Synthesis of Polyhydroxylated Aminocyclopentanes

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Dedicated to Prof. R. W. Hoffmann on the occasion of his 70th birthday

Keywords: Aldol reactions / Amino acids / Carbasugars / Enolates / Inhibitors

Polyhydroxylated aminocyclopentanes are an interesting class of glycosidase inhibitors. The reactions between chelated α-allylglycine esters and crotonaldehyde gave the corresponding aldol products in good yields and selectivities. Those compounds could be converted into enantiopure polyhydroxylated aminocyclopentanes by ring-closing metathesis, enzymatic separation and dihydroxylation. In the final deprotection step, three different protection groups were removed simultaneously in excellent yield, either by reduction or by basic hydrolysis.
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Introduction

Carbasugars are a family of synthetic and naturally occurring carbohydrate mimics which are attracting great attention among chemists and biochemists.[1] They are topologically similar to normal sugars, particularly in the arrangement of their hydroxy groups, but they have the ring oxygen replaced by a methylene group. Because of their lack of an easily hydrolysable glycosidic function, these sugar derivatives are much more stable towards hydrolysis. The first example, 5a-carba-α-D-galactose (**A**), was synthesized almost thirty years ago.[2] Many different types of naturally occurring carbasugars have been isolated so far, one hydroxy group very often being replaced by an amino group. A few examples such as validamine (**B**),[3] validoxylamine A (**C**),[4] mannostatin A (**D**)[5] and aristeromycin (**E**)[6] are shown in Figure 1. The usefulness of these compounds is illustrated well by the fact that the discovery of the strong trehalase inhibition potency of the natural product validoxylamine A (**C**) has resulted in the development of the strong synthetic glycohydrolase inhibitor voglibose (**F**),[7] which is used clinically as anti-diabetic.

A few years ago, it was found that aminocyclopentitols such as L-64[8] (**H**) and L-69[9] (**I**) act as analogues of the flattened half-chair conformation of the glucosyl oxo-carbenium ion (**G**), which is probably formed during enzymatic hydrolysis of glucosides (Figure 2). Some derivatives of this type are among the strongest known competitive inhibitors for their respective enzymes. Polyhydroxylated aminocyclopentanes are therefore interesting candidates for the development of new glycosidase inhibitors.[10] In this paper we present a short and high-yielding approach to enantiomerically pure aminocyclopentanetetrols.

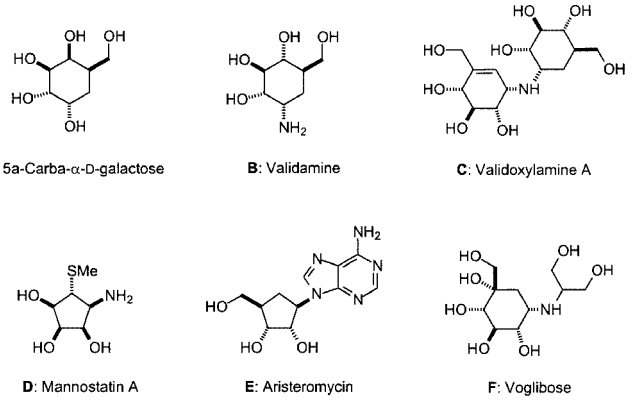

Figure 1. Examples of naturally occurring (**A**−**E**) and synthetic (**F**) (amino) carbasugars

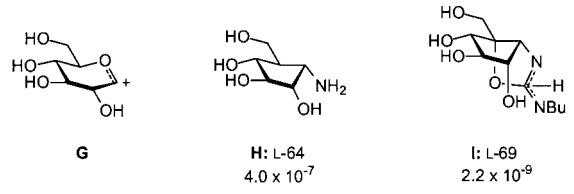

Figure 2. α-Glucosidase inhibitors (IC_{50}/M) against bakers' yeast

Results and Discussion

Our retrosynthetic approach to polyhydroxylated aminocyclopentane derivatives is presented in Scheme 1. The first step illustrates the intention to create the primary hydroxy

