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Synthesis of Naphthyl A-B Disaccharides Corresponding to Olivomycin A and Mithramycin

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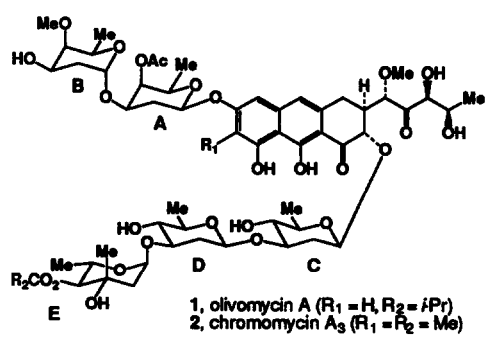
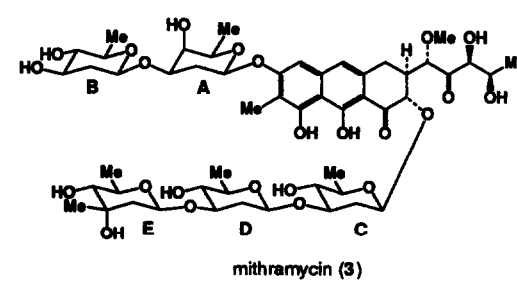
Abstract. Highly stereoselective syntheses of naphthyl disaccharides 4 and 5, which correspond to the A-B disaccharide units of olivomycin A and mithramycin, are described.

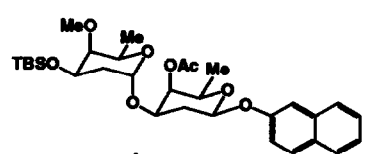
Olivomycin A (**1**), chromomycin A_3 (**2**) and mithramycin (**3**) are the most well known members of the aureolic acid antitumor antibiotic family.[1] In the presence of Mg^{+2} ions, the aureolic acids bind as 2 : 1 antibiotic : Mg^{+2} complexes in the DNA minor groove with selectivity for GC rich sequences.[2] While the aureolic acids have been used as chemotherapeutic agents, they are highly toxic and have found limited application except in severe cases.[1] With the goal of developing less toxic analogs and understanding the role of the oligosaccharides in the DNA binding event, several groups have focused on the synthesis of these challenging targets.[3] Thus far, our synthesis of olivin is the only approach that provides an aglycone in fully deprotected form.[3,4] Concerning the oligosaccharides, Thiem has reported pioneering syntheses of the A-B disaccharides and C-D-E trisaccharides of **1**-**3**.[5] Binkley, Franck, and Crich have also made important contributions towards the synthesis of these substructures.[6] We have reported syntheses of the olivomycin A-B disaccharide[7] and the C-D-E trisaccharide,[8] and have also developed a highly stereoselective procedure for the synthesis of β-aryl-2-deoxy-glycosides (the linkage that occurs between the A-B disaccharides and the aglycones) via the Mitsunobu reaction.[9,10] In continuation of our work on the total synthesis of these antibiotics,[4,7-9] we report herein highly stereoselective syntheses of olivomycin A and mithramycin model A-B disaccharides **4** and **5**. Notably, these syntheses proceed by way of the reducing A-B disaccharides (**11** and **15**) that are properly functionalized for coupling with advanced aglycone synthetic intermediates.[4b]



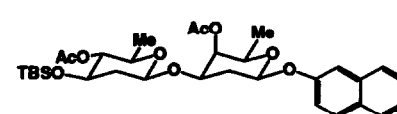
1, olivomycin A (R_1 = H, R_2 = *i*Pr)
2, chromomycin A_3 (R_1 = R_2 = Me)



mithramycin (3)

