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Reagent-Controlled α-Selective Dehydrative Glycosylation of 2,6-Dideoxy Sugars: Construction of the Arugomycin Tetrasaccharide

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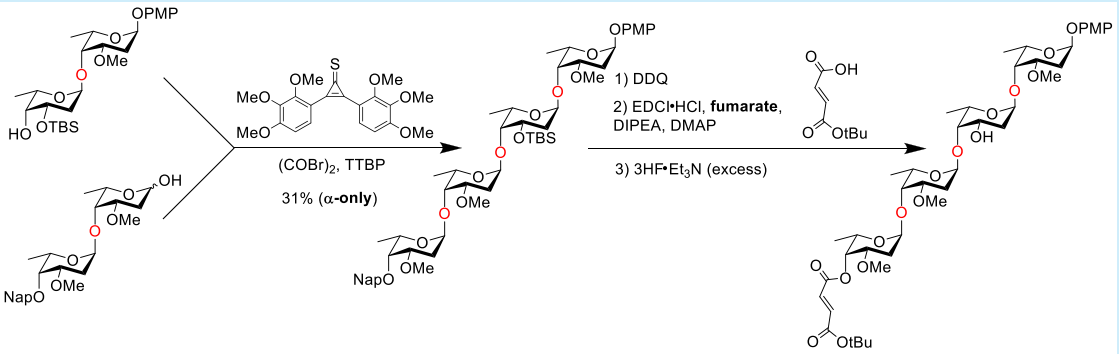
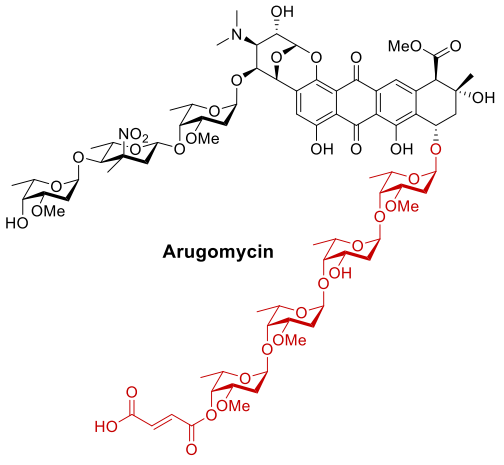


ABSTRACT: The first synthesis of the tetrasaccharide fragment of the anthracycline natural product Arugomycin is described. A reagent controlled dehydrative glycosylation method involving cyclopropenium activation was utilized to synthesize the α-linkages with complete anomeric selectivity. The synthesis was completed in 20 total steps, and in 2.5% overall yield with a longest linear sequence of 15 steps.

2,6-Dideoxy sugars are often found in natural products of therapeutic significance,[1,2] and alterations of the sugar composition of these natural products have been shown to significantly impact their biological activity.[3−7] While this approach holds promise for new avenues for therapeutic development, it is impeded by the inherent difficulties in deoxy-sugar oligosaccharide synthesis.[2,8] Conducting α-selective glycosylations of 2,6-dideoxy sugars is a synthetic challenge, primarily due to the lack of chemical handles at both the C-6 position to promote conformational bias[9,10] and at the C-2 position for the use of a chiral auxiliary.[11−13] Deoxy sugar donor intermediates are also more sensitive to hydrolysis than their fully substituted sugar counterparts,[14] and species such as halides and trichloroacetimidates have to be either freshly prepared and used immediately or generated *in situ* to function as effective donors in direct glycosylations.[15−20] A variety of novel direct,[21−30] indirect,[31−39] and *de novo*[40−46] glycosylation methods have emerged in recent years to address these drawbacks, but the extension of these methods to complex oligosaccharide synthesis remains at the frontier of carbohydrate synthesis.

