Halogenation of 4-Phenyl-3-(phenylsulfonyl)-2-azetidinones with *N*-Halosuccinimides. Kinetic vs Thermodynamic Control

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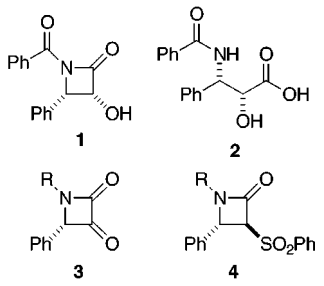
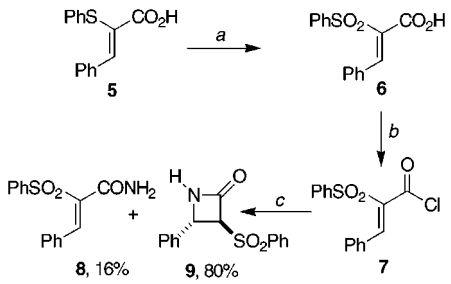
The development of synthetic routes to monocyclic 2-azetidinones (β-lactams) was stimulated by the antibacterial activity of monobactams and norcardicins.[1] Although interest in 2-azetidinones as antibiotics has waned, 2-azetidinones have served as important intermediates in many other applications. Monocyclic 2-azetidinones have been used as precursors to β-amino alcohols and β-amino acids, useful building blocks for peptides containing nonprotein amino acids.[2−4] 2-Azetidinones have served as precursors to γ-lactones via *N*- to *O*-acyl migration as demonstrated in the total synthesis of the macrolide antitumor antibiotic Lankacidin C.[5] Certain 2-azetidinones have also displayed potent cholesterol absorption inhibitory activity.[6]

Interest in the chemistry of 2-azetidinones increased with the use of 3-hydroxy-4-phenyl-2-azetidinones **1** (Chart 1) as alternatives to *N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine (**2**) for adding the side chain in the semisynthesis of paclitaxel.[7] These azetidinones have been prepared by an ester enolate−imine condensation (a [2 + 2] cycloaddition) to yield the correct stereochemistry in greater than 96% ee. Other azetidinones with the correct alcohol streochemistry have been prepared from the addition of organometallic agents to 4-phenylazetidine-2,3-diones **3**.[8]

Chart 1



Scheme 1



[a] Key: (a) H_2O_2, AcOH, 65%; (b) oxalyl chloride, 0.1 mol % DMF, $CHCl_3$, 100%; (c) NH_3, CH_2Cl_2

We have recently described the synthesis of *trans*-3-(arylsulfonyl)-4-phenylazetidinones **4** from the [3 + 1] addition of ammonia or primary amines to 2-(arylsulfonyl)cinnamic acid derivatives[9] as well as an enantioselective route to the same molecules.[10] Oxidation of compounds **4** to the equivalent oxidation state of dione **3** might provide useful precursors to novel side chains. Herein, we describe the halogenation of C3 in compounds **4** with *N*-halosuccinimides, which proceeds with surprisingly high diastereoselectivity in several cases.

Results and Discussion

Preparation of *trans*-3-(Phenylsulfonyl)-4-phenyl-2-azetidinone. *Z*-3-Phenyl-2-(phenylthio)propenoic acid (**5**) was prepared by the addition of thiophenol to ethyl phenylpropiolate followed by saponification of the resulting ethyl *Z*-3-phenyl-2-(phenylthio)propenoate.[9] Oxidation of **5** with hydrogen peroxide in acetic acid[11] gave *Z*-3-phenyl-2-(phenylsulfonyl)propenoic acid (**6**) in 65% isolated yield following recrystallization from EtOAc (Scheme 1). Compound **6** had previously been prepared in two steps involving the isolation of the sulfoxide intermediate.[9] Compound **6** was converted to the acid chloride **7** with oxalyl chloride in anhydrous chloroform in the presence of 0.1 mol % DMF. The addition of ammonia to **7** gave amide **8** in 16% isolated yield and

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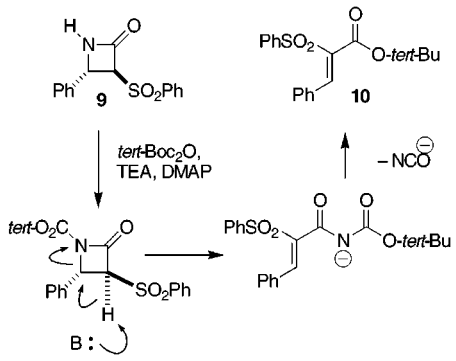
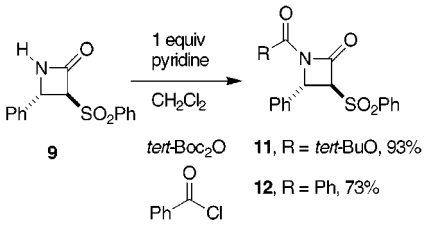
Scheme 2



Scheme 3



trans-3-(phenylsulfonyl)-4-phenyl-2-azetidinone (**9**) in 80% isolated yield.

