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Organocatalytic asymmetric syntheses of functionalized tetrahydropyridazines

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ABSTRACT

Four tetrahydropyridazines, respectively, substituted at the C-3 position with hydroxymethyl, a silyloxymethyl, a carboxylic acid, and a methyl ester have been prepared in good yields and high enantiomeric purities using organocatalytic α-amination of aldehydes as the key step. These compounds have then been tested as organocatalysts for the same reaction.

1. Introduction

The unsaturated variant of piperazic acid, namely 2,3,4,5-tetrahydropyridazine 3-carboxylic acid ('PCA'),[1] is an interesting structure, which has been found in several bioactive peptides.[2] These peptides have been used in the development of antagonists of bioactive molecules[3] and can be regarded as a conformationally fixed proline equivalent, with the potential to favor a β-turn in a peptide chain.[4] Furthermore, their interest can be explained by their analogy with the parent piperazic acid, a basic structure for bioactive molecule, in which they can be easily reduced.[5–7]

For their preparation, in addition to the possible direct oxidation of saturated to unsaturated piperazic acids when the *N*-2 position is acylated,[1,3] access to the PCA subunit can also be achieved by the cyclization of an α-hydrazino acid or ester intermediate, itself obtained from chiral[7] or prochiral sources.[4,8–14] In these cases, the C-3 stereocenter is introduced by the amination of enolates derived from Evans' chiral auxiliaries,[4,8–11] or by the asymmetric hydrogenation of an α,β-insaturated α-amino ester.[12]

The PCAs with asymmetric carbon atoms at C-3 and C-4 have also been prepared by this methodology: the two consecutive stereocenters are then controlled by a reduction or catalytic hydrogenation of a β-ketoester/electrophilic amination[6,13] tandem reaction, or again by the opening of an epoxide by hydrazine.[14] Stoodley reported an asymmetric hetero Diels–Alder reaction, followed by hydrogenation and then trifluoroacetolysis, leading to PCA with an excellent diastereoselectivity.[15,16] A route to 3-hydroxymethyl-4-hydroxy-2,3,4,5-tetrahydropyridazine, which relies on the aza-Achmatowicz methodology, has also been reported.[17]

In our studies to enlarge upon the range of organocatalysts for the electrophilic α-amination of aldehydes and ketones,[18] we prepared via an organocatalytic way, PCA and three derivatives; the 2,3,4,5-tetrahydropyridazines bearing a 3-hydroxymethyl, a 3-silyloxymethyl, and a 3-methyl ester functionality. Herein, we report the synthesis of these four cyclic hydrazones, and their use as catalysts for the reaction of α-amination of aldehydes.

2. Results and discussion

Organocatalytic electrophilic α-amination of carbonyl compounds is usually performed at room temperature using 10–20 mol% of proline.[19] The syntheses of piperazic acid, pipecolic acid, and proline have been reported starting from functionalized aldehydes.[20,18b] We recently described that 4-*trans*-*t*-butoxy-L-proline could be a useful catalyst for the electrophilic α-amination of carbonyl compounds: the reaction could be run at 0 °C using a low loading of catalyst (5%).[18c]

The 3-*tert*-butyldiphenylsiloxymethyl- and the 3-hydroxymethyltetrahydropyridazine, respectively, **4** and **5**, were prepared using these conditions for the electrophilic amination step (Scheme 1). The amination of 5,5-dimethoxypentanal **1**[21] with di-*t*-butyl azodicarboxylate (DTBAD) in the presence of 5 mol% of 4-*trans*-*t*-butoxy-L-proline at 0 °C followed by a reduction in situ led to the expected hydrazinoalcohol **2** with a yield of 69%. Alcohol **2** was protected as its *t*-butyldiphenylsilyl ether to give **3** with a good yield of 89%. At this stage, the enantiomeric excess was measured by HPLC analysis using a Chiralpak AD-H column (ee = 97%). Compound **3** was transformed into the hydrazone **4** upon treatment with trifluoroacetic acid in dichloromethane and cyclization of the intermediate hydrazine in an aqueous medium: **4** was then isolated in 70% yield. The treatment of **4** with tetra-*n*-butylammonium fluoride removed the silyl ether to give 3-hydroxymethyl tetrahydropyridazine **5** in 96% yield.

