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Diversity-Oriented Synthesis of 13- to 18-Membered Macrolactams via Ring-Closing Metathesis

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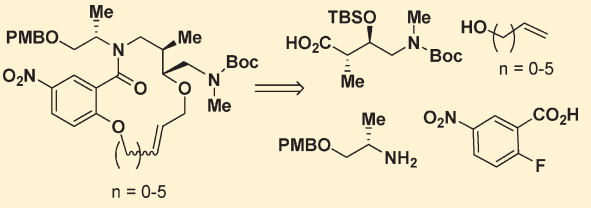
Supporting Information

ABSTRACT: An efficient build/couple/pair approach to diversity-oriented synthesis was employed to access several structurally complex macrolactams. In this paper, we describe the successful evaluation of ring-closing metathesis toward the systematic generation of skeletal diversity. By appropriately varying the nature and chain length of the alkenol fragment, a diverse collection of 13- to 18-membered macrolactams were obtained.



Diversity-oriented synthesis (DOS) has been a topic of increasing interest among both academic and industrial sectors.[1] This interest has stemmed, in large extent, from the apparent lack of structural complexity in known screening collections.[2,3] It has been suggested that this lack of diversity has limited the number of drugs to come to market in the recent past due to the narrow cross section of biological space accessible by these small molecules.[4] This leaves a large area of potential molecular targets such as transcription factors, regulatory RNA, and protein−protein and protein−DNA interactions relatively underexplored in the arena of drug discovery/development.[5] In an effort to access these so-called undruggable targets, several DOS-based libraries have recently been created to help increase the overall complexity of the screening collections in the hopes of modulating some of these more elusive targets.[6]

The build/couple/pair (B/C/P) algorithm has found increasing use in the development of DOS-based chemical libraries.[7] Our attempts to incorporate this strategy in recent library design focused on a diastereoselective aldol reaction to access **2** in the initial stages of the synthesis (*build phase*) (Figure 1).[7a] By coupling this amino acid with a complementary amino alcohol, **1**, we were able to access all stereochemical combinations of amine **3**, which has been applied in several library campaigns[7a,8] to gain access to stereo/structure−activity relationships (SSAR).[9] In our initial study[7a] we applied ring-closing metathesis (RCM)[10,11] as a pairing strategy to access the 14-membered macrolactams in all stereochemical combinations (16 stereoisomers total). Macrocycles in general are appealing in the context of drug discovery as they have been used successfully on a variety of important target classes, including proteases, G protein-coupled receptors (GPCRs), and protein−protein interactions.[12] The goal of the present study is to explore the feasibility of accessing different macrocyclic ring sizes using RCM as a pairing strategy. The ability to systematically vary the ring size of the RCM-derived macrocycle would potentially be useful in exploring the influence of skeletal diversity on biological activity.

Herein we demonstrate that 13- to 18-membered rings can be successfully formed with the RCM pairing strategy. Focusing on a single stereoisomer (2*S*,5*R*,6*R*) for this study, the pair phase involves the application of an intermolecular S_NAr reaction with aryl fluoride **5**[13] and commercially available alkenols.[14] Our plan called for systematically varying the alkenols to gain access to increasingly larger rings (Scheme 1). This approach would allow for the direct access to a number of ring sizes without the need for changing the overall synthetic strategy.

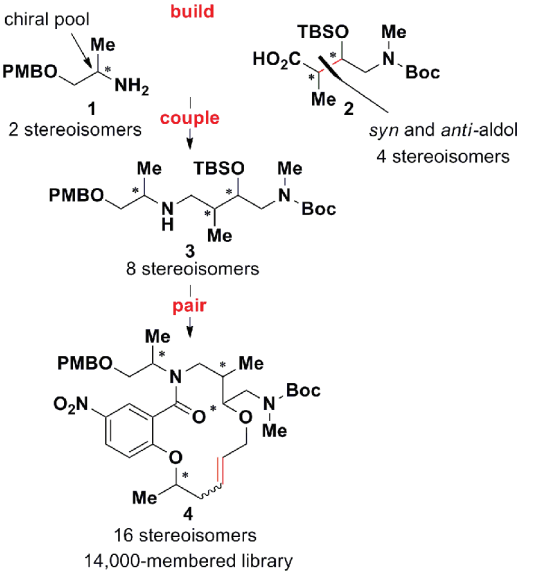


Figure 1. Build/couple/pair strategy for the synthesis of stereochemically diverse macrolactams.

It was found that exposure of enantio-enriched **5** to a solution of sodium hydride and requisite alcohols in THF at 0 °C provided the desired S_NAr products in excellent yields (82−91%). The reaction was found to work well with several different alcohols,

