

Dimethyl 3-Hydroxy-4-hydroxymethylcyclopentane-1,1-dicarboxylate: an Optically Pure Precursor of Spiro Carbocylic Deoxyribonucleosides

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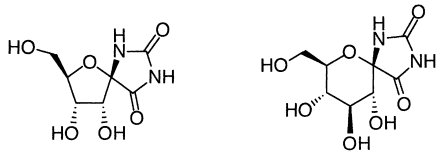
A concise, two-step preparation of dimethyl 3-hydroxy-4-hydroxymethylcyclopentane-1,1-dicarboxylate, an optically pure precursor of spiro carbocyclic nucleosides is described.

Nucleoside analogues are useful compounds as bases for important therapies including antiviral and anticancer treatments.[1] The interest in spiro nucleosides, a class of structurally constrained compounds, has primarily arisen from the discovery of hydantocidin **1** (Fig. 1), a natural product isolated from *Streptomyces hygroscopicus*.[2] This spiro hydantoin ribofuranose derivative **1** has demonstrated high herbicidal activity without animal toxicity. The origin of this activity has been shown to be inhibition of adenylosuccinate synthase, an enzyme involved in the de novo purine synthesis.[3] Also a newly synthesized spiro pyranoside **2** has been shown to possess some inhibitory activity against glycogen phosphorylase, thus providing a new approach to the treatment of diabetes.[4]

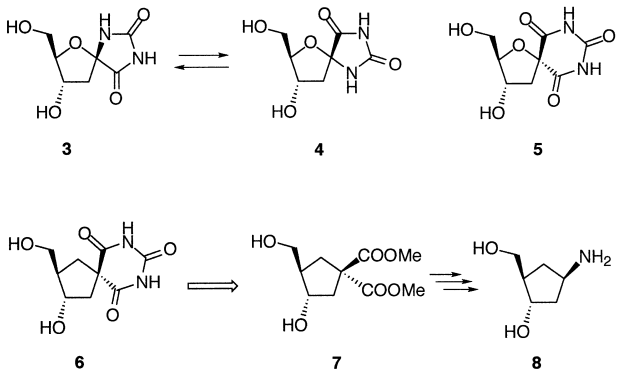


1 (+)-Hydantocidin **2**

Fig. 1. The Hydantocidin and the corresponding spiro pyranoside.

We recently reported that the deoxy derivative **3** of hydantocidin and its spiro epimer **4** were shown to interchange in basic medium.[5] We also designed new spiro barbiturates **5** and **6** in which the hydantoin ring is replaced by the barbiturate ring that also possesses thymine-like hydrogen bonding capacity against adenine derivatives.[6] The spiro barbituric deoxyribofuranose **5** exhibited rapid nucleophilic ring opening in aqueous medium, while its carbocyclic analogue **6** showed much greater stability (Scheme 1).

To prepare compound **6**, it was necessary to develop a synthetic approach to the optically active synthon (−)-**7**. In this article, we describe the synthesis of the optically pure chiral dihydroxy diester (−)-**7**. We report the determination of the absolute configuration of (−)-**7** by its transformation into the known chiral amino diol (+)-**8**. This series of reactions also



Scheme 1.

represents a new access to the amino diol **8**, that is used as a precursor in the synthesis of important carbocyclic nucleosides.[7]

