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Application of an isomerization-ring-closing metathesis strategy to the synthesis of unsaturated seven-membered, benzo-fused heterocycles containing two heteroatoms

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ABSTRACT

An isomerization-RCM approach was utilized to synthesize a number of seven-membered benzo-fused heterocycles containing two heteroatoms (*N*,*O*, *N*,*S*, and *S*,*O*). This approach utilized the ruthenium catalyst [RuClH(CO)(PPh_3)$_3$] for the isomerization of allyl groups, eventually followed by the use of the Grubbs second generation catalyst for the formation of the desired products. In most instances thermal RCM conditions were sufficient; however, in a number of cases where this methodology did not give the desired product a high temperature, short time microwave approach afforded the desired ring-closed products. In this manner, the following substituted benzo-fused scaffolds were successfully synthesized: 4,5-dihydro-1,5-benzoxazepine, 4,5- and 2,5-dihydro-1,5-benzothiazepine and 2*H*-1,5-benzoxathiepine.

1. Introduction

A structure-based literature search soon reveals that benzo-fused heterocycles are very popular motifs in medicinal chemistry. It is because of this phenomenon that they have been labeled 'privileged structures'.[1] Of these, there are a number of known seven-membered benzannulated compounds containing the heteroatoms oxygen, nitrogen, and sulfur. These include the mono-heteroatom containing compounds 2,3,4,5-tetrahydro-1-benzoxepine **1**, 2,3,4,5-tetrahydro-1*H*-1-benzazepine **2**, and 2,3,4,5-tetrahydro-1-benzothiepine **3** (Fig. 1). Examples containing different combinations of two heteroatoms in the heterocyclic portion of the annulated molecules include 3,4-dihydro-2*H*-1,5-benzodioxepine **4**, 2,3,4,5-tetrahydro-1*H*-1,5-benzodiazepine **5**, 3,4-dihydro-2*H*-1,5-benzodithiepine **6**, 2,3,4,5-tetrahydro-1,5-benzoxazepine **7**, 3,4-dihydro-2*H*-1,5-benzoxathiepine **8**, and 2,3,4,5-tetrahydro-1,5-benzothiazepine **9**.[2]

A number of the scaffolds with two heteroatoms, as shown in Fig. 1, have found utilization in medicinal studies. Examples shown in Fig. 2 include the benzodiazepine **10** and benzoxazepine **11**, both of which demonstrated activity as non-peptide vasopressin V_2 receptor agonists.[3] The benzothiazepine class of compounds is represented by molecule **12**, a compound with interesting muscular contractile activity.[4] Finally, benzoxathiepine **13**, containing a sulfone and an ether functional group in the benzannulated heterocycle, were studied as part of a set of Na^+/H^+ antiporter inhibitors.[5]

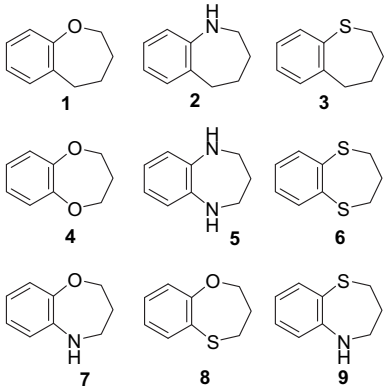

Fig. 1. Seven-membered benzo-fused heterocycles with two heteroatoms.

The application of ring-closing metathesis (RCM)[6] to the synthesis of benzo-fused seven-membered heteroatom-containing compounds containing an alkene functionality has been relatively

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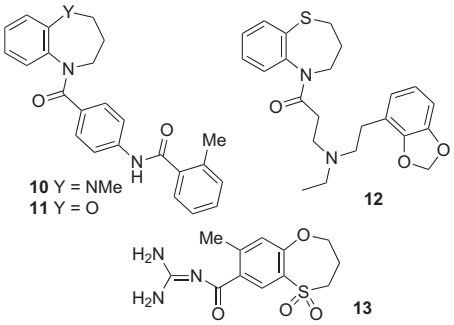
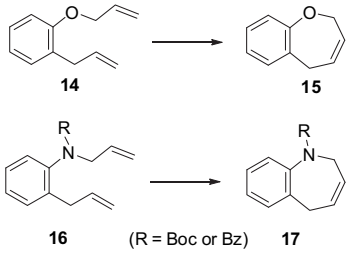


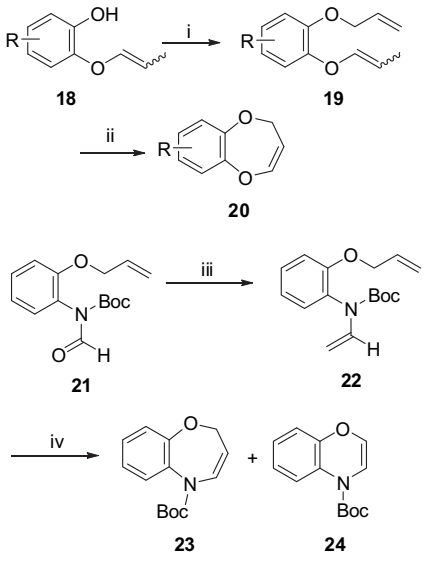
Fig. 2. Examples of bioactive seven-membered benzo-fused heterocycles with two heteroatoms.

straight-forward. In fact, precursor **14** has regularly been used as a 'test substrate' for novel metathesis catalysts, resulting in the synthesis of 2,5-dihydro-1-benzoxepine **15** (Scheme 1).[7] In addition, the 2,5-dihydro-1*H*-1-benzazepine **17** backbone has also been synthesized in a similar way from compound **16** (R=Boc,[8] R=Bz[9]).

To the best of our knowledge however, only two papers have reported the synthesis of seven-membered benzo-fused compounds containing two heteroatoms, making use of an RCM strategy. In 2004, Guillaumet and co-workers efficiently demonstrated the synthesis of substituted 2*H*-1,5-benzodioxepins **20** from precursors **19**, which were readily prepared from **18** (Scheme 2).[10] In



Scheme 1. Previous RCM approaches.



