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A combined, 6-*exo*-*dig* radical cyclization-palladium catalyzed allylic amination, approach to aminocarbasugar analogs: synthesis of novel *N*-substituted aminocyclitols from D-mannose

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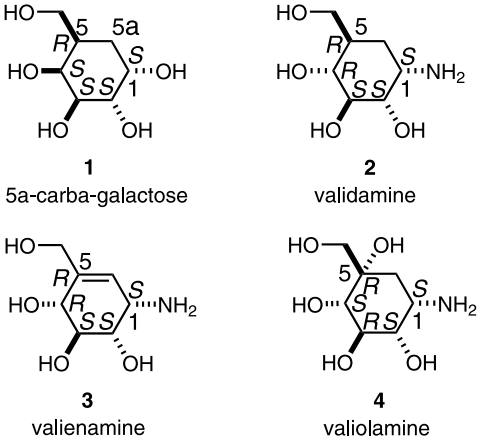
Abstract—A novel approach, which features a stereoselective 6-*exo*-*dig* radical cyclization and a palladium-catalyzed allylic amination, permits a six steps synthesis of aminocyclitol analogs from D-mannose.

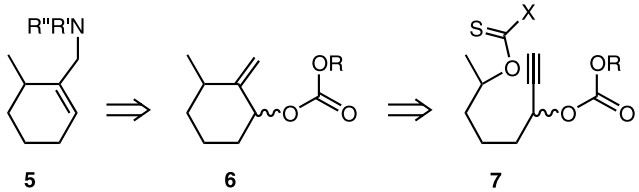
Carbocyclic polyols are important constituents of many biologically active molecules. They display a variety of biological effects, which range from cellular regulation to the selective inhibition of enzymes, which play key roles in living organisms.[1] Accordingly, structures which incorporate the cyclohexitol (polyhydroxylated cyclohexanoids) or the aminocyclohexitol core have raised widespread synthetic interest.[2] In this context, carbasugars,[3] e.g. **1**,[4,5] and aminocarbasugars, e.g. **2**, **3**, **4**, have proved to be potent glycomimics (Scheme 1).[6] Validamine **2**, valienamine **3** and valiolamine **4**, were first isolated by the chemical or microbial degradation of validamycins,[7] and some of their derivatives have found commercial use. Although in aminocarbasugars **2**–**4**, the amino group is located at C-1, many new types of aminocarbasugars or aminocyclitols have been synthesized in recent years and subjected to biological evaluation.[8]

Our group has recently been interested in the synthesis of carbasugars from monosaccharides,[9,10] and in this context we disclose herein a synthetic approach to the preparation of a novel class of homologated *N*-substituted aminocarbasugar analogs **14**. Our approach (Scheme 2), which is not only confined to carbohydrate derivatives, correlates retrosynthetically the aminomethyl group in **5**, with an allylic carbonate in a methylenecyclohexane (e.g. **6**). The latter could thus be obtained by 6-*exo*-*dig* radical cyclization[11] of a propargylic carbonate (e.g. **7**).

Accordingly, our synthetic route starts with the preparation of **11**, in four steps from D-mannose (Scheme 3).[9b] Mannose-diacetonide, **8** (Scheme 2), prepared in one single step from D-mannose by kinetic acetonation,[12] was treated with lithium trimethylsilylacetylide to yield after work-up, alkyne **9** as a 2:1 epimeric mixture at C-1 in 68% isolated yield. Chemoselective



Scheme 1. Carbasugars and aminocarbasugars.



Scheme 2. Synthesis of aminomethyl cyclohexanes from acyclic precursors.

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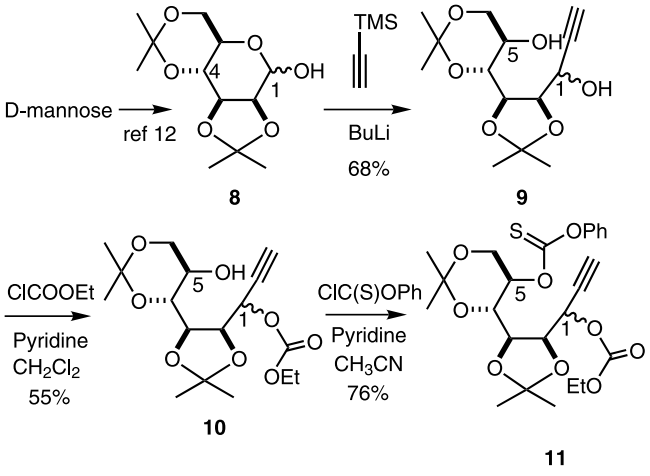
protection of the propargylic hydroxyl group was accomplished by use of ethyl chloroformate (55%).[13] The hydroxyl group at C-5 in **10** was next treated with phenylchlorothionoformate[14] to furnish cyclization precursor **11** (76%).

