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Brønsted Acid-Promoted Glycosylations of Disaccharide Glycal Substructures of the Saccharomicins

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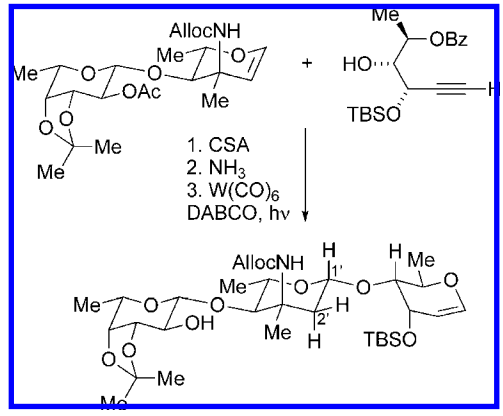
ABSTRACT



An acid-promoted glycosylation and alkynol cycloisomerization sequence provided direct access to the 2-deoxytrisaccharide corresponding to the fucose−saccharosamine−digitoxose substructure of saccharomicin B. In the course of this work, the absolute stereochemistry of the repeating fucose−saccharosamine disaccharide of saccharomicins was also confirmed.

The heptadecasaccharide antibiotics saccharomicins A and B were first isolated from the actinobacteria *Saccharothrix espanaensis* (Figure 1) and were found to have activity against a wide array of Gram-positive and Gram-negative bacteria. Cross resistance was not observed with many other antibiotics, including vancomycin, piperacillin, or ciprofloxacin.[1]

The saccharomicins possess several structural features of interest as synthetic targets. In addition to the 2-deoxysugar digitoxose (dig, Figure 1), the rare pyranosides saccharosamine (sac) and 4-*epi*-vancosamine (eva) are 2,6-dideoxysugars bearing 3-amino and 3-methyl substituents. On the basis of our earlier work that established the absolute stereochemistry of the terminal D-fucose (fuc-1) attached to the aglycon,[2] as well as a synthesis of saccharosamine glycal via tungsten-catalyzed alkynol cycloisomerization,[3] we now report the synthesis of a protected form of the fucose−saccharosamine disaccharide (**3**) present in several sectors of saccharomicins, specifically fuc-3/sac-2, fuc-5/sac-4, fuc-8/sac-7, and fuc-12/sac-11. In addition, we demonstrate the viability of Brønsted acid-promoted glycosylations to form 2-deoxyglycosides corresponding to the trisaccharides fuc-8/sac-7/rha-6 and the fuc-12/sac-11/rha-10 of saccharomicin A as well as fuc-12/sac-11/dig-10 of saccharomicin B.

(1) (a) Kong, F.; Zhao, N.; Siegel, M. M.; Janota, K.; Ashcroft, J. S.; Koehn, F. E.; Borders, D. B.; Carter, G. T. *J. Am. Chem. Soc.* **1998**, *120*, 13301. (b) Singh, M. P.; Petersen, P. J.; Weiss, W. J.; Kong, F.; Greenstein, M. *Antimicrob. Agents Chemother.* **2000**, *44*, 2154.

(2) Pletcher, J. M.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 4749.

(3) Cutchins, W. W.; McDonald, F. E. *Org. Lett.* **2002**, *4*, 749.

(4) (a) Schmidt, R. R.; Wegmann, B.; Jung, K.-H. *Liebigs Ann. Chem.* **1991**, 121. (b) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21.

(5) The identity of glycosides **6** and **7** was confirmed by X-ray crystallography (Supporting Information).