Results and Discussion

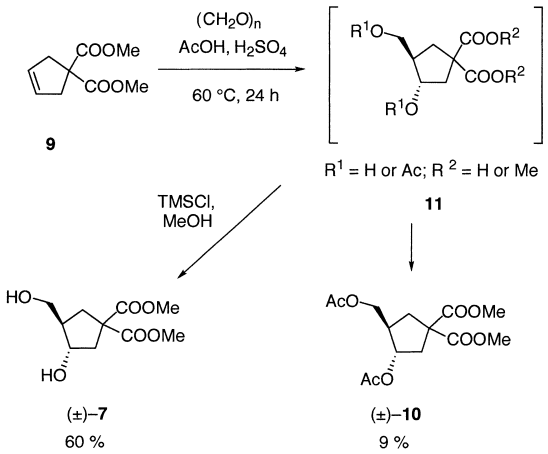
Racemic diol (±)-**7** was synthesized from the cyclopentene diester **9** which is easily accessible by condensation of dimethyl malonate and *cis*-1,4-dichloro-2-butene.[8] Upon treatment of **9** under Prins reaction conditions[9] (paraformaldehyde, AcOH, H_2SO_4, 60 °C, 24 h), a complex mixture was obtained from which the diacetate **10** was isolated in 9% yield (Scheme 2). We postulated that in the drastic reaction conditions used, formation of a mixture of compounds **11** resulting from hydrolysis of the methyl esters and/or acetylation of the alcohol functions could occur. Indeed when the crude reaction mixture was treated directly in transesterification conditions, i.e., refluxing in methanol in the presence of TMSCl, the dihydroxy diester (±)-**7** was obtained from **9** in 60% yield.

We next focused on the optical resolution of this diol (±)-**7**. Among the number of enzyme catalyzed transformations studied in organic synthesis, lipase catalyzed transesterifications have been widely used for the kinetic resolution of varieties of chiral racemic alcohols.[10] This method seemed quite attractive in the present case, in particular because the structurally related cyclopentane diol derivatives **12** have been resolved by this technique.[11] Using vinyl acetate as the acetyl donor, we stud-

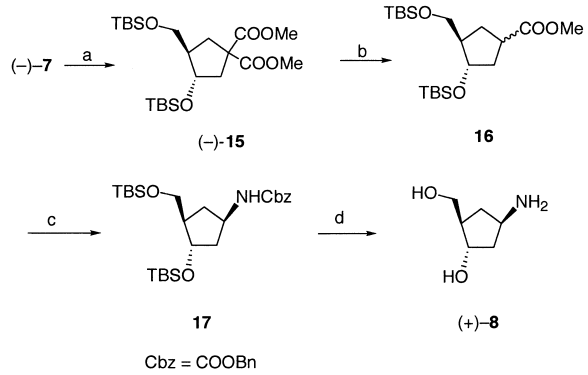
Table 1. Enzyme Catalyzed Optical Resolution of Diol (±)-**7**.

Enzyme	Time/h	% Conv[a)]	% ee of **14**[b)]	E value[c)]
Lipase from *Pseudomonas cepacia*	10	39	78	13.2
Lipase from hog *pancreas*	1	53	73	16.1
Pancreatin from *porcine pancreas*	4	41	76	12.3

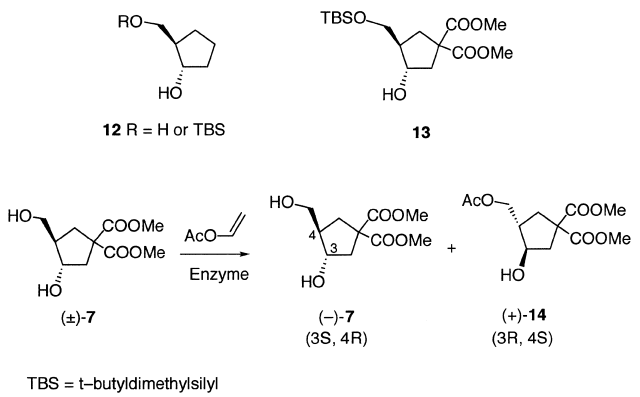
a) Conversion ratios were determined by ^{13}C NMR. b) The enantiomeric excess values (% ee) of **14** were determined by ^{1}H NMR spectroscopy using a chiral shift reagent [Eu(hfc)]. c) Index of enantioselectivity, see Ref. 19



Scheme 2. Synthesis of (±)-**7**.



Scheme 4. Conversion of (−)-**7** to (+)-8.
(a) TBSCl, imidazole, 90%. (b) NaCl, DMSO, 170 °C, 89%. (c) KOH; $(PhO)_2P(O)N_3$; BnOH; separation, 27%. (d) TBAF; H_2, Pd–C; 71%.



Scheme 3. Enzymatic resolution of (±)-**7**.

ied resolution of diol (±)-**7** with three enzymes of different sources (Scheme 3).

