Formation of medium-size bridged ring systems *via* ring-closing metathesis of 2,5-disubstituted-2,3-dihydro-1*H*-pyrroles

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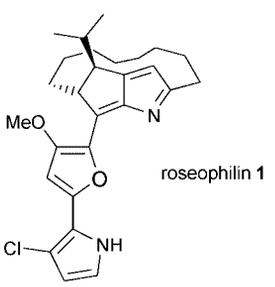
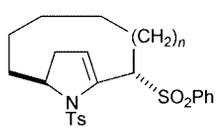
A series of 2,5-disubstituted-2,3-dihydro-1*H*-pyrroles were prepared *via* diastereoselective alkylations of sulfone **10**. Ring-closing metathesis (RCM), using Grubbs' catalyst, provided bridged ring systems with newly formed 9- to 12-membered rings in moderate to good yields. The 9-membered ring was formed as a single *Z*-isomer whereas the 10- to 12-membered rings were formed as mixtures of *E*- and *Z*-isomers. It was shown that the minor diastereomer obtained from the alkylation product **11c** failed to undergo RCM, illustrating the crucial aspect of substrate conformation.

Introduction

In conjunction with our studies towards the total synthesis of roseophilin **1** we set out to investigate the formation of



roseophilin **1**

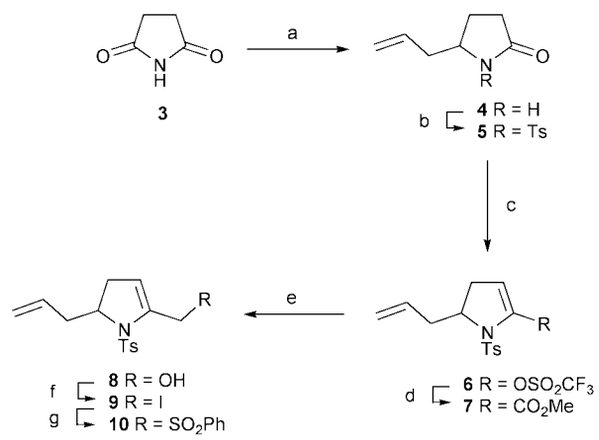


2a *n* = 1
2b *n* = 2
2c *n* = 3
2d *n* = 4

medium-size bridged rings.[1] Due to its interesting structural and biological properties roseophilin is currently a target for many synthetic groups.[2] Roseophilin possesses a core bridged tricyclic structure and our aim was to develop an efficient methodology for the construction of such systems. RCM now offers one of the most effective ways of constructing medium-size rings, but as yet we are unable to accurately predict the suitability of a substrate for RCM and relatively little is known about the construction of bridged ring systems.[3] Studies concerning the formation of bridged ring systems are thus of great value in assimilating a store of knowledge that will aid our understanding of the RCM process. Initially we have chosen to explore the formation of model bridged bicyclic rings. The substrates for the RCM reactions are diastereomerically enriched 2,5-disubstituted-2,3-dihydro-1*H*-pyrroles, possessing an allyl substituent at the 5-position and a sulfone substituted alkyl chain with a terminal double bond at the 2-position. Herein we describe the synthesis of [6.2.1], [7.2.1], [8.2.1] and [9.2.1] bridged bicycles **2a**–**d** using RCM as the key ring forming reaction.

Results and discussion

The synthesis of sulfone **10**, starting from succinimide, is illustrated in Scheme 1. In order to explore the scope of the RCM reaction in our system we required a route to the RCM precursors that allowed a series of compounds to be readily accessed.



Scheme 1 *Reagents and conditions*: a) allylmagnesium bromide, Et_2O, 0 °C, 3 h; $NaBH_3CN$, 6 M HCl, rt, 24 h, 79%; b) *n*BuLi, THF, −78 °C, 2 h; TsCl, −78 °C to rt, 16 h, 68%; c) KHMDS, THF, −78 °C, 2 h; Comins' reagent, −78 °C to 0 °C, 1 h; d) Pd_2dba_3, $AsPh_3$, CO, MeOH, Et_3N, THF, 60 °C, 19 h, 68% over 2 steps; e) DIBAL-H, THF, −78 °C to 0 °C, 1.5 h, 96%; f) PPh_3, imidazole, I_2, Et_2O, MeCN, 0 °C, 1 h, 88%; g) $PhSO_2Na$, DMF, 50 °C, 3 h, 81%.

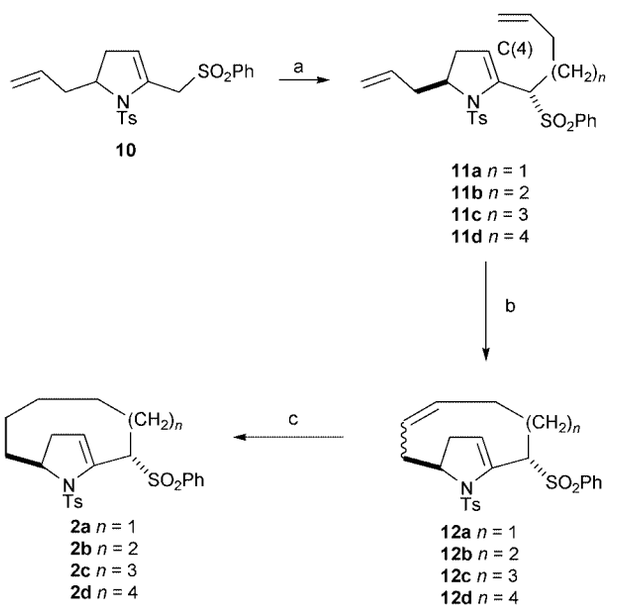
A one-pot procedure was used for introduction of the allyl group and reduction to form the allylated lactam **4**.[4] Grignard addition occurred at only one of the carbonyl groups and after acidification the intermediate iminium ion was reduced *in situ* with $NaBH_3CN$. Recently we have reported the value of enol triflate chemistry for the functionalisation of *N*-protected lactams and we wished to utilise this methodology for incorporating the second substituent onto the 5-membered ring.[5] We found that palladium-catalysed methoxycarbonylation of enol triflate **6** readily provided multigram quantities of ester **7**. When this reaction was performed at room temperature in DMF up to 60% of lactam **5** was also recovered and this caused problems due to the difficult chromatographic separation of ester **7** and lactam **5**. However, in THF at 60 °C no lactam was recovered and ester **7** was obtained in 68% yield over 2 steps. Standard procedures then gave iodide **9**, which sometimes contained up to 20% of the regioisomer obtained *via* an S_N2' process. However, during formation of the sulfone equilibration to the desired thermodynamically favoured regioisomer was observed.

Sulfone **10** was then alkylated with four alkenyl iodides ranging from 1-iodobut-3-ene to 1-iodohept-6-ene to provide

Table 1 Yields and product ratios of reactions a–c in Scheme 2[a]

n	Reaction a yield (%) (crude diastereomeric ratio)[b] (ratio submitted to reaction b)	Reaction b yield (%) (*Z*:*E* ratio)	Reaction c yield (%)
1	90 (95:5) (95:5)	48 (0:100)	100
2	99 (93:7) (100:0)	81 (21:79)	100
3	65 (87:13) (100:0)	84 (31:69)	100
4	82 (79:21) (79:21)	77 (40:60)	89

[a] All yields are isolated yields; see Scheme 2 for reactions a, b and c. [b] All ratios determined from crude 400 MHz ^{1}H NMR spectra.



Scheme 2 *Reagents and conditions*: a) *n*BuLi, THF, HMPA, −78 °C, 1 h; $I(CH_2)_nCH_2CH{=}CH_2$, −78 °C to 0 °C, 1.5 h; b) $(Cy_3P)_2Cl_2Ru{=}CHPh$, DCM, 40 °C, 16 h, 1 mM; c) PtO_2, H_2, EtOAc, rt, 16 h. Yields and product ratios given in Table 1.

the metathesis precursors **11a**–**d** (Scheme 2, Table 1). In all cases a high yield and a high level of diastereoselectivity was observed. Only partial separation of the diastereomers was possible by careful column chromatography. However, a proportion of the major isomer could often be obtained diastereomerically pure. The major and minor diastereomer obtained from the alkylation reactions can be differentiated by their characteristic chemical shift of the C(4)-hydrogen (Scheme 2) in the ^{1}H NMR spectra and from these results we can confidently predict that the major diastereomer of products **11a**–**d** all possess the same relative configuration at the two stereogenic centres. The stereochemistry of the major product was eventually determined after RCM and hydrogenation by using X-ray crystallography (*vide infra*).

