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Synthesis of Functional "Top-Half" Partial Structures of Azinomycin A and B

Robert S. Coleman,* Mark T. Tierney, Sarah B. Cortright, and Daniel J. Carper

Department of Chemistry, The Ohio State University, 100 West 18th Avenue, Columbus, Ohio 43210

coleman@chemistry.ohio-state.edu

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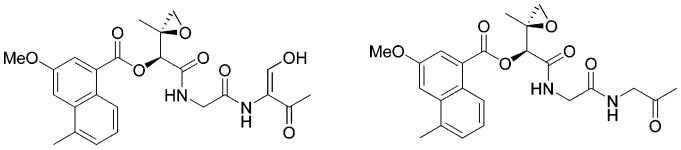

The design and synthesis of a detailed series of functional "top-half" substructures of azinomycin A and B is described.

Introduction

Antitumor agents that covalently modify duplex DNA[1] form the armamentarium of cancer chemotherapy.[2] Despite significant advances in intervention in uncontrolled cell growth,[3] these agents are often the first line of therapy for the majority of cancers. Of critical importance to the clinical use of such agents is the issue of selectivity and the associated problem of toxicity, and much effort has been spent on improving the therapeutic index of chemotherapeutic agents.

The azinomycins (Figure 1) are cytotoxic natural products[4] that are structurally and mechanistically unrelated to other families of antitumor agents.[5] These agents possess a novel and densely functionalized 1-azabicyclo[3.1.0]hexane (aziridino[1,2-*a*]pyrrolidine) ring system appended as part of a dehydroamino acid system to the referent "top-half" backbone. Azinomycin B bears an additional carbon (C4)—the role of which has not been defined—that is part of an unprecedented 2-amino-1,3-dicarbonyl system.

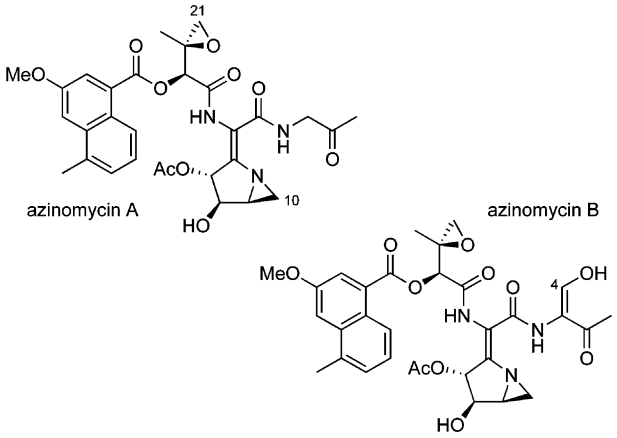

FIGURE 1. Structures of azinomycin A and B.

Azinomycins apparently exert their biological effect by the formation of covalent, interstrand cross-links[6] within the major groove of duplex DNA, presumably via electrophilic epoxide and aziridine rings. Considerable progress has recently been made on understanding the in vitro mechanism of action of these agents, both experimentally with natural compounds and analogues[7,8] and by computer modeling.[9] In addition, biosynthetic studies[10] and biological evaluation of several series of analogues have been reported.[11,12] In experimental studies on

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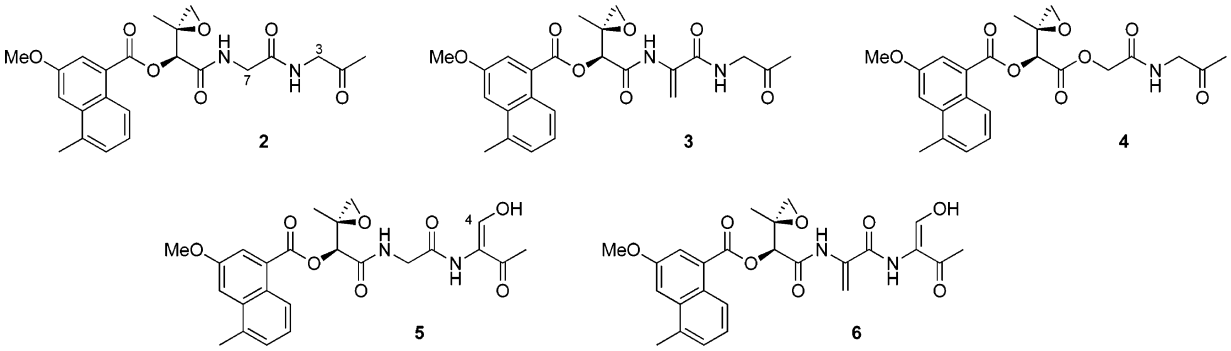

FIGURE 2. "Top-half" azinomycin partial structures.

azinomycin B,[8a] we established the sequence preferences for DNA cross-link formation and demonstrated the lack of intercalation by the aromatic naphthoate group. Prior work by Gates and Zang[8b] demonstrated a weak intercalative binding by this group, and to date, the role of the naphthoate in recognition and affinity of DNA binding has not been convincingly demonstrated. In previous work on azinomycin partial structures,[12] we established that the naphthoate was critical for effective DNA alkylation and cytotoxicity. Partial structures bearing the epoxide but lacking the naphthoate were devoid of activity. The importance of other structural features of the natural products remain to be demonstrated, among them the role of the intact backbone system in providing binding affinity for effective covalent bond formation, and what role, if any, the C1−C4 dicarbonyl system of azinomycin B plays in biological activity.

These structurally complex and unstable agents have attracted considerable attention from the synthetic organic community,[13] starting with early reports on approaches to the naphthoyl

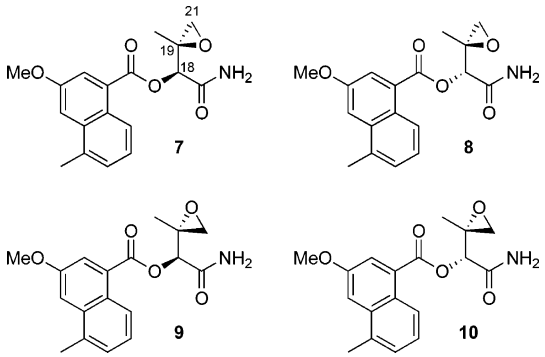

FIGURE 3. Stereoisomeric epoxy amides.

epoxide fragment[14] and azabicyclic system[15] and culminating in the total synthesis of azinomycin A in 2001.[16] A total synthesis of azinomycin B has not been reported, although partial syntheses exist.[17] Without a doubt, the greatest synthetic challenge is the introduction of the reactive azabicyclic system, particularly with respect to protecting group issues for the C12 hydroxyl group. Because of the modular nature of our synthetic strategy for construction of the azinomycins,[16] ready access to partial structures and modified versions thereof is available.

Most analogue synthesis has focused on the naphthoic epoxy amide (left-hand) moiety, often truncating the 1-azabicyclo-[3.1.0]hexane subunit. Recent work in this area has provided several left-hand partial structures that exhibit a greater stability than the natural agents. Replacement of the aziridine with a nitrogen mustard moiety led to left-hand partial analogues that could cross-link DNA and intercalate into DNA but had lower activities than the natural left-hand fragment.[18] Omission of the epoxide along with nitrogen mustard incorporation provided

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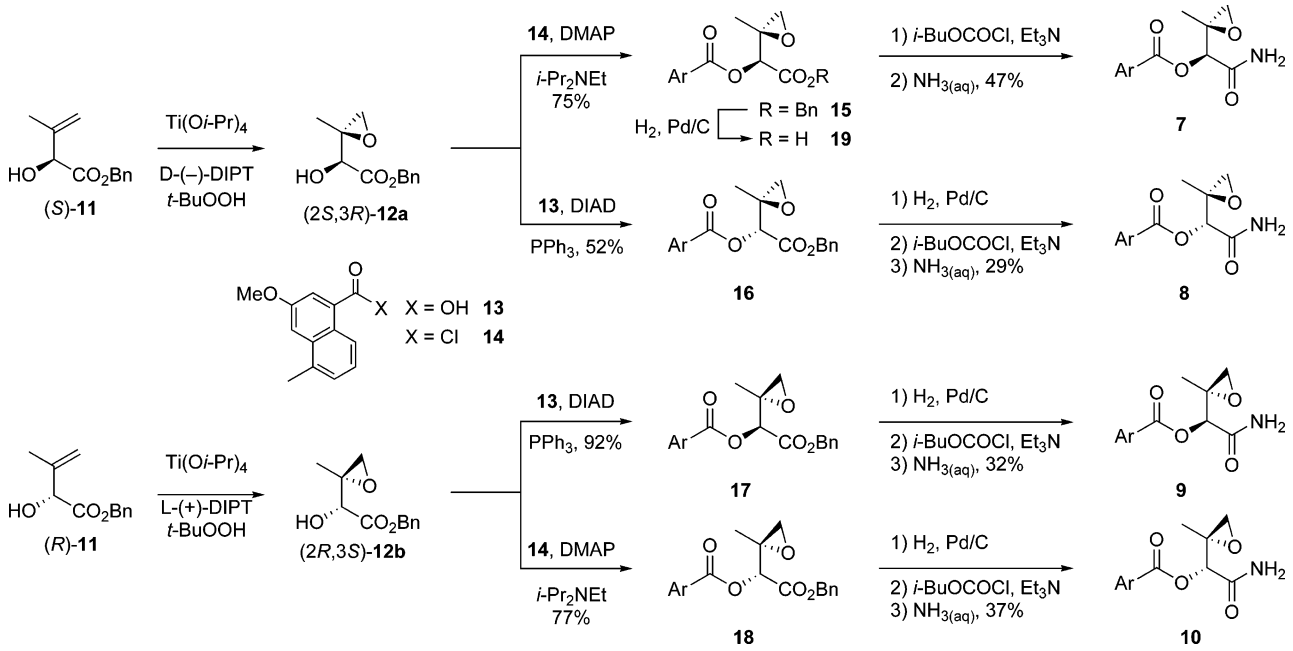
SCHEME 1

