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A new stereoselective approach to aminocyclohexitols using a Grignard addition on to an *N*-benzyl sugar imine and RCM

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ABSTRACT

A new stereoselective approach for the synthesis of cyclohexitols using a Grignard addition on to an *N*-benzyl sugar imine and RCM from D-glucose has been described; the glycosidase inhibitory activity of these amino cyclohexitols has also been studied.

1. Introduction

The development of inhibitors for glycosidases is an important challenge toward the treatment of diseases, such as diabetes, cancer, viral infections, lysosomal disorders[1] and so on. Recently amino cyclohexitols have drawn considerable attention as potent glycosidase inhibitors. Some of the naturally occurring and biologically active amino cyclohexitols include valiolamine **1**, validamine **2**, and valienamine **3**. Voglibose **4** (Fig. 1), which is a derivative of valiolamine shows excellent inhibitor activity against α-glycosidases[2] and is used as a drug in the treatment of diabetes.[3] Therefore, the synthesis and biological evaluation of analogues of valiolamine is an important area of research.[4] The key structural feature that appears in most of these compounds is the presence of amino and hydroxymethyl units at the 1- and 3-positions on a polyhydroxy cyclohexane moiety. In the context of glycosidase inhibition, these compounds can be considered as structural analogs of monosaccharides containing a basic nitrogen function at the anomeric center. In particular, the amino group mimics the protonated form of the leaving group oxygen atom in the α- and β-orientation in the transition state of glycosidase catalyzed reactions.[5] However, glycosidase inhibition of aminocyclitols as a function of the various structural and stereochemical features still remains to be fully understood. Hence, the synthesis of new analogs can provide not only a better understanding of glycosidase function but also lead to inhibitors with improved therapeutic activity.

2. Results and discussions

Over the last few years, our group has been involved in the development of new synthetic strategies for carbasugars and imino sugars. Recently, we developed an approach for the synthesis of bicyclic imino sugars using a stereoselective Grignard addition onto sugar imines and RCM.[6] Herein, we report the application of the above strategy for the synthesis of two new aminocarbapyranoses **5** and **6**, which are structural analogs of valiolamine **1**. Our synthesis started from aldehyde **7**, which can be prepared from commercially available D-glucose using a known procedure.[7] Condensation of aldehyde **7** with benzylamine in the presence of 4 Å molecular sieves afforded chiral imine **8**, which was used as such for the next step without any purification. Treatment of imine **8** with allyl magnesium bromide in THF at 0 °C gave *syn*-amino olefin **9** as the exclusive isomer (Scheme 1). The stereochemistry of the newly generated stereogenic center was confirmed at a later stage

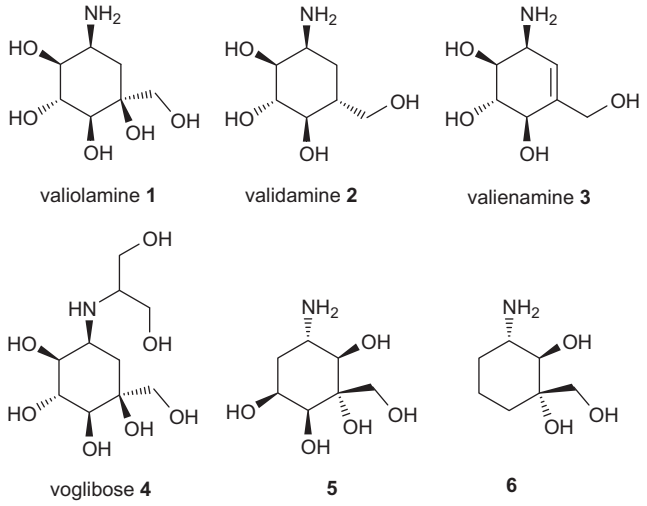

Figure 1.

