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PII: S0040-4020(15)01073-X

DOI: [10.1016/j.tet.2015.07.036](https://doi.org/10.1016/j.tet.2015.07.036)

Reference: TET 26981

To appear in: *Tetrahedron*

Received Date: 4 May 2015

Revised Date: 24 June 2015

Accepted Date: 13 July 2015

Please cite this article as: Marjanovic J, Ferjancic Z, Saicic RN, Organocatalyzed synthesis of (-)-4-*epi*-fagomine and the corresponding pipercolic acids, *Tetrahedron* (2015), doi: 10.1016/j.tet.2015.07.036.

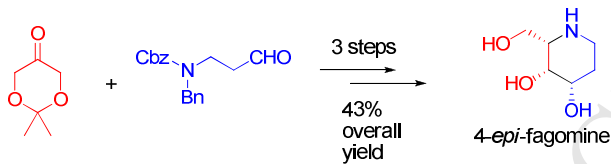
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## Graphical Abstract

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## Organocatalyzed synthesis of (-)-4-*epi*-fagomine and the corresponding pipecolic acids

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### ARTICLE INFO

#### Article history:

Received

Received in revised form

Accepted

Available online

Dedicated to Professor Sam Zard, on the occasion of his 60<sup>th</sup> birthday.

#### Keywords:

Organocatalysis

Iminosugars

Fagomine

Pipecolic acids

Glycolipid storage disorders

### ABSTRACT

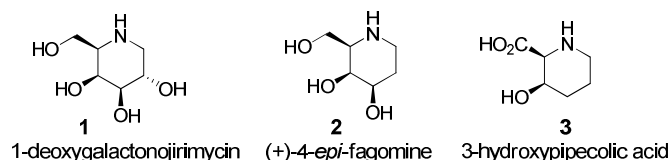
The enantioselective synthesis of 4-*epi*-fagomine was accomplished starting from dioxanone and Cbz-protected benzylamine, in 4 steps, with 18% overall yield. The key feature of this synthetic approach is the tactical combination of reactions: organocatalyzed aldolization/reductive amination, which allows for a quick formation of heterocyclic rings with defined absolute configuration of all stereogenic centers. Two hydroxypipecolic acids and a reduced fagomine analogue were also synthesized.

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### 1. Introduction

Iminosugars (also known as polyhydroxylated alkaloids or iminocyclitols) are a class of compounds that allow for selective inhibition of sugar-processing enzymes. This property offers a wide range of therapeutic applications, such as in the fight against diabetes, cancer, HIV, obesity, and viral and prion infections.<sup>1</sup> The malfunctions of one glycosidase enzyme result in a relatively rare glycolipid storage disorder, known as Fabry disease.<sup>2</sup> This is a disorder of glycosphingolipid metabolism caused by the deficiency of lysosomal  $\alpha$ -galactosidase, which results in deposition of excess globotriaosylceramide in blood vessels and other organs, with life-threatening consequences. Counterintuitively, glycosidase inhibitors could help in treating diseases resulting from glucosidase deficiency (from the deficiency of these enzymes): at subinhibitory concentrations, some iminosugars stabilize the proper folding of the mutated enzyme (the active site-specific-chaperone effect), thus allowing its transport out of the endoplasmatic reticulum and enhancing its glycolytic activity several times.<sup>3</sup> 1-Deoxy-galactonojirimycin (**1**) was found to be the most active compound for this purpose; however, the 1,2-dideoxy-derivative **2**, also known as 4-*epi*-fagomine, was also found to have considerable  $\alpha$ -galactosidase A inhibiting activity. In addition, it was found to inhibit non-

lysosomal glucosylceramidase (GAB-2),<sup>4</sup> and to suppress the level of cytokines, which are associated with inflammation and diabetes.<sup>5</sup> The corresponding pipecolic acids, such as 3-hydroxypipecolic acid (**3**), are constituents of several natural products with important biological activity, as well as intermediates in the syntheses of biologically active compounds; for these reasons, they have attracted considerable attention from synthetic chemists.<sup>6</sup> Therefore, we set out to develop efficient syntheses of these compounds.



**Figure 1.** 1-deoxygalactonojirimycin (**1**), 4-*epi*-fagomine (**2**) and (-)-*cis*-(2*S*,3*R*)-3-hydroxypipecolic acid (**3**).

Several syntheses of 4-*epi*-fagomine have been reported, most of which use the chiron approach. Chattopadhyay and collaborators prepared the compound from D-glucose (14 steps, 0.3% overall yield); in addition to 4-*epi*-fagomine, they also

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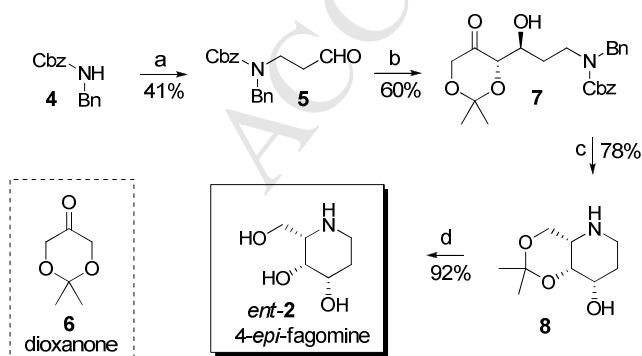
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prepared the corresponding piperelic acid.<sup>5</sup> Takahata, Kato and coworkers synthesized a series of fagomine-type analogues (including 4-*epi*-fagomine), starting from the Garner aldehyde (12 steps, 9% yield).<sup>7</sup> Aerts, Overkleeft and coworkers prepared a series of deoxyojirimycine derivatives, where 4-*epi*-fagomine was obtained from the Garner aldehyde (7 steps, yield not indicated).<sup>4,8</sup> Fan and coworkers prepared 4-*epi*-fagomine by the isomerisation of fagomine (experimental details not provided).<sup>3b</sup> Vankar and collaborators prepared fagomine analogues of both L- and D-series; 4-*epi*-fagomine was prepared from tri-*O*-benzylgalactal (7 steps, 28% overall yield).<sup>9</sup> The most efficient synthesis of 4-*epi*-fagomine, so far, is reported by Timmer, Stocker and collaborators: starting from 2-deoxygalactose, the target compound was obtained in 6 steps and with 60% overall yield.<sup>10</sup>

## 2. Results and discussion

We designed a catalytic asymmetric synthesis of 4-*epi*-fagomine (*ent*-2), that hinges on a tactical combination of reactions: organocatalyzed aldolization/reductive amination, which allows for a rapid access to heterocyclic systems with defined absolute configuration of all stereogenic centers. The synthesis starts from achiral, commercially available small molecules, so both enantiomers of the target compound could be obtained by a proper choice of a chiral organocatalyst (*R*- or *S*-proline). Recently, we have demonstrated the feasibility of this approach in total syntheses of natural products (+)-swainsonine<sup>11</sup> and hyacinthacine derivatives.<sup>12</sup> Some time ago, Joglar, Clapes and coworkers have reported a conceptually similar, two-step synthesis of fagomine, starting from dihydroxyacetone and a  $\beta$ -aminopropanal derivative.<sup>13</sup> In their synthesis the aldolization step was catalyzed by D-fructose-6-phosphate aldolase, and has resulted in *syn*-stereochemistry of the product, characteristic for chemoenzymatic aldolizations.

