JOC The Journal of Organic Chemistry

Note

The Titanium-Mediated Double Reductive Cleavage of Cyclic Sulfonamides for the Synthesis of Aryl Pyrrolidines

Aisha Khalifa, and Paul Evans

J. Org. Chem., **Just Accepted Manuscript** • DOI: 10.1021/acs.joc.8b02827 • Publication Date (Web): 25 Jan 2019

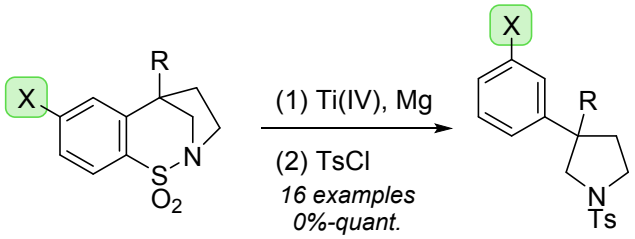
ACS Publications

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

The Titanium-Mediated Double Reductive Cleavage of Cyclic Sulfonamides for the Synthesis of Aryl Pyrrolidines

Aisha Khalifa and Paul Evans*

School of Chemistry, Centre for Synthesis and Chemical Biology, University College Dublin, Dublin D04, N2E5, Ireland. Email: paul.evans@ucd.ie; ORCID: 0000-0002-0584-876X

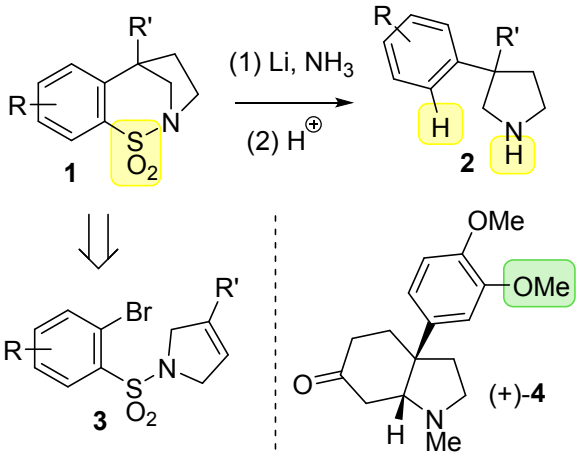


Abstract-Reduction of a range of benzo-fused cyclic sulfonamides has been accomplished using low-valent titanium. This operationally simple method generates the corresponding aryl substituted cyclic amines, typically, with good conversion. Notably, unlike our previous Li-NH_3-based method, loss of heteroatom-based substituents (X) on the aromatic ring does not readily occur and the robustness of this method was demonstrated with a synthesis of the *Sceletium* alkaloid mesembrane.

Keywords-sulfonamide, sultam, aryl amine, reduction, low-valent titanium

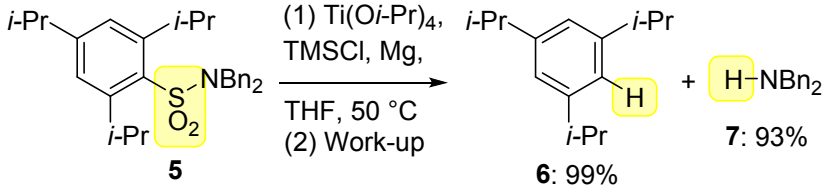
Introduction

The sulfonamide represents a useful functional group. It is an integral part of several pharmaceuticals and is used in the design of biologically active compounds more generally. It also occupies a niche in synthetic organic chemistry as a chemically robust nitrogen protecting group.[1] In this context the fate of the sulfonyl portion of the protecting group has, typically, been ignored, since the amino group represents the portion of interest. However, several years ago our group speculated that, if a cyclic sulfonamide of the type **1** was employed, a double reductive excision of the sulfonyl group might produce an aryl amine of the type **2** (see Scheme 1).[2] Compounds of type **1** can be formed from RCM derived dihydropyrroles **3**, *via* a reductive intramolecular Heck reaction sequence.[3] Furthermore, where applicable (R' ≠ H), we have shown that this carbon-carbon bond forming process favours generation of the more sterically encumbered quaternary product.[3,4] Overall, we felt that the sequence **3** → **2**, featuring a traceless *N*-protecting group which facilitates the formation of an sp^2-sp^3 carbon-carbon bond (that may be quaternary), constitutes an efficient and attractive means for the construction of aryl amines (**2**).



Scheme 1. The "double" reduction of cyclic sulfonamides (**1**) to access aryl pyrrolidines (**2**).

Apart from the novel sulfonyl excision aryl amines themselves are also of interest. They are a motif present in a variety of natural products and pharmaceutical agents, and we have applied the strategy outlined in Scheme 1 for the synthesis of members of the *Sceletium* alkaloid family (eg. **4**).[5] In this work we used Li (or Na) in liquid ammonia[2] to achieve the key sulfonyl excision.[6] Apart from the relative inconvenience associated with the use of ammonia gas, one issue with this method is that if a methoxy group is positioned *para*- to the sulfonyl moiety it is partially lost (group highlighted with a box in structure **4**, Scheme 1).[2,5,7] As a consequence we were keen to investigate alternative reaction conditions for this type of process. Among the several alternative methods available for the reductive cleavage of sulfonamides[8] we were attracted to the low-valent titanium technique reported in 2011 by Okamoto.[9] In this work it was shown that alkyl and aryl sulfonamides undergo cleavage by an undefined low-valent titanium species[10] produced by the *in situ* reduction of Ti(IV) with Mg. In one example from this work the fate of the aromatic portion was also considered. From this it was evident that, during reaction of **5**, reductive cleavage of both the N-S and the C-S bonds had taken place to produce **6** in addition to expected secondary amine **7** (Scheme 2).[9]

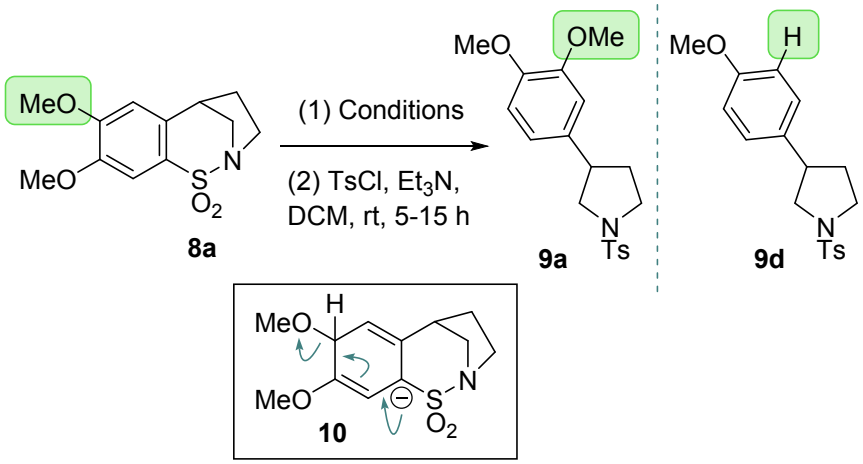


Scheme 2. Okamoto's low-valent titanium-based sulfonamide reduction.[9]

Results and Discussion

In order to study whether the low-valent titanium method successfully converted our cyclic sulfonamides into aryl amines, compound **8a** was selected (Table 1). Previously we reported[2] that use of Li in liquid NH_3 produced a mixture of di- and mono-methoxy-substituted aryl amines, which in order to purify and characterize, were converted into their *N*-tosyl sulfonamides.

Table 1. The reduction of dimethoxy-containing cyclic sulfonamide **8a**.