Protection of the Azetidinone Nitrogen. The proton on C3 of azetidinone **9** should be relatively acidic due to the electron-withdrawing nature of both the carbonyl and the phenylsulfonyl groups. Oxidation of **9** with positive halogen sources such as the *N*-halosuccinimides should be possible in the presence of a base to assist in deprotonation. The free amine proton of **9** may be oxidized as well in the presence of *N*-halosuccinimides, which necessitated protection of the azetidinone nitrogen.

Surprisingly, our initial attempts to protect the azetidinone nitrogen with the *tert*-butoxycarbonyl (*t*-Boc) protecting group under standard conditions failed to give the desired azetidinone.[12] Azetidinone **9** was treated with 1 equiv of triethylamine (TEA), 1 equiv of *N*,*N*-(dimethylamino)pyridine (DMAP), and 2 equiv of di-*tert*-butyl dicarbonate in CH_2Cl_2 to give *tert*-butyl ester **10** in 93% isolated yield. As shown in Scheme 2, the desired product **11** most likely is formed, but ring-opening promoted by the second equivalent of base would relieve the strain of the four-membered ring. The subsequent loss of isocyanate would lead to the observed product.

The *N*-protected azetidinone **11** could be isolated using 1 equiv each of base and di-*tert*-butyl dicarbonate in CH_2Cl_2 to minimize the formation of **10**. Potassium carbonate was sluggish as a base giving a 13% isolated yield of **11** following 17 h at reflux, while either DMAP or TEA gave **11** in 66% isolated yield. The best results were obtained using 1 equiv of pyridine as base, which gave **11** in 93% isolated yield (Scheme 3).

Protection of the azetidinone nitrogen of **9** with the *N*-benzoyl group using benzoyl chloride in CH_2Cl_2 was also dependent upon the base employed. The use of one equiv of TEA gave azetidinone **12** in 46% isolated yield. The use of one equiv of DMAP gave **12** in 27% isolated yield. Again, the use of pyridine as a base gave the best results for the formation of **12**, which was isolated in 73% yield (Scheme 3).

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Halogenation of Azetidinones 11 and 12 with *N*-Halosuccinimides. The addition of *N*-bromosuccinimide to 1-benzoylazetidinone **12** in the presence of $NaHCO_3$ gave two products in a 78:22 ratio that were separable via chromatography on silica gel (Scheme 3). The two products were isomeric based on NMR and mass spectral data as well as on the elemental analyses for the individual compounds. The spectral and analytical data were consistent with the two diastereomers of **13**, which we designate as *trans*-**13** and *cis*-**13** in reference to the orientation of the phenyl substituent on C4 relative to the halogen substituent on C3. The major component was unambiguously assigned the *trans*-stereochemistry (*trans*-**13**) by X-ray crystallography. The protons at C4 appeared at distinctly different chemical shifts in the ^{1}H NMR spectra for the *trans*- and *cis*-stereoisomers, which allowed the assignment of stereochemistry in the other halogenation products. The C4 proton appeared at δ 5.92 for *trans*-**13** and at δ 6.23 for *cis*-**13**.

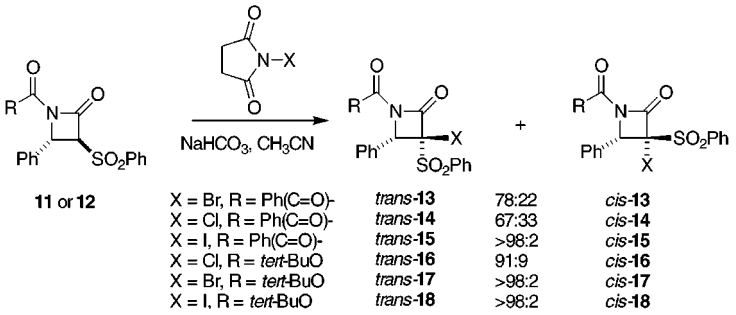
Chlorination of **12** with *N*-chlorosuccinimide gave an inseparable 67:33 mixture of monochloro products **14** with chemical shifts for the C4 proton of δ 5.78 for the major product and δ 6.32 for the minor product. Iodination of **12** with *N*-iodosuccinimide gave monoiodo product **15** as a single stereoisomer (>98% by ^{1}H NMR) with a chemical shift of δ 5.93 for the proton at C4. By analogy to diastereomers **13**, the major component is assigned the *trans*-stereochemistry (*trans*-**14** and *trans*-**15**, respectively), and the minor component is assigned the *cis*-stereochemistry (*cis*-**14**) based on the chemical shifts of the C4 protons.

Halogenation of the *t*-Boc-protected azetidinone **11** gave similar products, but with even greater diastereoselectivity for the *trans*-halogenated products than was observed with azetidinone **12**. The addition of *N*-chlorosuccinimide to **11** gave a 91:9 mixture of the two, monochloro diastereomers **16** with chemical shifts for the C4 proton of δ 5.45 for the major product and δ 6.02 for the minor product. Bromination of **11** with *N*-bromosuccinimide and iodination with *N*-iodosuccinimide gave only one detectable diastereomer in each case (>98% diastereoselectivity by ^{1}H NMR) with chemical shifts for the C4 proton of δ 5.90 for the monobromo product **17** and δ 5.62 for the monoiodo product **18**. By analogy to the stereochemical assignments for **13**−**15**, the major components of the **16**−**18** mixtures were assigned the *trans*-stereochemistry based on the upfield chemical shift of the protons at C4.

