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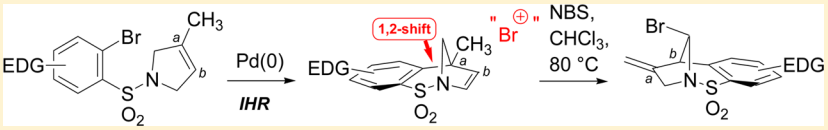
Halonium Ion Triggered Rearrangement of Unsaturated Benzo-Annulated Bi- and Tricyclic Sulfonamides

Kimberly Geoghegan, Shaun Smullen, and Paul Evans*

Centre for Synthesis and Chemical Biology, School of Chemistry and Chemical Biology, University College Dublin, Dublin 4, Ireland

Supporting Information



ABSTRACT: The halonium ion mediated 1,2-Wagner–Meerwein-type rearrangement of a series of benzo-fused bi- and tricyclic sulfonamides is reported. During this rearrangement the carbon–carbon bond that migrates was selectively set in the intramolecular Mizoroki–Heck (IHR) synthesis of the starting materials. Consequently, this method constitutes a means to access the regioisomeric series of cyclic sulfonamides not observed during the Mizoroki–Heck reaction.

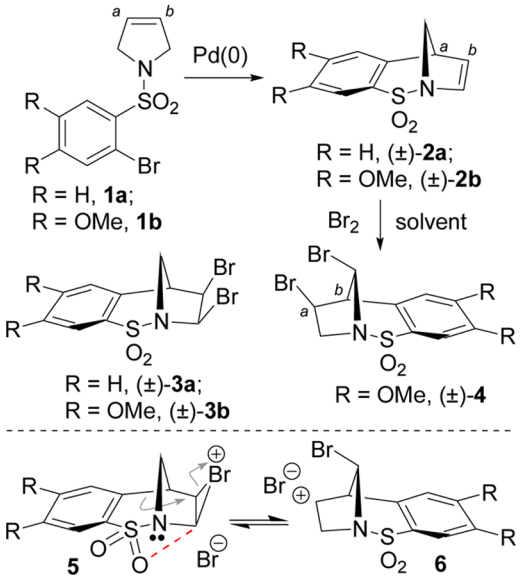
INTRODUCTION

Cyclic sulfonamides (sultams) are of interest from both a chemical and a pharmacological perspective.[1] An effective method for their construction, particularly when benzo-annulated, is the intramolecular Heck reaction (IHR), a process that results in formation of the cyclic sulfonamide and a new alkene (Scheme 1, **1a** to **2a**, for example).[2] We have investigated this tactic as a means to assemble functionalized cyclic sulfonamides, which can then be treated under reductive conditions to excise the sulfonyl group and form a functionalized amine.[3] During this study, following a report from Paquette, the derivatization of the Heck-derived alkene **2a** was also considered.[4] In accordance with Paquette's findings, the *cis*-1,2-dibromination of **2a** took place predominantly leading to **3a**, in solvents such as chloroform. The stereochemical outcome was ascribed to bromide interception of a carbocation from the less hindered convex face of the intermediate, as opposed to the ring-opening of the bromonium ion (e.g., **5**) from the more hindered, concave face.[5]

When nonpolar solvents were employed, the same outcome was observed for dimethoxy-substituted **2b** and the *cis*-1,2-dibromide **3b** was isolated. However, use of chloroform led to formation of compound **4** as the major product.[5] It was reasoned that **4** resulted from a 1,2-Wagner–Meerwein (W-M) rearrangement of intermediate **5**, whereby the aryl–benzylic carbon bond, which is appropriately aligned to the C–Br bromonium ion bond (or the carbocation),[6] shifts, generating secondary carbocation **6** (in a process that may be reversible), which then is subsequently intercepted, diastereoselectively, by a bromide ion. The fact that this rearrangement-derived product was not observed for nonsubstituted alkene **2a** indicates that the methoxy substituents exert influence on the bond migration.[7] Following the rearrangement described, it should be noted that the bond formed during the IHR (denoted carbon-*a* in Scheme 1) migrates to, what was, the other alkenyl carbon atom in the reaction precursor **1** (i.e., carbon-*b*).

This latter aspect attracted our attention, since, recently, we have uncovered that during the IHR of a series of alkyl and aryl trisubstituted alkenes, carbon–carbon bond formation takes place with high selectivity at the most substituted alkenyl carbon (i.e., **7** to **8**, Scheme 2).[8] During this work, in which the substitution pattern on the alkenyl carbon dictates bond formation rather than the size of the newly formed cycle,

Scheme 1. Formation of Benzo-Annulated Cyclic Sulfonamides by the Intramolecular Heck Reaction and Their Bromination



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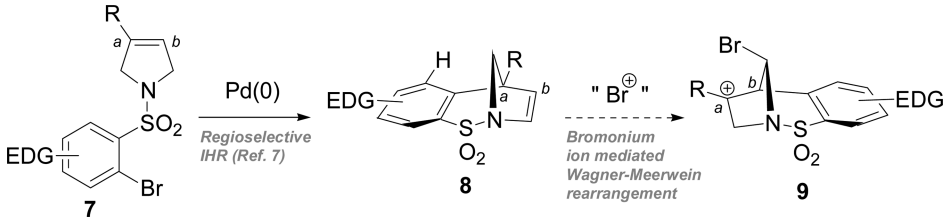
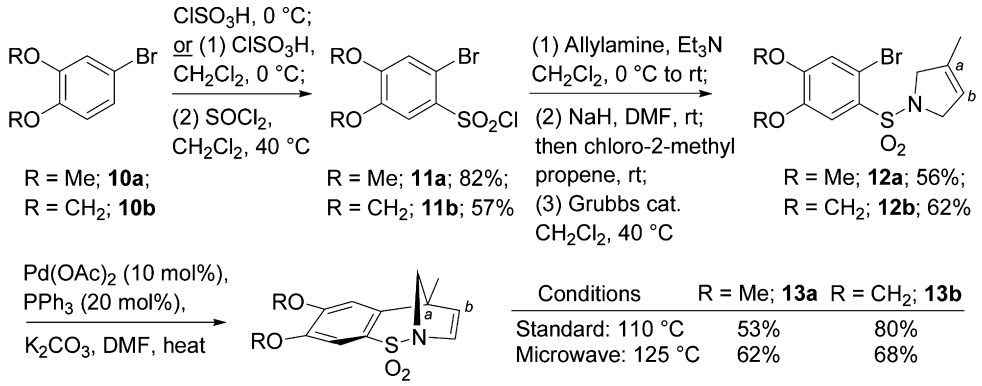
Scheme 2. Alkene Substituent Control in the IHR of Cyclic Sulfonamides and the Proposed Application of the 1,2-Wagner–Meerwein Rearrangement[a]



[a]EDG = electron donating group.

Scheme 3. Synthesis of Cyclic Sulfonamides 13a and 13b Possessing a Quaternary Center



conditions to reliably overturn the selectivity could not be identified. Therefore, it was of interest to investigate whether the bromonium ion triggered 1,2-shift of Heck adducts **8** could be used to access formally the isomeric series of compounds not obtainable following IHR.

It was, in fact, felt that the rearrangement of molecules such as **8** might actually proceed more readily than the example discussed above (**1b** to **4**), since in going from **8** to **9** steric compression between the bridgehead substituent (R) and the *peri*-aromatic hydrogen would be ameliorated and in addition the resultant carbocationic intermediate would be tertiary as opposed to secondary (e.g., **6**).

