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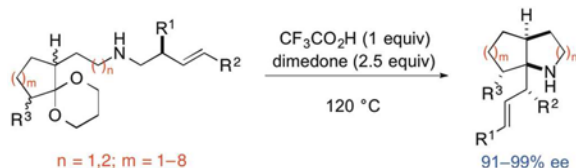
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Enantioselective Synthesis of Angularly Substituted 1-Azabicyclic Rings: Coupled Dynamic Kinetic Epimerization and Chirality Transfer

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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 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. 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 amino acids of the type depicted in Figure 1 in peptidomimetics or as organocatalysts.

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

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 non-aromatic 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-azabicyclic molecules **1**.⁶ The method is illustrated in Scheme 1 for the preparation *cis*-cyclopentapyrrolidine **4** from aminoketal **2**. In this synthesis, a mixture of aminoketal **2**, 1 equiv of tri-fluoroacetic 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 CD₃OD containing 3 equiv of D₂O, deuterium was incorporated into the angular methine (C3a) and C7 methylene positions of product d₃-**8** (Scheme 2).⁶ This deuterium incorporation signified that the initially formed iminium ion **D** equilibrated with enamonium ion isomers **E** and **F** more rapidly than formaldiminium ion intermediate **G** was trapped to yield *cis*-octahydroindole product **8**.

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.

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**.

In our initial study, the reaction temperature and the effect of the homoallylic substituent on chirality transfer was examined (Table 1). All reactions were conducted neat by heating mixtures of the aminoketal **9**, 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 CD₃OD 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*-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* stereoisomer 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

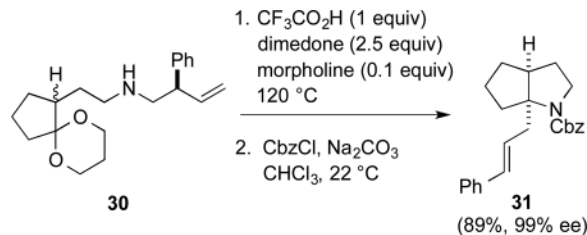
Although chirality transfer was typically high with substrates having an aryl substituent at the homoallylic position, we entertained the possibility that this selectivity might be even higher with substrates having a substituent at the allylic carbon. We initiated these studies by developing an enantioselective synthesis of (*R*)-2-phenylbut-2-enylamine. In order 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). Using a microwave modification¹⁶ of a method first introduced by Trost,¹⁷ molybdenum-catalyzed enantioselective allylic alkylation of cinnamyl methyl carbonate (**21**) with dimethyl sodiomalonate gave (*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 alkylation of allylbromide **27** (available in one step from (*E*)-1,4-dibromobut-2-ene)²⁰ with methylmagnesium bromide, catalyzed by 1 mol % CuBr•SMe₂ 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 cyclo-alkanone 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%).



(1)

We next examined whether dimedone was essential to the success of the transformation shown in eq 1 (Table 2). In the 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*-hexahydrocyclopenta[*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, 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 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/enamionium 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* stereoisomer 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 trifluoro-acetic acid at 120 °C for 30 min, followed by Cbz protection gave *cis*-hexahydrocyclopenta[*b*]pyrrole **40** as a single stereoisomer in 75% yield. 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 dia-stereomeric 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

-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 the more rigid analog, *oc*-tahydroindole-2-carboxylic acid, has been exploited in several bradykinin B₂ 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 transformations²⁶ with recent examples exemplifying 3-pyrrolidinecarboxylic acid catalysts.²⁷ Oxidative cleavage of the angular-allyl side chain of

the 1-azabicyclic molecules prepared in the manner reported herein would provide a variety of new, potentially useful, α -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 α -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/enamionium equilibration occurring faster than the [3,3]-sigmatropic rearrangement step. The rapid tautomerization of iminium ion and enamionium 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 CD₃OD (Scheme 10). As expected, azabicyclic carbamate **31** was isolated with deuterium incorporated in the angular C3a and C6 methylene positions; analysis of this 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 CD₃OD 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 CD₃OD 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 ¹³C NMR signal at 221 ppm), with additional products assigned as enamionium ions **P** and **Q** (diagnostic vinylic ¹³C 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.

Based upon 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 enamionium 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 in order to form the 3*a*,5,6*a**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 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 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/enamionium 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 bi-cyclic 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 α -amino acids of high enantiomeric purity, molecules of potential utility for the synthesis of peptidomimetics and 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 (*2R*)-2-phenyl-2-[(1*R*)-1-phenylbut-3-enylamino]ethanol¹² (2.26 g, 8.45 mmol), CH₂Cl₂ (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 CH₂Cl₂ (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 Et₂O (30 mL), treated with 10% NaOH until pH 14, and extracted with Et₂O (30 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄), 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:Et₂NH = 900:100:1; λ = 254 nm; major enantiomer t_R = 10.5 min; minor enantiomer t_R = 14.3 min].

$[\alpha]_{589}^{23} + 42.5$, $[\alpha]_{577}^{23} + 43.2$, $[\alpha]_{546}^{23} + 50.8$, $[\alpha]_{435}^{23} + 85.5$ (*c* 1.15, CH₂Cl₂).

(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:Et₂NH = 900:100:1; λ = 254 nm; major enantiomer t_R = 13.1 min; minor enantiomer t_R = 16.8 min].

$[\alpha]_{589}^{23} + 31.0$, $[\alpha]_{577}^{23} + 32.2$, $[\alpha]_{546}^{23} + 36.7$, $[\alpha]_{435}^{23} + 66.5$ (*c* 2.64, CH₂Cl₂).

(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:Et₂NH = 950:50:1; λ = 254 nm; major enantiomer t_R = 14.6 min; minor enantiomer t_R = 14.0 min].

$[\alpha]_{589}^{23} + 38.1$, $[\alpha]_{577}^{23} + 39.6$, $[\alpha]_{546}^{23} + 44.9$, $[\alpha]_{435}^{23} + 78.5$ (*c* 2.13, CH₂Cl₂).

(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:Et₂NH = 950:50:1; λ = 254 nm; major enantiomer t_R = 11.9 min; minor enantiomer t_R = 11.4 min].

$[\alpha]_{589}^{23} + 72.2$, $[\alpha]_{577}^{23} + 75.4$, $[\alpha]_{546}^{23} + 87.1$, $[\alpha]_{435}^{23} + 155$ (*c* 1.27, CH₂Cl₂).

