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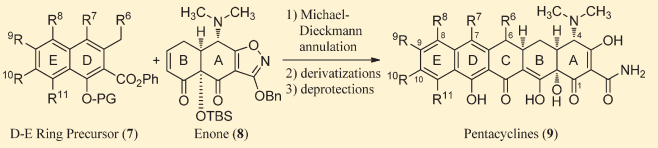
Synthesis and Antibacterial Activity of Pentacyclines: A Novel Class of Tetracycline Analogs

Cuixiang Sun, Diana K. Hunt, Roger B. Clark, Denene Lofland, William J. O'Brien, Louis Plamondon, and Xiao-Yi Xiao*

Tetraphase Pharmaceuticals, 480 Arsenal Street, Watertown, Massachusetts 02472, United States

ABSTRACT: Employing a highly efficient total synthesis approach, we synthesized and evaluated for antibacterial activity diverse and novel pentacycline analogs with systematic variations at C7, C8, C9, and C10. Certain substitution groups, as well as substitution patterns at various positions, were found to be preferred for increased antibacterial activity. A number of pentacycline analogs displayed potent activity *in vitro* and *in vivo*, especially against Gram-positive organisms. Several analogs have also shown promising oral bioavailability in rats and cynomolgus monkey.



INTRODUCTION

Tetracyclines are a class of antibiotics with broad spectrum antibacterial activity.[1] Since the isolation of its first member, chlorotetracycline (**1**, Figure 1), from the culture broth of *Streptomyces*,[2] several generations of tetracycline analogs have been discovered and used to treat infections caused by a wide range of pathogens. These tetracyclines include oxytetracycline (**2**),[3] tetracycline (**3**),[4] doxycycline (**4**),[5] and minocycline (**5**),[6] all discovered before the early 1970s, as well as the recently approved analog tigecycline (**6**).[7]

After a half century's use of tetracyclines, a high rate of resistance has emerged leading to dramatically decreased efficacy.[8] There are two main tetracycline-resistance mechanisms: (1) active drug efflux (*tet*A−*tet*D, and *tet*K−*tet*L) and (2) ribosomal protection (*tet*M−*tet*O).[9] The efflux mechanism is mainly observed in Gram-negative organisms such as *Escherichia coli* and *Pseudomonas* spp.,[9,10] while ribosomal protection is more common in Gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus* spp.[11]

Since the discovery of the first generation of natural tetracyclines (chlorotetracycline, oxytetracycline, and tetracycline), several generations of non-natural tetracycline antibiotics have been produced to overcome tetracycline resistance. These include the clinically important doxycycline, minocycline, and tigecycline, which are derived from fermentation products through semisynthesis. However, due to the structural complexity and chemical sensitivity of the tetracycline scaffold, chemical modifications of tetracyclines in the past 50 years have been largely limited to substitution at C7 and C9, and very few modifications at C4, C5, and C6.

The total synthesis approach, recently developed by Myers et al.,[12] can modify positions inaccessible (or difficult to access) by semisynthetic methods. Its unique "right-to-left" (ring A to D) mode of construction provides the most efficient means to widely vary substitutions, as well as ring structures, in the D-ring region.[12,17] Structure−activity relationships (SAR) of tetracycline analogs accumulated in the last few decades[14] and the recently solved tetracycline−30S ribosome cocrystal structure[15] indicate that the "southeast" portion of the molecule is directly involved in interactions (mainly H-bonding) with the bacterial ribosome and should be largely conserved in order to retain high levels of ribosomal binding. In contrast, the "northwest" portion of the molecule does not directly interact with the ribosome and can be modified without substantial loss of activity. Structural variations in the D-ring region have emerged as one of the most promising approaches to modify tetracyclines for improved potency and pharmacological properties[13] as shown by previous generations of tetracyclines such as tigecycline, which is highly potent and capable of overcoming tetracycline resistance.[7]

Myers et al.[12,17] recently reported a series of pentacyclic analogs with promising antibacterial activity against both Gram-positive and Gram-negative organisms. These analogs were based on a "pentacycline" scaffold (**9**, Figure 2),[12,17] which has an additional benzene ring (E-ring) fused in a linear fashion to the C8 and C9 carbons on the tetracycline D-ring. The added E-ring not only produces a unique tetracycline scaffold but also presents several additional derivatization sites believed to have minimum effect on ribosomal binding as expected from the binding mode of tetracycline with the 30S ribosome. We believe this unique pentacyclic scaffold, coupled with optimal substitutions and substitution patterns, has the potential to uncover new tetracycline analogs that are potent, are capable of overcoming tetracycline resistance, and have improved pharmacological properties such as oral bioavailability. We therefore decided to expand the pentacycline series to include a much wider range of substitutions and substitution patterns. We evaluated the antibacterial activity of the new pentacycline analogs against a wide range of organisms including Gram-positive, Gram-negative, and tetracycline-resistant strains. We also studied *in vivo* efficacy and pharmacokinetic

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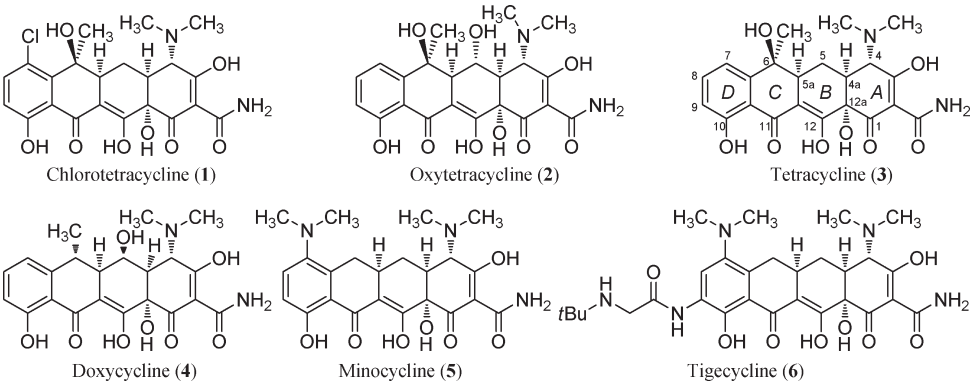

Figure 1. Structures of known tetracyclines.

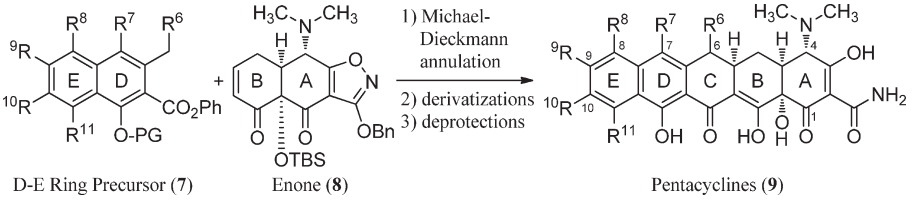

Figure 2. Synthesis of pentacyclines via Michael−Dieckmann annulations.

properties of several new pentacycline analogs in appropriate mouse, rat, and monkey models.

CHEMISTRY

We applied Myers' general synthetic approach[12,17] for the pentacyclines (**9**) as outlined in Figure 2, involving the coupling of various D−E ring precursors (**7**) and enone **8**[16] via Michael−Dieckmann annulations. Several subseries of pentacyclines with systematic modifications at C7−C10 were designed and synthesized according to Schemes 1−10.

Several 10-substituted pentacycline analogs with no substitution at C7 (7-H pentacyclines) or with a dimethylamino group at C7 (7-dimethylamino pentacyclines) were reported recently by Myers et al.[12,17] and showed promising antibacterial activity against both Gram-positive and Gram-negative organisms. In order to study the effect of different substitutions and substitution patterns on the antibacterial activity of the pentacyclines, we expanded the 7,10-disubstituted pentacycline class to include additional C7 substituents (Cl, F, and CH_3O), as well as a wide range of C10 substituents (Scheme 1).

Thus, 6-bromophthalide (**10**) was treated with lithium diisopropylamide (LDA) and methyl crotonate, followed by treatment with boron trifluoride diethyl etherate according to the Broom and Sammes procedures[18] to yield 7-bromonaphthol **11** (22% yield over two steps). Naphthol **11** was methylated with dimethylsulfate to give naphthalene **12**, which was converted to phenyl ester **13** by saponification with aqueous sodium hydroxide, acid chloride formation with oxalyl chloride, and reaction with phenol (86% yield over three steps). The methyl ether of compound **13** was cleaved with BBr_3, and the resulting phenol was protected using di-*tert*-butyl dicarbonate ($(Boc)_2O$), 4-dimethylaminopyridine (DMAP), and diisopropylethylamine (DIEA), affording the D−E ring precursor **14a** (89% yield over two steps). Michael−Dieckmann annulation[12] was carried out by deprotonation of **14a** with LDA in the presence of enone **8** and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) at −78 °C, yielding the desired hexacyclic intermediate **15a** (47% yield). Deprotonation with phenyllithium and lithium−halogen exchange with *n*-butyllithium at −78 °C, followed by reaction with *N*,*N*-dimethylformamide (DMF) converted **15a** to aldehyde **16a** in 84% yield. Reductive amination of aldehyde **16a** with a series of amines using sodium triacetoxyborohydride gave secondary and tertiary amines **17a**. The secondary amine intermediates were also further derivatized by acylation and sulfonylation. Finally, desylilation with aqueous hydrofluoric acid (HF) gave intermediates **18a**, which were subjected to palladium-catalyzed hydrogenation to yield the desired 7-H-10-aminomethyl pentacycline analogs **19a** after reverse-phase HPLC purification in about 45−55% overall yields.

A series of 7-chloro, 7-fluoro, and 7-dimethylamino-10-aminomethyl pentacycline analogs were also prepared starting from naphthalene **13** according to Scheme 1. Thus, to prepare the 7-chloro D−E ring precursor (**14b**) required for the 7-chloro pentacyclines (**19b**), compound **13** was regioselectively chlorinated with *N*-chlorosuccinimide (NCS) to yield phenyl 7-bromo-4-chloro-1-methoxy-3-methylnaphthalene-2-carboxylate, which was demethylated and protected with $(Boc)_2O$ to give D−E ring precursor **14b** (80% yield over three steps). The 7-fluoro D−E ring precursor (**14c**) was prepared as follows. Intermediate **13** was regioselectively iodinated with *N*-iodosuccinimide (NIS) and trifluoroacetic acid (TFA) in refluxing acetonitrile to give phenyl 7-bromo-4-iodo-1-methoxy-3-methylnaphthalene-2-carboxylate. Selective metal−iodine exchange with *n*-butyllithium at −100 °C followed by quenching with *N*-fluorobenzenesulfonimide (NFSI)[19] yielded phenyl 7-bromo-4-fluoro-1-methoxy-3-methylnaphthalene-2-carboxylate (51% yield over two steps), which was converted to D−E ring precursor **14c** by the two-step sequence of demethylation and Boc protection (78% yield over two steps). For the preparation of the 7-dimethylamino D−E ring precursor (**14d**), intermediate **13** was nitrated with a mixture of concentrated nitric acid and sulfuric acid in methylene chloride to yield

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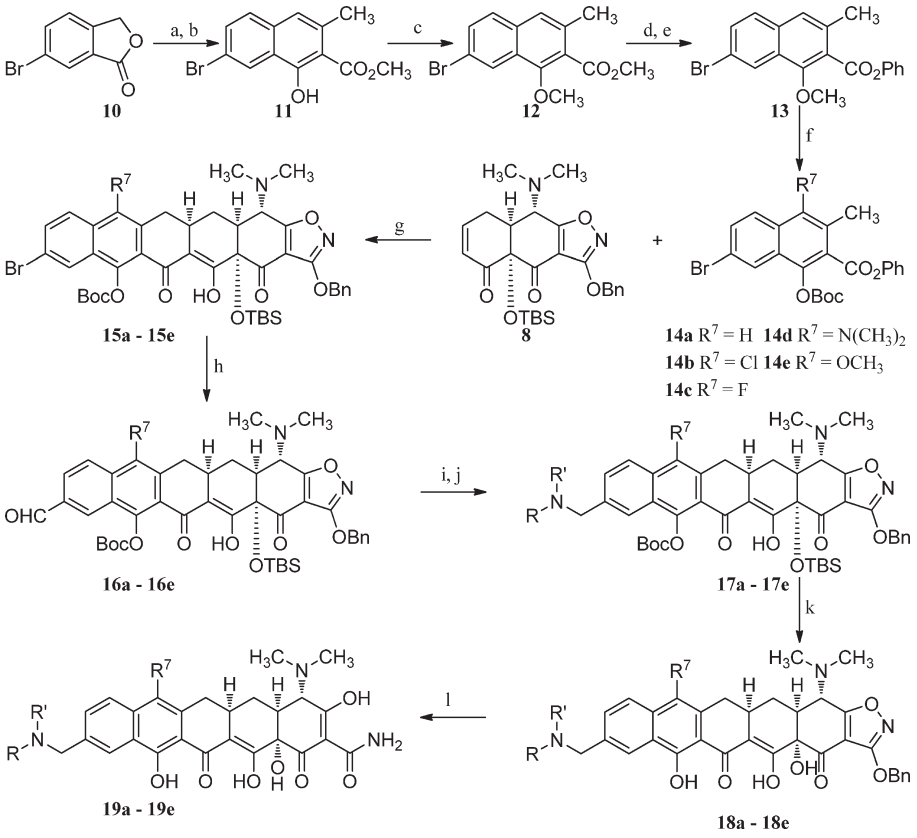
Scheme 1. Synthesis of 7-R-10-Aminomethyl Pentacycline Analogs[a]



[a] Reagents: (a) LDA, then methyl crotonate, THF; (b) BF_3—Et_2O, CH_2Cl_2; (c) $(CH_3)_2SO_4$, Cs_2CO_3, acetone; (d) NaOH, H_2O, EtOH; (e) $(COCl)_2$, DMF, CH_2Cl_2, then PhOH, DMAP, pyridine, CH_2Cl_2; (f) for **14a**, (1) BBr_3, CH_2Cl_2; (2) $(Boc)_2O$, DMAP, DIEA, CH_2Cl_2; for **14b**, (1) NCS, CH_3CN; (2) BBr_3, CH_2Cl_2; (3) $(Boc)_2O$, DMAP, CH_2Cl_2; for **14c**, (1) NIS, TFA, CH_3CN; (2) *n*-BuLi, then NFSI, THF; (3) BBr_3, CH_2Cl_2; (4) $(Boc)_2O$, DMAP, CH_2Cl_2; for **14d**, (1) HNO_3, H_2SO_4, CH_2Cl_2; (2) BBr_3, CH_2Cl_2; (3) Zn dust, HOAc, THF; (4) HCHO, $Na(OAc)_3BH$, CH_3CN, THF; (5) $(Boc)_2O$, DMAP, CH_2Cl_2; for **14e**, starting with phenolic precursor of **14d**, (1) $PhI(OAc)_2$, CH_3OH, 1,4-dioxane, then Zn dust, HOAc; (2) $(Boc)_2O$, DMAP, CH_2Cl_2; (g) enone **8**, TMEDA, LDA, THF; (h) PhLi, *n*-BuLi, then DMF, THF; (i) RR′NH, $Na(OAc)_3BH$, HOAc, 1,2-dichloroethane; (j) acylation or sulfonylation when RNH_2 was used in step i; (k) aq HF, CH_3CN; (l) H_2, Pd—C, CH_3OH.

phenyl 7-bromo-1-methoxy-3-methyl-4-nitronaphthalene-2-carboxylate. The methyl ether was cleaved with BBr_3, and the nitro group was reduced with zinc dust to give phenyl 4-amino-7-bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate. Reductive dimethylation with formaldehyde followed by Boc protection provided D—E ring precursor **14d** in high overall yield. The 7-methoxy D—E ring precursor (**14e**) was prepared as follows. Oxidation of phenyl 4-dimethylamino-7-bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate with $PhI(OAc)_2$ in methanol/1,4-dioxane followed by treatment with zinc dust in acetic acid afforded phenyl 4-methoxy-7-bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate,[20] which was protected with $(Boc)_2O$ to give the desired D—E ring precursor **14e** (80% yield over two steps). Final analogs (7-chloro, 7-fluoro, and 7-dimethylamino-10-aminomethyl pentacyclines, **19b**—**19e**) were then prepared from these D—E ring precursors (**14b**—**14e**) using similar procedures as described for the synthesis of **19a** in moderate to good yields.

To study the effect of different alkylamino groups at C7, a set of 7-alkylamino-10-azetidinomethyl pentacyclines were synthesized according to Scheme 2. Phenyl 7-bromo-1-methoxy-3-methyl-4-nitronaphthalene-2-carboxylate (**20**) was reduced to aniline **21** with zinc dust in 86% yield. Diallylation with excess phenyllithium and allylbromide led to diallylamine **22** (82% yield), which was demethylated with BBr_3 and protected with $(Boc)_2O$ to yield D—E ring precursor **23c** (46% yield over two steps). Additionally, D—E ring precursor **23b** was derived from intermediate **21** by monoallylation with phenyllithium and allylbromide, demethylation with BBr_3, and protection of the hydroxyl and secondary amino groups with $(Boc)_2O$ (39% yield over three steps). Furthermore, intermediate **20** was demethylated with BBr_3 and reduced with Zn dust as described above for the synthesis of analogs **19d**. The resulting hydroxyaniline was then protected as the tri-Boc intermediate by treatment with excess $(Boc)_2O$ in DMF, followed by monodeprotection with dilute TFA in methylene chloride to yield the di-Boc-protected intermediate (34% yield). Methylation of the resulting carbamate by deprotonation with lithium bis(trimethylsilyl)amide (LHMDS) followed by treatment with iodomethane yielded D—E ring precursor **23a** (67% yield over two steps). These three D—E ring precursors (**23a**—**23c**) were then annulated with enone **8** to give the bromo intermediates (**24a**—**24c**) in good yields. Formylation afforded aldehydes **25a**—**25c**, which were reductively aminated with azetidine and deprotected to yield the final products **26a**—**26c** in moderate yields.

Scheme 3 outlines the preparation of a series of 7-alkoxy-10-azetidinomethyl pentacycline analogs. Oxidation[20] of phenyl

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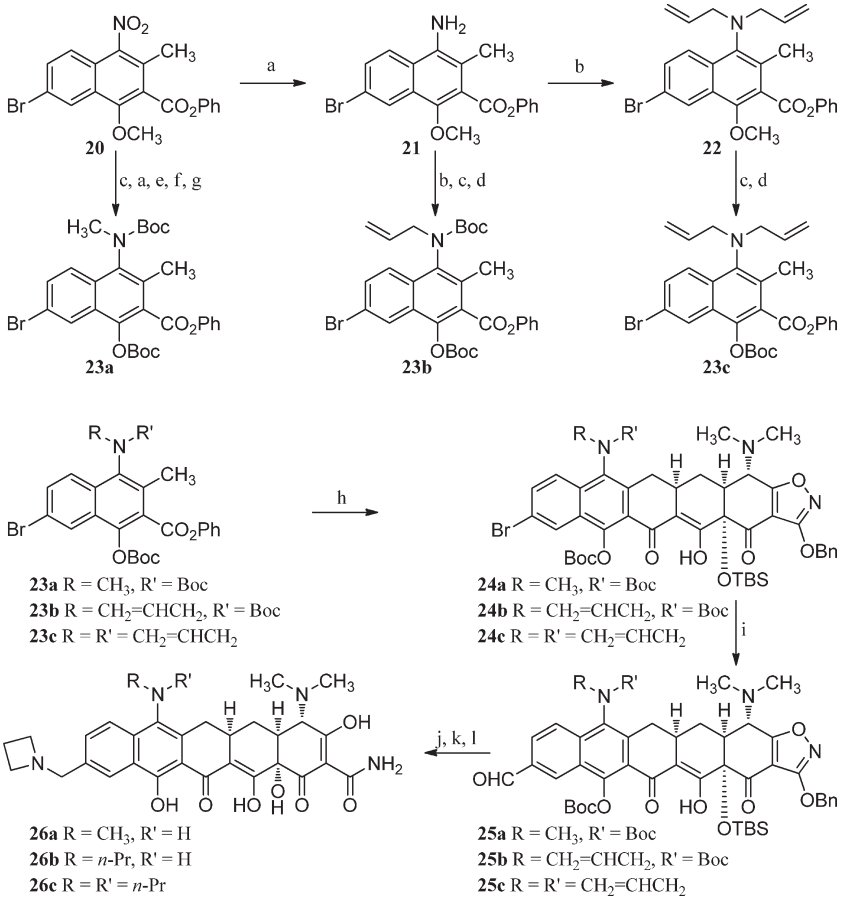
Scheme 2. Synthesis of 7-Alkylamino-10-azetidinomethyl Pentacycline Analogs[a]



[a] Reagents: (a) Zn dust, HOAc, THF; (b) PhLi, then allylbromide, THF; (c) BBr_3, CH_2Cl_2; (d) $(Boc)_2O$, DMAP, DIEA, CH_2Cl_2; (e) $(Boc)_2O$, DMAP, DMF; (f) TFA, CH_2Cl_2; (g) LHMDS, CH_3I, THF; (h) enone **8**, TMEDA, LDA, THF; (i) PhLi, *n*-BuLi, then DMF, THF; (j) azetidine, $Na(OAc)_3BH$, HOAc, 1,2-dichloroethane; (k) aq HF, acetonitrile; (l) H_2, Pd−C, CH_3OH.

4-dimethylamino-7-bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate (**27**) with $PhI(OAc)_2$ in the presence of allyl alcohol followed by treatment with zinc dust in acetic acid afforded the corresponding 4-allyloxy naphthol, which was protected with $(Boc)_2O$ under standard conditions to yield the desired D−E ring precursor **28** (80% yield over two steps). Michael−Dieckmann annulation with enone **8** gave intermediate **29** (47% yield). Formylation and reductive amination with azetidine yielded the allyl-protected intermediate **30** in good yields. Deallylation with $Pd(PPh_3)_4$ and *N*,*N*-dimethylbarbituric acid gave the naphthol intermediate **32** (86% yield). Compound **32** was reacted with isocyanates followed by deprotections to give carbamate analogs **33** in moderate overall yields. Intermediate **32** was also alkylated with a series of alcohols under Mitsunobu[21] conditions (PPh_3, diisopropyl azodicarboxylate (DIAD)) to yield the 7-alkoxy intermediates **34**. Desilylation with aqueous HF, enol ether cleavage with HCl, and hydrogenation gave the desired 7-alkoxy-10-azetidinomethyl pentacycline analogs **35** (25% yield over four steps). Intermediate **30** was also deprotected to give analog **31**.

Intermediate **30** was also treated with OsO_4 and *N*-methylmorpholine-*N*-oxide (NMO) to give the 1,2-diol **36** (Scheme 4). Oxidative cleavage of **36** with $NaIO_4$ yielded aldehyde **37**. Reductive amination followed by deprotection gave the desired 7-aminoexthoxy-10-azetidinomethyl pentacycline analogs **40** in moderate overall yields. Intermediate **36** was also deprotected to yield analog **38** (28% yield over three steps).

The effect of substitutions at C8 was probed with a set of 8-amino, 8-methoxy, and 8-aminomethyl pentacycline analogs prepared according to Schemes 5, 6, and 7. Thus, 4-bromophthalide **41** (Scheme 5) was converted to 5-bromonaphthol **42** under similar conditions to those used for the preparation of 7-bromonaphthol **11** in 27% overall yield. Naphthol **42** was benzylated with benzyl bromide and potassium carbonate to give compound **43** (77% yield), which was transformed to the corresponding phenyl ester **44** by hydrolysis and ester formation under standard conditions (73% over two steps). Buchwald amination[22] of **44** with $BocNH_2$ (74% yield), debenzylation by hydrogenation, and reprotection with $(Boc)_2O$ afforded the tri-Boc-protected intermediate **45** (49% yield over two steps). Benzylic bromination under radical conditions using NBS and dibenzoyl peroxide (BPO) gave the desired D−E ring precursor **46** in 81% yield. Lithium−halogen exchange of benzyl bromide **46** in the presence of enone **8** at −100 °C in THF gave the desired cyclized product **47** in 53% yield. Aqueous HF treatment of **47** followed by hydrogenation in the presence or absence of aldehydes yielded the desired 8-amino pentacycline analogs **49** (29% yield over two steps).

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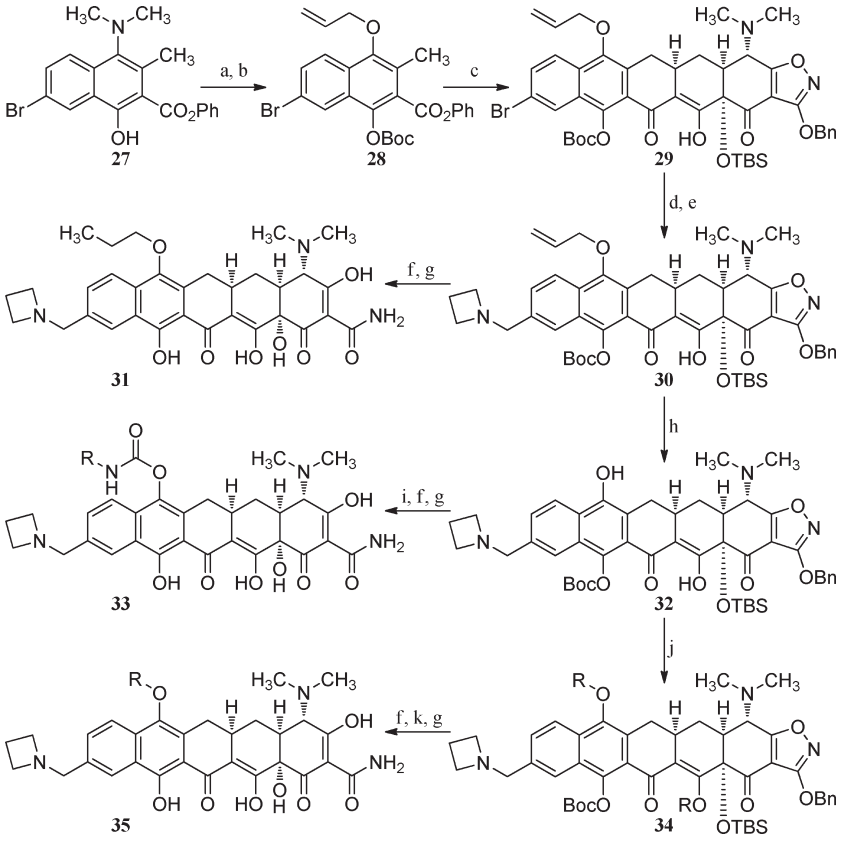
Scheme 3. Synthesis of 7-Alkoxy-10-azetidinomethyl Pentacycline Analogs[a]



[a] Reagents: (a) $PhI(OAc)_2$, allyl alcohol, 1,4-dioxane, then Zn dust, HOAc; (b) $(Boc)_2O$, DMAP, DIEA, CH_2Cl_2; (c) enone **8**, TMEDA, LDA, THF; (d) PhLi, *n*-BuLi, then DMF, THF; (e) azetidine, $Na(OAc)_3BH$, HOAc, 1,2-dichloroethane; (f) aq HF, CH_3CN; (g) H_2, Pd−C, CH_3OH; (h) $Pd(PPh_3)_4$, *N*,*N*-dimethylbarbituric acid, CH_2Cl_2; (i) RNCO, 2,6-lutidine, CH_2Cl_2; (j) ROH, PPh_3, DIAD, THF; (k) HCl, CH_3OH.

An 8-methoxy-pentacycline analog was synthesized according to Scheme 6. Bromonaphthalene **44** was treated with bis-(pinacolato)diboron, potassium acetate, and $PdCl_2(dppf)-CH_2Cl_2$ in hot 1,4-dioxane, followed by oxidation with H_2O_2 to yield the corresponding naphthol (67% yield),[23] which was methylated to give compound **50** (74% yield). Debenzylation by hydrogenation and protection with $(Boc)_2O$ gave intermediate **51** (90% yield over two steps), which was brominated with NBS and 2,2′-azobis(2-methylpropionitrile) (AIBN) to afford the desired D−E ring precursor **52** (82% yield). Lithium−halogen exchange with *n*-butyllithium in the presence of enone **8** at −100 °C in THF yielded the desired cyclized product **53** (61% yield), which was deprotected to give the desired 8-methoxy analog **54** (16% yield over two steps).

For the 8-aminomethyl pentacycline analogs (Scheme 7), naphthol **42** was methylated with dimethylsulfate and cesium carbonate to give compound **55**, which was converted to the desired D−E ring precursor **57** through hydrolysis, phenyl ester formation, demethylation, and Boc protection under conditions described previously (76% overall yield). Michael−Dieckmann annulation of **57** with enone **8** yielded bromo intermediate **58**, which was subjected to formylation, reductive amination, desilylation, and hydrogenation to yield the desired 8-aminomethyl pentacycline analogs **61** in moderate yields.

