A Novel Approach to the Synthesis of N-Substituted 1-*C*-Aminomethyl Glycofuranosides

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Abstract: Reductive amination of formyl *C*-glycofuranosides, easily available from hexose-derived equatorial-2-OH-glycopyranosides by DAST-promoted ring contraction, afforded N-substituted 1-*C*-aminomethyl glycofuranosides in most cases in high yields.

Key words: 1-*C*-aminomethyl glycofuranosides, formyl *C*-glycofuranosides, reductive amination, DAST-promoted ring contraction, sugar diamines

The stereoselective synthesis of functionalized *C*-glycosides has become an important area of carbohydrate research, as many naturally occurring *C*-glycosides show useful antibacterial, antiviral, and antitumoral properties.[1] One significant type of *C*-glycoside derivatives are 1-*C*-aminomethyl glycosides. These compounds are key intermediates for glycoconjugate syntheses, and a number of them have proved to be glycosidase inhibitors.[2] Sugar amino acids **2**[3] and **3**,[4] which containing the substructure **1** (Figure 1), are dipeptide isosters and have been used as secondary structure inducing elements for the generation of peptide-based drugs. This kind of substructure is also found in the naturally occurring alkaloid muscarine (**4**), a rigid muscarinic agonist of acetylcholine,[5] for which a renewed interest is due, in part, to the suggestion that various subtypes of muscarinic receptors seem to be implicated[6] in Alzheimer's disease.

Syntheses of 1-*C*-aminomethyl glycosides so far described rely on the introduction of a CH_2NH_2 equivalent at the anomeric position: (a) as CH_3NO_2 via nucleophilic aldol reaction,[7] (b) by reducing the corresponding glycosyl cyanide[8] or, (c) by degradation of a *C*-vinyl glycoside and subsequent formation of the azidomethyl intermediate.[3b] Alternatively, rearrangement involving 5-*exo* S_N2-opening of a terminal aziridine ring, and transformation of a primary hydroxyl function into the corresponding azide gave access to the 2,5-anhydro derivatives **3**[4] and **4**,[9] respectively. These routes are rather complicated, and for those involving an anomeric carbon–carbon bond-forming reaction, chemical efficiency and stereocontrol remain a difficult task. Moreover, for reaching an N-substituted 1-*C*-aminomethyl glycoside, additional N-alkylation process would be still required.

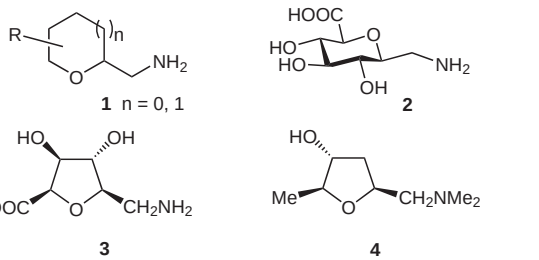
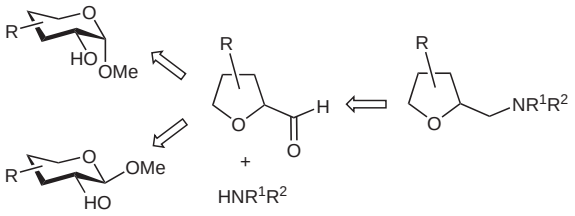


Figure 1

Here we introduce a straightforward approach to N-substituted 1-*C*-aminomethyl glycofuranosides from hexose-derived equatorial-2-OH-glycopyranosides (Scheme 1). The strategy takes advantage of a diethylaminosulfur trifluoride (DAST)-promoted ring contraction that, under remarkably mild conditions, leads to formyl *C*-glycofuranosides.[10] The use of these compounds in standard coupling reactions with nucleophiles should provide a ready access to hydrolytically stable *C*-glycofuranoside-based molecules (*C*-oligosaccharides and *C*-glycoconjugates). With this aim, our first goal has been to explore their coupling with biologically relevant amines as nitrogen-containing nucleophiles.



