Journal of Medicinal Chemistry Article

J. Med. Chem. **2010,** *53,* 2443–2463 **2443**
DOI: 10.1021/jm9015526

Discovery of Vaniprevir (MK-7009), a Macrocyclic Hepatitis C Virus NS3/4a Protease Inhibitor

John A. McCauley,*,† Charles J. McIntyre,† Michael T. Rudd,† Kevin T. Nguyen,† Joseph J. Romano,† John W. Butcher,† Kevin F. Gilbert,† Kimberly J. Bush,† M. Katharine Holloway,‡ John Swestock,† Bang-Lin Wan,† Steven S. Carroll,§ Jillian M. DiMuzio,§ Donald J. Graham,§ Steven W. Ludmerer,§ Shi-Shan Mao,§ Mark W. Stahlhut,§ Christine M. Fandozzi,∥ Nicole Trainor,∥ David B. Olsen,§ Joseph P. Vacca,† and Nigel J. Liverton†

†*Department of Medicinal Chemistry,* ‡*Department of Molecular Systems,* §*Department of Antiviral Research, and* ∥*Department of Drug Metabolism, Merck Research Laboratories, West Point, Pennsylvania, 19486*

Received October 19, 2009

A new class of HCV NS3/4a protease inhibitors which contain a P2 to P4 macrocyclic constraint was designed using a molecular-modeling derived strategy. Exploration of the P2 heterocyclic region, the P2 to P4 linker, and the P1 side chain of this class of compounds via a modular synthetic strategy allowed for the optimization of enzyme potency, cellular activity, and rat liver exposure following oral dosing. These studies led to the identification of clinical candidate **35b** (vaniprevir, MK-7009), which is active against both the genotype 1 and genotype 2 NS3/4a protease enzymes and has good plasma exposure and excellent liver exposure in multiple species.

Introduction

Hepatitis C virus (HCV[a]) is a chronic infection that affects an estimated 130−170 million people worldwide.[1] The positive RNA strand *Flaviviridae* family virus replicates primarily in the liver, and while disease progression is typically a slow process, a significant fraction of those infected develop serious liver disease including cirrhosis and hepatocellular carcinoma.[2] HCV is currently a leading cause of death in HIV coinfected patients[3] and is the most common indication for liver transplantation.[4] HCV displays a high degree of genetic heterogeneity and can be classified into six major genotypes that have different geographic distributions: genotypes 1, 2, and 3 account for more than 90% of the infections in the developed world, with genotype 1 being predominant (∼70%) in the U.S., Europe and Japan. Current standard treatment for HCV is based on combination therapy with pegylated interferon-α and ribavirin.[5] Pegylated interferon is dosed by once weekly injection and ribavirin orally. Duration of therapy and response rates are genotype-dependent. Sustained viral response is seen in ∼45% of HCV genotype 1-infected patients treated for 48 weeks and in ∼80% of genotype 2- and 3-infected patients treated for 24 weeks. Pegylated interferon and ribavirin therapy is also associated with a number of serious side effects, which limit the number of patients who may be treated.[6]

There is a compelling medical need for new oral therapeutic agents with improved efficacy and tolerability. Several promising antiviral targets for HCV have emerged in recent years,[7] with NS3/4a protease inhibitors showing perhaps the most dramatic antiviral effects.[8] Clinical proof-of-concept for this mechanism was first achieved with BILN-2061 (**1**, Figure 1), a rapidly reversible NS3 inhibitor.[9] Other compounds have entered clinical trials, including the slowly reversible covalent binders **2** (telaprevir, VX-950)[10] and **3** (boceprevir, SCH 503034)[11] and the rapidly reversible inhibitors **4** (ITMN-191)[12] and **5** (TMC 435350).[13]

We have recently disclosed a molecular-modeling derived strategy that led us to design HCV NS3/4a protease inhibitors which contain the P2 to P4 macrocyclic constraint.[14] This strategy arose from an analysis of the full crystal structure of NS3 with and without inhibitors docked in the active site.[15] A key observation was that in the absence of inhibitor, the C-terminus of the helicase domain occupies the protease active site. The side chain of Glu628 in this C-terminal region was the inspiration for, and occupies the same space as, the P2 to P4 linker in this class of inhibitors. With our P2 to P4 macrocyclization strategy validated by the attractive potency and pharmacokinetic profile of compound **6** (Figure 1),[14] we set out to explore the P2 heterocyclic portion of this class of compounds. In the literature, there was a significant variety of substituents in the P2 region which could be broken into two main classes. First were the directly linked heterocycles such as **1** and **5** (Figure 1) and **7** (Figure 2)[16] and second were those linked through a carbamate, including **4** (Figure 1), **8**, and **9**

*To whom correspondence should be addressed. Phone: 215-652-4133. Fax: 215-652-3971. E-mail: john_mccauley@merck.com.

[a] Abbreviations: APCI, atmospheric pressure chemical ionization; Boc, *t*-butoxycarbonyl; CDI, carbonyldiimazole; DCE, 1,2-dichloroethane; DIPEA, diisopropylethylamine; DMAP, 4-dimethylamino pyridine; DMEM, Dulbecco's modified eagle's medium; DMF, dimethylformamide; DMSO, dimethyl sulfoxide; DTT, dithiothreitol; ESI, electrospray ionization; EtOAc, ethyl acetate; EtOH, ethanol; FBS, fetal bovine serum; FTICR, Fourier transform ion cyclotron resonance; HATU, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl uronium hexafluorophosphate; HCV, hepatitis C virus; HEPES, 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid sodium salt; LAH, lithium aluminum hydride; MES, 2-(*N*-morpholino)ethanesulfonic acid; MeCN, acetonitrile; MeOH, methanol; NBS, *N*-bromosuccinimide; NHS, normal human serum; PEG400, polyethyleneglycol 400; RCM, ring-closing metathesis; RT, room temperature; SAR, structure−activity relationship; TEA, triethylamine; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TRF, time-resolved fluorescence; Zhan 1b catalyst, [1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene[2-(*i*-propoxy)-5-(*N*,*N*-dimethylaminosulfonyl)phenyl] methyleneruthenium(II) dichloride].

Published on Web 02/17/2010

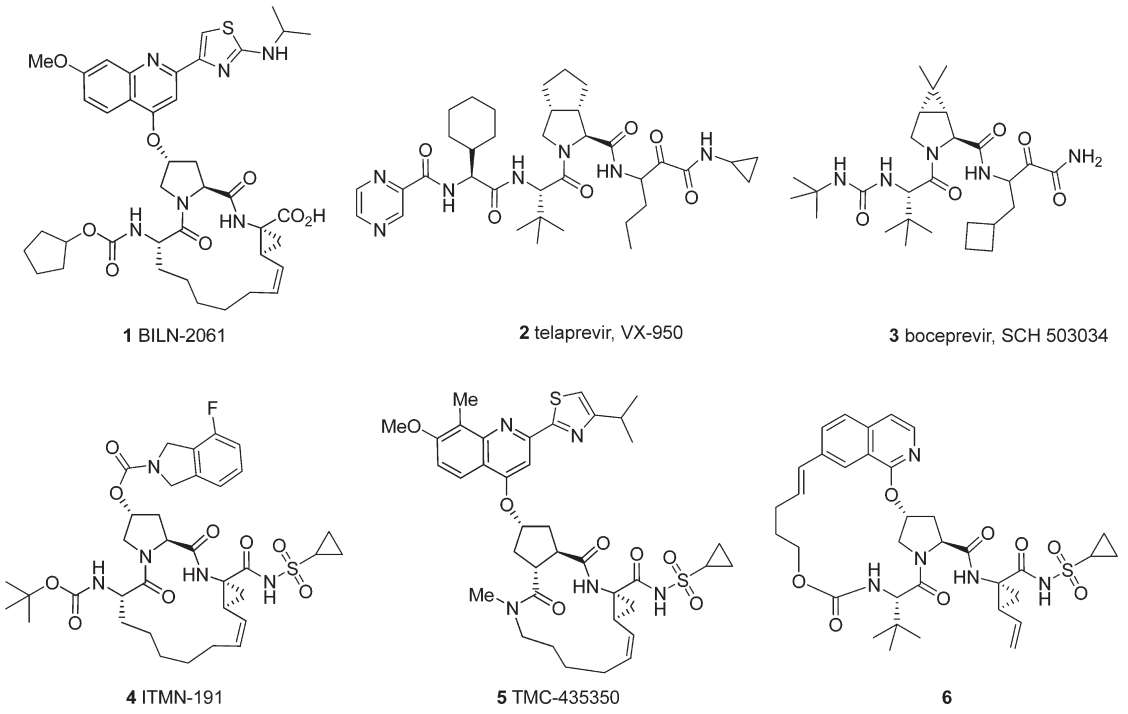


Figure 1. HCV NS3/4a protease inhibitors.

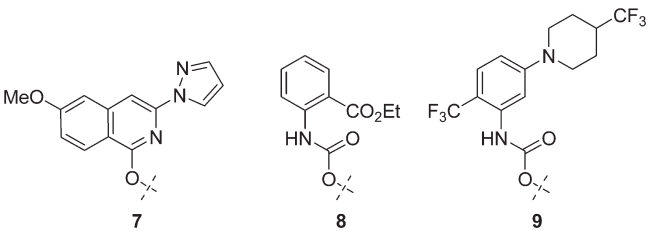


Figure 2. P2 substituents employed in representative HCV NS3/4a protease inhibitors.

(Figure 2).[17] In both of these classes, the P2 group ranged from the relatively simple to the very complex. Our modular synthetic approach, which relies on a key ring-closing metathesis (RCM) reaction,[18,19] allowed for the rapid exploration of a number of regions of these molecules, and herein, we report studies that led to the identification of a clinical candidate.[20]

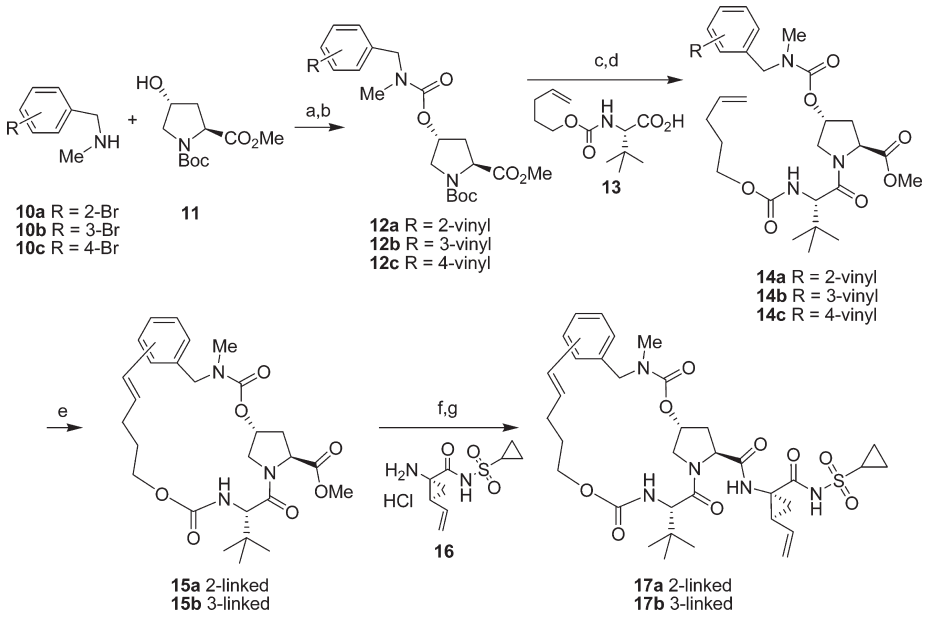
Chemistry

Compounds **12a**−**c** (Scheme 1) could be prepared by reaction of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (**11**)[21] first with carbonyldiimidazole (CDI), then by treatment with the ortho-, meta- and para-isomers of *N*-methyl-bromobenzylamine (**10a**−**c**), followed by vinylation with vinyltributyltin via palladium catalysis. Removal of the *t*-butoxycarbonyl (Boc) protecting group and amide formation under standard conditions with carboxylic acid **13** provided RCM precursors **14a**−**c**. Exposure of dilute solutions (3 mM) of the bis-olefins to the Zhan 1b catalyst [1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene-[2-(*i*-propoxy)-5-(*N*,*N*-dimethylaminosulfonyl)phenyl] methyleneruthenium(II) dichloride][22] in dichloroethane (DCE) at 70 °C provided macrocycles **15a** and **15b** cleanly via the RCM reaction and with selective (>10:1) formation of the trans olefins.[23] Compound **14c**, however, did not cyclize to give the desired product and, under forcing conditions, decomposed. We attribute this reaction failure to the strain associated with having a 1,4-substituted phenyl contained in a potentially rigid macrocycle. Compounds **15a** and **15b** were converted to **17a** and **17b**, respectively, by hydrolysis of the methyl ester and amide coupling with the vinyl P1 fragment **16**.[24]

Access to the intermediate required for the 5-tetrahydroisoquinoline P2 macrocycle (Scheme 2) started with the coupling of 5-bromotetrahydroisoquinoline (**18a**) to **11** through a CDI mediated carbamate formation followed by vinylation yielding **19a**. The 8-linked isomer synthesis began with demethylation of 8-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**18b**) to give the corresponding phenol,[25] which could be coupled to **11** in a similar manner. Installation of the vinyl group through the intermediate triflate provided **19b**. The linker region was installed via amide formation with **13** to give RCM precursors **20a** and **20b**. RCM with the Zhan 1b catalyst[22] formed the *trans*-olefins selectively and yielded the macrocycles (**21a** and **21b**), which could be further elaborated to **22a** and **22b** via hydrolysis and attachment of the P1 side chain (**16**).

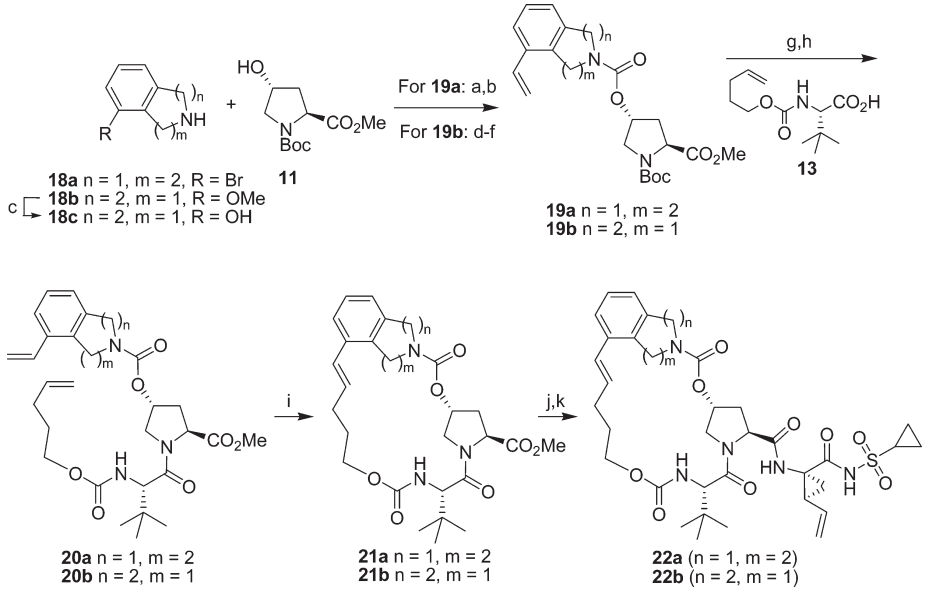
The isoindoline P2 synthesis starts with 3-bromo-*o*-xylene (**23**), which was dibrominated with *N*-bromosuccinimde (NBS) and benzoyl peroxide (Scheme 3).[26] Displacement of the bromines with benzylamine with concomitant ring closure gave 2-benzyl-4-bromoisoindoline. Installation of the vinyl group and removal of the benzyl protective group with 1-chloroethyl chloroformate[27] and methanol (MeOH) provided the required P2 heterocycle (**24**). Standard carbamate forming conditions and removal of the Boc protecting group gave key intermediate **25** as the hydrochloride salt, which is a stable white powder. Compound **25** was coupled to a variety of linker acids **13** and **26b**−**i** as shown in Scheme 3 to form bis-olefins **27a**−**i**. The Zhan 1b metathesis catalyst[22] was used to affect macrocyclization providing **28a**−**i** selectively as trans isomers. These intermediates were transformed to the ultimate

Scheme 1[a]



[a] Reagents and conditions: (a) **11**, carbonyldiimidazole, DMF; **10a**−**c**, DIPEA, 50 °C; (b) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, toluene, 100 °C; (c) HCl, dioxane; (d) **13**, HATU, DIPEA, DMAP, DMF; (e) Zhan 1b catalyst,[22] DCE, ∼3 mM, 70 °C; (f) LiOH, THF, MeOH, H_2O; (g) **16**, HATU, DIPEA, DMAP, DMF.

Scheme 2[a]



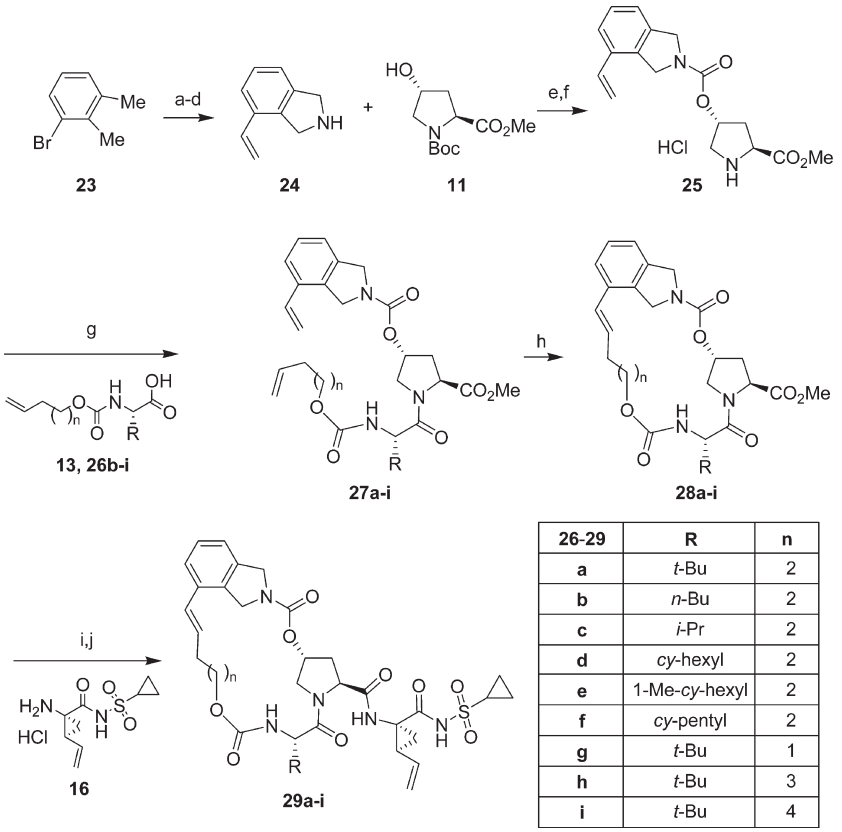
[a] Reagents and conditions: (a) **11**, carbonyldiimidazole, DMF; **18a**, DIPEA, 50 °C; (b) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, toluene, 100 °C, 75%; (c) HBr/H_2O, 120 °C, 81%; (d) carbonyldiimidazole, DMF; **18c**, DIPEA, 50 °C, 69%; (e) Tf_2O, TEA, CH_2Cl_2, 69%; (f) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, LiCl, toluene, 25 °C, 74%; (g) HCl, dioxane; (h) **13**, HATU, DIPEA, DMAP, DMF; (i) Zhan 1b catalyst,[22] DCE, ∼3 mM, 70 °C; (j) LiOH, THF, MeOH, H_2O; (k) **16**, HATU, DIPEA, DMAP, DMF.

targets by hydrolysis and amide formation with **16** to give a series of compounds that contained both the ring and side chain olefins and varied with regard to macrocycle size and P3 substituent (**29a**−**i**).

Scheme 4 describes the synthesis of a series of macrocycles similar to **29a** but with varying levels of saturation of the olefins contained in the macrocycle and the P1 side chain. Compound **31a** was prepared by hydrogenation of **28a**, followed by hydrolysis and coupling to the vinyl P1 side chain **16**. Macrocycle **31b** was prepared directly from **28a** by hydrolysis and addition of the ethyl P1 side chain **30**,[28] whereas **28a** first underwent reduction of the macrocyclic olefin before the final hydrolysis and ethyl P1 (**30**) coupling steps to give **31c**.

A second series of isoindoline P2 compounds containing a saturated linker and the ethyl cyclopropane P1 side chain was prepared using similar chemistry (Scheme 5). Amine hydrochloride **25** was coupled with a series of acids (**26h** and **32b**−**i**) to provide **27h** and **33b**−**i** which was then cyclized to give **28h** and **34b**−**i**. The newly formed olefin could be hydrogenated

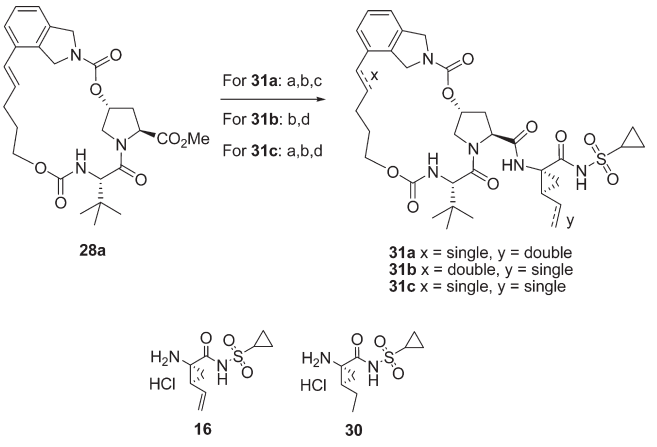
Scheme 3[a]



26-29	R	n
a	*t*-Bu	2
b	*n*-Bu	2
c	*i*-Pr	2
d	*cy*-hexyl	2
e	1-Me-*cy*-hexyl	2
f	*cy*-pentyl	2
g	*t*-Bu	1
h	*t*-Bu	3
i	*t*-Bu	4

[a] Reagents and conditions: (a) NBS, benzoyl peroxide, CCl_4, reflux, 92%; (b) K_2CO_3, benzylamine, MeCN, 77 °C, 50%; (c) $Bu_3SnCH{=}CH_2$, $Pd(PPh_3)_4$, toluene, 100 °C, 83%; (d) 1-chloroethyl chloroformate, DCE, reflux; MeOH, reflux, 86%; (e) **11**, carbonyldiimidazole, DMF; **24**, 60 °C, 81%; (f) HCl, dioxane, 90%; (g) **13**, **26b**−**i**, HATU, DIPEA, DMF; (h) Zhan 1b catalyst,[22] DCE, ~5 mM, 75 °C; (i) LiOH, THF, MeOH, H_2O; (j) **16**, HATU, DIPEA, DMF.

Scheme 4[a]



[a] Reagents and conditions: (a) H_2, 10% Pd/C, EtOAc; (b) $LiOH{\cdot}H_2O$, THF, MeOH, H_2O; (c) **16**, HATU, DIPEA, DMAP, DMF; (d) **30**, HATU, DIPEA, DMAP, DMF.