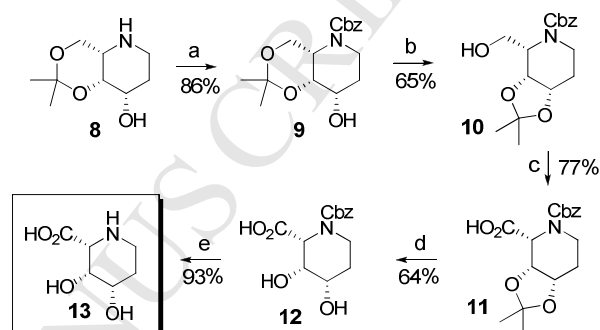
Our synthesis commenced with hetero-Michael addition of the commercially available carbamate **4** to acrolein (41%; Scheme 1).<sup>14</sup> The resulting adduct **5** was then submitted to the (*S*)-proline-organocatalyzed aldol reaction<sup>15</sup> with dioxanone (**6**).<sup>16</sup> The reaction could be performed in either DMF or DMSO, where the use of DMF as a solvent gave slightly higher yield (60%). However, we preferred the reaction in DMSO, for the reason of the superior purity of the product **7** (50-52%), which was obtained with complete diastereoselectivity (*i.e.*, exclusively *anti*-isomer). The only side-product of the reaction was the product of self-addition of dioxanone, which is easily separable by chromatography.



**Scheme 1.** Synthesis of 4-*epi*-fagomine *ent*-2. Reagents and conditions: a) acrolein (10 equiv), CSA (20 mol %), CH<sub>2</sub>Cl<sub>2</sub>, 0 ° to rt, 3 h, 41%; b) **6** (1.5 equiv), (*S*)-Proline (30 mol %), DMF (or DMSO with 5 equiv of H<sub>2</sub>O), 4 °C, 24 h, 60% (52% in DMSO); c) H<sub>2</sub>, 10% Pd/C, EtOH, 2 h, 78%; d) 3M HCl, MeOH, reflux, 4 h, 92%.

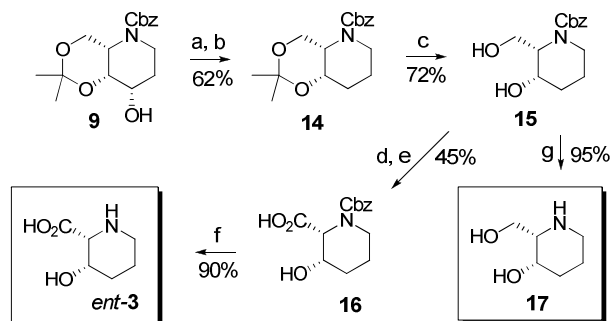
Upon exposure of aldol **7** to a hydrogen atmosphere in the presence of palladium on charcoal, double deprotection followed by the reductive amination afforded piperidine derivative **8** (78%). Acid-catalyzed deprotection of the dioxane unit then completed the shortest synthesis of 4-*epi*-fagomine (**2**), so far (4 steps, 16% overall yield).

With piperidine derivative **8** in hand, we turned our attention towards the synthesis of piperelic acids (Scheme 2). Protection of amine was followed by the acid-catalyzed rearrangement of dioxane **9** into thermodynamically more stable dioxolane **10**. The primary hydroxyl group was sequentially oxidized, first with DMP to the aldehyde, and then to the carboxylate **11** by Pinnick-Lindgren oxidation. Acid-catalyzed removal of the dioxolane in **11**, followed by reductive decarboxybenzylation of **12**, gave piperelic acid **13**.



**Scheme 2.** Synthesis of piperelic acid **13**. Reagents and conditions: a) CbzCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>, 0 °C to rt, 24 h, 86%; b) *p*-TsOH (0.15 equiv), acetone, rt, 24 h, 65%; c) i) DMP (2 equiv), CH<sub>2</sub>Cl<sub>2</sub>, 30 min; ii) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O, H<sub>2</sub>O<sub>2</sub>, CH<sub>3</sub>CN, 0 ° to rt, 3 h, 77% over two steps; d) 3M HCl, MeOH, rt, 2.5 h, 64%; e) H<sub>2</sub>, Pd/C, EtOH, 1 h, 93%.

Carbamate **9** could also be converted into a more interesting synthetic target, namely 3-hydroxypiperelic acid (*ent*-3; Scheme 3). To this end, the corresponding xanthate was submitted to Barton-McCombie deoxygenation with hypophosphorous acid, as a convenient reducing agent. After the acid-catalyzed deprotection of dioxane **14**, the resulting diol **15** could be selectively oxidized to acid **16** by a sequence of reactions involving PIDA oxidation followed by the Pinnick-Lindgren oxidation. Alternatively, hydrogenolytic deprotection of carbamate **15** yielded (-)-4-deoxyfagomine **17**.



**Scheme 3.** Synthesis of piperelic acid *ent*-3 and deoxyzasugar **17**. Reagents and conditions: a) NaH, CS<sub>2</sub>, THF, MeI, rt, 30 min, 80%; b) H<sub>3</sub>PO<sub>2</sub>, Et<sub>3</sub>N, AIBN (cat.), 1,4-dioxane, reflux, 30 min, 77%; c) 3M HCl, MeOH, rt, 1 h, 72%; d) TEMPO (cat.), PIDA, CH<sub>2</sub>Cl<sub>2</sub>, rt, 3 h; e) NaClO<sub>2</sub>, NaH<sub>2</sub>PO<sub>4</sub>·H<sub>2</sub>O, 30% H<sub>2</sub>O<sub>2</sub>, -10 °C to rt, 3 h, 45% from **15**; f) H<sub>2</sub>, 10% Pd/C, EtOH, 1 h, 90%; g) H<sub>2</sub>, 10% Pd/C, EtOH, 2 h, 95%.

dried over anh. MgSO<sub>4</sub> and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO<sub>2</sub>; eluent: toluene/EtOAc = 85/15) afforded the title aldol **7** (335.8 mg, 60%) as a pale yellow viscous oil.

**Method B:** Dioxanone **6** (390 mg, 3.00 mmol) and water (180.0 μL, 10.00 mmol) were added to a cold (0 °C) solution of aldehyde **5** (601 mg, 2.02 mmol) and proline (66 mg, 0.57 mmol, 30 mol %) in DMSO (7.8 mL), and the mixture was vigorously stirred for 24 h at 4 °C. The reaction was quenched by addition of brine followed by extraction with EtOAc. The aqueous phase was extracted with EtOAc (3 × 15 mL). The combined organic extract was dried over anh. MgSO<sub>4</sub>, filtered and concentrated under reduced pressure. Purification of the crude product by dry-flash chromatography (SiO<sub>2</sub>; eluent: toluene/EtOAc = 85/15) afforded the title aldol **7** (864.2 mg, 52%) as a pale yellow viscous oil. [α]<sub>D</sub><sup>20</sup> -85.6 (c 1.00, CHCl<sub>3</sub>); <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>, 65 °C) δ 7.39–7.19 (m, 10H), 5.13 (s, 2H), 4.68 (bd, *J*=5.3 Hz, 1H), 4.47 (s, 2H), 4.23 (d, *J*=3.8 Hz, 1H), 4.20 (d, *J*=17.2 Hz, 1H), 3.95 (d, *J*=16.8 Hz, 1H), 3.89–3.83 (m, 1H), 3.40–3.24 (m, 2H), 1.80–1.65 (m, 2H), 1.39 (s, 3H), 1.37 (s, 3H); <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>, 65 °C) δ 207.6 (C), 155.4 (C), 137.9 (C), 136.7 (C), 128.1 (CH), 128.0 (CH), 127.4 (CH), 127.1 (CH), 126.9 (CH), 126.7 (CH), 99.7 (C), 77.8 (CH), 67.0 (CH), 66.4 (CH<sub>2</sub>), 66.0 (CH<sub>2</sub>), 49.7 (CH<sub>2</sub>), 43.6 (CH<sub>2</sub>), 30.2 (CH<sub>2</sub>), 24.3 (CH<sub>3</sub>), 22.8 (CH<sub>3</sub>); IR (ATR) ν 3448, 2987, 2939, 1742, 1698, 1423, 1226, 1088, 736, 700 cm<sup>-1</sup>; HRMS (ESI) for C<sub>24</sub>H<sub>30</sub>NO<sub>6</sub> [M+H]<sup>+</sup> calculated: 428.2068; found: 428.2059.

