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Synthesis of 2-C-Branched Oligo(glyco–amino acid)s (OGAAs) by Ring Opening of 1,2-Cyclopropanecarboxylated Sugar Donors

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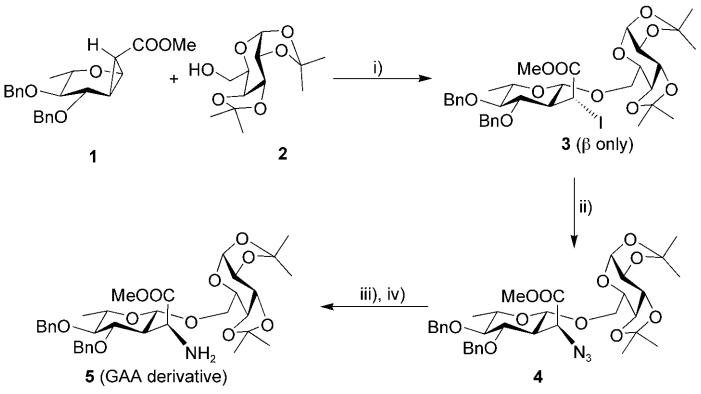
Dedicated to Professor S. Chandrasekaran

Carbohydrates decorated with amino acids are becoming an important area of glyco-chemistry research.[1] Possessing the architecture of a sugar and an amino acid in a single molecule, these glyco–amino acids (GAAs)[2] are expected to exhibit the characteristics of both carbohydrates and amino acids, which are both biological polymer precursors. C-branched glyco–α-amino acid moieties are found in a variety of nucleoside antibiotics, such as polyoxins,[3] miharamycins,[4] nikkomycin[5] and amipuramycin.[6] Very few methods are available in the literature for the synthesis of monosaccharide-derived C-branched GAA derivatives.[7] Linking an α-amino acid at C-2 or C-4 through a C–C bond has been found to be very difficult. For this reason, the biological importance of these GAAs is not yet fully understood. It has been shown that unnatural 2-C-acetonylsugars serve as metabolic substrates for cell surface engineering by mimicking 2-*N*-acetylsugars.[8] Similarly, a 2-C-*N*-hydroxyacetamide mimic of GlcNAc was synthesised and shown to be an inhibitor of the biosynthesis of lipid A.[9] Herein, we report the first stereoselective synthesis of 2-C-branched oligo(glyco–amino acid)s (OGAAs) by ring opening of 1,2-cyclopropanecarboxylated sugar donors.

The high reactivity and regioselectivity of donor–acceptor cyclopropanes has been well documented in the literature.[10] 1,2-cyclopropanecarboxylated sugars have been used as donor–acceptor cyclopropanes in the synthesis of 2-*C*-branched monosaccharides through electrophilic C1–C7 cyclopropane ring opening or by transition-metal-catalysed glycosylation.[11] Recently, a four-component Pavarov reaction and a transition-metal-mediated radical reaction were developed for the direct synthesis of 2-C-branched carbohydrate derivatives from glucals.[7a,12] These branched glycosides were further derivatised to bicyclic carbohydrate 1,2-lactones.[13] Glucal-derived donor–acceptor cyclopropanes have also been used as 1,3-dipoles under acidic conditions, which result in (3+2) cycloaddition reactions in presence of dipolarophiles.[14] By using the ability of 1,2-cyclopropanecarboxylated sugars to undergo electrophilic ring opening assisted by the adjacent oxygen in presence of an electrophile,[15] we herein present the *N*-iodosuccinimide (NIS)-mediated ring opening of 1,2-cyclopropanecarboxylated glycosyl donors with carbohydrate *O*-nucleophilic glycosyl bond acceptors.

To achieve this novel glycosylation reaction, we began by using 1,5-anhydro-2,6-dideoxy-1,2-C-(*exo*-carbomethoxymethylene)-3,4-di-*O*-benzyl-α-L-rhamnal **1**[7b] as the donor and 1,2-3,4-diisopropylidine-α-D-galactose **2** as the acceptor with NIS as the electrophile at 0 °C in acetonitrile. However, no expected disaccharide was observed under these reaction conditions, even with an excess of acceptor **2** (>3 equiv). Similar reaction conditions with dichloromethane as the



Scheme 1. Synthesis of 2-C-branched GAA disaccharides. i) NIS, TMSOTf, CH_2Cl_2, 0 °C–RT, 74% yield; ii) NaN_3, DMF, 96% yield; iii) Ph_3P, THF; iv) H_2O, reflux, 91% yield.