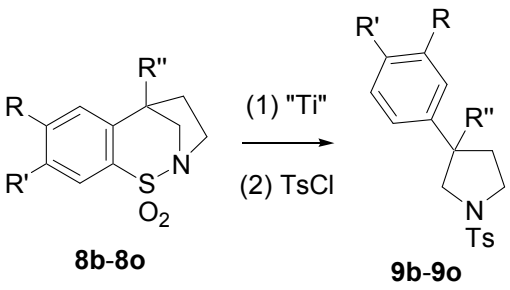


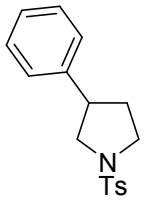
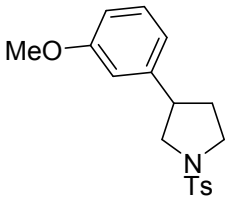
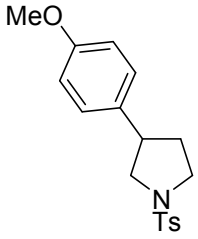
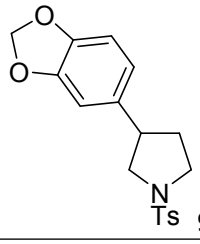
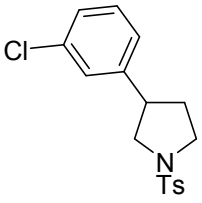
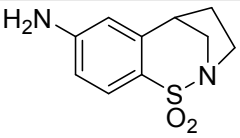
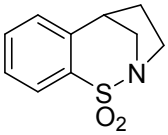
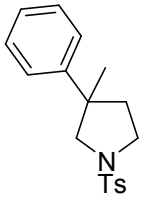
Entry	Conditions	8a	9a	9d
1[2]	Li (20 equiv.), NH_3, -78 °C, 0.5 h then NH_4Cl	-	28%	36%
2	Li (4 equiv.), $C_{10}H_8$ (4 equiv.), THF, -78 °C, 0.5 h	-	20%	-
3	Ti(O*i*-Pr)$_4$ (1.1 equiv.), Mg (6 equiv.), TMSCl (2 equiv.), THF, 80 °C, 15 h (under Ar)	-	83-100%	-
4	Mg (35 equiv.), EtOH-THF (5:1), rt-55 °C, 18 h	100%	-	-

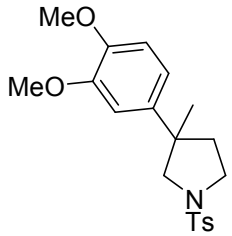
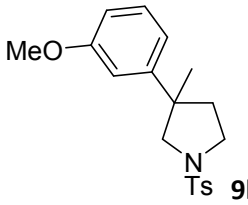
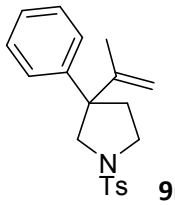
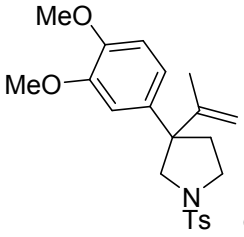
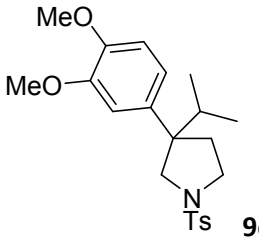
Thus, as shown in Entry 1, **9a** and **9d** were isolated in 28% and 36% respectively. It is likely that the regioselective partial loss of the methoxy-substituent highlighted stems from a Birch-type radical anionic intermediate.[11] This undergoes protonation (from NH_3) and re-aromatisation *via* a species of the type **10**. Subsequent sulfonamide reduction then ultimately generates the mono-methoxy compound **9d**. Based on this hypothesis it was felt that if the reaction was performed under aprotic conditions then perhaps the loss of the methoxy group would not occur. Therefore, the use of lithium naphthalenide in THF (or DME) was considered. As shown in Entry 2, this did successfully negate the formation of **9d**, however, the yields of **9a** were poor.

In contrast, when the low-valent titanium method was used[9] we were delighted to find that **9a** was not only the sole product and that it was also produced in excellent yields (Entry 3). Optimal results for this process were found when the process was conducted in a sealed reaction vessel under an argon atmosphere. Entry 4 demonstrates that unlike the successful outcome of the reaction combining Ti(IV) and Mg, the use of Mg alone in a mixture of EtOH or MeOH and THF (due to the poor solubility of **8a** in alcoholic solvents), with, or without sonication, was unsuccessful and only starting material **8a** was recovered.[8h,12]

Table 2. The titanium-mediated reduction of cyclic sulfonamides **8b-8o**.



Entry	Substrate	R	R'	R''	Product[a]	Yield[b]
1	**8b**	H	H	H	 **9b**	79%
2	**8c**	OMe	H	H	 **9c**	89%
3	**8d**	H	OMe	H	 **9d**	79%
4	**8e**	OCH_2O		H	 **9e**	74%
5	**8f**	Cl	H	H	 **9f**	61%
6	**8g**	NO_2	H	H	 **8h**	28%
7	**8i**	SO_2Me	H	H	 **8b**	65%
8	**8j**	H	H	Me	 **9j**	83%

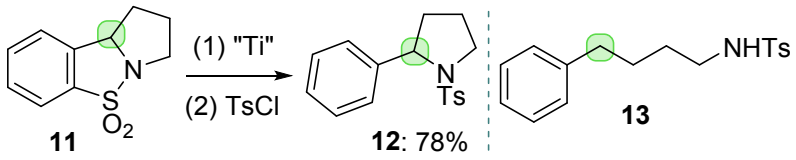
9	**8k**	OMe	OMe	Me	 **9k**	76%
10	**8l**	OMe	H	Me	 **9l**	85%
11	**8m**	H	H	*i*-C_3H_5	 **9m**	80%
12	**8n**	OMe	OMe	*i*-C_3H_5	 **9n**	60%
13	**8o**	OMe	OMe	*i*-Pr	 **9o**	62%

[a]Conditions: (1) Ti(*i*-OPr)$_4$ (1.1 equiv.), Mg (6.0 equiv.), TMSCl (2.0 equiv.), THF, 80 °C (oil bath temperature), 15 h, under Ar; (2) TsCl, Et_3N, DCM, rt, 15 h; [b]Yields obtained after purification by flash column chromatography.

In the light of the success with the low-valent titanium method a range of alternative examples bearing different aromatic (R and R') and benzylic (R'') substituents were considered (Table 2). Substrates **8b-8o** were prepared according to our previously reported[3] Heck-hydrogenation sequence and applying the conditions outlined in Table 1 above their behaviour in the presence of low valent titanium was evaluated. As shown in Table 2, Entry 1, the unsubstituted cyclic amide **8b** smoothly gave **9b** in a yield comparable to the Li-NH_3 method.[2] Regioisomeric methoxy substituted cyclic sulfonamides **8c** and **8d** and 1,3-dioxolane **8e** were next considered (Entries 2-4). Again, in these examples, no loss of the oxygen-based substituents was detected and the 3-aryl pyrrolidines **9c**-**9e** were isolated in good yields. In Okamoto's original report one example of an aryl chloride-containing sulfonamide was included, and the chloride unit survived the reaction. Based on this finding we were keen to evaluate how sulfonamide **8f**, containing a 4-chloro substituent, behaved. As shown in Entry 5 the chloro group *para*-to the sulfonyl unit did indeed survive the reduction process and **9f** was isolated in reasonable