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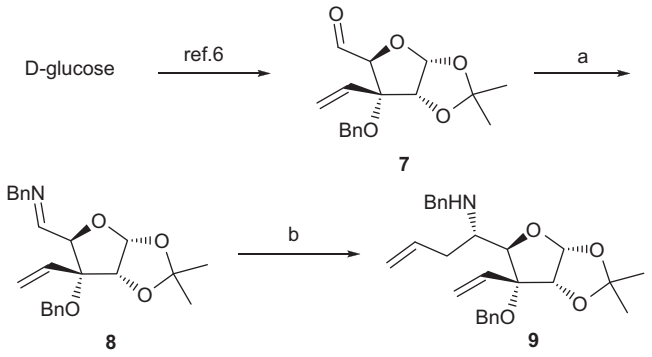
by ^{1}H NMR chemical shifts and coupling constants and also by NOE experiments. The formation of the *syn*-isomer is in accordance with our earlier observation, wherein the ring oxygen, the chelates with the Grignard reagent directs the nucleophile to undergo addition with high stereoselectivity[8] (Fig. 2). The amino functionality in compound **9** was protected as its Cbz derivative by treating it with benzyloxy carbonyl chloride in the presence of $NaHCO_3$ in MeOH to afford compound **10** in 92% yield. Next, 1,2-isopropylidene group in compound **10** was removed using TFA–H_2O to give hemiacetal **11**. Hemiacetal **11** was treated with $NaIO_4$ in CH_2Cl_2–H_2O to give the aldehyde, which was reduced to diol **12** with $NaBH_4$ in methanol in 74% yield. The *N*-Cbz protecting group was advantageously utilized for the selective protection of the secondary hydroxyl group of **12**. Thus, treatment of compound **12** with NaH in THF gave oxazolidinone **13**. Reduction of **13** with Na/liquid NH_3[9] furnished compound **14**. This diene **14**, upon reaction with Grubbs' second generation catalyst[10] in toluene at reflux afforded the aminocyclitol **15**. Isopropylidenation of **15** with 2,2-DMP in the presence of PTSA (catalyst) at room temperature gave **16**.



Scheme 1. Reagents and conditions: (a) $BnNH_2$, 4 Å molecular sieves, CH_2Cl_2, 0 °C, 4 h; (b) allyl magnesium bromide, ether, 0 °C, overnight, 92%.

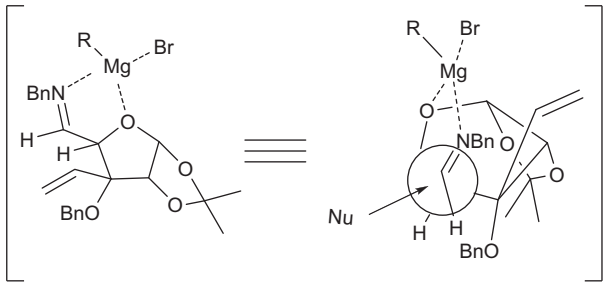


Figure 2.

The stereoselective dihydroxylation of **16** with osmium tetraoxide in the presence of NMO in acetone/water (3:1) gave the dihydroxylated compound **17** as the exclusive isomer.[11,12] Global deprotection of isopropylidene and the oxazolidine rings in compound **17** with 6 M HCl in methanol at reflux[12] afforded amino carbasugar **5**. Reduction of the olefin in compound **15** with H_2, Pd/C in methanol followed by deprotection of the oxazolidine ring with 6 M HCl in methanol at reflux gave **6** in 75% yield (Scheme 2). The new two amino carbasugars **5** and **6** were confirmed by using 1D NOE and coupling constants. The coupling constant $J_{Ha\text{-}Hb}$ = 10.0 Hz in compound **5** confirms the axial orientation of the H_a and H_b protons. The strong NOE between H_c–H_b, H_c–H_d and H_c–H_e further confirmed the structure of compound **5** (Fig. 3).

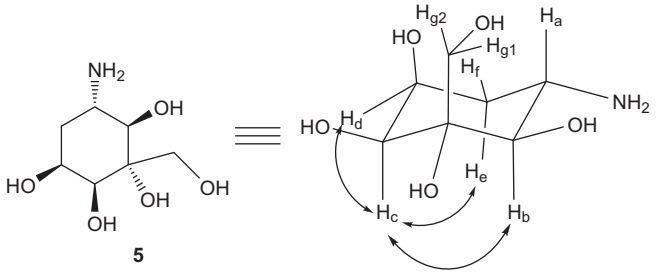


Figure 3.

3. Glycosidase inhibitory study

The inhibitory activities of compounds **5** and **6** were tested against a few enzymes, and the results are shown in Table 1. The glycosidase inhibitory activity against α-glucosidase (yeast), β-glucosidase (almonds), α-galactosidase (green coffee beans) and β-galactosidase (Kluyveromyces lactis) for compounds **5** and **6** were studied and the IC_{50} values are summarized in Table 1. The residual hydrolytic activities of the glycosidases were measured spectrometrically on the corresponding chromogenic nitrophenyl glycosides as substrates in an aqueous phosphate buffer at pH 6.8. All enzymes and substrates were purchased from Sigma–Aldrich Co., USA. The assays were performed with a fixed concentration of the substrate (1.6 mM) in a phosphate buffer and the enzyme concentration was 100 μl (1 mg/ml) in 20 ml of substrate solution. The substrate and compounds were preincubated for 1 min and the reaction was started by the addition of the enzyme. The reaction for the enzyme activity was followed for 5 min at 405 nm. Compound **5** was found to show moderate inhibition of α-glucosidase and α-galactosidase at concentrations of 0.82 and 1.2 mM respectively, whereas it showed no inhibition of β-glucosidase and β-galactosidase. On the other hand, compound **6** showed no inhibition of β-glucosidase, α-galactosidase, and β-galactosidase, but exhibited inhibition of α-glucosidase at a concentration of 1.02 mM.

