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Scalable Synthesis of Enantiomerically Pure *cis*-1,2-Cyclohexanediamine Derivatives and Conformationally Rigid 7-Azabicyclo[2.2.1]heptan-2-amines

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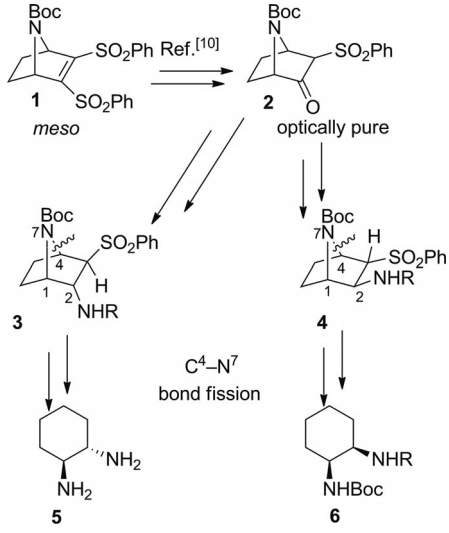
A scalable approach to the syntheses of enantiomerically pure *cis*-1,2-cyclohexanediamines as well as *exo*- and *endo*-7-azabicyclo[2.2.1]heptan-2-amines is reported that utilizes *meso*-*tert*-butyl 2,3-bis(phenylsulfonyl)-7-azabicyclo[2.2.1]-hept-2-ene-7-carboxylate as a starting material.

Introduction

1,2-Diamines are important scaffolds in organic chemistry and are routinely used as ligands[1a–1e] in metal-catalyzed asymmetric organic transformations as well as for the design of thiourea-based organocatalysts.[2a,2b] Such diamines are also abundant in a large number of naturally occurring organic compounds.[3] In particular, cyclohexane-1,2-diamines constitute a distinct subclass that has diverse applications in organic chemistry. For example, C_2-symmetric *trans*-1,2-diaminocyclohexane (**5**) has been used as a ligand[1c–1e] in metal-catalyzed asymmetric reactions, and there are several important organocatalysts[4a–4m] based on this structural framework. On the other hand, *cis*-1,2-diaminocyclohexanes **6** have shown great promise as therapeutic agents in medicinal chemistry.[5a–5l] More recently, *cis*-diaminocyclohexane derivatives have emerged as excellent pseudoenantiomeric organocatalysts to produce both enantiomers of a product.[6a,6b] Although **5** is obtained by resolution of its racemic mixture by either using chiral reagents or enzymes,[7a,7b] the corresponding compound **6** is obtained from either *trans*-2-aminocyclohexanol[5b,5i,5k] or acrylate cycloaddition with butadiene, using D-pantolactone as a chiral auxiliary[8a,8b] and employing a long reaction sequence. *cis*-1,2-Diaminocyclohexanes have also been obtained through the desymmetrization of the corresponding *meso*-vicinal cyclohexanediamines.[9a,9b]

Considering the importance of 1,2-diamines in general and 1,2-diaminocyclohexanes in particular, we visualized conformationally rigid 7-azabicyclo[2.2.1]heptane-2-amines **3** and **4** as ideal precursors for the syntheses of 1,2-diaminocyclohexanes (see Scheme 1). This idea originated from our ongoing exploitation of **2** in the syntheses of a variety of natural products/scaffolds[10,11] and the presence of the phenylsulfonyl moiety at C-3 to act as a handle to trigger a C-4–N-7 bond cleavage. In this paper, we disclose our explorations to synthesize 1,2-diaminocyclohexanes from **2** and our success to realize the synthesis of **6** in up to a multigram scale without the loss of yield or selectivity.



Scheme 1. Proposed sequence for the synthesis of 1,2-cyclohexanediamines (Boc = *tert*-butoxycarbonyl).

Results and Discussion

To transform **2** into either **3** or **4**, the corresponding alcohols were selectively obtained by reduction of **2** under different reaction conditions (see Scheme 2). For example, **7** (*exo*/*endo*, 9:1) was preferentially prepared by carrying out the reduction with $LiBH_4$ in tetrahydrofuran (THF) at ambient temperature, whereas **8** (*exo*/*endo*, 3:7) was obtained by performing the reduction at –78 °C. The individual alcohols were purified by simple column chromatography