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, then diluted with hexanes (25 mL), washed with H₂O (10 mL), dried (MgSO₄), 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, CDCl₃) δ 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); ¹³C NMR (125 MHz, CDCl₃) δ 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 C₁₅H₁₈O₃: 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 ace-tonitrile (160 mL) at 0 °C was added scandium triflate (77 mg, 0.16 mmol). The reaction was maintained at 0 °C for 30 min, then quenched with saturated aqueous NaHCO₃ (~ 5 mL) and extracted with Et₂O (3 × 75 mL). The combined organic layers were washed with water (3 × 50 mL) and brine (25 mL), dried (MgSO₄), filtered, concentrated *in vacuo* and purified on silica gel by flash chromatography (1:9 Et₂O: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 Debonylation 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), NaHCO₃ (1.82 g, 21.7 mmol), and Pd(OH)₂/C (182 mg, 20 % on carbon, wet) in EtOAc (60 mL) was evacuated and backfilled three times with N₂, then three times with H₂. The mixture was stirred at room temperature under a balloon atmosphere of H₂ 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 CH₂Cl₂ (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, CDCl₃) 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, 2H), 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₃₀NO₃ 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, CDCl₃) 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 (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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₂H₃₂NO₄ 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; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 $\text{C}_{21}\text{H}_{29}\text{ClNO}_3$ 378.1836; Found: 378.1834.

N*-[**(1*R*)-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; ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[M + \text{Na}]^+$ Calcd for $\text{C}_{21}\text{H}_{28}\text{ClNO}_3\text{Na}$ 400.1655; Found: 400.1659.

2-(1,5-Dioxaspiro[5.5]undec-7-yl)-*N*-[(1*R*)-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; ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[M + \text{Na}]^+$ Calcd for $\text{C}_{18}\text{H}_{31}\text{NO}_3\text{Na}$ 332.2202; found: 332.2210.

General Procedure E for Reduction of an Amide with Lithium Aluminum Hydride

***(1*R*)-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 cooling 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%). ^1H NMR (500 MHz, CDCl_3) 7.23 (dd, $J = 8.7, 3.9$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.71 (dtd, $J = 17.4, 10.0, 7.2$ 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) 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 $\text{C}_{22}\text{H}_{34}\text{NO}_3$ 360.2539; Found: 360.2536.

***(1*R*)-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). ^1H NMR (500 MHz,

CDCl₃) 7.32–7.31 (m, 4H), 7.26–7.21 (m, 1H), 5.76–5.608 (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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₃₂NO₂ 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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₃₀ClNO₂Na 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 hex-anes:EtOAc:Et₃N). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₃₁ClNO₂ 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 oi. ¹H NMR (500 MHz, CDCl₃) 5.80 (ddt, $J = 17.0, 10.0, 7.5$ Hz, 1H), 5.10–04 (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), 0.91–0.88 (m, 6H); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₈H₃₄NO₂ 296.2590; Found: 296.2585.

Representative Procedure for the Synthesis of Octahydroindole *ent*-8 from Aminoacetals 9

(3a*R*,7a*S*)-7a-Allyloctahydro-1*H*-indole (*ent*-8): A stirring mixture of **9a** (0.20 g, 0.62 mmol), TFA (47 μ L, 0.62 mmol), and morpholine (5.4 μ 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 Et₂O (10 mL). The mixture was extracted with 1 N HCl (2 \times 10 mL), and the combined aqueous layers were washed with Et₂O (30 mL), treated with 10% NaOH until pH 14, and extracted with Et₂O (30 mL). The organic layer was washed with brine (20 mL), dried (MgSO₄), filtered, and concentrated *in vacuo* to afford *ent*-8 as yellow oil (94 mg, 0.57 mmol, 92%).

$[\alpha]_{589}^{23} + 18.2$, $[\alpha]_{577}^{23} + 16.2$, $[\alpha]_{546}^{23} + 19.2$, (*c* 0.450, CH₂Cl₂); HPLC analysis of the derived benzoyl protected amine **S1** indicated an enantiomeric excess of 88% (see below). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₁H₂₀N 166.1596; Found: 166.1594.

7a-Allyl-1-benzoyloctahydro-1*H*-indole (S1): Benzoyl chloride (37 mg, 0.26 mmol) was added to a solution of *ent*-8 (31 mg, 0.19 mmol), Et₃N (40 mg, 0.40 mmol) and CH₂Cl₂ (0.5 mL) at room temperature. The solution was maintained at room temperature for 1 h. After the addition of Et₂O (10 mL), the organic layer was washed with water (5 mL), 1N HCl (5 mL), 10% NaOH (5 mL) and brine (5 mL). The organic layer was dried (MgSO₄), 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; λ = 220 nm; major enantiomer *t*_R = 28.3 min; minor enantiomer *t*_R = 25.5 min minor enantiomer *t*_R = 25.5 min]. mp 46-47 °C;

$[\alpha]_{589}^{23} + 76.8$, $[\alpha]_{577}^{23} + 79.5$, $[\alpha]_{546}^{23} + 90.8$, $[\alpha]_{435}^{23} + 171$ (*c* 1.04, CH₂Cl₂). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₈H₂₃NONa 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₇H₂₂O₄Na 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₀H₂₇NO₃Na 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₀H₃₀NO₂ 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, 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; Anal. Calcd for C₁₅H₁₈O₃: C, 73.15; H, 7.37. Found: C, 73.26; H, 7.40; HRMS (ES) *m/z*: [M + Na]⁺ Calcd for C₁₅H₁₈O₃Na 269.1154; Found: 269.1144.

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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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; Anal. Calcd for C₁₈H₂₄O₄: C, 71.03; H, 7.95. Found: C, 71.12; H, 7.94; HRMS (ES) *m/z*: [M + Na]⁺ Calcd for C₁₈H₂₄O₄Na 327.1572; Found: 327.1564.

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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_3\text{Na}$ 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 mmol, 88%) was obtained as a colorless oil. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{32}\text{NO}_2$ 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 μmol), 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, 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. ^1H NMR (500 MHz, CDCl_3) 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) 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; Anal. Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$: C, 73.82; H, 7.72. Found: C, 73.88; H, 7.72; HRMS (ES) m/z : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3\text{Na}$ 283.1310; Found: 283.1297.

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. ^1H NMR (500 MHz, CDCl_3) 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) 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 $\text{C}_{19}\text{H}_{26}\text{O}_4$: 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. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{22}\text{H}_{32}\text{NO}_3$ 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₂H₃₄NO₂ 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 μL, 0.722 mmol) and morpholine (6.30 μL, 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 CHCl₃ (5 mL). A saturated aqueous solution of Na₂CO₃ (2.4 mL), water (2.4 mL) and benzyl chloroformate (310 μL, 2.17 mmol) was added and the biphasic solution was stirred at room temperature for 18 h. The aqueous layer was extracted with CH₂Cl₂ (3 × 10 mL) and the combined organic layer was dried (Na₂SO₄), 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; λ = 220 nm; major enantiomer *t*_R = 6.7 min; minor enantiomer *t*_R = 8.5 min].

[α]₅₈₉²³ – 11.4, [α]₅₇₇²³ – 11.0, [α]₅₄₆²³ – 12.2, [α]₄₃₅²³ – 18.5 (*c* 1.99, CH₂Cl₂). ¹H NMR (500 MHz, DMSO-*d*₆, 388 K) 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); ¹³C NMR (125 MHz, DMSO-*d*₆, 388 K) 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 C₁₈H₂₃NO₂Na 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:Et₂O). HPLC analysis indicated an enantiomeric excess of 89% [CHIRALCEL OJ column; flow: 1.0 mL/min; 96% *n*-hexane/4% *i*-PrOH; λ = 220 nm; major enantiomer *t*_R = 7.8 min; minor enantiomer *t*_R = 11.6 min].

