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Evolution of a Protecting-Group-Free Total Synthesis: Studies en Route to the Neuroactive Marine Macrolide (−)-Palmyrolide A

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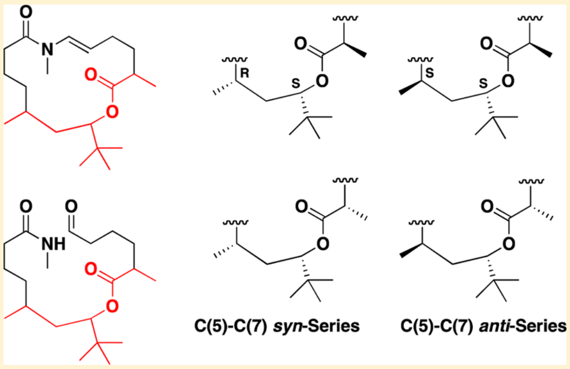
Supporting Information

ABSTRACT: A full account of our synthetic work toward the first total synthesis of the neuroactive marine macrolide (−)-palmyrolide A is described. Our first-generation approach aimed to unlock the unknown C(5)−C(7) stereochemical relationship via the synthesis of four diastereomers of palmyrolide A aldehyde, a known degradation product. When these efforts provided inconclusive results, recourse to synthesizing all possible stereocombinations of the 15-membered macrolide was undertaken. These studies were critical in confirming the absolute stereochemistry, yielding the first total synthesis of (+)-*ent*-palmyrolide A. Subsequent to this work, the first protecting-group-free total synthesis of natural (−)-palmyrolide A is also reported.



■ INTRODUCTION

In 2010, Gerwick and co-workers reported the isolation and structural elucidation of palmyrolide A [(−)-**1**],[1] a neuroactive macrolide found in a cyanobacterial assemblage composed of *Leptolyngbya* and *Oscillatoria* species collected in the Northern Pacific at Palmyra Atoll. Initial biological studies revealed **1** to be a potent inhibitor of calcium ion oscillations in murine cerebrocortical neurons and to possess a sodium ion channel blocking ability in neuroblastoma cells.[1] Importantly, (−)-palmyrolide A displays no appreciable cytotoxicity when screened against human lung adenocarcinoma cells.[1]

The connectivity of (−)-palmyrolide A was determined by detailed NMR studies.[1] However, as a result of the increased hydrolytic stability imparted to the lactone due to the neighboring *tert*-butyl group, the authors were unable to degrade the macrolide into acyclic fragments that would prove useful in determining the absolute stereochemistry. As a result, the Murata *J*-based configurational analysis[2] was applied to the 15-membered macrocycle in order to determine the relative stereochemistry between the C(5) methyl and the C(7) *tert*-butyl centers. This data, in conjunction with NOE correlations, suggested that the relationship between C(5) and C(7) was *syn*. An important detail to emerge from these degradation/hydrolysis studies is that the authors were able to induce ring-opening of the macrolide to yield palmyrolide A aldehyde (cf. **2** or **3**, Scheme 1).[1]

We became interested in (−)-palmyrolide A as a synthetic target not only because of its interesting biological profile but also due to the presence of two unique structural elements: the rare *tert*-butyl moiety and the *trans*-*N*-methyl enamide. A search of the literature reveals few examples of isolated natural products that contain a sterically encumbered *tert*-butyl group *α* to the lactone ester,[3] with (−)-apratoxin A[3a] being the sole example confirmed by total synthesis.[4] It should be noted that, for apratoxin, (1) the relative stereochemistry between its C(37) methyl and C(39) *tert*-butyl is *anti*,[5a] and (2) this stereochemical relationship was first proposed employing the Murata *J*-based configurational analysis on the macrocycle, and later confirmed by total synthesis.

N-Methyl enamide macrocycles[3b−d] are exceedingly rare in the natural product literature, with few reported examples; until recently,[6] none have been confirmed by total synthesis. Of note, these compounds all contain a *tert*-butyl group *α* to the lactone ester within their molecular framework and are likely derived from the same genus of cyanobacteria. A related family of macrolides possesses an *N*-H enamide,[7] although with *cis*-olefin geometry. Several other compounds have side chains decorated with *N*-H enamides;[8] however, to the best of our knowledge, only one class features an *N*-methyl enamide subunit.[8f]

Because of the uncertainty regarding the absolute configuration of palmyrolide A, at the outset of our synthetic campaign, we decided to target all possible C(5)−C(7) diastereomeric combinations. While Gerwick identified the relative configuration between the C(5) methyl and the C(7) *tert*-butyl to be *syn*, based on the apratoxin A literature,[3a,4] we believed that the relationship between these two groups could also be *anti*. During the design of our first-generation synthetic route, and after noting the scant literature references regarding the formation of enamide-containing macrocycles,[9] we sought to first determine the unknown absolute stereochemistry of **1** by synthesizing all possible diastereocombinations of palmyrolide A aldehyde, a compound we believed to be an easier to achieve subgoal, and whose three stereocenters were anticipated to be identical to the

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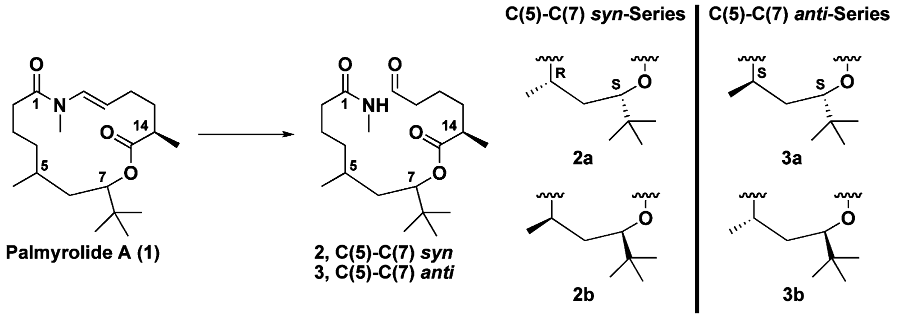
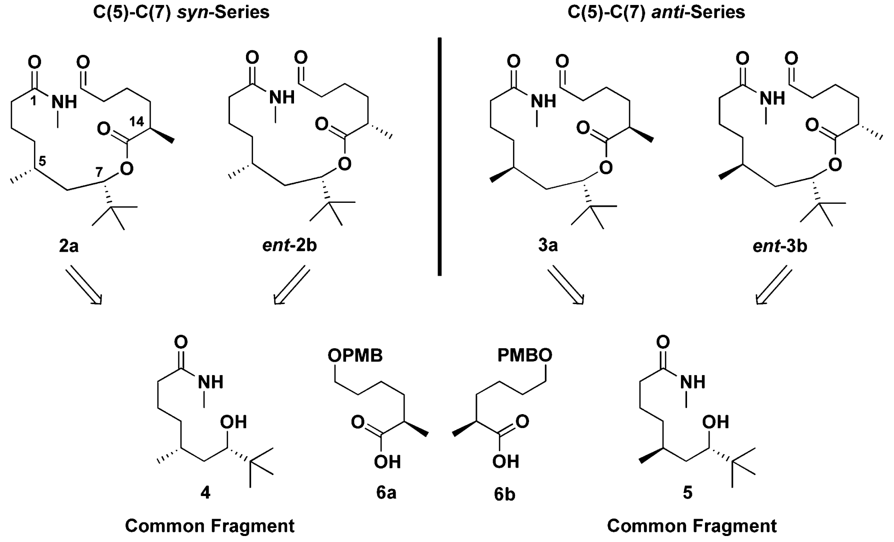
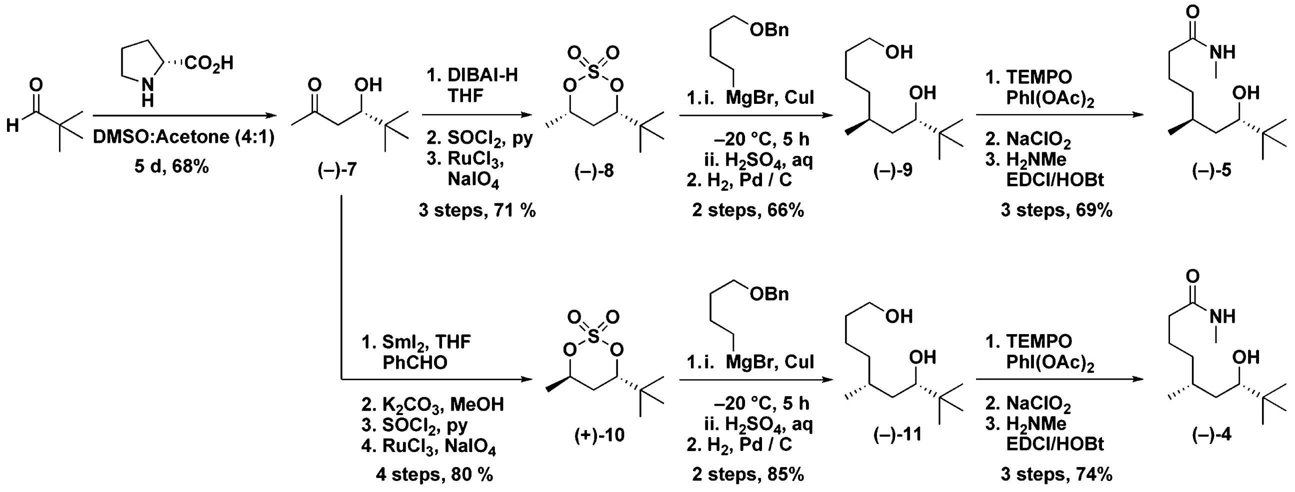
Scheme 1. Stereochemical Combinations of Natural Palmyrolide A Aldehyde



Scheme 2. Retrosynthetic Analysis



Scheme 3. Divergent Syntheses of Fragments 4 and 5

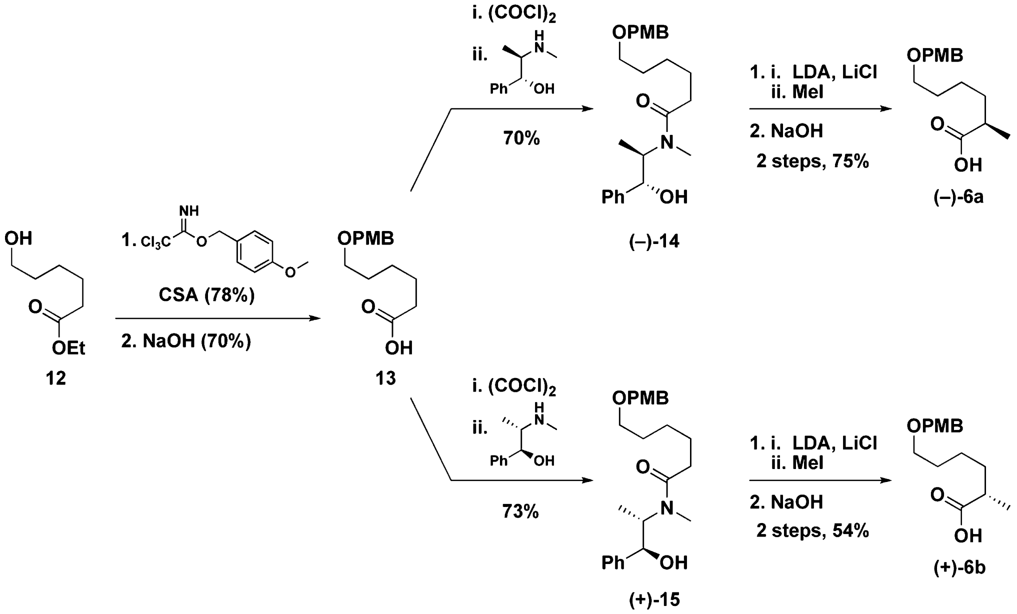


macrolide. Once the correct stereochemistry had been assigned, our plan was to then target only the *N*-methyl enamide macrocycle that would correspond to the correct structure of palmyrolide A.

■ RESULTS AND DISCUSSION

Aldehyde Studies. In the isolation report, the absolute stereochemistry of the C(14)[5b] methyl group was unequivocally assigned to be in the *R* configuration.[1] This is a critical point, and we used it to our advantage in planning a unique synthetic strategy aimed to target the different stereocombinations concurrently. Rather than design our synthesis around the known C(14) center, we thought that a more economical approach would be to target only one C(5)−C(7) *syn* enantiomer and one C(5)−C(7) *anti* enantiomer, and then pair each of these with the two stereochemical combinations of the C(14) methyl. In this way, we would utilize a common fragment for each series (cf. **4** and **5**) to gain access to all four

Scheme 4. Synthesis of Acids 6a and 6b



possible diastereomeric combinations of palmyrolide A aldehyde (cf. **2a**, *ent*-**2b**, **3a**, *ent*-**3b**, Scheme 2), representing one *seco*-aldehyde from each enantiomeric set. We chose to set C(7) in the (*S*) arrangement to coincide with the absolute stereochemistry found in an analogous position in apratoxin A.

For the syntheses of fragments **4** and **5**, we relied on elegant chemistry developed by Cavelier and co-workers[10] during their recent synthesis of oxoapratoxin, an oxazoline analogue of apratoxin A. The syntheses of fragments **4** and **5** commenced with a D-proline-catalyzed asymmetric aldol union between pivaldehyde and acetone to furnish *β*-hydroxy ketone (−)-**7**, following the known literature account (Scheme 3).[10] This reaction was critical in establishing the C(7) *tert*-butyl stereocenter and is the point at which the synthesis of the *syn* diastereomer diverged from the *anti*.

In the Cavelier studies,[10] stereoselective *syn* reduction of (−)-**7** was affected using diethylmethoxyborane/NaBH$_4$,[11] which provided an acceptable mixture of *syn* and *anti* diastereomers (95:5). Unfortunately, in our hands, this reduction strategy did not yield a synthetically workable mixture of isomers. Chromatographic separation also proved difficult. Pleasingly, recourse to the stereoselective Kiyooka reduction using 2.5 equiv of DIBAl-H[12] provided the requisite diol in excellent yield and high diastereoselectivity (Scheme 3). This modification also obviated the need for a challenging silica gel purification step. Next, in two synthetic operations involving (1) treatment with thionyl chloride in pyridine and (2) oxidation using RuO$_4$,[13] the *syn*-diol was easily converted into *syn*-cyclic sulfate (−)-**8** in good overall yield.

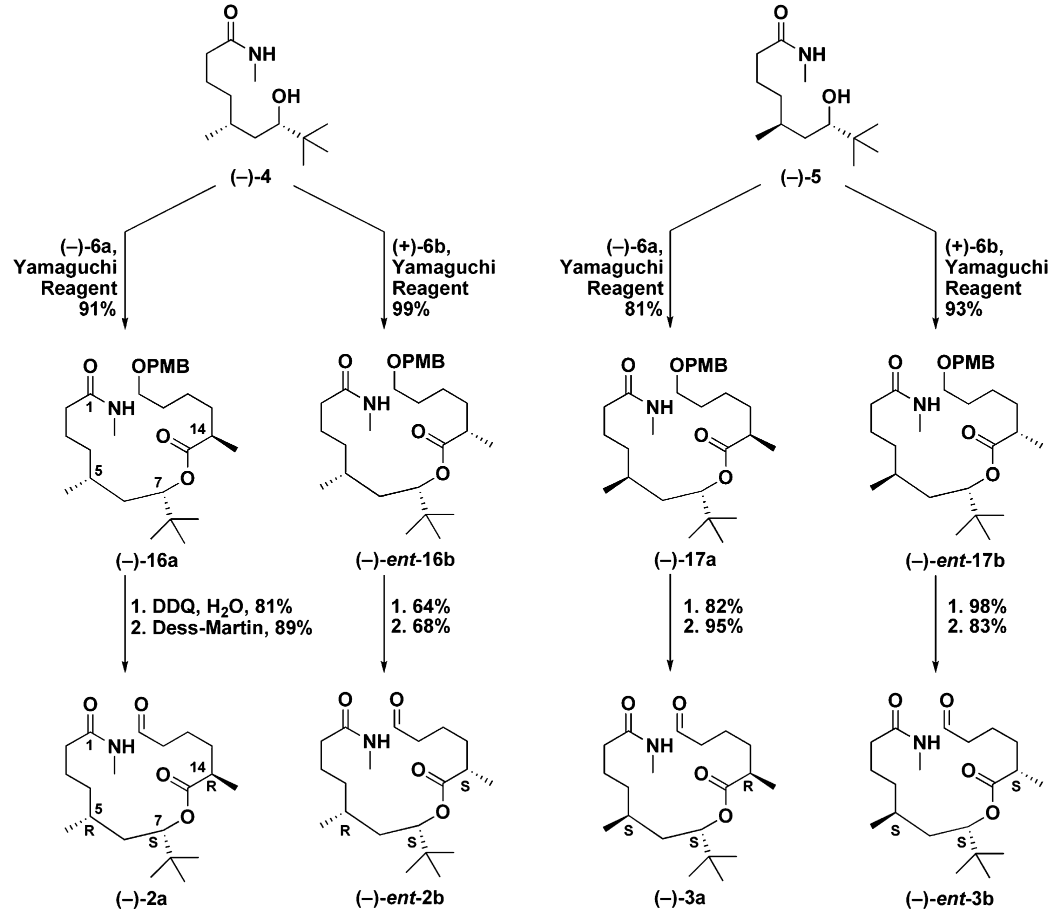
To synthesize *anti*-cyclic sulfate (+)-**10**, we relied on the Evans−Tishchenko reduction[14] using freshly prepared samarium(II) iodide in THF,[15] which provided the requisite *anti*-diol stereochemistry in greater than 99% diastereoselectivity. Unfortunately, the one-step Evans tetramethylammonium triacetoxyborohydride [Me$_4$NHB(OAc)$_3$] method[16] produced diastereomeric mixtures that were difficult to separate (vide supra). The Evans−Tishchenko reduction, while necessitating an extra synthetic operation (i.e., hydrolysis), was useful in providing high yields of the *anti*-diol precursor. Hydrolysis of the benzoyl ester, followed by sulfite formation and oxidation, provided *anti*-cyclic sulfate (+)-**10** in comparable yield to (−)-**8** (Scheme 3).

Nucleophilic ring-opening of the *syn*-cyclic sulfate using a mixed organometallic reagent derived from allylmagnesium chloride and copper(I) iodide has already been documented to occur at the least-hindered site,[10] resulting in complete inversion of configuration at that center. During our first-generation synthesis, we found that a Grignard derived from commercially available benzyl-4-bromobutyl ether, using copper(I) iodide as catalyst, could also serve as an efficient nucleophile in this process. Pleasingly, ring-opening and subsequent hydrogenolysis of *syn*-(−)-**8** occurred in good overall yield and provided *anti*-diol (−)-**9** as a single diastereomer (Scheme 3).

We believed that nucleophilic ring-opening of *anti*-(+)-**10** using the same mixed organometallic species would likewise produce the analogous *syn*-alcohol; however, there have been no literature reports of such a reaction. In the event, ring-opening, followed by hydrogenolysis, led to the formation of *syn*-diol (−)-**11** as a single regioisomer and in >99% diastereoselectivity (Scheme 3). We believe this to be the first example of the nucleophilic ring-opening of an *anti*-1,3-cyclic sulfate.

At this stage, the chemistry employed for the construction of either amide **4** or **5** was the same for both the *syn* and the *anti* series. Chemoselective oxidation of the primary alcohol with TEMPO/PhI(OAc)$_2$,[17] followed by Pinnick (Lindgren−Kraus)[18] oxidation, obviated the need for excessive protecting group manipulations, and afforded both carboxylic acids in good yield (Scheme 3). In the final step, each acid was separately transformed into the respective secondary amide [cf. (−)-**5** and (−)-**4**, Scheme 3] via treatment with methylamine and EDCI/HOBt. Amide formation proceeded smoothly and occurred with no lactone byproduct formation resulting from the undesired nucleophilic attack of the pendant alcohol on the activated carbonyl eight atoms away. We believe this to be due to (1) sterics surrounding the alcohol as a result of the neighboring *tert*-butyl group and (2) the enhanced nucleophilicity of methylamine compared to the secondary alcohol. Of note, the only protecting group employed during the synthesis of fragments

Scheme 5. Synthesis of All Four Diastereomeric Combinations of Palmyrolide A Aldehyde



(−)-**4** and (−)-**5** was the benzyl ether required during the ring-opening operation.