#### 4.4. (4*aS*,8*S*,8*aR*)-2,2-Dimethylhexahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridin-8-ol (**8**)

A mixture of aldol **7** (58.5 mg, 0.14 mmol) and 10% Pd/C (30.3 mg, 0.03 mmol) in ethanol (14.0 mL) was stirred for 2 h under a hydrogen atmosphere (5 bar). The mixture was filtered and concentrated under reduced pressure. Purification of the residue by column chromatography (SiO<sub>2</sub>; eluent: dichloromethane/methanol = 1/1) afforded compound **8** (20.0 mg, 78%) as a white solid. mp 128–130 °C; [α]<sub>D</sub><sup>20</sup> -45.3 (c 1.00, MeOH); <sup>1</sup>H NMR (500 MHz, MeOD) δ 4.17 (dd, *J*=12.2, 2.3 Hz, 1H), 4.12–4.11 (m, 1H), 3.66 (dd, *J*=12.2, 1.6 Hz, 1H), 3.61 (ddd, *J*=11.8, 4.8, 3.1 Hz, 1H), 3.11 (ddd, *J*=13.8, 4.4, 2.1 Hz, 1H), 2.59 (td, *J*=13.3, 3.0 Hz, 1H), 2.44–2.41 (m, 1H), 1.76 (ddd, *J*=24.7, 12.6, 4.4 Hz, 1H), 1.63–1.56 (m, 1H), 1.49 (s, 3H), 1.41 (s, 3H); <sup>13</sup>C NMR (126 MHz, MeOD) δ 100.5 (C), 70.7 (CH), 70.0 (CH), 65.2 (CH<sub>2</sub>), 52.8 (CH), 44.7 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>), 30.0 (CH<sub>3</sub>), 19.0 (CH<sub>3</sub>); IR (ATR) ν 3366, 2991, 2943, 1458, 1381, 1198, 1057, 971, 837 cm<sup>-1</sup>; HRMS (ESI) for C<sub>9</sub>H<sub>18</sub>NO<sub>3</sub> [M+H]<sup>+</sup> calculated: 188.1281; found: 188.1283.

#### 4.5. (2*S*,3*R*,4*S*)-2-(Hydroxymethyl)piperidine-3,4-diol (*ent*-4-*epi*-fagomine) (*ent*-**2**)

A solution of amine **13** (27.7 mg, 0.15 mmol) in solvent mixture methanol/3M HCl (5.7 mL, *v/v* = 2/1) was stirred and heated to reflux for 4 h. After the volatiles were removed under reduced pressure, the residue was purified by ion exchange column chromatography (acidic resin DOWEX 50WX8-100), to give the title compound *ent*-**2** (20.1 mg, 92%) as a white solid. mp 219–221 °C, [lit.<sup>17</sup> mp 220–222 °C]; [α]<sub>D</sub><sup>20</sup> -15.5 (c 1.00, H<sub>2</sub>O), [lit.<sup>17</sup> [α]<sub>D</sub><sup>20</sup> -10.4 (c 1.02, H<sub>2</sub>O)]; <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O) δ 3.93–3.91 (m, 1H), 3.75 (ddd, *J*=11.0, 6.1, 2.9 Hz, 1H), 3.65 (ddd, *J*=18.0, 11.5, 6.7 Hz, 2H), 3.13–3.05 (m, 1H), 2.75 (td, *J*=6.7, 1.5 Hz, 1H), 2.66–2.58 (m, 1H), 1.75–1.65 (m, 2H); <sup>13</sup>C NMR (126 MHz, D<sub>2</sub>O) δ 72.5 (CH), 70.3 (CH), 64.3 (CH<sub>2</sub>), 61.7 (CH), 45.5 (CH<sub>2</sub>), 30.0 (CH<sub>2</sub>); IR (ATR) ν 3355, 2938, 1446, 1358, 1057,

### 3. Conclusions

To summarize, enantioselective syntheses of 4-*epi*-fagomine (*ent*-**2**), *cis*-3-hydroxypipercolic acid (**13**), as well as their two 4-deoxy analogues (**17** and *ent*-**3**), are described. These syntheses rely on the organocatalyzed aldol addition/reductive amination reaction cascade, which allows for the efficient, stereocontrolled formation of functionalized nitrogen heterocycles.

### 4. Experimental

#### 4.1. General methods

All chromatographic separations were performed on silica gel, 10–18 μm, 60 Å (dry-flash), 100–200 μm 60 Å (column chromatography), ICN Biomedicals, 60 (0.063–0.200 mm) (column chromatography), Merck and ion exchange column chromatography (acidic resin DOWEX 50WX8-100). Standard techniques were used for the purification of reagents and solvents. Petroleum ether (PE) refers to the fraction boiling at 70–72 °C. NMR spectra were recorded on Bruker Avance III 500 (<sup>1</sup>H NMR at 500 MHz, <sup>13</sup>C NMR at 126 MHz). Chemical shifts are expressed in ppm (δ) using TMS as the internal standard. IR spectra were recorded on a Nicolet 6700 FT instrument, and are expressed in cm<sup>-1</sup>. Mass spectra were obtained on Agilent technologies 6210 TOF LC/MS instrument (LC: series 1200) and LTQ Orbitrap XL hybrid FTMS (Thermo Scientific). Melting points were determined on a Electrothermal apparatus and are uncorrected. Optical rotations were determined on a Rudolph Research Analytical AUTOPOL IV Automatic Polarimeter.

#### 4.2. Benzylbenzyl(3-oxopropyl)carbamate (**5**)<sup>14</sup>

Freshly distilled acrolein (7.0 mL, 104.81 mmol) was added with stirring to a cold (0 °C) solution of *N*-benzylbenzylcarbamate **4** (2.5 g, 10.36 mmol) and (+)-camphorsulfonic acid (0.5 g, 2.15 mmol, 20 mol %) in dichloromethane (10 mL). After 20 min cooling bath was removed and the reaction mixture was stirred for an additional 3.5 h at room temperature. The reaction mixture was diluted with dichloromethane and washed with sat. aq. NaHCO<sub>3</sub> (10 mL). The organic extract was concentrated in vacuo, diluted with Et<sub>2</sub>O (20 mL), washed with water, dried over anh. MgSO<sub>4</sub> and concentrated. Purification of the residue by dry-flash chromatography (SiO<sub>2</sub>; eluent: petroleum ether/EtOAc = 8/2) afforded aldehyde **5** (1.3 g, 41 %) as a colorless liquid. <sup>1</sup>H NMR (500 MHz, DMSO-*d*<sub>6</sub>, 65 °C): δ 9.64 (t, *J*=1.7 Hz, 1H), 7.38–7.22 (m, 10H), 5.15 (s, 2H), 4.50 (s, 2H), 3.55 (t, *J*=6.8 Hz, 2H), 2.65 (td, *J*=6.8, 1.7 Hz, 2H); <sup>13</sup>C NMR (126 MHz, DMSO-*d*<sub>6</sub>, 65 °C): δ 201.0 (CH), 155.3 (C), 137.7 (C), 136.6 (C), 128.1 (CH), 128.0 (CH), 127.4 (CH), 127.2 (CH), 127.0 (CH), 126.8 (CH), 66.3 (CH<sub>2</sub>), 50.1 (CH<sub>2</sub>), 42.1 (CH<sub>2</sub>), 40.6 (CH<sub>2</sub>); IR (ATR) ν 3063, 3032, 2950, 1670, 1473, 1422, 1238, 1123, 737, 700 cm<sup>-1</sup>; HRMS (ESI) for C<sub>18</sub>H<sub>20</sub>NO<sub>3</sub> [M+H]<sup>+</sup> calculated: 298.1443; found: 298.1429.

