Synthesis of Macrolide Analogues of Sanglifehrin by RCM: Unique Reactivity of a Ruthenium Carbene Complex Bearing an Imidazol-2-ylidene Ligand

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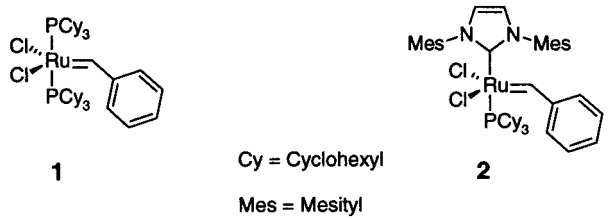
Introduction

Sanglifehrin A (SFA) was isolated from *Streptomyces flaveolus* in 1995 by scientists at Novartis.[1] The compound is a potent immunosuppressant and has a remarkably high affinity for an intracellular binding protein called cyclophilin ($IC_{50} = 2-4$ nM). Degradation studies on sanglifehrin and X-ray analysis of the cyclophilin−sanglifehrin complex showed that the binding was essentially mediated through the 22-membered macrolide.[2] To clarify the importance of the various functionalities attached to the macrocyclic core, we embarked on the synthesis of a series of simplified analogues containing the tripeptide fragment as well as an alkene or a conjugated 1,3-diene (Figure 1).

A retrosynthetic analysis shows that the macrocyclic core can be approached via different routes including macrolactonization, macrolactamization, or Stille coupling. The latter has been used successfully in the total synthesis of sanglifehrin A.[3] Early on, we considered the ring-closing metathesis (RCM) reaction as a convergent and flexible route to construct these unsaturated macrocyclic structures.[4] The approach was successful using Grubbs's ruthenium catalyst **1**, and we demonstrated for the first time that macrolides containing a conjugated 1,3-diene system can be obtained directly by RCM.[5] More recently, this methodology was shown to be extendable to the synthesis of other natural products, namely asteriscanolide and griseoviridin.[6,7] Even though catalyst **1** exhibits a remarkably wide scope and excellent compatibility with a range of functional groups, it is very sensitive toward the substitution pattern on the alkene. Tri- and tetrasubstituted alkenes cannot be formed by using catalyst **1**. This gap promises to be filled by a new generation of ruthenium catalysts bearing *one* bulky imidazol-2-ylidene ligand. Among these new catalysts, complex **2** has been most widely used.[8] This reagent allows the formation of tri- and tetrasubstituted cycloalkenes while retaining excellent stability toward heat and moisture.[9] These very interesting properties combined with its user-friendly character prompted us to test **2** on our system.



Herein, a detailed account of the synthesis of unsaturated sanglifehrin macrolide analogues by RCM in high yields is described. The methodology provides an efficient and convergent route toward macrolides containing either an alkene or a conjugated 1,3-diene. Additionally, an unexpected difference in reactivity between catalysts **1** and **2** with regard to conjugated dienes was observed.

Results and Discussion

The synthesis of the precursors for the RCM reaction is shown in Scheme 1. Two separate series of structures are described, each containing one unnatural amino acid: hexahydropyridazine-3-carboxylic acid (piperazic acid, Piz) or piperidine-3-carboxylic acid (nipecotic acid, Nip). The fully protected piperazic acid derivative **3** was obtained in an optically pure form and on a multigram scale according to the procedure published by Hale et al.[10] On the other hand, resolution of racemic nipecotic acid ethyl ester was achieved by recrystallization with tartaric acid.[11] With the protected unnatural amino acids **3** and **4** in our hands, the tripeptides **6a**,**b** were assembled by using carbodiimide-based coupling procedures. In the case of **5b**, preactivation of the carboxylic acid by the

