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# Enantioselective Synthesis of Angularly Substituted 1-Azabicylic Rings: Coupled Dynamic Kinetic Epimerization and Chirality Transfer

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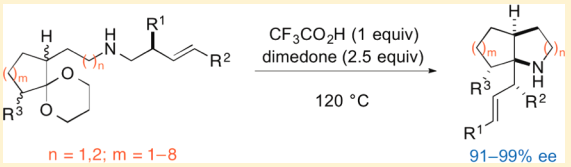
Supporting Information

**ABSTRACT:** A new strategy for enantioselective synthesis of azacyclic molecules in which dynamic kinetic equilibration of diastereomeric iminium ions precedes a stereochemistry-determining sigmatropic rearrangement is reported. The method is illustrated by the synthesis, in high enantiomeric purity (generally 95−99% ee), of a variety of 1-azabicyclic molecules containing angular allyl or 3-substituted 2-propenyl side chains adjacent to nitrogen and up to three stereogenic centers. In these products, the size of the carbocyclic ring is varied widely (5−12 membered); however, useful yields are obtained in forming 1-azabicyclic products containing only fused pyrrolidine and piperidine rings. Chirality transfer from substituents at carbons 1 and 2 of the 3-butenylamine fragment of the starting material is investigated, with methyl and phenyl substituents at the allylic position shown to provide exquisite stereocontrol (generally 98−99% chirality transfer). An attractive feature of the method is the ability to carry out the key transformation in the absence of solvent. Illustrated also is the high yielding conversion of four such products to a new family of bicyclic β-amino acids of high enantiomeric purity.




## INTRODUCTION

1-Azabicyclic rings having an angular substituent adjacent to nitrogen (**1**, Figure 1) have a variety of potential applications.

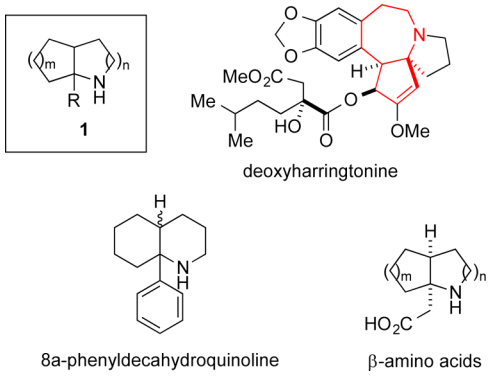



**Figure 1.** Angularly substituted 1-azabicyclic ring systems **1** and examples of compounds containing this ring system.

These ring systems are found in natural products exhibiting potentially useful therapeutic properties such as deoxyharringtonine[1] and in a few molecules of medicinal chemistry significance, such as 8a-phenyldecahydroquinolines (Figure 1).[2] One can also readily envisage applications of conformationally constrained β-amino acids of the type depicted in Figure 1 in peptidomimetics or as organocatalysts. Nonetheless, there are remarkably few reports of applications of angularly substituted nitrogen heterocycles **1**,[3] particularly in light of the presence of other substituted 1-azabicyclic nonaromatic heterocycles in marketed drugs and exploratory drug candidates.[4] The lack of general methods for the synthesis of heterocycles of type **1**, particularly in high enantiomeric purity, could be responsible for their limited use to date.[5]

We reported earlier a general method for the synthesis of racemic, angularly substituted, 1-azabicylic molecules **1**.[6] The method is illustrated in Scheme 1 for the preparation of *cis*-cyclopentapyrrolidine **4** from aminoketal **2**. In this synthesis, a mixture of aminoketal **2**, 1 equiv of trifluoroacetic acid (TFA), and 2.5 equiv of dimedone is heated for several hours at 120 °C. The tetrasubstituted iminium ion **A** is formed initially and upon heating undergoes [3,3]-sigmatropic equilibration with iminium ion isomer **B**. The inclusion of dimedone (5,5-dimethylcyclohexane-1,3-dione, **3**) selectively traps the less-stable formaldiminium ion isomer **B** to give presumably adduct **C**, which upon fragmentation delivers the *cis*-cyclopentapyrrolidine product **4**.[7] To aid in purification, this product is converted to benzyloxy (Cbz) derivative **5**, which was isolated in 86—96% yield. The exomethylene fragment of the iminium ion intermediate eventually emerges as the well-known dimedone-formaldehyde adduct **6**.

During the development of this method, we discovered that when the synthesis of the corresponding *cis*-octahydroindole **8** was carried out in $CD_3OD$ containing 3 equiv of $D_2O$, deuterium was incorporated into the angular methine (C3a) and C7 methylene positions of product **8**-$d_3$ (Scheme 2).[6] This deuterium incorporation signified that the initially formed iminium ion **D** equilibrated with enamonium ion iomers **E** and **F** more rapidly than formaldiminium ion intermediate **G** was trapped to yield *cis*-octahydroindole product **8**.

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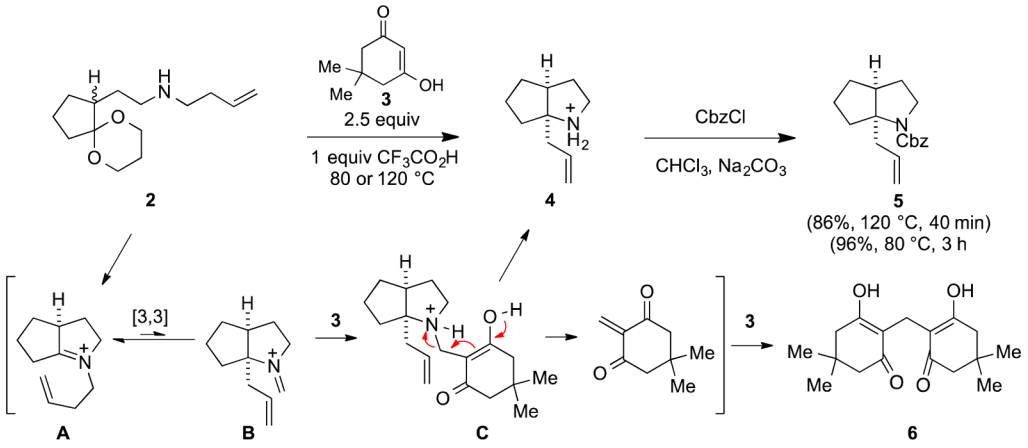
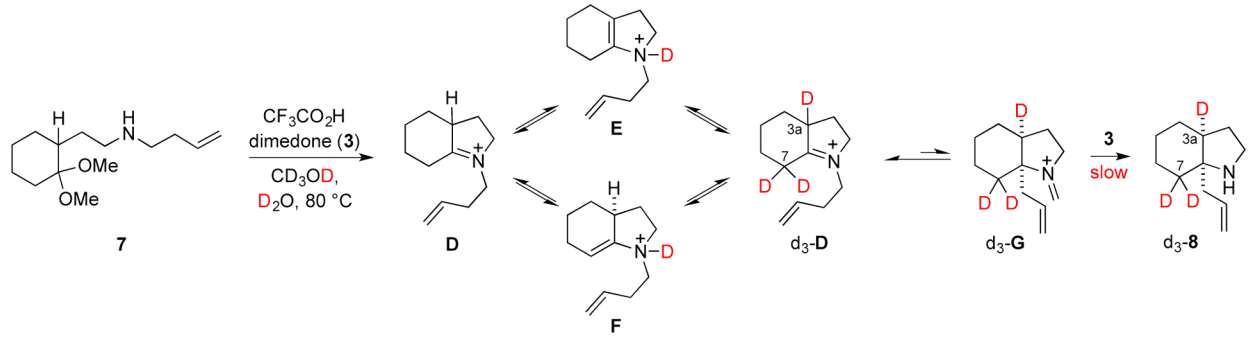
**Scheme 1. Methylene Transfer-Driven Cationic 2-Aza-Cope Rearrangement**

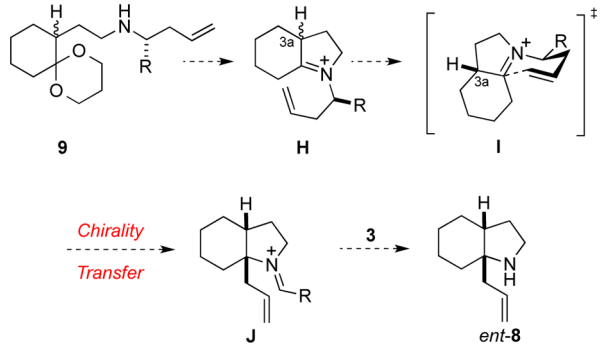



**Scheme 2. Deuterium Incorporation by Iminium/Enamonium Ion Tautomerization**




On the basis of the rapid pre-equilibrium that occurs between iminium ion and enamonium ion intermediates in this synthesis of angularly substituted heterocycles, we postulated that incorporating a nonracemic stereocenter on the homoallylic side chain of an aminoketal precursor such as **9** should result in the [3,3]-sigmatropic rearrangement occurring faster with one C3a epimer to deliver potentially one enantiomer of the azabicyclic product (Scheme 3). For this process to occur with high chirality transfer, the C3a epimers of iminium ion intermediate **H** must equilibrate rapidly, one epimer must preferentially undergo [3,3]-sigmatropic rearrangement, and dimedone trapping also must occur more rapidly than product iminium ion **J** equilibrates with its enantiomer.[8] At the outset, we anticipated that sigmatropic rearrangement via transition state geometry **I** would be preferred, because bond formation from the convex face and placement of the substituent R in a quasi-equatorial orientation should be favored.

**Scheme 3. Potential Synthesis of Enantiomerically Enriched *cis*-Octahydroindole 8 by Coupled Dynamic Kinetic Epimerization and Chirality Transfer**




In this article, we describe the development of this new strategy into a general method for enantioselective synthesis of angularly substituted 1-azabicyclic molecules.[9] Experiments that illuminate some of the mechanistic details of the cationic 2-aza-Cope rearrangement and other steps in the sequence are discussed also.

## RESULTS AND DISCUSSION

**Synthesis of Aminoketals Containing Enantiomerically Enriched 1-Substituted 3-Butenyl Fragments and Their Conversion to 1-Azabicyclic Products.** Our investigations began by preparing five aminoketal precursors **9** that varied in the nature of the homoallylic substituent. The synthesis begins with benzyl 2-oxocyclohexaneacetate (**11**),[10] which we found most convenient to prepare by fluoride-mediated alkylation of 1-(trimethylsiloxy)cyclohexene (**10**) with benzyl 2-bromoacetate (Scheme 4).[11] Ketalization of **11** catalyzed by scandium triflate yielded dioxolane derivative **12** in 68% overall yield from **10**. Cleavage of the benzyl ester by hydrogenolysis, followed by carbodiimide-promoted coupling with (*R*)-1-substituted-3-butenylamines **13a−e** provided amides **14a−e**. The enantiomerically enriched (*R*)-1-substituted-3-butenylamines **13a−e** were available in three steps from the corresponding aldehyde and (*R*)-phenylglycinol by the method of Vilaivan and co-workers.[12,13] Reduction of amide intermediates **14a−e** with lithium aluminum hydride delivered aminoketals **9a−e** in good overall yields from ketal ester **12**.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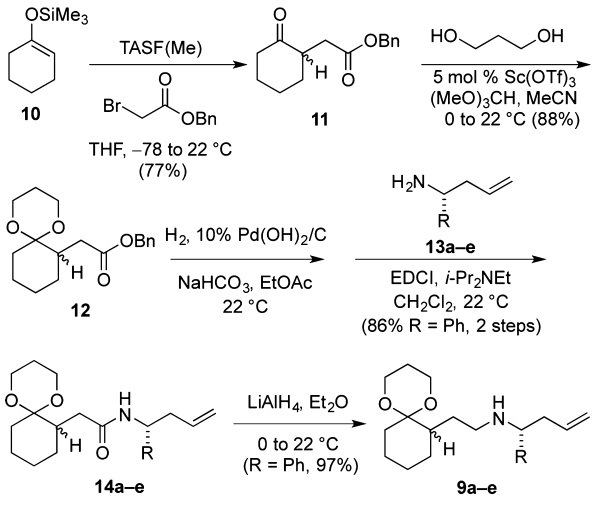
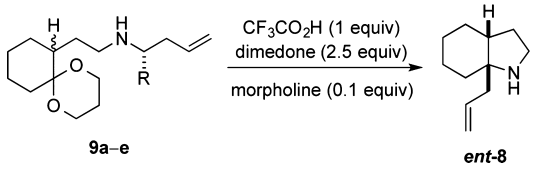
**Scheme 4. Synthesis of Aminoketals 9**




In our initial study, the reaction temperature and the effect of the homoallylic substituent on chirality transfer were examined (Table 1). All reactions were conducted neat by heating

**Table 1. Enantioselective Synthesis of Octahydroindole 8 from Aminoketals 9a–e**



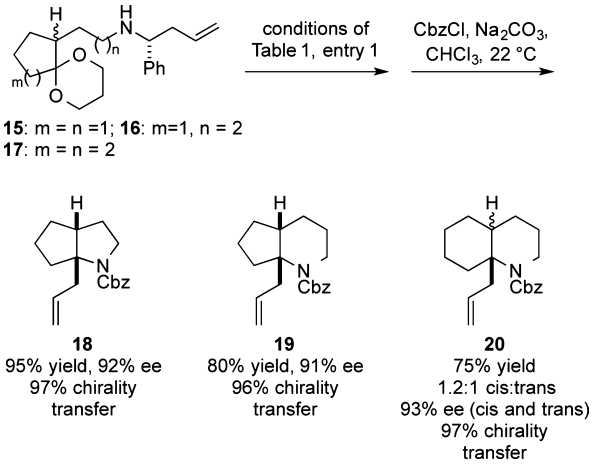

| entry | R | ee (%) **9**[a] | temp (°C) | time (h) | yield (%) | ee (%) *ent*-**8**[b] | chirality transfer (%) |
|---|---|---|---|---|---|---|---|
| 1 | Ph (**9a**) | 93 | 120 | 5 | 92 | 89 | 96 |
| 2 | Ph (**9a**) | 93 | 100 | 22 | 84 | 88 | 95 |
| 3 | Ph (**9a**) | 93 | 80 | 1 | 0 | | |
| 4 | 4-OMeC$_6$H$_4$ (**9b**) | 92 | 120 | 5 | 92 | 82 | 89 |
| 5 | 4-ClC$_6$H$_4$ (**9c**) | 94 | 120 | 5 | 90 | 89 | 95 |
| 6 | 2-ClC$_6$H$_4$ (**9d**) | 94 | 120 | 5 | 88 | 87 | 93 |
| 7 | *i*-Pr (**9e**) | 46 | 120 | 22 | 51 | 24 | 52 |

[a]Enantiomeric purity of the homoallylic amine fragment of **9** was determined by enantioselective HPLC. [b]Enantiomeric purity was determined by enantioselective HPLC analysis of the corresponding *N*-benzoyl derivative.

mixtures of the aminoketal **9**, trifluoroacetic acid (TFA) (1.0 equiv), and dimedone (2.5 equiv). In these small-scale reactions, 0.1 equiv of morpholine was added to ensure that excess TFA was not present, because dimedone is decomposed at elevated temperatures in the presence of this acid. At 120 °C, phenyl-substituted aminoketal **9a** was converted to *cis*-octahydroindole *ent*-**8** in 92% yield with 96% chirality transfer (entry 1).[14] When this reaction was conducted at 100 °C, the rearrangement was significantly slower (entry 2); however, the extent of chirality transfer was not enhanced. No reaction was observed at 80 °C after 1 h (entry 3). The degree of chirality transfer was affected to only a small extent by the incorporation of *p*-Cl or *o*-Cl substituents or a *p*-OMe group in the aryl fragment (entries 4–6). Most notable was the significant decrease in chirality transfer observed when the homoallylic substituent was isopropyl (entry 7). In addition, carrying out the reaction in $CD_3OD$ at 110 °C in a sealed tube (1 equiv of TFA and 2.5 equiv dimedone) provided *ent*-**8** in 75% yield, however with unsatisfactory (68%) chirality transfer. The absolute configuration of *ent*-**8** was secured by single crystal X-ray analysis of its hydrobromide salt.

We briefly investigated the scope of this enantioselective construction of allyl-substituted 1-azabicyclic molecules by examining three additional precursors containing a (*R*)-1-phenyl-3-butenyl fragment. Aminoacetal substrates **15**–**17** were prepared by sequences identical (or analogous) to that reported in Scheme 4.[15] As summarized in Scheme 5, *cis*-

**Scheme 5. Enantioselective Synthesis of Allyl-Substituted Heterocycles 18–20**




hexahydrocyclopenta[*b*]pyrrole carbamate **18** and *cis*-octahydrocyclopenta[*b*]pyridine carbamate **19** were formed in 95% and 80% yield from precursors **15** and **16**, respectively, and with 96–97% chirality transfer. In each case, only the cis steroisomer of the product was detected. In contrast, decahydroquinoline carbamate **20** was produced as a nearly 1:1 mixture of cis and trans epimers. These isomers could be separated, and each was shown to have an enantiomeric purity of 93% ee, corresponding to 97% chirality transfer. The absolute configuration of **18** was determined by single crystal X-ray analysis of the hydrobromide salt of the parent hexahydrocyclopenta[*b*]pyrrole;[9] the absolute configuration for **19** and **20** was assigned in analogy to that of related products **8** and **18**.

**Synthesis of 2-Substituted 3-Butenylamines of High Enantiomeric Purity.** Although chirality transfer was typically high with substrates having an aryl substituent at the homoallylic position, we entertained the possibility that this selectivity might be even higher with substrates having a substituent at the allylic carbon. We initiated these studies by developing an enantioselective synthesis of (*R*)-2-phenylbut-2-enylamine. To have convenient access to both enantiomers, we chose a route wherein the stereocenter is set by a catalytic enantioselective reaction using a catalyst for which both enantiomers are commercially available (Scheme 6). Through the use of a microwave modification[16] of a method first introduced by Trost,[17] molybdenum-catalyzed enantioselective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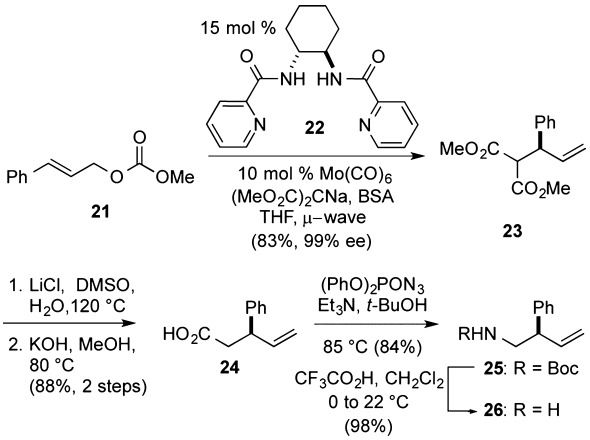
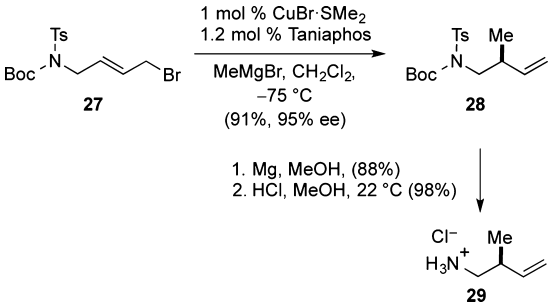
**Scheme 6. Synthesis of (*R*)-2-Phenylbut-2-en-1-amine**




allylic alkylation of cinnamyl methyl carbonate (**21**) with dimethyl sodiomalonate to give (*S*)-pentenoate **23** in high yield and 99% ee. Krapcho decarboxylation of the malonate,[18] followed by saponification of the carboxylic ester delivered (*R*)-acid **24**.[19] Curtius rearrangement of **24** with diphenylphosphoryl azide in *t*-BuOH, followed by cleavage of the Boc group with trifluoroacetic acid delivered (*R*)-2-phenylbut-2-enylamine (**26**) in 83% yield from the precursor acid. This sequence has been demonstrated on multigram scale.

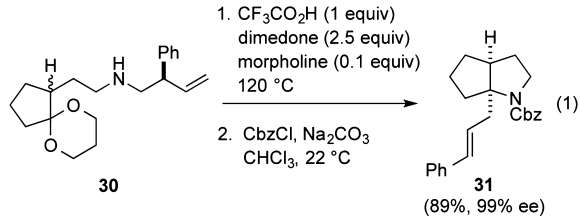
To explore the effect of the 2-butenyl substituent on chirality transfer of reactions of the corresponding aminoacetals, a short synthesis of (*S*)-2-methylbut-3-en-1-ammonium chloride (**29**) was developed also (Scheme 7). Enantioselective allylic

**Scheme 7. Synthesis of (*S*)-2-Methylbut-3-en-1-ammonium Chloride**



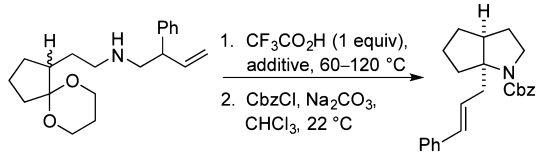

alkylation of allylbromide **27** (available in one step from (*E*)-1,4-dibromobut-2-ene)[20] with methylmagnesium bromide, catalyzed by 1 mol % CuBr·$SMe_2$ and 1.2 mol % Taniaphos delivered allylic carbamate **28** in 91% yield and in 95% ee.[21] Subsequent removal of the tosyl and *tert*-butoxycarbonyl groups gave the enantiomerically enriched butenylamine hydrochloride salt **29** in 78% overall yield from allylic bromide **27**.

**Synthesis of Enantiomerically Enriched Aminoacetal Precursors Containing 2-Substituted 3-Butenyl Fragments and Their Conversion to 1-Azabicyclic Products.** From homoallylic amine **26** or ammonium salt **29**, a variety of aminoacetal precursors were prepared from the corresponding cycloalkanone acetal acids by the general method shown in Scheme 4.[15] Our initial studies focused on the reaction of aminoacetal **30** and used the conditions utilized in our earlier studies with the analogous substrate **15** having the phenyl substituent at the homoallylic position. In this way, *cis*-hexahydrocyclopenta[*b*]pyrrole carbamate **31** was formed in 89% yield and a remarkable 99% ee, corresponding to complete chirality transfer (eq 1). When the morpholine buffer was omitted, the yield was depressed slightly (80%).




We next examined whether dimedone was essential to the success of the transformation shown in eq 1 (Table 2). In the

**Table 2. Reaction of Aminoacetal 30 with Trifluoroacetic Acid to Form Product 31 in the Presence of Various Additives[a]**




| entry | additive | temp (°C) | time (h) | yield (%) |
|---|---|---|---|---|
| 1[b] | dimedone (2.5 equiv) | 120 | 0.5 | 80 |
| 2 | dimedone (2.5 equiv), morpholine (0.1 equiv) | 120 | 0.5 | 89 |
| 3[c] | none | 120 | 0.5 | 21 |
| 4 | 1,3-propanediol (3 equiv) | 120 | 0.5 | 21 |
| 5 | MeOH[d] | 60 | 24 | 24 |
| 6 | 5% $H_2O$ in MeOH[d] | 60 | 24 | 7 |

[a]Reactions used a 1:1 molar ratio of *rac*-**30** and trifluoroacetic acid and the indicated additive(s). [b]Reactant **30** was prepared from (*S*)-butenylamine **26** (99% ee). [c]When enantioenriched **30** was used, product **31** was formed with >98% chirality transfer. [d]Methanol was the solvent in these reactions; the starting concentration of *rac*-**30** was 0.5 M.

absence of dimedone (and morpholine), product **31** was formed in 21% yield (entry 3). On the assumption that 1,3-propanediol was the agent trapping what would be in this case a formaldiminium ion of the 2-aza-Cope rearrangement product, the reaction was carried out in the presence of 3 equiv of this additive. However, the yield of **31** was not improved (entry 4). Methanol was considered also to be a potential trap for the formaldiminium ion intermediate; however, carrying out the reaction in methanol did not result in appreciably higher yields after 24 h at 60 °C (entries 5 and 6). Although we believe that other trapping agents as efficacious as dimedone could likely be found, we decided to explore instead the scope of the efficient, highly enantioselective, reaction shown in eq 1.