#### 4.3. Benzylbenzyl(*S*)-3-((*S*)-2,2-dimethyl-5-oxo-1,3-dioxan-4-yl)-3-hydroxypropyl)carbamate (**7**)

**Method A:** A solution of dioxanone **6** (250 mg, 1.92 mmol), aldehyde **5** (389 mg, 1.31 mmol) and (*S*)-proline (48 mg, 0.42 mmol, 30 mol %) in DMF (3.4 mL) was stirred overnight at 4 °C. The reaction mixture was diluted with water, extracted with EtOAc, the combined organic extract was washed with water,

1025, 805  $\text{cm}^{-1}$ ; HRMS (ESI) for  $\text{C}_6\text{H}_{14}\text{NO}_3$   $[\text{M}+\text{H}]^+$  calculated: 148.0968; found: 148.0972.

#### 4.6. (4a*S*,8*S*,8a*R*)-Benzyl 8-hydroxy-2,2-dimethyltetrahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine-5(4a*H*)-carboxylate (**9**)

Benzyl chloroformate (104.7 mg, 0.61 mmol) was added dropwise (over a period of 20 min) to a cold (0 °C) solution of amine **8** (104.5 mg, 0.56 mmol) and triethyl amine (75.6 mg, 0.75 mmol) in dichloromethane (0.6 mL). The reaction was warmed to room temperature and stirred overnight, then diluted with water (10 mL). The mixture was extracted with dichloromethane (3 × 20 mL), and the combined organic extract was washed with sat. aq.  $\text{NaHCO}_3$  (2 × 20 mL), brine (20 mL), dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under reduced pressure. Purification of the residue by column chromatography ( $\text{SiO}_2$ ; eluent: dichloromethane/methanol = 95/5) afforded the title compound **9** (154.3 mg, 86%) as a colorless viscous oil.  $[\alpha]_{\text{D}}^{20} +106.1$  (*c* 1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 65 °C)  $\delta$  7.40–7.29 (m, 5H), 5.08 (dd, *J*=21.7, 12.6 Hz, 2H), 4.52 (d, *J*=5.8 Hz, 1H), 4.18 (dd, *J*=4.4, 2.3 Hz, 1H), 3.98 (dd, *J*=12.0, 4.0 Hz, 1H), 3.87 (ddd, *J*=13.0, 9.0, 2.0 Hz, 1H), 3.73 (dd, *J*=12.3, 3.4 Hz, 1H), 3.67 (dd, *J*=8.0, 4.0 Hz, 1H), 3.60 (tdd, *J*=8.5, 5.8, 2.3 Hz, 1H), 3.53 (ddd, *J*=13.1, 9.8, 7.5 Hz, 1H), 2.02 (ddd, *J*=18.3, 12.8, 9.1 Hz, 1H), 1.60–1.50 (m, 1H), 1.40 (s, 3H), 1.33 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ , 65 °C)  $\delta$  154.5 (C), 136.6 (C), 128.0 (CH), 127.4 (CH), 127.2 (CH), 97.8 (C), 67.7 (CH), 65.9 (CH<sub>2</sub>), 65.5 (CH), 61.4 (CH<sub>2</sub>), 48.9 (CH), 38.2 (CH<sub>2</sub>), 27.8 (CH<sub>3</sub>), 27.4 (CH<sub>2</sub>), 19.7 (CH<sub>3</sub>); IR (ATR)  $\nu$  3440, 2988, 2936, 1695, 1424, 1381, 1262, 1075, 771, 700  $\text{cm}^{-1}$ ; HRMS (ESI) for  $\text{C}_{17}\text{H}_{24}\text{NO}_5$   $[\text{M}+\text{H}]^+$  calculated: 322.1649; found: 322.1647.

#### 4.7. (3a*R*,4*S*,7a*S*)-Benzyl 4-(hydroxymethyl)-2,2-dimethyltetrahydro-[1,3]dioxolo[4,5-*c*]pyridine-5(6*H*)-carboxylate (**10**)

$p\text{TsOH}\cdot\text{H}_2\text{O}$  (14.0 mg, 0.07 mmol) was added to a solution of alcohol **9** (153.7 mg, 0.48 mmol) in acetone (6.9 mL), and the mixture was stirred at room temperature for 24 h. The reaction mixture was treated with triethylamine (14.6 mg, 0.14 mmol) and concentrated under reduced pressure. The residue was purified by column chromatography ( $\text{SiO}_2$ ; eluent: petroleum ether/EtOAc = 6/4), to afford alcohol **10** (99.9 mg, 65%) as a colorless viscous oil.  $[\alpha]_{\text{D}}^{20} +29.4$  (*c* 1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 65 °C)  $\delta$  7.39–7.28 (m, 5H), 5.09 (s, 2H), 4.42 (dd, *J*=6.8, 5.8 Hz, 1H), 4.33–4.28 (m, 2H), 4.07 (dd, *J*=12.8, 6.8 Hz, 1H), 3.74–3.65 (m, 2H), 3.53 (ddd, *J*=13.1, 6.4, 5.0 Hz, 1H), 3.29 (ddd, *J*=13.2, 9.2, 4.1 Hz, 1H), 1.88–1.80 (m, 1H), 1.76–1.69 (m, 1H), 1.37 (d, *J*=0.5 Hz, 3H), 1.28 (d, *J*=0.5 Hz, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ , 65 °C)  $\delta$  155.3 (C), 136.8 (C), 128.0 (CH), 127.3 (CH), 127.0 (CH), 107.0 (C), 71.4 (CH), 70.3 (CH<sub>2</sub>), 65.9 (CH<sub>2</sub>), 59.6 (CH), 54.2 (CH), 36.9 (CH<sub>2</sub>), 27.3 (CH<sub>2</sub>), 26.0 (CH<sub>3</sub>), 24.3 (CH<sub>3</sub>); IR (ATR)  $\nu$  3462, 2985, 2936, 1697, 1418, 1256, 1212, 1063, 869, 700  $\text{cm}^{-1}$ ; HRMS (ESI) for  $\text{C}_{17}\text{H}_{24}\text{NO}_5$   $[\text{M}+\text{H}]^+$  calculated: 322.1649; found: 322.1647.

#### 4.8. (3a*R*,4*R*,7a*S*)-5-(Benzyloxycarbonyl)-2,2-dimethylhexahydro-[1,3]dioxolo[4,5-*c*]pyridine-4-carboxylic acid (**11**)

Dess-Martin's periodinane (268 mg, 0.63 mmol) was added to a solution of alcohol **10** (96.7 mg, 0.30 mmol) in dichloromethane (3.0 mL) and the reaction mixture was stirred at room temperature for 30 min. The reaction mixture was diluted with dichloromethane, washed with 5%  $\text{Na}_2\text{S}_2\text{O}_3$  and sat. aq.  $\text{NaHCO}_3$ , dried over anh.  $\text{MgSO}_4$ , filtered and concentrated under

reduced pressure. The residue was further used without purification.