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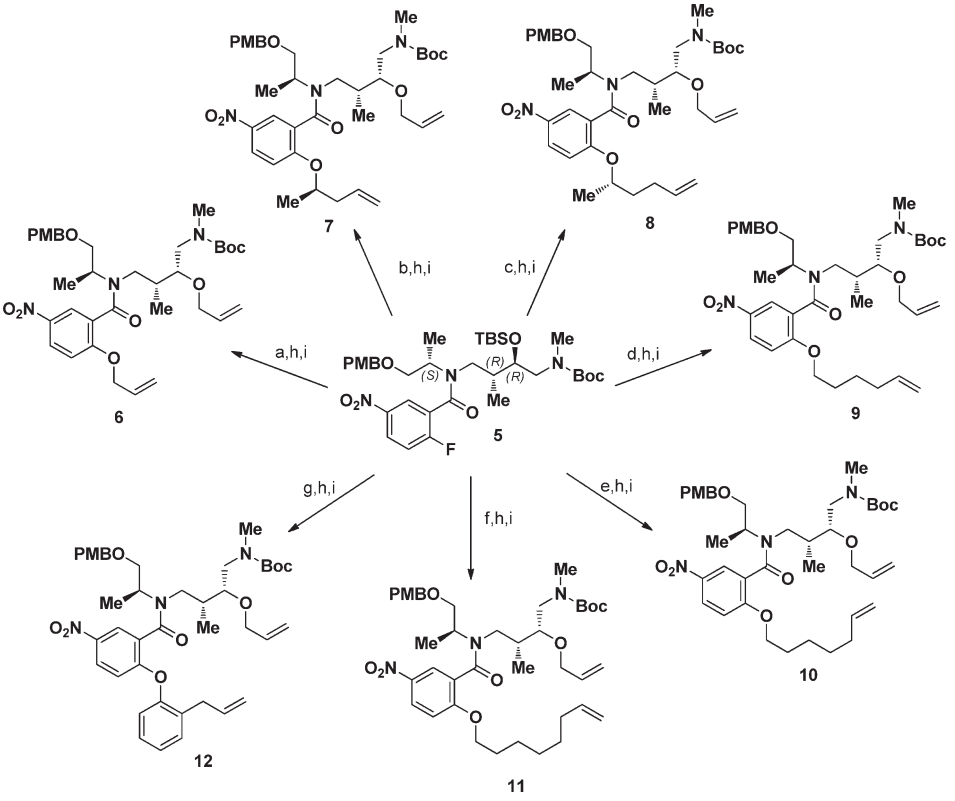
Scheme 1. Synthesis of RCM Precursors[a]



[a] Reagents and conditions: (a−g) alcohol, NaH, THF, 0−23 °C, [(a) allyl alcohol, 88%; (b) (*S*)-4-penten-2-ol, 82%; (c) (*R*)-5-hexen-2-ol, 89%; (d) 5-hexenol, 91%; (e) 6-heptenol, 91%; (f) 7-octenol, 91%; (g) 2-allyl phenol, 83%]; (h) TBAF, THF, 0−25 °C (82−99%); (i) NaH, allyl bromide, DMF, 0−25 °C (80−95%).

including primary, secondary, and aryl systems. Deprotection of the TBS silyl ether using TBAF followed by allylation of the resulting secondary alcohol with allyl bromide afforded the respective RCM precursors **6**−**12** in excellent overall yields (80−95%).

At this stage we began to investigate the scope and limitations of the RCM reaction. To this end, we tested the metathesis reaction on all our substrates with three commercially available ruthenium-based catalysts. Compounds **6**−**12** were subjected to Grubbs first generation (G1) and second generation (G2) and Grubbs−Hoveyda second generation (GH2) catalysts at 65 °C in toluene (Table 1). Little variation was noticed among the three catalysts with respect to overall chemical conversion for each of the ring sizes (Table 1, entries 1−18). Moreover, the product to dimer ratio was found to be independent of the catalyst employed in the reaction.[15] The 14- through 18-membered ring systems gave the best product to dimer ratios (98:2 to 100:0) using G1 catalyst with isolated yields ranging from 69−88% (Table 1, entries 7, 10, 13, and 16). A notable exception to this trend was the 13-membered ring system, which was found to give 85−88% conversion using various catalysts (Table 1, entries 1−3). Also, the 13-membered ring was found to be the most difficult system to close, with substantial amounts of dimers observed under all three catalyst conditions. G1 proved to be the best catalyst, with nearly 20% dimer and a 55% overall yield for the desired macrocycle (Table 1, entry 1).

Further optimization of the 13-membered system was undertaken in an effort to improve the yield and decrease dimerization. We chose to focus on Grubbs first generation catalyst since this reagent performed best in our initial screening for this ring system (Table 1, entries 1−3). In an attempt to improve the product to dimer ratio, we carried out the reaction in a range of solvents, and the results are summarized in Table 2. Aromatic solvents, including benzene, chlorobenzene, trifluorotoluene and xylenes, gave product to dimer ratios similar to that observed for toluene (Table 2, entries 2−5) as did the non-aromatic solvent ethyl acetate (entry 6). Finally it was found that DCM provided full conversion of the starting materials, albeit with product to dimer ratios identical to those for toluene (Table 2, entry 7). Though the product to dimer ratio remained the same, the overall isolated yield was significantly improved (from 55% to 79%).

We next surveyed the role of known additives that have been shown to affect the outcome of metathesis reactions.[16] Unfortunately, neither 1,4-benzoquinone nor acetic acid improved the overall selectivity of the reaction and in fact lowered the overall conversion (Table 2, entries 8 and 9).

In an effort to add additional structural diversity to the backbone of the macrocycle, we sought to incorporate a biaryl ether linkage. This is a common structural motif in a number of biologically active compounds, including vancomycin, K-13, bouvardin, OF4949-III, or biphenomycin-A.[17] Exposure of **8** to G1, G2, or GH2 provided excellent conversion and minimal dimer formation (Table 3).

In summary, application of the ring-closing metathesis reaction provided rapid entry to complex macrocyclic core systems

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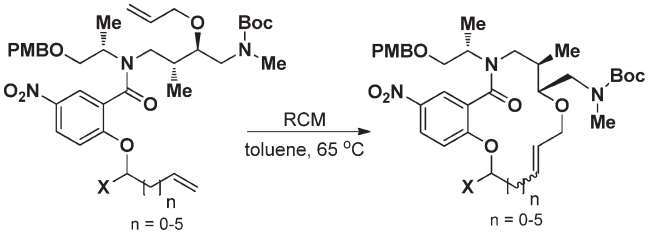
Table 1. Ring Size Variation via RCM



entry[a]	SM → P (ring size, X)	catalyst[b]	time (h)	conversion[c] (%)	UV ratio product:dimers[c]	yield[d] (%)
1	**6** → **13** (13, H)	G1	1	88	81:19	55
2		G2	1	88	60:40	
3		GH2	1	85	54:46	
4	**7** → **14** (14, Me)	G1	1	100	100:0	
5		G2	1	100	100:0	
6		GH2	1	100	100:0	85
7	**8** → **15** (15, Me)	G1	3	100	98:2	73
8		G2	2	99	95:5	
9		GH2	2	98	90:10	
10	**9** → **16** (16, H)	G1	3	99	98:2	88
11		G2	2	100	95:5	
12		GH2	2	100	90:10	
13	**10** → **17** (17, H)	G1	1	98	98:2	83
14		G2	1	98	98:2	
15		GH2	1	98	98:2	
16	**11** → **18** (18, H)	G1	1	100	98:2	69
17		G2	1	100	98:2	
18		GH2	1	100	91:9	