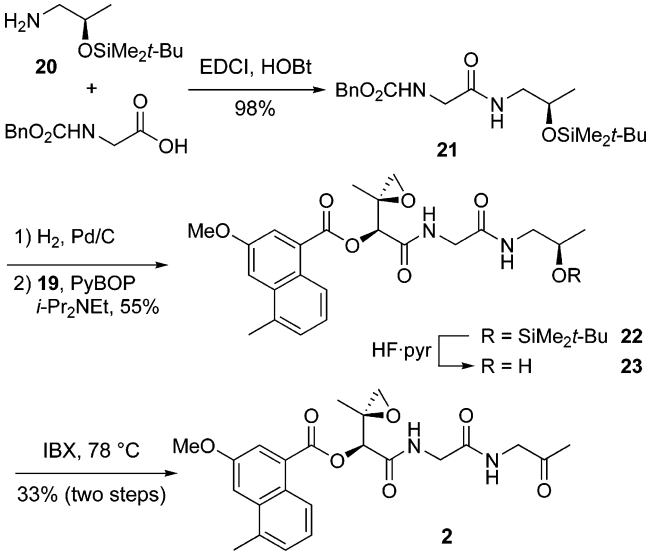


non-cross-linking compounds that were capable of monoalkylation.[18] Variations in substitution of the aromatic group for a series of left-hand primary amides showed significant effects on the cytotoxic potency of the analogues.[19] The amide substitution pattern for the naphthyl epoxy amide subunit has been explored by the synthesis of a small series of secondary amides, resulting in a loss of cytotoxic activity.[19] Bis-epoxides, with variations in linker structure, based on the naphthoyl epoxide moiety of naturally occurring azinomycins, have been synthesized to examine their merit as DNA cross-linkers.[20] Further "top-half" truncated analogues have included variations of the azabicyclic system, without the C12/C13 hydroxy groups.[21]

In this paper, we detail the synthetic efforts at the preparation of analogues of the "top-half" of azinomycin A and B. Compounds **2**−**4** are variations on the azinomycin A backbone. Compound **2** possesses a glycine methylene at C7 in place of the dehydroamino acid, whereas **3** bears a simple dehydroalanine in place of the pyrrolidine ring. Ester **4** is designed to examine hydrogen-bonding effects on epoxide ring opening. Previous results with less elaborate systems demonstrated the importance of the amide linkage at this position.[12] The azinomycin B series **5** and **6**, each possessing the characteristic azinomycin B C4-enol, are analogous to **2** and **3** (Figure 2), where the azabicyclic system has been truncated.

In a second series of modified azinomycin partial structures (Figure 3), we have constructed the complete series of stereoisomeric epoxy amides (**7**−**10**) to examine the effect of absolute and relative stereochemistry at the C18 and C19 stereogenic centers on DNA alkylation and cytotoxicity. A recent report described the synthesis of these diastereomeric epoxy amides for biological studies, using a nonstereoselective epoxide formation with *m*-CPBA.[22]

SCHEME 2



Previous work with **7** demonstrated that this azinomycin partial structure binds DNA in a mode different from that observed with the native agent.[12] These results indicated that the azinomycin naphthoate plays an important role in increasing sequence selective binding affinity and cytotoxic activity. As compared to the native agent, partial structure **7** altered the sequence selectivity while retaining a substantial portion of cytotoxic activity. Therefore, the complete stereoisomeric series

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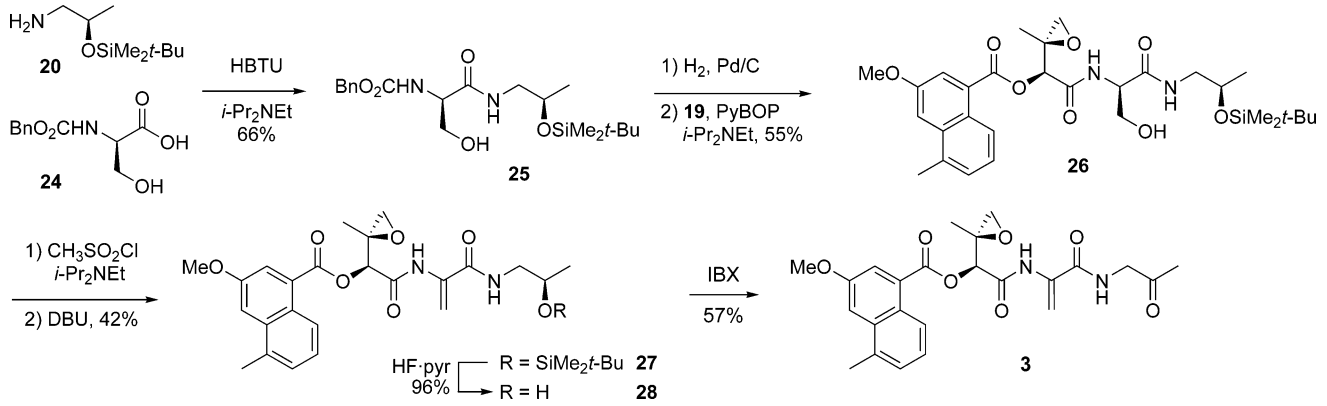
SCHEME 3



of **7**−**10** were synthesized to complete this study of the naphthoate portion of the azinomycins.

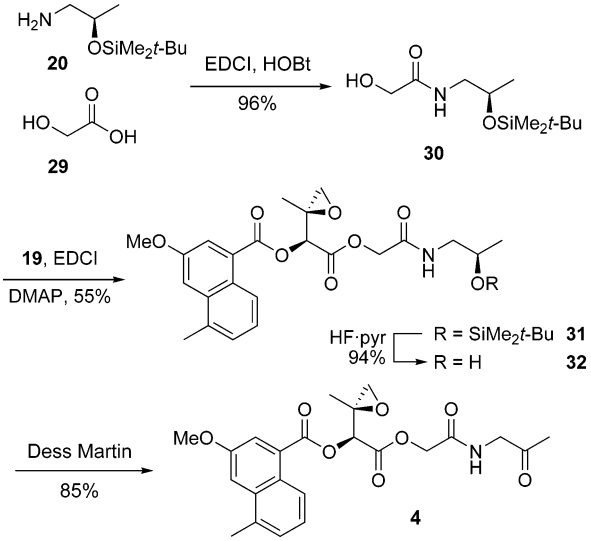
Results and Discussion

Preparation of Epoxide-Bearing Partial Structures. Synthesis of the desired epoxy amide compounds **7**−**10**[22] (Scheme 1) commenced with enantiomerically pure epoxides (+)-**12a** and (−)-**12b**, obtained via Sharpless epoxidation[23] of the respective enantiomerically enriched allylic alcohol **11**.[24,25] Esterification of epoxy alcohol **12a** with naphthoic acid chloride **14**[16,26] (CH_2Cl_2, 25 °C, 12 h) afforded the (2*R*,3*S*)-diester **15**, as a single diastereomer, bearing the native azinomycin epoxide stereochemistry. Hydrogenolysis of the benzyl ester (1 atm H_2, 10% Pd/C, THF, 25 °C) followed by activation of the resulting carboxylic acid **19** with isobutylchloroformate (THF, 0 °C, 30 min) and treatment with aqueous ammonia (0 °C) afforded epoxy amide **7** in modest yield. Following this same procedure, amide **10** was obtained from epoxy alcohol **12b.** Mitsunobu esterification of the (2*S*,3*R*)- and (2*R*,3*S*)-epoxy alcohols **12a** and **12b** (THF, 25 °C, 4 h) proceeded smoothly to yield the (2*R*,3*R*)- and (2*S*,3*S*)-epoxy diesters **16** and **17**, respectively. Conversion of the epoxy diesters to their respective amides was accomplished as stated previously and afforded **8** and **9** in modest yields.

Preparation of Complete "Top-Half" Structural Analogues of Azinomycin A. Structurally related complete "top-half" azinomycin A compounds were prepared with a convergent, modular approach using naphthoic epoxy acid **19** and elaborated aminopropanol fragments. (*R*)-1-Aminopropan-2-ol was utilized due to its relatively low cost and the subsequent simplification of ^{1}H and ^{13}C NMR spectra. For convenience of handling, it was protected with a *t*-butyldimethylsilyl group, and the protected amine (**20**) was used in all synthetic routes.

Synthesis of glycine methylene derivative **2** started with the EDCI coupling of amine **20** with benzylcarbamate-protected glycine (2:1 CH_2Cl_2/THF, 25 °C, 4 h) to afford amide **21** (Scheme 2). Hydrogenolysis of the benzylcarbamate of **21** (1 atm H_2, 10% Pd/C, MeOH, 25 °C) afforded the corresponding amine, which was coupled with naphthoic epoxy acid **19** (Scheme 1) using PyBOP or EDCI (CH_2Cl_2, 25 °C, 12 h) to provide **22** in modest yields. Deprotection of the silyl group of **22** with HF·pyridine (CH_3CN, −10 °C, 4 h) provided secondary alcohol **23**, which was subsequently oxidized with IBX (EtOAc, 78 °C, 7 h) to provide partial structure **2**.