Kinetic vs Thermodynamic Control in the Halogenations. The major product in each of the halogenation reactions of **11** and **12** with *N*-halosuccinimides has the bulky C4 phenyl and C3 phenylsulfonyl substituents *cis* to one another. One might expect a *trans*-orientation of these two groups and a *cis*-orientation of the C4 phenyl and C3 halogen to have smaller steric interactions overall and to be favored energetically. Simple MM2 calculations on both diastereomers of **13**−**18** favor the *cis*-orientation of halogen and phenyl relative to the *trans*-diastereomer by 0.35−1.1 kcal mol^{-1}. The high diastereoselectivities observed for all three halogenations of **11** and for iodination of **12** were somewhat surprising.

We observed that heating the 3-halo azetidinones in DMSO gave equilibration of *cis*- and *trans*-diastereomers. Heating a DMSO solution of either the pure *trans*-diastereomer of **13** or the pure *cis*-diastereomer of **13** at 80 °C for 15 h gave a 17:83 mixture of *trans*-**13** to *cis*-**13** at equilibrium, which indicates that the *cis*-diastereomer

Scheme 4



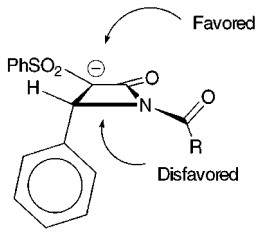


Figure 1. Favored approach for kinetic control of azetidinone halogenation.

Scheme 5

is favored by approximately 0.9 kcal mol^{-1}. It follows that the initial bromination proceeds under kinetic control to give the 78:22 mixture of *trans*- to *cis*-**13**.

As shown in Figure 1, deprotonation of azetidinone **11** or **12** would lead to an sp^2-hybridized, delocalized carbanion. The phenyl substituent would block approach of the electrophile on the same face of the azetidinone, and the *trans*-orientation of halogen and phenyl would result as the kinetic product.

The bromides **17** derived from the *t*-Boc-protected azetidinone **12** were more sluggish to equilibrate in DMSO at 80 °C. However, a new singlet at δ 6.21 slowly grew over 40 h at 80 °C (a 45:55 mixture of *trans*- to *cis*-**17** at this point, but decomposition products were also beginning to appear). The chlorides **14** and **16** were even slower to equilibrate in DMSO at 80 °C while decomposition of iodides **15** and **18** was competitive with the equilibration of diastereomers. At higher temperatures in DMSO, all of the halides **13**−**18** gave decomposition products.

Reductive Ring-Opening Products under Oxidative Conditions. We sought to accelerate the equilibration of the diastereomers through the addition of silver(I) salts such as silver tetrafluoroborate and silver nitrate. The addition of the silver(I) salt to DMSO solutions of **13** not only accelerated the equilibration of diastereomers, but also gave a new product that was identified as the 1-amino-2-(phenylsulfonyl)ethane derivative **19** (Scheme 5). Compound **19** was isolated in 40−45% yield under a variety of reaction conditions including silver tetrafluoroborate or silver nitrate in the presence of DMSO, triphenylphosphine oxide, or pyridine *N*-oxide (all compounds that transfer oxygen via nucleophilic addition). In addition to **19**, TLC analysis of the product mixture was indicative of myriad other products that were not characterized. Compound **19** was obtained in 50% isolated yield by the reaction of either diastereomer of **13** with silver nitrate in DMF at 80 °C.

The structure of **19**, which was isolated as an oil, followed from its spectral data. The IR spectrum of **19** indicated a carbonyl band at 1637 cm^{-1} as did the ^{13}C NMR spectrum with a peak at δ 166.7, which are consistent with the amide functional group. The 12 carbon signals in the aromatic region of the ^{13}C NMR spectrum are consistent with the three phenyl groups with two aliphatic carbons at δ 60.55 and 50.23. The aliphatic region of the ^1H NMR spectrum displayed an ABX pattern with signals centered at δ 3.53, 3.88, and 5.46 while the amide N−H was buried under the aromatic protons. The mass spectrum gave a parent ion consistent with the $C_{21}H_{19}NO_3S$ molecular formula of **19**.

Compound **19** is formally a reduction product of **13** under oxidative conditions. We assume that the 50% maximum yield is consistent with half of the reactant being oxidized to products unkown while half of the reactant is reduced to **19** in the process.

Summary and Conclusions

N-Benzoyl-protected azetidinone **11** and *t*-Boc-protected azetidinone **12** are readily halogenated by *N*-halosuccinimides in CH_3CN in the presence of $NaHCO_3$ to give 3-halo-3-(phenylsulfonyl)-4-phenylazetidinones **13**−**18** in 64−84% isolated yield. The major products in the halogenation reactions have the C4 phenyl substituent and the C3 halogen substituents *trans* to one another. Heating the *trans*-diastereomers in DMSO at 80 °C leads to isomerization to the more stable *cis*-diastereomer, which indicates that halogenation proceeds under kinetic control. The isomerization is accelerated in the presence of silver(I) salts, but a new ring-opened product **19** is formed in the process.