To a stirred solution of the crude aldehyde (obtained from **10** (96.7 mg, 0.30 mmol)) in  $\text{CH}_3\text{CN}$  (2.1 mL) was added a solution of  $\text{NaH}_2\text{PO}_4\cdot\text{H}_2\text{O}$  (8.2 mg, 0.06 mmol) in  $\text{H}_2\text{O}$  (0.4 mL) and 30%  $\text{H}_2\text{O}_2$  (45.0  $\mu\text{L}$ , 0.57 mmol).<sup>5</sup> The mixture was cooled to 0 °C, and  $\text{NaClO}_2$  (45.0 mg, 0.50 mmol) in  $\text{H}_2\text{O}$  (0.9 mL) was added dropwise over a period of 30 minutes. The reaction mixture was stirred at 15 °C. After 3 h, the reaction was quenched by the addition of a small amount of  $\text{Na}_2\text{SO}_4$  (50.0 mg) and extracted with EtOAc (3 × 5 mL). Evaporation of the solvent followed by column chromatography of the residue ( $\text{SiO}_2$ ; eluent: dichloromethane/methanol = 95/5) afforded compound **11** (77.7 mg, 77% over two steps) as a white solid. mp 45–47 °C;  $[\alpha]_{\text{D}}^{20} +15.5$  (*c* 1.00,  $\text{CHCl}_3$ );  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 65 °C)  $\delta$  7.40–7.26 (m, 5H), 5.12–5.01 (m, 2H), 4.66 (dd, *J*=6.9, 5.2 Hz, 1H), 4.42–4.34 (m, 2H), 3.74 (bd, *J*=12.2 Hz, 1H), 3.25 (bs, 1H), 1.75–1.64 (m, 2H), 1.38 (s, 3H), 1.27 (s, 3H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ , 65 °C)  $\delta$  169.9 (C), 154.9 (C), 136.5 (C), 128.0 (CH), 127.3 (CH), 127.0 (CH), 106.8 (C), 71.5 (CH), 69.8 (CH), 66.0 (CH<sub>2</sub>), 54.6 (CH), 36.1 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 26.2 (CH<sub>3</sub>), 23.9 (CH<sub>3</sub>); IR (ATR)  $\nu$  3741, 2988, 2936, 1702, 1422, 1259, 1214, 1040, 738  $\text{cm}^{-1}$ ; HRMS (ESI) for  $\text{C}_{17}\text{H}_{20}\text{NO}_6$   $[\text{M}-\text{H}]^-$  calculated: 334.1296; found: 334.1309.

#### 4.9. (2*R*,3*R*,4*S*)-1-(Benzyloxycarbonyl)-3,4-dihydropiperidine-2-carboxylic acid (**12**)

A solution of compound **11** (93.5 mg, 0.28 mmol) in solvent mixture methanol/3M HCl (12.6 mL, *v/v* = 2/1) was stirred at room temperature for 2 h. After the volatiles were removed under reduced pressure, the residue was purified by column chromatography ( $\text{SiO}_2$ ; eluent: dichloromethane/methanol = 9/1), to give the title compound **12** (53.1 mg, 64%) as a colorless, viscous oil.  $[\alpha]_{\text{D}}^{20} +40.8$  (*c* 0.7, MeOH);  $^1\text{H}$  NMR (500 MHz,  $\text{DMSO}-d_6$ , 65 °C)  $\delta$  7.38–7.27 (m, 5H), 5.08 (s, 2H), 4.47 (bs, 1H), 3.84 (bs, 1H), 3.78–3.62 (m, 2H), 3.30 (bs, 1H), 1.69–1.54 (m, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{DMSO}-d_6$ , 65 °C)  $\delta$  172.6 (C), 155.1 (C), 136.8 (C), 128.0 (CH), 127.3 (CH), 127.0 (CH), 69.5 (CH), 66.7 (CH), 65.9 (CH<sub>2</sub>), 55.1 (CH), 35.0 (CH<sub>2</sub>), 30.3 (CH<sub>2</sub>); IR (ATR)  $\nu$  3371, 2951, 1678, 1610, 1413, 1154, 746, 603  $\text{cm}^{-1}$ ; HRMS (ESI) for  $\text{C}_{14}\text{H}_{18}\text{NO}_6$   $[\text{M}+\text{H}]^+$  calculated: 296.1134; found: 296.1123.

#### 4.10. (2*R*,3*R*,4*S*)-3,4-Dihydropiperidine-2-carboxylic acid (3,4-Dihydropipecolic Acid) (**13**)

A suspension of **12** (21.9 mg, 0.07 mmol) and 10% Pd/C (5.3 mg, 0.005 mmol) in methanol (1.5 mL) was stirred under a hydrogen atmosphere (1 bar) for 2 h at room temperature. The reaction mixture was filtered through celite, concentrated under reduced pressure and purified by column chromatography ( $\text{SiO}_2$ ; eluent: EtOAc/EtOH/ $\text{H}_2\text{O}$  = 4/4/2), to give the title compound **13** (11.1 mg, 93%) as a white solid. mp 240–242 °C, [lit.<sup>5</sup> for *ent*-**13** mp 245–247 °C];  $[\alpha]_{\text{D}}^{20} +6.8$  (*c* 0.65,  $\text{H}_2\text{O}$ ), [lit.<sup>5</sup>  $[\alpha]_{\text{D}}^{25} +7.5$  (*c* 2.10,  $\text{H}_2\text{O}$ )];  $^1\text{H}$  NMR (500 MHz,  $\text{D}_2\text{O}$ )  $\delta$  4.43–4.40 (m, 1H), 3.97 (ddd, *J*=11.5, 5.2, 2.8 Hz, 1H), 3.75 (d, *J*=1.6 Hz, 1H), 3.46 (ddd, *J*=13.1, 4.6, 2.3 Hz, 1H), 3.05 (td, *J*=13.2, 3.8 Hz, 1H), 2.07–1.90 (m, 2H);  $^{13}\text{C}$  NMR (126 MHz,  $\text{D}_2\text{O}$ )  $\delta$  171.6 (C), 67.8 (CH), 67.5 (CH), 61.9 (CH), 41.2 (CH<sub>2</sub>), 23.6 (CH<sub>2</sub>); IR (ATR)  $\nu$  3395, 3313, 3109, 2957, 2926, 2856, 1732, 1458, 1269, 1074  $\text{cm}^{-1}$ ; HRMS (ESI) for  $\text{C}_6\text{H}_{12}\text{NO}_4$   $[\text{M}+\text{H}]^+$  calculated: 162.0761; found: 162.0758.

