Tandem Radical Cyclizations on Iodoaryl Azides: Synthesis of the Core Tetracycle of *Aspidosperma* Alkaloids

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A new stereoselective approach to the tetracyclic core of *Aspidosperma* alkaloids is described. Selective attack by tristrimethylsilylsilyl radicals on the aryl carbon−iodine bond of iodoaryl azides was first demonstrated on the simple model **15**, thus both extending the recent discoveries of Kim and co-workers on aliphatic C−I bonds and demonstrating that the selectivity can be exploited in cascade radical cyclizations. Extension to the more complex substrate **25** afforded the core **ABCE** tetracyclic skeleton of the alkaloids in excellent yield and with efficient control of relative stereochemistry.

Introduction

Indoline-containing alkaloids[1] have long been the subjects of intense interest because of their wide-ranging biological activities and also because of the challenge posed by their complex structures. The complexity arises from three factors: (i) the polycyclic nature of the structures, (ii) the number and arrangement of stereocenters, and (iii) the presence of tetrasubstituted carbon atoms. Considering these points, radical chemistry has shown considerable success in the preparation of fused carbocycles; this results from the rapid rates of cyclization to form five-membered rings. Furthermore, whereas the formation of tetrasubstituted carbon centers poses steric problems for many types of reaction,[2] the early transition state[3] which prevails in radical additions to unsaturated carbon atoms, together with the unsolvated nature of the radicals, gives a definite advantage to radical approaches to molecules containing tetrasubstituted carbons.

We propose a novel approach to the *Aspidosperma* and related alkaloids such as aspidospermidine[4] **1** which would involve stereoselective tandem formation of both C−C and C−N bonds, shown in Scheme 1 as the conversion **2** → **4**. The indoline formation is guaranteed to produce a *cis* ring junction from the extensive precedent in radical reactions[5] in which [5,6] fused ring systems are formed. This places the side chain bearing the nitrogen-containing group on the top face of the molecule as shown, and this should guarantee the stereochemistry of the C−N bond. It has already been observed that *cis*-fused cyclohexindolines[6] such as **3** show a strong bias for attack on the top face at the atom adjacent to the *cis*-ring fusion.

Discussion

At the outset, the difficulty lay in proposing the most suitable nitrogen-containing group, represented above as NX_2. Our attention was then drawn to the elegant research of Kim et al.,[7] who demonstrated that trialkylsilylsilyl radicals selectively attack aliphatic carbon−iodine bonds in the presence of azide groups. Thus compounds related to **5** undergo initial removal of iodine to afford a carbon radical, which then attacks the azide group to afford **6**. This suggested that the azide group would be an excellent candidate to terminate our proposed tandem cyclization.[8,9] However these plans in-

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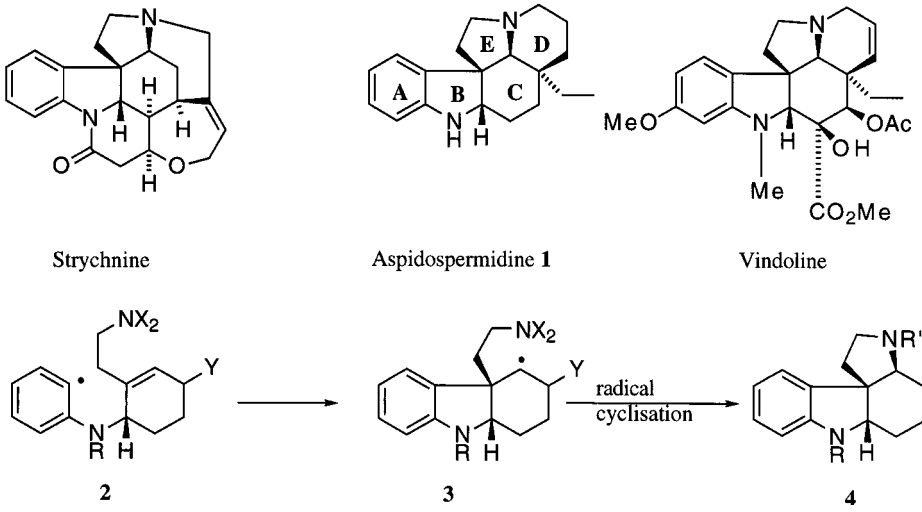
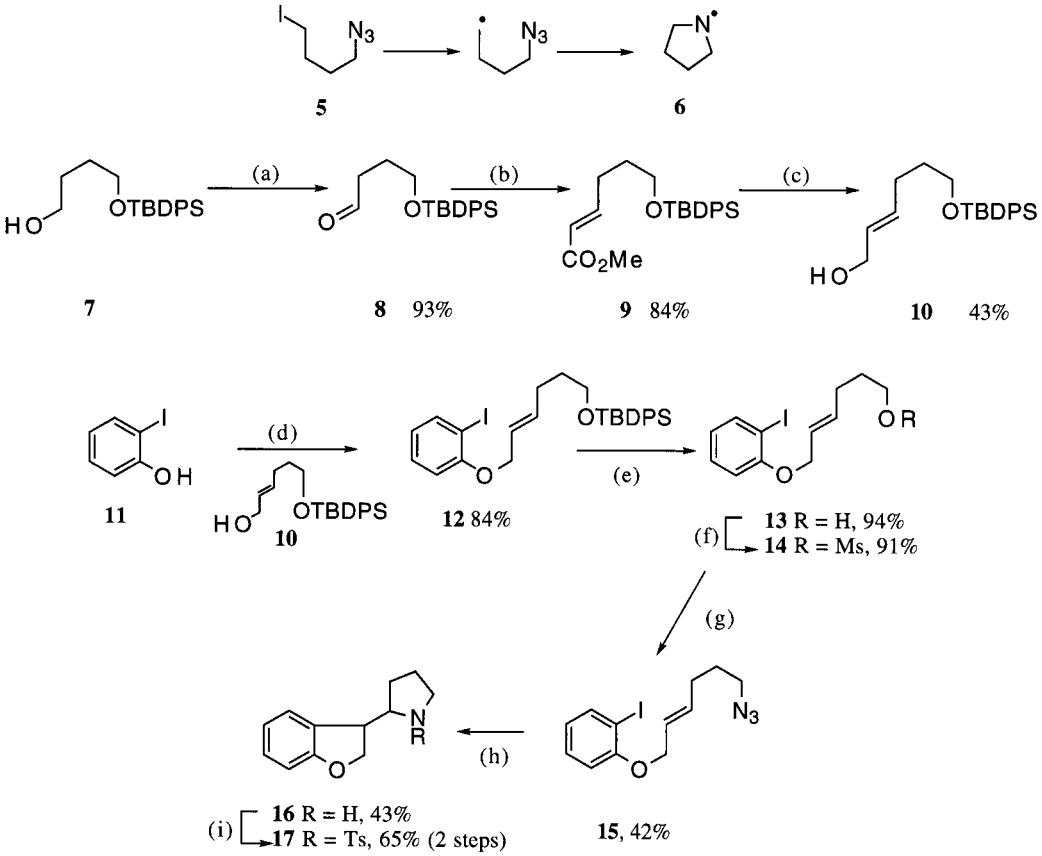
Scheme 1