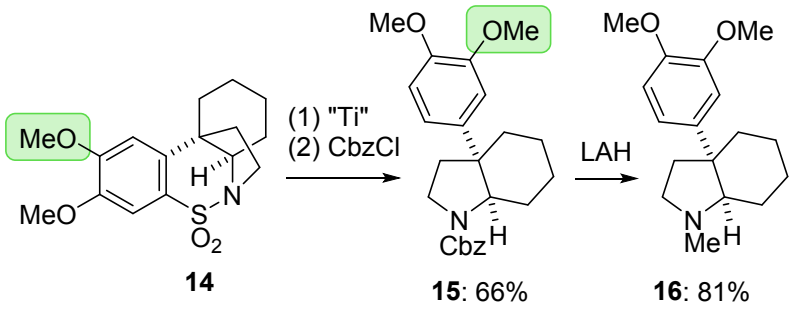
yield. Partly this outcome is notable because one might expect the aromatisation of an intermediate resembling **10** (Table 1) to readily occur and then because 6 equiv. of Mg are present one might also anticipate that competitive aryl magnesium reagent formation (either from **8f**, or the pyrrolidine product) might ensue over the course of the reaction. Next substrate **8g** was considered in which a nitro substituent is positioned *para*- to the sulfonyl group (Entry 6). In this case the nitro group does not survive the reduction process and the corresponding aniline (R = NH_2) was produced and isolated in a low yield. In this case, under the standard reaction conditions (i.e. 1.1 equiv. of Ti(IV) etc.), additional sulfonamide reduction was not clearly detected. Following the trend of positioning a potentially reactive moiety *para*- to the sulfonamide unit, sulfone **8i** was studied. This compound, prepared by nucleophilic aromatic substitution using nitro sulfonamide **8g**, underwent C-S sulfone bond cleavage and not the desired sulfonamide reduction (Entry 7). Interestingly, under the reaction conditions employed the resultant sulfonamide does not undergo further reaction to form the pyrrolidine and **8b** was isolated in 65% yield. Again, in this case the use of more equivalents of Ti(IV) was not studied. In the final set of examples we incorporated a substituent into the R'' position taking advantage of the high degree of regioselectivity[3,4] that can be obtained for intramolecular Heck reactions of trisubstituted dihydropyrroles of the type **3** (Scheme 1). As Entries 8-13 indicate, in all cases reasonable to good yields of the resultant pyrrolidine compounds, **9j**-**9o** were obtained. The unsaturated isopropenyl substitutent (R'' = *i*-C_3H_5) deserves mention because in these cases (Entries 11 and 12) the alkene does not react competitively and does not interfere with the overall sulfonamide reduction process and **9m** and **9n** were isolated in good to reasonable yield. Saturated isopropyl derivative **8o** also gave the product of double reduction **9o** without event.

Another interesting observation associated with chemoselectivity in Okamoto's original report is that benzylic bonds are not reductively cleaved under the low-valent titanium reaction conditions (see formation of **7** in Scheme 2).[9] Therefore, compound **11**,[2] an isomer of the 3-aryl cyclic sulfonamide **8b**, was subjected to the titanium reduction under the standard conditions outlined in Tables 1 and 2. As shown in Scheme 3, this was converted smoothly into 2-phenylpyrrolidine **12**, with none of the product of a further benzylic reduction detected. The additional benzylic reduction was observed when an excess of Li in liquid NH_3 was used, ultimately producing **13**. [2]



Scheme 3. The formation of 2-phenylpyrrolidine **12** from cyclic sulfonamide **11**.

The finding that the methoxy group *para*- to the sulfonyl group does not undergo cleavage during the titanium-mediated process (Tables 1 and 2) encouraged us to re-visit our syntheses of the *Sceletium* alkaloids, of which mesembrane (**16**) is a representative member. Thus, racemic cyclic sulfonamide **14**[4] was converted in reasonably good yield to carbamate protected octahydroindole **15** with no evidence of any loss of the methoxy-substituent highlighted (Scheme 4). This then gave racemic mesembrane **16** in a considerably more efficient overall sequence than that achieved previously with Li-NH_3 – which was hampered by the partial loss of the methoxy group highlighted.



Scheme 4. The synthesis of mesembrane **16** by reduction of cyclic sulfonamide **14**.

In summary, we have shown that low-valent titanium sulfonamide reduction can be effectively applied to a range of benzo-fused cyclic sulfonamides. In this process the sulfonyl group is excised and the N-S and C-S bonds are converted into N-H and C-H bonds respectively. We have shown that this method is generally applicable and can tolerate a range of different aromatic (R and R') and benzylic (R'') substituents. Substrates were selected in which a potential leaving group/reactive group (R = OMe, Cl, NO_2, SO_2Me) is located *para*- to the sulfonyl group and only in the case of the nitro and sulfone substituted compounds, **8g** and **8i** was competitive reaction, during the hoped for sulfonamide cleavage, observed. Unsaturation in the shape of a benzylic isopropenyl group (**8m** and **8n**), was unchanged over the course of the sulfonamide reduction and substrate **11**, with a potentially reactive benzylic C-N bond, gave only the hoped for sulfonamide cleavage process. Finally, the synthesis of mesembrane **16**, without loss of the vulnerable ether substituents, demonstrates the improvement of the described method for the double reduction of cyclic sulfonamides over the alternative Li, or Na-NH_3 method.

Experimental Section

General directions: Reagents from commercial suppliers were used without further purification and anhydrous DMF. ^{1}H and ^{1}H-decoupled ^{13}C NMR spectra were recorded on a Varian Unity 400 MHz spectrometer and coupling constants (*J*) are quoted in Hertz. All values are reported in ppm and were referenced to either tetramethylsilane or residual protonated chloroform. Assignment was aided by two-dimensional NMR (g-COSY and HSCQ). High resolution mass spectra were carried out on a VG analytical 70-E mass spectrometer under electrospray ionisation conditions (ESI) and a time-of-flight (TOF) analyser. Infrared spectra were recorded on a Bruker Alpha FTIR spectrometer. Melting points were recorded on a Gallenkamp electrothermal melting point apparatus. Thin-layer chromatography was performed on silica coated aluminium sheets and compounds were visualized with UV light and aqueous potassium permanganate, followed by heating. Merck silica gel (0.040-0.063 mm) was used for the flash column chromatography. The preparation of compounds **8a-g**,[3b] **8j-n**,[3b] **11**[2] and **14**[4a] were performed according to literature procedures.

General procedure for the Ti-based preparation and isolation of aryl pyrrolidines from cyclic sulfonamides: Under argon in oven-dry glassware the unsaturated sulfonamide substrate (0.185 mmol, 1 equiv.) was dissolved in anhydrous THF (3 mL). The solution was degassed under a steady flow of argon (*ca.* 10 min). Mg powder (6 equiv.) [activated by heating at 80°C for 30 min under Ar], Ti(O*i*-Pr)$_4$ (1.1 equiv.) and Me_3SiCl (2 equiv.) were added sequentially. After approx. 0.5 h the mixture turned black and was heated with stirring at 80 -100 °C (oil bath temperature) for 15 h. TLC analysis can be used to judge reaction completion. After cooling to room temperature, aqueous 1 M NaOH

(0.4 mL), Et_2O (15 mL), anhydrous NaF (1.0 g) and Celite (1.0 g) were sequentially added. The mixture was stirred for 30 min, decanted and the residue washed with Et_2O (3 x 15 mL) [alternatively, this mixture can be filtered through a Celite pad, washing with Et_2O (2 x 15 mL)]. After initial extraction the resultant aqueous phase was re-extracted with Et_2O (3 x 15 mL) and the organic extracts were combined. Drying over $MgSO_4$, followed by filtration and solvent removal gave the crude amine. A solution of the crude amine in CH_2Cl_2 (10 mL) was treated with triethylamine (0.39 mmol, 2 equiv.) and p-TsCl (0.204 mmol, 1.1 equiv.) at 0 °C. Stirring was continued for 15 h and the reaction gradually warmed to room temperature. Silica (*ca*. 2.0 g) was added to the reaction mixture and the solvent was removed under reduced pressure. Purification by flash column chromatography afforded the desired reduced cyclic amine.

