Chemoenzymatic Synthesis of Enantiopure 1-Azafagomine

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A new chemoenzymatic synthesis of both enantiomeric forms of the glycosidase inhibitor 1-azafagomine (**1**) is reported. The synthesis starts from the achiral starting materials pentadienol and methylurazol with the key steps being a hetero-Diels−Alder reaction followed by a lipase R/Novozym 435-catalyzed enantioselective esterification of the Diels−Alder adduct.

Introduction

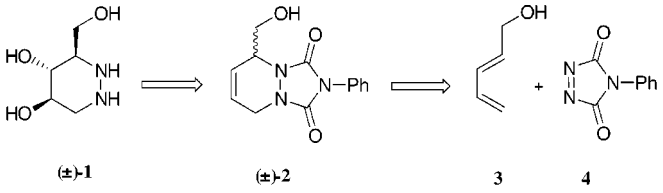
Potent glycosidase inhibitors are important compounds both as potential drug candidates and biochemical tools. Recently, our group reported the strong, racemic glycosidase inhibitor 1-azafagomine (**1**);[1] subsequently, we have found, by synthesis of both enantiomers from D- and L-xylose, that only the (−)-**1** form is biological active.[2,3] The synthesis of (−)-**1** is relatively long,[3] and the starting material L-xylose is relatively expensive compared to the exceptionally short synthesis of (±)-**1** starting from achiral materials.[1] We therefore in this paper report an alternative synthesis of enantiopure **1** that combines the Diels−Alder strategy of the racemic synthesis with a lipase-catalyzed resolution step.

Results and Discussion

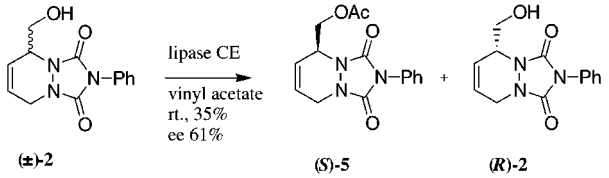
The previous synthesis of (±)-**1** consisted of four steps: (1) Diels−Alder reaction of 2,4-pentadienol (**3**) and 4-phenyltriazoline-3,5-dione (**4**) to give (±)-**2**, (2) epoxidation, (3) hydrolysis, and (4) deprotection (Scheme 1). Since the overall yield was good (32%), this synthesis was an attractive basis for an improved synthesis of enantiopure **1**, if, in some way, one of the intermediates in the racemic synthesis could be resolved. We chose to attempt biocatalytic kinetic resolution using lipases, and for this purpose, (±)-**2** seemed the best candidate, since it is a monool. This was previously attempted using lipase-catalyzed esterification with vinyl acetate as acetyl donor.[3] Over 20 lipases were screened, and lipase CE showed the best stereoselectivity. With this enzyme, the transesterification of (±)-**2** gave (*S*)-**5** in 35% yield and 61% ee (Scheme 2). The stereoselectivity of this reaction was, however, far too modest to be practically useful.

It was now suggested that the moderate selectivity was due to the fact that the phenyl group is too bulky to be well accommodated in the enzyme-binding pocket. A number of reports describe successful kinetic resolution with lipases of hydroxymethylated piperidines,[4,5] but in all cases the substrates had less bulky substituents on nitrogen. Therefore, we decided to replace the phenyl group with a methyl group to reduce the steric bulk in this region.

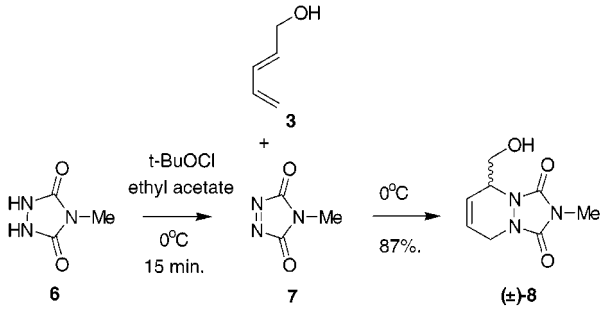
Scheme 1. Strategy for the Synthesis of 1-Azafagomine



Scheme 2. Lipase-Catalyzed Transesterification of Racemic 2



Scheme 3. Preparation of (±)-8



The substrate (±)-**8** was easily obtained using our method for synthesis of (±)-**2**. Thus, 4-methyl-1,2,4-triazoline-3,5-dione (**7**) was prepared in situ by *tert*-butyl hypochlorite oxidation of 4-methylurazol (**6**). This compound and pentadienol[6] (**3**) underwent Diels−Alder reaction to provide **8** as a colorless solid in 87% yield (Scheme 3).