We next turned our attention to the synthesis of enantiomer acids **6a** and **6b** (Scheme 4); each could be easily prepared relying on the Myers pseudoephedrine method[19] to install the requisite stereochemistry at what will become the C(14) site. Commercially available alcohol **12** was first protected as a *p*-methoxybenzyl ether[20] and then saponified to yield acid **13**[20b] (Scheme 4). Treatment with oxalyl chloride, followed by (*R*,*R*)-pseudoephedrine, led to amide (−)-**14**, which could be selectively alkylated with iodomethane and hydrolyzed to produce acid (−)-**6a** in good yield and in high enantioselectivity. In a similar manner, **13** could be converted to the acid chloride, reacted with (*S*,*S*)-pseudoephedrine and the resultant amide [(+)-**15**] subjected to the same alkylation/hydrolysis protocol to produce acid (+)-**6b** (Scheme 4). It is also possible to synthesize amide (−)-**14** directly from the PMB-protected ethyl ester. Direct displacement using the disodium salt of (*R*,*R*)-pseudoephedrine gave the desired product in 73% yield. While this yield is higher, it required the use of 2 equiv of the PMB-protected version of **12**, a compound that was difficult to manufacture in pure form. The two-step method [(1) saponification, (2) i. acid chloride formation, ii. addition of (*R*,*R*)-pseudoephedrine], while time-consuming, allowed us to conserve precious starting material with only a modest loss in yield (~25% overall).

We now had the necessary fragments in hand to assemble the four diastereomeric combinations of palmyrolide A aldehyde. This required the combination of alcohols (−)-**4** and (−)-**5** separately with acid (−)-**6a** and then with acid (+)-**6b** (Scheme 5). We found this to be readily achieved by first forming anhydrides via premixing each acid with 2,4,6-trichlorobenzoyl chloride (the Yamaguchi reagent),[21] and then adding these to their respective alcohol coupling partners (Scheme 5). In this way, we were able to manufacture amides (−)-**16a**/(−)-*ent*-**16b** and (−)-**17a**/(−)-*ent*-**17b** (Scheme 5). For the conversion to *seco*-aldehydes, each amide was separately treated with DDQ/H_2O, followed by alcohol oxidation with the Dess−Martin periodinane[22] (Scheme 5). Using this route, we were able to synthesize the two C(5)−C(7) *syn* combinations [cf. (−)-**2a** and (−)-*ent*-**2b**], and the two C(5)−C(7) *anti* [cf. (−)-**3a** and (−)-*ent*-**3b**], representing one aldehyde from each enantiomeric set.

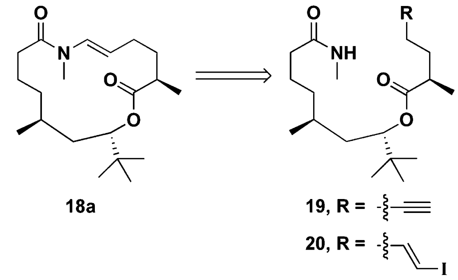
As each aldehyde was synthesized, we compared its ^1H NMR spectrum with the authentic palmyrolide A aldehyde spectrum reported by Gerwick.[1] An examination of the spectra showed that the synthetic C(5)−C(7) *syn*-aldehydes had major discrepancies with the reported aldehyde spectrum; the C(5)−C(7) *anti* series were a closer match. On the basis of this data, we believed that the relative stereochemistry between C(5) and C(7) could, in fact, be *anti*, contrary to the studies documented in the isolation report.[1] To distinguish between the two *anti*-aldehydes, which were very similar by ^1H NMR, we considered the *J*-coupling data for the C(7)−H. In the Gerwick report, this proton is split into a doublet of doublets with coupling constants of 2.2 and 9.8 Hz. The *J* values of aldehyde (−)-**3a** are 2.7 and 9.3 Hz; (−)-*ent*-**3b** has coupling constants of 3.6 and 8.4 Hz.

The chemical shift information, in conjunction with the coupling data, seemed to suggest that aldehyde (−)-**3a** was the best fit to the literature values. However, we were not confident that it was a close enough match to claim we had solved the stereochemical issue.[23] We were encouraged that, for (−)-**3a**, the C(14)-methyl was in the *R* configuration, matching what Gerwick determined in the isolation report,[1] and the stereochemistry at C(5) and C(7) matched the absolute stereochemistry found in apratoxin A.[3a,4] However, rather than risk assigning the absolute stereochemistry of palmyrolide A based on these data, we decided it would be in our best interest to unambiguously determine the stereochemistry via synthesis of the macrolide corresponding to aldehyde (−)-**3a**.

Cyclization Studies 1. After attempts at a dehydrative cyclization of (−)-**3a**,[24] we next sought to transform the aldehyde into a *trans*-vinyl triflate, which we believed would be an optimal coupling partner with the pendant secondary amide. Unfortunately, efforts to form the vinyl triflate, using known methods,[25] only resulted in the complete decomposition of starting material. When these studies did not prove feasible, a redesign of the ring-closing strategy was undertaken.

Our first thought was that cyclization to form the *trans-N*-methyl enamide could be affected exploiting an intramolecular version of the well-studied Goossen ruthenium-catalyzed conditions[26] to unite a secondary amide with a terminal alkyne. Unfortunately, when we synthesized alkyne **19**, and treated it with the optimized reaction conditions, using [Ru(methallyl)$_2$(COD)] as catalyst,[26a] no macrolide product was observed (Scheme 6). According to Goossen, the mechanism for the amide/alkyne union is proposed to involve the oxidative addition of the amide nitrogen onto the metal, followed by insertion of the alkyne and subsequent formation of a vinyl−ruthenium complex. This intermediate rearranges into a ruthenium−vinylidene species before migration of the amide occurs, followed by reductive elimination. We believe that formation of the vinyl ruthenium or the vinylidene intermediate in our cyclic system may require too high a strain barrier. This may be the reason we observed no desired macrolide product.

Scheme 6. Retrosynthetic Analysis of Our First-Generation Cyclization Studies

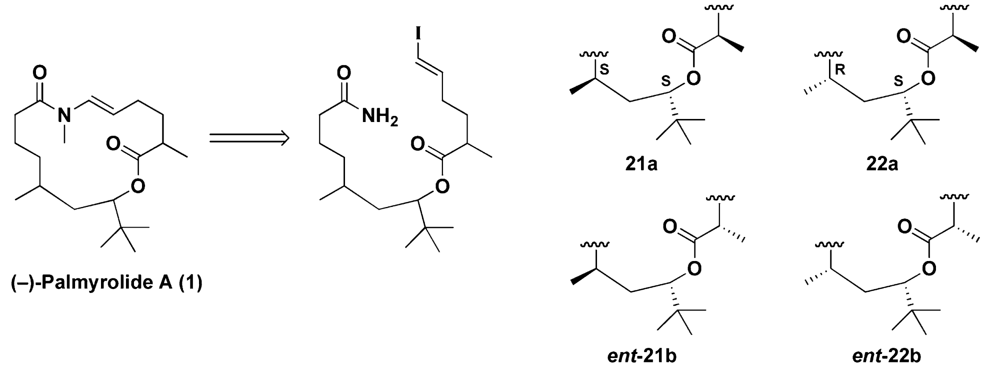


We then turned our attention to the possible union of the secondary amide with a pendant vinyl iodide coupling partner (cf. **20**, Scheme 6). This strategy would call upon a metal-catalyzed process to unite the vinyl iodide with the amide. Unfortunately, when we treated vinyl iodide **20** under palladium-catalyzed conditions,[27] using Pd(dba)$_3$/*t*-bu-XPhos,[27b] no cyclization occurred. The failure in this process may be due to the methyl substituent on the reacting nitrogen of the amide. While *N*-methyl amides have been documented to be competent coupling partners for Pd-catalyzed C−N bond forming processes,[27] primary amides are superior when using copper catalysis. Therefore, we decided to synthesize the corresponding vinyl iodide/primary amide macrocyclization precursor and attempt a copper-promoted strategy, similar to a method recently reported by Evano and co-workers.[9c] This route proved successful (vide infra).

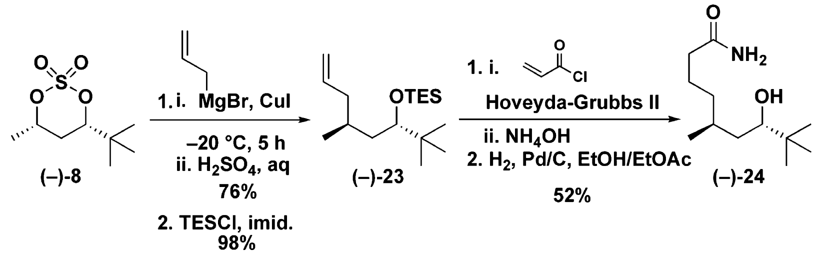
Cyclization Studies 2. After the disappointing attempts at enamide formation, we turned our attention to the production of a primary amide-containing macrocyclization precursor (cf. **21a**, Scheme 7). This strategy would require the synthesis of amide **24**, a compound similar to (−)-**5**, differing only in substitution at the amide nitrogen (Scheme 8). The synthesis of this fragment was straightforward and made use of the Cavelier precedent[10] for the construction of TES-protected alcohol (−)-**23** from *syn*-cyclic sulfate (−)-**8**. We chose to switch from 4-benzyloxybutylmagnesium bromide (Scheme 3) to allylmagnesium bromide (Scheme 8) because this approach would potentially shave off one linear operation from the overall synthetic route (deprotection). Cross metathesis of (−)-**23** with freshly distilled acryloyl chloride employing the Hoveyda−Grubbs II precatalyst,[28] followed by in situ addition of ammonium hydroxide, allowed access to the α,β-unsaturated primary amide in 58% yield.[29] This product was easily converted to amide alcohol (−)-**24** via hydrogenation, which occurred, due to solvent effects, with concomitant loss of the labile triethylsilyl group[30] (Scheme 8).

With the necessary fragment in hand [(−)-**24**], we turned our attention to the construction of vinyl iodide **28** (Scheme 9). The synthesis began employing known alcohol **25**, produced in three literature operations from commercially available 3-butyn-1-ol.[31] Alcohol-to-iodide interconversion proceeded in high yield, and the resultant diiodide (**26**) was used in the Myers alkylation[19]

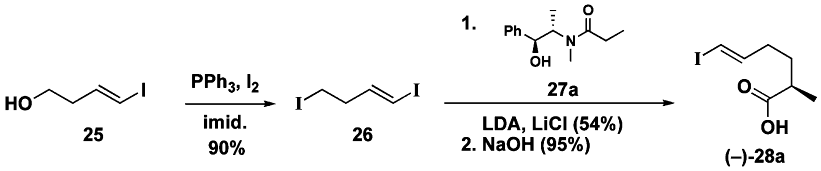
Scheme 7. Retrosynthetic Analysis of Our Second-Generation Cyclization Studies



Scheme 8. Synthesis of the C(5)−C(7) *anti* Primary Amide



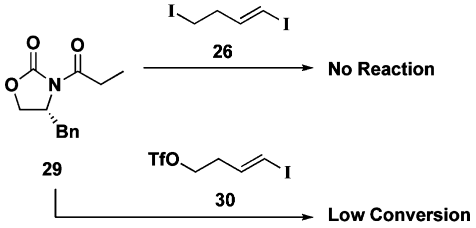
Scheme 9. Synthesis of Vinyl Iodide 28



with (*S*,*S*)-propionamide (**27a**), which produced the desired product in good yield and high diastereoselectivity (>20:1 by ^{1}H NMR). Subsequent hydrolysis with NaOH provided acid (−)-**28a** with negligible loss of stereopurity, and complete preservation of the *trans*-vinyl iodide unit.[32]

Earlier attempts to manufacture iodide (−)-**28a** employed the Evans oxazolidinone[33] as a chiral auxiliary (cf. **29**, Scheme 10).

Scheme 10. Unsuccessful Alkylation Attempts

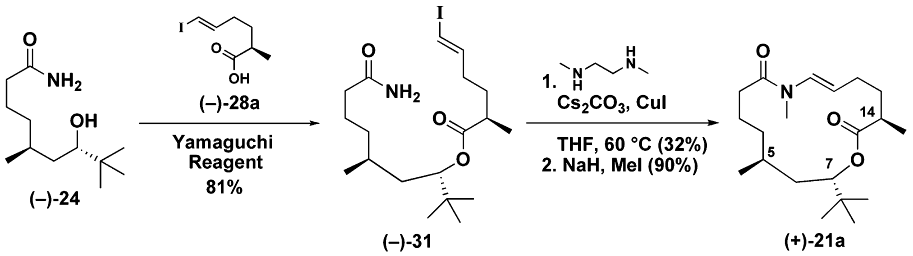


Unfortunately, when **29** was treated with NaHMDS, followed by diiodide **26**, no reaction was observed (Scheme 10). When **26** was replaced by triflate **30**,[34] we did observe alkylation;[35] however, the yield was low and the product obtained was contaminated with a significant amount of starting material, which could not be separated by silica gel chromatography (Scheme 10).

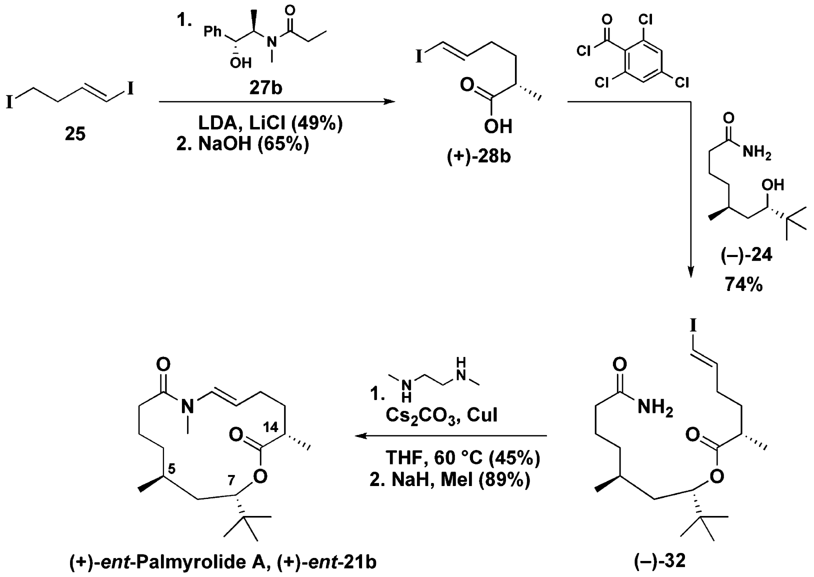
Similar to our aldehyde studies (vide supra), union of amide alcohol (−)-**24** with (−)-**28a**, employing 2,4,6-trichlorobenzoyl chloride as a coupling agent, provided vinyl iodide (−)-**31** in good yield (Scheme 11). For the critical macrocyclization step, we relied on the intramolecular copper(I) iodide/Cs_2CO_3/*N*,*N*′-dimethylethylenediamine conditions exploited by Evano and coworkers during their recent synthesis of the 13-membered cyclopeptide paliurine F.[9c] Even though paliurine F features a *cis*-*N*-H enamide, we believed that these optimized conditions could also be used for the construction of a *trans*-*N*-H enamide within the larger macrocycle of palmyrolide A. Formation of the 15-membered macrocycle, using a high-dilution modification (0.01 M) to coupling conditions developed by Buchwald,[36] afforded the *trans*-*N*-H enamide product in modest yield and as a mixture of rotational isomers. In the final step, treatment with sodium hydride, followed by N-alkylation with iodomethane,[26c] provided *trans*-*N*-methyl enamide (+)-**21a** in excellent yield (Scheme 11).

A comparison with the reported spectra of palmyrolide A was made. Compound (+)-**21a**, featuring the natural C(14)-*R* stereochemistry, did not match the literature values reported by Gerwick for the 15-membered macrolide.[1] This was a suprising result, especially since this macrolide stereochemistry corresponded directly with aldehyde (−)-**3a**, which seemed to be the best fit of the Gerwick aldehyde data (vide supra). Undeterred, we decided to quickly invert the stereochemistry at C(14) and manufactured the macrolide that would correspond to aldehyde (−)-*ent*-**3b**. This was accomplished via (1) synthesis of vinyl iodide (+)-**28b** exploiting the Myers alkylation, (2) joining this fragment with *anti*-(−)-**24**, and then subjecting the resultant amide [(−)-**32**] to the same end game protocol as was employed for (+)-**21a** (Scheme 12). Pleasingly, there was a complete ^{1}H and ^{13}C NMR match with macrolide (+)-*ent*-**21b**, where the C(14) methyl group is inverted relative to the natural macrolide. On the basis of the known configuration at this center, this would mean that our palmyrolide should be enantiomeric to the natural product: optical rotation comparison confirmed that we had indeed synthesized the enantiomer of (−)-palmyrolide A,

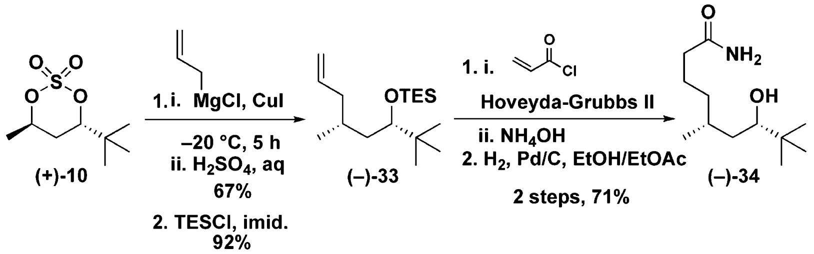
Scheme 11. Synthesis of *anti*-Macrolide 21a



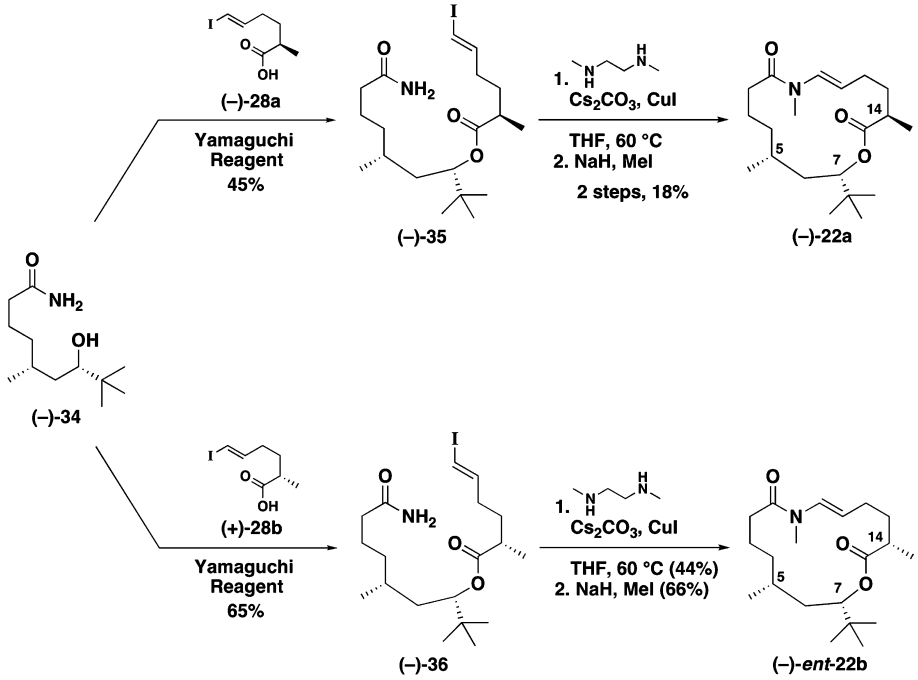
Scheme 12. Synthesis of *anti*-Macrolide *ent*-21b



Scheme 13. Synthesis of the C(5)−C(7) *syn* Primary Amide



Scheme 14. Synthesis of Both C(5)−C(7) *syn*-Macrolides



(+)-*ent*-palmyrolide A {$[\alpha]_D$ = +23 (c = 0.65, $CHCl_3$), lit. $[\alpha]_D$ = −29 (c = 0.9, $CHCl_3$)}.

These data reveal that the relative stereochemistry between the C(5) methyl and C(7) *tert*-butyl centers is *anti*, and not *syn*, as originally proposed by Gerwick.[1,6] Also of interest, the absolute stereochemistry between these two sites is enantiomeric to the absolute stereochemistry found in an analogous location in apratoxin A.[3a,4]

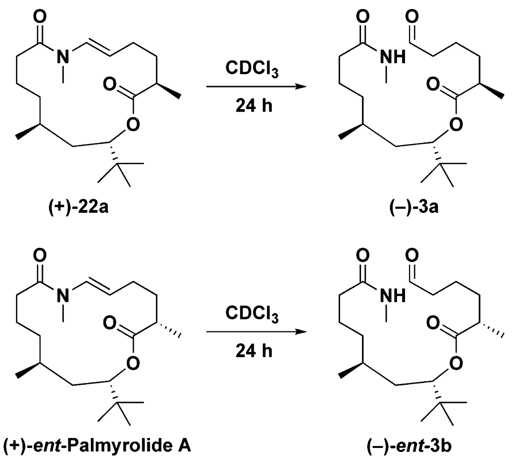
While working on the C(5)−C(7) *anti*-macrolides, we were also simultaneously synthesizing the C(5)−C(7) *syn* series (vide infra). At the time, we were still uncertain if our aldehyde studies had been correct in allowing us to assign the relative stereochemistry as *anti*, especially in light of the Gerwick NOE and *J*-based coupling analysis, which suggested a *syn* relationship. The synthesis of the requisite C(5)−C(7) *syn*-amide (cf. **34**) was accomplished, utilizing similar chemistry as before (Scheme 13). Once in hand, amide (−)-**34** was separately joined with acids (−)-**28a** and (+)-**28b**, and subjected to macrocyclization/*N*-methyl formation, producing (−)-**22a** and (−)-*ent*-**22b**, respectively (Scheme 14).

