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Novel strategies for the preparation of aminocarbasugar analogues: syntheses of *N*-substituted aminocyclitols from D-mannose

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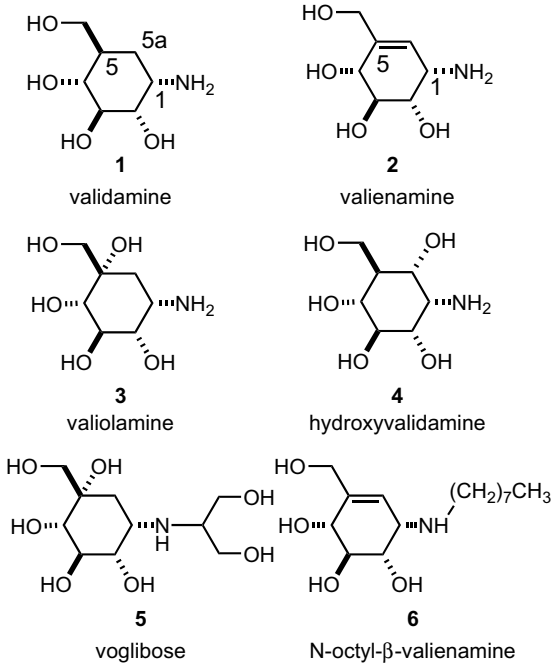
Abstract—Two strategies, based on the Pd-catalyzed allylic amination and the epoxidation-nucleophilic opening, have been described for the preparation of aminocarbasugar analogues from an *exo*-methylene cyclohexane derivative readily accessible in five steps from D-mannose by 6-*exo*-*dig*-radical cyclization as the key transformation.

1. Introduction

Carbocyclic polyols, for example, inositols (cyclohexanehexols),[1] conduritols (cyclohex-5-ene-1,2,3,4-tetrols)[2] and carba-hexopyranoses (hydroxymethyl)cyclohexanepolyols,[3] are important constituents of many biologically active molecules. These display a variety of biological effects, which range from cellular regulation and signal transduction to the selective inhibition of enzymes, which play key roles in living organisms.[4] Accordingly structures, which incorporate the cyclohexitol (polyhydroxylated cyclohexanoids) or the aminocyclohexitol core, have raised widespread synthetic interest.[5]

In this context, 5a-carbaaminosugar derivatives **1**–**4** are biologically relevant compounds (Scheme 1). Validamine **1**,[6,7] valienamine **2**,[6,8] valiolamine **3**,[6,8] and hydroxyvalidamine **4**,[6,8] were first isolated by the chemical or microbial degradation of validamycins,[6] with some of their derivatives finding commercial use. The search for new aminocarbasugar derivatives, which could function as either *glycomimetics*[9] or *carbohydrate mimetics*[10] has included, at least, two general approaches: the *N*-alkylation of amino carbasugar derivatives; and the use of stereoisomeric aminocarbasugars. For instance, in an attempt at developing new α-glucosidase inhibitors, Horii et al. screened a series of *N*-substituted valiolamine derivatives;[11] and one of



Scheme 1. 5a-Carba-aminosugars and derivatives.

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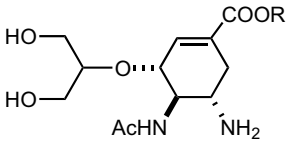


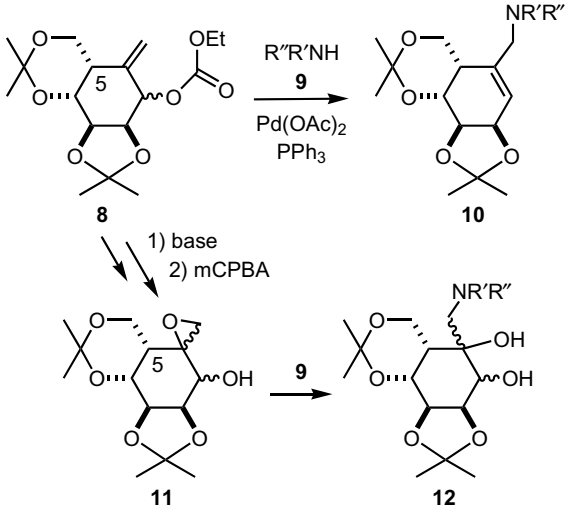
7

a: R =H GS4071
b: R =Et GS4104

Figure 1. Neuraminidase inhibitors **7**.