Lipase-catalyzed transesterification of (±)-**8** using vinyl acetate as acetyl donor was tested first (Scheme 4). Over 20 different enzymes were screened; many enzymes showed no reaction or low rate, but four enzymes were

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Scheme 4. Lipase-Catalyzed Transesterification of (±)-8

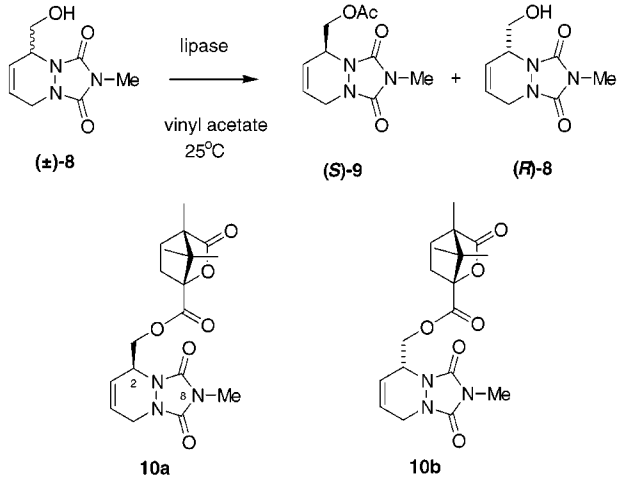


Table 1

enzyme[a] (mg)	(±)-**1** (mg)	time	P (major)	vinyl acetate (mL)	conversn (%)	ee (%)	*E*
Novozym 435 (30 mg)	150	8 d	(*S*)-**9**	5	47	60	6.7
Lipase CE (25 mg)	100	8 d	(*S*)-**9**	5	4	25	1.7
PPL (25 mg)	100	48 h	(*S*)-**9**	5	12	31	2.0
Lipase R (25 mg)	100	17 h	(*S*)-**9**	5	12	96	56

[a]Novozym 435: lipase from *Candida antarctica*. Lipase CE: lipase from *Humicola langinosa*. PPL: lipase from hog pancreas. Lipase R: lipase from *Penicillium roqueforti*.

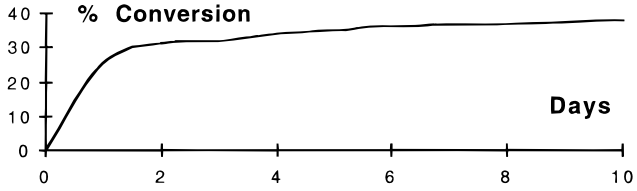


Figure 1. Conversion of **8** to (*S*)-**9** catalyzed by lipase R in vinyl acetate as a function of time.

selected for further screening (Table 1). The selectivities of PPL and lipase CE were very low, while Novozym 435 showed a practical conversion rate but relatively poor selectivity ($E = 6.7$). The best selectivity was achieved using lipase R (lipase from *Penicillium roqueforti*, 17 h, 12% conversion, 96% ee). This corresponds to a selectivity of 56:1 between the two enantiomers (Table 1).

At long reaction times, particularly when the reaction was scaled up, the reaction rate went drastically down (Figure 1). The reaction did not run to completion in a reasonable time and was stopped at ca. 40% conversion. The typical preparative lipase R catalyzed kinetic resolution provided (*S*)-**9** in 38% yield and 86% ee and (*R*)-**8** in 60% yield and 59% ee. The enantiopurity of (*S*)-**9** could not be enhanced by recrystallization. However, after saponification of the enantiomerically enriched (*S*)-**9**, recrystallization of (*S*)-**8**, provided enantiopure alcohol with 76% mass recovery.

