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A facile, one-pot synthesis of *Ephedra*-based aziridines

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ABSTRACT

A series of enantiomerically and diastereomerically enriched *N*-sulfonylaziridines have been prepared by a single-pot process from (1*R*,2*S*)- and (1*S*,2*R*)-norephedrine and (1*S*,2*S*)-pseudonorephedrine. The cyclization process involved N-sulfonylation of the *Ephedra* alkaloid followed by O-sulfonylation with methanesulfonyl chloride. The bis(sulfonyl)*Ephedra* derivatives were treated with either hydrazine or sodium hydroxide to afford the *N*-sulfonylaziridines.

1. Introduction

The application of enantiomerically enriched aziridines as chiral building blocks[1] and as chemical reagents[2] continues to enjoy widespread exposure in asymmetric organic synthesis. There are a wide variety of methods that can be employed in the synthesis of these valuable intermediates.[3] In 1992, Craig and Berry[4] demonstrated that *N*-tosylaziridines could be prepared by a three-step sequence from commercially available chiral α-amino acids (Scheme 1). The process involved N-tosylation of the amino acid **1** and subsequent reduction to generate the *N*-tosylamino alcohol **2**, which in turn was sulfonylated and cyclized under basic conditions (triethylamine) to afford the *N*-tosylaziridine **3**. In 2003, Leighton and Krauss[5] employed a more effective, single-step process that allowed the formation of chiral *N*-sulfonylaziridines from either L-valinol or L-*tert*-leucinol. More recently, in 2007, Badía et al.[6] further refined this process so that such aziridines could be obtained on a large scale in high yield.

We were interested in preparing a series of aziridines derived from (1*R*,2*S*)-norephedrine and (1*S*,2*S*)-pseudonorephedrine. Previously, in 2004, Zhang et al. prepared *N*-sulfonylaziridines possessing the *Ephedra* constitution by iron-catalyzed aziridination of *trans*-β-methylstyrene (Scheme 2).[7] Later, in 2007, Vinod et al. reported a two-step synthetic process involving sulfonylation of (1*R*,2*S*)-norephedrine followed by a Mitsunobu cyclization to yield a series of *N*-sulfonylaziridines (Scheme 2).[8]

The methods described in Schemes 1 and 2 serve as the inspiration for the development of a flexible, one-pot method for the preparation of enantiomerically and diastereomerically pure *Ephedra*-based aziridines. The most efficient of these processes is the one developed by Badía et al. However, this process is limited in terms of the sulfonyl group that is introduced into the system. Two equivalents of the sulfonyl chloride must be employed in order to obtain the product. If the desired sulfonyl group is valuable, for example, D-(+)-10-camphorsulfonyl, then the route of 2 equiv would not be the optimal synthetic pathway as 1 equiv would be lost as a sulfonate leaving group, resulting in poor atom economy. Based on this analysis, it would be favorable to develop a one-pot process where the *N*-sulfonyl group would be distinct from the *O*-sulfonyl leaving group. We envisioned a process that would first substitute the nitrogen with the desired alkyl- or arylsulfonyl chloride, followed by the activation of the alcohol with methanesulfonyl chloride, generating an inexpensive and sacrificial sulfonate for the cyclization stage of the aziridine formation. We report on the development of a process that addresses the facile preparation of a variety of *Ephedra*-based *N*-sulfonylaziridines in a single-pot system.

2. Results and discussion

This research was initiated by conducting a simple experiment to determine the viability of preparing *Ephedra*-based aziridines by a multistep, one-pot method similar to the one refined by Bádia et al.[6] (1*R*,2*S*)-Norephedrine **7** was treated with 2 equiv of methanesulfonyl chloride and excess triethylamine and allowed to stir to form the putative *N*,*O*-bis(methanesulfonyl) derivative **10** within 1 h (Scheme 3). As had been observed in the study by Berry and Craig,[4] it was expected that the presence of triethylamine would stimulate the formation of the aziridine **9a**. The cyclization process did indeed occur, but not in a timely fashion. There have been numerous literature examples where triethylamine, sodium hydride, or an alkali carbonate had been employed in the formation of sulfonamide aziridines.[9] Among the bases that were explored for this process, it was determined that when hydrazine was added to the mixture, there was an immediate acceleration of the cyclization as observed by thin layer chromatography. We