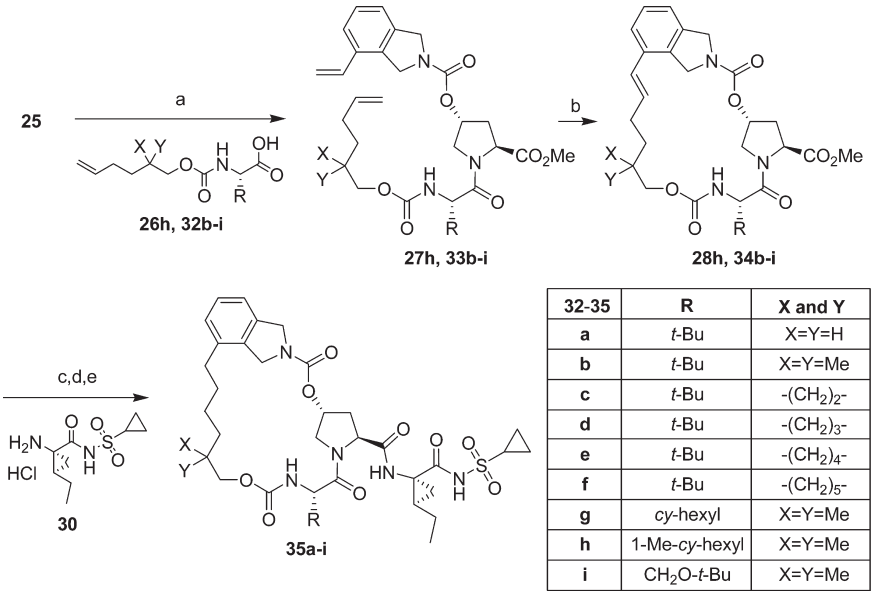
and the synthesis completed via hydrolysis and addition of the saturated P1 side chain **30** to give compounds **35a**−**i**.

Results and Discussion

Compounds were evaluated in an enzyme binding assay using the genotype 1b NS3/4a enzyme and selected compounds were also tested versus the genotype 2a enzyme with results reported as K_i values.[29] The cellular activity was determined using the replicon system expressing genotypes 1b or 2a, and compounds were tested in the presence of 10% fetal bovine serum (FBS) and 50% normal human serum (NHS).[30] Initial pharmacokinetic analysis focused on liver concentration of compounds in rats after a single 5 mg/kg oral dose.

For one of our initial efforts aimed at exploring the P2 region of our novel macrocycles, we chose to explore simple benzylamine derived carbamates. The 2-linked isomer **17a** had modest activity in both the 1b enzyme and cellular replicon assays (Table 1). This level of activity could be greatly improved by moving the linker to the three position as in compound **17b**, resulting in a 3.5-fold increase in replicon activity. This level of activity led us to constrain the P2 region of the compounds by cyclizing to the two corresponding isomers of tetrahydroisoquinoline **22a** and **22b**, which demonstrated an even greater difference in 1b enzyme potency of >50-fold. Further constraint of **22b** to the isoindoline (**29a**) led to a highly potent compound with 50 pM activity versus the genotype 1b enzyme and 7 nM activity in the replicon assay. Compound **29a** also showed liver exposure in rat of 910 nM at the 4 h time point following a single 5 mg/kg oral dose. As previously communicated, we have used rat liver concentration as the primary pharmacokinetic readout for evaluating compounds.[14,20] On the basis of these data, **29a** became an important lead and our focus turned toward evaluating structure−activity relationships (SAR) in other parts of the molecule while leaving the P2 isoindoline intact.

Scheme 5[a]



32-35	R	X and Y
a	*t*-Bu	X=Y=H
b	*t*-Bu	X=Y=Me
c	*t*-Bu	-$(CH_2)_2$-
d	*t*-Bu	-$(CH_2)_3$-
e	*t*-Bu	-$(CH_2)_4$-
f	*t*-Bu	-$(CH_2)_5$-
g	*cy*-hexyl	X=Y=Me
h	1-Me-*cy*-hexyl	X=Y=Me
i	CH_2O-*t*-Bu	X=Y=Me

[a] Reagents and conditions: (a) **26h**, **32b−i**, HATU, DIPEA, DMF; (b) Zhan 1b catalyst,[22] CH_2Cl_2, ~3 mM; (c) H_2, 10% Pd/C, EtOH, EtOAc; (d) $LiOH \cdot H_2O$, THF, MeOH, H_2O; (e) **30**, HATU, DIPEA, DMAP, CH_2Cl_2.

Table 1. In Vitro Activity

compd	1b K_i (nM)[a]	1b replicon IC_{50} (nM)[b] 10% FBS	1b replicon IC_{50} (nM)[b] 50% NHS	rat [liver] @ 4 h (μM)[c]
17a	1.60 ± 0.93	98 ± 72	610 ± 60	nd
17b	0.14 ± 0.06	28 ± 4	42 ± 5	0.45 ± 0.14
22a	8.30 ± 1.23	730 ± 82	2900 ± 900	nd
22b	0.15 ± 0.05	26 ± 4	140 ± 19	3.5 ± 0.2
29a	0.05 ± 0.01	7 ± 2	32 ± 4	0.91 ± 0.65
29b	0.05 ± 0.01	6 ± 3	26 ± 1	0.46 ± 0.32
29c	0.04 ± 0.01	12 ± 3	28 ± 3	0.44 ± 0.13
29d	0.02 ± 0.01	3 ± 1	24 ± 4	2.8 ± 0.8
29e	0.06 ± 0.01	4 ± 1	38 ± 3	1.6 ± 0.5
29f	0.04 ± 0.01	4 ± 1	23 ± 5	nd
29g	0.10 ± 0.03	16 ± 3	390 ± 65	nd
29h	0.03 ± 0.01	5.0 ± 0.3	19 ± 4	0.23 ± 0.12
29i	<0.02 ± 0	3.0 ± 0	23 ± 1	0.14 ± 0.05

[a] NS3/4a protease time-resolved fluorescence assay, mean ± standard deviation of at least $n = 3$ measurements. [b] Cell-based replicon assay, mean ± standard deviation of at least $n = 3$ measurements. [c] Liver levels from PK experiments carried out as described in the Experimental Section.

The investigation of the role of the P3 amino acid side chain was carried out via the synthesis of the series of compounds **29a−29f** (Table 1). Very little difference in potency was seen with various alkyl and cycloalkyl substituents. Rat liver concentrations after oral dosing were again similar for this series of compounds, with a slight trend toward increased liver exposure for the most lipophilic substituents. For example, cyclohexyl derivatives **29d** and **29e** showed 2.8 and 1.6 μM liver concentrations in rat liver at 4 h, while the isopropyl derivative **29c** showed a ~5-fold lower concentration at 0.44 μM. All three compounds, however, showed comparable enzyme and cellular activity. Contraction of the macrocyclic ring constraint by one carbon gave **29g** and led to a decrease in potency as well as cellular activity. Expansion of the linker by 1 and 2 carbons to the 6-carbon linked **29h** and 7-carbon linked **29i** gave overall profiles similar to the lead **29a**. The SAR summarized in Table 1 showed that there was good flexibility with regard to the P3 substituent and that a linker of 5 to at least 7 carbons was also tolerated. However, none of these changes led to a dramatic increase in activity or liver exposure.

We then undertook a study of the effect of saturation of each of the two olefins present in **29a**. Reduction of the macrocyclic olefin provided **31a**, which had a virtually identical potency and pharmacokinetic profile to that of **29a** (Table 2). Saturation of the P1 vinyl group to the P1 ethyl (**31b**) led to a ~4-fold increase in rat liver concentration, but this was accompanied by a ~10-fold loss in potency. The fully saturated compound (**31c**) however, maintained much of the potency of **29a** but now showed improved liver exposure (10.7 μM) at a 5 mg/kg oral dose to rats. We were encourged by this result; however, upon further profiling of **31c**, we found that the replicon activity, when measured against the genotype 2a system, was suboptimal. In fact, only **31a** in this series was below 100 nM in the genotype 2a replicon assay.

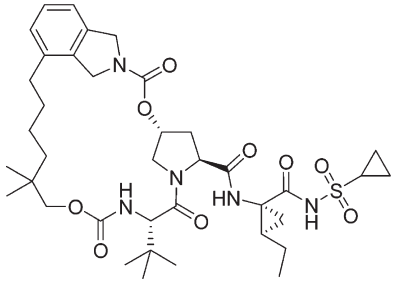
Knowing that there was flexibility with regard to macrocyclic ring size (vide supra), we expanded the ring of **31c** by one carbon to give **35a** (Table 2). This change gave a small boost in genotype 1b replicon activity but fortunately led to a greater than 10-fold increase in genotype 2a replicon activity. Somewhat unexpectedly, the liver exposure seen with **35a** was about 5-fold lower than **31c** even though the structures only differ by one methylene unit in the linker. In an attempt to regain liver exposure, we sought to introduce added lipophilicity on the linker. Installation of a dimethyl group β to the carbamate oxygen gave compound **35b**, which showed a concentration of 9.9 μM in rat liver at 4 h following a 5 mg/kg oral dose. Furthermore, replicon activity at both genotypes 1b and 2a was under 10 nM in the presence of 10% FBS and in the presence of 50% NHS the genotype 1b replicon activity showed a very small protein shift to 19 nM. A series of spiro-cycloalkyl substituents, from cyclopropane to cyclohexane (**35c−f**), showed that increasing the steric bulk and lipophilicity in this region of the molecule led to a decrease in enzyme potency and a marked erosion in replicon activity in

Table 2. In Vitro Activity

compd	1b K_i (nM)[a]	2a K_i (nM)[a]	replicon IC_{50} (nM)[b] 1b 10% FBS	1b 50% NHS	2a 10% FBS	rat [liver] @ 4 h (μM)[c]
29a	0.05 ± 0.01	2.6 ± 0.9	7 ± 2	32 ± 4	150 ± 20	0.91 ± 0.65
31a	0.04 ± 0.01	0.9 ± 0.1	7 ± 0	27 ± 5	66 ± 16	0.52 ± 0.01
31b	0.45 ± 0.07	19 ± 5	29 ± 8	110 ± 16	720 ± 110	3.8 ± 1.2
31c	0.18 ± 0.07	4.0 ± 0.8	10 ± 2	35 ± 20	140 ± 40	10.7 ± 0.5
35a	0.06 ± 0.01	0.9 ± 0.2	5.0 ± 0.3	27 ± 11	13 ± 2	1.9 ± 0.8
35b	0.05 ± 0.01	0.9 ± 0.3	3.0 ± 1.0	19 ± 6	9.0 ± 2.6	9.9 ± 5.4
35c	0.10 ± 0.03	4.3 ± 0.5	6 ± 1	41 ± 15	35 ± 4	4.6 ± 2.0
35d	0.09 ± 0.02	3.6 ± 1.0	3.0 ± 0.6	30 ± 9	20 ± 9	45 ± 8
35e	0.09 ± 0.01	5.1 ± 0.2	7 ± 1	85 ± 47	20 ± 3	6.6 ± 2.9
35f	1.22 ± 0.39	63 ± 8	43 ± 14	860 ± 60	270 ± 90	25 ± 16
35g	0.09 ± 0.02	nd	16 ± 12	75 ± 21	nd	7.5 ± 2.1
35h	0.08 ± 0.02	nd	10 ± 1	90 ± 9	nd	2.0 ± 0.5
35i	0.30 ± 0.09	nd	16 ± 6	180 ± 40	nd	13 ± 9.5

[a] NS3/4a protease time-resolved fluorescence assay, mean ± standard deviation of at least $n = 3$ measurements. [b] Cell-based replicon assay, mean ± standard deviation of at least $n = 3$ measurements. [c] Liver levels from PK experiments carried out as described in the Experimental Section.

Table 3. Pharmacokinetic Parameters for **35b**[a]



35b vaniprevir, MK-7009

species	Cl (mL/min/kg)	V_d (L/kg)	$T_{1/2}$ (h)	PO C_{max} (μM)	PO AUC (μM·h)	PO [liver] 2 h (μM)	PO [liver] 24 h (μM)
rat	74 ± 9	1.9 ± 1.6	0.9 ± 0.7	0−0.1	0−0.1	9.9 @ 4 h	0.4
dog	11 ± 2	0.3 ± 0.1	1.2 ± 0	0.5 ± 0.2	1.2 ± 0.4	34	0.5
rhesus	18 ± 2	0.4 ± 0.1	1.3 ± 0.2	0.01−0.2	0.05−0.2	3	nd
chimpanzee	nd	nd	nd	0.9	5.2	nd	31 @ 12 h

[a] Rat, dog, and rhesus iv (2 mg/kg, $n = 3$, DMSO), po (5 mg/kg, $n = 3$, PEG400), chimpanzee (po, 10 mg/kg, $n = 2$, chocolate milk).

the presence of 50% human serum (Table 2). Liver exposure, however, was affected in a less predictable manner. The change from a dimethyl substituent (**35b**) to a spiro-cyclohexyl group (**35f**) increased liver exposure by 2.5-fold but decreased replicon activity in the presence of 50% NHS by 50-fold. Although it has reduced potency, the spiro-cyclobutyl compound (**35d**) showed remarkable rat liver exposure of $> 40\,\mu$M after the 5 mg/kg oral dose and illustrates the difficulty of predicting this parameter.

Next, we sought to revisit the P3 amino acid side chain as in **29a**−**f** where varying the P3 group had little effect on activity but modulated liver exposure. In the case of compounds **35g**−**i**, however, larger more lipophilic P3 groups were not tolerated. For example, the cyclohexyl substituent used in compound **35g** led to good liver exposure, but this change was accompanied by a 4-fold loss in the serum-shifted replicon IC_{50}. This result is in contrast to the result with **29d**, which did not suffer a loss in activity with the P3 cyclohexyl group. The requirement for liver exposure needs to be carefully balanced with cellular activity. Perhaps the increase in lipophilicity of the linker that gives compounds **35b**−**i** good liver exposure precludes a further increase in lipophilicity at P3. On the basis of the exploration of the macrocyclic scaffold in the P2 isoindoline series, we concluded that **35b** was an optimal compound in this series and was subsequently selected for further development.

The pharmacokinetic properties of compound **35b** were evaluated in multiple species (Table 3). In rat, **35b** showed a plasma clearance of 74 mL/min/kg and a plasma half-life of ~1 h. When dosed orally at 5 mg/kg, the plasma exposure of **35b** was modest with an AUC of 0.1 μM·h. In contrast to the plasma exposure data, the liver exposure of the compound is quite good and **35b** remains in liver 24 h after a single 5 mg/kg oral dose. At 24 h, the liver concentration of **35b** is 0.4 μM, which is 130-fold greater than the replicon IC_{50} (10% FBS) and is >20-fold higher than the IC_{50} in the replicon assay in the presence of 50% NHS.

When dosed to dogs, the plasma pharmacokinetics of **35b** were greatly improved (Table 3). The compound shows moderate clearance of 11 mL/min/kg and a 1.2 h half-life after iv dosing and has good plasma exposure (AUC = 1.2 μM·h) after a 5 mg/kg oral dose. Dog liver biopsy studies showed that the liver concentrations of **35b** after the 5 mg/kg oral dose are 34 and 0.5 μM at the 2 and 24 h time points, respectively. Similar to its behavior in rats, **35b** demonstrates effective partitioning into liver tissue and maintains high liver

concentration, relative to potency, 24 h after oral dosing in dogs. In contrast to rat, **35b** demonstrates good plasma exposure after dosing a 5 mg/kg oral dose in dogs.

Rhesus pharmacokinetic parameters were generally similar to that of rat and characterized by good liver exposure and poor plasma exposure after a 5 mg/kg oral dose (Table 3). As a prelude to efficacy experiments which will be described elsewhere, we dosed **35b** to chimpanzees to evaluate plasma and liver pharmacokinetics. Following an oral dose of 10 mg/kg in chimpanzees, **35b** shows excellent plasma exposure with an AUC of 5.2 μM·h and a C_{max} of 0.9 μM. Furthermore, a liver biopsy at this dose level shows a liver concentration of 31 μM at 12 h postdose for **35b**. This concentration is >1500-fold greater than the serum-shifted replicon IC_{50} and clearly supported a dosing regimen of, at most, twice per day in chimpanzees.

Conclusions

Investigation of a series of P2−P4 macrocycles containing a hydroxy-proline carbamate led to the identification of 3-linked isoindoline as a promising P2 substituent for a new class of HCV NS3/4a protease inhibitors. Optimization of this series, including exploration of linker length and P3 amino acid side chains, showed that a number of different compounds maintained good activity versus the genotype 1b enzyme but that rat liver exposure was modest. Through a study of the effects of saturation of the macrocyclic and P1 side chain olefin, it was discovered that the fully saturated compounds preferentially partitioned into rat liver and provided high liver concentrations. Further optimization of the fully reduced compounds with regard to linker length and substitution was performed in an effort to maintain rat liver exposure and achieve balanced activity against both the 1b and 2a genotypes of NS3/4a protease, and these efforts led to the identification of **35b**. Compound **35b** shows good to excellent liver exposure across species and poor plasma exposure in rats and rhesus following a 5 mg/kg oral dose. In contrast, good plasma exposure was observed in dogs. In chimpanzees, at a 10 mg/kg oral dose, excellent plasma and liver exposure were observed with a liver concentration at 12 h 1500-fold greater than the serum-shifted replicon IC_{50}. Further studies of **35b** (vaniprevir, MK-7009), including clinical investigations of the pharmacokinetic and efficacy profile, are ongoing.[20]

Experimental Section

General. All reagents and solvents were of commercial quality and used without further purification unless indicated otherwise. All reactions were carried out under an inert atmosphere of nitrogen. ^{1}H NMR spectra were obtained on a Varian Unity Inova 400 spectrometer or a Varian Unity Inova 500 spectrometer. Chemical shifts are reported in parts per million relative to TMS as internal standard. Samples provided for accurate mass measurement were taken up in acetonitrile:water (50/50). The solutions were analyzed by use of electrospray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on either a Bruker Daltonics 3T or 7T Fourier transform ion cyclotron resonance (FTICR) mass spectrometer. External calibration was accomplished with polypropylene glycol (425 or 750). Elemental analyses were performed by Quantitative Technologies Inc., Whitehouse, NJ, and Robertson Microlit Laboratories, Madison, NJ. Silica gel chromatography was carried out with an ISCO CombiFlash Sg 100c or ISCO CombiFlash Companion purification system using ISCO silica gel RediSep or Analytical Sales and Products Aspire Flash-Ready cartridges. Preparative reverse-phase HPLC was performed using a Gilson 215 liquid handler and a Phenomenex Luna C18 column (150 mm × 20 mm i.d.) with a linear gradient over 15 min (95:5 to 0:100 H_2O containing 0.15% trifluoroacetic acid:acetonitrile). Compound purity was determined to be >95% by analytical HPLC analysis on an Agilent 1090 HPLC with binary pump and diode array detector with area quantification performed at 214 nm (Method 1: Zorbax RX-C18, 75 mm × 4.6 mm, 3.5 μM, 98% A/2% B to 100% B over 5.5 min then 100% B to 6.0 min (A = 0.1% H_3PO_4/water v/v; B = acetonitrile). Method 2: Luna C8(2), 75 mm × 4.6 mm, 3 μM, 98% A/2% B to 100% B over 5.5 min then 100% B to 6.0 min (A = 0.1% H_3PO_4/water v/v; B = acetonitrile)).

Enzymatic Assays. Compound inhibitory potencies were determined with use of a time-resolved fluorescence assay for NS3/4A protease activity.[29] The NS3 protease assay was performed in a final volume of 100 μL in assay buffer containing 50 mM 4-(2-hydroxyethyl)piperazine-1-ethanesulfonic acid sodium salt (HEPES), pH 7.5, 150 mM NaCl, 15% glycerol, 0.15% Triton X-100, 10 mM dithiothreitol (DTT), and 0.1% PEG8000. The NS3 protease was preincubated with various concentrations of inhibitors in dimethyl sulfoxide (DMSO) for 30 min. The reaction was initiated by adding the time-resolved fluorescence (TRF) peptide substrate (final concentration 100 nM). NS3 mediated hydrolysis of the substrate was quenched after 1 h at RT with 100 μL of 500 mM 2-(*N*-morpholino)ethanesulfonic acid (MES), pH 5.5. Product fluorescence was detected using either a Victor V2 or Fusion fluorophotometer (Perkin-Elmer Life and Analytical Sciences) with excitation at 340 nm and emission at 615 nm with a 400 μs delay. The inhibition constants were derived using a standard four-parameter fit to the data. Full length NS3/4A protease with the sequence from genotype 1b (BK strain) and genotype 2a (JFH strain) was overexpressed in and purified from *E. coli*.

Replicon Assay. Inhibition of viral replication was determined with use of the HCV bicistronic replicon assay[30] adapted for quantitative analysis using in situ hybridization.[31] Huh-7 cells that were stably transfected with HCV replicon RNA (genotype 1b con1 sequence;[31] genotype 2a JFH sequence[32]) were seeded into 96-well plates impregnated with scintillant (Cytostar-T, GE Healthcare) at a density of 20000 cells per well and incubated at 37 °C/5%CO_2 for 24 h in the presence of Dulbecco's modified eagle's medium (DMEM) supplemented with either 10% FBS or 50% NHS. Compound in DMSO was added to 1%, and incubated for a further 24 h. Cells were fixed by treatment with 10% formaldehyde and permeabilized by treatment with 0.25% Triton X100. A radiolabeled RNA probe that hybridizes to the neomycin resistance gene of the replicon was added and hybridized at 50 °C for 18 h, followed by RNase A treatment to remove unhybridized probe and washing. The plate was then counted in a Topcount NXT (Packard). The inhibition constants were derived using a standard four-parameter fit to the data.

Pharmacokinetics. Pharmacokinetic characterization of test agents was conducted in conscious male Sprague−Dawley rats (300−500 g; n = 2−3/study) or male and female beagle dogs (13−15 kg; n = 3/study) or male rhesus (4−6 kg, n = 3/study) or chimpanzees (~60 kg; 1 male and 1 female). The housing, maintenance, and care of the chimpanzees (*Pan troglodytes*) used in the study were in compliance with all relevant guidelines and requirements at Merck Research Laboratories, and at New Iberia Research Center (University of Louisiana at Lafayette). The study protocols were reviewed and approved by the Institutional Animal Care and Use Committees at both sites. Compounds were dosed intravenously to fasted rats, dogs, and rhesus monkeys. Compounds in DMSO were administered as a bolus (1.0, 0.1, 0.1 mL/kg respectively) in DMSO. For oral studies in rat, dog, and rhesus, compounds were dosed as a solution in polyethyleneglycol 400 (PEG400) (2.0 mL/kg).

Two chimpanzees were dosed orally by voluntary ingestion of test agent in a chocolate milk vehicle (Nestle brand, 0.67 mL/kg). Typical doses were 2 mg/kg iv and 5 mg/kg po to rats, 1 mg/kg iv and 5 mg/kg po to dogs, and 1 mg/kg iv and 5 mg/kg po to rhesus and 10 mg/kg po to chimpanzees. Blood samples for the determination of test agent plasma concentration were obtained at multiple time points up to 24 h after single dose test agent administration. Liver samples were taken at terminal time points for rats and as liver biopsies in dog, rhesus monkey, and chimpanzee. Liver samples were homogenized in buffer prior to analysis. Plasma and liver samples were analyzed using liquid−liquid extraction and LC/MS with appropriate standards and QCs. Pharmacokinetic parameters were calculated using Watson software.

All procedures related to the use of animals in these studies were reviewed and approved by the Institutional Animal Care and Use Committee at Merck Research Laboratories at West Point and conform with the Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources, Commission on Life Sciences, National Research Council, 1996).

1-*tert*-Butyl 2-Methyl (2*S*,4*R*)-4-({[Methyl(2-vinylbenzyl)amino]carbonyl}oxy)pyrrolidine-1,2-dicarboxylate (12a). To a 0 °C solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (**11**) (2.00 g, 8.15 mmol) in dimethylformamide (DMF) (16 mL) under nitrogen was added CDI (1.32 g, 8.15 mmol) and the mixture was stirred at RT for 2 h. 2-Bromo-*N*-methylbenzylamine (**10a**) (1.63 g, 8.15 mmol) and diisopropylethyl amine (DIPEA) (1.42 mL, 8.15 mmol) were added, and the reaction mixture was heated to 50 °C and stirred for 18 h. The reaction mixture was diluted with ethyl acetate (EtOAc) (50 mL), washed with 10% $KHSO_4$ (50 mL), 10% $NaHCO_3$ (50 mL), and brine (50 mL). The organic extract was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (gradient elution, 30−60% EtOAc in hexanes) to yield 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-({[(2-bromobenzyl)(methyl)amino]carbonyl}oxy)pyrrolidine-1,2-dicarboxylate as a clear oil (1.80 g, 47% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 7.8 Hz, 1 H), 7.31 (t, J = 7.5 Hz, 1 H), 7.24−7.06 (m, 2 H), 5.28 (m, 1 H), 4.55 (m, 2 H), 4.30−4.00 (m, 1 H), 3.70−3.50 (m, 5 H), 2.90 (m, 3 H), 2.50−2.10 (m, 2 H), 1.40 (m, 9 H) ppm. HRMS (ESI) m/z 471.1117 [(M + H)$^+$; calcd for $C_{20}H_{28}BrN_2O_6$: 471.1125].

