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Studies toward the syntheses of pluramycin natural products. The first total synthesis of isokidamycin

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ABSTRACT

We report the first total synthesis of the complex *C*-aryl glycoside isokidamycin, the epimer of the naturally-occurring pluramycin antibiotic kidamycin. The synthesis features a highly efficient Diels–Alder reaction between a substituted naphthyne and a glycosylated furan to form the anthracene core bearing a pendent angolosamine *C*-glycoside. The regiochemical outcome of the Diels–Alder reaction was controlled by employing a disposable silicon tether to link the reactive naphthyne and the glycosyl furan, rendering the cycloaddition intramolecular. The benzopyranone moiety of the aromatic nucleus was appended by cyclization of a functionalized vinylogous amide onto an advanced anthrol intermediate. The vancosamine amino glycoside was introduced by an *O*→*C*-glycoside rearrangement that produced the β-anomer. Subsequent refunctionalizations then led to isokidamycin.

1. Introduction

The pluramycin family of natural products are an important group of complex *C*-aryl glycoside antibiotics that possess the tetracyclic 4*H*-anthra[1,2-*b*]pyran-4,7,12-trione moiety A–D as an aromatic core (Fig. 1).[1] The D-ring is adorned with two deoxyaminosugars that are appended by *C*-aryl glycosidic linkages. The E-ring sugar is angolosamine, a carbohydrate that is also found in the antibiotic angolamycin.[2] The F-ring sugar is the *N*,*N*-dimethyl derivative of vancosamine, which is the sugar found in the glycopeptide antibiotic vancomycin.[3]

Kidamycin (**1**), which was isolated as a secondary metabolite from *Streptomyces phaeoverticillatus*, is the member of the pluramycin class that has been most extensively studied.[4] Its structure was unequivocally determined by NMR and X-ray analysis.[4b,5] These investigations revealed that the conformation of the E-ring sugar exists in a typical chair-conformation, with all of the substituents in an equatorial orientation. However, the conformation of the F-ring sugar has been the source of some confusion. Furukawa initially proposed that the F-ring of **1** resided in a boat conformation similar to that observed in the X-ray structure of a trimethylammonium derivative of kidamycin.[5a] The assumption that the underivatized natural product also adopted this conformation in solution was shown, however, likely to be incorrect when the analysis of an underivatized sample of hedamycin (**3**) revealed that the F-ring sugar existed in a chair-conformation, with the

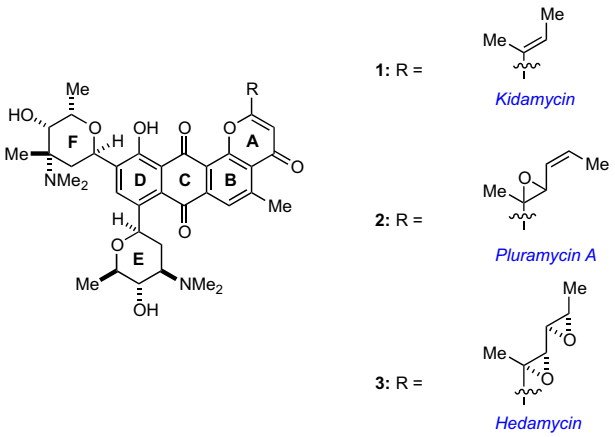

Fig. 1. The pluramycin family of natural products.

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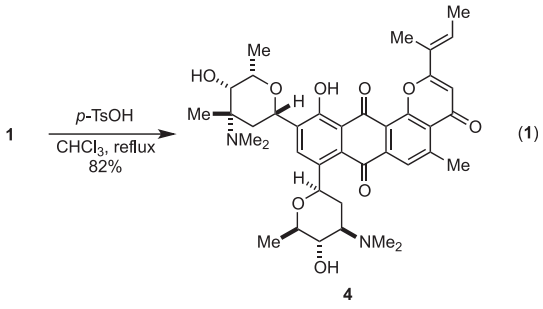
bulky aryl substituent in an axial position.[6] In order to relieve the strain associated with this orientation, the chair conformer was slightly flattened.

In addition to its interesting structure, kidamycin (**1**) has an intriguing biological profile. It is active against gram positive bacteria, and it exhibits anticancer activity against Ehrlich ascites carcinoma, leukemia L1210, sarcoma-180, NF-sarcoma, and Yoshida sarcoma.[7] Hurley and co-workers, who have extensively studied the mode of action of the pluramycin natural products,[8] found that the pluramycins intercalate into the DNA helix by positioning the carbohydrate residues in both the major and minor grooves of the helix. The complex is stabilized by hydrogen-bonds between the protonated dimethylamino groups of the sugar moieties and the DNA strand. The side-chain epoxide of pluramycin A then alkylates N7 of a guanine residue leading to the formation of a cationic lesion in the DNA that can lead to single strand cleavage in the presence of a base. Kidamycin has been shown to be cardiotoxic and possesses an LD_{50} of 18 mg/kg in mice;[7a] however, it also significantly prolongs the life of mice bearing Ehrlich ascites tumors at single doses (ip) as low as one-sixteenth of the LD_{50}. Kidamycin is the only member of the pluramycin family to have been derivatized in an attempt to increase the therapeutic index.[9]

Members of the pluramycin family of natural products exhibit striking chemical lability. They are heat-sensitive, and readily undergo decomposition when heated above 60 °C.[10] They are unstable toward UV or even daylight in solution.[11] Only one major degradation reaction has been reported for kidamycin.[4b] Kidamycin undergoes epimerization at the anomeric center of the vancosamine-derived sugar upon heating under reflux in chloroform in the presence anhydrous *p*-TsOH to give isokidamycin (**4**) in which the aromatic nucleus occupies the more stable equatorial orientation (Eq. 1). Because these are the only conditions reported, it is unclear how easily kidamycin might be epimerized under milder acidic conditions. The potential of kidamycin (**1**) to serve as an anticancer agent, coupled with its challenging structure have led to a number of synthetic investigations, but no member of the pluramycin family has been synthesized via these approaches.[12,13]



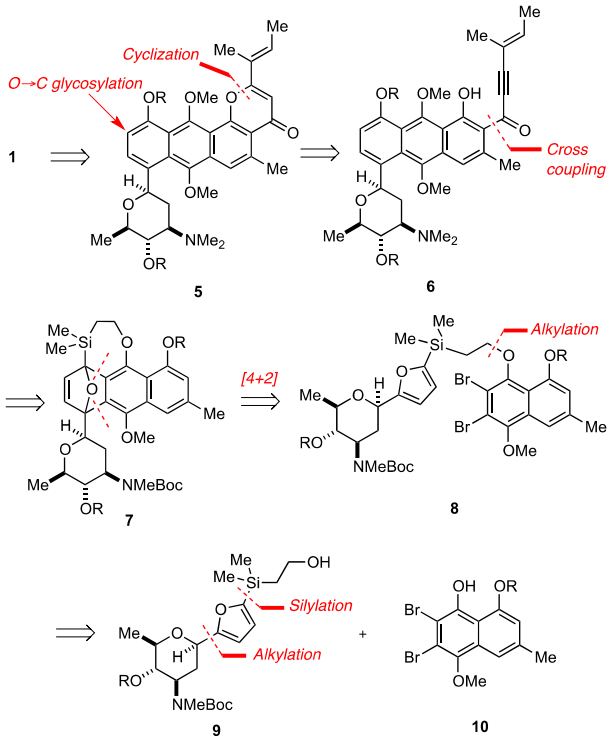
(1)

We have long been interested in developing new entries to oxygenated natural products, and we have disclosed a unified strategy for the synthesis of the four major classes of *C*-aryl glycosides.[14] The approach features the ring opening of cycloadducts obtained from the Diels–Alder reactions of substituted arynes with glycosyl furans. The power and utility of this approach has been demonstrated by the successful syntheses of a number of *C*-aryl glycoside natural products.[15] However, despite these successes, we had not applied this general method to the synthesis of any bis-*C*-aryl glycoside antibiotics, such as those of the complex pluramycin family. Accordingly, we embarked on the challenge of preparing kidamycin (**1**), an endeavor that ultimately resulted in a total synthesis of isokidamycin (**4**).[16] We now wish to disclose the details of this successful campaign.

2. Results and discussion

2.1. Development of the synthetic approach

The major elements of our plan for completing the synthesis of kidamycin (**1**) are outlined in retrosynthetic format in Scheme 1. The end-game relied on the stereoselective introduction of the vancosaminyl moiety onto the intermediate **5** by the *O*→*C*-glycoside rearrangement pioneered by Suzuki,[17] which should deliver the requisite α-anomer if the reaction were conducted under kinetically-controlled conditions. We reasoned that the incorporation of this residue late in the synthesis would minimize the opportunity for deleterious epimerization of the anomeric center. The benzopyranone ring in **5** would be formed by cyclization of an acetylenic ketone that would be introduced onto the tricyclic core **6** by a cross-coupling reaction.[18] The anthrol moiety in **6** would emanate from complete removal of the silicon tether in **7** and ring opening of the oxabicycle. The key intermediate **7** would be produced by an intramolecular Diels–Alder cycloaddition of the glycosyl furan ring in **8** with a naphthyne generated in situ from the dibromonaphthalene subunit in **8**. Assembly of **8** would then entail alkylation of **10** with **9**, a furyl glycoside that would be prepared using methods previously developed in our group.[14,15]

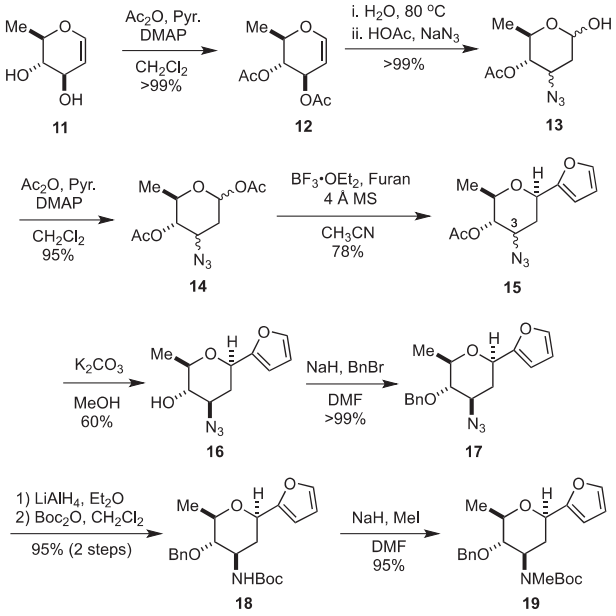


Scheme 1.

2.2. Synthesis of glycosyl furan and naphthalene precursors

The synthesis of the glycosyl furan **9** commenced with acetylation of D-rhamnal (**11**)[19] to furnish diacetate **12** in excellent yield (Scheme 2). Hydration of **12**, followed by treatment of the intermediate lactol with hydrazoic acid provided **13** in near quantitative yield as a mixture of four diastereomers that were not separated.[20] O-Acetylation of the anomeric hydroxyl group furnished **14** (95% yield), which underwent facile Friedel–Crafts alkylation with furan in the presence of $BF_3{\cdot}OEt_2$ and 4 Å MS to afford furyl glycoside **15** in 78% yield, at which point the desired β-

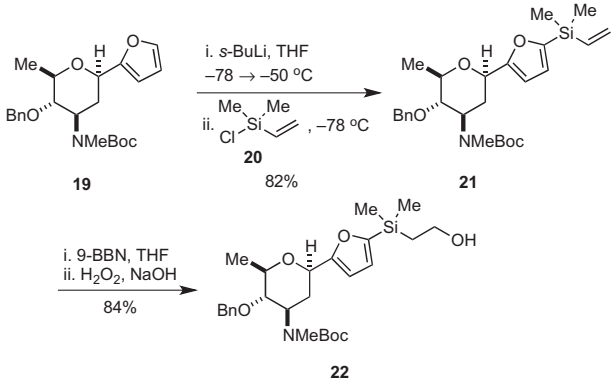
anomer was isolated, as a mixture (72:28) of diastereomers at C3. The relative configuration at the anomeric position of **15** was assigned based upon the observed coupling constants of 11.9 and 2.0 Hz for the anomeric proton; the ratio of C3 epimers was determined through ^{1}H NMR spectroscopy by integration of the equatorial methyl substituent at C5.



Scheme 2.

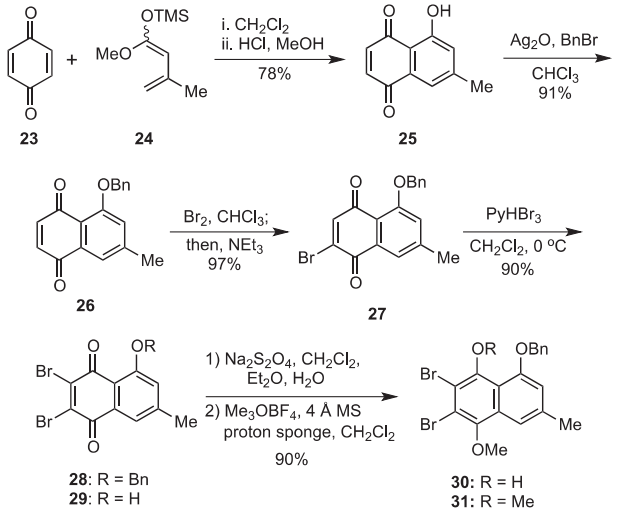
Although it was possible to separate the C3 epimers of **15**, it was more convenient to carry the mixture forward, because separation of the derived alcohols **16** was more facile. In the event, treatment of **15** with K_2CO_3 in MeOH, followed by separation of the diastereomers delivered the azido alcohol **16**, in 60% yield. The structure of **16** was established by X-ray analysis.[21] O-Benzylation of **16** gave **17** in nearly quantitative yield. Reduction of the azide and protection of the intermediate amine as its *tert*-butyl carbamate (Boc) afforded **18** in 95% yield over two steps. N-Alkylation of carbamate **18** with MeI provided the furyl glycoside **19** in 95% yield.

With quantities of furyl glycoside **19** in hand, we turned to its transformation into the silyl ethanol derivative **22** (Scheme 3). Metalation of **19** with *s*-BuLi gave a furyllithium intermediate that was allowed to react with chlorodimethylvinylsilane (**20**) to afford vinyl silane **21** in 82% yield. Although the deprotonation step was faster at 0 °C, the isolated yield of **21** was only 63%, and numerous unidentifiable side-products were formed. Hydroboration of **21** with 9-BBN, followed by oxidation then delivered alcohol **22** in 84% yield.



Scheme 3.

The next stage of the synthesis required preparation of the dibromonaphthalene **30** that would then be coupled with **22**. The synthesis of **30** commenced with the naphthoquinone **25**, which was obtained by the Diels–Alder reaction of benzoquinone (**23**) with the diene **18**[22] according to a known procedure (Scheme 4).[23] O-Benzylation of **25** to provide **26** was most efficiently achieved using the combination of Ag_2O and benzyl bromide; lower yields were obtained when various bases and benzyl bromide or chloride were employed. Furthermore, attempted O-benzylation of **25** under acidic conditions utilizing benzyltrichloroacetimidate was ineffective. Dibromination of **26** was accomplished in a two-step procedure. The first bromination was effected by exposing naphthoquinone **26** to 1 equiv of molecular bromine followed by dehydrobromination with NEt_3 to deliver bromonaphthoquinone **27** in 97% yield. The second bromination to give **28** was more problematic as significant quantities of the debenzylated product **29** were observed under standard bromination protocols. We postulated that this side reaction was promoted by the HBr that was formed during the reaction. Indeed, when **27** was allowed to react with Br_2 in the presence of K_2CO_3 to sequester the liberated HBr, **28** was isolated in 65% yield; however, lesser quantities of the debenzylated naphthoquinone **29** were still obtained. After some experimentation, we discovered that reproducibly high yields of dibromonaphthoquinone **28** could be obtained by treating **27** with 1 equiv of pyridinium bromide perbromide ($PyHBr_3$) in CH_2Cl_2. Reduction of **28** with sodium dithionite and subsequent monomethylation of the sterically less encumbered hydroxyl group using 1 equiv of methyl Meerwein's salt (Me_3OBF_4) then delivered dibromonaphthol **30** in 90% yield over the two steps. When 2 equiv of Me_3OBF_4 were used, the dimethyl ether **31** could be isolated in about 50% (unoptimized) yield.