these analogues, voglibose **5**, was developed as a blood glucose ameliorating agent.[6,12] Along similar lines, Ogawa et al. synthesized a series of *N*-alkyl-β-valienamine derivatives and found that *N*-octyl-β-valienamine **6** was a potent β-glucocerebrosidase inhibitor.[13] Finally, manno- and galacto-validamine derivatives have been prepared and found to display potent inhibition towards their corresponding glycosidase.[14] Conversely in aminocarbasugars **2**–**4**, the amino group is located at C-1, many new types of aminocarbasugars and aminocyclitols have been synthesized in recent years and subjected to biological evaluation.[15] For instance, the potent influenza neuraminidase inhibitor GS4104 **7b** has been selected as a clinical candidate for the oral treatment and prophylaxis of influenza-virus infection (Fig. 1).[16]

We are currently interested in the synthesis of carbasugars and derivatives from monosaccharides. We have reported two strategies for the preparation of carbasugars by radical cyclizations[17,18] and more recently described the preparation of bicyclic carbasugar derivatives via a Diels–Alder approach.[19] As a further extension of our work on radical cyclizations, we have become involved in the preparation of aminocarbasugar derivatives from some of our highly functionalized synthetic key intermediates. Herein, we report on the utility of methylenecyclohexane derivative **8**, as a starting material in the preparation of homologated *N*-substituted aminocarbasugar derivatives **9** and **11**. In our approaches (Scheme 2), which are not only confined to carbohydrate starting materials, the exocyclic double bond in **8** plays a pivotal role in the genesis of the aminomethyl group in compounds **10** and **12**. A preliminary communication of part of this work has already appeared.[20]

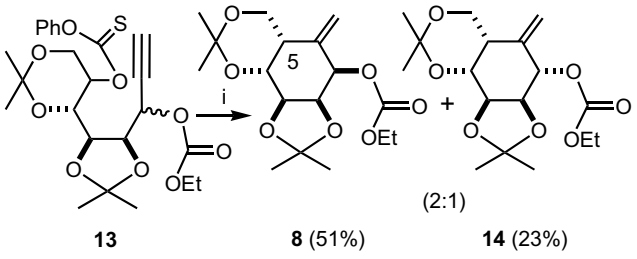


Scheme 2. Synthetic approaches to aminocyclitol analogues from methyleneclohexane **8**.

2. Results and discussion

2.1. 6-*Exo-digonal* radical cyclization. Synthesis of methylenecyclohexane 8

The key intermediate, methylenecyclohexane derivative **8**, is readily accessible from commercially available D-mannose through a five-step synthetic sequence.[20] The critical transformation in the synthesis is the 6-*exo-dig* radical cyclization[17a] of propargylic carbonate **13** (Scheme 3). The radical ring closure furnished a mixture of epimeric methylenecyclohexanes **8** and **14**.[17a] Although the transformations reported herein could have been applied to either of them, or even to the mixture, we chose for the sake of simplicity, to carry out the transformations with the major isomer **8.**



i) Bu_3SnH, AIBN, toluene, 85 °C

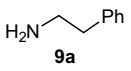
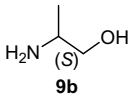
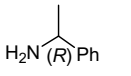
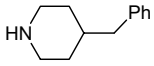
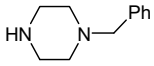
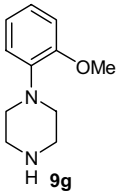
Scheme 3. Synthesis of methylenecyclohexane **8**.