The azetidinones **11** and **12** remain intact during the halogenation process. We are currently investigating reactions of **11**−**18** that lead to the formation of diones **3** in our quest for novel side-chain precursors for paclitaxel.

Experimental Section

General Methods. Solvents and reagents were used as received from Sigma-Aldrich Chemical Co (St. Louis, MO) unless otherwise noted. Concentration in vacuo was performed on a Büchi rotary evaporator. Elemental analyses were conducted by Atlantic Microanalytical, Inc. *Z*-3-Phenyl-2-(phenylthio)propenoic acid (**5**) was prepared as reported in ref 9.

Preparation of *Z*-3-Phenyl-2-(phenylsulfonyl)propenoic Acid (6). Acid **5**[9] (5.00 g, 21.2 mmol) was dissolved in glacial acetic acid (25 mL) with mild heating. Hydrogen peroxide (8.27 mL of a 30% solution, 73 mmol) was added via syringe. The reaction was heated to reflux with stirring for 2 h. A color change from deep yellow to pale yellow was noted. The reaction mixture

was diluted with ether, washed with water, dried over $MgSO_4$, and concentrated. Crystallization from EtOAc gave 3.99 g (65%) of **6** as a white crystalline solid, mp 70−73 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (s, 1 H), 7.93 (m, 2 H), 7.49 (m, 5 H), 7.34 (m, 3 H); ^{13}C NMR ($CDCl_3$) δ 165.6, 145.0, 140.4, 135.0, 134.2, 132.1, 131.9, 130.7, 129.6, 129.4, 129.1; IR (KBr) 3000 (br), 1727, 1615 cm^{-1}; FAB MS, *m*/*z* 289 (C_{15},$H_{12}O_4S$ + H^+), 244 (M − CO_2), 102 (base peak, $HCCPh^+$). Anal. Calcd for $C_{15}H_{12}O_4S$: C, 62.48; H, 4.20. Found: C. 62.59; H, 4.26.

Preparation of *Z*-3-Phenyl-2-(phenylsulfonyl)propenoyl Chloride (7). Acid **3** (1.00 g, 3.49 mmol) was dissolved in anhydrous $CHCl_3$ (10 mL). Oxalyl chloride (10 mL) was added followed by the addition of 10 μL of *N*,*N*-dimethylformamide. The resulting solution was heated at reflux for 4 h. The reaction mixture was concentrated in vacuo and was used without further purification. For **7**: ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1 H), 7.85 (m, 2 H), 7.65 (m, 1 H), 7.55 (m, 2 H), 7.45−7.30 (m, 5 H).

Addition of Ammonia to 7. Propenoyl chloride **7** (1.07 g, 3.49 mmol) was dissolved in dry CH_2Cl_2 (35 mL) in a flask equipped with a gas condenser containing a dry ice−acetone cooling bath. Approximately 0.50 g (≈30.0 mmol) of ammonia was condensed into the reaction mixture. The resulting solution was stirred at ambient temperature for 0.5 h. Ammonia was allowed to evaporate, and the reaction mixture was concentrated. The products were separated by chromatography on SiO_2 eluted with 20% EtOAc−CH_2Cl_2 to give 0.14 g (14%) of propenamide **8** (mp 177−178 °C from CH_3CN) and 0.80 g (80%) of *trans*-azetidinone **9** (mp 167−168 °C from CH_3CN).

For *Z*-3-phenyl-2-(phenylsulfonyl)propenoyl amide (8): ^{1}H NMR ($CDCl_3$) δ 7.93 (m, 2 H), 7.86 (s, 1 H), 7.45−7.65 (m, 5 H), 7.39 (m, 3 H), 6.42 (br s, 1 H), 5.70 (br s, 1 H); IR (CDCl3) 1687, 1620 cm^{-1}; FAB MS, *m*/*z* 288 ($C_{15}H_{13}O_3SN$ + H^+). Anal. Calcd for $C_{15}H_{13}O_3SN$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.76; H, 4.61; N, 4.83.

For *trans*-4-phenyl-3(phenylsulfonyl)azetidin-2-one (9): ^{1}H NMR ($CDCl_3$) δ 8.03 (d, 2 H), 7.70 (m, 1 H), 7.59 (m, 2 H), 7.36 (m, 5 H), 6.32 (br s, 1 H), 5.26 (d, 1 H, J = 2 Hz), 4.38 (d, 1 H, J = 2 Hz); ^{13}C NMR ($CDCl_3$) δ 159.3, 138.3, 137.2, 135.2, 130.0,129.7, 129.6, 129.5, 126.3, 79.4, 53.4; IR (KBr) 2983, 1791 cm^{-1}; FAB MS, *m*/*z* 288 ($C_{15}H_{13}O_3SN$ + H^+). Anal. Calcd for $C_{15}H_{13}O_3SN$: C, 62.70; H, 4.56; N, 4.87. Found: C, 62.25; H, 4.60; N, 4.83.

