Studies on the Synthesis of Aureolic Acid Antibiotics: Acyloin Glycosidation Studies

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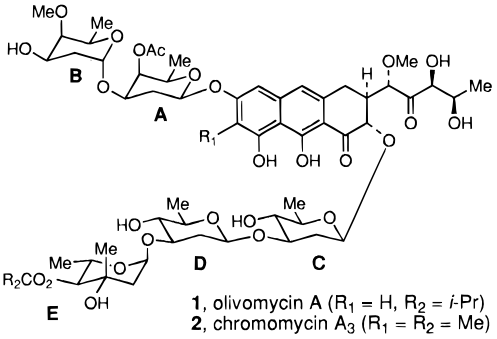
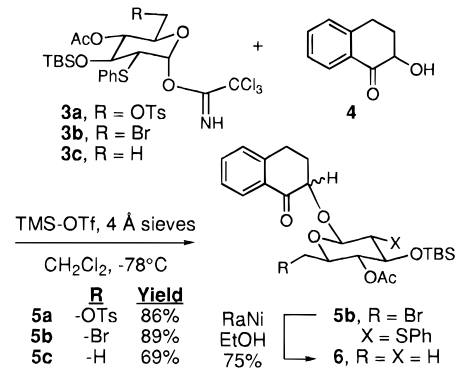
Several recent reports have detailed our progress toward the total synthesis of olivomycin A, a representative member of the aureolic acid family of antitumor antibiotics.[1,2] We have developed highly stereoselective syntheses of the aglycon, olivin,[3] the A−B disaccharide,[4] and the C−D−E trisaccharide.[5] We have also demonstrated that the Mitsunobu glycosidation protocol is suitable for coupling of the A−B disaccharide to the C(6)-phenol of advanced synthetic intermediates.[4] We report herein studies on the remaining problem, namely the glycosidation of the aglycone C(2)-acyloin unit.

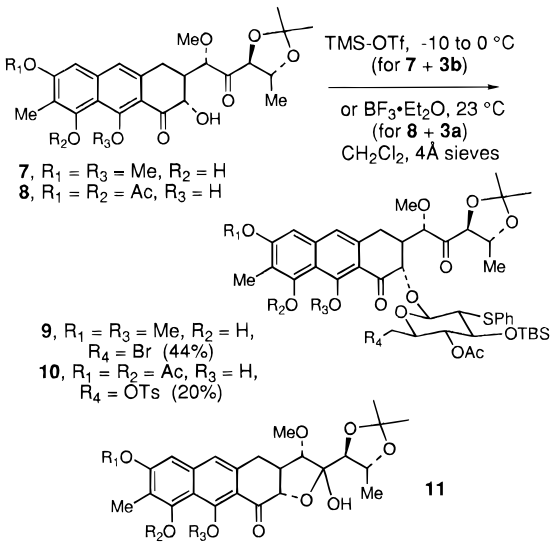


Several studies on the synthesis of 2-deoxyglycosides of acyloins have been reported.[6−9] Franck has demonstrated that the electrophilic addition reactions of glycals with the naphthylsulfenate ester of 2-hydroxytetralone, or with 2-hydroxytetralone in the presence of arylbis-(arylthio)sulfonium salts, provide the desired β-glycosides with excellent selectivity.[7,8] More recently, Ikegami has shown that the reaction of 2-hydroxytetralone with 2-(arylthio)-α-D-glucosyl tetramethylphosphoramidates is highly selective for the β-glycosidic product.[9] Franck also cites unpublished work from Thiem's laboratory in which a modified Koenigs−Knorr glycosidation of a 2-bromo-2-deoxyglucose unit with the C(2) acyloin of an olivin derivative provides the β-glycoside in 21% yield.[10]

We began by exploring the reactions of racemic 2-hydroxytetralone **4** with 2-(phenylthio)glucosyl imidates **3a**−**3c**.[5,11] In all three cases, a ca. 1:1 mixture of diastereomeric β-anomers **5** was obtained in good (**5c**) to excellent (**5a**, **5b**) yield, with α-anomers not being detected. One of the diastereomers of **5b** (R = Br) was smoothly elaborated to the 2,6-dideoxyglycoside **6** upon treatment with RaNi in EtOH (75% yield).