The enatiomeric ratios of the products were determined by converting the alcohol **8** to a pair of diastereomeric esters **10a** and **10b** with optically active camphanic acid. Samples of **8** were reacted with camphanoyl chloride in DMAP/Et_3N/CH_2Cl_2 to form **10a** and **10b**. These two esters had very large differences of chemical shift on a number of protons, especially those neighboring the ester (Table 2). The enantiomeric ratio of **9** was determined in the same way, by first saponifying the acetate to form **8**.

Table 2. Chemical Shift Differences in 10a and 10b

	$\Delta\delta$ = **10a** − **10b** in ppm
2′a-H	0.17
2′b-H	0.16
2-H	0.07
8-CH_3	−0.04

As mentioned above, the unreacted **8** from the enzymatic esterification was now enatiomerically enriched with (*R*)-alcohol. It was subjected to another enzymatic resolution step using the *Candida antartica* (Novozyme) lipase. This enzyme had a lower selectivity than lipase R but was chosen because of its greater reaction rate. After about 50% conversion, 48% of the starting material (*R*)-**8** was isolated with 99% ee. Thus both enantiopure (*R*)-**8** and (*S*)-**8** were obtainable.

With both enantiomers in the hand, we could complete the synthesis. Alkenol (*S*)-**8** was epoxidized using (trifluoromethyl)methyldioxirane, which was generated in situ, to give two possible diastereomers (−)-**11** and (−)-**12** in a 3:1 ratio (according to ^{1}H NMR). The two diastereomers were separable by chromatography (silica gel, ethyl acetate) to give (−)-**11** (68%) and (−)-**12** (13%), respectively. *trans*-Epoxide (−)-**11** was regioselectively hydrolyzed in the presence of perchloric acid to give crude triol **13a**. Finally, reaction of **13a** with hydrazine hydrate provided (−)-**1** (51% over two steps, Scheme 5).

The specific rotation of the product was −8.6° and thus close to the −9.8° obtained on material synthesized from L-xylose.[3] To check the optical purity of (−)-**1** it was converted into the derivative **14**, which was analyzed by chiral HPLC. This showed the optical purity of (−)-**1** to be 99% ee. This value is identical to the value determined for **8**. Thus, there is no loss in enantiomeric purity during the synthesis.

Similarly to the synthesis of (−)-**1**, (*R*)-**8** was epoxided to (+)-**11** and (+)-**12** in essentially identical yields. These were separated, and (+)-**11** was hydrolyzed to give **13b**, which finally was hydrazinolyzed to (+)-**1**. The product had a rotation of +10.2° as compared with +10° obtained on material synthesized from D-xylose.[2,3] Given the knowledge that no loss of enantiomeric purity occurred during the synthesis, and the fact that the optical rotation of (+)-**1** fitted perfectly with the literature value, it was pointless to check the enantiomeric purity further.

From the comparison of the rotations the absolute configuration of **1** and absolute configurations of compounds **8**, **9**, (−)-**11**/(+)-**11,** (−)-**12**/(+)-**12,** and **13a**/**13b** were determined (Scheme 6).