RESULTS AND DISCUSSION

To investigate the feasibility of the process outlined in Scheme 2, the synthesis of alkenes **13a** and **13b** was considered. Dimethoxy-containing **13a** was reported in our previous work[8b] and was assembled in four steps from 2-bromo-4,5-dimethoxybenzenesulfonyl chloride **11a** (Scheme 3). It proved more challenging to assemble dioxolane analogue **13b** due to difficulties associated with the synthesis of the acid-sensitive 2-bromo-4,5-(methylenedioxy)benzenesulfonyl chloride **11b**. After some optimization it was found that exposure of a cold dichloromethane solution of 1-bromo-3,4-(methylenedioxy)-benzene **10b** to chlorosulfonic acid led to formation of the required sulfonic acid, which immediately precipitated from solution. In turn, this sulfonic acid could be converted to sulfonyl chloride **11b** with thionyl chloride in dichloromethane at reflux. A ring-closing metathesis strategy gave the asymmetrical 3-methyl dihydropyrrole **12b**. Subsequent IHR gave **13b** as the sole isolable product, the structure of which was confirmed by X-ray crystallography.[9] Microwave irradiation was briefly investigated as an alternative to standard conductive heating. Irradiation at 300 W and 125 °C for 25 min under otherwise identical reaction conditions gave an isolated yield of 62% and 68% of **13a** and **13b**, respectively.

With alkenes **13a** and **13b** in hand, their behavior in the presence of bromine was studied (Scheme 4). Treatment of a chloroform solution of **13a** with bromine (10 equiv), which was warmed from −60 °C to room temperature over a 15 h period, gave a mixture of products (entry 1). 1,2-Dibromide **16a** was isolated in 33% yield along with 55%[10] of a mixture of rearranged di- and tribromides **14a** and **15a** (ca. 1:1) that proved inseparable by flash column chromatography. The formation of **14a** was consistent with diastereoselective interception of the tertiary carbocation **9** (as observed previously,[5] **2b** to **4**) and it was reasoned that tribromide **15a** formed as a result of bromination of the corresponding alkene **17a** (not observed in this reaction), which itself formed on loss of a proton from the same tertiary carbocation. On reducing the polarity of the medium, slightly diminished amounts of rearranged products (**14a** and **15a**) and more of the 1,2-dibromide **16a** (entry 2) were observed. The *cis*-1,2-dibromo relationship in **16a** was confirmed by NOE. However, increasing polarity can only be successfully employed in these reactions to a certain degree, since polar protic solvents competitively intercept reaction intermediates,[5] and solvents such as DMF, acetonitrile, and propylene carbonate failed to generate products of bromination in meaningful amounts. Since the inseparable mixture of rearranged di- and tribromides (**14a** and **15a**) served to complicate the understanding of this process, it was felt that if a basic silver salt was added, then the rate of bromide interception of the tertiary carbocation would diminish versus alkene formation and that consequently more tribromide **15a** would be isolated. As entry 3 indicates, this supposition proved incorrect and bromine treatment of **13a** in the presence of silver(I) acetate gave a mixture of **14a** and **15a** in approximately the same ratio as observed in the absence of Ag(I). Reducing the effective bromine concentration[11] (entries

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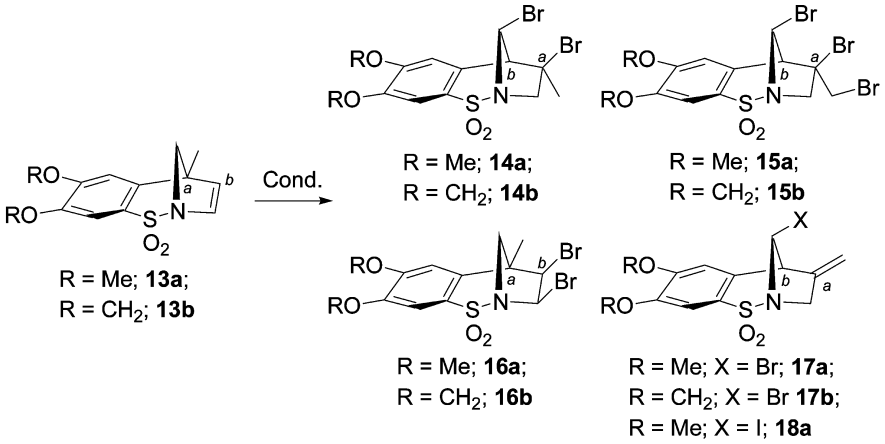
Scheme 4. Rearrangement of Cyclic Sulfonamides 13a and 13b



Entry	R	Conditions	Products (%)
1	Me	Br_2 (10 equiv.), $CHCl_3$, -60 °C to rt, 15 h	**14a**:**15a** (55%, 1:1); **16a** (33%)
2	Me	Br_2 (10 equiv.), CH_2Cl_2, -78 °C to rt, 15 h	**14a**:**15a** (44%, 1:1.1); **16a** (49%)
3	Me	Br_2 (10 equiv.), AgOAc (1 equiv.), $CHCl_3$, -60 °C to rt, 15 h	**14a**:**15a** (25%, 1:1.2); **16a** (28%)
4	Me	Br_2 (1.4 equiv.), $CHCl_3$, -60 °C to rt, 15 h	**14a**:**15a** (50%, 1:1); **16a** (45%)
5	Me	Br_2 (0.55 equiv.), $CHCl_3$, -60 °C to rt, 15 h	**16a** (3%); **17a** (50%)
6	Me	NBS (1.1 equiv.), $CHCl_3$, reflux, 15 h	**13a** (35%); **17a** (66%)
7*	Me	NBS (1.1 equiv.), $CHCl_3$, 80 °C, 15 h	**17a** (90%)
8*	Me	NIS (1.25 equiv.), $CHCl_3$, 80 °C, 15 h	**18a** (82%)
9*	Me	NCS (1.5 equiv.), $CHCl_3$, 80 °C, 15 h	**13a** (95%)
10	CH_2	Br_2 (10 equiv.), $CHCl_3$, -60 °C to rt, 15 h	**14b**:**15b** (32%, 1:3); **16b** (38%)
11*	CH_2	NBS (10 equiv.), $CHCl_3$, 80 °C, 15 h	**13b** (22%); **17b** (42%)

*Reactions performed in a sealed tube

4 and 5) did prove to influence product outcome, particularly when 0.55 equiv of bromine was used. Whereas use of 1.4 equiv of bromine (entry 4) gave essentially an identical outcome as the use of 10 equiv (entry 1), 0.55 equiv (entry 5) gave only a trace of 1,2-dibromide **16a**, none of the rearranged di- and tribromides (**14a** and **15a**), and the rearranged alkene **17a** (in 50% of a maximum 55% yield) as the major product.

This latter observation indicated that proton loss from the putative intermediate **9** was indeed feasible, and as long as the resultant alkene could be protected from subsequent dibromination, it could be effectively isolated. On the basis of this, the use of *N*-halosuccinimides was considered in order to both serve as a source of electrophilic halogen at low concentration and, due to the shape of the succinimide anion, a conjugate base to accept a proton from the methyl group flanking the tertiary carbocation. At room temperature no reaction with *N*-bromosuccinimide was realized; however, in chloroform at reflux **17a** was isolated in 66% yield (entry 6). In a sealed tube (held at 80 °C, oil bath temperature, for 15 h), 90% of **17a** was isolated as the sole reaction product. Similarly, use of NIS (entry 8) gave 82% of **18a**. However, the use of NCS, under otherwise identical reaction conditions, led only to recovery of starting material (entry 9). Dibromination of **17a** was performed, which gave an isolable sample of **15a** (without **14a** as a contaminant), serving to confirm both the origin of **15a** and its structure assignment.

