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Efficient Methodology for the Synthesis of 2-C-Branched Glyco-amino Acids by Ring Opening of 1,2-Cyclopropanecarboxylated Sugars

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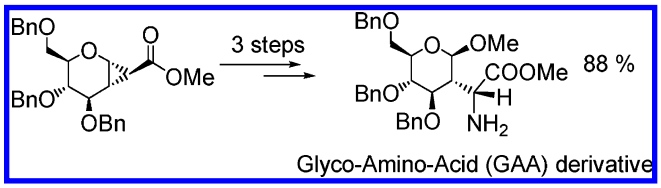
ABSTRACT



An efficient methodology for the synthesis of 2-C-branched glyco-amino acid derivatives by diastereoselective ring opening of 1,2-cyclopropanecarboxylated sugars in good yields is reported.

The past decade has seen several methods being introduced for the stereocontrolled cyclopropanation of glycals.[1] 1,2-Cyclopropanated sugars undergo ring opening to give 2-C-branched sugars when subjected to solvolysis in the presence of a stoichiometric amount of mercury(II) salts,[2] strong acid,[3] or halonium ions.[4] Recently, Madsen et al.,[5] synthesized 2-C-branched carbohydrate derivatives using a Zeise reagent ($[Pt(C_2H_4)Cl_2]_2$) catalyzed ring opening of 1,2-cyclopropanated sugars with *O*-nucleophiles. Their results prompted us to use 1,2-cyclopropanecarboxylated sugars as synthons for the synthesis of glyco-amino acids (GAAs),[6] utilizing their ability to undergo, in the presence of a protic solvent, electrophilic ring opening assisted by the adjacent oxygen to furnish a 2-deoxy-2-C-branched glycoside with defined C-2 stereochemistry, inherently present in the cyclopropanecarboxylate.

Toward this end, tri-*O*-benzyl-D-glucal **1** was treated with methyl diazoacetate (MDA) in dichloromethane with catalytic rhodium acetate (rt, 90 min) to furnish the 1,5-anhydro-2-deoxy-1,2-*C*-(*exo*-carbomethoxymethylene)-3,4,6-tri-*O*-benzyl-α-D-glucitol **2**[9] in 59% yield. Treatment of **2** with NIS/MeOH (28 °C, 8 h) afforded methyl-3,4,6-tri-*O*-benzyl-2-deoxy-2-*C*-(iodomethyl acetate)-*β*-D-glucopyranoside **3** in 75% yield as a single diastereomer[7] in which two new stereocenters were introduced in a single reaction (Scheme 1). Further reaction of **3** with NaN_3/DMF (28 °C, 24 h) afforded azide **4** in 96% yield. The reduction of azide **4** to the amine was unsuccessful under various hydrogenation conditions when 5% Pd/C was used as the catalyst. Reduction did occur satisfactorily using Ph_3P/THF/H_2O (Staudinger reaction conditions), the amine **5** typically being isolated in 95% yield. It is interesting to note that our benzyltriethylammonium tetrathiomolybdate reduction methodology[8] was

(1) For a recent review on the preparation and ring opening of cyclopropanated carbohydrates, see: Cousins, G. S.; Hoberg. J. O. *Chem. Soc. Rev.* **2000**, *29*, 165.
(2) Scott, R. W.; Heathcock, C. H. *Carbohydr. Res.* **1996**, *291*, 205.
(3) (a) Kim, C.; Hoang, R.; Theodorakis, E. A. *Org. Lett.* **1999**, *1*, 1295. (b) Hoberg, J. O.; Lcaffey, D. J. *Tetrahedron Lett.* **1996**, *37*, 2533.
(4) (a) Ramana, C. V.; Nagarajan, M. *Carbohydr. Lett.* **1998**, *3*, 117. (b) Ramana, C. V.; Nagarajan, M. *Synlett* **1997**, 763. (c) Bertinato, P.; Sorensen, E. J.; Meng, D.; Danishefsky, S. J. *J. Org. Chem.* **1996**, *61*, 8000.
(5) (a) Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137. (b) Beyer, J.; Skaanderup, R.; Madsen, R. *J. Am. Chem. Soc.* **2000**, *122*, 9575.
(6) A glyco-amino acid (GAA) is a saccharide attached to a single amino acid by any kind of covalent bond. McDevitt, J. P., Jr.; Lansbury, P. T. *J. Am. Chem. Soc.* **1996**, *118*, 3818.
(7) The ^{13}C NMR spectra of compound **3** showed only 13 lines in addition to the aromatic signals.
(8) Sridhar, P. R.; Prabhu, K. R.; Chandrasekaran, S. *J. Org. Chem.* **2003**, *68*, 5261.

