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Ring-closing metathesis: a powerful tool for the synthesis of simplified salicylihalamide-based V-ATPase inhibitors

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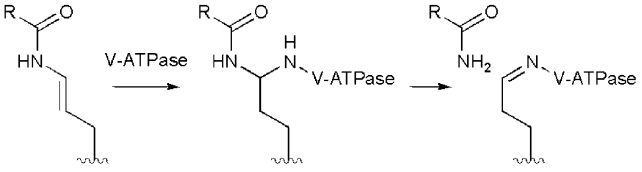
Abstract—Based on our synthetic strategy developed for the total synthesis of the macrocyclic salicylate natural product salicylihalamide, we describe herein the synthesis of a series of simplified salicylihalamide-based analogs. Alterations in the aromatic fragment, the macrolactone scaffold and side-chain were evaluated for in vitro inhibition of V-ATPase activity and human tumor cell growth.

1. Introduction

The past seven years has witnessed the disclosure of a variety of marine and terrestrial metabolites grouped into a common structural family by virtue of a signature *N*-acyl-enamine appended macrocyclic salicylate–salicylihalamide A (**1**) the first to be isolated (Fig. 1).[1–5] These compounds have been attributed growth-inhibitory activities against cultured human tumor cells and oncogene-transformed cell-lines through mechanisms distinct from standard clinical antitumor agents.[1–3,5] Boyd and co-workers subsequently found that the NCI 60 cell-line profiles of salicylihalamides, lobatamides, oximidines and apicularens gave consistently high correlations with the historical database profiles of bafilomycin and concanamycin, prototypical vacuolar (H^+)-ATPase (V-ATPase) inhibitors.[6] Biochemical studies have confirmed the ability of these compounds to inhibit mammalian V-ATPase activity, but unlike any previously known inhibitor of this enzyme, not those of yeast or other fungi.[6] V-ATPases are potential therapeutic targets for the development of pharmacological agents to treat a variety of diseases, notably osteoporosis and cancer.[7,8] Despite substantial efforts, the lack of tissue specificity, structural complexity and chemical stability associated with previous inhibitors has hampered progress towards the development of clinically useful compounds.[8]

The prospect to target specific subsets of V-ATPases with compounds potentially resulting from a chemical program around these structurally novel macrocyclic salicylates has prompted intense research activities by us, as well as others.[9,10] Based on a synthetic blueprint that resulted in the total synthesis of salicylihalamide by our group, we have prepared and evaluated numerous side-chain modified derivatives for structure-function studies.[11] Biochemical studies have further revealed that salicylihalamides bind to the *trans*-membranous proton-translocating domain (Vo) of the V-ATPase through a mechanism distinct from bafilomycin.[12] They are conditionally irreversible inhibitors, and experimental information gathered with carefully crafted side-chain modifications has led us to suggest a covalent binding mechanism initiated by enamine protonation and capture of a transient *N*-acyl iminium by an active site lysine residue, followed by a fragmentation to a covalent protein/small molecule imine complex with loss of the side chain (Eq. (1)).[12]



(1)

Total synthesis has been crucial to advance our knowledge of salicylihalamide's molecular pharmacology and define the structure-function boundaries related to the side chain.[13] The aspiration to advance a synthetic salicylihalamide-like

Keywords: Olefin-metathesis; Macrocyclic; Natural product; Vacuolar ATPase; Cancer.
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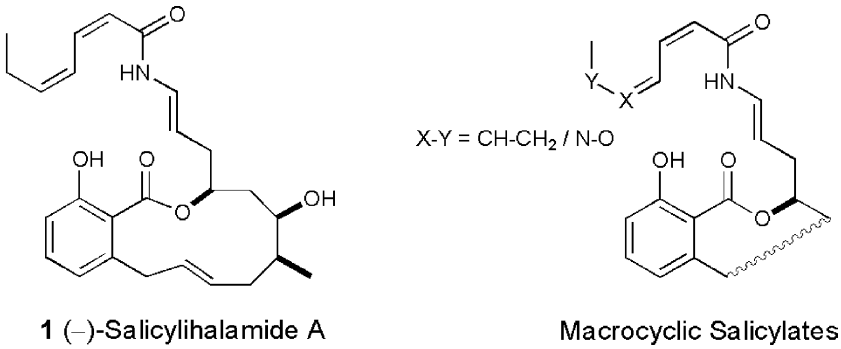


Figure 1.

small molecule through preclinical development prompted us to investigate simplified macrolactone scaffolds that could be prepared by shorter, scalable routes. Initial results related to this goal are detailed in this manuscript.

2. Results and discussion

Our scaffold selection and synthetic approach are depicted in Figure 2. Smith and co-workers have shown that deletion of the C_{12}-Me and C_{13}-OH substituents had no dramatic impact on activity at the cell-based level.[14] A direct consequence of our RCM approach, the endocyclic double bond was perceived as a beneficial conformation-restricting unit. Incorporation of the cyclic ether derives from synthetic considerations. Influenced by our earlier work,[11] a convergent combination of an allyl-substituted (hetero)cyclic carboxylic acid (**B**) and an allylated 1,3,5-pentanetriol derivative (**C**) via Mitsunobu esterification / RCM and final installation of the side chain was projected to efficiently generate the desired targets (**A**).

As shown in Scheme 1, we selected a series of readily accessible aryl, indole, cyclohexenyl and proline derived carboxylic acid building blocks **B** (**1**–**5**)[15] for incorporation into the macrocyclic scaffolds. The acyclic fragment **7** was prepared in three steps from aldehyde **6**,[11] an intermediate for the synthesis of salicylihalamide A, via reduction, allylation and silyl deprotection. Treatment of alcohol **7** with the respective carboxylic acids **1**–**5** under Mitsunobu reaction conditions cleanly afforded the bis-olefins **8a**,**c**–**f** in 76–99% yields.[16] The phenol in salicylate ester **8a** was protected as the acetate **8b** prior to the subsequent ring-closing olefin metathesis.

Ring-closing olefin metathesis with ruthenium carbene complexes was shown to be a powerful method to form the macrocyclic skeleton of the salicylihalamides.[9,17] In line with a highly significant study from the Grubbs lab,[18] which provided the inspiration for our RCM studies, we had observed that first generation pre-catalyst **i** induces kinetic selectivity whereas the H_2IMes-containing pre-catalyst **ii** affords thermodynamic selectivity. Not expected however, was the highly selective formation of the *E*-isomer under kinetic conditions (9–10:1, *E*/*Z*) contrasting the rather non-selective thermodynamic ratio (2:1) obtained with the second generation catalyst.[11b] In addition, Fürstner and co-workers reported a dramatic influence of the phenolic protecting group on *E*/*Z* ratios in their synthetic work on salicylihalamides.[19] In light of these results, we explored the

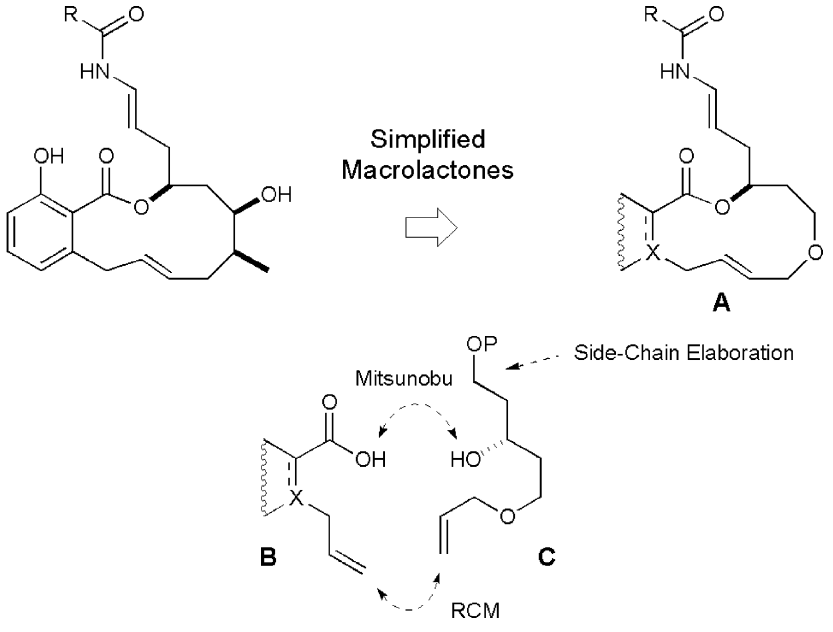
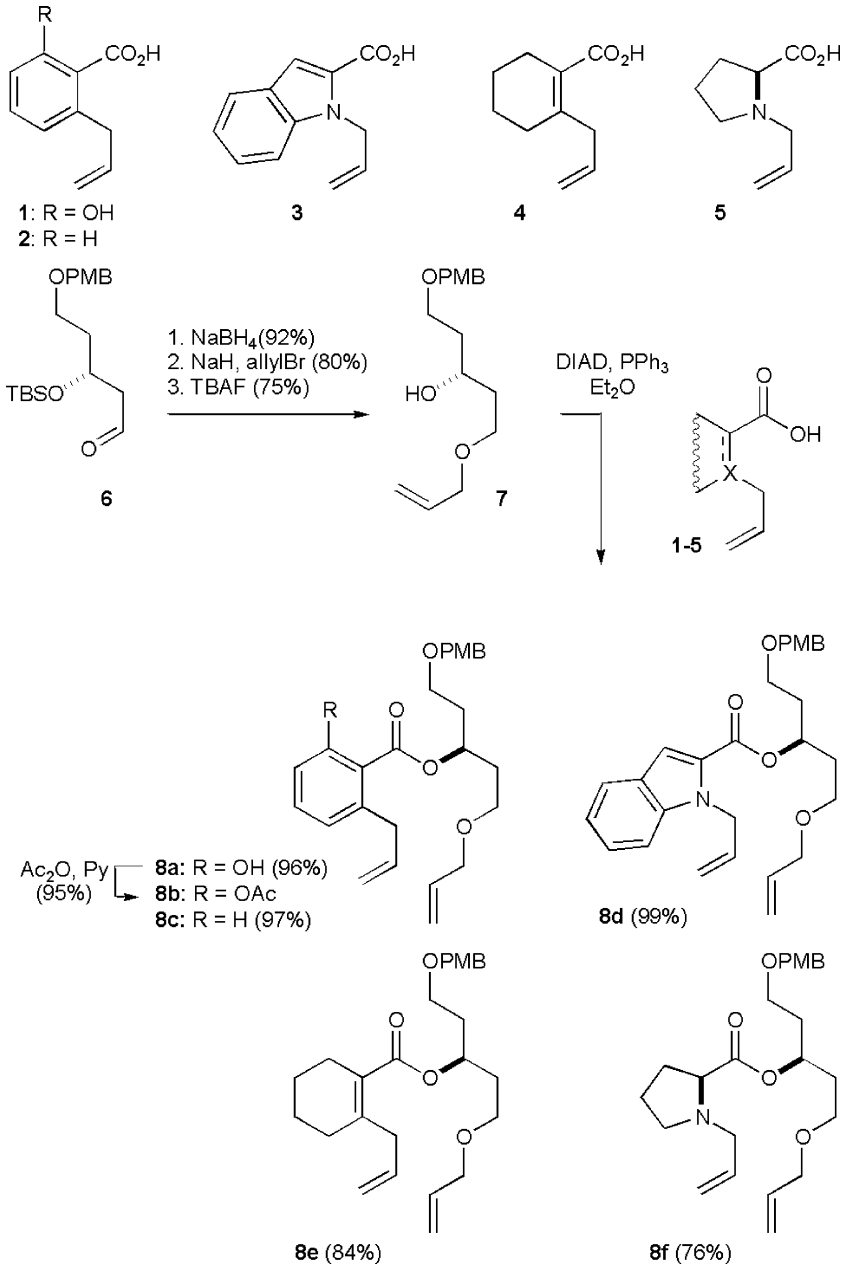
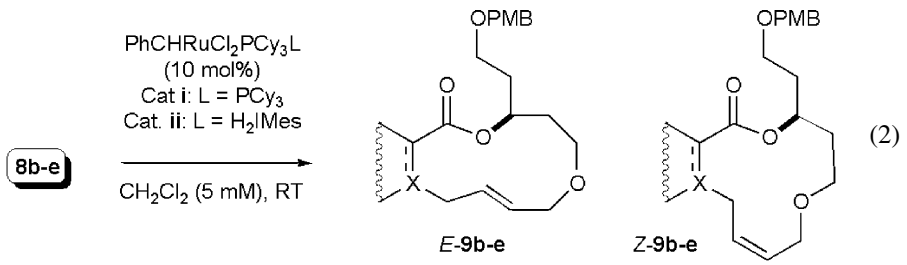


Figure 2.



