JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

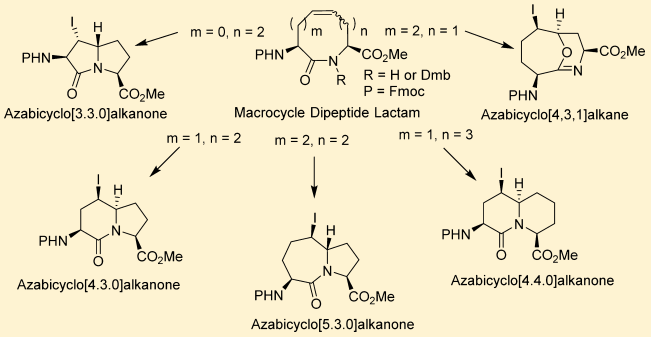
Insight into Transannular Cyclization Reactions To Synthesize Azabicyclo[*X.Y.Z*]alkanone Amino Acid Derivatives from 8-, 9-, and 10-Membered Macrocyclic Dipeptide Lactams

N. D. Prasad Atmuri and William D. Lubell*

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Centre-ville, Montréal, Québec H3C 3J7, Canada

Supporting Information

ABSTRACT: An efficient method for synthesizing different functionalized azabicyclo[*X.Y.*0]alkanone amino acid derivatives has been developed employing electrophilic transannular cyclizations of 8-, 9-, and 10-membered unsaturated macrocycles to form 5,5-, 6,5-, 7,5-, and 6,6-fused bicylic amino acids, respectively. Macrocycles were obtained by a sequence featuring peptide coupling of vinyl-, allyl-, homoallyl-, and homohomoallylglycine building blocks followed by ring-closing metathesis. X-ray crystallographic analyses of the 8-, 9-, and 10-membered macrocyclic lactam starting materials as well as certain bicyclic amino acid products provided insight into their conformational preferences as well as the mechanism for the diastereoselective formation of specific azabicycloalkanone amino acids by way of transannular iodolactamization reactions.



INTRODUCTION

Azabicyclo[*X.Y.*0]alkane structures, such as pyrrolizidines, indolizidines, and qunolizidines, are found in numerous biologically active alkaloid natural products.[1,2] The related azabicyclo[*X.Y.*0]alkanone amino acid counterparts are rigid dipeptide surrogates that have been employed to study conformation−activity relationships of biologically active peptides.[3,4] Inherent to the syntheses of both classes of heterocycles has been the stereocontrolled construction of the bicyclic ring system in a way that provides for effective introduction of ring functionality. Among various synthetic strategies,[5] transannular reactions featuring amine nucleophiles reacting on macrocyclic olefin and epoxide precursors have exhibited considerable utility for the stereoselective construction of the bicyclic amines,[6,7] albeit few examples of the related cyclizations of macrocyclic lactams have been reported.[8] In both cases, regioselective formation of specific bicycles has often been observed to occur with high diastereoselectivity. Limited mechanistic understanding exists however to predict the outcome of such transannular cyclization reactions, because they have been typically performed on a restricted number of ring sizes with substituents that have varied greatly both in functional group and in location. Generally, in cycloalkanes of 8−11 ring atoms, unfavorable interactions of ring substituents can cause significant strain, so-called "Prelog strain".[9,10] Moreover, nitrogen lone pair electrons have been reported to prefer an antiorientation with respect to the olefin π-bond to minimize repulsive interactions.[11] Such steric and electronic interactions serve likely in part as driving forces for preferred macrocycle conformations and favored regioselective cyclizations.

In the interest of developing a general strategy for synthesizing azabicyclo[*X.Y.*0]alkanone amino acids of varying ring sizes, we have pursued electrophilic transannular lactamizations of unsaturated macrocyclic dipeptides.[8a] This strategy is appealing, because a variety of macrocycles may be generated by coupling various ω-unsaturated amino acids, followed by ring-closing metathesis (RCM; Figure 1). Moreover, after transannular iodolactamization, the resulting iodide has served as a handle for introducing various side chain functional groups onto the bicyclic system.[12]

Considering that both bicycle and macrocycle constraints serve to rigidify the peptide backbone,[5c,13] efforts have focused on studying the synthesis and conformational analysis of a series of ring systems in which the same dipeptide motif is maintained as the ring size and olefin orientation are modulated. Employing X-ray crystallography and NMR spectroscopy, insight has now been gained with respect to the conformational preferences of the macrocyclic and bicyclic dipeptide motifs, as well as the regioselective nature of the transannular lactamization. Exploring five different macrocycles, we have found conditions to prepare regioselectively and stereoselectively five distinct bicyclic dipeptide mimics, validating the effectiveness of this approach for peptidomimetic synthesis.

RESULTS AND DISCUSSION

Iodoazabicyclo[4.3.0]- and iodoazabicyclo[5.3.0]alkanones **1** and **2** were previously made by the diastereoselective

Received: February 1, 2015
Published: April 1, 2015

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

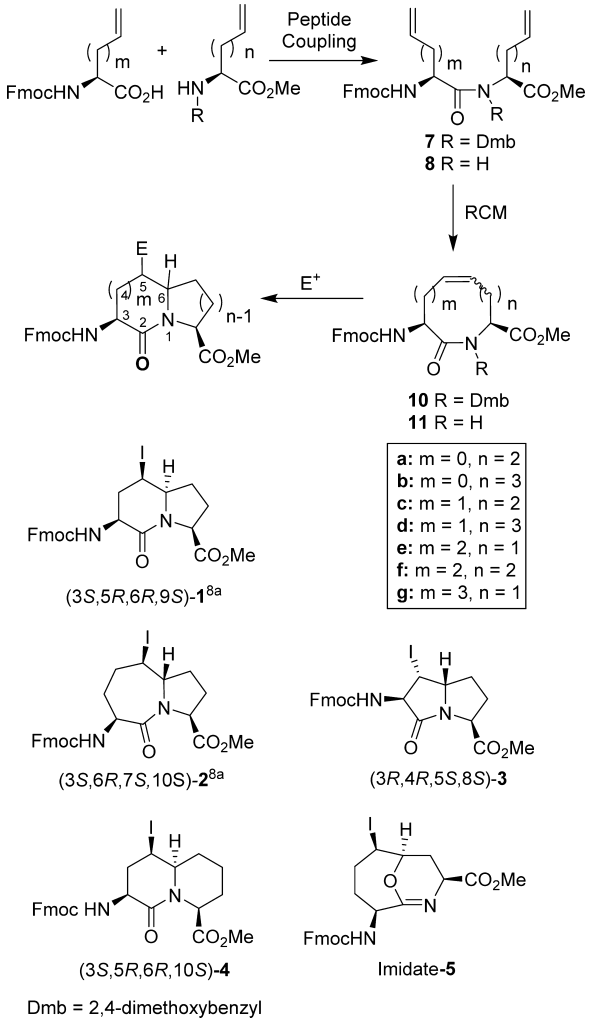


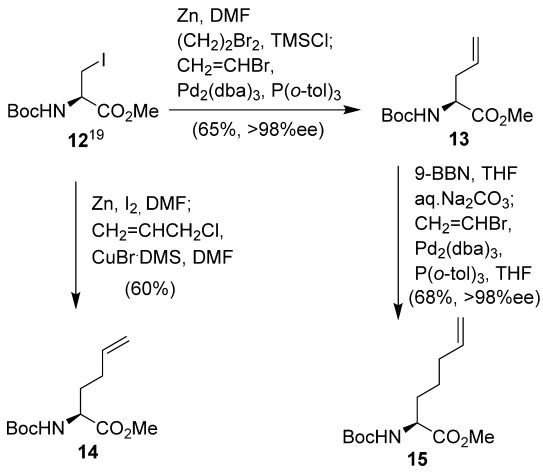
Figure 1. General synthetic plan for making azabicyclo[*X.Y.*0]alkanones and representative examples of previously prepared bicycles **1** and **2**, as well as new examples, **3**–**5**, prepared herein.

iodolactamization of 9- and 10-membered macrocycles (*Z*)-**10c** and (*E*)-**11f**, respectively (Figure 1).[8a,12,14] Macrocycles (*Z*)-**10c** and (*E*)-**11f** had been made from allyl- and homoallylglycine building blocks.[14] Herein, vinyl- and homohomoallylglycines were added to provide a set of four ω-unsaturated amino acids for RCM/electrophilic transannular cyclizations that have now given access to the new 5,5- and 6,6-fused bicyclic ring systems **3** and **4**, as well as anti-Bredt imidate **5** (Figure 1). The latter bridgehead imidate represents a rare substituted heterocycle example that challenges Bredt's rules.[15] From all five of these related transannular cyclizations, only a single heterocyclic system was typically formed diastereoselectively.

The enantiomerically pure ω-unsaturated amino acid starting materials with lengths of 4–7 carbons were synthesized efficiently by atom economical routes. Many synthetic approaches exist for making these building blocks;[14,16,17] however, they often require long reaction sequences, especially in the cases of 2-aminopent-4-enoate (allylglycine) and 2-aminohept-6-enoate (homohomoallylglycine).

Inspired by the relatively efficient synthesis of methyl 2-(*N*-Boc-amino)hex-5-enoate (**14**),[18] which featured the copper-catalyzed cross-coupling of allyl chloride and the zincate derived from iodoalanine **12** (Scheme 1),[19] related transition-metal cross-coupling methods were developed to make the higher and lower

Scheme 1. Synthesis of 2-Aminopent-4-enoate 13, 2-Aminohex-5-enoate 14, and 2-Aminohept-6-enoate 15



amino acid homologues. Methyl 2-(*N*-Boc-amino)pent-4-enoate (**13**) and methyl 2-(*N*-Boc-amino)hept-6-enoate (**15**) were thus respectively prepared by using vinyl bromide in the Pd-catalyzed reactions on the zincate derived from iodoalanine **12** and the boronate derived from **13**.

Starting from L-serine as a chiral educt, protected enantiomerically pure ω-unsaturated amino acids with chain lengths of 5–7 carbons were prepared by a common sequence. Methyl *N*-Boc-iodoalanine (**12**; Scheme 1) was assembled in three steps from serine and used in the synthesis of the five- and six-carbon analogues.[19] On treatment with zinc, iodoalanine **12** was converted to the corresponding zincate, which was coupled with vinyl bromide and $Pd_2(dba)_3$[20] or allyl chloride and CuBr·DMS,[18] respectively, to give pentenoate **13** and hexenoate **14** in 65% and 60% yields. Heptenoate **15** was synthesized from pentenoate **13** in 68% yield by hydroboration of the terminal alkene using 9-borabicyclo[3.3.1]nonane (9-BBN) and cross-coupling to vinyl bromide using $Pd_2(dba)_3$.

After the syntheses of pentenoate **13** and heptenoate **15**, their enantiomeric purities were respectively evaluated by conversion to diastereomeric dipeptides on removal of the Boc group with HCl gas in dichloromethane and coupling to L- and D-*N*-Boc-alanine with HATU (Supporting Information). Examination of the diastereotopic methyl ester singlets by ^{1}H NMR spectroscopy in CD_3CN during incremental addition of the (*S,R*)-diastereomer to the (*S,S*)-diastereomer demonstrated in both cases a >99:1 dr. Hence, pentenoate **13** and heptenoate **15** are both assumed to be of >98% enantiomeric purity.

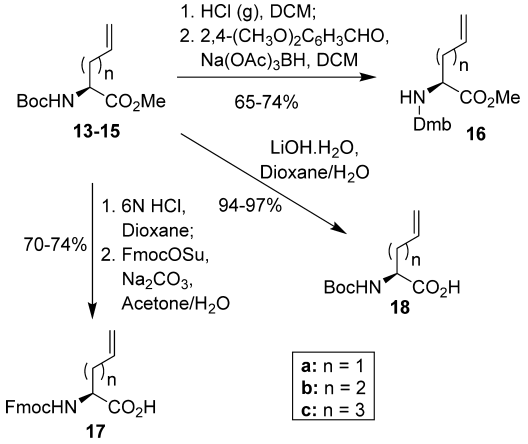
Suitably protected 2-(*N*-Dmb-amino) ester **16** and 2-(*N*-Boc-amino) and 2-(*N*-Fmoc-amino) acids **17** and **18** were prepared from 2-(*N*-Boc-amino) esters **13**–**15** using previously described protocols (Scheme 2).[14] 2-(*N*-Fmoc-amino)but-3-enoic acid (vinylglycine **19**) was synthesized as previously described.[21,22]

Dipeptides **6** and **7** were synthesized by coupling ester **16** and acids **17** and **18** using HATU and *N*-ethylmorpholine in 70–80% yield (Scheme 3).[14] Double bond migration occurred during coupling of but-3-enoic acid **19** to 2-(*N*-Dmb-amino)hex-5-oate **16b** using HATU and DIEA and gave dehydropeptide **20** (Scheme 4). Double bond migration was avoided by converting vinylglycine **19** to the corresponding acid chloride, which reacted with **16b** and **16c** in the absence of base to afford dipeptides **7a** and **7b** in 50–60% yield.

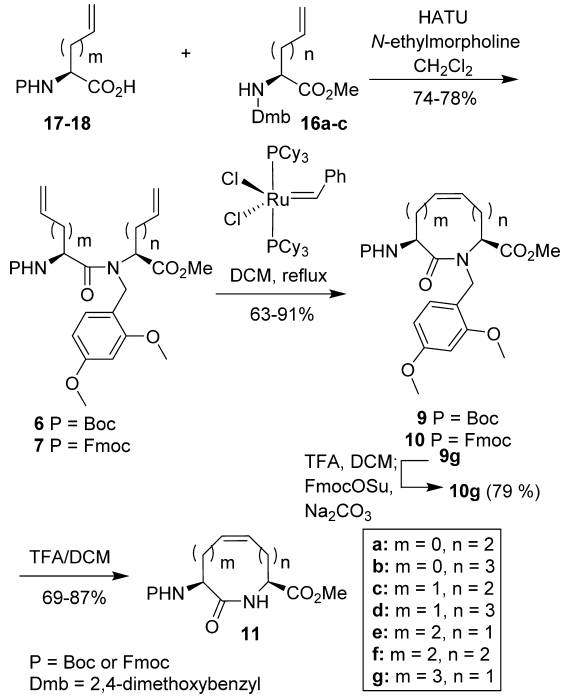
Macrocycles **9** and **10** were prepared from dipeptides **6** and **7** in 60–90% yields in solution using RCM employing the

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904–4918

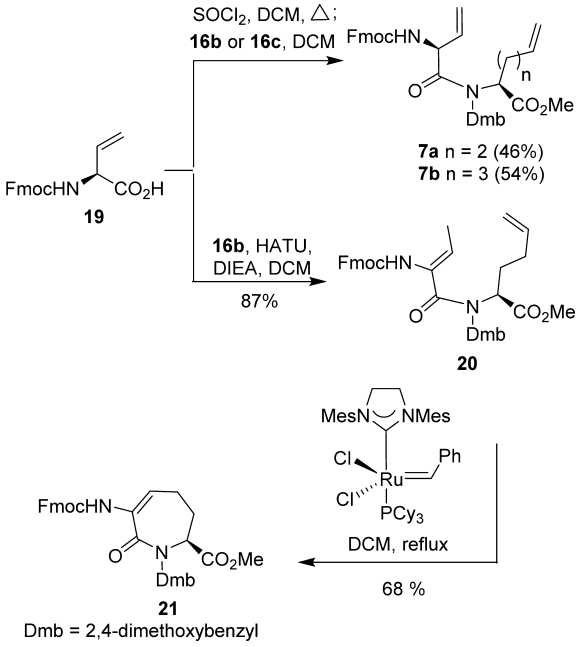
Scheme 2. Protecting Group Shuffle To Make Boc, Fmoc, and Dmb Building Blocks



Scheme 3. Syntheses of Dipeptides 6 and 7 and Macrocycles 9−11



Scheme 4. Coupling with Vinylglycine 19 and Synthesis of Dehydroazepinone 21



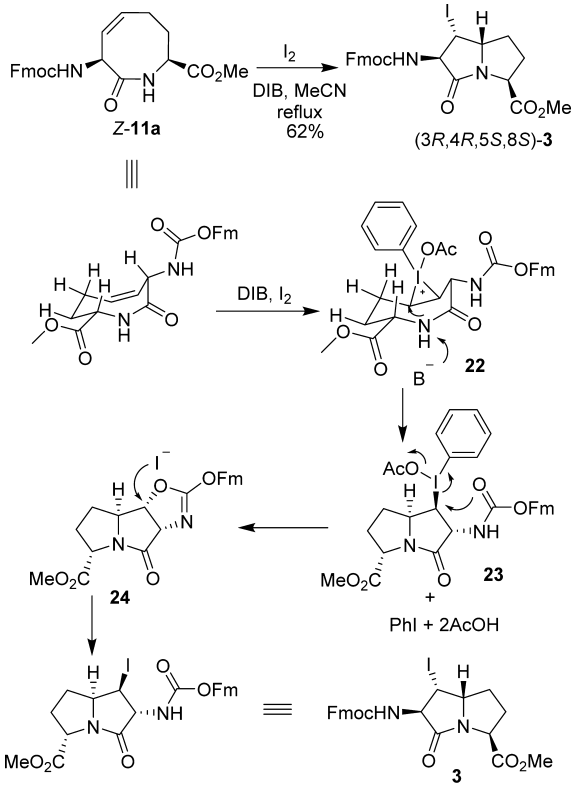
Grubbs first-generation catalyst in dichloromethane at reflux (Scheme 3).[23,24] Dehydroamino acid analogue **20** failed to react using the first generation of the Grubbs catalyst, but could be converted to dehydroazepinone **21** with the Grubbs second-generation catalyst (Scheme 4).[25] In spite of the acid sensitivity of the Dmb group, the Boc group could be selectively removed from macrocycle **9g** using 50% TFA in DCM for 2 h to afford the corresponding amine, which was converted to its Fmoc counterpart **10g** using Fmoc-OSu and Na_2CO_3 (Scheme 3).[14] To remove the Dmb group, *N*-Fmoc-amino lactams **10** were treated with 50% TFA/DCM for 18 h, which afforded macrocycles **11** in 70−80% yields. In the case of 10-membered *N*-Dmb-amino lactam **10d**, starting material was however not consumed even after treatment for 3 days, when lactam **11d** was afforded in 69% yield after chromatography. The olefin and amide isomer geometries of macrocycles **9**−**11** were established by NMR spectroscopy and X-ray analysis (vide infra).

