Tetrahedron: *Asymmetry* 22 (2011) 1320–1324

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

2-Hydroxy-3-[(*S*)-prolinamido]pinanes as novel bifunctional organocatalysts for asymmetric aldol reactions in aqueous media

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ARTICLE INFO

Article history:
Received 16 May 2011
Accepted 14 July 2011
Available online 11 August 2011

ABSTRACT

Novel (*S*)-prolinamides with stereoisomeric 2-hydroxy-3-aminopinane units have been synthesized. In the presence of (1*R*,2*R*,3*S*,5*R*)-2-hydroxy-3-[(*S*)-prolinamido]pinane (5 mol %) cyclic ketones reacted with (hetero-)aromatic aldehydes in aqueous media to afford chiral aldols in high yields. The reaction had moderate to high diastereo- (dr up to 91/9) and enantioselectivities (up to 83% ee).

1. Introduction

Asymmetric organocatalysis is a rapidly growing area of modern organic chemistry.[1] One of the most important organocatalytic transformations is the asymmetric aldol reaction,[2a–d] which is used for the synthesis of chiral natural compounds and pharmacologically active substances.[2e,f] Natural or synthetic α-amino acids,[3a] their amides,[3b] β-amino acids,[3c–e] alkaloid,[3f,g] 1,2-diaminocyclohexane,[3h–j] or imidazolidinone[3k] derivatives and some other chiral organic compounds[3l] are suitable catalysts for this reaction. Among them, prolinamides bearing β-aminoalcohol units provide a high-level of catalytic activity and selectivity due to the hydroxyl group being able to generate an additional stereocontrolling hydrogen bond in the enamine transitional state (bifunctional catalysis).[4] Prolinamide derivatives incorporating β-aminoalcohol fragments of natural origin (e.g., aminocarbohydrate units[5a,b]) are generally inferior to their synthetic analogues (e.g., to *N*-prolyl α,α-diphenylvalinole[5c]) in terms of activity and/or selectivity, which may be attributed to their conformational flexibility and/or specific solvation affects.[5d,5e] Some effective *N*-prolyl-β-hydroxyamine catalysts have been obtained from chiral α,β-diols.[5f]

We assumed that chiral *N*-prolyl-β-hydroxyamines with a natural rigid polycyclic skeleton would efficiently catalyze asymmetric aldol reactions. Furthermore, one might expect that their catalytic properties would depend on the orientation (*syn* or *anti*) of the amido and hydroxy groups in the catalyst. 2-Hydroxypinan-3-ones (+)-**1** and (−)-**1** readily available from softwood pitch may serve as convenient building-blocks for their synthesis. 2-Hydroxypinan-3-one derivatives have been used as chiral auxiliaries in the asymmetric synthesis of α-substituted benzylamines,[6a] 2-amino-2-phenylethanol,[6b] γ-fluorinated α-aminoacids,[6c] (*S*)-dolaphenine,[6d] as well as chiral ligands in catalytic cyclopropanation[6e] or hydrogenation reactions.[6f] However, prolinamides containing β-hydroxypinane unit have not been reported so far.

2. Results and discussion

To verify this hypothesis, we synthesized isomeric 2-hydroxy-3-aminopinanes **2a–d** from 2-hydroxypinan-3-one antipodes (+)-(**1**) and (−)-(**1**) by known procedures[6f,7] and converted them into the N-protected amides **4a–d** via treatment with (*S*)-Cbz-proline **3** in the presence of a $ClCO_2Et/Et_3N$ system. The catalytic deprotection of **4a–d** afforded isomeric prolinamides **5a–d** with different orientations of the hydroxy and amido groups (*syn*- or *anti*-) and different absolute configurations of the four stereocenters in the pinane fragment (Scheme 1).

At first, we compared the catalytic properties of amides **5a–d** in the model reaction between cyclohexanone **6a** and 4-nitrobenzaldehyde **7a** in the presence of water (90 equiv) which has been widely used over the last decade as an environmentally friendly medium in an organic synthesis.[8] The reactions were carried out for twenty hours at ambient temperature in the presence of a catalyst (5 mol %); the molar ratio of the reagents **6a**/**7a** was 3:1. Under these conditions, the reactions ran with a high conversion (92–98%) affording *anti*-diastereomeric aldol **8a** as the major product. The best diastereo- (*anti*/*syn* 91:9) and enantioselectivities (ee *anti*-**8a** 78%) were obtained in the presence of prolinamide **5b** containing the (1*R*,2*R*,3*S*,5*R*)-2-hydroxy-3-aminopinane unit (Table 1). We assumed that catalyst **5b**, which has *syn*-orientated NH– and OH– groups, had more efficient hydrogen bonding with the aldehyde oxygen atom in the transition state than isomeric compounds **5a**,**c**,**d**, thus lowering its energy.