Scheme 1.

RCM reactions of substrates **8b–f** with both first and second generation catalysts to empirically identify the most *E*-selective conditions.[20]



(2)

Our results are presented in Eq. (2) and Table 1. In contrast to salicylihalamide, salicylic macrocycle **9b** was obtained as an almost equimolar mixture of *E*/*Z*-isomers under kinetic RCM conditions, despite displaying the same ring-size, olefin position, and aromatic fragment as the salicylihalamide macrocycle. Similar results were obtained for the non-substituted benzoate counterpart **9c**. In both of these cases, a thermodynamic cyclization with second generation catalyst **ii** was now significantly favoring formation of the *E*-isomer. Re-exposure of isomerically pure *E*-**9c** and *Z*-**9c** to the reaction conditions confirmed that thermodynamic

Table 1. Ring-closing olefin metathesis studies

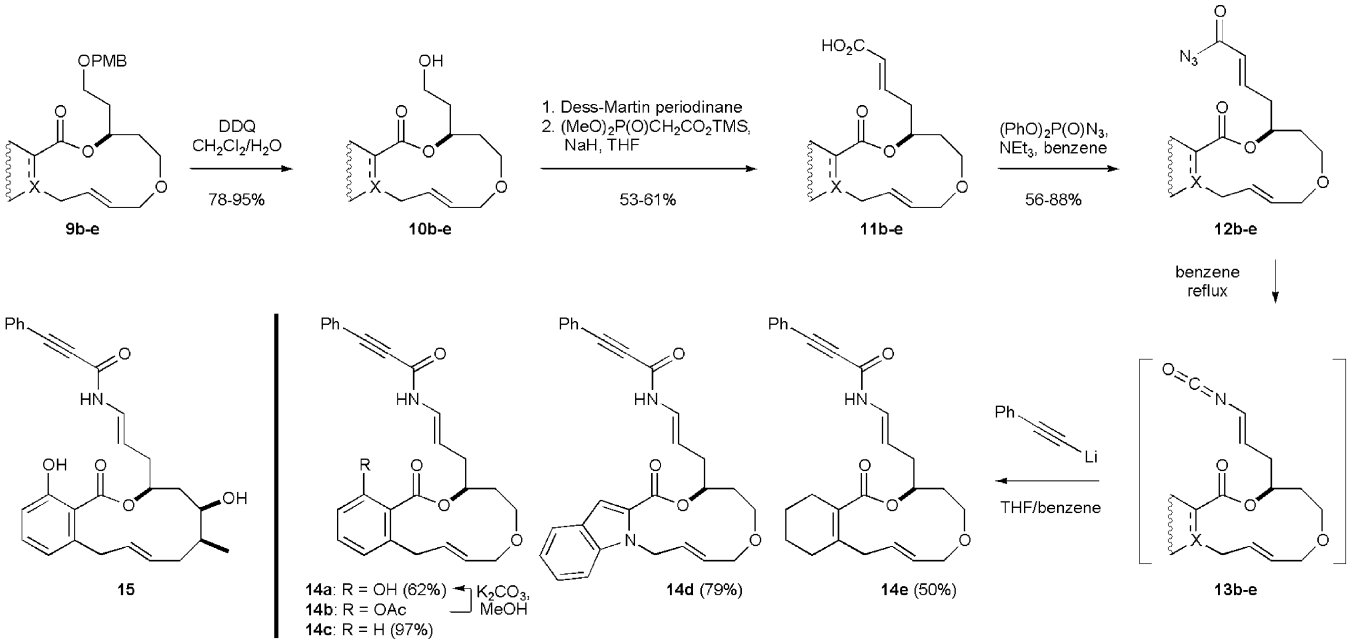
Substrate	*t* (h)	Product	*E*/*Z* ratio[a] (% conversion)[a]	
			Catalyst **i**	Catalyst **ii**
8b	1.3	**9b**	42:48 (80)	95:5 (95)
8b	6.3	**9b**	54:46 (92)[b]	98:2 (100)[b]
8c	1.3	**9c**	52:48 (>80)	82:18 (>90)
8c	6.3	**9c**	54:46 (100)[b]	84:16 (100)[b]
8d	6.3	**9d**	45:55 (80)[c]	32:68 (80)[c]
8e	4	**9e**	29:71 (70)	49:51 (90)[d]
8f	4	—[e]	—	—
E-**9c**	5	**9c**	98:2 (−)	89:11 (−)
Z-**9c**	5	**9c**	11:89 (−)	82:18 (−)

[a] Determined by ^{1}H NMR analysis of crude product mixtures.
[b] Isolated yields between 90–99%.
[c] Some decomposition occurred; 34–41% isolated yield.
[d] 75% Isolated yield.
[e] No reaction; higher temperatures or the addition of $BF_3 \cdot OEt_2$ or $Ti(O^iPr)_4$ led to decomposition of the starting material.

equilibrium was reached with catalyst **ii**, but not with catalyst **i**. Interestingly, cyclohexenyl- and indolyl-tethered substrates **8d** and **8e** respectively, behaved quite differently and no *E*-selective conditions could be identified—*Z*-selectivity predominated with catalyst **ii** for indolyl substrate **8d** and with catalyst **i** for the cyclohexenyl substrate **8e**. Also, reaction with the indolyl substrate **8d** gave low yields of product **9d**, the remainder accounted for as starting material and decomposition products. These results are fascinating because all these products (**9b–e**) have an identical macrocycle fused with the smaller ring through sp^2-hybridized atoms. Evidently, subtle effects influenced by the nature of the fused ring are at play here. The proline-derived bis-olefin **8f** was not a viable substrate for RCM under all conditions explored.

With four macrocyclic lactones **9b–e** at hand, we were set to complete the synthesis by appending an *N*-acyl enamide side chain following our sequence described previously (Scheme 2).[11] Thus, oxidative deprotection of the primary *p*-methoxybenzyl ether provided four primary alcohols **10b–e** in 78–95% yield. Dess–Martin periodinane oxidation delivered the corresponding aldehydes,[21] which were subsequently homologated via HWE-reaction with trimethylsilyl dimethylphosphonoactetate. Aqueous work-up provided the α,β-unsaturated acids **11b–e** with high *E*-selectivity in 53–61% yield for the two steps. These materials were converted to acylazides **12b–e**, precursors for the corresponding isocyanates **13b–e**. For the first series of analogs, we opted for the addition of lithium phenylacetylide. The corresponding analog **15** with salicylihalamide's macrolactone was found to be equipotent to salicylihalamide (**1**) but prepared in higher yields and more resistant to decomposition.[11] In the event, addition of in situ prepared isocyanate **13b–e** (benzene, reflux) to a cold (−78 °C) solution of freshly deprotonated phenylacetylene (BuLi, THF) resulted in a clean conversion to compounds **14b–e** (50–97% yields). A portion of acetate **14b** was stirred in a basic methanol solution (K_2CO_3) to liberate the free phenol **14a**.

Comparing the biological activity of this series of compounds with the corresponding analog **15** would (1) indicate if the endocyclic allyl ether presents a viable alternative to the more complex macrocyclic backbone of salicylihalamide, and (2) provide the first SAR-data related to the nature of the fused ring (aryl, indole, cyclohexenyl). As shown in Table 2, direct comparison of analogs **14a** and **15** indicates that this simplified allyl ether scaffold (**14a**) retains the ability to potently inhibit proton-pumping of purified V-ATPase (~4.5-fold less than **15**). Larger differences (~10-fold) are observed in the growth inhibition assay with two selected lung tumor cell lines, perhaps related to altered drug transport and availability characteristics. Compared to phenol **14a**, the similar cytotoxicity, but not in vitro potency of the corresponding acetate **14b**, is likely a manifestation of esterase-mediated release of phenol **14a** in the cell-based assay. Any other permutation



Scheme 2.

Table 2. Biological properties of selected compounds

Compound	V-ATPase inhibition (H^+-pumping) IC_{50} (nM)[a]	Cell growth inhibition[b]	
		A549 IC_{50} (μM)	NCI-H460 IC_{50} (μM)
15	1.0	0.086	0.018
14a	4.5	1.03	0.20
14b	125	1.38	0.31
14c	No inhibition[c]	—[d]	—[d]
14d	>1000[e]	—[d]	—[d]
14e	No inhibition[c]	—[d]	—[d]
16[f]	16	3.05	1.03
17	2300	1.50	1.23
18	1000	0.88	0.55
19	30	4.62	1.62
20	4	—[d]	—[d]
21	1900	>10[g]	>10[g]

[a] Assay performed as in Ref. 12.
[b] See Section 3 for details.
[c] Up to 1 μM.
[d] Not measured.
[e] 10% Inhibition at 1 μM.
[f] Racemic mixture.
[g] 20–29% Inhibition at 10 μM.

of the aromatic phenol (i.e. compounds **14c–e**) virtually abrogated in vitro V-ATPase inhibition, manifesting the importance for a fused *ortho*-hydroxy benzoate (i.e. salicylate) scaffold.

Having identified a promising, highly simplified salicylate scaffold, we next prepared and evaluated a variety of side-chain modifications in this series. To this end, we added isocyanate **13b** (from **12b**) to a 2-fluorophenyl-, 2-pyridinyl-, or 2-oxazoyl-substituted acetylide followed by acetate hydrolysis (K_2CO_3, MeOH) to deliver the corresponding analogs **16–18** (Scheme 3). Benzyl-, pentyl-, and 2-oxazoylmethyl carbamates **19–21** are obtained directly from heating acylazide **12b** in the presence of the corresponding alcohols and acetate hydrolysis as before.

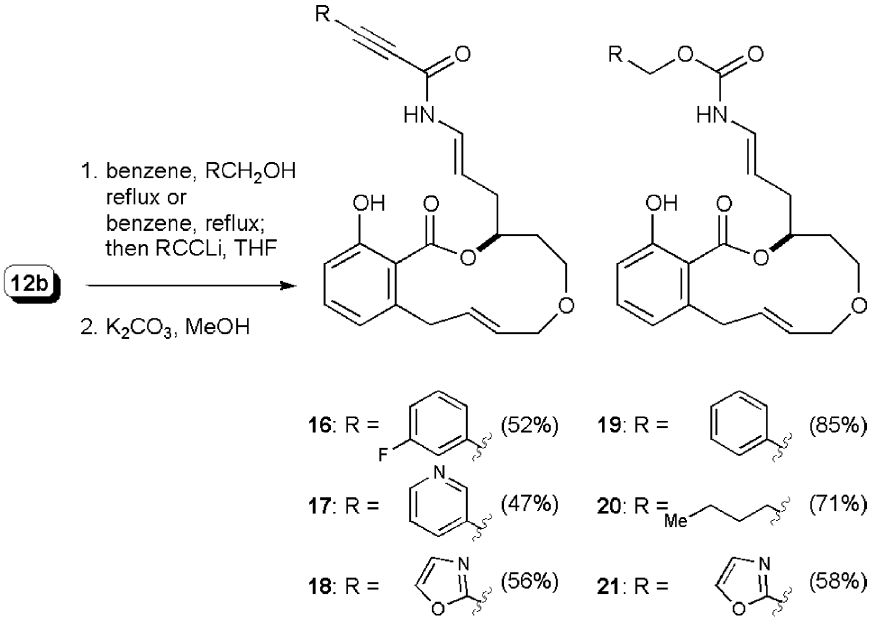
While compounds **16**, **19** and **20** still inhibit V-ATPase activity (4–30 nM) in line with our previous observations within the salicylihalamide series,[11,12] heteroaromatic substituents (**17**, **18**, **21**) are deleterious. The more surprising result however, is that this 'heteroatom effect' does not translate to the cytotoxicity assay. Pyridinyl and oxazoyl substituted derivatives **17** and **18** are still able to inhibit cell growth at similar concentrations to compound **14a**. These observations might indicate that **17** and **18** induce cytotoxicity through a different mechanism, or that they target a different V-ATPase isoform than the one used in this study.[22]

In conclusion, we have identified a series of simplified analogs (**14a**,**b**, **16**, **19**, **20**) of the macrocyclic salicylate natural product salicylihalamide A that retain the ability to potently inhibit the V-ATPase. These and other derivatives were conveniently prepared via a convergent assembly of a series of allyl-substituted carboxylic acids **1–4** and the allyl ether derivative **7** via Mitsunobu esterification and ring-closing olefin metathesis. We also uncovered subtle effects on *E*/*Z*-stereochemistry during RCM related to the nature of the small ring fused to the macrocycle. Finally, structure-function studies indicate that the salicylate moiety is indispensable for activity and that heteroaryl terminating side-chains behave differently than other inhibitors in the salicylate family. Continuing efforts to study this intriguing family of compounds are ongoing.

