

Synthesis of the Saccharomicin Fucose–Aglycon Conjugate and Determination of Absolute Configuration

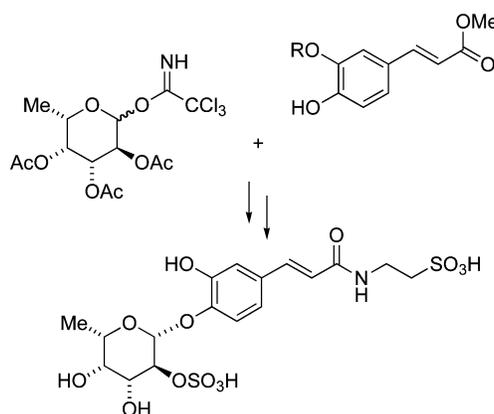
Joseph M. Pletcher and Frank E. McDonald*

Department of Chemistry, Emory University, Atlanta, Georgia 30322

fmcadona@emory.edu

Received August 15, 2005

ABSTRACT



Schmidt glycosylation of the appropriately protected 3,4-dihydroxycinnamate methyl ester with 2,3,4-triacetoxylfucopyranosyltrichloroacetimidate gives aryl glycoside in high yield and diastereoselectivity. 2-Sulfation of fucose, installation of taurine, and global deprotection of the remaining protecting groups affords the fucose–aglycon conjugate of saccharomicin. This synthesis which arises from L-fucose also establishes the absolute configuration of the reducing terminus of the saccharomicin oligosaccharide.

Saccharomicins A and B were isolated in 1998 by Kong and co-workers from the antibiotic complex designated LL-C19004, produced by the rare actinomycete *Saccharothrix espanaensis*.¹ This new class of antibiotics exhibits in vitro and in vivo antibacterial activity against a panel of pathogenic Gram-positive organisms, including strains of multiresistant staphylococci and enterococci bacteria.² The mechanism of action is currently unclear, but studies suggest that the saccharomicin oligosaccharide disrupts the bacterial cell membrane, allowing for intracellular potassium leakage and subsequent cell death. Although the saccharomicins have a small therapeutic window with regard to lethal dosage, the oligosaccharide backbone and its conformation appears to

be critical to the observed biological activity and may provide a template for the design of future therapeutics. Aside from the medicinal impetus for a study of the saccharomicins, their molecular architectures present a myriad of synthetic challenges worthy of exploration and an opportunity for development of new methods of chemical synthesis.

Chemical degradation and spectroscopic characterization were the primary techniques used for structural elucidation of saccharomicins A and B, revealing connectivity patterns and relative configurations of all 17 sugars. However, the absolute stereochemistry of each monosaccharide unit was arbitrarily assigned based on their most abundant natural forms and remains ambiguous. As a starting point, we sought to synthesize the reported structures of degradation products and compare their optical rotations to the naturally derived materials, thereby providing information vital to the pursuit of a stereoselective total synthesis.

(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) Shi, S. D.-H.; Hendrickson, C. L.; Marshall, A. G.; Siegel, M. M.; Kong, F.; Carter, G. T. *J. Am. Soc. Mass. Spectrom.* **1999**, *10*, 1285.

(2) Singh, M. P.; Petersen, P. J.; Weiss, W. J.; Kong, F.; Greenstein, M. *Antimicrob. Agents Chemother.* **2000**, *44*, 2154.