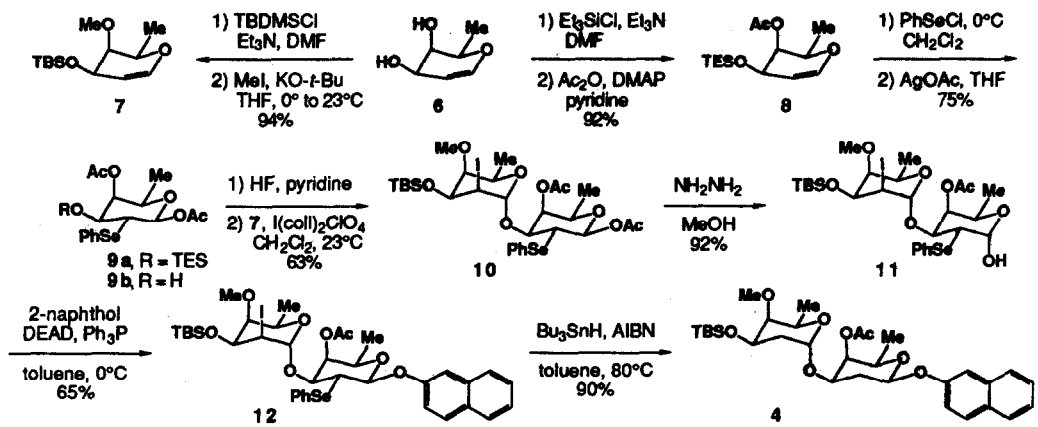


4



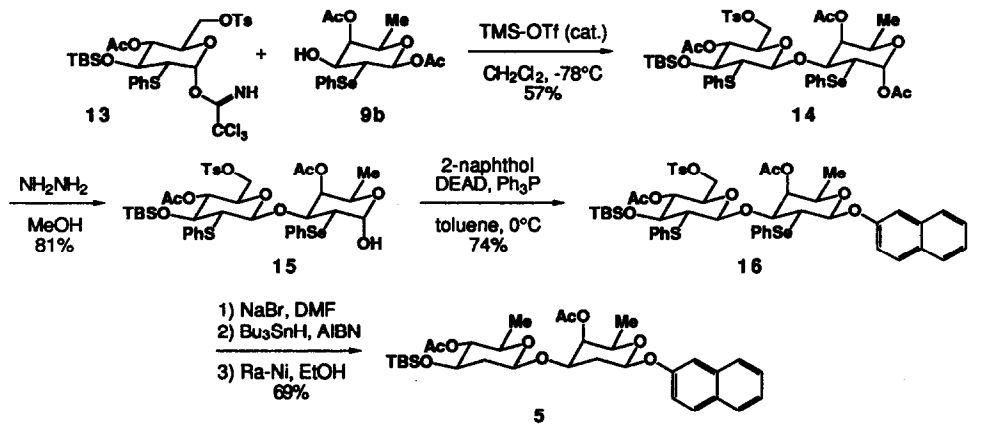
5

These syntheses were undertaken with the knowledge that construction of the aryl β-glycosidic linkage via the Mitsunobu procedure requires the presence of a thiophenyl or selenophenyl substituent at C(2) of the pyranose donor.[9,10] Unfortunately, we were not able to devise an efficient protocol for functionalizing C(2) of the 2,6-dideoxy-*lyxo*-hexose intermediates that we used in our first synthesis of the olivomycin A-B disaccharide.[7] We therefore elected to use readily available D-fucal (**6**) as the starting material in the syntheses of **4** and **5** reported herein.[11] Thus, selective mono-silylation of **6** (1.2 equiv. TBDMS-Cl, Et_3N, DMF) followed by methylation of the axial hydroxyl group (KO-*t*-Bu, MeI, THF, 23°C) provided glycal **7**,[12a,b] a precursor to the B residue of **4**, in 94% overall yield. Alternatively, **6** was elaborated into glycal **8**,[12a,b] a precursor to the A residues of **4** and **5**, in 92% overall yield by protection as a mono TES ether (1.1 equiv. Et_3SiCl, Et_3N, DMF) and acylation of the axial hydroxyl group (Ac_2O, DMAP, Et_3N, CH_2Cl_2). It should be noted that the same silyl protecting group could not be used for **7** and **8** since a TES group in the B residue (**7**) is incompatible with chemistry planned for completion of the synthesis, while a TBDMS group could not be removed at the stage of **9** without competitive migration of the acetyl group from C(4) to C(3). A more significant problem concerned the definition of a suitable strategy for differentiating the glycal units of **7** and **8** in such a way that **8** also emerged in a form suitable for use in the subsequent Mitsunobu glycosidation reaction.[13] This was accomplished by treating **8** with PhSeCl (1.5 equiv.) in CH_2Cl_2 at 0°C followed by AgOAc (3 equiv.) in THF, which provided the *galacto* 2-phenylseleno acetate **9a**[12a,b] in 75% overall yield.[14] Removal of the TES protecting group by treatment of **9a** with excess HF-pyridine in THF provided alcohol **9b**[12a] (88% yield) which was coupled with **7** (1.5 equiv.) by using $I(coll)_2ClO_4$ (1.5 equiv.) in CH_2Cl_2 at 0° to 23°C over 8 h.[15] This reaction provided **10**[12a,b] in 72% yield (63% from **9a**) along with 6% of an isomer with an equatorial iodide in the B residue. Selective cleavage of the anomeric acetate was accomplished by treating **10** with 1.6 equiv. of hydrazine in MeOH at 23°C overnight, thereby providing **11**[12a,b] in 92% yield.[16] This intermediate exists predominantly (≥8 : 1) as the α,α anomer by ^1H NMR analysis. The Mitsunobu coupling[9] of **11** and 2-naphthol (1.2 equiv.) then provided the aryl β-glycoside **12**[12a,b] in 65% yield along with 4% of the α,α-anomer which was separated chromatographically (11 : 1 selectivity by ^1H NMR analysis). Finally, reductive removal (Bu_3SnH, AIBN, toluene, 80°C) of the iodo and phenylseleno substituents completed the synthesis of the olivomycin A model AB disaccharide **4**.[12a,b]