Transannular cyclization of 8-membered macrocyclic lactam (*Z*)-**10a** was initially studied by treatment with iodine in THF and MeCN at room temperature to reflux; however, only loss of the Dmb group was observed, and macrocycle (*Z*)-**11a** was isolated. 8-Membered lactam (*Z*)-**11a** proved resistant to transannular iodoamidation using I_2 in THF buffered with $NaHCO_3$, as well as using I_2 in acetonitrile at reflux. Transannular cyclization was achieved by treating (*Z*)-**11a** with (diacetoxyiodo)-benzene (DIB; 1.5 equiv) and 4 equiv of iodine in acetonitrile at reflux for 30 min (Scheme 5). Although DIB has been used in oxidative cyclizations of *o*-hydroxystyrenes to benzofurans, to the best of our knowledge, this is the first use of this reagent in a transannular iodolactamization. (3*R*,4*R*,5*S*,8*S*)-Pyrrolizidinone **3** was isolated as a single diastereomer in 62% yield after chromatography (Scheme 5). In the mechanism for the formation of **3**, hypervalent iodine may activate the double bond as a 3-membered iodonium species, **22**,[26] which undergoes intramolecular reaction with the amide nitrogen to form intermediate **23**. Displacement of the hypervalent iodine by the neighboring carbamate may occur by way of an oxazole intermediate **24**, which is opened by iodide to give iodopyrrolizidinone **3** with retention of configuration. The structure of **3** was confirmed by NMR spectroscopy and X-ray diffractometry as described below.

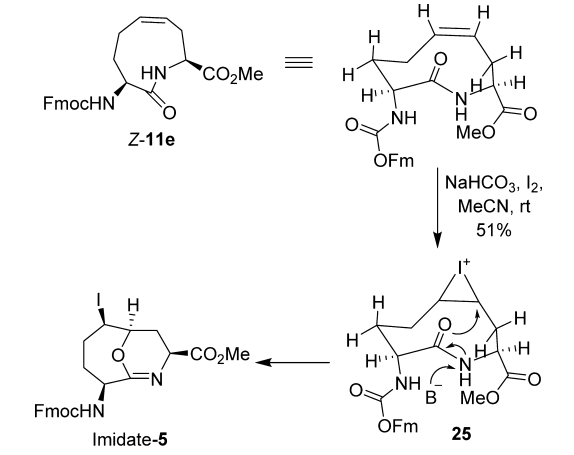
Although the related double bond isomer (*Z*)-**10c** (m = 1, n = 2) underwent iodolactamization to provide iodoindolizidinone **1** in 86% yield using I_2 in THF at 80 °C (Figure 1),[8a] treatment of unsaturated macrocyclic lactam (*Z*)-**10e** (m = 2, n = 1) under analogous conditions only caused removal of the Dmb group to provide lactam (*Z*)-**11e**. Moreover, attempts to induce transannular cyclization of 9-membered lactam (*Z*)-**11e** using alternative conditions (I_2 in MeCN;[12] DIB and I_2 in MeCN, rt to reflux; Lewis base-catalyzed[27] iodolactamization using $Ph_3P{=}S$, NIS/DCM) produced a relatively less polar spot on TLC compared to the iodobicycles. The reaction proceeded cleanly, and the starting material was all consumed within 1 h as indicated by TLC. After the usual aqueous workup with $Na_2S_2O_3$, and purification by silica gel chromatography in the dark, imidate

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

Scheme 5. Proposed Mechanism for the Synthesis of Iodoazabicyclo[3.3.0]alkanone Amino Ester 3



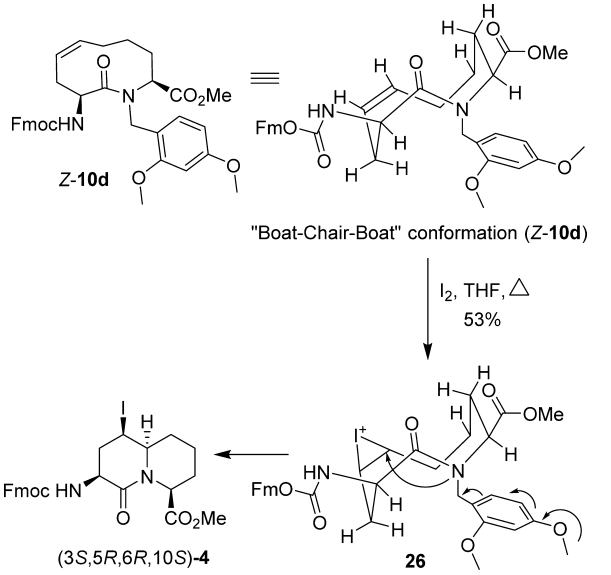
Scheme 6. Synthesis of Azabicyclo[4.3.1]alkane 5



5 was characterized using NMR spectroscopy and X-ray crystallography (Scheme 6). Imidate formation has been observed commonly in halocyclizations of linear unsaturated amides, and avoided using methods employing *N,O*-bis-silylation, *N*-tosyl and *N*-alkoxycarbonyl substitution, and strong bases.[28] On the other hand, transannular iodolactamization has favored azabicycloalkanone.[8b,12] Albeit light-sensitive, imidate **5** is a unique anti-Bredt heterocycle formed by attack of the lactam oxygen on iodonium intermediate **25**.[29,30]

Previously, iodoazabicyclo[5.3.0]alkanone **2** (Figure 1) was prepared diastereoselectively from 10-membered lactam (*E*)-**11f** (m = 2, n = 2) using 4 equiv of I_2 in THF at reflux.[8a] Iodolactamization of 10-membered *N*-Dmb-lactam (*Z*)-**10d** (m = 1, n = 3) has now given diastereoselective access to the first example of a substituted quinolizidinone amino acid,

Scheme 7. Synthesis of Iodoazabicyclo[4.4.0]alkanone Amino Ester 4



(3*S*,5*R*,6*R*,10*S*)-5-iodoazabicyclo[4.4.0]alkanone **4**, in 53% yield using I_2 in THF at reflux (Scheme 7).

Stereochemical Assignment Using NMR Spectroscopy. The assignment of the structure and stereochemistry of bicycles **3**–**5** was accomplished by 2D NMR spectroscopy and X-ray crystallography (Supporting Information). Typically, a COSY spectrum was used to assign the ring proton through-bond connectivities starting from the downfield carbamate NH proton. The observation of magnetization transfer between the peptide backbone protons and ring protons in the NOESY and ROESY spectra was then used to assign the relative stereochemistry at the ring-fusion and iodide-bearing carbons (Figure 2). For example,

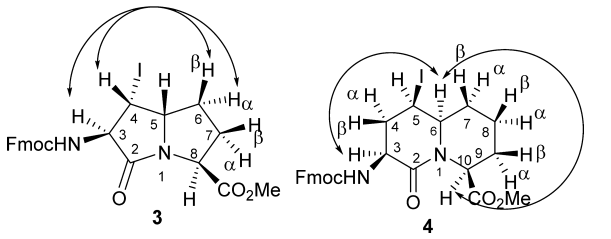


Figure 2. NOESY and ROESY correlations used to assign the relative configurations of bicycles **3** and **4**.

(4*R*,5*S*)-4-iodopyrrolizidinone *N*-Fmoc-amino ester **3** exhibited a transfer of magnetization between the backbone C3α and the ring C6α protons in C_6D_6. A second long-range NOE between the ring C4 and C6 β-protons established the relative stereochemistry of the iodide-bearing carbon. Long-range transfer of magnetization was observed between the ring-fusion C6 and backbone C3 and C10 protons in the ROESY spectrum of (3*S*,5*R*,6*R*,10*S*)-5-iodoquinolizidinone **4**. The stereochemistry of the ring-fusion carbon of pyrrolizidinone **3** and the iodide-bearing carbon of **4** were subsequently inferred on the basis of mechanistic considerations that placed the protons from the *cis*-double bond of the macrocycle on the same face of the bicycle.

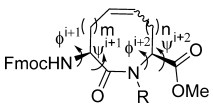
Although through-bond couplings of azabicyclo[4,3,1]alkane **5** could be used to assign all of the ring protons, no clear long-range NOEs were observed to assign the relative stereochemistry.

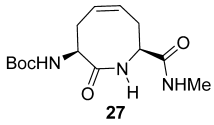
DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904–4918

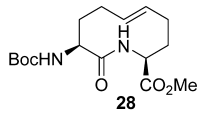
In the infrared spectrum of **5**, a C═N stretching band at 1657 cm^{-1} was observed, indicative of an imidate structure. Examination of the coupling pattern (ddd, J = 2.7, 5.4, 11.0 Hz) for the proton on the iodide-bearing carbon, before and after saturation of the neighboring bridgehead proton, and application of the Karplus equation[31] gave torsion angels that were consistent with those observed in the crystal structure.

Crystal Structures of 8-, 9-, and 10-Membered Macrocyclic Dipeptide Lactams. Lactams (*Z*)-**11a**, (*Z*)-**11e**, and (*Z*)-**10d** were crystallized by a common method (Supporting Information). In all three cases, the (*Z*)-double bond geometry was observed. In 8-membered lactam (*Z*)-**11a**, the *cis*-(*E*)-amide isomer was observed, as was previously described in the X-ray structure of the related olefin regioisomer 8-membered macrocycle **27** (Table 1).[32] On the other hand, the *trans*-(*Z*)-amide isomer was detected in the crystal structures of 9- and 10-membered lactams (*Z*)-**11e** and (*Z*)-**10d**.

Table 1. Comparison of Dihedral Angles of Macrocyclic and Bicyclic Peptidomimetics with Ideal Secondary Structures







type of β-turn[33]	ϕ_1, deg	ψ_1, deg	ϕ_2, deg	ψ_2, deg
I	−60	−30	−90	0
II	−60	120	80	0
II′	60	−120	−80	0
VIb	−135	135	−75	160

antiparallel β-sheet[38]	ϕ = −140	ψ = 135
parallel β-sheet[38]	ϕ = −120	ψ = 115

Peptidomimetic Dihedral Angles	ϕ^{i+1}, deg	ψ^{i+1}, deg	ϕ^{i+2}, deg	ψ^{i+2}, deg
8-membered lactam (*Z*)-**11a**	−142	156	−158	172
8-membered lactam **27**[32]	−93	177	−148	90
9-membered lactam (*Z*)-**11e**	−109	−27	−145	−28
10-membered lactam (*Z*)-**10d**	−161	171	63	23
10-membered lactam (*E*)-**28**[39]				
chair−chair	−107	−1	−130	23
chair−boat	120	−64	−131	−43
4-iodoazabicyclo[3.3.0]alkanone **3**	−120	−140	−109	173
6-hydroxyazabicyclo[3.3.0]alkanone[5a]	14	−141	−40	133
iodoazabicyclo[5.3.0]alkanone **2**[8a]	−138	−64	−49	136
azabicyclo[4,3,1]alkane **5**	−166	−1	175	74

Examination of the backbone dihedral angles found in the crystal structures of lactams (*Z*)-**11a**, (*Z*)-**11e**, and (*Z*)-**10d** may provide an understanding of their potential for mimicry of natural peptide structures, albeit ^{1}H NMR spectroscopy of macrocyclic lactams (*Z*)-**11e** and (*Z*)-**10d** did show doubling of some peaks, indicative of conformational isomers in $CDCl_3$. The torsion angles of lactams (*Z*)-**11a**, (*Z*)-**11e**, and (*Z*)-**10d** were compared with those for ideal turn and sheet structures (Table 1).[33] Notably, 8-membered lactam (*Z*)-**11a** possesses a dihedral angle geometry similar to that observed for the central residues of an ideal type VIb β-turn, similar to its olefin regioisomer **27**. The torsion angle values of 9-membered lactam (*Z*)-**11e** are similar to those of an ideal type I β-turn. Previously, 10-membered lactam **28** possessing a *trans*-olefin geometry had also been found to exhibit backbone dihedral angles similar to those of an ideal type I β-turn (Table 1). In the case of 10-membered lactam (*Z*)-**10d**, which possesses a *cis*-olefin at a different ring position, the backbone conformation was more similar to an ideal type II β-turn, albeit the dihedral angles of the *N*-terminal residue resembled an extended parallel β-pleated sheet. In summary, lactams (*Z*)-**11a**, (*Z*)-**11e**, and (*Z*)-**10d** appear to have potential for mimicry of three different β-turn conformations.

Crystal Structures of Azabicyclo[*X.Y.Z*]alkanes 3 and 5. The stereochemical assignments made for iodopyrrolizidinone **3** were confirmed by the X-ray structure (Figure 3). The dihedral angle values of the peptide backbone in the 5,5-fused bicycle **3** resembled those of an extended rather than a turn structure. In this respect, the peptide backbone geometry in azabicyclo[3.3.0]-alkanone **3** differed from those observed in X-ray analyses of larger azabicyclo[4.3.0]alkanone and iodoazabicyclo[5.3.0]-alkanone (**2**) amino ester counterparts, which were respectively similar to ideal type II′ and type I β-turns.[34,12] In addition, the X-ray structure of 4-iodopyrrolizidinone **3** exhibited dihedral angles different from those of the X-ray structure of the related 6-hydroxypyrrolizidinone, which closely resembled those of a type II′ β-turn (Table 1).[5a]

In the X-ray structure of cyclic imidate **5** (Figure 3), the (*Z*)-*anti*-periplanar isomer was observed. Although related structures of such anti-Bredt heterocycles were not found, the bond lengths of bridging imidate **5** (C−O, 1.39 Å; C═N, 1.24 Å) compared well with those from the crystal structures of cyclic imidates (C−O, 1.36 ± 0.2 Å; C═N, 1.25 ± 0.01 Å),[35,36] indicating that little distortion was induced by the bridgehead geometry of **5**. In addition, the dihedral angle values of **5** resembled those of an ideal type II β-turn.

Mechanistic Considerations. Transannular iodolactamizations have been studied using a series of related macrocycles of 8−10 ring atoms. In spite of the structural similarities of the starting macrocyclic lactams, many factors may influence this reaction, including the ring conformation and cyclization conditions. In related iodolactamizations, regioselectivity has previously been considered to be a consequence of the macrocycle conformation.[37] In this light, the flexibility of the macrocycle ring may contribute to mixtures of bicyclic products, yet ring substituents that orient to avoid allylic strain with the olefin substituents and diaxial interactions will significantly reduce the number of cyclization pathways. Typically, a relaxed conformer may orient the lactam and olefin to give regio- and stereoselective pathways.[37,8f,d] In such cases, the iodide substituent ends up on the lactam ring. In one case, a thermodynamically less stable 9-membered lactam has been found to give an alternative regio- and stereochemical indolizidinone featuring a 5-membered lactam and a piperidine ring bearing the iodide.[37] In addition, 9-membered lactam (*Z*)-**11e** gave imidate **5** instead of a fused 7,4-bicycle with the iodide on the 7-membered lactam or a 6,5-bicycle with the iodide on the 5-membered pyrrolidine.