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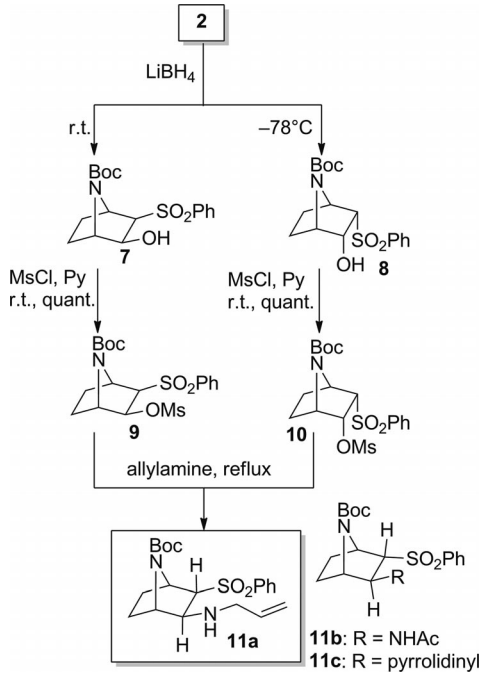
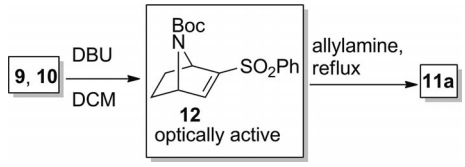
and were individually and quantitatively converted into the corresponding mesylates **9** and **10** by treatment with mesyl chloride (MsCl) in pyridine at room temperature. These mesylates were very stable solids [m.p. 172.4–174.9 °C (for **9**), m.p. 177.3–181.6 °C (for **10**)]. Initially, we heated **9** at reflux with allylamine for 30 min and, surprisingly, isolated **11a** in 95% yield. The identical reaction with **10** also gave **11a**. To probe this unexpected result further, a mixture of both **9** and **10** was heated at reflux with allylamine, which also exclusively produced **11a**. The reaction with acetamide and pyrolidine derivatives also yielded the corresponding products **11b** and **11c**, respectively.



Scheme 2. Preparation of *exo*-7-azabicyclo[2.2.1]heptanediamines.

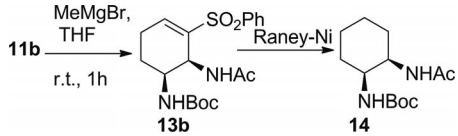
Mechanistically, the possibility of this reaction occurring through an S_N2-type displacement can be ruled out, and an S_N1-type reaction would involve an energetically uphill task because of the presence of the α-phenylsulfonyl moiety. Therefore, we hypothesized that this reaction might proceed through an *exo* attack of the amine on intermediate **12**, which is produced by elimination of the mesyl group through an E1cB mechanism (see Scheme 3). To confirm the involvement of **12** as an intermediate, both **9** and **10** were stirred with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in dichloromethane (DCM) at room temperature for 1 h, and the resultant **12** was heated with allylamine to give **11a** exclusively.

By applying an identical procedure, **11b** was prepared on a multigram (40 g) scale. To effect the C-4–N-7 cleavage, **11b** was stirred with 4.0 equiv. of MeMgBr (1.4 M solution in THF) at room temperature for 1 h, and the usual workup was followed by crystallization of the reaction mixture to give **13b** in 80% yield (m.p. > 240 °C, decomposition; see



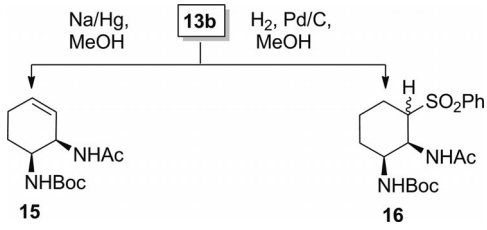
Scheme 3. Support of **12** as an intermediate in amination reaction.

Scheme 4). Removal of the phenylsulfonyl moiety[12] by heating to reflux in absolute ethanol with Raney-Ni quantitatively gave **14** {$[\alpha]_D^{27}$ = 5 (*c* = 1, chloroform)}.



Scheme 4. Synthesis of 1,2-diaminocyclohexane **14**.

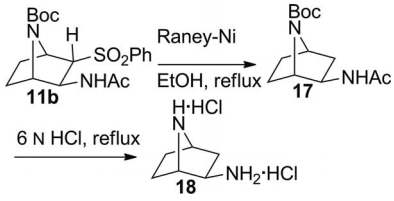
In addition to transforming **13b** into **14**, it was also converted into **15** and **16** by performing simple steps as shown in Scheme 5. Both compounds **15** and **16** provide the required structural features for further functionalizations. The reduction of **13b** by treatment with Na/Hg and H_2, Pd/C produced **15** {$[\alpha]_D^{24}$ = –31.1 (*c* = 0.9, chloroform)} and **16**, respectively, in good yields.



Scheme 5. Exploration of the methodology for other cyclohexanediamine analogues.