3. Experimental

3.1. General procedures

Commercially available materials were used without further purification. All solvents used were of HPLC- or ACS-grade. Solvents used for moisture sensitive operations were distilled from drying agents under a nitrogen atmosphere: Et_2O and THF from sodium benzophenone ketyl; benzene



Scheme 3.

from sodium; CH_2Cl_2 and NEt_3 from CaH_2. All moisture sensitive reactions were carried out under a nitrogen atmosphere with magnetic stirring. Flash chromatography (FC) was performed using E Merck silicagel 60 (240–400 mesh). Thin Layer chromatography was performed using precoated plates purchased from E. Merck (silicagel 60 PF254, 0.25 mm) that were visualized using a $KMnO_4$ or Ce(IV) stain.

Nuclear magnetic resonance (NMR) spectra were recorded on either a Varian Inova-400 or Mercury-300 spectrometer at operating frequencies of 400/300 MHz (^{1}H NMR) or 100/75 MHz (^{13}C NMR). Chemical shifts (δ) are given in ppm relative to residual solvent and coupling constants (J) in Hz. Multiplicity is tabulated as s for singlet, d for doublet, t for triplet, q for quadruplet, and m for multiplet, whereby the prefix app is applied in cases where the true multiplicity is unresolved, and br when the signal in question is broadened. High-resolution mass spectra (HRMS) were recorded at the NIH regional mass spectrometry facility at the University of Washington, St. Louis, MO. Optical rotations were measured at 23 °C on a Perkin–Elmer 241 MC polarimeter.

3.1.1. 3-(*tert*-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-pentan-1-ol. To a solution of aldehyde **6** (8.95 g, 25.38 mmol) in absolute ethanol (300 mL) at 0 °C was added sodium borohydride (2.40 g, 63.45 mmol) portionwise. After stirring at rt for 45 min, the reaction mixture was cooled down to 0 °C and quenched with water (300 mL) and acetic acid to pH ~ 5. Following removal of EtOH in vacuo, the mixture was extracted with EtOAc (2×300 mL). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by FC (20% EtOAc in hexanes) to give 8.3 g (92%) of the desired alcohol as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.8 Hz), 4.44 (1H, d, J=11.2 Hz), 4.39 (1H, d, J=11.2 Hz), 4.09 (1H, quent, J=5.2 Hz), 3.82–3.77 (1H, m), 3.80 (3H, s), 3.73–3.67 (1H, m), 3.49 (2H, app.t, J=6.4 Hz), 2.43 (1H, t, J=5.0 Hz), 1.89–1.76 (3H, m), 1.65 (1H, dddd, J=16.0, 6.0, 6.0, 3.6 Hz), 0.89 (9H, s), 0.08 (6H, d, J=8.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 130.6, 129.5, 114.0, 72.9, 69.2, 66.7, 60.2, 55.5, 38.5, 36.9, 26.0, 18.1, −4.4; MS (ES) m/z 377.25 $[M+Na]^+$; calcd for $C_{19}H_{34}O_4SiNa$: 377.21.

3.1.2. [1-(2-Allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propoxy]-tert-butyl-dimethyl-silane. To a suspension of sodium hydride (902 mg, 22.56 mmol, prewashed with benzene) in THF (30 mL) was added 3-(tert-Butyl-dimethyl-silanyloxy)-5-(4-methoxy-benzyloxy)-pentan-1-ol (2 g, 5.64 mmol). After stirring at rt for 45 min, a solution of allylbromide (1.95 mL, 22.56 mmol) in THF (5 mL) was added dropwise and the reaction was stirred for another 20 h. The mixture was quenched with water (5 mL) and brine (150 mL) was added. The separated aqueous phase was extracted with EtOAc (2×150 mL). The combined organic layers were washed with brine (2×150 mL), dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by FC (5% EtOAc in hexanes) to give 1.73 g (78%) of the desired product as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.8 Hz), 6.87 (2H, d, J=8.8 Hz), 5.90 (1H, dddd, J=17.2, 10.8, 5.2, 5.2 Hz), 5.26 (1H, dd, J=17.2, 1.6 Hz), 5.16 (1H, dd, J=10.4, 1.6 Hz), 4.42 (1H, d, J=11.2 Hz), 4.39 (1H, d, J=11.2 Hz), 3.98 (1H, app.t, J=6.0 Hz), 3.93 (2H, d, J=6.0 Hz), 3.80 (3H, s), 3.51 (2H, t, J=6.8 Hz), 3.48 (2H, t, J=6.8 Hz), 1.82–1.68 (4H, m), 0.87 (9H, s), 0.04 (6H, d, J=2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 135.2, 130.9, 129.5, 116.9, 113.9, 72.8, 72.0, 67.1, 66.9, 59.8, 55.5, 37.6, 37.5, 26.1, 18.3, −4.4; MS (ES) m/z 417.20 $[M+Na]^+$; calcd for $C_{22}H_{38}O_4SiNa$: 417.24.

3.1.3. 1-Allyloxy-5-(4-methoxy-benzyloxy)-pentan-3-ol 7. To a solution of [1-(2-Allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propoxy]-tert-butyl-dimethyl-silane (1.65 g, 4.18 mmol) in THF (30 mL) at 0 °C was added TBAF (1.0 M in THF, 12.54 mL, 12.54 mmol). The reaction was stirred at rt for 5 h and water (200 mL) was added. The mixture was extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were washed with brine (300 mL) and dried over $MgSO_4$. After concentration in vacuo, the residue was purified by FC (20% EtOAc in hexanes) to give 866 mg (74%) of **7** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, J=8.8 Hz), 6.86 (2H, d, J=8.8 Hz), 5.88 (1H, dddd, J=16.8, 10.4, 5.2, 5.2 Hz), 5.26 (1H, dd, J=17.6, 1.6 Hz), 5.17 (1H, dd, J=10.0, 1.6 Hz), 4.44 (2H, s), 3.97 (2H, dt, J=5.6, 1.2 Hz), 3.97–3.93 (1H, m), 3.78 (3H, s), 3.68–3.55 (4H, m), 3.38 (1H, br.s), 1.78–1.71 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.3, 134.7, 130.3, 129.4, 117.0, 113.9, 76.8, 72.1, 69.4, 68.4, 68.3, 55.3, 36.9; MS (ES) m/z 303.10 $[M+Na]^+$; calcd for $C_{16}H_{24}O_4Na$: 303.15.

3.1.4. Mitsunobu coupling. To a solution of acid **1**–**5** (1.5 equiv), alcohol **7** (1.0 equiv), and PPh_3 (1.6 equiv) in Et_2O (0.1 M with respect to the alcohol) at 0 °C was added diisopropylazodicarboxylate (1.6 equiv). The reaction was stirred at rt until all alcohol reacted (2–12 h). The reaction mixture was filtrated off and washed with Et_2O. The filtrate was washed with water. The aqueous phase was extracted twice with Et_2O. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was then purified by FC (EtOAc in hexanes) to give the corresponding ester **8a**–**f**.

3.1.4.1. 2-Allyl-6-hydroxy-benzoic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8a. In the case of compound **8a**, a 1:6 adduct:product resulted from esterification of the phenolic group, which was hydrolyzed in MeOH in the presence of K_2CO_3 (1 equiv) over 1 h. After adding water, an extraction was performed with EtOAc. The combined extracts were dried, concentrated in vacuo, and purified by FC (20% EtOAc in hexanes) to give 1.26 g (96% yield) of product **8a** as pale yellowish oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.1 (1H, s), 7.31 (1H, t, J=8.0 Hz), 7.20 (2H, d, J=8.8 Hz), 6.87 (1H, d, J=8.8 Hz), 6.82 (2H, d, J=8.8 Hz), 6.72 (1H, d, J=7.2 Hz), 5.96 (1H, dddd, J=16.4, 10.4, 6.4, 6.4 Hz), 5.85 (1H, dddd, J=16.0, 10.4, 5.6, 5.6 Hz), 5.59–5.53 (1H, m), 5.22 (1H, dd, J=16.8, 1.2 Hz), 5.13 (1H, dd, J=10.4, 1.2 Hz), 5.00 (1H, dd, J=10.0, 1.2 Hz), 4.90 (1H, dd, J=16.8, 1.6 Hz), 4.42 (1H, d, J=11.6 Hz), 4.38 (1H, d, J=11.6 Hz), 3.92 (2H, d, J=5.6 Hz), 3.77 (3H, s), 3.64 (2H, br.d, J=6.0 Hz), 3.55–3.47 (4H, m), 2.05–1.97 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7, 162.5, 159.4, 142.7, 138.0, 134.8, 134.2, 130.3, 129.6, 122.6, 117.3, 116.4, 115.6, 113.9, 113.0, 73.0, 72.2, 72.0,

66.7, 66.4, 55.4, 40.1, 34.7; MS (ES) *m/z* 463.20 $[M+Na]^+$; calcd for $C_{26}H_{32}O_6Na$: 463.21.

3.1.4.2. 2-Allyl-benzoic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8c. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 295 mg (97% yield) of product **8c**. $[\alpha]_D=-9.9$ ($c=1.60$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (1H, d, $J=7.6$ Hz), 7.43 (1H, t, $J=7.6$ Hz), 7.28–7.22 (4H, m), 6.83 (2H, d, $J=8.4$ Hz), 6.00 (1H, dddd, $J=16.4$, 10.0, 6.4, 6.4 Hz), 5.87 (1H, dddd, $J=16.8$, 10.0, 5.6, 5.6 Hz), 5.42–5.36 (1H, m), 5.23 (1H, dd, $J=17.2$, 1.6 Hz), 5.13 (1H, dd, $J=10.4$, 1.6 Hz), 5.02 (1H, dd, $J=10.0$, 1.6 Hz), 4.99 (1H, dd, $J=17.2$, 1.6 Hz), 4.41 (2H, s), 3.93 (2H, br.d, $J=5.6$ Hz), 3.77 (3H, s), 3.74 (2H, d, $J=6.4$ Hz), 3.56–3.49 (4H, m), 2.04–1.97 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2, 159.3, 141.6, 137.7, 135.0, 132.0, 131.1, 130.6, 130.3, 129.5, 126.3, 117.1, 115.8, 113.9, 72.9, 72.1, 70.4, 66.9, 66.6, 55.4, 38.4, 34.9; MS (ES) *m/z* 447.20 $[M+Na]^+$; calcd for $C_{26}H_{32}O_5Na$: 447.22.