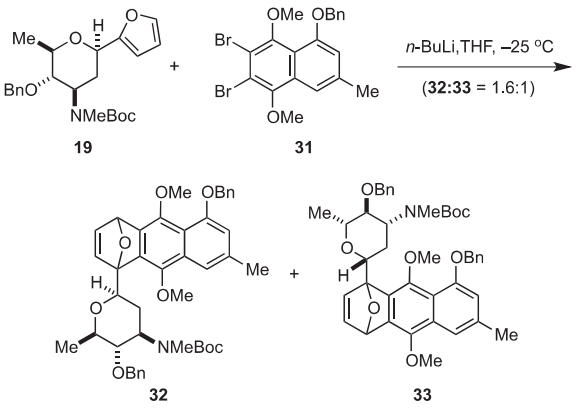


Scheme 4.

2.3. Diels–Alder reactions to form the anthrone subunit

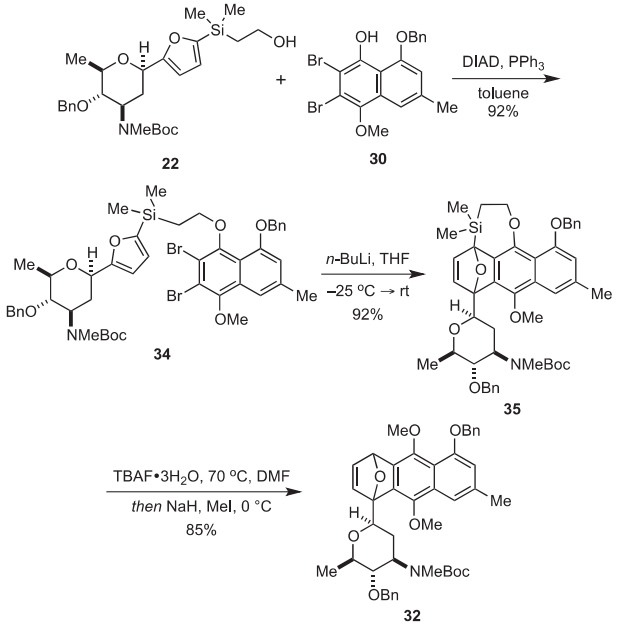
Our original synthetic plan called for an intramolecular Diels–Alder reaction of a glycosyl furan with a substituted naphthyne to assemble a precursor of the anthrone subunit of kidamycin (see Scheme 1, 8→7). This strategy was based upon our reasoned hypothesis that the regiochemistry of an intermolecular cycloaddition reaction would not be high. It occurred to us that this rationale, compelling as it was based upon our prior experience, should be tested by experiment. Toward this objective, equal molar solutions of **31** and *n*-BuLi were added dropwise to a solution of furan **19** at −25 °C to deliver a mixture of the four possible cycloadducts in good overall yield (Scheme 5). Based upon integration of

the oxabicyclic bridgehead protons of **32** and **33** in the ^{1}H NMR spectrum of the crude reaction mixture, the ratio of regioisomers **32** and **33** was 1.6:1. The desired regioisomers **32** could be isolated in 35% yield after careful column chromatography.



Scheme 5.

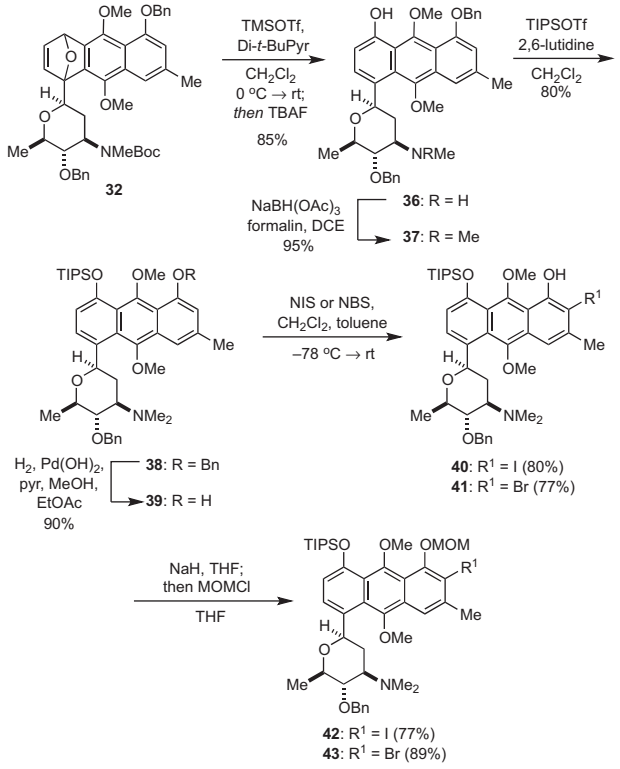
The question to be resolved at this juncture was whether an intramolecular Diels–Alder reaction might be more efficient. In the event, coupling the alcohol **22** with the dibromonaphthol **30** under Mitsunobu conditions furnished **34** in 92% yield (Scheme 6). Optimizing the conditions for inducing the intramolecular cycloaddition of the naphthyne derived from **34** required extensive optimization of the reaction temperature, time, and alkyllithium reagent, and it was necessary to rigorously dry **34** prior to the reaction. We eventually found that treatment of **34** with *n*-BuLi in THF at −25 °C for 15 min, followed by slow warming to ambient temperature delivered the oxabicycle **35** in 92% yield. Complete removal of the silicon-derived tether using fluoride anion, followed by methylation of the intermediate naphthol in a one-pot protocol delivered oxabicycle **32** in 85% yield. The inherent advantages associated with the intramolecular cycloaddition approach are thus evident. In particular, the overall yield of the intramolecular route to **32** (Scheme 6) is 50% based upon the more valuable starting material **19**, whereas the intermolecular approach (Scheme 5) provided **32** in a 35% overall yield from **19**. The total number of chemical operations in the intramolecular route is only two more than the intermolecular pathway, as the latter required an additional step to prepare **31**.



Scheme 6.

2.4. Synthesis of the tetracyclic core of kidamycin

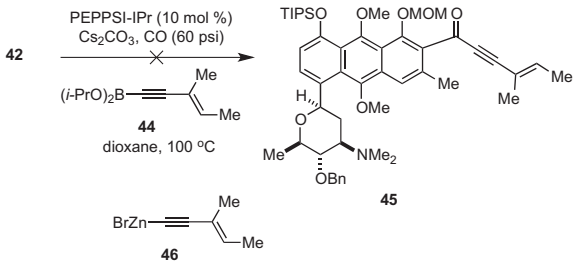
With the oxabicycle **32** in hand, we turned our focus to opening of the oxabicyclic ring and installing the benzopyranone A-ring. After an extensive screen of Brønsted and Lewis acidic conditions, we found that exposure of **32** to TMSOTf, in the presence of 2,6-di-*tert*-butylpyridine induced the requisite ring opening with concomitant loss of the *tert*-butyl carbamate protecting group to afford amino anthrol **36** in 85% yield (Scheme 7). Reductive N-methylation of the secondary amino group on the sugar residue under standard conditions gave tertiary amine **37** in near quantitative yield.



Scheme 7.

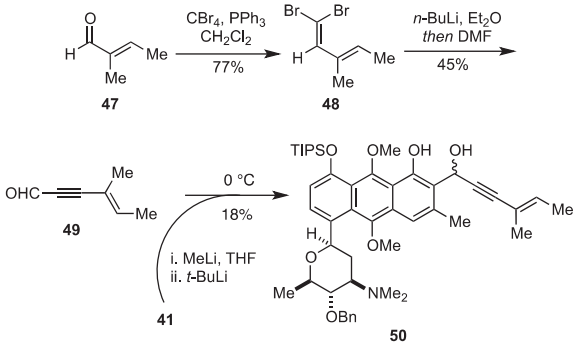
In anticipation of installing the benzopyranone ring, several functional group manipulations were now required. In the event, silylation of anthrol **37**, followed by selective hydrogenolysis of the anthrolic benzyl ether gave **39**. Because a functional handle was needed to introduce the pyranone ring, **39** was converted into the corresponding iodide **40** and bromide **41** by *ortho*-selective iodination or bromination, respectively. Protection of these anthrols as their MOM-ethers then provided **42** and **43**.

We first explored methods to convert the iodide **42** into the ketone **45** using carbonylative cross-coupling protocols that were developed in our laboratories specifically for the synthesis of sterically hindered *ortho*-disubstituted aryl alkynyl ketones.[24] Unfortunately, when **42** was treated with the boronate ester **44** and CO in the presence of PEPPSI–IPr[25] under our optimized conditions, we were unable to obtain any of the desired **45** (Scheme 8); only unreacted starting material was recovered. Similar attempts using the alkynyl zinc reagent **46** were also unsuccessful. This disappointing setback notwithstanding, we turned to other possibilities, even though these would not benefit from the same level of step economy.



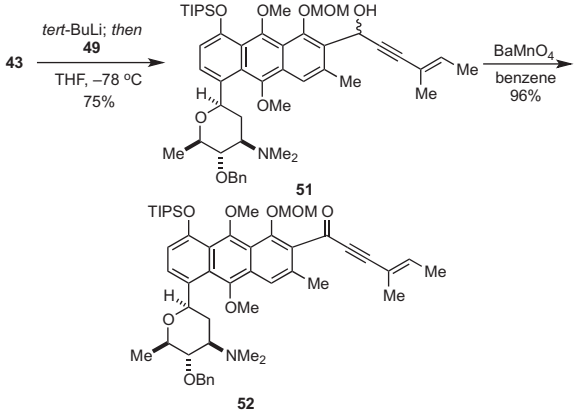
Scheme 8.

In one such effort, we attempted to install the enyne side-chain by generating the dianion from bromide **41** and trapping it with the aldehyde **49**, which was prepared by Corey–Fuchs homologation of tiglic aldehyde (**47**) and trapping of the resultant alkynyl anion with DMF (Scheme 9). Despite numerous efforts, we were able to obtain **50** in at best an 18% yield.



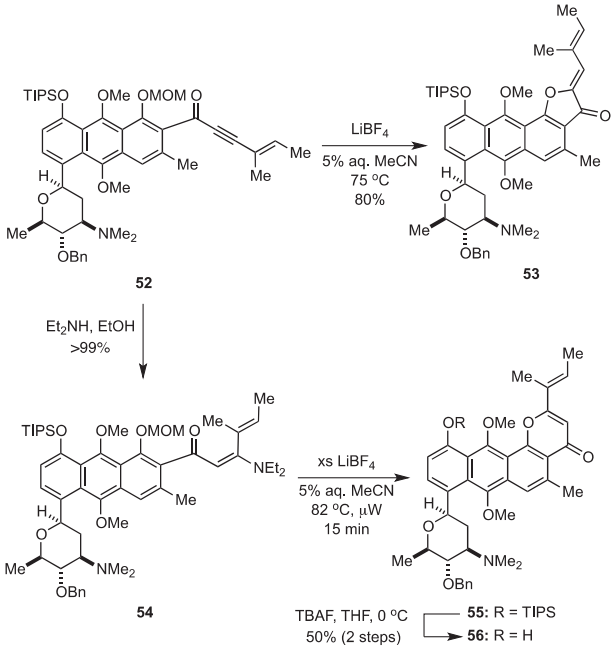
Scheme 9.

In light of these results, we reasoned that the protected bromide **43** might be a better substrate for introducing the enyne side-chain. In the event, treatment of **43** with a slight excess of *t*-BuLi in THF, followed by addition of aldehyde **49** gave **51** in 75% yield (Scheme 10); about 14% of dehalogenated anthracene was obtained that could be recycled. Oxidation of **51** with $BaMnO_4$ gave **52** in 96% yield; other oxidants, such as IBX, Dess–Martin periodinane, TPAP, and MnO_2 furnished lower yields of **52**.



Scheme 10.

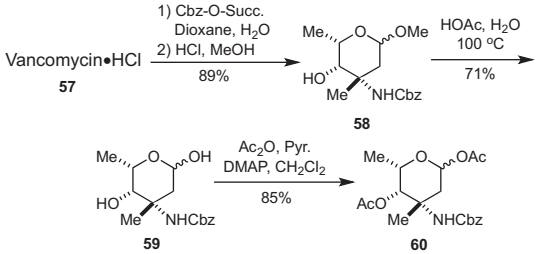
The stage was now set for forming the pyranone ring on **52** by removal of the MOM-ether protecting group, and cyclization of the unmasked anthrol onto the alkynyl ketone.[13c–e,26] Although treating **52** with a variety of Brønsted acids led largely to recovered starting material under most of the conditions examined, we discovered that heating **52** in aqueous acetonitrile containing $LiBF_4$ gave the benzofuranone **53** in 80% yield (Scheme 11); the undesired 5-*exo*-digonal cyclization completely dominated in complete preference to the desired 6-*endo*-digonal cyclization mode. The cyclizations of phenolic ynones to give benzofuranones was known,[26] and in some cases may be avoided by first converting the ynone to a vinylogous amide.[18b] Accordingly, **52** was converted into vinylogous amide **54** in virtually quantitative yield. When a solution of **54** in aqueous acetonitrile containing $LiBF_4$ was heated briefly with microwave irradiation, the 6-*endo*-digonal ring closure occurred to give benzopyranone **55**, which was treated directly with fluoride ion to remove the TIPS protecting group and furnish **56** in 50% overall yield from **54**.



Scheme 11.

2.5. Introduction of vancosaminyl residue by *O*→*C*-glycoside rearrangement

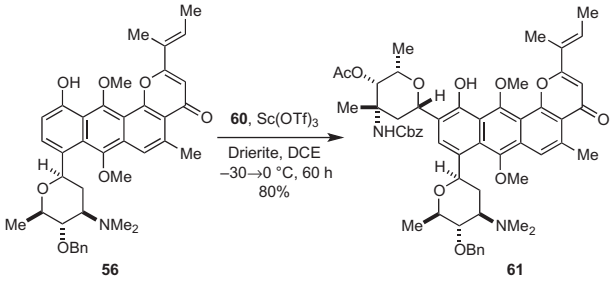
In order to introduce a vancosaminyl residue on the D-ring (**1**), it was first necessary to prepare a suitably protected vancosamine donor. In consideration of the prevailing protecting group strategy for the anthrapyran core, we concluded that the vancosamine derivative **60** would likely meet our needs. Although there are a number of routes to vancosamine derivatives of the general type **60**,[27] the expediency of using vancomycin as a starting material was attractive. Accordingly, vancomycin hydrochloride (**57**) was subjected to Cbz-protection followed by acidic methanolysis to deliver **58** in good yield (Scheme 12).[28] Hydrolysis of the methyl acetal and acetylation of the resultant lactol delivered vancosamine donor **60** as a mixture (10:1) of α- and β-anomers, respectively.



Scheme 12.