Scheme 1

We describe herein the synthesis of enantiopure orthogonally protected *C*-glycofuranosyl diamines by reductive amination of formyl *C*-glycofuranosides, easily obtained as their synthetic equivalents **6** and **12** from the methyl equatorial-2-OH-glycohexopyranosides **5** and **11**, respectively, by DAST methodology.[10,11]

Treatment of the crude aldehyde obtained in situ by hydrolysis (9:1 TFA–H_2O, r.t., 1 h) of the dimethyl acetal **6**, with diverse primary or secondary amines (1.4 mol equiv)

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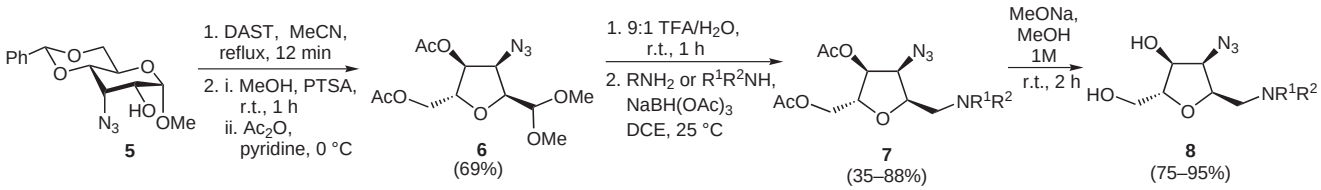


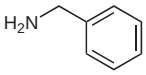
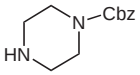
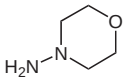
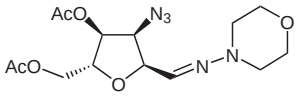
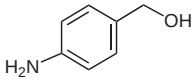
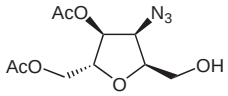
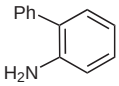
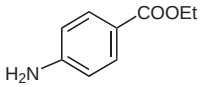
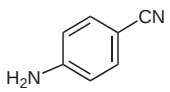
Scheme 2

in dry 1,2-dichloroethane, and subsequent reduction of the respective, not isolated, imine using sodium triacetoxyborohydride (1.4 mol equiv), afforded the respective compounds **7a**–**h** in moderate to high yields (Scheme 2, Table 1).[12] Their deprotection with 1 M NaMeO–MeOH gave the corresponding products **8a**–**h**.[13]

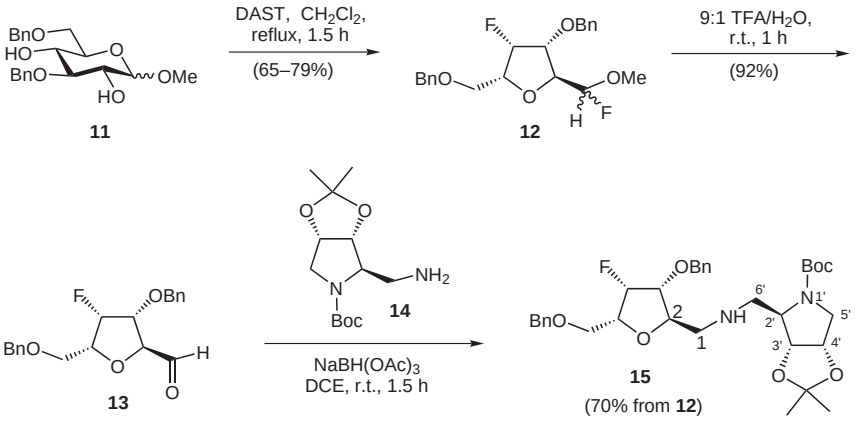
As shown in Table 1, primary and secondary aliphatic amines (benzylamine, piperidine, benzyloxycarbonyl piperazine, and morpholine, entries 1–4), as well as the aromatic amine 4-hydroxymethyl aniline (entry 6), gave the corresponding reductive amination compounds **7a**–**e** as the sole product. In the case of the other aniline derivatives (2-biphenylamino, ethyl 4-aminobenzoate and 4-aminobenzonitrile, entries 8–10), however, reductive amination products **7f**–**h** were obtained together with the primary alcohol **10**.

