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Synthesis of the HCV Protease Inhibitor Vaniprevir (MK-7009) Using Ring-Closing Metathesis Strategy

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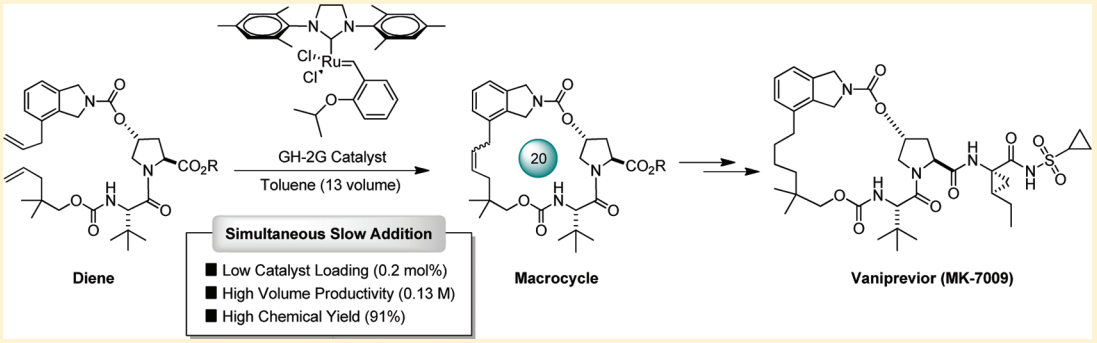
Supporting Information



ABSTRACT: A highly efficient synthesis of Vaniprevir (MK-7009) has been accomplished in nine linear steps and 55% overall yield. The key features of this synthesis include a cost-effective synthesis of the isoindoline subunit and efficient construction of the 20-membered macrocyclic core of Vaniprevir (MK-7009) utilizing ring-closing metathesis technology. A high-performing ring-closing metathesis protocol has been achieved by simultaneous slow addition of the ruthenium catalyst (0.2 mol %) and the diene substrate at a concentration of 0.13 M.

INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is a worldwide epidemic, affecting approximately 180 million individuals around the globe. HCV is a positive-strand RNA virus of the flaviviridae family and replicates primarily in the liver. While disease progression is typically a slow process that occurs over many years, a significant fraction of patients ultimately develops serious liver disease, including cirrhosis and hepatocellular carcinoma.[1] Currently, HCV is a leading cause of death in HIV-coinfected patients and is also the most common indication for liver transplantation surgery. The existing care for HCV combines Pegylated Interferon and Ribavirin but only provides a modest cure rate.[2] This low cure rate is partially attributed to the fact that patient response is highly dependent on the genotype of the virus. As such, a variety of gene targets have been evaluated to identify new modes of treatment. The launch of two new drugs, Boceprevir and Telaprevir, shows promise to improve the success rate in HCV therapy.[3] Despite these tremendous accomplishments, additional improvements in the area of genotype coverage, drug dose, and cure rate are still desired. Vaniprevir (MK-7009) is a potent HCV NS3/4a protease inhibitor that is being evaluated for the treatment of HCV at the late stage of clinical studies (Figure 1).[4] To ensure the supply of the drug for ongoing clinical studies, a chemical process amenable to production of multikilogram quantities of MK-7009 was required.

The primary challenges to develop a scalable, cost-effective synthesis for Vaniprevir (MK-7009) are identifying an efficient macrocyclization strategy and concise and efficient syntheses of the key intermediates needed to construct the macrocycle precursor. Ideally, these key components could be assembled together in a convergent manner with minimal linear steps. The first practical synthesis of Vaniprevir (MK-7009) on a large scale was based on macrolactamization to install the 20-membered macrocycle.[5] The macrocycle precursor **3** was synthesized via a Heck coupling of two chiral building blocks (Scheme 1). The process proceeded in 10 linear steps and 21 total steps with 30% overall yield and has served as a practical means of producing large quantities of Vaniprevir (MK-7009) to support the safety and clinical studies of this compound.

In recent years, ring-closing metathesis (RCM) has emerged as a powerful tool for forming macrocyclic compounds.[6] This methodology has been widely used in academic research and has been shown great promise for large scale pharmaceutical applications.[7] Herein, we report a new synthetic route for Vaniprevir (MK-7009) based on RCM for the construction of the 20-membered macrocycle (Scheme 2). We have developed a practical RCM protocol which employs low catalyst loading (0.2 mol%) and relatively high concentrations for RCM (0.13

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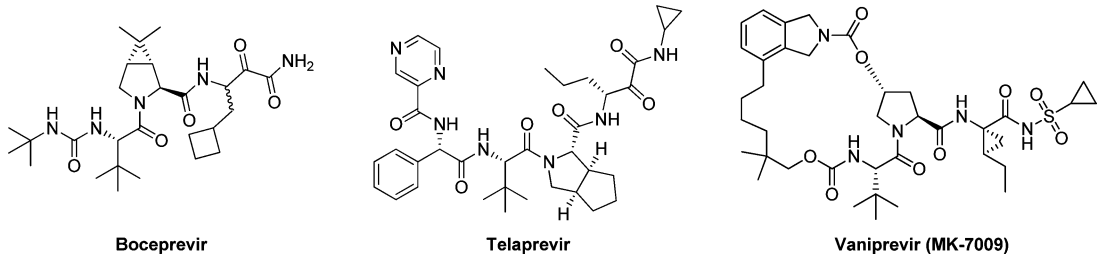
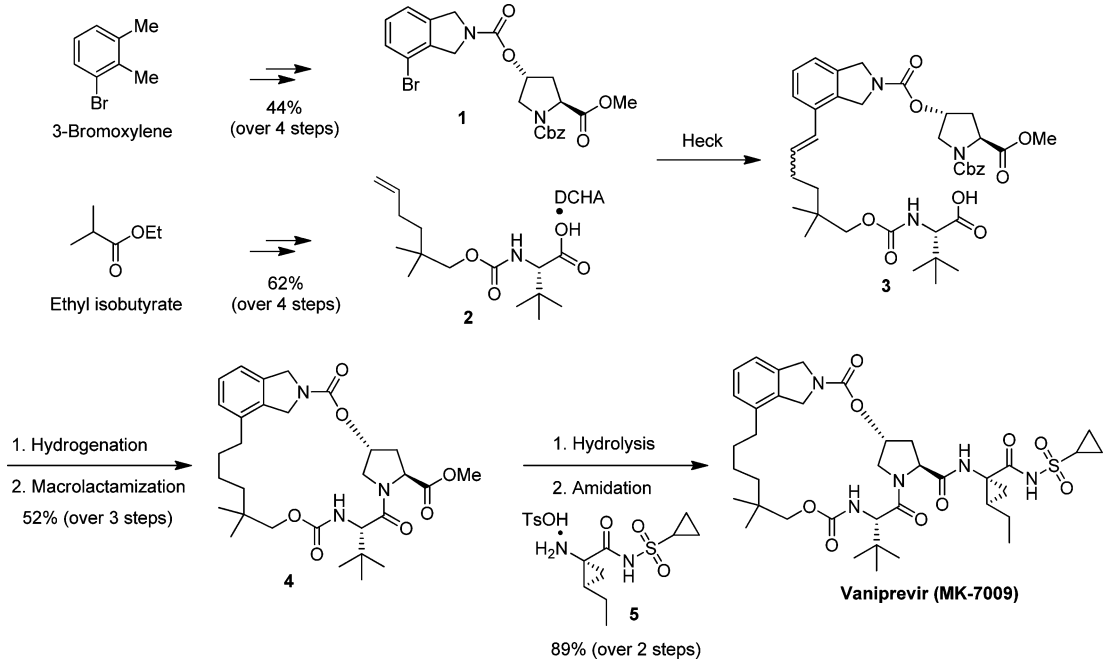
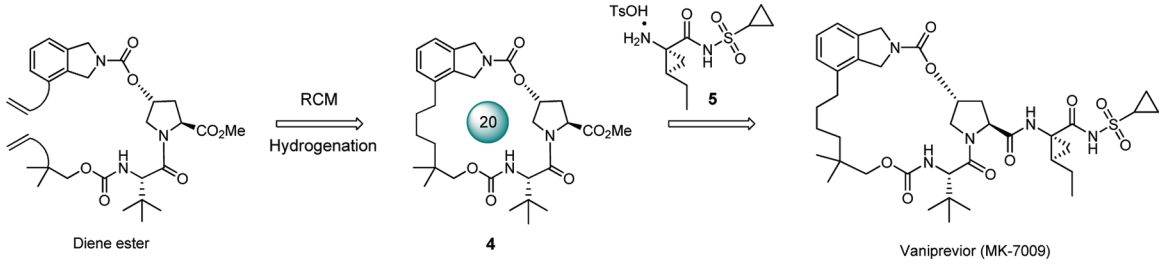


