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Stereoselective Synthesis of S-Linked Hexasaccharide of Landomycin A via Umpolung S-Glycosylation

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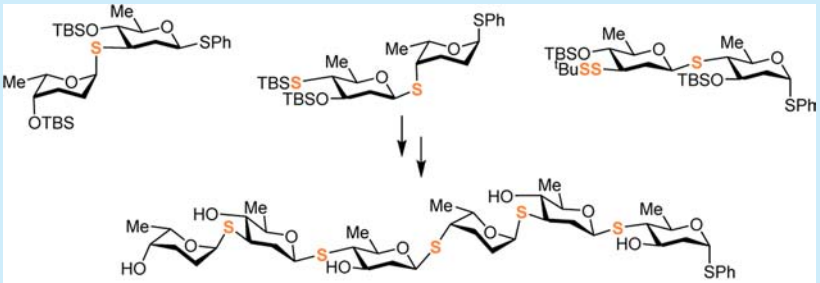
Supporting Information



ABSTRACT: Stereoselective synthesis of carbohydrate mimics resistant toward acid-mediated or enzymatic hydrolysis is chemically challenging and biologically interesting. In this Letter, the first stereoselective synthesis of a "non-hydrolyzable" S-linked hexasaccharide of antitumor antibiotic landomycin A is described. This synthesis was accomplished through the utilization of our recently developed umpolung reactivity-based S-glycosylation−sulfenylation of stereochemically defined glycosyl lithium species with asymmetric sugar-derived disulfides.

The landomycins are a family of angucycline antitumor antibiotics isolated from *Streptomyces cyanogenus*.[1] In particular, landomycin A (cf. **1**, Figure 1) possesses a broad spectrum antitumor activity against 60 cancer cell lines.[1a,2] Structurally, landomycin A contains an angular tetracyclic core as well as a hexasaccharide subunit consisting of two repeat units of trisaccharide (α-L-rhodinose-(1 → 3)-β-D-olivose-(1 → 4)-β-D-olivose). Although it is known that landomycin A inhibits DNA synthesis and G1/S cell cycle progression,[3] the specific mechanism of action on cancer cells has not yet been determined. SAR studies suggested that cytotoxic activity of the landomycins depends on the length of the glycan subunit. In this respect, landomycin A with the longest sugar chain was the most potent congener, while landomycins B, D, E, I, and J with shorter sugar chains showed diminished cytotoxic activities.[1,3] The initial structure of landomycin A proposed by Rohr[1a] in 1990 was revised in 1994[4] and later confirmed through synthetic studies by Roush[5] and a recent total synthesis from the Yu group.[6] The hexasaccharide subunit of landomycin A has also been previously synthesized by three independent groups including Sulikowski,[7] Roush,[8] and Yu.[9] In addition, the repeating trisaccharide has been prepared by Kirschning[10] and O'Doherty.[11] Furthermore, stereoselective synthesis of a combinatorial library of 16 deoxyhexasaccharides related to the landomycin A sugar moiety has also been recently reported.[12]

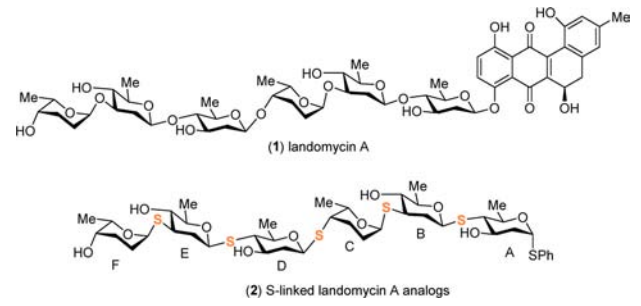


Figure 1. Landomycin A (**1**) and its associated S-linked hexasaccharide (**2**).

It is well-known that 2-deoxy glycosidic linkages are susceptible to acid-mediated or enzymatic hydrolysis. In order to access carbohydrate mimics resistant toward hydrolysis, recently our laboratory has developed an umpolung reactivity-based S-glycosylation[13] for the stereoselective preparation of S-linked 2-deoxy glycosides[14] (2-deoxy thioglycosides).[15] Herein, we describe the first total synthesis of the S-linked hexasaccharide of landomycin A (cf. **2**, Figure 1) employing the aforementioned umpolung reactivity-based S-glycosylation.