Table 1 summarizes the results obtained. Good enantioselectivities for monoacetylation were observed for all three enzymes examined (as judged by the% ee of monoacetate formed **14**). It is to be noticed that even when operating with a large excess of enzyme and a prolonged reaction time, acetylation of the secondary alcohol was never observed (data not shown). Also, our initial attempts to perform resolution via the monosilylated derivative **13** were unsuccessful, leading to full recovery of the starting material.

We estimated that the observed enantioselectivities of the enzyme catalyzed acetylation of **7** were satisfactory to operate gram-scale resolution of diol (±)-**7**. Racemic diol (±)-**7** (10.7 g) was treated under the pancreatin catalyzed transesterification conditions until about 70% conversion was achieved (3.5 h, 25 °C). After chromatographic separation of monoacetate **14**, the optically pure[12] diol (−)-**7** was recovered with **25**% yield (2.70 g, ee > 98%).

The absolute configuration of (−)-**7** was determined by its conversion to the known amino diol (+)-**8**.[13] Diol (−)-**7** was first converted to the disilylated derivative **15** and treated subsequently under the Krapcho dealkoxycarbonylation conditions[14] to give a 1:1 mixture of the two epimeric monoesters **16**.[15] Without separation of the two diastereoisomers, the ester function was saponified and transformed to the benzyl carbamate **17** by a Curtius-type reaction using diphenoxyphosphoryl azide.[16] The two isomers were separated ((1*R*)-**17**: 27%, (1*S*)-**17**: 31%).[17] Deprotection of the (1*R*)-isomer **17** was performed by successive treatments with TBAF in THF and H_2/Pd-C to give the amino diol (+)-**8**, that was unambiguously identified as the (1*R*, 3*S*, 4*R*)-isomer by all analytical data ($[\alpha]_D^{25}$ = +30.8 (*c* = 0.86, DMF), lit.[7b] $[\alpha]_D^{25}$ = +31.0 (*c* = 1.0, DMF)). This series of transformations established without ambiguity the absolute (3*S*, 4*R*) configuration of diol (−)-**7**.

The optically pure diol **7** obtained in three steps from dimethyl malonate and *cis*-1,4-dichloro-2-butene represents a useful precursor for building up spiro carbocyclic nucleosides, as exemplified by synthesis of the spiro barbiturate **6**.[18] In addition, further transformation of (−)-**7** by the reaction sequence outlined in Scheme 4 constitutes a new route to amino diol (+)-**8** which is a key intermediate in the preparation of important carbocyclic nucleosides.[7]

Experimental

General. All chemicals and solvents were purchased from Fluka, Aldrich, Merck, SDS, or Carlo-Elba. They were of analytical or HPLC grade, and otherwise distilled before use. Lipases from *Pseudomonas cepacia* (Ref. 62309) and lipase from *hog pancreas* (Ref. 62300) were purchased from Fluka, pancreatin from *porcine pancreas* (Ref. P7545) was purchased from Sigma. TLC: Merck Kieselgel 60 F_{254}, layer thickness 0.25 mm. Visualization by UV light (254 nm), H_2SO_4 solution, and/or phosphomolybdic acid solution. Preparative column chromatographies: Merck Kieselgel, 230–400 mesh. Mp: Reichert Thermovar (uncorrected). Optical rotations: Perkin-Elmer polarimeter 341. IR: Nicolet Impact 400. UV/Vis: Perkin-Elmer lambda 5. NMR: Bruker WP80, AM200, WP250, AM300, and Varian U+500 spectrometers. NMR spectra were referenced to the residual solvent peak; chemical shifts δ in ppm; apparent scalar coupling constants J in Hz. MS: Delsi-Nermag R10-10. Elemental analyses were performed by "Service central de microanalyse du CNRS".

