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Tandem intramolecular benzyne–furan cycloadditions. Total synthesis of vineomycinone B_2 methyl ester

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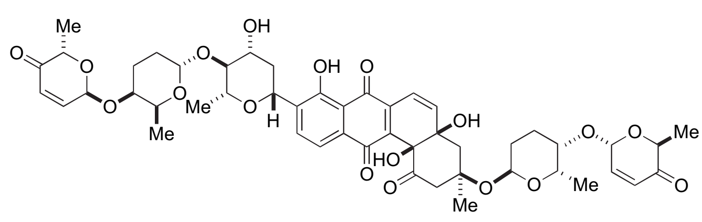
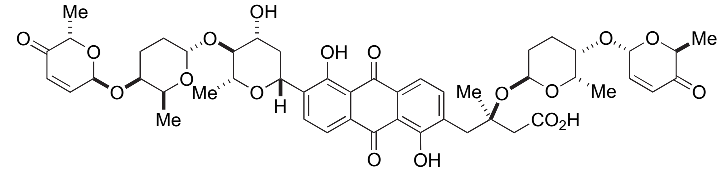
Abstract—We have exploited tandem intramolecular benzyne–furan cycloadditions employing three different benzyne precursors to generate substituted bisoxabenzonorbornadienes in a *single* operation. The regiochemical outcomes in these Diels–Alder reactions were effectively controlled by using disposable silicon tethers to link the reacting benzyne and furan moieties. Two different methods for converting the intermediate bisoxabenzonorbornadienes to substituted anthrarufins were developed. The first tactic entails the initial cleavage of the silicon tethers followed by regioselective ring opening of the oxabicycloheptadienes and oxidation of the central ring giving the target anthrarufin, whereas the second features the regioselective ring opening of the oxabicycloheptadienes followed by protiodesilylation and oxidation. When the starting furans bear carbohydrate substitutents, this new methodology enables the rapid assembly of the glycosyl-substituted aromatic cores of complex *C*-aryl glycoside antibiotics from simple starting materials. The utility of this novel approach to anthrarufins and *C*-aryl glycosides is exemplified in a triply convergent synthesis of vineomycinone B_2 methyl ester.

1. Introduction

The vineomycins A_1, A_2, B_1, and B_2 comprise a group of 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] Although the structures of vineomycins A_1 and B_2 have been determined as **1** and **2**, respectively, vineomycins A_2 and B_1 have not been fully characterized. Vineomycin A_1 has been shown to be identical with a *Streptomyces* metabolite P-1894B that was previously reported as a potent inhibitor of prolyl hydroxylase (IC_{50}=2.2 μM),[2] which as one of the key enzymes in collagen biosynthesis catalyzes the hydroxylation at the 4-position of specific prolyl residues in the peptide precursor of collagen.[3] Vineomycin A_1 has been shown to be effective for treating hypertrophic scar tissue or keloid in vivo,[4] and vineomycin B_2 (**2**) has been used as a biochemical tool to study collagen prolyl hydroxylase.[5] There are a number of natural products that are structurally similar to those of the vineomycin family. These compounds, which also exhibit significant biological activities, include: balmoralmycin, an inhibitor of protein kinase C-α,[6] saquaymycins A and B, which are active against several lines of tumor cells,[7] amicenomycins A and B, which exhibit antimicrobial activity,[8] and the antibacterial agents himalomycins A and B.[9]



Vineomycin A_1 (**1**)



Vineomycin B_2 (**2**)

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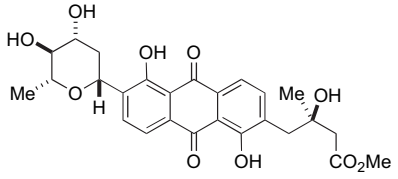
Owing to their intriguing structures and biological activities, a number of studies have been performed with members of the vineomycin family. The biosynthesis of the vineomycins was first studied by Ōmura and co-workers.[10] In their pioneering work, they performed feeding experiments with singly and doubly ^{13}C-labeled acetate and found that the tetracyclic ring system of vineomycinone A_1 (**1**) and all of the carbon atoms of the central core of vineomycinone B_2 (**2**) were derived from a single decaketide chain.[11]

During the course of structural studies of the vineomycins, it was discovered that when either **1** or **2** was heated in methanolic HCl, the degradation product vineomycinone B_2 methyl ester (**3**) was obtained.[1b] Interestingly, **3** was also generated from the acid-catalyzed methanolysis of aquayamycin.[12] Vineomycinone B_2 methyl ester (**3**) bears an olivose residue appended to one ring of the anthrarufin core and is thus a representative member of the *C*-aryl glycoside family of natural products.[13] The other ring of the anthrarufin core is further endowed with a 3(*R*)-hydroxyisovaleryl side chain, thereby making vineomycinone B_2 methyl ester an intriguing natural product of modest complexity. Indeed, the structure of **3** coupled with the potential anticancer activity of the vineomycins and related compounds has rendered vineomycinone B_2 methyl ester the object of a number of investigations, four of which have culminated in its total synthesis.[14,15]



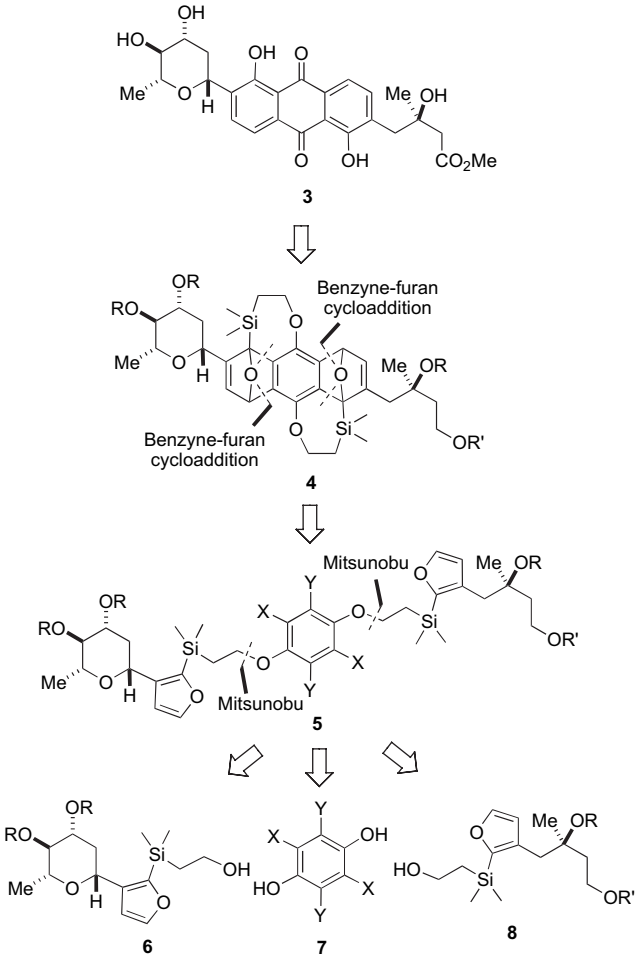
Vineomycinone B_2 methyl ester (**3**)

Like many natural products that have been previously prepared, **3** remains an inspiration for the design and development of new chemistries. In this context, it is noteworthy that we recently developed a general entry to the four major classes of *C*-aryl glycoside natural products by an approach that features the ring opening of cycloadducts that are obtained from Diels–Alder cycloadditions of substituted benzynes with glycosyl furans.[16] We demonstrated the utility of this methodology by its application to a formal synthesis of galtamycinone[17] and 2-aryl naphthol derivatives.[18] Owing to the unsymmetrical arrangement of carbohydrate and functionalized side-chain substituents on the anthrarufin nucleus, it was apparent that vineomycinone B_2 methyl ester (**3**) posed a significant challenge to our methodology. Hence, we decided to embark on the total synthesis of **3** as a more demanding test of the general efficacy of our approach to *C*-aryl glycosides, and we now report the details of these investigations.[19]

2. Results and discussion

2.1. Development of the synthetic plan

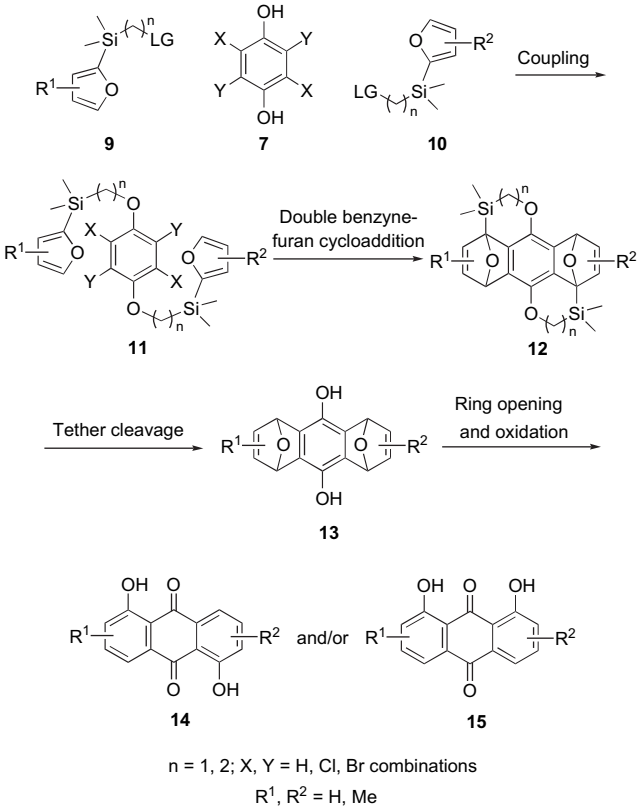
The successful application of our methodology for preparing *C*-aryl glycosides to the synthesis of vineomycinone B_2 methyl ester (**3**) relies on being able to control the regiochemical outcome of two Diels–Alder reactions of unsymmetrical benzyne and furan substrates to assemble the substituted aromatic framework. Although unsymmetrical benzynes are known to undergo regioselective Diels–Alder reactions, such cycloadditions more typically proceed with poor regioselectivity,[20,21] so our entry to *C*-aryl glycosides that involved using disposable silicon tethers to link the reacting benzyne and furan moieties was of particular interest.[16c,22] After considering a number of possibilities, a novel and highly convergent strategy eventuated for the synthesis of vineomycinone B_2 methyl ester (**3**) (Scheme 1). The approach features tandem intramolecular benzyne–furan cycloadditions originating from the key intermediate **5** to generate the bisoxabenzonorbornadiene **4**, thereby swiftly assembling the entire skeletal framework in a single operation. The conversion of **4** into **3** requires cleavage of the silicon tethers, regioselective ring opening of the oxabenzonorbornene core, global removal of the oxygen protecting groups, and adjustment of the oxidation level in the alkyl side chain. The precursor **5** for the tandem cycloaddition sequence would be prepared by the iterative Mitsunobu coupling of a hydroquinone **7**, which would be suitably substituted to serve as a bis-benzyne precursor, with the silicon-substituted furans **6** and **8**, both of which would be derived from readily available starting materials.



Scheme 1. Retrosynthetic analysis.

2.2. Feasibility of tandem benzyne–furan cycloadditions

Given the somewhat speculative nature of our strategy for the synthesis of vineomycinone B_2 methyl ester, we deemed it advisable to conduct some simple model studies to evaluate the underlying efficacy of preparing anthrarufins via tandem benzyne–furan cycloadditions and ring opening. Several important issues were to be evaluated in these preliminary investigations. The first task was to identify a substituted hydroquinone derivative **7** that would twice serve as a benzyne precursor. We and others have found that halohydroquinone derivatives could be readily converted into benzynes upon regioselective deprotonation with alkyllithium reagents,[16,23] so **7** (X=H; Y=Cl or Br) emerged as likely candidates. Hart has shown that tetrabromobenzenes can serve as bis-benzyne precursors in Diels–Alder reaction,[24] so **7** (X=Y=Br) might also be a suitable starting material. In earlier work, we developed silicon tethers containing one and two carbon atoms, so a second undertaking would be to ascertain which of these would be optimal in tandem benzyne–furan reactions. Hence, we would need to prepare substituted furans of the general structure **9** and **10** (n=1, 2; R^1, R^2=H, Me) and couple these with **7** to provide compounds of the general form **11** (Scheme 2). We would then be in a position to establish the feasibility of the key tandem benzyne–furan Diels–Alder reactions to give **12**. The specific tactic used to remove the silicon tethers of **12** to give **13** would depend upon the nature of the tether itself, but the requisite protocols had been developed in previous work.[16c]

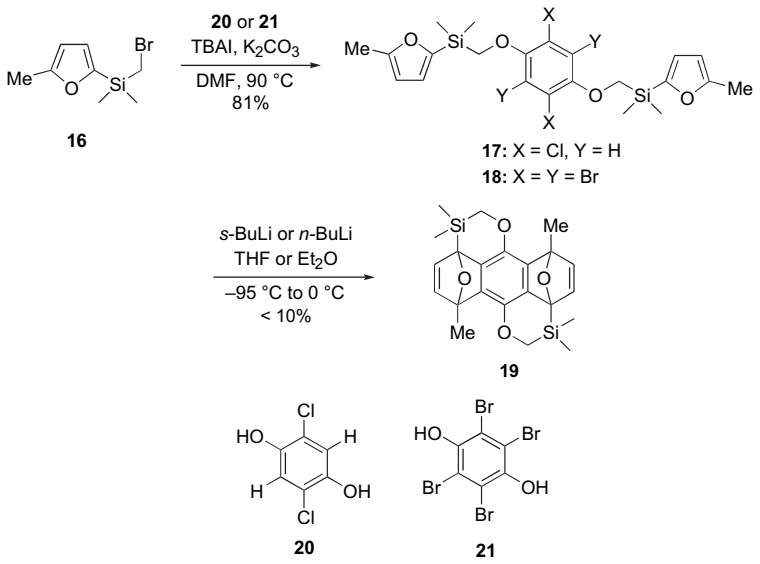


Scheme 2. Planning for model studies.