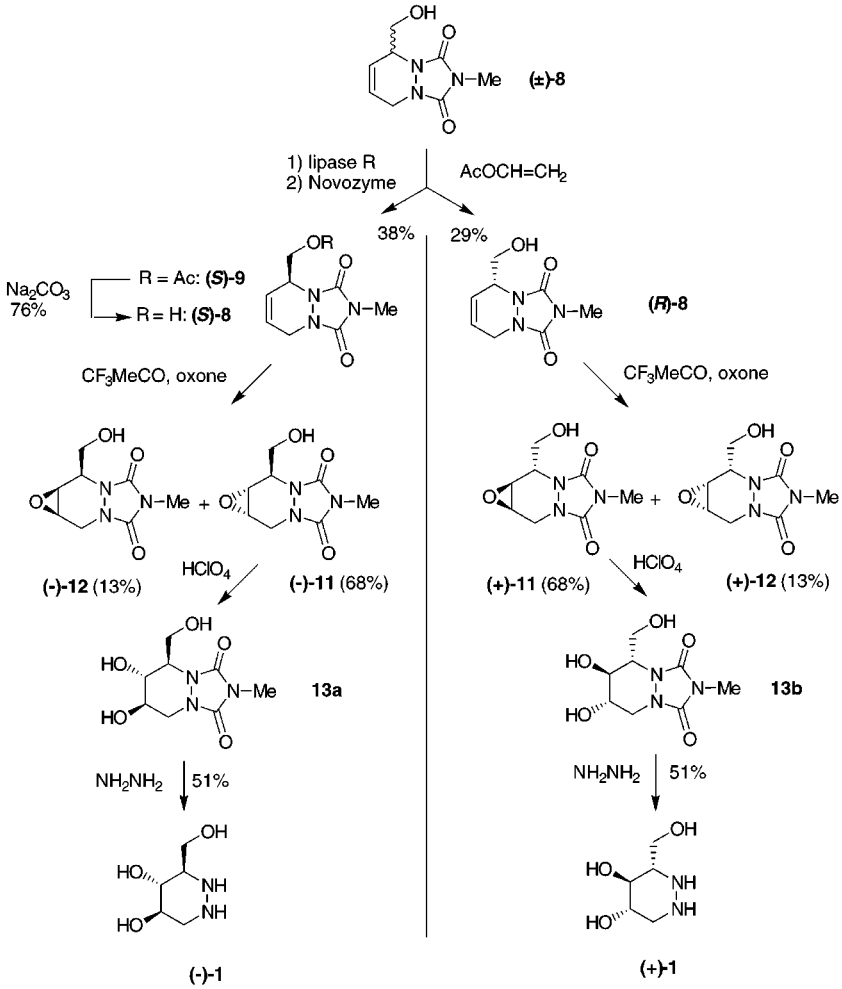
In summary, we have developed a short enantioselective synthesis of a biologically important compound. The synthesis has a overall yield of 18% (9% for each stereoisomer) over five steps, which compares favorably with the synthesis of **1** from xylose.

Experimental Section

The general procedures were as previously described.[3]

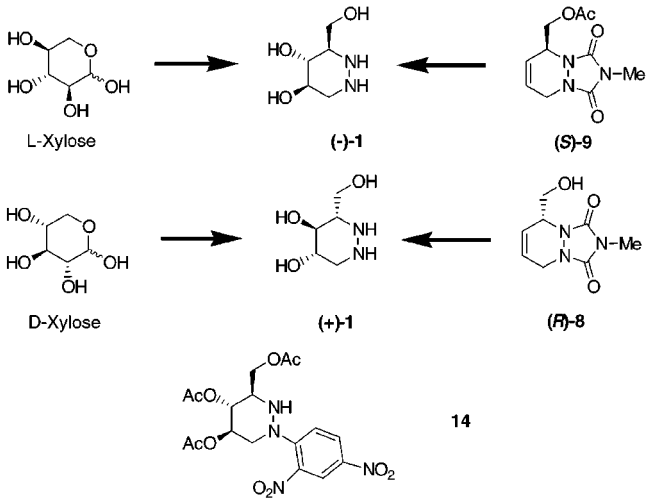
(±)-2-Hydroxymethyl-8-methyl-1,6,8-triazabicyclo[4.3.0]-non-3-ene-7,9-dione ((±)-8). 4-Methylurazole (**6**) (2.30 g, 20.0 mmol) was suspended in ethyl acetate (50 mL). *tert*-Butyl

Scheme 5. Synthesis of (−)- and (+)-1[a]



[a] All compounds (except (±)-**8**) have 99% ee.