3.1.4.3. 1-Allyl-1*H*-indole-2-carboxylic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8d. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 755 mg (100% yield) of product **8d** as pale yellowish oil. $[\alpha]_D=-11.2$ ($c=1.18$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (1H, d, $J=8.0$ Hz), 7.37–7.31 (2H, m), 7.28 (1H, s), 7.20 (2H, d, $J=8.8$ Hz), 7.15 (1H, ddd, $J=8.0$, 6.4, 1.6 Hz), 6.78 (2H, d, $J=8.4$ Hz), 5.99 (1H, dddd, $J=16.8$, 10.0, 4.8, 4.8 Hz), 5.86 (1H, dddd, $J=17.2$, 10.8, 5.6, 5.6 Hz), 5.44–5.37 (1H, m), 5.22 (1H, dd, $J=17.2$, 3.2 Hz), 5.21–5.20 (2H, m), 5.12 (1H, dd, $J=10.4$, 2.8 Hz), 5.08 (1H, dd, $J=10.8$, 2.4 Hz), 4.89 (1H, dd, $J=17.2$, 3.26 Hz), 4.39 (2H, s), 3.93 (2H, ddd, $J=5.6$, 1.2, 1.2 Hz), 3.71 (3H, s), 3.57–3.50 (4H, m), 2.05–1.98 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.6, 159.3, 139.4, 135.0, 134.2, 130.5, 129.5, 127.7, 126.2, 125.2, 122.8, 120.9, 117.1, 116.1, 113.9, 110.8, 110.7, 73.0, 72.2, 70.0, 66.8, 66.6, 55.4, 47.0, 35.0, 21.8; MS (ES) *m/z* 486.15 $[M+Na]^+$; calcd for $C_{28}H_{33}NO_5Na$: 486.23.

3.1.4.4. 2-Allyl-cyclohex-1-enecarboxylic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8e. Reaction mixture purified by FC (5% EtOAc in hexanes) to give 272 mg (84% yield) of product **8e**. ^1H NMR (400 MHz, $CDCl_3$) δ 7.24 (2H, d, $J=8.4$ Hz), 6.86 (2H, d, $J=8.4$ Hz), 5.88 (1H, dddd, $J=17.2$, 10.8, 5.6, 5.6 Hz), 5.80 (1H, dddd, $J=16.8$, 10.0, 6.8, 6.8 Hz), 5.25 (1H, dd, $J=17.2$, 1.6 Hz), 5.22–5.17 (1H, m), 5.15 (1H, dd, $J=10.4$, 1.6 Hz), 5.02 (1H, dd, $J=17.2$, 1.6 Hz), 4.99 (1H, dd, $J=10.4$, 1.6 Hz), 4.4 (2H, s), 3.93 (2H, dt, $J=5.6$, 1.6 Hz), 3.80 (3H, s), 3.50–3.43 (4H, m), 3.08 (2H, br.d, $J=6.4$ Hz), 2.25–2.19 (2H, m), 2.13–2.08 (2H, m), 1.91 (4H, app.quent., $J=6.4$ Hz), 1.60–1.56 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 159.3, 146.1, 142.8, 136.3, 135.1, 130.7, 129.5, 125.8, 117.1, 115.9, 114.0, 72.9, 72.1, 69.3, 67.0, 66.6, 55.5, 39.9, 34.9, 30.9, 26.8, 22.5; MS (ES) *m/z* 451.20 $[M+Na]^+$; calcd for $C_{26}H_{36}O_5Na$: 451.25.

3.1.4.5. 1-Allyl-pyrrolidine-2-carboxylic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8f. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 305 mg (72% yield) of product **8f**. $[\alpha]_D=-36.3$ ($c=1.23$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, $J=8.8$ Hz), 6.86 (2H, d, $J=8.8$ Hz), 5.96–5.83 (2H, m), 5.24 (1H, dd, $J=17.2$, 1.6 Hz), 5.20–5.15 (1H, m), 5.16 (1H, dd, $J=17.6$, 1.2 Hz), 5.15 (1H, dd, $J=10.4$, 1.2 Hz), 5.07 (1H, dd, $J=10.4$, 1.2 Hz), 4.42 (1H, d, $J=11.6$ Hz), 4.39 (1H, d, $J=11.6$ Hz), 3.92 (2H, dt, $J=5.6$, 1.6 Hz), 3.80 (3H, s), 3.51–3.39 (4H, m), 3.32 (1H, ddt, $J=13.2$, 6.4, 1.2 Hz), 3.16–3.10 (2H, m), 3.07 (1H, app.ddt, $J=13.2$, 7.2, 1.2 Hz), 2.37 (1H, app.q, $J=8.0$ Hz), 2.13–2.06 (1H, m), 1.93–1.76 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9, 159.4, 135.7, 135.0, 130.6, 129.5, 117.5, 117.2, 113.9, 72.9, 72.1, 69.8, 66.7, 66.5, 65.4, 57.7, 55.4, 53.5, 34.8, 29.7, 23.2, 22.1; MS (ES) *m/z* 418.25 $[M+H]^+$; calcd for $C_{24}H_{36}NO_5$: 418.26.

3.1.5. 2-Acetoxy-6-allyl-benzoic acid 1-(2-allyloxy-ethyl)-3-(4-methoxy-benzyloxy)-propyl ester 8b. To a solution of phenol **8a** (1.23 g, 2.79 mmol) equiv) in CH_2Cl_2 (20 mL) at 0 °C was added pyridine (243 mg, 3.07 mmol), acetic anhydride (314 mg, 3.07 mmol) and a catalytic amount of DMAP. After stirring at rt for 3 h the reaction mixture was concentrated in vacuo, and purified by FC (10% EtOAc in hexanes) to give 1.28 g (95% yield) of the product **8b** as a colorless oil. $[\alpha]_D=-7.5$ ($c=0.15$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, t, $J=8.0$ Hz), 7.25 (2H, d, $J=8.4$ Hz), 7.12 (1H, d, $J=7.6$ Hz), 7.01 (1H, d, $J=7.6$ Hz), 6.86 (2H, d, $J=8.4$ Hz), 5.97–5.84 (2H, m), 5.37 (1H, app.quint, $J=6.0$ Hz), 5.26 (1H, dd, $J=16.8$, 1.2 Hz), 5.16 (1H, dd, $J=10.4$, 1.2 Hz), 5.07 (1H, dd, $J=10.0$, 1.2 Hz), 5.04 (1H, dd, $J=17.2$, 1.2 Hz), 4.45 (1H, d, $J=11.6$ Hz), 4.41 (1H, d, $J=11.6$ Hz), 3.95 (2H, d, $J=5.6$ Hz), 3.80 (3H, s), 3.58–3.49 (4H, m), 3.44 (2H, d, $J=6.4$ Hz), 2.24 (3H, s), 2.04–1.95 (4H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 166.2, 159.4, 148.2, 139.6, 136.4, 134.9, 130.7, 130.5, 129.5, 127.5, 127.0, 121.1, 117.1, 117.0, 114.0, 72.9, 72.1, 71.5, 66.6, 66.5, 55.5, 37.7, 34.6, 34.5, 21.1; MS (ES) *m/z* 505.25 $[M+Na]^+$; calcd for $C_{28}H_{34}O_7Na$: 505.22.

3.1.6. Ring closure metathesis. A solution of bis-olefin **8b–e** in degassed CH_2Cl_2 (0.07 M) and a solution of Grubbs catalyst (10 mol%) in degassed CH_2Cl_2 (0.01 M) were added dropwise simultaneously to a flask containing degassed CH_2Cl_2 (0.07 M with respect to bis-olefin). The reaction was stirred at rt until no further evolution (as monitored by TLC) was observed (4–6 h). The solvent was removed in vacuo and the residue was purified by FC to give the corresponding lactone **9b–e**.

3.1.6.1. Acetic acid 7-[2-(4-methoxy-benzyloxy)-ethyl]-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-4-yl ester *E*-9b. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 93 mg (94% yield, catalyst **ii**) of product *E*-**9b** as a colorless oil. $[\alpha]_D=-34.0$ ($c=1.29$, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, t, $J=8.0$ Hz), 7.26 (2H, d, $J=8.4$ Hz), 7.11 (1H, d, $J=7.2$ Hz), 7.03 (1H, d, $J=8.4$ Hz), 6.88 (2H, d, $J=8.4$ Hz), 5.62 (1H, dddd, $J=14.8$, 10.0, 4.0, 1.6 Hz), 5.49 (1H, ddd, $J=14.8$, 10.8, 3.2 Hz), 5.22 (1H, dddd, $J=12.8$, 6.4, 6.4, 2.0 Hz), 4.48 (1H, d, $J=11.6$ Hz), 4.43 (1H, d, $J=11.6$ Hz), 4.13 (1H, br.dd, $J=11.6$, 3.2 Hz), 3.90 (1H, dd, $J=14.0$, 11.2 Hz), 3.80 (3H, s), 3.61–3.58 (2H, m), 3.46 (1H, ddd, $J=10.4$, 3.6, 2.4 Hz), 3.37 (1H, dd,

J=12.0, 10.4 Hz), 3.28 (1H, ddd, J=12.0, 10.8, 1.2 Hz), 3.20 (1H, dddd, J=14.0, 3.6, 1.6, 1.6 Hz), 2.21 (3H, s), 2.08–2.00 (1H, m), 1.94–1.83 (2H, m), 1.54 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 166.6, 159.4, 148.2, 139.6, 133.1, 130.6, 130.5, 129.7, 129.6, 127.9, 127.7, 121.6, 114.0, 73.0, 70.6, 69.8, 67.0, 61.9, 55.4, 37.7, 36.2, 35.1, 21.0; MS (ES) m/z 477.15 $[M+Na]^+$; calcd for $C_{26}H_{30}O_7Na$: 477.19.

3.1.6.2. 7-[2-(4-Methoxy-benzyloxy)-ethyl]-8,9,11,14-tetra-hydro-7*H*-6,10-dioxa-benzocyclododecen-5-one *E*-9c. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 237 mg of product *E*-**9c** (94% yield, catalyst **ii**) as a colorless oil. $[\alpha]_D=-72.8$ (c=1.66, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (1H, app.t, J=8.0 Hz), 7.29 (1H, d, J=7.6 Hz), 7.26 (2H, d, J=8.4 Hz), 7.21 (1H, d, J=8.8 Hz), 7.20 (1H, app.t, J=8.0 Hz), 6.85 (2H, d, J=8.8 Hz), 5.63 (1H, dddd, J=14.8, 10.4, 4.4, 1.6 Hz), 5.44 (1H, ddd, J=14.8, 10.8, 3.6 Hz), 5.35 (1H, dddd, J=11.6, 4.8, 4.8, 2.0 Hz), 4.45 (1H, d, J=11.6 Hz), 4.41 (1H, d, J=11.6 Hz), 4.13 (1H, dd, J=12.0, 4.4 Hz), 4.02 (1H, dd, J=14.0, 11.2 Hz), 3.79 (3H, s), 3.60 (2H, app.t, J=6.8 Hz), 3.45 (1H, dt, J=12.8, 2.8 Hz), 3.36 (1H, dd, J=12.0, 10.4 Hz), 3.28 (1H, ddd, J=12.0, 10.4, 1.6 Hz), 3.15 (1H, br.d, J=14.0 Hz), 2.05–1.95 (2H, m), 1.87 (1H, dddd, J=14.8, 12.0, 3.6, 2.4 Hz), 1.63 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 159.3, 138.3, 134.6, 133.3, 130.6, 130.4, 129.8, 129.6, 127.8, 126.6, 113.9, 73.0, 70.7, 69.4, 67.0, 62.1, 55.4, 37.7, 35.6, 35.1; MS (ES) m/z 419.15 $[M+Na]^+$; calcd for $C_{24}H_{28}O_5Na$: 419.18.

