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Total Synthesis of the Cyclopeptide Alkaloid Paliurine E. Insights into Macrocyclization by Ene−Enamide RCM

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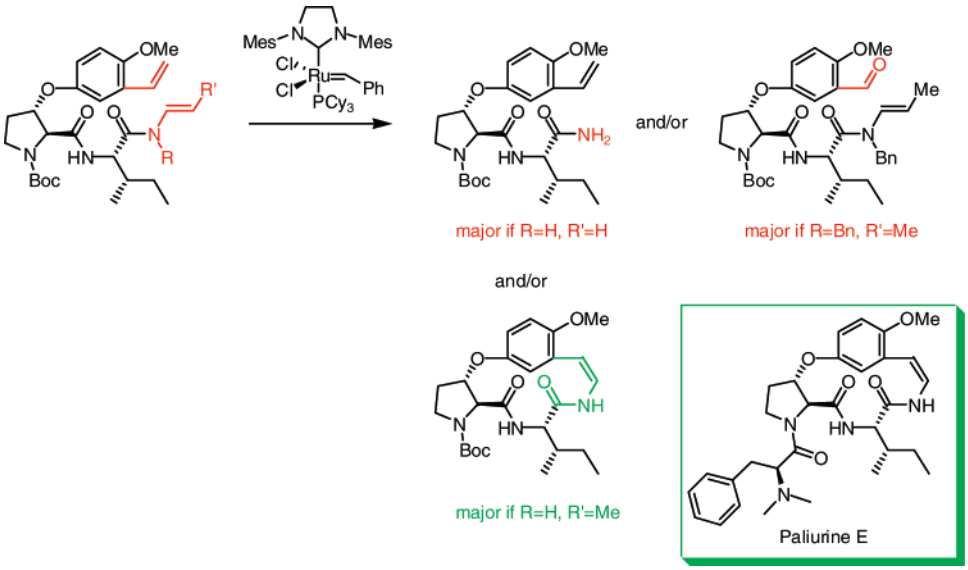

The total synthesis of (−)-paliurine E is described in 14 steps and 11% overall yield. The first successful application of ene−enamide ring-closing metathesis for macrocyclization serves as the foundation for this synthesis and allowed for a straightforward installation of the challenging cyclic enamide together with the macrocycle. In the course of these synthetic studies, we also found that very subtle and minor structural modification of the enamide resulted in dramatic and unexpected changes of their reactivity since a primary amide or an aromatic aldehyde can be obtained after reaction with Grubbs' second-generation catalyst. Further insights on the macrocyclization by ene−enamide RCM are also discussed.

Introduction

Over the last 10 years, ring-closing metathesis (RCM) has emerged as a major tool for the synthesis of complex molecules due to the development of well-defined metathesis catalysts which are tolerant to many functional groups and reactive toward a wide range of substrates.[1] With the advent of these catalysts, the reproducibility and yields have markedly improved and so has functional group tolerance. If especially efficient for the synthesis of medium-sized rings, RCM is now also recognized as one of the most straightforward and reliable methods for the formation of large ring systems. It compares favorably to all current synthetic alternatives and has been used as key step in the synthesis of an impressive number of macrocyclic natural products.[2,3]

Alkenes, alkynes, dienes, and enynes have been used as substrates for RCM, and the selective formation of one or more rings has been reported in numerous publications.[1] In contrast,

(1) For recent reviews on metathesis reactions, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012−3043. (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18−29. (c) Connon, S. J.; Blechert, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1900−1923. (d) Schrock, R. E.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592−4633. (e) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117−7140. (f) Schrodi, Y.; Pederson, R. L. *Aldrichim. Acta* **2007**, *40*, 45−52.

(2) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 4490−4527.

(3) Gradillas, A.; Pérez-Castells, J. *Angew. Chem., Int. Ed.* **2006**, *45*, 6086−6101.

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the metathesis of heteroatom-substituted olefins, which offers vast functionalization possibilities and clearly increases further the versatility of this reaction, has been studied only recently.[4] While vinylsilanes,[5] ethers,[6] boronates,[7] phosphonates,[8] chlorides,[9] fluorides,[10] vinylazinium salts,[11] as well as enamides[12] have been shown to participate in RCM to form small- to medium-sized ring systems, although with generally decreased reactivity, there are still no reports on their use for the formation of macrocyclic systems. In this contribution, we report on the first successful use of a macrocyclization by ene−enamide RCM, culminating in the first total synthesis of the 13-membered ring cyclopeptide alkaloid paliurine E. In the course of these studies, we also found that small changes in the metathesis substrates can have a dramatic impact on the course of the metathesis reaction. Investigation of the scope of the macrocyclic enamide-forming reaction also provided some insights into macrocyclization by ene−enamide RCM.

Strategic Considerations. Cyclopeptide alkaloids are natural products that have been isolated from the leaves, stem bark, root bark, and seeds of a wide variety of plant species throughout the world. They are distinguished by their structural similarity and possess a 13- (e.g., ziziphine Q), 14- (e.g., frangufoline), or 15-membered (e.g., abyssenine A) cycle containing an aromatic ring. The remainder of the macrocycle consists of a peptide unit connected to the aromatic ring in either a 1,4- or a 1,3-orientation by enamide and alkyl aryl ether (or methylene) linkages (Figure 1). To date, over 200 structures have been described and these natural products, which have been used historically for the treatment of a variety of ailments, have also been shown to display numerous biological activities including sedative, antibacterial, antifungal, and antiplasmodic.[13]

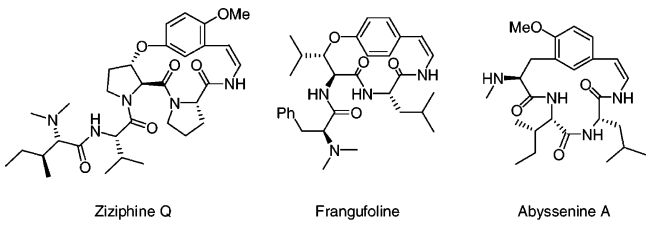

FIGURE 1. Cyclopeptide alkaloids family of natural products.

The interesting topology of these natural products coupled with their restricted natural availability (0.0002−1% of dried plants) and interesting bioactivities have drawn significant interest from the synthetic community. Several strategies have been used for the key macrocyclization step. The first synthesis of these compounds by Schmidt[14] utilized the macrolactamization of a pentafluorophenyl ester, a strategy which was later on used in the total syntheses of cyclopeptide alkaloids by Joullié[15] and Han.[16] The synthesis of sanjoinine G1 and mauritines by Zhu incorporated an intramolecular S_NAr reaction for macrocyclization.[17] A common feature of the previous synthetic efforts was the use of a four-step sequence to install the enamide (starting from the corresponding amino alcohol via thermal elimination of an intermediate selenoxide) after the crucial macrocyclization step, which somehow reduced the overall efficiency of the syntheses. More recently, we reported the use of a copper-mediated intramolecular amidation reaction to form this enamide with concomitant macrocyclization.[18,19] In the course of these synthetic studies, we considered forming the macrocyclic enamide in the recently isolated cyclopeptide alkaloid paliurine E **1**,[20] after installation of the side chain from precursor **2**, via a challenging macrocyclization by RCM starting

(4) For a review, see: Van de Weghe, P.; Bisseret, P.; Blanchard, N.; Eustache, J. *J. Organomet. Chem.* **2006**, *691*, 5078−5108.

(5) For examples, see: (a) Chang, S.; Grubbs, R. H. *Tetrahedron Lett.* **1997**, *38*, 4757−4760. (b) Denmark, S. E.; Yang, S.-M. *J. Am. Chem. Soc.* **2002**, *124*, 15196−15197. (c) Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158−3159.

(6) For examples, see: (a) Fujimura, O.; Fu, G. C.; Grubbs, R. H. *J. Org. Chem.* **1994**, *59*, 4029−4031. (b) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623−9626. (c) Rainier, J. D.; Allwein, S. P.; Cox, J. M. *J. Org. Chem.* **2001**, *66*, 1380−1386. (d) Clark, J. S.; Kimber, M. C.; Robertson, J.; McErlean, C. S. P.; Wilson, C. *Angew. Chem., Int. Ed.* **2005**, *44*, 6157−6162. (e) Liu, L.; Postema, M. H. D. *J. Am. Chem. Soc.* **2001**, *123*, 8602−8603. (f) Hekking, K. F. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751−6758. (g) Taillier, C.; Gille, B.; Bellosta, V.; Cossy, J. *J. Org. Chem.* **2005**, *70*, 2097−2108. (h) Oliver, S. F.; Högenauer, K.; Simic, O.; Antonello, A.; Smith, M. D.; Ley, S. V. *Angew. Chem., Int. Ed.* **2003**, *42*, 5996−6000. (i) Lee, A.-L.; Malcolmson, S. J.; Puglisi, A.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 5153−5157.

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(8) For examples, see: (a) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1999**, *40*, 3297−3300. (b) Stoianava, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769−1772. (c) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 8635−8638. (d) Rivard, M., Blechert, S. *Eur. J. Org. Chem.* **2003**, 2225−2228.

(9) For examples, see: (a) Chao, W.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2505−2507. (b) De Matteis, V.; van Delft, F. L.; de Gelder, R.; Tiebes, J.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2004**, *45*, 959−963. (c) Chao, W.; Mahajan, Y. R.; Weinreb, S. M. *Tetrahedron Lett.* **2006**, *47*, 3815−3818.

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(15) (a) Heffner, R. J.; Jiang, J.; Joullié, M. M. *J. Am. Chem. Soc.* **1992**, *114*, 10181−10189. (b) Xiao, D.; East, S. P.; Joullié, M. M. *Tetrahedron Lett.* **1998**, *39*, 9631−9632. (c) East, S. P.; Shao, F.; Williams, L.; Joullié, M. M. *Tetrahedron* **1998**, *54*, 13371−13390.

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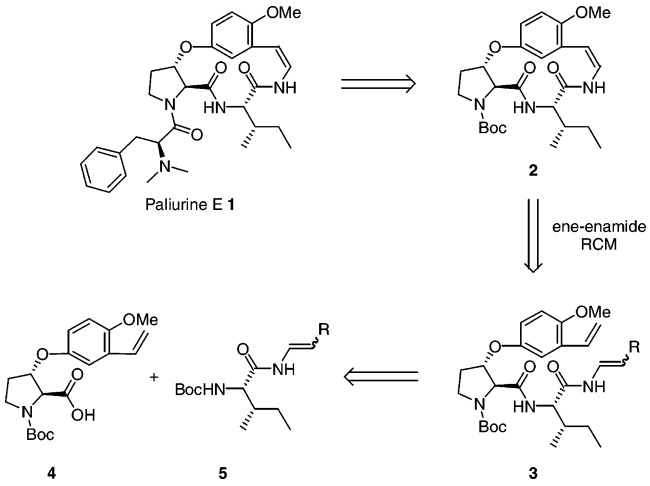
SCHEME 1. Ene−Enamide RCM-Based Retrosynthetic Analysis of Paliurine E (1)



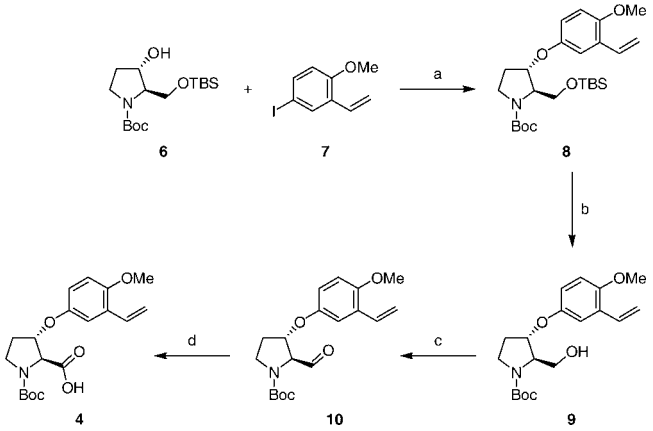
from ene−enamide **3** (Scheme 1). Despite many examples of macrocyclization using this transformation starting from dienes as substrates,[2] this strategic decision bore considerable risk and might even seem somewhat counterintuitive due to the low reactivity of enamides in RCM reactions and the presence of polar substituents in the substrate at positions where they can chelate the incipient metal carbene intermediates, which usually strongly impacts the effectiveness of the reaction.[21] However, we felt that if successful, this macrocyclization strategy would afford a straightforward entry to cyclopeptide alkaloids and could further increase the usefulness of RCM-based macrocyclizations.

