Studies on the Synthesis of Landomycin A: Synthesis and Glycosidation Reactions of L-Rhodinosyl Acetate Derivatives

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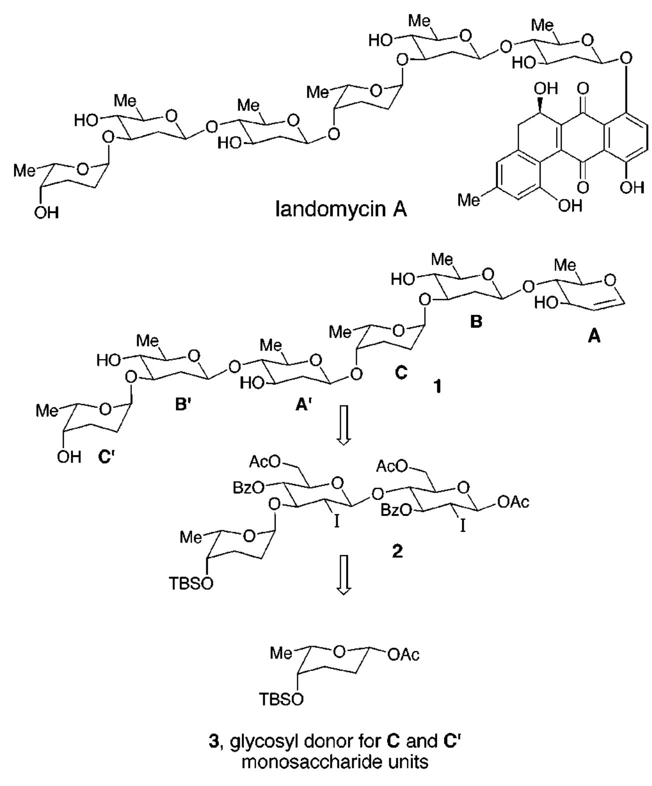
An efficient, eight-step synthesis of L-rhodinosyl acetate derivative **3** is described. The synthesis originates from methyl (*S*)-lactate and involves a highly stereoselective, chelate-controlled addition of allyltributylstannane to the lactaldehyde derivative **7**. The β-anomeric configuration of **3** was established with high selectivity by acetylation of the pyranose precursor with Ac_2O and Et_3N in CH_2Cl_2. Preliminary studies of glycosidation reactions of **3** and L-rhodinosyl acetate **10** containing a 3-*O*-TES ether revealed that these compounds are highly reactive glycosidating agents and that trialkylsilyl triflates are effective glycosylation promoters. The best conditions for reactions with **15** as the acceptor involved use of diethyl ether as the reaction solvent and 0.2 equiv of TES-OTf at −78 °C. However, the TES ether protecting group of **10** proved to be too labile under these reaction conditions, and mixtures of **16a**, **17**, and **18a** are obtained in reactions of **10** and **15**. Disaccharide **17** arises via in situ cleavage of the TES ether of disaccharide **16a**, while trisaccharide **18a** results from a glycosidation of in situ generated **17** (or of **16a** itself) with a second equivalent of **10**. These problems were largely suppressed by using **3** with a 3-*O*-TBS ether protecting group as the glycosyl donor and 0.2 equiv of TES-OTf as the reaction promoter. Attempts to selectively glycosylate the C(3)-OH of diol acceptors **20** or **28** gave a 70:30 mixture of **21** and **22** in the reaction of **20** and a 43:27:30 mixture of regioisomeric trisaccharides **29** and **30** and tetrasaccharide **31** from the glycosidation reaction of **28**. However, excellent results were obtained in the glycosidation of differentially protected disaccharide **34** using 1.5 equiv of **3** and 0.05 equiv of TBS-OTf in CH_2Cl_2 at −78 °C. The latter step is an important transformation in the recently reported synthesis of the landomycin A hexasaccharide unit.