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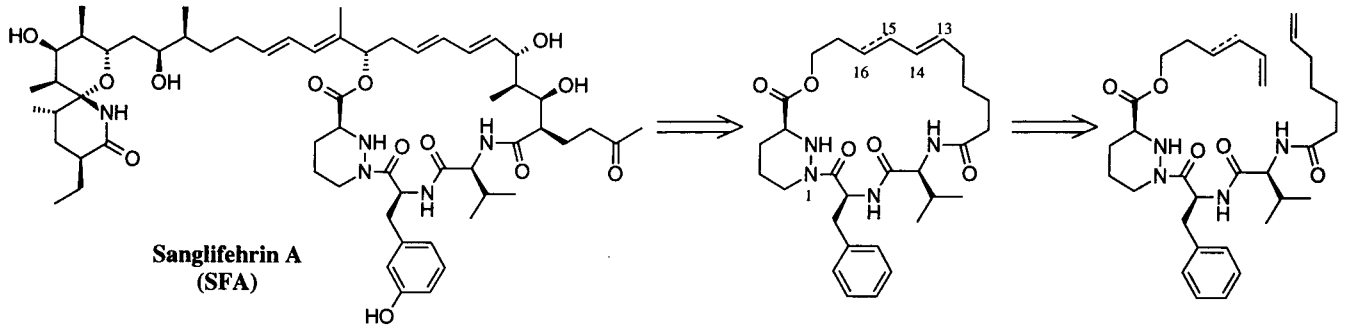
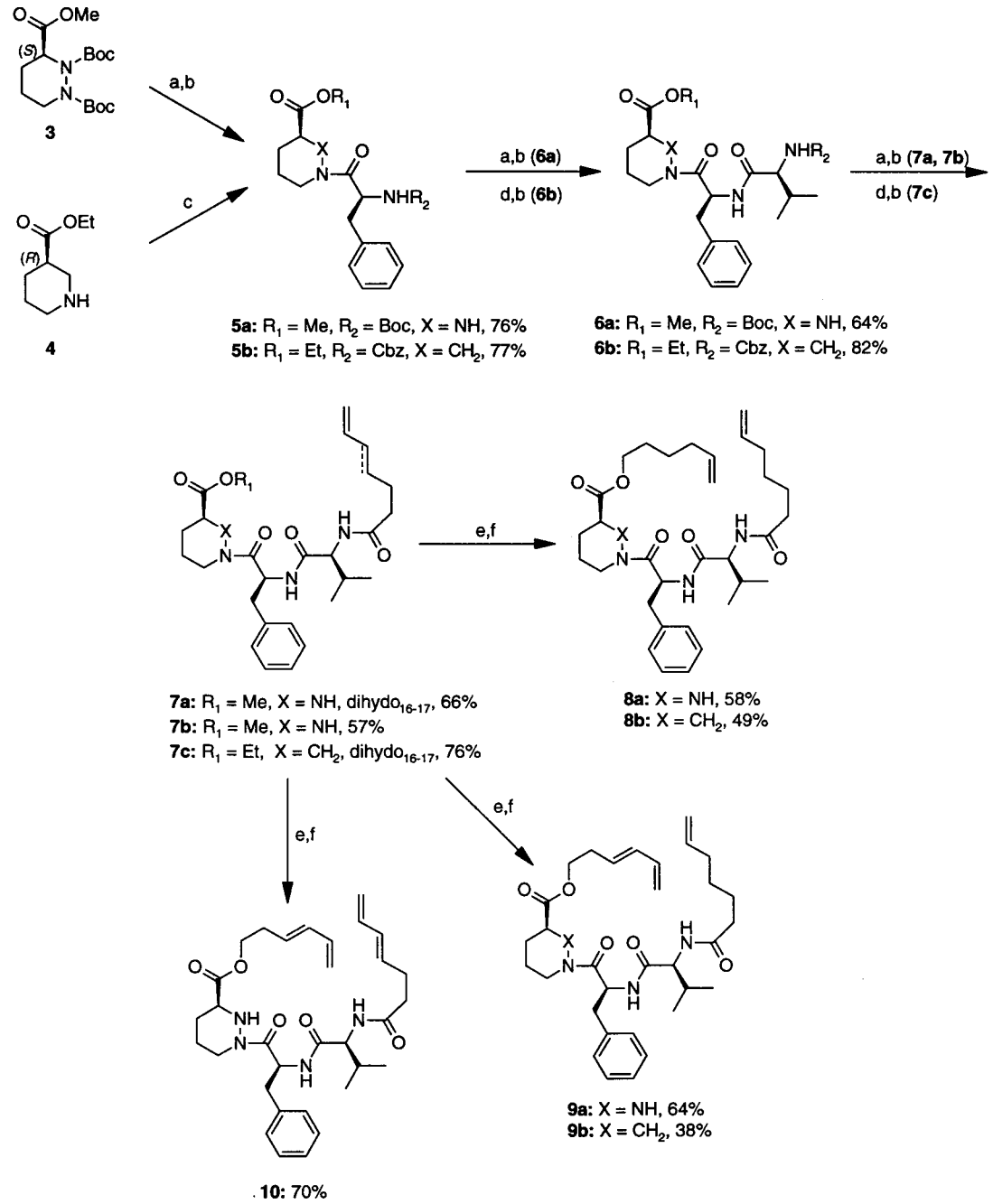


