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C-Aryl Glycosides via Tandem Intramolecular Benzyne−Furan Cycloadditions. Total Synthesis of Vineomycinone B_2 Methyl 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 B_2 furnished the aglycone vineomycinone B_2 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 B_2 methyl ester an intriguing target of modest complexity. Indeed, the structure of **1** coupled with its potential anticancer activity has rendered vineomycinone B_2 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 benzynes 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 B_2 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] On the basis of 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.

Preparation of **4** commenced by 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

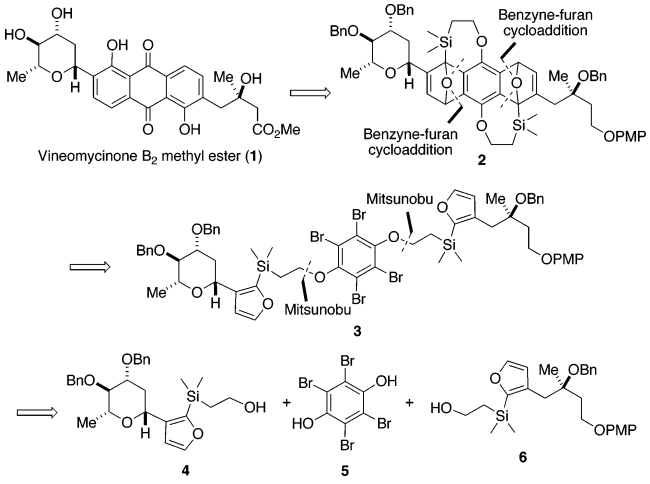
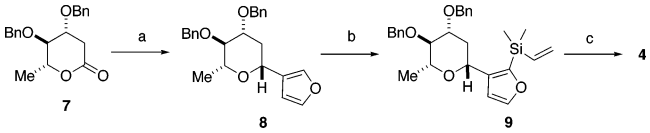


Figure 1. Retrosynthesis of vineomycinone B_2 methyl ester (**1**).

Scheme 1 [a]



[a] Reaction conditions: (a) 3-lithiofuran, THF, −78 °C; HCl, EtOH then $NaCNBH_3$, HCl, 50 °C, 80%; (b) LDA, THF, −78 °C; $Me_2Si(Cl)CH{=}CH_2$, 70%; (c) 9-BBN, THF; H_2O_2, NaOH, 94%.

heating with $NaCNBH_3$ in ethanolic HCl to form glycosylfuran **8** in 80% overall yield.[6] Regioselective metalation[4d,7] of **8** followed by trapping with chlorodimethylvinylsilane furnished the vinyl silane **9**, which was subjected to hydroboration/oxidation[8] 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 $BF_3{\bullet}OEt_2$ to provide the tertiary alcohol **12** in 76% overall yield. *O*-Benzylation 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 PPh_3 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

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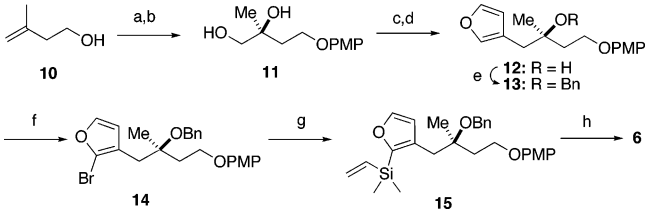
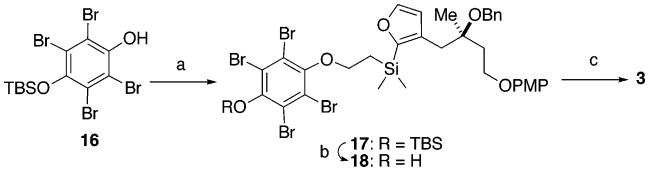
Scheme 2 [a]



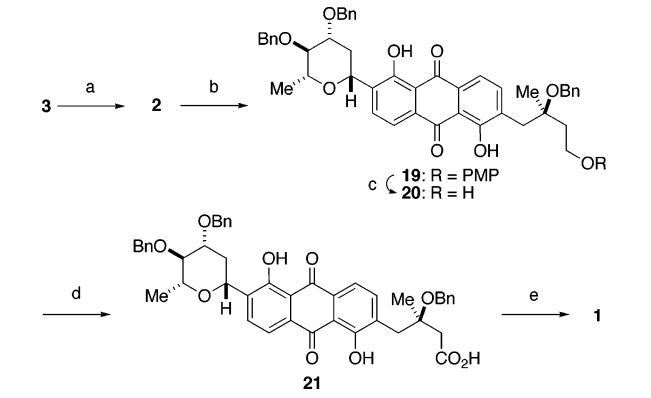
[a] Reaction conditions: (a) *p*-MeO−C_6H_4OH, DIAD, PPh_3, THF, 98%; (b) AD-Mix α, H_2O, *t*-BuOH, 95%, 96% ee; (c) TsCl, Et_3N, DMAP, CH_2Cl_2; (d) *n*-BuLi, −78 °C; 3-lithiofuran, $BF_3{\cdot}OEt_2$, THF, −78 °C, 76% (2 steps); (e) KH, DMF, 0 °C; BnBr, 100%; (f) NBS, DMF, 0°C, 86%; (g) *n*-BuLi, THF, −78 °C; $Me_2Si(Cl)CH{=}CH_2$, 87%; (h) 9-BBN, THF; H_2O_2, NaOH, 96%.

Scheme 3 [a]



[a] Reaction conditions: (a) **6**, DIAD, PPh_3, THF, 75%; (b) HF·py, THF, 0°C, 85%; (c) **4**, DIAD, PPh_3, THF, 85%.