The chemistry studied and optimized for the dimethoxy-substituted cyclic sulfonamide **13a** was next considered for dioxolane **13b**. Use of 10 equiv of bromine in chloroform at −60 °C to room temperature (entry 10) led to isolation of 1,2-dibromide **16a** in 38% yield along with a mixture of rearranged products comprising, predominantly, tribromide **15b** and dibromide **14b** (**14b**:**15b**, 1:3, 32%). It was interesting to note that significantly smaller quantities of the rearranged 1,3-dibromide **14b** was observed for the dioxolane series. Pleasingly, use of NBS also led to the rearrangement, and in this case alkene **17b**, formed in 42% yield, could be isolated from starting material **13b**. Stereoelectronic factors serve to diminish the interaction between the lone pairs on dioxolane-substituted aromatic species versus their methoxy-substituted analogues, which are not similarly conformationally constrained.[12] This is a possible explanation for the reduction in amounts of rearrangement products for the dioxolane-substituted material and the different ratios of di- and tribromides (**14** to **15**). It should be noted that the nonsubstituted analogue (not shown) does not undergo this type of rearrangement, demonstrating the influence the +M dimethoxy and dioxolane substituents play in this 1,2-carbon−carbon bond shift.

Following the work outlined in Scheme 4, a means to access the regioisomeric material, albeit brominated (or iodinated), from the IHR had been developed.[7] To exemplify this, as shown in Scheme 5, **17a** was treated with tri-*n*-butyltin hydride in the presence of 2,2′-azoisobutyronylnitrile, leading to the hoped for reduction of the carbon−bromine bond; however, this reaction was not clean and the product directly obtained

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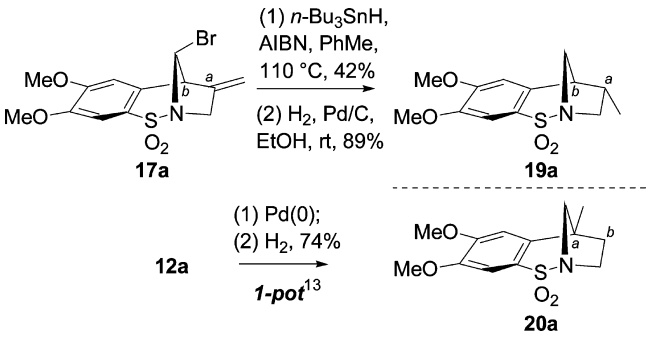
Scheme 5. Reduction of Rearranged Bromide 17a: Reversal of IHR Regiochemistry



from the reaction was contaminated with **13a**, which we presume arises following fragmentation of the secondary radical containing intermediate in a process involving a phenyl shift and generation of a primary radical. Nevertheless, the hoped for alkene could be obtained in 42% yield following careful purification to remove **13a** and then diastereoselectively further reduced to afford **19a**, the regioisomer of the product of our one-pot Heck-hydrogenation sequence,[13] **20a** (Scheme 5).

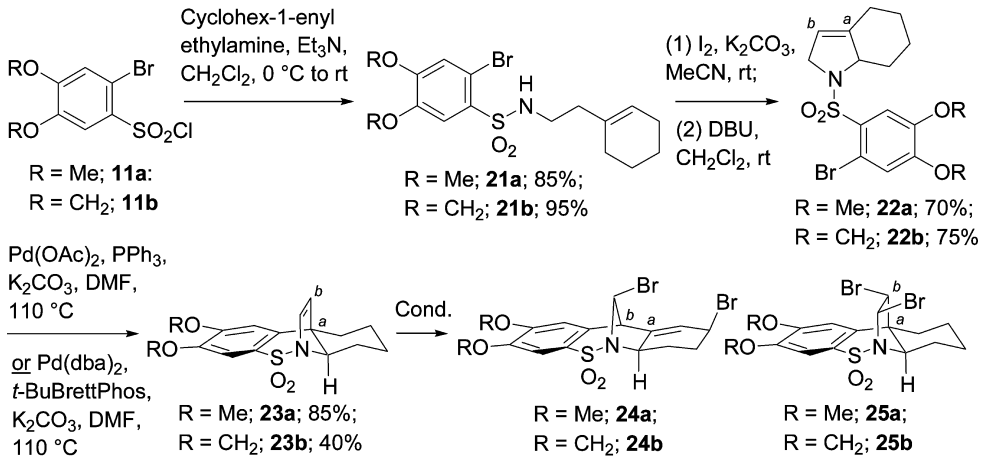
On the basis of the success of the rearrangements for bicyclic sulfonamides **13a** and **13b** (Scheme 4), we next turned our attention to the corresponding tricyclic analogues in which the quaternary center set following IHR comprises part of a fused cyclohexyl ring. Compounds required to study the halogen-triggered rearrangement (**23a** and **23b**) were assembled in four steps using an iodo-amino cyclization based on a report by Knight[14] and developed by us[8a] for these compounds. As before, IHR gave high selectivity for bond formation at the most substituted carbon atom, although dioxolane **22b** gave poorer conversion than **23a**. Optimum yields for this transformation were achieved using Pd(0) with an electron-rich phosphine, following which only 40% of **23b** was isolated (along with 50% of recovered starting material, **22b**).

As shown in Scheme 6, exposure of **23a** to bromine (10 equiv) using the procedure uncovered (Scheme 4) led to the reproducible formation of a major product along with two minor compounds (entry 1). Analysis of the spectroscopic data recorded for the major product, purified by flash column chromatography, indicated that its structure was dibromide **24a** (41% yield). Nuclear Overhauser effects were used to correlate the characteristic methine proton adjacent to nitrogen around the cyclohexenyl ring to the *cis*-allylic methine proton. In terms of mass balance for this reaction, two additional minor reaction products formed that proved to corun chromatographically. However, analysis of their nuclear magnetic resonance spectra indicated that the main component of this mixture was a 1,2-dibromide, the structure of which was tentatively assigned as *trans*-**25a**. In addition, a diastereoisomer of **24a** (epimeric at the allylic bromide) was also identified. Pleasingly, on increasing the concentration of bromine to 20 equiv (entry 2) synthetically useful yields of **24a** were observed.

Two aspects associated with the observation and isolation of **24a** warrant mention: first, it seems that following the hoped for rearrangement the initially formed trisubstituted alkene is reluctant to participate in further 1,2-dibromination, unlike the 1,1-disubstituted alkene **17** formed during the rearrangement of the bicyclic sulfonamides (as discussed above). Second, the initially formed trisubstituted alkene evidently undergoes a fast regio- and diastereoselective allylic bromination.[15] Trace amounts of 1,2-dibromide **25a** were detected, and for this case, again, unlike the bicyclic sulfonamides, NOE indicated that the 1,2-dibromide was predominantly formed as the *trans*-diastereoisomer. On the basis of this it seems reasonable to speculate that this occurs due to the effect that the additional cyclohexyl fused ring has on both the stereochemical sense of bromonium ion formation and on its subsequent reactivity.

The dioxolane containing sulfonamide **23b** was next considered. As indicated in entry 3, use of bromine (10 equiv) gave the desired rearranged product **24b**, again featuring diastereoselective allylic bromination in 33% yield. On the basis

Scheme 6. Synthesis and Rearrangement of Benzo-Annulated Tricyclic Sulfonamides 23a and 23b



Entry	R	Conditions	Product(s) (%)
1	Me	Br_2 (10 equiv.), $CHCl_3$, -60 °C, 4 h	**24a** (41%); **25a** (52%)
2	Me	Br_2 (20 equiv.), $CHCl_3$, -60 °C, 1.5 h	**24a** (77%); **25a** (3%)
3	CH_2	Br_2 (10 equiv.), $CHCl_3$, -60 °C to rt, 4 h	**24b** (33%); **25b** (45%)
4	CH_2	Br_2 (20 equiv.), $CHCl_3$, -60 °C, 1.5 h	**24b** (40%); **25b** (16%)

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of the indication that the efficiency of this process was improved using 20 equiv of bromine, the yield of **24b** was slightly increased (entry 4). Single crystal X-ray crystallography[16] served to confirm the relative stereochemistry of the major dibrominated product (Figure 1).

