Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 4737–4747

The synthesis of 2-benzazocines using ring-closing metathesis as a key step

Jenny-Lee Panayides,[a] Rakhi Pathak,[a] Helen Panagiotopoulos,[b] Hajierah Davids,[b,†] Manuel A. Fernandes,[a,‡] Charles B. de Koning[a] and Willem A. L. van Otterlo[a,*]

[a]*Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, PO Wits, 2050, 1 Jan Smuts Avenue, Johannesburg, Gauteng, South Africa*
[b]*Department of Pharmacy and Pharmacology, University of the Witwatersrand, 7 York Road, Parktown, 2193, Gauteng, South Africa*

Received 8 December 2006; revised 22 February 2007; accepted 15 March 2007
Available online 18 March 2007

Abstract—A number of protected 7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocines were synthesized from 2-allyl-3-isopropoxy-4-methoxybenzaldehyde using ring-closing metathesis as the key step. In addition, two 9-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocines were synthesized from 5-isopropoxy-4-methoxy-2-[(1*E*)-3-phenyl-2-propenyl]benzaldehyde, which in turn was obtained from the thermal Claisen–Cope rearrangement of 4-methoxy-3-{[(2*E*)-3-phenyl-2-propenyl]oxy}benzaldehyde. Finally, five of the 2-benzazocine compounds were tested for anti-cancer activity.

1. Introduction

The benzacocines are a class of benzo-fused nitrogen-containing compounds with an eight-membered heterocyclic ring. Members of this family of compounds include the 1-benzazocine **1** and 2-benzazocine **2** skeletons as shown in Figure 1.

Benzo-fused heterocycles have long been considered privileged structures in medicinal chemistry.[1] Examples include compound **3** (Fig. 2), an unsaturated 1-benzazocine analogue that has previously been synthesized by way of a ring-closing metathesis (RCM) reaction. This compound was investigated alongside a number of other pharmaceutically interesting benzo-fused scaffolds containing 7-, 8-, 9- and 10-membered heterocycles.[2] The literature also describes the use of 1,2,3,4,5,6-hexahydro-2-benzazocine **1** (Fig. 1) as a bicyclic

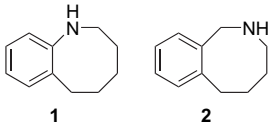


Figure 1.

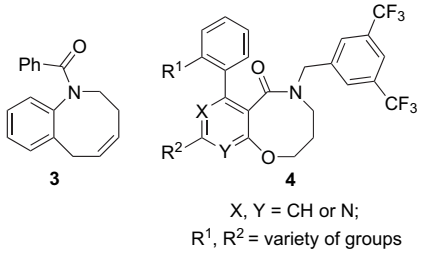


Figure 2.

benzylamine-type inhibitor of phenylethanolamine *N*-methyltransferase.[3] This compound was made as an analogue of some potent known 1,2,3,4-tetrahydroisoquinoline inhibitors and still displayed reasonable activity in inhibiting the *N*-methyltransferase enzyme. Other compounds containing an annulated eight-membered nitrogen-containing heterocycle can be represented by the generalized example **4** (Fig. 2). These compounds have been recently used as selective NK_1 antagonists[4] and this demonstrates that related structures frequently contain other heteroatoms (in this case oxygen) and other features (e.g., an additional carbonyl group).

In terms of natural products, a number of interesting compounds with structural similarities to **2**, have been isolated. Examples include buflavin **5** and its demethylated derivative **6** (Fig. 3), compounds isolated from an endemic South African Amaryllidaceae species.[5] In addition, compounds

* Corresponding author. Tel.: +27 11 717 6707; fax: +27 11 717 6749; e-mail: willem@chem.wits.ac.za
† Author for anti-cancer activity correspondence. E-mail: hajierah.davids@wits.ac.za
‡ Author for crystallographic correspondence. E-mail: manuel@hobbes.gh.wits.ac.za

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.03.087

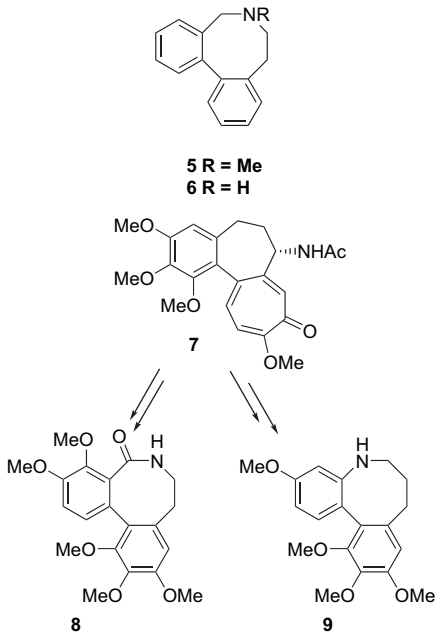


Figure 3.

8 and **9**, with similar structures to **5** and **6**, have been synthesized from the well-known naturally-occurring anti-cancer agent colchicine **7**.[6] These compounds were then tested for their ability to inhibit tubulin assembly and some were tested for their cytotoxicity.

Thus it should come as no surprise that strategies towards the synthesis of these scaffolds have seen much development in the last few years. As one of the plethora of approaches, the synthesis of benzo-fused ring systems has been readily accomplished using RCM.[7] A number of research groups, including ours,[8] have been successful in applying RCM, mediated by catalysts such as the Grubbs second generation catalyst **10** (Fig. 4), for the synthesis of annulated ring systems. However, the synthesis of the benzazocine skeletons by RCM in particular, has seen little investigation with, to the best of our knowledge, only one synthesis of the 1-benzacocine,[2a] 2-benzacocine[8g] and 2-benzazocin-1(2*H*)-one[9] being reported. In this paper we will describe our synthetic endeavours towards the development of general methodology affording the 2-benzacocines using a RCM reaction as the key step. In addition, results concerning the anti-cancer activity of a small set of 2-benzacocines will also be disclosed.

2. Discussion

The first step in our synthetic strategy[8g] involved the conversion of the readily accessible building block **11**[10] to the bis-allyl product **13** using a two-step reductive amination

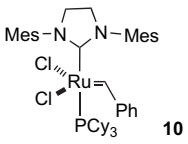
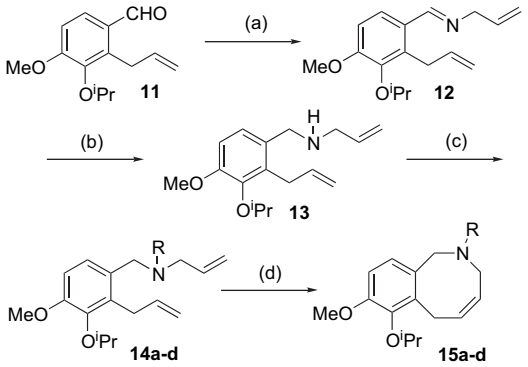


Figure 4.

procedure (Scheme 1).[11] At this point we decided to protect the secondary amine **13** with a variety of protecting groups. This was done so that we could investigate the impact of the various amine-protecting groups on the subsequent metathesis reactions, as well as to allow us to investigate the ease of deprotection of the final benzo-fused heterocycles. Compound **13** was successfully converted to the corresponding acetyl-**14a**, Boc-**14b**, benzyl sulfonamide-**14c** and tosyl-protected **14d** derivatives. The key RCM step, involving the precursors **14a–d**, proceeded smoothly within 1 h, to furnish the 2-benzazocines **15a–d** in good yields ranging from 82 to 99%.



Scheme 1. *Reagents and conditions*: (a) allyl amine, 0.1 equiv *p*-TsOH, benzene, Dean–Stark, reflux, 18 h; (b) $NaBH_4$, MeOH, 0 °C, 1 h (90% over two steps) or (a) allyl amine, solvent-free, rt, 24 h; (b) $NaBH_4$, MeOH, 0 °C, 1.5 h (81% over two steps); (c) R=Ac, acetic anhydride, pyridine, rt, 3 h, **14a** (92%), R=Boc, Boc_2O, DMAP, THF, rt, 3 h, **14b** (97%), R=SO_2Bn, benzylsulfonyl chloride, NEt_3, CH_2Cl_2, rt, 3 h, **14c** (62%), R=Ts, tosyl chloride, NEt_3, CH_2Cl_2, 0 °C, 3.5 h, **14d** (94%); (d) 5 mol % catalyst **10**, toluene, 60 °C, 1 h, **15a**, R=Ac (82%), **15b**, R=Boc (99%), **15c**, R=SO_2Bn (84%), **15d**, R=Ts (98%).

A single-crystal X-ray diffraction experiment on a suitable crystal of **15c** confirmed the formation of the eight-membered ring by way of the RCM reaction (see the ORTEP diagram in Fig. 5).[12]

At this point we were able to test the suitability of the various protecting groups on **15a–d** by applying specific conditions known to remove some of these groups. Unfortunately, it proved difficult to remove the sulfonamide groups of **15c** and **15d** under a variety of conditions. However, the Boc-protecting group of compound **15b** was readily cleaved with trifluoroacetic acid to afford 7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **16** in near quantitative yield (Scheme 2). In another experiment designed to

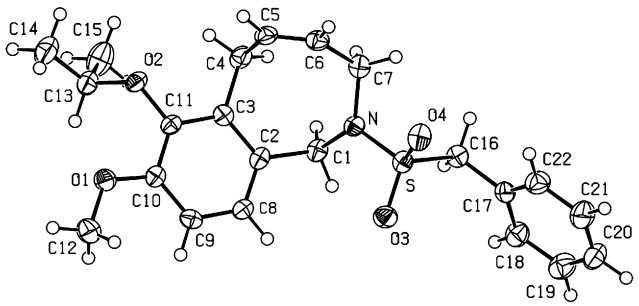
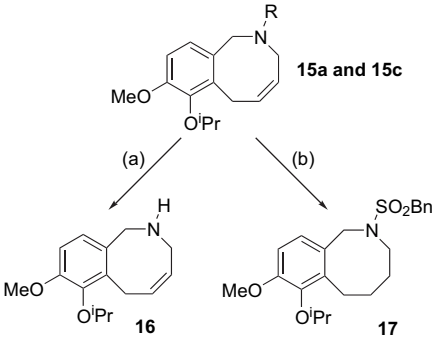


