

SHORT  
COMMUNICATIONS

## Synthesis of New Iminosugar Derivatives Based on (*S*)-(1,2,3,6-Tetrahydropyridazin-3-yl)methanol

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**Abstract**—(*S*)-(1,2,3,6-Tetrahydropyridazin-3-yl)methanol was synthesized in two steps by the Diels–Alder reaction of penta-2,4-dien-1-ol with diethyl azodicarboxylate in the presence of (*S*)-BINOL as chiral catalyst. The subsequent Boc-protection of the 2-position of the pyridazine ring, ring-closing carbonylation of the hydroxy group, and deprotection afforded a bicyclic iminosugar analog. The structure of the isolated compounds was proved by NMR, IR, and mass spectra and elemental analyses.

**Keywords:** pyridazine, imino sugars, 1-azafagomine, Diels–Alder reaction, *S*-BINOL, Boc protection.

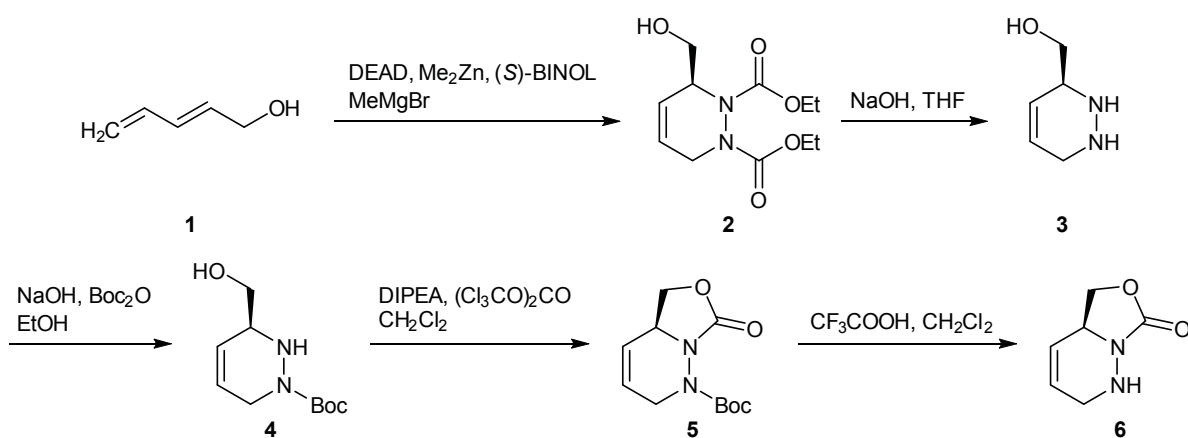
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Azasugars or iminosugars are organic compounds containing a ring nitrogen atom that have attracted keen interest in recent time [1–3]. The reason is that shift of the nitrogen atom to the pseudoanomeric position (which corresponds to the anomeric position in a monosaccharide) in a classical nojirimycin type iminosugar glucosidase inhibitor sharply enhances the inhibitory activity; therefore, such glucosidase inhibitors were discerned as a separate class, so-called 1-azasugars [4, 5]. Among this class of compounds, 1-azafagomine was shown to efficiently inhibit both  $\alpha$ - and  $\beta$ -glucosidases [6, 7]. The biological activity of 1-azafagomine originates from the fact that it mimics transition states in the cleavage of  $\alpha$ - and  $\beta$ -glucosides in the protonated form [8]. This stimulated development of methods for the synthesis of new iminosugar analogs. Concurrently, *in vivo* assays revealed broad spectrum of biological activity of these compounds, in particular antiviral, antibacterial, antiprotozoal, anti-parasitic, antipsoriatic, antifungal, nematocidal, insecticidal, anti-inflammatory, and antitumor [10–15]. Glycosidase inhibitors were found to be useful in the treatment of lysosomal memory disorders (Gaucher, Fabry, Sandhoff, and Tay-Sachs diseases); they can also be used as antidiabetic, antimicrobial, anticancer, and immunosuppressive agents [8, 9]. Obviously, the scope of application of iminosugars has become very interesting for both chemical and biological studies.

