A Highly Stereoselective Synthesis of the Landomycin A Hexasaccharide Unit

William R. Roush* and Chad E. Bennett

Department of Chemistry, University of Michigan
Ann Arbor, Michigan 48109

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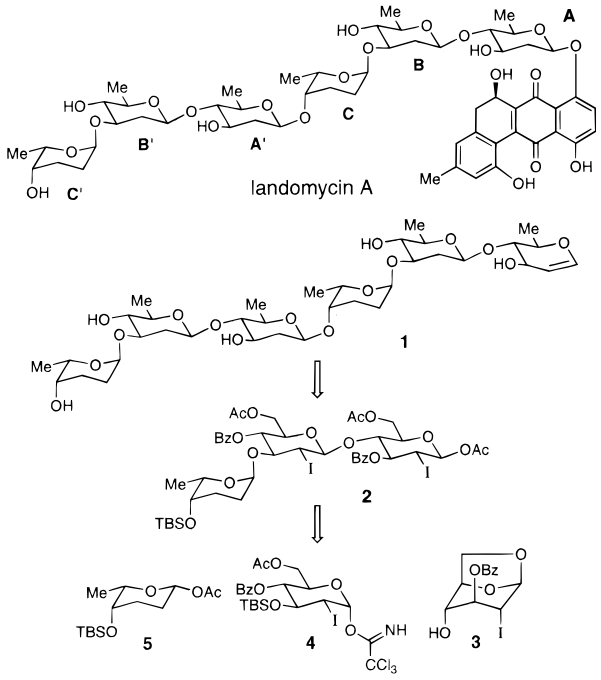
Landomycin A[1] is a member of the angucycline antibiotic family that exhibits a range of biological activities.[2,3] Landomycin A in particular has been studied as a potential antitumor agent.[1,4,5] Although the mode of action of landomycin A has not been established unequivocally, it is known that the natural product interacts with DNA,[5] and inhibits DNA synthesis and G_1/S cell cycle progression.[6] It is also known that the cytostatic activities of other members of the landomycin family (e.g., landomycins A−E) depend on the length of the oligosaccharide chain.[4]



The landomycin A hexasaccharide is a structurally complex deoxyoligosaccharide[7] containing four 2,6-dideoxy-β-glycosidic linkages and two 2,3,6-trideoxy-α-glycosidic linkages. This hexasaccharide exists as a head-to-tail dimer of a repeating A−B−C trisaccharide subunit. In view of the role played in DNA binding by the oligosaccharide units of several families of natural products, including the aureolic acids and the calicheamicins,[8−13] we became interested in developing a synthesis of landomycin A to probe the structure−function relationships of the structurally novel hexasaccharide. Sulikowski has reported a pioneering synthesis of the landomycin A hexasaccharide by a route featuring his glycosyl tetrazole and glycosyl phosphite glycosidation methodology.[14] More recently, Kirschning outlined a synthesis of the landomycin A−B−C repeat trisaccharide that features use of a 2-deoxy-2-iodo-glucosyl acetate donor for construction of the A−B glycosidic linkage.[15,16] We report herein a highly stereoselective synthesis of hexasaccharide glycal **1** using our recently introduced 2-deoxy-2-iodo-glucopyranosyl trichloroacetimidate glycosidation technology.[17,18] Each of the three 2-deoxy-β-glycosidic linkages in **1** was established with ≥95% selectivity using this technology. This is the most highly stereoselective synthesis of a structurally complex deoxyoligosaccharide containing 2,6-dideoxy-β-glycosidic linkages reported to date.

In planning the synthesis of **1**, we focused on the coupling of two advanced trisaccharide intermediates (ultimately, **8** and **9**) that could be derived from a common precursor such as **2**. Anticipating that our Mitsunobu glycosidation protocol will be useful for connecting the hexasaccharide to the phenolic aglycon,[19] we targeted **12** as a key intermediate. On the basis of our previous studies of the stereochemistry of PhSeCl additions to glycals (a step required to activate **12** for Mitsunobu coupling with the aglycon),[20] it was necessary to retain C(6)-heteroatom substituents on the A residue of **12**, and hence also the repeat trisaccharide precursor **2**. In turn, intermediate **2** would be assembled from the conformationally inverted 2-iodo-1,6-anhydroglucose derivative **3**[18] (precursor to the A and A′ residues), 2-iodoglycosyl trichloroacetimidate **4**[18] (precursor to the B and B′ residues), and the L-rhodinosyl acetate **5**[21] (precursor to the C and C′ residues). Intermediates **3** and **4** also derive from a common precursor, and the C(6)-acetoxy substituents of **2** are an artifact of this lineage. Concerns about the acid lability of the B−C and B′−C′ α-glycosidic linkages involving the L-rhodinose residue dictated that we use our 2-deoxy-2-iodo-glycosyl trichloroacetimidate glycosidation protocol for the late stage coupling of **8** and **9**.[22] Furthermore, we considered it prudent to defer the deoxygenation of the C(6) positions of **2** (and hence also of **8** and **9**) until after the hexasaccharide was fully assembled, since past experience

