sample of amino acid (+)-**6** {80:20 *er*; $[\alpha]_D^{20}$ = +60.8 (*c* = 1.08, MeOH); m.p. 140–142 °C} was subjected to the Pomeranz–Fritsch–Bobbitt sequence of transformations under the above reaction conditions, the hydrochloride salt of the tetrahydroisoquinoline carboxylic acid, (+)-**1**·HCl, was isolated in 66% yield {$[\alpha]_D^{20}$ = +43.7 (*c* = 1.1, MeOH)} as a hygroscopic foam after evaporation of the filtrate. An additional amount of (+)-**1**·HCl was recovered in 33% yield by washing the catalyst with 20% hydrochloric acid and water, but the sample showed a low the specific rotation value {$[\alpha]_D^{20}$ = +11.2 (*c* = 1.00, MeOH)}. The treatment of (+)-**1**·HCl {$[\alpha]_D^{20}$ = +43.7 (*c* = 1.1, MeOH)} with dilute ammonium hydroxide to pH ≈ 6 deposited (+)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1**). Recrystallization of the crude product from ethanol/water (50:50) afforded **1** as a crystalline compound in 41% yield with 95:5 *er* {$[\alpha]_D^{20}$ = +53.4 (*c* = 0.305, H_2O); m.p. 234.5–235 °C}.

A sample of the dextrorotatory enantiomer (93%*ee*), as described by Fülöp and co-workers,[6] was characterized by $[\alpha]_D^{25}$ = +62 (*c* = 0.30, H_2O), m.p. 265–267 °C, and spectroscopic data. These data were in full accordance with that of our product (+)-**1**.

Conclusions

The diastereoselective total synthesis of (+)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1**, 90%*ee*) was achieved by using a combination of two synthetic methods, that is, the Petasis synthesis of amino acids and the Pomeranz–Fritsch–Bobbitt synthesis of tetrahydro-

isoquinoline derivatives. The stereoselectivity of the synthesis was directed by chiral aminoacetaldehyde acetals **2a**–**2d**, which were used as the amine components of the Petasis reaction. Acetals **2a**–**2d**, which contained chiral *N*-substituents (i.e., α-phenylethyl, α-naphthylethyl, 1-tetrahydronaphthyl, and 1-indanyl groups), were transformed into arylglycine derivatives **5a**–**5d**, which were precursors for the Pomeranz–Fritsch–Bobbitt step of the synthesis. After removal of the nitrogen substituent, the *N*-dealkylated derivative (+)-**6** was subjected to the cyclization/hydrogenolysis procedure to afford the target (+)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1**) in two simple operations.

Experimental Section

General Methods: Melting points were measured with a Kofler block. IR spectra were recorded with a Bruker FT-IR IFS 113V spectrometer. The NMR spectroscopic data were recorded with a Varian Gemini 300 spectrometer, and TMS was used as the internal standard. Mass spectra were recorded with an AMD402 mass spectrometer. Optical rotation data were measured with a Perkin–Elmer polarimeter 242B at 20 °C. Elemental analyses were carried out with a Vario EL III elemental analyzer. Analytical HPLC data were recorded with a Waters HPLC system with a Chiralcel OD-H column and using a flow rate of 0.5 mL/min. Merck DC-Alufolien Kieselgel 60_{254} was used for the TLC analysis, and Kieselgel 60 (70–230 mesh ASTM) was employed for column chromatography. All compounds were purchased from Aldrich Chemical Co. and used as received.

Preparation of Aminoacetaldehyde Acetals 2a–2d. General Procedure: The chiral amine (10 mmol) and dimethoxyacetaldehyde (60 wt.-% solution in water, 3 mL, 20 mmol) were dissolved in benzene (50 mL), and the solution was heated at reflux (Dean–Stark trap) for 3 h. After that time, benzene was evaporated, and the residue was dissolved in methanol (10 mL). The resulting solution was cooled to 0 °C and then treated with $NaBH_4$ (15 mmol). The reaction mixture was stirred at room temperature for 18 h and then treated with water (5 mL) and 20% HCl (5 mL). The resulting mixture was stirred for 1 h. Then, the pH of the solution was adjusted to alkaline by the addition of 20% NaOH. After extraction with diethyl ether, drying over Na_2SO_4 and evaporation of the solvent, product **2** was obtained as a colorless oil, which was purified by bulb-to-bulb distillation.