Our group has had an enduring interest in developing methods for reagent-controlled direct dehydrative glycosylation using shelf-stable 2-deoxy hemiacetal donors. In these approaches, the stereochemical outcome of the reaction is controlled by the promoter system, with sulfonyl chloride promoters affording β-linked structures[47,48] and a combination



of a cyclopropene-1-thione and oxalyl bromide affording α-linked compounds.[49−51] Both our lab and other groups have applied the former approach to complex β-linked 2-deoxy

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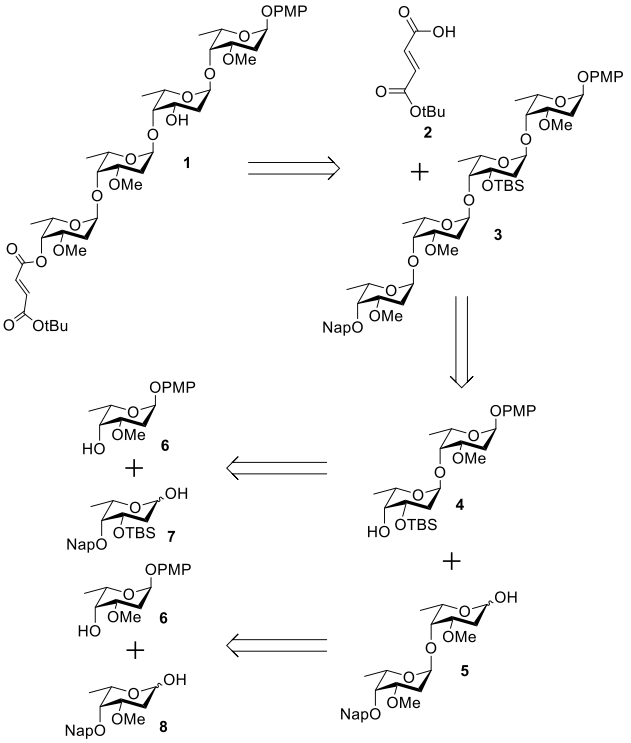
oligosaccharide synthesis,[52−56] but the utility of the latter method in α-linked oligosaccharide synthesis has yet to be established. In order to determine if this chemistry would be useful in oligosaccharide synthesis, we decided to apply it to the synthesis of the tetrasaccharide fragment of Arugomycin (Scheme 1).