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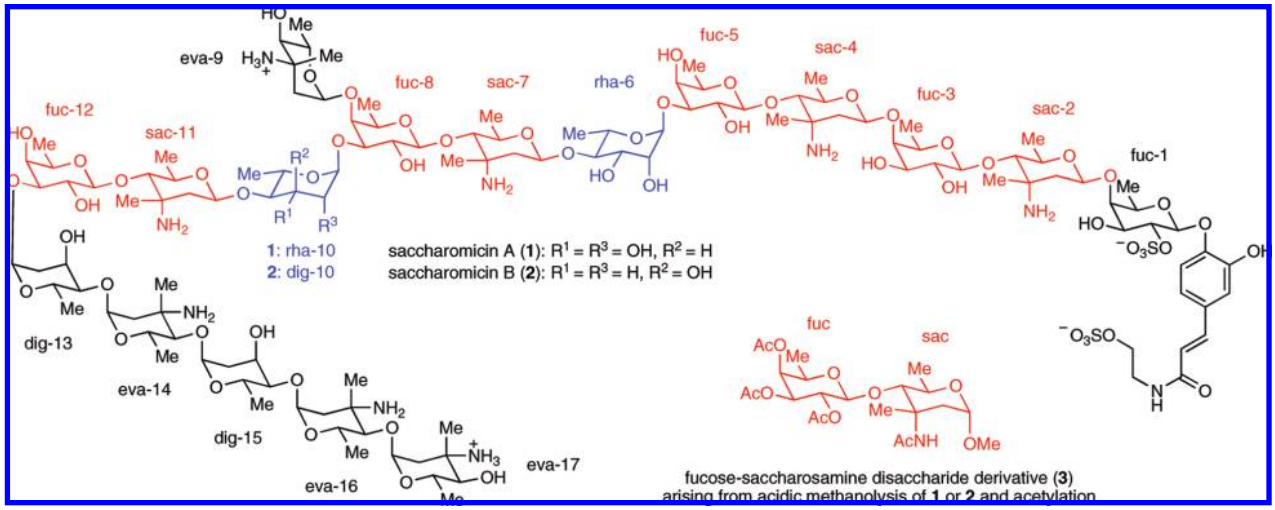
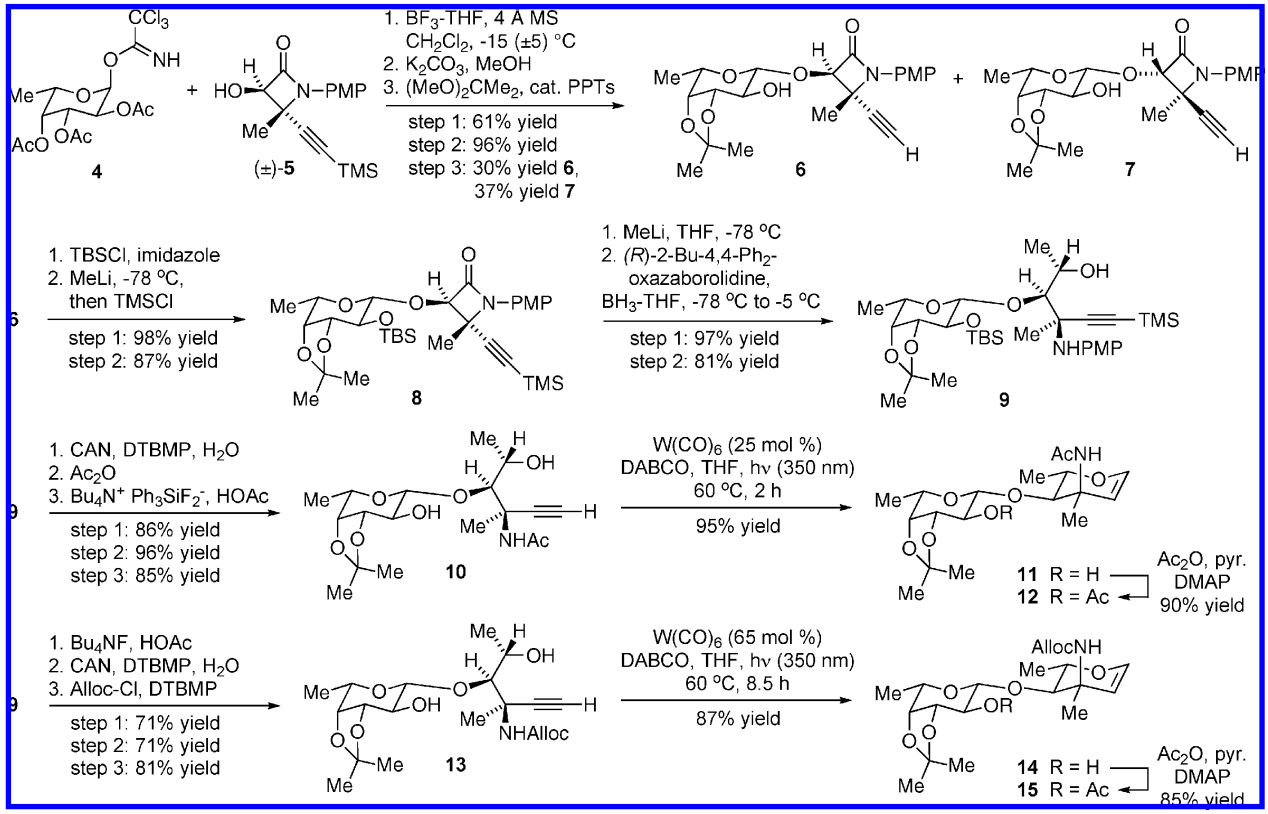