SCHEME 4



The azinomycin A partial structure **3** containing a dehydroamino acid moiety was prepared with a similar covergent approach (Scheme 3). (*R*)-2-Amino-1-(*t*-butyldimethylsiloxy)-propane (**20**) was coupled with benzylcarbamate-protected L-serine **24** using HBTU (CH_2Cl_2, 25 °C, 2.5 h) to afford **25**. Hydrogenolysis of the benzylcarbamate of **25** (1 atm H_2, 10% Pd/C, MeOH, 25 °C, 4 h) followed by PyBOP coupling with naphthoic epoxy acid **19** (CH_2Cl_2, 0−23 °C, 12 h) provided **26**, the complete azinomycin A top piece skeleton. Treatment with methanesulfonylchloride (CH_2Cl_2, −40 °C, 3 h) followed by DBU (CH_2Cl_2, 22 °C, 1.5 h) then afforded the eliminated product **27**. Deprotection of the silyl group with HF·pyridine (CH_3CN, 0−25 °C, 45 min) provided alcohol **28**, which was subjected to IBX oxidation (CH_3CN, 50 °C, 6 h) to provide partial structure **3**.

An ester analogue of the azinomycin A "top-half" partial structure was also prepared (Scheme 4).[12] (*R*)-2-Amino-1-(*t*-butyldimethylsiloxy)propane (**20**) was coupled with glycolic acid

(23) (a) Katsuki, T.; Martin, V. S. *Org. React.* **1996**, *48*, 1. (b) Johnson, R. A.; Sharpless, K. B. In *Comprehensive Organic Synthesis*; Trost, B. M., Ley, S. V., Eds.; Pergamon Press: New York, 1991; Vol. 7, p 389. (c) Martin, V. S.; Woodard, S. S.; Katsuki, T.; Yamada, Y.; Ikeda, M.; Sharpless, K. B. *J. Am. Chem. Soc.* **1981**, *103*, 6237.

(24) These epoxides were also obtained via the kinetic resolution/epoxidation of racemic allylic alcohol **11**.

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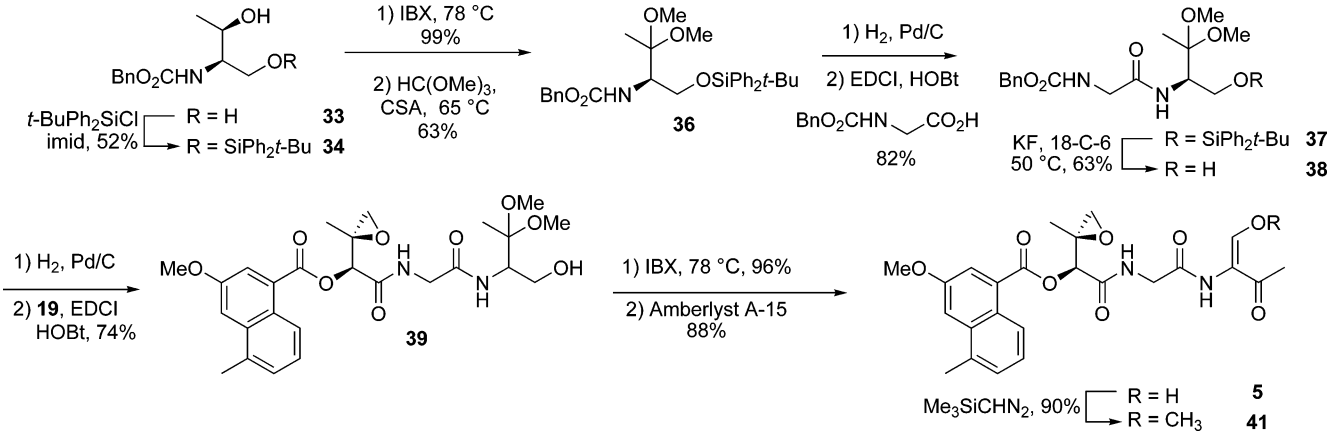
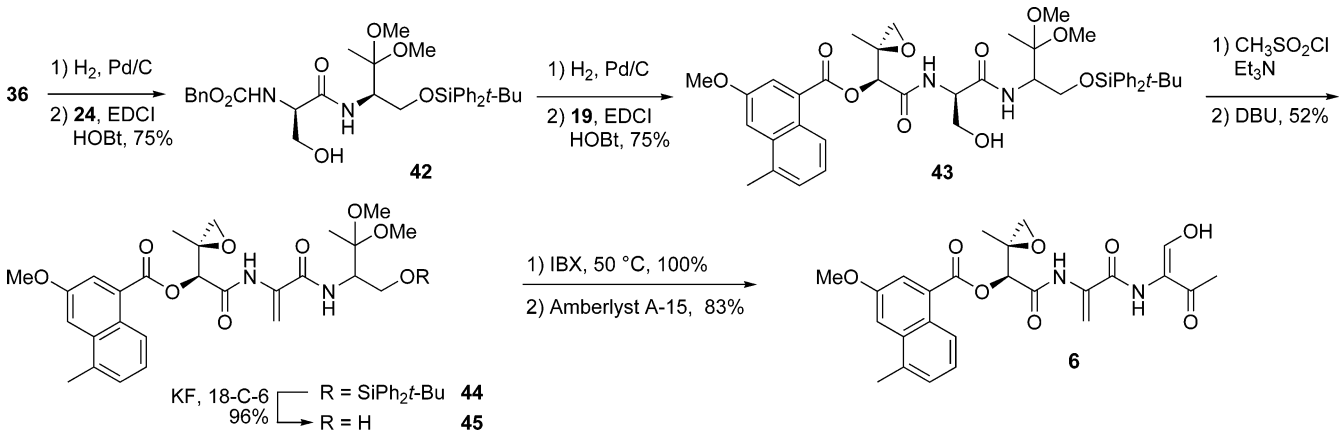
SCHEME 5



SCHEME 6



(**29**) using EDCI (2:1 CH_2Cl_2/THF, 25 °C, 12 h) to afford amido alcohol **30**. Next, **30** was coupled with naphthoic epoxy acid **19** using EDCI (CH_2Cl_2, 25 °C, 12 h) to afford **31**, the completed ester structural skeleton. Deprotection of the silyl group of **31** with HF·pyridine (CH_3CN, −5 °C, 45 min) provided alcohol **32**, which was followed by Dess−Martin oxidation (CH_2Cl_2, 25 °C, 1 h) of the secondary alcohol to provide partial structure **4**.

Preparation of Complete "Top-Half" Structural Analogues of Azinomycin B. Preparation of the 1,3-dicarbonyl system of azinomycin B presented considerable synthetic difficulty. Numerous attempts at introducing this moiety such as late stage oxidation of 1,3-diols resulted in elimination of either the 1- or the 3-alcohol to afford an olefin. However, introduction of a protected carbonyl early in the synthesis allowed for late stage oxidation and introduction of the second carbonyl.

Scheme 5 presents the synthesis of the azinomycin B "top-half" analogue **5**. Benzylcarbamate-protected L-threoninol (**33**) was obtained in several steps from L-threonine.[27] Silylation of the primary alcohol with *t*-butyldiphenylsilyl chloride (imidazole, DMF, 25 °C, 24 h) provided **34** and was followed by IBX oxidation (EtOAc, 78 °C, 14 h) to afford the desired ketone **35**. Dimethylacetal **36** was formed by treatment of ketone **35** with trimethylorthoformate (CSA, MeOH, 65 °C, 6 h) to afford the fully derivatized threonine-based 1,3-dicarbonyl precursor **36**. Hydrogenolysis of the benzylcarbamate of **36** (1 atm H_2, 10% Pd/C, MeOH, 25 °C, 2 h) followed by EDCI coupling with benzylcarbamate-protected glycine (CH_2Cl_2, 25 °C, 12 h) provided amido acetal **37**. Removal of the silyl group with KF·H_2O/18-crown-6 (CH_3CN, 50 °C, 24 h) provided alcohol **38**. Hydrogenolysis of the benzylcarbamate of **38** (1 atm H_2, 10% Pd/C, MeOH, 25 °C, 3 h) and coupling with naphthoic epoxy acid **19** using EDCI and HOBt (CH_2Cl_2, 25 °C, 12 h) afforded **39**, the fully elaborated top-piece skeleton. Oxidation of the primary alcohol of **39** with IBX (EtOAc, 78 °C, 6 h) provided crude aldehyde **40**. Treatment with Amberlyst A-15 resin in aqueous acetone (23 °C, 6.5 h) afforded the desired 1,3-dicarbonyl system and azinomycin partial structure **5**. The corresponding methyl ether **41** was formed upon treatment of **5** with trimethylsilyldiazomethane (1:1 toluene/MeOH, 25 °C, 20 min).