A comparison of phenyl and methyl stereocontrolling groups and results of our initial exploration of this route to functionalized 1-azacyclic ring systems is summarized in Table 3. Angularly substituted *cis*-hexahydropenta[*b*]pyrroles **31**, *cis*-octahydroindoles **32**, and *cis*-octahydrocyclopenta[*b*]-pyridines **33** containing a (*E*)-3-substituted-2-propenyl side chain were obtained in good yields (71–89% yields) and high 95–99% ee (entries 1–6). Chirality transfer was complete,


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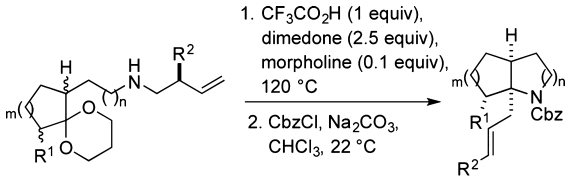
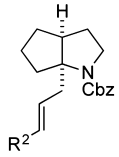
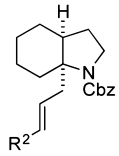
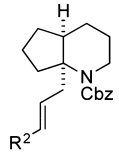
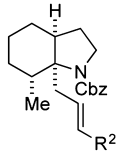
**Table 3. Enantioslective Synthesis of 1-Azabicyclic Molecules Containing an Angular 3-Phenyl or 3-Methylpropenyl Substituents**




| entry | product | $R^2$ | yield (%) | ee (%)[a] | chirality transfer (%) |
|---|---|---|---|---|---|
| 1 |  | Ph, **31a** | 89 | 99 | >98 |
| 2 | | Me, **31b** | 73 | 95 | >98 |
| 3 |  | Ph, **32a** | 82 | 99 | >98 |
| 4 | | Me, **32b** | 74 | 95 | >98 |
| 5 |  | Ph, **33a** | 89 | 99 | >98 |
| 6 | | Me, **33b** | 71 | 95 | >98 |
| 7 |  | Ph, **34a** | 81 | 99 | >98 |
| 8 | | Me, **34b** | 70 | 91[b] | 96 |

[a]Enantiomeric excess was determined by enantioselective HPLC. [b]This product was a 9:1 mixture of epimers at the angular methine carbon.

within experimental uncertainty, regardless of the nature of the allylic substituent on the butenyl fragment. Carrying out the synthesis of **31a** (87% yield, 99% ee) on a gram scale gave the product in comparable yield with no reduction in enantioselectivity, demonstrating the practicality of this method. The high-yield formation of *cis*-octahydroindole **34a** as exclusively a single C7 methyl epimer indicates that both stereogenic centers of the carbocyclic aminoacetal precursor epimerized by iminium/enamonium tautomerization prior to 2-aza-Cope rearrangement/dimedone trapping. In this case, the methyl-substituted aminoketal provided *cis*-octahydroindole **34b** in slightly diminished diastereoselectivity (9:1 dr) and chirality transfer (96%, entry 8). The absolute configuration of *cis*-octahydrocyclopenta[*b*]pyridine **33a** was determined by X-ray analysis of the corresponding secondary amine hydrobromide salt,[9] whereas the absolute configuration of products **31a** and **32a** was determined by chemical correlation with azacyclic products **18** and **8**. Absolute configurations of the other azabicyclic products reported in Table 3 were assigned by analogy.

Results of our further investigations of the scope of this chemistry using precursors containing a (*R*)-2-phenylbutenylamine fragment are summarized in Table 4. At 120 °C, decahydroquinoline **35** was formed as a 1.7:1 mixture of cis and trans stereoisomers (entry 1). Stereoselectivity was increased slightly when the reaction was conducted in methanol at 60 °C (entry 2).[22] Both the *cis*- and *trans*-decahydroquinoline products were formed in 99% ee. 1-Azabicyclic products containing an (*E*)-3-phenyl-2-propenyl side chain adjacent to nitrogen can be prepared with various sized rings carbocyclic rings (entries 3−5). The cis steroisomer of the product was strongly favored when the azacyclic ring is five-membered. Extension of this chemistry to the synthesis of 1-azabicyclic molecules in which the azacyclic unit is a medium ring appears problematic. For example, decahydrocyclopenta[*b*]azocine **38** was formed in only 16% yield after an extended reaction time of 22 h at 120 °C (entry 6). We attribute this low conversion to low efficiency in forming the initial 8-membered-ring iminium ion.

As the stereocontrolling step in this construction of 1-azacyclic molecules is an iminium ion [3,3]-sigmatropic rearrangement, the organized six-membered chair-transition structure should allow the geometry of a double bond in the starting material to be transformed to a new stereocenter at C1 of the allylic side chain of the product. To examine this possibility, three unsaturated aminoacetal substrates, **39a−c**, were prepared from (*R*)-2-phenyl-3(*E*)-alkenylamines having Me, Ph, or cyclohexyl substituents at C4. Exposure of aminoketal **39a**, prepared from (*R*)-2-phenyl-3(*E*)-pentenylamine of 87% ee, to trifluoroacetic acid at 120 °C for 30 min, followed by Cbz protection gave *cis*-hexahydrocyclopenta[*b*]-pyrrole **40** as a single stereoisomer in 75% yield (Scheme 8). The enantiomeric purity (87% ee) of **40** indicated again that chirality transfer was essentially complete. Similar results were obtained in the formation of products **41** and **42**, with the exception of their higher enantiomeric purity (99% ee) resulting from the greater diastereomeric purity of precursors **39b** and **39c**.[23] However, the yields of **41** and **42** were diminished, presumably because the larger size of the phenyl and cyclohexyl substituents results in destabilizing steric interactions in the iminium ion [3,3]-sigmatropic rearrangement.

**Synthesis of Uncommon *β*-Amino Acids in High Enantiomeric Purity.** *β*-Amino acids are valuable building blocks in peptide-based drug design, as proteolytic degradation is greatly reduced in vivo, increasing their bioavailability.[24] For example, replacing proline with a more rigid analog, octahydroindole-2-carboxylic acid, has been exploited in several bradykinin $B_2$ antagonists to improve both enzymatic stability and potency.[25] Moreover, proline-based catalysts have been shown to be powerful catalysts for a wide variety of transformations[26] with recent examples exemplifying 3-pyrrolidinecarboxylic acid catalysts.[27] Oxidative cleavage of the angular-allyl side chain of the 1-azabicyclic molecules


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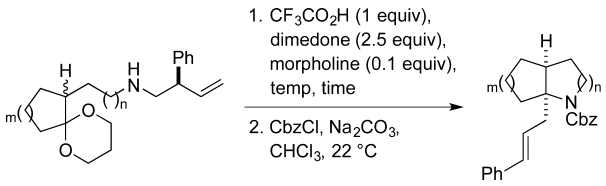
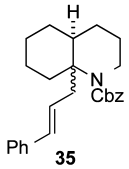
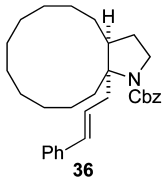
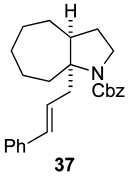
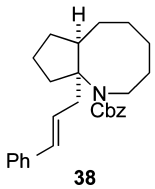
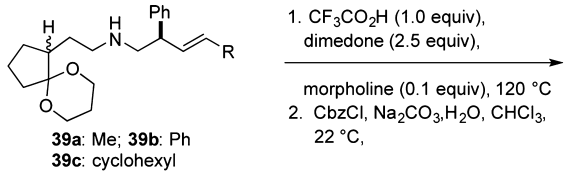
**Table 4. Further Scope of the Enantioselective Synthesis of 1-Azabicyclic Molecules Containing an Angular 3-Phenylpropenyl Substituent**



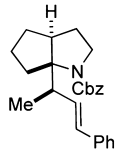

| entry | product | temp (°C) | time (h) | dr (cis:trans)[a] | yield (%) | ee (%)[b] |
|---|---|---|---|---|---|---|
| 1 |  **35** | 120 | 0.5 | 1.7:1 | 86 | 99[c] |
| 2 | | 60[c] | 20 | 2:1 | 72 | 99[d] |
| 3 |  **36** | 120 | 0.5 | 9:1 | 74 | 99[e] |
| 4 | | 60[c] | 20 | 15.2:1 | 70 | 99[e] |
| 5 |  **37** | 120 | 0.5 | >10:1 | 79 | 99 |
| 6 |  **38** | 120 | 22 | >10:1 | 16[f] | nd |

[a]Diastereoselectivities were determined by analysis of the $^1$H NMR spectra. [b]Enantiomeric excess was determined by enantioselective HPLC. [c]Reaction carried out in methanol (0.5 M). [d]Both isomers were obtained in 99% ee. [e]Enantiomeric excess of the major isomer; the enantiomeric excess of the minor isomer was not determined. [f]Enantiomeric excess was not determined.

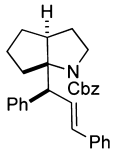
**Scheme 8. Enantioselective Synthesis of *cis*-Hexahydrocyclopenta[*b*]pyrrole Carbamates Having Chiral Allylic Side Chains**



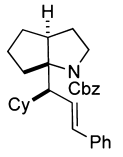

**39a**: Me; **39b**: Ph
**39c**: cyclohexyl



**40**
75% yield,
87% ee,
>98% chirality
transfer



**41**
65% yield,
99% ee,
>98% chirality
transfer



**42**
49% yield,
99% ee,
>98% chirality
transfer

prepared in the manner reported herein would provide a variety of new, potentially useful, *β*-amino acids. To demonstrate this potential, we optimized a high-yielding, two-step sequence to achieve this objective. Application of this sequence to prepare four Cbz-protected *β*-amino acids is reported in Scheme 9.

**Mechanistic Discussion.** Our current understanding of the high transfer of chirality observed in the azacyclic construction reported in this article is derived in part from our studies of the transformation of aminoketal **30** to *cis*-hexahydrocyclopenta-[*b*]pyrrole **47**. The success of this dynamic kinetic epimerization rearrangement sequence was predicated on iminium/enamonium equilibration occurring faster than the [3,3]-sigmatropic rearrangement step. The rapid tautomerization of iminium ion and enamonium ion intermediates **K**–**M** was confirmed to occur more rapidly than the 2-aza-Cope rearrangement when the reaction of aminoketal **30** was carried out in $CD_3OD$ (Scheme 10). As expected, azabicyclic carbamate **31** was isolated with deuterium incorporated in the angular C3a and C6 methylene positions; analysis of this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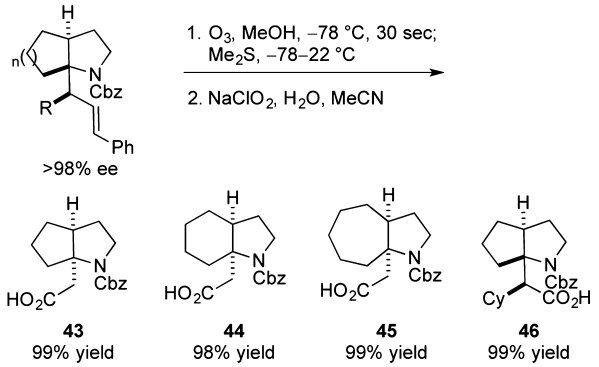
**Scheme 9. Synthesis of Four Representative Cbz-Protected *β*-Aminoacids**




product by electrospray mass spectrometry indicated an 8:4:0:1 ratio of $d_3$:$d_2$:$d_1$:$d_0$ deuterium incorporation.[28]

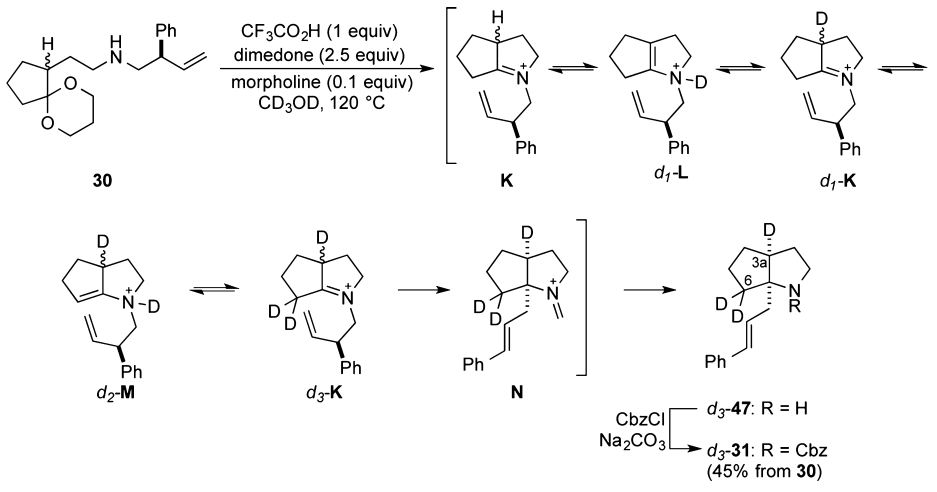
We next probed the reversibility of the aza-Cope rearrangement and methylene transfer steps (Scheme 11). The irreversibility of the methylene transfer step was demonstrated by heating secondary amine **47** with dimedone–formaldehyde adduct **6** (1.25 equiv), trifluoroacetic acid (1 equiv), and morpholine (0.1 equiv) at 120 °C in $CD_3OD$ for 48 h. Benzyloxycarbonyl protection of recovered **47** and mass spectrometric analysis showed that deuterium had not been incorporated. In contrast, heating *cis*-hexahydrocyclopenta[*b*]-pyrrole **47** in $CD_3OD$ at 120 °C for 24 h with paraformaldehyde (3 equiv), trifluoroacetic acid (1 equiv), and morpholine (0.1 equiv), followed by the addition of excess dimedone at 120 °C provided, after Cbz protection, carbamate **31** containing extensive deuterium incorporation ($d_3$:$d_2$:$d_1$:$d_0$ = 36:15:2:1). This latter result establishes that *in the absence of dimedone*, iminium ion isomers **K** and **N** (see Scheme 10) equilibrate under the reaction conditions.

To gain additional insight into this chemistry, the reaction of amino acetal *ent*-**48** with 1 equiv of TFA was studied by NMR (Scheme 12). Within 3 min at room temperature, *ent*-**48** was converted to a 1:1 mixture of diastereomeric bicyclic isomers **49** and **50**. This mixture was essentially unchanged after 12 h at room temperature. At temperatures above 40 °C, loss of 1,3-propanediol occurred to generate a mixture of products. The major component is iminium ion **O** (diagnostic $^{13}C$ NMR signal at 221 ppm), with additional products assigned as enamonium ions **P** and **Q** (diagnostic vinylic $^{13}C$ NMR signals between 132–123 ppm). This mixture was largely unchanged after heating at 60 °C for 12 h or at 120 °C for 5 min. Addition of excess dimedone to the latter sample and further heating at 130 °C generated *ent*-**51** as the major azacyclic product.

On the basis of the studies reported in Schemes 10–12, we propose the following mechanism (Scheme 13). In the presence of 1 equiv of TFA, an aminoketal such as **30** is transformed at elevated temperatures, by way of enamonium tautomer **L**, into an equilibrium mixture composed largely of tetrasubstituted iminium ions **R** and **S**. In the slow step of the sequence, iminium ion diastereomer **S** preferentially undergoes [3,3]-sigmatropic rearrangement via favored chair-transition structure **T** having the phenyl substituent pseudoequatorial to give *cis*-hexahydrocyclopenta[*b*]pyrrole formaldiminium ion **U**. The exquisite chirality transfer observed in the transformations reported herein requires that intermediate **U**, once formed, does not equilibrate with isomers **S** and **R**, because [3,3]-sigmatropic rearrangement of the latter (vide infra) would generate *ent*-**U** and erode enantioselectivity. Thus, trapping of intermediate **U** by dimedone and fragmentation of the dimedone adduct must be irreversible to form the 3a*S*,6a*R* product **47** in high enantioselectivity.[29]

The mechanism proffered in Scheme 13 ascribes the high chirality transfer (>98%) observed in the transformation of **30** to **47** to preferential [3,3]-sigmatropic rearrangement of iminium ion diastereomers **S** via transition structure **T**. As depicted in Figure 2, *ent*-**47** would be the result of [3,3]-sigmatropic rearrangement of diastereomer **R** from the convex face via boat geometry **V**.[30] The near perfect chirality transfer observed in forming **47** is consistent with transition structure **V** being at least 3 kcal/mol (more likely 3.5 kcal/mol) higher in energy than that of the chair-transition structure **T**.[31] In addition to the high enantioselectivity observed in forming *cis*-hexahydrocyclopenta[*b*]pyrrole **47**, the side chain of **47** is introduced with high *E* stereoselectivity. Quantitative HPLC analysis calibrated with an authentic sample of the (*Z*)-3-phenyl-2-propenyl isomer of the Cbz derivative **30**[32] demonstrated that stereoselectivity in forming product **47** having a (*E*)-3-phenyl-2-propenyl side chain was 150:1. This

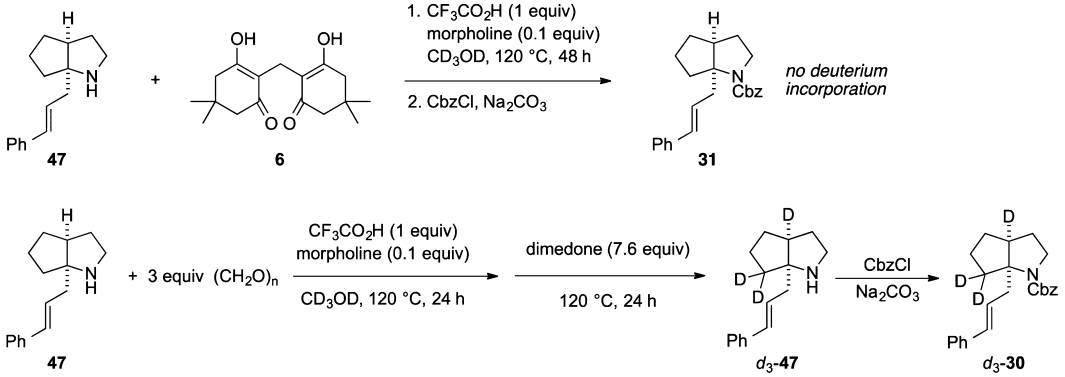
**Scheme 10. Deuterium Incorporation in *cis*-Hexahydrocyclopenta[*b*]pyrrole 47 via Rapid Iminium/Enamonium Ion Equilibratium**



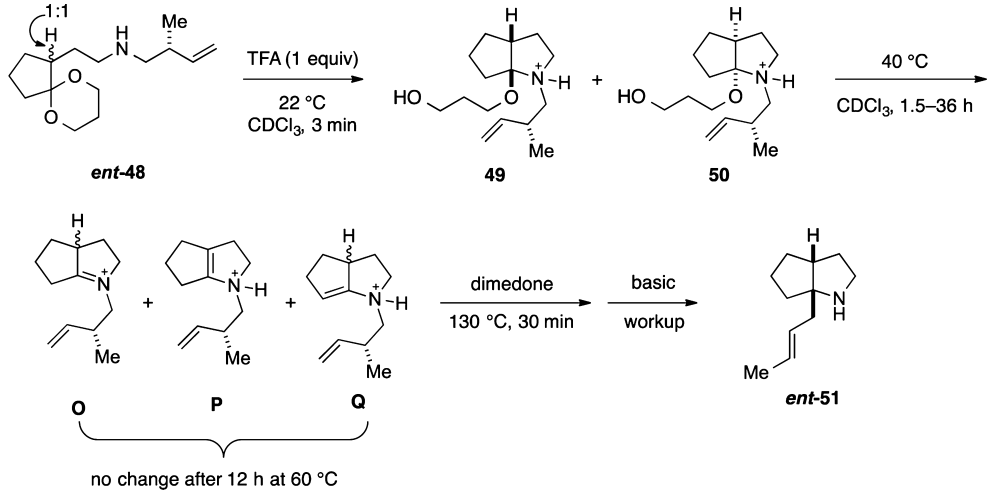


dx.doi.org/10.1021/jo4018099 | J. Org. Chem. 2013, 78, 9929–9948

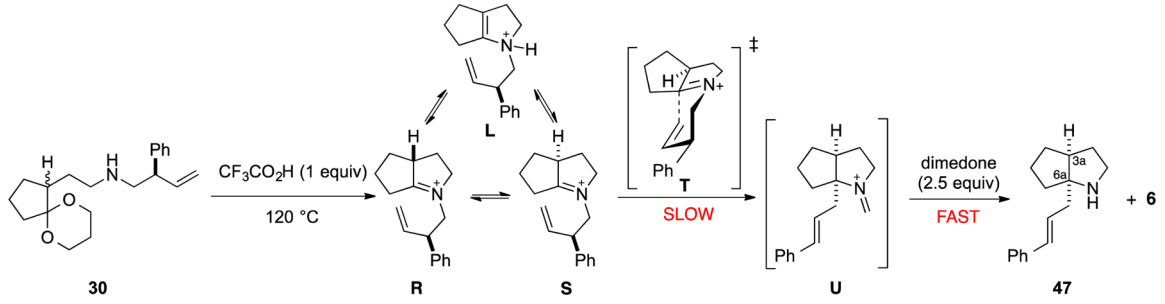
**Scheme 11. Probing the Reversibility of the Aza-Cope Rearrangement and Dimedone-Trapping Steps**




**Scheme 12. Intermediates Formed During the Formation of *cis*-Hexahydrocyclopenta[*b*]pyrrole *ent*-51**




**Scheme 13. Proposed Mechanism for the Formation of (3a*S*,6a*R*)-*cis*-Hexahydrocyclopenta[*b*]pyrrole 47 from Amino Acetal 30**




isomer ratio establishes that chair-transition structure **W** for [3,3]-sigmatropic rearrangement of iminium ion diastereomer **R** is similarly disfavored (by 3.9 kcal/mol relative to the favored transition structure **T**).

## ■ CONCLUSIONS AND OUTLOOK

In summary, a method of some generality for the enantioselective synthesis of angularly substituted 1-azabicyclic structures having up to three stereocenters is reported. This synthesis illustrates a new strategy for enantioselective synthesis of azacyclic molecules in which dynamic kinetic equilibration of diastereomeric iminium ions precedes a stereochemistry-determining sigmatropic rearrangement. Critical to the success of this method is the facility of iminium ion/enamonium ion interconversions, and identifying an irreversible step—in this case trapping of the less-stable iminium isomer of a 2-aza-Cope equilibration by reaction with dimedone—to dictate stereoselection.

The method was illustrated by the enantioselective synthesis of a variety of 1-azabicyclic molecules containing angular allyl or 3-substituted 2-propenyl side chains. In these structures, the size of the carbocyclic ring was varied widely (5−12 membered); however, useful yields were obtained in forming bicyclic products containing only fused pyrrolidine and piperidine rings. A notable aspect of the method is formation of the structurally rare 1-azacyclic products in high enantiomeric purity (95−99% ee). Also demonstrated is the high yielding conversion of four such products to a new family of bicyclic $\beta$-amino acids of high enantiomeric purity, molecules of potential utility for the synthesis of peptidomimetics, and


dx.doi.org/10.1021/jo4018099 | J. Org. Chem. 2013, 78, 9929−9948

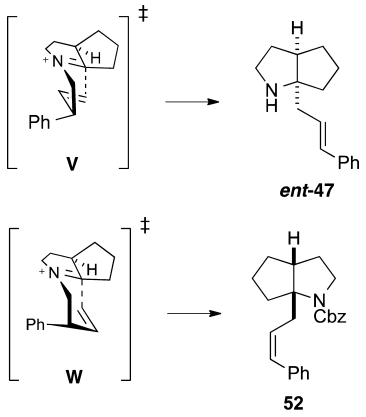



**Figure 2.** Higher energy pathways leading to azacyclic products *ent*-**47** and **52**.

scaffolds for medicinal chemistry (Scheme 9). An attractive feature of the method is the ability to carry out the key transformation in the absence of solvent. An unappealing feature of the method as currently practiced is the stoichiometric formation of the dimedone-formaldehyde adduct. The potential to mitigate this drawback by identifying alternate, more attractive, iminium ion trapping steps is suggested by preliminary studies but to date has not been realized in a high-yielding manner.

