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Stereoselective Syntheses of (+)-2-*epi*-Deoxoprosopinine, (−)-Deoxoprosophylline, (+)-*cis*-195A, and 2,5-Di-*epi*-*cis*-195A from a Common Chiral Nonracemic Building Block

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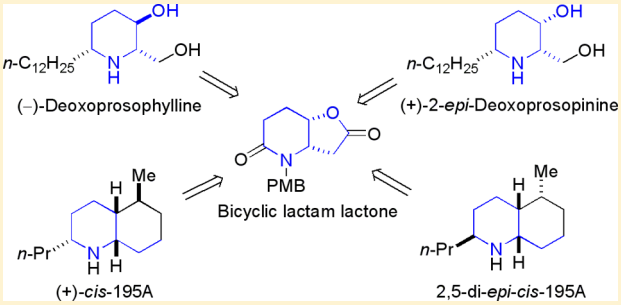
Supporting Information

ABSTRACT: Approaches toward the syntheses of alkaloids belonging to the 2,6-disubstituted 3-hydroxypiperidine and *cis*-decahydroquinoline (*cis*-DHQ) classes of alkaloids are developed, starting from a common chiral nonracemic bicyclic lactam lactone (BLL). Two key δ-lactam intermediates, (5*S*,6*S*)-5-hydroxy-6-hydroxymethyl- and (5*S*,6*S*)-5-hydroxy-6-methyl-piperidin-2-ones, are prepared; the latter δ-lactam is obtained via a direct decarbonylation of a bicyclic lactam lactol. The BLL is also used to prepare (4a*R*,5*R*,8a*S*)- and (4a*R*,5*S*,8a*S*)-5-methyl-octahydroquinolin-2-ones, which involved a 6-*exo*-*trig* free-radical conjugate addition reaction. The stereoselectivity observed in the free-radical cyclization step is found to be governed by allylic 1,2-strain arising from the interaction of the *N*-(*p*-methoxybenzyl) group and the C6 substituent in the lactam ring of the free-radical intermediate. The effectiveness of the developed approaches is demonstrated by the asymmetric syntheses of (+)-2-*epi*-deoxoprosopinine, (−)-deoxoprosophylline, (+)-*cis*-195A, and 2,5-di-*epi*-*cis*-195A.



INTRODUCTION

The piperidine ring is an important feature that is commonly found in alkaloids isolated, typically in minute amounts, from marine and terrestrial plants and animals.[1] Many of these alkaloids exhibit not only diverse structures that contain interesting stereochemistries but also biological activities that have potential applications in medicine.[2] For these reasons, piperidine-containing alkaloids are attractive targets for synthesis, and much interest has been aimed at developing approaches and methodologies for their stereoselective construction.[1e,3]

We previously described a method for the preparation of bicyclic lactam lactones (BLLs) in both enantiomeric forms[4] and showed that the BLLs are versatile building blocks for application in the synthesis of piperidine and indolizidine alkaloids. Accordingly, we have reported the enantioselective total syntheses of (+)-isofebrifugine, (−)-sedacryptine, (+)-(8*S*,8a*S*)-octahydroindolizidin-8-ol, and (+)-(1*S*,8a*S*)-octahydroindolizidin-1-ol.[4,5] Now, we describe approaches toward piperidine-containing alkaloids belonging to two different structural classes, the 2,6-disubstituted 3-hydroxypiperidines and the 2,5-disubstituted decahydroquinolines, starting from a common BLL building block. The realization of these two approaches is shown by the total syntheses of (−)-deoxoprosophylline and (+)-2-*epi*-deoxoprosopinine, and (+)-*cis*-195A (pumiliotoxin C) and its 2,5-di-*epi* diastereomer. These syntheses also demonstrate the synthetic flexibility afforded through the use of BLLs in readily preparing chiral nonracemic δ-lactam intermediates.

RESULTS AND DISCUSSION

The 2,6-disubstituted 3-hydroxypiperidine structure is commonly encountered in alkaloids of the *Prosopis* and *Cassia* families (Figure 1; **1**−**6**).[1a] These alkaloids are characterized by a long-chain, structurally varied hydrophobic group at C6 and a polar C2 methyl or hydroxymethyl substituted 3-hydroxypiperidine unit. Consequently, these alkaloids are sometimes referred to as alkaloid lipids. In addition to their unique structures, these

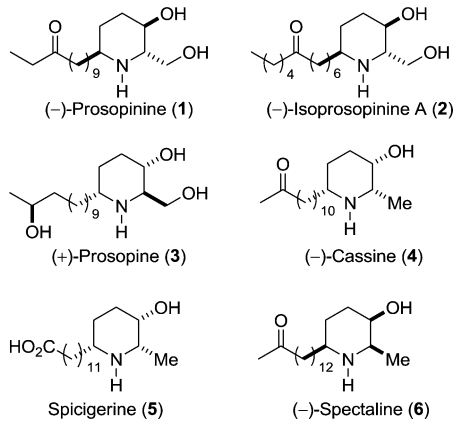


Figure 1. Representative examples of alkaloid lipids.

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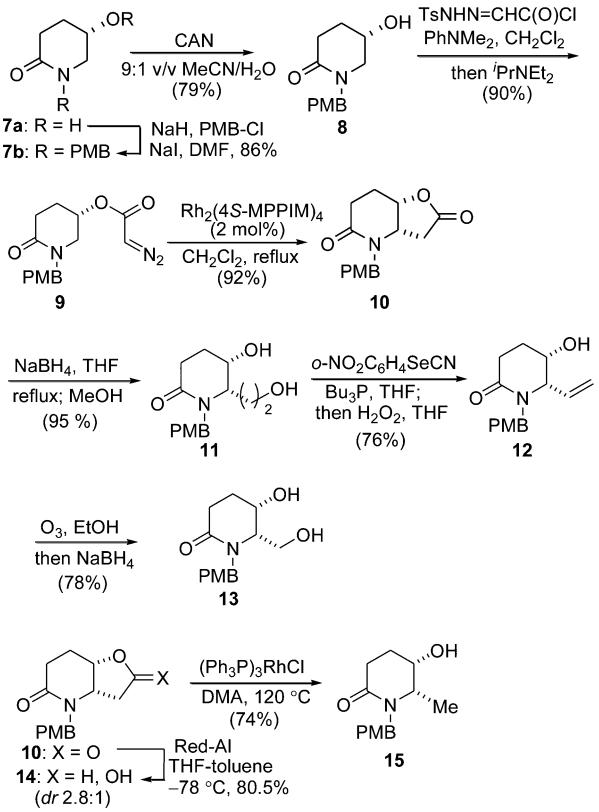
alkaloids exhibit a range of interesting biological activities such as antioxidant properties,[6a] anti-inflammatory activity,[6b] acetylcholinesterase,[6c] and plant growth inhibitory[6d] activities. Because of these attributes, the alkaloid lipids are often chosen as synthetic targets for evaluating new approaches and methodologies.[7]

A survey of the literature indicated that 6-substituted-5-hydroxy δ-lactams, such as **13** and **15** (Scheme 1), are often used as advanced intermediates in the synthesis of the alkaloid lipids.[8] However, some of the routes reported for their preparation are not flexible[8b] and suffer from regio-[8c] and stereoselectvity[8d] issues. In this context, we have investigated a route to readily prepare the δ-lactam intermediates **13** and **15** from the BLL-**10** (Scheme 1).

Scheme 1. Preparation of BLL-10 and δ-Lactam Intermediates 13, 15



The bicyclic lactam lactone **10** required for the synthesis of δ-lactam intermediates **13** and **15** was prepared using a route that is similar to the one we had reported[4] for the *N*-benzyl analog. Thus, the known[4] δ-lactam alcohol **7a** was first converted to the *N*,*O*-di(*p*-methoxybenzyl) derivative **7b** in 86% yield. Selective removal of the *O*-PMB group in **7b** was effected by CAN oxidation in a 9:1 v/v MeCN−H_2O mixture to give **8** (79%). Treatment of **8** with the House−Blankley[9,4b] reagent gave the diazoacetate **9**, which upon exposure to Rh_2(4*S*-MPPIM)$_4$ underwent efficient intramolecular C−H insertion to give BLL-**10**.

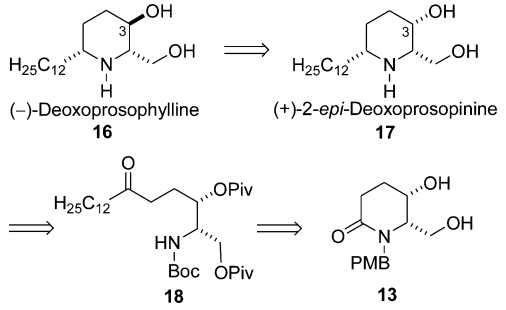
Reduction[10] of the lactone moiety in **10** to the diol was accomplished using $NaBH_4$ in refluxing THF containing MeOH. The diol was subjected to regioselective *o*-nitrophenylselenation followed by oxidation−*o*-nitrophenylselenoxide elimination[11] to provide the alkenol **12** in 76% yield. Subsequent ozonolysis of **9** followed by reductive workup yielded the diol (5*S*,6*S*)-**13** in 78% yield.

The chemoselective reduction of BLL-**10** with Red-Al, using slightly modified reaction conditions to our previously reported procedure[4] (see Experimental Section), furnished the lactol **14**, which was treated with 1 equiv of Wilkinson's catalyst[12] in *N*,*N*-dimethylacetamide (DMA) at 120 °C. Efficient decarbonylation of **14** was observed, which led directly to the formation of (5*S*,6*S*)-**15**. The conversion of **14** to (5*S*,6*S*)-**15** represents one of the few examples of the direct decarbonylation reaction of lactols,[12,13] and the first to be used on a bicyclic lactam lactol.

With ready access to the key δ-lactam intermediates **13** and **15**, we turned our attention to the syntheses of (−)-deoxoprosophylline (**16**) and (+)-2-*epi*-deoxoprosopinine (**17**) starting from δ-lactam **13** to demonstrate its synthetic utility.

Enantioselective syntheses of deoxoprosophylline[14] and 2-*epi*-deoxoprosopinine[14k,15] were reported previously starting from either chiral pool[14a−k,15b] or synthesis-derived[14l−s,15a] starting materials. Our retrosythetic plan for (−)-**16** and (+)-**17** is shown in Scheme 2. (−)-Deoxoprosophylline (**16**) can be obtained via C3 epimerization of alkaloid **17**. Alkaloid **17** is to be formed from amino ketone **18**, which is to be prepared from the δ-lactam diol **13**; the δ-lactam carbonyl unit will serve as the chemical handle for installing the dodecyl side chain.

Scheme 2. Retrosynthetic Plan of (−)-16 and (+)-17



The synthesis of (+)-2-*epi*-deoxoprosopinine (**17**) began with the preparation of the *N*-Boc δ-lactam **21** (Scheme 3) from **13** in order to enhance the electrophilicity[16] of the lactam carbonyl unit for installation of the dodecyl side chain. First, we investigated the removal of the *N*-PMB group under Birch[17] conditions (Na, liq. NH_3; NH_4Cl), which turned out to be unproductive. A 36% yield of the 1,4-cyclohexadiene derivative **25**[18] was isolated, and the remainder of the material balance was an intractable mixture of polar components. Thus, diol **13** was converted to the dipivalate **19** in 91% yield, and the *N*-PMB group in **19** was removed by CAN oxidation (3:1 v/v MeCN−H_2O) under optimized conditions,[19] to give a 1:1 mixture of the δ-lactams **20a**,**b** which, without separation, was treated with Hunig's base in MeOH at 55 °C. This yielded **20a** in an overall yield of 75%.

The lithio anion derived from **20a** was acylated (Boc_2O) to give the *N*-Boc derivative **21**, which was reacted with freshly prepared *n*-$C_{12}H_{25}MgBr$ in THF to furnish the acyclic ketone **18** as the only product in 72% yield. No products that could arise from nucleophilic acyl substitution at either one or both of the pivalate groups were detected.

Reductive cyclization of **18** to form the trisubstituted piperidine **22** was achieved via concomitant acid mediated *N*-Boc removal and condensation of the released primary amino function with the ketone carbonyl to give the corresponding

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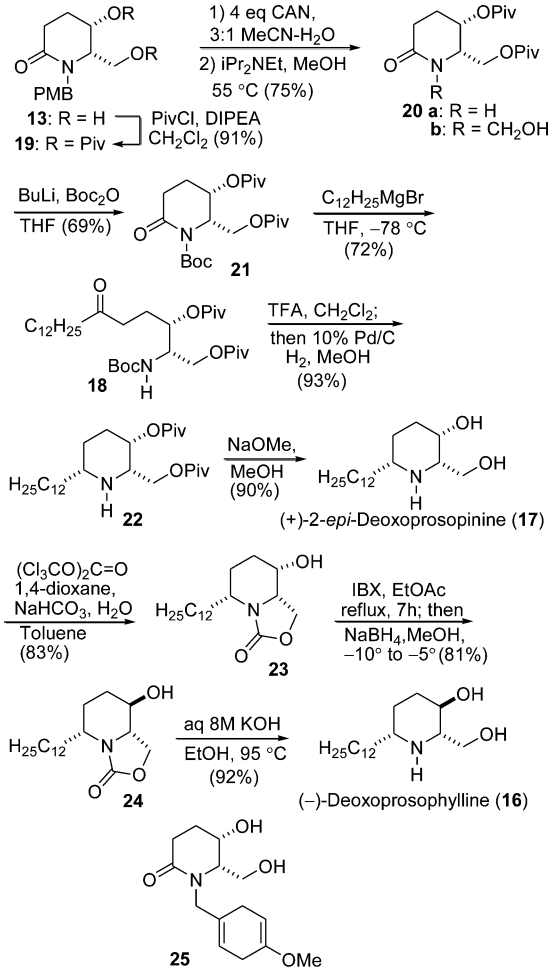
Scheme 3. Synthesis of (−)-16 and (+)-17



cyclic iminium triflate salt. Hydrogenation (1 atm, balloon) of the crude salt over 10% Pd/C gave only **22** in 92% yield. ^{1}H NMR analysis of the crude reaction mixture indicated that the hydrogenation of the cyclic iminium salt had proceeded with excellent *cis*-diastereoselectivity; the C6 epimer was not detected. The C2/C6 relative stereochemistry and the absolute configuration of C6 were confirmed by the conversion of **22** to (+)-**17**, whose $[\alpha]_D^{24}$ +3.0° (*c* 0.84, MeOH) {lit.[14k] $[\alpha]_D^{28}$ +3.3° (*c* 0.6, MeOH) lit.[15a] $[\alpha]_D^{20}$ +3.0° (*c* 0.6, MeOH)} and ^{1}H and ^{13}C NMR data are in accord with those reported in the literature.[14k,15]

To prepare (−)-deoxoprosophylline (**16**), the configuration at C3 in (+)-2-*epi*-deoxoprosopinine (**17**) was inverted, and this was achieved by first converting **17** to the cyclic carbamate **23** by treatment with triphosgene. Epimerization of hydroxyl groups in bicyclic carbamates similar to **23** via an oxidation−reduction protocol has precedence in the literature.[14r,20] Thus, heating a solution of **23** and IBX in ethyl acetate at reflux for 7 h cleanly gave the corresponding ketone,[14r] which was not purified but was immediately reduced[20b] with $NaBH_4$ in methanol to afford a separable mixture of the desired epimer **24** (82%) and starting **23** (6.5%). We found that the oxidation of **23** with the Dess-Martin periodinane[21] (1.6 mol equiv, CH_2Cl_2, 0 °C to rt) was "not clean" as judged by TLC analysis; the overall yield of the desired alcohol **24** (39%) after $NaBH_4$ reduction was low, and 12% of starting alcohol **23** was regenerated. Subsequent base hydrolysis (KOH, EtOH) of the carbamate **24** gave (−)-deoxoprosophylline (**16**) in 92% yield. Its $[\alpha]_D^{24}$ −14.2° (*c* 0.45, $CHCl_3$) {lit.[14h] $[\alpha]_D^{24}$ −14.2° (*c* 0.58, $CHCl_3$); lit.[14e] $[\alpha]_D^{22}$ −15.2° (*c* 0.55, $CHCl_3$); lit.[14a] $[\alpha]_D^{24}$ −14.0° (*c* 0.24, $CHCl_3$)} and ^{1}H and ^{13}C NMR data are in excellent agreement with reported data.[14]

