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A Synthesis of 6-Azabicyclo[3.2.1]octanes. The Role of *N*-Substitution

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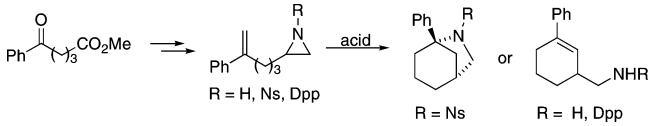

The intramolecular cyclization reactions of aziridines with π-nucleophiles can be a useful route to a number of heterocyclic and carbocyclic ring systems. We were particularly interested in the use of this cyclization reaction for the synthesis of 6-azabicyclo[3.2.1]octanes. We report here the development of a new synthesis of the aziridine necessary for the aziridine−π-nucleophile cyclization. We also report on the cyclization of aziridines with three different substitutions on the aziridine nitrogen. We have found that *N*-diphenylphospinyl and N−H aziridines, while participating in the initial ring-opening reaction, do not lead to the desired bicyclic ring systems. In contrast, a nosyl group on the aziridine nitrogen leads efficiently to the bicyclic ring system and can be readily deprotected.

Introduction

The 6-azabicyclo[3.2.1]octane skeleton is found in a wide variety of naturally occurring and synthetic pharmacologically active molecules. Some examples include natural products such as the $GABA_A$ receptor antagonist securinine[1,2] and analgesic aphanorphine.[3] Nonnatural molecules containing the 6-azabicyclo[3.2.1]octane system are also well-known. These range from very simple molecules such as the bicyclic proline analogue **1**[4] to the more complex aphanorphine analogue **2**.[5] Other examples include **3**, which was prepared as a ring-deleted analogue of the alkaloid methyllycaconitine,[6] and **4**, a potent inhibitor of dopamine reuptake (Figure 1).[7] We were interested in such molecules as potential ligands for the nicotinic acetylcholine receptor.

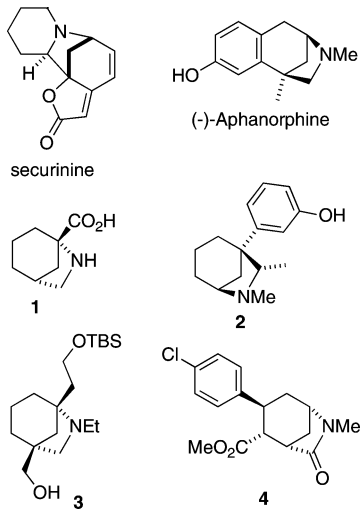

FIGURE 1. Azabicyclo[3.2.1]octanes.

We have recently reported on a method for the synthesis of 5-substituted 6-tosylazabicyclo[3.2.1]octanes.[8,9] This method involves the intramolecular cyclization of a π-nucleophile with

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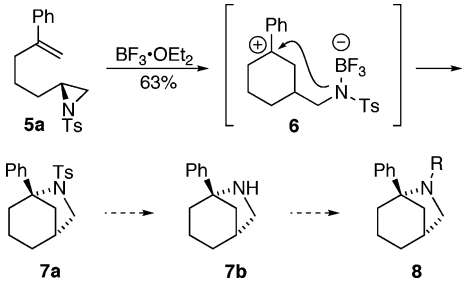
SCHEME 1. Attempted Synthesis To Make Unprotected Azabicyclo[3.2.1]octane



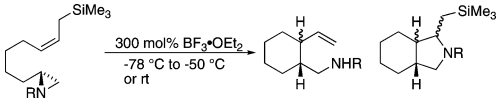
an *N*-tosyl aziridine. This reaction proceeds via an initial attack of the double bond on the aziridine ring leading to a carbocationic intermediate **6**. The nitrogen then cyclizes on the stabilized carbocation to provide the bicyclic product **7a**. This method works well with both an aryl- and an alkyl-substituted olefin as the π-nucleophile. In related cyclizations, substitution on the aromatic ring is generally well tolerated. For our project on the conversion of such molecules into ligands for the nAChR we wished to remove the toluenesulfonyl group to generate **7b** and replace this protecting group with an alkyl or aryl group yielding **8** (Scheme 1).

Our attempts to remove the toluenesulfonyl group of **7a** under a wide variety of conditions failed to provide **7b** in reasonable yield.[10−13] It seems likely that the reductive conditions used to remove the tosyl group may also cleave the benzyl−amine bond giving rise to several products.