In a strategy similar to that used for the azinomycin A partial structure **4** featuring the dehydroamino acid of the truncated azabicyclic system, the synthesis of azinomycin B partial structure **6** employed a late stage elimination of water from a serine residue (Scheme 6). Hydrogenolysis of dimethylacetal **36** (1 atm H_2, 10% Pd/C, MeOH, 25 °C, 3 h) followed by EDCI coupling with benzylcarbamate-protected L-serine (**24**) (CH_2Cl_2, 25 °C, 12 h) afforded amido acetal **42**. Hydrogenolysis of the carbamate of **42** (1 atm H_2, 10% Pd/C, MeOH, 25 °C, 2 h) followed by EDCI coupling with naphthoic epoxy acid **19** (CH_2Cl_2, 25 °C, 12 h) afforded diamide **43**. The primary alcohol of **43** was transformed into the corresponding methanesulfonate (CH_2Cl_2, Et_3N, −45−22 °C, 2 h), which underwent base-promoted elimination upon treatment with DBU (0−22 °C, 1 h) to provide alkene **44**. Removal of the *t*-butyldiphenylsilyl

(27) Jeffery, A. L.; Kim, J.-H.; Wiemer, D. F. *Tetrahedron* **2000**, *56*, 5077.

group of **44** was accomplished by treatment with KF/18-crown-6 (CH_3CN, 5% aqueous HOAc, 50 °C, 2 h). Oxidation of the resulting alcohol **45** with IBX (DMSO, 50 °C, 6 h) provided the corresponding aldehyde (**46**). Immediate treatment with Amberlyst A-15 resin in aqueous acetone (23 °C, 6.5 h) removed the dimethylacetal to afford the desired azinomycin B partial structure **6**.

Conclusion

We have described the synthesis of several key partial "top-half" structures of azinomycin A and B. Currently, DNA alkylation studies with these partial structures are in progress. Details of such studies with the stereoisomeric epoxy amides **7**−**10** have recently been reported, providing insight into the role of the epoxy amide stereochemistry in DNA alkylation and cytotoxicity.[12d] Alkylation studies with "top-half" structures **2**−**6** will demonstrate the significance of the complete azinomycin A and B backbone and provide valuable information on the in vitro mechanism of the azinomycins.

Experimental Section

Benzyl(2*R*,3*S*)-3,4-epoxy-2-(3-methoxy-5-methylnaphthoyloxy)-3-methylbutanoate (16). A solution of naphthoic acid **13** (0.402 g, 1.86 mmol), epoxy alcohol **12a** (0.138 g, 0.621 mmol), and triphenylphosphine (0.408 g, 1.55 mmol) in THF (20 mL) was cooled to −25 °C. Diethylazodicarboxylate (0.11 mL, 0.68 mmol) was added dropwise. The reaction mixture was warmed to 25 °C and stirred for 72 h. After being poured into EtOAc, the mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl; dried (Na_2SO_4); and concentrated. Purification of the residue by flash chromatography (1.5 cm × 10 cm silica; 20% EtOAc/hexane) afforded the diester as an oil (0.134 g, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (m, 1H), 7.92 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.40−7.30 (m, 7H), 5.32 (d, J = 12 Hz, 1H), 5.25 (d, J = 12 Hz, 1H), 5.06 (s, 1H), 3.94 (s, 3H), 3.07 (d, J = 4.5 Hz, 1H), 2.76 (d, J = 4.5 Hz, 1H), 2.65, (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.1, 166.9, 155.8, 135.0, 134.3, 133.1, 128.6, 128.5, 128.3, 128.2, 127.6, 126.8, 125.0, 123.8, 122.0, 108.4, 77.5, 67.5, 55.8, 55.5, 52.1, 20.02, 17.0; HRMS (ESI), *m*/*z* calculated for $C_{25}H_{24}O_6Na$: 443.1471; found: 443.1498.

Benzyl(2*S*,3*R*)-3,4-epoxy-2-(3-methoxy-5-methylnaphthoyloxy)-3-methylbutanoate (17). Triphenylphosphine (0.20 g, 0.76 mmol) was dissolved in THF (3 mL), and the reaction mixture was cooled to −20 °C. Diisopropylazodicarboxylate (0.14 mL, 0.69 mmol) was added dropwise. The reaction mixture was cooled to −78 °C, and a solution of naphthoic acid **13** (0.20 g, 0.95 mmol) and epoxy alcohol **12b** (0.14 g, 0.63 mmol) in THF (2 mL) was added rapidly via cannula. The reaction mixture was stirred at 25 °C for 4 h, when it was diluted with EtOAc and washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (1.5 cm × 10 cm silica, 20% EtOAc/hexane) afforded the diester as an oil (0.245 g; 92%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (m, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.47 (d, J = 2.6 Hz, 1H), 7.40−7.30 (m, 7H), 5.32 (d, J = 12 Hz, 1H), 5.24 (d, J = 12 Hz, 1H), 5.06 (s, 1H), 3.94 (s, 3H), 3.07 (d, J = 4.6 Hz. 1H), 2.76 (d, J = 4.6 Hz, 1H), 2.66, (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.3, 155.8, 135.0, 134.3, 133.1, 128.6, 128.5, 128.3, 128.2, 127.7, 126.8, 125.1, 123.8, 122.0, 108.4, 77.6, 67.5, 55.9, 55.5, 52.1, 20.1, 17.1: HRMS (ESI), *m*/*z* calculated for $C_{25}H_{24}O_6Na$: 443.1471; found: 443.1477.

Benzyl(2*R*,3*R*)-3,4-epoxy-2-(3-methoxy-5-methylnaphthoyloxy)-3-methylbutanoate (18). Epoxy alcohol **12b** (30 mg, 0.14 mmol) was added to a solution of naphthoic acid chloride **14** (40 mg, 0.17 mmol), diisopropylethylamine (30 μL, 0.17 mmol), and DMAP (2 mg) in CH_2Cl_2 (20 mL) at −65 °C. The reaction mixture was allowed to warm to 25 °C and was stirred 12 h. The reaction mixture was washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl, and the organic extract was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (1.5 cm × 10 cm silica; 20% EtOAc/hexane) afforded the diester as an oil (55 mg; 77%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60−8.59 (dd, J = 7.6, 2.0 Hz, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.51 (d, J = 2.6 Hz, 1H), 7.40−7.30 (m, 7H), 5.32 (d, J = 12 Hz, 1H), 5.24 (d, J = 12 Hz, 1H), 5.22 (s, 1H), 3.94 (s, 3H), 2.97 (d, J = 4.6 Hz, 1H), 2.68 (d, J = 4.6 Hz, 1H), 2.65, (s, 3H), 1.45 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.2, 166.3, 155.9, 135.0, 134.3, 133.1, 128.6, 128.5, 128.3, 128.2, 127.7, 126.8, 125.1, 123.8, 122.0, 108.4, 77.6, 67.5, 55.9, 55.5, 52.1, 20.1, 17.1; HRMS (ESI), *m*/*z* calculated for $C_{25}H_{24}O_6Na$: 443.1471; found: 443.1445.

General Procedure for Preparation of Epoxy Amides 7−10. The respective epoxy diester was dissolved in THF to a concentration of 5 mg/mL, and 10% Pd/C (10% w/w loading) was added. Hydrogen gas was bubbled into the mixture for approximately 3 h. After filtration through Celite, the filtrate was cooled to 0 °C, and diisopropylethylamine (2.2 equiv) and isobutylchloroformate (2 equiv) were added. After stirring for 30 min, the mixture was treated with 30% aqueous NH_3, and the reaction mixture was stirred for an additional 5 min. The mixture was partitioned between EtOAc and 5% aqueous acetic acid, and the organic extract was washed with water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. Flash chromatography (1.5 cm × 10 cm silica, 80% EtOAc/hexane) afforded the respective epoxy amides.

(2*S*,3*R*)-3,4-Epoxy-2-(3-methoxy-5-methylnapthoyloxy)-3-methylbutanamide (7). Yield (28 mg; 47%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (m, 1H), 7.90 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 2.6 Hz, 1H), 7.35 (m, 2H), 6.14 (br s, 1H), 5.67 (br s, 1H), 5.20 (s, 1H), 3.96 (s, 3H), 3.01 (d, J = 4.6 Hz, 1H), 2.78 (d, J = 4.6 Hz, 1H), 2.66 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.7, 165.5, 155.8, 134.3, 133.2, 128.1, 127.8, 126.9, 125.2, 123.7, 122.1, 108.4, 75.9, 55.8, 55.5, 53.3, 20.1, 17.6; HRMS (ESI), *m*/*z* calculated for $C_{18}H_{19}NO_5Na$: 352.1161; found: 352.1167.

(*R*)-2-(*t*-Butyldimethylsilanyloxy)propylamine (20). A solution of (*R*)-1-aminopropan-2-ol **20** (0.662 g, 8.81 mmol) and DBU (1.61 g, 10.6 mmol) in CH_3CN (10 mL) was cooled to 0 °C. *t*-Butyldimethylsilylchloride (1.59 g, 10.6 mmol) was added in one portion, and the reaction mixture was allowed to warm to 22 °C and stirred for 12 h. Methanol (0.1 mL) was added, and the solvent was removed under a stream of N_2. The residue was dissolved in Et_2O (25 mL), washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under N_2. This afforded amine **20** as an oil (1.39 g, 83%), which was used without further purification: IR (film) 3321, 3277, 2944, 1594 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.75 (m, 1H), 2.61 (m, 2H), 1.26 (br s, 2H), 1.09 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 70.8, 53.5, 26.9, 20.5, 18.1, −4.6, −4.8; ESI-HRMS, *m*/*z* calculated for $C_9H_{23}NOSiNa$: 212.1447; found: 212.1444.