Scheme 1. Retrosynthesis of Arugomycin Tetrasaccharide

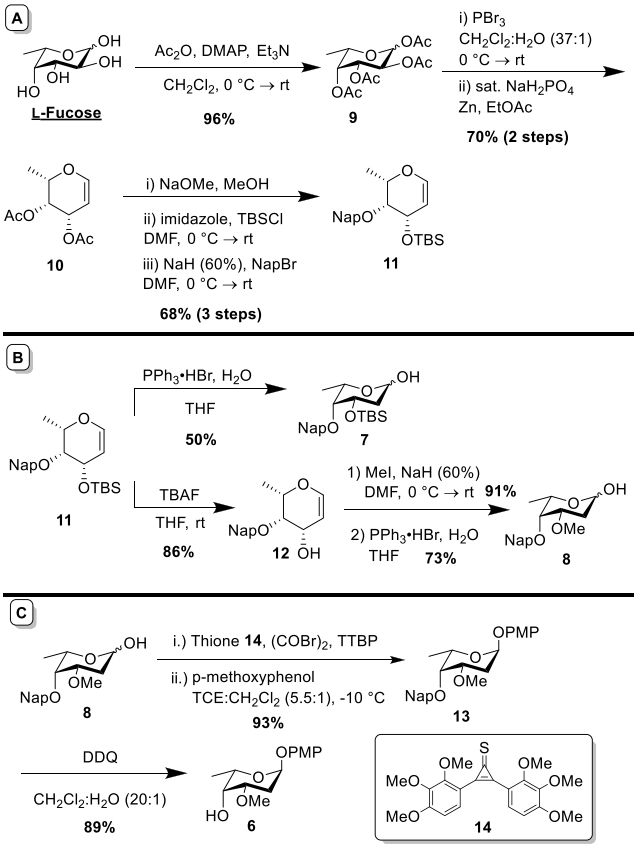


Arugomycin, first isolated from the bacteria *Streptomyces violaceochromogenes* in 1983, was shown to have moderate activity against Gram-Positive bacteria (*S. aureus*, *B. subtilis*, *M. luteus*, MIC = 12.5 μg/mL),[57−59] and it also has potential as an antitumor agent from its ability to intercalate DNA similar to other anthracyclines.[60] Notably, this compound possesses tetrasaccharide and trisaccharide deoxy-sugar chains, which represent challenging synthetic targets for reasons outlined above. We particularly viewed the tetrasaccharide chain, which consists of α-linked L-oliose configured residues with a fumaric acid moiety at the nonreducing end, as an ideal model system to test our method. Here we report the first synthesis of this tetrasaccharide, complete with fumarate attachment, starting from L-fucose.

From our retrosynthetic analysis of target compound **1**, we considered an approach where the fumarate moiety could be appended to tetrasaccharide **3** at the later stage. Tetrasaccharide **3** could then arise from a [2 + 2] coupling of disaccharide donor **5** and acceptor **4**. Both disaccharides could originate from monosaccharide coupling partners **6**, **7**, and **8**, which would in turn be derived from L-fucal.

We began our synthesis with the construction of L-fucal derivative **11** as a precursor to the monosaccharide coupling partners (Scheme 2A). Commercially available L-fucose was peracetylated with acetic anhydride and DMAP to afford compound **9** in 96% yield. Compound **9** was then halogenated at the anomeric position with PBr_3 and subsequently subjected to a modified Fischer−Zach protocol to afford fucal **10** in 70% yield.[61] Compound **10** was then deacetylated with catalytic sodium methoxide, silylated at the C3 position with *tert*-butyldimethylsilyl chloride (TBSCl), and then C-4 was protected as a 2-naphthylmethyl (Nap) ether using 2-naphthylmethyl bromide (NapBr) and sodium hydride to afford common core fucal **11** in 68% yield over three steps.[62]

Scheme 2. Synthesis of the Starting Monosaccharides: Common Core Fucal 9 (A), Oliose Donors 7 and 8 (B), and Oliose Acceptor 6 (C)



With the requisite fucal in hand, we turned our attention to the synthesis of the monosaccharide coupling partners. Hemiacetal donor **7** was produced by hydration of fucal **11** with catalytic triphenylphosphine hydrobromide (Scheme 2B).[44] To obtain **8**, fucal **11** was desilylated with tetrabutylammonium fluoride (TBAF) to afford fucal **12** in 84% yield, followed by methylation at the C3 position with methyl iodide in 91% yield.[63] Finally, hydration of the glycal with catalytic triphenyl phosphine hydrobromide provided **8** in 73% yield.[64]

Synthesis of monosaccharide acceptor **6** commenced with dehydrative glycosylation of donor **8** using a coactivation-based variant of our published methodology for secondary alcohol acceptors.[62] To this end, thione **14** was activated with oxalyl bromide in (5.5:1) TCE/CH_2Cl_2, followed by the sequential addition of *para*-methoxyphenol (PMP) at −10 °C, and donor **8**. This order of activation minimized the formation of trehalose byproducts and afforded **13** in 93% yield exclusively as the α-anomer (Scheme 2C). Subsequent deprotection of the Nap group at C4 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) produced monosaccharide acceptor **6** in 89% yield. With the necessary monosaccharides in hand, we turned our attention to disaccharide synthesis.

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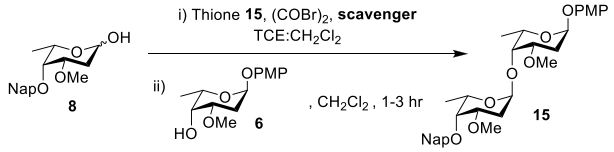
We initially investigated coupling of **8** and **6** using our previously optimized conditions for secondary alcohol acceptors at rt.[51] These conditions afforded α-linked disaccharide **15** in a low yield of 14% (Table 1, entry 1). The major byproducts