We were now poised to install the vancosamine glycoside using an *O*→*C*-glycoside rearrangement as pioneered by Suzuki.[17] Toward this end, the anthrol **56** was first treated with 1.5 equiv of

vancosamine donor **60** in the presence of 4 equiv of $Sc(OTf)_3$, but no *C*-aryl glycoside was isolated from the mixture. Although the anthrol **56** could be recovered, the vancosamine donor could not. Increasing the amount of **60** to 4 equiv and using 8 equiv of $Sc(OTf)_3$ led to the formation of a bis-*C*-aryl glycoside in 80% yield (Scheme 13). This initially exciting result was tempered by the realization that the *O*→*C*-glycoside rearrangement had given **61**, which is the undesired β-anomer of the vancosaminyl glycoside. This stereochemical assignment was made based on analysis of the 1D and 2D ^{1}H NMR spectra. The coupling constants of the vancosamine anomeric proton (J=11.7, 2.4 Hz, DMSO-d_6, 100 °C), as well as its chemical shift (5.32 ppm)[5b,12b] confirmed that the vancosamine glycoside was in its β-configuration. Furthermore, an NOE interaction was not observed between the anomeric proton and the methyl substituent at C5 on the vancosamine residue.



Scheme 13.

In an attempt to retard any equilibration of the α-anomer that was presumably formed as the kinetic product in the reaction of **56** with **60** to the undesired β-anomer, the reaction temperature was maintained at −30 °C; however, under these conditions no C-glycosylation of **56** was observed. We then explored other conditions that we reasoned might not enable deleterious α→β-equilibration. Suzuki had reported that the $Cp_2HfCl_2/AgClO_4$ promoter was a much more reactive promoter than $Sc(OTf)_3$ for inducing *C*-glycosylations via the *O*→*C*-glycoside rearrangement.[17c,29] When **56** and **60** were allowed to react in the presence of this dual promoter system, no glycosylated **56** was isolated. We also examined the utility of $SnCl_4$ as a promoter in accord with the findings of McDonald, who prepared a vancosamine-derived α-*C*-aryl glycoside.[12b] Under these conditions, **61** was again produced, albeit in only 28% yield.

The obtention of the undesired β,β-bis-*C*-aryl glycoside **61** was somewhat surprising and merits brief analysis. It is possible that the desired α-anomer of the vancosamine glycoside was formed, but rapidly underwent epimerization under the reaction conditions. Because we never observed any product other than **61** in the reaction mixture by TLC, this explanation is not completely satisfying. Alternatively, our initial predictions of the preferred transition state geometry of the vancosaminyl donor cation could be flawed. The putative intermediate oxonium ion **62** can adopt several different conformations in solution; representative conformers include **62A**–**62D** (Fig. 2). Axial attack on conformers **62B** and **62D** would give the desired α-anomeric *C*-aryl glycoside, whereas axial attack on **62A** and **62C** would afford the undesired β-anomeric *C*-aryl glycoside.

We originally predicted that the *N*-carbamyl group would reside in an equatorial orientation as in either **62B** or **62D**, thereby leading to the α-anomer; however, a retrospective analysis of various factors leads to a different conclusion. Namely, the geminal substitution of the methyl and *N*-carbamate groups requires that the axis of the *C*-methyl bond be approximately orthogonal to the plane of the carbamate array to minimize unfavorable interactions similar to those found in 1-methyl-1-phenylcyclohexane.[30] Placement of the carbamate moiety in an equatorial position as shown in **62B** and **62D** should thus be disfavored due to resulting *gauche* interactions with the adjacent acetoxy substituent and C–H bond on

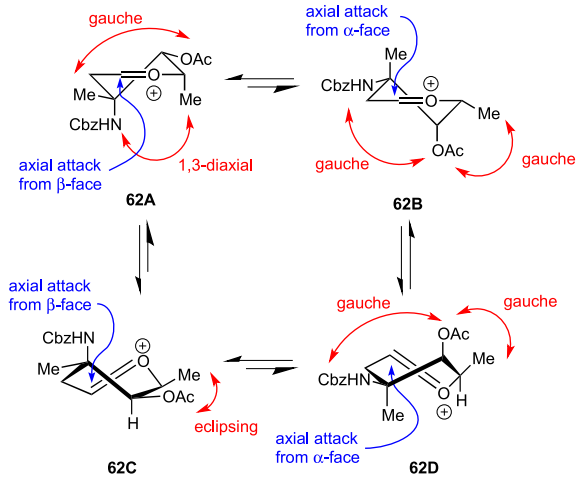


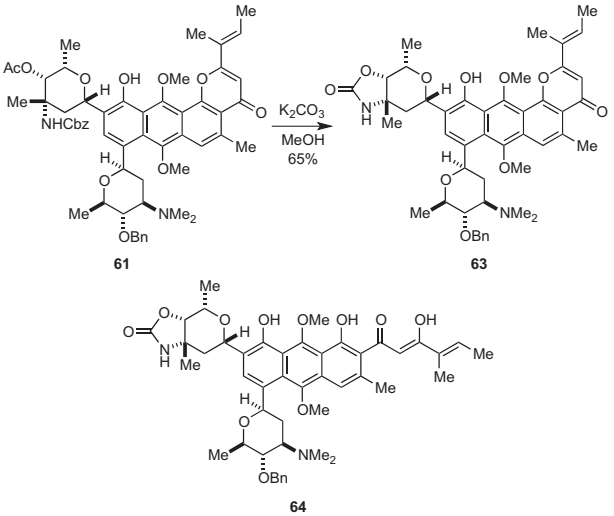
Fig. 2. Conformational analysis of oxonium ion **62**.

the pyran ring. If the carbamate is in an axial orientation as in **62A** and **62C**, these interactions are relieved. Although axial attack on either **62A** or **62C** will give the undesired β-anomer, a destabilizing 1,3-diaxial interaction between the carbamate and the methyl group on the pyran ring in **62A** suggests that attack may occur on the twist boat conformation **62C**. This analysis suggests an alternative protecting group strategy might bias the formation of the desired α-*C*-aryl glycoside.[12b,31]

2.6. Total synthesis of isokidamycin: the end game

Although the *O*→*C*-glycoside rearrangement did not deliver the desired α-anomer of the vancosamine *C*-aryl glycoside, it was apparent that **61** would be a viable intermediate in a total synthesis of isokidamycin (**4**). We envisioned that conversion of **61** into **4** could be realized following cleavage of the acetate protecting group, hydrogenolysis of the benzyl and Cbz protecting groups, reductive methylation of the primary amine, and oxidation of the central anthracene ring. Though ultimately successful, this superficially straightforward undertaking was littered with numerous pitfalls.

We initiated our efforts with removal of the acetate protecting group of **61** using catalytic amounts of K_2CO_3 in MeOH. However, these and related attempts to saponify this ester did not provide the expected secondary alcohol; rather the cyclic carbamate **63** was invariably isolated (Scheme 14). Attempts to hydrolyze the

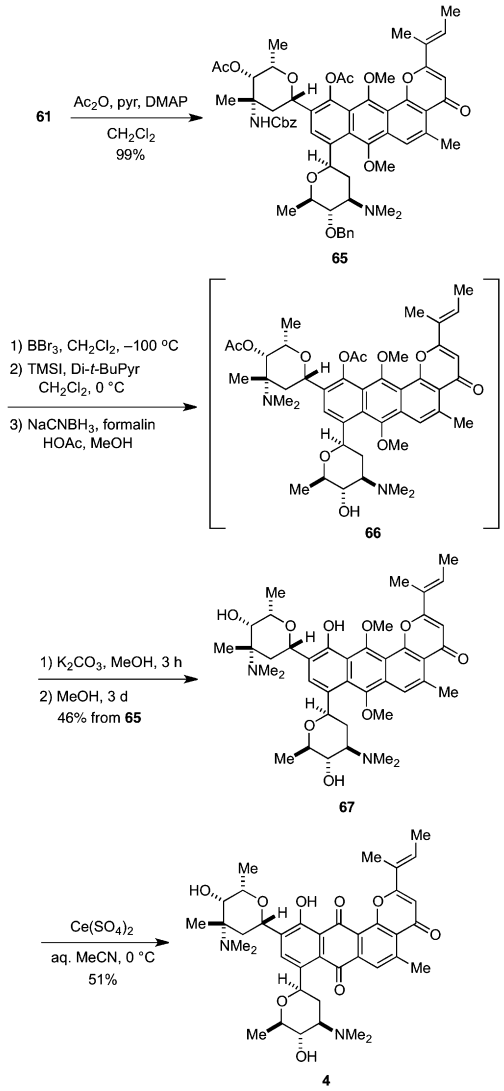


Scheme 14.

carbamate under more forcing conditions led to cleavage of the pyranone ring and formation of **64**. Treating **61** with methanol under mildly acidic conditions simply returned starting material.

In order to obviate the formation of cyclic carbamates upon removing the acetate group, we elected to remove the Cbz and benzyl protecting groups from the vancosamine and angolosamine subunits in **61** first. Although there was ample precedent for the hydrogenolysis of benzyl-derived protecting groups in the presence of olefins,[32] we were unable to selectively remove these groups from **61** without concomitant reduction of the alkenyl side-chain and/or formation of an amide in the vancosamine ring via *O*→*N*-acetyl migration.

The aforegoing reactions provided us some critical insights for planning the sequential removal of the various protecting groups. Armed with this information, we then examined conditions for the Lewis acid-promoted removal of the *O*-benzyl and *N*-Cbz groups. During these experiments, we found that the presence of the free phenol group on the D-ring of **61** rendered it unstable to many Lewis acids. However, after acetylation of this hydroxy group, the resulting acetate **65** could be treated with BBr_3 at low temperatures to cleave the angolosaminyl benzyl protecting group (Scheme 15). The crude alcohol thus obtained was treated with TMSI to effect cleavage of the *N*-Cbz protecting group. Key to the success of this reaction was the discovery that quenching the reaction with pH=7 phosphate buffer prevented migration of the vancosaminyl acetate onto the newly formed primary amine. Because of its propensity to suffer *O*→*N*-acetyl migration, the crude amine was immediately dimethylated by reductive amination to afford **66**, which was used without purification.



Scheme 15.

Removal of the vancosaminyl and phenolic acetate protecting groups from **66** proved unexpectedly difficult, as saponification of the former acetate group was slow. Prolonged exposure of **66** to base led to cleavage of the benzopyranone subunit. We eventually discovered that short treatment of **66** with K_2CO_3 in MeOH cleaved the phenolic acetate; stirring the crude monoacetate in MeOH for 3 days[33] led to transesterification of the remaining acetate group, delivering the penultimate intermediate **67** in 46% overall yield from **65**.

All that remained to complete the synthesis of isokidamycin (**4**) was the oxidative demethylation of the C-ring of **67** to form the anthraquinone. Although reaction of **67** with ceric ammonium nitrate (CAN) furnished quantities of isokidamycin (**4**), the use of cerium (IV) sulfate proved to be superior, delivering **4** in 51% yield. The synthetic sample of isokidamycin thus obtained exhibited physical properties and ^1H and ^{13}C NMR data identical with those of an authentic sample and those reported in the literature.[1,6b]

3. Conclusion

In summary, we have completed the first total synthesis of isokidamycin (**4**) and thus the synthesis of a bis-*C*-aryl glycoside from the pluramycin family of natural products. The synthesis highlights our unified strategy for the synthesis of *C*-aryl glycosides using silicon tethers as disposable linkers in intramolecular aryne–furan cycloadditions to combine a benzene annelation with the installation of a *C*-aryl glycoside. Although the use of an *O*→*C*-glycoside rearrangement to install the vancosamine glycoside did not give the requisite stereochemistry for synthesis of kidamycin (**1**), modification of the protecting group strategy of the vancosamine donor may lead to a solution to this problem.

4. Experimental

4.1. General

Tetrahydrofuran and diethyl ether were dried by filtration through two columns of activated, neutral alumina according to the procedure described by Grubbs.[34] Methanol, acetonitrile, and dimethylformamide were dried by filtration through two columns of activated molecular sieves, and toluene was dried by filtration through one column of activated, neutral alumina followed by one column of Q5 reactant. Benzene was distilled from sodium and benzophenone. Methylene chloride, diisopropylamine, triethylamine, and diisopropylethylamine were distilled from calcium hydride immediately prior to use. Pyridine was distilled from potassium hydroxide (KOH) and calcium hydride and stored over KOH. $BaMnO_4$, the quality of which was supplier dependent, was purchased from Aldrich and was ground with a mortar and pestle immediately before use. All solvents were determined to have less than 50 ppm H_2O by Karl Fischer coulometric moisture analysis. All 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. Volatile solvents were removed under reduced pressure using a Büchi rotary evaporator (20 mmHg, 25 °C). Thin layer chromatography was performed on pre-coated plates of silica gel with a 0.25 mm thickness containing 60F-254 indicator (Merck) unless otherwise noted. Purification by column chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on

230–400 mesh silica gel (E. Merck reagent silica gel 60) unless otherwise noted.

Infrared (IR) spectra were obtained either neat on sodium chloride or as solutions in the solvent indicated. Proton nuclear magnetic resonance (^{1}H NMR) spectra were obtained as solutions in the indicated solvent at the indicated field strength. Chemical shifts are reported in parts per million (ppm) and are referenced to the indicated deuterated solvent. Coupling constants (J) are reported in hertz and the splitting abbreviations used are: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; comp, overlapping multiplets of magnetically non-equivalent protons; br, broad; app, apparent. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were obtained at the indicated field strength using the solvent indicated as the internal reference. Reaction temperatures refer to the temperature of the cooling bath.

4.2. Experimental procedures

*4.2.1. (1R,3R,4S,5R)-3-Azido-1-(furan-1′-yl)-tetrahydro-5-methyl-2H-pyran-4-ol (**16**).* Boron trifluoride diethyl etherate ($BF_3{\cdot}OEt_2$) (18.6 g, 16.6 mL, 131 mmol) was added to a stirred solution of **14** (30.7 g, 119 mmol) and freshly distilled (KOH) furan (43.4 mL, 597 mmol) in MeCN (595 mL) at room temperature. Stirring was continued for 30 min, whereupon saturated $NaHCO_3$ (150 mL) and H_2O (150 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×300 mL). The combined organic layers were washed with brine (1000 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (9:1) to give 22.5 g (71%) of the furyl glycoside as a mixture of epimers at C3 (dr=72:28). This mixture was dissolved in MeOH (170 mL) containing anhydrous K_2CO_3 (0.59 g, 4.2 mmol), and the resultant mixture was stirred at room temperature for 20 h. The solvent was removed under reduced pressure, at which point the desired epimeric azide was isolated by flash column chromatography, eluting with hexanes/EtOAc (9:1) to afford 11.4 g (60%) of alcohol **16** as a white solid: mp=85–86 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (dd, J=1.8, 0.9 Hz, 1H), 6.32 (dd, J=3.2, 1.8 Hz, 1H), 6.29 (dt, J=3.2, 0.7 Hz, 1H), 4.53 (dd, J=11.8, 1.0 Hz, 1H), 3.53 (ddd, J=12.0, 9.3, 4.8 Hz, 1H), 3.46 (dq, J=9.0, 6.2 Hz, 1H), 3.21 (td, J=9.2, 3.7 Hz, 1H), 2.28 (ddd, J=12.8, 4.9, 1.8 Hz, 1H), 2.22 (d, J=3.8 Hz, 1H), 2.02 (dt, J=13.1, 12.0 Hz, 1H), 1.34 (d, J=6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7, 142.6, 110.2, 107.3, 76.3, 75.6, 70.8, 64.0, 34.2, 18.0; IR (neat) 3433 (br), 2877, 2102, 1255, 1071 cm^{-1}; mass spectrum (CI) m/z 224.1039 [$C_{10}H_{14}N_3O_3$ (M+1) requires 224.1035], 137 (base), 224.

