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Highly diastereoselective 1,3-dipolar cycloaddition reactions of *trans*-2-methylene-1,3-dithiolane 1,3-dioxide with 3-oxidopyridinium and 3-oxidopyrylium betaines: a route to the tropane skeleton

Varinder K. Aggarwal,*[a] Richard S. Grainger,[b] Gary K. Newton,[b] Peter L. Spargo,[c] Adrian D. Hobson[d] and Harry Adams[b]

[a] *School of Chemistry, Bristol University, Cantock's Close, Bristol, UK BS8 1TS*
[b] *Department of Chemistry, University of Sheffield, Brook Hill, Sheffield, UK S3 7HF*
[c] *Process R&D Department, Pfizer Central Research, Sandwich, Kent, UK CT13 9NJ*
[d] *Knoll Pharmaceuticals, Pennyfoot Street, Nottingham, UK*

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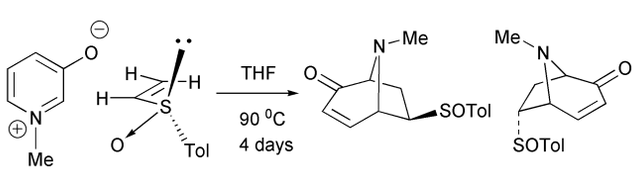
The C2-symmetric vinyl sulfoxide, *trans*-2-methylene-1,3-dithiolane 1,3-dioxide, was found to react with a range of 3-oxidopyridinium betaines (bearing different substituents on nitrogen) in high yield and with total diastereoselectivity. A 2.3 : 1 mixture of regioisomers was formed with all of the 3-oxidopyridinium betaines but the ratio was found to change over prolonged periods of time due to reversibility of the minor regioisomer. 3-Oxidopyridinium betaines bearing methyl substituents at either the 2- or 6-position were also tested in the cycloaddition process. Improved regioselectivity (8 : 1) and again high diastereoselectivity were observed with the betaine having an additional substituent at the 2-position, but with betaines having a substituent in the 6-position although high regioselectivity was observed (9.9 : 1), the major isomer was formed with low diastereoselectivity (5.5 : 4.4). The origin of the regio- and diastereo-selectivity with all the betaines is discussed. Finally, the C2-symmetric vinyl sulfoxide, *trans*-2-methylene-1,3-dithiolane 1,3-dioxide was reacted with an oxidopyrylium betaine in moderate yield. Good regioselectivity and moderate diastereoselectivity were observed.

Introduction

The tropane alkaloids are a family of natural products containing a common structural unit, the 8-azabicyclo[3.2.1]octane skeleton. They possess a wide range of biological activity making them attractive synthetic targets.[1] One of the most efficient methods of synthesising the tropane skeleton is the 1,3-dipolar cycloaddition of 3-oxidopyridinium betaines and olefins.[2] However, attempts to develop an asymmetric variant of this reaction have barely been explored.[3–5] Takahashi *et al.* reported the use of vinyl sulfoxide **2**, and although relatively high asymmetric induction was observed, a near 1 : 1 mixture of *endo* and *exo* adducts was produced (Scheme 1).[3]



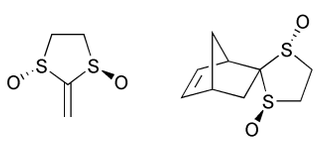
1 **2** **3** **4**

36%, 68% d.e

29% 100% d.e.

Scheme 1

We have recently reported the asymmetric synthesis of the C2-symmetric vinyl sulfoxide (1*R*, 3*R*)-2-methylene-1,3-dithiolane 1,3-dioxide **5** and its use in a number of cycloaddition reactions (Fig. 1). The presence of the C2-symmetry element renders the *endo* and *exo* approaches identical, thereby reducing the number of competing transition states. Indeed, high levels of diastereoselectivity have been achieved in both Diels–Alder reactions[6] and 1,3-dipolar cycloadditions with nitrones.[7,8] Furthermore, we were able to demonstrate that **5** could be used as a chiral ketene equivalent by synthesising



5 **6**

Fig. 1

enantiopure (+)-norbornenone from Diels–Alder adduct **6** (Fig. 1).[6] We report herein our results of the cycloadditions of **5** with a number of 3-oxidopyridinium betaines, and discuss those factors that effect selectivity.

Results and discussion

Racemic **5** was readily prepared in 4 steps[7] and its cycloaddition chemistry subsequently investigated. We were delighted to find that reaction of a stoichiometric amount of **5** with 1.1 equivalents of pyridinium salt **7** and triethylamine at room temperature furnished two regioisomeric cycloadducts **11** and **12** in good yield, in an approximate 2.3 : 1 ratio and with complete diastereoselectivity (Scheme 2). Evidently, **5** is a highly reactive dipolarophile, and able to impart high stereocontrol. Proof that the two isomers were regio- and not stereoisomers was obtained by reduction of the bis-sulfoxide moiety, which gave two thioacetals **19** and **20**, rather than a single compound. The two adducts **11** and **12** were separated by flash chromatography and their structures assigned by ^{1}H-NMR. H-7$_{endo}$ in the major and H-6$_{endo}$ in the minor regioisomer show very small or no coupling to the adjacent bridgehead proton (H-1 or H-5 respectively) due to a dihedral angle near 90°.[9] This results in a number of characteristic signals that can be used to assign the regiochemistry. In **11**, H-1 appears as a doublet due to coupling with 7-H$_{exo}$ with additional fine coupling, and H-5 shows coupling to H-4. In **12**, H-1 shows only fine coupling,

