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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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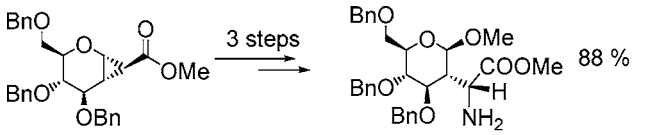
ABSTRACT



Glyco-Amino-Acid (GAA) derivative

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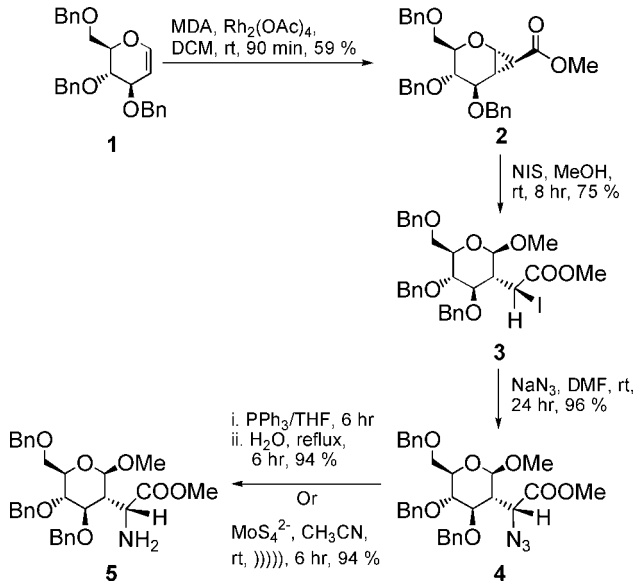
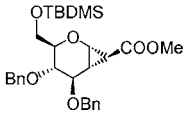
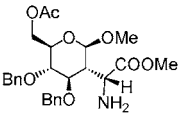
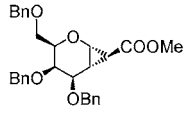
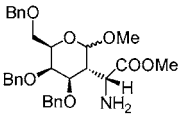
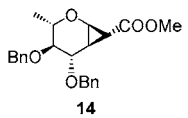
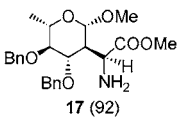
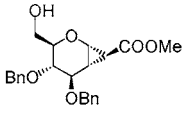
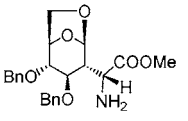
Scheme 1. General Strategy for the Synthesis of a Gluco-amino Acid from 3,4,6-Tri-*O*-benzyl-D-glucal



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

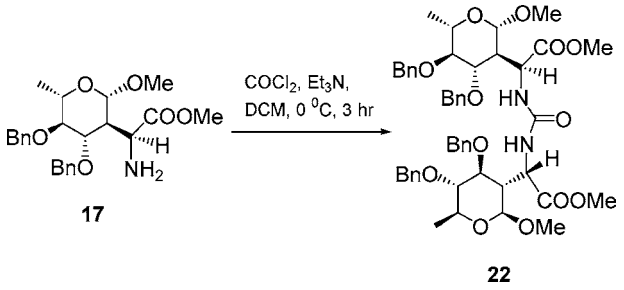
The aforementioned ring-opening of 1,2-cyclopropanecarboxylates could also be extended to the sugar derivatives. Thus, **6**, **10**, and **14** gave rise to the 2-C-branched gluco-amino acid derivatives **9**, **13**, and **17**, respectively, in good yields (65−85%) and with very high diastereoselectivity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



17 **22**

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]

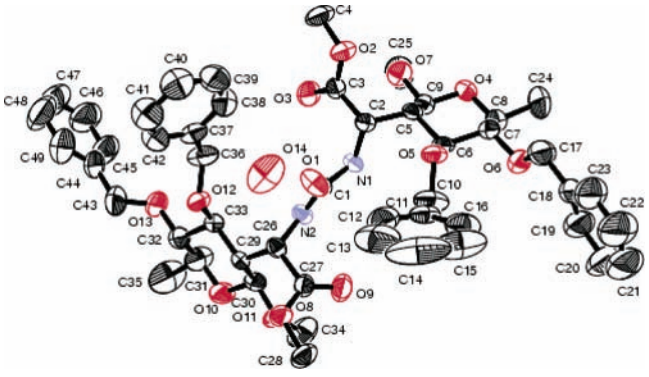


Figure 1. ORTEP diagram of compound **22**[12].

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.

Acknowledgment. P.R.S. thanks the Council of Scientific and Industrial Research, India, for a senior research fellowship.

(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).