Convergent de novo synthesis of vineomycinone B2 methyl ester†

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An efficient de novo synthesis of vineomycinone B2 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 BBr3 one-pot debenzylation, demethylation and air oxidation provided vineomycinone B2 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 B2 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 B2 afforded its aglycon vineomycinone B2 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 B2 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, metatation-stannylation reaction, Bradsher cycloaddition and Cp2HfCl2/AgClO4 promoted C-glycosylation to the use of tandem intramolecular benzene-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 B2.6 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 B2 methyl ester, which is based upon our de novo Achmatowicz approach to carbohydrates6 and our successful syntheses of fridamycin E8 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 B2 methyl ester (1) is depicted in Scheme 1. We envisioned that 1 could be accessed from a protected β-olivose or β-digitoxose sugar 2 as the glycosyl donor and the methyl ester of the natural product fridamycin E.

![Scheme 1 Retrosynthesis of vineomycinone B2 methyl ester.](https://www.rsc.org/chemcomm)

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(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. 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.

Previously, we have shown that the required Pd glycosyl donor β-ν-pyranone 6, as well as its enantiomer and ν-diastereoisomers, could be prepared from acyl furan 4 (Scheme 2). The stereodivergent route employed an enantioselective Noyori reduction, an Achmatowicz oxidation, and diastereoselective tert-butyl carbonate formation. The protected β-ν-digitoxose 9 was then completed by a 4-step sequence (Scheme 2). This began with Pd-catalyzed glycosylation of PMBOH and β-ν-pyranone 6 to form the β-benzylxy pyranone 7. A Luche reduction (NaBH₄/ CeCl₃) of 7 followed by the Myers’ reductive rearrangement to form 8 and the Upjohn dihydroxylation gave β-ν-digitoxose sugar 9 (Scheme 2). The two hydroxyl groups were protected as acetate groups (Ac₂O/Pyr) to form 10, which was followed by cenic 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 ν-digitoxose glycosyl donor 17 with an anomeric acetate (Scheme 3). This began with a highly regio- and stereospecific Mitsunobu like reaction (ρ-N₂O-PPh₃/H/DIAD/PPh₃) 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 (α:β = 1.6:1). Finally, acylation of 16 gave β-ν-olivose acetate 17 (99%, α:β = 2.8:1) in near quantitative yield.

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 site of convergence. Previously, we have also developed the asymmetric synthesis of fridamycin E. In this route, the β-lactone 19 was prepared in 7 steps and in 19% overall yield. The synthesis began with the monomethylation of anthrarufin, followed by a redox promoted Claisen rearrangement and benzyl protection to afford ortho-methylated 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 methanalysis (MeOH/K₂CO₃, 96% yield) smoothly afforded β-hydroxy carbocyclic 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 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., BF₃·Et₂O, TMSOTf and Cp₂HfCl₂/AgClO₄) 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. This led to the choice of the arene 23 with the
In contrast, the C-glycosylation between 23 and 12 was less successful, as only trace amount of the digitoxoside isomer was observed.

In summary, the convergent de novo synthesis of vineomycinone B₂ 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 L.³ 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 B₂ methyl ester that uses asymmetric catalysis to install all of its diastereomer and congeners should further enable their biochemical/medicinal chemistry study. Further vineomyccins synthetic/biological investigations are ongoing and will be reported in due course.

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Notes and references