3-(3,4-Dimethoxyphenyl)-1-tosylpyrrolidine 9a: Under argon gas, to a mixture of alkane **8a** (50 mg, 0.185 mmol, 1 equiv.) and Mg powder (31 mg, 1.28 mmol, 7 equiv.) in THF (3 mL) was added Ti(O*i*-Pr)$_4$ (0.060 mL, 0.203 mmol, 1.1 equiv.) and Me_3SiCl (0.052 mL, 0.410 mmol, 2.2 equiv.). The resulting mixture was stirred at 80 °C (oil bath temperature) for 15 h. Aqueous 1 M NaOH (0.4 mL), Et_2O (15 mL), anhydrous NaF (1.0 g) and Celite (1.0 g) were added at room temperature. After stirring for 30 min, the mixture was filtered through a pad of Celite. To the resulting filtrate was added aqueous 1 M NaOH (15 mL) and the mixture was extracted with Et_2O (15 mL). The organic layer was washed with aqueous 1 M NaOH (0.4 mL) and dried over anhydrous Na_2SO_4. Filtration followed by solvent removal under reduced pressure afforded the crude amine. A solution of the crude amine in CH_2Cl_2 (10 mL) was treated with triethylamine (0.057 mL, 0.41 mmol, 2.2 equiv.) and p-TsCl (46 mg, 0.24 mmol, 1.3 equiv.) at 0 °C. Stirring was continued for 15 h and the reaction gradually warmed to room temperature. Silica (*ca*. 2.0 g) was added to the reaction mixture and solvent removal under pressure. Purification by flash column chromatography (*c*-Hex-EtOAc; 2:1) gave **9d** (67 mg, 100 %) as a tan colored viscous oil. R_f = 0.5 (*c*-Hex-EtOAc; 1:1); ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.81-1.91 (1H, m, CH_2), 2.15-2.23 (1H, m, CH_2), 2.46 (3H, s, CH_3), 3.15-3.24 (2H, m, CH, CH_2), 3.31-3.37 (1H, m, CH_2), 3.53-3.59 (1H, m, CH_2), 3.66-3.75 (1H, m, CH_2), 3.83 (3H, s, CH_3), 3.84 (3H, s, CH_3), 6.64 (1H, s, ArH), 6.66 (1H, d, *J* = 8.0 Hz, ArH), 6.76 (1H, d, *J* = 8.0 Hz, ArH), 7.34 (2H, d, *J* = 8.0 Hz, ArH), 7.76 (2H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 21.5 (CH_3), 33.0 (CH_2), 43.8 (CH), 47.8 (CH_2), 54.1 (CH_2), 55.8 (CH_3), 55.85 (CH_3), 110.1 (CH), 111.1 (CH), 118.8 (CH), 127.5 (CH), 129.6 (CH), 133.1 (C), 133.9 (C), 143.4 (C), 147.9 (C), 148.9 (C) ppm. Data consistent with literature.[2]

3-Phenyl-1-tosylpyrrolidine 9b: Following the general procedure, **8b** (50 mg, 0.24 mmol, 1 equiv.) was converted into **9b**. Purification by flash column chromatography (*c*-Hex-EtOAc; 3:1) gave of **5b** (57 mg, 79 %) as a colorless solid. M.p. 65 C; R_f = 0.3 (*c*-Hex-EtOAc; 3:1). ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.82-1.94 (1H, m, CH_2), 2.17-2.25 (1H, m, CH_2), 2.46 (3H, s, CH_3), 3.18-3.29 (2H, m, CH, CH_2), 3.37 (1H, dd, *J* = 10.0, 7.0 Hz, CH_2), 3.54 (1H, ddd, *J* = 10.0, 8.5, 3.5 Hz, CH_2), 3.70-3.78 (1H, m, CH_2), 7.11 (2H, d, *J* = 7.0 Hz, ArH), 7.18-7.30 (3H, m, ArH), 7.35 (2H, d, *J* = 8.0 Hz, ArH), 7.77 (2H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 21.5 (CH_3), 32.9 (CH_2), 43.8 (CH), 47.8 (CH_2), 54.1 (CH_2), 126.9 (CH), 126.95 (CH), 127.6 (CH), 128.6 (CH), 129.7 (CH), 134.1 (C), 140.7 (C), 143.4 (C) ppm. Data consistent with literature.[2]

3-(3-Methoxyphenyl)-1-tosylpyrrolidine 9c: Following the general procedure, **8c** (50 mg, 0.21 mmol, 1 equiv.) was converted into **9c**. Silica (*ca*. 2.0 g) was added to the reaction mixture and solvent removal under pressure. Purification by flash column chromatography (*c*-Hex-EtOAc; 2:1) gave **9c** (61 mg, 89 %) as a tan colored viscous oil. R_f = 0.6 (c-Hex-EtOAc; 1:1); $\overline{\nu}_{max}$ 2921, 2889, 2834, 1930, 1726,

1595, 1493, 1464, 1453, 1430, 1336, 1287, 1257, 1152, 1111, 1028, 1014, 966, 845, 818, 783, 757, 692, 660, 587, 546, 511, 457 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.78-1.89 (1H, m, CH_2), 2.15-2.23 (1H, m, CH_2), 2.47 (3H, s, CH_3), 3.13-3.25 (2H, m, CH, CH_2), 3.32-3.40 (1H, m, CH_2), 3.51-3.57 (1H, m, CH_2), 3.69-3.74 (1H, m, CH_2), 3.77 (3H, s, CH_3), 6.65-6.63 (1H, m, ArH), 6.67 (1H, d, *J* = 7.5 Hz, ArH), 6.75 (1H, dd, *J* = 7.5, 1.5 Hz, ArH), 7.18 (1H, t, *J* = 7.5 Hz, ArH), 7.34 (2H, d, *J* = 8.0 Hz, ArH), 7.75 (2H, d, *J* = 8.0 Hz, ArH), ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 21.6 (CH_3), 33.2 (CH_2), 44.2 (CH), 48.2 (CH_2), 54.4 (CH_2), 55.6 (CH_3), 112.3 (CH), 113.4 (CH), 119.6 (CH), 127.9 (CH), 130.1 (CH), 130.1 (CH), 134.1 (C), 142.6 (C), 143.8 (C), 160.1 (C) ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{22}NO_3S$ 332.1320; Found 332.1305.