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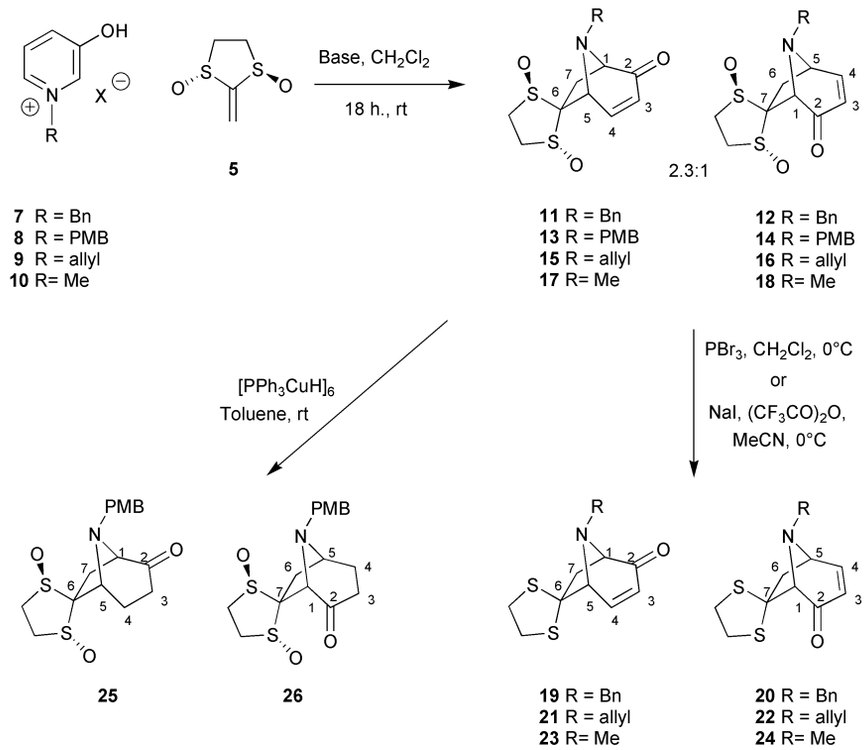


5

7 R = Bn
8 R = PMB
9 R = allyl
10 R= Me

11 R = Bn
13 R = PMB
15 R = allyl
17 R= Me

12 R = Bn
14 R = PMB
16 R = allyl
18 R= Me

25 **26**

19 R = Bn
21 R = allyl
23 R= Me

20 R = Bn
22 R = allyl
24 R= Me

Scheme 2

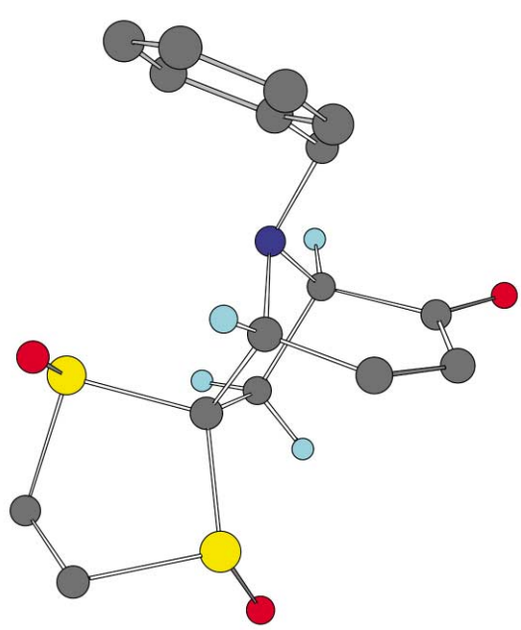


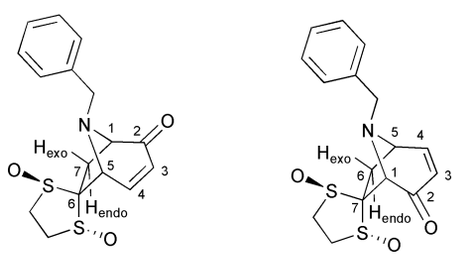
Fig. 2 Chem 3D representation of major cycloadduct **11** from X-ray coordinates (selected hydrogen atoms omitted for clarity).

whereas H-5 couples to both H-6$_{exo}$ (6 Hz) and H-4 (5 Hz). The stereochemistry of the major cycloadduct **11** was unambiguously determined by X-ray crystallography (Fig. 2).†

Cycloaddition of alkene **5** with a series of *N*-alkyl betaines generated cycloadducts (**13**–**18**, Scheme 2) in high yields with *identical levels of regioselectivity* (2.3 : 1). *In all cases the diastereoselectivity for each regioisomer was complete, no other diastereoisomers were detected.*