[a] Reactions run on 20 mg of material, 0.01 M in toluene, 65 °C, and 10 mol % catalyst. [b] G1 = Grubbs catalyst (first generation), G2 = Grubbs catalyst (second generation), and GH2 = Grubbs−Hoveyda catalyst (second generation). [c] From LC−MS analysis. [d] Yields based on products isolated after flash chromatography.

starting from a common intermediate, **5**. This synthetic sequence has been shown to be general for varying ring sizes (13- through 18-membered) and structural types (linear and branched alkyl and biaryl ethers). The two key steps of our approach are (i) an efficient intermolecular S_NAr reaction of a number of commercially available alkenyl alcohols to allow direct access to any number of bisallylated building blocks and (ii) a high-yielding ring-closing metathesis showing utility over a wide range of ring sizes. The ability to access a collection of such related ring systems is beneficial for library development and for providing structure−activity relationships once a hit is identified from one of the ring sizes.

EXPERIMENTAL SECTION

General Experimental Methods. All oxygen- and/or moisture-sensitive reactions were carried out under a N_2 atmosphere in glassware that had been flame-dried under vacuum (~0.5 mmHg) and purged with N_2 prior to use. All reagents and solvents were purchased from commercial vendors and used as received or synthesized according to the footnoted references. NMR spectra were recorded on a 300 MHz (^{1}H)/75 MHz (^{13}C) or 500 MHz (^{1}H)/125 MHz (^{13}C) spectrometer. Unless otherwise indicated, NMR data were collected at 25 °C. Flash chromatography was performed using 40−60 μm silica gel (60 Å mesh) on an automated medium-pressure liquid chromatography instrument. Analytical thin layer chromatography (TLC) was performed on commercially available plates with 0.25 mm of silica gel. Visualization was accomplished with UV light and aqueous potassium permanganate ($KMnO_4$) stain followed by heating.

General Procedure for the Synthesis of RCM Precursors. *S_NAr Reaction.* A solution of the alcohol (4.0 equiv) in THF (0.38 M) was cooled to 0 °C in an ice bath. Sodium hydride (60% dispersion in mineral oil, 4.0 equiv) was added portionwise, and the reaction was stirred for 20 min at 0 °C. A solution of compound **5**[7a] (2.45 mmol) in THF (2 M) was added via cannula over 2 min. The solution turned yellow over the addition of the amine. The reaction was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was quenched with water, and the aqueous layer was extracted two times with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by chromatography over silica gel to provide the S_NAr product.

TBS Deprotection. A solution of S_NAr product from the previous step (1.0 equiv) in THF (0.1 M) was cooled to 0 °C in an ice bath. A solution of tetrabutylammonium fluoride in THF (1.0 M, 2.0 equiv) was added dropwise over 3 min, and the reaction was stirred for 12 h, slowly warming to room temperature. The reaction was quenched with saturated aqueous NH_4Cl and water and extracted three times with EtOAc. The combined organic layers were dried ($MgSO_4$), filtered, and concentrated to provide the crude product, which could be purified by flash chromatography on silica gel to get a pure secondary alcohol.

Allylation. A solution of the secondary alcohol (1.0 equiv) in DMF (0.1 M) was cooled to 0 °C in an ice bath. Allyl bromide (10.0 equiv) was

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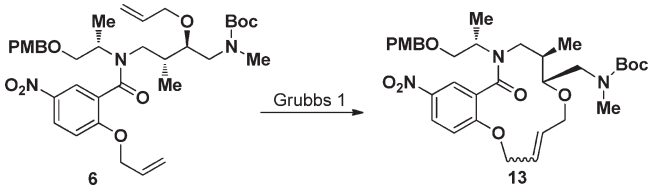
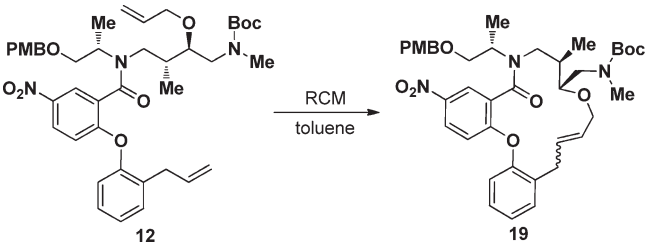
Table 2. Optimization of the RCM To Form the 13-Membered Macrolactam



entry[a]	solvent[b]	additive	T (°C)	time (h)	conversion[c] (%)	UV ratio product:dimers[c]	yield[d] (%)
1	PhMe		65	3	85	81:19	55
2	PhH		65	3	84	73:27	
3	PhCI		65	3	86	78:22	
4	$PhCF_3$		65	3	71	72:28	
5	xylenes		65	3	77	77:23	
6	EtOAc		40	3	78	74:26	
7	CH_2CI_2		40	4	100	85:15	79
8	CH_2CI_2	BQ	40	5	93	81:19	
9	CH_2CI_2	AcOH	40	5	89	85:15	

[a] Reactions run on 20 mg of material, 0.01 M in toluene, 65 °C, and 10 mol % catalyst. [b] G1 = Grubbs catalyst (first generation), G2 = Grubbs catalyst (second generation), and GH2 = Grubbs−Hoveyda catalyst (second generation). [c] From LC−MS analysis. [d] Yields based on products isolated after flash chromatography.