Scheme 2[a]



[a] Reagents and conditions: (a) $(COCl)_2$, DMSO, Et_3N; (b) NaH, $(MeO)_2PO{\cdot}CH_2CO_2Me$, 16 h; (c) DIBALH, 30 min, −78 °C then rt; (d) DEAD, PPh_3, THF, rt, 48h; (e) TBAF, THF, 12 h; (f) $MeSO_2Cl$, NEt_3, CH_2Cl_2, DMAP, rt, 5 h; (g) NaN_3, DMF, 60 °C, 5 h; (h) TTMSS, AIBN, 80 °C, benzene, 5 h; (i) p-TsCl, pyridine, DMAP, 110 °C, 12 h.

volved competition between an *aryl* iodide and an azide, whereas Kim's work had involved an alkyl iodide. Our own semiempirical calculations (AM1) suggest that an aryl carbon−iodine bond is considerably stronger than an aliphatic C−I bond [e.g., C−I bond in iodobenzene is calculated as 17 kcal/mol stronger than that in iodoethane], and thus the selectivity observed by Kim was at risk of being overturned. To probe this question of selectivity, a very simple model compound, **15**, was prepared as shown in Scheme 2.

The scheme used the known intermediates **7**,[11] **8**,[12] **9**,[13] and **10**,[13,14] and all steps proceeded well until the forma-

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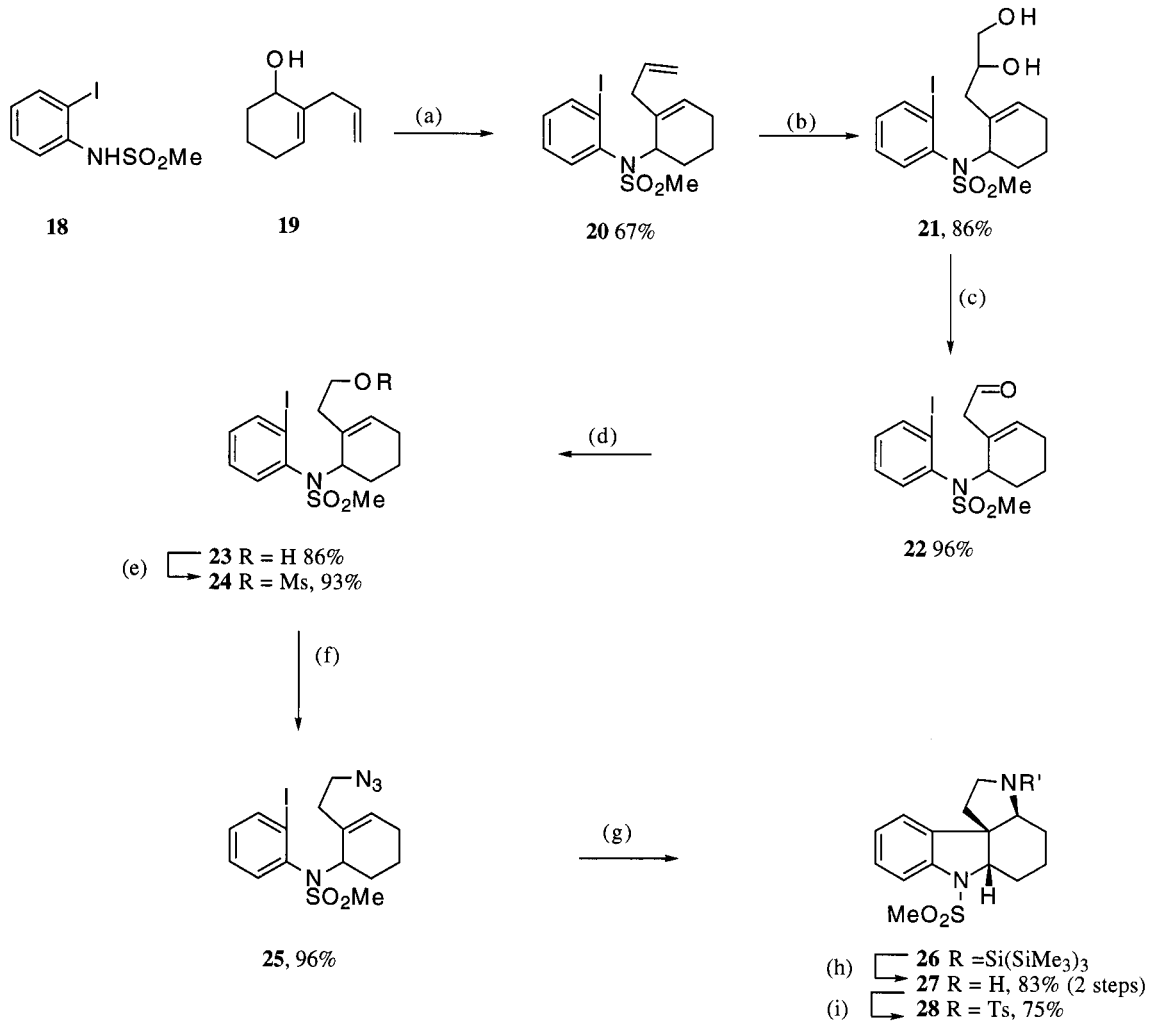
Scheme 3[a]



[a] Reagents and conditions: (a) DEAD, PPh_3, THF, rt, 48 h; (b) OsO_4, NMO, acetone: water (9:1), rt, 12 h; (c) $NaIO_4$, Et_2O, H_2O, rt, 12 h; (d), $NaBH_4$, MeOH, 10 min; (e) $MeSO_2Cl$, NEt_3, CH_2Cl_2, DMAP, rt, 5 h; (f) NaN_3, DMF, 60 °C, 6 h; (g) TTMSS, AIBN, 80 °C, benzene, 5 h; (h) H_2O; (i) *p*-TsCl, pyridine, DMAP, 110 °C, 12 h.

tion of **15**. The low yield observed in this step is attributed to the ease of allylic displacement of the phenolic leaving group in such reactions, and in line with this hypothesis, 2-iodophenol was isolated from this reaction in 20% yield.

Treatment of **15** with tristrimethysilylsilane afforded the desired dihydrobenzofuranpyrrolidine **16**, albeit in a low yield of 43%. However, the low yield of this reaction was likely due to the difficulty in chromatographic purification of the product, which, as with the cyclization products of Kim, was extremely polar. When the reaction was repeated and the crude product mixture subjected to tosylation, then the sulfonamide **17** was isolated in a much more promising 65% yield from the azide **15**. Rather than optimize the cyclization of this azide, it was decided to prepare the more advanced precursor **25**, the direct precursor of the target tetracycle.