Landomycin A,[2,3] a member of the angucycline antibiotic family,[4,5] is of considerable interest as a potential antitumor agent.[3,6,7] It is known that landomycin A inhibits DNA synthesis and G_1/S cell cycle progression[5,6] and that the cytostatic properties of other members of the landomycin family depend on the length of the oligosaccharide chain.[5,6] While syntheses of the landomycin A aglycone have not yet been reported, syntheses of the hexasaccharide unit have been reported by us[8] and by Sulikowski,[9] while Kirschning has reported a synthesis of the repeat A−B−C trisaccharide unit (Scheme 1).[10]

During the course of our work on the synthesis of hexasaccharide **1**,[8] we needed a convenient source of the L-rhodinosyl acetate derivative **3** for introduction of the C residue in the repeat trisaccharide **2**. L-Rhodinose, a 2,3,6-trideoxy-L-hexose, is a constituent of several classes of natural products including landomycin A, streptolydigin, and vineomycin B_2.[11−13] Numerous syntheses of rhodinose and its derivatives are known in the litera-

Scheme 1



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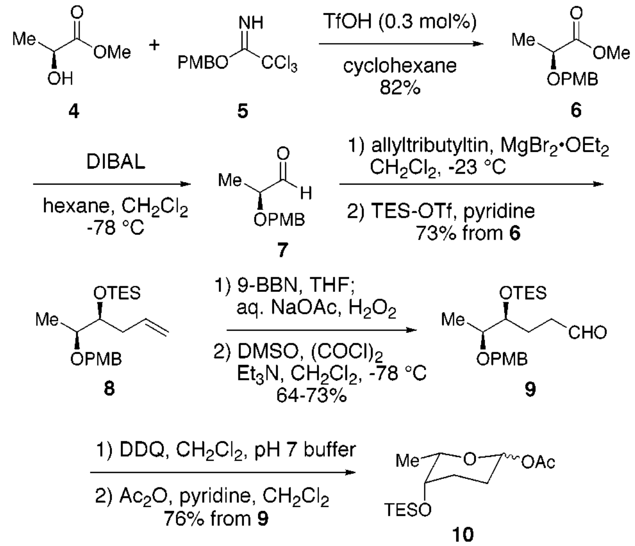
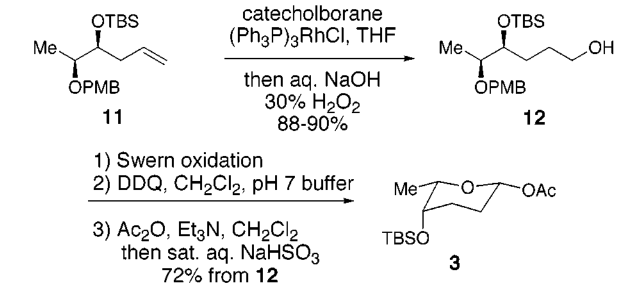
Scheme 2



Scheme 3



ture,[14−23] including several that originate from more readily available sugars.[24−28] We were most attracted to the routes that originated from methyl (*S*)-lactate[14,19,20] and adopted modifications of Schlessinger's route for synthesis of **3**.[20,29]

We initially targeted the triethylsilyl (TES)-protected **10** as the rhodinosyl acetate donor for the landomycin A synthesis. Accordingly, commercially available methyl (*S*)-lactate (**4**) was protected as a *p*-methoxybenzyl (PMB) ether by treatment with *p*-methoxybenzyl trichloroacetimidate (**5**) and 0.3 mol % of TfOH in cyclohexane, giving PMB ether **6** in 82% yield (Scheme 2).[30] Controlled reduction of **6** with 1.2 equiv of DIBAL in a 1:1 mixture of CH_2Cl_2−hexane solvent mixture at −78 °C provided lactaldehyde **7** in excellent yield. Treatment of **7** with $MgBr_2$•OEt_2 and allyltributylstannane in CH_2Cl_2 at −23 °C provided the expected homoallylic alcohol in 84% yield with excellent stereoselectivity.[20,31] This alcohol was then silylated with triethylsilyl triflate (TES-OTf) and pyridine, thereby providing TES ether **8** in 73% yield overall from **6**. Hydroboration of **8** with 9-BBN in THF followed by careful oxidation of the organoborane intermediate with hydrogen peroxide and sodium acetate afforded the primary alcohol in 69−79% yield. Unfortunately, the TES ether of this and subsequent intermediates proved to be very sensitive to cleavage. Subsequent Swern oxidation[32] of the primary alcohol then gave the corresponding aldehyde **9** in good yield. Oxidative cleavage of the *p*-methoxybenzyl ether with DDQ[33] in a CH_2Cl_2−water mixture then yielded a 1:1 anomeric mixture of lactols with $J_{4,5}$ = 1.3 Hz. These lactols were acetylated by treatment with Ac_2O and pyridine in CH_2Cl_2 to provide a 1:1 anomeric mixture of rhodinosyl acetates **10** in 76% yield over the last two steps. The stereochemistry of the rhodinosyl acetate derivatives **10**α and **10**β was confirmed by the observation of $J_{4,5}$ coupling constants of 1.2 Hz for the α-anomer and 1.4 Hz for the β-anomer, indicating an axial−equatorial relationship of the C(4) and C(5) protons, and hence syn stereochemistry in **8**.