(*S*)-(–)-(1-Phenylethylamino)acetaldehyde Dimethyl Acetal (2a): (1.96 g, 93% yield). $[\alpha]_D^{20}$ = –33 (*c* = 1.20, $CHCl_3$); ref.[13] $[\alpha]_D^{20}$ = –31 (*c* = 2.09, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3331, 2960, 2831 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36 (d, *J* = 6.7 Hz, 3 H), 2.59 (dABq, *J* = 12.1, 5.4 Hz, 2 H), 3.31 (s, 3 H), 3.35 (s, 3 H), 3.75 (q, *J* = 6.7 Hz, 1 H), 4.43 (t, *J* = 5.4 Hz, 1 H), 7.21–7.34 (m, 5 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.3, 49.0, 53.5, 54.0, 58.3, 103.9, 126.5, 126.9, 128.4, 145.3 ppm. MS (EI): *m*/*z* (%) = 209 (5) $[M]^+$, 194 (26), 178 (13), 134 (85), 105 (90), 75 (100). HRMS: calcd. for $C_{12}H_{19}NO_2$ $[M]^+$ 209.14159; found 209.14114. HPLC (*n*-hexane/*i*PrOH, 98:2): t_R = 11.1 min.

(*S*)-(–)-(1-Naphthylethylamino)acetaldehyde Dimethyl Acetal (2b): (1.95 g, 75% yield); $[\alpha]_D^{20}$ = –33 (*c* = 0.99, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3336, 2959, 2831 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.50 (d, *J* = 6.6 Hz, 3 H), 1.66 (s, which disappeared upon treatment with D_2O, 1 H), 2.66–2.74 (m, 2 H), 3.32 (s, 3 H), 3.36 (s, 3 H), 4.49 (t, *J* = 5.4 Hz, 1 H), 4.64 (q, *J* = 6.6 Hz, 1 H), 7.45–7.53 (m, 3 H), 7.66 (d, *J* = 6.5 Hz, 1 H), 7.74 (d, *J* = 8.2 Hz, 1 H), 7.85–7.88 (m, 1 H), 8.18 (d, *J* = 8.4 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 49.2, 53.5, 53.6, 54.0, 104.0, 122.7, 122.9, 125.3, 125.7, 125.7, 127.2, 128.9, 131.3, 133.9, 140.8 ppm. MS (EI): *m*/*z* (%) = 259 (7) $[M]^+$, 244 (11), 184 (16), 155 (100), 75 (18). HRMS: calcd. for $C_{16}H_{21}NO_2$ $[M]^+$ 259.15723; found 259.15711. HPLC (*n*-hexane/*i*PrOH, 80:20): t_R = 10.50 min.

(*S*)-(+)-[1-(1,2,3,4-Tetrahydronaphthylamino)]acetaldehyde Dimethyl Acetal (2c): Preparation on a 5 mmol scale afforded compound **2c** (0.85 g, 72% yield) as an unstable oil; $[\alpha]_D^{20}$ = +2.97 (*c* = 1.16, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.42 (br. s, which disappeared upon treatment with D_2O, 1 H), 1.71–1.75 (m, 1 H), 1.84–1.88 (m, 2 H), 1.95–1.99 (m, 1 H), 2.72–2.88 (m, 4 H), 3.38 (s, 6 H), 3.78 (t, *J* = 5.0 Hz, 1 H), 4.50 (t, *J* = 5.5 Hz, 1 H), 7.06–7.18 (m, 3 H), 7.32–7.36 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 18.9, 28.3, 29.3, 48.5, 53.7, 53.9, 55.3, 104.2, 125.7, 126.6, 128.7, 129.0, 137.4, 138.9 ppm. MS (EI): *m*/*z* (%) = 235 (7) $[M]^+$, 203 (5), 160 (19), 132 (14), 131 (100), 106 (18), 91 (20), 75 (21). HRMS: calcd. for $C_{14}H_{19}NO_2$ $[M]^+$ 235.15723; found 235.15632. HPLC (*n*-hexane/*i*PrOH, 90:10): t_R = 12.00 min.