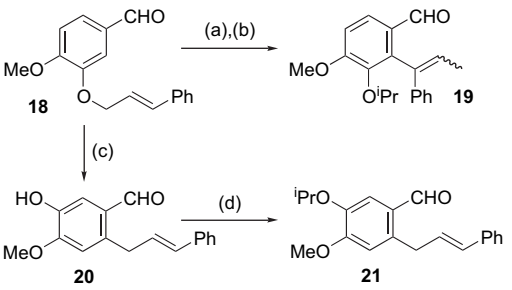
Figure 5. ORTEP diagram of compound **15c** (showing the 50% probability thermal ellipsoids for all non-hydrogen atoms).

evaluate the ease with which we could manipulate the heterocyclic ring, the alkene functionality of **15c** was readily hydrogenated with Pd/C, under 5 atm of hydrogen gas, to afford the saturated benzo-fused heterocycle **17** in an excellent yield. The structure of the hydrogenated compound **17** was also confirmed by a single-crystal X-ray diffraction study.[13]



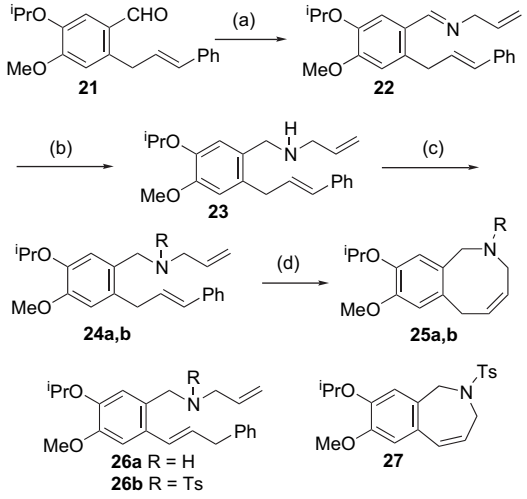
Scheme 2. *Reagents and conditions*: (a) for R=Boc, trifluoroacetic acid, CH_2Cl_2, rt, 1 h (99%); (b) for R=SO_2Bn, 10% Pd/C, 5 atm H_2, EtOH, rt, 18 h (98%).

In a related project we were interested in synthesizing annulated heterocycles containing an aryl substituent attached to the heterocyclic ring portion. Under thermal conditions (DMF at reflux), the readily available compound **18** has been shown to give, after protection of the resultant phenol as the isopropyloxy group, predominantly the product of a Claisen rearrangement followed by a double bond isomerization, compound **19** in acceptable yield (Scheme 3).[10] However, when we attempted the Claisen rearrangement of compound **18** in a microwave reactor, we were interested to find that compound **18** had undergone a subsequent Cope rearrangement to give the related regioisomer **21** as the major product, after phenolic protection of **20** with isopropyl bromide. This reaction has also been observed by Wang and co-workers who obtained compound **20** after heating substrate **18** in *N*,*N*-diethylaniline at a much higher temperature of 217 °C.[14] Optimization of the microwave procedure eventually allowed us to isolate quantitative yields of product **21** from **18**, in short reaction times. An additional benefit of this methodology was that **21** required no further purification. With this efficient procedure to synthesize **21** we decided to attempt the synthesis of 2-benzazocines with a different oxygenation pattern on the aromatic core, using the methodology previously established for compounds **15a–d**.



Scheme 3. *Reagents and conditions*: (a) DMF, 190 °C; (b) ^{i}PrBr, K_2CO_3, 60 °C, 51% over two steps;[10] (c) microwave, 200 °C, 50 W, 150 psi max, 5 min run, 5 min hold (quantitative); (d) ^{i}PrBr, K_2CO_3, 60 °C, 76% over two steps from **18**.

The benzaldehyde functional group of compound **21** was then cooled into the corresponding amine **23**, by way of **22**, using the two-step reductive amination procedure described previously (Scheme 4). A problem encountered in this transformation was that the major product **23** was contaminated with a small amount of another compound (<10% by NMR analysis), which we were unable to remove by silica gel column chromatography. We postulated that this compound had structure **26a** in which the alkene had isomerized into conjugation with the more electron-rich aromatic ring and this was later confirmed after the RCM reaction.



Scheme 4. *Reagents and conditions*: (a) allyl amine, solvent-free, rt, 21.5 h (quantitative); (b) $NaBH_4$, MeOH, 0 °C–rt, 4.5 h (75%); (c) **24a** R=Ts, tosyl chloride, NEt_3, CH_2Cl_2, 0 °C–rt, 2.5 h (72%), **24b** R=Boc, Boc_2O, 0.1 equiv DMAP, THF, rt, 3 h (79%); (d) 5 mol % catalyst **10**, toluene, 60 °C, 20–22.5 h, **25a** R=Ts (39%), **25b** R=Boc (73%).

Compound **23** was initially protected as the sulfonamide **24a** (R=Ts) in an acceptable yield of 72% (Scheme 4). The metathesis reaction was then performed on this substrate to afford the 8,9-substituted 2-benzazocine **25a** in a poor, unoptimized yield of only 39%. Analysis of the HRMS showed evidence of compound **27** arising from the RCM of impurity **26b**.

Compound **23** was also converted into the corresponding Boc-protected product **24b** in good yield (Scheme 4). This time the RCM reaction gave a more favourable result as **25b** was isolated in a reasonable yield of 73%. Characterization of compound **25b** by ^{1}H NMR spectroscopy proved to be difficult as the spectrum was complex caused by the presence of rotamers due to hindered rotation about the bulky Boc-protecting group. However, the ^{13}C NMR spectrum of this compound readily allowed us to account for all the necessary carbon signals.

It would thus appear that the presence of a bulky group, such as the isopropyloxy group, adjacent to the aromatic allyl group is beneficial to the RCM process.[15] Perhaps this occurs as a result of a reduction in the degree of freedom associated with this alkene fragment, as the metathesis yields for **15a–d** were high without fail and the reactions were all deemed complete within an hour. In contrast the metathesis of the substrates **24a** and **24b** required much longer

reaction times (20–22 h) for the reaction to be deemed complete (by TLC). These long reaction times also seemed to contribute to the formation of side products such as dimers. In light of the complications associated with the metathesis of the scaffolds **24a** and **24b**, we did not pursue this route any further.

3. Cytotoxicity testing

Since compounds such as **8** and **9** (Fig. 3) have been tested for tubulin inhibition and cytotoxicity, we decided to investigate whether some of our synthesized compounds had any anti-cancer properties. To this end, the cytotoxic effects of the benzo-fused compounds **15a–d** and **17** were evaluated on two adherent cell lines (i.e., HT-29 and MCF-7 cells) and two suspension cell lines (HL-60 and K562 cells) using the tetrazolium-based MTT assay (Fig. 6).[17] At an initial dose of 100 μM, **15d** and **17** were cytotoxic against the MCF-7 cells, reducing cell viability by 12% and 30%, respectively. No significant decrease in cell viability was noted when the MCF-7 cells were treated with **15a–c**. Similarly, no significant cytotoxic effect was exerted against the HT-29 cells when treated with **15a**, **15c–d** and **17**, where **15b** decreased cell viability by 8%. As none of the compounds tested reduced cell viability to less than 50% at 100 μM, IC_{50} values for these compounds could not be calculated and were thus determined to be in excess of 100 μM.

The HL-60 cells appeared to be the most sensitive cell line to the compounds, with reductions in cell viability ranging from approximately 34 to 48%. Finally, all compounds, with the exception of **15a**, decreased K562 cell viability by 10–40%. As with the adherent cell lines, none of the compounds tested reduced cell viability to less than 50%. IC_{50} values for these compounds could not be calculated and are determined to be in excess of 100 μM.

4. Conclusion

In this paper we have successfully demonstrated that the 2-benzazocine skeleton can be readily constructed by using RCM as the key step. In this way, benzaldehyde **11**, was transformed into the acetyl-, Boc-, benzyl sulfonyl- and tosyl-protected 7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocines **15a–d**. In addition, substrate **18** was converted into 9-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine derivatives **25a** and **25b**, albeit with less success. Lastly, cytotoxic testing proved the benzo-fused derivatives **15a–d** and **17** to only have slight activity against HL-60 and K562 cancer cell lines. Our future research will endeavour to utilize these 2-benzazocine derivatives as scaffolds for potentially bioactive molecules.

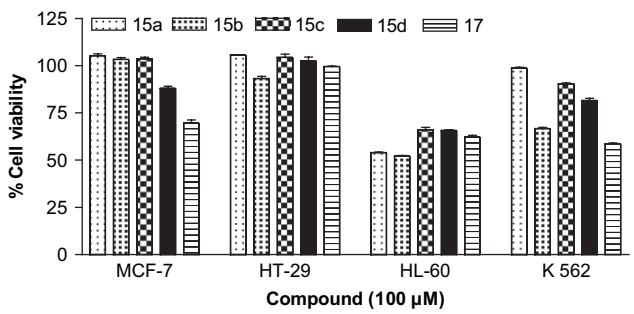


Figure 6. Percentage cell viability of four cell lines exposed to 100 μM **15a–d** and **17** for 24 h as determined by the MTT assay.[17]

5. Experimental

5.1. General

^1H NMR and ^{13}C NMR spectra were recorded either on a Bruker AC-200, Bruker 300 or Bruker DRX 400 spectrometer at the frequency indicated. For most compounds COSY and CH correlated spectra were utilized to assign the NMR signals. Most ^{13}C signals in the aromatic/alkene region have been assigned as quaternary (C) or non-quaternary (CH). In the ^1H NMR and ^{13}C NMR spectra assignments with same superscript may be interchanged. 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 a VG 70 SEQ 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 according to established procedures.[18]