{[2-(*t*-Butyldimethylsilanyloxy)propylcarbamoyl]methyl}-carbamic Acid Benzyl Ester (21). A solution of amine **20** (164 mg, 0.866 mmol), benzylcarbamate-protected glycine (181 mg, 0.866 mmol), and HOBt (117 mg, 0.866 mmol) in 2:1 CH_2Cl_2/THF at 25 °C was treated with EDCI (183 mg, 0.953 mmol), and the reaction mixture was stirred for 4 h. The mixture was poured onto water (10 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with 5% aqueous HOAc, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl and were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (3 cm × 10 cm silica; 50% EtOAc in hexanes) to afford the product as a white solid (324 mg; 98%). IR (film) 3422, 3322, 2956, 1711, 1667 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.29 (m, 5H), 6.17 (br s, 1H), 5.34 (br s, 1H), 5.12 (s, 3H), 3.92−3.81 (m, 2H), 3.43−3.38 (m, 1H), 3.12−3.06 (m, 1H), 1.11 (d, J = 6.1 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 164.9, 156.1, 135.7, 127.9, 127.2, 126.7,

73.3, 61.2, 47.3, 43.1, 27.5, 20.4, 18.2, −4.4, −4.5; ESI-HRMS, *m*/*z* calculated for $C_{19}H_{32}N_2O_4SiNa$: 403.2029; found: 403.2025.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid ({[2-(*t*-Butyldimethylsilanyloxy)propylcarbamoyl]methyl}carbamoyl)-(2-methyloxiranyl)methyl Ester (22). Hydrogen gas was bubbled through separate solutions of benzyl ester **15** (181 mg, 0.431 mmol) and glycine derivative **21** (164 mg, 0.327 mmol) in MeOH (25 mL each), each as a mixture with 10% Pd/C (10% w/w loading), for 4 h. Both mixtures were filtered through Celite, and the filtrate was concentrated. The residues were dissolved in CH_2Cl_2 (25 mL each), cooled to −20 °C, and combined. The resulting solution was treated with PyBOP (247 mg, 0.475 mmol) and diisopropylethylamine (61 mg, 0.475 mmol), and the reaction mixture was allowed to warm to 25 °C and was stirred 12 h. The mixture was poured onto EtOAc (100 mL) and washed with equal portions of 5% aqueous HOAc, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (3 cm × 10 cm silica; 50% EtOAc in hexanes) afforded the product as a solid (195 mg) that could not be separated from a minor impurity and was used directly in the next step.

(2-Methyloxiranyl)-{[(2-oxo-propylcarbamoyl)methyl]-carbamoyl}methyl Ester (2). IBX (29.8 mg, 0.106 mmol) was added to a solution of alcohol **23** (31.4 mg, 0.071 mmol) in EtOAc (4 mL). The resulting heterogeneous solution was stirred at reflux for 7 h. The cooled solution was then filtered, diluted with EtOAc (10 mL), washed with $Na_2S_2O_3$ (2 × 5 mL) and brine (2 × 5 mL), dried (Na_2SO_4), and concentrated. Column chromatography (1.5 cm × 10 cm silica, 2% MeOH/CH_2Cl_2) afforded ketone **2** as a white solid (17.1 mg, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.62 (m, 1H), 7.94 (d, J = 2.5 Hz, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.36 (m, 2H), 6.86 (m, 1H), 6.82 (m, 1H), 5.35 (s, 1H), 4.13 (m, 3H), 3.98 (s, 3H), 3.96 (m, 1H), 3.07 (d, J = 4.4 Hz, 1H), 2.80 (d, J = 4.4 Hz, 1H), 2.68 (s, 3H), 2.17 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 202.5, 168.4, 167.3, 165.8, 156.0, 134.5, 133.4, 127.98, 127.93, 127.1, 125.4, 123.8, 122.3, 108.8, 76.2, 56.2, 55.7, 53.3, 49.8, 42.9, 27.4, 20.3, 18.0; ESI-HRMS, *m*/*z* calculated for $C_{23}H_{26}N_2O_7Na$: 465.1638; found: 465.1656.

{1-[2*S*-(*t*-Butyldimethylsilanyloxy)propylcarbamoyl]-2*R*-hydroxyethyl}carbamic Acid Benzyl Ester (25). A solution of benzylcarbamate-protected L-serine (**24**) (0.619 g, 2.59 mmol) and (*R*)-2-amino-1-(*t*-butyldimethylsiloxy)propane (**20**) (0.512 g, 2.70 mmol) in CH_2Cl_2 (25 mL) was cooled to 0 °C. HBTU (1.08 g, 2.85 mmol) and diisopropylethylamine (0.50 mL, 2.85 mmol) were added, and the reaction mixture was warmed to 25 °C and stirred for 2.5 h. The mixture was diluted with EtOAc (150 mL) and washed successively with water, 10% aqueous HCl, water, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4) and concentrated. Purification of the residue by flash chromatography (3 cm × 10 cm silica; 0−5% MeOH/CH_2Cl_2) afforded the product as a white solid (0.701 g, 66%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (m, 5H), 6.70 (br s, 1H), 5.71 (br s, 1H), 5.07 (m, 2H), 4.20 (m, 1H), 3.90 (m, 1H), 3.64 (m, 1H), 3.34 (m, 1H), 3.12 (m, 1H), 3.00 (br s, 1H), 2.79 (m, 1H), 1.14 (d, J = 6.2 Hz, 3H), 0.89 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 155.6, 134.3, 133.2, 127.8, 126.8, 67.1, 62.6, 55.8, 53.7, 53.1, 25.7, 21.2, 18.2, −4.6, −4.9; HRMS (ESI), *m*/*z* calculated for $C_{20}H_{34}N_2O_5SiNa$: 433.2129; found: 433.2125.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {1-[2*S*-(*t*-Butyldimethylsilanyloxy)propylcarbamoyl]-2*R*-hydroxyethylcarbamoyl}-(2-methyloxiranyl)methyl Ester (26). Hydrogen gas was bubbled through solutions of benzyl ester **15** (125 mg, 0.298 mmol) and serine derivative **25** (135 mg, 0.327 mmol) in MeOH (10 mL each), each as a mixture with 10% Pd/C (10% w/w loading), for 4 h. Both mixtures were filtered through Celite, and the filtrates were concentrated. The residues were dissolved in CH_2Cl_2 (5 mL each) and combined. The resulting solution was cooled to 0 °C and treated with PyBOP (170 mg, 0.327 mmol) and diisopropylethylamine (0.057 mL, 0.327 mmol) and stirred for 12 h at 23 °C. The reaction mixture was poured onto EtOAc (100 mL) and washed with 5% aqueous HOAc, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (3 cm × 10 cm silica; 0−3% MeOH/CH_2Cl_2) to afford **26** as a solid (97 mg, 55%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59−8.57 (m, 1H), 7.91 (d, J = 2.6 Hz, 1H), 7.46 (d, J = 2.5 Hz, 1H), 7.34−7.32 (m, 2H), 7.28 (d, J = 7.4 Hz, 1H), 6.81 (t, J = 5.7 Hz, 1H), 5.22 (s, 1H), 4.50−4.46 (m, 1H), 4.10−4.06 (m, 1H), 3.95 (s, 3H), 3.92−3.88 (m, 1H), 3.72−3.65 (m, 1H), 3.34−3.27 (m, 2H), 3.14−3.08 (m, 1H), 2.99 (d, J = 4.6 Hz, 1H), 2.74 (d, J = 4.6 Hz, 1H), 2.64 (s, 3H), 1.50 (s, 3H), 1.08 (d, J = 6.2 Hz, 3H), 0.85 (s, 9H), 0.034 (s, 3H), 0.027 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 167.4, 165.6, 155.8, 134.3, 133.2, 127.8, 127.7, 126.8, 125.2, 123.6, 122.0, 108.6, 75.9, 67.0, 62.4, 55.8, 55.5, 53.8, 53.1, 46.8, 25.7, 21.2, 20.0, 18.0, 17.6, −4.6, −4.9; HRMS (ESI), *m*/*z* calculated for $C_{30}H_{44}N_2O_8SiNa$: 611.2765; found: 611.2786.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {1-[2*R*-(*t*-Butyldimethylsilanyloxy)propylcarbamoyl]vinylcarbamoyl}-(2-methyloxiranyl)methyl Ester (27). Diisopropylethylamine (12 mg, 96 μmol) and methanesulfonylchloride (6.6 mg, 58 μmol) were added to a solution of alcohol **26** (29 mg, 48 μmol) in CH_2Cl_2 (5 mL) at 0 °C and stirred for 3 h. The reaction mixture was warmed to 23 °C. DBU (15 mg, 0.10 mmol) was added, and the reaction mixture was stirred for 1.5 h. The mixture was poured onto saturated aqueous $NaHCO_3$ (3 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water and saturated aqueous NaCl and were dried (Na_2SO_4) and concentrated. Purification of the residue by preparative TLC (5% MeOH/CH_2Cl_2) afforded **27** as a solid (12 mg, 42%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.98 (s, 1H), 8.64 (m, 1H), 7.99 (d, J = 2.5 Hz, 1H), 7.49 (d, J = 2.5 Hz, 1H), 7.34 (m, 2H), 6.50 (s, 1H), 6.42 (br t, 1H), 5.26 (s, 1H), 5.21 (s, 1H), 3.97 (m, 4H), 3.50 (m, 1H), 3.10 (m, 1H), 3.01 (d, J = 4.5 Hz, 1H), 2.79 (d, J = 4.5 Hz, 1H), 2.66 (s, 3H), 1.52 (s, 3H), 1.13 (m, 3H), 0.88 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 165.5, 165.4, 163.2, 155.9, 134.4, 133.9, 133.3, 127.9, 127.7, 127.0, 125.2, 123.8, 121.9, 108.9, 101.4, 76.1, 67.1, 55.9, 55.6, 53.1, 47.1, 25.8, 21.3, 20.1, 17.9, 17.6, −4.4, −4.8; HRMS (ESI), *m*/*z* calculated for $C_{30}H_{42}N_2O_7SiNa$: 593.2653; found: 593.2670.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid (2-Methyloxiranyl)-[1-(2-oxopropylcarbamoyl)vinylcarbamoyl]-methyl Ester (3). A solution of alcohol **28** (8.0 mg, 17 μmol) in CH_3CN was treated with IBX (15 mg, 53 μmol) and was warmed at 50 °C for 6 h. Aqueous 10% $Na_2S_2O_3$ (2 mL) was added, and the mixture was stirred at 20 °C for 1 h. The resulting mixture was extracted with EtOAc and washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4) and concentrated, and the residue was purified by preparative TLC (silica, 3% MeOH/CH_2Cl_2) to afford **3** as a solid (4.3 mg, 57%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.85 (br s, 1H), 8.64 (m, 1H) 7.98 (d, J = 2.7 Hz, 1H), 7.49 (d, J = 2.7 Hz, 1H), 7.35 (m, 2H), 6.87 (br t, 1H), 6.54 (d, J = 2.3 Hz, 1H), 5.41 (br m, 1H), 5.25 (s, 1H), 4.22 (d, J = 4.4 Hz, 2H), 3.97 (s, 3H), 3.01 (d, J = 4.5 Hz, 1H), 2.78 (d, J = 4.5 Hz, 1H), 2.66 (s, 3H), 2.23 (s, 3H), 1.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 165.4, 165.4, 163.2, 155.9, 134.4, 133.2, 133.1, 127.9, 127.7, 127.0, 125.2, 123.8, 121.9, 108.8, 103.0, 76.2, 55.8, 55.6, 53.2, 50.1, 27.3, 20.1, 17.6; HRMS (ESI), *m*/*z* calculated for $C_{24}H_{26}N_2O_7Na$: 477.1638; found: 477.1648.