Our plan therefore was to examine the use of different protecting groups on the aziridine nitrogen with respect to the direct formation of the 6-azabicyclo[3.2.1]octane skeleton. We would expect that the nature of the group on the aziridine ring nitrogen should be quite important, both with respect to the initial ring opening as well as to the subsequent formation of the bicyclic ring system. The need for an electron-stabilizing group on the nitrogen in order to promote the initial ring opening (**5** → **6**) is well documented.[14−20] It is not clear what role this group would play in the subsequent ring closure to form **7a**.

Results and Discussion

Our goal of changing the activating group on the nitrogen of the aziridine so as to still generate the 6-azabicyclo[3.2.1]octane ring and then remove that activating group requires a consideration of multiple factors. This activating group must first activate the aziridine toward nucleophilic attack by the π-nucleophile. Second this activating group must allow the formation of the bicyclic ring system. Finally, the activating group should be readily removed without harming the products, especially the benzylic C−N bond. In considering activating groups on the nitrogen, three general classes generally have been used.[21] The first of these are *N*-carbonyl-type activating groups. Of this group, amides (e.g., benzamide, trifluoroacetamide) and carbamates (e.g., Cbz, Boc) are the most widely used. This type of activating group can be problematic in activating an aziridine.[22] Under acidic conditions, the carbonyl will often act as a nucleophile and open the aziridine ring leading to oxazoline ring systems.[23−25] Consequently we do not plan to examine this type of activating group for this reaction. Sulfonyl activating groups are excellent for acid-catalyzed aziridine reactions as there is no carbonyl to subsequently open the aziridine ring. The subsequent removal of sulfonyl activating groups is largely dependent upon the alkyl or aryl group attached to the sulfonyl. We have already seen that removal of the toluenesulfonyl group under strongly reducing conditions is not viable for compounds such as **7a**. The *p*-nitrophenylsulfonyl (Ns) group is reported to be useful in aziridine ring-opening reactions[26] and readily removed via thiolysis.[27] This should be an excellent choice of activating group in that it is acid stable and has been used to activate aziridines for ring opening. Another class of aziridine nitrogen activating groups that should be amenable to these reaction conditions and is readily removed is the diphenylphosphinyl ($Ph_2P(O)$ or Dpp) group. The Dpp group has been used to activate aziridine rings toward nucleophilic ring opening.[28−31]



We have examined a number of different substitutions on the nitrogen of the aziridine in the related aziridine−allylsilane cyclization. Of the groups examined in this study, the carbonyl-based activating groups (Cbz, benzoyl, and phenylacetyl) provided product in the lowest yields (17−35%). At room temperature a significant distinction was found between aryl sulfonyl groups that were either electron rich (e.g., 4-$OMeC_6H_4$) and those that were electron poor (e.g., Ns). The Ns group provided no bicyclic product only the monocyclic product in 96% yield. The 4-$OMeC_6H_4SO_2$ in contrast gave a 60:40 mix of monocyclic product to bicyclic product. However, at −50 °C we obtain a roughly 1:1 mixture of the olefin to bicycle. This suggested that at room temperature, the better electron-stabilizing group (i.e., Ns) more readily undergoes a β-elimination to provide the monocyclic product while the 4-OMe derivative does not. An examination of additional arylsulfonyl groups (with intermediate electron stabilizing ability) also indicated a roughly 1:1 ratio of the monocycle to bicycle ratio. This indicated that the stability of the sulfonamide anion had no significant effect on the initial bicycle formation.

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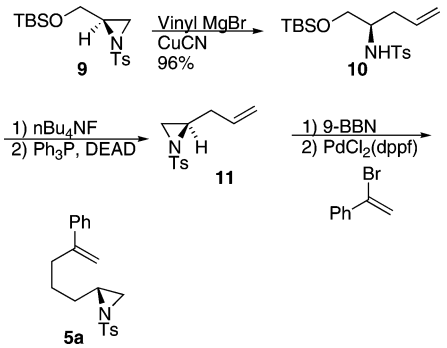
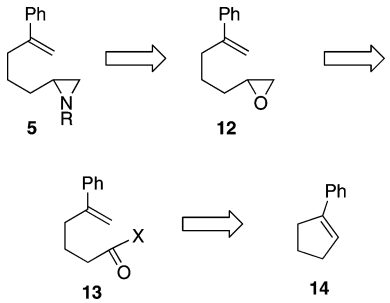
SCHEME 2. Initial Attempt To Prepare Differentially Substituted Aziridines