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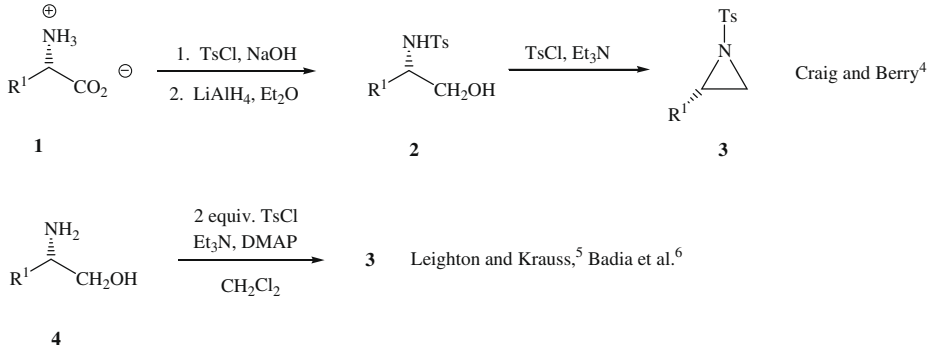
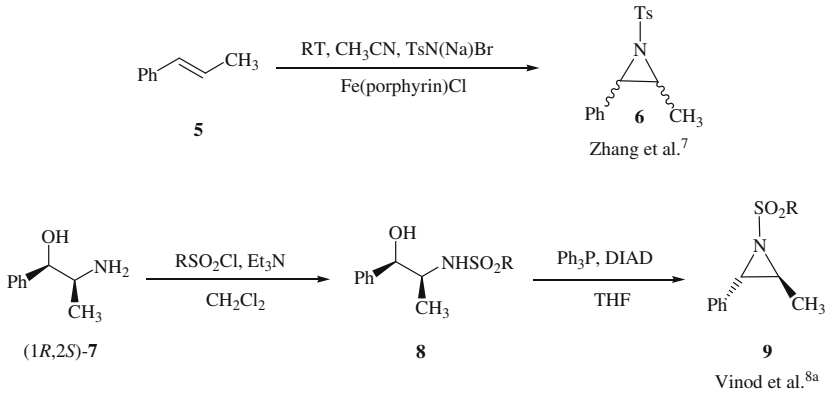


Scheme 1. Aziridine literature syntheses.

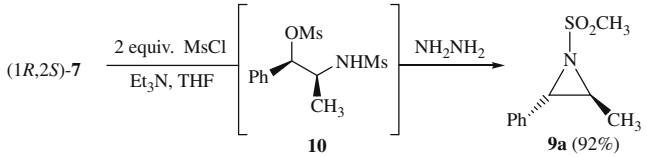


Scheme 2. *Ephedra* aziridine synthesis.

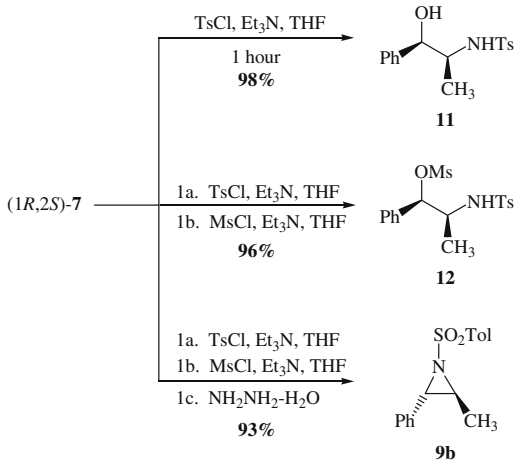
were gratified to learn that the hydrazine-mediated cyclization of **10** to the corresponding aziridine **9a** was nearly quantitative and occurred more quickly than the triethylamine-mediated reaction, presumably due to steric differences as the pK_a of the conjugate acid of triethylamine (10.75)[10a,b] is reported to be higher than that of hydrazine (8.07).[10c]

Encouraged by this result, we opted to design a multistep, single-pot process that would allow for the formation of other *N*-sulfonylaziridines but would not require the use of 2 equiv of a potentially valuable sulfonyl group. The use of methanesulfonyl chloride to form the *O*-sulfonate leaving group was considered to be ideal as it is commercially inexpensive and very atom economical. This synthetic route was explored in a stepwise fashion using (1*R*,2*S*)-**7** as a test case (Scheme 4). Treatment of (1*R*,2*S*)-**7** with *p*-toluenesulfonyl chloride and triethylamine formed the *N*-*p*-toluenesulfonyl derivative **11** in 98% yield within 1 hr as evidenced by thin layer chromatography. With this time parameter set, (1*R*,2*S*)-**7** was treated again with *p*-toluenesulfonyl chloride and triethylamine and then, after 1 h, was treated with methanesulfonyl chloride and triethylamine and allowed to stir for an hour to form the *O*-methanesulfonyl-*N*-toluenesulfonylnorephedrine derivative **12** in 96% yield. Finally, (1*R*,2*S*)-**7** was treated under the same conditions and after the expected formation of **12** in situ, hydrazine was added to the reaction mixture to induce the formation of the *N*-toluenesulfonylaziridine **9b** within 1 h in 93% yield after flash chromatography.