As we examined glycosidations of **10**, it became apparent that the TES ether protecting group was too labile under the glycosidation conditions (vide infra). Consequently, the rhodinose derivative **3** containing a much more robust *tert*-butyldimethylsilyl (TBS) protecting group was also synthesized. Intermediate **11** was prepared in 74% overall yield from **6** by substituting *tert*-butyldimethylsilyl chloride, imidazole and DMF for the TES ether protection step in the sequence employed for synthesis of **8**. Hydroboration of **11** using catecholborane in the presence of Wilkinson's catalyst ($(Ph_3P)_3RhCl$)[34] produced a boronic ester that was oxidized by treatment with aqueous NaOH and H_2O_2, thereby giving primary alcohol **12** in 88−90% yield (Scheme 3). Oxidation of this alcohol under Swern conditions,[32] followed by deprotection of the PMB ether by treatment with DDQ in wet CH_2Cl_2, provided a mixture of hemiacetals. Acylation of this mixture with Ac_2O and Et_3N afforded a mixture of β-rhodinosyl acetate **3** and anisaldehyde. None of the α-anomer of **3** was observed under these conditions.[35] The contaminating anisaldehyde was removed by extraction of this mixture with aqueous $NaHSO_3$ to form a water-soluble bisulfite adduct. Rhodinosyl acetate **3** was thus obtained in 72% yield over the last three steps. In this way, rhodinose derivative **3** was prepared on multigram scale in eight steps from commercially available methyl (*S*)-lactate in 38% overall yield.

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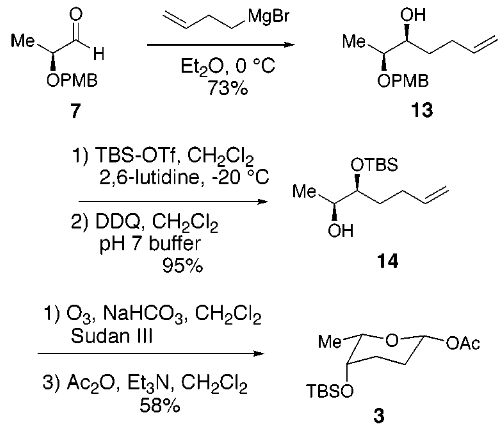
Scheme 4



A second route to **3** was also explored in which lactaldehyde derivative **7** was subjected to a chelate controlled reaction with 3-butenylmagnesium bromide.[36,37] Best results were obtained when this reaction was performed in Et_2O at 0 °C, and the diastereoselectivity of the reaction under these conditions was ca. 20:1. Protection of the major diastereomer **13** as a TBS ether and deprotection of the C(5)-PMB ether then gave **14** in high yield (Scheme 4). Finally, ozonolysis of **14** and acylation of the resulting mixture of hemiacetals provided L-rhodinosyl acetate **3** in 58% yield for the final two steps. Although this synthesis is one step shorter than the route that proceeds by way of **11**, the diastereoselectivity of the key carbonyl addition step is lower and the two isomers are difficult to separate especially on large scale. Consequently, this route was never scaled up to provide significant quantities of **3** for use in glycosylation studies.

In contrast to the numerous syntheses of rhodinose derivatives that have been developed, there are fewer reports of glycosidation reactions of rhodinosyl donors.[13,38−40] In an early example, Boeckman treated a protected rhodinosyl acetate with $BF_3{\cdot}OEt_2$ in pyrrolidine as solvent at 23 °C to afford a β-*N*-rhodinosyl pyrrolidine in 90% yield.[19] Schlessinger has reported the conversion of a rhodinose lactol to a β-hemiaminal in quantitative yield simply by stirring the lactol and amine in MeOH.[41] In his syntheses of the landomycin A hexasaccharide and a trisaccharide fragment of PI-080, Sulikowski used rhodinosyl tetrazoles to construct 2-deoxy-α-glycosidic linkages.[9,42] Rhodinose glycals have also been used as donors by Kirschning[43] and McDonald.[44] Kirschning activated the glycal with NIS in the presence of an acceptor to provide α-glycosides in good yields,[45,46] while McDonald activated the glycal with *p*-TsOH in the presence of an acceptor to afford α-glycosides in good yields.