SCHEME 3. Retrosynthesis of Aziridine 5



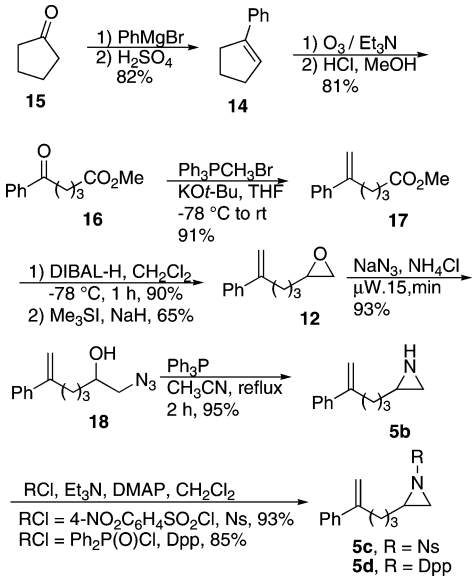
This group is readily removed under acidic conditions.[32−34] Given our need to only use activating groups that could be readily removed we have chosen to use only the Ns and Dpp groups. In addition to their easy removal, we have also successfully used these groups in previous aziridine−π-nucleophile cyclizations.[22]

Aziridine **5a** was previously prepared from aziridine **9** via a five-step sequence. As shown in Scheme 2, an initial ring opening/ring closing sequence was used to convert **9** into olefinic aziridine **11**.[35] This olefin was then converted to **5a** via a Suzuki−Miyaura cross-coupling reaction with 1-bromostyrene.[36]

The modification of this reaction sequence to use either the Ns or Dpp groups was unsuccessful. We were able to prepare aziridines corresponding to **9** in which the toluenesulfonyl group was replaced with either a Ns or a Dpp group. However, with both aziridines (*N*-Ns and *N*-Dpp) the initial ring opening of aziridine **9** failed to provide significant amounts of ring-opened product **10**.

Given our interest in exploring different activating groups on the nitrogen of the aziridine ring we decided to develop an alternate synthesis of aziridine **5** that proceeds through an N-unsubstituted aziridine. Such a synthetic route would be amenable to the introduction of a number of different activating groups on the aziridine nitrogen. As outlined in Scheme 3, the requisite aziridine **5b** (R = H) should be readily obtained from epoxy olefin **12** via an azide opening/ring formation sequence. The epoxide should be available from the corresponding aldehyde **13** (X = H) via sulfur ylide chemistry. This aldehyde should be available from cyclopentene **14**, via an ozonolysis/functional group modification sequence.

SCHEME 4. Synthesis of Aziridines 5b, 5c, and 5d



The reduction of this route to practice is shown in Scheme 4. The known cyclopentene **14** was prepared by the reported route via addition of PhMgBr to cyclopentanone followed by dehydration to provide 1-phenylcyclopentene **14**.[37] Ozonolysis of **14** followed by treatment of the ozonide with excess Et_3N provided the keto acid in excellent yield.[38] Subsequent esterification with HCl and methanol provided the ester **16** in 81% overall yield. Wittig reaction of ketoester **16** provided the olefinic ester **17** in 91% yield. DIBAL-H reduction of this ester in dichloromethane at −78 °C gave a 90% yield of the corresponding aldehyde.[39] The aldehyde was directly converted into epoxide **12** in 65% yield by reaction with dimethylsulfonium methylide.[40−43] Ring opening of epoxide with sodium azide followed by ring closing with Ph_3P gave the aziridine **5b** in 88% overall yield. This aziridine was then treated with *p*-nitrophenylsulfonyl chloride and diphenylphosphinyl chloride to provide the *N*-Ns and *N*-Dpp aziridines **5c** and **5d** in 93% and 85% yields, respectively.

With the necessary aziridine substrates in hand we examined the cyclization reactions using different reaction conditions (Table 1). As noted previously (entry 1) the *N*-Ts aziridine **5a** provides a good yield of the desired bicyclic product upon treatment with 300 mol % of $BF_3{\cdot}OEt_2$ at room temperature for 2 h.[9] The use of 100 mol % of $BF_3{\cdot}OEt_2$ provides roughly the same yield.