Figure 1. HCV NS3/4a protease inhibitors.

Scheme 1. Heck Route for Synthesis of Vaniprevir (MK-7009)[5]



Scheme 2. RCM Route for Synthesis of Vaniprevir (MK-7009)



M). Efficient synthesis of the key intermediates will also be described.

As shown in Scheme 3, there are three possible RCM options for the construction of the macrocycle on the basis of different positions of olefin metathesis: styryl-homoallyl, allyl-allyl, and homoallyl-vinyl diene. According to prior results, the use of the styryl-homoallyl diene **9** for RCM required high catalyst loading to obtain a satisfactory yield.[5] Unfortunately, the efficiency of RCM with diene **9** could not be improved with a variation of catalysts and reaction conditions. Hence, this substrate was not further investigated. We envisioned that the preparation of allyl-allyl diene **10** would be more straightforward as compared to that of the homoallyl vinyl substrate **11**. The introduction of two allylic moieties to the diene from a more readily available allylic starting material would likely be more cost-effective as well.

The retrosynthetic analysis of the diene-ester **10** is shown in Scheme 4. We conceived that diene-ester **10** could be derived from the coupling of ene-alcohol **13** with the allyl isoindoline HCl salt **12**. The ene-alcohol **13**, in turn, could be prepared from the coupling of the commercially available prolinol ester **14** and ene-acid **15**.

RESULTS AND DISCUSSION

Preparation of Diene-Ester 10. We started the synthesis of diene-ester **10** by investigation of a cost-effective preparation of allylisoindoline **12** from bromoisoindoline **18** via a Kumada coupling reaction using allylmagnesium chloride. The bromoisoindoline **18** was previously prepared in four steps from

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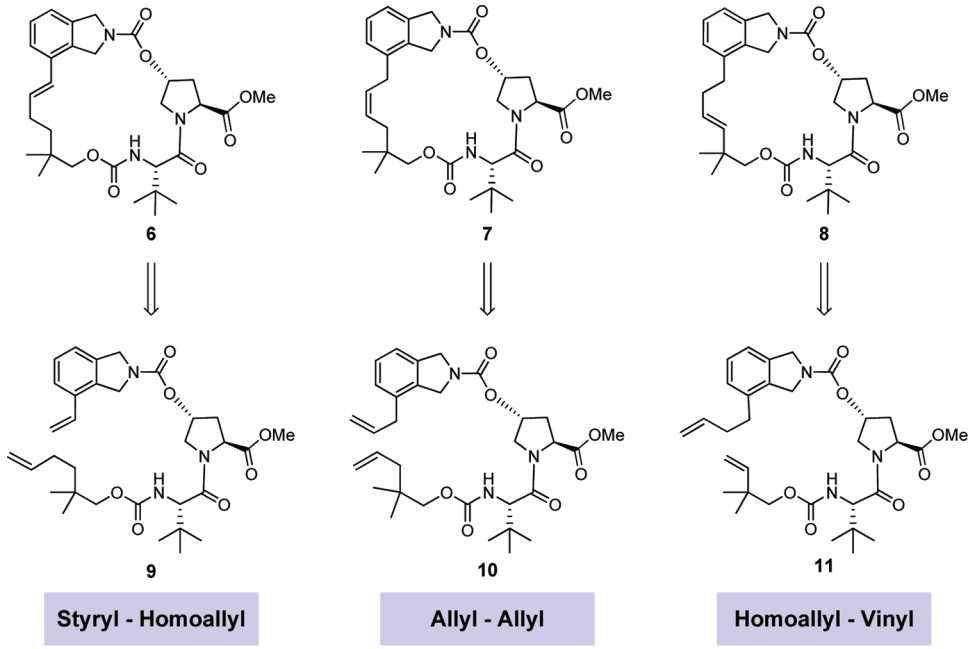
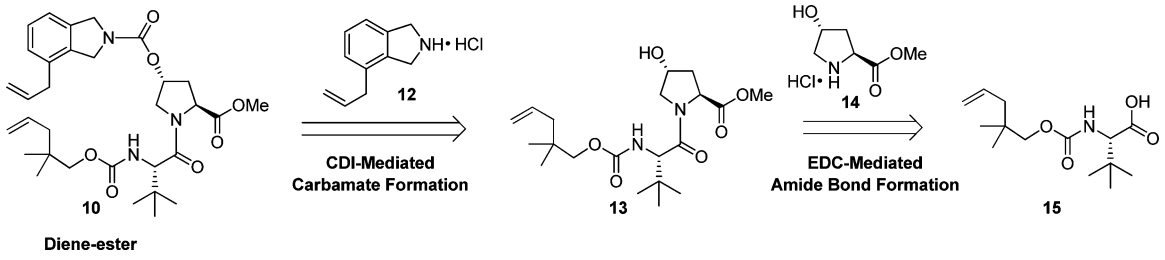
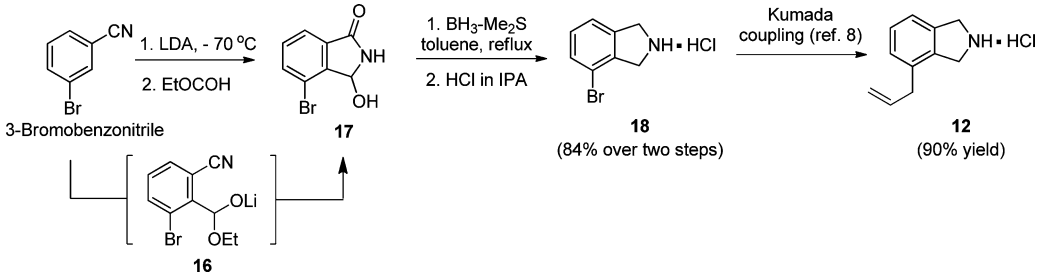
Scheme 3. Three Possible Options for RCM Route