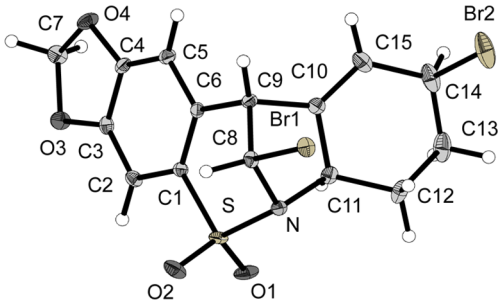

Figure 1. X-ray crystallographic structure of **24b**.

As shown in Figure 2, the type of functionalized 3-aryl-2,3,5,6,7,7a-hexahydroindole skeleton produced is found in a

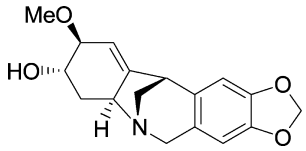

Figure 2. (−)-Montanine.

family belonging to the amaryllidaceae alkaloid class (montanine, brunsvigine, and pancracine).[17]

CONCLUSION

In summary, the bromonium ion triggered[18] rearrangement of a series of cyclic benzo-annulated sulfonamides has been reported. This process features the migration of the benzylic bond, presumably to generate a tertiary carbocation, which can then lose a proton to give a new exocyclic alkene. Depending on the amount of bromine present and the structure of this alkene, additional 1,2-dibromination may (**15**), or may not (**24**), occur. An additional feature is that for the tricyclic sulfonamides **23** a further, diastereoselective allylic bromination is evidently facile.

EXPERIMENTAL SECTION

General Directions. Reactions with anhydrous solvents were carried out under an atmosphere of N_2. Glassware was either dried in an oven or with a heat-gun before use, assembled hot, and cooled to room temperature under a stream of N_2. Anhydrous dichloromethane (CH_2Cl_2) and acetonitrile (MeCN) were distilled from CaH_2; anhydrous dimethylformamide (DMF) and chloroform were used as purchased. Thin layer chromatography (TLC) was carried out using silica-coated aluminum sheets (60 F_{254}), and silica gel (60 Å, 0.040−0.063 mm) was used for flash column chromatography, which was performed at medium pressure. ^1H and ^{13}C NMR spectra were recorded using 300 and 400 MHz instruments as indicated. Reported assignments are based on a combination of two-dimensional $^1H-^1H$ (gCOSY), $^1H-^{13}C$ (HMQC), and NOESY correlation spectra. Samples for infrared spectroscopy were recorded as films on KBr plates using an FT-IR spectrometer. Melting points are uncorrected and were recorded on recrystallized material (from indicated solvent) or material directly obtained following purification by flash column chromatography. High-resolution mass spectra (ESI-HRMS) were obtained using a mass spectrometer with a TOF mass analyzer. Experimental details concerning the preparation of compounds **13a**,[8b] **20a**,[13] and **21a−23a**[8a] have been previously reported.

6-Bromobenzo[*d*][1,3]dioxole-5-sulfonyl Chloride 11b. At 0 °C solution of 5-bromobenzo[*d*][1,3]dioxole **10b** (1.0 mL, 8.3 mmol, 1.0 equiv) in CH_2Cl_2 (40 mL) was treated with a solution of HSO_3Cl (0.7 mL, 10.4 mmol, 1.25 equiv) in CH_2Cl_2 (5 mL) dropwise over 5 min. Stirring was continued for a further 5 min before the reaction mixture was filtered under suction and the solid washed repeatedly with CH_2Cl_2 (5 × 10 mL) to afford 6-bromobenzo[*d*][1,3]dioxole-5-sulfonic acid (1.97 g, 85%) as a gray solid. [Mp: 87−89 °C. IR [KBr, deposited (dep) from CH_2Cl_2]: 1613, 1503, 1485, 1372, 1337, 1251, 1174, 1038, 938 cm^{-1}. HRMS (ESI): calcd for $C_7H_4O_4S^{79}Br$ ($[M - H]^-$) 278.8963, found 278.8964. ^1H NMR (DMSO-d_6, 400 MHz): δ 7.38 (s, 1H), 7.12 (s, 1H), 6.06 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz): δ 148.0, 145.9, 140.9, 113.4, 110.7, 109.0, 102.1.] A mixture of the above sulfonic acid (1.07 g, 3.81 mmol, 1.0 equiv) and $SOCl_2$ (2.76 mL, 38.1 mmol, 10 equiv) in CH_2Cl_2 (40 mL) was heated to reflux for 15 h. The reaction mixture was cooled and filtered, and the filtrate was washed with sat. $NaHCO_3$ (20 mL). The aqueous layer was re-extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and reduced under pressure to give sulfonyl chloride **11b** (643 mg, 57%) as a pale brown oil, which gradually solidified. R_f = 0.5 (*c*-Hex:EtOAc, 3:1). Mp: 54−56 °C. IR (KBr, dep from CH_2Cl_2): 3056, 2984, 2917, 1608, 1507, 1476, 1384, 1251, 1180 cm^{-1}. HRMS (ESI): calcd for $C_7H_4O_4S^{79}Br^{35}ClNa$ ($[M + Na]^+$) 320.8594, found 320.8624. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.62 (s, 1H), 7.23 (s, 1H), 6.16 (s, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.6, 147.6, 136.6, 115.7, 115.1, 110.6, 103.8.

1-[(6-Bromobenzo[*d*][1,3]dioxol-5-yl)sulfonyl]-3-methyl-2,5-dihydro-1*H*-pyrrole 12b. A solution of **11b** (1.00 g. 3.31 mmol, 1.0 equiv) and allylamine (0.34 mL, 4.30 mmol, 1.3 equiv) in CH_2Cl_2 (50 mL) was treated with Et_3N (0.6 mL, 4.30 mmol, 1.3 equiv) in a dropwise fashion at 0 °C. Stirring was continued for 15 h during which period room temperature was reached. HCl (1 M, 20 mL) was added to the reaction mixture, and the layers were separated. The organic layer was washed with H_2O (20 mL) and brine (20 mL) and dried over $MgSO_4$. Filtration followed by solvent removal under pressure afforded the *N*-allyl sulfonamide (862 mg, 81%) as a pale yellow solid. [R_f = 0.4 (*c*-Hex:EtOAc, 3:1). Mp: 101−104 °C. IR (KBr, dep from CH_2Cl_2): 2921, 2853, 1505, 1475, 1329, 1243, 1167, 1034, 924 cm^{-1}. HRMS (ESI): calcd for $C_{10}H_{11}NO_4S^{79}Br$ ($[M + H]^+$) 319.9592, found 319.9599. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.58 (s, 1H), 7.13 (s, 1H), 6.10 (s, 2H), 5.74−5.63 (m, 1H), 5.25−5.06 (m, 3H), 3.54 (t, J = 6.0, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 151.6, 147.7, 135.0, 132.9, 118.5, 114.7, 112.8, 111.7, 102.6, 45.9.] *N*-Allyl-6-bromobenzo[*d*][1,3]-dioxole-5-sulfonamide (400 mg, 1.25 mmol, 1.0 equiv) was dissolved in DMF (5 mL) and cooled to 0 °C. Sodium hydride (60% w/w in mineral oil, 75 mg, 1.89 mmol, 1.5 equiv) was added and the mixture was stirred for 0.5 h. 3-Chloro-2-methylprop-1-ene (0.16 mL, 1.63 mmol, 1.3 equiv) was added in a dropwise fashion. Stirring was continued for 15 h during which time room temperature was reached. EtOAc (10 mL) and H_2O (10 mL) were added and the phases separated. The aqueous layer was further extracted with EtOAc (2 × 10 mL). The combined organic layers were dried over $MgSO_4$. The crude product, obtained after filtration and solvent removal, was purified by column chromatography (*c*-Hex:EtOAc, 6:1 → 3:1), which gave (430 mg, 93%) as a colorless solid. [R_f = 0.5 (*c*-Hex:EtOAc, 3:1). Mp: 39−40 °C. IR (KBr, dep from CH_2Cl_2): 3081, 2981, 2916, 1505, 1475, 1369, 1329, 1243, 1164, 1143, 1033, 925 cm^{-1}. HRMS (ESI): calcd for $C_{14}H_{18}NO_4S^{79}Br$ ($[M + H]^+$) 374.0062, found 374.0069. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.63 (s, 1H), 7.12 (s, 1H), 6.09 (s, 2H), 5.63−5.53 (m, 1H), 5.19−5.10 (m, 2H), 4.95−4.86 (m, 2H), 3.88 (s, 2H), 3.83 (d, J = 6.5 Hz, 2H), 1.65 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.5, 147.3, 140.1, 133.2, 132.3, 119.5, 115.0, 114.9, 113.5, 112.4, 103.1, 53.2, 48.8, 19.9.] Under N_2, a degassed solution of diallyl compound (430 mg, 1.15 mmol, 1.0 equiv) in anhydrous CH_2Cl_2 (50 mL) was treated with Hoveyda−Grubbs' second-generation catalyst (14 mg, 0.023 mmol, 2.0 mol %). Stirring was continued at 40 °C for 15 h. Once cooled, the solvent was removed under reduced pressure. Purification by flash column chromatography (*c*-Hex:EtOAc, 3:1) gave