[α]₅₈₉²³ – 11.4, [α]₅₇₇²³ – 11.0, [α]₅₄₆²³ – 12.2, [α]₄₃₅²³ – 18.5 (*c* 1.99, CH₂Cl₂). ¹H NMR (500 MHz, DMSO-*d*₆, 398 K) 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); ¹³C NMR (125 MHz, DMSO-*d*₆, 398 K) 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 C₁₉H₂₅NO₂Na 322.1783; Found: 322.1777.

(4aR, 7aS)-Benzyl 7a-allyloctahydro-1 H-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:Et₂O). 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 $t_R = 7.3$ min].

$[\alpha]_{589}^{23} + 63.8$, $[\alpha]_{577}^{23} + 64.8$, $[\alpha]_{546}^{23} + 72.9$, $[\alpha]_{435}^{23} + 124$ (*c* 0.79, CH₂Cl₂). ¹H NMR (500 MHz, DMSO-*d*₆, 298 K) 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); ¹³C NMR (125 MHz, DMSO-*d*₆, 298 K) 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 C₁₉H₂₅NO₂Na 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:Et₂O). *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, CH₂Cl₂). ¹H NMR (500 MHz, DMSO-*d*₆, 348 K) 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); ¹³C NMR (125 MHz, DMSO-*d*₆, 348 K) 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 C₂₀H₂₇NO₂Na 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, CH₂Cl₂). ¹H NMR (500 MHz, DMSO-*d*₆) 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); ¹³C NMR (125 MHz, DMSO-*d*₆, 298 K) 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 C₂₀H₂₇NO₂Na 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 Et₃N (42 μ L) to the amide-coupling step. ¹H NMR (500 MHz, CDCl₃) 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) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{26}\text{NO}_3$ 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. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{15}\text{H}_{28}\text{NO}_2$ 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. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_3\text{Na}$ 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. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{21}\text{H}_{32}\text{NO}_2$ 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 μL) to the amide coupling step. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_3\text{Na}$ 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₃₀NO₂ 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₉NO₃Na 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₃₂O₂N 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 Et₃N (45 μL) to the amide-coupling step. ¹H NMR (500 MHz, CDCl₃) 5.95 (broad s, 1H), 5.73–5.66 (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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₂₇NO₃Na 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{30}\text{NO}_2$ 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 μL) to the amide coupling step. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{17}\text{H}_{29}\text{NO}_3\text{Na}$ 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. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{17}\text{H}_{32}\text{NO}_2$ 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 μL , 0.011 mmol), TFA (13 μL , 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, dissolved in CHCl_3 (1 mL) and 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 μL , 0.34 mmol). The reaction was vigorously stirred at room temperature for 24 h, 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 $t_{\text{R}} = 11.25$ min; minor enantiomer $t_{\text{R}} = 13.89$ min].

$[\alpha]_{577}^{23} - 7.88$, $[\alpha]_{546}^{23} - 6.81$, $[\alpha]_{435}^{23} - 14.0$ (c 0.45, CH_2Cl_2). ^1H NMR (500 MHz, $\text{DMSO}-d_6$, 393K) 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, $J = 12.7$ Hz, 1H).

= 5.8 Hz, 3H), 1.43–1.37 (m, 1H); ^{13}C NMR (125 MHz, DMSO- d_6 , 393K) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{19}\text{H}_{26}\text{NO}_2$ 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].

$[\alpha]_{589}^{23} - 47.2$, $[\alpha]_{577}^{23} - 48.0$, $[\alpha]_{546}^{23} - 54.7$, $[\alpha]_{435}^{23} - 94.3$ (c 0.43, CH_2Cl_2). ^1H NMR (500 MHz, DMSO- d_6 , 393K) 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 , 393K) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_2\text{Na}$ 336.1939; Found: 336.1934.

(4aS,7aR)-Benzyl 7a-((E)-but-2-en-1-yl)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 $t_R = 5.46$ min (for the opposite enantiomer as shown above)].

$[\alpha]_{589}^{23} - 13.0$, $[\alpha]_{577}^{23} - 13.8$, $[\alpha]_{546}^{23} - 14.9$, $[\alpha]_{435}^{23} - 28.8$ (c 0.36, CH_2Cl_2). ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_2\text{Na}$ 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)].

$[\alpha]_{589}^{23} - 34.3$, $[\alpha]_{577}^{23} - 39.4$, $[\alpha]_{546}^{23} - 44.8$, $[\alpha]_{435}^{23} - 78.3$ (c 0.87, CH_2Cl_2); data is for the opposite enantiomer as shown above). ^1H NMR (500 MHz, DMSO- d_6 , 393K) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{21}\text{H}_{29}\text{NO}_2\text{Na}$ 350.2096; Found: 350.2098.

Synthesis and Characterization Data of 1-Azabicyclics Reported in Table 4 and Their Precursors

N-(*(R)*-2-phenylbut-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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₂H₃₁NO₃Na 380.2202; Found: 380.2200.

(2*R*)-*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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₂H₃₄NO₂ 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; ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₃₀O₃Na 353.2093; Found: 353.2084.

(1,5-Dioxa-spiro[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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₄H₃₆O₄Na 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C

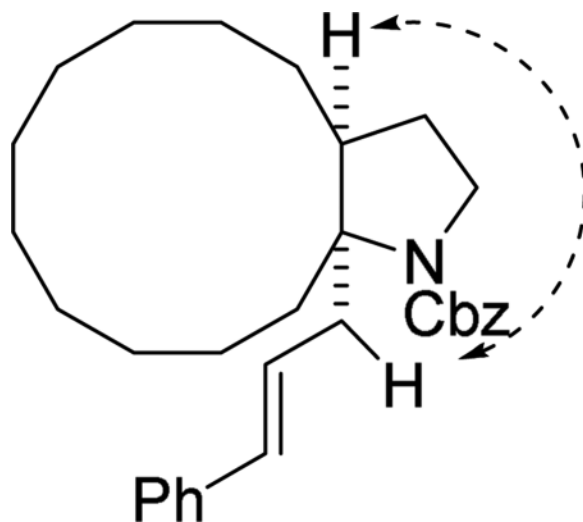
NMR (125 MHz, CDCl₃) 174.9, 174.8, 141.64, 141.58, 139.6, 139.5, 128.87, 128.85, 128.03, 127.99, 126.9, 116.2, 116.1, 102.9, 59.64, 59.58, 59.3, 49.6, 49.4, 43.5, 43.4, 39.5, 39.4, 37.5, 37.4, 27.2, 27.1, 26.4, 26.3, 25.5, 24.5, 23.6, 22.74, 22.65, 22.47, 22.45, 22.1, 19.3; IR (thin film, cm⁻¹) 3323, 2931, 2863, 1647, 1140, 1117, 1089; HRMS (ESI) m/z: [M + Na]⁺ Calcd for C₂₇H₄₁NO₃Na 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₇H₄₄O₂N 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 μmol, 74%) was obtained as a colorless amorphous solid (9:1 mixture of diastereomers by ¹H NMR). The major diastereomer was partially purified by preparatory TLC (9:1 hexanes/EtOAc) for characterization. HPLC analysis indicated an en-antiomeric excess of 99% [CHIRALCEL OD column; flow: 1.0 mL/min; 99.5% *n*-hexane/0.5% *i*-PrOH; λ = 254 nm; major enantiomer t_R = 19.16 min; minor enantiomer t_R = 27.21 min]. ¹H NMR (500 MHz, DMSO-*d*₆, 393 K) 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); ¹³C NMR (125 MHz, DMSO, 393 K) 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 C₃₁H₄₁NO₂Na 482.3035; Found: 482.3034. The ring fusion geometry was assigned by ¹H NOE analysis as depicted in the drawing below.