Scheme 4. Retrosynthetic Analysis for Allyl−Allyl Diene Synthesis



Scheme 5. Synthesis of Allylisoindoline HCl Salt 12



bromoxylene.[5] To develop a more efficient and cost-effective route for bromoisoindoline synthesis, we started with an inexpensive starting material, 3-bromobenzonitrile. Hence, the regioselective deprotonation of 3-bromobenzonitrile at the 2-position followed by addition of ethyl formate gave rise to alkoxide intermediate **16**. Upon reverse quenching of the reaction mixture in aqueous media, the alkoxide was readily converted to hydroxyl lactam **17**. Borane reduction of the hydroxyl lactam followed by HCl salt formation afforded bromoisoindoline HCl salt **18** in 84% overall yield over two steps. The bromoisoindoline HCl salt **18** was converted to the allylisoindoline HCl salt **12** in 90% yield via a one-pot process employing a Kumada coupling using 2 equiv of allylmagnesium chloride (Scheme 5).[8]

The other olefin piece for the diene synthesis was prepared via carbamate formation between alcohol **19**[9] and *tert*-leucine **21** (Scheme 6). The alcohol was first activated with DSC to afford the succinamide intermediate **20**. The intermediate is stable in aqueous media so that the coupling reaction can be run in aqueous DMF.[10] The solubility of *tert*-leucine in aqueous DMF was substantially improved, and hence the coupling reaction proceeded smoothly at ambient temperature to afford ene-acid **15** in 94% yield. Subsequent EDC-pyridine mediated coupling of ene-acid **15** with prolinol ester HCl salt **14** afforded ene-alcohol **13** in 97% yield.[11] Activation of the hydroxyl group with CDI followed by coupling with allylisoindoline HCl **12** completed the synthesis of diene-ester **10** in high overall yield.

Optimization of Ring-Closing Metathesis of Diene Ester 10. With diene-ester **10** secured, attention was turned

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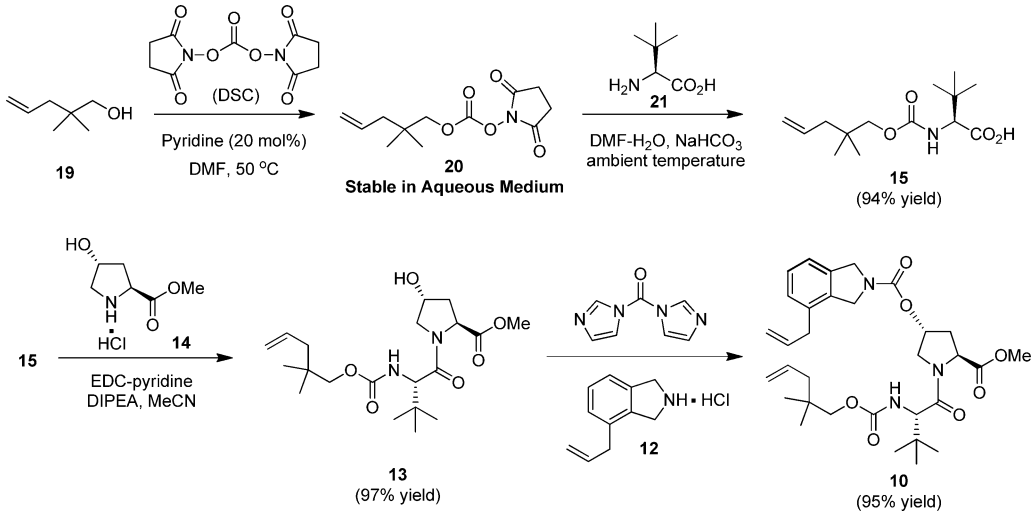
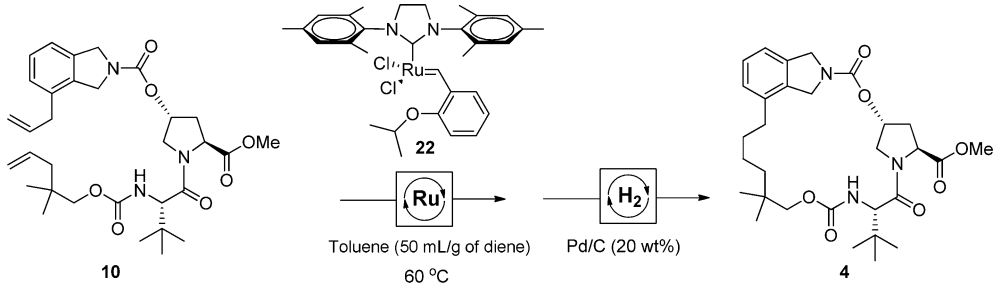
Scheme 6. Synthesis of Allyl-Allyl Diene



Scheme 7. Catalyst Slow Addition Effect on RCM



Addition mode	Catalyst loading	Yield
one-pot	1 mol%	57%
one-pot	5 mol%	67%
slow addition of catalyst	1 mol%	82%

toward optimization of the RCM with particular focus on two aspects of this macrocyclization process. First, the high-dilution conditions typically employed for RCM presented a severe limitation for material throughput/volume productivity when operating at a manufacturing scale. Second, the relatively high expense of RCM catalysts would necessitate a very low catalyst loading in order to maintain an economically viable process. With these challenges in mind, we began study of the RCM using diene-ester **10** using 1 mol % of the Grubbs–Hoveyda second-generation catalyst **22** under high-dilution conditions to gain proof of concept and gauge the catalyst activity. The reaction, however, only afforded the desired macrocyclic ester **4** in 57% yield after hydrogenation. Increasing the catalyst loading to 5 mol % only marginally improved the yield to 67%. Obviously, the reaction called for significant optimization to achieve high efficiency. Profiling of the RCM reaction showed that the catalytic activity was very high at the beginning of the reaction but quickly diminished as the reaction proceeded further. At the end, many side products including oligomers were formed. Given this fact, we envisioned that slow addition of the catalyst may sustain the catalyst activity during the reaction. Delightfully, this simple modification increased the yield to 82% when 1 mol % of catalyst was added over 1 h at 60 °C to diene-ester **10** in toluene (50 mL/g of diene) (Scheme 7).

We next shifted our attention to address the common high-dilution problem associated with macrocyclization by implementing slow addition of the catalyst but at higher reaction concentration. The reaction run under 30 mL/g of diene (0.058 M), however, afforded the desired 20-membered product **23** in only 61% yield. The 19-membered macrocyclic ester **24** was formed in 9% yield as a major side product (Scheme 8). We postulated that the 19-membered macrocycle was derived from the RCM of the styryl isomer **25**, which in turn was generated from the isomerization of allylic diene **10** (Scheme 8). It is known that Ru-H complex generated through decomposition of the Ru catalyst **22** is responsible for the isomerization of the olefin.[12] This isomerization pathway could be suppressed by addition of quinone additives which inhibit the decomposition of the catalyst or suppress Ru-H catalyzed olefin isomerization.[13] After screening a few quinone additives,[14] we found that 2,6-dichloroquinone effectively decreased the formation of the 19-membered ring to <1% without loss of conversion when the reaction was run at 20 mL/g diene concentration (Table 1, entry 2). More importantly, the catalyst loading was lowered to 0.2 mol %, which was viable for our large-scale production (Table 1, entry 3). Continuing studies revealed that higher temperature positively impacted on RCM to increase the yield to 84% (Table 1, entry 4).[15] Moreover, to suppress undesired thermodynamic equilibration in the end of the reaction due to a