Table 3. Accessing Macrocyclic Biaryl Ether through RCM



entry	catalyst[a,b]	time (h)	conversion[c] (%)	UV ratio product: dimers[c]	yield[d] (%)
1	G1	1	100	98:2	87
2	G2	1	100	98:2	
3	GH2	1	100	91:9	

[a] G1 = Grubbs catalyst (first generation), G2 = Grubbs catalyst (second generation), GH2 = Grubbs−Hoveyda catalyst (second generation). [b] Reactions run on 20 mg of material, 0.01 M in toluene, 65 °C, and 10 mol % catalyst. [c] From LC−MS analysis. [d] Yields based on products isolated after flash chromatography.

then added, followed by sodium hydride (60% dispersion in mineral oil, 2.4 equiv) as a solid in one portion, and the reaction was stirred for 12 h, slowly warming to room temperature. The reaction mixture was quenched with aqueous saturated NH_4Cl solution and extracted three times with ethyl acetate. The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product, which was purified by chromatography on silica gel to give pure allylated products **6**−**12**.

***tert*-Butyl ((2*R*,3*R*)-2-(Allyloxy)-4-(2-(allyloxy)-*N*-((*S*)-1-((4-methoxybenzyl)oxy)prop-2-yl)-5-nitrobenzamido)-3-methylbutyl)(methyl)carbamate (6).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -40.9$ (c 1.02, $CHCl_3$); IR (cm^{-1}) 2974, 2934, 1690, 1635, 1612, 1587, 1514, 1484, 1454, 1391, 1365, 1340, 1270, 1247, 1157, 1077; ^{1}H NMR (500 MHz, DMSO-d_6, 140 °C) δ 8.20 (dd, J = 8.5, 2.5 Hz, 1H), 7.97 (d, J = 3.0 Hz, 1H), 7.27 (d, J = 9.5, Hz, 1H), 7.20 (br s, 2H), 6.90 (d, J = 8.0 Hz, 2H), 6.02 (ddt, J = 16.5, 11.0, 5.5 Hz, 1H), 5.85 (br s, 1H), 5.43 (dd, J = 17, 1.5 Hz, 1H), 5.30 (d, J = 10.5 Hz, 1H), 5.20 (br s, 1H), 5.10 (s, 1H), 4.75 (d, J = 5.0 Hz, 1H), 4.40 (br s, 2H), 3.96 (br s, 2H), 3.90−3.70 (obsc br s, 1H), 3.79 (s, 3H), 3.70−3.00 (br, 4H), 3.35 (d, J = 11 Hz, 1H), 2.84 (s, 3H), 2.17 (br s, 1H), 1.44 (s, 9H), 1.23 (br s, 3H), 0.96 (br s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 166.4, 158.5, 158.3, 154.4, 140.6, 134.8, 134.8, 131.6, 129.8, 128.1, 128.1, 124.8, 122.9, 117.5, 114.8, 113.3, 112.6, 79.9, 77.9, 71.5, 70.7, 70.1, 69.2, 54.6, 53.6, 49.3, 42.6, 34.9, 34.5, 27.5, 15.0, 12.7; HRMS (ESI) m/z calcd for $C_{35}H_{49}N_3O_9$ $[M + H]^+$ 656.3542, found 656.3549.

***tert*-Butyl ((2*R*,3*R*)-2-(Allyloxy)-4-(*N*-((*S*)-1-((4-methoxybenzyl)oxy)prop-2-yl)-5-nitro-2-((*S*)-pent-4-en-2-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate (7).** Synthesis and characterization of this compound has been previously reported.[7a]

***tert*-Butyl ((2*R*,3*R*)-2-(Allyloxy)-4-(2-((*R*)-hex-5-en-2-yloxy)-*N*-((*S*)-1-((4-methoxybenzyl)oxy)prop-2-yl)-5-nitrobenzamido)-3-methylbutyl)(methyl)carbamate (8).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -63.4$ (c 1.13, $CHCl_3$); IR (cm^{-1}) 2976, 2934, 1688, 1635, 1610, 1587, 1513, 1481, 1452, 1390, 1365, 1337, 1268, 1247, 1152, 1111, 1075, 1034; ^{1}H NMR (500 MHz, DMSO-d_6, 140 °C) δ 8.20 (dd, J = 9.0, 3.0 Hz, 1H), 7.98 (d, J = 3.0 Hz, 1H), 7.24 (d, J = 9.0, Hz, 2H), 7.22 (br s, 1H), 6.90 (d, J = 8.5 Hz, 2H), 5.85 (ddt, J = 17.0, 10.5, 6.5 Hz, 2H), 5.19 (br s, 1H), 5.08 (br s, 1H), 5.01 (dd, J = 17.0, 1.5 Hz, 1H), 4.96 (d, J = 10.0 Hz, 1H), 4.72 (q, J = 6.5 Hz, 1H), 4.41 (br s, 2H), 3.98 (br s, 2H), 3.87−3.78 (br s, 1H), 3.78 (s, 3H), 3.74−3.00 (br s, 4H), 3.35 (d, J = 11.5 Hz, 2H), 2.86 (s, 3H), 2.16 (m, 3H), 1.81 (m, 1H), 1.73 (m, 1H), 1.42 (s, 9H), 1.34 (d, J = 6.0 Hz, 3H), 1.26 (obsc br s, 3H), 1.01 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 158.5, 157.9, 154.4, 140.1, 137.0, 134.7, 128.5, 128.0, 124.7, 123.2, 114.7, 114.0, 113.3, 112.6, 80.0, 77.9, 74.3, 71.5, 70.8, 70.2, 54.5, 53.4, 49.4, 42.3, 35.5, 34.5, 34.4, 27.9, 27.4, 18.4, 15.1, 12.8; HRMS (ESI) m/z calcd for $C_{38}H_{55}N_3O_9$ $[M + H]^+$ 698.4011, found 698.4002.