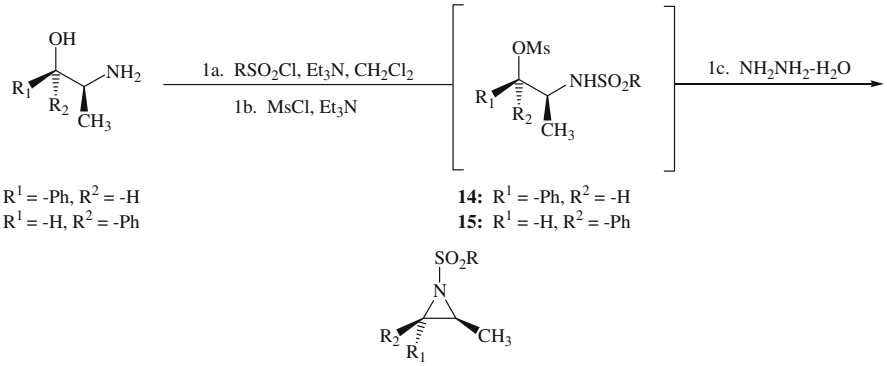
With the test case established for the multistep, one-pot reaction process, other examples were considered. Thus, (1*R*,2*S*)-norephedrine **7** and (1*S*,2*S*)-pseudonorephedrine **13** were reacted first with either *p*-toluenesulfonyl chloride or *o*-nitrobenzenesulfonyl chloride and 1 equiv of triethylamine and were allowed to stir for 1 h (Scheme 5). An additional equivalent of triethylamine and 1 equiv of methanesulfonyl chloride were then added and the reaction mixture was stirred for 1 h. An excess of hydrazine hydrate



Scheme 3. Multistep, single-pot synthesis of aziridine **9a**.



Scheme 4. Development of the single-pot process.

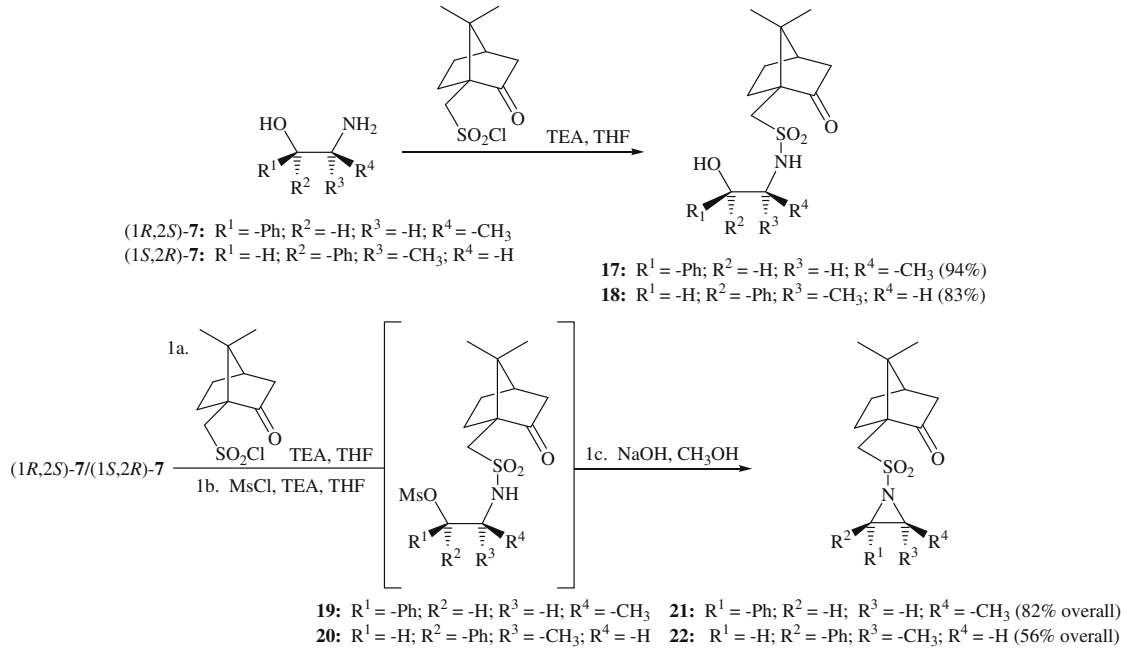


Scheme 5. Multistep, one-pot synthesis of norephedrine and pseudonorephedrine aziridines.

was then added and the reactions were stirred until complete product formation was determined by thin layer chromatography. The isolated chemical yield for the formation of the aziridines **9c**, **16a**, and **16b** was 73%, 87% and 60%, respectively. The yields for the *N*-*o*-nitrobenzenesulfonyl aziridines **9c** and **16b** were lower due to nucleophilicity of the hydrazine–hydrate being used. This was perhaps due to the enhanced electrophilicity of the benzylic carbon of the aziridine by way of the sulfonyl group.

In all cases of aziridine formation by inversion of the benzylic position through nucleophilic substitution, there was no detectable stereochemical scrambling as determined by ^{1}H NMR spectroscopic analysis. Ultimately, the isolation of diastereomerically pure aziridines (*cis*-aziridines, J = 7.4–7.7 Hz; *trans*-aziridines, J = 4.3–4.7 Hz) suggested that the process of the displacement of the methanesulfonate group proceeded through an 'S_N2' type transition state rather than an 'S_N1' type ionized intermediate.