2.2. Palladium catalyzed allylic amination of 8

To the best of our knowledge, there are no previous examples in the literature for the general transformation of **8**→**10** outlined in Scheme 2. Other methods have, however, been used in the synthesis of the allylic aminomethyl moiety in cyclohexane polyol systems. For example, Jotterand and Vogel described the nucleophilic displacement of allylic bromides with azide anion followed by catalytic (Pd/C) hydrogenation,[21] while Brown et al. utilized a reductive amination process on a cyclohexene aldehyde.[22]

The Pd-catalyzed allylic amination reaction of allylic carbonate **8** with different amines took place smoothly with the results shown in Table 1. The reaction with primary amines (Table 1, entries i–iii) furnished the expected *N*-alkyl substituted allylic derivatives in fair to moderate yields. The steric hindrance appears to be responsible for the decreasing yields observed in going from **10a** to **10b** and **10c** (entries i–iii). Secondary amines, **9d**–**h**, were also useful nucleophiles in this transformation and pyrrolidine (entry iv), piperidine (entry

Table 1. Preparation of *N*-substituted analogues of aminocyclitols **10**, by palladium-catalyzed allylic amination of allylic carbonate **8** with amines **9**

Entry	Amine	Reaction time	Product	Yield (%)
i	 **9a**	Overnight	**10a**	65
ii	 **9b**	3.5 h	**10b**	51
iii	 **9c**	5 days	**10c**	35
iv	 **9d**	Overnight	**10d**	51
v	 **9e**	Overnight	**10e**	52
vi	 **9f**	Overnight	**10f**	84
vii	 **9g**	Overnight	**10g**	52
viii	 **9h**	Overnight	**10h**	80

v), piperazines (entries vi and vii) and morpholine (entry viii) gave allylic amines, **10c–h**, in moderate to good yields.

2.3. Epoxidation-nucleophilic ring opening of 8

An alternative strategy for the introduction of the amino moiety in the carbasugar core is outlined in Scheme 2 with the transformation **8**→**11**→**12**. We thought that an oxirane, readily available from the exocyclic olefin, could be used as a handle for the introduction of the *N*-substituted aminomethyl moiety. Accordingly, treatment of allylic carbonate **8** with potassium carbonate in methanol gave allylic alcohol **15**, which on treatment with *m*-chloroperoxybenzoic acid in dichloromethane yielded a mixture of epimeric epoxides **16** and **17**. Reaction of **16** with 2-phenethylamine **9a** in refluxing ethanol overnight promoted the regioselective ring opening of the oxirane and furnished branched aminocarbasugar **18** in 80% yield. The stereochemistry at the quaternary center (C-5a) of **18**, and hence that of **16**, was unambiguously proven by an observed NOE between H5 and H7 as shown in Scheme 4. A similar reaction carried out on the epimeric epoxide **17** gave raise to aminocarbasugar **19** in 72% yield. Several attempts at the opening of these oxiranes under acidic conditions, which could have reversed the regiochemistry of the ring opening, left the starting oxiranes unaltered.

3. Conclusion

Two new methods for gaining access to novel branched *N*-substituted aminomethyl carbasugars, for example, **10**, **12**, have been developed. These processes illustrate the usefulness of our highly functionalized methylenecyclohexane intermediate **8** readily accessible from D-mannose in five steps. In the first method, an allylic carbonate is used to generate a π-allyl palladium complex that can be effectively coupled with a variety of primary and secondary amines. In the second, the exocyclic double bond is correlated with a spyrocyclic oxirane, which underwent smooth regioselective ring opening with phenetylamine. Thus, two novel kinds of 5a-carba aminosugar derivatives are now accessible by synthetic routes consisting of six and eight steps from inexpensive D-mannose.