## EXPERIMENTAL SECTION

**Preparation of Aminoketals Containing a Homoallylic Stereogenic Center.** *General Procedure A for Oxidative Cleavage of the Chiral Auxiliary. (R)-1-Phenylbut-3-en-1-amine (**13a**).*[12] Lead acetate (4.50 g, 10.1 mmol) was added to a solution of (2*R*)-2-phenyl-2-[(1′*R*)-1′-phenylbut-3′-enylamino]ethanol[12] (2.26 g, 8.45 mmol), $CH_2Cl_2$ (15 mL), and MeOH (15 mL) at 0 °C. The mixture was stirred at 0 °C for 30 min. Hydroxylamine hydrochloride (5.87 g, 84.5 mmol) was added, and the mixture was stirred at 0 °C for 30 min before concentration in vacuo. The residue was washed with hexanes (50 mL) and suspended in $CH_2Cl_2$ (50 mL) followed by filtration of the lead precipitate. The filtrate was extracted with 1 N HCl (3 × 30 mL). The combined aqueous layers were washed with $Et_2O$ (30 mL), treated with 10% NaOH until pH 14, and extracted with $Et_2O$ (30 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), and concentrated in vacuo to afford **13a** as a pale yellow oil (890 mg, 6.08 mmol, 72%). Characterization data were consistent with previously reported values.[12] HPLC analysis indicated an enantiomeric excess of 93% [CHIRALCEL OD-H column; flow, 0.5 mL/min; hexanes:*i*-PrOH:$Et_2NH$ = 900:100:1; $\lambda$ = 254 nm; major enantiomer $t_R$ = 10.5 min; minor enantiomer $t_R$ = 14.3 min]: $[\alpha]^{23}_{589}$ + 42.5, $[\alpha]^{23}_{577}$ +43.2, $[\alpha]^{23}_{546}$ +50.8, $[\alpha]^{23}_{435}$ +85.5 (*c* 1.15, $CH_2Cl_2$).

*(R)-1-(4-Methoxyphenyl)but-3-en-1-amine (**13b**).* Following general procedure A, **13b** (1.08 g, 6.11 mmol, 74% yield) was obtained as a yellow oil. Characterization data were consistent with previously reported values.[12] HPLC analysis indicated an enantiomeric excess of 92% [CHIRALCEL OD-H column; flow, 0.5 mL/min; hexanes:*i*-PrOH:$Et_2NH$ = 900:100:1; $\lambda$ = 254 nm; major enantiomer $t_R$ = 13.1 min; minor enantiomer $t_R$ = 16.8 min]: $[\alpha]^{23}_{589}$ +31.0, $[\alpha]^{23}_{577}$ +32.2, $[\alpha]^{23}_{546}$ +36.7, $[\alpha]^{23}_{435}$ +66.5 (*c* 2.64, $CH_2Cl_2$).

*(R)-1-Butyl-3-butenyl-1-(4-chlorophenyl)amine (**13c**).* Following general procedure A, **13c** (1.21 g, 6.70 mmol, 72% yield) was obtained as a colorless oil. Characterization data were consistent with previously reported values.[12] HPLC analysis indicated an enantiomeric excess of 94% [CHIRALCEL AD column; flow, 0.5 mL/min; hexanes:*i*-PrOH:$Et_2NH$ = 950:50:1; $\lambda$ = 254 nm; major enantiomer $t_R$ = 14.6 min; minor enantiomer $t_R$ = 14.0 min]: $[\alpha]^{23}_{589}$ +38.1, $[\alpha]^{23}_{577}$ +39.6, $[\alpha]^{23}_{546}$ +44.9, $[\alpha]^{23}_{435}$ +78.5 (*c* 2.13, $CH_2Cl_2$).

*(R)-1-Butyl-3-butenyl-1-(2-chlorophenyl)amine (**13d**).* Following general procedure A, **13d** (1.10 g, 6.11 mmol, 73% yield) was obtained as a colorless oil. Characterization data were consistent with previously reported values.[12] HPLC analysis indicated an enantiomeric excess of 94% [CHIRALCEL AD column; flow, 0.5 mL/min; hexanes:*i*-PrOH:$Et_2NH$ = 950:50:1; $\lambda$ = 254 nm; major enantiomer $t_R$ = 11.9 min; minor enantiomer $t_R$ = 11.4 min]: $[\alpha]^{23}_{589}$ +72.2, $[\alpha]^{23}_{577}$ +75.4, $[\alpha]^{23}_{546}$ +87.1, $[\alpha]^{23}_{435}$ +155 (*c* 1.27, $CH_2Cl_2$).

*General Procedure B for the Fluoride-Mediated Alkylation of Enoxysilanes. Benzyl 2-(2-Oxocyclohexyl)acetate (**11**).* To a stirred suspension of TASF(Me) (330 mg, 1.20 mmol) in THF (1.2 mL) at −78 °C was added a solution of 1-cyclohexenyloxytrimethylsilane (200 mg, 1.20 mmol) and benzyl 2-bromoacetate (0.22 mL, 1.4 mmol) in THF (1.8 mL) dropwise via syringe over 5 min. The resulting mixture was stirred at room temperature for 24 h and then diluted with hexanes (25 mL), washed with $H_2O$ (10 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude residue by flash chromatography on silica gel (9:1 hexanes:EtOAc) provided **11** as a colorless oil (0.22 g, 0.91 mmol, 77%): $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.37−7.30 (m, 5H), 5.18−5.08 (m, 2H), 2.94−2.80 (m, 2H), 2.48−2.32 (m, 2H), 2.26−2.07 (m, 3H), 1.92−1.85 (m, 1H), 1.79−1.58 (m, 2H), 1.44 (qd, *J* = 12.6, 3.7 Hz, 1H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 210.8, 172.4, 136.0, 128.5, 128.09, 128.05, 66.2, 47.1, 41.8, 34.4, 33.8, 27.7, 25.1; IR (film, $cm^{-1}$) 3066, 3035, 2937, 2861, 1733, 1710. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 72.89; H, 7.47.

*General Procedure C for Ketalization of Cycloalkanones. (1,5-Dioxaspiro[5.5]undec-7-yl)acetic Acid Benzyl Ester (**12**).* To a solution of ketoester **11** (3.9 g, 16 mmol), 1,3-propanediol (22 mL, 39 mmol), and trimethylorthoformate (8.6 mL, 78 mmol) in acetonitrile (160 mL) at 0 °C was added scandium triflate (77 mg, 0.16 mmol). The reaction was maintained at 0 °C for 30 min and then quenched with saturated aqueous $NaHCO_3$ (∼5 mL) and extracted with $Et_2O$ (3 × 75 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (25 mL), dried ($MgSO_4$), filtered, concentrated in vacuo, and purified on silica gel by flash chromatography (1:9 $Et_2O$:pentane) to provide **12** (4.2 g, 14 mmol, 88%) as a colorless oil. Characterization data were consistent with previously reported values.[6]

*General Procedure D for Sequential Debenzylation and Amide Bond Formation. 2-(1,5-Dioxaspiro[5.5]undec-7-yl)-N-[(1R)-1-phenylbut-3-en-1-yl]acetamide (**14a**).* Ketal ester **12** (1.82 g, 5.98 mmol), $NaHCO_3$ (1.82 g, 21.7 mmol), and $Pd(OH)_2/C$ (182 mg, 20% on carbon, wet) in EtOAc (60 mL) were evacuated and backfilled three times with $N_2$ and then three times with $H_2$. The mixture was stirred at room temperature under a balloon atmosphere of $H_2$ for 2.5 h before filtering the solution over Celite, eluting with EtOAc (30 mL). The filtrate was concentrated to give the resulting acid, which was used without further purification.

*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide hydrochloride (EDCI, 1.9 g, 7.2 mmol) was added to a solution of the crude acid, amine **13a** (0.88 g, 5.9 mmol), and DMAP (73 mg, 0.60 mmol) in $CH_2Cl_2$ (13 mL). The solution was maintained at room temperature for 21 h and concentrated in vacuo. The crude residue was purified by flash chromatography (1:3 EtOAc:hexanes) to afford **14a** (1.8 g, 5.1 mmol, 86%) as a colorless solid: mp 128−130 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.22 (m, 5H), 6.30 (app dd, *J* = 31.7, 8.3 Hz, 1H), 5.70−5.65 (m, 1H), 5.12−5.05 (m, 3H), 4.07−4.05 (m, 1H), 3.92−3.89 (m, 1H), 3.80−3.66 (m, 2 H), 2.81−2.77 (m, 1H), 2.60−2.54 (m, 3H), 2.10−2.00 (m, 1H), 2.00−1.80 (m, 2H), 1.65−1.55 (m, 3H), 1.40−1.05 (m, 5H); $^{13}C$ NMR (125 MHz, $CDCl_3$) $\delta$ 173.1, 142.4, 142.3, 134.44, 134.41, 128.7, 127.3, 126.70, 126.67, 118.2, 118.1, 98.94, 98.92, 59.3, 59.18, 59.17, 52.5, 52.4, 41.0, 40.9, 37.1, 29.2, 28.2, 25.89, 25.85, 25.0, 22.4; IR (thin film, $cm^{-1}$) 3290, 1644, 1536, 1447, 1337; HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{21}H_{30}NO_3$ 344.2226, found 344.2237.

*2-(1,5-Dioxaspiro[5.5]undec-7-yl)-N-[(1R)-1-(4-methoxyphenyl)-but-3-en-1-yl]acetamide (**14b**).* Following general procedure D, **14b** (1.75 g, 4.71 mmol, 88% yield) was obtained as a colorless solid: mp 79−80 °C; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$ 7.33−7.23 (m, 2H), 6.81 (app d, *J* = 7.0 Hz, 2H), 6.30 (app dd, *J* = 35.0, 7.8 Hz, 1H), 5.77−5.70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(m, 1H), 5.15−5.06 (m, 3H), 3.99 (app ds, $J$ = 11.7, 2.9 Hz, 1H), 3.84 (app dq, $J$ = 15.6, 5.2 Hz, 1H), 3.84 (s, 3H), 3.73−3.71 (m, 1H), 2.74 (app dt, $J$ = 15.1, 5.0 Hz, 1H), 2.51−2.48 (m, 3H), 2.01−1.80 (m, 3H), 1.59−1.52 (m, 3H), 1.47−1.23 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.0, 172.9, 158.8, 134.57, 134.55, 134.5, 134.4, 127.81, 127.79, 118.0, 117.9, 114.1, 114.04, 114.02, 98.90, 98.89, 98.88, 98.87, 59.2, 59.1, 55.45, 52.0, 51.88, 40.9, 40.8, 37.01, 36.99, 29.10, 28.14, 5.9, 25.8, 25.0, 22.4; IR (thin film, cm$^{-1}$) 3296, 2935, 1638, 1513, 1246; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{22}H_{32}NO_4$ 374.2331, found 374.2334.

*N-[(1R)-1-(4-Chlorophenyl)but-3-en-1-yl]-2-(1,5-dioxaspiro[5.5]-undec-7-yl)acetamide (**14c**).* Following general procedure D, **14c** (1.80 g, 4.76 mmol, 89% yield) was obtained as a colorless solid: mp 135−138 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.27 (app t, $J$ = 8.4 Hz), 7.20 (app t, $J$ = 6.8 Hz, 2H), 6.38 (dd, $J$ = 21.4, 7.6 Hz, 1H), 5.68−5.61 (m, 1H), 5.10−5.02 (m, 3H), 4.04 (app q, $J$ = 11.8, 2.8 Hz, 1H), 3.90 (app q, $J$ = 10.3, 2.5 Hz, 1H), 3.80−3.75 (m, 2H), 2.80 (ddd, $J$ = 19.5, 9.4, 6.8 Hz, 1H), 2.63 (broad s, 1H), 2.50 (t, $J$ = 6.8 Hz, 2H), 2.03−1.84 (m, 3H), 1.72−1.56 (m, 3H), 1.43−1.15 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.2, 173.1, 141.1, 141.0, 133.99, 133.96, 133.0, 128.82, 128.80, 128.2, 128.0, 118.6, 118.5, 99.0, 98.9, 59.3, 59.21, 59.19, 52.0, 51.8, 40.8, 37.0, 28.1, 25.9, 22.4; IR (thin film, cm$^{-1}$) 3288, 2935, 1638, 1542, 1493; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{21}H_{29}ClNO_3$ 378.1836, found 378.1834.

*N-[(1R)-1-(2-Chlorophenyl)but-3-en-1-yl]-2-(1,5-dioxaspiro[5.5]-undec-7-yl)acetamide (**14d**).* Following general procedure D, **14d** (1.81 g, 4.78 mmol, 91% yield) was obtained as a colorless solid: mp 86−88 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34 (dt, $J$ = 7.7, 1.5 Hz, 1H), 7.27−7.16 (m, 3H), 6.50 (t, $J$ = 6.5 Hz, 1H), 5.73−5.65 (m, 1H), 5.39 (dtd, $J$ = 13.5, 7.9, 5.5 Hz, 1H), 5.13−5.07 (m, 2H), 4.05 (dtd, $J$ = 18.5, 12.0, 3.0 Hz, 1H), 3.92 (qd, $J$ = 11.5, 2.5 Hz, 1H), 3.83−3.68 (m, 2H), 2.82 (ddd, $J$ = 15.0, 10.0, 5.0 Hz, 1H), 2.63−2.49 (m, 3H), 2.10−2.02 (m, 1H), 2.00−1.84 (m, 2H), 1.66−1.54 (m, 3H), 1.44−1.15 (m, 5H);$^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.1, 173.0, 139.70, 139.65, 134.21, 134.17, 133.0, 132.9, 130.22, 130.21, 128.4, 128.0, 127.9, 127.0, 126.96, 126.95, 118.4, 118.3, 98.93, 98.92, 98.91, 98.90, 59.23, 59.18, 59.17, 50.6, 50.5, 39.3, 39.2, 36.83, 36.82, 29.14, 29.08, 28.2, 25.9, 25.8, 25.0, 22.4; IR (thin film, cm$^{-1}$) 3319, 3070, 1642, 1538, 1478; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{28}ClNO_3Na$ 400.1655, found 400.1659.

*2-(1,5-Dioxaspiro[5.5]undec-7-yl)-N-[(1R)-1-isopropylbut-3-en-1-yl]-acetamide (**14e**).* Following general procedure D, **14e** (747 mg, 2.40 mmol, 68% yield) was obtained as a colorless solid from (*R*)-2-methylhex-5-en-3-amine (51% ee):[33] mp 88−92 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.80−5.73 (m, 2H), 5.07−5.03 (m, 2H), 4.06 (tt, $J$ = 12.0, 3.0 Hz, 1H), 3.95−3.84 (m, 2H), 3.83−3.77 (m, 2H), 2.80 (dt, $J$ = 14.5, 3.0 Hz, 1H), 2.61 (br s, 1H), 2.26 (dt, $J$ = 15.0, 5.0 Hz, 1H), 2.15−2.10 (m, 2H), 1.93 (ddd, $J$ = 14.6, 7.5, 2.8 Hz, 2H), 1.78−1.71 (m, 2H), 1.69−1.63 (m, 1H), 1.62−1.55 (m, 2H), 1.43−1.18 (m, 5H), 0.90 (ddd, $J$ = 14.5, 6.8, 2.2 Hz, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.41, 173.38, 135.4, 117.24, 117.21, 99.0, 98.9, 59.3, 59.22, 59.19, 53.4, 53.3, 37.12, 37.09, 37.0, 31.5, 31.4, 29.1, 29.0, 28.3, 28.2, 25.9, 25.0, 22.5, 19.48, 19.46, 18.1; IR (thin film, cm$^{-1}$) 3294, 2941, 1654, 1538, 1108; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{18}H_{31}NO_3Na$ 332.2202, found 332.2210.

*General Procedure E for Reduction of an Amide with Lithium Aluminum Hydride. (1R)-N-[2-(1,5-Dioxaspiro[5.5]undec-7-yl)ethyl]-1-(4-methoxyphenyl)but-3-en-1-amine (**9b**).* Under an atmosphere of dry $N_2$, $LiAlH_4$ (1.64 g, 43.1 mmol) was added to a solution of **14b** (1.61 g, 4.31 mmol) and $Et_2O$ (110 mL) at 0 °C. The suspension was stirred at room temperature for 22 h. After the suspension was cooled to 0 °C, water (3 mL), 10% NaOH (3 mL), and water (3 mL) were slowly added sequentially, and the mixture was stirred at room temperature for 0.5 h. After filtration, the filtrate was dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified by flash chromatography (100:1 EtOAc:$Et_3N$) to afford **9b** as a colorless oil (1.31 g, 3.66 mmol, 85%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.23 (dd, $J$ = 8.7, 3.9 Hz, 2H), 6.86 (d, $J$ = 8.7 Hz, 2H), 5.71 (ddt, $J$ = 17.4, 10.0, 7.2 Hz, 1H), 5.09−5.01 (m, 2H), 4.01 (td, $J$ = 11.5, 2.5 Hz, 1H), 3.88 (td, $J$ = 11.5, 3.0 Hz, 1H), 3.81−3.73 (m, 5H), 3.62 (q, $J$ = 6.6 Hz, 1H), 2.53−2.42 (m, 2H), 2.40−2.34 (m, 3H), 1.99−1.84 (m, 2H), 1.54−1.47 (m, 5H), 1.43−1.15 (m, 7H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 158.68, 158.67, 136.5, 136.0, 128.41, 128.38, 117.40, 117.36, 113.80, 113.79, 99.17, 99.16, 62.4, 62.2, 59.13, 59.12, 59.07, 59.06, 55.42, 55.41, 46.9, 46.4, 43.29, 43.25, 28.8, 28.44, 28.35, 28.0, 27.8, 25.9, 22.48, 22.46; IR (thin film, cm$^{-1}$) 2933, 2860, 1511, 1245, 1106; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{22}H_{34}NO_3$ 360.2539, found 360.2536.

*(1R)-N-[2-(1,5-Dioxaspiro[5.5]undec-7-yl)ethyl]-1-phenylbut-3-en-1-amine (**9a**).* Following general procedure E, **9a** (1.56 g, 1.62 mmol, 97% yield) was obtained as a pale yellow oil; changes from the standard procedure include the use of THF (70 mL) and $Et_2O$ (30 mL) as the solvent mixture (to assist in the solubility of the amide): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32−7.31 (m, 4H), 7.26−7.21 (m, 1H), 5.76−5.68 (m, 1H), 5.10−5.02 (m, 2H), 4.01 (td, $J$ = 11.5, 3.0 Hz, 1H), 3.88 (td, $J$ = 11.0, 2.5 Hz, 1H), 3.80−3.74 (m, 2H), 3.66 (q, $J$ = 6.2 Hz, 1H), 2.54−2.45 (m, 2H), 2.44−2.36 (m, 3H), 2.00−1.84 (m, 2H), 1.63−1.47 (m, 7H), 1.44−1.16 (m, 7H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 144.4, 135.9, 128.42, 128.41, 128.39, 128.38, 127.44, 127.43, 127.42, 127.39, 127.38, 127.01, 126.99, 117.53, 117.49, 99.14, 99.13, 63.0, 62.8, 59.12, 59.11, 59.05, 59.0, 47.0, 46.4, 43.3, 43.2, 28.8, 28.5, 28.4, 28.3, 28.0, 27.8, 25.8, 22.5, 22.4; IR (thin film, cm$^{-1}$) 2931, 2860, 1453, 1245, 1108; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{21}H_{32}NO_2$ 330.2433, found 330.2426.

*(1R)-1-(4-Chlorophenyl)-N-[2-(1,5-dioxaspiro[5.5]undec-7-yl)-ethyl]but-3-en-1-amine (**9c**).* Following general procedure E, **9c** (1.50 g, 4.13 mmol, 98% yield) was obtained as a colorless oil; changes from the standard procedure include the use of THF (16 mL) as the solvent mixture (to assist in the solubility of the amide): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32−7.24 (m, 4H), 5.69 (ddt, $J$ = 10.5, 7.5 Hz, 1H), 5.08−5.02 (m, 2H), 4.01 (tt, $J$ = 11.0, 2.0 Hz, 1H), 3.88 (td, $J$ = 11.5, 3.0 Hz, 1H), 3.77−3.75 (m, 2H), 3.64 (q, $J$ = 6.5 Hz, 1H), 2.50−2.45 (m, 2H), 2.38−2.33 (m, 3H), 1.99−1.84 (m, 2H), 1.55−1.46 (m, 5H), 1.42−1.15 (m, 7H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 143.0, 142.9, 135.34, 135.33, 132.47, 132.45, 128.81, 128.80, 128.79, 128.78, 128.77, 128.75, 128.74, 128.73, 128.72, 128.52, 128.50, 117.9, 117.8, 99.08, 99.07, 99.06, 62.36, 62.35, 62.19, 62.18, 62.17, 59.10, 59.09, 59.03, 59.01, 47.0, 46.4, 43.21, 43.19, 30.5, 28.8, 28.4, 28.3, 28.2, 28.1, 27.8, 25.8, 24.5, 22.42, 22.40; IR (thin film, cm$^{-1}$) 2933, 2860, 1490, 1245, 1108; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{30}ClNO_2Na$ 386.1863, found 386.1860.

*(1R)-1-(2-Chlorophenyl)-N-[2-(1,5-dioxaspiro[5.5]undec-7-yl)-ethyl]but-3-en-1-amine (**9d**).* Following general procedure E, **9d** (1.35 g, 3.69 mmol, 83% yield) was obtained as a colorless oil; changes from the standard procedure include the use of THF (16 mL) as a solvent (to assist in the solubility of the amide) and the purification of **9d** on silica gel by flash chromatography (100:100:1 hexanes:EtOAc:$Et_3N$): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.55 (ddd, $J$ = 7.8, 4.2, 1.7 Hz, 1H), 7.34 (dt, $J$ = 7.9, 0.9 Hz, 1H), 7.27 (tt, $J$ = 7.5, 1.5 Hz, 1H), 7.17 (td, $J$ = 7.4, 1.7 Hz, 1H), 5.83−5.75 (m, 1H), 5.14−5.06 (m, 2H), 4.25 (ddd, $J$ = 12.5, 8.0, 5.0 Hz, 1H), 4.06−4.00 (m, 1H), 3.90 (tt, $J$ = 11.0, 3.0 Hz, 1H), 3.82−3.76 (m, 2H), 2.55−2.48 (m, 3H), 2.44−2.36 (m, 1H), 2.30 (dt, $J$ = 14.0, 8.0 Hz, 1H), 2.03−1.95 (m, 1H), 1.94−1.86 (m, 1H), 1.57−1.53 (m, 4H), 1.42 (dq, $J$ = 13.0, 2.5 Hz, 1H), 1.38−1.28 (m, 2H), 1.27−1.17 (m, 4H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 141.39, 141.36, 135.43, 135.42, 133.8, 133.7, 129.58, 129.56, 128.32, 128.25, 127.86, 127.85, 127.1, 127.0, 117.9, 117.8, 99.13, 99.12, 59.13, 59.11, 59.05, 59.0, 58.4, 58.2, 46.8, 46.4, 41.5, 41.4, 31.8, 31.1, 28.8, 28.5, 28.4, 28.3, 28.0, 27.8, 25.83, 25.82, 24.5, 22.8, 22.5, 22.4, 14.3; IR (thin film, cm$^{-1}$) 2933, 2860, 1461, 1441, 1108; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{21}H_{31}ClNO_2$ 364.2043, found 364.2043.