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12b (324 mg, 82%) as a white solid. R_f = 0.4 (*c*-Hex:EtOAc, 3:1). Mp: 71−73 °C. IR (KBr, dep from CH_2Cl_2): 2918, 1483, 1331, 1260, 1164, 1136, 1036, 936, 737 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{13}NO_4S^{79}Br$ $([M + H])^+$ 345.9749, found 345.9751. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.54 (s, 1H), 7.15 (s, 1H), 6.09 (s, 2H), 5.36−5.34 (m, 1H), 4.22−4.18 (m, 2H), 4.15−4.04 (m, 2H), 1.73 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): 151.5, 147.4, 135.0, 132.0, 119.1, 115.2, 113.4, 111.7, 103.1, 57.8, 55.3, 14.3.

5-Methyl-5*H*-2,5-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*f*][1,2]thiazepine 1,1-Dioxide 13b. Under N_2, a solution of **12b** (100 mg, 0.29 mmol, 1.0 equiv) in anhydrous DMF (3.0 mL) was degassed under a steady stream of nitrogen (ca. 0.5 h). To this solution was added $Pd(OAc)_2$ (6.5 mg, 0.029 mmol, 10 mol %), PPh_3 (15 mg, 0.058 mmol, 20 mol %), and K_2CO_3 (80 mg, 0.58 mmol, 2.0 equiv), and the mixture was heated to 110 °C for 15 h. The reaction vessel was cooled, and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 2:1), affording the Heck product **13b** (72 mg, 80%) as a colorless solid. R_f = 0.3 (*c*-Hex:EtOAc, 3:1). Mp: 130−132 °C. IR (KBr, dep from CH_2Cl_2): 3055, 2915, 2859, 1610, 1504, 1475, 1368, 1330, 1243, 1168, 1148, 1094, 1034, 922, 664 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{12}NO_4S$ $([M + H])^+$ 266.0487, found 266.0475. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.14 (s, 1H), 6.71 (s, 1H), 6.34 (d, J = 4.0 Hz, 1H), 6.22 (d, J = 4.0 Hz, 1H), 6.01−6.00 (m, 2H), 4.36 (d, J = 12.0 Hz, 1H), 3.74 (d, J = 12.0 Hz, 1H), 1.49 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.1, 148.1, 140.7, 138.2, 133.8, 125.8, 107.6, 103.9, 102.1, 68.9, 45.2, 17.7.

(4*R,5*S**,10*S**)-4,10-Dibromo-7,8-dimethoxy-4-methyl-4,5-dihydro-3*H*-2,5-methanobenzo[*f*][1,2]thiazepine 1,1-Dioxide 14a and (4*R**,5*S**,10*S**)-4,10-Dibromo-4-(bromomethyl)-7,8-dimethoxy-4,5-dihydro-3*H*-2,5-methanobenzo[*f*][1,2]-thiazepine 1,1-Dioxide 15a.** A solution of alkene **13a** (40 mg, 0.142 mmol, 1 equiv) in $CHCl_3$ (0.8 mL) was treated with bromine (0.7 mL, 1.42 mmol, 10 equiv) at −60 °C (dry ice−acetone cold bath) and allowed to stir for 15 h during which time room temperature was reached. The reaction was quenched with aq sat. $Na_2S_2O_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$). Filtration, followed by solvent removal under reduced pressure, gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 5:1), affording compounds **14a** and **15a** (37 mg, 55%) as a chromatographically inseparable mixture (**14a**:**15a**; 1:1). R_f = 0.5 (*c*-Hex:EtOAc, 3:1). IR (KBr, dep from CH_2Cl_2): 3010, 2960, 2937, 2849, 1598, 1509, 1464, 1347, 1271, 1154 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{16}NO_4S^{79}Br_2$ $([M + H])^+$ 439.9167, found 439.9146 (**14a**). HRMS (ESI): calcd for $C_{13}H_{14}NO_4S^{79}Br_2$ $([M - HBr + H])^+$ 437.9010, found 437.9019 (**15a**). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.21 (s, 1H), 7.19 (s, 1H), 6.94 (s, 1H), 6.67 (s, 1H), 6.36 (s, 1H), 6.35 (s, 1H), 4.58 (d, J = 15.5 Hz, 1H), 4.49 (d, J = 15.0 Hz, 1H), 4.38−4.35 (m, 1H), 4.33−4.31 (m, 1H), 4.18−4.14 (m, 1H), 4.12−4.11 (m, 1H), 4.05 (s, 1H), 3.97−3.92 (m, 13H), 3.41 (d, J = 11.5 Hz, 1H), 3.04 (d, J = 11.5 Hz, 1H), 1.48 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.8, 152.1, 150.9, 150.4, 128.4, 126.9, 126.7, 126.3, 112.6, 110.5, 107.4, 65.8, 65.6, 65.5, 64.0, 62.8, 61.7, 60.7, 56.7, 43.3, 33.6. Further elution gave (3*R**,4,*R**,5*S**)-3,4-dibromo-7,8-dimethoxy-5-methyl-4,5-dihydro-3*H*-2,5-methanobenzo[*f*][1,2] thiazepine 1,1-dioxide **16a** (21 mg, 33%) as a white solid. R_f = 0.5 (*c*-Hex:EtOAc, 2:1). HRMS (ESI): calcd for $C_{13}H_{15}NO_4S^{79}Br_2Na$ $([M + Na])^+$ 461.8981, found 461.8988.