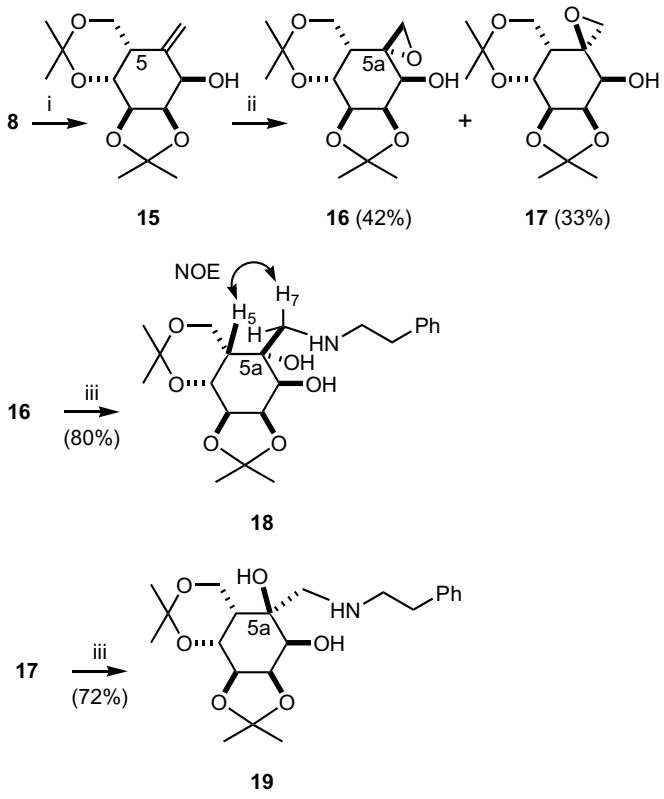
4. Experimental

4.1. General

All reactions were performed in dry flasks fitted with a glass stopper or rubber septa under a positive pressure of argon, unless otherwise noted. Air and moisture sensitive liquids and solutions were transferred via syringe or stainless steel cannula. Flash column chromatography was performed employing 230–400 mesh silica gel. Thin-layer chromatography was conducted in Kieselgel 60 F_{254} (Merck). Detection was first by UV (254 nm) then charring with a solution of 20% aqueous sulfuric acid (200 mL) in acetic acid (800 mL). Anhydrous magnesium sulfate ($MgSO_4$) or sodium sulfate (Na_2SO_4) was used to dry the organic solutions during work-ups, while the removal of the solvents was done under vacuum with a rotoevaporator. Solvents were dried and purified using standard methods. ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 300, 400 or 500 and 75 or 50 MHz, respectively. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to residual protium in the NMR solvent ($CHCl_3$: δ 7.25).

4.2. General procedure for the palladium-catalyzed allylic amination of 8

To a solution of compound **8** (100 mg, 0.29 mmol) in acetonitrile (10 mL) under argon, $Pd(OAc)_2$ (13 mg, 0.058 mmol), PPh_3 (76 mg, 0.29 mmol) and the corresponding amine **9** (0.38 mmol) were added. The reaction was then heated to 85 °C for the time indicated in Table 1. After cooling, the organic solvent was evaporated and the residue dissolved in ethyl acetate and washed with water. The organic layer was then dried over Na_2SO_4 and evaporated to furnish a residue, which was purified by flash chromatography using hexane/ethyl acetate mixtures as eluent.



Scheme 4. Synthesis of 5a-carba aminopyranose analogues **17** and **18**.

4.3. Amino carbasugar 10a

Solvent system for chromatography; hexane/ethyl acetate 6:4. $[\alpha]_D^{21} = +42.3$ (*c* 0.50, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 7.27–7.15 (m, 5H); 5.70 (s, 1H, H-1); 4.60 (m, 1H, H-2); 4.46 (t, $J = 3.3$ Hz, 1H, H-4); 4.18–4.12 (m, 2H, H-3, H-6); 3.95 (dd, $J = 3.3$, 12.4 Hz, 1H, H-6); 3.43 (d, $J = 13.5$ Hz, 1H, H-7); 3.26 (d, $J = 13.5$ Hz, 1H, H-7); 2.87–2.75 (m, 4H); 2.18 (m, 1H, H-5); 1.45 (s, 3H); 1.36 (s, 3H); 1.34 (s, 3H); 1.28 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 140.3, 135.4, 132.1 (×2), 128.6 (×2), 126.3, 124.4, 108.8, 98.7, 74.3, 72.2, 68.6, 60.7, 53.2, 50.8, 36.5, 31.9, 29.5, 28.2, 26.7, 19.3. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.47. Found: C, 71.03; H 8.38.