*(1R)-N-[2-(1,5-Dioxaspiro[5.5]undec-7-yl)ethyl]-1-isopropylbut-3-en-1-amine (**9e**).* Following general procedure E, **9e** (488 mg, 1.65 mmol, 85% yield) was obtained as a pale yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.80 (ddt, $J$ = 17.0, 10.0, 7.5 Hz, 1H), 5.10−5.04 (m, 2H), 4.03 (td, $J$ = 11.0, 3.0 Hz, 1H), 3.90 (td, $J$ = 11.5, 3.0 Hz, 1H), 3.82−3.79 (m, 2H), 2.68−2.62 (m, 1H), 2.55−2.45 (m, 2H), 2.37−2.33 (m, 1H), 2.23−2.18 (m, 1H), 2.08−2.01 (m, 1H), 1.99−1.87 (m, 2H), 1.84−1.77 (m, 1H), 1.66−1.53 (m, 6H), 1.45−1.21 (m, 8H),


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0.91−0.88 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 137.2, 116.7, 99.19, 99.18, 62.92, 62.91, 62.89, 59.10, 59.09, 59.03, 47.1, 47.0, 42.8, 35.34, 35.31, 30.2, 30.1, 28.9, 28.8, 28.42, 28.36, 27.9, 25.9, 24.4, 22.47, 22.46, 19.0, 18.9, 18.19, 18.17; IR (thin film, cm$^{-1}$) 2935, 2863, 1465, 1445, 1109; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{18}H_{34}NO_2$ 296.2590, found 296.2585.

*Representative Procedure for the Synthesis of Octahydroindole ent-**8** from Aminoacetals **9** (3aR,7aS)-7a-Allyloctahydro-1H-indole (ent-**8**).* A stirring mixture of **9a** (0.20 g, 0.62 mmol), TFA (47 $\mu$ L, 0.62 mmol), and morpholine (5.4 $\mu$L, 0.062 mmol) was heated at 120 °C. Dimedone (0.22 g, 1.5 mmol) was added, and the solution was maintained at 120 °C for 5 h. After cooling to room temperature, the reaction mixture was dissolved in $Et_2O$ (10 mL). The mixture was extracted with 1 N HCl (2 × 10 mL), and the combined aqueous layers were washed with $Et_2O$ (30 mL), treated with 10% NaOH until pH 14, and extracted with $Et_2O$ (30 mL). The organic layer was washed with brine (20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo to afford *ent*-**8** as a yellow oil (94 mg, 0.57 mmol, 92%): $[\alpha]^{23}_{589}$ +18.2, $[\alpha]^{23}_{577}$ +16.2, $[\alpha]^{23}_{546}$ +19.2 (*c* 0.450, $CH_2Cl_2$); HPLC analysis of the derived benzoyl protected amine **S1** indicated an enantiomeric excess of 88% (see below); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.87−5.79 (m, 1H), 5.09−5.02 (m, 2H), 3.03−2.91 (m, 2H), 2.25 (ddt, $J$ = 13.9, 8.0, 1.2 Hz, 1H), 2.11 (ddt, $J$ = 15.1, 7.0, 6.3 Hz, 1H), 1.89−1.82 (m, 1H), 1.76−1.63 (m, 3H), 1.57−1.50 (m, 1H), 1.48−1.27 (m, 7H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 135.0, 117.8, 61.9, 42.8, 42.5, 42.3, 31.4, 29.8, 26.8, 22.5, 22.1; IR (thin film, cm$^{-1}$) 3300, 2923, 1667, 1407; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{11}H_{20}N$ 166.1596, found 166.1594.

*7a-Allyl-1-benzoyloctahydro-1H-indole (**S1**).* Benzoyl chloride (37 mg, 0.26 mmol) was added to a solution of *ent*-**8** (31 mg, 0.19 mmol), $Et_3N$ (40 mg, 0.40 mmol), and $CH_2Cl_2$ (0.5 mL) at room temperature. The solution was maintained at room temperature for 1 h. After the addition of $Et_2O$ (10 mL), the organic layer was washed with water (5 mL), 1 N HCl (5 mL), 10% NaOH (5 mL), and brine (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (1:10 EtOAc:hexanes) to afford the title compound as a colorless solid (44 mg, 0.17 mmol, 87%). HPLC analysis indicated an enantiomeric excess of 89% [CHIRALCEL AD column; flow, 1.0 mL/min; 96.5% *n*-hexane/3.5% *i*-PrOH; $\lambda$ = 220 nm; major enantiomer $t_R$ = 28.3 min; minor enantiomer $t_R$ = 25.5 min]: mp 46−47 °C; $[\alpha]^{23}_{589}$ +76.8, $[\alpha]^{23}_{577}$ +79.5, $[\alpha]^{23}_{546}$ +90.8, $[\alpha]^{23}_{435}$ +171 (*c* 1.04, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.41−7.35 (m, 5H), 5.91−5.83 (m, 1H), 5.16−5.13 (m, 2H), 3.33−3.30 (m, 2H), 3.25 (dd, $J$ = 13.9, 6.5 Hz, 1H), 2.60−2.53 (m, 2H), 2.28−2.23 (m, 1H), 1.91−1.83 (m, 1H), 1.77 (td, $J$ = 13.1, 4.1 Hz, 1H), 1.71−1.56 (m, 4H), 1.50−1.30 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 170.0, 139.0, 134.7, 129.4, 128.4, 126.6, 118.3, 65.5, 50.7, 39.7, 37.5, 32.8, 27.3, 25.2, 22.8, 21.5; IR (thin film, cm$^{-1}$) 1630, 1403, 1218, 1189, 1138; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{18}H_{23}NONa$ 292.1677, found 292.1680.

*Synthesis and Characterization of Aminoketals 15−17 and Their Precursors. Benzyl 2-(2-Oxocyclopentyl)acetate (**S2**).* Following general procedure B, **S2** (2.3 g, 9.9 mmol, 78%) was obtained as a colorless oil. This product was purified on silica gel by flash chromatography (19:1 hexanes:EtOAc to 9:1 hexanes:EtOAc). Characterization data were consistent with previously reported values.[34]

*Benzyl 2-(6,10-Dioxaspiro[4.5]decan-1-yl)acetate (**S3**).* Following general procedure C, **S3** (5.8 g, 20 mmol, 96%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.37−7.28 (m, 5H), 5.14 (d, $J$ = 12.4 Hz, 1H), 5.08 (d, $J$ = 12.4 Hz, 1H), 3.90−3.77 (m, 4H), 2.71 (dd, $J$ = 15.0, 3.8 Hz, 1H), 2.38−2.25 (m, 2H), 2.11 (ddd, $J$ = 13.1, 8.7, 6.9 Hz, 1H), 1.96−1.86 (m, 2H), 1.82 (ddd, $J$ = 13.1, 9.4, 6.1 Hz, 1H), 1.71−1.62 (m, 2H), 1.39−1.31 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.5, 136.3, 128.4, 128.1, 128.0, 108.1, 65.9, 62.1, 60.6, 45.1, 33.8, 29.9, 28.6, 25.8, 20.8; IR (thin film, cm$^{-1}$) 2958, 2867, 1733; HRMS (ES) $m/z$ [M + Na]$^+$ calcd for $C_{17}H_{22}O_4Na$ 313.1416, found 313.1420.

*2-(6,10-Dioxaspiro[4.5]dec-1-yl)-N-[(1R)-1-phenylbut-3-en-1-yl]-acetamide (**S4**).* Following general procedure D, **S4** (1.5 g, 4.5 mmol, 89%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.33−7.23 (m, 5H), 7.07 (br s, 0.5H), 6.90 (br s, 0.5H), 5.74−5.66 (m, 1H), 5.11−5.01 (m, 3H), 3.94−3.78 (m, 4H), 3.75−3.71 (m, 1H), 2.69 (ddd, $J$ = 15.7, 7.8, 3.6 Hz, 1H), 2.62−2.52 (m, 2H), 2.29−2.03 (m, 3H), 1.96−1.81 (m, 3H), 1.75−1.57 (m, 3H), 1.39−1.24 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.5, 142.3, 142.1, 134.5, 128.64, 128.63, 127.4, 127.3, 126.9, 126.73, 126.70, 126.69, 117.90, 117.89, 108.2, 108.1, 62.4, 62.3, 60.7, 60.6, 52.9, 52.7, 46.2, 46.1, 41.0, 40.7, 36.2, 36.1, 30.7, 30.54, 30.53, 30.2, 30.0, 25.9, 25.7, 21.5, 21.3; IR (thin film, cm$^{-1}$) 3292, 1638, 1542, 1152; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{20}H_{27}NO_3Na$ 352.1889, found 352.1894.

*N-[2-(6,10-Dioxaspiro[4.5]dec-1-yl)-ethyl]-(1R)-1-phenylbut-3-en-1-amine (**S5**).* Following general procedure E, **S5** (1.15 g, 3.67 mmol, 93%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.27−7.22 (m, 4H), 7.19−7.16 (m, 1H), 5.67 (ddt, $J$ = 16.9, 9.4, 7.5 Hz, 1H), 5.04−4.97 (m, 2H), 3.85−3.75 (m, 4H), 3.62 (t, $J$ = 6.9, 1H), 2.50−2.34 (m, 4H), 2.10−1.99 (m, 1H), 1.90−1.49 (m, 8H), 1.39−1.27 (m, 2H), 1.24−1.13 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 144.44, 144.38, 135.8, 128.36, 128.35, 127.41, 127.40, 127.0, 126.9, 117.4, 108.83, 108.81, 62.83, 62.75, 62.19, 62.17, 60.7, 46.9, 46.8, 46.6, 46.5, 43.21, 43.20, 30.7, 29.4, 29.22, 29.17, 29.1, 26.07, 26.05, 21.28, 21.25; IR (thin film, cm$^{-1}$) 2954, 2861, 1453, 1246, 1108; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{20}H_{30}NO_2$ 316.2277, found 316.2282.

*Benzyl 3-(2-Oxocyclopentyl)propanoate (**S6**).* Ketone **S6** was prepared using an adaptation of the procedure of Cotarco and co-workers.[35] A stirring solution of cyclopentanone (19 mL, 0.21 mol), 4-methoxyphenol (0.17 g, 1.4 mmol), cyclohexylamine (1.7 mL, 15 mmol), and acetic acid (0.15 mL, 2.5 mmol) was heated to 80 °C for 10 min and then warmed to 130 °C over 30 min. Benzyl acrylate (16 mL, 0.11 mol) was added via syringe pump at a rate of 6.8 mL/h. Upon complete addition, the reaction was cooled to 25 °C, and the residue was purified directly on silica gel by flash chromatography (1:9−1:4 EtOAc:hexanes) to provide **S6** (13 g, 52 mmol, 47%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.40−7.31 (m, 5H), 5.15 (s, 2H), 2.55−2.45 (m, 2H), 2.31 (dd, $J$ = 18.8, 8.6 Hz, 1H), 2.23−2.17 (m, 1H), 2.16−2.07 (m, 3H), 2.05−1.97 (m, 1H), 1.82−1.73 (m, 1H), 1.73−1.63 (m, 1H), 1.56−1.46 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 219.9, 172.7, 135.8, 128.3, 128.1, 128.0, 65.9, 47.9, 37.7, 31.9, 29.2, 24.6, 20.3; IR (thin film, cm$^{-1}$) 2960, 2877, 1733; HRMS (ES) $m/z$ [M + Na]$^+$ calcd for $C_{15}H_{18}O_3Na$ 269.1154, found 269.1144. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.37. Found: C, 73.26; H, 7.40.

*Benzyl 3-(6,10-Dioxaspiro[4.5]decan-1-yl)propanoate (**S7**).* Following general procedure C, **S7** (4.6 g, 16 mmol, 56%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.38−7.27 (m, 5H), 5.14−5.08 (m, 2H), 3.90−3.79 (m, 4H), 2.54−2.42 (m, 2H), 2.09 (dt, $J$ = 13.3, 8.5 Hz, 1H), 1.90−2.01 (m, 2H), 1.87−1.74 (m, 3H), 1.70−1.53 (m, 3H) 1.37−1.24 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.7, 136.2, 128.3, 128.2, 128.0, 108.3, 65.8, 61.9, 60.4, 47.9, 32.8, 30.5, 28.7, 25.7, 23.7, 20.9; IR (thin film, cm$^{-1}$) 2956, 2865, 1733; HRMS (ES) $m/z$ [M + Na]$^+$ calcd for $C_{18}H_{24}O_4Na$ 327.1572, found 327.1564. Anal. Calcd for $C_{18}H_{24}O_4$: C, 71.03; H, 7.95. Found: C, 71.12; H, 7.94.

*3-(6,10-Dioxaspiro[4.5]dec-1-yl)-N-[(1R)-1-phenylbut-3-en-1-yl]-propionamide (**S8**).* Following general procedure D, **S8** (1.66 g, 4.85 mmol, 97%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.30−7.22 (m, 5H), 6.41 (app br d, $J$ = 20.8 Hz, 1H), 5.71−5.63 (m, 1H), 5.08−5.05 (m, 3H), 3.87−3.80 (m, 4H), 2.53−2.51 (m, 2H), 2.48−2.41 (m, 1H), 2.29−2.22 (m, 1H), 2.18−2.10 (m, 1H), 2.02−1.74 (m, 5H), 1.69−1.49 (m, 3H), 1.41−1.36 (m, 1H), 1.31−1.19 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.19, 173.16, 142.3, 142.2, 134.5, 134.4, 128.74, 128.69, 128.6, 127.4, 127.33, 127.27, 126.8, 126.7, 126.6, 118.2, 118.03, 118.00, 109.0, 108.9, 62.39, 62.36, 62.1, 60.5, 52.6, 52.4, 47.5, 47.4, 40.9, 35.3, 34.3, 31.0, 30.9, 29.6, 29.5, 26.2, 25.0, 21.34, 21.25; IR (thin film, cm$^{-1}$) 3288, 2956, 1638, 1542, 1248; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{29}NO_3Na$ 366.2045, found 366.2037.

*N-[3-(6,10-Dioxaspiro[4.5]dec-1-yl)-propyl]-(1R)-1-phenylbut-3-en-1-amine (**16**).* Following general procedure E, **16** (1.27 g, 3.84


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mmol, 88%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.30−7.27 (m, 4H), 7.21−7.18 (m, 1H), 5.72−5.64 (m, 1H), 5.06−4.99 (m, 2H), 3.87−3.79 (m, 4H), 3.62 (t, $J$ = 6.9 Hz, 1H), 2.43−2.36 (m, 4H), 2.06−2.00 (m, 1H), 1.95−1.88 (m, 1H), 1.84−1.68 (m, 6H), 1.34 (dq, $J$ = 7.9, 2.6 Hz, 1H), 1.26−1.19 (m, 1H), 1.17−1.08 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 144.31, 144.26, 135.8, 128.4, 127.39, 127.37, 127.0, 117.5, 108.9, 62.9, 62.8, 62.11, 62.10, 60.8, 48.9, 48.8, 48.4, 48.3, 43.2, 43.1, 30.71, 30.68, 29.1, 29.02, 28.99, 28.9, 26.34, 26.27, 26.1, 21.12, 21.09; IR (thin film, cm$^{-1}$) 2952, 2860, 1453, 1246, 1109; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{21}H_{32}NO_2$ 330.2433, found 330.2433.

*Benzyl 3-(2-oxocyclohexyl)propanoate (**S9**).* Ketone **S9** was prepared using an adaptation of the procedure of Cotarco and co-workers.[35] A stirring solution of cyclohexanone (24 mL, 0.21 $\mu$mol), 4-methoxyphenol (0.17 g, 1.4 mmol), cyclohexylamine (1.7 mL, 15 mmol), and acetic acid (0.15 mL, 2.5 mmol) was heated to 80 °C for 10 min and then warmed to 130 °C over 30 min. Benzyl acrylate (16 mL, 0.11 mol) was added via syringe pump at a rate of 6.8 mL/h. Upon complete addition, the reaction was cooled to 25 °C, and the residue was purified directly on silica gel by flash chromatography (1:9−1:4 EtOAc:hexanes) to provide **S9** (23 g, 87 mmol, 83%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32−7.24 (m, 5H), 5.06 (s, 2H), 2.45−2.1 (m, 5H), 2.09−1.95 (m, 3H), 1.83−1.74 (m, 1H), 1.64−1.49 (m, 3H), 1.31 (dq, $J$ = 8.9, 3.7 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 211.0, 173.0, 135.8, 128.2, 128.0, 127.9, 65.8, 49.3, 41.8, 33.8, 31.5, 27.7, 24.8, 24.5; IR (thin film, cm$^{-1}$) 2935, 2861, 1733, 1708; HRMS (ES) $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{20}O_3Na$ 283.1310, found 283.1297. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.72. Found: C, 73.88; H, 7.72

*Benzyl 3-(1,5-Dioxaspiro[5.5]undecan-7-yl)propanoate (**S10**).* Following general procedure C, **S10** (4.1 g, 13 mmol, 78%) was obtained as a colorless oil; changes from the standard procedure include the exposure of this substrate to reaction conditions at 25 °C for 3 h: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36−7.27 (m, 5H), 5.08 (s, 2H), 3.98 (app td, $J$ = 11.5, 2.7 Hz, 1H), 3.85 (app td, $J$ = 11.3, 2.7 Hz, 1H), 3.77−3.72 (m, 2H), 2.49−2.40 (m, 1H), 2.39−2.30 (m, 1H), 2.22−2.13 (m, 1H), 1.93−1.83 (m, 1H), 1.62−1.46 (m, 6H), 1.41−1.26 (m, 3H), 1.25−1.12 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 174.0, 136.2, 128.4, 128.1, 128.0, 98.9, 65.9, 58.8, 58.7, 44.0, 32.9, 28.0, 27.3, 25.5, 24.2, 23.4, 22.2; IR (thin film, cm$^{-1}$) 2935, 2861, 1735. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.62; H, 8.39.

*3-(1,5-Dioxaspiro[5.5]undec-7-yl)-N-[(1R)-1-phenylbut-3-en-1-yl]-propionamide (**S11**).* Following general procedure D, **S11** (1.45 g, 4.03 mmol, 99%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.24 (m, 5H), 6.51 (app t, $J$ = 9.4 Hz, 1H), 5.76−5.67 (m, 1H), 5.17−5.08 (m, 3H), 4.07 (tdd, $J$ = 11.9, 5.9, 3.0 Hz, 1H), 3.92 (td, J = 11.7, 2.8 Hz, 1H), 3.82−3.73 (m, 2H), 2.62−2.59 (m, 1H), 2.57−2.52 (m, 2H), 2.44−2.38 (m, 1H), 2.25−2.14 (m, 2H), 2.02−1.90 (m, 1H), 1.66−1.50 (m, 4H), 1.44−1.11 (m, 7H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$172.8, 172.7, 142.4, 142.3, 134.7, 134.5, 128.7, 128.6, 127.4, 127.3, 126.8, 126.7, 118.0, 99.53, 99.52, 59.19, 59.17, 59.1, 52.51, 52.45, 41.0, 40.8, 35.3, 35.2, 28.4, 28.1, 28.0, 25.9, 24.3, 24.2, 22.44, 22.4; IR (thin film, cm$^{-1}$) 3305, 2935, 1640, 1541, 1448; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{22}H_{32}NO_3$ 358.2382, found 358.2390.

*N-[3-(1,5-Dioxaspiro[5.5]undec-7-yl)-propyl]-(1R)-1-phenylbut-3-en-1-amine (**17**).* Following general procedure E, **17** (1.17 g, 3.41 mmol, 89%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.31 (m, 4H), 7.25−7.22 (m, 1H), 5.76−5.67 (m, 1H), 5.10−5.03 (m, 2H), 4.01 (td, $J$ = 11.4, 3.1 Hz, 1H), 3.88 (td, $J$ = 10.5, 2.7 Hz, 1H), 3.79−3.75 (m, 2H), 3.65 (t, $J$ = 6.8 Hz, 1H), 2.49−2.41 (m, 5H), 1.91−1.83 (m, 1H), 1.78−1.70 (m, 1H), 1.66−1.62 (m, 1H), 1.57−1.46 (m, 4H), 1.44−1.30 (m, 3H), 1.27−1.20 (m, 3H), 1.14−1.06 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 144.2, 135.8, 128.5, 127.43, 127.40, 127.1, 117.6, 99.3, 62.8, 62.7, 59.10, 59.09, 59.0, 48.3, 48.1, 43.1, 28.7, 28.4, 28.34, 28.29, 27.33, 27.25, 25.8, 25.2, 25.1, 24.3, 22.5; IR (thin film, cm$^{-1}$) 2933, 2860, 1453, 1244, 1107; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{22}H_{34}NO_2$ 344.2590, found 344.2581.

*General Procedure F for 2-Aza-Cope Rearrangement and Cbz Protection To Yield 1-Azabicyclic Products ent-**8** and **18**−**20**.* *Preparation of (3aR,6aS)-Benzyl 6a-Allylhexahydrocyclopenta[b]-pyrrole-1(2H)-carboxylate (**18**).* A stirring mixture of **15** (228 mg, 0.722 mmol), TFA (56.0 $\mu$L, 0.722 mmol), and morpholine (6.30 $\mu$L, 0.0722 mmol) was heated to 120 °C. Dimedone (253 mg, 1.81 mmol) was added, and the solution was maintained at 120 °C for 2 h. After cooling to room temperature, the reaction mixture was dissolved in $CHCl_3$ (5 mL). A saturated aqueous solution of $Na_2CO_3$ (2.4 mL), water (2.4 mL), and benzyl chloroformate (310 $\mu$L, 2.17 mmol) was added, and the biphasic solution was stirred at room temperature for 18 h. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 10 mL), and the combined organic layer was dried ($Na_2SO_4$), filtered, and concentrated in vacuo. The crude residue was purified by flash chromatography (1:20 EtOAc:hexanes) to afford **18** as a colorless oil (196 mg, 95%). HPLC analysis indicated an enantiomeric excess of 92% [CHIRALCEL OJ column; flow, 1.0 mL/min; 96% $n$-hexane:4% $i$-PrOH; $\lambda$ = 220 nm; major enantiomer $t_R$ = 6.7 min; minor enantiomer $t_R$ = 8.5 min]: $[\alpha]^{23}_{589}$ −11.4, $[\alpha]^{23}_{577}$ −11.0, $[\alpha]^{23}_{546}$ −12.2, $[\alpha]^{23}_{435}$ −18.5 ($c$ 1.99, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 388 K) $\delta$ 7.36 (app d, $J$ = 4.5 Hz, 4H), 7.32−7.28 (m, 1H), 5.79−5.71 (m, 1H), 5.13−5.00 (m, 2H), 3.53−3.42 (m, 2H), 2.81−2.77 (m, 2H), 2.50−2.44 (m, 1H), 2.37 (dd, $J$ = 18.8, 7.5 Hz, 1H), 2.16 (dt, $J$ = 12.3, 6.3 Hz, 1H), 1.93 (dq, $J$ = 12.6, 8.1 Hz, 1H), 1.87−1.80 (m, 1H), 1.72−1.65 (m, 1H), 1.64−1.51 (m, 3H), 1.45−1.38 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 388 K) $\delta$ 152.6, 136.7, 134.2, 127.4, 126.7, 126.6, 116.4, 73.1, 64.9, 47.3, 47.0, 40.5, 40.0, 39.8, 39.7, 39.5, 39.3, 39.2, 39.0, 37.3, 31.1, 27.8, 24.0; IR (thin film, cm$^{-1}$) 2946, 1696, 1405, 1355; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{18}H_{23}NO_2Na$ 308.1626, found 308.1622.