5.1.1. *N*-[(2-Allyl-3-isopropoxy-4-methoxyphenyl)-methylidene]-2-propen-1-amine 12. 2-Allyl-3-isopropoxy-4-methoxybenzaldehyde **11** (7.98 mmol, 1.87 g) was transferred directly to a round-bottomed flask and to this was added allyl amine (0.90 cm^3, 11.2 mmol). The reaction mixture was placed under N_2 atmosphere and was allowed to stir at rt for 3 h. After this period of time the excess allyl amine was removed in vacuo to yield a yellow oil (2.22 g, 99%). The product **12** was >95% pure by ^1H NMR spectroscopy and no further purification was required. ν_{max}/cm^{-1} (NaCl plate) 1682, 1637, 1591, 1520, 1487, 1465, 1440, 1383, 1373; δ_H (300 MHz, $CDCl_3$) 1.27 (6H, d, J=6.0 Hz, $OCH(CH_3)_2$), 3.69 (2H, dd, J=1.5 and 4.0 Hz, $ArCH_2$), 3.86 (3H, s, OCH_3), 4.21 (2H, dd, J=5.5 and 1.5 Hz, NCH_2), 4.49 (1H, sept, J=6.0 Hz, $OCH(CH_3)_2$), 4.86–5.24 (4H, m, $NCH_2CH{=}CH_2$ and $ArCH_2CH{=}CH_2$), 5.90–6.09 (2H, m, $NCH_2CH{=}CH_2$ and $ArCH_2CH{=}CH_2$), 6.83 (1H, d, J=8.5 Hz, 5-H), 7.73 (1H, d, J=8.5 Hz, 6-H), 8.44 (1H, s, N=CH); δ_C (100 MHz, $CDCl_3$) 22.6 and 22.7 ($OCH(CH_3)_2$), 30.7 ($ArCH_2$), 55.6 (OCH_3), 63.7 (NCH_2), 74.4 ($OCH(CH_3)_2$), 109.9 (5-C), 114.6 ($NCH_2CH{=}CH_2$),[a] 115.8 ($ArCH_2CH{=}CH_2$),[a] 124.1 (6-C), 131.7 (C), 132.5 ($NCH_2CH{=}CH_2$),[b] 136.9 (C), 137.5 ($ArCH_2CH{=}CH_2$),[b] 145.0 (C), 151.8 (C), 160.4 (N=CH); δ_N (40.6 MHz, $CDCl_3$) −62.9; *m/z* 272 (M^+, 67%), 258 (32), 231 (68), 230 (98), 218 (100), 216 (42), 190 (30), 176 (91), 175 (75), 174 (31), 144 (20), 143 (86), 115 (39), 43 (28), 41 (61); HRMS calculated for $C_{17}H_{23}NO_2$: 272.1729, found: 272.1722.

5.1.2. *N*-(2-Allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine 13. *N*-[(2-Allyl-3-isopropoxy-4-methoxyphenyl)methylidene]-2-propen-1-amine **12** (3.70 mmol, 1.01 g) was dissolved in MeOH (10 cm^3) and cooled to

0 °C (ice-water bath) before the addition of the $NaBH_4$ (4.44 mmol, 0.167 g). The solution was allowed to stir for 90 min before the addition of H_2O (10 cm^3), followed by HCl solution (1 M) until the pH was ~7. The MeOH was removed under reduced pressure to yield a yellow oil on the aqueous layer. This was then extracted with EtOAc (2×25 cm^3) and the combined organic fractions were dried ($MgSO_4$). The solvent was removed in vacuo to yield the product **13** as a yellow oil (0.828 g, 81%), which was used without further purification. ν_{max}/cm^{-1} (NaCl plate) 1637, 1599, 1272; δ_H (300 MHz, $CDCl_3$) 1.26 (6H, d, J=6.0 Hz, $OCH(CH_3)_2$), 1.42 (1H, s, NH), 3.26 (2H, dt, J=6.0 and 1.0 Hz, $ArCH_2CH{=}CH_2$),[a] 3.54 (2H, dt, J=6.0 and 1.5 Hz, $NHCH_2CH{=}CH_2$),[a] 3.69 (2H, s, $ArCH_2NH$), 3.81 (3H, s, OCH_3), 4.51 (1H, sept, J=6.0 Hz, $OCH(CH_3)_2$), 4.94–4.98 (2H, m, $ArCH_2CH{=}CH_2$),[b] 5.11–5.21 (2H, m, $NHCH_2CH{=}CH_2$),[b] 5.88–5.99 (2H, m, $ArCH_2CH{=}CH_2$ and $NHCH_2CH{=}CH_2$), 6.75 (1H, d, J=8.5 Hz, 5-H), 7.01 (1H, d, J=8.5 Hz, 6-H); δ_C (50 MHz, $CDCl_3$) 22.5 ($OCH(CH_3)_2$), 29.5 ($ArCH_2CH{=}CH_2$), 44.6 ($ArCH_2NH$), 55.5 (OCH_3), 63.6 ($NHCH_2CH{=}CH_2$), 74.6 ($OCH(CH_3)_2$), 110.2 (5-C), 115.7 ($ArCH_2CH{=}CH_2$),[a] 115.8 ($NHCH_2CH{=}CH_2$),[a] 123.0 (6-C), 127.9 (C), 133.6 (C), 136.2 ($NHCH_2CH{=}CH_2$),[b] 137.1 ($ArCH_2CH{=}CH_2$),[b] 144.4 (C), 154.6 (C); m/z 274 (M^+, 67%), 232 (18), 177 (42), 176 (100), 175 (25), 161 (34), 144 (23), 115 (21); HRMS calculated for $C_{17}H_{24}NO_2$ (M^+-H): 274.1807, found: 274.1809.

5.1.3. *N*-Allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-acetamide 14a. A solution of *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **13** (5.47 mmol, 1.51 g) in pyridine (5.47 mmol, 0.45 cm^3) was cooled to 0 °C (ice-water bath). To this was added dropwise, a solution of Ac_2O (8.20 mmol, 0.80 cm^3) in pyridine (8.20 mmol, 0.65 cm^3). The ice-water bath was then removed and the reaction mixture was stirred at rt under an Ar atmosphere for 3 h. After this time EtOAc (15 cm^3) was added and the reaction mixture was extracted with brine (3×10 cm^3). The combined aqueous layers were then extracted with CH_2Cl_2 (3×10 cm^3). The organic layers were combined and washed with a saturated NH_4Cl solution that had been basified to pH 10 with 25% NH_3 solution (15 cm^3). The combined organic portions were then dried ($MgSO_4$) and the solvent was removed in vacuo. The residue was purified by column chromatography (10–30% EtOAc–Hexane, R_f 0.22 in 30% EtOAc–Hexane) to yield the desired product **14a** as a yellow oil (1.59 g, 92%). The NMR spectra proved the compound to consist of a mixture of rotamers in 1:1 ratio. ν_{max}/cm^{-1} (NaCl plate) 1637, 1520, 1481, 1429, 1374, 1269, 1216; δ_H (300 MHz, $CDCl_3$, 1:1 rotameric ratio) 1.26–1.28 (6H, m, $OCH(CH_3)_2$), 2.05 and 2.14 (3H, 2×s, CH_3), 3.44 (2H, br d, J=5.5 Hz, $ArCH_2CH{=}CH_2$), 3.71 and 3.72 (1H, 2×s, $NCH(H)CH{=}CH_2$), 3.82 and 3.83 (3H, 2×s, OCH_3), 3.97 and 3.99 (1H, 2×s, $NCH(H)CH{=}CH_2$), 4.40 (1H, s, $ArCH(H)N$), 4.52 (1H, sept, J=6.0 Hz, $OCH(CH_3)_2$), 4.57 (1H, s, $ArCH(H)N$), 4.82–5.21 (4H, m, $ArCH_2CH{=}CH_2$ and $NCH_2CH{=}CH_2$), 5.74–5.90 (2H, m, $ArCH_2CH{=}CH_2$ and $NCH_2CH{=}CH_2$), 6.75–6.82 (2H, m, 5-H and 6-H); δ_C (50 MHz, $CDCl_3$) 21.4 (CH_3), 22.6 ($OCH(CH_3)_2$), 30.0 and 30.5 ($ArCH_2CH{=}CH_2$), 45.1 ($ArCH_2N$), 48.1 and 49.2 ($NCH_2CH{=}CH_2$), 55.5 (OCH_3), 74.5 and 74.6 ($OCH(CH_3)_2$), 110.0 and 110.1 (5-C), 114.7 and 115.1 ($NCH_2CH{=}CH_2$), 116.5 and 117.3 ($ArCH_2CH{=}CH_2$), 119.9 (6-C), 123.4 (1-C), 127.5 and 128.2 (2-C), 132.6 and 133.1 ($NCH_2CH{=}CH_2$),[a] 135.8 and 136.5 ($ArCH_2CH{=}CH_2$),[a] 145.2 and 145.4 (3-C),[b] 152.1 (4-C),[b] 170.8 and 171.2 (C=O); m/z 317 (M^+, 30%), 218 (41), 192 (53), 177 (35), 176 (100), 174 (27), 161 (28), 143 (40), 115 (20); HRMS calculated for $C_{19}H_{27}NO_3$: 317.1991, found: 317.1997.

5.1.4. *tert*-Butyl allyl(2-allyl-3-isopropoxy-4-methoxybenzyl)carbamate 14b. *N*-(2-Allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **13** (5.47 mmol, 1.51 g) was dissolved in THF (150 cm^3) and to this solution was added Boc_2O (6.56 mmol, 1.55 cm^3). The solution was stirred for 5 min before the addition of DMAP (0.547 mmol, 0.0669 g). The reaction mixture was allowed to stir at rt under an Ar atmosphere for 3 h after which time the solvent was removed in vacuo. The resultant orange oil was purified by column chromatography (5–10% EtOAc–Hexane, R_f 0.80 in 30% EtOAc–Hexane) to yield the desired product **14b** as a pale yellow oil (1.99 g, 97%). ν_{max}/cm^{-1} (NaCl plate) 1689, 1661, 1549, 1532, 1514, 1481, 1463, 1410, 1265; δ_H (300 MHz, $CDCl_3$) 1.26 (6H, d, J=6.0 Hz, $OCH(CH_3)_2$), 1.46 (9H, br s, $OC(CH_3)_3$), 3.45 (2H, br d, J=5.5 Hz, $ArCH_2CH{=}CH_2$), 3.60–3.70 (2H, very br s, $NCH_2CH{=}CH_2$), 3.82 (3H, s, OCH_3), 4.38 (2H, br s, $ArCH_2N$), 4.51 (1H, sept, J=6.0 Hz, $OCH(CH_3)_2$), 4.90–4.98 (2H, m, $ArCH_2CH{=}CH_2$),[a] 5.00–5.11 (2H, m, $NCH_2CH{=}CH_2$),[b] 5.72 (1H, br s, $NCH_2CH{=}CH_2$),[b] 5.70–5.99 (1H, m, $ArCH_2CH{=}CH_2$), 6.75 (1H, d, J=8.5 Hz, 5-H), 6.83 (1H, d, J=8.5 Hz, 6-H); δ_C (50 MHz, $CDCl_3$) 22.6 ($OCH(CH_3)_2$), 28.3 ($OC(CH_3)_3$), 30.3 (br, $ArCH_2CH{=}CH_2$), 46.6 (br, $ArCH_2N$),[a] 48.2 ($NCH_2CH{=}CH_2$),[a] 55.5 (OCH_3), 74.4 ($OCH(CH_3)_2$), 80.0 ($OC(CH_3)_3$), 109.9 (5-C), 114.8 ($ArCH_2CH{=}CH_2$),[b] 116.4 (br, $NCH_2CH{=}CH_2$),[b] 122.8 (6-C), 124.6 (C), 128.9 (br, C), 133.7 ($ArCH_2CH{=}CH_2$),[c] 136.2 (br, $NCH_2CH{=}CH_2$),[c] 145.1 (C), 151.8 (C), 155.6 (C=O); m/z 375 (M^+, 16%), 278 (32), 236 (29), 177 (38), 176 (100), 175 (32), 163 (26), 143 (36), 70 (50), 57 (54); HRMS calculated for $C_{22}H_{33}NO_4$: 375.2410, found: 375.2403.