A 'chiral relay effect', whereby the non-stereogenic *N*-tosyl group acts to relay and amplify the chirality of the allyl ring substituent, can be invoked to explain the diastereoselectivity of the alkylation reaction (Fig. 1).[6] The tosyl group is forced, due to steric factors, into a pseudo-*trans* orientation relative to the allyl substituent of the ring. (More precisely, the endocyclic double bond, the nitrogen, and the sulfur of the tosyl group are approximately planar, whilst the sulfur–oxygen bonds of the tosyl group point upwards and the aryl group points downward.) The sulfone group adopts an orientation so as to avoid steric interactions with the tosyl group, and the electrophile then approaches the planar delocalised anion from the opposite face of the ring to that in which the tosyl group lies.

The four RCM precursors **11a**–**d** were then treated with Grubbs' catalyst, the ratio of diastereomers present in the RCM substrates is indicated in Table 1. The RCM reactions were all

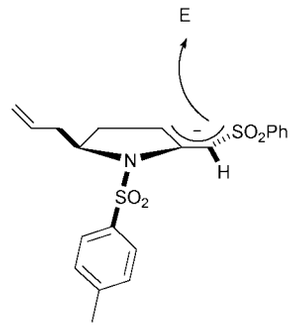


Fig. 1 Model illustrating the stereochemical outcome of the alkylation reactions of sulfone **10**.

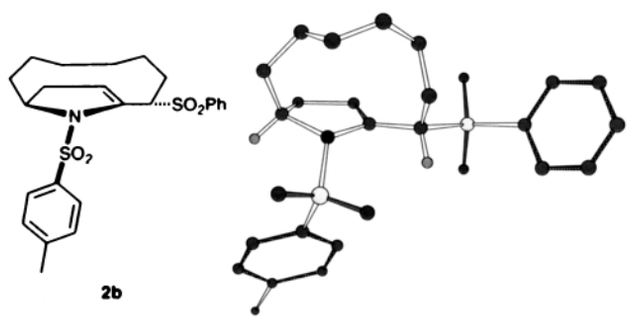


Fig. 2 X-Ray crystallographic structure of **2b**.

carried out using 20 mol% Grubbs' catalyst in dichloromethane at 40 °C for 16 h, at a concentration of 1 mM. Cyclisation to the bridged ring system was successful in each case, with newly formed ring sizes of 9- to 12-membered rings (Scheme 2, Table 1). The bridged ring containing a 9-membered ring (**12a**) was formed as a single *Z*-isomer, presumably due to the high level of ring strain that would be involved in forming the *E*-isomer. Formation of product **12a** proceeded in a significantly lower yield than the remaining RCM reactions. No other products, including starting material or dimeric species were isolated from the reaction, thus we hypothesise that polymerisation reactions occurred. The increased strain energy present in the 9-membered ring makes the RCM process less efficient and this result suggests that we are approaching the lower limit of the newly formed ring size that can be formed in such systems.

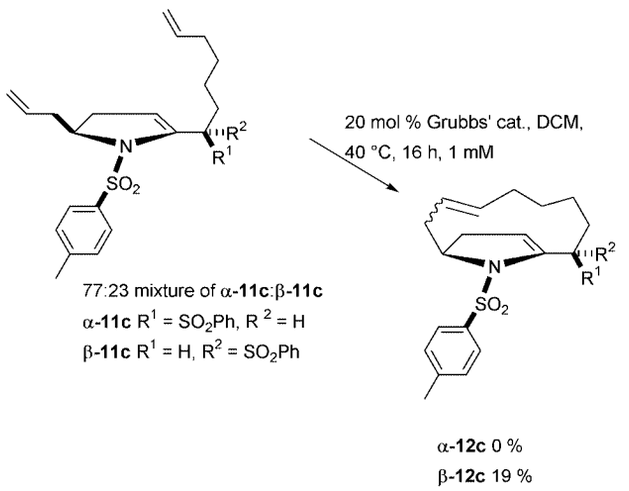
The bridged rings **12b**–**d** were all formed in high yield as mixtures of *E*- and *Z*-isomers, with increasing proportions of the *E*-isomer as the ring size increased. NOE experiments were performed to determine the ratio of *E*- and *Z*-isomers as the alkene signals in the 400 MHz ^{1}H NMR spectra were either unresolved or overlapping.

Finally, hydrogenation of the RCM products in the presence of platinum(IV) oxide resulted in the selective reduction of the disubstituted double bond to give the products **2a**–**d** as single diastereomers (Scheme 2, Table 1).

The X-ray crystallographic structure of compound **2b** is shown in Fig. 2. This shows the relative stereochemistry of the two stereogenic centres that is determined during the alkylation reaction. The observed stereochemistry is that which would be predicted if the 'chiral relay effect' was operating in the alkylation reaction.

In all of the RCM reactions performed where there was a mixture of diastereomers present in the starting material no cyclised product from the minor alkylation diastereomer was isolated. In order to confidently ascertain the fate of the minor alkylation products in the RCM reaction we set out to obtain one of these compounds as the major component. Thus, an experiment was performed whereby the alkylation product **11c** was deprotonated with *n*-butyllithium in THF and HMPA at −78 °C, and after one hour was quenched rapidly with a large excess of methanol. This gave a 69:31 mixture of diastereo-

mers, in favour of that previously obtained as the major diastereomer from the alkylation reaction. However, careful flash column chromatography allowed the attainment of a 77 : 23 mixture in favour of the previous minor diastereomer **α-11c** (Scheme 3). Upon subjection of this mixture to the stand-



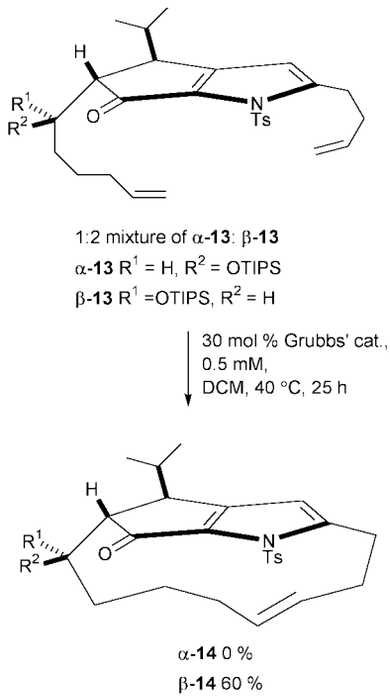
Scheme 3

ard RCM conditions **α-11c** was recovered, with no RCM products, whilst **β-11c** expectedly underwent RCM and gave **12c**. We hypothesise that, in the case of the unreactive diastereomer, the sulfone substituent serves to force the terminal double bonds out of proximity and no RCM can take place under the reaction conditions employed, whilst the major alkylation diastereomer has a low energy conformation in which the double bonds participating in the metathesis reaction are relatively close in space.

We anticipate that the lowest energy conformation of the major isomer of the alkylation products **11a**–**d** will be as shown in Scheme 3 for **β-11c**, whereby one of the groups of the stereogenic centre lies perpendicular to the plane of the ring, thus minimising allylic strain, and the smallest substituent (H) is placed in proximity to the *N*-tosyl group. In the case of the minor diastereomer obtained from the alkylation reactions a conformation suitable for RCM, one in which the terminal double bonds are placed in close proximity, would also place the sulfone and the tosyl groups into close proximity. It seems the high energy of such a reaction conformation inhibits RCM.

A related example of this phenomenon was reported by Fuchs and co-workers during their studies on the synthesis of roseophilin (Scheme 4).[2] Only one of the two diastereomers of **13** underwent RCM upon treatment with Grubbs' catalyst. They tentatively assigned the stereochemistry of the reactive diastereomer **β-13** as shown. **β-13** is able to adopt a low energy conformation in which the terminal double bonds are close in space. Conversely, in **α-13** steric interactions between the carbonyl oxygen and the OTIPS groups occur in the conformation in which the terminal double bonds are proximal. These results illustrate the same concept as that used to explain our results, that is, one of the two diastereomers of a RCM substrate possesses a low energy conformation in which the double bonds participating in the reaction are close in space, whereas the strain involved in placing the reacting centres together in the alternative diastereomer is sufficiently great to inhibit RCM.

In summary, we have synthesised a series of bicyclic bridged compounds possessing [6.2.1], [7.2.1] [8.2.1] and [9.2.1] ring structures, using RCM to form the 9- to 12-membered rings. We have also demonstrated the importance of substrate conformation in the RCM reaction.