A solution of the above bromide (1.60 g, 3.39 mmol) in toluene (20 mL) was degassed with nitrogen for 30 min. Vinyltributyltin (1.20 mL, 4.07 mmol) and $Pd(PPh_3)_4$ (0.39 g, 0.34 mmol) were added, and the reaction mixture was heated to 100 °C and stirred for 3 h. The reaction mixture was cooled, concentrated, and purified by silica gel chromatography (gradient elution, 20−60% EtOAc in hexanes) to provide **12a** as a clear oil (1.40 g, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.43 (m, 1 H), 7.30−6.80 (m, 3 H), 5.62 (dd, J = 7.3, 1.2 Hz, 1 H), 5.30 (m, 2 H), 4.70−4.10 (m, 4 H), 3.90−3.60 (m, 5 H), 3.00−2.10 (m, 5 H), 1.41 (m, 9 H) ppm. HRMS (ESI) m/z 419.2183 [(M + H)$^+$; calcd for $C_{22}H_{31}N_2O_6$: 419.2177].

1-*tert*-Butyl 2-Methyl (2*S*,4*R*)-4-({[Methyl(3-vinylbenzyl)amino]carbonyl}oxy)pyrrolidine-1,2-dicarboxylate (12b). Using the above procedure for **12a** with 3-bromo-*N*-methylbenzylamine (**10b**) provided **12b** (60% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37−7.26 (m, 2 H), 7.21−7.00 (m, 2 H), 6.71 (dd, J = 17.6, 10.9 Hz, 1 H), 5.75 (d, J = 17.6 Hz, 1 H), 5.34−5.21 (m, 2 H), 4.49−4.28 (m, 3 H), 3.74 (s, 6 H), 3.01−2.71 (m, 3 H), 1.48−1.36 (m, 10 H) ppm. HRMS (ESI) m/z 419.2183 [(M + H)$^+$; calcd for $C_{22}H_{31}N_2O_6$: 419.2177].

1-*tert*-Butyl 2-Methyl (2*S*,4*R*)-4-({[Methyl(4-vinylbenzyl)amino]carbonyl}oxy)pyrrolidine-1,2-dicarboxylate (12c). Using the above procedure for **12a** with 4-bromo-*N*-methylbenzylamine (**10c**) provided **12c** (67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.34 (m, 2 H), 7.24−7.08 (m, 2 H), 6.70 (dd, J = 17.6, 10.9 Hz, 1 H), 5.74 (d, J = 17.6 Hz, 1 H), 5.29 (s, 1 H), 5.24 (d, J = 10.9 Hz, 1 H), 4.50−4.27 (m, 3 H), 3.81−3.67 (m, 4 H), 2.99−2.71 (m, 3 H), 2.47−2.34 (m, 1 H), 2.30−2.07 (m, 1 H), 1.46−1.26 (m, 10 H) ppm. HRMS (ESI) m/z 419.2183 [(M+H)$^+$; calcd for $C_{22}H_{31}N_2O_6$: 419.2177].

3-Methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valine (13). DIPEA (9.85 g, 76.2 mmol) was added dropwise to a 0 °C solution of 4-penten-1-ol (7.22 g, 83.9 mmol) and triphosgene (11.3 g, 38.1 mmol) in dioxane (160 mL). The resulting white suspension was stirred for 5 min at 0 °C and then allowed to warm to room temperature (RT) over 1 h. The suspension was recooled to 0 °C and 1 N NaOH (76.2 mL, 76.2 mmol) and L-*tert*-butylglycine (10.0 g, 76.2 mmol) were added. The reaction mixture was allowed to warm to RT and stirred for 18 h. The dioxane was removed in vacuo, and the reaction mixture was basified to pH 12 with 1 N NaOH and washed with CH_2Cl_2. The aqueous phase was acidified to ~pH 1 with 6 N HCl and extracted with CH_2Cl_2 (3 × 150 mL). The organic layers were dried over $MgSO_4$ and concentrated to give **13** as a tan oil (13.7 g, 74% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 5.20 (br d, J = 9.7 Hz, 1 H), 5.03 (dd, J = 17.2, 1.7 Hz, 1 H), 4.98 (dd, J = 10.2, 1.7 Hz, 1 H), 4.19 (br d, J = 9.4 Hz, 1 H), 4.09 (apparent t, J = 7.1 Hz, 2 H), 2.15−2.09 (m, 2 H), 1.76−1.69 (m, 2 H), 1.03 (s, 9 H) ppm. HRMS (ESI) m/z 244.1541 [(M + H)$^+$; calcd for $C_{12}H_{22}NO_4$: 244.1543].

Methyl 3-Methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-({[methyl(2-vinylbenzyl)amino]carbonyl}oxy)-L-prolinate (14a). A solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-({[methyl(2-vinylbenzyl)amino]carbonyl}oxy)pyrrolidine-1,2-dicarboxylate (**12a**) (1.30 g, 3.11 mmol) in HCl/dioxane (4 M, 50 mL) was stirred at RT for 24 h. The reaction mixture was concentrated, triturated in ether/hexane, and concentrated to give methyl (4*R*)-4-({[methyl-(2-vinylbenzyl)amino]carbonyl}oxy)-L-prolinate hydrochloride as a white solid (1.1 g, 100% yield).

To a mixture of the above amine hydrochloride (1.17 g, 3.29 mmol), 3-methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valine (**13**) (800 mg, 3.29 mmol), 4-dimethylamino pyridine (DMAP) (201 mg, 1.64 mmol), and DIPEA (1.73 mL, 9.86 mmol) in DMF (5 mL) was added *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyl uronium hexafluorophosphate (HATU) (1.63 g, 4.27 mmol). The reaction mixture was stirred at RT for 24 h, diluted with aq $KHSO_4$, and extracted with EtOAc. The organic layer was washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (gradient elution, 20% to 60% EtOAc in hexanes) to yield **14a** as a clear oil (800 mg, 45% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60−7.40 (m, 1 H), 7.20−6.80 (m, 4 H), 5.77 (m, 1 H), 5.62 (d, J = 17.3 Hz, 1 H), 5.32 (m, 3 H), 4.98 (m, 2 H), 4.70−4.20 (m, 4 H), 4.00 (m, 4 H), 3.72 (m, 4 H), 2.85−2.00 (m, 6 H), 1.65 (m, 2 H), 1.04 (s, 9 H) ppm. HRMS (ESI) m/z 544.2992 [(M + H)$^+$; calcd for $C_{29}H_{42}N_3O_7$: 544.3017].

Methyl 3-Methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-({[methyl(3-vinylbenzyl)amino]carbonyl}oxy)-L-prolinate (14b). Using the above procedure for **14a** with 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-({[methyl(3-vinylbenzyl)amino]carbonyl}oxy)pyrrolidine-1,2-dicarboxylate (**12b**) provided **14b** (51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.25 (m, 2 H), 7.19−7.00 (m, 2 H), 6.71 (dd, J = 17.6, 11.0 Hz, 1 H), 5.75 (d, J = 17.3 Hz, 2 H), 5.40−5.29 (m, 2 H), 5.27 (d, J = 11.0 Hz, 1 H), 5.04−4.92 (m, 2 H), 4.67−4.37 (m, 3 H), 4.29−3.85 (m, 5 H), 3.74 (m, 3 H), 2.91−2.71 (m, 3 H), 2.51−2.36 (m, 1 H), 2.26−1.99 (m, 3 H), 1.72−1.55 (m, 2 H), 1.04 (m, 9 H) ppm. HRMS (ESI) m/z 544.3026 [(M + H)$^+$; calcd for $C_{29}H_{42}N_3O_7$: 544.3017].

Methyl 3-Methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-({[methyl(4-vinylbenzyl)amino]carbonyl}oxy)-L-prolinate (14c). Using the above procedure for **14a** with 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-({[methyl(4-vinylbenzyl)amino]carbonyl}oxy)pyrrolidine-1,2-dicarboxylate (**12c**) provided **14c** (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45−7.31 (m, 2 H), 7.21 (d, J = 7.8 Hz, 1 H), 7.09 (d, J = 7.8 Hz, 1 H), 6.70 (dd, J = 17.6, 10.9 Hz, 1 H),

5.82−5.65 (m, 2 H), 5.42−5.27 (m, 2 H), 5.24 (d, J = 10.9 Hz, 1 H), 5.05−4.91 (m, 2 H), 4.69−4.37 (m, 2 H), 4.32−3.85 (m, 5 H), 3.80−3.71 (m, 4 H), 2.96−2.68 (m, 3 H), 2.52−2.37 (m, 1 H), 2.26−1.99 (m, 3 H), 1.69−1.56 (m, 2 H), 1.05 (s, 9 H) ppm. HRMS (ESI) m/z 544.3038 [(M + H)$^+$; calcd for $C_{29}H_{42}N_3O_7$: 544.3017].

Methyl (1*R*,12*E*,20*S*,23*S*)-20-*tert*-Butyl-4-methyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatricyclo[20.2.1.0^{6,11}]pentacosa-6,8,10,12-tetraene-23-carboxylate (15a). A solution of methyl 3-methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-({[methyl-(2-vinylbenzyl)amino]carbonyl}oxy)-L-prolinate (**14a**) (600 mg, 1.10 mmol) in DCE (180 mL) was degassed with nitrogen for 15 min. Zhan 1b catalyst[22] (80 mg, 0.11 mmol) was added, and the reaction mixture was heated to 70 °C, stirred for 2 h, cooled, and concentrated. The crude product was purified by silica gel chromatography (gradient elution, 30−80% EtOAc in hexanes) to provide **15a** as a clear oil (420 mg, 74% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.50 (m, 1 H), 7.40−7.10 (m, 2 H), 7.00 (m, 1 H), 6.80−6.40 (m, 1 H), 6.20−5.90 (m, 1 H), 5.50−5.20 (m, 1 H), 4.72 (d, J = 17.1 Hz, 1 H), 4.52 (m, 1 H), 4.60−4.30 (m, 8 H), 2.97 (s, 3 H), 2.6−1.60 (m, 7 H), 1.04 (m, 9 H) ppm. HRMS (ESI) m/z 516.2710 [(M + H)$^+$; calcd for $C_{27}H_{38}N_3O_7$: 516.2704].

Methyl (6*R*,8*S*,11*S*,18*E*)-11-*tert*-Butyl-3-methyl-4,10,13-trioxo-5,14-dioxa-3,9,12-triazatricyclo[18.3.1.1^{6,9}]pentacosa-1(24),18,20,22-tetraene-8-carboxylate (15b). Using the above procedure for **15a** with methyl 3-methyl-*N*-[(pent-4-en-1-yloxy)-carbonyl]-L-valyl-(4*R*)-4-({[methyl(3-vinylbenzyl)amino]carbonyl}oxy)-L-prolinate (**14b**) provided **15b** (68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.20 (m, 1 H), 7.03−6.92 (m, 2 H), 6.43−5.93 (m, 2 H), 5.43−5.21 (m, 3 H), 4.86 (d, J = 14.9 Hz, 1 H), 4.70−4.52 (m, 1 H), 4.37−4.20 (m, 2 H), 4.08−3.93 (m, 2 H), 3.88−3.82 (m, 1 H), 3.80−3.71 (m, 4 H), 2.92−2.75 (m, 3 H), 2.50−2.14 (m, 4 H), 1.96−1.80 (m, 1 H), 1.68−1.62 (m, 1 H), 1.10−1.00 (m, 9 H) ppm. HRMS (ESI) m/z 516.2711 [(M + H)$^+$; calcd for $C_{27}H_{38}N_3O_7$: 516.2704].

(1*R*,12*E*,20*S*,23*S*)-20-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-4-methyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatricyclo[20.2.1.0^{6,11}]pentacosa-6,8,10,12-tetraene-23-carboxamide (17a). To a solution of methyl (1*R*,12*E*,20*S*,23*S*)-20-*tert*-butyl-4-methyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatricyclo[20.2.1.0^{6,11}]pentacosa-6,8,10,12-tetraene-23-carboxylate (**15a**) (200 mg, 0.39 mmol) in tetrahydrofuran (THF) (4 mL), MeOH (4 mL), and water (4 mL) was added LiOH (37.2 mg, 1.55 mmol) and the reaction mixture was stirred at 40 °C for 2 h. Upon complete hydrolysis, 3 N HCl (0.52 mL, 1.55 mmol) was added and the reaction mixture was concentrated to give (1*R*,12*E*,20*S*,23*S*)-20-*tert*-butyl-4-methyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatricyclo[20.2.1.0^{6,11}]-pentacosa-6,8,10,12-tetraene-23-carboxylic acid.

To a solution of the above crude carboxylic acid and (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (**16**)[24] (128 mg, 0.48 mmol) in DMF (2 mL) at RT was added DMAP (24 mg, 0.20 mmol), DIPEA (0.21 mL, 1.20 mmol), and HATU (200 mg, 0.52 mmol). The reaction mixture was stirred for 18 h, diluted with water (30 mL), and the resulting solids were filtered and washed with water. The crude solids were purified by silica gel chromatography (gradient elution, 50% to 100% EtOAc in hexanes) to provide **17a** as a white solid (240 mg, 84% yield, 2 steps). ^{1}H NMR (400 MHz, CD_3OD) δ 9.20−8.80 (m, 1 H), 7.60−7.00 (m, 4 H), 6.51 (m, 1 H), 6.00 (m, 1 H), 5.72 (m, 1 H), 5.30 (m, 2 H), 5.12 (m, 1 H), 4.70−3.60 (m, 9 H), 3.00−1.60 (m, 13 H), 1.40 (m, 1 H), 1.21 (m, 2 H), 1.04 (m, 11 H) ppm. HRMS (ESI) m/z 714.3194 [(M + H)$^+$; calcd for $C_{35}H_{48}N_5O_9S$: 714.3167]. Anal. ($C_{35}H_{47}N_5O_9S\cdot 1.5H_2O$) C, H, N.

(6*R*,8*S*,11*S*,18*E*)-11-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3-methyl-4,10,13-trioxo-5,14-dioxa-3,9,12-triazatricyclo[18.3.1.1^{6,9}]pentacosa-1(24),18,20,22-tetraene-8-carboxamide (17b). Using the above procedure for **17a** with methyl (6*R*,8*S*,11*S*,18*E*)-11-*tert*-butyl-3-methyl-4,10,13-trioxo-5,14-dioxa-3,9,12-triazatricyclo[18.3.1.1^{6,9}]pentacosa-1(24),18,20,22-tetraene-8-carboxylate (**15b**) provided **17b** (68% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.53−10.41 (m, 1 H), 9.04 (s, 1 H), 7.45−7.23 (m, 3 H), 7.21−6.95 (m, 4 H), 6.53−6.13 (m, 3 H), 5.63 (s, 1 H), 5.27−4.87 (m, 4 H), 4.38−3.72 (m, 7 H), 2.93 (s, 1 H), 2.82−2.67 (m, 3 H), 2.44−2.12 (m, 4 H), 1.90−1.62 (m, 3 H), 1.40−1.32 (m, 1 H), 1.12−0.83 (m, 11 H) ppm. HRMS (ESI) m/z 714.3220 [(M + H)$^+$; calcd for $C_{35}H_{48}N_5O_9S$: 714.3167]. Anal. ($C_{35}H_{47}N_5O_9S\cdot 0.25$ TFA) C, H, N.

8-Hydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide (18c). A mixture of 8-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (**18b**)[33] (3.00 g, 15.0 mmol) and 48% aqueous HBr (45 mL) was heated at 120 °C for 18 h. The resulting brown suspension was filtered and dried to provide **18c** (2.8 g, 81% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.89 (s, 1 H), 8.98 (s, 2 H), 7.08 (t, J = 7.8 Hz, 1 H), 6.72 (d, J = 7.8 Hz, 1 H), 6.66 (d, J = 7.8 Hz, 1 H), 4.07 (m, 2 H), 3.34 (m, 2 H), 2.94 (t, J = 6.14 Hz, 2 H). HRMS (ESI) m/z 150.0904 [(M + H)$^+$; calcd for $C_9H_{12}NO$: 150.0913].

1-*tert*-Butyl 2-Methyl (2*S*,4*R*)-4-{[(5-Vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (19a). Using the above procedure for **12a** with 5-bromo-1,2,3,4-tetrahydroisoquinoline (**18a**) provided **19a** (75% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, J = 8.0 Hz, 1 H), 7.19 (t, J = 7.5 Hz, 1 H), 7.05 (m, 1 H), 6.89 (dd, J = 17.5, 11.0 Hz, 1 H), 5.63 (dd, J = 17.5, 1.0 Hz, 1 H), 5.33 (dd, J = 11.0, 1.0 Hz, 1 H), 5.29 (br s, 1 H), 4.6 (m, 2 H), 4.45 and 4.36 (2 × t, J = 7.5 Hz, 1 H), 3.75 (s, 3 H), 3.60 (m, 4 H), 2.86 (br s, 2 H), 2.41 (m, 1 H), 2.22 (m, 1 H), 1.46 and 1.43 (2 × s, 9 H) ppm. HRMS (ESI) m/z 431.2179 [(M + H)$^+$; calcd for $C_{23}H_{31}N_2O_6$: 431.2182].

1-*tert*-Butyl 2-Methyl (2*S*,4*R*)-4-{[(8-Vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (19b). A mixture of CDI (0.176 g, 1.09 mmol) and 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (**11**) (0.21 g, 0.87 mmol) in DMF (5 mL) was stirred at RT for 45 min. 8-Hydroxy-1,2,3,4-tetrahydroisoquinoline hydrobromide (**18c**) (0.20 g, 0.87 mmol) and triethylamine (TEA) (0.18 g, 1.74 mmol) were added, and the resulting solution was heated at 50 °C for 2 h. The reaction mixture was poured onto aqueous saturated NH_4Cl and extracted with EtOAc, dried over Na_2SO_4, and concentrated. The residue was purified by column chromatography on silica gel (gradient elution, 10−80% EtOAc in hexanes) to give 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-{[(8-hydroxy-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (0.25 g, 0.60 mmol, 69% yield) as a colorless foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.04 (t, J = 7.8 Hz, 1 H), 6.72 (d, J = 7.8 Hz, 1 H), 6.64 (d, J = 7.8 Hz, 1 H), 5.62 (m, 1 H), 5.30 (m, 1 H), 4.50 (m, 2 H), 4.37 (m, 1 H), 3.75 (s, 3 H), 3.66 (m, 3 H), 2.83 (m, 2 H), 2.43 (m, 1 H), 2.21 (m, 1 H), 1.43 (s, 9 H) ppm. HRMS (ESI) m/z 421.1990 [(M + H)$^+$; calcd for $C_{21}H_{29}N_2O_7$: 421.1969].

To a solution of the above coupled product (1.81 g, 4.30 mmol) and TEA (1.31 g, 12.90 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added trifluoromethanesulfonic anhydride (1.76 g, 6.24 mmol). The resulting mixture was stirred for 18 h and was poured onto saturated aqueous $NaHCO_3$ and extracted into CH_2Cl_2. The organic layer was washed with 10% citric acid solution, dried over Na_2SO_4, and concentrated. The oil was purified by column chromatography on silica gel (gradient elution, 10−70% EtOAc in hexanes) to give 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-({[8-{[(trifluoromethyl)sulfonyl]oxy}-3,4-dihydroisoquinolin-2(1*H*)-yl]carbonyl}oxy)pyrrolidine-1,2-dicarboxylate (1.65 g, 69% yield) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (m, 1 H), 7.18 (m, 2 H), 5.30 (s, 2 H), 4.65 (m, 2 H), 4.41 (m, 1 H), 3.77 (s, 3 H), 3.59 (m, 1 H), 2.91 (m, 2 H), 2.44 (m, 1 H), 2.22 (m, 1 H), 2.01 (s, 1 H), 1.55 (m, 1 H), 1.49 (m, 9 H) ppm. HRMS (ESI) m/z 575.1303 [(M+Na)$^+$; calcd for $C_{22}H_{27}F_3N_2NaO_9S$: 575.1282].

A solution of the above triflate (1.74 g, 3.15 mmol), vinyltributyltin (1.10 g, 1.46 mmol), and lithium chloride (0.40 g, 9.45 mmol) in DMF (25 mL) was purged with nitrogen for 10 min.

Bis(triphenylphosphine)palladium(II) chloride (0.22 g, 0.32 mmol) was added, and the mixture was stirred at RT under nitrogen for 18 h. The mixture was partitioned between EtOAc and saturated $NaHCO_3$, the organic layer separated and washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The oil was purified by column chromatography on silica gel (gradient elution, 10 to 65% EtOAc in hexanes) to give **19b** (1.00 g, 74% yield) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.6 Hz, 1 H), 7.18 (t, J = 7.4 Hz, 1 H), 7.08 (m, 1 H), 6.78−6.90 (m, 1 H), 5.65 (d, J = 7.2 Hz, 1 H), 5.36 (d, J = 10.4 Hz, 1 H), 5.30 (m, 1 H), 4.60 (m, 2 H), 4.39 (t, J = 7.9 Hz, 1 H), 3.75 (m, 5 H), 3.62 (m, 2 H), 2.85 (m, 2 H), 2.43 (m, 1 H), 2.21 (m, 1 H), 1.43 (s, 9 H) ppm. HRMS (ESI) m/z 331.1669 [(M-Boc + H)$^+$; calcd for $C_{18}H_{23}N_2O_4$: 331.1707].

Methyl 3-Methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-{[(5-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]oxy}-L-prolinate (20a). Using the above procedure for **14a** with 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-{[(5-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)-carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (**19a**) provided **20a** (87% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, J = 7.2 Hz, 1 H), 7.18 (t, J = 7.2 Hz, 1 H), 7.06 (m, 1 H), 6.88 (dd, J = 17.0, 11.0 Hz, 1 H), 5.75 (br s, 1 H), 5.63 (d, J = 17.0 Hz, 1 H), 5.39 (br s, 1 H), 5.33 (d, J = 11.0 Hz, 2 H), 4.96 (m, 2 H), 4.65−4.52 (m, 3 H). 4.25 (d, J = 9.2 Hz, 1 H), 4.15−3.8 (m, 4 H), 3.75 (s, 3 H), 3.7−3.5 (m, 2 H), 2.87 (m, 2 H), 2.47 (m, 1 H), 2.19 (m, 1 H), 2.09 (m, 2 H), 1.64 (m, 2 H), 1.04 (s, 9 H) ppm. HRMS (ESI) m/z 556.3016 [(M + H)$^+$; calcd for $C_{30}H_{42}N_3O_7$: 556.3017].

Methyl 3-Methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-{[(8-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]oxy}-L-prolinate (20b). Using the above procedure for **14a** with 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-{[(8-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (**19b**) provided **20b** (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, J = 7.3 Hz, 1 H), 7.17 (t, J = 7.3 Hz, 1 H), 7.06 (m, 1 H), 6.84 (m, 1 H), 5.76 (m, 1 H), 5.64 (m, 1 H), 5.38 (m, 3 H), 4.99 (m, 2 H), 4.64 (m, 2 H), 4.26 (m, 1 H), 4.09 (m, 1 H), 3.92 (m, 2 H), 3.75 (s, 3 H), 3.62 (m, 2 H), 3.41 (m, 1 H), 2.82 (m, 2 H), 2.55 (m, 1 H), 2.23 (m, 1 H), 2.10 (m, 2 H), 1.81 (m, 1 H), 1.64 (m, 2 H), 1.05 (s, 9 H) ppm. HRMS (ESI) m/z 556.3042 [(M + H)$^+$; calcd for $C_{30}H_{42}N_3O_7$: 556.3017].