Dimethyl (3*S,4*R**)-3-Hydroxy-4-(hydroxymethyl)cyclopentane-1,1-dicarboxylate ((±)-7).** A stirred mixture of **9** (20.2 g, 110 mmol), paraformaldehyde (6.60 g, 220 mmol), Ac_2O (16.5 mL), and H_2SO_4 (5.5 mL) in AcOH (110 mL) was heated at 60 °C for 16 h. The solution was cooled at r.t., then H_2O (300 mL) and AcOEt (500 mL) were added. The aqueous phase was extracted four times with AcOEt and the combined organic phase was dried over $MgSO_4$. The solvents were then removed under vacuum and the resulting residue was co-evaporated three times with toluene and dissolved in MeOH (700 mL). After TMSCl (60 mL) was added, the mixture was stirred under reflux for 3 h. The volatile materials were removed under vacuum and to the resulting residue was added a saturated solution of NaCl (300 mL) and AcOEt (500 mL). The aqueous phase was extracted three times with AcOEt and the combined organic phase was dried over $MgSO_4$. After concentration under vacuum, the crude material was chromatographed on silica gel (MeOH/CH_2Cl_2 8:92) to afford (±)-**7** as a colorless oil (16.0 g, 69.0 mmol, 60%). TLC (MeOH/CH_2Cl_2 8:92): R_f 0.24. ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.79 (dd, J = 9.6, 13.7 Hz, 1 H, H-2′ or H-6′), 1.95–2.25 (m, 2H, H-4, H-2 or H-6), 2.40–2.65 (m, 2 H, H-2 or H-6), 3.53 (dd, J = 7.2, 10.6 Hz, 1 H, H-5), 3.6–3.75 (m, 1 H, H-5), 3.68 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 4.06 (m, 1 H, H-3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = 34.1 (C-6′), 41.7 (C-2), 48.8 (C-4), 52.8, 52.9 (2 CH_3), 57.2 (C-1), 64.2 (C-5), 75.2 (C-3), 172.5, 172.9 (2 C=O). MS (FAB+, glycerol) m/z 233 $[M + H]^+$. Anal. Calcd for $C_{10}H_{16}O_6$·0.25 H_2O: C 50.74 , H 7.03%; Found: C 50.80, H 6.88%.

Monosilylation of the Diol (±)-7 to (±)-13. To a stirred mixture of diol (±)-**7** (2.32 g, 10.0 mmol) and imidazole (1.69 g, 24.8 mmol) in DMF (20 mL) was added TBSCl (1.68 g, 11.2 mmol) at 4 °C. The solution was stirred at 4 °C for 1.5 h. The solvent was removed under vacuum and H_2O (40 mL) and AcOEt (50 mL) were added to the residue. The aqueous phase was extracted three times with 40 mL of AcOEt. The combined organic phase was dried over $MgSO_4$ and the solvent was removed under vacuum. The resulting foam was chromatographed on silica gel (AcOEt/cyclohexane 2:3) to afford the monosilylated diol (±)-**13** as a foam (2.7 g, 78%). TLC (AcOEt/hexane 2:3): R_f 0.30. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.02, 0.03 (2s, 6 H, $Si(CH_3)_2$), 0.85 (s, 9 H, $SiC(CH_3)_3$), 1.80 (dd, J = 10.0, 14.0 Hz, 1 H, H-6), 2.09 (m, 1 H, H-4), 2.16 (dd, J = 7.0, 14.0 Hz, 1 H, H-2), 2.46 (dd, J = 7.8, 14.0 Hz, 1 H, H-2), 2.57 (dd, J = 7.0, 13.5 Hz, 1 H, H-6), 2.66 (d, 1 H, OH), 3.51 (dd, J = 8.1, 10.0 Hz, 1 H, H-5), 3.54–3.70 (m, 1 H, H-5), 3.69, 3.71 (2s, 6 H, OCH_3), 4.04 (m, 1 H, H-3). ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.1 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 34.0 (C-6), 41.7 (C-2), 48.8 (C-4), 52.6, 52.8 (2 OCH_3), 57.3 (C-1), 64.8 (C-5), 74.2 (C-3), 172.4, 172.9 (2 C=O). MS (DCI, NH_3 + isobutane) m/z 347 $[M + H]^+$. Anal. Calcd for $C_{16}H_{30}O_6Si$: C 55.66, H 8.73%; Found: C 55.57, H 8.66%.