Scheme 2. Reagents and conditions: (i) allyl bromide, K_2CO_3, acetone, 10 h (80–86%);[10] (ii) Grubbs first generation catalyst or **25** (10–20 mol %), C_6H_6, 55 °C, 6–17 h (0–82% for Grubbs first generation catalyst, 53–98% for **25**);[10] (iii) Cp_2TiMe_2 (1.5 mol equiv), toluene/pyridine, reflux, 4 h;[11] (iv) **25** (3×10%), benzoquinone (0.3 mol equiv), 80 °C, 58 h, **23**/**24** (1:3 over two steps, no yield specified).[11]

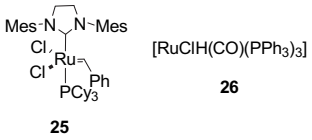
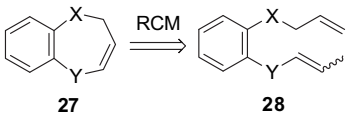


Fig. 3. Ruthenium catalysts used in this work.

addition, Bennasar and co-workers described the formation of *tert*-butyl 1,5-benzoxazepine-5(2*H*)-carboxylate **23** from diene **22**, alongside the formation of the related 4*H*-1,4-benzoxazine **24**, due to the undesired isomerization of the allyl ether prior to metathesis, under the reaction conditions employed.[11]

Over the last number of years, the synthesis of benzo-fused aromatic systems has been one of the central themes of the research performed in our group. We have made extensive use of the well-known ruthenium-mediated ring-closing metathesis (RCM) reaction, utilizing the Grubbs second generation compound **25** as our catalyst of choice,[12] to build a number of benzannulated compounds (Fig. 3).[13] In addition, we have successfully applied an isomerization-RCM[14] reaction sequence (sequential or one-pot), to afford various benzo-fused aromatic systems not always easily obtained by other synthetic approaches.[15,16] To accomplish the isomerizations we have often applied the robust catalyst **26**, with dependable results (Fig. 3).[17]

In this paper we will disclose the details of the successful application of a sequential isomerization-RCM strategy for the synthesis of a number of novel seven-membered annulated heterocycles containing two heteroatoms, X and Y, as well as a carbon–carbon double bond in the heterocyclic ring, as shown in the disconnection **27**→**28** (Scheme 3).[18] This paper will thus describe the application of the methodology to systems where X,Y = N,O, S,N, and S,O, respectively.[19] It should be clear from the disconnection in Scheme 3 that the synthetic strategy will involve the metathesis of a vinyl group conjugated to a heteroatom, a particular type of ene–ene metathesis reaction seeing increased use over the last number of years.[20]



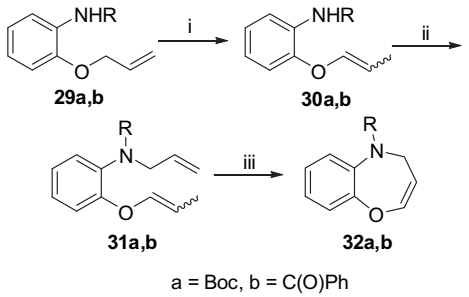
Scheme 3. Retrosynthetic analysis of the work described in this paper.

2. Results and discussion

2.1. Synthesis of 4,5-dihydro-1,5-benzoxazepines

Since Bennasar[11] and co-workers had been successful in demonstrating that RCM could be utilized to synthesize the 2,5-dihydro-1,5-benzoxazepine structure **23** from precursor **22**, albeit in a low yield, it was decided to focus the synthetic efforts on the regioisomeric 4,5-dihydro-1,5-benzoxazepine analogue. The readily synthesized precursor **29a**[21] was therefore exposed to the isomerization catalyst [RuClH(CO)(PPh_3)$_3$] **26**, to give the vinyloxy ether **30a** as a 2:1 mixture of *E*/*Z* isomers (Scheme 4). Subsequent allylation of this product afforded diene **31a**, also without any problems. Finally, RCM using 10% of catalyst **25** then readily afforded the desired seven-membered heterocyclic compound *tert*-butyl 1,5-benzoxazepine-5(4*H*)-carboxylate **32a** in a reasonable yield of 60%.

To demonstrate the versatility of this approach we also synthesized the corresponding benzoyl-protected derivative **32b** (Scheme 4). The synthetic pathway, **29b**→**30b**→**31b**→**32b** was accomplished according to the reaction conditions described in the



Scheme 4. Reagents and conditions: (i) (a) R=Boc, **26** (5 mol %), toluene, Ar, 80–100 °C, 18 h (98%), (b) R=C(O)Ph, **26** (4 mol %), neat, Ar, 65 °C, 24 h (92%); (ii) NaH, DMF, allylBr, N_2, rt, 18 h, [(a) R=Boc, 83%; (b) R=C(O)Ph, 95%]; (iii) (a) R=Boc, **25** (10 mol %), toluene, 60 °C, Ar, 18 h, (60%), (b) R=C(O)Ph, **25** (5 mol %), toluene, 80 °C, Ar, 8 h, (50%).

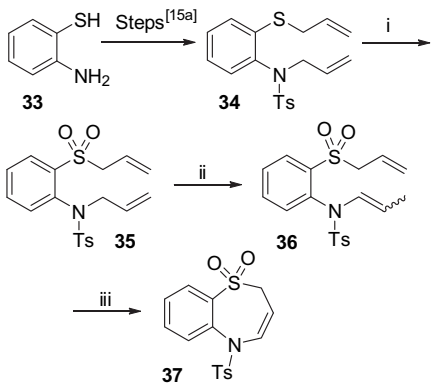
legend of Scheme 4 and afforded the desired benzoyl-protected 4,5-dihydro-1,5-benzoxazepine **32b** in reasonable yield of 44% over three synthetic steps.

2.2. Synthesis of 4,5-dihydro-1,5-benzothiazepine, 2,5-dihydrobenzo[*b*][1,4]thiazepine and derivatives

The RCM of substrates containing sulfur atoms has become more important in the last few years.[22] In addition, the application of RCM to synthesize benzo-fused *S*-containing heterocycles has seen more investigation.[8,23] We thus decided to test whether we could synthesize the seven-membered benzo-fused ring systems containing sulfur, in addition to nitrogen or oxygen.