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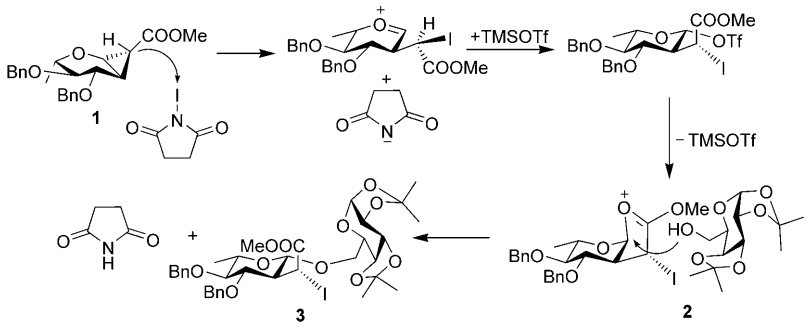
solvent did not improve the glycosylation reaction. We then looked for promoters and after several attempts found that trimethylsilyl trifluoromethanesulfonate (TMSOTf; 15 mol%) is the best promoter for this glycosylation reaction.[16] Treatment of **1** and **2** with NIS/TMSOTf in dichloromethane (0–28°C, 8 h) afforded 2′-C-branched disaccharide **3** in 74% yield as a single diastereomer[17] in which two new stereocenters were introduced at C1′ and C7′ in a single reaction. It is worth noting that only 1.1 equivalents of acceptor, with respect to the donor, were used for this glycosylation reaction. Substitution of α-iodocarboxylate **3** with NaN_3/DMF (28°C, 24 h; DMF = *N*,*N*-dimethylformamide) afforded azidocarboxylate **4** in 96% yield. Reduction of the azide under Staudinger reaction conditions (Ph_3P/THF/H_2O) produced disaccharide GAA derivative **5** in 91% isolated yield (Scheme 1).

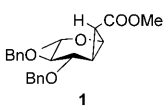
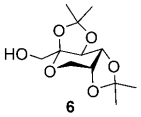
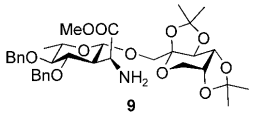
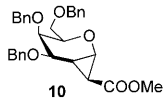
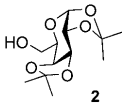
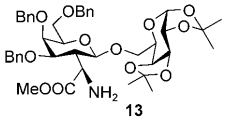
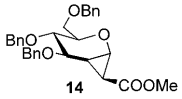
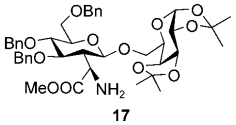
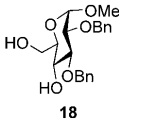
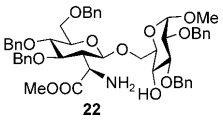
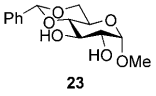
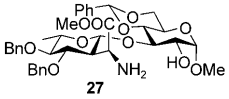
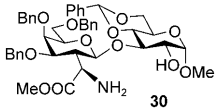
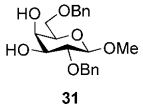
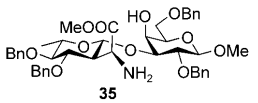
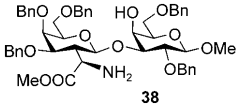
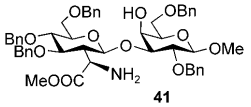
The proposed mechanism of NIS-mediated ring opening involves a stereospecific "edge attack" of iodine on 1,2-cyclopropanecarboxylate **1** to generate an oxocarbenium ion that is immediately trapped with triflate. The triflate is released by neighbouring-group participation of the C7-carboxylate to generate a second oxocarbenium ion intermediate, which is sufficiently long lived that it can be intercepted with a nucleophile. Nucleophilic attack by a glycosyl acceptor oxygen at the anomeric carbon gives disaccharide product **3** (Scheme 2).

The generality of this method has been proved by successfully applying it to a number of 1,2-cyclopropanated glycosyl donors and differentially protected sugar acceptors. Thus, the reaction of cyclopropanecarboxylates **1**, **10** and **14** with acceptors **6** and **2** gave the ring-



Scheme 2. Proposed mechanism for the NIS-mediated ring opening of 1,2-cyclopropanecarboxylated sugar derivatives.