We then obtained carboxylic acid **8** and its methyl ester derivative **9** (Scheme 2). The hydrazinoaldehyde **6** was prepared from **1** as previously reported and engaged in two different ways. In the first one, the oxidation of **6** with potassium permanganate followed by the cyclization of the intermediate afforded tetrahydropyridazine carboxylic acid **8** in very good yield (95% for the two steps). In the second method, aldehyde **6** was oxidized, and the intermediate was esterified to give compound **7** in 89% yield. Deprotection of the *t*-butylcarbamates, and cyclization in water

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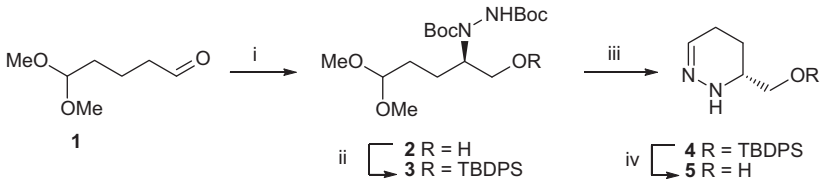
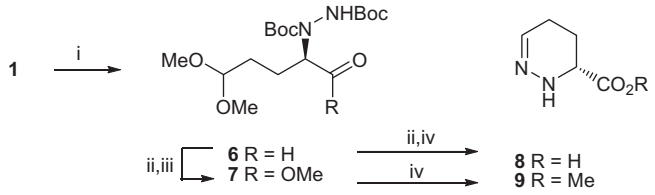


Scheme 1. Synthesis of compounds **4** and **5**. Reagents and conditions: (i) (a) *trans*-4-*tert*-butoxy-L-proline (5 mol%), DTBAD, DCM, 0 °C; (b) $NaBH_4$, EtOH, 0 °C; 69%; (ii) TBDPSCl, Im., DMF, 50 °C; 89%, ee = 97%; (iii) (a) TFA/DCM (1/1), 40 °C; (b) H_2O/MeOH (1/1); 70%; (iv) TBAF, THF; 96%.



Scheme 2. Synthesis of compounds **8** and **9**. Reagents and conditions: (i) *trans*- 4-*tert*-butoxyproline (5 mol%), DBAD, DCM, 0 °C; 80%; (ii) NaH_2PO_4 1 M, $KMnO_4$ 1 M, *t*-BuOH; (iii) $TMSCHN_2$, Tol/MeOH (3/1); 89% (2 steps); (iv) (a) TFA, 40 °C; (b) H_2O; **8**: 95% (2 steps); **9**: 72%.

gave tetrahydropyridazine methyl ester **9** in 72% yield. The physical properties of compounds **8** and **9** are in agreement with those described in the literature of their enantiomers.[8–11,15,16]

Next, we tested the four tetrahydropyridazines as catalysts for the electrophilic amination reaction. To the best of our knowledge, only the use of amines has been reported and hydrazones have never been tried due to the poor nucleophilicity of the secondary nitrogen atom.[1] However, the structure of the tetrahydropyridazine ring could be interesting in a catalytic mechanism.

The compounds **4**, **5**, **8**, and **9** were screened as catalysts for the enantioselective α-amination of two aldehydes; 6,6-dimethoxyhexanal **10** and the 5,5-dimethoxypentanal **1**. In all cases, the aldehydes were treated with DBAD in the presence of 10 mol % of catalyst in dichloromethane and at room temperature and were directly reduced in situ with sodium borohydride in ethanol at 0 °C. After purification by chromatography on silica gel, the enantiomeric ratios were determined by chiral HPLC analysis.