Less predictable was the regiochemical issue related to opening of the two oxabenzonorbornene rings in **13** to give, subsequent to oxidation, the desired anthrarufin **14** or its undesired isomer **15**. Although there was no direct precedent that could be used to predict the regiochemistry of opening of anthracene-derived oxabicycloheptadienes, there was information that provided some guidance. Namely, prior art in our laboratories revealed that the regiochemistry of acid-catalyzed ring openings of oxabicycloheptadienes was directed by the orientation of substituents on the bicyclic ring.[16c] The directing effect of bridgehead substituents in such openings is absolute as only one cleavage mode leads to a naphthol ring. When the substituent is on the carbon–carbon double bond, its effect on the direction of ring opening is not as strong, but the product in which the substituent is *ortho* to the naphthol hydroxyl group is generally the major product.[25] Thus, the regiochemistry of ring opening of an adduct **12** in which the substituents R^1 and R^2 were located on the carbon–carbon double bond would be expected to be different from that of comparably substituted **13**. Hence, we reasoned that the orientation of R^1 and R^2 on **13** would be expected to play a significant role in determining whether **14** or **15** was formed preferentially. In the context of the eventual application of this chemistry to the synthesis of vineomycinone B_2 methyl ester, it appeared likely that the substitution pattern (e.g., on **4**) would lead to the preferential formation of the anthrarufin core.

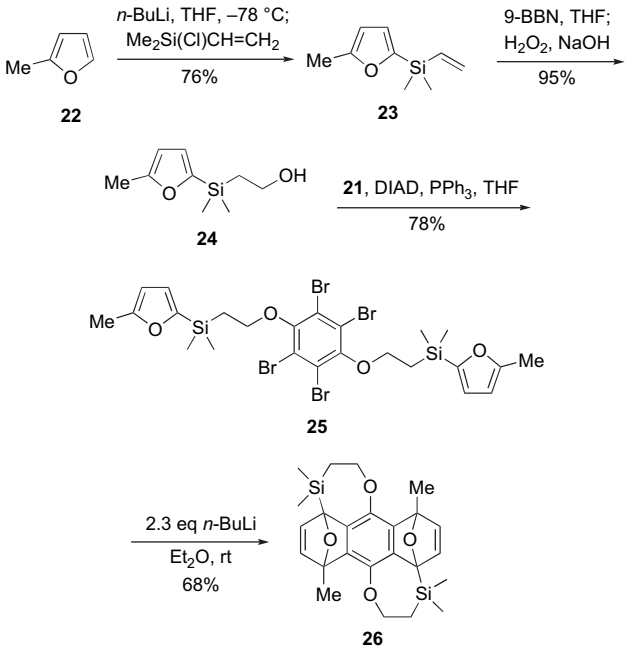
We thus first set to the task of determining what kinds of substrates of the general type **11** would undergo efficient tandem benzyne–furan cycloadditions. Namely, what haloarene would best serve as a bis-benzyne precursor and what was the optimal length of the silicon tether. Toward addressing these questions, we first prepared **17** and **18** by coupling dicholorohydroquinone (**20**)[26] and 2,3,5,6-tetrabromohydroquinone (**21**) with furan **16** using K_2CO_3 and tetra-*n*-butylammonium iodide (TBAI) in DMF at 90 °C (Scheme 3). Although we had previously found that acetone was a good solvent for related alkylations,[16c] its use in these reactions provided only small quantities of the alkylated phenols. It is worth noting that the use of acetone as the solvent, which was successful for the alkylation of 2,6-dichoro-4-methoxyphenol with alkyl bromides, failed to provide the coupling products. The methyl group on the furan rings in **17** and **18** would obviate any possible side reactions associated with deprotonation of the furan ring during the benzyne generating step(s). When **17** was treated with 2 equiv of either *s*-BuLi or *n*-BuLi at low temperatures in accord with our prior work,[16] only trace amounts at best of the cycloadduct **19** were isolated, despite considerable experimentation. Reaction of **18** with *n*-BuLi in Et_2O also produced a complex mixture, but **19** could be reliably isolated in about 5–10% yield. However, all attempts to increase the yield by varying solvent (THF, toluene), temperature (0 °C to room temperature), or by using additives (TMEDA) were fruitless.

These failures naturally led us to query the origin of our unexpected difficulties. Examination of models of **19** suggested that it might be highly strained, so we decided to explore the potential of silicon tethers containing two methylene groups. Toward this objective, we used methods previously developed in our laboratories to convert 2-methylfuran (**22**) into **24**.[16c] Namely, lithiation of **22** followed by reaction with commercially available chlorodimethylvinylsilane gave **23**, which was hydroborated employing 9-BBN



Scheme 3. Probing the feasibility of one-carbon silicon tethers.

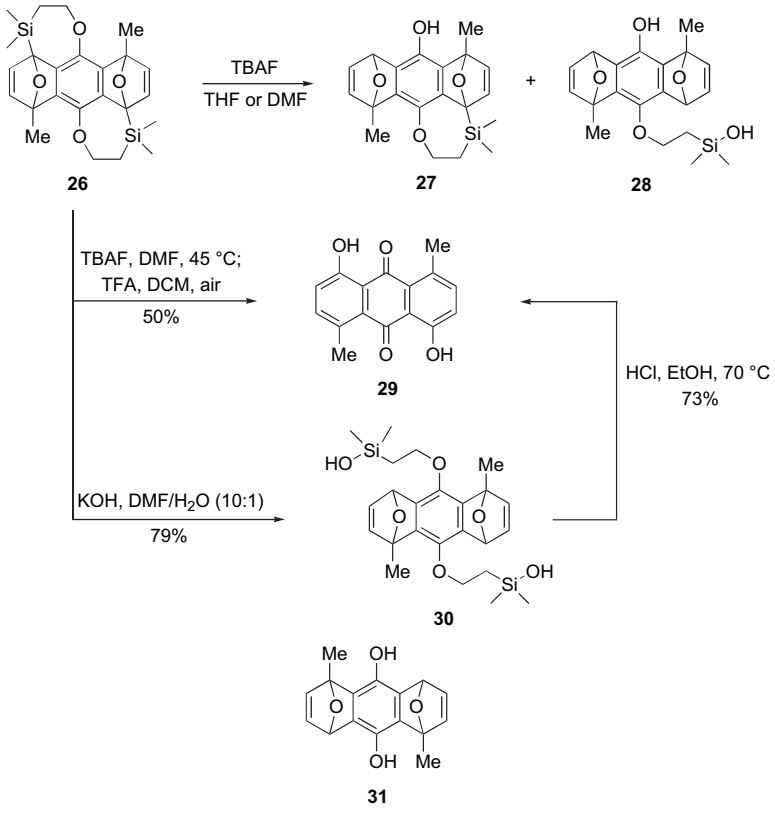
and oxidized (NaOH, H_2O_2) to afford **24** in 72% yield over two steps (Scheme 4).[27] We found in ancillary studies that derivatives of **20** did not serve effectively as precursors of bis-benzynes, so we focused on alkylated tetrabromohydroquinones. Accordingly, **24** was coupled with **21** by a double Mitsunobu reaction using diisopropylazodicarboxylate and triphenylphosphine to give **25** in 78% yield. After some experimentation, we discovered that when **25** was treated with a slight excess of *n*-BuLi in Et_2O (0.02 M) at room temperature the bis-cycloadduct **26** could be isolated as a mixture of diastereomers in 68% yield. To our knowledge, this constituted the first example of a tandem intramolecular benzyne–furan Diels–Alder reaction.



Scheme 4. Probing the feasibility of two-carbon silicon tethers.

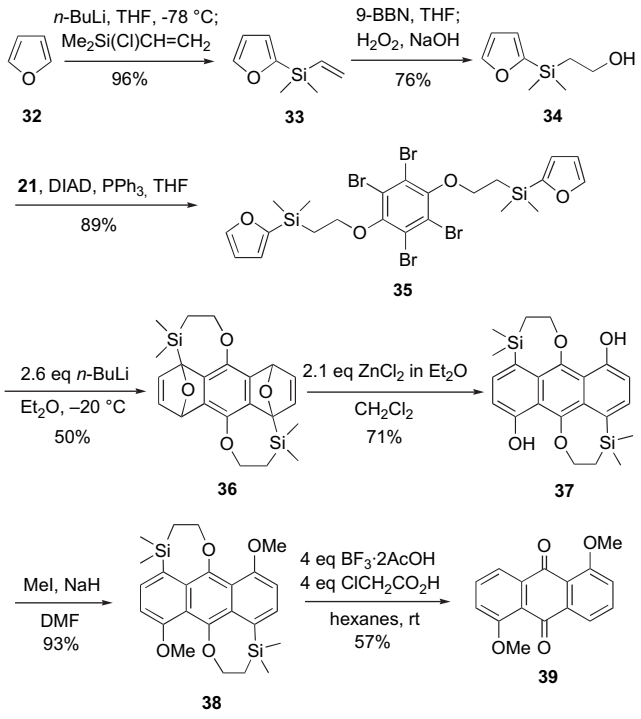
With the cycloadduct **26** in hand, it remained to explore tactics for its elaboration into an anthraquinone. We initially hoped to remove the β-dimethylsilylethyl tethers in cycloadduct **26** to afford the hydroquinone **31** (Scheme 5). However, treatment of **26** in THF with excess tetra-*n*-butylammonium fluoride (TBAF) provided a mixture of diastereomeric phenols **27**, arising from removal of only one β-dimethylsilylethyl tether from **26**. When the reaction was run in DMF, diastereomeric phenols **28** were isolated, even when the solution was warmed. We were thus unable to effect complete removal of the silicon tethers in a single step. We did find that exposure of **28** to acid led to anthrarufin **29**, presumably by the facile oxidation of the intermediate anthrol, and we developed a simple two-step procedure for converting **26** into **29** in up to 50% yield. Because this procedure was somewhat irreproducible, we turned to an alternative tactic to cleave bridgehead silicon–carbon bonds using KOH or KO-*t*-Bu in DMSO that was reported by Rickborn.[28] Indeed, we found that under the Rickborn conditions **26** underwent desilylation to give **30**, but the reaction was relatively slow and was accompanied by some decomposition. After extensive screening of various combinations of bases (KOH, NaOH, K_2CO_3) and solvents (DMSO, DMF, water), we developed a modification of the Rickborn protocol and discovered that the use of KOH in DMF/H_2O (10:1) was faster and more effective and provided **30** in 79% yield. Subsequent ring opening of **30** with HCl in ethanol and aerial oxidation delivered **29** in 73% yield. We had thus established the viability of our entry to anthrarufins by a procedure that featured tandem intramolecular benzyne–furan cycloadditions.

Because the furan rings in intermediates related to **5** lack substitution at the 5-position, we decided to conduct one more model study to ascertain whether an acidic proton on the furan might compromise the efficiency of the key tandem intramolecular benzyne–furan Diels–Alder reactions. In the event, furan (**32**) was converted into **35** in three steps and 65% overall yield following the same procedure used to prepare **25** (Scheme 6). Gratifyingly, the tandem benzyne–furan cycloadditions were then induced by treating **35** with excess *n*-BuLi (2.6 equiv) in Et_2O (0.02 M) at −20 °C to afford **36** in 50% yield, thereby establishing that acidic protons at the 5-position of the furan are compatible with the sequence.



Scheme 5. Synthesis of a simple anthrarufin.

The conversion of **26** into **29** was accomplished by tether cleavage, followed by acid-catalyzed rearrangement of the oxabicycloheptadienes and oxidation. We queried whether the alternate sequence of rearrangement, followed by tether cleavage and oxidation might also be a viable protocol for generating anthrarufins. After screening several conditions and acids (TMSOTf, 2,6-lutidine, CH_2Cl_2; CF_3CO_2H, CH_2Cl_2), we discovered that $ZnCl_2$ was an effective catalyst for converting **36** into **37**.[29] Because **37** was unstable, it was methylated to give **38**. We anticipated that fluoride would induce the cleavage of all silicon–carbon bonds in **38**, but were disappointed to find that treatment of **38** with excess TBAF at 70 °C, followed by oxidation gave **39** in only 22% yield. On the other hand, reaction of **38** with boron trifluoride–acetic acid complex and chloroacetic acid in hexanes at room temperature gave **39** in 57% yield;[30] yields were lower when ether or EtOAc was used as solvent.



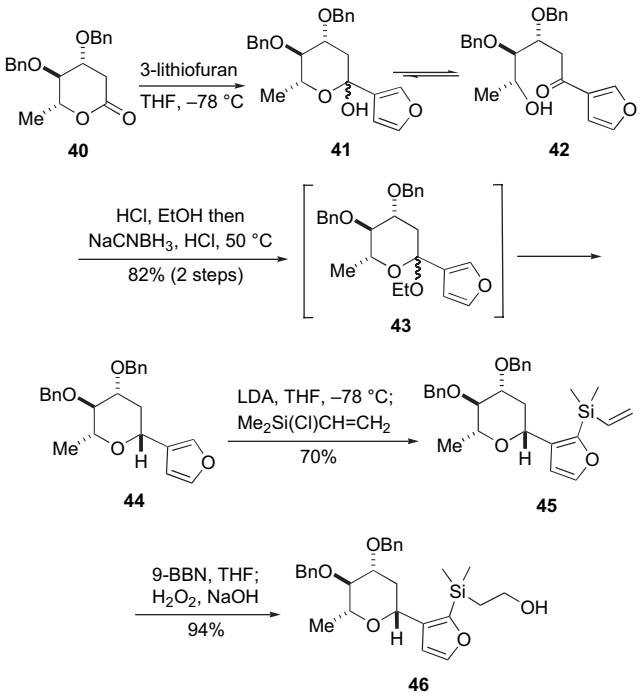
Scheme 6. Alternate route to a simple anthrarufin.

In summary, we had convincingly demonstrated the feasibility of conducting tandem intramolecular double benzyne–furan cycloadditions of substrates in which the hydroquinone and furan moieties of the precursor were linked using silicon tethers containing two carbon atoms. The cycloadducts thus obtained could be converted into anthrarufins by two protocols that varied with respect to the ordering of the steps involving tether cleavage and ring opening of the oxabenzonorbornene rings. Based upon these advances, we turned to the more challenging task of the total synthesis of vineomycinone B_2 methyl ester (**3**) according to the plan outlined in Scheme 1.