Table 1
Glycosidase inhibitory activity, IC_{50} values in mM

Enzymes	5	6
α-Glucosidase	0.82 mM	1.02 mM
β-Glucosidase	NI*	NI*
α-Galactosidase	1.2 mM	NI*
β-Galactosidaes	NI*	NI*

NI: no inhibition at 2 mM concentration.

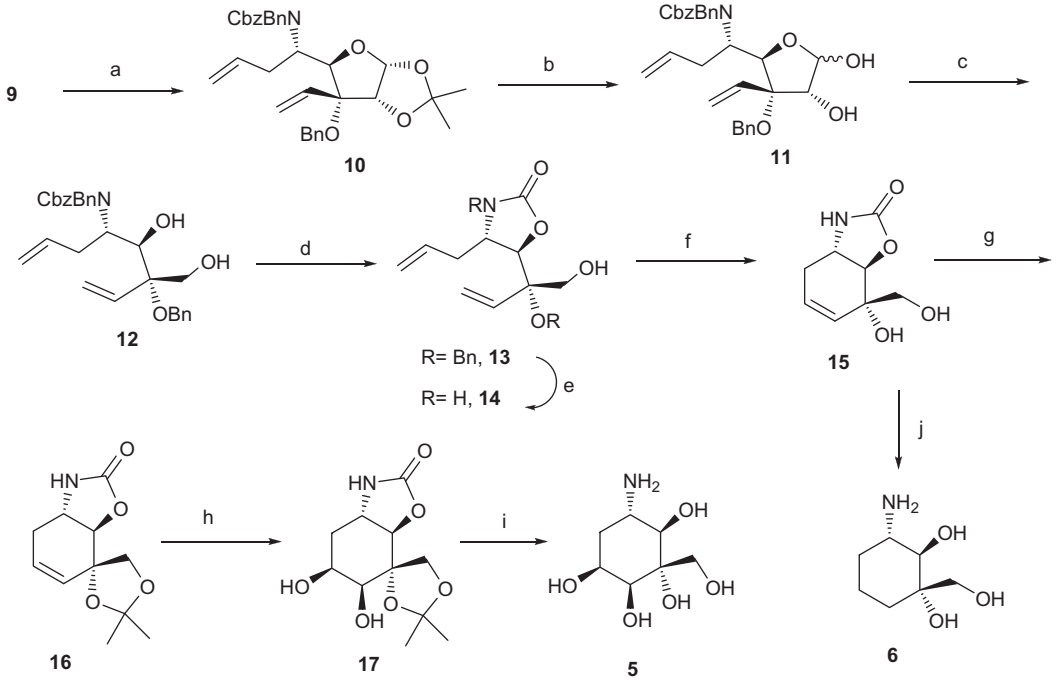
4. Conclusion

In conclusion, we have developed an efficient synthetic strategy for the preparation of two new aminocarbapyranoses using a Grignard reaction on a chiral imine, ring closing metathesis and dihydroxylation as key steps; their glycosidase inhibition was also studied. The extension of this approach for the preparation of other aminocyclitols is currently in progress in our laboratory.

5. Experimental

5.1. General

TLC was performed on Merck Kiesel gel 60; F254 plates (layer thickness 0.25 mm). Column chromatography was performed on



Scheme 2. Reagents and conditions: (a) CbzCl, $NaHCO_3$, MeOH, rt, 4 h, 92%; (b) TFA/H_2O (2:1), rt, 3 h, 74%; (c) $NaIO_4$, MeOH–H_2O, 6 h, then $NaBH_4$, MeOH, rt, 1 h, 74%; (d) NaH, THF, 0 °C, 20 min, 92%; (e) Na, liquid NH_3, THF, −78 °C, 20 min, 64%; (f) Grubbs' second generation catalyst, toluene, reflux, 4 h, 61%; (g) 2,2-DMP, PTSA, CH_2Cl_2, 0 °C, 1 h, 71%; (h) OsO_4, NMO, acetone/H_2O (3:1), 0 °C, 24 h, 94%; (i) 6 M HCl, MeOH, reflux, 12 h, 73%; (j) 10% Pd/C, MeOH, 1 h, then 6 M HCl, MeOH, H_2, reflux, 12 h, 75%.