For the sake of flexibility and to easily evaluate the reactivity and influence of the enamide group toward RCM, it was decided to incorporate this enamide residue at the very end of the synthesis by coupling of fragments **4** and **5**, after formation of the aryl alkyl ether in **4** (Scheme 1).

Results and Discussion

Synthesis of the Hydroxyproline−Styrene Fragment. The synthesis of the hydroxyproline−styrene fragment **4** closely followed the one we reported for the synthesis of paliurine F[18a] and commenced with an Ullmann-type copper-mediated arylation[22] between the highly functionalized hydroxyprolinol derivative **6**[18a] and iodostyrene **7**[23] using catalytic CuI and 1,10-phenanthroline, with cesium carbonate as base and a modest excess (1.6 equiv) of iodide **7** in toluene at 110 °C (Scheme 2). Under these conditions, pyrrolidinyl aryl ether **8** was obtained in 79% yield and was transformed into the corresponding carboxylic acid **4** after TBS deprotection and two-step oxidation (Swern/buffered $NaClO_2$) of the resulting primary alcohol **9**.

SCHEME 2. Synthesis of the Hydroxyproline−Styrene Fragment 4[a]



[a] Reagents and conditions: (a) CuI (10%), 1,10-phenanthroline (20%), Cs_2CO_3, toluene, 110 °C, 79%; (b) TBAF, THF, −20 °C to rt, 89%; (c) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, −78 to 0 °C; (d) $NaClO_2$, NaH_2PO_4, 2-methylbut-2-ene, *t*-BuOH/THF/H_2O, rt, 86% (two steps).

Synthesis of Enamide Fragments. To evaluate in detail the reactivity of ene−enamides toward RCM, several substituted enamides were prepared from *N*-Boc-isoleucine **11**. To this end, **11** was first cleanly converted to its amide derivative **12** by activation of the carboxylic acid in **11** as a mixed anhydride followed by reaction with ammonia (Scheme 3). Monosubstituted enamide derivative **5a** could then be obtained in excellent yield using a palladium-catalyzed vinyl transfer from butyl vinyl ether,[24,25] while ene−enamide **5b** was more conveniently synthesized by reacting **12** with (*E*)-1-iodohepta-1,6-diene in the presence of catalytic amounts of copper iodide and *N*,*N*′-dimethylethylene-1,2-diamine.[26] To access propenylamide **5c** as well as its benzyl-protected derivative **5d**, we found that they were best obtained using an isomerization of the corresponding allylamides **13** and **14**: amidation of **11** respectively with allylamine or allylbenzylamine followed by isomerization with $RuClH(CO)(PPh_3)_3$[27] efficiently gave the desired enamides **5c** and **5d** in excellent overall yields (Scheme 3).

Preparation of Acyclic Ene−Enamides. At this stage, the preparation of the acyclic substrates for the ene−enamide RCM was completed by coupling of phenoxyproline **4** with enamide fragments **5**. To this end, the Boc group of enamides **5a−d** was first carefully deprotected with anhydrous zinc bromide in dichloromethane and the resulting unstable free amines **15a−d** were coupled with carboxylic acid **4** using EDC and HOBt. Using this sequence, ene−enamides **16a−d** were obtained in good overall yields (Scheme 4).

Macrocyclization by Ene−Enamide Ring-Closing Metathesis. Completion of the preparation of acyclic ene−enamides finally set the stage for the crucial ene−enamide ring closing metathesis reaction.[12a] Acyclic substrates **16a−d** were reacted with 10 mol % of Grubbs' second-generation catalyst **GII** in refluxing 1,2-dichloroethane for 24 h, followed by addition of

(20) (a) Lin, H. Y.; Chen, C. H.; You, B. J.; Liu, K. C. S. C.; Lee, S. S. *J. Nat. Prod.* **2000**, *63*, 1338−1343. (b) Lee, S. S.; Su, W. C.; Liu, K. C. S. C. *Phytochemistry* **2001**, *58*, 1271−1276.

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(22) Wolter, M.; Nordmann, G.; Job, G. E.; Buchwald, S. L. *Org. Lett.* **2002**, *4*, 973−976.

(23) Obtained in three steps and 77% overall yield from salicyladehyde using an iodination (ICl, AcOH)−methylation (Me_2SO_4, K_2CO_3, acetone)−Wittig sequence. See the Experimental Section for more details.

(24) Brice, J. L.; Meerdink, J. E.; Stahl, S. S. *Org. Lett.* **2004**, *6*, 1845−1849.

(25) In contrast, all attempts at copper-mediated amidation of **12** with vinyl bromide using various catalytic systems failed to give the desired unsubstituted enamide in good and reproducible yields.

(26) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669.

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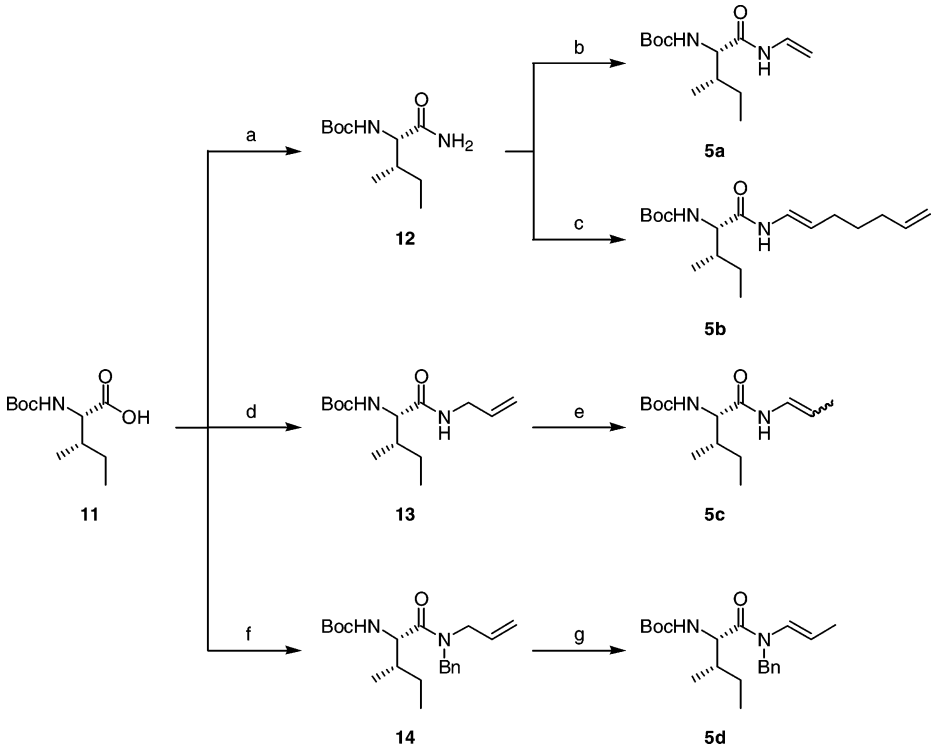
SCHEME 3. Synthesis of Enamide Fragments 5[a]



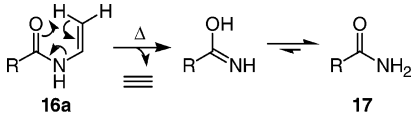
[a] Reagents and conditions: (a) isobutyl chloroformate, *N*-methylmorpholine, DME, 0 °C, then ammonia, quant; (b) butyl vinyl ether, (1,10-phenanthroline)Pd($OCOCF_3$)$_2$ (10%), 75 °C, 81%; (c) (*E*)-1-iodohepta-1,6-diene, CuI (10%), *N*,*N*′-dimethylethylene-1,2-diamine (20%), K_2CO_3, THF, 70 °C, 69%; (d) isobutyl chloroformate, *N*-methylmorpholine, DME, 0 °C, then allylamine, quant; (e) RuClH(CO)(PPh_3)$_3$ (2.5%), THF, reflux, 92%, dr: 6:4; (f) allylbenzylamine, EDC, HOBt, *N*-methylmorpholine, DMF, 0 °C to rt, 90%; (g) RuClH(CO)(PPh_3)$_3$ (2.5%), THF, reflux, 86%, dr >95:5.

another 10 mol % of the catalyst and further reaction for 24 h under high dilution conditions (0.005 M).[28] As can be seen from the results collected in Scheme 5, a dramatic difference in the reactivity of acyclic ene−enamides was observed. When reacted with **GII** in refluxing 1,2-dichloroethane, monosubstituted enamide **16a** furnished only 8% of the desired cyclopeptide core **2**, and amide **17** was obtained as the major product. Formation of **17** could be attributed to the thermal instability of **16a** since a similar transformation was noticed without the catalyst.[29] Encouraged by the formation of the desired macrocyclic compound, though in trace amounts, we decided to use ene−enamide **16b** bearing an additional methyl group, hoping for some stabilization of the enamide moiety. We were therefore delighted to see that when submitted to the crucial macrocyclization step, this enamide gave 49% isolated yield of the desired cyclopeptide **2** and the amount of amide **17** was considerably reduced (only 13%).[28,29] This result brings this first successful example of macrocyclization by ene−enamide RCM at a useful synthetic level (Scheme 5). In an attempt to further increase the yield of the desired cyclopeptide core **2**, the influence of various additives,[30] which would either prevent chelation of the substrate with the catalyst or degradation of the latter, was studied. However, all of the additives evaluated failed to bring any noticeable improvement (2,6-dichloro-1,4-benzoquinone, copper chloride, triphenylarsine, triphenylphosphine oxide) or were not compatible with the presence of the enamide group in **16b** (chlorocatecholborane, titanium isopropoxide).

In an attempt to improve the formation of the macrocyclic enamide, two additional strategies were evaluated. Since the problem in this macrocyclization clearly is the low reactivity of the enamide, we first considered forcing the formation of an alkylidene complex at this position using Hoye's relay RCM strategy starting from diene−enamide **16c**.[31] This relay approach involves temporary incorporation of a tether containing a sterically unencumbered terminal olefin for initiation of the catalytic cycle. The olefin is positioned such that a kinetically favorable formation of a five-membered ring is used to deliver the ruthenium onto the sterically hindered or less reactive position with concomitant extrusion of the ring. While this strategy has proven to be successful for macrocyclization in a

(28) Grubbs' first-generation catalyst was also evaluated but failed to give even traces of the desired cyclic compound.

(29) A [3,3]-sigmatropic rearrangement might account for the thermal instability of enamide **16a**. The presence of the additional methyl group in propenyl amide **16b** (mixture of *E* and *Z* isomers) would therefore block the rearrangement of *Z*-**16b**, which could explain the greater thermal stability of **16b**. The presence of this additional methyl group might also change the electronic properties of the enamide and account for its reactivity.



