JOC The Journal of Organic Chemistry

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Converting Cycloalkanones into *N*-Heterocycles: Formal Synthesis of (−)-Gephyrotoxin 287C

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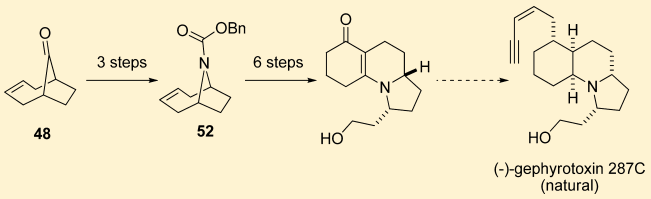
Supporting Information

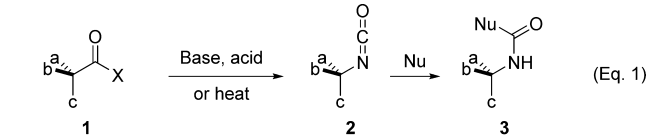
ABSTRACT: The photochemical rearrangement of *N*-activated lactams enables their ring contraction concomitant with the migration of a carbon onto a nitrogen atom. When coupled with the Beckmann rearrangement, this photochemical ring contraction converts cycloalkanones into *N*-heterocycles in a few steps and in a stereospecific manner. To showcase the method, we performed an efficient formal synthesis of (−)-gephyrotoxin 287C.



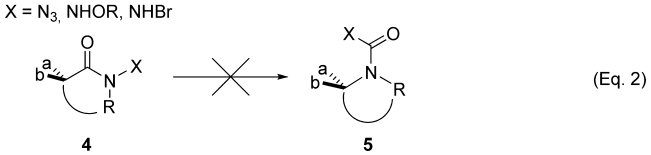
INTRODUCTION

In the last 40 years, over 850 lipophilic alkaloids were reported to have been isolated from the skin secretion of several species of poison frogs.[1] Those compounds were organized into several classes on the basis of their respective structures.[2] Even if the carbon framework can differ greatly from one class to another, there is one characteristic that can be found in each member of all families: the presence of at least one stereogenic center α to the nitrogen atom. In Figure 1 is represented a member of each of the five largest classes of poison frog alkaloids, namely, the disubstituted indolizidines (205A), the trisubstituted indolizidines (193G), the tricyclics (205B), the pumiliotoxins (225F), and the decahydroquinolines (195J). In addition to these main categories, there are several other classes, each containing only a small number of alkaloids. This is the case of the gephyrotoxin family of alkaloids, which comprises only two molecules, namely, gephyrotoxins 287C and 289B, differing only by the nature of their side chain situated on the *cis*-decaline fragment (Figure 1).

The Schmidt-type rearrangements, including the Lossen, Hofmann, and Curtius rearrangements, are well-known reactions that are frequently used in total syntheses of natural alkaloids (eq 1).[3] They reliably and stereospecifically convert a



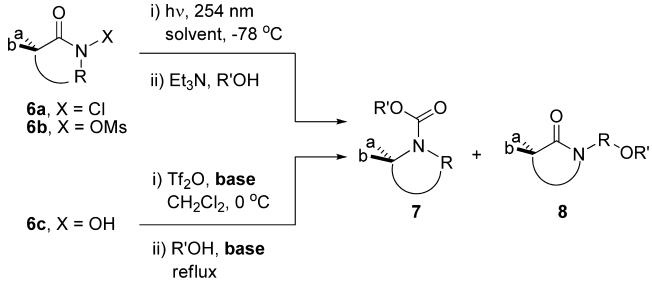
(Eq. 1)



(Eq. 2)

carbon−carbon bond adjacent to a carbonyl (as in **1**) into a carbon−nitrogen bond (as in **2**). Typically, an alcohol or amine is then added to give the corresponding carbamate (**3**, Nu = OR) or urea (**3**, Nu = NR_2). The main difference among these rearrangements is the nature of the primary amide derivative that is used. In the Hofmann and Lossen rearrangements, the nitrogen atom is oxidized (N−Br or N−OR) and a base is used to generate the reactive intermediate, while in the Schmidt and Curtius rearrangements, an acyl azide is generated and heated to initiate the reaction, perhaps via a nitrene intermediate.[4] In all of these rearrangements, the starting amide, acyl azide, or carbamic acid is *necessarily primary*. Secondary amides or lactams could not contain the necessary functionalities for the rearrangement to occur (eq 2).[5] Recently, we have added a unique complement to this list of reactions: the photochemical and/or thermal rearrangement of *N*-activated lactams **6** to give *N*-heterocycle **7** or a new lactam **8**, depending on the carbon that migrates (Scheme 1).[6,7] This ring-contraction reaction complements the Schmidt-type rearrangements because it converts lactams **6a**−**c**, thus *secondary amide derivatives*, to *N*-heterocycle **7** or **8**, and it is unique because its mechanism, though not yet completely understood, is different, perhaps involving a high-energy *N*-acylnitrenium ion.[8] Notably, the Beckmann rearrangement (a ring-expansion reaction) and our

Scheme 1. Rearrangements of *N*-Activated Lactams



Received: October 5, 2013
Published: November 4, 2013

   dx.doi.org/10.1021/jo402217e | J. Org. Chem. 2013, 78, 12532−12544

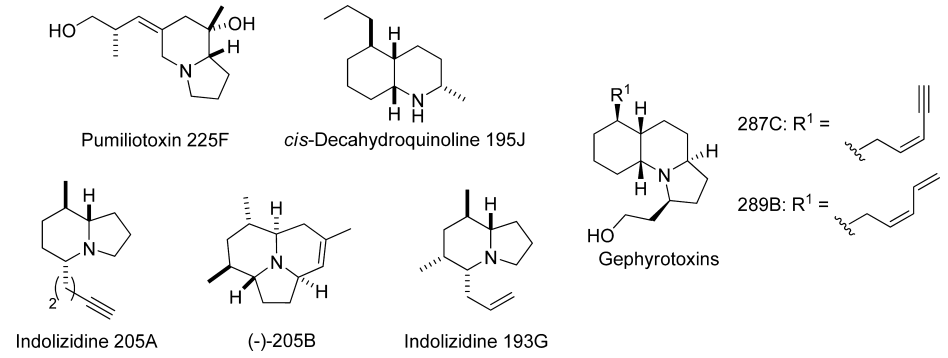
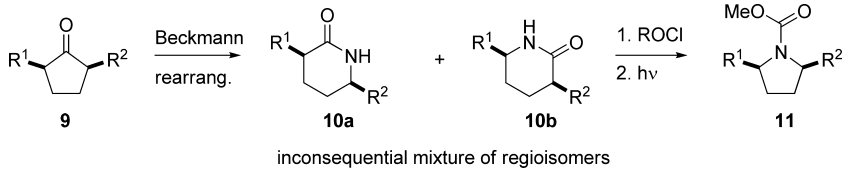
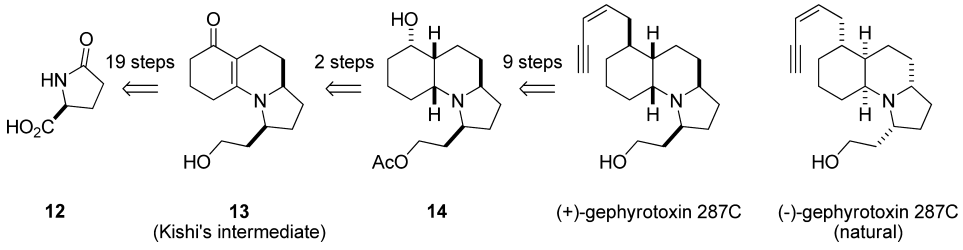


Figure 1. Lipophilic alkaloids from poison frog skin secretion.

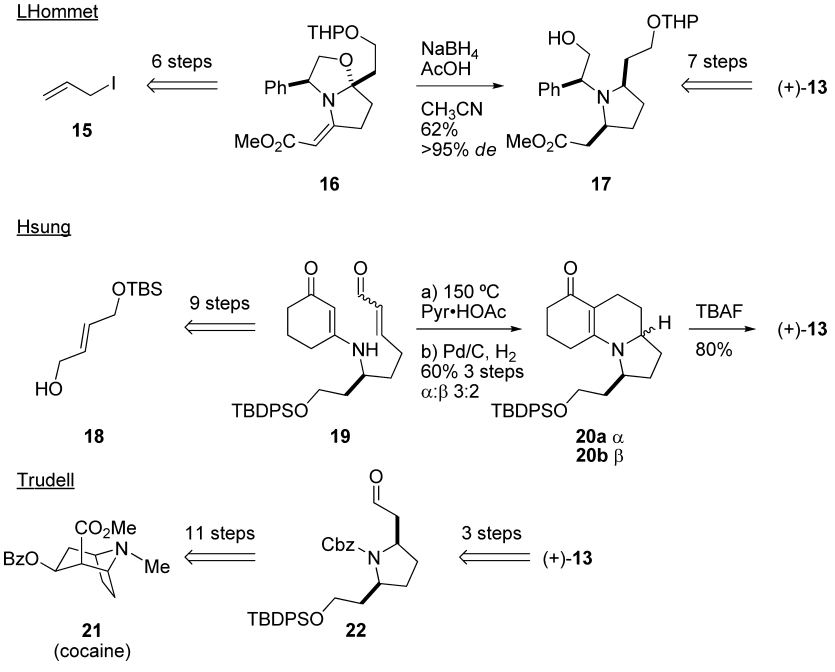
Scheme 2. Beckmann Ring-Expansion/Photochemical Ring-Contraction Sequence



Scheme 3. Retrosynthesis of (+)-Gephyrotoxin 287C by Kishi and His Group



Scheme 4. Retrosyntheses of (+)-Gephyrotoxin 287C by Three Different Research Groups



ring-contraction together constitute a formidable sequence capable of transforming in three steps a cycloalkanone (**9**) into an *N*-heterocycle of the same ring size (**11**) with retention of the stereochemistry on either side of the starting carbonyl **9** (Scheme 2). We herein wish to showcase this strategy with a short and efficient formal synthesis of (−)-gephyrotoxin 287C.

This neurotoxic alkaloid,[9] isolated from skin extracts of the neotropical frog *Dendrobates histrionicus*, was first named

dx.doi.org/10.1021/jo402217e | J. Org. Chem. 2013, 78, 12532−12544

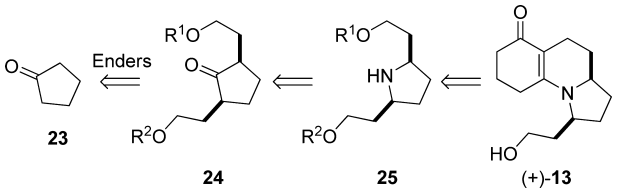
histrionicotoxin D (HTX-D) and then renamed gephyrotoxin 287C when analysis revealed its decahydroquinoline structure.[10] It is in very short supply (<50 mg isolated from thousands of frog skins), making its efficient synthesis a worthwhile goal. (±)-Gephyrotoxin 287C was first synthesized in the laboratory by Kishi and co-workers in 1980.[11a] Their retrosynthesis is shown in Scheme 3. Daly and co-workers had previously assigned the absolute configuration of natural (−)-gephyrotoxin 287C as that shown in Scheme 3 for (+)-gephyrotoxin 287C on the basis of X-ray analysis.[10a] Kishi's synthesis of (+)-gephyrotoxin 287C established the absolute stereochemistry of natural (−)-gephyrotoxin 287C as the one shown in Scheme 3.[11b] There have since been three other formal syntheses of (+)-gephyrotoxin 287C, all of which targeted Kishi's intermediate **13**, and their key steps are summarized in Scheme 4.[12,13] Lhommet's approach involves a highly diasteroselective reduction of pyrrolo[2,1-*b*]oxazole **16** into pyrrolidine **17** to achieve a 14-step synthesis of **13** starting from allyl iodide (**15**).[12a] In their approach, Hsung and co-workers used a poorly diastereoselective (3:2 ratio) intramolecular [3 + 2] cycloaddition of **19** to give **20** in order to achieve an 11-step synthesis of **13** from alcohol **18**.[12b] Lastly, Trudell and his colleagues achieved the synthesis of **13** in 14 steps from (−)-cocaine (**21**) via pyrrolidine **22**.[12c]