Taking into account the significance of iminosugars, we set ourselves the goal of obtaining new bicyclic 1-azafagomine analogs on the basis of (*S*)-(1,2,3,6-tetrahydropyridazin-3-yl)methanol (**3**). The starting compound was penta-2,4-dien-1-ol (**1**) which was prepared from penta-2,4-dienoic acid according to [16]. [4+2]-Cycloaddition of **1** and diethyl azodicarboxylate (DEAD) in the presence of (*S*)-BINOL as chiral catalyst gave enantiomerically pure adduct **2** with the *S* configuration of C<sup>3</sup> [17]. The carbamate moieties were removed from **2** by heating in boiling dioxane for 3 h in the presence of 2 M sodium hydroxide, followed by acidification with an acidic ion exchanger (Amberlite<sup>®</sup>, H-form). Pure compound **3** was isolated in 91% yield by recrystallization from acetone (Scheme 1). The 2-position in **3** was protected by treatment with Boc<sub>2</sub>O, and new *N*-Boc-1-azafagomine **4** thus obtained (yield 93%) was reacted with triphosgene in the presence of DIPEA in an inert atmosphere. As a result, bicyclic compound **5** was formed in 5 min and was isolated in 90% yield after purification by column chromatography. Finally, deprotection of **5** by the action of trifluoroacetic acid in methylene chloride at room temperature afforded target product **6**.

(**2E**)-Penta-2,4-dien-1-ol (**1**) was synthesized according to the procedure described in [16]. Yield 5 g (31.4%). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>),  $\delta$ , ppm: 3.12 br.s

Scheme 1.



(1*H*, OH), 4.07 m (2*H*, CH<sub>2</sub>OH), 5.01 d (1*H*, CH,  $J = 9.6$  Hz), 5.13 d (1*H*, CH,  $J = 16.4$  Hz), 5.74 d.t (1*H*, CH=CH<sub>2</sub>OH,  $J = 14.7, 5.7$  Hz), 6.25 m (2*H*, CH<sub>2</sub>=CH). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ<sub>C</sub>, ppm: 62.3 (CH<sub>2</sub>), 116.9 (CH<sub>2</sub>), 131.2 (CH), 132.5 (CH), 136.2 (CH). Found, %: C 71.47; H 9.48. C<sub>5</sub>H<sub>8</sub>O. Calculated, %: C 71.42; H 9.52.

**Diethyl (3*S*)-3-(hydroxymethyl)pyridazine-1,2-(3*H*,6*H*)-dicarboxylate (2).** A 1.2 M solution of Me<sub>2</sub>Zn in toluene (991 μL, 1.19 mmol) was added at 0°C to a solution of 0.100 g (1.19 mmol) of penta-2,4-dien-1-ol (1) in anhydrous toluene (6 mL), and the mixture was stirred for 5 min. Solution A was thus obtained. A 1.4 M solution of MeMgBr in toluene/THF (849 μL, 1.19 mmol) was added at 0°C to a solution of 0.340 g (1.19 mmol) of (*S*)-BINOL in 6 mL of anhydrous toluene, and the mixture was stirred for 5 min to obtain solution B. Solution A was diluted with anhydrous toluene (10 mL) and added to solution B, and the mixture was stirred for 5 min and cooled to -78°C. A solution of diethyl azodicarboxylate (543 μL, 1.19 mmol) in anhydrous toluene (10 mL) was added, and the mixture was stirred for 5 min at -78°C, allowed to slowly warm up to room temperature, and stirred for 18 h. The mixture was then quenched with a saturated solution of sodium hydrogen carbonate (1 mL) and filtered, and the precipitate was washed with ethyl acetate (3×20 mL). The filtrate was combined with the washings and evaporated under reduced pressure, and the residue (yellow oil) was purified by column chromatography using petroleum ether–diethyl ether (1:1) as eluent. In addition, (*S*)-BINOL, 0.200 g (69%), was partially recovered during chromatographic purification. Yield of 2 0.225 g (73%), yellow oil, [α]<sub>D</sub><sup>20</sup> = -23.4° ( $c = 1.25$ , CHCl<sub>3</sub>). IR spectrum, ν, cm<sup>-1</sup>: 3483 (OH), 1707 (C=O). <sup>1</sup>H NMR spectrum (CDCl<sub>3</sub>) δ,