Table 1. Ring opening of 1,2-cyclopropanecarboxylated carbohydrate donors with sugar acceptors; synthesis of 2-C-branched GAA disaccharides.

Entry	Donor cyclopropane	Acceptor	Iodide ([%])	Azide ([%])	GAA derivative	Yield[a] [%]
1	 **1**	 **6**	**7** (75)	**8** (95)	 **9**	92
2	 **10**	 **2**	**11** (72)	**12** (96)	 **13**	90
3	 **14**	**2**	**15** (72)	**16** (92)	 **17**	89
4	**14**	 **18**	**19** (70)	**20** (95) **21**[b] (98)	 **22**	85
5	**1**	 **23**	**24** (67)	**26** (92) **25**[c] (96)	 **27**	94
6	**10**	**23**	**28** (63)	**29** (90)	 **30**	92
7	**1**	 **31**	**32** (70)	**33** (93) **34**[d] (97)	 **35**	97
8	**10**	**31**	**36** (69)	**37** (92)	 **38**	90
9	**14**	**31**	**39** (65)	**40** (88)	 **41**	88

[a] Yield of GAA derivative. Only β-glycosides were formed, and no trace of α product was observed. [b] The free hydroxyl group of azide **20** was acetylated. [c] The free hydroxyl group of iodide **24** was acetylated. [d] The free hydroxyl group of azide **33** was acetylated.

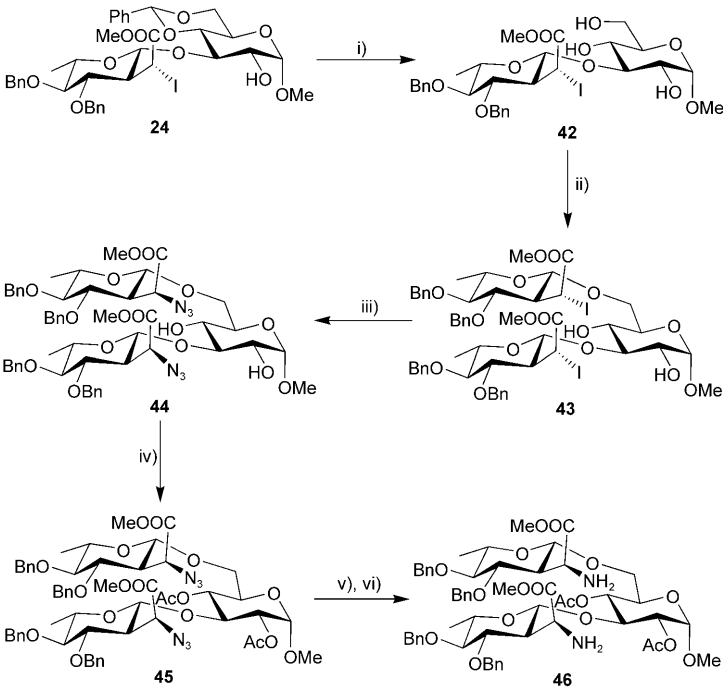
opened 2-C-branched GAA disaccharide derivatives **9**, **13** and **17**, respectively, in good yields with very high diastereoselectivity at the newly formed C1′ and C7′ stereocenters (Table 1, entries 1, 2 and 3). The stereochemistry at C1′ was confirmed by observing a large coupling constant ($J \approx 8.8$ Hz) for the C1′ proton, which indicates a 1,2-trans configuration for all the ring-opened disaccharide derivatives. The stereochemistry at C2′ was defined on the basis of the stereochemistry present in the 1,2-cyclopropanecarboxylated sugar precursor. The stereochemistry at C7′ was assigned based on the proposed mechanism and on one of the GAA derivative crystal structures we reported previously.[7b]

Our next investigations focused on regioselective glycosylation reactions based on the relative reactivity between two hydroxyls on a single sugar acceptor. Towards this goal, cyclopropanecarboxylate **14** was treated with methyl-2,3-di-*O*-benzyl-α-D-glucopyranoside **18** in the presence of NIS/TMSOTf in dichloromethane at 0 °C. The reaction produced a single product, **19**, that was converted to azide **20**. The regioselectivity at the 6-*O* position was assigned by acetylating the free hydroxyl group in **20** with Ac_2O/pyridine and observing a downfield shift in the signal of the C4 proton in acetylated disaccharide **21**. Similarly, reactivity-based glycosylation of 1,2-cyclopropanecarboxylates **1** and **10** with methyl-4,6-*O*-benzylidine-α-D-glucopyranoside **23** produced the 2-C-branched disaccharide derivatives **24** and **28**, respectively, in good yield. Interestingly, C3−OH was involved in the glycosylation step of these reactions.[18]