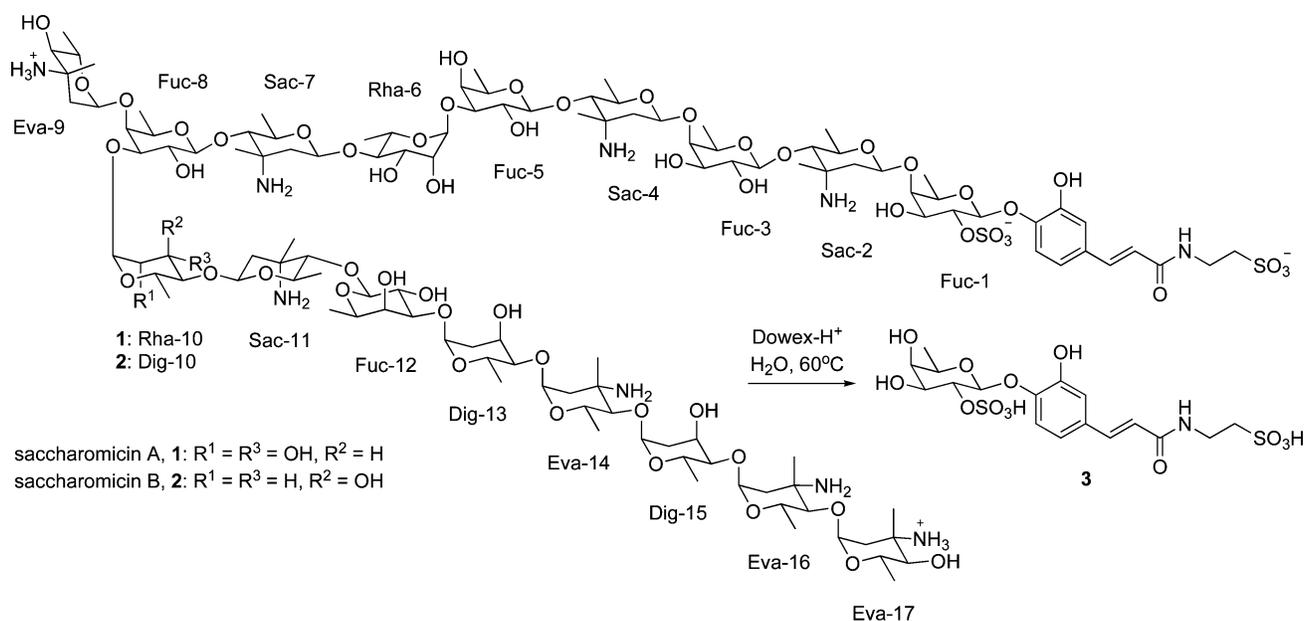


Figure 1. Structures of saccharomicins A and B (**1**, **2**) and the fucose–aglycon conjugate **3** from mild acidic hydrolysis.

The fucose–aglycon conjugate (**3**) (Figure 1) was one of two UV-active degradation products isolated from mild acid hydrolysis, and although Kong and co-workers assigned a D-configuration to the fucose, for convenience we chose to prepare the antipode *ent*-**3**, containing readily available L-fucose. The fucose–aglycon β -linkage led us to envision a stereoselective glycosylation between an activated fucosyl donor and a selectively protected cinnamic acid derivative. Strategic protective group manipulations would then permit selective installation of the 2'-sulfate and taurine moieties of the degradation product **3**.

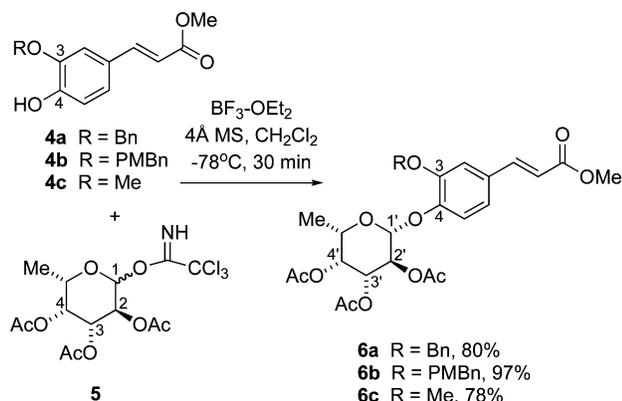
Stereoselective glycosylations of several 3-protected derivatives of 3,4-dihydroxycinnamate methyl ester **4**³ were accomplished with the 2,3,4-tri-*O*-acetyl L-fucosyl trichloroacetimidate **5**⁴ to give good yields of the β -fucosides **6** (Scheme 1). By way of contrast, the 1,2-glycal epoxide from dimethyldioxirane epoxidation of 3,4-bis-*O*-TBS-fucal af-

forded the undesired α -glycoside as the major product under a variety of conditions,⁵ consistent with precedents involving glycosylation of phenols with glycal epoxides.⁶ We also observed that the 3,4-acetonide-protected analogue of **5** was unreactive to glycosylation with phenolic nucleophile **4c**.

As removal of the methyl ether of **6c** ($R = \text{Me}$) was difficult to achieve in the presence of the glycosidic linkage, the majority of our successful efforts stemmed from the benzylic ether-protected glycosides **6a,b**. Removal of acetate protective groups and acid-catalyzed reaction of the resulting triols with 2,2-dimethoxypropane⁷ afforded regioselective protection of the *cis*-3' and 4'-hydroxyls in **7a,b** (Scheme 2). The remaining hydroxyl substituent at C2' was then converted into the sulfate esters **8a,b** in excellent yield.