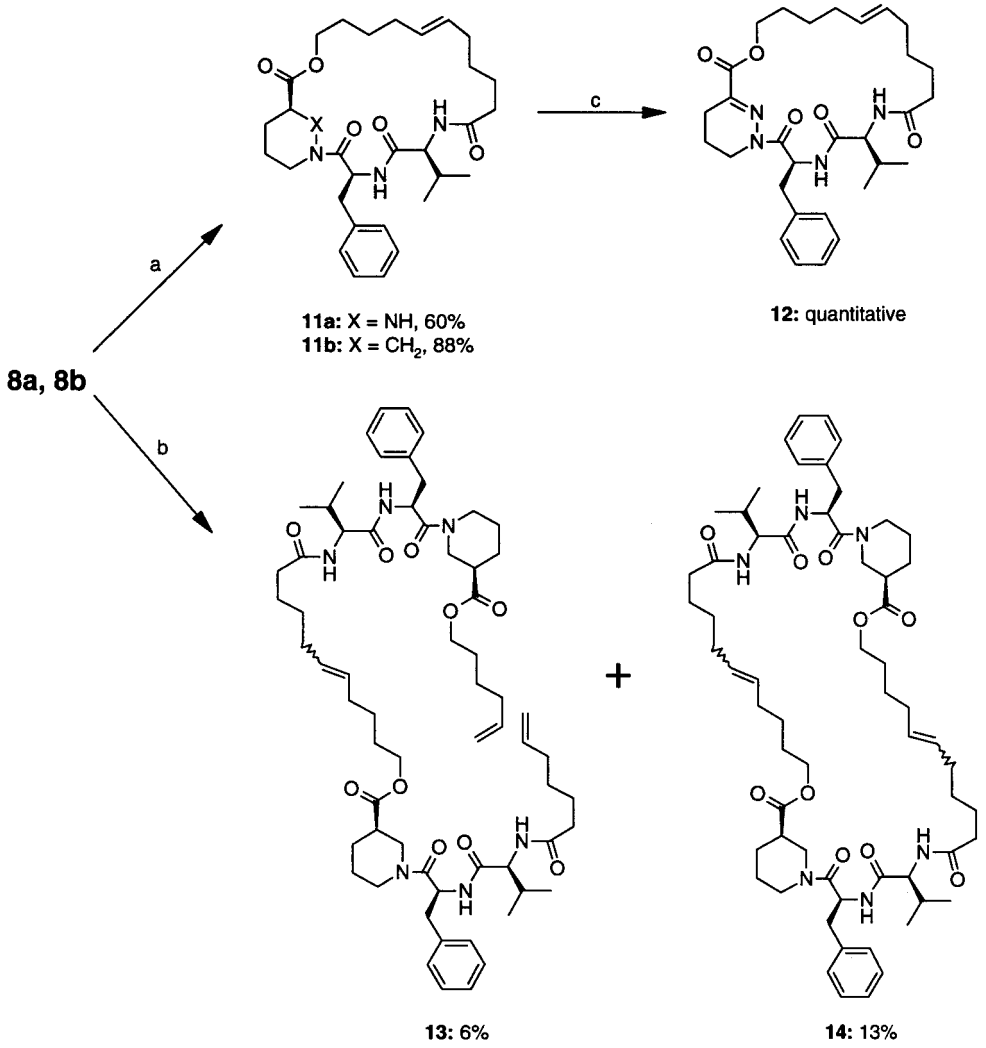
Figure 1.

Scheme 1[a]



[a] (a) TFA, CH_2Cl_2; (b) EDC, HOBT, NMM, RCO_2H (Boc-L-XX-OH, Cbz-L-XX-OH, 6-heptenoic acid or 4,6-heptadienoic acid), CH_2Cl_2; (c) NMM, isobutyl chloroformate, Cbz-L-Phe-OH, THF; (d) Pd/C, H_2, EtOH; (e) LiOH, THF/H_2O; (f) Ph_3P, DEAD, hexen-5-ol-1 or hexadien-3,5-ol-1, THF.

Scheme 2[a]



[a] (a) Catalyst **1** (0.15 equiv), CH_2Cl_2, concentration: 6 mM, reflux; (b) catalyst **1** (0.15 equiv), CH_2Cl_2, concentration: 40 mM, reflux; (c) air.

anhydride method was required for coupling the less reactive nipecotic acid derivative **4** in good yield.

In the next step, the N-terminus of the tripeptide was coupled to 6-heptenoic acid or 4,6-heptadienoic acid to afford **7a**−**c**.[12] Modification of the N-terminus had to be performed first, because partial isomerization of the diene moiety in **9a**,**b** occurred under the acidic Boc-cleavage conditions. Finally, saponification of the methyl ester of **7a**−**c** provided the corresponding acids, which were esterified with 5-hexenol or 3,5-hexadien-1-ol under Mitsunobu conditions.[13] Similar yields of the esterification could be obtained using DCC and DMAP, but in this case a careful removal of the urea side-product was important to avoid deactivation of the ruthenium catalyst in the following step. The metathesis precursors **8a**, **8b**, **9a**, **9b**, and **10** for the RCM reaction were thus obtained in good overall yield (11−33%) and allowed the study of the formation of 22-membered macrolides containing an alkene, a conjugated diene, or a triene unit.