Having demonstrated the utility of BLL-**10** in the synthesis of 2,6-disubstituted 3-hydroxypiperidine, we turned our attention toward the use of BLL-**10** in the synthesis of the decahydroquinoline (DHQ) alkaloids. The DHQ ring system is a central feature found in many alkaloids that have been isolated from frogs (*Dendrobatidae* and *Mantellidae*), ants (*Myrmicinae*), toads (*Bufonidae*), marine tunicates, and flatworms.[1d,22] Structurally, 2,5-disubstituted DHQ alkaloids are the most commonly encountered ones wherein the decahydroquinoline ring can have either a *cis*- or *trans*- ring junction (Figure 2). Biological activity studies on several DHQ

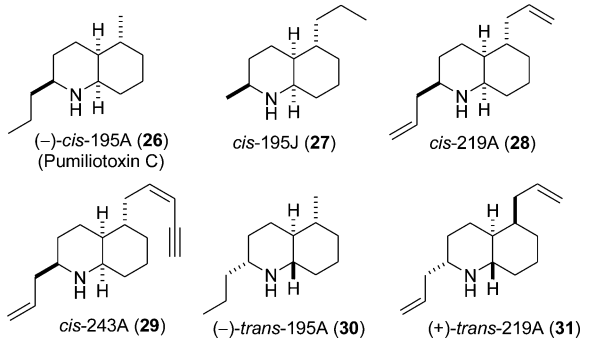


Figure 2. Representative examples of DHQ alkaloids.

alkaloids revealed that they act as noncompetitive blockers of nicotinic acetylcholine receptors.[23] These alkaloids are often only obtained in minute quantities from animal sources (some of which may be endangered) and, consequently, are available in insufficient amounts for more comprehensive biological studies. These limitations have spurred the development of many methods for their synthesis.[24−32]

Many ingenious methods have been devised with a focus on the synthesis of *cis*-DHQ alkaloids on account of the fact that *cis*-195A (pumiliotoxin C), a *cis*-DHQ alkaloid, was the first of the DHQ family of alkaloids to be isolated and structurally characterized.[24g,33] The reported approaches for constructing *cis*-DHQ alkaloids were based on Diels−Alder[24] and 1,3-dipolar cycloadditions,[25] intramolecular cyclizations (enamine-cyclization,[26c,d,g,h] aza-annulation,[26b,f,i,j] reductive amino-cyclization[26a]), ring closing and ring rearrangement metathesis,[27] tandem reactions,[28] metal catalysis,[29] free-radical cyclizations,[30] and *N*-heterocyclic intermediates.[31] However, some of these methods are limited by low stereoselectivity,[26a] lack of flexibility,[26c] and low yield[30a] and, therefore, new methods are constantly being sought.

The use of appropriately substituted *cis*-octahydroquinolin-2-ones[30a,32] as intermediates for the synthesis of *cis*-DHQ alkaloids has received less attention, but offers a practical alternative method. In this context, we reasoned that BLL-**7** would be especially suited for the asymmetric construction of the *cis*-octahydroquinolin-2-one (**32**) (Scheme 4). The presence of the phenylsulfonyl group in **32** allows for functionalization or chain extension[31d,34] at the α-methylene position. The lactam carbonyl and phenylsulfonyl units, together, would provide increased options for further synthetic transformations thereby increasing the synthetic utility of **32**.

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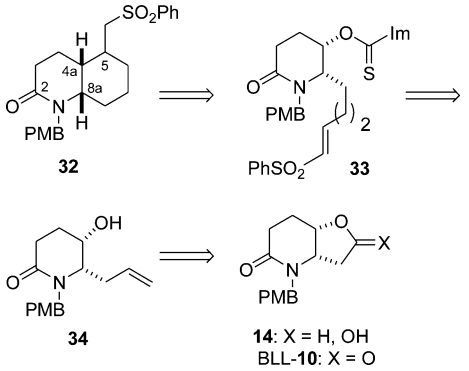
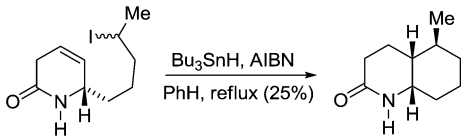
Scheme 4. Retrosynthetic Plan for *cis*-Octahydroquinolin-2-one (32)



cis-Octahydroquinolin-2-one (**32**) is to be formed from a 6-*exo-trig*, free-radical cyclization of the precursor **33**. The free-radical precursor **33** is to be made by (phenylsulfonyl)-vinylation of the terminal double bond in **34**, and the C5 hydroxyl group will serve as a latent carbon-centered free radical. Terminal alkene **34** is to be obtained via olefination of lactol **14**.

The crucial step in this plan is the formation of **32** by the free-radical mediated cyclization of **33**. In 2008, Spino and co-workers had reported an intramolecular free-radical cyclization route to the *cis*-decahydroquinoline ring of *cis*-195A (Scheme 5).[30a] Although highly stereoselective, they found the

Scheme 5. Spino's Free-Radical Cyclization Route to *cis*-DHQ

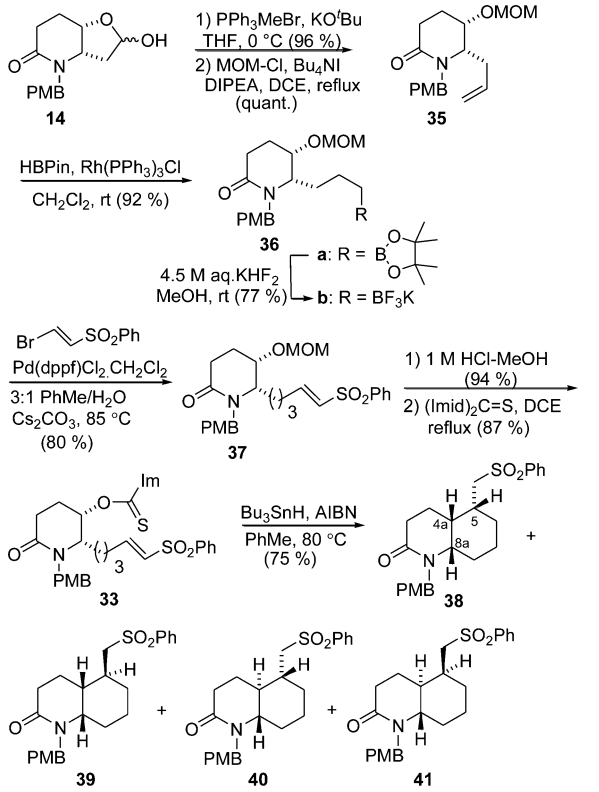


cyclization to be inefficient and was plagued by competing reduction, dimerization, and aromatization of the free-radical intermediate. Nonetheless, their work represents the only report, to date, of a free-radical cyclization approach to construct the *cis*-decahydroquinoline ring system of *cis*-195A.[30b] In our plan, the free-radical center is potentially nucleophilic in character and we reasoned that the use of an electrophilic double bond should facilitate and improve the efficiency of cyclization. Further, we were also interested in determining the diastereoselectivity of the cyclization especially with regard to the formation of the two new stereocenters at C4a and C5 in the presence of the pre-existing, stereochemically defined C8a.

The synthesis of the octahydroquinolin-2-one ring commenced with the Wittig olefination of lactol **14** (vide supra, Scheme 1) using methylidene(triphenyl)phosphorane to give alkene alcohol **34** in 96% yield (Scheme 6), which was then converted to the corresponding MOM-ether **35** in quantitative yield. With alkene **35** in hand, the preparation of the α,β-unsaturated phenylsulfone **37** was undertaken and we chose to investigate the use of a B-alkyl Suzuki–Miyaura coupling reaction for this purpose.[35]

Attempts at the hydroboration of alkene **35** with 9-BBN-H, under a variety of conditions (e.g., different solvents and reaction temperatures), were in vain, and only starting alkene

Scheme 6. Synthesis of *cis*-Octahydroquinolin-2-one from Lactol 14



was recovered. Thus, we investigated the hydroboration[36] of **35** with pinacolatoborane (HBPin) catalyzed by $[Ir(cod)Cl]_2$[36a] (1.5 mol %), and in the presence of 3 mol % of dppe. The reaction was found to proceed with high regioselectivity to give the pinacolboronic ester **36a** but only in 62% yield. After further investigations of reaction conditions to improve the yield of **36a** we found that hydroboration of **35** catalyzed by 2 mol % of Wilkinson's catalyst[36b] afforded the desired **36a** in high yield (92%).

Informed by the studies[37] of Suzuki and co-workers, who found that organoboronates are ineffective in B-alkyl coupling reactions, pinacolboronic ester **36a** was, therefore, first converted to the potassium trifluoroborate salt **36b** in 77% yield by treatment with 4.5 M aqueous KHF_2.[38] Subsequent Suzuki–Miyaura coupling[39] of **36b** with (*E*)-(2-bromovinyl) phenyl sulfone[40] using 10 mol % of $Pd(dppf)Cl_2$ in the presence of 3 equiv of Cs_2CO_3 gave the desired product **37**[41] in 80% yield. Hydrolytic removal of the MOM protecting group in **37** followed by reaction of the corresponding alcohol with *N*,*N*′-thiocarbonyldiimidazole efficiently provided the free-radical precursor **33** (Scheme 6). Thioimidazolide **33** was then treated with AIBN and Bu_3SnH (80 °C, 3 h, degassed toluene, slow addition) to effect cyclization[42] leading to two major diastereomers, **38** and **39**, and two minor diastereomers, **40** and **41**, in 75% combined yield and in a ratio of 12.6:5.8:1.6:1.0. Compounds **39** and **41** were closely moving (R_f [**39**] = 0.22, R_f [**41**] = 0.26; 5 × Et_2O), but were separable by careful chromatography. Compounds **38** and **40** were obtained as an 8:1 mixture, but because **38** was the major product we were able to obtain an analytically pure sample of **38** after repeated careful chromatographic separation of the mixture.

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All of the four possible octahydroquinolin-2-one diastereomers were formed in the free-radical cyclization of thioimidazolide **33**. The stereochemistries of the ring junction (C8a/C4a) in diastereomers **38**, **39**, **40**, and **41** were assigned on the basis of ^{1}H NMR spectral data analysis, and using the stereochemically well-defined C8a as a reference point. In particular, the H8a signal appeared as a *ddd* (δ 3.14 in **38**, δ 3.16 in **39**, δ 3.24 in **40**, and δ 2.74 in **41**) and was found to be diagnostic. The stereochemistry at C5 of **38**, **39**, **40**, and **41** was assigned by converting them (desulfonylation and *N*-PMB deprotection; see Supporting Information) to the known compounds **42**,[26b,32c,43] **43**,[24c,d,29a,32c,e] **44**,[24c,29a,32c] and **45**,[24d] respectively (Figure 3); the ^{1}H and ^{13}C NMR spectral data of each of the four octahydroquinolin-2-ones are in good agreement to those reported in the literature.

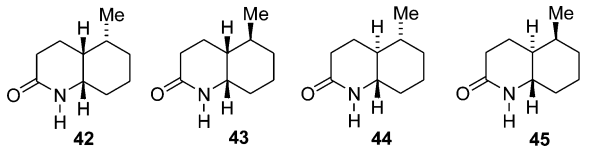

Figure 3. N-Deprotected−desulfonylated octahydroquinolin-2-ones **42**−**45**.

To gain an understanding of the observed distribution of products **38**, **39**, **40**, and **41** in the free-radical cyclization step, gas-phase DFT computational studies were performed to model the transition states involved in the reaction pathway. We used the *N*-benzyl instead of the *N*-(*p*-methoxybenzyl) in **46** for our calculations. The six transition state structures, **TS-46a**−**f**, were obtained, and the Gibbs free energies of activation ($\Delta G^{\ddagger}$) were derived from the difference in the free energies of each of the six transition state structures and the most stable free-radical precursor (local minima) which had resulted from the "plus-and-minus-displacement"[44] minimization calculations performed on the six transition state structures (Figure 4). The computed transition state structures revealed the δ-lactam unit has adopted a half-chair conformation in **46**, and the cyclization of the C5-centered radical onto the phenylsulfonylvinyl moiety has occurred via six-membered, chairlike transition states.[45] For **TS-46a**,**b**, the C6 α,β-unsaturated phenylsulfonyl side chain is located in the pseudoaxial position, which alleviates A^{1,2}-strain interaction between the *N*-PMB group and the C6 side chain. However, **TS-46b** is destabilized by a nonbonding interaction between the vinylic α-hydrogen and the pseudoaxial δ-hydrogen (side chain labeling) in the incipient six-membered ring. With **TS-46c**−**f**, the C6 α,β-unsaturated phenylsulfonyl side chain occupies the pseudoequatorial position and, consequently, these transition states are destabilized by an inherent A^{1,2}-strain between the *N*-PMB group and the C6 substituent. Moreover, in each of the **TS-46c**,**f**, a destabilizing, nonbonding interaction identical to the one found in **TS-46b** is present. Transition state **46c** is also further destabilized due to the orientation of the phenylsulfonylvinyl unit on the concave side of the forming bicycle. The calculated $\Delta G^{\ddagger}$ for cyclization proceeding via each of the six transition states supports our experimental results regarding product distribution. The major diastereomers, **38** and **39**, are formed via **TS-46a** and **TS-46b**, respectively. Reaction via **TS-46d** may be a very minor contributor toward the formation of **39**, and the involvement of **TS-46c** is expected to be negligible. Further, the $\Delta G^{\ddagger}$ for free-radical cyclization via **TS-46a** is 1.3 kcal/mol lower in energy than via **TS-46b** indicating that formation of **38** is more favored. The minor diastereomers, **40** and **41**, are formed via **TS-46e** and **TS-46f**, respectively.

As mentioned above, *cis*-195A is the first of the DHQ family of alkaloids to be isolated and characterized. As a result, *cis*-195A is often a target of choice for synthetic chemists to develop and test new methods for the stereoselective construction of DHQs. Many syntheses of *cis*-195A and/or its stereoisomers have been reported in both racemic[24a−f,25,26a−d,28,32a−g] and enantiomerically[24g−i,26d−f,29,30a,31a−c,32h,i] pure forms. With the *cis*-octahydroquinolin-2-ones **38** and **39** in hand, the enantioselective syntheses of (+)-*cis*-195A (**26**)[24c,30a] and 5-*epi*-*cis*-195A (**47**)[26b,43] were examined, and the retrosynthetic plan is summarized in Scheme 7.

