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Efficient Large-Scale Synthesis of BILN 2061, a Potent HCV Protease Inhibitor, by a Convergent Approach Based on Ring-Closing Metathesis

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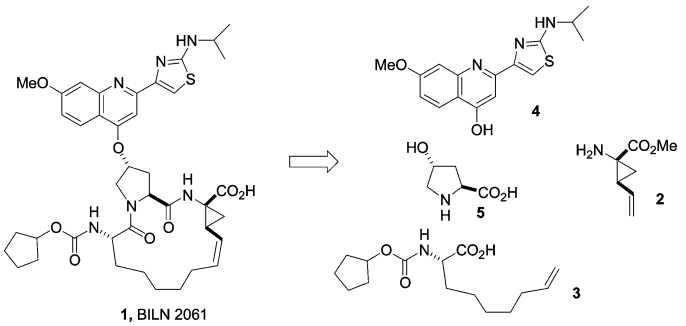

A multistep scalable synthesis of the clinically important hepatitis C virus (HCV) protease inhibitor BILN 2061 (**1**) is described. The synthesis is highly convergent and consists of two amide bond formations, one etherification, and one ring-closing metathesis (RCM) step, using readily available building blocks **2**−**5**. The optimization of each step is described at length. The main focus of the paper is the study of the RCM step and the description of the main problems faced when scaling up to pilot scale this highly powerful but very challenging synthetic operation. Eventually, the RCM reaction was smoothly scaled up to produce >400 kg of cyclized product.

Introduction

In the search for small molecules that could block replication of the hepatitis C virus (HCV), our discovery group has designed a series of peptidomimetics that are potent inhibitors of the HCV NS3 protease, an enzyme that is crucial to viral replication.[1] These inhibitors, characterized by three unnatural amino acid residues (P1, P2, P3), which are strung together in a macrocycle and are substituted with a very large hydrophobic heterocyclic moiety at the P2 residue, constitute a formidable challenge for the process chemist who is responsible for designing a practical

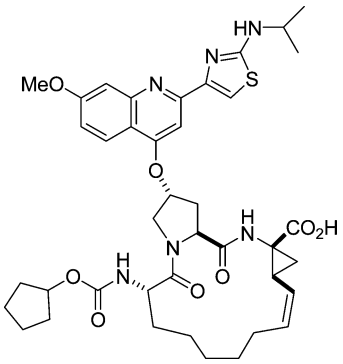

FIGURE 1. Structure of BILN 2061 (**1**).

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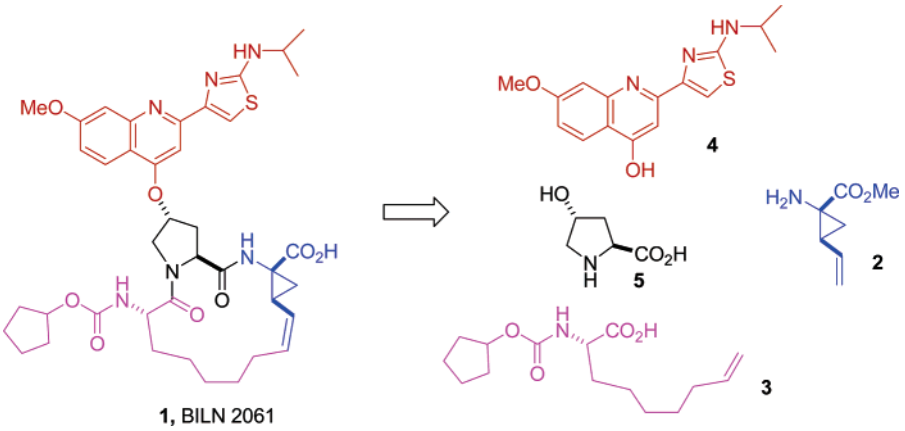

FIGURE 2. Retrosynthesis of BILN 2061.[4]

process that can be scaled to provide multi-kilogram amounts of these substances in a very high degree of purity.

A prototype of these HCV protease inhibitors, which recently has been tested in humans, is BILN 2061 (**1**, Figure 1).[2]

The new inhibitor has demonstrated antiviral response in HCV patients.[3] The molecule features a 15-membered ring bearing a (*Z*)-1,2-disubstituted alkene subunit, as well as five stereocenters. The obvious disconnections involve scission of two amide bonds and an ether function (Figure 2). Closure of the macrocycle can be effected by a Ru-catalyzed ring-closing metathesis (RCM) reaction,[4] a synthetic operation that has been used widely in recent years[5] but which still represents a formidable challenge in a manufacturing plant setting because of a variety of factors that we will discuss below.

In addition, preparation of the building blocks necessary for such an assembly presents considerable synthetic challenges. In the other papers in the series, we have described practical, large-scale approaches to building blocks **2**,[6] **3**,[7] and **4**,[8] whereas **5** is commercially available in large quantities.

In the final paper of this series, we now describe two related strategies to the assembly of this challenging target and report the details of our optimization studies leading to the smooth synthesis of BILN 2061 in multikilogram amounts.

Results and Discussion

Strategic Considerations. The initial goal of the program was to streamline the highly convergent discovery synthesis so we could rapidly prepare initial quantities of **1** for safety studies in animals and for formulation work. To make the synthesis more convergent, we decided to prepare quinoline subunit **4** and attempt to couple it directly with the peptidic core. This is a departure from the discovery synthesis that used a less functionalized version of **4** and introduced the thiazole ring through a multistep sequence.[4] The challenges encountered with the scale-up of this assembly were associated with defining the purification strategy along the way, that is, the strategic placement of crystallizations to obtain pure BILN 2061 without resorting to chromatography. The scale-up of the RCM step also was associated with considerable challenges because of the high cost of the Ru catalysts, the large volumes involved, and the long reaction times. Finally, it was imperative to track the Ru content of all post-RCM intermediates and ensure that the final target was free from Ru contamination (<10 ppm).

An equally important goal was to develop a more cost-effective assembly, that is, devise a strategy that would be suitable for late development and eventually commercial manufacturing. In addition, all the steps involved had to be explored in much more detail, and a certain level of optimization was imperative. One of the challenges associated with a change of assembly is that the purification strategy had to be completely worked out again, since the reaction intermediates were mostly different and had a different impurity content with respect to the first assembly. The problem of manufacturing a reproducibly pure active pharmaceutical ingredient (API)[9] while minimizing the number of purifications and avoiding chromatographic techniques, is a standard facet of the art of process development.[10]

Expedient Synthesis of BILN 2061. Our initial approach is detailed in Scheme 1. Simple strategic considerations dictated that the RCM step should not be the final or penultimate step of the synthesis, because of the high catalyst load likely to be

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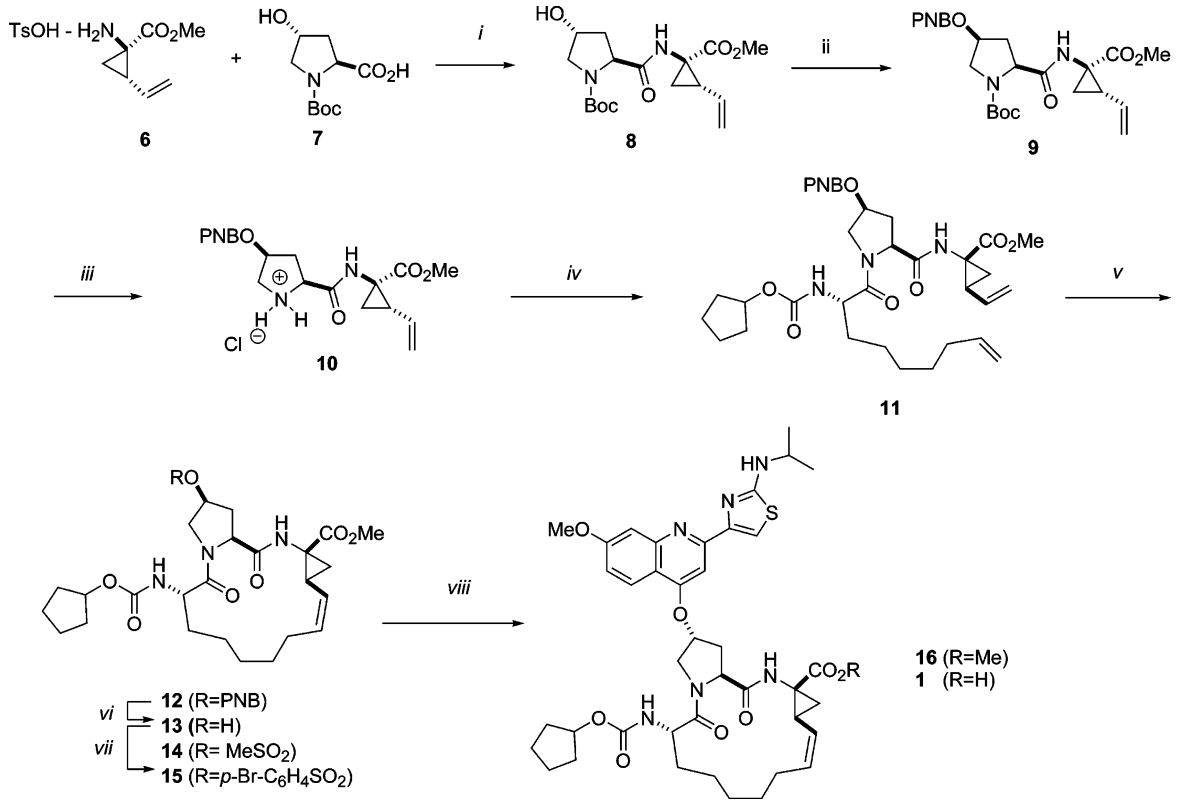
(5) Grubbs, R. H., Ed. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003.

SCHEME 1. Expedient Assembly of BILN 2061[a]



[a] **Conditions**: (i) EDC, HOBT, MeCN, *i*Pr$_2$NEt, rt (83%); (ii) *p*-$NO_2C_6H_4CO_2H$, PPh_3, DIAD, THF, 0 °C to rt; (iii) 4 N HCl, dioxane, rt (88%) from **8**; (iv) **3**, TBTU, *i*Pr$_2$NEt, CH_2Cl_2, rt (95%); (v) 5 mol % **18**, CH_2Cl_2, 40 °C (87%); (vi) 1.3 equiv LiOH, THF, 0−5 °C (89%); (vii) *p*-$BrC_6H_4SO_2Cl$, NEt_3, cat. DMAP, CH_2Cl_2, rt (93%); (viii) **4**, Cs_2CO_3, NMP, 50 °C, (84%); then 2 equiv LiOH, THF, H_2O, 40−45 °C (90%).

necessary and the associated difficulties in removing the Ru from the API. The synthesis, in addition to the RCM, also included two inversion steps at C-4 of the 4-hydroxy proline core to build the ether functionality and two amide-forming reactions.