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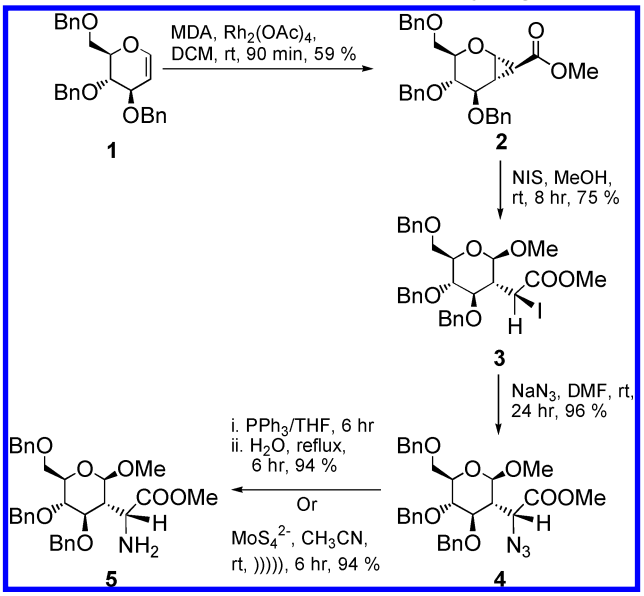
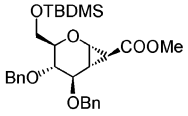
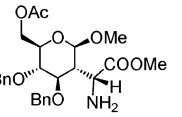
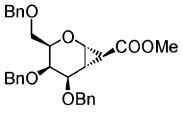
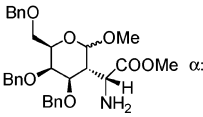
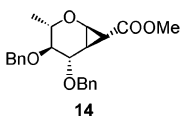
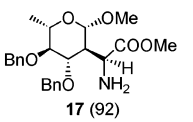
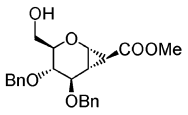
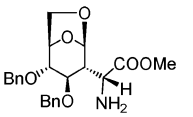
Scheme 1. General Strategy for the Synthesis of a Gluco-amino Acid from 3,4,6-Tri-*O*-benzyl-D-glucal



also effective for converting **4** into **5** (CH_3CN,))))), 28 °C, 6 h, 94%) (Scheme 1).

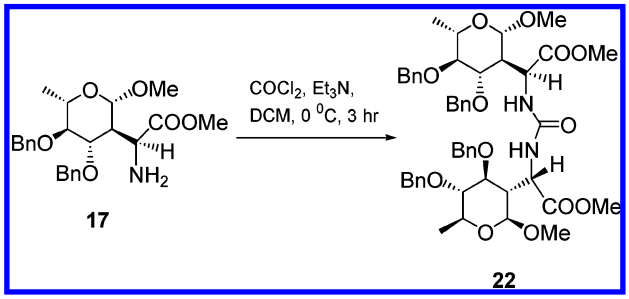
The aforementioned ring-opening of 1,2-cyclopropanecarboxylates could also be extended to the sugar derivatives. Thus, **6**, **10**, and **14** gave rise to the 2-C-branched gluco-amino acid derivatives **9**, **13**, and **17**, respectively, in good yields (65−85%) and with very high diastereoselectivity at

Table 1. Ring Opening of 1,2-Cyclopropanecarboxylated Sugar Derivatives: Synthesis of GAAs

entry	cyclopropane	iodide (%)[b]	azide (%)[b]	GAA (%)[b]	α:β ratio
1	 **6**	**7** (65)[a]	**8** (96)[c]	 **9** (90)	Only β
2	 **10**	**11** (72)	**12** (94)	 **13** (88)	α:β (3:7)
3	 **14**	**15** (85)	**16** (98)	 **17** (92)	Only α
4	 **18**	**19** (65)	**20** (98)	 **21** (95)	only β

[a] TBDMS has been completely deprotected under NIS-mediated solvolytic ring opening of 1,2-cyclopropanecarboxylated sugar **6**. [b] Isolated yield after column chromatography. [c] The free OH in **8** was acetylated prior to reduction of the azide.

