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Total Synthesis of Olivomycin A

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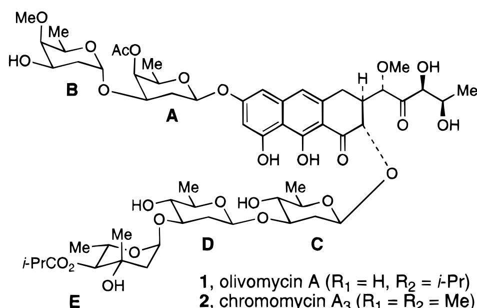
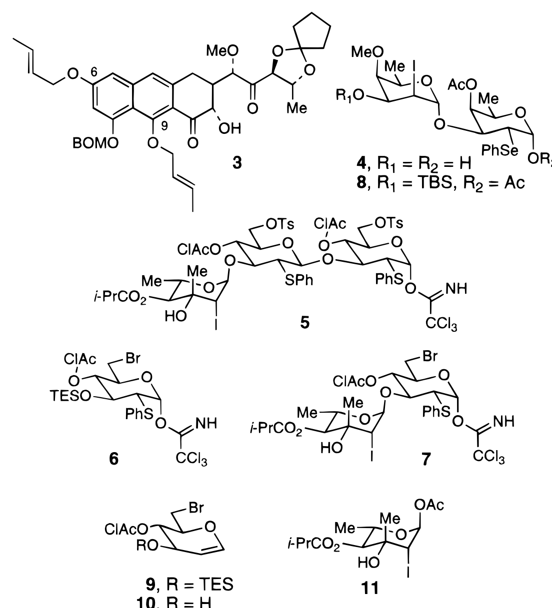
Olivomycin A (**1**) is a prominent member of the aureolic acid family of antitumor antibiotics, a group of clinically active agents that also includes mithramycin and chromomycin A_3 (**2**).[2−4] The



aureolic acids are known to bind in the minor groove of double stranded DNA as 2:1 antibiotic:Mg^{2+} complexes, with selectivity for GC rich sequences.[5−8] Recently, the GC rich promoter regions of the c-myc protooncogene and the dihydrofolate-reductase gene have been identified as possible biological targets of mithramycin.[9,10] We report herein a highly stereoselective total synthesis of olivomycin A, constituting the first chemical synthesis of any member of the aureolic acid group.[11]

Our original plan called for olivomycin A to be assembled by the late stage coupling of a protected version of the aglycon, olivin,[12] and activated forms of the A-B disaccharide[13] and the C-D-E trisaccharide units.[14,15] However, because earlier studies indicated that the efficiency of the glycosidation of protected aureolic acid aglycons with several fully elaborated C-D-E trisaccharides (e.g., **5**) was poor (typically less than 15% yield of the desired β-glycoside),[15] we have developed an alternative approach in which the C residue **6** is first coupled to the aglycon, followed by sequential addition of the D-E disaccharide **7** and the A-B disaccharide **4**. The protected aglycon, **3**, was synthesized via modifications of our second generation olivin synthesis,[12] specifically involving the use of crotyl ether protecting groups for the C(6) and C(9) phenols and a cyclopentylidene ketal for the side chain diol unit.[16] The reducing A-B disaccharide **4** was synthesized in two steps from the protected precursor **8**[13] ((i) HF−Et_3N, CH_3CN, 65 °C, 81%; (ii) NH_2NH_2, MeOH, 0 to 25 °C, 82%), while both **6** and **7** originated from glycal **9**.[17] The selection of **9** as the precursor to the C and D monosaccharide units was dictated by our observation that a polar substituent at C(6) is required to maximize stereoselectivity of the electrophilic addition of PhSCl to glucal derivatives,[17] as well as the fact that 6-bromo-glycosyl-1α-trichloroacetimidates[18] have consistently given higher β-selectivity in glycosylation reactions[19,20] than the corresponding 6-tosyl-1α-trichloroacetimidates used in most of our earlier studies.[14,15] The use of C(2)-heteroatom substitutents (e.g., −Br, −SAr, −SePh) to direct β-glycosidation reactions is a well-established strategy for synthesis of 2-deoxy-β-glycosides.[21−23]