Our assignment of the stereochemistry of the minor cycloadduct is based on ^{1}H-NMR analysis. In both cycloadducts **11** and **12**, the *endo* proton (H-7$_{endo}$ in **11**, H-6$_{endo}$ in **12**), appears downfield of the *exo* proton (Table 1, entries 1 and 2). Upon reduction of sulfoxide to sulfides **19** and **20**, this order is reversed (entries 9 and 10) *i.e. exo* protons appear downfield of *endo*. Katritzky and co-workers noted that in related systems derived from a large range of dipolarophiles, *exo*-protons are typically deshielded by 0.6–1 ppm with respect to their *endo*

Table 1 Chemical shifts of C6 and C7 protons of cycloadducts/reduced cycloadducts



11 **12**

Entry	Compound	δ 7-H$_{endo}$	δ 7-H$_{exo}$	δ 6-H$_{endo}$	δ 6-H$_{exo}$
1	**11**	2.55	2.22		
2	**12**			2.69	2.38
3	**13**	2.56	2.22		
4	**14**			2.71	2.43
5	**15**	2.56	2.24		
6	**16**			2.72	2.42
7	**17**	2.54	2.25		
8	**18**			2.71	1.45
9	**19**	2.39	3.13		
10	**20**			2.44	2.98
11	**21**	2.39	3.11		
12	**22**			2.44	2.93
13	**23**	2.38	3.09		
14	**24**			2.42	2.92
15	**25**	2.75	1.98		
16	**26**			2.65	2.15
17	**30**	2.78	1.83		
18	**42**			2.75	2.43
19	**43**	2.59	2.25		
20	**44**	1.83	3.15		

† CCDC reference number 206042. See http://www.rsc.org/suppdata/ob/b3/b302834h/ for crystallographic data in .cif or other electronic format.

counterparts, due to "the enhanced anisotropy of the bridgehead nitrogen".[10] Why then is the "expected" order of *endo* and *exo* reversed in the case of **11** and **12**? The X-ray crystal structure of **11** provides an answer: the H-7_{endo} proton is in close proximity (*syn*-axial) to a sulfoxide oxygen, and so experiences a pronounced anisotropic effect characteristic of the sulfoxide group on a 1,3-parallel hydrogen.[11] In contrast, H-7_{exo} is in the proximity of a sulfoxide lone pair and will not be affected. The pronounced downfield shift of H-6_{endo} in the minor isomer **12** must therefore be due to a similar anisotropic effect from the sulfoxide, and so its stereochemistry must be as shown. Similar effects are seen for all cycloadducts **13**–**18** and in the reduced forms **19**–**24**. Chemical shifts are tabulated in Table 1.

The excellent diastereoselectivity for the formation of adduct **11** (and **13**, **15** and **17**) can be rationalised by considering the two possible transition state models **TS1** and **TS2** (Fig. 3). **TS2** is destabilised by a combination of electronic repulsion, between one of the sulfinyl oxygens and the π-system of the betaine, and steric repulsion, between this same oxygen and one of the methine protons on the aromatic ring. Consequently only the cycloadduct **11** arising from **TS1** is observed.

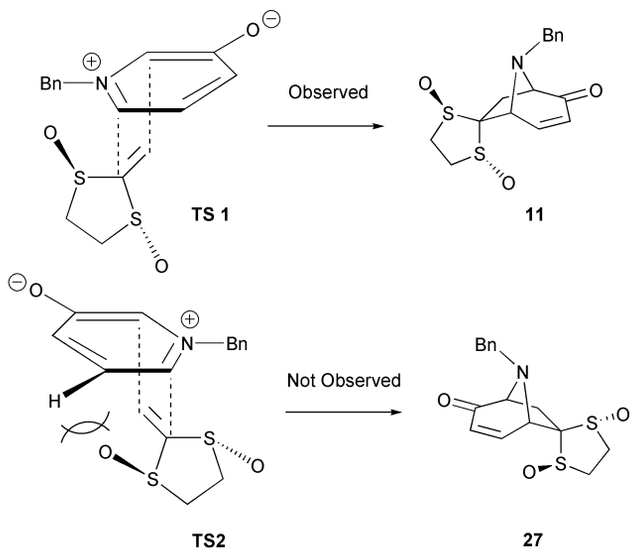


Fig. 3

The moderate regioselectivity was completely unexpected as a survey of the literature shows that 7-regioisomers are rarely observed in this type of cycloaddition, and such results have been rationalised using FMO calculations.[10] With alkene **5** it is possible that an attractive interaction can occur between the oxygen of the betaine and one of the sulfoxides (**TS3**), which could account for the unexpected formation of the 7-adduct **12** (Fig. 4). This attractive interaction could either be electrostatic in origin or result from overlap of the filled orbital on oxygen of the betaine with the antibonding orbital of the sulfoxide. Analogous to **TS2**, **TS4** is again destabilised by a combination of steric and electronic repulsion, and so adduct **28** is disfavoured. The stereochemical outcome of this model is also consistent with our assignment of stereochemistry for the minor adduct **12**.