Mitsunobu coupling of sulfonamide **18** with the cyclohexenol **19** gave alkene **20**. The spectroscopic data for this compound and subsequent compounds in the series were more complicated than might be expected. Specifically, many of the signals in the NMR spectra (^1H and ^{13}C) were doubled, indicating the possible presence of rotational isomers. This was confirmed when **20** was subjected to variable-temperature NMR in $(CD_3)_2SO$. In the ^1H NMR spectrum, the peaks due to the NC*H* and the C=C*H*−CH_2 protons appeared as doubled signals which were simple in pattern, easily assigned, and clearly separated from other signals. Heating of the NMR sample to 100 °C caused complete coalescence of the multiplet pairs assigned to these protons; recooling the NMR sample restored the orginal spectrum.

Alkene **20** was oxidized via diol **21** to the aldehyde **22**. This oxidation was performed as a two-step process, since attempts to oxidize analogous compounds in one step had led, in our hands, to complicated mixtures. Aldehyde **22** was efficiently reduced to the corresponding alcohol **23**, and mesylation and azidation both proceeded smoothly to give azide **25**. Formation of the azide occurred in high yield with no apparent byproducts, in contrast to the oxygen-linked substrate **15**.

Cyclization of the iodoazide **25** with tristrimethylsilylsilane and AIBN afforded, after workup, tetracycle **27** as a single diastereoisomer in an excellent 83% yield. It should be noted that the crude reaction mixture appeared to contain not the amine **27** but the tristrimethylsilylsilyl derivative **26** [formed by reaction of the amine **27** with

tristrimethylsilylsilyl iodide], which is apparently hydrolyzed during workup (Scheme 3).

To confirm the stereochemistry of amine **27**, it was converted into its toluenesulfonamide **28**, which was subjected to single-crystal X-ray analysis. [As shown in the Supporting Information, the relative stereochemistry is confirmed.]

In summary, it has been shown that the tetracyclic core of the *Aspidosperma* alkaloids can be conveniently prepared with excellent stereoselectivity by a novel tandem cyclization route. This route complements our recently reported approach using the radical-polar crossover reaction.[10] These twin novel approaches will afford flexibility in the design of both the alkaloids themselves and their analogues, which will be important for biological and medicinal studies.

Experimental Section

General Information. Where necessary, solvents were dried and/or distilled before use. Tetrahydrofuran was distilled from sodium benzophenone. Acetonitrile was distilled from phosphorus(V) oxide. Dichloromethane (DCM) was distilled from calcium hydride. Diethyl ether, toluene, and benzene were dried over sodium wire. Unless otherwise stated all petrol was of boiling range 40−60 °C and was distilled before use. Chromatography was performed using Sorbsil C60 (May and Baker), Kieselgel 60 (Art 9385), or Kieselgel HF254 silica gels.

2-[(6-*tert*-Butyldiphenylsilyloxy)hex-2-enyloxy]iodobenzene, 12. 2-Iodophenol **11** (1.22 g, 5.5 mmol, 1.5 equiv) and triphenylphosphine (1.45 g, 5.5 mmol, 1.5 equiv) were dissolved in dry THF (100 mL). (6-*tert*-Butyldiphenylsilyloxy)-hex-2-enol[11] (1.30 g, 3.67 mmol, 1.0 equiv) was added, and the mixture was cooled to 0 °C. Diethyl azodicarboxylate (0.96 g, 0.87 mL, 5.5 mmol, 1.5 equiv) was added dropwise over a 15 min period. After 16 h the mixture was evaporated to dryness, dissolved in DCM, and washed with NaOH (2 M), aqueous sodium carbonate (saturated), and water. The organic layer was dried over sodium sulfate, followed by filtration and removal of the solvent under reduced pressure to give a yellow solid. This was purified by column chromatography on silica gel eluted with 90% petroleum ether/10% EtOAc to give **12** as a clear yellow oil (1.71 g, 3.09 mmol, 84%); R_f 0.76 (petroleum ether/EtOAc = 85:15); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.05 (9H, s), 1.67 (2H, tt, *J* 7.4, 6.3 Hz), 2.20 (2H, td, *J* 7.4, 6.6 Hz), 3.68 (2H, t, *J* 6.3 Hz), 4.49 (2H, d, *J* 5.4 Hz), 5.67 (1H, dt, *J* 15.6, 5.4 Hz), 5.85 (1H, dt, *J* 15.6, 6.6 Hz), 6.67 (1H, dd, *J* 7.4, 7.8 Hz), 6.77 (1H, d, *J* 8.2 Hz), 7.25 (1H, m, ArH), 7.39 (6H, m, ArH), 7.66 (4H, m, ArH), 7.75 (1H, d, *J* 7.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 20.2 (s), 27.9 (q), 29.6 (t), 32.8 (t), 64.2 (t), 70.8 (t), 87.9 (s), 113.7 (d), 123.5 (d), 125.6 (d), 128.6 (d), 130.3 (d), 130.5 (d), 135.0 (s), 135.6 (d), 136.5 (d), 140.5 (d), 158.3 (s); MS (CI) *m*/*z* 574 [$(M + NH_4)^+$, 40]; HRMS for $C_{28}H_{33}IO_2Si$ calcd $(M + NH_4)^+$, 574.1638, found $(M + NH_4)^+$ (CI), 574.1629.

2-[(6-Hydroxy)hex-2-enyloxy]iodobenzene, 13. To a solution of **12** (1.47 g, 2.65 mmol, 1.0 equiv) in dry THF (50 mL) under nitrogen was added TBAF (1M solution in THF, 5.3 mL, 5.3 mmol, 2.0 equiv) and the mixture stirred for 3 h. THF was then removed in vacuo and the oily residue partitioned between water and DCM. The aqueous layer was extracted with further portions of DCM, and the combined organic extracts were washed with water, dried over magnesium sulfate, filtered, and evaporated to dryness. The residue was purified by column chromatography on silica gel eluted with 70% petroleum ether/30% EtOAc to give **13** as a yellow oil (814 mg, 2.5 mmol, 94%); R_f 0.25 (petroleum ether/EtOAc = 4:1); IR (neat) 3351 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.56 (1H, br s), 1.68 (2H, tt, *J* 7.6, 6.3 Hz), 2.19 (2H, dt, *J* 6.7, 7.4 Hz), 3.66 (2H, t, *J* 6.3 Hz), 4.54 (2H, d, *J* 5.5 Hz), 5.74 (1H, dtt, *J* 15.5, 5.5, 1.2 Hz), 5.90 (1H, dt, *J* 15.5, 6.7 Hz), 6.69 (1H, ddd, *J* 7.8, 7.3, 1.2 Hz), 6.80 (1H, dd, *J* 8.3, 1.2 Hz), 7.26 (1H, ddd, *J* 8.3, 7.3, 1.6 Hz), 7.76 (1H, dd, *J* 7.8, 1.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.6 (t), 31.8 (t), 62.2 (t), 69.7 (t), 86.9 (s), 112.8 (d), 122.6 (d), 124.9 (d), 129.3 (d), 134.3 (d), 139.5 (d), 157.2 (s); MS (CI) *m*/*z*: 318 (M^+, 5); HRMS for $C_{12}H_{15}IO_2$ calcd M^+, 318.0117; found M^+ (CI), 318.0128.