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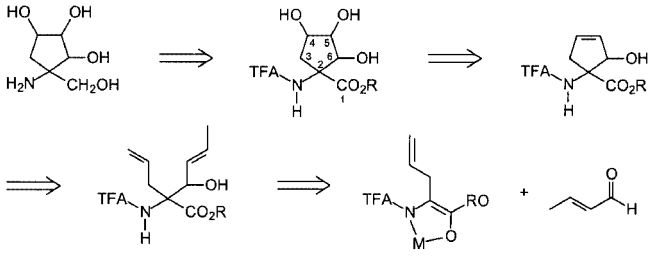


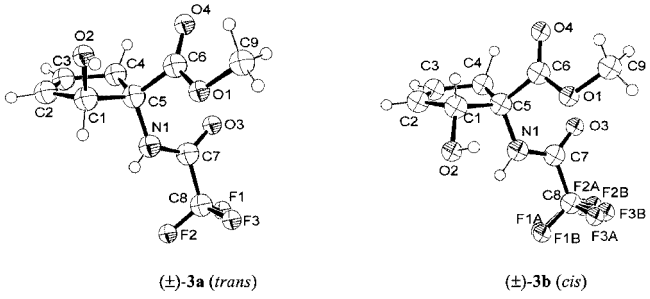
Scheme 1. Retrosynthesis of polyhydroxylated aminocyclopentanes

group out of an amino acid. The two hydroxy groups at C-4 and C-5 should be introduced by dihydroxylation or epoxidation of a cyclic allylic alcohol precursor, while it was planned that the ring should be formed by ring-closing metathesis.[11,12] The key step of the synthesis is an aldol reaction, in which a chelated amino acid ester enolate reacts with an α,β-unsaturated aldehyde.[13] The trifluoroacetyl (TFA) group was chosen as a protecting group, as the corresponding enolates usually show high reactivities and selectivities,[14] and it is possible to deprotect TFA amides either by hydrolysis or under reductive conditions.[15]

The TFA-protected α-allyl glycine ester **1** (Scheme 2), the starting material for the aldol reaction, was easily synthesized from glycine allyl ester through a chelate-enolate Claisen rearrangement.[16] It is known from previous work in our group[13] that reactions between chelated amino acid ester enolates and α,β-unsaturated aldehydes take place exclusively at the carbonyl group and no 1,4-addition (Michael reaction) product is observed. The reaction was complete after 1 h at −78 °C. The ratio of the *anti* and *syn* diastereomers **2a** and **2b** was determined by ^{1}H NMR spectroscopy to be 3:1. Though it was possible to separate the diastereomers by flash chromatography at this stage, it turned out later that separation after the ring-closing metathesis was far easier.

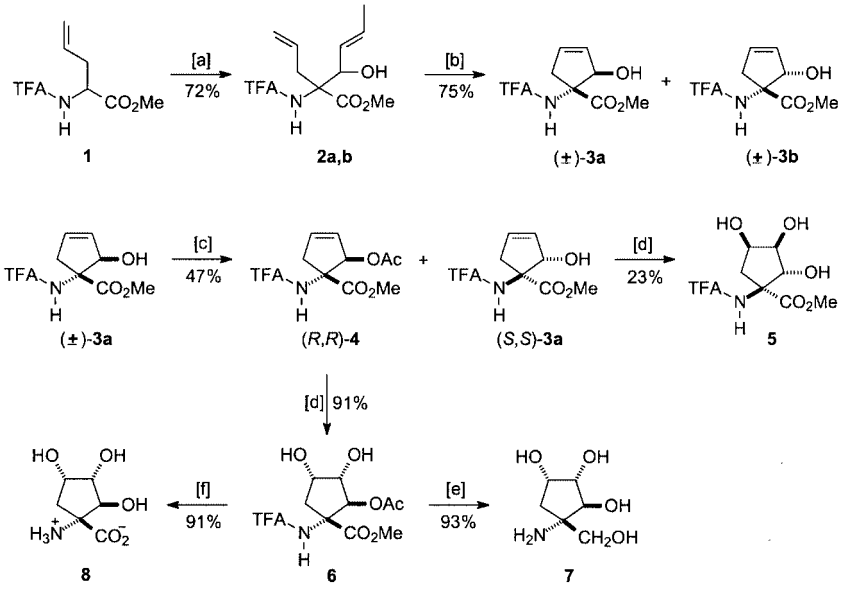
The mixture of diastereomers **2a** and **2b** was therefore treated with Grubbs catalyst.[11] The reaction was carried out in CH_2Cl_2 with 3 mol % catalyst and was complete after 10 h at room temperature. As mentioned above, the separation of the diastereomers (±)-**3a** and (±)-**3b** was easily achieved by column flash chromatography, but unfortunately both product fractions contained impurities originating from the decomposed catalyst. Analytically pure products could be obtained after sublimation in a bulb-to-bulb distillation apparatus. The overall yield of both diastereomers was 75%.