To probe the effect of substitutions at C9, a set of 9-amino-pentacycline analogs were prepared according to Scheme 8. 5-Bromonaphthalide (**62**) was converted to 6-bromonaphthol **63** in 20% yield over two steps. Benzylation, hydrolysis, and phenyl ester formation yielded intermediate **64** (46% yield over three steps). Buchwald amination with $BocNH_2$ gave compound **65** (64% yield), which was debenzylated by hydrogenation and reprotected with $(Boc)_2O$ to yield compound **66** (90% over two steps). Radical bromination of **66** using NBS and BPO afforded the desired D−E ring precursor **67** (74% yield). Lithium−halogen exchange of benzyl bromide **67** with *n*-butyllithium in the presence of enone **8** at −100 °C in THF gave the cyclized compound **68** (20% yield). Aqueous HF treatment, followed by hydrogenation in the presence or absence of aldehydes yielded the desired 9-amino pentacycline analogs **69** (34−36% yield).

The effect of C10 substitutions was explored with a set of 10-fluoro pentacycline analogs prepared according to Scheme 9. Bromonaphthalene **14d** was treated with *n*-butyllithium followed by NFSI to afford D−E ring precursor **70** (60% yield), which was cyclized with enone **8** to give compound **71d** in low yield (9%). Bromo intermediates **15a**, **15b**, and **15e** were also converted to the corresponding fluoro intermediates **71a**, **71b**, and **71c** in moderate yields under similar conditions. Desilylation and hydrogenation of **71a**−**71d** yielded the desired 10-fluoro pentacycline analogs **72a**−**72d** in 60−70% yields over two steps.

Scheme 10 outlines the synthesis of a series of 10-aryl pentacyclines. Suzuki coupling of bromo intermediate **15a** with aryl boronic acids afforded intermediates **73** in good yields.

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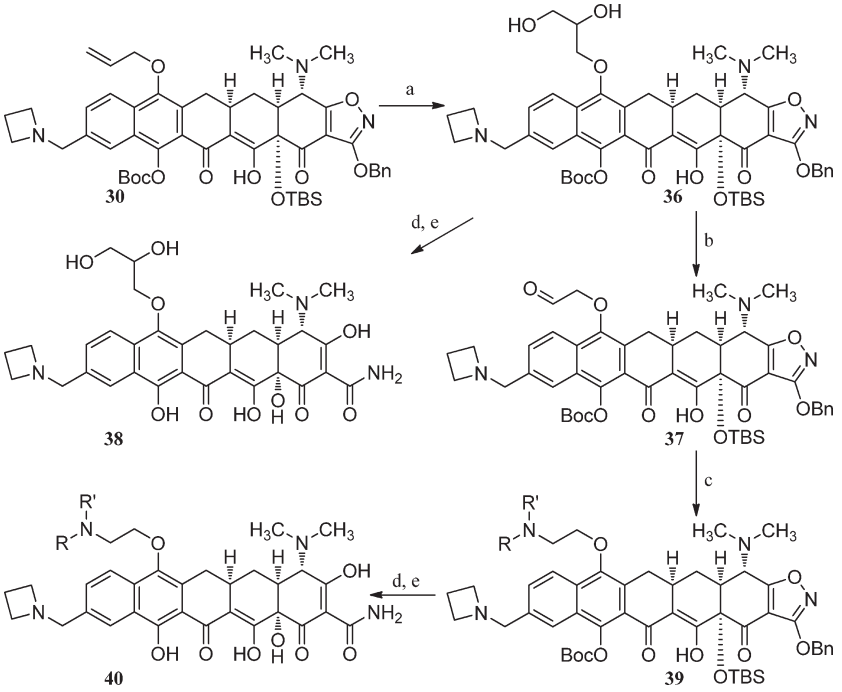
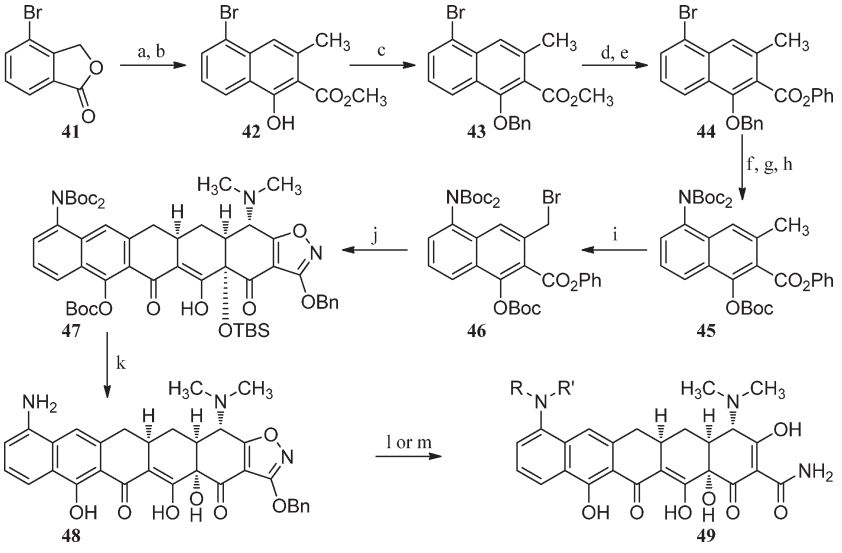
Scheme 4. Synthesis of 7-(2-Aminoethoxy)-10-azetidinomethyl Pentacycline Analogs[a]



[a] Reagents: (a) OsO_4, NMO, H_2O, THF; (b) $NaIO_4$, H_2O, THF; (c) RR′NH, $Na(OAc)_3BH$, HOAc, 1,2-dichloroethane; (d) aq HF, CH_3CN; (e) H_2, Pd−C, CH_3OH.

Scheme 5. Synthesis of 8-Amino Pentacycline Analogs[a]



[a] Reagents: (a) LDA, HMPA, then methyl crotonate, THF; (b) BF_3−Et_2O, CH_2Cl_2; (c) BnBr, K_2CO_3, acetone; (d) NaOH, H_2O, EtOH; (e) $(COCl)_2$, DMF, CH_2Cl_2, then PhOH, DMAP, pyridine, CH_2Cl_2; (f) $BocNH_2$, $Pd_2(dba)_3$, P(*t*-Bu)$_3$, NaOPh, toluene; (g) H_2, Pd−C, CH_3OH; (h) $(Boc)_2O$, DMAP, CH_2Cl_2; (i) NBS, BPO, CCl_4; (j) enone **8**, *n*-BuLi, THF; (k) aq HF, THF; (l) H_2, Pd−C, HCl, CH_3OH; (m) aldehyde, H_2, Pd−C, HCl, CH_3OH.

These were deprotected as described above to yield the desired 10-aryl pentacycline analogs **75** in moderate yields.

RESULTS AND DISCUSSION

The synthesized pentacycline analogs were evaluated for antibacterial activity using a panel of tetracycline-sensitive and tetracycline-resistant Gram-positive and Gram-negative bacteria strains, and their minimum inhibitory concentrations (MICs) are shown in Tables 1−4.

Table 1 shows the MIC data for analogs with the C10 substituent fixed as an azetidinomethyl group in combination with various C7 substituents (7-substituted-10-azetidinomethyl

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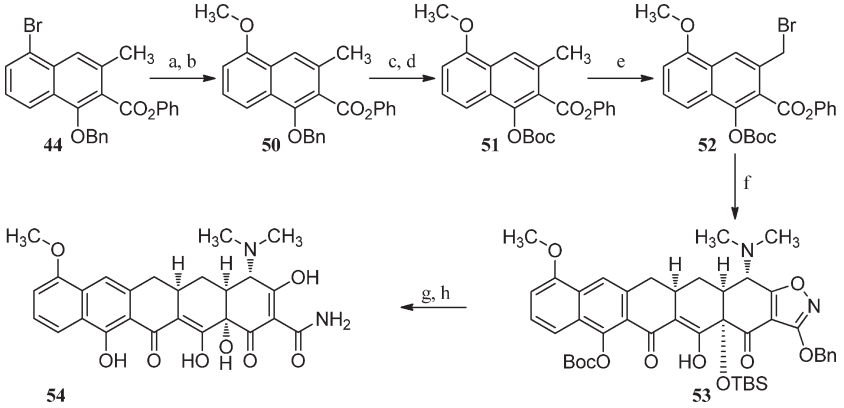
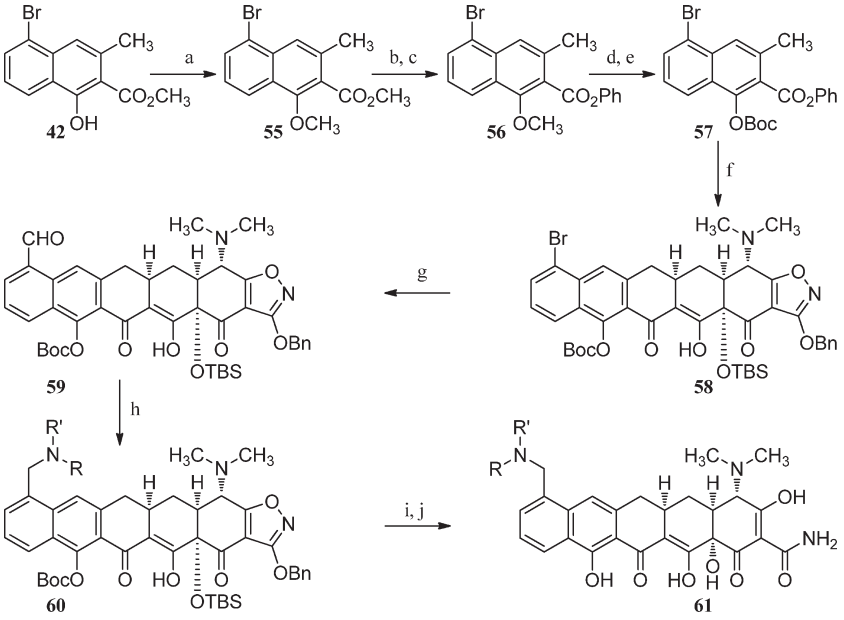
Scheme 6. Synthesis of an 8-Methoxy Pentacycline Analog[a]



[a] Reagents: (a) bis(pinacolato)diboron, KOAc, $PdCl_2(dppf)-CH_2Cl_2$, 1,4-dioxane, then H_2O_2, HOAc, THF; (b) CH_3I, K_2CO_3, acetone; (c) H_2, Pd−C, CH_3OH; (d) $(Boc)_2O$, DMAP, CH_2Cl_2; (e) NBS, AIBN, CCl_4; (f) enone **8**, *n*-BuLi, THF; (g) aq HF, CH_3CN; (h) H_2, Pd−C, HCl, CH_3OH.

Scheme 7. Synthesis of 8-Aminomethyl Pentacycline Analogs[a]



[a] Reagents: (a) $(CH_3)_2SO_4$, Cs_2CO_3, acetone; (b) NaOH, H_2O, EtOH; (c) $(COCl)_2$, DMF, CH_2Cl_2, then PhOH, DMAP, pyridine, CH_2Cl_2; (d) BBr_3, CH_2Cl_2; (e) $(Boc)_2O$, DMAP, DIEA, CH_2Cl_2; (f) enone **8**, TMEDA, LDA, THF; (g) PhLi, *n*-BuLi, then DMF, THF; (h) RR′NH, $Na(OAc)_3BH$, HOAc, 1,2-dichloroethane; (i) aq HF, CH_3CN; (j) H_2, Pd−C, CH_3OH.

pentacyclines). While the 7-Cl analog (**19b-1**) was slightly less potent than the parent compound (**19a-9**) and the 7-F analog (**19c-5**) was equipotent to **19a-9**, the 7-CH_3O and 7-$(CH_3)_2N$ analogs (**19e-6** and **26d**) were more potent than the parent against most Gram-positive strains, with the 7-CH_3O analog (**19e-6**) being the most potent compound in the series. Higher alkoxy groups at C7 (**31** and **35a**) did not improve potency, while alkoxy groups containing additional polar or basic groups (**35b**, **38**, **40a**, and **33a**) greatly reduced potency against most strains in the panel. Among the 7-amino pentacyclines (**26a**−**26d**), the 7-$(CH_3)_2N$ analog (**26d**) was the most potent overall. It is clear that tertiary amines (**26c** and **26d**) at C7 are preferred over secondary amines (**26a** and **26b**). Potency against Gram-negative strains decreases with increasing alkyl group size among the 7-alkoxy and 7-alkylamino analogs. The 7-alkoxy analogs appear to have better activity against Gram-negative organisms. It is important to note that several analogs, especially the 7-CH_3O analog (**19e-6**), displayed good potency against all Gram-positive resistant strains (*tet*K and *tet*M) in the panel (MIC = 0.0625−2 μg/mL) and their *tet*M activity is usually better than that of minocycline. However, these analogs are not as potent as tigecycline against most strains in the panel.

Table 2 outlines the antibacterial activity of analogs in which the C10 substitution was varied while keeping C7 constant as H. Among the 10-aryl analogs, compounds **75a** and **75b** (10-phenyl and 10-(3-pyridinyl)) had similar activity to the unsubstituted parent compound (**19a-1**) against most strains except *S. pneumoniae*, while the *p*-dimethylaminophenyl analog (**75c**) had almost no

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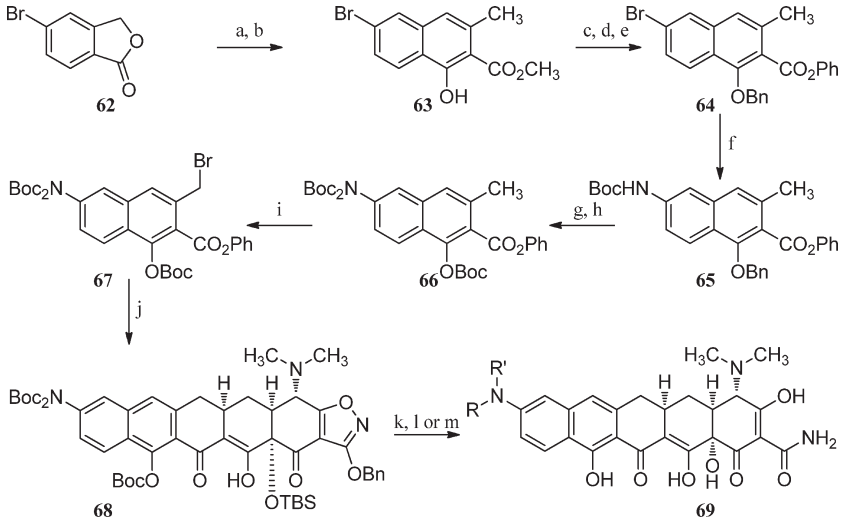
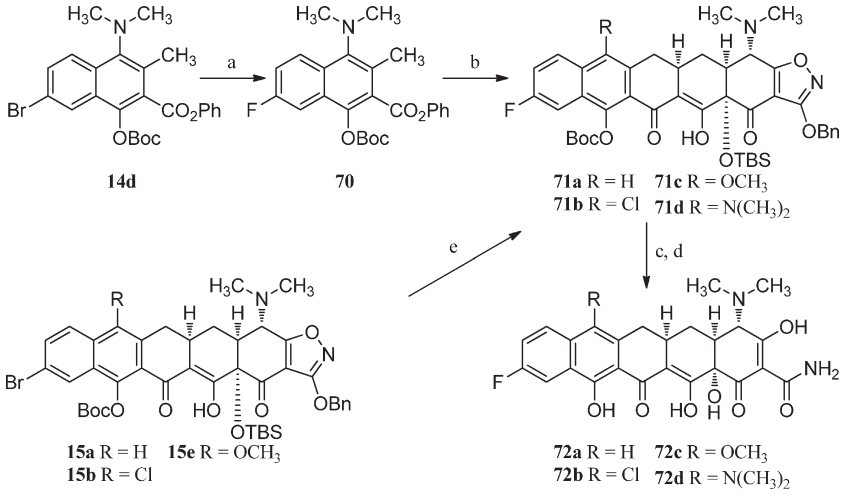
Scheme 8. Synthesis of 9-Amino Pentacycline Analogs[a]



[a] Reagents: (a) LDA, then methyl crotonate, THF; (b) BF_3—Et_2O, CH_2Cl_2; (c) BnBr, K_2CO_3, acetone; (d) NaOH, H_2O, EtOH; (e) $(COCl)_2$, DMF, CH_2Cl_2, then PhOH, DMAP, pyridine, CH_2Cl_2; (f) $BocNH_2$, $Pd_2(dba)_3$, P(*t*-Bu)$_3$, Cs_2CO_3, toluene; (g) H_2, Pd—C, EtOAc, CH_3OH; (h) $(Boc)_2O$, DMAP, CH_2Cl_2; (i) NBS, BPO, CCl_4; (j) enone **8**, *n*-BuLi, THF; (k) aq HF, CH_3CN; (l) H_2, Pd—C, HCl, CH_3OH; (m) aldehyde, H_2, Pd—C, HCl, CH_3OH.

Scheme 9. Synthesis of 10-Fluoro Pentacycline Analogs[a]



[a] Reagents: (a) *n*-BuLi, then NFSI, THF; (b) enone **8**, TMEDA, LDA, THF; (c) aq HF, CH_3CN; (d) H_2, Pd—C, CH_3OH; (e) PhLi, *n*-BuLi, then NFSI, THF.

activity across the board. On the other hand, the various 10-aminomethyl analogs, especially the 10-$(CH_3)_2NCH_2$ analog (**19a-6**), displayed good antibacterial activity, particularly against the Gram-positive strains. Aromatic aminomethyl substituents (**19a-8**), as well as nonbasic aminomethyl groups at C10 (**19a-19**), lead to decreased potency. It is clear that small basic alkylamines (C1—C6) are preferred at the C10 benzylic position for improved activity against both Gram-positive and Gram-negative organisms. Introduction of additional polar or basic groups decreased activity in general (**19a-12** to **19a-16**). It is interesting that while the 3-F-azetidinomethyl analog (**19a-17**) had similar activity to the parent compound (**19a-1**) against Gram-positive strains and better activity against Gram-negative strains, the 3,3-di-F-azetidinomethyl analog (**19a-18**) had almost no activity against Gram-negative strains. It is likely that the azetidine nitrogen is only weakly basic due to the *gem*,*gem*-difluoro substitutions.

Table 3 shows the antibacterial activity of analogs with various combinations of C7 and C10 substituents. All 10-aminomethyl pentacycline analogs bearing a F, Cl, CH_3O, or $(CH_3)_2N$ group at C7 had good potency in general, especially against Gram-positive bacteria. While the 7-CH_3O-10-azetidinomethyl analog (**19e-6**) was the most active analog and the 7-Cl analog (**19b-1**) had the least activity among this 10-aminomethyl pentacycline series, the variation at C7 from F to Cl, CH_3O, and $(CH_3)_2N$ did not drastically alter the analogs' potency. As for the C10 substituents, the analogs were able to maintain good potency as

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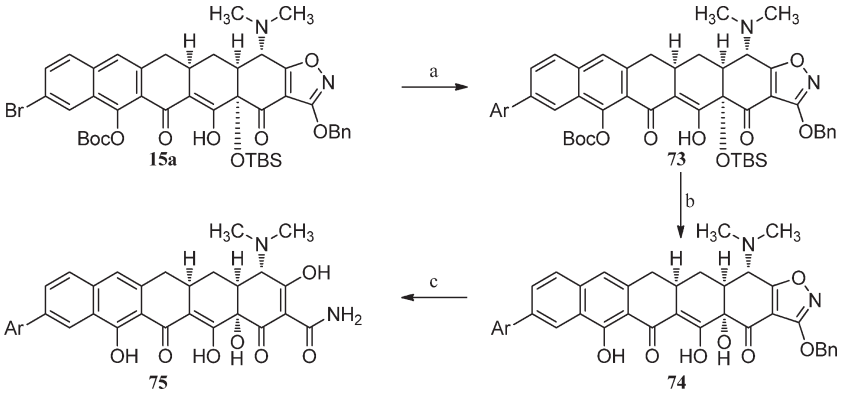
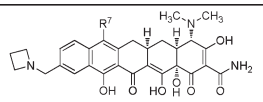
Scheme 10. Synthesis of 10-Aryl Pentacycline Analogs[a]



[a] Reagents: (a) $ArB(OH)_2$, $PdCl_2(dppf)-CH_2Cl_2$, Na_2CO_3, H_2O, toluene; (b) aq HF, CH_3CN; (c) H_2, Pd−C, CH_3OH.

Table 1. *In Vitro* Antibacterial Activity of 7-Substituted-10-Azetidinomethyl Pentacyclines



		MIC (μg/mL)[a]													
		SA101	SA161[b]	SA158[c]	EF103	EF159[c]	SP106	SP160[c]	EC107	EC155[c]	AB110	PA111	ECl108	KP109	KP153[c]
Compound	**R^7**	29213	MRSA, *tet* M	*tet* K	29212	*tet* M	49619	*tet* M	25922	*tet* A	19606	27853	13047	13883	*tet* A
19a-9[d]	H	0.5	2	0.5	0.5	4	0.125	0.25	1	8	1	32	2	4	8
19c-5	F	0.25	1	0.25	0.25	2	0.0625	0.125	1	4	0.5	32	2	2	4
19b-1	Cl	1	2	1	0.25	2	0.25	0.5	2	16	2	>32	8	4	8
19e-6	CH_3O	0.0625	0.5	0.0625	0.0625	1	0.0156	0.0625	0.25	8	1	32	1	1	8
31	$CH_3(CH_2)_2O$	0.125	2	0.25	0.25	2	0.0156	0.0625	2	16	1	32	16	8	32
35a	$(CH_3)_2CHO$	0.125	4	0.25	0.5	4	0.0313	0.0625	4	16	2	>32	16	16	32
35b	$CH_3O(CH_2)_2O$	0.25	2	0.5	0.5	2	0.0313	0.25	2	32	4	>32	8	8	>32
38	$HOCH_2CH(OH)CH_2O$	>32	>32	>32	32	>32	4	16	>32	>32	>32	>32	>32	>32	>32
40a	$(CH_3)_2N(CH_2)_2O$	4	8	4	8	16	1	2	8	>32	>32	>32	16	32	>32
33a	$CH_3NHC(O)O$	8	32	32	8	32	1	4	32	>32	>32	>32	>32	>32	>32
26a	CH_3NH	2	8	2	4	8	0.25	1	4	>32	>32	>32	32	32	>32
26d[d]	$(CH_3)_2N$	1	2	0.0625	0.125	2	≤0.0156	0.125	2	8	1	32	8	4	16
26b	$CH_3(CH_2)_2NH$	4	ND	4	4	16	0.5	2	16	>32	16	>32	>32	32	>32
26c	$[CH_3(CH_2)_2]_2N$	0.5	ND	0.5	0.5	4	0.125	0.5	32	>32	8	>32	>32	>32	>32
minocycline		0.0625	8	0.0313	1	16	≤0.0156	2	0.5	8	0.0625	16	2	1	8
tigecycline		0.0625	0.125	0.0625	0.0313	0.0625	0.0156	0.0156	0.0313	0.5	0.25	8	0.25	0.125	1

[a] Strains were obtained from the American Type Culture Collection (ATCC, Manassas, VA) unless otherwise noted. The first seven strains from the left are Gram-positive strains. The last seven strains are Gram-negative strains. Strains with "*tet*A", "*tet*K", or "*tet*M" noted underneath are tetracycline-resistant strains. SA, *Staphylococcus aureus*; EF, *Enterococcus faecalis*; SP, *Streptococcus pneumoniae*; EC, *Escherichia coli*; AB, *Acinetobacter baumannii*; PA, *Pseudomonas aeruginosa*; ECl, *Enterobacter cloacae*; KP, *Klebsiella pneumoniae*. [b] Obtained from Micromyx (Kalamazoo, MI). [c] Obtained from Marilyn Roberts' laboratory at the University of Washington. [d] See ref 17.

long as a small alkylaminomethyl group (C1−C6) is present, as also indicated by data in Table 2. Heterosubstitutions on this C10 moiety decrease overall activity as shown by analog **19d-2**. While the 10-fluoro analogs (**72a**−**72d**) maintained potency against most Gram-positive strains, they are much less active than the corresponding 10-aminomethyl analogs against the two *S. pneumoniae* strains and all the Gram-negative strains. Although the 7-CH_3O-10-azetidinylmethyl analog (**19e-6**) had comparable activity to tigecycline against most Gram-positive strains (except EF159), most other analogs were less potent in general, especially against Gram-negative organisms.

The antibacterial activity of the 8-aminomethyl, 8-amino, 8-CH_3O, and 9-amino pentacycline analogs is shown in Table 4. Most had similar or decreased activity relative to the parent compound (**19a-1**). Analogs with an 8-aminomethyl group (**61a**−**61c**) had decreased activity against the *tet*M strains (SA161, EF159, and SP160) but maintained activity against the *tet*K strain (SA158). While analogs with an amino group at C8 or C9 (**49a**−**49c**, **69a**, **69b**) had decreased potency overall, the 8-methoxy analog (**54**) maintained activity against the *S. aureus* and *E. faecalis* strains but had significantly decreased activity against the *S. pneumoniae* strains. As data in previous tables has shown, a proper combination of substitutions at the C7 and C10 positions, particularly a methoxy group at C7 and a small aminomethyl group at C10, is preferred for increased overall potency. Since analogs in Table 4 do not have any

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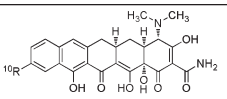
Table 2. *In Vitro* Antibacterial Activity of 7-H-10-Substituted Pentacyclines



		MIC (μg/mL)[a]													
		SA101	SA161[b]	SA158[c]	EF103	EF159[c]	SP106	SP160[c]	EC107	EC155[c]	AB110	PA111	ECl108	KP109	KP153[c]
Compound	**R^{10}**	29213	MRSA,tetM	tetK	29212	tetM	49619	tetM	25922	tetA	19606	27853	13047	13883	tetA
19a-1[d]	H	1	1	0.5	0.5	0.5	0.25	0.25	>32	>32	8	>32	ND	ND	ND
75a	Ph	2	8	4	2	0.5	>32	>32	>32	>32	>32	>32	>32	>32	>32
75b	3-pyridinyl	1	1	0.5	0.5	0.25	>32	>32	>32	>32	>32	>32	>32	>32	>32
75c	4-$(CH_3)_2$N-Ph	>32	>32	16	>32	16	>32	>32	>32	>32	>32	>32	>32	>32	>32
19a-2	CH_3NHCH_2	0.5	4	1	0.5	4	0.0625	1	1	16	4	16	2	4	8
19a-3	$CH_3(CH_2)_2NHCH_2$	0.5	2	0.25	0.5	4	0.0156	0.25	1	4	1	32	2	2	4
19a-4	$(CH_3)_2CHCH_2NHCH_2$	0.25	4	0.25	0.5	4	0.0156	0.25	1	4	0.5	32	2	4	4
19a-5	$CH_3O(CH_2)_2NHCH_2$	0.25	4	0.5	0.5	8	0.0156	0.5	1	8	1	32	2	4	8
19a-6	$(CH_3)_2NCH_2$	0.25	1	0.25	0.25	1	0.0313	0.125	1	4	2	>32	2	2	4
19a-7	$CH_3CH_2N(CH_3)CH_2$	0.25	2	0.5	0.5	4	0.125	0.25	2	16	2	>32	4	8	32
19a-8	$PhN(CH_3)CH_2$	1	8	1	4	4	2	2	>32	>32	>32	>32	>32	>32	>32
19a-9	azetidinomethyl	0.5	2	0.5	0.5	4	0.125	0.25	1	8	1	32	2	4	8
19a-10	pyrrolidinomethyl	0.5	2	0.25	0.25	2	0.0625	0.125	1	4	1	>32	4	4	4
19a-11	piperidinomethyl	0.5	2	0.5	0.5	2	0.125	0.25	2	8	1	>32	8	8	8
19a-12	3-hdyroxy-azetidinomethyl	0.5	4	1	0.5	4	0.0625	0.5	1	8	4	32	2	4	8
19a-13	3-CH_3O-azetidinomethyl	1	4	0.5	1	8	0.0625	0.5	2	16	2	>32	8	4	16
19a-14	3-$(CH_3)_2$N-azetidinomethyl	2	8	1	1	8	0.0625	1	4	16	4	>32	8	8	8
19a-15	3-AcNH-azetidinomethyl	2	8	2	2	16	0.25	2	4	16	16	>32	8	16	16
19a-16	3-CN-azetidinomethyl	1	2	1	1	4	0.25	1	4	>32	8	>32	8	8	32
19a-17	3-F-azetidinomethyl	0.5	2	0.5	0.5	2	0.125	0.25	2	8	1	>32	8	8	16
19a-18	3,3-di-F-azetidinomethyl	1	1	1	1	1	2	4	>32	>32	>32	>32	>32	>32	>32
19a-19	$CH_3SO_2N(CH_3)CH_2$	2	2	2	2	2	1	4	>32	>32	>32	>32	>32	>32	>32
minocycline		0.0625	8	0.0313	1	16	≤0.0156	2	0.5	8	0.0625	16	2	1	8
tigecycline		0.0625	0.125	0.0625	0.0313	0.0625	0.0156	0.0156	0.0313	0.5	0.25	8	0.25	0.125	1

[a] Strains were obtained from the American Type Culture Collection (ATCC, Manassas, VA) unless otherwise noted. The first seven strains from the left are Gram-positive strains. The last seven strains are Gram-negative strains. Strains with "*tet*A", "*tet*K", or "*tet*M" noted underneath are tetracycline-resistant strains. SA, *Staphylococcus aureus*; EF, *Enterococcus faecalis*; SP, *Streptococcus pneumoniae*; EC, *Escherichia coli*; AB, *Acinetobacter baumannii*; PA, *Pseudomonas aeruginosa*; ECl, *Enterobacter cloacae*; KP, *Klebsiella pneumoniae*. [b] Obtained from Micromyx (Kalamazoo, MI). [c] Obtained from Marilyn Roberts' laboratory at the University of Washington. [d] See ref 17.

substitution at C10, it is possible that additional substitution at C10 would result in analogs with increased activity.