Our initial retrosynthesis of S-linked hexasaccharide **2** is depicted in Scheme 1. In this, **2** would be obtained by 3 + 3 coupling of trisaccharide donor **3** (fragment DEF) with trisaccharide-derived asymmetric disulfide acceptor **4** (fragment

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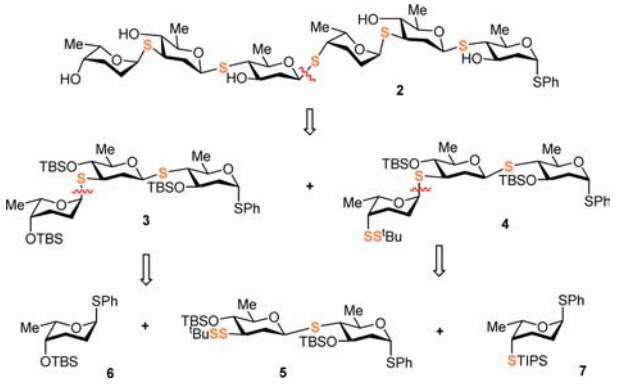
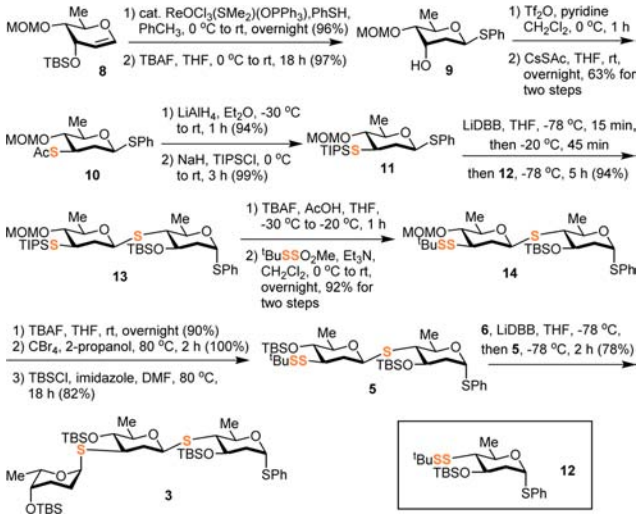
Scheme 1. Initial Retrosynthesis of S-Linked Hexasaccharide of Landomycin A (2)



ABC) via our previously reported umpolung S-glycosylation.[13] In turn, donor **3** would be obtained from disaccharide-derived disulfide **5** and donor **6**,[13a] while acceptor **4** would be accessed from disaccharide-derived disulfide **5** and donor **7**.

In order to synthesize trisaccharide donor **3**, known protected 6-deoxy-D-allal **8**[16] underwent Re(V)-catalyzed thioglycosylation[14b] with thiophenol followed by desilylation to furnish compound **9** (Scheme 2). Triflation of the C3-

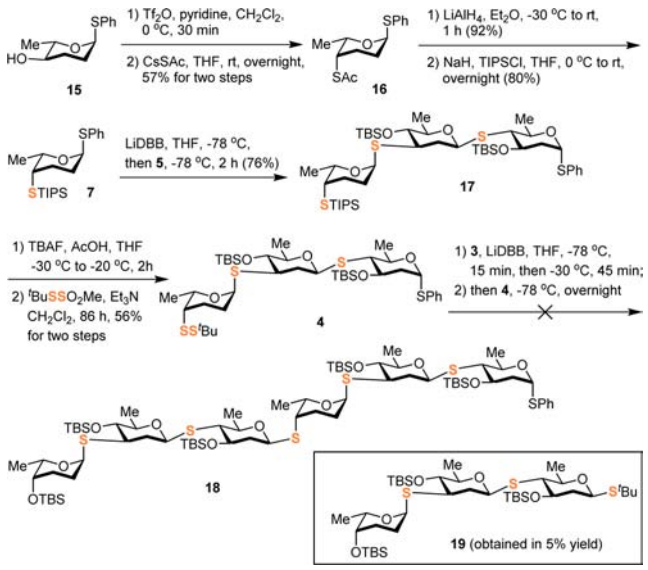
Scheme 2. Synthesis of Trisaccharide Donor (3)



alcohol of **9** followed by S_N2 substitution with cesium thioacetate gave desired product **10**. Reductive removal of the S-acetyl group afforded the corresponding free thiol which was subsequently protected as triisopropylsilyl thioether **11**. Next, lithium 4,4′-di-*tert*-butylbiphenyl (LiDBB)-mediated reductive lithiation of the glycosyl phenylsulfide of **11** followed by anomerization (−20 °C)[13] afforded the corresponding equatorial lithium which reacted with asymmetric disulfide acceptor **12**[13a] to give rise to the desired *β*-S-linked disaccharide **13** in 94% yield. Selective deprotection of triisopropylsilyl thioether of **13** in the presence of TBS ether led to the formation of the free thiol which reacted with S-*tert*-butylmethanethiosulfonate to afford asymmetric disulfide **14**. Despite several attempts, the selective deprotection of methoxymethyl (MOM) ether of **14** in the presence of TBS ether was unsuccessful. Thus, TBAF-mediated cleavage of the TBS ether of **14** followed by MOM-deprotection and global TBS protection gave rise to disaccharide disulfide acceptor **5**. Finally, LiDBB-mediated reductive lithiation of the L-rhodinosyl phenylsulfide of **6**[13a] at −78 °C afforded the corresponding axial glycosyl lithium which then reacted with asymmetric disulfide acceptor **5** to give the desired trisaccharide donor **3** in 78% yield.