As anticipated, the C(5)−C(7) *syn*-macrolides did not match the NMR data provided in the isolation report. The most diagnostic peak was the C(7) methine proton: for natural (−)-palmyrolide A, the chemical shift is δ 4.88 ppm and the signal is split into a doublet of doublets with coupling constants of 1.5 and 11.0 Hz. For (−)-**22a**, the value we observed was δ 4.79 ppm (J = 0.3, 9.9 Hz), and for the all-*syn* diastereomer, (−)-*ent*-**22b**, the value was δ 4.86 ppm (J = 0.9, 10.2 Hz).

Stability Studies. After unambiguously determining the relative and absolute stereochemistry of palmyrolide A, we were still intrigued that our aldehyde spectra did not perfectly correlate with the degradation spectrum reported by Gerwick. Our studies seemed to suggest that the best match to the macrolide would be the relative stereochemistry contained in aldehyde (+)-**3a**; however, through total synthesis, we learned that this did not map onto the natural macrolide stereochemistry. Our initial thought was that the synthetic experiments employed to set the absolute stereochemistry in our aldehyde series were incorrect; this line of reasoning was quickly ruled out. Upon sitting in aged chloroform overnight, the *trans*-*N*-methyl enamide moiety rapidly hydrolyzes to the corresponding aldehyde. A comparison of (−)-**3a** and *ent*-(−)-**3b** formed in this manner (Scheme 15) to the corresponding aldehydes prepared via synthesis (Scheme 5) revealed a perfect match in each case, meaning our stereochemical assignments had been sound.

We next decided to study the isolation report in greater detail.[1] After close examination of the conditions used to degrade palmyrolide A into palmyrolide A aldehyde, we reasoned that ring-opening of natural palmyrolide A could also be accompanied by epimerization at the C(14) site. In this way, we might be able to argue the discrepancy observed between our aldehyde and macrolide series. To test this hypothesis, a simple epimerization experiment with concentrated HCl in methanol would demonstrate how palmyrolide A aldehyde could invert the stereochemistry at C(14). Unfortunately, after replicating the same conditions found in the Gerwick account (6N HCl/MeOH),[1] we were not able to observe any evidence to suggest that aldehyde *ent*-(−)-**3b** could convert into (−)-**3a**.

Scheme 15. Trace-Acid-Catalyzed Ring-Opening



We now speculate that there may be a concentration dependence giving rise to the minor anomalies observed via NMR. Another explanation may be that some unknown impurity in the authentic sample could produce a hydrogen-bonding effect that would cause the molecule to twist in such a way as to alter the chemical shift and coupling values slightly relative to our pure, synthetic compounds.[23] Unfortunately, at this stage, we do not have strong evidence to support either argument. However, we do know the absolute stereoidentities of the aldehydes prepared via synthesis, and those formed via ring-opening at the enamide site; neither are a perfect match to the Gerwick aldehyde data.

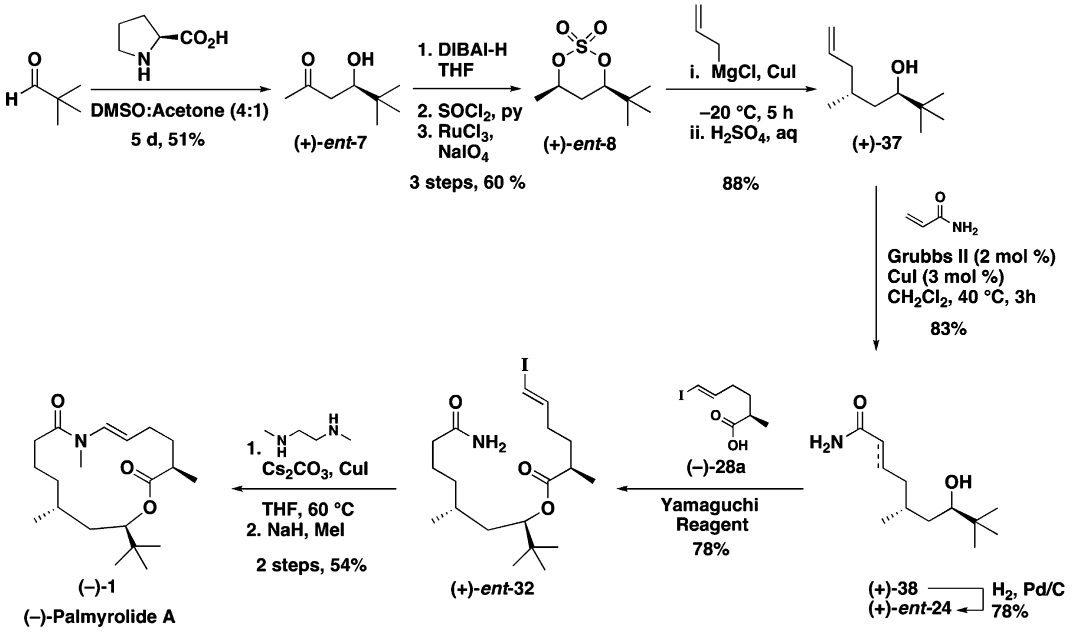
Second-Generation Synthesis. After the successful completion of the first phase of our work, namely, the determination of the relative stereochemistry of palmyrolide A, we set out to confirm the absolute stereochemistry via total synthesis of the natural (−)-enantiomer. We also took this opportunity to address two shortcomings of our initial route: the overall number of steps and the low-yielding cross-metathesis processes.[37]

To manufacture the (−)-enantiomer of palmyrolide A, our second-generation approach would exploit L-proline in the initial organo-catalyzed asymmetric aldol union to set the stereochemistry at the C(7) *tert*-butyl site as *R* (Scheme 16). Similar to our earlier studies, stereoselective Kiyooka *syn* reduction of (+)-*ent*-**7** was affected using 2.5 equiv of DIBAl-H, which provided the requisite diol in good yield and high diastereoselectivity (Scheme16). The *syn*-cyclic sulfate [(+)-*ent*-**8**] could be made in a similar fashion as (−)-**8**, and nucleophilic ring-opening using the mixed organometallic reagent derived from allylmagnesium chloride and copper(I) iodide was critical in allowing access to the natural C(5)−C(7) *anti*-stereochemical combination [cf. (+)-**37**, Scheme 16].

In our first-generation synthesis, the alcohol was protected as a triethylsilyl-ether before cross-metathesis with acryloyl chloride (Scheme 8). Wanting to obviate the need for any protecting groups in our second-generation approach, we decided to attempt cross-metathesis directly on alcohol (+)-**37**. This strategy would be extremely difficult using acryloyl chloride, as we anticipated that the free alcohol at C(7) would readily react with the acid chloride that is employed in an excess amount. By substituting acryloyl chloride with acrylamide, we would avoid the possibility of alcohol protection and directly arrive at the requisite amide product (cf. **38**) in a single synthetic operation.

In the event, cross-metathesis between (+)-**37** and acrylamide, using the Grubbs II precatalyst (5 mol %) in dichloroethane at 70 °C, gave smooth conversion to the desired amide after 18 h; however, the yield for this process was moderate (52%). Regardless, this modification had allowed us to operate directly on free alcohol (+)-**37**. Encouraged by this result, we decided to employ copper(I) iodide as cocatalyst (2 mol % Grubbs II, 3 mol % CuI, Scheme 16), calling upon the recently reported studies of Lipshutz and co-workers.[38] This modification was critical in allowing us to lower the catalyst loading using a moderately unreactive coupling partner (acrylamide) and achieve a high yield of the desired amide product [cf. (+)-**38**, 83% isolated, 92% by ^{1}H NMR] in only 3 h.[39] To the best of our knowledge, we believe this to be the first reported example of a cross-metathesis

Scheme 16. Second-Generation Synthesis Applied to (−)-Palmyrolide A



reaction using acrylamide under the modified Lipshutz CuI conditions.[40,41]

Hydrogenation of (+)-**38**, followed by union of (+)-*ent*-**24** with acid (−)-**28a**, led to the formation of macrocyclization precursor (+)-*ent*-**32**, which was smoothly closed to the *N*-H enamide using the modified Buchwald conditions.[42] In the final step, N-alkylation using sodium hydride/iodomethane allowed access to the natural enantiomer, (−)-palmyrolide A $\{[\alpha]_D = -27$ (c = 0.86, $CHCl_3$), lit. $[\alpha]_D = -29$ (c = 0.9, $CHCl_3$)$\}$. Of signifigant note, this second-generation synthesis employs no protecting groups[43] and allows access to the desired macrolide in only 10 linear steps, with 7% overall yield.

In summary, we have described efficient total syntheses for both natural (−)-palmyrolide A and its optical enantiomer, (+)-*ent*-palmyrolide A, the former being accomplished for the first time. *En route* to this structurally interesting, biologically active molecule, we have also revealed the syntheses of all four possible stereocombinations of palmyrolide A aldehyde and three additional diastereocombinations of the palmyrolide A macrolide. Critical to the success of this work was the first reported application of the Buchwald CuI/Cs_2CO_3/*N*,*N*′-dimethylethylenediamine strategy to form a 15-membered macrocycle at the *trans*-*N*-H enamide junction. Also of note, the first use of acrylamide as a competent cross-metathesis partner, using the CuI/Grubbs II precatalyst conditions of Lipshutz, allowed us to achieve an efficient, protecting-group-free synthesis in only 10 linear operations. Future work from our laboratory will focus on analogue development, as well as the synthesis of a related family of enamide-containing natural products.

■ EXPERIMENTAL SECTION

General Remarks. Unless otherwise noted, reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Reaction solvents (CH_2Cl_2, THF, and Et_2O) were purified before use in a solvent purification system under a flow of dry nitrogen. Dimethylsulfoxide (DMSO) and toluene were distilled from CaH_2. All other solvents and reagents were purchased from commercial suppliers and used as received, unless otherwise specified. Thin-layer chromatography (TLC) was performed using plates precoated with silica gel 60 Å F-254 (250 μm) and visualized by UV light, $KMnO_4$, or anisaldehyde stains, followed by heating. Silica gel (particle size = 40−63 μm) was used for flash chromatography. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or at 400 and 100 MHz, respectively, and are reported relative to residual solvent peak (δ 7.26 and δ 77.0 for ^{1}H and ^{13}C in $CDCl_3$). Data for ^{1}H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Spectra obtained are described using the following abbreviations: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. IR samples were prepared by evaporation from $CHCl_3$ or CH_2Cl_2 on NaCl plates. High-resolution mass spectra were obtained using positive electrospray ionization.

(*S*)-4-Hydroxy-5,5-dimethylhexan-2-one [(−)-7)]. (−)-**7** was prepared following the literature procedure of Cavelier and co-workers. A screw-top flask was charged with pivaldehyde (5.89 mL, 54.3 mmol) and D-proline (2.50 g, 21.7 mmol) dissolved in DMSO (183.0 mL) and reagent grade acetone (51.0 mL). The reaction flask was then sealed, and the mixture was allowed to stir for 5 days at room temperature before being quenching with a half-saturated NH_4Cl solution (100 mL). The reaction mixture was then extracted with EtOAc, dried over $MgSO_4$, filtered, and concentrated to afford crude aldol product (−)-**4**, which was purified by flash column chromatography (4:1 hexanes/EtOAc) to afford 5.28 g (68%) of a slightly yellow oil. ^{1}H, ^{13}C, and optical rotation data were in agreement with literature values.[10]

(2*S*,4*S*)-5,5-Dimethylhexane-2,4-diol [(−)-S1]. A solution of (−)-**7** (1.63 g, 11.3 mmol) in dry THF (220.0 mL) was cooled to −78 °C and treated with a solution of DIBAl-H (1.0 M in heptane, 28.36 mL, 28.4 mmol) slowly, allowing each drop to run down the side of the flask. The reaction mixture was allowed to stir at −78 °C for 3.5 h before being quenched by the addition of a 10% HCl aqueous solution (30 mL). After the cooling bath was removed, the contents of the flask were warmed to room temperature and allowed to stir for an additional 3 h. The crude reaction mixture was then partitioned between ether (50 mL) and brine (50 mL), and the aqueous phase was re-extracted with additional ether washes. The combined organic phases were then dried over $MgSO_4$, filtered, and concentrated to afford crude diol as a 10:1 mixture of diastereomers, which were purified by flash column chromatography (9:1 → 8:2 hexanes/EtOAc) to afford 1.38 g (83%) of clean *syn*-diol (−)-**S1** as an amorphous white solid. ^{1}H, ^{13}C, and optical rotation data were in agreement with literature values.[10]

(4*S*,6*S*)-4-(*tert*-Butyl)-6-methyl-1,3,2-dioxathiane 2,2-dioxide [(−)-8]. (−)-**8** was prepared following the literature procedure of

Cavelier and co-workers. A solution of diol (−)-**S1** (0.403 g, 2.76 mmol) in dry pyridine (12.5 mL) was cooled to 0 °C and treated with $SOCl_2$ (1.00 mL, 13.8 mmol). The reaction mixture was allowed to stir at 0 °C for 45 min before being quenched by the addition of water. The contents of the flask were then extracted with CH_2Cl_2 and washed with a saturated aqueous $KHSO_4$ solution, followed by a saturated aqueous $NaHCO_3$ solution. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated to afford the crude sulfite, which was taken on to the next step without further purification. The crude sulfite was then dissolved a 2:1:1 mixture of water/MeCN/CCl_4 (22 mL:22 mL:11 mL) and treated with $RuCl_3 \cdot xH_2O$ (0.030 g) and $NaIO_4$ (0.884 g, 4.14 mmol). The biphasic reaction mixture was then vigorously stirred at room temperature for 2 h before being diluted with Et_2O and extracted from a saturated aqueous $NaHCO_3$ solution. The crude sulfate was purified by flash column chromatography (8:2 hexanes/EtOAc) to afford 0.491 g (85% over two steps) of *syn*-cyclic sulfate (−)-**8** as an amorphous white solid. ^1H, ^{13}C, and optical rotation data were in agreement with literature values.[10]

(3*S*,5*S*)-9-(Benzyloxy)-2,2,5-trimethylnonan-3-ol [(−)-S2]. Freshly ground magnesium turnings (0.030 g, 1.24 mmol) were flame-dried under vacuum and, upon cooling, were suspended in dry THF (2 mL). A small piece of iodine was added, and the flask was cooled to 0 °C before 4-bromobutyl benzyl ether (2.20 mL, 1.04 mmol, 90%) was added dropwise via syringe. The reaction mixture was allowed to warm to room temperature and then warmed by hand until it reached a gentle reflux. The yellow/gray suspension was allowed to stir for 1 h before being added, via cannula, to a flask containing a solution of cyclic sulfate (−)-**8** (0.064 g, 0.300 mmol) and CuI (0.060 g, 0.310 mmol) in dry THF (4.0 mL) at −25 °C. Upon addition, the reaction mixture immediately turned purple and was allowed to stir at −25 °C for 5 h before being warmed to room temperature and concentrated in vacuo. The solid residue was dissolved in ether (30 mL) and treated with a 20% aqueous H_2SO_4 solution (10 mL). The contents of the flask were then stirred vigorously for 12 h before the phases were separated and the aqueous layer extracted with ether, dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (9:1 hexanes/EtOAc) to afford 0.060 g (66%) of alcohol (−)-**S2** as a colorless oil. $[\alpha]_D^{22.6} = -38.5$ (c = 1.06, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 7.15−7.28 (m, 5H), 4.43 (s, 2H), 3.40 (t, J = 6.6 Hz, 2H), 3.19 (d, J = 9.9 Hz, 1H), 1.45−1.68 (m, 4H), 1.31−1.44 (m, 2H), 1.17−1.30 (m, 2H), 1.09 (ddd, J = 4.2, 10.2, 14.2 Hz, 1H), 0.90−1.03 (m, 1H), 0.86 (d, J = 6.6 Hz, 3H), 0.80 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 138.6, 128.3, 127.6, 127.4, 77.6, 72.8, 70.4, 39.3, 35.3, 34.9, 30.0, 29.9, 25.6, 23.4, 21.0; IR (neat, thin film) ν 3469, 2950, 2866, 1454, 1363, 1101 cm^{-1}; HRMS m/z calcd for $C_{19}H_{32}O_2Na$ $[M + Na]^+$, 315.2294; found, 315.2293.

(5*S*,7*S*)-5,8,8-Trimethylnonane-1,7-diol [(−)-9]. Benzyl ether (−)-**S2** (0.239 g, 0.810 mmol) was dissolved in a 1:1 EtOAc/EtOH mixture (20 mL) and treated with 10% Pd/C (0.080 g). The reaction mixture was then flushed with hydrogen gas and allowed to stir under an atmosphere of hydrogen (using a balloon). After TLC showed the complete consumption of starting material (24 h), the reaction mixture was diluted with EtOAc and filtered through a short plug of Celite, rinsing several times with fresh EtOAc. The filtrate was concentrated in vacuo and purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.166 g (99%) of diol (−)-**9** as a colorless oil. $[\alpha]_D^{21.8} = -55.6$ (c = 1.09, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 3.62 (t, J = 6.4 Hz, 2H), 3.27 (dd, J = 1.8, 10.2 Hz, 1H), 0.97−1.73 (m, 11H), 0.92 (d, J = 6.6 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 77.5, 62.8, 39.2, 35.1, 34.9, 32.9, 29.9, 25.6, 23.0, 20.9; IR (neat, thin film) ν 3351, 2950, 2868, 1463, 1364, 1074, 985 cm^{-1}; HRMS m/z calcd for $C_{12}H_{26}O_2Na$ $[M + Na]^+$, 225.1825; found, 225.1823.

(5*S*,7*S*)-7-Hydroxy-5,8,8-trimethylnonanamide [(−)-5]. Diol (−)-**9** (0.166 g, 0.810 mmol) was dissolved in dry CH_2Cl_2 (12 mL) and treated with TEMPO (0.013 g, 0.081 mmol), followed by iodobenzene diacetate (0.313 g, 0.970 mmol). The reaction mixture was allowed to stir at room temperature for 6 h before being quenched by the addition of a saturated aqueous solution of sodium thiosulfate ($Na_2S_2O_3$). The contents of the flask were then extracted with CH_2Cl_2, and the combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude aldehyde was purified by flash column chromatography (85:15 hexanes/EtOAc) to afford 0.154 g (93%) of the purified material, which was taken directly on to the next step without characterization. In a separate flask, a mixture of sodium chlorite ($NaClO_2$, 0.122 g) and sodium phosphate (NaH_2PO_4, 0.086 g) was dissolved in water (2 mL), and this solution was added to a mixture of aldehyde in *t*-BuOH (1 mL) and 2-methyl-2-butene (0.5 mL). The reaction mixture was allowed to stir at room temperature for 45 min before being quenched with water and extracted using ethyl acetate. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide the crude acid, which was taken directly on to the next step without characterization. The acid (ca. 0.76 mmol) was dissolved in dry CH_2Cl_2 (15.2 mL) and sequentially treated with (in this order) methylamine hydrochloride (0.051 g, 0.760 mmol), HOBt (0.103 g, 0.760 mmol), DMAP (0.093 g, 2.28 mmol), and EDCI (0.146 g, 0.760 mmol). The reaction mixture was allowed to stir at room temperature for 12 h before being diluted with CH_2Cl_2 and washed with a half-saturated aqueous solution of citric acid. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (100:1 EtOAc/Et_3N) to afford 0.130 g (74% over two steps) of amide (−)-**5** as an amorphous white solid. $[\alpha]_D^{21.6} = -50.8$ (c = 1.04, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 5.68 (bs, 1H), 3.26 (dd, J = 1.9, 10.2 Hz, 1H), 2.79 (d, J = 4.8 Hz, 3H), 2.16 (dd, J = 7.0, 7.8 Hz, 2H), 1.61−1.80 (m, 3H), 1.40−1.61 (m, 2H), 1.34 (ddd, J = 1.9, 9.2, 14.0 Hz, 1H), 1.20 (td, J = 1.0, 4.0, 14.0 Hz, 1H), 1.05 (ddd, 4.4, 8.8, 17.7 Hz, 1H), 0.93 (d, J = 6.7 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 173.8, 77.2, 39.0, 36.6, 34.9, 34.6, 29.3, 26.2, 25.7, 23.0, 20.9; IR (thin film) ν 3305, 2952, 1651, 1562, 1411, 1363 cm^{-1}; HRMS m/z calcd for $C_{13}H_{27}NO_2Na$ $[M + Na]^+$, 252.1934; found, 252.1931.