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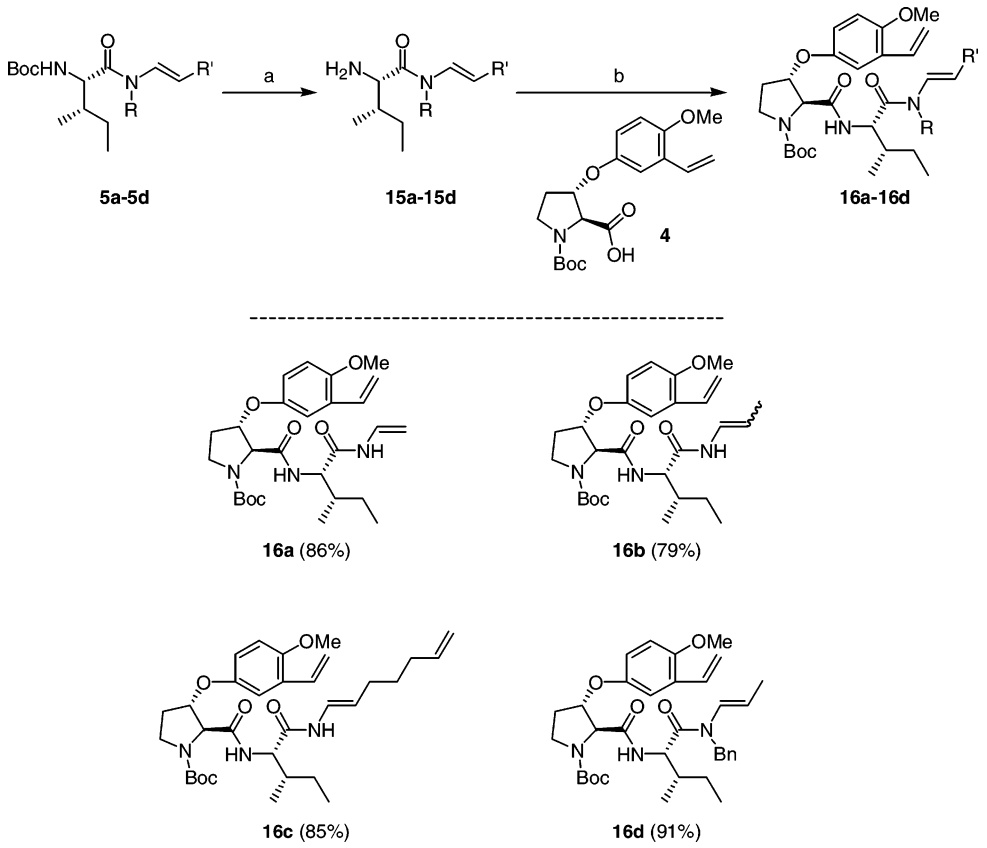
(31) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210−10211.

SCHEME 4. Fragment Assembly: Preparation of Acyclic Ene−Enamides[a]



[a] Reagents and conditions: (a) $ZnBr_2$ (4.5 equiv), CH_2Cl_2, 0 °C to rt; (b) EDC, HOBt, *N*-methylmorpholine, DMF, 0 °C to rt.

couple of cases,[32,33] it failed using **16c** and a complex mixture of unidentified and inseparable compounds was obtained.[34,35] Alternatively, the ring-closing metathesis of benzyl-protected ene−enamide **16d** was envisioned: the presence of an additional benzyl group was expected to stabilize the enamide which could then react with the catalyst before decomposition. The tertiary enamide in **16d** was, indeed, considerably more stable since no trace of amide could be observed in the crude reaction mixture and starting material was mainly recovered along with trace amounts of aldehyde **18**. Surprised by the formation of this most unexpected byproduct, we tried to force this reaction by using a stoichiometric amount of the catalyst. Using these conditions, a 1:1 mixture of starting material and aldehyde **18** was now isolated. A rationale for the formation of **18** is the formation of a relatively stable Hoveyda−Grubbs-like alkylidene complex[36] **19** by reaction of the ruthenium catalyst with the methoxystyrene group (Scheme 6). Steric hindrance or a change in the conformation of the enamide[37] due to the presence of the benzyl group on the enamide probably prevents the second [2 + 2] cycloaddition to occur. Alkylidene complex **19** being unable to react with the enamide olefin, it finally reacts with water from the air to give aldehyde **18**.[38,39]

This study not only demonstrated the feasibility of ene−enamide RCM-based macrocyclization but also showed that small changes in the substitution pattern of the ene−enamide can have a dramatic impact on the outcome of this reaction (Scheme 5). Pleased to observe that the ene−enamide RCM proceeded starting from substrate **16b**, affording macrocyclic enamide **2**, we next decided to investigate the possibility to obtain this macrocyclic compound using a one-pot isomerization/ene−enamide RCM sequence starting from an allylic amide in place of the enamide.

Macrocyclization by Isomerization/Ene−Enamide Ring-Closing Metathesis Sequence. Considering that the enamide moiety in the *N*-Boc-isoleucine-propenylamide fragment **5c** was installed by isomerization of the corresponding allylamide **13** (Scheme 3) and since ruthenium carbenes have been recently

(32) For a review, see: Wallace, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912−1915.

(33) For examples of macrocyclization using relay ring-closing metathesis, see: (a) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601−3605. (b) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960−8961.

(34) Not a trace of the macrocyclic enamide could be detected in the crude reaction mixture.

(35) For examples of substrates failing to undergo relay ring-closing metathesis, see: (a) Hoye, T. R.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 6950−6951. (b) Helmboldt, H.; Kohler, D.; Hiersemann, M. *Org. Lett.* **2006**, *8*, 1573−1576. (c) Trost, B. M.; Yang, H.; Thiel, O. R.; Frontier, A. J.; Brindle, C. S. *J. Am. Chem. Soc.* **2007**, *129*, 2206−2207. (d) Fürstner, A.; Fasching, B.; O'Neil, G. W.; Fenster, M. D. B.; Godbout, C.; Ceccon, J. *Chem. Commun.* **2007**, 3045−3047.

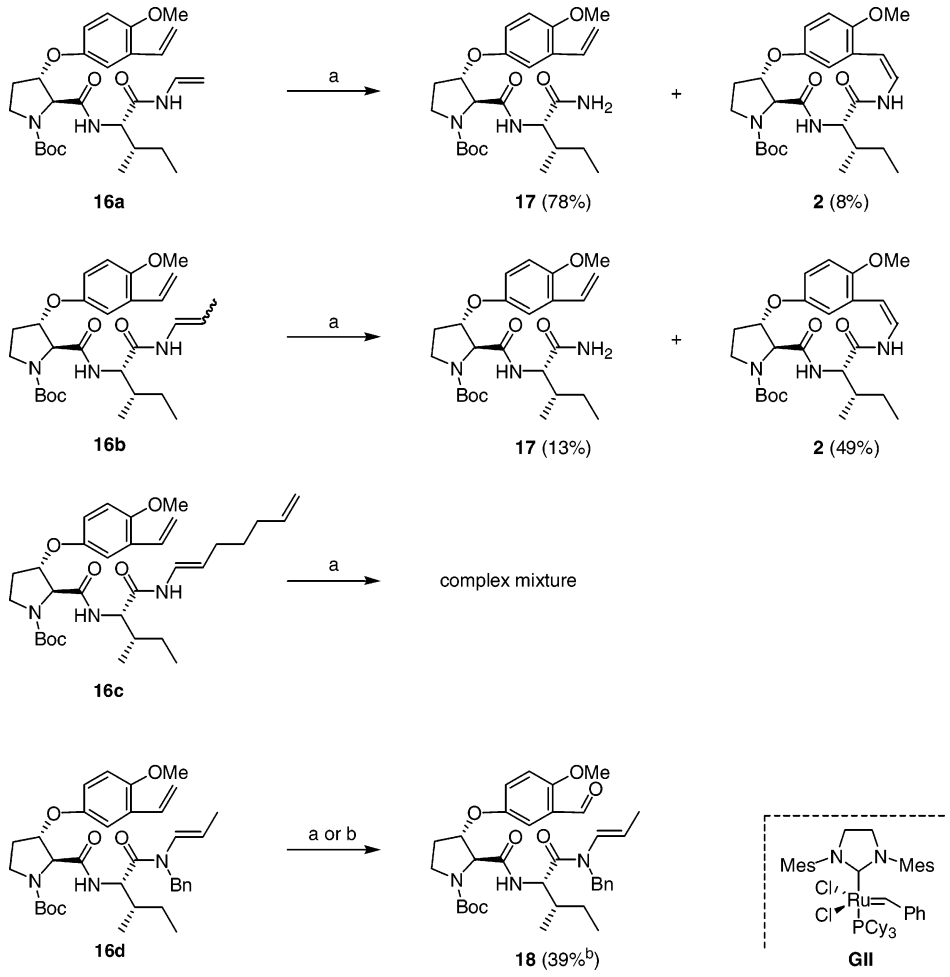
(36) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.

(37) As pointed out by one of the reviewers, the bulk of the benzyl group can cause the alkene moiety to adopt a conformation where it is parallel to the carbonyl. In this conformation, it appears the alkene will not be able to approach the Ru-alkylidene with a favorable geometry for orbital overlap.

(38) Kim, M.; Eum, M.-S.; Jin, M. Y.; Jun, K.-W.; Lee, C. W.; Kuen, K. A.; Kim, C. H.; Chin, C. S. *J. Organomet. Chem.* **2004**, *689*, 3535−3540.

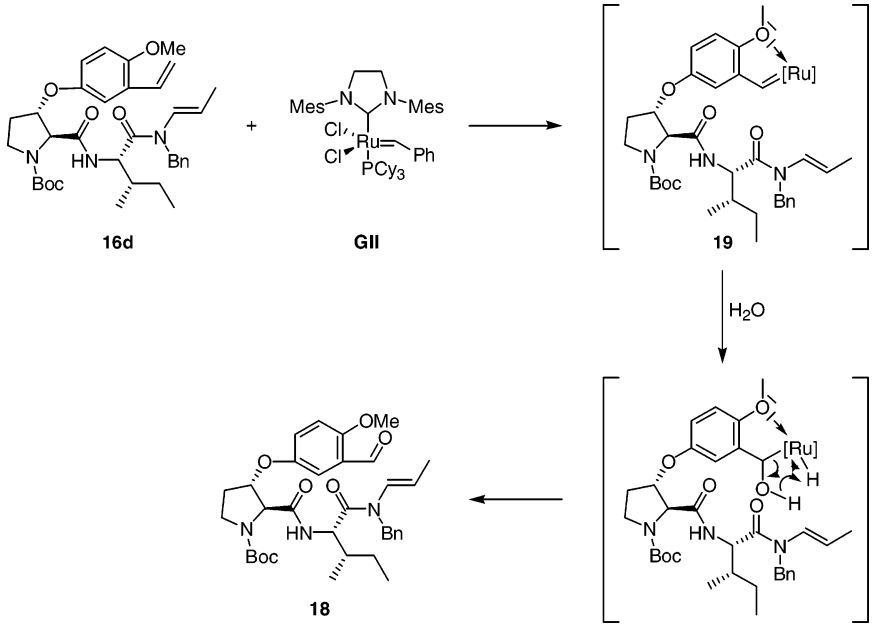
(39) All attempts at characterization of an intermediate alkylidene ruthenium complex in the crude reaction mixture, or at its isolation, even in the presence of copper chloride to trap the tricyclohexylphosphine, failed.

SCHEME 5. Ene−Enamide Ring-Closing Metathesis[a]

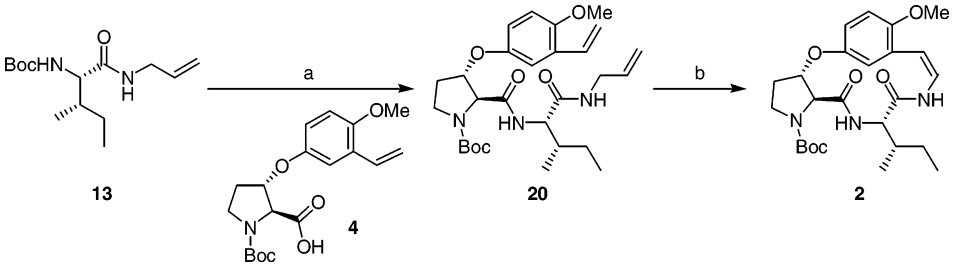


[a] Reagents and conditions: (a) Grubbs' second-generation catalyst **GII** (2 × 10%), 1,2-dichloroethane (0.005 M), reflux; (b) **GII** (1 equiv), 1,2-dichloroethane (0.005 M), reflux [b]Isolated yield with 1 equiv of **GII** (conditions b); traces only with 20% of **GII**.