We next examined the glycosidation reactions of chromomycinone derivatives **7**[12] and **8**.[13] In the event, treatment of **7** with 1.8 equiv of imidate **3b** in the presence of TMSOTf at −10 to 0 °C provided a ca. 15:1 mixture of β- and α-glycosides in 44% yield, with the desired β-anomer **9** predominating. The reaction of chromomycinone diacetate derivative **8** with **3a** in the presence of $BF_3{\cdot}Et_2O$ was similarly selective for the β-anomer **10**; however, the yield in this case was only 20%. The efficiency of these glycosidations is hampered by steric hindrance of the 2-hydroxy group and by the fact that especially **8** exists as a mixture with the hemiketal isomer **11** (**8**:**11** = 50:50 in CD_3CN; 75:25 in $CDCl_3$; 90:10 in toluene-d_8 at 20 °C). We anticipate that the efficiency of these glycosidations will be improved by using aglycon derivatives with the side chain C(2′) ketone masked as an alcohol derivative.



Encouraged by these results, we initiated glycosidation studies using the fully elaborated C−D−E-trisaccharide imidate **13**. Treatment of C−D−E glycal **12**[14] with PhSCl

(1) Remers, W. A.; Iyengar, B. S. In *Cancer Chemotherapeutic Agents*; Foye, W. O., Ed.; American Chemical Society: Washington, DC, 1995; p 578.
(2) Leading references to the work of Weinreb, Franck, Thiem, Binkley, Crich, and Toshima, who have made important contributions to the synthesis of the aureolic acid antibiotics, are provided in ref 4.
(3) Roush, W. R.; Murphy, M. *J. Org. Chem.* **1992**, *57*, 6622.
(4) Roush, W. R.; Lin, X.-F. *J. Am. Chem. Soc.* **1995**, *117*, 2236 and references cited therein.
(5) Sebesta, D. P.; Roush, W. R. *J. Org. Chem.* **1992**, *57*, 4799.
(6) Thiem, J.; Gerken, M.; Snatzke, G. *Liebigs Ann. Chem.* **1983**, 448.
(7) Ramesh, S.; Franck, R. W. *J. Chem. Soc., Chem. Commun.* **1989**, 960.
(8) Grewal, G.; Kaila, N.; Franck, R. W. *J. Org. Chem.* **1992**, *57*, 2084.
(9) Hashimoto, S.; Yanagiya, Y.; Honda, T.; Ikegami, S. *Chem. Lett.* **1992**, 1511.
(10) See footnote 4b in ref 7 and ref 7 in: Ramish, S.; Kaila, N.; Grewal, G.; Franck, R. W. *J. Org. Chem.* **1990**, *55*, 5.
(11) Preuss, R.; Schmidt, R. R. *Synthesis* **1988**, 694.
(12) Miyamoto, M.; Morita, K.; Kawamatsu, Y.; Noguchi, S.; Marumoto, R.; Sasai, M.; Nohara, A.; Nakadaira, Y.; Lin, Y. Y.; Nakanishi, K. *Tetrahedron* **1966**, *22*, 2761.
(13) Chromomycinone derivative **8** was synthesized by treatment of chromomycinone acetonide[12] with 2 equiv of AcCl and 2.2 equiv of DBU in CH_2Cl_2.

