Tetrahedron Letters 125 (2023) 154615

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Synthesis of the branched tetrasaccharide fragment of saccharomicin B

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ARTICLE INFO

Article history:
Received 24 May 2023
Accepted 13 June 2023
Available online 20 June 2023

Keywords:
Carbohydrates
Glycosylation
Synthesis
Amino sugars
Antibiotics

ABSTRACT

A synthesis of the branched tetrasaccharide fragment of saccharomicin B through a [2+2] strategy is reported. Stereoselective coupling of a saccharosamine *ortho*-alkynyl benzoate to a digitoxose thioglycoside acceptor afforded the Sac-11-Digi-10 donor in 50% yield. This latter compound was then united with our previously reported Fuc-8-Eva-9 disaccharide under $AgPF_6$ promotion to afford the target tetrasaccharide in 20% yield. The resulting tetrasaccharide can serve as a linchpin for assembling the target molecule.

Introduction

Many natural products contain deoxy sugar mono-, di-, or oligosaccharides which play key roles in modulating their biological activity. While altering the composition of these sugars through glycodiversification can lead to improved pharmacological activities, the challenges in deoxy sugar oligosaccharide synthesis have limited the use of this approach in drug discovery [1–4]. Many glycosylation reactions have been developed for selective reactions with deoxy sugars in model systems, however, the broader application of these chemistries in complex molecule synthesis is less common [5]. As a consequence, many questions remain about the best methods to use for glycodiversification, which could be answered by studying the glycosylation reactions in more complicated settings.

Among deoxy sugar oligosaccharides, the saccharomicins represent the most complex structures reported to date (Fig. 1). Saccharomicin B (**1**) is a heptadecasaccharide natural product which possesses antimicrobial properties against both Gram-positive and Gram-negative bacteria [6]. This molecule is composed of several unusual deoxy-sugars, including the 2,3,6-trideoxy-3-amino-3-methyl sugars D-saccharosamine (Sac) and 4-*epi*-L-vancosamine (Eva), as well as D-fucose and L-digitoxose [7,8]. Given the synthetic challenges associated in controlling selectivity in glycosylation reactions with deoxy sugars, the complex molecular architecture of the target, and its potent activity, these molecules have attracted considerable attention from the synthetic community [9–13]. Our own lab has had an ongoing interest in the synthesis of these molecules, which has previously resulted in the construction of the Fuc-5-Sac-7, and Fuc-12-Eva-17 fragments of both saccharomicin A and B, as well as the Eva-9-Dig-10 fragment of saccharomicin B and the Eva-9-Sac-11 fragment of saccharomicin A [14–17]. Since toxicology studies on the molecule were conducted with mixtures of saccharomicin A and saccharomicin B, we have sought to develop routes to the molecule flexible enough to produce both targets for further study [6]. Here we report the synthesis of the central linchpin of saccharomicin B (**2**) possessing functionality for elaboration from both ends to the natural product.

Results and discussion

Retrosynthetically, we envisioned that **2** would arise through a [2+2] coupling between disaccharides **3** and **4** (Scheme 1). Disaccharide **3** could in turn be obtained from the reaction 1-O-TBS glycoside **6** and thioglycoside **5**. **6** would be synthesized using our previously published route starting from D-rhamnal [16]. In turn **5** would be obtained from L-rhamnal [15] and disaccharide **4** would be synthesized using our recently published approach [17].

In the forward direction, **7** was synthesized using our previously published procedure [15]. **5** was synthesized in 88% yield through an oxidative deprotection of **7** using 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) (Scheme 2) [18]. With both coupling partners in hand, we turned our attention to the construction of disaccharide donor **3**. Unfortunately, all attempts to unite **5** and **6** under the Lewis acidic conditions led to substrate degradation and intramolecular aglycone transfer of the thiophenol from **5** to **6** (Scheme 2) [16,17].