Table 1. Optimization of Disaccharide 15



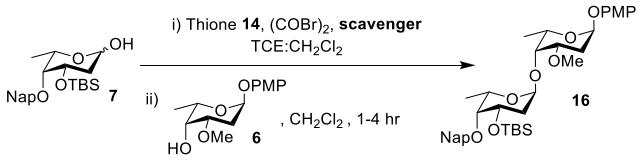
entry	donor/acceptor	scavenger	temp	yield (α-only)
1[a]	2:1	TTBP	rt	14%[b]
2[a]	2:1	TTBP	0 °C	44%[b]
3[a]	2:1	DTBMP	0 °C	11%[b]
4[c]	2:1	TTBP	0 °C	18%[b]
5[d]	1:2	TTBP	0 °C	47%[b]
6[d]	1:3	TTBP	0 °C	64%[b]
7[d]	1:3	TTBP	−10 °C	74%[e]
8[d,f]	1:3	TTBP	−10 °C	69%[e]

[a]TCE/CH_2Cl_2 (2.7:1). [b]NMR yield, product identified in a complex with α,α-trehalose. [c]TCE/CH_2Cl_2/THF (6.5:1:3.2). [d]TCE/CH_2Cl_2 (1.6:1). [e]Isolated yield. [f]300 mg scale of **8**.

of the reaction were an α,α-trehalose derivative of **8**, and a α-PMP glycoside derivative of **8**, which we posit arose from aglycone elimination/transfer from acceptor **6**.[65] Lowering the temperature to 0 °C led to a slight increase in yield (Table 1, entry 2). Switching to a more basic proton scavenger 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) negatively impacted the yield and led to increased formation of PMP transfer byproduct (Table 1, entry 3). The use of THF as a cosolvent, a beneficial practice in our prior study with thione promoter reagent **14**,[51] also led to aglycone transfer and decreased our yield relative to the TCE/CH_2Cl_2 solvent condition (Table 1, entry 4). Unable to limit the formation of byproducts by solvent or scavenger adjustments, we elected to switch the stoichiometry of the glycosylation to make the donor the limiting reagent, which led to a slight drop in byproduct formation (Table 1, entry 5). Further increasing the stoichiometry of the acceptor resulted in a marked increase in yield to 64% (Table 1, entry 6). Reducing the temperature to −10 °C led to a further increase in yield to 74% (Table 1, entry 7). These latter conditions were used to scale up the reaction (Table 1, entry 8).

We applied a similar optimization strategy to the coupling of donor **7** and acceptor **6**. Applying a 1:3 donor/acceptor ratio at 0 °C afforded α-linked disaccharide **16** in 55% yield by NMR integration (Table 2, entry 1). Again α,α-trehalose and derivatives of the donor **7** arising from intramolecular aglycone transfer were the major byproducts of the reaction. Furthermore, free *p*-methoxyphenol coeluted with **16** and could not be separated. Running the reaction at room temperature increased byproduct formation, and the use of THF as a cosolvent did not improve the yield (Table 2, entries 2 and 3). Rationalizing that byproduct formation was the result of inefficient proton scavenging, we again tried DTBMP, but this was again detrimental to the yield (Table 2, entry 4). Seeing the detrimental effect of increasingly Lewis basic scavengers on our substrates, we then investigated the alkene 4-allyl-1,2-dimethoxybenzene (ADB) as an alternate type of

Table 2. Optimization of Disaccharide 16



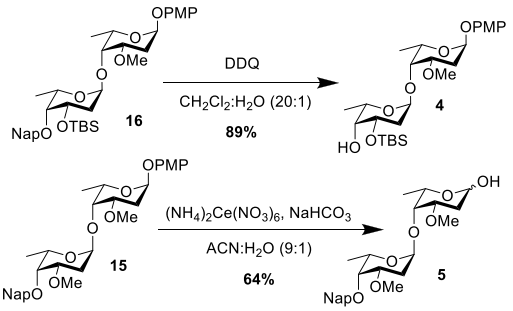
entry	donor/acceptor	scavenger	temp	yield (α-only)[a]
1[b]	1:3	TTBP	0 °C	55%
2[b]	1:3	TTBP	rt	11%
3[c]	1:3	TTBP	0 °C	53%
4[b]	1:3	DTBMP	0 °C	38%
5[b]	1:3	ADB	0 °C	2%
6[b]	1:3	TTBP	−10 °C	87%
7[b,d]	1:3	TTBP	−10 °C	74%
8[b,e]	1:3	TTBP	−10 °C	65%

