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A new stereoselective approach to aminocyclohexitols using RCM

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ABSTRACT

A new stereoselective approach for the synthesis of carbamannopyranosylamine and *epi*-valiolamine by using stereoselective allylation on lactamine and RCM from D-ribose has been described.

1. Introduction

Carbasugars[1] are analogues of monosaccharides, in which the ring oxygen is replaced with a methylene group. Similarly aminocarbasugars are carbasugars in which the C-1 hydroxy is replaced with an amino group; these compounds are generally glycosidase inhibitors.[2] Glycosidases are involved in several metabolic pathways, and the development of inhibitors for glycosidases is an important challenge toward the treatment of diseases, such as diabetes, cancer, viral infections, and lysosomal storage disorder.[3] Six membered aminocarbasugars (aminocyclohexitols) are found in Nature as part of complex molecules arising from the secondary metabolism of several microorganisms; examples include valienamine **1**, validamine **2,** and valiolamine **3** (Fig. 1). Valiolamine **3** possesses very potent activity against maltase and sucrase. Chemical modification of this compound has led to voglibose **4**, which is presently used for the treatment of diabetes.[4] Different types of validamine analogues have been prepared and tested with regard to their glycosidase inhibitory activity.[5] In these types of compounds, the amino group mimics the protonated form of the leaving group oxygen atom in the α- or β-orientation in the transition state of a glycosidase catalyzed reaction.[5] Recently, Ogawa and co-workers reported the importance of NOV **5** and NOEV **6** in chaperone therapy.[6] Tamiflu is also related to the aminocyclohexitols, which is used in the treatment of bird flu.[7] Due to the interesting biological activity and structural features, there has been a remarkable growth in the design, synthesis, and evaluation of new aminocyclohexitols as glycosidase inhibitors.[8,9]

In continuation of our efforts in the area of 'carbohydrate mimics' such as carbasugars,[10] aminocarbasugars,[11] and iminosugars,[12] we herein report the stereoselective synthesis of carbamannopyranosylamine **7**[13] and valiolamine analogue **8**.[14] In our previous communication, we reported an RCM[15] based approach for the synthesis of *N*-benzyl aminocyclopentitols,[11] where we utilized Eschenmoser's salt for the efficient preparation of a diene precursor, and the amino group was generated from the nucleophilic addition onto a ribosylamine.

2. Results and discussion

Herein we report the application of our aforementioned strategy for the synthesis of aminocyclohexitols **7** and **8**. The starting material 5-*O*-*tert*-butyl dimethylsilyl-2,3-*O*-isopropylidene-D-ribofuranose **9**, which was required for our synthesis was prepared from D-ribose using reported procedure (Scheme 1).[16] The reaction of **9** with benzylamine gave ribosylamine; treatment of the crude ribosylamine with allylbromide and zinc furnished amino alcohol **10** exclusively as a single isomer in 70% yield over two steps.[11] The formation of erythro isomer **10** can be explained by nucleophilic addition onto the imine generated from the ribosalamine of **9** via a seven membered transition state resulting from the chelation of hydroxyl and an imine, or a Felkin-Anh model, as per our earlier observations.[11] The secondary hydroxyl group of compound **10** was protected as its triethylsilyl ether to give **11** in 93% yield. The amino functionality in **11** was converted into a carbamate with CbzCl to give **12** in 85% yield. The hydroboration of olefin **12** gave alcohol **13** in 85% yield. The primary alcohol in compound **13** was oxidized with TEMPO/BAIB in CH_2Cl_2, to give aldehyde **13a** which upon treatment with Et_3N/Eschenmoser's salt[17] in the same pot yielded the α-methylene aldehyde **13b**. Compound **13b** was carried through to the next step immediately without any purification. Reduction of the crude α-methylene aldehyde **13b** under Luche conditions at −78 °C in methanol gave allylic alcohol **14** in 75% yield from **13**. Allylic alcohol **14** was protected as the MOM–ether to provide **15** in 94% yield. Deprotection of the silyl groups in **15** with TBAF furnished diol **16** in 93% yield. The 1,2-diol functionality in compound **16** was converted into olefin **17** in 75% yield by using Garreg's protocol.[18]

Ring closing metathesis of diene **17** with 10 mol % Grubbs II generation catalyst[15] in toluene at reflux gave aminocyclohexene **18** in 85% yield. The stereoselective hydroboration of aminocyclohexene **18** yielded the hydroxyl compound **19** in 68% yield. Dihydroxylation of **18** gave diol **20** in 80% yield. Hydrogenation of **19** and **20** using Pd/C under acidic conditions yielded carbamannopyrano-

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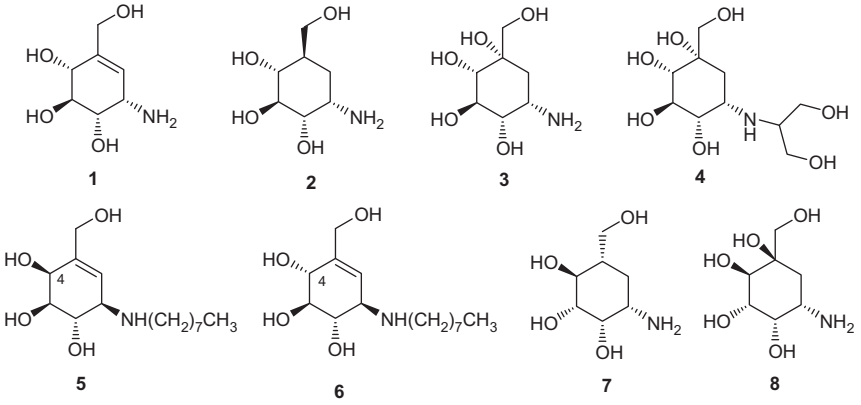


Figure 1.

sylamine **7** and (1*S*,2*S*)-valiolamine **8**, respectively. The crude mixture of **7** and **8** upon acetylation afforded peracetyl derivatives **21** and **22** in 80% yield over two steps. The physical and spectroscopic data of **21**[13] and **22**[14] were in good agreement with the reported values (Scheme 2).