We first examined the *N*-Ns aziridine **5c** under this set of reaction conditions. All reactions were carried out in CD_2Cl_2

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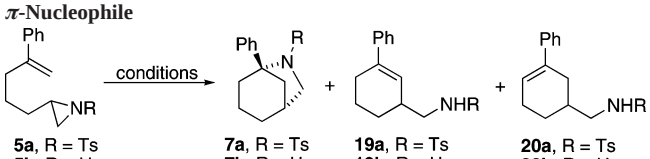
TABLE 1. Intramolecular Cyclization of Aziridines with a π-Nucleophile



5a, R = Ts; **5b**, R = H; **5c**, R = Ns; **5d**, R = Dpp

7a, R = Ts; **7b**, R = H; **7c**, R = Ns; **7d**, R = Dpp

19a, R = Ts; **19b**, R = H; **19c**, R = Ns; **19d**, R = Dpp

20a, R = Ts; **20b**, R = H; **20c**, R = Ns; **20d**, R = Dpp

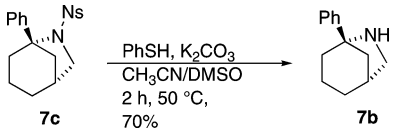
entry	substrate	conditions[a]	products
1	**5a**	$BF_3{\cdot}OEt_2$, 300 mol %, 2 h	**7a** (63%)[b]
2	**5a**	$BF_3{\cdot}OEt_2$, 100 mol %, 2 h	**7a** (60%)[b]
2	**5b**	$BF_3{\cdot}OEt_2$, 15 mol %, 8 h	no reaction
3	**5b**	$BF_3{\cdot}OEt_2$, 100 mol %, 8 h	decomposition
4	**5b**	$B(C_6F_5)_3$, 15 mol %, 24 h	no reaction
5	**5b**	$B(C_6F_5)_3$, 100 mol %, 8 h	**19b** (73%)[b]
6	**5b**	CF_3COOH, 15 mol %, 24 h	**5b**:**19b** (1:1)[a]
7	**5b**	CF_3COOH, 100 mol %, 8 h	**19b** (65%)[b]
8	**5c**	$BF_3{\cdot}OEt_2$, 15 mol %, 24 h	**7c**:**19c**:**20c** (1.5:1:1.7)[a]
9	**5c**	$BF_3{\cdot}OEt_2$, 100 mol %, 2 h	**7c**:**19c**:**20c** (1.8:1:1.8)[a]
10	**5c**	$B(C_6F_5)_3$, 15 mol %, 24 h	**5c**:**7c** (3:2)[a]
11	**5c**	$B(C_6F_5)_3$, 100 mol %, 2 h	**7c** (95%)[b]
12	**5c**	CF_3COOH, 15 mol %, 24 h	no reaction
13	**5c**	CF_3COOH, 100 mol %, 2 h	**7c**:**19c**:**20c** (5.3:1:1.3)[a]
14	**5d**	$BF_3{\cdot}OEt_2$, 15 mol %,24 h	**5d**:**19d**:**20d** (1:3:6.5)[a]
15	**5d**	$BF_3{\cdot}OEt_2$, 100 mol %, 8 h	**19d**:**20d** (2.3:1)(55%)[b]
16	**5d**	$B(C_6F_5)_3$, 15 mol %, 24 h	no reaction
17	**5d**	$B(C_6F_5)_3$, 100 mol %, 10 h	**19d**:**20d** (2:1) (72%)[b]
18	**5d**	CF_3COOH, 15 mol %, 8 h	**19b** (64%)[b]

[a] Product ratio determined by ^{1}H NMR. [b] Isolated yield

in an NMR tube so that reaction progress could be directly monitored by ^{1}H NMR. The initial reaction of **5c** with a catalytic amount of $BF_3{\cdot}OEt_2$ provided a 1:2 mixture of the desired bicycle (**7c**) to a mixture of two isomeric monocyclic products, **19c** and **20c**. Increasing the amount of $BF_3{\cdot}OEt_2$ to 100 mol % provided essentially the same product ratio. While additional Lewis acids might be considered, our previous experience suggests that $BF_3{\cdot}OEt_2$ and related Lewis acids are the optimum catalyst for this type of reaction.[44] On the basis of the work of Yudin et al. the Lewis acid $B(C_6F_5)_3$ was examined and provided considerably better results.[45] Treatment of **5c** with 15 mol % of $B(C_6F_5)_3$ showed only a 3:2 mixture of starting material to bicyclic product. However, none of the monocyclic product was observed. Increasing the amount of $B(C_6F_5)_3$ to 100 mol % provided the bicyclic product **7c** in a 95% isolated yield. We also examined the use of a protic acid with these substrates. The use of a catalytic amount of trifluoroacetic acid yielded no product, while increasing the amount of acid did lead to the formation of bicycle **7c** as a 5:2 mixture with the monocyclic product **19c** and **20c**.