There was also an interest in the synthesis of camphorsulfonyl-based derivatives **21** and **22** (Scheme 6). In this context, (1*R*,2*S*)-**7** and (1*S*,2*R*)-**7** were each reacted with D-camphorsulfonyl chloride and triethylamine to afford the sulfonylated derivatives **17** and **18** in 94% and 83% yields, respectively, after only 1 hr as judged by thin layer chromatography. This established a time window to ensure that complete sulfonylation had occurred. At this stage, the two-step process of forming bis(sulfonylated) intermediates **19** and **20** was investigated. It was determined that the complete formation of the *N*-camphorsulfonyl-*O*-methanesulfonyl *Ephedra* derivatives **19** and **20** occurred in a 4-h. time frame. Attempts to chromatographically purify these intermediates were not successful due to their reactive nature, that is, aziridine formation. The one-pot bis(sulfonylation) was carried out to yield the putative intermediates **19** and **20** and these compounds were treated with hydrazine–hydrate to effect the cyclization. Unfortunately, the cyclization stage of the reaction proved to be sluggish under these conditions and the reactions were not complete even after 12 h. We were gratified to learn that the use of sodium hydroxide/methanol mixture was considerably more effective for the cyclization process and ultimately led to the formation of the target aziridines **21** and **22** in 82% and 56% overall yield, respectively, for the three



Scheme 6. D-Camphorsulfonylaziridine synthesis.

step, one-pot process. The use of the methanolic base solution required an overnight process to reach completion as determined by the TLC analysis. The lower yield of **22** is attributed to potential conformational differences between intermediates **19** and **20** that may interfere with the ring-closing process.

3. Conclusion

A three-step, one-pot process for the formation of *N*-sulfonylaziridines derived from either norephedrine or pseudonorephedrine was developed. The combined reactions of the introduction of the selected arylsulfonyl or camphorsulfonyl group at nitrogen, followed by formation of the nucleofuge mesylate, and the base-mediated cyclization (hydrazine–hydrate or NaOH/MeOH) proved to be successful in creating synthetically valuable aziridines.

4. Experimental

4.1. General information

Enantiomerically enriched (1*R*,2*S*)- and (1*S*,2*R*)-norephedrine was purchased from Sigma–Aldrich. All reaction vessels were flame dried and purged under a nitrogen atmosphere. Triethylamine (TEA) was distilled over calcium hydride. All extractions were dried over anhydrous magnesium sulfate, gravity filtered, and the solvents were removed under vacuum. Infrared data were acquired using a Perkin–Elmer Spectrum BX FT-IR spectrophotomer on NaCl plates and were reported in reciprocal centimeters (cm^{-1}). All NMR spectra were recorded in $CDCl_3$ and reported in parts per million (δ scale) with tetramethylsilane as an internal standard (δ = 0 ppm, ^1H) or deuterated chloroform as a standard (δ = 77.0 ppm, ^{13}C). On some ^1H NMR spectra, the OH and NH peaks on the spectrum were not observed due to broadening. Optical rotation data were collected on a JASCO P-1010 digital polarimeter operating at 589 nm in an 8 × 100 mm cell. Melting points were determined using a Laboratory Devices Mel-Temp apparatus and are uncorrected. Mass Spectral data were collected by the University of Illinois at Urbana-Champaign.

4.2. (2*S*,3*S*)-2-Methyl-1-(methanesulfonyl)-3-phenylaziridine 9a

In a flame-dried, nitrogen purged reaction vessel containing (1*R*,2*S*)-norephedrine, in a 0.3 M THF solution, 2.2 equiv of triethylamine was added and the solution was cooled in an ice bath. To this solution, 2.1 equiv of methanesulfonyl chloride was added and the reaction was allowed to proceed for an hour after which 5 equiv of hydrazine was added to afford aziridine **9a** as a colorless oil in 92% yield after chromatography. The reaction was monitored by TLC (R_f = 0.36, 9:1, hex/EtOAc). $[\alpha]_D^{25} = -95.2$ (*c* 0.99, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 1.78 (3H, d, *J* = 5.9 Hz), 2.90 (1H, dq, *J* = 4.3, 5.9 Hz), 3.07 (3H, s), 3.70 (1H, d, *J* = 4.3 Hz), 7.26–7.38 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 42.5, 48.8, 48.9, 126.1, 128.2, 128.6, 135.4. IR (neat): 3063, 3031, 1602, 1150, 805, 776, 749, 700 cm^{-1}. HRMS (ESI) calcd for $C_{10}H_{14}NO_2S$ ($M+H^+$): 212.0745. Found: 212.0743.

4.3. *N*-((1*R*,2*S*)-1-Hydroxy-1-phenyl-2-propyl)-*p*-toluenesulfonamide 11

(1*R*,2*S*)-Norephedrine was dissolved in THF to afford a 0.3 M solution with 1.1 equiv of TEA and the solution was placed in an ice bath. To this solution, 1.05 equiv of *p*-toluenesulfonyl chloride was added and the water bath was removed after several minutes. After 1 h, the reaction was quenched with saturated bicarbonate and the THF removed under vacuum after which the sulfonamide was extracted with ethyl acetate and the solvents were removed. The resulting white solid was triturated with diethyl ether to afford the title compound in 98% yield. $[\alpha]_D^{24} = -2.3$ (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (3H, d, *J* = 7.0 Hz), 2.38 (3H, s), 3.27 (1H, br s), 3.49 (1H, dq, *J* = 5.5, 7.0 Hz), 4.80 (1H, d, *J* = 5.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.6, 21.5, 54.9, 75.7, 126.0, 126.9, 127.6, 128.3, 129.7, 137.7, 140.2, 143.5. IR (Nujol): 3509, 3208, 1598, 1324, 1160, 1092, 702 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{20}NO_3S$ ($M+H^+$): 306.1164. Found: 306.1168.