To this end, aminothiol **33** was thus readily converted into compound **34** (Scheme 5).[15a] This substrate was then oxidized to the corresponding sulfone **35** using *m*CPBA at −5 °C. We were then able to perform a selective alkene isomerization on **35** to obtain compound **36**, in which only the *N*-allyl group had been isomerized. Kuźnik and co-workers have shown that allyl sulfones can be isomerized to the thermodynamically more stable internal form,[24] but under our reaction conditions only the *N*-allyl group was affected by the ruthenium catalyst **26**. Subsequently, when compound **36** was treated with Grubbs catalyst **25**, the seven-membered 1,5-benzothiazepine **37** was obtained, although the reaction was particularly slow. This led to the desired product **37** being isolated in 41% yield, in addition to unreacted starting material **36** in 59% yield.[13e]

A single-crystal X-ray diffraction study confirmed the structure of compound **37**, with the sulfonamide-protected enamine functionality clearly in place. In addition, it was evident that the



Scheme 5. Reagents and conditions: (i) *m*CPBA (2.2 equiv), CH_2Cl_2, −5 °C, N_2, 48 h (71%); (ii) **26** (10 mol %), toluene, Ar, 105 °C, 24 h (84%); (iii) **25** (5 mol %), toluene, 50 °C, Ar, 24 h, then further **25** (5 mol %), 80 °C, Ar, 24 h, **37** (41%) and **36** (59%).

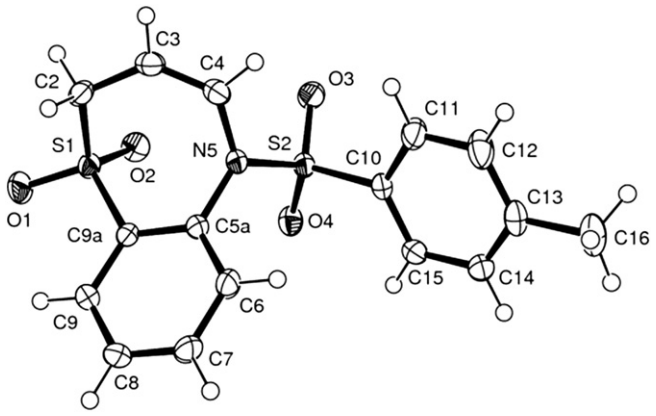
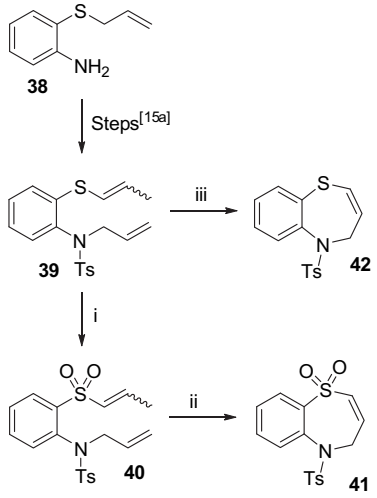


Fig. 4. ORTEP representation of compound **37**.

metathesis reaction had successfully afforded the seven-membered 2,5-dihydro-1,5-benzothiazepine skeleton, with the double bond clearly between C3 and C4 (numbering as shown in Fig. 4).

Next, it was decided to synthesize the regiosiomeric 1,5-benzothiazepine skeleton, in which the alkene was now a vinyl sulfide, by using a modified approach. To this end, 2-(allylsulfanyl)aniline **38** was readily converted into the *N*-[2-(1-propenylsulfanyl)phenyl] benzenesulfonamide **39** (Scheme 6) as described before.[15a] Once again, this particular compound was converted to the sulfone **40** and when this was treated with the metathesis catalyst **25** under the previously utilized conditions, none of the desired product was formed; prolonged reaction times only led to decomposition of the starting material. Hence, it was decided to apply microwave heating as described in the literature,[25] but unfortunately the usual moderate conditions described were unsuccessful in providing desired compound **41**. Finally, the application of a high temperature (145 °C), short duration (10 min) microwave heating regime[26] (80 W) did give more satisfactory results with **41** being obtained in 67% yield. It should be noted that it was found to be necessary to use higher catalyst loadings (20%) under these conditions to get a reasonable yield of product. Comparison of the NMR spectra of this compound with that obtained for regioisomer **37** clearly indicated that the double bond was now between C2 and C3.

We were delighted to observe that the sulfide **39** (Scheme 6), when subjected to the short time, high temperature metathesis

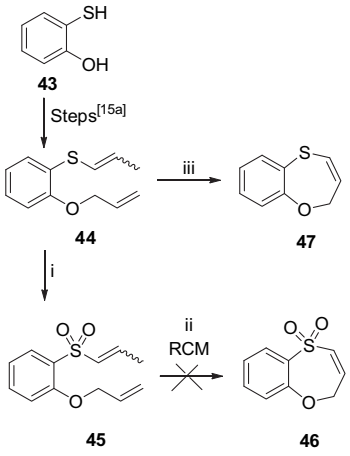


Scheme 6. Reagents and conditions: (i) *m*CPBA (2.2 equiv), CH_2Cl_2, −5 °C–0 °C, N_2, 24 h (84%); (ii) **25** (20 mol %), toluene, MW, Ar, 145 °C, 80 W, 10 min (67%); (iii) **25** (20 mol %), toluene, MW, Ar, 145 °C, 80 W, 10 min (92%).

microwave conditions,[26] furnished the desired product **42** in an excellent yield of 92% (of note is that under the milder metathesis conditions no cyclized product was formed). It would thus appear that these harsh conditions allow for the metathesis of the more hindered propenyl derivatives, as well as overcoming potential catalyst disrupting chelations from donor atoms, such as sulfur, which could be problematic under 'normal' thermal RCM conditions.

2.3. Synthesis of 2*H*-1,5-benzoxathiepine and derivatives

The final set of substrates used in this approach required the conversion of 2-mercaptophenol **43** into bis-alkene **44** according to established procedures. This compound was then oxidized to the corresponding sulfone **45** but unfortunately we were unable to accomplish the desired RCM reaction to yield **46**, even under the high temperature-short time microwave conditions. We are unable to explain this result in light of the other successes with this methodology. However, treatment of substrate **44** under the high temperature microwave conditions did give the benzoxathiepine **47** in acceptable yield (62%), although the use of a larger than normal amount of catalyst **25** was required (2×20%) to ensure depletion of all the starting material **44** (Scheme 7).



Scheme 7. Reagents and conditions: (i) *m*CPBA (2.2 equiv), CH_2Cl_2, −5 °C–0 °C, N_2, 24 h (70%); (ii) **25** (20+20 mol %), toluene, MW, Ar, 145–225 °C, 80–150 W, 30 min, no product obtained; (iii) **25** (20+20 mol %), toluene, MW, Ar, 150 °C, 100 W, 20 min, (62%).