Unlike the *N*-Ts and *N*-Ns aziridines, the *N*-Dpp aziridine **5d** provided none of the desired bicyclic product **7d**. Reaction of **5d** with a catalytic amount of $BF_3{\cdot}OEt_2$ provided only a mixture of starting material and monocyclic products **19d** and **20d**. Increasing the amount of $BF_3{\cdot}OEt_2$ to 100 mol % provided only the monocyclic products **19d** and **20d** in a 2:1 ratio. The mixture of compounds **19d** and **20d** was isolated in 55% yield. The use of 100 mol % of $B(C_6F_5)_3$ again provided only a 2:1 mixture of **19d** to **20d** albeit in a better isolated yield than with the $BF_3{\cdot}OEt_2$. Interestingly, the use of a protic acid (TFA) instead of a Lewis acid provided **19b**, a product in which an initial cyclization has occurred and the Dpp group has been removed. Since the Dpp group can be removed by acid it was not clear if the Dpp group was removed before or after the cyclization occurred. However, on the basis of this result we decided to examine the *N*-H aziridine **5b** in this cyclization reaction.

SCHEME 5. Removal of the Ns Group



7c **7b**

The use of *N*-H or *N*-alkyl aziridines in reactions with π-nucleophiles has not been observed to date. Consequently such cyclizations are of significant interest. Reaction of aziridine **5b** with $BF_3{\cdot}OEt_2$ provided no identifiable product of any kind. However, the reaction of **5b** with both TFA and $B(C_6F_5)_3$ did provide reasonable (65% and 73%) isolated yields of the monocyclic product **19b** as a single olefin regioisomer. To the best of our knowledge this is the first example of an unactivated aziridine being opened by a π-nucleophile. Clearly, the more basic nature of the amine generated from the N−H aziridine seems to have prevented the formation of the bicyclic ring system.

Having identified an aziridine substitution that leads to the bicyclic product **7**, we next examined the removal of the aziridine substitution to obtain the unsubstituted bicycle **7b**. Treatment of **7c** with $PhSH/K_2CO_3$ cleanly provided the desired product **7b** (Scheme 5) in 70% isolated yield.

Conclusions

In summary, we discovered that N-substitution plays an important role in the intramolecular cyclization of aziridines with π-nucleophiles. Both Dpp and N−H aziridines underwent monocyclization. Cyclization of the N−H aziridine is unique in that ring opening of an unactivated aziridine with a π-nucleophile has not been observed to date. An aziridine protected with a nosyl group successfully underwent ring opening and cyclization to provide the desired 6-azabicyclo[3.2.1]octane skeleton. The conversion of the N−H product into a variety of substituted bicyclic compounds is underway and results will be reported in due course.

Experimental Section

Methyl 5-Oxo-5-phenylpentanoate (16). Ozone was passed through a solution of 1-phenylcyclopentene **14**[37] (15 g, 0.1 mol) in CH_2Cl_2 (200 mL) at −78 °C until a blue color appeared. The reaction mixture was then treated with Et_3N (42.1 g, 0.42 mol) and the reaction stirred at room temperature overnight. The reaction mixture was acidified with 1 M HCl and the brown precipitate that formed was filtered, washed with water, and dried under vacuum to provide 16.5 g (83%) of 5-oxo-5-phenylpentanoic acid, which matched the reported spectra.[38] To a 0 °C solution of the crude acid in MeOH (100 mL) was added acetyl chloride (7.2 g, 96.7 mmol), then the reaction was warmed to room temperature and stirred overnight. This reaction was diluted with CH_2Cl_2 (200 mL) and washed with saturated $NaHCO_3$ solution, brine, and water. The organic layer was dried over $MgSO_4$, filtered, and concentrated to provide 17.1 g (96%) of ester **16** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.94 (d, 2H, J = 7.1 Hz), 7.42 (m, 3H), 3.67 (s, 3H), 3.02 (t, 2H, J = 6.2 Hz), 2.42 (t, 2H, J = 7.2 Hz), 2.03 (m, 2H, J

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= 7.1 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 199.3, 173.6, 136.9, 132.9, 128.6, 128.3, 127.9, 51.5, 37.4, 33.1, 19.4.