To determine if the rhodinosyl acetate derivatives **3** and **10** would undergo highly stereoselective α-glycosidation reactions with a relatively hindered secondary hydroxyl acceptor,[38−40] we explored the reactions of **3** and **10** with glucopyranose **15**[47] (see Table 1). These reactions were performed at −78 °C typically in Et_2O using a slight excess of **15** (1.2−1.6 equiv). We initially used TES ether **10** as the glycosyl donor and TMS-OTf as the catalyst. However, as shown in the first entry of Table 1, a 52:36:12 mixture of three products was obtained in 41% yield when the reaction was performed in CH_2Cl_2/disaccharide **16a**, disaccharide **17** in which the C(4′)-hydroxyl had been deprotected under the reaction conditions, and trisaccharide **18a** resulting from glycosidation of the intermediate **17** (or **16a**) with a second equivalent of **10**. All three products had α-configurations at the new glycosidic centers. The ratio of products **16a**:**17**:**18a** improved to 77:11:12 when the reaction was performed in Et_2O, which presumably attenuates the Lewis acidity of the TMS-OTf catalyst (Table 1, entry 2). An improved product ratio of 86:10:4 was obtained for products **16a**, **17**, and **18a** when **10** was used as the donor with TES-OTf as the glycosidation catalyst (Table 1, entry 3). Unfortunately, these products were isolated in a lower combined yield (58%) under from this reaction.

These results established that the TES ether of **10** was too labile under the reaction conditions. Accordingly, we decided to employ the TBS-protected rhodinosyl acetate **3** instead. The TMS-OTf-promoted glycosidation of **3** and **15** still afforded three products: **16b**, **17**, and **18b**; but they were isolated in a combined yield of 65% and in a 94:3:3 ratio (Table 1, entry 4). We have previously used TBS-OTf as the promoter of glycosidation reactions of sensitive substrates,[48−50] in all cases taking advantage of the diminished Lewis acidity of this reagent compared to TMS-OTf to minimize production of unwanted side products (including trans-silylation of silyl ether protecting groups). We were surprised, therefore, that the ratio of products from the TBS-OTf-catalyzed glycosidation of **3** and **15** was reduced to 83:7:10 (Table 1, entry 6). However, use of TES-OTf as the Lewis acid provided the products in a 96:3:1 ratio and a combined yield of 68% (Table 1, entry 5).

In contemplating the synthesis of the landomycin A hexasaccharide, we initially considered the possibility that disaccharide **19**[51] could serve as the A−B (and A′B′) disaccharide unit. We hoped that the derived diol **20** could be selectively glycosylated at the C(3)-hydroxyl, since the electron withdrawing properties of the pyran ring oxygen should make the C(4)-hydroxyl less nucleophilic than the C(3)-hydroxyl. Accordingly, deprotection of the TBS ethers of disaccharide **19** using $Et_3N{\cdot}HF$ in CH_3CN at 65 °C gave diol **20** in 85% yield (Scheme 5). However, treatment of a mixture of diol **20** and TBS-protected rhodinosyl acetate **3** with TES-OTf (0.1 equiv) in Et_2O at −78 °C afforded a 70:30 mixture of the desired

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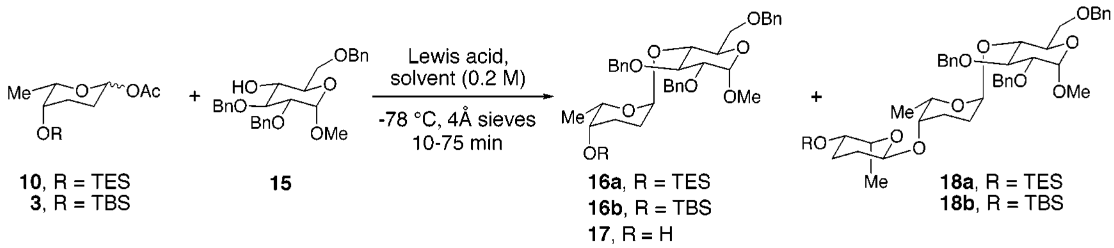
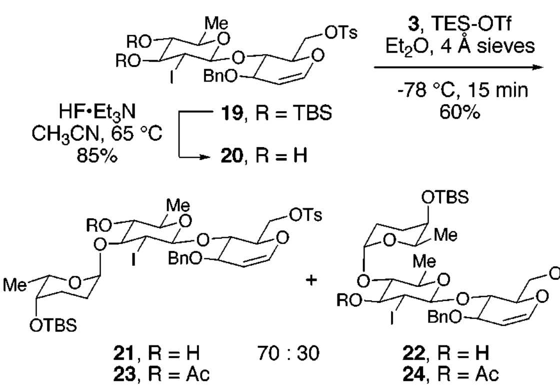
Table 1. Glycosidations of L-Rhodinosyl Acetates 3 and 10 with Acceptor 15