Scheme 6. Absolute Configuration Determination of (*S*)-9 and (*R*)-8



hypochlorite (2.40 g, 22.0 mmol) was added at 0 °C, and the obtained mixture was stirred for 15 min to give a red, homogeneous solution. Penta-2,4-dien-1-ol (**3**) (1.95 g, 22.0 mmol) was added dropwise until the red color disappeared, and the colorless solution was stirred for 1 h. After the solution had been left standing for 1 h at room temperature, the crystals was filtered to give (±)-**8** as a colorless product (1.69 g), mp 101 °C. The mother liquid was concentrated in vacuo, and the residue was purified by chromatography to give further 1.73 g of (±)-**8**. The total yield was 87% (3.42 g). ^{1}H NMR (200 MHz, $CDCl_3/D_2O$): δ 6.00 (dddd, $J_{2,4}$ 2.5, $J_{4,5a} = J_{4,5b}$ 3.2, $J_{4,5a}$ $J_{3,4}$ 10.4, H-4), 5.78 (dddd, $J_{2,3} = J_{3,5a} = J_{3,5b}$ 2.5, H-3), 4.46 (dddddd, $J_{2'a,2}$ 3.0, $J_{2'b,2}$ 6.2, $J_{2,5a} = J_{2,5b}$ 2.5, H-2), 4.14 (dddd, $J_{5a,5b}$ 16.6, H-5a), 4.00 (dddd, H-5b), 3.88 (dd, $J_{2a,2b}$ 12.3, H-2′a), 3.79 (dd, H-2′b), 3.13 (s, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 154.3, 153.5 (2×C=O), 122.6, 122.2 (C-3, C-4), 64.3 (C-2′), 58.0 (C-2), 43.0 (C-5), 25.1 (CH_3). MS(EI) *m/z*: 197.0800, calcd for $C_8H_{11}N_3O_3$ 197.0800.

(2*S*)-8-Methyl-2-[(1″*S*)-3-oxo-4″,7″,7″-trimethyl-2″-oxabicyclo-[2.2.1]heptane-1″-carboxy]methyl-1,6,8-triazabicyclo-[4.3.0]non-3-ene-7,9-dione (10a)/(2*R*)-8-methyl-2-[(1″*S*)-3-oxo-4″,7″,7″-trimethyl-2″-oxabicyclo[2.2.1]heptane-1″-carboxy]-methyl-1,6,8-triazabicyclo[4.3.0]non-3-ene-7,9-dione (10b). To a solution of (±)-**8** (5 mg, 0.025 mmol), DMAP (2 mg), and Et_3N (0.05 mL) in CH_2Cl_2 (3 mL) was added (*S*)-(−)-camphanic acid chloride (11 mg, 0.05 mmol) at room temperature. After total conversion (ca. 10 min, TLC control: ethyl acetate, R_f 0.39), the reaction solution was concentrated in vacuo. The residue was filtered through a short column (silica gel, ethyl acetate) to provide quantitatively **10a**/**10b**. ^{1}H NMR (200 MHz, C_6D_6): δ 5.35−5.13 (m, H-3, H-4, **10a**, **10b**), 4.67 (dd, $J_{2,2'a}$ 3.6, $J_{2'a,2'b}$ 11.6, H-2′a, **10a**), 4.50 (dd, $J_{2,2'a}$ 3.6, $J_{2'a,2'b}$ 11.6, H-2′a, **10b**), 4.40 (m, H-2, **10a**), 4.33 (m, H-2, **10b**), 4.12 (dd, $J_{2,2'b}$ 5.1, H-2′b, **10a**), 3.94 (dd, $J_{2,2'b}$ 5.1, H-2′b, **10b**), 3.90−3.71 (m, H-5a, **10a**, **10b**), 3.44−3.26 (m, H-5b, **10a**, **10b**), 2.94 (s, CH_3-8, **10b**), 2.90 (s, CH_3-8, **10a**), 2.40−1.81, 1.51−1.29 (m, 4H, H-5″, H-6″, **10a**, **10b**), 1.00−0.71 (s, 9H, CH_3-4″, CH_3-7″a, CH_3-7″b, **10a**, **10b**).