*(3aR,7aS)-Benzyl 7a-Allyloctahydro-1H-indole-carboxylate (Cbz-ent-**8**).* Following general procedure F, (164 mg, 0.549 mmol, 85%) was obtained as a colorless oil; changes from the standard procedure include heating **9a** at 120 °C for 5 h and purification by flash chromatography on silica gel (20:1 hexanes:$Et_2O$). HPLC analysis indicated an enantiomeric excess of 89% [CHIRALCEL OJ column; flow, 1.0 mL/min; 96% $n$-hexane:4% $i$-PrOH; $\lambda$ = 220 nm; major enantiomer $t_R$ = 7.8 min; minor enantiomer $t_R$ = 11.6 min]: $[\alpha]^{23}_{589}$ −11.4, $[\alpha]^{23}_{577}$ −11.0, $[\alpha]^{23}_{546}$ −12.2, $[\alpha]^{23}_{435}$ −18.5 ($c$ 1.99, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 398 K) $\delta$ 7.36−7.28 (m, 5H), 5.78−5.70 (m, 1H), 5.12−5.00 (m, 4H), 3.62−3.57 (m, 1H), 3.34−3.29 (m, 1H), 2.72 (dd, $J$ = 15.0, 7.1 Hz, 1H), 2.50−2.44 (m, 1H), 2.14−2.09 (m, 1H), 1.94−1.60 (m, 5H), 1.51−1.28 (m, 5H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 398 K) $\delta$ 152.9, 136.8, 133.8, 127.4, 126.6, 126.5, 116.3, 64.7, 63.1, 45.4, 39.0, 38.8, 31.3, 25.4, 24.8, 20.7, 20.4 ; IR (thin film, cm$^{-1}$) 2927, 1696, 1401, 1337; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{25}NO_2Na$ 322.1783, found 322.1777.

*(4aR,7aS)-Benzyl 7a-Allyloctahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**19**).* Following general procedure F, **19** (155 mg, 0.517 mmol, 80%) was obtained as a colorless oil; changes from the standard procedure include heating at 120 °C for 5 h and purification of the product by silica gel column chromatography (10:1 hexanes:$Et_2O$). HPLC analysis indicated an enantiomeric excess of 91% [CHIRALCEL OJ column; flow, 1.0 mL/min; 96% $n$-hexane:4% $i$-PrOH; $\lambda$ = 220 nm; major enantiomer $t_R$ = 5.8 min; minor enantiomer $t_R$ = 7.3 min]: $[\alpha]^{23}_{589}$ +63.8, $[\alpha]^{23}_{577}$ +64.8, $[\alpha]^{23}_{546}$ +72.9, $[\alpha]^{23}_{435}$ +124 ($c$ 0.79, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 298 K) $\delta$ 7.38−7.29 (m, 5H), 5.80 (ddt, $J$ = 16.7, 10.4, 7.5 Hz, 1H), 5.08−4.96 (m, 4H), 3.81 (ddd, $J$ = 13.4, 6.4, 3.3 Hz, 1H), 2.96 (ddd, $J$ = 13.4, 11.2, 5.0 Hz, 1H), 2.61 (dd, $J$ = 13.8, 7.4 Hz, 1H), 2.26 (dd, $J$ = 13.8, 7.6 Hz, 1H), 2.20−2.14 (m, 1H), 2.04−1.97 (m, 2H), 1.78−1.71 (m, 1H), 1.67−1.34 (m, 7H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 298 K) $\delta$ 155.3, 137.1, 134.7, 128.3, 127.6, 127.5, 117.5, 66.6, 65.7, 41.7, 40.9, 40.1, 37.5, 28.7, 24.0, 21.1, 20.7; IR (thin film, cm$^{-1}$) 2948, 1702, 1410, 1218; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{19}H_{25}NO_2Na$ 322.1783, found 322.1778.

*(4aR,8aS)-Benzyl 8a-Allyloctahydroquinoline-1(2H)-carboxylate (cis-20) and (4aR,8aR)-Benzyl 8a-Allyloctahydroquinoline-1(2H)-carboxylate (trans-20).* Octahydroquinoline *cis*-**20** was isolated as a colorless oil (80 mg, 0.25 mmol, 41%) and *trans*-**20** was isolated as a colorless oil (66 mg, 0.21 mmol, 34%). Changes from the standard procedure include heating at 120 °C for 5 h and separation of the products by flash chromatography on silica gel (20:1 hexanes:$Et_2O$).


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*cis*-**20**. HPLC analysis indicated an enantiomeric excess of 93% [CHIRALCEL OJ column; flow, 1.0 mL/min; 96% *n*-hexane/4% *i*-PrOH; $\lambda$ = 220 nm; major enantiomer $t_R$ = 6.2 min; minor enantiomer $t_R$ = 7.9 min]: $[\alpha]_{589}^{23}$ +50.1, $[\alpha]_{577}^{23}$ +53.2, $[\alpha]_{546}^{23}$ +60.4, $[\alpha]_{435}^{23}$ +104 (*c* 1.05, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 348 K) $\delta$ 7.39−7.28 (m, 5H), 5.76 (ddt, *J* = 17.5, 10.0, 7.3 Hz, 1H), 5.07−5.00 (m, 4H), 3.79 (dt, *J* = 13.2, 4.7 Hz, 1H), 3.26−3.20 (m, 1H), 2.68 (dt, *J* = 7.3, 1.2 Hz, 1H), 2.33 (ddd, *J* = 12.7, 8.3, 3.8 Hz, 1H), 1.83−1.64 (m, 4H), 1.60−1.48 (m, 5H), 1.46−1.27 (m, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 348 K) $\delta$ 154.9, 136.9, 133.8, 127.8, 127.1, 127.0, 116.9, 65.3, 60.1, 40.8, 38.3, 35.7, 32.2, 27.3, 23.1, 21.9, 21.7, 20.6; IR (thin film, cm$^{-1}$) 2934, 1697, 1398, 1261; HRMS (ESI) *m*/*z*: [M + Na]$^+$ calcd for $C_{20}H_{27}NO_2Na$ 336.1939, found 336.1938. *trans*-**20**: HPLC analysis indicated an enantiomeric excess of 93% [CHIRALCEL OJ column; flow, 1.0 mL/min; 96% *n*-hexane:4% *i*-PrOH; $\lambda$ = 220 nm; major enantiomer $t_R$ = 6.5 min; minor enantiomer $t_R$ = 8.0 min]; $[\alpha]_{589}^{23}$ +20.3, $[\alpha]_{577}^{23}$ +20.5, $[\alpha]_{546}^{23}$ +22.7, $[\alpha]_{435}^{23}$ +35.7 (*c* 1.17, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$) $\delta$ 7.37−7.28 (m, 5H), 5.69 (ddt, *J* = 17.2, 10.1, 7.2 Hz, 1H), 5.10 (d, *J* = 17.1 Hz, 1H), 5.00−4.93 (m, 3H), 3.97 (dt, *J* = 14.0, 4.4 Hz, 1H), 3.08 (ddd, *J* = 14.3, 11.4, 3.0 Hz, 1H), 2.88 (br d, *J* = 13.1 Hz, 1H), 2.64 (dd, *J* = 15.0, 7.6 Hz, 1H), 2.40 (dd, *J* = 14.8, 6.9 Hz, 1H), 1.64−1.52 (m, 5H), 1.51−1.30 (m, 5H), 1.29−1.18 (m, 2H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 298 K) $\delta$ 155.1, 137.3, 134.0, 128.3, 127.6, 127.4, 117.2, 65.5, 62.5, 45.2, 41.2, 35.0, 30.7, 29.6, 26.6, 25.3, 24.8, 22.7; IR (thin film, cm$^{-1}$) 2930, 1702, 1391, 1160; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{27}NO_2Na$ 336.1939, found 336.1947.

**Preparation and Characterization of Aminoketals Employed in the Transformations Reported in Table 3.** The direct precursors of 1-azabicyclic products **31a** and **34a** have been reported previously.[9]

*N-((S)-2-Methylbut-3-en-1-yl)-2-(6,10-dioxaspiro[4.5]decan-1-yl)-acetamide (**S12**).* Following general procedure D, **S12** (63 mg, 0.24 mmol, 85%) was obtained as a colorless solid; changes to the general procedure involve adding $Et_3N$ (42 $\mu$L) to the amide-coupling step: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 6.35 (broad s, 1H), 5.72−5.69 (m, 1H), 5.08−5.03 (m, 2H), 3.94−3.87 (m, 4H), 3.32−3.29 (m, 1H), 3.09−3.08 (m, 1H), 2.62 (dd, *J* = 15.6, 7.0 Hz, 1H), 2.38−2.31 (m, 1H), 2.28−2.21 (m, 1H), 2.14−2.07 (m, 2H), 2.02−1.85 (m, 3H), 1.70−1.65 (m, 2H), 1.42−1.25 (m, 2H), 1.03 (d, *J* = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 173.3, 141.83, 141.78, 115.1, 115.0, 108.3, 62.4, 60.8, 60.8, 46.19, 46.15, 44.67, 44.65, 38.2, 38.1, 36.2, 30.6, 29.85, 28.82, 26.06, 26.05, 21.3, 17.79, 17.75; IR (thin film, cm$^{-1}$) 3304, 3079, 2962, 1735, 1103; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{26}NO_3$ 268.1913, found 268.1915.

*(2S)-N-(2-(6,10-Dioxaspiro[4.5]decan-1-yl)ethyl)-2-methylbut-3-en-1-amine (**S13**).* Following general procedure E, **S13** (28 mg, 0.11 mmol, 46%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.70−5.63 (m, 1H), 5.07−4.99 (m, 2H), 3.93−3.84 (m, 4H), 2.72−2.61 (m, 2H), 2.56−2.46 (m, 2H), 2.39−2.33 (m, 1H), 2.11 (dddd, *J* = 7.7, 7.7, 7.7, 7.7 Hz, 1H), 2.02−1.97 (m, 1H), 1.87−1.79 (m, 3H), 1.68−1.57 (m, 3H), 1.43−1.25 (m, 4H), 1.00 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR (125 MHz) $\delta$ 143.0, 114.6, 114.5, 108.9, 62.2, 60.79, 55.77, 55.76, 49.1, 48.9, 47.1, 47.0, 38.5, 38.4, 30.70, 30.66, 29.4, 29.3, 29.2, 26.2, 21.3, 18.50, 18.46; IR (thin film, cm$^{-1}$) 3315, 3075, 2955, 1111; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{28}NO_2$ 254.2120, found 254.2127.

*N-((R)-2-Phenylbut-3-enyl)-2-(1,5-dioxaspiro[5.5]undecan-7-yl)-acetamide (**S14**).* Following general procedure D, **S14** (307 mg, 0.893 mmol, 55%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, *J* = 7.5 Hz, 2H), 7.25−7.21 (m, 3H), 6.00−5.93 (m, 2H), 5.15−5.09 (m, 2H), 3.98 (t, *J* = 11.7 Hz, 1H), 3.86 (t, *J* = 11.7 Hz, 1H), 3.74−3.58 (m, 3H), 3.55−3.44 (m, 2H), 2.72 (d, *J* = 14.6 Hz, 1H), 2.59 (d, *J* = 11.7 Hz, 1H), 1.95 (broad s, 1H), 1.89−1.75 (m, 2H), 1.57 (app d, *J* = 9.9 Hz, 3H), 1.39−1.22 (m, 4H), 1.12 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.9, 173.8, 141.54, 141.46, 139.3, 128.9, 128.03, 127.99, 127.0, 116.4, 116.3, 98.8, 98.7, 59.13, 59.10, 49.7, 49.6, 43.7, 43.6, 36.9, 36.8, 29.1, 28.9, 28.1, 25.8, 25.0, 22.4; IR (thin film, cm$^{-1}$) 3301, 2933, 1644, 1108; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{29}NO_3Na$ 366.2045, found 366.2051.

*(2R)-N-(2-(1,5-Dioxaspiro[5.5]undecan-7-yl)ethyl)-2-phenylbut-3-en-1-amine (**S15**).* Following general procedure E, **S15** (228 mg, 0.692 mmol, 80%) was obtained as a light yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, *J* = 7.9 Hz, 2H), 7.24−7.21 (m, 3H), 6.01−5.94 (m, 1H), 5.15−5.10 (m, 2H), 4.01 (tt, *J* = 11.4, 3.2 Hz, 1H), 3.88 (t, *J* = 10.1 Hz, 1H), 3.78−3.76 (m, 2H), 3.55 (q, *J* = 7.6 Hz, 1H), 2.95−2.87 (m, 2H), 2.72−2.65 (m, 1H), 2.62−2.55 (m, 1H), 2.46 (app broad s, 1H), 1.99−1.86 (m, 2H), 1.59−1.52 (m, 3H), 1.45−1.22 (m, 8H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.7, 140.40, 140.37, 128.9, 128.8, 127.94, 127.92, 126.77, 126.75, 116.0, 115.9, 99.2, 59.14, 59.08, 54.7, 54.6, 50.1, 48.92, 48.86, 28.6, 28.3, 28.1, 25.8, 24.5, 22.5; IR (thin film, cm$^{-1}$) 3319, 3080, 2933, 1108; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{32}NO_2$ 330.2433, found 330.2437.

*N-((S)-2-Methylbut-3-en-1-yl)-2-(1,5-dioxaspiro[5.5]undecan-7-yl)acetamide (**S16**).* Following general procedure D, **S16** (83 mg, 0.29 mmol, 80%) was obtained as a colorless solid; changes to the general procedure involve the addition of $Et_3N$ (56.0 $\mu$L) to the amide coupling step: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.92 (broad s, 1H), 5.71−5.64 (m, 1H), 5.07−5.05 (m, 2H), 4.05 (app dt, *J* = 11.8, 2.8 Hz, 1H), 3.93 (app dt, *J* = 11.8, 2.8 Hz, 1H), 3.80−3.78 (m, 2H), 3.35−3.27 (m, 1H), 3.07−2.98 (m, 1H), 2.76 (dd, *J* = 14.3, 4.6 Hz, 1H), 2.61 (broad d, *J* = 12.9 Hz, 1H), 2.35−2.29 (m, 1H), 2.04−1.95 (m, 1H), 1.94−1.87 (m, 2H), 1.65−1.58 (m, 3H), 1.41−1.18 (m, 5H), 1.01 (d, *J* = 6.9 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.80, 173.79, 141.84, 141.82, 115.14, 115.09, 98.8, 59.20, 59.15, 44.51, 44.48, 38.34, 38.26, 36.9, 36.8, 29.03, 28.98, 28.2, 25.8, 25.0, 22.4, 17.8, 17.7; IR (thin film, cm$^{-1}$) 3079, 2933, 1643; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{16}H_{27}NO_3Na$ 304.1889, found 304.1881.

*(2S)-N-(2-(1,5-Dioxaspiro[5.5]undecan-7-yl)ethyl)-2-methylbut-3-en-1-amine (**S17**).* Following the general procedure, **S17** (24 mg, 0.095 mmol, 74%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.65−5.61 (m, 1H), 5.06−4.98 (m, 2H), 4.01 (app dt, *J* = 11.5, 2.8 Hz, 1H), 3.88 (app dt, *J* = 11.2, 2.1 Hz, 1H), 3.78−3.76 (m, 2H), 2.66−2.29 (m, 1H), 2.57−2.43 (m, 4H), 2.36−2.33 (m, 1H), 1.96−1.88 (m, 2H), 1.60−1.55 (m, 4H), 1.42−1.24 (m, 7H), 0.99 (d, *J* = 6.7 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 143.0, 114.6, 114.5, 99.2, 59.2, 59.1, 55.83, 55.76, 49.2, 49.0, 38.5, 38.4, 28.7, 28.6, 28.4, 28.3, 28.1, 25.8, 24.4, 22.5, 18.53, 18.48; IR (thin film, cm$^{-1}$) 2933, 2862, 1446; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{30}NO_2$ 268.2277, found 268.2271.

*N-((R)-2-Phenylbut-3-enyl)-3-(6,10-dioxaspiro[4.5]decan-1-yl)-propanamide (**S18**).* Following general procedure D, **S18** (408 mg, 1.19 mmol, 73%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, *J* = 7.5 Hz, 2H), 7.24−7.21 (m, 3H), 5.99−5.92 (m, 2H), 5.14−5.09 (m, 2H), 3.88 (tt, *J* = 11.7, 2.4 Hz, 1H), 3.83−3.78 (m, 2H), 3.77−3.72 (m, 1H), 3.70−3.61 (m, 1H), 3.54−3.46 (m, 2H), 2.41−2.35 (m, 1H), 2.24−2.17 (m, 1H), 2.14−2.08 (m, 1H), 1.98−1.87 (m, 1H), 1.85−1.66 (m, 4H), 1.64−1.52 (m, 3H), 1.34 (dt, *J* = 13.2, 2.4 Hz, 1H), 1.29−1.19 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.98, 173.97, 141.5, 139.34, 139.28, 128.84, 128.82, 128.02, 127.98, 127.0, 116.33, 116.31, 108.8, 62.31, 62.28, 60.5, 49.62, 49.57, 47.5, 43.5, 35.2, 30.81, 30.77, 29.55, 29.54, 26.1, 25.1, 21.29, 21.27; IR (thin film, cm$^{-1}$) 3299, 3083, 2958, 1646; HRMS (ESI) *m*/*z* [M + Na]$^+$ calcd for $C_{21}H_{29}NO_3Na$ 366.2045, found 366.2044.

*(2R)-N-(3-(6,10-Dioxaspiro[4.5]decan-1-yl)propyl)-2-phenylbut-3-en-1-amine (**S19**).* Following general procedure E, **S19** (330 mg, 1.00 mmol, 88% yield) was obtained as light yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, *J* = 7.6 Hz, 2H), 7.24−7.21 (m, 3H), 6.01−5.94 (m, 1H), 5.15−5.11 (m, 2H), 3.93−3.82 (m, 4H), 3.55 (q, *J* = 7.4 Hz, 1H), 2.90 (d, *J* = 7.4 Hz, 2H), 2.68−2.59 (m, 2H), 2.11−2.05 (m, 1H), 2.03−1.93 (m, 1H), 1.89−1.37 (m, 9H), 1.30−1.12 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.6, 140.3, 128.9, 127.9, 126.8, 116.1, 109.0, 62.2, 60.8, 54.5, 50.3, 50.1, 48.9, 30.7, 29.0, 28.9, 26.3, 26.2, 21.2; IR (thin film, cm$^{-1}$) 3332, 3081, 2863, 1148, 1109; HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{32}O_2N$ 330.2433, found 330.2429.

*N-((S)-2-Methylbut-3-en-1-yl)-3-(6,10-dioxaspiro[4.5]decan-1-yl)-propanamide (**S20**).* Following general procedure D, **S20** (59 mg, 0.21 mmol, 72%) was obtained as a colorless solid; changes in the procedure include the addition of $Et_3N$ (45 $\mu$L) to the amide-coupling step: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.95 (broad s, 1H), 5.73−5.66


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(m, 1H), 5.08−5.03 (m, 2H), 3.95−3.87 (m, 4H), 3.32 (ddd, $J$ = 12.7, 6.0, 6.0 Hz, 1H), 3.08−3.03 (m, 1H), 2.41−2.39 (m, 1H), 2.31−2.29 (m, 1H), 2.26−2.22 (m, 1H), 2.18−2.12 (m, 1H), 2.02−2.00 (m, 1H), 1.90−1.81 (m, 3H), 1.78−1.76 (m, 1H), 1.66−1.60 (m, 3H), 1.39 (d, $J$ = 13.3 Hz, 1H), 1.31−1.27 (m, 1H), 1.02 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.9, 141.8, 141.7, 115.1, 115.0, 108.9, 62.3, 60.5, 47.72, 47.71, 44.5, 44.4, 38.2, 38.1, 35.4, 30.9, 30.8, 29.50, 29.46, 26.1, 25.1, 25.0, 21.29, 21.27, 17.72, 17.68; IR (thin film, cm$^{-1}$) 3298, 3080, 2960, 1644; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{27}NO_3Na$ 304.1889, found 304.1882.

*(2S)-N-(3-(6,10-Dioxaspiro[4.5]decan-1-yl)propyl)-2-methylbut-3-en-1-amine (**S21**).* Following general procedure E, **S21** (26 mg, 0.097 mmol, 46%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.69−5.62 (m, 1H), 5.11−5.00 (m, 2H), 3.93−3.85 (m, 4H), 2.62−2.52 (m, 3H), 2.49−2.45 (m, 1H), 2.38−2.35 (m, 1H), 2.11−2.05 (m, 1H), 1.98−1.96 (m, 1H), 1.89−1.78 (m, 3H), 1.65−1.51 (m, 5H), 1.39 (d, $J$ = 14.7 Hz, 1H), 1.32−1.12 (m, 2H), 1.00 (d, $J$ = 6.7 Hz, 3H), 0.89−0.88 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.8, 114.69, 114.68, 108.9, 62.1, 60.6, 55.50, 55.49, 60.4, 48.87, 48.85, 38.3, 36.8, 30.6, 30.4, 29.8, 28.9, 28.8, 28.6, 26.2, 26.1, 24.9, 23.7, 21.1, 18.5, 18.4, 17.8; IR (thin film, cm$^{-1}$) 3076, 2955, 2863; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{16}H_{30}NO_2$ 268.2277, found 268.2271.

*2-(11-Methyl-1,5-dioxaspiro[5.5]undecan-7-yl)-N-((S)-2-methylbut-3-en-1-yl)acetamide (**S22**).* Following general procedure D, **S22** (31 mg, 0.11 mmol, 70%) was obtained as a colorless solid; changes to the general procedure include addition $Et_3N$ (23 $\mu$L) to the amide coupling step: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.85 (broad d, $J$ = 26.6 Hz, 1H), 5.69−5.66 (m, 1H), 5.07−5.04 (m, 2H), 3.95−3.80 (m, 4H), 3.34−3.29 (m, 1H), 3.04−3.01 (m, 1H), 2.78−2.58 (m, 1H), 2.50−2.44 (m, 1H), 2.35−2.29 (m, 1H), 2.19−2.10 (m, 1H), 2.03 (dd, $J$ = 14.3, 4.6 Hz, 1H), 1.98−1.90 (m, 1H), 1.85−1.81 (m, 1H), 1.67−1.52 (m, 2H), 1.52−1.42 (m, 1H), 1.39−1.32 (m, 3H), 1.02 (d, $J$ = 6.6 Hz, 3H), 0.96 (d, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 172.0, 141.7, 141.6, 115.24, 115.16, 58.7, 58.6, 48.13, 48.11, 45.6, 44.50, 44.46, 44.4, 38.31, 38.30, 38.24, 38.19, 37.4, 37.12, 37.11, 36.8, 35.58, 35.56, 25.51, 25.48, 19.7, 17.69, 17.65, 14.6, 13.7; IR (thin film, cm$^{-1}$) 3296, 3078, 2963, 1640; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{17}H_{29}NO_3Na$ 318.2045, found 318.2047.

*(2S)-2-Methyl-N-(2-(11-methyl-1,5-dioxaspiro[5.5]undecan-7-yl)-ethyl)but-3-en-1-amine (**S23**).* Following general procedure E, **S23** (42 mg, 0.15 mmol, 48%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 5.71−5.63 (m, 1H), 5.08−5.00 (m, 2H), 3.84 (broad s, 4H), 2.71−2.63 (m, 1H), 2.60−2.45 (m, 3H), 2.39−2.34 (m, 1H), 1.90−1.51 (m, 7H), 1.44−1.36 (m, 5H), 1.01 (d, $J$ = 6.6 Hz, 3H), 0.93 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 143.0, 114.61, 114.56, 100.7, 58.7, 58.5, 55.74, 55.67, 49.1, 48.9, 38.5, 38.4, 25.6, 19.7, 18.5, 18.4, 13.9; IR (thin film, cm$^{-1}$) 3076, 2931, 2861; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{17}H_{32}NO_2$ 282.2433, found 282.2428.