Benzyl 2-(2-oxocycloheptyl)acetate (S30): Keto ester **S30** was prepared using an adapted procedure from Cotarco and co-workers.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 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) and 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 Et₂O (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 (MgSO₄), filtered, concentrated *in vacuo* and the residue was purified by flash chroma-tography on silica gel (2:25–3:25 EtOAc:hexanes) to give **S30** (6.3 g, 24 mmol, 45%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₂₀O₃: 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₉H₂₆O₄: 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₂H₃₁NO₃Na 380.2202; Found: 380.2201.

(2*R*)-*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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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.

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%). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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]dec-1-yl)pentanamide (S36): Following general procedure D, **S36** (242 mg, 0.651 mmol, 72%) as a colorless oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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]dec-1-yl)pentan-1-amine (S37): Following general procedure E, **S37** (146 mg, 0.408 mmol, 66%) was obtained as a light-yellow oil. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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-Azabicyclic 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 acid³⁶ (0.29 g, 1.5 mmol) and Et₃N (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 H₂O (10 mL), saturated aqueous NaHCO₃ (10 mL), and brine (10 mL). The organic layer was dried

(MgSO₄), 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]. $[\alpha]_{589}^{24} - 17.7$, $[\alpha]_{577}^{24} - 19.6$, $[\alpha]_{546}^{23} - 24.0$, $[\alpha]_{435}^{23} - 45.6$ ($c = 1.0$, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₁₆H₂₃NO₂Na 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 CH₂Cl₂ (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 Et₂O (3 × 15 mL). The organic layers were combined, dried (MgSO₄), 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₂₉NO₃Na 366.2045; Found: 366.2044.

(2*R,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. ¹H NMR (500 MHz, CDCl₃) 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, 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); ¹³C NMR (125 MHz, CDCl₃) 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 C₂₁H₃₂NO₂ 330.2433; Found: 330.2423.

(3*aS*,6*aS*)-Benzyl 6*a*-((*R,E*)-4-phenylbut-3-en-2-yl)hexahydrocyclopenta[*b*]pyrrole-1(2*H*)-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]. ¹H NMR (500 MHz, CDCl₃) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{25}\text{H}_{29}\text{NO}_2\text{Na}$ 398.2096; Found: 398.2097.

(*R,E*)-tert-Butyl (2,4-diphenylbut-3-en-1-yl)carbamate (S41)—To a solution of the catalyst HG-II³⁷ (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); ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{21}\text{H}_{25}\text{O}_2\text{NNa}$ 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); ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{16}\text{H}_{18}\text{N}$ 224.1439; Found: 224.1445.

***N*-(*R,E*)-2,4-Diphenylbut-3-en-1-yl)-2-(6,10-dioxaspiro[4.5]decan-1-yl)acetamide (S43)**—Following general procedure D, **S43** (45 mg, 0.11 mmol, 65%) was obtained as a colorless solid. ^1H NMR (500 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{26}\text{H}_{31}\text{NO}_3\text{Na}$ 428.2202; Found: 428.2203.

(2*R,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. ^1H NMR (500 MHz, CDCl_3) 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), 1.7–1.65 (m, 3H), 1.50–1.22 (m, 4H); ^{13}C NMR (125 MHz) 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 : $[\text{M} + \text{H}]^+$ Calcd for $\text{C}_{26}\text{H}_{34}\text{NO}_2$ 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 μmol , 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 en-antiomer $t_R = 23.72$ 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). ^1H NMR (500 MHz, DMSO-d_6 , 393K) 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 , 393K) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{30}\text{H}_{31}\text{NO}_2\text{Na}$ 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-II³⁷ (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:Et₂O) 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. ^1H NMR (600 MHz, CDCl_3) 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) 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 : $[\text{M} + \text{Na}]^+$ Calcd for $\text{C}_{21}\text{H}_{31}\text{NO}_2\text{Na}$ 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 minutes. 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 warmed to room temperature and ex-tracted with Et₂O (3 × 50 mL). The organic layers were combined, dried with MgSO_4 , filtered and con-centrated to provide the amine as a colorless oil. The crude material could be used without further puri-fication or purified to obtain an analytically pure sample (>98% *E* olefin isomer) by flash chromatog-raphy on silica gel (99:1 Et₂O:Et₃N) to yield **S45** as a colorless oil (25 mg, 0.11 mmol.

73%). $[\alpha]_{23}^{589} - 25.1$, $[\alpha]_{23}^{577} - 27.0$, $[\alpha]_{23}^{546} - 30.7$, $[\alpha]_{23}^{435} - 56.4$ (*c* 1.3, CH_2Cl_2); ^1H NMR (500 MHz, CDCl_3) 7.34–7.23 (m, 5H), 5.52–5.51 (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) 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 C₁₆H₂₄N 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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz) 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 C₂₆H₃₇NO₃Na 434.2671; Found: 434.2680.

(2*R,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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz) 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 C₂₆H₄₀NO₂ 398.3059; Found: 398.3053.

(3*aS*,6*aS*)-Benzyl 6*a*-((*R,E*)-1-cyclohexyl-3-phenylallyl)hexahydrocyclopenta[*b*]pyrrole-1(2*H*)-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; λ = 254 nm; major enantiomer t_R = 28.77 min; minor enantiomer t_R = 32.53 min].

[α]₂₃⁵⁸⁹ +41.9, [α]₂₃⁵⁷⁷ +42.1, [α]₂₃⁵⁴⁶ +49.7, [α]₂₃⁴³⁵ +92.1 (*c* = 0.34, CH₂Cl₂); ¹H NMR (500 MHz, DMSO-*d*₆, 393K) 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), 1.771.73 (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); ¹³C NMR (125 MHz, DMSO-*d*₆, 393K) 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 C₃₀H₃₇NO₂Na 466.2722; Found: 466.2714.