*4.2.2. (1R,3R,4S,5R)-3-Azido-4-benzyloxy-1-(furan-1′-yl)-tetrahydro-5-methyl-2H-pyran (**17**).* NaH (1.95 g, 48.7 mmol) was added in one portion to a stirred solution of **16** (9.05 g, 40.6 mmol) and benzyl bromide (5.79 mL, 48.7 mmol) in DMF (200 mL) at 0 °C. After gas evolution had subsided, the cooling bath was removed and stirring was continued for 2 h. The mixture was recooled to 0 °C, whereupon saturated NH_4Cl (100 mL) and H_2O (100 mL) were added. The layers separated, and the aqueous layer was extracted with EtOAc (3×100 mL). The combined organics were washed with H_2O (3×400 mL), brine (4100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (9:1) to afford 12.6 g (99%) of **17** as a white solid: mp=85–88 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39–7.34 (comp, 5H), 7.32–7.28 (comp, 1H), 6.32 (dd, J=3.2, 1.8 Hz, 1H), 6.28 (d, J=3.2 Hz, 1H), 4.88 (d, J=10.6 Hz, 1H), 4.65 (d, J=10.6 Hz, 1H), 4.49 (dd, J=11.8, 2.0 Hz, 1H), 3.65 (ddd, J=12.1, 9.2, 4.9 Hz, 1H), 3.51 (dq, J=9.2, 6.2 Hz, 1H), 3.08 (app t, J=9.3 Hz, 1H), 2.26 (ddd, J=13.1, 4.9, 2.0 Hz, 1H), 1.98 (dt, J=13.1, 12.1 Hz, 1H), 1.35 (d, J=6.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 142.5, 137.5, 128.5, 128.3, 128.1, 110.2, 107.2, 83.4, 76.2, 75.3, 70.8, 63.6, 35.0, 18.4; IR (neat) 2878, 2097, 1080, 742 cm^{-1}; mass spectrum (CI) m/z 314.1507 [$C_{17}H_{20}N_3O_3$ (M+1) requires 314.1505], 227 (base), 271, 286, 314.

*4.2.3. tert-Butyl-(1R,3R,4S,5R)-4-benzyloxy-1-(furan-1′-yl)-tetrahydro-5-methyl-2H-pyran-3-ylcarbamate (**18**).* $LiAlH_4$ (1.55 g, 40.7 mmol) was added to a suspension of **17** (11.6 g, 37.0 mmol) in Et_2O (185 mL) at 0 °C in a 1 L round bottom flask. Caution: voluminous amounts of gas are evolved. The slurry was stirred at 0 °C until gas evolution subsided, whereupon the cooling bath was removed and the solution stirred at room temperature for 1.5 h. The solution was recooled to 0 °C, and H_2O (1.55 mL), 15% $NaOH_{(aq)}$ (1.55 mL), then H_2O (4.65 mL) were added sequentially, dropwise. The slurry was filtered through a pad of Celite, eluting with EtOAc. The combined filtrate and washings were dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Boc_2O (12.1 g, 55.5 mmol) was then added in one portion to a solution of the crude amine in CH_2Cl_2 (74 mL) at room temperature and stirring was continued for 18 h, whereupon the solvent was removed under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (19:1→4:1) to afford 13.6 g (95%) of **18** as a white solid: mp=86–87 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.52 (dd, J=1.8, 0.8 Hz, 1H), 7.34–7.25 (comp, 5H), 6.64 (s, 1H), 6.37 (dd, J=3.3, 1.8 Hz, 1H), 6.29 (d, J=3.3 Hz, 1H), 4.70 (d, J=11.3 Hz, 1H), 4.60 (d, J=11.3 Hz, 1H), 4.52 (dd, J=11.7, 2.1 Hz, 1H), 3.74 (dtd, J=11.9, 9.3, 4.8 Hz, 1H), 3.48 (dq, J=9.2, 6.1 Hz, 1H), 3.13 (app t, J=9.5 Hz, 1H), 2.00 (ddd, J=13.0, 4.8, 2.3 Hz, 1H), 1.88 (m, 1H), 1.40 (s, 9H), 1.21 (d, J=6.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 154.6, 153.5, 141.5, 138.4, 127.5, 127.0, 126.7, 109.6, 105.9, 81.9, 77.3, 75.1, 72.8, 70.1, 52.1, 35.9, 27.8, 18.0; IR (neat) 3345, 1683, 1594, 1159, 1099 cm^{-1}; mass spectrum (CI) m/z 388.2126 [$C_{22}H_{30}NO_5$ (M+1) requires 388.2124], 169 (base), 388.

*4.2.4. tert-Butyl-(1R,3R,4S,5R)-4-benzyloxy-1-(furan-1′-yl)-tetrahydro-5-methyl-2H-pyran-2-ylmethylcarbamate (**19**).* NaH (1.50 g, 36.4 mmol) was added in one portion to a solution of **18** (12.8 g, 33.1 mmol) and MeI (2.50 mL, 39.8 mmol) in DMF (166 mL) at room temperature. The resultant slurry was stirred for 1 h and then cooled to 0 °C, whereupon saturated NH_4Cl (60 mL), H_2O (60 mL), and Et_2O (100 mL) were sequentially added. The layers were separated, and the aqueous layer was extracted with Et_2O (3×100 mL). The combined organics were washed with H_2O (4×400 mL), brine (400 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc (9:1) to afford 12.6 g (95%) of **19** as a clear oil, which slowly solidified to a white solid upon standing: mp=70–73 °C; ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.53 (s, 1H), 7.34–7.25 (comp, 5H), 6.38 (dd, J=3.1, 1.8 Hz, 1H), 6.34 (d, J=3.3 Hz, 1H), 4.60–4.53 (comp, 3H), 4.19–4.06 (br, 1H), 3.53 (dq, J=8.9, 6.1 Hz, 1H), 3.41 (app t, J=9.3 Hz, 1H), 2.80 (s, 3H), 2.17 (app q, J=12.4 Hz, 1H), 1.87 (comp, 1H), 1.41 (s, 9H), 1.27 (d, J=6.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 154.4, 153.4, 141.6, 138.2, 127.5, 126.9, 126.8, 109.6, 106.1, 78.9, 78.3, 75.4, 72.0, 70.4, 57.5, 32.6, 30.1, 27.7, 18.1; IR (neat) 2974, 2359, 1691, 1365, 1155 cm^{-1}; mass spectrum (CI) m/z 402.2276 [$C_{23}H_{32}NO_5$ (M+1) requires 402.2280], 302, 346 (base), 402.

*4.2.5. tert-Butyl-(1R,3R,4S,5R)-4-benzyloxytetrahydro-5-methyl-1-(4′-(dimethylvinylsilyl)furan-1′-yl)-2H-pyran-3-ylmethylcarbamate (**21**).* s-BuLi (28.5 mL, 36.5 mmol, 1.28 M solution in cyclohexane) was added dropwise to a stirred solution of **19** (12.22 g, 3.4 mmol) in THF (152 mL) at −78 °C. The yellow solution was stirred at −78 °C for 2 h, then at −50 °C for 30 min. The solution was recooled to −78 °C, whereupon chlorodimethylvinylsilane (6.3 mL, 45.6 mmol) was added slowly dropwise. The cooling bath was kept in place and

allowed to warm to room temperature. A saturated solution of $NaHCO_3$ (100 mL) was added, and the mixture was diluted with EtOAc (100 mL). The layers were separated, and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/Et_2O (9:1) to afford 12.05 g (82%) of **21** as a clear oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.33–7.25 (comp, 5H), 6.66 (d, J=3.1 Hz, 1H), 6.33 (d, J=3.3 Hz, 1H), 6.24 (dd, J=20.3, 14.7 Hz, 1H), 6.04 (dd, J=14.7, 3.7 Hz, 1H), 5.78 (dd, J=20.3, 3.7 Hz, 1H), 4.61–4.54 (comp, 3H), 4.18–4.02 (br, 1H), 3.53 (dq, J=8.8, 6.2 Hz, 1H), 3.43 (app t, J=9.6 Hz, 1H), 2.81 (s, 3H), 2.16 (app q, J=12.2 Hz, 1H), 1.88 (ddd, J=12.9, 4.2, 2.0 Hz, 1H), 1.42 (s, 9H), 1.27 (d, J=6.1 Hz, 3H), 0.31 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 158.2, 156.6, 154.4, 138.2, 136.1, 132.8, 127.5, 126.9, 126.8, 120.9, 106.1, 79.0, 78.3, 75.4, 72.1, 70.6, 68.7, 32.8, 27.7, 18.1, −3.9; IR (neat) 2973, 1693, 1152, 1109 cm^{-1}; mass spectrum (ESI) m/z 486.26703 [$C_{27}H_{40}NO_5Si$ (M+1) requires 486.2679], 524, 508, 486.

*4.2.6. tert-Butyl-(1R,3R,4S,5R)-4-benzyloxytetrahydro-1-(4′-((8′-hydroxyethyl)dimethylsilyl)-furan-1′-yl)-5-methyl-2H-pyran-3-ylmethylcarbamate (**22**).* 9-BBN (0.94 g, 7.67 mmol) was added to a stirred solution of **21** (1.24 g, 2.56 mmol) in THF (28 mL) at room temperature. The solution was stirred for 6 h and then cooled to 0 °C, whereupon 3 M NaOH (2.56 mL) and 30% H_2O_2 (0.74 mL, 7.67 mmol) were added sequentially. The solution was stirred at room temperature for 1 h, and H_2O (10 mL) was added. The layers were separated, and the aqueous portion was extracted with Et_2O (3×15 mL). The combined organic layers were washed with brine (30 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (4:1) to afford 1.08 g (84%) of alcohol **22** as a clear oil: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.34–7.25 (comp, 5H), 6.64 (d, J=3.3 Hz, 1H), 6.31 (d, J=3.1 Hz, 1H), 4.60–4.53 (comp, 3H), 4.20–4.02 (br, 2H), 3.59–3.50 (comp, 2H), 3.42 (app t, J=9.2 Hz, 1H), 2.80 (s, 3H), 2.16 (app q, J=11.6 Hz, 1H), 1.87 (comp, 1H), 1.42 (s, 9H), 1.27 (d, J=6.1 Hz, 3H), 1.05 (comp, 2H), 0.24 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 157.9, 157.8, 154.4, 138.2, 127.5, 126.9, 126.8, 120.3, 106.1, 79.0, 78.3, 75.4, 72.1, 70.7, 56.8, 56.7, 32.8, 27.7, 19.6, 18.1, −3.4; IR (neat) 3453, 2974, 1692, 1366, 1108 cm^{-1}; mass spectrum (CI) m/z 504.2785 [$C_{27}H_{41}NO_6Si$ (M+1) requires 504.2781], 170 (base), 487, 503.

*4.2.7. 5-Benzyloxy-7-methylnaphthalene-1,4-dione (**26**).* Ag_2O (135 g, 585 mmol) was added to a solution of **25** (27.5 g, 146 mmol) and benzyl bromide (52.0 mL, 438 mmol) in $CHCl_3$ (730 mL) at room temperature. The mixture was vigorously stirred (mechanical stirring) for 72 h in the dark. The mixture was then filtered through a pad of Celite, eluting with CH_2Cl_2. The combined filtrate and washings were concentrated under reduced pressure, and the crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc (9:1) to afford 37.0 g (91%) of **26** as a yellow solid: mp=90–93 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59–7.57 (comp, 2H), 7.53 (s, 1H), 7.42–7.31 (comp, 3H), 7.12 (s, 1H), 6.82 (s, 2H), 5.25 (s, 2H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.5, 183.9, 158.7, 146.3, 141.0, 136.1, 136.0, 133.8, 128.6, 128.5, 127.9, 126.9, 126.6, 120.3, 120.0, 118.0, 70.8, 22.3; IR (neat) 3500, 3064, 2920, 1658, 1599 cm^{-1}; mass spectrum (CI) m/z 279.1018 [$C_{18}H_{15}O_3$ (M+1) requires 279.1021], 297, 279, 183, 165.

*4.2.8. 5-Benzyloxy-2-bromo-7-methylnaphthalene-1,4-dione (**27**).* Bromine (7.65 mL, 149 mmol) in $CHCl_3$ (74 mL) was added dropwise to a solution of **26** (41.0 g, 147 mmol) in $CHCl_3$ (735 mL) at 0 °C. Stirring was continued for 1 h, whereupon the solution was sparged with dry nitrogen for 15 min. NEt_3 (22.1 mL, 159 mmol) was then added dropwise and stirring was continued at 0 °C for an additional 15 min. The cooling bath was then removed and the solution was warmed to room temperature, whereupon saturated $Na_2S_2O_3$ (700 mL) was added. The layers were separated, and the organic layer was washed with H_2O (700 mL), brine (700 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was recrystallized from EtOH to afford 50.9 g (97%) of **27** as an orange solid: mp=108–109 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (s, 1H), 7.56 (comp, 2H), 7.43–7.39 (comp, 2H), 7.34–7.32 (comp, 2H), 7.14 (s, 1H), 5.24 (s, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.9, 178.4, 158.9, 146.5, 142.3, 136.5, 135.8, 132.7, 128.6, 127.9, 126.5, 121.7, 120.3, 117.4, 70.7, 22.2; IR (neat) 3064, 1651, 1599, 1252 cm^{-1}; mass spectrum (CI) m/z 357.0125 [$C_{18}H_{14}BrO_3$ (M+1) requires 357.0126], 357, 358, 359, 360.

*4.2.9. 5-Benzyloxy-2,3-dibromo-7-methylnaphthalene-1,4-dione (**28**).* Pyridinium bromide perbromide (42.7 g, 134 mmol) was added to a solution of **27** (43.4 g, 122 mmol) in CH_2Cl_2 (1.2 L) at 0 °C. Stirring was continued for 50 min, at which point TLC analysis showed that starting material was consumed. Saturated $Na_2S_2O_3$ (1 L) was added, the cooling bath was removed, and the mixture was warmed to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (700 mL). The combined organic layers were washed with H_2O (1 L), brine (1 L), dried ($MgSO_4$), filtered, and concentrated. The crude residue was filtered through a short pad of silica gel, eluting with CH_2Cl_2 to afford 47.9 g (90%) of **28** as an orange solid: mp=161–163 °C (orange needles from EtOH); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (comp, 1H), 7.57–7.55 (comp, 2H), 7.42–7.39 (comp, 2H), 7.31 (tt, J=7.3, 1.3 Hz, 1H), 7.15 (s, 1H), 5.26 (s, 2H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.5, 173.5, 159.7, 147.1, 145.2, 139.5, 135.7, 132.8, 128.8, 126.8, 122.1, 120.3, 116.6, 71.1, 22.3; IR (neat) 2360, 1673, 1599, 1571, 1326, 1233 cm^{-1}; mass spectrum (CI) m/z 434.9233 [$C_{18}H_{13}Br_2O_3$ (M+1) requires 434.9231], 100.96 (base), 434, 435, 436, 437.

