New Synthetic Technology for the Stereocontrolled Construction of 1,1′-Disaccharides and 1,1′:1″,2-Trisaccharides. Synthesis of the FG Ring System of Everninomicin 13,384-1

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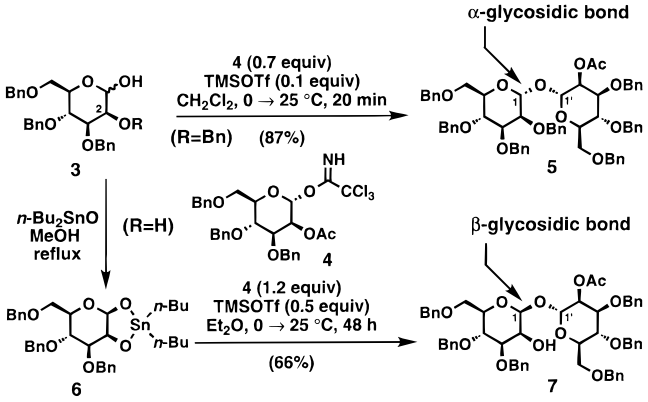
With its imposing molecular structure, everninomicin 13,384-1 (**1**, Figure 1) poses considerable challenge to the synthetic chemist. Isolated[1] from *Micromonospora carbonacea* var. *africana* (collected from the banks of the Nyiro river in Kenya), this antibiotic shows promising antibacterial properties against drug-resistant pathogens (e.g., methicillin-resistant *Staphylococci* and vancomycin-resistant *Streptococci* and *Enterococci*)[2] and, therefore, constitutes a unique opportunity for discovery and invention in the areas of chemical synthesis, biology, and medicine. Among its challenging features[3] are the 1,1′-disaccharide bridge, linking carbohydrate units F and G (see shaded area in Figure 1), its two orthoester frameworks, and its nitro sugar moiety. In this Communication we report new synthetic technology for the stereoselective construction of 1,1′-disaccharides[4] and 1,1′:1″,2-trisaccharides, and its application to the synthesis of the FG ring system (compound **2**, Scheme 3) of everninomicin 13,384-1 (**1**).

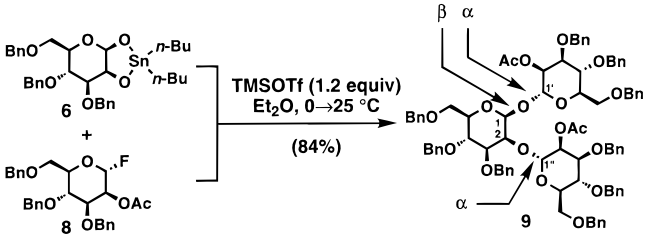
As expected[4i,j,l−p], the reaction of carbohydrate acceptor **3** (R = Bn, Scheme 1) with trichloroacetimidate donor **4** in the presence of TMSOTf led to the disaccharide **5** (87% yield) with the 1α,1′α-stereochemistry. This result calls attention to the problem of simultaneously controlling the stereochemistry at two anomeric centers while forming the glycosidic linkage of

Scheme 1. Stereoselective Construction of 1,1′-Disaccharides **5** and **7**[a]



[a] Bn = $PhCH_2$; TMSOTf = $Me_3SiOSO_2CF_3$.

Scheme 2. Stereocontrolled Construction of 1,1′;1″,2-Trisaccharide **9**



the FG ring system of everninomicin 13,384-1 (see shaded area in Figure 1 and compound **2**, Scheme 3). Compounding the challenge, one of the sugars is linked in a β-mannoside fashion. To circumvent this problem, the C-2 hydroxyl group in **3** (R = H) was utilized to fix the anomeric oxygen in the desired β-configuration via a five-membered ring stannane[5] (e.g., compound **6**, Scheme 1). Subsequent reaction with trichloroacetimidate **4** in the presence of TMSOTf resulted in the stereoselective formation of the 1β,1′α-disaccharide **7** (66% yield) with no trace of 1α,1′α-linked stereoisomer. More impressively, reaction of the corresponding glycosyl fluoride **8** (see Scheme 2 and Table 1) in excess (2.2 equiv) with stannane **6** led to trisaccharide **9** (84% yield), in which all three glycosidic bonds were formed stereoselectively.[6]

The generality of these glycosidation reactions was explored and selected results are shown in Table 1.[7] It was found that (a) both disaccharides and trisaccharides can be formed in stereocontrolled fashion, (b) trichloroacetimidate donors lead to good yields of disaccharides under the proper stoichiometry (entries 1, 5, 9, 13, and 15), and (c) glycosyl fluorides used in excess favor trisaccharide formation (entries 4, 8, 12, and 18).[8]

The application of the present technology to the stereocontrolled synthesis of FG ring system **2** of everninomicin

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(7) Coupling of tin acetal **6** with a variety of other donors and conditions (e.g., thioglycosides/DMTST,[6c] glycophosphates/TMSOTf) was also investigated but gave inferior yields. Moreover, fully acetylated imidates and fluorides were found to be inert under the applied reaction conditions.

(8) As expected, TMSOTf-induced coupling of imidate **4** with the tin acetal derived from 3,4,6-tri-*O*-benzyl-D-glucopyranose afforded a mixture of products consisting primarily of the corresponding 1α,1′α-disaccharide and the 2-*O*-substituted disaccharide in ca. 1:2 ratio.