RESULTS AND DISCUSSION

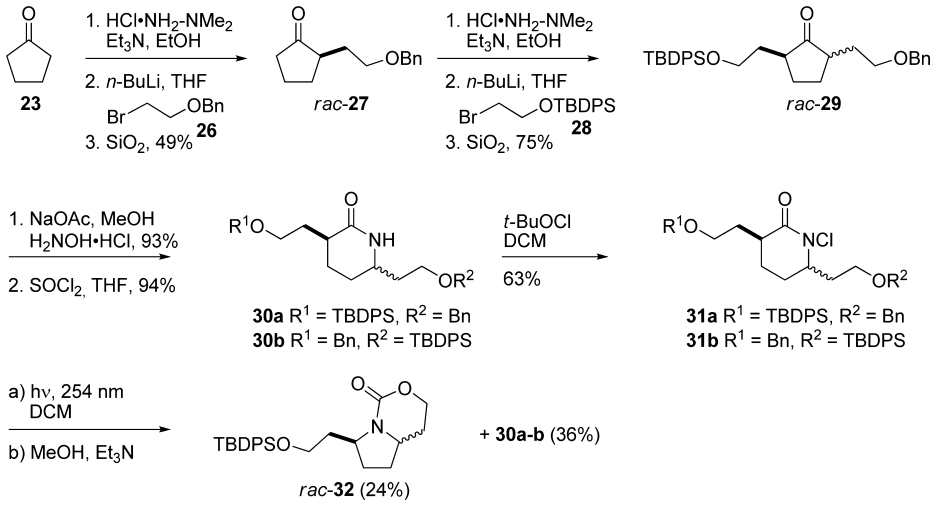
Our initial plan was to alkylate stereoselectively cyclopentanone (**23**) with two different two-carbon chains using Enders' chiral hydrazones (Scheme 5).[14] The *syn* stereochemistry of the two alkyl chains in **24** would be controlled by Enders' hydrazones. Our strategy then called for the conversion of the alkylated cyclopentanone **24** to the corresponding pyrrolidine **25** in three chemical steps. Intermediate **25** could then be converted to **13** by a number of routes. The racemic version of the synthesis began by alkylation of cyclopentanone **23** via its corresponding *N*′,*N*′-dimethylhydrazone with benzyl-protected bromoethanol **26** to furnish the racemic alkylated product **27** (Scheme 6). At this point, we decided not to optimize each reaction until the pivotal photochemical rearrangement proved to proceed in good yield. Alkylation of *rac*-**27**, this time with TBDPS-protected bromoethanol **28**, procured racemic product **29**, for which the ratio of *cis* and *trans* products was not determined, although the presence of both stereoisomers could be detected by ^{1}H NMR spectroscopy. Only the *cis* product was required for the synthesis of gephyrotoxin 287C, but we saw no harm in testing both isomers in the photochemical ring contraction. We thus made no effort to improve this diastereomeric ratio, as we did not expect this to be an issue in the nonracemic version of the alkylation using Enders' hydrazone auxiliary. The diastereomeric and enantiomeric ratios would then be controlled by the chiral auxiliary.[14] The Beckmann rearrangement of **29** gave **30a** and **30b** as a mixture of regioisomers, a fact that bore no consequence as both would give the same final pyrrolidine derivative after the photochemical rearrangement. Chlorination of amides **30a** and **30b** and irradiation of the resulting *N*-chloroamides **31a** and **31b** at 254 nm gave a disappointing 24% yield of the desired pyrrolidine **32** along with 36% recovery of amides **30a** and **30b**. The latter were expected, as the parent lactam nearly always accompanies, to varying degrees, the ring-contraction product when *N*-chlorolactams are used. The rest of the mass balance consisted of a complex mixture of unidentified chlorinated products, many having one or more chlorine atoms in their structure. Those were also anticipated, but in smaller amounts than what was actually observed.

The second unusual observation was that the benzyl-protected alcohol had cyclized onto either the *N*-acylium ion **33a** or the corresponding carbamoyl chloride to yield carbamate *rac*-**32** after dealkylation of the benzyl group in **33b** (Scheme 7).[7b] While free alcohols and amines add readily to such intermediates, weaker nucleophiles usually do not, and the cyclization of the benzyl ether was a surprise.[15] This in itself was not a problem, but the low yield was. To try and improve

Scheme 5. First Retrosynthetic Analysis of Kishi's Intermediate 13



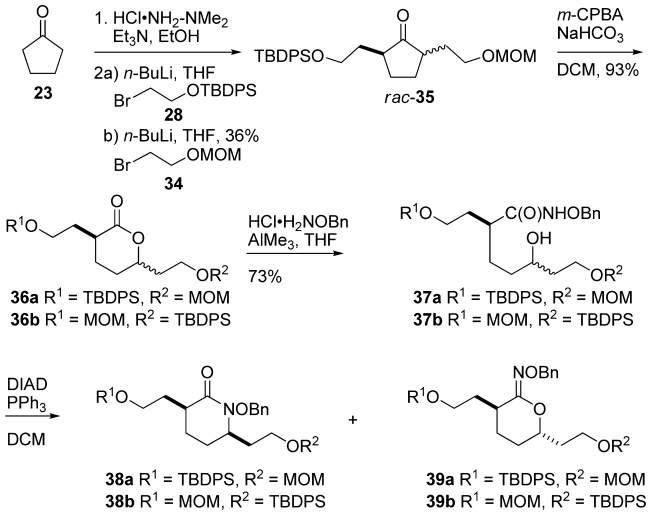
Scheme 6. Synthesis of Pyrrolidine 32



dx.doi.org/10.1021/jo402217e | J. Org. Chem. 2013, 78, 12532−12544

Scheme 7. Cyclization of the Benzyl Ether onto the *N*-Acylium Ion in 33a

Scheme 8. Synthetic Sequence To Give Cyclic Hydroxamic Acid Derivatives 38



it, we made a number of derivatives in which the alcohols in **31** were protected with various groups, including acetates, MOM ethers, and various silyl ether derivatives. All led to similarly low yields of the desired ring-contraction product, a 30−40% yield of the corresponding parent lactam, and an invariably larger than expected quantity of chlorinated products.

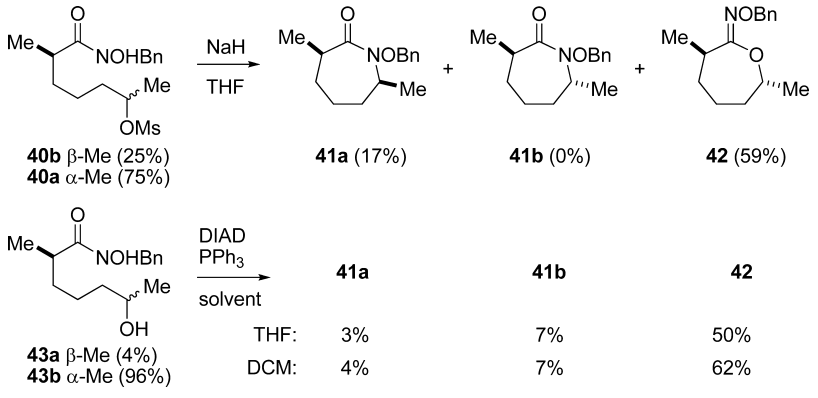
We envisaged two ways to circumvent this problem. First, we could use our second-generation ring-contraction methodology, namely, the photochemical rearrangement of *N*-mesyloxylactams: the yields of rearrangement products are invariably higher, and no parent lactam or radical-derived products were ever isolated in these cases.[6] The caveat with this solution is that it is not yet possible to directly and efficiently oxidize lactams to cyclic hydroxamic acids.[16] Therefore, a detour would have to be taken to make the required cyclic hydroxamic acid (vide infra). The second way to circumvent the problem of low yield would be to use an *N*-chlorolactam derivative in which the two alkyl chains at the 2- and 5-positions are tied together into a more rigid bicyclic system. Rigid bicyclic *N*-chlorolactams usually rearrange in higher yields.[6a,b] We decided to investigate both solutions.

While making the required modifications to synthesize the corresponding cyclic hydroxamic acid, we improved the yield of the first steps of the synthetic sequence. The two successive alkylations of cyclopentanone **23**, which were previously achieved in four steps and 29% overall yield, were combined into a two-step process where the hydrazine intermediate derived from **23** was alkylated twice, once with bromide **28** and next with bromide **34**, in a one-pot procedure to give the required doubly alkylated product **35** as a mixture of *cis* and *trans* isomers in 36% isolated yield (Scheme 8). Again, the *cis*:*trans* ratio was difficult to determine because of overlapping signals, but both isomers were clearly present in the ^{1}H NMR spectrum. A Baeyer−Villiger ring expansion of cyclopentanones **35** to give the corresponding lactones **36a** and **36b** and opening of these lactones with *O*-benzylhydroxylamine supplied **37a** and **37b** as a mixture of regio- and stereoisomers. Cyclization under the Mitsunobu conditions gave a surprising result: one stereoisomer of **37** gave the *cis*-disubstituted cyclic hydroxamic acids **38a** and **38b**, the result of an *N*-alkylation, while the other stereoisomer of **37** afforded the *trans*-disubstituted oximes **39a** and **39b**, the result of an *O*-alkylation. The regioisomeric cyclic hydroxamic acids **38a** and **38b** were later separately rearranged to the same *cis*-pyrrolidine, the stereochemistry of which was established by NOESY (vide infra). By inference, the stereochemistry of the regioisomeric oximes **39a** and **39b** was determined to be *anti*. Not surprisingly, oximes **39a** and **39b** did not rearrange upon irradiation.

We have observed this phenomenon (*O*- vs *N*-alkylation) on two other occasions (Scheme 9), and there are reported examples of this occurrence in the literature.[17] Hydroxamic acid isomers **40a** and **40b**, for example, cyclized to give a 17% yield of *cis* cyclic hydroxamic acid **41a**, none of the *trans* isomer **41b**, and a 59% yield of oxime **42**.[6c] The **41a**:**42** ratio corresponds to the ratio of the starting isomers **40a** and **40b**. Cyclization of the related alcohols **43a** and **43b** under the Mitsunobu conditions also gave similar results, this time with a small amount of the *trans* cyclic hydroxamic acid **41b** accompanying oxime **42**.[6c]

The desired regioisomeric cyclic hydroxamic acid derivatives **38a** and **38b** have the correct stereochemistry for the synthesis of gephyrotoxin 287C, and we realized that this phenomenon would help us procure pure *cis*-**38** in the nonracemic version of

Scheme 9. *N*- versus *O*-Alkylation of Hydroxamic Acid



dx.doi.org/10.1021/jo402217e | J. Org. Chem. 2013, 78, 12532−12544

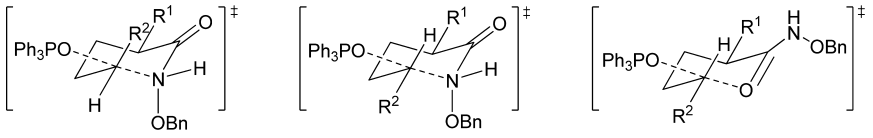
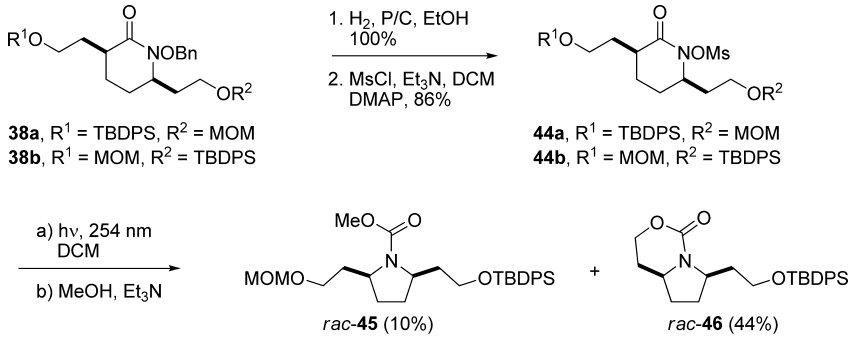


Figure 2. *O*- or *N*-cyclization of the different stereoisomers of **37**.