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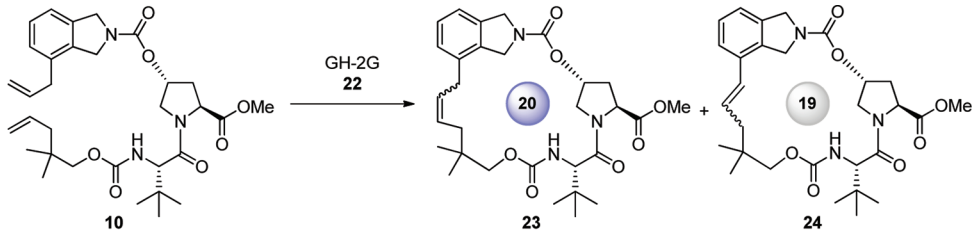
Scheme 8. Generation of 19-Membered Macrocycle at Higher Concentration



Reaction conditions	Volume Ratio (mL/g diene)	20-Mac Ester	19-Mac Ester
1 mol% GH-2G Slow addition of catalyst over 1 h toluene, 60 °C	50	82%	< 1%
	30	61%	9%

■ **Proposed pathway for generation of 19-membered macrocycle**

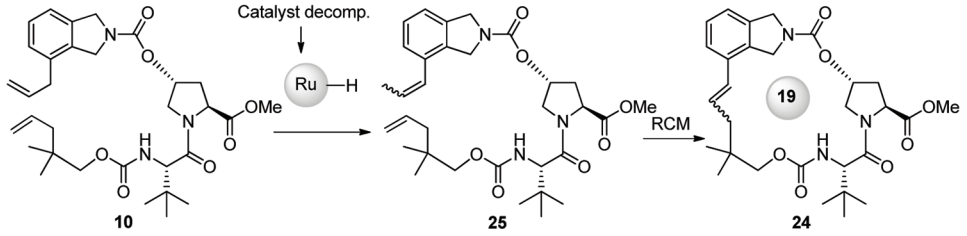
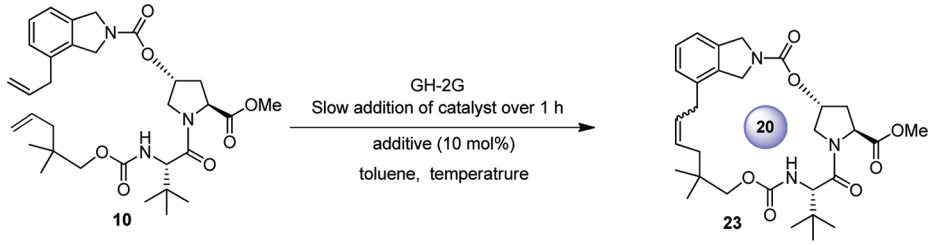


Table 1. Optimization of RCM with Diene-Ester 10



							yield (%)		
entry	amt of **3** (mol %)	temp (°C)	additive	method[a]	volume ratio (mL/g diene)	concn (M)	**23**	**24**	dimers/oligomers
1		70	none	A	20	0.086	62	8	5
2	0.5	70	2,6-dichloroquinone	A	20	0.086	72	<1	5
3	0.2	70	2,6-dichloroquinone	A	20	0.086	72	<1	5
4	0.2	100	2,6-dichloroquinone	A	20	0.086	84	1.5	5
5	0.2	100	2,6-dichloroquinone	B	20	0.086	88	1.5	5
6	0.2	100	2,6-dichloroquinone	B	13.5	0.13	78	2	>15
7	**0.2**	**100**	**2,6-dichloroquinone**	C	**13.5**	**0.13**	**91**	**2**	**5**

[a]Method A, no additional operation; method B, subsurface N_2 gas bubbling; method C, simultaneous addition of diene substrate.

high concentration of ethylene, we attempted to actively remove the evolving ethylene during RCM by sparging the reaction mixture with a gentle stream of nitrogen gas. Indeed, a simple subsurface nitrogen gas bubbling further increased the yield to 88% (Table 1, entry 5). However, at a higher concentration (13.5 mL of toluene/g of diene), the yield of the RCM product was significantly decreased due to the formation of a high level of dimers and oligomers (Table 1, entry 6). To circumvent this issue, we decided to mimic high-dilution conditions by implementing simultaneous slow addition of both catalyst and diene. Gratifyingly, the efficiency of the reaction was maintained at a higher concentration (0.13 M, 13.5 mL/g of diene) to produce the product **23** in 91% yield (Table 1, entry 7). Hydrogenation of RCM product **23** was conveniently carried out in a 9:1 mixture of toluene and IPA. A solvent switch to IPA from a toluene–IPA mixture followed by crystallization provided the key intermediate, macrocyclic ester **4**, in 89% yield with high purity (>99% HPLC purity). It should also be noted that single crystallization of the macrocyclic ester from IPA–water resulted in extremely low levels of residual metals (both ruthenium and palladium content <10 ppm). With the optimization conditions in hand, we successfully demonstrated the process of ring-closing metathesis followed by hydrogenation on a 100 g scale using 0.2 mol % of the Grubbs–Hoveyda second-generation catalyst at 13.5 mL/g (0.13 M) concentration in toluene. The demonstration of the optimized process featuring ring-closing metathesis as a means for the construction of the macrocycle forms the basis for the

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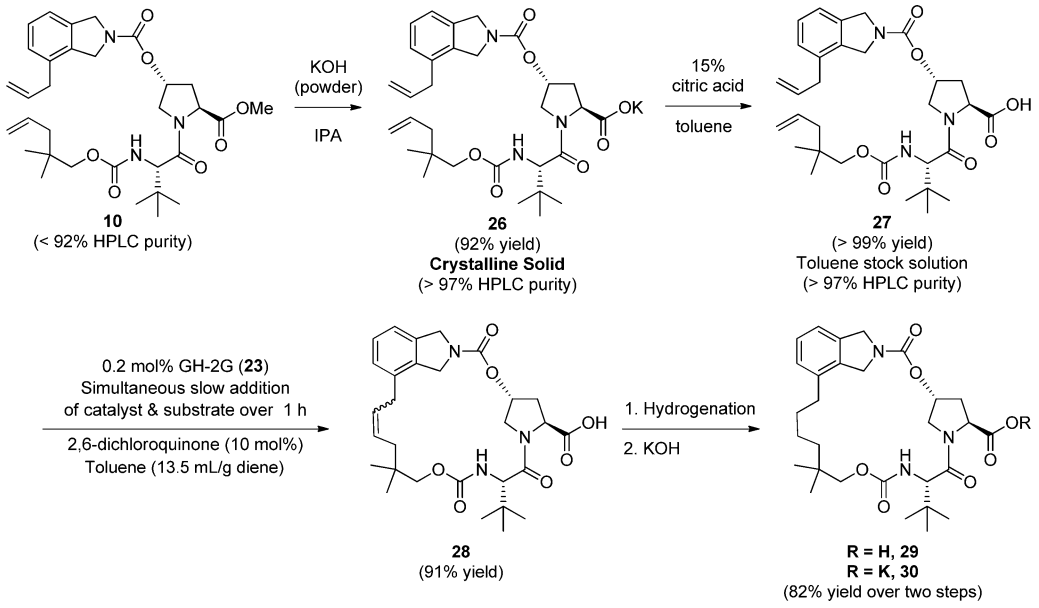
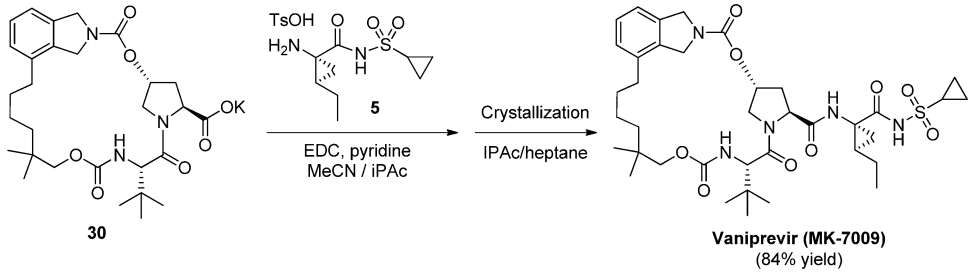
Scheme 9. Second-Generation RCM Route with Diene-Acid 27



Scheme 10. Synthesis of Vaniprevir (MK-7009)[5]



development of the manufacturing process of Vaniprevir (MK-7009).