3. Total synthesis of vineomycinone B_2 methyl ester

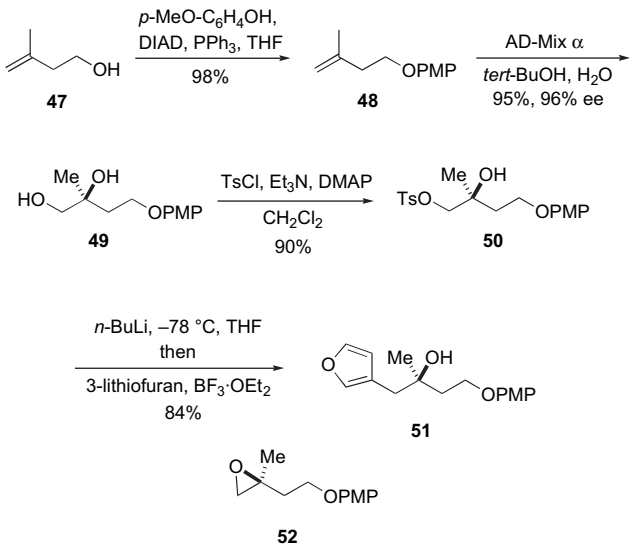
The first phase of the synthesis of vineomycinone B_2 methyl ester (**3**) was initiated by the preparation of substituted furans related to **6** and **8**. Because we had prepared similar compounds in other work, the basic chemistry had been

established. The basic problem, as in many efforts in total synthesis of complex natural products, was one of selecting the proper protecting groups. Inasmuch as our plan involved a global removal of all hydroxyl protecting groups as the final step in the synthesis, we envisioned that benzyl ethers would be well suited to the task. The glycosyl furan **46** thus emerged as an initial subgoal. The synthesis of **46**, which closely followed our previous work,[16] commenced with the addition of 3-lithiofuran to the known lactone **40**[16c] to afford a mixture of lactols **41**, which were in equilibrium with the open chain keto-alcohol **42** as evidenced by the ^{1}H NMR spectrum (Scheme 7). When this mixture was treated with ethanolic HCl, a mixture of ethyl acetals **43** was produced. Subsequent stereoselective reduction of **43** was induced by heating in ethanolic HCl in the presence of $NaCNBH_3$ to afford **44** in 82% overall yield. Regioselective deprotonation of **44** followed by trapping the furyl anion thus formed with chlorodimethylvinylsilane furnished the vinylsilane **45**, hydroboration and oxidation of which delivered **46** in 66% yield over two steps.



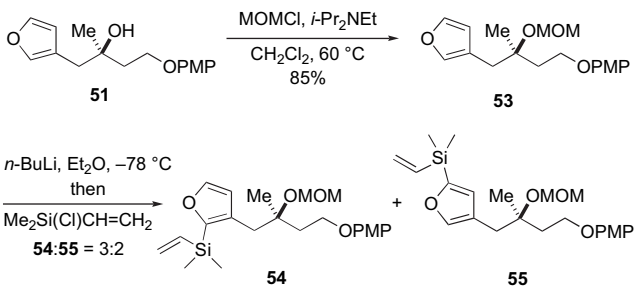
Scheme 7. Synthesis of a glycosyl furan with disposable tether.

The next phase of the synthesis required the synthesis of a substituted furan related to **8**. Toward this objective, the first task was the enantioselective preparation of the 3-substituted furan **51**, which we envisaged would result from the reaction of 3-lithiofuran with the epoxide **52**. We considered two possible approaches to **52**. The first would rely upon a useful protocol for the enantioselective epoxidation of homoallylic alcohols using chiral vanadium catalyst that was reported by Yamamoto.[31] Relevant to the task at hand was the observation that epoxidation of 3-methyl-3-butenol (**47**) under these conditions provided the corresponding epoxy alcohol in 58% yield and 84% enantiomeric excess. Alternatively, Corey expanded the scope of Sharpless asymmetric dihydroxylation to homoallylic alcohol derivatives and found that dihydroxylation of 1-(4-methoxyphenoxy)-3-methyl-3-butene **48** using $(DHQD)_2PYDZ\cdot OsO_4$ as the catalyst provided the enantiomer of **49** in 99% yield and 96% enantiomeric excess.[32] Thus, for the specific problem at hand, the Sharpless asymmetric dihydroxylation appeared to be the method of choice. Accordingly, 3-methyl-3-butenol **47** was first protected as its *p*-methoxyphenyl (PMP) ether **48** and subjected to Sharpless asymmetric dihydroxylation conditions using AD-mix α to afford diol **49** in 93% yield over two steps (96% ee) (Scheme 8). Treatment of diol **49** with tosyl chloride and triethylamine in the presence of a catalytic amount of DMAP selectively afforded the primary tosylate **50**. In initial studies **50** was converted into **51** in two steps via cyclization to the epoxide **52** (K_2CO_3, MeOH, 89%; 3-lithiofuran, $BF_3\cdot OEt_2$, THF, 89%). However, we discovered a more expeditious one-pot procedure that involved cyclization of **50** by deprotonation with *n*-BuLi followed by facile opening of the intermediate **52** formed in situ with 3-lithiofuran in the presence of $BF_3\cdot OEt_2$ to provide the tertiary alcohol **51** in 84% yield.



Scheme 8. Synthesis of 3-substituted furan.

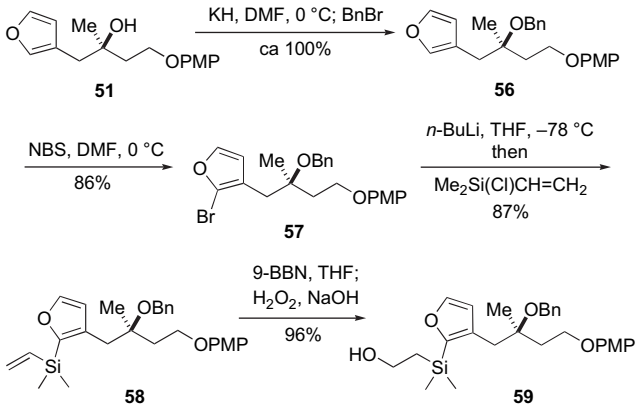
Having established a reliable method for preparing the 3-alkyl furan **51**, the next task involved selective introduction of the silicon-derived tether at the 2-position. We envisioned that selective deprotonation at the 2-position might be effected through the agency of a suitable directing group that would also serve as the protecting group for the tertiary alcohol of **51**. Indeed, we had performed related selective deprotonations in earlier work in the area.[16c] Because of the known ability of MOM ethers to direct deprotonations,[33] **51** was protected accordingly to give **53** (Scheme 9). To our



Scheme 9. Attempted selective functionalization of **51**.

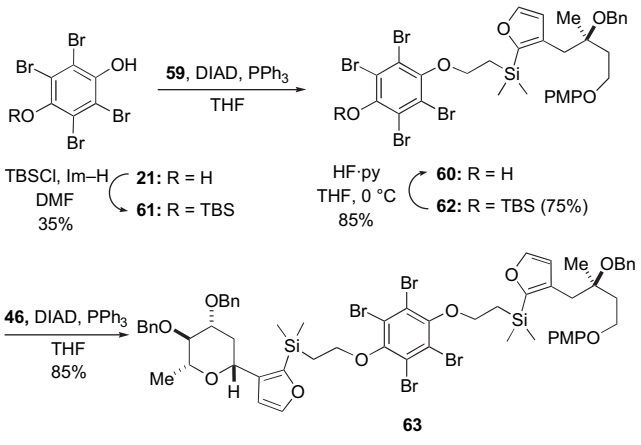
considerable disappointment, however, sequential reaction of furan **53** with *n*-BuLi in Et_2O at −78 °C and then chlorodimethylvinylsilane provided a mixture (3:2) of furans **54** and **55** in modest yield.

Although the directed deprotonation of **53** was not selective, we discovered that electrophilic bromination was. However, since protecting the tertiary alcohol in **51** as its MOM ether would not be compatible with our goal to effect a global deprotection as the final step of the synthesis, **51** was converted into **56** by O-benzylation (Scheme 10). Highly regioselective bromination of **56** was then effected by reaction with NBS to furnish **57** in 86% yield from **51**.[34] Subjection of **57** to metal–halogen exchange and reaction of the intermediate anion with chlorodimethylvinylsilane delivered exclusively the vinylsilane **58** in 87% yield. Subsequent hydroboration and oxidation of the vinyl moiety as before furnished the furan **59**.



Scheme 10. Preparing a 3-substituted furan with disposable tether.

With the requisite furans **46** and **59** in hand, it remained to assemble the appropriate precursor for tandem benzyne–furan Diels–Alder reaction. In an attempt to assemble **63** from **21**, **46**, and **59** without any protection steps, **59** was treated with 4 equiv of **21**, triphenylphosphine, and diisopropylazodicarboxylate in THF, but a complex mixture of products was obtained from which little **60** could be isolated (Scheme 11). In order to circumvent this problem, hydroquinone **21** was monoprotected by reaction with TBSCl and imidazole in DMF to give phenol **61**. Subsequent reaction of **61** with **59** via Mitsunobu coupling furnished aryl ether **62** in 75% yield. Removal of the silyl protecting group with HF·pyridine in THF gave the phenol **60**, which was then coupled with furan **46** via a second Mitsunobu reaction to deliver **63** in 72% yield over two steps.

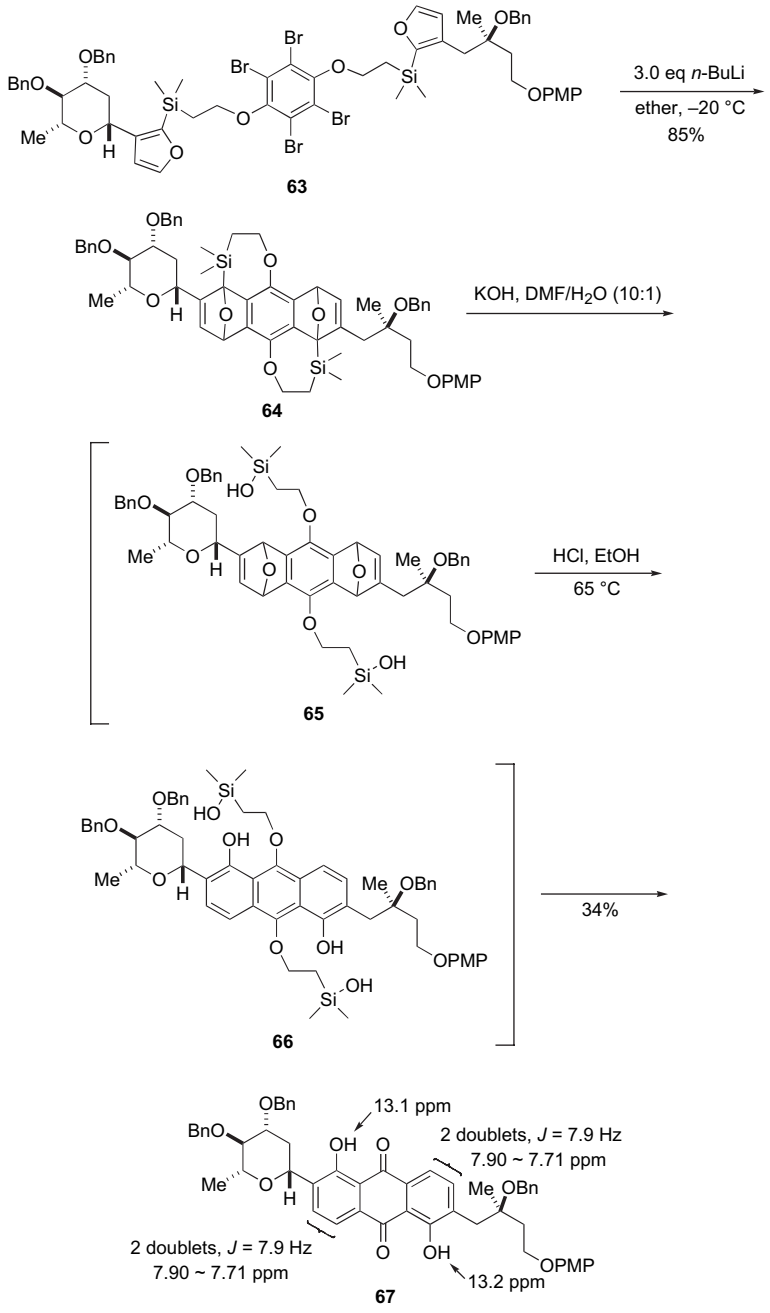


Scheme 11. Setting stage for tandem benzyne–furan cycloaddition.

The stage was now appropriately set for the pivotal tandem benzyne–furan cycloaddition of **63**. In our initial studies, we found that dropwise addition of 2.6 equiv of *n*-BuLi (0.23 M) to a solution of tetrabromide **63** in Et_2O at −20 °C afforded the desired bis-cycloadduct **64** as a mixture of diastereomers in variable and irreproducible yields ranging from 30 to 60% (Scheme 12). It became evident that these variable yields arose from traces of water remaining in the tetrabromide **63** that quenched the aryllithium intermediates. In order to ensure that there was no adventitious water to undermine the yield, **63** was dried in a Kügelrohr oven under vacuum for 2 h at 140 °C. When this dried material was treated with 3.0 equiv of *n*-BuLi (0.23 M) in Et_2O at −20 °C, the diastereomeric mixture of bis-cycloadducts **64** was obtained in 85% yield. The temperature at which this reaction was performed was found to be important. For example, if **63** was treated with *n*-BuLi at −78 °C or −50 °C, the yield of **64** plummeted to less than 30%, and other products, which were not characterized, were also obtained. It thus appears that the benzyne must be generated at a temperature where the cycloaddition is sufficiently rapid as to avoid deleterious side reactions of the intermediate benzynes.[24]

The tricky task of cleaving the silicon tethers and opening the two oxabicycloheptadiene rings to unveil the anthrarufin core was now at hand. As we had observed in our model studies with **26**, complete removal of the tethers from **64** with various fluoride sources (e.g., TBAF, TBAT, CsF, HF·Py) in different solvents (e.g., DMF, THF, dichloromethane, DMSO) at several temperatures (e.g., room temperature, 45 °C, 60 °C, 80 °C) was problematic. When these mixtures were then treated with various acids (e.g., TFA, TMSOTf, and $BF_3 \cdot Et_2O$) in several solvents (e.g., THF, dichloromethane, toluene) to complete the removal of the tether and open the oxabicycloheptadienes, complex mixtures containing isomeric anthraquinones and other unidentified compounds were obtained. Inspection of the ^1H NMR spectra of these mixtures revealed some signals that might arise from the desired product **67**, but these were minor. However, we again found that the modified Rickborn conditions that we had developed for converting **26** into **29** were also best suited for cleaving the silyl tethers as the first step in transforming **64** into **65**. In the event, reaction of **64** with KOH in DMF/H_2O (10:1) proceeded cleanly to provide a mixture of diastereomers **65**.