Although it was anticipated that the formation of adducts **11** to **18** were under kinetic control, 1,3-dipolar cycloadditions can be reversible, and hence the ratio of products may change over a period of time. Indeed, when 1-methyl-3-hydroxypyridinium iodide **10** and alkene **5** were allowed to stir at room temperature for 5 days an improved ratio of cycloadducts was obtained (3.3 : 1), albeit in slightly diminished yield (77%). Consequently a series of experiments were performed in order to determine the extent of reversibility in these reactions. An initial 2.3 : 1 mixture of methyl cycloadducts **17** and **18** in deuterated chloroform was placed into 4 NMR tubes with triphenylmethane as an internal standard, so that the relative amounts of the two isomers could be quantified. Two of the NMR tubes were left at room temperature and the other two heated at 50 °C. In addition, protonated DIPEA was added to two of the samples in order to investigate whether the tertiary ammonium salts generated by deprotonation of the pyridinium salts could promote retro-cycloaddition. Dennis *et al.* have demonstrated that betaine dimers undergo retro-cycloaddition in the presence of acid.[12] The results of these experiments are shown in Tables 2 and 3. The experiments clearly demonstrated that the 6-regioisomer **17** was the more stable and reversibility was indicated by the appearance of both betaine and alkene in the ^{1}H-NMR spectra. Furthermore, another set of characteristic methylene signals was observed in the spectra of those samples that had been left at 50 °C, indicating the presence of a third cycloadduct. Unfortunately the amount of 6-regioisomer **17** did not appear to increase relative to the internal standard and the improved ratios were a consequence of reversal of the (minor) 7-regioisomer **18** back to starting materials followed by degradation of **5** with adventitious water. As expected, the degree of reversibility increased with temperature and in the presence of protonated DIPEA.

It is thought that the increased stability of **17** over its regioisomer **18** may arise from a lower overall dipole moment. The electron withdrawing carbonyl group and bis-sulfoxide moieties have their dipoles opposed in **17**, whereas both groups have

Table 2 Amount of cycloadduct relative to triphenylmethane at 20 °C

	Without protonated DIPEA			With protonated DIPEA		
Time	**17**	**18**	Ratio	**17**	**18**	Ratio
0	1.00	0.39	2.5 : 1	1.00	0.41	2.4 : 1
12 days	0.95	0.33	2.8 : 1	0.94	0.32	2.9 : 1
19 days	0.95	0.32	3.0 : 1	0.91	0.28	3.2 : 1
27 days	0.95	0.29	3.3 : 1	0.89	0.21	4.2 : 1

Table 3 Amount of cycloadduct relative to triphenylmethane at 50 °C

	Without protonated DIPEA			With protonated DIPEA		
Time	**17**	**18**	Ratio	**17**	**18**	Ratio
0	1.00	0.40	2.5 : 1	1.00	0.41	2.4 : 1
12 hours	0.97	0.29	3.3 : 1	0.84	0.25	3.4 : 1
36 hours	0.97	0.25	3.9 : 1	0.82	0.20	4.2 : 1
4 days	0.97	0.24	4.1 : 1	0.87	0.20	4.4 : 1
12 days	1.00	0.18	5.5 : 1	0.74	0.13	5.6 : 1
16 days	1.00	0.15	6.4 : 1	0.66	0.11	5.7 : 1

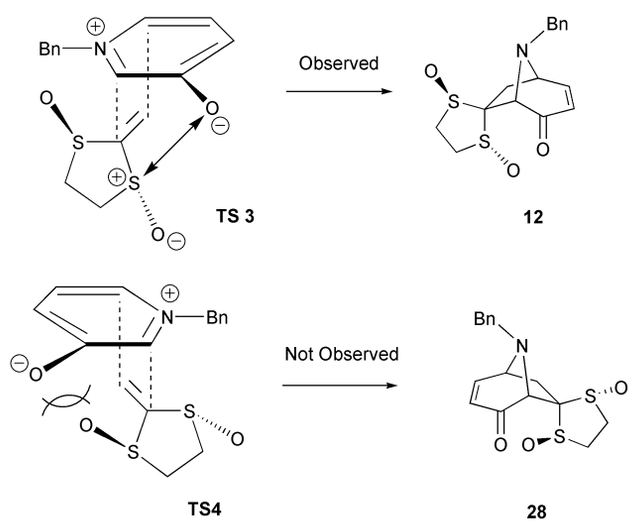


Fig. 4

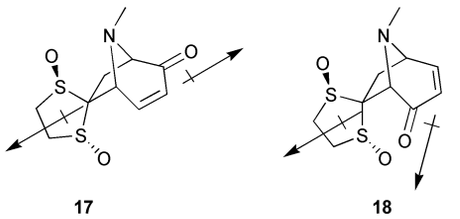


Fig. 5

a cumulative effect on the dipole moment in regioisomer **18** (Fig. 5). It is anticipated that a similar effect would be observed for adducts **11** to **16**.