Scheme 10. Rearrangement of Hydroxamic Acids 45 and 46



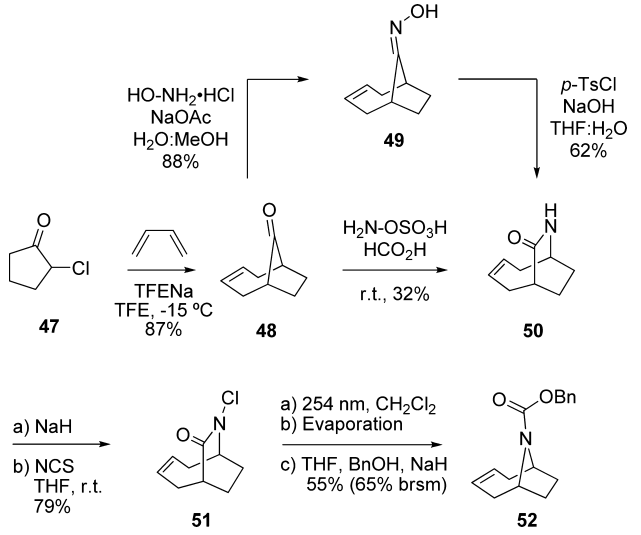
the synthesis. Any amount of the wrong *anti* isomer of nonracemic **35** produced would end up as the *trans* oxime **39** and could be removed.

This phenomenon could arise from an unfavorable steric interaction between R^2 and OBn in the transition state leading to *trans*-**38** (Figure 2). This interaction is alleviated in the TS leading to *trans*-oxime **39** and is not present in the TS leading to *cis*-**38**.

The two regioisomers **38a** and **38b** were separately debenzylated by hydrogenolysis and mesylated under standard conditions to give *N*-mesyloxylactams **44a** and **44b** (Scheme 10). Separate irradiation of the regioisomers **44a** and **44b** gave the same pyrrolidines **45** and **46** in a combined yield of 54%. This yield was now acceptable, and we believed that we could increase this yield by modifying the protecting groups for each alcohol. Moreover, the selective *cis*-*N*-cyclization of the Mitsunobu reaction would ensure a high stereochemical purity in favor of the desired *cis*-disubstituted pyrrolidine **46**. The only drawback was the detour via the Baeyer–Villiger reaction brought about by the difficulty in oxidizing lactams directly to cyclic hydroxamic acids. As mentioned earlier, we decided also to explore the next strategy, namely, the photochemical rearrangement of a bicyclic *N*-chlorolactam. Often, these more rigid structures give good yields of the product in the photochemical rearrangement, and we could take advantage of the direct chlorination of lactams. Another advantage is that a bicyclic structure would also provide a pure *cis* stereochemical relationship between the two carbon chains on the pyrrolidine ring.

Two methods for the synthesis of bicyclic ketone **48** have been published. In the method published by Still in 1976, the enamine of cyclopentanone reacts with *cis*-1,4-dichloro-2-butene to yield the desired compound in 38%.[18] Unfortunately, this method proved to be ineffective in our hands. The second method, published by Föhlisch and Joachimi in 1987, gave satisfactory results (Scheme 11).[19] In the event, a [4 + 3] cycloaddition took place between 1,3-butadiene and the Favorskii intermediate generated from 2-chlorocyclopentanone (**47**). After some optimization, in particular the fact that the addition of the base must be really slow, the yield of bicyclic

Scheme 11. Synthesis of Carbamate 52



ketone **48** was increased to 87%, which compares favorably to the 44% yield reported by Föhlisch and Joachimi.[19]

Next, we initiated the Beckmann ring-expansion/photochemical ring-contraction sequence (Scheme 11). After trying several sets of reaction conditions, we found that we could effect a direct Beckmann rearrangement to afford bicyclic lactam **50** in 32% yield by treating bicyclic ketone **48** with hydroxylamine-*O*-sulfonic acid in formic acid. We obtained a higher yield using a two-step procedure: formation of oxime **49** from bicyclic ketone **48** followed by a Beckmann rearrangement under basic conditions afforded lactam **50** in 55% yield over two steps. Chlorination of lactam **50** under standard conditions afforded the desired *N*-chlorolactam **51** in 79% yield. This product was then dissolved in dichloromethane, cooled to −78 °C, and irradiated with 254 nm UV light in order to effect the desired ring contraction reaction (Scheme 11). Evaporation and treatment with benzyl alcohol and base gave benzyl carbamate **52** in 55% yield (65% brsm), one of the highest yields obtained for the ring contraction of an *N*-chlorolactam. The yield of rearrangement of **51** was the same as

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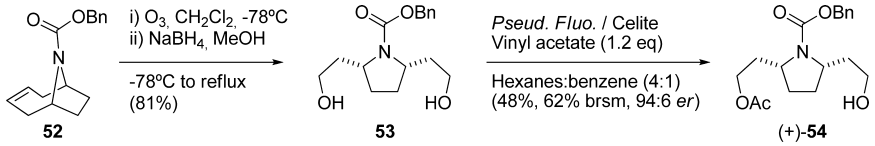
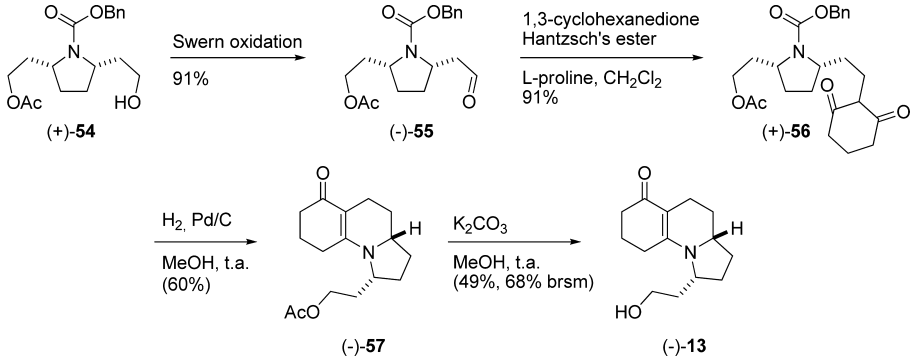
Scheme 12. Ozonolysis of 52 and Enzymatic Desymmetrization of Diol 53



Scheme 13. Formal Synthesis of (−)-Gephyrotoxin 287C



the yield of rearrangement of *N*-mesyloxylactams **44**, its synthesis was shorter, and no *trans* isomer or side products were formed. Therefore, if the desymmetrization of **52** proved to be possible, this synthetic strategy would be the better one.

Ozonolysis of the double bond present in benzyl carbamate **52** followed by a reductive quench afforded *meso*-diol **53** in 56% yield (Scheme 12). Room-temperature reduction of the ozonide generated from **52** yielded a lactol intermediate that was difficult to reduce. Heating the reaction mixture to reflux in the presence of the hydride was necessary to ensure a complete reduction to give **53**. We then turned our efforts toward the enzymatic desymmetrization of *meso*-diol **53**. Our initial choice of the reaction conditions was inspired by the results obtained by other research groups that had successfully desymmetrized similar diols.[20] However, in their molecules both hydroxyl groups were on the carbons next to the stereogenic centers. We were concerned about obtaining poor results because the hydroxyl groups in our case were two carbons removed from the stereogenic centers. To the best of our knowledge, no enzymatic desymmetrization of such substrates has been reported in the literature. After much optimization with three different enzymes (PS, PPL, and PFL), we were successful in obtaining monoacetate **54** in 48% yield and 94:6 *er* using a lipase isolated from *Pseudomonas fluorescens* (PFL) and vinyl acetate. This was quite a remarkable result, as the other enzymes afforded nearly racemic products. Some unreacted diol **53** remained, and the rest of the mass balance was mostly composed of the corresponding diacetate product (not shown). The recovered diol **53** was resubmitted to the desymmetrization conditions, thus further increasing the yield of **54** to 58% after two desymmetrization runs.

Oxidation of the alcohol in **54** using the Swern conditions proceeded with a yield of 91% (Scheme 13). Following the protocol utilized by Trudell,[12c] we synthesized compound **56** in 91% yield using a reductive Knoevenagel reaction starting from aldehyde **55**. Next, the benzyl carbamate in **56** was cleaved using hydrogen and a palladium catalyst. The resulting secondary amine immediately condensed onto one of the carbonyl groups, affording a 60% yield of tricyclic compound **57**. Kishi's intermediate (−)-**13** was obtained in 49% yield (68% brsm) after methanolysis of the acetate under basic conditions. It displayed a negative sign in its optical rotation measurement, confirming the absolute stereochemistry shown for the chiral structures in Schemes 12 and 13. This absolute stereochemistry corresponds to the one needed to make natural (−)-gephyrotoxin 287C.

In summary, we have developed a short and efficient synthesis of Kishi's intermediate to gephyrotoxin 287C, compound (−)-**13**, using the powerful combination of the Beckmann ring expansion and our photochemical ring contraction to stereospecifically convert a cyclopentanone into a pyrrolidine.

EXPERIMENTAL SECTION

All of the reactions were performed under an inert atmosphere of argon in glassware that was flame-dried. Solvents were distilled neat (hexanes), from potassium/benzophenone ketyl (THF), from calcium hydride (CH_2Cl_2, toluene, benzene, Et_3N), and from 4 Å molecular sieves (MeOH) prior to use. Triflic anhydride and benzyl alcohol were also freshly distilled before use. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a 300 or 400 MHz spectrometer. NMR samples were dissolved in chloroform-*d* (unless specified otherwise), and chemical shifts are reported in parts per million relative to the residual undeuterated solvent. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 75.5 or 100.7 MHz spectrometer. NMR samples were dissolved in chloroform-*d* (unless specified otherwise), and chemical shifts are reported in parts per million relative to the solvent. LRMS analyses were performed on a GC system spectrometer (30 m length, 25 μ OD, DB-5 ms column) coupled with a mass spectrometer. High-resolution mass spectrometry was performed by electrospray time-of-flight. Reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel-coated UV254 glass plates. Silica gel (particle size 230−400 mesh) was used for flash chromatography. Melting points are uncorrected.

((2-Bromoethoxy)methyl)benzene (26). Compound **26** was prepared from 2-(benzyloxy)ethanol following the literature procedure of Hammerschmidt and Kählig.[21] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.44−7.28 (m, 5H), 4.60 (s, 2H), 3.79 (t, 2H, J = 6.3 Hz), 3.50 (t, 2H, J = 6.3 Hz).

2-(2-(Benzyloxy)ethyl)cyclopentanone (27). *N*,*N*-Dimethylhydrazine hydrochloride (0.746 g, 7.73 mmol) and triethylamine (1.08 mL, 7.73 mmol) were added to a stirring solution of cyclopentanone (**23**) (0.500 g, 5.94 mmol) in EtOH (20 mL). The resulting solution was refluxed for 3.5 h. The solution was concentrated under reduced pressure to give a brown-orange paste. The paste was dissolved in

dx.doi.org/10.1021/jo402217e | J. Org. Chem. 2013, 78, 12532−12544

diethyl ether (200 mL) and washed with water (100 mL). The aqueous layer was then extracted with diethyl ether twice (100 mL). The organic layers were then combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield cyclopentanone dimethylhydrazone as an orange oil (0.669 g, 89%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 2.48 (s, 6H), 2.38 (dt, 4H, J = 6.9, 15.1 Hz), 1.82−1.67 (m, 4H). This compound is known.[22]

n-BuLi in hexanes (11.6 mL, 2.40 M, 28.0 mmol) was added to a stirring solution of cyclopentanone dimethylhydrazone (3.21 g, 25.4 mmol) in THF (85 mL) at 0 °C. The resulting mixture was allowed to stir for 1 h at this temperature, and then a solution of bromide **26** (5.63 g, 26.2 mmol) in THF (40 mL) was added using a cannula. The solution was then allowed to stir at rt for 45 min. The solution was then quenched with water and extracted with diethyl ether (3 × 100 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a brown oil. The oil was dissolved in dichloromethane (500 mL) and stirred with SiO_2 (60 g) for 48 h. The solution was then filtered, and the silica was washed with copious amounts of EtOAc. The resulting solution was concentrated under reduced pressure to give a yellow oil. The oil was purified by flash chromatography on silica gel (6:1 to 2:1 hexanes/diethyl ether) to yield *rac*-**27** as a colorless solid (2.70 g, 49%). **m.p.** 39−41 °C. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37−7.25 (m, 5H), 4.53−4.45 (AB quartet, 2H), 3.63−3.50 (m, 2H), 2.34−1.94 (m, 6H), 1.83−1.67 (m, 1H), 1.63−1.45 (m, 2H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 221.1 (s), 138.5 (s), 128.3 (d), 127.5 (d), 72.7 (t), 68.2 (t), 46.5 (d), 37.9 (t), 29.6 (t), 29.6 (t), 20.8 (t). Note: one carbon (d) was missing in the aromatic region (128.3−127.5 ppm) since it overlapped with another signal.