ppm: 1.23–1.30 m (12*H*, CH<sub>3</sub>), 2.58 br.s (1*H*, OH), 3.35 d.d (1*H*,  $J = 12.3, 9.5$  Hz), 3.45 d.d (1*H*,  $J = 12.0, 9.8$  Hz), and 3.56–3.69 m (2*H*) (CH<sub>2</sub>OH); 3.77 d.d (1*H*, 6-*H*,  $J = 13.5, 4.3$  Hz), 3.91 br.s (1*H*, 6-*H*), 4.11–4.26 m (8*H*, OCH<sub>2</sub>), 4.30 t.d.d (1*H*, 6-*H*,  $J = 6.0, 3.9, 2.2$  Hz), 4.34–4.44 m (1*H*, 6-*H*), 4.72 br.s (2*H*, 3-*H*), 5.66–5.88 m (4*H*, 4-*H*, 5-*H*). <sup>13</sup>C NMR spectrum (CDCl<sub>3</sub>), δ<sub>C</sub>, ppm: 14.30 and 14.40 (CH<sub>3</sub>CH<sub>2</sub>), 42.20 and 43.60 (C<sup>6</sup>), 55.90 and 56.90 (C<sup>3</sup>), 61.90 (CH<sub>2</sub>OH); 62.60, 62.70, 62.80, and 62.90 (CH<sub>2</sub>CH<sub>3</sub>); 123.40, 124.20, 124.60, and 125.20 (C<sup>4</sup>, C<sup>5</sup>); 154.90, 155.70, 156.20, and 156.30 (C=O). Mass spectrum:  $m/z$  281.1108 [ $M + Na$ ]<sup>+</sup>. Found, %: C 51.21; H 6.91; N 10.81. C<sub>11</sub>H<sub>18</sub>N<sub>2</sub>O<sub>5</sub>. Calculated, %: C 51.16; H 6.97; N 10.85.

**(*S*)-(1,2,3,6-Tetrahydropyridazin-3-yl)methanol (3).** Compound 2, 0.119 g (0.461 mmol), was dissolved in 2 mL of THF, 2 mL of 2 M aqueous sodium hydroxide was added, and the mixture was refluxed for 3 h. The mixture was cooled, 2 mL of THF and a suspension of Amberlite® (H-form) in water were added, the mixture was stirred and filtered with suction, and the solvent was distilled off from the filtrate. Yield 0.048 g (91.0%), yellow oil, [α]<sub>D</sub><sup>20</sup> = -20° ( $c = 0.3$ , EtOH). IR spectrum, ν, cm<sup>-1</sup>: 3422 (N–H), 1643 (C=C). <sup>1</sup>H NMR spectrum (D<sub>2</sub>O), δ, ppm: 3.24 d.d.d (1*H*, 6-*H*,  $J = 2.6, 3.2, 17.2$  Hz), 3.35 d.d.d (1*H*, 6-*H*,  $J = 2.8, 5.2, 17.6$  Hz), 3.48–3.54 m (1*H*, 3-*H*), 3.57–3.65 m (2*H*, CH<sub>2</sub>OH), 5.79 d.d.d (1*H*, 4-*H*,  $J = 2.0, 4.4, 10.4$  Hz), 6.01 d.d.d (1*H*, 5-*H*,  $J = 2.4, 5.6, 10.4$  Hz). <sup>13</sup>C NMR spectrum (D<sub>2</sub>O), δ<sub>C</sub>, ppm: 44.2 (C<sup>6</sup>), 54.8 (C<sup>3</sup>), 62.5 (CH<sub>2</sub>OH), 125.0 (C<sup>4</sup>), 127.4 (C<sup>5</sup>). Mass spectrum:  $m/z$  114.0793 [ $M + H$ ]<sup>+</sup>. Found, %: C 52.67; H 8.74; N 24.51. C<sub>5</sub>H<sub>10</sub>N<sub>2</sub>O. Calculated, %: C 52.63; H 8.77; N 24.56.