Attempts to improve the regioselectivity by changing the solvent and temperature were unsuccessful. In addition, the use of a range of Lewis acids resulted in poor yields of cycloadduct. This effect is commonly observed in 1,3-dipolar cycloadditions, where the Lewis acid can bind to the dipole thereby reducing its reactivity.[13]

In order to investigate the scope of this cycloaddition chemistry with alkene **5**, a series of modifications were made to the structure of the betaine. Molecular modelling suggested that placing a substituent in the 2-position of the betaine would destabilise the transition state leading to the minor regioisomer (**TS6**), and hence could improve the regioselectivity (Fig. 6).

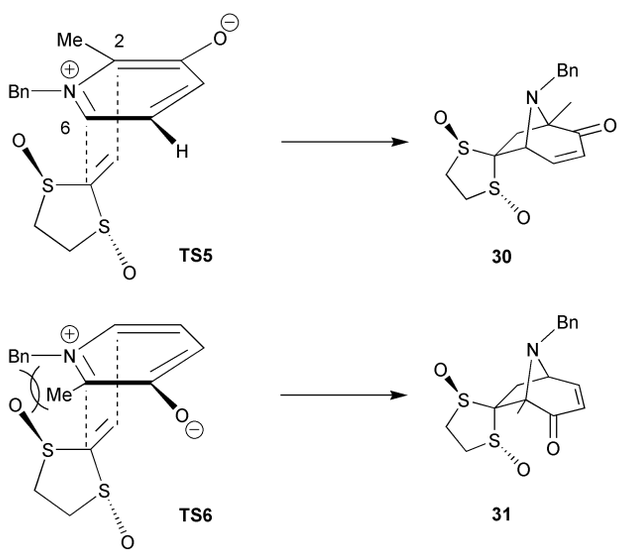
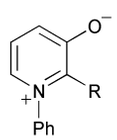


Fig. 6

It had previously been shown that 2-substituted betaines tend to give larger amounts of 7-regioisomer. For example only 6-substituted adducts were produced from the reaction of betaine **32** with either methyl acrylate or acrylonitrile (Fig. 7), whereas the methyl betaine **33** gave a mixture of regioisomers and the phenyl betaine **34** gave only 7-substituted tropanes.[14] This selectivity can be rationalised using FMO calculations. Evidently, the cycloadditions are dominated by FMO interactions when the alkenes are flat and hence steric effects are minimal.



32 R = H
33 R = Me
34 R = Ph

Fig. 7

Conversely, it was anticipated that placing a substituent at the 6-position of the betaine would lead to an increase in the amount of 7-adduct in these cycloaddition reactions (**TS8**) (Fig. 8).

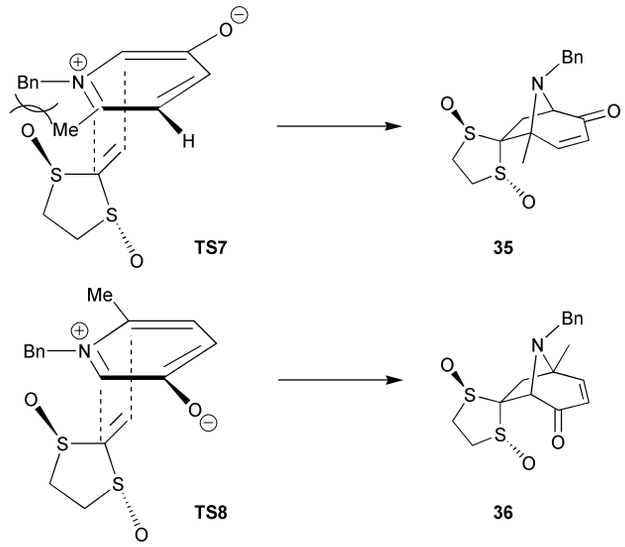


Fig. 8

The pyridinium salts **37** and **38** were prepared from the corresponding 3-hydroxypyridines and benzyl bromide. Subsequent cycloaddition of **37** with alkene **5** gave a mixture of cycloadducts with an improved ratio in favour of the 6-regioisomer **30**, as expected (Scheme 3). The yield could not be improved by leaving the reaction for a longer period of time. It is believed that the ratio of products reflects the kinetic ratio, as reversion to the betaine was not observed when the pure cycloadducts were left in solution for the same period of time.

Cycloaddition of the betaine derived from **38** with alkene **5** resulted in the formation of three cycloadducts in a 5.5 : 4.4 : 1 ratio (Scheme 4). These were identified by ^{1}H-NMR as the two 6-regioisomers **35** and **39** and the 7-regioisomer **36**. In the 6-regioisomers **35** and **39** the 7-H$_{endo}$ appears as a doublet and 7-H$_{exo}$ as a double doublet. In the 7-regioisomer **36** there is no H-5 so both 6-H$_{endo}$ and 6-H$_{exo}$ appear as doublets. Assignment of the stereochemistry of the 6-diasteromers **35** and **39** was based upon the relative chemical shifts of the 7-H *endo* and *exo* protons.

A high degree of reversibility was observed in the cycloaddition and after only 1 week in chloroform the major cycloadduct **35** disappeared to leave a 3.5 : 1 ratio of **39** and **36** respectively. A crossover experiment with 1-benzyl-3-hydroxypyridinium bromide **7** and the three cycloadducts **35**, **36** and **39** gave a mixture of cycloadducts **36** and **39** as well as the two desmethylcycloadducts **11** and **12**, confirming that the cycloaddition was reversible. Simple molecular models suggested that a severe 1,3-diaxial interaction existed between one of the sulfinyl oxygens and the methyl group in **35**, which could account for its relative instability (Fig. 9). Cycloadducts **36** and **39** did not show such rapid reversibility and the ratio of these two compounds probably reflects the kinetic ratio.

