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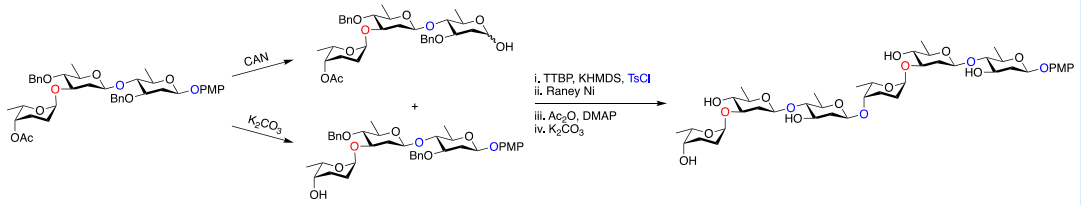
Synthesis of the Hexasaccharide Fragment of Landomycin A Using a Mild, Reagent-Controlled Approach

Subbarao Yalamanchili, Dina Lloyd, and Clay S. Bennett*

Department of Chemistry, Tufts University, 62 Talbot Avenue, Medford, Massachusetts 02155, United States

Supporting Information



ABSTRACT: The synthesis of the hexasaccharide fragment of landomycin A is reported. Using *p*-toluenesulfonyl chloride mediated dehydrative glycosylation, we constructed the deoxy-sugar linkages in a stereoselective fashion without the need for temporary prosthetic groups to control selectivity. Through this approach, the hexasaccharide was obtained in 28 steps and 8.9% overall yield, which is an order of magnitude higher than that of previously reported approaches.

Although there have been several advances in the field of carbohydrate chemistry, controlling selectivity in chemical glycosylation reactions remains one of the most challenging endeavors in organic synthesis.[1] In typical reactions, selectivity is dictated by the nature of the coupling partners.[2] This is especially true in reactions using 2-deoxy-sugar donors, which, due to the lack of functionality at the C-2 position, often requires the use of temporary prosthetic groups to control selectivity.[3−9] As a consequence, glycosylation reactions with deoxy-sugar donors frequently provide products as a mixture of α,β-anomers.[10−13] This issue has led to recent increased interest in developing new approaches for the direct stereospecific installation of β-linked 2-deoxyglycosidic linkages.[14−31] Despite the potential of these newer chemistries, however, their utility in complex molecule synthesis remains to be established.

Our own approach to deoxy-sugar synthesis has been to develop promoters that are able to exert absolute control over the stereochemical outcome of glycosylation reactions.[32−37] This approach has the potential to simplify oligosaccharide synthesis by eliminating the need to use highly specialized protecting group patterns and temporary prosthetic groups to control the stereochemical outcome of the reaction. To assess the utility of our chemistry in oligosaccharide synthesis, we turned our attention to the construction of the hexasaccharide fragment of landomycin A. Landomycin A (Figure 1) was first isolated from the bacteria *Streptomyces cyanogenus* and has been shown to possess potent antitumor activity.[38−41] The only total synthesis of landomycin A reported by Yu was achieved in 63 steps and 0.34% overall yield.[42] More pertinent to the current discussion, the synthesis of the hexasaccharide fragment of landomycin A has also drawn considerable attention, with the Sulikowski,[43] Roush,[44] Yu,[45] and Takahashi[46] groups reporting syntheses that delivered differentially protected versions of the target molecule in 0.01−0.72% overall yield. Smaller fragments

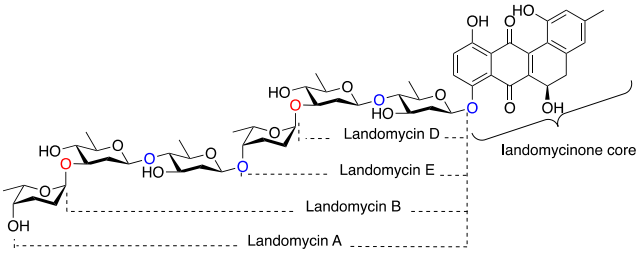


Figure 1. Landomycin series of angucycline antibiotics.

of this molecule have also attracted the attention of several groups, resulting in the construction of landomycin E trisaccharides by the Kirschning,[47] O'Doherty,[21] Mong,[6] and Zhu[23] groups and a disaccharide fragment of the molecule by the McDonald[20] group. Given the large number of synthetic studies on the landomycin hexasaccharide, we felt that it would represent an excellent testing ground for assessing the utility of our reagent-controlled glycosylation methodology.