General Procedure for Lipase-Catalyzed Transesterification of (±)-8. A mixture of (±)-**8** and a lipase in vinyl

acetate was stirred at room temperature. After the mixture was stirred for several days at room temperature, the lipase was filtered off and the obtained solution was concentrated in vacuo (the conversion was determined by chromatography). The residue was separated by chromatography (silica gel, ethyl acetate, R_f 0.18 for **8** and 0.35 for **9**) to give (*S*)-**9** and (*R*)-**8**. The ee's of (*S*)-**9** were determined by the camphanic ester derivative of (*S*)-**8** after saponification of (*S*)-**9** to (*S*)-**8**.

(*R*)-2-Hydroxymethyl-8-methyl-1,6,8-triazabicyclo[4.3.0]-non-3-ene-7,9-dione ((*R*)-8) and (*S*)-2-Acetoxymethyl-8-methyl-1,6,8-triazabicyclo[4.3.0]non-3-ene-7,9-dione ((*S*)-9). A mixture of (±)-**8** (1.0 g, 5.07 mmol) and lipase R (2 g) in vinyl acetate (100 mL) was stirred for 11 days at 42 °C. The enzyme was filtered off, and the obtained solution was concentrated in vacuo. The residue was separated by chromatography (silica gel, ethyl acetate) to provide (*R*)-**8** (604 mg, 60%, 59% ee) and (*S*)-**9** (461 mg, 38%, 86% ee) as colorless solids.

A mixture of (*R*)-**8** (604 mg, 59% ee) and Novozym 435 (200 mg) in vinyl acetate was stirred at room temperature for 48 h. Workup of the reaction mixture gave (*R*)-**8** (291 mg, 48%, 99% ee) as a colorless solid, mp 101 °C (crystallized from ethyl acetate/petane), and **9** (341 mg, 47%) as colorless oil. (*R*)-**8**. $[\alpha]^{22}_D = +51.9°$ (*c* 0.51 in $CHCl_3$). (*S*)-**9**. ^{1}H NMR (200 MHz, $CDCl_3$): δ 6.03 (dm, $J_{3,4}$ 10.0, H-4), 5.90 (dm, H-3), 4.74 (m, H-2), 4.40 (dd, $J_{2'a,\ 2'b}$ 12.0, $J_{2,2'a}$ 4.0, H-2′a), 4.23 (dm, $J_{5a,5b}$ 17.0, H-5a), 4.21 (dd, $J_{2,2'b}$ 6.6, H-2′b), 3.91 (dm, H-5b), 3.08 (s, NCH_3), 2.01 (s, COCH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ 193.6 (C═O, Ac), 154.7, 152.6 (7,8-C═O), 123.1, 122.0 (C-3, C-4), 62.4 (C-2′), 52.3 (C-2), 43.8 (C-5), 25.0 (8-CH_3), 20.6 (CH_3, Ac). MS-(EI) *m*/*z*: 239.0905, calcd for $C_{10}H_{13}N_3O_4$ 239.0906.

(*S*)-2-Hydroxymethyl-8-methyl-1,6,8-triazabicyclo[4.3.0]-non-3-ene-7,9-dione ((*S*)-8). A mixture of (*S*)-**9** (468 mg, 86%ee, 1.96 mmol) and Na_2CO_3 (46 mg, 0.38 mmol) in MeOH (10 mL) was stirred for 4 h at room temperature. After total conversion (TLC control, ethyl acetate), the mixture was concentrated in vacuo, and the residue was filtered through a short column of silica gel (ethyl acetate) to give (*S*)-**8** (382 mg, 99%,) as a colorless solid. The enantiomer enriched (*S*)-**8** was recrystallized from ethyl acetate/pentane to give enantiopure (*S*)-**8** (293 mg, 76%). Mp: 101 °C. $[\alpha]^{22}_D = -50.2°$ (*c* 0.51 in $CHCl_3$).