Pharmacokinetic (PK) measurements in Sprague−Dawley rats and *in vivo* efficacy studies in a mouse septicemia model were performed on a selected set of pentacycline analogs (Table 5). The 7-H analogs appear to have lower clearances and higher AUC's than the 7-CH_3O and 7-F analogs. While compounds **19a-17** and **19c-5** are closely related analogs, differing only in the position of the fluorine atom, their V_z and other PK parameters are quite different. Due to the extremely poor exposure of **19c-5**, its exceptionally large V_z probably has little meaning. In terms of oral bioavailability, three out of the four analogs with oral bioavailability (%F) of greater than 10% are compounds with fluorine either at C7 or on the C10 side chain (**19a-17**, **19c-6**, and **19e-7**), with both **19a-17** and **19e-7** having oral bioavailability of about 18%. Compound **19a-17** also showed similar oral bioavailability in cynomolgus monkeys. A number of analogs displayed very good *in vivo* efficacy in the mouse septicemia model with PD_{50} values ranging from less than 0.3 to 0.62 mg/kg when dosed intravenously, while both tetracycline and tigecycline had a similar PD_{50} of 0.35 mg/kg in the same model. Compound **19a-17** was also dosed orally in the septicemia model and showed a PD_{50} of 12.2 mg/kg. As a comparison, tetracycline had an oral bioavailability of 12% and an oral PD_{50} of 8.1 mg/kg in these models, while tigecycline had almost no oral bioavailability in the rats.

CONCLUSIONS

Employing a highly efficient total synthesis approach, we have prepared diverse and novel pentacycline analogs with systematic variations at C7, C8, C9, and C10. The *in vitro* and *in vivo* antibacterial activities of these pentacycline analogs were evaluated, and their structure−activity relationships (SAR) were analyzed. All pentacycline analogs retain a varying degree of activity against most strains used in the screening panel, especially Gram-positive organisms. This provides additional evidence that the "northwest" portion of the molecule is not directly involved in binding with the ribosome. It is observed that certain combinations of substitutions at both C7 and C10 can enhance the pentacyclines' overall potency. For example, analogs with a methoxy group at C7 and a small basic alkylaminomethyl group at C10 are the most potent pentacyclines against both susceptible and resistant Gram-positive organisms, while nonbasic substituents at C10 generally do not improve potency. These observations should prove to be valuable for further SAR studies of pentacyclines and other tetracycline classes. Although all pentacycline analogs prepared so far are less potent *in vitro* than tigecycline, a number of analogs showed *in vivo* efficacy comparable to tigecycline when dosed intravenously in a mouse septicemia model. Several analogs had promising oral bioavailability in rats and cynomolgus monkeys, while tigecycline had almost no oral bioavailability in rats. Moreover, compound **19a-17**, a

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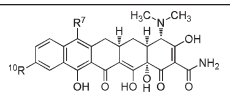
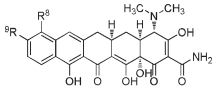
Table 3. *In Vitro* Antibacterial Activity of 7,10-Disubstituted Pentacyclines



			MIC (μg/mL)[a]													
			SA101	SA161[b]	SA158[c]	EF103	EF159[c]	SP106	SP160[c]	EC107	EC155[c]	AB110	PA111	ECl108	KP109	KP153[c]
Compound	**^{7}R**	**^{10}R**	29213	MRSA, tetM	tetK	29212	tetM	49619	tetM	25922	tetA	19606	27853	13047	13883	tetA
19c-1	F	$CH_3CH_2NHCH_2$	0.5	2	0.25	0.25	2	0.0313	0.25	1	8	1	16	2	4	8
19c-2	F	cyclopropyl-$NHCH_2$	0.5	2	0.25	0.5	2	0.0625	0.5	2	8	0.25	>32	4	4	8
19c-3	F	$(CH_3)_3CNHCH_2$	0.5	1	0.0156	0.0313	1	0.0156	0.0313	2	4	0.25	16	2	2	4
19c-4	F	$(CH_3)_2NCH_2$	0.5	1	0.25	0.25	1	0.0156	8	1	4	0.5	32	4	2	4
19c-5	F	azetidinomethyl	0.25	1	0.25	0.25	2	0.0625	0.125	1	4	0.5	32	2	2	4
19c-6	F	3-F-azetidinomethyl	0.5	1	0.25	0.25	1	0.25	0.5	4	8	1	>32	8	4	8
19c-7	F	pyrrolidinomethyl	0.25	1	0.125	0.125	1	0.0313	0.0313	1	4	0.25	32	4	2	4
19b-1	Cl	azetidinomethyl	1	2	1	0.25	2	0.25	0.5	2	16	2	>32	8	4	8
19e-1	CH_3O	$CH_3(CH_2)_2NHCH_2$	0.25	2	0.0625	0.125	2	0.0156	0.125	1	8	1	16	1	1	8
19e-2	CH_3O	cyclopropyl-$NHCH_2$	0.0625	2	0.0313	0.0625	2	0.0156	0.125	0.5	8	0.25	16	4	2	8
19e-3	CH_3O	$(CH_3)_2CHCH_2NHCH_2$	0.25	2	0.016	0.0625	2	0.0156	0.125	1	4	0.25	16	2	1	8
19e-4	CH_3O	$(CH_3)_3CNHCH_2$	0.25	2	0.25	0.25	2	0.0156	0.5	1	8	2	16	2	2	8
19e-5	CH_3O	$(CH_3)_2NCH_2$	0.25	2	0.25	0.25	4	0.0156	0.25	1	8	1	32	4	4	8
19e-6	CH_3O	azetidinomethyl	0.0625	0.5	0.0625	0.0625	1	0.0156	0.0625	0.25	8	1	32	1	1	8
19e-7	CH_3O	3-F-azetidinomethyl	0.25	1	0.125	0.125	2	0.0156	0.0313	2	8	0.25	32	8	4	8
19e-8	CH_3O	pyrrolidinomethyl	0.25	2	0.125	0.25	4	0.0156	0.25	1	8	1	16	4	4	8
19d-1	$(CH_3)_2N$	CH_3NHCH_2	0.25	2	0.5	0.5	4	0.125	0.5	2	32	2	>32	8	4	32
19d-2	$(CH_3)_2N$	$CH_3O(CH_2)_2NHCH_2$	0.5	8	0.5	1	8	0.0625	1	4	32	2	>32	16	16	32
19d-3	$(CH_3)_2N$	$(CH_3)_2NCH_2$	0.25	2	0.25	0.25	2	≤0.0156	0.25	2	8	16	>32	32	8	16
19d-4	$(CH_3)_2N$	pyrrolidinomethyl	0.5	2	0.5	0.25	2	≤0.0156	0.5	2	8	16	>32	16	8	32
72a	H	F	0.5	0.5	0.25	0.25	0.5	2	8	16	>32	4	>32	>32	>32	>32
72b	Cl	F	2	2	2	2	2	>32	>32	>32	>32	>32	>32	>32	>32	>32
72c	CH_3O	F	0.125	0.5	0.125	0.5	1	1	8	16	16	1	>32	>32	32	>32
72d	$(CH_3)_2N$	F	0.25	1	0.125	0.25	0.25	2	4	>32	>32	16	>32	>32	>32	>32
minocycline			0.0625	8	0.0313	1	16	≤0.0156	2	0.5	8	0.0625	16	2	1	8
tigecycline			0.0625	0.125	0.0625	0.0313	0.0625	0.0156	0.0156	0.0313	0.5	0.25	8	0.25	0.125	1

[a] Strains were obtained from the American Type Culture Collection (ATCC, Manassas, VA) unless otherwise noted. The first seven strains from the left are Gram-positive strains. The last seven strains are Gram-negative strains. Strains with "*tet*A", "*tet*K", or "*tet*M" noted underneath are tetracycline-resistant strains. SA, *Staphylococcus aureus*; EF, *Enterococcus faecalis*; SP, *Streptococcus pneumoniae*; EC, *Esherichia coli*; AB, *Acinetobacter baumannii*; PA, *Pseudomonas aeruginosa*; ECl, *Enterobacter cloacae*; KP, *Klebsiella pneumoniae*. [b] Obtained from Micromyx (Kalamazoo, MI). [c] Obtained from Marilyn Roberts' laboratory at the University of Washington.

Table 4. *In Vitro* Antibacterial Activity of 8-Substituted and 9-Substituted Pentacyclines



			MIC (μg/mL)[a]													
			SA101	SA161[b]	SA158[c]	EF103	EF159[c]	SP106	SP160[c]	EC107	EC155[c]	AB110	PA111	ECl108	KP109	KP153[c]
Compound	**^{8}R**	**^{9}R**	29213	MRSA, tetM	tetK	29212	tetM	49619	tetM	25922	tetA	19606	27853	13047	13883	tetA
19a-1[d]	H	H	1	1	0.5	0.5	0.5	0.25	0.25	>32	>32	8	>32	ND	ND	ND
61a	cyclopropyl-$NHCH_2$	H	2	16	1	4	16	0.5	4	16	>32	4	>32	>32	32	>32
61b	$(CH_3)_2NCH_2$	H	1	16	0.5	1	32	0.25	2	4	>32	16	>32	>32	16	>32
61c	azetidino-CH_2	H	1	4	0.5	2	32	0.25	2	8	>32	32	>32	32	16	>32
49a	H_2N	H	2	4	2	4	8	2	8	>32	>32	8	>32	>32	>32	>32
49b	CH_3NH	H	2	4	2	4	4	4	16	>32	>32	32	>32	>32	>32	>32
49c	$(CH_3)_2N$	H	1	2	1	1	2	4	8	>32	>32	16	>32	>32	>32	>32
54	CH_3O	H	0.5	0.5	0.5	0.5	1	2	4	>32	>32	32	>32	>32	>32	>32
69a	H	H_2N	2	8	2	4	8	2	8	>32	>32	16	>32	>32	>32	>32
69b	H	$(CH_3)_2N$	2	4	2	4	4	16	32	>32	>32	>32	>32	>32	>32	>32
minocycline			0.0625	8	0.0313	1	16	≤0.0156	2	0.5	8	0.0625	16	2	1	8
tigecycline			0.0625	0.125	0.0625	0.0313	0.0625	0.0156	0.0156	0.0313	0.5	0.25	8	0.25	0.125	1

[a] Strains were obtained from the American Type Culture Collection (ATCC, Manassas, VA) unless otherwise noted. The first seven strains from the left are Gram-positive strains. The last seven strains are Gram-negative strains. Strains with "*tet*A", "*tet*K", or "*tet*M" noted underneath are tetracycline-resistant strains. SA, *Staphylococcus aureus*; EF, *Enterococcus faecalis*; SP, *Streptococcus pneumoniae*; EC, *Esherichia coli*; AB, *Acinetobacter baumannii*; PA, *Pseudomonas aeruginosa*; ECl, *Enterobacter cloacae*; KP, *Klebsiella pneumoniae*. [b] Obtained from Micromyx (Kalamazoo, MI). [c] Obtained from Marilyn Roberts' laboratory at the University of Washington. [d] See ref 17.

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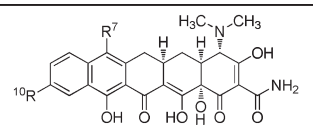
Table 5. Pharmacokinetic Profiles and *in Vivo* Efficacy of Pentacyclines

			PK (IV)[a]					%F[a]	MIC[b]	PD_{50}[c]	
			C_{max}	$AUC_{\infty obs}$	Cl	V_z	$T_{1/2}$		SA100	PO	IV
Compound	R^7	R^{10}	ng/mL	ng*hr/mL	mL/min/kg	L/kg	hr		μg/mL	mg/kg	mg/kg
19a-4	H	$(CH_3)_2CHCH_2NHCH_2$	891	2682	6.22	3.16	5.87	1.9	1	ND	0.62 (0.09-12)
19a-5	H	$CH_3O(CH_2)_2NHCH_2$	633	1978	8.43	3.78	5.19	2.8	1	ND	0.43 (0.37-0.5)
19a-17	H	3-F-azetidinomethyl	814	3457	4.82	1.4	3.35	18	1	12.2 (3.6-20.8)	0.36 (0.17-0.55)
19c-3	F	$(CH_3)_3CNHCH_2$	278	975	17.7	11.9	7.82	1.2	0.5	ND	0.35 (0.34-0.37)
19c-5	F	azetidinomethyl	73	354	52.4	41.9	8.01	ND	0.5	ND	0.3 (N.D.)
19c-6	F	3-F-azetidinomethyl	358	1043	16.1	3.06	2.22	16.7	1	ND	ND
19e-3	CH_3O	$(CH_3)_2CHCH_2NHCH_2$	414	815	20.5	9.6	5.4	2.7	0.5	ND	< 0.3 (N.D.)
19e-2	CH_3O	cyclopropyl-$NHCH_2$	124	385	45.4	8.4	2.17	12.5	0.25	ND	0.6 (N.D.)
19e-6	CH_3O	azetidinomethyl	618	1648	10.2	4.65	5.26	ND	0.0625	>20	0.36 (0.17-0.55)
19e-7	CH_3O	3-F-azetidinomethyl	237	451	63.9	5.06	1.5	17.7	1	ND	ND
tetracycline			583	802	20.5	3.68	4.5	12	0.25	8.1 (0.25-16)	0.35 (0.34-0.37)
tigecycline			428	1052	15.5	6.12	4.6	1.1	0.0625	ND	0.35 (0.24-0.47)

[a] Measured in Sprague−Dawley rats ($n = 3$). Animals were fasted overnight (minimum of 12 h) and given a single oral (10 mg/kg) or iv (1 mg/kg) dose followed by a sampling scheme for 24−48 h. Sterile water was used as vehicle. PK parameters were calculated by noncompartmental analysis using WinNonlin. ND = not determined. [b] SA, *Staphylococcus aureus*. [c] Determined in a mouse septicemia model (SA100, ATCC 13709). See Experimental Section for details. Numbers in parentheses are 95% CI values.

10-(3-fluoroazetidino)methyl pentacycline analog, showed promising *in vivo* efficacy comparable to tetracycline when dosed orally in the mouse septicemia model. We believe pentacycline analogs such as compound **19a-17**, or future analogs derived from this unique scaffold, have the potential to be further developed as oral and iv agents against resistant Gram-positive pathogens. This study demonstrates that the total synthesis approach can give access to novel and potent tetracycline analogs, such as the pentacyclines and azatetracyclines,[24] that would be inaccessible through semisynthetic methods.

EXPERIMENTAL SECTION

Chemistry. All commercially available solvents, including anhydrous solvents, and reagents were used without further purification. All reactions under dry conditions were performed under nitrogen atmospheres. Reductive aminations with amine salts were performed in the presence of equal equivalents of triethylamine in addition to other reagents. ^1H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded on a 400 MHz JEOL ECX-400 spectrometer. Thin layer chromatography (TLC) analysis was performed on Merck silica-gel 60 F_{254} and visualized under UV light. Flash chromatography was performed on Merck silica gel 60 (40−43 μm). Purity of tested compounds was determined to be ≥95% by reverse-phase analytical HPLC/MS analysis (high performance liquid chromatography/mass spectrometry) performed on a Waters Alliance system (column, SunFire C18, 5 μm, 4.6 × 50 mm^2; solvent A, water with 0.1% formic acid; solvent B, acetonitrile with 0.1% formic acid; MS detector, Waters 3100). Reverse-phase preparative HPLC was performed on a Waters Autopurification system (for purification of intermediates, column, SunFire Prep C18 OBD, 5 μm, 19 × 50 mm^2; flow rate, 20 mL/min; solvent A, water with 0.1% formic acid; solvent B, acetonitrile with 0.1% formic acid; fraction collection, mass-directed; for purification of final products, column, Polymerx RP-1 100A, 10 μm, 150 × 21.20 mm^2; flow rate, 20 mL/min; solvent A, water with 0.05 N HCl; solvent B, acetonitrile; fraction collection, mass-directed).

Methyl 7-Bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate (***11***). A solution of *n*-butyllithium in hexanes (2.50 M, 48.4 mL, 121.1 mmol, 1.2 equiv) was added to a solution of diisopropylamine (17.0 mL, 121.1 mmol, 1.2 equiv) in THF (400 mL) at −78 °C. The solution was vigorously stirred at −78 °C for 30 min, warmed to 0 °C for 5 min, and cooled back to −78 °C. A solution of 6-bromophthalide[25] (**10**, 21.5 g, 100.9 mmol, 1.0 equiv) in THF (200 mL) was added slowly via a cannula. The resulting dark solution was allowed to slowly warm to −50 °C over 3 h. Methyl crotonate (11.8 mL, 111.0 mmol, 1.1 equiv) was added slowly, and the resulting mixture was allowed to warm to rt

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without removing the cooling bath. The reaction mixture was poured into 1 N HCl (600 mL) and extracted with ethyl acetate (200 mL × 3). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated and dried under high vacuum, providing an orange foamy solid (27.5 g), which was used for the next reaction without further treatment.

The above crude product was dissolved in methylene chloride (250 mL). BF_3-Et_2O (2.52 mL, 20.2 mmol, 0.2 equiv) was added dropwise at rt. The resulting brownish mixture was stirred at rt for 1 h and poured into 0.5 N HCl (600 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (200 mL × 2). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing a thick brownish oil. Purification by flash column chromatography (5% → 10% ethyl acetate−hexanes) afforded compound **11** as an off-white solid (6.32 g, 22%, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.68 (s, 1 H), 8.52 (s, 1 H), 7.63−7.61 (d, J = 8.5 Hz, 1 H), 7.52−7.50 (d, J = 8.5 Hz, 1 H), 7.07 (s, 1 H), 4.01 (s, 3 H), 2.63 (s, 3 H).

*Methyl 7-Bromo-1-methoxy-3-methylnaphthalene-2-carboxylate (**12**).* Cesium carbonate powder (9.06 g, 27.8 mmol, 1.3 equiv) and dimethyl sulfate (2.43 mL, 25.7 mmol, 1.2 equiv) were added to a solution of **11** (6.31 g, 21.0 mmol, 1.0 equiv) in acetone (60 mL). The mixture was heated at reflux for 1 h, cooled to rt, and filtered through a short pad of Celite. The Celite cake was washed thoroughly with acetone. The filtrate was concentrated to afford **12** as a white solid, which was used for the next reaction directly without further purification.

*Phenyl 7-Bromo-1-methoxy-3-methylnaphthalene-2-carboxylate (**13**).* A mixture of ethanol (10 mL) and 4 N aqueous sodium hydroxide (10 mL) was added to compound **12**. The suspension was stirred at 85 °C overnight. The resulting clear solution was cooled to rt, acidified with 4 N HCl (pH 3, 11 mL), and extracted with methylene chloride (30 mL × 4). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated to afford the carboxylic acid as a pale solid.

Oxalyl chloride (2.24 mL, 25.7 mmol, 1.2 equiv) was added to a solution of the above carboxylic acid in anhydrous methylene chloride (100 mL) at rt, followed by a couple of drops of DMF (gas evolution). The mixture was stirred at rt for 1 h and the volatiles evaporated under reduced pressure. The residue was dried under high vacuum to give the crude acid chloride. This was redissolved in dry methylene chloride (100 mL). Pyridine (3.46 mL, 42.8 mmol, 2.0 equiv), phenol (2.11 g, 22.5 mmol, 1.05 equiv), and DMAP (catalytic amount) were added. The reaction mixture was stirred for several hours at rt, diluted with 1 N HCl (100 mL), and extracted with methylene chloride (50 mL × 3). The combined organic extracts were washed with brine (40 mL) and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (5% → 10% ethyl acetate−hexanes) to afford the desired product **13** as a white solid (6.86 g, 86%, three steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 1.8 Hz, 1 H), 7.60−7.52 (m, 2 H), 7.44−7.39 (m, 3 H), 7.27−7.24 (m, 3 H), 4.05 (s, 3 H), 2.53 (s, 3 H).

*Phenyl 7-Bromo-1-[(tert-butoxycarbonyl)oxy]-3-methylnaphthalene-2-carboxylate (**14a**).* A solution of BBr_3 in methylene chloride (1.0 M, 5.83 mL, 5.83 mmol, 2.0 equiv) was added slowly over 4 min to a solution of compound **13** (1.08 g, 2.91 mmol, 1.0 equiv) in methylene chloride (60 mL) at −70 °C. The resulting orange solution was allowed to warm to −45 °C over 5 h and poured into saturated aqueous sodium bicarbonate (100 mL). The mixture was stirred at rt for 10 min and extracted with methylene chloride (60 mL × 3). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing the naphthol intermediate as a white solid, which was used in the next reaction without further purification.

$(Boc)_2O$ (670 mg, 3.20 mmol, 1.1 equiv), DIEA (1.01 mL, 5.82 mmol, 2.0 equiv), and DMAP (20 mg, 0.16 mmol, 0.05 equiv) were added to a solution of the above intermediate in methylene chloride (60 mL). The mixture was stirred at rt overnight and concentrated under reduced pressure. The residue was purified by flash column chromatography (5% ethyl acetate−hexanes) to afford the desired product **14a** as a white solid (1.19 g, 89%, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, J = 1.8 Hz, 1 H), 7.63−7.55 (m, 3 H), 7.43−7.39 (m, 2 H), 7.28−7.24 (m, 3 H), 2.60 (s, 3 H), 1.44 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 151.2, 150.5, 144.9, 134.0, 133.4, 131.6, 129.5, 128.9, 126.9, 126.7, 126.3, 124.5, 124.0, 121.7, 120.9, 84.6, 27.5, 20.7.

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-9-bromo-4a-{[tert-butyl(dimethyl)-silyl]oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,-14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**15a**). Michael−Dieckmann Cyclization, General Procedure A.* A solution of LDA (1.8 M, 4.30 mL, 7.74 mmol, 3.0 equiv) in heptane/ethylbezene/THF was added dropwise via a syringe to a solution of compound **14a** (2.36 g, 5.16 mmol, 2.0 equiv), enone **8** (1.24 g, 2.58 mmol, 1.0 equiv), and TMEDA (2.32 mL, 15.5 mmol, 6.0 equiv) in THF (100 mL) at −78 °C. The resulting red-orange solution was allowed to warm to −10 °C over 2 h and diluted with aqueous potassium phosphate buffer (pH 7.0, 0.2 M, 50 mL) and saturated aqueous ammonium chloride. The mixture was extracted with ethyl acetate (200 mL × 2). The organic extracts were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure to give the crude product, which was purified by flash column chromatography (5% → 10% ethyl acetate−hexanes) to afford the Michael−Dieckmann cyclization product **15a** as an orange solid (1.02 g, 47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.98 (br s, 1 H), 8.24 (br s, 1 H), 7.64 (s, 2 H), 7.51−7.49 (m, 3 H), 7.39−7.33 (m, 3 H), 5.37 (d, J = 12.0 Hz, 1 H), 5.34 (d, J = 12.0 Hz, 1 H), 3.96 (d, J = 10.5 Hz, 1 H), 3.11−3.06 (m, 2 H), 2.93 (t, J = 15.5 Hz, 1 H), 2.56 (dd, J = 11.0, 5.0 Hz, 1 H), 2.49 (s, 6 H), 2.49−2.46 (m, 1 H), 2.14 (d, J = 14.0 Hz, 1 H), 1.59 (s, 9 H), 0.82 (s, 9 H), 0.27 (s, 3 H), 0.12 (s, 3 H); MS (ESI) m/z 845.70 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-9-formyl-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,-14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**16a**). Formylation, General Procedure B.* A solution of phenyllithium in di-*n*-butyl ether (1.8 M, 0.20 mL, 0.36 mmol, 2.0 equiv) was added dropwise to a solution of compound **15a** (153 mg, 0.18 mmol, 1.0 equiv) in THF (9 mL) at −78 °C. The resulting red solution was stirred at −78 °C for 5 min. *n*-Butyllithium (94 μL, 2.5 M/hexanes, 0.24 mmol, 1.3 equiv) was added dropwise at −78 °C. The reaction was stirred at −78 °C for 5 min. Dry DMF (69 μL, 0.90 mmol, 5.0 equiv) was added. The deep red reaction mixture was stirred at −78 °C for 1 h. Saturated aqueous ammonium chloride (10 mL) was added dropwise at −78 °C. Aqueous potassium phosphate buffer (pH 7.0, 0.2 M, 10 mL) was added. The reaction mixture was allowed to warm to rt and extracted with methylene chloride (30 mL × 3). The organic extracts were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The residue was purified by preparative reverse-phase HPLC to afford the desired product **16a** (121 mg, 84%) as a yellow solid: R_f = 0.15 (25% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.98 (br s, 1 H), 10.17 (s, 1 H), 8.60 (br s, 1 H), 8.06 (dd, J = 8.4, 1.6 Hz, 1 H), 7.88 (d, J = 8.4 Hz, 1 H), 7.62 (s, 1 H), 7.52−7.50 (m, 2 H), 7.41−7.34 (m, 3 H), 5.38 (d, J = 12.4 Hz, 1 H), 5.35 (d, J = 12.4 Hz, 1 H), 3.98 (d, J = 10.4 Hz, 1 H), 3.18−3.13 (m, 2 H), 3.03−2.96 (m, 1 H), 2.61−2.56 (m, 1 H), 2.51 (s, 6 H), 2.50−2.48 (m, 1 H), 2.18 (d, J = 14.4 Hz, 1 H), 1.62 (s, 9 H), 0.84 (s, 9 H), 0.29 (s, 3 H), 0.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 187.2, 181.7, 167.5, 140.5, 138.7, 135.0, 134.7, 129.5, 128.5, 128.48, 128.45, 128.42, 126.8, 126.0, 123.9, 120.7, 108.5, 108.4, 84.9, 81.8, 72.5, 61.2, 46.4, 41.8, 39.9, 28.4, 27.7, 26.0, 22.7, 19.0, −2.6, −3.8; MS (ESI) m/z 795.7 (M + H).

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*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-[(dimethylamino)methyl]-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-6**).* *Reductive Amination, General Procedure C.* Dimethylamine (44 μL, 2.0 M/THF, 0.088 mmol, 7.0 equiv), acetic acid (5 μL, 0.088 mmol, 7.0 equiv), and sodium triacetoxyborohydride (19 mg, 0.088 mmol, 7.0 equiv) were added to a solution of aldehyde **16a** (10 mg, 0.012 mmol, 1.0 equiv) in 1,2-dichloroethane (1 mL) at rt. After being stirred for 2 h, the reaction mixture was poured into aqueous potassium phosphate buffer (pH = 7.0, 10 mL). The mixture was extracted with methylene chloride (15 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give the crude product.

Desilylation, General Procedure D. Concentrated aqueous hydrofluoric acid (48 wt %, 0.3 mL) was added to a solution of the above crude product in acetonitrile (0.6 mL) in a polypropylene reaction vessel at rt. The mixture was vigorously stirred at rt overnight and poured into aqueous dipotassium hydrogen phosphate (3.6 g in 25 mL water). The mixture was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated to give the crude product as a yellow solid.