*4.2.10. 8-Benzyloxy-2,3-dibromo-4-methoxy-6-methylnaphthalen-1-ol (**30**).* A biphasic mixture of **28** (26.0 g, 59.9 mmol) in CH_2Cl_2 (600 mL) and Et_2O (600 mL) and $Na_2S_2O_4$ (156 g, 899 mmol) in H_2O (1200 mL) was vigorously stirred for 2 h with mechanical stirring. The layers were separated, and the organic layer was washed with H_2O (500 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to furnish a light yellow solid. Molecular sieves (4 Å, 2.80 g) and Me_3OBF_3 (9.00 g, 60.8 mmol) were added to the crude hydroquinone in the glove box. The flask was removed from the glove box and put under an atmosphere of dry nitrogen and the mixture was then dissolved in dry CH_2Cl_2 (600 mL) and cooled to 0 °C. Proton sponge (13.8 g, 64.4 mmol) was then added in one portion to the stirred solution. The resultant mixture was stirred at 0 °C for 1 h, whereupon the ice bath was removed and the solution stirred at room temperature for 14 h. H_2O (500 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3×200 mL). The combined organics were washed with 1 M $HCl_{(aq)}$ (500 mL), brine (500 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc (9:1 to 2:1), to afford 24.4 g (90%) of **30** as an orange solid: mp=154–156 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.04 (s, 1H), 7.47–7.40 (comp, 6H), 6.81 (dd, J=1.0 Hz, 1H), 5.23 (s, 2H), 3.88 (s, 3H), 2.48 (s, 3H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 154.6, 148.7, 146.1, 137.5, 134.5, 129.7, 129.2, 128.4, 118.2, 115.4, 113.0, 109.0, 105.8, 72.1, 61.2, 22.3; IR (neat) 3324, 2933, 2360, 1599, 1393, 1048 cm^{-1}; mass spectrum (CI) m/z 449.9466 [$C_{19}H_{16}Br_2O_3$ requires 449.9469], 372, 452 (base).

*4.2.11. 5-Benzyloxy-2,3-dibromo-1,4-dimethoxy-7-methylnaphthalene (**31**).* A biphasic mixture of **28** (1.0 g, 2.30 mmol) in Et_2O (58 mL) and CH_2Cl_2 (58 mL) and $Na_2S_2O_4$ (6.02 g, 34.6 mmol) in H_2O (115 mL) was shaken vigorously in a separatory funnel for

15 min. The layers were separated, and the organic layer was washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated. MS (4 Å, 0.10 g) and Me_3OBF_4 (0.71 g, 4.83 mmol) were added to the crude hydroquinone, and the solids were dissolved in CH_2Cl_2 (58 mL). The mixture was cooled to 0 °C, whereupon proton sponge (1.04 g, 4.83 mmol) was added in one portion. The solution was stirred for 30 min, whereupon the cooling bath was removed. Stirring was continued for 1 h, and H_2O (50 mL) was then added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×50 mL). The combined organics were washed with 1 M HCl (2×150 mL), H_2O (150 mL), brine (150 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified via flash column chromatography, eluting with hexanes/EtOAc (9:1) to afford 0.519 g (48%) of **31** as an off white solid: mp=103 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J=7.4 Hz, 2H), 7.50 (s, 1H), 7.42 (t, J=7.2 Hz, 2H), 7.36 (t, J=7.2 Hz, 1H), 6.87 (s, 1H), 5.17 (s, 2H), 3.94 (s, 3H), 3.72 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 151.1, 150.0, 137.8, 136.5, 130.6, 128.4 (2C), 127.9, 127.5 (2C), 119.0, 116.9 (2C), 114.4, 111.1, 71.4, 61.7, 61.0, 22.2; IR (neat) 2932, 1620, 1552, 1342 cm^{-1}; mass spectrum (CI) m/z 463.9618 [$C_{20}H_{18}Br_2O_3$ requires 463.9623], 469, 468, 467, 466, 465, 464, 389, 388, 387, 386.

*4.2.12. tert-Butyl-(1R,3R,4S,5R)-1-(4′-(8′-(5″-benzyloxy-2″,3″-dibromo-1″-methoxy-7″-methylnaphthalen-4″-yloxy)ethyldimethylsilyl)furan-1′-yl)-4-benzyloxytetrahydro-5-methyl-2H-pyran-3-ylmethylcarbamate (**34**).* DIAD (4.65 g, 4.53 mL, 23.0 mmol) was added dropwise to a stirred solution of **30** (7.96 g, 17.7 mmol), **22** (9.08 g, 18.0 mmol), and PPh_3 (6.03 g, 23.0 mmol) in toluene (450 mL) at room temperature. The solution was stirred for 40 min, and the solvent was removed under reduced pressure. The residue was purified by flash column chromatography, eluting with hexanes/EtOAc (6:1) to afford 15.27 g (92%) of **34** as an orange glass: ^{1}H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.51 (d, J=7.2 Hz, 2H), 7.46 (s, 1H), 7.41–7.25 (comp, 8H), 7.08 (s, 1H), 6.57 (d, J=3.2 Hz, 1H), 6.29 (d, J=3.1 Hz, 1H), 5.20 (s, 2H), 4.59–4.51 (comp, 3H), 4.09 (br, 1H), 3.92 (app t, J=6.8 Hz, 2H), 3.88 (s, 3H), 3.50 (dq, J=8.8, 5.8 Hz, 1H), 3.37 (app t, J=6.8 Hz, 2H), 2.75 (s, 3H), 2.45 (s, 3H), 2.12 (app q, J=13.1 Hz, 1H), 1.83 (comp, 1H), 1.40 (s, 9H), 1.23 (d, J=6.1 Hz, 3H), 1.11 (app t, J=8.2 Hz, 2H), 0.14 (s, 6H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 157.9, 156.9, 154.4, 154.3, 149.5, 149.3, 138.2, 137.6, 136.2, 129.8, 127.8, 127.7, 127.5, 127.4, 126.9, 126.8, 120.6, 118.6, 115.8, 113.5, 111.5, 110.2, 109.8, 106.1, 81.3, 78.3, 75.4, 72.1, 71.0, 70.8, 70.6, 60.5, 32.7, 27.7, 21.1, 18.1, 16.3, −3.80, −3.83; IR (neat) 2930, 1693, 1551, 1337, 1152 cm^{-1}; mass spectrum (CI) m/z 936.2146 [$C_{46}H_{56}Br_2NO_8Si$ (M+1) requires 936.2142], 911, 938 (base), 941.

*4.2.13. Cycloadduct **35**.* Compound **34** (4.56 g, 4.88 mmol) was dried by azeotropic distillation from toluene (3×100 mL) and then by heating at 120 °C under high vacuum for 2 h. *n*-BuLi (2.04 mL, 5.12 mmol, 2.51 M solution in hexanes) was then added dropwise to a stirred solution of **34** in THF (120 mL) at −25 °C. Stirring was continued for 15 min, whereupon saturated NH_4Cl (50 mL), H_2O (50 mL), and EtOAc (100 mL) were added. The cooling bath was removed, and the solution was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic layers were washed with brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with toluene/EtOAc (96:4→92:8) to afford 3.80 g (92%) of cycloadduct **35** as a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.25 (comp, 11H), 6.98–6.90 (comp, 1H), 6.78 (s, 1H), 5.18–5.08 (comp, 2H), 4.68–4.55 (comp, 3H), 4.42–4.35 (comp, 1H), 3.95–3.86 (comp, 2H), 3.80 (s, 3H), 2.90–2.60 (br, 4H), 2.44 (s, 3H), 2.00–1.84 (comp, 2H), 1.50–1.38 (comp, 14H), 0.96–0.88 (comp, 2H), 0.48–0.44 (comp, 3H), 0.22–0.16 (comp, 3H); IR (neat) 2930, 2361, 1691, 1366, 1154 cm^{-1}; mass spectrum (CI) m/z 778.3776 [$C_{46}H_{56}NO_8Si$ (M+1) requires 778.3775], 346 (base), 402, 777.

*4.2.14. Oxabicycle **32**. Method A.* A solution of TBAF·3H_2O (5.11 g, 16.2 mmol) and **35** (2.1 g, 2.70 mmol) in DMF (27 mL) was placed into a 70 °C oil bath and heated with stirring for 1.5 h. The solution was cooled to 0 °C, and MeI (1.68 mL, 27.0 mmol) and NaH (0.54 g, 13.5 mmol) were sequentially added. The cooling bath was removed, and the slurry was stirred at room temperature for 20 min. The slurry was then poured into a mixture of EtOAc (100 mL) and saturated NH_4Cl (25 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (3×20 mL), and the combined organic layers were washed with H_2O (4×200 mL), brine (200 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc (17:3→3:1), to afford 1.62 g (85%) of **32** as a pale orange oil, and as a mixture of diastereomers: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56–7.25 (comp, 9H), 6.98–6.92 (comp, 2H), 6.84–6.79 (comp, 1H), 5.99 (s, 1H), 5.14 (s, 2H), 4.80–4.50 (comp, 4H), 3.90–3.80 (comp, 3H), 3.75–3.60 (comp, 4H), 2.90–2.72 (comp, 2H), 2.70–2.55 (comp, 2H), 2.45 (s, 3H), 2.05–1.85 (comp, 2H), 1.62–1.55 (comp, 2H), 1.50–1.32 (comp, 12H); IR (neat) 2928, 1691, 1454, 1366 cm^{-1}; mass spectrum (CI) m/z 707.3458 [$C_{43}H_{49}NO_8$ requires 707.3458], 577, 608, 652, 707 (base).

Method B. A solution of **31** (0.096 g, 0.239 mmol) in THF (0.3 mL, 0.8 M) and a solution of *n*-BuLi (0.098 mL, 0.8 M) were added simultaneously via syringe pump to a solution of **19** (0.096 g, 0.239 mmol) in THF (2.4 mL) over 10 min at −30 °C over 10 min. Stirring was continued for 5 min, whereupon saturated $NaHCO_3$ (3 mL) and EtOAc (5 mL) were added. The layers were separated, and the aqueous layer was extracted with EtOAc (3×5 mL). The combined organic layers were washed with H_2O (15 mL), brine (15 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc (99:1→4:1) to afford 0.060 g (35%) of **32** and 0.037 g (22%) of **33** as orange oils.

*4.2.15. (E)-4-Methylhex-4-en-2-ynal (**49**).* A solution of PPh_3 (10.9 g, 41.6 mmol) in CH_2Cl_2 (26 mL) was transferred via cannula to a solution of freshly sublimed CBr_4 (6.87 g, 20.7 mmol) in CH_2Cl_2 (26 mL) at −20 °C. Stirring was continued for 20 min, then the solution was cooled to −78 °C. Tiglic aldehyde (1.0 mL, 10.4 mmol) was added dropwise. Stirring was continued for 10 min, whereupon the cooling bath was removed and the mixture was allowed to warm to room temperature. The mixture was poured into pentane (700 mL) and the resulting mixture was filtered through a pad a Celite, eluting with pentane. The combined filtrate and washings were concentrated under reduced pressure to ~10% of the original volume, and the precipitated solids were removed by vacuum filtration through a plug of Celite washing with additional pentane. The filtrate was again concentrated to ~10% of the original volume and was purified by passage through a plug of silica gel, eluting with pentane to give 1.95 g (79%) of (*E*)-1,1-dibromo-3-methylpenta-1,3-diene (**48**) as a colorless oil that was identical in all respects to the reported compound.[35]

n-BuLi (7.1 mL, 19.4 mmol, 2.74 M solution in hexanes) was added dropwise to a solution of a portion of the previously prepared vinyl dibromide (2.20 g, 9.25 mmol) in Et_2O (46 mL) at −78 °C. Stirring was continued for 1 h at −78 °C, and then at 0 °C for 1 h. The solution was recooled to −78 °C, whereupon DMF (0.86 mL, 11.1 mmol) was added dropwise. Stirring was continued for 5 min, whereupon the cooling bath was removed and the solution was warmed to room temperature. The reaction mixture was diluted with saturated NH_4Cl (5 mL), then Et_2O (20 mL). The layers were

separated, and the aqueous layer was extracted with Et_2O (2×10 mL). The combined organics were washed with H_2O (2×20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure while keeping the vacuum ~300 mmHg or higher. The crude material was purified by flash column chromatography, eluting with pentane/Et_2O (95:5). The eluant was then concentrated to a volume of ca. 6 mL. MS (4 Å) were added (2 spatula tips) and the mixture was stirred under N_2 for 2 h. The solution was then filtered into a dry flask using a syringe fitted with a 0.45 μm nitrocellulose filter tip and the resultant solution was used immediately as aldehyde **49** was quite unstable. The eluant could also be concentrated to deliver 0.449 g (45%) of the unstable aldehyde **49** as a yellow oil:[36] ^{1}H NMR (400 MHz, C_6D_6) δ 8.93 (s, 1H), 5.89 (qq, J=7.2, 1.4 Hz, 1H), 1.39 (dq, J=2.7, 1.4 Hz, 3H), 1.16 (dq, J=7.2, 1.0 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6) δ 175.8, 141.0, 116.9, 97.4, 86.7, 15.6, 14.2; IR (neat) 3412, 2925, 2854, 2182, 1662 cm^{-1}; mass spectrum (CI) m/z 109.0651 [C_7H_9O (M+1) requires 109.0653].

*4.2.16. 8-Benzyloxy-4-((1′R,3′R,4′S,5′R)-4′-benzyloxytetrahydro-5′-methyl-3′-methylamino-2H-pyran-1′-yl)-9,10-dimethoxy-6-methylanthracen-1-ol (**36**).* TMSOTf (4.64 g, 3.78 mL, 20.9 mmol) was added dropwise to a stirred solution of **32** (2.96 g, 4.18 mmol) and di-*t*-BuPy (4.77 g, 5.6 mL, 25.1 mmol) in CH_2Cl_2 (42 mL) at 0 °C. Stirring was continued at 0 °C for 5 min, whereupon the cooling bath was removed and stirring was continued for an additional 1.75 h. The solution was recooled to 0 °C, TBAF (5.5 g, 20.9 mmol) was added, and stirring was continued for 10 min. Saturated $NaHCO_3$ (50 mL) was added, and the solution was allowed to warm to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with H_2O (100 mL), brine (100 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude reside was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (70:25:5→60:35:5) to afford 2.16 g (85%) of **36** as a yellow oil: ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.61 (s, 1H), 7.72 (d, J=7.9 Hz, 1H), 7.63 (s, 1H), 7.57–7.59 (comp, 2H), 7.45–7.24 (comp, 8H), 6.80 (d, J=8.1 Hz, 1H), 6.73 (s, 1H), 5.64 (d, J=10.3 Hz, 1H), 5.24 (s, 2H), 4.79 (d, J=11.0 Hz, 1H), 4.72 (d, J=11.0 Hz, 1H), 3.84 (s, 3H), 3.82 (s, 3H), 3.77 (dq, J=9.2, 6.1 Hz, 1H), 3.18 (app t, J=9.0 Hz, 1H), 2.97–2.92 (comp, 1H), 2.52 (s, 3H), 2.39–2.46 (comp, 1H), 2.36 (s, 3H), 1.48 (d, J=6.2 Hz, 1H), 1.45–1.35 (comp, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.7, 154.0, 149.6, 148.5, 138.3, 136.7, 135.8, 128.7, 128.6, 128.5, 128.1, 127.94, 127.90, 127.5, 127.4, 126.1, 124.4, 117.1, 115.6, 114.2, 108.8, 108.2, 85.4, 76.5, 75.7, 75.1, 71.4, 64.9, 62.7, 62.2, 39.0, 33.2, 22.6, 19.2; IR (neat) 3275, 2931, 2279, 1633, 1447, 1356 cm^{-1}; mass spectrum (CI) m/z 608.3009 [$C_{38}H_{42}NO_6$ (M+1) requires 608.3012], 608, 302, 208, 125, 113.