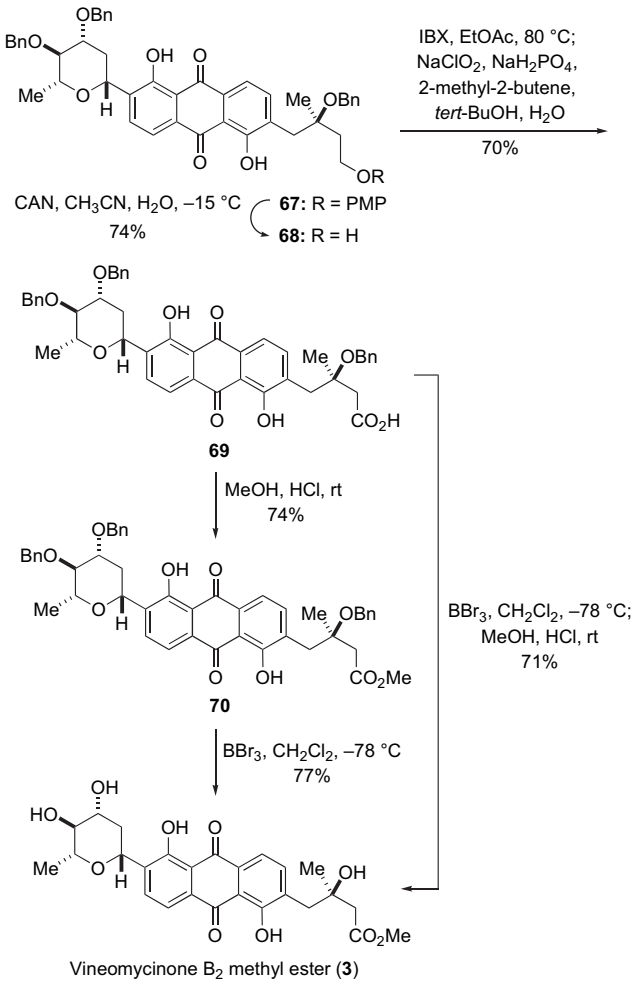
Optimizing the acid-catalyzed reaction to open the oxabicycloheptadienes present in **65** also required some experimentation. A quick survey of various Lewis acids (e.g., $ZnCl_2$, $BF_3 \cdot Et_2O$, and $TiCl_4$) revealed that they were not very effective in promoting the desired ring opening of **65** leading to **67**. A more promising result was obtained upon stirring **65** with TFA in CH_2Cl_2 to give a complex mixture from which **67** could be isolated in about 7–20% yield. However, when **65** was heated in ethanolic HCl under carefully defined conditions the desired anthrarufin **67** was



Scheme 12. Construction of substituted anthrarufin core of **3**.

reproducibly isolated in 34% overall yield, likely via aerial oxidation of **66** or a related intermediate.[35] An inseparable mixture of several other products was also obtained, and although these compounds could not be fully characterized, an analysis of the ^{1}H NMR spectrum of the mixture suggested that some of these were isomers of **67**. That **67** possessed the requisite substitution pattern on the anthrarufin core was supported by its ^{1}H NMR spectrum. Namely, the *ortho* relationship of the phenolic hydroxyl groups and the carbohydrate and alkyl substituents on the two rings was evident from the appearance of four doublets (J=7.9 Hz) at 7.90–7.71 ppm. The downfield chemical shift of the phenolic protons, which appeared as two singlets at 13.1 and 13.2 ppm, is in accord with their being hydrogen bonded to the adjacent carbonyl groups.

Completing the synthesis of vineomycinone B_2 methyl ester (**3**) required adjusting the oxidation level of the aliphatic side chain to a carboxylic acid, followed by global deprotection that proceeded largely in accord with our original plan. Namely, the PMP group was first cleaved from **67** under oxidative conditions with CAN (20:1 acetonitrile/H_2O, −15 °C) to give alcohol **68** in 74% yield (Scheme 13). Use of other typical solvent systems (e.g., 1:1 CH_2Cl_2/H_2O, 4:1 acetonitrile/H_2O, and 3:1:1 acetonitrile/pyridine/H_2O) gave lower yields of product. Although we found that oxidation of the primary alcohol function in **68** to give the acid **69** could be achieved in one step using PDC in DMF, the yields were modest. On the other hand, treatment of **68** with IBX followed by oxidation of the intermediate aldehyde with $NaClO_2$ gave **69** cleanly in 70% overall yield.



Scheme 13. Completion of the total synthesis of **3**.

Although reaction of **69** with methanolic hydrogen chloride gave the methyl ester **70** in 74% yield, we were unable to cleanly remove all of the benzyl protecting groups by hydrogenolysis with either 10% Pd/C or 10% $Pd(OH)_2$/C at pressures up to 9 atm. On the other hand, reaction of **70** with BBr_3 in dichloromethane at −78 °C quickly cleaved all of the benzyl groups and furnished vineomycinone B_2 methyl ester (**3**) in 77% yield. Alternatively, we developed a one-step procedure for converting **69** into **3** that involved global deprotection of all of the *O*-benzyl groups using BBr_3 followed by work-up with methanolic hydrogen chloride to deliver synthetic vineomycinone B_2 methyl ester (**3**) in 71% yield. The synthetic **3** thus obtained gave ^1H and ^{13}C NMR spectra identical to those of an authentic sample kindly provided by Professor Tius, and it exhibited an optical rotation and melting point identical to those reported in the literature.[14d]

4. Conclusion

We have demonstrated the feasibility of performing tandem benzyne–furan intramolecular Diels–Alder cycloadditions using compounds in which the benzyne precursor and the reactant furans were linked with silicon tethers containing two methylene groups. The bisoxabenzonorbornadienes thus obtained can be converted into substituted anthraquinones by two different tactics that differed in the order of tether cleavage and acid-catalyzed opening of the two oxabicycloheptadienes. The practical utility of such constructions was then established by their incorporation as a key step in a novel and highly convergent synthesis of vineomycinone B_2 methyl ester (**3**) via a process that required a longest linear sequence of 16 steps and proceeded with 2.9% overall yield in the longest linear sequence. This synthesis thus represents the first application of our general procedure for the regioselective synthesis of *C*-aryl glycosides using silicon tethers as disposable linkers to control the regiochemistry in Diels–Alder reactions of substituted benzynes and furans. Other applications of this strategy for the rapid assembly of the glycosyl-substituted aromatic cores found in complex *C*-aryl glycoside antibiotics are in progress and will be reported in due course.

5. Experimental

5.1. General

Tetrahydrofuran, dimethylformamide, acetonitrile, and toluene were dried according to the procedure described by Grubbs.[36] All solvents were determined to contain less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. Triethylamine was distilled from calcium hydride prior to use. Reactions involving air or moisture sensitive reagents or intermediates were performed under an inert atmosphere of nitrogen or argon in glassware that was flame dried. Thin layer chromatography was run on pre-coated silica gel plates with a 0.25 mm thickness containing 60 F_{254} indicator (Merck), and the plates were visualized by staining with AMCAN (ammonium molybdate/cerium ammonium nitrate), potassium permanganate, or *p*-anisaldehyde. Flash chromatography was performed using the indicated solvent system on 230–400 mesh silica gel (E. Merck reagent silica gel 60) according to Still's protocol.[37] Melting points are uncorrected. Infrared (IR) spectra were obtained as solutions in the solvent indicated. Proton nuclear magnetic resonance spectra (^1H NMR) were obtained in $CDCl_3$ solutions, and chemical shifts are reported in parts per million (ppm) referenced to the solvent. Coupling constants (*J*) are reported in hertz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; app t, apparent triplet; q, quartet; m, multiplet; comp, complex multiplet; br, broad. Carbon nuclear magnetic resonance spectra (^{13}C NMR) were obtained using $CDCl_3$ as the internal reference.

5.2. Model studies of benzyne–furan cycloadditions leading to anthrarufins

5.2.1. Bromomethyldimethyl-(5-methyl-furan-2-yl)-silane (16). *n*-BuLi (6.6 mL of a 1.5 M solution in hexanes, 10.0 mmol) was added dropwise to a solution of 2-methylfuran **22** (0.82 g, 10.0 mmol) in THF (20 mL) at 0 °C, and the reaction was stirred for 1 h. (Bromomethyl)chlorodimethylsilane (1.5 mL, 11.0 mmol) was added dropwise over 3 min and stirring continued for 30 min. The mixture was diluted with Et_2O (30 mL) and poured onto a mixture of H_2O (15 mL) and brine (15 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The resulting oil

was purified by flash chromatography eluting with pentane to provide 1.98 g (85%) of silane **16** as a colorless oil. ^{1}H NMR (400 MHz) δ 6.61 (d, J=2.8 Hz, 1H), 5.96 (dt, J=2.8, 0.8 Hz, 1H), 2.60 (s, 2H), 2.31 (d, J=0.8 Hz, 3H), 0.37 (s, 6H); ^{13}C NMR (100 MHz) δ 157.3, 154.4, 122.5, 105.9, 16.1, 13.7, −4.3; IR (neat) 2961, 2924, 1593, 1494, 1384, 1252, 1215, 1188, 1018, 812 cm^{-1}; mass spectrum (CI) m/z 233.0009 [$C_8H_{14}OSiBr$ (M+1) requires 232.9997], 225 (base).

5.2.2. Dimethyl(5-methylfuran-2-yl)vinylsilane (23). n-BuLi (7.0 mL of a 2.6 M solution in hexanes, 18.2 mmol) was added dropwise to a solution of 2-methylfuran **22** (1.50 g, 18.3 mmol) in THF (8 mL) at 0 °C, and the reaction was stirred for 1 h. Chlorodimethylvinylsilane (7.64 mL, 55.3 mmol) was added dropwise over 3 min and stirring continued for 15 min. The mixture was diluted with Et_2O (30 mL) and poured onto a mixture of H_2O (15 mL) and brine (15 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated to a volume of 6 mL. The resulting red oil was purified by distillation at atmospheric pressure to provide 2.30 g (76%) of vinylsilane **23** as a colorless oil. ^{1}H NMR (250 MHz) δ 6.54 (d, J=3.0 Hz, 1H), 6.24 (dd, J=19.8, 14.7 Hz, 1H), 6.02 (dd, J=14.7, 4.1 Hz, 1H), 5.95 (d, J=3.0 Hz, 1H), 5.77 (dd, J=19.8, 4.1 Hz, 1H), 2.32 (s, 3H), 0.32 (s, 6H); ^{13}C NMR (62.5 MHz) δ 156.9, 156.4, 136.9, 133.0, 121.7, 105.7, 13.7, −3.3; IR (NaCl) 3050, 2960, 1493, 1250 cm^{-1}; mass spectrum (CI) m/z 167.0888 [$C_9H_{15}OSi$ (M+1) requires 167.0892], 167 (base), 151.

5.2.3. 2-[Dimethyl-(5-methylfuran-2-yl)silanyl]ethanol (24). The vinylsilane **23** (2.30 g, 13.8 mmol) was added to a solution of 9-BBN (2.53 g, 20.7 mmol) in THF (42 mL) and stirred for 5 h at ambient temperature. The reaction was cooled to 0 °C and 3 N NaOH (8.2 mL) and 30% H_2O_2 (8.2 mL) were added sequentially. The mixture was stirred for 30 min at 0 °C, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2× 20 mL). The combined organics were dried (Na_2SO_4), concentrated, and the crude product was purified by flash chromatography eluting with hexanes/EtOAc (4:1) to provide 2.42 g (95%) of alcohol **24** as a colorless oil. ^{1}H NMR (250 MHz) δ 6.54 (d, J=3.1 Hz, 1H), 5.95 (d, J=3.1 Hz, 1H), 3.82–3.72 (comp, 2H), 2.32 (s, 3H), 1.50 (br, 1H), 1.22–1.12 (comp, 2H), 0.26 (s, 6H); ^{13}C NMR (62.5 MHz) δ 156.8, 156.7, 121.4, 105.7, 59.8, 20.7, 13.6, −3.0; IR (NaCl) 3434, 2956, 1495, 1035 cm^{-1}; mass spectrum (CI) m/z 184.0923 [$C_9H_{16}O_2Si$ requires 184.0920], 184 (base), 139.

5.2.4. 5-Methylfuran-2-yl-dimethyl[2-(2,3,5,6-tetrabromo-4-phenoxy)ethyl]-4-(2-dimethylsilanyl-5-methylfuran-2-yl)ethoxysilane (25). DIAD (0.16 g, 0.79 mmol) was added to a solution of tetrabromohydroquinone (0.17 g, 0.40 mmol), alcohol **24** (0.15 g, 0.81 mmol), and PPh_3 (0.21 g, 0.80 mmol) in THF (3 mL). The reaction was stirred for 3 h at room temperature and then concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (50:1) to afford 0.24 g (78%) of **25** as a pale yellow oil. ^{1}H NMR (250 MHz) δ 6.55 (d, J=3.0 Hz, 2H), 5.96 (d, J=3.0 Hz, 2H), 4.13–4.04 (comp, 4H), 2.32 (s, 6H), 1.55–1.46 (m, 4H), 0.31 (s, 12H); ^{13}C NMR (62.5 MHz) δ 156.9, 156.2, 151.9, 121.7, 121.5, 105.8, 71.4, 17.6, 13.7, −2.9; IR (NaCl) 2955, 2884, 1347, 1057 cm^{-1}; mass spectrum (CI) m/z 752.8322 [$C_{24}H_{29}Br_4O_4Si_2$ (M−1) requires 752.8338], 731, 621 (base).