***tert*-Butyl ((2*R*,3*R*)-2-(Allyloxy)-4-(2-(hex-5-en-1-yloxy)-*N*-((*S*)-1-((4-methoxybenzyl)oxy)-prop-2-yl)-5-nitrobenzamido)-3-methylbutyl)(methyl)carbamate (9).** This compound was synthesized

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by the general procedure described above: $[\alpha]_D^{20} = -39.2$ (*c* 1.27, $CHCl_3$); IR (cm^{-1}) 2935, 1689, 1635, 1611, 1587, 1513, 1454, 1391, 1365, 1338, 1269, 1246, 1153, 1075, 1033; ^1H NMR (500 MHz, DMSO-d_6, 140 °C) δ 8.20 (dd, *J* = 9.5, 3.0 Hz, 1H), 7.98 (d, *J* = 3.0 Hz, 1H), 7.24 (d, *J* = 9.5, Hz, 2H), 7.21 (br s, 1H), 6.90 (d, *J* = 9.0 Hz, 2H), 5.85 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 2H), 5.20 (br s, 1H), 5.08 (br s, 1H), 5.02 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.97 (d, *J* = 9.5, 0.5 Hz, 1H), 4.41 (br s, 2H), 4.18 (m, 1H), 3.97 (br s, 2H), 3.84 (br s, 1H), 3.78 (s, 3H), 3.74−3.00 (br s, 4H), 3.37 (d, *J* = 11.5 Hz, 2H), 2.86 (br, s, 3H), 2.16 (br s, 1H), 2.11 (q, *J* = 7.5 Hz, 2H), 1.79 (pent, *J* = 7 Hz, 1H), 1.55 (pent, *J* = 7.5 Hz, 1H), 1.44 (s, 9H), 1.25 (br s, 3H), 0.98 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 158.8, 158.5, 154.4, 140.3, 137.4, 134.4, 129.8, 128.0, 127.9, 124.8, 122.9, 114.7, 113.8, 113.3, 112.2, 80.0, 77.9, 71.5, 70.8, 70.1, 68.7, 54.5, 53.5, 49.3, 42.2, 35.0, 34.5, 31.8, 27.4, 27.3, 23.9, 14.9, 12.7; HRMS (ESI) *m*/*z* calcd for $C_{38}H_{55}N_3O_9$ $[M + H]^+$ 698.4011, found 698.4005.

***tert*-Butyl ((2*R*,3*R*)-2-(Allyloxy)-4-(2-(hept-6-en-1-yloxy)-*N*-((*S*)-1-((4-methoxybenzyl)-oxy)prop-2-yl)-5-nitrobenzamido)-3-methylbutyl)(methyl)carbamate (10).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -36.1$ (*c* 1.42, $CHCl_3$); IR (cm^{-1}) 2932, 1689, 1636, 1611, 1587, 1513, 1455, 1391, 1365, 1338, 1269, 1246, 1154, 1110, 1075, 1034; ^1H NMR (500 MHz, DMSO-d_6, 130 °C) δ 8.20 (dd, *J* = 9.5, 3.0 Hz, 1H), 7.98 (d, *J* = 3.0 Hz, 1H), 7.25 (d, *J* = 9.5, Hz, 2H), 7.21 (br s, 1H), 6.90 (d, *J* = 8.5 Hz, 2H), 5.83 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 2H), 5.20 (br s, 1H), 5.08 (br s, 1H), 5.01 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.95 (d, *J* = 9.5, Hz, 1H), 4.41 (br s, 2H), 4.17 (m, 2H), 3.97 (br s, 2H), 3.84 (br s, 1H), 3.78 (s, 3H), 3.74−3.00 (br s, 4H), 3.37 (d, *J* = 11.5 Hz, 2H), 2.86 (br, s, 3H), 2.18 (br s, 1H), 2.07 (apt. d, *J* = 6.5 Hz, 2H), 1.77 (pent, J = 7 Hz, 2H), 1.55 (pent, J = 6.5 Hz, 2H), 1.45 (s, 13H), 1.25 (br s, 3H), 0.98 (br s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.4, 158.8, 158.4, 154.3, 140.3, 137.7, 134.7, 129.8, 128.0, 128.0, 124.8, 122.8, 114.7, 113.5, 113.3, 112.2, 79.9, 77.9, 71.5, 70.8, 70.1, 68.8, 54.5, 53.5, 49.4, 42.2, 35.0, 34.5, 32.1, 27.7, 27.4, 27.2, 24.1, 14.8, 12.7; HRMS (ESI) *m*/*z* calcd for $C_{39}H_{57}N_3O_9$ $[M + H]^+$ 711.4095, found 711.4157.

***tert*-Butyl ((2*R*,3*R*)-2-(Allyloxy)-4-(*N*-((*S*)-1-((4-methoxybenzyl)-oxy)prop-2-yl)-5-nitro-2-(oct-7-en-1-yloxy)benzamido)-3-methylbutyl)(methyl)carbamate (11).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -34.1$ (*c* 1.44, $CHCl_3$); IR (cm^{-1}) 1931, 2857, 1690, 1636, 1611, 1587, 1513, 1455, 1391, 1365, 1337, 1269, 1246, 1154, 1110, 1076, 1034; ^1H NMR (500 MHz, DMSO-d_6, 130 °C) δ 8.20 (dd, *J* = 9.5, 2.5 Hz, 1H), 7.97 (d, *J* = 3.0 Hz, 1H), 7.25 (d, *J* = 9.5, Hz, 2H), 7.21 (br s, 1H), 6.89 (d, *J* = 8.5 Hz, 2H), 5.83 (ddt, *J* = 17.5, 10.5, 7.0 Hz, 2H), 5.18 (br s, 1H), 5.09 (br s, 1H), 5.01 (dd, *J* = 17.0, 1.5 Hz, 1H), 4.95 (d, *J* = 10.5, Hz, 1H), 4.41 (br s, 2H), 4.17 (m, 2H), 3.97 (obsc br s, 2H), 3.83 (obsc br s, 1H), 3.78 (s, 3H), 3.74−3.00 (br s, 4H), 3.37 (d, *J* = 11.5 Hz, 2H), 2.85 (br, s, 3H), 2.18 (br s, 1H), 2.05 (q, *J* = 6.5 Hz, 2H), 1.76 (pent, *J* = 7 Hz, 2H), 1.45 (s, 15H), 1.25 (br s, 3H), 0.97 (br s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 166.4, 158.8, 158.5, 154.3, 140.3, 137.9, 134.7, 129.7, 128.0, 127.9, 124.8, 122.9, 114.7, 113.4, 113.3, 112.2, 79.9, 77.9, 71.5, 70.8, 70.1, 68.8, 54.5, 53.5, 49.4, 42.2, 35.0, 34.5, 32.1, 27.8, 27.4, 27.4, 27.3, 24.4, 14.8, 12.7; HRMS (ESI) *m*/*z* calcd for $C_{40}H_{59}N_3O_9$ $[M + H]^+$ 726.4324, found 726.4311.