**Preparation and Characterization Data of 1-Azabicyclic Products Reported in Table 3.** Characterization data for azabicyclic compounds **31a**, **32a**, **33a**, and **34a** have been described.[9]

*General Procedure G for the 2-Aza-Cope Rearrangement and Subsequent Cbz Protection to Provide Products Reported in Tables 3 and 4. (3aS,6aR)-Benzyl 6a-((E)-But-2-en-1-yl)-hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (**31b**).* A mixture of aminoketal **S13** (28 mg, 0.12 mmol), morpholine (1 $\mu$L, 0.011 mmol), TFA (13 $\mu$L, 0.11 mmol), and dimedone (29 mg, 0.28 mmol) was stirred at 120 °C in a sealed 1-dram vial using an aluminum heating block. After 30 min, the reaction vessel was cooled in an ice bath for approximately 1 min. The reaction mixture was allowed to warm to room temperature and was dissolved in $CHCl_3$ (1 mL), and the solution was transferred to a larger reaction vessel. To this flask was added saturated aqueous $Na_2CO_3$ (0.5 mL), $H_2O$ (0.5 mL), and benzyl chloroformate (57 $\mu$L, 0.34 mmol). The reaction was vigorously stirred at room temperature for 24 h and then extracted with $CH_2Cl_2$ (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. The crude residue was purified on silica gel (1:19 EtOAc:hexanes) to provide 24 mg (0.081 mmol, 73%) of **31b** as a colorless oil. HPLC analysis indicated an enantiomeric excess of 95% [CHIRALCEL AD column; flow, 1 mL/min; 98% $n$-hexane:2% $i$-PrOH; $\lambda$ = 210 nm; major enantiomer $t_R$ = 11.25 min; minor enantiomer $t_R$ = 13.89 min]: $[\alpha]^{23}_{577}$ −7.88, $[\alpha]^{23}_{546}$ −6.81, $[\alpha]^{23}_{435}$ −14.0 ($c$ 0.45, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 393 K) $\delta$ 7.36−7.28 (m, 5H), 5.46−5.32 (m, 2H), 5.11 (d, $J$ = 12.7 Hz, 1H), 5.06 (d, $J$ = 12.7 Hz, 1H), 3.52−3.46 (m, 1H), 3.43−3.39 (m, 1H), 2.69 (dd, $J$ = 12.1, 6.3 Hz, 1H), 2.43 (dddd, $J$ = 8.6, 8.6, 5.3, 5.3 Hz, 1H), 2.27 (dd, $J$ = 15.8, 8.4 Hz, 1H), 2.15−2.11 (m, 1H), 1.93−1.86 (m, 1H), 1.81 (dddd, $J$ = 15.4, 7.3, 7.3, 7.3 Hz, 1H), 1.72−1.45 (m, 4H), 1.62 (d, $J$ = 5.8 Hz, 3H), 1.43−1.37 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 393 K) $\delta$ 152.8, 136.9, 127.5, 126.8, 126.70, 126.67, 125.8, 125.0, 73.4, 64.9, 47.3, 47.1, 37.3, 31.2, 27.8, 24.1, 16.7; IR (thin film, cm$^{-1}$) 2948, 1699; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{19}H_{26}NO_2$ 300.1964, found 300.1960.

*(3aS,7aR)-Benzyl 7a-((E)-But-2-en-1-yl)octahydro-1H-indole-1-carboxylate) (**32b**).* Following general procedure G, **32b** (25 mg, 0.078 mmol, 75%) was obtained as a colorless oil. HPLC analysis indicated an enantiomeric excess of 95% [CHIRALCEL AD column; flow, 1.0 mL/min; 98% $n$-hexane:2% $i$-PrOH; $\lambda$ = 210 nm; major enantiomer $t_R$ = 13.47 min; minor enantiomer $t_R$ = 17.22 min]: $[\alpha]^{23}_{589}$ −47.2, $[\alpha]^{23}_{577}$ −48.0, $[\alpha]^{23}_{546}$ −54.7, $[\alpha]^{23}_{435}$ −94.3 ($c$ 0.43, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 393 K) $\delta$ 7.38−7.27 (m, 5H), 5.41−5.37 (m, 1H), 5.30−5.29 (m, 1H), 5.07 (d, $J$ = 12.7 Hz, 1H), 5.01 (d, $J$ = 12.2 Hz, 1H), 3.56−3.52 (m, 1H), 3.24 (app dd, $J$ = 16.3, 7.9 Hz, 1H), 2.43 (dd, $J$ = 16.2, 6.0 Hz, 1H), 2.33 (dd, $J$ = 13.6, 7.8 Hz, 1H), 2.06−2.02 (m, 1H), 1.89−1.64 (m, 4H), 1.58 (d, $J$ = 5.6 Hz, 3H), 1.46−1.26 (m, 6H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 393 K) $\delta$ 152.9, 137.0, 127.6, 126.8, 126.7, 126.3, 124.9, 64.8, 63.3, 45.5, 40.1, 37.4, 31.5, 25.4, 24.8, 21.0, 20.6, 16.8; IR (thin film, cm$^{-1}$) 3029, 2928, 2857, 1701; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{20}H_{27}NO_2Na$ 336.1939, found 336.1934.

*(4aS,7aR)-Benzyl 7a-((E)-But-2-en-1-yl)octahydro-1H-cyclopenta[b]pyridine-1-carboxylate (**33b**).* Following general procedure G, **33b** (42 mg, 0.13 mmol, 71%) was obtained as a colorless oil. HPLC analysis indicated an enantiomeric excess of 95% [CHIRALCEL OJ column; flow, 0.5 mL/min; 99.9% $n$-hexane:0.1% $i$-PrOH; $\lambda$ = 210 nm; major enantiomer $t_R$ = 44.40 min; minor enantiomer $t_R$ = 55.46 min (for the opposite enantiomer as shown above)]: $[\alpha]^{23}_{589}$ −13.0,$[\alpha]^{23}_{577}$ −13.8, $[\alpha]^{23}_{546}$ −14.9, $[\alpha]^{23}_{435}$ −28.8 ($c$ 0.36, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.35−7.31 (m, 5H), 5.46−5.38 (m, 2H), 5.15 (d, $J$ = 12.4 Hz, 1H), 3.96 (d, $J$ = 12.6 Hz, 1H), 3.96 (app dd, $J$ = 13.4, 5.7 Hz, 1H), 2.97 (app dt, $J$ = 13.2, 4.8 Hz, 1H), 2.62 (dd, $J$ = 12.7, 4.4 Hz, 1H), 2.19−2.12 (m, 3H), 2.10−2.08 (m, 1H), 1.77−1.67 (m, 3H), 1.64 (d, $J$ = 4.9 Hz, 3H), 1.57−1.42 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.6, 137.3, 128.53, 128.52, 128.49, 128.2, 128.0, 127.9, 127.1, 67.6, 66.7, 42.3, 41.4, 39.5, 38.3, 29.5, 24.7, 21.8, 21.4, 18.2; IR (thin film, cm$^{-1}$) 3031, 2922, 2851, 1745; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{20}H_{27}NO_2Na$ 336.1939, found 336.1931.

*(3aS,7R,7aS)-Benzyl 7a-((E)-But-2-en-1-yl)-7-methyloctahydro-1H-indole-1-carboxylate (**34b**).* Following general procedure G, **34b** (12 mg, 0.035 mmol, 70%) was obtained as a colorless oil. HPLC analysis indicated an enantiomeric excess of 91% [CHIRALCEL AD column; flow, 1.0 mL/min; 98% $n$-hexane:2% $i$-PrOH; $\lambda$ = 210 nm; major enantiomer $t_R$ = 9.02 min; minor enantiomer $t_R$ = 20.11 min (for the opposite enantiomer as shown above)]: $[\alpha]^{23}_{589}$ −34.3, $[\alpha]^{23}_{577}$ −39.4, $[\alpha]^{23}_{546}$ −44.8, $[\alpha]^{23}_{435}$ −78.3 ($c$ 0.87, $CH_2Cl_2$; data is for the opposite enantiomer as shown above); $^1$H NMR (500 MHz, DMSO-$d_6$, 393K) $\delta$ 7.42−7.34 (m, 5H), 5.49−5.47 (m, 1H), 5.23−5.19 (m, 1H), 5.13 (d, $J$ = 12.1 Hz, 1H), 5.07 (d, $J$ = 12.6 Hz, 1H), 3.54−3.51 (m, 1H), 3.40−3.33 (m, 1H), 3.26−3.22 (m, 1H), 2.21−2.14 (m, 2H), 1.98−1.90 (m, 2H), 1.71−1.42 (m, 7H), 1.61 (d, $J$ = 23.9 Hz, 3H), 1.00 (broad s, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 393K) $\delta$ 154.4, 128.7, 128.5, 128.2, 128.1, 127.8, 127.64, 127.55, 125.7, 67.4, 65.7, 46.4, 37.1, 31.8, 29.9, 24.9, 24.7, 24.4, 20.2, 17.8, 17.1; IR (thin film, cm$^{-1}$) 3028, 2826, 2885, 1704; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{29}NO_2Na$ 350.2096, found 350.2098.

**Synthesis and Characterization Data of 1-Azabicyclics Reported in Table 4 and Their Precursors.** *N-((R)-2-Phenylbut-*


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*3-enyl)-3-(1,5-dioxaspiro[5.5]undecan-7-yl)propanamide (**S24**).* Following general procedure D, **S24** (496 mg, 1.39 mmol, 86%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.5 Hz, 2H), 7.27−7.21 (m, 3H), 6.00−5.93 (m, 2H), 5.15−5.10 (m, 2H), 4.03−3.97 (m, 1H), 3.88 (tt, $J$ = 11.7, 3.1 Hz, 1H), 3.77−3.60 (m, 3H), 3.53−3.46 (m, 2H), 2.54 (app d, $J$ = 12.7 Hz, 1H), 2.35−2.28 (m, 1H), 2.15−2.02 (m, 2H), 1.96−1.83 (m, 1H), 1.59−1.53 (m, 3H), 1.39−1.07 (m, 7H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.65, 173.63, 141.54, 141.52, 139.29, 139.25, 128.9, 128.8, 128.01, 127.97, 126.99, 126.98, 116.41, 116.37, 99.3, 59.15, 59.13, 59.0, 49.6, 49.5, 44.7, 43.7, 35.4, 35.3, 28.2, 28.0, 25.8, 24.8, 24.43, 24.41, 22.4; IR (thin film, cm$^{-1}$) 3299, 3083, 2861, 1644; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{22}H_{31}NO_3Na$ 380.2202, found 380.2200.

*(2R)-N-(3-(1,5-Dioxaspiro[5.5]undecan-7-yl)propyl)-2-phenylbut-3-en-1-amine (**S25**).* Following general procedure E, **S25** (229 mg, 0.667 mmol, 49%) was obtained as a light yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.6 Hz, 2H), 7.23−7.22 (m, 3H), 5.99−5.93 (m, 1H), 5.14−5.11 (m, 2H), 4.02 (t, $J$ = 11.2 Hz, 1H), 3.89 (dt, $J$ = 11.3, 2.3 Hz, 1H), 3.78 (app broad s, 2H), 3.54 (q, $J$ = 7.5 Hz, 1H), 2.90 (d, $J$ = 7.4 Hz, 2H), 2.64−2.60 (m, 2H), 2.45 (broad d, $J$ = 8.8 Hz, 1H), 1.90−1.10 (m, 15H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.6, 140.3, 128.8, 128.0, 127.9, 126.8, 116.0, 99.3, 59.1, 59.0, 54.5, 50.3, 50.1, 28.5, 28.3, 27.3, 25.8, 25.2, 24.4, 22.5; IR (thin film, cm$^{-1}$) 3315, 3081, 2933; HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{22}H_{34}NO_2$ 344.2589, found 344.2583.

Characterization data for azabicyclic compound **35** has been described.[9]

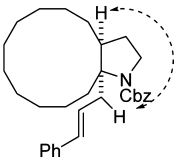
*Benzyl 2-(2-Oxocyclododecyl)acetate (**S26**).* Following general procedure B, **S26** (825 mg, 2.50 mmol, 64%) was obtained as a colorless solid: mp 64−65 °C; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.38−7.31 (m, 5H), 5.13−5.06 (m, 2H), 3.18−3.13 (m, 1H), 2.96−2.87 (m, 2H), 2.32 (dd, $J$ = 16.7, 5.2 Hz, 1H), 2.25 (ddd, $J$ = 17.7, 5.8, 3.6 Hz, 1H), 2.04−1.98 (m, 1H), 1.89−1.83 (m, 1H), 1.60−1.53 (m, 1H), 1.42−1.17 (m, 14H), 1.08−1.06 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 212.4, 172.7, 136.1, 128.8, 128.43, 128.40, 66.6, 47.3, 37.6, 34.3, 28.6, 26.3, 24.1, 23.3, 22.7, 22.4, 21.8, 21.2; IR (thin film, cm$^{-1}$) 3033, 2931, 2864, 1735, 1709, 1164; HRMS (ES) $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{30}O_3Na$ 353.2093, found 353.2084.

*(1,5-Dioxaspiro[5.11]heptadec-7-yl)acetic acid benzyl ester (**S27**).* Following general procedure C, ketal **S27** was obtained as a colorless oil (430 mg, 1.10 mmol, 91%). This product was purified by flash chromatography on silica gel (100:0 to 98:2 to 95:5 hexanes:EtOAc): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.40−7.29 (m, 5H), 5.15−5.08 (m, 2H), 4.00 (t, $J$ = 11.5 Hz, 1H), 3.78−3.73 (m, 2H), 3.53 (dd, $J$ = 11.0, 4.1 Hz, 1H), 2.82 (dd, $J$ = 15.3, 8.7 Hz, 1H), 2.43 (t, $J$ = 8.7 Hz, 1H), 2.30−2.23 (m, 1H), 2.10 (dd, $J$ = 15.3, 2.4 Hz, 1H), 1.98−1.90 (m, 1H), 1.61−1.22 (m, 19H), 1.11−1.06 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 174.7, 136.9, 128.5, 128.3, 128.0, 102.4, 65.8, 59.6, 59.5, 39.1, 34.4, 26.43, 26.37, 25.8, 25.4, 24.6, 23.6, 22.9, 22.7, 22.4, 22.2, 19.3; IR (thin film, cm$^{-1}$) 3063, 2931, 2862, 1736, 1248, 1142; HRMS (ES) $m/z$ [M + Na]$^+$ calcd for $C_{24}H_{36}O_4Na$ 411.2511, found 411.2515.

*N-((R)-2-Phenylbut-3-enyl)-2-(1,5-dioxaspiro[5.11]heptadecan-7-yl)acetamide (**S28**).* Following general procedure D, **S28** (171 mg, 0.400 mmol, 71%) was obtained as an amorphous colorless solid: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.9 Hz, 2H), 7.23 −7.21 (m, 3H), 6.31 (d, $J$ = 18.8 Hz, 1H), 5.96 (dddd, $J$ = 17.2, 9.9, 6.9, 2.5 Hz, 1H), 5.14 −5.07 (m, 2H), 3.99 (t, $J$ = 12.1 Hz, 1H), 3.80−3.69 (m, 3H), 3.64−3.42 (m, 4H), 2.78 (dt, $J$ = 15.1, 5.8 Hz, 1H), 2.25 (ddd, $J$ = 14.8, 11.7, 7.5 Hz, 1H), 2.06 (t, $J$ = 7.7 Hz, 1H), 1.93 (ddd, $J$ = 15.3, 7.6, 2.6 Hz, 1H), 1.88−1.77 (m, 2H), 1.56−1.20 (m, 17H), 1.09−1.04 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 174.9, 174.8, 141.64, 141.58, 139.6, 139.5, 128.87, 128.85, 128.03, 127.99, 126.9, 116.2, 116.1, 102.9, 59.64, 59.58, 59.3, 49.6, 49.4, 43.5, 43.4, 39.5, 39.4, 37.5, 37.4, 27.2, 27.1, 26.4, 26.3, 25.5, 24.5, 23.6, 22.74, 22.65, 22.47, 22.45, 22.1, 19.3; IR (thin film, cm$^{-1}$) 3323, 2931, 2863, 1647, 1140, 1117, 1089; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{27}H_{41}NO_3Na$ 450.2984, found, 450.2972.

*(2R)-N-(2-(1,5-Dioxaspiro[5.11]heptadecan-7-yl)ethyl)-2-phenylbut-3-en-1-amine (**S29**).* Following general procedure E, **S29** (81 mg, 0.20 mmol, 58%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.5 Hz, 2H), 7.25−7.20 (m, 3H), 6.01−5.95 (m, 1H), 5.14−5.10 (m, 2H), 4.02 (t, $J$ = 11.9 Hz, 1H), 3.84 (q, $J$ = 11.4 Hz, 1H), 3.77−3.69 (m, 2H), 3.57 (q, $J$ = 7.3 Hz, 1H), 2.92 (d, $J$ = 7.3 Hz, 2H), 2.72−2.69 (m, 2H), 2.32−2.26 (m, 1H), 2.07−1.93 (m, 2H), 1.56−1.23 (m, 22H), 1.12−1.08 (m, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.77, 142.75, 140.52, 140.48, 128.8, 127.94, 127.90, 126.7, 115.9, 115.8, 103.31, 103.27, 59.5, 59.4, 54.6, 50.3, 50.2, 50.1, 39.9, 39.8, 29.93, 29.91, 27.1, 27.0, 26.6, 26.4, 25.6, 25.11, 25.09, 24.0, 23.14, 23.10, 23.0, 22.6, 22.3, 19.5; IR (thin film, cm$^{-1}$) 3327, 3026, 2929, 2861, 1467, 1245, 1112; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{27}H_{44}O_2N$ 414.3372, found 414.3362.

*(3aS,13aR)-Benzyl 13a-((Z)-3-Phenylallyl)tetradecahydro-1H-cyclododeca[b]pyrrole-1-carboxylate (**36**).* Following general procedure E, **36** (41 mg, 89 $\mu$mol, 74%) was obtained as a colorless amorphous solid (9:1 mixture of diastereomers by $^1$H NMR). The major diastereomer was partially purified by preparatory TLC (9:1 hexanes/EtOAc) for characterization. HPLC analysis indicated an enantiomeric excess of 99% [CHIRALCEL OD column; flow, 1.0 mL/min; 99.5% $n$-hexane:0.5% $i$-PrOH; $\lambda$ = 254 nm; major enantiomer $t_R$ = 19.16 min; minor enantiomer $t_R$ = 27.21 min]: $^1$H NMR (500 MHz, DMSO-$d_6$, 393 K) $\delta$ 7.32−7.25 (m, 9H), 7.19−7.18 (m, 1H), 6.28 (d, $J$ = 15.4 Hz, 1H), 6.15−6.11 (m, 1H), 5.12 (d, $J$ = 12.6 Hz, 1H), 5.03 (d, $J$ = 12.6 Hz, 1H), 3.51 (t, $J$ = 9.8 Hz, 1H), 3.30−3.24 (m, 1H), 2.82−2.68 (m, 2H), 2.32 (dd, $J$ = 14.0, 7.4 Hz, 1H), 2.26−2.22 (m, 1H), 2.09−2.07 (m, 1H), 1.90 (td, $J$ = 12.8, 7.1 Hz, 1H), 1.69 (t, $J$ = 11.8 Hz, 1H), 1.51−1.27 (m, 18H); $^{13}$C NMR (125 MHz, DMSO, 393 K) $\delta$ 137.2, 131.1, 127.9, 127.7, 127.1, 126.3, 125.2, 67.2, 65.0, 46.7, 26.3, 25.9, 25.1, 23.5, 21.59, 21.56, 21.4, 21.1, 17.9; IR (thin film, cm$^{-1}$) 3027, 2925, 2852, 1702, 1459, 1402; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{31}H_{41}NO_2Na$ 482.3035, found 482.3034. The ring fusion geometry was assigned by $^1$H NOE analysis as depicted in the drawing below.




*Benzyl 2-(2-Oxocycloheptyl)acetate (**S30**).* Keto ester **S30** was prepared by using an adapted procedure from Cotarco and coworkers.[35] A 250 mL round-bottom flask with stir bar fitted with a Dean−Stark trap was charged with cycloheptanone (11 mL, 89 mmol), pyrrolidine (6.4 g, 89 mmol), and benzene (60 mL) and the solution was heated to reflux. After 20 h, the reaction was concentrated in vacuo at 55 °C for 1 h. The resultant red oil was dissolved in benzene (45 mL), 2-bromobenzylacetate (8.0 mL, 12 mmol) was added, and the reaction was heated to reflux. After 24 h, the reaction was allowed to cool to 22 °C, concentrated in vacuo, taken up in MeOH (30 mL) and water (6 mL), heated to reflux for 2 h, allowed to cool to 22 °C, and partitioned between $Et_2O$ (400 mL) and 1 M HCl (200 mL). The organic layer was washed with 1 M HCl (2 × 100 mL), saturated aqueous sodium bicarbonate (1 × 50 mL), and brine (1 × 15 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo, and the residue was purified by flash chromatography on silica gel (2:25−3:25 EtOAc:hexanes) to give **S30** (6.3 g, 24 mmol, 45%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.36−7.27 (m, 5H), 5.12−5.05 (m, 2H), 3.10 (dddd, $J$ = 10.9, 8.5, 5.7, 2.9 Hz, 1H), 2.87 (dd, $J$ = 16.8, 8.4 Hz, 1H), 2.59 (dt, $J$ = 16.3, 7.8 Hz, 1H), 2.50−2.38 (m, 1H), 2.33 (dd, $J$ = 16.8, 5.7 Hz, 1H), 1.92−1.76 (m, 3H), 1.76−1.63 (m, 2H), 1.57−1.47 (m, 1H), 1.40−1.22 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 213.8, 172.2, 135.8, 128.4, 128.02, 127.98, 66.1, 47.2, 43.2, 36.5, 31.0, 29.1, 28.8, 23.3; IR (thin film, cm$^{-1}$) 2925, 2854, 1733, 1702. Anal. Calcd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.72. Found: C, 73.49; H, 7.73.

*Benzyl 2-(1,5-Dioxaspiro[5.6]dodecan-7-yl)acetate (**S31**).* Following general procedure C, **S31** (5.2 g, 16 mmol) was isolated as a colorless oil in 84% yield; changes from the general procedure include the exposure of the substrate to the reaction conditions for 2 h: $^1$H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NMR (500 MHz, $CDCl_3$) $\delta$ 7.37−7.25 (m, 5H), 5.15 (d, $J$ = 12.4 Hz, 1H), 5.07 (d, $J$ = 12.4 Hz, 1H), 3.94 (td, $J$ = 11.9, 2.9 Hz, 1H), 3.81 (td, $J$ = 11.7, 2.4 Hz, 1H), 3.73−3.67 (m, 2H), 2.92−2.84 (m, 1H), 2.27−2.18 (m, 2H), 2.09 (ddd, $J$ = 14.8, 9.6, 2.2 Hz, 1H), 1.96−1.80 (m, 2H), 1.76−1.63 (m, 2H), 1.58−1.35 (m, 6H), 1.28 (dt, $J$ = 10.9, 2.2 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.8, 136.2, 128.1, 127.9, 127.7, 101.2, 65.5, 59.04, 58.96, 45.8, 35.8, 29.4, 28.0, 27.8, 26.6, 25.3, 20.3; IR (thin film, cm$^{-1}$) 2931, 2863, 1733. Anal. Calcd for $C_{19}H_{26}O_4$: C, 71.67; H, 8.23. Found: C, 71.45; H, 8.34.