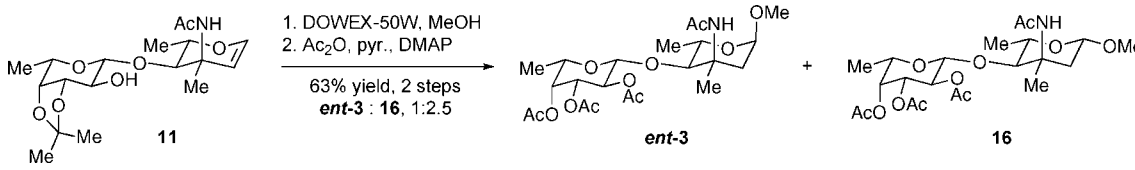
Figure 1. Saccharomicins A and B.

Although the stereochemistry of fucose-1 in saccharomicins was established as the D-isomer,[2] we chose to prepare fragments and develop methods based on the antipodal structures, due to the ready availability of L-fucose. Thus, our synthesis began with the resolution of racemic β-lactam **5** by glycosylation with the L-fucose-derived trichloroacetimidate **4** (Scheme 1).[4] The success of this transformation was particularly sensitive to temperature, so that temperatures below −45 °C favored orthoester formation, whereas temperatures above 0 °C produced a greater proportion of the α-glycoside anomers. After acetate ester removal and selective protection of the *cis*-diols as acetonide esters, the diastereomers **6** and **7** were chromatographically separated.[5]

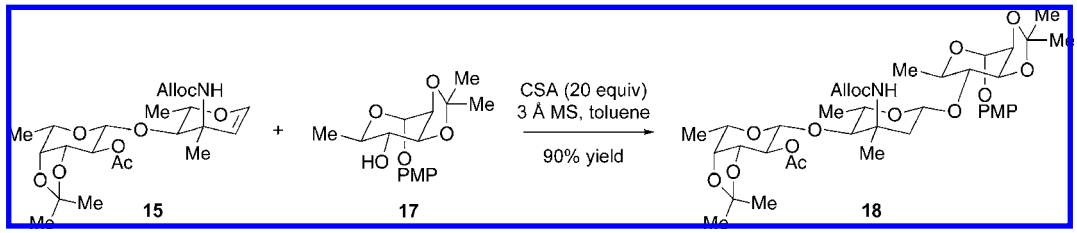
Scheme 1. Preparation of Fucose−Saccharosamine Disaccharide Glycals **11**−**12** and **14**−**15**



Scheme 2. Synthesis of Disaccharides *ent*-**3** and **16**



Scheme 3. Acid-Promoted Glycosylations of Disaccharide **15** with Rhamnose Acceptor **17**



The acidic protons of the fucosyl C2-hydroxyl and the terminal alkyne of compound **6** were protected to provide compound **8** bearing TBS ether and TMS−alkyne. From β-lactam **8**, sequential addition of methyl and hydride nucleophiles[3] afforded the secondary alcohol **9**, although stereoselective hydride addition was achieved only with the chiral oxazaborolidine reagent.[6,7] Two protocols for protective group manipulations were explored to diminish basicity of the nitrogen substituent for the alkynol cycloisomerization step. Originally, we first removed the *para*-methoxyphenyl (PMP) substituent from **9** and formed the acetamide, followed by desilylations with tetrabutylammonium difluorotriphenyl-silane and acetic acid.[8] Subsequently, we observed that desilylations proceeded more cleanly from compound **9**, followed by oxidative removal of the PMP substituent and N-acylation.