3-(4-Methoxyphenyl)-1-tosylpyrrolidine 9d: Following the general procedure, **8d** (50 mg, 0.21 mmol, 1 equiv.) was converted into **9d**. Purification by flash column chromatography (*c*-Hex-EtOAc; 2:1) gave **9d** (55 mg, 79 %) as a yellow colored viscous oil. R_f = 0.15 (*c*-Hex-EtOAc; 4:1); $\overline{\nu}_{max}$ 3054, 2958, 2927, 1599, 1492, 1454, 1436, 1340, 1264, 1157, 816, 780, 731, 699, 661, 590, 547 cm^{-1}. ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.78-1.89 (1H, m, CH_2), 2.15-2.23 (1H, m, CH_2), 2.47 (3H, s, CH_3), 3.13-3.25 (2H, m, CH, CH_2), 3.32-3.40 (1H, m, CH_2), 3.51-3.57 (1H, m, CH_2), 3.69-3.74 (1H, m, CH_2), 3.80 (3H, s, CH_3), 6.83 (2H, d, *J* = 8.0 Hz, ArH), 7.05 (2H, d, *J* = 8.0 Hz, ArH), 7.37 (2H, d, *J* = 8.0 Hz, ArH), 7.78 (2H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 21.6 (CH_3), 33.2 (CH_2), 43.2 (CH), 47.8 (CH_2), 54.4 (CH_2), 55.2 (CH_3), 113.9 (CH), 127.5 (CH), 127.9 (CH), 129.7 (CH), 132.5 (C), 133.8 (C), 143.4 (C), 158.4 (C) ppm. Data consistent with literature.[2]

3-(Benzo[d][1,3]dioxol-5-yl)-1-tosylpyrrolidine 9e: Following the general procedure alkane **8e** (50 mg, 0.197 mmol, 1 equiv.) was converted into **9e** which after conversion of the intermediate amine was purified by flash column chromatography (*c*-Hex-EtOAc; 2:1). This gave **9e** (50 mg, 74 %) as white solid. M.p. 100-103 °C; R_f = 0.6 (*c*-Hex-EtOAc; 2:1); $\overline{\nu}_{max}$ 2944, 2858, 2848, 1698, 1596, 1503, 1488, 1234, 1159, 1126, 1038, 785, 672, 589, 569 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.76-1.86 (1H, m, CH_2), 2.13-2.21 (1H, m, CH_2), 2.48 (3H, s, CH_3), 3.09-3.20 (2H, m, CH, CH_2), 3.30-3.35 (1H, m, CH_2), 3.49-3.52 (1H, m, CH_2), 3.66-3.72 (1H, m, CH_2), 5.94 (2H, s, CH_2), 6.55 (1H, s, ArH), 6.57 (1H, d, *J* = 7.5 Hz, ArH), 6.71 (1H, d, *J* = 7.5 Hz, ArH), 7.36 (2H, d, *J* = 8.0 Hz, ArH), 7.76 (2H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 21.1 (CH_3), 33.0 (CH_2), 43.9 (CH), 48.0 (CH_2), 54.1 (CH_2), 101.2 (CH_2), 107.4 (CH), 108.4 (CH), 120.2 (CH), 127.4 (CH), 129.8 (CH), 134.0 (C), 134.7 (C), 143.7 (C), 146.6 (C), 148.0 (C) ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{20}NO_4S$ 346.1113; Found 346.1107.

3-(3-Chlorophenyl)-1-tosylpyrrolidine 9f: Following the general procedure, **8f** (50 mg, 0.21 mmol, 1 equiv.) was converted into **9f**. Purification by flash column chromatography (*c*-Hex-EtOAc; 6:1) gave **9f** (43 mg, 61 %) as a pale viscous oil. R_f = 0.15 (*c*-Hex-EtOAc; 6:1); $\overline{\nu}_{max}$ 3054, 2984, 2971, 2901, 1597, 1572, 1480, 1344, 1264, 1160, 1046, 895, 731, 703, 662, 591, 549 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.78-1.89 (1H, m, CH_2), 2.15-2.23 (1H, m, CH_2), 2.47 (3H, s, CH_3), 3.13-3.25 (2H, m, CH, CH_2), 3.32-3.40 (1H, m, CH_2), 3.51-3.57 (1H, m, CH_2), 3.69-3.74 (1H, m, CH_2), 6.99-7.03 (1H, m, ArH), 7.05 (1H, s, ArH), 7.18-7.23 (2H, m, ArH), 7.35 (2H, d, *J* = 8.0 Hz, ArH), 7.75 (2H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 21.6 (CH_3), 32.9 (CH_2), 43.3 (CH), 47.5 (CH_2), 53.0 (CH_2), 125.1 (CH), 126.9 (CH), 127.3 (CH), 127.6 (CH), 129.6 (CH), 129.9 (CH), 133.5 (C), 134.2 (C), 142.7 (C), 143.4 (C) ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{17}H_{19}NO_2S^{35}Cl$ 336.0825; Found 336.0840.

4-Amino-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-dioxide 8h: Following the general procedure **8g** (50 mg, 0.19 mmol, 1 equiv.) gave aniline **8h** (12 mg, 28%) with data corresponding to literature.[3b]

4-(Methylsulfonyl)-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-dioxide 8i: A solution of 4-nitro sulfonamide **8g**[3b] (116 mg, 0.46 mmol, 1 equiv.) in anhydrous DMF (4 mL) was treated with NaSMe (60 mg, 0.86 mmol, 1.9 equiv.). Stirring was continued at room temperature for 18 h before the mixture was diluted with water (15 mL) and extracted with EtOAc (2 x 15 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Purification by flash column chromatography (*c*-Hex-EtOAc; 3:1 to 1:1) gave 4-(methylthia)-8-thia-9-aza-tricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-dioxide (80 mg, 68 %) as a viscous oil [R_f = 0.15 (*c*-Hex-EtOAc; 3:1); $\overline{\nu}_{max}$ 3045, 2966, 2899, 1584, 1328, 1295, 1163, 1107, 920 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.88-1.98 (1H, m, CH_2), 2.20-2.31 (1H, m, CH_2), 2.48 (3H, s, CH_3), 3.16-3.23 (2H, m, CH, CH_2), 3.48 (1H, ddd, *J* = 14.5, 10.5, 4.0 Hz, CH_2), 3.82-3.90 (1H, m, CH_2), 4.23 (1H, d, *J* = 12.5 Hz, CH_2), 7.02 (1H, d, *J* = 1.5 Hz, ArH), 7.18 (1H, dd, *J* = 8.5, 1.5 Hz, ArH), 7.65 (1H, d, *J* = 8.5 Hz, ArH), ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 14.9 (CH_3), 33.1 (CH_2), 39.8 (CH), 46.8 (CH_2), 56.9 (CH_2), 123.5 (CH), 125.1 (CH), 126.5 (CH), 131.4 (C), 141.3 (C), 145.2 (C) ppm; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{11}H_{14}NO_2S_2$ 256.0466; Found 256.0473]. Oxone® (1.00 g, 1.63 mmol, 5.3 equiv.) was added in one portion to a solution of the above sulfide (80 mg, 0.31 mmol, 1 equiv.) in MeOH (15 mL). Stirring was maintained for 2 days at rt. At this point most of the solvent was removed under reduced pressure and water (25 mL) and DCM (15 mL) were added. The resultant aqueous layer was further extracted with DCM (2 x 15 mL) and the combined organic extracts were dried over $MgSO_4$. After filtration and solvent removal under reduced pressure the crystalline residue was purified by gradient elution flash column chromatography (*c*-Hex-EtOAc; 3:1 to 1:3) to afford **8i** (84 mg, 94 %) as a colorless crystalline solid. R_f = 0.25 (*c*-Hex-EtOAc; 1:3); M.p = 198-200 °C; $\overline{\nu}_{max}$ 3073, 3020, 2932, 1402, 1327, 1312, 1297, 1161, 1095, 969 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.94- 2.02 (1H, m, CH_2), 2.29-2.38 (1H, m, CH_2), 3.06 (3H, s, CH_3), 3.28 (1H, dd, *J* = 13.0, 3.0 Hz, CH_2), 3.42 (1H, dd, *J* = 6.5, 3.0 Hz, CH), 3.55 (1H, ddd, *J* = 14.5, 10.5, 4.0 Hz, CH_2), 3.84-3.92 (1H, m, CH_2), 4.28 (1H, d, *J* = 13.0 Hz, CH_2), 7.84 (1H, d, *J* = 1.5 Hz, ArH), 7.94 (1H, dd, *J* = 8.0, 1.5 Hz, ArH), 7.99 (1H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 32.9 (CH_2), 39.7 (CH), 44.3 (CH_3), 46.7 (CH_2), 56.9 (CH_2), 126.6 (CH), 127.3 (CH), 127.9 (CH), 140.8 (C), 142.5 (C), 144.0 (C) ppm; HRMS (ESI-TOF) m/z: [M+H]$^+$ Calcd for $C_{11}H_{14}NO_4S_2$ 288.0364; Found 288.0372; $C_{11}H_{13}NO_4S_2$ Requires C: 45.98, H: 4.56, N: 4.87%; Found C: 46.21, H: 4.55, N: 4.62%.