***ent*-2c:** $[\alpha]_D^{20}$ = –2.26 (*c* = 1.23, $CHCl_3$). HPLC (*n*-hexane/*i*PrOH, 90:10): t_R = 11.22 min.

(*R*)-(–)-(1-Indanamino)acetaldehyde Dimethyl Acetal (2d): Preparation on a 5 mmol scale afforded compoound **2d** (0.83 g, 75.5% yield); $[\alpha]_D^{20}$ = –23 (*c* = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3320, 2940, 2832 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.52 (br. s, which disappeared upon treatment with D_2O, 1 H), 1.79–1.88 (m, 1 H), 2.34–2.42 (m, 1 H), 2.77–2.85 (m, 3 H), 2.96–3.04 (m, 1 H), 3.38 (s, 3 H), 3.39 (s, 3 H), 4.26 (t, *J* = 6.6 Hz, 1 H), 4.50 (t, *J* = 5.6 Hz, 1 H), 7.17–7.25 (m, 3 H), 7.32–7.35 (m, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 30.3, 33.3, 48.5, 53.7, 54.1, 63.0, 104.2, 124.1, 124.7, 126.1, 127.3, 143.5, 144.8 ppm. MS (EI): *m*/*z* (%) = 221 (4) $[M]^+$, 146 (19), 117 (100), 115 (14), 75 (28). HRMS: calcd. for $C_{13}H_{19}NO_2$ $[M]^+$ 221.14159; found 221.14231. HPLC (*n*-hexane/*i*PrOH, 90:10): t_R = 11.11 min.

Synthesis of Petasis Reaction Products 5a–5d. General Procedure: In a round-bottomed flask, a suspension of 3,4-dimethoxyphenylboronic acid (**3**) and glyoxylic acid monohydrate (**4**) in 1:1 molar ratio in DCM (5 mL/mmol) was stirred at room temperature for 7–10 min under argon, and then aminoacetaldehyde acetal **2** (1 molar equiv.) was added. The clear solution was stirred at room temperature for 72 h. After that time, the inorganic solid precipitate was removed by filtration, and the solvent was removed under reduced pressure. The crude reaction product was triturated with hexane to give amino acids **5** as an inseparable mixture of diastereomers. Attempts to prepare **5** in crystalline form by crystallization or chromatographic purification and separation failed, and the latter resulted in a substantial loss of yield. However, crude compound **5** was pure enough to be used in the next step of the synthesis without further purification. Analytical samples for characterization were prepared by chromatographic purification (silica gel column; DCM/methanol, 100:1 to 100:5).

***N*-2,2-Dimethoxyethyl-*N*-methylbenzyl-2-(3,4-dimethoxyphenyl)-glycine (5a):** Following the general procedure, boronic acid **3**, glyoxylic acid monohydrate (**4**), and aminoacetaldehyde dimethyl acetal **2a** were employed on a 10 mmol scale to afford **5a** (1.90 g, 90% yield, approximately 70:30 *dr*) as a foam. IR (film): $\tilde{\nu}$ = 3412 (br.), 2916, 2848, 1738 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, major isomer, diagnostic area): δ = 1.47 (d, *J* = 6.9 Hz), 3.24 (s), 3.27 (s), 3.78 (s), 3.85 (s), 4.26 (q, *J* = 6.9 Hz), 4.72 (s) ppm. ^1H NMR (300 MHz, $CDCl_3$, minor isomer, diagnostic area): δ = 1.58 (d, *J* = 6.9 Hz),

3.17 (s), 3.26 (s), 3.66 (s), 3.82 (s), 4.39 (q, J = 6.9 Hz), 4.84 (s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7, 16.6, 48.6, 48.7, 53.9, 54.9, 55.1, 55.73, 55.75, 55.79, 55.8, 61.3, 61.4, 66.6, 68.7, 103.2, 103.5, 110.7, 110.9, 112.6, 112.9, 122.0, 122.6, 126.7, 126.8, 127.5, 128.1, 128.2, 128.3, 128.6, 128.7, 140.4, 148.8, 148.9, 149.0, 149.2, 173.0, 173.9 ppm. MS (EI): m/z (%) = 403 (0.7) $[M]^+$, 328 (26), 327 (16), 269 (31), 268 (13), 254 (21), 195 (86), 178 (15), 151 (14), 105.0 (100), 79 (13), 77 (13), 75 (20). HRMS: calcd. for $C_{22}H_{29}NO_6$ $[M]^+$ 403.19949; found 403.19837. HPLC (after derivatization with diazomethane; *n*-hexane/*i*PrOH, 98:2): t_R = 32.64 (minor isomer) and 36.70 min (major isomer).