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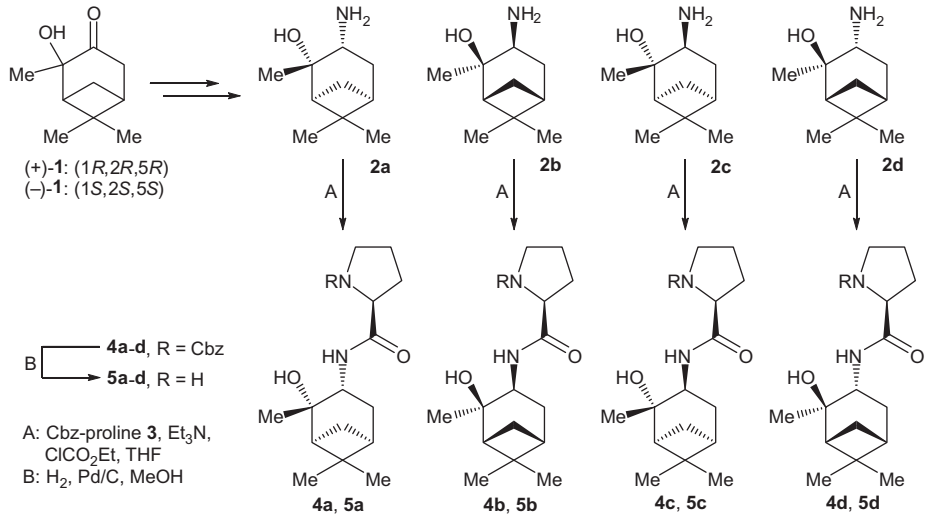
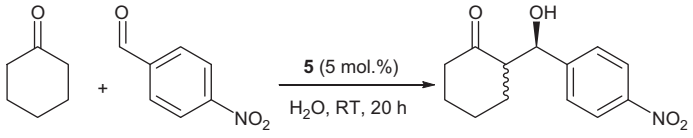
doi:10.1016/j.tetasy.2011.07.013



Scheme 1. Synthesis of 2-hydroxy-3-[(*S*)-prolinamino]pinanes **5a**–**d** from 2-hydroxypinane-3-ones (+)-**1** and (−)-**1**.

Table 1
Asymmetric aldol reaction between cyclohexanone **6a** and 4-nitrobenzaldehyde **7a** in the presence of amides **5a**–**d** in aqueous media[a]



6a **7a** **8a**

Entry	**5**	Conv.[b] (%)	dr (*anti*/*syn*)[b]	ee (*anti*/*syn*)[c]
1	**a**	94	84/16	64/30
2	**b**	98	91/9	78/18
3	**c**	92	86/14	57/14
4	**d**	96	85/15	72/38

[a] Reactions were carried out on a molar ratio of 3:1 (**6a**/**7a**) in the presence of water (0.09 mL, 90 equiv).
[b] ^{1}H NMR data for crude **8a**.
[c] Chiral HPLC data.

Next, in order to optimize the reaction conditions, we studied the amide **5b**-catalyzed reaction between **6a** and **7a** at rt in various solvents (THF, PhMe, DMSO, MeCN, EtOH, $CHCl_3$) and under neat conditions (Table 2). In most cases, the conversion was close to complete, however, in DMSO it was only 71%, which was in accordance with the reported data on the lower activity of some prolinamides or thioprolinamides in a DMSO solution[9] (entry 4). The highest *dr* (*anti*/*syn* 91:9) and ee values of product **8a** (78%) were obtained in aqueous media (entry 8). Furthermore, we succeeded in improving the ee value up to 80–83% by carrying out the reaction in the presence of benzoic (entry 10) or 4-nitrobenzoic acid (entry 11) additives (5 mol %). Reducing the amount of water to 45 or 22 equiv slightly diminished the ee of **8a** (entries 12 and 13).