4.4. Aminocarbasugar 10b

Solvent system for chromatography; ethyl acetate. $[\alpha]_D^{21} = +52.3$ (*c* 0.51, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.77 (s, 1H, H-1); 4.61 (s, 1H); 4.49 (t, $J = 3.0$ Hz, 1H); 4.19 (m, 2H); 4.02 (dd, $J = 2.6$, 11.8 Hz, 1H, H-6); 3.60–3.53 (m, 2H); 3.30–3.23 (m, 2H); 2.79 (m, 1H); 2.25 (s, 2H); 2.15 (s, 2H); 1.47 (s, 3H); 1.36 (s, 6H); 1.30 (s, 3H); 1.06 (d, $J = 6.1$ Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 134.7, 125.0, 108.6, 98.6, 74.0, 71.8, 68.4, 65.8, 60.4, 53.4, 49.9, 31.7, 29.2, 27.8, 26.3, 19.0, 16.5. Anal. Calcd for $C_{17}H_{29}NO_5$: C, 62.36; H, 8.93. Found: C, 62.56; H, 8.78.

4.5. Aminocarbasugar 10c

(Hexane/ethyl acetate; 6:4). $[\alpha]_D^{21} = +72.6$ (*c* 0.82, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33–7.25 (m, 5H); 5.70 (s, 1H, H-1); 4.60 (m, 1H); 4.48 (t, $J = 3.4$ Hz, 1H); 4.18 (t, $J = 4.4$ Hz, 1H); 4.04 (dd, $J = 2.2$, 12.4 Hz, 1H, H6); 3.94 (dd, $J = 3.4$, 12.4 Hz, 1H, H-6); 3.73 (q, $J = 6.6$ Hz, 1H, H-8); 3.19 (d, $J = 13.3$ Hz, 1H, H-7); 3.07 (d, $J = 13.3$ Hz, 1H, H-7); 2.28 (m, 1H, H-5); 1.45 (s, 3H); 1.41 (s, 3H); 1.38 (s, 3H); 1.33 (d, $J = 6.6$ Hz, 3H, CH_3 side chain); 1.26 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 145.4, 135.5, 128.4 (×2), 126.9, 126.6 (×2), 124.1, 108.6, 98.5, 74.1, 72.0, 68.2, 60.4, 57.9, 51.1, 31.6, 29.1, 28.0, 26.4, 24.5, 19.1. Anal. Calcd for $C_{22}H_{31}NO_4$: C, 70.75; H, 8.37. Found: C, 70.94; H, 8.19.

4.6. Aminocarbasugar 10d

(Hexane/ethyl acetate; 6:4) $[\alpha]_D^{21} = +36.1$ (*c* 0.64, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.67 (s, 1H), 4.57 (m, 1H), 4.49 (t, $J = 3.3$ Hz, 1H), 4.27 (dd, $J = 1.8$, 12.4 Hz, 1H), 4.16 (t, $J = 4$ Hz), 3.98 (dd, $J = 3.3$, 12.4 Hz, 1H), 3.63 (d, $J = 13$ Hz, 1H), 2.68 (d, $J = 13$ Hz, 1H), 1.44 (s, 4H), 2.23 (m, 1H), 1.73 (s, 4H), 1.45 (s, 3H), 1.36 (s, 6H), 1.28 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 134.8, 124.5, 108.4, 98.2, 74.0, 73.0, 68.1, 60.6, 60.4, 53.8 (×2), 31.6, 29.0, 27.7, 26.3, 23.5 (×2), 19.0. *M/e* = 323.2 (M^+), 308.2

(M^+-15), 265.2. Anal. Calcd for $C_{18}H_{29}NO_4$: C, 66.84; H, 9.04; N, 4.33. Found: C, 67.12; H, 8.91; N, 4.19.