The results of the RCM leading to macrolides containing an isolated double bond are summarized in Scheme 2. Under dilute conditions (<5 mM), the macrocycles **11a**,**b** were obtained using Grubbs's ruthenium catalyst **1** in refluxing CH_2Cl_2 in excellent yields after HPLC purification. Other solvents, e.g., benzene and toluene, gave lower yields. The configuration of the newly formed double bond was predominantly trans as assessed by IR (absorption band at 971 cm^{-1}) and ^1H NMR in benzene-d_6 (J_{13-14} = 15.5 Hz). In both cases, approximately 5% of the cis isomer could be detected by ^1H NMR and/or HPLC. To our surprise, the unprotected α nitrogen in the piperazic acid ring **8a** did not affect the rate of the RCM, even though the ruthenium catalysts are known to be highly sensitive to free nitrogen groups. The nitrogen atom is either sterically hindered or involved in a strong intramolecular hydrogen bond, which prevents interaction with the catalyst. This explanation is supported by the fact that attempts to use a monoprotected piperazic acid ester in a cross-metathesis reaction failed, whereas the reaction with the corresponding diprotected substrate succeeded. Compound **11a** is unstable and is slowly oxidized to **12** in the presence of oxygen even at low temperatures (−18 °C). This stands in sharp contrast to the stability of the parent molecule,

(12) 4,6-Heptadienoic acid was prepared according to: Hudlicky, T.; Koszyk, F. J.; Kutchan, T. M.; Sheth, J. P. *J. Org. Chem.* **1980**, *45*, 5020.

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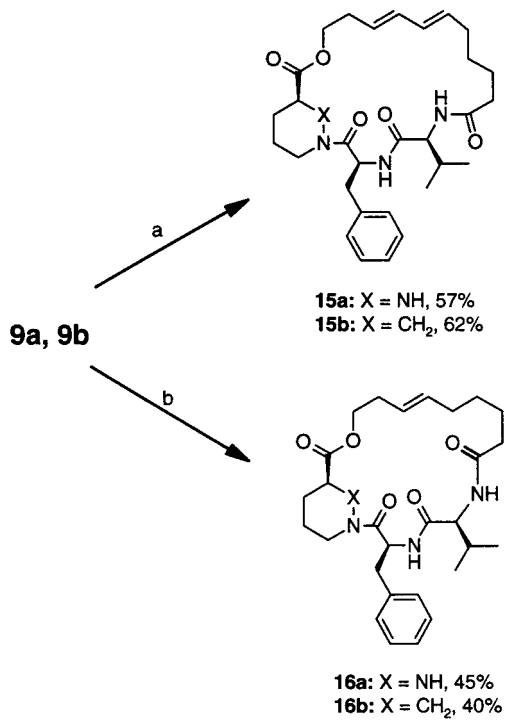
Scheme 3[a]



[a] (a) Catalyst **1** (0.15 equiv), CH_2Cl_2, reflux; (b) catalyst **2** (0.15 equiv), CH_2Cl_2, reflux.

sanglifehrin A, under the same conditions. Performing the RCM at higher concentrations (>40 mM) yielded two dimeric products, **13** and **14**, in low yield without cis/trans selectivity as revealed by ^{1}H NMR.

Scheme 3 shows the results of the RCM leading to macrolides containing a conjugated 1,3-diene system. Surprisingly, catalysts **1** and **2** displayed a very different reactivity toward the diene. Using Grubbs's ruthenium catalyst **1**, the desired *E*,*E*-dienes **15a**,**b** were formed in excellent yields of 57% and 62%, respectively. Best results were obtained under conditions (dilution, solvent, temperature) similar to those described for **11a**,**b**. The *E*,*Z* isomer was present as a minor component (<5%), but we could not detect any product resulting from metathesis of the internal diene double bond. On the other hand, the new ruthenium catalyst **2** showed the opposite selectivity, reacting preferentially with the internal diene double bond of **9a**,**b** to give **16a**,**b** as the major products in 45% and 40% yield, respectively. In this case, the dienes **15a**,**b** represented ~10% of the crude mixture as determined by HPLC analysis. Again, in both cases the trans alkene was formed predominantly as determined by IR (absorption band at 970 cm^{-1}) and ^{1}H NMR in pyridine-d_5 (J_{13-14} = 15.4 Hz). The product distribution was not affected by running the reaction at a higher temperature (reflux in 1,2-dichloroethane).

Finally, the possibility of forming a conjugated triene system directly was tested by submitting precursor **10** to the same RCM conditions in the presence of catalyst **1**. The sluggish reaction resulted in a complex mixture of products. HPLC-MS confirmed that the desired triene (MW = 536.68) had been formed in small amounts along with several peaks (MW = 510.64) corresponding to various isomeric dienes. Further experimentation would be needed to transform the latter results into an experimentally useful protocol for the synthesis of conjugated trienes.

Conclusion

Simplified macrolide analogues of sanglifehrin could be prepared in excellent yields via a convergent and flexible route. The crucial step was the RCM reaction, which lead selectively to 22-membered macrocycles containing either *E*-alkenes (**11a**,**b**) or conjugated *E*,*E*-dienes (**15a**,**b**). The attempt to form *E*,*E*,*E*-trienes was not successful. In the case of the diene formation, the reactivity of the two ruthenium catalysts **1** and **2** was compared. Surprisingly, the catalysts had opposite selectivity with respect to the double bond of the initial diene undergoing metathesis. Catalyst **1** reacted selectively with the less sterically hindered terminal double bond, whereas catalyst **2**, bearing an imidazol-2-ylidene ligand, predominantly reacted with the more substituted, electron-rich internal double. One explanation could be that the higher reactivity of catalyst **2** counterbalances the steric effect, resulting in a preferential attack of the electron-richer internal double bond of the diene.