Although electrophile-induced intramolecular cyclization reactions may proceed by formation of a dihalide that is subsequently displaced by the lactam to form the ring,[8e] cyclizations of macrocycles (*Z*)-**11a**, (*Z*)-**11e**, and (*Z*)-**10d** are presumed to proceed by way of iodonium-like intermediates based on their stereochemical outcomes.[40] The ambidentate nucleophilic nature of the amide group has been observed to give imidates in iodocyclizations of simpler olefins,[41,42] and such *O*-selectivity has been explained on the basis of hard−soft

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

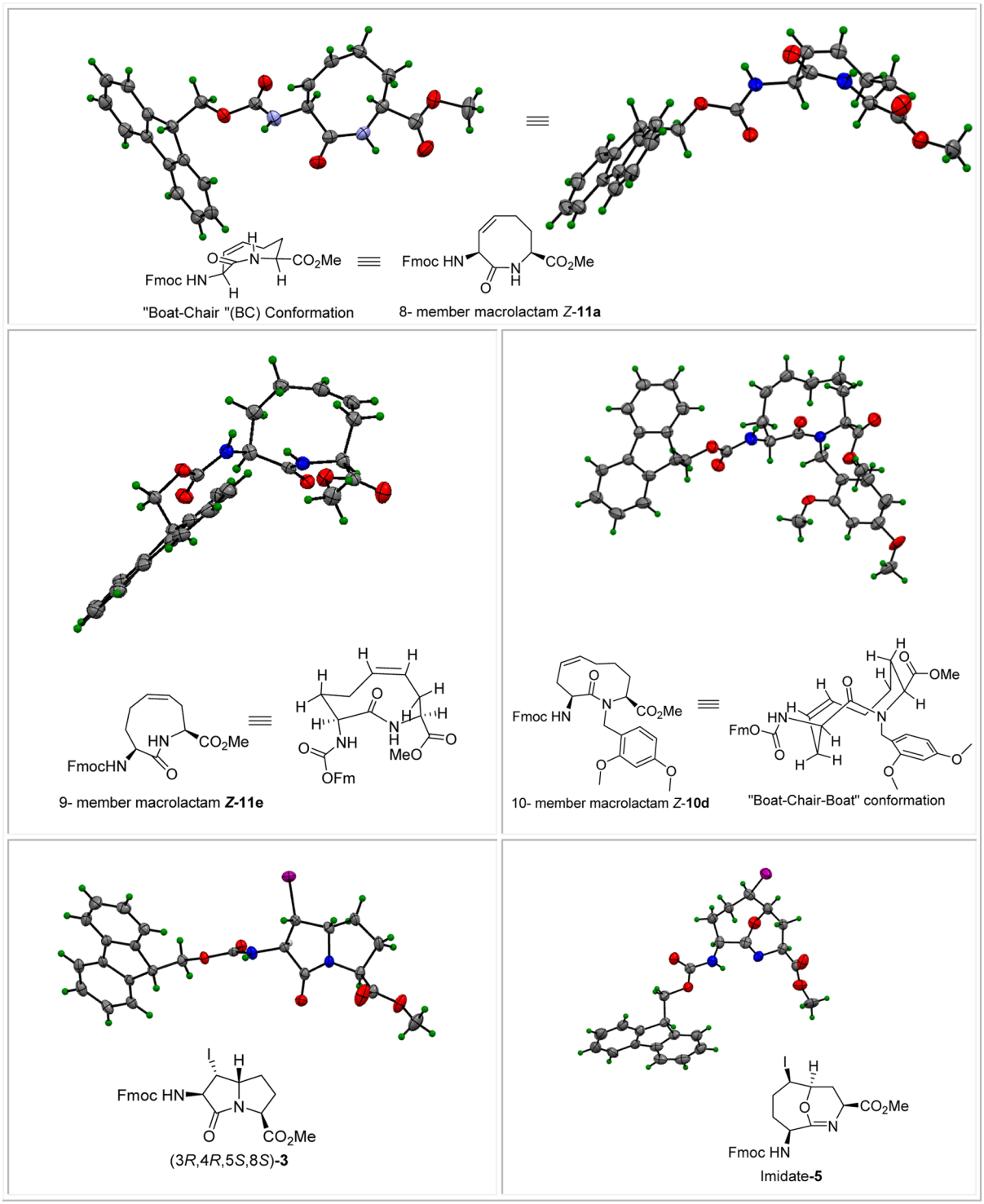


Figure 3. X-ray structures of macrocyclic dipeptide lactams and iodoazabicyclo[*X.Y.Z*]alkanes (C, gray; H, green; N, blue; O, red; I, magenta).

acid−base theory considering the iodine−olefin π-complex to be a hard electrophile.[43,44] However, transannular attack of oxygen would result in an anti-Bredt bridgehead heterocycle,[45] which may be relatively disfavored due to ring strain. Given the choices between placing iodide on the nonlactam ring, forming a strained *N*-acylazetidine or forming the anti-Bredt imidate, the latter product **5** was favored.

Notably, the respective proximities of the amide nitrogen and oxygen to the double bond carbons on the amine (C^N) and carbonyl (C^{CO}) sides of the macrocycle did not correlate with the mode of cyclization except in the case of the 8-membered lactam going to the fused 5,5-bicycle (Table 2).

A working hypothesis for the selectivity of the transannular iodolactamization begins with a favored macrocycle conformation that minimizes ring strain. Approach of iodine to the less sterically hindered face of the olefin provides the iodonium intermediate, which is typically attacked on the carbon (C^N) on the amide nitrogen side of the macrocycle to provide a bicycle having the iodide on the lactam ring. Attack of the iodonium carbon (C^{CO}) on the carbonyl side of the macrocycle is likely

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

Table 2. Comparison of Transannular Distances (Å) in Macrocyclic Lactams

bond	8-membered (Z)-**11a**	9-membered (Z)-**11e**	10-membered (Z)-**10d**
N to C^N	3.11	3.23	3.45
N to C^{CO}	3.40	3.01	3.47
O to C^N	3.14	3.33	3.29
O to C^{CO}	4.12	3.38	3.63

disfavored due to the need to avoid allylic strain between the carboxylate and the lactam carbonyl as well as potential diaxial interactions between the carboxylate and the iodide. In the case of **5**, the combination of the factors mentioned above and ring strain to make a 4-membered azetidine lead to a preferred attack by oxygen, giving the imidate. Computational analyses are currently being pursued to provide additional support of these mechanistic considerations.

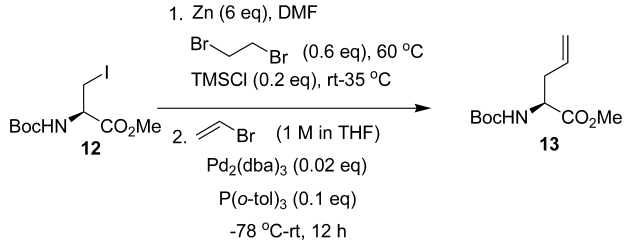
CONCLUSIONS

A variety of azabicyclo[*X.Y.*0]alkanone amino acids have been prepared using a common approach featuring effective assembly of macrocyclic lactams of 8−10-membered ring sizes by the synthesis and coupling of ω-unsaturated amino acids and RCM of their dipeptide derivatives, followed by regio- and stereoselective electrophilic transannular cyclization. Employing X-ray crystallographic and NMR spectroscopic analyses, we have demonstrated that the macrocyclic and bicyclic structures offer ample potential to mimic peptide secondary structures, in particular types I, II′, and VI β-turn geometries contingent on ring size. Moreover, such conformational analyses have also provided insight into the mechanism of transannular iodolactamization. Considering the potential of this method for effectively making a series of related dipeptide mimics to explore peptide conformation−activity relationships, as well as the opportunity for replacing the iodide with other side chains to examine functional group influences on activity, this method should have a significant impact on peptidomimetic approaches for studying biologically active peptides, particularly for the discovery of therapeutic agents.

EXPERIMENTAL SECTION

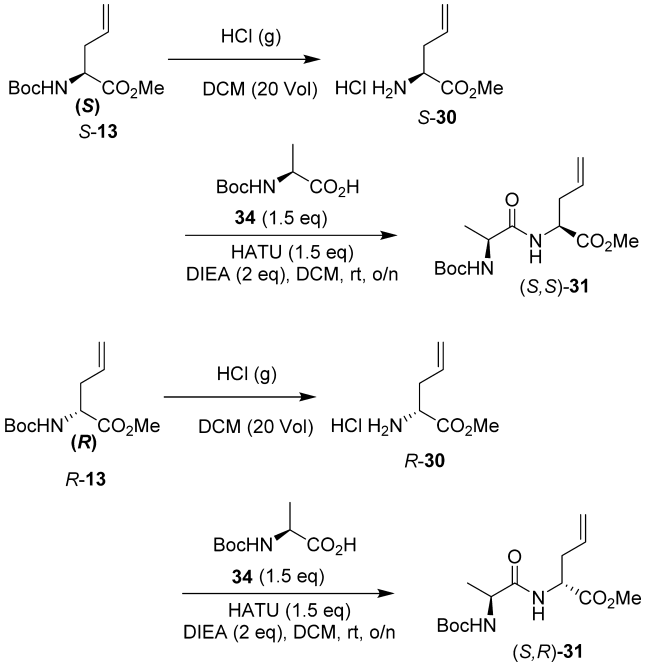
General Methods. Unless otherwise noted, all reactions were performed under an argon atmosphere and distilled solvents were transferred by syringe. Anhydrous CH_2Cl_2 (DCM), THF, and diethyl ether were obtained by passage through a solvent filtration system. Final reaction mixture solutions were dried over anhydrous $MgSO_4$ or Na_2SO_4, filtered, and rotary-evaporated under reduced pressure. Flash chromatography[46] was on 230−400 mesh silica gel, and thin-layer chromatography was performed on silica gel 60 F254 plates. Specific rotations, $[\alpha]_D$ values, were calculated from optical rotations measured at 20 °C in $CHCl_3$ or MeOD at the specified concentrations (c, g/100 mL) using a 1 dm cell (l) on a polarimeter, using the general formula $[\alpha]_D^{20} = 100\alpha/lc$. Accurate mass measurements were performed on an LC-MSD instrument in electrospray ionization (ESI-TOF) mode. Sodium adducts $[M + Na]^+$ were used for empirical formula confirmation. ^{1}H NMR spectra were measured in $CDCl_3$ (7.26 ppm), CD_3OD (3.31 ppm), or DMSO-d_6 (2.50 ppm). ^{13}C NMR spectra were measured in $CDCl_3$ (77.16 ppm) or DMSO-d_6 (39.52 ppm). ^{1}H NMR spectra for the dipeptides **7a**, **7b**, **6d**, **7d**, **6g**, **11g**, **11d**, and **20** were recorded at 100 °C to coalesce signals due to conformational isomers. Coupling constant J values were measured in hertz and chemical shift values in parts per million. Infrared spectra were recorded for neat samples on an FT-IR apparatus. Syntheses and characterization of compounds **7e**, **10e**, **11e**, **17a**, **17b**, **16a**, and **16b** have been previously reported.[14]

(*S*)-Methyl 2-(*N*-Boc-amino)pent-4-enoate (13).



To a stirred solution of zinc dust (11.92 g, 182.3 mmol, 6 equiv) in dry DMF (20 mL) was added 1,2-dibromoethane (1.57 mL, 3.42 g, 18.2 mmol, 0.6 equiv) via a syringe. The resulting mixture was heated to 60 °C, stirred for 45 min, and cooled to room temperature, and the slurry was treated with chlorotrimethylsilane (0.77 mL, 6.0 mmol). After being stirred for 40 min at room temperature, the activated zinc was treated with a solution of methyl (*R*)-*N*-Boc-iodoalaninate (**12**; 10 g, 30.39 mmol) in dry DMF (20 mL), heated to 35 °C, and stirred for 60 min, when insertion was judged complete by TLC analysis [2:1 hexanes/ethyl acetate, using 254 nm UV light to visualize the starting material **12** (R_f = 0.7) and organozinc reagent (R_f = 0.1)]. After complete zinc insertion, the reaction mixture was cooled to room temperature, charged with $Pd_2(dba)_3$ (779 mg, 0.85 mmol, 0.028 equiv) and tri-*o*-tolylphosphine (925 mg, 3.03 mmol, 0.1 equiv), cooled to −78 °C, and treated dropwise via a cannula with a solution of vinyl bromide in THF (1 M, 42.5 mL, 42.5 mmol, 1.4 equiv). After complete addition of the vinyl bromide solution, the cold bath was removed, and the reaction mixture was allowed to warm to room temperature with stirring for 12 h. The reaction mixture was diluted with ethyl acetate (200 mL) and water (200 mL), and filtered through a pad of Celite. The pad was washed with ethyl acetate (300 mL). The filtrate and washings were combined and transferred to a separating funnel. The organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 200 mL). The combined organic layers were washed with brine (400 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give 8.2 g of brown oil, which was purified by column chromatography on silica gel (8−10% EtOAc in hexane) to give olefin **13** (4.50 g, 19.64 mmol, 65%) as a brown oil: R_f = 0.29 (9:1 hexanes/ethyl acetate, visualized as a UV inactive and $KMnO_4$ active spot on heating); $[\alpha]_D^{20}$ +20.2 (c 1.5, $CHCl_3$); FT-IR (neat) ν_{max} 2978, 1744, 1712, 1499, 1437, 1365, 1159, 1021, 868, 779 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.63−5.71 (m, 1H), 5.09−5.12 (m, 2H), 5.03−5.04 (br d, 1H), 4.34−4.37 (m, 1H), 3.71 (s, 3H), 2.50−2.55 (m, 1H), 2.42−2.47 (m, 1H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 155.3, 132.4, 119.1, 79.9, 53.0, 52.3, 36.9, 28.4; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{11}H_{19}NO_4Na$ 252.1215, found 252.1217. Anal. Calcd for $C_{11}H_{19}NO_4$: C, 57.62; H, 8.35; N, 6.11. Found: C, 57.13; H, 8.51; N, 5.93. Attempts to ascertain the enantiomeric purity of olefin **13**, as well as the hydrochloride **30** obtained on treating **13** with HCl gas in dichloromethane, were both unsuccessful using supercritical fluid chromatography on a chiral column. To assess enantiomeric purity, diastereomeric amides were synthesized as described below. The crude residue was examined by ^{1}H NMR spectroscopy in CD_3CN at 700 MHz. Incremental addition of (*S*,*R*)-**31** to (*S*,*S*)-**31** and observation of the methyl ester singlets at 3.697 and 3.691 ppm demonstrated the diastereomers were of >99:1 dr. Hence, olefin **13** is assumed to be of >98% enantiomeric purity.

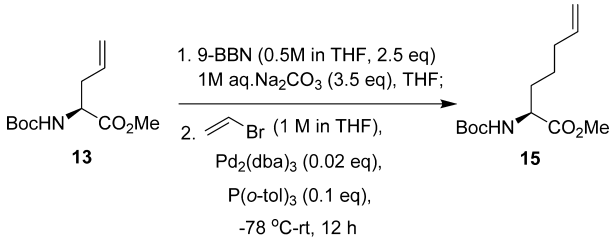
DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918



(*S*)-Methyl 2-Aminopent-4-enoate Hydrochloride (30). Dry HCl gas was bubbled into a stirred solution of (*S*)-**13** (70 mg, 0.30 mmol) in dichloromethane at room temperature. Consumption of (*S*)-**13** was observed by TLC after 3 h. The resulting solution was concentrated under reduced pressure to give (*S*)-**30** as a brown solid: ^{1}H NMR (400 MHz, CD_3OD) δ 2.68−2.75 (m, 2H), 3.86 (s, 3H), 4.16−4.19 (m, 1H), 5.27−5.33 (m, 2H), 5.77−5.81 (m, 1H). (*R*)-**30** was made from (*R*)-**13** by a method analogous to that used to prepare (*S*)-**30**.