(4*R,5*S**,11*S**)-4,11-Dibromo-4-methyl-4,5-dihydro-3*H*-2,5-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*f*][1,2]thiazepine 1,1-Dioxide 14b and (4*R**,5*S**,11*S**)-4,11-Dibromo-4-(bromomethyl)-4,5-dihydro-3*H*-2,5-methano[1,3]-dioxolo[4′,5′:4,5]-benzo[1,2-*f*][1,2]thiazepine 1,1-Dioxide 15b.** A solution of alkene **13b** (30 mg, 0.094 mmol, 1 equiv) in $CHCl_3$ (1 mL) was treated with bromine (0.05 mL, 0.94 mmol, 10 equiv) at −60 °C (dry ice−acetone cold bath) and allowed to stir for 15 h, over which time room temperature was reached. An aq sat. $Na_2S_2O_3$ solution (10 mL) was added and the mixture extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$). Filtration, followed by solvent removal under reduced pressure, gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 6:1), affording compounds **14b** and **15b** (15 mg, 32%) as a chromatographically inseparable mixture (**14b**:**15b**, 1:3). R_f = 0.6 (*c*-Hex:EtOAc, 3:1). IR (NaCl, dep from CH_2Cl_2): 3053, 2921, 2855, 1504, 1483, 1347, 1251, 1175, 1036, 931 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{12}NO_4S^{79}Br_2$ $([M + H])^+$ 423.8854, found 423.8835 (**14b**). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.20 (s, 1H), 7.18 (s, 1H), 6.89 (s, 1H), 6.70 (s, 1H), 6.34 (d, 1H, J = 1.0 Hz), 6.35 (d, 1H, J = 1.0 Hz), 6.13−6.11 (m, 4H), 4.54 (d, J = 15.0 Hz, 1H), 4.48 (d, J = 15.0 Hz, 1H), 4.38−4.34 (m, 1H), 4.17−4.14 (m, 1H), 4.12−4.11 (m, 1H), 4.01 (s, 1H), 3.88 (s, 1H), 3.36 (d, J = 11.5 Hz, 1H), 3.14 (d, J = 11.5 Hz, 1H), 1.51 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.5, 149.9, 128.5, 127.4, 110.0, 108.4, 105.6, 103.0, 102.8, 65.9, 65.2, 64.9, 63.9, 63.7, 62.9, 61.5, 60.1, 42.3, 33.5. Coincident carbon peaks. Further elution gave (3*R**,4*R**,5*S**)-3,4-dibromo-5-methyl-4,5-dihydro-3*H*-2,5-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*f*][1,2]thiazepine 1,1-dioxide **16b** (15 mg, 38%) as a white solid. R_f = 0.5 (*c*-Hex:EtOAc, 3:1). HRMS (ESI): calcd for $C_{12}H_{12}NO_4S^{79}Br_2$ $([M + H])^+$ 423.8854, found 423.8844.

(5*S,10*S**)-10-Bromo-7,8-dimethoxy-4-methylene-4,5-dihydro-3*H*-2,5-methanobenzo[*f*][1,2]thiazepine 1,1-Dioxide 17a.** A mixture of **13a** (40 mg, 0.14 mmol, 1 equiv) and *N*-bromosuccinimide (27 mg, 0.154 mmol, 1.1 equiv) in $CHCl_3$ (0.8 mL, 0.178 M) was heated (oil bath temperature 80 °C) in a sealed tube for 15 h. Once cooled, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers partitioned. The organic layer was washed successively with H_2O and brine and dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 4:1) affording the title compound **17a** (45 mg, 90%) as a colorless solid. R_f = 0.3 (*c*-Hex:EtOAc, 2:1). Mp: 48−50 °C. IR (KBr, dep from CH_2Cl_2): 3063, 2938, 2848, 1704, 1599, 1511, 1343, 1268, 1173, 1151, 1047, 1047, 916, 753 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{15}NO_4S^{79}Br$ $([M + H])^+$ 359.9905, found 359.9918. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (s, 1H), 6.64 (s, 1H), 6.30 (s, 1H), 5.35 (s (br), 1H), 5.11 (s (br), 1H), 4.43−4.25 (m, 2H), 3.93 (s, 3H), 3.90 (s, 3H), 3.87 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 153.2, 149.9, 144.6, 130.6, 125.6, 109.4, 108.3, 107.5, 67.3, 57.7, 56.5, 50.1. Anal. Calcd for $C_{13}H_{14}NO_4BrS$: C, 43.35; H, 3.92; N, 3.89. Found: C, 43.20; H, 3.62; N, 3.71.

Method Using Bromine. A solution of alkene **13a** (30 mg, 0.107 mmol, 1 equiv) in $CHCl_3$ (0.6 mL) was treated with bromine (3.0 μL, 0.058 mmol, 0.55 equiv) at −60 °C (dry ice−acetone cold bath) and allowed to stir for 15 h. Over this period room temperature was reached and the reaction was quenched with aq sat. $Na_2S_2O_3$ solution (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried ($MgSO_4$). Filtration, followed by solvent removal under reduced pressure, gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 4:1) affording the title compound **17a** (19 mg, 50%) as a colorless solid with data as above.

(5*S,10*S**)-10-Iodo-7,8-dimethoxy-4-methylene-4,5-dihydro-3*H*-2,5-Methanobenzo[*f*][1,2]thiazepine 1,1-Dioxide 18a.** A mixture of **13a** (40 mg, 0.14 mmol, 1 equiv) and *N*-iodosuccinimide (39 mg, 0.18 mmol, 1.25 equiv) in $CHCl_3$ (0.8 mL, 0.178 M) was heated (oil bath temperature 80 °C) in a sealed tube for 15 h. Once cooled, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers partitioned. The organic layer was washed successively with H_2O and brine and dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 4:1), affording the title compound **18a** (47 mg, 82%) as a colorless solid. R_f = 0.3 (*c*-Hex:EtOAc, 2:1). Mp: 174−176 °C. IR (KBr, dep from CH_2Cl_2): 2882, 1598, 1508, 1463, 1339, 1267, 1219, 1150, 1046, 1011, 912, 746, 639 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{14}NO_4SINa$ $([M + Na])^+$ 429.9599, found 429.9586. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.18 (s, 1H), 6.61 (s, 1H), 6.60 (s, 1H), 5.34−5.33 (m, 1H), 5.13 (s, 1H),

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4.42−4.29 (m, 2H), 3.95−3.89 (m, 7H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.8, 149.9, 145.5, 130.8, 125.6, 109.0, 107.9, 107.7, 59.8, 56.4, 50.4, 42.4.

(5*S,11*S**)-11-Bromo-4-methylene-4,5-dihydro-3*H*-2,5-methano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*f*][1,2]thiazepine 1,1-Dioxide 17b.** A mixture of **13b** (40 mg, 0.15 mmol, 1 equiv) and *N*-bromosuccinimide (269 mg, 1.51 mmol, 10 equiv) in $CHCl_3$ (0.85 mL, 0.178 M) was heated (oil bath temperature 80 °C) in a sealed tube for 15 h. Once cooled, CH_2Cl_2 (10 mL) and H_2O (10 mL) were added and the layers partitioned. The organic layer was washed successively with H_2O and brine and dried over $MgSO_4$. Filtration, followed by solvent removal under reduced pressure, gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 4:1), affording the title compound **17b** (22 mg, 42%) as a light brown solid. R_f = 0.5 (*c*-Hex:EtOAc, 3:1). Mp: 211−213 °C. IR (KBr, dep from CH_2Cl_2): 2918, 1614, 1504, 1481, 1342, 1246, 1159, 1120, 1036, 916, 668 cm^{-1}. HRMS (ESI): calcd for $C_{12}H_{11}NO_4S^{79}Br$ ($[M + H]$)$^+$ 343.9583, found 343.9592. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.16 (s, 1H), 6.66 (s, 1H), 6.29 (s, 1H), 6.06 (d, J = 1.5 Hz, 1H), 6.05 (d, J = 1.5 Hz, 1H), 5.33−5.31 (m, 1H), 5.12 (s (br), 1H), 4.43−4.25 (m, 2H), 3.83 (s, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.8, 148.5, 144.4, 132.3, 127.1, 109.2, 106.2, 105.6, 102.6, 66.9, 57.9, 49.9.