Methyl (4*R*,6*S*,9*S*,16*E*)-9-*tert*-Butyl-2,8,11-trioxo-3,12-dioxa-1,7,10-triazatetracyclo[20.3.1.1^{4,7}.0^{18,23}]heptacosa-16,18,20,22-tetraene-6-carboxylate (21a). Using the above procedure for **15a** with methyl 3-methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-{[(5-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]-oxy}-L-prolinate (**20a**) provided **21a** (67% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 7.5 Hz, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 6.97 (d, J = 7.5 Hz, 1 H), 6.45 (d, J = 16.0 Hz, 1 H), 5.90 (m, 1 H), 5.58 (t, J = 3.5 Hz, 1 H), 5.37 (d, J = 10.0 Hz, 1 H), 5.0 (d, J = 17.0 Hz, 1 H), 4.68 (dd, J = 10.7, 7.5 Hz, 1 H), 4.25 (d, J = 16.5 Hz, 1 H), 4.18 (d, J = 9.5 Hz, 1 H), 4.00 (m, 2 H), 3.92 (m, 1 H), 3.78−3.72 (m, 2 H), 3.77 (s, 3 H), 3.04 (m, 1 H), 2.77 (m, 1 H), 2.61 (m, 1 H), 2.48 (m, 1 H), 2.30 (m, 1 H), 2.20−2.10 (m, 2 H), 1.93 (m, 1 H), 1.65 (m, 1 H), 1.01 (s, 9 H) ppm. HRMS (ESI) m/z 528.2704 [(M + H)$^+$; calcd for $C_{28}H_{38}N_3O_7$: 528.2705].

Methyl (4*R*,6*S*,9*S*,16*E*)-9-*tert*-Butyl-2,8,11-trioxo-3,12-dioxa-1,7,10-triazatetracyclo[16.6.2.1^{4,7}.0^{22,26}]heptacosa-16,18(26),19,21-tetraene-6-carboxylate (21b). Using the above procedure for **15a** with methyl 3-methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-{[(8-vinyl-3,4-dihydroisoquinolin-2(1*H*)-yl)carbonyl]-oxy}-L-prolinate (**20b**) provided **21b** (82% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.6 Hz, 1 H), 7.01 (t, J = 7.6 Hz, 1 H), 7.13 (d, J = 7.6 Hz, 1 H), 6.35 (d, J = 15.6 Hz, 1 H), 6.02 (m, 1 H), 5.44 (m, 1 H), 5.38 (m, 1 H), 4.61 (m, 2 H), 4.41 (m, 2 H), 4.30 (m, 2 H), 3.84 (m, 2 H), 3.81 (m, 2 H), 3.75 (s, 3 H), 3.52 (m, 1 H), 2.87 (m, 1 H), 2.60 (m, 1 H), 2.28 (m, 2 H), 2.19 (m, 1 H), 1.94 (m, 1 H), 1.62 (m, 1 H), 1.07 (s, 9 H) ppm. HRMS (ESI) m/z 528.2729 [(M + H)$^+$; calcd for $C_{28}H_{38}N_3O_7$: 528.2705].

(4*R*,6*S*,9*S*,16*E*)-9-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-2,8,11-trioxo-3,12-dioxa-1,7,10-triazatetracyclo[20.3.1.1^{4,7}.0^{18,23}]heptacosa-16,18,20,22-tetraene-6-carboxamide (22a). Using the above procedure for **17a** with methyl (4*R*,6*S*,9*S*,16*E*)-9-*tert*-butyl-2,8,11-trioxo-3,12-dioxa-1,7,10-triazatetracyclo[20.3.1.1^{4,7}.0^{18,23}]-heptacosa-16,18,20,22-tetraene-6-carboxylate (**21a**) provided **22a** (45% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.35 (d, J = 8.0 Hz, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.01 (br d, J = 9.0 Hz, 1 H), 6.97 (d, J = 7.5 Hz, 1 H), 6.50 (d, J = 15.5 Hz, 1 H), 6.03 (m, 1 H), 5.78 (m, 1 H), 5.54 (br s, 1 H), 5.34 (d, J = 17.0 Hz, 1 H), 5.14 (d, J = 10.0 Hz, 1 H), 4.95 (d, J = 16.5 Hz, 1 H), 4.50 (dd, J = 11.5 Hz, 6.5 Hz, 1 H), 4.29 (d, J = 16.0 Hz, 1 H), 4.22 (m, 3 H), 3.90 (m, 3 H), 3.15 (m, 1 H), 2.94 (m, 1 H), 2.74 (m, 2 H), 2.38−2.10 (m, 6 H), 2.00 (m, 1 H), 1.85 (m, 1 H), 1.68 (m, 1 H), 1.48 (m, 1 H), 1.26 (m, 2 H), 1.08 (m, 2 H), 0.99 (s, 9 H) ppm. HRMS (ESI) m/z 726.3151 [(M + H)$^+$; calcd for $C_{36}H_{48}N_5O_9S$: 726.3167].

(4*R*,6*S*,9*S*,16*E*)-9-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-2,8,11-trioxo-3,12-dioxa-1,7,10-triazatetracyclo[16.6.2.1^{4,7}.0^{22,26}]heptacosa-16,18(26),19,21-tetraene-6-carboxamide (22b). Using the above procedure for **17a** with methyl (4*R*,6*S*,9*S*,16*E*)-9-*tert*-butyl-2,8,11-trioxo-3,12-dioxa-1,7,10-triazatetracyclo[16.6.2.1^{4,7}.0^{22,26}]heptacosa-16,18(26),19,21-tetraene-6-carboxylate (**21b**) and purification by reverse phase HPLC provided **22b** (56% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, J = 7.4 Hz, 1 H), 7.14 (t, J = 7.4 Hz, 1 H), 7.01 (d, J = 7.4 Hz, 1 H), 6.42 (d, J = 15.2 Hz, 1 H), 5.98 (m, 1 H), 5.79 (m, 2 H), 5.19 (m, 2 H), 4.95 (m, 1 H), 4.59 (m, 2 H), 4.42 (m, 1 H), 4.31 (m, 1 H), 4.19 (m, 1 H), 3.90 (m, 1 H), 3.81 (m, 2 H), 3.77 (m, 1 H), 3.36 (m, 1 H), 2.90 (m, 1 H), 2.81 (m, 1 H), 2.59 (m, 1 H), 2.38 (m, 1 H), 2.22 (m, 2 H), 1.90 (m, 2 H), 1.73 (s, 9 H), 1.68 (m, 1 H), 1.03 (m, 8 H), 0.74 (m, 1 H) ppm. HRMS (ESI) m/z 726.3169 [(M + H)$^+$; calcd for $C_{36}H_{48}N_5O_9S$: 726.3167]. Anal. ($C_{36}H_{47}N_5O_9S\cdot 2.6H_2O\cdot 0.9$TFA) C, H, N.

1-Bromo-2,3-bis(bromomethyl)benzene (23). A suspension of 3-bromo-*o*-xylene (196 g, 1.06 mol), *N*-bromosuccinimide (377 g, 2.15 mol), and benzoyl peroxide (0.26 g, 1.0 mmol) in carbon tetrachloride (1800 mL) was heated to reflux under nitrogen for 15 h. The contents of the reaction flask were cooled, filtered, and the filtrate evaporated. The crude material was distilled under high vacuum with major fractions collected between 88 and 152 °C to give **23** (108 g, 35% yield) and 182 g of 95% pure material (57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 1 H), 7.16 (t, J = 8.0 Hz, 1 H), 4.84 (s, 2 H), 4.64 (s, 2 H) ppm.

4-Vinylisoindoline (24). Postassium bicarbonate (204 g, 2.04 mol) was suspended in acetonitrile (12 L), and the mixture was heated to 80 °C. Solutions of 1-bromo-2,3-bis(bromomethyl)-benzene (**23**) (280 g, 0.82 mol) in acetonitrile (MeCN) (500 mL) and benzylamine (87.5 g, 0.82 mol) in MeCN (500 mL) were added concurrently via addition funnels over 1 h. The reaction mixture was stirred at 77 °C for 16 h, cooled to RT, and concentrated. The reaction mixture was partitioned between 1 M K_2CO_3 and EtOAc. The organics were washed with brine, dried over Na_2SO_4, filtered, and concentrated. Silica gel chromatography (gradient elution, heptane to 10% EtOAc in heptane) gave 2-benzyl-4-bromoisoindoline (118 g, 50% yield) as a pale oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.31 (m, 4 H), 7.29−7.23 (m, 2 H), 7.07−7.02 (m, 2 H), 3.99 (s, 2 H), 3.94 (s, 2 H), 3.88 (s, 2 H) ppm. HRMS (ESI) m/z 288.0385 [(M + H)$^+$; calcd for $C_{15}H_{15}BrN$: 288.0383]. Anal. ($C_{15}H_{14}BrN\cdot 0.2H_2O$) C, H, N.

A solution of 2-benzyl-4-bromoisoindoline (4.0 g, 13.9 mmol) and vinyltributyltin (4.9 mL, 16.7 mmol) in toluene (80 mL) was degassed with nitrogen for 15 min. $Pd(PPh_3)_4$ (0.32 g, 0.28 mmol) was added, and the resulting solution was heated at 100 °C under nitrogen for 24 h. The reaction mixture was cooled, concentrated, and purified by silica gel chromatography (5% EtOAc in hexane) to give 2-benzyl-4-vinylisoindoline as a pale oil (2.7 g, 83% yield). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.39 (m, 2 H), 7.33 (m, 2 H), 7.25 (m, 2 H), 7.14 (apparent t, J = 7.5 Hz, 1 H), 7.05 (d, J = 7.4 Hz, 1 H), 6.63 (dd, J = 17.6, 11.2 Hz, 1 H), 5.57 (d, J = 17.6 Hz, 1 H), 5.24 (d, J = 11.2 Hz, 1 H), 4.00 (s, 2 H), 3.91 (m, 4 H) ppm. HRMS (ESI) m/z 236.1434 [(M + H)$^+$; calcd for $C_{17}H_{18}N$: 236.1434].

To a solution of 2-benzyl-4-vinylisoindoline (2.9 g, 12.3 mmol) in 1,2-dichloroethane (50 mL) at 0 °C was added a solution of 1-chloroethyl chloroformate (2.11 g, 14.8 mmol) in 1,2-dichloroethane (10 mL) dropwise over 20 min, keeping the internal reaction temperature <5 °C. The reaction mixture was then warmed to RT, heated to reflux for 1 h, cooled, and concentrated. Methanol (50 mL) was added, and the reaction mixture was heated to reflux for 30 min, cooled, and concentrated and partitioned between EtOAc and water. The aqueous layer was basified with 2 N NaOH and extracted with CH_2Cl_2 (3×). The combined organic extracts were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (gradient elution, CH_2Cl_2 to 90:10:1 CH_2Cl_2:MeOH:NH_4OH) to yield **24** as a brown oil (1.54 g, 86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (d, J = 7.5 Hz, 1 H), 7.16 (apparent t, J = 7.4 Hz, 1 H), 7.12 (d, J = 7.3 Hz, 1 H), 6.67 (dd, J = 17.7, 11.1 Hz, 1 H), 5.61 (d, J = 17.7 Hz, 1 H), 5.28 (d, J = 11.1 Hz, 1 H), 4.27 (s, 2 H), 4.21 (s, 2 H) ppm. HRMS (ESI) m/z 146.0976 [(M + H)$^+$; calcd for $C_{10}H_{12}N$: 146.0964]. Anal. ($C_{10}H_{11}N \cdot 0.7H_2O$) C, H, N.

(3*R*,5*S*)-5-(Methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride (25). To a solution of 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-hydroxypyrrolidine-1,2-dicarboxylate (**11**) (10.1 g, 41.4 mmol) in DMF (90 mL) at 0 °C was added CDI (6.70 g, 41.4 mmol). The reaction mixture was warmed to RT and stirred for 2 h. A solution of 4-vinylisoindoline (**24**) (6.00 g, 41.4 mmol) in DMF (10 mL) was added, and the reaction mixture was heated at 60 °C for 2 h. The reaction mixture was cooled and poured into water and 5% potassium bisulfate and the resulting mixture was extracted with EtOAc (4 × 250 mL). The combined organics were washed with brine, dried with Na_2SO_4, filtered, and concentrated. Purification by silica gel chromatography (30% EtOAc in hexane) gave 1-*tert*-butyl 2-methyl (2*S*,4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}pyrrolidine-1,2-dicarboxylate (13.9 g, 81% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (m, 1 H), 7.23 (m, 1 H), 7.14−7.08 (m, 1 H), 6.62 (dd, J = 17.6, 11.2 Hz, 1 H), 5.66 (m, 1 H), 5.33 (d, J = 11.2 Hz, 1 H), 5.29 (br s, 1 H), 4.78−4.61 (m, 4 H), 4.50−4.32 (m, 1 H), 3.72 (s, 3 H), 3.72−3.58 (m, 2 H), 2.45 (m, 1 H), 2.20 (m, 1 H), 1.42−1.40 (m, 9 H) ppm. HRMS (ESI) m/z 417.2008 [(M + H)$^+$; calcd for $C_{22}H_{29}N_2O_6$: 417.2020].

The above protected amine (15.0 g, 36.0 mmol) was dissolved in a solution of HCl in dioxane (4 M, 36.0 mL, 144 mmol), and the reaction mixture was stirred at RT for 2 h. The reaction mixture was concentrated, suspended in Et_2O, and filtered to give **25** as a white solid (11.5 g, 90% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.40 (dd, J = 7.5, 3.03 Hz, 1 H), 7.27 (apparent t, J = 8.2 Hz, 1 H), 7.18 (apparent t, J = 9.0 Hz, 1 H), 6.70 (ddd, J = 17.6, 11.2, 3.4 Hz, 1 H), 5.70 (dd, J = 17.6, 10.3 Hz, 1 H), 5.41 (br s, 1 H), 5.33 (dd, J = 11.2. 3.0 Hz, 1 H), 4.82−4.70 (m, 5 H), 3.85 (s, 3 H), 3.70−3.58 (m, 2 H), 2.68 (m, 1 H), 2.43 (ddd, J = 14.8, 10.7, 4.9 Hz, 1 H) ppm. HRMS (ESI) m/z 317.1497 [(M + H)$^+$; calcd for $C_{17}H_{21}N_2O_4$: 317.1496]. Anal. ($C_{17}H_{20}N_2O_4 \cdot HCl$) C, H, N.

***N*-[(Pent-4-en-1-yloxy)carbonyl]-L-norleucine (26b).** To a solution of 1-penten-4-ol (0.95 g, 11.0 mmol) in DMF (15 mL) at 0 °C was added CDI (1.79 g, 11.0 mmol). The reaction mixture was warmed to RT and stirred for 30 min. L-Norleucine methyl ester hydrochloride (2.00 g, 11.0 mmol) was added, and the reaction mixture was heated to 50 °C and stirred for 15 min. Upon cooling, the reaction mixture was diluted with Et_2O and washed twice with water. The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (gradient elution, 10 to 90% EtOAc in hexanes) to afford methyl *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucinate (2.10 g, 74% yield) as a clear oil.

To a stirred solution of methyl *N*-[(pent-4-enyloxy)carbonyl]-L-norleucinate (8.50 g, 33.0 mmol) in THF (20 mL) was added 1 N NaOH (20 mL). This reaction mixture was stirred at RT for 3 h and then acidified to pH 3 with 1 N HCl and extracted with EtOAc (3 × 250 mL). The combined EtOAc layer was washed with water, brine, dried over Na_2SO_4, filtered, and concentrated to give **26b** (7.09 g, 88% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.12 (s, 1 H), 5.04 (d, J = 17.1 Hz, 1 H), 4.99 (d, J = 10.3 Hz, 1 H), 4.37 (q, J = 5.4 Hz, 1 H), 4.10 (m, 2 H), 2.12 (m, 2 H), 1.88 (s, 1 H), 1.73 (m, 3 H), 1.36 (m, 4 H), 0.91 (t, J = 7.4 Hz, 3 H) ppm. HRMS (ESI) m/z 244.1549 [(M + H)$^+$; calcd for $C_{12}H_{22}NO_4$: 244.1544].

***N*-[(Pent-4-en-1-yloxy)carbonyl]-L-valine (26c).** Using the above procedure for **26b** with L-valine methyl ester hydrochloride provided **26c** (80% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.00 (m, 1 H), 5.88−5.78 (m, 1 H), 5.06−4.95 (m, 2 H), 4.11−4.03 (m, 3 H), 2.17−2.12 (m, 3 H), 1.76−1.69 (m, 2 H), 0.99−0.93 (m, 6 H) ppm. HRMS (ESI) m/z 230.1396 [(M + H)$^+$; calcd for $C_{11}H_{20}NO_4$: 230.1387].

(2*S*)-Cyclohexyl{[(pent-4-en-1-yloxy)carbonyl]amino}acetic Acid (26d). Using the above procedure for **26b** with methyl (2*S*)-amino-(cyclohexyl)acetate hydrochloride provided **26d** (75% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.01 (d, J = 8.4 Hz, 1 H), 5.88−5.77 (m, 1 H), 5.06−5.01 (m, 1 H), 4.98−4.95 (m, 1 H), 4.05−4.02 (m, 3 H), 3.74−3.70 (m, 1 H), 2.14 (dd, J = 15, 7.0 Hz, 2 H), 1.88−1.65 (m, 8 H), 1.34−1.09 (m, 5 H) ppm. HRMS (ESI) m/z 270.1732 [(M + H)$^+$; calcd for $C_{14}H_{24}NO_4$: 270.1700].

(2*S*)-(1-Methylcyclohexyl){[(pent-4-en-1-yloxy)carbonyl]amino}acetic Acid (26e). Using the above procedure for **13** with (2*S*)-amino(1-methylcyclohexyl)acetic acid hydrochloride[34] provided **26e** (30% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 6.89 (br d, J = 9.5 Hz, 1 H), 5.83 (m, 1 H), 5.05 (d, J = 17.0 Hz, 1 H), 4.95 (d, J = 10.0 Hz, 1 H), 4.23 (br s, 1 H), 4.04 (t, J = 6.5 Hz, 2 H), 2.14 (m, 2 H), 1.72 (m, 2 H), 1.61−1.30 (m, 10 H), 0.96 (s, 3 H) ppm. HRMS (ESI) m/z 284.1854 [(M + H)$^+$; calcd for $C_{15}H_{26}NO_4$: 284.1862].

(2*S*)-Cyclopentyl {[(Pent-4-en-1-yloxy)carbonyl]amino}acetic Acid (26f). Using the above procedure for **26b** with methyl (2*S*)-amino(cyclopentyl)acetate hydrochloride provided **26f** (86% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 5.88−5.78 (m, 1 H), 5.06−4.95 (m, 2 H), 4.06−3.89 (m, 4 H), 2.29−2.11 (m, 2 H), 1.80−1.29 (m, 11 H) ppm. HRMS (ESI) m/z 256.1542 [(M + H)$^+$; calcd for $C_{13}H_{22}NO_4$: 256.1471].

***N*-[(But-3-en-1-yloxy)carbonyl]-3-methyl-L-valine (26g).** Using the above procedure for **13** with but-3-en-1-ol provided **26g** (51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.83−5.74 (m, 1 H), 5.24 (d, J = 9.2, 1 H), 5.14−5.06 (m, 2 H), 4.20−4.12 (m, 3 H), 2.42−2.36 (m, 2 H), 1.03 (s, 9 H) ppm. HRMS (ESI) m/z 230.1387 [(M + H)$^+$; calcd for $C_{11}H_{20}NO_4$: 230.1314].

***N*-[(Hex-5-en-1-yloxy)carbonyl]-3-methyl-L-valine (26h).** Using the above procedure for **13** with hex-5-en-1-ol provided **26h** (60% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 5.25 (d, J = 9.5 Hz, 1 H), 5.02 (d, J = 17.1 Hz, 1 H), 4.96 (d, J = 9.3 Hz, 1 H), 4.19 (d, J = 9.5 Hz, 1 H), 4.08 (m, 2 H), 2.07 (m, 2 H), 1.64 (quint, J = 7.1 Hz, 2 H), 1.46 (quint, J = 7.4 Hz, 2 H), 1.03 (s, 9 H) ppm. HRMS (ESI) m/z 258.1709 [(M + H)$^+$; calcd for $C_{13}H_{24}NO_4$: 258.1700].

***N*-[(Hept-6-en-1-yloxy)carbonyl]-3-methyl-L-valine (26i).** Using the above procedure for **13** with hept-6-en-1-ol provided **26i** (68% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.22 (m, 1 H), 5.02 (m, 1 H), 4.97 (m, 1 H), 4.18 (m, 1 H), 4.08 (m, 2 H), 2.11 (m, 2 H), 1.63 (m, 2 H), 1.39 (m, 4 H), 1.03 (s, 9 H) ppm. HRMS (ESI) m/z 272.1858 [(M + H)$^+$; calcd for $C_{14}H_{26}NO_4$: 272.1856].

Methyl 3-Methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (27a). To a solution of (3*R*,5*S*)-5-(methoxycarbonyl)-pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride (**25**) (200 mg, 0.57 mmol) and 3-methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valine (**13**) (152 mg, 0.62 mmol) in

DMF (5 mL) at RT was added DIPEA (0.30 mL, 1.70 mmol) and HATU (259 mg, 0.68 mmol). After 1 h, the reaction mixture was poured onto Et_2O and extracted with 0.5 N HCl. The aqueous layer was back-extracted with Et_2O, and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by silica gel chromatography (gradient elution, 5% to 90% EtOAc in hexanes) to yield **27a** (290 mg, 94% yield) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (apparent t, J = 7.3 Hz, 1 H), 7.23 (m, 1 H), 7.14−7.05 (m, 1 H), 6.62 (ddd, J = 17.6, 10.7, 10.7 Hz, 1 H), 5.70−5.63 (m, 2 H), 5.36−5.30 (m, 2 H), 5.23 (br d, J = 9.3 Hz, 1 H), 4.95−4.59 (m, 7 H), 4.21−4.14 (m, 2 H), 3.89−3.82 (m, 2 H), 3.73 (s, 3 H), 3.63 (m, 1 H), 2.48 (dd, J = 13.6, 7.9 Hz, 1 H), 2.19 (m, 1 H), 1.94 (m, 2 H), 1.50 (m, 2 H), 1.01 (s, 9 H) ppm. HRMS (ESI) m/z 542.2853 [(M + H)$^+$; calcd for $C_{29}H_{40}N_3O_7$: 542.2861].

Methyl *N*-[(Pent-4-enyloxy)carbonyl]-L-norleucyl-(4R)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate (27b). Using the above procedure for **27a** with *N*-[(pent-4-en-1-yloxy)carbonyl]-L-norleucine (**26b**) provided **27b** (89% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 (apparent t, J = 7.1 Hz, 1 H), 7.25 (m, 1 H), 7.14−7.06 (m, 1 H), 6.62 (ddd, J = 17.5, 11.2, 6.1 Hz, 1 H), 5.75−5.63 (m, 2 H), 5.39 (m, 1 H), 5.35−5.31 (m, 2 H), 4.95−4.60 (m, 7 H), 4.40 (m, 1 H), 4.05 (m, 1 H), 3.92−3.75 (m, 3 H), 3.72 (s, 3 H), 2.48 (m, 1 H), 2.18 (m, 1 H), 1.98 (m, 2 H), 1.80−1.55 (m, 4 H), 1.40−1.27 (m, 4 H), 0.88 (t, J = 7.0 Hz, 3 H) ppm. HRMS (ESI) m/z 542.2851 [(M + H)$^+$; calcd for $C_{29}H_{40}N_3O_7$: 542.2861].