Enzymatic Resolution of Diol (±)-7. A mixture of (±)-**7** (10.7 g, 46.0 mmol), vinyl acetate (43 mL), and pancreatine (8.6 g) in *t*BuOMe (176 mL) was vigorously stirred at 25 °C for 3.5 h. This suspension was then filtered on celite and the solid was thoroughly washed with *t*BuOMe (300 mL). The filtrate was concentrated under vacuum and the resulting residue was chromatographed on silica gel (MeOH/CH_2Cl_2 2:98 to 10:90) to give the diol (−)-**7** (2.7 g, 11.6 mmol, 25%, ee > 98%) and the monoacetylated alcohol (+)-**14** (8.1 g, 29.5 mmol, 64%, ee 49%). Data for diol (−)-**7**: TLC (MeOH/ CH_2Cl_2 8:92): R_f 0.24. $[\alpha]_D^{25}$ −12.5 (*c* 2.23, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.79 (dd, J = 9.6, 13.7 Hz, 1 H, H-2 or H-6), 1.95–2.25 (m, 2H, H-4, H-2 or H-6), 2.40–2.65 (m, 2 H, H-2 or H-6), 3.53 (dd, J = 7.2, 10.6 Hz, 1 H, H-5), 3.6–3.75 (m, 1 H, H-5), 3.68 (s, 3 H, CH_3), 3.70 (s, 3 H, CH_3), 4.06 (m, 1 H, H-3). ^{13}C NMR (50 MHz, $CDCl_3$) δ 34.1 (C-6), 41.7 (C-2), 48.8 (C-4), 52.8, 52.9 (2 CH_3), 57.2 (C-1), 64.2 (C-5), 75.2 (C-3), 172.5, 172,9 (2 C=O). MS (DCI, NH_3 + isobutane) m/z 233 $[M+H]^+$. Anal. Calcd for $C_{10}H_{16}O_6$·0.20 H_2O: C 50.93, H 7.01%; Found: C 51.13, H 6.92%.

Data for monoacetylated alcohol (−)-**14**: TLC (MeOH/ CH_2Cl_2 8:92): R_f 0.51. $[\alpha]_D^{25}$ +3.9 (*c* 2.53, $CHCl_3$). ^{1}H NMR (200 MHz,$CDCl_3$) δ 1.89 (dd, J = 9.6, 13.6 Hz, 1 H, H-2 or H-6), 2.03 (s, 3 H, CH_3CO), 2.15–2.25 (m, 2H, H-4, H-2 or H-6), 2.36 (d, 1 H, OH), 2.45–2.65 (m, 2 H, H-2 or H-6), 3.70 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 4.07 (m, 2 H, H-5). ^{13}C NMR (50 MHz, $CDCl_3$) δ 20.81 (CH_3CO), 34.7 (C-6), 41.7 (C-2), 46.5 (C-4), 52.9, 53.0 (2 OCH_3), 57.2 (C-1), 64.9 (C-5), 74.3 (C-3), 171.2, 172.1, 172.9 (3 C=O). MS (DCI, NH_3 + isobutane) m/z 274 $[M]^+$.