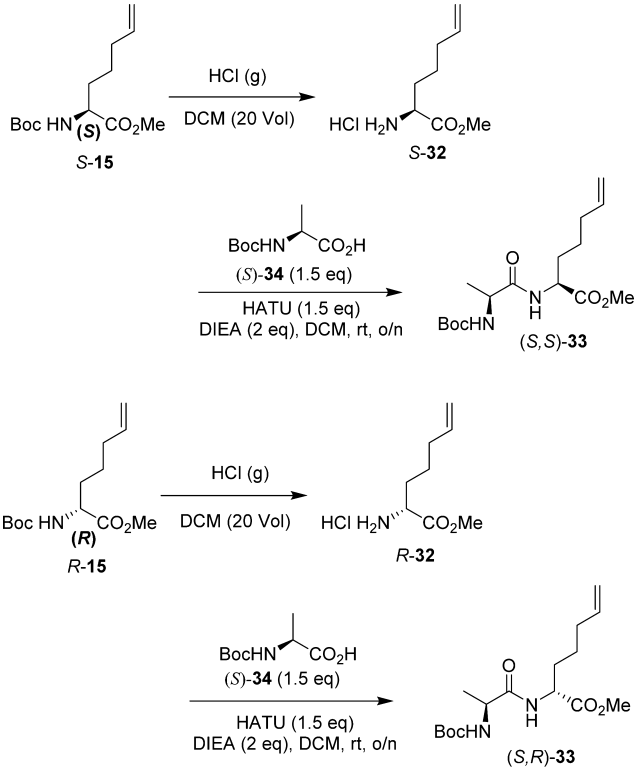
(*S,S*)-Methyl 2-[(*N*-Boc-alaninyl)aminopent-4-enoate [(*S,S*)-31]. A stirred solution of Boc-L-Ala (**34**; 86 mg, 0.45 mmol, 1.5 equiv) in DCM (5 mL) was treated with amine hydrochloride (*S*)-**30** (50 mg, 0.30 mmol, 1 equiv), DIEA (78 mg, 0.6 mmol, 2 equiv), and HATU (173 mg, 0.45 mmol, 1.5 equiv), stirred at room temperature for 16 h, diluted with DCM (∼10 mL), and washed with saturated aqueous $NaHCO_3$. The layers were separated. The aqueous layer was extracted with DCM (∼10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (*S,S*)-**31** as a brown oil, which was analyzed without further purification: ^{1}H NMR (400 MHz, CD_3CN) δ 1.27−1.28 (d, J = 7.2, 3H), 1.44 (s, 9H), 2.43−2.51 (m, 1H), 2.53−2.60 (m, 1H), 3.71 (s, 3H), 4.06−4.10 (m, 1H), 4.44−4.49 (m, 1H), 5.10−5.19 (m, 2H), 5.63 (br s, 1H), 5.72−5.82 (m, 1H), 6.91 (br s, 1H). (*S,R*)-**31** was made using (*R*)-**30** by a method analogous to that used to prepare (*S,S*)-**31**: ^{1}H NMR (400 MHz, CD_3CN) δ 1.26−1.28 (d, J = 7.2, 3H), 1.44 (s, 9H), 2.42−2.50 (m, 1H), 2.53−2.60 (m, 1H), 3.70 (s, 3H), 4.05−4.09 (m, 1H), 4.44−4.49 (m, 1H), 5.10−5.18 (m, 2H), 5.62 (br s, 1H), 5.68−5.81 (m, 1H), 6.90 (br s, 1H).

(*S*)-Methyl 2-(*N*-Boc-amino)hept-6-enoate (15).



A solution of 9-BBN in THF (0.5 M, 109 mL) was added to a 0 °C solution of methyl pent-4-enoate **13** (5 g, 21.8 mmol) in anhydrous THF (40 mL). The mixture was warmed to room temperature, stirred for 3 h, and quenched with 1 M aqueous Na_2CO_3 in H_2O (76.3 mL) with agitation using argon bubbles for 20 min. To a second round-bottomed flask containing a stirred suspension of $Pd_2(dba)_3$ (393 mg, 0.43 mmol) and tri-*o*-tolylphosphine (663 mg, 2.18 mmol) in THF at −78 °C was added a 1 M solution of vinyl bromide in THF (87 mL, 87 mmol), followed by a degassed solution of boronate. The resulting mixture was stirred at room temperature overnight, quenched with water (100 mL), and extracted using ethyl acetate (150 mL × 2). The combined organic extracts were washed with brine (100 mL), dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give 7.8 g of brown oil, which was twice purified by column chromatography on silica gel using 4−6% EtOAc in hexane. Evaporation of the collected fractions gave olefin **15** (3.81 g, 14.81 mmol, 68%) as a light brown oil: R_f = 0.29 (9:1 hexanes/ethyl acetate, visualized as a UV inactive and $KMnO_4$ active spot on heating); $[\alpha]_D^{22}$ +14.6 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2977, 1742, 1712, 1501, 1365, 1160. 1050, 909 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.70−5.80 (m, 1H), 4.93−5.01 (m, 3H), 4.27−4.28 (m, 1H), 3.71 (s, 3H), 2.00−2.09 (m, 2H), 1.74−1.82 (m, 1H), 1.56−1.65 (m, 1H), 1.37−1.48 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 155.5, 138.1, 115.2, 79.9, 53.4, 52.3, 33.2, 32.3, 28.3, 24.7; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{13}H_{23}NO_4Na$ 280.1519, found 280.1533.

Attempts to ascertain the enantiomeric purity of olefin **15**, as well as the hydrochloride **32** that was obtained on treating **15** with HCl gas in dichloromethane, were both unsuccessful using SFC on a chiral column. To assess enantiomeric purity, diastereomeric amides were synthesized as described below. Crude residue was examined by ^{1}H NMR spectroscopy in CD_3CN at 700 MHz. Incremental addition of (*S,R*)-**33** to (*S,S*)-**33** and observation of the methyl ester singlets at 3.6578 and 3.6622 ppm demonstrated the diastereomers were of >99:1 dr. Hence, olefin **15** is assumed to be of >98% enantiomeric purity.



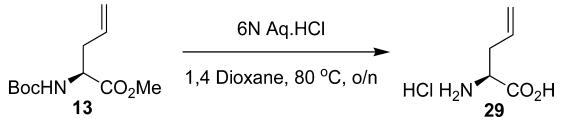
(*S*)-Methyl 2-Aminohept-6-enoate Hydrochloride [(*S*)-32]. Dry HCl gas was bubbled into a stirred solution of (*S*)-**15** (100 mg, 0.38 mmol) in dry dichloromethane at room temperature. Consumption of (*S*)-**15** was observed by TLC after 3 h. The resulting solution was concentrated under reduced pressure to give (*S*)-**32** as a white solid: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.78−5.86 (m, 1H), 4.99−5.09 (m, 2H), 4.06−4.09 (t, 1H, J = 6.4 Hz), 3.85 (s, 3H), 2.11−2.16 (m, 2H), 1.86−1.99 (m, 2H), 1.45−1.63 (m, 2H). (*R*)-**32** was made from (*R*)-**15** by a method analogous to that used to prepare (*S*)-**32**.

(*S,S*)-Methyl 2-[(*N*-Boc-alaninyl)amino]hept-6-enoate [(*S,S*)-33]. A stirred solution of **34** (87 mg, 0.46 mmol, 1.5 equiv) in DCM (5 mL) was treated with amine hydrochloride (*S*)-**32** (60 mg, 0.31 mmol,

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

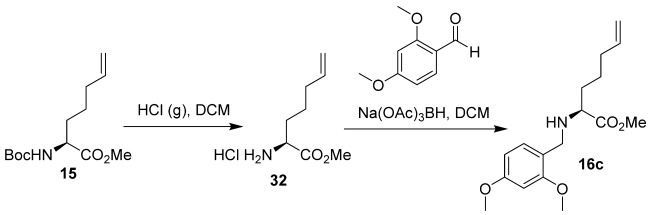
1 equiv), DIEA (80 mg, 0.62 mmol, 2 equiv), and HATU (180 mg, 0.45 mmol, 1.5 equiv), stirred at room temperature for 16 h, diluted with DCM (~10 mL), and washed with saturated aqueous $NaHCO_3$. The layers were separated. The aqueous layer was extracted with DCM (~10 mL). The combined organic layers were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure to give (*S*,*S*)-**33** as a brown oil, which was analyzed without further purification: ^{1}H NMR (700 MHz, CD_3CN) δ 6.86 (br s, 1H), 5.77−5.83 (m, 1H), 5.57 (br s, 1H), 4.99−5.03 (m, 1H), 4.94−4.96 (m, 1H), 4.34−4.37 (m, 1H), 4.03−4.05 (m, 1H), 3.65 (s, 3H), 2.03−2.06 (m, 2H), 1.75−1.80 (m, 1H), 1.61−1.68 (m, 1H), 1.38−1.42 (m, 11H), 1.24−1.25 (d, J = 7.1 Hz, 3H). Amide (*S*,*R*)-**33** was made using (*R*)-**32** by a method analogous to that used to prepare (*S*,*S*)-**33**: ^{1}H NMR (700 MHz, CD_3CN) δ 6.86 (br s, 1H), 5.76−5.82 (m, 1H), 5.57 (br s, 1H), 5.01−5.02 (m, 1H), 4.99−5.00 (m, 1H), 4.33−4.36 (m, 1H), 4.01−4.03 (m, 1H), 3.66 (s, 3H), 2.01−2.08 (m, 2H), 1.75−1.80 (m, 1H), 1.60−1.66 (m, 1H), 1.39−1.40 (m, 11H), 1.24−1.25 (d, J = 7.1 Hz, 3H).

(*S*)-2-Aminopent-4-enoic Acid Hydrochloride (29).



A stirred solution of (*S*)-**13** (4 g, 17.4 mmol) in 1,4-dioxane at 0 °C was treated with 6 N HCl (80 mL), heated to 80 °C overnight, cooled, and evaporated to a reside that was dissolved in water and washed with dichloromethane. The aqueous layer was concentrated to off-white solid **29** (2.51 g, 16.61 mmol, 95%): mp 206−208 °C, $[\alpha]_D^{20}$ +7.6 (*c* 1, CH_3OH); FT-IR (neat) ν_{max} 2914, 1730, 1490, 1427, 1215, 1174, 1124, 993, 933, 873 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.76−5.87 (m, 1H), 5.26−5.34 (m, 2H), 4.06−4.09 (m, 1H), 2.63−2.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 131.8, 121.4, 53.4, 35.7 ; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_5H_9ClNO_2$ 150.0327, found 150.0330.

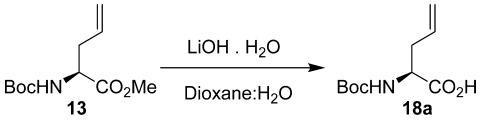
(*S*)-Methyl 2-[(2,4-Dimethoxybenzyl)amino]hept-6-enoate (16c).



A stirred solution of (*S*)-**15** (3 g, 11.7 mmol) in dichloromethane (60 mL) was treated with HCl gas bubbles for 3 h. The volatiles were removed by rotary evaporation to give (*S*)-**32** (2.19 g, 11.34 mmol, 97%) as a white solid: mp 112−114 °C; $[\alpha]_D^{24}$ +24.6 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2922, 2134, 1745, 1438, 1234, 912 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 5.78−5.86 (m, 1H), 4.99−5.09 (m, 2H), 4.06−4.09 (t, 1H, J = 6.4 Hz), 3.85 (s, 3H), 2.11−2.16 (m, 2H), 1.86−1.99 (m, 2H), 1.45−1.63 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 170.9, 138.6, 116.0, 53.9, 53.6, 34.0, 30.9, 25.1; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_8H_{16}NO_2$ 158.1175, found 158.1179.

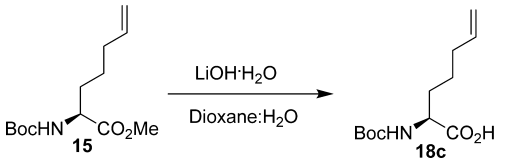
Amino ester hydrochloride **32** (2 g, 10.35 mmol) was partitioned between a saturated $NaHCO_3$ solution (50 mL) and CH_2Cl_2 (50 mL). The aqueous phase was extracted with CH_2Cl_2 (2 × 50 mL), and the combined organic layers were washed with 30 mL of brine, dried over Na_2SO_4, filtered, and concentrated to a volume of ~30 mL. The solution of free base was treated with 2,4-dimethoxybenzaldehyde (2.23 g, 13.45 mmol) and $NaBH(OAc)_3$ (3.28 g, 15.5 mmol), stirred for 18 h at room temperature, treated with 40 mL of saturated $NaHCO_3$, and stirred for 30 min. The aqueous layer was separated and washed with 20 mL of CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography on silica gel (20−25% EtOAc in hexane) to give *N*-Dmb-amino ester **16c** (2.09 g, 6.80 mmol, 65%) as a colorless oil: R_f = 0.35 (7:3 hexanes/ethyl acetate, visualized by UV), $[\alpha]_D^{20}$ −3.1 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2943, 1732, 1612, 1587, 1505, 1457, 1437, 1287, 1260, 1206, 1154, 1035, 913 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.11−7.12 (d, 1H, J = 8.25 Hz), 6.40−6.42 (m, 2H), 5.71−5.78 (m, 1H), 4.91−4.99 (m, 2H), 3.79 (s, 3H), 3.78 (s, 3H), 3.68−3.71 (d, 1H, J = 13.2 Hz), 3.64 (s, 3H), 3.61−3.64 (d, 1H, J = 13.2 Hz), 3.22−3.25 (t, 1H, J = 6.65 Hz), 1.99−2.01 (m, 2H), 1.59−1.65 (m, 2H), 1.39−1.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.9, 160.1, 158.6, 138.3, 130.3, 120.5, 114.7, 103.7, 98.5, 60.7, 55.4, 55.3, 51.5, 47.1, 33.5, 33.0, 25.0; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{17}H_{25}NO_4Na$ 330.1675, found 330.1691.

(*S*)-2-(*N*-Boc-amino)pent-4-enoic Acid (18a).



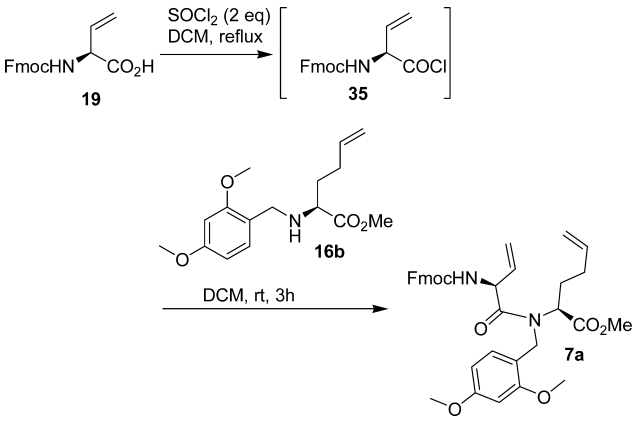
A solution of (*S*)-**13** (1.2 g, 5.23 mmol) in 1:1 H_2O/dioxane (48 mL) was treated with LiOH·H_2O (219 mg, 5.23 mmol), stirred for 3 h, and evaporated to a residue that was partitioned between H_2O (20 mL) and EtOAc (20 mL). The aqueous phase was acidified with 1 M HCl to pH 4 and extracted twice with EtOAc (20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated to afford acid **18a** (1.09 g, 5.06 mmol, 97%) as a colorless oil: $[\alpha]_D^{22}$ +12.3 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2978, 1698, 1699, 1507, 1393, 1367, 1248, 1158, 1050, 869, 754 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 5.74−5.83 (m, 1H,), 5.07−5.15 (m, 2H), 4.13−4.16 (m, 1H), 2.52−2.53 (m, 1H), 2.38−2.42 (m, 1H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 175.4, 157.9, 134.7, 118.5, 80.5, 54.6, 37.1, 28.7; HRMS (ESI-TOF) m/z $[M + Na]^+$ calcd for $C_{10}H_{17}NO_4Na$ 238.1049, found 238.1050.

(*S*)-2-(*N*-Boc-amino)hept-6-enoic Acid (18c).



Employing the procedure described for acid **8a**, methyl hept-6-enoate **15** (500 mg, 1.94 mmol) was converted to acid **18c** (445 mg, 1.83 mmol, 94%) as a colorless oil: $[\alpha]_D^{20}$ +11.5 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2977, 2929, 1711, 1508, 1393, 1367, 1245, 1160, 910 cm^{-1}; ^{1}H NMR (500 MHz, CD_3OD) δ 5.76−5.84 (m, 1H,), 4.94−5.04 (m, 2H), 4.05−4.08 (m, 1H), 2.03−2.12 (m, 2H), 1.77−1.84 (m, 1H), 1.59−1.67 (m, 1H), 1.51−1.46 (m, 2H), 1.44 (s, 9H); ^{13}C NMR (125 MHz, CD_3OD) δ 176.3, 158.1, 139.4, 115.3, 80.4, 54.7, 34.3, 32.3, 28.7, 26.2; HRMS (ESI-TOF) m/z $[M - H]^-$ calcd for $C_{12}H_{20}NO_4$ 242.1397, found 242.1409.