Retrosynthetically, we chose to take a convergent approach using a [3 + 3] glycosylation strategy (Scheme 1), taking advantage of the fact that the landomycin hexasaccharide **1** is a repeat of two trisaccharides. Accordingly, it can be divided into acceptor **2** and donor **3**. Both of these compounds can be obtained from the three monosaccharides **4**, **5**, and **6**, which could in turn be obtained from D- and L-rhamnal.

The synthesis of the hexasaccharide commenced with the construction of D-rhamnal **8** using a modification of Takahashi and Tanaka's approach to this molecule.[24] First, commercially available **7**, which can be readily made in three steps from D-

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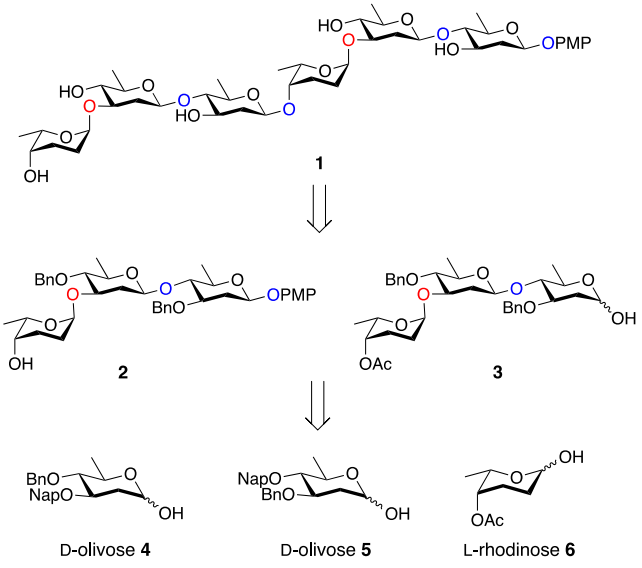
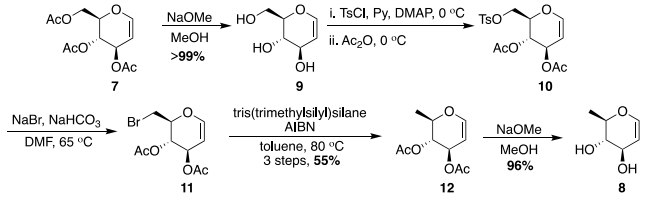
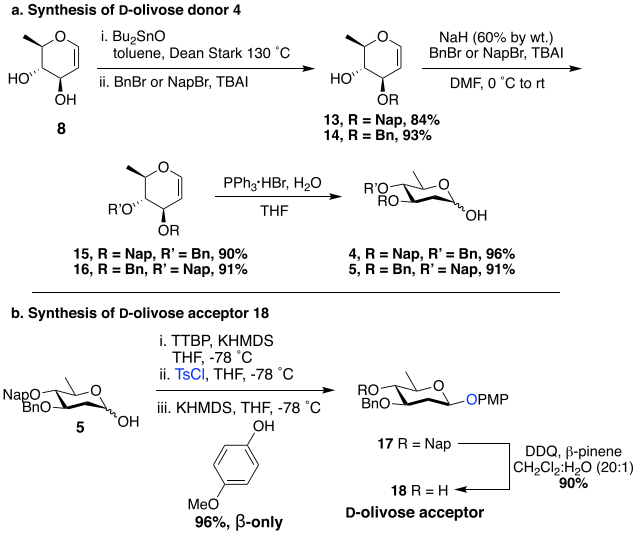
Scheme 1. Retrosynthetic Analysis of 1, the Hexasaccharide Portion of Landomycin A