**4.11. (4a*S*,8a*S*)-Benzyl 2,2-dimethyltetrahydro-4*H*-[1,3]dioxino[5,4-*b*]pyridine-5(4a*H*)-carboxylate (**14**)**

To a solution of compound **8** (62.0 mg, 0.19 mmol) in THF (0.2 mL) was added sodium hydride (12.0 mg, 0.50 mmol) under an argon atmosphere. After stirring for 15 minutes at room temperature, carbon disulfide (0.3 mL, 5.10 mmol) was added, followed after 0.5 h by iodomethane (65  $\mu$ L, 1.04 mmol). The resulting solution was stirred for 30 minutes and the reaction was quenched by addition of water. The mixture was extracted with EtOAc, the extract was washed with water, dried over anhydrous  $MgSO_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography ( $SiO_2$ ; eluent: petroleum ether/EtOAc = 85/15), to give the xanthate (63.5 mg, 80%) as a pale yellow viscous oil.  $[\alpha]_D^{20} +41.8$  (c 1.00,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.39–7.30 (m, 5H), 5.60 (td,  $J=8.8, 2.3$  Hz, 1H), 5.12 (q,  $J=12.3$  Hz, 2H), 4.56 (dd,  $J=4.1, 2.2$  Hz, 1H), 4.18–4.09 (m, 1H), 4.04 (dd,  $J=12.2, 3.6$  Hz, 1H), 3.96–3.83 (m, 2H), 3.79–3.69 (m, 1H), 2.56 (s, 3H), 2.49–2.40 (m, 1H), 1.94–1.82 (m, 1H), 1.44 (s, 3H), 1.42 (s, 3H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  215.6 (C), 155.2 (C), 136.3 (C), 128.6 (CH), 128.1 (CH), 128.0 (CH), 99.1 (C), 78.0 (CH), 67.4 ( $CH_2$ ), 65.3 (CH), 62.2 ( $CH_2$ ), 49.1 (CH), 38.3 ( $CH_2$ ), 27.9 ( $CH_3$ ), 24.5 ( $CH_2$ ), 20.0 ( $CH_3$ ), 19.1 ( $CH_3$ ); IR (ATR)  $\nu$  2989, 2940, 1670, 1422, 1220, 1058, 980, 736, 700  $cm^{-1}$ ; HRMS (ESI) for  $C_{19}H_{25}NO_5S_2Na$   $[M+Na]^+$  calculated: 434.1066; found: 434.1055.

AIBN (74 mg; 0.45 mmol) was added to a refluxing solution of xanthate (412 mg, 1.00 mmol), hypophosphorous acid (0.56 mL of the 50% aqueous solution, 5.12 mmol) and triethylamine (0.8 mL, 5.73 mmol) in dioxane (9.1 mL) and the reaction mixture was stirred for 30 minutes at room temperature.<sup>18</sup> Upon completion, the reaction mixture was diluted with dichloromethane (20 mL) and washed with water. The organic extract was dried over anhydrous  $MgSO_4$ , filtered and concentrated under reduced pressure. Purification by column chromatography ( $SiO_2$ ; eluent: petroleum ether/EtOAc = 85/15), afforded the title compound **14** (236.8 mg, 77%) as a colorless oil.  $[\alpha]_D^{20} +128.7$  (c 1.00,  $CHCl_3$ );  $^1H$  NMR (500 MHz,  $DMSO-d_6$ , 65  $^\circ C$ )  $\delta$  7.40–7.28 (m, 5H), 5.09 (q,  $J=12.6$  Hz, 2H), 4.24–4.19 (m, 1H), 3.92 (dd,  $J=12.1, 4.3$  Hz, 1H), 3.85 (ddd,  $J=10.0, 6.8, 2.8$  Hz, 1H), 3.77 (dd,  $J=12.1, 4.1$  Hz, 1H), 3.70 (q,  $J=4.4$  Hz, 1H), 3.39 (ddd,  $J=13.1, 10.0, 6.8$  Hz, 1H), 1.82–1.75 (m, 1H), 1.68–1.59 (m, 2H), 1.58–1.49 (m, 1H), 1.38 (d,  $J=0.5$  Hz, 3H), 1.32 (d,  $J=0.5$  Hz, 3H);  $^{13}C$  NMR (126 MHz,  $DMSO-d_6$ , 65  $^\circ C$ )  $\delta$  154.6 (C), 136.7 (C), 128.0 (CH), 127.4 (CH), 127.1 (CH), 97.6 (C), 65.9 ( $CH_2$ ), 63.7 (CH), 61.0 ( $CH_2$ ), 49.0 (CH), 37.9 ( $CH_2$ ), 27.7 ( $CH_3$ ), 23.3 ( $CH_2$ ), 20.5 ( $CH_3$ ), 18.0 ( $CH_2$ ); IR (ATR)  $\nu$  2989, 2941, 2874, 1699, 1423, 1379, 1232, 1033, 768, 699  $cm^{-1}$ ; HRMS (ESI) for  $C_{17}H_{23}NO_4Na$   $[M+Na]^+$  calculated: 328.1519; found: 328.1525.

**4.12. (2*S*,3*S*)-Benzyl 3-hydroxy-2-(hydroxymethyl)piperidine-1-carboxylate (**15**)**

A solution of amine **14** (220.0 mg, 0.72 mmol) in solvent mixture methanol/3M HCl (31.5 mL, v/v = 2/1) was stirred at room temperature for 1 h. After the volatiles were removed under reduced pressure, the residue was purified by column chromatography ( $SiO_2$ ; eluent: dichloromethane/methanol = 95/5), to give the title compound **15** (137.6 mg, 72%) as a colorless viscous oil.  $[\alpha]_D^{20} +20.3$  (c 1.00,  $CH_2Cl_2$ ), [lit.<sup>19</sup> ent  $[\alpha]_D^{25} +6.24$  (c 0.25,  $H_2O$ )];  $^1H$  NMR (500 MHz,  $CDCl_3$  + drop of  $D_2O$ )  $\delta$  7.39–7.28 (m, 5H), 5.12 (d,  $J=2.4$  Hz, 2H), 4.52–4.43 (m, 1H), 4.16–4.07 (m, 1H), 3.97–3.84 (m, 2H), 3.82–3.73 (m, 1H), 3.44 (bs, 1H), 2.92 (bs, 1H), 1.87–1.80 (m, 1H), 1.75–1.68 (m, 1H), 1.62 (ddd,  $J=23.9, 12.4, 4.0$  Hz, 1H), 1.53–1.41 (m, 1H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  156.1 (C), 136.4 (C), 128.5 (CH),

128.0 (CH), 127.7 (CH), 69.2 (CH), 67.4 ( $CH_2$ ), 59.1 ( $CH_2$ ), 56.6 (CH), 39.8 ( $CH_2$ ), 28.3 ( $CH_2$ ), 23.6 ( $CH_2$ ); IR (ATR)  $\nu$  3394, 2936, 1675, 1432, 1258, 1074, 999, 738, 699  $cm^{-1}$ ; HRMS (ESI) for  $C_{14}H_{20}NO_4$   $[M+H]^+$  calculated: 266.1387; found: 266.1383.

**4.13. (2*R*,3*S*)-1-(Benzyloxycarbonyl)-3-hydroxypiperidine-2-carboxylic acid (**16**)**

A solution of compound **15** (52.0 mg, 0.20 mmol), (diacetoxy)iodobenzene (71.6 mg, 0.22 mmol) and TEMPO (8.0 mg, 0.05 mmol, 25 mol%) in abs. dichloromethane (3.4 mL) was stirred at room temperature for 3 h, under an argon atmosphere.<sup>20</sup> The reaction was quenched by the addition of sat. aq.  $Na_2S_2O_3$  (5 mL) and stirred for 30 min. The mixture was extracted with dichloromethane (3  $\times$  20 mL) and the combined organic extract was dried over anhydrous  $MgSO_4$ , filtered and concentrated under reduced pressure. The residue was used without further purification.