(3*S*,5*R*)-5-Hydroxy-2,2-dimethylhexan-3-yl Benzoate [(+)-S3]. A solution of (−)-**7** (0.500 g, 3.50 mmol) in dry THF (14 mL) was cooled to −10 °C (ice/brine) and treated with freshly distilled benzaldehyde (1.06 mL, 10.5 mmol), followed by a freshly prepared solution of SmI_2 in THF (17.3 mL, ca. 0.1 M). The reaction mixture was allowed to stir at −10 °C for 2 h before being quenched with a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$), and extracted using ether. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (7:3 hexanes/EtOAc) to afford 0.989 g (99%) of benzoate (+)-**S3** as a colorless oil. $[\alpha]_D^{23.0} = +2.3$ (c = 1.25, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 8.04−8.10 (m, 2H), 7.54−7.62 (m, 1H), 7.41−7.50 (m, 2H), 5.07 (m, 1H), 3.49−3.64 (m, 1H), 3.30 (d, J = 3.5 Hz, 1H), 1.54−1.67 (m, 2H), 1.11 (d, J = 6.2 Hz, 3H), 0.94 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 167.8, 133.2, 129.8, 129.7, 128.4, 79.1, 63.2, 39.1, 34.4, 26.1, 22.8; IR (neat, thin film) ν 3494, 2965, 1700, 1284, 1273, 1125, cm^{-1}; HRMS m/z calcd for $C_{15}H_{22}O_3Na$ $[M + Na]^+$, 273.1461; found, 273.1457.

(2*R*,4*S*)-5,5-Dimethylhexane-2,4-diol [(+)-S4]. To a solution of benzoate (+)-**S3** (0.876 g, 3.50 mmol) in MeOH (20 mL) was added K_2CO_3 (5.50 g, 39.7 mmol) in a single portion at room temperature. After TLC showed the complete consumption of starting material, the reaction was quenched by the addition of water and concentrated in vacuo. The residue was then extracted using ethyl acetate, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford 0.532 g (93%) of diol (+)-**S4** as an amorphous white solid. ^1H, ^{13}C, and optical rotation data were in agreement with literature values.[10]

(4*S*,6*R*)-4-(*tert*-butyl)-6-methyl-1,3,2-dioxathiane-2,2-dioxide [(+)-10]. (+)-**10** was prepared in a similar manner as *syn*-cyclic sulfate (−)-**8**. The crude product was purified by flash column chromatography (8:2 hexanes/EtOAc) to afford 0.309 g (89% over two steps) of *anti*-cyclic sulfate (+)-**10** as an amorphous white solid. $[\alpha]_D^{23.0} = +0.19$ (c = 0.93, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 4.94 (ddq, J = 4.6, 6.6, 13.0 Hz, 1H), 4.60 (dd, J = 3.6, 11.3 Hz, 1H), 2.30 (ddd, J = 6.0, 11.3, 14.1 Hz, 1H), 1.75 (ddd, J = 3.7, 4.5, 14.1 Hz, 1H), 1.64 (d, J = 6.6 Hz, 3H), 1.02 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 88.4, 81.0, 34.2, 29.9, 25.0, 19.5; IR (neat, thin film) ν 2972, 1469, 1369, 1194, 1051, 1041, 950, 916, 856 cm^{-1}; HRMS *m*/*z* calcd for $C_8H_{16}O_4SNa$ [M + Na], 231.0661; found, 231.0659.

(3*S*,5*R*)-9-(Benzyloxy)-2,2,5-trimethylnonan-3-ol [(−)-S5]. (−)-**S5** was prepared in a similar manner as benzyl ether (−)-**S2**. The crude product was purified by flash column chromatography (8:2 hexanes/EtOAc) to afford 0.309 g (94%) of benzyl ether (−)-**S5** as a colorless oil. $[\alpha]_D^{22.8} = -23.1$ ($c = 2.4$, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 7.25−7.36 (m, 5H), 4.50 (s, 2H), 3.47 (t, $J = 6.6$ Hz, 2H), 3.29 (dd, $J = 1.7$, 10.4 Hz, 1H), 1.55−1.72 (m, 3H), 1.09−1.49 (m, 7H), 0.89 (d, $J = 6.4$ Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 138.6, 128.3, 127.6, 127.4, 77.2, 78.8, 70.4, 38.9, 38.2, 34.8, 30.0, 29.5, 25.6, 23.6, 18.9; IR (neat, thin film) ν 2956, 2875, 1455, 1362, 1093, 1029, 1011, 895 cm^{-1}; HRMS *m*/*z* calcd for $C_{19}H_{32}O_2Na$ $[M + Na]^+$, 315.2294; found, 315.2291.

(5*R*,7*S*)-5,8,8-Trimethylnonane-1,7-diol [(−)-11]. (−)-**11** was prepared in a similar manner as diol (−)-**9**. The crude product was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford 0.101 g (90%) of diol (−)-**11** as a colorless oil. $[\alpha]_D^{22.7} = -39.8$ ($c = 0.92$, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 3.64 (t, $J = 6.5$ Hz, 2H), 3.28 (d, $J = 10.3$ Hz, 1H), 1.50−1.75 (m, 3H), 1.11−1.48 (m, 8H), 0.88 (δ, $J = 6.4$ Hz, 3H), 0.88, (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz) 77.4, 63.0, 38.8, 38.0, 34.8, 33.0, 29.6, 25.7, 23.2, 19.0; IR (neat, thin film) ν 3351, 2934, 2869, 1460, 1364, 1073, 979 cm^{-1}; HRMS *m*/*z* calcd for $C_{12}H_{26}O_2Na$ $[M + Na]^+$, 225.1825; found, 225.1823.

(5*R*,7*S*)-7-Hydroxy-*N*,5,8,8-tetramethylnonanamide [(−)-4]. (−)-**4** was prepared in a similar manner as amide (−)-**5**. The crude product was purified by flash column chromatography (100:1 EtOAc/Et_3N) to afford 0.020 g (74% over three steps) of amide (−)-**4** as an amorphous white solid. $[\alpha]_D^{22.9} = -32.9$ ($c = 1.64$, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 5.68 (bs, 1H), 3.25 (dd, $J = 1.7$, 10.4 Hz, 1H), 2.78 (d, $J = 4.7$ Hz, 3H), 2.15 (t, $J = 7.8$ Hz, 2H), 1.51−1.78 (m, 4H), 1.06−1.39 (m, 4H), 0.87 (d, overlapped, 3H), 0.87 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 173.9, 77.3, 38.6, 37.8, 36.7, 34.8, 29.3, 26.2, 25.7, 23.1, 19.0; IR (neat, thin film) ν 3304, 2952, 1652, 1562, 1410, 1075 cm^{-1}; HRMS *m*/*z* calcd for $C_{13}H_{27}NO_2Na$ $[M + Na]^+$, 252.1934; found, 252.1931.

Ethyl 6-((4-Methoxybenzyl)oxy)hexanoate (S7). A suspension of NaH (0.037 g, 0.920 mmol, 60% dispersion in mineral oil) in dry ether (18 mL) was treated with *p*-methoxybenzyl alcohol (1.14 mL, 9.22 mmol) dropwise. The reaction mixture was allowed to stir at room temperature for 30 min before being cooled to 0 °C. Trichloroacetonitrile (0.92 mL, 9.22 mmol) was added dropwise, and the reaction flask was allowed to gradually warm to room temperature. After 5 h, the contents of the flask were concentrated, and the resultant orange oil was suspended in hexanes (25 mL) and MeOH (0.1 mL). The solid precipitate was then filtered through a short plug of Celite, rinsing several times with fresh hexanes, and the filtrate was concentrated. The crude trichloroacetimidate was dissolved in dry CH_2Cl_2 (30 mL) and cooled to 0 °C. To this was added ethyl-6-hydroxyhexanoate (1.00 mL, 6.14 mmoL), followed by camphor sulfonic acid (CSA, 0.143 g, 0.610 mmol). The contents of the flask were allowed to gradually warm to room temperature and stir for 12 h. A saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) was then added, and the mixture was extracted using CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford 1.35 g (78%) of ester **S7** as a colorless oil. ^1H and ^{13}C were in agreement with literature values.[20]

6-((4-Methoxybenzyl)oxy)hexanoic Acid (13). Ester **S7** was dissolved a 2:2:1 mixture of THF/MeOH/H_2O (30 mL) and treated with NaOH (0.902 g, 22.6 mmol). A condenser was attached, and the reaction mixture was heated to 60 °C overnight. The flask was allowed to cool before the contents were concentrated in vacuo. The aqueous residue was acidified using concentrated HCl to pH ∼3 and then saturated with solid NaCl before being extracted using EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (7:3 hexanes/EtOAc) to afford 1.41 g (70%) of acid **13** as a thick colorless oil. ^1H and ^{13}C were in agreement with literature values.[20b]

***N*-((1*R*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)-6-((4-methoxybenzyl)oxy)-*N*-methylhexanamide [(−)-14].** To a solution of acid **13** (0.300 g, 1.18 mmol) in dry CH_2Cl_2 (12 mL) was added oxalyl chloride (0.11 mL, 1.30 mmol) dropwise, followed by a single drop of DMF; gas evolution immediately occurred. The reaction mixture was allowed to stir at room temperature overnight before being concentrated in vacuo. In a separate flask, (−)-pseudoephedrine (0.196 g, 1.18 mmol) was dissolved in dry THF (3 mL), treated with triethylamine (0.21 mL, 1.54 mmol), and cooled to 0 °C. To this was added the recently prepared acid chloride in dry THF (3 mL) via canula. The reaction mixture was allowed to stir at 0 °C for 1 h before being quenched with brine and extracted using EtOAc. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford 0.335 g (70%) of amide (−)-**14** as an amorphous white solid. $[\alpha]_D^{24.0} = -56.2$ ($c = 2.26$, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz, mixture of rotamers) 7.17−7.41 (m, 7H), 6.80−6.91 (m, 2H), 4.50−4.35 (m, 5H), 4.42−4.60 (m, 0.6H), 4.39−4.41 (s, 2H), 3.96 (m, 0.3H), 3.77 (s, 3H), 3.42 (t, $J = 6.5$ Hz, 2H), 2.87 (s, 0.8H), 2.76 (s, 2H), 2.32−2.43 (m, 0.4H), 2.20−2.29 (m, 1H), 1.50−1.68 (m, 4H), 1.30−1.45 (m, 2H), 1.07 (d, $J = 6.8$, 2H), 0.95 (d, $J = 6.8$, 2H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz, mixture of rotamers) 175.5, 174.3, 159.3, 142.8, 141.9, 130.9, 129.5, 128.8, 128.5, 127.8, 127.1, 126.6, 114.0, 77.8, 77.7, 75.6, 72.8, 70.3, 70.2, 58.5, 55.5, 34.5, 33.8, 33.0, 29.8, 27.0, 26.4, 26.2, 25.4, 25.0, 15.7, 14.6; IR (neat, thin film) ν 3391, 2935, 1614, 1513, 1454, 1247, 1094, 1034 cm^{-1}; HRMS *m*/*z* calcd for $C_{24}H_{33}NO_4Na$ $[M + Na]^+$, 422.2301; found, 422.2295.

(*R*)-*N*-((1*R*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)-6-((4-methoxybenzyl)oxy)-*N*,2-dimethylhexanamide [(−)-S8]. Lithium chloride (0.2133 g, 5.03 mmol) was placed in a round-bottom flask under vacuum and flame-dried before use. Once cooled, the flask was placed under an atmosphere of nitrogen and charged with diisopropylamide (0.26 mL, 1.88 mmol) and dry THF (4 mL). The contents of the flask were cooled to 0 °C and treated with *n*BuLi (2.5 M in hexanes, 0.75 mL, 1.89 mmol) dropwise. After 20 min, the LDA solution was cooled to −78 °C before a solution of amide (−)-**14** (0.335 g, 0.83 mmol) in dry THF (3 mL) was added dropwise via cannula. After 1 h at −78 °C, the flask was allowed to warm to 0 °C for 15 min, and then room temperature for 5 min. The flask was then cooled back down to 0 °C, and iodomethane (78 μL, 1.82 mmol) was added neat. The reaction mixture was allowed to stir at 0 °C for 20 min before being quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The phases were separated, and the aqueous phase was extracted with EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford 0.280 g (80%) of amide (−)-**S8** as an amorphous white solid. $[\alpha]_D^{23.3} = -74.2$ ($c = 1.46$, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz, mixture of rotamers) 7.16−7.40 (m, 7H), 6.80−6.89 (m, 2H), 4.86 (bs, 0.4H), 4.59 (t, $J = 7.0$ Hz, 0.7H), 4.51 (dd, $J = 8.3$, 2.4 Hz, 0.3H), 4.40 (s, 1.3H), 4.37 (s, 0.5H), 4.32 (t, $J = 6.8$ Hz, 0.3H), 4.00−4.11 (m, 0.2H), 3.40 (t, $J = 6.4$ Hz, 1.8H), 2.53 (s, 3H), 2.87 (s, 0.6H), 2.75 (s, 2H), 2.48−2.60 (m, 0.6H), 1.47−1.71 (m, 2.5H), 1.21−1.39 (m, 2H), 1.15 (d, $J = 6.9$ Hz, 2H), 1.09 (d, $J = 6.6$ Hz, 1H), 98 (d, $J = 6.7$ Hz, 2H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz, mixture of rotamers) 178.5, 177.5, 158.9, 142.4, 141.6, 130.4, 129.0, 128.4, 128.0, 127.2, 126.7, 113.5, 76.0, 75.1, 72.3, 69.7, 59.2, 57.8, 55.0, 36.2, 35.4, 34.2, 33.5, 29.5, 26.9, 23.9, 23.8, 17.5, 17.1, 15.5, 14.2; IR (neat, thin film) ν 3389, 2935, 2860, 1613, 1513, 1453, 1247, 1097, 1035 cm^{-1}; HRMS *m*/*z* calcd for $C_{25}H_{35}NO_4Na$ $[M + Na]^+$, 436.2458; found, 436.2456.

(*R*)-6-((4-Methoxybenzyl)oxy)-2-methylhexanoic Acid [(−)-6a]. To a solution of amide (−)-**S8** (0.280 g, 0.670 mmol) in *t*-BuOH (6 mL) and MeOH (6 mL) was added an aqueous solution of NaOH (3.22 N, 12 mL). A condenser was attached, and the reaction mixture was heated to 85 °C overnight. The flask was allowed to cool before the contents were partitioned between water (30.0 mL) and CH_2Cl_2 (30.0 mL). The phases were separated, and the organic layer containing recovered pseudoephedrine was set aside. The aqueous layer was acidified using concentrated HCl to pH ∼3 before being extracted using CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product [0.168 g (93%)], as a thick colorless oil, was sufficiently clean to use in the next step without further purification. $[\alpha]_D^{22.2}$ = −7.9 (c = 1.27, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 10.50 (bs, 1H), 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.44 (t, J = 6.5 Hz, 2H), 2.46 (ddq, J = 7.0, 7.0, 13.0 Hz, 1H), 1.55−1.77 (m, 3H), 1.34−1.5 (m, 3H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$, 100 MHz) 183.0, 159.1, 130.6, 129.2, 113.7, 72.5, 69.7, 55.2, 39.3, 33.2, 29.5, 23.8, 16.8; IR (neat, thin film) ν 2937, 2862, 1700, 1612, 1513, 1247, 1097, 1035 cm^{-1}; HRMS m/z calcd for $C_{15}H_{22}O_4Na$ $[M + Na]^+$, 289.1410; found, 289.1409.

***N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-6-((4-methoxybenzyl)oxy)-*N*-methylhexanamide [(+)-15].** (+)-**15** was prepared in a similar manner as amide (−)-**14**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.350 g (73%) of amide (+)-**15** as an amorphous white solid. $[\alpha]_D^{23.2}$ = +66.9 (c = 1.27, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz, mixture of rotamers) 7.17−7.41 (m, 7H), 6.80−6.91 (m, 2H), 4.42−4.60 (m, 0.6H), 4.39−4.41 (s, 2H), 3.96 (m, 0.3H), 3.77 (s, 3H), 3.42 (t, J = 6.5 Hz, 2H), 2.87 (s, 0.8H), 2.76 (s, 2H), 2.32−2.43 (m, 0.4H), 2.20−2.29 (m, 1H), 1.50−1.68 (m, 4H), 1.30−1.45 (m, 2H), 1.07 (d, J = 6.8, 2H), 0.95 (d, J = 6.8, 2H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz, mixture of rotamers) 175.5, 174.3, 159.3, 142.8, 141.9, 130.9, 129.5, 128.8, 128.5, 127.8, 127.1, 126.6, 114.0, 77.8, 77.7, 75.6, 72.8, 70.3, 70.2, 58.5, 55.5, 34.5, 33.8, 33.0, 29.8, 27.0, 26.4, 26.2, 25.4, 25.0, 15.7, 14.6; IR (neat, thin film) ν 3391, 2935, 1614, 1513, 1454, 1247, 1094, 1034 cm^{-1}; HRMS m/z calcd for $C_{24}H_{33}NO_4Na$ $[M + Na]^+$, 422.2301; found, 422.2292.

(*S*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-6-((4-methoxybenzyl)oxy)-*N*,2-dimethylhexanamide [(+)-S9]. (+)-**S9** was prepared in a similar manner as amide (−)-**S8**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.263 g (72%) of amide (+)-**S9** as an amorphous white solid. $[\alpha]_D^{23.8}$ = +77.1 (c = 1.0, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz, mixture of rotamers) 7.16−7.40 (m, 7H), 6.80−6.89 (m, 2H), 4.86 (bs, 0.4H), 4.59 (t, J = 7.0 Hz, 0.7H), 4.51 (dd, J = 2.4, 8.3 Hz, 0.3H), 4.40 (s, 1.3H), 4.37 (s, 0.5H), 4.32 (t, J = 6.8 Hz, 0.3H), 4.00−4.11 (m, 0.2H), 3.40 (t, J = 6.4 Hz, 1.8H), 2.53 (s, 3H), 2.87 (s, 0.6H), 2.75 (s, 2H), 2.48−2.60 (m, 0.6H), 1.47−1.71 (m, 2.5H), 1.21−1.39 (m, 2H), 1.15 (d, J = 6.9 Hz, 2H), 1.09 (d, J = 6.6 Hz, 1H), 0.98 (d, J = 6.7 Hz, 2H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz, mixture of rotamers) 178.5, 177.5, 158.9, 142.4, 141.6, 130.4, 129.0, 128.4, 128.0, 127.2, 126.7, 113.5, 76.0, 75.1, 72.3, 69.7, 59.2, 57.8, 55.0, 36.2, 35.4, 34.2, 33.5, 29.5, 26.9, 23.9, 23.8, 17.5, 17.1, 15.5, 14.2; IR (neat, thin film) ν 3389, 2935, 2860, 1613, 1513, 1453, 1247, 1097, 1035 cm^{-1}; HRMS m/z calcd for $C_{25}H_{35}NO_4Na$ $[M + Na]^+$, 436.24583; found, 436.24583.

(*S*)-6-((4-Methoxybenzyl)oxy)-2-methylhexanoic acid [(+)-6b]. (+)-**6b** was prepared in a similar manner as acid (−)-**6a**. The crude product [0.127 g (75%)], as a thick colorless oil, was sufficiently clean to use in the next step without further purification. $[\alpha]_D^{24.7}$ = +9.4 (c = 1.80, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 11.24 (bs, 1H), 7.26 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.44 (t, J = 6.5 Hz, 2H), 2.46 (ddq, J = 7.0, 7.0, 13.0 Hz, 1H), 1.55−1.77 (m, 3H), 1.34−1.5 (m, 3H), 1.18 (d, J = 7.0 Hz, 3H); ^{13}C NMR (δ, $CDCl_3$, 75 MHz) 183.0, 159.0, 130.5, 129.2, 113.7, 72.4, 69.7, 55.2, 39.3, 33.2, 29.5, 23.8, 16.7; IR (neat, thin film) ν 2937, 2862, 1700, 1612, 1513, 1247, 1097, 1035 cm^{-1}; HRMS m/z calcd for $C_{15}H_{22}O_4Na$ $[M + Na]^+$, 289.1410; found, 289.1407.