Tungsten-catalyzed alkynol cycloisomerization of compound **10** proceeded efficiently to afford the disaccharide glycal **11**, and O-acetylation of the fucosyl 2-hydroxyl gave compound **12**. With an eye to facile late-stage deprotection of the amino substituent, we also prepared substrate **13** bearing an *N*-allyloxycarbonyl (Alloc) protective group. In this case, the alkynol cycloisomerization reaction was noticeably slower, and a relatively high loading of tungsten carbonyl was required for complete conversion to the disaccharide glycal **14**. The *N*-Alloc alkene may have coordinated with tungsten carbonyl,[9] as *N*-benzyloxycarbonyl and *N*-butoxycarbonyl-protected substrates are considerably more reactive in alkynol cycloisomerizations.[3,10]

As the methyl glycoside of a peracetylated derivative of the fucose−saccharosamine disaccharide (**3**) had been reported as a degradation product arising from acidic methanolysis of saccharomicins, we sought to prepare the antipode of this compound to conclusively establish the absolute stereochemistry of the natural product-derived material.[1a] Acidic methanolysis of disaccharide glycal **11** was accompanied by acetonide removal, and acetylation of the hydroxyl groups of fucose provided a mixture of *ent*-**3** and the β-anomer, **16** (Scheme 2). After chromatographic separation of the anomers, the minor α-anomer *ent*-**3** matched the spectroscopic data provided for the antipode of this structure, thus confirming that the fucose and saccharosamine sugars in the repeating unit of the natural product saccharomicins both possessed D-stereochemistry.[11] Furthermore, the major β-anomer of **16** was also characterized by X-ray crystallography, thus unambiguously establishing the structure of our synthetic material.[12,13]

Having previously established a viable acid-catalyzed glycosylation of a disaccharide glycal in our synthesis of

(6) (a) Corey, E. J.; Bakshi, R. K. *Tetrahedron Lett.* **1990**, *31*, 611. (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(7) A variety of substrate-controlled reduction methods gave poor stereoselectivity; see Supporting Information for a summary of these results. The (*R*)-diastereomer was produced in approximately 5% yield in the oxazaborolidine reduction and was recycled by IBX oxidation to the methyl ketone.

(8) (a) Evans, C. M.; Kirby, A. J. *J. Chem. Soc., Perkin Trans. II* **1984**, 1269. (b) Hecker, S. J.; Heathcock, C. H. *J. Am. Chem. Soc.* **1986**, *108*, 4586. (c) Desilylation with tetrabutylammonium fluoride in the presence of acetic acid gave byproducts consistent with hydration of the alkyne, possibly from 5-*exo*-cyclization of the alkynyl alcohol and hydrolysis of the exocyclic enol ether, whereas the desilylation with tetrabutylammonium difluorotriphenylsilane afforded good yields of alkynyl alcohol **10**.

(9) (a) Barluenga, J.; Diéguez, A.; Rodríguez, F.; Fananás, F. J.; Sordo, T.; Campomanes, P. *Chem.—Eur. J.* **2005**, *11*, 5735. (b) Katz, T. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 3010. (c) Fuchibe, K.; Iwasawa, N. *Chem.—Eur. J.* **2003**, *9*, 905.