5.2.5. Cycloadduct 26. n-BuLi (1.1 mL of a 2.6 M solution in hexanes, 2.8 mmol) was added dropwise at 1.0 mL/h to a solution of **25** (0.91 g, 1.20 mmol) in Et_2O (240 mL) at room temperature. After the addition was complete, the reaction mixture was washed with H_2O (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (9:1 to 4:1) to provide 0.36 g (68%) of cycloadduct **26** as a pale yellow solid; mp 172–173 °C; ^{1}H NMR (500 MHz) δ 7.00 (d, J=5.2 Hz, 1H), 6.98 (d, J=5.2 Hz, 1H), 6.84 (d, J=5.2 Hz, 1H), 6.82 (d, J=5.2 Hz, 1H), 4.48 (ddd, J=12.0, 7.5, 2.2 Hz, 1H), 4.42 (ddd, J=12.0, 7.5, 2.2 Hz, 1H), 3.90 (dt, J=12.0, 4.0 Hz, 1H), 3.76 (dd, J=12.5, 4.0 Hz, 1H), 1.97 (s, 3H), 1.95 (s, 3H), 1.56–1.44 (m, 2H), 1.10–1.03 (m, 2H), 0.34 (s, 3H), 0.31 (s, 3H), 0.24 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (125 MHz) δ 146.9, 146.6, 146.5, 146.3, 146.1, 145.2, 144.8, 144.4, 141.5, 140.6, 91.6, 91.4, 85.0, 84.7, 72.3, 71.5, 17.0, 16.9, 16.7, 16.6, −3.4, −4.0, −4.1, −4.2; IR (neat) 2934, 1477, 1448, 1365, 1248, 1108, 1040 cm^{-1}; mass spectrum (CI) m/z 438.1677 [$C_{24}H_{30}O_4Si_2$ requires 438.1683], 339 (base).

5.2.6. Cycloadduct 30. Potassium hydroxide (two pellets) and H_2O (0.3 mL) were added to a solution of cycloadduct **26** (80 mg, 0.18 mmol) in DMF (3 mL), and the mixture was stirred for 2 h at room temperature. The mixture was diluted with 50% Et_2O/hexanes (50 mL) and washed with brine (5×5 mL). The organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (1:2) to afford 68 mg (79%) of **30** as a yellowish oil. ^{1}H NMR (400 MHz) δ 7.02–6.96 (m, 2H), 6.81 (d, J=5.6 Hz, 2H), 5.69 (dd, J=4.0, 2.0 Hz, 2H), 4.05–3.96 (m, 4H), 1.96 (s, 7H, 2CH_3 and OH), 1.62–1.57 (br, 1H, OH), 1.25–1.12 (m, 4H), 0.20 (s, 12H); ^{13}C NMR (125 MHz) δ 146.6, 146.4, 144.1, 144.0, 143.5, 143.3, 142.7, 142.7, 142.1, 141.9, 90.1, 80.2, 80.2, 72.0, 71.6, 19.8, 19.8, 16.9, 16.9, 0.3, 0.3; IR (neat) 3388, 2915, 2853, 1463, 1249 cm^{-1}; mass spectrum (CI) m/z 474.1874 [$C_{24}H_{34}O_6Si_2$ requires 474.1894].

5.2.7. 1,5-Dihydroxy-4,8-dimethylanthraquinone (29). Cycloadduct **30** (68 mg, 0.14 mmol) in MeOH (4 mL) containing concentrated HCl (five drops) was stirred in air for 3 h at 75 °C. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (10:1) to afford 28 mg (73%) of **29** as a reddish solid; mp 237–238 °C; ^{1}H NMR (500 MHz) δ 13.40 (s, 2H), 7.43 (d, J=8.7 Hz, 2H), 7.19 (d, J=8.7 Hz, 2H), 2.72 (s, 6H); ^{13}C NMR (125 MHz) δ 190.6, 161.8, 141.0, 134.1, 129.4, 124.8, 117.2, 23.5; IR ($CDCl_3$) 3155, 2984, 1641, 1470, 1382, 1096 cm^{-1}; mass spectrum (CI) m/z 269.0816 [$C_{16}H_{13}O_4$ (M+1) requires 269.0814] (base), 253.

5.2.8. 2-[(Furan-2-yl)dimethylsilanyl]ethanol (34). n-BuLi (27.0 mL of a 2.05 M solution in hexanes, 55.4 mmol) was

added dropwise to a solution of furan (8.0 mL, 110.0 mmol) in ether (160 mL) at −78 °C and stirred for 1 h. Chlorodimethylvinylsilane (7.64 mL, 55.3 mmol) was added dropwise over 3 min. The reaction was stirred at −78 °C for 15 min and then quenched with EtOH (4 mL). The mixture was diluted with Et_2O (200 mL) and washed with brine (2× 80 mL). The organic layer was separated, dried (Na_2SO_4), and concentrated to provide 8.1 g (96%) of **33** as a colorless oil. A portion of **33** (1.30 g, 8.5 mmol) thus obtained was dissolved in THF (34 mL), 9-BBN (2.50 g, 20.5 mmol) was added, and the solution was stirred at ambient temperature for 12 h. The reaction was cooled to 0 °C, and 3 N NaOH (3.90 mL) and 30% H_2O_2 (3.90 mL) were added. The mixture was stirred for 25 min at 0 °C, the organic layer was separated, and the aqueous layer was extracted with Et_2O (2× 20 mL). The combined organics were dried (Na_2SO_4), concentrated, and the crude product was purified by flash chromatography eluting with EtOAc/hexanes (1:3) to afford 1.13 g (76%) of alcohol **34** as a colorless oil. ^{1}H NMR (250 MHz) δ 7.66 (d, J=1.6 Hz, 1H), 6.65 (d, J=3.3 Hz, 1H), 6.38 (dd, J=3.3, 1.6 Hz, 1H), 3.81–3.75 (comp, 2H), 1.39 (br, 1H), 1.23–1.16 (comp, 2H), 0.29 (s, 6H); ^{13}C NMR (62.5 MHz) δ 158.8, 146.8, 120.2, 109.4, 59.6, 20.6, −3.1; IR (neat) 3364, 2957, 2926, 1412, 1253, 1035 cm^{-1}; mass spectrum (CI) m/z 170.0766 [$C_8H_{14}O_2Si$ requires 170.0763], 125, 75 (base).

5.2.9. Furan-2-yl-dimethyl[2-(2,3,5,6-tetrabromo-4-ethoxyphenoxy)ethyl]-4-(2-dimethylsilanylfuran-2-yl)-ethoxysilane (35). Diisopropylazodicarboxylate (0.24 g, 1.19 mmol) was added to a solution of tetrabromohydroquinone (0.25 g, 0.59 mmol), alcohol **34** (0.20 g, 1.17 mmol), and triphenylphosphine (0.31 g, 1.18 mmol) in THF (6.0 mL). The reaction was stirred for 2 h at ambient temperature and then concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/EtOAc (20:1) to provide 0.38 g (89%) of **35** as a colorless oil. ^{1}H NMR (250 MHz) δ 7.62 (d, J=1.6 Hz, 2H), 6.64 (d, J=3.1 Hz, 2H), 6.35 (dd, J=3.1, 1.6 Hz, 2H), 4.09–4.02 (comp, 4H), 1.53–1.46 (comp, 4H), 0.31 (s, 12H); ^{13}C NMR (62.5 MHz) δ 158.1, 151.9, 147.0, 121.5, 120.4, 109.4, 71.2, 17.5, −3.0; IR (neat) 2955, 1406, 1348, 1252, 1179, 1056 cm^{-1}; mass spectrum (CI) m/z 726.8187 [$C_{22}H_{27}Br_4O_4Si_2$ (M+1) requires 726.8181], 667, 529 (base), 281.

5.2.10. Cycloadduct 36. A solution of n-BuLi (111 μL of a 1.95 M solution in hexanes, 0.22 mmol) was added dropwise to a solution of **35** (61 mg, 0.08 mmol) in Et_2O (14 mL) at room temperature. Brine (4 mL) was added, and the organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography eluting with hexanes/EtOAc (6:1) to afford 17 mg (50%) of cycloadduct **36** as a yellowish solid; mp 185–186 °C; ^{1}H NMR (250 MHz) δ 7.10–7.00 (comp, 4H), 5.81–5.77 (comp, 2H), 4.62–4.43 (comp, 2H), 3.91–3.70 (comp, 2H), 1.61–1.41 (comp, 2H), 1.17–1.07 (comp, 2H), 0.33 (s, 3H), 0.30 (s, 3H), 0.24 (s, 3H), 0.21 (s, 3H); ^{13}C NMR (62.5 MHz) δ 146.3, 145.1, 145.1, 144.4, 144.1, 143.2, 142.0, 141.1, 139.9, 139.2, 85.7, 85.5, 81.4, 81.2, 72.5, 71.3, 17.1, 16.9, −3.5, −4.0, −4.1, −4.1; IR ($CDCl_3$) 2959, 1482, 1035 cm^{-1}; mass spectrum (CI) m/z 410.1368 [$C_{22}H_{26}O_4Si_2$ requires 410.1370], 411 (base), 383, 355.

5.2.11. Anthracenediol (37). A solution of $ZnCl_2$ (2.92 mL of 1 M solution in Et_2O, 2.92 mmol) was added to a solution of **36** (571 mg, 1.39 mmol) in CH_2Cl_2 (28 mL) at −78 °C. The reaction was allowed to warm to 0 °C over 1 h, and stirring was continued for 40 min at 0 °C. The mixture was diluted with hexanes (70 mL), washed with H_2O (15 mL) and brine (15 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (15:1) to afford 403 mg (71%) of **37** as an orange solid; mp 170–171 °C; ^{1}H NMR (300 MHz) δ 10.53 (s, 2H), 7.58 (d, J=7.5 Hz, 2H), 6.84 (d, J=7.5 Hz, 2H), 5.10–3.98 (br, 4H), 1.80–1.38 (br, 4H), 0.44 (s, 12H); ^{13}C NMR (62.5 MHz) δ 155.8, 152.0, 135.6, 129.5, 123.2, 117.0, 108.6, 78.3, 19.6, 3–0 (br); IR (NaCl) 3402, 2954, 2897, 1463, 1280, 1251, 1082, 1023 cm^{-1}; mass spectrum (CI) m/z 409.1284 [$C_{22}H_{25}O_4Si_2$ (M−1) requires 409.1291], 397 (base), 367.

5.2.12. Anthracenediol dimethyl ether (38). Sodium hydride (235 mg of a 60% suspension in mineral oil, 5.88 mmol) was added to a solution of **37** (403 mg, 0.98 mmol) and CH_3I (2.90 g, 20.4 mmol) in DMF (20 mL) at 0 °C. The reaction was allowed to warm to room temperature over 20 min and stirred for 40 min. H_2O (2 mL) and Et_2O (100 mL) were added, and the mixture was washed with brine (4×15 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (15:1) to afford 400 mg (93%) of **38** as a light orange solid; mp 153–154 °C; ^{1}H NMR (300 MHz) δ 7.57 (d, J=7.5 Hz, 2H), 6.75 (d, J=7.5 Hz, 2H), 5.00–4.60 (br, 2H), 4.40–4.00 (br, 2H), 4.01 (s, 6H), 1.70–1.30 (br, 4H), 0.41 (s, 12H); ^{13}C NMR (75 MHz) δ 157.3, 150.9, 133.7, 133.5, 127.9, 118.9, 103.9, 74.6, 56.2, 19.5, 2–(−1) (br); IR (NaCl) 2955, 2896, 1384, 1331, 1073 cm^{-1}; mass spectrum (CI) m/z 438.1686 [$C_{24}H_{30}O_4Si_2$ requires 438.1683], 411 (base), 395, 382.

5.2.13. 1,5-Dimethoxyanthra-9,10-quinone (39). $BF_3 \cdot 2AcOH$ (17 mg, 0.09 mmol) was added to a solution of **38** (10 mg, 0.02 mmol) and $ClCH_2CO_2H$ (8.6 mg, 0.09 mmol) in hexane (0.5 mL). The reaction was stirred for 40 min at room temperature, whereupon EtOAc (7 mL) was added. The mixture was washed with brine (3×1 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with $CHCl_3$ to afford 3.5 mg (57%) of **39** as a yellowish solid (mp 234–235 °C; lit.[38] mp 234–235 °C) whose ^{1}H and ^{13}C NMR spectral data were consistent with those reported.[38]

5.3. Synthesis of vineomycinone B_2 methyl ester

5.3.1. 3(*R*),4(*R*)-Bisbenzyloxy-6(*R*)-furan-3-yl-2(*R*)-methyltetrahydropyran (44). A solution of 3-bromofuran (0.20 g, 1.36 mmol) in THF (9 mL) was cooled to −78 °C and n-BuLi (0.57 mL of a 2.4 M solution in hexanes, 1.36 mmol) was added dropwise. The reaction was stirred for 10 min, and a solution of lactone **40**[16c] (0.41 g, 1.25 mmol) in THF (3 mL) was added dropwise over 3 min. The reaction was stirred for an additional 30 min and then poured onto saturated $NaHCO_3$ (2 mL). The mixture was diluted with H_2O (20 mL) and extracted with EtOAc (30 mL). The organics were dried ($MgSO_4$) and

concentrated to a colorless oil. The oil was dissolved in EtOH (5 mL) and one drop of HCl in EtOH (prepared from 0.4 mL of AcCl and 5 mL of EtOH) was added. The mixture was stirred for 10 min and then poured onto saturated $NaHCO_3$ (20 mL) layered with EtOAc (20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated to an oil, which solidified upon standing to a colorless solid. The solid was dissolved in EtOH (13 mL) and heated to 50 °C. Bromocresol green (1 mg) was added followed by $NaCNBH_3$ (0.71 g, 11.3 mmol). A solution of HCl in EtOH (prepared from 0.4 mL of AcCl and 5 mL of EtOH) was added dropwise until no acetal remained (~2 mL) as determined by TLC (10% EtOAc/hexanes). The solution was cooled and poured onto saturated $NaHCO_3$ (20 mL) and water (20 mL) and extracted with EtOAc (30 mL). The organics were dried ($MgSO_4$), concentrated, and the resulting residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (9:1) to afford 0.39 g (82%) of glycosyl furan **44** as a colorless oil that was identical in all respects to that reported.[39] ^{1}H NMR (250 MHz) δ 7.41–7.25 (comp, 12H), 6.42 (dd, J=1.6, 0.7 Hz, 1H), 5.00 (d, J=10.8 Hz, 1H), 4.74 (d, J=11.6 Hz, 1H), 4.70 (d, J=10.8 Hz, 1H), 4.66 (d, J=11.6 Hz, 1H), 4.38 (dd, J=11.7, 2.0 Hz, 1H), 3.74 (ddd, J=11.4, 8.7, 5.0 Hz, 1H), 3.49 (dq, J=9.3, 6.2 Hz, 1H), 3.20 (dd, J=9.3, 8.7 Hz, 1H), 2.37 (ddd, J=12.8, 5.0, 2.0 Hz, 1H), 1.78 (ddd, J=12.8, 11.7, 11.4 Hz, 1H), 1.36 (d, J=6.2 Hz, 3H); ^{13}C NMR (75 MHz) δ 143.1, 139.2, 138.5, 128.4, 128.4, 128.4, 128.0, 127.7, 127.6, 127.6, 126.1, 108.8, 84.0, 80.6, 75.6, 75.3, 71.5, 70.0, 37.6, 18.5; IR (neat) 3063, 2973, 2922, 2863, 1952, 1875, 1810, 1604, 1498, 1454, 1364, 1300, 1208, 1162, 1113, 1027, 996 cm^{-1}; mass spectrum (CI) m/z 379.1916 [$C_{24}H_{27}O_4$ (M+1) requires 379.1909].