Methyl *N*-[(Pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (27c). Using the above procedure for **27a** with *N*-[(pent-4-en-1-yloxy)carbonyl]-L-valine (**26c**) provided **27c** (77% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.45−7.41 (m, 1 H), 7.30−7.26 (m, 1 H), 7.23−7.15 (m, 1 H), 7.07 (d, J = 7.6 Hz, 1 H), 6.78−6.67 (m, 1 H), 5.72 (dd, J = 17.4, 3.8 Hz, 1 H), 5.68−5.62 (m, 1 H), 5.37−5.33 (m, 2 H), 4.94−4.82 (m, 3 H), 4.79−4.64 (m, 4 H), 4.50 (t, J = 10.4 Hz, 1 H), 3.97 (t, J = 8.4 Hz, 1 H), 3.83−3.78 (m, 1 H), 3.74 (s, 3 H), 3.66−3.62 (m, 1 H), 3.45−3.39 (m, 1 H), 2.60−2.55 (m, 1 H), 2.26−2.18 (m, 1 H), 2.00−1.95 (m, 1 H), 1.85 (m, 2 H), 1.41−1.37 (m, 2 H), 1.10−0.99 (m, 6 H) ppm. HRMS (ESI) m/z 528.2703 [(M + H)$^+$; calcd for $C_{28}H_{38}N_3O_7$: 528.2705].

(3*R*,5*S*)-1-((2*S*)-2-Cyclohexyl-2-{[(pent-4-en-1-yloxy)carbonyl]-amino}acetyl)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-Vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (27d). Using the above procedure for **27a** with (2*S*)-cyclohexyl{[(pent-4-en-1-yloxy)-carbonyl]amino}acetic acid (**26d**) provided **27d** (73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 (d, J = 7.2 Hz, 1 H), 7.29−7.24 (m, 1 H), 7.17−7.08 (m, 1 H), 6.70−6.60 (m, 1 H), 5.77−5.66 (m, 2 H), 5.42−5.34 (m, 2 H), 5.27−5.23 (m, 1 H), 4.99−4.59 (m, 7 H), 4.30−4.10 (m, 2 H), 3.93−3.84 (m, 2 H), 3.79−3.69 (m, 4 H), 2.54−2.48 (m, 1 H), 2.28−2.18 (m, 1 H), 2.01−1.95 (m, 2 H), 1.85−1.52 (m, 8 H), 1.28−1.00 (m, 5 H) ppm. HRMS (ESI) m/z 568.3012 [(M + H)$^+$; calcd for $C_{31}H_{42}$-N_3O_7: 568.3018].

(3*R*,5*S*)-5-(Methoxycarbonyl)-1-((2*S*)-2-(1-methylcyclohexyl)-2-{[(pent-4-en-1-yloxy)carbonyl]amino}acetyl)pyrrolidin-3-yl 4-Vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (27e). Using the above procedure for **27a** with (2*S*)-(1-methylcyclohexyl){[(pent-4-en-1-yloxy)carbonyl]amino}acetic acid (**26e**) provided **27e** (51% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (m, 1 H), 7.27 (m, 1 H), 7.17 and 7.08 (2 × d, J = 7.5 Hz, 1 H), 6.64 (m, 1 H), 5.67 (m, 1 H), 5.36 (m, 2 H), 5.05−4.6 (m, 5 H), 4.24 (m, 1 H), 4.07 (m, 1 H), 3.88 (m, 2 H), 3.76 (s, 3 H), 3.65 (m, 1 H), 2.51 (m, 1 H), 2.21 (m, 1 H), 2.11 (m, 1 H), 1.95 (m, 1 H), 1.69 (m, 1 H), 1.62−1.30 (m, 14 H), 1.18 (m, 1 H), 1.04 (s, 3 H) ppm. HRMS (ESI) m/z 582.3162 [(M + H)$^+$; calcd for $C_{32}H_{44}N_3O_7$: 582.3179].

(3*R*,5*S*)-1-((2*S*)-2-Cyclopentyl-2-{[(pent-4-en-1-yloxy)carbonyl]amino}acetyl)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (27f). Using the above procedure for **27a** with (2*S*)-cyclopentyl {[(pent-4-en-1-yloxy)-carbonyl]amino}acetic acid (**26f**) provided **27f** (86% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (m, 1 H), 7.17 (d, J = 7.2 Hz, 1 H), 7.10 (d, J = 7.6 Hz, 1 H), 6.70−6.61 (m, 2 H), 5.75−5.65 (m, 2 H), 5.37 (m, 1 H), 5.29 (m, 1 H), 4.99−4.59 (m, 8 H), 4.31−4.24 (m, 3 H), 3.95−3.82 (m, 2 H), 3.74 (m, 1 H), 2.73 (br s, 1 H), 2.56−2.51 (m, 1 H), 2.26−2.16 (m, 1 H), 1.94 (m, 1 H), 1.83−1.48 (m, 10 H), 1.35 (m, 1 H) ppm. HRMS (ESI) m/z 554.2888 [(M + H)$^+$; calcd for $C_{30}H_{40}N_3O_7$: 554.2788].

Methyl *N*-[(But-3-en-1-yloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (27g). Using the above procedure for **27a** with *N*-[(but-3-en-1-yloxy)carbonyl]-3-methyl-L-valine (**26g**) provided **27g** (96% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.37 (m, 1 H), 7.29−7.24 (m, 1 H), 7.18−1.08 (m, 1 H), 6.70−6.61 (m, 1 H), 5.69 (dd, J = 17.6 Hz, 4.8 Hz, 1 H), 5.60 (m, 1 H), 5.40−5.31 (m, 3 H), 5.03−4.98 (m, 2 H), 4.88−4.59 (m, 5 H), 4.25−4.19 (m, 2 H), 3.98−3.64 (m, 5 H), 2.55−2.50 (m, 1 H), 2.26−2.18 (m, 4 H), 1.04 (s, 9 H) ppm. HRMS (ESI) m/z 528.2704 [(M + H)$^+$; calcd for $C_{28}H_{38}N_3O_7$: 528.2632].

Methyl *N*-[(Hex-5-en-1-yloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (27h). Using the above procedure for **27a** with *N*-[(hex-5-en-1-yloxy)carbonyl]-3-methyl-L-valine (**26h**) provided **27h** (82% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.42 (t, J = 8.2 Hz, 1 H), 7.28 (sext, J = 3.8 Hz, 1 H), 7.18 (2 × d, J = 7.3 Hz, 1 H), 6.77−6.66 (m, 1 H), 5.72 (m, 2 H), 5.36 (t, J = 9.9 Hz, 1 H), 5.32 (m, 1 H), 4.91 (m, 2 H), 4.79−4.65 (m, 5 H), 4.42 (t, J = 11.1 Hz, 1 H), 4.17 (s, 1 H), 3.79 (m, 1 H), 3.74 (s, 3 H), 3.60 (m, 1 H), 3.35 (m, 1 H), 2.58 (m, 1 H), 2.21 (m, 1 H), 1.89 (q, J = 5.9 Hz, 2 H), 1.28 (m, 2 H), 1.16 (m, 2 H), 1.04 (s, 9 H) ppm. HRMS (ESI) m/z 556.3063 [(M + H)$^+$; calcd for $C_{30}H_{42}N_3O_7$: 556.3018].

Methyl *N*-[(Hept-6-en-1-yloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (27i). Using the above procedure for **27a** with *N*-[(hept-6-en-1-yloxy)carbonyl]-3-methyl-L-valine (**26i**) provided **27i** (83% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, J = 7.4 Hz, 1 H), 7.25 (t, J = 7.4 Hz, 1 H), 7.10 (2 × d, J = 7.4 Hz, 1 H), 6.63 (m, 1 H), 5.79 (m, 1 H), 5.69 (dd, J = 17.7, 4.4 Hz, 1 H), 5.37 (m, 2 H), 5.29 (m, 1 H), 4.94 (m, 2 H), 4.82−4.68 (m, 3 H), 4.64−4.56 (m, 2 H), 4.23 (d, J = 4.7 Hz, 2 H), 3.89 (m, 2 H), 3.76 (s, 3 H), 3.81 (m, 1 H), 2.52 (m, 1 H), 2.21 (m, 1 H), 2.00 (m, 2 H), 1.42 (m, 2 H), 1.31 (m, 2 H), 1.14 (m, 2 H), 1.04 (s, 9 H) ppm. HRMS (ESI) m/z 570.3174 [(M + H)$^+$; calcd for $C_{31}H_{44}N_3O_7$: 570.3174].

Methyl (1*R*,12*E*,20*S*,23*S*)-20-*tert*-Butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (28a). A solution of methyl 3-methyl-*N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (**27a**) (230 mg, 0.43 mmol) in DCE (85 mL) was degassed with N_2 for 15 min. The Zhan 1b catalyst[22] (31 mg, 0.042 mmol) was added, and the reaction mixture was heated to 75 °C for 1 h. The reaction mixture was concentrated and the crude product was purified by silica gel chromatography (gradient elution, 10−90% EtOAc/hexane) to provide **28a** (198 mg, 91% yield) as an off-white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.18 (m, 2 H), 7.07 (d, J = 7.3 Hz, 1 H), 6.24 (d, J = 15.9 Hz, 1 H), 5.97 (ddd, J = 15.9, 8.0, 5.9 Hz, 1 H), 5.40−5.36 (m, 2 H), 4.68−4.50 (m, 5 H), 4.36 (d, J = 9.8 Hz, 1 H), 4.27 (dd, J = 11.5, 1.8 Hz, 1 H), 4.21 (dd, J = 10.9, 4.6 Hz, 1 H), 3.85 (m, 1 H), 3.73 (s, 3 H), 3.69 (dd, J = 11.5, 3.1 Hz, 1 H), 2.58 (ddd, J = 14.2, 8.1, 1.6 Hz, 1 H), 2.33−2.25 (m, 2 H), 2.09 (ddd, J = 14.0, 10.1, 3.8 Hz, 1 H), 1.95 (m, 1 H), 1.63, 1 H), 1.05 (s, 9 H) ppm. HRMS (ESI) m/z 514.2546 [(M + H)$^+$; calcd for $C_{27}H_{36}N_3O_7$: 514.2548].

Methyl (1*R*,12*E*,20*S*,23*S*)-20-Butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (28b). Using the above procedure for **28a** with methyl *N*-[(pent-4-enyloxy)carbonyl]-L-norleucyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2H-isoindol-2-yl)carbonyl]oxy}-L-prolinate (**27b**) provided **28b** (78% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24−7.17 (m, 2 H), 7.07 (d, J = 7.2 Hz, 1 H), 6.28 (d, J = 16.1 Hz, 1 H), 5.98 (ddd, J = 16.1, 7.4, 6.0 Hz, 1 H), 5.37

(apparent t, J = 3.3 Hz, 1 H), 5.16 (d, J = 8.9 Hz, 1 H), 4.68−4.38 (m, 6 H), 4.27 (m, 1 H), 3.84 (m, 1 H), 3.72 (s, 3 H), 3.71 (m, 1 H), 2.60 (ddd, J = 14.1, 7.9, 1.6 Hz, 1 H), 2.31−2.23 (m, 2 H), 2.10 (ddd, J = 14.0, 10.1, 3.8 Hz, 1 H), 1.92 (m, 1 H), 1.78 (m, 1 H), 1.70−1.59 (m, 3 H), 1.43−1.30 (m, 4 H), 0.90 (t, J = 6.9 Hz, 3 H) ppm. HRMS (ESI) m/z 514.2545 [(M + H)$^+$; calcd for $C_{27}H_{36}N_3O_7$: 514.2548].

Methyl (1*R*,12*E*,20*S*,23*S*)-20-Isopropyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (28c). Using the above procedure for **28a** with methyl *N*-[(pent-4-en-1-yloxy)carbonyl]-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (**27c**) provided **28c** (84% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.31−7.29 (m, 1 H), 7.26−7.22 (m, 1 H), 7.16−7.14 (m, 1 H), 6.44−6.40 (m, 1 H), 6.15−6.07 (m, 1 H), 5.34 (m, 1 H), 4.77−4.73 (m, 1 H), 4.68 (m, 3 H), 4.63−4.57 (m, 1 H), 4.51−4.48 (m, 1 H), 4.33−4.26 (m, 1 H), 4.16−4.13 (m, 1 H), 3.92−3.87 (m, 1 H), 3.81−3.79 (m, 1 H), 3.73 (s, 3 H), 2.63−2.58 (m, 1 H), 2.40−2.21 (m, 2 H), 2.20−2.14 (m, 1 H), 2.05−1.90 (m, 2 H), 1.80−1.68 (m, 1 H), 1.05 (d, J = 6.8 Hz, 6 H) ppm. HRMS (ESI) m/z 500.2380 [(M + H)$^+$; calcd for $C_{26}H_{34}N_3O_7$: 500.2392].

Methyl (1*R*,12*E*,20*S*,23*S*)-20-Cyclohexyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (28d). Using the above procedure for **28a** with (3*R*,5*S*)-1-((2*S*)-2-cyclohexyl-2-{[(pent-4-en-1-yloxy)-carbonyl]amino}acetyl)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (**27d**) provided **28d** (84% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.29 (d, J = 7.6 Hz, 1 H), 7.23 (t, J = 7.6 Hz, 1 H), 7.14 (d, J = 7.6 Hz, 1 H), 6.40 (d, J = 16.0 Hz, 1 H), 6.10 (dt, J = 16.0, 6.5 Hz, 1 H), 5.32 (t, J = 3.0 Hz, 1 H), 4.74−4.55 (m, 5 H), 4.47 (d, J = 11.6 Hz, 1 H), 4.29−4.24 (m, 1 H), 4.20 (d, J = 9.6 Hz, 1 H), 3.91−3.85 (m, 1 H), 3.78 (dd, J = 11.6, 2.8 Hz, 1 H), 3.72 (s, 3 H), 2.62−2.56 (m, 1 H), 2.40−2.22 (m, 2 H), 2.16 (ddd, J = 14.2, 10.4, 3.8 Hz, 1 H), 2.02−1.90 (m, 3 H), 1.82−1.66 (m, 5 H), 1.34−1.22 (m, 3 H), 1.12−1.00 (m, 2 H) ppm. HRMS (ESI) m/z 540.2689 [(M + H)$^+$; calcd for $C_{29}H_{38}N_3O_7$: 540.2705].

Methyl (1*R*,12*E*,20*S*,23*S*)-20-(1-Methylcyclohexyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (28e). Using the above procedure for **28a** with (3*R*,5*S*)-5-(methoxycarbonyl)-1-((2*S*)-2-(1-methylcyclohexyl)-2-{[(pent-4-en-1-yloxy)carbonyl]amino}acetyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (**27e**) provided **28e** (90% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (m, 2 H), 7.11 (d, J = 7.5 Hz, 1 H), 6.26 (d, J = 15.5 Hz, 1 H), 5.98 (m, 1 H), 5.45 (d, J = 10.0 Hz, 1 H), 5.42 (t, J = 3.5 Hz, 1 H), 4.7 (m, 3 H), 4.6 (m, 2 H), 4.42 (d, J = 10.0 Hz, 1 H), 4.32 (dd, J = 11.5, 2.0 Hz, 1 H), 4.24 (dt, J = 11.0, 4.5 Hz, 1 H), 3.88 (m, 1 H), 3.76 (s, 3 H), 3.74 (m, 1 H), 2.60 (m, 1 H), 2.3 (m, 2 H), 2.12 (m, 1 H), 1.97 (m, 1 H), 1.67−1.35 (m, 11 H), 1.07 (s, 3 H) ppm. HRMS (ESI) m/z 554.2846 [(M + H)$^+$; calcd for $C_{30}H_{40}N_3O_7$: 554.2866].

Methyl (1*R*,12*E*,20*S*,23*S*)-20-Cyclopentyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (28f). Using the above procedure for **28a** with (3*R*,5*S*)-1-((2*S*)-2-cyclopentyl-2-{[(pent-4-en-1-yloxy)-carbonyl]amino}acetyl)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (**27f**) provided **28f** (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.21 (m, 2 H), 7.12 (d, J = 6.8 Hz, 1 H), 6.31 (d, J = 16.0 Hz, 1 H), 6.03−5.96 (m, 1 H), 5.40 (t, J = 3.2 Hz, 1 H), 5.24 (d, J = 8.8 Hz, 1 H), 4.76−4.64 (m, 4 H), 4.59−4.55 (m, 1 H), 4.47 (dd, J = 11.4 Hz, 1.8 Hz, 1 H), 4.34−4.25 (m, 2 H), 3.90−3.85 (m, 1 H), 3.79−3.75 (m, 4 H), 2.67−2.62 (m, 1 H), 2.35−2.21 (m, 2 H), 2.17−2.11 (m, 1 H), 1.99−1.93 (m, 1 H), 1.87−1.83 (m, 2 H), 1.72−1.57 (m, 6 H), 1.44−1.26 (m, 2 H) ppm. HRMS (ESI) m/z 526.2563 [(M + H)$^+$; calcd for $C_{28}H_{36}N_3O_7$: 526.2475].

Methyl (1*R*,12*E*,19*S*,22*S*)-19-*tert*-Butyl-3,17,20-trioxo-2,16-dioxa-4,18,21-triazatetracyclo[19.2.1.1^{4,7}.0^{6,11}]pentacosa-6,8,10,12-tetraene-22-carboxylate (28g). Using the above procedure for **28a** with methyl *N*-[(but-3-en-1-yloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (**27g**) provided **28g** (64% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 7.6 Hz, 1 H), 7.11 (t, J = 7.0 Hz, 2 H), 6.41 (d, J = 16.8 Hz, 1 H), 5.96−5.90 (m, 1 H), 5.59 (d, J = 9.6 Hz, 1 H), 5.28 (t, J = 3.4 Hz, 1 H), 4.84−4.68 (m, 5 H), 4.57 (d, J = 15.2 Hz, 1 H), 4.49 (d, J = 9.6 Hz, 1 H), 4.32 (dd, J = 11.6, 2.0 Hz, 1 H), 3.91 (dt, J = 11.0, 3.3 Hz, 1 H), 3.76−3.71 (m, 4 H), 2.81−2.75 (m, 1 H), 2.67 (m, 1 H), 2.39 (m, 1 H), 2.19−2.12 (m, 1 H), 1.07 (s, 9 H) ppm. HRMS (ESI) m/z 500.2409 [(M + H)$^+$; calcd for $C_{26}H_{34}N_3O_7$: 500.2319].

Methyl (1*R*,12*E*,21*S*,24*S*)-21-*tert*-Butyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxylate (28h). Using the above procedure for **28a** with methyl *N*-[(hex-5-en-1-yloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (**27h**) provided **28h** (80% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (m, 2 H), 7.15 (dd, J = 5.9, 2.7 Hz, 1 H), 6.38 (d, J = 16.0 Hz, 1 H), 6.08 (dt, J = 16.1, 6.3 Hz, 1 H), 5.39 (t, J = 3.8 Hz, 1 H), 4.75 (m, 1 H), 4.69 (d, J = 1.2 Hz, 2 H), 4.58 (m, 3 H), 4.39 (s, 1 H), 4.25 (d, J = 12.0 Hz, 1 H), 3.91 (dd, J = 12.0, 4.0 Hz, 1 H), 3.77 (m, 1 H), 3.72 (s, 3 H), 2.64 (m, 1 H), 2.23 (m, 3 H), 1.70 (m, 2 H), 1.54 (m, 2 H), 1.06 (s, 9 H) ppm. HRMS (ESI) m/z 528.2688 [(M + H)$^+$; calcd for $C_{28}H_{38}N_3O_7$: 528.2705].

Methyl (1*R*,12*E*,22*S*,25*S*)-22-*tert*-Butyl-3,20,23-trioxo-2,19-dioxa-4,21,24-triazatetracyclo[22.2.1.1^{4,7}.0^{6,11}]octacosa-6,8,10,12-tetraene-25-carboxylate (28i). Using the above procedure for **28a** with methyl *N*-[(hept-6-en-1-yloxy)carbonyl]-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (**27i**) provided **28i** (67% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (t, J = 7.4 Hz, 1 H), 7.23 (t, J = 7.4 Hz, 1 H), 7.11 (d, J = 7.4 Hz, 1 H), 6.25 (d, J = 15.8 Hz, 1 H), 6.10 (m, 1 H), 5.63 (t, J = 3.6 Hz, 1 H), 5.33 (d, J = 9.5 Hz, 1 H), 4.73 (m, 2 H), 4.61 (m, 3 H), 4.33 (m, 2 H), 4.22 (m, 1 H), 3.86 (dd, J = 11.5, 3.8 Hz, 1 H), 3.77 (s, 3 H), 3.74 (m, 1 H), 2.57 (m, 1 H), 2.34 (m, 1 H), 2.24−2.19 (m, 2 H), 1.71 (m, 1 H), 1.48 (m, 3 H), 1.29 (m, 2 H), 1.07 (s, 9 H) ppm. HRMS (ESI) m/z 542.2884 [(M + H)$^+$; calcd for $C_{29}H_{40}N_3O_7$: 542.2861].

(1*R*,12*E*,20*S*,23*S*)-20-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxamide (29a). To a solution of methyl (1*R*,12*E*,20*S*,23*S*)-20-*tert*-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (**28a**) (460 mg, 0.90 mmol) in THF (10 mL), MeOH (2.5 mL), and water (5 mL) was added LiOH (215 mg, 8.96 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h. The mixture was then diluted with 0.5 N HCl and EtOAc, and the layers were separated. The organic layer was dried over Na_2CO_3, filtered, and concentrated to give (1*R*,12*E*,20*S*,23*S*)-20-*tert*-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo-[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylic acid (440 mg, 98% yield).

To a solution of the above crude acid (55 mg, 0.11 mmol) in DMF (1 mL) was added (1*R*,2*S*)-1-amino-*N*-(cyclopropylsulfonyl)-2-vinylcyclopropanecarboxamide hydrochloride (**16**)[24] (42 mg, 0.15 mmol), HATU (59 mg, 0.15 mmol), and DIPEA (0.06 mL, 0.33 mmol). The reaction mixture was stirred at RT for 2 h and then directly purified by reverse phase HPLC [Waters SunFire Prep C18 OBD 5 μm, 30 mm × 100 mm column, 5−95% MeCN/0.15% trifluoroacetic acid (TFA) in water]. The fractions containing product were concentrated to give **29a** as a white solid (42 mg, 54% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.89 (br s, 1 H), 7.29−7.22 (m, 2 H), 7.17−7.11 (m, 2 H), 6.29 (d, J = 16.0 Hz, 1 H), 6.03 (ddd, J = 16.0, 6.1, 6.1 Hz, 1 H), 5.73 (m, 1 H), 5.46−5.44 (m, 2 H), 5.27 (d, J = 17.0 Hz, 1 H), 5.14 (d, J = 10.3 Hz, 1 H), 4.75−4.65 (m, 3 H), 4.53 (d, J = 15.0 Hz, 1 H), 4.46 (dd, J = 9.7, 7.7 Hz, 1 H), 4.37 (apparent t, J = 9.6 Hz, 2 H), 4.25 (m, 1 H), 3.91 (m, 1 H), 3.73 (dd, J = 11.6, 3.1 Hz, 1 H), 2.91 (m, 1 H), 2.47−2.41 (m, 2 H), 2.34−2.29 (m, 2 H), 2.10−1.95 (m, 5 H), 1.71 (m, 1 H), 1.44 (dd, J = 9.3, 5.8 Hz, 1 H), 1.39−1.35 (m, 2 H), 1.07 (s, 9 H) ppm. HRMS (ESI) m/z

712.3041 [(M + H)$^+$; calcd for $C_{35}H_{46}N_5O_9S$: 712.3011]. Anal. ($C_{35}H_{45}N_5O_9S \cdot 0.5TFA$) C, H, N.