Contrary to our expectation, deterioration in the diastereoselectivity was observed, while we did not see the anticipated

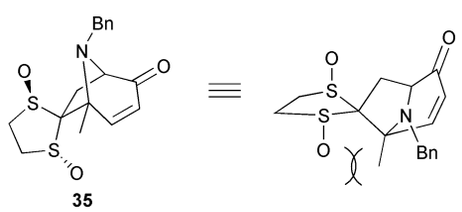
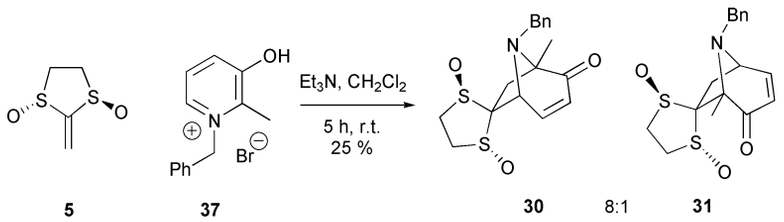
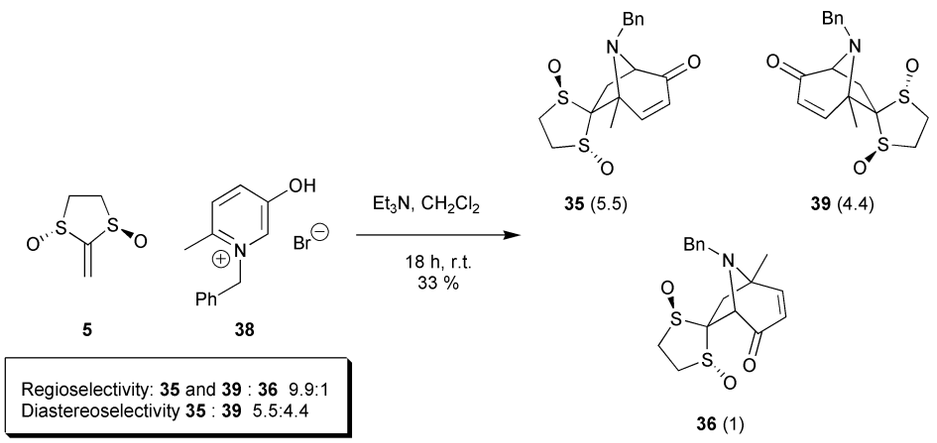


Fig. 9



Scheme 3



Scheme 4

increase in the proportion of the 7-adduct **36**. Whereas destabilisation of **TS7** was correctly predicted, the outcome was not. The methyl group does not destabilise **TS9** (Fig. 10) to the same extent, however it is still destabilised by steric and electronic repulsive interactions leading to an approximate 1 : 1 ratio of **35** and **39**. The improved regioselectivity cannot be explained using steric arguments. A survey of the literature shows that 6-substituted betaines tend to give 6-adducts, however as far as we are aware nobody has performed any calculations to show the effect a 6-substituent has on the FMOs of the betaine.

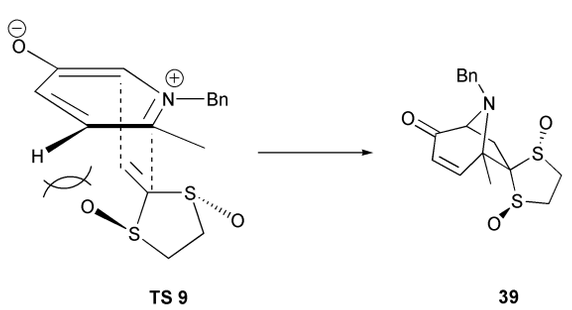


Fig. 10

1,3-Dipolar cycloadditions of 5 with oxidopyrylium betaines

We also decided to investigate the cycloaddition of **5** with the related, but much more difficult, 3-oxidopyrylium betaine **41**. Such betaines are readily generated from acetoxypyrones in the presence of base, although they tend to dimerise more rapidly than they undergo cycloaddition reactions.[15] Hence most intermolecular cycloadditions have been performed at high temperatures or in the presence of a large excess of alkene. Acetoxypyrone **40** was prepared in 2 steps in accordance with the literature.[16,17] Cycloaddition at room temperature with only 1 equivalent of alkene **5** led to the formation of three out of the four possible cycloadducts in moderate overall yield, further demonstrating the high reactivity of alkene **5** in 1,3-dipolar cycloadditions (Scheme 5). Diminished diastereoselectivity but improved regioselectivity was observed compared with the cyclisation of **5** with the pyridinium betaines derived from **7**–**10**. The former may simply be a result of the increased reactivity of the betaine. By replacing the nitrogen of the betaine with a second oxygen atom the amount of charge on the 3-oxygen will be reduced. This is likely to result in a decrease in the proposed interaction between the oxygen of the betaine and the sulfur of the dipolarophile (see **TS3**), and account for the improved regioselectivity. Consistent with our model for assigning stereochemistry, H-7_{endo} in diastereomer **44** does not experience the pronounced downfield shift of H-7_{endo} in **43** and H-6_{endo} in **42**, due to the lack of a *syn*-[1,3]diaxial relationship with a sulfoxide oxygen (Table 1, entries 18–20).