3. Conclusion

This paper has demonstrated that the utilization of an isomerization-RCM approach is of specific use in the synthesis of seven-membered benzo-fused heterocycles containing two heteroatoms in the heterocyclic ring. In particular, the approach produced examples of compounds containing *N*,*O*- (viz. a substituted 4,5-dihydro-1,5-benzoxazepine), *N*,*S*- (viz. a substituted 4,5- and 2,5-dihydro-1,5-benzothiazepine), and also a *S*,*O*-containing compound (viz. 2*H*-1,5-benzoxathiepine). In addition, it was found that with certain substrates the application of a short duration-high temperature microwave protocol was required for the formation of the desired cyclized products.

4. Experimental

4.1. General

^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker 300 or Bruker DRX 400 spectrometer at the frequency indicated. Infra-red spectra were recorded on either a Bruker IFS 25 Fourier Transform spectrometer or on a Bruker Vector 22 Fourier Transform spectrometer. Mass spectra were recorded on a Kratos MS 9/50, VG 70E MS or VG 70 SEQ mass spectrometer or a WatersAPI Q-TOF Ultima or Waters GCT Premier mass spectrometer. Macherey–Nagel kieselgel 60 (particle size 0.063–0.200 mm) was used for conventional silica gel chromatography. All solvents used for reactions and chromatography were distilled prior to use. Reactions were performed under a blanket of inert gas (Ar or N_2) unless specified. All microwave reactions were performed in a CEM Corporation Discover Focused Microwave Synthesis system using CEM microwave reactor vials, which were sealed with the CEM Discover pressure/infra red attenuator.

*4.1.1. tert-Butyl 2-(1-propenyloxy)phenylcarbamate **30a**.* *tert*-Butyl 2-(allyloxy)phenylcarbamate[27] **29a** (0.20 g, 0.80 mmol) was dissolved in toluene (8 mL) and [RuClH(CO)(PPh_3)$_3$] **26** (5 mol %, 0.038 g, 0.40 mmol) was added. The reaction was then heated at 80–100 °C for 18 h, under Ar. H_2O (20 mL) was then added and the crude product was extracted with EtOAc (2×100 mL). The solvent was removed under vacuum and silica gel column chromatography (10% EtOAc/hexane) was performed on the crude product to afford the product **30a** as a brown oil (0.19 g, 98%). NMR spectroscopy showed that the compound was a mixture of *E*/*Z* isomers (2:1). R_f (10% EtOAc/hexanes) 0.73; IR: ν_{max} (film)/cm^{-1} 3442, 2987, 1732, 1671, 1606, 1524, 1478, 1450, 1393, 1368, 1328; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.53 and 1.54 [9H, s, C(CH_3)$_3$], 1.67 and 1.73 (3H, d, *J* 6.7 Hz, OCHCHCH_3), 4.95–5.00 and 5.35–5.46 (1H, m, OCH*C*HCH$_3$), 6.17–6.34 (1H, m, O*C*HCHCH$_3$), 6.88–7.01 (4H, m, 4× ArH), 8.09 (1H, br s, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 9.4 and 12.1 (CH_3), 28.3 [C(*C*H$_3$)$_3$], 80.5 [*C*(CH$_3$)$_3$], 108.8 and 109.2 (CH), 114.2 and 114.7 (CH), 118.6 (CH), 122.3 and 122.4 (CH), 122.9 and 123.0 (CH), 128.6 (C), 140.7 and 141.8 (CH), 145.3 and 145.5 (C), 152.0 (C=O); *m*/*z* (EI): 249 (M$^+$, 9%), 193 (60), 149 (31), 120 (37), 108 (19), 57 (100); HRMS, required for $C_{14}H_{19}NO_3$ 249.1365, found 249.1356.

*4.1.2. tert-Butyl allyl[2-(1-propenyloxy)phenyl]carbamate **31a**.* Carbamate **30a** (0.13 g, 0.52 mmol) was dissolved in DMF (10 mL) and NaH (60% in oil, 0.025 g, 0.63 mmol) was added, followed by allyl bromide (0.050 mL, 0.63 mmol). The reaction was stirred at rt, under N_2, for 18 h, after which H_2O (20 mL) was added. The crude product was subsequently extracted with EtOAc (4×100 mL), which was removed under reduced pressure. Column chromatography (5% EtOAc/hexane) was then performed to afford the product **31a** as a yellow oil (0.12 g, 83%). The product was found to be a mixture of *E*/*Z* isomers by NMR spectroscopy in a ratio 2:1. R_f (5% EtOAc/hexanes) 0.35; IR: ν_{max} (film)/cm^{-1} 1701, 1526, 1499, 1454, 1386; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.34 and 1.50 [9H, br s, C(CH_3)$_3$], 1.64 and 1.70 (3H, d, *J* 6.7 Hz, CHCHCH_3), 4.13 (2H, br s, NCH_2CHCH$_2$), 4.84–4.88 and 5.27–5.36 (1H, m, OCH*C*HCH$_3$), 5.02–5.11 (2H, m, NCH$_2$CHCH_2), 5.80–5.95 (1H, m, NCH$_2$*C*HCH$_2$), 6.31–6.34 (1H, m, O*C*HCHCH$_3$), 6.96–7.01 (2H, m, 2× ArH), 7.11–7.26 (2H, m, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$, 1 carbon signal not observed): δ (ppm) 9.4 and 12.1 (CH_3), 28.1 [C(*C*H$_3$)$_3$], 52.2 (NCH_2), 79.7 (C–O), 107.2 and 108.0 (CH), 115.7 and 116.3 (CH), 116.8 (CH), 122.3 (CH), 128.0 (CH), 129.6 and 129.7 (CH), 131.9 (C), 134.2 (CH), 140.9 and 142.2 (C), 154.7 and 159.8 (C=O); *m*/*z* (EI): 289 (M$^+$, 9%), 233 (11), 189 (20), 163 (35), 160 (25), 148 (11), 120 (13), 57 (100); HRMS, required for $C_{17}H_{23}NO_3$ 289.1678, found 289.1670.