Treatment of **9**[17] with PhSCl in CH_2Cl_2 (0 to 23 °C) followed by hydrolysis of the intermediate glycosyl chloride (Ag_2CO_3, THF, H_2O) provided the 2-thiophenyl pyranose in 81−96% yield, which was converted to the trichloroacetimidate derivative **6** by exposure to excess NaH in Cl_3CCN (as solvent) at −40 to −20 °C (57−66% yield following chromatographic purification).[17,18] Desilylation of **9** with HF−pyridine in THF gave monosaccharide **10**,[18] which was coupled with the olivomycose derivative **11** (TMSOTf, 4 Å molecular sieves, CH_2Cl_2, −78 °C, 74% yield).[24] The resulting

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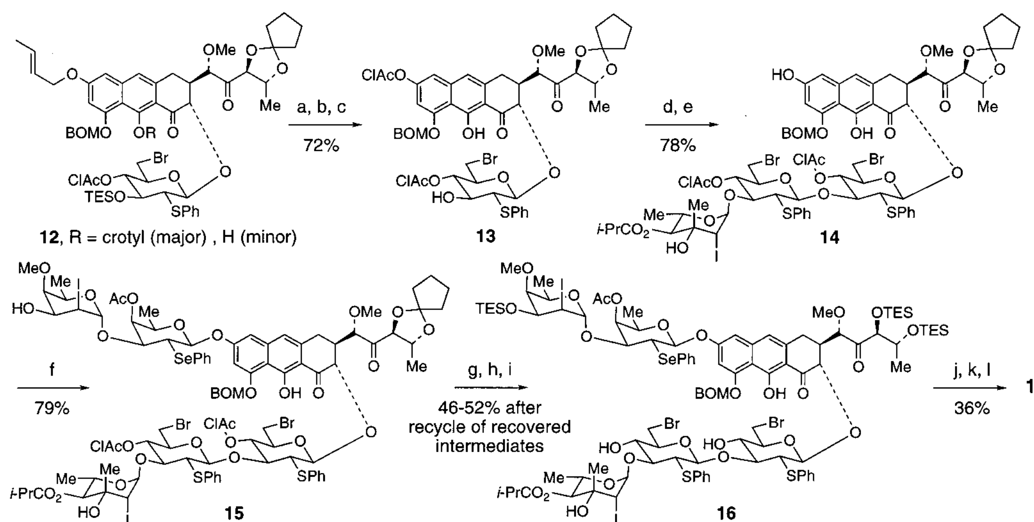
Scheme 1



Key: (a) Bu_3SnH, $Pd(PPh_3)_4$, HOAc, toluene, 25 °C, 90%; (b) $(ClCH_2CO)_2O$, pyridine, CH_2Cl_2, 84%; (c) HF-pyridine, THF, 0 °C, 95%; (d) **7** (3 equiv), TBS-OTf (0.3 equiv), 4 Å molecular sieves, 1 : 1 hexane-CH_2Cl_2, -35 °C; (e) NH_3, MeOH, 0°C (78%, two steps); (f) **4**, PPh_3, DEAD, CH_2Cl_2, 4 Å molecular sieves, 79%; (g) CSA, MeOH, 54% after HPLC, plus 14% recovered starting material; (h) TES-OTf, pyridine, CH_2Cl_2, -60 °C, 95%; (i) NH_3, MeOH, 78% plus 9% monochloroacetate; (j) Bu_3SnH, Et_3B, toluene, 25° to 45 °C, 84%; (k) RaNi, THF, EtOH, sonication, 25° to 50 °C, 57%; (l) HF-pyridine, THF-pyridine, 76%.