(4*S,5*S**)-7,8-Dimethoxy-4-methyl-4,5-dihydro-3*H*-2,5-methanobenzo[*f*][1,2]thiazepine 1,1-Dioxide 19a.** A solution of **17a** (100 mg, 0.28 mmol, 1 equiv) in anhydrous toluene (6 mL) was treated with *n*-Bu_3SnH (0.097 mL, 0.363 mmol, 1.3 equiv) and AIBN (cat.). The reaction mixture was heated to reflux for 15 h (oil bath temperature 110 °C). Once cooled, Et_2O (50 mL) and 2% KF solution (100 mL) were added, and the reaction mixture was stirred for 2 h, after which the layers were separated. The aqueous layer was extracted with Et_2O (2 × 50 mL), and the combined ethereal layers were dried ($MgSO_4$). Filtration followed by solvent removal gave the crude material, which was purified by column chromatography (*c*-Hex:EtOAc, 4:1) to afford the debrominated compound (33 mg, 42%) as a brown viscous oil. [7,8-Dimethoxy-4-methylene-4,5-dihydro-3*H*-2,5-methanobenzo[*f*][1,2] thiazepine 1,1-dioxide: R_f = 0.3 (*c*-Hex:EtOAc, 2:1). HRMS (ESI): calcd for $C_{13}H_{16}NO_4S$ ($[M + H]$)$^+$ 282.0800, found 282.0812. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.20 (s, 1H), 6.65 (s, 1H), 5.19 (s, 1H), 4.93 (s, 1H), 4.29 (dd, J = 12.5 Hz, 2.5 Hz, 1H), 4.02−3.97 (m, 1H), 3.93 (s, 3H), 3.90 (s, 4H), 3.53−3.51 (m, 1H), 3.44 (dd, J = 12.5, 3.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 152.5, 149.9, 148.3, 132.6, 125.7, 108.7, 108.1, 106.7, 57.6, 56.4, 56.3, 52.3, 47.1.] A mixture of the alkene (18 mg, 0.064 mmol, 1.0 equiv) and 20% w/w Pd/C (1.4 mg, 0.013 mmol) in EtOH:EtOAc (1:1, 10 mL) was stirred under an atmosphere of hydrogen (1 atm) for 15 h. The mixture was filtered through Celite (washed with EtOAc, 3 × 20 mL) and solvent removal afforded the alkane compound **19a** (16 mg, 89%) as a colorless viscous oil. R_f = 0.3 (*c*-Hex:EtOAc, 2:1). IR (KBr, dep from CH_2Cl_2): 2958, 2924, 2853, 1602, 1509, 1463, 1322, 1264, 1146 cm^{-1}. HRMS (ESI): calcd for $C_{13}H_{17}NO_4SNa$ ($[M + Na]$)$^+$ 306.0776, found 306.0768. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.22 (s, 1H), 6.56 (s, 1H), 4.26 (dd, J = 12.5, 1.5 Hz, 1H), 3.90 (s, 6H), 3.66 (dd, J = 13.5, 9.5 Hz, 1H), 3.34 (dd, J = 3.0, 1.5 Hz, 1H), 3.26−3.22 (m, 1H), 2.94−2.92 (m, 1H), 2.69−2.60 (m, 1H), 0.78 (d, J = 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.7, 149.1, 129.9, 127.3, 111.2, 108.2, 58.2, 56.3, 54.0, 44.6, 38.9, 16.4.

6-Bromo-*N*-(2-(cyclohex-1-en-1-yl)ethyl)benzo[*d*][1,3]-dioxole-5-sulfonamide 21b. A mixture of sulfonyl chloride **11b** (600 mg, 2.02 mmol, 1.0 equiv) and 2-cyclohex-1-enyethylamine (0.37 mL, 2.42 mmol, 1.2 equiv) in CH_2Cl_2 (15 mL) was treated with Et_3N (0.34 mL, 2.42 mmol, 1.2 equiv) in a dropwise fashion at 0 °C. Stirring was continued for 15 h during which period room temperature was reached. HCl (1 M, 10 mL) was added to the reaction mixture, and the layers were separated. The organic layer was washed successively with sat. $NaHCO_3$ (10 mL), H_2O (10 mL), and brine and was dried over $MgSO_4$. Filtration followed by solvent removal under pressure afforded the crude product. Purification through a plug of silica (*c*-Hex:EtOAc, 2:1) afforded the title compound (743 mg, 95%) as a brown viscous oil. R_f = 0.2 (*c*-Hex:EtOAc, 4:1). IR (KBr, dep from CH_2Cl_2): 2925, 1504, 1475, 1369, 1329, 1243, 1167, 1136, 1034, 653 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{19}NO_4S^{79}Br$ ($[M + H]$)$^+$ 388.0218, found 388.0235. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.60 (s, 1H), 7.13 (s, 1H), 6.10 (s, 2H), 5.47 (s (br), 1H), 5.06 (t, J = 6.0 Hz, 1H), 2.94 (q, J = 6.0 Hz, 2H), 2.11 (t, J = 6.0 Hz, 2H), 1.99 (s (br), 2H), 1.76 (s (br), 2H), 1.67−1.48 (m, 4H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.5, 147.4, 133.3, 131.9, 125.1, 114.4, 112.2, 111.6, 102.9, 40.6, 37.1, 27.5, 25.2, 22.6, 22.2.

1-((6-Bromobenzo[*d*][1,3]dioxol-5-yl)sulfonyl)-2,4,5,6,7,7a-hexahydro-1*H*-indole 22b. A solution of **21b** (1.0 g, 2.58 mmol, 1.0 equiv) in distilled MeCN (20 mL) was treated with powdered K_2CO_3 (1.31 g, 9.48 mmol, 3.6 equiv). The mixture was stirred for 1 h at room temperature. Finely ground I_2 (907 mg, 9.48 mmol, 3.6 equiv) was added in one portion and the reaction stirred for 4 h. A solution of sat. Na_2SO_3 (50 mL) was added and the combined mixture was extracted with CH_2Cl_2 (2 × 50 mL). The combined extracts were dried over $MgSO_4$, filtered, and reduced under pressure to afford the crude iodide. The crude material was directly dissolved in CH_2Cl_2 (30 mL) and treated with DBU (0.77 mL, 5.16 mmol, 2.0 equiv) at room temperature. Stirring was maintained for 2 h before 1 M HCl (15 mL) was added, and the layers were separated. The resulting aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL), and the combined organic layers were dried over $MgSO_4$. The crude product, obtained after filtration, solvent removal, and purification by column chromatography (*c*-Hex:EtOAc, 4:1), was **22b** (750 mg, 75%), a brown viscous oil. R_f = 0.5 (*c*-Hex:EtOAc, 2:1). IR (KBr, dep from CH_2Cl_2): 2933, 2853, 1610, 1505, 1475, 1368, 1327, 1242, 1166, 1142, 1082, 1034, 922, 671 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{16}NO_4S^{79}BrNa$ ($[M + Na]$)$^+$ 407.9876, found 407.9880. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.51 (s, 1H), 7.14 (s, 1H), 6.08 (s, 2H), 5.26 (s (br), 1H), 4.31−4.25 (m, 2H), 4.22−4.18 (m, 2H), 2.50−2.44 (m, 2H), 2.20−2.16 (m, 2H), 2.00−1.96 (m, 2H), 1.32−1.19 (m, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.4, 147.8, 142.1, 132.8, 115.2, 114.3, 113.6, 111.3, 102.9, 66.5, 55.5, 35.6, 28.6, 26.5, 24.0.

