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Convergent *de novo* synthesis of vineomycinone B_2 methyl ester†

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An efficient *de novo* synthesis of vineomycinone B_2 methyl ester has been achieved. The longest linear route required only 14 steps from achiral commercially available starting materials (4.0% overall yield). The key transformations included the *de novo* asymmetric synthesis of two key fragments, which were joined by a convergent late stage Suzuki's glycosylation for the construction of the aryl β-C-glycoside. A subsequent BBr_3 one-pot debenzylation, demethylation and air oxidation provided vineomycinone B_2 methyl ester.

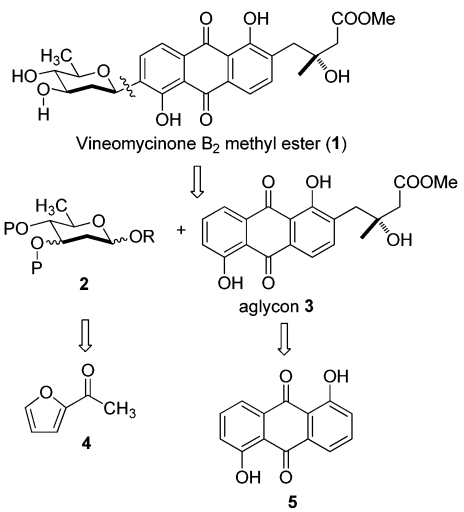
The anthraquinone containing vineomycin members of the angucycline family of antibiotics have been of particular interest to both the synthetic and biological communities due to their unique structures and potent antitumor and antibacterial activities.[1] Vineomycin B_2 is a secondary metabolite of *Streptomyces matensis* subsp. *vineus*, which displays potent antitumor/antibiotic activity with a pharmacologic profile similar to that of the clinically important anthracyclines.[2,3] Acid-catalyzed methanolysis of vineomycin B_2 afforded its aglycon vineomycinone B_2 methyl ester (**1**) which is the result of *ortho*-C-glycosylation (β-D-olivose) of the methyl ester of fridamycin E (**3**).[4]

The total synthesis of vineomycinone B_2 methyl ester has been achieved by several groups.[5] While these approaches vary in terms of overall efficiency, the routes tend to focus on the construction of the aglycon portion, rather than β-C-glycoside. These methods varied from the use of cycloadditions with siloxydienes, metalation–stannylation reaction, Bradsher cycloaddition and $Cp_2HfCl_2/AgClO_4$ promoted C-glycosylation to the use of tandem intramolecular benzyne–furan cycloadditions.[5] Despite the success and range of these previous approaches, we felt there was room for a convergent *de novo* asymmetric approach to this class of C-aryl glycoside natural products. In additions to being able to provide access to enantio- and diastereomeric isomers, a convergent *de novo* approach could provide material in a reduced number of steps.

Previously, we described the synthesis and anticancer activity of a sans-C-glycoside trisaccharide portion of vineomycin B_2.[6] More recently, we finished the asymmetric synthesis of both enantiomers of fridamycin E. These synthetic efforts enable the biological evaluation of these natural product structural motifs. Ultimately we envision these efforts leading to a generalizable late stage C-glycosylation strategy for the synthesis and structure activity relationship studies of this class of C-glycoside natural products.[7]

Herein we describe our successful approach to vineomycinone B_2 methyl ester, which is based upon our *de novo* Achmatowicz approach to carbohydrates[6] and our successful syntheses of fridamycin E[8] from achiral starting materials (acyl furan and anthrarufin, respectively). We believe this convergent *de novo* asymmetric approach that utilizes a late stage Suzuki's glycosylation to install the β-C-glycoside provides synthetic material in a more efficient manner than the previous routes.

Our approach to vineomycinone B_2 methyl ester (**1**) is depicted in Scheme 1. We envisioned that **1** could be accessed from a protected D-olivose or D-digitoxose sugar **2** as the glycosyl donor and the methyl ester of the natural product fridamycin E



Scheme 1 Retrosynthesis of vineomycinone B_2 methyl ester.