3.1.6.3. 7-[2-(4-Methoxy-benzyloxy)-ethyl]-8,9,11,14-tetra-hydro-7*H*-6,10-dioxa-benzocyclododecen-5-one *Z*-9c. $[\alpha]_D=-73.2$ (c=1.0, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (1H, d, J=7.6 Hz), 7.35 (1H, t, J=7.6 Hz), 7.29 (1H, d, J=7.6 Hz), 7.25 (2H, d, J=8.4 Hz), 7.12 (1H, t, J=7.6 Hz), 6.82 (2H, d, J=8.4 Hz), 5.78 (1H, dt, J=10.8, 6.0 Hz), 5.64–5.58 (1H, m), 5.51 (1H, dddd, J=12.8, 9.2, 4.0, 1.6 Hz), 4.52 (1H, dd, J=12.0, 12.0 Hz), 4.48 (1H, d, J=11.6 Hz), 4.42 (1H, d, J=11.6 Hz), 4.03 (1H, t, J=9.2 Hz), 3.77 (1H, app.t, J=10.8 Hz), 3.72 (3H, s), 3.64–3.55 (4H, m), 3.20 (1H, dd, J=12.8, 6.0 Hz), 2.04–1.88 (3H, m), 1.76 (1H, dddd, J=15.6, 4.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 159.3, 140.3, 137.5, 132.3, 131.1, 130.8, 130.4, 129.9, 129.6, 125.8, 124.1, 114.0, 73.0, 71.8, 69.2, 66.0, 65.1, 55.4, 35.7, 35.5, 30.6; MS (ES) m/z 419.15 $[M+Na]^+$; calcd for $C_{24}H_{28}O_5Na$: 419.18.

3.1.6.4. 12-[2-(4-Methoxy-benzyloxy)-ethyl]-5,8,11,12-tetrahydro-10*H*-9,13-dioxa-4b-aza-cyclododeca[a]-inden-14-one *E*-9d. Reaction mixture purified by FC (20% EtOAc in hexanes) to give 86 mg of product *E*-**9d** (18% yield *E*-isomer, catalyst **i**; 41% combined yield $E+Z$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.33 (1H, app.t, J=8.0 Hz), 7.27 (2H, d, J=8.8 Hz), 7.15 (1H, t, J=8.0 Hz), 6.91 (1H, s), 6.85 (2H, d, J=8.8 Hz), 5.80 (1H, ddd, J=15.2, 10.0, 4.4 Hz), 5.49–5.43 (1H, m), 5.38 (1H, ddd, J=14.8, 10.0, 3.6 Hz), 5.02 (1H, dd, J=14.4, 10.0 Hz), 4.88 (1H, br.d, J=14.4 Hz), 4.47 (1H, d, J=11.6 Hz), 4.43 (1H, d, J=11.6 Hz), 4.10 (1H, dd, J=12.0, 4.8 Hz), 3.78 (3H, s), 3.60 (2H, ddd, J=6.4, 2.0, 2.0 Hz), 3.45 (1H, ddd, J=10.0, 3.6, 3.6 Hz), 3.39 (1H, dd, J=12.4, 10.4 Hz), 3.27 (1H, ddd, J=11.6, 9.6, 2.0 Hz), 2.03–1.89 (3H, m), 1.69 (1H, dddd, J=14.4, 12.0, 2.4, 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 159.3, 138.4, 132.8, 131.4, 130.6, 130.2, 129.6, 126.9, 124.3, 122.5, 120.8, 114.0, 110.0, 107.3, 73.1, 70.0, 66.8, 62.6, 55.4, 46.1, 35.6, 35.4; MS (ES) m/z 458.15 $[M+Na]^+$; calcd for $C_{26}H_{29}NO_5Na$: 458.19.

3.1.6.5. 7-[2-(4-Methoxy-benzyloxy)-ethyl]-1,2,3,4,8,9,11,14-octahydro-7*H*-6,10-dioxa-benzocyclododecen-5-one *E*-9e. Reaction mixture purified by FC (15% EtOAc in hexanes) to give 172 mg of non-separable *E*- and *Z*-isomers (75% combined yield, catalyst **ii**) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (2H, d, J=8.0 Hz), 6.86 (2H, d, J=8.0 Hz), 5.48–5.34 (2H, m), 5.15 (1H, dddd, J=11.6, 6.0, 6.0, 2.0 Hz), 4.43 (1H, d, J=11.6 Hz), 4.38 (1H, d, J=11.6 Hz), 4.09 (1H, br.dd, J=11.2, 3.2 Hz), 3.80 (3H, s), 3.50–3.35 (6H, m), 2.27 (2H, br.d, 14.0), 2.15 (2H, br.s), 2.0–1.92 (1H, m), 1.87 (2H, app.dt, J=6.8, 6.4 Hz), 1.82 (1H, dddd, J=16.4, 14.8, 3.6, 2.4 Hz), 1.66–1.61 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1, 159.3, 138.8, 132.4, 130.5, 129.6, 128.5, 114.0, 73.0, 70.6, 69.3, 66.8, 61.9, 55.4, 36.9, 35.6, 35.1, 32.4, 27.0, 22.7, 21.8; MS (ES) m/z 423.15 $[M+Na]^+$; calcd for $C_{24}H_{32}O_5Na$: 423.21.

3.1.7. PMB deprotection. To a solution of the lactone **9b–e** (1 equiv) in CH_2Cl_2 (0.05 M with respect to the lactone) and water (1.0 M with respect to the lactone) was added DDQ (1.2 equiv). After stirring for 2–3 h, the slurry was poured into sat. aq. $NaHCO_3$ and water and extracted with EtOAc (4×). The combined organic layers were dried, concentrated in vacuo, and purified by FC.

3.1.7.1. Acetic acid 7-(2-hydroxy-ethyl)-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-4-yl ester 10b. Reaction mixture purified by FC (60% EtOAc in hexanes) to give 760 mg (95% yield) of product **10b**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, t, J=8.0 Hz), 7.14 (1H, d, J=7.6 Hz), 7.05 (1H, d, J=7.6 Hz), 5.63 (1H, dddd, J=14.8, 10.4, 4.0, 1.6 Hz), 5.51 (1H, ddd, J=14.8, 11.2, 3.6 Hz), 5.33 (1H, dddd, J=10.8, 8.4, 2.4, 2.4 Hz), 4.15 (1H, br.d, J=12.4 Hz), 3.92 (1H, dd, J=13.6, 10.8 Hz), 3.77–3.73 (2H, m), 3.48 (1H, dt, J=10.0, 2.8 Hz), 3.38 (1H, dd, J=12.0, 10.0 Hz), 3.28 (1H, ddd, J=12.0, 10.4, 1.6 Hz), 3.22 (1H, ddt, J=14.0, 3.2, 1.6 Hz), 2.94 (1H, dd, J=7.6, 6.0 Hz), 2.22 (3H, s), 1.99–1.91 (1H, m), 1.82 (1H, dddd, J=16.4, 12.8, 3.6, 2 Hz), 1.69 (1H, ddt, J=13.6, 10.0, 3.2 Hz), 1.62–1.56 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 168.4, 148.3, 139.8, 133.3, 130.9, 129.7, 128.0, 127.2, 121.7, 70.5, 69.3, 61.8, 58.3, 39.0, 37.6, 35.6, 21.0; MS (ES) m/z 357.10 (100%) [$(M+Na)^+$; calcd for $C_{18}H_{22}O_6Na$: 357.13].

3.1.7.2. 7-(2-Hydroxy-ethyl)-8,9,11,14-tetrahydro-7*H*-6,10-dioxa-benzocyclododecen-5-one 10c. Reaction mixture purified by FC (50% EtOAc in hexanes) to give 155 mg (94% yield) of product **10c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (1H, app.t, J=7.6 Hz), 7.37 (1H, d, J=7.6 Hz), 7.27 (1H, app.t, J=7.6 Hz), 7.25 (1H, d, J=7.6 Hz), 5.63 (1H, dddd, J=15.2, 10.4, 4.4, 1.6 Hz), 5.46 (1H, ddd, J=14.8, 11.2, 3.2 Hz), 5.42–5.35 (1H, m), 4.15 (1H, br.dd, J=10.8,

4.0 Hz), 4.02 (1H, dd, J=13.6, 10.8 Hz), 3.76–3.64 (2H, m), 3.48 (1H, dt, J=10.0, 2.8 Hz), 3.37 (1H, dd, J=12.0, 10.4 Hz), 3.29 (1H, ddd, J=12.0, 10.4, 1.6 Hz), 3.15 (1H, br.d, J=13.6 Hz), 3.07 (1H, br. s), 1.99–1.80 (2H, m), 1.78 (1H, dddd, J=13.6, 10.0, 3.6, 3.6 Hz), 1.65 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0, 138.3, 134.0, 133.5, 130.8, 130.5, 129.6, 127.7, 126.6, 70.6, 68.7, 62.0, 58.5, 38.4, 37.5, 35.5; MS (ES) m/z 299.00 $[M+Na]^+$; calcd for $C_{16}H_{20}O_4Na$: 299.13.

3.1.7.3. 12-(2-Hydroxy-ethyl)-5,8,11,12-tetrahydro-10*H*-9,13-dioxa-4b-aza-cyclododeca[a]inden-14-one 10d. Reaction mixture purified by FC (40% EtOAc in hexanes) to give 36 mg (94% yield) of product **10d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.33 (1H, ddd, J=8.0, 7.2, 1.2 Hz), 7.16 (1H, dd, J=7.2, 7.2 Hz), 6.99 (1H, s), 5.80 (1H, ddd, J=15.2, 10.0, 4.4 Hz), 5.47 (1H, dddd, J=11.2, 11.2, 2.4, 2.4 Hz), 5.38 (1H, ddd, J=14.0, 10.0, 3.2 Hz), 5.00 (1H, dd, J=14.4, 10.0 Hz), 4.87 (1H, br d, J=14.4 Hz), 4.14 (1H, dd, J=11.6, 4.0 Hz), 3.76–3.70 (2H, m), 3.47 (1H, dt, J=10.0, 3.2 Hz), 3.36 (1H, dd, J=12.4, 10.4 Hz), 3.25 (1H, ddd, J=12.0, 10.0, 1.6 Hz), 2.79 (1H, br.s), 1.99–1.83 (2H, m), 1.81 (1H, dddd, J=14.4, 10.8, 3.6 Hz), 1.71 (1H, dddd, J=14.0, 11.6, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.7, 138.5, 132.7, 131.1, 130.4, 126.9, 124.6, 122.5, 121.0, 110.0, 107.6, 70.0, 69.7, 62.6, 58.6, 46.1, 38.1, 35.6; MS (ES) m/z 338.10 $[M+Na]^+$; calcd for $C_{18}H_{21}NO_4Na$: 338.14.

3.1.7.4. 7-(2-Hydroxy-ethyl)-1,2,3,4,8,9,11,14-octahydro-7*H*-6,10-dioxa-benzocyclododecen-5-one 10e. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 42 mg (35% yield, 78% combined yield E+Z) of the *E*-isomer **10e**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.48–5.36 (2H, m), 5.25–5.18 (1H, m), 4.10 (1H, br.d, J=11.6 Hz), 3.64–3.61 (1H, m), 3.52–3.43 (3H, m), 3.39–3.32 (2H, m), 3.10 (1H, br. s), 2.36 (1H, br.d, J=17.6 Hz), 2.68 (1H, br.d, J=14.0 Hz), 2.17 (2H, m), 2.06 (1H, br.d, J=16.8 Hz), 1.84 (1H, dddd, J=17.2, 10.4, 5.6, 2.8 Hz), 1.79 (1H, dddd, J=16.0, 12.0, 3.2, 2.0 Hz), 1.69–1.56 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 139.7, 132.6, 129.4, 128.4, 70.6, 67.3, 61.8, 58.3, 38.4, 36.7, 35.6, 32.4, 26.8, 22.6, 21.8; MS (ES) m/z 303.05 $[M+Na]^+$; calcd for $C_{16}H_{24}O_4Na$: 303.16.