5.1.5. *N*-Allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)phenylmethanesulfonamide 14c. *N*-(2-Allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **13** (2.82 mmol, 0.780 g) was dissolved in CH_2Cl_2 (8 cm^3) and stirred for 5 min under an Ar atmosphere. To this was added NEt_3 (7.05 mmol, 1.00 cm^3) and the reaction mixture was stirred at rt for a further 15 min before the dropwise addition of benzylsulfonyl chloride (3.10 mmol, 0.593 g), which had been dissolved in CH_2Cl_2 (4 cm^3). The reaction mixture was stirred for 3 h at rt and then the solvent was removed in vacuo. The residue was purified by column chromatography (5% EtOAc–Hexane, R_f 0.35 in 30% EtOAc–Hexane) to yield the product **14c** as a yellow oil (0.710 g, 62%). ν_{max}/cm^{-1} (NaCl plate) 1594, 1487, 1439, 1375, 1337, 1273; δ_H (300 MHz, $CDCl_3$) 1.23 (6H, d, J=6.0 Hz, $OCH(CH_3)_2$), 3.41 (2H, br d, J=5.5 Hz, $ArCH_2CH{=}CH_2$),[a] 3.64 (2H, br d, J=6.5 Hz, $NCH_2CH{=}CH_2$),[a] 3.80 (3H, s, OCH_3), 4.07 (2H, s, $ArCH_2N$),[b] 4.25 (2H, s, SO_2CH_2),[b] 4.48 (1H, sept, J=6.0 Hz, $OCH(CH_3)_2$), 4.80 (1H, dd, J=1.5 and 17.0 Hz, $ArCH_2CH{=}C(H)H$),[c] 4.93 (1H, dd, J=1.5 and 10.0 Hz, $ArCH_2CH{=}C(H)H$),[c] 5.02–5.11 (2H, m, $NCH_2CH{=}CH_2$),[c] 5.57–5.67 (1H, m, $NCH_2CH{=}CH_2$),[d] 5.75–5.85

(1H, m, $ArCH_2CH{=}CH_2$),[d] 6.76 (1H, d, J=8.5 Hz, 5-H), 7.04 (1H, d, J=8.5 Hz, 6-H), 7.35–7.40 (5H, m, 5×ArH); δ_C (50 MHz, $CDCl_3$) 22.4 ($OCH(CH_3)_2$), 30.0 ($ArCH_2CH{=}CH_2$), 48.1 ($ArCH_2NH$),[a] 50.0 ($NHCH_2CH{=}CH_2$),[a] 55.5 (OCH_3), 58.9 (SO_2CH_2), 74.4 ($OCH(CH_3)_2$), 110.0 (5-C), 115.0 ($NHCH_2CH{=}CH_2$),[b] 119.0 ($ArCH_2CH{=}CH_2$),[b] 123.8 (6-C), 127.1 (CH), 128.6 (C), 128.7 (2×ArH), 129.0 (C), 130.7 (2×ArH), 132.2 (C),[c] 132.8 ($NHCH_2CH{=}CH_2$),[c] 136.3 ($ArCH_2CH{=}CH_2$), 144.9 (C), 152.2 (C); m/z 429 (M^+, 28%), 274 (11), 232 (32), 176 (100), 161 (12), 160 (11), 144 (10), 91 (80), 41 (10); HRMS calculated for $C_{24}H_{31}NO_4S$: 429.1974, found: 429.1971.

5.1.6. *N*-Allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methylbenzenesulfonamide 14d. To a stirred solution of *N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-2-propen-1-amine **13** (1.45 mmol, 0.410 g) in CH_2Cl_2 (20 cm^3) were added NEt_3 (2.03 mmol, 0.300 cm^3) and previously recrystallized TsCl (1.74 mmol, 0.333 g) at 0 °C under N_2 atmosphere. The reaction mixture was allowed to stir at 0 °C for 3.5 h and then at rt for 40 min. Afterwards the reaction mixture was diluted with water (20 cm^3) and then CH_2Cl_2 (20 cm^3) was added. The combined organics were washed with H_2O (2×20 cm^3) and dried ($MgSO_4$). The solvent was removed in vacuo and the residue was purified by column chromatography (20% EtOAc–Hexane, R_f 0.70 in 30% EtOAc–Hexane). The product **14d** was obtained as a pale yellow oil that solidified on standing (0.58 g, 94%). Mp 46–52 °C; ν_{max}/cm^{-1} (NaCl plate) 1599, 1487, 1439, 1341, 1273, 1216; δ_H (300 MHz, $CDCl_3$) 1.25 6H, d, J=6.0 Hz, $OCH(CH_3)_2$), 2.44 (3H, s, CH_3), 3.50 (2H, br, J=5.5 Hz, $ArCH_2CH{=}CH_2$), 3.70 (2H, d, J=6.5 Hz, $NCH_2CH{=}CH_2$), 3.82 (3H, s, OCH_3), 4.25 (2H, s, $ArCH_2N$), 4.49 (1H, sept, J=6.0 Hz, $OCH(CH_3)_2$), 4.82–4.98 (4H, m, $ArCH_2CH{=}CH_2$ and $NHCH_2CH{=}CH_2$), 5.38–5.47 (1H, m, $NCH_2CH{=}CH_2$),[a] 5.82–5.91 (1H, m, $ArCH_2CH{=}CH_2$),[a] 6.73 (1H, d, J=8.5 Hz, 5-H), 6.98 (1H, d, J=8.5 Hz, 6-H), 7.32 (2H, d, J=8.0 Hz, 2×ArH), 7.73 (2H, d, J=8.0 Hz, 2×ArH); δ_C (50 MHz, $CDCl_3$) 21.5 (CH_3), 22.5 ($OCH(CH_3)_2$), 30.1 ($ArCH_2CH{=}CH_2$), 48.3 ($ArCH_2N$),[a] 49.7 ($NCH_2CH{=}CH_2$),[a] 55.5 (OCH_3), 74.5 ($OCH(CH_3)_2$), 109.9 (5-C), 115.0 ($NHCH_2CH{=}CH_2$),[b] 118.6 ($ArCH_2CH{=}CH_2$),[b] 124.3 (6-C), 126.7 (C), 127.4 (2×ArCH), 129.7 (2×ArCH), 132.6 ($NCH_2CH{=}CH_2$),[c] 132.8 (C), 136.5 ($ArCH_2CH{=}CH_2$),[c] 137.0 (C), 143.2 (C), 145.1 (C), 152.3 (C); m/z 429 (M^+, 17%), 274 (27), 232 (38), 177 (58), 176 (100), 161 (37), 144 (32); HRMS calculated for $C_{24}H_{31}NO_4S$: 429.1974, found: 429.1975.

5.2. General metathetic approach to eight-membered rings

The diene precursors **14a–d** were dissolved in distilled toluene (10 cm^3), after which the solution was degassed by bubbling N_2 through it for 20 min. The solution was then heated to 60 °C before the addition of Grubbs II catalyst **10** (5 mol %). The reaction mixture was then stirred at 60 °C under an Ar atmosphere for 1 h. After this time the solvent was removed in vacuo to yield a dark brown oil that was purified by column chromatography (5–10% EtOAc–Hexane) to afford the desired cyclized products **15a–d**. The products synthesized in this manner are listed below.

5.2.1. 1-[7-Isopropoxy-8-methoxy-3,6-dihydro-2-benzazocin-2(1*H*)-yl]-1-ethanone 15a. *N*-Allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)acetamide **14a** (0.288 mmol, 0.0914 g) in toluene (10 cm^3), was reacted with Grubbs II catalyst **10** (5 mol %, 0.0144 mmol, 0.0133 g). Purification by column chromatography (5–10% EtOAc–Hexane, R_f 0.05 in 30% EtOAc–Hexane) then afforded the product **15a** as a clear oil (0.0682 g, 82%), showing evidence of rotamers due to the amide functionality. ν_{max}/cm^{-1} (NaCl plate) 1631, 1522, 1481, 1427, 1378, 1333, 1216; δ_H (300 MHz, $CDCl_3$) 1.27 (6H, d, J=6.0 Hz, $OCH(CH_3)_2$), 2.00 and 2.09 (3H, 2×s, $COCH_3$), 3.49 and 3.53 (2H, 2×d, J=7.5 Hz, 6-H), 3.81 and 3.82 (3H, 2×s, OCH_3), 3.84 (under OCH_3) and 4.17 (2H, 2×d, J=5.0 Hz, 3-H), 4.46 and 4.48 (1H, 2×sept, J=6.0 Hz, $OCH(CH_3)_2$), 4.59 and 4.68 (2H, 2×s, 1-H), 5.71–6.01 (2H, m, 4-H and 5-H), 6.82 (1H, d, J=8.5 Hz, 9-H), 6.99 (1H, d, J=8.5 Hz, 10-H); δ_C (50 MHz, $CDCl_3$) 22.0 and 22.4 ($COCH_3$), 22.5 and 22.6 ($OCH(CH_3)_2$), 24.7 and 25.3 (6-C), 44.1 and 45.4 (3-C), 50.9 and 52.8 (1-C), 55.5 and 55.6 (OCH_3), 74.4 and 74.8 ($OCH(CH_3)_2$), 109.5 and 109.7 (9-C), 123.7 and 125.5 (10-C), 126.9 and 127.6 (5-C),[a] 128.6 and 128.2 (C), 129.3 (4-C),[a] 132.2 and 132.6 (C), 133.1 (4-C),[a] 144.2 and 145.0 (C), 152.6 and 152.7 (C), 170.4 and 170.9 (C=O); m/z 289 (M^+, 100%), 218 (61), 204 (30), 188 (95), 175 (43), 173 (54), 156 (37), 143 (95), 115 (34), 73 (25), 43 (55); HRMS calculated for $C_{17}H_{23}NO_3$: 289.1678, found: 289.1687.