Various cyclic or heterocyclic ketones **6a**–**d** reacted with aromatic (heteroaromatic) aldehydes **7a**–**e** under optimal conditions and generated the respective aldols **8a**–**f** with enantioselectivities of 62–80% ee (Table 3). In general, the yields of products **8** were high. 2-Thienylcarboxaldehyde was less active under the conditions studied and the yield of product **8f** after 120 h did not exceed 54% (entry 6). Six-membered cyclic or heterocyclic ketones **6a**,**c**,**d** predominantly afforded the *anti*-diastereomers of the corresponding aldols **8a**,**b**,**d**,**f** (*anti*/*syn* 78:22–91:9), however, cyclopentanone **6b** gave the *syn*-diastereomer of aldol **8c** as the major product (*anti*/*syn* 32/68). In general, aldol reactions in the presence of catalyst **5b** afforded the respective aldols in an aqueous environment in higher yields but with somewhat lower enantioselectivities than the corresponding reactions promoted by the most efficient β-aminoalcohol-derived proline amide catalysts. Proline itself and the majority bearing carboxyl group water-soluble derivatives efficiently catalyzed the aldol reactions in organic solvents but exhibited poor catalytic properties in the presence of water.[10]

3. Conclusion

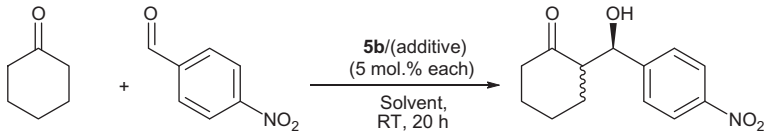
In conclusion, we have for the first time synthesized (*S*)-prolinamides bearing stereoisomeric 2-hydroxy-3-aminopinane units and shown that in the presence of (1*R*,2*R*,3*S*,5*R*)-2-hydroxy-3-[(*S*)-prolinamido]pinane **5b** cyclic ketones react with (hetero-)aromatic aldehydes in aqueous media to afford their respective aldols in high yields. The reaction took place with moderate to high diastereo- and enantioselectivities. Research aimed at novel efficient organocatalysts and ligands based on plant-derived chiral β-aminoalcohols is currently underway in our laboratory.

4. Experimental

4.1. General

The NMR spectra were recorded on a Bruker AM300 NMR spectrometer (300.13 MHz for ^{1}H, 75.5 MHz for ^{13}C) in $CDCl_3$. Chemical

Table 2
Influence of solvents and acidic additives on the amide **5b**-catalyzed aldol reaction between **6a** and **7a**[a]

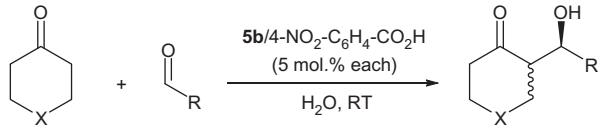


6a **7a** **8a**

Entry	Solvent	Additive	Conv.[b] (%)	dr (*anti*/*syn*)[b]	ee (*anti*/*syn*)[c]
1	—	—	99	74/26	46/10
2	THF	—	98	67/33	60/29
3	PhMe	—	99	75/25	54/22
4	DMSO	—	71	69/31	69/28
5	MeCN	—	99	76/24	56/15
6	EtOH	—	97	73/27	61/22
7	$CHCl_3$	—	99	75/25	50/31
8	H_2O	—	98	91/9	78/18
9	H_2O	AcOH	97	90/10	76/48
10	—//—	$PhCO_2H$	99	89/11	80/3
11	—//—	4-NO_2–C_6H_4–CO_2H	98	91/9	83/7
12[d]	—//—	—//—	99	91/9	81/3
13[e]	—//—	—//—	99	91/9	80/1

[a] Reactions were carried out at a molar ratio of 3:1 (**6a**/**7a**) in 0.09 mL of the respective solvent (90 equiv for water).
[b] ^{1}H NMR data for crude **8a**.
[c] Chiral HPLC data.
[d] 45 equiv of water was used.
[e] 22 equiv of water was used.