P1−P2 Subunit (6 → 10). Compound **10**, the deprotected P1−P2 subunit, is an ideal candidate for purification by crystallization. Our goal became, therefore, to process **8** and **9** without isolation and, if possible, obtain **10** in a high degree of purity by direct precipitation. Thus, coupling between **6** and **7** was carried out using EDC/HOBT as reagents in dichloromethane. A slight excess (5%) of the less expensive **7** was used, to ensure consumption of the more precious **6**. Consumption of **6** was achieved after 1 h at rt, and the solution yield of **8** was found to be 95% (by a quantitative HPLC assay). Removal of EDC urea and excess **7** by aqueous washes was not a problem. Unfortunately, this operation only partially removed HOBT. We found that HOBT reacts as a Mitsunobu nucleophile[11] by forming an adduct with **7**. Thus, the procedure was modified to include washing the ethyl acetate (EtOAc) extracts of **8** with a dilute sodium hydroxide (NaOH) solution. The resulting solution was analyzed, and the specification of <1% HOBT content was met with the use of two washes. A quantitative HPLC assay indicated that the yield of **8** was now 83% because of product losses during the washes. However, this solution, after a solvent switch to THF and azeotropic drying, was of suitable quality to carry out the Mitsunobu inversion.[11] This was carried out in dry THF with 1.2 equiv each of *p*-nitrobenzoic acid and triphenylphosphine, upon slow addition of 1.2 equiv of diisopropyl azodicarboxylate (DIAD) (THF solution) at 0 °C. After 2 h at rt, the solution was assayed by HPLC, which indicated a 98% yield. The removal of the Mitsunobu reaction coproducts is always a challenge, especially if chromatography is not an option. Work-up with EtOAc and bicarbonate removed the excess *p*-nitrobenzoic acid. The other impurities could not be removed by washes, and the crude solution was partially evaporated. A solvent screen demonstrated that dioxane is an ideal solvent for the deprotection reaction because it dissolves HCl quite well and causes almost complete

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(9) Current guidelines make it imperative to control, in the final API, all organic impurities exceeding 0.1% (w/w), and current practices suggest that impurities >0.05% should be monitored.

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(11) Hughes, D. L. *Org. React.* **1992**, *42*, 2. The role of HOBT as a Mitsunobu nucleaophile is, as far as we know, unreported. In our case, product (**i**) was obtained from **7** and characterized by ^{1}H NMR and mass spectroscopy.

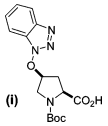
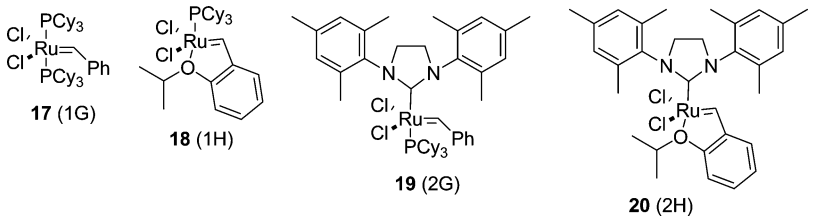
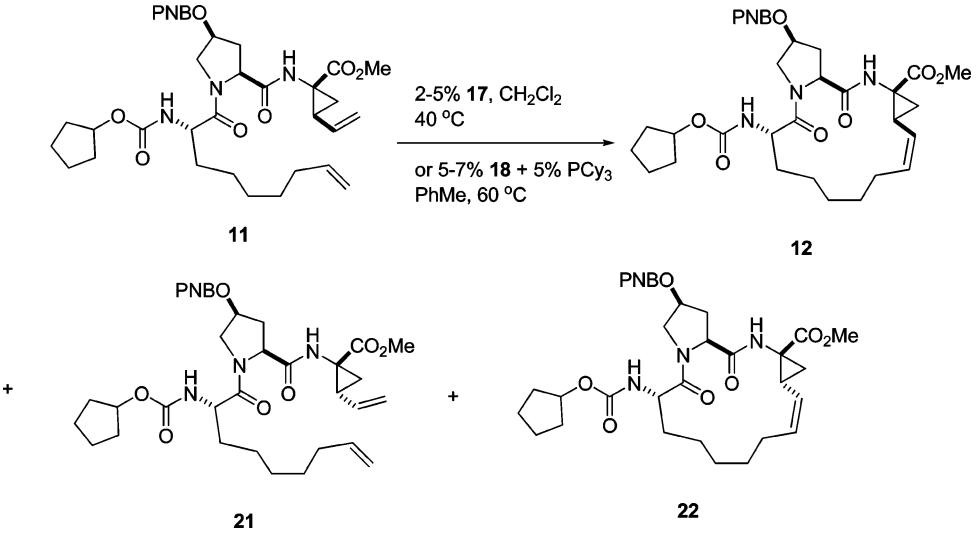


CHART 1. RCM Catalysts Used in This Study



SCHEME 2. RCM of 11 Using Catalyst 17



precipitation of **10**. A solvent switch to dioxane and treatment with a 4 N HCl dioxane solution at rt gave rise to a copious precipitate. After 2 h, filtration yielded crude **10** that was slurried with EtOAc to remove the Mitsunobu coproducts.

Triphenylphosphine oxide (TPPO) proved to be the main challenge because washes removed this impurity with difficulty. The acceptable levels of TPPO in **10** could be determined only by carrying mixtures through the next steps and comparing reaction profiles against those obtained with highly purified materials. After carrying through mixtures that contained up to 2% TPPO in **10** (w/w), it was found that the rate of the RCM step was adversely affected by such a small amount of this impurity, whereas lower levels of TPPO could be tolerated. A specification of 0.5% (w/w) was set for TPPO as a contaminant in **10**. Usually, one reslurry was sufficient to obtain **10** with an absolute (that is, measured against a pure standard) HPLC purity over 98%. The isolated yield was 88% for the two steps. The overall yield for the three-step assembly of highly pure **10** was 73−74%. This allowed us to tackle the coupling of the P3 unit with material of relatively high purity.

P3 Attachment (10 → 11). The next step involved the formation of the second peptidic bond, which was not a problem. Rather, the challenge consisted in identifying the minimum quality of **11** that would lead to a smooth RCM reaction without requiring complex purification procedures. We found that crude **3**, obtained from its dicyclohexylamine salt, couples with **10** using *O*-(benzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate (TBTU) and Hünig's base in dichloromethane at rt (5−6 h). The HPLC yield before work-up is typically 98−99%. It was found that extensive washes were needed to remove HOBT. Once again, this impurity interfered with the subsequent step, which in this case was the RCM reaction. After several washes (acid, bicarbonate, then water) to remove HOBT and tetramethylurea, the purity of **11** in solution was usually >98% (92−95% HPLC yield for the transformation), which, in a typical run, was satisfactory for the following RCM reaction. The low boiling point of dichloromethane was ideal for the next step, because the RCM in a variety of solvents could be attempted without isolation of **11**, that is, by simple evaporative solvent replacement (for example, toluene).

RCM Reaction. A number of catalysts for this transformation have been described recently in the literature.[5,12] Our initial screen focused on four of the most established Ru catalysts, which are illustrated in Chart 1.

Catalyst **17**, also referred to as "first-generation Grubbs catalyst" (1G), represents the original Grubbs catalyst design,[13] whereas **18** (1H) represents a catalyst prototype first introduced by Hoveyda et al., that is, a catalyst bearing only one phosphane ligand, which is endowed with improved robustness and recyclability.[14] Species **19** (2G) and **20** (2H) represent second-generation catalysts, that is, catalysts that have been made more active in the RCM reactions by the imidazolium ligands.[15]

(12) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117.
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(14) Kingsbury, J. S.; Harrity, J. P. A.; Bonitatebus, P. J., Jr.; Hoveyda, A. H. *J. Am. Chem. Soc*. **1999**, *121*, 791.
(15) (a) Scholl, M.; Trnka, T. M.; Morgan, J. P.; Grubbs, R. H. *Tetrahedron Lett*. **1999**, *40*, 2247. (b) Weskamp, T.; Kohl, F. J.; Hieringer, W.; Gleich, D.; Herrmann, W. A. *Angew. Chem., Int. Ed*. **1999**, *38*, 2416. (c) Huang, J.; Stevens, E. D.; Nolan, S. P.; Petersen, J. L. *J. Am. Chem. Soc*. **1999**, *121*, 2674. (d) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2000**, *122*, 8168.

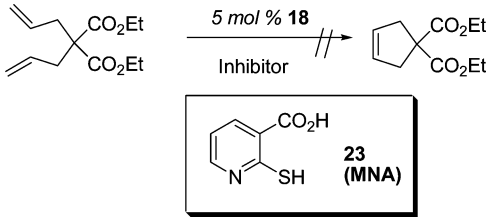
Early results had shown that the reaction produces only cis-isomers, presumably because of the higher thermodynamic stability of cis vs trans.[16] On the other hand, variable amounts of epimerization at one of the cyclopropane carbons were observed with catalyst **17** (Scheme 2). The exact proportion of the RCM product **12** was difficult to control and reproduce.

Control experiments suggest that free PCy_3, liberated by the catalyst during the metathesis, may be the culprit for this isomerization. The 1H catalyst **18** (5 mol % load) did not produce any (<0.5%) **22**, whereas simple addition of 5 mol % PCy_3 to the RCM catalyzed by **18** led, under typical conditions, to a low yield (54%) of the expected **12**, and 13% of the epimeric diene **21** and 27% of the epimerized RCM product **22**. Further observations suggest that this epimerization also can be promoted by secondary amines. This was dramatically evidenced in a metathesis run using catalyst **18**, which, quite unexpectedly, led to >15% **22**. Examination of the quality of starting material **11** showed the presence of 2−3% unacylated **10**, which had not been removed sufficiently by acidic washes and was responsible for the extensive isomerization of **11**. Small amounts (2%) of **21** also were produced. Thus, epimerization appears to take place on **11** prior to the RCM. Continued subjection of these mixtures to RCM conditions led to the disappearance of **21**, which was quantitatively transformed into **22**. At this point, no further epimerization took place. Although the mechanism of this epimerization has not been clarified yet, it is interesting that vinylcyclopropanes have been described to undergo RCM reaction without the complications we encountered,[17] whereas alkene migration and *Z/E* isomerizations during RCM are commonplace.[18] Ru(II) compounds are capable of isomerizing alkenes by Ru−H addition/elimination sequences.[19] Further studies aimed at understanding the origin of this novel epimerization are ongoing and will be reported.[20]

In general, 1H catalyst **18** led to the cleanest RCM product. Typically, >90% yields (HPLC quantitation) were obtained. There were four major problems with the use of **18** and the scale-up of the RCM.