4.7. Aminocarbasugar 10e

(Hexane/ethyl acetate; 85:15) $[\alpha]_D^{21} = +27.3$ (*c* 0.49, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.31–7.09 (m, 5H); 5.64 (s, 1H, H-1); 4.57 (m, 1H); 5.00 (t, *J* = 3.3 Hz, 1H); 4.27 (dd, *J* = 1.7 Hz, 12.3 Hz, 1H, H-6); 4.17 (t, *J* = 4 Hz, 1H); 4.00 (dd, *J* = 3.3, 12.3 Hz, 1H, H-6); 3.35 (d, *J* = 13.2 Hz, 1H, H-7); 2.75 (m, 2H); 2.62 (d, *J* = 13.2 Hz, 1H, H-7); 2.49 (m, 2H); 2.15 (s, 1H, H-5); 1.93 (t, *J* = 11.4 Hz, 1H); 1.73–1.50 (m, 6H); 1.47 (s, 3H); 1.36 (s, 3H); 1.34 (s, 3H); 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 141.0, 134.7, 129.3 (×2), 128.4 (×2), 125.9, 125.3, 108.8, 98.6, 74.3, 72.4, 68.4, 63.4, 61.0, 55.2, 52.9, 43.5, 38.2, 32.7, 32.4, 31.9, 29.5, 28.2, 26.3, 19.3. Anal. Calcd for $C_{26}H_{37}NO_4$: C, 73.03; H, 8.72. Found: C, 73.12; H, 8.91.

4.8. Aminocarbasugar 10f

(Hexane/ethyl acetate; 6:4) $[\alpha]_D^{21} = +26.7$ (*c* 0.94, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.31–7.26 (m, 5H); 5.67 (s, 1H, H-1); 4.57 (m, 1H); 4.49 (t, *J* = 3.3 Hz, 1H); 4.25 (dd, *J* = 1.7, 12.3 Hz, 1H, H-6); 4.16 (t, *J* = 4.3 Hz, 1H); 3.97 (dd, *J* = 3.4, 12.3 Hz, 1H, H-6); 3.48 (m, 2H); 3.38 (d, *J* = 13.3 Hz, 1H, H-7); 2.69 (d, *J* = 13.3 Hz, 1H, H-7); 2.42 (m, 6H); 2.13 (s, 1H, H-5); 1.46 (s, 3H); 1.35 (s, 3H); 1.32 (s, 3H); 1.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 138.0, 133.9, 129.1 (×2), 128.1 (×2), 126.9, 125.4, 108.5, 98.3, 74.0, 72.0, 68.1, 62.9, 62.7, 60.6, 53.1 (×4), 31.6, 29.2, 27.9, 26.4, 19.0. Anal. Calcd for $C_{25}H_{36}N_2O_4$: C, 70.06; H, 8.47. Found: C, 70.32; H, 8.71.

4.9. Aminocarbasugar 10g

(Hexane/ethyl acetate; 9:1) $[\alpha]_D^{21} = +27.4$ (*c* 1.2, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.02–6.82 (m, 5H), 5.73 (s, 1H), 4.60 (m, 1H), 4.51 (t, *J* = 3.3 Hz, 1H), 4.31 (dd, *J* = 1.6, 12.3 Hz, 1H), 4.19 (t, *J* = 4.4 Hz, 1H), 4.01 (dd, *J* = 3.3, 12.3 Hz, 1H), 3.86 (s, 3H, OMe), 3.44 (d, *J* = 13.2 Hz, 1H), 3.03 (m, 4H), 2.78 (d, *J* = 13.2 Hz, 1H), 2.62–2.55 (m, 4H), 2.20 (s, 1H), 1.49 (s, 3H), 1.39 (s, 6H), 1.31 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 152.4, 141.6, 134.1, 125.6, 122.7, 121.0, 148.2, 111.5, 108.5, 98.4, 74.2, 72.1, 68.3, 62.9, 60.8, 56.4, 53.4, 50.7, 31.9, 29.2, 27.9, 26.4, 19.2. *M/e* = 444.4 (M^+), 429.35 (M^+-15), 386.3, 371.3, 357.3, 308.3. Anal. Calcd for $C_{25}H_{36}N_2O_5$: C, 67.54; H, 8.16. Found: C, 67.82; H, 7.91.