Second-Generation RCM Route with Diene-Acid 27. The sensitivity of the RCM to impurities is a key challenge for developing a robust manufacturing process.[16] The success of the RCM under low catalyst loading was highly dependent on the purity of the starting material. The diene-ester **10**, on the other hand, was an oil which limited purification options for purity upgrade. To reinforce the robustness of our RCM route, we sought to find a crystalline substrate for RCM. To our delight, potassium salt **26** was found as a crystalline solid. Moreover, the potassium salt was conveniently prepared by treatment of diene-ester **10** with powdered KOH in IPA.[17] Upon saponification, potassium salt **26** crystallized spontaneously from the reaction media. Treatment of potassium salt **26** with 10% citric acid smoothly converted the salt to free acid **27** and upgraded the purity as well. For example, the purity could be readily upgraded from ester (<92% HPLC purity) to salt or free acid (>97% HPLC purity) using these two simple procedures. The direct use of potassium salt **26** for RCM was not suitable, due to its poor solubility in organic solvents such as toluene and IPAc. However, the RCM of diene acid **27** under the conditions defined for diene-ester **10** proceeded smoothly to produce the desired product, macrocyclic acid **28**, in 91% yield. Subsequent hydrogenation followed by salt formation afforded potassium salt **30** in 82% yield with excellent purity upgrade (Scheme 9). The potassium salt **30** also serves as the penultimate species for the efficient synthesis for Vaniprevir (MK-7009).

Synthesis of Vaniprevir (MK-7009). With the availability of both potassium salt **30** and cyclopropyl sulfonamide **5** as tosylate,[18] direct coupling of both species without salt breaking of each component was investigated. Delightfully, EDC-pyridine mediated amidation[11] proceeded cleanly to afford Vaniprevir (MK-7009) in 84% yield with excellent purity after crystallization from IPAc/heptane (Scheme 10).

■ CONCLUSIONS

In summary, we have defined and developed a highly efficient synthesis of Vaniprevir (MK-7009) featuring ring-closing metathesis (RCM) of a fully elaborated diene. The synthesis proceeds with the longest sequence of nine steps, combining four important components, *tert*-leucine unit **15**, hydroxy proline unit **14**, isoindoline unit **12**, and cyclopropyl amino acid side chain **5**. Simultaneous slow addition of the ruthenium catalyst and the diene substrate enables the ring-closing metathesis for the construction of a 20-membered ring to proceed at low catalyst loading (0.2 mol %) without employing high-dilution conditions. The strategy was successfully applied to the efficient synthesis of Vaniprevir (MK-7009).

■ EXPERIMENTAL SECTION

Chemical reagents were used as received from suppliers. NMR spectra were taken on 400 or 500 MHz spectrometers. High-resolution mass spectra (HRMS) were obtained on a Fourier transform ion cyclotron

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resonance (FTICR) mass spectrometer and are reported as m/z (relative intensity). Accurate masses are reported for the molecular ion (M + 1).

4-Bromoisoindoline Hydrochloride 18. To a 500 mL round-bottom flask equipped with a magnetic stirrer, thermocouple, and nitrogen inlet was added diisopropylamine (8.61 mL, 60.4 mmol) and then THF (50 mL). The solution was cooled to −20 °C. *n*-BuLi (24.1 mL of 2.50 M in hexane, 60.4 mmol) was slowly added. The resulting solution was aged over 5 min at −20 °C and then cooled to −70 °C. In the meantime, 3-bromobenzonitrile (10.0 g, 54.9 mmol) was dissolved in THF (20 mL) at room temperature. The 3-bromobenzonitrile solution in THF was transferred to LDA solution while controlling the temperature below −65 °C. The resulting solution was aged over 5 min around −70 °C. Then the reaction was quenched with ethyl formate (6.04 mL, 74.2 mmol). The resulting solution was aged over 5 min at −70 °C. The reaction solution was reversely quenched into 50 mL of water in ice bath. After quenching was completed, 50 mL of EtOAc was added. The resulting solution was acidified to pH 4 using concentrated HCl (9 mL). The aqueous layer was extracted with EtOAc (2 × 50 mL). Concentration of the combined organic layers under reduced pressure provided 11.67 g of the desired product. Without further purification, the crude lactam (5 g, 21.93 mmol) was dissolved in toluene (20 mL). The resulting solution was heated to 55 °C. Borane ethyl sulfide complex (4.58 mL, 48.2 mmol) was slowly added to the reaction solution for 10 min. After addition, the reaction mixture was heated to 110 °C and aged overnight at 110 °C. The reaction mixture was cooled to around 75 °C and quenched by adding 5 N HCl in IPA (10 mL). The resulting slurry was aged over 1 h at 75 °C. Finally, the slurry was cooled to room temperature and aged at that temperature over 30 min. The slurry was filtered, and the wet cake was washed with two 10 mL portions of toluene. After overnight drying of the wet cake under vacuum with N_2 gas sweep, 4.32 g of compound **18** was obtained as an off-white solid (84% yield). ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.15 (br s, 2H), 7.59 (d, J = 10.0 Hz, 1H), 7.44 (d, J = 10.0 Hz, 1H), 7.35 (d, J = 10.0 Hz, 1H), 4.63 (s, 2H), 4.48 (s, 2H). ^{13}C NMR (125 MHz, DMSO-d_6): δ 137.9, 136.0, 131.6, 131.2, 122.9, 116.8, 51.6, 51.6. The NMR data match literature values.[5]