First, the catalyst load needed to reach reaction completion was quite high and depended on the degree of purity of the diene. Typically, crude **11** required 5−7 mol % **18** to reach completion in refluxing dichloromethane. A charcoal/silica pad filtration produced better quality **11**, which required only 2−3 mol % **18** to undergo RCM. It was very difficult to complete the reaction with lower catalyst loads. In addition, it proved impossible to recycle any of the catalyst. Active catalyst left after the RCM was evidenced by our attempts to concentrate the RCM solution for work-up (vide infra), but this was not enough to warrant catalyst recovery.

SCHEME 3. Screen for Ru Catalyst Inactivators and Structure of 23 (MNA)



The second problem associated with **18** was the reaction time. Typically, the RCM took 24 h at reflux, which is an impractically long time in a manufacturing setting. This limitation is due to the slow kinetics using **18** and, presumably, could be overcome only by using more active catalysts.

The third problem was the dilution factor. The reaction yield was inversely proportional to the initial concentration of diene. Thus, a 0.01 M solution of **11** led to >90% yield of **12**, a 0.03−0.05 M solution led to **12** in 60−64% yield, and a 0.1 M solution led to **12** in only 45% yield. The balance probably is constituted by oligomers and dimers. In later experiments, the presence of cyclic dimers was elucidated clearly by LC−MS techniques. Thus, the effective molarity of this reaction is such that a concentration of 0.01 M cannot be exceeded, if a high yield is desired.

The fourth problem was closely related: the RCM was reversible. This first was evidenced by our attempts to scale-up the reaction. On a small scale, the reaction mixture could be evaporated safely or distilled to a small volume in preparation for work-up and isolation, whereas on a large scale, evaporation led to extensive decomposition. Quantitative experiments showed that when some of the solvent was distilled off, the HPLC yield of **12** dropped with time. Reasoning that ethylene, the coproduct of this metathesis, may be involved in product ring-opening and dimerization, we bubbled nitrogen through the solution prior to and during the distillation. This had little or no effect. We rationalized the results by hypothesizing that, in some cases, an active form of the catalyst is still present at the end of the reaction and this active form is apparently capable of ring-opening **12**. In other cases, the catalyst accidentally is completely consumed as **11** reacts, and the concentration of the solution to the small volume causes no harm to the product. Therefore, the presence of a still active catalytic species at the end of the RCM was a major hurdle toward the isolation of our product, and it became imperative to devise a means for catalyst inactivation.

Extensive screening suggested that mercaptonicotinic acid (MNA, **23**) is both capable of inactivating **18** (using 5 mol equiv at 30 °C for 6 h) and of being extracted by aqueous bicarbonate. MNA was discovered by screening potential RCM inhibitors using an easy substrate, diallyl diethyl malonate (Scheme 3). This method was applied to the synthesis of **12**, and thereafter, no decomposition was experienced upon distillation. In addition, this provided us with a tool for removing some of the Ru from the product, occasionally in conjunction with other Ru-removing agents described in the literature.

In an effort to overcome the low reactivity and low TON associated with catalyst **18**, we tested the performance of the more active second-generation catalysts **19** and **20** on the RCM reaction of **11**. Some key results are shown in Table 1.

The trend that emerges is quite clear: both second generation catalysts are kinetically more active than **18**, but they also form

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TABLE 1. RCM Reaction of 11 with Catalysts 18−20[a]

entry	catalyst (equiv)	solvent	temp (°C)	time (h)	HPLC yield **12**	% dimer content
1	**18** (5%)	CH_2Cl_2	40	24	90	<0.5
2	**18** (3.5%)	PhMe	60	20	90	<0.5
3	**19** (0.5%)	PhMe	60	4	87	8
4	**20** (1%)	PhMe	55	1	85	10

[a] Experiments were carried out with 1.0 mmol of RCM substrate in 100 mL of selected solvent under the specified conditions. The product yields were determined by quantitative HPLC assay.

considerable amounts of dimers. Although the yield of the RCM reaction is still suitable, the problem of separating 8−10 mol % cyclic dimers from **12** is significant, at least by nonchromatographic methods, and **18** becomes the catalyst of choice among the ones discussed so far. From a mechanistic standpoint, this suggests that the reaction is reversible under the conditions used and that more active catalysts (**19** and **20**) are responsible both for rapid ring closure as well as rapid reopening and dimerization.

To confirm the reversibility of the reaction under our conditions, we carried out a simple test; that is, we probed the ring-opening of **12** to **11** under typical RCM conditions. To create the appropriate conditions, we ran the RCM reaction of **11** in the same container as the ring-opening (i.e., reverse RCM) of a similar substrate (**24**), guaranteeing the presence of RCM-active catalysts, presumably Ru methylidenes (Scheme 4).

When **11** was treated with **18** under standard conditions in dichloromethane, the reaction was slow ($t_{1/2}$ > 500 min) and ethylene evaporation probably took place, thereby driving the equilibrium toward the RCM product. Usually <1% **11** was left. To study the presumed equilibrium, we chose to study the reaction using a more active catalyst under sealed tube conditions. Thus, **11** was treated with 2.5 mol % **19** in the presence of 1 equiv of RCM product **24**. Interestingly, the reaction was very rapid ($t_{1/2} \approx 0.5$ min) and reached an apparent equilibrium in less than 10 min. When the vessels were cooled, opened, and quickly analyzed, it was shown that both systems, **11**/**12** and **24**/**25**, reached a 17.5:1 molar ratio of RCM product/diene. Also, in both cases a 7% dimer content (by HPLC area %) was estimated. These dimers comprise the homodimers originating from **11** and **25** as well as the heterodimers originating from cross metathesis. No attempt was made to separate, analyze, and quantitate all these dimers, and their presence was confirmed, by LC−MS (Figure 3). When these experiments were conducted in an open system and ethylene was swept away, the RCM reaction quickly proceeded to completion, but the dimers consistently were formed and their concentration did not change with time.

Finally, when the major component of the dimeric mixture was isolated by preparative HPLC (exact structure unknown) and was submitted to typical reaction conditions in the presence of **19** and ethylene, **12** was obtained in better than 60% conversion (Scheme 5).

All these experiments prove that the more active catalysts **19** and **20** lead to a rapid equilibration of the system. Both the RCM and ring-opening occur in a matter of minutes. Therefore, it is likely that the concentrations represented in **Figure 3** are equilibrium concentrations under the particular conditions employed. Although removal of ethylene can drive the RCM to completion, the dimer formation also is fast with these systems. As shown in Scheme 5, dimer reopening also is quite smooth. This is only a qualitative experiment, because the ethylene concentration was not measured and the dimer concentration and composition were not rigorously determined. Nevertheless, the qualitative picture presented here is very informative.

In contrast to **19** and **20**, **18** is less active under these conditions and leads to very little or no dimer formation; that is, the RCM products are more kinetically stable under the conditions used. From a preparative standpoint it is clear that the less active Hoveyda Ru species **18** represents the best catalyst for our system, despite the longer reaction times needed.

Ether Formation and Completion of the Synthesis (12 → 1). Careful basic hydrolysis of **12** easily produced **13** under conditions that minimized hydrolysis of the methyl ester (typically lithium hydroxide, LiOH, in THF at subambient temperatures). Mitsunobu displacement with **4** in THF led directly to **16** in variable yields (35−50%). A typical problem in the Mitsunobu reaction was the consumption of **13** to a myriad of products, whereas up to 50−60% of **4** remained unreacted. Our assumption was that solvolysis of the Mitsunobu intermediate derived from **13** was competing with the S_N2 displacement. The most sensible solution was to use an intermediate less prone to solvolysis, and a sulfonate ester seemed like a reasonable candidate. In addition, if the side reactions are truly caused by solvolysis (i.e., S_N1 reaction), and product formation is the result of an S_N2 displacement, it is possible that different sulfonates may lead not only to different reaction rates but also to different product distributions, because it is unlikely that the relative abilities of different sulfonate esters to undergo S_N1 vs S_N2 reaction are absolutely identical.

This idea proved fruitful. A number of sulfonates were prepared and subjected to etherification under a variety of conditions. The mesylate (**14**, Scheme 1) was used initially and the reaction was partially optimized. *N*-Methyl-pyrrolidininone (NMP) at 50−80 °C and the use of cesium carbonate as base represent one of the best set of conditions possible. Organic bases such as LiHMDS, tertiary amines, or other inorganic bases, such as potassium or sodium carbonate, gave lower yields. Under the best conditions, the displacement using **14** led to 54% isolated yield of **16**. The yield with the corresponding tosylate was not much better (55%), whereas the triflate proved extremely unstable and led to no etherification. Finally, brosylate **15** proved to be the ideal intermediate, leading to >85% HPLC yields of the final intermediate **16**, with isolated yields of 81−83%.

The concentration effect also was elucidated. When the reaction was run at 0.4−0.5 M concentration for each of the two reactants, an optimal HPLC yield of 85% was obtained. More concentrated batches could not be conveniently run; the yield dropped to ca. 78% at 0.2 M concentration and even further at lower concentrations. This supports our hypothesis of a unimolecular reaction being responsible for the decomposition of **15**, whereas the etherification is second order. Compound **15** degraded, in a blank experiment (NMP, 50 °C) via first-order kinetics with a $t_{1/2}$ of 21 h.