2-[(6-Methanesulfonyloxy)hex-2-enyloxy]iodobenzene, 14. To a solution of **13** (2.35 g, 7.4 mmol, 1.0 equiv), DMAP (90 mg, 0.74 mmol, 0.1 equiv), and triethylamine (900 mg, 1.23 mL, 8.89 mmol, 1.2 equiv) in DCM (100 mL) under nitrogen at 0 °C was added methanesulfonyl chloride (930 mg, 0.63 mL, 8.15 mmol, 1.1 equiv) dropwise over 10 min. After a further 2 h stirring at 0 °C, the mixture was warmed to room temperature and stirred for a further 3 h. The reaction mixture was washed with aqueous HCl (0.5 M), and the aqueous phase was then extracted with DCM. The combined organic phases were washed with aqueous sodium hydrogen carbonate solution (saturated), dried over magnesium sulfate, filtered, evaporated to dryness, and purified by column chromatography on silica gel eluted with 70% petroleum ether/30% EtOAc to give **14** as a yellow oil (1.82 g, 6.76 mmol, 91%); R_f 0.53 (petroleum ether/EtOAc = 7:3); IR (neat) 1351(SO_2^-), 1173 (SO_2^-) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.88 (2H, tt, *J* 6.9, 6.4 Hz), 2.24 (2H, tdd, *J* 7.0, 7.0, 0.8 Hz), 2.99 (3H, s), 4.23 (2H, t, *J* 6.4 Hz), 4.54 (2H, dd, *J* 5.2, 0.9 Hz), 5.73−5.79 (1H, m), 5.84−5.91 (1H, m), 6.71 (1H, ddd, *J* 7.8, 7.3, 1.3 Hz), 6.80 (1H, dd, *J* 8.3, 1.3 Hz), 7.27 (1H, m), 7.77 (1H, dd, *J* 7.8, 1.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.1 (t), 28.3 (t), 37.2 (q), 69.1 (t), 69.3 (t), 86.7 (s), 112.7 (d), 122.7 (d), 126.0 (d), 129.3 (d), 132.5 (d), 139.4 (d), 157.1 (s); MS (FAB) *m*/*z* 396 (M^+, 6); HRMS for $C_{13}H_{17}IO_4S$ calcd M^+, 395.9892; found M^+ (FAB), 395.9908.

2-[(6-Azido)hex-2-enyloxy]iodobenzene, 15. 2-[(6-Methanesulfonyloxy)hex-2-enyloxy]iodobenzene **14** (760 mg, 2.82 mmol, 1.0 equiv) and sodium azide (368 mg, 5.65 mmol, 2.0 equiv) were dissolved in DMF (15 mL) and heated at 60 °C under nitrogen, for 5 h. The reaction mixture was then poured into water and extracted into diethyl ether. The combined organic extracts were then washed with water, dried over magnesium sulfate, filtered, evaporated to dryness, and purified by column chromatography on silica gel eluted with 90% petrol/10% EtOAc to give **15** as a yellow oil (400 mg, 1.16 mmol, 42%); R_f 0.63 (petroleum ether/EtOAc = 4:1); IR (neat) 2096, 1678 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.69 (2H, tt, *J* 7.3, 6.8 Hz), 2.21 (2H, td, *J* 7.3, 6.7 Hz), 3.28 (2H, t, *J* 6.8 Hz), 4.54 (2H, d, *J* 5.4 Hz), 5.75 (1H, dt, *J* 15.5, 5.4 Hz), 5.88 (1H, dt, *J* 15.5, 6.7 Hz), 6.72 (1H, dd, *J* 7.8, 7.3 Hz), 6.81 (1H, d, *J* 8.2 Hz), 7.26 (1H, ddd, *J* 8.2, 7.3, 1.6 Hz), 7.78 (1H, d, *J* 7.8 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 28.1 (t), 29.2 (t), 50.6 (t), 69.4 (t), 86.6 (s), 112.7 (d), 122.7 (d), 125.7 (d), 129.3 (d), 133.0 (d), 139.5 (d), 157.2 (s); MS (EI) *m*/*z* 343 (M^+, 100); HRMS for $C_{12}H_{14}IN_3O$ calcd M^+, 343.0181; found M^+ (CI), 343.0178. Further elution of the column gave 2-iodophenol (127 mg, 0.57 mmol, 20%), identical to an authentic sample.

Reaction of 2-[(6-Azido)hex-2-enyloxy]iodobenzene 15 with Tristrimethylsilylsilane/AIBN in Benzene. To a stirred solution of **15** (127 mg, 0.37 mmol, 1.0 equiv) in refluxing dry degassed benzene (10 mL) were added tris-(trimethylsilyl)silane (92 mg, 120 μL, 0.37 mmol, 1.0 equiv) and AIBN (10 mg, 0.037 mmol, 0.1 equiv) under nitrogen. The mixture was refluxed for 5 h and evaporated to dryness. The mixture then dissolved in EtOAc and extracted with aqueous HCl (2 M). The aqueous layer was basified with NaOH (2 M) and then the aqueous layer extracted with EtOAc, dried over magnesium sulfate, filtered, evaporated to dryness, and purified by column chromatography on silica gel eluting with 80% DCM/20% MeOH to give 2-(2,3-dihydrobenzofuran-3-yl)pyrrolidine (**16**) as a clear yellow oil (30 mg, 0.15 mmol, 43%), which was a 2:1 mixture of diastereoisomers: R_f 0.35 (DCM/MeOH = 4:1); IR ($CHCl_3$) 3206 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38−1.49 (1H, m), 1.66−1.99 (3H, m), 2.13 (1H, br s), 2.81−3.03 (2H, m), 3.24 (1H, m), 3.43 (1H, m), 4.35−4.38 and 4.49−4.62 (2H, 2 × m), 6.77−6.86 (2H, m), 7.18 (1H, dd, *J* 7.7, 7.7 Hz), 7.25 and 7.30 (1H, 2 × d, *J* 7.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 24.9 (t), 25.7 (t), 28.8 (t), 29.7 (t), 46.5 (t), 46.6 (t), 47.3 (d), 47.4 (d), 62.0 (d), 62.3 (d), 74.1 (t), 74.5 (t), 109.6 (d), 109.6 (d), 119.8 (d), 120.1 (d), 120.2 (d), 124.8 (d), 125.1 (d), 128.4 (d), 128.7 (s), 129.3 (s), 160.2 (s), 160.5 (s);

MS (FAB) *m/z* 190 [$(M + H)^+$, 17]; HRMS for $C_{12}H_{15}NO$ calcd $(M + H)^+$, 190.1232; found $(M + H)^+$ (FAB), 190.1231.