5.2.2. *tert*-Butyl 7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxylate 15b. *tert*-Butyl allyl-(2-allyl-3-isopropoxy-4-methoxybenzyl)carbamate **14b** (1.07 mmol, 0.402 g) was dissolved in toluene (40 cm^3) before the addition of Grubbs II catalyst **10** (5 mol %, 0.053 mmol, 0.051 g). Purification by column chromatography (5% EtOAc–Hexane, R_f 0.63 in 20% EtOAc–Hexane) afforded the desired product **15b** as a clear oil (0.366 g, 99%). NMR spectroscopy showed the product to be a mixture of amide rotamers (ratio 60:40). ν_{max}/cm^{-1} (NaCl plate) 1682, 1566, 1550, 1532, 1514, 1464, 1411, 1376, 1266; δ_H (300 MHz, $CDCl_3$) 1.27 (6H, d, J=6.0 Hz, $OCH(CH_3)_2$), 1.34 and 1.42 (9H, 2×s, $OC(CH_3)_3$), 3.51–3.56 (2H, m consisting of 2×overlapping d, 6-H), 380 and 3.81 (3H, 2×s, OCH_3), 3.81–3.84 (under OCH_3) and 4.00 (2H, d, J=4.5 Hz, 3-H), 4.47 and 4.54 (2H, 2×s, 1-H), 4.54 (1H, under 1-H, $OCH(CH_3)_2$), 5.66–5.90 (2H, m, 4-H and 5-H), 6.66–6.71 (1H, 2×overlapping d, J=7.5 Hz, 9-H), 6.83 and 6.95 (1H, 2×d, J=7.5 Hz, 10-H); δ_C (50 MHz, $CDCl_3$) 22.5 and 22.6 ($OCH(CH_3)_2$), 25.2 and 25.3 (6-C), 28.4 ($OC(CH_3)_3$), 44.5 and 44.9 (3-C), 51.7 (1-C), 55.6 (OCH_3), 74.5 and 74.6 ($OCH(CH_3)_2$), 79.4 and 79.5 ($OC(CH_3)_3$), 109.2 and 109.6 (9-C), 124.5 and 125.2 (10-C), 128.1 and 128.4 (5-C),[a] 129.4 (C), 130.3 and 130.6 (4-C),[a] 132.9 and 133.2 (C), 144.4 (C), 152.2 and 152.4 (C), 155.2 and 155.5 (C=O); m/z 347 (M^+, 43%), 249 (20), 204 (25), 188 (47), 175 (39), 162 (20), 143 (48), 57 (100); HRMS calculated for $C_{20}H_{29}NO_4$: 347.2097, found: 347.2095.

5.2.3. 2-(Benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine 15c. *N*-Allyl-*N*-(2-allyl-3-isopropoxy-4-methoxy-benzyl)phenylmethanesulfonamide **14c** (0.466 mmol, 0.205 g) was dissolved in toluene (20 cm^3) and Grubbs II catalyst **10** (5 mol %, 0.0233 mmol,

0.0194 g) was added. Column chromatography (10% EtOAc–Hexane, R_f 0.49 in 30% EtOAc–Hexane) afforded white crystals of compound **15c** (0.157 g, 84%). Mp 119–122 °C; ν_{max}/cm^{-1} (NaCl plate) 1691, 1647, 1463, 1372, 1333; δ_H (300 MHz, $CDCl_3$) 1.28 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 3.63 (2H, d, J=7.5 Hz, 6-H), 3.83–3.86 (7H, m, OCH_3, ArCH_2N and NCH_2C), 4.48–4.56 (3H, m, OCH(CH_3)$_2$ and SO_2CH_2Ar), 5.58–5.64 (1H, m, 4-H),[a] 6.02–6.08 (1H, m, 5-H),[a] 6.75 (1H, d, J=8.5 Hz, 9-H), 6.98 (1H, d, J=8.5 Hz, 10-H), 7.23–7.26 (2H, m, 2×ArH), 7.30–7.32 (3H, m, 3×ArH); δ_C (50 MHz, $CDCl_3$) 22.6 (OCH(CH_3)$_2$), 26.8 (6-C), 44.8 (3-C), 52.8 (SO_2CH_2Ar), 55.6 (OCH_3), 59.4 (1-C), 74.6 (OCH(CH_3)$_2$), 109.8 (9-C), 125.6 (CH), 126.0 (CH), 127.7 (C), 128.3 (CH), 128.5 (2×CH), 129.1 (C), 130.7 (2×CH), 134.4 (C), 135.4 (CH), 144.5 (C), 152.8 (C); m/z 401 (M^+, 47%), 284 (70), 265 (19), 253 (15), 252 (16), 246 (15), 204 (100), 188 (16), 175 (20), 143 (17), 91 (88); HRMS calculated for $C_{22}H_{27}NO_4S$: 401.1661, found: 401.1666.

5.2.4. 7-Isopropoxy-8-methoxy-2-[(4-methylphenyl)-sulfonyl]-1,2,3,6-tetrahydro-2-benzazocine 15d. *N*-Allyl-*N*-(2-allyl-3-isopropoxy-4-methoxybenzyl)-4-methyl-benzenesulfonamide **14d** (0.364 mmol, 0.156 g) was dissolved in toluene (15 cm^3) and Grubbs II catalyst **10** (5 mol %, 0.0182 mmol, 0.0161 g) was added. Purification by column chromatography (5–10% EtOAc–Hexane, R_f 0.54 in 30% EtOAc–Hexane) afforded the desired product **15d** as a pale yellow oil (0.139 g, 95%). ν_{max}/cm^{-1} (NaCl plate) 1598, 1489, 1439, 1383, 1334, 1279; δ_H (300 MHz, $CDCl_3$) 1.23 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 2.40 (3H, s, CH_3), 3.54 (2H, d, J=6.5 Hz, 6-H), 3.75 (2H, d, J=6.5 Hz, 3-H), 3.82 (3H, s, OCH_3), 4.41 (1H, sept, J=6.0 Hz, OCH(CH_3)$_2$), 4.47 (2H, s, 1-H), 5.43-5.49 (1H, m, 4-H),[a] 5.75–5.81 (1H, m, 5-H),[a] 6.71 (1H, d, J=8.5 Hz, 9-H), 6.89 (1H, d, J=8.5 Hz, 10-H), 7.23 (2H, d, J=8.0 Hz, 2×ArH), 7.62 (2H, d, J=8.0 Hz, 2×ArH); δ_C (50 MHz, $CDCl_3$) 21.5 ($ArCH_3$), 22.5 (OCH(CH_3)$_2$), 26.5 (6-C), 43.3 (3-C), 50.8 (1-C), 55.6 (OCH_3), 74.8 (OCH(CH_3)$_2$), 110.0 (9-C), 124.5 (10-C),[a] 125.4 (CH),[a] 127.3 (2×CH), 127.7 (C), 129.4 (2×CH), 133.2 (C), 133.4 (CH), 136.9 (C), 143.0 (C), 144.3 (C), 152.9 (C); m/z 401 (M^+, 22%), 246 (50), 204 (100), 189 (43), 175 (52), 161 (22), 143 (35); HRMS calculated for $C_{22}H_{27}NO_4S$: 401.1661, found: 401.1663.

5.2.5. 7-Isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine 16. *tert*-Butyl 7-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxylate **15b** (0.300 mmol, 0.104 g) was dissolved in CH_2Cl_2 (2 cm^3) and to this solution was added triflouroacetic acid (0.45 mmol, 0.035 cm^3). The reaction mixture was allowed to stir at rt under an Ar atmosphere for 1 h, after which time the solution had gone dark brown. To the reaction mixture was added distilled H_2O (2 cm^3) and the solution was diluted with EtOAc (2 cm^3). It was then neutralized using a saturated solution of $NaHCO_3$ and 10% aqueous AcOH. The organic layer was kept aside and the aqueous layer was extracted with EtOAc (3×10 cm^3). The combined organics were then dried ($MgSO_4$) and the solvent was removed in vacuo to yield **16** as a dark orange semi-solid (0.0731 g, 99%), which was sufficiently pure by ^{1}H NMR spectroscopy and no further purification was performed. ν_{max}/cm^{-1} (NaCl plate) 3618, 1674, 1603, 1520, 1440; δ_H (400 MHz, $CDCl_3$) 1.17 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 3.17 (2H, d, J=8.0 Hz, 6-H), 3.66 (2H, br s, 3-H), 3.76 (3H, s, OCH_3), 4.21 (2H, br s, 1-H), 4.34 (1H, sept, J=6.0 Hz, OCH(CH_3)$_2$), 5.47–5.54 (1H, m, 4-H),[a] 6.11–6.16 (1H, m, 5-H),[a] 6.76 (1H, d, J=8.5 Hz, 9-H), 7.00 (1H, d, J=8.5 Hz, 10-H), 8.84 (1H, br s, NH); δ_C (50 MHz, $CDCl_3$) 22.5 (OCH(CH_3)$_2$), 29.1 (6-C), 36.8 (3-C), 45.3 (1-C), 55.6 (OCH_3), 75.2 (OCH(CH_3)$_2$), 111.2 (9-C), 117.7 (10-C), 121.6 (C), 127.0 (C), 133.4 (CH), 140.1 (CH), 144.6 (C), 154.2 (C); m/z 247 (M^+, 68%), 204 (100), 190 (32), 188 (43), 176 (60), 175 (35), 162 (25), 161 (28), 143 (39), 115 (31); HRMS calculated for $C_{15}H_{21}NO_2$: 247.1572, found: 247.1565.