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https://doi.org/10.1016/j.tetlet.2023.154615
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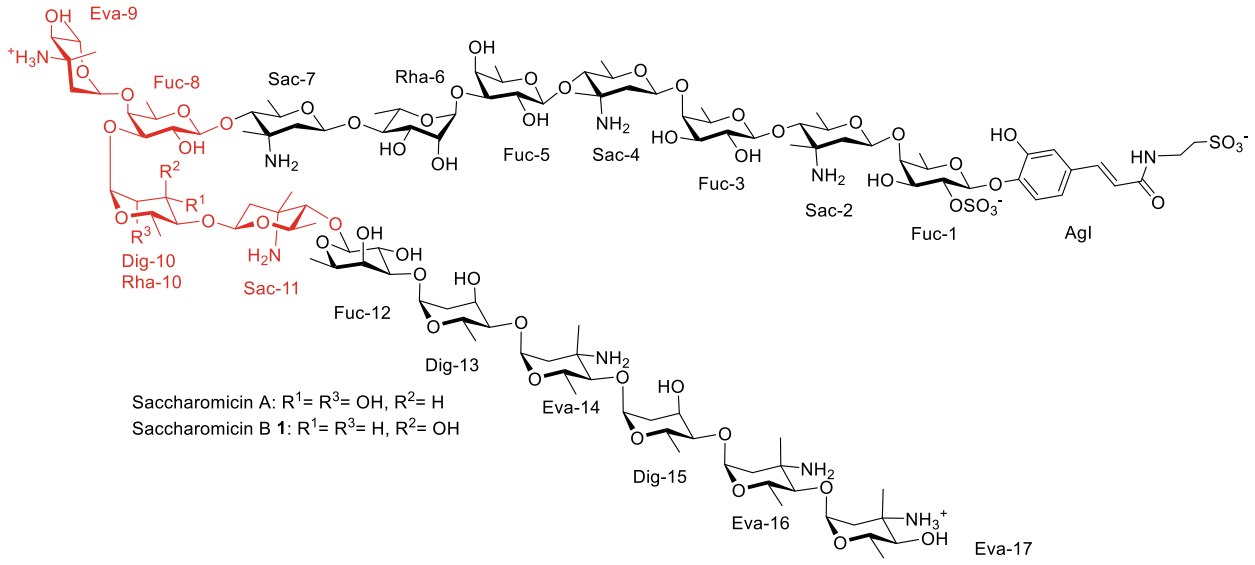
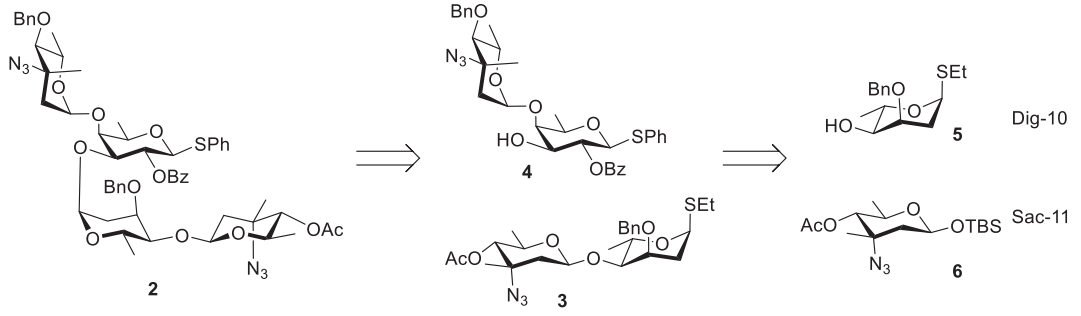
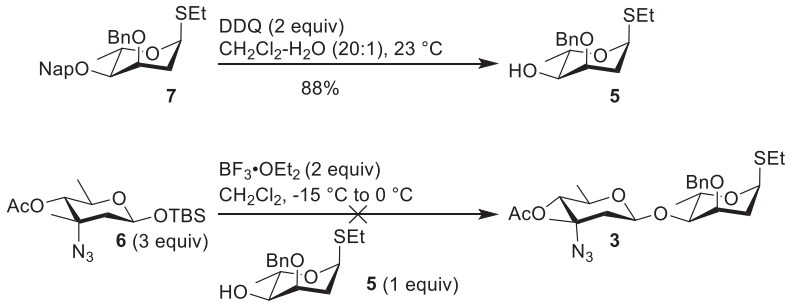


Fig. 1. Structure of Saccharomicin B **1**. The target branched tetrasaccharide is highlighted in red. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