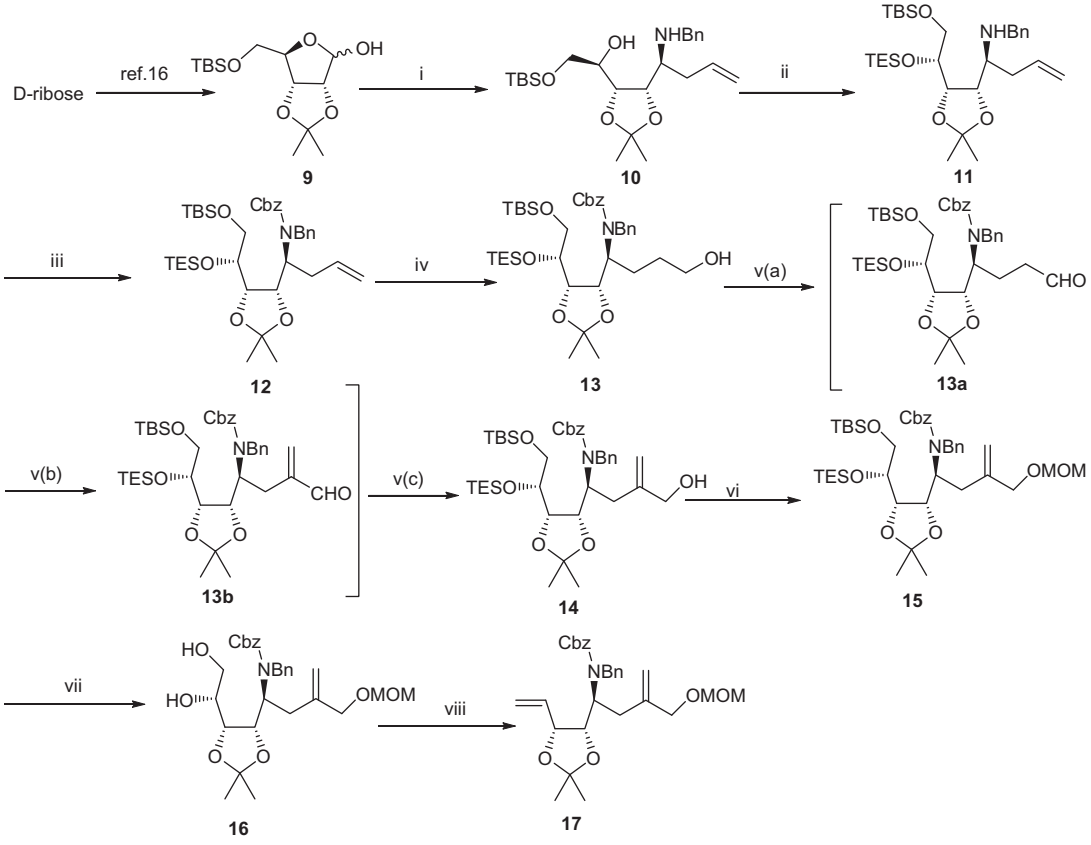
3. Conclusions

In conclusion, we have successfully reported the application of our strategy for the synthesis of aminocyclohexitols using RCM. Further studies of the applications of this strategy for the synthesis of more complex systems are currently in progress.

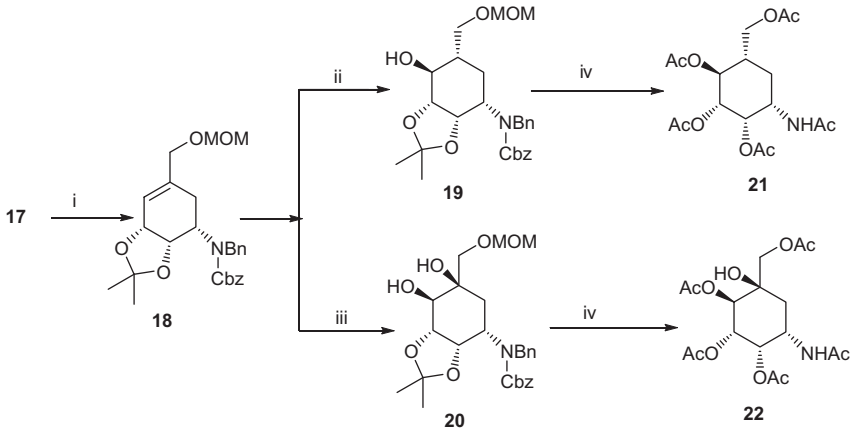
4. Experimental

4.1. General

TLC was performed on Merck Kiesel gel 60, F254 plates (layer thickness 0.25 mm). Column chromatography was performed on silica gel (60–120 mesh) using ethyl acetate and hexane mixture as the eluent. Melting points were determined on a Fisher John's melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin–Elmer RX-1 FT-IR system. ^{1}H NMR and ^{13}C NMR spectra were recorded using Varian Gemini-200 MHz and 400 MHz or a Bruker Avance-300 MHz spectrometer. ^{1}H NMR data