5.2.6. 2-(Benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,4,5,6-hexahydro-2-benzazocine 17. 2-(Benzylsulfonyl)-7-isopropoxy-8-methoxy-1,2,3,6-tetrahydro-2-benzazocine **15c** (0.275 mmol, 0.109 g) was dissolved in absolute ethanol (10 cm^3) by sonication. To the resultant emulsion was added 10% Pd/C (0.15 g/mmol, 0.0430 g) and this mixture was subjected to hydrogenation in an autoclave at 5 atm H_2 for 18 h at rt. The reaction mixture was then filtered through Celite and rinsed with CH_2Cl_2 (3×50 cm^3). The solvent was then removed in vacuo to yield a cream-white solid. This was then recrystallized by dissolving the compound in the minimum amount of EtOAc and then adding hexane dropwise to the solution until it became cloudy. The solution was then left to stand overnight and the recrystallized material was collected by filtration. The pure product **17** was obtained as colourless crystals (0.108 g, 98%). Mp 141–147 °C; ν_{max}/cm^{-1} (NaCl plate) 1521, 1490, 1425, 1332, 1212; δ_H (300 MHz, $CDCl_3$) 1.25 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 1.51–1.52 (2H, m, 4-H),[a] 1.66–1.68 (2H, m, 5-H),[a] 2.87–2.91 (2H, m, 6-H),[b] 3.09–3.12 (2H, m, 3-H),[b] 3.82 (3H, s, OCH_3), 4.18 (2H, s, 1-H),[c] 4.22 (2H, s, SO_2CH_2Ar),[c] 4.53 (1H, sept, J=6.0 Hz, OCH(CH_3)$_2$), 6.73 (1H, d, J=8.5 Hz, 9-H), 6.94 (1H, d, J=8.5 Hz, 10-H), 7.35–7.37 (5H, m, 5×ArH); δ_C (50 MHz, $CDCl_3$) 22.6 (OCH(CH_3)$_2$), 24.0 (5-C),[a] 27.9 (4-C),[a] 29.3 (6-C),[a] 46.9 (3-C),[b] 49.7 (SO_2CH_2),[b] 55.5 (OCH_3), 58.7 (1-C), 74.3 (OCH(CH_3)$_2$), 110.0 (9-C), 125.6 (10-C), 128.1 (C), 128.5 (CH), 128.7 (2×CH), 129.5 (C), 130.7 (2×CH), 135.4 (C), 144.3 (C), 152.6 (C); m/z 403 (M^+, 36%), 361 (28), 253 (19), 206 (71), 205 (20), 178 (17), 177 (22), 176 (21), 120 (17), 91 (100), 30 (13), 28 (19); HRMS calculated for $C_{22}H_{29}NO_4S$: 403.1817, found: 403.1818.

5.2.7. 5-Hydroxy-4-methoxy-2-[(1*E*)-3-phenyl-2-propenyl]benzaldehyde 20. The Claisen–Cope rearrangement was effected by placing the 4-methoxy-3-{[(2*E*)-3-phenyl-2-propenyl]oxy}benzaldehyde **18** (0.939 mmol, 0.249 g) neat in a sealed tube for the microwave reactor. The program was set up with the power output at 50 W, the maximum temperature at 200 °C, the maximum allowable pressure at 150 psi with no cooling and continuous stirring. The run time was set to 5 min with a hold time of 5 min. This yielded the desired compound **20** as a dark brown oil that was deemed acceptably pure by spectroscopy and no further purification was required (0.249 g, 100%). The NMR spectra of this compound correlated well with that published in the literature.[14]

5.2.8. 5-Isopropoxy-4-methoxy-2-[(1*E*)-3-phenyl-2-propenyl]benzaldehyde 21.[16] The 4-methoxy-3-{[(2*E*)-3-phenyl-2-propenyl]-oxy}benzaldehyde **18** (9.35 mmol,

2.51 g) was placed in a sealed tube for the microwave reactor in 0.250 g batches and the Claisen–Cope rearrangement was performed under solvent-free conditions. The program was set up with the power output at 50 W, the maximum temperature at 200 °C, the maximum allowable pressure at 150 psi with no cooling and continuous stirring. The run time was set to 5 min, with a hold time of 5 min, for each of the 0.250 g batches of aldehyde. All the products were combined in a round-bottomed flask and were dissolved in DMF (25 cm^3). The solution was placed under an Ar atmosphere and then heated to 60 °C. Then K_2CO_3 (23.4 mmol, 3.24 g) was added and the solution was stirred until a suspension formed. Isopropyl bromide (23.4 mmol, 2.20 cm^3) was finally added and the reaction mixture was allowed to stir at 60 °C under an Ar atmosphere for 19 h. After this time the reaction mixture was cooled to rt and the inorganic solids were filtered off through a Celite pad, which was rinsed with CH_2Cl_2 (50 cm^3). The solvent was then removed in vacuo. The crude mixture was then purified by column chromatography (5–10% EtOAc–Hexane, R_f 0.63 in 30% EtOAc–Hexane) to obtain the desired product **21** as a dark yellow oil (2.20 g, 76% over two steps). ν_{max}/cm^{-1} (NaCl plate) 1679, 1594, 1510, 1423, 1266, 1216; δ_H (300 MHz, $CDCl_3$) 1.39 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 3.90–3.92 (5H, m, CH_2 and OCH_3), 4.62 (1H, sept, J=6.0 Hz, OCH(CH_3)$_2$), 6.38–6.39 (2H, m, CH=CHPh and CH=CHPh), 6.77 (1H, s, 3-H), 7.16–7.32 (5H, m, 5×ArH), 7.42 (1H, s, 6-H), 10.20 (1H, s, CHO); δ_C (50 MHz, $CDCl_3$) 21.9 (OCH(CH_3)$_2$), 35.0 ($ArCH_2$), 56.1 (OCH_3), 71.5 (OCH(CH_3)$_2$), 113.5 (3-C), 115.6 (6-C), 126.1 (2×CH), 126.8 (C), 127.3 (CH), 128.5 (2×CH), 128.8 (CH), 131.4 (CH), 137.1 (C), 137.6 (C), 146.1 (C), 155.2 (C), 190.1 (CHO); m/z 310 (M^+, 46%), 268 (50), 239 (18), 219 (54), 178 (15), 177 (100), 163 (82), 152 (16), 136 (33), 91 (23); HRMS calculated for $C_{20}H_{22}O_3$: 310.1569, found: 310.1583.

5.2.9. *N*-((*E*)-{5-Isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]phenyl}methylidene)-2-propen-1-amine 22.[16] The 5-isopropoxy-4-methoxy-2-[(1*E*)-3-phenyl-2-propenyl]-benzaldehyde **21** (6.41 mmol, 1.99 g) was transferred to the reaction flask using the minimum amount of Et_2O and the solvent was removed under high vacuum. To the aldehyde was then added allyl amine (8.97 mmol, 0.700 cm^3) and the reaction mixture was stirred at rt under an Ar atmosphere for 21.5 h. After this time the excess allyl amine was removed under reduced pressure and imine formation was confirmed by ^1H NMR spectroscopy. The product **22** was obtained as a yellow oil (2.24 g, 100%) and no further purification was performed. ν_{max}/cm^{-1} (NaCl plate) 1677, 1645, 1598, 1508, 1465, 1445, 1385, 1266, 1216; δ_H (300 MHz, $CDCl_3$, only major isomer listed) 1.37 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 3.71 (2H, d, J=2.5 Hz, $ArCH_2$), 3.86 (3H, s, OCH_3), 4.22 (2H, br d, J=5.5 Hz, NCH_2C), 4.65 (1H, sept, J=6.0 Hz, OCH(CH_3)$_2$), 5.06–5.22 (2H, m, $ArCH_2CH$=CH_2), 5.98–6.10 (1H, m, $ArCH_2CH$=CH_2), 6.31–6.32 (2H, m, CH=CHPh and CH=CHPh), 6.70 (1H, s, 3-H), 7.17–7.33 (5H, m, 5×ArH), 7.59 (1H, s, 6-H), 8.52 (1H, s, N=CH); δ_C (50 MHz, $CDCl_3$, only major isomer listed) 22.0 (OCH(CH_3)$_2$), 35.4 ($ArCH_2$), 55.9 (OCH_3), 63.7 (NCH_2CH=CH_2), 71.3 (OCH(CH_3)$_2$), 113.2 (3-C), 113.6 (6-C), 115.7 (CH), 126.1 (2×CH), 126.7 (C), 127.1 (CH), 128.6 (2×CH), 129.3 (CH=CHPh),[a] 130.9 (CH=CHPh),[a] 133.1 (C), 136.3 (CH), 137.3 (C), 146.1 (C), 152.3 (C), 159.5 (N=CH); m/z 349 (M^+, 18%), 348 (25), 310 (37), 268 (44), 258 (50), 219 (45), 216 (31), 177 (100), 164 (85), 136 (35), 91 (46), 41 (28); HRMS calculated for $C_{23}H_{27}NO_2$: 349.2042, found: 349.2034.

5.2.10. *N*-{5-Isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]-benzyl}-2-propen-1-amine 23.[16] The *N*-((*E*)-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]-phenyl}methylidene)-2-propen-1-amine **22** (6.26 mmol, 2.19 g) was dissolved in MeOH (200 cm^3) and cooled to 0 °C in an ice-water bath. Then sodium borohydride (7.52 mmol, 0.294 g) was added and the reaction mixture was allowed to warm to rt, with stirring, under an Ar atmosphere for 4.5 h. After this time thin layer chromatography showed no further change so distilled water (200 cm^3) was added to the reaction mixture. The pH was then neutralized using 1 M HCl and saturated $NaHCO_3$ solutions. The volatiles were removed in vacuo before the aqueous layer was extracted with CH_2Cl_2 (4×100 cm^3). The combined organics were then extracted with distilled H_2O (200 cm^3) and dried over anhydrous $MgSO_4$. The solvent was then removed in vacuo to give the desired product **23** as a dark yellow oil (1.66 g, 75%). The compound contained a minor impurity (presumed to be the isomerized compound **26**) but it proved impossible to remove this by chromatography. ν_{max}/cm^{-1} (NaCl plate) 1513, 1446, 1216; δ_H (300 MHz, $CDCl_3$, only major isomer listed) 1.36 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 1.58 (1H, br s, NH), 3.25–3.28 (2H, m, NCH_2CH=CH_2), 3.55 (2H, br s, $ArCH_2CHCH$), 3.73 (2H, br s, $ArCH_2N$), 3.82 (3H, s, OCH_3), 4.53 (1H, sept, J=6.0 Hz, OCH(CH_3)$_2$), 5.07–5.20 (2H, m, NCH_2CH=CH_2), 5.85–5.98 (1H, m, NCH_2CH=CH_2), 6.32–6.35 (2H, m, CH=CHPh and CH=CHPh), 6.74 (1H, s, 3-H), 6.93 (1H, s, 6-H), 7.18–7.34 (5H, m, 5×ArH); δ_C (50 MHz, $CDCl_3$, only major isomer listed) 22.0 (OCH(CH_3)$_2$), 35.8 ($ArCH_2CH$), 50.2 ($ArCH_2N$),[a] 51.9 (NCH_2CH=CH_2),[a] 56.1 (OCH_3), 71.6 (OCH(CH_3)$_2$), 114.0 (3-C), 115.9 (CH), 117.7 (6-C), 125.9 (C), 126.0 (2×CH), 127.0 (CH), 127.9 (C), 128.4 (2×CH), 129.6 (CH), 130.5 (CH), 136.8 (CH), 137.4 (C), 145.6 (C), 149.5 (C); m/z 351 (M^+, 18%), 294 (33), 253 (22), 252 (100), 251 (14), 237 (12), 219 (12), 204 (11), 161 (24), 91 (25); HRMS calculated for $C_{23}H_{29}NO_2$: 351.2198, found: 351.2193.