Scheme 2. Synthesis of 3,4-Dihydroxy-D-rhamnal 8



Scheme 3. Synthesis of D-Olivose Donor 5 and D-Olivose Acceptor 18



glucose,[48] was deacetylated under Zemplén conditions to afford triol **9** in >99% yield. The primary alcohol at C-6 was sulfonylated with *p*-toluenesulfonyl chloride (tosyl chloride or TsCl), and the remaining two alcohols were acetylated in situ. Without any further purification, the tosyl group was displaced using sodium bromide, and the resulting primary halide was subjected to radical dehalogenation using tris(trimethylsilyl)-silane and AIBN to yield diacetal-D-rhamnal **12** in 55% over three steps.[49] Finally, compound **12** was deacetylated under Zemplén conditions to afford **8** (Scheme 2).

With diol **8** in hand, we turned our attention to the construction of D-olivose building blocks **4** and **5**. First, the allylic position of diol **8** was regioselectively alkylated using

Scheme 4. Synthesis of L-Rhodinose Donor 6

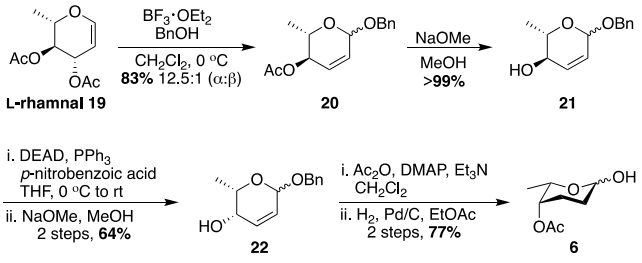
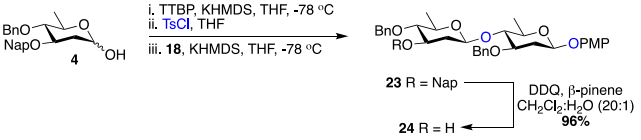


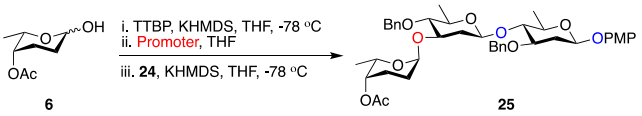
Table 1. Reaction Optimization of Disaccharide 23



entry	donor/acceptor	activation time (h)	yield[c] (%)	β/α[c]
1[a]	1.5:1	0.5	51	10:1
2[a]	1.5:1	1.0	64	18:1
3[a]	1.5:1	1.5	74	14:1
4[a]	2:1	1.5	78	16:1
5[b]	2:1	1.5	81	16:1

[a]With 500 mg of acceptor. [b]With 1.0 g of acceptor. [c]Based on isolated product.

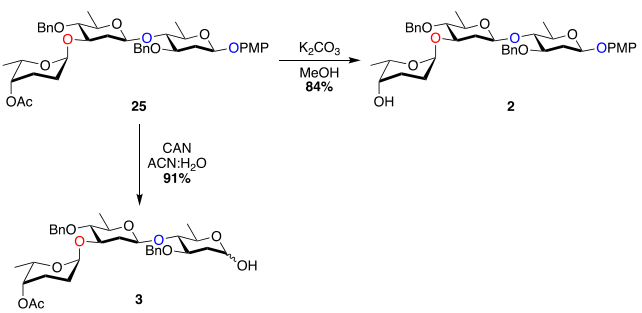
Table 2. Reaction Optimization of Trisaccharide 16



entry	donor/acceptor	promoter	yield[c] (%)	β/α
1	2:1	trisylCl	38	α only
2	2:1	TsCl	39	α only
3	3:1	TsCl	37	α only
4	5:1	TsCl	38	α only
5[a]	2:1	TsCl	47	α only
6[b]	2:1	TsCl	59	α only
7[a,b]	2:1	TsCl	76	α only

[a]Addition of promoter at −78 °C. [b]Portion-wise addition of KHMDS to donor. [c]Based on isolated product.