**tert-Butyl (S)-3-(hydroxymethyl)-3,6-dihydropyridazine-1(2*H*)-carboxylate (4).** Sodium hydrox-

ide, 0.015 g (0.385 mmol), and  $\text{Boc}_2\text{O}$ , 0.015 g (0.385 mmol), were added to a mixture of 0.044 g (0.385 mmol) of compound **3** and 10 mL of ethanol. The mixture was stirred for 1 h at room temperature and filtered, and the precipitate was thoroughly washed with ethanol. The solution was concentrated to obtain a yellow solid which was dissolved in acetone, and the solution was filtered and evaporated. Yield 0.077 g (93%), yellow oil,  $[\alpha]_{\text{D}}^{20} = +67^\circ$  ( $c = 0.78$ ,  $\text{CH}_2\text{Cl}_2$ ). IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 3269 (OH), 1694 (CO).  $^1\text{H}$  NMR spectrum ( $\text{D}_2\text{O}$ ),  $\delta$ , ppm: 1.50 s (9H, *t*-Bu), 3.56–3.68 m (3H, 3-H, 3- $\text{CH}_2$ ), 3.96 br.d and 4.09 br.d (1H each, 6-H,  $J = 10.0$  Hz), 5.90 br.d (1H, 4-H,  $J = 8.8$  Hz), 5.96 br.d (1H, 5-H,  $J = 8.8$  Hz).  $^{13}\text{C}$  NMR spectrum ( $\text{D}_2\text{O}$ ),  $\delta_{\text{C}}$ , ppm: 27.6 [ $\text{C}(\text{CH}_3)_3$ ], 55.9 ( $\text{C}^3$ ), 61.8 (3- $\text{CH}_2$ ), 82.7 [ $\text{C}(\text{CH}_3)_3$ ], 125.0 ( $\text{C}^5$ ), 125.1 ( $\text{C}^4$ ), 156.8 ( $\text{C}=\text{O}$ ). Mass spectrum:  $m/z$  214.1317 [ $M + \text{H}$ ] $^+$ . Found, %: C 56.11; H 8.37; N 13.05.  $\text{C}_{10}\text{H}_{18}\text{N}_2\text{O}_3$ . Calculated, %: C 56.07; H 8.41; N 13.08.

**tert-Butyl (4a*S*)-7-oxo-4a,5-dihydro-7*H*-oxazolo[3,4-*b*]pyridazine-1(2*H*)-carboxylate (5).** Compound **4**, 0.114 g (0.532 mmol), was mixed with 10 mL of anhydrous methylene chloride, 0.93 mL (0.532 mmol) of DIPEA and 0.077 g (0.532 mmol) of triphosgene were added, and the mixture was stirred for 5 min at room temperature in a nitrogen atmosphere. The solvent was distilled off, and the residue was purified by column chromatography using ethyl acetate–petroleum ether (1:1) as eluent. Yield 0.077 g (90%), yellow oil,  $[\alpha]_{\text{D}}^{20} = +30^\circ$  ( $c = 0.4$ ,  $\text{CH}_2\text{Cl}_2$ ). IR spectrum:  $\nu$  1717  $\text{cm}^{-1}$  ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR spectrum ( $\text{DMSO-}d_6$ ),  $\delta$ , ppm: 3.46 d (1H,  $J = 11.2$ , 7.2 Hz), 3.55 d.d (1H,  $J = 11.2$ , 4.8 Hz), 3.71 br.s (1H), 4.02 d.d (2H,  $J = 4.8$ , 2.4 Hz), 5.86 d.d.d (1H,  $J = 8.4$ , 4.8, 2.0 Hz), 5.89 d.m (1H,  $J = 8.8$  Hz).  $^{13}\text{C}$  NMR spectrum ( $\text{DMSO-}d_6$ ),  $\delta_{\text{C}}$ , ppm: 27.4, 27.7, 27.8, 27.9 ( $\text{CH}_3$ ), 43.3, 43.8 ( $\text{CH}_2\text{N}$ ), 53.0, 55.6, 56.2 (CH), 59.9, 60.4 ( $\text{CH}_2\text{O}$ ), 81.6, 83.0 ( $\text{C}=\text{O}$ ), 123.8–124.5 (CH), 152.6 ( $\text{C}=\text{O}$ ), 153.6 ( $\text{C}=\text{O}$ ). Mass spectrum:  $m/z$  240.0793 [ $M + \text{H}$ ] $^+$ . Found, %: C 55.05; H 6.63; N 11.69.  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_4$ . Calculated, %: C 55.00; H 6.66; N 11.66.