Final hydrolysis using LiOH again, this time at rt, yielded BILN 2061 (**1**) in ca. 94−95% isolated yield after crystallization from EtOH/water. The product was typically 98.5−99.0% pure according to a quantitative assay vs an analytical standard, which was sufficient for initial preclinical studies. The balance was constituted by organic volatile impurities and a small number of organic impurities each accounting for <0.15% by HPLC. Thus, a convergent, scalable synthesis of BILN 2061 that

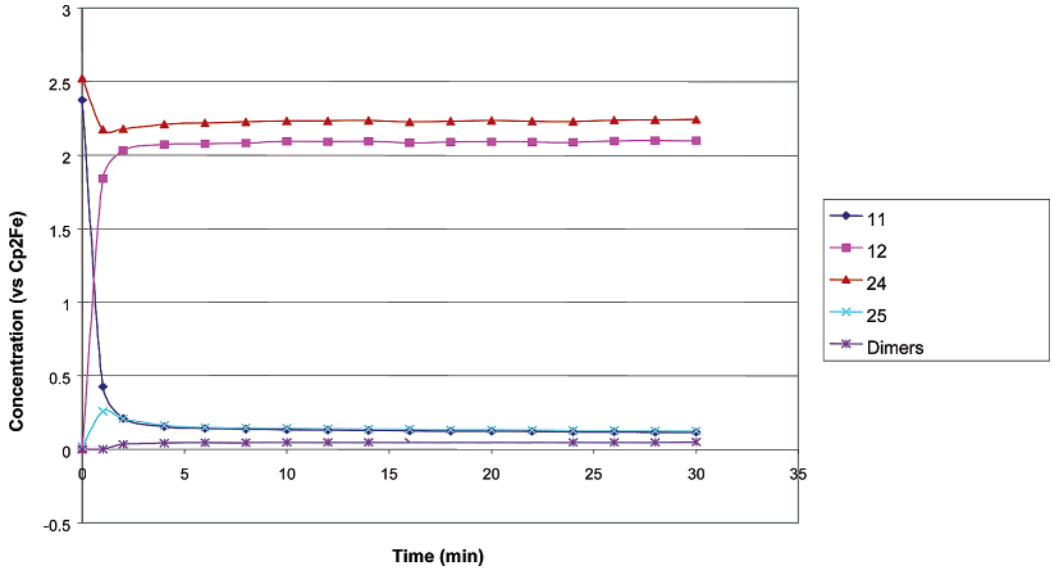
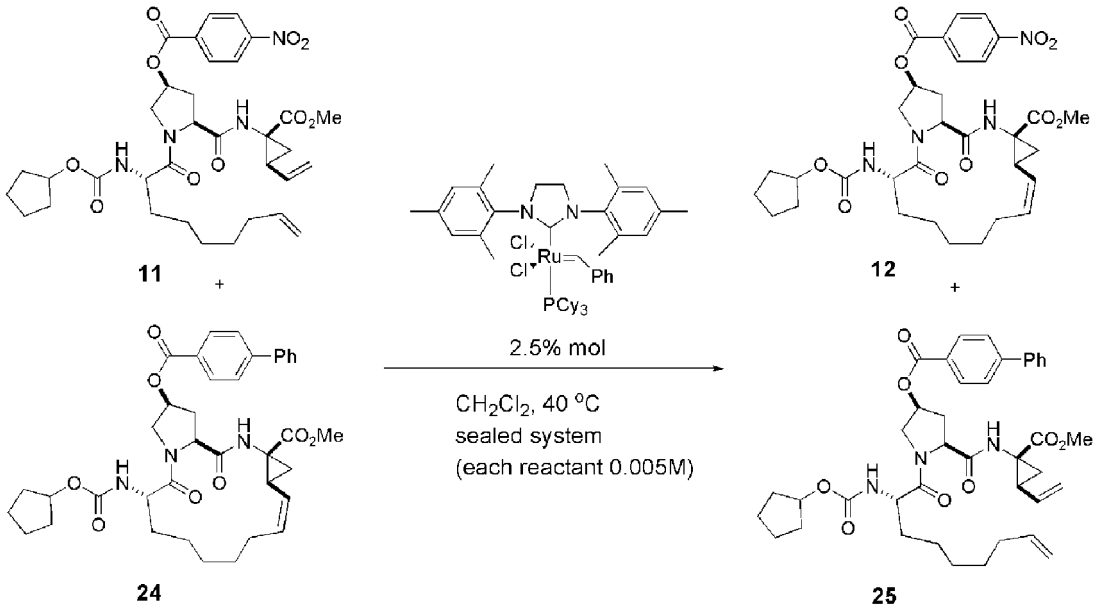


FIGURE 3. Reversibility experiment for the RCM reaction of **11** and **25**.

SCHEME 4. Reversibility Test for the RCM Reaction of 11



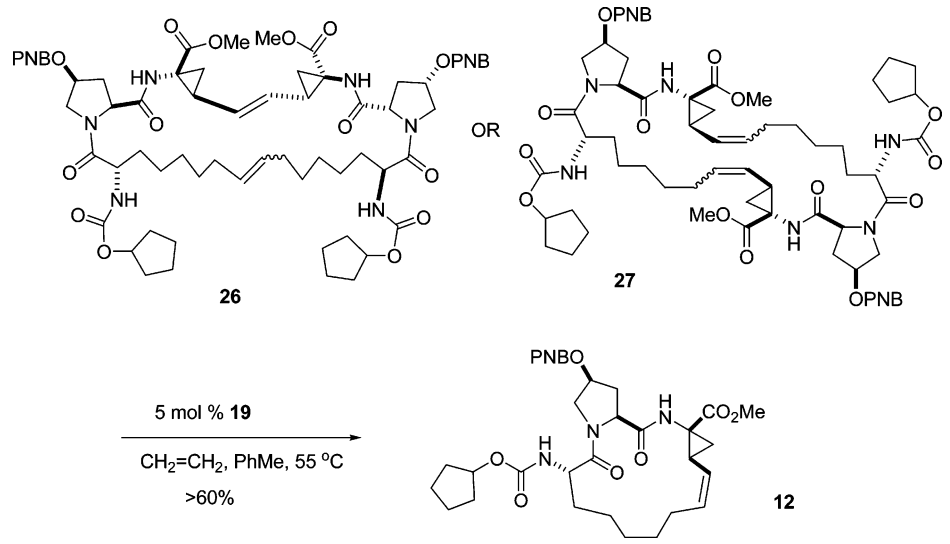
minimizes purifications and avoids chromatographies was at hand. The next challenge was to streamline the assembly and improve the practicality and the productivity of the process.

Ru Removal. A variety of techniques were used throughout our work to remove the Ru from the final API.[21] Levels of Ru in all intermediates post-RCM were measured by inductively coupled plasma (ICP) spectroscopy using a validated assay. It was important to track the level of Ru all the way to **1** and assess the ability of each step (purification and work-up) to reduce the Ru content. Many assays were run under a large variety of reaction and purification conditions. For example, a 30 g lab run using the synthesis in Scheme 1 yielded the following Ru values: in **12**, after double wash with **23** and silica pad filtration, 159 ppm Ru; after hydrolysis and brosylation, **15** had 145 ppm Ru (little or none removed); after ether formation, **16** contained 124 ppm Ru; charcoal treatment in EtOAc and crystallization of **16** led to purified product in ca. 90% yield and only 4 ppm Ru. Slight variations on this best scenario (i.e., using different grades of charcoal, different solvents) gave levels of Ru around 5−30 ppm. After hydrolysis and crystallization, the API (**1**) had typically <5 ppm Ru. Thus, Ru removal did not prove to be an insurmountable problem here. The strategy of carrying out the final purification at the stage of crystalline **16** eliminated most organic impurities and also dramatically reduced the Ru levels.

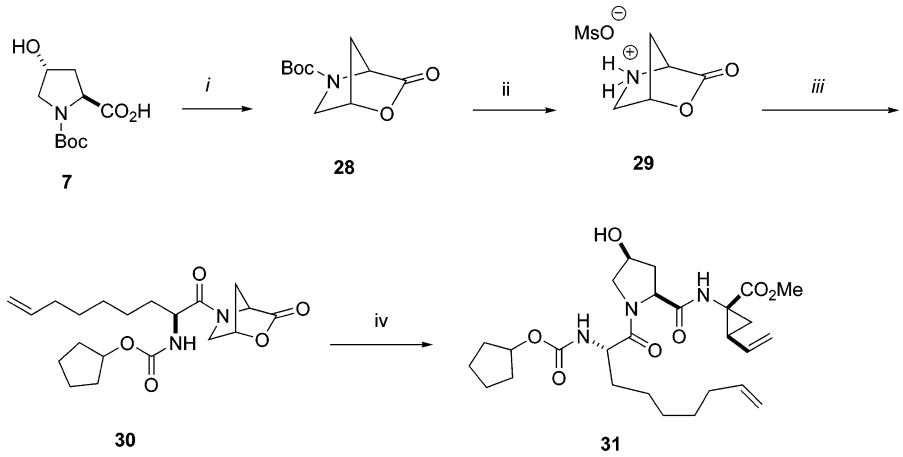
Pilot Plant Synthesis of BILN 2061. Our expedient assembly of BILN 2061 features a Mitsunobu reaction, which was marred by low mass and volume efficiency. In addition, extensive protection/deprotection operations (Boc and PNB groups) were

(21) For references on Ru removal see: (a) Ahn, Y. M.; Yang, K.; Georg, G. I. *Org. Lett*. **2001**, *3*, 1411. (b) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett*. **1999**, *40*, 4137. (c) Paquette, L. A.; Schloss, J. D.; Efremov, I.; Fabris, F.; Gallou, F.; Mendez-Andino, J.; Yang, J. *Org. Lett*. **2000**, *2*, 1259. (d) Cho, J. H.; Kim, B. M. *Org. Lett.* **2003**, *5*, 531.

SCHEME 5. Reversibility of Dimer Formation



SCHEME 6. Final Assembly of RCM Precursor[a]



[a] **Conditions**: (i) MsCl, *N*-methylpyrrolidine, THF, −10 °C; then *i*Pr$_2$NEt, dioxane, reflux (70%); (ii) MsOH, MeOAc, 50 °C (91%); (iii) **3**, EDC, *i*Pr$_2$NEt, CH_2Cl_2, rt (98%); (iv) 1.4 equiv of Na ethyl hexanoate, **6**, H_2O, rt (92%).

rendered necessary. Attachment of costly vinylcyclopropane amino acid **6** also was carried out as the first step, which was undesirable. We sought, therefore, an assembly strategy that reduced the number of steps and improved the overall throughput and cost scenario.

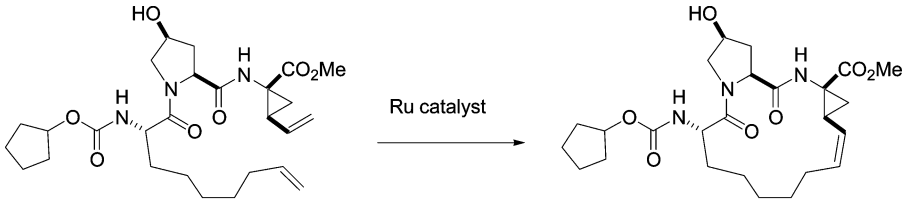
Our most efficient synthetic route for the RCM precursor is depicted in Scheme 6. To avoid the inefficient Mitsunobu reaction, we resorted to formation of lactone **28.**[22] The mesylate derived from **7** can be cyclized in situ to **28** and easily purified by crystallization directly from the reaction mixture by addition of water, in acceptable yield (ca. 70%) and excellent quality (>98% purity).