Table 3
Amide **5b**-catalyzed aldol reactions between cyclic ketones **6a**–**d** and (hetero-)aromatic aldehydes **7a**–**e** in the presence of water[a]



6a-d **7a-e** **8b-f**

Entry	**6** (X)	**7** (R)	**8**	Time (h)	Yield (%)	dr (anti/syn)[b]	ee (%) (*anti*/*syn*)[c]
1	**a** (–CH_2–)	**a** (4-NO_2–C_6H_4–)	**a**	20 (72)[d] (20–48)[e] (24)[f] (24–48)[g]	95 (85)[d] (69–85)[e] (89)[f] (65)[g]	91/9 (90/10)[d] (87:13)[e] (99/1)[f] (63/37)[g]	78/18 (92/nd)[d] (91/nd)[e] (96/nd)[f] (89/67)[g]
2	**a** (–CH_2–)	**b** (4-MeO_2C–C_6H_4–)	**b**	40	81	85/15	79/16
3	**b** (–)	**a** (4-NO_2–C_6H_4–)	**c**	16	96	32/68	76/34
4	**c** (–O–)	**c** (4-CN–C_6H_4–)	**d**	16	71	85/15	80/6
5	**d** (–S–)	**d** (4-F–C_6H_4–)	**e**	40	80	89/11	62/14
6	**a** (–CH_2–)	**e** (2-thienyl)	**f**	120	54	78/22	62/3

[a] Reactions were carried out at a molar ratio of 3:1 (**6a**/**7a**) in the presence of water (0.09 mL, 90 equiv). Reported data for respective reactions promoted by other catalysts in aqueous medium are given in brackets.
[b] ^{1}H NMR data for isolated products **8a**–**f**.
[c] Chiral HPLC data.
[d] Catalyst: *N*-(*S*)-prolyl-chitosan.[5b]
[e] Catalyst: *N*-(*S*)-prolyl-α,α-diphenyl-β-phenylglycinol.[4a]
[f] Catalyst: *N*-(*S*)-prolyl-α,β-diphenyl-β-aminoethanol.[11a]
[g] Catalyst: (*S*)-proline, DMSO as the solvent.[11b]

shifts are given in ppm and referenced to an internal TMS standard for ^{1}H and $CDCl_3$ for ^{13}C. Elemental analyses were conducted on a Perkin–Elmer 2400 microanalyser. High resolution mass spectra (HRMS) were measured on a Bruker microTOF II instrument using electrospray ionization (ESI).[12] The measurements were carried out in a positive ion mode (interface capillary voltage 4500 V); mass range from *m*/*z* 50 to *m*/*z* 3000 Da; external or internal calibration was done with Electrospray Calibrant Solution (Fluka). A syringe injection was used for a solution in methanol (flow rate 3 mL/min). Nitrogen was applied as a dry gas; interface temperature was set at 180 °C. The IR spectra (KBr pellets) were recorded with a Specord M82. Specific optical rotations $[\alpha]_D^{t,^\circ C}$ were measured with a Jasco DIP-360 polarimeter at 589 nm. Compounds **8a**,[13a] **8b**,[13a] **8c**,[13a] **8d**,[13b] **10e**,[13c] and **10f**[13d] were identified by comparing the NMR spectra with literature data. The dr values of the aldols were evaluated by ^{1}H NMR spectra and diastereomer signals were assigned in accordance with $^3J_{H(1),H(2)}$ values: $J < 3$ Hz ($\delta = 5.51$–5.59 ppm) for *syn*- and $J = 6.6$–9.5 Hz ($\delta = 5.02$–5.24 ppm) for the *anti*-diastereomer. Enantiomeric excess values (ee) of the aldols were determined by HPLC on a Stayer chromatograph with the

chiral phase Chiralcel OD-H, OJ-H, or Chiralpak AD-H. Racemic forms of the corresponding aldols were obtained with racemic proline in the ketone medium. Silica gels 0.060–0.200 and 0.035–0.070 nm (Acros) were used for column chromatography. Solvents were purified by standard methods.

4.2. General procedure for the aldol reaction

Ketone **6** (0.3 mmol) and aldehyde **7** (0.1 mmol) were added to a solution or suspension of catalyst **5** (0.005 mmol, 1.3 mg) in the corresponding media (0.09 mL by default or specified otherwise in Table 2). The reaction mixture was stirred for 16 h or the period given in Table 3. Aldols **8a–f** and the remaining starting materials were extracted with Et_2O (2 × 3 mL). The combined extracts were filtered through a silica gel pad (1 g) and the residue was washed with Et_2O (2 mL). The resulting solution was evaporated under reduced pressure (15 Torr) to afford crude product **8**. Aldols **8a–f** were isolated by column chromatography (Silica Gel Acros, 60A, 0.035–0.070 mm, eluent: hexane–EtOAc 3:1).