Because of the cyclic structure of the metathesis product, it was now possible to determine the relative configuration of the stereocenters by NOESY experiments [coupling of N*H* to H-2 in the case of major isomer (±)-**3a**] and also by X-ray structure analysis (Figure 3).[17] As was expected from the previous work[13,18] the configuration was *trans* in the major diastereomer (±)-**3a** and *cis* in the minor diastereomer (±)-**3b**.



(±)-**3a** (*trans*) (±)-**3b** (*cis*)

Figure 3. X-ray structure of the diastereomeric metathesis products (±)-**3a** and (±)-**3b**



Scheme 2. Synthesis of polyhydroxylated aminocyclopentane 7 and amino acid **8**; conditions: [a] i) 2.5 equiv. LHMDS, 2.5 equiv. $ZnCl_2$, THF, −78 °C, ii) crotonaldehyde, −78 °C, 1 h, [b] 3 mol % Grubbs cat., CH_2Cl_2, room temp., 10 h. [c] Novozym 435, vinyl acetate, room temp., 14 d. [d] K_2OsO4 (cat.), NMO, acetone/H_2O, room temp., 48 h. [e] 5 equiv. $NaBH_4$, 5 equiv. $CaCl_2$, THF/EtOH, 0 °C, [f] 15 equiv. LiOH, THF/MeOH/H_2O

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Up to this point, the synthesis had been carried out under achiral conditions. It was now likely, however, that the cyclic allyl alcohols **3** should be well suited for an enzyme-catalysed kinetic resolution. According to the literature,[19] Novozym 435®, a lipase isolated from the bacterium *Candida antarctica*, should be able to acetylate the (*R*) enantiomer containing the hydroxy group with good selectivity (Kazlauskas rule).[20] Treatment of the major *trans* isomer (±)-**3a** with immobilized Novozym 435® was carried out in vinyl acetate at room temperature and was monitored by gas chromatography on a chiral cyclodextrin column. The reaction was complete within 14 d, and both the acylated product (*R*,*R*)-**4** and the unchanged alcohol (*S*,*S*)-**3a** showed enantiomeric purities > 99% *ee*. The remaining alcohol (*S*,*S*)-**3a** could be isolated in 47% yield, the acetate (*R*,*R*)-**4** also in 47% yield.

To investigate the subsequent dihydroxylation of the double bond, we first treated the recovered (*S*,*S*)-alcohol **3a** with catalytic amounts of K_2OsO_4 and *N*-methylmorpholine *N*-oxide (NMO) as co-oxidant.[21] The reaction was complete within 48 h but after the aqueous workup the desired product **5** could only be isolated in very poor yield (23%), probably because of the high solubility of the triol. However, two encouraging results were obtained from this reaction. Firstly, according to ^{1}H NMR, only one stereoisomer was formed, and secondly, it was possible to crystallize the product and determine the configuration by X-ray structure analysis (Figure 4).[22] As expected, the configuration of the two incoming hydroxy groups turned out to be *trans* in relation to the directing alcohol function.

The poor yield could be explained by the high polarity of the product and the consequent problems in the aqueous workup. To increase the yield, the reaction was carried out with acetate (*R*,*R*)-**4** under the same conditions, and the dihydroxylated product **6** could indeed now be isolated in 91% yield, again as a single diastereomer.

In order to complete the synthesis of the aminocyclopentanetetrol **7**, the methyl ester **6** had to be reduced and the TFA and the acetyl group cleaved in as few steps as possible. We found that it was possible to accomplish this task in one single step by use of a mixture of $NaBH_4$ and $CaCl_2$ in THF/EtOH.[23] The isolation and purification of the free aminosugar was achieved by use of the strongly acidic ion-exchange resin Dowex 50WX8. After optimisation of the reaction conditions and the purification procedure the final product **7** was isolated in 93% yield. The protecting groups of methyl ester **6** could also be hydrolysed under basic conditions in one step with LiOH. The resulting polyhydroxylated amino acid **8** was also purified by use of Dowex 50WX8 and isolated in 91% yield.