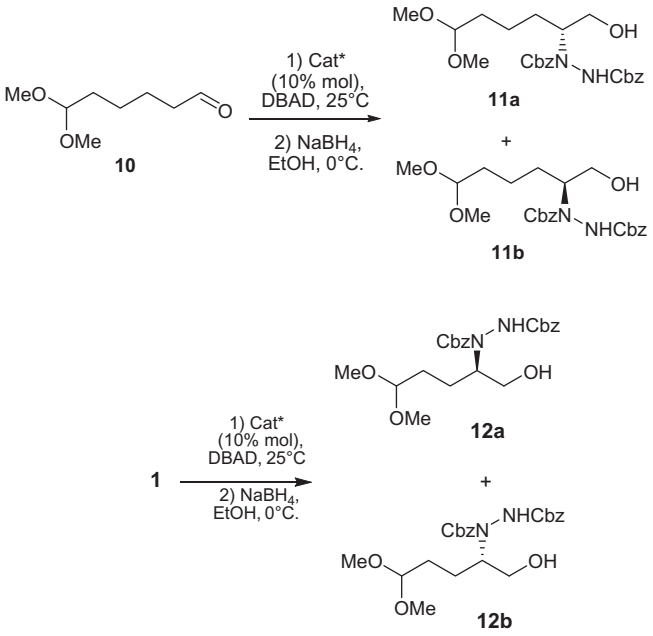
The four chiral tetrahydropyridazines were initially screened as catalysts for the amination–reduction of aldehyde **10**, leading to the hydrazino derivatives (*R*)-**11a** and/or (*S*)-**11b** (Scheme 3).[18b] The results are summarized in the Table 1.

Table 1
Formation of the hydrazino alcohols **11a** and **11b** from **10**

Entry	Catalyst	Time (h)	Yield	**11a**/**11b**[a]	ee (%)
1	**4**	2.5	55	82/18	64
2	**5**	21	11	64.5/35.5	29
3	**8**	3	45	46/54	8
4	**9**	21	53	71/29	42

[a] Determined by HPLC in a Chiralpak AD-H column. Eluant heptane/*i*-PrOH (90:10) + 0.2% TFA; flow 0.5 mL/min; λ = 260 nm; T = 25 °C; t_r(**11b**) = 52.07 min; t_r(**11a**) = 55.31 min.

The use of tetrahydropyridazine **4** led mainly to **11a** with 55% yield and an enantiomeric ratio of 82/18 for **11a**/**11b** after 2.5 h (entry 1). It is interesting to note that a longer reaction time (21 h) gave similar values. The selectivity could be explained with the model described by Houk, where steric hindrance is the main promoter of the stereoselectivity.[22] In this case, the bulky *t*-butyldiphenylsilyl ether group prevents the approach of the electrophile DBAD on the same face and the new C–N bond is formed on the opposite face to preferentially induce an (*R*)-configuration for the product. The use of 3-hydroxymethyl tetrahydropyridazine **5** led to the same major enantiomer with a poor yield and with no significant enantioselectivity (entry 2). We attempted to reverse the enantiomeric ratio to obtain **11b** as the major enantiomer using the catalyst bearing a carboxylic acid **8**. In this case, the selectivity should be controlled by the formation of a hydrogen bond between the carboxylic acid and the electrophile.[22] The reaction was run for 3 h in dichloromethane (entry 3). The yield was moderate (45%) and a weak inversion of the enantiomeric ratio was observed (**11a**/**11b**: 46/54). No significant improvement was observed when changing the solvent. Finally, catalyst **9** led mainly to compound **11a** with an acceptable yield and an enantiomeric ratio of 71/29 (entry 4).



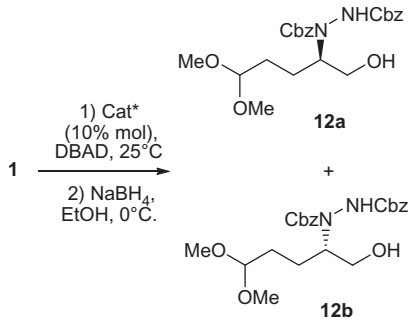
Scheme 3.