*4.1.3. tert-Butyl 1,5-benzoxazepine-5(4H)-carboxylate **32a**.* Carbamate **31a** (0.097 g, 0.33 mmol) was dissolved in toluene (5 mL) and Grubbs second generation catalyst **25** (10 mol %, 0.014 g, 0.04 mmol) was added under Ar. The reaction was then stirred at 60 °C for 18 h. The solvent was removed under vacuum and column chromatography (10% EtOAc/hexane) was performed on the crude residue to afford the

cyclized compound **32a** as a brown solid (0.036 g, 60%). Mp: 59–61 °C; R_f (10% EtOAc/hexanes) 0.25; IR: ν_{max} (film)/cm^{-1} 1703, 1612, 1498, 1454, 1380; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.38 [9H, br s, C(CH_3)$_3$], 4.22 (2H, br s, NCH_2), 4.80–4.85 (1H, m, NCH_2CHCH), 6.42 (1H, d, J 6.0 Hz, OC*H*CH), 7.07 (2H, br s, 2× ArH), 7.17–7.20 (2H, m, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 28.2 [C(CH_3)$_3$], 45.2 (CH_2), 80.6 (C–O), 105.2 (CH), 121.0 (CH), 123.7 (C), 123.9 (CH), 127.9 (CH), 129.8 (CH), 133.2 (C), 142.7 (CH), 154.3 (C=O); m/z (EI): 247 (M^+, 20%), 214 (5), 191 (50), 174 (12), 147 (16), 146 (16), 120 (21), 91 (6), 57 (100); HRMS, required for $C_{14}H_{17}NO_3$ 247.1208, found 247.1204.

4.1.4. N-[2-(1-Propenyloxy)phenyl]benzamide ***30b****.* *N*-[2-(Allyloxy) phenyl]benzamide[28] **29b** (0.401 g, 1.58 mmol) and [RuClH(CO) (PPh_3)$_3$] **26** (4 mol %, 0.060 g, 0.063 mmol) were stirred under neat (solventless) conditions. The reaction mixture was subsequently heated at 65 °C for 24 h under Ar. The reaction solution was then diluted with a 5% EtOAc/hexane mixture (20 mL) and filtered through a compacted Celite plug (3×20 mL) to remove the catalyst; the solvent was then removed under reduced pressure. The resulting crude residue was passed through a silica gel column (10% EtOAc/hexane) to afford the desired product **30b** as a yellow oil (0.37 g, 92%) as a mixture of *E*/*Z* isomers (ratio 3:1). R_f (20% EtOAc/ hexanes) 0.57; IR: ν_{max} (ATR)/cm^{-1}: 1672, 1604, 1525, 1477, 1453, 1332, 1256, 1205; ^{1}H NMR (300 MHz; $CDCl_3$): δ (ppm) 1.68 and 1.75 (3H, dd and dd, J 6.9, 1.4 Hz and J 6.9, 1.6 Hz, OCHCHC*H*$_3$), 4.92–5.10 and 6.33–6.43 (1H, 2× m, OCHC*H*CH$_3$), 6.34–6.40 (1H, m, OC*H*CHCH$_3$), 6.98–7.10 (3H, m, 3× ArH), 7.43–7.58 (3H, m, 3× ArH), 7.89 (2H, dd, J 6.5, 1.6 Hz, 2× ArH), 8.46–8.59 (2H, m, ArH and NH); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 9.3 and 12.0 (CH_3), 108.7 and 109.6 (CH), 114.0 and 114.6 (CH), 120.3 (CH), 122.9 (CH), 123.8 (CH), 126.8 (2× CH), 128.3 (C), 128.7 (2× CH), 131.7 (CH), 135.0 (C), 140.4 and 141.5 (CH), 146.0 (C), 165.0 (C=O); m/z (EI): 253 (M^+, 34%), 196 (35), 105 (100), 77 (23), 51 (8); HRMS, required for $C_{16}H_{15}NO_2$ 253.1103, found 253.1091.

4.1.5. N-Allyl-N-[2-(1-propenyloxy)phenyl]benzamide ***31b****.* Benzamide **30b** (0.297 g, 1.17 mmol) was dissolved in dry DMF (30 mL) under N_2, and the temperature of the mixture lowered to 0 °C, followed by the sequential addition of NaH (60% in oil, 0.054 g, 1.4 mmol) and allyl bromide (0.28 g, 2.3 mmol, 0.20 mL). The reaction mixture was then stirred at rt for 24 h under N_2. H_2O (80 mL) was then added to quench the reaction mixture, after which it was extracted with EtOAc (3×50 mL) and the combined fractions dried ($MgSO_4$). The solvent was then removed under reduced pressure. The resulting crude residue was passed through a silica gel column (20% EtOAc/hexane) to afford compound **31b** as a pale yellow oil (0.33 g, 95%) and as a mixture of *E*/*Z* isomers (ratio 65:35). R_f (10% EtOAc/hexanes) 0.17; IR: ν_{max} (ATR)/cm^{-1}: 1639, 1496, 1384, 1255, 1213; ^{1}H NMR (300 MHz; $CDCl_3$) δ (ppm) 1.63 and 1.69 (3H, dd and dd, J 6.9, 1.5 Hz, and J 6.9, 1.6 Hz, OCHCHC*H*$_3$), 4.20–4.60 (2H, br m, NC*H*$_2$CHCH$_2$), 4.84–4.94 and 5.29–5.41 (1H, 2× m, OCHC*H*CH$_3$), 5.09–5.15 (2H, m, NCH_2CHCH_2), 5.86–6.12 (2H, m, 2× CH_2CHCH_2), 6.80–6.92 (2H, m, 2× ArH), 7.03–7.23 (5H, m, 5× ArH), 7.32–7.36 (2H, m, 2× ArH); ^{13}C NMR (75 MHz; $CDCl_3$): δ (ppm) 9.4 and 12.1 (CH_3), 52.3 and 52.2 (NCH_2), 108.6 and 109.8 (CH), 115.5 and 115.6 (CH), 117.7 and 117.6 (CH), 122.4 and 122.3 (CH), 127.3 (CH), 128.1 (CH), 128.6 and 128.5 (CH), 129.4 (CH), 130.0 and 129.9 (CH), 132.4 and 132.3 (C), 133.2 and 133.3 (CH), 136.1 and 136.2 (C), 140.0 and 140.9 (CH), 152.6 (C), 171.0 (C=O); m/z (EI): 293 (M^+, 28%), 236 (38), 188 (5), 160 (28), 105 (100), 77 (44), 51 (6); HRMS, required for $C_{19}H_{19}NO_2$ 293.1416, found 293.1424.