***N*-[2-(*t*-Butyldimethylsilanyloxy)propyl]-2-hydroxyacetamide (30)**. Glycolic acid (0.965 g, 12.7 mmol) was added to a solution of **20** (2.40 g, 12.7 mmol) in CH_2Cl_2/THF (2:1, 150 mL) at 25 °C. Solid EDCI (2.70 g, 13.9 mmol) and HOBt (1.71 g, 12.7 mmol) were added, and the reaction mixture was stirred for 12 h. The mixture was poured onto EtOAc (400 mL) and extracted with water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4) and concentrated,

and the residue was purified by flash chromatography (5 cm × 15 cm silica; 10% diethyl ether in hexanes) to afford **30** as an oil (3.02 g, 96%): IR (film) 3400, 3300, 2944, 2856, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (br s, 1H), 4.18 (s, 2H), 3.95 (m, 2H), 3.51 (m, 1H), 3.12 (m, 1H), 1.18 (d, 3 H), 0.90 (s, 9H), 0.10 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 67.3, 62.0, 46.1, 25.8, 21.3, 18.0, −4.5, −4.9; HRMS (ESI), *m*/*z* calculated for $C_{11}H_{25}NO_3SiNa$: 270.1501; found: 270.1503.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {[2-(*t*-Butyldimethylsilanyloxy)propylcarbamoyl]methoxycarbonyl}-(2-methyloxiranyl)methyl Ester (31). Hydrogen gas was bubbled through a mixture of benzyl ester **19** (30 mg, 71 μmol) and 10% Pd/C (10% w/w loading) in MeOH (10 mL) for 4 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (5 mL) and combined with alcohol **30** (19 mg, 79 μmol). The resulting solution was cooled to 0 °C and was treated with solid EDCI (15 mg, 79 μmol) and DMAP (1 mg) and was stirred for 12 h at 25 °C. The mixture was poured onto EtOAc (100 mL) and washed with equal portions of 5% aqueous HOAc, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (3 cm × 10 cm silica; 0−3% MeOH/CH_2Cl_2) to afford **31** as a solid (25 mg, 55%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (m, 1H), 7.92 (dd, J = 2.7, 3.3 Hz, 1H), 7.50 (d, J = 2.5 Hz, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 6.92 (br t, 1H), 5.09 (d, J = 2.8 Hz, 1H), 4.82 (dd, J = 3.6, 15.4 Hz, 1H), 4.66 (dd, J = 10.1, 15.4 Hz, 1H), 3.97 (s, 3H), 3.96−3.91 (m, 1H), 3.37−3.31 (m, 1H), 3.19−3.15 (m, 1H), 3.00 (t, J = 5.0 Hz, 1H), 2.79 (t, J = 4.3 Hz, 1H), 2.67 (s, 3H), 1.53 (d, J = 5.7 Hz, 3H), 1.10 (d, J = 6.1 Hz, 3H), 0.86 (s, 9H), 0.04 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 166.3, 166.2, 155.8, 134.4, 133.4, 127.8, 127.2, 126.9, 125.3, 123.6, 122.6, 108.7, 75.7, 67.1, 63.3, 55.5, 55.3, 52.7, 46.6, 25.8, 21.3, 20.1, 18.0, 17.6, −4.7, −4.9; HRMS (ESI), *m*/*z* calculated for $C_{29}H_{41}NO_8SiNa$: 582.2494; found: 582.2493.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid (2-Methyloxiranyl)-[(2-oxopropylcarbamoyl)methoxycarbonyl]-methyl Ester (4). Dess−Martin periodinane (54 mg, 0.13 mmol) was added in one portion to a solution of **32** (38 mg, 0.085 mmol) in CH_2Cl_2 (4 mL) at 25 °C. After 1 h, a saturated aqueous solution of $NaHCO_3$ (2 mL) was added, and the reaction mixture was stirred for 10 min. The layers were separated, and the organic phase was washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (1.5 cm × 10 cm silica, 0−3% MeOH in CH_2Cl_2) to afford **4** (0.032 g, 85%): ^1H NMR (400 MHz, $CDCl_3$) δ 8.58 (m, 1H), 7.93 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 2.5 Hz, 1H), 7.33 (m, 2H), 5.27 (s, 1H), 5.18 (br s, 1H), 4.78 (d, J = 1.3 Hz, 2H), 4.13 (d, J = 2.3 Hz, 1H), 4.12 (d, J = 2.3 Hz, 1H), 3.96 (s, 3H), 3.06 (d, J = 4.4 Hz, 1H), 3.05 (d, J = 4.4 Hz, 1H), 2.65 (s, 3H), 2.14 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 202.0, 166.6, 166.2, 166.2, 155.8, 134.4, 133.3, 127.8, 127.3, 126.8, 125.3, 123.5, 122.5, 108.8, 75.8, 63.1, 55.5, 55.4, 52.9, 49.2, 27.1, 20.1, 17.6; HRMS (ESI), *m*/*z* calculated for $C_{23}H_{25}NO_8Na$: 466.1472; found: 466.1459.

[1-(*t*-Butyldiphenylsilanyloxymethyl)-2-oxopropyl]carbamic Acid Benzyl Ester (35). A solution of alcohol **30** (2.54 g, 5.32 mmol) in EtOAc (100 mL) was treated with IBX (2.24 g, 7.98 mmol), and the reaction mixture was warmed at reflux for 14 h. The mixture was filtered, and the filtrate was poured onto 10% aqueous $Na_2S_2O_3$ (2.5 mL) and stirred at 23 °C for 1 h. The mixture was extracted with EtOAc (4 × 25 mL), and the combined organic extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and dried (Na_2SO_4) and concentrated to afford the crude product as a solid (2.50 g, 99%), which was used without further purification: ^1H NMR (400 MHz, $CDCl_3$) δ 7.61 (m, 4H), 7.45−7.35 (m, 11H), 6.83 (br d, 1H), 5.08 (s, 2H), 4.39 (m, 1H), 4.11 (m, 1H), 3.92 (m, 1H), 2.15 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.4, 155.7, 136.3, 135.5, 132.5, 129.9, 128.5, 128.1, 128.0, 127.8, 66.8, 63.8, 62.1, 27.2, 26.7, 19.2,; HRMS (ESI), *m*/*z* calculated for $C_{28}H_{33}NO_4SiNa$: 498.2071; found: 498.2077.

[1-(*t*-Butyldiphenylsilanyloxymethyl)-2,2-dimethoxypropyl]-carbamic Acid Benzyl Ester (36). A solution of ketone **35** (2.50 g, 5.26 mmol) in MeOH (100 mL) was treated with trimethylorthoformate (0.840 g, 7.89 mmol) and camphorsulfonic acid (10 mg). The reaction mixture was warmed at reflux for 6 h. The solvent was removed, and the residue was dissolved in EtOAc (100 mL) and water (50 mL). The organic extract was washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (3 cm × 10 cm silica; 0−5% MeOH/CH_2Cl_2) to afford **36** (1.70 g, 63%) as a solid: ^1H NMR δ 7.69−7.65 (m, 4H), 7.44−7.31 (m, 11H), 5.18 (d, J = 12.4 Hz, 1H), 5.10 (d, J = 12.0 Hz, 1H), 5.03 (m, 1H), 4.13−4.05 (m, 1H), 3.87 (dd, J = 4.0, 10.4 Hz, 1H), 3.78 (dd, J = 5.6, 10.8 Hz, 1H), 3.21 (s, 3H), 3.17 (s, 3H), 1.29 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 136.6, 135.5, 133.1, 129.6, 128.4, 128.0, 127.9, 127.6, 101.2, 66.7, 63.0, 60.2, 48.5, 48.5, 26.8, 19.1, 18.4; HRMS (ESI), *m*/*z* calculated for $C_{30}H_{39}NO_5SiNa$: 544.2490; found: 544.2521.