We first investigated the synthesis of (+)-*cis*-195A (**26**, Scheme 8). Initially, an approach similar to the one used in the synthesis of (+)-2-*epi*-deoxoprosopinine (**17**, Scheme 3, **21** → **18**) was investigated in order to install the *n*-propyl substituent. Therefore, the octahydroquinolin-2-one **43** was converted to the *N*-Boc derivative and then subjected to reaction with *n*-PrMgBr. Surprisingly, preferential addition of *n*-PrMgBr occurred mainly at the *N*-Boc carbonyl moiety resulting in the regeneration of starting **43**. As a result, the route originally reported by Oppolzer was used (Scheme 8). Thus, the octahydroquinolin-2-one **43** was converted to the corresponding methyl imidate[24c] with freshly washed Me_3OBF_4. Due to the instability of the methyl imidate toward hydrolysis, it was not isolated but used crude in its reaction with *n*-PrMgBr to form the imine **48**. Hydrogenation of the crude imine **48** over 10% PtO_2 (1 atm H_2, balloon) in the presence of 2 M aqueous HCl in ethanol was found to be stereospecific and yielded (+)-*cis*-195A (**26**) in 45% yield over three steps; some unreacted **43** (13%) was also recovered. The $[\alpha]_D^{21}$ −2.1° (*c* 0.33, MeOH) [lit.[29d] $[\alpha]_D^{20}$ −2.2° (*c* 1.34, MeOH)] and ^{1}H and ^{13}C NMR spectral data of **26** are in excellent agreement with those reported in literature.[29d] We also prepared the hydrochloride salt of (+)-*cis*-195A by treating a solution of **26** in methanol with concentrated HCl. The ^{1}H and ^{13}C NMR spectral data of **26·HCl** and its $[\alpha]_D^{22}$ +12.9° (*c* 0.34, MeOH) [lit.[29d] $[\alpha]_D^{20}$ +12.9° (*c* 0.36, MeOH)] are also in accord with the reported data.[29d]

For the synthesis of 5-*epi*-*cis*-195A (**47**) from octahydroquinolin-2-one **42** the same steps as those described for the synthesis of *cis*-195A were used. Thus, **42** was converted via the methyl imidate (Scheme 9) to imine **49** followed by hydrogenation of **49** over 10% PtO_2. However, the ^{1}H and ^{13}C NMR spectral data of the product were found to be incongruent with the data reported by Stille and Paulvannan[26b,43] for their synthesis of 5-*epi*-*cis*-195A, which was prepared from (±)-**42**. In their studies, reduction of **49** with DIBAL-H was reported to occur from the sterically less hindered *Si*-face of the imine π-bond to give 5-*epi*-cis-195A as the only product. Puzzled by this outcome, we revisited the reduction of the imine **49**, but employing DIBAL-H as the reductant under the reported[26b,43] conditions. In our hands, the DIBAL-H reduction step resulted in a mixture of products, which after careful chromatographic purification afforded a compound with ^{1}H and ^{13}C NMR spectral data that were again not in agreement with the reported data for **47**. Reduction of imine **49** with $Na(OAc)_3BH$[46] in the presence of AcOH in THF also gave the same product as that obtained from the DIBAL-H reduction. These results suggested that the reduction

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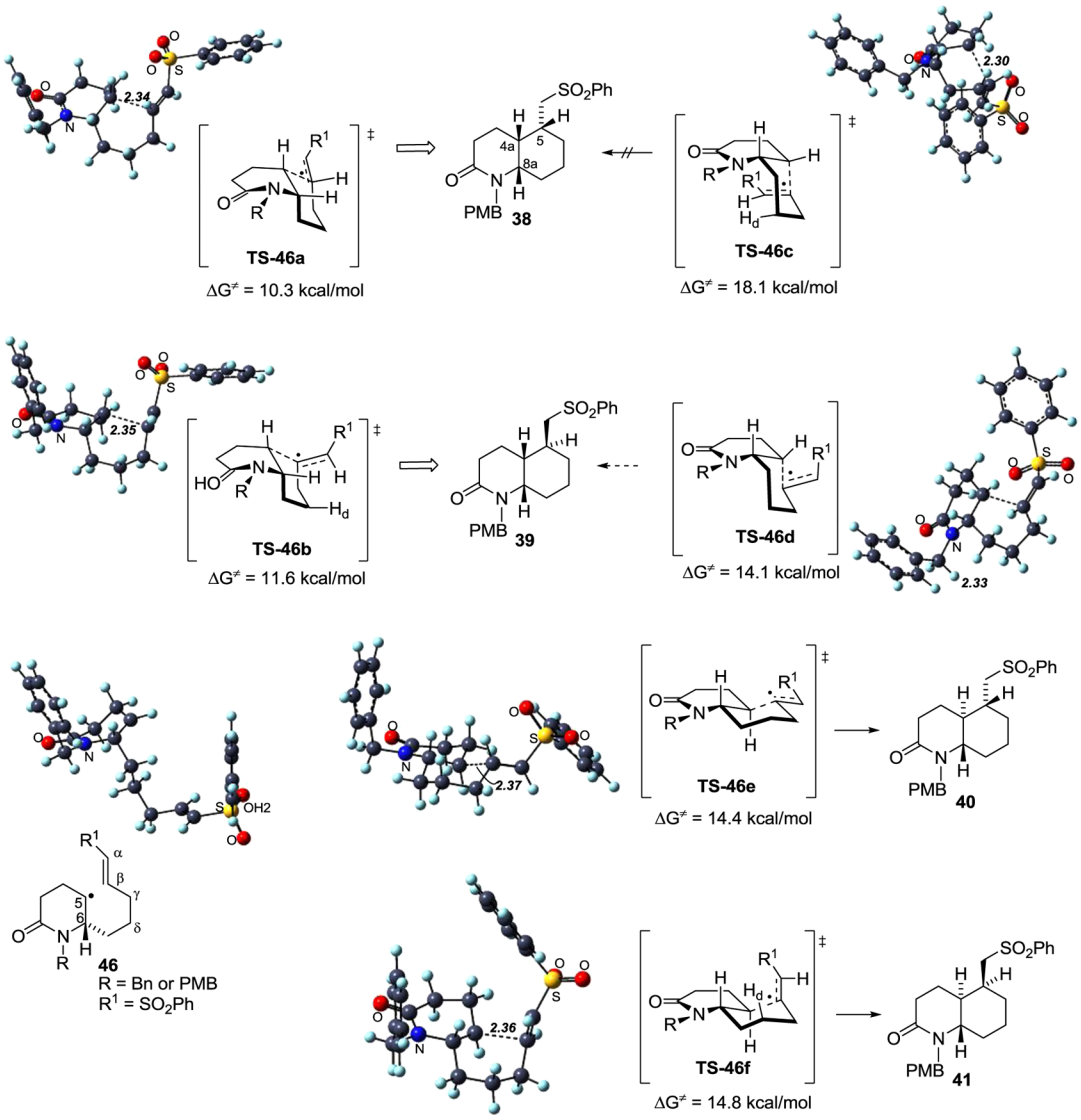
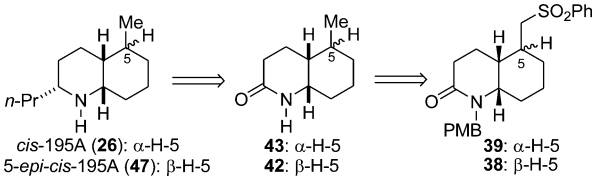
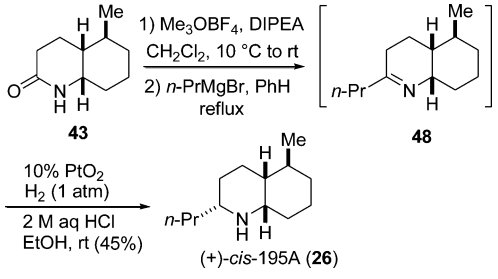


Figure 4. Transition state structures for the free-radical cyclization of **46**.

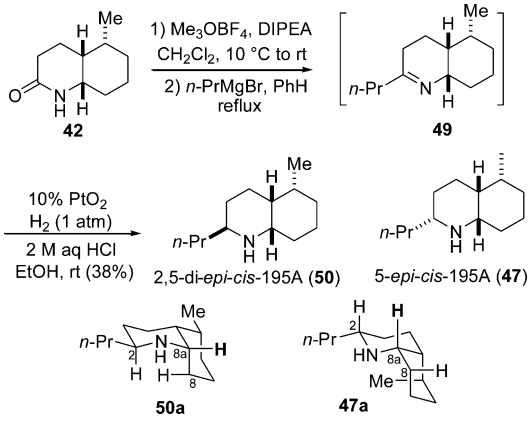
Scheme 7. Retrosynthetic Approach to (+)-*cis*-195A and 5-*epi*-*cis*-195A



Scheme 8. Synthesis of (+)-*cis*-195A from (+)-43



Scheme 9. Synthesis of 2,5-Di-*epi*-*cis*-195A from (−)-42



of **49** in our case must have occurred from the sterically more hindered *Re*-face of the imine π-bond. This product was assigned as 2,5-di-*epi*-*cis*-195A (**50**) based on the ^{1}H NMR spectral data analysis.

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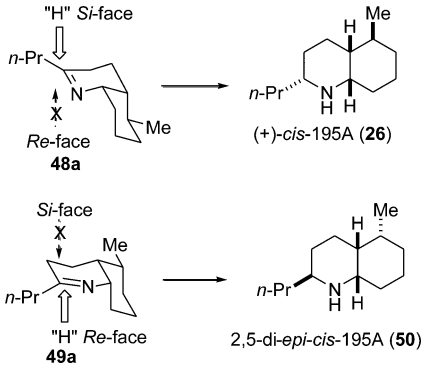
In particular, the H8a in **50** showed a characteristic *ddd* signal at δ 2.88 with $^{3}J_{vic}$ values of 12.1, 3.9, and 3.9 Hz. The large $^{3}J_{8a\text{-}8ax}$ and two small $^{3}J_{8a\text{-}8eq}$ and $^{3}J_{8a\text{-}4a}$ couplings are indicative of the expected coupling behavior of H8a in the preferred conformer **50a**. If the reduced product were 5-*epi*-*cis*-195A (**47**), as shown[24h,47] in its preferred conformer **47a** (Scheme 9), H8a is not expected to show a large vicinal coupling constant. Further support for the assigned structure of **50** was deduced from NOESY1D experiments, which showed signal enhancement of H2 when $H8_{ax}$ was irradiated and vise versa.[48] In addition to these studies, a comparison of the ^{1}H and ^{13}C NMR data of hydrochloride salt of **50** with those reported by Husson and co-workers[32d] for (±)-**50·HCl** also showed very good agreement. Hsung et al. also had reported[26f] the synthesis of (−)-4a,8a-di-*epi*-pumiliotoxin C, which is equivalent to 2,5-di-*epi*-*cis*-195A. The ^{1}H and ^{13}C NMR spectral data of (−)-**50·HCl** reported by Hsung et al. were not in accord with our and Husson's spectral data. Interestingly, 2,5-di-*epi*-*cis*-195A (**50**) showed $[\alpha]_D^{21}$ 0.0 (*c* 0.69, MeOH) and **50·HCl** showed $[\alpha]_D^{21}$ +0.4 (*c* 0.73, MeOH).

The observed stereoselectivity in the reduction of imines **48** and **49** leading to (+)-*cis*-195A (**26**) and 2,5-di-*epi*-*cis*-195A (**50**), respectively, is interesting and can be understood by considering the reaction conformers of **48a** and **49a** (Scheme 10) in which the C5-methyl substituent occupies the equatorial

Scheme 10. Proposed Stereochemical Course of Reduction of Imines 48 and 49



position. For **48a**, the delivery of hydrogen or hydride ("H") occurs from the less hindered *Si*-face of the imine π-bond via a chairlike transition state leading to the formation of (+)-**26**. On the other hand, the delivery of "H" to reaction conformer **49a** preferentially occurs from the *Re*-face of the imine π-bond to form **50** as our results indicate. The approach of "H" from the *Si*-face of **49a** is favored on steric grounds, but would lead to an energetically less stable twist boat transition state whereas the "H" approach from the *Re*-face, although sterically hindered, proceeds via a lower energy chairlike transition state[24e] to give **50**.

CONCLUSIONS

The utility of the BLL-**10** as a chiral building block is demonstrated by the approaches that have been developed for the syntheses of alkaloids belonging to two structural classes, the 2,6-disubstituted-3-hydroxypiperidines and the *cis*-decahydroquinolines (*cis*-DHQs). Our studies on the synthesis of 2,6-disubstituted-3-hyroxypiperidines involved the efficient conversion of BLL-**10** to the advanced intermediates (5*S*,6*S*)-5-hydroxy-6-hydroxymethylpiperidin-2-one (**13**) and (5*S*,6*S*)-5-hydroxy-6-methylpiperidin-2-one (**15**). The (5*S*,6*S*)-**13** was successfully converted to (+)-2-*epi*-deoxoprosopinine (**17**) and (−)-deoxoprosophylline (**16**). The overall yields of (+)-**17** and (−)-**16** starting from the BLL-**10** are 16% (10-steps) and 10% (13-steps), respectively. For the synthesis of *cis*-DHQs, BLL-**10** was transformed to the *cis*-octahydroquinolin-2-ones **38** and **39** using an intramolecular free-radical conjugate addition reaction as the key step. A rationalization of the observed stereoselectivity and product distribution in the free-radical cyclization is proposed and is supported by the Gibbs free energies of the computed transition state structures leading to *cis*- and *trans*-octahydroquinolin-2-ones. Compounds **38** and **39** were converted to octahydroquinolin-2-ones **42** and **43**, which are advanced intermediates used in the syntheses of (+)-*cis*-195A (**26**) and 2,5-di-*epi*-*cis*-195A (**50**). Compounds (+)-**26** and **50** were obtained in overall yields of 2.2% (14-steps) and 4% (14-steps), respectively, starting from the BLL-**10**.

The overall yields realized for (+)-2-*epi*-deoxoprosopinine (**17**) and (−)-deoxoprosophylline (**16**) are comparable to the yields reported in the literature. On the other hand, the overall yields of (+)-*cis*-195A (**26**) and 2,5-di-*epi*-*cis*-195A (**50**) were slightly lower and this is attributed to the modest diastereoselectivity realized during the formation of the C5 stereocenter bearing the (phenylsulfonyl)methyl group in the octahydroquinolin-2-ones **38** and **39**. Nonetheless, the synthetic approaches developed here have the advantage of flexibility. The functionalized lactam intermediates **13**, **15**, **38**, and **39** prepared from BLL-**10** will find applications in the syntheses of other members of these two classes of alkaloids. Further, either of the enantiomers of BLL-**10** is readily accessible,[4] which would allow the syntheses of the 2,6-disubstituted-3-hydroxypiperidine and *cis*-DHQ alkaloids in either of their enantiomeric forms.

EXPERIMENTAL SECTION

General. Only the diagnostic absorptions in the infrared spectrum are reported. ^{1}H (300 or 500 MHz) and $^{13}C\{^{1}H\}$ (75 or 125 MHz) NMR spectra were recorded in $CDCl_3$ unless stated otherwise. The residual $CHCl_3$ singlet at δ_H = 7.26 and the $CDCl_3$ triplet centered at δ_C = 77.0 were used as internal references for ^{1}H and ^{13}C NMR spectra, respectively. $^{11}B\{^{1}H\}$ (96.3 MHz) and $^{19}F\{^{1}H\}$ (282.4 MHz) NMR spectra were recorded in either $CDCl_3$ or CD_3CN and were calibrated with reference to δ_B = 0.0 and δ_F = −153.0 using $BF_3{\cdot}Et_2O$ as the external standard. High-resolution mass spectra in electron impact (EI) and chemical ionization (CI) modes were recorded on a double focusing sector field mass spectrometer and in the electrospray ionization (ESI) mode using a quadrupole time-of-flight mass spectrometer. Optical rotations were recorded at the Na_D line. Reaction progress was monitored by thin-layer chromatography on silica gel 60_{F254} precoated (0.25 mm) on aluminum backed sheets. Air and moisture sensitive reactions were conducted under a static pressure of argon. All organic extracts were dried over anhydrous Na_2SO_4. Chromatographic purification implies flash column chromatography, which was performed on silica gel 60 Å (230−400 mesh). Dichloromethane, DMF, DMA, toluene, chloroform, methanol, and acetonitrile were dried by distillation from calcium hydride. THF and diethyl ether were dried by distillation from sodium using sodium benzophenone ketyl as the indicator. Ethanol was dried by distillation form $Mg(OEt)_2$. The commercial trimethyloxonium tetrafluoroborate obtained was washed successively with CH_2Cl_2 and Et_2O prior to use.

Computational Methods. Geometry optimizations and vibrational frequency DFT calculations were conducted using the Gaussian09 (revisions B.01/D.01) program suite[49] using the unrestricted B3LYP/6-31G(d) level of theory.[50] All optimizations used tight convergence criteria and an ultrafine grid. Transition state structures were located using opt = (ts, noeigentest, calcFC)

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algorithms.[51] Optimized transition state structures were submitted to vibrational frequency analysis to confirm that they had only one imaginary frequency. Further, each of the transition states was confirmed to be on the correct reaction coordinate by "plus-and-minus-displacement"[43] minimization runs: the transition state was displaced ~0.05 Å along the imaginary frequency normal mode in both directions, and the two displaced structures (starting free-radical and product free-radical intermediates) were optimized to the nearest minima structures.

(*S*)-1-(*p*-Methoxybenzyl)-5-(*p*-methoxybenzyloxy)piperidin-2-one (7b). Sodium hydride (1.95 g, 46.8 mmol, 60% dispersed in mineral oil) was washed with hexane and dried. It was suspended in DMF (34 mL) and then treated with the known[4] lactam alcohol **7a** (2.0 g, 17.4 mmol) in DMF (16 mL) via cannula at 0 °C under Ar. To this brown colored reaction mixture was added sodium iodide (260 mg, 10 mol %), and the mixture was stirred at rt for 30 min. Then *p*-methoxybenzyl chloride (6.70 mL, 48.6 mmol) was added dropwise to the brown mixture, and the resulting light yellow suspension was stirred overnight at rt. DMF was removed by Kugelrohr distillation, and the oily residue was diluted with Et_2O and washed with brine. The organic layer was dried over sodium sulfate, filtered, and concentrated. Purification by chromatography (1:4 petroleum ether/EtOAc then EtOAc) afforded **7b** (5.31 g, 86%) as a white solid: mp 37−40 °C; $[\alpha]_D^{24}$ +23.2° (*c* 1.35, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 1676, 1644 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.20 (m, 4 H), 6.78−6.87 (m, 4 H), 4.54 (d, *J* = 14.5 Hz, 1 H), 4.46 (d, *J* = 14.5 Hz, 1 H), 4.38 (d, *J* = 11.4 Hz, 1 H), 4.31 (d, *J* = 11.4 Hz, 1 H), 3.69−3.81 (m, 7 H), 3.18−3.32 (m, 2 H), 2.58−2.73 (m, 1 H), 2.39 (ddd, *J* = 17.5, 6.2, 6.2 Hz, 1 H), 1.85−2.05 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 159.2, 158.9, 130.0, 129.3, 128.9, 113.9, 113.8, 70.2, 69.9, 55.1(9), 55.1(7), 50.4, 49.2, 28.2, 25.8; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{21}H_{25}NO_4$ 355.1784; Found 355.1776.