(1*R*,12*E*,20*S*,23*S*)-20-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxamide (29b). Using the above procedure for **29a** with methyl (1*R*,12*E*,20*S*,23*S*)-20-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (**28b**) provided **29b** (44% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 7.29−7.22 (m, 2 H), 7.12 (d, J = 7.2 Hz, 1 H), 7.07 (s, 1 H), 6.39 (d, J = 16.1 Hz, 1 H), 6.08 (ddd, J = 16.1, 6.2, 6.2 Hz, 1 H), 5.77 (m, 1 H), 5.43 (apparent t, J = 2.7 Hz, 1 H), 5.38 (d, J = 8.3 Hz, 1 H), 5.25 (d, J = 17.0 Hz, 1 H), 5.13 (d, J = 10.3 Hz, 1 H), 4.80−4.67 (m, 3 H), 4.59 (d, J = 15.2 Hz, 1 H), 4.46−4.35 (m, 3 H), 4.29 (m, 1 H), 3.94 (m, 1 H), 3.77 (dd, J = 11.4, 3.1 Hz, 1 H), 2.94 (m, 1 H), 2.52−2.36 (m, 2 H), 2.31−2.25 (m, 2 H), 2.10−1.70 (m, 8 H), 1.39−1.24 (m, 5 H), 1.04 (m, 2 H), 0.92 (m, 3 H) ppm. HRMS (ESI) m/z 712.3028 [(M + H)$^+$; calcd for $C_{35}H_{46}N_5O_9S$: 712.3011]. Anal. ($C_{35}H_{45}N_5O_9S \cdot 0.6TFA$) C, H, N.

(1*R*,12*E*,20*S*,23*S*)-*N*-((1*R*,2*S*)-1-{[(Cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-20-isopropyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxamide (29c). Using the above procedure for **29a** with methyl (1*R*,12*E*,20*S*,23*S*)-20-isopropyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (**28c**) provided **29c** (78% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 9.26 (s, 1 H), 7.34−7.24 (m, 2 H), 7.17−7.15 (m, 1 H), 6.43−6.39 (m, 1 H), 6.13−6.10 (m, 1 H), 5.80−5.72 (m, 1 H), 5.37−5.29 (m, 2 H), 5.12 (d, J = 10.0 Hz, 1 H), 4.80−4.65 (m, 4 H), 4.54−4.48 (m, 1 H), 4.42−4.37 (m, 1 H), 4.36−4.30 (m, 1 H), 4.08−4.03 (m, 1 H), 3.91−3.82 (m, 2 H), 2.99−2.93 (m, 1 H), 2.47−2.42 (m, 1 H), 2.37−2.06 (m, 5 H), 1.99−1.94 (m, 1 H), 1.92−1.86 (m, 1 H), 1.78−1.70 (m, 1 H), 1.42−1.37 (m, 1 H), 1.31−1.16 (m, 3 H), 1.09−0.96 (m, 8 H) ppm. HRMS (ESI) m/z 698.2858 [(M + H)$^+$; calcd for $C_{34}H_{44}N_5O_9S$: 698.2854]. Anal. ($C_{34}H_{43}N_5O_9S \cdot 0.25H_2O \cdot 1.2EtOAc$) C, H, N.

(1*R*,12*E*,20*S*,23*S*)-20-Cyclohexyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxamide (29d). Using the above procedure for **29a** with methyl (1*R*,12*E*,20*S*,23*S*)-20-cyclohexyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]-hexacosa-6,8,10,12-tetraene-23-carboxylate (**28d**) provided **29d** (79% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 9.24 (s, 1 H), 7.30 (d, J = 7.5 Hz, 1 H), 7.25 (t, J = 7.5 Hz, 1 H), 7.16 (d, J = 7.0 Hz, 1 H), 6.42 (d, J = 16.0 Hz, 1 H), 6.11 (dt, J = 16.0, 6.6 Hz, 1 H), 5.76 (m, 1 H), 5.35 (s, 1 H), 5.30 (m, 2 H), 5.12 (dd, J = 10.5, 1.5 Hz, 1 H), 4.79−4.63 (m, 4 H), 4.49 (d, J = 11.5 Hz, 1 H), 4.39 (dd, J = 10.5, 6.5 Hz, 1 H), 4.32 (sext, J = 5.3 Hz, 1 H), 4.15 (d, J = 10.5 Hz, 1 H), 3.90−3.86 (m, 1 H), 3.84 (dd, J = 11.5, 3.0 Hz, 1 H), 2.98−2.93 (m, 1 H), 2.44 (dd, J = 13.7, 7.2 Hz, 1 H), 2.39−2.14 (m, 4 H), 1.98−1.66 (m, 9 H), 1.40 (dd, J = 9.2, 5.2 Hz, 1 H), 1.31−1.21 (m, 5 H), 1.10−1.02 (m, 4 H) ppm. HRMS (ESI) m/z 738.3176 [(M + H)$^+$; calcd for $C_{37}H_{48}N_5O_9S$: 738.3167]. Anal. ($C_{37}H_{47}N_5O_9S \cdot 1.8H_2O \cdot 0.55EtOAc$) C, H, N.

(1*R*,12*E*,20*S*,23*S*)-*N*-((1*R*,2*S*)-1-{[(Cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-20-(1-methylcyclohexyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxamide (29e). Using the above procedure for **29a** with methyl (1*R*,12*E*,20*S*,23*S*)-20-(1-methylcyclohexyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo-[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (**28e**) provided **29e** (83% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.32 (d, J = 7.5 Hz, 1 H), 7.25 (t, J = 8.0 Hz, 1 H), 7.17 (d, J = 7.5 Hz, 1 H), 7.15 (d, J = 9.5 Hz, 1 H), 6.37 (d, J = 16.0 Hz, 1 H), 6.10 (m, 1 H), 5.72 (m, 1 H), 5.37 (s, 1 H), 5.28 (dd, J = 17.0, 1.5 Hz, 1 H), 5.12 (dd, J = 10.0, 1.5 Hz, 1 H), 4.67 (m, 4 H), 4.42 (m, 3 H), 4.28 (m, 1 H), 3.87 (m, 2 H), 2.93 (m, 1 H), 2.40 (m, 2 H), 2.31 (m, 1 H), 2.22 (m, 1 H), 2.12 (m, 1 H), 2.0 (m, 1 H), 1.88 (dd, J = 8.3, 5.5 Hz, 1 H), 1.71 (m, 1 H), 1.63−1.36 (m, 10 H), 1.30−1.19 (m, 4 H), 1.09 (s, 3 H), 1.08 (m, 2 H) ppm. HRMS (ESI) m/z 752.3303 [(M + H)$^+$; calcd for $C_{38}H_{50}N_5O_9S$: 752.3329].

(1*R*,12*E*,20*S*,23*S*)-20-Cyclopentyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxamide (29f). Using the above procedure for **29a** with methyl (1*R*,12*E*,20*S*,23*S*)-20-cyclopentyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]-hexacosa-6,8,10,12-tetraene-23-carboxylate (**28f**) provided **29f** (98% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.29−7.12 (m, 3 H), 6.40 (d, J = 16.0 Hz, 1 H), 6.10 (m, 1 H), 5.57 (br s, 1 H), 5.31−5.07 (m, 3 H), 4.79−4.14 (m, 10 H), 3.86 (m, 2 H), 2.95 (br s, 1 H), 2.42−2.22 (m, 6 H), 1.91−1.58 (m, 8 H), 1.38−1.04 (m, 8 H) ppm. HRMS (ESI) m/z 724.3029 [(M + H)$^+$; calcd for $C_{36}H_{46}N_5O_9S$: 724.3011].

(1*R*,12*E*,19*S*,22*S*)-19-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,17,20-trioxo-2,16-dioxa-4,18,21-triazatetracyclo[19.2.1.1^{4,7}.0^{6,11}]pentacosa-6,8,10,12-tetraene-22-carboxamide (29g). Using the above procedure for **29a** with methyl (1*R*,12*E*,19*S*,22*S*)-19-*tert*-butyl-3,17,20-trioxo-2,16-dioxa-4,18,21-triazatetracyclo[19.2.1.1^{4,7}.0^{6,11}]-pentacosa-6,8,10,12-tetraene-22-carboxylate (**28g**) provided **29g** (91% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.23 (m, 1 H), 7.13 (m, 2 H), 6.48 (d, J = 16.4 Hz, 1 H), 6.00 (m, 1 H), 5.80 (br s, 1 H), 5.24 (m, 2 H), 5.05 (m, 1 H), 4.79−4.57 (m, 5 H), 4.51 (s, 1 H), 4.42 (br s, 1 H), 4.33 (d, J = 12.0 Hz, 1 H), 3.99−3.83 (m, 2 H), 2.84 (br s, 1 H), 2.70−2.63 (m, 2 H), 2.44−2.40 (m, 1 H), 2.29−2.10 (m, 2 H), 1.83 (m, 1 H), 1.39−0.90 (m, 16 H) ppm. HRMS (ESI) m/z 698.2854 [(M + H)$^+$; calcd for $C_{34}H_{44}N_5O_9S$: 698.2781].

(1*R*,12*E*,21*S*,24*S*)-21-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxamide (29h). Using the above procedure for **29a** with methyl (1*R*,12*E*,21*S*,24*S*)-21-*tert*-butyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]-heptacosa-6,8,10,12-tetraene-24-carboxylate (**28h**) provided **29h** (70% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.25 (t, J = 7.5 Hz, 1 H), 7.22 (d, J = 7.0 Hz, 1 H), 7.15 (d, J = 6.5 Hz, 1 H), 6.37 (d, J = 16.0 Hz, 1 H), 6.07 (dt, J = 16.0, 6.4 Hz, 1 H), 5.77 (dt, J = 17.0, 9.0 Hz, 1 H), 5.37 (m, 1 H), 5.28 (d, J = 17.5 Hz, 1 H), 5.11 (d, J = 10.5 Hz, 1 H), 4.75 (d, J = 14.3 Hz, 1 H), 4.66 (m, 5 H), 4.41 (s, 1 H), 4.37 (dd, J = 10.7, 6.8 Hz, 1 H), 4.23 (d, J = 11.5 Hz, 1 H), 3.95 (dd, J = 12.0, 4.0 Hz, 1 H), 3.77 (quint, J = 5.6 Hz, 1 H), 2.93 (m, 1 H), 2.51 (dd, J = 14.0, 6.5 Hz, 1 H), 2.23 (m, 4 H), 1.86 (dd, J = 8.2, 5.7 Hz, 1 H), 1.68 (m, 2 H), 1.53 (quint, J = 7.2 Hz, 2 H), 1.44 (dd, J = 9.2, 5.8 Hz, 1 H); 1.24 (m, 3 H); 1.06 (m, 2 H), 1.05 (s, 9 H) ppm. HRMS (ESI) m/z 726.3137 [(M + H)$^+$; calcd for $C_{36}H_{48}N_5O_9S$: 726.3167]. Anal. ($C_{36}H_{47}N_5O_9S \cdot 2H_2O$) C, H, N.

(1*R*,12*E*,22*S*,25*S*)-22-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,20,23-trioxo-2,19-dioxa-4,21,24-triazatetracyclo[22.2.1.1^{4,7}.0^{6,11}]octacosa-6,8,10,12-tetraene-25-carboxamide (29i). Using the above procedure for **29a** with methyl (1*R*,12*E*,22*S*,25*S*)-22-*tert*-butyl-3,20,23-trioxo-2,19-dioxa-4,21,24-triazatetracyclo[22.2.1.1^{4,7}.0^{6,11}]-octacosa-6,8,10,12-tetraene-25-carboxylate (**28i**) provided **29i** (61% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 (t, J = 7.7 Hz, 1 H), 7.25 (t, J = 7.7 Hz, 1 H), 7.11 (d, J = 7.7 Hz, 1 H), 6.26 (d, J = 15.6 Hz, 1 H), 6.11 (m, 1 H), 5.82 (m, 1 H), 5.48 (m, 1 H), 5.27 (m, 1 H), 4.91 (m, 1 H), 4.89−4.60 (m, 5 H), 4.36−4.13 (m, 4 H), 3.79 (m, 2 H), 2.58 (m, 1 H), 2.26 (m, 2 H), 2.19 (m, 1 H), 2.03 (s, 3 H), 1.83 (m, 2 H), 1.69 (m, 1 H), 1.49 (m, 3 H), 1.33 (m, 2 H), 1.21 (m, 2 H), 1.02 (s, 9 H), 0.79 (m, 2 H) ppm. HRMS (ESI) m/z 740.3320 [(M + H)$^+$; calcd for $C_{37}H_{50}N_5O_9S$: 740.3324]. Anal. ($C_{37}H_{49}N_5O_9S \cdot 3.8H_2O$) C, H, N.

(1*R*,20*S*,23*S*)-20-*tert*-Butyl-*N*-((1*R*,2*S*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-vinylcyclopropyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10-triene-23-carboxamide (31a). To a solution of methyl (1*R*,12*E*,

20*S*,23*S*)-20-*tert*-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (**28a**) (100 mg, 0.20 mmol) in EtOAc (7 mL) was added 10% palladium on carbon (10 mg). The reaction mixture was stirred under a balloon of hydrogen for 5 h at RT. The reaction mixture was filtered through celite and the filtrate evaporated to give methyl (1*R*,20*S*,23*S*)-20-*tert*-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10-triene-23-carboxylate (90 mg, 90% yield), which was used with no further purification.

Using the procedure for **29a** with the above crude ester provided **31a** (28% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 9.14 (s, 1 H), 7.23 (t, J = 7.4 Hz, 1 H), 7.13 (d, J = 7.2 Hz, 1 H), 7.10 (d, J = 7.2 Hz, 1 H), 5.75 (m, 1 H), 5.53 (s, 1 H), 5.30 (d, J = 16.8 Hz, 1 H), 5.12 (d, J = 10.0 Hz, 1 H), 4.75−4.59 (m, 4 H), 4.42 (m, 2 H), 4.34 (s, 1 H), 4.30 (d, J = 12.0 Hz, 1 H), 3.88 (d, J = 9.5 Hz, 1 H), 3.75 (m, 1 H), 3.60 (q, J = 6.9 Hz, 2 H), 2.95 (sept, J = 4.6 Hz, 1 H), 2.63 (m, 1 H), 2.41 (m, 2 H), 2.23 (q, J = 8.9 Hz, 1 H), 2.15 (m, 1 H), 1.88 (m, 1 H), 1.79 (m, 1 H), 1.56 (m, 3 H), 1.41 (m, 3 H), 1.25 (m, 2 H), 1.17 (t, J = 7.0 Hz, 2 H), 1.06 (s, 9 H) ppm. HRMS (ESI) m/z 714.3188 [(M + H)$^+$; calcd for $C_{35}H_{48}N_5O_9S$: 714.3167]. Anal. ($C_{35}H_{47}N_5O_9S\cdot 2H_2O$) C, H, N.

(1*R*,12*E*,20*S*,23*S*)-20-*tert*-Butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxamide (31b). To a solution of methyl (1*R*,12*E*,20*S*,23*S*)-20-*tert*-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (**28a**) (60 mg, 0.12 mmol) in THF (1 mL), MeOH (0.5 mL) and water (0.5 mL) was added LiOH (28 mg, 1.17 mmol). The reaction mixture was heated to 40 °C and stirred for 1 h. The reaction mixture was then diluted with 0.5 N HCl and EtOAc, and the layers were separated. The organic layer was dried over Na_2SO_4, filtered, and concentrated to give (1*R*,12*E*,20*S*,23*S*)-20-*tert*-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylic acid (51 mg, 87% yield).

To a solution of the above carboxylic acid (51 mg, 0.10 mmol) in DMF (1 mL) was added (1*R*,2*R*)-1-amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride (**30**)[28] (32 mg, 0.12 mmol), HATU (48 mg, 0.15 mmol), and DIPEA (0.04 mL, 0.25 mmol). The reaction mixture was stirred at RT for 2 h and then directly purified by reverse phase HPLC [Waters SunFire Prep C18 OBD 5 μm, 30 mm × 100 mm column, 5−95% MeCN/0.15% TFA in water]. The fractions containing product were concentrated to give **31b** as a white solid (55 mg, 77% yield). ^{1}H NMR (400 MHz, CD_3OD) δ 7.33 (d, J = 7.2 Hz, 1 H), 7.26 (t, J = 7.6 Hz, 1 H), 7.16 (d, J = 8.0 Hz, 1 H), 6.39 (d, J = 15.7 Hz, 1 H), 6.13 (m, 1 H), 5.37 (s, 1 H), 4.69 (m, 5 H), 4.47−4.28 (m, 5 H), 3.89 (m, 1 H), 3.83 (d, J = 11.6 Hz, 1 H), 2.98 (m, 1 H), 2.40 (m, 2 H), 2.31 (m, 1 H), 2.10 (t, J = 12.0 Hz, 1 H), 1.99 (s, 1 H), 1.73 (m, 1 H), 1.60 (m, 2 H), 1.52 (m, 1 H), 1.29−1.15 (m, 4 H), 1.08 (s, 9 H), 0.98 (m, 4 H) ppm. HRMS (ESI) m/z 714.3189 [(M + H)$^+$; calcd for $C_{35}H_{48}N_5O_9S$: 714.3167]. Anal. ($C_{35}H_{47}N_5O_9S\cdot 0.60TFA$) C, H, N.

(1*R*,20*S*,23*S*)-20-*tert*-Butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10-triene-23-carboxamide (31c). To a solution of methyl (1*R*,12*E*,20*S*,23*S*)-20-*tert*-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]hexacosa-6,8,10,12-tetraene-23-carboxylate (**28a**) (100 mg, 0.20 mmol) in EtOAc (7 mL) was added 10% palladium on carbon (10 mg). The reaction mixture was stirred under a balloon of hydrogen for 5 h at RT. The reaction mixture was filtered through celite and the filtrate evaporated to give methyl (1*R*,20*S*,23*S*)-20-*tert*-butyl-3,18,21-trioxo-2,17-dioxa-4,19,22-triazatetracyclo[20.2.1.1^{4,7}.0^{6,11}]-hexacosa-6,8,10-triene-23-carboxylate (90 mg, 90% yield), which was used with no further purification.

Using the procedure for **31b** with the above crude ester provided **31c** (82% yield, 3 steps). ^{1}H NMR (500 MHz, CD_3OD) δ 7.23 (t, J = 7.5 Hz, 1 H), 7.13 (d, J = 7.5 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 7.02 (d, J = 9.0 Hz, 1 H), 5.52 (s, 1 H), 4.74−4.60 (m, 5 H), 4.48−4.30 (m, 4 H), 3.88 (d, J = 11.5 Hz, 1 H), 3.75 (m, 1 H), 2.99 (sept, J = 4.3 Hz, 1 H), 2.62 (m, 1 H), 2.41 (m, 2 H), 2.14 (m, 1 H), 1.79 (m, 1 H), 1.65−1.51 (m, 7 H), 1.47−1.19 (m, 6 H), 1.10 (m, 1 H), 1.07 (s, 9 H), 0.99 (t, J = 6.8 Hz, 3 H) ppm. HRMS (ESI) m/z 716.3321 [(M + H)$^+$; calcd for $C_{35}H_{50}N_5O_9S$: 716.3324]. Anal. ($C_{35}H_{49}N_5O_9S\cdot 0.75H_2O$) C, H, N.

***N*-{[(2,2-Dimethylhex-5-enyl)oxy]carbonyl}-3-methyl-L-valine (32b).** To a stirred solution of 2,2-dimethylhex-5-en-1-ol[35] (10.8 g, 83.9 mmol) in anhydrous 1,4-dioxane (100 mL), at 0 °C and under nitrogen, was added triphosgene (13.7 g, 46.1 mmol) and DIPEA (14.6 mL, 83.9 mmol) cautiously. The reaction mixture was stirred at RT for 1 h, cooled to 0 °C, and 1 N NaOH (83.9 mL, 83.9 mmol) was added slowly. L-*tert*-Leucine (11.0 g, 83.9 mmol) was then added, and the reaction mixture was stirred at RT for 20 h. The reaction solution was basified to pH 10 with 1 N NaOH, washed with CH_2Cl_2 (3 × 100 mL), acidified to pH 5 with 1 N HCl, and extracted with CH_2Cl_2 (3 × 150 mL). The combined CH_2Cl_2 layer was washed with water, dried over Na_2SO_4, filtered, and concentrated to give **32b** (20.3 g, 85% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50 (br s, 1 H), 5.85−5.76 (m, 1 H), 5.25−5.23 (m, 1 H), 5.04−4.99 (m, 1 H), 4.95−4.92 (m, 1 H), 4.23−4.20 (m, 1 H), 3.89−3.79 (m, 2 H), 2.05−2.00 (m, 2 H), 1.38−1.34 (m, 2 H), 1.05 (s, 9 H), 0.93 (s, 6 H) ppm. HRMS (ESI) m/z 286.2014 [(M + H)$^+$; calcd for $C_{15}H_{28}NO_4$: 286.2013]. Anal. ($C_{15}H_{27}NO_4\cdot 0.65H_2O$) C, H, N.

***N*-{[(1-But-3-en-1-ylcyclopropyl)methoxy]carbonyl}-3-methyl-L-valine (32c).** To a stirred solution of 1 M lithium aluminum hydride (LAH) in ether (65.4 mL, 65.4 mmol), at 0 °C and under nitrogen, was added a solution of ethyl 1-but-3-en-1-ylcyclopropanecarboxylate[36] (5.0 g, 29.7 mmol) in anhydrous ether (25 mL) dropwise over 1 h. The reaction solution was then stirred at RT for 15 h, carefully quenched at 0 °C with water (3 mL), 1 M NaOH (11 mL), and water (9 mL). The resulting mixture was dried over Na_2SO_4, filtered, and concentrated to give (1-but-3-en-1-ylcyclopropyl)methanol (3.45 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (m, 1 H), 5.05−4.92 (m, 2 H), 3.43 (br s, 2 H), 2.17 (m, 2 H), 1.50 (m, 2 H), 0.37 (m, 4 H) ppm.

Using the above procedure for **13** with (1-but-3-en-1-ylcyclopropyl)methanol provided **32c** (64% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.29 (m, 1 H), 5.01 (d, J = 15.5 Hz, 1 H), 4.93 (d, J = 10.5 Hz, 1 H), 4.19 (d, J = 9.5 Hz, 1 H), 3.97 (d, J = 11.0 Hz, 1 H), 3.89 (d, J = 11.5 Hz, 1 H), 2.15 (m, 2 H), 2.07 (m, 1 H), 1.45 (m, 2 H), 1.03 (s, 9 H), 0.48 (t, J = 5.0 Hz, 1 H), 0.39 (t, J = 5.3 Hz, 2 H) ppm. HRMS (ESI) m/z 284.1767 [(M + H)$^+$; calcd for $C_{15}H_{26}NO_4$: 284.1817].

***N*-{[(1-But-3-en-1-ylcyclobutyl)methoxy]carbonyl}-3-methyl-L-valine (32d).** To a stirred solution of DIPEA (12.1 mL, 85.8 mmol) in anhydrous THF (50 mL), at −70 °C under nitrogen, was slowly added a solution of *n*-BuLi (2.5 M in hexane, 33.1 mL, 82.7 mmol). The reaction mixture was stirred for 20 min, and a solution of ethyl cyclobutanecarboxylate (10.8 mL, 78.0 mmol) in THF (50 mL) was added dropwise over 30 min. The reaction mixture was warmed to 0 °C and recooled to −70 °C, and then a solution of 4-bromobut-1-ene (8.87 mL, 87.4 mmol) in HMPA (20 mL) was added dropwise. The reaction mixture was slowly warmed to RT and stirred for 2 h and then quenched with water (100 mL). The aqueous layer was extracted with ether, and the combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel chromatography (gradient elution, 0 to 25% EtOAc in hexane) to give ethyl 1-but-3-en-1-ylcyclobutanecarboxylate (6.11 g, 43% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84−5.76 (m, 1 H), 5.01 (m, 1 H), 4.91 (m, 1 H), 4.51 (q, J = 7.2 Hz, 2 H), 2.42 (m, 2 H), 1.94 (m, 2 H), 1.89 (m, 6 H), 1.26 (t, J = 7.0 Hz, 3 H) ppm. LRMS (ESI) m/z 183.3 [(M + H)$^+$; calcd for $C_{11}H_{19}O_2$: 183.1].