*4.2.17. 8-Benzyloxy-4-((1′R,3′R,4′S,5′R)-4′-benzyloxytetrahydro-3′-dimethylamino-5′-methyl-2H-pyran-1′-yl)-9,10-dimethoxy-6-methylanthracen-1-ol (**37**).* $NaBH(OAc)_3$ (1.34 g, 6.32 mmol) was added in one portion to a solution of **36** (1.28 g, 2.11 mmol) and 37% aqueous formaldehyde (0.47 mL, 6.32 mmol) in DCE (42 mL) at room temperature. Stirring was continued for 5 min, whereupon saturated $NaHCO_3$ (40 mL) and CH_2Cl_2 (40 mL) were sequentially added. The biphasic solution was stirred vigorously for 10 min. The layers were separated, and the organic layer was washed with saturated $NaHCO_3$ (2 mL), H_2O (2 mL), brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to afford 1.25 g (95%) of **37** as an orange oil that needed no further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.62 (s, 1H), 7.72 (d, J=8.0 Hz, 1H), 7.65–7.64 (comp, 1H), 7.60–7.58 (comp, 2H), 7.47–7.26 (comp, 8H), 6.80 (d, J=8.0 Hz, 1H), 6.75 (d, J=1.0 Hz, 1H), 5.52 (d, J=10.3 Hz, 1H), 5.24 (s, 2H), 5.03 (d, J=10.7 Hz, 1H), 4.68 (d, J=10.7 Hz, 1H), 3.833 (s, 3H), 3.828 (s, 3H), 3.69–3.76 (comp, 1H), 3.21 (app t, J=9.4 Hz, 1H), 3.09–3.03 (comp, 1H), 2.53 (s, 3H), 2.36 (s, 6H), 2.24–2.28 (comp, 1H), 1.46 (d, J=6.1 Hz, 3H), 1.42–1.31 (comp, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.7, 153.8, 149.5, 148.5, 139.0, 136.7, 135.8, 128.6, 128.5, 128.3, 128.1, 127.5, 125.4, 124.2, 117.0, 115.6, 114.2, 108.7, 108.1, 80.4, 76.9, 76.2, 74.3, 71.4, 67.2, 64.84, 64.83, 62.7, 40.9, 32.6, 22.5, 19.3; IR (neat) 2931, 1633, 1452, 1356 cm^{-1}; mass spectrum (CI) m/z 622.3170 [$C_{39}H_{44}NO_6$ (M+1) requires 622.3169], 623, 622, 621, 249, 222.

*4.2.18. (1R,3R,4S,5R)-4-Benzyloxy-1-(6′-benzyloxy-5′,10′-dimethoxy-8′-methyl-4′-triisopropyloxyanthracen-1′-yl)-N,N,5-trimethyltetrahydro-2H-pyran-3-amine (**38**).* TIPSOTf (0.84 mL, 3.11 mmol) was added dropwise to a solution of anthrol **37** (1.76 g, 2.83 mmol) and 2,6-lutidine (0.43 mL, 3.68 mmol) in CH_2Cl_2 (14 mL) at 0 °C. The cooling bath was removed, and stirring was continued for 21 h, whereupon CH_2Cl_2 (10 mL) and saturated $NaHCO_3$ (20 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×10 mL). The combined organics were washed with H_2O (40 mL), brine (40 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (90:9:1) to afford 1.73 g (80%) of **38** as a yellow oil: ^{1}H NMR (600 MHz, C_6D_6) δ 8.20 (d, J=7.5 Hz, 1H), 7.80 (s, 1H), 7.64 (d, J=7.0 Hz, 2H), 7.47 (d, J=7.6 Hz, 2H), 7.36 (t, J=7.5 Hz, 2H), 7.24–7.21 (comp, 3H), 7.14–7.12 (comp, 1H), 6.97 (d, J=7.5 Hz, 1H), 6.48 (s, 1H), 5.66 (d, J=10.1 Hz, 1H), 5.15 (d, J=11.2 Hz, 1H), 4.98–4.82 (br s, 2H), 4.67 (d, J=11.2 Hz, 1H), 3.99 (dq, J=8.3, 6.0 Hz, 1H), 3.74 (s, 3H), 3.54 (s, 3H), 3.26–3.20 (comp, 2H), 2.54 (d, J=11.8 Hz, 1H), 2.29 (s, 3H), 2.15 (s, 6H), 1.71 (d, J=6.0 Hz, 3H), 1.47–1.35 (comp, 4H), 1.21–1.18 (br s, 18H); ^{13}C NMR (150 MHz, C_6D_6) δ 156.6, 152.84, 147.8, 140.3, 138.2, 135.8, 131.2, 129.4, 128.5, 128.4, 128.3, 128.1, 127.9, 127.7, 127.4, 127.3, 125.7, 124.5, 121.8, 118.3, 114.5, 113.1, 109.3, 80.7, 77.5, 77.4, 74.5, 71.3, 68.2, 63.8, 62.4, 40.7, 32.9, 22.4, 19.8, 18.4, 13.7; IR (neat) 2941, 2865, 1568, 1356 cm^{-1}; mass spectrum (CI) m/z 778.44974 [$C_{48}H_{63}NO_6Si$ (M+1) requires 778.4495], 780, 779, 778.

*4.2.19. 5′-((1R,3R,4S,5R)-4-Benzyloxy-3-dimethylamino-5-methyltetrahydro-2H-pyran-1-yl)-9′,10′-dimethoxy-3′-methyl-8′-triisopropylsilyloxyanthracen-1′-ol (**39**).* A mixture of **38** (1.73 g, 2.22 mmol) and pyridine (0.09 mL, 1.11 mmol) in MeOH (44 mL) and EtOAc (4.0 mL) was sonicated for 60 min until all solids had dissolved. $Pd(OH)_2$ (0.31 g, 0.44 mmol; 20% on carbon) was added in one portion, and the mixture was vigorously stirred under an atmosphere of H_2 (balloon pressure) for 2 h. The resultant mixture was filtered through a pad of Celite, eluting with EtOAc. The yellow solution was concentrated under reduced pressure, and the crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (90:9:1) to deliver 1.37 g (90%) of **39** as a yellow oil: ^{1}H NMR (600 MHz, DMSO-d_6) δ 10.14 (s, 1H), 7.60 (d, J=7.9 Hz, 1H), 7.43 (s, 1H), 7.38–7.33 (comp, 4H), 7.27 (tt, J=6.9, 1.8 Hz, 1H), 6.79 (d, J=7.9 Hz, 1H), 6.65 (d, J=1.5 Hz, 1H), 5.38 (d, J=8.1 Hz, 1H), 4.91 (d, J=11.3 Hz, 1H), 4.64 (d, J=11.3 Hz, 1H), 3.84 (s, 3H), 3.81 (s, 3H), 3.62 (dq, J=8.7, 6.1 Hz, 1H), 3.18 (app t, J=9.3 Hz, 1H), 2.97–2.93 (comp, 1H), 2.44 (s, 3H), 2.25 (s, 6H), 2.22–2.14 (comp, 1H), 1.37 (septet, J=7.6 Hz, 3H), 1.33 (d, J=6.1 Hz, 3H), 1.25–1.15 (comp, 1H), 1.14–1.00 (br s, 18H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 153.8, 150.4, 149.6, 147.6, 139.2, 137.2, 130.3, 128.1, 127.48, 127.37, 127.2, 124.2, 124.0, 118.3, 114.8, 112.1, 111.5, 110.5, 79.6, 76.0, 75.7, 73.0, 66.4, 64.4, 62.8, 40.4, 32.0, 21.9, 19.0, 17.78, 17.75, 17.74, 12.5; IR (neat) 3309, 2941, 2865, 1640, 1449, 1362, 1031 cm^{-1}; mass spectrum (CI) m/z 687.3950 [$C_{41}H_{57}NO_6Si$ (M+0) requires 687.3955], 688, 532, 222.

*4.2.20. 5′-((1R,3R,4S,5R)-4-Benzyloxy-3-dimethylamino-5-methyltetrahydro-2H-pyran-1-yl)-2′-bromo-9′,10′-dimethoxy-3′-methyl-8′-triisopropylsilyloxyanthracen-1′-ol (**41**).* A solution of freshly recrystallized and rigorously dried NBS (0.083 g,

0.467 mmol) in CH_2Cl_2 (12 mL) was added dropwise to a solution of **39** (0.318 g, 0.463 mmol) in CH_2Cl_2 (12 mL) −78 °C. The cooling bath was left in place, and the mixture was allowed to slowly warm to room temperature for 4 h, whereupon saturated $NaHCO_3$ (20 mL) was added. The layers were separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organics were washed with H_2O (40 mL), brine (40 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (90:9:1) to afford 0.272 g (77%) of **41** as an orange foam; ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.04 (s, 1H), 7.65 (d, J=8.1 Hz, 1H), 7.64 (s, 1H), 7.38–7.33 (comp, 4H), 7.29–7.26 (comp, 1H), 6.84 (d, J=8.1 Hz, 1H), 5.45–5.30 (br, 1H), 4.91 (d, J=11.3 Hz, 1H), 4.65 (d, J=11.3 Hz, 1H), 3.89 (s, 3H), 3.83 (s, 3H), 3.63 (dq, J=8.7, 6.2 Hz, 1H), 3.19 (app t, J=9.2 Hz, 1H), 3.00–2.91 (comp, 1H), 2.54 (s, 3H), 2.26 (s, 6H), 2.24–2.15 (br, 1H), 1.44–1.26 (comp, 6H), 1.28–1.18 (br, 1H), 1.12–0.91 (comp, 18H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 150.3, 150.1, 148.3, 148.1, 139.0, 136.4, 130.3, 128.1, 127.5, 127.3, 125.2, 124.6, 118.8, 114.5, 113.2, 106.5, 79.3, 76.0, 75.4, 74.2, 72.9, 66.3, 64.7, 63.3, 40.3, 32.0, 23.8, 18.9, 17.8, 12.5; IR (neat) 3249, 2941, 2866, 1628, 1447, 1103 cm^{-1}; mass spectrum (ESI) m/z 766.31331 [$C_{41}H_{56}BrNO_6Si$ (M+1) requires 766.3124], 770, 769, 768, 767, 766.

*4.2.21. (2R,3S,4R,6R)-3-Benzyloxy-6-(6′-bromo-9′,10′-dimethoxy-5′-methoxymethoxy-7′-methyl-4′-triisopropylsilyloxyanthracen-1′-yl)-N,N,2-trimethyltetrahydro-2H-pyran-4-amine (**43**).* NaH (0.21 g, 0.53 mmol; 60% dispersion in mineral oil) was added in one portion to a solution of **41** (0.272 g, 0.355 mmol) and MOMCl (0.058 mL, 0.533 mmol) in THF (3.6 mL) at 0 °C. After gas evolution has subsided, the cooling bath was removed, and stirring was continued for 25 min. The mixture was recooled to 0 °C, whereupon saturated NH_4Cl (8 mL), Et_2O (20 mL) and H_2O (10 mL) were sequentially added. The layers were separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organics were washed with H_2O (40 mL), brine (40 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (90:9:1) to afford 0.258 g (89%) of **43** as a yellow oil: ^{1}H NMR (600 MHz, C_6D_6) δ 8.18 (d, J=7.5 Hz, 1H), 7.91 (s, 1H), 7.47 (d, J=7.6 Hz, 2H), 7.23 (app t, J=7.5 Hz, 2H), 7.14–7.10 (comp, 1H), 6.94 (d, J=7.5 Hz, 1H), 5.60 (d, J=10.2 Hz, 1H), 5.49–5.32 (br, 2H), 5.15 (d, J=11.2 Hz, 1H), 4.67 (d, J=11.2 Hz, 1H), 4.05–3.94 (comp, 1H), 3.75 (s, 3H), 3.68–3.62 (br s, 3H), 3.43 (s, 3H), 3.23–3.19 (comp, 2H), 2.50 (d, J=12.0 Hz, 1H), 2.42 (s, 3H), 2.16 (s, 6H), 1.70 (d, J=6.0 Hz, 3H), 1.41–1.32 (comp, 4H), 1.21–1.08 (comp, 18H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 152.6, 150.2, 148.5, 140.2, 136.5, 131.3, 125.6, 124.7, 122.4, 119.9, 119.3, 113.5, 101.2, 80.6, 77.5, 77.2, 75.8, 74.5, 74.1, 68.1, 67.5, 65.9, 63.6, 62.5, 58.3, 40.8, 32.8, 24.6, 19.8, 18.3, 13.7; IR (neat) 2942, 2866, 1607, 1451, 1033 cm^{-1}; mass spectrum (CI) m/z 810.33952 [$C_{43}H_{60}BrNO_7Si$ (M+1) requires 810.3395], 814, 813, 811, 809, 649, 647, 593, 592, 590.

*4.2.22. (E)-1′-(5″-((2R,4R,5S,6R)-5-Benzyloxy-4-dimethylamino-6-methyltetrahydro-2H-pyran-2-yl)-9″,10″-dimethoxy-1″-methoxymethoxy-3″-methyl-8″-triisopropylsilyloxyanthracen-2″-yl)-4′-methylhex-4′-en-2′-yn-1′-ol (**51**).* t-BuLi (1.21 mL, 1.6 M solution in pentane) was added at a fast, dropwise rate to a solution of **43** (0.75 g, 0.925 mmol) in THF (9.3 mL) at −78 °C. Stirring was continued for 10 s, whereupon a solution of **49** (0.50 g, 4.63 mmol) in THF (6 mL) was quickly added. Stirring was continued for 2 min, whereupon the cooling bath was removed, and the solution was warmed to room temperature. H_2O (10 mL) and Et_2O (10 mL) were then added. The layers were separated, and the aqueous layer was extracted with Et_2O (3×10 mL). The combined organics were washed with H_2O (30 mL), brine (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (90:9:1) to afford 0.581 g (75%) of **51** as a mixture of C1′ epimers; ^{1}H NMR (400 MHz, C_6D_6) δ 8.16 (s, 1H), 8.01 (s, 1H), 7.46 (d, J=7.2 Hz, 2H), 7.22 (t, J=7.6 Hz, 2H), 7.14–7.11 (comp, 1H), 7.00–6.92 (comp, 2H), 6.00–5.88 (comp, 1H), 5.62–5.61 (comp, 1H), 5.22 (d, J=6.1 Hz, 1H), 5.13 (d, J=11.2 Hz, 1H), 4.65 (d, J=11.2 Hz, 1H), 4.00–3.92 (comp, 1H), 3.80–3.65 (comp, 3H), 3.47–3.40 (comp, 4H), 3.30–3.21 (comp, 4H), 3.15–3.00 (comp, 2H), 2.98–2.82 (comp, 2H), 2.53 (d, J=12.5 Hz, 1H), 2.20–2.10 (br s, 6H), 1.69–1.67 (comp, 6H), 1.43–1.30 (comp, 8H), 1.25–1.05 (br s, 18H); ^{13}C NMR (100 MHz, C_6D_6) δ 152.4, 151.1, 148.3, 140.1, 136.8, 135.1, 132.2, 131.2, 128.1, 128.4, 127.5, 125.5, 124.4, 122.0, 118.9, 113.2, 101.6, 80.6, 77.4, 77.3, 74.4, 68.0, 63.4, 62.5, 59.0, 57.4, 45.7, 40.7, 32.6, 30.2, 21.4, 19.7, 18.3, 13.8, 10.7; IR (neat) 3416, 2932, 2866, 2350, 1602, 1451, 1358, 1026 cm^{-1}; mass spectrum (ESI) m/z 840.48652 [$C_{50}H_{70}NO_8Si$ (M+1) requires 840.4865], 842, 841, 840.