Scheme 1. Reagents and conditions: (i) (a) $BnNH_2$, MeOH, reflux, overnight; (b) allylbromide, Zn, THF, 0 °C to rt, 12 h, 70% (over two steps); (ii) TES-Cl, imidazole, cat. DMAP, CH_2Cl_2, 0 °C, 10 min, 93%; (iii) NaH, CbzCl, THF, 0 °C, 1 h, 85%; (iv) BH_3.DMS, THF, 0 °C, 2 h, NaOH, H_2O_2, 0 °C, 85%; (v) (a) TEMPO, BAIB, CH_2Cl_2, 0 °C, 2 h; (b) Et_3N, Eschenmoser's salt, rt, 4 h; (c) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, −78 °C, 30 min, 75% (from **13**); (vi) MOM–Cl, DIPEA, cat. DMAP, CH_2Cl_2, 0 °C, 94%; (vii) TBAF, THF, rt, 1 h, 93%, (viii) TPP, I_2, imidazole, toluene, reflux, 4 h, 75%.



Scheme 2. Reagents and conditions: (i) 10 mol % Grubbs second generation catalyst, toluene, reflux, 12 h, 85%; (ii) BH_3·DMS, H_2O_2, NaOH, THF, 0 °C, 3 h, 68%; (iii) OsO_4, NMO, acetone/water, 4:1, rt, 3 h, 80%; (iv) (a) 10% Pd/C, H_2, concd HCl, rt, 12 h; (b) Ac_2O, pyridine, cat. DMAP, rt, 12 h, 80% (over two steps).

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 JASCO digital polarimeter. Accurate mass measurement was performed on Q STAR mass spectrometer (Applied Biosystems, USA).

4.2. (*R*)-1-((4*R*,5*S*)-5-((*S*)-1-(Benzylamino)-but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(*tert*-but-yldimethylsilyloxy) ethanol 10

To a stirred solution of ribofuranose **9** (10 g, 32.89 mmol) in dry MeOH (100 mL), 4 Å molecular sieves, Na_2SO_4, and $BnNH_2$ (8.9 mL, 82.23 mmol) were added at rt. The reaction mixture was refluxed overnight. The reaction mixture was filtered on a Celite pad and the solvent was evaporated under reduced pressure. To this crude lactamine (12.9 g, 32.89 mmol) in dry THF (120 mL), at −15 °C, allylbromide (41.6 mL, 493.42 mmol) was added and then Zn (27.86 g, 426.71 mmol) was added portionwise over a period of 15 min at 0 °C. After stirring overnight at room temperature, the reaction mixture was quenched with a saturated NH_4Cl solution and filtered on a Celite pad. The filtrate was extracted into ethylacetate (3 × 100 mL). The collected organic layers were combined, washed with aq 1 M HCl, separated then dried over Na_2SO_4, concentrated under reduced pressure, and purified through column chromatography on silica gel using hexane/ethyl acetate (9:1) to afford the corresponding amino alcohol **10** as a colorless oil (10.0 g, 70% over two steps). $[\alpha]_D^{25} = +11.5$ (*c* 1.9, $CHCl_3$); IR (neat) ν_{max} 3445, 3071, 2929, 1637, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.10 (s, 6H), 0.93 (s, 9H), 1.32 (s, 3H), 1.40 (s, 3H), 2.50–2.68 (m, 2H), 3.03–3.13 (m, 1H), 3.61–3.73 (m, 2H), 3.76 (dd, 1H, *J* = 4.5, 10.7 Hz); 3.82–3.98 (m, 3H), 4.19–4.30 (m, 1H), 5.18–5.28 (m, 2H), 5.76–5.96 (m, 1H), 7.21–7.38 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): -5.2, -5.3, 18.5, 25.6, 26.0, 28.1, 32.4, 50.4, 54.9, 65.0, 69.5, 77.1, 77.6, 108.2, 119.7, 127.5, 128.7, 133.0, 138.0; ESI/MS (*m*/*z*): 436 $(M+H)^+$; HRMS Calcd for $C_{24}H_{42}NO_4Si$ $(M+H)^+$ 436.2883. Found: 436.2867.

