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TOTAL SYNTHESIS OF THE AB DISACCHARIDE UNIT OF OLIVOMYCIN A

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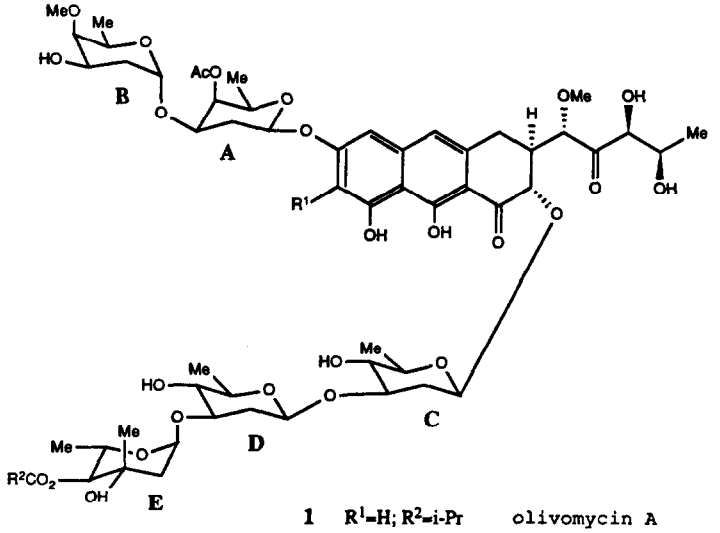
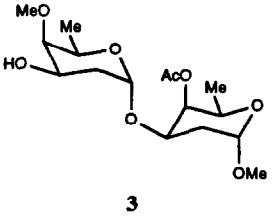
Abstract. An efficient (10 step, 17% overall yield), highly diasteroselective total synthesis of disaccharide 3, corresponding to the AB disaccharide unit of olivomycin A, is described.

Olivomycin A (1) is a clinically active member of the aureolic acid family of anticancer agents.[2] Other important members of this group are chromomycin A_3 (2) and mithramycin, which has the same aglycone as 2 but differs in the structures of the di- and trisaccharide units.[3] Considerable effort has been devoted recently to the synthesis of the aglycones (olivin and chromomycinone respectively)[4], and Thiem has performed significant pioneering studies on the structure and synthesis of the di- and trisaccharides.[3,5] As an extension of our earlier studies on the synthesis of 1,[4e,6] we have developed and report herein an efficient total synthesis of the AB disaccharide 3.





3

1 R^1=H; R^2=i-Pr olivomycin A

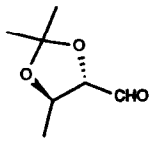
2 R^1=R^2=Me chromomycin A_3

In our initial work on the synthesis of 2,6-dideoxyhexoses, epoxyalcohols prepared by the Sharpless kinetic resolution - enantioselective epoxidation technology served as the key synthetic intermediates.[6,7] Although this approach proved to be reasonably direct and efficient in the cases reported thus far, it suffers from two major drawbacks: (i) since a resolution is involved, the maximum yield of useable chiral intermediates is 50%; and (ii) the generality is restricted since the efficiency of the kinetic resolution (e.g., relative rate of epoxidation of the enantiomeric allylic alcohols) and the diastereoselectivity of the epoxidation step are poor for secondary (Z)-allylic alcohols, an important class of substrates. Our recent development of the tartrate ester modified allylboronates[8] suggested that a more general solution to this problem would involve the reaction of a chiral aldehyde with a chiral allylboronate ("double asymmetric synthesis")[9] as a means of establishing the stereochemistry of the sugar backbone. It is this new approach that is featured in this communication.