silica gel (60–120 mesh) using ethyl acetate and hexane mixture as eluents. Melting points were determined on a Fisher John's melting point apparatus. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Bruker Avance-300 MHz, Varian-400, and 500 MHz spectrometers. ^{1}H NMR data are expressed as chemical shifts in ppm followed by multiplicity (s—singlet; d—doublet; t—triplet; q—quartet; m—multiplet), number of proton (s) and coupling constant (s) *J* (Hz). ^{13}C NMR chemical shifts are expressed in ppm. Optical rotations were measured with a JASCO digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA). Compounds were analyzed by using proton 1D NMR techniques. Here the conformations are fixed by considering the observed coupling constants and NOEs.

5.1.1. (*S*)-*N*-Benzyl-1-((3*aR*,5*R*,6*R*,6*aR*)-6-(benzyloxy)-2,2-dimethl-6-vinyl-tetra hydrofuro[2,3-*d*][1,3]dioxol-5yl)but-3en-1-amine 9

To a solution of aldehyde **7** (4.0 g, 13.11 mmol) in dry CH_2Cl_2 (40 mL) and molecular sieves 4 Å (0.8 g) was added benzylamine (1.43 mL, 13.11 mmol) at room temperature and kept at 0 °C for 4 h. The reaction mixture was filtered and concentrated to give crude imine **8**, which was used as such for the next step. To a solution of allyl magnesium bromide prepared from Mg (3.07 g, 128.12 mmol) and allyl bromide (10.86 mL, 128.12 mmol) in ether (40 mL), was added chiral imine **8** (5.05 g,12.81 mmol) in ether (50 mL) at 0 °C. After stirring overnight at room temperature, the reaction mixture was poured into saturated aqueous NH_4Cl (150 mL) and extracted with ethylacetate (3 × 150 mL). The combined organic layers were washed with water, brine, then dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (hexane/ethyl acetate 8:2) to afford the corresponding amino olefin **9** as a yellow oil (5.15 g, 92% for two steps). $[\alpha]_D^{30} = +47.1$ (*c* 1.46, $CHCl_3$); IR ν_{max} 3448, 3066, 3028, 2985, 2926, 1637, 1494, 1455, 1377, 1215, 1166, 1102, 1030, 737 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34–7.13 (m, 10H), 5.94–5.72 (m, 3H), 5.39 (d, 1H, *J* = 11.3 Hz), 5.26 (d, 1H, *J* = 17.9 Hz), 5.07–4.98 (m, 2H), 4.70 (d, 1H, *J* = 11.1 Hz), 4.60–4.52 (m, 2H), 4.14 (d, 1H, *J* = 8.6 Hz), 3.8 (d, 1H, *J* = 12.6 Hz), 3.7 (d, 1H, *J* = 12.6 Hz), 2.78 (m, 1H), 2.47 (m, 1H), 2.27 (m, 1H), 1.60 (s, 3H), 1.36 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 140.6, 138.5, 135.4, 134.6, 128.2, 128.07, 128.04, 127.0, 126.7, 126.5, 117.5, 116.8, 112.5, 103.3, 85.3, 82.6, 81.8, 66.9, 55.7, 50.5, 33.1, 26.7, 26.6; ESIMS *m*/*z*: 436 [M+H]$^+$; HRMS (ESI) calcd for $C_{27}H_{33}NO_4$ [M+H]$^+$ 436.2487, found 436.2484.

5.1.2. Benzyl benzyl ((*S*)-1-(3*aR*,5*R*,6*R*,6*aR*)-6-(benzyloxy)-2,2-dimethyl-6-vinyl-tetra hydrofuro[2,3-*d*][1,3]dioxol-5-yl)but-3-enyl)carbamate 10