(2-Bromoethoxy)(*tert*-butyl)diphenylsilane (28). Compound **28** was prepared from 2-bromoethanol following the literature procedure of Buchwald and co-workers.[23] **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.69−7.66 (m, 4H), 7.47−7.36 (m, 6H), 3.92 (t, 2H, J = 6.6 Hz), 3.42 (t, 2H, J = 6.6 Hz), 1.07 (s, 9H).

2-(2-(Benzyloxy)ethyl)-5-(2-(*tert*-butyldiphenylsilyloxy)-ethyl)cyclopentanone (29). *N*,*N*-Dimethylhydrazine hydrochloride (2.65 g, 27.4 mmol) and triethylamine (3.6 mL, 26 mmol) were added to a stirring solution of **27** (3.99 g, 18.3 mmol) in EtOH (120 mL). The resulting mixture was refluxed for 16 h. The solution was concentrated under reduced pressure to give an orange paste. The paste was dissolved in diethyl ether (200 mL) and washed with water (100 mL). The aqueous layer was then extracted with diethyl ether twice (100 mL). The organic layers were then combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield the corresponding hydrazone as a yellow oil (4.68 g, 98%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 7.33−7.23 (m, 5H), 4.52−4.45 (AB quartet, 2H), 3.57 (t, 2H, J = 6.9 Hz), 2.53−2.37 (m, 2H), 2.44 (s, 6H), 2.29 (dtd, 1H, J = 18.1, 8.5, 1.5 Hz), 2.14−2.06 (m, 1H), 1.97−1.91 (m, 1H), 1.85−1.76 (m, 1H), 1.64−1.54 (m, 2H), 1.42−1.33 (m, 1H). **^{13}C NMR** (100.7 MHz, $CDCl_3$): δ 176.9 (s), 138.9 (s), 128.5 (d), 127.8 (d), 127.6 (d), 73.0 (t), 69.1 (t), 47.3 (q), 42.0 (d), 33.2 (t), 31.1 (t), 29.5 (t), 23.1 (t). **IR** (neat, NaCl) ν (cm^{-1}): 3032, 2958, 2854, 2812, 1735, 1648, 1457, 1101. **LRMS** (*m*/*z*, relative intensity): 260 (M^+, 20), 126 (100), 91 (75). **HRMS**: calcd for $C_{16}H_{24}N_2O$ 260.1889, found 260.1886.

n-BuLi in hexanes (4.0 mL, 2.4 M, 9.5 mmol) was added to a stirring solution of the hydrazone (2.25 g, 8.64 mmol) in THF (30 mL) at 0 °C. The resulting mixture was stirred for 1 h at this temperature, and then a solution of bromide **28** (3.45 g, 9.50 mmol) in THF (10 mL) was added using a cannula. The solution was allowed to stir at rt for 18 h. The solution was then quenched with water and extracted with EtOAc (3 × 100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give an orange oil. The oil was dissolved in dichloromethane (140 mL) and stirred with SiO_2 (20 g) for 48 h. The solution was filtered, and the silica was washed with copious amounts of EtOAc. The resulting solution was concentrated under reduced pressure to give an orange oil. The oil was purified by flash chromatography on silica gel (4:1 to 2:1 hexanes/diethyl ether) to yield *rac*-**29** as a colorless oil (2.89 g, 67% (75% brsm)) as a mixture of diastereomers. Note: only the major isomer is reported. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.80−7.77 (m, 4H), 7.52−7.25 (m, 11H), 4.62−4.52 (AB quartet, 2H), 3.92−3.77 (m, 2H), 3.71−3.54 (m, 2H), 2.43−2.09 (m, 6H), 1.73−1.37 (m, 4H), 1.16 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 221.7 (s), 138.5 (s), 135.6 (d), 133.8 (s), 129.7 (d), 128.4 (d), 127.8 (d), 127.6 (d), 72.8 (t), 68.3 (t), 62.1 (t), 46.6 (d), 46.5 (d), 33.1 (t), 30.1 (t), 28.0 (t), 27.0 (q), 22.8 (t), 19.3 (s). Note: one carbon (d) was missing since it overlapped with another signal in the aromatic region (138.5−127.6 ppm). **IR** (neat, NaCl) ν (cm^{-1}): 3072, 3037, 2940, 2856, 1734, 1470, 1452, 1430, 1359, 1103. **LRMS** (*m*/*z*, relative intensity): 500 (M^+, 1), 336 (100), 275 (85), 199 (95), 182 (80). **HRMS**: calcd for $C_{32}H_{40}O_3Si$ 500.2747, found 500.2750.

6-(2-(Benzyloxy)ethyl)-3-(2-(*tert*-butyldiphenylsilyloxy)-ethyl)piperidin-2-one (30a) and 3-(2-(Benzyloxy)ethyl)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)piperidin-2-one (30b). Sodium acetate (0.375 g, 4.57 mmol) and hydroxylamine hydrochloride (0.318 g, 4.57 mmol) were added to a stirring solution of **29** (0.572 g, 1.14 mmol) in methanol (11 mL). The solution was stirred at rt for 20 h, quenched with a 7.2 pH phosphate buffer (20 mL), and extracted with DCM (3 × 100 mL). The organic layers were then combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a clear oil. The oil was purified by flash chromatography on silica gel (2:1 to 1:2 hexanes/diethyl ether) to yield four oximes (two diastereomeric pairs, one for each regioisomer) as a clear oil (0.546 g, 93%). Note: the four compounds were difficult to separate, and their characterization as a mixture was difficult. We therefore separated only one of them and report its characterization. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 8.94 (br s, 1H), 7.76−7.71 (m, 4H), 7.48−7.26 (m, 11H), 4.59−4.49 (AB quartet, 2H), 3.86−3.69 (m, 2H), 3.65−3.58 (m, 2H), 3.19−3.08 (m, 1H), 2.72−2.62 (m, 1H), 2.52−2.42 (m, 1H), 2.24−2.13 (m, 1H), 2.06−1.92 (m, 2H), 1.67−1.24 (m, 4H), 1.10 (s, 9H). **^{13}C NMR** (100.7 MHz, $CDCl_3$): δ 170.2 (s), 138.8 (s), 135.9 (d), 135.9 (d), 134.3 (s), 134.2 (s), 129.8 (d), 128.6 (d), 127.9 (d), 127.9 (d), 127.8 (d), 73.1 (t), 68.9 (t), 62.7 (t), 40.7 (d), 37.3 (d), 34.6 (t), 31.5 (t), 30.6 (t), 29.5 (t), 27.1 (q), 19.5 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3585−3108 (br), 3068, 2936, 2856, 1452, 1421, 1103. **LRMS** (*m*/*z*, relative intensity): 515 (M^+, 1), 459 (100), 260 (30), 199 (20), 91 (25). **HRMS**: calcd for $C_{32}H_{41}NO_3Si$ 515.2856, found 515.2860.

Thionyl chloride (120 μL, 1.59 mmol) was added to a stirring solution of the mixture of oximes (0.546 g, 1.06 mmol) in THF (11 mL) at 0 °C. The solution was stirred for 1 h and then quenched with a saturated aqueous solution of $NaHCO_3$ (10 mL). The solution was allowed to stir for 1 h and then extracted three times with $CHCl_3$ (50 mL). The organics were combined, washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give a light-yellow oil. The oil was purified by flash chromatography on silica gel (2:1 to 1:1 hexanes: EtOAc) to yield **30a** and **30b** as a clear oil (0.513 g, 94%). Note: the four compounds were difficult to separate, and their characterization as a mixture was difficult. We therefore separated only one of them and report its characterization. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.71−7.67 (m, 4H), 7.45−7.26 (m, 11H), 6.42 (br s, 1H), 4.52 (s, 2H), 3.84−3.71 (m, 2H), 3.68−3.48 (m, 3H), 2.48−2.37 (m, 2H), 1.99−1.52 (m, 7H), 1.06 (s, 9H). **^{13}C NMR** (100.7 MHz, $CDCl_3$): δ 174.5 (s), 138.1 (s), 135.8 (d), 134.2 (s), 134.1 (s), 129.8 (d), 128.7 (d), 128.0 (d), 127.9 (d), 127.9 (d), 73.5 (t), 68.4 (t), 61.9 (t), 53.2 (d), 38.2 (d), 37.0 (t), 34.2 (t), 29.8 (t), 27.1 (q), 26.6 (t), 19.5 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3209, 3072, 2931, 2865, 1659, 1465, 1421, 1112. **LRMS** (*m*/*z*, relative intensity): 515 (M^+, 2), 500 (5), 440 (100). **HRMS**: calcd for $C_{32}H_{41}NO_3Si$ 515.2856, found 515.2855.

6-(2-(Benzyloxy)ethyl)-3-(2-(*tert*-butyldiphenylsilyloxy)-ethyl)-1-chloropiperidin-2-one (31a) and 3-(2-(Benzyloxy)-ethyl)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-1-chloropiperidin-2-one (31b). *tert*-Butyl hypochlorite (66 μL, 0.55 mmol) was added dropwise to a stirring solution of **30a** and **30b** (0.191 g, 0.369 mmol) in dichloromethane (1.5 mL) in the dark at 0 °C. The solution was stirred for 2 h, whereupon additional *tert*-butyl hypochlorite was added (22 μL, 0.18 mmol) and the mixture was stirred for 15 min. The solution was then concentrated under reduced pressure to give a light-

yellow oil. The oil was purified by flash chromatography on silica gel (2:1 to 1:1 hexanes/diethyl ether) to yield **31a** and **31b** as a clear oil (0.128 g, 63%). Note: the four compounds were difficult to separate, and their characterization as a mixture was difficult. We therefore separated only two of them and report their characterization as a mixture. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.69−7.67 (m, 8H), 7.46−7.26 (m, 22H), 4.57−4.46 (AB quartet, 2H), 4.53−4.47 (AB quartet, 2H), 3.90−3.69 (m, 6H), 3.67−3.54 (m, 4H), 2.76−2.59 (m, 2H), 2.48−2.27 (m, 4H), 2.16−2.07 (m, 2H), 1.98−1.47 (m, 10H), 1.08 (s, 9H), 1.07 (s, 9H). ^{13}**C NMR** (75.5 MHz, $CDCl_3$): δ 171.3 (s), 171.2 (s), 138.4 (s), 138.0 (s), 135.6 (d), 135.6 (d), 133.7 (s), 133.4 (s), 129.8 (d), 129.8 (d), 129.7(d), 129.7 (d), 128.4 (d), 128.4 (d), 127.8 (d), 127.8 (d), 73.1 (t), 72.9 (t), 68.1 (t), 66.3 (t), 64.4 (d), 64,3 (d), 61.6 (t), 60.1 (t), 41.2 (d), 41.0 (d), 36.6 (t), 34.4 (t), 34.1 (t), 32.0 (t), 28.9 (t), 28.5 (t), 26.9 (q), 26.9 (q), 24.7 (t), 24.4 (t), 19.2 (s), 19.2 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3072, 3033, 2931, 2852, 1677, 1430, 1275, 1187, 1112. **LRMS** (*m*/*z*, relative intensity): 549 (M^+, 1), 492 ($M^+ - C_4H_9$, 2), 458 ($M^+ - C_7H_7$, 100), 350 (30), 199 (25), 91 (85). **HRMS**: calcd for $C_{28}H_{31}NO_3SiCl$ ($M^+ - C_4H_9$) 492.1762, found 492.1763.