Experimental Section

General Methods. All reactions were monitored by TLC carried out on glass plates precoated (0.25 mm) with silica gel 60 F_{254}. Materials were detected by visualization under a UV lamp (254 nm) and/or using molybdenum solution followed by heat as developing agent. Flash column chromatography (FCC) was performed with Merck silica gel 60 (230−400 mesh). All mixed solvent systems are reported as v/v solutions. The purity of the compounds was analyzed by reverse-phase HPLC using the following conditions: C18 column; 10 min linear gradient followed by 5 min isocratic; elution 30−100% (H_2O/CH_3CN (1:9) in H_2O/CH_3CN (9:1)); flow rate 1.5 mL/min. The retention time (rt) is indicated in min. All reagents were purchased at highest commercial quality and used without further purification.

General Procedures for Deprotection/Coupling Reactions

Method A: (*tert*-Butoxycarbonyl)-L-phenylalanine-hexahydropyridazine-3*S*-carboxylic Acid Methyl Ester (5a). *N*,*N*′-Bis(*tert*-butoxycarbonyl)-hexahydro-pyridazine-3*S*-carboxylic acid methyl ester **3** (41.7 g, 0.12 mol) was dissolved in CH_2Cl_2 (500 mL) and cooled to 0 °C. Trifluoroacetic acid (70 mL) was added dropwise, and the mixture was stirred for 2 h at room temperature. All volatile materials were evaporated under high vacuum, and the residue was redissolved in CH_2Cl_2 (500 mL). To this solution were added *N*-methylmorpholine (61.2 g, 0.6 mol), EDC (25.0 g, 0.13 mol), HOBT (24.5 g, 0.18 mol), and Boc-L-Phe-OH (35.3 g, 0.13 mol). The mixture was stirred overnight. The reaction was diluted with CH_2Cl_2 (500 mL) and washed with 1.0 M aqueous tartaric acid (2 × 200 mL), 1.0 M aqueous $NaHCO_3$ (2 × 200 mL), and brine (100 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by FCC (AcOEt/hexane 1:1) to afford **5a** (36.0 g, 76%) as a white solid. $[\alpha]^{20}_D$ = +2.8 (*c* = 1.0, $CHCl_3$); rt = 4.96 min; ^{1}H NMR ($CDCl_3$) δ 1.41 (s, 9H), 1.40−1.49 (m, 2H), 1.73−1.76 (m, 2H), 2.32−2.41 (m, 1H), 2.69−2.78 (m, 1H), 2.86−3.00 (m, 2H), 3.54 (m, 1H), 3.71 (s, 3H), 4.29 (m, 1H), 5.26 (d, *J* = 8.5 Hz, 1H), 5.54 (m, 1H), 7.15−7.31 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 23.0, 28.6, 28.7, 40.6, 42.1, 50.9, 52.5, 58.3, 79.7, 127.1, 128.7, 130.1, 137.4, 155.4, 171.9, 173.4; IR (KBr) ν_{max} 3292, 1740, 1705, 1655, 705; ESI-MS 392 $(M + H)^+$. Anal. Calcd for $C_{20}H_{29}N_3O_5$ (391.47): C 61.36, H 7.47, N 10.73. Found: C 61.29, H 7.51, N 10.73.

Method B: (Benzyloxycarbonyl)-L-valine-L-phenylalanine-piperidine-3*R*-carboxylic Acid Ethyl Ester (6b). Compound **5b** (21.0 g, 48.0 mmol) was dissolved in EtOH (500 mL), and 10% Pd/C (1.2 g, 1.13 mmol) was added. The mixture was hydrogenated overnight and filtered through Celite. The solvent was evaporated to afford the crude amine (13.2 g). To a solution