The aforementioned acceptor-reactivity-based glycosylation of 1,2-cyclopropanecarboxylated sugar donors could also be extended to the other sugar derivatives. Thus, treatment of cyclopropanecarboxylated donors **1**, **10** and **14** with methyl-2,6-di-*O*-benzyl-β-D-galactopyranoside **31** gave disaccharide derivatives **32**, **36** and **39**, respectively, in good yields. All the disaccharide α-iodocarboxylates (**24**, **28**, **32**, **36** and **39**) were converted to the corresponding azides (**26**, **29**, **33**, **37** and **40**, respectively) by using NaN_3/DMF to give excellent yields (≈90%). All these azides were further converted to the corresponding 2-C-branched GAA derivatives **27**, **30**, **35**, **38** and **41**, respectively, under Staudinger reaction conditions (Table 1, entries 5, 6, 7, 8, and 9).

Keeping the above-mentioned acceptor-reactivity-based regio- and stereoselective glycosylation of 1,2-cyclopropanecarboxylated sugar donors in mind, we further planned to synthesise an OGAA derivative. Towards this goal, the benzylidine protecting group in α-iodocarboxylate **24** was deprotected by using *p*-TsOH·H_2O/MeOH to give disaccharide triol **42**. A second acceptor-reactivity-based glycosylation was performed by treating **1** with triol **42** in presence of NIS/TMSOTf to give trisaccharide **43** in good yield as the only isolated product. Treatment of **43** with NaN_3/DMF gave diazide **44**. The free hydroxyls were acetylated to give compound **45**, which gave OGAA derivative **46** under Staudinger reaction conditions (Scheme 3).

In summary, a new glycosylation method that uses carbohydrate-derived donor–acceptor cyclopropanes as glycosyl acceptors has been developed. To the best of our knowledge, this method is the first report of the use of 1,2-cyclopropanecarboxylated sugars in traditional oligosaccharide synthesis. The novel glycosidation method was successfully applied to the synthesis of a number of 2-C-branched GAA disaccharides and to the preparation of an OGAA derivative. Mimicking natural glycosides with carbon-branched GAAs and determining the biological importance of these hybrid biomolecules are in progress.



Scheme 3. Synthesis of 2-C-branched OGAA derivatives. i) *p*-TsOH·H_2O, MeOH, 92% yield; ii) **1**, NIS, TMSOTf, CH_2Cl_2, 0 °C–RT, 62% yield; iii) NaN_3, DMF, 85% yield; iv) Ac_2O, pyridine, 93% yield; v) Ph_3P, THF; vi) H_2O, reflux, 80% yield.

Experimental Section

General procedure for the glycosylation of 1,2-cyclopropanecarboxylated sugar donors: *N*-iodosuccinimide (0.55 mmol) and trimethylsilyl trifluoromethane sulfonate (0.01 mmol) were added to a stirred suspension of 1,2-cyclopropanecarboxylated sugar derivative (0.50 mmol), glycosyl acceptor (0.55 mmol), and a 4-Å molecular sieve in dichloromethane (5 mL) at 0 °C under a nitrogen atmosphere. The temperature was slowly raised to 25 °C and the mixture was stirred for 6 h (until reaction completion, as determined by using TLC). The reaction mixture was diluted with dichloromethane, filtered and washed with aqueous sodium thiosulfate (5%), then the organic layer was dried over anhydrous sodium sulphate and concentrated under vacuum. Column chromatography of the crude product with ethyl acetate/hexane afforded the pure glycosidation product.

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Keywords: carbohydrates · donor–acceptor systems · glyco–amino acids · glycosylation · oligosaccharides

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[16] TMSOTf has been used as an activator in various reactions of donor–acceptor cyclopropanes.

[17] Based on the ^{1}H and ^{13}C NMR spectra.

[18] The site of reactivity was found by acetylating the free hydroxyl group in disaccharide **24** and observing a downfield shift in the signal of the C2 proton in compound **25**. Please see the Supporting Information.

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