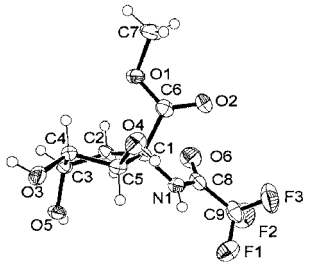

Figure 4. X-ray structure of triol **5**

Conclusion

In conclusion, we have developed a high-yielding and stereoselective route to polyhydroxylated aminocyclopentane derivatives, which can be regarded as amino-substituted carbasugars. Key steps of the synthesis were an aldol reaction between a chelated amino acid enolate and an α,β-unsaturated aldehyde and the deprotection step, in which three different protecting groups were removed simultaneously under either reductive or basic conditions in excellent yield.

Experimental Section

General Remarks: Most reactions were carried out under argon in oven-dried glassware (100 °C). All solvents were dried before use. THF was distilled from sodium benzophenone, dichloromethane from calcium hydride. Dowex 50WX8 was purchased from Aldrich. LHMDS solutions were prepared from freshly distilled hexamethyldisilazane (HMDS) and commercially available *n*-butyllithium solution (15% in hexane) in THF at −20 °C directly before use. The Grubbs catalyst was purchased from Fluka and used as supplied. The starting materials and the products were purified by flash chromatography on silica gel (32−63 μm). Mixtures of ethyl acetate (EtOAc) and petroleum ether (PE, 40−60 °C) were generally used as eluents. TLC: commercially precoated Polygram© SIL-G/UV 254 plates (Macherey−Nagel). Viewing was accomplished with use of UV light, iodine, and potassium permanganate solution. Enantiomeric ratios were determined on Varian 3400 gas chromatograph on a CP-Cyclodextrin-B-2,3,6-M19 column. ^{1}H and ^{13}C NMR: Bruker DRX 500, Bruker Avance 500 and Bruker Aspect 3000 spectrometers. Optical rotations were measured with a Perkin−Elmer PE 341 polarimeter.

Methyl 2-Allyl-3-hydroxy-2-(2,2,2-trifluoroacetylamino)-4-hexenoate (2a, 2b): HMDS (9.56 mL, 45.6 mmol) was diluted in THF (60 mL). After the flask had been cooled to −78 °C, *n*BuLi solution (25.0 mL, 40 mmol) was added slowly. The yellowish solution was stirred at −78 °C for 10 min and at room temperature for 20 min . During this time, methyl 2-(2,2,2-trifluoroacetylamino)-4-pentenoate (**1**, 3.60 g, 16.0 mmol) and anhydrous $ZnCl_2$ (5.45 g, 40.0 mmol) were dissolved in THF (60 mL). This solution was also cooled to −78 °C. The LHMDS solution was now added slowly, by use of a transfer needle. The mixture was stirred at −78 °C for 30 min, after which freshly distilled crotonaldehyde (1.46 g, 17.6 mmol), diluted in THF (30 mL), was added slowly. The mixture was stirred at −78 °C for 1 h, and was then diluted with EtOAc. $KHSO_4$ (1 N aq., 100 mL) was added to hydrolyse the enolate. The two phases were separated and the aqueous phase was extracted twice with EtOAc. The combined organic phases were washed with brine and dried with Na_2SO_4. The solvent was evaporated in vacuo and the relative ratio of the *syn* and *anti* diastereomers was determined from the crude product by ^{1}H NMR spectroscopy to be 1:3. The product diastereomers were purified without separation by flash chromatography (PE/EtOAc, 9:1, 8:2), giving a mixture of **2a** and **2b** (3.39 g, 11.5 mmol, 72%) as a colour-