Scheme 4 [a]



[a] Reaction conditions: (a) 3.0 equiv of *n*-BuLi, ether, −20 °C, 85%; (b) KOH, DMF/H_2O (10:1); HCl, EtOH, 70 °C, 34%; (c) CAN, CH_3CN, H_2O, −15 °C, 74%; (d) IBX, EtOAc, 80 °C; $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, *t*-BuOH, H_2O, 70%; (e) BBr_3, CH_2Cl_2, −78 °C; MeOH, HCl, rt, 71%.

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 Et_2O 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 Rickborn[12] conditions using KOH in DMF/H_2O (10:1). Treatment of the crude mixture thus obtained with hydrochloric acid resulted in the regioselective opening[4a−d] of the two bicyclooxaheptene rings, and subsequent air oxidation furnished the anthrarufin **19** in 34% overall yield together with several unidentified products.

Completion of the synthesis of vineomycinone B_2 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 $NaClO_2$. Global deprotection of the benzyl groups with BBr_3 followed by workup with methanolic hydrogen chloride provided synthetic vineomycinone B_2 methyl ester (**1**) in 71% yield. The synthetic material thus obtained gave ^1H and ^{13}C NMR spectra identical to those of an authentic sample.

In summary, a novel and highly convergent synthesis of vineomycinone B_2 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 benzynes 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.

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Supporting Information Available: Experimental procedures for **2**−**4**, **9**, **17**, and **19**, 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 ^{13}C NMR data for synthetic and authentic **1**. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Ōmura, S.; Tanaka, H.; Ōiwa, R.; Awaya, J.; Masuma, R.; Tanaka, K. *J. Antibiot.* **1977**, *30*, 908. (b) Imamura, N.; Kakinuma, K.; Ikekawa, N.; Tanaka, H.; Omura, S. *J. Antibiot.* **1981**, *34*, 1517.

(2) For general reviews of *C*-aryl glycosides, see: (a) Jaramillo, C.; Knapp, S. *Synthesis* **1994**, 1. (b) Levy, D. E.; Tang, C. In *The Chemistry of C-Glycosides*; Elsevier Science: Tarrytown, NY, 1995. (c) Nicotra, F. *Top. Curr. Chem.* **1997**, *187*, 55. (d) Du, Y.; Linhardt, R. J.; Vlahov, I. R. *Tetrahedron* **1998**, *54*, 9913. (e) Liu, L.; McKee, M.; Postema, M. H. D. *Curr. Org. Chem.* **2001**, *5*, 1133.

(3) For total syntheses of vineomycinone B_2 methyl ester, see: (a) Danishefsky, S.; Uang, B. J.; Quallich, G. *J. Am. Chem. Soc.* **1985**, *107*, 1285. (b) Tius, M. A.; Gomez-Galeno, J.; Gu, X. Q.; Zaidi, J. H. *J. Am. Chem. Soc.* **1991**, *113*, 5775. (c) Bolitt, V.; Mioskowski, C.; Kollah, R. O.; Manna, S.; Rajapaksa, D.; Falck, J. R. *J. Am. Chem. Soc.* **1991**, *113*, 6320. (d) Matsumoto, T.; Katsuki, M.; Jona, H.; Suzuki, K. *J. Am. Chem. Soc.* **1991**, *113*, 6982.

(4) For syntheses of *C*-aryl glycosides based on furan−benzyne cycloadditions, see: (a) Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *J. Am. Chem. Soc.* **2001**, *123*, 6937. (b) Martin, S. F. *Pure Appl. Chem.* **2003**, *75*, 63. (c) Apsel, B.; Bender, J. A.; Escobar, M.; Kaelin, D. E., Jr.; Lopez, O. D.; Martin, S. F. *Tetrahedron Lett.* **2003**, *44*, 1075. (d) Kaelin, D. E., Jr.; Sparks, S. M.; Plake, H. R.; Martin, S. F. *J. Am. Chem. Soc.* **2003**, *125*, 12994. (e) Chen, C.-L.; Martin, S. F. *Org. Lett.* **2004**, *6*, 3581.

(5) See also: Hart, H.; Lai, C.-Y.; Nwokogu, G. C.; Shamouilian, S. *Tetrahedron* **1987**, *43*, 5203.

(6) (a) Czernecki, S.; Ville, G. *J. Org. Chem.* **1989**, *54*, 610. (b) Boyd, V. A.; Drake, B. E.; Sulikowski, G. A. *J. Org. Chem.* **1993**, *58*, 3191.

(7) Goldsmith, D.; Liotta, D.; Saindane, M.; Waykole, L.; Bowen, P. *Tetrahedron Lett.* **1983**, *24*, 5835.

(8) Soderquist, J. A.; Brown, H. C. *J. Org. Chem.* **1980**, *45*, 3571.

(9) The enantiomer of **11** is known. See: Corey, E. J.; Guzman-Perez, A.; Noe, M. C. *J. Am. Chem. Soc.* **1995**, *117*, 10805.

(10) For regioselective brominations, see: (a) Mitchell, R. H.; Lai, Y.-H.; Williams, R. V. *J. Org. Chem.* **1979**, *44*, 4733. (b) Bock, I.; Bornowski, H.; Ranft, A.; Theis, H. *Tetrahedron* **1990**, *46*, 1199.

(11) Prepared in 35% yield by silylation of 1.25 equiv of **5** (Sigma-Aldrich) with 1.0 equiv of TBSCl and imidazole in DMF.

(12) (a) The reaction using KOH in DMF/H_2O (10:1) was more efficient than in DMSO, but use of TBAF gave multiple unidentified products. (b) Netka, J.; Crump, S. L.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 1189. (c) Camenzind, R.; Rickborn, B. *J. Org. Chem.* **1986**, *51*, 1914.

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