[a]NMR yield, product identified in a complex with *p*-methoxyphenol. [b]TCE/CH_2Cl_2 (1.6:1). [c]TCE/CH_2Cl_2/THF (9.5:1:4.5). [d]400 mg scale 7. [e]1 g scale 7.

scavenger,[66] but the use of this scavenger led to a complex mixture (Table 2, entry 5). Inspired by our last optimization, we then lowered the temperature of the system to −10 °C and we were pleased to observe an increase in yield of **16** to 87% with no decrease in α-selectivity (Table 2, entry 6). These latter conditions were used for scale-up with minimal impact on the yield (Table 2, entries 7 and 8).

With disaccharides **15** and **16** in hand, we turned our attention to converting them to the requisite disaccharide coupling partners **5** and **4** (Scheme 3). To this end, DDQ

Scheme 3. Disaccharide Deprotections



deprotection of the Nap group of **16** gave disaccharide acceptor **4** in 89% yield, and we gratifyingly did not observe anomerization of the PMP group in the absence of a proton scavenger for this reaction.[64] Disaccharide donor **5** was then generated with ceric ammonium nitrate in 64% yield. In this latter reaction we found that addition of sodium bicarbonate to this reaction was essential to limit the acid-catalyzed hydrolysis of the disaccharide.[67]

With the stage set for tetrasaccharide formation, we initially examined the [2 + 2] glycosylation using the optimal conditions for disaccharide **16** formation. Using our preactivation protocol, we reacted donor **5** and acceptor **4** in a 1:3 ratio at −10 °C and obtained tetrasaccharide **3** as a single α-anomer in 28% yield (Table 3, entry 1). Under these conditions donor **5** was not fully consumed, and we identified the major byproduct of this reaction as the α,α-trehalose derivative of donor **5**. We additionally could quantitatively recover and reuse excess acceptor **4** through flash chromatog-

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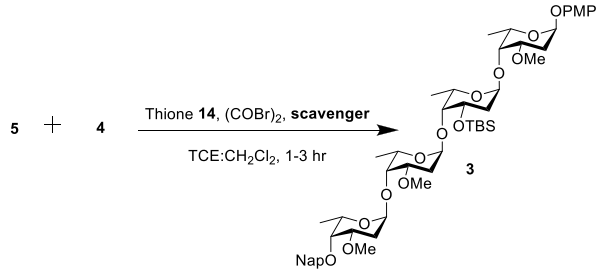
Table 3. Tetrasaccharide Optimization



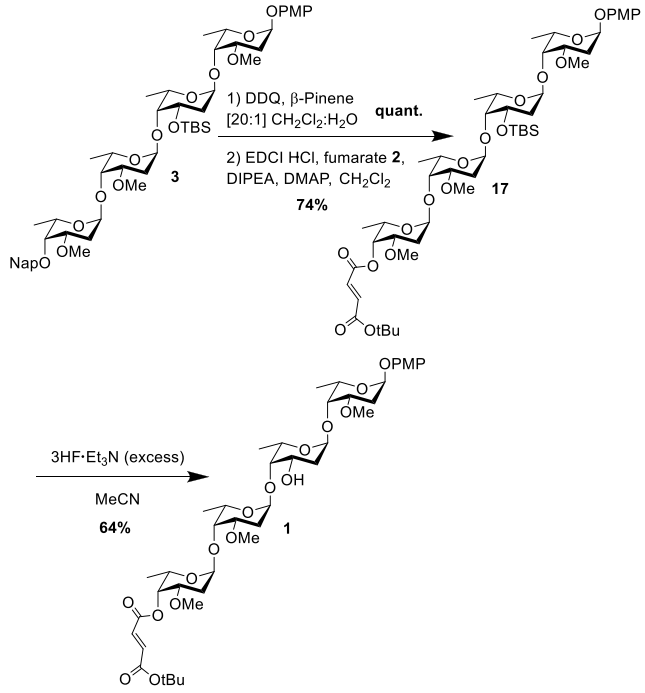
entry[d]	activation method	scavenger	temp	yield (α-only)[a]
1	preactivation	TTBP	−10 °C	28%
2	coactivation	TTBP	−10 °C	trace
3[b]	preactivation	TTBP	−30 °C → −10 °C	31%
4[c]	preactivation	TTBP	−10 °C	30%
5	preactivation	IBO	−10 °C	trace
6	preactivation	β-Pinene	−10 °C	trace