Scheme 4

Experimental

General methods and materials

Unless otherwise noted materials were obtained from commercial suppliers and used without further purification. Tetrahydrofuran and dichloromethane were freshly distilled from sodium–benzophenone and calcium hydride, respectively. Petroleum ether (bp 60–80 °C) was distilled before use. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide pellets under an atmosphere of nitrogen.

2-[*N*,*N*-Bis(trifluoromethylsulfonyl)amino]-5-chloropyridine was Kugelrohr distilled before use and stored at 0 °C under an atmosphere of nitrogen. All reactions were stirred under an inert atmosphere of dry nitrogen unless otherwise indicated. During workup, where drying of the organic solutions is indicated, Na_2SO_4 was used with subsequent filtration in all cases. Column chromatography was performed by using Acros Chimica silica gel (0.030–0.075 mm).

Infrared spectra were recorded from $CHCl_3$ solutions using a Bruker IFS 28 spectrophotometer and the frequency absorptions are reported in units of cm^{-1}. Nuclear magnetic resonance (NMR) spectra were obtained using a Bruker ARX 400 (400 MHz) and measured in $CDCl_3$ unless otherwise indicated. Chemical shifts are reported in units of ppm on the δ scale relative to an internal standard of residual chloroform (7.27 ppm for ^{1}H NMR and 77.0 for ^{13}C NMR). *J* values are in hertz. All diastereomeric ratios were obtained from ^{1}H NMR spectra. Carbon resonances were detected by using attached proton test (ATP). Mass spectra and accurate mass determinations were determined using the electron-impact method unless otherwise indicated; with data reported as *m*/*z* (relative intensity). Measurements were performed on a JEOL JMS SX/SX102A four-sector mass spectrometer, coupled to a JEOL MS-MP7000 data system. Elemental analyses were performed by Dornis u. Kolbe Mikroanalytisches Laboratorium, Mülheim a.d. Ruhr, Germany. Melting points are uncorrected.

Crystal structure determination of 2b

A crystal with dimensions $0.25 \times 0.40 \times 0.45$ mm approximately was used for data collection, recrystallised from ethyl acetate.

Crystal data for 2b. $C_{24}H_{29}NO_4S_2$, $M_R = 459.6$, triclinic, $P\bar{1}$, $a = 8.2243(5)$, $b = 10.4546(8)$, $c = 14.535(3)$ Å, $\alpha = 80.443(7)$, $\beta = 84.476(8)$, $\gamma = 70.578(5)°$, $V = 1161.1(3)Å^3$, $Z = 2$, $D_x = 1.315$ g cm^{-3}, λ(Cu-Kα) = 1.5418 Å, μ(Cu-Kα) = 23.3 cm^{-1}, $F(000)$ = 488, room temperature, final $R = 0.069$ for 3749 observed reflections. CCDC reference number 207/387. See http://www.rsc.org/suppdata/p1/a9/a908272g for crystallographic files in .cif format.

5-Allylpyrrolidin-2-one (4)[7]

To a solution of succinimide (10.0 g, 101 mmol) in tetrahydrofuran (300 ml) at 0 °C was added dropwise allylmagnesium bromide (303 ml of a 1.0 M solution in diethyl ether, 303 mmol, 3.0 equiv.) and the mixture was stirred for 3 h. Sodium cyanoborohydride (7.60 g, 121 mmol, 1.2 equiv.) was added and then a solution of hydrochloric acid (6 M) until pH 2–3 was reached. After addition of more sodium cyanoborohydride (3.50 g, 55.7 mmol, 0.55 equiv.) the thick white solution was mechanically stirred for 24 h. The reaction mixture was neutralised with an aqueous solution of potassium hydroxide (2 M) and the aqueous layer was extracted with dichloromethane (6 × 200 ml). The combined organic layers were dried and the solvent was removed *in vacuo*. Column chromatography (ethyl acetate→1 : 1 ethyl acetate–acetone) afforded lactam **4** (10.0 g, 79%) as a colourless oil: ^{1}H NMR (400 MHz) δ 6.10–5.94 (1H, br s, N*H*), 5.80–5.69 (1H, m, CH_2CH=CH_2), 5.15–5.11 (2H, m, CH_2CH=CH_2), 3.75–3.68 (1H, m, 5-H), 2.36–2.16 (4H, m, 3-H_2, CH_2CH=CH_2), 1.80–1.68 (2H, m, 4-H_2).

5-Allyl-1-(4-tolylsulfonyl)pyrrolidin-2-one (5)

To a solution of lactam **4** (5.00 g, 40.0 mmol) in tetrahydrofuran (250 ml) at −78 °C was added dropwise *n*BuLi (31.0 ml of a 1.6 M solution in hexanes, 49.6 mmol, 1.2 equiv.) and the solution was stirred for 2 h. A solution of toluene-*p*-sulfonyl chloride (9.66 g, 50.6 mmol, 1.3 equiv.) in the minimum amount of tetrahydrofuran was added dropwise and the reaction mixture was warmed to room temperature overnight. A saturated solution of ammonium chloride (40 ml) was added and the aqueous layer was extracted with diethyl ether (4 × 200 ml). The combined organic layers were dried and the solvent was removed *in vacuo*. Column chromatography (2 : 3 ethyl actetate–petroleum ether) afforded *N*-tosyllactam **5** (7.58 g, 68%) as a white solid: mp 102–103 °C (from ethyl acetate); ν_{max}/cm^{-1} 2961, 1732, 1597, 1358, 1168; ^{1}H NMR (400 MHz) δ 7.92 (2H, d, *J* 8.2, Ar-H), 7.29 (2H, d, *J* 8.2, Ar-H), 5.71–5.60 (1H, m, CH_2CH=CH_2), 5.11–5.07 (2H, m, CH_2CH=CH_2), 4.45–4.41 (1H, m, 5-H), 2.67–2.62 (1H, m, CH_2CH=CH_2), 2.52–2.43 (2H, m, 3-H, CH_2CH=CH_2), 2.39 (3H, s, CH_3), 2.30–2.23 (1H, m, 3-H), 2.16–2.06 (1H, m, 4-H), 1.90–1.87 (1H, m, 4-H); ^{13}C NMR (100 MHz) δ 173.5 (2), 144.9, 135.7, 129.4, 128.2 (Ar-C), 132.2 (CH_2CH=CH_2), 119.4 (CH_2CH=CH_2), 59.3 (5), 38.9, 30.6, 22.8 (3, 4, CH_2CH=CH_2), 21.5 (CH_3); *m*/*z* 280 (M$^+$, 40%), 240 (100), 174 (100), 91 (100) (Found: C, 60.2; H, 6.2; N, 5.1. Calc. for $C_{14}H_{17}NO_3S$: C, 60.2; H, 6.1; N, 5.0%).

Trifluoromethanesulfonic acid 5-allyl-1-(4-tolylsulfonyl)-4,5-dihydro-1*H*-pyrrol-2-yl ester (6)

To a solution of potassium bis(trimethylsilyl)amide (23.0 ml of a 0.5 M solution in toluene, 11.5 mmol, 1.4 equiv.) in tetrahydrofuran (45 ml) at −78 °C was added lactam **5** (2.23 g, 7.99 mmol) in tetrahydrofuran (20 ml) and the pale yellow solution was stirred for 2 h. A solution of 2-[*N*,*N*-bis(trifluoromethylsulfonyl)amino]-5-chloropyridine (3.69 g, 9.39 mmol, 1.2 equiv.) in tetrahydrofuran (10 ml) was added in one portion. The solution was stirred for 75 min at −78 °C and then warmed to 0 °C. A saturated solution of ammonium chloride (30 ml), followed by dichloromethane (75 ml) and water (30 ml) were added, and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 60 ml). The combined organic layers were dried and most of the solvent was removed *in vacuo*. The remaining solvent was removed using an oil pump with no water bath so that the evaporating solvent cooled the crude sample maintaining the internal temperature at 0–10 °C. The triflate was dissolved in benzene (20 ml) and filtered through cotton-wool (to remove the excess of Comins' reagent) and the solvent was removed as described above. The cold triflate was used without further purification. On one occasion column chromatography (1 : 5→1 : 1 dichloromethane–petroleum ether) afforded the pure triflate **6** in 85% yield as a colourless oil: ^{1}H NMR (400 MHz, C_6D_6) δ 7.67 (2H, d, *J* 8.3, Ar-H), 6.69 (2H, d, *J* 8.3, Ar-H), 5.72 (1H, ddt, *J* 17.2, 10.2, 7.0, CH_2CH=CH_2), 5.03–4.93 (2H, m, CH_2CH=CH_2), 4.42 (1H, dd, *J* 3.1, 2.2, 3-H), 3.98 (1H, m, 5-H), 2.33 (1H, m, CH_2CH=CH_2), 2.17 (1H, m, CH_2CH=CH_2), 1.83 (3H, s, CH_3), 1.56 (1H, m, 4-H), 1.32 (1H, m, 4-H).