(*S*)-5-Hydroxy-1-(*p*-methoxybenzyl)piperidin-2-one (8). To **7b** (510 mg, 1.44 mmol) in a mixture of MeCN and distilled water (9:1 v/v, 20 mL) at 0 °C was added CAN (1.58 g, 2.88 mmol) in one portion, and the resultant yellow-orange solution was stirred at 0 °C for 1.5 h and then at rt for 1 h. The reaction mixture was recooled to 0 °C, a few drops of distilled water were added, and the reaction mixture was diluted with EtOAc. The mixture was washed successively with saturated aqueous $NaHCO_3$(2 × 5 mL) and distilled water (1 × 5 mL). The organic layer was separated, and the aqueous layer was saturated with solid NaCl and re-extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (1:4 petroleum ether/EtOAc, then 10:1 EtOAc/MeOH) to give the *N*-PMB alcohol **8** (270 mg, 79%) as white crystals. Starting **7b** (25 mg, 5%) was also recovered: mp 97−100 °C; $[\alpha]_D^{24}$ −12.4° (*c* 2.04, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3518−3178, 1654, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.08−7.17 (m, 2 H), 6.76−6.85 (m, 2 H), 4.51 (d, *J* = 14.5 Hz, 1 H), 4.36 (d, *J* = 14.5 Hz, 1 H), 3.97−4.0 (m, 1 H), 3.74 (s, 3 H), 3.23−3.35 (m, 2 H), 3.09 (dd, *J* = 12.4, 5.1 Hz, 1 H), 2.59 (ddd, *J* = 18.0, 7.1, 7.1 Hz, 1 H), 2.34 (ddd, *J* = 18.0, 6.2, 6.2 Hz, 1 H), 1.76−1.96 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 158.9, 129.3, 128.7, 113.9, 63.6, 55.2, 53.4, 49.5, 28.6, 28.1; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{17}NO_3$ 235.1208; Found 235.1207.

(*S*)-5-(α-Diazoacetoxy)-1-(*p*-methoxybenzyl)piperidin-2-one (9). The secondary alcohol **8** (0.75 g, 3.19 mmol) and α-(*p*-toluenesulfonylhydrazone)acetyl chloride (1.25 g, 4.78 mmol) were dissolved in CH_2Cl_2 (25 mL) under argon, and the solution was cooled to 0 °C. *N*,*N*-Dimethylaniline (0.73 mL, 5.73 mmol) was added dropwise, and the mixture was stirred for 40 min at rt. Then, the mixture was cooled to 0 °C, *N*,*N*-diisopropylethylamine (2.8 mL, 15.9 mmol) was added and stirred for 30 min. The reaction mixture was diluted with CH_2Cl_2, washed with saturated aqueous $NaHCO_3$(3 × 20 mL), water (2 × 20 mL), aqueous citric acid (3 × 20 mL), and finally water (20 mL), and dried over Na_2SO_4. The filtered solution was evaporated, and the crude residue was purified by chromatography (2:1 petroleum ether/EtOAc) to afford the diazoacetate **9** (0.88 g, 90%) as a yellow oil: $[\alpha]_D^{23}$ +24.2° (*c* 2.07, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 2115, 1700, 1686, 1654, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.08−7.17 (m, 2 H), 6.76−6.87 (m, 2 H), 5.11−5.2 (m, 1 H), 4.69 (s, 1 H), 4.58 (d, *J* = 14.4 Hz, 1 H), 4.38 (d, *J* = 14.4 Hz, 1 H), 3.75 (s, 3 H), 3.39 (dd, *J* = 13.1, 4.1 Hz, 1 H), 3.24 (ddd, *J* = 13.1, 3.8, 1.5 Hz, 1 H), 2.39−2.64 (m, 2 H), 1.90−2.11 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 168.5, 159.0, 129.3, 128.6, 114.0, 66.6, 55.2, 50.4, 49.2, 46.4, 46.3, 27.7, 25.6; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{17}N_3O_4$ 303.1219; Found 303.1214.

(3a*S*,7a*S*)-4-(*p*-Methoxybenzyl)tetrahydrofuro[3,2-*b*]-pyridine-2,5(3*H*,6*H*)-dione (10). Rh_2(4*S*-MPPIM)$_4$ (4*S*-MPPIM = methyl 1-(3-phenylpropanoyl)-2-oxoimidazolidine-4(*S*)-carboxylate) (30 mg, 2 mol %) was dried under vacuum at 80 °C for 1 h and then cooled to rt. CH_2Cl_2 (5 mL) was added, and the mixture was heated (oil bath) to reflux under argon. A solution of the diazoacetate **9** (310 mg, 1.02 mmol) in CH_2Cl_2 (10 mL) was added dropwise, via syringe pump, over a period of 3 h. After addition was complete, the mixture was refluxed for an additional 1 h and then cooled to rt. The solvent was removed under reduced pressure to give crude product **10** as a light purple oil. The crude product was purified by chromatography (1:1 petroleum ether/EtOAc) to afford BLL-**10** (260 mg, 92%): $[\alpha]_D^{24}$ +52.1° (*c* 1.66, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 1784, 1654, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.11−7.18 (m, 2 H), 6.82−6.89 (m, 2 H), 5.17 (d, *J* = 15.9 Hz, 1 H), 4.81 (ddd, *J* = 7.5, 3.7, 3.7 Hz, 1 H), 4.08 (ddd, *J* = 7.5, 7.5, 3.7 Hz, 1 H), 3.90 (d, *J* = 15.9 Hz, 1 H), 3.79 (s, 3 H), 2.72 (dd, *J* = 17.8, 7.5 Hz, 1 H), 2.40−2.63 (m, 3 H), 2.21−2.35 (m, 1 H), 1.88−2.05 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 173.9, 169.0, 159.3, 129.5, 128.0, 114.3, 75.6, 55.2, 54.4, 47.0, 35.6, 26.5, 24.0; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{17}NO_4$ 275.1158; Found 275.1164.

(5*S*,6*S*)-5-Hydroxy-6-(2-hydroxyethyl)-1-(*p*-methoxybenzyl)-piperidin-2-one (11). BLL-**10** (57 mg, 0.21 mmol) was dissolved in THF (1 mL) and $NaBH_4$ (20 mg, 0.52 mmol) was added at rt, under argon. The resulting white suspension was allowed to reflux (65 °C, oil bath), and MeOH (0.17 mL, 4.2 mmol) was added dropwise over a period of 1 h. The mixture was stirred for an additional 1 h at the same temperature. The reaction mixture was cooled to 0 °C, and 1 M aqueous HCl was added until the gas evolution was subsided. All the volatiles were evaporated under reduced pressure, and the crude residue obtained was diluted with CH_2Cl_2. The organic layer was washed once with 10% aqueous NaOH. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (10:1 EtOAc/MeOH) afforded the diol **11** (55 mg, 95%) as a colorless oil: $[\alpha]_D^{21}$ −83.1° (*c* 2.10, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3517−3096, 1654, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.06−7.16 (m, 2 H), 6.75−6.86 (m, 2 H), 5.20 (d, *J* = 15 Hz, 1 H), 3.90 (ddd, *J* = 8.7, 4.3, 4.3 Hz, 1 H), 3.71−3.82 (m, 6 H), 3.49−3.6 (m, 1 H), 3.40 (ddd, *J* = 8.7, 4.3, 4.3 Hz, 1 H), 2.34−2.63 (m, 2 H), 1.72−2.09 (m, 4 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 159.0, 129.2, 129.0, 114.0, 66.7, 60.2, 58.6, 55.2, 47.5, 31.9, 28.8, 25.2; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{21}NO_4$ 279.1471; Found 279.1472.

(5*S*,6*S*)-5-Hydroxy-1-(*p*-methoxybenzyl)-6-vinylpiperidin-2-one (12). To the diol **11** (56.2 mg, 0.20 mmol) in THF (4 mL) under argon was added 2-nitrophenylseleno cyanate (56 mg, 0.24 mmol), and the mixture was cooled to 0 °C. To this brown colored reaction mixture was then added tributylphosphine (60 μL, 0.24 mmol) dropwise, and the solution was allowed to rt. After stirring the reaction mixture for overnight, THF was removed under reduced pressure. The crude product was purified by chromatography (10:1 EtOAc/MeOH) to afford the selenide (74 mg, 80%) as a yellow oil. To a solution of the crude selenide in THF (4 mL) at 0 °C, under argon, was added 30% aqueous H_2O_2 (0.2 mL, 2.0 mmol) dropwise, and the mixture was stirred at rt for 5 h. The reaction mixture was cooled to 0 °C, saturated aqueous $NaHSO_3$ solution was added to quench excess H_2O_2, and THF was evaporated. Dichloromethane was added, and the organic layer was successively washed with saturated aqueous $NaHCO_3$ (2 × 5 mL) and brine (1 × 5 mL) and dried over Na_2SO_4. The crude mixture was purified by chromatography (1:4 petroleum ether/EtOAc then EtOAc) to give **12** (40 mg, 76% over two steps) as a colorless oil:

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$[\alpha]_D^{21}$ −182.9° (*c* 0.68, $CHCl_3$); IR (neat) ν_{max} 3573−3108, 2953, 2837, 1643 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.09−7.17 (m, 2 H), 6.79−6.87 (m, 2 H), 5.86 (ddd, *J* = 17.2, 10.3, 6.7 Hz, 1 H), 5.45 (d, *J* = 10.3 Hz, 1 H), 5.39 (d, *J* = 14.6 Hz, 1 H), 5.25 (d, *J* = 17.2 Hz, 1 H), 3.83−3.97 (m, 2 H), 3.78 (s, 3 H), 3.59 (d, *J* = 14.6 Hz, 1 H), 2.60 (ddd, *J* = 18.2, 5.2, 5.2 Hz, 1 H), 2.47 (ddd, *J* = 18.2, 8.8, 8.8 Hz, 1 H), 2.18 (br s, 1 H), 1.80−1.92 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 159.0, 133.2, 129.5, 129.2, 120.6, 114.0, 67.4, 61.9, 55.2, 47.1, 29.3, 25.9. HRMS data for compound **12** were obtained after converting it to the corresponding pivalate derivative; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{20}H_{27}NO_4$ 345.1940; Found 345.1937.

(5*S*,6*S*)-5-Hydroxy-6-(hydroxymethyl)-1-(*p*-methoxybenzyl)-piperidin-2-one (13). An ozone/oxygen stream was bubbled into a solution of olefin **12** (33 mg, 0.13 mmol) in EtOH (4 mL) at −40 °C. After about 2 min, TLC analysis showed the absence of starting material. Argon was bubbled into the reaction mixture to remove excess ozone, and then the mixture was warmed to 0 °C. $NaBH_4$ (20 mg, 0.50 mmol) was added, and the mixture was allowed to warm slowly to rt with stirring. After 2 h at rt, the reaction mixture was recooled to 0 °C and glacial AcOH was added dropwise to destroy excess $NaBH_4$, followed by evaporation of EtOH. The mixture was diluted with CH_2Cl_2, and distilled water (1 mL) was added. Aqueous NaOH (5%) was added, and the two layers were separated. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (10:1 EtOAc/MeOH) afforded **13** (26 mg, 78%) as a thick colorless oil: $[\alpha]_D^{22}$ −58.8° (*c* 0.84, $CHCl_3$); IR (neat) ν_{max} 3578−3065, 2947, 1615 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.06−7.15 (m, 2 H), 6.76−6.85 (m, 2 H), 5.22 (d, *J* = 14.9 Hz, 1 H), 4.04−4.14 (m, 1 H), 3.87−3.98 (m, 2 H), 3.74−3.82 (m, 1 H), 3.74 (s, 3 H), 3.32−3.40 (m, 1 H), 2.61 (ddd, *J* = 18.0, 6.5, 6.5 Hz, 1 H), 2.39 (ddd, *J* = 18.0, 6.3, 6.3 Hz, 1 H), 1.94−2.10 (m, 1 H), 1.77−1.93 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.8, 158.9, 129.0, 128.9, 114.0, 67.6, 60.4, 58.6, 55.2, 46.9, 28.3, 26.0. HRMS data for compound **13** were obtained after converting it to the corresponding dipivalate derivative **19**.

(3a*S*,7a*S*)-2-Hydroxy-4-(*p*-methoxybenzyl)hexahydrofuro-[3,2-*b*]pyridin-5(6H)-one (14). A stock solution of 0.15 M Red-Al in toluene was made by diluting Red-Al (3.0 mL, 65% w/w in toluene) with toluene (60 mL). To a stock solution of Red-Al (20.4 mL, 3.17 mmol) at −78 °C was added, under Ar, THF (1 mL), followed by a solution of BLL-**10** (1.23 g, 4.47 mmol) in THF (33 mL) via syringe pump (rate of addition ∼4 mL/min; the flask that held the solution of **10** and the syringe were rinsed with another 8.0 mL of THF). The reaction mixture was stirred at −78 °C for 1 h. The reaction mixture was quenched with a few drops of MeOH, followed by saturated aqueous NH_4Cl (4 mL), and allowed to warm to rt. All the volatiles were evaporated under reduced pressure; the remaining residue was diluted with CH_2Cl_2 (40 mL) and filtered through a pad of Celite. The two layers were separated, and the organic layer was washed once with brine. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Careful chromatography purification (packed with 1:4 petroleum ether/EtOAc, then EtOAc, followed by 10:1 EtOAc/MeOH) afforded the lactol **14** (997 mg, 80.5%; 93.5% based on recovered starting material) as an off-white solid; the diol **11** (31 mg, 2.5%) and starting material **10** (172 mg, 14%) were also recovered. The ratio of the diastereomeric lactols was ∼2.8:1, based on integration of the benzylic methylene protons at 5.04 and 5.32 ppm: mp 144−146 °C; $[\alpha]_D^{23}$ +27.4° (*c* 1.53, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3505−3104, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ (major diastereomer) 7.10−7.17 (m, 2 H), 6.77−6.87 (m, 2 H), 5.51−5.58 (m, 1 H), 5.04 (d, *J* = 14.6 Hz, 1 H) 4.44−4.51 (m, 1 H), 3.98−4.21 (m, 2 H), 3.95 (d, *J* = 14.6 Hz, 1 H), 3.76 (s, 3 H), 2.27−2.49 (m, 2 H), 1.94−2.25 (m, 2 H), 1.68−1.95 (m, 2 H); δ (discernible signals for minor diastereomer) 5.48 (m, 1 H), 5.32 (d, *J* = 14.8 Hz, 1 H), 4.24−4.33 (m, 1 H), 3.72−3.82 (m, 4 H), 2.65−2.79 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (major diastereomer) 171.0, 159.0, 129.5, 128.9, 114.0, 97.0, 72.5, 57.2, 55.2, 47.5, 41.7, 27.5, 24.8; δ (minor diastereomer) 170.9, 158.9, 129.4, 128.7, 113.9, 97.7, 75.3, 57.2, 55.2, 46.6, 39.0, 27.1, 24.4; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{15}H_{19}NO_4$ 277.1314; Found 277.1313.