SCHEME 6. Possible Intermediate for the Formation of Aldehyde 18 from Ene−Enamide 16d

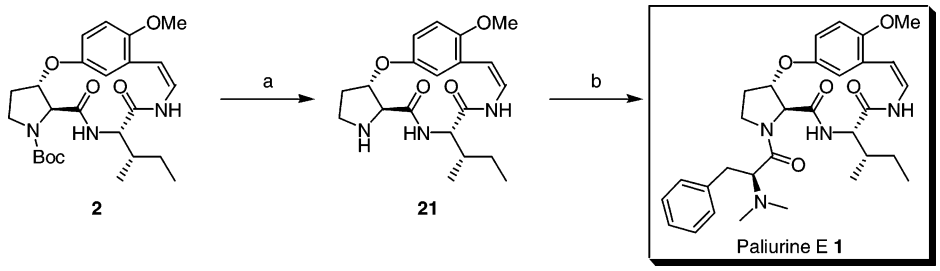


SCHEME 7. Macrocyclization by Isomerization/Ene−Enamide Ring-Closing Metathesis Sequence[a]



[a] Reagents and conditions: (a) $ZnBr_2$ (4.5 equiv), CH_2Cl_2, 0 °C to rt, then **4**, EDC, HOBt, *N*-methylmorpholine, DMF, 0 °C to rt, 92%; (b) Grubbs' second-generation catalyst **GII** (2 × 10%), 1,2-dichloroethane (0.005M), reflux, 36%.

SCHEME 8. Completion of the Synthesis[a]



[a] Reagents and conditions: (a) TMSOTf, 2,6-lutidine, CH_2Cl_2, −10 to 0 °C; (b) *N*,*N*-dimethyl-L-phenylalanine, HATU, HOAt, DIPEA, DMF, 0 °C to rt, 78% (two steps).

shown to be excellent catalysts for this kind of isomerization reactions,[40,41] it was reasoned that the macrocyclic enamide **2**, required for the preparation of paliurine E, might be obtained starting from acyclic allylic amide **20** using an isomerization/ene−enamide ring-closing metathesis sequence. This alternative to the ene−enamide RCM would shorten the synthesis and provide additional insights into the preparation of macrocyclic enamides using RCM-based strategies.

To test this opportunity, allylamide **20** was prepared by deprotection of **13** as before and condensed with acid **4**. When reacted with Grubbs' second-generation catalyst under high dilution, allylamide **20** was first smoothly isomerized to the corresponding enamide which then underwent the ene−enamide RCM to macrocycle **2** in 36% yield (Scheme 7).[42]

Completion of the Synthesis of Paliurine E. With useful quantities of the macrocyclic core **2** in hand, the synthesis of paliurine E was finally achieved in two steps. First, deprotection of the Boc group was achieved using TMSOTf and 2,6-lutidine. Finally, HATU/HOAt-mediated coupling of **21** with *N*,*N*-dimethyl-L-phenylalanine gave the desired paliurine E (**1**) in 78% over the two final steps (Scheme 8). The synthetic (−)-paliurine E exhibited physical, spectroscopic, and spectrometric characteristics (^{1}H NMR, ^{13}C NMR, IR, $[\alpha]_D$, UV, and MS) identical to those reported for the natural product.[20]

Conclusion

With their especially appealing molecular architectures and potent biological activities, the cyclopeptide alkaloids present an interesting challenge to the synthetic chemist and also an opportunity to test the scope and applicability of an important carbon−carbon bond-forming reaction in complex situations. Our flexible approach to these structures allowed us, with slight modifications, to test synthetic strategies based on ene−enamide ring-closing metathesis as a potential tool for their construction. Results of these investigations were somewhat surprising since very subtle changes on the enamides resulted in dramatic changes on their reactivity. This provided interesting insights on the macrocyclization by ene−enamide RCM and allowed for the completion of the first total synthesis of paliurine E in a limited number of steps featuring an installation of the challenging enamide concomitant with the macrocyclization. The exercise unearthed interesting chemistry and may also serve as a guide in future endeavors directed toward the construction of similar structures to the ones described here.

Experimental Section

General Information. All reactions were carried out in oven- or flame-dried glassware under an argon atmosphere employing standard techniques in handling air-sensitive materials.

All solvents were reagent grade. Tetrahydrofuran (THF) and toluene were freshly distilled from sodium/benzophenone under argon immediately prior to use. Dichloromethane, DMSO, and DMF were freshly distilled from calcium hydride. 1,2-Dichloroethane was successively distilled over phosphorus pentoxide and calcium hydride under argon and degassed before use. Methanol was distilled from magnesium turnings and iodine.

(40) (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204−2207. (b) Alcaide, B.; Almendros, P.; Alonso, J. M.; Aly, M. F. *Org. Lett.* **2001**, *3*, 3781−3784. (c) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2003**, *9*, 5793−5799. (c) Alcaide, B.; Almendros, P.; Alonso, J. M.; Luna, A. *Synthesis* **2005**, 668−672. (d) Alcaide, B.; Almendros, P.; Alonso, J. M. *Tetrahedron Lett.* **2003**, *44*, 8693−8695. (e) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865−1880. (f) McNaughton, B. R.; Bucholtz, K. M.; Camaano-Moure, A.; Miller, B. L. *Org. Lett.* **2005**, *7*, 733−736. (g) Alcaide, B.; Almendros, P.; Alonso, J. M. *Chem. Eur. J.* **2006**, *12*, 2874−2879.

(41) Allylamide **13** could easily be isomerized to the corresponding enamide **5c** using catalytic amounts of Grubbs' second-generation catalyst. See the Experimental Section for details.

(42) For a reverse ene−allylamide RCM/isomerization sequence which does not involve the loss of one carbon atom, see: Fustero, S.; Sánchez-Roselló, M.; Jiménez, D.; Sanz-Cervera, J. F.; del Pozo, C.; Acena, J. L. *J. Org. Chem.* **2006**, *71*, 2706−2714.

Allylamine, diisopropylethylamine, *N*-methylmorpholine, triethylamine, 2,6-lutidine, and *N*,*N*′-dimethylethylenediamine were distilled over calcium hydride. 1,2-Dimethoxyethane was synthesis grade and used as supplied. Copper(I) iodide (99,999% purity) and Grubbs' second-generation catalyst were purchased from a commercial supplier and used as supplied. Finely powdered potassium carbonate (325 mesh) and cesium carbonate were used for copper-mediated coupling reactions. All other reagents were used as supplied.

Unless otherwise noted, reactions were magnetically stirred and monitored by thin layer chromatography using $60F_{254}$ plates. Chromatography was performed with silica gel 60 (particle size 35−70 μm) supplied by SDS. Yields refer to chromatographically and spectroscopically pure compounds, unless otherwise noted.

Proton NMR spectra were recorded using an internal deuterium lock at ambient temperature on a Bruker 300 MHz spectrometer. Internal references of δ_H 7.26 and δ_H 2.50 were used for $CDCl_3$ and DMSO-d_6, respectively. Data are presented as follows: chemical shift (in ppm on the δ scale relative to $\delta_{TMS} = 0$), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintuplet, m = multiplet, br = broad, app = apparent), coupling constant (*J*/Hz) and integration. Resonances that are either partially or fully obscured are denoted obscured (obs). Carbon-13 NMR spectra were recorded at 75 MHz. Internal references of δ_C 77.16 and δ_C 39.52 were used for $CDCl_3$ and DMSO-d_6, respectively.

Due to the presence of complex rotameric mixtures, it was necessary to record ^{1}H and ^{13}C NMR spectra of dipeptides as well as acyclic ene−enamides in DMSO-d_6 at 345 K. Even at those temperatures, some ^{13}C peaks were poorly resolved and are denoted "broad" (br).

4-Iodo-1-methoxy-2-vinylbenzene 7. To a suspension of methyltriphenylphosphonium bromide (20.5 g, 57.3 mmol) in THF (200 mL) at −78 °C was added *n*-butyllithium (1.6 M in hexanes, 32.0 mL, 51.2 mmol). The resulting orange solution was stirred at −78 °C for 1 h and a solution of 5-iodo-2-methoxybenzaldehyde[18a] (5.0 g, 19.1 mmol) in THF (50 mL) was added via cannula. The reaction mixture was warmed to 0 °C over 2 h and quenched with 100 mL of saturated NH_4Cl aqueous solution. The organic layer was separated, and the aqueous layer was extracted with AcOEt. Combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel (Et_2O/petroleum ether: 2/8) to give the desired substituted styrene **7** (4.1 g, 15.8 mmol, 83%) as a pale yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.65 (d, *J* = 2.2 Hz, 1H), 7.42 (dd, *J* = 8.6, 2.2 Hz, 1H), 6.84 (dd, *J* = 17.7, 11.1 Hz, 1H), 6.54 (d, *J* = 8.6 Hz, 1H), 5.63 (d, *J* = 17.7 Hz, 1H), 5.21 (d, *J* = 11.1 Hz, 1H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.6, 137.4, 135.2, 130.4, 129.4, 115.8, 113.2, 83.2, 55.7; IR (neat) ν_{max} 2991, 1480, 1240, 1122, 1025 cm^{-1}. ESIMS (positive mode) 283.1; ESIHRMS *m*/*z* calcd for C_9H_9IONa $[M + Na]^+$ 282.9596, found 282.9603.

(2*R*,3*S*)-1-*tert*-Butoxycarbonyl-2-*tert*-butyldimethylsilyloxymethyl-3-(4-methoxy-3-vinylphenoxy)pyrrolidine 8. A 15 mL pressure tube was charged with 4-iodo-1-methoxy-2-vinylbenzene **7** (830 mg, 3.2 mmol), alcohol **6**[18a] (1.0 g, 3.0 mmol), cesium carbonate (1.95 g, 6.0 mmol), 1,10-phenanthroline (108 mg, 0.6 mmol), and copper(I) iodide (57 mg, 0.3 mmol). Toluene (2 mL) was added, the pressure tube was closed, and the brownish suspension was heated to 110 °C for 24 h. Another portion of 4-iodo-1-methoxy-2-vinylbenzene **7** (415 mg, 1.6 mmol) was then added, and the reaction mixture was heated for an additional 24 h and cooled to rt. Crude reaction mixture was finally filtered over a plug of silica gel (washed with AcOEt), concentrated, and purified by flash chromatography over silica gel (AcOEt/petroleum ether 15/85) to yield aryl ether **8** as a colorless oil (1.1 g, 2.4 mmol, 79%): $[\alpha]_D^{20}$ −2 (*c* 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.96−7.06 (m, 2H), 6.85−6.91 (m, 1H), 6.78 and 6.77 (rotamers, d, *J* = 8.8 Hz, d, *J* = 8.8 Hz, 1H), 5.72 and 5.71 (rotamers, d, *J* = 17.7 Hz, d, *J* = 17.7 Hz, 1H), 5.28 and 5.27 (rotamers, d, *J* = 11.1 Hz, d, *J* = 11.1 Hz, 1H), 4.84 and 4.80 (rotamers, d, *J* = 3.0 Hz, d, *J* = 4.1 Hz, 1H), 3.80−4.07 (m, 2H), 3.81 (s, 3H), 3.46−3.73 (m, 3H), 2.05−2.29 (m, 2H), 1.49 (s, 9H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.7, 151.6 and 151.3 (rotamers), 151.4, 131.5 and 131.4 (rotamers), 128.0, 115.5, 115.1 and 114.6 (rotamers), 115.0, 112.2 and 112.1 (rotamers), 80.0 and 79.8 (rotamers), 79.6 and 79.4 (rotamers), 64.2, 63.1 and 62.5 (rotamers), 56.3 and 56.2 (rotamers), 45.4 and 45.1 (rotamers), 30.1 and 28.9 (rotamers), 28.7, 26.0, 18.4, −5.3, −5.4; IR (neat) ν_{max} 1694, 1682, 1494, 1393, 1180 cm^{-1}; CIMS (NH_3 gas) 464 (37), 408 (31), 364 (26), 350 (100), 306 (12); ESIHRMS *m*/*z* calcd for $C_{25}H_{41}NO_5SiNa$ $[M + Na]^+$ 486.2652, found 486.2638.