The lactone ring formation provided the required inversion of configuration at the hydroxyl moiety of hydroxyproline in high diastereomeric excess. The cleavage of the Boc group was smooth using methanesulfonic acid in MeOAc to form the crystalline mesylate **29** in excellent yield and quality, whereas the corresponding hydrochloride and hydrobromide were highly hygroscopic. The lactone **29**, unstable to water, was completely transformed into the *cis*-hydroxyproline after 6 days of storage under wet air. Due to its hygroscopicity, polarity, and the lack of a chromophore in the molecule, the only way to measure reliably and reproducibly the yield of **29** was by quantitative ^{1}H NMR methods.

The peptide coupling with amino nonenoic acid derivative **3** was preferably carried out with EDC as the coupling reagent. Epimerization was shown to be of no concern when the reaction was performed at rt, and therefore, we could avoid the use of HOBT. The dipeptide **30** was recrystallized from PhMe/heptane. However, with a melting point of just 46 °C, the material could not be easily dried and handled. It also was not possible to isolate the product and use the crude substance, after simple aqueous work-up, for the next step. The lactone ring served in this reaction as an internal protecting group for the carboxylate moiety in hydroxyproline. The dipeptide **30** can be reacted with the amino acid derivative **6** directly, that is, without the use of any peptide coupling reagent, simply using sodium 2-ethylhexanoate as the base in water.[23] Evidently, the strain of the lactone ring was sufficient activation to attach the third amino acid in very good yield (95%). Therefore, the overall assembly

(22) (a) Bowers-Nemia, M. M.; Joullié, M. M. *Heterocycles* **1983**, *20*, 817. (b) Gomez-Vidal, J. A.; Silverman, R. B. *Org. Lett.* **2001**, *3*, 2481.

SCHEME 7. RCM of Alternative Substrate 31



31 **13**

TABLE 2. RCM Reaction of 31 under Selected Conditions[a]

entry	catalyst (mol %)	solvent	temp (°C)	time (h)	HPLC assay yield (%)	total dimers (area %)
1	**18** (2−5%)	CH_2Cl_2	40	20	75−82	12−13
2	**19** (2%)	CH_2Cl_2	40	20	78	13
3	**19** (2%)	PhMe	60	0.1−18	72	15−20
4	**20** (1%)	PhMe	55	1	65	9−11
5	**20** (1.2%)	1:4 PhMe/THF	60	8	88	6

[a] Experiments were carried out with 1.0 mmol of RCM substrate in 100 mL of selected solvent under the specified conditions. The product yields were determined by quantitative HPLC assay.

effort could be shortened substantially using the hydroxyproline lactone. This key intermediate provided the three most favorable features to our synthesis: it introduced the right C-4 stereochemistry at a very early stage, when no other amino acid was present in the substrate; it served as a protecting group in the first peptide coupling step and as an activating group in the second one. In addition, the lactone moiety was coupled without generating a molecular fragment and without the use of any peptide coupling reagent, which translated into a very atom-economical process.[24]

RCM with 31. We next examined the RCM reaction of **31** to **13** (Scheme 7). Diene **31** structurally differs from our previous substrate **11** only by the absence of the PNB protecting group at the hydroxyproline residue. Although there are examples of remote polar substituents affecting the rate and stereoselectivity of RCM reactions,[25] we hoped that **31** would behave exactly like **11**. To our dismay, the RCM reaction of **31,** using the even less reactive catalyst **18,** led to substantial amounts of cyclic dimers under the previously developed conditions (Table 2). Thus, dimerization of **31** was triggered even by the milder **18**.

A rationalization for this discrepancy is difficult to provide. It is possible that removal of the PNB protecting group brings about a conformational shift in the RCM precursor, or at least decreases the relative proportion of the conformers that lead to RCM, thereby favoring intermolecular reactions.

When we decided to screen cosolvents that would diminish the relative proportion of these dimers, we found that ethers slow the dimerization with only a slight retardation of the RCM reaction. After much experimentation, THF was found to be the best cosolvent. Under these conditions (Table 2, entry 5), the yield of **13** was quite suitable (88%), but the removal of 6% dimers without resorting to chromatography proved challenging (vide infra).

RCM with 32. An alternative to the metathesis of unprotected **31** would be the introduction of a protecting group at the free hydroxyl group of the 4-hydroxy proline moiety. This would add two steps to our assembly, therefore rendering the whole synthesis less efficient than the earlier one of Scheme 1. Therefore, we decided to switch the two final construction steps, that is, protect the hydroxyl group as a brosylate, and carry out the RCM on this species, followed by the ether formation. This strategy proved to be very successful. Thus, **31** was treated with brosyl chloride and 4-dimethylaminopyridine/triethylamine (DMAP/NEt_3) to yield brosylate **32** in about 90% yield. This typically was used in situ for the RCM reaction (Scheme 8). A similar study to that shown in Table 2 was carried out on **32** (Table 3).

The brosylate neither decomposed nor solvolysed in the nonpolar solvents we employed. These experiments confirmed that the course of the RCM depends on the substituent at the hydroxyl group of the proline moiety. In general, the milder catalyst **18** led to the smallest proportion of dimers (4−5%), whereas the second generation catalysts provided relatively high levels of dimers (>15%).

In this case, addition of THF to the system of entry 2 slowed the overall reaction without significantly reducing the proportion of dimers. Thus, the THF effect seems to require a free hydroxyl group, an observation that is extremely hard to rationalize, even speculatively. In the end, RCM of brosylate **32** was selected because it produced a slightly lower proportion of dimers vs **31** while leading to a comparable yield of RCM product.

Completion of the Synthesis and Removal of the Dimers. After some experimentation, we found that subjecting the crude RCM product to the etherification reaction led to final intermediate **16** in the customary yield (82−83%). Recrystallization of this intermediate from EtOAc/methylcyclohexane (1:1.5) removed most of the dimers. Purification of **16** obtained from RCM of **32** was easier than purification of **16** obtained from RCM of **31**. The extra 2% dimers obtained with the latter substrate often required a second recrystallization to reduce the content of the major dimer to <0.1%, which was required to match the quality of the batches previously obtained. Typically, recrystallization led to a recovery of ca. 90% with a total impurity content <0.25%, which was sufficient to use the API for clinical studies.[26]

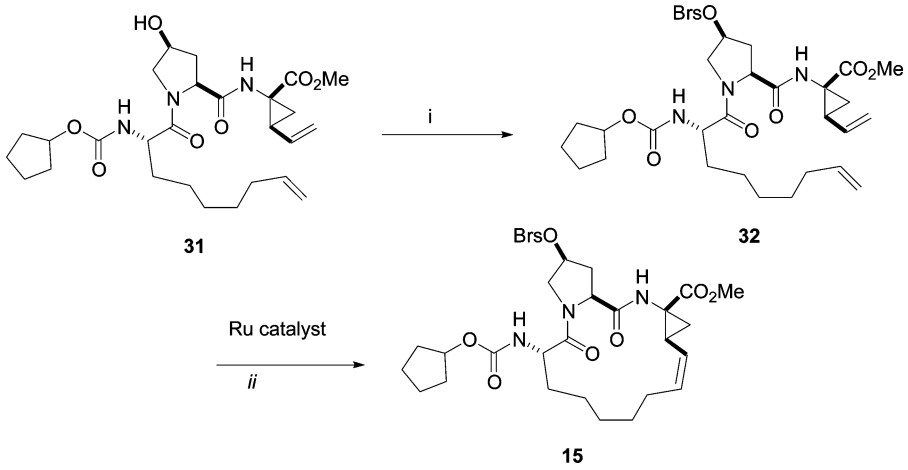
(23) Liu, W.; Xu, D. D.; Repiè, O.; Blacklock, T. J. *Tetrahedron Lett.* **2001**, *42*, 2439.

(24) Trost, B. M. *Science* **1991**, *254*, 1471.

(25) (a) Couladouros, E. A.; Mihou, A. P.; Bouzas, E. A. *Org. Lett*. **2004**, *6*, 977. (b) Bourgeois, D.; Pancrazi, A.; Ricard, L.; Prunet, J. *Angew. Chem., Int. Ed.* **2000**, *39*, 726. (c) Fürstner, A.; Thiel, O. R.; Blanda, G. *Org. Lett*. **2000**, *2*, 3731. (d) Lee, C. W.; Grubbs, R. H. *Org. Lett*. **2000**, *2*, 2145. (e) Meng, D.; Su, D.-S.; Balog, A.; Bertinato, P.; Sorensen, E. J.; Danishefsky, S. J.; Zheng, Y.-H.; Chou, T.-C.; He, L.; Horwitz, S. B. *J. Am. Chem. Soc*. **1997**, *119*, 2733.

(26) The procedure described here was scaled to multikilo levels in our pilot plant and was scaled to produce >100 kg of API in our Ingelheim production plants. See: Nicola, T.; Brenner, M.; Donsbach, K.; Kreye, P. *Org. Process Res. Dev*. **2005**, *9*, 513.

SCHEME 8. Synthesis and RCM Reaction of Brosylate 32[a]



[a] **Conditions**: (i) *p*-$BrC_6H_4SO_2Cl$ (BrsCl), *t*-BuOK, THF, −5 °C (95%); (ii) see Table 3.

TABLE 3. RCM Reaction of 32 under Selected Conditions[a]

entry	catalyst (mol %)	solvent	temp (°C)	time (h)	HPLC assay yield (%)	total dimers (area %)
1	**18** (4%)	CH_2Cl_2	40	20	83	4−5
2	**18** (4%)	PhMe	80	20	87	4−5
3	**18** (2%)	PhMe	60	20	85	5−6
4	**19** (2%)	PhMe	60	2	72	14−15
5	**20** (2%)	PhMe	60	2	69	16−17

[a] Experiments were carried out with 1.0 mmol of RCM substrate in 100 mL of selected solvent under the specified conditions. The product yields were determined by quantitative HPLC assay.