3.1.8. Oxidation and HWE olefination. To a solution of alcohol **10b–e** in CH_2Cl_2 (0.04 M) was added Dess Martin periodinane (3 equiv). The reaction was stirred at rt for 3–4 h, after which time the solvent was removed in vacuo and the residue was quickly passed through a short column of silica (50% EtOAc in hexanes) to give the aldehyde. To a suspension of NaH (60% in mineral oil, prewashed with benzene, 4.5 equiv with respect to alcohol) in THF (0.3 M) was added dimethyl(trimethylsiloxy-carbonylmethyl)-phosphonate (5.0 equiv) at 0 °C. After stirring for 30 min at the same temperature, the solution was added to a solution of the above prepared aldehyde (pre-washed with benzene) in THF (0.1 M with respect to aldehyde) and stirring was continued for 1 h after which time more phosphonate solution (same amounts) was added. The mixture was stirred at 0 °C for 30 min before being quenched with acetic acid. Water was added, and the solution was extracted with EtOAc (3×). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo and purified by FC.

3.1.8.1. 4-(4-Acetoxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoic acid 11b. Reaction mixture purified by FC (50% EtOAc in hexanes with 1% AcOH) to give 111 mg of product **11b** (61% yield for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, t, J=7.6 Hz), 7.16–7.09 (2H, m), 7.06 (1H, d, J=8.4 Hz), 5.96 (1H, d, J=15.6 Hz), 5.63 (1H, dddd, J=15.2, 10.4, 4.0, 1.6 Hz), 5.52 (1H, ddd, J=14.8, 10.8, 3.2 Hz), 5.24 (1H, dddd, J=11.6, 6.4, 4.8, 1.6 Hz), 4.16 (1H, br.dd, J=12.4, 3.6 Hz), 3.87 (1H, dd, J=13.6, 10.8 Hz), 3.53 (1H, ddd, J=10.0, 3.6, 2.4 Hz), 3.40 (1H, dd, J=12.4, 10.4 Hz), 3.29 (1H, ddd, J=12.0, 10.8, 1.2 Hz), 3.22 (1H, dddd, J=14.0, 3.2, 1.6, 1.6 Hz), 2.75–2.59 (2H, m), 2.27 (3H, s), 1.80 (1H, dddd, J=16.4, 12.8, 3.6, 1.6 Hz), 1.54 (1H, dddd, J=14.4, 12.8, 1.6, 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.6, 168.9, 166.6, 148.1, 146.1, 139.3, 133.6, 130.7, 130.4, 129.2, 128.7, 127.9, 127.5, 121.6, 70.7, 70.0, 61.9, 37.7, 34.1, 21.1; MS (ES) m/z 397.10 $[M+Na]^+$; calcd for $C_{20}H_{22}O_7Na$: 397.13.

3.1.8.2. 4-(5-Oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoic acid 11c. Reaction mixture purified by FC (40% EtOAc in hexanes with 1% AcOH) to give 100 mg (57% yield for 2 steps) of the product **11c**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 11.2 (1H, br.s), 7.37–7.22 (4H, m), 7.13 (1H, dt, J=15.6, 7.2 Hz), 5.96 (1H, d, J=15.6 Hz), 5.62 (1H, dddd, J=15.3, 10.5, 4.5, 1.8 Hz), 5.46 (1H, ddd, J=14.4, 10.8, 2.7 Hz), 5.37 (1H, dddd, J=11.7, 5.7, 5.7, 3.2 Hz), 4.17 (1H, br.dd, J=12.3, 4.2 Hz), 4.00 (1H, dd, J=13.8, 10.8 Hz), 3.52 (1H, dt, J=10.2, 2.4 Hz), 3.38 (1H, dd, J=12.3, 10.2 Hz), 3.29 (1H, ddd, J=12.3, 10.2, 2.1 Hz), 3.15 (1H, dddd, J=13.8, 3.3, 1.5, 1.5 Hz), 2.75–2.55 (2H, m), 1.85 (1H, dddd, J=15.9, 12.0, 3.3, 3.3 Hz), 1.63 (1H, dddd, J=14.4, 12.3, 2.1, 2.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 171.4, 146.4, 138.1, 134.2, 133.7, 130.7, 130.5, 129.4, 127.5, 126.7, 123.9, 70.7, 70.0, 62.0, 38.0, 37.5, 34.3; MS (ES) m/z 339.00 $[M+Na]^+$; calcd for $C_{18}H_{20}O_5Na$: 339.12.

3.1.8.3. 4-(14-Oxo-5,8,11,12-tetrahydro-10H,14H-9,13-dioxa-4b-aza-cyclododeca[a]inden-12-yl)-but-2-enoic acid 11d. Reaction mixture purified by FC (50% EtOAc in hexanes with 1% AcOH) to give 21.4 mg of product **11d** (53% yield for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.15 (1H, br s), 7.65 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.33 (1H, t, J=6.8 Hz), 7.16 (1H, t, J=7.2 Hz), 7.11 (1H, dt, J=15.2, 8.0 Hz), 6.9 (1H, s), 5.98 (1H, d, J=15.2 Hz), 5.79 (1H, ddd, J=14.8, 10.4, 4.0 Hz), 5.47 (1H, dddd, J=11.6, 6.0, 6.0, 2.0 Hz), 5.38 (1H, ddd, J=14.0, 10.0, 3.6 Hz), 5.00 (1H, dd, J=14.4, 10.0 Hz), 4.87 (1H, br.d, J=15.2 Hz), 4.12 (1H, dd, J=12.8, 6.0 Hz), 3.48 (1H, dt, J=10.0, 3.2 Hz), 3.38 (1H, dd, J=12.0, 10.0 Hz), 3.25 (1H, ddd, J=12.0, 10.0, 2.0 Hz), 2.70–2.61 (2H, m), 1.89 (1H, dddd, J=14.8, 12.0, 3.2, 3.2 Hz), 1.68 (1H, dddd, J=14.4, 12.0, 2.4, 2.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 146.3, 138.4, 132.7, 131.0, 130.4, 126.9, 124.5, 122.6, 120.9, 110.0, 107.5, 70.1, 69.8, 62.5, 46.1, 38.0, 34.7; MS (ES) m/z 378.05 $[M+Na]^+$; calcd for $C_{20}H_{21}NO_5Na$: 378.13.

3.1.8.4. 4-(5-Oxo-1,3,4,5,8,9,11,14-octahydro-2H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoic acid 11e. Reaction mixture purified by FC (30% EtOAc in hexanes with 1% AcOH) to give 25.5 mg of product **11e** (56% yield for 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, dt, J=15.6, 8.0 Hz), 5.84 (1H, d, J=15.6 Hz), 5.45–5.34 (2H, m), 5.19 (1H, dddd, J=11.6, 5.6, 5.6, 2.0 Hz), 4.10 (1H, br.d, J=11.2 Hz), 3.53 (1H, dt, J=10.0, 2.8 Hz), 3.44–3.32 (3H, m), 2.63–2.55 (1H, m), 2.45 (1H, dddd, J=14.4, 8.0, 7.2, 0.8 Hz), 2.33–2.25 (2H, m), 2.18–2.02 (3H, m), 1.78 (1H, dddd, J=16.4, 12.4, 3.6, 2.4 Hz), 1.68–1.56 (5H, m);); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 170.3, 146.8, 138.9, 132.7, 129.8, 128.3, 123.6, 70.8, 67.8, 61.9, 37.9, 36.9, 34.4, 32.4, 26.5, 22.7, 21.8; MS (ES) m/z 343.05 $[M+Na]^+$; calcd for $C_{18}H_{24}O_5Na$: 343.15.

3.1.9. Acyl azide formation. To a stirred solution of the acid **11b–e** and diphenylphosphorylazide (4 equiv) in benzene (0.03 M) was added triethylamine (4.7 equiv). The reaction mixture was stirred at rt for 2 h and concentrated in vacuo prior to purification by FC.

3.1.9.1. Acetic acid 7-(3-azidocarbonyl-allyl)-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-4-yl ester 12b. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 82 mg (77% yield) of product **12b** as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (1H, t, J=8.0 Hz), 7.12 (1H, d, J=7.2 Hz), 7.10 (1H, dt, J=15.6, 7.6 Hz), 7.06 (1H, d, J=8.4 Hz), 5.94 (1H, d, J=15.6 Hz), 5.62 (1H, dddd, J=14.8, 10.4, 4.4, 1.6 Hz), 5.51 (1H, ddd, J=14.8, 10.8, 3.6 Hz), 5.23 (1H, dddd, J=11.6, 6.4, 4.8, 1.6 Hz), 4.13 (1H, br.dd, J=12.0, 4.4 Hz), 3.87 (1H, dd, J=13.6, 10.4 Hz), 3.51 (1H, ddd, J=10.4, 3.2, 2.8 Hz), 3.39 (1H, dd, J=12.4, 10.4 Hz), 3.27 (1H, ddd, J=12.4, 10.8, 1.6 Hz), 3.21 (1H, dddd, J=14.0, 3.2, 1.6, 1.6 Hz), 2.71–2.55 (2H, m), 2.26 (3H, s), 1.78 (1H, dddd, J=16.4, 12.0, 3.6, 1.6 Hz), 1.53 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 168.8, 166.7, 148.1, 146.1, 139.4, 133.5, 130.7, 129.4, 127.9, 125.7, 122.9, 121.6, 70.7, 69.9, 61.8, 37.7, 34.4, 21.2; MS (ES) m/z 356.20 $[M-H]^-$; calcd for $C_{18}H_{18}N_3O_5$: 356.13.

3.1.9.2. 4-(5-Oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoyl azide 12c. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 61 mg (56% yield) of product **12c**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (1H, app.dt, J=7.6, 1.2 Hz), 7.33 (1H, d, J=7.6 Hz), 7.27 (1H, app.t, J=7.6 Hz), 7.23 (1H, d, J=7.6 Hz), 7.10 (1H, dt, J=15.2, 8.0 Hz), 5.95 (1H, d, J=15.2 Hz), 5.61 (1H, dddd, J=15.2, 10.4, 4.4, 1.6 Hz), 5.46 (1H, ddd, J=14.4, 10.8, 3.2 Hz), 5.37 (1H, dddd, J=12.0, 6.4, 6.4, 2.4 Hz), 4.14 (1H, dd, J=12.0, 4.4 Hz), 4.00 (1H, dd, J=14.0, 10.8 Hz), 3.49 (1H, dt, J=10.0, 2.8 Hz), 3.37 (1H, dd, J=12.4, 10.4 Hz), 3.27 (1H, ddd, J=12.0, 10.0, 1.6 Hz), 3.15 (1H, dddd, J=14.0, 3.2, 1.6, 1.6 Hz), 2.72–2.55 (2H, m), 1.82 (1H, dddd, J=16.4, 12.0, 3.6, 2.4 Hz), 1.61 (1H, dddd, J=13.6, 12.0, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.5, 169.0, 146.6, 138.2, 134.2, 133.6, 130.7, 130.6, 129.5, 127.4, 126.7, 125.6, 70.7, 68.9, 61.9, 38.3, 37.6, 34.6; MS (ES) m/z 368.10 $[M-N_2+MeOH+Na]^+$; calcd for $C_{19}H_{23}NO_5Na$: 368.15.

3.1.9.3. 4-(14-Oxo-5,8,11,12-tetrahydro-10H,14H-9,13-dioxa-4b-aza-cyclododeca[a]inden-12-yl)-but-2-enoyl azide 12d. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 20 mg (88% yield) of product **12d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (1H, d, J=8.0 Hz), 7.42 (1H, d, J=8.4 Hz), 7.34 (1H, ddd, J=8.0, 7.2, 0.8 Hz), 7.16 (1H, t, J=7.6 Hz), 7.10 (1H, dt, J=15.2, 7.6 Hz), 6.96 (1H, s), 5.97 (1H, d, J=15.2 Hz), 5.79 (1H, ddd, J=15.2, 10.4, 4.8 Hz), 5.47 (1H, dddd, J=11.6, 6.8, 6.8, 2.4 Hz), 5.38 (1H, ddd, J=14.4, 10.0, 3.6 Hz), 5.00 (1H, dd, J=14.4, 10.0 Hz), 4.87 (1H, br.d, J=14.0 Hz), 4.12 (1H, dd, J=10.8, 3.6 Hz), 3.47 (1H, dt, J=10.0, 3.2 Hz), 3.37 (1H, dd, J=12.4, 10.4 Hz), 3.24 (1H, ddd, J=11.6, 10.0, 1.6 Hz), 2.68–2.61 (2H, m), 1.88 (1H, dddd, J=14.4, 11.6, 3.2, 3.2 Hz), 1.67 (1H, dddd, J=14.4, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 146.3, 138.5, 132.7, 131.0, 130.3, 126.8, 125.8, 124.5, 122.6, 120.9, 110.0, 107.5, 70.1, 69.7, 62.4, 46.1, 38.2, 34.9; MS (ES) m/z 407.05 $[M-N_2+MeOH+Na]^+$; calcd for $C_{21}H_{24}N_2ONa$: 407.16.