Methyl 5-Phenylhex-5-enoate (17). To a slurry of methyltriphenylphosphonium bromide (17.8 g, 50 mmol) in THF (100 mL) at 0 °C was added potassium *tert*-butoxide (5.85 g, 50 mmol). After 1 h of stirring, the reaction was cooled to −78 °C and ester **16** (4.3 g, 20 mmol) was added to the reaction. The solution was warmed to room temperature and stirred for 30 min. It was then quenched with saturated aqueous NH_4Cl (30 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, concentrated, and chromatographed (5% EtOAc in hexanes) to provide 3.9 g (91%) of **17** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.15 (m, 5H), 5.2 (s, 1H), 4.9 (s, 1H), 3.5 (s, 3H), 2.42 (t, 2H, J = 7.7 Hz), 2.21 (t, 2H, J = 7.5 Hz), 1.64 (m, 2H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 128.3, 127.4, 126.1, 112.9, 51.4, 34.6, 33.4, 23.4. HRMS calcd for $C_{13}H_{16}O_2$ 204.1150, found 204.1156.

2-(4-Phenylpent-4-enyl)oxirane (12). DIBAL (5.94 mL of a 1 M solution in hexanes, 5.94 mmol) was slowly added to a solution of ester **17** (1 g, 4.89 mmol) in CH_2Cl_2 (10 mL) at −78 °C and stirring was continued for an additional 1 h. The reaction was quenched by adding methanol (10 mL) at −78 °C and warmed to room temperature. HCl (1 M, 50 mL) was added and the reaction was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated to provide 0.77 g (90%) of aldehyde, which was used immediately in the subsequent reaction: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.62 (t, 1H, J = 1.6 Hz), 7.14 (m, 5H), 5.2 (s, 1H), 4.96 (s, 1H), 2.43 (t, 2H, J = 7.7 Hz), 2.31 (dt, 2H, J = 7.3, 1.6 Hz), 1.66 (m, 2H, J = 7.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.2, 147.5, 140.8, 128.4, 127.5, 126.1, 113.1, 43.1, 34.6, 20.6. IR (neat) 1720 cm^{-1}.

DMSO (7 mL) was added to NaH (0.17 g of a 60% suspension in mineral oil, 4.16 mmol, washed with hexanes) and the mixture was stirred at 75 °C for 30 min. THF (10 mL) was added and the reaction was cooled to −10 °C. Trimethylsulfonium iodide (0.85 g, 4.16 mmol) in DMSO (4 mL) was added dropwise to the reaction over 10 min with the temperature of the reaction maintained at −5 °C during the addition. The aldehyde (0.613 g, 3.51 mmol) in THF (3 mL) was then added to the ylide solution over 5 min. The reaction was warmed to room temperature and stirred for 2 h. Water (25 mL) was added and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and chromatographed (20% EtOAc in hexanes) to provide 430 mg (65%) of epoxide **12** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.27 (m, 5H), 5.30 (s, 1H), 5.09 (s, 1H), 2.90 (m, 1H), 2.73 (t, 1H, J = 4.0 Hz), 2.57 (m, 2H), 2.45 (m, 1H), 1.55 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 128.3, 127.5, 126.1, 112.6, 52.1, 46.9, 35.3, 32.0, 24.6. HRMS calcd for $C_{13}H_{16}O$ 188.1201, found 188.1199.

1-Azido-6-phenylhept-6-en-2-ol (18). A mixture of epoxide **12** (1 g, 5.32 mmol), NaN_3 (3.4 g, 53.24 mmol), and NH_4Cl (0.57 g, 10.65 mmol) in MeOH (12 mL) and water (1.5 mL) was heated in a microwave for 10 min at 120 °C (0−300 W, 2.45 GHz microwave (Biotage Initiator), 10−20 mL vial size, 2−5 deg/min). The reaction mixture was cooled to room temperature, diluted with water (25 mL), and extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and chromatographed (15% EtOAc in hexanes) to provide 1.13 g (93%) of azido alcohol **18** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.28 (m, 5H), 5.31 (s, 1H), 5.09 (s, 1H), 3.73 (m, 1H), 3.20 (m, 2H), 2.5 (m, 2H), 1.98 (d, 1H, J = 4.6 Hz), 1.51 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.5, 138.5, 125.9, 124.9, 123.7, 110.3, 68.2, 54.6, 32.6, 31.3, 21.5. IR (neat) 3400, 2100 cm^{-1}. HRMS calcd for $C_{13}H_{17}N_3O{\cdot}Na^+$ 254.1269, found 254.1271.