In the course of our synthetic work, we were concerned about the eventual removal of protective groups in the presence of potentially sensitive functional groups. We were pleased to observe that the acetonide protective group could be removed by acidic hydrolysis at several stages of this synthesis. Although *p*-toluenesulfonic acid-catalyzed deprotection of **8a** gave a 37% yield of **9** (accompanied with byproducts resulting from hydrolysis of sulfate ester and/or glycoside), Dowex 50WX8 ion-exchange resin provided a 74% isolated yield of **9**. However, deprotection of the benzylic

Scheme 1. Synthesis of Phenolic Fucosides **6**



(3) (a) Compounds **4a** and **4b** were prepared by Wadsworth–Emmons olefination of the corresponding 3-protected derivative of 3,4-dihydroxybenzaldehyde (see the Supporting Information). (b) **4c**: Gu, W.; Jing, X.; Pan, X.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron Lett.* **2000**, *41*, 6079.

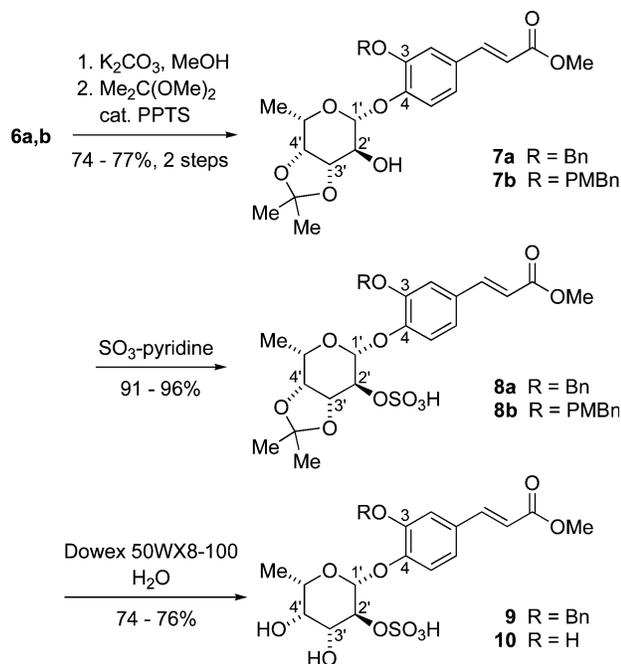
(4) (a) Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21. (b) Jiang, Z.-H.; Schmidt, R. R. *Liebigs Ann. Chem.* **1992**, *9*, 975.

(5) This unpublished work was conducted by Dr. Minglang Wu.

(6) Chiappe, C.; LoMoro, G.; Munforte, P. *Tetrahedron* **1997**, *53*, 10471.

(7) For acetonide protection in the presence of an aryl PMB-ether, see: Trost, B. M.; Dudash, J., Jr.; Dirat, O. *Chem. Eur. J.* **2002**, *8*, 259.

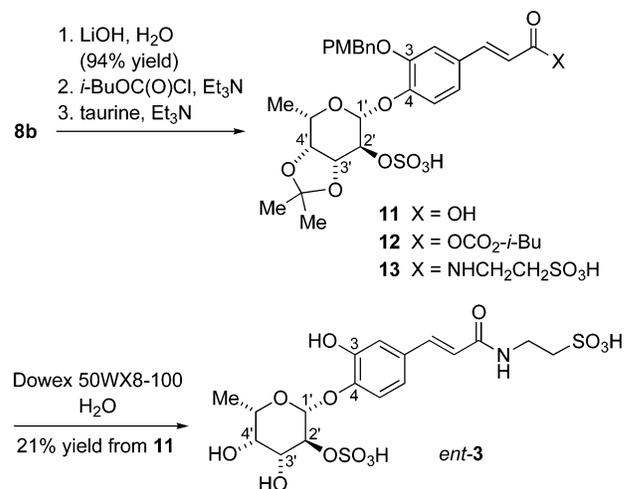
Scheme 2. Protective Group Studies Associated with Regioselective Introduction of Sulfate Ester



ether of **8a** or **9** was much more difficult. Despite precedents which suggested that selective removal of the benzyl ether might be achieved under transfer hydrogenation conditions,⁸ all attempts at reductive debenzoylation resulted in concomitant saturation of the conjugated alkene functionality. Other procedures for deprotection of benzyl ethers such as FeCl_3 ⁹ were incompatible with the glycosidic linkage. Fortunately, the *p*-methoxybenzyl (PMBn) ether **8b** was acid labile and could be cleanly deprotected at the same time as the removal of the acetonide to provide **10** in 76% isolated yield, without significant cleavage of the glycosidic linkage or sulfate ester.