Preparation of *tert*-Butyl *Z*-3-phenyl-2-(phenylsulfonyl)-propenoate (10). Azetidinone **9** (0.500 g, 1.75 mmol) was dissolved in dry CH_2Cl_2 (3.5 mL). Triethylamine (0.24 mL, 1.75 mmol), *N*,*N*-(dimethylamino)pyridine (0.214 g, 1.75 mmol), and di-*tert*-butyl dicarbonate (0.764 g, 3.50 mmol) were added. The solution was stirred under argon at ambient temperature for 2 h and then concentrated in vacuo. The product was isolated by chromatography on SiO_2 eluted with 10% hexanes−CH_2Cl_2. Crystallization from CH_2Cl_2 gave 0.56 g (93%) of **10** as a white crystalline solid, mp 96−97 °C: ^{1}H NMR ($CDCl_3$) δ 7.94 (d, 2 H), 7.87 (s, 1 H), 7.63 (t, 1 H), 7.54 (t, 2 H), 7.47 (d, 2 H), 7.38 (q, 3 H), 1.35 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 162.1, 142.3, 140.2, 136.1, 133.6, 131.9, 131.3, 130.0, 129.1, 128.8, 128.5, 84.2, 27.6; IR (KBr) 3068, 2982, 1718, 1618, 1142, 1032 cm^{-1}; EIMS *m*/*z* 344 ($C_{19}H_{20}O_4S$). Anal. Calcd for $C_{19}H_{20}O_4S$: C, 66.25; H, 5.85. Found: C, 66.39; H, 5.92.

Preparation of *trans*-*N*-(*tert*-Butoxycarbonyl)-4-phenyl-3-(phenylsulfonyl)-2-azetidinone (11). Method A. Azetidinone **9** (0.100 g, 0.350 mmol) was dissolved in dry CH_2Cl_2 (5 mL). Potassium carbonate (0.100 g) and di-*tert*-butyl dicarbonate (0.153 g, 0.700 mmol were added successively. The reaction mixture was allowed to stir for 17 h under argon at ambient temperature. Potassium carbonate was removed by filtration, and the filtrate was concentrated. The residue was purified by chromatography on SiO_2 eluted with 10% EtOAc−hexanes followed by recrystallization from EtOAc−hexanes to give 0.14 g (13%) of **11** as a white powder, mp 151−152 °C.

Method B. Azetidinone **9** (0.100 g, 0.350 mmol) was dissolved in dry CH_2Cl_2 (5 mL). Triethylamine (0.0488 mL, 0.350 mmol) and di-*tert*-butyl dicarbonate (0.153 g, 0.700 mmol) were added successively. The reaction mixture was stirred for 49.5 h under argon at ambient temperature. The reaction mixture was concentrated. The residue was purified by chromatography on SiO_2 eluted with 10% EtOAc−hexanes followed by recrystallization from EtOAc−hexanes to give 0.090 g (66%) of **11** as a white powder, mp 151−152 °C.

Method C. Azetidinone **9** (0.100 g, 0.350 mmol) was dissolved in dry CH_2Cl_2 (5 mL). *N*,*N*-(Dimethylamino)pyridine (0.0425 g, 0.350 mmol) and di-*tert*-butyl dicarbonate (0.0915 g, 0.417 mmol) were added successively. The reaction mixture was stirred for 1 h at ambient temperature and was then concentrated. The residue was purified by chromatography on SiO_2 eluted with 10% EtOAc−hexanes followed by recrystallization from EtOAc−hexanes to give 0.09 g (66%) of **11** as a white powder, mp 150−152 °C.

Method D. Azetidinone **9** (0.810 g, 2.82 mmol) was dissolved in dry CH_2Cl_2 (15 mL). Pyridine (0.229 mL, 2.82 mmol) and di-*tert*-butyl dicarbonate (0.744 g, 3.40 mmol) were added successively. The reaction mixture was allowed to stir for 22 h at ambient temperature and then concentrated. The residue was purified by chromatography on by chromatography on SiO_2 eluted with 20% EtOAc−hexanes. The product was recrystallized from EtOAc−hexanes to give 1.01 g (93%) of **11** as a white powder, mp 150−152 °C: ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 2 H), 7.71 (t, 1 H), 7.59 (t, 2 H), 7.33 (d, 5 H), 5.44 (s, 1 H), 4.38 (s, 1 H), 1.38 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 156.2, 146.8, 137.6, 135.4, 135.1, 129.8, 129.5, 129.4, 129.2, 126.0, 84.9, 77.7, 56.1, 27.9; IR (KBr) 3060, 2985, 1806, 1723, 1450, 1339, 1027, 1153 cm^{-1}; EI MS, *m*/*z* 244 ($C_{14}H_{12}O_2S^+$, M − CO_2 − HNCO − C_4H_8). Anal. Calcd for $C_{20}H_{21}O_5NS$: C, 61.99; H, 5.46; N, 3.62. Found: C, 61.94; H, 5.53; N, 3.54.