4.3. (*S*)-*N*-Benzyl-1-((4*S*,5*S*)-5-((*R*)-3,3-diethyl-8,8,9,9-tetramethyl-4,7-dioxa-3,8disiladecan -5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-1-amine 11

To an ice cooled stirred solution of amino alcohol **10** (4.50 g, 10.35 mmol) in dry CH_2Cl_2 (50 mL) was added imidazole (2.8 g, 41.4 mmol) and triethylsilylchloride (3.5 mL, 20.6 mmol) and stirred for 10 min. The reaction mixture was extracted in CH_2Cl_2 (100 mL) and washed with brine. The organic layer was separated, dried over anhydrous Na_2SO_4, concentrated, purified by column chromatography using hexane/ethyl acetate (19:1) to give **11** (5.30 g, 93%) as a syrup. $[\alpha]_D^{25} = +24.1$ (*c* 2.4, $CHCl_3$); IR (neat) ν_{max} 2978, 1698, 1385, 1083 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.02–0.08 (m, 6H), 0.52–0.65 (m, 6H), 0.86–0.95 (m, 18H), 1.30 (s, 3H), 1.41 (s, 3H), 2.25–2.48 (m, 2H), 2.92–3.03 (m, 1H), 3.64 (dd, 1H, *J* = 5.2, 10.7 Hz), 3.72 (d, 1H, *J* = 12.4 Hz), 3.75–3.87 (m, 2H), 3.95–40 (m, 1H), 4.08–4.22 (m, 2H), 5.03–5.15 (m, 2H), 5.81–5.96 (m, 1H), 7.16–7.32 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz): −5.4, −5.5, 5.0, 6.9, 18.3, 24.6, 25.7, 26.3, 34.5, 50.7, 55.7, 66.0, 73.3, 77.0, 78.8, 107.4, 117.7, 126.7, 127.9, 128.1, 134.8, 140.4; ESI/MS (*m*/*z*): 550 $(M+H)^+$; HRMS Calcd for $C_{30}H_{56}NO_4Si_2$ $(M+H)^+$ 550.3747. Found: 550.3722.

4.4. Benzyl benzyl((*S*)-1-((4*S*,5*S*)-5-((*R*)-3,3-diethyl-8,8,9,9-tetramethyl-4,7-dioxa-3,8-disiladecan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-enyl)carbamate 12

To an ice cooled, stirred solution of compound **11** (5.0 g, 9.10 mmol) in dry THF, NaH (0.72 g, 60% w/v dispersion in mineral oil, 18.2 mmol) and Cbz-Cl (3.88 mL, 50% in toluene, 13.6 mmol) were added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with a saturated NH_4Cl solution and extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, separated and then dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel by eluting with hexane/ethyl acetate (19:1) to give compound **12** (5.50 g, 85% yield) as a syrup. $[\alpha]_D^{25} = +5.4$ (*c* 0.19, $CHCl_3$); IR (neat) ν_{max} 2949, 2880, 1699, 1458, 1375, 1250, 1099 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.01–0.10 (m, 6H), 0.53–0.74 (m, 6H), 0.82–1.02 (m, 18H), 1.16 (s, 3H), 1.40 (s, 3H), 2.16–2.49 (m, 2H), 3.54–4.02 (m, 3H), 4.04–4.19 (m, 1H); 4.21–4.32 (m, 1H), 4.45–5.20 (m, 7H), 5.46–5.88 (m, 1H), 7.01–7.40 (m, 10H) (^1H NMR Spectra not resolved clearly due to rotameric mixture); ^{13}C NMR ($CDCl_3$, 75 MHz): −5.5, 5.1, 6.9, 18.4, 24.5, 26.1, 34.1, 46.7, 47.0, 55.6, 55.8, 65.1, 66.9, 67.3, 72.4, 77.1, 78.8, 79.3, 107.6, 116.5, 116.8, 126.4, 126.5, 127.1, 127.5, 127.7, 127.9, 125.1, 128.4, 135.4, 135.5, 136.6, 139.8, 140.0, 156.8, 157.0 (multiple peaks in the spectra are due to rotameric mixture); ESI/MS (*m*/*z*): 684 $(M+H)^+$; HRMS Calcd for $C_{38}H_{61}NO_6Si_2Na$ $(M+Na)^+$ 706.3930. Found: 706.3935.

4.5. Benzyl benzyl((*S*)-1-((4*S*,5*S*)-5-((*R*)-3,3-diethyl-8,8,9,9-tetramethyl-4,7-dioxa-3,8-disiladecan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-hydroxybutyl)carbamate 13

To the stirred solution of **12** (1.30 g, 1.90 mmol) in dry THF (10 mL), $BH_3.Me_2S$ (0.39 mL, 4.18 mmol) was added dropwise at −10 °C. Stirring was continued for 3 h at room temperature. The reaction mixture was quenched by the addition of 10% NaOH (10 mL) followed by 30% H_2O_2 (15 mL) at 0 °C and allowed to warm to room temperature, and stirred for another 2 h. The reaction mixture was extracted with ethyl acetate (2 × 100 mL). The combined organic layers were washed with brine, separated and dried over anhydrous Na_2SO_4, the solvent was removed on rotary evaporator. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (4.5:0.5) as the eluant to give pure compound **13** (1.13 g, 85%) as a syrup. $[\alpha]_D^{25} = -32.5$ (*c* 1.87, $CHCl_3$); IR (neat) ν_{max} 3435, 2948, 2878, 1695, 1458, 1414, 1375, 1252, 1098, 1006, 835, 734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.10–0.0.10 (m, 6H), 0.53–0.78 (m, 6H), 0.89 (s, 9H), 0.89–1.01 (m, 9H), 1.20 (s, 3H), 1.08–1.58 (m, 2H), 1.41 (s, 3H), 1.44–1.69 (m, 2H), 3.11–3.52 (m, 2H), 3.52–4.01 (m, 3H); 4.06–4.32 (m, 2H), 4.51–4.78 (m, 3H), 4.94–5.51 (m, 2H), 7.14–7.45 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): −5.5, 5.1, 6.9, 18.3, 24.5, 25.6, 25.8, 26.0, 29.1, 46.6, 56.0, 62.6, 65.1, 67.2, 72.4, 77.2, 79.6, 107.6, 126.6, 127.3, 127.7, 127.9, 128.0, 128.2, 128.3, 136.5, 136.6, 140.0, 156.9; ESI/MS (*m*/*z*): 702 $(M+H)^+$; HRMS Calcd for $C_{38}H_{63}NO_7Si_2Na$ $(M+Na)^+$ 724.4041. Found: 724.4040.