7-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (32). A mixture of **31a** and **31b** (0.250 g, 0.454 mmol) was dissolved in dichloromethane (30 mL) in a quartz reaction cell, which was lowered into into a Rayonet reactor chamber equipped with sixteen 254 nm UV lamps and exposed to UV light at −78 °C under a N_2 atmosphere until no more starting material was detected by TLC (2 h). The solution was then transferred to a flask containing a mixture of MeOH (10 mL) and Et_3N (1 mL). The reaction mixture was allowed to stir overnight (18 h). The reaction mixture was concentrated under reduced pressure to give an orange oil. The oil was dissolved in dichloromethane (30 mL) and washed with water (30 mL). The aqueous layer was extracted twice with dichloromethane (30 mL). The organic layers were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a light-yellow oil. The oil was taken up in dichloromethane and purified by flash chromatography on silica gel (4:1 to 1:1 hexanes/EtOAc) to yield **32** as colorless oil (47 mg, 24%) and the parent amides **30a** and **30b** as a clear oil (85 mg, 36%). One of the two stereoisomers of **32** could be obtained reasonably pure: ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.68−7.65 (m, 4H), 7.45−7.35 (m, 6H), 4.29 (ddd, 1H, J = 11.0, 3.9, 1.9 Hz), 4.13−4.01 (m, 2H), 3.73 (t, 2H, J = 6.3 Hz), 3.48 (ddd, 1H, J = 16.0, 11.0, 5.0 Hz), 2.41−2.31 (m, 1H), 2.18−2.04 (m, 3H), 1.72−1.54 (m, 3H), 1.44−1.31 (m, 1H), 1.04 (s, 9H). ^{13}**C NMR** (100.7 MHz, $CDCl_3$): δ 153.0 (s), 135.8 (d), 134.0 (s), 133.9 (s), 129.8 (d), 127.9 (d), 65.9 (t), 61.6 (t), 57.6 (d), 57.0 (d), 37.4 (t), 33.4 (t), 30.3 (t), 28.7 (t), 27.1 (q), 19.4 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3064, 2936, 2861, 1695, 1470, 1430, 1112. **LRMS** (*m*/*z*, relative intensity): 367 ($M^+ - C_4H_8$, 100), 320 (10), 294 (15). **HRMS**: calcd for $C_{21}H_{25}NO_3Si$ ($M^+ - C_4H_8$) 367.1604, found 367.1605.

1-Bromo-2-(methoxymethoxy)ethane (34). Compound **34** was prepared from 2-bromoethanol following the literature procedure of Ito and co-workers.[24] ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 4.68 (s, 2H), 3.87 (t, 2H, J = 6.1 Hz), 3.51 (t, 2H, J = 6.1 Hz), 3.39 (s, 3H).

2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-5-(2-(methoxymethoxy)ethyl)cyclopentanone (35). *n*-BuLi in hexanes (5.60 mL, 1.95 M, 10.9 mmol) was added to a stirring solution of cyclopentanone dimethylhydrazone (prepared in the same way as in the synthesis of compound **27**) (1.10 g, 8.74 mmol) in THF (30 mL) at 0 °C. The resulting mixture was allowed to stir for 30 min at this temperature, and then a solution of bromide **28** (3.81 g, 10.5 mmol) in THF (10 mL) was added using a cannula. The solution was then allowed to stir at rt for 30 min. The solution was then cooled down again to 0 °C, and *n*-BuLi in hexanes (5.60 mL, 1.95 M, 10.9 mmol) was added. The resulting mixture was allowed to stir for 30 min at this temperature, and then a solution of bromide **34** (1.77 g, 10.5 mmol) in THF (10 mL) was added using a cannula. The solution was allowed to stir at rt for 90 min and was then quenched with water and extracted into EtOAc (3 × 100 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a light-orange oil. The oil was dissolved in dichloromethane (145 mL) and stirred with SiO_2 (21 g) for 48 h. The solution was then filtered from the silica. The silica was then washed with copious amounts of EtOAc, and the resulting solution was concentrated under reduced pressure to give a yellow oil. The oil was purified by flash chromatography on silica gel (6:1 to 4:1 hexanes/diethyl ether) to yield compound **35** as a clear oil (1.43 g, 36%) as a mixture of inseparable diastereomers and 2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-cyclopentanone (the product of monoalkylation, 640 mg, 20%). One of the two stereoisomers of **35** could be obtained stereoisomerically pure: ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.70−7.68 (m, 4H), 7.44−7.35 (m, 6H), 4.61 (s, 2H), 3.85−3.72 (m, 2H), 3.71−3.56 (m, 2H), 3.35 (s, 3H), 2.39−1.97 (m, 6H), 1.69−1.37 (m, 4H), 1.07 (s, 9H). ^{13}**C NMR** (75.5 MHz, $CDCl_3$): δ 221.5 (s), 135.5 (d), 133.7 (d), 129.6 (d), 127.7 (d), 96.3 (t), 65.6 (t), 62.0 (t), 55.1 (q), 46.5 (d), 46.4 (d), 33.0 (t), 30.1 (t), 27.9 (t), 27.9 (t), 26.9 (q), 19.2 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3072, 3053, 2900, 2862, 1735, 1469, 1424, 1151, 1113, 1042. **LRMS** (*m*/*z*, relative intensity): 397 ($M^+ - C_4H_9$, 2), 365 ($M^+ - C_5H_{14}O$, 100), 275 (25), 199 (80). **HRMS**: calcd for $C_{23}H_{29}O_4Si$ ($M^+ - C_4H_9$) 397.1835, found 397.1844.

3-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-6-(2-(methoxymethoxy)ethyl)tetrahydro-2*H*-pyran-2-one (36a) and 6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-3-(2-(methoxymethoxy)ethyl)-tetrahydro-2*H*-pyran-2-one (36b). *m*CPBA (2.74 g, 12.2 mmol) and $NaHCO_3$ (1.03 g, 12.2 mmol) were added to a stirring solution of **35** (0.928 g, 2.04 mmol) in DCM (70 mL). The resulting mixture was stirred at rt for 24 h. The solution was then dissolved in DCM (50 mL) and washed with an aqueous solution of NaOH (25 mL, 1M). The phases were separated, and the aqueous phase was extracted twice with DCM (100 mL). The organic layers were then combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a light-yellow oil. The oil was purified on by flash chromatography on silica gel (2:1 to 1:1 hexanes/diethyl ether) to yield the mixture of stereo- and regioisomeric compounds **36a** and **36b** as a clear oil (0.575 g, 60%) as a mixture of inseparable regioisomers. Note: the four compounds were difficult to separate, and their characterization as a mixture was difficult. We therefore separated only one of them and report its characterization. ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 7.67−7.64 (m, 8H), 7.46−7.36 (m, 12H), 4.61 (s, 4H), 4.61−4.31 (m, 2H), 3.93−3.59 (m, 8H), 3.35 (s, 6H), 2.76−2.50 (m, 2H), 2.38−1.47 (m, 16H) 1.05 (s. 18H). ^{13}**C NMR** (75.5 MHz, $CDCl_3$): δ 173.7 (s), 173.5 (s), 135.5 (d), 135.5 (d), 133.6 (s), 133.5 (s), 129.7 (d), 129.7 (d), 127.7 (d), 127.7 (d), 96.5 (t), 96.4 (t), 78.5 (d), 78.3 (d), 64.9 (t), 63.3 (t), 60.9 (t), 59.6 (t), 55.3 (q), 55.3 (q), 39.1 (t), 38.0 (d), 37.7 (d), 36.4 (t), 34.2 (t), 31.7 (t), 29.2 (t), 29.2 (t), 26.8 (q), 26.8 (q), 25.9 (t), 25.5 (t), 19.2 (s), 19.2 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3076, 3050, 2930, 2885, 2855, 1731, 1473, 1428, 1185, 1151, 1113, 1035. **LRMS** (*m*/*z*, relative intensity): 439 ($M^+ - OC_1H_3$, 5), 413 ($M^+ - C_4H_9$, 40), 351 (25), 291 (45), 213 (50), 199 (100), 91 (55). **HRMS**: calcd for $C_{23}H_{29}O_5Si$ ($M^+ - C_4H_9$) 413.1784, found 413.1776.

***N*-(Benzyloxy)-2-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-5-hydroxy-7-(methoxymethoxy)heptanamide (37a) and *N*-(Benzyloxy)-7-(*tert*-butyldiphenylsilyloxy)-5-hydroxy-2-(2-(methoxymethoxy)ethyl)heptanamide (37b).** Trimethylaluminum (3.7 mL, 1.0 M in toluene, 3.7 mmol) was added to a stirring solution of *O*-benzylhydroxylamine (596 mg, 3.73 mmol) in anhydrous THF (12 mL) at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and 30 min at rt and then cooled again to −10 °C. A solution of lactone **36a** and 36**b** (586 mg, 1.24 mmol) in THF (12 mL) was transferred to the reaction mixture using a cannula. The solution was allowed to stir for 2 h at 0 °C. The resulting solution was cooled to 0 °C and then quenched with a 0.5 N aqueous HCl solution (20 mL) portionwise over 1 h. The resulting mixture was then extracted with EtOAc (3 × 50 mL). The organic layers were then combined, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give a clear oil. The oil was purified by flash chromatography on silica gel (2:1 to 1:2 hexanes/diethyl ether) to yield **37a** and **37b** as a clear oil (477 mg, 65% (73% brsm)) as a mixture of inseparable regioisomers (3:2). ^{1}**H NMR** (300 MHz, $CDCl_3$): δ 8.77 (br s, 1H), 8.47 (br s,

dx.doi.org/10.1021/jo402217e | *J. Org. Chem.* 2013, 78, 12532−12544

1H), 7.68−7.62 (m, 8H), 7.47−7.33 (m, 22H), 4.94−4.87 (AB quartet, 2H), 4.87−4.78 (AB quartet, 2H), 4.61 (s, 2H), 4.51 (s, 2H), 3.90−3.54 (m, 8H), 3.46−3.38 (m, 2H), 3.35 (s, 3H), 3.30 (s, 3H), 2.32−2.21 (m, 2H), 2.01−1.66 (m, 10H), 1.63−1.40 (m, 6H), 1.04 (s, 9H), 1.02 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 173.7 (s), 173.5 (s), 135.5 (d), 135.5 (d), 133.7 (s), 133.5 (s), 132.9 (s), 132.7 (s), 129.9 (d), 129.9 (d), 129.8 (d), 129.8 (d), 129.1 (d), 129.1 (d), 128.5 (d), 128.5 (d), 127.8 (d), 127.8 (d), 96.5 (t), 96.5 (t), 78.1 (t), 78.1 (t), 71.5 (d), 70.7 (d), 66.4 (t), 65.6 (t), 63.6 (t), 61.5 (t), 55.4 (q), 55.3 (q), 40.2 (d), 39.7 (d), 37.7 (t), 37.7 (t), 36.0 (t), 35.1 (t), 34.3 (t), 32.5 (t), 27.9 (t), 27.9 (t), 26.9 (q), 26.8 (q), 19.2 (s), 19.0 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3653−3323 (br), 3323−3106 (br), 3076, 3035, 2934, 2855, 1656, 1473, 1432, 1110, 1038. **LRMS** (*m*/*z*, relative intensity): 536 ($M^+ - C_4H_9$, 2), 518 ($M^+ - C_4H_{11}O$, 3), 413 (25), 291 (40), 199 (100), 91 (85). **HRMS**: calcd for $C_{30}H_{38}NO_6Si$ ($M^+ - C_4H_9$) 536.2468, found 536.2459.

***cis*-1-(Benzyloxy)-3-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-6-(2-(methoxymethoxy)ethyl)piperidin-2-one (38a), *cis*-1-(Benzyloxy)-6-(2-(*tert*-butyldiphenylsilyloxy)ethyl)-3-(2-(methoxymethoxy)ethyl)piperidin-2-one (38b), *trans*-3-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-6-(2-(methoxymethoxy)ethyl)-tetrahydro-2*H*-pyran-2-one *O*-Benzyl Oxime (39a), and *trans*-6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-3-(2-(methoxymethoxy)ethyl)tetrahydro-2*H*-pyran-2-one *O*-Benzyl Oxime (39b).** DIAD (0.17 mL, 0.84 mmol) was added to a stirring solution of PPh_3 (0.221 g, 0.843 mmol) in DCM (8 mL) at −10 °C. The solution was stirred for 30 min at this temperature, and then a solution of alcohols **37a** and **37b** (0.477 g, 0.804 mmol) in DCM (8 mL) was added to the reaction mixture using a cannula. The resulting solution was left to stir at rt for 16 h and then concentrated under reduced pressure to give a yellow oil. The oil was purified by flash chromatography on silica gel (6:1 to 1:1 hexanes/EtOAc) to yield the separable isomers **38a** and **38b** as a clear oil (products of *N*-cyclization, 120 mg, 26%) and two inseparable *O*-cyclization products **39a** and **39b** as a clear oil (146 mg, 38%).