4.4. (1*R*,2*S*)-2-(*p*-Toluenesulfonamido)-1-phenylpropyl methanesulfonate 12

To a flame-dried, nitrogen purged reaction vessel containing (1*R*,2*S*)-norephedrine, in a 0.3 M THF solution, was added 1.1 equiv of TEA and the solution was cooled in an ice bath. To this mixture, 1.05 equiv of *p*-toluenesulfonyl chloride was added and the ice bath was removed after several minutes. After a 1-h reaction time, 1.1 equiv of TEA was added to the reaction mixture with ice bath cooling. This was followed by the addition of 1.05 equiv of methanesulfonyl chloride and the bath was removed after several minutes. After 1 h, saturated sodium bicarbonate was added and the THF was removed. The sulfonamide was extracted with ethyl acetate and the solvents were removed to afford a white solid which was triturated with diethyl ether to provide **12** in 96% yield. Mp: decomposes >90 °C. $[\alpha]_D^{25} = -68.7$ (*c* 1.0, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$): δ 1.03 (3H, d, *J* = 7.0 Hz), 2.43 (3H, s), 2.91 (3H, s), 3.68 (1H, ddq, *J* = 3.5, 7.0, 8.6 Hz), 4.95 (1H, d, *J* = 8.6 Hz), 5.56 (1H, d, *J* = 3.5 Hz), 7.23–7.36 (7H, m), 7.76 (2H, d, *J* = 8.2 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, due to coincidental overlap, some peaks in the aromatic region are missing) δ 15.2, 21.5, 38.6, 53.9, 84.9, 126.3, 127.1, 128.9, 129.8, 135.2, 137.4, 143.7. IR (Nujol): 3305, 3030, 1595, 1454, 1377, 1172, 938, 749, 701 cm^{-1}. HRMS calcd for $C_{17}H_{25}N_2O_5S_2$ ($M+NH_4^+$): 401.1205. Found: 401.1196.

4.5. (2*S*,3*S*)-2-Methyl-3-phenyl-1-toluenesulfonylaziridine 9b

In a flame-dried, nitrogen purged reaction vessel containing (1*R*,2*S*)-norephedrine, in a 0.3 M THF solution, 1.1 equiv of TEA was added and the solution was cooled in an ice bath. To this, 1.05 equiv of *p*-toluenesulfonyl chloride was added and the water bath was removed after several minutes. After a 1-h reaction time, 1.1 equiv of TEA was added to the reaction mixture with ice bath cooling. This was followed by the addition of 1.05 equiv of methanesulfonyl chloride and the reaction was allowed to proceed for an additional hour after which 5 equiv of hydrazine was added to afford aziridine **9b** as a colorless oil in 93% yield after flash chromatography. The reaction was monitored by TLC. $[\alpha]_D^{25} = +66.2$ (*c* 1.06, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 1.82 (3H, d, *J* = 6.3 Hz), 2.36 (3H, s), 2.90 (1H, dq, *J* = 4.3, 6.3 Hz), 3.80 (1H, d, *J* = 4.3 Hz), 7.12–7.15 (5H, m), 7.23 (2H, d, *J* = 7.4 Hz), 7.82 (2H, d, *J* = 8.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 21.4, 49.0, 49.1, 126.2, 127.1, 127.9, 128.4, 129.4, 135.5, 137.8, 143.8. IR (neat) 3063, 3030, 1602, 748, 699 cm^{-1}. HRMS (ESI) calcd for $C_{16}H_{18}NO_2S$ ($M+H^+$): 288.1058. Found: 288.1052.

4.6. (2*S*,3*S*)-2-Methyl-1-(*o*-nitrobenzenesulfonyl)-3-phenylaziridine 9c

In a flame-dried, nitrogen purged reaction vessel containing (1*R*,2*S*)-norephedrine, in a 0.3 M THF solution, 1.1 equiv of triethylamine (TEA) was added and the solution was cooled in an ice bath. To this, 1.05 equiv of *o*-nitrobenzenesulfonyl chloride was added and the water bath was removed after several minutes. After a 1-h reaction time, 1.1 equiv of TEA was added to the reaction mixture with ice bath cooling. This was followed by the addition of

1.05 equiv of methanesulfonyl chloride and the reaction was allowed to proceed for an additional hour after which 5 equiv of hydrazine were added and the reaction was stirred for 6 h. This process afforded aziridine **9c** as a colorless oil in 72% yield after chromatography. The reaction was monitored by TLC. $[\alpha]_D^{24} = -93.5$ (*c* 0.77, CH_2Cl_2). ^1H NMR (400 MHz, $CDCl_3$) δ 1.86 (3H, d, *J* = 6.3 Hz), 3.09 (1H, dq, *J* = 4.7 Hz, *J* = 6.3 Hz), 3.94 (1H, d, *J* = 4.7 Hz), 7.22–7.30 (5H, m), 7.65–7.69 (2H, m), 8.19–8.21 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, due to coincidental overlap, some peaks in the aromatic region are missing) δ 15.0, 50.9, 51.4, 124.1, 126.3, 128.1, 128.3, 130.3, 132.1, 133.9, 135.1, 147.9. IR (neat): 3094, 3028, 2936, 1592, 1543, 1367, 1165, 747, 699 cm^{-1}. HRMS calcd for $C_{15}H_{15}N_2O_4S$ ($M+H^+$): 319.0753. Found: 319.0753.