*N-((R)-2-Phenylbut-3-enyl)-2-(1,5-dioxaspiro[5.6]dodecan-7-yl)-acetamide (**S32**).* Following general procedure D, **S32** (369 mg, 1.03 mmol, 66%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.4 Hz, 2H), 7.25−7.21 (m, 3H), 6.00−5.93 (m, 1H), 5.83 (app broad d, $J$ = 5.3 Hz, 1H), 5.15−5.10 (m, 2H), 3.96 (t, $J$ = 11.7 Hz, 1H), 3.82 (t, $J$ = 11.6 Hz, 1H), 3.76−3.59 (m, 3H), 3.56−3.45 (m, 2H), 2.66 (dd, $J$ = 14.6, 4.0 Hz, 1H), 2.10−2.04 (m, 2H), 2.01−1.95 (m, 2H), 1.91−1.76 (m, 2H), 1.70−1.61 (m, 2H), 1.52−1.32 (m, 6H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.90, 173.87, 141.50, 141.46, 139.3, 128.9, 128.0, 127.0, 116.39, 116.36, 102.1, 59.5, 59.43, 59.41, 49.7, 49.6, 46.43, 46.38, 43.7, 43.6, 38.14, 38.09, 29.79, 29.77, 28.4, 28.1, 28.0, 27.1, 25.6, 20.6; IR (thin film, cm$^{-1}$) 3296, 3080, 2928, 1643; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{22}H_{31}NO_3Na$ 380.2202, found 380.2201.

*(2R)-N-(2-(1,5-Dioxaspiro[5.6]dodecan-7-yl)ethyl)-2-phenylbut-3-en-1-amine (**S33**).* Following general procedure E, **S33** (225 mg, 0.655 mmol, 70%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.5 Hz, 2H), 7.24−7.21 (m, 3H), 6.02−5.95 (m, 1H), 5.15−5.11 (m, 2H), 3.97 (tt, $J$ = 11.3, 2.9 Hz, 1H) 3.86 (t, $J$ = 11.0 Hz, 1H), 3.81−3.74 (m, 2H), 3.56 (q, $J$ = 7.5 Hz, 1H), 2.97−2.88 (m, 2H), 2.71 (tt, $J$ = 10.1, 4.8 Hz, 1H), 2.64−2.57 (m, 1H), 2.25−2.18 (m, 1H), 1.97−1.84 (m, 2H), 1.77−1.72 (m, 4H), 1.61−1.26 (m, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.7, 140.4, 128.84, 128.82, 127.94, 127.92, 126.8, 126.7, 116.0, 115.9, 102.6, 59.5, 59.4, 54.73, 54.71, 50.2, 49.11, 49.08, 46.23, 46.19, 30.51, 30.49, 30.3, 28.74, 28.72, 27.20, 27.17, 27.0, 26.9, 25.7, 20.9; IR (thin film, cm$^{-1}$) 3027, 2929, 2861, 2809, 1454, 1108; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{22}H_{34}O_2N$ 344.2590, found 344.2581.

Characterization data for azabicyclic compound **37** has been described previously.[9]

*Benzyl 5-(2-Oxocyclopentyl)pentanoate (**S34**).* Following general procedure B, **S34** (385 mg, 1.40 mmol, 55%) was obtained as a colorless oil after flash chromatography on silica gel (19:1 hexanes:EtOAc to 9:1 hexanes:EtOAc to 4:1 hexanes:EtOAc): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.37−7.32 (m, 5H), 5.12 (s, 2H), 2.37 (t, $J$ = 7.4 Hz, 2H), 2.29 (dd, $J$ = 18.7, 8.4 Hz, 1H), 2.22−2.16 (m, 1H), 2.13−2.05 (m, 1H), 2.02−1.96 (m, 2H), 1.80−1.74 (m, 2H), 1.71−1.61 (m, 2H), 1.48 (qd, $J$ = 10.8, 6.7 Hz, 1H), 1.37 (app quintet, $J$ = 7.9 Hz, 2H), 1.26 (dq, $J$ = 16.1, 8.4 Hz, 1H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 221.5, 173.6, 136.3, 128.7, 128.37, 128.36, 66.3, 49.1, 38.3, 34.3, 29.7, 29.4, 27.2, 25.0, 20.9; IR (thin film, cm$^{-1}$) 3033, 2940, 2860, 1735, 1158; HRMS (ES) $m/z$ [M + Na]$^+$ calcd for $C_{17}H_{22}O_3Na$ 297.1467, found 297.1467.k

*5-(6,10-Dioxaspiro[4.5]dec-1-yl)pentanoic acid benzyl ester (**S35**).* Following general procedure C, ketal **S35** was obtained as a colorless oil (622 mg, 1.87 mmol, 64%): $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.39−7.32 (m, 5H), 5.12 (s, 2H), 3.93−3.82 (m, 4H), 2.38 (t, $J$ = 7.6 Hz, 2H), 2.09−2.05 (m, 1H), 2.05−1.88 (m, 1H), 1.86−1.76 (m, 3H), 1.70−1.59 (m, 5H), 1.41−1.19 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 174.0, 136.4, 128.7, 128.4, 128.3, 109.0, 66.2, 62.0, 60.8, 48.9, 34.6, 30.7, 29.0, 28.2, 28.1, 26.2, 25.6, 21.2; IR (thin film, cm$^{-1}$) 3066, 3034, 2950, 1737, 1151, 1106; HRMS (ES) $m/z$ [M + Na]$^+$ calcd for $C_{20}H_{28}O_4Na$ 355.1885, found 355.1884.

*N-((R)-2-Phenylbut-3-enyl)-5-(6,10-dioxaspiro[4.5]decan-1-yl)-pentanamide (**S36**).* Following general procedure D, **S36** (242 mg, 0.651 mmol, 72%) as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.31 (t, $J$ = 7.5 Hz, 2H), 7.23−7.18 (m, 3H), 5.98−5.91 (m, 1H), 5.54 (broad s, 1H), 5.14−5.09 (m, 2H), 3.90−3.82 (m, 4H), 3.59−3.58 (m, 1H), 3.51−3.48 (m, 2H), 2.11−2.03 (m, 3H), 1.97−1.93 (m, 1H), 1.85−1.73 (m, 3H), 1.64−1.54 (m, 5H), 1.38−1.14 (m, 5H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.3, 141.3, 139.0, 128.8, 127.9, 127.0, 116.5, 108.9, 62.0, 60.7, 49.5, 48.8, 43.6, 36.9, 30.6, 28.9, 28.13, 28.09, 26.2, 26.1, 21.0; IR (thin film, cm$^{-1}$) 3295, 3078, 2944, 1645; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{23}H_{33}O_3NNa$ 394.2358, found 394.2365.

*N-((R)-2-Phenylbut-3-enyl)-5-(6,10-dioxaspiro[4.5]decan-1-yl)-pentan-1-amine (**S37**).* Following general procedure E, **S37** (146 mg, 0.408 mmol, 66%) was obtained as a light-yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.4 Hz, 2H), 7.23−7.18 (m, 3H), 6.00−5.93 (m, 1H), 5.14−5.11 (m, 2H), 3.92−3.85 (m, 5H), 3.54 (q, $J$ = 6.9 Hz, 1H), 2.89 (d, $J$ = 7.4 Hz, 2H), 2.60 (t, $J$ = 7.2 Hz, 2H), 2.10−0.90 (m, 17H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 142.5, 140.3, 128.8, 127.8, 126.8, 116.0, 109.1, 62.1, 60.8, 54.6, 50.1, 49.9, 48.9, 30.7, 30.1, 28.9, 28.5, 28.4, 27.9, 26.2, 21.1; IR (thin film, cm$^{-1}$) 2930, 2858, 1453, 1149, 1111; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{23}H_{36}NO_2$ 358.2746, found 358.2741.

**Preparation and Characterization Data for 1-Azabicyclics Reported in Scheme 8 and Their Aminoketal Precursors.** *(R,E)-tert-Butyl 2-Phenylpent-3-enylcarbamate (**S38**).* Diphenylphosphoryl azide (0.33 mL, 1.5 mmol) was added dropwise via syringe to a solution of (*R,E*)-3-phenylhex-4-enoic acid[36] (0.29 g, 1.5 mmol) and $Et_3N$ (0.21 mL, 1.5 mmol) in *t*-BuOH (2.2 mL) at room temperature. The resulting solution was heated at 85 °C for 48 h, cooled to room temperature, diluted with EtOAc (50 mL), and washed sequentially with $H_2O$ (10 mL), saturated aqueous $NaHCO_3$ (10 mL), and brine (10 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude residue by flash chromatography on silica gel (19:1 hexanes:EtOAc to 9:1 hexanes:EtOAc) gave **S38** (0.31 g, 1.2 mmol, 77%) as a colorless solid (mp 47−48 °C). HPLC analysis indicated an enantiomeric excess of 84%. The product was recrystallized with *n*-hexane/*i*-PrOH to an enantiomeric excess of 87% [CHIRALCEL OD-H column; flow, 1.0 mL/min; 99.7% *n*-hexane/0.3% *i*-PrOH; $\lambda$ = 220 nm; major enantiomer $t_R$ = 44.75 min; minor enantiomer $t_R$ = 55.41 min]: $[\alpha]_{589}^{23}$ −17.7, $[\alpha]_{577}^{23}$ −19.6, $[\alpha]_{546}^{23}$ −24.0, $[\alpha]_{435}^{23}$ −45.6 ($c$ = 1.0, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.33 (t, $J$ = 7.4 Hz, 2H), 7.25−7.20 (m, 3H), 5.58−5.55 (m, 2H), 4.50 (broad s, 1H), 3.42−3.36 (m, 3H), 1.70 (d, $J$ = 4.5 Hz, 3H), 1.43 (s, 9H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.0, 142.3, 131.9, 128.9, 127.9, 127.4, 126.9, 79.4, 49.2, 45.5, 28.6, 18.3; IR (thin film, cm$^{-1}$) 3357, 2975, 2931, 1702, 1506, 1171; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{16}H_{23}NO_2Na$ 284.1626, found 284.1628.

*(R,E)-2-Phenylpent-3-en-1-amine (**S39**).* To a solution of *N*-Boc amine **S38** (180 mg, 0.690 mmol) in $CH_2Cl_2$ (3.4 mL) was added TFA (0.530 mL, 6.90 mmol) dropwise via syringe at 0 °C. The resulting solution was stirred at room temperature for 1.5 h and quenched with 10% aqueous NaOH at 0 °C until a pH of 14 was reached. The mixture was allowed to warm to room temperature and extracted with $Et_2O$ (3 × 15 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo to provide **S39** (140 mg) as a yellow oil that was used in subsequent reactions without further purification.

*N-((R,E)-2-Phenylpent-3-enyl)-2-(6,10-dioxaspiro[4.5]decan-1-yl)-acetamide (**S40**).* Following general procedure D, **S40** (35 mg, 0.10 mmol, 16%) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.32 (t, $J$ = 7.9 Hz, 2H), 7.24−7.21 (m, 3H), 6.26 (broad s, 1H), 5.57−5.54 (m, 2H), 3.87−3.75 (m, 4H), 3.63−3.44 (m, 3H), 2.56 (dd, $J$ = 14.9, 6.6 Hz, 1H), 2.20−2.08 (m, 1H), 2.08−2.04 (m, 2H), 1.87−1.80 (m, 3H), 1.69 (d, $J$ = 5.2 Hz, 3H), 1.65−1.62 (m, 1H), 1.33−1.26 (m, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 173.25, 173.23, 142.5, 142.4, 132.19, 132.16, 131.9, 128.9, 128.8, 127.93, 127.88, 127.2, 127.1, 127.0, 126.8, 108.3, 108.2, 62.30, 62.28, 60.74, 60.71, 48.8, 48.7, 46.03, 45.98, 44.23, 44.17, 36.05, 36.04, 30.47, 30.46, 29.6, 29.5, 26.0, 25.99, 21.2, 18.3; IR (thin film, cm$^{-1}$) 3299, 2961, 2932, 2867, 1642, 1544; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{29}NO_3Na$ 366.2045, found 366.2044.

*(2R,E)-N-(2-(6,10-Dioxaspiro[4.5]decan-1-yl)ethyl)-2-phenylpent-3-en-1-amine (**39a**).* Following general procedure E, **39a** (33 mg, 0.10 mmol, 98%) was obtained as a light-brown oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.31 (t, $J$ = 7.7 Hz, 2H), 7.23−7.19 (m, 3H), 5.58−5.55 (m, 2H), 3.92−3.82 (m, 4H), 3.49 (q, $J$ = 7.2 Hz, 1H), 2.88−2.85 (m,


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2H), 2.69−2.64 (m, 2H), 2.10−2.06 (m, 1H), 2.00−1.91 (m, 1H), 1.84−1.74 (m, 5H), 1.69−1.62 (m, 8H), 1.40−1.36 (m, 2H), 1.31−1.26 (m, 2H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 143.59, 143.55, 133.2, 133.1, 128.77, 128.75, 127.81, 127.79, 126.8, 126.7, 126.56, 126.55, 108.9, 62.2, 60.8, 55.2, 49.3, 48.9, 47.1, 30.6, 30.5, 29.9, 29.3, 29.1, 26.1, 21.3, 18.3; IR (thin film, cm$^{-1}$) 3305, 3206, 2954, 2861, 1451, 1149, 1110; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{21}H_{32}NO_2$ 330.2433, found 330.2423.

*(3aS,6aS)-Benzyl 6a-((R,E)-4-Phenylbut-3-en-2-yl)-hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (**40**).* Following general procedure G, **40** (28 mg, 0.075 mmol, 75%) was obtained as a colorless oil. HPLC analysis indicated an enantiomeric excess of 87% [CHIRALCEL OD-H column; flow, 1.0 mL/min; 99.8% *n*-hexane:0.2% *i*-PrOH; $\lambda$ = 254 nm; major enantiomer $t_R$ = 43.90 min; minor enantiomer $t_R$ = 40.20 min]: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.38−7.29 (m, 9H), 7.20 (t, $J$ = 7.3 Hz, 1H), 6.43 (d, $J$ = 15.8 Hz, 1H), 6.17 (dd, $J$ = 15.8, 8.5 Hz, 1H), 5.14−5.09 (m, 2H), 3.60−3.47 (m, 2H), 3.34 (m, 1H), 2.67−2.50 (m, 1H), 2.14−2.10 (m, 1H), 2.00−1.92 (m, 2H), 1.76−1.72 (m, 1H), 1.60−1.55 (m, 2H), 1.50−1.38 (m, 2H), 0.88 (d, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 152.7, 137.0, 136.8, 132.4, 129.8, 127.7, 127.6, 126.9, 126.6, 126.2, 125.3, 76.6, 65.0, 47.3, 44.1, 41.4, 36.7, 32.3, 28.6, 24.3, 15.2; IR (thin film, cm$^{-1}$) 3027, 2955, 2868, 1698, 1402; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{25}H_{29}NO_2Na$ 398.2096, found 398.2097.

*(R,E)-tert-Butyl (2,4-Diphenylbut-3-en-1yl)carbamate (**S41**).* To a solution of the catalyst HG-II[37] (13 mg, 0.02 mmol) in $CH_2Cl_2$ (1.3 mL) was added homoallylamine **25** (0.10 g, 0.40 mmol) and styrene (0.16 mL, 1.2 mmol). The green solution was heated to reflux for 12 h. After 12 h, the solution was cooled to room temperature and concentrated under reduced pressure to a brown solid. The crude material was purified by silica gel chromatography (100% hexanes to 4:1 hexanes:$Et_2O$) to yield **S41** as a colorless solid (92 mg, 0.28 mmol, 70%): mp 80−81 °C; $[\alpha]_{22}^{589}$ −6.35, $[\alpha]_{22}^{577}$ −7.12, $[\alpha]_{22}^{546}$ −8.15, $[\alpha]_{22}^{435}$ −7.48 ($c$ 1.3, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.21 (m, 10H), 6.49 (d, $J$ = 15.9 Hz, 1H), 6.34 (dd, $J$ = 15.9, 7.8 Hz, 1H), 4.57 (broad s, 1H), 3.69−3.68 (m, 1H), 3.57−3.56 (m, 1H), 3.52−3.48 (m, 1H), 1.43 (s, 9H); $^{13}$C NMR (125 MHz) $\delta$ 156.1, 141.7, 137.2, 131.7, 130.8, 129.0, 128.7, 128.0, 127.6, 127.1, 126.5, 79.5, 49.5, 45.5, 28.6; IR (thin film, cm$^{-1}$) 3430, 3358, 3060, 2979, 1710; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{25}O_2NNa$ 346.1783, found 346.1793.

*(R,E)-2,4-Diphenylbut-3-en-1-amine (**S42**).* To a solution of Boc-amide **S41** (89 mg, 0.28 mmol) in $CH_2Cl_2$ (1.3 mL) at 0 °C was added TFA (0.21 mL, 2.8 mmol) dropwise over 3 min. The resulting clear and colorless solution was warmed to room temperature and maintained for 1.5 h. The reaction was quenched by the addition of 10% aqueous solution of NaOH until the solution is basic (pH >10 analyzed by pH paper) at 0 °C. The solution was allowed to warm to room temperature and extracted with $Et_2O$ (3 × 50 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated to provide the amine **S42** as a slightly yellow oil (61 mg, 0.28 mmol). This amine was used without further purification: $[\alpha]_{22}^{589}$ +6.24, $[\alpha]_{22}^{577}$ +6.61, $[\alpha]_{22}^{546}$ +8.33, $[\alpha]_{22}^{435}$ +22.2 ($c$ 1.9, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.39−7.20 (m, 10H), 6.51 (d, $J$ = 15.7 Hz, 1H), 6.25 (dd, $J$ = 15.7, 8.1 Hz, 1H), 3.59 (broad d, $J$ = 7.2 Hz, 1H), 3.47 (broad s, 2H), 3.10 (broad s, 2H); $^{13}$C NMR (125 MHz) $\delta$ 141.1 136.9, 132.3, 130.1, 129.2, 128.8, 127.9, 127.8, 127.4, 126.5, 50.9, 46.0; IR (thin film, cm$^{-1}$) 3357, 3290, 2929; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{16}H_{18}N$ 224.1439, found 224.1445.

*N-((R,E)-2,4-Diphenylbut-3-en-1-yl)-2-(6,10-dioxaspiro[4.5]-decan-1yl)acetamide (**S43**).* Following general procedure D, **S43** (45 mg, 0.11 mmol, 65%) was obtained as a colorless solid: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.39−7.20 (m, 10H), 6.47 (dd, $J$ = 12.7, 4.5 Hz, 1H), 6.36−6.31 (m, 1H), 3.85−3.54 (m, 7H), 2.58 (dd, $J$ = 14.4, 6.8 Hz, 1H), 2.21−2.13 (m, 1H), 2.11−2.00 (m, 2H), 1.91−1.71 (m, 3H), 1.65−1.54 (m, 3H), 1.29−1.22 (m, 2H); $^{13}$C NMR (125 MHz) $\delta$ 173.38, 173.36, 141.9, 141.7, 137.3, 137.2, 131.4, 131.0, 129.0, 128.72, 128.71, 128.1, 128.0, 127.63, 127.60, 127.1, 126.4, 108.2, 62.3, 60.7, 49.04, 49.01, 46.09, 46.05, 44.2, 44.1, 36.08, 36.05, 30.52, 30.45, 30.4, 29.9, 29.7, 29.6, 26.0, 21.2, 21.2; IR (thin film, cm$^{-1}$) 3330, 3059, 2960, 2866, 1721; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{26}H_{31}NO_3Na$ 428.2202, found 428.2203.

*(2R,E)-N-(2-(6,10-Dioxaspiro[4.5]decan-1-yl)ethyl)-2,4-diphenylbut-3-en-1-amine (**39b**).* Following general procedure E, **39b** (204 mg, 0.520 mmol, 81% yield) was obtained as a light-yellow oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.46−7.26 (m, 10H), 6.55 (dd, $J$ = 15.9, 4.0 Hz, 1H), 6.42 (dd, $J$ = 15.9, 8.0 Hz, 1H), 3.97−3.76 (m, 5H), 3.08 (d, $J$ = 7.4 Hz, 2H), 2.78−2.68 (m, 2H), 2.18−2.12 (m, 1H), 2.02−2.00 (m, 1H), 1.94−1.83 (m, 3H), 1.73−1.65 (m, 3H), 1.50−1.22 (m, 4H); $^{13}$C NMR (125 MHz) $\delta$ 142.71, 142.67, 137.42, 137.39, 132.1, 132.0, 131.14, 131.07, 128.89, 128.88, 128.7, 128.65, 128.59, 128.4, 128.3, 127.96, 127.94, 127.7, 127.44, 127.43, 126.8, 126.84, 126.82, 126.4, 126.3, 108.8, 62.7, 62.2, 62.1, 60.8, 54.9, 49.41, 49.39, 48.84, 48.82, 46.97, 46.96, 30.53, 30.50, 29.23, 29.21, 29.0, 26.0, 21.2; IR (thin film, cm$^{-1}$) 3654, 3025, 2951, 1147; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{26}H_{34}NO_2$ 392.2590. found 392.2585.

*(3aS,6aS)-Benzyl 6a-((1S, E)-1,3-Diphenylallyl)-hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (**41**).* Following general procedure G, **41** (6 mg, 14 $\mu$mol, 65% yield) was obtained as a light colorless oil. HPLC analysis indicated an enantiomeric excess of 99% [CHIRALCEL AD column; flow, 1.0 mL/min; 98% *n*-hexane/2% *i*-PrOH; $\lambda$ = 254 nm; major enantiomer $t_R$ = 29.97 min; minor enantiomer $t_R$ = 23.72 min]: $[\alpha]_{22}^{589}$ −66.0, $[\alpha]_{22}^{577}$ −69.9, $[\alpha]_{22}^{546}$ −79.7, $[\alpha]_{22}^{435}$ −148.6 ($c$ 1.2, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 393 K) $\delta$ 7.50−7.40 (m, 6H), 7.35−7.30 (m, 3H), 7.24−7.15 (m, 6H), 6.73 (dd, $J$ = 15.6, 9.9 Hz, 1H), 6.48 (d, $J$ = 15.5 Hz, 1H), 5.22 (d, $J$ = 12.6, 1H), 5.12 (broad d, $J$ = 13.4 Hz, 1H), 4.50 (broad d, $J$ = 12.8 Hz, 1H), 3.30 (ddd, $J$ = 10.5, 8.0, 8.0 Hz, 1H), 3.02−2.97 (m, 1H), 2.69 (ddd, $J$ = 10.7, 8.8, 4.7 Hz, 1H), 2.24 (broad s, 1H), 2.04 (ddd, $J$ = 14.3, 7.3, 7.3 Hz, 1H), 1.90−1.84 (m, 1H), 1.60−1.46 (m, 2H), 1.42−1.37 (m, 1H), 1.31−1.28 (m, 1H), 1.18−1.12 (m, 1H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 393 K) $\delta$ 152.7, 141.4, 136.82, 136.78, 131.9, 129.5, 127.9, 127.8, 127.6, 127.1, 127.0, 126.9, 126.5, 125.6, 125.5, 77.5, 65.1, 51.6, 46.6, 43.9, 37.1, 32.6, 27.6, 24.3; IR (thin film, cm$^{-1}$) 3028, 2951, 1699, 1132; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{30}H_{31}NO_2Na$ 460.2252, found 460.2243.