*Data for **38a**.* **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70−7.67 (m, 4H), 7.47−7.33 (m, 11H), 4.94 (s, 2H), 4.57 (s, 2H), 3.87−3.60 (m, 3H), 3.56 (t, 2H, *J* = 6.3 Hz), 3.32 (s, 3H), 2.66−2.55 (m, 1H), 2.44−2.33 (m, 1H), 2.29−2.18 (m, 1H), 1.87−1.48 (m, 6H), 1.06 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 170.2 (s), 135.6 (d), 133.8 (s), 133.7 (s), 129.6 (d), 128.6 (d), 128.4 (d), 127.6 (d), 96.4 (t), 75.6 (t), 65.8 (t), 61.7 (t), 57.8 (d), 55.3 (q), 39.7 (d), 34.0 (t), 32.4 (t), 26.8 (q), 26.2 (t), 22.8 (t), 19.2 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3072, 3035, 2937, 2881, 2859, 1656, 1110, 1035. **LRMS** (*m*/*z*, relative intensity): 518 ($M^+ - C_4H_9$, 100), 91 (60). **HRMS**: calcd for $C_{30}H_{36}NO_5Si$ ($M^+ - C_4H_9$) 518.2363, found 518.2368.

*Data for **38b**.* **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.61−7.59 (m, 4H), 7.42−7.26 (m, 11H), 4.89 (s, 2H), 4.62−4.57 (AB quartet, 2H), 3.73−3.56 (m, 5H), 3.33 (s, 3H), 2.55−2.46 (m, 1H), 2.34−2.18 (m, 2H), 1.82−1.50 (m, 6H), 1.01 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 169.8 (s), 135.5 (d), 135.3 (s), 133.4 (s), 129.7 (d), 129.5 (d), 128.5 (d), 128.3 (d), 127.7 (d), 96.3 (t), 75.4 (t), 65.5 (t), 60.9 (t), 57.5 (d), 55.2 (q), 29.8 (d), 34.5 (t), 31.3 (t), 26.8 (q), 25.8 (t), 22.9 (t), 19.1 (s). IR (neat, NaCl) ν (cm^{-1}): 2986, 2937, 2877, 1653, 1510, 1465, 1110. **LRMS** (*m*/*z*, relative intensity): 544 (M^+ − OMe, 5), 518 ($M^+ - C_4H_9$, 15), 456 (25), 366 (50), 91 (100). HRMS: calcd for $C_{30}H_{36}NO_5Si$ ($M^+ - C_4H_9$) 518.2363, found 518.2352.

*Data for **39a/39b**.* **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.70−7.68 (m, 8H), 7.52−7.26 (m, 22H), 5.00 (s, 2H), 4.97 (s, 2H), 4.63 (s, 2H), 4.60−4.55 (AB quartet, 2H), 4.38−4.32 (m, 1H), 4.32−4.22 (m, 1H), 3.98−3.90 (m, 1H), 3.84−3.60 (m, 5H), 3.58 (t, 2H, *J* = 6.3 Hz), 3.35 (s, 6H), 2.71−2.55 (m, 2H), 2.22−1.73 (m, 10H), 1.72−1.50 (m, 6H), 1.08 (s, 18H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 157.1 (s), 156.7 (s), 138.6 (s), 138.4 (s), 135.6 (d), 135.6 (d), 134.0 (s), 133.9 (s), 133.8 (s), 133.6 (s), 129.6 (d), 129.6 (d), 128.1 (d), 128.1 (d), 127.7 (d), 127.7 (d), 127.4 (d), 127.4 (d), 96.5 (t), 96.5 (t), 75.7 (t), 75.7 (t), 75.0 (d), 74.8 (d), 65.4 (t), 63.8 (t), 61.5 (t), 60.0 (t), 55.2 (q), 55.2 (q), 38.1 (t), 35.5 (t), 34.2 (t), 33.3 (t), 31.2 (d), 31.0 (d), 26.9 (q), 26.9 (q), 25.2 (t), 25.2 (t), 24.9 (t), 24.9 (t), 19.2 (s), 19.2 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3072, 3031, 2930, 2855, 1641, 1469, 1424, 1102, 1050. **LRMS** (*m*/*z*, relative intensity): 575 (M^+, 2), 518 ($M^+ - C_4H_9$, 90), 293 (30), 199 (40), 91 (100). **HRMS**: calcd for $C_{34}H_{45}NO_5Si$ 575.3067, found 575.3077.

***cis*-3-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-6-(2-(methoxymethoxy)ethyl)-2-oxopiperidin-1-yl Methanesulfonate (44a).** To a solution of **38a** (77.1 mg, 0.134 mmol) in EtOH (13 mL) was added Pd/C (~25−50 mg, 10 wt % on activated carbon). The reaction mixture was then allowed to stir at rt under a positive pressure of hydrogen (1 atm) until no more starting material was seen by TLC (10 h). The solution was then filtered through Celite and concentrated under reduced pressure to give the cyclic hydroxamic acid as an orange oil (65 mg). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.63−7.60 (m, 4H), 7.42−7.31 (m, 6H), 4.59−4.54 (AB quartet, 2H), 3.93−3.85 (m, 1H), 3.79−3.53 (m, 4H), 3.31 (s, 3H), 2.58−2.45 (m, 1H), 2.29−2.12 (m, 2H), 1.90−1.73 (m, 3H), 1.70−1.50 (m, 3H), 1.01 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 166.9 (s), 135.5 (d), 133.4 (s), 129.7 (d), 127.7 (d), 96.3 (t), 65.3 (t), 60.9 (t), 56.6 (d), 55.2 (q), 37.8 (d), 34.8 (t), 31.5 (t), 26.8 (q), 25.4 (t), 23.0 (t), 19.1 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3469−3177 (br), 2982, 2941, 2881, 1626, 1514, 1237, 1106, 1035. **LRMS** (*m*/*z*, relative intensity): 485 (M^+, 1), 470 ($M^+ - CH_3$, 1), 428 ($M^+ - C_4H_9$, 100), 200 (20). **HRMS**: calcd for $C_{27}H_{39}NO_5Si$ 485.2597, found 485.2590.

Triethylamine (25 μL, 0.18 mmol), 4-dimethylaminopyridine (5.5 mg, 0.045 mmol), and methanesulfonyl chloride (13 μL, 0.17 mmol) were added to a cooled (0 °C) stirring solution of the cyclic hydroxamic acid (73 mg, 0.15 mmol) in dichloromethane (1.5 mL). The resulting mixture was stirred at 0 °C for 1 h. The resulting solution was quenched with a 0.5 N aqueous HCl solution (10 mL) and extracted with dichloromethane (3 × 25 mL). The organic layers were then combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield a pink oil. The oil was purified by flash chromatography on silica gel (1:1 to 1:2 hexanes/diethyl ether) to yield **44a** as a clear oil (44 mg, 52% (86% brsm)). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.66−7.64 (m, 4H), 7.46−7.37 (m, 6H), 4.63−4.58 (AB quartet, 2H), 4.28−4.24 (m, 1H), 3.77−3.56 (m, 4H), 3.35 (s, 3H), 3.22 (s, 3H), 2.74−2.64 (m, 1H), 2.34−2.21 (m, 2H), 2.17−2.02 (m, 2H), 1.93−1.83 (m, 1H), 1.72−1.56 (m, 3H), 1.05 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 171.7 (s), 135.5 (d), 133.3 (s), 133.2 (s), 129.8 (d), 127.7 (d), 96.4 (t), 65.0 (t), 62.5 (d), 60.7 (t), 55.3 (q), 40.5 (d), 39.0 (q), 33.0 (t), 30.8 (t), 26.8 (q), 26.2 (t), 22.7 (t), 19.1 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3072, 3042, 2941, 2855, 1701, 1372, 1185, 1110, 1038. **LRMS** (*m*/*z*, relative intensity): 532 ($M^+ - CH_3O$, 2), 506 ($M^+ - C_4H_9$, 5), 366 (100). **HRMS**: calcd for $C_{24}H_{32}NO_7SSi$ ($M^+ - C_4H_9$) 506.1669, found 506.1654.

***cis*-6-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-3-(2-(methoxymethoxy)ethyl)-2-oxopiperidin-1-yl Methanesulfonate (44b).** To a solution of **38b** (0.114 g, 0.197 mmol) in EtOH (7 mL) was added Pd/C (~25−50 mg, 10 wt % on activated carbon). The reaction mixture was then allowed to stir at rt under a positive pressure of hydrogen (1 atm.) until no more starting material was seen by TLC (6 h). The solution was then filtered through Celite and concentrated under reduced pressure to give the cyclic hydroxamic acid as an orange oil (94 mg, 98%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.67−7.65 (m, 4H), 7.44−7.36 (m, 6H), 4.63−4.59 (AB quartet, 2H), 3.91−3.62 (m, 5H), 3.36 (s, 3H), 2.73−2.55 (m, 1H), 2.35−2.21 (m, 2H), 1.97−1.69 (m, 4H), 1.63−1.50 (m, 2H), 1.05 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 167.3 (s), 135.5 (d), 133.7 (s), 133.6 (s), 129.6 (d), 127.7 (d), 96.4 (t), 64.7 (t), 61.5 (t), 56.6 (d), 55.3 (q), 37.6 (d), 34.1 (t), 32.6 (t), 26.8 (q), 25.7 (t), 22.8 (t), 19.2 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3398−3106 (br), 3068, 3050, 2934, 2859, 1731, 1634, 1473, 1102, 1038. **LRMS** (*m*/*z*, relative intensity): 485 (M^+, 1), 470 ($M^+ - CH_3$, 2), 428 ($M^+ - C_4H_9$, 100), 199 (20). **HRMS**: calcd for $C_{27}H_{39}NO_5Si$ 485.2597, found 485.2590.

Triethylamine (32 μL, 0.23 mmol), 4-dimethylaminopyridine (7.1 mg, 0.058 mmol), and methanesulfonyl chloride (16 μL, 0.21 mmol) were added to a cooled (0 °C) stirring solution of the cyclic hydroxamic acid (94 mg, 0.19 mmol) in dichloromethane (1.9 mL). The resulting mixture was stirred at 0 °C for 1 h. The resulting solution was quenched with a 0.5 N aqueous HCl solution (10 mL) and extracted with dichloromethane (3 × 25 mL). The organic layers

dx.doi.org/10.1021/jo402217e | J. Org. Chem. 2013, 78, 12532−12544

were then combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to yield a pink oil. The oil was purified by flash chromatography on silica gel (2:1 to 1:1 hexanes/diethyl ether) to yield **44b** as a clear oil (83 mg, 76%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.66−7.64 (m, 4H), 7.46−7.33 (m, 6H), 4.62−4.57 (AB quartet, 2H), 4.22−4.18 (m, 1H), 3.85−3.62 (m, 2H), 3.60 (t, 2H, J = 6.3 Hz), 3.35 (s, 3H), 3.22 (s, 3H), 2.81−2.71 (m, 1H), 2.38−2.25 (m, 2H), 2.19−1.95 (m, 2H), 1.93−1.53 (m, 4H), 1.05 (s, 9H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 171.9 (s), 135.5 (d), 133.6 (s), 133.5 (s), 129.7 (d), 127.7 (d), 96.5 (t), 64.4 (t), 62.4 (d), 61.2 (t), 55.4 (q), 40.3 (d), 39.1 (q), 33.5 (t), 31.1 (t), 26.8 (q), 26.5 (t), 22.7 (t), 19.2 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3080, 3050, 2934, 2877, 1694, 1473, 1428, 1376, 1185, 1106, 1035. **LRMS** (m/z, relative intensity): 506 ($M^+ - C_4H_9$, 100), 199 (30). **HRMS**: calcd for $C_{24}H_{32}NO_7SSi$ ($M^+ - C_4H_9$) 506.1669, found 506.1654.