In conclusion, we have shown two related assemblies of the tripeptide RCM precursor related to BILN 2061. We have studied in detail the RCM reaction and have shown that it proceeds in suitable yield and is readily scalable. We believe this is the first large-scale[26] pharmaceutical application described in the literature for this eminently popular and versatile synthetic transformation. Finally, etherification to provide the final drug candidate has been optimized. The main future challenges in this program are to improve the practicality of the RCM step, that is, lower the catalyst load, increase the reaction rate, and overcome the high dilution (0.01 M) conditions that plague the current RCM conditions. Our best solutions to the above problems will form the subject of future studies.

Experimental Section

(2S,4*R*)-4-Hydroxy-2-[(1*R*,2*S*)-1-methoxycarbonyl-2-vinylcyclopropylcarbamoyl]pyrrolidine-1-carboxylic Acid *tert*-butyl Ester (8). A suspension of **7** (1.215 kg, 5.254 mol) and **6** (1.65 kg, 5.254 mol) in MeCN (10.5 L) was stirred at rt as diisopropylethylamine (1.7 kg, 13.13 mol) was added. When the mixture became a clear solution, 1-hydroxybenzotriazole (HOBT) monohydrate (0.8 kg, 5.254 mol) was added followed by EDC (1.1 kg, 5.78 mol). The reaction mixture was stirred at 22 °C for 1 h, and HPLC analysis indicated that the reaction was complete. The reaction mixture was concentrated, the residue was diluted with EtOAc, and the solution was washed with a solution of 0.5 M NaOH/20% NaCl (1:1) twice. The organic layer was concentrated to give crude **8** (1.55 kg, 83% assay yield by HPLC). The crude product was used for the next step directly; $[\alpha]^{25}_D$ −46.4 (c = 0.93, MeOH). ^{1}H NMR (rotamers, DMSO-d_6, 400 MHz): δ 8.64 (s, 0.74 H), 8.59 (s, 0.26 H), 5.68−5.59 (m, 1 H), 5.29−5.23 (m, 1 H), 5.11−5.07 (m, 1 H), 5.02 (br d, J = 4.0 Hz, 1 H), 4.23 (br s, 1 H), 4.07 (br t, J = 8.0 Hz, 1 H), 3.58, 3.57 (2 s, 3 H), 3.46−3.38 (m, 1 H), 3.29−3.22 (m, 1 H), 2.18−1.99 (m, 2 H), 1.87−1.81 (m, 1 H), 1.68−1.60 (m, 1 H), 1.39 (s, 2.3 H), 1.34 (s, 6.7 H), 1.29−1.22 (m, 1 H). ^{13}C NMR (rotamers, DMSO-d_6, 100 MHz): δ 173.3, 173.0, 170.5, 170.4, 153.7, 153.4, 134.2, 134.1, 117.5, 117.3, 78.5, 78.4, 68.3, 67.6, 58.7, 58.6, 54.8, 54.6, 51.9, 51.8, 38.8, 38.1, 32.7, 30.1, 28.0, 27.9, 22.4, 22.3. HRMS calcd for $C_{17}H_{27}N_2O_6$ [M + H] 355.1791, found, 355.1850.

4-Nitro-benzoic Acid 5-(1-methoxycarbonyl-2-vinylcyclopropylcarbamoyl)pyrrolidin-3-yl Ester HCl (10). To a solution of crude dipeptide **8** (23 g by HPLC assay, 50.8 mmol) in anhydrous THF (150 mL), PPh_3 (16.65 g, 63.5 mmol) and *p*-nitrobenzoic acid (10.60 g, 63.5 mmol) were added. The resulting solution was cooled to 0−3 °C in an ice−water bath as a solution of DIAD (15.4 g, 76.2 mmol) in THF (30 mL) was added at such a rate to keep the internal temperature below 5 °C. The reaction mixture was allowed to warm to rt over 30 min and stirred at rt for 2 h, at which point HPLC analysis indicated the reaction was complete. The reaction mixture was concentrated under reduced pressure. The residue was diluted with ethyl acetate (200 mL), and the organic layer was washed with aq. 2% $NaHCO_3$ (2 × 100 mL) and concentrated. The residue was evaporated from EtOAc (2 × 100 mL) and dioxane (60 mL) to obtain 72 g of residue. The residue was diluted with dioxane (15 mL) and treated with 4 N HCl (76 mL) in dioxane. The reaction mixture was stirred at rt for 1 h, at which point HPLC analysis showed the reaction was complete. The mixture was concentrated to dryness and was evaporated from EtOAc (100 mL). The residue was slurried at rt with EtOAc to remove the residual PPh_3. The solids were filtered and dried at 45 °C under vacuum to give 19.4 g (88%) of **10**; $[\alpha]^{25}_D$ −9.6 (c = 1.98, MeOH). ^{1}H NMR (DMSO-d_6, 400 MHz): δ 9.66 (s, 1 H), 8.32 (d, J = 8.7 Hz, 2 H), 8.17 (d, J = 8.7 Hz, 2 H), 5.67−5.55 (m, 2 H), 5.27 (d, J = 17.1 Hz, 1 H), 5.11 (d, J = 10.4 Hz, 1 H), 4.41 (dd, J = 10.4, 3.6 Hz, 1 H), 3.63−3.52 (m, 2 H), 3.47 (s, 3 H), 2.79 (ddd, J = 15.4, 10.4, 5.5 Hz, 1 H), 2.35 (br d, J = 14.4 Hz, 1 H), 2.25 (q, J = 8.9 Hz, 1 H), 1.62 (dd, J = 7.9, 5.3 Hz, 1 H), 1.22 (dd, J = 9.5, 5.3 Hz, 1 H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 169.9, 169.0, 163.4, 150.3, 134.6, 133.8, 130.9, 123.5, 117.9, 73.9, 57.4, 52.1, 50.5, 35.9, 32.5, 22.1. HRMS calcd for $C_{19}H_{22}N_3O_7$ [M + H] 404.1380, found 404.1452.

Anal. Calcd for $C_{19}H_{22}ClN_3O_7$: C, 51.88; H, 5.04; N, 9.55. Found: C, 51.68; H, 4.90; N, 9.47.

4-Nitro-benzoic Acid 1-(2-Cyclopentyloxycarbonylamino-non-8-enoyl)-5-(1-methoxycarbonyl-2-vinylcyclopropylcarbamoyl)-pyrrolidin-3-yl Ester (11). A solution of **3** (12.73 g, 44.9 mmol), TBTU (15.3 g, 47.5 mmol), and diisopropylethylamine (7.5 mL) in dichloromethane (80 mL) was stirred at rt as a suspension of **10**

(19.0 g, 43.2 mmol), and diisopropylethylamine (7.5 mL) in dichloromethane (80 mL) was added over 20 min. Additional diisopropylethylamine (3.5 mL) was added, and the reaction was stirred at rt for 1.5 h, at which point the reaction was complete. The mixture was concentrated, and the residue was diluted with toluene (100 mL) and MTBE (200 mL). The organic layer was washed with half-saturated $NaHCO_3$ to remove HOBT and with water to remove tetramethylurea. The organic layer was concentrated, and the residue was stripped from toluene (160 mL) to give the crude product **11** (27.3 g by HPLC assay, 95%) as a thick oil; $[\alpha]^{25}_D$ +6.8 (*c* 1.98, MeOH). ^{1}H NMR (rotamers, $CDCl_3$, 500 MHz): δ 8.25−8.15 (m, 4 H), 7.81 (s, 1 H), 5.72−5.69 (m, 2 H), 5.62−5.58 (m, 1 H), 5.22−5.09 (m, 4 H), 4.95−4.88 (m, 2 H), 4.81 (d, J = 7.9 Hz, 1 H), 4.52−4.45 (m, 1 H), 4.25−4.15 (m, 1 H), 3.78 (d, J = 12.0 Hz, 1 H), 3.55, 3.38 (2s, 3 H), 3.00 (d, J = 13.8 Hz, 1 H), 2.30−2.20 (m, 1 H), 2.03−1.25 (m, 21 H). ^{13}C NMR (rotamers, $CDCl_3$, 125 MHz): δ 174.0, 170.3, 164.2, 156.3, 150.6, 138.5, 135.1, 133.5, 133.4, 131.1, 130.9, 123.4, 118.0, 114.6, 114.4, 78.1, 74.3, 72.7, 59.1, 53.2, 52.4, 52.0, 40.0, 33.8, 33.5, 33.4, 33.3, 32.8, 32.7, 31.2, 28.7, 28.6, 28.5, 25.1, 23.6, 23.0. HRMS calcd for $C_{34}H_{45}N_4O_{10}$ [M + H] 668.3057, found 669.3132.

(1*S*,4*R*,6*S*,7*Z*,14*S*,18*S*)-14-Cyclopentyloxycarbonylamino-18-(4-nitro-benzoyloxy)-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^{4,6}]-nonadec-7-ene-4-carboxylic Acid Methyl Ester (12). A solution of **11** (668.7 g, 1.0 mol) in CH_2Cl_2 (100 L) was degassed by bubbling nitrogen. Hoveyda catalyst **18** (30 g, 0.05 mol) was added at rt. The reaction mixture was heated at reflux for 24 h, at which point the HPLC analysis indicated that the reaction was complete. The reaction mixture was cooled to 30 °C and 2-mercaptonicotinic acid (155.2 g, 1.0 mol) was added followed by triethylamine (101.2 g, 1.0 mol). The mixture was stirred at 30 °C for 30 min and then concentrated. The residue was diluted with toluene (25 L), and the solution was stirred at 55 °C for 6 h. The solution was cooled to rt and washed with 0.5 M $NaHCO_3$ (2 × 25 L). Activated carbon (0.5 kg) was added to the organic layer, and the mixture was stirred at 35 °C overnight (15 h). The mixture was filtered and concentrated to give crude product **12** (557.3 g by HPLC assay, 87%). This crude product was used directly for the next step. ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.25 (AB d, J = 8.6 Hz, 2 H), 8.22 (AB d, J = 8.6 Hz, 2 H), 7.14 (s, 1 H), 5.63 (dd, J = 5.3, 5.3 Hz, 1H), 5.47 (dt, J = 10.9, 4.9 Hz, 1 H), 5.38 (d, J = 8.1 Hz, 1 H), 5.14 (t, J = 9.0 Hz, 1 H), 5.08 (br s, 1 H), 5.01 (d, J = 8.8 Hz, 1 H), 4.64 (br dd, J = 6.7, 6.7 Hz, 1 H), 4.37 (dd, J = 12.2, 5.5 Hz, 1 H), 3.86 (d, J = 12.9 Hz, 1 H), 3.29 (s, 3 H), 2.98 (d, J = 14.3 Hz, 1 H), 2.35−2. 22 (m, 2 H), 2.16 (q, J = 3.9 Hz, 1 H), 2.02−1.58 (m, 12 H), 1.52−1.18 (m, 7 H). HRMS calcd for $C_{32}H_{41}N_4O_{10}$ [M + H] 641.2744, found 641.2824.