donor	15 (equiv)	Lewis acid	solvent	yield[a] (%)	product (ratio)[b] **16**:**17**:**18**
10	1.3	TMS-OTf (0.1 equiv)	CH_2Cl_2	41	52:36:12
10	1.6	TMS-OTf (0.1 equiv)	Et_2O	71	77:11:12
10	1.3	TES-OTf (0.2 equiv)	Et_2O	58	86:10:4
3	1.5	TMS-OTf (0.25 equiv)	Et_2O	65	94:3:3
3	1.5	TES-OTf (0.2 equiv)	Et_2O	68	96:3:1
3	1.2	TBS-OTf (0.2 equiv)	Et_2O	66	83:7:10

[a] Yield of products isolated by chromatography. [b] Glycosides **16a** and **18a** derive from reactions with **10** as the donor, whereas **16b** and **18b** were obtained from reactions in which **3** was the glycosyl donor.

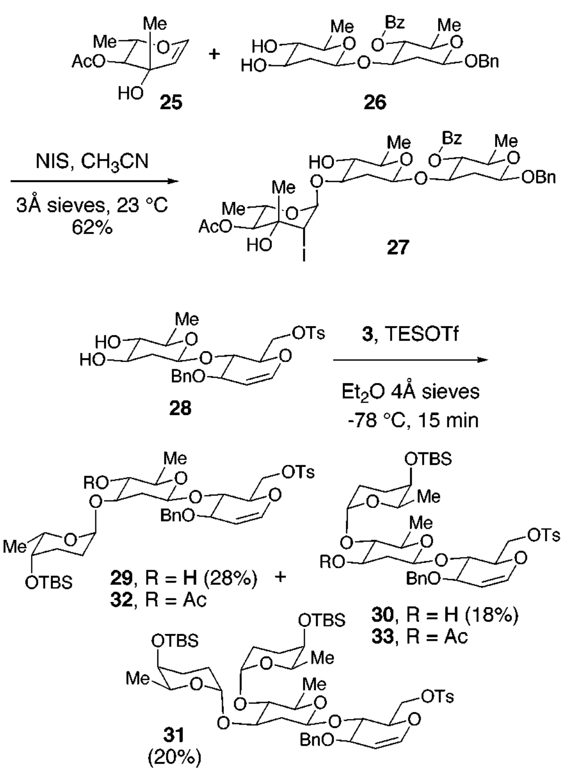
Scheme 5



α-1,3-trisaccharide **21** and the undesired α-1,4-trisaccharide **22** in a combined yield of 60%. Use of TBS-OTf as the Lewis acid under the same glycosidation conditions did not change the reaction regioselectivity. Lowering the reaction temperature to −100 °C with TES-OTf as catalyst also did not improve the selectivity of this experiment. The inter-glycosidic connectivities of **21** (δ 3.42 for H_3, δ 3.09 for H_4) and **22** (δ 3.61 for H_3, δ 3.04 for H_4) were established by acetylation of the free hydroxyl in each with Ac_2O in pyridine to afford the acetylated derivatives **23** (δ 3.77 for H_3, δ 4.71 for H_4) and **24** (δ 5.18 for H_3, δ 3.33 for H_4). The ^{1}H NMR data summarized here provide unequivocal confirmation of the connectivity of the new glycosidic bonds in **21** and **22**.