*(R,E)-tert-Butyl (4-Cyclohexyl-2-phenylbut-3-en-1-yl)carbamate (**S44**).* To a stirring solution of HG-II[37] (23 mg, 0.036 mmol) in $CH_2Cl_2$ (1.2 mL) was added homoallylic carbamate **25** (0.090 g, 0.36 mmol) and vinylcyclohexane (0.25 mL, 1.8 mmol). The green solution was heated to reflux for 12 h. After 22 h, the solution was cooled to room temperature and concentrated under reduced pressure to a brown solid. The crude material was purified by flash chromatography on silica gel (100% hexanes to 9:1 hexanes:$Et_2O$) to yield **S44** as a colorless solid (49 mg, 0.15 mmol, 41%) that was a 9:1 mixture of *E*:*Z* double-bond isomers: mp 83−84 °C; $^1$H NMR (600 MHz, $CDCl_3$) $\delta$ 7.33−7.31 (m, 2H), 7.24−7.20 (m, 3H), 5.54−5.48 (m, 2H), 5.44−5.39 (m, 0.18 H), 3.41 (broad s, 1H), 3.37−3.32 (m, 2H), 3.22−3.18 (m, 0.11H), 1.97−1.93 (m, 1H), 1.74−1.69 (m, 5H), 1.65−1.63 (1.3H), 1.43 (s, 10.5 H), 1.29−1.22 (m, 2.4 H), 1.18−1.10 (m, 3.3 H); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 156.0, 142.5, 138.8, 128.8, 128.0, 127.90, 127.88, 127.8, 127.6, 126.8, 79.3, 49.0, 45.7, 40.9, 33.2, 28.6, 26.2; IR (thin film, cm$^{-1}$) 3438, 3363, 2975, 1704, 1601, 1171; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{21}H_{31}NO_2Na$ 352.2252, found 352.2254.

*(R,E)-4-Cyclohexyl-2-phenylbut-3-en-1-amine (**S45**).* To a solution of Boc-amide **S44** (49 mg, 0.15 mmol) in $CH_2Cl_2$ (0.68 mL) at 0 °C was added TFA (0.12 mL, 1.5 mmol) dropwise over 3 min. The resulting clear and colorless solution was warmed to room temperature and maintained for 1.5 h. The reaction was quenched by the addition of 10% aqueous solution of NaOH until the solution was basic (pH >10 analyzed by pH paper) at 0 °C. The solution was warmed to room temperature and extracted with $Et_2O$ (3 × 50 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated to provide the amine as a colorless oil. The crude material could be used without further purification or purified to obtain an analytically pure sample (>98% *E* olefin isomer) by flash chromatography on silica gel (99:1 $Et_2O$:$Et_3N$) to yield **S45** as a colorless oil (25 mg, 0.11 mmol. 73%): $[\alpha]_{22}^{589}$ −25.1, $[\alpha]_{22}^{577}$ −27.0, $[\alpha]_{22}^{546}$ −30.7 $[\alpha]_{22}^{435}$ −56.4 ($c$ 1.3, $CH_2Cl_2$); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.34−7.16 (m, 5H), 5.52−


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5.51 (m, 2H), 3.23−3.19 (m, 1H), 2.95−2.87 (m, 2H), 2.00−1.92 (m, 1H), 1.73−1.63 (m, 5H), 1.47 (broad s, 1H), 1.28−1.07 (m, 6H); $^{13}$C NMR (125 MHz) $\delta$ 143.3, 138.7, 128.7, 128.6, 127.9, 126.5, 53.0, 47.7, 40.9, 33.4, 33.3, 26.3, 26.2, 25.1; IR (thin film, cm$^{-1}$) 3366, 3284, 3026, 2920, 2850, 1074, 1029; HRMS (ESI) $m/z$ [M + H]$^+$ calcd for $C_{16}H_{24}N$ 230.1909, found 230.1909.

*N-((R,E)-4-Cyclohexyl-2-phenylbut-3-en-1-yl)-2-(6,10-dioxaspiro-[4.5]decan-1-yl)acetamide (**S46**).* Following general procedure D, **S46** (27 mg, 0.065 mmol, 64% yield) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.38−7.35 (m, 2H), 7.28−7.25 (m, 3H), 6.23 (broad d, $J$ = 17.1 Hz, 1H), 5.55 (s, 1H), 5.54 (dd, $J$ = 3.0, 1.2 Hz, 1H), 3.93−3.76 (m, 4H), 3.71−3.60 (m, 1H), 3.56−3.41 (m, 2H), 2.60 (dd, $J$ = 15.1, 6.7 Hz, 1H), 2.67−2.20 (m, 1H), 2.13−2.07 (m, 2H), 2.10−1.90 (m, 1H), 1.91−1.58 (m, 12H), 1.41−1.05 (m, 5H); $^{13}$C NMR (125 MHz) $\delta$ 173.24, 173.21, 142.6, 142.5, 138.6, 138.5, 128.8, 128.3, 128.0, 127.9, 126.8, 108.3, 108.2, 62.30, 62.27, 60.73, 60.70, 48.7, 48.6, 46.1, 45.9, 44.33, 44.26, 40.9, 36.1, 33.21, 33.17, 30.51, 30.47, 29.9, 29.6, 29.5, 26.3, 26.2, 26.01, 25.99, 21.2; IR (thin film, cm$^{-1}$) 3296, 3061, 2920, 1644; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{26}H_{37}NO_3Na$ 434.2671, found 434.2680.

*(2R,E)-N-(2-(6,10-Dioxaspiro[4.5]decan-1-yl)ethyl)-4-cyclohexyl-2-phenylbut-3-en-1-amine (**39c**).* Following general procedure E, **39c** (18 mg, 0.045 mmol, 67% yield) was obtained as a colorless oil: $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 7.31−7.29 (m, 2H), 7.23−7.20 (m, 3H), 5.51−5.50 (m, 2H), 3.89−3.84 (m, 4H), 3.51−3.45 (m, 1H), 2.89−2.83 (m, 2H), 2.69−2.67 (m, 2H), 2.11−2.06 (m, 1H), 2.00−1.90 (m, 2H), 1.82−1.55 (m, 11H), 1.44−1.04 (m, 9H); $^{13}$C NMR (125 MHz) $\delta$ 138.4, 129.1, 128.7, 128.7, 127.8, 126.51, 126.49, 108.90, 108.88, 62.23, 62.22, 60.79, 60.77, 55.3, 55.2, 49.0, 48.82, 48.76, 47.0, 46.9, 41.0, 40.9, 33.33, 33.30, 33.24, 33.23, 30.7, 30.6, 29.31, 29.25, 29.0, 26.4, 26.27, 26.26, 26.15, 21.24, 21.23; IR (thin film, cm$^{-1}$) 3430, 3313, 3052, 2923, 1264; HRMS (ESI) $m/z$: [M + H]$^+$ calcd for $C_{26}H_{40}NO_2$ 398.3059, found 398.3053.

*(3aS,6aS)-Benzyl 6a-((R,E)-1-Cyclohexyl-3-phenylallyl)-hexahydrocyclopenta[b]pyrrole-1(2H)-carboxylate (**42**).* Following general procedure G, **42** (31 mg, 0.071 mmol, 49%) was obtained as a colorless oil. HPLC analysis indicated an enantiomeric excess of 99% [CHIRALCEL AD column; flow, 0.5 mL/min; 98% $n$-hexane:2% $i$-PrOH; $\lambda$ = 254 nm; major enantiomer $t_R$ = 28.77 min; minor enantiomer $t_R$ = 32.53 min]: $[\alpha]_{22}^{589}$ +41.9, $[\alpha]_{22}^{577}$ +42.1, $[\alpha]_{22}^{546}$ +49.7, $[\alpha]_{22}^{435}$ +92.1 ($c$ = 0.34, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 393 K) $\delta$ 7.42−7.35 (m, 6H), 7.32−7.29 (m, 3H), 7.22−7.19 (m, 1H), 6.34 (d, $J$ = 15.8 Hz, 1H), 6.14 (dd, $J$ = 15.7, 10.6, 1H), 5.15 (d, $J$ = 12.7 Hz, 1H), 5.06 (d, $J$ = 12.6 Hz, 1H), 3.62−3.51 (m, 1H), 2.97 (d, $J$ = 9.5 Hz, 1H), 2.09 (broad s, 1H), 2.00 (dddd, $J$ = 12.9, 8.5, 8.5, 8.5 Hz, 1H), 1.85 (dddd, $J$ = 7.7, 7.7, 7.7, 7.7 Hz, 1H), 1.77−1.73 (m, 2H), 1.69−1.66 (m, 1H), 1.63−1.39 (m, 8H), 1.31−1.29 (m, 1H), 1.23−1.14 (m, 3H), 1.11−1.01 (m, 3H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 393 K) $\delta$ 152.7, 137.0, 136.9, 132.0, 129.4, 127.8, 127.6, 126.9, 126.8, 126.2, 125.4, 76.7, 65.0, 53.3, 47.3, 44.6, 37.9, 33.03, 32.99, 29.4, 28.4, 25.9, 25.7, 25.3, 23.8; IR (thin film, cm$^{-1}$) 3028, 2925, 2851, 1699; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{30}H_{37}NO_2Na$ 466.2722, found 466.2714.

The synthesis and characterization of amino acids **43**−**45** have been reported previously.[9]

*(S)-2-((3aS,6aS)-1-((Benzyloxy)carbonyl)octahydrocyclopenta[b]-pyrrol-6a-yl)-2-cyclohexylacetic acid (**46**).* Ozone was bubbled through a solution of **42** (12 mg, 25 $\mu$mol) in MeOH (1.7 mL) at −78 °C for approximately 30 s until a persistent blue color was observed. The solution was purged with $O_2$ until colorless, quenched with dimethyl sulfide (81 $\mu$L, 1.1 mmol), and warmed to room temperature. After 24 h, the reaction mixture was concentrated in vacuo, dissolved in MeCN (1.8 mL) and $H_2O$ (0.17 mL), and the solution was cooled to 0 °C. Sodium chlorite (23 mg, 0.25 mmol) was added to the solution, and the reaction mixture was warmed to room temperature. After stirring for 24 h, the reaction mixture was concentrated in vacuo, diluted with brine (5 mL), and extracted with EtOAc (3 × 5 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated. Purification of the crude residue by flash chromatography on silica gel (100:100:1 hexanes:Et$_2$O:AcOH) provided **46** (10 mg, 25 $\mu$mol, 99% yield) as a colorless oil: $[\alpha]_{22}^{589}$ −2.90, $[\alpha]_{22}^{577}$ −3.46, $[\alpha]_{22}^{546}$ +1.24, $[\alpha]_{22}^{435}$ +1.88 ($c$ 0.31, $CH_2Cl_2$); $^1$H NMR (500 MHz, DMSO-$d_6$, 393 K) $\delta$ 11.56 (broad s, 1H), 7.36 (broad s, 4H), 7.30 (broad s, 1H), 5.16 (d, $J$ = 1.8 Hz, 1H), 5.06 (broad m, 1H), 3.53−3.41 (broad m, 2H), 3.27 (broad s, 1H), 2.09−2.03 (broad m, 1H), 1.92−1.84 (broad m, 2H), 1.73−1.38 (broad m, 11H), 1.32−0.86 (broad m, 6H); $^{13}$C NMR (125 MHz, DMSO-$d_6$, 393 K) $\delta$ 174.6, 152.6, 137.5, 128.4, 128.3, 128.0, 127.6, 127.1, 75.7, 65.2, 53.0, 47.0, 43.4, 38.5, 36.6, 33.5, 32.7, 30.9, 29.4, 26.3, 26.1, 25.8, 25.0; IR (thin film, cm$^{-1}$) 2921, 2851, 1214; HRMS (ESI) $m/z$ [M + Na]$^+$ calcd for $C_{23}H_{31}NO_4Na$ 408.2151, found 408.2153.

*2,2,2-Trifluoro-1,3-ethan-1-one, 6a-(3-Hydroxypropoxy)-1-((S)-2-methylbut-3-en-1-yl)octahydrocyclopenta[b]pyrrol-1-ium Salt (Diastereomers **49** and **50**).* $^1$H NMR (500 MHz, DMSO-d$_6$) $\delta$: 8.38−8.29 (br d, 2H), 5.73−5.66 (m, 1H), 5.13−5.05 (m, 2H), 3.85−3.74 (m, 4H), 2.98−2.84 (m, 1H), 2.84−2.83 (m, 2H), 2.52−2.48 (m, 1H), 2.11−2.06 (m, 2H), 1.81−1.69 (m, 5H), 1.55−1.50 (m, 3H), 1.34 (d, $J$ = 2.4 Hz, 1H), 1.18−1.16 (m, 1H), 0.98 (d, $J$ = 7.0 Hz, 3H). $^{13}$C NMR (125 MHz, DMSO-d$_6$, contains a mixture of diastereomers, signals observed are reported) $\delta$: 258.4, 158.2, 139.8, 139.8, 139.8, 116.2, 116.2, 107.7, 107.6, 61.5, 59.9, 51.5, 46.58, 46.55, 45.97, 45.96, 34.8, 29.9, 28.4, 25.5, 24.7, 24.7, 24.6, 20.72, 20.71, 14.5.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Copies of $^1$H and $^{13}$C NMR spectra for new compounds, HPLC traces used to determine enantiomeric purity, CIF files for compounds *ent*-**8** and **18**, and general experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

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## ■ REFERENCES

(1) (a) Morita, H.; Arisaka, M.; Yoshida, N.; Kobayashi, J. *Tetrahedron* **2000**, *56*, 2929−2934. Other examples of alkaloid natural products containing these structural frameworks: Huperzine B (b) Liu, J.-S.; Whu, Y.-L.; Yu, C.-M.; Zhou, Y.-Z.; Han, Y.-Y.; Wu, F.-

W.; Qi, N.-F. *Can. J. Chem.* **1986**, *64*, 837−839. Malycorin C (c) Hirasawa, Y.; Tanaka, T.; Kobayashi, J.; Kawahara, N.; Goda, Y.; Morita, H. *Chem. Pharm. Bull.* **2008**, *56*, 1473−1476. Serratine (d) Inubushi, Y.; Tsuda, Y.; Ishii, H.; Sano, T.; Hosokawa, M.; Harayama, T. *Yakugaski Zasshi* **1964**, *84*, 1108−1113.

(2) Chen, C.; Kozikowski, A. P.; Wood, P. L.; Reynolds, I. J.; Ball, R. G.; Pang, Y. P. *J. Med. Chem.* **1992**, *35*, 1634−1638.

(3) Substructure searches for **1** ($n$ = 0−2 and $m$ = 0−2) in SciFinder finds only 23 compounds for which an analysis criteria of biological study or use is recorded; 19 of these are 8a-substituted decahydroquinolines.

(4) Examples include moxifloxacin, which contains an octahydropyrrolopyridine fragment, and ramipril, which contains a hexahydropenta[*b*]pyrrole unit.

(5) For reports of the direct enantioselective construction of specific angularly substituted 1-azacyclic molecules, see: (a) Trauner, D.; Schwarz, J. B.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 3542−3545. (b) Carson, M. W.; Kim, G.; Hentemann, M. F.; Trauner, D.; Danishefsky, S. J. *Angew. Chem., Int. Ed.* **1999**, *38*, 4450−4452. (c) Aldous, D. J.; Drew, M. G. B.; Draffin, W. N.; Hamelin, E. M.-N.; Harwood, L. M.; Thurairatnam, S. *Synthesis* **2005**, 3271−3278. (d) Reggelin, M.; Junker, B.; Heinrich, T.; Slavik, S.; Bühle, P. *J. Am. Chem. Soc.* **2006**, *128*, 4023−4034. (e) Xu, S.; Arimoto, H.; Uemura, D. *Angew. Chem., Int. Ed.* **2007**, *46*, 5746−5749. (f) Keck, G. E.; Heumann, S. A. *Org. Lett.* **2008**, *10*, 4783−4786. (g) Ranatunga, S.; Del Valle, J. R. *Tetrahedron Lett.* **2009**, *50*, 2464−2466. (h) Sethofer, S. G.; Mayer, T.; Toste, F. D. *J. Am. Chem. Soc.* **2010**, *132*, 8276−8277. (i) Nama, K.; Inai, M.; Sundermeier, U.; Greshock, T. J.; Williams, R. M. *Tetrahedron Lett.* **2010**, *51*, 6557−6559. (j) Fustero, S.; Mateu, N.; Simón-Fuentes, A.; Aceña, Luis *J. Org. Lett.* **2010**, *12*, 3014−3017. (k) Yuan, C.; Chang, C.-T.; Axelrod, A.; Siegal, D. *J. Am. Chem. Soc.* **2010**, *132*, 5924−5925. Enantiomerically enriched angularly substituted 1-azabicyclic molecules have been accessed also by separation of a 1:1 mixtures of diastereomers or enantiomers, see: (l) Kozikowski, A. P.; Chen, C. *Tetrahedron* **1990**, *31*, 5869−5872. (m) Chen, C.; Kozikowski, A. P.; Wood, P. L.; Reynolds, I. J.; Ball, R. G.; Pang, Y.-P. *J. Med. Chem.* **1992**, *35*, 1634−1638. (n) Verbist, B. M. P.; De Borggraeve, W. M.; Toppet, S.; Compernolle, F.; Hoornaert, G. J. *Eur. J. Org. Chem.* **2005**, 2941−2950. (o) Meyer, U.; Bisel, P.; Weckert, E.; Frahm, A. W. *Chirality* **2006**, *18*, 383−394. (p) Kopylova, N. A.; Grygorenko, O. O.; Komarov, I. V.; Groth, U. *Tetrahedron: Asymmetry* **2010**, *21*, 2868−2871.

(6) Aron, Z. D.; Overman, L. E. *Org. Lett.* **2005**, *7*, 913−916.

(7) For representative examples of selective bimolecular trapping of one iminum ion isomer of a 2-aza-Cope rearrangement, see: (a) Overman, L. E.; Yokomatsu, T. *J. Org. Chem.* **1980**, *45*, 5229−5230. (b) Castelhano, A. L.; Krantz, A. *J. Am. Chem. Soc.* **1984**, *106*, 1877−1879. (c) Bennett, D. J.; Hamilton, N. M. *Tetrahedron Lett.* **2000**, *41*, 7961−7964.

(8) For a recent review of dynamic kinetic resolution, see: Pellissier, H. *Tetrahedron* **2011**, *67*, 3769−3802.

(9) Some of these studies were reported in a preliminary communication, see: Ito, T.; Overman, L. E.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 3272−3273.

(10) Previously prepared by alkylation of a gallium enolate of cyclohexanone: (a) Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* **2002**, *75*, 2049−2052. Or by transesterification of commercially available methyl 2-oxocyclohexaneacetate: (b) Meidong, L.;Gu, Q.; He, Y.; Huang, W.Faming Zhuanli Shenqing, CN 150049 A 20050105, 2005.

(11) The route utilized to prepare **11** is an optimization of previous disclosures.[6,9] TASF(Me) was found to promote the alkylation to afford ketoester **11** in the highest efficiency. The use of CsF, tetrabutylammonium diflurotriphenylstannate, tetrabutylammonium difluorotriphenylsilicate, or benzyltrimethylammonium fluoride as promoter afforded the product in lower yields (30%, 32%, 58%, and 60%, respectively).

(12) Vilaivan, T.; Winotapan, C.; Banphavichit, V.; Shinada, T.; Ohfune, Y. *J. Org. Chem.* **2005**, *70*, 3464−3471.

(13) We found it most convenient to determine the enantiomeric purity of these primary amines by enantioselective chromatography of the corresponding benzamides (see the Supporting Information).

(14) Enantioselectivities were determined by enantioselective HPLC after benzolylation of *ent*-**8**; details are provided in the Experimental Section and Supporting Information.

(15) Details are provided in the Experimental Section.

(16) Kaiser, N.-K. K.; Bremberg, U.; Larhed, M.; Moberg, C.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3596−3598.

(17) (a) Trost, B. M.; Hachiya, I. *J. Am. Chem. Soc.* **1998**, *120*, 1104−1105. (b) Palucki, M.; Um, J. M.; Conlon, D. A.; Yasuda, N.; Hughes, D. L.; Mao, B.; Wang, J.; Reider, P. J. *Adv. Synth. Catal.* **2001**, *343*, 46−50.

(18) Krapcho, A. P.; Weimaster, J. F.; Eldridge, J. M.; Jahngen, E. G. E., Jr.; Lovey, A. J.; Stephens, W. P. *J. Org. Chem.* **1978**, *43*, 138−147.

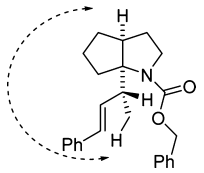
(19) (a) Brown, E.; Deroye, C.; Touet, J. *Tetrahedron: Asymmetry* **1998**, *9*, 1605−1614. (b) Mitsui, K.; Sato, T.; Urabe, H.; Sato, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 490−492. (c) Gao, M.; Wang, D.-X.; Zheng, Q.-Y.; Wang, M.-X. *J. Org. Chem.* **2006**, *71*, 9532−9535.

(20) Blanco, B.; Christensen, J.; Maurel, I.; Pleixats, R.; Serra, A.; Pla-Quintana, A.; Roglans, A.; Benet-Buchholz, J. *Synthesis* **2005**, 374−380.

(21) (a) van Zijl, A. W.; López, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558−2563. (b) The enantiomeric purity of **28** was determined by enantioselective HPLC analysis of the corresponding primary alcohol obtained by an ozonolysis/reduction sequence.

(22) This reaction could be carried out also neat; however, because the reaction is heterogeneous at this lower temperature, inconsistent reaction times were observed.

(23) The configuration assigned to the side chain stereocenter of **40** is consistent with the expectation that it would be established in the aza-Cope rearrangement step. This assignment is further supported by a strong $^1$H NOE enhancement observed between C3a−H and the methyl substituent of the side chain; The relative configuration of **40** was assigned by comparing the NOESY data to the lowest energy conformation calculated using ab initio studies with DFT/B3LYP/6-31G* as implemented in Spartan 2008.




(24) For recent representative applications, see: (a) Hanessian, S.; Auzzas, L. *Acc. Chem. Res.* **2008**, *41*, 1241−1251. (b) Seebach, D.; Gardiner, J. *Acc. Chem. Res.* **2008**, *41*, 1366−1375. (c) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2012**, *75*, 311−335.

(25) Sayago, F. J.; Laborda, P.; Calaza, M. I.; Jiménez, A. I.; Cativiela, C. *Eur. J. Org. Chem.* **2011**, 2011−2028.

(26) For a review, see: Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471−5569.

(27) For example, Tanaka and Barbas have found that (*R*)-3-pyrrolidinecarboxylic acid can efficiently catalyze a highly antiselective Mannich reactions, see: (a) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2008**, *130*, 875−886. See also (b) Armstrong, A.; Bhonoah, Y.; Colorless, A. J. P. *J. Org. Chem.* **2009**, *74*, 5041−5048.

(28) Isotopic analysis was performed using MassLynx mass spectrometry software.

(29) In our initial report of these transformations in the racemic series, we suggested on the basis of an experiment, which in hindsight was potentially flawed, that the allylic iminium ion sigmatropic isomers studied at that time were in equilibrium.[6] As already noted, the high chirality transfer observed in the substituted allyl series that is the subject of this report rigorously establishes that the sigmatropic isomers are not in equilibrium.

(30) See the Supporting Information of ref 9 for a scheme detailing all possible chair and boat transition structures for the 2-aza-Cope rearrangement and the corresponding products produced.
(31) Enantiomers **47** and *ent*-**47** exhibited baseline resolution in the enantioselective HPLC separation used in this study, allowing us to confidently say that less than 2% of *ent*-**47** (more likely < 1%) was formed. See the Supporting Information provided for ref 9.
(32) Wang, J. Ph.D. Dissertation, UC Irvine, Irvine, CA, 2011.
(33) van der Sluis, M.; Dalmolen, J.; de Lange, N.; Kaptein, B.; Kellogg, R. M.; Broxterman, Q. B. *Org. Lett.* **2001**, *3*, 3943−3946.
(34) Kohno, K.; Narasaka, K. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 322−329.
(35) Cotarco, L.; Delogu, P.; Maggioni, P.; Nardelli, A.; Bianchini, R.; Sguassero, S. *Synthesis* **1997**, 328−332.
(36) Ocejo, M.; Carrillo, L.; Badía, D. *J. Org. Chem.* **2009**, *74*, 4404−4407.
(37) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2000**, *122*, 8168−8179.