4.6. Benzyl benzyl((*S*)-1-((4*S*,5*S*)-5-((*R*)-3,3-diethyl-8,8,9,9-tetramethyl-4,7-dioxa-3,8-disila-decan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-3-(hydroxymethyl)but-3-enyl)carbamate 14

To an ice cooled stirred solution of alcohol **13** (1.0 g, 1.42 mmol) in CH_2Cl_2 (10 mL), TEMPO (0.02 g, 0.14 mmol) and BAIB (1.10 g, 2.84 mmol) were added. The reaction mixture was stirred at room temperature for 5 h. After conversion, the aldehyde, triethylamine (0.8 mL, 5.7 mmol), and Eschenmoser's salt (0.6 g, 3.2 mmol) were added at rt. The reaction mixture was stirred for another 3 h and extracted with CH_2Cl_2 (2 × 50 mL). The organic layer was washed with brine, separated, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the crude product aldehyde was taken to the next reaction.

To an ice cooled, stirred solution of $CeCl_3{\cdot}7H_2O$ (1.0 g, 2.81 mmol) in MeOH (15 mL), $NaBH_4$ (0.21 g, 5.6 mmol) was added portionwise. After being stirred at 0 °C for 10 min, the reaction mixture was further cooled to −78 °C. To it, the above crude aldehyde in MeOH (10 mL) was added. The reaction mixture was stirred for another 30 min at −78 °C. To this reaction mixture saturated $NaHCO_3$ solution was added, after which the solvent was removed under reduced pressure. The residue was taken in ethyl acetate, and filtered through a Celite pad. The filtrate was washed with brine, separated, and the combined organic layers were removed on a rotary evaporator. The residue was purified by column chromatography on silica gel using hexane/ethyl acetate (9:1) as the eluant to give pure compound **14** (0.76 g, 75% over two steps) as a colorless liquid. $[\alpha]_D^{25} = -21.1$ (*c* 2.44, $CHCl_3$); IR (neat) ν_{max} 3400, 2945, 2877, 1686, 1252, 1209, 1100, 996, 903, 837, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.02–0.08 (m, 6H), 0.58–0.72 (m, 6H), 0.88–0.97 (m, 18H), 1.19 (s, 3H), 1.43 (s, 3H), 2.07 (d, 1H, *J* = 13.9 Hz), 2.42 (dd, 1H, *J* = 2.2, 13.9 Hz), 3.66–3.75 (m, 1H), 3.78–3.88 (m, 1H), 3.93 (s, 2H), 4.01–4.09 (m, 1H), 4.14 (dd, 1H, *J* = 6.7, 14.7 Hz), 4.23 (br d, 1H, *J* = 7.1 Hz), 4.46–4.67 (m, 3H), 4.79 (br s, 1H), 4.90–4.92 (m, 1H), 5.03 (s, 2H), 7.04–7.39 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): −5.7, 5.0, 6.7, 18.1, 24.3, 25.6, 33.8, 46.2, 54.5, 64.9, 66.2, 66.9, 72.0, 76.8, 78.5, 107.7, 112.7, 126.7, 127.4, 127.7, 127.8, 128.7, 136.1, 139.4, 145.8, 157.0 (multiple peaks in the spectra are due to a rotameric mixture); ESI/MS (*m*/*z*): 714 $(M+H)^+$; HRMS Calcd for $C_{39}H_{64}NO_7Si_2$ $(M+H)^+$ 714.4223. Found: 714.4221.

4.7. Benzyl benzyl((*S*)-1-((4*S*,5*S*)-5-((*R*)-3,3-diethyl-8,8,9,9-tetramethyl-4,7-dioxa-3,8-disila-decan-5-yl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methoxymethoxy)methyl)but-3-enyl)carbamate 15