8-Thia-9-azatricyclo[7.2.1.02,7]dodeca-2(7),3,5-triene-8,8-dioxide 8b: Following the general procedure, **8i** (50 mg, 0.17 mmol, 1 equiv.) was converted into **8b**. Purification by flash column chromatography (*c*-Hex-EtOAc; 3:1) gave **8b** (23 mg, 65 %), which was isolated as a colorless crystalline solid. M.p. = 120-122°C; R_f = 0.4 (*c*-Hex-EtOAc; 1:1). Data corresponds to that previously reported.[2,3]

3-Methyl-3-phenyl-1-tosylpyrrolidine 9j: Following the general procedure alkane **8j** (50 mg, 0.22 mmol, 1 equiv.) converted to **9j** following purification by flash chromatography (*c*-Hex-EtOAc; 3:1) gave of **9j** (59 mg, 83 %) as a colorless oil. R_f = 0.4 (*c*-Hex-EtOAc; 3:1); $\overline{\nu}_{max}$ 2965, 2876, 1597, 1496, 1445, 1343, 1158, 1095, 663 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.20 (3H, s, CH_3), 1.96-2.10 (2H, m, CH_2), 2.41 (3H, s, CH_3), 3.39 (1H, d, *J* = 9.5 Hz, CH_2), 3.39-3.50 (2H, m, CH_2), 3.55 (1H, d, *J* = 9.5 Hz, CH_2), 7.14 (2H, d, *J* = 7.0 Hz, ArH), 7.20-7.22 (1H, m, ArH), 7.24-7.32 (4H, m, ArH), 7.73 (2H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 21.4 (CH_3), 27.7 (CH_3), 37.6 (CH_2), 45.9 (C), 46.5 (CH_2),

58.9 (CH_2), 125.9 (CH), 126.5 (CH), 127.6 (CH), 128.6 (CH), 129.7 (CH), 134.1 (C), 143.4 (C) 146.4 (C) ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{18}H_{22}NO_2S$ 316.1371; Found 316.1366.

3-(3,4-Dimethoxyphenyl)-3-methyl-1-tosylpyrrolidine 9k: As per the general procedure, a mixture of alkane **8k** (50 mg, 0.176 mmol, 1 equiv.) yielded **9k** (50 mg, 76 %) as a white solid following purification by flash column chromatography (*c*-Hex-EtOAc; 2:1). M.p. = 94-98 °C; R_f = 0.4 (*c*-Hex-EtOAc; 2:1); $\overline{\nu}_{max}$ 2960, 2917, 1520, 1464, 1340, 1255, 1158, 1094, 1027, 807, 663 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.19 (3H, s, CH_3), 1.90-2.12 (2H, m, CH_2), 2.46 (3H, s, CH_3), 3.51-3.39 (4H, m, CH_2), 3.83 (3H, s, CH_3), 3.84 (3H, s, CH_3), 6.66-6.70 (2H, m, ArH), 6.76 (1H, d, *J* = 8.0 Hz, ArH), 7.30 (2H, d, *J* = 8.0 Hz, ArH), 7.76 (2H, d, *J* = 8.0 Hz, ArH) ppm; $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 21.5 (CH_3), 27.6 (CH_3), 37.8 (CH_2), 45.7 (C), 46.6 (CH_2), 55.9 (CH_3), 55.95 (CH_3), 59.2 (CH_2), 109.3 (CH), 111.1 (CH), 117.5 (CH), 127.4 (CH), 129.6 (CH), 134.3 (C), 139.0 (C), 143.3 (C), 147.7 (C), 148.9 (C) ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{20}H_{26}NO_4S$ 376.1583; Found 376.1590.

3-(3-Methoxyphenyl)-3-methyl-1-tosylpyrrolidine 9l: Following the general procedure, alkane **8l** (50 mg, 0.197 mmol, 1 equiv.) yielded **9l** (58 mg, 85 %) as a viscous oil after purification by flash column chromatography (*c*-Hex-EtOAc; 6:1). R_f = 0.25 (*c*-Hex-EtOAc; 6:1); $\overline{\nu}_{max}$ 2961, 2924, 2874, 2854, 1598, 1582, 1488, 1451, 1336, 1290, 1154, 1090, 1043, 925, 804, 783, 701, 661, 592, 546 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.19 (3H, s, CH_3), 1.94-2.03 (2H, m, CH_2), 2.41 (3H, s, CH_3), 3.30 (1H, d, *J* = 9.5 Hz, CH_2), 3.34-3.41 (2H, m, CH_2), 3.46 (1H, d, *J* = 9.5 Hz, CH_2), 3.72 (3H, s, CH_3), 6.61 (1H, s, ArH), 6.64-6.70 (1H, m, ArH), 7.14 (1H, t, *J* = 7.5 Hz, ArH), 7.30 (2H, d, *J* = 8.0 Hz, ArH), 7.72 (2H, d, *J* = 8.0 Hz, ArH) ppm; $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 21.6 (CH_3), 27.3 (CH_3), 37.4 (CH_2), 45.9 (CH_2), 46.5 (C), 55.2 (CH_3), 58.3 (CH_2), 111.1 (CH), 112.1 (CH), 117.8 (CH), 127.4 (CH), 129.5 (CH), 129.6 (CH), 134.1 (C), 143.3 (C), 148.0 (C), 159.6 (C) ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{19}H_{24}NO_3S$ 346.1477; Found 346.1461.

3-Phenyl-3-(prop-1-en-2-yl)-1-tosylpyrrolidine 9m: Following the general procedure, **8m** (50 mg, 0.20 mmol, 1 equiv.) was converted into **9m**. Purification of the crude reaction product by flash column chromatography (*c*-Hex-EtOAc; 9:1) gave **9m** (55 mg, 80 %) as viscous oil. R_f = 0.45 (*c*-Hex-EtOAc; 3:1); $\overline{\nu}_{max}$ 3055, 3026, 2922, 2853, 1642, 1597, 1493, 1446, 1341, 1160, 1091, 1053, 898, 815, 763, 735, 700, 663, 599, 547 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.57 (3H, s, CH_3), 2.03-2.06 (1H, m, CH_2), 2.16-2.22 (1H, m, CH_2), 2.42 (3H, s, CH_3), 3.21-3.30 (1H, m, CH_2), 3.40-3.47 (1H, m, CH_2), 3.57 (1H, d, *J* = 9.5 Hz, CH_2), 3.69 (1H, d, *J* = 9.5 Hz, CH_2), 4.87 (1H, s, CH_2), 4.93 (1H, s, CH_2), 7.14-7.32 (5H, m, ArH), 7.29 (2H, d, *J* = 8.0 Hz, ArH), 7.70 (2H, d, *J* = 8.0 Hz, ArH) ppm; $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ = 20.7 (CH_3), 21.6 (CH_3), 35.5 (CH_2), 46.7 (C), 55.8 (CH_2), 56.0 (CH_2), 110.7 (CH_2), 126.1 (CH), 126.5 (CH), 127.1 (CH), 128.2 (CH), 129.5 (CH), 135.1 (C), 142.9 (C), 143.7 (C), 147.3 (C) ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{20}H_{23}NO_2NaS$ 364.1347; Found 364.1331.