Scheme 5. Preparation of Trisaccharide Acceptor 2 and Donor 3



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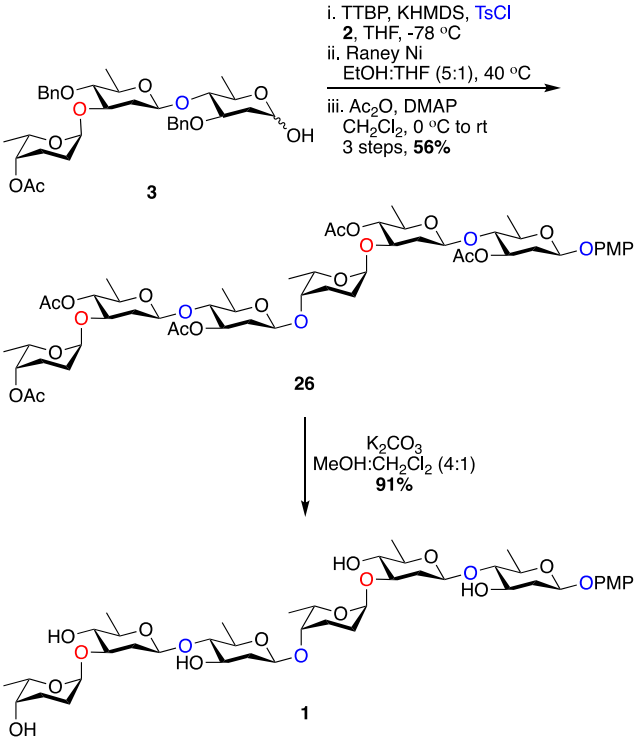
Scheme 6. Assembly of Hexasaccharide 1



dibutyltin oxide and either 2-naphthylmethyl bromide (NapBr) or benzyl bromide (BnBr) to afford **13** and **14** (Scheme 3a), respectively.[24] Protection of the C-4 hydroxyl under standard Williamson ether conditions proceeded smoothly to afford **15** and **16**. Finally, hydration of both glycals afforded D-olivose donor **4** and D-olivose hemiacetal **5**.[50] To prepare D-olivose acceptor **18**, hemiacetal **5** was glycosylated with *p*-methoxyphenol under our previously reported conditions to afford **17** in 96% yield as a single β-isomer. The Nap protecting group at C-3 was removed using DDQ in the presence of β-pinene to afford **18** in 90% yield (Scheme 3b).[51]

The synthesis of rhodinose **6** began with treatment of commercially available L-rhamnal **19** with benzyl alcohol and $BF_3{\cdot}OEt_2$ to afford Ferrier rearranged product **20** in 83% yield (12.5:1 α/β).[52] The C-4 acetate was removed under Zemplén conditions to afford **21** in >99% yield. Mitsonobu inversion on the C-4 alcohol with *p*-nitrobenzoic acid,[53] followed by methanolysis of the resulting ester, produced **22** in 64% yield over two steps. Acetylation under standard conditions followed by hydrogenation with 10% Pd/C to both reduce the alkene and remove the anomeric benzyl ether afforded the L-rhodinose hemiacetal **6** in 77% yield over two steps (Scheme 4).[37]

With the monosaccharide building blocks in hand, we turned our attention to oligosaccharide assembly. To this end, activation of donor **4** under our previously reported conditions followed by glycosylation with **18** afforded disaccharide **23** in 64% yield as an 18:1 (β/α) mixture of isomers (Table 1, entry 2). To improve the yield, we first examined the effect of activation time on the reaction. Through this study, we found that longer activation times led to an increase in yield, accompanied by a slight reduction in the selectivity (Table 1, entries 1 and 3). Further optimization by increasing the amount of donor in the reaction led to the production of disaccharide **23** in 81% yield as a 16:1 (β/α) mixture of isomers (Table 1, entries 4 and 5). This glycosylation could readily be scaled up, permitting the production of this disaccharide on gram scale (Table 1, entry 5).