5-Allyl-1-(4-tolylsulfonyl)-4,5-dihydro-1*H*-pyrrole-2-carboxylic acid methyl ester (7)

Tris(dibenzylideneacetone)dipalladium(0) (48 mg, 52 μmol, 0.05 equiv.) and triphenylarsine (77 mg, 0.25 mmol, 0.23 equiv.) were added to a solution of crude triflate **6** (*ca*. 0.45 g, 1.1 mmol) in tetrahydrofuran (6 ml) and the mixture was flushed with carbon monoxide for 10 min. Triethylamine (1.8 ml, 12.9 mmol, 12 equiv.) and methanol (2.1 ml, 51.8 mmol, 47 equiv.) were added and the solution was stirred under carbon monoxide and heated at 60 °C for 19 h. After the solution was flushed with air, ethyl acetate (15 ml) and water (10 ml) were added and the organic layer was separated. The aqueous layer was extraced with ethyl acetate (2 × 15 ml), the combined organic layers were washed with brine (2 × 15 ml) and dried, and the solvent was removed *in vacuo*. Column chromatography (5 : 2 ethyl acetate–petroleum ether) afforded ester **7** (240 mg, 68% over 2 steps) as a colourless oil: ν_{max}/cm^{-1} 2952, 1738, 1641, 1598, 1357, 1166; ^{1}H NMR (400 MHz) δ 7.73 (2H, d, *J* 8.2, Ar-H), 7.30 (2H, d, *J* 8.2, Ar-H), 6.05 (1H, dd, *J* 3.3, 2.9, 3-H), 5.78–5.68 (1H, m, CH_2CH=CH_2), 5.07–5.04 (2H, m, CH_2CH=CH_2), 4.19–4.13 (1H, m, 5-H), 3.86 (3H, s, OCH_3), 2.42 (3H, s, CH_3), 2.38–2.24 (2H, m, CH_2CH=CH_2), 2.15–1.96 (2H, m, 4-H); ^{13}C NMR (100 MHz) δ 162.5 (CO_2CH_3), 144.0, 136.5, 133.9, 129.4, 127.9 (2) (Ar-C), 132.7 (CH_2CH=CH_2), 126.8 (3), 118.4 (CH_2CH=CH_2), 61.8 (5), 52.3 (OCH_3), 40.0 (CH_2CH=CH_2), 33.3 (4), 21.5 (CH_3); *m*/*z* 321 (M$^+$, 11%), 280 (33), 91 (100) (Found M$^+$: 321.1037. Calc. for $C_{16}H_{19}NO_4S$: 321.1035).

[5-Allyl-1-(4-tolylsulfonyl)-4,5-dihydro-1*H*-pyrrol-2-yl]-methanol (8)

To a solution of ester **7** (636 mg, 1.98 mmol) in tetrahydrofuran (6 ml) at −78 °C was added diisobutylaluminum hydride (4.7 ml of a 1.5 M solution in toluene, 7.05 mmol, 3.5 equiv.) and the solution was warmed to 0 °C over 90 min. The reaction was carefully quenched with a saturated solution of potassium sodium tartrate. Water (250 ml) was added and the solution was extracted with ethyl acetate (4 × 80 ml). The combined organic layers were filtered through Celite®, dried, and the solvent was removed *in vacuo* to afford allylic alcohol **8** (565 mg, 96%) in virtually pure form as a yellow oil. On one occasion column chromatography (2 : 1 ethyl acetate–petroleum ether) afforded the pure alcohol **8** as a colourless oil: ν_{max}/cm^{-1} 3532 (br), 2927, 1597, 1346, 1162; ^{1}H NMR (400 MHz, C_6D_6) δ 7.76 (2H, d, *J* 8.2, Ar-H), 6.79 (2H, d, *J* 8.2, Ar-H), 5.84–5.75 (1H, m, CH_2CH=CH_2), 5.06–5.01 (2H, m, CH_2CH=CH_2), 4.80 (1H, s, 3-H), 4.51 (1H, d, *J* 14.3, CH_2OH), 4.42 (1H, d, *J* 14.3, CH_2-OH), 4.08–4.02 (1H, m, 5-H), 2.50–2.38 (2H, m, CH_2CH=CH_2), 1.91 (3H, s, CH_3), 1.89–1.82 (1H, m, 4-H), 1.64 (1H, m, 4-H); ^{13}C NMR (100 MHz, C_6D_6) δ 144.2, 144.1, 130.4, 128.3 (Ar-C), 134.3 (CH_2CH=CH_2), 128.9 (2), 118.7 (CH_2CH=CH_2), 114.0 (3), 62.8 (5), 60.3 (CH_2OH), 41.8 (CH_2CH=CH_2), 33.1 (4), 21.8

(CH_3); *m/z* 293 (M^+, 28%), 252 (90), 222 (100), 91(100), 80 (91) (Found M^+: 293.1083. Calc. for $C_{15}H_{19}NO_3S$: 293.1086).

2-Allyl-5-iodomethyl-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (9)

To a solution of the alcohol **8** (1.40 g, 4.78 mmol) in diethyl ether–acetonitrile (3:2, 22 ml) at 0 °C was added sequentially triphenylphosphine (2.44 g, 9.31 mmol, 1.9 equiv.), imidazole (700 mg, 10.3 mmol, 2.1 equiv.) and iodine (2.92 g, 11.5 mmol, 2.1 equiv.) and the solution was stirred for 1 h. Ethyl acetate (250 ml) was added and the organic layer was sequentially washed with an aqueous solution of sodium thiosulfate (5%, 150 ml), a saturated solution of copper sulfate (2 × 150 ml) and brine (150 ml), and dried. After removal of the solvent *in vacuo* column chromatography (1:5 ethyl acetate–petroleum ether) afforded iodide **9** (1.70 g, 88%) as a yellow oil: ^{1}H NMR (400 MHz) δ 7.66 (2H, d, *J* 8.2, Ar-H), 7.29 (2H, d, *J* 8.2, Ar-H), 5.92–5.82 (1H, m, CH_2CH=CH_2), 5.49 (1H, s, 4-H), 5.13–5.09 (2H, m, CH_2CH=CH_2), 4.61–4.58 (1H, m, 2-H), 4.20–4.11 (2H, m, CH_2I), 2.42 (3H, s, CH_3), 2.47–2.19 (2H, m, CH_2CH=CH_2), 1.85–1.78 (2H, m, 3-H_2); ^{13}C NMR (100 MHz) δ 143.9, 134.7, 133.3, 129.7, 127.4 (Ar-C, CH_2CH=CH_2), 141.0 (5), 118.3 (CH_2CH=CH_2), 117.8 (4), 62.2 (2), 40.1, 32.6 (3, CH_2CH=CH_2), 21.5 (CH_3), −1.9 (CH_2I).