With trisaccharide donor **3** in hand, we turned our attention to the synthesis of trisaccharide-derived asymmetric disulfide acceptor **4**. As shown in Scheme 3, the alcohol of known L-

Scheme 3. Attempted Synthesis of S-Linked Hexasaccharide (2)



amicetosyl phenylsulfide **15**[17] underwent triflation and subsequent S_N2 substitution with cesium thioacetate to furnish thioacetate **16**. Reductive removal of the S-acetyl group followed by silylation of the resulting free thiol afforded donor **7**. Likewise, our umpolung-based *α*-S-glycosylation[13] between donor **7** and disaccharide acceptor **5** furnished S-linked trisaccharide **17** in 76% yield. Next, selective deprotection of triisopropylsilyl thioether **17** in the presence of TBS ether led to the formation of the corresponding free thiol which was then converted to the trisaccharide asymmetric disulfide acceptor **4** in 56% yield over two steps. In order to prepare the target hexasaccharide **2**, reductive lithiation of trisaccharide donor **3** followed by anomerization (−30 °C)[13] afforded the corresponding equatorial glycosyl lithium which was subjected to the reaction with trisaccharide asymmetric disulfide acceptor **4** at −78 °C. However, it was very disappointing to find out that this 3 + 3 coupling did not provide the desired S-linked hexasaccharide **18**. Rather, a trisaccharide-derived *β*-*tert*-butylthioglycoside **19** was obtained in approximately 5% yield. Mechanistically, compound **19** may be formed by nucleophilic attack of the trisaccharide donor **3**-derived equatorial glycosyl lithium to the sulfur atom next to the *tert*-butyl group of disulfide acceptor **4**. In addition, we noticed that significant amounts of trisaccharide disulfide acceptor **4** were recovered, which indicated the low reactivity of trisaccharide disulfide acceptor **4** probably due to the steric bulkiness (the *tert*-butyl disulfide moiety is *cis*- to the C6-methyl group of the nonreducing sugar moiety of **4**).

We speculated that the reactivity of the disulfide acceptor might be enhanced by truncating the trisaccharide **4** to a

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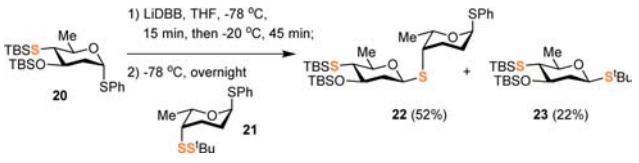
monosaccharide (cf. **21**, Scheme 4). In order to test this idea, we prepared monosaccharide donor **20** and monosaccharide-

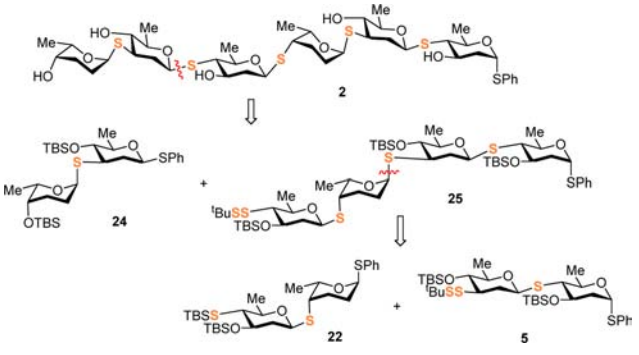
Scheme 4. Synthesis of S-Linked Disaccharide 22



derived asymmetric disulfide acceptor **21**.[18] Gratifyingly, reductive lithiation of donor **20** followed by anomerization (−20 °C)[13] afforded the corresponding equatorial glycosyl lithium which subsequently reacted with disulfide acceptor **21** to give desired *β*-S-linked disaccharide **22** in 52% yield together with *β*-*tert*-butylthioglycoside **23** (22% yield). Disaccharide **22** corresponds to the disaccharide fragment CD of hexasaccharide **2** (cf. Figure 1).