Hydrogenation, General Procedure E. Methanol (3 mL) was added to the above crude product. 10% Pd−C (catalytic amount) was added in one portion at rt. An atmosphere of hydrogen was introduced by briefly evacuating the flask and flushing with hydrogen (1 atm). The reaction mixture was stirred at rt for 4 h and filtered through a pad of Celite. The filtrate was concentrated to give the crude product, which was purified by preparative reverse-phase HPLC to yield the desired product (**19a-6**) as a yellow solid (3.6 mg, HCl salt, 51%, three steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (br s, 1 H), 7.83 (d, J = 7.9 Hz, 1 H), 7.74 (d, J = 6.9 Hz, 1 H), 7.16 (br s, 1 H), 4.49 (br s, 2 H), 4.10 (br s, 1 H), 3.03−2.95 (m, 9 H), 2.87 (s, 6 H), 2.64−2.57 (m, 1 H), 2.25−2.22 (m, 1 H), 1.60−1.58 (m, 1 H); MS (ESI) m/z 522.50 (M + H).

The following compounds were prepared similarly to **19a-6** using aldehyde **16a** and the respective amines according to general procedures C, D, and E.

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-[(methylamino)methyl]-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-2**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1 H), 7.86 (d, J = 8.5 Hz, 1 H), 7.71 (dd, J = 1.8, 8.5 Hz, 1 H), 7.21 (s, 1 H), 4.37 (s, 2 H), 4.10 (s, 1 H), 3.17−2.96 (m, 9 H), 2.77 (s, 3 H), 2.67 (t, J = 13.4 Hz, 1 H), 2.28−2.21 (m, 1 H), 1.69−1.57 (m, 1 H); MS (ESI) m/z 508.45 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-10-[(propylamino)methyl]-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-3**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1 H), 7.86 (d, J = 8.5 Hz, 1 H), 7.74 (dd, J = 1.8, 8.5 Hz, 1 H), 7.21 (s, 1 H), 4.38 (s, 2 H), 4.11 (s, 1 H), 3.17−2.96 (m, 11 H), 2.67 (t, J = 13.4 Hz, 1 H), 2.28−2.20 (m, 1 H), 1.82 1.71 (m, 2 H), 1.69−1.57 (m, 1 H), 1.04 (t, J = 7.9 Hz, 3 H); MS (ESI) m/z 536.50 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-10-[(isobutylamino)methyl]-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-4**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1 H), 7.84 (d, J = 8.5 Hz, 1 H), 7.74 (dd, J = 1.8, 8.5 Hz, 1 H), 7.19 (s, 1 H), 4.39 (s, 2 H), 4.10 (s, 1 H), 3.17−2.90 (m, 9 H), 2.66 (t, J = 14.0 Hz, 1 H), 2.28−2.18 (m, 1 H), 2.12−2.00 (m, 1 H), 1.70−1.57 (m, 1 H), 1.03 (d, J = 6.7 Hz, 6 H); MS (ESI) m/z 550.49 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-10-{[(2-methoxyethyl)amino]methyl}-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-5**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1 H), 7.84 (d, J = 8.5 Hz, 1 H), 7.72 (dd, J = 1.8, 8.5 Hz, 1 H), 7.18 (s, 1 H), 4.41 (s, 2 H), 4.11 (s, 1 H), 3.67 (t, J = 4.9 Hz, 2 H), 3.41 (s, 3 H), 3.28−3.24 (m, 2 H), 3.15−2.92 (m, 9 H), 2.65 (t, J = 14.0 Hz, 1 H), 2.27−2.18 (m, 1 H), 1.69−1.54 (m, 1 H); MS (ESI) m/z 552.47 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-{[ethyl(methyl)amino]-methyl}-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-7**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (br s, 1 H), 7.83 (d, J = 7.3 Hz, 1 H), 7.75 (d, J = 7.8 Hz, 1 H), 7.16 (br s, 1 H), 4.59 (m, 1 H), 4.41 (m, 1 H), 4.10 (br s, 1 H), 3.30−2.95 (m, 11 H), 2.78 (s, 3 H), 2.64−2.58 (m, 1 H), 2.28−2.18 (m, 1 H), 1.60−1.58 (m, 1 H), 1.38 (m, 3 H); MS (ESI) m/z 536.59 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-{[methyl(phenyl)amino]-methyl}-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-8**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (s, 1 H), 7.80 (d, J = 8.2 Hz, 1 H), 7.51−7.43 (m, 6 H), 7.13 (s, 1 H), 4.96 (s, 2 H), 4.08 (s, 1 H), 3.41 (s, 3 H), 3.03−2.96 (m, 9 H), 2.64 (t, J = 14.6 Hz, 1 H), 2.20−2.19 (m, 1 H), 1.67−1.57 (m, 1 H); MS (ESI) m/z 584.54 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-9**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.44 (s, 1 H), 7.70 (d, J = 8.7 Hz, 1 H), 7.68 (dd, J = 1.8, 8.7 Hz, 1 H), 7.13 (s, 1 H), 4.55 (s, 2 H), 4.29−4.22 (m, 2 H), 4.12−4.08 (m, 3 H), 3.10−2.96 (m, 9 H), 2.63−2.55 (m, 2 H), 2.50−2.46 (m, 1 H), 2.26−2.21 (m, 1 H), 1.65−1.56 (m, 1 H); MS (ESI) m/z 534.51 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-10-(pyrrolidin-1-ylmethyl)-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-10**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1 H), 7.81−7.78 (m, 2 H), 7.15 (s, 1 H), 4.54 (s, 2 H), 4.10 (s, 1 H), 3.49 (m, 2 H), 3.22 (m, 2 H), 3.03−2.95 (m, 9 H), 2.63−2.58 (m, 1 H), 2.25−2.17 (m, 3 H), 2.02−1.98 (m, 2 H), 1.64−1.54 (m, 1 H); MS (ESI) m/z 548.58 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-10-(piperidin-1-ylmethyl)-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-11**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (s, 1 H), 7.84−7.76 (m, 2 H), 7.17 (s, 1 H), 4.45 (s, 2 H), 4.10 (s, 1 H), 3.46−3.44 (m, 2 H), 3.10−2.96 (m, 11 H), 2.65−2.59 (m, 1 H), 2.25−2.17 (m, 1 H), 1.92−1.79 (m, 5 H), 1.60−1.52 (m, 2 H); MS (ESI) m/z 562.54 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-10-[(3-hydroxyazetidin-1-yl)methyl]-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-12**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1 H), 7.85 (d, J = 8.5 Hz, 1 H), 7.72−7.66 (m, 1 H), 7.19 (s, 1 H), 4.74−4.51 (m, 3 H), 4.42−4.28 (m, 2 H), 4.10 (s, 1 H), 4.08−3.94 (m, 2 H), 3.17−2.91 (m, 9 H), 2.66 (t, J = 14.7 Hz, 1 H), 2.28−2.18 (m, 1 H), 1.67−1.57 (m, 1H); MS (ESI) m/z 550.54 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-10-[(3-methoxyazetidin-1-yl)methyl]-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-13**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (s, 1 H), 7.84 (d, J = 8.5 Hz, 1 H), 7.76−7.70 (m, 1 H), 7.20−7.15 (m, 1 H), 4.61 (s, 3 H), 4.47−4.28 (m, 3 H), 4.16 (s, 1 H), 4.12−4.01 (m, 2 H), 3.17−2.92 (m, 9 H), 2.69−2.56 (m, 1 H), 2.33−2.23 (m, 1 H), 1.68−1.53 (m, 1 H); MS (ESI) m/z 564.57 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-{[3-(dimethylamino)-azetidin-1-yl]methyl}-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,-5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-14**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1 H), 7.89−7.76 (m, 2 H), 7.19 (s, 1 H), 4.91−4.74 (m, 4 H), 4.59−4.41 (m, 3 H), 4.15 (s, 1 H), 3.15−2.95 (m, 9 H), 2.91 (s, 6 H), 2.68−2.56 (m, 1 H), 2.32−2.23 (m, 1 H), 1.67−1.54 (m, 1 H); MS (ESI) m/z 577.60 (M + H).

*(4S,4aS,5aR,14aS)-10-{[3-(Acetylamino)azetidin-1-yl]methyl}-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,-13,14a-octahydropentacene-2-carboxamide (**19a-15**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.52−8.48 (m, 1 H), 7.89−7.82 (m, 1 H),

7.74−7.66 (m, 1 H), 7.23−7.16 (m, 1 H), 4.67−4.53 (m, 3 H), 4.47−4.21 (m, 4 H), 4.10 (s, 1 H), 3.16−2.92 (m, 9 H), 2.72−2.60 (m, 1 H), 2.27−2.18 (m, 1 H), 2.00 (s, 3 H), 1.69−1.56 (m, 1 H); MS (ESI) m/z 591.58 (M + H).

*(4S,4aS,5aR,14aS)-10-[(3-Cyanoazetidin-1-yl)methyl]-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-16**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (s, 1 H), 7.88 (d, J = 8.5 Hz, 1 H), 7.69 (dd, J = 1.8, 8.5 Hz, 1 H), 7.22 (s, 1 H), 4.64 (s, 2 H), 4.59−4.37 (m, 3 H), 4.10 (s, 1 H), 4.08−3.95 (m, 1 H), 3.12−2.93 (m, 10 H), 2.73−2.62 (m, 1 H), 2.28−2.18 (m, 1 H), 1.70−1.56 (m, 1 H); MS (ESI) m/z 559.47 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-[(3-fluoroazetidin-1-yl)-methyl]-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-17**).* Prepared from aldehyde **16a** (1.08 g, 1.36 mmol, 1.0 equiv) and 3-fluoroazetidine according to General Procedures C, D, and E. The final product was purified by preparative reverse-phase HPLC using water (with 0.5% trifluoroacetic acid (TFA)) and acetonitrile as the mobile phases (474 mg, 45%, three steps, TFA salt).

To a solution of the above TFA salt of compound **19a-17** (269 mg, 0.345 mmol, 1 equiv) in methanol (5 mL) was added methanesulfonic acid (44.8 μL, 0.691 mmol, 2 equiv). The solvent was removed under reduced pressure; the residue was dissolved in water (3.75 mL) and acetonitrile (1.25 mL) and then freeze-dried to provide the desired product as the dimesylate salt (256 mg, 100%): ^{1}H NMR (400 MHz, CD_3OD) δ 8.55−8.47 (m, 1 H), 7.87 (d, J = 8.5 Hz, 1 H), 7.73−7.65 (m, 1 H), 7.21 (s, 1 H), 5.58−5.28 (m, 1 H), 4.72−4.27 (m, 6 H), 4.09 (s, 1 H), 3.18−2.92 (m, 10 H), 2.74−2.62 (3, 7 H), 2.27−2.18 (m, 1 H), 1.71−1.57 (m, 1 H); MS (ESI) m/z 552.18 552.35 (M + H).

*(4S,4aS,5aR,14aS)-10-[(3,3-Difluoroazetidin-1-yl)methyl]-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-18**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.55 (s, 1 H), 7.86 (d, J = 8.5 Hz, 1 H), 7.82−7.74 (m, 1 H), 7.20 (s, 1 H), 4.90−4.52 (m, 5 H), 4.15 (s, 1 H), 4.11−3.70 (m, 1 H), 3.14−2.93 (m, 9 H), 2.68−2.56 (m, 1 H), 2.32−2.21 (m, 1 H), 1.67−1.52 (m, 1 H); MS (ESI) m/z 570.54 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy--10-{[methyl(methylsulfonyl)amino]methyl}-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19a-19**).* Methylamine (68 μL, 8.0 M/ethanol, 0.54 mmol, 7.0 equiv), acetic acid (31 μL, 0.54 mmol, 7.0 equiv), and sodium triacetoxyborohydride (115 mg, 0.54 mmol, 7.0 equiv) were added to a solution of aldehyde **16a** (62 mg, 0.078 mmol, 1.0 equiv) in 1,2-dichloroethane (4 mL) at rt. After being stirred for 5 h, the reaction mixture was quenched by saturated aqueous sodium bicarbonate (10 mL) and aqueous potassium phosphate buffer (pH 7.0, 0.2 M, 10 mL). The mixture was extracted with methylene chloride (15 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to give the methylamino intermediate.

2,6-Lutidine (4.3 μL, 0.037 mmol, 3.0 equiv) and methanesulfonyl chloride (2.9 μL, 0.037 mmol, 3.0 equiv) were added to a solution of the above methylamino intermediate (10 mg, 0.012 mmol, 1.0 equiv) in anhydrous methylene chloride (0.6 mL). The reaction was stirred at rt for 6 h and concentrated. The residue was purified by preparative reverse-phase HPLC to afford the desired methylsulfonamide intermediate, which was subjected to desilylation and hydrogenation according to General Procedures D and E to yield compound **19a-19** (2.4 mg, 34%, yellow solid): ^{1}H NMR (400 MHz, CD_3OD) δ 8.31 (s, 1 H), 7.75 (d, J = 8.2 Hz, 1 H), 7.66 (d, J = 8.2 Hz, 1 H), 7.13 (s, 1 H), 4.46 (s, 2 H), 4.08 (s, 1 H), 3.08−2.95 (m, 12 H), 2.77 (s, 3 H), 2.64 (t, J = 14.6 Hz, 1H), 2.24−2.19 (m, 1H), 1.67−1.57 (m, 1H); MS (ESI) m/z 586.44 (M + H).

Phenyl 7-Bromo-4-chloro-1-methoxy-3-methylnaphthalene-2-carboxylate. A suspension of NCS (396 mg, 2.96 mmol, 1.1 equiv) and compound **13** (1.00 g, 2.69 mmol, 1.0 equiv) in acetonitrile (27 mL) was heated at reflux for overnight. The reaction mixture was cooled to rt, and solvents were evaporated. The crude product (white solid) was dried under high vacuum and used directly for the next step.

*Phenyl 7-Bromo-1-[(tert-butoxycarbonyl)oxy]-4-chloro-3-methylnaphthalene-2-carboxylate (**14b**).* A solution of BBr_3 in methylene chloride (1.0 M, 5.38 mL, 5.38 mmol, 2.0 equiv) was added slowly to a solution of the above crude compound (2.69 mmol, 1.0 equiv) in methylene chloride (30 mL) at −65 °C. The resulting red solution was stirred at −65 °C for 55 min and was poured into saturated aqueous sodium bicarbonate (100 mL). The mixture was stirred at rt for 30 min and extracted with methylene chloride (60 mL × 4). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing the naphthol intermediate as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.06 (s, 1 H), 8.58 (d, J = 2.4 Hz, 1 H), 8.13 (d, J = 9.2 Hz, 1 H), 7.78 (dd, J = 2.4, 9.2 Hz, 1 H), 7.50−7.46 (m, 2 H), 7.34 (t, J = 7.3 Hz, 1 H), 7.25−7.22 (m, 2 H), 2.90 (s, 3 H); MS (ESI) m/z 389.03, 391.03 (M − H).

$(Boc)_2O$ (616 mg, 2.82 mmol, 1.05 equiv) and DMAP (10 mg, 0.08 mmol, 0.03 equiv) were added to a solution of the above naphthol intermediate in methylene chloride (30 mL). The mixture was stirred for 40 min at rt and concentrated. The residue was purified by flash column chromatography (1% → 5% ethyl acetate−hexanes) to afford compound **14b** (white solid, 1.06 g, 80%, three steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, J = 9.2 Hz, 1 H), 8.02 (d, J = 1.8 Hz, 1 H), 7.63 (dd, J = 1.8, 9.2 Hz, 1 H), 7.42−7.38 (m, 2 H), 7.27−7.22 (m, 3 H), 2.63 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.0, 150.8, 150.3, 142.7, 132.3, 131.2, 130.7, 129.9, 129.5, 127.3, 126.5, 126.3, 125.4, 124.5, 121.9, 121.5, 84.8, 27.4, 18.3; MS (ESI) m/z 489.18, 491.10 (M − H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-9-bromo-4a-{[tert-butyl(dimethyl)silyl]oxy}-12-chloro-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**15b**).* Compound **14b** (1.06 g, 2.16 mmol, 1.5 equiv) was reacted with enone **8** (694 mg, 1.44 mmol, 1.0 equiv) according to General Procedure A to yield compound **15b** as a yellow solid (773 mg, 61%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.74 (br s, 1 H), 8.19 (br s, 1 H), 8.04 (d, J = 9.2 Hz, 1 H), 7.66 (dd, J = 1.8, 9.2 Hz, 1 H), 7.43−7.41 (m, 2 H), 7.31−7.24 (m, 3 H), 5.30, 5.26 (ABq, J = 12.2 Hz, 2 H), 3.87 (d, J = 10.4 Hz, 1 H), 3.59 (dd, J = 4.3, 15.9 Hz, 1 H), 3.04−2.98 (m, 1 H), 2.60 (t, J = 15.3 Hz, 1 H), 2.54−2.39 (m, 8 H), 2.14 (d, J = 14.0 Hz, 1 H), 1.50 (s, 9 H), 0.75 (s, 9 H), 0.20 (s, 3 H), 0.06 (s, 3 H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]-oxy}-12-chloro-15-(dimethylamino)-9-formyl-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**16b**).* Compound **15b** (704 mg, 0.72 mmol, 1.0 equiv) was converted to compound **16b** according to General Procedure B (371 mg, yellow solid, 62%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.79 (br s, 1 H), 10.18 (d, J = 4.2 Hz, 1 H), 8.62 (br s, 1 H), 8.38 (br s, 1 H), 8.14 (br s, 1 H), 7.51−7.37 (m, 5 H), 5.37 (br s, 2 H), 3.97 (br s, 1 H), 3.73 (d, J = 14.0 Hz, 1 H), 3.14 (br s, 1 H), 2.27−2.54 (m, 9 H), 2.25 (d, J = 9.8 Hz, 1 H), 1.60 (s, 9 H), 0.84 (s, 9 H), 0.29 (s, 3 H), 0.15 (s, 3 H); MS (ESI) m/z 829.46 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-7-chloro-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19b-1**).* Compound **16b** (20 mg, 0.024 mmol, 1.0 equiv) was subjected to reductive amination with azetidine (6.5 μL, 0.096 mmol, 4.0 equiv), desilylation, and hydrogenation according to General Procedures C, D, and E to yield compound **19b-1** as a yellow solid (1.6 mg, from half of the crude desilylated intermediate, 24%, three steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1 H), 8.32 (d, J = 8.7 Hz, 1 H), 7.85 (dd, J = 1.4, 8.7 Hz, 1 H), 4.60

(s, 2 H), 4.27 (q, J = 9.6 Hz, 2 H), 4.16−4.10 (m, 3 H), 3.61 (dd, J = 4.1, 16.0 Hz, 1 H), 3.14−2.97 (m, 8 H), 2.61−2.46 (m, 3 H), 2.28 (ddd, J = 2.8, 5.0, 13.7 Hz, 1 H), 1.74−1.64 (m, 1 H); MS (ESI) m/z 568.37 (M + H).

Phenyl 7-Bromo-4-fluoro-1-methoxy-3-methylnaphthalene-2-carboxylate. NIS (2.57 g, 11.4 mmol, 1.3 equiv) and TFA (0.20 mL, 2.63 mmol, 0.3 equiv) were added to a suspension of compound **13** (3.26 g, 8.78 mmol, 1.0 equiv) in acetonitrile (90 mL) at rt. The mixture was then stirred at 80 °C for 25 h. The reaction mixture was cooled to rt, and solvents were evaporated. The resulting off-white solid was dissolved in methylene chloride (250 mL) and the methylene chloride solution was washed with saturated aqueous sodium bicarbonate (200 mL). The aqueous layer was extracted with methylene chloride (50 mL × 2). The combined organic phase was dried over magnesium sulfate, filtered, and concentrated to afford the iodo intermediate as a pale yellow solid (4.51 g): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, J = 1.8 Hz, 1 H), 8.17 (d, J = 9.2 Hz, 1 H), 7.66 (dd, J = 1.8, 9.2 Hz, 1 H), 7.48−7.44 (m, 2 H), 7.32−7.27 (m, 3 H), 4.08 (s, 3 H), 2.76 (s, 3 H).

To a solution of the above iodo intermediate in THF (135 mL) at −100 °C (liquid nitrogen/ethanol bath) was added *n*-butyllithium (4.25 mL, 1.6 M/hexanes, 6.80 mmol, 1.0 equiv) dropwise. After the mixture was stirred at that temperature for 5 min, a solution of NFSI (*N*-fluorobenzenesulfonimide, 2.57 g, 8.16 mmol, 1.2 equiv) in THF (17 mL) was added dropwise via a cannula. The resulting reaction mixture was warmed slowly to −78 °C and kept at that temperature for 1 h. Phosphate buffer (pH 7.0, 200 mL) was added to quench the reaction. The resulting mixture was warmed to rt and extracted with ethyl acetate (200 mL). The organic layer was separated, washed with saturated aqueous sodium bicarbonate (150 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and concentrated to afford a yellow solid, which was purified by flash column chromatography (0 → 1% ethyl acetate−hexanes) to afford phenyl 7-bromo-4-fluoro-1-methoxy-3-methylnaphthalene-2-carboxylate (pale yellow solid, 1.30 g, 51%, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (t, J = 1.8 Hz, 1 H), 7.93 (d, J = 9.2 Hz, 1 H), 7.66 (dd, J = 1.8, 9.2 Hz, 1 H), 7.48−7.44 (m, 2 H), 7.32−7.27 (m, 3 H), 4.06 (s, 3 H), 2.48 (d, J = 2.3 Hz, 3 H); MS (ESI) m/z 387.09 (M − H).

*Phenyl 7-Bromo-1-[(tert-butoxycarbonyl)oxy]-4-fluoro-3-methylnaphthalene-2-carboxylate (**14c**).* A solution of BBr_3 in methylene chloride (1.0 M, 3.67 mL, 3.67 mmol, 1.1 equiv) was added slowly to a solution of phenyl 7-bromo-4-fluoro-1-methoxy-3-methylnaphthalene-2-carboxylate (1.30 g, 3.34 mmol, 1.0 equiv) in methylene chloride (40 mL) at −78 °C. The resulting red solution was stirred at −78 °C for 45 min and was poured into saturated aqueous sodium bicarbonate (250 mL). The mixture was stirred at rt for 30 min and extracted with methylene chloride (300 mL × 1, 120 mL × 3). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing the crude product as an off-white solid.

$(Boc)_2O$ (765 mg, 3.51 mmol, 1.05 equiv) and DMAP (10 mg, 0.08 mmol, 0.02 equiv) were added to a solution of the above crude product in methylene chloride (40 mL). The reaction mixture was stirred for 50 min at rt and concentrated. The residue was purified by flash column chromatography (1% → 3% ethyl acetate−hexanes) to afford compound **14c** (off-white solid, 1.23 g, 78%, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1 H), 7.84 (d, J = 8.7 Hz, 1 H), 7.60 (dd, J = 1.8, 8.7 Hz, 1 H), 7.41−7.38 (m, 2 H), 7.26−7.24 (m, 3 H), 2.48 (d, J = 2.8 Hz, 3 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.6 (d, J = 2.9 Hz, 1 C), 154.0 (d, J = 249.2 Hz, 1 C), 151.1, 150.3, 140.4 (d, J = 3.8 Hz, 1 C), 131.8, 129.4, 127.3 (d, J = 4.8 Hz, 1 C), 126.3, 124.6 (d, J = 4.8 Hz, 1 C), 124.4, 123.3 (d, J = 20.1 Hz, 1 C), 122.3 (d, J = 5.8 Hz, 1 C), 122.0, 121.5, 117.8 (d, J = 19.2 Hz, 1 C), 84.6, 27.4, 12.0 (d, J = 5.8 Hz, 1 C); MS (ESI) m/z 473.16 (M − H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-9-bromo-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-12-fluoro-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**15c**).* Compound **14c** (1.23 g, 2.59 mmol, 1.2 equiv) was reacted with enone **8** (1.04 g, 2.16 mmol, 1.0 equiv) according to General Procedure A to afford product **15c** as a yellow solid (1.05 g, 56%; 481 mg of starting material **14c** and 262 mg of enone **8** were recovered): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.96 (s, 1 H), 8.24 (s, 1 H), 7.89 (d, J = 8.5 Hz, 1 H), 7.70 (dd, J = 1.8, 8.5 Hz, 1 H), 7.51−7.50 (m, 2 H), 7.39−7.31 (m, 3 H), 5.39, 5.35 (ABq, J = 12.2 Hz, 2 H), 3.97 (d, J = 10.4 Hz, 1 H), 3.48 (dd, J = 4.3, 15.3 Hz, 1 H), 3.14−3.07 (m, 1 H), 2.64−2.48 (m, 9 H), 2.23 (d, J = 14.0 Hz, 1 H), 1.61 (s, 9 H), 0.85 (s, 9 H), 0.30 (s, 3 H), 0.17 (s, 3 H); MS (ESI) m/z 863.43 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-12-fluoro-9-formyl-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**16c**).* Compound **15c** (1.05 g, 1.22 mmol, 1.0 equiv) was converted to compound **16c** according to General Procedure B (685 mg, 69%, yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.88 (s, 1 H), 10.18 (s, 1 H), 8.58 (s, 1 H), 8.17 (d, J = 8.5 Hz, 1 H), 8.11 (dd, J = 1.2, 8.5 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.39−7.32 (m, 3 H), 5.37, 5.34 (ABq, J = 12.2 Hz, 2 H), 3.94 (d, J = 10.4 Hz, 1 H), 3.52 (dd, J = 4.3, 15.3 Hz, 1 H), 3.14−3.08 (m, 1 H), 2.66−2.51 (m, 9 H), 2.22 (d, J = 14.6 Hz, 1 H), 1.59 (s, 9 H), 0.82 (s, 9 H), 0.26 (s, 3 H), 0.13 (s, 3 H); MS (ESI) m/z 813.50 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-7-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19c-5**).* Compound **16c** was subjected to reductive amination with azetidine (39 μL, 0.57 mmol, 3.0 equiv), desilylation, and hydrogenation according to General Procedures C, D, and E to yield the desired product **19c-5** as a yellow solid (57 mg, 47%, three steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (s, 1 H), 8.06 (d, J = 8.2 Hz, 1 H), 7.82 (dd, J = 1.8, 8.7 Hz, 1 H), 4.59 (s, 2 H), 4.27 (q, J = 9.6 Hz, 2 H), 4.16−4.10 (m, 3 H), 3.37 (dd, J = 4.1, 14.6 Hz, 1 H), 3.12−2.97 (m, 8 H), 2.63−2.55 (m, 1 H), 2.53−2.45 (m, 1 H), 2.38 (t, J = 14.6 Hz, 1 H), 2.27 (ddd, J = 2.8, 5.0, 13.7 Hz, 1 H), 1.72−1.62 (m, 1 H); MS (ESI) m/z 552.40 (M + H).

The following compounds were prepared similarly from compound **16c** and the respective amines.

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-[(ethylamino)methyl]-7-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19c-1**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (s, 1 H), 7.94 (d, J = 8.4 Hz, 1 H), 7.77 (d, J = 8.4 Hz, 1 H), 4.32 (s, 2 H), 4.04 (s, 1 H), 3.28−3.23 (m, 1 H), 3.12−3.07 (m, 2 H), 2.97−2.89 (m, 8 H), 2.32−2.18 (m, 2 H), 1.61−1.52 (m, 1 H), 1.29 (t, J = 7.2 Hz, 3 H); MS (ESI) m/z 540.2 (M + H).

*(4S,4aS,5aR,14aS)-10-[(Cyclopropylamino)methyl]-4-(dimethylamino)-7-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19c-2**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1 H), 8.08 (d, J = 8.7 Hz, 1 H), 7.86 (d, J = 8.7 Hz, 1 H), 4.53 (s, 2 H), 4.10 (s, 1 H), 3.38 (dd, J = 4.6, 15.6 Hz, 1 H), 3.12−2.97 (m, 8 H), 2.88−2.83 (m, 1 H), 2.40 (t, J = 14.2 Hz, 1 H), 2.28−2.24 (m, 1 H), 1.72−1.62 (m, 1 H), 0.97−0.91 (m, 4 H); MS (ESI) m/z 552.35 (M + H).