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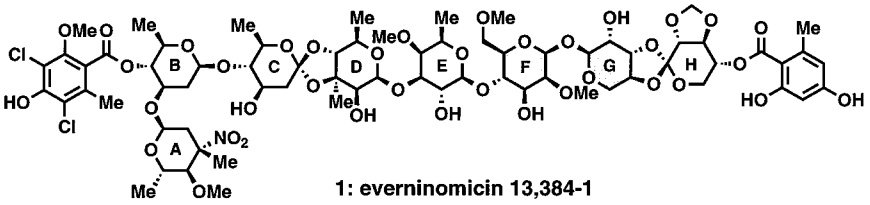


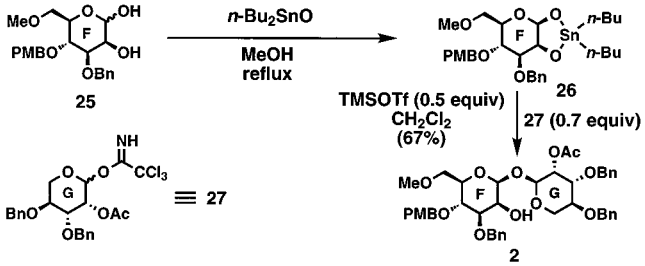
Figure 1. Structure of everninomicin 13,384-1. Rings F and G are shaded.

Table 1. Synthesis of β-Linked 1,1′-Disaccharides and 1,1′;1″,2-Trisaccharides[a]

Entry	Acceptor (equiv)	Donor	Solvent[b]	TMSOTf (equiv)[c]	Time (h)	Disaccharide (% Yield)[d]		Trisaccharide (% Yield)	
1	6 (1.5)	4: X=OC(NH)CCl$_3$	A	0.5	35		7 (66)		9 (9)
2	6 (0.45)	"	A	0.5	72		7 (-)		9 (-)
3	6 (1.5)	8: X=F	A	1.1	24		7 (10)		9 (70)
4	6 (0.45)	"	A	0.6	24		7 (-)		9 (84)
5	6 (1.5)	10: X=OC(NH)CCl$_3$	A	0.4	48		11 (68)		12 (-)
6	6 (0.45)	"	A	0.3	96		11 (22)		12 (47)
7	6 (1.5)	13: X=F	A	1.2	48		11 (64)		12 (-)
8	6 (0.45)	"	A	0.5	72		11 (23)		12 (32)
9	6 (1.5)	14: X=OC(NH)CCl$_3$	B	0.8	72		15 (57)		16 (22)
10	6 (0.45)	"	B	0.3	72		15 (58)		16 (14)
11	6 (1.5)	17: X=F	B	1.2	0.5		15 (59)		16 (5)
12	6 (0.45)	"	B	0.5	48		15 (-)		16 (33)
13	6 (1.5)	18: X=OC(NH)CCl$_3$	A	0.5	0.5		19 (72)		20 (8)
14	6 (1.5)	21: X=F	A	1.1	0.5		19 (70)		20 (12)
15	22 (1.5)	10 X=OC(NH)CCl$_3$	B	0.5	40		23 (58)		24 (-)
16	22 (0.45)	"	B	0.5	72		23 (-)		24 (-)
17	22 (1.5)	13: X=F	B	1.1	2		23 (52)		24 (9)
18	22 (0.45)	"	B	0.5	48		23 (7)		24 (11)

[a] All reactions were started at 0 °C and then allowed to proceed at ambient temperature for the indicated time. [b] Solvent system A=ether; B=ether:CH_2Cl_2, 3:1. [c] Based on donor. [d] Combined yield of disaccharide and its TMS derivative; removal of the TMS group was effected with PPTS in MeOH.

Scheme 3. Stereocontrolled Synthesis of FG Ring System **2** of Everninomicin 13,384-1[a]



[a] PMB = *p*-MeO-$C_6H_4CH_2$. Rings F and G are shaded.

13,384-1 (**1**) is shown in Scheme 3. Thus, conversion of the F-carbohydrate unit **25**[9] to its di-*n*-butylstannyl derivative **26** under standard conditions, followed by reaction with 0.7 equiv of ring G trichloroacetimidate donor **27**[9] in the presence of TMSOTf, furnished the desired 1β,1′α-disacccharide **2** in 67% yield as a single stereoisomer. The stereochemistry of the glycosidic linkages of compounds **5**, **7**, **9**, and **2** was assigned on the basis of the anomeric $^{13}C-^{1}H$ spin-coupling constants,[4m,10] measuring 174.1, 156.9, 151.2, and 159.1 Hz, respectively. Proof of anomeric configuration of the remaining substrates was found in the chemical shift of the mannose H-5 proton, typically appearing at $\delta \sim 3.4$ ppm for the β-linked glycoside.

The described chemistry is expected to find application in synthetic carbohydrate chemistry and facilitate a projected total synthesis of everninomicin 13,384-1 (**1**) and its congeners.[11]

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Supporting Information Available: Procedures for the preparation of the disaccharides and trisaccharides, schemes for the synthesis of compounds **25** and **27**, and a listing of selected data for compounds **2**, **5**, **7**, **9**, **11**, **12**, **13**α, **13**β, **15**, **16**, **18**α, **18**β, **19**, **20**, **23**−**25**, **27**, and **28** (21 pages). See any current masthead page for ordering and Internet access instructions.

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(9) For the preparation of this intermediate, see Supporting Information.

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(11) All new compounds exhibited satisfactory spectral and exact mass data.