To a stirred solution of **9** (5 g, 11.46 mmol) in dry methanol (50 mL) was added sodium bicarbonate (2.88 g, 34.39 mmol) followed by CbzCl (3.23 mL, 22.92 mmol) at 0 °C. The reaction mixture was stirred at rt for 4 h. Methanol was evaporated under reduced pressure and reaction mixture was diluted with water (50 mL) and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography (hexane/ethyl acetate 9:1) to give compound **10** (6.0 g, 91.8%) as a colorless syrup. $[\alpha]_D^{30} = +20.6$ (*c* 2.29, $CHCl_3$); IR ν_{max} 3432, 3065, 3030, 2985, 2929, 1697, 1455, 1378, 1247, 1219, 1108, 1043, 738, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz)* δ 7.39–7.10 (m, 14H), 6.95 (br s, 1H), 5.96–5.13 (m, 5H), 5.12–4.77 (m, 3H), 4.75–4.17 (m, 7H), 4.01 (m, 1H), 2.66–2.03 (m, 2H), 1.40–1.25 (br s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz)* δ 157.4, 157.2, 138.9, 138.7, 138.4, 138.2, 138.1, 137.7, 136.9, 136.4, 134.9, 134.4, 134.2, 134.0, 133.8, 133.4, 129.6, 128.0, 127.8, 127.5, 127.4, 127.3, 127.1, 126.9, 126.7, 126.4, 126.2, 118.5, 118.2, 116.8, 116.3, 112.4, 103.2, 103.1, 85.7, 85.4, 82.2, 82.0, 81.1, 80.1, 80.0, 77.2, 66.9, 66.8, 66.7, 58.5, 55.7, 55.2, 46.1, 45.8, 33.1, 31.8, 31.7, 26.5; ESIMS *m*/*z*: 570 [M+H]$^+$. HRMS (ESI) calcd for $C_{35}H_{39}NO_6$ [M+Na]$^+$ 592.2675, found 592.2694. *^{1}H and ^{13}C NMR showed a doubling of the signals due to a rotameric mixture.

5.1.3. Benzyl benzyl ((*S*)-1-(2*R*,3*S*,4*R*)-3-(benzyloxy)-4,5-dihydroxy-3-vinyltetra hydrofuran-2,-yl)but-3-enyl)-carbamate 11

To compound **10** (5.9 g, 10.35 mmol) TFA/H_2O (2:1, 40 ml) was added at 0 °C then the reaction mixture was warmed to room temperature and stirred for 3 h. The solvents were removed by three co-evaporations with toluene (3 × 30 mL), and the residual product was dissolved in water and neutralized with saturated $NaHCO_3$ and then extracted with ethyl acetate (2 × 100 mL). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure and the crude product was purified by column chromatography (hexane/ethyl acetate 1:1) to give the lactol **11** (4.1 g, 74.8%) as a syrup. $[\alpha]_D^{30} = +32.9$ (*c* 0.77, $CHCl_3$); IR ν_{max}, 3411, 3065, 3030, 2941, 1675, 1452, 1419, 1310, 1246, 1092, 1037, 737, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz)* δ 7.51–6.99 (m, 15H), 6.20–3.62 (m, 17H), 3.08–2.05 (m, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz)* δ 157.7, 138.8, 137.9, 137.6, 136.5, 136.2, 134.2, 134.1, 133.2, 133.0, 132.6, 129.6, 128.3, 128.1, 127.8, 127.6, 127.5, 127.4, 127.3, 127.0, 126.8, 126.5, 119.4, 119.0, 116.9, 116.7, 102.4, 102.2, 95.7, 95.4, 85.6, 85.5, 81.7, 80.0, 78.7, 77.2, 78.3, 78.3, 72.9, 67.0, 66.8, 56.1, 46.2, 32.4, 32.2, 31.8; ESIMS *m*/*z*: 530 $[M+H]^+$; HRMS (ESI) calcd for $C_{32}H_{35}NO_6$ $[M+Na]^+$ 552.2362, found 552.2386. *^1H and ^{13}C NMR showed a doubling of the signals due to a rotameric mixture.

5.1.4. Benzyl benzyl ((4*S*,5*R*,6*S*)-6-(benzyloxy)-5-hydroxy-6-(hydroxymethyl)octa-1,7-dien-4-yl)carbamate 12

To a solution of lactol **11** (4.0 g, 7.54 mmol) in methanol (40 mL) was added $NaIO_4$ (12.86 g, 60.37 mmol) in H_2O (40 mL) at 0 °C. The reaction mixture was stirred at rt for 4 h. Methanol was removed under reduced pressure. The reaction mixture was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic layers were washed with aq $NaHCO_3$ (50 mL), dried and concentrated to give the crude aldehyde, which was used as such for the next reaction without any purification. To a solution of the aldehyde in dry methanol (25 mL) was added $NaBH_4$ (0.38 g, 10.54 mmol) at 0 °C and stirred for 1 h. The reaction mixture was quenched by adding satd NH_4Cl after which MeOH was removed under reduced pressure and extracted with ethyl acetate (2 × 100 mL). The organic layer was dried over Na_2SO_4, concentrated, and purified by column chromatography (hexane/ethyl acetate 1:1) to afford diol **12** (2.8 g, 74% for 2 steps) as a thick liquid. $[\alpha]_D^{30} = +245.7$ (*c* 1.52, $CHCl_3$), IR ν_{max}, 3373, 3065, 3031, 2926, 1739, 1668, 1447, 1238, 1076, 736, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.22 (m, 10H), 7.20–7.09 (m, 3H), 6.89–6.78 (m, 2H), 6.02–5.79 (m, 2H), 5.40–5.17 (m, 3H), 5.08 (d, 1H, *J* = 12.2 Hz), 4.94–4.61 (m, 5H), 4.54 (d, 1H, *J* = 10.5 Hz), 4.02–3.90 (m, 2H), 3.83–3.70 (m, 2H), 3.35–3.23 (br s, 1H), 2.80–2.66 (m, 1H), 2.27–2.14 (br s, 1H), 1.94–1.82 (br s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 157.9, 138.5, 136.9, 136.2, 135.3, 134.6, 128.8, 128.4, 128.2, 128.1, 128.0, 127.7, 127.5, 117.3, 116.2, 82.2, 72.6, 67.6, 65.4, 63.2, 60.1, 54.0, 34.3; ESIMS *m*/*z*: 502 $[M+H]^+$; HRMS (ESI) calcd for $C_{31}H_{35}NO_5$ $[M+Na]^+$ 524.2412, found 524.2428.