5.3.2. (2*R*,4*R*,5*R*,6*R*)-[3-(4,5-Bisbenzyloxy-6-methyltetrahydropyran-2-yl)furan-2-yl]dimethylvinylsilane (45). A solution of furan **44** (0.17 g, 0.45 mmol) in THF (2.0 mL) was added to a solution of LDA (0.67 mmol) in THF (3.0 mL) at −78 °C and stirred for 3.5 h. Freshly distilled chlorodimethylvinylsilane (81 mg, 0.67 mmol) was added dropwise, and the mixture was stirred at −78 °C for 5 min. Saturated $NaHCO_3$ (2 mL) was added, and the mixture was extracted with EtOAc (3×5 mL). The combined extracts were dried ($MgSO_4$) and concentrated, and the residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (9:1) to afford 146 mg (70%) of furan **45** as a colorless oil and 50 mg (29%) of recovered **44**. ^{1}H NMR (500 MHz) δ 7.53 (d, J=1.7 Hz, 1H), 7.35–7.27 (comp, 10H), 6.39 (d, J=1.7 Hz, 1H), 6.24 (dd, J=20.4, 14.6 Hz, 1H), 6.01 (dd, J=14.6, 3.6 Hz, 1H), 5.75 (dd, J=20.4, 3.6 Hz, 1H), 4.97 (d, J=10.9 Hz, 1H), 4.69 (d, J=11.6 Hz, 1H), 4.67 (d, J=10.9 Hz, 1H), 4.62 (d, J=11.6 Hz, 1H), 4.43 (dd, J=11.7, 1.9 Hz, 1H), 3.68 (ddd, J=11.3, 8.6, 5.0 Hz, 1H), 3.42 (dq, J=9.2, 6.2 Hz, 1H), 3.17 (t, J=8.9 Hz, 1H), 2.23 (ddd, J=12.9, 5.0, 2.0 Hz, 1H), 1.77 (ddd, J=12.8, 11.6, 11.6 Hz, 1H), 1.32 (d, J=6.2 Hz, 3H), 0.34 (s, 3H), 0.33 (s, 3H); ^{13}C NMR (125.5 MHz) δ 154.4, 146.5, 138.6, 138.5, 136.9, 136.4, 133.1, 128.4, 128.4, 128.0, 127.7, 127.7, 127.6, 108.6, 84.0, 80.9, 75.7, 75.3, 71.5, 70.4, 38.1, 18.6, −2.9, −2.9; IR (NaCl) 2924, 2861, 1498, 1454, 1366, 1114, 1080 cm^{-1}; mass spectrum (CI) m/z 463.2297 [$C_{28}H_{35}O_4Si$ (M+1) requires 463.2304] (base).

5.3.3. (2*R*,4*R*,5*R*,6*R*)-2-{[3-(4,5-Bisbenzyloxy-6-methyltetrahydropyran-2-yl)-furan-2-yl]-dimethylsilanyl}ethanol (46). 9-BBN (47 mg, 0.39 mmol) was added to a solution of vinylsilane **45** (90 mg, 0.19 mmol) in THF (1.0 mL), and the mixture was stirred at room temperature for 2 h. The reaction was cooled to 0 °C, and 3 N NaOH (0.40 mL) and 30% H_2O_2 (0.20 mL) were added sequentially. The mixture was stirred vigorously for 15 min and then extracted with Et_2O (2×2 mL). The combined extracts were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (7:3) to afford 88 mg (94%) of alcohol **46** as a colorless oil. ^{1}H NMR (250 MHz) δ 7.56 (d, J=1.6 Hz, 1H), 7.40–7.26 (comp, 10H), 6.40 (d, J=1.6 Hz, 1H), 5.01 (d, J=10.8 Hz, 1H), 4.76–4.64 (comp, 3H), 4.46 (dd, J=11.6, 1.8 Hz, 1H), 3.81–3.68 (comp, 3H), 3.53–3.44 (comp, 1H), 3.21 (t, J=8.9 Hz, 1H), 2.31 (ddd, J=12.9, 5.0, 1.9 Hz, 1H), 1.83 (q, J=11.6 Hz, 1H), 1.58 (br, 1H), 1.37 (d, J=6.1 Hz, 3H), 1.30–1.14 (comp, 2H), 0.32 (s, 6H); ^{13}C NMR (62.5 MHz) δ 155.1, 146.4, 138.5, 138.4, 136.1, 128.4, 128.3, 127.9, 127.7, 127.6, 108.6, 83.9, 80.7, 75.8, 75.3, 71.5, 70.5, 59.6, 37.9, 20.8, 18.5, −2.5, −2.5; IR ($CDCl_3$) 3619, 2930, 2879, 1364, 1253, 1075 cm^{-1}; mass spectrum (CI) m/z 481.2390 [$C_{28}H_{37}O_5Si$ (M+1) requires 481.2410], 435 (base), 379.

5.3.4. (2*S*)-4-(4-Methoxy-phenoxy)-2-methyl-butane-1,2-diol (49). A solution of 1-(4-methoxyphenoxy)-3-methyl-3-butene **48**[32] (3 g, 15.6 mmol) in *tert*-BuOH (77 mL) was added to a solution of DHQ_2PHAL (120 mg, 0.16 mmol), $K_2OsO_2(OH)_4$ (11 mg, 0.03 mmol), $K_3Fe(CN)_6$ (15.4 g, 46.8 mmol), and K_2CO_3 (6.47 g, 46.8 mmol) in H_2O (77 mL) at 0 °C. The mixture was stirred for 24 h at 0 °C, and Na_2SO_3 (2 g, 15.9 mmol) was added. The mixture was stirred for 20 min, and brine (40 mL) was added. The mixture was extracted with EtOAc/hexanes (2:1, 4×150 mL). The combined organic layers were dried (Na_2SO_4), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with EtOAc to afford 3.35 g (95%) of diol **49** as a white solid (mp 57–58 °C; lit.[32] mp 57–58 °C) of 96% ee (determined by HPLC) whose ^{1}H and ^{13}C NMR spectral data were consistent with those reported.[32]

5.3.5. (2*S*)-Toluene-4-sulfonic acid 2-hydroxy-4-(4-methoxyphenoxy)-2-methylbutyl ester (50). A solution of *p*-toluenesulfonyl chloride (1.65 g, 8.65 mmol) in CH_2Cl_2 (6 mL) was added to a solution of diol **49**[32] (1.63 g, 7.3 mmol), triethylamine (1.50 mL, 10.76 mmol), and 4,4-dimethylaminopyridine (10 mg, 0.08 mmol) in CH_2Cl_2 (30 mL) at room temperature. The solution was stirred for 48 h and then washed with saturated aqueous $NaHCO_3$ (20 mL). The organic layer was separated, dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (7:3) to afford 2.46 g (90%) of tosylate **50** as a colorless oil. ^{1}H NMR (250 MHz) δ 7.78 (d, J=8.3 Hz, 2H), 7.34 (d, J=8.3 Hz, 2H), 6.83–6.74 (comp, 4H), 4.04 (t, J=5.9 Hz, 2H), 3.96 (d, J=9.6 Hz, 1H), 3.88 (d, J=9.6 Hz, 1H), 3.77 (s, 3H), 2.89 (s, 1H), 2.44 (s, 3H), 1.99 (td, J=5.8, 2.0 Hz, 2H), 1.25 (s, 3H); ^{13}C NMR (62.5 MHz) δ 154.2, 152.2, 145.0, 132.5, 129.9, 128.0, 115.4, 114.6, 75.5, 71.0, 64.9, 55.7, 36.9, 24.5, 21.6; IR ($CDCl_3$) 3525, 2935, 1506,

1227 cm^{-1}; mass spectrum (CI) *m/z* 380.1305 [$C_{19}H_{24}O_6S$ requires 380.1294], 380, 209, 191 (base).

5.3.6. (2*S*)-1-Furan-3-yl-4-(4-methoxyphenoxy)-2-methylbutan-2-ol (51). *Method A*. A solution of *n*-BuLi (0.87 mL of a 2.5 M solution in hexanes, 2.18 mmol) was added dropwise to a solution of tosylate **50** (0.83 g, 2.18 mmol) in THF (16 mL) at −78 °C. The reaction mixture was stirred for 10 min, and a solution of 3-lithiofuran (5.45 mmol) in THF (12 mL) at −78 °C was transferred to the mixture via cannula. $BF_3 \cdot Et_2O$ (0.60 mL, 4.74 mmol) was then added, and the reaction was stirred for 1 h. The reaction was quenched by addition of saturated $NaHCO_3$ (5 mL) and extracted with EtOAc (20 mL). The organic layer was washed with brine (2×15 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (3:1) to afford 0.50 g (84%) of furan **51** as a pale yellow oil. ^1H NMR (250 MHz) δ 7.38 (t, *J*=1.5 Hz, 1H), 7.31 (s, 1H), 6.90–6.80 (comp, 4H), 6.36 (s, 1H), 4.15 (t, *J*=6.3 Hz, 2H), 3.77 (s, 3H), 2.70 (d, *J*=14.3 Hz, 1H), 2.63 (d, *J*=14.3 Hz, 1H), 2.37 (br, 1H), 2.07–1.86 (comp, 2H), 1.26 (s, 3H); ^{13}C NMR (62.5 MHz) δ 154.0, 152.7, 142.7, 140.8, 120.1, 115.4, 114.7, 112.6, 71.7, 65.5, 55.7, 39.7, 38.0, 26.7; IR ($CDCl_3$) 3550, 2935, 1508, 1227 cm^{-1}; mass spectrum (CI) *m/z* 276.1368 [$C_{16}H_{20}O_4$ requires 276.1362], 276, 177 (base). *Method B*. Potassium carbonate (0.58 g, 4.20 mmol) was added to a solution of tosylate **50** (0.20 g, 0.53 mmol) in MeOH (10 mL) at room temperature. The reaction was stirred for 45 min and then poured onto Et_2O (80 mL) and water (20 mL). The organic layer was separated and washed with brine (20 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (4:1) to afford 97 mg (89%) of epoxide **52** as a colorless solid; mp 51–53 °C; ^1H NMR (250 MHz) δ 6.82 (s, 4H), 4.07–3.93 (comp, 2H), 3.76 (s, 3H), 2.73 (d, *J*=4.9 Hz, 1H), 2.63 (d, *J*=4.9 Hz, 1H), 2.14–1.93 (comp, 2H), 1.40 (s, 3H); ^{13}C NMR (62.5 MHz) δ 153.9, 152.7, 115.4, 114.6, 64.8, 55.7, 55.2, 53.9, 36.1, 21.6; IR ($CDCl_3$) 2957, 1508, 1230, 1039 cm^{-1}; mass spectrum (CI) *m/z* 208.1095 [$C_{12}H_{16}O_3$ requires 208.1099], 191 (base). A solution of 3-bromofuran (0.21 g, 1.43 mmol) in THF (4 mL) was cooled to −78 °C, and *n*-BuLi (0.68 mL of a 2.1 M solution, 1.43 mmol) was added dropwise. The solution was stirred for 15 min, and then a solution of epoxide **52** (0.10 g, 0.48 mmol) in THF (1.0 mL) was added dropwise. The solution was stirred for 5 min and $BF_3 \cdot Et_2O$ (0.11 g, 0.76 mmol) was added. The solution was stirred for 1.5 h, whereupon saturated aqueous $NaHCO_3$ (2 mL) was added. The mixture was extracted with Et_2O (2×5 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (3:1) to afford 116 mg (88%) of **51**.

5.3.7. 3-[2-Benzyloxy-4-(4-methoxyphenoxy)-2(*S*)-methylbutyl]furan (56). A solution of furan **51** (0.29 g, 1.05 mmol) in DMF (3 mL) was added dropwise to a suspension of KH (0.24 g of a 35% suspension, 2.09 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred for 10 min, and benzyl bromide (0.27 g, 1.58 mmol) was added. After 45 min, saturated aqueous $NaHCO_3$ (15 mL) was added, and the mixture was extracted with Et_2O (2×20 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (9:1) to afford 0.39 g (100%) of benzyl ether **56** as a pale yellow oil. ^1H NMR (500 MHz) δ 7.35–7.24 (comp, 7H), 6.84–6.78 (comp, 4H), 6.33 (dd, *J*=2.0, 1.0 Hz, 1H), 4.52 (s, 2H), 4.13–4.05 (m, 2H), 3.75 (s, 3H), 2.76 (s, 2H), 2.14–2.02 (m, 2H), 1.31 (s, 3H); ^{13}C NMR (100 MHz) δ 153.8, 153.1, 142.4, 140.8, 139.2, 128.4, 127.2, 127.2, 120.3, 115.4, 114.7, 112.6, 76.4, 64.6, 63.6, 55.8, 37.2, 34.5, 23.5; IR ($CDCl_3$) 2935, 1508, 1230 cm^{-1}; mass spectrum (CI) *m/z* 366.1827 [$C_{23}H_{26}O_4$ requires 366.1831], 366, 259, 177 (base).