(*S*,*S*)-Methyl 2-[*N*-[2-(*N*-Fmoc-amino)but-3-enoyl]-*N*-(2,4-dimethoxybenzyl)amino]hex-5-enoate (7a).

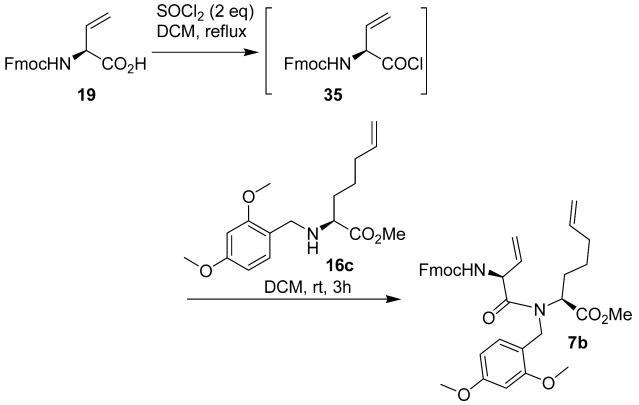


(*S*)-*N*-Fmoc-vinylglycine (**19**; 2.47 g, 7.64 mmol) was treated with thionyl chloride (1.1 mL, 15.32 mmol) in DCM at 0 °C. The resulting solution was then heated to reflux for 3 h and cooled, and the volatiles were evaporated. The residue was dissolved and evaporated three times from DCM. Without further purification, acid chloride **35** was dissolved in DCM (20 mL), cooled to 0 °C, and treated with *N*-Dmb-homoallylglycine (**16b**; 1.5 g, 5.12 mmol). The resulting mixture was stirred at room temperature for 3 h. The volatiles were evaporated, and

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

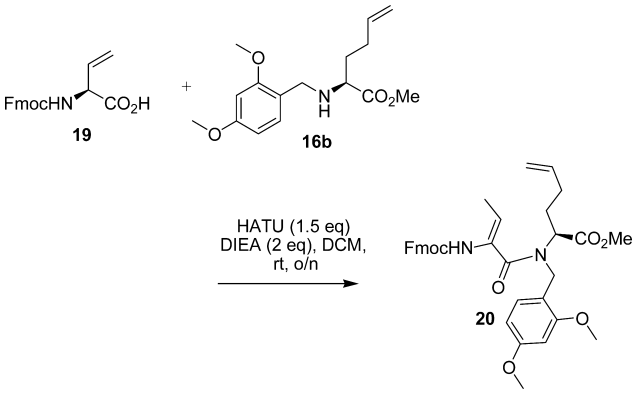
the residue was taken up in a minimum volume of DCM, applied onto a silica gel column, and eluted with 30−40% EtOAc/hexanes to give **7a** (1.42 g, 2.37 mmol, 46%) as a colorless oil that solidified on standing: R_f = 0.52 (4:6 EtOAc/hexanes, visualized by UV); $[\alpha]_D^{24}$ −40.1 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2947, 1719, 1647, 1612, 1588, 1506, 1207, 1156, 1032, 759, 738 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.84−7.85 (d, 2H, *J* = 7.5 Hz), 7.67−7.70 (t, 2H, *J* = 6.7 Hz), 7.38−7.42 (m, 2H), 7.29−7.32 (m, 2H), 7.18 (br s, 1H), 7.04 (br s, 1H), 6.55 (d, 1H, *J* = 2.0 Hz), 6.46−6.48 (dd, 1H, *J* = 2.2 Hz), 5.87−5.95 (m, 1H), 5.63−5.71 (m, 1H), 5.23−5.29 (m, 2H), 5.18−5.20 (br t, 1H), 4.92−4.93 (m, 1H), 4.90−4.91 (m, 1H), 4.55−4.58 (d, 1H, *J* = 16.4 Hz), 4.39−4.43 (m, 1H), 4.28−4.35 (m, 2H), 4.20−4.23 (m, 2H), 3.77 (s, 3H), 3.75 (s, 3H), 3.50 (s, 3H), 1.91−2.04 (m, 3H), 1.65−1.71 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 170.1, 169.8, 160.1, 157.9, 154.6, 143.4, 143.3, 140.2, 137.1, 133.5, 129.5, 127.2, 126.4, 124.6, 124.5, 119.3, 117.0, 114.5, 104.5, 98.2, 78.6, 65.6, 57,.5 54.9, 54.8, 53.7, 50.9, 46.4, 29.4, 27.6; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{38}N_2O_7Na$ 621.2571, found 621.2562.

(*S*,*S*)-Methyl 2-[*N*-[2-(*N*-Fmoc-amino)but-3-enoyl]-*N*-(2,4-dimethoxybenzyl)amino]hept-6-enoate (7b).



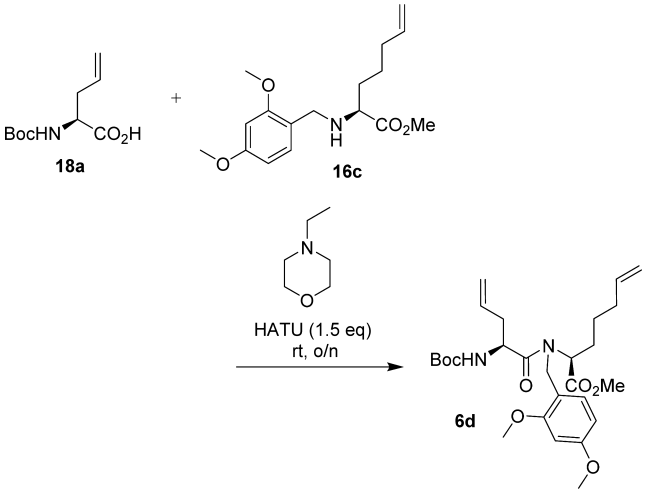
As described for the synthesis of dipeptide **7a**, (*S*)-2-(*N*-Fmoc-amino)but-3-enoic acid (**19**; 785 mg, 2.43 mmol) was coupled with **16c** (500 mg, 1.62 mmol). The residue was purified by chromatography on silica gel (30−40% EtOAc in hexane) to give dipeptide **7b** (540 mg, 0.88 mmol, 54%) as a colorless oil: R_f = 0.55 (4:6 EtOAc/hexanes, visualized by UV); $[\alpha]_D^{20}$ −30.6 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2947, 1719, 1647, 1612, 1588, 1506, 1207, 1156, 1032, 916, 758, 738 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.84−7.85 (d, 2H, *J* = 7.5 Hz), 7.67−7.70 (t, 2H, *J* = 6.6 Hz), 7.38−7.42 (m, 2H), 7.29−7.32 (m, 2H), 7.18−7.19 (m, 1H), 7.03 (br s, 1H) 6.55−6.56 (m, 1H), 6.45−6.47 (m, 1H), 5.84−5.96 (m, 1H), 5.62−5.71 (m, 1H), 5.24−5.29 (m, 2H), 5.17−5.20 (m, 1H), 4.88−4.94 (m, 2H), 4.53−4.57 (d, 1H, *J* = 16.4), 4.41−4.44 (m, 1H), 4.20−4.35 (m, 4H), 3.75 (s, 3H), 3.78 (s, 3H), 3.51 (s, 3H), 1.81−1.97 (m, 3H), 1.55−1.67 (m, 1H), 1.17−1.37 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 170.2, 160.1, 157.7, 154.6, 143.4, 143.3, 140.3, 137.6, 133.6, 129.4, 127.0, 126.4, 124.6, 124.5, 119.3, 117.0, 114.0, 104.5, 98.2, 78.6, 65.6, 57.9, 54.9, 54.8, 53.7, 50.9, 46.4, 45.3, 32.1, 27.7, 24.7; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{36}H_{40}N_2O_7Na$ 635.2727, found 635.2738.

(*Z*,*S*)-Methyl 2-[*N*-[2-(*N*-Fmoc-amino)but-2-enoyl]-*N*-(2,4-dimethoxybenzyl)amino]hex-5-enoate (20).



N-Fmoc-vinylglycine (**19**; 274 mg, 0.85 mmol) and methyl 2-(*N*-Dmb-amino)hex-5-enoate (**16b**; 170 mg, 0.57 mmol) were dissolved in DCM (10 mL), treated with DIEA (147 mg, 1.14 mmol) and HATU (323.1 mg, 0.85 mmol), stirred for 24 h, and diluted with water. The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (30−40% EtOAc in hexane) to give dipeptide **20** (302 mg, 0.50 mmol, 87%) as a colorless gummy oil: R_f = 0.27 (4.5:5.5 EtOAc/hexanes, visualized by UV); $[\alpha]_D^{20}$ −63.2 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2945, 1716, 1611, 1506, 1448, 1206, 1108, 1032, 757, 738 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 8.68 (br, s, 1H), 7.85−7.86 (d, 2H, *J* = 7.6 Hz), 7.71−7.72 (m, 2H), 7.40−7.43 (t, 2H, *J* = 7.4 Hz), 7.31−7.34 (m, 2H), 7.25−7.27 (d, 1H, *J* = 8.5 Hz), 6.52−6.53 (d, 1H, *J* = 2.4 Hz), 6.44−6.46 (dd, 1H, *J* = 2.4 Hz), 5.60−5.68 (m, 1H), 5.45−5.49 (m, 1H), 4.84−4.89 (m, 2H), 4.56−4.59 (d, 1H, *J* = 16 Hz), 4.47−4.50 (d, 1H, *J* = 15.9 Hz), 4.355−4.356 (d, 1H, *J* = 0.8 Hz), 4.34 (s, 1H), 4.23−4.26 (t, 1H, *J* = 13.9 Hz), 4.16 (br s, 1H), 3.77 (s, 3H), 3.7 (s, 3H), 3.51 (s, 3H), 1.88−2.07 (m, 3H), 1.71−1.81 (m, 1H), 1.64−1.66 (d, 3H, *J* = 7 Hz); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 170.5, 168.1, 159.6, 157.5, 153.3, 143.3, 143.3, 140.3, 137.3, 130.6, 129.3, 127.0, 126.4, 124.6, 119.4, 118.4, 117.2, 114.2, 104.6, 98.0, 78.6, 65.7, 58.2, 54.9, 54.8, 50.8, 46.4, 29.6, 27.9, 11.2; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{38}N_2NaO_7$ 621.2571, found 621.2573.

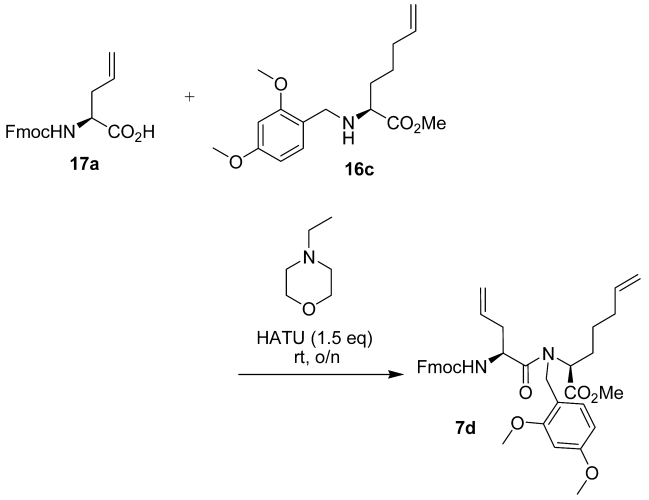
(*S*,*S*)-Methyl 2-[*N*-[2-(*N*-Boc-amino)pent-4-enoyl]-*N*-(2,4-dimethoxybenzyl)amino]hept-6-enoate (6d).



N-Boc-allylglycine (**18a**; 522 mg, 2.43 mmol) and *N*-Dmb-amino ester **16c** (500 mg, 1.62 mmol) were dissolved in DCM (10 mL), treated with *N*-ethylmorpholine (373 mg, 3.24 mmol) and HATU (923 mg, 2.43 mmol), stirred for 24 h, and diluted with water. The aqueous layer was extracted with DCM (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel (30−35% EtOAc in hexane) to give dipeptide **6d** (610 mg, 1.21 mmol, 74%) as a colorless gummy oil: R_f = 0.67 (4:6 EtOAc/hexanes, visualized by UV); $[\alpha]_D^{20}$ −33.1 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2975, 2932, 1739, 1708, 1639, 1613, 1507, 1437, 1208, 1158, 1033, 753 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.16 (br s, 1H), 6.56 (s, 1H), 6.47−6.49 (d, 1H, *J* = 7.7 Hz), 6.20 (brs, 1H), 5.63−5.77 (m, 2H), 5.01−5.09 (m, 2H), 4.88−4.95 (m, 2H), 4.61−4.62 (m, 2H), 4.43−4.48 (m, 1H), 4.23 (br s, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.51 (s, 3H), 2.30−2.39 (m, 2H), 1.86−1.95 (m, 3H), 1.58−1.70 (m, 1H), 1.39 (s, 9H), 1.20−1.26 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 171.6, 170.3, 160.1, 157.9, 154.2, 137.6, 133.5, 129.6, 116.8, 116.6, 114.0, 104.5, 98.2, 78.6, 77.9, 58.5, 54.9, 54.8, 50.8, 50.1, 36.1, 32.2, 28.1, 27.6, 24.6; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{27}H_{40}N_2NaO_7$ 527.2727, found 527.2732.

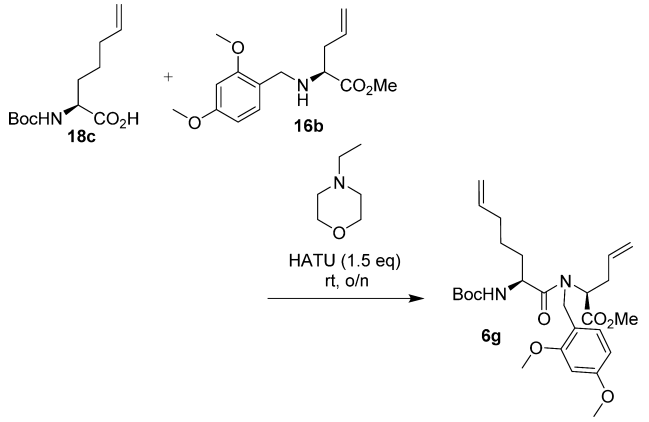
DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

(*S*,*S*)-Methyl 2-[*N*-[2-(*N*-Fmoc-amino)pent-4-enoyl]-*N*-(2,4-dimethoxybenzyl)amino]hept-6-enoate (7d).



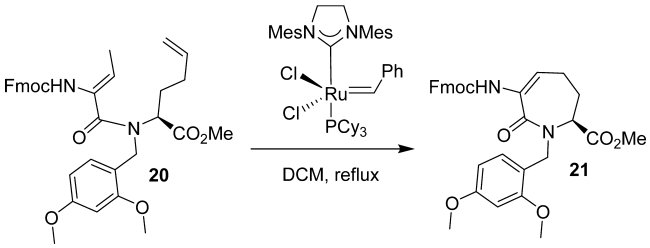
Employing the protocol described for the synthesis of dipeptide **6d**, (*S*)-2-(*N*-Fmoc-amino)pent-4-enoic acid (**17a**; 1.147 g, 3.40 mmol) was coupled with **16c** (700 mg, 2.27 mmol). The residue was purified by chromatography on silica gel (30−40% EtOAc in hexane) to give dipeptide **7d** (1.080 g, 1.72 mmol, 76%) as a colorless gummy oil: R_f = 0.57 (4:7 EtOAc/hexanes, visualized by UV); $[\alpha]_D^{20}$ −39.7 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2923, 1718, 1638, 1612, 1588, 1506, 1437, 1207, 1156, 758, 739538 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.82−7.85 (d, 2H, *J* = 7.5 Hz), 7.67−7.68 (m, 2H), 7.38−7.42 (m, 2H), 7.29−7.32 (t, 2H, *J* = 7.4 Hz), 7.15 (br s, 1H), 6.96 (br s, 1H), 6.54−6.55 (m, 1H), 6.44−6.46 (m, 1H), 5.62−5.75 (m, 2H), 5.02−5.10 (m, 2H), 4.87−4.93 (m, 2H), 4.67 (br s, 2H), 4.41 (br s, 1H), 4.28−4.34 (m, 2H), 4.19−4.22 (t, 2H, *J* = 13.9), 3.77 (s, 3H), 3.74 (s, 3H), 3.49 (s, 3H), 2.36−2.41 (m, 2H), 1.81−1.93 (m, 3H), 1.56−1.67 (m, 1H), 1.16−1.27 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 171.5, 170.3, 160.1, 158.0, 154.9, 143.4, 140.2, 137.7, 133.4, 129.5, 127.0, 126.4, 124.6, 119.4, 116.9, 114.0, 104.5, 98.2, 78.6, 66.2, 65.4, 57.8, 54.9, 54.8, 50.8, 50.5, 46.4, 45.1, 36.0, 32.1, 27.8, 24.6. HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{37}H_{42}N_2O_7Na$ 649.2884, found 649.2873.