(−)-(2*R*,3*R*,4*S*)- and (2*R*,3*S*,4*R*)-3,4-Epoxy-2-hydroxymethyl-8-methyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione ((−)-11 and (−)-12). Alkenol (−)-**8** (0.50 g, 2.54 mmol) was dissolved in CH_3CN/H_2O (30 mL/20 mL). The obtained solution was cooled to 0 °C. 1,1,1-Trifluoroacetone (4 mL) and $NaHCO_3$ (2.6 g) were added. Oxone (12.3 g) was added in portions (20 min.). The mixture was filtered, and the solution was extracted 30 times with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated in vacuo. The residue was separated twice by chromatography (silica gel, ethyl acetate) to give (−)-**11** (368 mg) and (−)-**12** (72 mg) as colorless solids. (−)-**11**. Mp: 153−155 °C. $[\alpha]^{22}_D = -76.8°$ (*c* 0.82, CH_3CN). ^{1}H NMR (200 MHz, $CDCl_3$): δ 4.41 (dd, $J_{2'a,2} = J_{2'b,2}$ 5.0, H-2), 4.24 (ddd, $J_{3,5a} = J_{4,5a}$ 0.7, $J_{5a,5b}$ 13.7, H-5a), 4.11 (ddd, $J_{2'a,2'b}$ 11.5, $J_{2'a,OH}$ 5.8, H-2′a), 3.95 (ddd, $J_{2'b,OH}$ 5.8, H-2′b), 3.76 (dd, $J_{4,5b}$ 1.7, H-5b), 3.52 (ddd, $J_{3,4}$ 4.3, H-4), 3.46 (dd, H-3), 3.25 (s, 3 H, CH_3), 2.97 (dd, OH). (D_2O): δ 4.54 (m, H-2), 4.16 (dm, $J_{5a,5b}$ 14.0, H-5a), 3.90 (dd, $J_{2'a,2'b}$ 13.0, $J_{2'a,OH}$ 3.7, H-2′a), 3.86 (dd, $J_{4,5b}$ 1.9, H-5b), 3.76 (dd, $J_{2,2'b}$ 4.2, H-2′b), 3.65 (m, H-4), 3.59 (m, H-3), 2.92 (s, CH_3). ^{13}C NMR (50 MHz, D_2O): δ 150.4 (2×C═O), 57.6 (C-2′), 51.6 (C-2), 48.3, 46.3 (C-3, C-4), 38.3 (C-5), 22.8 (CH_3). MS(EI) *m*/*z*: 213.0749, calcd for $C_8H_{11}N_3O_4$ 213.0749. (−)-**12**. Mp: 177−178 °C (crystallized from ethyl acetate). $[\alpha]^{22}_D = -121.1°$ (*c* 0.98, CH_3CN). ^{1}H NMR (200 MHz, D_2O): δ 4.42 (ddd, $J_{2'a,2}$ 5.1, $J_{2'b,2}$ 7.1, $J_{2,3}$ 4.3, H-2), 4.17 (dd, $J_{4,5a}$ 1.5, $J_{5a,5b}$ 13.4, H-5a), 3.86 (dd, $J_{2'a,2'b}$ 11.1, H-2′a), 3.76 (dd, H-2′b), 3.75 (dd, $J_{3,4}$ 4.3, H-3), 3.68 (ddd, $J_{4,5b}$ 1.5, H-4), 3.58 (dd, H-5b), 2.95 (s, 3 H, CH_3). ^{13}C NMR (50 MHz, D_2O): δ 154.3,151.3 (2×C═O), 55.9 (C-2′), 50.0 (C-2), 48.7, 47.6 (C-3, C-4), 41.0 (C-5), 22.8 (CH_3). MS(EI) *m*/*z*: 213.0749, calcd for $C_8H_{11}N_3O_4$ 213.0749.

(+)-(2*S*,3*S*,4*R*)- and (2*S*,3*R*,4*S*)-3,4-Epoxy-2-hydroxymethyl-8-methyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione ((+)-11 and (+)-12). Carried out as for (−)-**11** and (−)-**12**. (+)-**11**. $[\alpha]^{22}_D = +76.8°$ (*c* 0.82, CH_3CN). (+)-**12**: $[\alpha]^{22}_D = +117.8°$ (*c* 0.90, CH_3CN).

(2*R*,3*R*,4*R*)-3,4-Dihydroxy-2-hydroxymethylmethyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (13a). Epoxide (−)-**11** (328 mg) was dissolved in H_2O (25 mL, and $HClO_4$ (1 mL, 70%) was added. The obtained solution was heated under reflux for 5 h and then neutralized with $KHCO_3$ and concentrated in vacuo. The residue was purified by chromatography (silica gel, acetone) to give a crude **13a**, which was directly used in the next step.