(1*S*,4*R*,6*S*,7*Z*,14*S*,18*S*)-14-Cyclopentyloxycarbonylamino-18-hydroxy-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic Acid Methyl Ester (13). A solution of **12** (48.74 g by HPLC assay, 76.1 mmol) in THF (300 mL) was stirred at −5 °C as a solution of LiOH−H_2O (3.35 g, 79.9 mmol) in water (100 mL) was added over 2 h while the temperature was kept at −2 to 0 °C. After the reaction was stirred for another hour, HPLC analysis indicated that the reaction was complete. The reaction was neutralized with 1 N HCl (∼8 mL) at 0 °C until pH = 7. The reaction mixture was diluted with EtOAc (570 mL) and the organic layers were washed with 5% $NaHCO_3$ (2 × 250 mL) and 2% NaCl (200 mL) and concentrated to give crude product **13** as an oil (33.26 g by HPLC assay, 89%). ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.38 (br s, 1 H), 5.58 (dt, J = 9.5, 9.5 Hz, 1 H), 5.35 (d, J = 7.8 Hz, 1 H), 5.27 (t, J = 9.4 Hz, 1 H), 5.00−5.18 (m, 2 H), 4.73 (d, J = 9.3 Hz, 1 H), 4.42−4.50 (m, 2 H), 3.91 (dd, J = 11.1, 4.3 Hz, 1 H), 3.75 (d, J = 11.1 Hz, 1 H), 3.68 (s, 3 H), 2.43 (d, J = 14.4 Hz, 1 H), 2.30−2.00 (m, 4 H), 1.90−1.20 (m, 18 H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 174.4, 173.1, 169.7, 155.8, 134.4, 125.5, 77.9, 71.2, 59.5, 57.4, 52.4, 51.7, 41.2, 34.6, 32.8, 32.7, 32.1, 28.8, 27.5, 26.3, 25.4, 23.9, 23.6, 22.2. HRMS calcd for $C_{25}H_{38}N_3O_7$ [M + H] 492.2709, found 492.2704.

(1*S*,4*R*,6*S*,7*Z*,14*S*,18*S*)-18-(4-Bromo-benzenesulfonyloxy)-14-cyclopentyloxycarbonylamino-2,15-dioxo-3,16-diaza-tricyclo-[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic Acid Methyl Ester (15). A solution of brosyl chloride (6.90 g, 27.0 mmol) in CH_2Cl_2 (100 mL) was added to a solution of **13** (9.84 g by HPLC assay, 20.0 mmol), triethylamine (8.37 mL, 60 mmol), and DMAP (122 mg, 1.0 mmol) in toluene (30 mL) at ambient temperature. The reaction mixture was stirred at ambient temperature overnight (15 h). HPLC analysis indicated that the reaction was complete. The reaction mixture was diluted with toluene (40 mL), washed with 0.5 N HCl (94 mL) and 5% $NaHCO_3$ (94 mL), and concentrated to give crude **15** (13.24 g, 93% assay yield by HPLC). This crude product was used directly for the next step. ^{1}H NMR ($CDCl_3$, 600 MHz): δ 7.82 (dd, J = 8.6, 1.8 Hz, 2 H), 7.71 (dd, J = 8.6, 1.9 Hz, 2 H), 6.91 (br s, 1 H), 5.50 (dt, J = 10.9, 5.4 Hz, 1 H), 5.32 (br d, J = 7.9 Hz, 1 H), 5.22−5.16 (m, 2 H), 5.06 (m, 1 H), 4.77 (dd, J = 9.2, 1.8 Hz, 1 H), 4.53 (br t, J = 6.3 Hz, 1 H), 4.24 (dd, J = 12.1, 5.6 Hz, 1 H), 3.84 (dd, J = 12.1, 1.4 Hz, 1 H), 3.61 (s, 3 H), 2.65 (d, J = 14.5 Hz, 1 H), 2.30−2.20 (m, 1 H), 2.16−2.08 (m, 2 H), 2.05−1.91 (m, 3 H), 1.90−1.76 (m, 2 H), 1.70−1.20 (m, 14 H). ^{13}C NMR ($CDCl_3$, 150 MHz): δ 172.8, 169.7, 169.6, 155.9, 135.4, 134.1, 132.6, 129.5, 129.4, 125.5, 79.0, 78.1, 58.4, 53.3, 52.4, 51.6, 41.1, 32.7, 32.1, 31.4, 28.0, 27.9, 25.8, 25.3, 23.6, 22.5, 22.4. HRMS calcd for $C_{31}H_{41}BrN_3O_9S$ [M + H] 710.1747, found 710.1741.

(1*S*,4*R*,6*S*,7*Z*,14*S*,18*R*)-14-Cyclopentyloxycarbonylamino-18-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic Acid Methyl Ester (16). A suspension of brosylate **15** (13.24 g by HPLC assay, 18.64 mmol), **4** (5.88 g, 18.64 mmol), and Cs_2CO_3 (7.89 g, 24.23 mmol) in NMP (47 mL) was heated to 50 °C and stirred at 50 °C for 24 h. HPLC analysis indicated that the reaction was complete. After cooling to rt, EtOAc (200 mL) was added, and the suspension was washed with 2.5% $NaHCO_3$ (2 × 160 mL). NMP (80 mL) was added, and the organic layer was washed with 2.5% $NaHCO_3$ until all **4** was removed. The organic layer was washed with 2% NaCl (200 mL) and concentrated to give crude product **16** (12.3 g by HPLC assay, 84%).

The crude product **16** was dissolved with EtOAc (450 mL). The solution was heated to 40 °C and treated with charcoal (6 g) for 3 h. The mixture was filtered, and the filtrate was concentrated until the total weight was ∼85 g (∼80 mL EtOAc remained). The solution was heated to 65 °C, and heptane (120 mL) was added over 1 h.The solution then was stirred for an additional 30 min. After the suspension was cooled to rt over 2 h, was stirred at rt for 4 h and at 4−5 °C for 1 h, the crystalline solids **16** (10.7 g, >99% purity by HPLC) were collected by filtration. A full characterization of this compound was reported in ref 4; mp 176 °C; $[\alpha]^{25}_D$ +53.3 (*c* = 1.13, MeOH). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 172.9, 171.7, 170.6, 167.7, 160.65, 159.5, 155.6, 154.0, 150.8, 150.7, 132.9, 126.5, 123.0, 117.1, 115.0, 106.8, 105.4, 98.3, 76.7, 76.1, 58.1, 55.3, 52.6, 52.0, 51.8, 46.6, 40.0, 33.3, 32.1, 31.5, 30.1, 27.2, 26.8, 25.9, 24.4, 23.1, 22.3, 21.3.

(1*S*,4*R*,6*S*,7*Z*,14*S*,18*R*)-14-Cyclopentyloxycarbonylamino-18-[2-(2-isopropylamino-thiazol-4-yl)-7-methoxy-quinolin-4-yloxy]-2,15-dioxo-3,16-diaza-tricyclo[14.3.0.0^{4,6}]nonadec-7-ene-4-carboxylic Acid (1). A solution of **16** (20.0 g, 25.3 mmol) in THF (160 mL) was treated with a solution of LiOH−H_2O (2.45 g, 102 mmol) in water (54 mL) at 40−45 °C, and the mixture was stirred for 8 h at the same temperature. After complete conversion, the mixture was cooled to rt, the aqueous layer was separated, ethanol (54 mL) was added to the organic layer, and the pH was adjusted to pH 5.5−5.7 by addition of 1 M HCl. The mixture was heated to 40−45 °C, and water (80 mL) was added slowly. After precipitation started, additional water (80 mL) was added at 40−45 °C and the suspension was cooled to rt and then stirred for 1 h at the same temperature. After filtration, the precipitate was washed with water (3 × 20 mL) and dried under vacuum at 35 °C. Yield: 17.7 g (90%). A full characterization of this compound was reported in

ref 4. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.58 (s, 1 H), 8.04 (d, J = 7.5 Hz, 1H), 7.65 (d, J = 6.9 Hz, 1H), 7.44 (s, 2H), 7.29 (s, 1H), 7.19 (d, J = 5.6 Hz, 1H), 7.03 (dd, J = 9.1, 9.1 Hz, 1H), 5.55−5.42 (m, 2H), 5.29 (t, J = 9.2 Hz, 1H), 4.69 (br s, 1H), 4.47 (s, 1H), 4.50−3.93 (m, 2H), 4.15−4.09 (m, 1H), 3.90 (s, 3H), 3.85−3.81 (m, 1H), 2.50−2.38 (m, 2H), 2.22−2.16 (m, 1H), 1.90−1.70 (m, 2H), 1.75−1.16 (m, 19H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 172.8, 171.8, 171.7, 167.8, 160.7, 159.6, 155.6, 154.1, 150.8, 150.7, 132.4, 127.1, 123.1, 117.1, 115.0, 106.9, 105.4, 98.4, 76.8, 76.2, 58.2, 55.3, 52.6, 52.0, 46.7, 39.6, 33.5, 32.1, 32.1, 31.6, 29.7, 27.0, 25.9, 23.8, 23.1, 23.1, 22.3, 22.3, 21.5. IR (KBr) 3362, 3287, 2941, 2870, 1707, 1687, 1646, 1623, 1591−1332, 1444, 1421, 1279, 1218, 1140, 1052, 1025, 960, 845, 638; Anal. Calcd for $C_{40}H_{52}N_6O_9S$ (monohydrate): C, 60.59; H, 6.61; N, 10.60. Found: C, 60.54; H, 6.58; N, 10.56. HRMS (ES) calcd for $C_{40}H_{50}N_6O_8S$ [M] 774.3411, found 774.3429; $[\alpha]^{25}_D$ +39.0 (c = 1.98, MeOH); mp 200 °C.