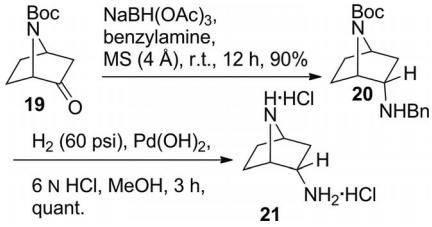
The presence of the phenylsulfonyl group at C-3 in **16** provides a handle for further transformation of this structural framework. Conformationally rigid diamines (CRDA) are important compounds because of their roles in biology, catalysis, and coordination and supramolecular chemistry.[13] Interestingly, *exo*- and *endo*-7-azabicyclo[2.2.1]-heptan-2-amines (**18** and **21**, respectively) are known substructures of many pharmacologically important compounds. For example, *N*-6-(*endo*-7-azabicyclo[2.2.1]hept-2-yl)adenosines are highly potent A1AR agonists,[14,15] whereas *exo*-7-azabicyclo[2.2.1]heptan-2-amine derivatives act as inhibitors against the plasmepsins of the malarial parasite Plasmodium falciparum.[16] In spite of the significant biological activities associated with these structural frameworks, their syntheses have mainly relied on the chiral resolution of racemic amines.[15,17] Although **21** has recently been synthesized[18] by an intramolecular cyclization of optically active 3,4-diaminocyclohexanol under Mitsunobu conditions, the strategy suffers from the need to purify the diastereomers. Therefore, we visualized the synthesis of **18** from **11b** by simply removing the phenylsulfonyl moiety. In this context, **11b** was heated to reflux in absolute ethanol

with Raney-Ni for 12 h to produce **17** in 81% yield (see Scheme 6). The global deprotection of **17** by heating at reflux with 6 N HCl quantitatively gave **18** {$[\alpha]_{27.5}^{D}$= –3 (*c* = 1.2, methanol)}.



Scheme 6. Synthesis of *exo*-7-azabicyclo[2.2.1]heptan-2-amine.

As we failed to transform **9** into its corresponding *endo* derivative, we decided to proceed with **19**, which was obtained easily from **2**. Towards this end, **19** was subjected to reductive amination with benzylamine in the presence of $NaBH(OAc)_3$ to give **20** in 90% yield (see Scheme 7). Hydrogenolysis of **20** in methanolic HCl gave **21** {$[\alpha]_{D}^{28}$ = –2.6 (*c* = 1.5, H_2O)} in 95% yield.



Scheme 7. Synthesis of *endo*-7-azabicyclo[2.2.1]heptan-2-amine.

Conclusions

We have developed a scalable, practical, and relatively inexpensive strategy towards the syntheses of *cis*-1,2-diaminocyclohexane derivatives and 7-azabicyclo[2.2.1]hept-2-amines. Explorations using *cis*-1,2-diaminocyclohexane derivatives as organocatalysts are currently underway in our laboratory and shall be disclosed in due course.

Experimental Section

General Methods: All reactions were performed under argon unless otherwise mentioned. All glassware was dried prior to use in an oven at 125 °C. Dry tetrahydrofuran was obtained by passing commercially available predried oxygen-free formulations through activated alumina columns and distilling from sodium benzophenone ketyl. DCM was distilled from calcium hydride and stored over molecular sieves (MS, 4 Å). Pyridine was distilled from KOH. The solvents for chromatography were distilled at their respective boiling points. All commercial reagents were obtained from Sigma–Aldrich Chemical Co. and S. D. Fine Chemical Co. (India). The reactions were monitored by thin layer chromatography (0.25 mm E. Merck silica gel plates, $60F_{254}$) and visualized by using UV light, an ethanolic solution of phosphomolybdic acid, and iodine. Column chromatography was performed on silica gel (60–120/100–200/230–400 mesh) that was obtained from S. D. Fine Chemical Co. India or SRL India. Typical syringe and cannula techniques were used to transfer air- and moisture-sensitive reagents. All melting points are reported in °C and were recorded with a Büchi melting point apparatus (B-450). IR spectra were recorded with Perkin–Elmer infrared spectrometer models 599-B and 1620 FTIR. ^{1}H NMR spectroscopic data were recorded in deuterated solvents with Bruker AC-200, AV-400, and DRX-500 instruments. Chemical shifts are reported in ppm. Proton coupling constants (*J*) are reported as absolute values in Hz, and the multiplicities are reported as br. (broad), s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), td (triplet of doublet), or m (multiplet). ^{13}C NMR spectroscopic data were recorded with Bruker AC-200, AV-400, and DRX-500 instruments that operated at 50, 100, and 125 MHz, respectively. The ^{13}C NMR chemical shifts are reported in ppm relative to the central line of $CDCl_3$ (δ = 77.0 ppm). High-resolution mass spectrometric data were obtained with a Thermo Scientific "Q-EXACTIVE" instrument. Optical rotations were measured with a JASCO P-1030 polarimeter.