5.1.5. (4*S*,5*R*)-4-Allyl-3-benzyl-5-((*S*)-2-(benzyloxy)-1-hydroxybut-3en-2-yl) oxazolidin-2-one 13

To a solution of **12** (2.1 g, 4.19 mmol) in dry THF (20 mL) was added sodium hydride [0.501 g (60% w/w in wax), 23.11 mmol] at room temperature and the mixture was stirred under nitrogen atmosphere for 20 min. The reaction mixture was quenched by adding saturated aqueous NH_4Cl and extracted with ethyl acetate (100 mL). The organic layer was dried over anhydrous Na_2SO_4, concentrated under reduced pressure and purified through column chromatography (hexane/ethyl acetate 4:6) to afford oxazolidine **13** (1.53 g, 92.8%) as a liquid. $[\alpha]_D^{30} = -6.1$ (*c* 2.0, $CHCl_3$); IR ν_{max} 3431, 3030, 2930, 1732, 1442, 1243, 1063, 738, 701 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.39–7.09 (m, 10H), 5.75–5.59 (m, 1H), 5.52–5.39 (dd, 1H, *J* = 10.5, 11.3 Hz), 5.27–5.09 (m, 4H), 4.72 (1H, *J* = 15.1 Hz), 4.54–4.43 (m, 3H), 3.99 (d, 1H, *J* = 15.1 Hz), 3.93–3.75 (m, 2H), 3.71–3.63 (m, 1H), 2.47–2.35 (m, 1H), 2.33–2.21 (m, 1H), 1.93–1.72 (br s, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 157.5, 138.2, 135.2, 132.4, 131.5, 128.5, 128.4, 128.3, 127.8, 127.5, 126.8, 120.6, 119.6, 80.5, 76.0, 64.8, 61.0, 53.6, 45.8, 36.2; ESIMS *m*/*z*: 394 $[M+H]^+$. HRMS (ESI) calcd for $C_{24}H_{27}NO_4$ $[M+Na]^+$ 416.1837, found 416.1833.

5.1.6. (4*S*,5*R*)-4-Allyl-5-((*S*)-1,2-hydroxybut-3en-2-yl)-oxazolidin-2-one 14

To a solution of sodium (2.45 g, 106.87 mmol) in liquid NH_3 (50 mL) at −78 °C was added compound **13** (1.4 g, 3.56 mmol) dissolved in dry THF (25 mL). After the addition the acetone/dry ice bath was replaced by a CCl_4/dry ice bath and stirred for 20 min and again cooled to −78 °C. The blue solution was stirred for 30 min and solid NH_4OAc (2 g) was added, after which the reaction mixture was brought to room temperature. After evaporation of the ammonia, the residue was partitioned between ethyl acetate (100 mL) and H_2O (100 mL). The aqueous layer was separated and extracted with ethyl acetate (2 × 100 mL) and the combined organic layers were washed with saturated NaCl, dried over anhydrous Na_2SO_4, concentrated under reduced pressure, and purified by column chromatography (hexane/ethyl acetate = 2:8) to afford compound **14** (0.49 g, 64.6%) as a colorless oil. $[\alpha]_D^{30} = -37.5$ (*c* 0.48, MeOH); IR ν_{max}, 3415, 2927, 1738, 1648, 1409, 1246, 1066, 1020, 764 cm^{-1}; ^1H NMR (CD_3OD, 300 MHz) δ 5.90–5.74 (m, 2H), 5.52 (d, 1H, *J* = 16.9 Hz), 5.34 (d, 1H, *J* = 11.1 Hz), 5.24–5.12 (m, 1H), 4.41 (d, 1H, *J* = 4.5 Hz), 3.81 (dd, 1H, *J* = 4.5, 10.9 Hz), 3.68 (d, 1H, *J* = 11.5 Hz), 3.45 (d, 1H, *J* = 11.5 Hz), 2.46–2.35 (m, 1H), 2.32–2.20 (m, 1H); ^{13}C NMR (CD_3OD, 300 MHz) δ 161.3, 136.5, 134.0, 119.3, 118.2, 81.9, 76.8, 66.4, 53.7, 41.3; ESIMS *m*/*z*: 214 $[M+H]^+$. HRMS (ESI) calcd for $C_{10}H_{15}NO_4$ $[M+Na]^+$ 236.0898, found 236.0887.