Starting from *N*-aminomorpholine as the amine (entry 5), the only isolated product was the hydrazone **9**, which could not be reduced by the reagent employed. When using imidazole as the starting amine (entry 7), the expected

Table 1 Reductive Amination Products **7** of the Formyl Azido-*C*-glycofuranoside Synthetic Equivalent **6** with Various Amines, and Their Deacetylated Products **8**[a]

Entry	Amines R^1R^2NH	Reaction time (h)	Products **7**[12] (yield after purification, %)	Products **8**[13] (yield, %)
1		3	**7a** (55)	**8a** (75)
2		5	**7b** (65)	**8b** (92)
3		2.5	**7c** (80)	**8c** (95)
4		6	**7d** (67)	**8d** (87)
5		1.5	 **9** (88)	–[b]
6		2	**7e** (77)	**8e** (90)
7		20	 **10**[11] (56)	–
8		18	**7f** (63) + **10** (19)	**8f** (85)
9		18	**7g**[11] (47) + **10** (34)	**8g** (86)
10		18	**7h** (35) + **10** (48)	**8h** (89)

[a] All products were fully characterized by their IR, ^{1}H NMR, ^{13}C NMR, and HRMS spectral data.[14]
[b] Complex mixture of products.



Scheme 3

2,5-anhydro-1-(imidazol-1-yl)-D-altritol derivative was not obtained, only **10** was obtained. The reason of this behavior of imidazole may be its weak nucleophilic character, much lower than those of the remainder amines used. In the same way, formation of the primary alcohol **10** as accompanying product of **7f**–**h**, arise from the lack of nucleophilicity provoked by the electron-withdrawing substituent at the *para* position of the anilines.

A shorter experimental protocol, in which a 2,5-anhydro-1-fluoro-1-*O*-methylhexitol (a formyl *C*-glycofuranoside synthetic equivalent directly formed in the ring-contraction reaction promoted by DAST) is subjected to hydrolysis and subsequent in situ reductive amination process, can be applied. Adopting this one-pot procedure, fluoro aldehyde **13** obtained in situ by hydrolysis (9:1 TFA–H_2O, r.t., 1 h) of (1*R*,1*S*)-2,5-anhydro-3,6-di-*O*-benzyl-4-deoxy-1,4-difluoro-1-*O*-methyl-D-talitol (**12**),[10a] was made react with diamine **14**,[15] furnishing fluoro-*C*-glycofuranosyl aminomethylpyrrolidine derivative **15** in good yield (Scheme 3).[16]

In conclusion, this work provides a simple approach to the synthesis of functionalized N-substituted aminomethyl *C*-glycofuranosides by reductive amination of formyl *C*-glycofuranosides, readily available by DAST methodology from hexose-derived equatorial-2-OH-glycopyranosides. The method works well with good nucleophilic amines and allows complete stereocontrol at the anomeric center. Stereo- and functional diversity on the furanoid ring could be achieved on starting from different equatorial-2-OH-glycohexopyranosides. Extension of this work to other substrates as well as studies with other nucleophiles is currently under investigation.

Acknowledgment

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(12) **General Procedure for the One-Pot Preparation of Compounds 7.**

Compound **6** (100 mg, 0.315 mmol) was dissolved in a 9:1 TFA–H_2O mixture (2.7 mL) and the solution was kept at r.t. for 1 h. The reaction mixture was poured into ice-water (100 mL) and extracted with CH_2Cl_2 (4 × 20 mL). The combined organic layers were successively washed with sat. aq $NaHCO_3$ and brine, then dried (Na_2SO_4), and concentrated. The residue (crude aldehyde) was dissolved in 1,2-dicloroethane (3.1 mL) and treated with the amine (0.437 mmol) and sodium triacetoxyborohydride (93.0 mg, 0.441 mmol). The reaction was stirred at r.t. for the appropriate time (Table 1). The mixture was then diluted with sat. aq $NaHCO_3$ (25 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure to give the crude product, which was purified by column chromatography using EtOAc–hexane, Et_2O–hexane or Et_2O–acetone as eluent.