5.3.8. 3-[2-Benzyloxy-4-(4-methoxyphenoxy)-2(*S*)-methylbutyl]-2-bromofuran (57). A solution of furan **56** (0.68 g, 1.86 mmol) in DMF (37 mL) was cooled to 0 °C, and freshly recrystallized *N*-bromosuccinimide (0.33 g, 1.85 mmol) was added. The reaction was stirred for 1 h, and saturated aqueous $NaHCO_3$ (40 mL) was added. The mixture was extracted with EtOAc (3×100 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (9:1) to afford 0.72 g (86%) of **57** as a colorless oil. ^1H NMR (250 MHz) δ 7.38–7.23 (comp, 6H), 6.85–6.78 (comp, 4H), 6.42 (d, *J*=2.0 Hz, 1H), 4.52 (s, 2H), 4.09 (app t, *J*=6.9 Hz, 2H), 3.75 (s, 3H), 2.70 (s, 2H), 2.14–2.04 (m, 2H), 1.32 (s, 3H); ^{13}C NMR (62.5 MHz) δ 153.8, 153.0, 143.6, 139.1, 128.3, 127.3, 127.2, 121.9, 119.9, 115.4, 114.6, 114.5, 76.8, 64.5, 63.7, 55.7, 37.3, 34.9, 23.3; IR (NaCl) 2934, 1508, 1231, 1040 cm^{-1}; mass spectrum (CI) *m/z* 444.0932 [$C_{23}H_{25}O_4Br$ (M+1) requires 444.0936], 444, 177 (base).

5.3.9. {3-[2-Benzyloxy-4-(4-methoxyphenoxy)-2(*S*)-methylbutyl]furan-2-yl}dimethylvinylsilane (58). A solution of bromofuran **57** (0.38 g, 0.84 mmol) in THF (13 mL) was cooled to −78 °C, and *n*-BuLi (0.43 mL of a 2.4 M solution, 1.03 mmol) was added dropwise. The solution was stirred for 25 min, and freshly distilled chlorodimethylvinylsilane (150 μL, 1.09 mmol) was added. The reaction was stirred for 25 min at −78 °C and then poured onto saturated $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (2×30 mL), and the combined organics were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (95:5) to furnish 0.34 g (88%) of vinylsilane **58** as a colorless oil. ^1H NMR (250 MHz) δ 7.54 (d, *J*=1.5 Hz, 1H), 7.38–7.23 (comp, 5H), 6.83–6.78 (comp, 4H), 6.43 (d, *J*=1.5 Hz, 1H), 6.28 (dd, *J*=20.0, 14.5 Hz, 1H), 6.03 (dd, *J*=14.5, 3.8 Hz, 1H), 5.77 (dd, *J*=20.0, 3.8 Hz, 1H), 4.51 (s, 2H), 4.08 (t, *J*=7.1 Hz, 2H), 3.75 (s, 3H), 2.87 (d, *J*=14.7 Hz, 1H), 2.78 (d, *J*=14.7 Hz, 1H), 2.20–1.99 (m, 2H), 1.26 (s, 3H), 0.36 (s, 6H); ^{13}C NMR (62.5 MHz) δ 154.0, 153.7, 153.0, 146.4, 139.2, 137.2, 133.1, 131.8, 128.3, 127.3, 127.2, 115.3, 114.6, 112.5, 76.6, 64.6, 63.6, 55.7, 37.8, 34.7, 23.5, −2.7; IR ($CDCl_3$) 3051, 2959, 1508, 1230 cm^{-1}; mass spectrum (CI) *m/z* 450.2233 [$C_{27}H_{34}O_4Si$ requires 450.2226], 451, 343 (base).

5.3.10. 2-({3-[2-Benzyloxy-4-(4-methoxyphenoxy)-2(*S*)-methylbutyl]furan-2-yl}dimethylsilanyl)ethanol (59). 9-BBN (0.36 g, 2.95 mmol) was added to a solution of

vinylsilane **58** (0.84 g, 1.86 mmol) in THF (9 mL) at room temperature. The reaction was stirred for 3 h and then cooled to 0 °C, whereupon 3 N NaOH (5 mL) and 30% H_2O_2 (5 mL) were added sequentially. The mixture was stirred for 30 min and then extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (7:3) to afford 0.84 g (96%) of alcohol **59** as a colorless oil. ^{1}H NMR (250 MHz) δ 7.49 (d, J=1.5 Hz, 1H), 7.34–7.22 (comp, 5H), 6.83–6.76 (comp, 4H), 6.39 (d, J=1.5 Hz, 1H), 4.49 (s, 2H), 4.07 (t, J=7.1 Hz, 2H), 3.72 (s, 3H), 3.69 (app t, J=8.2 Hz, 2H), 2.84 (d, J=14.6 Hz, 1H), 2.75 (d, J=14.6 Hz, 1H), 2.13–2.04 (m, 2H), 1.26 (s, 3H), 1.18–1.12 (m, 2H), 0.28 (s, 6H); ^{13}C NMR (62.5 MHz) δ 154.4, 153.8, 153.0, 146.3, 139.2, 131.6, 128.3, 127.3, 127.2, 115.4, 114.6, 112.6, 64.6, 63.7, 59.7, 55.7, 37.9, 35.0, 23.6, 21.2, −2.1; IR (NaCl) 3417, 2953, 1504, 1230, 1039 cm^{-1}; mass spectrum (CI) m/z 468.2339 [$C_{27}H_{36}O_5Si$ requires 468.2332], 469, 423, 259 (base).

5.3.11. 2,3,5,6-Tetrabromo-4-(*tert*-butyl-dimethylsilanyloxy)-1-phenol (61). Imidazole (0.19 g, 2.79 mmol) and TBSCl (0.17 g, 1.13 mmol) were added to a solution of **21** (0.6 g, 1.41 mmol) in DMF (1 mL) at room temperature. After stirring for 50 min, the mixture was loaded onto column and purified by chromatography on silica gel eluting with hexanes/EtOAc (9:1) to furnish 274 mg (35%) of phenol **61** as a yellowish oil. ^{1}H NMR (400 MHz) δ 5.85 (s, 1H, OH), 1.02 (s, 9H), 0.32 (s, 6H); ^{13}C NMR (100 MHz) δ 145.9, 145.8, 118.3, 112.4, 26.2, 19.0, −1.8; IR ($CDCl_3$) 3493, 2929, 2857, 1652, 1424, 1364, 1258, 1179 cm^{-1}; mass spectrum (CI) m/z 536.7726 [$C_{12}H_{17}O_2Br_4Si$ (M+1) requires 536.7731], 483 (base), 404.

5.3.12. 3-[2-Benzyloxy-4-(4-methoxyphenyl)-2(*S*)-methylbutyl]-2-(dimethyl-{2-[2,3,5,6-tetrabromo-4-(*tert*-butyldimethylsilanyloxy)phenoxy]ethyl}silanyl)furan (62). DIAD (9.1 mg, 0.05 mmol) was added to a solution of phenol **61** (24 mg, 0.04 mmol), alcohol **59** (21 mg, 0.05 mmol), and PPh_3 (11.8 mg, 0.05 mmol) in THF (0.5 mL), and the solution was stirred for 3 h at room temperature. The reaction mixture was concentrated under reduced pressure, and the residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (95:5) to furnish 33 mg (75%) of **62** as a colorless oil. ^{1}H NMR (400 MHz) δ 7.52 (d, J=1.2 Hz, 1H), 7.35–7.24 (comp, 5H), 6.83–6.77 (comp, 4H), 6.42 (d, J=1.6 Hz, 1H), 4.52 (s, 2H), 4.10 (t, J=6.8 Hz, 2H), 4.05 (t, J=6.8 Hz, 2H), 3.75 (s, 3H), 2.88 (d, J=14.8 Hz, 1H), 2.80 (d, J=14.8 Hz, 1H), 2.19–2.03 (comp, 2H), 1.54 (app t, J=8.4 Hz, 2H), 1.30 (s, 3H), 1.04 (s, 9H), 0.36 (s, 3H), 0.36 (s, 3H), 0.35 (s, 3H), 0.34 (s, 3H); ^{13}C NMR (100 MHz) δ 153.8, 153.5, 152.8, 149.4, 148.6, 146.3, 139.0, 131.7, 128.2, 127.1, 127.1, 121.3, 118.4, 115.2, 114.5, 112.4, 76.5, 71.1, 64.6, 63.7, 55.8, 37.9, 35.1, 26.3, 23.8, 19.1, 18.1, −1.5, −1.6,−1.8; IR ($CDCl_3$) 2930, 1508, 1419, 1368, 1252, 1230, 1041 cm^{-1}; mass spectrum (CI) m/z 985.9865 [$C_{39}H_{50}O_6Br_4Si_2$ requires 985.9879], 597, 483, 403 (base).

5.3.13. 4-[2-({3-[2-Benzyloxy-4-(4-methoxyphenoxy)-2(*S*)-methylbutyl]furan-2-yl}dimethylsilanyl)ethoxy]-2,3,5,6-tetrabromophenol (60). HF·pyridine (0.2 mL, 65–70%) was added to a solution of silyl ether **62** (0.32 g, 0.32 mmol) in THF (4.5 mL) at 0 °C in a Teflon vial. The reaction was stirred for 1 h and then poured into a mixture of saturated $NaHCO_3$ (10 mL) and EtOAc (15 mL). The organic layer was separated, washed with brine (10 mL), dried ($MgSO_4$), and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (4:1) to afford 0.25 g (89%) of phenol **60** as a colorless oil. ^{1}H NMR (400 MHz) δ 7.53 (d, J=2.0 Hz, 1H), 7.36–7.25 (m, 5H), 6.84–6.78 (comp, 4H), 6.43 (d, J=2.0 Hz, 1H), 5.98 (s, 1H), 4.52 (s, 2H), 4.10 (t, J=7.0 Hz, 2H), 4.08–4.02 (m, 2H), 3.76 (s, 3H), 2.88 (d, J=14.4 Hz, 1H), 2.80 (d, J=14.4 Hz, 1H), 2.19–2.05 (m, 2H), 1.53–1.50 (m, 2H), 1.30 (s, 3H), 0.36 (s, 3H), 0.35 (s, 3H); ^{13}C NMR (100 MHz) δ 153.9, 153.7, 153.0, 148.9, 148.0, 146.5, 112.6, 112.3, 76.5, 71.4, 64.5, 63.6, 55.7, 37.8, 35.0, 23.6, 18.0, −2.0; IR ($CDCl_3$) 3490, 2956, 1508, 1363, 1230, 1040 cm^{-1}; mass spectrum (CI) m/z 871.9028 [$C_{33}H_{36}O_6Br_4Si$ requires 871.9015], 876, 741, 483, 423 (base).

5.3.14. 3(*R*),4(*R*)-Bisbenzyloxy-6(*R*)-{2-[(2-{4-[2-({3-[2-benzyloxy-4-(4-methoxyphenoxy)-2(*S*)-methylbutyl]-furan-2-yl}dimethylsilanyl)ethoxy]-2,3,5,6-tetrabromophenoxy}ethyl)dimethylsilanyl]furan-3-yl}-2(*R*)-methyltetrahydropyran (63). DIAD (65 mg, 0.32 mmol) was added to a solution of phenol **60** (230 mg, 0.26 mmol), alcohol **46** (140 mg, 0.29 mmol), and PPh_3 (84 mg, 0.32 mmol) in THF (10 mL) and the reaction was stirred for 4 h at room temperature. The mixture was concentrated under reduced pressure and the residue was purified by chromatography on silica gel eluting with hexanes/EtOAc/Et_3N (93:5:2) to furnish 299 mg (85%) of aryl ether **63** as a colorless oil. ^{1}H NMR (400 MHz) δ 7.55 (d, J=1.6 Hz, 1H), 7.53 (d, J=1.6 Hz, 1H), 7.39–7.24 (m, 15H), 6.84–6.80 (comp, 4H), 6.44 (d, J=2.0 Hz, 1H), 6.38 (d, J=2.0 Hz, 1H), 4.99 (d, J=10.8 Hz, 1H), 4.72 (d, J=11.6 Hz, 1H), 4.69 (d, J=10.8 Hz, 1H), 4.66 (d, J=11.6 Hz, 1H), 4.53 (s, 2H), 4.46 (dd, J=11.6, 2.0 Hz, 1H), 4.15–4.04 (comp, 6H), 3.76 (s, 3H), 3.75–3.70 (m, 1H), 3.52–3.45 (m, 1H), 3.20 (t, J=8.8 Hz, 1H), 2.88 (d, J=14.4 Hz, 1H), 2.81 (d, J=14.4 Hz, 1H), 2.31 (ddd, J=12.8, 4.8, 1.6 Hz, 1H), 2.19–2.06 (m, 2H), 1.80 (dd, J=12.8, 11.6 Hz, 1H), 1.59–1.51 (m, 4H), 1.36 (d, J=6.0 Hz, 3H), 1.30 (s, 3H), 0.36 (s, 3H), 0.36 (s, 9H); ^{13}C NMR (100 MHz) δ 154.2, 153.9, 153.7, 153.0, 151.9, 146.5, 139.1, 138.5, 138.4, 136.6, 131.8, 128.4, 128.4, 128.3, 128.0, 127.7, 127.7, 127.6, 127.3, 121.5, 115.3, 114.6, 112.6, 108.7, 83.9, 80.8, 76.5, 75.8, 75.3, 71.5, 71.3, 71.2, 70.8, 64.5, 63.6, 55.7, 38.2, 37.8, 35.0, 23.6, 18.6, 18.0, 17.7, −2.0, −2.3; IR ($CDCl_3$) 3032, 2953, 2887, 1508, 1348, 1230, 1088 cm^{-1}; mass spectrum (CI) m/z 1338.1149 [$C_{61}H_{70}O_{10}Br_4Si_2$ requires 1338.1200], 1338, 655, 555 (base).