4.10. Aminocarbasugar 10h

(Hexane/ethyl acetate; 8:2) $[\alpha]_D^{21} = +28.1$ (*c* 0.39, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.69 (s, 1H), 4.57 (m, 1H), 4.49 (t, *J* = 3.4 Hz, 1H), 4.25 (dd, *J* = 1.6, 12.3 Hz, 1H), 4.17 (t, *J* = 4.5 Hz, 1H), 3.98 (dd, *J* = 3.4, 12.3 Hz, 1H), 3.64 (m, 4H), 3.37 (d, *J* = 13 Hz, 1H), 2.70 (d, *J* = 13 Hz, 1H), 2.35 (m, 3H), 2.10 (s, 1H), 1.46 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.29 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 133.3, 126.0, 108.4, 98.3, 74.0, 71.9, 68.1, 67.3 (×2), 63.1, 60.5, 53.5 (×2), 31.7, 29.1, 27.8, 26.3, 19.0. Anal. Calcd for $C_{18}H_{29}NO_5$: C, 63.69; H, 8.61. Found: C, 63.82; H, 8.52.

4.11. Preparation of allylic alcohol 15 from carbonate 8

A solution of compound **8** (1 g, 2.92 mmol) in methanol (100 mL) was treated with potassium carbonate (807 mg, 5.84 mmol) and left stirring overnight. The resulting solution was filtered and evaporated to a residue, which was dissolved in ethyl acetate and washed with water. The organic layer was then dried (sodium sulfate) and evaporated. Flash chromatography of the residue (hexane/ethyl acetate; 8:2) gave **15** (730 mg, 70%). $[\alpha]_D^{21} = +199.7$ (*c* 0.7, $CHCl_3$), mp 90–92 °C. ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.40 (s, 1H); 5.10 (s, 1H); 4.77 (m, 1H, H-1); 4.50 (dd, *J* = 4.0, 7.4 Hz, 1H, H-2); 4.38 (dd, *J* = 3.3, 7.4 Hz, 1H, H-3); 4.24 (t, *J* = 3.3 Hz, 1H, H-4); 4.14 (dd, *J* = 4.3 Hz, *J* = 11.7 Hz, 1H, H-6); 3.82 (dd, *J* = 3.2, 11.7 Hz, 1H, H-6); 2.52 (m, 1H, H-5); 2.16 (d, *J* = 7.2 Hz, 1H, OH); 1.43 (s, 3H); 1.35 (s, 3H); 1.34 (s, 3H); 1.33 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 146.3, 110.5, 109.1, 98.9, 76.1, 75.1, 69.0, 66.5, 65.6, 35.9, 28.4, 25.9, 24.3, 19.4. *M/e* = 255.1 (M^+-15), 212, 197. Anal. Calcd for $C_{14}H_{22}O_5$: C, 62.20; H, 8.20. Found: C, 62.42; H, 7.96.

4.12. Epoxidation of 15

A solution of allylic alcohol **15** (300 mg, 1.11 mmol) in dichloromethane (30 mL) was cooled to 0 °C under argon was treated with *m*-chloroperoxybenzoic acid (1.5 equiv). The resulting solution was allowed to warm to room temperature and kept with stirring overnight. The resulting solution was then diluted with CH_2Cl_2 and washed twice with a saturated solution of sodium thiosulfate containing sodium bicarbonate. The organic layer was dried (Na_2SO_4) filtered and evaporated. Flash chromatography of the residue (hexane/ethyl acetate; 8:2) gave, in order of elution, oxiranes **17** and **16**.

Data for **17** (104 mg, 33%) $[\alpha]_D^{21} = +94.8$ (*c* 1.09, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.55 (dd, *J* = 3.5, 7.3 Hz, 1H, H-2); 4.37 (dd, *J* = 2.9, 7.3 Hz, 1H, H-3); 4.33 (d, *J* = 3.5 Hz, 1H, H-1); 4.26 (t, *J* = 2.9 Hz, 1H, H-4); 3.99 (dd, *J* = 3.3, 12.4 Hz, 1H, H-6); 3.75 (dd, *J* = 2.6, 12.4 Hz, 1H, H-6); 2.98 (d, *J* = 4.5 Hz, 1H, H-7); 2.87 (d, *J* = 4.5 Hz, 1H, H-7); 2.09 (m, 1H, H-5); 1.55 (s, 3H); 1.46 (s, 3H); 1.39 (s, 3H); 1.37 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 109.5, 99.1, 74.9 (×2), 67.4, 65.2, 61.5, 56.9, 46.1, 34.7, 29.0, 26.0, 24.2, 19.0. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.53; H, 7.52.