5.1.7. (3a*S*,7*S*,7a*R*)-7-Hydroxy-7-(hydroxymethyl)-3a,4,7,7a-tetrahydrobenzo[*d*] oxazol-2(3*H*)-one 15

To diene **14** (0.45 g, 2.11 mmol) in dry toluene (80 mL), Grubbs' II generation catalyst (0.179 g, 0.211 mmol) was added and the resulting purple solution turned brown after 10 min. The reaction mixture was refluxed for 4 h, concentrated under reduced pressure, and the residue was purified by column chromatography (hexane/ethyl acetate: 2:8) to give compound **15** as a light brown oil (0.24 g, 61.5%). $[\alpha]_D^{30} = +101.8$ (*c* 0.77, MeOH); IR ν_{max}, 3416, 2925, 1947, 1746, 1632, 1388, 1230, 1038, 764 cm^{-1}; ^1H NMR (D_2O, 500 MHz) δ 5.98–5.93 (m, 1H), 5.63 (dd, 1H, *J* = 2.1, 10.4 Hz), 4.36 (d, 1H, *J* = 12.6 Hz), 4.08–4.04 (m, 1H), 3.85 (dd, 2H, *J* = 12.2, 6.1 Hz), 2.64–2.57 (m, 1H), 2.31–2.23 (m, 1H); ^{13}C NMR (D_2O, 300 MHz) δ 164.6, 131.4, 130.7, 89.6, 76.1, 65.9, 55.8, 32.5; ESIMS *m*/*z*: 208 $[M+Na]^+$. HRMS (ESI) calcd for $C_8H_{11}NO_4$ $[M+Na]^+$ 208.0585, found 208.0578.

5.1.8. (3a*S*,4′*S*,7a*R*)-2′,2′-Dimethyl-3,3a,4,7a-tetrahydro-2*H*-spiro[benzo[*d*]oxazole-7,4′-[1,3]dioxolan]-2-one 16

To a solution of compound **15** (0.21 g, 1.13 mmol) in CH_2Cl_2 (3 mL) was added 2,2-dimethoxy propane (0.41 mL, 3.40 mmol) and PTSA (catalyst) and then stirred for 1 h at room temperature. After evaporation of the solvents, water was added (2 mL) and extracted with ethyl acetate (2 × 10 mL). The combined organic layers were washed with brine (10 mL) dried over Na_2SO_4 and concentrated in vacuo. Purification by column chromatography (hexane/ethyl acetate, 8:2) afforded **16** as a white solid (0.18 g, 71.1%). Mp 148 °C $[\alpha]_D^{30} = +68.0$ (*c* 1.3, $CHCl_3$); IR ν_{max}, 3286, 2922, 2853, 1745, 1375, 1223, 1170, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 5.86 (br s, 1H), 5.80–5.73 (m, 1H), 5.69–5.64 (m, 1H),

4.34 (d, 1H, J = 8.6 Hz), 4.30 (d, 1H, J = 12.4 Hz), 3.84 (d, 1H, J = 8.6 Hz), 3.49 (m, 1H), 2.50 (m, 1H), 2.23 (m, 1H), 1.49 (S, 3H), 1.45 (S, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 159.8, 131.9, 125.9, 110.6, 83.6, 81.2, 67.6, 54.7, 30.4, 26.7, 26.0; ESIMS m/z 226 $[M+H]^+$; HRMS (ESI) calcd for $C_{11}H_{15}NO_4$ $[M+Na]^+$ 248.0898, found 248.0905.