Scheme 2



the newly formed C-1 and C-7 stereocenters (Table 1). The large coupling constant ($J \sim 8.8$ Hz) for the anomeric proton in all the ring-opened products showed that the sugar derivatives had a 1,2-*trans* configuration.[9] The stereochemistry at C-2 was defined on the basis of the stereochemistry present in the 1,2-cyclopropanecarboxylated sugar precursors.

However, in the case of 1,5-anhydro-2-deoxy-1,2-*C*-(*exo*-carbomethoxymethylene)-3,4,6-tri-*O*-benzyl-α-D-galactol **10**, the ring-opened product gave a mixture of α,*β*-diastereomers in a ratio of 30:70[10] (Table 1, entry 2). Treatment of compound **18** with NIS in anhydrous acetonitrile (4 Å molecular sieves) furnished the corresponding levoglucosan derivative **19** in good yield, which once again corroborated the 1,2-*trans* selectivity at the anomeric center. The iodide **19** was then converted to the azide **20** and this reduced under Staudinger reaction conditions or with tetrathiomolybdate to afford the levoglucosan-derived glyco-amino acid ester **21** in excellent yield (95%).

To ascertain the exact stereochemistry at C-7, the GAA derivative **17** was treated with phosgene (Et_3N/CH_2Cl_2, 0 °C, 3 h) to furnish the corresponding urea derivative **22** as a crystalline solid (Scheme 2), and it was subjected to X-ray crystallographic analysis. The crystal structure of compound **22** (Figure 1) was in accord with our stereochemical assignment for the ring-opened products.[11]

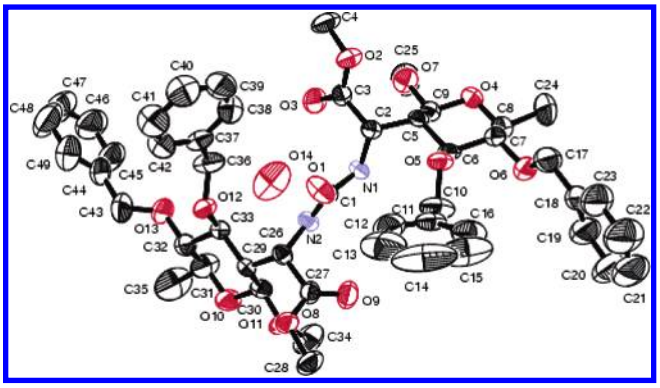


Figure 1. ORTEP diagram of compound **22**[12].

In conclusion, we have developed an effective method for the synthesis of 2-C-branched glyco-amino acid derivatives

by diastereoselective ring opening of 1,2-cyclopropane-carboxylated sugars. Further studies on the application of these new GAAs and the synthesis of glycopeptides by the above methodology are currently under investigation.

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(9) The high diastereoselectivity at the anomeric center may be attributed to the neighboring group (COOMe) participation.

(10) Based on HPLC and ^{1}H NMR spectroscopy.

(11) The configuration of all GAA derivatives were assigned on the basis of the coupling constants and also the structure of compound **22.**

Supporting Information Available: ^{1}H and ^{13}C NMR data for all the ring-opened products, azides, and GAA derivatives, ^{1}H ^{1}H COSY spectra for compounds **15**, **16**, and **17**, and crystallographic data for compound **22**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) One molecule of water was observed in the crystal structure. Crystal data for **22** ($C_{49}H_{62}N_2O_{14}$): $M_r = 908$, monoclinic, space group $P2_1$, $a = 12.1940$ Å, $b = 19.8738$ Å, $c = 17.5201$ Å, $\beta = 93.670(10)°$, $V = 2499.75(27)$ Å^3, $Z = 2$, Mo Kα radiation ($\lambda = 0.710\ 73$ Å), $T = 293(2)$ K; $R_1 = 0.0578$, w$R_2 = 0.115$ ($I > 2\sigma(I)$); $R_1 = 0.102$, w$R_2 = 0.132$ (all data).