of the amine in THF (200 mL) at 0 °C were added Cbz-L-Val-OH (13.4 g, 53.4 mmol), EDC (10.2 g, 53.4 mmol), and HOBT (7.2 g, 53.4 mmol). The mixture was stirred overnight at room temperature, and the solvent was evaporated. The residue was taken up in AcOEt (500 mL) and washed with H_2O (2 × 100 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by FCC (AcOEt/Hexane 1:1) to afford **6b** (21.0 g, 82%) as a colorless oil: $[\alpha]^{20}_D = -31.1$ ($c = 2.0$, EtOH); rt = 5.86 min; ^{1}H NMR (DMSO, 120 °C, 400 MHz) δ 0.82 (d, J = 6.6 Hz, 6H), 1.18 (t, J = 6.6 Hz, 3H), 1.25−1.38 (m, 1H), 1.50−1.65 (m, 2H), 1.81−1.90 (m, 1H), 1.96 (dsept, J = 6.8, 6.6 Hz, 1H), 2.03−2.18 (m, 1H), 2.85 (dd, J = 12.6, 6.3 Hz, 1H), 2.80−2.90 (m, 1H), 2.96 (dd, J = 12.6, 6.6 Hz, 1H), 2.91−3.02 (m, 1H), 3.75−3.85 (m, 1H), 3.89 (dd, J = 9.0, 6.2 Hz, 1H), 3.97−4.05 (m, 1H), 4.07 (q, J = 6.6 Hz, 2H), 5.01 (m, 1H), 5.03 (s, 2H), 6.68 (d, J = 7.8 Hz, 1H), 7.12−7.38 (m, 10H), 7.74 (d, J = 6.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.6 MHz, 1:1 mixture of two conformers) δ 14.1, 14.2, 17.5, 19.2, 23.7, 25.0, 26.9, 27.2, 31.2, 31.4, 39.7, 40.3, 40.6, 41.1, 42.4, 43.9, 45.7, 47.3, 49.9, 60.1, 60.2, 60.7, 66.9, 67.0, 127.0, 127.1, 128.0, 128.1, 128.4, 128.5, 128.6, 129.4, 129.7, 135.9, 136.1, 136.3, 156.3, 169.3, 169.5, 170.4, 170.5, 172.3, 172.9; IR (KBr) ν_{max} 3298, 2961, 1730, 1630, 699; HRMS: Calcd for $C_{30}H_{39}N_3O_6$ $[M + Na]^+$ 560.2736, found 560.2745.

Method C: (Benzyloxycarbonyl)-L-phenylalanine-piperidine-3*R*-carboxylic Acid Ethyl Ester (5b). To a solution of Cbz-L-Phe-OH (19.3 g, 64.5 mmol) and *N*-methylmorpholine (7.2 g, 71.0 mmol) in dry THF (200 mL) cooled to −15 °C was added isobutyl chloroformate (9.7 g, 71.0 mmol) dissolved in THF (50 mL). A white precipitate fell out immediately, and the suspension was stirred for 30 min at −15 °C. The tartaric acid salt of piperidine-3*R*-carboxylic acid ethyl ester **4** (19.8 g, 64.5 mmol) was dissolved in CH_2Cl_2 (100 mL) containing diisopropylethylamine (9.2 g, 71.0 mmol). The solution was added to the chloroformate, and the reaction was stirred overnight at room temperature. The solvent was evaporated, and the residue was redissolved in AcOEt (500 mL). The organic phase was washed with H_2O (2 × 150 mL), dried over Na_2SO_4, and evaporated. The residue was purified by FCC (AcOEt) to afford **5b** (21.7 g, 77%) as a colorless oil: $[\alpha]^{20}_D = -24.7$ ($c = 2.0$, EtOH); rt = 5.76 min; ^{1}H NMR (DMSO, 120 °C, 400 MHz) δ 1.21 (t, J = 7.5 Hz, 3H), 1.27−1.39 (m, 1H), 1.54−1.65 (m, 2H), 1.85−1.93 (m, 1H), 2.12−2.25 (m, 1H), 2.86 (dd, J = 13.2, 6.9 Hz, 1H), 2.94 (dd, J = 13.2, 6.6 Hz, 1H), 2.90−3.04 (m, 2H), 3.78−3.86 (m, 1H), 4.03−4.14 (m, 1H), 4.10 (q, J = 7.5 Hz, 2H), 4.74 (dd, J = 6.9, 6.6 Hz, 1H), 4.98 (d, J = 13.7 Hz, 1H), 5.03 (d, J = 13.7 Hz, 1H), 6.85 (br, 1H), 7.18−7.38 (m, 10H); ^{13}C NMR ($CDCl_3$, 100.6 MHz, mixture of two conformers) δ 14.6, 24.1, 25.4, 27.3, 27.6, 40.5, 41.1, 41.2, 41.5, 42.8, 44.3, 46.1, 47.7, 51.8, 52.1, 60.9, 61.0, 67.2, 127.4, 127.5, 128.4, 128.5, 128.9, 129.0, 129.9, 130.1, 136.4, 136.6, 136.8, 136.9, 155.9, 156.0, 170.1, 170.2, 172.7, 173.4; IR (film) ν_{max} 3291, 2942, 1728, 1642, 700; HRMS: Calcd for $C_{25}H_{30}N_2O_5$ $[M + Na]^+$ 461.2052, found 461.2052.

