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C-Aryl Glycosides via Tandem Intramolecular Benzyne-Furan Cycloadditions. Total Synthesis of Vineomycinone B₂Methyl Ester

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The vineomycins are a group of glycosidic antibiotics that were isolated from a culture of *Streptomyces matensis vineus* and found to be active against Gram-positive bacteria and sarcoma-180 solid tumors in mice.¹ Acid-catalyzed methanolysis of vineomycin B₂ furnished the aglycone vineomycinone B₂ methyl ester (**1**). Bearing an olivose residue appended to one ring of the anthrarufin core, **1** is a representative member of the C-aryl glycoside family of natural products.² A 3(*R*)-hydroxyisovaleryl side chain adorns the opposite side of the core making vineomycinone B₂ methyl ester an intriguing target of modest complexity. Indeed, the structure of **1** coupled with its potential anticancer activity has rendered vineomycinone B₂ methyl ester the object of a number of investigations, four of which have culminated in total syntheses.³ Despite these successes, there remains ample opportunity for the development of new chemistries.

In the context of an interest in C-aryl glycoside antibiotics, we recently developed a general entry to the four major classes of this family of natural products.⁴ The strategy features the ring opening of cycloadducts that are obtained from Diels—Alder cycloadditions of substituted benzyne with glycosyl furans. Having established the basic elements of the approach, we turned to the task of applying it to the syntheses of naturally occurring C-aryl glycosides as an obligatory test of its true utility. We now report the application of this methodology to a facile synthesis of vineomycinone B₂ methyl ester (**1**).

The two substituents on **1** are unsymmetrically positioned on the anthrarufin nucleus. Hence, the major challenge is controlling the regioselectivity in the Diels-Alder reactions that would simultaneously assemble the aromatic framework and introduce the carbohydrate and aliphatic residues. We had previously developed a practical solution to this problem by using disposable silicon tethers to link the reacting benzyne and furan moieties.^{4d} Based upon that advance, a novel and highly convergent strategy eventuated for preparing **1** (Figure 1). The synthesis features tandem intramolecular benzyne-furan cycloadditions originating from the key intermediate **3** to generate the bisoxabenzonorbornadiene **2** in a *single* operation.⁵ The conversion of **2** into **1** requires cleavage of the silicon tethers, ring opening of the bisoxabenzonorbornene core, global removal of the oxygen protecting groups, and adjustment of the oxidation level in the alkyl side chain. The cycloaddition precursor **3** would be prepared by iterative Mitsunobu coupling of tetrabromohydroquinone (**5**) with the silicon-substituted furans **4** and **6**, both of which would be derived from readily available starting materials.

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Supporting Information Available: Experimental procedures for **2**–**4**, **9**, **17**, and **19** as well as spectral data and copies of ¹H NMR spectra for all new compounds together with copies of ¹H NMR spectra of synthetic and authentic **1** and a tabular comparison of ¹³C NMR data for synthetic and authentic **1**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

Preparation of **4** commenced with adding 3-lithiofuran to the known lactone **7**^{4c} to afford a mixture of lactols, which were in equilibrium with the open chain keto-alcohol (Scheme 1). This mixture was treated directly with ethanolic-HCl to furnish an intermediate ethyl acetal that was stereoselectively reduced upon heating with NaCNBH₃ in ethanolic-HCl to form glycosylfuran **8** in 80% overall yield.⁶ Regioselective metallation^{4d,7} of **8** followed by trapping with chlorodimethylvinylsilane furnished the vinyl silane **9**, which was subjected to hydroboration/oxidation⁸ to deliver furan **4** in 66% yield over two steps.

Turning to the synthesis of furan **6**, 3-methyl-3-butenol was first protected as its PMP ether and subjected to Sharpless asymmetric dihydroxylation conditions to afford diol **11** in 93% yield over two steps (96% ee) (Scheme 2).⁹ The primary tosylate derived from **11** was cyclized by deprotonation with *n*-BuLi to give an intermediate epoxide that underwent facile opening *in situ* with 3-lithiofuran in the presence of BF₃•OEt₂ to provide the tertiary alcohol **12** in 76% overall yield. *O*-Benzoylation of the hydroxyl group in **12** gave **13**, regioselective bromination of which with NBS furnished bromide **14** in 86% yield over two steps.¹⁰ The furyl bromide was subjected to metal-halogen exchange, and the resulting anion was trapped with chlorodimethylvinylsilane to afford the vinylsilane **15** in 87% yield. Subsequent hydroboration and oxidation of the vinyl moiety as before delivered the furan **6**.