*(4S,4aS,5aR,14aS)-10-[(tert-Butylamino)methyl]-4-(dimethylamino)-7-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19c-3**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.60 (s, 1 H), 8.08 (d, J = 8.7 Hz, 1 H), 7.88 (dd, J = 1.8, 8.7 Hz, 1 H), 4.42 (s, 2 H), 4.12 (s, 1 H), 3.38 (dd, J = 4.1, 14.6 Hz, 1 H), 3.12−2.98 (m, 8 H), 2.88−2.83 (m, 1 H), 2.39 (t, J = 14.2 Hz, 1 H), 2.28 (ddd, J = 2.8, 5.0, 13.7 Hz, 1 H), 1.72−1.63 (m, 1 H), 1.51 (s, 9 H); MS (ESI) m/z 568.41 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-[(dimethylamino)methyl]-7-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19c-4**).* ^{1}H NMR (400 MHz, CD_3OD)

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δ 8.53 (s, 1 H), 8.03 (d, *J* = 8.4 Hz, 1 H), 7.83 (d, *J* = 8.4 Hz, 1 H), 4.55−4.48 (m, 2 H), 4.09 (s, 1 H), 3.34−3.25 (m, 1 H), 3.07−2.94 (m, 8 H), 2.88 (s, 3 H), 2.87 (s, 3 H), 2.36−2.23 (m, 2 H), 1.67−1.55 (m, 1 H); MS (ESI) *m*/*z* 540.3 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-7-fluoro-10-[(3-fluoroazetidin-1-yl)methyl]-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19c-6**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.57−8.54 (m, 1 H), 8.07 (d, *J* = 8.7 Hz, 1 H), 7.88−7.82 (m, 1 H), 5.55−5.34 (m, 1 H), 4.73−4.30 (m, 6 H), 4.12 (s, 1 H), 3.37 (dd, *J* = 4.1, 15.6 Hz, 1 H), 3.13−2.97 (m, 8 H), 2.38 (t, *J* = 14.6 Hz, 1 H), 2.28 (ddd, *J* = 2.8, 5.0, 13.7 Hz, 1 H), 1.72−1.62 (m, 1 H); MS (ESI) *m*/*z* 570.36 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-7-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-10-(pyrrolidin-1-ylmethyl)-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19c-7**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.61 (s, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.92 (d, *J* = 8.8 Hz, 1 H), 4.63 (s, 2 H), 4.14 (s, 1 H), 3.55−3.41 (m, 2 H), 3.36−3.33 (m, 1 H), 3.28−3.00 (m, 10 H), 2.44−2.21 (m, 4 H), 2.19−2.05 (m, 2 H), 1.74−1.61 (m, 1 H); MS (ESI) *m*/*z* 566.1 (M + H).

*Phenyl 7-Bromo-1-methoxy-3-methyl-4-nitronaphthalene-2-carboxylate (**20**).* A mixture of freshly mixed nitric acid (68−70%) and concentrated sulfuric acid (4:5 v/v, 0.6 mL) was added dropwise to a solution of compound **13** (2.74 g, 7.38 mmol, 1.0 equiv) in methylene chloride (25 mL) at 0 °C. The resulting yellow solution was stirred at 0 °C for 25 min. Additional nitric acid (68−70%) and concentrated sulfuric acid (4:5 v/v, 0.66 mL) were added dropwise. The reaction mixture was stirred at 0 °C for 1.5 h and neutralized with 6 N aqueous sodium hydroxide (5.5 mL). Saturated aqueous sodium bicarbonate (100 mL) was added. The organic layer was separated, and the aqueous layer was extracted with methylene chloride (80 mL × 2). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing the title compound **20** as a light yellow solid: ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 7.72 (d, *J* = 8.7 Hz, 1 H), 7.55 (d, *J* = 8.7 Hz, 1 H), 7.44−7.42 (m, 2 H), 7.30−7.28 (m, 1 H), 7.24−7.22 (m, 2 H), 4.09 (s, 3 H), 2.48 (s, 3 H).

Phenyl 4-Amino-7-bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate. A solution of BBr_3 in methylene chloride (1.0 M, 14.8 mL, 14.8 mmol, 2.0 equiv) was added slowly over 7 min to a solution of phenyl 7-bromo-1-methoxy-3-methyl-4-nitronaphthalene-2-carboxylate (**20**) in methylene chloride (74 mL) at −70 °C. The resulting red solution was allowed to warm to −45 °C in 2 h and was poured into saturated aqueous sodium bicarbonate (200 mL). The mixture was stirred at rt for 30 min and extracted with methylene chloride (300 mL × 2). The aqueous layer was further extracted with ethyl acetate (150 mL × 2). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered through a short plug of silica gel, and the filtrate was concentrated, providing the crude product as a yellow solid (2.62 g).

Zinc dust (1.93 g, 29.52 mmol, 4.0 equiv) was added slowly to a solution of the above intermediate in a mixture of THF (30 mL) and acetic acid (6 mL) in one portion at 0 °C. The mixture was stirred vigorously for 60 h at rt. The reaction mixture was filtered through a pad of Celite. The Celite cake was washed thoroughly with ethyl acetate. The filtrate was washed with saturated aqueous sodium bicarbonate (350 mL) and brine (100 mL). The organic phase was dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing the title compound as a yellow solid (2.73 g, quantitative).

*Phenyl 7-Bromo-1-[(tert-butoxycarbonyl)oxy]-4-(dimethylamino)-3-methyl-2-naphthoate (**14d**).* Formic acid (37 wt % in water, 0.78 mL, 10.5 mmol, 5.4 equiv), acetic acid (0.60 mL, 10.5 mmol, 5.4 equiv), and sodium triacetoxyborohydride (2.23 g, 10.5 mmol, 5.4 equiv) were added to a solution of phenyl 4-amino-7-bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate (730 mg, 1.96 mmol, 1.0 equiv) in acetonitrile (35 mL) and THF (20 mL). The reaction mixture was stirred at rt for 3.5 h and quenched by slowly adding saturated aqueous sodium bicarbonate (80 mL). The resulting clear mixture was extracted with ethyl acetate (50 mL × 3). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated to give the crude intermediate phenyl 7-bromo-1-hydroxy-4-(dimethylamino)-3-methyl-2-naphthoate (**27**).

$(Boc)_2O$ (470 mg, 2.16 mmol, 1.1 equiv), DIEA (0.61 mL, 3.50 mmol, 1.8 equiv), and DMAP (20 mg, 0.16 mmol, 0.08 equiv) were added to a solution of the above intermediate **27** in methylene chloride (35 mL). The reaction mixture was stirred for 1 h at rt, diluted with methylene chloride (100 mL), and washed with a mixture of brine and saturated aqueous sodium bicarbonate (1:1, 100 mL). The organic phase was separated and dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (1% → 5% ethyl acetate−hexanes) to afford compound **14d** as a yellow foamy solid (976 mg, quantitative, two steps): ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.14−8.10 (m, 2 H), 7.68−7.66 (m, 1 H), 7.52−7.55 (m, 2 H), 7.39−7.37 (m, 3 H), 3.05 (s, 6 H), 2.58 (s, 3 H), 1.57 (s, 9 H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]-oxy}-12,15-bis(dimethylamino)-9-formyl-5-hydroxy-4,6-dioxo-4,4a,-6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**16d**).* Compound **14d** (760 mg, 1.52 mmol, 2.0 equiv) was reacted with enone **8** (366 mg, 0.76 mmol, 1.0 equiv) according to General Procedure A to afford the cyclized product **15d** (430 mg, 64%) as a yellow solid, which was converted to compound **16d** according to General Procedure B (214 mg, 53%, yellow solid): R_f = 0.45 (35% ethyl acetate−hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.85 (br s, 1H), 10.17 (s, 1H), 8.60 (br s, 1H), 8.24 (d, *J* = 8.8 Hz, 1H), 8.06 (dd, *J* = 8.8, 1.2 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.2 Hz, 2H), 7.40−7.33 (m, 3H), 5.39 (d, *J* = 12.0 Hz, 1H), 5.35 (d, *J* = 12.0 Hz, 1H), 4.04 (d, *J* = 10.4 Hz, 1H), 3.36 (dd, *J* = 15.6, 4.0 Hz, 1H), 3.03 (br s, 6H), 3.08−2.97 (m, 1H), 2.71 (t, *J* = 15.2 Hz, 1H), 2.63−2.54 (m, 8H), 2.23 (d, *J* = 10.0 Hz, 1H), 1.61 (s, 9H), 0.86 (s, 9H), 0.30 (s, 3H), 0.17 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.7, 187.2, 182.5, 181.7, 167.5, 151.3, 145.3, 143.6, 138.4, 134.9, 134.4, 129.8, 128.5, 128.4, 127.3, 125.8, 125.4, 121.3, 108.3, 84.7, 81.7, 72.5, 61.0, 46.4, 43.2, 41.8, 35.7, 28.2, 27.6, 26.0, 22.7, 18.9, −2.6, −3.8; HRMS−ESI (*m*/*z*) $[M + H]^+$ calcd for $C_{46}H_{56}N_3O_{10}Si$, 838.3735; found, 838.3721.

*(4S,4aS,5aR,14aS)-4,7-Bis(dimethylamino)-3,12,14,14a-tetrahydroxy-10-[(methylamino)methyl]-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19d-1**).* Compound **16d** was subjected to reductive amination with methylamine (33 wt % in ethanol, 14 μL, 0.11 mmol, 7.0 equiv), desilylation, and hydrogenation according to General Procedures C, D, and E to yield compound **19d-1** as a yellow solid (4.4 mg, 41% for three steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.72 (br s, 1 H), 8.47 (br s, 1 H), 8.02 (br s, 1 H), 4.42 (br s, 2 H), 4.17 (br s, 1 H), 3.66−3.54 (m, 8 H), 3.26−3.20 (m, 1 H), 3.06−2.90 (m, 7 H), 2.77 (s, 3 H), 2.69 (m, 1 H), 2.42 (br s, 1 H), 1.70 (br s, 1 H); MS (ESI) *m*/*z* 551.45 (M + H).

The following compounds were prepared similarly from compound **16d** and the respective amines.

*(4S,4aS,5aR,14aS)-4,7-Bis(dimethylamino)-3,12,14,14a-tetrahydroxy-10-{[(2-methoxyethyl)amino]methyl}-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19d-2**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.65 (br s, 1 H), 8.37 (br s, 1 H), 7.94 (br s, 1 H), 4.37 (br s, 2 H), 4.08 (br s, 1 H), 3.59−3.45 (m, 10 H), 3.30 (s, 4 H), 2.96−2.86 (m, 8 H), 2.61 (m, 1 H), 2.34 (m, 1 H), 1.62 (m, 1 H); MS (ESI) *m*/*z* 595.48 (M + H).

*(4S,4aS,5aR,14aS)-4,7-Bis(dimethylamino)-10-[(dimethylamino)-methyl]-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19d-3**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (s, 1 H), 8.50 (br s, 1 H), 8.07 (br s, 1 H), 4.57 (s, 2

H), 4.18 (s, 1 H), 3.68−3.56 (m, 7 H), 3.06−2.90 (m, 14 H), 2.71−2.70 (m, 1 H), 2.43 (m, 1 H), 1.70 (m, 1 H); MS (ESI) *m/z* 565.54 (M + H).

*(4S,4aS,5aR,14aS)-4,7-Bis(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-10-(pyrrolidin-1-ylmethyl)-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19d-4**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.76 (s, 1 H), 8.45 (br s, 1 H), 8.08 (d, *J* = 6.4 Hz, 1 H), 4.62 (s, 2 H), 4.17 (s, 1 H), 3.63−3.51 (m, 10 H), 3.30−2.95 (m, 9 H), 2.69 (m, 1 H), 2.40 (m, 1 H), 2.18−2.01 (m, 4 H), 1.69 (m, 1 H); MS (ESI) *m/z* 591.56 (M + H).

Phenyl 7-Bromo-1-hydroxy-4-methoxy-3-methylnaphthalene-2-carboxylate. $PhI(OAc)_2$ (2.20 g, 6.84 mmol, 2.0 equiv) was added in one portion to a solution of phenyl 7-bromo-1-hydroxy-4-(dimethylamino)-3-methyl-2-naphthoate (**27**, 1.37 g, 3.42 mmol, 1.0 equiv) in a mixture of methanol (20 mL) and 1,4-dioxane (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 8 min. Acetic acid (4 mL) and zinc dust (1.34 g, 20.5 mmol, 6.0 equiv) were added at 0 °C. The reaction mixture was stirred at 0 °C for 10 min and filtered through a pad of Celite. The Celite cake was washed thoroughly with ethyl acetate. The filtrate was washed with 6 N aqueous sodium hydroxide (11 mL), saturated aqueous sodium bicarbonate (120 mL), and brine (50 mL). The organic phase was dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing the title compound as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.10 (s, 1 H), 8.06 (d, *J* = 9.2 Hz, 1 H), 8.02 (d, *J* = 1.8 Hz, 1 H), 7.63 (dd, *J* = 1.8, 9.2 Hz, 1 H), 7.42−7.38 (m, 2 H), 7.27−7.22 (m, 3 H), 2.63 (s, 3 H), 1.43 (s, 9 H); MS (ESI) *m/z* 385.21 (M − H).

*Phenyl 7-Bromo-1-[(tert-butoxycarbonyl)oxy]-4-methoxy-3-methyl-2-naphthoate (**14e**).* $(Boc)_2O$ (784 mg, 3.59 mmol, 1.05 equiv) and DMAP (12 mg, 0.10 mmol, 0.03 equiv) were added to a solution of phenyl 7-bromo-1-hydroxy-4-methoxy-3-methylnaphthalene-2-carboxylate in methylene chloride (30 mL). The mixture was stirred at rt for 25 min and concentrated. The residue was purified by flash column chromatography (5% → 10% ethyl acetate−hexanes) to afford the Boc-protected product **14e** (white solid, 1.33 g, 80%, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 1.8 Hz, 1 H), 7.94 (d, *J* = 8.7 Hz, 1 H), 7.62 (dd, *J* = 1.8, 8.7 Hz, 1 H), 7.43−7.39 (m, 2 H), 7.27−7.24 (m, 3 H), 3.84 (s, 3 H), 2.51 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 152.4, 151.3, 150.5, 140.5, 131.5, 129.5, 128.1, 127.8, 126.3, 125.3, 124.8, 124.7, 124.2, 121.6, 121.4, 84.6, 61.7, 27.5, 13.4.

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-9-bromo-4a-{[tert-butyl(dimethyl)-silyl]oxy}-15-(dimethylamino)-5-hydroxy-12-methoxy-4,6-dioxo-4,4a,-6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**15e**).* Compound **14e** (1.56 g, 3.20 mmol, 1.5 equiv) was reacted with enone **8** (1.03 g, 2.13 mmol, 1.0 equiv) according to General Procedure A to yield compound **15e** as a yellow solid (829 mg, 45%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.94 (br s, 1 H), 8.23 (br s, 1 H), 7.94 (d, *J* = 8.5 Hz, 1 H), 7.67 (dd, *J* = 2.4, 8.5 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.39−7.32 (m, 3 H), 5.37, 5.33 (ABq, *J* = 12.2 Hz, 2 H), 3.98 (d, *J* = 11.0 Hz, 1 H), 3.85 (s, 3 H), 3.48 (dd, *J* = 4.9, 15.3 Hz, 1 H), 3.06−2.98 (m, 1 H), 2.62−2.44 (m, 9 H), 2.20 (d, *J* = 14.0 Hz, 1 H), 1.58 (s, 9 H), 0.82 (s, 9 H), 0.27 (s, 3 H), 0.13 (s, 3 H); MS (ESI) *m/z* 875.55 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]-oxy}-15-(dimethylamino)-9-formyl-5-hydroxy-12-methoxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**16e**).* Compound **15e** (589 mg, 0.67 mmol, 1.0 equiv) was converted to compound **16e** according to General Procedure B (366 mg, 66%, yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.90 (br s, 1 H), 10.17 (s, 1 H), 8.58 (br s, 1 H), 8.18 (d, *J* = 8.5 Hz, 1 H), 8.08 (dd, *J* = 1.2, 8.5 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.39−7.32 (m, 3 H), 5.37, 5.33 (ABq, *J* = 12.2 Hz, 2 H), 3.97 (d, *J* = 11.0 Hz, 1 H), 3.89 (s, 3 H), 3.54 (dd, *J* = 4.3, 15.3 Hz, 1 H), 3.07−3.02 (m, 1 H), 2.67−2.45 (m, 9 H), 2.21 (d, *J* = 14.0 Hz, 1 H), 1.59 (s, 9 H), 0.82 (s, 9 H), 0.27 (s, 3 H), 0.13 (s, 3 H); MS (ESI) *m/z* 825.80 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-7-methoxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19e-6**).* Compound **16e** (273 mg, 0.33 mmol, 1.0 equiv) was subjected to reductive amination with azetidine (45 μL, 0.66 mmol, 2.0 equiv) to afford compound **17e-6** (MS (ESI) *m/z* 866.76 (M + H)), followed by desilylation and hydrogenation according to General Procedures C, D, and E to yield compound **19e-6** as a yellow solid (156 mg, 74%, three steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, *J* = 1.8 Hz, 1 H), 8.07 (d, *J* = 8.7 Hz, 1 H), 7.80 (dd, *J* = 1.8, 8.7 Hz, 1 H), 4.59 (s, 2 H), 4.27 (q, *J* = 10.0 Hz, 2 H), 4.17 (s, 1 H), 4.15−4.10 (m, 2 H), 3.79 (s, 3 H), 3.39 (dd, *J* = 4.1, 15.6 Hz, 1 H), 3.08−2.98 (m, 8 H), 2.63−2.56 (m, 1 H), 2.53−2.45 (m, 1 H), 2.37−2.30 (m, 2 H), 1.69−1.60 (m, 1 H); MS (ESI) *m/z* 564.42 (M + H).

The following compounds were prepared similarly from compound **16e** and the respective amines.

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-7-methoxy-1,13-dioxo-10-[(propylamino)methyl]-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19e-1**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, *J* = 1.8 Hz, 1 H), 8.11 (d, *J* = 8.7 Hz, 1 H), 7.81 (dd, *J* = 1.8, 8.7 Hz, 1 H), 4.40 (s, 2 H), 4.13 (s, 1 H), 3.81 (s, 3 H), 3.41 (dd, *J* = 4.1, 15.6 Hz, 1 H), 3.09−2.97 (m, 10 H), 2.38 (t, *J* = 13.7 Hz, 1 H), 2.28 (ddd, *J* = 2.8, 4.6, 13.7 Hz, 1 H), 1.82−1.74 (m, 2 H), 1.72−1.62 (m, 1 H), 1.04 (t, *J* = 7.3 Hz, 3 H); MS (ESI) *m/z* 566.42 (M + H).

*(4S,4aS,5aR,14aS)-10-[(Cyclopropylamino)methyl]-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-7-methoxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19e-2**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, *J* = 1.8 Hz, 1 H), 8.11 (d, *J* = 8.7 Hz, 1 H), 7.82 (dd, *J* = 1.8, 8.7 Hz, 1 H), 4.52 (s, 2 H), 4.13 (s, 1 H), 3.80 (s, 3 H), 3.41 (dd, *J* = 4.6, 15.6 Hz, 1 H), 3.06−2.97 (m, 8 H), 2.86−2.81 (m, 1 H), 2.38 (t, *J* = 13.7 Hz, 1 H), 2.30−2.25 (m, 1 H), 1.72−1.62 (m, 1 H), 0.94−0.92 (m, 4 H); MS (ESI) *m/z* 564.53 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-10-[(isobutylamino)methyl]-7-methoxy-1,13-dioxo-1,4,4a,5,5a,6,13,-14a-octahydropentacene-2-carboxamide (**19e-3**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (d, *J* = 1.8 Hz, 1 H), 8.12 (d, *J* = 8.7 Hz, 1 H), 7.81 (dd, *J* = 1.8, 8.7 Hz, 1 H), 4.41 (s, 2 H), 4.08 (s, 1 H), 3.81 (s, 3 H), 3.42 (dd, *J* = 4.1, 15.6 Hz, 1 H), 3.07−2.94 (m, 10 H), 2.41 (t, *J* = 13.7 Hz, 1 H), 2.29−2.24 (m, 1 H), 2.11−2.01 (m, 1 H), 1.73−1.64 (m, 1 H), 1.04 (d, *J* = 6.4 Hz, 6 H); MS (ESI) *m/z* 580.48 (M + H).

*(4S,4aS,5aR,14aS)-10-[(tert-Butylamino)methyl]-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-7-methoxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19e-4**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.59 (s, 1 H), 8.13 (d, *J* = 8.2 Hz, 1 H), 7.82 (d, *J* = 8.2 Hz, 1 H), 4.39 (s, 2 H), 4.12 (s, 1 H), 3.82 (s, 3 H), 3.42 (dd, *J* = 3.2, 15.6 Hz, 1 H), 3.05−2.97 (m, 8 H), 2.40 (t, *J* = 14.6 Hz, 1 H), 2.29−2.25 (m, 1 H), 1.73−1.63 (m, 1 H), 1.50 (s, 9 H); MS (ESI) *m/z* 580.64 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-[(dimethylamino)methyl]-3,12,14,14a-tetrahydroxy-7-methoxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19e-5**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.57 (s, 1 H), 8.14 (d, *J* = 8.7 Hz, 1 H), 7.81 (dd, *J* = 1.8, 8.7 Hz, 1 H), 4.52 (s, 2 H), 4.12 (s, 1 H), 3.82 (s, 3 H), 3.42 (dd, *J* = 4.1, 15.6 Hz, 1 H), 3.05−2.97 (m, 8 H), 2.91 (s, 6 H), 2.40 (dd, *J* = 13.7, 15.1 Hz, 1 H), 2.30−2.25 (m, 1 H), 1.73−1.63 (m, 1 H); MS (ESI) *m/z* 552.55 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-[(3-fluoroazetidin-1-yl)-methyl]-3,12,14,14a-tetrahydroxy-7-methoxy-1,13-dioxo-1,4,4a,5,5a,-6,13,14a-octahydropentacene-2-carboxamide (**19e-7**).* ^{1}H NMR (400 MHz, CD_3OD, TFA salt) δ 8.53 (d, *J* = 1.8 Hz, 1 H), 8.11 (d, *J* = 8.7 Hz, 1 H), 7.75 (dd, *J* = 1.8, 8.7 Hz, 1 H), 5.51−5.36 (m, 1 H), 4.65 (s, 2 H), 4.65−4.53 (m, 1 H), 4.42−4.34 (m, 1 H), 4.10 (s, 1 H), 3.80 (s, 3 H), 3.40 (dd, *J* = 4.1, 15.1 Hz, 1 H), 3.06−2.94 (m, 8 H), 2.38

(t, J = 15.1 Hz, 1 H), 2.28−2.24 (m, 1 H), 1.72−1.62 (m, 1 H); MS (ESI) m/z 582.38 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-7-methoxy-1,13-dioxo-10-(pyrrolidin-1-ylmethyl)-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**19e-8**).* ^{1}H NMR (400 MHz, CD_3OD) δ 8.58 (s, 1 H), 8.12 (d, J = 8.2 Hz, 1 H), 7.85 (d, J = 8.2 Hz, 1 H), 4.59 (s, 2 H), 4.12 (s, 1 H), 3.81 (s, 3 H), 3.56−3.51 (m, 2 H), 3.41 (dd, J = 4.1, 15.1 Hz, 1 H), 3.27−3.21 (m, 2 H), 3.06−2.97 (m, 8 H), 2.38 (t, J = 14.6 Hz, 1 H), 2.29−2.21 (m, 3 H), 2.05−2.02 (m, 2 H), 1.72−1.62 (m, 1 H); MS (ESI) m/z 578.59 (M + H).

*Phenyl 4-Amino-7-bromo-1-methoxy-3-methylnaphthalene-2-carboxylate (**21**).* Acetic acid (2 mL) and zinc dust (622 mg, 9.52 mmol, 4 equiv) were added to a solution of compound **20** (990 mg, 2.38 mmol, 1.0 equiv) in THF (10 mL) at rt. The reaction mixture was stirred at rt for 15 h. More zinc dust (311 mg, 4.76 mmol, 2 equiv) was added. The reaction mixture was stirred for another 5 h and filtered through a Celite pad. The Celite cake was washed with ethyl acetate. The filtrate was washed with saturated aqueous sodium bicarbonate and brine. The organic phase was dried over sodium sulfate and filtered. The filtrate was concentrated. The residue was purified by flash column chromatography (20% ethyl acetate−hexanes containing 10% methylene chloride) to afford the aniline product **21** (791 mg, 86%) as a yellow solid.

*Phenyl 4-[Allyl(tert-butoxycarbonyl)amino]-7-bromo-1-[(tert-butoxycarbonyl)oxy]-3-methyl-2-naphthoate (**23b**).* A solution of phenyllithium in di-*n*-butyl ether (1.8 M, 0.61 mL, 1.10 mmol, 1.2 equiv) was added dropwise to a solution of aniline **21** (354 mg, 0.92 mmol, 1.0 equiv) in THF (18 mL) at −78 °C. After 5 min, allylbromide (0.11 mL, 1.28 mmol, 1.4 equiv) was added dropwise at −78 °C. The reaction mixture was allowed to warm up to rt over 1 h 40 min, and saturated aqueous ammonium chloride was added. The resulting mixture was stirred for 5 min and extracted with ethyl acetate (40 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate and filtered. The filtrate was concentrated, and the residue was purified by flash column chromatography (0% → 5% ethyl acetate/hexanes) to afford the monoallyl intermediate (325 mg, 83%) as a colorless solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (d, J = 1.8 Hz, 1 H), 7.99 (d, J = 9.2 Hz, 1 H), 7.60 (dd, J = 1.8, 9.2 Hz, 1 H), 7.49−7.44 (m, 2 H), 7.32−7.28 (m, 3 H), 6.11−6.01 (m, 1 H), 5.39−5.34 (m, 1 H), 5.21−5.18 (m, 1 H), 4.06 (s, 3 H), 3.69 (dt, J = 6.0, 1.4 Hz, 2 H), 2.49 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 150.6, 148.5, 139.7, 136.0, 130.4, 129.7, 129.3, 128.2, 126.3, 126.2, 125.6, 125.1, 123.4, 121.5, 120.3, 116.4, 63.8, 53.0, 15.1.

A solution of BBr_3 in methylene chloride (1.0 M, 0.61 L, 0.61 mmol, 2.0 equiv) was added dropwise to a solution of the above monoallyl intermediate (130 mg, 0.30 mmol, 1.0 equiv) in methylene chloride (3 mL) at −30 °C. The resulting yellow solution was stirred between −30 to −25 °C for 1.5 h and was poured into saturated aqueous sodium bicarbonate. The mixture was warmed to rt and extracted with methylene chloride (25 mL × 3). The organic extracts were combined, dried over anhydrous sodium sulfate, and filtered. The filtrate was concentrated to give the crude product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.77 (s, 1 H), 8.58 (d, J = 1.8 Hz, 1 H), 7.94 (d, J = 9.2 Hz, 1 H), 7.71 (dd, J = 1.8, 9.2 Hz, 1 H), 7.50−7.46 (m, 2 H), 7.36−7.32 (m, 1 H), 7.26−7.23 (m, 2 H), 6.13−6.03 (m, 1 H), 5.39−5.34 (m, 1 H), 5.21−5.18 (m, 1 H), 3.60 (dt, J = 5.5, 1.4 Hz, 2 H), 2.73 (s, 3 H).

$(Boc)_2O$ (96 mg, 0.44 mmol, 2.0 equiv) and DMAP (3 mg, 0.02 mmol, 0.1 equiv) were added to a solution of the above intermediate in DMF (1 mL). The reaction was stirred at rt overnight, diluted with ethyl acetate (50 mL), and washed with water (30 mL × 4). The organic phase was dried over anhydrous sodium sulfate. The dried solution was filtered and concentrated. The residue was purified by flash column chromatography (5% → 7% ethyl acetate−hexanes) to afford compound **23b** (colorless oil, 88 mg, 47%, two steps, 3:1 rotamers): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (m, 1 H), 7.68−7.67 (m, 2 H), 7.49−7.45 (m, 2 H), 7.34−7.28 (m, 3 H), 6.02−5.90 (m, 1 H), 5.09−5.04 (m, 2 H), 4.21 (d, J = 6.9 Hz, 1.5 H), 4.12 (d, J = 6.9 Hz, 1 H), 2.49 (s, 0.75 H), 2.48 (s, 2.25 H), 1.57 (s, 2.25 H), 1.48 (s, 9 H), 1.25 (s, 6.75 H).

*Phenyl 7-Bromo-4-(diallylamino)-1-methoxy-3-methyl-2-naphthoate (**22**).* A solution of phenyllithium in di-*n*-butyl ether (1.8 M, 0.35 mL, 0.64 mmol, 1.2 equiv) was added dropwise to a solution of aniline **21** (206 mg, 0.53 mmol, 1.0 equiv) in THF (10 mL) at −78 °C. After 3 min, allylbromide (0.16 mL, 1.86 mmol, 1.5 equiv) was added dropwise at −78 °C. The reaction mixture was allowed to warm up to rt over 30 min. The reaction was recooled to −78 °C. Additional phenyllithium in di-*n*-butyl ether (0.35 mL, 1.8 M/di-*n*-butyl ether, 0.636 mmol, 1.2 equiv) and allylbromide (0.16 mL, 1.86 mmol, 1.5 equiv) were added. The reaction was allowed to warm to rt over 40 min and quenched with saturated aqueous ammonium chloride. The mixture was stirred for 5 min and extracted with ethyl acetate (40 mL × 3). The organic extracts were combined and dried over anhydrous sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue was purified by flash column chromatography (0% → 2% ethyl acetate/hexanes) to afford the diallyl compound **22** (205 mg, 82%) as a pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 1.8 Hz, 1 H), 8.06 (d, J = 9.2 Hz, 1 H), 7.60 (dd, J = 1.8, 9.2 Hz, 1 H), 7.49−7.44 (m, 2 H), 7.32−7.28 (m, 3 H), 5.82−5.91 (m, 2 H), 5.14−5.04 (m, 4 H), 4.06 (s, 3 H), 3.84−3.75 (m, 4 H), 2.51 (s, 3 H).