2-(2,3-Dihydrobenzofuran-3-yl)-*N*-(4-methylbenzenesulfonyl) pyrrolidine, 17. To a stirred solution of **15** (130 mg, 0.38 mmol, 1.0 equiv) in refluxing dry degassed benzene (10 mL) were added tris(trimethylsilyl)silane (95 mg, 123 μL, 0.38 mmol, 1.0 equiv) and AIBN (11 mg, 0.038 mmol, 0.1 equiv) under nitrogen. The mixture was refluxed for 5 h and evaporated to dryness. To a solution of crude product (as obtained above) in pyridine (15 mL) were added 4-(dimethylamino)pyridine (6 mg, 0.03 mmol, 0.1 equiv) and *p*-toluenesulfonyl chloride (73 mg, 0.38 mmol, 1.0 equiv). The resulting mixture was heated to reflux (110 °C) for 16 h. The mixture was warmed to room temperature, and the whole mixture was taken into aqueous HCl (2 M) and extracted with DCM. The organic extract was dried over magnesium sulfate, filtered, evaporated to dryness, and purified by column chromatography on silica gel eluted with 90% petrol/10% EtOAc to give **17** as a colorless oil and a mixture of diastereoisomers [85 mg, 0.24 mmol, 65% (for two steps)]. Crystallization from 20% diethyl ether/80% petroleum ether afforded a pure single isomer; mp 126−127 °C; data quoted below for single isomer: R_f 0.63 (petroleum ether/EtOAc = 4:1);. IR ($CHCl_3$) 1349 (SO_2^-), 1157 (SO_2^-) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.10−1.28 (2H, m), 1.53−1.65 (2H, m), 2.45 (3H, s), 3.15−3.27 (2H, m), 3.82 (1H, ddd, *J* 7.7, 5.2, 5.2 Hz), 4.08 (1H, m), 4.39 (1H, dd, *J* 9.4, 3.4 Hz), 4.58 (1H, dd, *J* 9.4, 9.4 Hz), 6.76 (1H, d, *J* 8 Hz), 6.86 (1H, ddd, *J* 7.4, 7.4, 0.7 Hz), 7.17 (1H, ddd, *J* 8.0, 7.4, 0.7 Hz), 7.35 (2H, d, *J* 8 Hz), 7.43 (1H, d, *J* 7.4 Hz), 7.76 (2H, d, *J* 8.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 21.5 (q), 24.2 (t), 26.9 (t), 46.0 (d), 49.7 (t), 62.9 (d), 74.3 (t), 109.4 (d), 120.6 (d), 126.7 (d), 126.7 (s), 127.6 (d), 128.9 (d), 129.8 (d), 134.4 (s), 143.6 (s), 160.9 (s); MS (FAB) *m/z* 344 [$(M + H)^+$, 6]; HRMS for $C_{19}H_{21}NO_3S$ Calcd $(M + H)^+$, 344.1320; found $(M + H)^+$, 344.1373.

***N*-(2-Iodophenyl)methanesulfonamide, 18.** Methanesulfonyl chloride (14.50 g, 9.8 mL, 126 mmol, 1.2 equiv), 2-iodoaniline (23 g, 105 mmol, 1.0 equiv), and DMAP (1.30 g, 10.5 mmol, 0.1 equiv) were dissolved in pyridine (75 mL), and the resulting mixture was heated under reflux for 12 h. The cooled reaction mixture was diluted with DCM and washed with aqueous HCl (2 M) and aqueous sodium hydroxide (2 M). The combined aqueous extracts were acidified with concentrated hydrocloric acid and then extracted with DCM. The combined organic extracts were dried over magnesium sulfate, filtered, and evaporated to dryness to give **18** as a yellow crystalline solid (20 g, 70.9 mmol, 68%); mp 96−98 °C (diethyl ether); R_f 0.66 (petroleum ether/EtOAc = 1:1); IR (KBr) 3329, 1343 (SO_2^-), 1151 (SO_2^-) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.02 (3H, s), 6.64 (1H, br), 6.95 (1H, ddd, *J* 8.0, 8.0, 1.5 Hz), 7.37 (1H, ddd, *J* 8.0, 8.0, 1.3 Hz), 7.65 (1H, dd, *J* 8.0, 1.5 Hz), 7.82 (1H, dd, *J* 8.0, 1.4 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 40.0 (q), 92.1 (s), 122.4 (d), 127.2 (d), 129.7 (d), 137.4 (s), 139.3 (d); MS (EI) *m/z* 297 (M^+, 40); HRMS for $C_7H_8INO_2S$ calcd M^+, 296.9320; found M^+ (EI), 296.9314.

***N*-(2-Allyl-2-cyclohexen-1-yl)-*N*-(2-iodophenyl)methanesulfonamide, 20.** *N*-(2-Iodophenyl)methanesulfonamide (**18**) (5.43 g, 19.2 mmol, 1.0 equiv) and triphenylphosphine (7.55 g, 28.8 mmol, 1.5 equiv) were dissolved in dry THF (100 mL). 2-(Prop-2′-enyl)-cyclohex-2-en-1-ol (**19**) (3.98 g, 28.8 mmol, 1.5 equiv) was added[15] and the mixture cooled to 0 °C. Diethyl azodicarboxylate (5.01 g, 4.53 mL, 28.8 mmol, 1.5 equiv) was added dropwise over a 15 min period. After 2 h the mixture was evaporated to dryness, dissolved in DCM (100 mL), and washed with NaOH, aqueous sodium carbonate (saturated), and water. The solution was dried over sodium sulfate, followed by filtration and removal of the solvent under reduced pressure to give a yellow solid. This was purified by column chromatography on silica gel eluted with 80% petrol/20% EtOAc to give **20** as a colorless solid that was a 4:1 mixture of rotamers (5.34 g, 12.8 mmol, 67%); R_f 0.38 (petroleum ether/ethyl acetate = 4:1); mp 90−91 °C (diethyl ether/petroleum ether); IR (KBr) 1334 (SO_2^-), 1150 (SO_2^-) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.72−0.83 and 1.07−1.19 (1H, m), 1.30−1.43 (1H, m), 1.73−2.13 (3H, m), 2.21−2.72 (1H, m), 3.07 (2H, m), 3.06 and 3.25 (3H, 2 × s), 4.68 (1H, m), 5.12−5.27 (2H, m), 5.72 and 5.84 (1H, 2 × m), 5.90−6.05 (1H, m), 7.05−7.20 (1H, ddd, *J* 7.9, 7.9, 1.5 Hz), 7.26 (1H, dd, *J* 7.9, 1.5 Hz), 7.39 (1H, ddd, *J* 7.9, 7.9, 1.5 Hz), 8.03 (1H, dd, *J* 7.9, 1.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.8 (t), 18.0 (t), 24.6 (t), 24.8 (t), 28.4 (t), 30.0 (t), 39.0 (t), 40.6 (t), 41.0 (q), 42.3 (q), 56.5 (d), 57.6 (d), 102.8 (s), 104.7 (s), 116.1 (t), 116.3 (t), 128.7 (d), 129.0 (d), 129.9 (d), 130.1 (d), 131.4 (d), 133.0 (s), 133.8 (d), 134.2 (d), 134.8 (s), 136.5 (d), 136.9 (d), 140.4 (s), 140.8 (d), 141.2 (s), 141.3 (d); MS (FAB) *m/z* 418 [$(M + H)^+$, 3]; HRMS for $C_{16}H_{20}INO_2S$ calcd $(M + H)^+$, 418.0338; found $(M + H)^+$ (FAB), 418.0326.