***tert*-Butyl ((2*R*,3*R*)-2-(Allyloxy)-4-(2-(2-allylphenoxy)-*N*-((*S*)-1-((4-methoxybenzyl)oxy)prop-2-yl)-5-nitrobenzamido)-3-methylbutyl)(methyl)carbamate (12).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -33.7$ (*c* 1.05, $CHCl_3$); IR (cm^{-1}) 2974, 2934, 1690, 1635, 1612, 1514, 1454, 1340, 1270, 1247, 1157, 1077. ^1H NMR (500 MHz, DMSO-d_6, 130 °C) δ 8.16 (m, 2H), 7.38 (d, *J* = 7.0 Hz, 1H), 7.32 (t, *J* = 6.0 Hz, 1H), 7.26 (t, *J* = 6.5 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.87 (d, *J* = 8.0 Hz, 2H), 6.83 (d, *J* = 10.5 Hz, 1H), 5.92 (ddt, *J* = 16.5, 10.5, 6.5 Hz, 1H), 5.84 (br s, 1H), 5.18 (br d, J = 14.5 Hz, 1H), 5.07 (apt. AB, J_A = 12.0 Hz, 1H), 5.01 (apt. AB, J_B = 10.0 Hz, 1H), 4.46 (s, 2H), 4.04 (q, J = 6.0 Hz, 1H), 3.97 (br s, 1H), 3.78 (s, 3H), 3.70−3.40 (br s, 4H), 3.35 (d, *J* = 6.0 Hz, 2H), 3.21 (br s, 1H), 2.87 (s, 3H), 2.21 (br s, 1H), 1.43 (s, 9H), 1.30 (br s, 3H), 0.99 (br s, 3H); ^{13}C NMR (125 MHz, DMSO) δ 166.0, 158.5, 157.6, 154.3, 151.5, 141.8, 135.1, 134.7, 131.3, 130.2, 129.7, 128.7, 128.0, 127.3, 125.0, 124.7, 123.5, 119.6, 115.3, 115.3, 114.8, 113.3, 79.9, 77.9, 71.6, 70.7, 70.2, 54.5, 53.8, 49.4, 42.5, 35.0, 34.5, 32.4, 27.4, 15.0, 12.8; HRMS (ESI) *m*/*z* calcd for $C_{41}H_{53}N_3O_9Na$ $[M + Na]^+$ 754.3679, found 754.3653.

General Procedure for RCM/Hydrogenation. *RCM.* A solution of allylated product synthesized by the first general procedure described above (1.0 equiv) and G1, G2, or GH2 catalyst (0.10 equiv) in toluene (0.01 M with respect to starting material) was degassed with dry nitrogen. The reaction was heated and stirred for 4 h at 65 °C. The solvent was evaporated under reduced pressure and purified by flash chromatography on silica gel. The resulting products (a mixture of geometric isomers) were redissolved in ethyl acetate (0.02 M) and stirred overnight with activated carbon. The mixture was then filtered over Celite and concentrated to provide the cyclized products **13**−**19**. Since the product was isolated as a mixture of *E* and *Z* isomers, full characterization was carried out after hydrogenation.

Hydrogenation. To a solution of the RCM products **13**−**19** (1.0 equiv) in methanol (0.02 M) was added 10% Pd on activated carbon (0.065−0.10 equiv). Into the mixture was bubbled hydrogen gas for 30 min, after which the reaction was placed under a static H_2 environment (balloon pressure) for 12−15 h. The reaction mixture was filtered through Celite, washing the filter cake with EtOAc, DCM, and finally hot EtOAc. The filtrate was concentrated, and the crude residue was purified by flash chromatography on silica gel using MeOH in DCM to provide the pure anilines **13H**−**19H** (structures not shown), which were suitable for characterization.

***tert*-Butyl (((7*R*,8*R*)-13-Amino-10-((*S*)-1-((4-methoxybenzyl)-oxy)prop-2-yl)-8-methyl-11-oxo-3,4,5,7,8,9,10,11-octahydro-2*H*-benzo[*b*][1,9,5]dioxaazacyclotridec-7-yl)methyl)(methyl)-carbamate (13H).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -27.4$ (*c* 0.27, $CHCl_3$); IR (cm^{-1}) 3348, 3232, 2964, 2931, 2871, 1683, 1610, 1512, 1455, 1245, 1157, 1085, 1033; ^1H NMR (500 MHz, DMSO-d_6) δ 8.01 (br s, 1H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.89 (d, *J* = 8.5 Hz, 2H), 6.59 (d, *J* = 8.5 Hz, 1H), 6.50 (dd, *J* = 8.4, 2.6 Hz, 1H), 6.40 (d, *J* = 2.5 Hz, 1H), 4.38 (d, *J* = 3 Hz, 2H), 4.16 (s, 2H), 4.01 (dq, *J* = 13.1, 6.5, 1H), 3.77 (s, 3H), 3.64 (dd, *J* = 9.8, 6.8, 1H), 3.50 (dd, *J* = 10.0, 6.0, 1H), 3.39 (t, *J* = 6.3, 2H), 3.35 (dd, *J* = 8.1, 4.3 Hz, 1H), 3.32−3.22 (m, 3H), 3.15 (dd, *J* = 14.3, 8.1 Hz, 1H) 2.83 (s, 3H), 2.12 (m, 1H), 1.50−1.42 (obs. m, 2H), 1.43 (s, 9H), 1.34 (td, *J* = 14.3, 7.0 Hz, 2H), 1.21 (d, *J* = 6.8 Hz, 3H), 0.89 (m, 5H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.1, 158.4, 154.4, 144.1, 139.9, 130.0, 128.1, 128.1, 125.0, 116.2, 115.7, 113.3, 113.3, 113.2, 113.1, 80.0, 77.8, 71.4, 69.0, 54.7, 54.6, 53.1, 53.0, 49.2, 44.8, 34.8, 34.5, 34.4, 31.3, 27.6, 27.5, 18.0, 15.2, 15.1, 12.7, 12.6; HRMS (ESI) *m*/*z* calcd for $C_{33}H_{49}N_3O_7$ $[M + H]^+$ 600.3649, found 6 00.3640.