To an ice cooled, stirred solution of alcohol **14** (0.50 g, 0.7 mmol) in CH_2Cl_2 (20 mL) were added DIPEA (0.48 mL, 2.8 mmol), MOM–Cl (0.17 mL, 2.1 mmol), and DMAP (cat). The reaction mixture was allowed to warm at room temperature and then stirred for 12 h. The reaction mixture was then extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with brine, separated and dried over anhydrous Na_2SO_4 and the solvent was concentrated under reduced pressure. The crude product was purified by column chromatography using hexane/ethyl acetate (9:1) to afford compound **15** (0.50 g, 94%) as a yellow oil. $[\alpha]_D^{25} = -19.9$ (*c* 1.67, $CHCl_3$); IR (neat) ν_{max} 2922, 2856, 1699, 1253, 1103, 838, 738, 692 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.00–0.10 (m, 6H), 0.53–0.76 (m, 6H), 0.84–1.0 (m, 18H), 1.20 (s, 3H), 1.42 (s, 3H), 2.11–2.44 (m, 2H), 3.24–3.37 (m, 3H), 3.44–4.24 (m, 5H), 4.30 (d, 1H, *J* = 7.1 Hz), 4.39–4.90 (m, 5H), 4.88–5.15 (m, 3H), 7.04–7.43 (m, 10H) (multiple peaks in the spectra are due to a rotameric mixture); ^{13}C NMR ($CDCl_3$, 75 MHz): −5.7, 3.9, 5.0, 6.5, 6.7, 18.1, 24.3, 25.6, 32.4, 46.3, 46.8, 53.3, 53.7, 54.8, 64.5, 64.9, 66.6, 67.1, 69.4, 69.7, 71.9, 76.3, 76.8, 79.2, 79.7, 95.0, 107.5, 112.9, 113.9, 126.1, 126.8, 127.4, 127.7, 127.8, 128.0, 128.5, 136.2, 139.5, 139.7, 141.4, 142.0, 156.4, 156.8 (doubling of peaks in the spectra due to rotameric mixture); ESI/MS (*m*/*z*): 758 $(M+H)^+$; HRMS Calcd for $C_{41}H_{67}NO_8Si_2Na$ $(M+Na)^+$ 780.4311. Found: 780.4302.

4.8. Benzyl benzyl((*S*)-1-((4*S*,5*R*)-5-((*R*)-1,2-dihydroxyethyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methoxymethoxy)methyl)but-3-enyl)carbamate 16

To a stirred solution of compound **15** (0.4 g, 0.52 mmol) in dry THF (7 mL) was added a 1 M solution of TBAF (1.5 mL, 1.58 mmol) at room temperature and stirred for 1 h. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (1:1) as the eluant to give pure compound diol **16** (0.26 g, 93%) as a colorless liquid. $[\alpha]_D^{25} = +0.9$ (*c* 1.97, $CHCl_3$); IR (neat) ν_{max} 3405, 2921, 2852, 1676, 1211, 1051, 910, 735, 697 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.10 (s, 3H), 1.38 (s, 3H), 2.44 (d, 2H, *J* = 7.1 Hz), 3.35 (s, 3H), 3.50 (dd, 1H, *J* = 2.6, 8.3 Hz), 3.71 (dd, 1H, *J* = 2.6, 8.3 Hz), 3.79–3.96 (m, 2H), 4.02–4.25 (m, 2H), 4.40 (d, 1H, *J* = 15.8 Hz), 4.52–4.69 (m, 2H), 4.75–4.97 (m, 1H), 4.99–5.16 (m, 3H), 7.04–7.43 (m, 10H) (multiple peaks in the spectra are due to a rotameric mixture); ^{13}C NMR ($CDCl_3$, 75 MHz): 24.7, 27.0, 32.9, 46.2, 52.6, 55.4, 64.8, 67.6, 68.8, 69.5, 78.0, 78.7, 95.4, 108.1, 115.3, 126.9, 127.8, 127.9, 128.2, 136.1, 138.7, 141.9, 157.8; ESI/MS (*m*/*z*): 530 $(M+H)^+$; HRMS Calcd for $C_{29}H_{39}NO_8Na$ $(M+Na)^+$ 552.2560. Found: 552.2573.

4.9. Benzyl benzyl((*S*)-1-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)-3((methoxy methoxy)methyl)but-3-enyl)carbamate 17

To a stirred solution of diol **16** (0.20 g, 0.37 mmol) in dry toluene (8 mL) were added triphenylphosphine (0.40 g, 1.5 mmol), and imidazole (0.10 g, 1.5 mmol) at room temperature, after which it was heated to 60 °C. Next, iodine (0.14 g, 1.13 mmol) was added in small portions. The reaction was further heated at reflux for 4 h. The reaction mixture was quenched with an excess $Na_2S_3O_3$ solution and extracted into ethyl acetate (2 × 25 mL). The combined

organic layers were washed with brine, separated and dried over anhydrous Na_2SO_4, and the solvent was concentrated under reduced pressure. The crude product was purified by column chromatography using elutant hexane/ethyl acetate (9:1) to afford olefin **17** (0.14 g, 75%) as a pale yellow liquid. $[\alpha]_D^{25} = +13.7$ (*c* 1.86, $CHCl_3$); IR (neat) ν_{max} 2985, 2935, 1694, 1452, 1415, 1245, 1213, 1046, 739, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.20 (s, 3H), 1.38 (s, 3H), 2.46–2.48 (m, 2H), 3.33–3.35 (m, 3H), 3.63–4.03 (m, 2H), 4.08–4.40 (m, 2H), 4.49–4.61 (m, 2H), 4.55–4.68 (m, 1H), 4.73–4.91 (m, 1H), 4.96–5.32 (m, 5H), 5.64–5.96 (m, 1H), 7.13–7.41 (m, 10H) (spectra not resolved clearly due to a rotameric mixture); ^{13}C NMR ($CDCl_3$, 75 MHz): 24.7, 27.0, 32.2, 46.8, 53.9, 55.2, 67.2, 67.5, 69.3, 69.6, 78.9, 79.0, 79.9, 95.4, 95.5, 108.3, 114.2, 115.0, 118.7, 119.0, 126.9, 127.2, 127.4, 128.1, 128.3, 128.4, 133.5, 133.8, 139.0, 142.1 (doubling of peaks in the spectra are due to a rotameric mixture); ESI/MS (*m*/*z*): 496 $(M+H)^+$; HRMS Calcd for $C_{29}H_{37}NO_6Na$ $(M+Na)^+$ 518.2493. Found: 518.2518.