**(*S*)-1,2,4a,5-Tetrahydro-7*H*-oxazolo[3,4-*b*]pyridazin-7-one (6).** Trifluoroacetic acid, 2.76 mL (0.574 mmol), was added to a solution of 0.138 g (0.574 mmol) of compound **5** in 11 mL of methylene chloride, and the mixture was stirred for 2 h at room temperature. The mixture was then treated with a saturated solution of sodium hydrogen carbonate and extracted with ethyl acetate (3×30 mL). The organic phase was dried over  $\text{MgSO}_4$ , the solvent was distilled off, and the residue was purified by column chromatography using ethyl acetate–petroleum ether (2:1) as

eluent. Yield 0.061 g (76%), yellow oil. IR spectrum,  $\nu$ ,  $\text{cm}^{-1}$ : 2926 (N–H), 1788 ( $\text{C}=\text{C}$ ), 1729 ( $\text{C}=\text{O}$ ).  $^1\text{H}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta$ , ppm: 3.90–4.03 d.d.d (1H,  $J = 18.4$ , 3.6, 2.0 Hz), 4.20–4.26 m (2H), 4.45–4.50 m (1H), 4.52–4.58 m (1H), 4.62 d.d (1H,  $J = 8$ , 1.2 Hz), 5.87 br.d (1H,  $J = 8.4$  Hz), 6.00–6.10 m (1H).  $^{13}\text{C}$  NMR spectrum ( $\text{CDCl}_3$ ),  $\delta_{\text{C}}$ , ppm: 39.7 ( $\text{CH}_2\text{N}$ ), 47.6 ( $\text{CH}_2\text{N}$ ), 52.9, 53.7 (CH), 67.10, 67.12 ( $\text{CH}_2\text{O}$ ), 124.3, 124.7, 125.8, 125.9 (CH), 156.4–156.6 ( $\text{C}=\text{O}$ ). Mass spectrum:  $m/z$  140.0586 [ $M + \text{H}$ ] $^+$ . Found, %: C 51.42; H 5.75; N 19.99.  $\text{C}_6\text{H}_8\text{N}_2\text{O}_2$ . Calculated, %: C 51.48; H 5.81; N 19.91.

All commercially available reagents (Merck) were used without further purification. The progress of reactions was monitored by TLC on Silufol UV-254 plates. The optical rotations were measured on an Autopol III polarimeter. Elemental analysis was performed with a Carlo Erba 1108 analyzer. The NMR spectra were recorded on a Bruker Avance 400 spectrometer (Germany) at 400 and 100.6 MHz, respectively. The IR spectra were recorded in the range 4000–400  $\text{cm}^{-1}$  on a Bomem MB 104 spectrometer at room temperature. The high-resolution mass spectra (electrospray ionization) were obtained on Varian 500-MS LC Ion Trap and VG AutoSpec-M mass spectrometers.

## CONFLICT OF INTERESTS

The authors declare the absence of conflict of interests.

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