4.1.6. 5-Benzoyl-4,5-dihydro-1,5-benzoxazepine ***32b****.* Benzamide **31b** (0.301 g, 1.03 mmol) and Grubbs second generation catalyst **25** (5 mol %, 0.0436 g, 0.0513 mmol) were dissolved in distilled, degassed toluene (15 mL). The reaction mixture was then stirred at 80 °C for 8 h under Ar. After cooling, the reaction mixture was diluted with a 10% EtOAc/hexane mixture (20 mL) and filtered through a compacted Celite plug (3×20 mL) to remove the catalyst; the solvent was then removed under reduced pressure. The resulting crude residue was passed through a silica gel column (10% EtOAc/hexane) to afford the cyclized **32b** as a low melting point solid (0.13 g, 50%). Mp 27–28 °C; R_f (10% EtOAc/hexanes) 0.14; IR: ν_{max} (ATR)/cm^{-1}: 1657, 1593, 1537, 1469, 1414, 1364, 1325, 1287, 1264, 1202; ^{1}H NMR (300 MHz, $CDCl_3$, one proton for NCH_2 not observed in spectrum due to very broad peaks caused by amide rotamers): δ (ppm) 3.76 and 5.36 (1H, 2× br s, NCH_2), 4.94 (1H, d, J 3.1 Hz, NCH_2CH), 6.51–6.58 (1H, m, OCH), 6.70 (1H, br s, ArH), 6.80 (1H, br s, ArH), 7.10–7.31 (7H, m, 7× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 44.5 (br, NCH_2), 105.0 (NCH_2CH), 121.1 (CH), 124.5 (CH), 127.8 (CH), 128.0 (CH), 128.4 (CH), 129.5 (CH), 129.9 (CH), 134.8 (C), 135.4 (C), 142.9 (CH), 153.2 (C), 169.8 (C=O); m/z (EI): 252 (M^++H, 94%), 251 (M^+, 30%), 196 (8), 154 (40), 136 (38), 131 (15), 120 (9), 105 (100); HRMS, required for $C_{16}H_{14}NO_2$ 252.1025, found 252.1012.

4.1.7. N-Allyl-N-[2-(allylsulfonyl)phenyl]-4-methyl-benzenesulfonamide ***35****.* The diene **34**[15a] (0.471 g, 1.31 mmol) was dissolved in dry CH_2Cl_2 (15 mL) and cooled to −5 °C under N_2. *m*CPBA (70%, 0.497 g, 2.88 mmol) was added in one portion and stirring was continued for 36 h at 0 °C. The reaction mixture was then poured into a saturated solution of $NaHCO_3$ (20 mL) and extracted with additional CH_2Cl_2 (20 mL). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a thick yellow oil. Column chromatography (20% EtOAc/hexane) subsequently afforded the desired product **35** (0.364 g, 71% yield) as a pale yellow oil that started to solidify on standing. R_f (40% EtOAc/hexanes) 0.48; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.49 (3H, s, CH_3), 4.16–4.58 (4H, m, 2× CH_2), 4.87–5.03 (2H, m, CH_2CHCH_2), 5.37–5.46 (2H, m, CH_2CHCH_2), 5.63–5.74 (1H, m, CH_2CHCH_2), 5.77–5.93 (1H, m, CH_2CHCH_2), 6.90–6.96 (1H, m, ArH), 7.38 (2H, d, J 8.1 Hz, 2× ArH), 7.49–7.56 (2H, m, 2× ArH), 7.38 (2H, d, J 8.1 Hz, 2× ArH), 8.05–8.10 (1H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.6 (CH_3), 56.1 (CH_2), 60.2 (CH_2), 120.5, (CH), 124.5 (CH), 125.1 (CH), 128.4 (2 CH), 128.9 (CH), 129.8 (2 CH), 131.5 (CH), 131.6 (CH), 133.2 (CH), 133.9 (CH), 136.5 (C), 138.5 (C), 139.0 (C), 144.4 (C); m/z (ESI): 282 (M^++H, 100%), 235 (15); HRMS, required for $C_{19}H_{22}NO_4S_2$ 392.0984, found 392.0985.

4.1.8. N-[2-(Allylsulfonyl)phenyl]-4-methyl-N-(1-propenyl)benzenesulfonamide ***36****.* The sulfone **35** (0.11 g, 0.29 mmol) was dissolved in a degassed solution (Ar) of toluene-d_8 (0.50 mL) in an NMR tube containing the isomerization catalyst **26** (0.003 g, 0.003 mmol, 1 mol %). The tube was then sealed and heated in an oil bath at 95 °C for 16 h. A further portion of catalyst **26** (0.030 g, 0.03 mmol, 10 mol %) was added and the NMR tube was heated for an additional 16 h. Silica gel column chromatography (20% EtOAc/hexane) then afforded the product **36** (0.094 g, 84%) as a brown solid. The NMR spectra of compound **36** were very complex because of the mixtures of *E* and *Z* isomers so the product was utilized in the next reaction without further characterization.

4.1.9. 5-[(4-Methylphenyl)sulfonyl]-2,5-dihydro-1,5-benzothiazepine 1,1-dioxide ***37****.* Sulfone **36** (0.065 g, 0.17 mmol) was dissolved in toluene (10 mL) and Grubbs second generation catalyst **25** (5 mol %, 0.007 g, 0.008 mmol) was added under Ar. The reaction was then stirred at 50 °C for 24 h after which an additional amount of Grubbs second generation catalyst **25** (5 mol %, 0.007 g, 0.008 mmol) was added. The reaction was then stirred at 80 °C under Ar for an additional 24 h after which it was stirred under air at rt for 16 h. The solvent was removed under vacuum and column chromatography (20% EtOAc/hexane) was performed on the crude residue to afford

the cyclized compound **37** as a white solid (0.026 g, 41%) and starting material (0.0392 g, 59%). R_f (40% EtOAc/hexanes) 0.41; IR: ν_{max} (film)/cm^{-1} 1794, 1713, 1663, 1598, 1474, 1361, 1328, 1292, 1170; Mp: 191–192 °C with decomposition; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.41 (3H, s, CH_3), 3.70 (2H, dd, *J* 4.7, 1.4 Hz, CH_2S), 4.97–5.03 (1H, m, NHCC*H*CH_2), 6.95 (1H, d, *J* 9.8 Hz, N*H*CCH), 7.26 (2H, d, *J* 8.2 Hz, 2× ArH), 7.51–7.56 (1H, m, ArH), 7.64 (2H, d, *J* 8.2 Hz, 2× ArH), 7.70–7.75 (1H, m, ArH), 7.86 (1H, d, *J* 8.0 Hz, ArH), 8.01 (1H, d, *J* 7.8 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.7 ($ArCH_3$), 53.6 (CH_2), 104.1 (CH), 127.8 (CH), 128.5 (4× CH), 129.3 (2× CH), 131.3 (CH), 134.4 (CH), 134.8 (C), 135.5 (C), 136.5 (C), 144.7 (C); *m*/*z* (EI): 349 (M^+, 6%), 285 (38), 221 (23), 194 (18), 155 (5), 130 (100), 91 (30), 65 (11), 39 (8); HRMS, required for $C_{16}H_{15}NO_4S_2$ 349.0443, found 349.0446.