Variable temperature studies were performed on this compound: ^1H NMR [400 MHz, $(CD_3)_2SO$ at 25 °C] δ 0.38 and 0.92−0.97 (1H, m), 1.17−1.19 and 1.34−1.37 (1H, m), 1.60−1.80 (3H, m), 2.21−2.32 and 2.50−2.54 (1H, 2 × m*****), 3.05−3.20 (2H, m), 3.15 and 3.35 (3H, 2 × s), 4.41 and 4.50 (1H, 2 × m*****), 5.01−5.21 (2H, m), 5.56 and 5.65 (1H, 2 × m*****), 5.84−5.95 (1H, m), 7.04−7.14 and 7.68−7.72 (2H, 2 × m), 7.34−7.45 (1H, m), 7.95−7.97 (1H, m); on heating to 100 °C, essentially complete coalescence was observed for the multiplet pairs marked "*****"; partial coalescence was observed in other regions of the spectrum. On recooling to 25 °C, the spectrum returned to its previous appearance at that temperature.

***N*-[2-(2,3-Dihydroxypropyl)-2-cyclohexen-1-yl]-*N*-(2-iodophenyl)methanesulfonamide, 21.** To a stirred solution of **20** (24.60 g, 59.0 mmol, 1.0 equiv) in acetone/water (1000 mL, 9:1) was added a solution of osmium tetroxide (20 mL of a 10 mg/mL solution in *tert*-butyl alcohol, 200 mg, 0.78 mmol, 1.3 mol %) followed by *N*-methylmorpholine *N*-oxide (8.27 g, 71.9 mmol, 1.2 equiv), and the mixture was stirred for 16 h. Sodium bisulfite solution (15 g in 50 mL) was then added, the mixture was stirred for 1 h and filtered through Celite, and the filtrate was evaporated to remove acetone before extracting with DCM. The organic phase was washed with HCl (2 M) and water, dried over magnesium sulfate, evaporated to dryness, and purified by column chromatography on silica gel eluted with 90% DCM/10% MeOH to give **21** as a colorless solid, formed as a mixture of diastereoisomers and rotamers (22.89 g, 50.75 mmol, 86%); R_f 0.24 (DCM/MeOH = 4:1); mp 125−129 °C; IR ($CHCl_3$) 3543 (O−H), 1322 (SO_2^-), 1143 (SO_2^-) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.50−0.52 and 1.01−1.03 (1H, m), 1.20−1.29 and 1.39−1.44 (1H, m), 1.70−2.01 (3H, m), 2.11−2.54 (2H, m), 2.63−2.88 (2H, m), 2.92−3.23 (1H, m), 3.04, 3.07, 3.32 and 3.36 (3H, 4 × s), 3.50−3.94 (3H, m), 4.67 and 4.80 (1H, 2 × br m), 5.80 and 5.85 (1H, 2 × br m), 7.00−7.61 (3H, m), 7.94 (1H, d, *J* 7.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.6 (t), 17.7 (t), 18.0 (t), 18.1 (t), 24.7 (t), 24.8 (t), 24.9 (t), 25.0 (t), 28.3 (t), 28.4 (t), 29.9 (t), 30.0 (t), 38.7 (t), 38.8 (t), 40.8 (t), 40.8 (t), 40.5 (q), 40.6 (q), 42.7 (q), 54.9 (d), 56.1 (d), 57.3 (d), 58.4 (d), 66.5 (t), 66.6 (t), 66.7 (t), 66.8 (t), 70.5 (d), 70.6 (d), 73.1 (d), 73.5 (d), 103.3 (s), 103.4 (s), 104.5 (s), 104.6 (s), 128.9 (d), 128.9 (d),130.2 (d), 130.2 (d), 130.5 (d), 131.1(s), 131.2 (d), 132.1 (d), 132.3 (s), 132.7 (s), 133.5 (d), 133.6 (d), 133.7 (s), 134.0 (d), 134.4 (d), 134.7 (d), 140.0 (s), 140.1 (s), 140.8 (s), 140.8 (s), 140.9 (d), 141.0 (d), 141.6 (d), 141.7 (d); MS (CI) *m/z* 469 [$(M + NH_4)^+$, 10]; HRMS for $C_{16}H_{22}INO_4S$ calcd M^+, 451.0314; found M^+ (EI), 451.0310. Anal. Calcd for $C_{16}H_{22}INO_4S$: C, 42.58; H, 4.91; N, 3.10; S, 7.1. Found: C, 42.47; H, 4.94; N, 3.36; S, 7.1.

***N*-(2-Iodophenyl)-*N*-[2-(oxoethyl)cyclohex-2-enyl] methanesulfonamide, 22.** To a stirred solution of **21** (20 g, 44 mmol, 1.0 equiv) in diethyl ether (500 mL) and ethanol (50 mL) was added sodium periodate (11.76 g, 55 mmol, 1.25 equiv) followed by water (60 mL). The resulting mixture was stirred for 5 h under nitrogen atmosphere. The mixture was then diluted with EtOAc (250 mL) and washed with water. The aqueous phase was then extracted with EtOAc, and the combined organic extracts were washed with water, dried over magnesium sulfate, filtered, evaporated to dryness, and puri-

(15) (a) Hong, C. H.; Kado, N.; Overman, L. E. *J. Am. Chem. Soc.* **1993**, *115*, 11028. (b) Taber, D. F. *J. Org. Chem.* **1976**, *41*, 2649. (c) Taber, D. F.; Gunn, B. P.; Chiu, I.-C. *Organic Syntheses*; Wiley: New York, 1990; Collect. Vol. VII, p 249.

fied by column chromatography on silica gel eluted with 50% petroleum ether/50% EtOAc to give **22** as a yellow oil, formed as a mixture of rotamers (17.70 g, 42.24 mmol, 96%); R_f 0.49 (petroleum ether/ethyl acetate = 1:1); IR (neat) 2724, 1720, 1330, 1149 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 0.56 and 1.03 (1H, m), 1.15−1.46 (1H, m), 1.70−2.45 (4H, m), 3.00 and 3.25 (3H, 2 × s), 3.18 (1H, m), 3.93 (d, *J* 17.3 Hz), and 4.08 (1H, br m), 4.55 and 4.60 (1H, 2 × br s), 5.72 and 5.75 (1H, 2 × br s), 7.04 (1H, m), 7.12−7.53 (2H, m), 7.93 (1H, br d, *J* 7.9 Hz), 9.75 (1H, br s); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 18.0 (t), 18.1 (t), 24.6 (t), 24.9 (t), 27.9 (t), 29.1 (t), 40.1 (q), 42.5 (q), 49.3 (t), 51.1 (t), 57.2 (d), 58.4 (d), 103.2 (s), 104.8 (s), 127.6 (s), 128.9 (d), 130.2 (d), 130.4 (d), 133.0 (d), 133.4 (d), 134.2 (d), 135.3 (d), 140.0 (s), 140.9 (d), 141.5 (d), 200.1 (d), 201.3 (d); MS (CI) *m*/*z* 437 $(M + NH_4)^+$ 100]; HRMS for $C_{15}H_{18}INO_3S$ calcd M^+, 419.0052; found M^+ (CI), 419.0072.