4.7. (2*S*,3*R*)-2-Methyl-3-phenyl-1-toluenesulonylaziridine 16a

In a flame-dried, nitrogen purged reaction vessel containing (1*S*,2*S*)-pseudonorephedrine in a 0.3 M THF solution, 1.1 equiv of TEA was added and the solution was cooled in an ice bath. To this, 1.05 equiv of *p*-toluenesulfonyl chloride was added and the water bath was removed after several minutes. After a 1-h reaction time, 1.1 equiv of TEA was added to the reaction mixture with ice bath cooling. This was followed by the addition of 1.05 equiv of methanesulfonyl chloride and the reaction was allowed to proceed for an additional hour after which 5 equiv of hydrazine was added to afford the title compound as a colorless oil in 87% yield after flash chromatography. ^1H NMR (300 MHz, $CDCl_3$) δ 1.01 (3H, d, *J* = 6.1 Hz), 2.42 (3H, s), 3.18 (1H, dq, *J* = 6.1, 7.7 Hz), 3.92 (1H, *J* = 7.7 Hz), 7.19–7.28 (5H, m), 7.32 (2H, d, *J* = 8.2 Hz), 7.88 (2H, d, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, due to coincidental overlap, some peaks in the aromatic region were not observed) δ 11.9, 21.6, 41.5, 46.0, 127.5, 127.7, 128.2, 129.7, 132.7, 135.2, 144.4. IR (neat): 1603, 1593, 1319, 1161, 889, 759, 700 cm^{-1}. HRMS calcd for $C_{16}H_{17}NO_2S$ ($M+H^+$): 288.1058. Found: 288.1057.

4.8. (2*S*,3*R*)-2-Methyl-1-(*o*-nitrobenzenesulfonyl)-3-phenylaziridine 16b

To a flame-dried, nitrogen purged reaction vessel containing (1*S*,2*S*)-pseudonorephedrine in a 0.3 M THF solution, 1.1 equiv of TEA was added and the solution was cooled in an ice bath. To this mixture, 1.05 equiv of *o*-nitrobenzenesulfonyl chloride was added and the water bath was removed after several minutes. After a 1-h reaction time, 1.1 equiv of TEA was added to the reaction mixture with ice bath cooling. This was followed by the addition of 1.05 equiv of methanesulfonyl chloride and the reaction was allowed to proceed for an additional hour after which 5 equiv of hydrazine was added to afford the title compound as a colorless oil in 60% yield after chromatography. $[\alpha]_D^{24} = -129.1$ (*c* 1.0, CH_2Cl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 1.12 (3H, d, *J* = 5.9 Hz), 3.42 (1H, dq, *J* = 5.9, 7.4 Hz), 4.22 (1H, d, *J* = 7.4 Hz), 7.27–7.35 (5H, m), 7.75–7.78 (2H, m), 8.27–8.29 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$ due to coincidental overlap, some peaks in the aromatic region are missing) δ 11.6, 44.6, 47.1, 124.2, 127.9, 131.8, 132.2, 132.2, 134.5, 148.3. IR (neat): 3094, 3029, 2933, 1732, 1591, 1537, 1335, 1163, 765, 699 cm^{-1}. HRMS calcd for $C_{15}H_{15}N_2O_4S$ ($M+H^+$): 319.0753. Found: 319.0740.

4.9. 1-(7,7-Dimethyl-2-oxobicyclo[2.2.1]-1-heptyl)-*N*-((1*R*,2*S*)-1-hydroxy-1-phenyl-2-propyl) methanesulfonamide 17