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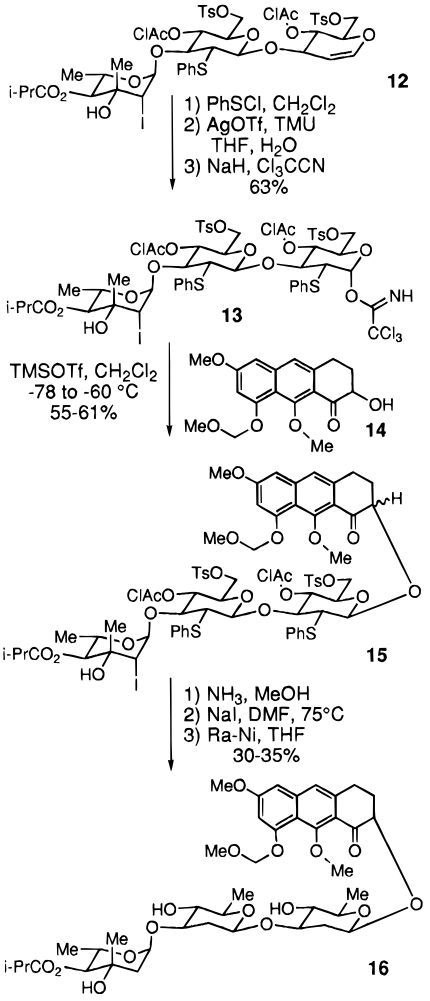
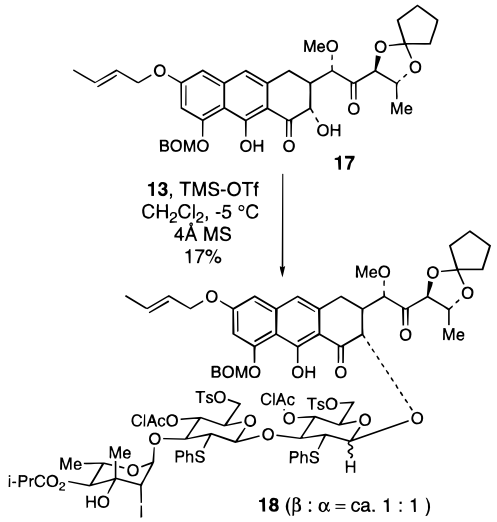
followed by hydrolysis of the anomeric chlorides (AgOTf, tetramethylurea, THF, H_2O) and activation of the resulting pyranose by treatment with excess NaH and Cl_3CCN (as solvent) provided imidate **13** in 63% overall yield.[11] Treatment of racemic acyloin **14**[15] (2 equiv) with **13** (1 equiv) in CH_2Cl_2 at −78 to −60 °C in the presence of TMS−OTf (0.2 equiv) and 4 Å molecular sieves then provided β-glycoside **15** in 55−61% yield as a ca. 1.4:1 mixture of epimers at C(2) of the aglycon; α-glycosides were not detected. The C(2) epimers were separated chromatographically, and each was individually elaborated to the respective epimers of **16** by sequential



treatment with 2 M NH_3 in MeOH to remove the two chloroacetyl groups, NaI in DMF to displace the two tosylate groups, and finally Ra-Ni in THF to reductively remove the three iodo and the two phenylthio substituents. There was no evidence of epimerization of C(2) during this sequence. The overall yield of **16** was 30−35% from **15**.

We have also demonstrated that glycosidation of synthetic aglycon **17** with trisaccharide imidate **13** (1.8 equiv) at −5 °C provides **18** in 17% yield as a ca. 1:1 mixture of β and α anomers. Efforts to improve the stereoselectivity and efficiency of this coupling are underway.[16]



In summary, we have established that the reactions of acyloins **4**, **7**, **8**, and **14** and 2-(arylthio)-α-D-glucosyl trichloroacetimidates **3** and **13** give β-glycosides with excellent diastereoselectivity. The first glycosidation of an aureolic acid aglycon with an intact C−D−E trisaccharide has also been accomplished. Further progress toward the completion of an olivomycin total synthesis will be reported in due course.

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Supporting Information Available: Experimental procedures and characterization data for all new compounds (58 pages).

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(14) Trisaccharide **12** with chloroacetate groups in the C and D residues was synthesized by using appropriate modifications of our published procedure (ref 5); details of the synthesis of **12** are provided in the Supporting Information. Acetate protecting groups in the C and D residues could not be removed selectively in the presence of the isobutyrate in the E residue.

(15) Details of the synthesis of acyloin **14** are provided in the supporting information.

(16) Glycosidation (**13**, TMSOTf, −40 to −10 °C) of an analog of aglycon **17** with the C(2′) carbonyl replaced by a 2′-(R)-OAc unit provided a 1:1 mixture of α and β trisaccharide derivatives in 35% yield. However, at −78 °C the β isomer was obtained with good selectivity (ca. 10−15% yield). Glycosidation of **7** with **13** ($BF_3{\cdot}Et_2O$, CH_2Cl_2, −5 to 23 °C, 4 Å sieves) gave the β-trisaccharide conjugate in ca. 10% yield, while attempted glycosidations of **8** with **13** were unsuccessful.