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# Total Synthesis of the Trisaccharide of Olivomycin A

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***Abstract:*** *The total synthesis of the trisaccharide of olivomycin A, which is one of the aureolic acid antitumor antibiotics, has been achieved. Our approach involves highly stereocontrolled glycosidations using 2,6-ahnydro-2-thio glycosyl donors. The 2,6-anhydro-2-thio trisaccharide* ***21*** *was constructed from* ***4*** *and* ***5****, and then converted into the 2,6-dideoxy trisaccharide of olivomycin A* ***3*** *by hydrogenolysis and deprotection.*

Olivomycin A (**1**, Figure 1) is one of the most prominent members of the aureolic acid family along with chromomycin (**2**, Figure 1) and mithramycin.[1] These antibiotics clinically demonstrate effective antitumor activities which are assumed to result from the strong and selective inhibitions of the DNA-dependent RNA synthesis.[2] The mechanism of the inhibitions involves the selective binding of these agents to two contiguous GC rich regions of DNA duplexes in the minor groove and in the presence of $Mg^{2+}$ ions.[2] The DNA binding site and the RNA synthesis inhibitory effect are influenced more by the carbohydrate moieties than their aglycon parts.[2,3] Because of the stimulant biological background many groups have focused on the synthesis of the di- and trisaccharide units of these antibiotics.[4] Both are constituted from several types of 2,6-dideoxy sugar; however, a highly stereocontrolled glycosidation of this sugar is still a formidable problem in organic synthesis.[5] We report herein the highly stereoselective total synthesis of the trisaccharide of olivomycin A by the successful application of stereocontrolled α- and β-glycosylation methods utilizing 2,6-anhydro-2-thio sugars.[6]

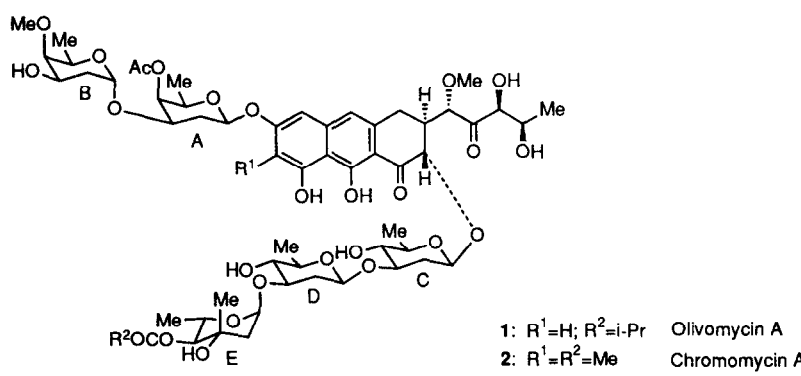


**Figure 1**. Molecular structure of olivomycin A (**1**) and chromomycin $A_3$ (**2**).

2,6-Anhydro-2-thio D-sugar **4** was selected for the C and D residue glycosyl donors and another 2,6-anhydro-2-thio L-sugar **5** was chosen for the E ring donor in the present synthesis. Cyclohexanol (**6**), a secondary alcohol, was employed as a model alcohol of the aglycon, olivin.[7] The key intermediates **4** and **5** were synthesized from the corresponding enantiomers of **7** by modifications and extensions of procedures previously reported from our laboratories.[8] Crucial to the success of this synthesis were (a) highly stereoselective α-or β-glycosidation of each key glycosyl donor; (b) highly stereoselective creations of the C-3 configuration of each ring; and (c) high-yielding reactions as described below (Figure 2).