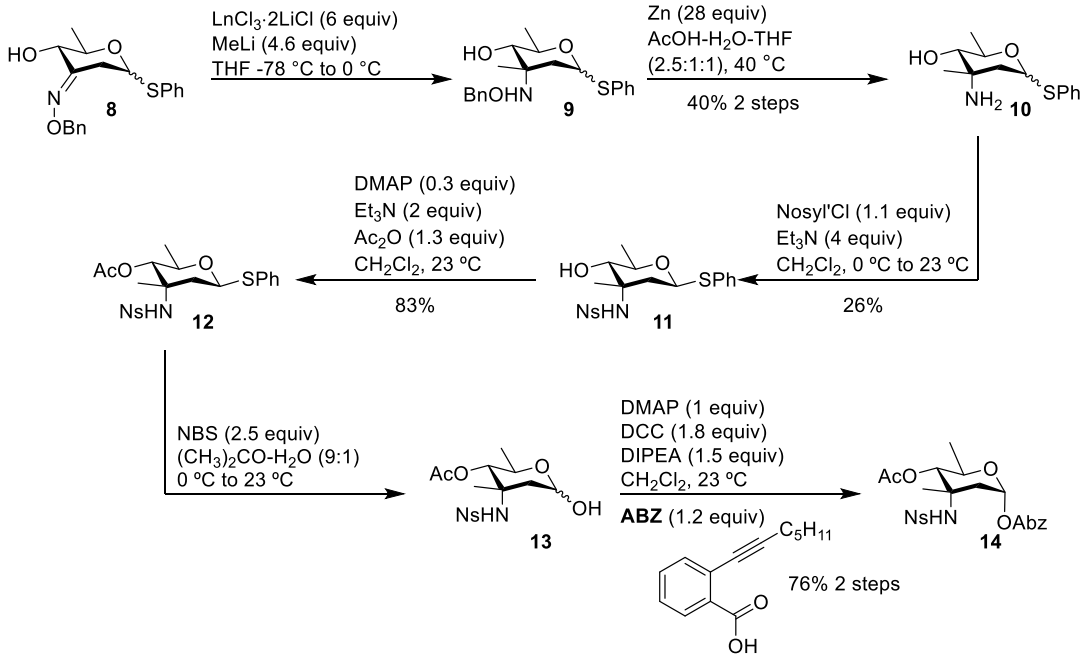


Scheme 1. Retrosynthesis of the branched tetrasaccharide fragment **2** in saccharomicin B.



Scheme 2. Synthesis of L-digitoxose **5** and initial attempt for the synthesis of β(1,4)-linked D-saccharosamine L-digitoxose disaccharide **3**.

In our search for a milder method to synthesize the Sac-11-Dig-10 disaccharide coupling partner, we were attracted to a recent report from Wan, which described activation of *ortho*-alkynyl benzoates in the presence of triaryl phosphines for β-selective glycosylation reactions with 2-deoxy sugars [12]. We therefore turned out attention to the synthesis of *ortho*-alkynyl benzoate donor **14**. The synthesis of **14** began with **8** which was synthesized from D-rhamnal using our previously published method (Scheme 3) [16]. Using the method described by Knochel, the C-3 methyl group was installed using methyl lithium (MeLi), followed by cleavage of the N—O bond on the resulting amine using zinc and acetic acid to afford **10** in 40% yield over 2 steps [19]. Installation of the nosylate sulfonamide to the amine of **10** using 4-nitrobenzenesulfonyl chloride (NsCl) afforded **11** in 26% yield as a single β-anomer (Scheme 3) [12]. The α-anomer of **11** was not isolated due to purification difficulties. Acetylation of **11** using acetic anhydride (Ac_2O) afforded **12** in 83% yield. Notably, when acetylating the C-4 position of **11** careful control of stoichiometry was needed to prevent acetate migration from the C-4 hydroxyl to the C-3 nitrogen. Finally, hydrolysis of the anomeric thiophenol using *N*-bromosuc-

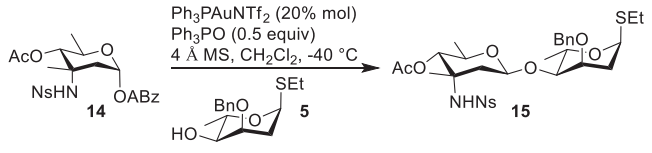


Scheme 3. Synthesis of D-saccharosamine **14**.

cinimide (NBS) and subsequent esterification of the hemiacetal species with **ABZ** afforded compound **14** in 76% yield over two steps (Scheme 3) [12].