From these first assays, silyloxymethyl tetrahydropyridazine **4** was shown to be an efficient catalyst. We tested it for the electrophilic amination of **1** with DBAD, followed by the in situ reduction, giving (*R*)-**12a** and/or its enantiomer (*S*)-**12b** (Scheme 4). The main results with catalyst **4** are summarized in Table 2.

Table 2
α-Amination of **1** in the presence of the catalyst **4**

Entry	Time (h)	Yield	**12a**/**12b**[a]	ee (%)
1	2.5	7	93/7	86
2	6.5	44	85/15	70
3	24	69	85/15	70

[a] Determined by HPLC in a Chiralpak AS-H column. Eluant heptane/*i*-PrOH (90:10); flow 0.8 mL/min; λ = 260 nm; t_r(**12b**) = 20.9 min; t_r(**12a**) = 53.6 min.



Scheme 4.

After 2.5 h of reaction, derivative **12a** was obtained as the major enantiomer (**12a**/**12b:** 93/7, entry 1). Nevertheless, the yield was very low (7%). Increasing the reaction time increased the yield to 69% with a small decrease in the enantiomeric ratio (**12a**/**12b**: 85/15, entries 2 and 3).

3. Conclusion

In conclusion, we have prepared four 3-functionalized tetrahydropyridazines **4**, **5**, **8**, and **9** in very good overall yields with short stereoselective synthetic sequences. The organocatalytic α-hydrazination of the aldehyde in the presence of *trans*-4-*t*-butoxy-L-proline allowed the control of the newly created stereogenic aminated center. The obtained tetrahydropyridazine derivatives have been screened as organocatalysts for the electrophilic α-amination of aldehydes. In particular, the 3-silyloxymethyl tetrahydropyridazine **4** promoted the direct asymmetric α-amination of aldehydes with azodicarboxylate with good yields and enantioselectivities. Further developments are currently in progress.

4. Experimental

4.1. General

Solvents were distilled according to *Purification of Laboratory Chemicals*, 4th Ed., W.L.F. Aramarego and D.D. Perrin, Butterwoth Heinemann, 1996. Flash chromatography was performed on silica gel chromagel 60 ACC 35–70 μm. Analytical TLC was performed using aluminum-backed silica gel Merck 60 F_{254} and was visualized by UV radiation (254 nm) and/or a solution of phosphomolybdic acid in MeOH and heating. Optical rotations were measured at 25 °C on a Perkin-Elmer 241 polarimeter (1 dm cell) using a sodium lamp as the light source (589 nm). NMR spectra were recorded on a Brucker AC 200 or Avance 300 apparatus with chemical shift values (δ) in ppm downfield from tetramethylsilane. Infrared spectra were recorded on a Nicolet OPUS IR (impact 400D) spectrophotometer. Melting points were performed with a Büchi B-545 apparatus. Mass spectra were obtained on a HP MS 5989B spectrometer. Analytical HPLC was performed on a Jasco LC-NetII/ADC with Chiralpak AD-H, AS-H, or OD-H columns (0.46 × 25 cm). Microanalyses were performed by the Service de Microanalyse of ICSN, Gif-sur-Yvette, France. HRMS were performed by the Service de Spectrométrie de Masse of ICSN, Gif-sur-Yvette, France.

4.2. General procedure for the α-amination of aldehydes

To a solution of aldehyde (0.68 mmol, 1.5 equiv) and catalyst (5% or 10 mol %) in CH_2Cl_2 (2 mL) was added di-*t*-butyl azodicarboxylate (1.0 equiv) or dibenzylazodicarboxylate (1.0 equiv) at 0 °C. After 14 h at 0 °C, the mixture was treated with EtOH (2 mL) and $NaBH_4$ (26 mg, 0.68 mg) and was stirred for 15 min at 0 °C. The reaction was quenched with aqueous saturated NH_4Cl (2 mL), and extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel to provide the α-hydrazino alcohol. For physical analysis of derivatives **11** and **12**, see the literature.[18b,c]