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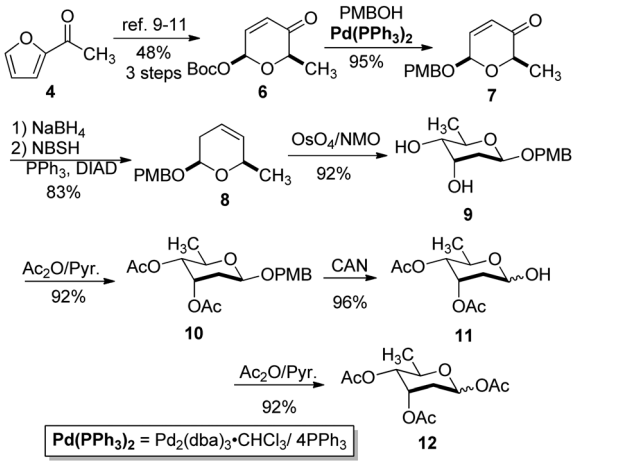
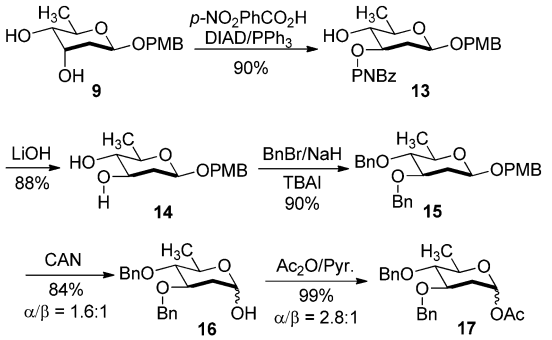


Scheme 2 Approach to glycosyl donor **12**.

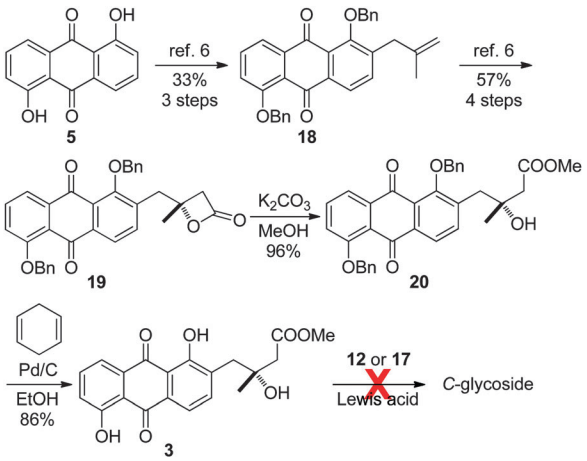
(**3**) as the aglycon. A Lewis acid promoted β-C-glycosylation could be used to install the glycosidic bond of **1**. While the olivose sugar is more direct synthetically, the digitoxose diastereomer has the potential for directing group effects that might be required for selectivity in the C-glycosylation. Conveniently, our *de novo* Achmatowicz strategy was envisioned to produce both diastereomers of the glycosyl donor **2** from commercially available acyl furan **4**.[5a] So, the synthetic advantage to the olivose diastereomer boils down to a step before *versus* after the point of convergence. Building upon our fridamycin E work, we imagined an aglycon subunit suitable for coupling (*e.g.*, **3**) could be prepared from commercially available anthrarufin **5**.[8]

Previously, we have shown that the required Pd glycosyl donor β-D-pyranone **6**, as well as its enantiomer and α-diastereoisomers, could be prepared from acyl furan **4** (Scheme 2). The stereodivergent route employed an enantioselective Noyori reduction,[9,10] an Achmatowicz oxidation, and diastereoselective *tert*-butyl carbonate formation.[11,12] The protected β-D-digitoxose **9** was then completed by a 4-step sequence (Scheme 2).[6] This began with Pd-catalyzed glycosylation of PMBOH and β-D-pyranone **6** to form the β-benzyloxy pyranone **7**. A Luche reduction ($NaBH_4$/$CeCl_3$) of **7** followed by the Myers' reductive rearrangement to form **8** and the Upjohn dihydroxylation gave β-D-digitoxose sugar **9** (Scheme 2). The two hydroxyl groups were protected as acetate groups (Ac_2O/Pyr) to form **10**, which was followed by ceric ammonium nitrate (CAN) oxidative deprotection of the PMB-group to afford lactol **11**. Finally the anomeric hydroxyl group was acylated to produce the desired glycosyl donor **12**.