General Procedures for Saponification/Esterification

Method A: Hept-6-en-1-oyl-L-valine-L-phenylalanine-hexahydropyridazine-3*S*-carboxylic Acid Hex-5-enyl Ester (8a). To a solution of **7a** (61 mg, 0.12 mmol) in THF (5 mL) was added 1.0 M aqueous LiOH (0.3 mL). The mixture was stirred for 4 h at room temperature, neutralized with 1.0 M aqueous HCl, and concentrated. The residue was taken up in AcOEt (30 mL) and washed with 2.0 M aqueous HCl (5 mL), H_2O (5 mL), and brine (2 mL). The aqueous phases were reextracted with AcOEt (2 × 10 mL). The combined organic phases were dried over Na_2SO_4 and evaporated to afford the crude acid. To a solution of the acid in CH_2Cl_2 (15 mL) were added 5-hexen-1-ol (12.3 mg, 0.12 mmol), DCC (26.5 mg, 0.13 mmol), and DMAP (12.6 mg, 0.12 mmol). The mixture was stirred overnight at room temperature, diluted with CH_2Cl_2 (15 mL), and filtered over Celite. The organic phase was washed with 1.0 M aqueous tartaric acid (5 mL) and brine (2 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by FCC (AcOEt/Hexane 4:1) to afford **8a** (40 mg, 58%) as a white foam: $[\alpha]^{20}_D = -24.0$ ($c = 1.11$, $CHCl_3$); rt = 8.51 min; ^{1}H NMR (DMSO, 400 MHz) δ 0.78, 0.80 (2d, J = 6.7 Hz, 6H), 1.28−1.81 (m, 12H), 1.88−2.23 (m, 7H), 2.75 (dd, J = 13.1, 7.4 Hz, 1H), 2.81−3.01 (m, 3H), 3.89−4.20 (m, 4H), 4.91−5.07 (m, 4H), 5.14 (d, J = 10.4 Hz, 1H), 5.46 (m, 1H), 5.72−5.87 (m, 2H), 7.12−7.26 (m, 5H), 7.66 (d, J = 7.8 Hz, 1H), 7.75 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125.6 MHz) δ 18.0, 19.2, 22.7, 25.0, 25.2, 27.9, 28.4, 28.5, 31.5, 33.2, 33.4, 36.6, 39.5, 41.8, 49.9, 57.9, 58.0, 64.9, 114.6, 115.0, 126.8, 128.4, 129.7, 136.6, 138.1, 138.4, 170.5, 171.1, 172.1, 172.7; IR (KBr) ν_{max} 3288, 2933, 1742, 1635, 911, 697; HRMS: Calcd for $C_{32}H_{48}N_4O_5$ $[M + Na]^+$ 591.3522, found 591.3523.

Method B: Hept-6-en-1-oyl-L-valine-L-phenylalanine-hexahydropyridazine-3*S*-carboxylic Acid Hexa-3,5-dienyl Ester (9a). To a solution of **7a** (700 mg, 1.4 mmol) in THF (30 mL) at 0 °C was added 1.0 M aqueous LiOH (3.5 mL). The reaction was stirred at room temperature for 2 h, neutralized with 1.0 M aqueous HCl, and evaporated. The residue was redissolved in AcOEt (50 mL) and washed with 1.0 M aqueous HCl (10 mL). The organic phase was dried over Na_2SO_4 and evaporated to afford the crude acid. To a solution of the crude acid in THF (20 mL) were added 3,5-hexadien-1-ol (358 mg, 3.64 mmol), triphenylphosphine (460 mg, 1.75 mmol), and DEAD (275 μL, 1.75 mmol). The reaction was stirred overnight at room temperature and concentrated. The residue was taken up in AcOEt (50 mL) and washed with 1.0 M aqueous $NaHCO_3$ (10 mL). The organic phase was dried over Na_2SO_4 and evaporated. The residue was purified by FCC (AcOEt/Hexane 4:1) to afford **9a** (507 mg, 64%) as a white foam: $[\alpha]^{20}_D = -26.0$ ($c = 1.0$, $CHCl_3$); rt = 7.54 min; ^{1}H NMR (DMSO, 400 MHz) δ 0.78, 0.80 (2d, J = 6.5 Hz, 6H), 1.28−1.58 (m, 6H), 1.62−1.80 (m, 2H), 1.95 (m, 1H), 2.01 (m, 2H), 2.07−2.23 (m, 2H), 2.41 (m, 2H), 2.75 (dd, J = 13.3, 7.5 Hz, 1H), 2.87 (dd, J = 13.3, 6.0 Hz, 1H), 2.92 (br, 2H), 3.92 (br, 1H), 4.14 (m, 3H), 4.90−5.10 (m, 3H), 5.14 (m, 2H), 5.48 (m, 1H), 5.66−5.85 (m, 2H), 6.14 (dd, J = 15.3, 10.5 Hz, 1H), 6.32 (dt, J = 17.0, 10.5 Hz, 1H), 7.12−7.27 (m, 5H), 7.64 (d, J = 8.0 Hz, 1H), 7.76 (d, J = 9.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.4, 19.6, 23.0, 25.6, 28.7, 28.9, 31.9, 32.2, 33.8, 37.0, 39.9, 42.2, 50.2, 58.2, 58.4, 64.4, 115.1, 116.8, 127.3, 128.8, 129.5, 130.1, 134.2, 136.9, 137.0, 138.9, 170.8, 171.4, 172.5, 173.1; IR (KBr) ν_{max} 3288, 2930, 1743, 1635, 1550, 909, 698; ESI-MS 589 $(M + Na)^+$, 567 $(M + H)^+$. Anal. Calcd for $C_{32}H_{46}N_4O_5$ (566.75): C 67.82, H 8.18, N 9.89. Found: C 67.48, H 8.16, N 9.71.