X-ray crystal structure details of compound **37**: crystallized from EtOAc/hexane, formula: $C_{16}H_{15}NO_4S_2$, *M*=349.41, colour of crystal: colourless, needle, crystal size 0.38×0.36×0.32 mm, *a*=7.8710(4) Å, *b*=14.5770(7) Å, *c*=13.7102(6) Å, β=96.093(3)°, *V*=1564.16(13) Å^3, ρ_{calcd}=1.484 Mg/m^3, μ=0.360 mm^{-1}, *F*(000)=728, *Z*=4, monoclinic, space group P2(1)/n, *T*=173(2) K, 10,989 reflections collected, 3783 independent reflections, θ_{max} 28.00°, 209 refined parameters, maximum residual electron density 0.435 and −0.375 e Å^{-3}. R_1=0.0319, wR_2=0.0876. Crystallographic data for the structure have been deposited with the Cambridge Crystallographic Data Centre as deposition No. CCDC-791247.

*4.1.10. N-Allyl-4-methyl-N-[2-(1-propenylsulfonyl)-phenyl]benzenesulfonamide **40**.* The diene **39**[15a] (0.799 g, 2.22 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to 0 °C under N_2. *m*CPBA (70%, 1.15 g, 4.66 mmol) was added in portion-wise and stirring was continued for 4 h during which the reaction warmed to rt. CH_2Cl_2 (50 mL) was added and the organic phase was washed with H_2O (50 mL) and saturated $NaHCO_3$ (50 mL). The organic extracts were dried over Na_2SO_4, filtered and evaporated to afford a thick yellow oil. Flash column chromatography (20% EtOAc/hexane) subsequently afforded the desired product **40** (0.729 g, 84% yield) as a white solid. Mp: 116–119 °C; ^{1}H NMR spectroscopy showed that compound **40** consisted of a 1:1 mixture of *E*/*Z* isomers. R_f (30% EtOAc/hexanes) 0.26; IR: ν_{max} (film)/cm^{-1} 1733, 1642, 1594, 1493, 1473, 1348, 1335, 1318, 1220, 1180, 1145, 1123, 1018; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.02 and 2.17 (3H, 2× dd, *J* 6.9, 1.6, and 7.4, 1.6 Hz, CH_3), 2.48 (3H, s, CH_3), 4.27–4.45 (2H, m, CH_2), 4.92–4.99 (2H, m, CHCH_2), 5.57–5.72 (1H, m, C*H*CH_2), 6.46–6.57 (0.5H, m, CH), 6.74–6.83 (1.5H, m, ArH and CH), 6.87–6.99 (0.5H, m, CH), 7.06–7.18 (0.5H, m, CH), 7.38 (2H, br d, *J* 8.3, 2× ArH), 7.42–7.63 (2H, m, 2× ArH), 7.66–7.83 (2H, m, 2× ArH), 8.11–8.32 (1H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.4 and 17.5 ($CHCH_3$), 21.6 ($ArCH_3$), 55.4 and 55.5 (CH_2), 120.3 and 120.4 (CH), 128.3 and 128.4 (2× CH_2), 129.1 and 129.2 (CH), 129.8 (2× CH_2), 130.5 (CH), 130.9 and 131.0 (CH), 131.2 (CH), 131.4 and 131.5 (CH), 133.4 and 133.5 (CH), 136.9 and 137.0 (C), 138.1 and 138.2 (C), 141.5 (C), 142.5 (C), 143.2 (CH), 144.1 and 144.2 (CH), 144.6 (CH); *m*/*z* (EI): 414 (M^++Na, 100%), 287 (25), 236 (74), 130 (10); HRMS, required for $C_{19}H_{22}NO_4S_2$ (M^++H) 392.0972, found 392.0984.

4.2. General procedure for RCM reactions performed in the CEM discover microwave

To a flame dried 10 mL microwave vial, equipped with a stirring bar, were added the diene and anhydrous toluene, all under Ar gas. The Grubbs second generation catalyst **25** was subsequently added under Ar to the vial after which it was sealed. The vial was then irradiated in a microwave reactor for the recorded period and reaction conditions. After cooling the crude product was purified by column chromatography on silica gel.

*4.2.1. 5-[(4-methylphenyl)sulfonyl]-4,5-dihydro-1,5-benzothiazepine 1,1-dioxide **41**.* According to the general procedure described above the Grubbs second generation catalyst **25** (20 mol %, 0.043 g) was added to the sulfone **40** (0.10 g, 0.26 mmol) dissolved in dry toluene (5 mL). The irradiation was then performed for a period of 10 min at conditions of 145 °C and 80 W. The desired cyclised compound **41** was then obtained after silica gel column chromatography (30% EtOAc/hexane) as an off-white solid (0.060 g, 67%). Mp: 203–206 °C; R_f (30% EtOAc/hexanes) 0.21; IR: ν_{max} (film)/cm^{-1} 1734, 1656, 1597, 1493, 1446, 1391, 1295, 1209, 1157, 1124; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.41 (3H, s, $ArCH_3$), 3.69 (2H, dd, *J* 4.8, 1.5 Hz, NCH_2), 4.97–5.03 (1H, m, C*H*CH_2), 6.94 (1H, d, *J* 9.6 Hz, SCH), 7.19–7.26 (2H, m, 2× ArH), 7.51–7.56 (1H, m, ArH), 7.64 (2H, d, *J* 8.1 Hz, 2× ArH), 7.69–7.75 (1H, m, ArH), 7.86 (1H, d, *J* 8.1 Hz, ArH), 8.00 (1H, dd, *J* 7.8, 1.2 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.7 ($ArCH_3$), 53.6 (CH_2), 104.1 (CH), 127.8 (CH), 128.5 (4× CH), 129.4 (2× CH), 131.3 (CH), 134.4 (CH), 134.8 (C), 135.5 (C), 136.5 (C), 144.7 (C); *m*/*z* (EI): 350 (M^++H, 55%), 294 (5), 155 (5); HRMS, required for $C_{16}H_{16}NO_4S_2$ (M^++H) 350.0521, found 350.0526.