(1*S*,2*S*,3*R*,4*R*)-*tert*-Butyl 2-[(Methylsulfonyl)oxy]-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (9): To a solution of **7** (20.0 g, 56.59 mmol) in pyridine (91.3 mL, 1.13 mol) in a round-bottom flask was added methanesulfonyl chloride (10.95 mL, 141.47 mmol) at 0 °C, and the reaction mixture was stirred at room temperature for 24 h until TLC revealed no starting material. The reaction was quenched with water (500.0 mL). The resulting mixture was extracted with EtOAc (3 × 150.0 mL), and the combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was dried in vacuo to give **9** (24.4 g, 99.9%) as a white solid; m.p. 172.4–174.9 °C. $[\alpha]_{D}^{27.5}$ = +18.0 (*c* = 0.525, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1704, 1366, 1177, 1141, 1007, 968, 868 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 8.05–7.94 (m, 2 H), 7.73–7.48 (m, 3 H), 4.92 (d, *J* = 7.1 Hz, 1 H), 4.67 (d, *J* = 3.2 Hz, 1 H), 4.40 (br. s, 1 H), 3.56 (d, *J* = 7.2 Hz, 1 H), 3.18 (s, 3 H), 1.78 (s, 2 H), 1.39 (s, 11 H) ppm. ^{13}C NMR (100 MHz, [D_6]DMSO, 25 °C): δ = 153.7, 139.7, 134.4, 129.5, 129.4, 80.2, 70.3, 61.6, 58, 37.6, 28.3, 28.2, 23.3 ppm. HRMS (ESI): calcd. for $C_{18}H_{29}N_2O_7S_2$ [M + NH_4]$^+$ 449.1411; found 449.1411.

(1*S*,2*R*,3*S*,4*R*)-*tert*-Butyl 2-[(Methylsulfonyl)oxy]-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (10): By applying the above-mentioned procedure, the corresponding mesylate **10** (99.5% yield) was obtained as a white solid; m.p. 177.3–181.6 °C. $[\alpha]_{D}^{27.6}$ = 13.0 (*c* = 0.475, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1706, 1638, 1364, 1152, 1029, 863 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.89 (d, *J* = 7.6 Hz, 2 H), 7.74–7.67 (m, 1 H), 7.65–7.56 (m, 2 H), 5.22 (dd, *J* = 4.4, 9.3 Hz, 1 H), 4.56–4.47 (m, 1 H), 4.05 (t, *J* = 4.4 Hz, 1 H), 3.72 (ddd, *J* = 1.5, 4.3, 9.8 Hz, 1 H), 3.20 (s, 3 H), 2.80–2.71 (m, 1 H), 2.40–2.30 (m, 1 H), 1.85–1.71 (m, 2 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 154.0, 139.8, 134.3, 129.6, 128.0, 81.5, 73.9, 64.0, 60.9, 58.5, 38.7, 28.1, 23.0, 21.9 ppm. HRMS (ESI): calcd. for $C_{18}H_{29}N_2O_7S_2$ [M + NH_4]$^+$ 449.1411; found 449.1409.

(1*S*,2*S*,3*R*,4*R*)-*tert*-Butyl 2-(Allylamino)-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (11a): A solution of **9** (10.0 g, 23.2 mmol) in allylamine (34.7 mL, 463.5 mmol) was heated to 55 °C for 1 h. When TLC revealed that there was no starting material, the allylamine was evaporated under reduced pressure to obtain **11a** (8.75 g, 96%) as a colorless liquid. $[\alpha]_{D}^{25}$ = +29.3 (*c* = 1.1, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1699, 1639, 1368, 1149 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.87 (d, *J* = 7.3 Hz, 2 H), 7.67–7.59 (m, 1 H), 7.59–7.51 (m, 2 H), 5.65 (br. s, 1 H), 5.11–4.96 (m, 2 H), 4.29 (br. s, 1 H), 4.17 (br. s, 1 H), 3.41–2.91 (m, 4 H), 2.39 (t, *J* = 9.2 Hz, 1 H), 1.90–1.78 (m, 1 H), 1.66–1.49 (m, 2 H), 1.38 (s, 9 H)

ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 155.3, 139.7, 135.9, 133.8, 129.3, 127.9, 116.3, 80.4, 72.9, 63.7, 61.3, 57.3, 50.0, 28.1, 28.0, 26.0, 23.9 ppm. HRMS (ESI): calcd. for $C_{20}H_{29}N_2O_4S$ [M + H]$^+$ 393.1843; found 393.1847.