4.10. Benzyl benzyl((3aS,4S,7aR)-6-((methoxymethoxy)methyl)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate 18

To a solution of diene **17** (0.10 g, 0.20 mmol) in toluene (25 mL), Grubbs second generation catalyst (0.018 g, 0.02 mmol) was added at rt. The reaction mixture was refluxed for 12 h. Toluene was removed under reduced pressure and the crude mixture was purified by column chromatography using hexane/ethyl acetate (7:3) as elutant to provide aminocyclohexene **18** (0.08 g, 85%) as an oil. $[\alpha]_D^{25} = -23.2$ (c 0.5, $CHCl_3$); IR (neat) ν_{max} 2961, 1696, 1455, 1371, 1227, 1106, 1033, 859, 737, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.19 (s, 3H), 1.32 (s, 3H), 1.96 (dd, 1H, *J* = 3.0, 13.9 Hz), 2.35 (dd, 1H, *J* = 13.9 Hz), 3.28 (s, 3H), 3.89 (s, 2H), 4.25–4.36 (m, 1H), 4.46–4.84 (m, 6H), 5.07–5.29 (m, 2H), 5.48–5.60 (m, 1H), 7.09–7.42 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): 24.9, 26.5, 27.9, 47.3, 52.9, 55.2, 67.4, 69.9, 74.6, 75.3, 95.4, 109.7, 122.7, 126.3, 126.4, 126.8, 127.8, 128.0, 128.2, 135.6, 139.8, 156.7; ESI/MS (*m*/*z*): 468 $(M+H)^+$; HRMS Calcd for $C_{27}H_{33}NO_6Na$ $(M+Na)^+$ 490.2207. Found: 490.2205.

4.11. Benzyl benzyl((3aS,4S,6S,7S,7aR)-7-hydroxy-6-((methoxymethoxy)methyl)-2,2-dimethyl-hexahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate 19

To a solution of **18** (0.10 g, 0.21 mmol) in THF (4 mL), $BH_3{\cdot}Me_2S$ (0.04 mL, 0.47 mmol) was added dropwise at −10 °C. Stirring was continued for 30 min at room temperature. The reaction mixture was quenched by the addition of 10% NaOH (1 mL) followed by 30% H_2O_2 (2 mL) at 0 °C. The mixture was allowed to warm at room temperature and stirred for another 2 h. The reaction mixture was extracted with ethyl acetate (2 × 20 mL) and the combined organic extracts were washed with brine, separated, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (1:1) as the eluant to give pure compound **19** (0.07 g, 68%) as a colorless liquid. $[\alpha]_D^{25} = -32.5$ (*c* 1.87, $CHCl_3$); IR (neat) ν_{max} 3422, 2925, 1692, 1455, 1244, 1042, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.23 (s, 3H), 1.50 (s, 3H), 1.59–1.75 (m, 3H), 2.86 (br s, 1H), 3.22 (s, 3H), 3.50–3.59 (m, 3H), 3.85–3.96 (m, 1H), 4.28–4.42 (m, 1H), 4.54 (s, 3H), 4.66–4.77 (m, 2H), 5.10–5.31 (m, 2H), 7.05–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$, 75 MHz): 26.0, 26.5, 25.5, 29.6, 39.9, 47.7, 53.2, 55.2, 67.4, 69.2, 74.3, 76.4, 82.0, 96.4, 109.9, 126.1, 126.3, 126.4, 127.8, 128.1, 139.9, 156.8; ESI/MS (*m*/*z*): 486 $(M+H)^+$; HRMS Calcd for $C_{27}H_{35}NO_7Na$ $(M+Na)^+$ 508.2297. Found: 508.2311.

4.12. Benzyl benzyl((3aS,4S,6R,7R,7aR)-6,7-dihydroxy-6-((methoxymethoxy)methyl)-2,2-dimethyl-hexahydrobenzo[*d*][1,3]dioxol-4-yl)carbamate 20