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(16) The Kirschning trisaccharide synthesis appeared while our work was in progress. We have also explored the use of 2-deoxy-2-iodo-glycosyl acetate donors in a first generation synthesis of the A−B−C trisaccharide, but have found it advantageous to use the 2-deoxy-2-iodo-glycosyl imidate technology described herein, in view of the much greater reactivity of these donors. A discussion of our first generation synthesis of the A−B−C trisaccharide will be deferred to a full paper on the synthesis of **1**.
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(21) Our synthesis of L-rhodinose derivative **7** and studies of its glycosidation reactions will be reported elsewhere.
(22) The 6-acetyl-2-deoxy-2-iodo-glycosyl trichloroacetimidates undergo glycosidation reactions at −78 °C under silyl triflate catalysis, while the corresponding 6-acetyl-2-deoxy-2-iodo-glycosyl acetates require reaction temperatures around 0 °C. For example, glycosyl imidate **8** reacted with *p*-methoxybenzyl alcohol at −78 °C to provide the corresponding β-*p*-methoxybenzyl trisaccharide in 79% yield. However, when attempts were made to couple 2-deoxy-2-iodo-glycosyl acetate **2** with *p*-methoxybenzyl alcohol and TBSOTf at 0 °C, the B−C α-glycosidic linkage to the L-rhodinose unit was cleaved cleanly to afford glycosyl acetate **7** in 99% yield along with *p*-methoxybenzyl α-rhodinoside in near quantitative yield.

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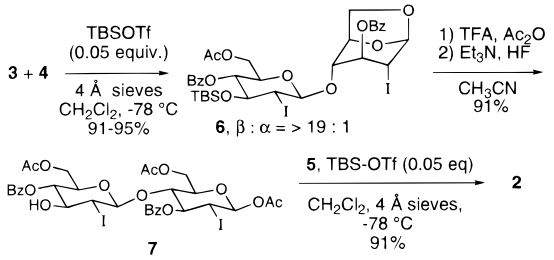
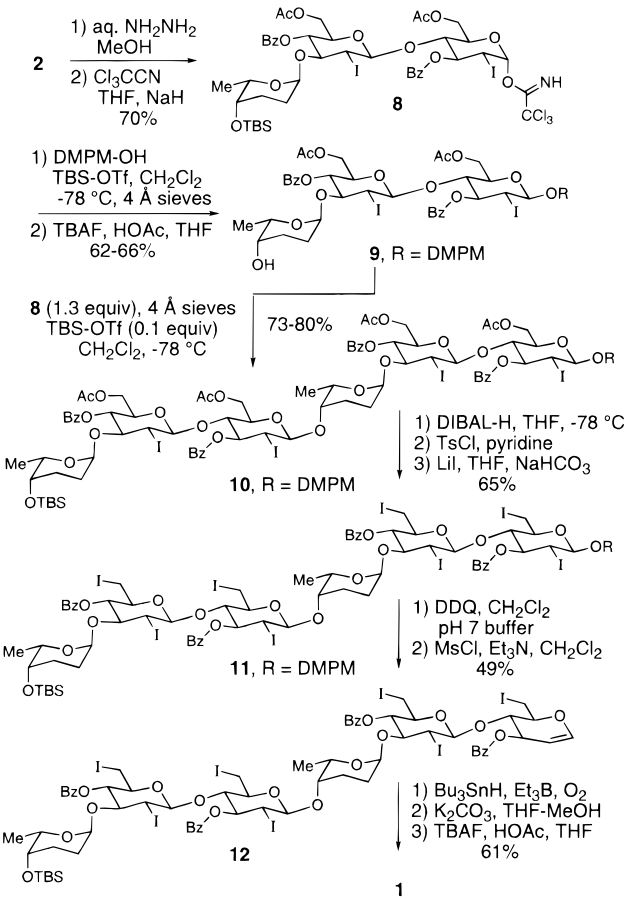
indicated that 6-deoxy-glycosyl trichloroacetimidates are extremely reactive and difficult to prepare without decomposition.[23] The C(6)-heteroatom substituents of **2** thus play a key strategic role in this synthesis by functioning as glycosyl donor stabilizing elements.[24]