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

(*S*)-2-((3*aS*,6*aS*)-1-((Benzoyloxy)carbonyl)octahydrocyclopenta[*b*]pyrrol-6*a*-yl)-2-cyclohexylacetic acid (46)—Ozone was bubbled through a solution of **42** (12 mg, 25 μmol) in MeOH (1.7 mL) at –78 °C for approximately 30 seconds until a persistent blue color was observed. The solution was purged with O₂ until colorless, quenched with dimethyl sulfide (81 μL, 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 H₂O (0.17 mL), and 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 (MgSO₄), filtered, and concentrated. Purification of the crude residue by flash chromatography on silica gel (100:100:1 hexanes:Et₂O:AcOH) provided **46** (10 mg, 25 μmol, 99% yield) as a colorless oil.

$[\alpha]_{23}^{589} - 2.90$, $[\alpha]_{23}^{577} - 3.46$, $[\alpha]_{23}^{546} + 1.24$, $[\alpha]_{23}^{435} + 1.88$ (*c* 0.31, CH₂Cl₂); ¹H NMR (500 MHz, DMSO-*d*₆, 393K) 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); ¹³C NMR (125 MHz, DMSO-*d*₆, 393K) 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 C₂₃H₃₁NO₄Na 408.2151; Found: 408.2153.

2,2,2-trifluoro-113-ethan-1-one, 6a-(3-hydroxypropoxy)-1-((S)-2-methylbut-3-en-1-yl)octahydrocyclopenta[b]pyrrol-1-ium salt (diastereomers 49 and 50) —¹H NMR (500 MHz, DMSO-*d*₆) 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); ¹³C NMR (125 MHz, DMSO-*d*₆, contains a mixture of diastereomers, signals observed are reported): 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

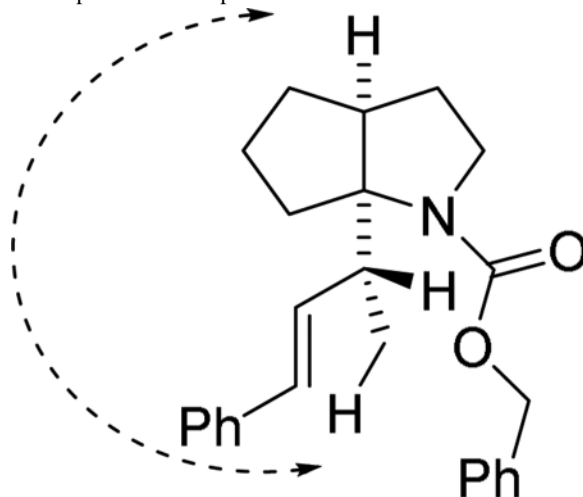
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 11. The route utilized to prepare **11** is an optimization of previous disclosures.^{6,9} TASF(Me) was found to promote the alkylation to afford ketoester **11** in the highest efficiency. The use of CsF, tetrabutylammonium difluorotriphenylstannate, tetrabutylammonium difluorotriphenylsilicate, or benzyltrimethylammonium fluoride as promoters afforded the product in lower yields (30%, 32%, 58%, and 60%, respectively).
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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 ^1H 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 con-formation calculated using ab initio studies with DFT/B3LYP/6-31G* as implemented in Spartan 2008.



The relative configuration of products **41** and **42** were assigned by analogy.

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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 Supporting Information of reference 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 reference 9.
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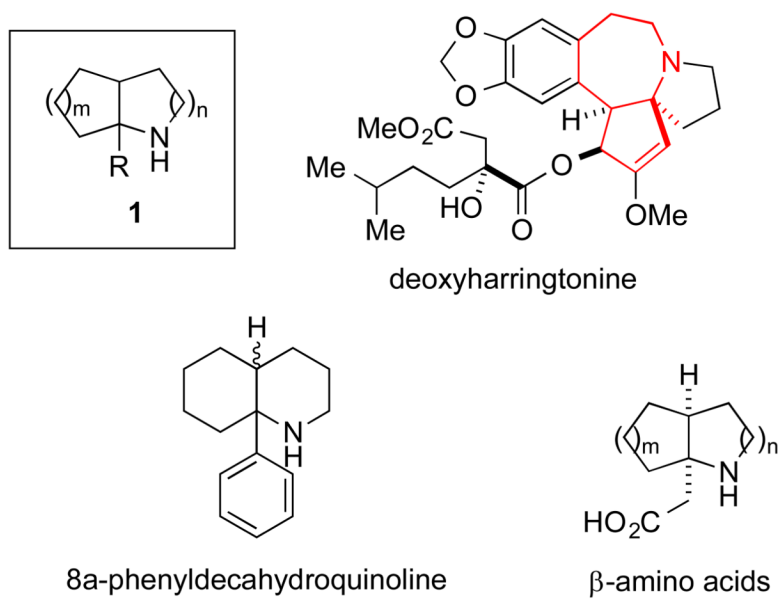


Figure 1. Angularly Substituted 1-Azabicyclic Ring Systems 1 and Examples of Compounds Containing this Ring System

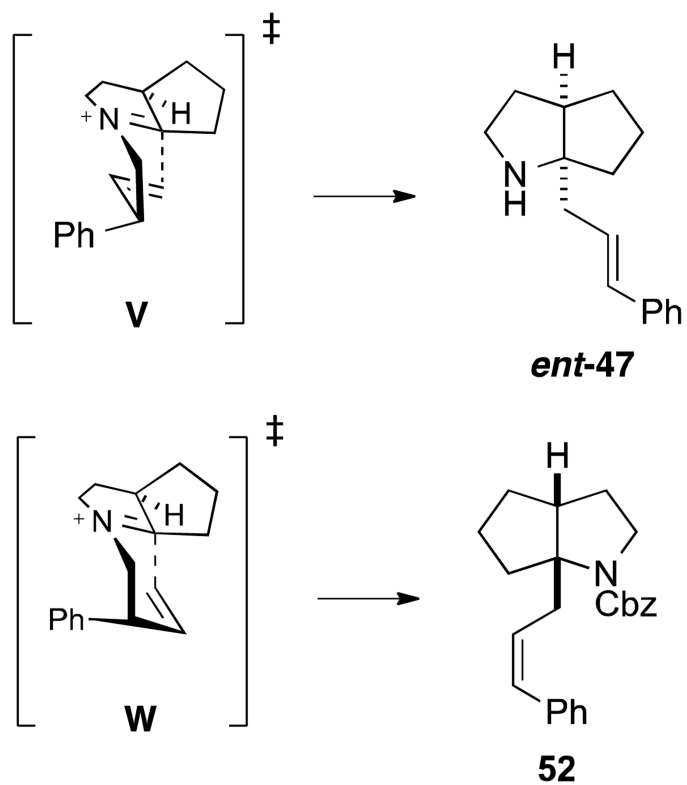
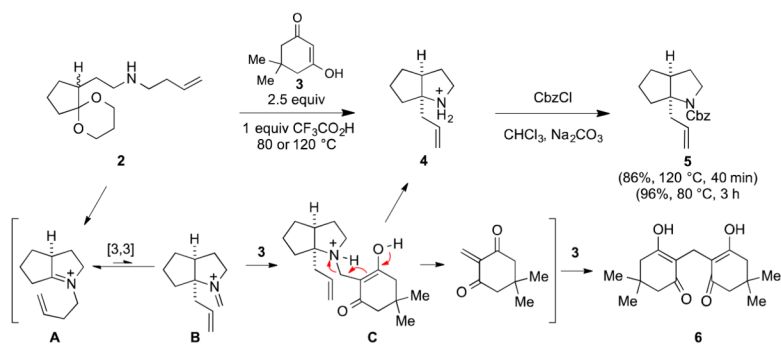
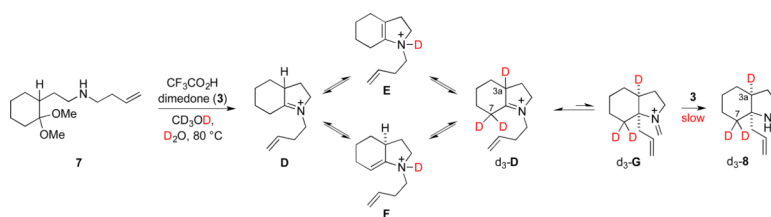