To an ice cooled, stirred solution of compound **18** (0.10 g, 0.21 mmol) in acetone/water (4:1) (2 mL) were added NMO (0.043 g, 0.32 mmol) and OsO_4 (0.25 g in 20 mL toluene) (0.43 mL, 0.02 mmol). The reaction was allowed to return to room temperature and stirred for another 3 h. The reaction mixture was quenched with solid $Na_2S_2O_3$. The solvent was removed under reduced pressure and extracted with ethyl acetate (2 × 25 mL). The combined organic extracts were washed with brine, separated, and dried over anhydrous Na_2SO_4. The solvent was removed on a rotary evaporator and the residue was purified by column chromatography on silica gel using hexane/ethyl acetate (1:1) as the eluant to give pure compound **20** (0.08 g, 80%) as a colorless liquid. $[\alpha]_D^{25} = -4.6$ (*c* 1.33, $CHCl_3$); IR (neat) ν_{max} 1430, 2922, 2854, 1697, 1458, 1245, 1045, 966 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.15 (s, 3H), 1.50 (s, 3H), 1.54–1.68 (m, 1H), 1.86 (t, 1H, *J* = 13.6 Hz), 2.75–3.07 (m, 2H), 3.19 (s, 3H), 3.46 (s, 2H), 3.54 (d, 1H, *J* = 6.7 Hz), 3.97–4.16 (m, 1H), 4.23–4.43 (m, 1H), 4.54 (s, 2H), 4.68–4.93 (m, 2H), 4.93–5.38 (m, 3H), 7.01–7.46 (m, 10H) (multiple peaks in the spectra are due to rotameric mixture); ^{13}C NMR ($CDCl_3$, 75 MHz): 25.9, 28.4, 31.3, 47.8, 47.9, 49.1, 55.3, 67.3, 73.0, 73.5, 73.8, 76.1, 80.5, 96.7, 109.6, 126.0, 126.3, 127.7, 128.2, 139.9, 156.7; ESI/MS (*m*/*z*): 502 $(M+H)^+$; HRMS Calcd for $C_{27}H_{36}NO_8$ $(M+H)^+$ 502.2416. Found: 502.2440.

4.13. (1S,2R,3S,4S,6S)-4-Acetamido-6-(acetoxymethyl)cyclohexane-1,2,3-triyl triacetate 21

To a solution of **19** (0.02 g, 0.04 mmol) in MeOH (2 mL) was added concentrated HCl (0.2 mL) and 10% Pd/C (cat), after which the reaction mixture was hydrogenated overnight at rt. The reaction mixture was filtered through a Celite pad, the solvent was evaporated after which pyridine (2 mL), Ac_2O (0.1 mL), and catalytic amount of DMAP were added at rt and stirred overnight. The solvent was removed under reduced pressure. The crude product was purified by column chromatography with 5% MeOH in $CHCl_3$ to afford pentaacetate **21** (0.012 g, 80% over two steps) as a white solid. mp 175–178 °C; $[\alpha]_D^{25} = -14.7$ (*c* 0.54, $CHCl_3$); IR (neat) ν_{max} 3370, 2923, 1742, 1657, 1541, 1371, 1228, 1047, 958 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 1.56–1.63 (m, 1H), 1.96 (s, 6H), 1.97–2.10 (m, 2H), 2.04 (s, 3H), 2.06 (s, 3H), 2.21 (s, 3H), 3.98 (dd, 1H, *J* = 3.7, 11.0 Hz), 4.05 (dd, 1H, *J* = 6.0, 11.0 Hz), 4.27 (m, 1H), 4.94 (dd, 1H, *J* = 2.6, 10.2 Hz), 5.18 (t, 1H, *J* = 10.2 Hz), 5.45 (t, 1H, *J* = 2.6 Hz), 5.49 (d, 1H, *J* = 8.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.5, 20.7, 23.2, 28.7, 37.9, 46.7, 63.7, 68.9, 71.5, 72.6, 169.2, 169.7, 170.1, 170.3, 170.7; ESI/MS (*m*/*z*): 386 $(M+H)^+$; HRMS Calcd for $C_{17}H_{25}NO_9Na$ $(M+Na)^+$ 410.1410. Found: 410.1427.

4.14. (1S,2S,3R,4R,6S)-6-Acetamido-4-(acetoxymethyl)-4-hydroxycyclohexane-1,2,3-triyl triacetate 22

To a solution of **20** (0.02 g, 0.039 mmol) in MeOH (4 mL) was added concentrated HCl (0.2 mL) and 10% Pd/C (cat), the reaction mixture was hydrogenated overnight at rt. The reaction mixture was filtered through celite pad, the solvent was evaporated under reduced pressure. To this crude product, pyridine (2 mL), Ac_2O (0.1 mL), a catalytic amount of DMAP were added at rt, and then stirred overnight. The solvent was removed under reduced pressure, the crude product was purified by column chromatography with 5% MeOH in $CHCl_3$ as an elutant to afford penta acetate **22** (0.015 g, 80% over two steps) as a white solid. mp 265–269 °C; $[\alpha]_D^{25} = +19.6$ (*c* 0.61, $CHCl_3$) {lit.,[13] $[\alpha]_D^{22}$ of enantiomer = −15.6 (*c* 0.6, $CHCl_3$)}; IR (neat) ν_{max} 3371, 1743, 1650, 1540, 1459,

1373, 1229, 1053 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 1.78 (dd, 1H, J = 4.4, 13.2 Hz), 1.96 (s, 6H), 2.03 (dd, 1H, J = 4.4, 13.2 Hz), 2.09 (s, 6H), 2.20 (s, 3H), 2.70 (br s, 1H), 4.00 (ABq, 2H, J = 11.7 Hz), 4.62–4.70 (m, 1H), 5.27 (d, 1H, J = 10.2 Hz), 5.35 (dd, 1H, J = 2.9, 10.2 Hz), 5.44 (d, 1H, J = 8.3 Hz), 5.50 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): 20.5, 20.7, 20.74, 21.0, 23.2, 34.0, 43.6, 67.3, 69.9, 70.2, 71.5, 71.9, 169.2, 169.7, 169.9, 170.3, 170.5; ESI/MS (m/z): 426 $(M+Na)^+$; HRMS Calcd for $C_{17}H_{26}NO_{10}$ $(M+H)^+$ 404.1537. Found: 404.1556.

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