(5*S*,6*S*)-5-Hydroxy-1-(*p*-methoxybenzyl)-6-methylpiperidin-2-one (15). To the lactol **14** (22 mg, 0.08 mmol) was added $Rh(PPh_3)_3Cl$ (83 mg, 0.09 mmol) and the flask was evacuated and flushed with nitrogen three times. DMA (1 mL) was added, and the resulting brown color solution was stirred at 120 °C (oil bath) for 12 h. After cooling the reaction mixture to rt, DMA was removed by Kugelrohr distillation. Purifaction by chromatography (1:4 petroleum ether/EtOAc) gave **15** (14.6 mg, 74%) as a colorless oil: $[\alpha]_D^{22}$ −112.7° (*c* 1.56, $CHCl_3$); IR (neat) ν_{max} 3563−3092, 2955, 1613 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10−7.17 (m, 2 H), 6.79−6.86 (m, 2 H), 5.22 (d, *J* = 14.8 Hz, 1 H), 3.86−3.95 (m, 1 H), 3.83 (d, *J* = 14.8 Hz, 1 H), 3.77 (s, 3 H), 3.35−3.46 (m, 1 H), 2.57 (ddd, *J* = 18.3, 7.4, 4.0 Hz, 1 H), 2.42−2.53 (br m, 1 H), 2.44 (ddd, *J* = 18.3, 9.0, 8.0 Hz, 1 H), 1.77−2.05 (m, 2 H), 1.19 (d, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 158.9, 129.4, 129.2, 114.0, 67.4, 55.2, 54.5, 47.0, 29.0, 24.8, 13.1; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{14}H_{19}NO_3$ 249.1365; Found 249.1358.

(5*S*,6*S*)-1-(*p*-Methoxybenzyl)-5-pivaloyloxy-6-(pivaloyl-oxymethyl)piperidin-2-one (19). To the diol **13** (26 mg, 0.13 mmol) in CH_2Cl_2 (3 mL), under argon at rt, were added DMAP (15 mg, 0.13 mmol), *N*,*N*-diisopropylethylamine (0.11 mL, 0.65 mmol), and pivaloyl chloride (40 μL, 0.32 mmol) successively, and the solution was stirred overnight. The reaction mixture was cooled to 0 °C, distilled water (1 mL) was added, and the mixture was stirred for 20 min. The mixture was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by chromatography (1:1 petroleum ether/EtOAc) to afford dipivalate **19** (39 mg, 91%) as a colorless oil: $[\alpha]_D^{23}$ −25.5° (*c* 2.57, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 1734, 1654, 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.19 (m, 2 H), 6.81−6.87 (m, 2 H), 5.18 (d, *J* = 15.0 Hz, 1 H), 5.05 (ddd, *J* = 9.2, 4.6, 4.6 Hz, 1 H), 4.30 (dd, *J* = 11.7, 5.3 Hz, 1 H), 4.19 (dd, *J* = 11.7, 3.9 Hz, 1 H), 4.06 (d, *J* = 15.0 Hz, 1 H), 3.78 (s, 3 H), 3.64−3.72 (m, 1 H), 2.5−2.72 (m, 2 H), 1.9−2.18 (m, 2 H), 1.18 (s, 9 H), 1.17 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.9, 177.0, 169.3, 159.0, 128.9, 128.7, 114.2, 67.3, 60.9, 55.7, 55.2, 47.4, 38.8, 38.7, 28.7, 27.1, 27.0, 23.6; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{35}NO_6$ 433.2464; Found 433.2463.

(5*S*,6*S*)-5-Pivaloyloxy-6-(pivaloyloxymethyl)piperidin-2-one (20a). To the *N*-PMB lactam **19** (34.5 mg, 0.08 mmol) in acetonitrile (0.95 mL) at 0 °C was added aqueous cerium(IV) ammonium nitrate (0.32 mL, 1 M) dropwise (final $MeCN/H_2O$ = 3:1 v/v). The resulting orange solution was stirred at the same temperature for 30 min, followed by 1 h at rt. The reaction mixture was diluted with EtOAc, and saturated $NaHCO_3$ was added. The resulting suspension was stirred for 30 min at rt and then was vacuum filtered through a pad of Celite. After the two layers were separated, the organic layer was washed once with brine. The combined aqueous layers were saturated with solid NaCl and back-extracted into EtOAc. The two organic layers were combined and dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:1 petroleum ether/EtOAc then 25:1 EtOAc/MeOH) afforded **20a** and **20b** (20 mg) in a ratio of 1:1, and in a combined 76% yield.

The mixture of **20a** and **20b** (20 mg) was treated with *N*,*N*-diisopropylethylamine (0.06 mL, 0.32 mmol) in MeOH (2 mL) at 55 °C (oil bath) for 1 h. After evaporating the solvent under reduced pressure, the crude product was purified by chromatography (1:4 petroleum ether/EtOAc) to afford **20a** (25 mg, 75%) as a colorless oil. Characterization data for compounds **20a** and **20b** were previously reported.[19]

(5*S*,6*S*)-1-(*tert*-Butyloxycarbonyl)-5-pivaloyloxy-6-(pivaloyl-oxymethyl)piperidin-2-one (21). To the lactam **20a** (27.2 mg, 0.08 mmol) in THF (4 mL) at −78 °C under argon were added a few crystals of 2,2′-bipyridine indicator, followed by dropwise addition of *n*-BuLi (0.05 mL, 0.09 mmol, 1.9 M in hexanes) until a bright red solution resulted. The mixture was stirred for 10 min, and then a solution of Boc_2O (29 mg, 0.13 mmol) in THF (2 mL) was added via

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cannula. The mixture was stirred at −78 °C for 30 min and then at −20 °C for 30 min. The reaction mixture was recooled to −78 °C, quenched with saturated aqueous NH_4Cl, and warmed slowly to rt. THF was evaporated, the crude residue was diluted with EtOAc, washed once with brine, and dried over Na_2SO_4. EtOAc was removed under reduced pressure, and the crude product was purified by chromatography (9:1 petroleum ether/EtOAc, then 8:1 petroleum ether/EtOAc) to afford **21** (24.7 mg, 69%) as a colorless oil: $[\alpha]_D^{23}$ +25.2° (*c* 2.32, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 1773, 1732 cm^{-1}; 1H NMR ($CDCl_3$, 300 MHz) δ 5.16−5.27 (m, 1 H), 4.39−4.52 (m, 2 H), 4.15−4.26 (m, 1 H), 2.57−2.68 (m, 2 H), 1.95−2.19 (m, 2 H), 1.50 (s, 9 H), 1.20 (s, 9 H), 1.17 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.9, 177.1, 169.9, 152.1, 83.8, 67.0, 61.3, 54.8, 38.9, 38.8, 31.9, 27.9, 27.05, 27.02, 23.9; HRMS (ESI-QTOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{21}H_{35}NO_7Na$ 436.2305; Found 436.2300.

(2*S*,3*S*)-2-(*tert*-Butyloxycarbonylamino)-6-oxo-1,3-di-*O*-pivaloyloctadecane-1,3-diol (18). To a solution of the *N*-Boc lactam **21** (148 mg, 0.35 mmol) in THF (7 mL) at −78 °C under argon was added freshly prepared *n*-$C_{12}H_{25}MgBr$ in THF (1.2 mL, 0.46 mmol, 0.39 M) dropwise, and the reaction mixture was stirred at the same temperature for 2.5 h. The reaction was quenched with 0.5 M aqueous HCl at −78 °C, and the solution was concentrated under reduced pressure. The resulting mixture was diluted with CH_2Cl_2 (5 mL) and washed with saturated aqueous $NaHCO_3$ (1 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (10:1 petroleum ether/EtOAc then 6:1 petroleum ether/EtOAc) to give starting **21** (10 mg, 7%) and the desired *N*-Boc ketone **18** (150 mg, 72%; 77% based on recovered **21**) as a colorless oil: $[\alpha]_D^{24}$ −8.1° (*c* 2.34, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3434, 1736, 1718 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.98 (ddd, *J* = 7.9, 6.3, 3.9 Hz, 1 H), 4.50−4.63 (br d, 1 H), 3.84−4.16 (m, 3 H), 2.26−2.56 (m, 4 H), 1.74−1.97 (m, 2 H), 1.37−1.59 (m, 12 H), 1.14−1.32 (m, 35 H), 0.86 (t, *J* = 6.7 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 209.4, 178.1, 177.7, 155.4, 79.9, 71.2, 63.0, 51.8, 42.9, 39.0, 38.8, 38.0, 31.9, 29.6, 29.59, 29.58, 29.4, 29.3, 29.2, 28.3, 27.3, 27.2, 27.1, 25.1, 23.8, 22.7, 14.1; HRMS (CI-double focusing sector field) *m*/*z*: $[M + H]^+$ Calcd for $C_{33}H_{62}NO_7$ 584.4526; Found 584.4531.

(2*S*,3*S*,6*R*)-6-Dodecyl-3-pivaloyloxy-2-(pivaloyloxymethyl)-piperidine (22). To the *N*-Boc ketone **18** (26 mg, 0.04 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C under argon was added trifluoroacetic acid (0.17 mL, 2.21 mmol) dropwise, and the reaction mixture was stirred at rt for 3 h. CH_2Cl_2 and TFA were evaporated under reduced pressure, and the crude residue was dried over P_2O_5 under high vacuum. The crude iminium salt was dissolved in MeOH (3 mL) and subjected to the catalytic hydrogenation (1 atm H_2, balloon) over 10% palladium on carbon (18 mg). After stirring overnight, the mixture was filtered through a pad of Celite, and MeOH was evaporated under reduced pressure. The reaction mixture was diluted with CH_2Cl_2 (5 mL), washed with saturated aqueous $NaHCO_3$ (2 × 5 mL), and dried over Na_2SO_4. The filtered solution was evaporated under reduced pressure, and the crude product was purified by chromatography (9:1 petroleum ether/EtOAc) to afford **22** (19.3 mg, 92.5%) as a colorless oil: $[\alpha]_D^{24}$ +21.7° (*c* 1.08, $CHCl_3$); IR (neat) ν_{max} 2926, 2853, 1734 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.82−4.90 (m, 1 H), 3.95 (dd, *J* = 10.7, 7.5 Hz, 1 H), 4.01 (dd, *J* = 10.7, 7.5 Hz, 1 H), 3.08 (ddd, *J* = 6.3, 6.3, 1.4 Hz, 1 H), 2.47−2.61 (m, 1 H), 1.94−2.07 (m, 1 H), 1.11−1.66 (m, 44 H), 0.86 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 178.1, 177.6, 66.5, 64.2, 57.1, 56.1, 39.1, 38.7, 37.2, 31.9, 29.7, 29.66, 29.65, 29.62, 29.61, 29.3, 28.7, 27.5, 27.2, 27.1, 25.9, 22.7, 14.1; HRMS (CI-double focusing sector field) *m*/*z*: $[M + H]^+$ Calcd for $C_{28}H_{54}NO_4$ 468.4053; Found 468.4063.

(+)-2-*epi*-Deoxoprosopinine (17). Sodium (18 mg, 0.8 mmol) was washed with hexanes, weighed into a flask to which MeOH (2 mL) was added at 0 °C under argon. The dipivalate **22** (46.2 mg, 0.1 mmol) in MeOH (1 mL) was added to the above solution via cannula at the same temperature, and the resulting mixture was stirred at rt overnight. The reaction was quenched with water at 0 °C, and MeOH was evaporated under reduced pressure. The aqueous layer was saturated with solid NaCl and was repeatedly extracted into CH_2Cl_2. The organic layer was dried over Na_2SO_4 and filtered. Removal of the solvent under reduced pressure gave **17** (26.5 mg, 89.5%) as an off-white solid whose ^1H and ^{13}C NMR spectra showed it to be pure. Recrystallization from aqueous MeOH afforded 20.5 mg (77%) of the pure (+)-2-*epi*-deoxoprosopinine: mp 55−57 °C (lit.[14k] mp 57−58 °C; lit[15a] mp 56−57 °C); $[\alpha]_D^{24}$ +3.0° (*c* 0.84, MeOH), {lit.[14k] $[\alpha]_D^{28}$ +3.3° (*c* 0.6, MeOH); lit.[15a] $[\alpha]_D^{20}$ +3.0° (*c* 0.6, MeOH)}; IR (CH_2Cl_2) ν_{max} 3548−3188, 3056 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.59−3.90 (m, 3 H), 2.12−2.92 (m, 5 H), 1.77−1.99 (m, 1 H), 1.09−1.70 (m, 25 H), 0.74−1.00 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 66.2, 64.7, 61.1, 56.8, 37.0, 31.9, 31.87, 29.8, 29.66, 29.65, 29.63, 29.61, 29.3, 26.5, 25.8, 22.7, 14.1; HRMS (CI-double focusing sector field) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{38}NO_2$ 300.2903; Found 300.2902.

(5*R*,8*S*,8a*S*)-5-Dodecyl-tetrahydro-8-hydroxy-1*H*-oxazolo-[3,4-*a*]pyridin-3(5*H*)-one (23). To the 2-*epi*-deoxoprosopinine (**17**) (32 mg, 0.10 mmol) in a 1:1:1 ratio of 1,4-dioxane (1.4 mL), distilled water (1.4 mL), and saturated aqueous $NaHCO_3$ (1.4 mL) at 0 °C triphosgene (36 mg, 0.11 mmol) in toluene (2.8 mL) was added dropwise via syringe. The resulting biphasic solution was vigorously stirred at rt overnight. The reaction mixture was then cooled to 0 °C, and saturated aqueous $NaHCO_3$ (1 mL) was added. This mixture was gradually warmed to rt and repeatedly extracted with CH_2Cl_2. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (1:2 petroleum ether/EtOAc) to give the carbamate **23** (29 mg, 83%) as a white crystalline solid: mp 108−110 °C; $[\alpha]_D^{23}$ +9.2° (*c* 0.5, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3520−3240, 1724 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.16−4.31 (m, 2 H), 3.74−3.84 (m, 1 H), 3.63 (ddd, *J* = 8.1, 6.3, 1.8 Hz, 1 H), 3.00−3.14 (m, 1 H), 2.35−2.51 (m, 1 H), 2.13−2.28 (br m, 1 H), 1.95−2.07 (m, 1 H), 1.50−1.82 (m, 4 H), 1.12−1.44 (m, 20 H), 0.86 (t, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.5, 64.9, 62.9, 60.9, 57.5, 31.9, 31.3, 31.0, 29.68, 29.67, 29.64, 29.3, 26.7, 24.8, 22.7, 14.1; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{35}NO_3$ 325.2617; Found 325.2610.

(5*R*,8*R*,8a*S*)-5-Dodecyl-tetrahydro-8-hydroxy-1*H*-oxazolo-[3,4-*a*]pyridin-3(5*H*)-one (24). To the carbamate **23** (18.5 mg, 0.05 mmol) in EtOAc (1.5 mL) at rt was added 2-iodoxybenzoic acid (40 mg, 0.14 mmol) in one portion. The resulting white suspension was refluxed at 80 °C for 7 h, by which time the reaction was complete as indicated by TLC analysis. The reaction mixture was allowed to cool to rt, and it was filtered through a pad of Celite. Ethyl acetate was evaporated under reduced pressure to give the crude product as an off-white solid (20 mg), which was immediately reduced in the next step.

The ketone (20 mg) was dissolved in MeOH (1 mL) and cooled (−10 to −5 °C) in an ice−salt bath. $NaBH_4$ (3.3 mg, 0.08 mmol based on starting **23**) was added in one portion, and the mixture was stirred at 0 °C for 1 h. Distilled water (0.5 mL) was added, and the reaction mixture was slowly allowed to warm to rt. Methanol was evaporated, and the resulting residue was diluted with CH_2Cl_2. The organic layer was washed once with brine, and the aqueous layer was saturated with solid NaCl and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (4:1 petroleum ether/EtOAc then 3:1 petroleum ether/EtOAc) to give the desired alcohol **24** (15 mg, 81%) as an off-white solid, and starting alcohol **23** (1.2 mg, 6.5%) was also regenerated. Compound **24**: mp 68−70 °C; $[\alpha]_D^{23}$ −24.6° (*c* 1.42, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3560−3200, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.30 (dd, *J* = 8.8, 7.3 Hz, 1 H), 4.18 (dd, *J* = 8.8, 3.8 Hz, 1 H), 3.43−3.58 (m, 1 H), 3.29 (ddd, *J* = 9.5, 7.3, 3.8 Hz, 1 H), 2.95−3.08 (m, 1 H), 2.19−2.44 (m, 2 H), 2.07−2.18 (m, 1 H), 1.60−1.83 (m, 2 H), 1.17−1.54 (m, 22 H), 0.86 (t, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 156.1, 69.5, 65.1, 62.7, 57.3, 33.5, 31.9, 30.9, 29.9, 29.67, 29.65, 29.63, 29.62, 29.60, 29.56, 29.3, 27.0, 22.7, 14.1; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{19}H_{35}NO_3$ 325.2617; Found 325.2610.