To a stirred solution of crude aldehyde (obtained from **15** (52.0 mg, 0.20 mmol)) in acetonitrile (1.1 mL) was added the solution of  $NaH_2PO_4 \cdot H_2O$  (6.1 mg, 0.04 mmol) in water (0.3 mL) and 30%  $H_2O_2$  (40.0  $\mu$ L, 0.51 mmol). The mixture was stirred and cooled at -10  $^\circ C$ ,  $NaClO_2$  (31.2 mg, 0.34 mmol) in water (0.6 mL) was added dropwise over 30 min, the reaction mixture was then stirred at 15  $^\circ C$ . After 3 h, the reaction was quenched by addition of a small amount of  $Na_2SO_3$  (11.3 mg) and acidified with 10% aq HCl (5 mL). The organic layer was separated, aqueous layer was extracted with EtOAc (4  $\times$  5 mL), the combined organic extract was evaporated, and the residue was dissolved in 10% aq.  $NaHCO_3$  (15 mL). The bicarbonate layer was washed with EtOAc (15 mL) and then made acidic to pH 2 and extracted with EtOAc (3  $\times$  15 mL). The organic extract was dried over anhydrous  $MgSO_4$ , filtered and concentrated under reduced pressure. The residue was purified by column chromatography ( $SiO_2$ ; eluent: dichloromethane/methanol = 8/2), to give 24.7 mg (45% over two steps) of the title compound **16**, as a colorless viscous oil.  $[\alpha]_D^{20} +13.4$  (c 0.42,  $CH_2Cl_2$ ), [lit.<sup>19</sup> ent  $[\alpha]_D^{25} -13.9$  (c 0.42,  $CH_2Cl_2$ )];  $^1H$  NMR (500 MHz,  $CDCl_3$ )  $\delta$  7.39–7.28 (m, 5H), 7.25–6.60 (bs, 1H), 5.20–5.12 (m, 2H), 5.12–4.98 (m, 1H), 4.10–3.94 (m, 1H), 3.92–3.83 (m, 1H), 2.98–2.74 (m, 1H), 2.06–1.96 (m, 1H), 1.77–1.66 (m, 1H), 1.58–1.43 (m, 2H);  $^{13}C$  NMR (126 MHz,  $CDCl_3$ )  $\delta$  172.2 (C), 156.7 (C), 135.8 (C), 128.5 (CH), 128.2 (CH), 127.8 (CH), 68.6 (CH), 68.1 ( $CH_2$ ), 57.6 (CH), 40.8 ( $CH_2$ ), 29.6 ( $CH_2$ ), 23.4 ( $CH_2$ ); IR (ATR)  $\nu$  3336, 2952, 2869, 1702, 1423, 1260, 1155, 975, 751, 699  $cm^{-1}$ ; HRMS (ESI) for  $C_{14}H_{17}NO_5Na$   $[M+Na]^+$  calculated: 302.0999; found: 302.0996.

**4.14. (2*R*,3*S*)-3-Hydroxypiperidine-2-carboxylic acid (3-hydroxypipicolinic acid, *ent*-3)**

A suspension of compound **16** (13.2 mg, 0.05 mmol) and 10% Pd/C (2.0 mg, 0.002 mmol) in methanol (0.7 mL) was stirred for 1 h under a hydrogen atmosphere (1 bar). The reaction mixture was filtered through celite, concentrated under reduced pressure and purified by column chromatography ( $SiO_2$ ; eluent: EtOAc/EtOH/ $H_2O$  = 4/4/2), to give the title compound *ent*-**3** (6.1 mg, 90%) as a colorless, viscous oil.  $[\alpha]_D^{20} +48.3$  (c 0.3,  $H_2O$ ), [lit.<sup>21</sup>  $[\alpha]_D^{27} +51.0$  (c 0.75,  $H_2O$ )];  $^1H$  NMR (500 MHz,  $D_2O$ )  $\delta$  4.56–4.51 (m, 1H), 3.70 (d,  $J=1.8$  Hz, 1H), 3.47–3.41 (m, 1H), 3.08–2.99 (m, 1H), 2.08–1.95 (m, 2H), 1.86–1.72 (m, 2H);  $^{13}C$  NMR (126 MHz,  $D_2O$ )  $\delta$  172.3 (C), 64.1 (CH), 62.2 (CH), 43.6 ( $CH_2$ ), 28.7 ( $CH_2$ ), 15.8 ( $CH_2$ ); IR (ATR)  $\nu$  3060, 2928, 2856, 1630, 1405, 1254, 1113, 998, 735  $cm^{-1}$ ; HRMS (ESI) for  $C_6H_{12}NO_3$   $[M+H]^+$  calculated: 146.0812; found: 146.0809.

## 4.15. (2S,3S)-2-(Hydroxymethyl)piperidin-3-ol (17)

A suspension of **15** (12.9 mg, 0.05 mmol) and 10% Pd/C (3.2 mg, 0.003 mmol) in methanol (0.7 mL) was stirred for 2 h under a hydrogen atmosphere (1 bar). The reaction mixture was filtered through celite, concentrated under reduced pressure and purified by ion exchange column chromatography (acidic resin DOWEX 50WX8-100), to give the title compound **17** (6.1 mg, 95%), as a pale yellow, viscous oil.  $[\alpha]_{\text{D}}^{20} +13.3$  (c 0.60, H<sub>2</sub>O),  $[\text{lit.}^{19} \text{ent} [\alpha]_{\text{D}}^{25} -13.2$  (c 2.51, H<sub>2</sub>O)],  $[\alpha]_{\text{D}}^{20} +10.8$  (c 0.38, MeOH),  $[\text{lit.}^{22} [\alpha]_{\text{D}}^{28} +10.8$  (c 0.50, MeOH)]; <sup>1</sup>H NMR (500 MHz, D<sub>2</sub>O)  $\delta$  4.03–3.99 (m, 1H), 3.67 (ddd,  $J=19.0, 11.5, 6.7$  Hz, 2H), 3.15–3.08 (m, 1H), 2.90 (ddd,  $J=11.1, 7.2, 3.6$  Hz, 1H), 2.72 (td,  $J=12.4, 3.2$  Hz, 1H), 1.93–1.86 (m, 1H), 1.82–1.68 (m, 2H), 1.60–1.53 (m, 1H); <sup>13</sup>C NMR (126 MHz, D<sub>2</sub>O)  $\delta$  64.4 (CH), 61.4 (CH<sub>2</sub>), 59.5 (CH), 44.3 (CH<sub>2</sub>), 29.7 (CH<sub>2</sub>), 18.9 (CH<sub>2</sub>); IR (ATR)  $\nu$  3308, 2937, 2863, 1596, 1440, 1099, 1037, 993, 734 cm<sup>-1</sup>.

## Acknowledgments

This work was supported by the Serbian Ministry of Education, Science and Technological Development (project No. 172027) and the Serbian Academy of Sciences and Arts (Proj. No. F193). The authors gratefully acknowledge the support of the humanitarian foundation "Hrast" and the support of Dr. Ivan Trifunovic. The authors acknowledge the support of the FP7 RegPot project FCUB ERA GA No. 256716. The EC does not share responsibility for the content of the article.

## Supplementary Material

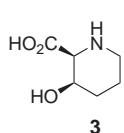
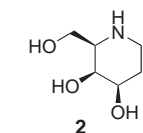
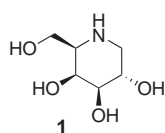
Copies of NMR spectra for all compounds are available as the electronic version at: <http://XXXXX>.