Thus, the synthesis was successfully completed from the PMBn-protected glycoside **8b**, which was converted into the carboxylic acid **11** by basic hydrolysis of the methyl ester (Scheme 3). The taurine amide was then introduced by employing the intermediacy of an isobutyl mixed anhydride **12**^{10,11} to provide **13**. This synthetic intermediate was difficult to purify from triethylammonium salts, but subsequent treatment with Dowex 50WX8 in water at room-temperature affected removal of both the acetonide and PMBn protecting groups to afford the saccharomicin fucose-aglycon conjugate, as the L-enantiomer (*ent*-**3**). The modest yield of *ent*-**3** is attributed to incomplete formation and/or

Scheme 3. Introduction of Taurine and Removal of Protective Groups



partial hydrolysis of mixed anhydride **12**, as some of the carboxylic acid **11** was recovered albeit contaminated with triethylammonium salts. Compound *ent*-**3** was obtained pure after C_{18} silica gel chromatography with slow elution $\text{H}_2\text{O}/\text{MeOH}$ (9:1) and gives identical ^1H and ^{13}C NMR spectra when compared to the naturally derived fucose-aglycon conjugate.¹²

Optical rotation of the synthetic fucose-aglycon conjugate *ent*-**3** derived from L-fucose gave a positive sign of rotation: $[\alpha]_{\text{D}} = +63$ (*c* 0.22 in MeOH); $[\alpha]_{\text{D}} = +53$ (*c* 0.26 in H_2O), whereas that of the naturally derived material was $[\alpha]_{\text{D}} = -60.1$ (*c* 0.052 in H_2O),¹³ indicating an absolute configuration of D-fucose in the saccharomicins. While D-fucose is considerably more expensive than L-fucose, we note that D-fucose glycal can be easily prepared using alkynyl alcohol cycloisomerization methodology¹⁴ and can likely be incorporated in a projected synthesis of saccharomicin oligosaccharides.

In conclusion, we have completed a short synthesis of the fucose-aglycon substructure of saccharomicins, which compares favorably to the enantiomer of compound **3** arising from acid-catalyzed degradation of saccharomicins.

Acknowledgment. We thank the National Institutes of Health (CA 59703) for support of this research. We also acknowledge use of shared instrumentation provided by grants from the National Institutes of Health, National Science Foundation, and the Georgia Research Alliance

(8) (a) Felix, A. M.; Heimer, E. P.; Lambros, T. J.; Tzougraki, C.; Meienhofer, J. *J. Org. Chem.* **1978**, *21*, 4194. (b) Knapp, S.; Nandan, S. R. *J. Org. Chem.* **1994**, *59*, 281. (c) Kawada, T.; Asano, R.; Hayashida, S.; Sakuno, T. *J. Org. Chem.* **1999**, *64*, 9268.

(9) (a) Park, M. H.; Takeda, R.; Nakanishi, K. *Tetrahedron Lett.* **1987**, *28*, 3823. (b) Rodebaugh, R.; Debenham, J. S.; Fraser-Reid, B. *Tetrahedron Lett.* **1996**, *37*, 5477.

(10) Lebel, H.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *63*, 9624.

(11) Attempted introduction of taurine by other methods, such as dehydrative carbodiimide coupling of the carboxylic acid or acylation of the corresponding acid chloride, were unsuccessful.

(12) We thank Dr. Fangming Kong (Wyeth Research) for providing ^1H and ^{13}C NMR spectra of **3**.

(13) The optical rotation data (unpublished) was graciously provided by Dr. Fangming Kong. In a private communication, he notes some uncertainty with the magnitude of the rotations measured in his work, but the sign of the rotation of **3** derived from naturally occurring saccharomicin is consistently negative.

(14) (a) McDonald, F. E.; Reddy, K. S.; Díaz, Y. *J. Am. Chem. Soc.* **2000**, *122*, 4304. (b) McDonald, F. E.; Reddy, K. S. *Angew. Chem., Int. Ed.* **2001**, *40*, 3653. (c) McDonald, F. E.; Wu, M. *Org. Lett.* **2002**, *4*, 3979. (d) Koo, B.; McDonald, F. E. *Org. Lett.* **2005**, *7*, 3621.

(NMR spectroscopy, mass spectrometry) as well as the University Research Committee of Emory University (polarimeter). We are particularly appreciative to Dr. Fangming Kong (Wyeth Research) for providing copies of NMR spectra and unpublished data regarding the optical rotation of compound **3**.

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

OL051971S