(2*R*,3*S*)-1-*tert*-Butoxycarbonyl-2-hydroxymethyl-3-(4-methoxy-3-vinylphenoxy)pyrrolidine 9. A solution of **8** (1.5 g, 3.2 mmol) in THF (30 mL) was treated with a solution of TBAF (1 M solution in THF, 4.9 mL, 4.9 mmol) at −20 °C. The resulting light yellow mixture was warmed to rt over 2 h and quenched with water. The aqueous layer was extracted with Et_2O, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel (AcOEt/petroleum ether: 1/1) to give the unprotected alcohol **9** (1.0 g, 2.9 mmol, 89%) as a white solid: mp 82 °C; $[\alpha]_D^{20}$ −12 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (br s, 1H), 7.00 (dd, *J* = 17.3, 11.1 Hz, 1H), 6.78 (br s, 2H), 5.70 (d, *J* = 17.3 Hz, 1H), 5.26 (d, *J* = 11.1 Hz, 1H), 4.81 and 4.59 (rotamers, br s, br s, 1H), 4.11 and 3.94 (rotamers, br m, br m, 1H), 3.79 (s, 3H), 3.70−3.86 (m, 2H), 3.44−3.61 (m, 2H), 2.05−2.16 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.0, 151.7, 151.0, 131.4, 127.9, 115.9, 115.0, 114.2, 112.3, 80.5, 79.2, 65.2, 64.8, 56.3, 45.8, 30.0, 28.6; IR (KBr) ν_{max} 3410, 2952, 1675, 1484, 1214, 1042, 872 cm^{-1}; ESIMS (positive mode) 721.4; ESIHRMS *m*/*z* calcd for $C_{19}H_{27}NO_5Na$ $[M + Na]^+$ 372.1787, found 372.1803.

(2*S*,3*S*)-1-*tert*-Butoxycarbonyl-2-formyl-3-(4-methoxy-3-vinylphenoxy)pyrrolidine 10. DMSO (430 μL, 6.1 mmol) was added to a solution of oxalyl chloride (450 μL, 5.1 mmol) in dichloromethane (15 mL) at −78 °C. The resulting solution was stirred at −78 °C for 30 min, and a solution of **9** (850 mg, 2.43 mmol) in dichloromethane (20 mL) was added dropwise via cannula. The reaction mixture was stirred for 30 min at −78 °C before adding triethylamine dropwise (1.5 mL, 10.7 mmol), and the mixture was warmed to 0 °C over 4 h. The reaction was next quenched at 0 °C with water and diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the desired aldehyde **10** as an orange oil (850 mg, 2.43 mmol, quant) which was used without purification in the next step: $[\alpha]_D^{20}$ −31 (*c* 2.4, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.68 and 9.62 (rotamers, s, s, 1H), 7.10 and 7.09 (rotamers, s, s, 1H), 7.01 and 6.99 (rotamers, dd, *J* = 17.7, 11.1, dd, *J* = 17.7, 11.1 Hz, 1H), 6.81−6.83 (m, 2H), 5.75 and 5.73 (rotamers, d, *J* = 17.7 Hz, d, *J* = 17.7 Hz, 1H), 5.29 and 5.25 (rotamers, d, *J* = 11.1 Hz, d, *J* = 11.1 Hz, 1H), 4.86 (br s, 1H), 4.49 and 4.30 (rotamers, s, s, 1H), 3.61−3.85 (m, 2H), 3.80 (s, 3H), 2.18−2.26 (m, 1H), 1.90−2.04 (m, 1H), 1.49 and 1.42 (rotamers, s, s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.3 and 200.1 (rotamers), 155.1 and 154.0 (rotamers), 152.0, 150.5, 131.2, 128.0, 115.8, 115.2, 114.1, 112.3, 81.0 and 80.7 (rotamers), 79.1 and 77.8 (rotamers), 70.9 and 70.6 (rotamers), 56.2, 45.9 and 45.0 (rotamers), 31.1 and 30.5 (rotamers), 28.5; IR (neat) ν_{max} 2949, 1738, 1712, 1693, 1494, 1393, 1217, 911 cm^{-1}; CIMS (NH_3 gas) 370.0 (22), 242.3 (67), 186.3 (100); ESIHRMS *m*/*z* calcd for $C_{19}H_{25}NO_5Na$ $[M + Na]^+$ 370.1630, found 370.1637.

(2*S*,3*S*)-1-*tert*-Butoxycarbonyl-3-(4-methoxy-3-vinylphenoxy)-proline 4. To a solution of **10** (850 mg, 2.43 mmol) in a mixture of THF (7 mL) and *tert*-butanol (24 mL) was added 2-methylprop-2-ene (2.6 mL), followed by a solution of sodium chlorite (80%, 660 mg, 5.8 mmol) and sodium dihydrogen phosphate dihydrate

(796 mg, 5.1 mmol) in water (7 mL). The yellow reaction mixture was then stirred for 1 h, carefully quenched with a 1 M HCl solution, and diluted with ether. The aqueous layer was extracted with ether, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel (CH_2Cl_2/EtOH: 98/2) to give the acid **4** as a yellow oily solid (762 mg, 2.10 mmol, 86% over two steps): $[\alpha]_D^{20}$ −30 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.51 (br s, 1H), 7.06 and 7.04 (rotamers, s, s, 1H), 6.95 and 6.93 (rotamers, dd, J = 17.2, 11.1 Hz, dd, J = 17.2, 11.1 Hz, 1H), 6.71−6.77 (m, 2H), 5.68 and 5.66 (rotamers, d, J = 17.2 Hz, d, J = 17.2 Hz, 1H), 5.21 and 5.19 (rotamers, d, J = 11.1 Hz, d, J = 11. Hz, 1H), 4.96 and 4.82 (rotamers, s, s, 1H), 4.50 and 4.38 (rotamers, s, s, 1H), 3.55−3.68 (m, 1H), 3.73 (s, 3H), 3.54−3.60 (m, 1H), 2.10−2.14 (m, 2H), 1.42 and 1.33 (rotamers, s, s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0 and 173.1 (rotamers), 156.1 and 154.1 (rotamers), 151.8, 150.4, 131.1, 127.9, 115.6 and 115.4 (rotamers), 115.1, 113.8 and 113.7 (rotamers), 112.4, 81.6, 80.8, 80.3 and 78.9 (rotamers), 64.8, 56.2, 45.3 and 44.7 (rotamers), 30.4 and 29.8 (rotamers), 28.4 and 28.3 (rotamers); IR (neat) ν_{max} 3437, 3211, 2981, 1696, 1414, 1209 cm^{-1}; CIMS (NH_3 gas) 381 (9), 363 (100), 325 (94), 308 (56), 264 (60), 150 (49); ESIHRMS *m*/*z* calcd for $C_{19}H_{25}NO_6Na$ $[M + Na]^+$ 386.1580, found 386.1562.

***N*-Boc-isoleucinamide 12.** To a solution of *N*-Boc-isoleucine **11** (5.0 g, 21.6 mmol) and *N*-methylmorpholine (2.85 mL, 25.9 mmol) in DME (100 mL) was added isobutyl chloroformate (3.35 mL, 25.9 mmol) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 min, and a solution of ammonia (30 wt % aqueous solution, 8 mL) was then added. The resulting white slurry was vigorously stirred at rt for 1 h and quenched with water. Dichloromethane was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. Combined organic layers were successively washed with a 1 M HCl aqueous solution and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to yield the desired amide **12** as a white solid (5.0 g, 21.6 mmol, quant): mp 153 °C; $[\alpha]_D^{20}$ −7 (*c* 2.3, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.26 (s, 1H), 6.99 (s, 1H), 6.55 (d, J = 9.0 Hz, 1H), 3.75 (app t, J = 9.0 Hz, 1H), 1.60−1.70 (m, 1H), 1.32−1.42 (m, 1H), 1.38 (s, 9H), 1.00−1.13 (m, 1H), 0.82 (d, J = 6.7 Hz, 3H), 0.81 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.4, 155.3, 77.8, 58.6, 36.4, 28.1, 24.3, 15.5, 11.0; IR (KBr) ν_{max} 3380, 3350, 3201, 2955, 1680, 1639, 1516, 1311, 1250, 1157, 661 cm^{-1}; CIMS (NH_3 gas) 361 (37), 316 (42), 248 (11), 186 (100), 175 (51), 131 (67), 86 (27); ESIHRMS *m*/*z* calcd for $C_{11}H_{22}N_2O_3$-Na $[M + Na]^+$ 253.1528, found 253.1519.

***N*-Boc-isoleucine-vinylamide 5a.** A slurry of *N*-Boc-isoleucinamide **12** (920 mg, 4.0 mmol) in butyl vinyl ether (10 mL) was treated with (1,10-phenanthroline)Pd($OCOCF_3$)$_2$[43] (205 mg, 0.4 mmol) at 75 °C. The resulting brownish slurry was left open to air and stirred at 75 °C for 4 h, concentrated, and directly purified by flash chromatography over silica gel (petroleum ether/AcOEt: 7/3) to yield the desired vinylamide **5a** as a white solid (830 mg, 3.2 mmol, 81%): mp 137 °C; $[\alpha]_D^{20}$ +5 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (d, J = 9.4 Hz, 1H), 6.89 (app dt, J = 15.7, 9.4 Hz, 1H), 5.53 (d, J = 8.3 Hz, 1H), 4.59 (d, J = 15.7 Hz, 1H), 4.36 (d, J = 9.4 Hz, 1H), 4.03 (app t, J = 8.3 Hz, 1H), 1.76−1.83 (m, 1H), 1.46−1.60 (m, 1H), 1.41 (s, 9H), 1.08−1.18 (m, 1H), 0.92 (d, J = 6.7 Hz, 3H), 0.86 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 156.4, 128.5, 96.6, 80.1, 59.3, 37.2, 28.4, 25.0, 15.5, 11.1; IR (KBr) ν_{max} 3293, 1675, 1634, 1527, 1245, 1168, 856, 840 cm^{-1}; CIMS (NH_3 gas) 257(100), 201 (57), 186 (22), 157 (49), 130 (12), 86 (17); ESIHRMS *m*/*z* calcd for $C_{13}H_{24}N_2O_3$-Na $[M + Na]^+$ 279.1685, found 279.1694.

(*E*)-*N*-Boc-isoleucine-hepta-1,6-dienylamide 5b. A 15 mL pressure tube was charged with *N*-Boc-isoleucinamide **12** (920 mg, 4.0 mmol), (*E*)-1-iodo-hepta-1,6-diene[44] (890 mg, 4.0 mmol), copper(I) iodide (76 mg, 0.4 mmol), and potassium carbonate (830 mg, 6.0 mmol). The tube was evacuated under high vacuum, backfilled with argon, and closed with a rubber septa. Dry and degassed THF (4 mL) and *N*,*N*′-dimethylethylene-1,2-diamine (85 μL, 0.8 mmol) were next added, the rubber septa was replaced by a Teflon stopper, and the light blue suspension was sonicated for 2 min before being heated to 70 °C for 15 h. The reaction mixture was cooled to rt, filtered over a plug of silica gel (washed with AcOEt), and concentrated. The crude residue was purified by flash chromatography over silica gel (AcOEt/petroleum ether: 1/9) to give the desired enamide **5b** (899 mg, 3.1 mmol, 69%) as a white solid: mp 115 °C; $[\alpha]_D^{20}$ +5 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77−7.96 (m, 1H), 6.68 (dd, J = 13.8, 10.8 Hz, 1H), 5.71−5.85 (m, 1H), 5.11−5.20 (m, 2H), 4.92−5.01 (m, 2H), 3.95 (app t, J = 8.3 Hz, 1H), 1.98−2.07 (m, 4H), 1.84−1.92 (m, 1H), 1.38−1.57 (m, 3H), 1.43 (s, 9H), 1.03−1.16 (m, 1H), 0.93 (d, J = 6.6 Hz, 3H), 0.89 (t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 156.1, 138.6, 122.2, 114.7, 114.0, 80.1, 59.4, 37.0, 33.2, 29.2, 29.0, 28.3, 24.8, 15.6, 11.3; IR (KBr) ν_{max} 3319, 2955, 1680, 1649, 1521, 1168, 953, 646 cm^{-1}; CIMS (NH_3 gas) 327 (9), 325 (100), 269 (13), 225 (9); ESIHRMS *m*/*z* calcd for $C_{18}H_{32}N_2O_3Na$ $[M + Na]^+$ 347.2311, found 347.2323.