***N*-2,2-Dimethoxyethyl-*N*-(1-naphthyl)ethyl-2-(3,4-dimethoxyphenyl)glycine (5b):** Following the general procedure, boronic acid **3**, glyoxylic acid monohydrate (**4**), and aminoacetaldehyde dimethyl acetal **2b** were employed on a 0.75 mmol scale to afford **5b** (0.28 g, 83% yield, 79:21 *dr*). IR (KBr): $\tilde{\nu}$ = 3548 (br.), 2936, 2838, 2590 (br.), 1727, 1515 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer, diagnostic area): δ = 1.64 (d, J = 6.8 Hz, 3 H), 2.76–3.01 (m, 2 H), 3.16 (s, 3 H), 3.25 (s, 3 H), 3.87 (s, 3 H), 3.88 (s, 3 H), 4.70 (s, 1 H), 5.02 (q, J = 6.7 Hz, 1 H), 6.79 (d, J = 1.6 Hz, 1 H), 6.85–6.91 (m, 2 H), 7.47–7.62 (m, 4 H), 7.85–7.90 (m, 2 H), 8.42 (d, J = 8.6 Hz, 1 H) ppm. ^{1}H NMR (300 MHz, $CDCl_3$, minor isomer, diagnostic area): δ = 1.71 (d, J = 6.8 Hz, 3 H), 2.63–2.69 (m, 2 H), 3.00 (s, 3 H), 3.01 (s, 3 H), 3.82 (s, 3 H), 4.86 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, major isomer, diagnostic area): δ = 15.5, 50.4, 54.8, 54.8, 55.9, 57.5, 67.5, 103.7, 111.0, 113.1, 122.6, 123.7, 125.1, 125.3, 125.9, 126.3, 127.6, 129.0, 131.7, 134.1, 137.1, 148.9, 149.1, 173.4 ppm. MS (EI): m/z (%) = 422 (4) $[M - 31]^+$, 377 (16), 304 (24), 178 (18), 155 (100), 75 (12). $C_{26}H_{31}NO_6 \cdot 1/2H_2O$ (462.5): calcd. C 67.52, H 6.97, N 3.03; found C 67.28, H 6.67, N 2.94. HPLC (after derivatization with diazomethane; *n*-hexane/*i*PrOH, 98:2): t_R = 36.24 (minor isomer) and 37.82 min (major isomer).

***N*-2,2-Dimethoxyethyl-*N*-[1-(1,2,3,4-tetrahydro)naphthyl]-2-(3,4-dimethoxyphenyl)glycine (5c):** Following the general procedure, boronic acid **3**, glyoxylic acid monohydrate (**4**), and amino acetal **2c** were employed on a 3.4 mmol scale to afford **5c** (quantitative yield, 56:44 *dr*) as a foam. IR (film): $\tilde{\nu}$ = 3425 (br.), 2936, 2836, 2591 (br.), 1727, 1516 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer, diagnostic area): δ = 3.17 (s), 3.23 (s), 3.82 (t, J = 5.2 Hz), 3.84 (s), 3.87 (s), 4.44 (dd, J = 6.2, ~9.0 Hz), 4.72 (s), 7.58 (dd, J = 6.3, 8.9 Hz) ppm. ^{1}H NMR (300 MHz, $CDCl_3$, minor isomer, diagnostic area): δ = 3.29 (s), 3.38 (s), 3.86 (s), 3.87 (s), 4.17 (dd, J = 4.3, 6.2 Hz), 4.25 (dd, J = 6.1, 8.6 Hz), 4.69 (s), 7.51 (d, J = 7.5 Hz) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 22.0, 25.4, 26.2, 29.6, 29.7, 49.0, 50.4, 53.7, 54.8, 54.86, 54.91, 55.82, 55.84, 55.9, 60.2, 62.6, 67.7, 69.2, 103.4, 103.5, 110.7, 111.0, 112.6, 113.1, 122.3, 122.5, 125.9, 126.2, 127.2, 127.5, 128.0, 128.3, 128.8, 129.26, 129.29, 135.6, 135.8, 138.8, 139.4, 148.9, 149.1, 149.2, 173.7, 174.6 ppm. MS (EI): m/z (%) = 429 (1) $[M]^+$, 354 (16), 353 (17), 295 (12), 195 (29), 178 (14), 166 (30), 151 (11), 132 (14), 131 (100), 130 (37), 91 (15), 75 (15). HRMS: calcd. for $C_{24}H_{31}NO_6$ $[M]^+$ 429.21515; found 429.21274. HPLC (after derivatization with diazomethane, *n*-hexane/*i*PrOH, 98:2): t_R = 25.57 (major isomer) and 28.45 min (minor isomer).