(1*S*,4*S*)-3-Oxo-2-oxa-5-aza-bicyclo[2.2.1]heptane-5-carboxylic Acid *tert*-Butyl Ester (28). A solution of N-Boc hydroxyproline **7** (150.4 g, 0.65 mol) and *N*-methyl pyrrolidine (154.9 g, 1.82 mol) in THF (752 mL) was stirred (−10 °C) as MsCl (141.5 g, 1.24 mol) was added. After the mixture was stirred for 2 h, the reaction was complete and the mixture was washed with water (66 mL). After the reaction mixture was warmed to 5 °C, the layers were separated, and the organic layer was heated to 50 °C. THF (560 mL) was distilled off under vacuum. The reaction mixture was saturated with dioxane (752 mL), and the residual THF was distilled off from the mixture. Diisopropylethylamine (84 g, 0.65 mol) was added, and the reaction mixture was heated to 95 °C for 2 h. After the mixture was cooled to 60 °C, 300 mL of solvent was distilled off under vacuum. The mixture was treated with a solution of $KHSO_4$ (5.3 g) in water (752 mL) and cooled to rt. The crystals were collected, washed with water (2 × 150 mL), and dried in vacuo at 45 °C. Yield: 99.7 g (70%); mp 107−110 °C. The spectral data of **28** are identical to those reported.[22]

Anal. Calcd for $C_{10}H_{15}NO_4$: C, 56.33; H, 7.09; N, 6.57. Found: C, 56.15; H, 6.86; N, 6.48.

(1*S*,4*S*)-2-Oxa-5-aza-bicyclo[2.2.1]heptan-3-one Mesylate (29). A solution of N-Boc-lactone **28** (93.8 g, 0.44 mol) in MeOAc (375 mL) was heated to 45 °C, as methanesulfonic acid (84.6 mL, 0.88 mol) was slowly added over 1.5 h. The reaction mixture was cooled to rt; the crystals were collected, washed with MeOAc, and dried at 45 °C. Yield: 84.2 g (91.5%) colorless crystals; $[\alpha]^{25}_D$ +43.7 (c = 0.41, MeOH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 9.94 (br s, 2H), 5.42 (s, 1H), 4.60 (s, 1H), 3.54 (d, J = 12.0 Hz, 1H), 3.35 (d, J = 12.0 Hz, 1H), 2.60 (d, J = 12.0 Hz, 1H), 2.39 (s, 1H), 2.17 (d, J = 12.0 Hz, 1H). ^{13}C NMR (125.76 MHz, DMSO-d_6): δ 169.4, 79.0, 57.3, 48.6, 39.5, 38.2. HRMS (ES) calcd for $C_5H_7NO_2$ [M + H] 114.0550, found 114.0549.

Anal. Calcd for $C_6H_{11}NO_5S$: C, 34.44; H, 5.30; N, 6.69. Found: C, 34.37; H, 5.07; N, 6.63;

(1*R*,2*S*)-1-{[(2*S*,4*S*)-1-((*S*)-2-Cyclopentyloxycarbonylamino-oct-7-enoyl)-4-hydroxypyrrolidine-2-carbonyl]-amino}-2-vinylcyclopropanecarboxylic Acid Methyl Ester (31). A suspension of **3** dicyclohexylamine salt (521.4 g, 1.12 mol) in toluene (1.3 L) and water (0.95 L) was treated with concentrated H_2SO_4 (40.8 g, 0.4 mol) under vigorous stirring. The organic layer was washed with water (2 × 655 mL) and concentrated. The residue was dissolved in toluene (258 mL). A suspension of **29** (199.6 g, 0.95 mol) in CH_2Cl_2 (1 L) was treated with EDC−HCl (214.7 g, 1.12 mol). The above solution of **3** in toluene was added slowly at the rate to keep the internal temperature below 21 °C. The mixture was treated with diisopropylethylamine (130.3 g, 1.01 mol), and the reaction mixture was stirred for 1 h at rt. The reaction was quenched with water (634 mL), the reaction mixture was filtered, and the layers were separated. The organic layer was washed with a solution of acetic acid (10.2 g) in water (634 mL) and a solution of $NaHCO_3$ (14.3 g) in water (634 mL), dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was dissolved in toluene (634 mL) and slowly treated with *n*-heptane (2.5 L) over 1.5 h. The suspension was stirred for 1 h at rt, and the crystals were collected, washed with *n*-heptane (2 × 317 mL), and dried at room temperature in vacuo to give compound **30**. Yield: 314.6 g (98%); mp 46 °C.

A mixture of **30** (8.97 g, 23.7 mmol), **6** (7.80 g, 24.9 mmol), and sodium 2-ethylhexanoate (5.9 g, 35.6 mmol) in water (200 mL) was stirred at rt for 4 h. Toluene (200 mL) was added to the reaction mixture, and the layers were separated. The aqueous layer was extracted with toluene (50 mL). The combined organic layers were washed with aqueous Na_2CO_3 (50 mL), 0.5 N sulfuric acid (50 mL), and water (50 mL) and concentrated to dryness. Yield: 11.3 g, 21.8 mmol, 92%; $[\alpha]^{25}_D$ = −35.2 (c = 0.21, MeOH). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 7.86 (s, 1 H), 5.76−5.69 (m, 2 H), 5.27 (d, J = 17.1 Hz, 1 H), 5.17 (d, J = 8.3 Hz, 1 H), 5.12 (d, J = 10.3 Hz, 1 H), 5.04 (br s, 1 H), 4.97 (d, J = 17.3 Hz, 1 H), 4.92 (d, J = 10.2 Hz, 1 H), 4.70 (d, J = 8.9 Hz, 1 H), 4.52−4.46 (m, 1 H), 4.37−4.31 (m, 1 H), 3.85 (dd, J = 10.7, 3.7 Hz, 1 H), 3.64 (s, 3 H), 2.37 (d, J = 14.2 Hz, 1 H), 2.18−2.07 (m, 2 H), 2.05−1.99 (m, 2 H), 1.88−1.76 (m, 3 H), 1.75−1.50 (m, 8 H), 1.47−1.24 (m, 7 H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 173.6, 173.5, 169.7, 156.3, 138.6, 133.1, 118.2, 114.4, 78.0, 71.0, 59.5, 57.4, 52.3, 40.1, 34.5, 33.7, 33.5, 32.8, 32.7, 32.6, 28.8, 28.7, 28.6, 25.2, 23.6, 22.9; HRMS calcd for $C_{27}H_{42}N_3O_7$ [M + H] 520.3067, found 520.3017.

(1*R*,2*S*)-1-{[(2*S*,4*S*)-4-(4-Bromo-benzenesulfonyloxy)-1-((*S*)-2-cyclopentyloxycarbonylamino-oct-7-enoyl)pyrrolidine-2-carbonyl]-amino}-2-vinylcyclopropanecarboxylic Acid Methyl Ester (32). To a solution of **31** (9.61 g, 18.5 mmol) in toluene (50 mL), brosyl chloride (5.20 g, 20.4 mmol) was added at rt. After the mixture was cooled to 5 °C, potassium *tert*-butoxide (24% in THF, 2.49 g, 22.2 mmol) was added slowly and the mixture was stirred for an additional 15 min. The reaction mixture was washed with 1 N aqueous NaOH (20 mL), 0.5 N H_2SO_4 (20 mL), and water (20 mL), then filtered through charcoal, and concentrated. Yield: 13.0 g (95%); $[\alpha]^{25}_D$ −23.1 (c = 0.48, MeOH). ^{1}H NMR (rotamers, 500 MHz, $CDCl_3$): δ 8.20 (br s, 0.32 H), 7.74−7.62 (m, 4 H), 7.32 (br s, 0.64 H), 5.75−5.58 (m, 2 H), 5.38−5.31 (m, 1 H), 5.24−5.13 (m, 1 H), 5.09−5.00 (m, 2 H), 4.97−4.80 (m, 3 H), 4.53 (d, J = 8.8 Hz, 0.64 H), 33. 4.31 (d, J = 8.8 Hz, 0.34 H), 33. 4.28−4.20 (m, 0.60 H), 4.12−4.03 (m, 0.95 H), 3.85−3.79 (m, 0.35 H), 3.72−3.62 (m, 1 H), 3.55 (s, 1 H), 3.52 (s, 2 H), 2.64 (d, J = 14.5 Hz, 0.33 H), 2.52 (d, J = 14.5 Hz, 0.66 H), 2.26−1.88 (m, 4 H), 1.80−1.41 (m, 11 H), 1.38−1.10 (m, 7 H). ^{13}C NMR (125.76 MHz, $CDCl_3$): δ 172.8, 171.8, 170.0, 169.9, 169.8, 156.6, 155.9, 138.3, 138.1, 135.2, 135.1, 133.6, 133.2, 132.5, 132.4, 129.1, 129.0, 117.5, 117.3, 114.3, 114.2, 78.6, 78.1, 78.0, 77.7, 59.0, 58.4, 53.1, 52.9, 52.7, 52.3, 51.9, 39. 7, 39.6, 37.0, 33.6, 33.2, 33.2, 33.1, 32.5, 32.4, 32.2, 31.9, 31.1, 28.4, 28.4, 28.3, 28.2, 25.3, 24.8, 23.3, 22.6, 22.4. HRMS calcd for $C_{33}H_{45}BrN_3O_9S$ [M + H] 738.1986, found 738.2054.

Anal. Calcd for $C_{33}H_{44}BrN_3O_9S$: C, 53.66; H, 6.00; N, 5.69. Found: C, 53.09; H, 5.97; N, 5.58.

Metathesis of 32 to Compound 15. A solution of **32** (17.6 g, 23.8 mmol) in toluene (1.7 L) was degassed with nitrogen for 2 h, heated to 80 °C, and the Hoveyda catalyst **18** (605 mg, 1 mmol, 3 mol %) was added in one portion as a solid. The resulting mixture was stirred at 80 °C for 8 h, quenched by the addition of 2-mercaptonicotinic acid (**23**, 1.85 g, 11.9 mmol), and cooled to 30 °C. Toluene (1.3 L) was removed by distillation under reduced pressure to ∼1/4 of the original volume, and the organic solution was washed with a 0.5 M $NaHCO_3$ solution (400 mL). The layers were separated, and the organic layer was treated with 2-mercaptonicotinic acid (1.85 g, 11.9 mmol, 0.5 eq) at 25 °C for 1 h. The organic layer was washed with 0.5 M $NaHCO_3$ solution (2 × 400

mL) and filtered through a pad of charcoal (10 g), which was rinsed with toluene (200 mL). Concentration of the filtrate afforded 17.2 g (87% yield by HPLC assay) of crude product **15**. The spectral data are identical to those described previously for **15**.

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Supporting Information Available: ^{1}H NMR spectra of all new compounds **8**, **10**, **11**, **12**, **13**, **15**, **31**, and **32**. This material is available free of charge via Internet at http://pubs.acs.org.

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