5.3.15. Preparation of bis-cycloadduct 64. Tetrabromide **63** (800 mg, 0.60 mmol), which had been dried in the bulb of a Kügelrohr apparatus under vacuum for 2 h at 140 °C, was dissolved in Et_2O (30 mL), and a solution of *n*-BuLi (7.8 mL of a 0.23 M solution, 1.84 mmol, which was prepared by diluting 0.8 mL of 2.3 M *n*-BuLi in hexanes with 7.0 mL Et_2O) was added dropwise over 30 min at −20 °C. Once addition was complete, the reaction was stirred for

10 min at −20 °C. The mixture was quenched with EtOH (1 mL) and then poured onto saturated $NaHCO_3$ (30 mL) and Et_2O (300 mL). The organic layer was separated, washed with saturated $NaHCO_3$ (3×30 mL), dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (1:4) to afford 517 mg (85%) of a mixture of diastereomeric cycloadducts **64** as a yellowish oil. ^{1}H NMR (400 MHz) of an enriched diastereomer δ 7.35–7.20 (m, 15H), 6.99 (s, 1H), 6.82–6.70 (m, 5H), 5.74–5.71 (m, 2H), 4.98 (d, J=11.0 Hz, 1H), 4.69 (d, J=11.6 Hz, 1H), 4.66 (d, J=11.0 Hz, 1H), 4.59 (d, J=11.6 Hz, 1H), 4.60–4.45 (m, 3H), 4.37 (d, J=10.8 Hz, 1H), 4.25 (d, J=10.8 Hz, 1H), 4.00–3.81 (m, 4H), 3.76 (s, 3H), 3.66–3.58 (m, 1H), 3.42–3.35 (m, 1H), 3.14 (t, J=9.0 Hz, 1H), 2.76 (d, J=18.4 Hz, 1H), 2.49 (d, J=18.6 Hz, 1H), 2.26 (dd, J=11.8, 4.2 Hz, 1H), 2.12–1.98 (m, 2H), 1.68 (dd, J=12.4, 11.6 Hz, 1H), 1.53–1.43 (m, 1H), 1.40 (s, 3H), 1.36 (d, J=6.0 Hz, 3H), 1.27–1.17 (m, 1H), 1.12–1.03 (m, 2H), 0.36 (s, 3H), 0.33 (s, 3H), 0.16 (s, 3H), 0.06 (s, 3H); IR (NaCl) 2936, 2878, 1507, 1454, 1229, 1109, 1038 cm^{-1}; mass spectrum (CI) m/z 1019.4559 [$C_{61}H_{70}O_{10}Si_2$ (M+1) requires 1019.4585] (base), 992, 885, 694.

5.3.16. Anthraquinone 67. Potassium hydroxide (10 pellets) and H_2O (1 mL) were added to a solution of cycloadduct **64** (225 mg, 0.22 mmol) in DMF (10 mL), and the mixture was stirred for 24 h at room temperature. A mixture of 50% Et_2O/hexanes (300 mL) was added, and the solution was washed with brine (5×20 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was dissolved in EtOH (30 mL), and concentrated hydrochloric acid (40 drops) was added. The reaction was stirred for 4 h at 65 °C and then concentrated under reduced pressure. The residue was purified by chromatography on silica gel eluting with hexanes/EtOAc (8:1) to afford 64 mg (34%) of **67** as a yellowish oil. ^{1}H NMR (500 MHz) δ 13.19 (s, 1H, OH), 13.11 (s, 1H, OH), 7.90 (d, J=7.9 Hz, 1H), 7.85 (d, J=7.9 Hz, 1H), 7.74 (d, J=7.8 Hz, 1H), 7.71 (d, J=7.9 Hz, 1H), 7.36–7.24 (comp, 15H), 6.83–6.76 (comp, 4H), 4.99 (d, J=11.2 Hz, 1H), 4.86 (dd, J=11.5, 1.7 Hz, 1H), 4.72 (d, J=8.0 Hz, 1H), 4.70 (d, J=8.0 Hz, 1H), 4.64 (d, J=11.2 Hz, 1H), 4.55 (s, 2H), 4.17–4.08 (comp, 2H), 3.85 (ddd, J=13.5, 8.9, 4.7 Hz, 1H), 3.74 (s, 3H), 3.57 (dq, J=8.9, 6.2 Hz, 1H), 3.21 (t, J=8.9 Hz, 1H), 3.19 (d, J=13.6 Hz, 1H), 3.11 (d, J=13.6 Hz, 1H), 2.69 (ddd, J=12.8, 4.7, 1.7 Hz, 1H), 2.21–2.07 (comp, 2H), 1.48–1.39 (m, 1H), 1.39 (d, J=6.2 Hz, 3H), 1.34 (s, 3H); ^{13}C NMR (125 MHz) δ 188.3, 188.2, 161.5, 158.9, 153.8, 153.0, 139.4, 139.1, 138.6, 138.5, 138.4, 138.3, 135.5, 133.3, 131.9, 131.5, 128.4, 128.3, 128.2, 128.1, 128.0, 127.8, 127.7, 127.6, 127.5, 127.3, 127.1, 125.5. 119.4, 118.6, 115.5, 114.7, 84.0, 80.9, 77.5, 75.8, 75.3, 71.4, 71.2, 64.6, 63.8, 55.7, 37.7, 37.4, 37.3, 23.1, 18.6; IR (NaCl) 2918, 2848, 1625, 1507, 1431, 1372, 1284, 1261, 1231, 1107, 1090, 1072 cm^{-1}; mass spectrum (CI) m/z 849.3634 [$C_{53}H_{53}O_{10}$ (M+1) requires 849.3639], 742 (base), 726, 419, 293, 267.

5.3.17. Anthraquinone 68. A solution of ceric ammonium nitrate (48 mg, 0.09 mmol) in H_2O (0.1 mL) was added to a solution of **67** (25 mg, 0.03 mmol) in CH_3CN (2.9 mL) at −15 °C, and the reaction was stirred for 20 min. Et_2O (20 mL) was added, and the solution was washed with brine (4×3 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (2:1) to afford 16 mg (74%) of **68** as a yellowish oil. ^{1}H NMR (500 MHz) δ 13.22 (s, 1H, OH), 13.09 (s, 1H, OH), 7.91 (d, J=7.8 Hz, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.75 (d, J=7.8 Hz, 1H), 7.63 (d, J=7.8 Hz, 1H), 7.36–7.24 (comp, 15H), 4.99 (d, J=11.3 Hz, 1H), 4.86 (dd, J=11.4, 1.9 Hz, 1H), 4.72 (d, J=7.1 Hz, 1H), 4.70 (d, J=7.1 Hz, 1H), 4.64 (d, J=11.3 Hz, 1H), 4.61 (d, J=11.1 Hz, 1H), 4.58 (d, J=11.1 Hz, 1H), 3.91–3.80 (comp, 3H), 3.57 (dq, J=9.1, 6.1 Hz, 1H), 3.21 (t, J=9.1 Hz, 1H), 3.18 (d, J=13.6 Hz, 1H), 3.12 (d, J=13.6 Hz, 1H), 2.69 (ddd, J=13.0, 5.1, 1.9 Hz, 1H), 2.62 (t, J=4.8 Hz, 1H, OH), 1.98–1.90 (m, 1H), 1.88–1.82 (m, 1H), 1.48–1.39 (m, 1H), 1.39 (s, 3H), 1.38 (d, J=6.1 Hz, 3H); ^{13}C NMR (125 MHz) δ 188.2, 161.5, 158.9, 139.2, 138.6, 138.5, 138.4, 138.3, 135.1, 133.3, 131.8, 131.6, 128.5, 128.4, 128.3, 128.1, 127.7, 127.6, 127.5, 127.4, 127.3, 119.4, 118.7, 115.6, 115.5, 84.0, 80.8, 79.6, 75.8, 75.3, 71.4, 71.2, 64.1, 59.4, 40.3, 37.3, 36.9, 22.8, 18.6; IR (NaCl) 3428 (br), 2930, 2872, 1626, 1606, 1582, 1475, 1431, 1372, 1318, 1279, 1260, 1109, 1090, 1071 cm^{-1}; mass spectrum (CI) m/z 741.3059 [$C_{46}H_{45}O_9$ (M−1) requires 741.3064] (base), 633.

5.3.18. Anthraquinone 69. IBX (9 mg, 0.03 mmol) was added to a solution of alcohol **68** (8.0 mg, 0.01 mmol) in EtOAc (1 mL), and the resulting suspension was heated for 3 h at 80 °C with vigorous stirring. The reaction was allowed to cool to room temperature, and Et_2O (5 mL) was added. The mixture was filtered through a pad of Celite, and the filtrate was concentrated under reduced pressure. The crude aldehyde thus obtained was dissolved in t-BuOH/H_2O (3.5:1, 2 mL), and the solution was cooled to 0 °C. $NaH_2PO_4 \cdot 2H_2O$ (28 mg, 0.18 mmol), 2-methyl-2-butene (0.16 mL, 1.51 mmol), and $NaClO_2$ (21 mg, 0.23 mmol) were then added, and the mixture was stirred for 90 min at room temperature. The mixture was diluted with Et_2O (20 mL) and washed with brine (3×2 mL). The organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography on silica gel eluting with hexanes/EtOAc (1:2) to afford 5.7 mg (70%) of acid **69** as a yellowish oil. ^{1}H NMR (500 MHz) δ 13.24 (s, 1H, OH), 13.05 (s, 1H, OH), 9.80 (br, 1H), 7.91 (d, J=7.9 Hz, 1H), 7.85 (d, J=7.8 Hz, 1H), 7.78 (d, J=7.8 Hz, 1H), 7.63 (d, J=7.8 Hz, 1H), 7.38–7.25 (comp, 15H), 4.99 (d, J=11.0 Hz, 1H), 4.86 (dd, J=11.3, 1.3 Hz, 1H), 4.74–4.62 (comp, 5H), 3.85 (ddd, J=13.6, 8.8, 4.9 Hz, 1H), 3.57 (dq, J=8.8, 6.1 Hz, 1H), 3.29 (d, J=13.6 Hz, 1H), 3.21 (t, J=8.8 Hz, 1H), 3.18 (d, J=13.6 Hz, 1H), 2.71 (d, J=15.3 Hz, 1H), 2.71–2.67 (comp, 1H), 2.66 (d, J=15.3 Hz, 1H), 1.49 (s, 3H), 1.48–1.40 (m, 1H), 1.39 (d, J=6.1 Hz, 3H); ^{13}C NMR (125 MHz) δ 188.2, 188.1, 171.1, 161.4, 159.0, 139.2, 138.7, 138.6, 138.5, 137.2, 133.6, 133.4, 132.1, 131.7, 128.7, 128.5, 128.4, 128.2, 128.1, 127.8, 127.7, 127.6, 119.6, 118.8, 115.8, 115.4, 83.9, 80.8, 78.2, 75.8, 75.3, 71.4, 71.2, 64.9, 44.1, 37.3, 36.8, 22.7, 18.6; IR (NaCl) 2919, 2860, 1702, 1619, 1431, 1366, 1320, 1290, 1255, 1114, 1091, 1073 cm^{-1}; mass spectrum (CI) m/z 757.3013 [$C_{46}H_{45}O_{10}$ (M+1) requires 757.3013], 689, 621, 502 (base), 458, 355.

5.3.19. Vineomycinone B_2 methyl ester (3). BBr_3 in CH_2Cl_2 (0.2 mL of 1 M solution, 0.2 mmol) was added to a solution of acid **69** (5.5 mg, 7.27 μmol) in CH_2Cl_2 (2 mL) at −78 °C. The mixture was stirred for 10 min at −78 °C, and methanolic HCl (2 mL, prepared from 0.2 mL of AcCl and 5 mL MeOH) was added. The mixture was stirred for 6 h at room temperature and then concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with EtOAc to afford 2.6 mg (71%) of vineomycinone B_2 methyl ester (**3**) as an orange solid; mp 183–184 °C (lit.[14b,d] mp 183–184 °C); $[\alpha]_D^{24}$ +109.8 (*c* 0.00091, $CDCl_3$) (lit.[14b] $[\alpha]_D$ +109.1 (*c* 0.00066, $CDCl_3$)); ^{1}H NMR (500 MHz) δ 13.20 (s, 1H, OH), 13.09 (s, 1H, OH), 7.90 (d, *J*=7.9 Hz, 1H), 7.85 (d, *J*=7.9 Hz, 1H), 7.80 (d, *J*=7.8 Hz, 1H), 7.68 (d, *J*=7.9 Hz, 1H), 4.94 (dd, *J*=11.3, 1.8 Hz, 1H), 3.87 (s, 1H, OH), 3.86–3.81 (m, 1H), 3.70 (s, 3H), 3.52 (dq, *J*=9.0, 6.1 Hz, 1H), 3.21 (dt, *J*=9.0, 3.5 Hz, 1H), 3.09 (d, *J*=13.4 Hz, 1H), 3.01 (d, *J*=13.4 Hz, 1H), 2.57 (d, *J*=16.0 Hz, 1H), 2.53 (d, *J*=16.0 Hz, 1H), 2.52 (ddd, *J*=12.7, 4.8, 1.8 Hz, 1H), 2.20 (d, *J*=3.5 Hz, 1H, OH), 2.10 (d, *J*=3.7 Hz, 1H, OH), 1.51–1.42 (m, 1H), 1.41 (d, *J*=6.1 Hz, 3H), 1.29 (s, 3H); ^{13}C NMR (125 MHz) δ 188.2, 188.2, 173.3, 161.4, 159.0, 139.6, 138.3, 134.7, 133.3, 131.9, 131.8, 119.4, 118.9, 115.6, 115.5, 78.1, 75.9, 73.1, 71.8, 71.3, 51.7, 44.4, 40.5, 39.4, 27.3, 18.1; IR (NaCl) 3400 (br), 2930, 2860, 1733, 1626, 1433, 1374, 1260, 1090, 1070, 993, 971 cm^{-1}; mass spectrum (CI) *m*/*z* 501.1757 [$C_{26}H_{29}O_{10}$ (M+1) requires 501.1761] (base), 326.

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