5.1.9. (3a*S*,4′*R*,5*S*,6*S*,7a*R*)-5,6-Dihydroxy-2′,2′-dimethylhexahydro-2*H*-spiro[benzo[*d*]oxazole-7,4′-[1,3]dioxolan]-2-one 17

To a stirred solution of compound **16** (0.08 g, 0.35 mmol) in acetone/H_2O (3:1, 4 mL) was added NMO monohydrate (72 mg, 0.53 mmol) followed by OsO_4 (9 mg, 0.035 mmol) at 0 °C and stirred at room temperature for 24 h. After the addition of Na_2SO_3 (0.049 g, 0.39 mmol), acetone was removed under reduced pressure and the reaction mixture was diluted with water and extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under reduced pressure, purified by column chromatography (hexane/ethyl acetate, 2:8) to give compound **17** as a white solid (0.086 g, 94.5%). Mp 234 °C; $[\alpha]_D^{30} = -6.8$ (c 0.5, MeOH); IR ν_{max}, 3384, 3251, 2993, 2903, 1751, 1378, 1248, 1224, 1058, 944 cm^{-1}; ^{1}H NMR (CD_3OD, 300 MHz) δ 4.30 (d, 1H, J = 9.1 Hz), 4.11–4.07 (m, 1H), 4.05 (d, 1H, J = 9.1 Hz), 3.90 (d, 1H, J = 12.1 Hz), 3.79–3.67 (m, 1H), 3.66 (d, 1H, J = 3.0 Hz), 2.08 (td, 1H, J = 3.3, 12.8 Hz), 1.57 (dt, 1H, J = 2.6 Hz), 1.33 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 163.0, 110.0, 86.3, 85.6, 74.6, 71.2, 64.4, 54.1, 33.5, 26.65, 26.6; ESIMS m/z: 282 $[M+Na]^+$. HRMS (ESI) calcd for $C_{11}H_{17}NO_6$ $[M+Na]^+$ 282.0953, found 282.0941.

5.1.10. (1*R*,2*S*,3*S*,4*S*,6*S*)-6-Amino-2-(hydroxymethyl)-cyclohexane-1,2,3,4-tetraol 5

To a solution of compound **17** (0.055 g, 0.21 mmol) in MeOH, was added 6 M HCl (2 mL) at 0 °C, and then stirred at reflux for 12 h. Next the solution was concentrated under reduced pressure and purified by column chromatography using Dowex 50w X 8–400 to afford compound **5** as a white semi-solid (0.03 g, 73.1%), $[\alpha]_D^{30} = +27.2$ (c 0.2, H_2O), IR ν_{max},3424, 2922, 2852, 1630, 1571, 1462, 570 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 4.21–4.07 (m, 1H, H_d), 3.96–3.82 (s, 2H, H_{g1}, H_{g2}), 3.70 (d, 1H, $J_{Hc\text{-}Hd}$ = 3.0 Hz, H_c), 3.38 (d, 1H, $J_{Ha\text{-}Hb}$ = 10.0 Hz, H_b), 3.31–3.17 (m, 1H, H_a), 2.07 (td, 1H, J = 4.1, 13.9 Hz, H_f), 1.59 (dt, 1H, J = 2.2, 13.2 Hz, H_e); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 77.5, 76.7, 75.7, 67.7, 62.1, 49.1, 32.8; ESIMS m/z: 194 $[M+H]^+$. HRMS (ESI) calcd for $C_7H_{15}NO_5$ $[M+H]^+$ 194.1028, found 194.1022.

5.1.11. (1*S*,2*R*,3*S*)-3-Amino-1-(hydroxymethyl) cyclohexane-1,2-diol 6

To a solution of compound **14** (0.04 g, 0.17 mmol) in MeOH was added 10% Pd/C (cat) and stirred under an H_2 atmosphere for 1 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure, after which the crude reaction mixture was dissolved in MeOH. Next, 6 M HCl (1 mL) was added at 0 °C, and the reaction mixture was refluxed for 12 h. The reaction mixture was concentrated under reduced pressure and purified by column chromatography using Dowex 50w X 8–400 to afford the compound **6** as a white semi solid (0.021 g, 75%). $[\alpha]_D^{30} = +47.3$ (c 0.2, H_2O), IR ν_{max}, 3382, 2957, 2361, 2123, 1624, 1095, 1059, 619 cm^{-1}; ^{1}H NMR (D_2O, 300 MHz) δ 3.74 (d, 1H, J = 12.2 Hz), 3.62 (d, 1H, J = 12.2 Hz), 3.60 (d, 1H, J = 10.0 Hz), 3.29–3.17 (m, 1H), 2.09–1.90 (m, 2H), 1.76–1.26 (m, 4H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 76.2, 75.5, 62.3, 52.9, 31.6, 28.1, 19.0; ESIMS m/z: 162 $[M+H]^+$; HRMS (ESI) calcd for $C_7H_{15}NO_3$ $[M+H]^+$ 162.1130, found 162.1123.

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