4.3. (*R*)-2-(*N*,*N*′-Di-*tert*-butoxycarbonylhydrazino) 5′,5′-dimethoxypentanol 2

The general procedure of the α-amination was applied to 5,5-dimethoxypentanal[22] (100 mg, 0.68 mmol) in the presence of *trans*-4-*t*-butoxy-L-proline (5 mol %), and DTBAD followed by the classical treatment and a purification with (CH_2Cl_2/EtOAc: 5:1) as eluant gave the α-hydrazino alcohol **2** as a white solid in 69% isolated yield. mp: 124 °C; R_f = 0.14 (CH_2Cl_2/EtOAc: 5:1); $[\alpha]_D^{25} = -4$ (*c* 1.1, MeOH); IR (KBr): $\tilde{\nu}_{max}$ = 3396, 2980, 2935, 2832, 2520, 2366, 1706 cm^{-1}; ^1H NMR (300 MHz, CD_3OD, 25 °C): δ = 1.18–1.74 (m, 22 H, 3′-H, 4′-H and *t*Bu), 3.28–3.35 (m, 6 H, 2 OCH_3), 3.36–3.51 (m, 2 H, 1′-H), 4.16 (br s, 1 H, 2′-H), 4.37 (t, 1 H, *J* = 5.6 Hz, 5′-H) ppm; ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 23.9 (3′-C), 28.5 ($C(CH_3)_3$), 30.0 (4′-C), 49.0 and 49.6 (OCH_3), 59.1 (2′-C), 63.1 (1′-C), 82.3 and 82.6 ($C(CH_3)_3$), 106.0 (5′-C), 157.4 (CO) ppm; MS (ESI): *m*/*z* 401 $[M+Na]^+$; Calcd for $C_{17}H_{34}N_2O_7$ (378.46): C, 53.95; H, 9.06; N, 7.40. Found: C, 54.02; H, 9.11; N, 7.05.

4.4. (*R*)-1-*tert*-Butyldiphenylsilyl-2-(*N*,*N*′-di-*tert*-butoxycarbonylhydrazino) 5′,5′-dimethoxypentanol 3

To a solution of alcohol **2** (155 mg, 0.41 mmol) in DMF (2 mL) were added imidazole (84 mg, 1.23 mmol) and *t*-butylchlorodiphenylsilane (133 μL, 0.51 mmol). The reaction mixture was heated to 50 °C for 14 h. After cooling, the solution was hydrolyzed with aqueous saturated NH_4Cl (2 mL) and extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc: 5:1) to give **3** as a yellow oil in 89% isolated yield and 97% ee. R_f = 0.71 (CH_2Cl_2/EtOAc: 5:1); $[\alpha]_D^{25} = +11$ (*c* 1.2, MeOH); IR (NaCl): $\tilde{\nu}_{max}$ = 3355, 3068, 2970, 2919, 2377, 1962, 1890, 1747, 1710, 1588 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.05 (s, 9H, *t*Bu), 1.15–2.00 (m, 22H, 3′-H, 4′-H and *t*Bu), 3.29 (s, 6H, 2OCH_3), 3.45–3.69 (m, 2H, 1′-H), 4.03–4.47 (m, 2H, 2′-H and 5′-H), 5.63 (br s, 1H, NH), 7.32–7.50 (m, 6H, Ar), 7.58–7.71 (m, 4H, Ar) ppm; ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 20.0 ($SiC(CH_3)_3$), 24.3 (3′-C), 27.4 and 28.6 ($C(CH_3)_3$ and $SiC(CH_3)_3$), 30.2 (4′-C), 53.4 (OCH_3), 59.3 (2′-C), 65.4 (1′-C), 81.4 and 82.0 ($C(CH_3)_3$), 106.1 (5′-C), 128.8, 131.0, 134.6 and 136.7 (Ar), 157.1, 158.0 (CO) ppm; MS (ESI): *m*/*z* 639 $[M+Na]^+$; Calcd for $C_{33}H_{52}N_2O_7Si$ (616.86): C, 64.25; H, 8.50; N, 4.54. Found: C 63.46; H, 8.59; N, 4.43; the ee was determined by chiral HPLC using Chiralpak AD-H column (heptane/*i*-PrOH = 96:4 + TFA 0.3%, flow rate 0.2 mL/min; λ = 260 nm), t_r [(*R*)-**2**] = 67.0 min; t_r [(*S*)-**2**] = 55.0 min.