2-Allyl-5-phenylsulfonylmethyl-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (10)

To a solution of iodide **9** (200 mg, 496 μmol) in *N*,*N*-dimethylformamide (4 ml) at 50 °C was added benzenesulfonic acid sodium salt (163 mg, 993 μmol, 2.0 equiv.) and the solution was stirred for 3 h. Ethyl acetate was added and the organic layer was sequentially washed with water (3 × 20 ml), a saturated solution of sodium bicarbonate (20 ml), brine (20 ml) and dried. After removal of the solvent *in vacuo* column chromatography (2:5 ethyl actetate–petroleum ether) afforded sulfone **10** (168 mg, 81%) as a white solid: mp 124.5 °C (from ethyl acetate); ν_{max}/cm^{-1} 3019, 2976, 1599, 1350, 1322, 1166, 1046; ^{1}H NMR (400 MHz) δ 7.96 (2H, d, *J* 7.6, Ar-H), 7.65 (1H, t, *J* 7.5, Ar-H), 7.56 (4H, m, Ar-H), 7.26 (2H, d, *J* 7.6, Ar-H), 5.66–5.56 (2H, m, 4-H, CH_2CH=CH_2), 5.05–4.98 (2H, m, CH_2CH=CH_2), 4.98 (1H, d, *J* 15.2, CH_2SO_2Ph), 4.08 (1H, d, *J* 15.2, CH_2SO_2Ph), 3.95–3.88 (1H, m, 2-H), 2.40 (3H, s, CH_3), 2.22–2.15, 2.03–1.88 (4H, m, 3-H, CH_2CH=CH_2); ^{13}C NMR (100 MHz) δ 144.1, 139.0, 133.9, 133.8, 130.7 129.7, 129.0, 128.5, 127.4 (Ar-C, 5), 133.4 (CH_2CH=CH_2), 122.2 (4), 118.1 (CH_2CH=CH_2), 62.0 (2), 55.3 (CH_2SO_2Ph), 39.8, 32.9 (3, CH_2CH=CH_2), 21.5 (CH_3); *m/z* 417 (M^+, 11%), 376 (43), 262 (31), 234 (100), 162 (41), 91 (66) (Found: C, 60.4; H, 5.3; N, 3.25; S, 15.5. Calc. for $C_{21}H_{23}NO_4S_2$: C, 60.4; H, 5.55; N, 3.35; S, 15.4%).

General procedure A: preparation of RCM precursors 11a–d *via* alkylation of sulfone 10

To a solution of sulfone **10** (100 mg, 240 μmol) in tetrahydrofuran (3 ml) at −78 °C was added *n*BuLi (0.18 ml of a 1.6 M solution in hexanes, 288 μmol, 1.2 equiv.) and hexamethylphosphorous triamide (74 μl, 600 μmol, 2.5 equiv.) and the solution was stirred for 1 h. Iodoalkene (480 μmol, 2.0 equiv.) was added and after 90 min the solution was warmed to *ca*. 0 °C. Water (15 ml) and ethyl acetate (30 ml) were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 15 ml), the combined organic layers were washed with water (4 × 15 ml) and brine (15 ml) and dried. After removal of the solvent *in vacuo* column chromatography (1:5 ethyl acetate–petroleum ether) afforded metathesis precursors **11a**–**d**.

2-Allyl-5-(1-phenylsulfonylpent-4-enyl)-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (11a). According to general procedure A, the alkylation of sulfone **10** (100 mg, 240 μmmol) with 4-iodobut-1-ene (52 μl, >290 μmol, >1.2 equiv.) afforded **11a** (102 mg, 90%) as a white solid and as a 95:5 mixture of diastereomers: ν_{max}/cm^{-1} 3072, 2952, 1641, 1597, 1350, 1308, 1168, 1151; ^{1}H NMR (400 MHz, C_6D_6) major diastereomer (2*S**, 1′*S**) δ 8.01 (2H, d, *J* 7.5, Ar-H), 7.74 (2H, d, *J* 8.3, Ar-H), 7.70 (1H, t, *J* 7.5, Ar-H), 7.60 (2H, t, *J* 7.5, Ar-H), 7.23 (2H, d, *J* 8.3, Ar-H), 5.92 (1H, m, 4-H), 5.79–5.71 (1H, m, 4′-H or CH_2CH=CH_2), 5.70–5.61 (1H, m, 4′-H or CH_2CH=CH_2), 5.10–5.08 (2H, m, 5′-H or CH_2CH=CH_2), 5.06–5.04 (1H, m, 1′-H), 5.00–4.95 (2H, m, 5′-H or CH_2CH=CH_2), 3.89–3.87 (1H, m, 2-H), 2.49–2.40 (1H, m, CH_2CH=CH_2), 2.40 (3H, s, CH_3), 2.36–1.91 (7H, m CH_2); characteristic peak of minor diastereomer (2*S**, 1′*R**) δ 5.46 (1H, m, 4-H); ^{13}C NMR (100 MHz, C_6D_6) δ 143.8, 138.6, 136.3, 136.3, 134.5, 129.5, 129.2, 128.7, 127.9 (Ar-C, 5), 133.7, 133.2 (4′, CH_2CH=CH_2), 118.2 (5′ or CH_2CH=CH_2), 117.4 (4), 115.9 (5′ or CH_2CH= CH_2), 62.0, 61.1 (2, 1′), 39.6 (CH_2CH=CH_2), 32.7, 31.7, 29.9 (3, 2′, 3′), 21.5 (CH_3); *m/z* (FAB+) 472 (MH^+, 100%), 430 (35), 330 (67), 288 (70), 154 (92), 136 (80), 91 (75) (Found: C, 63.7; H, 6.2; N, 2.9; S, 13.7. Calc. for $C_{25}H_{29}NO_4S_2$: C, 63.7; H, 6.2; N, 3.0; S, 13.6%).

2-Allyl-5-(1-phenylsulfonylhex-5-enyl)-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (11b). According to general procedure A, the alkylation of sulfone **10** (102 mg, 245 μmol) with 5-iodopent-1-ene (72 μl, >370 μmol, >1.5 equiv.) afforded **11b** (118 mg, 99%) as a colourless oil and as a 93:7 mixture of diastereomers: ν_{max}/cm^{-1} 3072, 2934, 1640, 1597, 1349, 1308, 1162, 1151; ^{1}H NMR (400 MHz, C_6D_6) major diastereomer (2*S**, 1′*S**) δ 8.00 (2H, d, *J* 7.5, Ar-H), 7.74 (2H, d, *J* 8.2, Ar-H), 7.69 (1H, t, *J* 7.5, Ar-H), 7.59 (2H, t, *J* 7.5, Ar-H), 7.23 (2H, d, *J* 8.2, Ar-H), 5.89 (1H, m, 4-H), 5.80–5.68 (1H, m, 5′-H or CH_2CH=CH_2), 5.68–5.58 (1H, m, 5′-H or CH_2CH=CH_2), 5.09–5.05 (2H, m, 6′-H or CH_2CH=CH_2), 5.05–5.03 (1H, m, 1′-H), 4.92–4.84 (2H, m, 6′-H or CH_2CH=CH_2), 3.90–3.84 (1H, m, 2-H), 2.48–2.40 (1H, m, CH_2CH=CH_2), 2.39 (3H, s, CH_3), 2.25–2.17 (1H, m, CH_2CH=CH_2), 2.06–1.79 (6H, m, CH_2), 1.69–1.58 (1H, m, 3′-H), 1.49–1.43 (1H, m, 3′-H); characteristic peaks of minor diastereomer (2*S**, 1′*R**) δ 5.47 (1H, m, 4-H), 4.01–3.95 (1H, m, 2-H); ^{13}C NMR (100 MHz, C_6D_6) δ 143.8, 138.7, 137.3, 136.3, 134.5, 133.6, 133.3, 129.5, 129.1, 128.8, 127.9 (Ar-C, 5′, 5, CH_2CH=CH_2), 118.1 (6′ or CH_2CH=CH_2), 117.3 (4), 115.2 (6′ or CH_2CH=CH_2), 62.5, 61.1 (2, 1′), 39.6 (CH_2CH=CH_2), 32.9, 32.7, 31.5 (3, 2′, 4′), 25.0 (3′), 21.5 (CH_3); *m/z* (FAB) 486 (MH^+, 100%), 444, (63), 302 (55), 188 (53), 148 (60), 91 (70) (Found MH^+: 486.1768. Calc. for $C_{26}H_{32}NO_4S_2$: 486.1773).