***cis*-Methyl 2-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)-5-(2-(methoxymethoxy)ethyl)pyrrolidine-1-carboxylate (45) and *cis*-7-(2-(*tert*-Butyldiphenylsilyloxy)ethyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (46).** *N*-Mesyloxylactam **44a** (70 mg, 0.12 mmol) was dissolved in DCM (20 mL) in a quartz reaction cell, which was lowered into a Rayonet reactor chamber equipped with sixteen 254 nm UV lamps. The reaction mixture was then exposed to UV light at −78 °C under a N_2 atmosphere until no more starting material was seen by TLC (5.5 h). The solution was then transferred to a flask containing a mixture MeOH (5 mL) and Et_3N (0.5 mL). The reaction mixture was allowed to stir overnight (16 h). The reaction mixture was concentrated under reduced pressure to give an orange oil. The solution was then concentrated to give a light-yellow oil. The oil was dissolved in dichloromethane (30 mL) and washed with water (30 mL). The aqueous layer was extracted twice with dichloromethane (30 mL). The organic layers were then combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to give a yellow oil. The oil was taken up in dichloromethane and purified by flash chromatography on silica gel (4:1 to 1:2 hexanes/EtOAc) to yield **45** as a clear oil (6 mg, 10%) and **46** as light-yellow oil (23 mg, 44%). The same reaction starting from **44b** gave identical yields of products.

*Data for **45**.* **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.68−7.65 (m, 4H), 7.45−7.35 (m, 6H), 4.63−4.58 (AB quartet, 2H), 3.98−3.89 (m, 2H), 3.76−3.62 (m, 2H), 3.65 (s, 3H), 3.55 (t, 2H, J = 6.6 Hz), 3.36 (s, 3H), 2.27−1.99 (m, 4H), 1.95−1.44 (m, 4H), 1.05 (s, 9H). **^{13}C NMR** (100.7 MHz, $CDCl_3$): δ 156.2 (s), 135.8 (d), 134.1 (s), 129.8 (d), 127.9 (d), 96.6 (t), 65.6 (t), 61.9 (d), 61.9 (d), 55.4 (q), 52.3 (q), 52.3 (t), 35.9 (t), 35.9 (t), 30.1 (t), 27.1 (q), 26.3 (t), 19.4 (s). **IR** (neat, NaCl) ν (cm^{-1}): 2949, 2926, 2877, 2855, 1698, 1447, 1383, 1102. **LRMS** (m/z, relative intensity): 442 ($M^+ - C_4H_9$, 100), 412 (10), 366 (20), 294 (25), 213 (30), 183 (35). **HRMS**: calcd for $C_{24}H_{32}NO_5Si$ ($M^+ - C_4H_9$) 442.2050, found 442.2057.

*Data for **46**.* **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.67−7.65 (m, 4H), 7.44−7.36 (m, 6H), 4.37 (ddd, 1H, J = 12.9, 5.0, 1.1 Hz), 4.15 (ddd, 1H, J = 12.9, 12.9, 3.3 Hz), 3.98 (ddd, 1H, J = 8.8, 8.8, 2.2 Hz), 3.77−3.63 (m, 2H), 3.47 (ddt, 1H, J = 16.0, 8.8, 3.3 Hz), 2.43−2.34 (m, 1H), 2.13−1.94 (m, 3H), 1.89−1.76 (m, 1H), 1.69−1.41 (m, 3H), 1.04 (s, 9H). **^{13}C NMR** (77.5 MHz, $CDCl_3$): δ 151.8 (s), 135.6 (d), 133.6 (s), 129.6 (d), 127.6 (d), 67.1 (t), 62.1 (t), 56.8 (d), 56.7 (d), 35.0 (t), 30.6 (t), 29.0 (t), 28.3 (t), 26.8 (q), 19.1 (s). **IR** (neat, NaCl) ν (cm^{-1}): 3072, 3050, 2964, 2934, 2859, 1694, 1473, 1424, 1342, 1293, 1188, 1110, 1091 . **LRMS** (m/z, relative intensity): 366 ($M^+ - C_4H_9$, 100), 320 (15), 294 (60), 197 (30), 183 (35). **HRMS**: calcd for $C_{21}H_{24}NO_3Si$ ($M^+ - C_4H_9$) 366.1525, found 366.1533.

Bicyclo[4.2.1]non-3-en-9-one (48). 1,3-Butadiene (37 mL, 422 mmol) was condensed in a graduated cylinder at −78 °C before being added to a solution of 2-chlorocyclopentanone (**47**) (4.22 mL, 42.2 mmol) in trifluoroethanol (42 mL) at −15 °C. A solution of sodium trifluoroethoxide in trifluoroethanol (85 mL, 1.0 M, 84 mmol), previously prepared by the addition of sodium to trifluoroethanol, was added dropwise (7 h @ 0.2 mL/min), and the reaction mixture was allowed to stir at −15 °C for 18 h. A 1 N aqueous HCl solution was added until an acidic pH was obtained. The aqueous phase was extracted with dichloromethane (3 × 150 mL), and the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (2.5:97.5) as the eluent to give a colorless oil (5.00 g, 87%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.70−5.56 (m, 2H), 2.59−2.49 (m, 2H), 2.31−2.13 (m, 4H), 2.11−2.01 (m, 2H), 1.66 (AB quartet, 2H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 224.0 (s), 126.6 (d), 45.3 (d), 32.1 (t), 25.6 (t). **IR** ($CHCl_3$) ν (cm^{-1}): 3040, 2953, 2837, 1726, 1654, 1447, 1356, 1162, 1046. **LRMS** (m/z, relative intensity): 159 (MNa^+, 100). **HRMS**: calcd for $C_9H_{12}ONa$ 159.0780, found 159.0784.

Bicyclo[4.2.1]non-3-en-9-one, oxime (49). To a solution of ketone **48** (0.100 g, 0.734 mmol) in a 2:1 mixture of water (1.5 mL) and MeOH (0.75 mL) at rt were added sodium acetate (0.300 g, 3.65 mmol) and hydroxylamine hydrochloride (61.2 mg, 0.881 mmol). The reaction mixture was stirred at reflux for 18 h before being allowed to cool to rt. Water (25 mL) was added, and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (10:90) as the eluent to give compound **49** as a white solid (97.5 mg, 88%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.60−5.50 (m, 2H), 3.61−3.51 (m, 1H), 2.95−2.85 (m, 1H), 2.53−2.39 (m, 1H), 2.32−2.11 (m, 4H), 2.05−1.86 (m, 2H), 1.65−1.50 (m, 2H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 172.0 (s), 126.8 (d), 126.5 (d), 40.0 (d), 35.8 (t), 34.9 (d), 32.4 (t), 28.4 (t), 28.4 (t). **IR** ($CHCl_3$) ν (cm^{-1}): 3513−3018, 2950, 2903, 2837, 1595, 1444, 1347, 1303, 1178, 1043. **LRMS** (m/z, relative intensity): 174 (MNa^+, 100). **HRMS**: calcd for $C_9H_{13}NONa$ 174.0889, found 174.0894. **m.p.** 92−94 °C.

7-Azabicyclo[4.2.2]dec-3-en-8-one (50). To a solution of oxime **49** (0.100 g, 0.661 mmol) in a 1:1 mixture of water (1.5 mL) and THF (1.5 mL) at rt were added sodium hydroxide (0.264 g, 6.60 mmol) and *p*-toluenesulfonyl chloride (0.628 g, 3.30 mmol). The reaction mixture was stirred at reflux for 18 h before being allowed to cool to rt. Water (25 mL) was added, and the aqueous phase was extracted with dichloromethane (3 × 25 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using methanol and ethyl acetate (5:95) as the eluent to give bicyclic lactam **50** as a white solid (62.1 mg, 62%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 6.36 (br s, 1H), 5.44−5.24 (m, 2H), 3.81−3.72 (m, 1H), 2.84−2.67 (m, 2H), 2.64−2.33 (m, 3H), 2.10−1.94 (m, 2H), 1.93−1.74 (m, 2H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 177.6 (s), 124.5 (d), 123.8 (d), 47.7 (d), 39.5 (t), 38.4 (d), 36.6 (t), 24.6 (t), 23.7 (t). **IR** ($CHCl_3$) ν (cm^{-1}): 3497−3022, 3410, 3206, 2987, 2953, 2890, 2831, 1660, 1478, 1447, 1328, 1043. **LRMS** (m/z, relative intensity): 174 (MNa^+, 100). **HRMS**: calcd for $C_9H_{13}NONa$ 174.0889, found 174.0881. **m.p.** 130−132 °C.

Chloro-7-azabicyclo[4.2.2]dec-3-en-8-one (51). To a solution of lactam **50** (0.500 g, 3.31 mmol) in THF (35 mL) at rt was added sodium hydride (60% suspension in mineral oil, 0.172 g, 4.30 mmol). The reaction mixture was stirred 15 min at rt, and *N*-chlorosuccinimide (0.664 g, 4.97 mmol) was added. The solution was shielded from light and stirred at rt for another 15 min, after which a 1 N NaOH aqueous solution (100 mL) was added. The aqueous phase was extracted with dichloromethane (3 × 75 mL), and the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (25:75) as the eluent to give *N*-chlorolactam **51** as a white solid (0.488 g, 79%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 5.47−5.38 (m, 1H), 5.33−5.25 (m, 1H), 4.08−4.02 (m, 1H), 3.08−2.93 (m, 2H), 2.91−2.77 (m, 1H), 2.51−2.27 (m, 3H), 2.14−1.98 (m, 2H), 1.90−1.78 (m, 1H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 172.7 (s), 125.4 (d), 122.4 (d), 62.3 (d), 41.8 (d), 35.6 (t), 35.5 (t), 25.8 (t), 24.2 (t). **IR** ($CHCl_3$) ν (cm^{-1}): 3000, 2956, 2893, 2831, 1660, 1406, 1284, 1240, 1165, 1134, 1093, 1043. **LRMS** (m/z, relative intensity): 186 (MH^+, 15), 208 (MNa^+, 100) . **HRMS**: calcd for $C_9H_{12}ClNONa$ 208.0500, found 208.0499. **m.p.** 55−57 °C.

dx.doi.org/10.1021/jo402217e | *J. Org. Chem.* 2013, 78, 12532−12544

Benzyl 9-Azabicyclo[4.2.1]non-3-ene-9-carboxylate (52). *N*-Chlorolactam **51** (1.22 g, 6.57 mmol) was separated in four portions of 305 mg each. Those portions were separately dissolved in dichloromethane (110 mL). The solutions were transferred to quartz cells, cooled to −78 °C, and irradiated with 254 nm UV light. After irradiation at −78 °C for 45 min, the reaction mixtures were transferred and combined in a round-bottom flask, and the solvent was removed under reduced pressure. The residue was dissolved in THF (40 mL), and the solution was cooled to 0 °C, after which benzyl alcohol (0.36 mL, 3.4 mmol) was added. NaH (60% suspension in mineral oil, 0.151 g, 3.78 mmol) was added portionwise, and the reaction mixture was stirred at 0 °C for 15 min. A 1 N HCl aqueous solution (100 mL) was added. The aqueous phase was extracted with dichloromethane (3 × 75 mL), and the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (5:95) as the eluent to give bicyclic compound **52** as a colorless oil (1.16 g, 55%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.37−7.29 (m, 5H), 5.58−5.45 (m, 2H), 5.14 (AB quartet, 2H), 4.42 (d, 2H, J = 19.5 Hz), 2.71 (d, 1H, J = 20.6 Hz), 2.57 (d, 1H, J = 18.7 Hz), 2.21−2.02 (m, 4H), 1.69−1.58 (m, 2H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): **Rotamer A**: δ 153.4 (s), 137.1 (s), 128.4 (d), 127.7 (d), 127.7 (d), 126.8 (d), 66.5 (t), 55.1 (d), 37.2 (t), 29.8 (t). **Rotamer B**: δ 153.4 (s), 137.1 (s), 128.4 (d), 127.7 (d), 127.7 (d), 126.2 (d), 66.5 (t), 54.8 (d), 36.4 (t), 29.0 (t). **IR** (neat) ν (cm^{-1}): 3063, 3010, 2957, 2895, 2834, 1694, 1420, 1328, 1208, 1102, 1001, 758. **LRMS** (m/z, relative intensity): 280 (MNa^+, 100). **HRMS**: calcd for $C_{16}H_{19}NO_2Na$ 280.1308, found 280.1318.