Dimethyl (3*S*,4*R*)-3-(*t*-Butyldimethylsiloxy)-4-(*t*-butyldimethylsiloxymethyl)cyclopentane-1,1-dicarboxylate ((−)-15). To a solution of diol (−)-**7** (2.0 g, 8.6 mmol) in DMF (17 mL) were added imidazole (3.50 g, 52.0 mmol) and TBSCl (3.90 g, 26.0 mmol). The reaction mixture was stirred at r.t. under argon for 10 h. This solution was directly filtered on silica gel and the disilylated compound was eluted with AcOEt/pentane (1:5). The first 100 mL fraction was recovered and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel (AcOEt/pentane (5:95)) to afford (−)-**15** as a colorless oil (3.60 g, 90%). TLC (AcOEt/hexane (1:6)): R_f 0.40. $[\alpha]_D^{25}$ −8.3 (*c* 2.37, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01 (s, 12 H, MeSi), 0.8 (2s, 18 H, *t*BuSi), 1.76 (dd, J = 8.9, 13.7 Hz, 1 H, H-6), 1.95-2.25 (m, 2 H, H-4, H-2), 2.45–2.70 (m, 2 H, H-2, H- 6), 3.51 (d, J = 4.8 Hz, 2 H, H-5), 3.68 (s, 3 H, CH_3), 3.69 (s, 3 H, CH_3), 4.06 (q, J = 5.8 Hz, 1 H, H-3). ^{13}C NMR (50 MHz, $CDCl_3$) δ = −4.7 (4 C, MeSi), 17.9, 18.2 (s, 2 C, Me_3C), 25.7, 25.8 (2s, 6 C, MeSi), 33.5 (C-6), 42.3 (C-2), 49.7 (C-4), 52.5 (2 CH_3), 57.3 (C-1), 62.3 (C-5), 73.5 (C-3), 172.4, 172.9 (2 C=O). MS (DCI, NH_3 + isobutane) m/z 461 $[M+H]^+$. Anal. Calcd for $C_{22}H_{44}O_6Si_2$: C 57.35 , H 9.63%; found: C 57.44, H 9.78%.

Demethoxycarbonylation of (−)-15. To a solution of compound (−)-**15** (940 mg, 2.00 mmol) in DMSO (3 mL) were added H_2O (0.2 mL) and NaCl (400 mg) at r.t. The mixture was stirred at 170 °C for 8 h. The suspension was cooled at r.t. and H_2O (20 mL) was added. This solution was extracted three times with Et_2O

(50 mL) and the combined organic phase was washed with brine, then dried over $MgSO_4$. The solvent was removed under vacuum and the residue was chromatographed on silica gel (AcOEt/pentane 5:95) to afford the diastereoisomeric mixture **16** (1*R*:1*S* = 1:1) as an oil (720 mg, 89%). TLC (AcOEt/pentane 3:97): R_f 0.33. ^{1}H NMR: vide infra. ^{13}C NMR (62 MHz, $CDCl_3$) δ −5.4, −4.7, −4.6 (4 C, $Si(CH_3)_2$), 18.0, 18.3 (2 C, $SiC(CH_3)_3$), 25.8, 25.9 (6 C, $SiC(CH_3)_3$), 28.4, 30.4 (C-5), 38.2, 38.6 (C-2), 39.9, 40.9 (C-1), 49.1, 50.8 (CH_3O), 51.6, 51.7 (C-4), 62.7, 64.0 (C-6), 74.0, 74.6 (C-3), 176.4, 176.7 (C=O). MS (DCI, NH_3 + isobutane) *m*/*z* 403 $[M]^+$. Anal. Calcd for $C_{20}H_{42}O_4Si_2$: C 59.65, H 10.51%; Found: C 59.13, H 10.42%.

In order to determine the relative configuration at C-1 for each diastereoisomer, a pure sample of each isomer (1*R*)-**16** and (1*S*)-**16** was obtained by two successive chromatographies (using AcOEt/pentane 3:97 for the first column, CH_2Cl_2 for the second column). The compounds (1*R*)-**16** and (1*S*)-**16** were separately characterized by ^{1}H NMR 1D, NOE, and 2D COSY experiments.

Data for the isomer (1*R*)-**16**: TLC (CH_2Cl_2): R_f 0.59. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 12 H, $Si(CH_3)_2$), 0.84, 0.86 (2s, 18 H, $SiC(CH_3)_3$), 1.48 (m, 1 H, H-5), 1.79 (m, 1 H, H-2), 1.85–2.05 (m, 2 H, H-2, H-4), 2.13 (m, 1 H, H-5), 2.99 (m, 1 H, H-1), 3.48 (d, J = 5.8 Hz, 2 H, H-6), 3.64 (s, 3 H, CH_3O), 4.12 (m, 1 H, H-3).