***N*-2,2-Dimethoxyethyl-*N*-(1-indanyl)-1-(3,4-dimethoxyphenyl)glycine (5d):** Following the general procedure, boronic acid **3**, glyoxylic acid monohydrate (**4**), and amino acetal **2d** were employed on a 2 mmol scale to give **5d** (quantitative yield, 13:87 *dr*). IR (KBr): $\tilde{\nu}$ = 3437 (br.), 2938, 2836, 2594 (br.), 1727, 1515 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$, major isomer, diagnostic area): δ = 3.27 (s), 3.34 (s), 3.87 (s), 3.89 (s), 4.22 (t, J = 5.0 Hz), 4.67 (dd, J = 6.1, 7.8 Hz), 4.89 (s) ppm. ^{1}H NMR (300 MHz, $CDCl_3$, minor isomer, diagnostic area): δ = 3.19 (s), 3.24 (s), 3.82 (s), 3.86 (s), 4.53 (t, J = 5.6 Hz), 4.78 (dd, J = 6.1, 8.2 Hz), 4.70 (s) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.3, 30.6, 49.2, 54.7, 55.4, 55.8, 55.9, 66.5, 69.6, 103.9, 111.1, 113.1, 123.0, 124.9, 125.0, 126.9, 128.5, 141.3, 143.6, 149.0, 149.3, 172.9 ppm. MS: m/z (%) = 415 (1) $[M]^+$, 340 (14), 339 (12), 281 (28), 195 (33), 178 (11), 118 (12), 117 (100), 115 (14), 75 (14). HRMS: calcd. for $C_{23}H_{29}NO_6$ $[M]^+$ 415.19949; found 415.19746. HPLC (after derivatization with diazomethane; *n*-hexane/*i*PrOH, 98:2): t_R = 28.72 (minor isomer) and 36.93 min (major isomer).