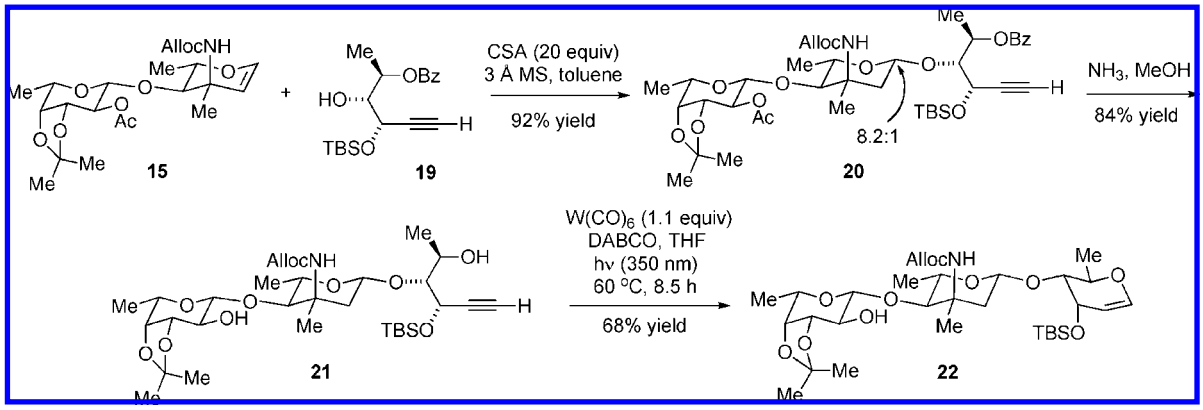
(10) Davidson, M. H.; McDonald, F. E. *Org. Lett.* **2004**, *6*, 1601.

(11) We thank Drs. Fangming Kong and Guy T. Carter (Wyeth Research) for providing ^{1}H and ^{13}C NMR spectra of compound **3** (Supporting Information).

(12) We thank Drs. Rui Cao and Kenneth I. Hardcastle (Emory University) for solving the crystal structure of compound **16** (Supporting Information).

(13) The L-fucosyl-D-saccharosamine diastereomer of **16** has also been prepared by a similar protocol beginning with compound **7** (Supporting Information).

Scheme 4. Acid-Promoted Glycosylation of Disaccharide **15** with Alkynyl Alcohol **19** and Cycloisomerization to Digitoxose-Terminated Trisaccharide **22**



digitoxin,[14] we explored the glycosylation of glycal **15** with the D-rhamnose acceptor **17**. In initial experiments, the yield of trisaccharide **18** was diminished by competitive hydration of the glycal due to adventitious water. However, excellent yields of **18** were obtained when the glycosylation was conducted in the presence of molecular sieves (Scheme 3). The optimized transformation required excess camphorsulfonic acid due to the mildly basic nature of the molecular sieves. Glycosylation occurred with complete stereoselectivity *trans* to the C3-acetamido substituent.[15]

Building on the concept of acyclic alkynyl alcohols as glycosyl acceptors,[14,16] we subsequently explored the glycosylation of disaccharide **15** with alkynyl alcohol **19** as the precursor to digitoxose (Scheme 4). In this case, the glycoside **20** was generated in excellent yield and with high stereoselectivity for the β-anomer. After removal of the ester protective groups, the alkynyl alcohol substrate **21** underwent cycloisomerization to the trisaccharide glycal **22**, although this transformation required stoichiometric tungsten carbonyl due to the *N*-Alloc substituent.

In summary, this work has confirmed the structure of the repeating fucose−saccharosamine disaccharide of saccharomicins and has provided insight into the viability of Brønsted acid-promoted glycosylations with this disaccharide to provide 2-deoxyglycoside trisaccharide substructures observed in the saccharomicins.

Acknowledgment. This work was initially supported by the National Institutes of Health, grant CA-59703.

Supporting Information Available: Experimental procedures and characterization and spectral data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) McDonald, F. E.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653.

(15) These results are consistent with anchimeric assistance from the *N*-carbonyl substituent at C3. For examples of glycosylations *trans*- to C3-ester substituents, see: (a) Tsai, T. Y. R.; Jin, H.; Wiesner, K. *Can. J. Chem.* **1984**, *62*, 1403. (b) Komarova, B. S.; Tsvetkov, Y. E.; Knivel, Y. A.; Zähringer, U.; Pier, G. B.; Nifantiev, N. E. *Tetrahedron Lett.* **2006**, *47*, 3583. (c) Chiba, S.; Kitamura, M.; Narasaka, K. *J. Am. Chem. Soc.* **2006**, *128*, 6931.

(16) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979.