(*S*,*S*)-Methyl 2-[*N*-[2-(*N*-Boc-amino)hept-6-enoyl]-*N*-(2,4-dimethoxybenzyl)amino]pent-4-enoate (6g).



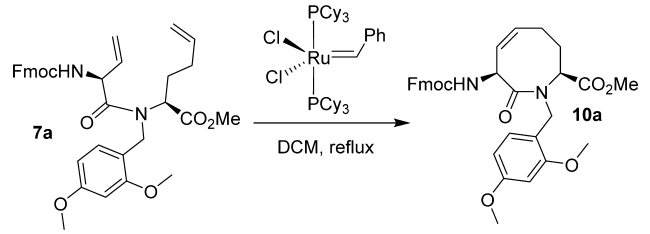
Employing the protocol described for the synthesis of dipeptide **6d**, **18c** (521 mg, 2.14 mmol) was coupled with **16b** (400 mg, 1.43 mmol). The residue was purified by chromatography on silica gel (30−40% EtOAc in hexane) to give dipeptide **6g** (561 mg, 1.11 mmol, 78%) as a colorless gummy oil: R_f = 0.72 (4:6 EtOAc/hexanes, visualized by UV); $[\alpha]_D^{22}$ −52.5 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2975, 2932, 1739, 1708, 1639, 1613, 1507, 1437, 1208, 1158, 1033, 753 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6, 100 °C) δ 7.19 (br s, 1H), 6.56 (s, 1H), 6.47−6.49 (m, 1H), 6.16 (br s, 1H), 5.73−5.81 (m, 1H), 5.60−5.70 (m, 1H), 4.91−5.02 (m, 4H), 4.42−4.55 (m, 3H), 4.19−4.21 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.50 (s, 3H), 2.60−2.68 (m, 1H), 2.40−2.46 (m, 1H), 1.95−2.04 (m, 2H) 1.59−1.65 (m, 1H), 1.49−1.57 (m, 1H), 1.44−1.35 (m, 11H); ^{13}C NMR (125 MHz, DMSO-d_6, 100 °C) δ 172.1, 169.8, 160.1,154.3, 137.8, 134.5, 129.3, 116.3, 114.0, 104.4, 98.2, 78.6, 77.8, 57.8, 54.9, 54.8, 50.9, 50.3, 32.8, 32.7, 32.1, 31.5, 27.6, 23.8, 23.7. HRMS (ESI-TOF) *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{41}N_2O_7$ 505.2908, found 505.2920.

(*S*)-Methyl 3-(*N*-Fmoc-amino)-1-(2,4-dimethoxybenzyl)-2-oxo-5,6,7-tetrahydro-1*H*-azepine-7-carboxylate (21).



Dipeptide **20** (150 mg, 0.25 mmol) was dissolved in DCM (300 mL), treated with the Grubbs second-generation catalyst (42 mg, 0.050 mmol), heated, and stirred at reflux for 2 days. The volatiles were removed under reduced pressure, and the residue was taken up in a minimum volume of DCM, applied onto a silica gel column, and eluted with 35−40% EtOAc in hexanes. Evaporation of the collected fractions gave macrocycle **21** (95 mg, 68%) as a white foam: R_f = 0.55 (4:6 EtOAc/hexanes); $[\alpha]_D^{20}$ +31.8 (*c* 0.5, $CHCl_3$); FT-IR (neat) ν_{max} 2947, 1718, 1654, 1612, 1505, 1206, 1154, 1123, 1032, 758, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75−7.77 (m, 2H); 7.59−7.63 (m, 2H), 7.37−7.43 (m, 2H), 7.27−7.34 (m, 3H), 7.05 (br s, 1H), 6.66 (br s, 1H), 6.45−6.49 (m, 2H), 5.16−5.20 (d, 1H, *J* = 14), 4.39−4.41 (m, 2H), 4.18−4.24 (m, 3H) 3.81 (s, 3H), 3.80 (s, 3H), 3.58 (s, 3H), 2.55−2.60 (m, 1H), 2.13−2.18 (m, 2H), 1.84−1.91 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 167.9, 161.0, 158.8, 153.6, 143.9, 143.9, 141.4, 141.4, 132.2, 131.5, 127.8, 127.8, 127.2, 125.2, 120.1, 120.0, 117.2, 116.2, 104.3, 98.5, 66.8, 59.5, 55.5, 55.3, 52.7, 47.2, 47.1, 32.8, 21.7; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{32}H_{32}N_2NaO_7$ 579.2107, found 579.2101.

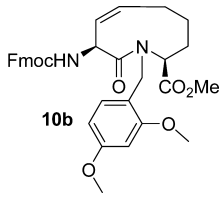
(3*S*,8*S*,*Z*)-Methyl 3-(*N*-Fmoc-amino)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,6,7,8-hexahydroazocine-8-carboxylate (10a).



Dipeptide **7a** (1 g, 1.67 mmol) was dissolved in DCM (2 L), treated with the Grubbs first-generation catalyst (412 mg, 0.50 mmol), heated, and stirred at reflux for 2 days. After 2 days, TLC showed remaining **7a**, and more catalyst (274 mg, 0.33 mmol) was added to the reaction mixture, which was heated at reflux and stirred for 2 days. The volatiles were removed under reduced pressure. The residue was taken up in a minimum volume of DCM, applied onto a silica gel column, and eluted with 35−40% EtOAc in hexanes. Evaporation of the collected fractions afforded macrocycle **10a** (605 mg, 1.06 mmol, 63%) as a colorless gummy oil: R_f = 0.45 (4:6 EtOAc/hexanes); $[\alpha]_D^{24}$ +8.7 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2947, 1718, 1654, 1612, 1505, 1447, 1206, 1154, 1123, 738 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75−7.77 (d, 2H, *J* = 7.5 Hz), 7.61−7.63 (d, 2H, *J* = 7.4 Hz), 7.37−7.42 (t, 2H, *J* = 7.5 Hz), 7.28−7.33 (m, 2H), 7.16−7.19 (d, 1H, *J* = 8.3 Hz), 6.40−6.45 (m, 2H), 6.17−6.19 (d, 1H, *J* = 7 Hz), 5.67−5.79 (m, 2H), 5.28−5.31 (d, 1H, *J* = 7 Hz), 4.71−4.81 (m, 2H), 4.33−4.43 (m, 2H), 4.12−4.26 (m, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 3.45 (s, 3H), 1.97−2.44 (m, 2H), 1.82−1.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.4, 169.9, 160.0, 157.7, 155.9, 144.1, 143.9, 141.4, 131.3, 129.2, 128.1, 127.8, 127.2, 125.7, 120.0, 116.8, 104.1, 98.2, 67.3, 57.6, 55.5, 55.4, 53.7, 52.2, 47.2, 41.0, 28.3, 21.4. HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{33}H_{34}N_2O_7Na$ 593.2258, found 593.2255.

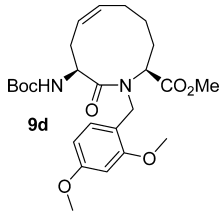
DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

(3*S*,9*S*,*Z*)-Methyl 3-(*N*-Fmoc-amino)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,6,7,8,9-heptahydro-1*H*-azonine-9-carboxylate (10b).



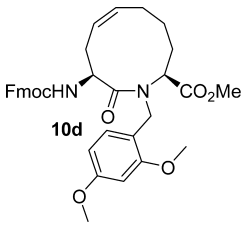
Dipeptide **7b** (200 mg, 0.32 mmol) was dissolved in DCM (400 mL), treated with the Grubbs first-generation catalyst (79 mg, 0.096 mmol), heated, and stirred at reflux for 2 days, when TLC indicated remaining **7b**, and another portion of catalyst (53 mg, 0.065 mmol) was added to the mixture, which was heated at reflux and stirred for 1 day. The volatiles were removed under reduced pressure. The residue was taken up in a minimum volume of DCM, applied onto a silica gel column, and eluted with 35−40% EtOAc in hexanes. Evaporation of the collected fractions afforded macrocycle **10b** (131 mg, 0.22 mmol, 69%) as a colorless gummy oil: R_f = 0.37 (4:6 EtOAc/hexanes); $[\alpha]_D^{20}$ +7.1 (*c* 0.22, $CHCl_3$); FT-IR (neat) ν_{max} 2946, 1718, 1637, 1612, 1587, 1505, 1447, 1288, 1206, 1034, 739 cm^{-1}; ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.75−7.77 (d, 2H, *J* = 7.4 Hz), 7.60−7.63 (m, 2H), 7.38−7.42 (t, 2H, *J* = 7.4 Hz), 7.30−7.33 (t, 2H, *J* = 7.4), 7.08−7.10 (d, 1H, *J* = 8.3 Hz), 6.35−6.42 (m, 3H), 5.69−5.73 (t, 1H, *J* = 7.8 Hz), 5.56−5.63 (m, 1H), 5.34−5.39 (t, 1H, *J* = 10 Hz), 4.87−4.91 (d, 1H, *J* = 15.1 Hz), 4.69−4.71 (d, 1H, *J* = 7.6 Hz), 4.36−4.38 (m, 2H), 4.22−4.31 (m, 2H), 3.76 (s, 3H), 3.78 (s, 3H), 3.59 (s, 3H), 2.62−2.73 (m, 1H), 2.23−2.2 6 (m, 1H), 2.06−2.11 (m, 1H), 1.63−1.69 (m, 1H), 1.47−1.57 (m, 1H), 1.31−1.39 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.3, 170.0, 160.5, 158.3, 155.8, 144.0, 144.0, 141.4, 130.8, 130.7, 129.1, 127.7, 127.1, 125.3, 125.3, 120.1, 120.0, 117.5, 104.1, 98.1, 67.1, 55.4, 55.3, 55.2, 52.4, 50.4, 47.2, 41.6, 28.3, 24.5, 23.7; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{34}H_{36}N_2O_7Na$ 607.2414, found 607.2425.

(3*S*,10*S*,*Z*)-Methyl 3-(*N*-Boc-amino)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,7,8,9,10-octahydroazecine-10-carboxylate (9d).



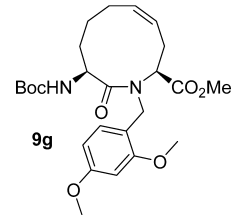
Dipeptide **6d** (600 mg, 1.18 mmol) was dissolved in DCM (1300 mL), treated with the Grubbs first-generation catalyst (189 mg, 0.23 mmol), heated, and stirred at reflux for 2 days. The volatiles were removed under reduced pressure, and the residue was taken up in a minimum volume of DCM, applied onto a silica gel column, and eluted with 30−35% EtOAc in hexanes to afford macrocycle **9d** (490 mg, 1.02 mmol, 86%) as a white solid: R_f = 0.55 (4:6 EtOAc/hexanes); mp 81−83 °C; $[\alpha]_D^{20}$ +15.1 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2944, 1706, 1644, 1612, 1490, 1433, 1363, 1209, 1157, 1130, 1030, 833 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04−7.06 (d, 1H, *J* = 8.2 Hz), 6.42−6.43 (d, 1H, *J* = 2.2 Hz), 6.34−6.39 (m, 1H), 5.85−5.86 (d, 1H, *J* = 7.1 Hz), 5.53−5.58 (m, 1H), 5.44−5.46 (m, 1H), 5.23 (br s, 1H), 4.97−4.99 (d, 1H, *J* = 14.2), 3.93−3.98 (m, 1H), 3.78 (s, 3H), 3.75 (s, 3H), 3.37−3.39 (d, 1H, *J* = 10.5 Hz), 3.30 (s, 3H), 2.79−2.81 (m, 1H), 2.44−2.45 (m, 1H), 2.25−2.37 (m, 2H), 2.02−2.05 (m, 1H), 1.93−1.96 (m, 1H), 1.65−1.66 (m, 1H), 1.46−1.41(m, 10H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.2, 169.9, 160.5, 159.0, 154.2, 132.1, 130.5, 123.1, 115.2, 102.3, 97.4, 78.3, 76.3, 61.2, 54.5, 54.1, 50.7, 50.4, 49.8, 28.5, 27.5, 25.0, 22.3; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{36}N_2O_7Na$ 499.2414, found 499.2409.

(3*S*,10*S*,*Z*)-Methyl 3-(*N*-Fmoc-amino)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,7,8,9,10-octahydroazecine-10-carboxylate (10d).



Dipeptide **7d** (1 g, 1.60 mmol) was dissolved in DCM (2000 mL), treated with the Grubbs first-generation catalyst (263.34 mg, 0.32 mmol), heated, and stirred at reflux for 2 days. The volatiles were removed under reduced pressure, and the residue was taken up in a minimum volume of DCM, applied onto a silica gel column, and eluted with 35−40% EtOAc in hexanes to afford macrocycle **10d** (872 mg, 1.45 mmol, 91%) as a white solid: R_f = 0.40 (4:6 EtOAc/hexanes); mp 89−92 °C; $[\alpha]_D^{20}$ −5.8 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 3005, 1717, 1640, 1611, 1588, 1505, 1207, 1156, 1034, 758, 739, 542 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76−7.78 (d, 2H, *J* = 7.5 Hz), 7.62−7.65 (m, 2H), 7.38−7.42 (t, 2H, *J* = 7.4), 7.30−7.33 (m, 2H), 7.06−7.08 (d, 1H, *J* = 8.2 Hz), 6.38−6.43 (m, 2H), 6.17−6.19 (d, 1H, *J* = 6.5 Hz), 5.49−5.60 (m, 2H), 5.26−5.28 (m, 1H), 4.97−5.01 (d, 1H, *J* = 14.4), 4.34−4.47 (m, 2H), 4.22−4.26 (m, 1H), 3.99−4.02 (m, 1H), 3.79 (s, 3H), 3.73 (s, 3H), 3.39−3.44 (m, 1H), 3.33 (s, 3H), 2.80−2.90 (m, 1H), 2.40−2.52 (m, 2H), 2.27−2.36 (m, 1H), 1.84−2.09 (m, 3H), 1.67−1.74 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 170.5, 161.5, 159.9, 155.5, 144.1, 144.0, 141.4, 131.5, 127.8, 127.2, 127.1, 125.4, 125.3, 123.8, 120.1, 116.0, 103.5, 98.4, 66.8, 62.3, 55.5, 55.4, 55.4, 55.3, 52.0, 51.7, 47.4, 47.3, 26.0; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{35}H_{38}N_2O_7Na$ 621.2571, found 621.2588.

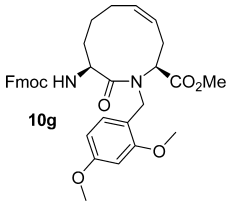
(3*S*,10*S*,*Z*)-Methyl 3-(*N*-Boc-amino)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,5,6,9,10-octahydroazecine-10-carboxylate (9g).



Dipeptide **6g** (550 mg, 1.09 mmol) was dissolved in DCM (1000 mL), treated with the Grubbs first-generation catalyst (173 mg, 0.21 mmol), heated, and stirred at reflux for 2 days. The volatiles were removed under reduced pressure, and the residue was taken up in a minimum volume of DCM, applied onto a silica gel column, and eluted with 30−35% EtOAc in hexanes to afford macrocycle **9g** (460 mg, 0.96 mmol, 79%) as a white solid: R_f = 0.62 (4:6 EtOAc/hexanes); mp 79−82 °C; $[\alpha]_D^{22}$ −40.5 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 2943, 1735, 1706, 1637, 1612, 1589, 1506, 1438, 1363, 1208, 1156, 1034, 750, 533 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.03−7.05 (d, 1H, *J* = 8.16 Hz), 6.37−6.42 (m, 2H), 5.87−5.88 (d, 1H, *J* = 6.76 Hz), 5.48−5.60 (m, 2H), 5.02−5.05 (t, 1H, *J* = 6.36 Hz), 4.81−4.85 (d, 1H, *J* = 14.2 Hz), 3.78 (s, 3H), 3.75 (s, 3H), 3.44−3.49 (m, 1H), 3.42 (m, 3H), 3.26−3.35 (m, 1H), 2.46−2.55 (m, 1H), 2.25−2.31 (m, 1H), 1.98−2.04 (m, 1H), 1.84−1.93 (m, 2H), 1.74−1.78 (m, 1H), 1.39−1.53 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 170.8, 161.3, 159.9, 155.2, 135.3, 131.4, 125.0, 115.9, 103.4, 98.5, 79.2, 57.9, 55.4, 55.2, 51.8, 50.7, 50.1, 28.5, 27.7, 25.0, 24.1, 21.5; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ calcd for $C_{25}H_{36}N_2O_7Na$ 499.2414, found 499.2409.