(1*S*,2*S*,3*R*,4*R*)-*tert*-Butyl 2-Acetamido-3-(phenylsulfonyl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (11b): Acetamide (13.7 g, 231.7 mmol) was added to **9** (5.0 g, 11.6 mmol) in a round-bottomed flask, and the mixture was heated until the acetamide melted (approximately 90 °C). Potassium carbonate (0.320 g, 2.3 mmol) was then added, and the reaction mixture was stirred at that temperature for 2 h. The reaction was quenched by the addition of water (200.0 mL), and the resulting solution was extracted with EtOAc (3 × 100.0 mL). The combined organic layers were dried with sodium sulfate and concentrated to give **11b** (4.0 g, 87%) as a white solid. The reaction with a mixture of **9** and **10** (50.0 g, 115.9 mmol) gave **11b** (40 g, 87%); m.p. 138.5–140 °C. $[\alpha]_D^{27.2}$ = +24.7 (*c* = 2.1, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1651, 1371, 1308, 1151 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.92 (d, *J* = 7.5 Hz, 2 H), 7.68–7.61 (m, 1 H), 7.59–7.52 (m, 2 H), 5.57 (d, *J* = 9.0 Hz, 1 H), 4.63–4.52 (m, 2 H), 4.09 (d, *J* = 5.3 Hz, 1 H), 3.25 (t, *J* = 3.8 Hz, 1 H), 2.46 (ddd, *J* = 3.1, 8.5, 12.2 Hz, 1 H), 1.94–1.83 (m, 1 H), 1.76 (t, *J* = 5.5 Hz, 2 H), 1.70 (s, 3 H), 1.43 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 168.6, 155.2, 139.5, 134.0, 129.3, 128.2, 81.1, 73.5, 64.2, 58.1, 54.8, 28.1, 26.0, 24.1, 22.9 ppm. HRMS (ESI): calcd. for $C_{19}H_{27}N_2O_5S$ [M + H]$^+$ 395.1635; found 395.1632.

(1*R*,2*S*,3*S*,4*S*)-*tert*-Butyl 2-(Phenylsulfonyl)-3-(pyrrolidin-1-yl)-7-azabicyclo[2.2.1]heptane-7-carboxylate (11c): To a stirring solution of pyrrolidine (11.40 mL, 139.0 mmol) was added **9** (6.0 g, 13.90 mmol), and the reaction mixture was heated to 90 °C for 1 h. The reaction mixture was concentrated under reduced pressure to give **11c** (5.5 g, 97%) as a pale yellow solid; m.p. 123–124 °C. $[\alpha]_D^{25}$ = +15.2 (*c* = 2.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 2972, 2067, 1637, 1447, 1367 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.90 (dd, *J* = 1.1, 8.4 Hz, 2 H), 7.66–7.60 (m, 1 H), 7.58–7.51 (m, 2 H), 4.31 (br. s, 1 H), 4.18 (br. s, 1 H), 3.59 (br. s, 1 H), 3.06 (br. s, 1 H), 2.50–2.27 (m, 5 H), 1.91–1.82 (m, 1 H), 1.68–1.52 (m, 6 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 155.3, 139.9, 133.7, 129.2, 128.1, 80.0, 70.3, 69.3, 61.5, 57.5, 51.4, 28.1, 26.2, 24.4, 23.2 ppm. HRMS (ESI): calcd. for $C_{21}H_{31}N_2O_4S$ [M + H]$^+$ 407.1999; found 407.2002.

(1*R*,4*S*)-*tert*-Butyl 2-(Phenylsulfonyl)-7-azabicyclo[2.2.1]hept-2-ene-7-carboxylate (12): To a solution of **9** and **10** (1.0 g, 2.32 mmol) in dichloromethane was added DBU (0.7 mL, 4.64 mmol) at room temperature, and the reaction mixture was stirred for 1 h, in which time TLC revealed no starting material. The reaction was quenched with water (10.0 mL), and the resulting solution was extracted with of EtOAc (3 × 10.0 mL). The combined organic layers were concentrated, and the crude material was dried in vacuo to give **12** (0.77 g, 99%) as a white solid. $[\alpha]_D^{25.4}$ = +6 (*c* = 2.5, $CHCl_3$) To this was added allylamine (1.72 mL, 23.0 mmol), and the reaction mixture was heated at 55 °C for 1 h. When TLC revealed no starting material, the reaction mixture was concentrated under reduced pressure. The crude material was dried in vacuo to give **11a** (0.860 g, 95%) as a colorless liquid. The analytical data matched that of previously synthesized **11a**.