(*R*)-(3*S*,5*R*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-((4-methoxy benzyl)oxy)-2-methylhexanoate [(−)-16a]. A solution of acid (−)-**3a** (0.070 g, 0.260 mmol) in dry THF (2.6 mL) was treated with freshly distilled DIPEA (64.1 μL, 0.36 mmol), followed by 2,4,6-trichlorobenzoyl chloride (72.7 μL, 0.41 mmol). The mixture was stirred at room temperature for 3 h, and the resulting mixed anhydride was then concentrated in vacuo. The residue was dissolved in dry toluene (5.2 mL) and was added, via cannula, to a separate flask containing amide (−)-**4** (0.037 g, 0.150 mmol) and DMAP (0.032 g, 0.260 mmol). The reaction mixture was allowed to stir at room temperature for 12 h before CH_2Cl_2 (20 mL) was added, and the mixture was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL). The phases were separated, and the aqueous layer was extracted with additional CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.069 g (91%) of amide (−)-**16a** as a colorless oil. $[\alpha]_D^{23.0}$ = −14.3 (c = 2.31, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 7.25 (d, J = 8.5 Hz, 2H), 6.87 (d, J = 8.5 Hz, 2H), 5.68 (bs, 1H), 4.83 (d, J = 10.6 Hz, 1H), 4.42 (s, 2H), 3.80 (s, 3H), 3.44 (t, J = 6.5 Hz, 2H), 2.74 (d, J = 4.8 Hz, 3H), 2.36−2.49 (m, 1H), 2.08 (t, J = 7.6 Hz, 2H), 1.48−1.72 (m, 6H), 1.30−1.48 (m, 4H), 1.19−1.30 (m, 3H), 1.16 (d, J = 7.0 Hz, 3H), 0.88 (d, overlapped, 3H), 0.87 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 176.5, 173.6, 159.1, 130.5, 129.2, 113.7, 78.0, 74.4, 69.9, 55.2, 39.9, 37.7, 36.9, 36.7, 34.6, 33.5, 29.6, 29.2, 26.2, 25.9, 24.0, 23.2, 19.0, 17.5; IR (neat, thin film) ν 3307, 2937, 2868, 1727, 1651, 1513, 1248, 1171, 1098, 1036, 821 cm^{-1}; HRMS m/z calcd for $C_{28}H_{47}NO_5Na$ $[M + Na]^+$, 500.3346; found, 500.3336.

(*R*)-(3*S*,5*R*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-hydroxy-2-methylhexanoate [(−)-S10]. To a solution of amide (−)-**16a** (0.069 g, 0.017 mmol) in CH_2Cl_2/water (20:1, 2.0 mL) at room temperature was added DDQ (0.050 g, 0.210 mmol). The reaction mixture was allowed to vigorously stir for 1 h before being diluted with CH_2Cl_2 and washed with a saturated aqueous solution of sodium bicarbonate ($NaHCO_3$) and brine. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated.The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes → 100:1 EtOAc/Et_3N) to afford 0.043 g (82%) of alcohol (−)-**S10** as a colorless oil. $[\alpha]_D^{23.6}$ = −28.7 (c = 2.15, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 5.88 (bs, 1H), 4.80 (d, J = 10.6 Hz, 1H), 3.61 (t, J = 6.1 Hz, 2H), 2.77 (d, J = 4.7 Hz, 3H), 2.77 (s, overlapped, 1H), 2.38−2.52 (m, 1H), 2.11 (t, J = 7.6 Hz, 2H), 1.46−1.77 (m, 6H), 1.30−1.44 (m, 3H), 1.17−1.29 (m, 4H), 1.14 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.1 Hz, 3H), 0.85 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 176.8, 173.9, 78.1, 62.4, 39.8, 37.7, 37.0, 36.6, 34.5, 33.7, 32.6, 29.5, 26.2, 25.9, 23.7, 23.5, 19.1, 17.7; IR (neat, thin film) ν 3306, 2956, 2936, 1729, 1649, 1562, 1461, 1381, 1161 cm^{-1}; HRMS m/z calcd for $C_{20}H_{39}NO_4Na$ $[M + Na]^+$, 380.2771; found, 380.2764.

(*R*)-(3*S*,5*R*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-2-methyl-6-oxohexanoate [(−)-2a]. A solution of alcohol (−)-**S10** (0.026 g, 0.072 mmol) in dry CH_2Cl_2 (2 mL) was treated with $NaHCO_3$ (0.061 g, 0.72 mmol), followed by the Dess−Martin periodinane (0.154 g, 0.360 mmol). The resulting suspension was allowed to stir at room temperature for 1 h before being quenched with a saturated aqueous solution of sodium thiosulfate ($Na_2S_2O_3$). The contents of the flask were then stirred vigorously for 1 h, and then the layers were separated. The aqueous layer was extracted using CH_2Cl_2, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes → 9:1 EtOAc/hexanes) to afford 0.023 g (89%) of aldehyde (−)-**2a** as a colorless oil. $[\alpha]_D^{23.2}$ = −19.5 (c = 1.15, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 9.76 (t, J = 1.2 Hz, 1H), 5.77 (bs, 1H), 4.82 (dd, J = 1.0, 11.3 Hz, 1H), 2.79 (d, J = 4.7 Hz, 3H), 2.38−2.51 (m, 3H), 2.13 (t, J = 7.6 Hz, 2H), 1.34- 1.79 (m, 7H), 1.13−1.29 (m, 4H), 1.17 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 5.8 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 202.4, 176.2 (2C), 78.3, 43.8, 39.8, 37.7, 36.9, 36.7, 34.6, 33.0, 29.3, 26.2, 25.9, 23.3, 19.9, 19.0, 17.6; IR (neat, thin film) ν 3305, 2960, 1727, 1650, 1551, 1366, 1163, 1075 cm^{-1}; HRMS m/z calcd for $C_{20}H_{37}NO_4Na$ $[M + Na]^+$, 378.26148; found, 378.26145.

(*S*)-(3*S*,5*R*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-((4-methoxy benzyl)oxy)-2-methylhexanoate [(−)-*ent*-16b]. (−)-*ent*-**16b** was prepared in a similar manner as amide (−)-**16a**, using acid (+)-**6b** and amide (−)-**4**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.072 g (99%) of amide (−)-*ent*-**16b** as an amorphous white solid. $[\alpha]_D^{24.1}$ = −8.8 (c = 1.0, $CHCl_3$); ^1H NMR (δ, ppm, $CDCl_3$, 300 MHz) 7.24 (d, J = 8.6 Hz, 2H), 6.86 (d, J = 8.6 Hz, 2H), 5.60 (bs, 1H), 4.81 (dd, J = 10.9, 1.3 Hz, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 3.42 (t, J = 6.5 Hz, 2H), 2.76 (d, J = 4.8 Hz, 3H), 2.35−2.48 (m, 1H), 2.09 (t, J = 7.6 Hz, 2H), 1.47−1.75 (m, 6H), 1.3−1.46 (m, 3H), 1.14−1.29 (m, 4H), 1.14 (d, J = 6.9 Hz, 3H), 0.88 (d, J = 6.0 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 176.4, 173.6, 159.1, 130.6, 129.2, 113.7, 77.9, 72.5, 69.9, 55.2, 40.1, 37.8, 36.9, 36.8, 34.5, 33.5, 29.6, 29.3, 26.2, 26.0, 24.0, 23.3, 19.0, 17.5; IR (neat, thin film) ν 3306, 2936, 1727, 1650, 1513, 1462, 1366, 1247, 1171, 1098, 1036, 821 cm^{-1}; HRMS *m*/*z* calcd for $C_{28}H_{47}NO_5Na$ $[M + Na]^+$, 500.3346; found, 500.3336.

(*S*)-(3*S*,5*R*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-hydroxy-2-methylhexanoate [(−)-S11]. (−)-**S11** was prepared in a similar manner as alcohol (−)-**S10**, using amide (−)-*ent*-**16b**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes → 100:1 EtOAc/Et$_3$N) to afford 0.034 g (64%) of alcohol (−)-**S11** as a colorless oil. $[\alpha]_D^{24.1} = -18.0$ ($c = 1.70$, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 5.85 (bs, 1H), 4.80 (d, *J* = 10.6 Hz, 1H), 3.59 (t, *J* = 6.5 Hz, 2H), 2.76 (d, 4.8 Hz, 3H), 2.36−2.48 (m, 1H), 2.10 (t, *J* = 7.5 Hz, 2H), 1.46−1.76 (m, 7H), 1.29−1.45 (m, 3H), 1.09−1.29 (m, 4H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.2 Hz, 3H), 0.85 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 75 MHz) 176.3, 173.9, 78.0, 62.4, 40.5, 37.8, 37.0, 36.7, 34.5, 33.6, 32.7, 29.5, 26.2, 25.9, 23.7, 23.5, 19.0, 17.7; IR (neat, thin film) ν 3305, 2936, 1729, 1651, 1563, 1462, 1366, 1163, 1074 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{39}NO_4Na$ $[M + Na]^+$, 380.2771; found, 380.2767.

(*S*)-(3*S*,5*R*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-2-methyl-6-oxohexanoate [(−)-*ent*-2b]. (−)-*ent*-**2b** was prepared in a similar manner as aldehyde (−)-**2a**, using alcohol (−)-**S11**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes → 9:1 EtOAc/hexanes) to afford 0.022 g (68%) of aldehyde (−)-*ent*-**2b** as a colorless oil. $[\alpha]_D^{24.1} = -16.7$ ($c = 1.08$, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 9.74 (t, *J* = 1.5 Hz, 1H), 5.67 (bs, 1H), 4.81 (dd, *J* = 1.2, 11.2 Hz, 1H), 2.78 (d, *J* = 4.8 Hz, 3H), 2.39−2.49 (m, 3H), 2.11 (d, *J* = 7.5 Hz, 2H), 1.34−1.78 (m, 7H), 1.13−1.29 (m, 4H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 5.8 Hz, 3H), 0.85 (s, 9H); ^{13}C NMR (δ, CDCl$_3$, 75 MHz) 202.2, 175.9, 173.6, 78.2, 43.7, 40.0, 37.8, 36.9, 36.8, 34.5, 33.0, 29.4, 26.2, 25.9, 23.4, 19.9, 19.0, 17.5; IR (neat, thin film) ν 3305, 2960, 1727, 1651, 1552, 1366, 1257, 1164, 1076 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{37}NO_4Na$ $[M + Na]^+$, 378.2615; found, 378.2614.

(*R*)-(3*S*,5*S*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-((4-methoxy benzyl)oxy)-2-methylhexanoate [(−)-17a]. Was prepared in a similar manner as amide (−)-**16a**, using acid (−)-**6a** and amide (−)-**5**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.078 g (81%) of amide (−)-**17a** as an amorphous white solid. $[\alpha]_D^{22.0} = -40.1$ ($c = 1.90$, CHCl$_3$); ^{1}HNMR (δ, ppm, CDCl$_3$, 300 MHz) 7.24 (d, *J* = 8.7 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 6.11 (bs, 1H), 4.75, (dd, *J* = 1.1, 8.8 Hz, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 3.42 (t, *J* = 6.5 Hz, 2H), 2.78 (d, *J* = 4.7 Hz, 3H), 2.35−2.50 (m, 1H), 1.97−2.20 (m, 2H), 1.20−1.85 (m, 12H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.91−1.08 (m, 1H), 0.86 (d, *J* = 6.0 Hz, 3H), 0.86 (s, 9H); ^{13}CNMR (δ, ppm, CDCl$_3$, 75 MHz) 176.9, 173.9, 159.1, 130.6, 129.2, 113.7, 78.6, 72.5, 69.8, 55.2, 39.9, 37.6, 36.1, 34.5, 34.4, 33.4, 29.6, 28.8, 26.1, 25.9, 24.0, 22.8, 20.8, 17.5; IR (neat, thin film) ν 3306, 2955, 1727, 1651, 1513, 1248, 1171, 1099 cm^{-1}; HRMS *m*/*z* calcd for $C_{28}H_{47}NO_5Na$ $[M + Na]^+$, 500.3346; found, 500.3350.

(*R*)-(3*S*,5*S*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-hydroxy-2-methylhexanoate [(−)-S12]. (−)-**S12** was prepared in a similar manner as alcohol (−)-**S10**, using amide (−)-**17a**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes → 100:1 EtOAc/Et$_3$N) to afford 0.048 g (82%) of alcohol (−)-**S12** as a colorless oil. $[\alpha]_D^{21.6} = -54.8$ ($c = 1.2$, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 6.25 (bs, 1H), 4.76 (dd, *J* = 9.9, 1.6 Hz, 1H), 3.55−3.70 (m, 2H), 2.77 (d, *J* = 4.8 Hz, 3H), 2.37−2.50 (m, 1H), 2.27 (bs, 1H), 2.00−2.20 (m, 2H), 1.63−1.83 (m, 2H), 1.21−1.60 (m, 10H), 1.16 (d, 7.0 Hz, 3H), 0.92−1.04 (m, 1H), 0.86 (d, overlapped, 3H), 0.85 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 75 MHz) 177.0, 174.1, 78.4, 62.2, 40.0, 37.5, 36.2, 34.6, 34.5, 33.1, 32.4, 28.8, 26.1, 25.9, 23.6, 23.1, 20.7, 17.7; IR (neat, thin film) ν 3304, 2950, 1729, 1649, 1560, 1462, 1366, 1163, 1074 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{39}NO_4Na$ $[M + Na]^+$, 380.2771; found, 380.2764.

(*R*)-(3*S*,5*S*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-2-methyl-6-oxohexanoate [(−)-3a]. (−)-**3a** was prepared in a similar manner as aldehyde (−)-**2a**, using alcohol (−)-**S12**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes → 9:1 EtOAc/hexanes) to afford 0.008 g (95%) of aldehyde (−)-**3a** as a colorless oil. $[\alpha]_D^{23.6} = -51.2$ ($c = 0.92$, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 9.75 (t, *J* = 1.3 Hz, 1H), 6.11 (bs, 1H), 4.75 (dd, *J* = 2.7, 9.3 Hz, 1H), 2.78 (d, *J* = 4.7 Hz, 3H), 2.38−2.50 (m, 2H), 1.94−2.22 (m, 2H), 1.55−1.83 (m, 4H), 1.32−1.53 (m, 4H), 1.20−1.32 (m, 3H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.93−1.07 (m, 1H), 0.86 (d, overlapped, 3H), 0.85 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 100 MHz) 202.0, 176.4, 173.8, 78.8, 43.7, 39.8, 37.6, 36.2, 34.6, 34.6, 32.9, 29.0, 26.1, 25.9, 22.9, 20.7, 19.8, 17.4; IR (neat, thin film) ν 3305, 2957, 1722, 1648, 1552, 1462, 1366, 1164 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{37}NO_4Na$ $[M + Na]^+$, 378.2614; found, 378.2615.

(*S*)-(3*S*,5*S*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-((4-methoxy benzyl)oxy)-2-methylhexanoate [(−)-*ent*-17b]. (−)-*ent*-**17b** was prepared in a similar manner as amide (−)-**16a**, using acid (+)-**6b** and amide (−)-**5**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.039 g (93%) of amide (−)-*ent*-**17b** as an amorphous white solid. $[\alpha]_D^{22.0} = -29.4$ ($c = 1.82$, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 7.24 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.08 (bs, 1H), 4.74 (dd, *J* = 8.3, 3.5 Hz, 1H), 4.41 (s, 2H), 3.79 (s, 3H), 3.41 (t, *J* = 6.5 Hz, 2H), 2.79 (d, *J* = 4.8 Hz, 3H), 2.36−2.50 (m, 1H), 1.98−2.21 (m, 2H), 1.52−1.82 (m, 4H), 1.19−1.50 (m, 7H), 1.15 (d, *J* = 7.0 Hz, 3H), 0.93−1.07 (m, 2H), 0.86 (d, overlapped, 3H), 0.85 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 75 MHz) 176.9, 173.8, 159.1, 130.6, 129.2, 113.7, 78.6, 72.5, 69.8, 55.2, 40.1, 37.6, 36.1, 34.48, 34.45, 33.5, 29.6, 28.8, 26.1, 25.9, 24.0, 22.8, 20.8, 17.4; IR (neat, thin film) ν 3292, 2954, 1727, 1650, 1513, 1462, 1245, 1171, 1098 cm^{-1}; HRMS *m*/*z* calcd for $C_{28}H_{47}NO_5Na$ $[M + Na]^+$, 500.3346; found, 500.3340.

(*S*)-(3*S*,5*S*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-6-hydroxy-2-methylhexanoate [(−)-S13]. (−)-**S13** was prepared in a similar manner as alcohol (−)-**S10**, using amide (−)-*ent*-**17b**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes → 100:1 EtOAc/Et$_3$N) to afford 0.028 g (98%) of alcohol (−)-**S13** as a colorless oil. $[\alpha]_D^{21.6} = -34.82$ ($c = 1.37$, CHCl$_3$); ^{1}H NMR (δ, ppm CDCl$_3$, 300 MHz) 6.10 (bs, 1H), 4.76 (dd, *J* = 2.2, 9.5 Hz, 1H), 3.63 (t, *J* = 6.4 Hz, 2H), 2.79 (d, *J* = 4.8 Hz, 3H), 2.39−2.51 (m, 1H), 2.00−2.23 (m, 2H), 1.91 (bs, 1H), 1.63−1.80 (m, 2H), 1.22−1.60 (m, 10H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.87 (d, overlapped, 3H), 0.86 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 75 MHz) 176.8, 174.0, 78.6, 62.5, 40.2, 37.6, 36.2, 34.5, 33.3, 32.5, 28.8, 26.2, 25.9, 25.9, 23.5, 23.0, 20.8, 17.4; IR (neat, thin film) ν 3296, 2956, 1728, 1651, 1562, 1462, 1366, 1164 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{39}NO_4Na$ $[M + Na]^+$, 380.2771; found, 380.2764.

(*S*)-(3*S*,5*S*)-2,2,5-Trimethyl-9-(methylamino)-9-oxononan-3-yl-2-methyl-6-oxohexanoate [(−)-*ent*-3b]. (−)-*ent*-**3b** was prepared in a similar manner as aldehyde (−)-**2a**, using alcohol (−)-**S13**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes → 9:1 EtOAc/hexanes) to afford 0.019 g (83%) of aldehyde (−)-*ent*-**3b** as a colorless oil. $[\alpha]_D^{23.6} = -40.6$ ($c = 1.01$, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 9.76 (s, 1H), 6.03 (bs, 1H), 4.76 (dd, *J* = 3.6, 8.4 Hz, 1H), 2.80 (d, *J* = 4.9 Hz, 3H), 2.45 (t, *J* = 6.5 Hz, 3H), 2.00−2.23 (m, 2H), 1.55−1.83 (m, 5H), 1.21−1.54 (m, 5H), 1.17 (d, *J* = 7.0 Hz, 3H), 0.94−1.10 (m, 1H), 0.87 (d, overlapped, 3H), 0.86 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 75 MHz) 202.0, 176.4, 173.8, 78.9, 78.8, 43.7, 40.0, 37.6, 36.2, 34.5, 34.5, 33.0, 28.8, 25.9, 22.9, 22.9, 19.8, 17.4; IR (neat, thin film) ν 3305, 2957, 1726, 1649, 1552, 1366, 1195, 1164 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{37}NO_4Na$ $[M + Na]^+$, 378.2615; found, 378.2614.