The assembly of **3** then proceeded uneventfully (Scheme 3). Alcohol **6** and the monoprotected phenol **16**¹¹ underwent Mitsunobu coupling employing DIAD and PPh₃ to furnish the aryl ether **17** in 75% yield. Removal of the silyl protecting group utilizing HF•pyridine in THF released the phenol **18** that was then coupled with furan **4** via a second Mitsunobu reaction to deliver **3** in 72% yield over two steps.

With the Diels-Alder precursor **3** in hand, the stage was set for the pivotal domino benzyne-furan cycloaddition. Gratifyingly, dropwise addition of *n*-BuLi (0.23 M, 3.0 equiv) to a solution of tetrabromide **3** in Et₂O at -20 °C afforded biscycloaddition product **2** in 85% yield as a mixture of diastereomers (Scheme 4). After some experimentation, we discovered that the bonds between the silicon atoms and the bridgehead carbon atoms in **2** were most efficiently cleaved under modified Rickborn¹² conditions using KOH in DMF/H₂O (10:1). Treatment of the crude mixture thus obtained with hydrochloric acid resulted in the regioselective opening^{4a-d} of the two bicycloheptene rings, and subsequent air oxidation furnished the anthrurufin **19** in 34% overall yield together with several unidentified products.

Completion of the synthesis of vineomycinone B₂ methyl ester then required removal of the various protecting groups and adjustment of the oxidation level of the aliphatic side chain. The PMP group was thus cleaved under oxidative conditions with CAN to give alcohol **20** in 74% yield. Subsequent oxidation of alcohol **20** with IBX generated an aldehyde intermediate, which was transformed into acid **21** in 70% yield by reaction with NaClO₂. Global deprotection of the benzyl groups with BBr₃ followed by work-up with methanolic hydrogen chloride provided synthetic vineomycinone B₂ methyl ester (**1**) in 71% yield. The synthetic material thus obtained gave ¹H and ¹³C NMR spectra identical with an authentic sample.

In summary, a novel and highly convergent synthesis of vineomycinone B₂ methyl ester (**1**) has been completed by a process that required 16 steps, the same length as the shortest previous synthesis of **1**,^{3b} in the longest linear sequence. The synthesis features the first application of our strategy for using silicon tethers as disposable linkers to control the regiochemistry in Diels-Alder reactions of substituted benzyne and furans. Such constructions enable the rapid assembly of the glycosyl-substituted aromatic cores of complex *C*-aryl glycoside antibiotics from simple starting materials. Other applications of this strategy are in progress and will be reported in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
Retrosynthesis of vineomycinone B₂ methyl ester (1)

Scheme 1a.

a Reaction conditions: (a) 3-lithiofuran, THF, -78 °C; HCl, EtOH then NaCNBH₃, HCl, 50 ° C, 80%; (b) LDA, THF, -78 °C; Me₂Si(Cl)CH=CH₂, 70%; (c) 9-BBN, THF; H₂O₂, NaOH, 94%.

Scheme 2a.

a Reaction conditions: (a) *p*-MeO-C₆H₄OH, DIAD, PPh₃, THF, 98%; (b) AD-Mix α , H₂O, *t*-BuOH, 95%, 96% ee; (c) TsCl, Et₃N, DMAP, CH₂Cl₂; (d) *n*-BuLi, -78 °C; 3-lithiofuran, BF₃·OEt₂, THF, -78 °C, 76% (2 steps); (e) KH, DMF, 0 °C; BnBr, 100%; (f) NBS, DMF, 0 °C, 86%; (g) *n*-BuLi, THF, -78 °C; Me₂Si(Cl)CH=CH₂, 87%; (h) 9-BBN, THF; H₂O₂, NaOH, 96%.

Scheme 3a.

a Reaction conditions: (a) **6**, DIAD, PPh₃, THF, 75%; (b) HF·py, THF, 0 °C, 85%; (c) **4**, DIAD, PPh₃, THF, 85%.

Scheme 4a.

a Reaction conditions: (a) 3.0 eq. *n*-BuLi, ether, -20 °C, 85%; (b) KOH, DMF/H₂O (10:1); HCl, EtOH, 70 °C, 34%; (c) CAN, CH₃CN, H₂O, -15 °C, 74%; (d) IBX, EtOAc, 80 °C; NaClO₂, NaH₂PO₄, 2-methyl-2-butene, *t*-BuOH, H₂O, 70%; (e) BBr₃, CH₂Cl₂, -78 °C; MeOH, HCl, rt, 71%.