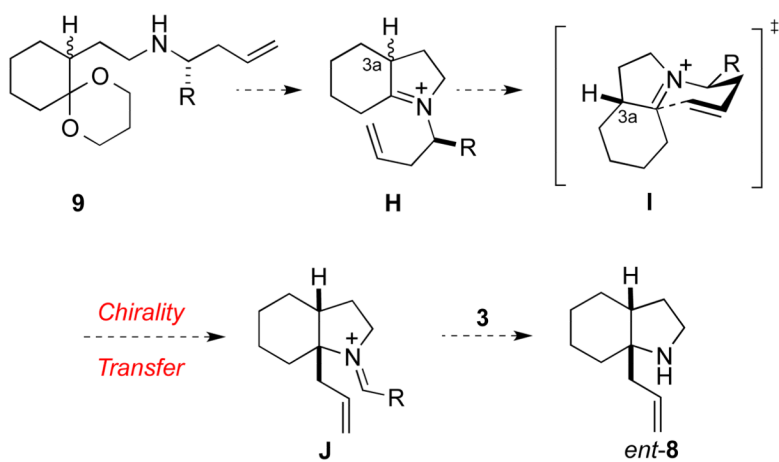
Figure 2. Higher Energy Pathways Leading to Azacyclic Products *ent-47* and **52**



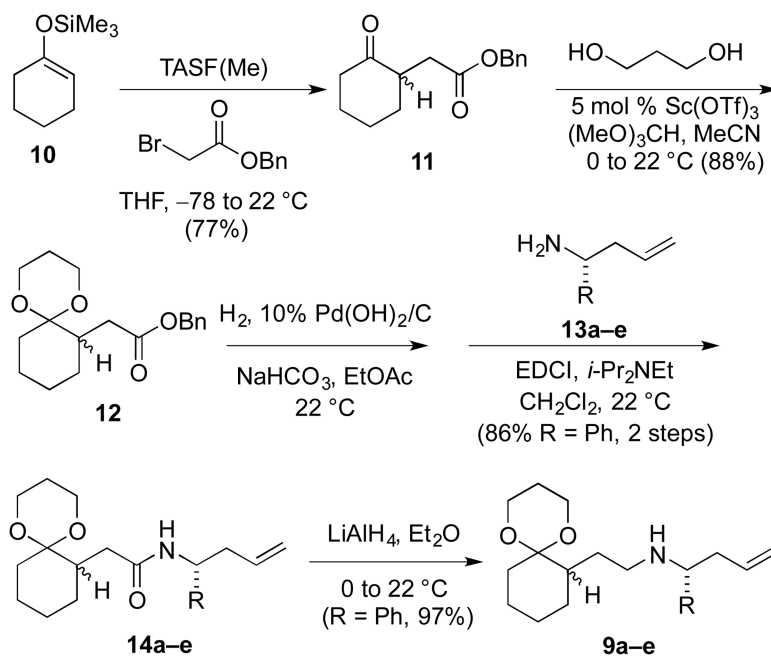
Scheme 1. Methylene Transfer-Driven Cationic 2-Aza-Cope Rearrangement



Scheme 2. Deuterium Incorporation by Iminium/Enamionium Ion Tautomerization

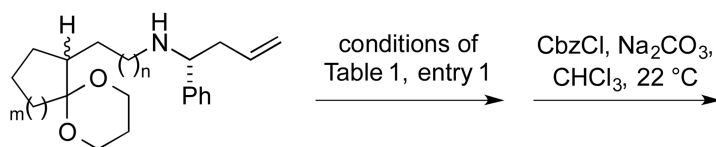


Scheme 3. Potential Synthesis of Enantiomerically Enriched *cis*-Octahydroindole 8 by Coupled Dynamic Kinetic Epimerization and Chirality Transfer

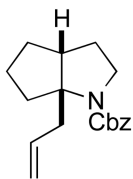


R: **a** = Ph, **b** = 4-MeOC₆H₄, **c** = 4-ClC₆H₄, **d** = 2-ClC₆H₄, **e** = *i*-Pr

Scheme 4. Synthesis of Aminoketals **9**

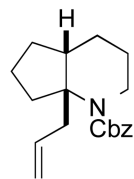


15: m = n = 1; **16:** m=1, n = 2
17: m = n = 2



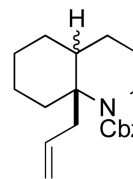
18

95% yield, 92% ee
 97% chirality transfer



19

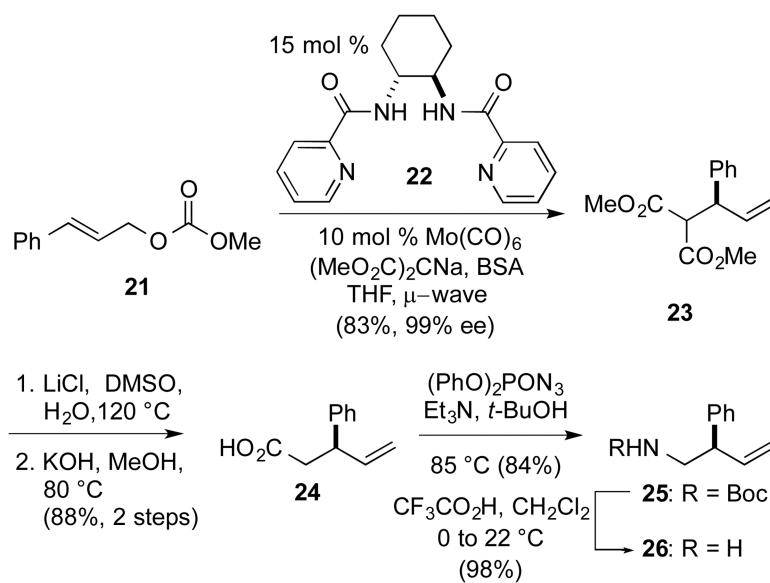
80% yield, 91% ee
 96% chirality transfer