Preparation of *trans*-*N*-Benzoyl-4-phenyl-3-(phenylsulfonyl)-2-azetidinone (12). Method A. Azetidinone **9** (0.200 g, 0.777 mmol) was dissolved in dry CH_2Cl_2. TEA (0.078 g, 0.78 mmol) and benzoyl chloride (0.108 mL, 0.933 mmol) were added successively. The reaction mixture was allowed to stir for 28 h under argon at ambient temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on SiO_2 eluted with CH_2Cl_2 followed by recrystallization from EtOAc to give 0.14 g (46%) of **12** as a white solid, mp 149−150 °C

Method B. Azetidinone **9** (0.110 g, 0.386 mmol) was dissolved in dry CH_2Cl_2 (5 mL). *N*,*N*-(Dimethylamino)pyridine (0.0417 g, 0.386 mmol) and benzoyl chloride (0.0538 mL, 0.463 mmol) were added successively. The reaction mixture was allowed to stir for 4 h under argon at ambient temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on SiO_2 eluted with CH_2Cl_2 followed by recrystallization from EtOAc to give 0.40 g (27%) of **12** as a white, flakey solid, mp 149−150 °C.

Method C. Azetidinone **9** (1.10 g, 3.86 mmol) was dissolved in dry CH_2Cl_2 (25 mL). Pyridine (0.305 g, 3.86 mmol) and benzoyl chloride (0.538 mL, 4.63 mmol) were added successively. The reaction mixture was allowed to stir for 4 h under argon at ambient temperature. The reaction mixture was diluted with water and extracted with CH_2Cl_2. The organic layers were combined, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by chromatography on SiO_2 eluted with CH_2Cl_2 followed by recrystallization from EtOAc to give 1.10 g (73%) of **12** as a white, flakey solid, mp 149−150 °C; ^{1}H NMR ($CDCl_3$) δ 7.99 (t, 4 H), 7.75 (t, 1 H), 7.65 (q, 3 H), 7.48 (t, 2 H), 7.36 (s, 5 H), 5.8 (d, 1 H, J = 3.3), 4.52 (d, 1 H, J = 3.6); ^{13}C NMR ($CDCl_3$) δ 165.9, 155.8, 135.7, 135.1, 134.9, 133.9, 130.9, 129.9, 129.2, 129.1, 128.9, 128.4, 125.7, 75.6, 54.3; IR (KBr) 1816, 1685, 1448, 1294, 1156 cm^{-1}; EI MS *m*/*z* 250 ($C_{16}H_{12}O_2N^+$, M − $C_6H_5SO_2$). Anal. Calcd for $C_{22}H_{17}O_4NS$: C, 67.50; H, 4.38; N, 3.58; S, 8.19. Found: C, 67.58; H, 4.31; N, 3.58; S, 8.10.

Preparation of 1-Benzoyl-3-bromo-4-phenyl-3-(phenylsulfonyl)azetidin-2-ones (13). Azetidinone **12** (0.500 g, 1.28 mmol) was dissolved in CH_3CN (8.0 mL). *N*-Bromosuccinimide (0.273 g, 1.53 mmol) was added followed by saturated $NaHCO_3$ solution (2.0 mL). The reaction mixture was stirred at 40 °C for 5 h. Water was added, and the resulting mixture was extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on SiO_2 eluted with 50% CH_2Cl_2−hexanes to give 0.300 g (50%) of a white crystalline solid identified as the *trans*-isomer

(*trans*-**13**) and 0.0843 g (14%) of a white powder identified as the *cis*-isomer (*cis*-**13**) following recrystallization from EtOAc−hexanes.

For *trans*-**13**: mp 198 °C (dec); ^{1}H NMR ($CDCl_3$) δ 8.13 (d, 2 H), 7.70 (m, 5 H), 7.56 (t, 2 H), 7.42 (m, 6 H), 5.92 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 165.2, 156.8, 135.9, 135.0, 134.6, 130.7, 130.4, 129.7, 129.1, 128.8, 128.4, 128.2, 72.4, 69.0; IR (KBr) 3063, 2361, 1805, 1685, 1294, 1155, 726 cm^{-1}; FAB(+) MS *m*/*z* 470 ($C_{22}H_{16}O_4{}^{79}BrNS + H^+$). Anal. Calcd for $C_{22}H_{16}O_4BrNS$: C, 56.18; H, 3.43; Br, 16.99; N, 2.98; S, 6.82. Found: C, 56.30; H, 3.44; Br, 17.11, N, 3.01; S, 6.72.

For *cis*-**13**: mp 167−168 °C; ^{1}H NMR ($CDCl_3$) δ 8.02 (t × d, 4 H), 7.76−7.49 (m, 6 H), 7.38 (m, 3 H), 7.26 (m, 2 H), 6.23 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 165.2, 156.4, 135.5, 134.3, 134.1, 132.7, 131.1, 130.7, 130.6, 130.1, 129.5, 129.1, 128.8, 128.5, 126.9, 59.2; IR (KBr) 3066, 2960, 1797, 1683, 1260, 1149, 711 cm^{-1}; FAB MS *m*/*z* 470 ($C_{22}H_{16}O_4{}^{79}BrNS + H^+$). Anal. Calcd for $C_{22}H_{16}O_4BrNS$: C, 56.18; H, 3.43; Br, 16.99; N, 2.98; S, 6.82. Found: C, 56.03; H, 3.34; Br, 17.10, N, 2.91; S, 6.72.