The first β-selective glycosidation of **4** (1 equiv) prepared by acetolysis of the D-sugar of **7**[8] ($Ac_2O$, cat. TMSOTf, 0°C, 1h, 70%) with **6** (2 equiv) was achieved by using 1.1 equiv. of TMSOTf in $CH_2Cl_2$ at -40→ -20°C for 20 min to afford the desired glycoside **8** in 90% yield without any chromatographic evidence for the formation of an α-anomer. The inversion of the configuration of the C-3 position of the 2,6-anhydro-2-thio-altropyranoside **8** was selectively performed by a method previously reported[8] to give 2,6-anhydro-2-thio-mannopyranoside **11** in three steps (1. 1.5 equiv. NaOMe, MeOH, 25°C, 1h, 99%; 2. 4.0 equiv. Dess-Martin periodinane,[9] $CH_2Cl_2$, 25°C, 1h, 99%; 3. 3.0 equiv. DIBALH, PhMe, -78°C, 75 min, 86% along with 6% of the isomer) in 84% overall yield. Because the β-selective glycosylation reaction of **4** with a Lewis acid in $CH_2Cl_2$ proceeded under thermodynamic control and was reversible,[6d] **11** was transformed into the corresponding deactivated 2,6-anhydro-2-sulfinyl glycoside **12**[6c] by oxidation of the sulfide in **11** (1.0 equiv. m-CPBA, $CH_2Cl_2$, 0°C, 75 min, 99%). The *m*-CPBA oxidation proceeded stereospecifically owing to the induction of the hydroxyl group at the C-3 position of **11**.[10] The second glycosidation of **12** (1 equiv) with **4** (2 equiv) that was performed in a manner similar to that for **8** ( 1.1 equiv. TMSOTf, $CH_2Cl_2$, -30→0°C, 1.5h) was found to produce the 2,6-anhydro-2-thio disaccharide **13** ($[\alpha]29_D$ -67.7° (c 0.47, $CHCl_3$)) in 89% yield without the detectable α-isomer. Next, the disaccharide **13** was converted into the glycosyl acceptor **16** ($[\alpha]27_D$ -55.0° (c 1.05, $CHCl_3$)) in 72% overall yield *via* stereoselective inversion of the C-3 position of D-ring by a way similar to that described above (1. 1.5 equiv. LAH, THF, 0°C, 1.5h, 96%; 2. 4.0 equiv. Dess-Martin periodinane, $CH_2Cl_2$, 25°C, 30 min, 96%; 3. 3.0 equiv. DIBALH, PhMe, -78°C, 2.5h, 78% along with 9% of the isomer), followed by the reduction[6e] of sulfoxide of the C-ring. At this stage, deactivation of **16** was not necessary because the final α-selective glycosylation reaction of 2,6-anhydro-2-thio sugar **5** possessing a thiophenyl group with NBS proceeded under kinetic control and was an irreversible reaction.[6a-c]

On the other hand, the E-ring donor **5** was prepared from **17** which was effectively synthesized from the L-series of **7** *via* stereoselective creation of the C-3 configuration.[8] Thus, debenzylation of **17**[8] ($H_2$, $Pd(OH)_2$, MeOH, 40°C, 1h, 75%) followed by selective protection of the C-4 hydroxyl group (1.1 equiv. *i*-PrCOCl, Py, cat. 4-DMAP, 25°C, 1.5h, 100%) afforded **19** in 75% overall yield. The compound **19** was then converted into the corresponding thioglycoside **20** by Nicolaou's method[6a,11] (5.0 equiv. $Me_3SiSPh$, 1.2 equiv. TMSOTf, $CH_2Cl_2$, 25°C, 1.5h) in 87% yield as a mixture of the α- and β-anomers in a ratio 1:3. Silylation of **20** (3.0 equiv. DEIPSOTf, 3.5 equiv. 2,6-lutidine, $CH_2Cl_2$, 25°C, 3h) with a diethylisopropylsilyl (DEIPS) group[12,13] produced **5** in a quantitative yield. The final glycosidation of **16** (1 equiv) with **5** (1.7 equiv) was completed by using 1.1 equiv. of NBS and MS 4A in $CH_2Cl_2$ at -30→-20°C for 30min to give the 2,6-anhydro-2-thio trisaccharide **21** ($[\alpha]28_D$ -54.9° (c 0.79, $CHCl_3$)) in 89% yield as a sole isolated anomer. Finally, hydrogenolysis ($H_2$, Raney-Ni, EtOH-dioxane (3:1), 50°C, 24h, 76%) of **21** followed by desilylation (3.0 equiv. TBAF, THF, 25°C, 1.5h, 85%) furnished the targeted 2,6-dideoxy trisaccharide **3** ($[\alpha]28_D$ -84.1° (c 0.44, $CHCl_3$)) with three correct anomeric configurations.[14]