4.3. General procedure for the synthesis of compounds 4a–d

A solution of ethylchloroformate (0.34 mL, 3.55 mmol) in THF (10 mL) was added over 10 min to a stirred solution of *N*-Cbz-proline **2** (0.88 g, 3.55 mmol) and Et_3N (0.50 mL, 3.55 mmol) in THF (15 mL) at 0–5 °C. After 20 min a solution of corresponding β-hydroxyamine **3a–d** (0.60 g, 3.55 mmol) in THF (10 mL) was added dropwise over 10 min. The resulting mixture was stirred for 1 h at 0–5 °C, then for 2 h at ambient temperature and then was refluxed for 30 min. After cooling to room temperature, the reaction mixture was filtered off. The precipitate was washed with THF (20 mL). The combined organic extracts were evaporated, after which the residue was dissolved in EtOAc and the organic solution was successively washed with aqueous solutions of K_2CO_3 (20%) and 1 M HCl and then with water. The organic layer was separated, dried over anhydrous Na_2SO_4, and evaporated. The residue was washed with hexane (2 × 20 mL) and dried in vacuo (0.5 Torr) for 2 h to afford **4a–d** (0.93 g, 66% / 1.00 g, 71% 1.13 g, 80% 1.17 g, 83%) as white solid.

4.3.1. (*S*)-Benzyl 2-((1*S*,2*S*,3*R*,5*S*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylcarbamoyl)-pyrrolidine-1-carboxylate 4a

White solid, mp 99–101 °C, $[\alpha]_D^{23} = -24.25$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.02 (s, 3H), 1.19 (s, 3H), 1.25 (s, 3H), 1.08–1.30 (m, 2H), 1.37–1.50 (m, 1H), 1.79–1.99 (m, 3H), 2.00–2.26 (m, 3H), 2.33–2.47 (m, 1H), 3.42–3.64 (m, 2H), 4.05–4.19 (m, 1H), 4.34–4.48 (m, 1H), 5.01–5.26 (m, 2H), 6.56 (br, 1H), 7.21–7.38 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ 23.6, 24.7, 28.1, 28.6, 29.3, 29.9, 35.6, 38.6, 40.5, 47.0, 48.0, 54.2, 61.1, 67.2, 74.9, 127.3, 127.9, 128.4, 136.5, 155.2, 171.8 ppm. Anal. Cacld for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 69.20; H, 8.09; N, 6.96. HRMS(ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_4$ ($[M+Na]^+$): 423.2254, found: 423.2255. IR (KBr, cm^{-1}): 3424, 3307, 2917, 1708, 1658, 1542, 1418, 1355, 1119, 752, 697.

4.3.2. (*S*)-Benzyl 2-((1*R*,2*R*,3*S*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylcarbamoyl)-pyrrolidine-1-carboxylate 4b

White solid, mp 102–104 °C, $[\alpha]_D^{24} = -86.95$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.06 (s, 3H), 1.28 (s, 6H), 1.12–1.50 (m, 2H), 1.80–2.06 (m, 4H), 2.08–2.30 (m, 3H), 2.38–2.52 (m, 1H), 3.43–3.70 (m, 2H), 4.19–4.51 (m, 2H), 5.08–5.28 (m, 2H), 6.73 (br, 1H), 7.22–7.44 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ 23.6, 24.4, 28.1, 28.7, 29.4, 29.7, 36.0, 38.7, 40.5, 47.2, 47.8, 54.3, 61.3, 67.3, 74.5, 128.0, 128.1, 128.5, 136.3, 155.1, 171.3 ppm. Anal. Cacld for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 69.16; H, 8.11; N, 6.94. HRMS(ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_4$ ($[M+Na]^+$): 423.2254, found: 423.2256. IR (KBr, cm^{-1}): 3424, 3307, 2917, 1708, 1658, 1542, 1418, 1355, 1119, 752, 697.