***tert*-Butyl [(1*S*,2*S*)-2-(Allylamino)-3-(phenylsulfonyl)cyclohex-3-en-1-yl]carbamate (13a):** To a solution of **11a** (2.0 g, 5.10 mmol) in THF (20 mL) in a round-bottom flask equipped with a magnetic stir bar was added dropwise methylmagnesium bromide solution (1.4 M solution in THF, 14.6 mL, 20.4 mmol) at room temperature. After a period of time, the solution changed from colorless to yellow. The reaction was quenched with a saturated solution of ammonium chloride (20 mL) after 4 h. The resulting mixture was extracted with EtOAc (3 × 25.0 mL), and the combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified by column chromatography (petroleum ether/ethyl acetate, 70:30) to give **13a** (1.72 g, 86%) as a white crystalline solid; m.p. 137–138 °C. $[\alpha]_D^{27}$ = –52.4 (*c* = 0.35, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 2927, 1637, 1149 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$, 25 °C): δ = 7.86 (d, *J* = 7.6 Hz, 2 H), 7.66–7.59 (m, 1 H), 7.58–7.50 (m, 2 H), 7.14 (dd, *J* = 2.7, 4.6 Hz, 1 H), 5.88–5.73 (m, 1 H), 5.22–5.10 (m, 2 H), 5.05 (d, *J* = 10.1 Hz, 1 H), 3.51 (dd, *J* = 6.0, 13.6 Hz, 1 H), 3.45–3.37 (m, 1 H), 3.32 (br. s, 1 H), 3.22 (dd, *J* = 6.0, 13.6 Hz, 1 H), 2.48–2.26 (m, 2 H), 1.76–1.60 (m, 2 H), 1.41 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$, 25 °C): δ = 155.1, 142.0, 141.0, 139.6, 136.5, 133.4, 129.3, 127.8, 116.1, 79.3, 52.9, 52.4, 49.7, 28.3, 25.3, 23.0 ppm. HRMS (ESI): calcd. for $C_{20}H_{29}N_2O_4S$ [M + H]$^+$ 393.1843; found 393.1847.

***tert*-Butyl [(1*S*,2*S*)-2-Acetamido-3-(phenylsulfonyl)cyclohex-3-en-1-yl]carbamate (13b):** To a solution of **11b** (0.5 g, 1.27 mmol) in THF (5 mL) in a round-bottomed flask equipped with a magnetic stir bar was added dropwise methylmagnesium bromide solution (1.4 M solution in THF, 3.6 mL, 5.07 mmol) at room temperature. After a period of time, the solution changed from colorless to yellow. The reaction was quenched with a saturated solution of ammonium chloride (10.0 mL) after 1 h. The reaction mixture was extracted with EtOAc (3 × 15.0 mL), and the combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was recrystallized (EtOAc/petroleum ether, 90:10) to give **13b** (0.4 g, 80%) as a white solid; m.p. 243–245 °C (decomposition). $[\alpha]_D^{27.5}$ = 154 (*c* = 0.8, MeOH). IR (neat): $\tilde{\nu}_{max}$ = 1645, 1306, 1146, 1025 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.92–7.79 (m, 2 H), 7.70–7.50 (m, 3 H), 7.32 (t, *J* = 3.6 Hz, 1 H), 5.81–5.60 (m, 1 H), 5.32–5.08 (m, 1 H), 4.87–4.70 (m, 1 H), 3.60–3.40 (m, 1 H), 2.56–2.39 (m, 2 H), 2.11–1.89 (m, 5 H), 1.39 (s, 9 H) ppm. ^{13}C NMR (125 MHz, $[D_6]$DMSO, 25 °C): δ = 168.7, 154.7, 142.6, 140.1, 137.9, 133.3, 129.0, 127.6, 77.6, 49.6, 42.5, 28.3, 25.3, 22.4, 21.1 ppm. HRMS (ESI): calcd. for $C_{19}H_{27}N_2O_5S$ [M + H]$^+$ 395.1635; found 395.1632.

***tert*-Butyl [(1*S*,2*R*)-2-Acetamidocyclohexyl]carbamate (14):** To a stirred solution of **13b** (100 mg, 0.254 mmol) in absolute ethanol (5 mL) was added Raney-Ni (38 mg, 0.632 mmol) in one portion, and the reaction mixture was heated at reflux for 12 h. The reaction mixture was cooled and then passed through a pad of Celite. The filtrate was concentrated by rotary evaporation to give **14** (65 mg, 100%) as a colorless liquid. $[\alpha]_D^{27}$ = +5 (*c* = 1, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3333, 2933, 2859, 1694, 1645, 1532, 1455, 1367, 1335, 1312, 1249, 1172, 1050, 979, 755 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 6.42 (br. s, 1 H), 5.01 (br. s, 1 H), 3.94 (br. s, 1 H), 3.81 (br. s, 1 H), 1.95 (s, 3 H), 1.84–1.53 (m, 4 H), 1.43 (s, 13 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.1, 156.3, 79.7, 50.6, 50.1, 29.4, 28.3, 27.8, 23.4, 22.8, 21.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{25}N_2O_3$ [M + H]$^+$ 257.1860; found 257.1853.