2-Allyl-5-(1-phenylsulfonylhept-6-enyl)-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (11c). According to general procedure A, the alkylation of sulfone **10** (108 mg, 259 μmol) with 6-iodohex-1-ene (0.12 ml, >570 μmol, >2.2 equiv.) afforded **11c** (84 mg, 65%) as a colourless oil and as a 87:13 mixture of diastereomers: ν_{max}/cm^{-1} 3072, 2930, 1641, 1598, 1349, 1308, 1168, 1152; ^{1}H NMR (400 MHz, C_6D_6) major diastereomer (2*S**, 1′*S**) δ 8.02 (2H, d, *J* = 7.5, Ar-H), 7.77 (2H, d, *J* = 8.2, Ar-H), 7.70 (1H, t, *J* = 7.5, Ar-H), 7.61 (2H, t, *J* = 7.5, Ar-H), 7.26 (2H, d, *J* = 8.2, Ar-H), 5.89 (1H, m, 4-H), 5.76–5.68 (2H, m, 6′-H, CH_2CH=CH_2), 5.10–5.07 (2H, m, 7′-H or CH_2CH=CH_2), 5.06–5.03 (1H, m, 1′-H), 4.95–4.89 (2H, m, 7′-H or CH_2CH=CH_2), 3.88–3.86 (1H, m, 2-H), 2.48–2.41 (1H, m, CH_2CH=CH_2), 2.40 (3H, s, CH_3), 2.25–2.20 (1H, m, CH_2-CH=CH_2), 2.04–1.82 (5H, m, CH_2), 1.58–1.53 (1H, m, CH_2), 1.42–1.25 (4H, m, CH_2); characteristic peaks of minor diastereomer (2*S**, 1′*R**) δ 5.61 (1H, m, 4-H), 4.34–4.29 (1H, m, 2-H); ^{13}C NMR (100 MHz, C_6D_6) δ 143.7, 138.8, 136.3, 134.6, 133.6, 129.5, 129.1, 128.7, 127.9 (Ar-C, 5), 138.3, 133.3 (6′, CH_2-CH=CH_2), 118.1 (7′ or CH_2CH=CH_2), 117.2 (4), 114.6 (7′ or CH_2CH=CH_2), 62.5 (1′), 61.1 (2), 39.6 (CH_2CH=CH_2), 33.1, 32.6, 31.2, 28.2, 25.3 (3, 2′, 3′, 4′, 5′), 21.5 (CH_3); *m/z* (FAB) 500, (MH^+, 70%), 458 (43), 358 (45), 316 (55), 202 (92), 162

(92), 91 (100) (Found MH^+: 500.1911. Calc. for $C_{27}H_{34}NO_4S_2$: 500.1929).

2-Allyl-5-(1-phenylsulfonyloct-7-enyl)-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (11d). According to general procedure A, the alkylation of sulfone **10** (120 mg, 288 μmol) with 7-iodohept-1-ene (0.13 ml, >570 μmol, >2.0 equiv.) afforded **11d** (121 mg, 82%) as a colourless oil and as a 79 : 21 mixture of diastereomers: ν_{max}/cm^{-1} 3071, 2926, 1641, 1598, 1350, 1308, 1168, 1152; ^{1}H NMR (400 MHz, C_6D_6) major diastereomer (2*S**, 1′*S**) δ 8.02 (2H, d, *J* 7.4, Ar-H), 7.76 (2H, d, *J* 8.2, Ar-H), 7.70 (1H, t, *J* 7.4, Ar-H), 7.61 (2H, t, *J* 7.4, Ar-H), 7.30 (2H, d, *J* 8.2, Ar-H), 5.89 (1H, m, 4-H), 5.81–5.70 (2H, m, 7′-H, CH_2CH=CH_2), 5.10–5.07 (2H, m, 8′-H or CH_2CH=CH_2), 5.06–5.03 (1H, m, 1′-H), 4.98–4.90 (2H, m, 8′-H or CH_2CH=CH_2), 3.91–3.85 (1H, m, 2-H), 2.49–2.40 (1H, m, CH_2CH=CH_2), 2.40 (3H, s, CH_3), 2.25–2.18 (1H, m, CH_2CH=CH_2), 2.06–1.77, 1.56–1.27 (12H, m, CH_2); characteristic peaks of minor diastereomer (2*S**, 1′*R**) δ 5.46 (1H, m, 4-H), 3.97–3.94 (1H, m, 2-H); ^{13}C NMR (100 MHz, C_6D_6) δ 143.8, 138.9, 138.8, 136.5, 134.7, 133.7, 133.4, 129.6, 129.2, 128.8, 128.0 (Ar-C, 5, 7′), 118.2 (8′ or CH_2CH=*C*H_2), 117.3 (4), 114.4 (8′ or CH_2CH=*C*H_2), 62.6, 61.2 (2, 1′), 39.7 (*C*H_2CH=CH_2), 33.5, 32.8, 32.6, 28.6, 28.4, 25.8 (*C*H_2), 21.6 (*C*H_3); *m*/*z* 513 (M^+, 10%), 472 (32), 330 (43), 234 (37), 162 (60), 91 (100) (Found M^+: 513.2017. Calc. for $C_{28}H_{35}NO_4S_2$: 513.2008).

General procedure B: preparation of macrocycles 12a–d *via* ring-closing metathesis

A solution of triene **11a** (71 mg, 0.15 mmol) in dichloromethane (150 ml, 1 mM concentration) was thoroughly degassed with a vigorous stream of nitrogen and Grubbs' catalyst $(Cy_3P)_2Cl_2Ru$=CHPh (25 mg, 0.20 equiv.) was added. The solution was heated at 40 °C for 16 h. After cooling to room temperature a stream of air was bubbled through the solution and the solvent was removed *in vacuo*. Column chromatography (1 : 6 ethyl acetate–petroleum ether) afforded macrocycle **12a**.

(2*S,8*S**,*Z*)-2-Phenylsulfonyl-11-(4-tolylsulfonyl)-11-aza-bicyclo[6.2.1]undeca-1(10),5-diene (12a).** According to General procedure B, a metathesis reaction on triene **11a** (71 mg, 0.15 mmol) afforded bicycle **12a** (32 mg, 48%) as a white solid and as a single *Z*-isomer: mp 183–184 °C (from ethyl acetate); ν_{max}/cm^{-1} 2924, 2853, 1597, 1347, 1307, 1165, 1149; ^{1}H NMR (400 MHz, C_6D_6) δ 8.01 (2H, d, *J* 7.5, Ar-H), 7.71 (1H, t, *J* 7.5, Ar-H), 7.62 (2H, t, *J* 7.5, Ar-H), 7.49 (2H, d, *J* 8.2, Ar-H), 7.19 (2H, d, *J* 8.2, Ar-H), 5.92 (1H, m, 10-H), 5.57–5.55 (1H, m, 5-H or 6-H), 5.48–5.44 (1H, m, 5-H or 6-H), 5.15–5.11 (1H, m, 2-H), 3.99–3.97 (1H, m, 8-H), 2.90–2.87 (1H, m, 4-H), 2.66–2.61 (1H, m, 7-H), 2.40 (3H, s, CH_3), 2.14–1.91 (4H, m, CH_2), 1.79–1.74 (1H, m, 9-H), 1.67–1.60 (1H, m, 9-H); ^{13}C NMR (100 MHz, C_6D_6) δ 143.7, 138.5, 134.5, 133.7, 133.7, 129.4, 129.1, 129.1, 127.8 (Ar-C, 1), 137.1 (5 or 6), 123.7, 122.9 (5 or 6, 10), 62.0, 61.0 (2, 8), 32.7, 30.8, 28.9, 23.6 (3, 4, 7, 9), 21.5 (*C*H_3); *m*/*z* 443 (M^+, 67%), 378 (15), 303 (100), 248 (60), 234 (53), 210 (30), 146 (100), 91 (100) (Found M^+: 443.1217. Calc. for $C_{23}H_{25}NO_4S_2$: 443.1225).

(2*S,9*S**,*E*)- and (2*S**,9*S**,*Z*)-2-Phenylsulfonyl-12-(4-tolylsulfonyl)-12-azabicyclo[7.2.1]dodeca-1(11),6-diene (12b).** According to general procedure B, a metathesis reaction on triene **11b** (150 mg, 309 μmol) afforded bicycle **12b** (114 mg, 81%) as a colourless oil and as a 21 : 79 mixture of *E*/*Z*-isomers: ν_{max}/cm^{-1} 2927, 2854, 1597, 1343, 1308, 1163, 1152; ^{1}H NMR (400 MHz, C_6D_6) *Z*-isomer δ 8.02 (2H, d, *J* 7.6, Ar-H), 7.93 (2H, d, *J* 8.2, Ar-H), 7.67 (1H, t, *J* 7.6, Ar-H), 7.59 (2H, t, *J* 7.6, Ar-H), 7.27 (2H, d, *J* 8.2, Ar-H), 5.85 (1H, br s, 11-H), 5.41 (2H, m, 6-H, 7-H), 4.79 (1H, d, *J* 10.3, 2-H), 4.14–4.09 (1H, m, 9-H), 3.09–3.04 (1H, m, 5-H), 2.80–2.75 (1H, m, 8-H), 2.41 (3H, s, CH_3), 2.13–1.51 (8H, m, CH_2); *E*-isomer δ 7.99 (2H, d, *J* 7.5, Ar-H), 7.78–7.76 (2H, m, Ar-H), 7.69 (1H, t, *J* 7.5, Ar-H), 7.59 (2H, t, *J* 7.5, Ar-H), 7.22 (2H, d, *J* 8.1, Ar-H), 5.88–5.86 (1H, m, 11-H), 5.82–5.74 (1H, m, 6-H or 7-H), 5.34–5.30 (1H, m, 6-H or 7-H), 4.91–4.89 (1H, m, 2-H), 4.03–4.01 (1H, m, 9-H), 2.40 (3H, s, CH_3), 2.41–2.33, 2.24–2.17, 2.04–1.99, 1.92–1.87, 1.79–1.73 (10H, 5 × m, CH_2); ^{13}C NMR (100 MHz, C_6D_6) both isomers δ 143.6, 138.5, 135.5, 134.8, 133.6, 129.5, 129.1, 128.7, 128.1 (Ar-C, 1), 137.5 (6 or 7), 123.0, 120.3 (6 or 7, 11), 64.1, 61.6 (2, 9), 35.6, 32.1, 31.3, 26.9, 25.8 (*C*H_2), 21.5 (*C*H_3); *m*/*z* 457 (M^+, 20%), 316 (90), 149 (75), 91 (100) (Found M^+: 457.1390. Calc. for $C_{24}H_{27}NO_4S_2$ 457.1382).