## References and notes

- <sup>1</sup> (a) Asano, N.; Nash, R. J.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **2000**, *11*, 1645; (b) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265; (c) *Iminosugars: From Synthesis to Therapeutic Applications*; P. Compain, O. R. Martin Eds.; Wiley: Chichester, 2007; (d) Nash, R. J.; Kato, A.; Yu, C.-Y.; Fleet, G. W. J. *Future Med. Chem.* **2011**, *3*, 1513; (e) Li, J.; Browning, S.; Mahal, S. P.; Oelschlegel, A. M.; Weissmann, C. *Science* **2010**, *327*, 869; (e) Lahiri, R.; Ansari, A. A.; Vankar, Y. D. *Chem. Soc. Rev.* **2013**, *42*, 5102.
- <sup>2</sup> (a) Butters, T. D.; Dwaek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683; (b) Kolter, T.; Sandhoff, K. *Angew. Chem. Int. Ed.* **1999**, *38*, 1532.
- <sup>3</sup> (a) Fan, J.-Q.; Ishii, S.; Asano, N.; Suzuki, Y. *Nature Med.* **1999**, *5*, 112; (b) Asano, N.; Ishii, S.; Kizu, H.; Ikeda, K.; Yasuda, K.; Kato, A.; Martin, O. R.; Fan, J.-Q. *Eur. J. Biochem.* **2000**, *267*, 4179.
- <sup>4</sup> van den Berg, R. J. B. H. N.; Wennekes, T.; Ghisaidoobe, A.; Donker-Koopman, W. E. Strijland, A.; Boot, R. G.; van der Marel, G. A.; Aerts, J. M. F. G.; Overkleef, H. S. *ACS Med. Chem. Lett.* **2011**, *2*, 519.
- <sup>5</sup> Ajish Kumar, K. S.; Rathee, J. S.; Subramanian, M.; Chattopadhyay, S. *J. Org. Chem.* **2013**, *78*, 7406.
- <sup>6</sup> For a review article on syntheses of 3-hydroxyproline acids, see: Cochi, A.; Pardo, D. G.; Cossy, J. *Eur. J. Org. Chem.* **2013**, 809.
- <sup>7</sup> (a) Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H.; Kato, A.; Adachi, I. *J. Org. Chem.* **2003**, *68*, 3606; (b) Kato, A.; Miyauchi, S.; Kato, N.; Nash, R. J.; Yoshimura, Y.; Nakagome, I.; Hirono, S.; Takahata, H.; Adachi, I. *Bioorg. Med. Chem.* **2011**, *19*, 3558.
- <sup>8</sup> Takahata, H.; Banba, Y.; Ouchi, H.; Nemoto, H. *Org. Lett.* **2003**, *5*, 2527.
- <sup>9</sup> Kumari, N.; Gopal Reddy, B.; Vankar, Y. D. *Eur. J. Org. Chem.* **2009**, 160.
- <sup>10</sup> Corkran, H. M.; Munneke, S.; Dangerfield, E. M.; Stocker, B. L.; Timmer, M. S. M. *J. Org. Chem.* **2013**, *78*, 9791.
- <sup>11</sup> Trajkovic, M.; Balanac, V.; Ferjancic, Z.; Saicic, R. N. *RSC Adv.* **2014**, *4* (96), 53722.
- <sup>12</sup> Marjanovic, J.; Divjakovic, V.; Matovic, R.; Ferjancic, Z.; Saicic, R. N. *Eur. J. Org. Chem.* **2013**, 5555.
- <sup>13</sup> Castillo, J. A.; Calveras, J.; Casas, J.; Mitjans, M.; Vinardell, M. P.; Parella, T.; Inoue, T.; Sprenger, G. A.; Joglar, J.; Clapes, P. *Org. Lett.* **2006**, *8*, 6067.
- <sup>14</sup> Pohjakallio, A.; Pihko, P. M. *Chem. Eur. J.* **2009**, *15*, 3960. Alternatively, aldehyde **5** can be prepared from commercially available benzyl-3-butenyl amine, via a benzyloxycarbonylation/ozonolysis sequence, in 80% yield: Brands, K. M. J.; Meekel, A. A. P.; Pandit, U. K. *Tetrahedron* **1991**, *47*, 2005.
- <sup>15</sup> For selected review articles on enamine organocatalyzed aldol reactions, see: (a) Notz, W.; Tanaka, F.; Barbas, C. F. III, *Acc. Chem. Res.* **2004**, *37*, 580; (b) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471; (c) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131; (d) Heravi, M. M.; Asadi, S. *Tetrahedron: Asymmetry* **2012**, *23*, 1431; (e) Bisai, V.; Bisai, A.; Singh, V. K. *Tetrahedron* **2012**, *68*, 4541.
- <sup>16</sup> For the first examples of organocatalyzed aldol reactions with dioxanone, see: (a) Suri, J. T.; Ramachary, D. B.; Barbas, C. F., III *Org. Lett.* **2005**, *7*, 1383. (b) Enders, D.; Grondal, C. *Angew. Chem. Int. Ed.* **2005**, *44*, 1210. (c) Ibrahim, I.; Cordova, A. *Tetrahedron Lett.* **2005**, *46*, 3363.
- <sup>17</sup> Kato, A.; Miyauchi, S.; Kato, N.; Nash, R. J.; Yoshimura, Y.; Nakagome, I.; Hirono, S.; Takahata, H.; Adachi, I. *Bioorg. Med. Chem.* **2011**, *19*, 3558.
- <sup>18</sup> Maslak, V.; Matovic, R.; Saicic, R. N. *Tetrahedron.* **2004**, *60*, 8957.
- <sup>19</sup> Kalamkar, N. B.; Kasture, V. M.; Dhaval, D. D. *J. Org. Chem.* **2008**, *73*, 3619.
- <sup>20</sup> Meister, A. C.; Nieger, M.; Bräse, S. *Chem. Eur. J.* **2013**, *19*, 10836.
- <sup>21</sup> Yoshimura, Y.; Ohara, C.; Imahori, T.; Saito, Y.; Kato, A.; Miyauchi, S.; Adachi, I.; Takahata, H. *Bioorg. Med. Chem.* **2008**, *16*, 8273.
- <sup>22</sup> Kim, I. S.; Oh, J. S.; Zee, O. P.; Jung, Y. H. *Tetrahedron*, **2007**, *63*, 2622.



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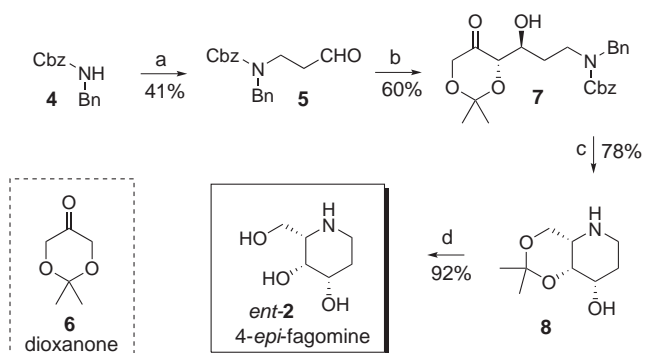


1-deoxygalactonojirimycin

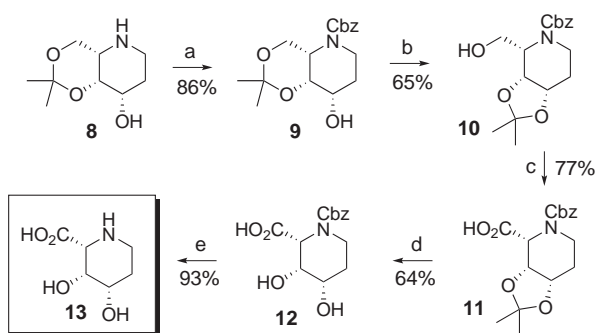
(+)-4-epi-fagomine

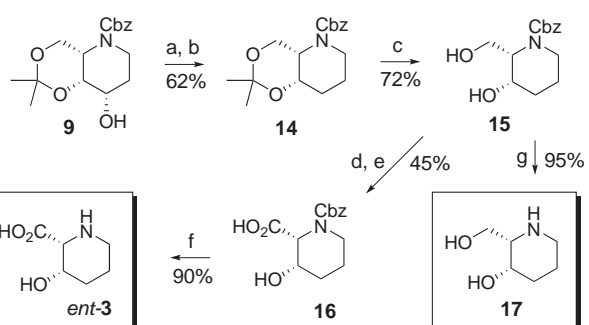
3-hydroxypipercolic acid

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## Organocatalyzed synthesis of (-)-4-*epi*-fagomine and the corresponding pipercolic acids

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