Data for the isomer (1*S*)-**16**: TLC (CH_2Cl_2): R_f 0.53. ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 12 H, $Si(CH_3)_2$), 0.84, 0.86 (2s, 18 H, $SiC(CH_3)_3$), 1.68 (m, 1 H, H-5), 1.83 (m, 1 H, H-2), 1.95 (m, 1 H, H-4), 2.05–2.15 (m, 2 H, H-2, H-5), 2.13 (m, 1 H, H-5), 2.62 (m, 1 H, H-1), 3.53 (d, J = 4.3 Hz, 2 H, H-6), 3.64 (s, 3 H, CH_3O), 3.97 (m, 1 H, H-3).

Benzyl (+)-(1*R*, 3*S*, 4*R*)-*N*-[3-(*t*-Butyldimethylsiloxy)-4-(*t*-butyldimethylsiloxymethyl)cyclopentyl]carbamate (17). A solution of the diastereoisomeric mixture **16** (680 mg, 1.7 mmol) in ethanolic KOH (310 mg in 17 mL) was stirred at 30 °C for 20 h. The solvent was then removed under vacuum and the resulting residue was dissolved in Et_2O (100 mL). This solution was cooled at 4 °C, then washed with a solution of 0.05 M HCl (100 mL). The aqueous phase was extracted three times with Et_2O, and the combined organic phase was dried over $MgSO_4$. The solvent was then removed under reduced pressure to give the intermediate crude acid (660 mg, 99%).

To a solution of the above acid in toluene (17 mL) were added at 0 °C, diphenoxyphosphoryl azide (0.42 mL) and Et_3N (0.28 mL). The mixture was stirred at 0 °C for 30 min, then at r.t. for 1 h, and finally at 80 °C for 2 h. The solution was cooled at 10 °C and benzyl alcohol (0.40 mL) and dibutyltin dilaurate (40 μL) were added. This solution was stirred at 80 °C for 3 h, then at 100 °C for 30 min. After being cooled to r.t., the mixture was diluted with Et_2O. The organic phase was washed with a solution of 1 M $NaHCO_3$. The aqueous phase was extracted three times with Et_2O, the combined organic phase was washed with brine, and then dried over $MgSO_4$. The solvent was removed under reduced pressure and the resulting residue was chromatographed on silica gel (CH_2Cl_2, three successive columns) to afford the (1*R*)-isomer **17** (201 mg, 27%) and the (1*S*)-isomer (220 mg, 31%), both as oils.

Data for the (1*R*)-isomer **17**: TLC (CH_2Cl_2): R_f 0.33. $[\alpha]_D^{25}$ +26.4 (*c* 0.97, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01, 0.03, 0.04, 0.05 (4s, 12 H, $SiCH_3$), 0.84, 0.86 (2s, 18 H, $SiC(CH_3)_3$), 1.23 (m, 1 H, H-5), 1.65–2.10 (m, 3 H, H-2, H-4), 2.16 (m, 1 H, H-5), 3.55 (m, 2 H, H-6), 4.05–4.22 (m, 2 H, H-1 and H-3), 5.06 (s, 2 H, CH_2), 7.25–7.35 (m, 5 H, arom. H). ^{13}C NMR (62 MHz, $CDCl_3$) δ −5.3, −4.7, −4.4 (4 C, $SiCH_3$), 18.0, 18.5 (2 C, $SiC(CH_3)_3$), 25.9, 26.0 (6 C, $SiC(CH_3)_3$), 33.8 (C-5), 43.0 (C-2), 48.9 (C-1), 50,2 (C-4), 63.4 (C-5), 66.4 (CH_2Ar), 73.3 (C-3), 127.9, 128.3, 136.6 (arom. C), 155.5 (C=O). MS (FAB+, glycerol) *m*/*z* 494 $[M+H]^+$. Calcd for $C_{26}H_{47}N_1O_4Si_2$: C 63.24, H 9.59 , N 2.84% ; Found: C 63.20 H 9.54 , N 2.89%.