(*S*)-2-((((2,2-Dimethylpent-4-en-1-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoic Acid (Ene-Acid 15). A 1 L round-bottom flask was charged with DMF (270 mL), alcohol **19** (44 g, 0.385 mol), DSC (109 g, 0.424 mol), and pyridine (6.21 mL, 0.077 mol) at room temperature. The resulting solution was heated to 45−50 °C and aged until the amount of starting material was <2.0% (ca. 1 h). The reaction mixture was cooled to 5 °C, and water (270 mL) was slowly added while controlling the temperature below 10 °C. After addition, the mixture was stirred for 30 min. L-*tert*-Leucine (50.60 g, 0.385 mol) was added to the reaction mixture in one portion and then $NaHCO_3$ was added in four portions. (*Note: upon adding solid $NaHCO_3$, carbon dioxide (CO_2) gas was generated. To avoid the vigorous CO_2 gas generation, slow addition of $NaHCO_3$ was needed. $NaHCO_3$ can be replaced by K_3PO_4.*) The reaction mixture was aged at 15−25 °C over 12 h. A 450 mL amount of heptane was added. The layers were separated, and the organic layer was discarded. The aqueous layer was acidified to around pH 1−2 by adding 3 N HCl (ca. 500 mL) at around 20 °C. The acidic aqueous layer was extracted with 450 mL of IPAc. The organic layer was washed with two 450 mL portions of water. The organic solvent was removed under reduced pressure. Ene-acid **15** was obtained as a white solid (97 g, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$, mixture of two rotamers): δ 11.10 (br s, 1H), 6.26 and 5.27 (d, J = 9.5 Hz, 0.3H and d, J = 6.0 Hz, 0.7H), 5.83−5.75 (m, 1H), 5.06−5.00 (m, 2H), 4.21 and 3.97 (d, J = 9.5 Hz, 0.7H and d, J = 6.0 Hz, 0.3H), 3.85 (d, J = 10.5 Hz, 1H), 3.79 (d, J = 10.5 Hz, 1H), 2.02 (d, J = 7.5 Hz, 2H), 1.04 (s, 9H), 0.91 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.5, 156.6, 134.4, 117.6, 72.98, 62.0, 43.4, 34.6, 34.3, 26.5, 24.0. HRMS (ESI$^+$): exact mass calcd for $[M + 1]^+$ ($C_{14}H_{26}NO_4$) m/z 272.1856, found m/z 272.1871.

(2*S*,4*R*)-Methyl 1-((*S*)-2-((((2,2-Dimethylpent-4-en-1-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoyl)-4-hydroxypyrrolidine-2-carboxylate (Ene-Alcohol 13). A 2 L round-bottom flask with overhead stirring was charged with ene-acid **15** (335 g, 1.23 mol) and MeCN (1 L). To this was added *trans*-4-hydroxy-L-proline methyl ester hydrochloride (256.6 g, 96 wt % contaminated with 4% of carboxylic acid, 1.36 mol). Pyridine (146.5 g, 1.85 mol) was added via addition funnel over 45 min. The resulting slurry was aged for 1 h. EDC·HCl (319.5 g, 1.667 mol) was then added as a solid. The resulting solution was warmed to 45 °C and stirred at that temperature. (*Note: the ene-acid starting material was not detected by HPLC after 4 h.*) The reaction was inversely quenched into a 6 L extractor with overhead stirring and a drop valve that had been charged with 2.0 L of 15 wt % aqueous citric acid and 2.5 L of toluene. The biphasic mixture was stirred for 30 min, and then stirring was stopped. The aqueous layer was discarded. The extractor was charged with 0.5 L of 15% aqueous NaCl (half brine), and the resulting biphasic mixture was stirred for 30 min. The aqueous layer was discarded, and theorganic layer was collected. The organic phase was concentrated to ∼2 L and then dried via azeotrope with toluene (50 °C bath and 45−50 mmHg pressure) under constant-volume conditions. The final total volume was adjusted to 3.5 L. This solution was transferred via in-line filtration to a separate vessel. The resulting solution was measured to have KF = 100 ppm of H_2O. The toluene stream was assayed to contain 475.5 g of ene-alcohol **13** (97% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.78−5.67 (m, 1H), 5.49 (d, J = 12.0 Hz, 1H), 5.00−4.95 (m, 2H), 4.60 (t, J = 8.0 Hz, 1H), 4.46 (br s, 1H), 4.23 (d, J = 12.0 Hz, 1H), 3.80−3.76 (m, 2H), 3.72−3.70 (m, 1H), 3.71 (s, 3H), 2.29 (dd, J = 12.0, 8.0 Hz, 1H), 1.99−1.92 (m, 3H), 0.99 (s, 9H), 0.84 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7, 171.0, 157.1, 134.5, 117.7, 73.1, 70.2, 59.2, 58.0, 56.6, 52.3, 43.5, 37.6, 35.9, 34.3, 26.4, 24.7, 24.1. HRMS (ESI$^+$): exact mass calcd for $[M + 1]^+$ ($C_{20}H_{35}N_2O_6$) m/z 399.2490, found m/z 399.2505.

(3*R*,5*S*)-1-((*S*)-2-((((2,2-Dimethylpent-4-en-1-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoyl)-5-(methoxycarbonyl)-pyrrolidin-3-yl 4-Allylisoindoline-2-carboxylate (Diene-Ester 10). A 10 L three-neck flask with overhead stirring was charged with the ene-alcohol **13** (475.5 g, 1.193 mol) as a solution in toluene (3.5 L total volume), followed by a 75 mL toluene rinse. 1,1′-Carbonyldiimidazole (CDI; 223 g, 1.372 mol) was charged into the ambient-temperature (T_i = 22 °C) solution, followed by a 5 mL toluene rinse. The resulting solution was aged at 22−26 °C for 1 h. Formation of the CDI adduct was monitored by HPLC by conversion to the corresponding carbamate. (*Note: 0.1 mL of the* reaction *was added to 0.5 mL of $BuNH_2$ neat, and the resulting solution was heated to 50 °C for 2−3 min. This solution was then diluted to 10 mL and assayed by HPLC.*) After 1 h, over 99% conversion was observed. A 450 mL portion of H_2O was then added to the reaction solution, and the resulting biphasic solution was aged for 1 h. 4-Allylisoindoline·HCl (285 g, 98 wt %, 1.46 mol) was then added as a solution in H_2O (1.95 L). The resulting biphasic solution was heated to 50 °C and aged at 50 °C for 10 h. The phases were allowed to settle, and HPLC assay of the organic phase showed that conversion was over 99%. The aqueous phase (pH 7−8) was separated and discarded. The organic phase was washed with 1.0 L of 15 wt % aqueous citric acid below 25 °C. The organic phase was washed with 0.5 L of 5 wt % aqueous $NaHCO_3$. The organic phase was concentrated to ∼1.4 L total volume (conditions: 50 mmHg pressure and T = 35 °C). The final volume was adjusted to make an approximately 50 wt % stock solution for the next step, RCM. Diene-ester **10** was obtained as a 50 wt % solution in toluene (662 g, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 (dd, J = 15.0, 5.0 Hz, 1H), 7.10−7.01 (m, 2H), 5.91−5.82 (m, 1H), 5.69−5.61 (m, 1H), 5.35 (br s, 1H), 5.31 (dd, J = 10.0, 5.0 Hz, 1H), 5.04 (dd, J = 25.0, 15.0 Hz, 2H), 4.95 (dd, J = 30.0, 20.0 Hz, 2H), 4.76−4.50 (m, 5H), 4.24 (dd, J = 10.0, 5.0 Hz, 1H), 4.16 (t, J = 12.5 Hz, 1H), 3.90−3.83 (m, 1H), 3.72 (s, 3H), 3.63 (dd, J = 25.0, 10.0 Hz, 1H), 3.33−3.25 (m, 3H), 2.49 (dd, J = 15.0, 10.0 Hz, 1H), 2.22 −2.11 (m, 1H), 1.89−1.81 (m, 2H), 1.02 (s, 9H), 0.73 (d. J = 5.0 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, mixture of two rotamers): δ 172.1 and 172.1, 171.3 and 171.2, 156.8 and 156.7, 153.9, 136.9 and 136.6, 135.6, 135.5 and 135.4, 134.8, 134.6 and 134.5, 128.1 and 128.1, 127.8 and 127.7, 120.6 and 120.5, 117.5, 116.6 and 116.5, 73.5 and 73.5, 72.6 and 72.6, 59.2 and 59.1, 58.0 and 57.9, 54.1 and 53.6, 52.8, 52.4 and 52.3,

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51.5 and 51.1, 43.3, 37.7 and 37.4, 35.6 and 35.4, 35.1 and 35.0, 34.1, 26.3, 24.0 and 23.9. HRMS (ESI$^+$): exact mass calcd for $[M + 1]^+$ ($C_{32}H_{46}N_3O_7$) m/z 584.3330, found m/z 584.3347.