The repeat trisaccharide **2** was synthesized starting with the β-glycosidation of the readily available alcohol **3**[18] with the glycosyl imidate **4**.[18] This reaction, performed with 0.05 equiv of TBS-OTf[25] as the activating agent in CH_2Cl_2 at −78 °C, provided disaccharide **6** in 91−95% yield with ≥19:1 selectivity. Acetolysis of the 1,6-anhydro linkage was accomplished by treatment of **6** with trifluoroacetic acid and acetic anhydride at ambient temperature. Deprotection[26] of the TBS ether using Et_3N-$(HF)_3$ in CH_3CN provided disaccharide **7** as a ca. 3:1 mixture of anomeric acetates favoring the β-isomer shown (91% over two steps). Finally, coupling of disaccharide **7** with the L-rhodinosyl acetate **5**[21] using TBS-OTf (0.05 equiv) in CH_2Cl_2 at −78 °C provided **2** in 91% yield, again as a ca. 3:1 mixture of anomeric acetates favoring **2**β.[27]

Trisaccharide **2** was easily converted into the targeted trichloroacetimidate derivative **8** in 70% yield by selective cleavage of the anomeric acetate using aqueous hydrazine in MeOH,[28] and then treatment of a THF solution of the lactols with excess NaH in Cl_3CCN at 0 °C.[23]



DMPM ether **9**[29] was synthesized by treatment of trisaccharide trichloroacetimidate **8** and 1.0 equiv of 3,4-dimethoxybenzyl alcohol (DMPM-OH) in CH_2Cl_2 with 0.1 equiv of TBS−OTf as the activating agent (75−80%), followed by removal of the TBS ether using HOAc-buffered TBAF. This sequence afforded **9** in 62−66% overall yield, with ca. 25:1 selectivity for the β-anomer. TBS-OTf promoted coupling of **9** with trichloroacetimidate **8** (1.3 equiv) then provided hexasaccharide **10** in 73−80% yield, again with β-selectivity of ≥25:1. The four primary acetates were cleaved uneventfully upon treatment of hexasaccharide **10** with a large excess of DIBAL-H in THF. The four primary alcohols were then simultaneously converted to tosylates, which were displaced without complication by treatment with LiI in THF heated to reflux in the presence of $NaHCO_3$, giving **11** in 65% overall yield. Next, the anomeric DMPM ether was cleaved by treatment of **11** with DDQ in CH_2Cl_2 containing pH 7 phosphate buffer.[30] This provided the hexasaccharide lactols in 56% yield, along with 21% of the corresponding reducing pentasaccharide in which the terminal (C′ residue) rhodinose unit had been cleaved. Treatment of the hexasaccharide lactols with methanesulfonyl chloride (MsCl) and Et_3N resulted in spontaneous reductive elimination of the 2-iodo substituent from the A residue (87% yield), and provided the hexasaccharide glycal **12** in 49% yield for the two steps. Reductive removal of the seven iodide substituents was accomplished in 88% yield by treatment of **12** with Bu_3SnH in toluene at ambient temperature, using Et_3B (and a trace amount of air) as the radical initiator.[31] Exposure of the resulting tetrabenzoate to K_2CO_3 in a boiling mixture of THF and MeOH (78% yield) and removal of the TBS ether by treatment with HOAc-buffered TBAF in boiling THF (89% yield) completed the synthesis of hexasaccharide glycal **1**.

In summary, we have developed a highly stereoselective synthesis of hexasaccharide glycal **1**. The exceptional stereocontrol (>95:5) achieved at each of the five glycosidic linkages is noteworthy, especially the control exercised over the three 2-deoxy-β-glycosidic linkages.[32] Also of interest is the reduction of a 2-iodopyranose with MsCl and Et_3N (cf., **11** to **12**). Further progress toward the completion of a total synthesis of landomycin A will be reported in due course.

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Supporting Information Available: Experimental details for the synthesis of **1** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(32) A referee requested that we provide a statistical comparison of Sulikowski's and our syntheses of the landomycin A hexasaccharide fragments. This is not necessarily a meaningful exercise, since different molecules were synthesized by the two groups. Nevertheless, our synthesis of **1** proceeds in a total of 35 steps and 0.6% overall yield, including 8 steps for the synthesis of rhodinose derivative **5** from methyl (*S*)-lactate (unpublished). The longest linear sequence is 25 steps starting from commercially available triacetyl D-glucal (precursor to **3** and **4**), with an overall yield of 1.5% and ≥87% stereoselectivity for this sequence. Sulikowski's synthesis involves 33 steps starting from L-rhamnal (precursor of the L-rhodinose units) and D-rhamnal (precursor of the A, B, A′, and B′ residues), in an overall yield of <0.01% and 27% stereoselectivity. The longest linear sequence in this work is 18 steps (0.4% yield) starting from L-rhamnal (which is not commercially available).