*Phenyl 7-Bromo-1-[(tert-butoxycarbonyl)oxy]-4-(diallylamino)-3-methyl-2-naphthoate (**23c**).* A solution of BBr_3 in methylene chloride (1.0 M, 2.22 mL, 2.22 mmol, 2.0 equiv) was added dropwise to a solution of compound **22** (517 mg, 1.11 mmol, 1.0 equiv) in methylene chloride (11 mL) at −40 °C. The resulting light orange suspension was stirred between −40 and −30 °C for 1 h and was poured into saturated aqueous sodium bicarbonate. The mixture was warmed to rt and stirred for 30 min. The mixture was extracted with methylene chloride (60 mL × 3). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered and concentrated. The crude product was used directly for the next reaction.

$(Boc)_2O$ (291 mg, 1.33 mmol, 1.2 equiv), DIEA (0.23 mL, 1.33 mmol, 1.2 equiv), and DMAP (16 mg, 0.13 mmol, 0.1 equiv) were added to a solution of the above intermediate in methylene chloride (20 mL). The mixture was stirred at rt for 20 min and concentrated. The residue was purified by flash column chromatography (0% → 5% ethyl acetate−hexanes) to afford compound **23c** (pale yellow solid, 280 mg, 46%, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 9.2 Hz, 1 H), 8.02 (d, J = 1.8 Hz, 1 H), 7.62 (dd, J = 1.8, 9.2 Hz, 1 H), 7.47−7.43 (m, 2 H), 7.31−7.27 (m, 3 H), 5.90−5.80 (m, 2 H), 5.15−5.04 (m, 4 H), 2.54 (s, 3 H), 1.48 (s, 9 H).

*Phenyl 7-Bromo-4-[(tert-butoxycarbonyl)(methyl)amino]-1-[(tert-butoxycarbonyl)oxy]-3-methyl-2-naphthoate (**23a**).* Phenyl 4-amino-7-bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate (2.0 g, 5.37 mmol, 1.0 eq, crude) was dissolved in DMF (30 mL). $(Boc)_2O$ (2.34 g, 10.75 mmol, 2.0 equiv) and DMAP (30 mg, 0.24 mmol, 0.04 equiv) were added. The brownish reaction mixture was stirred at rt for 3.5 h. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with brine (150 mL × 3). The organic phase was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. TLC analysis indicated incomplete reaction. The residue was then redissolved in DMF (30 mL). $(Boc)_2O$ (2.34 g, 10.75 mmol, 2.0 equiv) and DMAP (20 mg, 0.16 mmol, 0.03 equiv) were added. The mixture was stirred at rt for 42 h. The reaction mixture was diluted with ethyl acetate (300 mL) and washed with water (200 mL × 2) and brine (200 mL). The organic phase was dried over magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (15% → 25% ethyl acetate−hexanes) to afford the tri-Boc-protected product (white solid, 1.24 g, 34%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (t, J = 1.4 Hz, 1 H), 7.69 (d, J = 1.4 Hz, 2 H), 7.47−7.43 (m, 2 H), 7.32−7.25 (m, 3 H), 2.47 (s, 3 H), 1.46 (s, 9 H), 1.32 (s, 18 H).

TFA (0.71 mL, 9.22 mmol, 5.0 equiv) was added to a solution of the above tri-Boc-protected compound (1.24 g, 1.84 mmol, 1.0 equiv) in methylene chloride (60 mL) at 0 °C. The solution was stored in a refrigerator (4 °C) overnight. Saturated aqueous sodium bicarbonate was added slowly at 0 °C, and the mixture was warmed to rt. The mixture was extracted with methylene chloride (50 mL × 3). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing the *O*-Boc and *N*-mono-Boc intermediate as a white foamy solid.

The above crude compound was dissolved in THF (30 mL). A solution of LHMDS in THF (1.0 M, 2.76 mL, 2.76 mmol, 1.5 equiv) was added dropwise to the reaction at −78 °C. The resulting orange mixture was stirred at −78 °C for 20 min. Iodomethane (0.23 mL, 3.68 mmol, 2.0 equiv) was added slowly. The reaction mixture was slowly warmed to rt and stirred overnight. Saturated ammonium chloride was added. The reaction mixture was extracted with ethyl acetate (100 mL × 1, 50 mL × 2). The organic extracts were combined and dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash column chromatography (10% → 20% ethyl acetate−hexanes) to give compound **23a** (6.5:1 rotamers, yellow foamy solid, 724 mg, 67%, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06−8.05(m, 1 H), 7.66−7.59 (m, 2 H), 7.42−7.36 (m, 2 H), 7.26−7.21 (m, 3 H), 3.15 (s, 2.6 H), 3.147 (s, 0.4 H), 2.43 (s, 2.6 H), 2.427 (s, 0.4 H), 1.42 (s, 9 H), 1.38 (s, 1.2 H), 1.21 (s, 7.8 H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-9-bromo-12-[(tert-butoxycarbonyl)(methyl)amino]-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno-[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**24a**).* Compound **23a** (772 mg, 1.32 mmol, 2.0 equiv) was reacted with enone **8** (318 mg, 0.66 mmol, 1.0 equiv) according to General Procedure A to yield compound **24a** (560 mg, 87%, a mixture of rotamers) as a yellow solid: ^{1}H NMR of the major rotamer (400 MHz, $CDCl_3$) δ 15.82 (br s, 1 H), 8.29 (br s, 1 H), 7.74 (dd, J = 1.8, 8.5 Hz, 1 H), 7.64 (dd, J = 8.5 Hz, 1 H), 7.55−7.51 (m, 2 H), 7.42−7.35 (m, 3 H), 5.36, 5.39 (ABq, J = 12.2 Hz, 2 H), 3.93 (d, J = 10.7 Hz, 1 H), 3.15 (s, 3 H), 3.12−3.09 (m, 1 H), 3.04−2.98 (m, 1 H), 2.62−2.46 (m, 9 H), 2.19−2.15 (m, 1 H), 1.61 (s, 9 H), 1.27 (s, 9 H), 0.82 (s, 9 H), 0.28 (s, 3 H), 0.15 (s, 3 H); MS (ESI) m/z 974.62 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-12-[(tert-butoxycarbonyl)(methyl)-amino]-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-9-formyl-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**25a**).* Compound **24a** (93 mg, 0.096 mmol, 1.0 equiv) was converted to compound **25a** according to General Procedure B. The crude product was purified by preparative reverse-phase HPLC (45 mg, 51%, a mixture of rotamers, yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.84, 15.97 (s, 1 H), 10.21, 10.19 (s, 1 H), 8.69, 8.65 (s, 1 H), 8.16−8.14 (m, 1 H), 7.90−7.84 (m, 1 H), 7.53−7.50 (m, 2 H), 7.42−7.35 (m, 3 H), 5.38 (s, 2 H), 4.02, 3.99 (d, J = 10.4 Hz, 1 H), 3.28, 3.19 (s, 3 H), 3.28−2.99 (m, 2 H), 2.68−2.49 (m, 9 H), 2.18−2.14 (m, 1 H), 1.62, 1.61 (s, 9 H), 1.27, 1.24 (s, 9 H), 0.85, 0.82 (s, 9 H), 0.26, 0.25 (s, 3 H), 0.16 (s, 3 H); MS (ESI) m/z 924.68 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-7-(methylamino)-1,13-dioxo-1,4,4a,5,5a,6,-13,14a-octahydropentacene-2-carboxamide (**26a**).* Compound **25a** was subjected to reductive amination with azetidine, followed by desilylation and hydrogenation according to general procedures C, D, and E to yield compound **26a** (23% over three steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.68 (br s, 1 H), 8.17 (br d, J = 7.3 Hz, 1 H), 8.01 (br s, J = 7.3 Hz, 1 H), 4.62 (br s, 2 H), 4.27−4.25 (m, 2 H), 4.17−4.12 (m, 3 H), 3.20−2.98 (m, 12 H), 2.60−2.38 (m, 4 H), 1.62−1.72 (m, 1 H); MS (ESI) m/z 563.50 (M + H).

*(4aS,13aR,14aS,15S)-12-[Allyl(tert-butoxycarbonyl)amino]-3-(benzyloxy)-9-bromo-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**24b**).* Prepared from compound **23b** according to General Procedure A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.90, 15.82 (s, 1 H), 8.32−8.26 (m, 1 H), 7.74−7.69 (m, 1 H), 7.65−7.62 (m, 1 H), 7.52−7.50 (m, 2 H), 7.41−7.33 (m, 3 H), 6.04−5.87 (m, 1 H), 5.40−5.34 (m, 2 H), 5.09−4.95 (m, 2 H), 4.56−4.45 (m, 1 H), 3.96−3.81 (m, 2 H), 3.22−3.09 (m, 1 H), 3.01−2.91 (m, 1 H), 2.62−2.35 (m, 9 H), 2.19−2.10 (m, 1 H), 1.61, 1.60 (s, 9 H), 1.27, 1.26 (s, 9 H), 0.84, 0.81 (s, 9 H), 0.29, 0.28 (s, 3 H), 0.15, 0.14 (s, 3 H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-9-bromo-4a-{[tert-butyl(dimethyl)silyl]oxy}-12-(diallylamino)-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**24c**).* Prepared from compound **23c** according to General Procedure A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.88 (br s, 1 H), 8.25 (br s, 1 H), 7.80 (d, J = 9.2 Hz, 1 H), 7.66 (dd, J = 1.8, 9.2 Hz, 1 H), 7.52−7.50 (m, 2 H), 7.41−7.34 (m, 3 H), 5.96−5.89 (m, 1 H), 5.79−5.72 (m, 1 H), 5.36 (s, 2 H), 5.19−4.99 (m, 4 H), 4.00 (d, J = 10.4 Hz, 1 H), 3.86−3.67 (m, 4 H), 3.45 (dd, J = 4.3, 15.3 Hz, 1 H), 3.00−2.92 (m, 1 H), 2.62−2.48 (m, 9 H), 2.18 (d, J = 14.6 Hz, 1 H), 1.60 (s, 9 H), 1.26 (s, 9 H), 0.85 (s, 9 H), 0.29 (s, 3 H), 0.15 (s, 3 H).

*(4aS,13aR,14aS,15S)-12-[Allyl(tert-butoxycarbonyl)amino]-3-(benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-9-formyl-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**25b**).* Prepared from compound **24b** according to General Procedure B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.86, 15.79 (s, 1 H), 10.21, 10.19 (s, 1 H), 8.66−8.62 (m, 1 H), 8.14−8.10 (m, 1 H), 7.90−7.81 (m, 1 H), 7.52−7.50 (m, 2 H), 7.41−7.30 (m, 3 H), 6.05−5.87 (m, 1 H), 5.41−5.32 (m, 2 H), 5.10−4.95 (m, 2 H), 4.60−4.48 (m, 1 H), 4.06−3.84 (m, 2 H), 3.28−3.15 (m, 1 H), 3.04−2.94 (m, 1 H), 2.76−2.44 (m, 9 H), 2.21−2.12 (m, 1 H), 1.62, 1.61 (s, 9 H), 1.27, 1.26 (s, 9 H), 0.84, 0.82 (s, 9 H), 0.29, 0.28 (s, 3 H), 0.16, 0.14 (s, 3 H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]-oxy}-12-(diallylamino)-15-(dimethylamino)-9-formyl-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**25c**).* Prepared from compound **24c** according to General Procedure B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.85 (br s, 1 H), 10.18 (s, 1 H), 8.61 (br s, 1 H), 8.23 (d, J = 8.5 Hz, 1 H), 8.07 (dd, J = 1.2, 8.5 Hz, 1 H), 7.52−7.50 (m, 2 H), 7.41−7.34 (m, 3 H), 5.99−5.89 (m, 1 H), 5.83−5.73 (m, 1 H), 5.39, 5.35 (ABq, J = 12.2 Hz, 2 H), 5.20−5.01 (m, 4 H), 4.00 (d, J = 10.4 Hz, 1 H), 3.94−3.71 (m, 4 H), 3.52 (dd, J = 4.3, 15.9 Hz, 1 H), 3.02−2.97 (m, 1 H), 2.67−2.46 (m, 9 H), 2.20 (d, J = 14.0 Hz, 1 H), 1.61 (s, 9 H), 0.86 (s, 9 H), 0.30 (s, 3 H), 0.16 (s, 3 H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-7-(propylamino)-1,4,4a,5,5a,6,-13,14a-octahydropentacene-2-carboxamide (**26b**).* Prepared from compound **25b** according to General Procedures C, D, and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.69 (d, J = 1.4 Hz, 1 H), 8.14 (dd, J = 1.4, 8.7 Hz, 1 H), 8.00 (d, J = 8.7 Hz, 1 H), 4.63 (br s, 2 H), 4.31−4.24 (m, 2 H), 4.16−4.12 (m, 3 H), 3.63−2.98 (m, 11 H), 2.68−2.34 (m, 4 H), 1.94−1.86 (m, 2 H), 1.72−1.42 (m, 1 H), 1.06−1.00 (m, 3 H); MS (ESI) m/z 591.47 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-7-(dipropylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,-6,13,14a-octahydropentacene-2-carboxamide (**26c**).* Prepared from compound **25c** according to General Procedures C, D, and E: ^{1}H NMR (400 MHz, D_2O) δ 8.35 (br s, 1 H), 8.05 (d, J = 8.2 Hz, 1 H), 7.61 (d, J = 8.2 Hz, 1 H), 4.31 (br s, 2 H), 3.98−3.86 (m, 5 H), 3.58−3.40 (m, 2 H), 3.12 (dd, J = 3.7, 15.6 Hz, 1 H), 2.96−2.85 (m, 2 H), 2.76 (s, 3 H), 2.72−2.71 (m, 2 H), 2.67 (s, 3 H), 2.42−2.26 (m, 2 H), 2.22−2.14 (m, 1 H), 2.06−2.00 (m, 1 H), 1.52−1.43 (m, 1 H), 1.34−1.18 (m, 2 H),

1.06−0.80 (m, 2 H), 0.55 (t, J = 7.3 Hz, 3 H), 0.42 (t, J = 7.1 Hz, 3 H); MS (ESI) m/z 633.50 (M + H).

*Phenyl 4-(Allyloxy)-7-bromo-1-[(tert-butoxycarbonyl)oxy]-3-methyl-2-naphthoate (**28**).* $PhI(OAc)_2$ (2.58 g, 8.00 mmol, 2.0 equiv) was added in one portion to a solution of **27** (1.60 g, 4.00 mmol, 1.0 equiv) in a mixture of allylalcohol (20 mL) and 1,4-dioxane (20 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min. Acetic acid (4 mL) and zinc dust (1.57 g, 24.0 mmol, 6.0 equiv) were added at 0 °C. The reaction mixture was stirred at 0 °C for 25 min and filtered through a pad of Celite. The Celite cake was washed thoroughly with ethyl acetate. The filtrate was washed with 6 N aqueous sodium hydroxide (11 mL), saturated aqueous sodium bicarbonate (120 mL), and brine (50 mL). The organic phase was dried over anhydrous magnesium sulfate. The dried solution was filtered, and the filtrate was concentrated, providing the allyloxy intermediate as an orange solid.

$(Boc)_2O$ (917 mg, 4.20 mmol, 1.05 equiv) and DMAP (catalytic amount) were added to a solution of the above intermediate in methylene chloride (40 mL). The mixture was stirred for 10 min at rt and concentrated. The residue was purified by flash column chromatography (1% → 4% ethyl acetate−hexanes) to afford compound **28** (white solid, 1.64 g, 80%, two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (s, 1 H), 7.92 (d, J = 8.7 Hz, 1 H), 7.60 (dd, J = 1.8, 8.7 Hz, 1 H), 7.42−7.38 (m, 2 H), 7.26−7.18 (m, 3 H), 6.16−6.07 (m, 1 H), 5.46 (d, J = 17.4 Hz, 1 H), 5.28 (d, J = 10.5 Hz, 1 H), 4.41 (d, J = 5.5 Hz, 2 H), 2.50 (s, 3 H), 1.43 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 151.3, 151.2, 150.4, 140.5, 133.1, 131.4, 129.5, 128.3, 127.7, 126.3, 125.2, 125.0, 124.6, 124.3, 121.6, 121.4, 118.0, 84.5, 75.0, 27.4, 13.7.

*(4aS,13aR,14aS,15S)-12-(Allyloxy)-3-(benzyloxy)-9-bromo-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**29**).* Compound **28** (150 mg, 0.29 mmol, 1.5 equiv) was reacted with enone **8** (94 mg, 0.19 mmol, 1.0 equiv) according to General Procedure A to give compound **29** as a yellow solid (83 mg, 47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.93 (br s, 1 H), 8.23 (br s, 1 H), 7.92 (d, J = 9.2 Hz, 1 H), 7.67 (dd, J = 1.8, 9.2 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.39−7.30 (m, 3 H), 6.20−6.10 (m, 1 H), 5.45 (dd, J = 1.2, 15.1 Hz, 1 H), 5.38−5.32 (m, 3 H), 4.47−4.38 (m, 2 H), 3.96 (d, J = 11.0 Hz, 1 H), 3.49 (dd, J = 4.3, 15.3 Hz, 1 H), 3.03−2.98 (m, 1 H), 2.60−2.44 (m, 9 H), 2.17 (d, J = 14.6 Hz, 1 H), 1.58 (s, 9 H), 0.81 (s, 9 H), 0.26 (s, 3 H), 0.12 (s, 3 H); MS (ESI) m/z 901.77 (M + H).

*(4aS,13aR,14aS,15S)-12-(Allyloxy)-9-(azetidin-1-ylmethyl)-3-(benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno-[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**30**).* Compound **29** (769 mg, 0.85 mmol, 1.0 equiv) was converted to the corresponding aldehyde according to General Procedure B (519 mg, 72%, yellow solid): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.90 (br s, 1 H), 10.16 (s, 1 H), 8.58 (br s, 1 H), 8.17 (d, J = 8.5 Hz, 1 H), 8.07 (dd, J = 1.2, 8.5 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.39−7.30 (m, 3 H), 6.22−6.12 (m, 1 H), 5.48 (dd, J = 1.2, 17.1 Hz, 1 H), 5.38−5.32 (m, 3 H), 4.51−4.45 (m, 2 H), 3.98 (d, J = 10.4 Hz, 1 H), 3.55 (dd, J = 4.3, 15.3 Hz, 1 H), 3.08−3.00 (m, 1 H), 2.65−2.45 (m, 3 H), 2.51 (s, 6 H), 2.19 (d, J = 14.6 Hz, 1 H), 1.60 (s, 9 H), 0.82 (s, 9 H), 0.27 (s, 3 H), 0.13 (s, 3 H); MS (ESI) m/z 851.67 (M + H).

The above aldehyde intermediate was then subjected to reductive amination with azetidine according to General Procedure C to yield compound **30** as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.02 (br s, 1 H), 8.00 (d, J = 8.5 Hz, 1 H), 7.91 (br s, 1 H), 7.57 (d, J = 8.5 Hz, 1 H), 7.49−7.48 (m, 2 H), 7.38−7.30 (m, 3 H), 6.21−6.12 (m, 1 H), 5.46 (d, J = 17.1 Hz, 1 H), 5.38−5.27 (m, 3 H), 4.43 (d, J = 5.5 Hz, 2 H), 3.98 (d, J = 11.0 Hz, 1 H), 3.72 (q, J = 12.8 Hz, 2 H), 3.50 (dd, J = 4.3, 15.3 Hz, 1 H), 3.23 (t, J = 7.3 Hz, 4 H), 3.01−2.96 (m, 1 H), 2.62−2.43 (m, 3 H), 2.49 (s, 6 H), 2.17 (d, J = 14.0 Hz, 1 H), 2.08 (p, J = 7.3 Hz, 2 H), 1.58 (s, 9 H), 0.81 (s, 9 H), 0.26 (s, 3 H), 0.12 (s, 3 H); MS (ESI) m/z 892.83 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-7-propoxy-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**31**).* Prepared from compound **30** by desilylation and hydrogenation according General Procedure D and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (br s, 1 H), 8.11 (d, J = 8.7 Hz, 1 H), 7.75 (d, J = 8.7 Hz, 1 H), 4.56 (s, 2 H), 4.26 (q, J = 9.6 Hz, 2 H), 4.12−4.10 (m, 3 H), 3.85−3.79 (m, 2 H), 3.42 (dd, J = 4.1, 15.6 Hz, 1 H), 3.12−2.96 (m, 8 H), 2.62−2.55 (m, 1 H), 2.52−2.47 (m, 1 H), 2.40 (t, J = 14.6 Hz, 1 H), 2.28−2.24 (m, 1 H), 1.94−1.85 (m, 2 H), 1.73−1.63 (m, 1 H), 1.31 (t, J = 7.8 Hz, 3 H); MS (ESI) m/z 592.42 (M + H).

*(4aS,13aR,14aS,15S)-9-(Azetidin-1-ylmethyl)-3-(benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5,12-dihydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**32**).* A mixture of crude product **30** (0.33 mmol, 1.0 equiv), $Pd(PPh_3)_4$ (7.6 mg, 0.0066 mmol, 0.02 equiv) and *N*,*N*-dimethylbarbituric acid (256 mg, 1.64 mmol, 5.0 equiv) was dissolved in degassed methylene chloride (8 mL) under nitrogen. The resulting orange solution was stirred at rt for 1 h and diluted with saturated aqueous sodium bicarbonate. The mixture was extracted with methylene chloride (15 mL × 3). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by preparative reverse-phase HPLC. Fractions with the desired MW were collected and concentrated at rt under reduced pressure. The residue was neutralized with saturated aqueous sodium bicarbonate and extracted with methylene chloride (15 mL × 3). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to afford the desired product **32** as an orange solid (263 mg, 86% over two steps): ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.05 (br s, 1 H), 7.81 (br s, 1 H), 7.68−7.65 (m, 1 H), 7.49−7.47 (m, 2 H), 7.38−7.29 (m, 3 H), 7.12−7.10 (m, 1 H), 5.32, 5.35 (ABq, J = 12.2 Hz, 2 H), 3.97 (d, J = 11.0 Hz, 1 H), 3.67 (s, 2 H), 3.44−3.41 (m, 1 H), 3.32 (t, J = 7.3 Hz, 4 H), 3.05−3.00 (m, 1 H), 2.55−2.42 (m, 3 H), 2.46 (s, 6 H), 2.16−2.10 (m, 3 H), 1.58 (s, 9 H), 0.81 (s, 9 H), 0.26 (s, 3 H), 0.12 (s, 3 H); MS (ESI) m/z 852.94 (M + H).

*(6aR,7aS,8S,11aS)-10-(Aminocarbonyl)-2-(azetidin-1-ylmethyl)-8-(dimethylamino)-9,11a,12,14-tetrahydroxy-11,13-dioxo-6,6a,7,7a,8,-11,11a,13-octahydropentacen-5-yl Methylcarbamate (**33a**).* 2,6-Lutidine (6.3 μL, 0.055 mmol, 3.0 equiv) and methylisocyanate (3.2 μL, 0.055 mmol, 3.0 equiv) were added to a solution of compound **32** (16 mg, 0.018 mmol, 1.0 equiv) in methylene chloride (1 mL) at rt. The reaction mixture was stirred at rt for 1 h. Additional methylisocyanate (5.0 μL, 0.085 mmol, 4.7 equiv) was added. The reaction mixture was stirred at rt for 3 h, diluted with saturated aqueous sodium bicarbonate (10 mL) and potassium phosphate buffer solution (pH 7.0, 10 mL), and extracted with methylene chloride (15 mL × 3). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to give the carbamate intermediate (MS (ESI) m/z 909.86 (M + H)), which was subjected to desilylation and hydrogenation according to General Procedures D and E to yield compound **33a** as a yellow solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.53 (d, J = 1.8 Hz, 1 H), 7.87 (d, J = 8.2 Hz, 1 H), 7.77 (dd, J = 1.8, 8.2 Hz, 1 H), 4.56 (s, 2 H), 4.25 (q, J = 9.6 Hz, 2 H), 4.14−4.08 (m, 3 H), 3.14−3.09 (m, 1 H), 3.06−2.96 (m, 8 H), 2.82 (s, 3 H), 2.64−2.54 (m, 1 H), 2.52−2.43 (m, 1 H), 2.32 (dd, J = 13.7, 14.6 Hz, 1 H), 2.24−2.21 (m, 1 H), 1.68−1.58 (m, 1 H); MS (ESI) m/z 607.47 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-7-(2-methoxyethoxy)-1,13-dioxo-1,4,4a,5,-5a,6,13,14a-octahydropentacene-2-carboxamide (**35b**).* DIAD (27 μL, 0.14 mmol, 5.0 equiv) was added dropwise to a solution of compound **32** (24 mg, 0.028 mmol, 1.0 equiv), PPh_3 (37 mg, 0.14 mmol, 5.0 equiv), and 2-methoxyethanol (11 μL, 0.14 mmol, 5.0 equiv) in THF (1 mL) at 0 °C. The resulting dark red solution was stirred at 0 °C for 1 h. Saturated aqueous sodium bicarbonate and brine (1:1, 20 mL) were added. The

mixture was extracted with methylene chloride (15 mL × 3). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude product (MS (ESI) *m/z* 968.81 (M + H)).

The above crude product was subjected to desilylation according to General Procedure D, and the crude desliylated product was purified by preparative reverse-phase HPLC. This intermediate was dissolved in methanol (0.5 mL). Concentrated HCl (0.5 mL) was added slowly at rt. The reaction mixture was stirred at rt for 36 h and poured into aqueous dipotassium hydrogenphosphate (3 g dissolved in 30 mL water). The mixture was extracted with methylene chloride (15 mL × 5). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was subjected to hydrogenation according to General Procedure E to yield compound **35b** (4.3 mg, 25% over four steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.51 (d, J = 1.4 Hz, 1 H), 8.22 (d, J = 8.7 Hz, 1 H), 7.76 (dd, J = 1.4, 8.7 Hz, 1 H), 4.57 (s, 2 H), 4.26 (q, J = 9.6 Hz, 2 H), 4.15−4.10 (m, 3 H), 4.09−4.04 (m, 1 H), 3.99−3.94 (m, 1 H), 3.79−3.70 (m, 2 H), 3.47 (dd, J = 4.1, 15.6 Hz, 1 H), 3.45 (s, 3 H), 3.05−2.97 (m, 8 H), 2.63−2.55 (m, 1 H), 2.53−2.45 (m, 1 H), 2.36 (dd, J = 13.7, 15.1 Hz, 1 H), 2.28−2.25 (m, 1 H), 1.71−1.62 (m, 1 H); MS (ESI) *m/z* 608.47 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-7-isopropoxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**35a**).* Prepared similarly to compound **35b** from compound **32** and isopropanol: ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (d, J = 1.8 Hz, 1 H), 8.12 (d, J = 8.7 Hz, 1 H), 7.73 (dd, J = 1.8, 8.7 Hz, 1 H), 4.56 (s, 2 H), 4.29−4.22 (m, 3 H), 4.15−4.10 (m, 3 H), 3.42 (dd, J = 4.1, 15.1 Hz, 1 H), 3.04−2.91 (m, 8 H), 2.62−2.55 (m, 1 H), 2.53−2.44 (m, 1 H), 2.37 (t, J = 14.4 Hz, 1 H), 2.27−2.22 (m, 1 H), 1.72−1.62 (m, 1 H), 1.32 (d, J = 6.4 Hz, 3 H), 1.27 (d, J = 6.4 Hz, 3 H); MS (ESI) *m/z* 592.53 (M + H).