Ring-Closing Metathesis with Diene-Ester 10 (RCM Product 23). In a 3 L round-bottom flask equipped with a magnetic stirrer, thermocouple, nitrogen inlet, and reflux condenser was added 2,6-dichloroquinone (3.03 g, 0.0173 mol) and degassed toluene (1.03 L). In the meantime, we prepared the diene-ester **10** stock solution (200 g, 0.171 mol, 50 wt % in toluene) and Grubbs−Hoveyda-II catalyst stock solution by dissolving the catalyst (0.215 g, 0.343 mmol) in 100 mL of toluene. A 10 vol % amount of diene-ester **10** stock solution was charged into the reaction solution. The resulting solution was heated over 100 °C with gentle N_2 gas bubbling through the solution. Grubbs−Hoveyda-II catalyst stock solution in toluene and the remaining 90 vol % of diene-ester **10** stock solution were slowly and simultaneously added to the reaction solution over 1 h. After the addition was completed, the reaction mixture was stirred for 1 h more to achieve the complete consumption of diene-ester substrate. The reaction mixture was cooled to room temperature and assayed (86.4 g, 91% yield). The crude reaction mixture was carried over to the next step.

Hydrogenation of RCM Product 23. The RCM product **23** (86.4 g, 0.1556 mol) in toluene (1.35 L) was transferred to a shaker can. The remaining RCM product was rinsed with two 75 mL portions of IPA and transferred to a shaker can. The catalyst 5% Pd/C-Shell (25 g, 25 wt %) was charged. The reaction vessel was purged three times with nitrogen gas followed by three purges of hydrogen gas at 45 psi. The reaction mixture was aged for 24 h under 45 psi of hydrogen. After 24 h, the reaction was stopped and the heterogeneous solution was transferred to a 1 L plastic container. The shaker was rinsed with two 30 mL portions of toluene/IPA (9/1), and this solution was combined with the main solution. The catalyst was filtered through Sloka Floc (20 wt %). The pad was washed with two 30 mL portions of toluene/IPA (9/1) mixed solvent (30 mL). The crude macrocyclic ester **4** in toluene/IPA (9/1) was carried over to the crystallization step (4.26 wt % in toluene/IPA (9/1)).

Purification/Crystallization of Mac-Ester 4. The solvent was switched to IPA. The IPA solution (460 mL) was heated to 45 °C and aged at 45 °C over 15 min. A 60 mL portion of water was slowly added to the IPA solution over 30 min at 45 °C, and the resulting solution was further stirred over 15 min. At that point, 10 mg of Mac-ester (0.1 wt %) was charged as a seed. Once crystallization started, the batch was cooled to 40 °C and aged over 15 min at that temperature. A second portion of water (60 mL) was added over 1 h at 40 °C. The slurry was cooled to room temperature slowly over 1 h and then aged overnight at room temperature. The slurry was further cooled to 0 °C and aged over 1 h at 0 °C. The slurry was filtered and washed with 100 mL of precooled IPA/water (2/1 at 0 °C). The solid was dried over 24 h at 45 °C under vacuum with an N_2 sweep. A 77.5 g amount of the desired macrocyclic ester **4** was obtained as a white solid (89% for hydrogenation followed by crystallization, 81% yield over two steps from diene-ester **10**; >99% HPLC purity; Ru <10 ppm and Pd <10 ppm). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (dd, J = 10.0, 5.0 Hz, 1H), 7.08 (d, J = 10.0 Hz, 1H), 7.04 (d, J = 5.0 Hz, 1H), 5.53 (d, J = 5.0 Hz, 1H), 5.31 (t, J = 5.0 Hz, 1H), 4.71 (dd, J = 25.0, 15.0 Hz, 2H), 4.62 (t, J = 10.0 Hz, 1H), 4.54−4.48 (m, 2H), 4.42 (t, J = 10.0 Hz, 2H), 4.13 (d, J = 15.0 Hz, 1H), 3.81 (d, J = 15.0 Hz, 1H), 3.75 (s, 3H), 3.24 (d, J = 15.0 Hz, 1H), 2.76−2.72 (m, 1H), 2.54−2.48 (m, 1H), 2.43−2.37 (m, 1H), 2.14 (dq, J = 15.0, 5.0 Hz, 1H), 1.53−1.43 (m, 2H), 1.33−1.25 (m, 3H), 1.20−1.11 (m, 1H), 1.50 (s, 9H), 0.95 (s, 3H), 0.78 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 170.7, 156.2, 153.4, 137.5, 136.1, 134.9, 127.9, 127.5, 120.2, 74.1, 72.4, 59.0, 57.5, 54.0, 52.4, 52.2, 50.8, 36.8, 36.5, 35.4, 34.0, 33.5, 30.6, 26.2, 25.0, 23.7, 23.3. The NMR data match literature values.[5]

Potassium (2*S*,4*R*)-4-((4-Allylisoindoline-2-carbonyl)oxy)-1-((*S*)-2-((((2,2-dimethylpent-4-en-1-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoyl)pyrrolidine-2-carboxylate (Diene-Acid K Salt 26). A 2 L three-neck flask with overhead stirring and an addition funnel was charged with diene-ester **10** (100 g, 171.4 mmol) as a solution in *i*-PrOH (0.8 L total volume, 0.7 L of *i*-PrOH). A solution of KOH pellets that had been dissolved in *i*-PrOH (0.3 L) was added dropwise while controlling the temperature below 30 °C. The solution was aged at ambient temperature. After 16 h, the slurry was filtered and the wet cake was washed with 400 mL of *i*-PrOH. The cake was dried via vacuum suction under a N_2 tent. A 96.0 g amount of compound **26** was obtained as a white solid (92% yield, 98.2 HPLC purity). ^{1}H NMR (500 MHz, CD_3COOD, mixture of rotamers): δ 7.27−7.23 (m, 1H), 7.18−7.10 (m, 1.8H), 7.05 (dd, J = 10.0, 3.0 Hz, 0.1H), 6.90 (dd, J = 10.0, 6.0 Hz, 0.1H), 5.97−5.87 (m, 1H), 5.87−5.80 (m, 0.2H), 5.73−5.67 (m, 0.8H), 5.45 (d, J = 2.5 Hz, 1H), 5.11−4.91 (m, 3H), 4.83 −4.58 (m, 5H), 4.48−4.37 (m, 2H), 4.07 (t, J = 12.5 Hz, 0.2H), 3.88 (ddd, J = 15.0, 12.5, 5.0 Hz, 0.8H), 3.62 (ddd, J = 30.0, 30.0, 10.0 Hz, 0.8H), 3.36−3.22 (m, 3H), 2.79−2.75 (m, 0.2H), 2.68−2.64 (m, 0.8H), 2.52−2.45 (m, 0.2H), 2.36−2.30 (m, 0.8H), 2.07−2.03 (m, 1H), 1.92−1.83 (m, 2H), 1.80 (s, 7.9H), 1.05 (s, 1.1H), 0.92 (s, 1.3H), 0.74 (s, 4.7H). ^{13}C NMR (125 MHz, $CDCl_3$, mixture of rotamers): δ 176.6, 173.9 and 173.8, 158.8 and 158.8, 155.7, 137.9 and 137.5, 136.6 and 136.5, 136.5 and 136.3, 135.8 and 135.6, 135.6 and 135.5, 129.1 and 129.0, 128.6 and 128.4, 121.5 and 121.4, 117.9, 117.0 and 116.8, 75.5 and 75.5, 73.5, 60.7 and 60.7, 59.3 and 59.2, 55.6, 53.3 and 53.1, 52.1 and 51.9, 43.8 and 43.8, 38.3 and 38.2, 36.0 and 35.8, 35.5 and 35.5, 34.9 and 34.7, 26.7, 24.1, and 24.0. HRMS (ESI$^+$): exact mass calcd for $[M + 1]^+$ ($C_{31}H_{43}KN_3O_7$) m/z 608.2733, found m/z 608.2756.