We then turned to the preparation of the diastereomeric D-digitoxose glycosyl donor **17** with and anomeric acetate (Scheme 3). This began with a highly regio- and stereospecific Mitsunobu like reaction (*p*-NO_2PhCO_2H/DIAD/PPh_3) on *cis*-diol **9** to provide **13** in excellent overall yield. Hydrolysis of the nitrobenzoate **13** with LiOH afforded the *trans*-diol **14** (88%). The two hydroxyl groups were then protected as benzyl ethers (BnBr, NaH/TBAI, 88% yield). A subsequent deprotection of the PMB-group in **15** with CAN smoothly converted it into lactol **16** in 84% yield as an equilibrating mixture of diastereomers ($\alpha:\beta$ = 1.6 : 1). Finally, acylation of **16** gave β-D-olivose acetate **17** (99%, $\alpha:\beta$ = 2.8 : 1) in near quantitative yield.



Scheme 3 Caption approach to glycosyl donor **17**.



Scheme 4 C-glycosylation attempts of fridamycin E methyl ester **3** with **12** and **17**.

With the glycosyl donor in hand, we then turned to the synthesis of the aglycon **3**, the methyl ester of fridamycin E (Scheme 4), this was chosen as it would lead to the latest possible sight of convergence. Previously, we have also developed the asymmetric synthesis of fridamycin E.[8] In this route, the β-lactone **19** was prepared in 7 steps and in 19% overall yield. The synthesis began with the monomethallylation of anthrarufin, followed by a redox promoted Claisen rearrangement and benzyl protection to afford *ortho*-methallylated product, was asymmetrically epoxidized in a 3-step protocol (Sharpless dihydroxylation–tosylation–ring-closure) to give epoxide **18**. A subsequent Coates carbonylation regio- and stereospecifically provided β-lactone **19**, which after methanolysis ($MeOH/K_2CO_3$, 96% yield) smoothly afforded β-hydroxyl carboxylic acid methyl ester **20** in excellent yield (96%) with the requisite tertiary alcohol. Finally, a reductive debenzylation of **20** with 1,4-cyclohexadiene and Pd/C in ethanol gave the methyl ester of fridamycin E **3** in 86% yield.

With both glycosyl donor and aglycon in hand, we explored the possibility of a Lewis acid promoted C-glycosylation of **3** with **12** or **17** (Scheme 4). Unfortunately, our exhaustive survey of various Lewis acids and conditions (*e.g.*, $BF_3{\cdot}Et_2O$, TMSOTf and $Cp_2HfCl_2/AgClO_4$)[5e] met with no success. No signs of the desired C-glycoside product were detected.

Thus, we decided to target an earlier synthetic intermediate that would (1) possess a more electron rich aromatic ring and (2) be suitably protected to reveal the aglycon portion of the natural product in a single step.[7e] This led to the choice of the arene **23** with the