(−)-Deoxoprosophylline (16). To a solution of carbamate **24** (13 mg, 0.04 mmol) in 95% EtOH (1 mL) was added aqueous KOH (0.5

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mL, 8 M), and the reaction mixture was heated to 95 °C (oil bath) for 18 h. The reaction mixture was cooled to rt, and EtOH was evaporated under reduced pressure. The crude residue was diluted with CH_2Cl_2 (6 mL), and the organic layer was washed once with distilled water. Dichloromethane was removed under reduced pressure, the residue was dissolved in EtOH (2 mL), and a few drops of concentrated HCl were added. Ethanol was evaporated under reduced pressure, the resulting white solid was taken into CH_2Cl_2 (5 mL), and aqueous NaOH (5 mL, 2.5 M solution) was added. The organic layer was separated, and the aqueous layer was repeatedly extracted into CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (6:1 CH_2Cl_2/MeOH) afforded (−)-deoxoprosophylline (11 mg, 92%) as a white solid, whose ^1H and ^{13}C NMR spectra showed it to be pure. Recrystallization (Et_2O/hexanes) gave (−)-deoxoprosophylline (**16**) as a white crystalline solid: mp 89−90 °C (lit.[14h] mp 88−89 °C, lit.[14e] mp 85−86 °C, lit.[14a] mp 90.5 °C); $[\alpha]_D^{24}$ −14.2° (*c* 0.45, $CHCl_3$) {lit.[14h] $[\alpha]_D^{24}$ −14.2° (*c* 0.58, $CHCl_3$); lit.[14a] $[\alpha]_D^{24}$ −14.0° (*c* 0.24, $CHCl_3$); lit.[14e] $[\alpha]_D^{22}$ −15.2° (*c* 0.55, $CHCl_3$)}; IR (KBr) ν_{max} 3567−3042, 2921, 2851 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.82 (dd, *J* = 10.7, 4.9 Hz, 1 H), 3.69 (dd, *J* = 10.7, 5.4 Hz, 1 H), 3.39−3.50 (ddd, *J* = 9.1, 9.1, 4.6 Hz, 1 H), 2.09−2.64 (m, 5 H), 1.98−2.09 (m, 1 H), 1.68−1.79 (m, 1 H), 1.01−1.50 (m, 24 H), 0.87 (t, *J* = 6.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 70.8, 64.8, 63.2, 56.0, 36.6, 34.0, 31.9, 31.2, 29.8, 29.67, 29.66, 29.64, 29.60, 29.58, 29.3, 26.2, 22.7, 14.1; HRMS (CI-double focusing sector field) *m*/*z*: $[M + H]^+$ Calcd for $C_{18}H_{38}NO_2$ 300.2903; Found 300.2893.

(5*S*,6*S*)-1-[(4-Methoxycyclohexa-1,4-dienyl)methyl]-5-pivaloyloxy-6-(pivaloyloxymethyl)piperidin-2-one (25·dipivalate). Na metal was cut into small pieces and washed three times with hexanes. To the liquid NH_3 (5 mL) at −78 °C under argon was added Na metal (58 mg, 2.5 mmol) portionwise (~5 min), and the resulting blue colored solution was stirred at −78 °C for 30 min. To the above solution was then added the diol **13** (33.6 mg, 0.13 mmol) in THF (2 mL) via cannula, and the reaction mixture was stirred at the same temperature for 6 h. Solid NH_4Cl (60 mg) was added to the above solution at −78 °C, and the reaction temperature was allowed to gradually warm to rt, by which time all of the ammonia had evaporated. The crude residue was extracted with CH_2Cl_2 (3 × 5 mL), followed by 4:1 v/v CH_2Cl_2/MeOH (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (10:1 EtOAc/MeOH) afforded **25** (12 mg, 36%) as a colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 5.48−5.56 (m, 1 H), 4.67 (d, *J* = 15.1 Hz, 1 H), 4.56−4.61 (m, 1 H), 4.24 (ddd, *J* = 8.7, 4.1, 4.1 Hz, 1 H), 3.98 (dd, *J* = 11.9, 6.7 Hz, 1 H), 3.84 (dd, *J* = 11.9, 2.4 Hz, 1 H), 3.53 (s, 3 H), 3.41−3.51 (m, 2 H), 2.55−2.79 (m, 5 H), 2.43 (ddd, *J* = 17.9, 7.4, 7.4 Hz, 1 H), 2.01−2.17 (m, 1 H), 1.86−1.99 (m, 1 H). The diol **25** was fully characterized after converting it to the corresponding dipivalate derivative.

To the diol **25** (12 mg, 0.045 mmol) in CH_2Cl_2 (2 mL), under argon at rt, were added DMAP (5.5 mg, 0.045 mmol), *N*,*N*-diisopropylethylamine (47 μL, 0.27 mmol), and pivaloyl chloride (16 μL, 0.13 mmol) successively, and the solution was stirred overnight. The reaction mixture was cooled to 0 °C, distilled water (1 mL) was added, and the mixture was stirred for 20 min. The mixture was washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (2:1 petroleum ether/EtOAc) afforded **25·dipivalate** (16.5 mg, 85%) as a colorless oil: IR (CH_2Cl_2) ν_{max} 2973, 2875, 1732, 1648 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.49−5.55 (m, 1 H), 5.13 (ddd, *J* = 9.7, 4.6, 4.6 Hz), 4.62 (d, *J* = 15.1 Hz, 1 H), 4.57−4.61 (m, 1 H), 4.38 (dd, *J* = 11.8, 5.2 Hz, 1 H), 4.18 (dd, *J* = 11.8, 3.8 Hz, 1 H), 3.67−3.74 (m, 1 H), 3.53 (s, 3 H), 3.49 (d, *J* = 15.1 Hz, 1 H), 2.52−2.79 (m, 4 H), 1.92−2.18 (m, 4 H), 1.21 (s, 9 H), 1.19 (s, 9 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 177.9, 177.2, 169.2, 152.6, 130.6, 120.8, 89.9, 67.3, 60.7, 55.4, 53.9, 49.1, 38.9, 38.7, 29.0, 28.6, 27.4, 27.1, 27.0, 23.5; HRMS (ESI-QTOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{24}H_{37}NO_6Na$ 458.2513; Found 458.2530.

(5*S*,6*S*)-6-Allyl-5-hydroxy-1-(*p*-methoxybenzyl)piperidin-2-one (34). $Ph_3P^+MeBr^-$ (1.93 g, 5.41 mmol) was dried under vacuum at 110 °C for 1 h and cooled to rt. The above salt was suspended in THF (24 mL), and it was cooled to 0 °C under argon. KO*t*-Bu (639 mg, 5.41 mmol) was added, in one portion, to the above suspension to give a bright yellow suspension. After 45 min at 0 °C a solution of the lactol **14** (600 mg, 2.16 mmol) in THF (16 mL) was added, via cannula, and the reaction mixture was stirred for 1 h. Saturated aqueous NH_4Cl (5 mL) was added, and the THF was evaporated under reduced pressure. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL), dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by chromatography (1:1 petroleum ether/EtOAc) to afford **34** (572 mg, 96%) as a white crystalline solid: mp 83−85 °C; $[\alpha]_D^{23}$ −78.9° (*c* 2.01, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3543−3110, 1653 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.04−7.12 (m, 2 H), 6.75−6.82 (m, 2 H), 5.74−5.90 (m, 1 H), 5.28 (d, *J* = 14.8 Hz, 1 H), 5.01−5.17 (m, 2 H), 3.82−3.92 (m, 1 H), 3.78 (d, *J* = 14.8 Hz, 1 H), 3.74 (s, 3 H), 3.30−3.38 (m, 1 H), 3.18 (br d, 1 H), 2.49−2.64 (m, 2 H), 2.25−2.46 (m, 2 H), 1.75−2.01 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.7, 158.8, 135.6, 129.1, 117.6, 113.9, 66.9, 58.8, 55.1, 47.7, 33.5, 28.6, 25.3; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{16}H_{21}NO_3$ 275.1521(4); Found 275.1521(3).

(5*S*,6*S*)-6-Allyl-1-(*p*-methoxybenzyl)-5-(methoxymethoxy)-piperidin-2-one (35). To the alcohol **34** (1.18 g, 4.29 mmol) in DCE (30 mL) under Ar at rt were added tetrabutylammonium iodide (24 mg, 1.5 mol %), *N*,*N*-diisopropylethylamine (4.50 mL, 25.71 mmol), and MOM-Cl (0.98 mL, 12.86 mmol) successively, and the resulting solution was allowed to reflux, overnight. The reaction mixture was cooled to 0 °C and diluted with CH_2Cl_2 (10 mL), and saturated aqueous Na_2CO_3 (10 mL) was added. After the mixture stirred for 15 min at the same temperature, the biphasic solution was transferred into a separatory funnel. The two layers were separated, and the organic layer was washed once with brine. The aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. Purification by chormatography (2:1 petroleum ether/EtOAc) afforded **35** (1.37 g, 100%) as a colorless oil: $[\alpha]_D^{21}$ −74.8° (*c* 1.05, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3054, 2951, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.09−7.17 (m, 2 H), 6.78−6.86 (m, 2 H), 5.74−5.90 (m, 1 H), 5.34 (d, 1 H, *J* = 14.8 Hz), 5.01−5.16 (m, 2 H), 4.56 (d, 1 H, *J* = 6.9 Hz), 4.51 (d, 1 H, *J* = 6.9 Hz), 3.81 (d, *J* = 14.8 Hz, 1 H), 3.76 (s, 3 H), 3.69−3.77 (m, 1 H), 3.42 (dd, *J* = 11.1, 5.5 Hz, 1 H), 3.27 (s, 3 H), 2.41−2.69 (m, 3 H, H-3), 2.31 (ddd, *J* = 14.4, 7.2, 7.2 Hz, 1 H), 1.85−2.07 (m, 2 H); ^{13}C NMR (CDCl3, 75 MHz) δ 169.2, 158.8, 135.5, 129.2, 129.1, 117.5, 95.6, 72.9, 57.5, 55.5, 55.1, 48.0, 33.8, 28.8, 23.2; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{25}NO_4$ 319.1784; Found 319.1780.

(5*S*,6*S*)-1-(*p*-Methoxybenzyl)-5-(methoxymethoxy)-6-(3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propyl)piperidin-2-one (36a). To the alkene **35** (1.41 g, 4.43 mmol) in CH_2Cl_2 (25 mL) under argon at rt was added $[Rh(PPh_3)_3Cl]$ (82 mg, 2 mol %) in one portion resulting in an orange-red color solution. Pinacolborane (1.32 mL, 8.86 mmol) was added dropwise to the above mixture, during which time the color of solution has changed to yellow-orange. After the reaction mixture was stirred at the same temperature overnight, it was cooled to 0 °C and distilled water (5 mL) was added. The organic layer was separated, and the aqueous layer was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by chromatography (Et_2O) to afford boronate ester **36a** (1.82 g, 92%) as a colorless oil: $[\alpha]_D^{22}$ −48.4° (*c* 0.67, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 2943, 1642 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.10−7.17 (m, 2 H), 6.76−6.83 (m, 2 H), 5.35 (d, *J* = 14.7 Hz, 1 H), 4.52 (d, *J* = 6.8 Hz, 1 H), 4.47 (d, *J* = 6.8 Hz, 1 H), 3.74 (s, 3 H), 3.74 (d, *J* = 14.7 Hz, 1 H), 3.65−3.75 (m, 1 H), 3.26−3.33 (m, 1 H), 3.24 (s, 3 H), 2.57 (ddd, *J* = 18.2, 7.9, 5.0 Hz, 1 H), 2.44 (ddd, *J* = 18.2, 7.9, 7.9 Hz, 1 H), 1.69−2.03 (m, 3 H), 1.40−1.62 (m, 3 H), 1.20 (s, 12 H), 0.75 (t, *J* = 7.4 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 158.7, 129.3, 129.1, 113.8, 95.2, 82.8, 72.8, 57.4, 55.4, 55.0, 48.1, 32.0, 30.1, 28.7, 24.69, 24.67, 23.0, 21.9; ^{11}B NMR ($CDCl_3$, 96.3 MHz) δ 33.5; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{38}BNO_6$ 447.2792(2); Found 447.2792(4).

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Potassium (5*S*,6*S*)-1-(*p*-Methoxybenzyl)-5-(methoxymethoxy)-6-(3-(trifluoroborato)propyl)piperidin-2-one (36b). To the boronate ester **36a** (1.82 g, 4.03 mmol) in MeOH (26 mL) at rt was added aqueous KHF_2 (4.10 mL, 4.5 M) dropwise, and the resultant solution was vigorously stirred at the same temperature, overnight. All the volatiles were removed under reduced pressure, and the crude residue was dissolved in a mixture of MeOH and water (2:1 v/v, 20 mL) for azeotropic evaporation of the pinacol byproduct. The solvent was removed, and the evaporation cycles were continued until TLC showed the absence of the pinacol (6 cycles). The crude residue was washed with acetone (4 × 20 mL), dried over Na_2SO_4, filtered, concentrated, and redissolved in CH_2Cl_2. To this solution was added Et_2O down the sides of the flask to effect the precipitation of potassium trifluoroborate salt. The solvent was decanted carefully from the flask, and the remaining white precipitate was washed with Et_2O (3 × 10 mL). Evaporation of Et_2O under reduced pressure gave the trifluoroborate salt **36b** (1.33 g, 77%, 70.5% from **35**) as a white solid: mp 72−74 °C; $[\alpha]_D^{23}$ −45.9° (*c* 0.44, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3055, 2943, 1625 cm^{-1}; ^1H NMR (CD_3CN, 300 MHz) δ 7.12−7.21 (m, 2 H), 6.81−6.90 (m, 2 H), 5.16 (d, *J* = 14.9 Hz, 1 H), 4.54 (d, *J* = 6.8 Hz, 1 H), 4.49 (d, *J* = 6.8 Hz, 1 H), 3.86 (d, *J* = 14.9 Hz, 1 H), 3.75 (s, 3 H), 3.69−3.79 (m, 1 H), 3.31−3.40 (m, 1 H), 3.22 (s, 3 H), 2.49 (ddd, *J* = 18.0, 8.5, 5.3 Hz, 1 H), 2.34 (ddd, *J* = 18.0, 7.7, 7.7 Hz, 1 H), 1.78−2.02 (m, 2 H), 1.64−1.77 (m, 1 H), 1.48−1.63 (m, 1 H), 1.32 (tt, *J* = 7.8, 7.8 Hz, 2 H), 0.00−0.21 (m, 2 H); ^{13}C NMR (CD_3CN, 75 MHz) δ 170.8, 160.2, 131.8, 130.4, 118.8, 115.2, 96.5, 74.0, 59.7, 56.35, 56.33, 49.4, 34.4, 29.9, 24.5, 24.4 (q, *J* = 8.9 Hz, ^{13}C-^{11}B); ^{11}B NMR (CD_3CN, 96.3 MHz) δ 2.9; ^{19}F NMR (CD_3CN, 282.4 MHz) δ −141.0; HRMS (ESI-QTOF) *m*/*z*: $[M - K^+]^-$ Calcd for $C_{18}H_{26}BF_3NO_4$ 388.1912; Found 388.1928.

(5*S*,6*S*)-1-(*p*-Methoxybenzyl)-5-(methoxymethoxy)-6-((*E*)-5-(phenylsulfonyl)pent-4-enyl)piperidin-2-one (37). Cs_2CO_3 (3.0 g, 9.21 mmol), $[Pd(dppf)Cl_2]$ (251 mg, 0.31 mmol), and (*E*)-(2-bromovinyl) phenyl sulfone (835 mg, 3.38 mmol) were successively added to the trifluoroborate salt **36b** (1.31 g, 3.07 mmol), and the flask was evacuated and flushed with nitrogen. To the above reaction flask under argon at rt was added a degassed mixture of toluene and water (3:1 v/v, 26 mL), and the suspension was allowed to warm to 85 °C (oil bath). The solution is orange-red in color at the beginning and was turned into dark brown within 2 h, by which time all of the trifluoroborate was consumed. The reaction mixture was diluted with EtOAc (20 mL) and washed successively with water (1 × 5 mL) and brine (1 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (1:2 petroleum ether/EtOAc, then 1:4 petroleum ether/EtOAc) afforded **37** (1.19 g, 80%) as a yellow oil: $[\alpha]_D^{21}$ −21.6° (*c* 0.63, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 2947, 2900, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84−7.91 (m, 2 H), 7.49−7.66 (m, 3 H), 7.07−7.17 (m, 2 H), 6.94 (dt, *J* = 15.1, 6.8 Hz, 1 H), 6.79−6.88 (m, 2 H), 6.31 (d, *J* = 15.1 Hz, 1 H), 5.26 (d, *J* = 14.8 Hz, 1 H), 4.55 (d, *J* = 6.8 Hz, 1 H), 4.50 (d, *J* = 6.8 Hz, 1 H), 3.70−3.80 (m, 1 H), 3.79 (d, *J* = 14.8 Hz, 1 H), 3.78 (s, 3 H), 3.22−3.34 (m, 1 H), 3.26 (s, 3 H), 2.40−2.65 (m, 2 H), 2.20 (dt, *J* = 6.8, 6.8 Hz, 2 H), 1.70−2.0 (m, 3 H), 1.43−1.64 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.2, 158.9, 145.9, 140.5, 133.2, 130.9, 129.2, 129.1, 129.0, 127.5, 114.0, 95.3, 72.9, 57.6, 55.6, 55.2, 48.5, 31.6, 29.1, 28.7, 25.5, 22.9; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{26}H_{33}NO_6S$ 487.2029; Found 487.2021.