Removal of the Nap group in **23** under standard conditions afforded disaccharide acceptor **24** in 96% yield.[51] With a scalable method for producing this acceptor established, we next examined the synthesis of trisaccharide **25**. We had previously found that activating the trideoxy-sugar amicetose with triisopropylbenzenesulfonyl chloride (trisylCl) led to α-selective glycosylation reactions, and we wanted to see if a similar transformation could be achieved with rhodinose **6**.[37] Indeed, when **6** was activated under these conditions and treated with acceptor **2**, we were able to obtain trisaccharide **25** as a single α-isomer, albeit in a modest 38% yield (Table 2, entry 1). Reasoning that the yield may be the result of the bulky trisylate group leading to incomplete activation, we next examined the use of the less sterically encumbered tosyl chloride as a promoter. Surprisingly, a similar yield and selectivity were observed with both promoters, in contrast to what we had previously observed with amicetose (Table 2, entry 2). Increasing the donor/acceptor stoichiometry had no effect on the reaction (Table 2, entries 3 and 4). We therefore turned our attention to examining different modes of adding the promoter. To this end, we found that precooling the sulfonate promoter to −78 °C before addition to the reaction mixture increased the yield 47% (Table 2, entry 5). Further optimization revealed that portion-wise addition of KHMDS to the donor led to a significant increase in yield (59%, Table 2, entry 6). Finally, the combined conditions of portion-wise addition of KHMDS and precooling the promoter to −78 °C before addition to the reaction led to the production of **25** in 76% yield as a single α-isomer (Table 2, entry 7).

With the trisaccharide intermediate in hand, we were ready to prepare the donor and acceptor required for the key [3 + 3] glycosylation needed to construct the hexasaccharide. To this end, a portion of **25** was treated with K_2CO_3 to remove the acetate protecting group at the C-3 position of the rhodinose residue to produce trisaccharide acceptor **2** in 84% yield (Scheme 5). To prepare trisaccharide hemiacetal **3**, a second portion of **25** was treated with ceric ammonium nitrate to remove the *p*-methoxyphenol group at the reducing end of the sugar in 91% yield.[54]

In our initial attempts to couple **2** and **3**, we found that we could produce the target hexasaccharide; however, attempts to purify this compound led to decomposition. We therefore opted to carry the crude product forward in the hopes that replacement of benzyl ethers with disarming acetate protecting groups would help stabilize the glycosidic linkages and facilitate purification. To this end, we subjected the crude hexasaccharide glycosylation product directly to several different conditions for benzyl ether removal. Unsurprisingly, several attempts to remove the benzyl ethers using Pd- or Rh-catalyzed hydrogenolysis led to either no reactivity or substrate decomposition.[46] Gratifyingly, however, we were able to successfully remove the benzyl ethers using Raney Ni at 40 °C, as described by Yu and co-workers.[45] Upon completion of the debenzylation, the crude mixture was treated with acetic anhydride and DMAP to afford peracetylated hexasaccharide **26** in 56% yield over three steps (Scheme 6). Finally, removal of the acetate protecting groups led to the formation of the landomycin A hexasaccharide **1** in 91% yield.

In summary, we have completed the synthesis of the landomycin A hexasaccharide. The synthesis proceeds in 28 total steps and 8.9% overall yield, with a convergent linear

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sequence of 18 steps starting from commercially available tri-*O*-acetal glucal. This route is both scalable and the highest yielding approach to this molecule reported to date by about an order of magnitude. Central to the success of this approach was the use of our TsCl-mediated reagent-controlled glycosylation chemistry, which allowed us to directly construct the β-linked deoxy-sugars in the landomycin hexasaccharide in a stereoselective fashion without the need for prosthetic groups. These studies demonstrate that reagent-controlled approaches hold enormous promise for streamlining and simplifying oligosaccharide synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01118.

Experimental details and ^{1}H NMR, ^{13}C NMR, COSY, and HSQC spectra data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: clay.bennett@tufts.edu.

ORCID

Clay S. Bennett: 0000-0001-8070-4988

Notes

The authors declare no competing financial interest.

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