Compound **7a**: R_f = 0.37 (5:1 Et_2O–acetone); $[\alpha]_D^{26}$ +19.3 (*c* 0.56, CH_2Cl_2). IR: ν_{max} = 3324 (NH), 2106 (N_3), 1746 (CO), 1231 and 1119 (CO) cm^{-1}. ^1H NMR (300 MHz, acetone-d_6): δ = 7.25–7.08 (m, 5 H, Ph), 5.31 (dd, 1 H, $J_{4,5}$ = 7.8 Hz, $J_{3,4}$ = 5.1 Hz, H-4), 4.48 (dd, 1 H, $J_{2,3}$ = 3.9 Hz, H-3), 4.32 (ddd, 1 H, $J_{1,2}$ = $J_{1',2}$ = 6.6 Hz, H-2), 4.23 (dd, 1 H, $J_{6,6'}$ = 10.8 Hz, $J_{5,6}$ = 2.4 Hz, H-6), 4.07–3.95 (m, 2 H, H-5 and H-6′), 3.83 (d, 1 H, $J_{H,H'}$ = 13.5 Hz, C*H*^{a}Ph), 3.78 (d, 1 H, $J_{H,H'}$ = 13.8 Hz, C*H*^{b}Ph), 2.82 (d, 2 H, H-1 and H-1′), 2.11 and 2.02 (each 2 s, 3 H, 2 CO*Me*) ppm. ^{13}C NMR (75.4 MHz, acetone-d_6): δ = 170.8, 170.7 (2 CO), 141.8–127.5 (Ph), 80.0 (C-2), 78.1 (C-5), 75.8 (C-4), 64.6 (C-6), 64.4 (C-3), 54.4 (*C*H_2Ph), 49.4 (C-1), 20.7 and 20.4 (2 CO*Me*) ppm. HRMS (CI): *m/z* calcd for $C_{17}H_{22}N_4O_5$ + H: 363.1668; found 363.1671.

(13) **General Procedure for Deacetylation of 7 and Preparation of Compounds 8.**

The corresponding reductive amination product **7** (0.070 mmol) was dissolved in: (i) (2 mL of 1:1 MeOH–$CHCl_3$), (ii) (2 mL of MeOH), or (iii) (2 mL of EtOH abs.), and 5 drops of 1 M MeONa–MeOH were added to the solution [for the deprotection of **7g** was used EtONa–EtOH abs. (1 M)]. The reaction mixture was kept at r.t. for 2 h. Work-up was done by one of the following procedures.

Procedure 1 (**8b**–**d**,**f**): the reaction mixture was cooled and 600 μL TFA was added. The residue was purified by a Dowex 50 × 8 W column, using MeOH (50 mL), H_2O (50 mL) and NH_4OH (10% aq soln; 100 mL) as eluents.

Procedure 2 (**8a**,**e**,**g**,**h**): the reaction mixture was neutralized with Amberlyst 15, the resin was removed by filtration and the solvent under reduced pressure.