5.2.11. *N*-Allyl-*N*-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}-4-methylbenzenesulfonamide 24a.[16] *N*-{5-Isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]-benzyl}-2-propen-1-amine **23** (1.43 mmol, 0.503 g) was dissolved in CH_2Cl_2 (25 cm^3) and the solution was cooled to 0 °C in an ice-water bath. NEt_3 (2.00 mmol, 0.300 cm^3) was then added and the reaction mixture was allowed to stir for 5 min before the addition of the TsCl (1.72 mmol, 0.331 g). The reaction mixture was then warmed to rt with stirring for 2.5 h, before being diluted with distilled H_2O (25 cm^3). The aqueous layer was then extracted with CH_2Cl_2 (25 cm^3); then the organic layers were combined and washed with distilled H_2O (2×25 cm^3) before being dried over anhydrous $MgSO_4$. The solvent was removed in vacuo to yield a dark orange oil that was then purified by column chromatography (5–10% EtOAc–Hexane, R_f 0.60 in 30% EtOAc–Hexane). The desired compound **24a** was obtained as a yellow oil (0.521 g, 72%) that slowly solidified into a yellow wax on standing. Mp 79–82 °C;

ν_{max}/cm^{-1} (NaCl plate) 1599, 1513, 1447, 1343, 1275; δ_H (300 MHz, $CDCl_3$, only major isomer listed) 1.32 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 2.43 (3H, s, ArCH_3), 3.48 (2H, br d, J=5.0 Hz, ArCH_2C), 3.70–3.74 (2H, m, NCH_2CH=CH_2), 3.83 (3H, s, OCH_3), 4.28–4.42 (3H, m, ArCH_2N and OCH(CH_3)$_2$), 4.84–5.00 (2H, m, NCH$_2$CH=CH_2), 5.41–5.52 (1H, m, CH=CH$_2$), 6.25–6.35 (2H, m, CH=CHPh and CH=CHPh), 6.70 (1H, s, 3-H), 6.81 (1H, s, 6-H), 7.20–7.31 (7H, m, 7×ArH), 7.73 (2H, d, J=8.0 Hz, 2×ArH); δ_C (50 MHz, $CDCl_3$, only major isomer listed) 21.5 (ArCH_3), 22.1 (OCH(CH_3)$_2$), 35.5 (ArCH_2C), 47.8 (ArCH_2N),[a] 49.5 (NCH_2CHCH$_2$),[a] 56.0 (OCH_3), 71.5 (OCH(CH_3)$_2$), 113.9 (3-C), 117.3 (CH), 118.7 (6-C), 125.4 (C), 126.1 (2×CH), 127.1 (CH), 127.3 (2×CH), 128.3 (C), 128.5 (2×CH), 129.7 (2×CH), 130.8 (CH), 131.4 (CH), 132.6 (C), 137.0 (CH), 137.4 (C), 143.2 (C), 145.6 (C), 149.9 (C); m/z 505 (M$^+$, 7%), 350 (13), 295 (15), 294 (53), 262 (39), 253 (23), 252 (100), 224 (12), 161 (22), 91 (42), 41 (15); HRMS calculated for $C_{30}H_{35}NO_4S$: 505.2287, found: 505.2284.

5.2.12. *tert*-Butyl allyl{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]benzyl}carbamate 24b.[16] The *N*-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-prop-enyl]-benzyl}-2-propen-1-amine **23** (1.47 mmol, 0.517 g) was dissolved in freshly distilled THF (50 cm^3). To this solution was added Boc_2O (1.76 mmol, 0.400 cm^3) and it was stirred for 5 min. Then DMAP (0.147 mmol, 0.0180 g) was added and the reaction mixture was left to stir at rt under an Ar atmosphere for 3 h. After this time thin layer chromatography showed consumption of the starting material so the solvent was removed in vacuo to yield an orange oil. This was then purified by column chromatography (5–10% EtOAc–Hexane, R_f 0.74 in 30% EtOAc–Hexane) to obtain the desired product **24b** as a yellow oil (0.525 g, 79%). The NMR spectra of compound **24b** showed that it consisted of a complex mixture of rotamers due to the Boc-protecting group. ν_{max}/cm^{-1} (NaCl plate) 1681, 1603, 1513, 1460, 1416, 1368, 1212; δ_H (300 MHz, $CDCl_3$) 1.35 (6H, d, J=6.0 Hz, OCH(CH_3)$_2$), 1.45 and 1.48 (9H, 2×s, OC(CH_3)$_3$), 3.47 (2H, br d, J=4.0 Hz, ArCH_2C),[a] 3.53–3.76 (2H, very br m, NCH_2CHCH$_2$),[a] 3.93 (3H, s, OCH_3), 4.43–4.49 (3H, m, ArCH_2N and OCH(CH_3)$_2$), 5.02–5.10 (2H, m, CH=CH_2), 5.71–5.73 (1H, br m, CH=CH$_2$), 6.30 (1H, br s, CH=CHPh),[b] 6.73 (1H, br s, CH=CHPh),[b,c] 6.77 (1H, br s, 3-H),[c] 7.16–7.33 (6H, m, 6-H and 5×ArH); δ_C (50 MHz, $CDCl_3$) 22.1 (OCH(CH_3)$_2$), 28.4 (OC(CH_3)$_3$), 35.6 (ArCH_2C), 46.2 (br, ArCH_2N), 48.0 (NCH_2C), 56.1 (OCH_3), 71.6 (OCH(CH_3)$_2$), 79.7 (OC(CH_3)$_3$), 109.9 (3-C), 114.0 (CH), 116.4 (6-C), 126.0 (2×CH), 127.0 (CH), 127.8 (C), 128.3 (C), 128.4 (2×CH), 128.6 (CH), 130.6 (CH), 133.7 (CH), 137.4 (C), 145.6 (C), 149.6 (C), 155.5 (C=O); m/z 451 (M$^+$, 22%), 295 (17), 294 (42), 281 (83), 253 (26), 252 (100), 251 (24), 239 (57), 161 (26), 91 (37), 70 (25), 57 (37); HRMS calculated for $C_{28}H_{37}NO_4$: 451.2723, found: 451.2721.

5.2.13. 9-Isopropoxy-8-methoxy-2-[(4-methylphenyl)-sulfonyl]-1,2,3,6-tetrahydro-2-benzazocine 25a. The *N*-allyl-*N*-{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-prop-enyl]benzyl}-4-methylbenzenesulfonamide **24a** (0.411 mmol, 0.208 g) was dissolved in distilled toluene (20 cm^3) and the solution was heated to 60 °C before the addition of Grubbs II catalyst **10** (5 mol %, 0.0206 mmol, 0.0176 g). The reaction mixture was then stirred at 60 °C under an Ar atmosphere for 20 h. After this time the solvent was removed in vacuo and the crude mixture was purified by column chromatography (5–10% EtOAc–Hexane, R_f 0.40 in 30% EtOAc–Hexane) to give the desired compound **25a** as a milky yellow oil (0.0649 g, 39%) as well as a number of other compounds, which were uncharacterizable in our hands. ν_{max}/cm^{-1} (NaCl plate) 1600, 1517, 1425, 1334, 1216; δ_H (300 MHz, $CDCl_3$) 1.32–1.39 (6H, m, OCH(CH_3)$_2$), 2.41 (3H, br s, ArCH_3), 3.41 (2H, br d, J=6.5 Hz, 6-H), 3.73–3.77 (2H, m, 3-H), 3.83 (3H, s, OCH_3), 4.39–4.47 (3H, m, 1-H and OCH(CH_3)$_2$), 5.41–5.48 (1H, m, 4-H),[a] 5.76–5.84 (1H, m, 5-CH),[a] 6.61 (1H, s, 7-H),[b] 6.70 (1H, s, 10-H),[b] 7.21–7.27 (2H, m, 2×ArH), 7.65 (2H, d, J=8.0 Hz, 2×ArH); δ_C (50 MHz, $CDCl_3$) 21.5 (ArCH_3), 22.1 (OCH(CH_3)$_2$), 34.3 (6-C), 43.3 (3-C), 50.5 (1-C), 56.0 (OCH_3), 71.6 (OCH(CH_3)$_2$), 113.9 (CH), 118.1 (CH), 124.0 (CH), 127.2 (2×CH), 128.9 (C), 129.5 (2×CH), 131.1 (C), 133.3 (CH), 136.8 (C), 143.0 (C), 145.9 (C), 150.1 (C); m/z 401 (M$^+$, 79%), 246 (47), 214 (21), 204 (100), 189 (23), 188 (21), 176 (47), 175 (63), 163 (24), 137 (26), 91 (68); HRMS calculated for $C_{22}H_{27}NO_4S$: 401.1661, found: 401.1672.