The synthesis of the mithramycin model AB disaccharide originated with the trimethylsilyl triflate catalyzed β-selective glycosidation of **9b** with trichloroacetimidate donor **13**.[8,17,18] It is interesting to note that the trichloroacetimidate unit of **13** is selectively activated in the presence of the β-seleno acetate substructure of **9b**, which is known to serve as a glycosyl donor under very similar conditions.[14] Best results

were obtained by using 1.0 equiv. of **9b**, 1.3 equiv. of **13** and 0.1 equiv. of TMS-OTf in the presence of 4Å molecular sieves (50 mg/mL) in CH_2Cl_2 at -78°C for 10 min. Under these conditions, the selectivity for the new β-glycosidic linkage was 10 : 1, but the anomeric acetate in the A unit emerged as a 7 : 3 mixture with the indicated β,α-anomer **14**[12a,b] predominating (the yield of the mixture was 57%).[19] Selective deprotection of the anomeric acetate by using anhydrous NH_2NH_2 in MeOH provided the reducing disaccharide **15** (81%) which was coupled with 2-naphthol under our standard Mitsunobu conditions, thereby providing the fully protected aryl disaccharide **16**[12a,b] in 74% yield. The selectivity for the aryl β-glycoside was 10 : 1 according to ^1H NMR analysis. Finally, treatment of **16** with NaBr in DMF (80°C, 20 h, 91%), followed by Bu_3SnH (3 equiv., AIBN, 80°C, toluene, 86%) and then Ra-Ni (excess, EtOH, 23°C, 10 min, 88%) provided the mithramycin model AB disaccharide **5**[12a,b] in 69% overall yield.



In conclusion, we have developed highly stereoselective syntheses of the olivomycin A and mithramycin reducing AB disaccharides **11** and **15** and have shown that these intermediates undergo highly stereoselective (≥10 : 1) β-glycosidations with 2-naphthol under standard Mitsunobu conditions. We believe that intermediates **11** and **15** are properly functionalized for use in completing total syntheses of the parent aureolic acid antitumor antibiotics, and our further progress towards this objective will be reported in due course.

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12. The spectroscopic properties (^{1}H NMR, IR, high resolution mass spectrum) of all new compounds are in compelete agreement with the assigned structures. (b) A correct C and H analysis was obtained for this intermediate.
13. The electronic properties of glycals **7** and **8** are too evenly matched for application of the "armed/disarmed" protocol for the direct coupling of these two fragments (see ref. 15).
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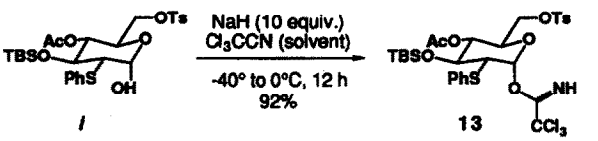
18. Dr. K. Briner of our laboratory has improved the synthesis of **13** as summarized below. It is necessary that Cl_3CCN be used as solvent to supress epimerization of C(2) that, otherwise, is a significant complication (see ref. 8).



1 **13**

19. Control experiments established that **14** rapidly decomposes when treated with catalytic TMS-OTf at -78°C. This instability presumably contributes to the moderate yield of **14** from this reaction.

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