***tert*-Butyl [(1*S*,2*R*)-2-Acetamidocyclohex-3-en-1-yl]carbamate (15):** To a stirred solution of **13b** (0.2 g, 0.51 mmol) in methanol (10 mL) at –20 °C was added in one portion 6% sodium amalgam (0.58 g, 1.52 mmol), and the resultant reaction mixture was stirred at that temperature for 24 h. The reaction was quenched with a saturated aqueous solution of ammonium chloride (10.0 mL), and the resultant solution was extracted with EtOAc (3 × 15.0 mL). The combined organic layers were dried with anhydrous sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material

was purified by column chromatography (EtOAc/petroleum ether, 70:30) to give **15** (0.11 g, 85%) as a colorless liquid. $[\alpha]_D^{24}$ = –31.1 (c = 0.9, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3435, 2094, 1642, 1369, 1169, 1048 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.88–5.80 (m, 1 H), 5.68 (br. s, 1 H), 5.62–5.50 (m, 1 H), 5.03 (br. s, 1 H), 4.62 (br. s, 1 H), 3.90 (tt, J = 4.0, 7.8 Hz, 1 H), 2.13 (br. s, 2 H), 2.02 (s, 3 H), 1.78 (br. s, 1 H), 1.68–1.61 (m, 1 H), 1.45 (s, 9 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 170.4, 155.9, 130.4, 126.2, 79.5, 48.8, 47.2, 28.3, 24.7, 23.5, 22.8 ppm. HRMS (ESI): calcd. for $C_{13}H_{22}N_2O_3Na$ $[M + Na]^+$ 277.1523; found 277.1517.

***tert*-Butyl [(1*S*,2*S*)-2-Acetamido-3-(phenylsulfonyl)cyclohexyl]carbamate (16):** To a solution of **13b** (200 mg, 0.507 mmol) in methanol (20 mL) in a round-bottomed flask equipped with a magnetic stir bar was added 10% Pd/C (54 mg, 0.05 mmol) at room temperature. A hydrogen balloon was then attached, and the reaction mixture was stirred vigorously for 24 h until TLC revealed no starting material. The reaction mixture was passed through a pad of Celite, and the filtrate was concentrated in vacuo to give **16** (0.2 g, 99%) as a colorless liquid. $[\alpha]_D^{26}$ = +24.8 (c = 1.3, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ = 7.89–7.79 (m, 2 H), 7.75–7.51 (m, 3 H), 6.38 (d, J = 7.3 Hz, 1 H), 4.33–4.19 (m, 1 H), 3.91 (t, J = 10.4 Hz, 1 H), 3.27 (dt, J = 3.9, 10.5 Hz, 1 H), 2.28–2.14 (m, 1 H), 1.98 (s, 3 H), 1.89–1.70 (m, 2 H), 1.61–1.49 (m, 1 H), 1.43 (s, 9 H) ppm. HRMS (ESI): calcd. for $C_{19}H_{29}N_2O_5S$ $[M + H]^+$ 397.1792; found 397.1799.

(1*S*,2*R*,4*R*)-*tert*-Butyl 2-Acetamido-7-azabicyclo[2.2.1]heptane-7-carboxylate (17): To a solution of **11b** (200 mg, 0.507 mmol) in absolute ethanol (10 mL) was added freshly prepared Raney-Ni (90 mg, 1.5 mmol). The reaction mixture was heated at reflux for 12 h until TLC revealed no starting material. The mixture was cooled and then passed through a pad of Celite. The filtrate was concentrated in vacuo to give **17** (105 mg, 81%) as a colorless liquid. $[\alpha]_D^{29.2}$ = +71.6 (c = 2, CH_3OH). IR (neat): $\tilde{\nu}_{max}$ = 2978, 1648, 1638, 1368, 1168, 1138, 1020 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.93 (br. s, 1 H), 4.22 (t, J = 4.9 Hz, 1 H), 4.07 (d, J = 5.0 Hz, 1 H), 3.97 (dt, J = 3.3, 7.9 Hz, 1 H), 1.94 (s, 3 H), 1.81–1.61 (m, 2 H), 1.53–1.46 (m, 2 H), 1.44 (s, 9 H), 1.40 (dd, J = 2.9, 17.2 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $[D_6]$DMSO, 25 °C): δ = 169.4, 156.4, 80.1, 61.3, 55.9, 53.0, 40.4, 28.3, 28.2, 25.9, 23.2 ppm. HRMS (ESI): calcd. for $C_{13}H_{23}N_2O_3$ $[M + H]^+$ 255.1703; found 255.1700.