(5*S*,6*S*)-1-(*p*-Methoxybenzyl)-6-((*E*)-5-(phenylsulfonyl)pent-4-enyl)-5-(thiocarbonylimidazolyl)-piperidin-2-one (33). Compound **37** (1.24 g, 2.54 mmol) was dissolved in HCl−MeOH (26 mL, 1 M), and the solution was heated to 60 °C (oil bath) for 3 h. The reaction mixture was cooled to 0 °C, and solid $NaHCO_3$ (2.18 g, 26 mmol) was added to quench the excess acid. MeOH was evaporated under reduced pressure, and the crude residue was diluted with CH_2Cl_2. The organic layer was washed once with brine. The aqueous solution was saturated with solid NaCl and back-extracted into CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was purified by chromatography (EtOAc, then 10:1 EtOAc/MeOH) to give the deprotected alcohol (1.06 g, 94%) as a thick colorless oil: $[\alpha]_D^{22}$ −32.6° (*c* 0.93, $CHCl_3$); IR (neat) ν_{max} 3650−3109, 2946, 1616 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, *J* = 7.4 Hz, 2 H), 7.47−7.66 (m, 3 H), 7.03−7.15 (m, 2 H), 6.92 (dt, *J* = 15.1, 6.7 Hz, 1 H), 6.76−6.86 (m, 2 H), 6.30 (d, *J* = 15.1 Hz, 1 H), 5.23 (d, *J* = 14.7 Hz, 1 H), 3.86−3.98 (m, 1 H), 3.77 (d, *J* = 14.7 Hz, 1 H), 3.76 (s, 3 H), 3.16−3.28 (m, 1 H), 2.64−2.77 (br m, 1 H), 2.55 (dt, *J* = 18.2, 6.0 Hz, 1 H), 2.42 (dt, *J* = 18.2, 7.7 Hz, 1 H), 2.19 (dt, *J* = 6.7 Hz, 2 H), 1.70−1.96 (m, 3 H), 1.40−1.68 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 158.6, 146.2, 140.2, 133.1, 130.4, 129.1, 128.8, 128.8, 127.2, 113.8, 66.3, 59.0, 55.0, 47.7, 31.3, 28.6, 28.4, 25.4, 25.0; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{24}H_{29}NO_5S$ 443.1766; Found 443.1769.

To the above alcohol (1.12 g, 2.53 mmol) in DCE (30 mL) under argon at rt was added 1,1-thiocarbonyldiimidazole (1.0 g, 5.05 mmol) in one portion, and the resultant reddish brown solution was stirred at 85 °C (oil bath) overnight. The reaction mixture was cooled to rt, distilled water (5 mL) was added, and the mixture was stirred for 10 min. The two layers were separated, and the organic layer was diluted with CH_2Cl_2 and washed successively with cold aqueous HCl (2 × 5 mL, 0.5 M), saturated aqueous $NaHCO_3$ (1 × 5 mL), and brine (1 × 5 mL). The organic layer was dried over Na_2SO_4, filtered, and concentrated. Purification by chromatography (EtOAc, then 20:1 EtOAc/MeOH) afforded **33** (1.22 g, 87%) as a thick foamy oil: $[\alpha]_D^{23}$ −2.3° (*c* 0.57, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3047, 2951, 1636 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.21−8.25 (m, 1 H), 7.80−7.87 (m, 2 H), 7.45−7.65 (m, 4 H), 7.09−7.18 (m, 2 H), 6.98−7.02 (m, 1 H), 6.77−6.90 (m, 3 H), 6.24 (dd, *J* = 15.1, 0.9 Hz, 1 H), 5.65 (ddd, 1 H, *J* = 8.7, 4.3, 4.3 Hz, 1 H), 5.23 (d, *J* = 14.9 Hz, 1 H), 3.96 (d, *J* = 14.9 Hz, 1 H), 3.77 (s, 3 H), 3.62−3.72 (m, 1 H), 2.62 (t, *J* = 7.2 Hz, 2 H), 2.06−2.35 (m, 4 H), 1.54−1.81 (m, 2 H), 1.35−1.52 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 182.3, 168.7, 159.1, 144.9, 140.3, 136.8, 133.3, 131.5, 131.3, 129.2, 129.1, 128.5, 127.5, 117.4, 114.2, 77.3, 56.1, 55.2, 47.9, 31.2, 29.3, 28.0, 24.6, 22.0; HRMS (ESI-QTOF) *m*/*z*: $[M + Na]^+$ Calcd for $C_{28}H_{31}N_3O_5S_2Na$ 576.1597; Found 576.1614.

Formation of Octahydroquinolin-2-ones 38−41 from Thioimidazolide 33. To a solution of the thioimidazolide **33** (483 mg, 0.87 mmol) in degassed toluene (30 mL) under argon at 85 °C (oil bath) was added a mixture of AIBN (45 mg, 0.17 mmol) and Bu_3SnH (0.36 mL, 1.31 mmol) in degassed toluene (30 mL) via syringe pump over 3 h. The reaction mixture was stirred at the same temperature for another 30 min and was allowed to reach rt. Toluene was evaporated under reduced pressure, and the crude residue was diluted with EtOAc. Aqueous KF (10 mL, 10% w/v) was added, and the biphasic mixture was vigorously stirred for 30 min. The solution was vacuum filtered through a pad of Celite, and the two layers were separated. The aqueous layer was re-extracted into EtOAc, and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The crude residue was carefully purified by chromatography (Et_2O, then 1:4 petroleum ether/EtOAc) to give **38** + **40** (189 mg, **38**:**40** = 8:1), **39** (58.6 mg), **41** (6.2 mg), and **39** + **41** (25 mg, **39**:**41** = 2.5:1) in an overall yield of 75%. The ratio of the mixture of **38** and **40** was determined based on the integration of benzylic methylene proton doublets at 3.89 and 4.25 ppm, whereas the ratio of the mixture of **39** and **41** was based on the integration of benzylic methylene proton doublets at 5.21 and 4.98 ppm. For characterization purposes, compound **38** was obtained after repeated chromatographic purification (1:4 petroleum ether/EtOAc) of the 8:1 mixture of **38** and **40**.

*(4a*R*,5*R*,8a*S*)-1-(p-Methoxybenzyl)-5-((phenylsulfonyl)methyl)-octahydroquinolin-2-one (**38**).* White solid: mp 52−54 °C; $[\alpha]_D^{22}$ −38.6° (*c* 0.28, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3047, 2940, 1629 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.86 (d, *J* = 7.5 Hz, 2 H), 7.64 (t, *J* = 7.3 Hz, 1 H), 7.53 (t, *J* = 7.3 Hz, 2 H), 7.07−7.17 (m, 2 H), 6.79−6.89 (m, 2 H), 5.21 (d, *J* = 14.8 Hz, 1 H), 3.84 (d, *J* = 14.8 Hz, 1 H), 3.80 (s, 3 H), 3.14 (ddd, *J* = 11.4, 4.0, 4.0 Hz, 1 H), 3.04 (dd, *J* = 14.0, 6.2 Hz, 1 H), 2.93 (dd, *J* = 14.0, 6.8 Hz, 1 H), 2.53 (dd, *J* = 18.0, 6.2 Hz, 1 H), 2.18−2.43 (m, 2 H), 1.99−2.12 (m, 1 H), 1.70−1.98 (m, 3 H), 1.58−1.70 (m, 1 H), 1.45−1.58 (m, 1 H), 1.09−1.44 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 158.9, 140.0, 133.8, 129.5, 129.3, 129.03, 127.6, 114.0, 59.4, 57.2, 55.2, 47.0, 37.6, 34.7, 30.9, 26.4, 26.1,

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24.0, 16.1; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{24}H_{29}NO_4S$ 427.1817; Found 427.1813.

*(4aR,5S,8aS)-1-(p-Methoxybenzyl)-5-((phenylsulfonyl)methyl)-octahydroquinolin-2-one (**39**).* Colorless oil: $[\alpha]_D^{23}$ −36.0° (*c* 1.60, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3057, 2941, 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.84 (d, *J* = 7.6 Hz, 2 H), 7.62−7.70 (m, 1 H), 7.55 (t, *J* = 7.6 Hz, 2 H), 7.05−7.14 (m, 2 H), 6.80−6.88 (m, 2 H), 5.19 (d, *J* = 15.0 Hz, 1 H), 3.89 (d, *J* = 15.0 Hz, 1 H), 3.80 (s, 3 H), 3.16 (ddd, *J* = 10.9, 4.4, 4.4 Hz, 1 H), 3.04 (dd, *J* = 14.2, 6.5 Hz, 1 H), 2.96 (dd, *J* = 14.2, 6.5 Hz, 1 H), 2.32−2.58 (m, 3 H), 2.0−2.17 (m, 1 H), 1.80−1.92 (m, 2 H), 1.51−1.74 (m, 3 H), 1.33−1.52 (m, 2 H), 1.14−1.29 (m, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.3, 158.8, 139.6, 133.9, 129.5, 129.4, 128.8, 127.8, 114.0, 59.3, 55.3, 53.4, 47.0, 38.4, 33.7, 31.2, 26.7, 25.2, 22.5, 19.9; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{24}H_{29}NO_4S$ 427.1817; Found 427.1801.

*(4aS,5R,8aS)-1-(p-Methoxybenzyl)-5-((phenylsulfonyl)methyl)-octahydroquinolin-2-one (**40**).* ^1H NMR ($CDCl_3$, 300 MHz) δ (discernible signals for **40** in a 8:1 mixture of **38** and **40**) 4.94 (d, *J* = 15.6 Hz, 1 H), 4.34 (d, *J* = 15.6 Hz, 1 H), 3.24 (d, *J* = 13.7, 13.7, 2.6 Hz, 1 H).

*(4aS,5S,8aS)-1-(p-Methoxybenzyl)-5-((phenylsulfonyl)methyl)-octahydroquinolin-2-one (**41**).* White solid: mp 205−208 °C (EtOAc); $[\alpha]_D^{22}$ +18.7° (*c* 0.98, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3058, 2931, 2858, 1634 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.85−7.92 (m, 2 H), 7.63−7.71 (m, 1 H), 7.53−7.62 (m, 2 H), 7.03−7.10 (m, 2 H), 6.78−6.85 (m, 2 H), 4.98 (d, *J* = 15.3 Hz, 1 H), 4.25 (d, *J* = 15.3 Hz, 1 H), 3.78 (s, 3 H), 2.98 (dd, *J* = 14.5, 8.3 Hz, 1 H), 2.92 (dd, *J* = 14.5, 3.1 Hz, 1 H), 2.74 (ddd, *J* = 11.2, 11.2, 3.4 Hz, 1 H), 2.57 (ddd, *J* = 18.0, 4.5, 3.0 Hz, 1 H), 2.35−2.52 (m, 2 H), 2.11−2.22 (m, 1 H), 1.85−1.95 (m, 1 H), 1.60−1.76 (m, 2 H), 1.16−1.52 (m, 4 H), 1.02 (dddd, *J* = 12.3, 12.3, 12.3, 3.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.1, 158.6, 139.3, 133.8, 129.6, 129.4, 128.5, 128.0, 114.0, 56.4, 55.2, 53.9, 44.9, 43.6, 33.6, 32.9, 31.7, 29.1, 24.6, 19.5; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{24}H_{29}NO_4S$ 427.1817; Found 427.1820.

Desulfonylation and Birch Reduction of Octahydroquinolin-2-ones 38−41. *General Procedure for Desulfonylation.* To the octahydroquinolin-2-ones **38**−**41** (1 mmol) in MeOH (30 mL) under argon at rt was added freshly dried Na_2HPO_4 (1.92 g, 13.5 mmol) in one portion. Na−Hg (14.5 g, 6% Na) amalgam was added to the above solution in three equal portions over 30 min. The resultant cloudy solution was stirred overnight at rt, after which time mercury was seen to settle at the bottom of the reaction flask. The reaction mixture was cooled to 0 °C in a salt−ice bath, and distilled water (8 mL) was added. To the above mixture was then added EtOAc (20 mL), and the resulting solution was vigorously stirred for 15 min at rt. The solution was carefully decanted into a separatory funnel leaving behind the mercury in the reaction flask. The organic and aqueous layers were separated, and the aqueous layer was saturated with solid NaCl and back-extracted into EtOAc. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the crude desulfonylated products.

General Procedure for Birch Reduction. Na metal was cut into small pieces and washed three times with hexanes. To the liquid NH_3 (15 mL) at −78 °C under argon, was added Na metal (276 mg, 12 mmol) portion wise (~5 min) and the resulting blue colored solution was stirred at −78 °C for 30 min. To the above solution was then added the desulfonylated compounds (1 mmol) in THF (7 mL) via cannula and the reaction mixture was stirred at the same temperature for 5 h. Solid NH_4Cl (280 mg) was added to the above solution at −78 °C and the reaction temperature allowed to gradually warm to rt, by which time all of the ammonia had evaporated. The crude residue was extracted with CH_2Cl_2 (3 × 12 mL), followed by 4:1 v/v CH_2Cl_2/MeOH (3 × 5 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated to afford the crude octahydroquinolin-2-ones **42**-**45**.

(4a*R*,5*R*,8a*S*)-5-Methyloctahydroquinolin-2-one (42). The desulfonylation of an 8:1 mixture of **38** and **40** (810 mg, 1.89 mmol) was conducted according to the above described general procedure. Purification by chromatography (1:2 petroleum ether/EtOAc, then 1:4 petroleum ether/EtOAc) afforded an inseparable 8:1 mixture of the corresponding desulfonylated products (414 mg, 76%, 84% brsm) as a colorless oil. Some unreacted mixture of **38** and **40** (74 mg, 9%) was also recovered. The diastereomeric ratio of the desulfonylated products was determined based on integration of the benzylic methylene proton doublets at 5.27 and 4.37 ppm in the ^1H NMR spectrum.

Pure **38** (43 mg, 0.1 mmol), previously obtained by repeated chromatographic purification of the mixture of **38** and **40**, was also treated with Na−Hg amalgam to obtain the corresponding desulfonylated product (21 mg, 73%, 89% based on recoverd **38**) which was used for spectral characterization. *(4aR,5R,8aS)-1-(p-Methoxybenzyl)-5-methyloctahydroquinolin-2-one.* Colorless oil: $[\alpha]_D^{23}$ −66.5° (*c* 1.94, $CHCl_3$); IR (neat) ν_{max} 2933, 2865, 1631 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.13−7.20 (m, 2 H), 6.80−6.87 (m, 2 H), 5.27 (d, *J* = 14.9 Hz, 1 H), 3.85 (d, *J* = 14.9 Hz, 1 H), 3.79 (s, 3 H), 3.12 (ddd, *J* = 11.7, 4.1, 4.1 Hz, 1 H), 2.51−2.63 (m, 1 H), 2.34−2.49 (m, 1 H), 1.54−1.97 (m, 6 H), 0.99−1.43 (m, 4 H), 0.89 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.8, 158.7, 123.0, 129.0, 113.9, 58.2, 55.2, 47.0, 39.6, 34.4, 31.3, 28.2, 26.3, 24.6, 19.1, 15.4; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{18}H_{25}NO_2$ 287.1885; Found 287.1886.