3.1.9.4. 4-(5-Oxo-1,3,4,5,8,9,11,14-octahydro-2H,7H-6,10-dioxa-benzocyclododecen-7-yl)-but-2-enoyl azide 12e. Reaction mixture purified by FC (10% EtOAc in hexanes) to give 17 mg (67% yield) of product **12e**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (1H, dt, J=15.2, 7.6 Hz), 5.84 (1H, d, J=15.2 Hz), 5.45–5.36 (2H, m), 5.19 (1H, dddd, J=11.6, 5.6, 5.6, 2.0 Hz), 4.10 (1H, br.d, J=11.2 Hz), 3.52 (1H, dt, J=9.6, 2.4 Hz), 3.44–3.31 (3H, m), 2.57 (1H, app.dt, J=14.0, 6.8 Hz), 2.43 (1H, app.dt, J=14.0, 7.6 Hz), 2.36–2.25 (2H, m), 2.16–1.99 (3H, m), 1.76 (1H, dddd, J=16.8, 12.4, 3.6, 2.4 Hz), 1.68–1.53 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.6, 170.3, 147.0, 139.1, 132.6, 129.7, 128.3, 125.4, 70.8, 67.7, 61.8, 38.3, 36.9, 34.6, 32.4, 26.5, 22.7, 21.8; MS (ES) m/z 372.10 $[M-N_2+MeOH+Na]^+$; calcd for $C_{19}H_{27}NO_5Na$: 372.18.

3.1.10. Curtius rearrangement and alkyne addition. A stirred solution of the acylazide **12b–e** in benzene (0.02 M) was heated at 80 °C for 5 h, after which the solvent was steamed off with nitrogen and the residue dried under vacuum for 10 min. To a solution of the alkyne (2.0 equiv) in THF (0.1 M) at −78 °C was added *n*-BuLi (2.5 M in hexanes, 1.7 equiv) or the alkyne was added to a freshly prepared solution of LDA in THF (0.1 M). The stirring was continued for 30 min, after which time a solution of the isocyanate mixture in THF was added. The reaction mixture was stirred at −78 °C for 30 min, and then quenched with saturated NH_4Cl and water. The mixture was extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. If no acetate group was present, the residue was purified by FC. When an acetate group was present, the residue was dissolved in MeOH and K_2CO_3 (1 equiv) was added. The mixture was stirred at rt for 1 h, after which time water was added and the mixture was extracted with Et_2O (3×). The combined organic layers were dried, concentrated in vacuo, and purified by FC.

3.1.10.1. 3-Phenyl-propynoic acid [3-(4-hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 14a. *n*-BuLi was used. Reaction mixture purified by FC (40% EtOAc in hexanes) to give 23.6 mg (62% yield) of product **14a**. $[\alpha]_D$=−19.3

($c=1.52$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.59 (2H, d, $J=7.2$ Hz), 7.48 (1H, t, $J=7.6$ Hz), 7.41 (2H, d, $J=8.0$ Hz), 7.15 (1H, t, $J=8.0$ Hz), 6.84 (1H, d, $J=14.4$ Hz), 6.77 (1H, d, $J=8.4$ Hz), 6.72 (1H, d, $J=7.6$ Hz), 5.56–5.53 (2H, m), 5.49 (1H, dt, $J=14.4$, 8.0 Hz), 5.11–5.05 (1H, m), 4.10 (1H, d, $J=10.8$ Hz), 3.71 (1H, dd, $J=13.2$, 10.0 Hz), 3.54 (1H, br d, $J=10.0$ Hz), 3.44 (1H, dd, $J=12.4$, 10.0 Hz), 3.38 (1H, d, $J=10.8$ Hz), 3.15 (1H, d, $J=13.2$ Hz), 2.49 (2H, dd, $J=6.4$, 6.4 Hz, m), 1.80 (1H, dd, $J=14.8$, 11.6 Hz), 1.60 (1H, dd, $J=14.4$, 12.4 Hz); ^{13}C NMR (75 MHz, CD_3OD_3) δ 170.5, 156.4, 152.4, 139.6, 135.3, 133.7, 131.7, 130.0, 129.9, 125.9, 123.9, 122.2, 121.5, 115.6, 111.7, 87.3, 83.7, 71.8, 71.6, 63.4, 38.7, 36.2, 34.7; MS (ES) m/z 454.20 $[M+Na]^+$; calcd for $C_{26}H_{25}NO_5Na$: 454.16.

3.1.10.2. 3-Phenyl-propynoic acid [3-(5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 14c. *n*-BuLi was used. Reaction mixture purified by FC (40% EtOAc in hexanes) to give 9.3 mg (97% yield) of product **14c**. $[\alpha]_D=-66.8$ ($c=0.63$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.58 (2H, d, $J=8.0$ Hz), 7.47 (1H, d, $J=7.2$ Hz), 7.43–7.37 (4H, m), 7.31–7.27 (2H, m), 6.89 (1H, d, $J=14.4$ Hz), 5.56 (1H, dddd, $J=15.2$, 10.4, 4.4, 1.6 Hz), 5.49 (1H, ddd, $J=14.4$, 10.0, 3.2 Hz), 5.45 (1H, dt, $J=15.2$, 8.4 Hz), 5.20 (1H, ddd, $J=11.6$, 6.0, 6.0, 2.0 Hz), 4.09 (1H, br.dd, $J=12.0$, 3.2 Hz), 3.92 (1H, dd, $J=14.0$, 10.8 Hz), 3.49 (1H, dt, $J=10.0$, 2.4 Hz), 3.40 (1H, dd, $J=12.0$, 9.6 Hz), 3.33–3.28 (1H, m), 3.19 (1H, br.d, $J=13.6$ Hz), 2.53–2.38 (2H, m), 1.84 (1H, dddd, $J=16.0$, 12.4, 3.6, 2.4 Hz), 1.60 (1H, dddd, $J=14.4$, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 152.5, 139.2, 135.8, 134.9, 133.7, 131.7, 131.6, 130.6, 130.0, 128.6, 127.8, 125.9, 122.5, 11.5, 87.4, 83.6, 71.5, 71.3, 63.3, 38.4, 36.9, 35.2; MS (ES) m/z 438.15 $[M+Na]^+$; calcd for $C_{26}H_{25}NO_4Na$: 438.17.

3.1.10.3. 3-Phenyl-propynoic acid [3-(14-oxo-5,8,11,12-tetrahydro-10H,14H-9,13-dioxa-4b-aza-cyclododeca[a]inden-12-yl)-propenyl]-amide 14d. *n*-BuLi was used. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 12 mg (79% yield) of product **14d**. $[\alpha]_D=-167.6$ ($c=0.50$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.62 (1H, d, $J=8.0$ Hz), 7.57 (2H, d, $J=8.0$ Hz), 7.52 (1H, d, $J=8.4$ Hz), 7.45 (1H, d, $J=7.2$ Hz), 7.40 (2H, d, $J=8.0$ Hz), 7.30 (1H, dd, $J=7.2$, 7.2 Hz), 7.11 (1H, t, $J=7.6$ Hz), 6.95 (1H, s), 6.89 (1H, d, $J=14.4$ Hz), 5.72 (1H, ddd, $J=14.8$, 10.0, 4.8 Hz), 5.46 (1H, ddd, $J=14.4$, 6.8, 6.8 Hz), 5.42–5.28 (2H, m), 5.01 (1H, br.d, $J=10.4$ Hz), 4.92 (1H, br.d, $J=14.8$ Hz), 4.11–4.04 (1H, m), 3.46 (1H, br.d, $J=9.2$ Hz), 3.42 (1H, dd, $J=12.0$, 10.0 Hz), 3.31–3.26 (1H, m), 2.49–2.42 (2H, m), 1.90 (1H, dddd, $J=14.4$, 11.6, 3.2, 3.2 Hz), 1.65 (1H, dddd, $J=14.4$, 12.0, 2.4, 2.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 173.1, 165.4, 152.5, 139.9, 133.7, 133.6, 132.6, 131.8, 130.1, 130.0, 128.2, 126.0, 125.4, 123.3, 121.8, 121.5, 111.4, 111.1, 108.0, 87.4, 83.7, 72.3, 70.8, 63.8, 47.0, 36.8, 35.5; MS (ES) m/z 477.20 $[M+Na]^+$; calcd for $C_{28}H_{26}N_2O_4Na$: 477.18.

3.1.10.4. 3-Phenyl-propynoic acid [3-(5-oxo-1,3,4,5,8,9,11,14-octahydro-2H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 14e. *n*-BuLi was used. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 10 mg (50% yield) of product **14e**. $[\alpha]_D=-65.1$ ($c=0.48$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.59 (2H, d, $J=8.4$ Hz), 7.49 (1H, app.t, $J=7.6$ Hz), 7.43 (2H, d, $J=7.6$ Hz), 6.76 (1H, d, $J=14.4$ Hz), 5.46 (1H, ddd, $J=14.8$, 10.8, 3.6 Hz), 5.39–5.33 (1H, m), 5.35 (1H, dt, $J=14.4$, 7.2 Hz), 5.03 (1H, dddd, $J=11.6$, 6.0, 6.0, 2.0 Hz), 4.05 (1H, br.dd, $J=12.0$, 3.6 Hz), 3.51 (1H, app.dt, $J=10.0$, 2.8 Hz), 3.40 (1H, dd, $J=12.0$, 10.0 Hz), 3.36–3.30 (2H, m), 2.40–2.16 (6H, m), 2.07–2.00 (1H, m), 1.78 (1H, dddd, $J=17.2$, 12.8, 4.0, 2.4 Hz), 1.68–1.60 (4H, m), 1.55 (1H, dddd, $J=14.4$, 12.4, 2.0, 2.0 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.6, 151.1, 138.6, 132.5, 132.4, 130.4, 129.9, 128.7, 128.0, 124.4, 120.1, 110.2, 86.0, 82.3, 70.2, 69.0, 61.8, 36.4, 35.4, 33.8, 31.9, 26.4, 22.5, 21.6; MS (ES) m/z 442.10 $[M+Na]^+$; calcd for $C_{26}H_{29}NO_4Na$: 442.20.