(3*S*,5*S*)-2,2,5-Trimethyloct-7-en-3-ol [(−)-S14]. (−)-**S14** was prepared following the literature procedure of Cavelier and co-workers. To a flask containing a solution of cyclic sulfate (−)-**8** (0.057 g, 0.27 mmol) and CuI (0.063 g, 0.32 mmol) in dry THF (0.5 mL) at −25 °C was added allylmagnesium bromide (1.0 M in ether, 1.36 mL, 1.36 mmol). The purple-colored reaction mixture was allowed to stir at −25 °C for 5 h before being warmed to room temperature and then concentrated in vacuo. The solid residue was dissolved in ether (10 mL) and treated with a 20% aqueous H$_2$SO$_4$ solution (2 mL). The contents of the flask were then stirred vigorously for 12 h before the phases were separated and the aqueous layer extracted with ether, dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (8:2 hexanes/EtOAc) to afford 0.036 g (76%

yield) of alcohol (−)-**S14** as a colorless oil. ^{1}H, ^{13}C, and optical rotation data were in agreement with literature values.[10]

Triethyl(((3*S*,5*S*)-2,2,5-trimethyloct-7-en-3-yl)oxy)silane [(−)-23]. Alcohol (−)-**S14** (0.713 g, 4.18 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and treated with imidazole (1.14 g, 16.7 mmol), DMAP (0.051 g, 0.4 mmol), and triethylsilyl chloride (0.84 mL, 5.02 mmol). The reaction mixture was allowed to stir overnight at room temperature before being diluted with CH_2Cl_2 and washed with a saturated aqueous $NaHCO_3$ solution and brine. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford 1.16 g (98% yield) of silyl ether (−)-**23** as a colorless oil. ^{1}H, ^{13}C, and optical rotation data were in agreement with literature values.[10]

(5*S*,7*S*,*E*)-5,8,8-Trimethyl-7-((triethylsilyl)oxy)non-2-enamide [(−)-S15]. To a solution of silyl ether (−)-**23** (0.049 g, 0.17 mmol) in dry CH_2Cl_2 (1 mL) was added freshly distilled acryloyl chloride (0.021 mL, 0.25 mmol), followed by the Hoveyda−Grubbs II precatalyst (0.0054 g, 0.0086 mmol). The flask was flushed with nitrogen, and the reaction mixture was allowed to stir overnight at room temperature. After the disappearance of starting material was noted by TLC, NH_4OH (1 mL) was added in a single portion. The contents of the flask were stirred vigorously for 1 h before the phases were separated and the aqueous phase extracted with CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 → 2:1 EtOAc/hexanes) to afford 0.033 g (58% yield) of amide (−)-**S15** as a pale yellow foam. $[\alpha]_D^{21.5} = -118.9$ (c = 1.12, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 300 MHz) 6.88−6.78 (m, 1H), 5.83 (d, J = 15 Hz, 1H), 3.33 (dd, J = 2.1, 8.1 Hz, 1H), 2.39−2.30 (m, 1H), 1.93−1.69 (m, 2H), 1.42−1.21 (m, 2H), 0.96 (t, J = 8.1 Hz, 9 H), 0.91 (d, J = 6.8 Hz, 3H), 0.84 (s, 9H), 0.60 (q, J = 7.6 Hz, 6H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 167.6, 144.9, 124.1, 78.6, 40.7, 38.4, 35.6, 29.5, 26.2, 21.0, 7.2, 5.8; IR (neat, thin film) ν 3348, 3183, 2956, 2913, 2876, 1674, 1646, 1617, 1414, 1107, 1086, 977, 737 cm^{-1}; HRMS m/z calcd for $C_{18}H_{37}NO_2SiNa$ $[M + Na]^+$, 350.2486; found, 350.2485.

(5*S*,7*S*)-7-Hydroxy-5,8,8-trimethylnonanamide [(−)-24]. Amide (−)-**S15** (0.026 g, 0.074 mmol) was dissolved in a 1:1 mixture of EtOH/EtOAc (2 mL) and treated with Pd/C (0.025 g). The reaction mixture was then flushed with hydrogen gas and allowed to stir overnight under an atmosphere of hydrogen (using a balloon). After TLC showed the complete consumption of starting material, the reaction mixture was diluted with EtOAc and filtered through a short plug of Celite, rinsing several times with fresh EtOAc. The filtrate was concentrated in vacuo and purified by flash column chromatography (100:1 EtOAc/Et_3N) to afford 0.014 g (89% yield) of amide (−)-**24** as an amorphous white solid. $[\alpha]_D^{24.1} = -54.9$ (c = 1.01, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 400 MHz) 5.64 (bs, 2H), 3.28 (dd, J = 2.0, 10.4 Hz, 1H), 2.22 (t, J = 7.2 Hz, 2H), 1.87−1.48 (m, 5H), 1.39−1.32 (m, 1H), 1.26−1.19 (m, 1H), 1.11−1.02 (m, 1H), 0.94 (d, J = 6.4 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (δ, ppm, $CDCl_3$, 100 MHz) 175.7, 77.2, 39.0, 35.9, 34.9, 34.6, 29.4, 25.7, 22.8, 20.9; IR (neat, thin film) ν 3352, 3195, 2953, 2870, 1667, 1615, 1479, 1463, 1394, 1364, 1072 cm^{-1}; HRMS m/z calcd for $C_{12}H_{25}NO_2Na$ $[M + Na]^+$, 238.1778; found, 238.1776.

(*E*)-1,4-Diiodobut-1-ene (26). Triphenylphosphine (2.15 g, 8.21 mmol) and imidazole (0.559 g, 8.21 mmol) were dissolved in dry CH_2Cl_2 (25 mL) and cooled to 0 °C. To this was added iodine crystals (2.08 g, 8.21 mmol), and the contents of the flask were allowed to stir at 0 °C for 15 min before a solution of alcohol **25**[31] (1.55 g, 7.82 mmol) in dry CH_2Cl_2 (15 mL) was added via cannula. The cooling bath was removed, and the reaction mixture was allowed to stir at room temperature for 4 h. The mixture was concentrated in vacuo and redissolved in ether. The triphenylphosphine oxide, which precipitated, was filtered over Celite, and the filtrate was washed several times with ether. The combined ether layers were again concentrated in vacuo and purified directly by flash column chromatography (100% hexanes) to afford 2.18 g (90% yield) of diiodide **26** as a slightly yellow oil. ^{1}H NMR (δ, ppm, $CDCl_3$, 300 MHz) 6.52−6.43 (m, 1H), 6.21 (d, J = 14.4, 1H), 3.15 (t, J = 6.0 Hz, 2H), 2.62 (q, J = 6.9 Hz, 2H); ^{13}C NMR (δ, ppm, $CDCl_3$, 75 MHz) 143.9, 78.0, 39.5, 2.9; IR (neat, thin film) ν 3045, 2956, 1602, 1419, 1246, 1199, 1167, 1117, 945. Because of volatility, we were not able to obtain an HRMS for diiodide **26**.

(*R*,*E*)-*N*-((1*S*,2*S*)-1-Hydroxy-1-phenylpropan-2-yl)-6-iodo-*N*,2-dimethylhex-5-enamide [(+)-S16]. Lithium chloride (0.147 g, 3.47 mmol) was placed in a round-bottom flask under vacuum and flame-dried before use. Once cooled, the flask was placed under an atmosphere of nitrogen and charged with diisopropylamide (0.18 mL, 1.30 mmol) and dry THF (1 mL). The contents of the flask were cooled to 0 °C and treated with *n*BuLi (2.5 M in hexanes, 0.52 mL, 1.30 mmol) dropwise. After 20 min, the LDA solution was cooled to −78 °C before a solution of amide **27a** (0.128 g, 0.57 mmol) in dry THF (2 mL) was added dropwise via cannula. After 1 h at −78 °C, the flask was allowed to warm to 0 °C for 15 min, and then room temperature for 5 min. The flask was then cooled back down to 0 °C, and a solution of diiodide **26** (0.446 g, 1.44 mmol) in dry THF (1 mL) was added slowly via cannula. The reaction mixture was allowed to stir at 0 °C for 30 min before being quenched by the addition of a saturated aqueous solution of NH_4Cl (10 mL). The phases were separated, and the aqueous phase was extracted with CH_2Cl_2, followed by EtOAc. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.127 g [54% (83% borsm)] of vinyl amide (+)-**S16** as an amorphous white solid and as a pair of rotamers (~3:1 ratio). $[\alpha]_D^{23.8}$ = +39.3 (c = 1.90, $CHCl_3$); ^{1}H NMR (mixture of rotamers, δ, ppm, $CDCl_3$, 400 MHz) 7.40−7.24 (m, 8H), 6.51 (minor, quintet, J = 6.8 Hz, 0.3H), 6.40 (major, quintet, J = 7.6 Hz, 1H), 6.02 (minor, d, J = 14.8 Hz, 0.3H), 5.8 (major, d, J = 14.4 Hz, 1H), 4.63−4.55 (m, 2H), 4.42 (bs, 1H), 4.07−4.00 (minor, m, 0.3H), 2.90 (minor, s, 1H), 2.84 (major, s, 3H), 2.67−2.53 (m, 1.4H), 2.07−1.85 (m, 3.3H), 1.80−1.72 (m, 1H), 1.45−1.33 (m, 1.5H), 1.14 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 4H), 1.01 (d, J = 6.8 Hz, 1.3H); ^{13}C NMR (mixture of rotamers, δ, ppm, $CDCl_3$, 100 MHz) 177.9, 176.9, 146.4, 145.8, 142.5, 141.4, 128.7, 128.3, 127.5, 126.9, 126.1, 76.1, 75.4, 75.0, 57.7, 35.5, 34.7, 33.7, 32.2, 27.1, 18.0, 17.4, 15.6, 14.3; IR (neat, thin film) ν 3377, 3061, 3029, 2968, 2933, 2873, 1616, 1453, 1409, 1374, 1108. 1082, 1050, 1027, 701 cm^{-1}; HRMS m/z calcd for $C_{17}H_{24}INO_2Na$ $[M + Na]^+$, 424.0744; found, 424.0738.

(*R*,*E*)-6-Iodo-2-methylhex-5-enoic acid [(−)-28a]. A solution of amide (+)-**S16** (0.095 g, 0.230 mmol) in *t*-BuOH (2 mL) and MeOH (2 mL) was treated with an aqueous NaOH solution (3.22 N, 4 mL). A condenser was attached, and the mixture was heated to 85 °C for 24 h. The flask was allowed to cool before the contents were concentrated in vacuo. The aqueous residue was diluted with water and washed with CH_2Cl_2. The aqueous layer was acidified with concentrated HCl solution and again extracted with CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated to afford 0.058 g (95%) of vinyl iodide (−)-**28a** as a colorless oil that would be used directly in the next step without further purification. $[\alpha]_D^{21.9} = -18.8$ (c = 0.82, $CHCl_3$); ^{1}H NMR (δ, ppm, $CDCl_3$, 400 MHz) 6.54−6.44 (m, 1H), 6.06 (td, J = 1.2, 14.4 Hz, 1H), 2.48 (sextet, J = 6.9 Hz, 1H), 2.12 (dq, J = 1.2, 7.5 Hz, 2H), 1.87−1.75 (m, 1H), 1.62−1.48 (m, 1H), 1.20 (d, J = 7.2 Hz, 3H); ^{13}C NMR (δ, ppm, $CDCl_3$, 100 MHz) 182.3, 145.2, 75.6, 38.4, 33.6, 31.9, 16.8; IR (neat, thin film) ν 3049, 2967, 2930, 1702 cm^{-1}; HRMS m/z calcd for $C_7H_{11}IO_2Na$ $[M + Na]^+$, 276.9696; found, 276.9694.

(*R*,*E*)-(3*S*,5*S*)-9-Amino-2,2,5-trimethyl-9-oxononan-3-yl-6-iodo-2-methylhex-5-enoate [(−)-31]. A solution of vinyl iodide (−)-**28a** (0.044 g, 0.17 mmol) in dry THF (1.7 mL) was treated with freshly distilled DIPEA (47.3 mL, 0.27 mmol), followed by 2,4,6-trichlorobenzoyl chloride (26.5 mL, 0.17 mmol). The mixture was stirred at room temperature for 3 h, and the resulting mixed anhydride was then concentrated in vacuo. The residue was dissolved in dry toluene (4.0 mL) and was added, via cannula, to a separate flask containing amide (−)-**24** (0.0157 g, 0.072 mmol) and DMAP (0.0142 g, 0.11 mmol). The reaction mixture was allowed to stir at room temperature for 18 h before CH_2Cl_2 (20 mL) was added, and the mixture was washed with a saturated aqueous solution of $NaHCO_3$ (20 mL). The phases were separated, and the aqueous layer was extracted with additional CH_2Cl_2. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.027 g (81% yield) of amide (−)-**31** as an amorphous white solid. $[\alpha]_D^{21.4}$ = −42.1 (c = 1.08, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 6.49 (dt, J = 7.2, 14.4 Hz, 1H), 6.02 (d, J = 14.4 Hz, 1H), 5.88 (bs, 1H), 5.46 (bs, 1H), 4.79 (dd, J = 4.5, 6.3 Hz, 1H), 2.45 (sextet, J = 6.9 Hz, 1H), 2.23−2.15 (m, 2H), 2.12−2.05 (m, 2H), 1.86−1.69 (m, 2H), 1.61−1.25 (m, 6H), 1.17 (d, J = 7.2 Hz, 3H), 1.11−0.99 (m, 1H), 0.91−0.87 (doublet/singlet overlapping, 12H); ^{13}C NMR (δ, ppm, CDCl$_3$, 75 MHz) 176.5, 175.8, 145.6, 79.0, 75.5, 39.3, 37.7, 35.7, 34.79, 34.77, 33.9, 32.3, 29.2, 26.1, 22.8, 21.1, 17.5; IR (neat, thin film) ν 3429, 3351, 3203, 2962, 2934, 2868, 1725, 1665, 1607, 1461, 1380, 1366, 1259, 1181, 1119, 1067, 957, 935 cm^{-1}; HRMS m/z calcd for $C_{19}H_{34}INO_3Na$ [M + Na]$^+$, 474.1476; found, 474.1471.

(3*R*,13*S*,15*S*,*E*)-15-(*tert*-Butyl)-3,8,13-trimethyl-1-oxa-8-aza-cyclopentadec-6-ene-2,9-dione [(+)-21a]. A mixture of amide (−)-**31** (0.022 g, 0.048 mmol), copper iodide (0.005 g, 0.026 mmol), and cesium carbonate (0.030 g, 0.092 mmol) was suspended in dry THF (5 mL). *N*,*N*′-Dimethylethylenediamine (20 μL, 0.026 mmol) was added, and the reaction flask was degassed by bubbling dry nitrogen gas for 10 min. The septum was quickly removed and replaced with a glass stopper. The contents of the flask were then heated at 60 °C overnight. The flask was allowed to cool to room temperature before being diluted with EtOAc and filtered through a short plug of silica gel. The crude *N*-H macrolide was then concentrated in vacuo and purified by flash column chromatography (8:2 hexanes/EtOAc) to afford 0.005 g (32%) of enamide **S17**, which was used in the next step without extensive characterization. Enamide **S17** (0.005 g, 0.015 mmol) was dissolved in dry THF (0.5 mL), cooled to 0 °C, and treated with sodium hydride (60% dispersion, 0.003 g, 0.077 mmol). The cooling bath was removed, and the flask was allowed to warm to room temperature and stir for 20 min. Iodomethane (0.1 mL, 1.61 mmol) was then added. After 20 min, the reaction mixture was diluted with EtOAc and quenched with water. The phases were separated, and the aqueous phase was extracted with additional EtOAc. The combined organic layers were then dried over MgSO$_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (8:2 hexanes/EtOAc) to afford 0.005 g (90%) of (+)-**21a** as a colorless oil. $[\alpha]_D^{21.4}$ = +2.7 (c = 0.39, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 400 MHz) 6.63 (d, J = 13.6 Hz, 1H), 4.92 (ddd, J = 5.2, 8.8, 13.6 Hz, 1H), 4.85 (dd, J = 2.0, 9.6 Hz, 1H), 3.05 (s, 3H), 2.60−2.42 (m, 3H), 2.32 (dt, J = 7.2, 13.6 Hz, 1H), 2.24−2.17 (m, 1H), 2.03−1.95 (m, 1H), 1.84−1.74 (m, 1H), 1.68−1.54 (m, 2H), 1.49−1.30 (m, 4H), 1.26 (d, J = 7.2 Hz, 3H), 1.03−0.93 (m, 1H), 0.89 (d, J = 6.4 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 100 MHz) 175.4, 172.8, 129.8, 110.2, 76.5, 37.2, 36.6, 35.4, 34.3, 33.6, 31.0, 29.8, 29.5, 27.3, 25.9, 24.9, 20.0, 19.2; IR (neat, thin film) ν 2959, 2927, 2873, 1728, 1675, 1646, 1466, 1413, 1384, 1366, 1333, 1298, 1240, 1205, 1193, 1171, 1121, 933 cm^{-1}; HRMS m/z calcd for $C_{20}H_{35}NO_3Na$ [M + Na]$^+$, 360.2509; found, 360.2503.

(*S*,*E*)-*N*-((1*R*,2*R*)-1-Hydroxy-1-phenylpropan-2-yl)-6-iodo-*N*,2-dimethylhex-5-enamide [(−)-S18]. (−)-**S18** was prepared in a similar manner as vinyl iodide (+)-**S16**, using amide **27b**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.969 g [50% (77% borsm)] of vinyl iodide (−)-**S18** as an amorphous white solid and as a pair of rotamers (~3:1 ratio). $[\alpha]_D^{23.8}$ = −35.1 (c = 1.23, CHCl$_3$); ^{1}H NMR (mixture of rotamers, δ, ppm, CDCl$_3$, 400 MHz) 7.40−7.24 (m, 8H), 6.51 (minor, quintet, J = 6.8 Hz, 0.3H), 6.40 (major, quintet, J = 7.6 Hz, 1H), 6.02 (minor, d, J = 14.8 Hz, 0.3H), 5.8 (major, d, J = 14.4 Hz, 1H), 4.63−4.55 (m, 2H), 4.42 (bs, 1H), 4.07−4.00 (minor, m, 0.3H), 2.90 (minor, s, 1H), 2.84 (major, s, 3H), 2.67−2.53 (m, 1.4H), 2.07−1.85 (m, 3.3H), 1.80−1.72 (m, 1H), 1.45−1.33 (m, 1.5H), 1.14 (d, J = 6.8 Hz, 3H), 1.05 (d, J = 6.8 Hz, 4H), 1.01 (d, J = 6.8 Hz, 1.3H); ^{13}C NMR (mixture of rotamers, δ, ppm, CDCl$_3$, 100 MHz) 177.9, 176.9, 146.4, 145.8, 142.5, 141.4, 128.7, 128.3, 127.5, 126.9, 126.1, 76.1, 75.4, 75.0, 57.7, 35.5, 34.7, 33.7, 32.2, 27.1, 18.0, 17.4, 15.6, 14.3; IR (neat, thin film) ν 3377, 3061, 3029, 2968, 2933, 2873, 1616, 1453, 1409, 1374, 1108. 1082, 1050, 1027, 701 cm^{-1}; HRMS m/z calc'd for $C_{17}H_{24}INO_2Na$ [M + Na]$^+$, 424.0744; found, 424.0738.

(*S*,*E*)-6-Iodo-2-methylhex-5-enoic Acid [(+)-28b]. (+)-**28b** was prepared in a similar manner as vinyl iodide (−)-**28a**, using vinyl iodide (−)-**S18**. The crude product [0.012 g (65%)], as an amorphous white solid, was sufficiently clean to use in the next step without further purification. $[\alpha]_D^{25.1}$ = +21.0 (c = 1.06, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 400 MHz) 6.54−6.44 (m, 1H), 6.06 (td, J = 1.2, 14.4 Hz, 1H), 2.48 (sextet, J = 6.9 Hz, 1H), 2.12 (dq, J = 1.2, 7.5 Hz, 2H), 1.87−1.75 (m, 1H), 1.62−1.48 (m, 1H), 1.20 (d, J = 7.2 Hz, 3H); ^{13}C NMR (δ, ppm, CDCl$_3$, 100 MHz) 182.3, 145.2, 75.6, 38.4, 33.6, 31.9, 16.8; IR (neat, thin film) ν 3049, 2967, 2930, 1702 cm^{-1}; HRMS m/z calcd for $C_7H_{11}IO_2Na$ [M + Na]$^+$, 276.9696; found, 276.9699.

(*S*,*E*)-(3*S*,5*S*)-9-Amino-2,2,5-trimethyl-9-oxononan-3-yl-6-iodo-2-methylhex-5-enoate [(−)-32]. (−)-**32** was prepared in a similar manner as amide (−)-**31**, using vinyl iodide (+)-**28b**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.098 g (74%) of amide (−)-**32** as an amorphous white solid. $[\alpha]_D^{23.2}$ = −20.5 (c = 1.01, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 400 MHz) 6.52−6.44 (m, 1H), 6.02 (d on top of a bs, J = 14.4 Hz, 3H), 4.78 (dd, J = 3.6, 8.4 Hz, 1H), 2.49−2.42 (m, 1H), 2.23−2.05 (m, 4H), 1.85−1.71 (m, 2H), 1.55−1.43 (m, 3H), 1.41−1.37 (m, 1H), 1.31−1.20 (m, 1H), 1.16 (d, J = 6.8 Hz, 3H), 1.10−0.99 (m, 1H), 0.98 (d, J = 6.8 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 100 MHz) 176.3 (2C), 145.4, 78.8, 75.3, 39.2, 37.5, 34.6, 34.5, 33.7, 33.6, 32.1, 28.9, 25.9, 22.6, 20.8, 17.4; IR (neat, thin film) ν 3423, 3350, 3200, 2964, 2872, 1724, 1667, 1607, 1462, 1397, 1379, 1366, 1222, 1186, 1123, 1065, 957 cm^{-1}; HRMS m/z calcd for $C_{19}H_{34}INO_3Na$ [M + Na]$^+$, 474.1476; found, 474.1463.