(1*S*,2*R*,4*R*)-7-Azabicyclo[2.2.1]heptan-2-amine Hydrochloride (18): A solution of **17** (100 mg, 0.393 mmol) in HCl (6 N solution, 5 mL) in a round-bottom flask equipped with a magnetic stir bar and a reflux condenser was heated to reflux for 12 h until TLC reveal no starting material. The reaction mixture was concentrated by rotary evaporation, and the crude material was dried in vacuo to give **18** (71 mg, 98%) as a brown solid. $[\alpha]_D^{27.5}$ = 3 (c = 1.2, CH_3OH). IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 3437, 1634, 1227, 1059 cm^{-1}. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 4.40 (d, J = 4.8 Hz, 1 H), 4.34 (t, J = 4.6 Hz, 1 H), 3.74 (dd, J = 4.4, 8.9 Hz, 1 H), 2.36 (dd, J = 8.9, 14.4 Hz, 1 H), 2.00–1.84 (m, 3 H), 1.78–1.64 (m, 2 H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 61.4, 58.5, 51.0, 34.4, 24.9, 24.2 ppm. HRMS (ESI): calcd. for $C_6H_{13}N_2$ $[M + H]^+$ 113.1073; found 113.1075.

(1*S*,2*S*,4*R*)-*tert*-Butyl 2-(Benzylamino)-7-azabicyclo[2.2.1]heptane-7-carboxylate (20): To a solution of **19** (0.20 g, 0.946 mmol) and anhydrous magnesium sulfate in dichloroethane (5.00 mL) in a round-bottomed flask equipped with a magnetic stir bar was added benzylamine (0.16 mL, 1.42 mmol). The flask was stirred under argon for 60 min, and then sodium triacetoxyborohydride (0.30 g, 1.42 mmol) was added. The reaction mixture was stirred at room temperature for 24 h until TLC showed complete conversion of the starting material and then was quenched with NaOH (2 N solution, 5.00 mL). The layers were separated, and the aqueous layer was extracted with DCM (3 × 10.0 mL). The combined organic layers were dried with sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified by column chromatography (EtOAc/petroleum ether, 60:40) to give **20** (0.27 g, 94%) as a colorless liquid. $[\alpha]_D^{28.9}$ = +12.2 (c = 0.5, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 3087, 3063, 3006, 2975, 2871, 2090, 1698, 1641, 1496, 1456, 1366, 1165 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.24–7.18 (m, 4 H), 7.18–7.12 (m, 1 H), 4.19–3.93 (m, 2 H), 3.59 (s, 2 H), 3.23–3.10 (m, 1 H), 2.13–2.01 (m, 1 H), 1.96 (ddd, J = 4.5, 9.2, 12.2 Hz, 1 H), 1.34 (s, 9 H), 0.78 (dd, J = 4.6, 12.1 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 155.7, 140.0, 128.4, 128.2, 127.1, 79.5, 58.8, 58.5, 56.8, 52.9, 37.9, 30.1, 28.3, 21.4 ppm. HRMS (ESI): calcd. for $C_{18}H_{27}N_2O_2$ $[M + H]^+$ 303.2067; found 303.2079.

(1*S*,2*S*,4*R*)-7-Azabicyclo[2.2.1]heptan-2-amine Hydrochloride (21): To a solution of **20** (100 mg, 0.33 mmol) in distilled methanol (5 mL) were added HCl (6 N solution, 5 mL) and $Pd(OH)_2/C$ (46 mg, 0.66 mmol), and the reaction mixture was put into a Parr shaker and shaken under hydrogen pressure (60 psi) at room temperature for 4 h. The solution was filtered, and the filtrate was concentrated under reduced pressure to give **21** (59 mg, 97%) as a colorless solid. $[\alpha]_D^{28}$ = +2.2 (c = 2, H_2O). IR (neat): $\tilde{\nu}_{max}$ = 2068, 1637, 1422, 1022 cm^{-1}. ^1H NMR (400 MHz, D_2O, 25 °C): δ = 4.43 (br. s, 1 H), 4.28 (t, J = 4.5 Hz, 1 H), 3.97–3.89 (m, 1 H), 2.50–2.39 (m, 1 H), 2.08–1.96 (m, 3 H), 1.87–1.77 (m, 1 H), 1.64 (dd, J = 4.4, 14.4 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O, 25 °C): δ = 59.4, 59.2, 48.2, 31.3, 26.3, 19.7 ppm. HRMS (ESI): calcd. for $C_6H_{13}N_2$ $[M + H]^+$ 113.1073; found 113.1044.

Supporting Information (see footnote on the first page of this article): NMR spectra for the compounds synthesized.

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