***N*-Boc-isoleucine-allylamide 13.** To a solution of *N*-Boc-isoleucine **11** (1.75 g, 7.6 mmol) and *N*-methylmorpholine (1.0 mL, 9.1 mmol) in DME (100 mL) was added isobutyl chloroformate (1.2 mL, 9.1 mmol) dropwise at 0 °C. The resulting mixture was stirred at 0 °C for 2 min, and allylamine (11.3 mL) was then added. The resulting white slurry was vigorously stirred at rt for 1 h and quenched with water. Dichloromethane was added, the organic layer was separated, and the aqueous layer was extracted with dichloromethane. Combined organic layers were successively washed with a 1 M HCl aqueous solution and brine, dried over $MgSO_4$, filtered, and concentrated under vacuum to yield the desired allylamide **13** as a white solid (2.1 g, 7.6 mmol, quant): mp 106 °C; $[\alpha]_D^{20}$ −13 (*c* 2.2, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.64 (s, 1H), 5.71−5.86 (m, 1H), 5.27 (d, J = 8.7 Hz, 1H), 5.14 (dd, J = 17.2, 1.4 Hz, 1H), 5.07 (d, J = 10.2 Hz, 1H), 3.96 (app t, J = 7.9 Hz, 1H), 3.84 (app q, J = 5.9 Hz, 2H), 1.77−1.85 (m, 1H), 1.45−1.55 (m, 1H), 1.39 (s, 9H), 1.01−1.15 (m, 1H), 0.89 (d, J = 6.2 Hz, 3H), 0.86 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.9, 156.0, 134.1, 116.4, 79.8, 59.4, 41.8, 37.2, 28.4, 24.8, 15.6, 11.4; IR (KBr) ν_{max} 3319, 2966, 2645, 1675, 1557, 1168, 922, 651 cm^{-1}; CIMS (NH_3 gas) 271 (100), 215 (52), 186 (13), 171 (17), 130 (8), 86 (24); ESIHRMS *m*/*z* calcd for $C_{14}H_{26}N_2O_3Na$ $[M + Na]^+$ 293.1841, found 293.1837.

***N*-Boc-isoleucine-prop-1-enylamide 5c.** To a solution of *N*-Boc-isoleucine-allylamide **13** (1.0 g, 3.7 mmol) in THF (5 mL) was added $RuClH(CO)(PPh_3)_3$ (88 mg, 0.09 mmol). The resulting solution was refluxed for 2 h and concentrated. The crude residue was directly purified by flash chromatography over silica gel (petroleum ether/AcOEt: 8/2) to yield the desired prop-1-enylamide **5c** (mixture of *E* and *Z* isomer in a 6:4 ratio) as a white solid (925 mg, 3.4 mmol, 92%): mp 92 °C; $[\alpha]_D^{20}$ −12 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.70 (d, J = 9.9 Hz, 0.6H), 9.25 (d, J = 10.2 Hz, 0.4H), 6.86 (d, J = 8.6 Hz, 0.4H), 6.78 (d, J = 8.6 Hz, 0.6H), 6.48−6.61 (m, 1H), 5.18 (dq, J = 6.8, 6.8 Hz, 0.6H), 4.69 (dq, J = 8.6, 7.1 Hz, 0.4H), 3.99 (app t, J = 8.6 Hz, 0.4H), 3.76 (app t, J = 8.6 Hz, 0.6H), 1.57−1.70 (m, 1H), 1.63 (dd, J = 7.4, 1.7 Hz, 1.8H), 1.61 (dd, J = 8.0, 1.4 Hz, 1.2H), 1.33−1.47 (m, 1H), 1.37 (s, 9H), 1.03−1.15 (m, 1H), 0.76−0.83 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.0 and 169.0 (isomers), 155.4 and 155.3 (isomers), 123.7 and 122.0 (isomers), 106.7 and 105.3 (isomers), 77.9, 58.7 and 58.3 (isomers), 36.2, 28.1, 24.5 and 24.4 (isomers), 15.3, 14.8 and 11.3 (isomers), 10.7; IR (KBr) ν_{max} 3309, 3053, 2971, 1685, 1542, 1240, 1173, 651 cm^{-1}; ESIMS (positive

(43) Prepared according to McKeon, J. E.; Fitton, P. *Tetrahedron* **1972**, *28*, 233−238.

(44) Iyer, R. S.; Kuo, G.-H.; Helquist, P. *J. Org. Chem.* **1985**, *50*, 5898−5900.

mode) 293.3 (100), 234.4 (33), 193.3 (57); ESIHRMS *m/z* calcd for $C_{14}H_{26}N_2O_3Na$ $[M + Na]^+$ 293.1841, found 293.1839.

Alternate Procedure for Isomerization of 13 to 5c Using Grubbs' Second-Generation Catalyst. A solution of *N*-Boc-isoleucine-allylamide **13** (405 mg, 1.5 mmol) in toluene (40 mL) was treated with benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (Grubbs' second-generation catalyst, 10 mg, 0.01 mmol) at 95 °C for 3 days. The resulting greenish solution was then concentrated and directly purified by flash chromatography over silica gel (CH_2Cl_2/MeOH: 95/5) to yield the desired prop-1-enylamide **5c** (mixture of *E* and *Z* isomer in a 6:4 ratio) as a white solid (351 mg, 1.3 mmol, 87%).

***N*-Boc-isoleucine-allylbenzylamide 14.** To a solution of *N*-Boc-isoleucine **11** (2.0 g, 8.3 mmol) and allylbenzylamine (1.35 g, 9.2 mmol) in DMF (50 mL) was added 1-hydroxybenzotriazole (HOBt, 1.3 g, 9.6 mmol). 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 1.8 g, 9.4 mmol) and *N*-methylmorpholine (1.8 mL, 16.6 mmol) were next added at 0 °C, and the solution was stirred for 16 h while being progressively warmed to rt. The yellow reaction mixture was quenched with water and diluted with ether. The aqueous layer was extracted with ether, and the combined organic layers were successively washed with a 1 M HCl aqueous solution, a saturated aqueous solution of $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel (AcOEt/petroleum ether: 2/8) to give the desired benzylallylamide **14** (2.8 g, 7.8 mmol, 90%) as a white solid: mp 48 °C; $[\alpha]_D^{20}$ −30 (*c* 2.9, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 365 K) δ 7.24−7.34 (m, 5H), 6.26 (d, J = 8.3 Hz, 1H), 5.74−5.84 (m, 1H), 5.13−5.17 (m, 2H), 4.58 (br s, 2H), 4.29 (app t, J = 8.3 Hz, 1H), 3.91−4.03 (m, 2H), 1.75−1.86 (m, 1H), 1.46−1.58 (m, 1H), 1.40 (s, 9H), 1.05−1.19 (m, 1H), 0.85 (d, J = 7.4 Hz, 3H), 0.84 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 365 K) δ 172.5, 155.7, 138.1, 134.2, 128.7, 127.9, 127.5, 117.4, 78.8, 55.1, 55.0, 37.1, 28.6, 24.4, 16.1, 11.1; IR (KBr) ν_{max} 3278, 2991, 1696, 1629, 1168 cm^{-1}; CIMS (NH_3 gas) 361 (100), 305 (12); ESIHRMS *m/z* calcd for $C_{21}H_{32}N_2O_3Na$ $[M + Na]^+$ 383.2311, found 383.2296.

(*E*)-*N*-Boc-isoleucine-benzylprop-1-enylamide 5d. To a solution of *N*-Boc-isoleucine-allylbenzylamide **14** (1.0 g, 2.8 mmol) in THF (7 mL) was added $RuClH(CO)(PPh_3)_3$ (67 mg, 0.07 mmol). The resulting solution was refluxed for 2 h and concentrated. The crude residue was purified by flash chromatography over silica gel (petroleum ether/AcOEt: 9/1) to yield the desired enamide **5d** (*E* isomer) as a white solid (860 mg, 2.4 mmol, 86%): mp 77 °C; $[\alpha]_D^{20}$ +80 (*c* 1.7 $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.13−7.33 (m, 6H), 6.97 (d, J = 13.5 Hz, 1H), 5.01 (dq, J = 13.5, 6.2 Hz, 1H), 4.88 (A of AB syst., J = 15.8 Hz, 1H), 4.75 (B of AB syst., J = 15.8 Hz, 1H), 4.49 (app t, J = 8.4 Hz, 1H), 1.78−1.85 (m, 1H), 1.60 (d, J = 6.2 Hz, 3H), 1.39−1.55 (m, 1H), 1.40 (s, 9H), 1.12−1.24 (m, 1H), 0.85 (d, J = 5.4 Hz, 3H), 0.84 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 171.1, 155.7, 137.4, 128.2, 126.6, 126.5, 108.3, 78.1, 55.1, 46.3, 35.9, 28.1, 24.1, 15.4, 15.1, 11.0; IR (KBr) ν_{max} 3350, 2955, 1649, 1527, 1163, 968, 738 cm^{-1}; CIMS (NH_3 gas) 361 (100), 305 (9); ESIHRMS *m/z* calcd for $C_{21}H_{32}N_2O_3Na$ $[M + Na]^+$ 383.2311, found 383.2323.

Typical Procedure for Fragment Coupling. To a solution of Boc-protected isoleucinamide enamide derivative **5a**−**d** (0.44 mmol) in CH_2Cl_2 (10 mL) was added anhydrous zinc(II) bromide (446 mg, 1.98 mmol) at 0 °C. The resulting white slurry was vigorously stirred at 0 °C for 1 h, slowly warmed to rt, stirred for another 1 h, and concentrated. Carboxylic acid **4** (150 mg, 0.41 mmol), 1-hydroxybenzotriazole (HOBt, 54 mg, 0.40 mmol), and DMF (8 mL) were next added to the resulting white solid. After complete dissolution of all solids, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 87 mg, 0.45 mmol) and *N*-methylmorpholine (115 μL, 1.04 mmol) were next added at 0 °C, and the solution was stirred for 16 h while being progressively warmed to rt. The yellow reaction mixture was quenched with water and diluted with ether. The aqueous layer was extracted with ether, and the combined organic layers were successively washed with a 1 M HCl aqueous solution, a saturated aqueous solution of $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was finally purified by flash chromatography over silica gel to give the desired substrates for RCM **16a**−**d**.

(2*S*,3*S*)-[1-*tert*-Butoxycarbonyl-3-(4-methoxy-3-vinylphenoxy)prolyl]isoleucine-vinylamide 16a. Solvent system for purification by flash chromatography over silica gel: AcOEt/petroleum ether 3/7; white solid (scale 253 mg of compound obtained; yield 86%): mp 75 °C; $[\alpha]_D^{20}$ −36 (*c* 0.1, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 345 K) δ 9.77 (d, J = 9.8 Hz, 1H), 7.78 (d, J = 8.6 Hz, 1H), 7.14 (d, J = 2.7 Hz, 1H), 6.87−6.97 (m, 3H), 6.79 (ddd, J = 15.9, 9.8, 8.8 Hz, 1H), 5.81 (dd, J = 17.7, 1.5 Hz, 1H), 5.26 (dd, J = 11.2, 1.5 Hz, 1H), 4.80 (br s, 1H), 4.72 (d, J = 15.9 Hz, 1H), 4.38 (s, 1H), 4.35 (d, J = 8.8 Hz, 1H), 4.25 (app t, J = 8.3 Hz, 1H), 3.77 (s, 3H), 3.37−3.61 (m, 2H), 2.00−2.13 (m, 2H), 1.78−1.86 (m, 1H), 1.38−1.51 (m, 1H), 1.40 (s, 9H), 1.08−1.26 (m, 1H), 0.84−0.90 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 345 K) δ 169.3, 168.9, 153.9, 151.6, 150.6, 131.1, 129.0, 127.1, 116.5, 115.1, 114.0, 113.2, 95.5, 80.5 (br), 79.3, 69.5, 66.2, 57.2, 44.8, 36.5, 28.0, 24.4, 18.8, 15.3, 10.7; IR (KBr) ν_{max} 3293, 2966, 2648, 1644, 1701, 1393, 1209, 1163 cm^{-1}; CIMS (NH_3 gas) 502 (100), 458 (72), 402 (52), 401 (43), 375 (8), 352 (9), 331 (8); ESIHRMS *m/z* calcd for $C_{27}H_{39}N_3O_6Na$ $[M + Na]^+$ 524.2737, found 524.2717.