***N*-[2-(2-Hydroxyethyl)-2-cyclohexen-1-yl]-*N*-(2-iodophenyl)methanesulfonamide, 23.** To a stirred solution of **22** (17.7 g, 39.2 mmol, 1.0 equiv) in MeOH (50 mL) was added $NaBH_4$ (1.48 g, 39.2 mmol, 1.0 equiv) and the mixture stirred for 5 min. Water (50 mL) was added and the mixture evaporated to remove MeOH before extracting with DCM. The organic phase was washed with water, dried over magnesium sulfate, evaporated to dryness, and purified by column chromatography on silica gel eluted with diethyl ether to give **23** as a colorless solid that was a mixture of rotamers (15.29 g, 36.3 mmol, 86%); R_f 0.33 (diethyl ether); mp 105−106 °C (EtOAc/petroleum ether); IR ($CHCl_3$) 3549, 1322, 1145 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.60 and 1.06 (1H, 2 × m), 1.25−1.46 (1H, m), 1.72−1.92 (3H, m), 2.00−2.08 (1H, m), 2.15−2.52 (2H, m), 2.83−2.99 (1H, m), 3.04, 3.31 (3H, 2 × s), 3.72−3.80 (2H, m), 4.71 (1H, m), 5.71 and 5.81 (1H, 2 × m), 7.01 (1H, ddd, *J* 7.9, 7.9, 1.5 Hz), 7.21 (1H, dd, *J* 8.0, 1.5 Hz), 7.32 (1H, ddd, *J* 8.0, 8.0, 1.3 Hz), 7.95 (1H, dd, *J* 7.9, 1.3 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.3 (t), 18.5 (t), 25.0 (t), 25.2 (t), 28.8 (t), 30.2 (t), 38.3 (t), 40.1 (t), 41.2 (q), 43.0 (q), 56.3 (d), 58.3 (d), 62.5 (t), 62.8 (t), 103.3 (s), 104.7 (s), 129.2 (d), 129.2 (d), 130.5 (d), 130.7 (d), 130.8 (d), 132.6 (s), 133.0 (d), 134.1 (d), 134.9 (d), 140.5 (s), 141.3 (d), 141.4 (s), 141.9 (d); MS (FAB) *m*/*z* 422 $[(M + H)^+$, 6]; HRMS for $C_{15}H_{20}INO_3S$ calcd 439.0552 $(M + NH_4)^+$; found $(M + NH_4)^+$ (CI), 439.0538.

2-{6-[2-Iodo(methylsulfonyl)anilino]-1-cyclohexen-1-yl} ethylmethanesulfonate, 24. To a stirred solution of **23** (15 g, 35.55 mmol, 1.0 equiv) and DMAP (475 mg, 3.56 mmol, 0.1 equiv) in DCM (400 mL) was added triethylamine (4.32 g, 5.90 mL, 42.52 mmol, 1.2 equiv) under nitrogen at 0 °C. Methanesulfonyl chloride (4.48 g, 3.07 mL, 39 mmol, 1.1 equiv) was added dropwise over 10 min. After a further 2 h stirring at 0 °C, the mixture was warmed to room temperature and stirred for a further 3 h. The reaction mixture was washed with aqueous HCl (0.5 M), and the aqueous phase was then extracted with DCM. The combined organic phases were washed with aqueous sodium hydrogen carbonate solution (saturated) and dried over magnesium sulfate, filtered, evaporated to dryness, and purified by column chromatography on silica gel eluted with 60% EtOAc/40% petrol to give **24** as a colorless crystalline solid, formed as a mixture of rotamers (16.4 g, 33.0 mmol, 93%); R_f 0.28 (petroleum ether/EtOAc = 1:1); mp 103−104 °C (decomp); IR ($CHCl_3$) 1354 (SO_2^-), 1324 (SO_2^-), 1146 (SO_2^-) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.51 and 1.01 (1H, 2 × m), 1.25 and 1.38−1.42 (1H, 2 × m), 1.77−1.94 (3H, m), 2.09−2.15 and 2.43−2.50 (1H, 2 × m), 2.57−2.74 (1H, 2 × m), 2.90−3.21 (1H, m), 3.02 (3H, s), 3.01 and 3.31 (3H, 2 × s), 4.39 (2H, m), 4.63 (1H, m), 5.76 and 5.85 (1H, 2 × m), 7.04 (1H, ddd, *J* 8.0, 8.0, 1.6 Hz), 7.16 (1H, dd, *J* 8.0, 1.6 Hz), 7.33 (1H, ddd, *J* 8.0, 8.0, 1.5 Hz), 7.96 (1H, dd, *J* 8.0, 1.6 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.9 (t), 18.4 (t), 25.0 (t), 25.3 (t), 28.5 (t), 30.0 (t), 34.9 (t), 36.7 (t), 37.9 (q), 38.0 (q), 40.6 (q), 43.3 (q), 54.9 (d), 57.5 (d), 69.7 (t), 69.8 (t), 103.8 (s), 104.5 (s), 129.3 (d), 130.0 (s), 130.7 (d), 130.9 (d), 131.5 (s), 132.7 (d), 133.6 (d), 134.9 (d), 135.0 (d), 140.3 (s), 141.0 (s), 141.3 (d), 142.0 (d); MS (FAB) *m*/*z* 422 $[(M - SO_2Me)^+$, 6]; HRMS for $C_{16}H_{22}INO_5S_2$ calcd $(M + NH_4)^+$, 517.0328; found $(M + NH_4)^+$ (CI), 517.0321. Anal. Calcd for $C_{16}H_{22}INO_5S_2$: C, 38.48; H, 4.44; N, 2.80; S, 12.84; I, 25.24. Found: C, 38.48; H, 4.53; N, 2.80; S, 12.51; I, 25.40.