(2*S,10*S**,*E*)- and (2*S**,10*S**,*Z*)-2-Phenylsulfonyl-13-(toluene-4-sulfonyl)-13-azabicyclo[8.2.1]trideca-1(12),7-diene (12c).** According to general procedure B, a metathesis reaction on triene **11c** (9.5 mg, 19 μmol) afforded bicycle **12c** (7.5 mg, 84%) as a colourless oil and as a 31 : 69 mixture of *E*/*Z*-isomers [the *Z*-isomer could be crystallised from the mixture: mp 217–221 °C (partial decomposition), (from ethyl acetate)]: ν_{max}/cm^{-1} 2930, 2854, 1597, 1346, 1307, 1166, 1117; ^{1}H NMR (400 MHz, C_6D_6) *Z*-isomer δ 8.03 (2H, d, *J* 7.6, Ar-H), 7.75 (1H, t, *J* 7.6, Ar-H), 7.65 (2H, t, *J* 7.6, Ar-H), 7.22 (2H, d, *J* 8.2, Ar-H), 7.08 (2H, d, *J* 8.2, Ar-H), 6.11 (1H, br s, 12-H), 5.57–5.45 (2H, m, 7-H, 8-H), 4.75 (1H, d, *J* 9.0, 2-H), 4.05–4.00 (1H, m, 10-H), 2.37 (3H, s, CH_3) 2.53–1.37 (12H, m, CH_2); characteristic peaks of *E*-isomer δ 6.06 (1H, br s, 12-H) 3.96–3.94 (1H, m, 10-H); ^{13}C NMR (100 MHz, C_6D_6) both isomers δ 143.7, 143.6, 139.2, 138.8, 138.2, 134.2, 134.0 (Ar-C, 1), 133.6, 133.2, 132.3 (Ar-C, 7 or 8), 129.5, 129.4, 129.0, 128.8, 127.5, 127.4 (Ar-C), 126.8, 124.1, 120.0, 118.9 (7 or 8, 12), 63.5, 63.3, 62.2, 61.1 (2, 10), 39.5, 33.3, 32.4, 29.7, 29.2, 28.2, 26.4, 24.8, 23.7, 23.2, 21.5, 21.1 (*C*H_2), 21.5 (*C*H_3); *m*/*z* 471 (M^+, 12%), 330 (90), 262 (38), 162 (92), 91 (100) (Found M^+: 471.1551. Calc. for $C_{25}H_{29}NO_4S_2$: 471.1538).

(2*S,11*S**,*E*)- and (2*S**,11*S**,*Z*)-2-Phenylsulfonyl-14-(4-tolylsulfonyl)-14-azabicyclo[9.2.1]tetradeca-1(13),8-diene (12d).** According to general procedure B, a metathesis reaction on triene **11d** (86 mg, 168 μmol) afforded bicycle **12d** (62 mg, 77%) as a colourless oil and as a 40 : 60 mixture of *E*/*Z*-isomers: ν_{max}/cm^{-1} 2924, 2855, 1598, 1343, 1307, 1152; ^{1}H NMR (400 MHz, C_6D_6) *Z*-isomer δ 8.12 (2H, d, *J* 8.2, Ar-H), 8.03 (2H, d, *J* 7.3, Ar-H), 7.67 (1H, t, *J* 7.3, Ar-H), 7.58 (2H, t, *J* 7.3, Ar-H), 7.30 (2H, d, *J* 8.2, Ar-H), 5.91 (1H, s, 13-H), 5.63–5.58 (1H, m, 8-H or 9-H), 5.46–5.40 (1H, m, 8-H or 9-H), 4.99–4.95 (1H, m, 2-H), 4.14–4.09 (1H, m, 11-H), 2.69–2.66 (1H, m, 10-H), 2.42 (3H, s, CH_3), 2.26–1.52 (13H, m, CH_2); characteristic peaks of *E*-isomer δ 5.19–5.24 (1H, m, 2-H), 4.01–3.96 (1H, m, 11-H); ^{13}C NMR (100 MHz, C_6D_6) both isomers δ 143.7, 138.7, 135.3, 135.1, 133.5, 129.4, 129.0, 128.6, 128.6 (Ar-C, 1), 135.6, 122.3 (8, 9), 114.9 (13), 62.1, 61.4 (2, 11), 34.4, 33.1, 32.9, 32.4, 27.4, 24.6, 23.8 (*C*H_2), 21.5 (*C*H_3); *m*/*z* (FAB) 486 (MH^+, 15%), 344 (15), 154 (35), 136 (37), 55 (100) (Found MH^+: 486.1782. Calc. for $C_{26}H_{32}NO_4S_2$ 486.1773).

General procedure C: preparation of reduced macrocycles 2a–d *via* hydrogenation reactions

To a solution of bicycle **12b** (17 mg, 37 μmol) in ethyl acetate (3 ml) was added platinum(IV) oxide (6 mg, 21 μmol, 0.57 equiv.) and the mixture was stirred under an atmosphere of hydrogen for 16 h. Filtration through Celite and silica and removal of solvent *in vacuo* afforded hydrogenated bicycle **2b**.

(2*S,8*S**)-2-Phenylsulfonyl-11-(4-tolylsulfonyl)-11-aza-bicyclo[6.2.1]undeca-1(10)-ene (2a).** According to general procedure C, hydrogenation of bicycle **12a** (19 mg, 43 μmol) afforded hydrogenated bicycle **2a** (19 mg, 100%) as a white solid: mp 186 °C (from ethyl acetate); ν_{max}/cm^{-1} 2935 (br), 1597,

1344, 1308, 1166, 1149; ^{1}H NMR (400 MHz, C_6D_6) δ 8.03 (2H, d, *J* 7.4, Ar-H), 7.73 (1H, t, *J* 7.4, Ar-H), 7.63 (2H, t, *J* 7.4, Ar-H), 7.33 (2H, d, *J* 8.1, Ar-H), 7.14 (2H, d, *J* 8.1, Ar-H), 6.14 (1H, m, 10-H), 4.83 (1H, m, 2-H), 4.00 (1H, m, 8-H), 2.39 (3H, s, CH_3), 2.39–2.34 (1H, m, 3-H), 2.03–2.02 (1H, m, CH_2), 1.84–1.54 (9H, m, CH_2), 1.36–1.33 (1H, m, CH_2); ^{13}C NMR (100 MHz, C_6D_6) δ 143.7, 138.8, 138.4, 133.7, 133.7, 129.4, 129.2, 129.1, 127.7 (Ar-C, 1), 122.7 (10), 64.3 (2), 61.0 (8), 35.9, 32.7, 30.3, 30.0, 22.9 (CH_2), 21.6 (CH_3), 20.0 (6); *m*/*z* (FAB) 446 (MH^+, 22%), 334 (25), 297 (100), 290 (38), 149 (78), 91 (90) (Found MH^+: 446.1463. Calc. for $C_{23}H_{28}NO_4S_2$: 446.1460).