Preparation of 1-Benzoyl-3-chloro-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (14). Azetidinone **12** (0.250 g, 0.638 mmol) was dissolved in CH_3CN (2.5 mL) and *N*-chlorosuccinimide (0.111 g, 0.830 mmol) was added in one portion followed by saturated $NaHCO_3$ (0.62 mL). The reaction mixture was stirred at 40 °C for 3 h. Water was added, and the products were extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. The residue was purified by chromatography on SiO_2 eluted with CH_2Cl_2 to give 0.187 g (69%) of **14** as an inseparable mixture of the two isomers in a 67:33 ratio by ^{1}H NMR. For *trans*-**14** (major component): ^{1}H NMR ($CDCl_3$) δ 8.14 (d, 2 H), 7.74−7.26 (m, 13 H), 6.32, (s, 1 H). For *cis*-**14**: ^{1}H NMR ($CDCl_3$) δ 8.03 (q, 2 H), 7.74−7.26 (m, 13 H), 5.78 (s, 1 H). For the mixture: IR (KBr) 3064, 2960, 2359, 1811, 1683, 1294, 1157, 688 cm^{-1}; FAB(+) MS *m*/*z* 426 ($C_{22}H_{16}O_4ClNS+H^+$). Anal. (of the mixture) Calcd for $C_{22}H_{16}O_4ClNS$: C, 62.05; H, 3.79; N, 3.29. Found: C, 61.89; H, 3.94; N, 3.16.

Preparation of 1-Benzoyl-3-iodo-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (15). Azetidinone **12** (0.200 g, 0.511 mmol) was dissolved in CH_3CN (2.0 mL), and *N*-iodosuccinimide (0.149 g, 0.664 mmol) was added in one portion followed by saturated $NaHCO_3$ (0.50 mL). The reaction was stirred at 40 °C for 3 h. The reaction was diluted with water (20 mL) and extracted with CH_2Cl_2 (30 mL × 2). The combined organic extracts were dried over $MgSO_4$ and concentrated. The ^{1}H NMR spectrum of the crude reaction mixture showed >98% of a single stereoisomer of **15** with perhaps a trace of the second diastereomer at δ 6.22. The residue was purified by chromatography on SiO_2 eluted with CH_2Cl_2 to give 0.215 g (71%) of *trans*-**15** as a white powder following recrystallization from EtOAc−hexanes: mp 156−157 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (t, 4 H), 7.74−7.51 (m, 7 H), 7.43 (d, 3 H), 7.25 (s, 1 H), 5.93 (s, 1 H); ^{13}C NMR ($CDCl_3$) δ 165.2, 157.6, 135.4, 135.3, 134.4, 134.2, 131.2, 130.7, 130.1, 129.5, 129.0, 128.7, 128.5, 126.4, 61.8, 58.9; IR (KBr) 3062, 2361, 1796, 1691, 1290, 1152, 561 cm^{-1}; FAB(+) MS *m*/*z* 518 ($C_{22}H_{16}O_4INS + H^+$). Anal. Calcd for $C_{22}H_{16}O_4INS$: C, 51.08; H, 3.12; N, 2.71. Found: C, 50.86; H, 3.16; N, 2.57.

Preparation of 1-(*tert*-Butoxycarbonyl)-3-chloro-4-phenyl-3-(phenylsulfonyl)azetidin-2-ones (16). Azetidinone **11** (0.250 g, 0.645 mmol) was dissolved in CH_3CN (2.5 mL) and *N*-chlorosuccinimide (0.112 g, 0.839 mmol) was added in one portion followed by saturated $NaHCO_3$ (0.62 mL). The reaction was stirred at 40 °C for 4 h. The reaction was diluted with water and extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. The ^{1}H NMR spectrum of the crude product mixture was indicative of a 91:9 mixture of the two diastereomers of **16** based on the C4 singlets at δ 5.45 for the major comonent and δ 6.05 for the minor component. The residue was purified by chromatography on SiO_2 eluted with CH_2Cl_2 to give 0.187 g (69%) of **16** as a white powder: mp 133−134 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (d, 2 H), 7.44 (m, 8 H), 5.45 (s, 1 H), 1.42 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 156.7, 146.5, 135.0, 130.6, 129.7, 129.2, 129.0, 128.8, 128.4, 128.1, 85.5, 70.4, 27.7; IR (KBr) 3084, 2978, 2338, 1820, 1735, 1326, 1159, 774 cm^{-1}; FAB(+) MS *m*/*z* 422 ($C_{20}H_{20}O_5ClNS + H^+$), 424.2. Anal. Calcd for $C_{20}H_{20}O_5ClNS$: C, 56.94; H, 4.78; N, 3.32. Found: C, 56.82; H, 4.86; N, 3.27.