4.5. (*R*)-3-((*tert*-Butyldiphenylsilyloxy) methyl)-2,3,4,5-tetrahydropyridazine 4

Trifluoroacetic acid (2 mL) was added dropwise to a solution of silyl ether **3** (88 mg, 0.14 mmol) in CH_2Cl_2 at 0 °C. After 15 min at 40 °C, the excess trifluoroacetic acid and solvent were removed under reduced pressure. The obtained residue was dissolved in a 1:1 mixture of MeOH/H_2O (4 mL). After 15 min at room temperature, the solution was adjusted to pH 9 with aqueous ammonia. The mixture was then extracted with Et_2O (3 × 2 mL). The combined organic layer was washed with brine, dried with Na_2SO_4, filtered,

and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc: 5:1) to provide **4** as a yellow oil in 70% isolated yield. R_f = 0.31 (CH_2Cl_2/EtOAc: 5:1); $[\alpha]_D^{25} = -13$ (*c* 1.2, MeOH); IR (NaCl): $\tilde{\nu}_{max}$ = 3380, 3334, 3068, 2976, 2930, 2853, 1962, 1890, 1824, 1624, 1588 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.07 (s, 9H, *t*Bu), 1.33–1.83 (m, 2H, 4-H), 1.97–2.40 (m, 2H, 5-H), 3.10–3.32 (m, 1H, 3-H), 3.55–3.69 (m, 2H, CH_2OSi), 6.77 (br s, 1H, 6-H), 7.32–7.43 (m, 6H, Ar), 7.56–7.83 (m, 4H, Ar) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 19.2 ($C(CH_3)_3$), 21.5 and 23.0 (4-C and 5-C), 26.8 ($C(CH_3)_3$), 52.8 (3-C), 66.3 (CH_2OSi), 127.8, 129.8, 133.2 and 135.5 (Ar), 140.5 (6-C) ppm; MS (ESI): *m*/*z* 375 $[M+Na]^+$; HRMS (ESI) Calcd for $C_{21}H_{28}N_2OSi$, 375.1869; found, 375.1880.

4.6. (*R*)-3-Hydroxymethyl-2,3,4,5-tetrahydropyridazine 5

To a solution of **4** (31 mg, 0.09 mmol) in THF (1 mL) at 0 °C was added TBAF 1 M in THF (0.26 mL, 0.26 mmol). After 1 h at room temperature, the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (EtOAc/MeOH: 9:1) to give **5** as a yellow oil in 96% isolated yield. R_f = 0.45 (EtOAc/MeOH: 1:1); $[\alpha]_D^{25} = -127$ (*c* 1.0, MeOH); IR (NaCl): $\tilde{\nu}_{max}$ = 3329, 2930, 2853, 1665, 1634 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.57–1.93 (m, 2H, 4-H), 1.97–2.40 (m, 2H, 5-H), 3.03–3.24 (m, 1H, 3-H), 3.28–3.78 (m, 3H, CH_2OH), 6.77 (br s, 1H, 6-H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 21.3 and 23.0 (4-C and 5-C), 52.7 (3-C), 64.6 (CH_2OSi), 141.0 (6-C) ppm; MS (ESI): *m*/*z* 137 $[M+Na]^+$; HRMS (ESI) calcd for $C_5H_{10}N_2O$, 137.0691; found, 137.0686.