2,3,4,4a-Tetrahydro-1*H*-5,11b-etheno[1,3]dioxolo[4′,5′:4,5]-benzo[1,2-e]benzo[*c*][1,2]thiazine 6,6-Dioxide 23b. Under N_2, a premixed solution (1 h at 50 °C) of $Pd(dba)_2$ (8 mg, 0.014 mmol, 10 mol %) and *t*-BuBrett-Phos (13 mg, 0.03 mmol, 21 mol %) in anhydrous DMF (2 mL) was treated with a solution of **22b** (53 mg, 0.14 mmol, 1 equiv) in anhydrous DMF (0.5 mL) and K_2CO_3 (39 mg, 0.28 mmol, 2 equiv), and the mixture was heated to 110 °C for 15 h. The reaction vessel was cooled, and EtOAc (10 mL) and H_2O (10 mL) were added. The resultant aqueous layer was further extracted with EtOAc (2 × 10 mL), and the combined organic extracts were dried over $MgSO_4$. Filtration followed by solvent removal under reduced pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 6:1→1:1), affording the Heck product **23b** (17 mg, 40%, 80% brsm) as a light brown viscous oil. R_f = 0.3 (*c*-Hex:EtOAc, 2:1). IR (KBr, dep from CH_2Cl_2): 2932, 1609, 1504, 1482, 1346, 1249, 1176, 1161, 1036, 944, 757, 673 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{16}NO_4S$ ($[M + H]$)$^+$ 306.0800, found 306.0809. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.14 (s, 1H), 6.70 (s, 1H), 6.20 (d, J = 3.5 Hz, 1H), 6.12 (d, J = 3.5 Hz, 1H), 6.00 (app. d, J = 4.5 Hz, 2H), 4.46−4.42 (m, 1H), 2.36 (d, J = 13.5 Hz, 1H), 2.16−2.10 (m, 1H), 1.88−1.49 (m, 4H), 1.42−1.09 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 150.1, 147.8, 140.8, 138.3, 132.8, 126.4, 107.4, 103.4, 102.1, 72.4, 48.6, 28.5, 27.7, 22.9, 21.7.

(6a*R,9*S**,11*S**,12*S**)-9,12-Dibromo-2,3-dimethoxy-7,8,9,11-tetrahydro-6a*H*-6,11-methanodibenzo[*c*,*f*][1,2]-thiazepine 5,5-Dioxide 24a.** A solution of **23a** (18 mg, 0.056 mmol, 1 equiv) in $CHCl_3$ (0.8 mL, 0.178 M) was treated with Br_2 (57 μL, 1.12 mmol, 20 equiv) at −60 °C (dry ice−acetone cold bath) and allowed to stir at this temperature for 1.5 h (reaction monitored by TLC). The reaction was quenched with aq sat. $Na_2S_2O_3$ solution (10 mL) and the reaction mixture allowed to warm to room temperature. The reaction micture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$). Filtration followed by solvent removal under reduced pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 4:1), affording initially (6a*R**,10a*R**,11*R**,12*S**)-11,12-dibromo-2,3-dimethoxy-7,8,9,10-tetrahydro-6a*H*-6,10a-ethanodibenzo[*c*,*e*][1,2]thiazine

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5,5-dioxide **25a** (3 mg, 11%) as a white solid. R_f = 0.6 (*c*-Hex:EtOAc, 2:1). HRMS (ESI): calcd for $C_{16}H_{19}NO_4S^{79}Br_2Na$ ($[M + Na]^+$ 501.9294, found 501.9314. Further elution gave title compound **24a** (21 mg, 77%) as a colorless solid. R_f = 0.5 (*c*-Hex:EtOAc, 2:1). Mp: 181−183 °C. IR (KBr, dep from CH_2Cl_2): 2932, 1609, 1504, 1482, 1346, 1249, 1176, 1161, 1036, 944, 757, 673 cm^{-1}. HRMS (ESI): calcd for $C_{16}H_{18}NO_4S^{79}Br_2$ ($[M + H]^+$ 477.9323, found 477.9332. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.19 (s, 1H), 6.62 (s, 1H), 6.35 (s, 1H), 6.17 (s, 1H), 4.90 (s, 1H), 4.38−4.32 (m, 1H), 3.92 (s, 3H), 3.91 (s, 3H), 3.86 (s (br), 1H), 2.46−2.39 (m, 2H), 2.33−2.26 (m, 1H), 2.18−2.08 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 159.2, 150.6, 140.2, 128.2, 126.1, 125.1, 109.6, 108.0, 66.8, 59.3, 56.6, 56.5, 56.1, 46.4, 32.3, 24.3.

(6a*R,9*S**,11*S**,13*S**)-9,13-Dibromo-7,8,9,11-tetrahydro-6a*H*-6,11-methano-[1,3]-dioxolo[4′,5′:4,5]benzo[1,2-*f*]benzo-[*c*][1,2]thiazepine 5,5-Dioxide 24b.** A solution of **23b** (20 mg, 0.066 mmol, 1 equiv) in $CHCl_3$ (0.35 mL, 0.178 M) was treated with Br_2 (64 μL, 1.24 mmol, 20 equiv) at −60 °C (dry ice−acetone cold bath) and allowed to stir at this temperature for 1.5 h. The reaction was quenched with aq sat. $Na_2S_2O_3$ solution (10 mL) and the solution allowed to warm to room temperature. The mixture was extracted with CH_2Cl_2 (3 × 10 mL), and the combined organic layers were dried ($MgSO_4$). Filtration followed by solvent removal under reduced pressure gave the crude product, which was purified by flash column chromatography (*c*-Hex:EtOAc, 4:1), affording initially (5a*R**,11b*R**,12*R**,13*S**)-12,13-dibromo-2,3,4,4a-tetrahydro-1*H*-5,11b-ethano[1,3]dioxolo[4′,5′:4,5]benzo[1,2-*e*]benzo[*c*][1,2]thiazine 6,6-dioxide **25b** (5 mg, 16%) as a colorless solid. R_f = 0.5 (*c*-Hex:EtOAc, 2:1). HRMS (ESI): calcd for $C_{15}H_{15}NO_4S^{79}Br_2$ ($[M + Na]^+$ 485.8981, found 485.8992. Further elution gave the title compound **24b** (12 mg, 40%) as a colorless solid. R_f = 0.4 (*c*-Hex:EtOAc, 2:1). Mp: 172−175 °C. IR (KBr, dep from CH_2Cl_2): 2960, 2923, 1609, 1504, 1481, 1342, 1249, 1178, 1160, 1036, 944, 821, 756 cm^{-1}. HRMS (ESI): calcd for $C_{15}H_{13}NO_4S^{79}Br_2Na$ ($[M + Na]^+$ 483.8824, found 483.8841. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.17 (s,1H), 6.65 (s, 1H),6.34 (s, 1H), 6.14 (s, 1H), 6.07−6.05 (m, 2H), 4.09 (s (br), 1H), 4.38−4.31 (m, 1H), 3.82 (s, 1H), 2.48−2.38 (m, 2H), 2.32−2.26 (m, 1H), 2.17−2.08 (m, 1H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 151.9, 148.7, 139.9, 129.9, 127.7, 125.7, 107.7, 106.2, 102.3, 66.4, 59.2, 56.8, 48.5, 32.5, 24.1. Crystals suitable for X-ray diffraction were obtained from (CH_2Cl_2−*c*-Hex).

■ ASSOCIATED CONTENT

Supporting Information

Copies of proton and carbon NMR spectra, NOE correlation for compounds **14**, **15**, and **19** and X-ray crystallographic data for **13b** and **24b**. This material is available free of charge via the Internet at: http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: paul.evans@ucd.ie. Tel: +353-1-716-2291

Notes

The authors declare no competing financial interest.

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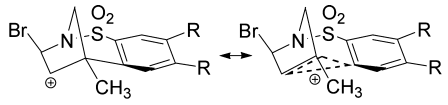

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