The synthesis of disaccharide 3 thus begins with the reaction of aldehyde 4 (prepared from L-threonine)[4e,10] and (S,S)-5 (1.3 equiv., 0.5 M in CH_2Cl_2, -78°C for 2.5 h, then overnight at 23°C) performed in the presence of 4Å molecular sieves (10 mg/mL). This provided the known homoallylic alcohol 6[11,12] in 93% yield and with greater than 98% diastereoselectivity. Benzylation of 6 under standard conditions (NaH, $C_6H_5CH_2Br$, THF-DMF, reflux, 2 h, 88%) smoothly afforded 7[12a] which was hydrolyzed by treatment with 4:1 HOAc-H_2O at 100°C for 4 h (98% yield). Ozonolysis of the resulting diol 8[12a,b] in MeOH at -20°C (Me_2S workup) then provided the desired 2,6-dideoxy-D-lyxo-hexose[12a] (72%) as a mixture of pyranose (9α,β) and furanose (10α,β) tautomers that was directly converted to the corresponding methyl glycosides by treatment with methanol containing 1 equiv. of acetyl chloride. This mixture was most conveniently separated after acylation (Ac_2O, pyridine, DMAP, 23°C). In this manner, pyranoside 11α[12a,b] (m.p. 70-73°C; $[\alpha]_D^{22}$ + 168° (c=0.38, $CHCl_3$); TLC, R_f 0.44, 1:1 ether-hexane) was obtained as the major product in 36% yield along with a mixture of pyranose 11β and furanoses 12α,β (48% combined). The latter mixture was recycled three times ((i) MeOH, AcCl; (ii) Ac_2O, pyridine, DMAP; (iii) chromatographic separation) bringing the total yield of 11α to 71%.

Intermediate 11α served as precursor to both of the monosaccharide units in 3. Thus, the A ring sugar 13[12a,b] (m.p. 89°C; $[\alpha]_D^{22}$ + 129° (c=0.50, $CHCl_3$)) was prepared in 84% yield by hydrogenation (1 atm) of 11α in EtOH over 10% Pd/C. Alternatively, treatment of 11α with powdered KOH in DMSO (23°C, 1.5 h) followed by excess CH_3I and catalytic 18-crown-6 (23°C, 4 h) gave 14[12a,b] ($[\alpha]_D^{22}$ + 108° (c=0.58, $CHCl_3$)) in 81% yield. This intermediate was then converted into thiosugar 15[12a,b] (anomeric mixture), a precursor to the B ring monosaccharide, in 92% yield by using the method described by Hanessian ($C_6H_5SSiMe_3$ (5 equiv.), ZnI_2 (3 equiv.), Bu_4NI (1.1 equiv.), CH_2Cl_2 25°C, 3 h).[13] Coupling of these two units was smoothly accomplished by treatment of a mixture of 13 (1.1 equiv.) and 15 with NBS

(1.2 equiv.) and 4Å molecular sieves (120 mg/mL) in CH_2Cl_2 for 45 min at 23°C.[14] Although a mixture of anomers was anticipated at the outset,[14,15] we were pleased to find that



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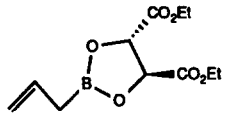
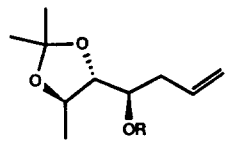
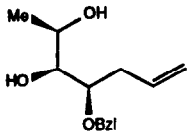


(S,S)-5



6 R=H
7 R=$CH_2C_6H_5$



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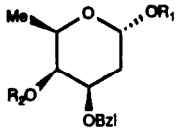
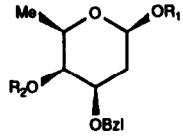
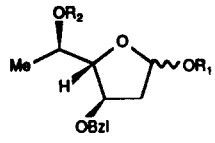


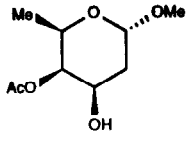
9 α R_1=R_2=H
11α R_1=Me
R_2=Ac
14 R_1=R_2=Me



9 β R_1=R_2=H
11β R_1=Me
R_2=Ac



10 α,β R_1=R_2=H
12 α,β R_1=Me
R_2=Ac



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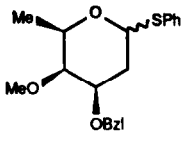

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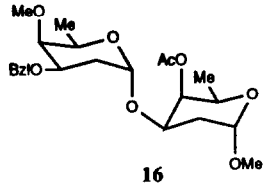

16

this method provided disaccharide 16[12a,b] in 61% yield a >6:1 mixture in which the α,α-anomer predominated. Finally, hydrogenation of 16 (H_2, EtOH, 10% Pd/C, 91% yield) gave disaccharide 3, the spectroscopic properties of which were in excellent agreement with literature values.[5b]

In summary, we have developed an efficient (10 step, 17% overall yield), highly diastereoselective synthesis of 3 which corresponds to the AB disaccharide unit of olivomycin A (1) and chromomycin A_3 (2). Future reports from our laboratory will describe additional applications of chiral allylic boronic esters in the synthesis of carbohydrates as well as further progress towards the synthesis of 1.

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