3-(3,4-Dimethoxyphenyl)-3-(prop-1-en-2-yl)-1-tosylpyrrolidine 9n: Following the general procedure, **8n** (39 mg, 0.126 mmol, 1 equiv.) was converted into **9n**. Purification by flash column chromatography (*c*-Hex-EtOAc; 6:1) gave **9n** (30.5 mg, 60 %) as light tan colored viscous oil. R_f = 0.35 (*c*-Hex-EtOAc; 3:1); $\overline{\nu}_{max}$ 2952, 2927, 2870, 1641, 1597, 1517, 1454, 1337, 1255, 1162, 1028, 814, 765, 664, 594, 548 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.47 (3H, s, CH_3), 1.94-2.04 (1H, m, CH_2), 2.10-2.18 (1H, m, CH_2), 2.42 (3H, s, CH_3), 3.21-3.30 (1H, m, CH_2), 3.40-3.46 (1H, m, CH_2), 3.54 (1H, d, *J* = 9.5 Hz, CH_2), 3.67 (1H, d, *J* = 9.5 Hz, CH_2), 3.82 (3H, s, CH_3), 3.85 (3H, s, CH_3), 4.88 (1H, s, CH_2), 4.91 (1H, s, CH_2), 6.66-6.73 (3H, m, ArH), 7.28 (2H, d, *J* = 8.0 Hz, ArH), 7.69 (2H, d, *J* = 8.0 Hz, ArH) ppm; $^{13}C\{^1H\}$-NMR (100 MHz, $CDCl_3$) δ =

20.2 (CH_3), 21.4 (CH_3), 35.1 (CH_2), 46.2 (CH_2), 54.9 (C), 55.6 (CH_2), 55.7 (CH_3), 55.75 (CH_3), 109.8 (CH), 110.5 (CH), 110.55 (CH_2), 118.3 (CH), 127.2 (CH), 129.4 (CH), 134.6 (C), 134.7 (C), 143.0 (C), 146.9 (C), 147.6 (C), 148.6 (C) ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{22}H_{27}NO_4NaS$ 424.1559; Found 424.1551.

4,5-Dimethoxy-1-(prop-2-yl)-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5-triene 8,8-dioxide 8o: 4,5-Dimethyoxy-1-(prop-1-en-2-yl)-8-thia-9-azatricyclo[7.2.1.0^{2,7}]dodeca-2(7),3,5,10-tetraene 8,8-dioxide (65 mg, 0.021 mmol) was dissolved in EtOAc (12 mL). This solution (0.018 M) was pumped (0.5 mL/min) through a ThalesNano H-cube® at *ca*. 13 Bar H_2 pressure containing 10% w/w Pd/C in a cartridge (70 x 4 mm) which was set to 30 °C. After one-pass the apparatus was washed through with EtOAC (12 mL) and the solvent was removed under reduced pressure to afford **8n** (65 mg, 99%) as a white solid. Proton NMR spectroscopy indicated that this compound did not require additional purification. M.p. = 130-133 °C; R_f = 0.35 (*c*-Hex-EtOAc; 1:1); $\overline{\nu}_{max}$ 2959, 2923, 2849, 1712, 1599, 1566, 1506, 1463, 1443, 1323, 11304,1263, 1214, 1157, 1033, 985, 913, 864, 773, 713, 695, 666, 604, 526, 516 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 1.02 (3H, d, *J* = 7.0 Hz,CH_3), 1.15 (3H, d, *J* = 7.0 Hz, CH_3), 1.63-1.78 (1H, m, CH_2), 2.18-2.30 (1H, m, CH_2), 2.53-2.68 (1H, m, CH), 3.18 (1H, d, *J* = 12.5 Hz, CH_2), 3.51-3.59 (1H, m, CH_2), 3.74 -3.84 (1H, m, CH_2), 3.92 (6H, s, CH_3), 4.08 (1H, d, *J* = 12.5 Hz, CH_2), 6.85 (1H, s, ArH), 7.25 (1H, s, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 17.2 (CH_3), 20.5 (CH_3), 28.4 (CH), 35.4 (CH_2), 48.0 (CH_2), 49.7 (C), 56.1 (CH_3), 56.2 (CH_2, CH_3), 106.8 (CH), 108.0 (CH), 127.3 (C), 136.3 (C), 148.1 (C), 152.0 (C) ppm; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{15}H_{21}NO_4NaS$ 334.1089; Found 334.1089.

3-(3,4-Dimethoxyphenyl)-3-(prop-2-yl)-1-tosylpyrrolidine 9o: Following the general procedure, **8o** (50 mg, 0.161 mmol, 1 equiv.) was converted into **9o**. Purification of the crude reaction mixture by flash column chromatography (*c*-Hex-EtOAc; 6:1) gave **9o** (40 mg, 62 %) as a light brown colored viscous oil. R_f = 0.3 (*c*-Hex-EtOAc; 3:1); $\overline{\nu}_{max}$ 3063, 2923, 2875, 2851, 2834, 1597, 1511, 1462, 1328, 1249, 1239, 1143, 1095, 1023, 812, 765, 734, 660, 592, 547 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ = 0.72-0.75 (6H, m, CH_3), 1.76 (1H, sept, *J* = 7.0 Hz, CH), 2.07-2.13 (2H, m, CH_2), 2.42 (3H, s, CH_3), 3.16-3.22 (1H, m, CH_2), 3.40-3.47 (1H, m, CH_2), 3.55 (1H, d, *J* = 10.0 Hz, CH_2), 3.58 (1H, d, *J* = 10.0 Hz, CH_2), 3.82 (3H, s, CH_3), 3.85 (3H, s, CH_3), 6.56-6.61 (2H, m, ArH), 6.71 (1H, d, *J* = 8.0 Hz, ArH), 7.24 (2H, d, *J* = 8.0 Hz, ArH), 7.64 (2H, d, *J* = 8.0 Hz, ArH) ppm; ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$) δ = 18.2 (CH_3), 18.6 (CH_3), 21.3 (CH_3), 33.9 (CH), 34.5 (CH_2), 46.3 (CH_2), 53.4 (C), 55.7 (CH_3), 55.8 (CH_3), 56.1 (CH_2), 110.2 (CH), 111.3 (CH), 119.6 (CH), 127.3 (CH), 129.5 (CH), 133.2 (C), 134.2 (C), 142.9 (C), 147.0 (C), 148.0 (C) ppm; HRMS (ESI-TOF) m/z: $[M+H]^+$ Calcd for $C_{22}H_{30}NO_4S$ 404.1896; Found 404.1886.