Data for **16** (133 mg, 42%) $[\alpha]_D^{21} = +111.6$ (*c* 1.38, $CHCl_3$), ^1H NMR (200 MHz, $CDCl_3$) δ (ppm): 4.68–4.64 (m, 2H, H-1, H-2); 4.39 (dd, *J* = 2.9, 6.8 Hz, 1H, H-3); 4.31 (t, *J* = 3.5 Hz, 1H, H-4); 3.96 (dd, *J* = 2.5, 12.0 Hz, 1H, H-6); 3.87 (dd, *J* = 3.9, 12.0 Hz, 1H, H-6); 3.28 (d, *J* = 5.1 Hz, 1H, H-7); 2.52 (d, *J* = 5.1 Hz, 1H, H-7); 2.11 (m, 1H, H-5); 2.00 (d, *J* = 4.9 Hz, 1H, OH); 1.56 (s, 3H); 1.44 (s, 3H); 1.40 (s, 3H); 1.37 (s,

3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 109.3, 98.7, 75.4, 75.1, 67.5, 65.5, 58.5, 56.8, 50.4, 33.5, 28.8, 26.0, 23.6, 19.0. Anal. Calcd for $C_{14}H_{22}O_6$: C, 58.73; H, 7.74. Found: C, 58.61; H, 7.49.

4.13. Oxirane opening with 2-phenethylamine

A solution of the oxirane (100 mg, 0.35 mmol) in ethanol (14 mL) under argon was treated with 2-phenethylamine (5 equiv) and refluxed overnight. The resulting solution was evaporated and the residue dissolved in ethyl acetate and then washed with water. The organic layer was dried over anhydrous sodium sulfate, filtered, evaporated and the resulting residue chromatographed with hexane/ethyl acetate (6:4) as eluant.

4.14. Amino alcohol 18

(114 mg, 80% yield) $[\alpha]_D^{21} = +30.2$ (c 0.99, $CHCl_3$), ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 7.29–7.22 (m, 3H); 7.21–7.18 (m, 2H); 4.58 (dd, J = 2.6, 7.5 Hz, 1H, H-2); 4.34 (m, 1H, H-1); 4.22–4.18 (m, 2H, H-3, H6); 4.01–3.98 (m, 2H, H-4, H-6); 3.22 (d, J = 11.3 Hz, 1H, H-7); 2.90–2.75 (m, 5H); 1.55 (m, 1H, H-5); 1.45 (s, 3H); 1.44 (s, 3H); 1.37 (s, 3H); 1.35 (s, 3H). ^{13}C NMR (50 MHz, $CDCl_3$) δ (ppm): 139.4, 128.4 (×2), 128.3 (×2), 126.0, 108.5, 99.6, 76.2, 75.9, 75.3, 72.0, 69.6, 61.3, 57.7, 50.8, 36.2, 36.0, 29.5, 26.0, 23.4, 18.4. M/e = 408.3 (M^++1), 392.25 (M^+−15), 342.2. Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16. Found: C, 64.97; H, 8.40.

4.15. Amino alcohol 19

(101 mg, 72% yield) $[\alpha]_D^{21} = +16.2$ (c 0.8, $CHCl_3$), ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.33–7.15 (m, 5H); 4.49 (dd, J = 3.0, 7.4 Hz, 1H); 4.27–4.10 (m, 4H); 3.90 (dd, J = 3.3, 12.8 Hz, 1H, H-6); 3.32 (d, J = 12.3 Hz, 1H, H-7); 2.97–2.77 (m, 5H); 2.04 (m, 1H, H-5); 1.52 (s, 3H), 1.42 (s, 3H); 1.36 (s, 3H); 1.30 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 139.8, 128.9 (×2), 128.8 (×2), 126.5, 109.2, 99.1, 75.8 (×2), 72.6, 71.4, 68.8, 60.0, 56.3, 51.5, 40.8, 36.6, 29.9, 26.3, 23.9, 18.6. Anal. Calcd for $C_{22}H_{33}NO_6$: C, 64.84; H, 8.16. Found: C, 65.08; H, 8.31.

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