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less oil. For analytical purposes a small quantity of the diastereomers was separated and characterized. ***anti*** **Diastereomer 2a:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67 (d, *J* = 6.4 Hz, 3 H), 2.68 (dd, *J* = 14.6, 6.9 Hz, 1 H), 3.08 (dd, *J* = 14.6, 8.0 Hz, 1 H), 3.59 (m, 1 H), 3.82 (s, 3 H), 4.55 (d, *J* = 6.9 Hz, 1 H), 5.06−5.14 (m, 2 H), 5.31 (ddq, *J* = 15.5, 6.9, 1.4 Hz, 1 H), 5.49 (m, 1 H), 5.76 (m, 1 H), 7.55 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.6, 35.8, 53.6, 69.8, 75.3, 115.7, 120.6, 127.5, 130.1, 130.5, 157.2, 171.2 ppm. ***syn*** **Diastereomer 2b:** ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.70 (d, *J* = 6.9 Hz, 3 H), 2.83 (dd, *J* = 14.6, 6.4 Hz, 1 H), 2.96 (dd, *J* = 14.1, 8.7 Hz, 1 H), 3.09 (m, 1 H), 3.82 (s, 3 H), 4.53 (d, *J* = 7.7 Hz, 1 H), 5.14−5.19 (m, 2 H), 5.36 (ddq, *J* = 15.1, 7.7, 1.4 Hz, 1 H), 5.56 (m, 1 H), 5.78 (m, 1 H), 7.02 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.8, 36.3, 53.4, 68.2, 75.4, 115.7, 120.9, 127.2, 131.0, 131.6, 156.7, 170.7 ppm. $C_{12}H_{16}F_3NO_4$ (295.26): calcd. C 48.82, H 5.46, N 4.68; found C 48.63, H 5.67, N 4.74.

Methyl 2-Hydroxy-1-(2,2,2-trifluoroacetylamino)cyclopent-3-enecarboxylate [(±)-3a,b]: The 3:1 mixture of diastereomers **2a** and **2b** (3.10 g, 10.5 mmol) was dissolved in CH_2Cl_2 (50 mL). Grubbs catalyst (259 mg, 0.32 mmol, 3 mol %) was added, and the mixture was stirred for 10 h at room temperature. The solvent was evaporated in vacuo and the diastereomers were separated by flash chromatography. In order to remove impurities originating from the decomposed catalyst, both products were purified by bulb-to-bulb distillation (160 °C, 4 × 10^{-3} mbar). After this procedure, the major isomer (±)-**3a** (1.50 g, 5.92 mmol, 56%) and the minor isomer (±)-**3b** (0.50 g, 1.98 mmol, 19%) were obtained, both as white crystalline solids, which were appropriate for X-ray structure analysis after recrystallization (CH_2Cl_2). ***trans*** **Diastereomer (±)-3a:** M.p. 156 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.53 (br. s, 1 H), 2.80 (dd, *J* = 17.3, 1.1 Hz, 1 H), 3.24 (dd, *J* = 17.5, 2.2 Hz, 1 H), 3.80 (s, 3 H), 5.12 (s, 1 H), 5.76 (m, 1 H), 6.00 (m, 1 H), 7.48 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.4, 52.5, 70.2, 83.0, 115.6, 129.6, 132.8, 157.7, 170.5 ppm. ***cis*** **Diastereomer (±)-3b:** M.p. 70−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.21 (br. s, 1 H), 2.80 (dd, *J* = 18.3, 1.8 Hz, 1 H), 3.36 (d, *J* = 18.3 Hz, 1 H), 3.77 (s, 3 H), 4.93 (s, 1 H), 5.72 (dd, *J* = 5.5, 1.8 Hz, 1 H), 6.01 (m, 1 H), 7.71 (br. s, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.4, 53.2, 65.4, 80.9, 115.6, 129.1, 133.8, 158.6, 172.0 ppm. $C_9H_{10}F_3NO_4$ (253.18): calcd. C 42.70, H 3.98, N 5.53; found C 43.07, H 3.91, N 5.44. HRMS (CI): [M + H]$^+$ calcd. 254.0640; found 254.0636.

Enzymatic Resolution of the Racemate (±)-3a: The racemic allyl alcohol (±)-**3a** (1.37 g, 5.41 mmol) was dissolved in vinyl acetate (10 mL). Immobilized Novozym 435® (200 mg) was added and the mixture was shaken at room temperature. The reaction was monitored by gas chromatography on a chiral cyclodextrin column. The reaction was complete after 14 d. The immobilized enzyme was filtered off and washed several times with dichloromethane. The combined organic solvents were evaporated in vacuo and the alcohol (*S*,*S*)-**3a** was separated from the acetate (*R*,*R*)-**4** by flash chromatography (PE/EtOAc, 8:2, 7:3, 1:1).