2-(4-Phenylpent-4-enyl)aziridine (5b). To a solution of azido alcohol **18** (0.7 g, 3.02 mmol) in dry acetonitrile (15 mL) was added Ph_3P (0.95 g, 3.6 mmol) and the reaction was heated to reflux for 1.5 h. The reaction mixture was cooled to room temperature, concentrated, and chromatographed (5% MeOH in CH_2Cl_2) to provide 538 mg (95%) of aziridine **5b** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.24 (m, 5H), 5.26 (s, 1H), 5.05 (s, 1H), 2.52 (t, 2H, J = 7.5 Hz), 1.88 (m, 1H), 1.71 (m, 1H), 1.57 (m, 2H), 1.38 (m, 2H), 1.27 (m, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4, 141.3, 128.2, 127.2, 126.1, 112.3, 35.1, 34, 30.0, 26.2, 24.9. HRMS calcd for $C_{13}H_{17}N{\cdot}Na^+$ 210.1259, found 210.1248.

1-Nosyl-2-(4-phenylpent-4-enyl)aziridine (5c). *p*-Nitrophenylsulfonyl chloride (0.14 g, 0.64 mmol) was added to a −78 °C solution of aziridine **5b** (0.1 g, 0.53 mmol) and Et_3N (0.11 g, 1.06 mmol) in CH_2Cl_2 (1 mL). After 5 min at −78 °C, the reaction was warmed to 0 °C over 20 min. The reaction was then diluted with CH_2Cl_2 and the organic phase was washed with 1 M HCl and saturated $NaHCO_3$, dried ($MgSO_4$), concentrated, and chromatographed (5% EtOAc in hexanes) to provide 184 mg (93%) of aziridine **5c**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.3 (d, 2H, J = 8.97 Hz), 8.08 (d, 2H, J = 9 Hz), 7.32 (m, 5H), 5.24 (s, 1H), 4.98 (s, 1H), 2.83 (m, 1H), 2.75 (d, 1H, J = 7.0 Hz), 2.47 (t, 2H, J = 6.7 Hz), 2.15 (d, 1H, J = 4.7 Hz), 1.61 (m, 1H), 1.35 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 150.5, 147.6, 143.9, 129.2, 128.4, 127.6, 126.0, 124.2, 112.8, 41.2, 34.6, 34.4, 30.7, 25.3. HRMS calcd for $C_{19}H_{20}N_2O_4S{\cdot}Na^+$ 372.1144, found 372.1134.

1-Diphenylphosphinyl-2-(4-phenylpent-4-enyl)aziridine (5d). To a −78 °C solution of aziridine **5b** (0.1 g, 0.53 mmol) and DMAP (6.5 mg, 0.053 mmol) in CH_2Cl_2 (1 mL) were added Et_3N (0.213 g, 2.13 mmol) and diphenylphosphinic chloride (0.195 g, 0.828 mmol). The reaction was warmed to 0 °C and stirred 20 min. The mixture was then diluted with CH_2Cl_2, and the organic phase was washed with 1 M HCl and saturated $NaHCO_3$ solution, dried ($MgSO_4$), concentrated, and chromatographed (10% EtOAc in hexanes) to provide 175 mg (85%) of pure Dpp protected aziridine **5d**: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8 (m, 5H), 7.28 (m, 10H), 5.21 (s, 1H), 4.92 (s, 1H), 2.62 (m, 1H), 2.5 (dd, 1H, J = 7.6, 5.9 Hz), 2.27 (t, 2H, J = 7.3 Hz), 1.89 (m, 1H), 1.46 (m, 2H), 1.24 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.3, 131.7, 131.6, 131.5, 128.7, 128.5, 128.4, 128.3, 128.3, 128.2, 127.4, 126.1, 112.5, 51.6, 34.8, 32.1, 29.7, 25.4. HRMS calcd for $C_{25}H_{26}NOP{\cdot}Na^+$ 410.1650, found 410.1645.

(3-Phenylcyclohex-2-enyl)methanamine (19b). To a 0 °C solution of aziridine **5b** (0.02 g, 0.106 mmol) or **5d** (0.02 g, 0.052 mmol) in CH_2Cl_2 (1 mL) was added trifluoroacetic acid (8 μL, 0.106 mmol for **5b** or 4 μL, 0.052 mmol for **5d**). The reaction was warmed to room temperature and stirred for 2 h. The reaction was diluted with CH_2Cl_2, washed with saturated aq Na_2CO_3 and brine, dried ($MgSO_4$), concentrated, and chromatographed (5% EtOAc in hexanes) to provide 13 mg (65%) from **5b** (or 6.2 mg (64%) from **5d**) of **19b** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (m, 5H), 6.03 (s, 1H), 2.69 (m, 2H), 2.41 (m, 2H), 2.31 (m, 1H), 1.86 (m, 2H), 1.7 (m, 1H), 1.34 (m, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 142.4, 138.1, 128.2, 126.8, 125.1, 47.7, 39.7, 27.8, 26.2, 21.8. HRMS calcd for $C_{13}H_{17}N{\cdot}Na^+$ 188.1432, found 188.1432.