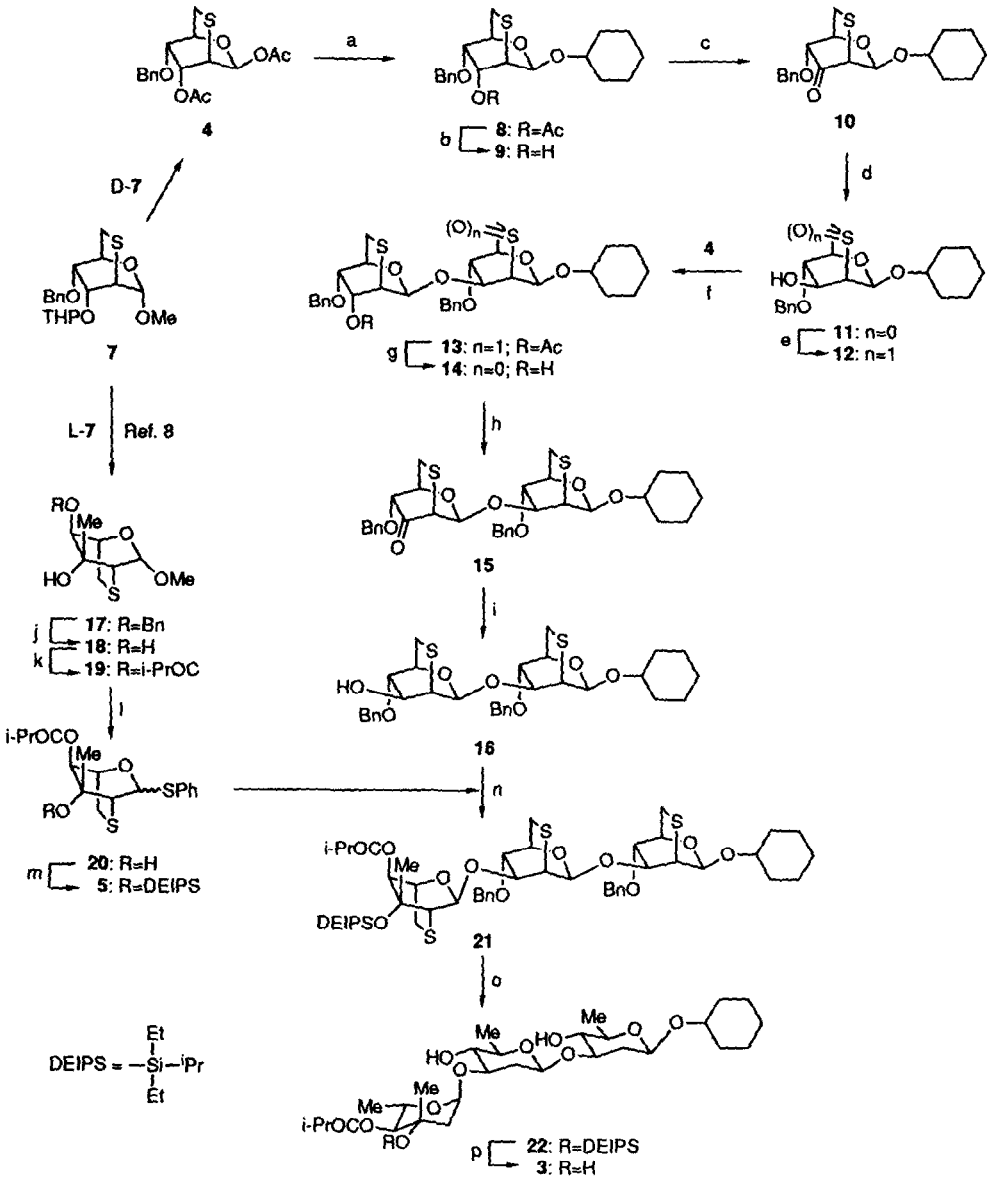


**Figure 2.** Total synthesis of the trisaccharide **3** of olivomycin A. Reagents and conditions: (a) 2.0 equiv of cyclohexanol (**6**),1.1 equiv of TMSOTf, $CH_2Cl_2$, -40→-20°C, 20min, 90%; (b) 1.5 equiv of NaOMe, MeOH, 25°C, 1h, 99%; (c) 4.0 equiv of Dess-Martin periodinane, $CH_2Cl_2$, 25°C, 1h, 99%; (d) 3.0 equiv of DIBALH, PhMe, -78°C, 75min, 86%; (e) 1.0 equiv of m-CPBA, $CH_2Cl_2$, 0°C, 1.5h, 99%; (f) 2.0 equiv of **4**, 1.1 equiv of TMSOTf, $CH_2Cl_2$, -30→-0°C, 1.5h, 89%; (g) 1.5 equiv of LAH, THF, 0°C, 1.5h, 96%; (h) 4.0 equiv of Dess-Martin periodinane, $CH_2Cl_2$, 25°C, 30min, 96%; (i) 3.0 equiv of DIBALH, PhMe, -78°C, 2.5h, 78%; (j) $H_2$, cat. $Pd(OH)_2$, MeOH, 40°C, 1h, 75%; (k) 1.1 equiv of i-PrCOCl, Py, cat. 4-DMAP, 25°C, 1.5h, 100%; (l) 5.0 equiv of $Me_3SiSPh$, 1.2 equiv of TMSOTf, $CH_2Cl_2$, 25°C, 1.5h, 87%(α/β=1/3); (m) 3.0 equiv of DEIPSOTf, 3.5 equiv of 2,6-lutidine, $CH_2Cl_2$, 25°C, 3h, 100%; (n) 1.7 equiv of **6**, 1.1 equiv of NBS, MS 4A, $CH_2Cl_2$, -30→-20°C, 40min, 89%; (o) $H_2$, cat. Raney-Ni, EtOH-dioxane (3:1), 50°C, 24h, 76%; (p) 3.0 equiv of TBAF, THF, 25°C, 1.5h, 85%.

In summary, the present work offers the total synthesis of the trisaccharide of olivomycin A with an intact form and also shows promising potential for our 2,6-anhydro-2-thio sugar glycosylation method in the synthesis of complex 2,6-dideoxy oligosaccharides which occur widely in useful antibiotics.

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13. The diethylisopropylsilyl (DEIPS) protecting group was shown to be superior in all respects to the *t*-buthyldimethylsilyl group in this synthesis.
14. All new compounds were purified by silica-gel column chromatography and were fully characterized by spectroscopic means and elemental analyses.


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