Methyl (1*S*,2*S*)-2-Hydroxy-1-(2,2,2-trifluoroacetylamino)cyclopent-3-enecarboxylate [(*S*,*S*)-3a]: After enzymatic resolution, (*S*,*S*)-**3a** (641 mg, 2.53 mmol, 47%, > 99% *ee*) was obtained as colourless crystals, m.p. 116 °C. $[\alpha]_D^{20}$ = +205.7 (*c* = 1.1, $CHCl_3$). GC: column: β-CD, temperature program: 120 °C starting temperature for 30 min, heating with 2 °C/min to final temperature 180 °C, hold for 3 min, injector: 200 °C, detector 250 °C; $t_{R(S,S\text{-}3a)}$ = 44.74 min [$t_{R(R,R\text{-}3a)}$ = 45.00 min].

Methyl (1*R*,2*R*)-2-Acetoxy-1-(2,2,2-trifluoroacetylamino)cyclopent-3-enecarboxylate [(*R*,*R*)-4]: The allylic acetate (*R*,*R*)-**4** (743 mg, 2.52 mmol, 47%, > 99% *ee*) was also obtained as colourless crystals, m.p. 99 °C. $[\alpha]_D^{20}$ = −51.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 2.70 (ddd, *J* = 17.3, 4.4, 2.2 Hz, 1 H), 3.47 (ddd, *J* = 17.3, 4.4, 2.2 Hz, 1 H), 3.75 (s, 3 H), 5.63 (m, 1 H), 6.04 (m, 1 H), 6.10 (m, 1 H), 8.00 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5, 41.9, 53.0, 69.8, 85.5, 115.5, 126.0, 135.0, 157.5, 169.3, 171.7 ppm. $C_{11}H_{12}F_3NO_5$ (295.22): calcd. C 44.75, H 4.10, N 4.74; found C 44.93, H 4.20, N 4.70. GC: column: β-CD, temperature program: 120 °C start temperature for 30 min, heating with 2 °C/min to final temperature 180 °C, hold for 3 min, injector: 200 °C, detector 250 °C; $t_{R,(R,R)\text{-}4}$ = 36.08 min [$t_{R,(S,S)\text{-}4}$ = 35.47 min].

Methyl (1*S*,2*R*,3*R*,4*R*)-2,3,4-Trihydroxy-1-(2,2,2-trifluoroacetylamino)cyclopentanecarboxylate (5): The allylic alcohol (*S*,*S*)-**3a** (50 mg, 0.20 mmol) was dissolved in a mixture of acetone (2 mL) and water (250 µl). *N*-Methylmorpholine *N*-oxide monohydrate (54 mg, 0.40 mmol) and potassium osmate dihydrate (4 mg, 0.01 mmol) were subsequently added, and the mixture was stirred for 10 h at room temperature. The black suspension was diluted with dichloromethane and poured into 10% $NaHSO_3$ solution. The aqueous phase was extracted three times with dichloromethane. The combined organic layers were dried with Na_2SO_4 and the solvents were removed in vacuo. Purification by flash chromatography (EtOAc) gave **5** (13 mg, 0.05 mmol, 23%) as a colourless, crystalline solid (m.p. 124−125 °C). After recrystallization, ($CHCl_3$/acetone) crystals appropriate for X-ray structure analysis were obtained. $[\alpha]_D^{20}$ = +1.1 (*c* = 1.1, EtOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.94 (m, 1 H), 2.77 (dd, *J* = 15.8, 6.0 Hz, 1 H), 3.58, 3.70 (2 br. s, 2 H), 3.75 (m, 1 H), 3.56 (s, 3 H), 3.96−4.03 (m, 2 H), 4.28 (d, *J* = 8.2 Hz, 1 H), 8.11 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 39.5, 52.6, 66.7, 68.8, 75.6, 80.7, 115.3, 157.0, 170.5 ppm. HRMS (CI): [M + H]$^+$ calcd. 288.0695; found 288.0691.