4.7. (*R*)-2-(*N*,*N*′-Di-*tert*-butoxycarbonylhydrazino) 5′,5′-dimethoxypentanal 6

To a solution of 5,5-dimethoxypentanal[22] **1** (100 mg, 0.68 mmol) and *trans*-4-*t*-butoxy-L-proline (4 mg, 0.02 mmol) in CH_2Cl_2 (2 mL) was added di-*t*-butyl azodicarboxylate (105 mg, 0.46 mmol) at 0 °C. After 14 h at 0 °C, the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc: 5:1) to provide the α-hydrazino aldehyde **6** as an oil in 80% isolated yield. R_f = 0.27 (CH_2Cl_2/EtOAc: 9:1); IR (NaCl): $\tilde{\nu}_{max}$ = 3283, 2970, 2930, 2832, 1736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.42 (s, 18H, *t*Bu), 1.54–2.13 (m, 4H, 3′-H and 4′-H), 3.28 (s, 6H, $2OCH_3$), 4.12–4.62 (m, 2H, 2′-H and 5′-H), 6.58 (br s, 1H, NH), 9.63 (br s, 1H, CHO) ppm; MS (ESI): *m*/*z* 399 $[M+Na]^+$.

4.8. (*R*)-Methyl 2-(*N*,*N*′-di-*tert*-butoxycarbonylhydrazino) 5′,5′-dimethoxypentanoate 7

To a solution of hydrazino aldehyde **6** (265 mg, 0.71 mmol) in *t*-butanol (4 mL) was added an aqueous solution of NaH_2PO_4 (1 M, 4.0 mL, 0.40 mmol) followed by an aqueous solution of $KMnO_4$ (1 M, 4.0 mL, 0.40 mmol). After stirring for 1 min, the excess $KMnO_4$ was quenched with an aqueous solution of Na_2SO_3 (4 mL). The reaction mixture was then cooled to 0 °C, and the solution was adjusted to pH 3 with aqueous HCl 1 M. The mixture was then extracted with EtOAc (3 × 20 mL). The combined organic layers were successively washed with water and brine, dried with Na_2SO_4, filtered, and concentrated in vacuo. The obtained crude hydrazino acid was dissolved in a 3:1 mixture of Tol/MeOH (8 mL), and (trimethylsilyl)diazomethane was added (668 μL, 1.34 mmol). After stirring for 10 min at room temperature, acetic acid was added until no more gas formation was observed. The solvent was then removed under reduced pressure, and the obtained crude product was purified by column chromatography on silica gel (CH_2Cl_2/EtOAc: 5:2) to give hydrazino ester **7** as a colorless oil in 89% isolated yield. R_f = 0.77 (CH_2Cl_2/EtOAc: 2:1); $[\alpha]_D^{25} = +26$ (*c* 1.0, MeOH); IR (NaCl): $\tilde{\nu}_{max}$ = 3319, 2980, 2930, 2827, 2351, 1742, 1706 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 1.44 (s, 18H, *t*Bu), 1.60–2.07 (m, 4H, 3′-H and 4′-H), 3.29 (s, 6H, $2OCH_3$), 3.69 (s, 3H, CO_2CH_3), 4.22–4.43 (m, 1H, 5′-H), 4.46–4.94 (m, 1H, 2′-H), 6.31 (br s, 1H, NH) ppm; ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 23.7 (3′-C), 28.1 ($C(CH_3)_3$), 29.0 (4′-C), 52.3 and 52.7 (OCH_3), 52.7 (CO_2CH_3), 59.5 (2′-C), 80.7 and 82.0 ($C(CH_3)_3$), 104.3 (5′-C), 154.9 and 155.6 (CO), 172.4 (CO_2CH_3) ppm; MS (ESI): *m*/*z* 429 $[M+Na]^+$; Calcd $C_{18}H_{34}N_2O_8$ (406.47): C, 53.19; H, 8.43; N, 6.89. Found: C, 53.67; H, 8.47; N, 6.52.