{[1-(*t*-Butyldiphenylsilanyloxymethyl)-2,2-dimethoxypropyl-carbamoyl]methyl}carbamic Acid Benzyl Ester (37). A mixture of threonine derivative **36** (300 mg, 0.575 mmol) and 10% Pd/C (50 mg) in MeOH (10 mL) was treated with H_2 (1 atm) for 2 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (20 mL) and benzylcarbamate-protected glycine (120 mg, 0.632 mmol), HOBt (89 mg, 0.63 mmol), diisopropylethylamine (0.1 mL), and EDCI (110 mg, 0.632 mmol) were added at 25 °C. The reaction mixture was stirred for 12 h and was poured onto water (100 mL) and extracted with EtOAc (3 × 90 mL). The combined organic extracts were washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (3 cm × 10 cm silica; 0−5% MeOH/CH_2Cl_2) to afford **37** (260 mg, 82%) as a foam: ^1H NMR (400 MHz, $CDCl_3$) δ 7.65 (m, 4H), 7.45−7.26 (m, 11H), 5.18 (d, J = 12 Hz, 1H), 5.10 (d, J = 12 Hz, 1H), 5.02 (br s, 1H), 4.23 (m, 3H), 4.09 (br s, 1H), 3.87 (dd, J = 3.8, 10.0 Hz, 1H), 3.79 (dd, J = 5.6, 10.0 Hz, 1H), 3.21 (s, 3 H), 3.17 (s, 3H), 1.29 (s, 3H), 1.06 (s, 9H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.1, 136.6, 135.6, 135.5, 133.2, 133.1, 129.6, 129.6, 128.4, 128.0, 127.9, 127.6, 101.2, 66.7, 63.0, 48.5, 48.5, 26.8, 19.1, 18.4; HRMS (ESI), *m*/*z* calculated for $C_{32}H_{42}N_2O_6SiNa$: 601.2710; found: 601.2716.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {[(1-Hydroxymethyl-2,2-dimethoxypropylcarbamoyl)methyl]carbamoyl}-(2-methyloxiranyl)methyl Ester (39). A mixture of benzyl ester **15** (80 mg, 0.19 mmol) and 10% Pd/C (25 mg) in MeOH (10 mL) was treated with H_2 (1 atm) for 3 h. Simutaneously, a mixture of benzylcarbamate-protected glycine derivative **38** (71 mg, 0.21 mmol) and 10% Pd/C (7 mg) in MeOH (10 mL) was treated with H_2 (1 atm). Both mixtures were filtered through Celite, and the filtrates were concentrated. The residues were dissolved in CH_2Cl_2 (5 mL each) and combined. HOBt (25 mg, 0.190 mmol) and EDCI (41 mg, 0.209 mmol) were added at 25 °C. The reaction mixture was stirred for 12 h and was poured into water (10 mL) and extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated. Purification of the residue by flash chromatography (1.5 cm × 10 cm silica; 0−5% MeOH/CH_2Cl_2) afforded **39** (73 mg, 74%) as a solid: ^1H NMR (400 MHz, $CDCl_3$) δ 8.60 (t, J = 4.8 Hz, 1H), 7.92 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 2.4 Hz, 1H), 7.33 (d, J = 4.8 Hz, 2H), 6.98 (br t, 1H), 6.60 (d, J = 7.6 Hz, 1H), 5.29 (s, 1H), 4.13 (m, 2H), 3.96 (s, 3H), 3.90 (dd, J = 16.8, 5.4 Hz, 1H), 3.70 (m, 2H), 3.45 (br s, 1H), 3.19 (s, 3H), 3.15 (s, 3H), 3.02 (d, J = 4.4 Hz, 1H), 2.74 (d, J = 4.4 Hz, 1H), 2.66 (s, 3H), 1.52 (s, 3H), 1.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 167.6, 165.7, 155.8, 134.4, 133.2, 127.8, 127.1, 126.9, 125.3, 123.7, 122.3, 108.6, 101.6, 76.3, 62.5, 56.0, 55.6,

55.2, 53.0, 49.0, 48.9, 43.4, 20.1, 17.8, 17.8; HRMS (ESI), *m*/*z* calculated for $C_{26}H_{34}N_2O_9Na$: 541.2162; found: 541.2172.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {[(1-Formyl-2,2-dimethoxypropylcarbamoyl)methyl]carbamoyl}(2-methyloxiranyl)methyl Ester (40). A solution of alcohol **39** (56 mg, 0.11 mmol) in EtOAc (10 mL) was treated with IBX (33 mg, 0.12 mmol), and the reaction mixture was warmed at reflux for 6 h. The reaction mixture was filtered, the filtrate was poured onto 10% aqueous $Na_2S_2O_3$ (2.5 mL), and the mixture was stirred at 23 °C for 1 h. The mixture was extracted with EtOAc (4 × 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl and were dried (Na_2SO_4) and concentrated to afford the crude product as a solid (54 mg, 96%), which was used without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.70 (s, 1H), 8.60 (t, J = 5.0 Hz, 1H), 7.93 (d, J = 2.8 Hz, 1H), 7.48 (d, J = 2.8 Hz, 1H), 7.33 (m, 2H), 6.90 (br t, 1H), 6.71 (t, J = 8.0 Hz, 1H), 5.37 (s, 1H), 4.86, (d, J = 8.0 Hz, 1H), 4.19 (dd, J = 16.8, 6.4 Hz, 1H), 3.92 (s, 3H), 3.25 (s, 3H), 3.22 (s, 3H), 3.04 (d, J = 4.4 Hz, 1H), 2.75 (d, J = 4.4 Hz, 1H), 2.66 (s, 3H), 1.54 (s, 3H), 1.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 168.3, 167.3, 165.5, 155.8, 134.4, 133.2, 127.8, 126.9, 125.5, 123.7, 122.2, 108.6, 101.6, 76.1, 61.9, 56.1, 55.6, 55.1, 52.9, 49.2, 49.1, 43.0, 20.1, 19.0, 17.9; HRMS (ESI), *m*/*z* calculated for $C_{26}H_{32}N_2O_9Na$: 539.2000; found: 539.2012.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {[(1-Acetyl-2-hydroxyvinylcarbamoyl)methyl]carbamoyl}-(2-methyloxiranyl)methyl Ester (5). Aldehyde **40** (54 mg, 0.10 mmol) was dissolved in 10% aqueous acetone (5 mL) and treated with Amberlyst A-15 resin (150 mg) for 6.5 h at 23 °C. The reaction mixture was filtered and concentrated, and the residue was purified by flash chromatography (1.5 cm × 5 cm silica; 3% MeOH/CH_2Cl_2) to afford **5** as a white solid (43 mg, 88%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.24 (d, J = 12 Hz, 1H), 8.60 (m, 2H), 7.91 (d, J = 2.8 Hz, 1H), 7.48 (d, J = 2.8 Hz, 1H), 7.35 (m, 3H), 6.83 (br t, 1H), 5.30 (s, 1H), 4.15 (d, J = 5.6 Hz, 2H), 3.96 (s, 3H), 3.04 (d, J = 4.4 Hz, 1H), 2.81 (d, J = 4.4 Hz, 1H), 2.66 (s, 3H), 2.27 (s, 3H), 1.55 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 168.3, 167.7, 165.5, 155.8, 150.0, 134.3, 133.3, 127.9, 127.8, 126.8, 125.2, 123.7, 122.1, 116.9, 108.5, 75.8, 56.0, 55.5, 53.2, 42.8, 23.8, 20.1, 17.7; HRMS (ESI), *m*/*z* calculated for $C_{24}H_{26}N_2O_8SiNa$: 493.1581; found: 493.1595.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {[(1-Acetyl-2-methoxyvinylcarbamoyl)methyl]carbamoyl}-(2-methyloxiranyl)methyl Ester (41). A solution of vinylogous acid **5** (5.0 mg, 0.011 mmol) in toluene/MeOH (1:1, 2 mL) at 25 °C was treated with trimethylsilyldiazomethane (0.011 mL of a 2.0 M solution in toluene, 0.021 mmol), and the reaction mixture was stirred for 20 min. The volatiles were removed under a stream of nitrogen, and the residue was purified by preparative TLC (5% MeOH/CH_2Cl_2) to afford the product (5.0 mg, 90%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (m, 1H), 7.93 (d, J = 2.8 Hz, 1H), 7.35 (d, J = 2.8 Hz, 1H), 7.32 (d, J = 7.2 Hz, 2H), 7.18 (s, 1H), 6.82 (br t, 1H), 5.35 (m, 2H), 5.28 (s, 3H), 4.18 (m, 1H), 4.05 (m, 1H), 3.90 (s, 3H), 3.83 (s, 3H), 3.05 (d, J = 4.4 Hz, 1H), 2.78 (d, J = 4.4 Hz, 1H), 2.67 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.8, 168.2, 167.8, 165.5, 155.8, 150.1, 134.4, 133.3, 127.9, 127.7, 126.8, 125.3, 123.7, 122.1, 116.8, 108.4, 75.8, 60.3, 56.1, 55.6, 53.2, 42.7, 23.8, 20.1, 17.8; HRMS (ESI), *m*/*z* calculated for $C_{25}H_{28}N_2O_8Na$: 507.1743; found: 507.1748.