To a stirred solution of ethyl 1-but-3-en-1-ylcyclobutanecarboxylate (6.00 g, 32.9 mmol) in Et_2O (50 mL), at −75 °C was

added a solution of LAH (1 M in Et_2O, 72.4 mL, 72.4 mmol) over 1 h. The reaction mixture was stirred at RT for 3 h and then cooled to −75 °C and quenched with successive slow additions of water (3 mL), 1 M NaOH (11 mL), and water (9 mL). The mixture was dried over Na_2SO_4, filtered, and concentrated to give (1-but-3-en-1-ylcyclobutyl)methanol (3.92 g, 85% yield) as a clear oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89−5.81 (m, 1 H), 5.02 (m, 1 H), 4.95 (m, 1 H), 3.56 (d, J = 6.0 Hz, 2 H), 2.00 (m, 2 H), 1.87 (m, 2 H), 1.77 (m, 4 H), 1.60 (m, 2 H) ppm.

Using the above procedure for **13** with (1-but-3-en-1-ylcyclobutyl)methanol provided **32d** (47% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1 H), 5.26 (d, J = 9.5 Hz, 1 H), 5.02 (d, J = 17.0 Hz, 1 H), 4.94 (d, J = 9.0 Hz, 1 H), 4.21 (d, J = 9.5 Hz, 1 H), 4.09 (d, J = 11.0 Hz, 1 H), 4.02 (d, J = 11.0 Hz, 1 H), 1.99 (m, 2 H), 1.86 (m, 4 H), 1.78 (m, 2 H), 1.58 (m, 2 H), 1.04 (s, 9 H) ppm. HRMS (ESI) m/z 298.2015 [$(M + H)^+$; calcd for $C_{16}H_{28}NO_4$: 298.2013].

***N*-{[(1-But-3-en-1-ylcyclopentyl)methoxy]carbonyl}-3-methyl-L-valine (32e).** Using the above procedure for **32d** methyl cyclopentanecarboxylate provided **32e** (42% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.82 (m, 1 H), 5.26 (d, J = 9.5 Hz, 1 H), 5.00 (d, J = 17.5 Hz, 1 H), 4.92 (d, J = 10.0 Hz, 1 H), 4.20 (d, J = 9.5 Hz, 1 H), 3.94 (d, J = 11.0 Hz, 1 H), 3.85 (d, J = 10.5 Hz, 1 H), 2.02 (m, 2 H), 1.60 (m, 4 H), 1.47 (m, 4 H), 1.39 (m, 2 H), 1.03 (s, 9 H) ppm. HRMS (ESI) m/z 312.2172 [$(M + H)^+$; calcd for $C_{17}H_{30}NO_4$: 312.2169].

***N*-{[(1-But-3-en-1-ylcyclohexyl)methoxy]carbonyl}-3-methyl-L-valine (32f).** Using the above procedure for **32d** with methyl cyclohexanecarboxylate provided **32f** (47% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 (m, 1 H), 5.22 (d, J = 9.5 Hz, 1 H), 5.01 (dq, J = 15.0, 1.7 Hz, 1 H), 4.92 (d, J = 10.0 Hz, 1 H), 4.21 (d, J = 10.0 Hz, 1 H), 3.98 (d, J = 11.0 Hz, 1 H), 3.90 (d, J = 10.5 Hz, 1 H), 1.97 (m, 2 H), 1.44 (m, 8 H), 1.33 (m, 4 H), 1.03 (s, 9 H) ppm. HRMS (ESI) m/z 326.2326 [$(M + H)^+$; calcd for $C_{18}H_{32}NO_4$: 326.2326].

(2*S*)-Cyclohexyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}-amino)acetic Acid (32g). Using the above procedure for **26b** with 2,2-dimethylhex-5-en-1-ol and methyl (2*S*)-amino(cyclohexyl)acetate hydrochloride provided **32g** (99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.88−5.74 (m, 1 H), 5.18 (d, J = 8.9 Hz, 1 H), 5.01 (d, J = 17.2 Hz, 1 H), 4.93 (d, J = 10.2 Hz, 1 H), 4.31 (dd, J = 9.0, 4.9 Hz, 1 H), 3.81 (s, 2 H), 2.11−1.61 (m, 8 H), 1.42−1.08 (m, 7 H), 0.92 (d, J = 6.1 Hz, 6 H) ppm. HRMS (ESI) m/z 312.2167 [$(M + H)^+$; calcd for $C_{17}H_{30}NO_4$: 312.2169].

(2*S*)-({[(2,2-Dimethylhex-5-en-1-yl)oxy]carbonyl}amino)(1-methylcyclohexyl)acetic Acid (32h). Using the above procedure for **13** with 2,2-dimethylhex-5-en-1-ol and (2*S*)-amino(1-methylcyclohexyl)acetic acid hydrochloride provided **32h** (97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.81 (m, 1 H), 5.20 (d, J = 12.0 Hz, 1 H), 5.01 (m, 1 H), 4.93 (d, J = 12.5 Hz, 1 H), 4.37 (d, J = 12.0 Hz, 1 H), 3.83 (m, 2 H), 2.02 (m, 2 H), 1.58−1.33 (m, 12 H), 0.97 (s, 3 H), 0.92 (s, 6 H) ppm. HRMS (ESI) m/z 326.2331 [$(M + H)^+$; calcd for $C_{18}H_{32}NO_4$: 326.2326].

***O*-(*tert*-Butyl)-*N*-{[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}-L-serine (32i).** Using the above procedure for **26b** with 2,2-dimethylhex-5-en-1-ol and methyl *O*-(*tert*-butyl)-L-serinate hydrochloride provided **32i** (61% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75−5.86 (m, 1 H), 4.90−5.04 (m, 2 H), 4.02 (m, 1 H), 3.57−3.90 (m, 4 H), 1.98−2.05 (m, 2 H), 1.27−1.36 (m, 2 H), 1.14 (s, 9 H), 1.01 (d, J = 6.5 Hz, 1 H), 6.09 (s, 6 H) ppm. HRMS (ESI) m/z 316.2114 [$(M + H)^+$; calcd for $C_{16}H_{30}NO_5$: 316.2118].

Methyl *N*-{[(2,2-Dimethylhex-5-en-1-yl)oxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]-oxy}-L-prolinate (33b). To a solution of (3*R*,5*S*)-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate hydrochloride (**25**) (400 mg, 1.13 mmol) and acid **32b** (324 mg, 1.13 mmol) in DMF (10 mL) at RT was added DIPEA (0.59 mL, 3.40 mmol) and HATU (604 mg, 1.59 mmol). After 18 h of stirring, the reaction mixture was poured into aqueous $NaHCO_3$ and extracted with EtOAc three times. The combined organic portions were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by silica gel chromatography (gradient elution, 5% to 90% EtOAc in hexanes) to yield **33b** (600 mg, 91% yield) as a white foam. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40−7.36 (m, 1 H), 7.29−7.24 (m, 1 H), 7.17−7.08 (m, 1 H), 6.70−6.60 (m, 1 H), 5.82−5.66 (m, 2 H), 5.44−5.34 (m, 2 H), 5.29−5.27 (m, 1 H), 4.99−4.59 (m, 7 H), 4.26−4.19 (m, 2 H), 3.92−3.85 (m, 1 H), 3.76 (m, 3 H), 3.66−3.63 (m, 1 H), 3.31 (t, J = 11.0 Hz, 1 H), 2.55−2.50 (m, 1 H), 2.28−2.15 (m, 1 H), 1.95−1.85 (m, 2 H), 1.22−1.17 (m, 2 H), 1.05−1.02 (m, 9 H), 0.76−0.74 (m, 6 H) ppm. HRMS (ESI) m/z 584.3332 [$(M + H)^+$; calcd for $C_{32}H_{46}N_3O_7$: 584.3331]. Anal. ($C_{32}H_{45}N_3O_7 \cdot 0.7H_2O$) C, H, N.

Methyl *N*-{[(1-But-3-en-1-ylcyclopropyl)methoxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)-carbonyl]oxy}-L-prolinate (33c). Using the above procedure for **27a** with *N*-{[(1-but-3-en-1-ylcyclopropyl)methoxy]carbonyl}-3-methyl-L-valine (**32c**) provided **33c** (89% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.43 (t, J = 6.5 Hz, 1 H), 7.30−7.26 (2 × d, J = 7.8 Hz, 1 H), 7.22−7.13 (2 × d, J = 7.5 Hz, 1 H), 6.73 (m, 1 H), 5.72 (m, 1 H), 5.37 (t, J = 11.0 Hz, 1 H), 5.30 (m, 1 H), 4.92 (d, J = 17.5 Hz, 2 H), 4.71 (m, 5 H), 4.43 (t, J = 11.5 Hz, 1 H), 4.17 (s, 1 H), 3.78 (m, 1 H), 3.74 (s, 3 H), 3.54 (dd, J = 11.5, 5.0 Hz, 1 H), 3.08 (dd, J = 17.5, 11.5 Hz, 1 H), 2.56 (m, 1 H), 2.20 (m, 2 H), 1.92 (m, 2 H), 1.26 (m, 3 H), 1.05 (s, 9 H), 1.04 (m, 1 H), 0.13 (m, 3 H) ppm. HRMS (ESI) m/z 582.3160 [$(M + H)^+$; calcd for $C_{32}H_{44}N_3O_7$: 582.3170].

Methyl *N*-{[(1-But-3-en-1-ylcyclobutyl)methoxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)-carbonyl]oxy}-L-prolinate (33d). Using the above procedure for **27a** with *N*-{[(1-but-3-en-1-ylcyclobutyl)methoxy]carbonyl}-3-methyl-L-valine (**32d**) provided **33d** (79% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.42 (t, J = 8.5 Hz, 1 H), 7.28 (m, 1 H), 7.23−7.15 (2 × d, J = 7.8, Hz, 1 H), 6.72 (m, 1 H), 5.72 (dd, J = 17.5, 5.5 Hz, 1 H), 5.36 (dd, J = 15.5, 11.5 Hz, 1 H), 5.31 (m, 1 H), 4.93 (m, 1 H), 4.87 (m, 1 H), 4.73 (m, 4 H), 4.46 (t, J = 11.0 Hz, 1 H), 4.19 (d, J = 4.0 Hz, 1 H), 3.80 (m, 1 H), 3.74 (s, 3 H), 3.69 (dd, J = 11.0, 5.0 Hz, 1 H), 3.23 (t, J = 11.0 Hz, 1 H), 2.58 (m, 1 H), 2.22 (m, 1 H), 1.90 (s, 1 H), 1.73 (m, 5 H), 1.55 (m, 4 H), 1.38 (t, J = 7.7 Hz, 2 H), 1.05 (s, 9 H) ppm. HRMS (ESI) m/z 596.3330 [$(M + H)^+$; calcd for $C_{33}H_{46}N_3O_7$: 596.3330].

Methyl *N*-{[(1-But-3-en-1-ylcyclopentyl)methoxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)-carbonyl]oxy}-L-prolinate (33e). Using the above procedure for **27a** with *N*-{[(1-but-3-en-1-ylcyclopentyl)methoxy]carbonyl}-3-methyl-L-valine (**32e**) provided **33e** (85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 8.5 Hz, 1 H), 7.27 (m, 1 H), 7.17−7.08 (2 × d, J = 7.0 Hz, 1 H), 6.65 (dt, J = 17.5, 12.3 Hz, 1 H), 5.76 (m, 1 H), 5.69 (dd, J = 17.5, 5.5 Hz, 1 H), 5.38 (m, 2 H), 5.29 (m, 1 H), 4.96 (d, J = 17.0 Hz, 1 H), 4.89 (m, 2 H), 4.84−4.62 (m, 4 H), 4.24 (m, 1 H), 3.89 (m, 1 H), 3.76 (s, 3 H), 3.74 (m, 1 H), 3.35 (dd, J = 13.5, 10.5 Hz, 1 H), 2.52 (dd, J = 14.0, 8.0 Hz, 1 H), 2.22 (m, 1 H), 2.01 (m, 1 H), 1.88 (m, 1 H), 1.48 (m, 5 H), 1.34 (m, 3 H), 1.25 (m, 3 H), 1.05 (s, 9 H) ppm. HRMS (ESI) m/z 610.3511 [$(M + H)^+$; calcd for $C_{34}H_{48}N_3O_7$: 610.3487].

Methyl *N*-{[(1-But-3-en-1-ylcyclohexyl)methoxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)-carbonyl]oxy}-L-prolinate (33f). Using the above procedure for **27a** with *N*-{[(1-but-3-en-1-ylcyclohexyl)methoxy]carbonyl}-3-methyl-L-valine (**32f**) provided **33f** (76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 (t, J = 9.0 Hz, 1 H), 7.27 (m, 1 H), 7.18−7.09 (2 × d, J = 7.2 Hz, 1 H), 6.66 (dt, J = 17.5, 11.3 Hz, 1 H), 5.76 (m, 1 H), 5.69 (dd, J = 17.5, 4.0 Hz, 1 H), 5.40 (s, 1 H), 5.37 (dd, J = 11.3, 2.8 Hz, 1 H), 5.27 (d, J = 9.5 Hz, 1 H), 4.99−4.62 (m, 6 H), 4.25 (d, J = 10.0 Hz, 1 H), 4.21 (t, J = 11.8 Hz, 1 H), 3.90 (m, 2 H), 3.82 (dd, J = 10.8, 8.2 Hz, 1 H), 3.77 (s, 3 H), 3.41 (dd, J = 10.8, 5.8 Hz, 1 H), 2.52 (dd, J = 13.5, 8.0 Hz, 1 H), 2.22 (m, 1 H), 1.85 (m, 2 H), 1.32 (m, 9 H), 1.17 (m, 3 H), 1.05 (s, 9 H) ppm. HRMS (ESI) m/z 624.3631 [$(M + H)^+$; calcd for $C_{35}H_{50}N_3O_7$: 624.3643].

(3*R*,5*S*)-1-[(2*S*)-2-Cyclohexyl-2-({[(2,2-dimethylhex-5-en-1-yl)-oxy]carbonyl}amino)acetyl]-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (33g). Using the above procedure for **27a** with (2*S*)-cyclohexyl({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino)acetic acid (**32g**) provided **33g** (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43−7.35 (m, 1 H), 7.17 (d, J = 7.6 Hz, 1 H), 7.10 (d, J = 7.6 Hz, 1 H), 6.71−6.58 (m, 2 H), 5.82−5.65 (m, 4 H), 5.45−5.22 (m, 3 H), 5.01−4.82 (m, 2 H), 4.85−4.57 (m, 4 H), 4.28−4.17 (m, 2 H), 3.90 (m, 1 H), 3.82−3.68 (m, 3 H), 3.67 (dd, J=10.5, 4.4 Hz, 1 H), 3.39 (dd, J = 17.1, 10.4 Hz, 1 H), 2.53 (dd, J = 13.6, 8.0 Hz, 1 H), 2.28−2.16 (m, 1 H), 1.96−1.49 (m, 7 H), 1.25−0.82 (m, 6 H), 0.77 (d, J = 3.4 Hz, 6 H) ppm. HRMS (ESI) m/z 610.3481 [(M + H)$^+$; calcd for $C_{34}H_{48}N_3O_7$: 610.3487].

(3*R*,5*S*)-1-[(2*S*)-2-({[(2,2-Dimethylhex-5-en-1-yl)oxy]carbonyl}-amino)-2-(1-methylcyclohexyl)acetyl]-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (33h). Using the above procedure for **27a** with (2*S*)-({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino) (1-methylcyclohexyl)acetic acid (**32h**) provided **33h** (89% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 (t, J = 10.0 Hz, 1 H), 7.26 (m, 1 H), 7.18−7.08 (2 × d, J = 9.5 Hz, 1 H), 6.65 (2 × t, J = 14.7 Hz, 1 H), 5.76 (m, 1 H), 5.69 (2 × d, J = 4.5 Hz, 1 H), 5.37 (m, 2 H), 5.29 (d, J = 10.5 Hz, 1 H), 4.99−4.61 (m, 7 H), 4.25 (m, 2 H), 3.90 (m, 1 H), 3.77 (s, 3 H), 3.63 (m, 1 H), 3.28 (t, J = 14.3 Hz, 1 H), 2.51 (m, 1 H), 2.19 (m, 1 H), 1.88 (m, 2 H), 1.55 (s, 6 H), 1.47 (m, 7 H), 1.18 (m, 2 H), 1.05 (s, 2 H), 0.74 (m, 4 H) ppm. HRMS (ESI) m/z 624.3686 [(M + H)$^+$; calcd for $C_{35}H_{50}N_3O_7$: 624.3643].

Methyl *O*-(*tert*-Butyl)-*N*-{[(2,2-dimethylhex-5-en-1-yl)oxy]-carbonyl}-L-seryl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)-carbonyl]oxy}-L-prolinate (33i). Using the above procedure for **27a** with *O*-(*tert*-butyl)-*N*-{[(2,2-dimethylhex-5-en-1-yl)oxy]-carbonyl}-L-serine (**32i**) provided **33i** (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42−7.35 (m, 1 H), 7.30−7.35 (m, 1 H), 7.20−7.05 (m, 1 H), 6.72−6.57 (m, 1 H), 5.84−5.65 (m, 2 H), 5.50 (m, 1 H), 5.44−5.33 (m, 2 H), 5.05−4.87 (m, 2 H), 4.80 (br s, 1 H), 4.76−4.53 (m, 5 H), 4.10−3.91 (m, 1 H), 3.83−3.68 (m, 5 H), 3.64−3.55 (m, 2 H), 3.55−3.37 (m, 1 H), 2.53−2.41 (m, 1 H), 2.31−2.19 (m, 1 H), 2.04−1.90 (m, 2 H), 1.37−1.29 (m, 1 H), 1.22−1.13 (m, 9 H), 1.09 (s, 1 H), 1.00−0.73 (m, 6 H) ppm. HRMS (ESI) m/z 614.3448 [(M + H)$^+$; calcd for $C_{33}H_{48}N_3O_8$: 614.3436].

Methyl (1*R*,12*E*,21*S*,24*S*)-21-*tert*-Butyl-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]-heptacosa-6,8,10,12-tetraene-24-carboxylate (34b). A solution of methyl *N*-{[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)-carbonyl]oxy}-L-prolinate (**33b**) (4.70 g, 8.05 mmol) in CH_2Cl_2 (1.4 L) was degassed with nitrogen for 15 min. Zhan 1b catalyst[22] (0.59 g, 0.81 mmol) was added, and the mixture was stirred at RT under a nitrogen atmosphere for 19 h. The reaction was complete, DMSO (57 μL, 0.805 mmol) was added, and the mixture was stirred for 2 h and concentrated. The crude product was then directly purified by silica gel chromatography (gradient elution, 0−50% EtOAc in hexanes) to yield **34b** (4.40 g, 98% yield) as a light-green oil. ^{1}H NMR (400 MHz, CD_3OD) δ 7.25−7.12 (m, 3 H), 6.79 (d, J = 9.2 Hz, 1 H), 6.33 (d, J = 16.0 Hz, 1 H), 6.05−5.99 (m, 1 H), 5.31−5.29 (m, 1 H), 4.72−4.55 (m, 6 H), 4.47 (d, J = 9.6 Hz, 1 H), 4.20−4.17 (m, 1 H), 3.89 (dd, J = 12.0, 3.6 Hz, 1 H), 3.72 (s, 3 H), 3.35 (d, J = 10.8 Hz, 1 H), 2.71−2.66 (m, 1 H), 2.30−2.10 (m, 3 H), 1.44−1.28 (m, 2 H), 1.06 (s, 9 H), 1.03 (s, 3 H), 0.89 (s, 3 H) ppm. HRMS (ESI) m/z 556.3023 [(M + H)$^+$; calcd for $C_{30}H_{42}N_3O_7$: 556.3018]. Anal. ($C_{30}H_{41}N_3O_7 \cdot 0.7\ H_2O$) C, H, N.

Methyl (1′*R*,12′*E*,21′*S*,24′*S*)-21′-*tert*-Butyl-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclopropane-1,16′-tetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′,12′-tetraene-24′-carboxylate (34c). Using the above procedure for **28a** with methyl *N*-{[(1-but-3-en-1-ylcyclopropyl)methoxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]-oxy}-L-prolinate (**33c**) provided **34c** (78% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.25 (t, J=7.7 Hz, 1 H), 7.17 (d, J=7.5 Hz, 1 H), 7.15 (d, J = 7.0 Hz, 1 H), 6.42 (d, J = 16.0 Hz, 1 H), 6.04 (dt, J = 16.0, 7.3 Hz, 1 H), 5.36 (t, J = 3.8 Hz, 1 H), 5.06 (d, J = 11.0 Hz, 1 H), 4.89 (d, J = 15.0 Hz, 1 H), 4.68 (m, 3 H), 4.61 (dd, J = 10.3, 7.8 Hz, 1 H), 4.42 (s, 1 H), 4.26 (d, J = 12.5 Hz, 1 H), 3.89 (dd, J = 12.3, 3.8 Hz, 1 H), 3.73 (s, 3 H), 3.05 (d, J = 11.0 Hz, 1 H), 2.70 (dd, J = 14.0, 7.5 Hz, 1 H), 2.40 (m, 1 H), 2.21 (m, 2 H), 1.84 (m, 1 H), 1.29 (s, 1 H), 1.11 (m, 1 H), 1.07 (s, 9 H), 0.90 (m, 1 H), 0.51 (m, 1 H), 0.43 (m, 2 H) ppm. HRMS (ESI) m/z 554.2881 [(M + H)$^+$; calcd for $C_{30}H_{40}N_3O_7$: 554.2861].

Methyl (1′*R*,12′*E*,21′*S*,24′*S*)-21′-*tert*-Butyl-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclobutane-1,16′-tetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′,12′-tetraene-24′-carboxylate (34d). Using the above procedure for **28a** with methyl *N*-{[(1-but-3-en-1-ylcyclobutyl)methoxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]-oxy}-L-prolinate (**33d**) provided **34d** (87% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (t, J = 7.8 Hz, 1 H), 7.16 (d, J = 7.5 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 6.32 (d, J = 16.5 Hz, 1 H), 5.93 (dt, J = 16.0, 6.8 Hz, 1 H), 5.54 (d, J = 9.5 Hz, 1 H), 5.32 (t, J = 3.7 Hz, 1 H), 4.76- 4.56 (m, 6 H), 4.40 (d, J = 9.5 Hz, 1 H), 4.15 (d, J = 11.5 Hz, 1 H), 3.83 (dd, J = 12.0, 3.5 Hz, 1 H), 3.76 (s, 3 H), 3.72 (d, J = 11.5 Hz, 1 H), 2.75 (dd, J = 14.8, 7.8 Hz, 1 H), 2.28 (sept, J = 7.1 Hz, 1 H), 2.17 (m, 2 H), 2.00 (m, 1 H), 1.86 (s, 4 H), 1.65 (m, 1 H), 1.51 (t, J = 8.2 Hz, 2 H), 1.07 (s, 9 H) ppm. HRMS (ESI) m/z 568.3040 [(M+H)$^+$; calcd for $C_{31}H_{42}N_3O_7$: 568.3017].