(+)-*N*-2,2-Dimethoxyethyl-2-(3,4-dimethoxyphenyl)glycine (6): Petasis amino acid **5a** (70:30 *dr*) was dissolved in absolute methanol (6 mL/mmol), and the solution was hydrogenated (hydrogen from a balloon) in the presence of the Pearlman's catalyst (20% w/w) at room temperature for 24 h. Then, the catalyst was removed by filtration, and the solvent was evaporated. The crude crystalline product was triturated with hexane to deposit (+)-**6** (85% yield, average value of several experiments; approximately 72:28 *er*). Crystallization of the crude product (2.0 g/22 mL of 96% ethanol) afforded the first crop of almost racemic crystals of **6** (33%), and the second crop contained enantiomerically enriched (+)-**6** (48% yield, approximately 80:20 *er*). HPLC (after derivatization with diazomethane to give *O*,*N*-dimethylated derivative, *n*-hexane/*i*PrOH, 90:10): t_R = 17.96 (major isomer) and 20.49 min (minor isomer). An enantiomerically pure sample of **6** was prepared by repeated crystallizations of enantiomerically enriched fractions by using 96% ethanol; m.p. 141–142 °C. $[a]_D^{20}$ = +85 (c = 1.15, MeOH), >99% *ee*. ^{1}H NMR (300 MHz, $[D_6]$DMSO): δ = 2.53 (dd, J = 12.3, 5.1 Hz, 1 H), 2.66 (dd, J = 12.5, 6.0 Hz, 1 H), 3.24 (s, 3 H), 3.26 (s, 3 H), 3.73 (s, 3 H), 3.74 (s, 3 H), 4.22 (s, 1 H), 4.48 (t, $J \approx$ 5.4 Hz, 1 H), 6.87–6.98 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO/$[D_4]CH_3OH$, 10:1 v/v): δ = 47.4, 53.5, 53.8, 55.5, 55.55, 64.7, 101.9, 111.5, 111.6, 120.6, 129.7, 148.55, 148.6, 171.5 ppm. MS (EI): m/z (%) = 255 (21) $[M - CO_2]^+$, 254 (63), 195 (85), 166 (50), 75 (100). $C_{14}H_{21}NO_6$ (299.32): calcd. C 56.18, H 7.07, N 4.68; found C 55.89, H 6.64, N 4.63. HPLC (after derivatization with diazomethane to give *O*,*N*-dimethylated derivative, *n*-hexane/*i*PrOH, 90:10): t_R = 17.09 min. The *N*-debenzylation of amino acids **5b** and **5d** was carried out under the reaction conditions described above for **5a**. Amino acid **5b** afforded (+)-**6** in 83% yield and 79:21 *er*. Amino acid **5d** afforded (–)-**6** in quantitative yield and 13:87 *er*.

(+)-6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic Acid (1): Compound (+)-**6** (80:20 *er*, 0.46 g, 1.5 mmol) was dissolved in 20% hydrochloric acid (15 mL), and the resulting solution was stirred at room temperature for 72 h under argon in darkness. After that time, the mixture was hydrogenated (hydrogen from a balloon) in the presence of 10% Pd/C (20% w/w) for 24 h. The catalyst was removed by filtration, and the filtrate was concentrated under high vacuum to deposit the hydrochloride salt of the isoquinoline carboxylic acid **1**·HCl (0.28 g, 66% yield) as a hygroscopic foam; $[a]_D^{20}$ = +43.7 (c = 1.1, MeOH). Washing the catalyst with 20% hydrochloric acid and water provided additional amounts of **1**·HCl (0.15 g, 33% yield) as creamy solid; $[a]_D^{20}$ = +11.2 (c = 1.00, MeOH). The **1**·HCl {0.25 g, 0.9 mmol; $[a]_D^{20}$ = +43.7 (c = 1.11, MeOH)} was treated with ammonium hydroxide (25%) that was diluted with chloroform/methanol ($NH_4OH/CHCl_3/CH_3OH$, 0.5:45:4.5 v/v/v) to pH ≈ 6 at room temp. for 30 min. Evaporation of solvents and crystallization of the crude product from ethanol/water (50:50) afforded pure, crystalline (*S*)-(+)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**1**, 0.1 g, 41% yield, 95:5 *er*); $[a]_D^{20}$ = +53.4 (c = 0.305, H_2O), m.p. 234.4–235 °C. ^{1}H NMR (300 MHz, D_2O): δ = 2.99 (t, J = 6.3 Hz, 2 H), 3.44 (td, J = 6.4, 12.7 Hz, 1 H), 3.58 (td, J = 6.3, 12.9 Hz, 1 H), 3.84 (s, 3 H), 3.87 (s, 3 H), 4.86 (s, 1 H), 6.85 (s, 1 H), 7.15 (s, 1 H) ppm. ^{13}C

NMR (75 MHz, D_2O): δ = 27.0, 42.7, 58.5, 58.6, 61.1, 113.4, 114.3, 123.1, 127.3, 149.8, 150.9, 175.0 ppm. MS (EI): *m*/*z* (%) = 237 (1.4) $[M]^+$, 236 (4), 193 (36), 192 (100), 191 (11), 190 (10), 177 (19), 176 (31), 148 (17), 147 (11), 146 (10), 134 (12), 131 (12), 118 (12), 77 (12). HRMS: calcd. for $C_{12}H_{15}NO_4$ $[M]^+$ 237.10011; found 237.09911. HPLC (after derivatization with diazomethane to give *O*,*N*-dimethylated derivative, *n*-hexane/*i*PrOH, 80:20): t_R = 29.17 min.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C NMR spectra of all compounds and HPLC data.