*(4aS,13aR,14aS,15S)-9-(Azetidin-1-ylmethyl)-3-(benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-12-(2,3-dihydroxypropoxy)-15-(dimethylamino)-5-(2-methoxyethoxy)-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**36**).* *N*-Methylmorpholine-*N*-oxide (60 mg, 0.52 mmol, 4.0 equiv) was added to a solution of compound **30** (115 mg, 0.129 mmol, 1.0 equiv) in THF (3 mL) and water (0.6 mL). A solution of OsO_4 in water (4 wt %, 30 μL, 0.04 equiv) was added. The reaction mixture was stirred at rt overnight, diluted with aqueous $Na_2S_2O_3$ (2 M, 10 mL) and brine (10 mL), and extracted with methylene chloride (20 mL × 2). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to give compound **36**: MS (ESI) *m/z* 926.92 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-7-(2,3-dihydroxypropoxy)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,-13,14a-octahydropentacene-2-carboxamide (**38**).* Prepared from compound **36** by desilylation and hydrogenation according to General Procedures D and E (28% over three steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.52 (s, 1 H), 8.27 (dd, J = 2.3, 8.2 Hz, 1 H), 7.75 (d, J = 8.2 Hz, 1 H), 4.56 (s, 2 H), 4.26 (q, J = 10.1 Hz, 2 H), 4.15−4.09 (m, 3 H), 4.06−4.02 (m, 1 H), 3.98 (dd, J = 3.2, 9.6 Hz, 0.5 H), 3.92−3.91 (m, 1 H), 3.84 (dd, J = 6.0, 9.6 Hz, 0.5 H), 3.73−3.70 (m, 2 H), 3.53−3.47 (m, 1 H), 3.05−2.97 (m, 8 H), 2.62−2.55 (m, 1 H), 2.52−2.45 (m, 1 H), 2.36 (dd, J = 14.2, 14.6 Hz, 1 H), 2.28−2.25 (m, 1 H), 1.71−1.62 (m, 1 H); MS (ESI) *m/z* 624.61 (M + H).

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-7-(2-oxoethoxy)-1,4,4a,5,5a,6,-13,14a-octahydropentacene-2-carboxamide (**37**).* $NaIO_4$ (72 mg, 0.34 mmol, 3.0 equiv) was added to a solution of compound **36** (0.11 mmol, 1.0 equiv) in THF (1.5 mL) and water (1.5 mL) at 0 °C. The reaction mixture was stirred between 0 and 8 °C for 24 h, diluted with aqueous $Na_2S_2O_3$ solution (2 M, 15 mL) and brine (15 mL), and extracted with methylene chloride (20 mL × 3). The organic extracts were combined, dried over anhydrous sodium sulfate, filtered, and concentrated to give compound **37**.

*(4S,4aS,5aR,14aS)-10-(Azetidin-1-ylmethyl)-4-(dimethylamino)-7-[2-(dimethylamino)ethoxy]-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**40a**).* Prepared from compound **37** and dimethylamine according to General Procedures C, D, and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, J = 1.8 Hz, 1 H), 8.15 (d, J = 8.2 Hz, 1 H), 7.83 (dd, J = 1.8, 8.2 Hz, 1 H), 4.58 (s, 2 H), 4.30−4.23 (m, 4 H), 4.15−4.09 (m, 3 H), 3.77−3.71 (m, 2 H), 3.43−3.38 (m, 1 H), 3.10−2.98 (m, 14 H), 2.63−2.55 (m, 1 H), 2.52−2.45 (m, 2 H), 2.39−2.36 (m, 1 H), 1.73−1.63 (m, 1 H); MS (ESI) *m/z* 621.66 (M + H).

*Methyl 5-Bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate (**42**).* A solution of *n*-butyllithium in hexane (2.5 M, 12.0 mL, 30.0 mmol, 1.2 equiv) was added slowly to a stirred solution of diisopropylamine (4.25 mL, 30.0 mmol, 1.2 equiv) in anhydrous THF (100 mL) at −78 °C. The solution was stirred at −78 °C for 30 min. 4-Bromophthalide[26] (5.38 g, 25 mmol, 1 equiv) in anhydrous THF (20 mL) was added dropwise. The mixture was then warmed to −50 °C over 3 h. Methyl crotonate (2.95 mL, 27.5 mmol, 1.1 equiv) was slowly added. The reaction mixture was gradually warmed to rt, stirred overnight, and poured into dilute HCl (1 N, 150 mL). The mixture was extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to give the crude intermediate.

The above crude intermediate was redissolved in methylene chloride (65 mL). BF_3−Et_2O (0.63 mL, 5.00 mmol, 0.2 equiv) was added dropwise. The reaction was stirred at rt for 1 h and quenched with water (100 mL). The organic layer was separated, and the aqueous layer was further extracted with methylene chloride (50 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (100:1 → 50:1, petroleum ether−ethyl acetate) to give the desired product **42** (2.0 g, 27%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.68 (s, 1 H), 8.29 (dd, J = 1.2, 8.4 Hz, 1 H), 7.78 (dd, J = 1.2. 8.4 Hz, 1 H), 7.41 (s, 1 H), 7.21 (t, J = 8.4 Hz, 1 H), 3.94 (s, 3 H), 2.63 (s, 3 H).

*Methyl 1-(Benzyloxy)-5-bromo-3-methylnaphthalene-2-carboxylate (**43**).* To a stirred solution of compound **42** (2.0 g, 6.8 mmol, 1.0 equiv) in acetone (25 mL) was added powdered potassium carbonate (1.2 g, 8.7 mmol, 1.3 equiv) and benzylbromide (1.4 g, 8.2 mmol, 1.2 equiv). The mixture was heated at reflux for 1.5 h, cooled to rt, and filtered through a short Celite pad. The filtrate was concentrated under reduced pressure, and the residue was purified by flash chromatography (100:1, petroleum ether−ethyl acetate) to give the desire product **43** (2.0 g, 77%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.4 Hz, 1 H), 7.80 (s, 1 H), 7.72 (d, J = 7.6 Hz, 1 H), 7.43−7.41 (m, 2 H), 7.37−7.29 (m, 3 H), 7.20 (t, J = 8.4 Hz, 1 H), 5.05 (s, 2 H), 3.83 (s, 3 H), 2.45 (s, 3 H).

*Phenyl 1-(Benzyloxy)-5-bromo-3-methylnaphthalene-2-carboxylate (**44**).* To a solution of compound **43** (2.0 g, 5.2 mmol) in absolute ethanol (10 mL) was added aqueous sodium hydroxide (4 N, 10 mL). The mixture was heated at reflux overnight. The reaction was cooled to rt, diluted with water (30 mL), and extracted with ethyl acetate (20 mL × 3, discarded). The aqueous phase was acidified with dilute HCl (1 N, 45 mL) to pH ≈ 6, and the mixture was extracted with ethyl acetate (40 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the carboxylic acid intermediate as a white solid.

To a solution of the above crude product in methylene chloride (20 mL) was added oxalyl chloride (0.57 mL, 6.5 mmol, 1.3 equiv) and a few drops of DMF (gas evolution). The solution was stirred at rt for 30 min, and the volatiles were evaporated under reduced pressure. The residue was further dried under high vacuum to afford the crude benzoyl chloride. This crude benzoyl chloride was redissolved in dry methylene chloride (20 mL). Pyridine (0.88 mL, 10.9 mmol, 2.1 equiv), phenol (0.54 g, 5.7 mmol, 1.1 equiv), and DMAP (catalytic amount) were added. The solution was stirred at rt for 1 h. The solvent was evaporated.

The residue was suspended in ethyl acetate and filtered. The filtrate was washed with 1 N HCl (three times), H_2O, saturated aqueous sodium bicarbonate, and brine, and dried over sodium sulfate. The dried solution was filtered, and the filtrate was concentrated. The residue was purified by flash chromatography (100:1, petroleum ether−ethyl acetate) to give compound **44** (1.7 g, 73%) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.4 Hz, 1 H), 7.94 (s, 1 H), 7.83 (dd, J = 1.2, 8.4 Hz, 1 H), 7.53−7.51 (m, 2 H), 7.42−7.35 (m, 5 H), 7.32−7.24 (m, 2 H), 7.16 (d, J = 7.6 Hz, 1 H), 5.22 (s, 2 H), 2.68 (s, 3 H).

*Phenyl 5-[Bis(tert-butoxycarbonyl)amino]-1-[(tert-butoxycarbonyl)-oxy]-3-methyl-2-naphthoate (**45**).* To a stirred solution of compound **44** (2.0 g, 4.48 mmol, 1.0 equiv) in anhydrous toluene (20 mL) was added $BocNH_2$ (786 mg, 6.7 mmol, 1.5 equiv), PhONa (779 mg, 6.7 mmol, 1.5 equiv), and $Pd_2(dba)_3\cdot CHCl_3$ (125 mg, 0.11 mmol, 0.025 equiv). The mixture was degassed. $(tBu)_3P$ (45 mg, 0.22 mmol, 0.05 equiv) was added. The mixture was heated at 95 °C for 2 h. The reaction was cooled to rt, quenched with water (50 mL), and extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by flash chromatography (100:1 → 50:1 → 20:1, petroleum ether−ethyl acetate) to give the aminated intermediate (1.6 g, 74%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.4 Hz, 1 H), 7.48−7.46 (m, 3 H), 7.42−7.31 (m, 7 H), 7.21−7.19 (m, 1 H), 7.09 (d, J = 8.4 Hz, 2 H), 5.16 (s, 2 H), 2.61 (s, 3 H), 1.51 (s, 9 H).

To a stirred solution of the above aminated intermediate (2.0 g, 4.13 mmol, 1.0 equiv) in methanol (20 mL) was added 10% Pd−C (300 mg). The suspension was briefly evacuated and refilled with hydrogen, and the mixture was stirred under a hydrogen atmosphere (1 atm) at rt for 1 h. The reaction mixture was filtered through a small Celite pad and the filtrate was concentrated under reduced pressure. The residue was redissolved in methylene chloride (20 mL). Boc_2O (1.25 g, 5.73 mmol, 1.4 equiv) and a catalytic amount of DMAP (30 mg, 0.25 mmol, 0.06 equiv) were added. The solution was stirred at rt for 2 h. The reaction was quenched with brine (50 mL) and extracted with methylene chloride (30 mL × 3). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography (50:1 → 15:1 → 10:1, petroleum ether−ethyl acetate) to give the desired product **45** (1.2 g, 49%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 8.4 Hz, 1 H), 7.61 (s, 1 H), 7.54−7.39 (m, 4 H), 7.32−7.26 (m, 3 H), 2.67 (s, 3 H), 1.46 (s, 9 H), 1.32 (s, 18 H).

*Phenyl 5-[Bis(tert-butoxycarbonyl)amino]-3-(bromomethyl)-1-[(tert-butoxycarbonyl)oxy]-2-naphthoate (**46**).* To a solution of compound **45** (1.1 g, 1.85 mmol, 1.0 equiv) in carbon tetrachloride (20 mL) was added NBS (347 mg, 1.95 mmol, 1.05 equiv) and BPO (895 mg, 3.70 mmol, 2.0 equiv). The mixture was refluxed for 2 h, cooled to rt, and concentrated. The residue was purified by flash chromatography (50:1 → 15:1, petroleum ether−ethyl acetate) to give the desired product **46** (1.0 g, 81%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.4 Hz, 1 H), 7.78 (s, 1 H), 7.62−7.56 (m, 1 H), 7.47−7.40 (m, 3 H), 7.40−7.35 (m, 2 H), 7.32−7.26 (m, 1 H), 4.92 (s, 1 H), 1.43 (s, 9 H), 1.30 (s, 18 H).

*Di-tert-butyl [(4aS,13aR,14aS,15S)-3-(Benzyloxy)-7-[(tert-butoxycarbonyl)oxy]-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-11-yl]imidodicarbonate (**47**).* A solution of *n*-butyllithium in hexane (2.5 M, 0.30 mL, 0.75 mmol, 3.2 equiv) was added dropwise to a solution of **46** (504 mg, 0.75 mmol, 3.2 equiv) and enone **8** (113 mg, 0.23 mmol, 1.0 equiv) in dry THF (10 mL) at −100 °C (liquid N_2/ethanol bath). The reaction was stirred at −100 °C for 30 min, allowed to warm to 0 °C gradually, quenched with brine (20 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography (30:1 → 20:1 → 10:1, petroleum ether−ethyl acetate) to give the desired product **47** (123 mg, 53%) as a yellow semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, J = 8.4 Hz, 1 H), 7.77−7.71 (m, 5 H), 7.66−7.48 (m, 6 H), 7.35 (d, J = 8.8 Hz, 2 H), 5.59 (s, 2 H), 4.27−4.18 (m, 1 H), 3.40−3.29 (m, 2 H), 3.20 (d, J = 10.4 Hz, 1 H), 2.90−2.68 (m, 9 H), 2.28−2.18 (m, 1 H), 1.56 (s, 9 H), 1.50 (s, 18 H), 1.08 (s, 9 H), 0.50 (s, 3 H), 0.37 (s, 3 H).

*(4S,4aS,5aR,14aS)-8-Amino-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**49a**).* Prepared from compound **47** (29 mg, 0.030 mmol) by desilylation and hydrogenation according to General Procedures D and E (4.3 mg, 29%, yellow solid): ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (d, J = 8.0 Hz, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.59 (t, J = 8.0 Hz, 1 H), 7.26 (s, 1 H), 4.16 (s, 1 H), 3.36−2.91 (m, 9 H), 2.78−2.66 (m, 1 H), 2.33−2.29 (m, 1 H), 1.71−1.61 (m, 1 H); MS (ESI) m/z 480.2 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-8-(methylamino)-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**49b**).* The Boc and TBS protection groups of compound **47** (70 mg, 0.071 mmol) were removed according to General Procedure D. One half of this crude product (20 mg, 0.035 mmol, 1.0 equiv) was dissolved in 1 N HCl/methanol (4 mL). Formalin (0.06 mL, 0.74 mmol, 21 equiv) and 10% Pd−C (7.0 mg) were added. The suspension was briefly evacuated and refilled with hydrogen. The mixture was stirred at rt under a hydrogen atmosphere (1 atm) for 3 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to yield the crude product. The crude product was purified by preparative HPLC to give the desired product **49b** (4.5 mg, 23%) as a yellow solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.33 (t, J = 8.4 Hz, 1 H), 7.65−7.46 (m, 2 H), 7.25 (s, 1 H), 4.03 (s, 1 H), 3.15−2.85 (m, 12 H), 2.69−2.56 (m, 1 H), 2.20−2.16 (m, 1 H), 1.62−1.49 (m, 1 H); MS (ESI) m/z 494.2 (M + H).

*(4S,4aS,5aR,14aS)-4,8-Bis(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**49c**).* Prepared from the same precursor (30 mg, 0.053 mmol, 1.0 equiv) under similar hydrogenation conditions used for compound **49b**, except that the reaction was performed at 40−50 °C overnight (4.0 mg, 15%, yellow solid): ^{1}H NMR (400 MHz, CD_3OD) δ 8.56 (d, J = 8.4 Hz, 1 H), 8.10 (d, J = 8.4 Hz, 1 H), 7.68 (t, J = 8.4 Hz, 1 H), 7.58 (s, 1 H), 4.13 (s, 1 H), 3.46 (s, 3 H), 3.44 (s, 3 H), 3.22−2.96 (m, 9 H), 2.81−2.73 (m, 1 H), 2.30−2.25 (m, 1 H), 1.70−1.59 (m, 1 H); MS (ESI) m/z 508.0 (M + H).

*Phenyl 1-(Benzyloxy)-5-methoxy-3-methyl-2-naphthoate (**50**).* A mixture of compound **44** (2.2 g, 4.93 mmol, 1.0 equiv), bis-(pinacolato)diboron (7.5 g, 29.5 mmol, 6.0 equiv), potassium acetate (3.0 g, 30.6 mmol, 6.2 equiv), and $PdCl_2$(dppf)−CH_2Cl_2 (400 mg, 0.5 mmol, 0.1 equiv) in 1,4-dioxane (50 mL) was degassed and stirred at 90 °C under a nitrogen atmosphere overnight. The reaction mixture was cooled to rt and filtered. The filtrate was concentrated. The residue was purified by column chromatography (100:1, petroleum ether−ethyl acetate) to afford the borate intermediate (2.1 g, 86%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (s, 1 H), 8.25 (d, J = 8.4 Hz, 1 H), 8.11 (d, J = 2.4 Hz, 1 H), 7.54−7.52 (m, 2 H), 7.46 (dd, J = 6.8, 8.4 Hz, 1 H), 7.41−7.37 (m, 5 H), 7.27−7.23 (m, 1 H), 7.17−7.15 (m, 2 H), 5.21 (s, 2 H), 2.66 (s, 3 H), 1.24 (s, 12 H).

To a solution of the above borate intermediate (2.0 g, 4.0 mmol, 1.0 equiv) in THF (20 mL) was carefully added H_2O_2 (30%, 2.0 mL, 17.6 mmol, 4.4 equiv), followed by acetic acid (1.2 mL, 20.0 mmol, 5.0 equiv). The reaction was stirred at rt overnight, quenched with saturated aqueous $NaHSO_3$ solution (until starch iodide test was negative), and extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography (50:1 → 40:1 → 10:1, petroleum ether−ethyl acetate) to give the desired naphthol intermediate (1.2 g, 78%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (s, 1 H), 7.66 (d, J = 8.4 Hz, 1 H), 7.47 (d, J = 6.8 Hz, 2 H), 7.36−7.28 (m, 5 H),

7.24−7.17 (m, 2 H), 7.09 (d, J = 7.6 Hz, 2 H), 6.78 (d, J = 7.2 Hz, 1 H), 5.51 (br s, 1 H), 5.16 (s, 2 H), 2.58 (s, 3 H).

To a stirred solution of the above naphthol intermediate (1.0 g, 2.6 mmol, 1.0 equiv) in acetone (15 mL) was added powdered potassium carbonate (0.9 g, 6.5 mmol, 2.5 equiv) and iodomethane (0.74 g, 5.2 mmol, 2.0 equiv). The reaction was stirred at rt overnight and quenched with water (50 mL). After evaporation of acetone, the residue was extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography (40:1, petroleum ether−ethyl acetate) to give the desired product **50** (760 mg, 74%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.65 (d, J = 8.4 Hz, 1 H), 7.48 (d, J = 7.6 Hz, 2 H), 7.36−7.28 (m, 6 H), 7.20−7.17 (m, 1 H), 7.09 (d, J = 8.4 Hz, 2 H), 6.82 (d, J = 7.6 Hz, 1 H), 5.16 (s, 2 H), 3.94 (s, 3 H), 2.57 (s, 3 H).

*Phenyl 1-[(tert-Butoxycarbonyl)oxy]-5-methoxy-3-methyl-2-naphthoate (**51**).* To a stirred solution of compound **50** (750 mg, 1.88 mmol, 1.0 equiv) in methanol (10 mL) and ethyl acetate (10 mL) was added 10% Pd−C (90 mg). The suspension was briefly evacuated, refilled with hydrogen, and stirred under a hydrogen atmosphere (1 atm) at rt for 2 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was redissolved in methylene chloride (20 mL). Boc_2O (430 mg, 1.97 mmol, 1.1 equiv) and DMAP (20 mg, 0.16 mmol, 0.09 equiv) were added. The reaction was stirred at rt for 50 min, quenched with water (50 mL), and extracted with ethyl acetate (30 mL × 3). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography (40:1, petroleum ether−ethyl acetate) to give the desired product **51** (690 mg, 90%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.44−7.35 (m, 4 H), 7.24−7.20 (m, 3 H), 6.82 (d, J = 7.6 Hz, 1 H), 3.94 (s, 3 H), 2.60 (s, 3 H), 1.40 (s, 9 H).

*Phenyl 3-(Bromomethyl)-1-[(tert-butoxycarbonyl)oxy]-5-methoxy-2-naphthoate (**52**).* A mixture of compound **51** (204 mg, 0.50 mmol, 1.0 equiv), NBS (99 mg, 0.56 mmol, 1.1 equiv), and AIBN (20 mg, 0.12 mmol, 0.24 equiv) in carbon tetrachloride (4 mL) was stirred at reflux for 3 h. After evaporation of the solvent, the residue was purified by flash chromatography (50:1, petroleum ether−ethyl acetate) to give the desired product **52** (200 mg, 82%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1 H), 7.56−7.46 (m, 4 H), 7.42−7.32 (m, 2 H), 7.35−7.30 (m, 1 H), 6.96 (d, J = 6.8 Hz, 1 H), 4.99 (s, 2 H), 4.03 (s, 3 H), 1.49 (s, 9 H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5-hydroxy-11-methoxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**53**).* A solution of n-butyllithium in hexane (2.5 M, 0.10 mL, 0.25 mmol, 4.0 equiv) was added dropwise to a solution of compound **52** (100 mg, 0.21 mmol, 3.3 equiv) and enone **8** (30 mg, 0.062 mmol, 1.0 equiv) in dry THF (2.5 mL) at −100 °C (liquid nitrogen/ethanol bath). The reaction was allowed to warm to 0 °C gradually over 1 h, quenched with brine (20 mL), and extracted with ethyl acetate (20 mL × 3). The combined organic extracts were dried, filtered, and concentrated. The residue was purified by flash chromatography (40:1 → 20:1, petroleum ether−ethyl acetate) to give the desired product **53** (30 mg, 61%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 7.62 (d, J = 8.4 Hz, 1 H), 7.46−7.44 (m, 2 H), 7.40−7.28 (m, 5 H), 6.87 (d, J = 6.8 Hz, 1 H), 5.31 (s, 2 H), 3.95 (s, 3 H), 3.11−3.03 (m, 2 H), 2.92 (d, J = 10.4 Hz, 1 H), 2.51−2.38 (m, 9 H), 2.11−2.05 (m, 1 H), 1.73−1.65 (m, 1 H), 1.53 (s, 9H), 0.80 (s, 9 H), 0.22 (s, 3 H), 0.09 (s, 3 H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-8-methoxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**54**).* Prepared from compound **53** (30 mg, 0.038 mmol) by desilylation and hydrogenation according the General Procedures D and E (8.0 mg, 16%, yellow solid): ^{1}H NMR (400 MHz, CD_3OD) δ 7.87 (d, J = 8.4 Hz, 1 H), 7.43 (s, 1 H), 7.39 (t, J = 8.4 Hz, 1 H), 7.07 (d, J = 8.4 Hz, 1 H), 4.07 (s, 1 H), 3.97 (s, 2 H), 3.09−2.89 (m, 9H), 2.65−2.58 (m, 1 H), 2.22−2.19 (m, 1 H), 1.65−1.59 (m, 1 H); MS (ESI) m/z 495.3 (M + H).

*Phenyl 5-Bromo-1-[(tert-butoxycarbonyl)oxy]-3-methylnaphthalene-2-carboxylate (**57**).* Prepared from compound **42** according to the same reaction sequence used for compound **14a** with an overall yield of 76%: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 1 H), 7.87 (d, J = 8.7 Hz, 1 H), 7.80 (dd, J = 1.4, 7.8 Hz, 1 H), 7.42−7.38 (m, 2 H), 7.31 (dd, J = 7.3, 8.2 Hz, 1 H), 7.26−7.23 (m, 3 H), 2.66 (s, 3 H), 1.41 (s, 9 H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-11-bromo-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno-[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**58**).* Prepared from compound **57** according to General Procedure A: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.99 (br s, 1 H), 8.09 (d, J = 8.5 Hz, 1 H), 7.97 (s, 1 H), 7.86 (d, J = 6.7 Hz, 1 H), 7.51−7.48 (m, 2 H), 7.39−7.33 (m, 4 H), 5.38, 5.34 (ABq, J = 12.0 Hz, 2 H), 3.97 (d, J = 11.0 Hz, 1 H), 3.23−3.11 (m, 2 H), 3.00 (t, J = 13.4 Hz, 1 H), 2.60−2.46 (m, 8 H), 2.22−2.16 (m, 1 H), 1.58 (s, 9 H), 0.82 (s, 9 H), 0.28 (s, 3 H), 0.14 (s, 3 H); MS (ESI) m/z 845.61 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-11-formyl-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**59**).* Prepared from compound **58** according to General Procedure B: ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.93 (br s, 1 H), 10.32 (s, 1 H), 9.04 (s, 1 H), 8.40 (d, J = 8.5 Hz, 1 H), 8.07 (d, J = 6.7 Hz, 1 H), 7.69 (dd, J = 7.3, 7.9 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.39−7.32 (m, 2 H), 5.37, 5.33 (ABq, J = 12.2 Hz, 2 H), 3.96 (d, J = 10.4 Hz, 1 H), 3.25−3.11 (m, 2 H), 3.00 (t, J = 14.0 Hz, 1 H), 2.58−2.40 (m, 8 H), 2.20−2.15 (m, 1 H), 1.57 (s, 9 H), 0.81 (s, 9 H), 0.26 (s, 3 H), 0.12 (s, 3 H); MS (ESI) m/z 795.58 (M + H).

*(4S,4aS,5aR,14aS)-8-[(Cyclopropylamino)methyl]-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**61a**).* Prepared from compound **59** by reductive amination with cyclopropylamine, followed by desilylation and hydrogenation according to General Procedures C, D, and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.47 (d, J = 8.2 Hz, 1 H), 7.83 (d, J = 8.2 Hz, 1 H), 7.54 (t, J = 8.2 Hz, 1 H), 7.46 (s, 1 H), 4.75 (s, 2 H), 4.11 (s, 1 H), 3.20−2.85 (m, 10 H), 2.69 (m, 1 H), 2.35−2.25 (m, 1 H), 1.67−1.58 (m, 1 H); MS (ESI) m/z 534.52 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-8-[(dimethylamino)methyl]-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**61b**).* Prepared from compound **59** by reductive amination with dimethylamine, followed by desilylation and hydrogenation according to General Procedures C, D, and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.52−8.49 (m, 1 H), 7.86 (s, 1 H), 7.55−7.51 (m, 2 H), 4.77 (s, 2 H), 4.10 (s, 1 H), 3.19−2.90 (m, 15 H), 2.67 (m, 1 H), 2.28 (m, 1 H), 1.62 (m, 1 H); MS (ESI) m/z 522.50 (M + H).

*(4S,4aS,5aR,14aS)-8-(Azetidin-1-ylmethyl)-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**61c**).* Prepared from compound **59** by reductive amination with azetidine, followed by desilylation and hydrogenation according to General Procedures C, D, and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.45 (d, J = 8.2 Hz, 1 H), 7.80 (d, J = 5.0 Hz, 1 H), 7.52−7.48 (m, 2 H), 4.82 (s, 2 H), 4.27 (s, 2 H), 4.10 (s, 3 H), 3.19−2.96 (m, 9 H), 2.66−2.45 (m, 3 H), 2.26 (m, 1 H), 1.62 (m, 1 H); MS (ESI) m/z 534.51 (M + H).

*Methyl 6-Bromo-1-hydroxy-3-methylnaphthalene-2-carboxylate (**63**).* A solution of n-butyllithium in hexane (2.5 M, 96 mL, 0.24 mol, 1.2 equiv) was added slowly to a stirred solution of diisopropylamine (33.8 mL, 0.24 mol, 1.2 equiv) in anhydrous THF (800 mL) at −78 °C. The mixture was stirred at −78 °C for 30 min. A solution of 5-bromophthalide (**62**, 42.6 g, 0.2 mol, 1.0 equiv) in anhydrous THF (200 mL) was added dropwise. The reaction mixture was then allowed to warm to −50 °C over 3 h. Methyl crotonate (23.4 mL, 0.22 mol, 1.1

equiv) was slowly added. The reaction was gradually warmed to rt with stirring overnight. The reaction mixture was poured into dilute HCl (1 N, 150 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic extracts were dried over anhydrous sodium sulfate, filtered, and concentrated to dryness.

The above crude intermediate was redissolved in methylene chloride (400 mL). BF_3-Et_2O (5.1 mL, 40 mmol, 0.2 equiv) was added dropwise. The reaction was stirred at rt for 1 h and quenched with water (200 mL). The organic layer was separated, and the aqueous layer was extracted with methylene chloride (100 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (50:1 → 30:1, petroleum ether−ethyl acetate) to give the desired product **63** (12 g, 20%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.67 (s, 1 H), 8.14 (d, J = 8.8 Hz, 1 H), 7.72 (d, J = 1.2 Hz, 1 H), 7.43 (dd, J = 1.6, 8.4 Hz, 1 H), 6.92 (s, 1 H), 3.93 (s, 3 H), 2.56 (s, 3 H).

*Phenyl 1-(Benzyloxy)-6-bromo-3-methylnaphthalene-2-carboxylate (**64**).* To a stirred solution of compound **63** (10.7 g, 36.3 mmol, 1.0 equiv) in acetone (250 mL) was added powdered potassium carbonate (10.0 g, 72.5 mmol, 2.0 equiv) and benzylbromide (7.4 g, 43.5 mmol, 1.2 equiv). The mixture was refluxed for 2 h, cooled to rt, and concentrated. The residue was purified by flash chromatography (1:0 → 10:1, petroleum ether−ethyl acetate) to give the benzyl ether intermediate (9.1 g, 65%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93−7.91 (m, 2 H), 7.50−7.46 (m, 3 H), 7.43−7.34 (m, 4 H), 5.10 (s, 2 H), 3.89 (s, 3 H), 2.45 (s, 3 H).