Data for the (1*S*)-isomer: TLC (CH_2Cl_2): R_f 0.40. $[\alpha]_D^{25}$ = + 25.3 (*c* 1.02, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.01, 0.03, 0.04, 0.05 (4s, 12 H, $SiCH_3$), 0.84, 0.86 (2s, 18 H, $SiC(CH_3)_3$), 1.45–2.70 (m, 2 H, H-5, H-2), 1.72–1.98 (m, 2 H, H-2, H-4), 2.17 (m, 1 H, H-5), 3.31 (dd, J = 6.9, 9.9 Hz, 1 H, H-6), 3.50 (dd, J = 5.1, 9.9 Hz, 1 H, H-6), 4.05–4.25 (m, 2 H, H-1 and H-3), 5.06 (s, 2 H, CH_2), 5.65 (m, 1 H, NH), 7.25–7.35 (m, 5 H, arom. H). MS (FAB+, glycerol) *m*/*z* 494 $[M+H]^+$.

(+)-(1*R*,3*S*,4*R*)-3-Hydroxy-4-(hydroxymethyl)cyclopentylamine ((+)-8). To a solution of (1*R*)-**17** (140 mg, 0.284 mmol) in THF (2 mL) was added a solution of 1 M TBAF in THF (0.70 mL). This solution was stirred at r.t. for 3.5 h. The solvent was then removed under reduced pressure and the resulting residue was chromatographed three times on silica gel ($MeOH/CH_2Cl_2$ 10:90) in order to remove residual TBAF. The intermediate benzyl carbamate was thus obtained as a white powder (55 mg, 72%): mp 86–88 °C. TLC ($MeOH/CH_2Cl_2$ 10:90): R_f 0.28. $[\alpha]_D^{25}$ +10.5 (*c* 0.82, $CHCl_3$). IR (KBr) 3390, 3339, 3281, 2960, 1680, 1537, 1352, 1284, 1267, 1218, 1155, 1036 cm^{-1}. ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.16 (m, 1 H, H-5), 1.62 (m, 1 H, H-2), 1.72–2.10 (m, 3 H, H-2, H-4 and OH), 2.10–2.30 (m, 2 H, H-5 and OH), 3.58 (dd, J = 7.9, 10.3 Hz, 1 H, H-6), 3.79 (dd, J = 4.7, 10.3 Hz, 1 H, H-6), 4.11, 4.28 (m, 2 H, H-1 and H-3), 4.92 (m, 1 H, NH), 5.05 (s, 2 H, CH_2), 7.22–7.35 (2s, 5 H, arom. H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 34.3 (C-5), 41.5 (C-2), 48.7 (C-4), 49.6 (C-1), 63.8 (C-6), 66.4 (CH_2Ar), 73.6 (C-3), 127.9, 128.4, 136.5 (arom. C), 155.9 (C=O). MS (FAB−, glycerol) *m*/*z* 264 [M−H]. Anal. Calcd for $C_{14}H_{19}NO_4$: C 63.38, H 7.22, N 5.28%; Found: C 63.22 H 7.52, N 5.08%.

A solution of the above benzyl carbamate (48 mg, 0.19 mmol) in MeOH (2 mL) was vigorously stirred for 2 h at r.t. under H_2 atmosphere with Pd/C-10% (20 mg). This suspension was then filtered on celite and the solid was thoroughly washed with MeOH. The filtrate was concentrated under reduced pressure and the oily residue was dried under high vacuum to afford (+)-**8** as an oil (24 mg, 99%). $[\alpha]_D^{25}$ +30.8 (*c* 0.86, DMF). (lit.[7b] $[\alpha]_D^{25}$ +31.0 (*c* 1.0, DMF)). ^{1}H NMR (300 MHz, MeOD-d_4) δ 1.14 (m, 1 H, H-5), 1.69 (m, 1 H, H-2), 1.82–2.05 (m, 2 H, H-2 and H-4), 2.21 (m, 1 H, H-5), 3.43–3.60 (m, 3 H, H-6 and H-1), 4.04 (m, 1 H, H-3). ^{13}C NMR (75 MHz, MeOD-d_4) δ 37.3 (C-5), 43.9 (C-2), 51.0 (C-4), 51.3 (C-1), 64.7 (C-6), 74.6 (C-3). MS (IE) *m*/*z* 131 $[M]^+$, 114 [M − OH], 100 [M − CH_2OH], 96 [M − 2OH], 72, 69, 56, 44.

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