5.2.14. *tert*-Butyl 9-isopropoxy-8-methoxy-3,6-dihydro-2-benzazocine-2(1*H*)-carboxylate 25b. The *tert*-butyl allyl{5-isopropoxy-4-methoxy-2-[(2*E*)-3-phenyl-2-propenyl]-benzyl}carbamate **24b** (0.476 mmol, 0.215 g) was dissolved in distilled toluene (20 cm^3) and the solution was heated to 60 °C. Then Grubbs II catalyst **10** (5 mol %, 0.0238 mmol, 0.0237 g) was added and the reaction mixture was stirred at 60 °C under an Ar atmosphere for 22.5 h. After this time the reaction mixture was cooled to rt and the solvent was removed in vacuo to yield a dark brown oil. This was then purified by column chromatography (5% EtOAc–Hexane, R_f 0.58 in 30% EtOAc–Hexane) to obtain the desired compound **25b** as a viscous yellow oil (0.121 g, 73%). Peak broadening was observed in the ^{1}H NMR spectrum due to the Boc-protecting group. ν_{max}/cm^{-1} (NaCl plate) 1683, 1603, 1513, 1464, 1411, 1369, 1268; δ_H (300 MHz, $CDCl_3$) 1.26–1.55 (15H, m, OCH(CH_3)$_2$ and OC(CH_3)$_3$), 3.36 (2H, d, J=8.0 Hz, 6-H), 3.83–3.85 (4H, m, OCH_3 and one of NCH_2CH),[a] 4.05 (1H, d, J=5.0 Hz, one of NCH_2CH),[a] 4.44–4.53 (3H, m, ArCH_2N and OCH(CH_3)$_2$), 5.65–5.91 (1H, m, 4-H),[b] 6.64–6.83 (1H, m, 5-H),[b] 7.26–7.30 (2H, m, 7-H and 10-H); δ_C (50 MHz, $CDCl_3$) 22.1 and 22.2 (OCH(CH_3)$_2$), 28.4 (OC(CH_3)$_3$), 32.6 and 33.0 (6-C), 45.0 and 45.3 (3-C), 51.6 (1-C), 56.0 (OCH_3), 71.4 and 71.9 (OCH(CH_3)$_2$), 79.6 (OC(CH_3)$_3$), 113.9 and 114.3 (CH), 118.3 and 118.5 (CH), 126.0 and 126.3 (C), 127.5 and 127.9 (CH), 128.4 and 128.5 (C), 129.1 and 130.6 (CH), 131.2 and 131.5 (C), 145.0 (C), 149.5 (C=O); m/z 347 (M$^+$, 100%), 291 (52), 290 (71), 249 (28), 204 (28), 188 (51), 179 (33), 176 (34), 175 (95), 137 (41), 57 (91), HRMS calculated for $C_{20}H_{29}NO_4$: 347.2097, found: 347.2093.

5.3. Cytotoxic effects—MTT assay

HT-29 (colon adenocarcinoma) cells were maintained in DMEM containing 0.2% 60 mg/l benzyl-penicillin/100 mg/l streptomycin and 10% foetal bovine serum (FBS). MCF-7 (breast carcinoma), K562 (chronic myelogenous leukaemia)

and HL-60 (acute promyelocytic leukaemia) cells were routinely maintained in RPMI-1640 medium supplemented with 10% foetal bovine serum (FBS). All cells, medium and supplements were obtained from Highveld Biological, South Africa.

The cells were seeded in 96-well plates at a density of 25,000 cells/well, in order to maintain the cells within the exponential growth phase during testing. Cells were exposed to a one-concentration primary screen of 100 μM compound for 24 h at 37 °C in a humidified incubator containing 5% CO_2. The effect of the compounds on cell viability was determined by the MTT [3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide] assay as described by Mosmann.[17] Briefly, 50 μl 0.5% MTT solution was added to the culture medium at the end of each experiment, and the cells were further incubated for 2 h. The yellow MTT dye is reduced by mitochondrial succinic dehydrogenase of viable cells to purple formazan crystals, which were solubilized in DMSO. The optical density was read at 540 nm against a DMSO blank. Cell numbers per well were extrapolated from calibration curves for individual cell lines. The percentage cell viability per well was calculated as follows: % cell viability=[number of viable treated cells]/[number of viable control cells]×100%. All experiments were conducted in triplicate.

Acknowledgements

This work was supported by the National Research Foundation (NRF, GUN 2053652), Pretoria and the University of the Witwatersrand (University and Science Faculty Research Councils, Friedel Sellschop Award). Prof. J. P. Michael is thanked for many helpful discussions. We also gratefully acknowledge Mr R. Mampa and Mr T. van der Merwe for providing the NMR and MS spectroscopy services, respectively.

References and notes

1. Horton, D. A.; Bourne, G. T.; Smythe, M. L. *Chem. Rev.* **2003**, *103*, 893–930.
2. (a) Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1545–1551; (b) Qadir, M.; Cobb, J.; Sheldrake, P. W.; Whittall, N.; White, A. J. P.; Hii, K. K.; Horton, P. N.; Hursthouse, M. B. *J. Org. Chem.* **2005**, *70*, 1552–1557.
3. Grunewald, G. L.; Dahanukar, V. H.; Ching, P.; Criscione, K. R. *J. Med. Chem.* **1996**, *39*, 3539–3546.
4. (a) Sato, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem.* **2005**, *13*, 5717–5732; (b) Sato, S.; Tanioka, A.; Ikeda, M.; Izawa, S. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1479–1484; (c) Sato, S. *Tetrahedron Lett.* **2004**, *45*, 8475–8478.
5. Viladomat, F.; Bastida, J.; Codina, C.; Campbell, W. E.; Mathee, S. *Phytochemistry* **1995**, *40*, 307–311.
6. (a) Bergemann, S.; Brecht, R.; Büttner, F.; Guénard, D.; Gust, R.; Seitz, G.; Stubbs, M. T.; Thoret, S. *Bioorg. Med. Chem.* **2003**, *11*, 1269–1281; (b) Brecht, R.; Seitz, G.; Guénard, D.; Thoret, S. *Bioorg. Med. Chem.* **2000**, *8*, 557–562.
7. See the following reviews and other reviews cited therein: (a) Schmidt, B.; Hermanns, J. *Curr. Org. Chem.* **2006**, *10*, 1363–1396; (b) McReynolds, M. D.; Dougherty, J. M.; Hanson, P. R. *Chem. Rev.* **2004**, *104*, 2239–2258; (c) Deiters, A.; Martin, S. F. *Chem. Rev.* **2004**, *104*, 2199–2238.
8. For the synthesis of benzo-fused compounds by RCM from our group, see the following recent examples and references cited therein: (a) Pathak, R.; Panayides, J.-L.; Jeftic, T. D.; de Koning, C. B.; van Otterlo, W. A. L. *S. Afr. J. Chem.* **2007**, *60*, 1–7 (http://blues.sabinet.co.za/sajchem/); (b) Coyanis, E. M.; Panayides, J.-L.; Fernandes, M. A.; de Koning, C. B.; van Otterlo, W. A. L. *J. Organomet. Chem.* **2006**, *691*, 5222–5239; (c) van Otterlo, W. A. L.; Ngidi, E. L.; Kuzvidza, S.; Morgans, G. L.; Moleele, S. S.; de Koning, C. B. *Tetrahedron* **2005**, *61*, 9996–10006; (d) van Otterlo, W. A. L.; Morgans, G. L.; Madeley, L. G.; Kuzvidza, S.; Moleele, S. S.; Thornton, N.; de Koning, C. B. *Tetrahedron* **2005**, *61*, 7746–7755; (e) van Otterlo, W. A. L.; Coyanis, E. M.; Panayides, J.-L.; de Koning, C. B.; Fernandes, M. A. *Synlett* **2005**, 501–505; (f) van Otterlo, W. A. L.; Ngidi, E. L.; de Koning, C. B.; Fernandes, M. A. *Tetrahedron Lett.* **2004**, *45*, 659–662; (g) van Otterlo, W. A. L.; Pathak, R.; de Koning, C. B. *Synlett* **2003**, 1859–1861; (h) van Otterlo, W. A. L.; Ngidi, E. L.; Coyanis, E. M.; de Koning, C. B. *Tetrahedron Lett.* **2003**, *44*, 311–313.
9. Lane, C.; Snieckus, V. *Synlett* **2000**, 1294–1296.
10. de Koning, C. B.; Michael, J. P.; Rousseau, A. L. *J. Chem. Soc., Perkin Trans. 1* **2000**, 787–797.
11. Synthetic work done by Ms J.-L. Panayides (MSc), and Ms R. Pathak (PhD) and biological testing by Ms H. Panagiotopoulos (MSc).
12. Crystallographic data for compound **15c**: $C_{22}H_{27}NO_4S$, crystal size 0.30×0.19×0.04 mm^3, crystal system monoclinic, space group $P2_1/c$, Z=4, unit cell dimensions: a=15.692(5) Å, b=14.617(5) Å, c=9.104(3) Å, β=95.042(6)°, V=2080.0(11) $Å^3$, D_x=1.282 Mg/m^3, collection temperature 173(2) K; θ_{max}=25.00°; 10,651 reflections collected with 3670 independent reflections (R_{int}=0.1309); 256 parameters; maximum residual electron density 0.536 and −0.550 e $Å^{-3}$; final R indices: R_1=0.0605, wR_2=0.1287. CCDC-626420 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax (internat.): +44 1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
13. Crystallographic data for compound **17**: $C_{22}H_{29}NO_4S$, crystal size 0.35×0.24×0.07 mm^3, crystal system triclinic, space group P_{-1}, Z=4, unit cell dimensions: a=10.4070(3) Å, b=12.4260(3) Å, c=16.5460(4) Å, α=99.2740(10)°, β=95.2530(10)°, γ=90.3040(10)°, V=2102.41(9) $Å^3$, D_x=1.275 Mg/m^3, collection temperature 173(2) K; θ_{max}=28.00°; 34,736 reflections collected with 10,153 independent reflections (R_{int}=0.0379); 291 parameters; maximum residual electron density 0.481 and −0.414 e$Å^{-3}$; final R indices: R_1=0.0511, wR_2=0.1332. CCDC-626421 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax (internat.): +44 1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].
14. Huang, K.-S.; Wang, E.-C.; Chen, H.-M. *J. Chin. Chem. Soc.* **2004**, *51*, 585–605.

15. For other papers commenting on the possibility of steric buttressing effects by *ortho*-groups in (i) RCM see: (a) Evans, P.; Grigg, R.; York, M. *Tetrahedron Lett.* **2000**, *41*, 3967–3970; (b) Evans, P.; Grigg, R.; Monteith, M. *Tetrahedron Lett.* **1999**, *40*, 5247–5250; (ii) For Pauson–Khand reactions see: (c) Lovely, C. J.; Seshadri, H.; Wayland, B. R.; Cordes, A. W. *Org. Lett.* **2001**, *3*, 2607–2610.
16. The product is assumed to be mainly the *E*-isomer but confirmation of this was difficult due to the overlapping nature of the alkene protons in the ^{1}H NMR spectrum, so that no coupling constants could be determined.
17. Mosmann, T. *J. Immunol. Methods* **1983**, *65*, 55–63.
18. Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*; Pergamon: London, 1988.