Because the regioselectivity of the glycosidation of **20** was poor, we decided to remove the C(2′)-iodide substituent so as to decrease the steric crowding of the C(3′)-hydroxyl group. This strategy seemed appropriate, since Thiem had demonstrated in his synthesis of the C−D−E trisaccharide unit of olivomycin A that glycosidation of diol **26** with glycal **25** provided trisaccharide **27** with glycosidation occurring exclusively on C(3)−OH (Scheme 6).[52] Accordingly, diol **28** was prepared in 52% yield by reduction of **20** with Bu_3SnH and AIBN in refluxing benzene.[53,54] However, TES-OTf-catalyzed glycosidation

Scheme 6



of diol **28** and rhodinosyl acetate **3** in Et_2O at −78 °C afforded three products: the desired α-1,3-trisaccharide **29** in 28% yield, the regioisomeric α-1,4-trisaccharide **30** in 18% yield, and tetrasaccharide **31** in 20% yield. Once again, the connectivity in **29** and **30** was determined by ^{1}H NMR analysis of the acetate derivatives prepared by acylation of the free hydroxyl groups. The structures of acetate derivative **32** [high-resolution FAB, calcd for

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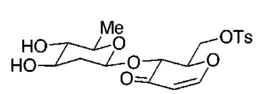
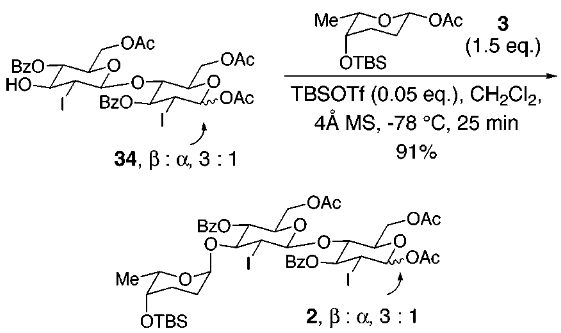
(54) The Bu_3SnH reduction of **20** was performed under standard conditions, and provided **28** in 52% yield. In addition, enone **i** was obtained in 30% yield.



i

Scheme 7



$C_{40}H_{58}O_{12}SSiNa$ $(M + Na)^+$ 813.3316, found 813.3318 *m/z*], acetate derivative **33** [high-resolution FAB, calcd for $C_{40}H_{58}O_{12}SSiNa$, $(M + Na)^+$ 813.3316, found 813.3282 *m/z*], and **31** [low resolution FAB spectrum for $C_{50}H_{80}O_{13}SSi_2Na$, $(M + Na)^+$ calcd 999, found 999 *m/z*] were also confirmed by mass spectral data.

It was apparent that the development of an efficient synthesis of the landomycin A repeat trisaccharide would require use of a fully differentially protected B (or B′) ring monosaccharide unit, such that the regioselectivity issues encountered in glycosidations of **20** and **28** would be avoided. Ultimately, this was accomplished by using disaccharide **34**,[8] a 3:1 mixture of anomers at the A ring glycosyl acetate, as the A−B disaccharide acceptor. Thus, treatment of **34** with 1.5 equiv of **3** and 0.05 equiv of TBS-OTf in CH_2Cl_2 at −78 °C in the presence of 4 Å molecular sieves provided the A−B−C repeat trisaccharide **2** in 91% yield (Scheme 7). The newly formed B−C glycosyl linkage to the rhodinose unit was exclusively α, and the 3:1 anomeric mixture in the A ring was unchanged. Disaccharide **34** was poorly soluble in Et_2O at −78 °C; consequently, we used CH_2Cl_2 for this reaction even though the preliminary studies (Table 1) suggested that these conditions would be less than optimal. It is also interesting to note that use of TBS-OTf (0.05 equiv) as the glycosidation promoter gave excellent results in this case, again in contrast to the results summarized in Table 1. Perhaps the excellent result in this case is due to the low catalyst loading and relatively short reaction time.

In summary, the examples presented here establish that the TBS-protected rhodinosyl acetate **3** is a highly reactive and highly stereoselective donor for synthesis of α-L-rhodinosyl glycosides. The best results have been obtained when TES−OTf or TBS−OTf are used as the glycosidation catalysts at −78 °C. Although it was not possible to achieve regioselective glycosidations of diols **20** and **28**, excellent results were obtained in the glycosidation of disaccharide **34**. Additional progress toward the synthesis of landomycin A and full details of our synthesis of hexasaccharide **1** will be reported separately.

Acknowledgment. We thank the National Institutes of Health (GM 38907) for financial support.

Supporting Information Available: Experimental details for synthesis of **3**, representative procedures for the glycosidation reactions, and ^1H NMR spectra of **2**α, **2**β, **3**, **6**, **10**α, **10**β, **36**, and **38**. This material is available free of charge via the Internet at http://pubs.acs.org.

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