(2*S*,3*S*)-[1-*tert*-Butoxycarbonyl-3-(4-methoxy-3-vinylphenoxy)prolyl]isoleucine-prop-1-enylamide 16b. Solvent system for purification by flash chromatography over silica gel: AcOEt/petroleum ether 35/65; white solid, obtained as a mixture of *E* and *Z* isomer in a 1:1 ratio (scale 146 mg of compound obtained; yield 79%): mp 62 °C; $[\alpha]_D^{20}$ −42 (*c* 0.5, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 345 K) δ 9.55 (d, J = 9.5 Hz, 0.5H), 9.17 (d, J = 9.7 Hz, 0.5H), 7.80 (d, J = 8.7 Hz, 0.5H), 7.75 (d, J = 8.6 Hz, 0.5H), 7.15 (br s, 1H), 6.88−6.97 (m, 3H), 6.50−6.62 (m, 1H), 5.81 (dd, J = 17.8, 1.0 Hz, 1H), 5.20−5.30 (m, 1.5H), 4.80 (br s, 1H), 4.69−4.79 (m, 0.5H), 4.43 (app t, J = 7.8 Hz, 0.5H), 4.39 (br s, 1H), 4.22 (app t, J = 8.0 Hz, 0.5H), 3.77 (s, 3H), 3.42−3.61 (m, 2H), 2.00−2.13 (m, 2H), 1.76−1.89 (m, 1H), 1.61−1.65 (m, 3H), 1.43−1.54 (m, 1H), 1.40 (s, 9H), 1.06−1.22 (m, 1H), 0.82−0.89 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 345 K) δ 169.0 and 168.9 (stereoisomers), 168.6 and 167.7 (stereoisomers), 154.4 (br), 151.2, 150.3, 130.7, 126.8, 123.4 and 121.7 (stereoisomers), 116.1, 114.7, 113.7, 112.9, 106.9 and 105.5 (stereoisomers), 80.4 (br), 78.9, 65.8, 56.7 and 56.3 (stereoisomers), 55.9 and 55.8 (stereoisomers), 44.4, 36.3, 29.0 (br), 27.6, 24.0 and 23.9 (stereoisomers), 14.9, 14.1 and 10.7 (stereoisomers), 10.4; IR (KBr) ν_{max} 3303, 2960, 1685, 1650, 1531, 1486, 1404, 1214, 1168 cm^{-1}; ESIMS (positive mode) 538.4; ESIHRMS *m/z* calcd for $C_{28}H_{41}N_3O_6Na$ $[M + Na]^+$ 538.2893, found 538.2890.

(*E*,2*S*,3*S*)-[1-*tert*-Butoxycarbonyl-3-(4-methoxy-3-vinylphenoxy)prolyl]isoleucine-hepta-1,6-dienylamide 16c. Solvent system for purification by flash chromatography over silica gel: AcOEt/petroleum ether 3/7; white foamy solid, obtained as *E* enamide isomer (scale 194 mg of compound obtained; yield 85%): $[\alpha]_D^{20}$ −37 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6, 345 K) δ 9.54 (d, J = 9.6 Hz, 1H), 7.75 (d, J = 8.7 Hz, 1H), 7.15 (d, J = 2.6 Hz, 1H), 6.87−6.97 (m, 3H), 6.57 (ddt, J = 14.3, 9.6, 1.3 Hz, 1H), 5.82−5.88 (m, 1H), 5.74−5.80 (m, 1H), 5.21−5.31 (m, 2H), 4.93−5.04 (m, 2H), 4.81 (br m, 1H), 4.38 (app s, 1H), 4.23 (t, J = 8.0 Hz, 1H), 3.77 (s, 3H), 3.53−3.62 (m, 1H), 3.42−3.52 (m, 1H), 1.96−2.08 (m, 6H), 1.77−1.86 (m, 1H), 1.38−1.52 (m, 2H), 1.40 (s, 9H), 1.08−1.21 (m, 2H), 0.86 (d, J = 6.8 Hz, 3H), 0.85 (app t, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 345 K) δ 169.3, 168.2, 153.9, 151.6, 150.6, 138.4, 131.1, 127.1, 123.1, 116.5, 115.1, 114.5, 114.0, 113.2, 112.4, 80.9, 79.3, 66.2, 57.2, 56.2, 44.8, 36.6, 32.4, 28.7, 28.6, 28.0, 24.4, 15.3, 10.7; IR (KBr) ν_{max} 3305, 1692,

1487, 1220; 1165 cm^{-1}; ESIMS (positive mode) 593.3; ESIHRMS *m*/*z* calcd for $C_{32}H_{47}N_3O_6Na$ $[M + Na]^+$ 592.3363, found 592.3379.

(*E*,2*S*,3*S*)-[1-*tert*-Butoxycarbonyl-3-(4-methoxy-3-vinylphenoxy)-prolyl]isoleucine-benzylprop-1-enylamide 16d. Solvent system for purification by flash chromatography over silica gel: AcOEt/petroleum ether 1/9; white oily solid, obtained as *E* enamide isomer (scale 284 mg of compound obtained; yield 91%): $[\alpha]_D^{20}$ +18 (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6, 345 K) δ 8.12 (d, J = 8.0 Hz, 1H), 7.10−7.28 (m, 6H), 6.84−6.97 (m, 4H), 5.78 (d, J = 17.8 Hz, 1H), 5.25 (dd, J = 11.2, 1.4 Hz, 1H), 5.15 (dq, J = 13.8, 6.5 Hz, 1H), 4.75−4.83 (m, 3H), 4.71 (br s, 1H), 4.43 (s, 1H), 3.77 (s, 3H), 3.57−3.64 (m, 1H), 3.40−3.53 (m, 1H), 2.04−2.11 (m, 2H), 1.87−1.98 (m, 1H), 1.63 (dd, J = 6.5, 1.4 Hz, 3H), 1.47−1.51 (m, 1H), 1.40 (s, 9H), 1.07−1.21 (m, 1H), 0.86 (br m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 345 K) δ 170.2, 169.4, 153.7, 151.6, 150.6, 137.4, 131.2, 131.1, 128.2, 127.1, 126.7, 116.5, 115.1, 114.1, 113.2, 110.5 (br), 81.0 (br), 79.2, 56.2, 53.7, 47.2, 44.8, 39.0, 29.2, 28.0, 23.9, 15.5, 14.9, 10.7; IR (KBr) ν_{max} 3297, 1668, 1642, 1173 cm^{-1}; CIMS (NH_3 gas) 606 (100), 532 (42), 458 (23), 376 (22), 287 (31), 170 (29), 148 (41); ESIHRMS *m*/*z* calcd for $C_{35}H_{47}N_3O_6Na$ $[M + Na]^+$ 628.3363, found 628.3347.

Typical Procedure for Ene−Enamide RCM Reaction. A 25 mL round-bottom flask was charged with vinyl enamide derivative **16a−d** (0.07 mmol). The flask was fitted with a condenser, evacuated under high vacuum, and backfilled with argon. Dry and degassed 1,2-dichloroethane (15 mL) and benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium (Grubbs' second-generation catalyst, 6 mg, 0.007 mmol) were successively added, and the resulting purple reaction mixture was refluxed for 24 h. Another portion of Grubbs' second-generation catalyst (6 mg, 0.007 mmol) was then added, and the reaction mixture was refluxed for 24 h, cooled to rt, left open to air for 1 h, concentrated, and directly purified by flash chromatography over silica gel.

(2*S*,3*S*)-[1-*tert*-Butoxycarbonyl-3-(4-methoxy-3-vinylphenoxy)prolyl]soleucinamide 17. Solvent system for purification by flash chromatography over silica gel: AcOEt/petroleum ether 8/2; white glassy solid (scale 72 mg of compound obtained from **16a**): mp 85 °C; $[\alpha]_D^{20}$ −25 (*c* 0.7, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6, 345 K) δ 7.61 (d, J = 8.7 Hz, 1H), 7.16 (d, J = 2.7 Hz, 1H), 6.88−7.12 (m, 4H), 5.82 and 5.26 (rotamers, dd, J = 17.7, 1.5 Hz, dd, J = 11.2, 1.5 Hz, 1H), 4.84 (br s, 1H), 4.39 (app s, 1H), 4.21 (dd, J = 8.5, 6.6 Hz, 1H), 3.78 (s, 3H), 3.57 (app tt, J = 10.6, 2.9 Hz, 1H), 3.42−3.51 (m, 1H), 2.07−2.10 (br m, 2H), 1.76−1.85 (m, 1H), 1.40−1.54 (m, 1H), 1.41 (s, 9H), 1.04−1.18 (m, 1H), 0.89 (d, J = 6.8 Hz, 3H), 0.86 (d, J = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, DMSO-d_6, 345 K) δ 172.1, 168.7, 153.5, 151.2, 150.3, 130.8, 127.5, 116.1, 114.8, 113.7, 112.9, 80.4 (br), 79.0, 65.9, 56.6, 55.9, 44.4, 36.4, 29.0 (br), 27.7, 24.0, 15.1, 10.6; IR (KBr) ν_{max} 3319, 2966, 1690, 1486, 1388, 1219, 1173 cm^{-1}; ESIMS (positive mode) 499.3, 498.3; ESIHRMS *m*/*z* calcd for $C_{25}H_{37}N_3O_6Na$ $[M + Na]^+$ 498.2580, found 498.2589.

Cyclopeptide Core 2. Solvent system for purification by flash chromatography over silica gel: Et_2O/EtOH 99/1; white solid (scale 67 mg of compound obtained from **16b**): mp 188 °C; $[\alpha]_D^{20}$ −436 (*c* 0.54, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 11.2 Hz, 1H), 7.22 (d, J = 5.0 Hz, 1H), 6.87 (dd, J = 6.9, 11.2 Hz, 1H), 6.83 (d, J = 9.2 Hz, 1H), 6.74 (dd, J = 2.9, 8.9 Hz, 1H), 6.65 (d, J = 2.9 Hz, 1H), 5.85 (d, J = 9.1 Hz, 1H), 5.43 (dt, J = 2.7, 8.1 Hz, 1H), 4.25 (app t, J = 4.6 Hz, 1H), 4.15 (d, J = 2.6 Hz, 1H), 3.70−3.78 (m, 1H), 3.73 (s, 3H), 3.30−3.39 (m, 1H), 2.39−2.50 (m, 1H), 2.14−2.24 (m, 1H), 2.00−2.10 (m, 1H), 1.38 (s, 9H), 1.05−1.32 (m, 2H), 0.93 (d, J = 7.0 Hz, 3H), 0.81 (t, J = 9.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 167.6, 155.3, 151.6, 151.4, 124.5, 121.7, 117.8, 113.9, 111.5, 106.7, 81.2, 78.0, 64.9, 60.4, 56.2, 46.0, 35.3, 32.2, 28.4, 24.6, 16.2, 11.9; IR (KBr) ν_{max} 3319, 2919, 1706, 1650, 1506, 1404, 1214, 1163, 1122, 1030, 764 cm^{-1}; CIMS (NH_3 gas) 491.0 (100), 473.0 (57), 418.0 (42); HRMS (CI, NH_3) *m*/*z* calcd for $C_{25}H_{36}N_3O_6$ $[M + H]^+$ 474.2604, found 474.2607.