Benzyl 2,5-Bis(2-hydroxyethyl)pyrrolidine-1-carboxylate (53). Carbamate **52** (89 mg, 0.35 mmol) was dissolved in dichloromethane (3 mL), and ozone was bubbled through the solution until it turned pale blue (5 min). Argon was then bubbled for 10 min, and $NaBH_4$ (0.132 g, 3.50 mmol) was added. The solution was stirred at reflux for 1.5 h, and a 1 N HCl aqueous solution (10 mL) was added. The aqueous phase was extracted with dichloromethane (3 × 25 mL), and the organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using ethyl acetate as the eluent to give diol **53** as a colorless oil (58 mg, 56%). **^{1}H NMR** (300 MHz, $CDCl_3$): **Rotamer A**: δ 7.41−7.29 (m, 5H), 5.24−5.08 (m, 2H), 4.32−4.18 (m, 1H), 4.13−4.03 (m, 1H), 3.70−3.49 (m, 4H), 2.16−1.34 (m, 8H). **Rotamer B**: δ 7.41−7.29 (m, 5H), 5.24−5.08 (m, 2H), 4.32−4.18 (m, 1H), 4.03−3.90 (m, 1H), 3.70−3.49 (m, 4H), 2.16−1.34 (m, 8H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): **Rotamer A**: δ 156.8 (s), 136.3 (s), 128.5 (d), 128.1 (d), 127.8 (d), 67.3 (t), 59.6 (t), 56.0 (d), 39.0 (t), 30.5 (t). **Rotamer B**: δ 156.8 (s), 136.3 (s), 128.5 (d), 128.1 (d), 127.8 (d), 67.3 (t), 59.1 (t), 55.7 (d), 38.8 (t), 30.2 (t). **IR** (neat) ν (cm^{-1}): 3699−3094 (br), 2953, 2873, 1677, 1412, 1354, 1111, 1054, 736, 696. **LRMS** (m/z, relative intensity): 316 (MNa^+, 100). **HRMS**: calcd for $C_{16}H_{23}NO_4Na$ 316.1519, found 316.1527.

(2*R*,5*S*)-Benzyl 2-(2-Acetoxyethyl)-5-(2-hydroxyethyl)pyrrolidine-1-carboxylate (54). *meso*-Diol **53** (250 mg, 0.852 mmol) was divided into five portions of 50 mg each. Those portions were dissolved in benzene (1.7 mL) and hexanes (6.8 mL) before Celite (500 mg), Amano lipase from *P. fluorescens* (Sigma-Aldrich, ≥20000 units/g, 500 mg), and vinyl acetate (0.018 mL, 0.20 mmol) were added. After being stirred at rt for precisely 20 min, the reaction mixtures were filtered using ethyl acetate. The solvent was removed under reduced pressure, and the crude product was purified by flash chromatography on silica gel using ethyl acetate and hexanes (75:25 and 100:0) as the eluent to give nonracemic **54** as a colorless oil (136 mg, 48%, 62% brsm). The enantiomeric excess was calculated to be 88% by HPLC using a chiral column. **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.40−7.29 (m, 5H), 5.15 (s, 2H), 4.34−4.20 (m, 1H), 4.17−3.88 (m, 3H), 3.69−3.55 (m, 2H), 2.29−1.88 (m, 3H), 1.96 (s, 3H), 1.85−1.39 (m, 5H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 170.9 (s), 156.9 (s), 136.3 (s), 128.5 (d), 128.1 (d), 127.9 (d), 67.4 (t), 61.8 (t), 59.0 (t), 56.0 (d), 55.6 (d), 38.8 (t), 35.4 (t), 30.5 (t), 30.2 (t), 20.8 (q). **IR** (neat) ν (cm^{-1}): 3637−3156 (br), 2957, 2878, 1734, 1685, 1412, 1354, 1239, 1107, 1041, 740, 696. **LRMS** (m/z, relative intensity): 358 (MNa^+, 100). **HRMS**: calcd for $C_{18}H_{25}NO_5Na$ 358.1625, found 358.1635. $[\alpha]_D^{20}$: + 8.12 ($CHCl_3$, c = 0.5).

(2*R*,5*S*)-Benzyl 2-(2-Acetoxyethyl)-5-(2-oxoethyl)pyrrolidine-1-carboxylate (55). Oxalyl chloride (0.11 mL, 1.2 mmol) was added to a solution of DMSO (0.22 mL, 3.1 mmol) in CH_2Cl_2 (15 mL) at −78 °C. The solution was stirred at that temperature for 15 min before a solution of monoacetate **54** (0.349 g, 1.04 mmol) in CH_2Cl_2 (5 mL) was added. After the mixture was stirred at −78 °C for 45 min, Et_3N (1.0 mL, 7.3 mmol) was added, and the reaction mixture was then allowed to stir at rt for 30 min. Water (20 mL) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 25 mL). The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexanes (35:65) as the eluent to give aldehyde **55** as a colorless oil (314 mg, 91%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 9.83−9.63 (m, 1H), 7.41−7.28 (m, 5H), 5.20−4.98 (m, 2H), 4.36−4.25 (m, 1H), 4.18−3.92 (m, 3H), 3.16−2.76 (m, 1H), 2.52 (ddd, 1H, J = 16.6, 7.7, 1.5 Hz), 2.30−2.12 (m, 2H), 2.10−1.88 (m, 4H), 1.78−1.54 (m, 3H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): **Rotamer A**: δ 200.4 (s), 170.8 (s), 155.1 (s), 136.4 (s), 128.4 (d), 128.0 (d), 127.9 (d), 66.9 (t), 61.9 (t), 56.6 (d), 54.07 (d), 49.9 (t), 34.5 (t), 30.0 (t), 29.6 (t), 20.8 (q). **Rotamer B**: δ 200.4 (s), 170.8 (s), 155.1 (s), 136.4 (s), 128.4 (d), 128.0 (d), 127.9 (d), 66.9 (t), 61.9 (t), 55.7 (d), 53.3 (d), 49.9 (t), 34.5 (t), 30.0 (t), 29.6 (t), 20.8 (q). **IR** (neat) ν (cm^{-1}): 3038, 2964, 2885, 1739, 1694, 1409, 1353, 1244, 1106, 1031. **LRMS** (m/z, relative intensity): 388 (MNa^+ + MeOH, 100), 356 (MNa^+, 60). **HRMS**: calcd for $C_{18}H_{23}NO_5Na$ 356.1468, found 356.1479. $[\alpha]_D^{20}$: −18.0 ($CHCl_3$, c = 0.5).

(2*R*,5*R*)-Benzyl 2-(2-Acetoxyethyl)-5-(2-(2,6-dioxocyclohexyl)ethyl)pyrrolidine-1-carboxylate (56). To a solution of aldehyde **55** (0.295 g, 0.885 mmol) in CH_2Cl_2 (3 mL) were successively added Hantzsch's ester (0.360 g, 1.42 mmol), 1,3-cyclohexanedione (0.159 g, 1.42 mmol), and L-proline (20.7 mg, 0.177 mmol). The reaction mixture was allowed to stir at rt for 3 h before the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of ethyl acetate and hexanes (60:40) as the eluent to give product **56** as a colorless oil (342 mg, 91%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 10.25 (br s, 1H), 7.39−7.28 (m, 5H), 5.16 (AB quartet, 2H), 4.16−4.02 (m, 2H), 4.01−3.93 (m, 1H), 3.86−3.74 (m, 1H), 2.61−2.34 (m, 5H), 2.31−2.11 (m, 2H), 2.05−1.87 (m, 4H), 1.93 (s, 3H), 1.84−1.50 (m, 6H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 199.5 (s), 173.9 (s), 171.0 (s), 156.4 (s), 136.2 (s), 128.4 (d), 128.4 (d), 127.8 (d), 114.8 (s), 67.4 (t), 66.5 (t), 61.9 (t), 58.7 (d), 56.1 (d), 35.8 (t), 34.9 (t), 30.4 (d), 29.9 (d), 29.6 (d), 20.8 (t), 20.7 (q), 18.8 (t). **IR** (neat) ν (cm^{-1}): 3495−3083 (br), 3027, 2960, 2881, 1735, 1698, 1409, 1353, 1237, 1106, 1027. **LRMS** (m/z, relative intensity): 452 (MNa^+, 100), 430 (MH^+, 10). **HRMS**: calcd for $C_{24}H_{31}NO_6Na$ 452.2044, found 452.2058. $[\alpha]_D^{20}$: +11.0 ($CHCl_3$, c = 0.5)

2-((1*R*,3a*R*)-6-Oxo-1,2,3,3a,4,5,6,7,8,9-decahydropyrrolo[1,2-*a*]quinolin-1-yl)ethyl Acetate (57). Diketone **56** (330 mg, 0.769 mmol) was dissolved in methanol (30 mL) at rt, and 5% Pd/C (100 mg) was added. After the solution was degassed with argon for 10 min, the argon was replaced by hydrogen, and the latter was bubbled into the solution for several seconds. The solution was stirred under hydrogen for 1 h, and argon was bubbled into the solution for another 10 min. The reaction mixture was filtered over Celite, and the filter cake was washed with methanol. The solvent was removed under reduced pressure to yield the crude product, which was purified by flash chromatography on silica gel using a mixture of methanol and ethyl acetate (10:90) as the eluent to give tricyclic compound **57** as a colorless oil (128 mg, 60%). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.15−3.97 (m, 2H), 3.94−3.83 (m, 1H), 3.32−3.17 (m, 1H), 2.70−2.50 (m, 2H), 2.47−2.24 (m, 3H), 2.21−1.75 (m, 7H), 2.07 (s, 3H), 1.71−1.50 (m, 3H), 1.29−1.09 (m, 1H). **^{13}C NMR** (75.5 MHz, $CDCl_3$): δ 193.7 (s), 170.8 (s), 158.3 (s), 107.2 (s), 61.6 (t), 59.1 (d), 55.5 (d), 36.1 (t), 34.6 (t), 29.4 (t), 28.8 (t), 28.2 (t), 27.0 (t), 21.8 (t), 21.2 (t), 20.8 (q). **IR** (neat) ν (cm^{-1}): 2945, 2877, 1739, 1608, 1432, 1233, 1185,

1050. **LRMS** (*m*/*z*, relative intensity): 316 (MK^+, 10), 300 (MNa^+, 100), 278 (MH^+, 50). **HRMS**: calcd for $C_{16}H_{23}NO_3Na$ 300.1570, found 300.1579. $[\alpha]_D^{20}$: −343 ($CHCl_3$, *c* = 0.49)

(1*R*,3a*R*)-1-(2-Hydroxyethyl)-1,2,3,3a,4,5,8,9-octahydropyrrolo[1,2-*a*]quinolin-6(7*H*)-one (13). To a solution of tricycle **57** (0.104 g, 0.375 mmol) in methanol (3 mL) was added K_2CO_3 (0.153 g, 1.12 mmol). The reaction mixture was stirred for 10 min at rt, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography on silica gel using a mixture of methanol and ethyl acetate (15:85) as the eluent to give the enantiomer of Kishi's intermediate, (−)-**13**, as a white solid (43 mg, 49% (68% brsm)). **^{1}H NMR** (300 MHz, $CDCl_3$): δ 4.13−4.07 (m, 1H), 3.80−3.73 (m, 1H), 3.66 (ddd, 1H, *J* = 11.0, 9.1, 4.6 Hz), 3.36−3.23 (m, 1H), 2.74−2.58 (m, 2H), 2.55−2.31 (m, 4H), 2.26−2.04 (m, 5H), 2.00−1.75 (m, 5H), 1.72−1.48 (m, 2H), 1.33−1.11 (m, 1H). **LRMS** (*m*/*z*, relative intensity): 258 (MNa^+, 50), 236 (MH^+, 100). **HRMS**: calcd for $C_{14}H_{22}NO_2$ 236.1645, found 236.1653. $[\alpha]_D^{20}$: −422 (EtOH, *c* = 0.5) (lit[11b] +538 (EtOH, *c* = 1.4)).

■ ASSOCIATED CONTENT

Supporting Information

Characterization data for all new 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.

■ ACKNOWLEDGMENTS

We thank the Natural Sciences and Engineering Research Council of Canada (NSERC), the Fonds de Recherche Québécois Nature et Technologies (FRQ-NT), and the Université de Sherbrooke for financial support. We also thank Dr. René Gagnon for helpful discussions regarding the enzymatic desymmetrization reaction.

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