To a flame-dried, nitrogen purged 100 mL flask containing (1*R*,2*S*)-norephedrine (1.00 g, 6.61 mmol) dissolved in a 0.30 M solution of THF (22.0 mL), 1.10 equiv of triethylamine (1.02 mL, 7.28 mmol) was added and the solution was cooled in an ice bath. To the cooled solution, 1.05 equiv of D-(+)-10-camphorsulfonyl chloride (1.74 g, 6.94 mmol) was added slowly. After several minutes, the ice bath was removed from the flask, and the reaction was allowed to proceed with stirring for 1 h. After 1 h, the reaction was quenched with 25 mL $NaHCO_3$, and the organic solvents were removed by rotary evaporation. The product sulfonamide was extracted with 3 portions, 50 mL each, of ethyl acetate and the combined solution were washed with 3 M HCl (50 mL) followed by brine solution (50 mL). The solution was then dried over magnesium sulfate, gravity filtered, and the solvents were removed under vacuum, which after flash chromatography (80% hexanes, 20% EtOAc) yielded a thick colorless oil (2.27 g, 6.21 mmol, 94% yield). $[\alpha]_D^{24} = +4.3$ (*c* 1.15 $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H,s), 1.06 (3H, s), 1.09 (3H, d, *J* = 6.8 Hz), 1.45 (1H, ddd, *J* = 3.9, 9.3, 12.9 Hz), 1.85 (1H, m), 1.95 (1H, d, *J* = 18.6 Hz), 2.00–2.09 (1H, m), 2.13 (1H, t, *J* = 4.4 Hz), 2.34–2.44 (2H, m), 2.82 (1H, d, *J* = 4.4 Hz), 2.97 (1H, d, *J* = 15.0 Hz), 3.49 (1H, d, *J* = 15.0 Hz), 3.88–3.96 (1H, m), 4.94 (1H, t, *J* = 4.0 Hz), 5.03 (1H, d, *J* = 8.5 Hz), 7.27–7.40 (5H, m). ^{13}C NMR (125 MHz, $CDCl_3$) δ 15.9, 19.6, 19.9, 25.7, 27.0, 42.7, 42.8, 48.5, 51.3, 55.3, 59.0, 75.8, 126.2, 127.7, 128.4, 216.6. IR (neat): 3500, 3296, 1741, 1325, 1137 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{28}NO_4S$ ($M+H^+$) 366.1739. Found: 366.1728.

4.10. 1-(7,7-Dimethyl-2-oxobicyclo[2.2.1]heptan-1-yl)-*N*-((1*S*,2*R*)-1-hydroxy-1-phenyl-2-propyl)methanesulfonamide 18

To a flame-dried, nitrogen purged 100 mL flask containing (1*S*,2*R*)-norephedrine (1.00 g, 6.61 mmol) dissolved in a 0.30 M solution of THF (22.0 mL), 1.10 equiv of triethylamine (1.02 mL, 7.28 mmol) was added and the solution was cooled in an ice bath. To the cooled solution, 1.05 equiv of D-(+)-10-camphorsulfonyl chloride (1.74 g, 6.94 mmol) was added slowly. After several minutes, the ice bath was removed from the flask, and the reaction was allowed to proceed with stirring for 1 h. After 1 h, the reaction was quenched with 25 mL $NaHCO_3$, and the organic solvents were removed by rotary evaporation. The product sulfonamide was extracted with 3 portions, 50 mL each, ethyl acetate and the solution were washed with 50 mL of 3 M HCl followed by 50 mL brine solution. The solution was then dried over magnesium sulfate, gravity filtered, and the solvents were removed under vacuum, which after flash chromatography (80% hexanes, 20% EtOAc) yielded a thick colorless oil (2.01 g, 5.50 mmol, 83% yield). $[\alpha]_D^{24} = +27.1$ (*c* 1.10, $CHCl_3$) ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, s), 1.03 (3H, s), 1.06 (3H, d, *J* = 6.9 Hz), 1.41–1.48 (1H, m), 1.93 (1H, d, *J* = 18.7 Hz), 1.94–2.08 (2H, m), 2.13 (1H, t, *J* = 4.4 Hz), 2.19–2.18 (1H, m), 2.39 (1H, ddd, *J* = 3.0, 4.6, 18.6 Hz), 2.74 (1H, d, *J* = 4.3 Hz), 2.99 (1H, d, *J* = 15.1 Hz), 3.40 (1H, d, *J* = 15.1 Hz), 3.77 -3.85 (1H, m), 4.97 (1H, t, *J* = 3.7 Hz), 5.47 (1H, d, *J* = 7.6 Hz), 7.27–7.39 (5H, m). ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.8, 19.6, 19.9, 26.5, 27.0, 42.8, 42.9, 48.6, 51.3, 55.6, 59.3, 76.2, 126.3, 127.6, 128.2, 140.4, 216.6. IR (neat): 3500, 3297, 1738, 3127, 1137 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{28}NO_4S$ ($M+H^+$): 366.1739. Found: 366.1749.

4.11. 7,7-Dimethyl-1-(((2*S*,3*S*)-2-methyl-3-phenylaziridin-1-ylsulfonyl)methyl)bicyclo [2.2.1]heptan-2-one 21

To a flame-dried, nitrogen purged 100 mL flask containing (1*R*,2*S*)-norephedrine (0.700 g, 4.62 mmol) dissolved in a 0.30 M solution of THF (15.4 mL), 1.10 equiv of triethylamine (0.71 mL, 5.1 mmol) was added and the solution was cooled in an ice bath. To the cooled solution, 1.05 equiv of D-(+)-10-camphorsulfonyl chloride (1.22 g, 4.86 mmol) was added slowly. After several minutes, the ice bath was removed from the flask, and the reaction was allowed to proceed with stirring for 1 h. After 1 h, an additional 1.10 equiv of triethylamine (0.515 g, 5.09 mmol) was added to the solution, and the solution was returned to an ice bath. To the