With saccharosamine donor **14** in hand, we set about coupling it to **5** [12]. Initial attempts to couple **14** and **5** using tris(3,5-dimethyl-4-methoxyphenyl)phosphine oxide and tetrakis[3,5-*bis*(*trifluoromethyl*)*phenyl*]borate) triphenylphosphine gold (I) ($Ph_3PAuBAr_4F$) failed to provide any product [12]. In an effort to improve the reaction we next conducted the glycosylation using triphenylphosphine oxide (Ph_3PO) and triphenylphosphine gold (I) bis(trifluoromethanesulfonyl)imidate ($Ph_3PAuNTf_2$) [12]. To our delight, under these conditions we were able to obtain disaccharide **15** in 50% yield as a single β-anomer (Table 1, entry 1). The major by-product of this glycosylation is the saccharosamine glycal which is consistent with the literature [12]. Notably, this glycosylation was sensitive to donor stoichiometry and we obtained lower yields using **5** in excess relative to donor **14** (Table 1, entry 2). Finally, warming the reaction to 23 °C resulted in the synthesis of **15** in 46% yield (Table 1, entry 3).

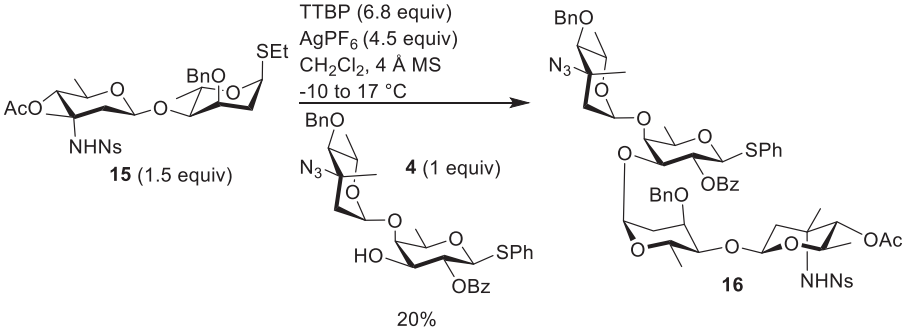
Table 1
Synthesis of β(1,4)-linked D-saccharosamine L-digitoxose disaccharide **15**.



Entry	**14**:**5** ratio	yield %, **15**
1	1.5:1	50, β-only
2	1:1.5	34, β-only
3[a]	1.5:1	46, β-only

[a] Reaction was stirred for 6 h at −40 °C before being warmed to 23 °C over 18 h.

With disaccharide **15** in hand, we turned our attention to the synthesis of the branched tetrasaccharide of saccharomicin B **16**. One of the major challenges in this plan was the selective activation of the digitoxose ethyl thioglycoside in the presence of the fucose thiophenyl glycoside. As a possible solution we were attracted to Hirama's silver hexafluorophosphate ($AgPF_6$)-mediated thioglycoside activation, as it had been reported to selectively activate deoxy sugars over their C-2-substituted counter-



Scheme 4. Synthesis of the branched tetrasaccharide fragment **16**.

parts [20–23]. To this end, we attempted the glycosylation between disaccharide **15** and disaccharide **4** using $AgPF_6$. Compound **16** was produced in the reaction, however, it was not stable to silica gel. Therefore, using reverse phase chromatography we were able to isolate tetrasaccharide **16** in 20% yield (scheme 4).

Conclusion

In conclusion, we report the first synthesis of the branched tetrasaccharide fragment of saccharomicin B **16**. To address issues arising from the need to couple highly reactive donors, we ultimately settled on Wan's triaryl phosphine modified *ortho*-alkynyl benzoate activation to forge the β-linked D-saccharosamine-L-digitoxose fragment of the molecule [12]. This disaccharide could then be directly united with the 4-*epi*-L-vancosamine-D-fucose fragment of the molecule using $AgPF_6$ to afford the target tetrasaccharide **16** in 20% yield. The advanced intermediate **16** is ready to be further elaborated into saccharomicin B. Perhaps more importantly, the lessons learned from this study provide valuable insights into the construction of deoxy-sugar oligosaccharides, which could help further efforts to adapt glycodiversification to drug discovery.

Data availability

Data will be made available on request.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We thank the National Science Foundation (CHE-1954841) for generous support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2023.154615.

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