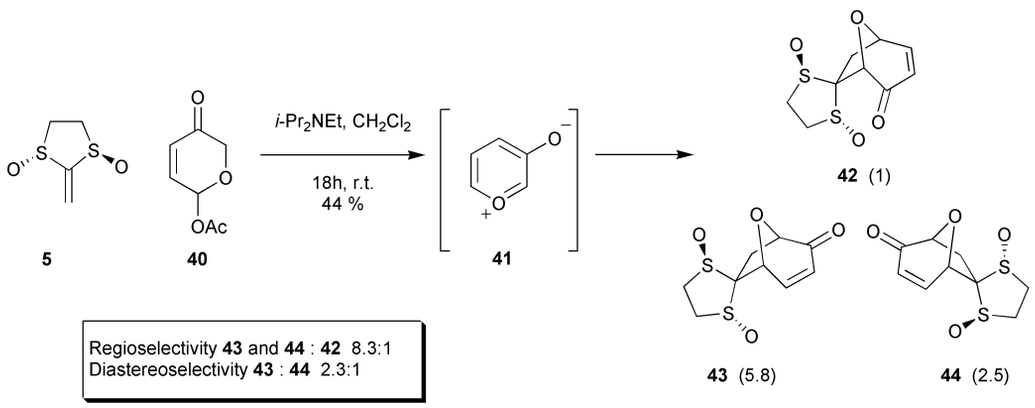
Conclusion

Alkene **5** has been shown to be a highly reactive dipolarophile in 1,3-dipolar cycloadditions with aromatic betaines. High yields coupled with complete diastereoselectivities have been achieved with simple 3-oxidopyridinium betaines. These reactions are under kinetic control, although over longer periods of time the ratio of regioisomers changed on account of the reversibility of the reaction. The regioselectivity in these reactions was moderate although this could be improved by placing an additional substituent at the 2-position of the betaine. Substitution at the 6-position of the betaine resulted in greater reversibility, and hence to mixtures of cycloadducts resulting from both kinetic and thermodynamic control. Furthermore, alkene **5** reacted with an oxidopyrylium betaine in moderate yield. Good regioselectivity and moderate diastereoselectivity were observed. To the best of our knowledge this is the first asymmetric, intermolecular 1,3-dipolar cycloaddition with this class of betaine.[11]

Experimental

General

Dichloromethane, acetonitrile and triethylamine were distilled from calcium hydride immediately prior to use. Toluene was distilled from $LiAlH_4$ immediately prior to use. Alkene **5** was prepared in 4 steps in accordance with our previously reported procedure.[7] Pyridinium salts **7**[18] and **10**[19] were made by reacting 3-hydroxypyridine with the corresponding alkyl halide, according to literature procedures. Acetoxypyrone **40** was made in



Scheme 5

2 steps from furfuryl alcohol according to the methods of Achmatowicz *et al.* [16] and Laliberté *et al.*[17] All other reagents are commercially available and were used as received. Proton and ^{13}C NMR spectra were recorded on a Bruker 250 MHz or Bruker 400 MHz instrument. Coupling constants are given in Hertz.

3-Hydroxy-1-(4-methoxybenzyl)pyridinium chloride (8). To a suspension of 3-hydroxypyridine (2 g, 21 mmol) in toluene (10.2 ml), 4-methoxybenzyl chloride (2.8 ml, 21 mmol) was added. The mixture was refluxed gently for 5 hours, after which time the solvent was removed under reduced pressure to yield a sticky solid. Recrystallisation from EtOH–EtOAc gave the *pyridinium salt* as light brown crystals (4.1 g, 78%), mp 175–177 °C; (Found: C, 61.9; H, 5.6; N, 5.4; Cl, 14.1. $C_{13}H_{14}NO_2Cl$ requires C, 62.0; H, 5.6; N, 5.6; Cl, 14.1%); ν_{max} (KBr)/cm^{-1} 3448 (O–H), 3057, 2992, 2676, 2561 and 2496 (C–H), 1610, 1577, 1516 and 1484 (Ar); δ_H (250 MHz; DMSO) 3.76 (3H, s, OCH_3), 5.68 (2H, s, CH_2), 6.96–7.03 (2H, m, Ar–H), 7.49–7.56 (2H, m, Ar–H), 7.93 (1H, dd, *J* 8.5 and 5.8, 5-H), 8.04 (1H, ddd, *J* 8.5, 1.9 and 1.0, 4-H), 8.66 (1H, dd, *J* 5.8 and 1.0, 6-H), 8.75 (1H, d, *J* 1.9, 2-H); δ_C (63 MHz; D_2O) 55.4 (q), 64.0 (t), 114.8 (d), 117.9 (d), 125.2 (s), 128.6 (d), 130.8 (d), 131.9 (d), 135.3, (d), 156.8 (s), 159.9 (s); *m*/*z* (EI) 215 ((M − H)$^+$, 11%), 121 (100), 95 (28), 78 (17).