4.9. (*R*)-2,3,4,5-Tetrahydropyridazine-3-carboxylic acid 8

To a solution of hydrazino aldehyde **6** (56 mg, 0.15 mmol) in *t*-butanol (1 mL) was added an aqueous solution of NaH_2PO_4 (1 M, 0.8 mL, 0.80 mmol) followed by an aqueous solution of $KMnO_4$ (1 M, 0.8 mL, 0.80 mmol). After stirring for 1 min, the excess of $KMnO_4$ was quenched with an aqueous solution of Na_2SO_3 (1 mL). The reaction mixture was then cooled to 0 °C, and the solution was adjusted to pH 3 with aqueous HCl (1 M). The mixture was then extracted with EtOAc (3 × 5 mL). The combined organic layers were successively washed with water and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The obtained crude product was dissolved in CH_2Cl_2 (1 mL) at 0 °C and trifluoroacetic acid (1 mL) was added dropwise. After 15 min at 40 °C, the excess trifluoroacetic acid and the solvent were removed under reduced pressure. The obtained residue was dissolved in H_2O (1 mL). After 15 min at room temperature, the solvent was removed under reduced pressure. $[\alpha]_D^{25} = -59$ (*c* 1.0, MeOH), lit[15,16]: +62 (0.3%; MeOH; enantiomer). The resulting salt was eluted on Dowex 50W-X4 ion exchange column (NH_4OH 1*M*) to give **8** as a yellow oil in 95% isolated yield; IR (KBr): $\tilde{\nu}_{max}$ = 3365, 2935, 1593 cm^{-1}; ^1H NMR (200 MHz, D_2O, 25 °C): δ = 1.79–2.44 (m, 4H, 4-H and 5-H), 3.63 (dd, 1H, *J* = 8.0 Hz and *J* = 3.8 Hz, 3-H), 7.04 (s, 1H, 6-H) ppm; ^{13}C NMR (75 MHz, D_2O, 25 °C): δ = 20.3 and 20.4 (4-C and 5-C), 54.8 (3-C), 149.9 (6-C), 177.2 (CO) ppm; MS (ESI): *m*/*z* 151 $[M+Na]^+$; HRMS (ESI) calcd for $C_5H_8N_2O_2$, 151.0483; found, 151.0490.

4.10. (*R*)-Methyl 2,3,4,5-tetrahydropyridazine-3-carboxylate 9

Trifluoroacetic acid (2 mL) was added dropwise to a solution of hydrazino ester **7** (84 mg, 0.21 mmol) in CH_2Cl_2 (2 mL) at 0 °C. After 15 min at 40 °C, the excess trifluoroacetic acid and solvent were removed under reduced pressure. The obtained residue was dissolved in H_2O (2 mL). After 15 min at room temperature, the reaction mixture was concentrated in vacuo. The crude product was purified by column chromatography on silica gel with EtOAc in the presence of triethylamine (2%) to provide **9** as a yellow oil in 72% isolated yield. R_f = 0.40 (EtOAc); $[\alpha]_D^{25} = -67$ (*c* 0.9, MeOH), lit[8,9]: +139 (*c* 0.8, MeOH; enantiomer), lit[16]: +86 to +124 (MeOH; enantiomer): the authors established the complete dissociation between the specific rotation and enantiomeric purity; IR (NaCl): $\tilde{\nu}_{max}$ = 3370, 2971, 2930, 2863, 1742 cm^{-1}; ^1H NMR (200 MHz, CD_3OD, 25 °C): δ = 1.90–2.37 (m, 4H, 4-H and 5-H), 3.74 (s, 3H, CO_2CH_3), 3.78–3.91 (m, 1H, 3-H), 6.69 (s, 1H, 6-H) ppm; ^{13}C NMR (75 MHz, CD_3OD, 25 °C): δ = 22.2 and 22.8 (4-C and 5-C), 52.7 and 54.5 (3-C and CO_2CH_3), 141.6 (6-C), 173.7 (CO) ppm; MS (ESI): *m*/*z* 165 $[M+Na]^+$; HRMS (ESI) calcd for $C_6H_{10}N_2O_2$, 165.0640; found, 165.0644.

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