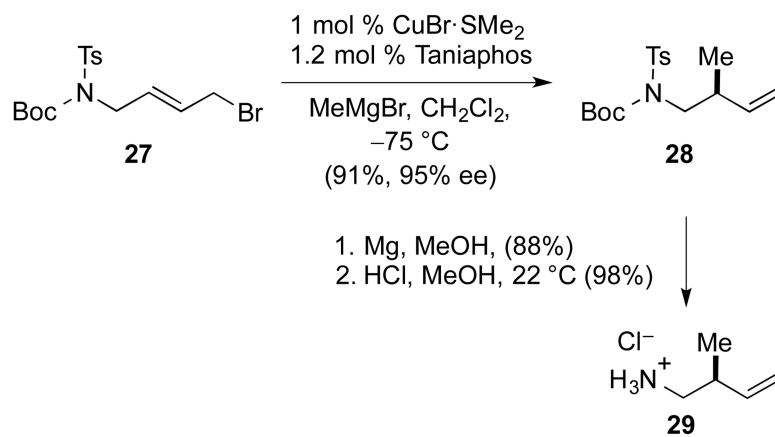


20

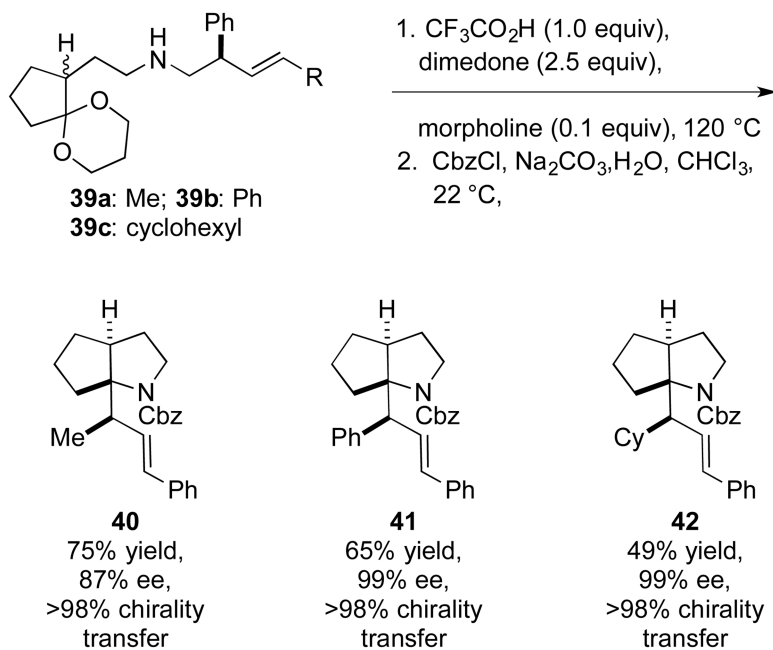
75% yield
 1.2:1 cis:trans
 93% ee (cis and trans)
 97% chirality transfer

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

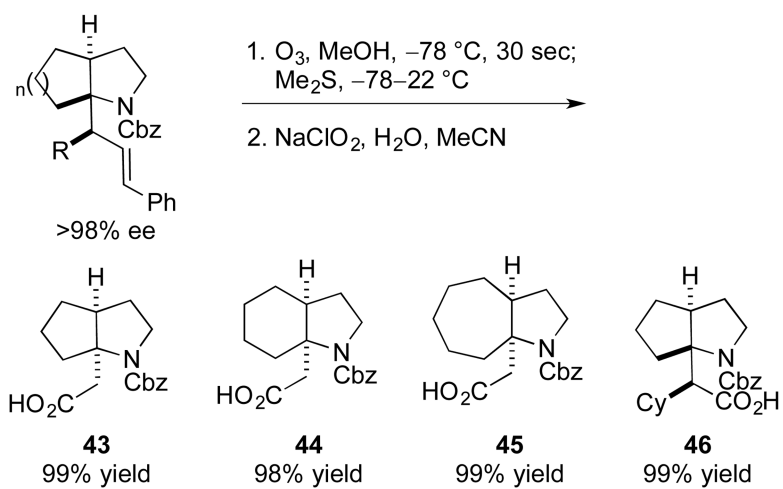
Scheme 6. Synthesis of (*R*)-2-Phenylbut-2-en-1-amine



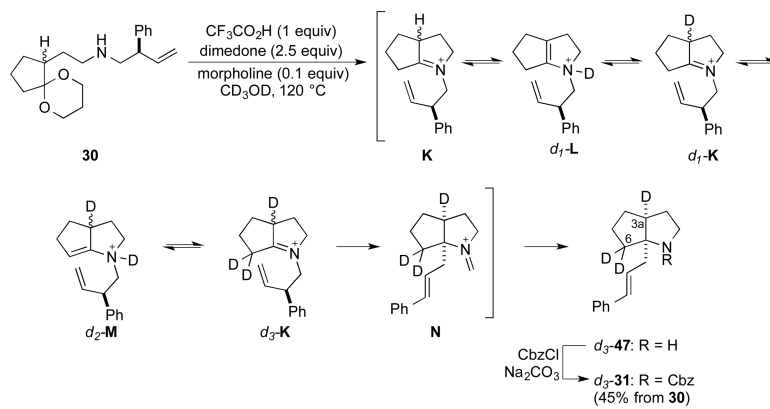
Scheme 7. Synthesis of (*S*)-2-Methylbut-3-en-1-ammonium Chloride



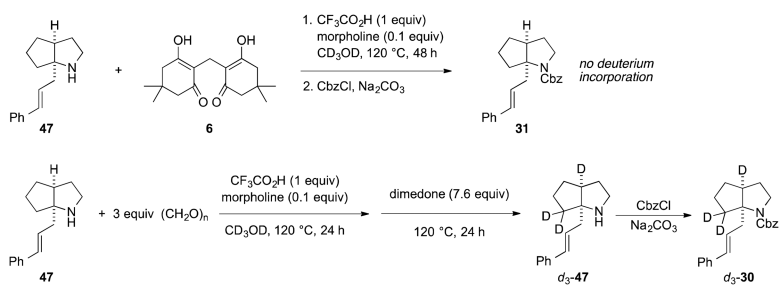
Scheme 8. Enantioselective Synthesis of *cis*-exahydrocyclopenta[*b*]pyrrole Carbamates Having Chiral Allylic Side Chains