***tert*-Butyl (((2*S*,8*R*,9*R*)-14-Amino-11-((*S*)-1-((4-methoxybenzyl)-oxy)prop-2-yl)-2,9-dimethyl-12-oxo-2,3,4,5,6,8,9,10,11,12-decahydrobenzo[*b*][1,9,5]dioxaazacyclotetradec-8-yl)methyl)-(methyl)carbamate (14H).** Synthesis and characterization of this compound has been previously reported.[7a]

***tert*-Butyl (((2*R*,9*R*,10*R*)-15-Amino-12-((*S*)-1-((4-methoxy-benzyl)oxy)prop-2-yl)-2,10-dimethyl-13-oxo-3,4,5,6,7,9,10,11,12,13-decahydro-2*H*-benzo[*b*][1,9,5]dioxaazacyclopentadec-9-yl)methyl)(methyl)carbamate (15H).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -80.0$ (*c* 0.36, $CHCl_3$); IR (cm^{-1}) 3428, 3349, 2970, 2933, 2872, 1684, 1226, 1153, 1084; ^1H NMR (500 MHz, DMSO-d_6) δ 7.20 (br s, 2H), 6.90 (d, *J* = 8.3 Hz, 2H), 6.70 (d, *J* = 8.6 Hz, 1H), 6.58 (d, *J* = 6.3 Hz, 1H), 6.41 (s, 1H), 4.37 (obsc br s, 2H), 4.27 (obsc br s, 1H), 3.95 (br s, 1H), 3.78 (s, 3H), 3.50 (br s, 1H), 3.34 (br s, 2H), 2.85 (s, 3H), 1.53 (obsc br m, 3H), 1.43 (s, 9H), 1.23 (obsc br s, 3H), 1.19 (d, *J* = 5.4, 3H), 0.88 (br s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.8, 158.4, 154.5, 144.2, 140.6, 130.0, 128.2, 128.1, 127.9,

114.9, 113.4, 113.3, 77.7, 71.4, 66.9, 54.7, 54.6, 53.2, 48.1, 34.8, 27.6, 27.5, 23.0, 21.6, 18.8, 15.1, 12.0; HRMS (ESI) m/z calcd for $C_{36}H_{56}N_3O_7$ $[M + H]^+$ 642.4118, found 642.4111.

***tert*-Butyl (((10*S*,11*R*)-16-Amino-13-((*S*)-1-((4-methoxybenzyl)-oxy)propan-2-yl)-11-methyl-14-oxo-2,3,4,5,6,7,8,10,11,12,13,14-dodecahydrobenzo[*b*][1,9,5]dioxaazacyclohexadec-10-yl)-methyl)(methyl)carbamate (16H).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -2.6$ (c 0.30, $CHCl_3$); IR (cm^{-1}) 3350, 2971, 2932, 2860, 1686, 1612, 1498, 1470, 1245, 1226, 1153, 1084; ^1H NMR (500 MHz, DMSO-d_6) δ 7.23 (d, J = 22.2 Hz, 2H), 6.90 (d, J = 7.3 Hz, 2H), 6.73 (s, 1H), 6.59 (dd, J = 8.6, 2.7 Hz 1H), 6.42 (s, 1H), 4.46 (obsc br s, 1H), 4.32 (obsc br s, 3H), 3.88 (s, 4H), 3.77 (s, 3H), 3.61 − 3.49 (m, 2H), 3.35 (d, J = 14.1, 3H), 3.14 (br s, 1H), 2.94 (obsc br s, 1H), 2.84 (br s, 3H), 1.83 (br s, 1H), 1.68 − 1.50 (br m, 4H), 1.43 (s, 12H), 1.15 (s, 3H), 1.01 − 0.86 (m, 3H), 0.70 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 158.4, 154.5, 145.6, 145.2, 141.4, 141.1, 130.2, 129.9, 128.8, 128.1, 127.3, 127.2, 114.7, 114.0, 113.4, 113.2, 112.6, 111.4, 81.8, 77.8, 71.4, 68.6, 67.7, 65.0, 54.7, 54.6, 52.8, 50.9, 50.4, 48.1, 44.2, 36.1, 35.3, 34.8, 34.1, 28.4, 28.1, 27.6, 27.5, 27.0, 26.3, 23.9, 23.2, 15.0, 14.5, 13.4; HRMS (ESI) m/z calcd for $C_{36}H_{56}N_3O_7$ $[M + H]^+$ 642.4118, found 642.4111.