Preparation of 1-(*tert*-Butoxycarbonyl)-3-bromo-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (17). Azetidinone **11** (0.200 g, 0.516 mmol) was dissolved in CH_3CN (2.0 mL) and *N*-bromosuccinimide (0.101 g, 0.568 mmol) was added followed by saturated $NaHCO_3$ (0.50 mL). The reaction mixture was stirred at 40 °C for 3 h and then was diluted with water. The products were extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. The ^{1}H NMR spectrum of the crude product mixture was indicative of >98% of a single diastereomer of **17**. The residue was purified by chromatography on SiO_2 eluted with 70% CH_2Cl_2−hexanes to give 0.194 g (81%) of **17** as a white powder following recrystallization from EtOAc−hexanes: mp 148−149 °C; ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 2 H), 7.74 (t, 1 H), 7.60 (t, 2 H), 7.40 (d, 3 H), 7.26 (s, 2 H), 5.90 (s, 1 H), 1.43 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 156.4, 147.6, 135.5, 134.2, 132.7, 131.1, 129.5, 129.1, 128.6, 127.1, 85.4, 78.6, 60.8, 27.8; IR (KBr) 3068, 2974, 2363, 1820, 1736, 1326, 1326, 1155, 559 cm^{-1}; FAB(+) MS *m*/*z* 466 ($C_{20}H_{20}O_5{}^{79}BrNS + H^+$). Anal. Calcd for $C_{20}H_{20}O_5BrNS$: C, 51.51; H, 4.32; Br, 17.14; N, 3.00; S, 6.88. Found: C, 51.62; H, 4.39; Br, 17.22; N, 2.92; S, 6.76.

Preparation of 1-(*tert*-Butoxycarbonyl)-3-iodo-4-phenyl-3-(phenylsulfonyl)azetidin-2-one (18). Azetidnone **11** (0.150 g, 0.387 mmol) was dissolved in CH_3CN (2.0 mL), and *N*-iodosuccinimide (0.113 g, 0.503 mmol) was added in one portion followed by saturated $NaHCO_3$ (0.50 mL). The reaction was stirred at 40 °C for 3 h and was then diluted with water. The products were extracted with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated. The ^{1}H NMR spectrum of the crude product mixture was indicative of >98% of a single diastereomer of **18**. The residue was purified by chromatography on SiO_2 eluted with 70% CH_2Cl_2−hexanes to give 0.165 g (84%) of **18** as a white powder following recrystallization from EtOAc−hexanes: mp 129−131 °C; ^{1}H NMR ($CDCl_3$) δ 8.04 (dxd, 2 H), 7.72 (txd, 1 H), 7.60 (t, 2 H), 7.41 (d, 3 H), 7.20 (d of d, 2 H), 5.62 (s, 1 H), 1.42 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 157.5, 146.6, 135.3, 135.2, 134.5, 131.1, 129.5, 128.9, 128.5, 126.6, 85.2, 62.9, 60.5, 27.7; IR (KBr) 3067, 2984, 2363, 1814, 1736, 1324, 1153, 544 cm^{-1}; FAB(+) MS *m*/*z* 514 ($C_{20}H_{20}O_5INS+H^+$). Anal. Calcd for $C_{20}H_{20}O_5INS$: C, 46.80; H, 3.93; N, 2.73. Found: C, 46.73; H, 4.01; N, 2.67.

Isomerization of 13. A 50-mg sample of either *trans*-**13** or *cis*-**13** was dissolved in 3 mL of dry DMSO, and the resulting solution was heated at 80 °C in a constant temperature oil bath for 15 h. The reaction mixture was diluted with water, and the products were extracted with ether. The combined ether extracts were washed with several portions of brine, dried over Na_2SO_4, and concentrated to give 45 mg (90% recovery) of *trans*- and *cis*-**13**. The ratio of diastereomers was determined from the ^{1}H NMR spectrum of the crude product mixture.

Reaction of 13 with Silver Nitrate in DMF. Preparation of *N*-Benzoyl-1-phenyl-2-(phenylsulfonyl)ethylamine (19). A mixture of silver nitrate (0.170 g, 1.00 mmol) and *cis*- or *trans*-**13** (0.235 g, 0.500 mmol) in 10 mL of DMF was stirred for 4 h at 80 °C. The reaction mixture was poured into water, and the products were extracted with CH_2Cl_2. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified via chromatography on SiO_2 eluted with CH_2Cl_2−hexanes (1:1) to give 0.092 mg (50%) of **19** as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 7.81 (t × d, 4 H), 7.59 (t, 1 H), 7.52−7.40 (m, 6 H), 7.24 (s, 5 H), 5.49−5.44 (m, 1 H), 3.83 (d × d, 1 H, J = 14.4), 3.58 (d × d, 1 H, J = 15 Hz), ^{13}C NMR (CD_2Cl_2) δ 166.70, 139.74, 134.38, 134.26, 132.42, 132.16, 129.80, 129.22, 128.98, 128.37, 128.31, 127.44, 126.65, 60.55, 50.23, IR (KBr) 3257, 3063, 2934, 1637, 1535, 1300, 1143 cm^{-1}; FAB(+)MS *m*/*z* 366 ($C_{21}H_{19}NO_3S + H^+$). Anal. Calcd for $C_{21}H_{19}NO_3S$: C, 69.02; H, 5.24; 3.83. Found: C, 68.74; H, 5.23; N, 3.80.

Supporting Information Available: ORTEP plot, experimental procedure, crystal data and structure refinement, atomic coordinates and equivalent isotropic displacement parameters, bond lengths and angles, anisotropic displacement parameters, and hydrogen coordinates and isotropic displacement parameters for *trans*-**13** and Cartesian coordinates and computed total energies for the MM2 calculations on *cis*- and *trans*-**13**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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