3.1.10.5. 3-(3-Fluoro-phenyl)-propynoic acid [3-(4-hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 16. *n*-BuLi was used. Reaction mixture purified by FC (40% EtOAc in hexanes) to give 9.2 mg (52% yield) of product **16**. ^1H NMR (400 MHz, CD_3OD) δ 7.47–7.40 (2H, m), 7.34 (1H, ddd, $J=9.2$, 2.8, 1.6 Hz), 7.25 (1H, dddd, $J=10.8$, 8.8, 2.8, 1.6 Hz), 7.15 (1H, t, $J=7.6$ Hz), 6.83 (1H, d, $J=14.4$ Hz), 6.75 (1H, d, $J=8.4$ Hz), 6.73 (1H, d, $J=7.2$ Hz), 5.57–5.53 (2H, m), 5.50 (1H, dt, $J=14.4$, 8.0 Hz), 5.08 (1H, dddd, $J=11.6$, 5.6, 5.6, 2.4 Hz), 4.10 (1H, d, $J=12.0$ Hz), 3.71 (1H, dd, $J=13.6$, 10.0 Hz), 3.54 (1H, ddd, $J=10.4$, 3.6, 2.4 Hz), 3.44 (1H, dd, $J=12.4$, 10.0 Hz), 3.37 (1H, ddd, $J=12.0$, 10.4, 1.6 Hz), 3.15 (1H, br.d, $J=13.6$ Hz), 2.49 (2H, ddd, $J=7.2$, 6.0, 1.2 Hz), 1.80 (1H, dddd, $J=16.4$, 12.8, 4.0, 2.4 Hz), 1.60 (1H, dddd, $J=14.4$, 12.0, 1.6, 1.6 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 165.6, 162.3, 156.5, 152.0, 139.6, 135.3, 132.1, 132.0, 131.7, 129.9, 125.8, 123.9, 122.1, 120.3, 120.0, 119.1, 118.8, 115.6, 112.0, 85.5, 84.3, 71.8, 71.6, 63.4, 38.7, 36.2, 34.8; MS (ES) m/z 472.25 $[M+Na]^+$; calcd for $C_{26}H_{24}FNO_5Na$: 472.15.

3.1.10.6. 3-Pyridin-3-yl-propynoic acid [3-(4-hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 17. LDA was used. Reaction mixture purified by PTLC (neat EtOAc) to give 1.8 mg (47% yield) of product **17**. $[\alpha]_D=-8.22$ ($c=0.18$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 8.75 (1H, d, $J=2.0$ Hz), 8.63 (1H, dd, $J=4.8$, 1.6 Hz), 8.04 (1H, ddd, $J=8.0$, 1.6, 1.6 Hz), 7.51 (1H, dd, $J=7.6$, 4.8 Hz), 7.16 (1H, t, $J=7.6$ Hz), 6.85 (1H, d, $J=14.4$ Hz), 6.76 (1H, d, $J=8.4$ Hz), 6.73 (1H, d, $J=7.6$ Hz), 5.58–5.49 (3H, m), 5.12–5.06 (1H, m), 4.11 (1H, d, $J=10.0$ Hz), 3.73 (1H, dd, $J=13.2$, 10.0 Hz), 3.56 (1H, br d, $J=10.0$ Hz), 3.45 (1H, dd, $J=12.4$, 10.0 Hz), 3.39 (1H, d, $J=10.4$ Hz), 3.16 (1H, br d, $J=13.2$ Hz), 2.51 (2H, dd, $J=6.4$, 6.4 Hz), 1.81 (1H, dd, $J=14.8$, 12.4 Hz), 1.62 (1H, dd, $J=14.8$, 12.0 Hz); MS (ES) m/z 455.10 $[M+Na]^+$; calcd for $C_{25}H_{24}N_2ONa$: 455.16.

3.1.10.7. 3-Oxazol-2-yl-propynoic acid [3-(4-hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-amide 18. LDA was used. Reaction mixture purified by FC (50% EtOAc in hexanes) to give 4.3 mg (56% yield) of product **18**.

$[\alpha]_D = -13.2$ ($c=0.25$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 8.08 (1H, d, $J=0.8$ Hz), 7.37 (1H, d, $J=0.8$ Hz), 7.15 (1H, t, $J=8.0$ Hz), 6.83 (1H, d, $J=14.4$ Hz), 6.77 (1H, d, $J=8.4$ Hz), 6.73 (1H, d, $J=7.6$ Hz), 5.59–5.51 (3H, m), 5.09 (1H, dddd, $J=11.2$, 6.8, 4.8, 2.0 Hz), 4.10 (1H, br.d, $J=12.0$ Hz), 3.71 (1H, dd, $J=13.6$, 10.0 Hz), 3.55 (1H, br.d, $J=9.2$ Hz), 3.45 (1H, dd, $J=12.0$, 10.0 Hz), 3.38 (1H, d, $J=10.8$ Hz), 3.16 (1H, br.d, $J=13.6$ Hz), 2.53–2.48 (2H, m), 1.80 (1H, dddd, $J=16.8$, 12.4, 4.0, 2.4 Hz), 1.61 (1H, dd, $J=14.4$, 12.4 Hz); ^{13}C NMR (75 MHz, CD_3OD_3) δ 170.5, 156.5, 150.1, 143.8, 139.6, 135.3, 131.7, 130.1, 129.9, 125.5, 123.9, 122.1, 115.6, 113.0, 84.8, 71.7, 71.6, 63.4, 38.7, 36.2, 34.7; MS (ES) *m/z* 445.10 $[M+Na]^+$; calcd for $C_{23}H_{22}N_2O_6Na$: 445.14.

3.1.11. Curtius rearrangement and alcohol addition. To a stirred solution of acylazide **12b** in benzene (0.02 M) was added the alcohol (20 equiv). The reaction mixture was heated at 80 °C for 5 h, after which the solvent was steamed off with nitrogen. The residue was dissolved in MeOH and K_2CO_3 (1 equiv) was added. The mixture was stirred at rt for 1 h, after which time water was added and the mixture was extracted with Et_2O (3×). The combined organic layers were dried over $MgSO_4$, concentrated in vacuo, and purified by FC.

3.1.11.1. [3-(4-Hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-carbamic acid benzyl ester 19. Reaction mixture purified by FC (30% EtOAc in hexanes) to give 6.5 mg (85% yield) of product **19**. $[\alpha]_D = -6.8$ ($c=0.34$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.37–7.30 (5H, m), 7.15 (1H, t, $J=8.0$ Hz), 6.74 (1H, d, $J=8.8$ Hz), 6.72 (1H, d, $J=8.0$ Hz), 6.52 (1H, d, $J=14.4$ Hz), 5.56–5.53 (2H, m), 5.17 (1H, dt, $J=14.0$, 8.0 Hz), 5.12 (2H, s), 5.05–4.99 (1H, m), 4.08 (1H, d, $J=10.8$ Hz), 3.70 (1H, dd, $J=13.6$, 10 Hz), 3.53 (1H, br d, $J=10$ Hz), 3.43 (1H, dd, $J=11.6$, 10 Hz), 3.36 (1H, br.t, $J=10.8$ Hz), 3.15 (1H, d, $J=13.2$ Hz), 2.45–2.39 (2H, m), 1.79 (1H, dd, $J=14.4$, 12.4 Hz), 1.57 (1H, dd, $J=13.6$, 13.2 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.6, 156.5, 139.6, 135.3, 131.7, 129.8, 129.7, 129.3, 129.1, 127.9, 124.0, 122.1, 115.6, 106.8, 101.8, 72.2, 71.6, 67.8, 63.5, 38.7, 36.0, 34.5; MS (ES) *m/z* 460.10 $[M+Na]^+$; calcd for $C_{25}H_{27}NO_6Na$: 460.17.

3.1.11.2. [3-(4-Hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-carbamic acid pentyl ester 20. $[\alpha]_D = -58.9$ ($c=2.21$, CH_2Cl_2); Reaction mixture purified by FC (20% EtOAc in hexanes) to give 7 mg (71% yield) of product **20**. ^1H NMR (400 MHz, CD_3OD) δ 7.16 (1H, t, $J=8.0$ Hz), 6.76 (1H, d, $J=8.0$ Hz), 6.74 (1H, d, $J=8.0$ Hz), 6.51 (1H, d, $J=14.4$ Hz), 5.57–5.54 (2H, m), 5.15 (1H, dt, $J=14.8$, 8.0 Hz), 5.03 (1H, dddd, $J=12.0$, 6.8, 4.4, 2.4 Hz), 4.12–4.06 (3H, m), 3.71 (1H, dd, $J=14.0$, 10.4 Hz), 3.55 (1H, ddd, $J=10.4$, 3.6, 2.4 Hz), 3.44 (1H, dd, $J=12.4$, 10.4 Hz), 3.37 (1H, ddd, $J=12.4$, 10.4, 2.0 Hz), 3.16 (1H, d, $J=13.6$ Hz), 2.46–2.38 (2H, m), 1.81 (1H, dddd, $J=16.8$, 12.4, 3.6, 2.4 Hz), 1.67–1.62 (2H, m), 1.58 (1H, ddt, $J=14.4$, 12.0, 2.4 Hz), 1.39–1.37 (4H, m), 0.94 (3H, t, $J=7.2$ Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 156.4, 139.6, 135.3, 131.7, 129.9, 128.0, 124.0, 122.1, 115.5, 106.4, 72.2, 71.6, 66.4, 63.5, 38.7, 36.1, 34.5, 30.0, 29.3, 23.6, 14.5; MS (ES) *m/z* 440.20 $[M+Na]^+$; calcd for $C_{23}H_{31}NO_6Na$: 440.20; 481.30 $[M+CH_3CN+Na]^+$; calcd for $C_{25}H_{34}N_2O_6Na$: 481.23.

3.1.11.3. [3-(4-Hydroxy-5-oxo-8,9,11,14-tetrahydro-5H,7H-6,10-dioxa-benzocyclododecen-7-yl)-propenyl]-carbamic acid oxazol-2-ylmethyl ester 21. Reaction mixture purified by FC (50% EtOAc in hexanes) to give 6.2 mg (58% yield) of product **21**. $[\alpha]_D = -11.0$ ($c=0.26$, CH_2Cl_2). ^1H NMR (400 MHz, CD_3OD) δ 7.94 (1H, s), 7.19 (1H, s), 7.15 (1H, t, $J=8.0$ Hz), 6.75 (1H, d, $J=8.0$ Hz), 6.72 (1H, d, $J=8.0$ Hz), 6.52 (1H, d, $J=14.4$ Hz), 5.56–5.54 (2H, m), 5.21 (1H, dt, $J=13.6$, 8.0 Hz), 5.20 (2H, s), 5.07–5.00 (1H, m), 4.10 (1H, br.d, $J=10.8$ Hz), 3.70 (1H, dd, $J=13.6$, 10.4 Hz), 3.54 (1H, ddd, $J=9.6$, 32, 2.4 Hz), 3.43 (1H, dd, $J=12.4$, 10.4 Hz), 3.36 (1H, ddd, $J=12.0$, 104, 1.6 Hz), 3.15 (1H, d, $J=13.6$ Hz), 2.44 (2H, app.t, $J=6.4$ Hz), 1.78 (1H, br.dd, $J=14.8$, 11.6 Hz), 1.59 (1H, br.dd, $J=14.4$, 12.4 Hz); ^{13}C NMR (75 MHz, CD_3OD) δ 170.5, 161.6, 156.4, 141.8, 139.6, 135.3, 131.7, 129.8, 128.2, 127.7, 124.0, 122.1, 115.5, 107.5, 72.1, 71.6, 63.4, 59.2, 38.7, 36.0, 34.5; MS (ES) *m/z* 451.10 $[M+Na]^+$; calcd for $C_{22}H_{24}N_2O_7Na$: 451.15.

3.2. Cytotoxicity assay

Human non-small cell lung tumor cells (A549 and NCI-H460) were plated in 96 well plates on Day 0. Cells were treated with serial dilutions of analogue between 0.1 nM and 10 μM (ranges were adjusted for the activity of each analogue) on Day 1. Control cells were treated with vehicle (DMSO) alone. The surviving fraction of cells in the presence of drug was calculated using the sulforhodamine B assay as previously described (Skehan, P. et al. New colorimetric cytotoxicity assay for anticancer-drug screening. *J. Natl. Cancer Inst.* **1990**, *82*, 1107–1112; Papazisis, K. T.; Geromichalos, G. D.; Dimitriadis, K. A.; Kortsaris, A. H. Optimization of the sulforhodamine B colorimetric assay. *J. Immunol. Methods* **1997**, *208*, 151–158). Briefly, the cells were fixed on Day 5 (96 h post-treatment) with 50% w/v trichloroacetic acid, dried overnight, and stained with 0.4% sulforhodamine B in 1% acetic acid. Fractional survival was determined by dividing the average absorbance (A_{492}) value of test wells by control wells. Each condition was replicated in 6 wells. The fractional survival values were plotted against the log[analog concentration] to determine the IC_{50} value for each analog and cell line.

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