{1-[1-(*t*-Butyldiphenylsilanyloxymethyl)-2,2-dimethoxypropylcarbamoyl]-2-hydroxyethyl}carbamic Acid Benzyl Ester (42). A solution of threonine derivative **36** (226 mg, 0.453 mmol) in MeOH (25 mL) was treated with 10% Pd/C (35 mg) and H_2 (1 atm) for 3 h. The reaction mixture was filtered through Celite, and the filtrate was concentrated. The residue was dissolved in CH_2Cl_2 (25 mL) at 25 °C, and benzylcarbamate-protected serine (**24**) (114 mg, 0.476 mmol), HOBt (64 mg, 0.45 mmol), and EDCI (91 mg, 0.48 mmol) were added sequentially. The reaction mixture was stirred for 12 h and then poured onto water (10 mL) and extracted with EtOAc (3 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl and were dried (Na_2SO_4) and concentrated to afford crude **42** (225 mg; 82%), which was used directly without purification.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {1-[1-(*t*-Butyldiphenylsilanyloxymethyl)-2,2-dimethoxypropylcarbamoyl]-2-hydroxyethylcarbamoyl}-(2-methyloxiranyl)methyl Ester (43). A mixture of benzyl ester **15** (35 mg. 83 μmol) and 10% Pd/C (10 mg) in MeOH (10 mL) was treated with H_2 (1 atm) for 2 h at 25 °C. Simultaneously, a mixture of benzylcarbamate-protected serine derivative **42** (51 mg, 84 μmol) and 10% Pd/C (5 mg) in MeOH (10 mL) was treated with H_2 (1 atm). Both reaction mixtures were filtered through Celite, and the filtrates were concentrated. The residues were dissolved in CH_2Cl_2 (3.0 mL each) and combined. HOBt (11 mg, 81 μmol) and EDCI (20 mg, 0.10 mmol) were added, and the reaction mixture was stirred for 12 h at 25 °C. The mixture was poured onto water (10 mL) and was extracted with EtOAc (3 × 30 mL). The combined organic extracts were washed with water and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography (1.5 cm × 5 cm silica; 0−5% MeOH/CH_2Cl_2) to afford **43** (49 mg, 75%) as a solid: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.26 (dd, J = 3.2, 7.2 Hz, 1H), 7.91 (d, J = 2.8 Hz, 1H), 7.63 (m, 5H), 7.47 (d, J = 2.8 Hz, 1H), 7.43−7.35 (m, 12H), 6.86 (d, J = 10.0 Hz, 1H), 5.23 (s, 1H), 4.45 (m, 1H), 4.32 (m, 1H), 3.95 (s, 3H), 3.80 (m, 2H), 3.64 (br s, 1H), 3.13 (m, 1H), 3.07 (s, 3H), 3.04 (s, 3H), 3.00 (d, J = 4.8 Hz, 1H), 2.76 (d, J = 4.8 Hz, 1H), 1.51 (m, 3H), 1.22 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 167.4, 165.7, 155.9, 135.7, 134.4, 133.2, 133.1, 129.8, 129.7, 128.3, 128.1, 127.7, 126.9, 125.1, 123.8, 121.9, 108.6, 101.1, 75.9, 55.9, 55.5, 53.8, 53.5, 53.3, 48.8, 48.6, 48.5, 26.8, 20.1, 19.1, 18.4, 17.4; HRMS (ESI), *m*/*z* calculated for $C_{43}H_{54}N_2O_{10}SiNa$: 809.3445; found: 809.3411.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid {1-[1-(*t*-Butyldiphenylsilanyloxymethyl)-2,2-dimethoxypropylcarbamoyl]-vinylcarbamoyl}(2-methyloxiranyl)methyl Ester (44). A solution of alcohol **43** (12 mg. 15 μmol) in CH_2Cl_2 (2 mL) was cooled to −45 °C. Triethylamine (0.010 mL, 73 μmol) was added followed by methanesulfonylchloride (2.6 mg, 23 μmol). The reaction mixture was allowed to warm to 22 °C and stirred for 2 h. After cooling to 0 °C, DBU (0.010 mL, 66 μmol) was added. The reaction mixture was warmed to 22 °C and stirred for 1 h. The reaction mixture was poured onto water and diluted with EtOAc. The organic extract was washed with 1% aqueous HOAc, water, saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl. The organic extract was dried (Na_2SO_4) and concentrated, and the residue was purified by flash chromatography (1 cm × 5 cm silica; 0−25% EtOAc in CH_2Cl_2) to afford **44** as an oil (6.0 mg, 52%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (br s, 1H), 8.64 (m, 1H), 7.99 (d, J = 2.6 Hz, 1H), 7.60 (m, 4H), 7.49 (d, J = 2.5 Hz, 1H), 7.45−7.30 (m, 8H), 6.51 (d, J = 2.0 Hz, 1H), 6.43 (d, J = 9.7 Hz, 1H), 5.26 (s, 1H), 5.21 (br t, 1 H), 4.31 (m, 1 H), 3.96 (s, 3H), 3.89 (dd, J = 10.1, 4.0 Hz, 1H), 3.77 (dd, J = 10.1, 4.0 Hz, 1 H), 3.16 (s, 3H), 3.14 (s, 3H), 3.01 (d, J = 4.8 Hz, 1H), 2.76 (d, J = 4.8 Hz, 1H), 2.66 (s, 3H), 1.53 (m, 3H), 1.34 (s, 3H), 1.02 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.5, 165.4, 162.7, 155.9, 135.6, 134.4, 133.1, 132.9, 132.8, 129.9, 128.6, 128.1, 127.9, 127.7, 127.0, 125.2, 123.8, 121.8, 108.9, 101.7, 101.2, 76.1, 62.4, 55.9, 55.6, 53.1, 53.0, 48.8, 26.8, 20.1, 19.1, 19.0, 17.6,; HRMS (ESI), *m*/*z* calculated for $C_{43}H_{52}N_2O_9SiNa$: 791.3340; found: 791.3320.

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid [1-(1-Formyl-2,2-dimethoxypropylcarbamoyl)vinylcarbamoyl](2-methyloxiranyl)methyl Ester (46). IBX (4.0 mg, 14 μmol) was added to a solution of alcohol **45** (6.0 mg, 11 μmol) in DMSO and warmed at 50 °C for 6 h. A 10% aqueous solution of $Na_2S_2O_3$ (0.5 mL) was added, and the mixture was stirred at 20 °C for 1 h. The mixture was extracted with EtOAc, and the organic extract was washed with saturated aqueous $NaHCO_3$ and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated to afford crude **46** as a white solid (6.0

mg, 100%), which was used directly without further purification: ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.73 (s, 1H), 8.81 (br s, 1H), 8.62 (m, 1H), 7.97 (d, J = 2.6 Hz, 1H), 7.48 (d, J = 2.6 Hz, 1H), 7.33 (m, 2H), 6.62 (br d, J = 8.0 Hz, 1H), 6.57 (d, J = 2.0 Hz, 1H), 5.46 (m, 1H), 5.25 (s, 1H), 4.88 (d, J = 8.0 Hz, 1H), 3.96 (s, 3H), 3.30 (s, 3H), 3.26 (s, 3H), 2.99 (d, J = 4.4 Hz, 1H), 2.76 (d, J = 4.4 Hz, 1H), 2.66 (s, 3H), 1.52 (s, 3H), 1.26 (s, 3H).

3-Methoxy-5-methylnaphthalene-1-carboxylic Acid [1-(1-Acetyl-2-hydroxyvinylcarbamoyl)vinylcarbamoyl]-(2-methyloxiranyl)methyl Ester (6). Amberlyst A-15 resin (50 mg) was added to a solution of aldehyde **46** in 10% aqueous acetone (1.5 mL) and stirred for 6.5 h at 23 °C. The reaction mixture was filtered and concentrated, and the residue was purified by preparative TLC (silica; 3% MeOH/CH_2Cl_2) to afford **6** as a white solid (5.0 mg; 83%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.06 (d, J = 12.4 Hz, 1H), 9.03 (br s, 1H), 8.72 (br s, 1H), 8.62 (m, 1H), 8.01 (d, J = 2.6 Hz, 1H), 7.50 (d, J = 2.6 Hz, 1H), 7.39−7.33 (m, 1H), 6.70 (d, J = 2.6 Hz, 1H), 5.60 (m, 1H), 5.28 (m, 3H), 3.98 (s, 3H), 3.02 (d, J = 4.5 Hz, 1H), 2.79 (d, J = 4.5 Hz, 1H), 2.67 (s, 3H), 2.32 (s, 3H), 1.53 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.0, 165.5, 165.2, 162.2, 155.9, 149.9, 134.4, 133.2, 132.6, 127.8, 127.6, 127.0, 125.3, 123.7, 122.3, 116.7, 108.7, 105.6, 76.1, 55.9, 55.6, 53.3, 23.8, 20.1, 17.6; HRMS (ESI), m/z calculated for $C_{25}H_{26}N_2O_8Na$: 505.1587; found: 505.1592.

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Supporting Information Available: Full experimental procedures and spectral characterization of intermediates and products. This material is available free of charge via the Internet at http://pubs.acs.org.

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