[a]Isolated yield. [b]**4** added at −30 °C. [c]rxn time 23 h, [d]1:3 donor/acceptor ratio for all reactions.

raphy, reducing the impact of these low yields. In an attempt to improve the reaction outcome, we switched to the coactivation protocol described above, which had limited trehalose formation in the PMP glycosylation of monosaccharide donor **8** (Scheme 2C). This method resulted in a complex mixture of products and a significant amount of α-PMP glycoside of donor **5** was produced, signifying aglycone transfer (Table 3, entry 2). Reasoning that the majority of trehalose would be formed during the activation of the donor in the absence of the acceptor, we then cooled the reaction to −30 °C and then allowed the system to warm to −10 °C upon addition of the acceptor, but this failed to increase the yield (Table 3, entry 3), and the donor consumption was sluggish at this lower temperature. Increasing the reaction time to 23 h did not improve the yield (Table 3, entry 4), and we again explored nonbasic proton scavengers as a means of controlling byproduct formation without causing elimination of the PMP substituent of 4. Isobutylene oxide (IBO), which was reported to be effective in preventing halo acid formation in direct glycosylation methods involving halide ion release,[27,68] did not benefit our system, instead affording a complex mixture of products (Table 3, entry 5). We next examined the strained alkene β-Pinene as an acid scavenger;[69−71] however, this too afforded a complex mixture (Table 3, entry 6). Having established a fully selective, albeit low-yielding [2 + 2] glycosylation method, we decided to move forward with the synthesis.

To complete the synthesis of tetrasaccharide **1**, compound **3** was first quantitatively deprotected at the nonreducing end with DDQ in the presence of β-Pinene, which was necessary to prevent PMP anomerization (Scheme 4).[64] The alcohol derivative of **3** was then coupled to fumarate monoester **2** using 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride (EDCI·HCl) and *N*,*N*-diisopropylethylamine (DIPEA) to give tetrasaccharide ester **17** in 74% yield.[72] The sensitivity of the glycosidic linkages of **17** made removal of the TBS masking group challenging, and several conventional approaches failed (e.g., acid-buffered TBAF, HF·pyridine complex). Fortunately, we were able to remove the TBS with an excess of triethylamine trihydrofluoride to afford alcohol-ester **1** in 64% yield.[73]

Scheme 4. Synthesis of Tetrasaccharide Ester 1



In conclusion, we have achieved the first synthesis of the Arugomycin tetrasaccharide fragment by a convergent [2 + 2] route, relying solely on our third-generation promoter system of aryl cyclopropene-1-thione and oxalyl bromide to conduct fully α-selective glycosylations with secondary alcohol acceptors. In our application of this method to more complex glycosylations of 2,6-dideoxy mono- and disaccharides, we addressed the formation of yield-limiting byproducts through adjustments to temperature, stoichiometry, and addition method to ensure good to excellent yields in our disaccharide couplings. Our challenges in extending this method further to tetrasaccharide glycosylation are illustrative of the sensitivity of 2-deoxy sugar linkages and the need for both effective and innocuous proton scavengers. Taken together, the strategies and results reported herein may inform the synthesis of other 2,6-dideoxy-sugar containing oligosaccharides.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01153.

Experimental details and characterization data (PDF)
FAIR data, including the primary NMR FID files, for compounds **1**−**10** (ZIP)
FAIR data, including the primary NMR FID files, for compounds **11**−**17**, **S3**, **S5**, and **S8** (ZIP)

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Notes

The authors declare no competing financial interest.

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