(*E*,2*S*,3*S*)-[1-*tert*-Butoxycarbonyl-3-(3-formyl-4-methoxyphenoxy)prolyl]isoleucine-benzylprop-1-enylamide 18. Solvent system for purification by flash chromatography over silica gel: AcOEt/petroleum ether 3/7; oily solid, obtained as *E* enamide isomer (scale: 18 mg of compound obtained; yield obtained using 1 equiv of **GII**: 39%): $[\alpha]_D^{20}$ +18 (*c* 0.3, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6, 345 K) δ 10.32 (s, 1H), 8.15 (br s, 1H), 7.16−7.31 (m, 9H), 5.14 (dq, J = 13.3, 6.6 Hz, 1H), 4.80−4.82 (m, 3H), 4.71 (br s, 1H), 4.43 (s, 1H), 3.90 (s, 3H), 3.54−3.61 (m, 1H), 3.40−3.49 (m, 1H), 2.00−2.07 (m, 2H), 1.87−1.96 (m, 1H), 1.63 (dd, J = 6.6, 1.5 Hz, 3H), 1.47−1.51 (m, 1H), 1.40 (s, 9H), 1.08−1.21 (m, 1H), 0.78−9.88 (br m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 345 K) δ 188.6, 170.1, 169.2, 156.7, 150.5, 137.4, 128.2, 126.6, 125.1, 124.7, 114.8, 114.2, 80.1 (br), 79.2, 56.6, 53.7, 47.2, 44.6, 36.2, 30.1 (br), 28.0, 23.9, 15.5, 14.9, 10.7; IR (KBr) ν_{max} 3281, 17235, 1278, 1145, 840 cm^{-1}; CIMS (CH_4 gas) 608 (100), 552 (53), 461 (13), 405 (12); ESIHRMS *m*/*z* calcd for $C_{34}H_{45}N_3O_7Na$ $[M + Na]^+$ 630.3155, found 630.3148.

(2*S*,3*S*)-[1-*tert*-Butoxycarbonyl-3-(4-methoxy-3-vinylphenoxy)prolyl]isoleucine-allylamide 20. To a solution of *N*-Boc-isoleucine-allylamide **13** (80 mg, 0.30 mmol) in CH_2Cl_2 (6 mL) was added anhydrous zinc(II) bromide (304 mg, 1.35 mmol) at 0 °C. The resulting white slurry was vigorously stirred at 0 °C for 1 h, slowly warmed to rt, stirred for another 1 h, and concentrated. Carboxylic acid **4** (100 mg, 0.275 mmol), 1-hydroxybenzotriazole (HOBt, 36 mg, 0.0.31 mmol), and DMF (5 mL) were next added to the resulting white solid. After complete dissolution of all solids, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC, 60 mg, 0.31 mmol) and *N*-methylmorpholine (76 μL, 0.69 mmol) were next added at 0 °C, and the solution was stirred for 16 h while being progressively warmed to rt. The yellow reaction mixture was quenched with water and diluted with ether. The aqueous layer was extracted with ether, and the combined organic layers were successively washed with a 1 M HCl aqueous solution, a saturated aqueous solution of $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was finally purified by flash chromatography over silica gel (petroleum ether/AcOEt: 3/7) to yield the desired acyclic allylamide **20** as a white glassy solid (130 mg, 0.252 mmol, 92%): $[\alpha]_D^{20}$ −31 (*c* 0.2, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6, 345 K) δ 8.00 (br s, 1H), 7.67 (d, J = 8.5 Hz, 1H), 7.14 (d, J = 2.8 Hz, 1H), 6.87−7.00 (m, 3H), 5.73−5.87 (m, 2H), 5.26 (dd, J = 11.2, 1.6 Hz, 1H), 5.13 (app dq, J = 17.2, 1.6 Hz, 1H), 5.04 (app dq, J = 10.2, 1.6 Hz, 1H), 4.81 (br m, 1H), 4.38 (app s, 1H), 4.22 (dd, J = 8.7, 7.3 Hz, 1H), 3.77 (s, 3H), 3.70−3.83 (m, 2H), 3.62 (app tt, J = 11.0, 3.2 Hz, 1H), 3.45−3.57 (m, 1H), 2.08 (br m, 1H), 1.76−1.90 (m, 1H), 1.38−1.51 (m, 1H), 1.40 (s, 9H), 1.04−1.18 (m, 2H), 0.82−0.90 (m, 6H); ^{13}C NMR (75 MHz, DMSO-d_6, 345 K) δ 170.3, 169.1, 153.9, 151.6, 150.6, 135.0, 131.1, 127.1, 116.5, 115.2, 114.7, 114.0, 113.2, 79.3, 69.8, 66.2, 57.2, 56.3, 44.8, 40.9, 36.8, 28.0, 24.4, 18.8, 15.4, 10.8; IR (KBr) ν_{max} 3301, 2984, 1686, 1532, 1170 cm^{-1}; ESIMS (positive mode) 539.3, 538.3; ESIHRMS *m*/*z* calcd for $C_{28}H_{41}N_3O_6Na$ $[M + Na]^+$ 538.2893, found 538.2880.

Cyclopeptide Core 2 via Isomerization/Ene−Enamide RCM Tandem Reaction. A 25 mL round-bottom flask was charged with allylamide derivative **20** (35 mg, 0.07 mmol). The flask was fitted with a condenser, evacuated under high vacuum, and backfilled with argon. Dry and degassed 1,2-dichloroethane (15 mL) and benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]-dichloro(tricyclohexylphosphine)ruthenium (Grubbs' second-generation catalyst, 6 mg, 0.007 mmol) were successively added, and the resulting purple reaction mixture was refluxed for 24 h. Another portion of Grubbs' second-generation catalyst (6 mg, 0.007 mmol) was then added, and the reaction mixture was refluxed for 24 h, cooled to rt, left open to air for 1 h, concentrated, and directly

purified by flash chromatography over silica gel (Et_2O/EtOH: 99/1) to yield the desired cyclopeptide core **2** (11.5 mg, 0.024 mmol, 36%) as a white solid (see characterization above).

Deprotected Cyclopeptide Core 21. To a solution of **2** (58 mg, 0.122 mmol) in dichloromethane (3 mL) were added at −10 °C 2,6-lutidine (15 μL, 0.122 mmol) and trimethylsilyl trifluoromethanesulfonate (1.4 M solution in dichloromethane, 350 μL, 0.49 mmol). The resulting light pink solution was stirred for 1 h while being progressively warmed to 0 °C. The mixture was next hydrolyzed at 0 °C by addition of a saturated aqueous solution of $NaHCO_3$ and diluted with dichloromethane. The aqueous layer was extracted with dichloromethane, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to give the desired *N*-deprotected macrocycle **21** as a white solid which was used without further purification for the next step (quantitative mass recovery): mp 218 °C; $[\alpha]_D^{20}$ −452 (*c* 0.49, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.50 (br s, 1H), 6.91 (dd, J = 9.2, 11.3 Hz, 1H), 6.92 (d, J = 9.1 Hz, 1H), 6.82 (dd, J = 2.9, 9.0 Hz, 1H), 6.65 (br s, 1H), 5.95 (d, J = 8.9 Hz, 1H), 5.09−5.11 (m, 1H), 4.32 (br s, 1H,), 3.79 (s, 3H), 3.43 (br s, 1H), 3.13−3.20 (m, 1H), 2.90−2.95 (m, 1H), 2.16−2.26 (m, 3H), 1.95−2.03 (br m, 1H), 1.37−1.47 (m, 1H), 1.02−1.14 (m, 1H), 0.94 (d, J = 6.9 Hz, 3H), 0.87 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 167.0 (br), 151.2, 151.1, 124.1, 121.5, 117.5, 113.8, 111.1, 107.2, 80.9, 69.6, 60.1 (br), 56.1, 47.5 (br), 35.6 (br), 32.0, 25.3, 16.0, 11.7; ESIMS (positive mode) 412.3; HRMS (CI, NH_3) *m*/*z* calcd for $C_{20}H_{28}N_3O_4$ $[M + H]^+$ 374.2080, found 374.2069.

Paliurine E 1. To a cooled solution of *N*,*N*-dimethyl-L-phenylalanine (36 mg, 0.18 mmol) and 1-hydroxyazabenzotriazole (HOAt, 30 mg, 0.22 mmol) in DMF (3 mL) were added *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU, 65 mg, 0.17 mmol) and diisopropylethylamine (90 μL, 0.51 mmol) at 0 °C. The resulting yellow solution was stirred at 0 °C for 20 min and added dropwise via cannula to a cooled solution of **21** (46 mg, 0.122 mmol) in DMF (2 mL) at 0 °C. The flask containing the activated acid was rinsed with an additional portion of DMF (1 mL), which was cannulated into the solution of the amine. The resulting yellow solution was warmed to rt and stirred overnight. The mixture was quenched at 0 °C with a saturated aqueous solution of NH_4Cl and diluted with ether. The aqueous layer was extracted with ether, and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated. The crude residue was purified by flash chromatography over silica gel (CH_2Cl_2/MeOH/30 wt % aqueous NH_3 95/3/2) to give the desired synthetic paliurine E **1** (52 mg, 95 μmol, 78% over two steps) as a white solid: R_f 0.56 (AcOEt/EtOH 95/5); mp 190 °C (lit. unreported); $[\alpha]_D^{20}$ −298 (*c* 0.6, CH_3CN) [lit.[20] natural paliurine E $[\alpha]_D^{20}$ −382 (*c* 0.9, CH_3CN)]; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (d, J = 11.4 Hz, 1H), 7.40 (d, J = 4.5 Hz, 1H), 7.15−7.24 (m, 3H), 7.06 (dd, J = 7.7, 1.7 Hz, 2H), 6.94 (dd, J = 9.2, 11.3 Hz, 1H), 6.88 (d, J = 9.0 Hz, 1H), 6.79 (dd, J = 9.0, 2.9 Hz, 1H), 6.68 (d, J = 2.9 Hz, 1H), 5.91 (d, J = 9.1 Hz, 1H), 5.41 (dt, J = 7.2, 3.0 Hz, 1H), 4.44 (d, J = 3.0 Hz, 1H), 4.24 (app t, J = 4.2 Hz, 1H), 4.00 (ddd, J = 10.9, 8.5, 2.7 Hz, 1H), 3.79 (s, 3H), 3.44 (dd, J = 10.3, 3.5 Hz, 1H), 3.06 (dd, J = 13.0, 10.6 Hz, 1H), 2.92 (dd, J = 13.0, 3.3 Hz, 1H), 2.86 (dt, J = 4.2, 10.7 Hz, 1H), 2.40 (s, 6H), 2.36−2.39 (m, 1H), 2.03−2.21 (m, 2H), 1.13−1.48 (m, 2H), 1.01 (d, J = 7.0 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 170.3, 167.4, 151.6, 151.2, 138.3, 129.1, 128.7, 126.7, 124.5, 121.7, 117.6, 113.9, 111.4, 106.7, 76.9, 68.2, 64.6, 60.5, 56.2, 46.0, 42.1, 35.7, 32.5, 32.4, 24.8, 16.4, 12.1; UV λ_{max} (log ϵ) 219 (4.81), 320 (4.51); IR (KBr) ν_{max} 3391, 3350, 2966, 2933, 2873, 1670, 1644, 1503, 1460, 1420, 1383, 1296, 1260, 1220, 1178, 1050, 810, 794, 748, 701 cm^{-1}; ESIMS (positive mode) 571.5 (100), 549.5 (83), 359.5 (11), 148.2 (34); ESIHRMS *m*/*z* calcd for $C_{31}H_{41}N_4O_5$ $[M + H]^+$ 549.3077, found 549.3069.

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Supporting Information Available: Characterization data and copies of ^{1}H and ^{13}C NMR spectra for all new compounds and paliurine E. Paliurine E spectral data compared to reported data. This material is available free of charge via the Internet at http://pubs.acs.org.

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