(4aS,5R,8aS)-1-(p-Methoxybenzyl)-5-methyloctahydroquinolin-2-one. ^1H NMR ($CDCl_3$, 300 MHz) of 8:1 product mixture, δ (discernible signals for desulfonylated compound formed from **40**) 4.96 (d, *J* = 15.6 Hz, 1 H), 4.37 (d, *J* = 15.6 Hz, 1 H), 2.81−2.91 (m, 1 H).

The 8:1 product mixture from the desulfonylation of **38** and **40** (414 mg, 1.44 mmol) was subjected to Birch reduction according to the general procedure. Purification by chromatography (20:1 EtOAc/MeOH) afforded an 8:1 mixture of octahydroquinolin-2-ones **42** and **44** (212 mg, 88%) as a white solid. Single recrystallization of the above mixture from Et_2O afforded pure **42** (144 mg) as a white solid: mp 145−146 °C (Et_2O) {lit.[32c] for (±)-**42**, mp 133−134 °C}; $[\alpha]_D^{23}$ −14.7° (*c* 2.20, $CHCl_3$); IR (CH_2Cl_2) ν_{max} 3201, 3051, 2932, 2865, 1659 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 6.50−6.75 (br s, 1 H), 3.29 (ddd, *J* = 12.3, 8.4, 4.2 Hz, 1 H), 2.43 (ddd, *J* = 18.0, 4.7, 2.3 Hz, 1 H), 2.27 (ddd, *J* = 18.00, 8.3, 8.3 Hz, 1 H), 1.89−1.97 (m, 1 H), 1.61−1.75 (m, 5 H), 1.34−1.48 (m, 2 H), 1.18−1.30 (m, 1 H), 1.03 (dddd, *J* = 13.0, 13.0, 13.0, 3.6 Hz, 1 H), 0.95 (d, *J* = 6.9 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.2, 54.1, 38.4, 34.2, 31.2, 30.5, 28.2, 24.3, 19.3, 15.0; HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{10}H_{17}NO$ 167.1310; Found 167.1309. Racemic **42** has been reported[32c,43] in the literature.

(4a*S*,5*R*,8a*S*)-5-Methyloctahydroquinolin-2-one (44). To obtain pure **44** for characterization purposes, the mixture of **42** and **44** (enriched in **44**) obtained in the desulfonylation−Birch reduction of an 8:1 mixture of **38** and **40** was converted to the corresponding *N*-Boc derivatives by treatment with *n*-BuLi and Boc_2O in THF at −78 °C. Gratifyingly, *N*-Boc-**44** was readily separated from *N*-Boc-**42** by column chromatography. Treatment of *N*-Boc-**44** with 1 M HCl−MeOH gave pure **44** as a white solid: IR (CH_2Cl_2) ν_{max} 3202, 3054, 2959, 2930, 2861, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 5.50 (br s, 1 H), 2.97 (ddd, *J* = 10.5, 10.5, 3.5 Hz, 1 H), 2.48 (ddd, *J* = 18.1, 6.4, 1.9 Hz, 1 H), 2.34 (ddd, *J* = 18.1, 11.9, 6.8 Hz, 1 H), 2.03−2.13 (m, 1 H), 1.66−1.83 (m, 3 H), 1.15−1.44 (m, 4 H), 0.94−1.10 (m, 2 H), 0.96 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 57.5, 46.2, 35.09, 35.11, 33.7, 31.6, 24.8, 24.0, 19.1 (the amide carbonyl signal was not detected due to low sample concentration); HRMS (EI-double focusing sector field) m/z: $[M]^+$ Calcd for $C_{10}H_{17}NO$ 167.1310; Found 167.1306.

The mp and $[\alpha]_D$ of **44** were not measured due to insufficient amounts of material. Racemic **44**[24c,32c] and (+)-**44**[29a] have been described in the literature.

(4a*R*,5*S*,8a*S*)-5-Methyloctahydroquinolin-2-one (43). Desulfonylation of **39** (355 mg, 0.83 mmol) was conducted according to the general procedure. Purification by chromatography (1:1 petroleum ether/EtOAc then 1:4 petroleum ether/EtOAc) afforded the desulfonylated compound (181 mg, 76%). Starting **39** (28.4 mg, 8%) was also recovered. *(4aR,5S,8aS)-1-(p-Methoxybenzyl)-5-methyl-*

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octahydroquinolin-2-one. Colorless oil: $[\alpha]_D^{21}$ −47.3° (*c* 1.22, $CHCl_3$); IR (neat) ν_{max} 2932, 2873, 1637 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.12−7.20 (m, 2 H), 6.80−6.88 (m, 2 H), 5.22 (d, *J* = 15.0 Hz, 1 H), 3.96 (d, *J* = 15.0 Hz, 1 H), 3.79 (s, 3 H), 3.38 (ddd, *J* = 8.9, 4.2, 4.2 Hz, 1 H), 2.39−2.61 (m, 2 H), 2.03−2.18 (m, 1 H), 1.36−1.89 (m, 8 H), 1.21 (ddd, *J* = 13.2, 8.8, 4.6 Hz, 1 H), 0.95 (d, *J* = 7.1 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 158.7, 130.0, 128.8, 113.9, 55.2, 54.0, 46.7, 40.3, 32.2, 31.0, 28.0, 27.8, 23.0, 19.7, 19.1; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{18}H_{25}NO_2$ 287.1885; Found 287.1888.

Birch reduction of the desulfonylated compound obtained from **39** (130 mg, 0.45 mmol) was conducted according to the general procedure. Purification by chromatography (1:4 petroleum ether/EtOAc) afforded the *cis*-octahydroquinolin-2-one **43** (65 mg, 86%) as a white solid: mp 143−144 °C (Et_2O) {lit.[29a] for *ent*-**43**, mp 146.5−147.5 °C}; $[\alpha]_D^{23}$ +65.3° (*c* 0.88, $CHCl_3$); {lit.[30a] for (+)-**43**; $[\alpha]_D^{20}$ +33.8° (*c* 0.08, $CHCl_3$); lit.[29a] for *ent*-**43**; $[\alpha]_D^{25}$ −60.4° (*c* 1.00, $CHCl_3$)}; IR (CH_2Cl_2) ν_{max} 3195, 3054, 2932, 1659, 1450 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 5.44−5.60 (br s, 1 H), 3.63 (ddd, *J* = 3.4, 3.4, 3.4 Hz, 1 H), 2.26−2.33 (m, 2 H), 2.05 (ddd, *J* = 13.7, 9.3, 4.2 Hz, 1 H), 1.39−1.74 (m, 8 H), 0.96−1.08 (m, 1 H), 0.93 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.9, 52.2, 39.7, 33.7, 31.8, 27.6, 27.3, 23.1, 20.0, 19.3; HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{10}H_{17}NO$ 167.1310; Found 167.1308. Compounds (±)-**43**,[24c,d,32c,e] (+)-**43**,[30a] and (−)-**43**[29a] have been reported in the literature.

(4a*S*,5*S*,8a*S*)-5-Methyloctahydroquinolin-2-one (45). Desulfonylation of a 2.5:1 mixture of **39** and **41** (131 mg, 0.31 mmol) was conducted according to the general procedure. Purification by chromatography (1:1 petroleum ether/EtOAc) afforded an inseparable mixture of the corresponding desulfonylated compounds (70 mg, 80%) in a 2.5:1 ratio. Characterization data for the major product, which was formed from the desulfonylation of **39**, is reported under the preparation of **43** described above. *(4aS,5S,8aS)-1-(p-Methoxybenzyl)-5-methyloctahydroquinolin-2-one.* ^1H NMR ($CDCl_3$, 300 MHz) of the 2.5:1 product mixture, δ (discernible signals for desulfonylated compound formed from **41**) 4.90 (d, *J* = 15.3 Hz, 1 H); 4.39 (d, *J* = 15.3 Hz, 1 H), 3.08 (ddd, *J* = 11.5, 11.5, 3.4 Hz, 1 H), 0.81 (d, *J* = 7.3 Hz, 3 H).

Birch reduction of the 2.5:1 desulfonylated products prepared from the mixture of **39** and **41** (70 mg, 0.24 mmol) was performed according to the general procedure. Purification by chromatography (1:4 petroleum ether/EtOAc) afforded an inseparable 2.5:1 mixture of **43** and **45** (20 mg, 50%). Characterization data for the major product **43** (from **39**) is described above: ^1H NMR ($CDCl_3$, 300 MHz) of the 2.5:1 mixture of **43** and **45**, δ (discernible signals for minor **45**) 6.05 (br s, 1 H), 3.20 (ddd, *J* = 11.0, 11.0, 3.9 Hz, 1 H), 2.46 (ddd, *J* = 17.8, 5.4, 2.9 Hz, 1 H), 1.74−1.83 (m, 1 H), 0.89 (d, *J* = 7.3 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) of the 2.5:1 mixture of **43** and **45**, δ (discernible signals for minor **45**) 172.1, 51.6, 42.6, 34.2, 32.7, 31.9, 31.7, 25.5, 18.8, 12.8. Compound **45** was inseparable from **43**, which prevented its full spectral characterization and measurement of its optical rotation. Racemic **45** has been reported[24d] in the literature.

(+)-*cis*-195A (26). A solution of the octahydroquinolin-2-one **43** (30 mg, 0.18 mmol) in CH_2Cl_2 (1 mL) was added to a stirred mixture of trimethyloxonium tetrafluoroborate (55 mg, 0.36 mmol) and *N*,*N*-diisopropylethylamine (1 drop) in CH_2Cl_2 (1 mL) under argon at 10 °C, and the solution was allowed to stir at rt for 1.5 h. The reaction mixture was cooled to 0 °C, and cold aqueous saturated $NaHCO_3$ (2 mL) was added. The two layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. ^1H NMR of the crude product (38 mg) showed the presence of the imidate ether and unreacted starting material in a 4:1 ratio. The crude product was used in the next step without any purification to avoid degradation.

A freshly prepared solution of *n*-C_3H_7MgBr in Et_2O (0.48 mL, 1.32 M) was added to benzene (1 mL) under argon, and the mixture was heated to 85 °C (oil bath) for 10 min. The imidate ether (38 mg) in benzene (2 mL) was added to the Grignard solution via cannula and refluxed for 12 h. The reaction mixture was diluted with Et_2O and cooled to 0 °C, and cold saturated aqueous $NaHCO_3$ (2 mL) was added. The two layers were separated, and the aqueous layer was re-extracted with Et_2O. The combined organic layers were dried over anhydrous K_2CO_3, filtered, and concentrated. The crude imine (36 mg) was hydrogenated in the next step without any further purification.

To the imine (36 mg) in 95% EtOH (1 mL) was added aqueous HCl (0.2 mL, 2 M), followed by PtO_2 (6 mg), and the mixture was stirred under H_2 (1 atm, balloon) for 8 h. The reaction mixture was filtered through a pad of Celite followed by washing with 95% EtOH, and the solvent was removed under reduced pressure. The crude hydrochloride salt was diluted with CH_2Cl_2 (10 mL) and aqueous NaOH (5 mL, 6 M) was added; the mixture was then stirred for 30 min. The two layers were separated, and the aqueous layer was re-extracted with CH_2Cl_2 (4 × 5 mL). The combined organic layers were dried over anhydrous K_2CO_3, filtered, and concentrated. The crude residue (22 mg) was purified by chromatography (10:1 CH_2Cl_2/MeOH, then 80:20:1 CH_2Cl_2/MeOH/^{i}PrNH$_2$) to give **26** (15.5 mg, 45% over 3 steps, 52% based on recovered **43**) as a pale yellow oil. The starting octahydroquinilin-2-one **43** (3.8 mg, 13%) was also recovered. Addition of concentrated aqueous HCl (2 drops) to a methanolic solution of **26**, followed by evaporation, gave the corresponding hydrochloride salt (18.8 mg) as an off-white solid.

Data for **26:** $[\alpha]_D^{21}$ −2.1° (*c* 0.33, MeOH) {lit[29d] $[\alpha]_D^{20}$ −2.2° (*c* 1.34, MeOH)}; IR (CH_2Cl_2) ν_{max} 3317, 3047, 2928, 2864, 1450, 1373, 1265 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.84 (q, *J* = 2.5 Hz, 1 H), 2.48−2.58 (m, 1 H), 1.77−2.00 (m, 2 H), 1.50−1.71 (m, 4 H), 1.23−1.49 (m, 7 H), 1.04−1.17 (m, 2 H), 0.88−1.03 (m, 2 H), 0.90 (t, *J* = 6.4 Hz, 3 H), 0.83 (d, *J* = 6.0 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 57.7, 56.0, 42.6, 39.8, 35.9, 33.4, 27.4, 27.1, 21.3, 19.9, 19.1, 14.3.

Data for **26·HCl:** mp 280−282 °C (sealed capillary) {lit[31a] mp 285−286 °C}; $[\alpha]_D^{22}$ = +12.9° (*c* 0.34, MeOH) {lit[29d] $[\alpha]_D^{20}$ +12.9° (*c* 0.36, MeOH)}; IR (KBr) ν_{max} 3173, 3121, 2969, 2955, 2930, 2872, 2821, 1584 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.50 (br s, 1 H), 8.40 (br s, 1 H), 3.23−3.36 (m, 1 H), 2.86−3.05 (m, 1 H), 2.26−2.54 (m, 2 H), 1.97−2.25 (m, 4 H), 1.69−1.92 (m, 2 H), 1.31−1.67 (m, 6 H), 1.14−1.31 (m, 1 H), 0.92−1.04 (m, 1 H), 0.90 (t, *J* = 6.9 Hz, 3 H), 0.88 (d, *J* = 5.6 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 60.2, 58.1, 40.9, 34.8, 34.3, 29.1, 27.1, 25.2, 23.1, 20.5, 19.7, 19.1, 13.7. HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{26}N$ 196.2060; Found 196.2063.

2,5-Di-*epi*-*cis*-195A (50). 2,5-Di-*epi*-*cis*-195A was synthesized from the *cis*-octahydraquinolin-2-one **42** (30 mg, 0.18 mmol) according to the same procedure described above for preparation of *cis*-195A; purification by chromatography (10:1 CH_2Cl_2/MeOH, then 80:20:1 CH_2Cl_2/MeOH/^{i}PrNH$_2$) afforded 2,5-di-*epi*-*cis*-195A (13.2 mg, 38% over three steps, 51% based on recovered **42**) as a pale yellow oil. The starting lactam **42** (7.6 mg, 25%) was also recovered. Addition of concentrated aqueous HCl (2 drops) to a methanolic solution of **50**, followed by evaporation of the solvent, gave the corresponding hydrochloride salt (15.5 mg) as an off-white solid.

Data for **50:** $[\alpha]_D^{21}$ 0.0° (*c* 0.69, MeOH); IR (neat) ν_{max} 3298, 2928, 2865, 1458 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 2.88 (ddd, *J* = 11.6, 3.4, 3.4 Hz, 1 H), 2.67−2.79 (m, 1 H), 1.89 (m, 1 H), 1.65−1.80 (m, 3 H), 1.14−1.65 (m, 11 H), 0.91−1.10 (m, 2 H), 0.88 (t, *J* = 6.0 Hz, 3 H), 0.86 (d, *J* = 6.4 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 56.3, 49.0, 41.6, 40.0, 35.3, 33.3, 28.5, 26.3, 25.5, 19.3, 19.1, 18.4, 14.2.

Data for **50·HCl:** mp 178−182 °C (decomp); $[\alpha]_D^{21}$ +0.41° (*c* 0.73, MeOH); IR (CH_2Cl_2) ν_{max} 3051, 2955, 2870, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 9.42 (br s, 1 H), 9.30 (br s, 1 H, NH), 3.40−3.54 (m, 1 H), 3.00−3.18 (m, 1 H), 2.15−2.27 (m, 1 H), 2.05−2.16 (m, 1 H), 1.90−2.05 (m, 2 H), 1.23−1.89 (m, 11 H), 0.97−1.13 (m, 1 H), 0.93 (t, *J* = 7.0 Hz, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 55.7, 51.0, 37.4, 35.3, 34.1, 28.1, 27.9, 22.0, 18.8, 18.6, 16.9, 13.9. HRMS (EI-double focusing sector field) *m*/*z*: $[M]^+$ Calcd for $C_{13}H_{26}N$ 196.2060; Found 196.2061.

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■ ASSOCIATED CONTENT

Supporting Information

Copies of the ^{1}H and ^{13}C NMR spectra for all products, stereochemical assignment data for compounds **38**−**41** and **42**−**45**, and Cartesian coordinates for computed structures **46**. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b00621.

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Notes

The authors declare no competing financial interest.

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