***tert*-Butyl (((11*S*,12*R*)-17-Amino-14-((*S*)-1-((4-methoxybenzyl)-oxy)prop-2-yl)-12-methyl-15-oxo-3,4,5,6,7,8,9,11,12,13,14,15-dodecahydro-2*H*-benzo[*b*][1,9,5]dioxaazacycloheptadec-11-yl)methyl)(methyl)carbamate (17H).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -12.3$ (c 0.34, $CHCl_3$); IR (cm^{-1}) 3431, 3349, 2961, 2929, 2856, 1688, 1612, 1496, 1258, 1154, 1086, 1031; ^1H NMR (500 MHz, DMSO-d_6) δ 7.20 (br s, 2H), 6.90 (d, J = 8.4 Hz, 2H), 6.73 (s, 1H), 6.57 (dd, J = 8.6, 2.8 Hz, 1H), 6.42 (s, 1H), 4.44 (obsc br s, 1H), 4.33 (br s, 3H), 3.87 (obsc br s, 2H), 3.83 (m, 2H), 3.77 (s, 3H), 3.66−3.26 (obsc br s, 2H), 3.59 (br s, 2H), 3.33 (s, 2H), 3.11 (s, 2H), 2.85 (br s, 3H), 1.63 (br s, 2H), 1.43 (s, 16H), 1.35 (s, 7H), 1.16 (br s, 3H), 0.97 (br s, 3H), 0.75 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.2, 158.4, 154.4, 145.5, 141.6, 130.0, 128.5, 128.1, 128.0, 127.6, 114.6, 114.2, 113.3, 113.3, 111.9, 80.9, 77.8, 71.6, 71.4, 69.1, 68.5, 54.7, 54.6, 54.5, 54.4, 53.0, 51.3, 49.7, 49.2, 44.6, 35.2, 34.6, 34.5, 28.5, 27.6, 27.5, 27.28, 26.8, 24.4, 23.9, 15.2, 14.2, 13.7, 12.4; HRMS (ESI) m/z calcd for $C_{37}H_{57}NaN_3O_7$ $[M + Na]^+$ 678.4094, found 678.4096.

***tert*-Butyl (((12*S*,13*R*)-18-Amino-15-((*S*)-1-((4-methoxybenzyl)-oxy)prop-2-yl)-13-methyl-16-oxo-2,3,4,5,6,7,8,9,10,12,13,14,15,16-tetradecahydrobenzo[*b*][1,9,5]dioxaazacyclooctadec-12-yl)methyl)(methyl)carbamate (18H).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -19.6$ (c 0.32, $CHCl_3$); IR (cm^{-1}) 3444, 3349, 2971, 2929, 2855, 1686, 1624, 1497, 1301, 1153, 1083, 1032. ^1H NMR (500 MHz, DMSO-d_6) δ 7.20 (br s, 2H), 6.90 (d, J = 8.0 Hz, 2H), 6.73 (d, J = 8.5 Hz, 1H), 6.57 (dd, J = 8.6, 2.7 Hz, 1H), 6.42 (s, 1H), 4.36 (br s, 4H), 3.84 (s, 3H), 3.77 (br s, 3H), 3.52 (br s, 2H), 3.38 (br s, 2H), 3.39 − 3.27 (m, 3H), 3.13 (br s, 2H), 2.86 (s, 3H), 2.26 (br s, 1H), 1.63 (obsc br s, 2H), 1.57 (obsc br s, 1H), 1.43 (s, 15H), 1.34 (br s, 10H), 1.18 (br s, 3H), 0.97 (s, 3H), 0.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 169.1, 158.4, 154.4, 145.5, 141.4, 129.9, 128.1, 128.0, 114.6, 114.0, 113.4, 113.3, 80.6, 77.8, 71.4, 69.1, 67.8, 54.7, 54.6, 52.9, 49.1, 43.9, 35.5, 34.7, 34.6, 28.4, 27.6, 27.5, 26.2, 25.0, 24.2, 15.3, 12.1; HRMS (ESI) m/z calcd for $C_{38}H_{59}N_3O_7$ $[M + H]^+$ 670.4431, found 670.4439.

***tert*-Butyl (((8*R*,9*R*)-3-Amino-6-((*S*)-1-((4-methoxybenzyl)-oxy)prop-2-yl)-8-methyl-5-oxo-6,7,8,9,11,12,13,14-octahydro-5*H*-dibenzo[*b*,*n*][1,9,5]dioxaazacyclopentadec-9-yl)methyl)-(methyl)carbamate (19H).** This compound was synthesized by the general procedure described above: $[\alpha]_D^{20} = -8.3$ (c 0.30, $CHCl_3$); IR (cm^{-1}) 3444, 3349, 2971, 2930, 2861, 1685, 1611, 1482, 1450, 1246, 1155, 1108, 1033; ^1H NMR (500 MHz, DMSO) δ 7.26 (s, 1H), 7.19 (d, J = 7.8, 3H), 7.12 − 6.95 (m, 2H), 6.86 (s, 3H), 6.55 (s, 2H), 4.56 (s, 1H), 4.37 (s, 2H), 4.04 (s, 1H), 3.77 (s, 3H), 3.42 (s, 2H), 3.28 (s, 3H), 2.83 (s, 3H), 2.67 (s, 4H), 1.40 (s, 9H), 1.30 (br s, 3H), 0.83 (d, J = 6.5, 3H); ^{13}C NMR (126 MHz, DMSO) δ 168.8, 158.4, 155.2, 154.5, 153.0, 143.6, 142.5, 134.4, 130.0, 128.2, 128.0, 126.1, 123.4, 121.6, 119.8, 118.7, 116.5, 115.0, 114.1, 113.3, 113.3, 82.1, 77.7, 75.8, 71.4, 68.4, 67.4, 54.7, 54.5, 53.2, 52.2, 50.7, 50.3, 47.6, 43.4, 36.8, 34.7, 31.0, 29.0, 27.6, 27.5, 26.6, 24.7, 21.1, 15.1, 14.5, 13.4, 12.7, 11.4; HRMS (ESI) m/z calcd for $C_{39}H_{53}N_3O_7$ $[M + H]^+$ 676.3962, found 676.3969.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^1H and ^{13}C NMR spectra of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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