Acknowledgments

This work was supported by a research grant from the National Science Centre, Poland (NCN 2011/01/D/ST5/06627).

[1] M. Chrzanowska, A. Grajewska, Z. Meissner, M. D. Rozwadowska, I. Wiatrowska, *Tetrahedron* **2012**, *68*, 3092–3097.
[2] M. Chrzanowska, A. Grajewska, M. D. Rozwadowska, *Heterocycles* **2012**, *86*, 1119–1127.
[3] a) N. R. Candeias, F. Montalbano, P. M. S. D. Cal, P. M. P. Gois, *Chem. Rev.* **2010**, *110*, 6169–6193; b) R. A. Batey, in: *Boronic Acids* (Ed.: D. G. Hall), Wiley-VCH, Weinheim, Germany, **2008**, p. 279; c) N. A. Petasis, *Aust. J. Chem.* **2007**, *60*, 795–798; d) S. G. Pyne, M. Tang, *Org. React.* **2014**, *83*, 211–498.
[4] a) M. Shamma, L. Moniot, *Isoquinoline Alkaloids Research*, Plenum Press, New York, **1978**; b) K. W. Bentley, *The Isoquinoline Alkaloids*, Harward Academic Publishers, Amsterdam, **1998**; c) M. Chrzanowska, M. D. Rozwadowska, *Chem. Rev.* **2004**, *104*, 3341–3370.
[5] R. M. Williams, J. A. Hendrix, *Chem. Rev.* **1992**, *92*, 889–917.
[6] T. A. Paál, A. Liljeblad, L. T. Kanerva, E. Forró, F. Fülöp, *Eur. J. Org. Chem.* **2008**, 5269–5276.
[7] E. Juaristi, Y. Bandala, *Aldrichimica Acta* **2010**, *43*, 65–78.
[8] a) H. Mandai, K. Murota, S. Suga, *Heterocycles* **2012**, *85*, 1655–1669; b) S. Lou, S. E. Schaus, *J. Am. Chem. Soc.* **2008**, *130*, 6922–6923; c) T. J. Southwood, M. C. Curry, C. A. Hutton, *Tetrahedron* **2006**, *62*, 236–242; d) H. Jourdan, G. Gouhier, L. Van Hijfte, P. Angibaud, R. Piettre, *Tetrahedron Lett.* **2005**, *46*, 8027–8031; e) B. Jiang, M. Xu, *Org. Lett.* **2002**, *4*, 4071–4080; f) B. Jiang, C.-G. Yang, X.-H. Gu, *Tetrahedron Lett.* **2001**, *42*, 2545–2547; g) N. A. Petasis, I. A. Zavialov, *J. Am. Chem. Soc.* **1997**, *119*, 445–446; h) N. A. Petasis, A. Goodman, I. A. Zavialov, *Tetrahedron* **1997**, *53*, 16463–16470.
[9] S. Sugiyama, S. Arai, K. Ishii, *Tetrahedron: Asymmetry* **2004**, *15*, 3149–3153.
[10] J. M. Bobbitt, A. J. Bourque, *Heterocycles* **1987**, *25*, 601–616.
[11] a) R. M. Williams, *Synthesis of Optically Active α-Amino Acids*, Pergamon, Oxford, UK, **1989**; b) R. O. Duthaler, *Tetrahedron* **1994**, *50*, 1539–1650.
[12] a) I. Schuster, A. Sztojkov-Ivanov, L. Lázár, F. Fülöp, *Lett. Org. Chem.* **2007**, 102–108; b) T. A. Paál, E. Forró, A. Liljeblad, L. T. Kanerva, F. Fülöp, *Tetrahedron: Asymmetry* **2007**, *18*, 1428–1433.
[13] F. Corelli, V. Summa, A. Brogi, E. Monteagudo, M. Botta, *J. Org. Chem.* **1995**, *60*, 2008–2015.

Received: September 16, 2014
Published Online: November 27, 2014