2-Phenyl-1-tosylpyrrolidine 12: Following the general procedure, **11** (50 mg, 0.23 mmol, 1 equiv.)[2] was converted into **12**. Purification by flash column chromatography (*c*-Hex-EtOAc; 5:1) yielded **12** (54.5 mg, 78 %) as a colorless solid. M.p = 70 -74°C; R_f = 0.3 (*c*-Hex-EtOAc; 3:1); data corresponds to that previously reported.[2]

2,3-Dimethoxy-7,8,9,10-tetrahydro-6a*H*-6,10a-ethanodibenzo[*c,e*][1,2]thiazine 5,5-dioxide 14: 2,3-Dimethoxy-7,8,9,10-tetrahydro-6a*H*-6,10a-ethenodibenzo[*c,e*][1,2]thiazine 5,5-dioxide (140 mg, 0.044 mmol)[4a] was dissolved in EtOAc (15 mL). This solution (0.03 M) was then pumped (0.5 mL/min) through a ThalesNano H-cube® at *ca.* 14 Bar H_2 pressure containing 10% w/w Pd/C at a temperature of 30 °C. Following the elution, the system was washed with EtOAc (15 mL) and the combined solvent removed under reduced pressure. This afforded **14** (141 mg, quant) as a white solid with data that corresponds to that previously reported.[4a]

(±)-3a-(3,4-Dimethoxyphenyl)-1-methyloctahydroindole (mesembrane) 16: Following the first phase of the general procedure, under argon gas a mixture of alkane **14** (100 mg, 0.31 mmol, 1 equiv.) and Mg powder (45 mg, 1.86 mmol, 6 equiv.) in THF (6 mL) was treated with $Ti(O\textit{i}\text{-}Pr)_4$ (0.1 mL, 0.34 mmol, 1.1 equiv.) and Me_3SiCl (0.078 mL, 0.62 mmol, 2 equiv.). The resulting mixture was stirred at 80 °C for 15 h. Work up as described afforded the crude amine. A solution of the crude amine in CH_2Cl_2 (5 mL) and powdered K_2CO_3 (342 mg, 2.48 mmol, 8 equiv.) was added followed by benzyl chloroformate (68.5mg, 0.40 mmol, 1.3 equiv.). Stirring was continued at room temperature for 4 h before addition of silica (*ca*. 2 g) and solvent removal under reduced pressure. Purification by flash column chromatography gave **15** (80 mg, 66 %) with data as reported.[4a] Under N_2, **15** (80 mg, 0.20 mmol, 1 equiv.) in dry THF (5 mL) was treated with $LiAlH_4$ (15.5 mg, 0.42 mmol, 2.1 equiv.). The reaction mixture was heated to reflux for 2 h. On cooling EtOAc (30 mL) was gradually added followed by 1 M NaOH solution (30 mL). The resultant aqueous layer was extracted with EtOAc (2 x 30 mL) and the combined organic extracts were dried over $MgSO_4$. Following filtration and solvent removal flash column chromatography ($CHCl_3$-MeOH; 19:1, 1 % Et_3N) afforded **16** (45 mg, 81 %) as a colorless oil. R_f = 0.1 ($CHCl_3$-MeOH; 19:1, 1 % Et_3N). Data corresponds to that previously reported.[4a]

Supporting Information

Copies of ^1H- and $^{13}C\{^1H\}$-NMR spectra (PDF) are available free of charge on the ACS Publications website at DOI:

Acknowledgments

We thank the Libyan Government, Department of Cultural Affairs for the provision of a postgraduate scholarship (AK, ref. IA8-490-45773) and Dr. Kimberly Geoghegan for useful advice.

References

1. For general reviews concerning the sulfonamide functional group, see: (a) Majumdar, K. C.; Mondal, S. Recent Developments in the Synthesis of Fused Sultams. *Chem. Rev.* **2011**, *111*, 7749-7773; (b) M. Szostak, M.; Aubé, J. Chemistry of Bridged Lactams and Related Heterocycles. *Chem. Rev*. **2013**, *113*, 5701-5765; (c) Kolaczek, A.; Fusiarz, I.; Lawecka, J.; Branowska, D. Biological Activity and Synthesis of Sulfonamide Derivatives: A Brief Review. *Chemik* **2014**, *68*, 620-628. For a discussion of the sulfonamide group as a protecting group in organic chemistry, see: (d) Greene's Protective Groups in Organic Synthesis, 4th Ed. Wuts, P. G. M.; Greene, T. W. J. Wiley and Sons, New York, **2007**; (e) Protecting Groups, Kocieński, P. J. Thieme, Stuttgart, **2005**.

2. Evans, P.; McCabe, T.; Morgan, B. S.; Reau, S. Double Reduction of Cyclic Aromatic Sulfonamides: A Novel Method for the Synthesis of 2- and 3-Aryl-Substituted Cyclic Amines. *Org. Lett*. **2005**, *7*, 43-46.

3. (a) Geoghegan, K.; Kelleher, S.; Evans, P. An Investigation into the One-Pot Heck Olefination-Hydrogenation Reaction. *J. Org. Chem.* **2011**, *76*, 2187-2194; (b) Khalifa, A.; Conway, L.; Geoghegan, K.; Evans, P. Ammonium Formate-Based One-Pot Reductive Heck Reactions for the Construction of Cyclic Sulfonamides. *Tetrahedron Lett*. **2017**, *58*, 4559-4562.

4. (a) Klein, J. E. M. N.; Geoghegan, K.; Méral, N.; Evans, P. Selective Generation of Quaternary All-Carbon-Centres Through Heck-Cyclisations: Synthesis of Mesembrane. *Chem. Commun.* **2010**, *46*, 937-939; (b) Geoghegan, K.; Evans, P.; Rozas, I.; Alkorta, I. Regioselectivity in the Intramolecular Heck

Reaction of a Series of Cyclic Sulfonamides: An Experimental and Computational Study. *Chem. Eur. J.* **2012**, *18*, 13379-13387.

5. Geoghegan, K.; Evans, P. Double Reduction of Cyclic Aromatic Sulfonamides: Synthesis of (+)-Mesembrine and (+)-Mesembranol. *J. Org. Chem*. **2013**, *78*, 3410-3415.

6. No Birch-type reduction of the newly formed phenyl group occurs (presumably due to the absence of a proton source, such as *t*-BuOH).

7. Zeng, W.; Chemler, S. R. Total Synthesis of (*S*)-(+)-Tylophorine *via* Enantioselective Intramolecular Alkene Carboamination. *J. Org. Chem*. **2008**, *73*, 6045-6047.

8. For a recent paper concerning sulfonamide cleavage see: Javorskis, T.; Orentas, E. Chemoselective Deprotection of Sulfonamides under Acidic Conditions: Scope, Sulfonyl Group Migration and Synthetic Applications. *J. Org. Chem*. **2017**, *82*, 13423-13439 (and also references 9-19 therein).

9. Shohji, N.; Kawaji, T.; Okamoto, S. Ti(O*i*-Pr)$_4$/Me$_3$SiCl/Mg-Mediated Reductive Cleavage of Sulfonamides and Sulfonates to Amines and Alcohols. *Org. Lett*. **2011**, *13*, 2626-2629.

10. For an overview of stoichiometric and catalytic titanium-based chemistry in the realm of organic synthesis, see: (a) Organotitanium Reagents in Organic Synthesis, Reetz, M. T. Springer-Verlag, Berlin Heidelberg, **1986**; (b) Fürstner, A.; Bogdanovic, B. New Developments in the Chemistry of Low-Valent Titanium. *Angew. Chem. Int. Ed. Engl*. **1996**, *35*, 2442-2469; (c) Davis-Gilbert, Z. W.; Tonks, I. A. Titanium Redox Catalysis: Insights and Applications of an Earth-Abundant Base Metal. *Dalton Trans.* **2017**, *46*, 11522-11528.

11. Lowenthal, H. J. E.; Gottlieb, L. Metal-Ammonia Reduction and Reductive Alkylation of *N*-Alkylnaphthalenesulfonamides. A New Route to Substituted Naphthalenes. *J. Org. Chem.* **1992**, *57*, 2631-2641.

12. For a general review concerning the use of Mg-MeOH, see: Lee, G. H.; Youn, I. K.; Choi, E. B.; Lee, H. K.; Yon, G. H.; Yang, H. C.; Pak, C. S. Magnesium in Methanol (Mg/MeOH) in Organic Syntheses. *Curr. Org. Chem.* **2004**, *8*, 1263-1287.