E-D glycal was then converted into the activated E-D-trichloroacetimidate **7** by the now familiar three-step sequence described for the conversion of **9** to **6** ((i) PhSCl, CH_2Cl_2, 0 to 25 °C; then AgOTf, tetramethylurea, THF, H_2O (80% yield); (ii) NaH, Cl_3CCN, −40 to −20 °C, 47% yield).

Treatment of the protected aglycon **3** with 7 equiv of **6** (added in two portions) and 0.3 equiv of TBS−OTf in 2:1 hexane−CH_2Cl_2 at −60 °C provided an 8:1 mixture of **12** and the corresponding α-glycoside anomer in 58% yield (51% isolated yield of **12**, R = crotyl, contaminated with ca. 10% of **12**, R = H). Because difficulties were subsequently encountered during attempts to remove the crotyl protecting groups in the presence of the iodo substituent of the C-D-E trisaccharide, the crotyl groups of **12** were removed ($Pd(PPh_3)_4$, Bu_3SnH, HOAc, 90%)[25] and the C(6) phenol reprotected as a chloroacetate (84%). The TES ether was then removed (95%) from the C monosaccharide unit, thereby providing **13** in 72% overall yield. The glycosylation of **13** with the E-D-imidate **7** (3 equiv of **7**, 0.3 equiv of TBS−OTf, 1:1 hexane−CH_2Cl_2, −35 °C) provided the trisaccharide derivative **14** in 78% yield following removal of the phenolic chloroacetate by brief treatment with methanolic NH_3. Intermediate **14** was then coupled with the reducing A-B disaccharide **4** (1.5 equiv) by using our previously described Mitsunobu glycosidation protocol,[13] which provided the targeted pentasaccharide **15** in 73−79% yield.

The final sequence of functional group manipulations required to complete the olivomycin synthesis was initiated by the acid-catalyzed cleavage of the cyclopentylidene ketal. This provided the requisite triol in 54% yield after HPLC purification, along with 14% of recovered **15** which could be recycled.[26] The triol was then per-triethylsilylated (in order to improve the solubility properties of subsequent intermediates, 95% yield) and the two chloroacetate units were removed by treatment with NH_3 in MeOH. In this way, the advanced intermediate **16** was obtained in 78% yield along with 9% of recovered mono-chloroacetate.[27] After recycling of recovered materials, the yield of **16** was 46−52%. Related advanced intermediates proved to be somewhat unstable at temperatures above 60 °C, and consequently standard[28] Bu_3SnH−AIBN reductive removal of the halogen and selenophenyl substituents gave mixtures of products. However, use of triethylborane as the radical initiator permitted the Bu_3SnH reduction of the iodo-, bromo-, and selenophenyl substituents of **16** to be performed in toluene at 25 to 45 °C (84% yield).[29] The two thiophenyl substituents and the BOM group were then excised by using freshly prepared RaNi[30] in a mixture of THF and EtOH with external sonication (57% yield). Finally, the three TES ethers were removed by treatment with HF−pyridine at 0 °C, thereby providing totally synthetic (−)-olivomycin A in 76% yield. The synthetic material was identified by comparison to an authentic sample of (−)-olivomycin A, and the two were found to be identical according to ^1H and ^{13}C NMR, HPLC, UV, mass spectroscopy, and TLC analysis in four different solvent systems.

In summary, the first total synthesis of olivomycin A has been completed by a route featuring three highly stereoselective *β*-glycosidation reactions. Applications of this methodology to the synthesis of aureolic acid analogues will be reported in due course.

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Supporting Information Available: Schemes for the synthesis of **3**, **4**, **6**, and **7**; experimental details for the synthesis of **12**−**16** and synthetic olivomycin A; and ^1H and ^{13}C NMR spectra for selected compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(26) If the ketal hydrolysis was allowed to proceed to completion, product(s) resulting from glycoside hydrolysis were also produced.

(27) The isobutyrate ester is also sensitive to cleavage by NH_3 in MeOH. If this reaction was allowed to proceed until both chloroacetates were completely removed, some cleavage of the isobutyrate ester on the E-sugar was observed.

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