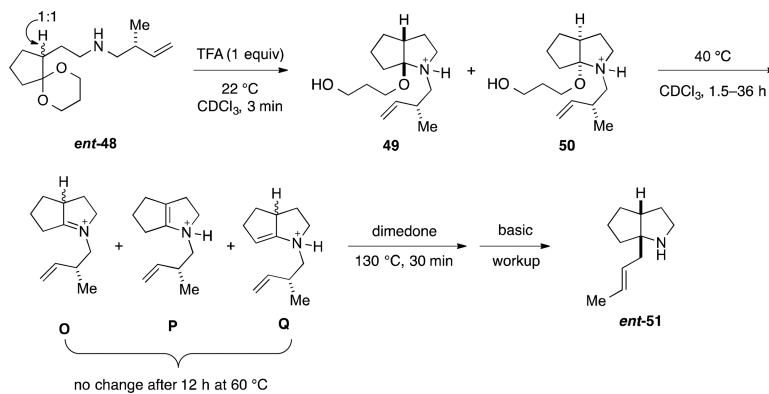
Scheme 9. Synthesis of Four Representative Cbz-Protected α -Aminoacids



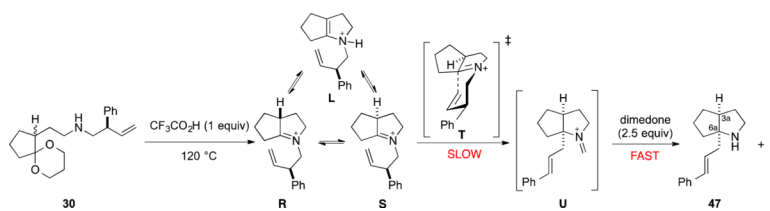
Scheme 10. Deuterium Incorporation in *cis*-Hexahydrocyclopenta[*b*]pyrrole 47 via Rapid Iminium/Enamionium Ion Equilibratium



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

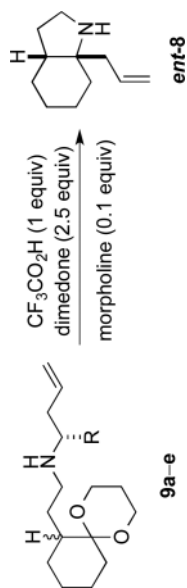


Scheme 12. Intermediates Formed During the Formation of *cis*-hexahydrocyclopenta[*b*]pyrrole *ent*-51



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

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

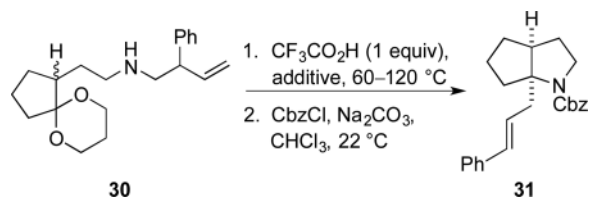


entry	R	ee (%) <i>9a</i>	temp (°C)	time(h)	yield (%)	ee (%) <i>ent-8</i> ^b	chirality transfer (%)
1	Ph (9a)	93	120	5	92	89	96
2	Ph (9a)	93	100	22	84	88	95
3	Ph (9a)	93	80	1	0	—	—
4	4-OMeC ₆ H ₄ (9b)	92	120	5	92	82	89
5	4-ClC ₆ H ₄ (9c)	94	120	5	90	89	95
6	2-ClC ₆ H ₄ (9d)	94	120	5	88	87	93
7	<i>i</i>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

^aEnantiomeric purity of the homoallylic amine fragment of **9** was determined by enantioselective HPLC.

^bEnantiomeric purity was determined by enantioselective HPLC analysis of the corresponding *N*-benzoyl derivative.

Table 2
The 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 ₂ O in MeOH ^d	60	24	7

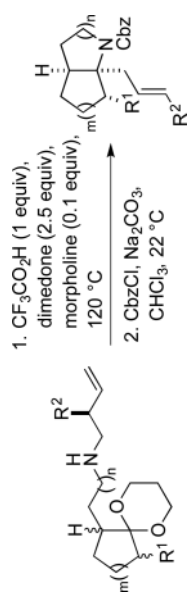
^aReactions used a 1:1 molar ratio of *rac*-**30** and trifluoroacetic acid and the indicated additive(s).

^bReactant **30** was prepared from (*S*)-butenylamine **26** (99% ee).

^cWhen enantioenriched **30** was used, product **31** was formed with >98% chirality transfer.

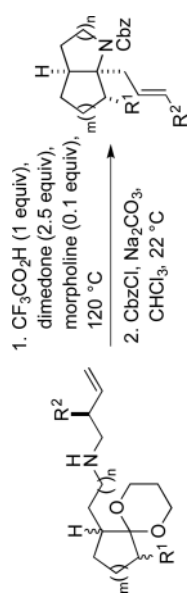
^dMethanol was the solvent in these reaction; the starting concentration of *rac*-**30** was 0.5 M.

Table 3
Enantioselective 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

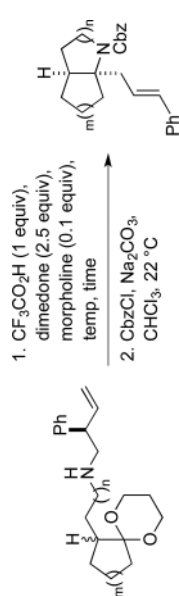
Aron et al.



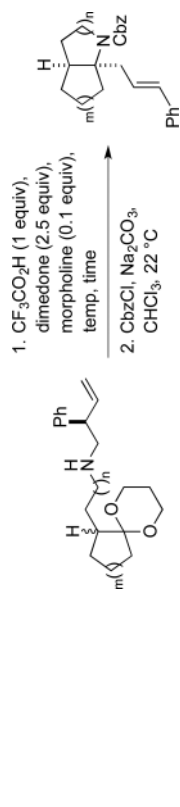
entry	product	R ²	yield (%)	ee (%) ^a	chirality transfer (%)
5		Ph, 33a	89	99	>98
6		Me, 33b	71	95	>98
7		Ph, 34a	81	99	>98
8		Me, 34b	70	91 ^b	96

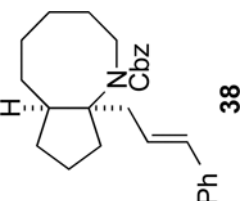
^aEnantiomeric excess was determined by enantioselective HPLC.^bThis product was a 9:1 mixture of epimers at the angular methine carbon.

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) ^d	yield (%)	ee (%) ^b
1		120	0.5	1.7:1	86	99 ^c
2		60 ^c	20	2:1	72	99 ^d
3		120	0.5	9:1	74	99 ^e
4		60 ^c	20	15.2:1	70	99 ^e
5		120	0.5	>10:1	79	99



entry	product	temp ($^\circ\text{C}$)	time (h)	dr (cis:trans) ^a	yield (%) ^b	ee (%) ^b
6		120	22	>10:1	16 ^f	nd

^aDiastereoselectivities were determined by analysis of the ^1H NMR spectra.

^bEnantiomeric excess was determined by enantioselective HPLC.

^cReaction carried out in methanol (0.5 M).

^dBoth isomers were obtained in 99% ee.

^eEnantiomeric excess of the major isomer; the enantiomeric excess of the minor isomer was not determined.

^fEnantiomeric excess was not determined.