To a solution of the above benzyl ether intermediate (12.5 g, 32.4 mmol) in absolute ethanol (50 mL) was added dilute aqueous sodium hydroxide (4 N, 50 mL). The mixture was heated at reflux overnight, cooled to rt, diluted with water (150 mL), and extracted with ethyl acetate (50 mL × 3, discarded). The aqueous phase was acidified with dilute HCl (1 N, 220 mL) to pH ≈ 6 and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give the carboxylic acid as a white solid.

To a solution of above crude product in methylene chloride (250 mL) was added oxalyl chloride (6.13 mL, 65.0 mmol, 2.0 equiv) and a few drops of DMF (gas evolution). The mixture was stirred at rt for 30 min, and the volatiles were evaporated under reduced pressure. The residue was further dried under high vacuum to afford the crude benzoyl chloride. This crude benzoyl chloride was redissolved in dry methylene chloride (200 mL). Pyridine (5.14 g, 65.0 mmol, 2.0 equiv), phenol (3.66 g, 39.0 mmol, 1.2 equiv), and a catalytic amount of DMAP were added. The mixture was stirred at rt for 1 h. The solvent was evaporated. The residue was suspended in ethyl acetate and filtered. The filtrate was washed with 1 N HCl (three times), H_2O, saturated aqueous sodium bicarbonate, and brine. The solution was dried over sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (1:0 → 10:1, petroleum ether−ethyl acetate) to give compound **64** (1.7 g, 71%) as an off-white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00−7.97 (m, 2 H), 7.56−7.51 (m, 3 H), 7.44−7.38 (m, 6 H), 7.30−7.26 (m, 1 H), 7.18−7.15 (m, 2 H), 5.23 (s, 2 H), 2.64 (s, 3 H).

*Phenyl 1-(Benzyloxy)-6-[(tert-butoxycarbonyl)amino]-3-methyl-2-naphthoate (**65**).* A mixture of compound **64** (3.5 g, 7.5 mmol, 1.0 equiv), $BocNH_2$ (1.32 g, 11.3 mmol, 1.5 equiv), cesium carbonate (3.68 g, 11.3 mmol, 1.5 equiv), $Pd_2(dba)_3$ (213 mg, 0.19 mmol, 0.025 equiv), and $P(tBu)_3$ (77 mg, 0.38 mmol, 0.05 equiv) in toluene (50 mL) was degassed and stirred between 90 and 100 °C overnight under a nitrogen atmosphere. After cooling to rt, the mixture was added with water (100 mL) and extracted with ethyl acetate (50 mL × 3). The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by flash chromatography (30:1 → 10:1, petroleum ether−ethyl acetate) to give the desired product **65** (2.3 g, 64%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, J = 9.2 Hz, 1 H), 7.99 (s, 1 H), 7.53 (dd, J = 1.2, 8.0 Hz, 2 H), 7.44−7.38 (m, 6 H), 7.31−7.24 (m, 2 H), 7.17 (d, J = 7.6 Hz, 2 H), 6.67 (s, 1 H), 5.23 (s, 2 H), 2.61 (s, 3 H), 1.56 (s, 9 H).

*Phenyl 6-[Bis(tert-butoxycarbonyl)amino]-1-[(tert-butoxycarbonyl)-oxy]-3-methyl-2-naphthoate (**66**).* To a stirred solution of compound **65** (2.0 g, 4.13 mmol, 1.0 equiv) in methanol (15 mL) and ethyl acetate (3 mL) was added 10% Pd−C (300 mg). The suspension was briefly evacuated and refilled with hydrogen and stirred under a hydrogen atmosphere (1 atm) at rt for 2 h. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure. The residue was redissolved in methylene chloride (20 mL). Boc_2O (2.5 g, 11.57 mmol, 2.8 equiv) and DMAP (50 mg, 0.42 mmol, 0.10 equiv) were added. The reaction was stirred at rt for 1 h and quenched with water (50 mL). The mixture was extracted with methylene chloride (20 mL × 3). The combined organic layers were dried, filtered, and concentrated. The residue was purified by flash chromatography (50:1 → 30:1, petroleum ether−ethyl acetate) to give the desired product **66** (2.2 g, 90%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.8 Hz, 1 H), 7.60 (s, 1 H), 7.55 (s, 1 H), 7.45−7.41 (m, 2 H), 7.30−7.26 (m, 4 H), 2.65 (s, 3 H), 1.44 (s, 9 H), 1.39 (s, 18 H).

*Phenyl 6-[Bis(tert-butoxycarbonyl)amino]-3-(bromomethyl)-1-[(tert-butoxycarbonyl)oxy]-2-naphthoate (**67**).* A mixture of compound **66** (2.2 g, 3.81 mmol, 1.0 equiv), NBS (691 mg, 3.88 mmol, 1.02 equiv), and BPO (1.84 g, 7.60 mmol, 2.0 equiv) in carbon tetrachloride (20 mL) was refluxed for 5 h. The reaction was cooled to rt and quenched with water (50 mL). The mixture was extracted with methylene chloride (20 mL × 3). The combined organic layers were dried, filtered, and concentrated. The residue was purified by flash chromatography (50:1 → 30:1, petroleum ether−ethyl acetate) to give the desired product **67** (1.9 g, 74%) as a white solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 8.8 Hz, 1 H), 7.78 (s, 1 H), 7.63 (d, J = 2.0 Hz, 1 H), 7.47−7.41 (m, 2 H), 7.40−7.33 (m, 2 H), 7.31−7.26 (m, 2 H), 4.93 (s, 2 H), 1.45 (s, 9 H), 1.40 (s, 18 H).

*Di-tert-butyl [(4aS,13aR,14aS,15S)-3-(Benzyloxy)-7-[(tert-butoxycarbonyl)oxy]-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-10-yl]imidodicarbonate (**68**).* A solution of *n*-butyllithium in hexane (2.5 M, 0.15 mL, 0.37 mmol, 3.6 equiv) was added dropwise to a solution of compound **67** (250 mg, 0.37 mmol, 3.6 equiv) and enone **8** (50 mg, 0.10 mmol, 1.0 equiv) in dry THF (5.0 mL) at −100 °C (liquid nitrogen/ethanol bath). The reaction was allowed to warm to 0 °C gradually over 1 h and quenched with brine (20 mL). The mixture was extracted with ethyl acetate (10 mL × 3). The combined organic layers were dried, filtered, and concentrated. The residue was purified by flash chromatography (40:1 → 20:1, petroleum ether−ethyl acetate) to give the desired product **68** (20 mg, 20%) as a yellow semisolid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 9.2 Hz, 1 H), 7.41 (s, 1 H), 7.38−7.36 (m, 3 H), 7.26−7.12 (m, 4 H), 5.23 (s, 2 H), 3.84 (d, J = 14.4 Hz, 1 H), 2.99−2.95 (m, 2 H), 3.01−2.92 (m, 1 H), 2.86−2.82 (m, 1 H), 2.46−2.30 (m, 9 H), 2.05−1.98 (m, 1 H), 1.44 (s, 9 H), 1.29 (s, 18 H), 0.70 (s, 9 H), 0.14 (s, 3 H), 0.08 (s, 3 H).

*(4S,4aS,5aR,14aS)-9-Amino-4-(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**69a**).* Prepared from compound **68** (18 mg, 0.018 mmol) according to General Procedures D and E (3.0 mg, 36%, yellow solid): ^{1}H NMR (400 MHz, CD_3OD) δ 8.42 (d, J = 8.8 Hz, 1 H), 7.61 (s, 1 H), 7.37 (d, J = 8.8 Hz, 1 H), 7.14 (s, 1 H), 4.11 (s, 1 H), 3.18−2.95 (m, 9 H), 2.68−2.61 (m, 1 H), 2.27−2.20 (m, 1 H), 1.69−1.57 (m, 1 H); MS (ESI) m/z 480.2 (M + H).

*(4S,4aS,5aR,14aS)-4,9-Bis(dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**69b**).* Compound **68** (45 mg, 0.046 mmol) was desilylated according to General Procedure D. The crude product was dissolved in HCl/

methanol (1 N, 6.0 mL). Formalin (0.10 mL, 1.23 mmol, 35 equiv) and 10% Pd−C (20 mg) were added. The suspension was briefly evacuated and refilled with hydrogen. The reaction was stirred under a hydrogen atmosphere (1 atm) at rt for 30 min. The catalyst was filtered off, and the filtrate was concentrated under reduced pressure to give the crude product. The crude product was purified by HPLC to yield the desired product **69b** (6.0 mg, 34%) as a yellow solid: ^{1}H NMR (400 MHz, CD_3OD) δ 8.35 (d, J = 9.2 Hz, 1 H), 7.40 (d, J = 9.2 Hz, 1 H), 7.06 (s, 1 H), 4.08 (s, 1 H), 3.26 (s, 6 H), 3.15−2.85 (m, 9 H), 2.65−2.58 (m, 1 H), 2.24−2.18 (m, 1 H), 1.68−1.54 (m, 1 H); MS (ESI) m/z 508.1 (M + H).

*Phenyl 1-[(tert-Butoxycarbonyl)oxy]-4-(dimethylamino)-7-fluoro-3-methyl-2-naphthoate (**70**).* A solution of *n*-butyllithium in hexanes (1.6 M, 0.35 mL, 0.55 mmol, 1.2 equiv) was added dropwise to a solution of compound **14d** (230 mg, 0.46 mmol, 1.0 equiv) in THF (10 mL) at −100 °C, forming a red solution. After 5 min, a solution of *N*-fluorobenzenesulfonimide (290 mg, 0.92 mmol, 2.0 equiv) in THF (1 mL) was added dropwise via a cannula. The reaction was allowed to warm to −78 °C and was stirred at that temperature for 1 h. Saturated aqueous ammonium chloride (5 mL) was added dropwise at −78 °C. The reaction mixture was allowed to warm to 23 °C, diluted with additional saturated aqueous ammonium chloride (30 mL), and extracted with ethyl acetate (60 mL). The organic phase was separated, washed with brine (20 mL), dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by preparative reverse-phase HPLC to yield compound **70** (95 mg, 60% based on recovered starting material (50 mg)): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (dd, J = 5.5, 9.2 Hz, 1 H), 7.48−7.42 (m, 3 H), 7.34−7.27 (m, 4 H), 2.98 (s, 6 H), 2.50 (s, 3 H), 1.46 (s, 9 H); MS (ESI) m/z 440.34 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)-silyl]oxy}-12,15-bis(dimethylamino)-9-fluoro-5-hydroxy-4,6-dioxo-4,-4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**71d**).* Prepared from compound **70** (15 mg, 0.033 mmol, 1.0 equiv) and enone **8** (16 mg, 0.033 mmol, 1.0 equiv) according to General Procedure A (2.4 mg, 9%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.88 (br s, 1 H), 8.13 (dd, J = 5.5, 9.2 Hz, 1 H), 7.68 (br d, J = 7.9 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.39−7.30 (m, 4 H), 5.37, 5.33 (ABq, J = 12.2 Hz, 2 H), 4.02 (d, J = 10.4 Hz, 1 H), 3.27 (dd, J = 4.3, 15.3 Hz, 1 H), 3.03−2.95 (m, 7 H), 2.65 (t, J = 15.3 Hz, 1 H), 2.58−2.49 (m, 8 H), 2.18 (d, J = 14.0 Hz, 1 H), 1.57 (s, 9 H), 0.83 (s, 9 H), 0.27 (s, 3 H), 0.13 (s, 3 H); MS (ESI) m/z 828.55 (M + H).

*(4S,4aS,5aR,14aS)-4,7-Bis(dimethylamino)-10-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**72d**).* Prepared from compound **71d** (2.4 mg, 0.003 mmol, 1.0 equiv) by desilylation and hydrogenation according to General Procedures D and E (1.1 mg, 60% for two steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.25 (br s, 1 H), 8.08 (br s, 1 H), 7.57 (br s, 1 H), 4.14 (s, 1 H), 3.44−3.39 (m, 1 H), 3.13−2.97 (m, 8 H), 2.56−2.50 (m, 1 H), 2.33−2.29 (m, 1 H), 1.74−1.64 (m, 1 H); MS (ESI) m/z 526.30 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-15-(dimethylamino)-9-fluoro-5-hydroxy-12-methoxy-4,6-dioxo-4,4a,-6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**71c**).* A solution of phenyllithium in di-*n*-butyl ether (1.8 M, 66 μL, 0.12 mmol, 2.0 equiv) was added dropwise to a solution of compound **15e** (52 mg, 0.06 mmol, 1.0 equiv) in THF (2 mL) at −78 °C, forming a dark red solution. After 5 min, a solution of *n*-butyllithium in hexanes (1.6 M, 45 μL, 0.072 mmol, 1.2 equiv) was added dropwise at −78 °C followed 3 min later by the addition of *N*-fluorobenzenesulfonimide (66 mg, 0.21 mmol, 3.5 equiv). The resulting red reaction mixture was stirred at −78 °C for 1 h. Saturated aqueous ammonium chloride solution (2 mL) was added dropwise at −78 °C. The reaction mixture was allowed to warm to 23 °C, diluted with saturated aqueous ammonium chloride solution (20 mL), and extracted with methylene chloride (15 mL × 3). The organic extracts were combined, and the combined solution was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by preparative reverse-phase HPLC to yield product **71c** as a yellow solid (17 mg, 34%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.95 (br s, 1 H), 8.08 (dd, J = 5.5, 9.2 Hz, 1 H), 7.69 (br d, J = 9.2 Hz, 1 H), 7.50−7.48 (m, 2 H), 7.41−7.32 (m, 4 H), 5.37, 5.33 (ABq, J = 12.2 Hz, 2 H), 3.98 (d, J = 10.4 Hz, 1 H), 3.87 (s, 3 H), 3.48 (dd, J = 4.9, 15.3 Hz, 1 H), 3.04−2.98 (m, 1 H), 2.63−2.47 (m, 9 H), 2.19 (d, J = 14.0 Hz, 1 H), 1.59 (s, 9 H), 0.81 (s, 9 H), 0.26 (s, 3 H), 0.12 (s, 3 H); MS (ESI) m/z 815.50 (M + H).

Compounds **71a** and **71b** were prepared from compound **15a** and **15b** using similar conditions.

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]-oxy}-15-(dimethylamino)-9-fluoro-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,-14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**71a**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.01 (br s, 1 H), 7.76 (dd, J = 5.5, 9.2 Hz, 1 H), 7.68 (br d, J = 9.2 Hz, 1 H), 7.53 (s, 1 H), 7.50−7.46 (m, 2 H), 7.39−7.29 (m, 4 H), 5.37, 5.33 (ABq, J = 12.2 Hz, 2 H), 3.97 (d, J = 11.0 Hz, 1 H), 3.10−3.05 (m, 2 H), 2.98−2.94 (m, 1 H), 2.58−2.46 (m, 8 H), 2.13 (d, J = 14.0 Hz, 1 H), 1.58 (s, 9 H), 0.81 (s, 9 H), 0.26 (s, 3 H), 0.12 (s, 3 H); ^{19}F NMR (400 MHz, $CDCl_3$) δ −111.7; MS (ESI) m/z 785.47 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]oxy}-12-chloro-15-(dimethylamino)-9-fluoro-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**71b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 15.82 (br s, 1 H), 8.30 (dd, J = 5.5, 9.2 Hz, 1 H), 7.75−7.69 (m, 1 H), 7.50−7.44 (m, 3 H), 7.39−7.32 (m, 3 H), 5.37, 5.33 (ABq, J = 12.2 Hz, 2 H), 3.94 (d, J = 11.0 Hz, 1 H), 3.66 (dd, J = 4.3, 15.9 Hz, 1 H), 3.10−3.05 (m, 1 H), 2.74−2.68 (m, 1 H), 2.61−2.45 (m, 8 H), 2.20 (d, J = 14.0 Hz, 1 H), 1.57 (s, 9 H), 0.82 (s, 9 H), 0.26 (s, 3 H), 0.12 (s, 3 H); MS (ESI) m/z 819.45 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-fluoro-3,12,14,14a-tetrahydroxy-7-methoxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**72c**).* Prepared from compound **71c** (17 mg, 0.020 mmol, 1.0 equiv) by desilylation and hydrogenation according to General Procedures D and E (8 mg, 70% for two steps): ^{1}H NMR (400 MHz, CD_3OD) δ 8.04 (dd, J = 5.0, 9.2 Hz, 1 H), 7.92 (dd, J = 2.8, 7.3 Hz, 1 H), 7.49 (dt, J = 2.3, 8.7 Hz, 1 H), 4.11 (s, 1 H), 3.78 (s, 3 H), 3.35 (dd, J = 4.1, 15.1 Hz, 1 H), 3.06−2.95 (m, 8 H), 2.32 (t, J = 14.2 Hz, 1 H), 2.28−2.24 (m, 1 H), 1.65 (q, J = 11.4 Hz, 1 H); MS (ESI) m/z 513.28 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**72a**).* Prepared from compound **71a** by desilylation and hydrogenation according to General Procedures D and E: ^{1}H NMR (400 MHz, CD_3OD) δ 7.92 (dd, J = 2.3, 9.6 Hz, 1 H), 7.79 (dd, J = 5.5, 9.2 Hz, 1 H), 7.44 (dt, J = 2.8, 8.7 Hz, 1 H), 7.17 (s, 1 H), 4.09 (s, 1 H), 3.09−2.96 (m, 9 H), 2.65 (t, J = 13.7 Hz, 1 H), 2.21 (ddd, J = 2.8, 4.6, 13.7 Hz, 1 H), 1.68−1.58 (m, 1 H); MS (ESI) m/z 483.26 (M + H).

*(4S,4aS,5aR,14aS)-7-Chloro-4-(dimethylamino)-10-fluoro-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**72b**).* Prepared from compound **71b** by desilylation and hydrogenation according to General Procedures D and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.28 (dd, J = 5.0, 9.2 Hz, 1 H), 8.05 (dd, J = 1.8, 9.6 Hz, 1 H), 7.62 (dt, J = 2.8, 9.2 Hz, 1 H), 4.11 (s, 1 H), 3.58 (dd, J = 4.6, 15.6 Hz, 1 H), 3.05−2.97 (m, 8 H), 2.78 (t, J = 14.6 Hz, 1 H), 2.27−2.24 (m, 1 H), 1.73−1.63 (m, 1 H); MS (ESI) m/z 517.23 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]-oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-9-phenyl-4,4a,6,13,13a,-14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**73a**).* Compound **15a** (20 mg, 0.024 mmol, 1.0 equiv), phenyl boronic acid (14 mg, 0.12 mmol, 5.0 equiv), sodium carbonate (12 mg, 0.12 mmol, 5.0 equiv), and $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (1.0 mg, 0.0012 mmol, 0.05 equiv)

were dissolved in a mixture of toluene (1 mL), 1,4-dioxane (1 mL), and water (0.2 mL). The reaction mixture was stirred at 80 °C for 1 h, cooled to rt, diluted with methylene chloride (30 mL), and washed with aqueous potassium phosphate buffer (pH 7.0, 0.2 M, 10 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified by preparative reverse-phase HPLC to afford compound **73a** (17 mg, 78%) as a yellow solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.09 (s, 1 H), 8.23 (s, 1 H), 7.83 (s, 2 H), 7.68−7.66 (m, 2 H), 7.56 (s, 1 H), 7.51−7.47 (m, 4 H), 7.41−7.32 (m, 4 H), 5.36 (s, 2 H), 4.01 (d, J = 10.4 Hz, 1 H), 3.15−3.08 (m, 2 H), 2.97 (t, J = 15.3 Hz, 1 H), 2.59−2.47 (m, 8 H), 2.15 (d, J = 14.0 Hz, 1 H), 1.58 (s, 9 H), 0.82 (s, 9 H), 0.27 (s, 3 H), 0.14 (s, 3 H); MS (ESI) m/z 843.78 (M + H).

Compounds **73b** and **73c** were prepared from compound **15a** and the respective boronic acids under similar conditions.

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]-oxy}-15-(dimethylamino)-5-hydroxy-4,6-dioxo-9-pyridin-3-yl-4,4a,6,-13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**73b**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.03 (s, 1 H), 8.93 (d, J = 1.8 Hz, 1 H), 8.64 (dd, J = 1.2, 4.9 Hz, 1 H), 8.24 (s, 1 H), 8.02 (dt, J = 7.9, 1.8 Hz, 1 H), 7.89 (d, J = 8.5 Hz, 1 H), 7.79 (dd, J = 8.5, 1.2 Hz, 1 H), 7.59 (s, 1 H), 7.50−7.46 (m, 3 H), 7.39−7.32 (m, 3 H), 5.37, 5.34 (ABq, J = 12.2 Hz, 2 H), 3.98 (d, J = 11.0 Hz, 1 H), 3.15−3.10 (m, 2 H), 2.98 (t, J = 15.3 Hz, 1 H), 2.58−2.48 (m, 8 H), 2.15 (d, J = 14.0 Hz, 1 H), 1.58 (s, 9 H), 0.82 (s, 9 H), 0.27 (s, 3 H), 0.13 (s, 3 H); MS (ESI) m/z 844.74 (M + H).

*(4aS,13aR,14aS,15S)-3-(Benzyloxy)-4a-{[tert-butyl(dimethyl)silyl]-oxy}-15-(dimethylamino)-9-[4-(dimethylamino)phenyl]-5-hydroxy-4,6-dioxo-4,4a,6,13,13a,14,14a,15-octahydropentaceno[2,3-d]isoxazol-7-yl tert-Butyl Carbonate (**73c**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 16.11 (s, 1 H), 8.16 (s, 1 H), 7.83−7.77 (m, 2 H), 7.61−7.59 (m, 2 H), 7.52−7.49 (m, 3 H), 7.39−7.32 (m, 3 H), 6.92−6.90 (m, 2 H), 5.37, 5.34 (ABq, J = 12.2 Hz, 2 H), 4.01 (d, J = 10.4 Hz, 1 H), 3.19−2.93 (m, 9 H), 2.58−2.46 (m, 8 H), 2.14 (d, J = 14.0 Hz, 1 H), 1.58 (s, 9 H), 0.82 (s, 9 H), 0.27 (s, 3 H), 0.13 (s, 3 H); MS (ESI) m/z 886.90 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-10-phenyl-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**75a**).* Prepared from compound **73a** by desilylation and hydrogenation according to General Procedures D and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.48 (d, J = 1.8 Hz, 1 H), 7.88 (dd, J = 1.8, 8.7 Hz, 1 H), 7.76 (d, J = 8.4 Hz, 1 H), 7.71 (d, J = 7.3 Hz, 2 H), 7.48 (t, J = 7.3 Hz, 2 H), 7.37 (t, J = 7.3 Hz, 1 H), 7.09 (s, 1H), 4.10 (s, 1 H), 3.09−2.93 (m, 9 H), 2.58 (t, J = 14.2 Hz, 1 H), 2.23−2.20 (m, 1 H), 1.64−1.54 (m, 1 H); MS (ESI) m/z 541.43 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-3,12,14,14a-tetrahydroxy-1,13-dioxo-10-pyridin-3-yl-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**75b**).* Prepared from compound **73b** by desilylation and hydrogenation according to General Procedures D and E: ^{1}H NMR (400 MHz, CD_3OD) δ 9.33 (s, 1 H), 9.07 (d, J = 6.4 Hz, 1 H), 8.87 (d, J = 6.4 Hz, 1 H), 8.76 (s, 1 H), 8.22 (t, J = 7.8 Hz, 1 H), 8.04 (d, J = 7.8 Hz, 1 H), 7.92 (d, J = 7.8 Hz, 1 H), 7.19 (s, 1H), 4.12 (s, 1 H), 3.12−2.97 (m, 9 H), 2.64 (t, J = 13.3 Hz, 1 H), 2.25−2.23 (m, 1 H), 1.67−1.58 (m, 1 H); MS (ESI) m/z 542.41 (M + H).

*(4S,4aS,5aR,14aS)-4-(Dimethylamino)-10-[4-(dimethylamino)phenyl]-3,12,14,14a-tetrahydroxy-1,13-dioxo-1,4,4a,5,5a,6,13,14a-octahydropentacene-2-carboxamide (**75c**).* Prepared from compound **73c** by desilylation and hydrogenation according to General Procedures D and E: ^{1}H NMR (400 MHz, CD_3OD) δ 8.49 (s, 1 H), 7.92−7.84 (m, 3 H), 7.77−7.75 (m, 3 H), 7.08 (s, 1H), 4.06 (s, 1 H), 3.30 (s, 6 H), 3.08−2.92 (m, 9 H), 2.57 (t, J = 13.7 Hz, 1 H), 2.20−2.17 (m, 1 H), 1.60−1.51 (m, 1 H); MS (ESI) m/z 584.51 (M + H).

Susceptibility Testing. Compound stocks were prepared and serially diluted in sterile deionized water. Tetracycline-susceptible isolates SA100 (*Staph. aureus* ATCC 13709, Smith), SA101 (*Staph. aureus* ATCC 29213), SP106 (*Strep. pneumoniae* ATCC 49619), EF103 (*Enc. faecalis* ATCC 29212), EC107 (*E. coli* ATCC 25922), KP109 (*Klebsiella pneumoniae* ATCC 13883), AB110 (*Acinetobacter baumannii* ATCC 19606), EC108 (*Enterobacter cloacae* ATCC 13047), and PA111 (*Pseudomonas aeruginosa* ATCC 27853) were obtained from the American Type Culture Collection (ATCC, Manassas, VA). Tetracycline-resistant isolates *Staph. aureus* SA158 (*tet*K), *Strep. pneumoniae* SP160 (*tet*M), *Enc. faecalis* EF159 (*tet*M), *E. coli* EC155 (*tet*A), and *K. pneumoniae* KP153 (*tet*A) were obtained from Marilyn Roberts' laboratory at the University of Washington. *Staph. aureus* SA161 (*tet*M) was obtained from Micromyx (Kalamazoo, MI). Minimal inhibitory concentration (MIC) determinations were performed in liquid medium in 96-well microtiter plates according to the methods described by the Clinical and Laboratory Standards Institute (CLSI).[27] Cation-adjusted Mueller Hinton broth was obtained from BBL (Cat. no. 212322, Becton Dickinson, Sparks, MD), prepared fresh and kept at 4 °C prior to testing. Defibrinated horse blood (Cat. no. A0432, PML Microbiologicals, Wilsonville, OR) was used to supplement medium, as appropriate. All test methods met acceptable standards based on recommended quality control ranges for all comparator antibiotics and the appropriate ATCC quality control strains.

PD_{50} Determination. *In vivo* efficacy was evaluated in a mouse systemic infection model against a susceptible *Staph. aureus* isolate, ATCC 13709. ATCC 13709 was mixed with 5% mucin and inoculated by intraperitoneal injection at 2.1×10^6 cfu/mouse. Mice received the test compounds 60 min postinfection via intravenous injection or oral gavage (0.3−30 mg/kg, 6 mice/dose group, vehicle = sterile water). Infection control groups did not receive treatment. Survival was assessed over a 48 h period. Percent survival was calculated, and PD_{50} values were determined using Probit analysis.

AUTHOR INFORMATION

Corresponding Author

*Phone: 617-715-3553. Fax: 617-926-3557. E-mail: xyxiao@tphase.com.

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ABBREVIATIONS

AIBN, 2,2′-azobis(2-methylpropionitrile); ATCC, American Type Culture Collection; AUC, area under curve; aq, aqueous; BPO, dibenzoyl peroxide; CI, confidence interval; Cl, clearance; C_{max}, maximum plasma concentration; dba, dibenzylideneacetone; DIEA, *N*,*N*-diisopropylethylamine; DMAP, 4-(dimethylamino)pyridine; DIAD, diisopropyl azodicarboxylate; dppf, (diphenylphosphino)ferrocene; ESI, electrospray ionization; %F, percent oral bioavailability; HMPA, hexamethylphosphoramide; iv, intravenous; LDA, lithium diisopropylamide; LHMDS, lithium bis(trimethylsilyl)amide; MIC, minimum inhibitory concentration; NBS, *N*-bromosuccinimide; NCS, *N*-chlorosuccinimide; NFSI, *N*-fluorobenzenesulfonimide; NIS, *N*-iodosuccinimide; NMO, *N*-methylmorpholine-*N*-oxide; PD_{50}, dose at which 50% protection was observed; PK, pharmacokinetic; po, oral; $T_{1/2}$, elimination half-life; TBS, *tert*-butyldimethylsilyl; TFA, trifluoroacetic acid; TMEDA, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; V_z, volume of distribution

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