***N*-(2-[2-Azidoethyl]cyclohex-2-enyl)-*N*-(2-iodophenyl)-methanesulfonamide, 25.** 2-{6-[2-Iodo(methylsulfonyl)anilino]-1-cyclohexen-1-yl} ethylmethanesulfonate (**24**) (15.45 g, 30.90 mmol, 1.0 equiv) and sodium azide (4.03 g, 61.5 mmol, 2.0 equiv) were dissolved in DMF (300 mL) and heated at 60 °C under nitrogen, for 5 h. The reaction mixture was concentrated by distilling off DMF (250 mL) under reduced pressure, diluted with diethyl ether (200 mL), and then washed with water and extracted into diethyl ether. The combined organic extracts were then washed with water, dried over magnesium sulfate, filtered, evaporated to dryness, and purified by column chromatography on silica gel eluted with 80% petroleum ether/20% EtOAc to give **25** as a white solid that was a mixture of rotamers (13.2 g, 29.59 mmol, 96%); R_f 0.32 (petroleum ether/EtOAc = 4:1); mp 92−93 °C; IR ($CHCl_3$) 2099, 1323 (SO_2^-), 1146 (SO_2^-) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.56 and 1.04 (1H, m), 1.26−1.48 (1H, m), 1.73−2.00 (3H, m), 2.13−2.58 (2H, m), 2.93 (1H, m), 3.03 and 3.29 (3H, 2 × s), 3.32−3.52 (2H, m), 4.64 (1H, br m), 5.74 and 5.84 (1H, 2 × m), 7.04 (1H, ddd, *J* 7.9, 7.9, 1.5 Hz), 7.17 (1H, dd, *J* 7.9, 1.5 Hz), 7.33 (1H, ddd, *J* 7.9, 7.9, 1.5 Hz), 7.95 (1H, dd, *J* 7.9, 1.5 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 18.1 (t), 18.4 (t), 25.1 (t), 25.3 (t), 28.6 (t), 30.1 (t), 34.9 (t), 36.6 (t), 40.9 (q), 43.2 (q), 50.7 (t), 50.9 (t), 55.2 (d), 57.4 (d), 103.5 (s), 104.6 (s), 129.2 (d), 130.6 (d), 130.8 (d), 131.6 (s), 131.7 (d), 133.2 (s), 133.9 (d), 134.0 (d), 135.0 (d), 140.4 (s), 141.1 (s), 141.3 (d), 141.9 (d); MS (CI) *m*/*z* 464 $[(M + NH_4)^+$, 20]; HRMS for $C_{15}H_{19}IN_4O_2S$ calcd $(M + NH_4)$, 464.0617; found $(M + NH_4)^+$ (CI), 464.0616. Anal. Calcd for $C_{15}H_{19}IN_4O_2S$: C, 40.37; H, 4.29; N, 12.55. Found: C, 40.75; H, 4.45; N, 12.32.

Reaction of *N*-(2-[2-Azidoethyl]cyclohex-2-enyl)-*N*-(2-iodophenyl)methanesulfonamide (25) with $(TMS)_3SiH$/AIBN in Benzene. To a stirred solution of **25** (576 mg, 1.28 mmol, 1.0 equiv) in refluxing dry degassed benzene (25 mL) were added tris(trimethylsilyl)silane (320 mg, 480 μL, 1.28 mmol, 1.0 equiv) and AIBN (24 mg, 0.128 mmol, 0.1 equiv) under nitrogen. The mixture was refluxed for 6 h and evaporated to dryness. The mixture was then dissolved in EtOAc (100 mL) and extracted with aqueous HCl (2 M). The aqueous layer was basified with sodium hydroxide (2 M) and then the aqueous layer extracted with EtOAc, dried over magnesium sulfate, filtered, and evaporated to dryness to give (±)-(3a*S**,6a*S**,11b*R**)-7-methanesulfonyl-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3,d]carbazole (**27**) as a colorless solid (310 mg, 1.06 mmol, 83%); mp 119−120 °C (diethyl ether/petroleum ether); R_f 0.21 (DCM/MeOH = 4:1); IR ($CHCl_3$) 3305, 1352, 1158 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.25−2.25 (9H, m), 3.02 (3H, s), 3.15−3.18 (2H, m), 3.70 (1H, br s), 4.13 (1H, dd, *J* 10.8, 5.4 Hz), 7.06 (1H, dd, *J* 7.6, 7.3 Hz), 7.17 (1H, d, *J* 7.3 Hz), 7.22 (1H, dd, *J* 7.9, 7.6 Hz), 7.33 (1H, d, *J* 7.9 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.1 (t), 27.0 (t), 29.9 (t), 39.6 (q), 42.7 (t), 44.8 (t), 53.1 (s), 59.2 (d), 68.7 (d), 114.3 (d), 123.0 (d), 124.3 (d), 128.8 (d), 136.6 (s), 140.9 (s); MS (EI) *m*/*z* 292 $(M^+$, 8); HRMS for $C_{15}H_{20}N_2O_2S$ calcd M^+, 292.1246; found M^+ (EI), 292.1250.

(±)-(3a*S,6a*S**,11b*S**)-3-Toluenesulfonyl-7-methanesulfonyl-2,3,3a,4,5,6,6a,7-octahydro-1*H*-pyrrolo[2,3,d]-carbazole, 28.** To a stirred solution of **30** (52 mg, 0.17 mmol, 1.0 equiv) and DMAP (3 mg, 0.017 mmol, 0.1 equiv) in pyridine (10 mL) under nitrogen was added *p*-toluenesulfonyl chloride (41 mg, 0.21 mmol, 1.2 equiv). The resulting mixture was heated to reflux (110 °C) for 16 h. The mixture was brought to room temperature, and the whole mixture was poured into aqueous HCl (2 M, 50 mL) and extracted with DCM. The organic extracts were dried (sodium sulfate), filtered, evaporated, and purified by column chromatography on silica gel eluted with 50% petroleum ether/50% EtOAc to give **28** as a white crystalline solid (60 mg, 0.13 mmol, 75%); R_f 0.42 (petroleum ether/EtOAc = 1:1); mp 185−186 °C (EtOAc/petrol); IR ($CHCl_3$) 1350, 1159, 1102 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20−1.28 (1H, m), 1.33−1.43 (1H, m), 1.51−1.64 (3H, m), 1.89−1.94 (1H, m), 2.14−2.18 (1H, m), 2.26−2.29 (1H, m), 2.46 (3H, s), 2.99 (3H, s), 3.48−3.53 (1H, m), 3.62−3.68 (1H, m),

3.94−3.95 (1H, br m), 4.05−4.10 (1H, dd, *J* 11.0, 6.0 Hz), 6.64 (1H, d, *J* 7.5 Hz), 6.89 (1H, ddd, *J* 7.5, 7.5, 1.0 Hz), 7.20 (1H, ddd, *J* 8.0, 7.5, 1.0 Hz), 7.25−7.28 (1H, d, *J* 8.0 Hz), 7.37 (2H, d, *J* 8.0 Hz), 7.79 (2H, d, *J* 8.0 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 17.0 (t), 22.1 (q), 27.9 (t), 28.8 (t), 38.6 (t), 40.0 (q), 47.9 (t), 54.1 (s), 61.7 (d), 67.8 (d), 114.4 (d), 122.9 (d), 124.2 (d), 127.9 (d), 129.5 (d), 130.4 (d), 134.0 (s), 135.3 (s), 140.5 (s), 144.4 (s); MS (EI) *m*/*z* 446 (M^+, 63); HRMS for $C_{22}H_{26}N_2O_4S_2$ calcd M^+, 446.1334; found M^+ (EI), 446.1321. Anal. Calcd for $C_{22}H_{26}N_2O_4S_2$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.38; H, 5.96; N, 6.61.

X-ray Crystallographic data for **28** are available in the Supporting Information.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of compounds **7**−**10**, **12**−**18**, **20**−**25**, **27**, and **28**; ^{1}H−^{1}H COSY spectrum of **17**; and X-ray structural data for **28**. This material is available free of charge via the Internet at http://pubs.acs.org.

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