(14) In comparison with the NMR spectra of each direct precursor, each acetylated compound **7a**–**h** lacked any signal of aldehyde proton and carbon, but showed instead the signals corresponding to the two new diastereotopic protons at C(1). For the compounds obtained from some primary amines (**7e**,**f**–**h**), the amine proton gave rise to the typical broad signal in the ^1H NMR spectrum at δ = 4.41 (**7e**), 4.44–4.38 (**7f**), 5.81 (**7g**), and 6.00 ppm (**7h**), values that can be correlated with the electron-withdrawing or electron-donating character of the substituent at the *para* position of the aromatic group. However, the amine proton signal of **7a** was not observed, probably because it is overlapped. The molecular weight found for **9** in its HRMS agreed with the aldimine structure assigned, while its NMR spectra showed the sp^2 (C)H signal at δ = 6.86 ppm and the imine carbon at δ = 134.1 ppm, thus corroborating the assignation. For the deacetylated compounds **8a**–**h**, their respective calculated molecular weights were in agreement with those found by HRMS. Furthermore, the ^1H NMR and ^{13}C NMR spectra of these compounds showed no signal corresponding to the *O*-acetyl groups present in the precursors **7a**–**h**, as expected.

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(16) Compound **15** was obtained from **12** (100 mg, 0.265 mmol) and diamine **14** (78 mg, 0.287 mmol) in the presence of $NaBH(OAc)_3$ (60.2 mg, 0.287 mmol) by a similar one-pot procedure to that described above for the preparation of compounds **7** from **6**.

More relevant data of **15**: R_f = 0.45 (Et_2O); $[\alpha]_D^{24}$ +14.6 (*c* 0.63, acetone). IR: ν_{max} = 3295 (NH), 1692 (CO), 1370 (NCO), 1157, 1059 (COC), and 991 (CF) cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6, 363 K): δ = 7.41–7.25 (m, 5 H, Ph), 5.27 (dt, 1 H, $^2J_{4,F}$ = 54.9 Hz, $J_{3,4}$ = $J_{4,5}$ = 3.0 Hz, H-4), 4.79, 4.63 (2 d, 1 H each, $J_{H,H'}$ = 11.5 Hz, C*H*$_2$Ph), 4.69 (dd, 1 H, $J_{4',3'}$ = $J_{4',5'b}$ = 5.7 Hz, H-4′), 4.62 (d, 1 H, H-3′), 4.55 (s, 2 H, C*H*$_2$Ph), 4.38 (dddd, 1 H, $^3J_{5,F}$ = 30.5 Hz, $J_{5,6a}$ = $J_{5,6b}$ = 6.0 Hz, H-5), 4.33–4.21 (m, 2 H, H-2 and H-2′), 4.17 (dt, 1 H, $^3J_{3,F}$ = 23.5 Hz, $J_{2,3}$ = 8.5 Hz, H-3), 3.75 (dd, 1 H, $J_{6a,6b}$ = 10.2 Hz, H-6a), 3.75 (d, 1 H, $J_{5'a,5'b}$ = 14.0 Hz, H-5′a), 3.60 (ddd, 1 H, $^4J_{6b,F}$ = 1.8 Hz, H-6b), 3.32 (dd, 1 H, H-5′b), 3.20–2.91 (m, 4 H, H-1a, H-1b, H-6′a, H-6′b), 1.41 (s, 9 H, C*Me*$_3$), 1.34 and 1.25 (each 2 s, 3 H, C*Me*$_2$) ppm. ^{13}C NMR (125.7 MHz, DMSO-d_6, 363 K): δ = 152 (CO), 137.7–126.8 (Ph), 110.6 (*C*Me$_2$), 89.1 (d, $^1J_{4,F}$ = 188.2 Hz, C-4), 81.6 (C-3′), 80.1 (d, $^2J_{3,F}$ = 16.2 Hz, C-3), 79.5 (C-4′), 78.4 (d, $^2J_{5,F}$ = 17.1 Hz, C-5), 78.3 (*C*Me$_3$), 74.7 (C-2), 72.2 and 71.2 (*C*H$_2$Ph), 67.0 (d, $^3J_{6,F}$ = 11.6 Hz, C-6), 59.8 (C-2′), 50.4 (C-5′), 49.0, 46.6 (C-1, C-6′), 27.6 (C*Me*$_3$), 26.3 and 26.2 (C*Me*$_2$). HRMS (CI): *m/z* calcd for $C_{33}H_{45}N_2O_7F$ + H: 601.3289; found: 601.3281.