Methyl (1*R*,2*S*,3*S*,4*S*)-2-Acetoxy-3,4-dihydroxy-1-(2,2,2-trifluoroacetylamino)cyclopentanecarboxylate (6): According to the synthesis of **5**, the allylic acetate (*R*,*R*)-**4** (58 mg, 0.20 mmol) was treated with NMO·H_2O (54 mg, 0.40 mmol) and K_2OsO_4·$2H_2O$ (4 mg, 0.01 mmol). Purification by flash chromatography (PE/EtOAc, 1:1) gave diol **6** (59 mg, 0.18 mmol, 91%) as a colourless oil. $[\alpha]_D^{20}$ = +28.6 (*c* = 1.1, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06 (s, 3 H), 2.16 (d, *J* = 16.2 Hz, 1 H), 3.09 (dd, *J* = 16.1, 6.1 Hz, 1 H), 3.24 (m, 1 H), 3.75 (m, 1 H), 3.78 (s, 3 H), 4.21 (m, 1 H), 4.27 (dd, *J* = 9.3, 5.1 Hz, 1 H), 5.44 (d, *J* = 9.3 Hz, 1 H), 8.17 (br. s, 1 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4, 40.1, 53.7, 65.4, 68.8, 74.0, 81.6, 115.3, 157.3, 169.9, 172.0 ppm. HRMS (CI): [M + H]$^+$ calcd. 330.0801; found 330.0767.

(1*S*,2*S*,3*S*,4*S*)-4-Amino-4-(hydroxymethyl)cyclopentane-1,2,3-triol (7): Anhydrous $CaCl_2$ (84 mg, 0.76 mmol) and $NaBH_4$ (58 mg, 1.52 mmol) were suspended in THF (1 mL) at 0 °C. The diol **6** (50 mg, 0.15 mmol) was dissolved in ethanol (1 mL) and the solution was added slowly to the suspension. The mixture was warmed to room temperature and stirred for 12 h. The reaction was quenched by addition of saturated NH_4Cl, and Dowex 50WX8 (1.0 g) was added. The resulting solution was shaken for three days. After filtration, the resin was washed thoroughly with water and methanol. The product was eluted with 2.5% NH_3 (aq). The aqueous solution was concentrated in vacuo, after which toluene was added. The solvents were now evaporated to dryness, giving aminocyclopentane **7** (23 mg, 0.14 mmol, 93%) as a colourless oil. $[\alpha]_D^{20}$ = +4.0 (*c* = 1.2, MeOH). ^{1}H NMR / HH-COSY (400 MHz, CD_3OD): δ = 1.65 (dd, *J* = 15.3, 3.0 Hz, 1 H), 2.05 (dd, *J* = 15.2,

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6.2 Hz, 1 H), 3.42 (d, J = 11.8 Hz, 1 H), 3.66 (d, J = 11.7 Hz, 1 H), 3.73 (m, 1 H), 3.95 (d, J = 5.9 Hz, 1 H), 3.99 (m, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD): δ = 38.7, 63.6, 64.9, 71.3, 79.5, 80.3 ppm. HRMS (CI): $[M + H]^+$ calcd. 164.0943; found 164.0933.

(1*R*,2*S*,3*S*,4*S*)-1-Amino-2,3,4-trihydroxycyclopentanecarboxylic Acid (8): Diol **6** (40 mg, 0.12 mmol) was dissolved in a mixture of THF (3 mL), methanol (3 mL) and water (1.5 mL). $LiOH·H_2O$ (76 mg, 1.82 mmol) was added, and the suspension was stirred at room temperature for 24 h. Dowex 50WX8 (1.0 g) was added, and the product was isolated according to the procedure described above. The amino acid **8** (20 mg, 0.11 mmol, 91%) was obtained as colourless crystals (m.p. > 250 °C). $[\alpha]_D^{20}$ = +29.9 (c = 1.0, EtOH/H_2O, 1:1). ^{1}H NMR (500 MHz, CD_3OD, D_2O): δ = 1.63 (dd, J = 14.8, 2.5 Hz, 1 H), 2.63 (dd, J = 14.8, 6.3 Hz, 1 H), 3.91 (d, J = 8.2 Hz, 1 H), 4.07 (dd, J = 8.2, 5.4 Hz, 1 H), 4.15 (m, 1 H) ppm. ^{13}C NMR (125 MHz, CD_3OD, D_2O): δ = 43.1, 65.4, 70.3, 78.2, 84.8, 180.7 ppm. HRMS (CI): $[M + H]^+$ calcd. 178.0715; found 178.0712.

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