*4.2.23. (E)-1″-(5′-((2R,4R,5S,6R)-5-Benzyloxy-4-dimethylamino-6-methyltetrahydro-2H-pyran-2-yl)-9′,10′-dimethoxy-1′-methoxymethoxy-3′-methyl-8′-(triisopropylsilyloxy)anthracen-2′-yl)-4″-methylhex-4″-en-2″-yn-1″-one (**52**).* Freshly ground $BaMnO_4$ (2.55 g, 9.96 mmol) was added in one portion to a solution of **51** (0.418 g, 0.498 mmol) in benzene (10 mL) at room temperature. Vigorous stirring was continued for 3.5 h, whereupon the mixture was filtered through a pad of Celite, eluting with CH_2Cl_3. The filtrate was concentrated to provide 0.401 g (96%) of **52** as an orange oil that needed no further purification: ^{1}H NMR (600 MHz, C_6D_6) δ 8.19 (d, J=7.8 Hz, 1H), 7.87 (s, 1H), 7.47 (d, J=7.0 Hz, 2H), 7.23 (t, J=7.5 Hz, 2H), 7.14–7.12 (comp, 1H), 6.94 (d, J=8.0 Hz, 1H), 6.01 (dq, J=7.2, 1.6 Hz, 1H), 5.60 (d, J=9.2 Hz, 1H), 5.45–5.48 (br, 2H), 5.16 (d, J=11.2 Hz, 1H), 4.67 (d, J=11.2 Hz, 1H), 3.99–3.94 (br, 1H), 3.82 (s, 3H), 3.61 (s, 3H), 3.43 (s, 3H), 3.26–3.20 (comp, 2H), 2.53 (d, J=13.6 Hz, 1H), 2.50 (s, 3H), 2.18 (s, 6H), 1.70 (d, J=6.0 Hz, 3H), 1.52 (s, 3H), 1.39–1.34 (br, 4H), 1.21 (d, J=7.2 Hz, 3H), 1.19–1.15 (br, 18H); ^{13}C NMR (150 MHz, C_6D_6) δ 181.0, 152.6, 151.8, 151.7, 148.5, 140.2, 139.8, 134.3, 133.0, 131.3, 128.8, 126.2, 125.0, 122.3, 119.7, 117.7, 113.5, 102.0, 95.3, 88.6, 80.6, 77.5, 77.3, 74.5, 68.1, 63.8, 62.5, 57.9, 40.8, 32.8, 30.2, 20.3, 19.8, 18.3, 15.9, 14.2, 13.7; IR (neat) 2932, 2866, 2183, 1650, 1451, 1360 cm^{-1}; mass spectrum (ESI) 838.47087 [$C_{50}H_{68}NO_8Si$ (M+1) requires 838.47190].

*4.2.24. (Z)-7′-((2R,4R,5S,6R)-5-Benzyloxy-4-dimethylamino-6-methyltetrahydro-2H-pyran-2-yl)-6′,11′-dimethoxy-4′-methyl-2′-((E)-2″-methylbut-2′-enylidene)-10′-triisopropylsilyloxyanthra[1,2,b]furan-3″(2H)one (**53**).* A freshly made solution of $LiBF_4$ (0.21 mL, 1.0 M in MeCN) was added to a solution of **52** (0.017 g, 0.021 mmol) in MeCN (1.0 mL) at room temperature. The resultant solution was heated to 75 °C for 2 h, whereupon H_2O (0.05 mL) was added. Stirring was continued for 30 min, and the solution was then cooled to room temperature. Saturated $NaHCO_3$ (2.0 mL) and Et_2O (2.0 mL) were added. The layers were separated, and the aqueous layer was extracted with Et_2O (3×1 mL). The combined organics were washed with H_2O (2.0 mL), brine (2.0 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (90:9:1) to afford 0.013 g (80%) of **53** as a red oil: ^{1}H NMR (600 MHz, C_6D_6) δ 8.25 (d, J=8.0 Hz, 1H), 7.58 (d, J=1.3 Hz, 1H), 7.49 (d, J=7.5 Hz, 2H), 7.24 (t, J=7.4 Hz, 2H), 7.14–7.12 (comp, 1H), 6.98 (d, J=8.0 Hz, 1H), 6.78 (s, 1H), 5.88 (qq, J=7.2, 1.3 Hz, 1H), 5.60 (d, J=9.8 Hz, 1H), 5.17 (d, J=11.1 Hz, 1H), 4.67 (d, J=11.1 Hz, 1H), 4.05–3.92 (comp, 1H), 3.78 (s, 3H), 3.44 (s, 3H), 3.26–3.20 (comp, 2H), 2.54–2.46 (comp, 1H), 2.28 (s, 3H), 2.17 (s, 6H), 1.69 (d, J=6.0 Hz, 3H), 1.51 (d, J=7.6 Hz, 3H), 1.41–1.29 (comp, 7H), 1.24–1.04 (br s, 18H); ^{13}C NMR (150 MHz, C_6D_6) δ 184.0, 167.7, 153.2, 153.0, 148.5, 147.8, 146.0, 140.1, 137.6, 133.5, 132.4, 129.7, 128.5, 127.6, 126.3, 121.7, 117.7, 116.81, 116.77, 114.2, 113.5, 80.5, 77.6, 77.1, 74.5,

68.0, 64.4, 62.7, 40.8, 33.1, 19.7, 18.3, 14.5, 14.4, 13.6; IR (neat) 2941, 2846, 1687, 1602, 1367, 1071 cm^{-1}; mass spectrum (low res ESI) *m/z* 794.22 [$C_{48}H_{63}NO_7Si$ (M+1) requires 794.10].

*4.2.25. (2″E,4″E)-1″-(((2R,4R,5S,6R)-5-Benzyloxy-4-dimethylamino-6-methyltetrahydro-2H-pyran-2-yl)-9′,10′-dimethoxy-1′-methoxymethoxy-3′-methyl-8′-(triisopropylsilyloxy)anthracen-2′-yl)-3″-diethylamino-4″-methylhexa-2″,4″-dien-1″-one (**54**).* Freshly distilled Et_2NH (0.92 mL, 8.86 mmol) was added to a solution of **52** (0.372 g, 0.443 mmol) in EtOH (4.4 mL) at room temperature. Stirring was continued for 3 h, whereupon the solution was concentrated under reduced pressure. The crude residue was dissolved in Et_2O (50 mL) and the resultant solution was washed with H_2O (50 mL), brine (50 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to provide 0.396 g (99%) of **54** as a yellow oil, which required no further purification: ^1H NMR (600 MHz, C_6D_6) δ 8.17 (d, *J*=7.9 Hz, 1H), 7.98 (s, 1H), 7.47 (d, *J*=6.9 Hz, 2H), 7.22 (t, *J*=7.4 Hz, 2H), 7.13–7.10 (comp, 1H), 6.96 (d, *J*=7.9 Hz, 1H), 5.64 (d, *J*=10.1 Hz, 1H), 5.55 (s, 1H), 5.50–5.44 (br, 3H), 5.16 (d, *J*=11.2 Hz, 1H), 4.67 (d, *J*=11.2 Hz, 1H), 3.98 (dq, *J*=8.0, 5.9 Hz, 1H), 3.93 (s, 3H), 3.67 (s, 3H), 3.50 (s, 3H), 3.26–3.19 (comp, 2H), 2.90–2.64 (br, 4H), 2.60 (s, 3H), 2.58–2.52 (br, 1H), 2.16 (s, 6H), 2.40–1.92 (br, 3H), 1.70 (d, *J*=6.1 Hz, 3H), 1.64–1.51 (br, 3H), 1.42–1.30 (comp, 4H), 1.25–1.10 (br comp, 18H), 0.83–0.70 (br, 6H); ^{13}C NMR (150 MHz, C_6D_6) δ 188.7, 163.7, 159.9, 152.5, 151.3, 151.2, 148.3, 148.1, 140.3, 139.2, 134.8, 133.4, 131.3, 128.7, 128.5, 127.6, 127.4, 125.2, 124.1, 122.0, 119.0, 113.2, 101.8, 97.1, 80.6, 77.5, 77.4, 74.4, 68.1, 63.8, 62.6, 57.9, 43.5, 40.8, 32.8, 22.8, 20.6, 19.8, 18.3, 16.5, 15.1, 13.8, 13.6; IR (neat) 2935, 1513, 1358, 1036 cm^{-1}; mass spectrum (ESI) 911.56002 *m/z* [$C_{54}H_{79}N_2O_8Si$ (M+1) requires 911.55881].

*4.2.26. 8′-((2R,4R,5S,6R)-5-Benzyloxy-4-dimethylamino-6-methyltetrahydro-2H-pyran-2-yl)-1′-((E)-but-2″-en-2″-yl)-11′-hydroxy-7′,12′-dimethoxy-5′-methyl-4H-naphtho[2,3-h]chromen-4′-one (**56**).* A solution of **54** (0.182 g, 0.200 mmol) and $LiBF_4$ (4.0 mL, 1.0 M solution in 5% aq MeCN) was heated at 82 °C in the microwave (with simultaneous cooling; ~12 W) for 15 min. The reaction was cooled, and the mixture was partitioned between Et_2O (2 mL) and saturated $NaHCO_3$ (2 mL). The layers were separated, and the organic layer was washed with H_2O (2 mL), brine (2 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (80:19:1 → 60:39:1) to afford 0.061 g, 38% of the TIPS protected anthrol as a yellow oil, along with 0.017 g, 14% of **56** as an orange oil.

A 1.0 M solution of TBAF·$3H_2O$ in THF (0.17 mL, 0.17 mmol) was added dropwise to a stirred solution of the TIPS protected anthrol (0.09 g, 0.114 mmol) in THF (11 mL) at 0 °C. Stirring was continued for 5 min, whereupon saturated $NaHCO_3$ (5 mL), Et_2O (20 mL), and H_2O (5 mL) were sequentially added. The layers were separated, and the organic layer was washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (80:18:2) to afford 0.065 g (90%) of **56** as an orange oil: ^1H NMR (600 MHz, C_6D_6) δ 10.64–10.54 (br, 1H), 8.27 (d, *J*=8.0 Hz, 1H), 7.82 (s, 1H), 7.49 (d, *J*=8.0 Hz, 2H), 7.29–7.23 (comp, 3H), 6.78 (q, *J*=7.3 Hz, 1H), 6.45 (s, 1H), 5.61 (d, *J*=9.5 Hz, 1H), 5.16 (d, *J*=11.2 Hz, 1H), 4.68 (d, *J*=11.2 Hz, 1H), 3.97–3.93 (comp, 1H), 3.46 (s, 3H), 3.30 (s, 3H), 3.22–3.20 (comp, 2H), 3.18 (s, 3H), 2.48–2.40 (br, 1H), 2.20 (s, 6H), 1.66 (d, *J*=6.1 Hz, 3H), 1.50 (s, 3H), 1.45 (d, *J*=7.2 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 179.2, 162.4, 155.2, 154.7, 150.6, 149.1, 140.1, 135.7, 129.7, 120.6, 120.2, 118.5, 114.1, 110.7, 110.3, 80.5, 77.6, 76.9, 74.5, 68.1, 65.9, 63.9, 62.6, 40.8, 33.3, 32.8, 30.2, 24.2, 19.7, 15.5, 14.1, 11.9; IR (neat) 3314, 2926, 1643, 1443, 1371, 1114 cm^{-1}; mass spectrum (ESI) 638.31123 [$C_{39}H_{44}NO_7$ (M+1) requires 638.3114].

*4.2.27. Benzyl (2S,3S,4S)-3-hydroxy-6-methoxy-2,4-dimethyltetrahydro-2H-pyran-4-ylcarbamate(**58**).* $NaHCO_3$ (1.0 g, 12.0 mmol) was added to a solution of vancomycin·HCl (**57**) (5.94 g, 4.0 mmol) in dioxane (33 mL) and H_2O (33 mL) at room temperature. Stirring was continued for 5 min, whereupon Cbz–*O*-Succinimide (3.99 g, 16.0 mmol) was added in one portion. Stirring was continued for 3 h. The resulting solution was poured into acetone (400 mL) and was sonicated for 30 min. The solids were collected in a medium porosity fritted funnel. The collected solids were azeotroped from toluene (3×200 mL) and placed under vacuum overnight. The resulting crude Cbz–vancomycin was dissolved in MeOH (133 mL), whereupon a solution of concentrated HCl (2.67 mL, 32.0 mmol) in dioxane (5.4 mL) was added dropwise at room temperature. White precipitate formed after ca. 1 min. Stirring was continued for 3 h, whereupon $NaHCO_3$ (2.72 g, 32.3 mmol) was added. Stirring was continued for 20 min, whereupon the mixture was concentrated to ca. 10% of its original volume. Acetone (400 mL) was added and the resultant mixture was sonicated for 30 min. The solids were collected in a medium porosity fritted funnel and the filtrate was concentrated under reduced pressure. The crude material thus obtained was absorbed onto silica gel and purified by flash column chromatography, eluting with hexanes/EtOAc (3:2) to afford 1.10 g (89%) of **58** as an inseparable mixture of α/β anomers (3:2): ^1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.27 (comp, 5H), 5.45–5.43 (comp, 1H), 5.12–5.02 (comp, 2H), 4.71–4.39 (comp, 1H), 4.12–3.80 (comp, 1H), 3.47 (s, 1H), 3.24–3.36 (comp, 3H), 2.36–2.04 (comp, 2H), 1.87–1.77 (comp, 1H), 1.62–1.51 (comp, 3H), 1.35–1.22 (comp, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.0, 136.5, 128.5, 128.0, 103.8, 100.2, 98.1, 88.7, 73.0, 72.5, 68.8, 66.2, 62.9, 60.2, 56.4, 55.0, 54.9, 53.6, 37.4, 35.2, 23.2, 21.6, 20.8, 17.2, 17.1; IR (neat) 3411 (br), 2937, 1714, 1502, 1222 cm^{-1}; mass spectrum (CI) *m/z* 310.1654 [$C_{16}H_{24}NO_5$ (M+1) requires 310.1658] 310, 279, 278.

*4.2.28. Benzyl (2S,3S,4S)-3,6-dihydroxy-2,4-dimethyltetrahydro-2H-pyran-4-ylcarbamate (**59**).* A solution of **58** (0.707 g, 2.29 mmol) in H_2O (2.3 mL) and HOAc (9.15 mL) was heated to 100 °C for 1 h, whereupon the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc (1:1 → 1:4) to afford 0.486 g (71%) of **59** as an inseparable mixture (ca. 2:1) of α/β anomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (comp, 5H), 5.66–5.46 (comp, 1H), 5.32–4.76 (comp, 4H), 3.76–3.36 (comp, 1H), 3.40–3.19 (comp, 1H), 2.80–1.94 (comp, 2H), 1.82–1.52 (comp, 2H), 1.48–1.36 (comp, 2H), 1.26–1.19 (comp, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.2, 136.3, 136.0, 128.4, 128.0, 97.7, 96.9, 93.1, 91.3, 72.9, 72.0, 69.1, 66.7, 66.2, 65.9, 63.2, 62.7, 59.6, 55.0, 53.5, 47.7, 46.9, 38.7, 35.2, 23.4, 22.1, 21.5, 21.0, 20.3, 17.23, 17.17; IR (neat) 3406 (br), 2939, 1705, 1503, 1276, 1068 cm^{-1}; mass spectrum (CI) *m/z* 296.1501 [$C_{15}H_{22}NO_5$ (M+1) requires 296.1498] 296, 279, 278.