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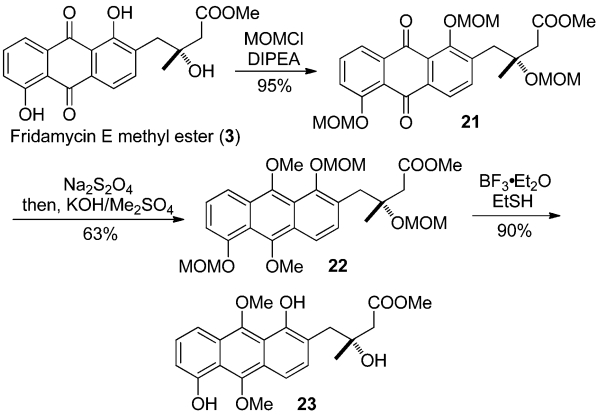
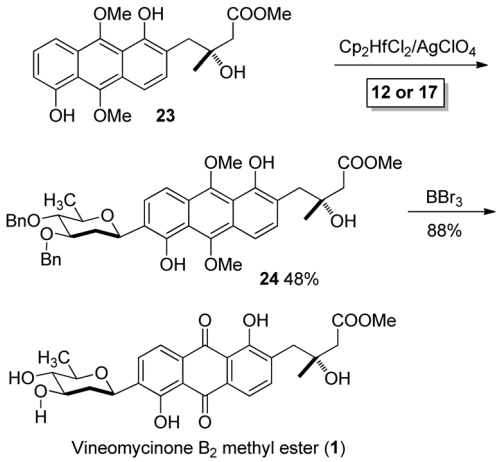


Scheme 5 Synthesis of the aglycon **23**.



Scheme 6 Synthesis of vineomycinone B_2 methyl ester (**1**).

reduced quinone ring protected as a bis-methyl ether (Scheme 5). The revised synthesis began with an MOM protection of **3**, then *in situ* dithionate reduction of **21** to an anthraquinol intermediate, followed by methylation (KOH/Me_2SO_4) to give **22** in 63% yield. Finally deprotection of **22** gave the bis-phenol **23** in 90% yield.

With the second-generation C-glycosylation coupling partner in hand, we turned our focused on the C-glycosylation of **23** with **12** and **17** (Scheme 6). To our delight, treatment of a 1 : 1 mixture of **17** and **23** under the typical Suzuki conditions ($Cp_2HfCl_2/AgClO_4$) led to formation of the desired β-C-glycoside **24** as a single regio- and diastereo-isomer in 48% yield. While the reaction is envisaged as proceeding through an *O*- to C-glycoside rearrangement,[5] no evidence of an *O*-glycoside product was detected. A clue as to how to best complete the synthesis came from careful observation of the crude reaction mixture. Specifically, under the Lewis acid conditions of the C-glycosylation reaction one can observe the conversion of the acid sensitive starting material **23** into a corresponding anthraquinone. As a result, a one-pot per-deprotection–oxidation was realized with the exposure of **24** to excess BBr_3. The bis-debenzylation, bis-demethylation and subsequent air oxidation of an anthraquinol intermediate afforded vineomycinone B_2 methyl ester **1** in 88% yield. This synthetic material had physical and spectroscopic data in good agreement with literature values (*e.g.*, $[\alpha]_D^{20} = +109$ (*c* = 0.27, dioxane), $[\alpha]_D^{29} = +118$ (*c* = 1.05, dioxane),[5e] $[\alpha]_D^{24} = +109.8$ (*c* = 0.00091, $CDCl_3$)).[5f]

In contrast, the C-glycosylation between **23** and **12** was less successful, as only trace amount of the digitoxose isomer was observed.

In summary, the convergent *de novo* synthesis of vineomycinone B_2 methyl ester was accomplished in only 14 steps with 4.0% overall yield in the longest linear sequence, which is a highly efficient route comparing the shortest previous synthesis (16 steps) of **1**.[5] The route shows the efficiency of the convergent *de novo* synthesis of coupling partners for a late stage convergent C-glycosylation followed by a single step deprotection–oxidation to yield the natural product. It is interesting to note that while this is the first synthesis of vineomycinone B_2 methyl ester that uses asymmetric catalysis to install all of the stereocenters, in terms of overall synthetic efficiency it compares quite favorably with the elegant work of Martin and predecessors.[5] Having this improved stereo-divergent assess to vineomycinone B_2 methyl ester, its diastereomer and congeners should further enable their biochemical/medicinal chemistry study. Further vineomycins synthetic/biological investigations are ongoing and will be reported in due course.

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