(3*S*,13*S*,15*S*,*E*)-15-(*tert*-Butyl)-3,8,13-trimethyl-1-oxa-8-aza-cyclopentadec-6-ene-2,9-dione [(+)-*ent*-21b]. (+)-*ent*-**21b** was prepared in a similar manner as macrolide (−)-**21a**, using amide (−)-**32**. The crude product was purified by flash column chromatography (8:2 hexanes/EtOAc) to afford 0.013 g (40% over two steps) of macrolide (+)-*ent*-**21b** as a colorless oil. $[\alpha]_D^{22.9}$ = +23.4 (c = 0.65, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 400 MHz) 6.47 (d, J = 14 Hz, 1H), 5.27 (dt, J = 7.2, 14 Hz, 1H), 4.88 (dd, J = 2.0, 10.8 Hz, 1H), 3.04 (s, 3H), 2.52−2.43 (m, 1H), 2.42−2.34 (m, 2H), 2.33−2.24 (m, 2H), 1.86−1.71 (m, 3H), 1.70−1.45 (m, 3H), 1.41−1.31 (m, 2H), 1.21 (d, J = 7.2 Hz, 3H), 1.11−1.02 (m, 1H), 0.90 (d, J = 6.4 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 100 MHz) 175.3, 172.9, 130.7, 117.3, 38.9, 35.8, 35.2, 34.5, 32.8, 31.7, 29.3, 27.0, 26.1, 24.3, 20.6, 16.8 [*Note*: At 100 MHz, we did not observe the C(7) CH signal at δ 76.9 ppm. At this frequency, the peak is buried under the CDCl$_3$ peak. Pleasingly, the peak is visible in the HMQC spectra]; IR (neat, thin film) ν 2963, 2873, 1725, 1676, 1649, 1465, 1366, 1250, 1180, 1127, 1072, 936 cm^{-1}; HRMS m/z calcd for $C_{20}H_{35}NO_3Na$ [M + Na]$^+$, 360.2509; found, 360.2503.

(3*S*,5*R*)-2,2,5-Trimethyloct-7-en-3-ol [(−)-S19]. (−)-**S19** was prepared in a similar manner as alcohol (−)-**S14**, using (+)-**10**. The crude product was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford 0.170 g (67%) of alcohol (−)-**S19** as a colorless oil. $[\alpha]_D^{22.1}$ = −51.1 (c = 1.19, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 5.79 (dddd, J = 7.0, 7.0, 10.9, 16.3 Hz, 1H), 5.02 (dddd, J = 1.5, 2.3, 3.7, 5.2 Hz, 1H), 4.98 (t, J = 1.5 Hz, 1H), 3.29 (dd, J = 1.9, 10.5 Hz, 1H), 1.90−2.12 (m, 2H), 1.76 (m, 1H), 1.36 (ddd, J = 3.3, 10.5, 13.9 Hz, 1H), 1.34 (bs, 1H), 1.19 (ddd, 1.8, 10.5, 13.9 Hz, 1H), 0.90 (d, J = 6.7 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 75 MHz) 137.5, 115.8, 77.4, 42.7, 38.4, 34.8, 29.6, 25.6, 18.7; IR (neat, thin film) ν 3398, 2957, 1824, 1639, 1477, 1465, 1377, 1305, 1073, 993, 909 cm^{-1}; HRMS m/z calcd for $C_{11}H_{22}ONa$ [M + Na]$^+$, 193.1563; found, 193.1562.

Triethyl(((3*S*,5*R*)-2,2,5-trimethyloct-7-en-3-yl)oxy)silane [(−)-33]. (−)-**33** was prepared in a similar manner as silyl ether (−)-**23**, using alcohol (−)-**S19**. The crude product was purified by flash column chromatography (95:5 hexanes/EtOAc) to afford 0.261 g (92%) of silyl ether (−)-**33** as a colorless oil. $[\alpha]_D^{23.4}$ = −32.9 (c = 1.13, CHCl$_3$); ^{1}H NMR (δ, ppm, CDCl$_3$, 300 MHz) 5.78 (dddd, J = 7.0, 7.0, 11.4, 16.0 Hz, 1H), 5.01 (bd, J = 5.9 Hz, 1H), 4.97 (s, 1H), 3.34 (dd, J = 1.5, 9.1 Hz, 1H), 1.86−2.07 (m, 2H), 1.55−1.71 (m, 1H), 1.38 (ddd, J = 2.6, 9.1, 13.6 Hz, 1H), 1.15 (ddd, J = 1.5, 10.9, 13.6 Hz, 1H), 0.97 (t, J = 7.8 Hz, 6H), 0.86 (d, J = 6.5 Hz, 3H), 0.84 (s, 9H), 0.61 (q, J = 7.8 Hz, 9H); ^{13}C NMR (δ, ppm, CDCl$_3$, 75 MHz) 137.5, 115.6, 78.8, 43.0, 40.2, 35.5, 29.6, 26.2, 19.0, 7.2, 5.8; IR (neat, thin film) ν 2955, 2876, 1640, 1460, 1238, 1092, 1029, 910, 737 cm^{-1}; HRMS *m*/*z* calcd for $(C_{17}H_{36}OSi)_2Na$ [2M + Na]$^+$, 591.4963; found, 591.4957.

(5*S*,7*S*,*E*)-5,8,8-Trimethyl-7-((triethylsilyl)oxy)non-2-enamide [(−)-S20]. (−)-**S20** was prepared in a similar manner as amide (−)-**S15**, using silyl ether (−)-**33**. The crude product was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford 0.135 g (82%) of amide (−)-**S20** as a pale yellow foam and as a ca. 25:1 mixture of *E*/*Z* olefin isomers that could not be separated by column chromatography. $[\alpha]_D^{22.8}$ = −23.6 (*c* = 2.33, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 6.82 (dt, *J* = 7.5, 15.2 Hz, 1H), 6.01 (bs, 1H), 5.82 (d, *J* = 15.2 Hz, 1H), 5.56 (bs, 1H), 3.32 (dd, *J* = 1.1, 9.0 Hz, 1H), 2.18 (ddd, *J* = 6.1, 6.1, 13.5 Hz, 1H), 2.04 (ddd, *J* = 8.0, 8.0, 14.5 Hz, 1H), 1.65−1.83 (m, 1H), 1.36 (ddd, *J* = 2.1, 9.0, 13.7 Hz, 1H), 1.13−1.25 (m, 1H), 0.95 (t, *J* = 7.8 Hz, 6H), 0.86 (d, *J* = 6.5 Hz, 3H), 0.82 (s, 9H), 0.59 (q, *J* = 7.8 Hz, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 168.0, 144.9, 123.9, 78.6, 41.1, 40.4, 35.5, 29.4, 26.2, 18.9, 7.2, 5.8; IR (neat, thin film) *ν* 3335, 3169, 2955, 1673, 1616, 1415, 1085, 739 cm^{-1}; HRMS *m*/*z* calcd for $C_{18}H_{37}NO_2SiNa$ [M + Na]$^+$, 350.2485; found, 350.2478.

(5*R*,7*S*)-7-Hydroxy-5,8,8-trimethylnonanamide [(−)-34]. (−)-**34** was prepared in a similar manner as amide (−)-**24**, using amide (−)-**S20**. The crude product was purified by flash column chromatography (100:1 EtOAc/Et$_3$N) to afford 0.074 g (87%) of amide (−)-**34** as an amorphous white solid. $[\alpha]_D^{22.0}$ = −13.7 (*c* = 0.43, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 5.40 (bs, 2H), 3.28 (dd, *J* = 1.7, 10.4 Hz, 1H), 2.22 (t, *J* = 7.6 Hz, 2H), 1.58−1.78 (m, 3H), 1.12−1.42 (m, 5H), 0.90 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 175.7, 77.3, 38.6, 37.7, 36.0, 34.8, 29.3, 25.7, 22.8, 19.0; IR (neat, thin film) *ν* 3351, 2953, 1666, 1462, 1394, 1075, 1007 cm^{-1}; HRMS *m*/*z* calcd for $C_{12}H_{25}NO_2Na$ [M + Na]$^+$, 238.1777; found, 238.1775.

(*R*,*E*)-(3*S*,5*R*)-9-Amino-2,2,5-trimethyl-9-oxononan-3-yl-6-iodo-2-methylhex-5-enoate [(−)-35]. (−)-**35** was prepared in a similar manner as amide (−)-**31**, using amide (−)-**34** and acid (−)-**28a**. The crude product was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford 0.033 g (45%) of amide (−)-**35** as an amorphous white solid. $[\alpha]_D^{21.7}$ = −16.9 (*c* = 1.63, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 6.48 (dt, *J* = 7.0, 14.4 Hz, 1H), 6.01 (d, *J* = 14.4 Hz, 1H), 5.75 (bs, 1H), 5.46 (bs, 1H), 4.82 (d, *J* = 10.6 Hz, 1H), 2.36−2.51 (m, 1H), 2.18 (t, *J* = 7.6 Hz, 2H), 2.08 (q, *J* = 7.5 Hz, 2H), 1.71−1.87 (m, 1H), 1.38−1.70 (m, 4H), 1.18−1.36 (m, 4H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 175.9, 175.6, 145.5, 78.2, 75.2, 39.0, 37.7, 36.8, 36.1, 34.6, 33.7, 32.1, 29.5, 26.0, 23.1, 19.0, 17.3; IR (neat, thin film) *ν* 3351, 2964, 1726, 1667, 1462, 1380, 1183, 1067, 935 cm^{-1}; HRMS *m*/*z* calcd for $C_{19}H_{34}INO_3Na$ [M + Na]$^+$, 474.1475; found, 474.1463.

(3*R*,13*R*,15*S*,*E*)-15-(*tert*-Butyl)-3,8,13-trimethyl-1-oxa-8-aza-cyclopentadec-6-ene-2,9-dione [(−)-22a]. (−)-**22a** was prepared in a similar manner as macrolide (−)-**21a**, using amide (−)-**35**. The crude product was purified by flash column chromatography (85:15 hexanes/EtOAc) to afford 0.005 g (18% over two steps) of macrolide (−)-**22a** as a colorless oil. $[\alpha]_D^{24.0}$ = −44.0 (*c* = 0.16, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 6.68 (d, *J* = 13.8 Hz, 1H), 4.86 (ddd, *J* = 4.3, 10.2, 4.7 Hz, 1H), 4.78 (dd, *J* = 0.3, 9.9 Hz, 1H), 3.07 (s, 3H), 2.64 (dt, *J* = 8.1, 13.6 Hz, 1H), 2.44−2.58 (m, 1H), 2.02−2.39 (m, 3H), 1.84−2.01 (m, 2H), 1.30−1.46 (m, 5H), 1.23 (d, *J* = 7.2 Hz, 3H), 1.03−1.13 (m, 2H), 0.94 (d, *J* = 4.8 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 175.8, 172.1, 129.9, 110.2, 78.6, 38.4, 37.0, 35.3, 34.9, 31.8, 31.7, 29.7, 29.1, 28.0, 25.9, 23.3, 19.6, 19.4; IR (neat, thin film) *ν* 2962, 1729, 1675, 1646, 1464, 1384, 1199, 1165, 1125, 1084, 930 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{35}NO_3Na$ [M + Na]$^+$, 360.2509; found, 360.2504.

(*S*,*E*)-(3*S*,5*R*)-9-Amino-2,2,5-trimethyl-9-oxononan-3-yl-6-iodo-2-methylhex-5-enoate [(−)-36]. (−)-**36** was prepared in a similar manner as amide (−)-**31**, using amide (−)-**34** and acid (+)-**28b**. The crude product was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford 0.052 g (65%) of amide (−)-**36** as an amorphous white solid. $[\alpha]_D^{22.2}$ = −4.1 (*c* = 0.26, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 6.48 (dt, *J* = 7.0, 14.4 Hz, 1H), 6.01 (d, *J* = 14.4 Hz, 1H), 5.79 (bs, 1H), 5.48 (bs, 1H), 4.82 (dd, *J* = 1.2, 10.7 Hz, 1H), 2.36−2.50 (m, 1H), 2.18 (t, *J* = 6.7 Hz, 2H), 2.07 (q, *J* = 7.4 Hz, 2H), 1.80 (ddd, *J* = 7.6, 13.6, 15.5 Hz, 1H), 1.37−1.68 (m, 5H), 1.13−1.33 (m, 3H), 1.15 (d, *J* = 7.1 Hz, 3H), 0.89 (d, *J* = 5.5 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 175.9, 175.6, 145.5, 78.2, 75.2, 39.2, 37.7, 36.9, 36.1, 34.5, 33.7, 32.1, 29.4, 26.0, 23.1, 19.0, 17.4; IR (neat, thin film) *ν* 3351, 2964, 1726, 1666, 1461, 1366, 1183, 1066 cm^{-1}; HRMS *m*/*z* calcd for $C_{19}H_{34}INO_3Na$ [M + Na]$^+$, 474.1475; found, 474.1462.

(3*S*,13*R*,15*S*,*E*)-15-(*tert*-Butyl)-3,8,13-trimethyl-1-oxa-8-aza-cyclopentadec-6-ene-2,9-dione [(−)-*ent*-22b]. (−)-*ent*-**22b** was prepared in a similar manner as macrolide (−)-**21a**, using amide (−)-**36**. The crude product was purified by flash column chromatography (9:1 hexanes/EtOAc) to afford 0.010 g (29% over two steps) of macrolide (−)-*ent*-**22b** as a colorless oil. $[\alpha]_D^{23.2}$ = −45.5 (*c* = 0.5, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 6.66 (d, *J* = 13.9 Hz, 1H), 5.13 (dt, *J* = 13.9, 6.8 Hz, 1H), 4.86 (dd, *J* = 0.9, 10.2 Hz, 1H), 3.06 (s, 3H), 2.36−2.66 (m, 3H), 2.03−2.36 (m, 2H), 1.50−1.97 (m, 5H), 1.23−1.40 (m, 3H), 1.19 (d, *J* = 6.9 Hz, 3H), 1.10−1.20 (m, 1H), 0.94 (d, *J* = 6.0 Hz, 3H), 0.90 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 175.6, 172.6, 131.0, 112.9, 79.0, 38.0, 36.5, 36.4, 34.9, 33.9, 33.0, 30.8, 27.7, 27.2, 26.1, 22.7, 20.6, 17.5; IR (neat, thin film) *ν* 2964, 1725, 1675, 1647, 1463, 1382, 1260, 1178, 1082, 935 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{35}NO_3Na$ [M + Na]$^+$, 360.2509; found, 360.2506.

(*R*)-4-Hydroxy-5,5-dimethylhexan-2-one [(+)-*ent*-7]. (+)-*ent*-**7** was prepared in a similar manner as alcohol (−)-**7**, using L-proline as organocatalyst. The crude product was purified by flash column chromatography (4:1 hexanes/EtOAc) to afford 2.16 g (51%) of alcohol (+)-*ent*-**7** as a slightly yellow oil. $[\alpha]_D^{23.6}$ = +71.1 (*c* = 1.11, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 3.68 (dd, *J* = 2.2, 10.1 Hz, 1H), 2.93 (bs, 1H), 2.59 (dd, *J* = 2.1, 17.1 Hz, 1H), 2.44 (dd, *J* = 10.1, 17.2 Hz, 1H), 2.16 (s, 3H), 0.87 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 210.4, 74.8, 45.0, 34.1, 30.8, 25.5; IR (neat, thin film) *ν* 3468, 2956, 2872, 1710, 1480, 1365, 1288, 1245, 1163, 1076 cm^{-1}; HRMS *m*/*z* calcd for $(C_8H_{16}O_2)_2Na$ [2M + Na]$^+$, 311.2193; found, 311.2193.

(2*R*,4*R*)-5,5-Dimethylhexane-2,4-diol [(+)-*ent*-S1]. (+)-*ent*-**S1** was prepared in a similar manner as diol (−)-**S1**, using alcohol (+)-*ent*-**7**. The crude product was purified by flash column chromatography (1:1 hexanes/EtOAc) to afford 0.626 g (65%) of diol (+)-*ent*-**S1** as an amorphous white solid. $[\alpha]_D^{23.5}$ = +1.9 (*c* = 1.15, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 4.04−3.92 (m, 1H), 3.46 (dd, *J* = 1.9, 10.6 Hz, 1H), 3.13 (bs, 1H), 2.67 (bs, 1H), 1.58 (ddd, *J* = 2.2, 2.2, 14.4 Hz, 1H), 1.39 (ddd, *J* = 9.7, 10.4, 14.4 Hz, 1H), 1.20 (d, *J* = 6.2 Hz, 3H), 0.33 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 81.0, 69.3, 38.6, 34.8, 25.5, 24.5; IR (neat, thin film) *ν* 3351, 2961, 2871, 1127, 1079 cm^{-1}; HRMS *m*/*z* calcd for $C_8H_{18}O_2Na$ [M + Na]$^+$, 169.1199; found, 169.1198.

(4*R*,6*R*)-4-(*tert*-Butyl)-6-methyl-1,3,2-dioxathiane 2,2-dioxide [(+)-*ent*-8]. (+)-*ent*-**8** was prepared in a similar manner as sulfate (−)-**8**, using diol (+)-*ent*-**S1**. The crude product was purified by flash column chromatography (8:1 hexanes/EtOAc) to afford 0.822 g (92% over two steps) of *syn*-cyclic sulfate (+)-*ent*-**8** as an amorphous white solid. $[\alpha]_D^{23.0}$ = +4.2 (*c* = 1.65, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 5.00−4.86 (m, 1H), 4.52 (dd, *J* = 5.6, 8.8 Hz, 1H), 1.85 (t, *J* = 5.5 Hz, 1H), 1.85 (t, *J* = 8.6 Hz, 1H), 1.47 (dd, *J* = 6.3, 8.8 Hz, 3H), 1.00 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 91.8, 81.0, 34.3, 31.6, 25.2, 20.8; IR (neat, thin film) *ν* 2966, 2877, 1386, 1370, 1187, 1045, 892, 876 cm^{-1}; HRMS *m*/*z* calcd for $C_8H_{16}O_4SNa$ [M + Na]$^+$, 231.0662; found, 231.0661.

(3*R*,5*R*)-2,2,5-Trimethyloct-7-en-3-ol [(+)-37]. (+)-**37** was prepared in a similar manner as alcohol (−)-**S14**, using sulfate (+)-*ent*-**8**. The crude product was purified by flash column chromatography (9:1 hexanes/EtOAc) to afford 0.80 g (88%) of alcohol (+)-**37** as a colorless oil. $[\alpha]_D^{23.0}$ = +37.3 (*c* = 1.07, CHCl$_3$); ^{1}H NMR (*δ*, ppm, CDCl$_3$, 300 MHz) 5.86−5.86 (m, 1H), 5.05−4.97 (m, 2H), 3.31 (dd, *J* = 1.8, 10.2 Hz, 1H), 1.93−1.70 (m, 2H), 1.42 (ddd, *J* = 1.8, 9.2, 14.3 Hz, 1H), 1.36 (bs, 1H), 1.19 (ddd, *J* = 5.1, 9.2, 19.4 Hz, 1H), 0.95 (d, *J* = 6.6, 3H), 0.88 (s, 9H); ^{13}C NMR (*δ*, ppm, CDCl$_3$, 75 MHz) 137.1, 116.0, 77.5, 39.8, 38.5, 35.0, 29.8, 25.6, 20.9; IR (neat, thin film) *ν* 3391, 3076, 2956, 2870, 1478, 1459 1364 1069, 992, 910 cm^{-1}; HRMS *m*/*z* calcd for $(C_{11}H_{22}O)_2Na$ [2M + Na]$^+$, 363.3233; found, 363.3234.

(5*R*,7*R*,*E*)-7-Hydroxy-5,8,8-trimethylnon-2-enamide [(+)-38]. To a solution of alcohol (+)-**37** (0.050 g, 0.29 mmol) in dry CH$_2$Cl$_2$ (4 mL) was added acrylamide (0.031 g, 0.44 mmol), CuI (0.002 g, 0.009 mmol), and the Grubbs II precatalyst (0.005 g, 0.006 mmol). The reaction mixture was first degassed by bubbling in dry nitrogen for 10 min before being heated to 40 °C for 3 h. The flask was then cooled to room temperature, and the solvent was removed under vacuum. The crude residue was diluted with EtOAc, transferred to a separatory funnel, and washed three times with water. The combined organic layers were then dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography (8:2 EtOAc/hexanes) to afford 0.052 g (83%) of amide (+)-**38** as a colorless oil. $[\alpha]_D^{24.9}$ = +40.2 (*c* = 1.01, $CHCl_3$); ^1H NMR (*δ*, ppm, $CDCl_3$, 400 MHz) 6.84 (dt, *J* = 7.1, 15.3 Hz, 1H), 5.84 (d, 15.3 Hz, 1H), 5.63 (bs, 2H), 3.28 (d, 9.8 Hz, 1H), 2.39−2.31 (m, 1H), 2.05−1.92 (m, 2H), 1.90 (bs, 1H), 1.39 (ddd, *J* = 1.7, 9.3, 14.3 Hz, 1H), 1.25 (ddd, *J* = 3.9, 10.3, 14.4 Hz, 1H), 0.95 (d, 6.6 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (*δ*, ppm, $CDCl_3$, 100 MHz) 157.5, 145.1, 124.0, 77.3, 38.5, 38.0, 34.9, 29.7, 25.6, 21.0; IR (neat, thin film) *ν* 3342, 3193, 2955, 2870, 1675, 1641, 1607, 1396, 1365, 1069 cm^{-1}; HRMS *m*/*z* calcd for $C_{12}H_{23}NO_2Na$ $[M + Na]^+$, 236.1621; found, 236.1620.