(+)-(2*S*,3*S*,4*S*)-3,4-Dihydroxy-2-hydroxymethylmethyl-1,6,8-triazabicyclo[4.3.0]nonane-7,9-dione (13b). Carried out as for **13a**, but starting from (+)-**11**.

(−)-(3*S*,4*S*,5*S*)-4,5-Dihydroxy-3-hydroxymethylhexahydropyridazine ((−)-1). 13a was dissolved in hydrazine hydrate (10 mL). The obtained solution was heated under reflux for 18 h and then concentrated in vacuo. The residue was dissolved in H_2O (100 mL) and put on a column of ion-exchange resin (Amberlite IR-120, H^+), washed with H_2O to neutral, and eluted with 2.5% aqueous NH_3 solution. Concentration followed by chromatography (silica gel, ethanol/25% NH_4OH 20:1, R_f 0.22) provided (−)-**1** (117 mg, 51% over two steps) as a yellowish solid. $[\alpha]^{22}_D = -8.6°$ (*c* 0.5, H_2O). ^{1}H NMR (200 MHz, D_2O): δ 3.71 (dd, $J_{3,3'a}$ 2.7, $J_{3'a,3'b}$ 12.0, H-3′a), 3.54 (dd, $J_{3,3'b}$ 5.9, H-3′b), 3.46 (ddd, $J_{4,5}$ 9.6, $J_{5,6eq}$ 5.3, $J_{5,6ax}$ 10.9, H-5), 3.20 (dd, $J_{3,4}$ 9.6, H-4), 3.06 (dd, $J_{6eq,6ax}$ 13.1, H-6eq), 2.55 (ddd, H-3), 2.44 (dd, H-6ax).^{13}C NMR (50 MHz, D_2O): δ 69.6, 69.1 (C-4, C-5), 60.7, 57.3 (C-3, C-3′), 49.4 (C-6).

(+)-(3*R*,4*R*,5*R*)-4,5-Dihydroxy-3-hydroxymethylhexahydropyridazine ((+)-1). Carried out as for (−)-**1**, giving $[\alpha]^{22}_D$ +10.2° (*c* 0.15, H_2O).

Analysis of the Enantiomerical Purity of 1. A sample of (−)-**1** (or (±)-**1**) was converted into the derivative **14** in the following manner: (−)-**1** (5−10 mg) was dissolved in EtOH (0.2 mL) and $NaHCO_3$-solution (0.1 mL, satd), and 2,4-dinitrophenyl fluoride (0.02 mL) was added. The mixture was stirred for 1 h and separated between CH_2Cl_2 (2 mL) and water (2 mL). The organic layer was discarded, while the water layer was extracted with EtOAc (3 × 2 mL). The combined EtOAc layers were dried, concentrated, and treated with Ac_2O (3 equiv), Et_3N (10 equiv), and DMAP (1 mg) in CH_2Cl_2 (1 mL). After 1 h at room temperature, the mixture separated between CH_2Cl_2 (2 mL) and water (2 mL). The water layer was further extracted with CH_2Cl_2 (2 × 2 mL). The combined CH_2Cl_2 layers were dried and concentrated to give **14** (ca. 10 mg).

The optical purity of **14** was assessed by HPLC using a CHIRALPAK OD coloumn (i.d. 0.46 cm × 25 cm) and a 1:1 mixture of *n*-hexane−2-propanol as mobile phase. The flow rate was 0.5 mL/min, and peaks were detected at 370 nm. Racemic **14** gave identical sized peaks at 25.07 min. and 32.3 min. The sample of **14** prepared from (−)-**1** gave the same two peaks, but the peak at 25.07 min was 144 times larger based on integrations. Thus, on the basis of this the ee of (−)-**1** was 99%.

Supporting Information Available: NMR data of (±)-**8**, **10a**,**b**, (−)-**11**, and (−)-**12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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