Methyl (1′*R*,12′*E*,21′*S*,24′*S*)-21′-*tert*-Butyl-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclopentane-1,16′-tetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′,12′-tetraene-24′-carboxylate (34e). Using the above procedure for **28a** with methyl *N*-{[(1-but-3-en-1-ylcyclopentyl)methoxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]-oxy}-L-prolinate (**33e**) provided **34e** (81% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.24 (t, J=7.5 Hz, 1 H), 7.17 (d, J=7.5 Hz, 1 H), 7.14 (d, J=7.5 Hz, 1 H), 6.37 (d, J=16.0 Hz, 1 H), 5.98 (dt, J = 16.0, 6.9 Hz, 1 H), 5.29 (t, J = 3.7 Hz, 1 H), 4.76 (d, J = 15.0 Hz, 1 H), 4.65 (m, 4 H), 4.58 (dd, J = 10.3, 7.7 Hz, 1 H), 4.46 (s, 1 H), 4.22 (dd, J = 12.0, 1.5 Hz, 1 H), 3.89 (dd, J = 12.3, 3.8 Hz, 1 H), 3.72 (s, 3 H), 3.45 (d, J = 11.0 Hz, 1 H), 2.71 (dd, J = 14.3, 7.8 Hz, 1 H), 2.32 (m, 1 H), 2.17 (m, 2 H), 1.82 (m, 1 H), 1.66 (m, 4 H), 1.52 (m, 2 H), 1.41 (m, 2 H), 1.29 (m, 2 H), 1.06 (s, 9 H) ppm. HRMS (ESI) m/z 582.3195 [(M + H)$^+$; calcd for $C_{32}H_{44}N_3O_7$: 582.3174].

Methyl (1′*R*,12′*E*,21′*S*,24′*S*)-21′-*tert*-Butyl-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclohexane-1,16′-tetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′,12′-tetraene-24′-carboxylate (34f). Using the above procedure for **28a** with methyl *N*-{[(1-but-3-en-1-ylcyclohexyl)methoxy]carbonyl}-3-methyl-L-valyl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (**33f**) provided **34f** (86% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.24 (t, J=7.7 Hz, 1 H), 7.15 (d, J=6.5 Hz, 1 H), 7.14 (d, J=6.0 Hz, 1 H), 6.39 (d, J=16.0 Hz, 1 H), 5.91 (m, 1 H), 5.27 (t, J=3.5 Hz, 1 H), 4.78 (m, 1 H), 4.66 (m, 3 H), 4.58 (d, J=11.0 Hz, 2 H), 4.47 (s, 1 H), 4.23 (d, J = 12.0 Hz, 1 H), 3.88 (dd, J = 12.0, 3.5 Hz, 1 H), 3.72 (s, 3 H), 3.58 (d, J = 11.0 Hz, 1 H), 2.73 (dd, J=14.2, 8.2 Hz, 1 H), 2.29 (m, 1 H), 2.20 (m, 1 H), 2.09 (m, 1 H), 1.47 (m, 9 H), 1.24 (m, 3 H), 1.06 (s, 9 H) ppm. HRMS (ESI) m/z 596.3304 [(M + H)$^+$; calcd for $C_{33}H_{46}N_3O_7$: 596.3331].

Methyl (1*R*,12*E*,21*S*,24*S*)-21-Cyclohexyl-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]-heptacosa-6,8,10,12-tetraene-24-carboxylate (34g). Using the above procedure for **28a** with (3*R*,5*S*)-1-[(2*S*)-2-cyclohexyl-2-({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino)acetyl]-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (**33g**) provided **34g** (65% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26−7.06 (m, 3 H), 6.32−6.20 (m, 1 H), 6.00−5.88 (m, 1 H), 5.54 (d, J=8.9 Hz, 1 H), 5.34−5.25 (m, 1 H), 4.74−4.42 (m, 7 H), 4.18−4.06 (m, 2 H), 3.82

(dd, J = 11.6, 3.5 Hz, 1 H), 3.76 (s, 3 H), 3.37−3.25 (m, 1 H), 2.76 (dd, J = 14.4, 7.7 Hz, 1 H), 2.30−2.10 (m, 3 H), 1.94−1.83 (m, 1 H), 1.85−1.64 (m, 4 H), 1.36−1.19 (m, 5 H), 1.24−1.01 (m, 4 H), 0.98 (s, 2 H), 0.86 (s, 2 H) ppm. HRMS (ESI) m/z 582.3187 [(M + H)$^+$; calcd for $C_{32}H_{44}N_3O_7$: 582.3174].

Methyl (1*R*,12*E*,21*S*,24*S*)-16,16-Dimethyl-21-(1-methylcyclohexyl)-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxylate (34h). Using the above procedure for **28a** with (3*R*,5*S*)-1-[(2*S*)-2-({[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}amino)-2-(1-methylcyclohexyl)acetyl]-5-(methoxycarbonyl)pyrrolidin-3-yl 4-vinyl-1,3-dihydro-2*H*-isoindole-2-carboxylate (**33h**) provided **34h** (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, J = 9.5 Hz, 1 H), 7.16 (d, J = 9.5 Hz, 1 H), 7.10 (d, J = 9.5 Hz, 1 H), 6.28 (d, J = 20.5 Hz, 1 H), 5.95 (dt, J = 20.0, 7.9 Hz, 1 H), 5.57 (d, J = 12.0 Hz, 1 H), 5.31 (t, J = 4.5 Hz, 1 H), 4.72−4.56 (m, 5 H), 4.41 (d, J = 12.0 Hz, 1 H), 4.13 (m, 1 H), 3.87 (dd, J = 14.8, 4.8 Hz, 1 H), 3.76 (s, 3 H), 3.29 (d, J = 13.5 Hz, 1 H), 2.73 (dd, J = 17.7, 9.2 Hz, 1 H), 2.16 (m, 3 H), 1.62 (m, 1 H), 1.57 (s, 6 H), 1.48−1.31 (m, 6 H), 1.05 (s, 3 H), 0.99 (s, 3 H), 0.86 (s, 3 H) ppm. HRMS (ESI) m/z 596.3323 [(M + H)$^+$; calcd for $C_{33}H_{46}N_3O_7$: 596.3330].

Methyl (1*R*,12*E*,21*S*,24*S*)-21-(*tert*-Butoxymethyl)-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxylate (34i). Using the above procedure for **28a** with methyl *O*-(*tert*-butyl)-*N*-{[(2,2-dimethylhex-5-en-1-yl)oxy]carbonyl}-L-seryl-(4*R*)-4-{[(4-vinyl-1,3-dihydro-2*H*-isoindol-2-yl)carbonyl]oxy}-L-prolinate (**33i**) provided **34i** (88% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (m, 2 H), 7.10 (d, J = 7.1 Hz, 1 H), 6.23 (d, J = 16.1 Hz, 1 H), 6.01 (dt, J = 16.1, 6.1 Hz, 1 H), 5.66 (d, J = 8.2 Hz, 1 H), 5.29 (m, 1 H), 4.85−4.77 (m, 1 H), 4.79−4.47 (m, 3 H), 4.16−4.08 (m, 2 H), 3.82 (m, 1 H), 3.83−3.67 (m, 3 H), 3.66−3.55 (m, 1 H), 3.48 (t, J = 8.6 Hz, 1 H), 3.27 (d, J = 10.9 Hz, 1 H), 2.73 (dd, J = 14.6, 8.0 Hz, 1 H), 2.30−2.06 (m, 3 H), 1.20 (s, 9 H), 1.17 (s, 1 H), 0.98 (s, 3 H), 0.93−0.82 (m, 6 H) ppm. HRMS (ESI) m/z 586.3127 [(M + H)$^+$; calcd for $C_{31}H_{44}N_3O_8$: 586.3123].

(1*R*,21*S*,24*S*)-21-*tert*-Butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10-triene-24-carboxamide (35a). Using the above procedure for **31c** with methyl (1*R*,12*E*,21*S*,24*S*)-21-*tert*-butyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxylate (**28h**) provided **35a** (71% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.23 (t, J = 7.5 Hz, 1 H), 7.14 (d, J = 7.5 Hz, 1 H), 7.09 (d, J = 7.5 Hz, 1 H), 7.02 (d, J = 9.5 Hz, 1 H), 5.36 (s, 1 H), 4.71 (m, 3 H), 4.64 (m, 1 H), 4.56 (sext, J = 4.9 Hz, 1 H), 4.40 (m, 2 H), 4.24 (d, J = 11.5 Hz, 1 H), 3.96 (dd, J = 12.0, 3.5 Hz, 1 H), 3.72 (m, 1 H), 2.98 (sept, J = 4.2 Hz, 1 H), 2.58 (m, 1 H), 2.49 (m, 2 H), 2.15 (m, 1 H), 1.69−1.19 (m, 16 H), 1.09 (m, 2 H), 1.06 (s, 9 H), 0.98 (t, J = 7.0 Hz, 3 H) ppm. HRMS (ESI) m/z 730.3478 [(M + H)$^+$; calcd for $C_{36}H_{52}N_5O_9S$: 730.3480]. Anal. ($C_{36}H_{51}N_5O_9S\cdot H_2O$) C, H, N.

(1*R*,21*S*,24*S*)-21-*tert*-Butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]-heptacosa-6,8,10-triene-24-carboxamide (Vaniprevir, 35b). To a solution of methyl (1*R*,12*E*,21*S*,24*S*)-21-*tert*-butyl-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxylate (**34b**) (17.8 g, 32.0 mmol) in ethanol (EtOH) (800 mL) and EtOAc (160 mL) was added 10% Pd/C (1.7 g, 1.60 mmol). The reaction mixture was then placed under balloon pressure hydrogen and stirred for 18 h. The reaction mixture was filtered through celite, and the filtrate was concentrated to give methyl (1*R*,21*S*,24*S*)-21-*tert*-butyl-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10-triene-24-carboxylate (17.9 g), which was used with no further purification. LRMS (ESI) m/z 558.4 [(M + H)$^+$; calcd for $C_{30}H_{44}N_3O_7$: 558.3].

To a solution of the above ester (17.9 g, 32.0 mmol) in THF (300 mL), MeOH (75 mL), and water (150 mL) at RT was added $LiOH\cdot H_2O$ (13.4 g, 320 mmol). The reaction mixture was stirred at RT for 1 h, concentrated to half volume, and diluted with Et_2O. The layers were separated, and the aqueous layer was acidified with 2 N HCl and then extracted with EtOAc three times. The combined organic layer was dried over Na_2SO_4, filtered, and concentrated to yield (1*R*,21*S*,24*S*)-21-*tert*-butyl-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10-triene-24-carboxylic acid (17.4 g), which was used with no further purification. LRMS (ESI) m/z 544.4 [(M + H)$^+$; calcd for $C_{29}H_{42}N_3O_7$: 544.3].

To a solution of the above carboxylic acid (17.4 g, 32.0 mmol) and (1*R*,2*R*)-1-amino-*N*-(cyclopropylsulfonyl)-2-ethylcyclopropanecarboxamide hydrochloride (**30**)[28] (10.3 g, 38.4 mmol) in CH_2Cl_2 (800 mL) was added DIPEA (16.8 mL, 96 mmol), DMAP (0.08 g, 0.02 mmol), and HATU (14.6 g, 38.4 mmol). The reaction mixture was stirred at RT for 20 h and then concentrated and partitioned between EtOAc and 1 N HCl. The organic layer was washed with water and brine, dried over Na_2SO_4, and concentrated. The crude material was then purified by silica gel chromatography (gradient elution, 40−100% EtOAc in hexanes) to yield **35b** (22.1 g, 91% yield, 3 steps) as a white powder. ^{1}H NMR (500 MHz, ppm, CD_3OD) δ 9.07 (s, 1 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.14 (d, J = 7.5 Hz, 1 H), 7.09 (d, J = 7.0 Hz, 1 H), 5.53 (s, 1 H), 4.75−4.56 (m, 4 H), 4.44−4.36 (m, 3 H), 4.19 (d, J = 11.7 Hz, 1 H), 3.92 (dd, J = 11.8, 3.3 Hz, 1 H), 3.33−3.27 (m, 2 H), 2.99−2.96 (m, 1 H), 2.60−2.42 (m, 3 H), 2.17−2.08 (m, 1 H), 1.68−1.48 (m, 6 H), 1.37−1.16 (m, 8 H), 1.13−0.94 (m, 17 H), 0.80 (s, 3 H). HRMS (ESI) m/z 758.3844 [(M + H)$^+$; calcd for $C_{38}H_{56}N_5O_9S$: 758.3793]. Anal. ($C_{38}H_{55}N_5O_9S\cdot 0.55H_2O$) C, H, N.

(1′*R*,21′*S*,24′*S*)-21′-*tert*-Butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclopropane-1,16′-tetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′-triene-24′-carboxamide (35c). Using the above procedure for **35b** with methyl (1′*R*,12′*E*,21′*S*,24′*S*)-21′-*tert*-butyl-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclopropane-1,16′-tetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′,12′-tetraene-24′-carboxylate (**34c**) provided **35c** (73% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.21 (t, J = 7.5 Hz, 1 H), 7.14 (d, J = 7.6 Hz, 1 H), 7.06 (d, J = 7.6 Hz, 1 H), 7.05 (d, J = 9.8 Hz, 1 H), 5.36 (m, 1 H), 4.86 (m, 1 H), 4.75−4.59 (m, 4 H), 4.45 (m, 1 H), 4.36 (d, J = 9.5 Hz, 1 H), 4.22 (d, J = 11.2 Hz, 1 H), 3.90 (dd, J = 12.0, 3.4 Hz, 1 H), 2.97 (sept, J = 4.0 Hz, 1 H), 2.86 (d, J = 11.5 Hz, 1 H), 2.54 (m, 3 H), 2.14 (m, 1 H), 1.74 (m, 1 H), 1.64−1.52 (m, 6 H), 1.45−1.19 (m, 6 H), 1.11−0.89 (m, 14 H), 0.55 (m, 1 H), 0.36 (m, 1 H), 0.30 (m, 2 H) ppm. HRMS (ESI) m/z 756.3630 [(M + H)$^+$; calcd for $C_{38}H_{54}N_5O_9S$: 756.3637]. Anal. ($C_{38}H_{53}N_5O_9S\cdot H_2O$) C, H, N.

(1′*R*,21′*S*,24′*S*)-21′-*tert*-Butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclobutane-1,16′-tetracyclo-[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′-triene-24′-carboxamide (35d). Using the above procedure for **35b** with methyl (1′*R*,12′*E*,21′*S*,24′*S*)-21′-*tert*-butyl-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclobutane-1,16′-tetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′,12′-tetraene-24′-carboxylate (**34d**) provided **35d** (74% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.21 (t, J = 7.5 Hz, 1 H), 7.13 (d, J = 7.3 Hz, 1 H), 7.07 (d, J = 7.1 Hz, 1 H), 7.06 (d, J = 10.3 Hz, 1 H), 5.35 (m, 1 H), 4.71 (m, 1 H), 4.66−4.57 (m, 3 H), 4.44−4.33 (m, 3 H), 4.21 (d, J = 11.0 Hz, 1 H), 3.89 (dd, J = 11.7, 3.2 Hz, 1 H), 3.68 (d, J = 10.7 Hz, 1 H), 2.96 (sept, J = 4.3 Hz, 1 H), 2.54 (m, 3 H), 2.13 (m, 1 H), 2.04 (m, 1 H), 1.85 (m, 2 H), 1.76 (q, J = 8.8 Hz, 2 H), 1.65−1.39 (m, 9 H), 1.32−1.16 (m, 5 H), 1.12−0.87 (m, 14 H) ppm. HRMS (ESI) m/z 770.3807 [(M + H)$^+$; calcd for $C_{39}H_{56}N_5O_9S$: 770.3793]. Anal. ($C_{39}H_{55}N_5O_9S\cdot 0.75H_2O$) C, H, N.

(1′*R*,21′*S*,24′*S*)-21′-*tert*-Butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclopentane-1,16′-tetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′-triene-24′-carboxamide (35e). Using the above procedure for **35b** with methyl (1′*R*,12′*E*,21′*S*,24′*S*)-21′-*tert*-butyl-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclopentane-1,16′-tetracyclo[21.2.1.1^{4,7}.0^{6,11}]-heptacosane]-6′,8′,10′,12′-tetraene-24′-carboxylate (**34e**) provided **35e** (97% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 9.08 (s, 1 H), 7.23 (t, J = 7.3 Hz, 1 H), 7.15 (d, J = 7.3 Hz, 1 H), 7.09 (d, J = 7.1 Hz, 1 H), 5.36 (s, 1 H), 4.75−4.58 (m, 5 H), 4.43 (m, 2 H), 4.34 (d, J = 10.5 Hz, 1 H), 4.21 (d, J = 11.7 Hz, 1 H), 3.91 (d, J = 10.0 Hz, 1 H), 3.35 (m, 1 H), 2.98 (br s, 1 H), 2.59−2.49 (m, 3 H), 2.14 (m, 1 H), 1.82 (m, 1 H), 1.62−0.94 (m, 34 H) ppm. HRMS (ESI) m/z 784.3944 [(M + H)$^+$; calcd for $C_{40}H_{58}N_5O_9S$: 784.3950]. Anal. ($C_{40}H_{57}N_5O_9S\cdot 1.50H_2O$) C, H, N.

(1′*R*,21′*S*,24′*S*)-21′-*tert*-Butyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclohexane-1,16′-tetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosane]-6′,8′,10′-triene-24′-carboxamide (35f). Using the above procedure for **35b** with methyl (1′*R*,12′*E*,21′*S*,24′*S*)-21′-*tert*-butyl-3′,19′,22′-trioxo-2′,18′-dioxa-4′,20′,23′-triazaspiro[cyclohexane-1,16′-tetracyclo[21.2.1.1^{4,7}.0^{6,11}]-heptacosane]-6′,8′,10′,12′-tetraene-24′-carboxylate (**34f**) provided **35f** (81% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 7.22 (t, J = 7.4 Hz, 1 H), 7.14 (d, J = 7.6 Hz, 1 H), 7.08 (d, J = 8.1 Hz, 1 H), 5.34 (s, 1 H), 4.74−4.57 (m, 4 H), 4.43 (m, 2 H), 4.26−4.18 (m, 2 H), 3.90 (d, J = 9.3 Hz, 1 H), 3.53 (d, J = 10.8 Hz, 1 H), 2.98 (m, 1 H), 2.62−2.46 (m, 3 H), 2.13 (m, 1 H), 1.64 (m, 2 H), 1.56−1.36 (m, 12 H), 1.30−1.23 (m, 9 H), 1.09 (m, 3 H), 1.05 (s, 9 H), 0.97 (m, 4 H) ppm. HRMS (ESI) m/z 798.4089 [(M + H)$^+$; calcd for $C_{41}H_{60}N_5O_9S$: 798.4106]. Anal. ($C_{41}H_{59}N_5O_9S\cdot H_2O$) C, H, N.

(1*R*,21*S*,24*S*)-21-Cyclohexyl-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]-heptacosa-6,8,10-triene-24-carboxamide (35g). Using the above procedure for **35b** with methyl (1*R*,12*E*,21*S*,24*S*)-21-cyclohexyl-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxylate (**34g**) provided **35g** (83% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.13 (s, 1 H), 7.22 (t, J = 7.5 Hz, 1 H), 7.10 (d, J = 7.5 Hz, 1 H), 7.05 (d, J = 7.5 Hz, 1 H), 6.73 (s, 1 H), 5.40 (d, J = 9.5 Hz, 1 H), 5.36 (m, 1 H), 4.67−4.76 (m, 2 H), 4.55 (d, J = 15.5 Hz, 1 H), 4.44 (d, J = 14.5 Hz, 1 H), 4.41 (d, J = 11.0 Hz, 1 H), 4.29−4.39 (m, 2 H), 4.16 (d, J = 11.0 Hz, 1 H), 3.85−3.82 (dd, J = 11.5, 3.5 Hz, 1 H), 3.25 (d, J = 11.0 Hz, 1 H), 2.95 (m, 1 H), 2.59−2.51 (m, 2 H), 2.44−2.36 (m, 2 H), 1.76−1.00 (m, 26 H), 0.99−0.90 (m, 6 H), 0.79 (br s, 3 H) ppm. HRMS (ESI) m/z 784.3950 [(M + H)$^+$; calcd for $C_{40}H_{58}N_5O_9S$: 784.3911].

(1*R*,21*S*,24*S*)-*N*-((1*R*,2*R*)-1-{[(Cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-16,16-dimethyl-21-(1-methylcyclohexyl)-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10-triene-24-carboxamide (35h). Using the above procedure for **35b** with methyl (1*R*,12*E*,21*S*,24*S*)-16,16-dimethyl-21-(1-methylcyclohexyl)-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxylate (**34h**) provided **35h** (79% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.97 (s, 1 H), 7.22 (m, 1 H), 7.09 (d, J = 7.5 Hz, 1 H), 7.06 (d, J = 7.3 Hz, 1 H), 6.70 (s, 1 H), 5.52 (d, J = 9.7 Hz, 1 H), 5.34 (m, 1 H), 4.72 (m, 2 H), 4.51−4.38 (m, 3 H), 4.31 (m, 1 H), 4.18 (d, J = 12.0 Hz, 1 H), 3.87 (dd, J = 11.8, 3.4 Hz, 1 H), 3.48 (q, J = 7.0 Hz, 2 H), 3.25 (d, J = 10.7 Hz, 1 H), 2.93 (m, 1 H), 2.63−2.50 (m, 2 H), 2.47−2.28 (m, 2 H), 1.64−1.33 (m, 13 H), 1.32−1.14 (m, 3 H), 1.11−1.08 (m, 11 H), 1.06 (s, 3 H), 0.96 (s, 3 H), 0.79 (s, 3 H) ppm. HRMS (ESI) m/z 798.4129 [(M + H)$^+$; calcd for $C_{41}H_{60}N_5O_9S$: 798.4106]. Anal. ($C_{41}H_{59}N_5O_9S\cdot H_2O$) C, H, N.

(1*R*,21*S*,24*S*)-21-(*tert*-Butoxymethyl)-*N*-((1*R*,2*R*)-1-{[(cyclopropylsulfonyl)amino]carbonyl}-2-ethylcyclopropyl)-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]-heptacosa-6,8,10-triene-24-carboxamide (35i). Using the above procedure for **35b** with methyl (1*R*,12*E*,21*S*,24*S*)-21-(*tert*-butoxymethyl)-16,16-dimethyl-3,19,22-trioxo-2,18-dioxa-4,20,23-triazatetracyclo[21.2.1.1^{4,7}.0^{6,11}]heptacosa-6,8,10,12-tetraene-24-carboxylate (**34i**) provided **35i** (76% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 1 H), 7.20 (t, J = 7.5 Hz, 1 H), 7.10 (d, J = 8.0 Hz, 1 H), 7.05 (d, J = 8.5 Hz, 1 H), 6.82 (s, 1 H), 5.75 (m, 1 H), 5.54 (d, J = 9.5 Hz, 1 H), 5.31 (m, 1 H), 5.20−5.10 (m, 1 H), 4.80 (m, 1 H), 4.68−7.76 (m, 2 H), 4.45−4.56 (m, 4 H), 4.17 (d, J = 11.5 Hz, 1 H), 3.78 (m, 1 H), 3.68−3.70 (m, 1 H), 3.58 (t, J = 9.0 Hz, 1 H), 3.25 (d, J = 11.0 Hz, 1 H), 2.95−2.98 (m, 1 H), 2.71−2.75 (m, 1 H), 2.49−2.51 (m, 1 H), 2.37−2.42 (m, 1 H), 1.64−1.71 (m, 3 H), 1.54 (s, 9 H), 1.45−1.33 (m, 3 H), 1.26−1.33 (m, 5 H), 1.20 (s, 6 H), 1.00 (t, J = 7.0 Hz, 2 H), 0.96 (s, 2 H), 0.80 (br s, 2 H) ppm. HRMS (ESI) m/z 788.4011 [(M + H)$^+$; calcd for $C_{39}H_{58}N_5O_{10}S$: 788.3860].

Acknowledgment. We thank Dr. Charles W. Ross, III, and Joan S. Murphy for determination of high-resolution mass spectra, and Sandor L. Varga for interpretation of NMR spectral data.

Supporting Information Available: ^{1}H NMR spectra and elemental analysis data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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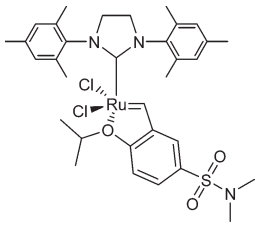

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