General Procedure for the Ring-Closing Metathesis Reaction

(*E*)-(3*S*,6*S*,21*S*)-3-Benzyl-6-isopropyl-19-oxa-1,4,7,25-tetraaza-bicyclo[19.3.1]-pentacos-13-ene-2,5,8,20-tetraone (*trans*-11a). To a solution of **8a** (700 mg, 1.23 mmol) in CH_2Cl_2 (250 mL) was added ruthenium catalyst **1** (150 mg, 0.18 mmol). The reaction was stirred under reflux overnight, and the solvent was evaporated. The residue was purified by reverse-phase preparative HPLC [C18 column, 25 min linear gradient followed by 10 min isocratic; elution 30−100% (H_2O/CH_3CN (1:9) in H_2O/CH_3CN (9:1)); flow rate 20 mL/min] to afford *trans*-**11a** (405 mg, 60%) as a white foam and containing ∼5% *cis*-**11a** as determined by ^{1}H NMR; $[\alpha]^{20}_D = +83.2$ ($c = 1.65$, $CHCl_3$); rt = 4.74 min; ^{1}H NMR (DMSO, 400 MHz) δ 0.81, 0.87 (2d, J = 6.6 Hz, 6H), 1.06−1.18 (m, 1H), 1.23−1.46 (m, 5H), 1.47−1.62 (m, 4H), 1.64−1.79 (m, 3H), 1.80−2.00 (m, 5H), 2.18−2.28 (m, 1H), 2.79 (dd, J = 13.8, 8.0 Hz, 1H), 2.85 (dd, J = 13.8, 5.6 Hz, 1H), 2.85−3.02 (m, 2H), 3.88−4.18 (m, 4H), 5.06 (d, J = 10.4 Hz, 1H), 5.19−5.34 (m, 2H), 5.50 (m, 1H), 7.11−7.25 (m, 5H), 7.60 (d, J = 9.0 Hz, 1H), 7.93 (d, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.6, 19.7, 23.3, 26.2, 26.6, 28.2, 28.6, 28.9, 31.3, 32.5, 32.8, 37.3, 38.9, 42.0, 50.0, 58.3, 59.9, 65.5, 127.4, 129.0, 129.9, 130.2, 130.4, 136.6, 170.7, 171.3, 172.6, 173.8; IR (KBr) ν_{max} 3318, 2927, 1736, 1644, 970, 700; HRMS: Calcd for $C_{30}H_{44}N_4O_5$ $[M + Na]^+$ 563.3209, found 563.3219.

(*E*)-(3*S*,6*S*)-3-Benzyl-6-isopropyl-19-oxa-1,4,7,25-tetraaza-bicyclo[19.3.1]-pentacosa-13,21(25)-diene-2,5,8,20-tetraone (12). 11a is slowly oxidized into the white foam **12** in the presence of air: $[\alpha]^{20}_D = +115.5$ ($c = 1.86$, $CHCl_3$); rt = 5.68 min; ^{1}H NMR (DMSO, 400 MHz) δ 0.82, 0.90 (2d, J = 6.6 Hz, 6H), 1.02−1.11 (m, 2H), 1.26−1.46 (m, 3H), 1.47−1.62 (m, 3H), 1.63−1.75 (m, 2H), 1.76−2.00 (m, 6H), 2.17−2.30 (m, 1H), 2.31−2.42 (m, 2H), 2.87 (d, J = 6.8 Hz, 2H), 3.41−3.54 (m, 1H), 3.64−3.75 (m, 1H), 3.91−4.02 (m, 1H), 4.21 (m, 1H), 4.31−4.40 (m, 1H), 5.16−5.33 (m, 2H), 5.57 (m, 1H), 7.09−7.26 (m, 5H), 7.64 (d, J = 9.0 Hz, 1H), 8.27 (d, J = 7.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.7, 18.7, 19.7, 21.9, 26.3, 27.1, 28.5, 29.2, 31.3, 32.3, 33.0, 37.3, 38.9, 39.6, 51.3, 58.6, 65.8, 127.4, 128.9, 129.7, 130.1, 136.3, 141.0, 164.6, 171.2, 172.8, 173.9; IR (KBr) ν_{max} 3312,

2933, 1694, 1645, 969, 700; HRMS: Calcd for $C_{30}H_{42}N_4O_5$ [M + Na]$^+$ 561.3053, found 561.3063.

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Supporting Information Available: Analytical data of compounds **6a**, **7a**−**c**, **8b**, **9b**, **10**, **11b**, **13**−**16**. Copies of ^{1}H NMR spectra of compounds **5**−**16**. This material is available free of charge via the Internet at http://pubs.acs.org.

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