(2*S,9*S**)-2-Phenylsulfonyl-12-(4-tolylsulfonyl)-12-aza-bicyclo[7.2.1]dodeca-1(11)-ene (2b).** According to general procedure C, hydrogenation of bicycle **12b** (17 mg, 37 μmol) afforded hydrogenated bicycle **2b** (18 mg, 100%) as a white solid: mp 191–195 °C (from ethyl acetate); ν_{max}/cm^{-1} 2935, 2851, 1597, 1346, 1308, 1165, 1150; ^{1}H NMR (400 MHz, C_6D_6) δ 8.00 (2H, d, *J* 7.5, Ar-H), 7.74 (1H, d, *J* 7.5, Ar-H), 7.63 (2H, d, *J* 7.5, Ar-H), 7.44 (2H, d, *J* 8.2, Ar-H), 7.16 (2H, d, *J* 8.2, Ar-H), 6.13 (1H, m, 11-H), 5.06 (1H, m, 2-H), 4.06 (1H, m, 9-H), 2.40 (3H, s, CH_3), 2.12–1.42 (14H, m, CH_2); ^{13}C NMR (100 MHz, C_6D_6) δ 143.6, 138.9, 134.7, 133.6, 133.3, 129.4, 129.2, 128.7, 127.4 (Ar-C, 1), 121.5 (11), 64.1, 61.3 (2, 9), 34.7, 33.7, 29.6, 26.6, 23.6, 18.5, 18.0 (CH_2), 21.4 (CH_3); *m*/*z* 459 (M^+, 10%), 318 (100), 304 (100), 254 (35), 163 (100), 162 (95), 91 (82) (Found M^+: 459.1510. Calc. for $C_{24}H_{29}NO_4S_2$: 459.1538).

(2*S,10*S**)-2-Phenylsulfonyl-13-(4-tolylsulfonyl)-13-aza-bicyclo[8.2.1]trideca-1(12)-ene (2c).** According to general procedure C, hydrogenation of bicycle **12c** (19 mg, 39 μmol) afforded hydrogenated bicycle **2c** (19 mg, 100%) as a white solid: mp 209 °C (from ethyl acetate); ν_{max}/cm^{-1} 1598; ^{1}H NMR (400 MHz, C_6D_6) δ 8.19 (2H, d, *J* 8.2, Ar-H), 8.08 (2H, d, *J* 6.6, Ar-H), 6.93–6.85 (5H, m, Ar-H), 6.11 (1H, d, *J* 1.8, 12-H), 5.28 (1H, d, *J* 8.5, 2-H), 3.86–3.80 (1H, m, 10-H), 2.30–2.24 (1H, m, CH_2), 2.11–2.04 (1H, m, CH_2), 1.88 (3H, s, CH_3), 1.88–1.80 (2H, m, CH_2), 1.78–1.65 (1H, m, CH_2), 1.56–1.40 (3H, m, CH_2), 1.30–1.03 (8H, m, CH_2); ^{13}C NMR (100 MHz, C_6D_6) δ 144.2, 140.5, 139.4, 136.5, 133.9, 130.4, 129.9, 129.6, 129.5 (Ar-C, 1), 121.0 (12), 64.9, 63.0 (2, 10), 35.4, 32.5, 30.8, 26.9, 26.8, 25.3, 23.4, 21.4 (CH_2), 21.8 (CH_3); *m*/*z* (FAB) (MH^+, 5%), 305 (40), 261 (50), 149 (38), 81 (73), 69 (100) (Found MH^+: 474.1744. Calc. for $C_{25}H_{32}NO_4S_2$: 474.1773).

(2*S,11*S**)-2-Phenylsulfonyl-14-(4-tolylsulfonyl)-14-aza-bicyclo[9.2.1]trideca-1(13)-ene (2d).** According to general procedure C, hydrogenation of bicycle **12d** (36 mg, 74 μmol) afforded hydrogenated bicycle **2d** (32 mg, 89%) as a white solid: mp 211–216 °C (partial decomposition) (from ethyl acetate); ν_{max}/cm^{-1} 2927, 2853, 1597, 1348, 1307, 1151; ^{1}H NMR (400 MHz, C_6D_6) δ 8.02 (2H, d, *J* 7.5, Ar-H), 7.73 (1H, t, *J* 7.5, Ar-H), 7.62 (2H, t, *J* 7.5, Ar-H), 7.52 (2H, d, *J* 8.2, Ar-H), 7.13 (2H, d, *J* 8.2, Ar-H), 6.08 (1H, br s, 13-H), 5.03 (1H, m, 2-H), 3.95 (1H, m, 11-H), 2.38 (3H, s, CH_3), 2.19–2.10 (1H, m, CH_2), 2.07–1.08 (17H, m, CH_2); ^{13}C NMR (100 MHz, C_6D_6) δ 143.6, 139.2, 134.5, 134.3, 133.5, 129.4, 129.1, 128.6, 127.6 (Ar-C, 1), 121.8 (13), 63.5, 62.5 (2, 11), 35.1, 31.2, 29.6, 28.1, 25.9, 25.2, 22.5, 22.3, 21.1 (CH_2), 21.5 (CH_3); *m*/*z* (FAB) 488 (MH^+, 15%), 307 (25), 289 (15), 154 (100), 136 (78) (Found MH^+: 488.1923. Calc. for $C_{26}H_{34}NO_4S_2$: 488.1929).

(2*S,1′*R**)-2-Allyl-5-(1-phenylsulfonylhept-6-enyl)-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (α-11c) and (2*S**,1′*S**)-2-allyl-5-(1-phenylsulfonylhept-6-enyl)-1-(4-tolylsulfonyl)-2,3-dihydro-1*H*-pyrrole (β-11c).** To a solution of **β-11c** (86 mg, 17 μmol) in tetrahydrofuran (2 ml) and hexamethylphosphorous triamide (50 μl) at −78 °C was added dropwise *n*BuLi (118 μl of a 1.6 M solution in hexanes, 19 μmol, 1.1 equiv.) and the mixture was stirred for 1 h. Methanol (0.1 ml) was then added rapidly and the reaction was allowed to warm to room temperature. Water (15 ml) and ethyl acetate (30 ml) were added and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (2 × 15 ml), the combined organic layers were washed with water (4 × 15 ml) and brine (15 ml) and dried. The solvent was removed *in vacuo* to afford **α-11c**–**β-11c** (84 mg, 98%) as a colourless oil and as a 31 : 69 mixture of diastereomers. Careful column chromatography (1 : 6 ethyl acetate–petroleum ether) afforded **α-11c**–**β-11c** (22 mg) as a 77 : 23 mixture of diastereomers.

Ring closing metathesis of α-11c and β-11c

According to general procedure B, a metathesis reaction on triene **α-, β-11c** (22 mg, 44 μmol) as a 77 : 23 mixture of diastereomers at C-1′ afforded starting material **α-11c** (15 mg, 68%) as a white solid and as a single diastereomer, and bicycle **12c** (4 mg, 19%) as a colourless oil and as a 38 : 62 mixture of *E*/*Z*-isomers. **α-11c**: ν_{max}/cm^{-1} 3073, 2924, 2853, 1446, 1339, 1307, 1148, 1086; ^{1}H NMR (400 MHz, C_6D_6) δ 8.03–8.00 (2H, m, Ar-H), 7.67 (2H, d, *J* 8.1, Ar-H), 6.96–6.94 (3H, m, Ar-H), 6.74 (2H, d, *J* 8.1, Ar-H), 5.73–5.62 (2H, m, 6′-H, CH_2CH=CH_2), 5.35–5.31 (2H, m, 4-H, 1′-H), 5.01–4.92 (4H, m, 7′-H, CH_2CH=CH_2), 4.13–4.08 (1H, m, 2-H), 2.44–2.38 (1H, m, CH_2CH=CH_2), 2.31–2.22 (1H, m, 3-H), 2.04–1.82 (4H, m, CH_2), 1.68–1.20 (6H, m, CH_2); ^{13}C NMR (100 MHz, C_6D_6) δ 144.2, 140.8, 137.6, 139.3, 135.1, 133.9, 130.3, 129.9, 129.7, 129.0, 119.4 (4, 6′, CH_2CH=CH_2, Ar-C), 130.0, (CH_2CH=CH_2), 118.5, 115.4 (5, 7′), 63.7, 63.3 (2, 1′), 40.9, 34.4, 33.6, 30.1, 29.8, 27.8 (CH_2), 21.7 (CH_3); *m*/*z* (FAB) 500 (MH^+, 62%), 458 (35), 358 (30), 316 (42), 304 (27), 234 (27), 202 (47), 162 (65), 91 (100) (Found MH^+: 500.1933. Calc. for $C_{27}H_{34}NO_4S_2$: 500.1929). Data for **12c** as reported above.

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