*4.2.29. (4S,5S,6S)-4-Benzyloxycarbonylamino-4,6-dimethyltetrahydro-2H-pyran-2,5-diyl acetate (**60**).* Ac_2O (0.62 mL 6.59 mmol) was added dropwise to a solution of **59** (0.486 g, 1.65 mmol), pyridine (0.80 mL, 9.9 mmol), and DMAP (0.02 g, 0.17 mmol) in CH_2Cl_2 (17 mL) at room temperature. Stirring was continued for 24 h, whereupon the solvent was removed under reduced pressure. The crude residue was dissolved in Et_2O (20 mL), and the resultant solution was washed with saturated $CuSO_4$ (2×20 mL), H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc (5:1 → 1:1) to afford 0.531 g (85%) of **60** as a mixture (9:1) of α/β anomers: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (comp, 5H), 5.87 (dd, *J*=10.2, 2.4 Hz, 1H), 5.14–4.82 (comp, 4H), 4.15–4.96 (comp, 1H), 2.18–2.05 (comp, 8H), 1.64 (s, 3H) 1.22–1.15 (comp, 3H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 170.9, 168.9, 168.0, 153.7, 136.7, 127.7, 127.1, 90.4,

71.2, 68.4, 64.4, 53.4, 36.0, 21.3, 20.2, 20.1, 19.8, 16.6; IR (neat) 3358, 2987, 1746, 1526, 1245, 1045 cm^{-1}; mass spectrum (CI) *m/z* 378.1555 [$C_{19}H_{24}NO_7$ (M−H) requires 378.1553] 667, 438, 414, 378, 293.

*4.2.30. (2″S,3″S,4″S,6″S)-6″-(8′((2R,4R,5S,6R)-5-Benzyloxy-4-dimethylamino-6-methyltetrahydro-2H-pyran-2-yl)-1′-((E)-but-2‴-en-2‴-yl)-11′-hydroxy-7′,12′-dimethoxy-5′-methyl-4′-oxo-4H-naphtho[2,3-h]chromen-10′-yl)-4″-benzyloxycarbonylamino-2″,4″-dimethyltetrahydro-2H-pyran-3″-yl acetate (**61**).* A solution of **56** (0.073 g, 0.115 mmol) and **60** (0.174 g, 0.460 mmol) in DCE (1.5 mL) was transferred dropwise, via cannula, to a stirred suspension of $Sc(OTf)_3$ (0.453 g, 0.920 mmol) and powdered Drierite (0.453 g) in DCE (2.3 mL) at −30 °C. The cooling bath was left in place, and the reaction mixture was allowed to reach 0 °C over 30 min. Stirring was continued at 0 °C for 67 h, whereupon saturated $NaHCO_3$ (3 mL) and EtOAc (5 mL) were added. Stirring was continued for 5 min, whereupon the mixture was filtered through a pad of Celite, eluting with EtOAc. The filtrate was washed with H_2O (20 mL), brine (20 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by two flash column chromatographic separations, eluting the first with CH_2Cl_2/MeOH (99:1→95:5), and the second with hexanes/EtOAc/NEt_3 (80:19:1→50:49:1) to afford 0.088 g (80%) of **61** as an orange oil, along with 0.014 g (19%) of recovered **56** [**61** exists as a mixture of rotomers, which decompose upon extended heating at 100 °C in DMSO-d_6]: ^{1}H NMR (600 MHz, DMSO-d_6, 100 °C) δ 8.06 (s, 1H), 7.80 (s, 1H), 7.40–7.26 (comp, 10H), 7.13 (dq, *J*=7.1, 1.3 Hz, 1H), 6.44 (s, 1H), 5.50 (d, *J*=10.0 Hz, 1H), 5.32 (dd, *J*=11.7, 2.4 Hz, 1H), 5.13–5.09 (comp, 1H), 5.04 (d, *J*=12.6 Hz, 1H), 4.93 (d, *J*=11.5 Hz, 1H), 4.90 (d, *J*=12.6 Hz, 1H), 4.70 (d, *J*=11.5 Hz, 1H), 4.08 (qd, *J*=6.2, 1.1 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.68 (dq, *J*=8.7, 6.2 Hz, 1H), 3.20 (t, *J*=9.2 Hz, 1H), 3.00 (td, *J*=9.2, 4.0 Hz, 1H), 2.90 (s, 3H), 2.33 (s, 6H), 2.16 (dd, *J*=13.8, 4.0 Hz, 1H), 2.08 (s, 3H), 2.06–2.02 (comp, 4H), 1.99–1.96 (comp, 4H), 1.82 (d, *J*=12.5 Hz, 1H), 1.73 (s, 3H), 1.36 (d, *J*=6.02 Hz, 3H), 1.12 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (150 MHz, C_6D_6) δ 179.2, 170.5, 170.1, 162.3, 155.1, 154.7, 150.5, 149.3, 149.0, 140.1, 137.5, 135.7, 129.7, 129.2, 125.9, 125.8, 122.7, 120.6, 120.2, 118.1, 114.2, 110.6, 92.8, 91.7, 80.4, 77.6, 76.9, 74.4, 73.6, 72.5, 71.4, 70.0, 68.1, 66.3, 63.8, 63.1, 54.7, 53.3, 40.9, 39.2, 36.3, 34.3, 32.8, 24.2, 21.7, 20.3, 19.5, 18.2, 14.2, 11.9; IR (neat) 3287, 2974, 1746, 1643, 1231 cm^{-1}; mass spectrum (ESI) 957.45320 *m/z* [$C_{56}H_{64}N_2O_{12}$ (M+1) requires 957.4538].

*4.2.31. 10′-((2″S,3″S,4″S,6″S)-3″-Acetoxy-4″-benzyloxycarbonylamino-2″,4″-dimethyltetrahydro-2H-pyran-6″-yl)-8′-((2R,4R,5S,6R)-5-benzyloxy-4-dimethylamino-6-methyltetrahydro-2H-pyran-2-yl)-1′-((E)-but-2‴-3n-2‴-yl)-7′,12′-dimethoxy-5′-methyl-4′-oxo-4H-naphtho[2,3-h]chromen-11′-yl acetate (**65**).* Ac_2O (39 μL, 0.412 mmol) was added dropwise to a solution of **61** (0.079 g, 0.082 mmol), pyridine (66 μL, 0.820 mmol), and DMAP (0.005 g, 0.041 mmol) in CH_2Cl_2 (1.64 mL) at room temperature. Stirring was continued for 30 min, whereupon the solution was concentrated and redissolved in Et_2O (5 mL). The ethereal solution was washed with H_2O (3×5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The resultant crude material was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (75:23:2→50:48:2) to afford 0.081 g (99%) of **65** as a yellow solid that existed as a mixture of rotomers that decompose upon extended heating at 100 °C in DMSO-d_6: mp=125–126 °C; ^{1}H NMR (600 MHz, DMSO-d_6, 100 °C) δ 8.13 (s, 1H), 7.81 (s, 1H), 7.40–7.26 (comp, 10H), 7.12 (dq, *J*=7.1, 1.3 Hz, 1H), 6.63 (s, 1H), 6.45 (s, 1H), 5.54 (d, *J*=10.1 Hz, 1H), 5.12 (s, 1H), 5.11–5.06 (comp, 1H), 5.04 (d, *J*=12.6 Hz, 1H), 4.93 (d, *J*=11.5 Hz, 1H), 4.90 (d, *J*=12.6 Hz, 1H), 4.70 (d, *J*=11.5 Hz, 1H), 4.09 (qd, *J*=6.3, 1.1 Hz, 1H), 3.91 (s, 3H), 3.77–3.69 (comp, 4H), 3.21 (app t, *J*=9.3 Hz, 1H), 3.03 (ddd, *J*=12.0, 9.8, 3.9 Hz, 1H), 2.91 (s, 3H), 2.44 (s, 3H), 2.35–2.31 (comp, 7H), 2.27 (ddd, *J*=12.6, 4.0, 1.5 Hz, 1H), 2.16–2.10 (comp, 1H), 2.08 (s, 3H), 1.98 (d, *J*=7.1 Hz, 3H), 1.72 (s, 3H), 1.45–1.42 (comp, 1H), 1.38 (d, *J*=6.0 Hz, 3H), 1.10 (d, *J*=6.3 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6, 100 °C) δ 179.4, 169.9, 168.4, 162.4, 155.8, 154.6, 150.8, 148.4, 142.1, 140.1, 137.4, 137.1, 136.2, 131.4, 129.6, 126.0, 124.2, 121.0, 120.8, 120.0, 119.8, 116.9, 110.5, 80.3, 77.5, 77.2, 74.5, 72.8, 71.4, 70.5, 68.2, 66.3, 63.1, 62.8, 54.1, 40.8, 39.8, 32.3, 30.2, 24.2, 21.2, 20.3, 20.1, 19.6, 18.2, 14.1, 11.7; IR (neat) 2933, 1747, 1642, 1440, 1200, 1081 cm^{-1}; mass spectrum (CI) 999.4637 *m/z* [$C_{58}H_{67}N_2O_{13}$ (M+1) requires 999.4643].

*4.2.32. 1′-((E)-But-2‴-en-2‴-yl)-10′-((2″S,3″S,4″S,6″S)-4″-dimethylamino-5″-hydroxy-4″,6″-dimethyltetrahydro-2H-pyran-6″-yl)-8′-((2R,4R,5S,6R)-4-dimethylamino-5-hydroxy-6-methyltetrahydro-2H-pyran-2-yl)-11′-hydroxy-7′,12′-dimethoxy-5′-methyl-4H-naphtho[2,3-h]chromen-4′-one (**67**).* A solution of BBr_3 (0.65 mL, 0.326 mmol, 0.5 M in CH_2Cl_2) was added dropwise to a stirred solution of **65** (0.054 g, 0.054 mmol) in CH_2Cl_2 (2.7 mL) at −90 °C. Stirring was continued for 5 min, whereupon MeOH (1.5 mL) and saturated $NaHCO_3$ (1.5 mL) were added. The cooling bath was removed, and the mixture was vigorously stirred while warming to room temperature. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with hexanes/EtOAc/NEt_3 (50:49:1)→hexanes/EtOAc/MeOH/NEt_3 (50:45:4:1) to afford a mixture of alcohols (ca. 1:1 by HPLC).

A portion of the above mixture of alcohols (0.021 g, 0.024 mmol) was dissolved in CH_2Cl_2 (0.5 mL) containing di-*t*-BuPy (0.019 g, 0.022 mL, 0.096 mmol) at 0 °C, and TMSI (0.027 mL, 0.191 mmol) was added with stirring. The solution was stirred for 45 min, whereupon MeOH (0.5 mL) and pH=7 phosphate buffer (0.5 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (2×1 mL). The combined organic layers were diluted with MeOH (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a volume of ca. 1.2 mL (it is important to keep the crude product in MeOH throughout the workup and not to concentrate the solution to dryness in order to avoid *O*→*N*-acetyl migration.) This solution was used immediately in the next reaction.

A solution of 37% aqueous formalin (0.011 mL, 0.144 mmol) and $NaCNBH_3$ (0.009 g, 0.144 mmol) were added to the above methanolic solution, and the pH was then adjusted to pH=4–5 with HOAc. The solution was stirred at room temperature for 15 min, whereupon saturated $NaHCO_3$ (1 mL) and CH_2Cl_2 (1 mL) were added. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3×1 mL). The combined organic layers were washed with H_2O (5 mL), brine (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was dissolved in MeOH (1.2 mL), K_2CO_3 (0.033 g, 0.240 mmol) was added, and the mixture was stirred at room temperature for 1.5 h. Saturated NH_4Cl (1.5 mL) and $CHCl_3$ (2 mL) were added and the layers separated, and the aqueous layer was extracted with $CHCl_3$ (4×2 mL). The combined organic layers were washed with brine (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The residue was dissolved in dry MeOH (1.2 mL), and the solution was stirred for 3 days. The solvent was removed under reduced pressure, and the residue was purified by flash column chromatography, eluting with toluene/NEt_3 (4:1) to obtain 0.010 g (46% over five steps) of **67** as a yellow solid: mp=150 °C (decomp.); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.84–10.60 (br, 1H), 8.13 (s, 1H), 7.79 (s, 1H), 7.15 (q, *J*=6.8 Hz, 1H), 6.46 (s, 1H), 5.56 (d, *J*=10.3 Hz, 1H), 5.15–4.92 (br, 1H), 4.00–3.80 (comp, 7H), 3.68–3.62 (comp, 1H), 3.32–3.25 (comp, 2H), 2.98 (s, 3H), 2.80–2.72 (comp, 1H), 2.30 (s, 6H), 2.23 (s,

6H), 2.03 (s, 3H), 1.98 (d, J=6.8 Hz, 3H), 1.50–1.44 (comp, 6H), 1.20 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 180.1, 162.8, 155.2, 148.6, 134.8, 130.4, 128.1, 127.1, 126.1, 125.6, 122.6, 120.1, 120.0, 117.8, 113.7, 110.3, 78.4, 77.9, 73.3, 72.2, 71.8, 70.4, 68.2, 64.5, 59.0, 58.6, 52.1, 40.4, 37.5, 36.6, 30.3, 29.7, 23.9, 18.8, 17.2, 14.7, 12.4, 11.0, 8.4; IR (neat); 3281, 2934, 1640, 1440, 1082 cm^{-1}; mass spectrum (CI) m/z 719.3895 [$C_{41}H_{55}N_2O_9$ (M+1) requires 719.3908].

*4.2.33. Isokidamycin (**4**).* A solution of $Ce(SO_4)_2$ (0.013 mL, 0.064 mmol, 0.5 M in H_2O) was added dropwise to a stirred solution of **67** (0.023 g, 0.032 mmol) in MeCN (0.058 mL) and H_2O (0.006 mL) at 0 °C. Stirring was continued for 10 min, whereupon the mixture was partitioned between saturated $NaHCO_3$ (1 mL) and $CHCl_3$ (1 mL). The layers were separated, and the aqueous layer was extracted with $CHCl_3$ (3×1 mL). The combined organic layers were washed with H_2O (4 mL), brine (4 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography, eluting with $CHCl_3$/hexanes/NEt_3 (3:2:1) to afford 0.011 g (51%) of isokidamycin (**4**) as a red solid: mp=199–200 °C (decomp.); ^{1}H NMR (600 MHz, $CDCl_3$) δ 13.94 (s, 1H), 8.39 (s, 1H), 7.94 (s, 1H), 7.45 (q, J=6.2 Hz, 1H), 6.36 (s, 1H), 5.29 (dd, J=8.7, 6.0 Hz, 1H), 4.89 (d, J=10.4 Hz, 1H), 3.81 (q, J=5.6 Hz, 1H), 3.48 (dq, J=8.7, 6.0 Hz, 1H), 3.32 (t, J=9.5 Hz, 1H), 3.28 (s, 1H), 2.99 (s, 3H), 2.87–2.82 (m, 1H), 2.38 (s, 6H), 2.30–2.24 (comp, 2H), 2.21 (s, 6H), 2.05–2.01 (comp, 2H), 2.00 (d, J=7.2 Hz, 3H), 1.99 (s, 3H), 1.48 (d, J=6.5 Hz, 3H), 1.37 (d, J=6.1 Hz, 3H), 1.18 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 188.1, 183.5, 179.7, 164.1, 158.8, 155.9, 149.7, 137.3, 134.1, 132.6, 127.4, 126.4, 126.0, 125.5, 119.1, 115.6, 108.9, 77.6, 75.5, 72.4, 71.3, 71.2, 70.3, 67.7, 40.5, 36.9, 36.7, 28.4, 24.1, 18.6, 18.0, 15.0, 12.2; IR (neat) 3390, 2928, 1643, 1085 cm^{-1}; mass spectrum (ESI) m/z 345.17513 [$C_{39}H_{50}N_2O_9$ (M+2)/2 requires 345.17527].

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