cool solution, methane sulfonyl chloride (0.583 g, 5.09 mmol) was added dropwise. After several minutes the ice bath was removed, and the reaction was left to proceed with stirring for 4 h. After 4 h, methanol (10 mL) was added to the reaction, and 2.00 equiv of 3 M sodium hydroxide (3.10 mL, 9.24 mmol) was added to the flask. The reaction was left to proceed for 6 h, after which the reaction was quenched with 25 mL $NaHCO_3$, and the organic solvents were removed by rotary evaporation. The product aziridine was extracted with 3 portions, 50 mL each, ethyl acetate and the solution were washed with 50 mL of 3 M HCl followed by 50 mL brine solution. The solution was then dried over magnesium sulfate, gravity filtered, and the solvents were removed under vacuum, which after flash chromatography (90% hexanes, 10% EtOAc) yielded a thick colorless oil (1.32 g, 3.81 mmol, 82% yield). $[\alpha]_D^{24} = +118.5$ (*c* 1.03, $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.84 (3H, s), 1.10 (3H, s), 1.41 (1H, ddd, *J* = 3.64, 9.2, 12.0 Hz), 1.71 (1H, ddd, *J* = 4.8, 9.4, 14.0 Hz), 1.78 (2H, d, *J* = 6.0 Hz), 1.92 (1H, d, *J* = 18.4), 1.99–2.06 (1H, m), 2.08 (1H, app. t, *J* = 4.4 Hz), 2.36 (1H, ddd, *J* = 3.6, 4.4, 18.4 Hz), 2.57–2.64 (1H, M), 2.93 (1H, dq, *J* = 4.4, 6.0 Hz), 3.18 (1H, d, *J* = 15.0 Hz), 3.58 (1H, d, *J* = 15.0 Hz), 3.75 (1H, d, *J* = 4.3 Hz), 7.27–7.38 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.1, 19.7, 19.9, 24.5, 26.9, 42.5, 42.7, 47.9, 49.0 (48.99), 49.0 (49.01), 51.5, 58.4, 126.4, 128.3, 128.7, 135.7, 214.5. IR (neat): 1747, 1324, 1149, 752, 700 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{26}NO_3S$ ($M+H^+$): 348.1633. Found: 348.1622.

4.12. 7,7-Dimethyl-1-(((2*R*,3*R*)-2-methyl-3-phenylaziridin-1-ylsulfonyl)methyl)bicyclo [2.2.1]heptan-2-one 22

To a flame-dried, nitrogen purged 100 mL flask containing (1*S*,2*R*)-norephedrine (1.00 g, 6.61 mmol) dissolved in a 0.30 M solution of THF (22.0 mL), 1.10 equiv of triethylamine (1.02 mL, 7.28 mmol) was added, and the solution was cooled in an ice bath. To the cooled solution, 1.05 equiv of D-(+)-10-camphorsulfonyl chloride (1.74 g, 6.94 mmol) was added slowly. After several minutes, the ice bath was removed from the flask, and the reaction was allowed to proceed with stirring for 1 h. After 1 h, an additional 1.10 equiv of triethylamine (1.02 mL, 7.28 mmol) was added to the solution, and the solution was returned to an ice bath. To the cool solution, methanesulfonyl chloride (0.56 mL, 7.28 mmol) was added dropwise. After several minutes the ice bath was removed, and the reaction was left to proceed with stirring for 4 h. After 4 h, methanol (10 mL) was added to the reaction, and 2.00 equiv of 3 M sodium hydroxide (4.41 mL, 13.2 mmol) was added to the flask. The reaction was left to proceed for 6 h, after which the reaction was quenched with 25 mL $NaHCO_3$, and the organic solvents were removed by rotary evaporation. The product aziridine was extracted with 3 portions, 50 mL each, ethyl acetate and the solution were washed with 50 mL of 3 M HCl followed by 50 mL brine solution. The solution was then dried over magnesium sulfate, gravity filtered, and the solvents were removed under vacuum, which after flash chromatography (90% hexanes, 10% EtOAc) yielded a thick colorless oil (1.29 g, 3.71 mmol, 56% yield). $[\alpha]_D^{24} = -79.0$ (*c* 0.91, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, s), 1.11 (3H, s), 1.41 (1H, ddd, *J* = 3.9, 9.4, 12.6 Hz), 1.70 (1H, ddd, *J* = 4.8, 9.4, 14.5 Hz), 1.78 (2H, d, *J* = 6.0 Hz), 1.92 (1H, d, *J* = 18.4 Hz), 1.97–2.06 (1H, m), 2.08 (1H, t, *J* = 4.3 Hz), 2.37 (1H, ddd, *J* = 4.3, 4.3, 18.4 Hz), 2.56 (1H, ddd, *J* = 3.9, 11.7, 14.5 Hz), 2.87–2.92 (1H, m), 3.05 (1H, d, *J* = 15.1 Hz), 3.71 (1H, d, *J* = 4.3 Hz), 3.81 (1H, d, *J* = 15.1 Hz), 7.27–7.38 (5H, m). ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 19.8, 20.0, 25.1, 26.9, 42.6, 42.8, 47.8, 49.06, 49.09, 51.6, 58.5, 126.4, 128.3, 128.7, 135.8, 214.3. IR (neat): 1747, 1324, 1149, 752, 700 cm^{-1}. HRMS (ESI) calcd for $C_{19}H_{26}NO_3S$ ($M+H^+$): 348.1633. Found: 348.1627.

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