With successful preparation of *β*-S-linked disaccharide **22**, we revised our synthetic strategy to that shown in Scheme 5. Thus,

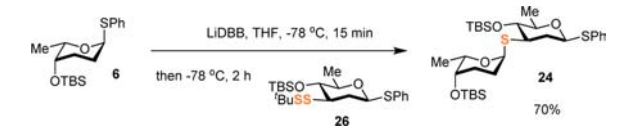
Scheme 5. Revised Retrosynthesis of S-Linked Hexasaccharide of Landomycin A (2)



S-linked hexasaccharide **2** could potentially be obtained by 2 + 4 coupling of disaccharide donor **24** and tetrasaccharide-derived asymmetric disulfide acceptor **25** via our reported umpolung S-glycosylation.[13] In turn, tetrasaccharide-derived asymmetric disulfide acceptor **25** might be obtainable from the previously prepared disaccharide donor **22** and disaccharide-derived disulfide **5**.

As shown in Scheme 6, *α*-S-disaccharide donor **24** can be readily prepared in 70% yield by reductive lithiation of L-

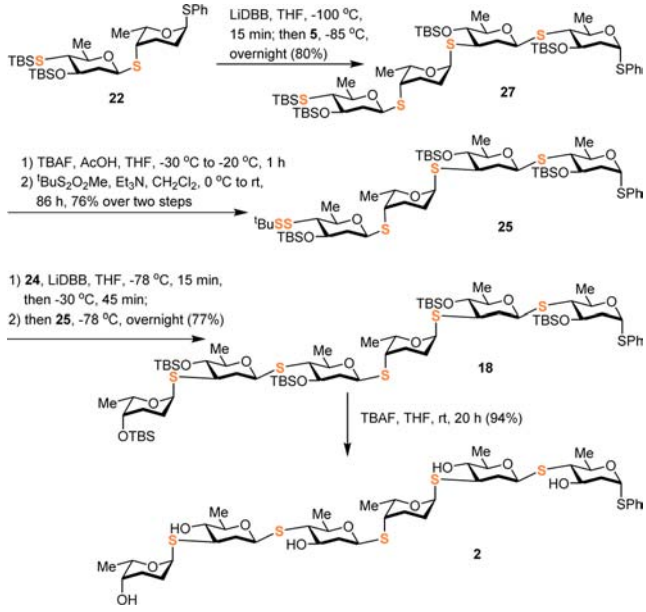
Scheme 6. Synthesis of Disaccharide Donor 24



rhodinosyl phenylsulfide **6**[13a] at −78 °C followed by reaction with asymmetric disulfide **26**.[19] Disaccharide **24** corresponds to the disaccharide fragment EF of hexasaccharide **2** (cf. Figure 1).

With disaccharide donors **22** and **24** as well as disaccharide disulfide acceptor **5** (fragment AB) available, we executed the final stages of our synthesis of S-linked hexasaccharide **2** (Scheme 7). Accordingly, reductive lithiation of disaccharide-derived phenylsulfide **22** at −100 °C gave the corresponding axial glycosyl lithium which then reacted with disaccharide-

Scheme 7. Revised Retrosynthesis of S-Linked Hexasaccharide of Landomycin A (2)



derived asymmetric disulfide **5** at −85 °C to afford desired tetrasaccharide **27** in 80% yield (fragment ABCD). Selective deprotection of the *tert*-butyldimethylsilyl thioether of **27** in the presence of three TBS ethers led to the formation of the free thiol which reacted with S-*tert*-butylmethanethiosulfonate to afford asymmetric disulfide acceptor **25**. Similarly, LiDBB-mediated reductive lithiation of the disaccharide-derived donor **24** followed by anomerization (−30 °C)[13] afforded the corresponding equatorial lithium which then reacted with the asymmetric disulfide acceptor **25** to give the desired fully protected *β*-S-linked hexasaccharide **18** in 77% yield. Finally, global deprotection of five *tert*-butyldimethylsilyl ethers using TBAF at room temperature afforded desired S-linked hexasaccharide **2**.

In conclusion, we have described the first stereoselective synthesis of an S-linked hexasaccharide subunit of landomycin A. This synthesis has been achieved using our previously reported umpolung reactivity-based S-glycosylation via sulfenylation of stereochemically defined glycosyl lithium species with asymmetric sugar-derived disulfides. Preparation of analogs of landomycin A bearing S-linked 2-deoxy sugar subunits and their biological evaluation is underway and will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02223.

Experimental procedure; characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(17) Synthesis of compound **15** was previously reported; see: Kahne, D. E.; Goodnow Jr, R. A.; Taylor, C. M.; Yan, L. U.S. Patent 5,700,916, 1997. In addition, we have described the details for the preparation and characterization of compound **15** in the Supporting Information.

(18) See Supporting Information for the preparation of donor **20** and acceptor **21**.

(19) See Supporting Information for the preparation of disulfide acceptor **26**.

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