(2*S*,4*R*)-4-((4-Allylisoindoline-2-carbonyl)oxy)-1-((*S*)-2-((((2,2-dimethylpent-4-en-1-yl)oxy)carbonyl)amino)-3,3-dimethylbutanoyl)pyrrolidine-2-carboxylic Acid (Diene-Acid 27). A 3 L flask with overhead stirring and a drop valve was charged with the solid diene K salt **26** and toluene. An aqueous solution of citric acid (15 wt %) was then added. The resulting biphasic solution was aged for 1 h with stirring at 25 °C. The aqueous phase was drained, and the organic phase was washed with 100 mL of water. The aqueous phase was drained and discarded. The resulting toluene stream was maintained as a 1000 mL solution and dried via azeotrope by distillation with toluene under constant-volume conditions (35 °C at 50 mmHg pressure) in order to meet the specification of KF ≤300 ppm. The toluene stream was transferred to a smaller vessel via in-line filtration and then concentrated to a 50 wt % solution in toluene. The diene-acid stock solution in toluene was directly used for RCM.

Ring-Closing Metathesis with Diene-Acid 27. A 500 mL three-neck round-bottom flask with overhead stirring and a reflux condenser was charged with 2,6-dichloro-1,4-benzoquinone (217 mg, 1.229 mmol) and toluene (200 mL) at room temperature. The reaction solution was then heated over 100 °C with gentle nitrogen gas bubbling. In the meantime, we prepared the diene-acid **27** stock solution (40.0 g, 30.68 mmol, 50 wt % in toluene) and Grubbs−Hoveyda-II catalyst stock solution by dissolving the catalyst (44 mg, 0.07 mmol) in 20 mL of toluene. Then 6 mL of diluted diene-acid stock solutioin (10 vol %) was added into the reaction vessel. The catalyst stock solution was transferred to a 20 mL syringe and set in a syringe pump. Grubbs−Hoveyda-II catalyst stock solution in toluene and the remaining 90 vol % of diene-acid stock solution was slowly and simultaneously added to the reaction solution for 1 h. After the addition of catalyst was complete, the reaction mixture was aged for an additional 30 min to achieve >98% conversion. The reaction mixture was cooled to room temperature. The toluene solution (270 mL, 13.5 mL/1 g of diene-acid) including cis/trans mixtures of RCM products was carried over to the next step without further purification (17.3 g, 91% yield, 7.2 wt % in toluene).

Hydrogenation of RCM Product 28. The RCM prduct **28** in toluene (17.3 g, 7.2 wt % in toluene) was transferred to a shaker can. The remaining RCM-acid was rinsed with two 15 mL portions of IPA and transferred to the shaker can. A 5% Pd/C-Shell catalyst (4.98 g, 30 wt %) was charged. The reaction vessel was purged three times with nitrogen gas followed by three purges of hydrogen gas at 45 psi. The reaction mixture was aged under 45 psi of hydrogen. After 24 h, the reaction was stopped and the heterogeneous solution was transferred to a 1 L plastic container. The shaker was rinsed with two 30 mL portions of mixed solvent (Tol/IPA 9/1), and this solution was combined with the main batch. The heterogeneous solution was

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filtered through Sloka Floc (4 g, 20 wt %). The pad was washed with two 30 mL portions of toluene/IPA (9/1) mixed solvent. The crude macrocyclic acid **29** in toluene/IPA (9/1) was carried over to the crystallization step (4.26 wt % in toluene/IPA (9/1)).

Isolation of Mac-Acid K Salt 30. The crude macrocyclic acid **29** (4.0 g, 7.36 mmol) in toluene/IPA (9/1) was concentrated. The solvent was switched to EtOH. The final volume of EtOH was adjusted to make about 8 mL (2 mL of EtOH/g of macrocyclic aicd **29**). KOH stock solution (418 mg, 7.45 mmol of KOH in 3.5 mL of EtOH) was slowly added to the reaction solution over 2 h. The resulting thick slurry was heated to 45 °C over 1 h. The slurry was slowly cooled to ambient temperature. The resulting slurry was aged overnight at ambient temperature. The slurry was filtered, and the wet cake was washed with 6 mL of EtOH. The cake was dried under vacuum with N_2 sweep. A 3.49 g amount of macrocyclic acid K-salt **30** was obtained as a white solid (82% yield over two steps from RCM product **28**). ^{1}H NMR (500 MHz, CD_3Cl): δ 7.19 (dd, J = 7.5, 7.7 Hz, 1H), 7.07 (d, J = 10.0 Hz, 1H), Hz, 1H), 7.02 (d, J = 10.0 Hz, 1H), 5.53 (d, J = 5.0 Hz, 1H), 5.21 (br s, 1H), 4.68 (dd, J = 30.0, 15.0 Hz, 2H), 4.49 (d, J = 10.0 Hz, 1H), 4.39 (d, J = 10.0 Hz, 1H), 4.18 (dd, J = 10.0, 5.0 Hz, 1H), 4.05 (d, J = 10.0 Hz, 1H), 3.81 (d, J = 10.0 Hz, 1H), 3.46 (br s, 1H), 3.23 (d, J = 10.0 Hz, 1H), 2.63 (dd, J = 15.0, 10.0 Hz, 1H), 2.50−2.37 (m, 2H), 2.21−2.15 (m, 1H), 1.50−1.42 (m, 2H), 1.38−1.28 (m, 3H), 1.21−1.10 (m, 1H), 0.98 (s, 9H), 0.97 (s, 3H), 0.81 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 170.4, 156.2, 153.8, 137.5, 136.4, 135.1, 127.9, 127.4, 120.1, 74.9, 72.6, 61.1, 58.9, 54.5, 52.4, 50.8, 36.8, 36.0, 34.1, 33.6, 30.8, 26.3, 25.2, 23.8, 23.3. HRMS (ESI$^+$): exact mass calcd for $[M + 1]^+$ ($C_{29}H_{40}KN_3O_7$) m/z 582.2576, found m/z 582.2593.

■ ASSOCIATED CONTENT

Supporting Information

Figures giving ^{1}H NMR and ^{13}C NMR spectra of compounds **4**, **10**, **13**, **15**, **18**, **26**, and **30**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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