(5*R*,7*R*)-7-Hydroxy-5,8,8-trimethylnonanamide [(+)-*ent*-24]. Amide (+)-**38** (0.052 g, 0.244 mmol) was dissolved in a 1:1 mixture of EtOH/EtOAc (2.4 mL) and treated with Pd/C (0.052 g). The reaction mixture was then flushed with hydrogen gas and allowed to stir overnight under an atmosphere of hydrogen (using a balloon). After 16 h, the reaction mixture was diluted with EtOAc and filtered through a short plug of Celite, rinsing several times with fresh EtOAc. The filtrate was concentrated in vacuo and purified by flash column chromatography (100:1 EtOAc/Et_3N) to afford 0.041 g (78%) of amide (+)-*ent*-**24** as a colorless oil. $[\alpha]_D^{23.4}$ = +40.5 (*c* = 1.01, $CHCl_3$); ^1H NMR (*δ*, ppm, $CDCl_3$, 300 MHz) 5.85 (bs, 1H), 5.76 (bs, 1H), 3.26 (dd, *J* = 2.1, 10.3 Hz, 1H), 2.20 (t, *J* = 7.2 Hz, 2H), 1.86 (bs, 1H), 1.79−1.44 (m, 4H), 1.34 (ddd, *J* = 1.9, 9.2, 14.0 Hz, 1H), 1.27−1.14 (m, 1H), 1.13−0.97 (m, 1H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.86 (s, 9H); ^{13}C NMR (*δ*, ppm, $CDCl_3$, 75 MHz) 175.8, 77.2, 39.0, 35.9, 34.9, 34.5, 29.3, 25.7, 22.8, 20.9; IR (neat, thin film) *ν* 3351, 2953, 1663, 1385 cm^{-1}; HRMS *m*/*z* calcd for $C_{12}H_{25}NO_2Na$ $[M + Na]^+$, 238.1778; found, 238.1776.

(*R*,*E*)-(3*R*,5*R*)-9-Amino-2,2,5-trimethyl-9-oxononan-3-yl-6-iodo-2-methylhex-5-enoate [(+)-*ent*-32]. (+)-*ent*-**32** was prepared in a similar manner as amide (−)-**31**, using vinyl iodide (−)-**28a**. The crude product was purified by flash column chromatography (1:1 EtOAc/hexanes) to afford 0.094 g (78%) of amide (+)-*ent*-**32** as a colorless oil. $[\alpha]_D^{24.5}$ = +19.4 (*c* = 1.03, $CHCl_3$); ^1H NMR (*δ*, ppm, $CDCl_3$, 300 MHz) 6.49 (dt, *J* = 7.1, 14.5 Hz, 1H), 6.03 (d, *J* = 14.4 Hz, 1H), 5.91(bs, 1H), 5.68 (bs, 1H), 4.79 (dd, *J* = 3.4, 7.8 Hz, 1H), 2.51−2.42 (m, 1H), 2.25−2.03 (m, 4H), 1.87−1.67 (m, 2H), 1.58−1.44 (m, 3H), 1.43−1.35 (m, 1H), 1.32−1.20 (m, 1H), 1.16 (d, *J* = 6.9 Hz, 3H), 1.10−0.99 (m, 1H), 0.89 (d, *J* = 6.8 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (*δ*, ppm, $CDCl_3$, 75 MHz) 176.3 (2C), 145.4, 78.8, 75.3, 39.2, 37.5, 34.54, 34.49, 33.7 (2C), 32.1, 28.9, 26.0, 22.7, 20.9, 17.4; IR (neat, thin film) *ν* 3428, 3349, 3196, 2963, 2871, 1725, 1665, 1608, 1462,1397,1379, 1223, 1186, 1123, 1065, 958, 937 cm^{-1}; HRMS *m*/*z* calcd for $C_{19}H_{34}INO_3Na$ $[M + Na]^+$, 474.1476; found, 474.1466.

(−)-Palmyrolide A [(−)-1]. (−)-**1** was prepared in a similar manner as macrolide (−)-**21a**, using amide (+)-*ent*-**32**. The crude product was purified by flash column chromatography (8:2 hexanes/EtOAc) to afford 0.017 g (54% over two steps) of Palmyrolide A (−)-**1** as a colorless oil. $[\alpha]_D^{23.6}$ = −26.7 (*c* = 0.86, $CHCl_3$); ^1H NMR (*δ*, ppm, $CDCl_3$, 400 MHz) 6.48 (d, *J* = 13.8 Hz, 1H), 5.28 (dt, *J* = 7.0, 13.9 Hz, 1H), 4.89 (dd, *J* = 1.9, 10.8 Hz, 1H), 3.08 (s, 3H), 2.53−2.43 (m, 1H), 2.43−2.34 (m, 2H), 2.34−2.24 (m, 2H), 1.86−1.72 (m, 3H), 1.71−1.43 (m, 3H), 1.42−1.31 (m, 2H), 1.22 (d, *J* = 7.1 Hz, 3H), 1.12−1.02 (m, 1H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.87 (s, 9H); ^{13}C NMR (*δ*, ppm, $CDCl_3$, 100 MHz) 175.3, 172.9, 130.6, 117.3, 38.9, 35.7, 35.2, 34.54, 34.46, 32.8, 31.7, 29.3, 27.0, 26.1, 24.3, 20.6, 16.8 [*Note*: At 100 MHz, we did not observe the C(7) CH signal at *δ* 76.9 ppm. At this frequency, the peak is buried under the $CDCl_3$ peak. Pleasingly, the peak is visible in the HSQC spectra]; IR (neat, thin film) *ν* 2928, 1722, 1647, 1384, 1072 cm^{-1}; HRMS *m*/*z* calcd for $C_{20}H_{35}NO_3Na$ $[M + Na]^+$, 360.2509; found, 360.2505.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of ^1H and ^{13}C NMR spectra of all new compounds and copies of ^1H NMR spectra of all known compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Pereira, A. R.; Cao, Z.; Engene, N.; Soria-Mercado, I. E.; Murray, T. F.; Gerwick, W. H. *Org. Lett.* **2010**, *12*, 4490−4493.

(2) (a) Matsumori, N.; Kaneno, D.; Murata, M.; Nakamura, H.; Tachibana, K. *J. Org. Chem.* **1999**, *64*, 866−876. (b) Paterson, I.; Britton, R.; Delgado, O.; Wright, A. E. *Chem. Commun.* **2004**, 632−633. (c) Hassfeld, J.; Farès, C.; Steinmetz, H.; Carlomagno, T.; Menche, D. *Org. Lett.* **2006**, *8*, 4751−4754. (d) Plaza, A.; Bewley, C. A. *J. Org. Chem.* **2006**, *71*, 6898−6907. (e) Plaza, A.; Bifulco, G.; Keffer, J. L.; Lloyd, J. R.; Baker, H. L.; Bewley, C. A. *J. Org. Chem.* **2009**, *74*, 504−512. (f) For review on the determination of relative configuration by NMR and computational methods, see: Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744−3779.

(3) (a) Luesch, H.; Yoshida, W. Y.; Moore, R. E.; Paul, V. J.; Corbett, T. H. *J. Am. Chem. Soc.* **2001**, *123*, 5418−5423. (b) Klein, D.; Braekman, J. C.; Daloze, D.; Hoffmann, L.; Demoulin, V. *Tetrahedron Lett.* **1996**, *37*, 7519−7520. (c) Klein, D.; Braekman, J. C.; Daloze, D.; Hoffmann, L.; Castillo, G.; Demoulin, V. *J. Nat. Prod.* **1999**, *62*, 934−936. (d) Matthew, S.; Salvador, L. A.; Schupp, P. J.; Paul, V. J.; Luesch, H. *J. Nat. Prod.* **2010**, *73*, 1544−1552.

(4) (a) Chen, J.; Forsyth, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 8734−8735. (b) Chen, J.; Forsyth, C. J. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 12067−12072. (c) Doi, T.; Numajiri, Y.; Munakata, A.; Takahashi, T. *Org. Lett.* **2006**, *8*, 531−534. (d) Ma, D.; Zou, B.; Cai, G.; Hu, X.; Liu, J. O. *Chem.*—*Eur. J.* **2006**, *12*, 7615−7626. (e) Numajiri, Y.; Takahashi, T.; Doi, T. *Chem.*—*Asian J.* **2009**, *4*, 111−125. (f) Doi, T.; Numajiri, Y.; Takahashi, T.; Takagi, M.; Shin-ya, K. *Chem.*—*Asian J.* **2011**, *6*, 180−188.

(5) (a) For the apratoxin numbering convention, see ref 3a. (b) The numbering convention for palmyrolide used throughout the text matches the numbering assigned in the isolation report (see ref 1); this numbering is not reflected in the correct IUPAC names for the macrolides found in the Experimental Section.

(6) Tello-Aburto, R.; Johnson, E. M.; Valdez, C. K.; Maio, W. A. *Org. Lett.* **2012**, *14*, 2150−2153.

(7) (a) For a review article showcasing several examples, see: Gournelis, D. C.; Laskaris, G. G.; Verpoorte, R. *Nat. Prod. Rep.* **1997**, *14*, 75−82. See also: (b) Rahbaek, L.; Anthoni, U.; Chrisophersen, C.; Nielsen, P.; Petersen, B. *J. Org. Chem.* **1996**, *61*, 887−889. (c) Lin, H.-Y.;

Chen, C.-H.; You, B.-J.; Liu, K. C. S. C.; Lee, S.-S. *J. Nat. Prod.* **2000**, *63*, 1338−1343.

(8) For several examples, see: (a) Erickson, K. L.; Beutler, J. A.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8188−8192. (b) Galinis, D. L.; McKee, T. C.; Pannell, L. K.; Cardellina, J. H., II; Boyd, M. R. *J. Org. Chem.* **1997**, *62*, 8968−8969. (c) McKee, T. C.; Galinis, D. L.; Pannell, L. K.; Cardellina, J. H., II; Laakso, J.; Ireland, C. M.; Murray, L.; Capon, R. J.; Boyd, M. R. *J. Org. Chem.* **1998**, *63*, 7805−7810. (d) Kim, J. W.; Shin-ya, K.; Furihata, K.; Hayakawa, Y.; Seto, H. *J. Org. Chem.* **1999**, *64*, 153−155. (e) Kohno, J.; Koguchi, Y.; Nishio, M.; Nakao, K.; Kuroda, M.; Shimizu, R.; Ohnuki, T.; Komatsubara, S. *J. Org. Chem.* **2000**, *65*, 990−995. (f) Nogle, L. M.; Gerwick, W. H. *Org. Lett.* **2002**, *4*, 1095−1098.

(9) (a) Sergeyev, S.; Hesse, M. *Helv. Chim. Acta* **2003**, *86*, 465−473. (b) Baran, P. S.; Shenvi, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 14028−14029. (c) Toumi, M.; County, F.; Evano, G. *Angew. Chem., Int. Ed.* **2007**, *46*, 572−575. (d) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2007**, *72*, 9003−9009. (e) Toumi, M.; Couty, F.; Evano, G. *J. Org. Chem.* **2008**, *73*, 1270−1281. (f) Toumi, M.; Couty, F.; Evano, G. *Synlett* **2008**, 29−32. (g) Toumi, M.; Rincheval, V.; Young, A.; Gergeres, D.; Turos, E.; Couty, F.; Mignotte, B.; Evano, G. *Eur. J. Org. Chem.* **2009**, 3368−3386. (h) Liang, S.; Xu, Z.; Ye, T. *Chem. Commun.* **2010**, *46*, 153−155.

(10) (a) Gilles, A.; Martinez, J.; Cavelier, F. *J. Org. Chem.* **2009**, *74*, 4298−4304. (b) Gilles, A.; Martinez, J.; Cavelier, F. *C. R. Chim.* **2011**, *14*, 437−440.

(11) Chen, K. M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, 1923−1926.

(12) (a) Kiyooka, S.-i.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009−3012. (b) Harrison, T. J.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 7308−7311. (c) Evans, D. A.; Starr, J. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1787−1790.

(13) Gao, Y.; Sharpless, K. B. *J. Am. Chem. Soc.* **1988**, *110*, 7538−7539 . Also see ref 10.

(14) Evans, D. A.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1990**, *112*, 6447−6449.

(15) Chopade, P. R.; Davis, T. A.; Prasad, E.; Flowers, R. A., II *Org. Lett.* **2004**, *6*, 2685−2688.

(16) (a) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939−5942. (b) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.

(17) (a) DeMico, A.; Margarita, R.; Parlanti, L.; Vescovi, A.; Piancatelli, G. *J. Org. Chem.* **1997**, *62*, 6974−6977. (b) Hansen, T. M.; Florence, G. J.; Lugo-Mas, P.; Chen, J.; Abrams, J. N.; Forsyth, C. J. *Tetrahedron Lett.* **2003**, *44*, 57−59.

(18) (a) Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, *27*, 888−890. (b) Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, *45*, 4825−4830. (c) Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091−2096.

(19) (a) Myers, A. G.; Yang, B. H.; Chen, H.; McKinstry, L.; Kopecky, D. J.; Gleason, J. L. *J. Am. Chem. Soc.* **1997**, *119*, 6496−6511. (b) For the latest modification that uses pseudoephenamine, see: Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568−4571.

(20) (a) Dias, L. C.; deOliveira, L. G.; Vilcachagua, J. D.; Nigsch, F. *J. Org. Chem.* **2005**, *70*, 2225−2234. (b) Sabitha, G.; Nayak, S.; Bhikshapathi, M.; Chittapragada, M.; Yadav, J. S. *Synthesis* **2011**, 3661−3668.

(21) Inanaga, J.; Hirata, K.; Saeki, H.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989−1993.

(22) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155−4156.

(23) The small anomalies we observed may be due to magnet strength (600 MHz vs 300 MHz) or possibly due to some unknown impurity in the authentic sample. In the isolation report, the authors note the presence of "several minor analogues in the crude reaction products", which can clearly be seen in the ^{1}H NMR spectrum provided in the Supporting Information of their manuscript. See ref 1.

(24) For an example using PPTS and 4 Å molecular sieves, see: Nicolaou, K. C.; Jiang, X.; Lindsay-Scott, P. J.; Corbu, A.; Yamashiro, S.; Bacconi, A.; Fowler, V. M. *Angew. Chem., Int. Ed.* **2011**, *50*, 1139−1144.

(25) (a) Stang, P. J.; Treptow, W. *Synthesis* **1980**, 283−284. (b) A possible explanation for our inability to form the vinyl triflate may be competing amide activation under these conditions. For a lead reference, see: Pelletier, G.; Bechara, W. S.; Charette, A. B. *J. Am. Chem. Soc.* **2010**, *132*, 12817−12819.

(26) (a) Goossen, L. J.; Rauhaus, J. E.; Deng, G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4042−4045. (b) Goossen, L. J.; Arndt, M.; Blanchot, M.; Rudolphi, F.; Menges, F.; Niedner-Schatteburg, G. *Adv. Synth. Catal.* **2008**, *350*, 2701−2707. (c) Goossen, L. J.; Blanchot, M.; Arndt, M.; Salih, K. S. M. *Synlett* **2010**, 1685−1687. (d) Arndt, M.; Salih, K. S.; Fromm, A.; Goossen, L. J.; Menges, F.; Niedner-Schatteburg, G. *J. Am. Chem. Soc.* **2011**, *133*, 7428−7449.

(27) (a) Huang., X; Anderson, K. W.; Zim, D.; Jiang, L.; Klapars, A.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, *125*, 6653−6655. (b) Willis, M. C.; Brace, G. N.; Holmes, I. P. *Synthesis* **2005**, 3229−3234. (c) Campos, K. R.; Chen, C.-y.; Volante, R. P. *Org. Lett.* **2005**, *7*, 1185−1188. (d) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734−7735. (e) Dooleweerdt, K.; Fors, B. P.; Buchwald, S. L. *Org. Lett.* **2010**, *12*, 2350−2353.

(28) Ferrié, L.; Bouzbouz, S.; Cossy, J. *Org. Lett.* **2009**, *11*, 5446−5448.

(29) Our initial attempts using acrylamide and the Grubbs II precatalyst gave good, but somewhat inferior, results compared to acryloyl chloride (36% vs 58%, respectively). For a lead reference, see: Choi, T.-L.; Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2001**, *40*, 1277−1279.

(30) Sajiki, H.; Ikawa, T.; Hattori, K.; Hirota, K. *Chem. Commun.* **2003**, 654−655.

(31) (a) Munakata, R.; Ueki, T.; Katakai, H.; Takau, K.; Tadano, K.-i. *Org. Lett.* **2002**, *3*, 3029−3033. (b) Trend, R. M.; Ramtohul, Y. K.; Stoltz, B. M. *J. Am. Chem. Soc.* **2005**, *127*, 17778−17788. (c) Alcohol 7 can also be prepared in one synthetic step from 3-butyn-1-ol. See: Huang, Z.; Negishi, E.-i. *Org. Lett.* **2006**, *8*, 3675−3678.

(32) Elimination of *Z*-vinyl iodides readily occurs upon treatment with NaOMe. For example, see ref 31a.

(33) Evans, D. A.; Bartroli, J.; Shih, T. L. *J. Am. Chem. Soc.* **1981**, *103*, 2127−2129.

(34) Bao, J.; Wulff, W. D.; Dragisich, V.; Wenglowsky, S.; Ball, R. G. *J. Am. Chem. Soc.* **1994**, *116*, 7616−7630.

(35) For the alkylation of triflates using a similar method, see: (a) Williams, D. R.; McGill, J. M. *J. Org. Chem.* **1990**, *55*, 3457−3459. (b) Decicco, C. P.; Grover, P. *J. Org. Chem.* **1996**, *61*, 3534−3541.

(36) For copper-catalyzed vinyl halide/amide unions, see: (a) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443−1446. (b) Shen, R.; Porco, J. A., Jr. *Org. Lett.* **2000**, *2*, 1333−1336. (c) Shen, R.; Lin, C. T.; Porco, J. A., Jr. *J. Am. Chem. Soc.* **2002**, *124*, 5650−5651. (d) Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667−3669. (e) Nakamura, R.; Tanino, K.; Miyashita, M. *Org. Lett.* **2003**, *5*, 3583−3586. (f) Han, C.; Shen, R.; Su, S.; Porco, J. A., Jr. *Org. Lett.* **2004**, *6*, 27−30. (g) Coleman, R. S.; Liu, P.-H. *Org. Lett.* **2004**, *6*, 577−580. (h) Pan, X.; Cai, Q.; Ma, D. *Org. Lett.* **2004**, *6*, 1809−1812. (i) Shen, R.; Inoue, T.; Forgac, M.; Porco, J. A., Jr. *J. Org. Chem.* **2005**, *70*, 3686−3692. (j) Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054−3131.

(37) We also wanted to address the low yield of the copper-mediated macrocyclization step. In our previous examples, enamide formation was only attempted once to obtain enough material for a ^{1}H NMR. However, we do note the variance in yield over these attempts (18−54%). Pleasingly, in every case, we were able to recover unreacted starting material, which could be recycled. We believe that the range in yields reflects small experimental deviations, from catalyst/ligand loading, oxygen content, and concentration; each could have a large impact on the overall outcome of the reaction. Unfortunately, we did not attempt a detailed study to quantify the role of these variables.

(38) (a) Voigtritter, K.; Ghorai, S.; Lipshutz, B. H. *J. Org. Chem.* **2011**, *76*, 4697−4702. (b) Venukadasula, P. K. M.; Chegondi, R.; Suryn, G. M.; Hanson, P. R. *Org. Lett.* **2012**, *14*, 2634−2637.

(39) The ratio of *E*/*Z* olefin isomers is at least 20:1, as seen in the crude ^{1}H NMR. Unfortunately, during column chromatography, the *Z* isomer was lost.

(40) We have observed faithful reproducibility for this union over several successful attempts.

(41) Acrylamide has been previously used in cross-metathesis processes employing the Grubbs II precatalyst alone (see ref 29); however, to obtain high yields, the olefin partner (typically Type 1) is used in excess amounts. This strategy would be unsuitable in our case, where olefin (+)-**37** is a precious metathesis partner.

(42) We also attempted macrocyclization using the CuTc [copper(I) thiophene-2-carboxylate] conditions developed by Porco. Unfortunately, using the optimized conditions, and either *N*-methylpyrrolidione or DMSO as solvent, we observed no desired product formation.

(43) Young, I. S.; Baran, P. S. *Nat. Chem.* **2009**, *1*, 193−205.