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

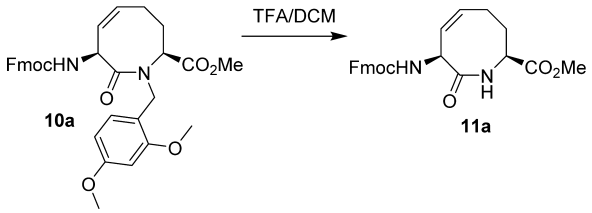
(3*S*,10*S*,*Z*)-Methyl 3-(*N*-Fmoc-amino)-1-(2,4-dimethoxybenzyl)-2-oxo-1,2,3,4,5,6,,9,10-octahydroazecine-10-carboxylate (10g).



10g

A stirred solution of Boc-protected dipeptide lactam **9g** (200 mg, 0.42 mmol) in 10 mL of DCM was treated with TFA (4 mL) at 0 °C and stirred for 2 h, and the volatiles were removed under reduced pressure to provide the trifluoroacetate salt, which was dissolved in 15 mL of a 1:1 water/acetone solution and treated with Fmoc-OSu (138 mg, 0.42 mmol) and Na_2CO_3 (90 mg, 0.84 mmol). After being stirred for 18 h at room temperature, the mixture was diluted with water and acidified to pH 3−4 with 10% $KHSO_4$ solution. This aqueous solution was extracted with ethyl acetate (3 × 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to a residue that was purified by chromatography on silica gel using 25−30% EtOAc in hexane as the eluent. Evaporation of the collected fractions gave Fmoc-protected dipeptide lactam **10g** (151 mg, 0.25 mmol, 60%) as a colorless oil: R_f = 0.50 (4:6 EtOAc/hexanes, visualized by UV); $[\alpha]_D^{20}$ −45.2 (*c* 0.5, $CHCl_3$); FT-IR (neat) ν_{max} 2944, 1715, 1636, 1612, 1588, 1506, 1440, 1207, 1156, 1130, 1035, 758, 739, 535 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.76−7.78 (d, 2H, *J* = 7.5 Hz), 7.63−7.66 (t, 2H, *J* = 6.0 Hz), 7.39−7.42 (t, 2H, *J* = 7.4 Hz), 7.30−7.34 (m, 2H), 7.05−7.07 (d, 1H, *J* = 8.1 Hz), 6.39−6.43 (m, 2H), 6.21−6.23 (d, 1H, *J* = 6.7), 5.52−5.64 (m, 2H), 5.08−5.12 (m, 1H), 4.83−4.87 (d, 1H, *J* = 14.3 Hz), 4.41−4.46 (m, 1H), 4.33−4.39 (m, 1H), 4.22−4.26 (t, 1H, *J* = 7.2 Hz), 3.79 (s, 3H), 3.75 (s, 3H), 3.48−3.54 (m, 1H), 3.45 (s, 3H), 3.30−3.40 (m, 1H), 2.50−2.62 (m, 1H), 2.30−2.35 (m, 1H), 2.05−211 (m, 1H), 1.80−1.98 (m, 3H), 1.75−1.49 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 170.7, 161.4, 159.8, 155.5, 144.1, 144.1, 141.5, 135.3, 131.4, 127.8, 127.1, 125.4, 125.3, 125.1, 120.1, 120.0, 115.7, 103.5, 98.5, 66.9, 58.0, 55.4, 55.4, 51.9, 50.7, 50.6, 47.4, 27.5, 25.0, 24.2, 21.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{35}H_{38}N_2O_7Na$ 621.2571, found 621.2576

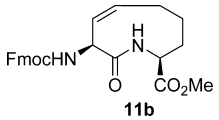
(3*S*,8*S*,*Z*)-Methyl 3-(*N*-Fmoc-amino)-2-oxo-1,2,3,6,7,8-hexahydroazocine-8-carboxylate (11a).



10a 11a

Lactam **10a** (155 mg, 0.27 mmol) was treated with TFA (2 mL) in DCM (5 mL) overnight. The volatiles were removed under vacuum, and the residue was purified by chromatography on silica gel (40−50% EtOAc in hexane) to give macrocycle **11a** (97 mg, 0.23 mmol, 85%) as a white solid: R_f = 0.2 (1:1 EtOAc/hexanes, visualized by UV); mp 183−185 °C, $[\alpha]_D^{24}$ +29.5 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 3377, 2955, 1728, 1696, 1663, 1528, 1432, 1255, 1050, 984, 721, 549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.74−7.76 (d, 2H, *J* = 7.5 Hz), 7.59−7.61 (m, 2H), 7.37−7.41 (t, 2H, *J* = 7.4 Hz), 7.29−7.32 (m, 2H), 6.17−6.19 (d, 1H, *J* = 7.7 Hz), 6.06−6.08 (d, 1H, *J* = 7.3 Hz), 5.77−5.84 (m, 1H), 5.63−5.68 (m, 1H), 5.15−5.19 (t, 1H, *J* = 6.5 Hz), 4.44−4.49 (m, 1H), 4.33−4.41 (m, 2H), 4.21−4.24 (t, 1H, *J* = 7.23 Hz), 3.79 (s, 3H), 2.46−2.51 (m, 2H), 2.16−2.21 (m, 1H), 1.56−1.65 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 171.8, 155.9, 144.0, 143.9, 141.4, 132.7, 129.2, 127.8, 127.2, 125.3, 125.2, 120.0, 67.3, 55.9, 53.2, 52.2, 47.2, 33.0, 25.5; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{24}N_2O_5Na$ 443.1577, found 443.1581.

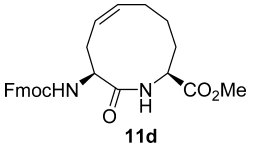
(3*S*,9*S*,*Z*)-Methyl 3-(*N*-Fmoc-amino)-2-oxo-1,2,3,6,7,8,9-heptahydro-1*H*-azonine-9-carboxylate (11b).



11b

Lactam **10b** (53 mg, 0.09 mmol) was treated as described for the synthesis of **11a** above with TFA (1 mL) in DCM overnight. Chromatography (30−40% EtOAc in hexane) gave **11b** (34 mg, 0.08 mmol, 87%) as a white solid: R_f = 0.2 (1:1 EtOAc/hexanes, visualized by UV); mp 202−204 °C; $[\alpha]_D^{20}$ +21.1 (*c* 1, $CHCl_3$); FT-IR (neat) ν_{max} 3325, 2922, 1736, 1660, 1521, 1434, 1318, 1240, 1204, 1032, 985, 882, 758 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.75−7.76 (d, 2H, *J* = 7.5 Hz), 7.58−7.60 (m, 2H), 7.37−7.41 (t, 2H, *J* = 7.4 Hz), 7.29−7.32 (t, 2H, *J* = 7.4 Hz), 6.37−6.39 (d, 1H, *J* = 9.0 Hz), 6.13−6.14 (d, 1H, *J* = 5.9 Hz), 5.68−5.75 (m, 1H), 5.39−5.43 (m, 2H), 4.31−4.39 (m, 3H), 4.20−4.23 (t, 1H, *J* = 7.2 Hz), 3.80 (s, 3H), 2.80−2.91 (m, 1H), 2.29−2.40 (m, 1H), 1.93−2.01 (m, 2H), 1.76−1.82 (m, 1H), 162−1.71 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 169.8, 155.6, 144.0, 143.9, 141.4, 131.5, 128.1, 127.8, 127.2, 125.2, 120.0, 67.2, 53.1, 50.2, 50.2, 47.2, 34.1, 29.8, 25.6, 23.4; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{26}N_2O_5Na$ 457.1733, found 457.1745.

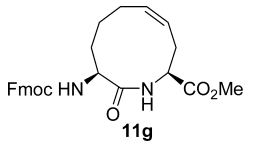
(3*S*,10*S*,*Z*)-Methyl 3-(*N*-Fmoc-amino)-2-oxo-1,2,3,4,7,8,9,10-octahydroazecine-10-carboxylate (11d).



11d

Lactam **10d** (100 mg, 0.17 mmol) was treated with TFA (2 mL) in DCM (5 mL) for 3 days. The volatiles were removed under vacuum, and the residue was purified by chromatography on silica gel (40−50% EtOAc in hexane) to give lactam **11d** (52 mg, 0.11 mmol, 69%) as a white solid: R_f = 0.2 (1:1 EtOAc/hexanes, visualized by UV); $[\alpha]_D^{20}$ +48.1 (*c* 0.16, $CHCl_3$); FT-IR (neat) ν_{max} 3327, 2920, 1723, 1649, 1505, 1437, 1349, 1221, 1022, 756 cm^{-1}; ^1H NMR (500 MHz, 100 °C DMSO-d_6) δ 7.86−7.87 (d, 2H, *J* = 7.5 Hz), 7.81−7.82 (m, 1H), 7.86−7.89 (d, 2H, *J* = 7.5 Hz), 7.40−7.43 (t, 2H, *J* = 7.4), 7.32−7.35 (m, 2H), 6.86 (br s, 1H), 5.35−5.46 (m, 2H), 4.34−4.40 (m, 2H), 4.23−4.26 (m, 1H), 4.08−4.18 (m, 2H) 3.65 (s, 3H), 2.36−2.39 (m, 1H), 2.27−2.28 (m, 1H), 1.97−2.15 (m, 2H), 1.66−1.91 (m, 3H), 1.55−1.57 (m, 1H); ^{13}C NMR (125 MHz, 100 °C DMSO-d_6) δ 172.0, 169.8, 144.4, 141.3, 134.3, 128.0, 127.5, 125.5, 123.8, 121.7, 120.6, 120.4, 120.3, 79.6, 66.4, 55.4, 54.3, 52.1, 47.5, 30.0, 26.1, 25.9, 25.6; HRMS (ESI-TOF) *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{28}N_2O_5Na$ 471.1890, found 471.1898.

(3*S*,10*S*,*Z*)-Methyl 3-(*N*-Fmoc-amino)-2-oxo-1,2,3,4,5,6,9,10-octahydroazecine-10-carboxylate (11g).



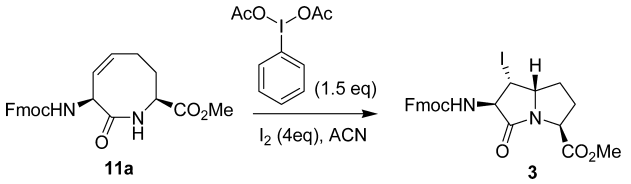
11g

Lactam **10g** (40 mg, 0.07 mmol) was treated as described for the synthesis of **11a** above with TFA (0.5 mL) in DCM overnight. Chromatography (40−50% EtOAc in hexane) gave lactam **11g** (24 mg, 0.05 mmol, 80%) as a white solid: R_f = 0.2 (1:1 EtOAc/hexanes, visualized by UV); mp 210−215 °C; $[\alpha]_D^{22}$ +2.4 (*c* 0.16, $CHCl_3$); FT-IR (neat) ν_{max} 3296, 2926, 1726, 1685, 1643, 1527, 1438, 1247, 1105, 1031, 755, 736 cm^{-1}; ^1H NMR (500 MHz, 100 °C, DMSO-d_6) δ 7.92 (br, s, 1H), 7.84−7.86 (d, 2H, *J* = 7.6 Hz), 7.67−7.69 (m, 2H), 7.39−7.42 (t, 2H, *J* = 7.4 Hz), 7.30−7.33 (t, 2H, *J* = 7. 5), 6.74 (br s, 1H), 5.48−5.53 (m, 1H), 5.34−5.41 (m, 1H), 4.32−4.33 (m, 2H), 4.21−4.24 (t, 1H, *J* = 6.9), 4.06−4.09 (m, 1H), 3.90 (br s, 1H), 3.65 (s, 3H), 2.75−2.82 (m, 1H), 2.42−2.43 (m, 1H), 2.12−2.20 (m, 1H), 1.83−1.89 (m, 2H), 1.74−1.78 (m, 2H), 1.44−1.48 (m, 1H); ^{13}C NMR (125 MHz, 100 °C, DMSO-d_6) δ 171.3, 170.4, 154.5, 143.4, 140.3, 134.4, 127.0, 126.5, 124.6, 124.2, 119.4, 65.4, 53.2, 51.7, 51.2, 46.5, 35.8, 29.4, 24.7, 23.7,

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

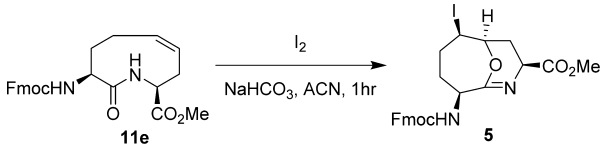
21.7, 16.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{28}N_2O_5Na$ 471.1890, found 471.1903.

(3*R*,4*R*,5*S*,8*S*)-Methyl 3-(*N*-Fmoc-amino)-4-iodo-2-oxohexahydro-5*H*-pyrrolizine-8-carboxylate (3).



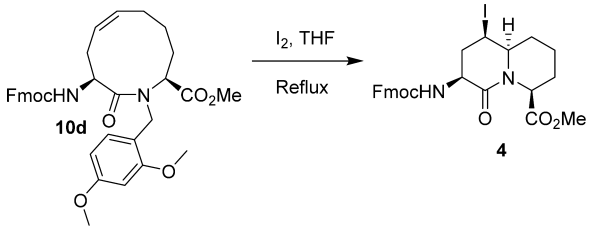
In the dark, a solution of macrocycle **11a** (100 mg, 0.24 mmol) in acetonitrile (4 mL) was treated with iodine (243 mg, 0.96 mmol) followed by (diacetoxyiodo)benzene (116 mg, 0.36 mmol). The resulting mixture was heated to 80 °C for 30 min and cooled to room temperature, and the volatiles were evaporated under reduced pressure. The residue was chromatographed on silica gel (40−50% EtOAc in hexane) to give pyrrolizidinone **3** (81 mg, 0.15 mmol, 62%) as a light-sensitive white solid: R_f = 0.45 (3:2 EtOAc/hexanes, visualized by UV); mp 94−96 °C; $[\alpha]_D^{20}$ −70.8 (c 1, $CHCl_3$); FT-IR (neat) ν_{max} 3374,1754, 1739, 1692, 1522, 1444, 1380, 1254, 1220, 1166, 1076, 1049, 818, 755, 741, 532 cm^{-1}; ^{1}H NMR (700 MHz, C_6D_6) δ 7.57−7.58 (d, 2H, J = 7.7 Hz), 7.43−7.44 (m, 2H), 7.17−7.24 (m, 4H), 4.92−4.93 (d, 1H, J = 7.6 Hz), 4.49−4.51 (t, 1H, J = 7.4), 4.40−4.43 (t, 1H, J = 7.6 Hz), 4.34−4.35 (d, 2H, J = 6.5 Hz), 3.96−3.98 (t, 1H, J = 6.5 Hz), 3.90−3.92 (t, 1H, J = 6.6 Hz), 3.26−3.29 (m, 1H), 3.22 (s, 3H), 1.70−1.78 (m, 1H), 1.43−1.48 (m, 1H), 1.32−1.34 (m, 1H), 0.80−0.83 (m, 1H); ^{13}C NMR (175 MHz, C_6D_6) δ 172.0, 171.0, 156.2, 144.5, 144.4, 141.8, 127.4, 127.4, 125.5, 120.2, 67.0, 63.9, 62.6, 57.6, 51.8, 47.5, 33.5, 30.3, 30.0, 22.5; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{24}H_{23}IN_2O_5Na$ 569.0543, found 569.0559.

Imidate 5.