4.3.3. (*S*)-Benzyl 2-((1*S*,2*S*,3*S*,5*S*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylcarbamoyl)-pyrrolidine-1-carboxylate 4c

White solid, mp 53–55 °C, $[\alpha]_D^{23} = -79.85$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.84 (s, 3H), 1.18 (s, 3H), 1.26 (s, 3H), 1.37–1.51 (m, 1H), 1.64–1.75 (m, 2H), 1.87–2.06 (m, 4H), 2.12–2.30 (m, 2H), 2.33–2.46 (m, 1H), 3.41–3.64 (m, 2H), 4.08–4.48 (m, 2H), 5.11–5.27 (m, 2H), 7.28–7.43 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): δ 23.1, 24.4, 25.1, 25.2, 27.6, 28.6, 30.8, 38.5, 39.8, 47.0, 53.2, 55.2, 60.0, 67.3, 76.5, 127.3, 127.9, 128.4, 136.8, 154.8, 174.0 ppm. Anal. Cacld for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 69.03; H, 8.18; N, 6.92. HRMS(ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_4$ ($[M+Na]^+$): 423.2254, found: 423.2258. IR (KBr, cm^{-1}): 3424, 3307, 2917, 1708, 1658, 1542, 1418, 1355, 1119, 752, 697.

4.3.4. (*S*)-Benzyl 2-((1*R*,2*R*,3*R*,5*R*)-2-hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-ylcarbamoyl)-pyrrolidine-1-carboxylate 4d

White solid, mp 108–110 °C, $[\alpha]_D^{24} = -54.35$ (*c* 2.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 0.78 (s, 3H), 1.06 (s, 3H), 1.26 (s, 3H), 1.62–1.75 (m, 2H), 1.83–1.45 (m, 4H), 1.90–2.03 (m, 2H), 2.14–2.24 (m, 2H), 3.41–3.66 (m, 2H), 4.05–4.30 (m, 1H), 4.38–4.50 (m, 1H), 5.08–5.28 (m, 2H), 7.29–7.40 (m, 5H) ppm. ^{13}C NMR ($CDCl_3$): 23.1, 24.9, 25.0, 27.7, 29.9, 30.9, 34.5, 38.4, 39.8, 46.9, 53.2, 55.0, 59.8, 67.2, 76.5, 127.7, 128.0, 128.4, 136.3, 154.2, 172.3 ppm. Anal. Cacld for $C_{23}H_{32}N_2O_4$: C, 68.97; H, 8.05; N, 6.99. Found: C, 69.18; H, 8.12; N, 6.94. HRMS(ESI) *m*/*z* calcd for $C_{23}H_{32}N_2O_4$ ($[M+Na]^+$): 423.2254, found: 423.2256. IR (KBr, cm^{-1}): 3424, 3307, 2917, 1708, 1658, 1542, 1418, 1355, 1119, 752, 697.

4.4. General procedure for the synthesis of compounds 5a–d

A mixture of **4a–d** (0.80 g, 2.00 mmol/0.88 g, 2.20 mmol/1.00 g, 2.50 mmol/1.00 g, 2.50 mmol) and Pd/C (5%, 0.08 g/0.09 g/0.10 g/0.10 g) in dry CH_3OH (25 mL) was stirred under H_2 (760 Torr) at ambient temperature for 3 h. The resulting precipitate was filtered off and then washed with CH_3OH (10 mL). The combined organic phases were evaporated, and the residue was dried under reduced pressure (0.5 Torr) for 2 h to afford **5a–d** (0.53 g, 99%/0.58 g, 98%/0.65 g, 97%/0.66 g, 99%) as white solids.

4.4.1. (*S*)-*N*-((1*S*,2*S*,3*R*,5*S*)-2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-pyrrolidine-2-carboxamide 5a

White solid, mp 167–169 °C, $[\alpha]_D^{24} = -32.25$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.07 (s, 3H), 1.27 (s, 3H), 1.29 (s, 3H), 1.39–1.57 (m, 2H), 1.64–1.80 (m, 2H), 1.86–2.04 (m, 3H), 2.06–2.29 (m, 2H), 2.40–2.56 (m, 1H), 2.90–3.09 (m, 2H), 3.75 (dd, *J* = 5.3, 8.9 Hz, 1H), 4.30 (q, *J* = 8.7 Hz, 1H), 7.99 (d, *J* = 6.0 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 23.6, 26.0, 28.2, 28.7, 29.8, 31.0, 36.0, 38.7, 40.6, 47.2, 47.8, 54.7, 60.9, 74.1, 174.6 ppm. Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.80; H, 9.91; N, 10.48. HRMS(ESI) *m*/*z* calcd for $C_{15}H_{26}N_2O_2$ ($[M+Na]^+$): 289.1886, found: 289.1876. IR (KBr, cm^{-1}): 3444, 3349, 2962, 2925, 2867, 1642, 1520, 1464, 1382, 1299, 1121, 1073, 899.