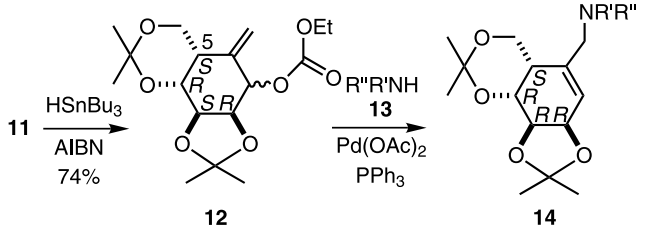
Radical cyclization of **11**[15] takes place with excellent stereoselectivity to afford carbonate **12**[16] (Scheme 4), which upon treatment with palladium acetate and triphenylphospine in acetonitrile, in the presence of a primary or a secondary amine **13a**–**h**, yields aminocyclitol analogs **14a**–**h**[17,18] (Table 1).

The results in Table 1 show the scope of the Pd-catalyzed reaction. Pyrrolidine (Table 1, entry iv), piperidine (entry v), piperazines (entries vi and vii), and morpholine (entry viii), as well as acyclic primary amines (entries i, ii, iii) were used as nucleophiles. The Pd-catalyzed amination, except in the case of (*R*)-(+)-α-methylbenzylamine (**13c**, Table 1 entry iii), took place in a few hours, giving moderate to good yields of allylic amines **14**.

In summary, we have reported an efficient strategy for the synthesis of a novel class of *N*-substituted aminocyclitol analogs, **14**, from D-mannose. The approach permits the above-mentioned transformation to be carried out in six steps, and benefits from a series of chemoselective transformations. D-Mannose diacetonide, **8**, leaves only the hemiacetal function exposed to reaction and, upon reaction with the alkynyl nucleophile, grants access to the 1,5-diol moiety in one step. The latter (e.g. **9**) is chemoselectively protected at the prop-2-ynilic hydroxy group (1-OH) as a carbonate, which plays a dual role in our strategy: As a protecting group (for 1-OH), and as an activator of the double bond in the forthcoming allylic amination. We have illustrated the synthetic potential of this approach with the preparation of compounds **14a**–**h** from D-mannose. Nevertheless, the use of different monosaccharide diacetonides,[19] as well as the use of nucleophiles other than amines in the Pd-catalyzed reaction[20–22] could give rise to a large variety of cyclitol analogs. Furthermore, the double bond is susceptible to chemical modifications. Use of the above strategy for the preparation of highly functionalized cyclitols and derivatives thereof is underway in our laboratory and will be described in due course.

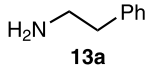
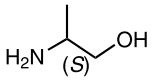
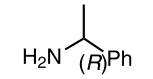
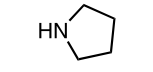
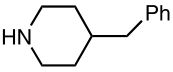
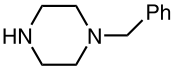
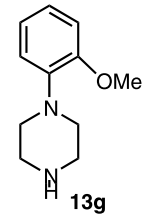
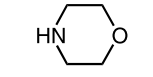


Scheme 3. Synthesis of alkynyl carbonates **11** from D-mannose.



Scheme 4. Synthesis of aminocyclitol analogs, **14**, from D-mannose.

Table 1. Preparation of *N*-substituted analogs of aminocyclitols **14**, by palladium-catalyzed allylic amination of allylic carbonate **12** with amines **13**

Entry	Amine	Reaction time	Product	Yield (%)
i	 **13a**	overnight	**14a**	65
ii	 **13b**	3.5 h	**14b**	51
iii	 **13c**	5 days	**14c**	35
iv	 **13d**	overnight	**14d**	51
v	 **13e**	overnight	**14e**	52
vi	 **13f**	overnight	**14f**	84
vii	 **13g**	overnight	**14g**	52
viii	 **13h**	overnight	**14h**	80

Acknowledgements

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15. ***Procedure for radical cyclization.*** A thoroughly degassed (argon) solution of thiocarbonate **11** in toluene (0.02 M) was heated to 85°C under argon. A solution of Bu_3SnH (1.6 equiv.) and AIBN (0.1 equiv.) in toluene (5 mL/mmol) was then added and the reaction mixture was kept at that temperature over 12 h. After cooling, the organic solvent was evaporated and the residue was purified by flash chromatography.
16. The configuration at C-5 in compounds **12** has been rigorously confirmed by their correlation with previously described carbasugars of known absolute configuration: Gómez, A. M.; Moreno, E.; Valverde, S.; López, J. C. *Tetrahedron Lett.* **2002**, *44*, 5559. The corresponding C-5-6-*epi* derivative (as an epimeric mixture at C-1) was also detected, albeit in low yield (<5%).
17. ***General procedure for palladium-catalyzed allylic amination.*** To a solution of compound **12** (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 **13** (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 (sodium sulfate) and evaporated to furnish a residue, which was purified by flash chromatography using hexane:ethyl acetate mixtures as eluent.
18. ***Data for selected compounds: Allylic amine 14b***. (ethyl acetate): $[\alpha]_{D21}$ +52.3 (*c* 0.51, $CHCl_3$), ^1H NMR (300 MHz, $CDCl_3$) δ (ppm): 5.77 (s, 1H), 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), 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. ***14d***. (hexane:ethyl acetate; 6:4): $[\alpha]_{D21}$ +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. ***14g***. (hexane:ethyl acetate; 9:1): $[\alpha]_{D21}$

+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; N, 6.30. Found: C, 67.82; H, 7.91; N, 6.16. ***14h***. (hexane:ethyl acetate; 8:2): $[\alpha]_{D21}$ +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; N, 4.13. Found: C, 63.82; H, 8.52; N, 3.97.

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