In the dark, a solution of macrocycle **11e** (50 mg, 0.11 mmol) in acetonitrile (4 mL) was treated with $NaHCO_3$ (27 mg, 0.33 mmol) followed by iodine (83.7 mg, 0.33 mmol) in three portions, stirred for 1 h at rt, and treated with 1 M $Na_2S_2O_3$ until the purple solution became clear. The mixture was extracted quickly with ethyl acetate (3 × 10 mL). The organic extractions were washed with brine, dried, and concentrated under reduced pressure to a residue that was chromatographed on silica gel (20−30% EtOAc in hexane). Evaporation of the collected fractions gave imidate **5** (33 mg, 0.06 mmol, 51%) as a white solid: R_f = 0.45 (4.5:6.5 EtOAc/hexanes, visualized by UV); mp 152−154 °C; $[\alpha]_D^{20}$ +48.4 (c 1, $CHCl_3$); FT-IR (neat) ν_{max} 3410, 2923, 1738, 1715, 1657, 1490, 1449, 1352, 1277, 1208, 1162, 1020, 958, 903, 739, 541 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.76−7.77 (d, 2H, J = 7.4 Hz), 7.60−7.63 (m, 2H), 7.39−7.41 (m, 2H), 7.31−7.33 (m, 2H), 6.17−6.18 (d, 1H, J = 5.9 Hz), 4.89−4.93 (m, 1H), 4.67−4.69 (m, 1H), 4.38−4.39 (d, 2H, J = 7 Hz), 4.26−4.29 (m, 1H), 4.21−4.23 (t, 1H, J = 6.9), 3.95−3.97 (m, 1H), 3.85 (s, 3H), 2.69−2.73 (m, 1H), 2.12−2.17 (m, 2H), 2.03−2.10 (m, 1H), 1.94−1.98 (m, 2H); ^{13}C NMR (175 MHz, $CDCl_3$) δ 172.0, 164.8, 155.7, 144.1, 143.9, 141.4, 141.4, 127.8, 127.2, 125.3, 125.2, 120.1, 120.1, 67.1, 55.3, 52.7, 51.3, 47.3, 36.7, 33.2, 30.3, 30.1, 14.1; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{25}H_{25}IN_2O_5Na$ 583.0700, found 583.0705.

(3*S*,5*R*,6*R*,10*S*)-Methyl 3-(*N*-Fmoc-amino)-5-iodo-2-oxooctahydro-6*H*-quinolizine-10-carboxylate (4).



In the dark, a solution of macrocycle **10d** (300 mg, 0.50 mmol) in THF (10 mL) was treated with iodine (508 mg, 2 mmol), heated to 80 °C for 8 h, and cooled to room temperature, and the volatiles were removed under reduced pressure to a residue that was chromatographed on silica gel (40−50% EtOAc in hexane) to give quinolizidinone **4** (151 mg, 0.26 mmol, 53%) as a white solid: R_f = 0.45 (3:2 EtOAc/hexanes); mp 98−101 °C; $[\alpha]_D^{20}$ +16.2 (c 1, $CHCl_3$); FT-IR (neat) ν_{max} 2947, 1717, 1655, 1508, 1446, 1324, 1226, 738, 538 cm^{-1}; ^{1}H NMR (700 MHz, $CDCl_3$) δ 7.75−7.76 (d, 2H, J = 7.1 Hz), 7.57−7.58 (d, 2H, J = 7.3 Hz), 7.38−7.40 (t, 2H, J = 7.4 Hz), 7.30−7.32 (t, 2H, J = 7.3 Hz), 5.75 (br s, 1H), 4.69−4.70 (m, 1H), 4.31−4.42 (m, 2H), 4.17−4.20 (m, 2H), 3.73 (s, 3H), 3.65−3.68 (m, 1H), 3.44−3.45 (m, 1H), 3.06−3.08 (m, 1H), 2.45−2.51 (m, 1H), 2.24−2.25 (m, 1H), 2.06−2.09 (m, 1H), 1.94−1.98 (m, 1H), 1.83−1.89 (m, 1H), 1.59−1.60 (m, 2H) ^{13}C NMR (175 MHz, $CDCl_3$) δ 169.6, 168.6, 156.2, 143.9, 143.8, 141.4, 141.4, 127.8, 127.2, 125.3, 120.1, 67.2, 62.9, 60.2, 52.6, 52.4,. 47.2, 37.7, 30.1, 24.8, 22.9, 20.3; HRMS (ESI-TOF) m/z [M + Na]$^+$ calcd for $C_{26}H_{27}IN_2O_5Na$ 597.0856, found 597.0861.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for all new compounds and X-ray data for compounds **10d**, **11a**, **11e**, **3**, and **5** (PDF and CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: william.lubell@umontreal.ca.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC), the Canadian Institutes of Health Research (CIHR; Grants TGC-114046 and CIP-79848), the Global Alliance to Prevent Prematurity and Stillbirth, an initiative of Seattle Children's, the Bill & Melinda Gates Foundation, the March of Dimes, and the Canadian Foundation for Innovation. We thank Dr. A. Fürtös, K. Venne, and M-C. Tang from the Regional Laboratory for Mass Spectrometry, Sylvie Bilodeau, Antoine Hamel, and Cedric Malveau from the Regional Laboratory for NMR Spectroscopy, and Francine Belanger-Gariepy from the Regional Laboratory for X-ray Analysis, at the Université de Montréal, for their assistance in compound analyses. Shastri Indo-Canadian Institute is thanked for a Quebec Tuition Fee Exemption grant to N.D.P.A.

■ REFERENCES

(1) (a) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556−1575. (b) Nukui, S.; Sodeoka, M.; Sasai, H.; Shibasaki, M. *J. Org. Chem.* **1995**, *60*, 398−404. (c) Rawal, V. H.; Michoud, C. *Tetrahedron Lett.* **1991**, *32*, 1695−1698.

(2) (a) Yang, C.-W.; Chen, W.-L.; Wu, P.-L.; Tseng, H.-Y.; Lee, S.-J. *Mol. Pharmacol.* **2006**, *69*, 749−758. (b) Michael, J. P. *Nat. Prod. Rep.* **2001**, *18*, 543−559. (c) Michael, J. P. *Nat. Prod. Rep.* **2002**, *19*, 719−741. (d) Grundon, M. F.; Saxton, J. E. *The Alkaloids*; Royal Society of Chemistry: London, 1971; Vol. *1*. (e) Wei, L.; Shi, Q.; Bastow, K. F.; Brossi, A.; Morris-Natschke, S. L.; Nakagawa-Goto, K.; Wu, T.-S.; Pan, S.-L.; Teng, C.-M.; Lee, K.-H. *J. Med. Chem.* **2007**, *50*, 3674−3680.

(3) (a) Sukhorukov, A. Y.; Boyko, Y. D.; Nelyubina, Y. V.; Gerard, S.; Ioffe, S. L.; Tartakovsky, V. A. *J. Org. Chem.* **2012**, *77*, 5465−5469. (b) Sun, H.; Nikolovska-Coleska, Z.; Yang, C.-Y.; Xu, L.; Liu, M.; Tomita, Y.; Pan, H.; Yoshioka, Y.; Krajewski, K.; Roller, P. P. *J. Am.*

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918

Chem. Soc. **2004**, *126*, 16686−16687. (c) Zhang, B.; Nikolovska-Coleska, Z.; Zhang, Y.; Bai, L.; Qiu, S.; Yang, C.-Y.; Sun, H.; Wang, S.; Wu, Y. *J. Med. Chem.* **2008**, *51*, 7352−7355. (d) Vagner, J.; Qu, H.; Hruby, V. J. *Curr. Opin. Chem. Biol.* **2008**, *12*, 292−296. (e) Bourguet, C. B.; Claing, A.; Laporte, S. A.; Hébert, T. E.; Chemtob, S.; Lubell, W. D. *Can. J. Chem.* **2014**, *92*, 1031−1040. (f) Haubner, R.; Schmitt, W.; Hölzemann, G.; Goodman, S. L.; Jonczyk, A.; Kessler, H. *J. Am. Chem. Soc.* **1996**, *118*, 7881−7891. (g) Nogawa, T.; Kawatani, M.; Uramoto, M.; Okano, A.; Aono, H.; Futamura, Y.; Koshino, H.; Takahashi, S.; Osada, H. *J. Antibiot.* **2013**, *66*, 621−623.

(4) (a) Bourguet, C. B.; Goupil, E.; Tassy, D.; Hou, X.; Thouin, E.; Polyak, F.; Hébert, T. E.; Claing, A.; Laporte, S. A.; Chemtob, S.; Lubell, W. D. *J. Med. Chem.* **2011**, *54*, 6085−6097. (b) Hanessian, S.; McNaughton-Smith, G.; Lombart, H.-G.; Lubell, W. D. *Tetrahedron* **1997**, *53*, 12789−12854. (c) Becker, J. A.; Wallace, A.; Garzon, A.; Ingallinella, P.; Bianchi, E.; Cortese, R.; Simonin, F.; Kieffer, B. L.; Pessi, A. *J. Biol. Chem.* **1999**, *274*, 27513−27522. (d) Estiarte, M. A.; Rubiralta, M.; Diez, A.; Thormann, M.; Giralt, E. *J. Org. Chem.* **2000**, *65*, 6992−6999.

(5) (a) Rao, M. H. R.; Pinyol, E.; Lubell, W. D. *J. Org. Chem.* **2007**, *72*, 736−743. (b) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **1998**, *63*, 5937−5949. (c) Polyak, F.; Lubell, W. D. *J. Org. Chem.* **2001**, *66*, 1171−1180. (d) Salvati, M.; Cordero, F. M.; Pisaneschi, F.; Bucelli, F.; Brandi, A. *Tetrahedron* **2005**, *61*, 8836−8847. (e) Hanessian, S.; Chattopadhyay, A. K. *Org. Lett.* **2013**, *16*, 232−235.

(6) Transannular cyclization reactions have been recently reviewed: Harutyunyan, S. R.; Rizzo, A. *Org. Biomol. Chem.* **2014**, *12*, 6570−6579.

(7) For examples of transannular aminations see: (a) White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129−9142. (b) White, J. D.; Hrnciar, P.; Yokochi, A. F. *J. Am. Chem. Soc.* **1998**, *120*, 7359−7360. (c) Jensen, T.; Mikkelsen, M.; Lauritsen, A.; Andresen, T. L.; Gotfredsen, C. H.; Madsen, R. *J. Org. Chem.* **2009**, *74*, 8886−8889. (d) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2012**, *14*, 4278−4281. (e) Brock, E. A.; Davies, S. G.; Lee, J. A.; Roberts, P. M.; Thomson, J. E. *Org. Lett.* **2011**, *13*, 1594−1597.

(8) For examples of transannular amidations see: (a) Surprenant, S.; Lubell, W. D. *Org. Lett.* **2006**, *8*, 2851−2854. (b) Edstrom, E. D. *J. Am. Chem. Soc.* **1991**, *113*, 6690−6692. (c) Edwards, O.; Paton, J.; Benn, M.; Mitchell, R.; Watanatada, C.; Vohra, K. *Can. J. Chem.* **1971**, *49*, 1648−1658. (d) Diederich, M.; Nubbemeyer, U. *Chem.—Eur. J.* **1996**, *2*, 894−900. (e) Edstrom, E. D. *Tetrahedron Lett.* **1991**, *32*, 5709−5712. (f) Sudau, A.; Münch, W.; Bats, J. W.; Nubbemeyer, U. *Chem.—Eur. J.* **2001**, *7*, 611−621.

(9) (a) Prelog, V. *J. Chem. Soc.* **1950**, 420−428. (b) Brown, H. C.; Ichikawa, K. *Tetrahedron* **1957**, *1*, 221−230.

(10) Still, W. C.; Galynker, I. *Tetrahedron* **1981**, *37*, 3981−3996.

(11) Yoshikawa, K.; Bekki, K.; Karatsu, M.; Toyoda, K.; Kamio, T.; Morishima, I. *J. Am. Chem. Soc.* **1976**, *98*, 3272−3281.

(12) Godina, T. A.; Lubell, W. D. *J. Org. Chem.* **2011**, *76*, 5846−5849.

(13) (a) Liu, Y.; Bolen, D. *Biochemistry* **1995**, *34*, 12884−12891. (b) Bean, J. W.; Kopple, K. D.; Peishoff, C. E. *J. Am. Chem. Soc.* **1992**, *114*, 5328−5334.

(14) Kaul, R.; Surprenant, S.; Lubell, W. D. *J. Org. Chem.* **2005**, *70*, 3838−3844.

(15) Buchanan, G. *Chem. Soc. Rev.* **1974**, *3*, 41−63.

(16) (a) Rémond, E.; Bayardon, J. R. M.; Ondel-Eymin, M.-J. L.; Jugé, S. *J. Org. Chem.* **2012**, *77*, 7579−7587. (b) Myers, A. G.; Gleason, J. L.; Yoon, T.; Kung, D. W. *J. Am. Chem. Soc.* **1997**, *119*, 656−673. (c) Xu, P.-F.; Lu, T.-J. *J. Org. Chem.* **2003**, *68*, 658−661. (d) Workman, J. A.; Garrido, N. P.; Sançon, J.; Roberts, E.; Wessel, H. P.; Sweeney, J. B. *J. Am. Chem. Soc.* **2005**, *127*, 1066−1067.

(17) Traoré, M.; Mietton, F.; Maubon, D. l.; Peuchmaur, M.; Francisco Hilário, F.; Pereira de Freitas, R.; Bougdour, A.; Curt, A. l.; Maynadier, M.; Vial, H. *J. Org. Chem.* **2013**, *78*, 3655−3675.

(18) Rodríguez, A.; Miller, D. D.; Jackson, R. F. *Org. Biomol. Chem.* **2003**, *1*, 973−977.

(19) Trost, B. M.; Rudd, M. T. *Org. Lett.* **2003**, *5*, 4599−4602.

(20) (a) Olsen, J. A.; Severinsen, R.; Rasmussen, T. B.; Hentzer, M.; Givskov, M.; Nielsen, J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 325−328. (b) Atmuri, N. D. P.; Lubell, W. D. *Org. Synth.* **2015**, *92*, 103−116.

(21) Sicherl, F.; Cupido, T.; Albericio, F. *Chem. Commun.* **2010**, *46*, 1266−1268.

(22) Organ, M. G.; Xu, J.; N'Zemba, B. *Tetrahedron Lett.* **2002**, *43*, 8177−8180.

(23) Grubbs, R. H. *Angew. Chem., Int. Ed.* **2006**, *45*, 3760−3765.

(24) Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855−5856.

(25) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601−3605.

(26) Singh, F. V.; Wirth, T. *Synthesis* **2012**, *44*, 1171−1177.

(27) Denmark, S. E.; Burk, M. T. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20655−20660.

(28) (a) Biloski, A. J.; Wood, R. D.; Ganem, B. *J. Am. Chem. Soc.* **1982**, *104*, 3233−3235. (b) Rajendra, G.; Miller, M. J. *J. Org. Chem.* **1987**, *52*, 4471−4477.

(29) Tang, Y.; Li, C. *Tetrahedron Lett.* **2006**, *47*, 3823−3825.

(30) Mehta, S.; Yao, T.; Larock, R. C. *J. Org. Chem.* **2012**, *77*, 10938−10944.

(31) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870−2871.

(32) Creighton, C. J.; Leo, G. C.; Du, Y.; Reitz, A. B. *Biorg. Med. Chem.* **2004**, *12*, 4375−4385.

(33) Hutchinson, E. G.; Thornton, J. M. *Protein Sci.* **1994**, *3*, 2207−2216.

(34) Lombart, H.-G.; Lubell, W. D. *J. Org. Chem.* **1996**, *61*, 9437−9446.

(35) Sauvaître, T.; Barlier, M.; Herlem, D.; Gresh, N.; Chiaroni, A.; Guenard, D.; Guillou, C. *J. Med. Chem.* **2007**, *50*, 5311−5323.

(36) Pandey, G. *Org. Lett.* **2011**, *13*, 4672−4675.

(37) Sudau, A.; Münch, W.; Nubbemeyer, U.; Bats, J. W. *J. Org. Chem.* **2000**, *65*, 1710−1720.

(38) Richardson, J. S.; Richardson, D. C. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 2754−2759.

(39) Fink, B. E.; Kym, P. R.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1998**, *120*, 4334−4344.

(40) Wilson, S. R.; Sawicki, R. A. *J. Org. Chem.* **1979**, *44*, 287−291.

(41) Bianchi, G.; Chiarini, M.; Marinelli, F.; Rossi, L.; Arcadi, A. *Adv. Synth. Catal.* **2010**, *352*, 136−142.

(42) Padwa, A.; Hasegawa, T.; Liu, B.; Zhang, Z. *J. Org. Chem.* **2000**, *65*, 7124−7133.

(43) Hu, T.; Liu, K.; Shen, M.; Yuan, X.; Tang, Y.; Li, C. *J. Org. Chem.* **2007**, *72*, 8555−8558.

(44) Fujita, M.; Kitagawa, O.; Suzuki, T.; Taguchi, T. *J. Org. Chem.* **1997**, *62*, 7330−7335.

(45) Detert, H.; Anthony-Mayer, C.; Meier, H. *Angew. Chem., Int. Ed.* **1992**, *31*, 791−792.

(46) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

DOI: 10.1021/acs.joc.5b00237
J. Org. Chem. 2015, 80, 4904−4918