4.4.2. (*S*)-*N*-((1*R*,2*R*,3*S*,5*R*)-2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-pyrrolidine-2-carboxamide 5b

White solid, mp 150–152 °C, $[\alpha]_D^{24} = -39.45$ (*c* 1.0, $CHCl_3$). ^1H NMR ($CDCl_3$): δ 1.05 (s, 3H), 1.26 (s, 33H), 1.27 (s, 3H), 11.36–1.46 (m, 1H), 1.61–1.77 (m, 2H), 1.79–2.03 (m, 4H), 2.05–2.27 (m, 2H), 2.40–2.52 (m, 1H), 2.85–3.05 (m, 2H), 3.74 (dd, *J* = 5.3, 9.0 Hz, 1H), 4.29 (q, *J* = 8.6 Hz, 1H), 7.97 (d, *J* = 7.7 Hz, 1H) ppm.

^{13}C NMR ($CDCl_3$): δ 23.6, 26.0, 28.1, 28.6, 29.9, 30.9, 36.3, 38.7, 40.5, 47.1, 47.6, 54.6, 60.8, 74.2, 174.7 ppm. Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.78; H, 9.90; N, 10.49. HRMS(ESI) m/z calcd for $C_{15}H_{26}N_2O_2$ ($[M+Na]^+$): 289.1886, found: 289.1882. IR (KBr, cm^{-1}): 3444, 3349, 2962, 2925, 2867, 1642, 1520, 1464, 1382, 1299, 1121, 1073, 899.

4.4.3. (*S*)-*N*-((1*S*,2*S*,3*S*,5*S*)-2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-pyrrolidine-2-carboxamide 5c

White solid, mp 62–64 °C, $[\alpha]_D^{25} = -62.4$ (c 1.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.87 (s, 3H), 1.17 (s, 3H), 1.28 (s, 3H), 1.57 (dd, J = 9.6, 12.8 Hz, 1H), 1.66–1.82 (m, 2H), 1.86–2.06 (m, 4H), 2.10–2.26 (m, 2H), 2.26–2.39 (m, 1H), 2.86–3.11 (m, 2H), 3.83 (dd, J = 5.2, 9.1 Hz, 1H), 4.19 (q, J = 8.4 Hz, 1H), 7.65 (br, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 23.1, 25.0, 25.1, 26.1, 27.6, 30.3, 30.8, 38.5, 39.8, 47.1, 53.2, 54.5, 59.9, 76.2, 177.2 ppm. Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.69; H, 9.97; N, 10.45. HRMS(ESI) m/z calcd for $C_{15}H_{26}N_2O_2$ ($[M+Na]^+$): 289.1886, found: 289.1874. IR (KBr, cm^{-1}): 3444, 3349, 2962, 2925, 2867, 1642, 1520, 1464, 1382, 1299, 1121, 1073, 899.

4.4.4. (*S*)-*N*-((1*R*,2*R*,3*R*,5*R*)-2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)-pyrrolidine-2-carboxamide 5d

White solid, mp 185–187 °C, $[\alpha]_D^{25} = -8.9$ (c 2.0, $CHCl_3$). ^{1}H NMR ($CDCl_3$): δ 0.87 (s, 3H), 1.14 (s, 3H), 1.28 (s, 3H), 1.51–1.61 (m, 1H), 1.65–1.82 (m, 2H), 1.85–2.45 (m, 2H), 1.89–2.06 (m, 2H), 2.10–2.25 (m, 2H), 2.25–2.39 (m, 1H), 2.86–3.10 (m, 2H), 3.71–3.82 (m, 1H), 4.11–4.24 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$): δ 23.2, 25.0, 25.1, 26.1, 27.7, 30.8, 30.9, 38.5, 40.0, 47.2, 53.3, 54.4, 60.1, 76.3, 177.5 ppm. Anal. Calcd for $C_{15}H_{26}N_2O_2$: C, 67.63; H, 9.84; N, 10.52. Found: C, 67.81; H, 9.93; N, 10.46. HRMS(ESI) m/z calcd for $C_{15}H_{26}N_2O_2$ ($[M+Na]^+$): 289.1886, found: 289.1880. IR (KBr, cm^{-1}): 3444, 3349, 2962, 2925, 2867, 1642, 1520, 1464, 1382, 1299, 1121, 1073, 899.

Acknowledgment

This work was supported by the Russian Foundation of Basic Research (Grant No. 09-03-00384).

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