*4.2.2. 5-[(4-Methylphenyl)sulfonyl]-4,5-dihydro-1,5-benzothiazepine **42**.* According to the general procedure described above the Grubbs second generation catalyst **25** (20 mol %, 0.037 g) was added to the sulfone **39** (0.080 g, 0.22 mmol) dissolved in dry toluene (4 mL). The irradiation was then performed for a period of 10 min at conditions of 145 °C and 80 W. The desired cyclized compound **42** was then obtained after silica gel column chromatography (30% EtOAc/hexane) as an off-white solid (0.065 g, 92%). Mp: 105–108 °C; R_f (30% EtOAc/hexanes) 0.53; IR: ν_{max} (film)/cm^{-1} 1732, 1625, 1597, 1492, 1469, 1438, 1396, 1313, 1230, 1184, 1127, 1070; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.40 (3H, s, $ArCH_3$), 4.44 (2H, d, *J* 1.8 Hz, NCH_2), 5.71 (1H, dt, *J* 10.8, 3.6 Hz, C*H*CH_2), 5.82 (1H, dt, *J* 10.8, 1.5 Hz, SCH), 7.18–7.31 (5H, m, 5× ArH), 7.34–7.47 (1H, m, ArH), 7.65 (2H, d, *J* 8.1 Hz, 2× ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 21.6 ($ArCH_3$), 49.5 (CH_2), 119.9 (CH), 122.9 (CH), 127.7 (2× CH), 128.4 (CH), 128.7 (CH), 129.2 (2× CH), 130.3 (CH), 131.6 (CH), 135.8 (C), 137.6 (C), 141.0 (C), 143.3 (C); *m*/*z* (EI): 318 (M^++H, 60%), 272 (2), 163 (30), 162 (100); HRMS, required for $C_{16}H_{16}NO_2S_2$ (M^++H) 318.0622, found 318.0638.

*4.2.3. 1-(Allyloxy)-2-(1-propenylsulfonyl)benzene **45**.* The bis-alkene **44**[15a] (0.50 g, 2.4 mmol) was dissolved in dry CH_2Cl_2 (20 mL) and cooled to −5 °C under N_2. *m*CPBA (0.92 g, 5.3 mmol) was added in one portion and stirring was continued for 24 h at 0 °C. The reaction mixture was then poured into a saturated solution of $NaHCO_3$ (25 mL) and extracted with additional CH_2Cl_2 (25 mL). The organic extracts were washed with brine (20 mL), dried over Na_2SO_4, filtered, and evaporated to afford a thick yellow oil. Column chromatography (30% EtOAc/hexane) subsequently afforded the desired product **45** (0.41 g, 70%) as an colorless thick liquid. ^{1}H NMR spectroscopy showed that compound **45** consisted of a 1:1 mixture of *E*/*Z* isomers. R_f (30% EtOAc/hexanes) 0.34; IR: ν_{max} (film)/cm^{-1} 1729, 1629, 1445, 1424, 1347, 1304, 1279, 1228, 1129, 1099, 1043; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.99 and 2.07 (3H, 2× dd, *J* 6.9, 1.5 Hz and 7.2, 1.5 Hz, CH_3), 4.67–4.70 (2H, m, OCH_2), 5.29–5.52 (2H, m, CHCH_2), 5.99–6.14 (1H, m, OCH_2C*H*CH_2), 6.32–6.38 (0.5H, m, SCH*CH*CH_3), 6.49–6.64 (1H, m, SCH), 6.97–7.11 (2.5H, m, 2× ArH and SCHCHCH_3), 7.50–7.56 (1H, m, ArH), 7.94–8.02 (1H, m, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 14.1 and 17.3 (CH_3), 58.8 (OCH_2), 113.4 and 113.5 (CH), 118.3 and 118.5 (CH_2), 120.6 and 120.7 (CH), 129.41 and 129.45 (C), 131.1 and 131.4 (CH), 132.0 (CH), 135.1 (CH), 141.6 (CH), 143.3 (CH), 156.2 and 156.3 (C); *m*/*z* (EI): 239 (M^++H, 100%), 197 (4); HRMS, required for $C_{12}H_{15}O_3S$ (M^++H) 239.0742, found 239.0742.

*4.2.4. 2H-1,5-benzoxathiepine **47**.* According to the general procedure described above the Grubbs second generation catalyst **25** (20 mol %, 0.041 g) was added to the sulfone **44** (0.050 g,

0.24 mmol) dissolved in dry toluene (3 mL). The irradiation was then performed for a period of 10 min at conditions of 150 °C and 100 W. After cooling the reaction mass, a further portion of Grubbs second generation catalyst (20 mol %, 0.041 g) was loaded and the sample was irradiated for a further 10 min (150 °C and 100W). The desired cyclised compound **47** was then obtained after silica gel column chromatography (5% EtOAc/hexane) as a pale yellow oil (0.025 g, 62%). R_f (5% EtOAc/hexanes) 0.50; IR: ν_{max} (film)/cm^{-1} 1725, 1623, 1572, 1439, 1469, 1375, 1345, 1232, 1154, 1121, 1070, 1039; ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.72 (2H, dd, *J* 3.6, 1.8 Hz, OCH_2), 5.85 (1H, dt, *J* 11.0, 3.6 Hz, C*H*CH_2), 6.13 (1H, dt, *J* 11.0, 1.8 Hz, SCH), 7.02–7.08 (2H, m, 2× ArH), 7.20–7.25 (1H, m, ArH), 7.32 (1H, dd, *J* 7.5, 1.5 Hz, ArH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 72.0 (CH_2), 120.2 (CH), 122.8 (CH), 124.4 (CH), 125.8 (CH), 128.9 (CH), 130.0 (CH), 130.1 (C), 160.1 (C); *m*/*z* (EI LCMS): 164 (M^+, 100%), 163 (80), 137 (85); HRMS, required for C_9H_8OS 164.0296, found 164.0299.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.02.035. These data include MOL files and InChiKeys of the most important compounds described in this article.

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