***N*-Diphenylphosphinyl(3-phenylcyclohex-2-enyl)methanamine (19d) and *N*-Diphenylphosphinyl(3-phenylcyclohex-3-enyl)methanamine (20d).** To a 0 °C solution of aziridine **5d** (0.02 g, 0.052 mmol) in CH_2Cl_2 (1 mL) was added $BF_3{\cdot}OEt_2$ (6.5 μL, 0.052 mmol). The reaction was warmed to room temperature and stirred for 2 h. The reaction was diluted with CH_2Cl_2, washed with saturated aq Na_2CO_3 and brine, dried ($MgSO_4$), concentrated, and chromatographed (5% EtOAc in hexanes) to provide 11 mg of a 2:1 mixture of **19d** and **20d** (55%) as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.8 (m, 4H), 7.4 (m, 6H), 7.05 (m, 6H), 6.03 (s, 0.3H), 5.95 (m, 0.63H), 2.8 (m, 3H), 2.51 (m, 1H), 2.05 (m, 2H), 1.86 (m, 2H), 1.7 (m, 1H), 1.34 (m, 3H, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.3, 131.7, 131.6, 131.5, 128.7, 128.5, 128.4, 128.3, 128.3, 128.2, 127.4, 126.1, 112.5, 51.6, 34.8, 32.1, 29.7, 25.4. HRMS calcd for $C_{25}H_{26}NOP{\cdot}Na^+$ 410.1650, found 410.1645.

***N*-(4-Nitrophenylsulfonyl)-5-phenyl-6-azabicyclo[3.2.1]-octane (7c).** $B(C_6F_5)_3$ (0.453 g, 0.885 mmol) was added to a 0 °C solution of nosyl aziridine **5c** (0.3 g, 0.805 mmol) in CH_2Cl_2 (3 mL) at 0 °C. The reaction was warmed to room temperature and

stirred for 2 h. The reaction was diluted with CH_2Cl_2, washed with saturated aq Na_2CO_3 and brine, dried ($MgSO_4$), concentrated, and chromatographed (10% EtOAc in hexanes) to provide 0.285 g (95%) of **7c** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.02 (d, 2H, J = 8.9 Hz), 7.34 (d, 2H, J = 8.9 Hz), 7.05 (m, 5H), 3.92 (d, 1H, J = 9.0 Hz), 3.56 (m, 1H), 2.79 (m, 1H), 2.43 (m, 1H), 2.20 (m, 1H), 1.71 (m, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 147.5, 145.8, 139.5, 126.1, 125.8, 125.6, 125.0, 121.8, 68.6, 53.2, 48.3, 32.7, 32.1, 23, 17.9. HRMS calculated for $C_{19}H_{20}N_2O_4S{\cdot}Na^+$ 395.1041 found 395.1058.

5-Phenyl-6-azabicyclo[3.2.1]octane (7b). PhSH (30 mg, 0.20 mmol) was added to a suspension of **7c** (20 mg, 0.053 mmol) and K_2CO_3 (30 mg, 0.212 mmol) in CH_3CN:DMSO (49:1) (1 mL) at room temparature. The reaction was heated to 50 °C and stirred for 2 h. The reaction was diluted with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), concentrated, and chromatographed (10% MeOH in CH_2Cl_2) to provide 7 mg (70%) of **7b** as a clear oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.04 (m, 5H), 3.01 (dd, 1H, J = 5.76 and 4.5 Hz), 2.83 (d, 1H, J = 10.29 Hz), 2.34 (m, 1H), 1.48 (m, 8H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.4, 128.23, 126.4, 125.5, 65.5, 51.5, 43.8, 41.7, 36.1, 30.6, 29.7, 20.3. HRMS calcd for $C_{13}H_{17}N{\cdot}H^+$ 188.1439 found 188.1434.

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Supporting Information Available: ^{1}H and ^{13}C NMR for compounds **5b**, **5c**, **5d**, **7b**, **7c**, **12**, **16**, **17**, **18**, **19b**, and **19d**/**20d** and COSY spectra for **7b**, **7c**, and **19b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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