1-Allyl-3-hydroxypyridinium bromide (9). The procedure used for the synthesis of **9** differed from the literature procedure so is included for completion. All spectral data were in accordance with the title compound. Allyl bromide (2.2 ml, 25 mmol) was added to a solution of 3-hydroxypyridine (2 g, 21 mmol) in acetonitrile (20 ml). After stirring at room temperature for 18 hours the solvent was evaporated. The brown gum that remained solidified after the addition of toluene and subsequent evaporation to dryness. The solid residue was then washed with a solution of 50% EtOAc–acetone (20 ml) and the solution decanted from the remaining insoluble material. The washing procedure was repeated several times until the decanted solution did not contain any 3-hydroxypyridine (indicated by TLC). The remaining brown solid was dried under vacuum to give the title compound, as a hygroscopic brown solid (3.87 g, 85%), mp 96–98 °C [lit.[19] mp 97–99 °C].

(1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′-6]-8-benzyl-8-azabicyclo[3.2.1]oct-3-en-2-one (11) and (1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′-7]-8-benzyl-8-azabicyclo[3.2.1]oct-3-en-2-one (12). Pyridinium salt **7** (1.7 g, 6.4 mmol) and triethylamine (0.9 ml, 6.4 mmol) were added to a solution of alkene **5** (870 mg, 5.8 mmol) in dry dichloromethane (11.6 ml) under nitrogen. The pyridinium salt was seen to dissolve over a period of 10 minutes giving a brown solution. The reaction mixture was stirred for 18 hours at room temperature then purified by flash chromatography, eluting with acetone. The title compounds were isolated as a 2.3 : 1 mixture (1.5 g, 79%). The two cycloadducts were separated by more careful flash chromatography, eluting with 5% EtOH–EtOAc. Cycloadduct **12** eluted first and was obtained as a yellow oily solid (410 mg, 21%). R_f (10% EtOH–EtOAc) 0.4; δ_H (400 MHz; $CDCl_3$) 2.38 (1H, dd, *J* 14 and 6, 6-H$_{exo}$), 2.69 (1H, d, *J* 14, 6-H$_{endo}$), 3.49 (1H, td, *J* 14 and 4, C*H*S(O)), 3.54–3.63 (2H, m, 2 × C*H*S(O)), 3.76 (1H, td, *J* 14 and 2, C*H*S(O)), 3.86 (1H, d, *J* 13, 9-H), 3.87–3.91 (1H, m, 5-H), 4.12 (1H, t, *J* 1, 1-H), 6.26 (1H, dd, *J* 10 and 1, 3-H), 7.10 (1H, dd, *J* 10 and 5, 4-H), 7.23–7.34 (5H, m, Ar–H); *m*/*z* (EI) 335 (M$^+$, 5%), 275 (10), 227 (11), 211 (37), 185 (18), 91 (100).

Further elution gave **11** (1.0 g, 52%) as a yellow crystalline solid. R_f (10% EtOH–EtOAc) 0.3, mp 160–161 °C. δ_H (250 MHz; $CDCl_3$) 2.22 (1H, dd, *J* 15.5 and 7.5, 7-H$_{exo}$), 2.55 (1H, dd, *J* 15.5 and 1, 7-H$_{endo}$), 3.40 (1H, td, *J* 14 and 4.5, 4′-H or 5′-H), 3.52–3.61 (2H, m, 4′-H and/or 5′-H), 3.75 (1H, ddt, *J* 7.5 and 2, 1, 1-H), 3.83 (2H, br s, 9-H), 3.92 (1H, dt, *J* 14 and 4.5, 4′-H or 5′-H), 4.21 (1H, br d, *J* 5, 5-H), 6.37 (1H, dd, *J* 10 and 2, 3-H), 6.97 (1H, dd, *J* 10 and 5, 4-H), 7.23–7.34 (5H, m, Ar–H); *m*/*z* (EI) 335 (M$^+$, 32%), 318 (33), 260 (41), 210 (33), 91 (100).

Crystal data for $C_{16}H_{17}NO_3S_2$; *M* = 335.43, crystallises from dichloromethane–pet ether as colourless blocks; crystal dimensions 0.54 × 0.33 × 0.28 mm. Monoclinic, *a* = 15.087(2), *b* = 6.443(2), *c* = 16.736(2) Å, b = 106.840(10)°, *U* = 1557.1(6) Å^3, *Z* = 4, D_c = 1.431 g cm^{-3}, space group $P2_1/c$ (No. 14), Mo–K$_\alpha$ radiation (λ = 0.71073 Å), μ(Mo–K$_\alpha$) = 0.353 mm^{-1}, *F*(000) = 704.

Three-dimensional, room temperature X-ray data were collected in the range $3.5 < 2\theta < 45°$ on a Siemens P4 diffractometer by the omega scan method. Of the 2748 reflections measured, all of which were corrected for Lorentz and polarisation effects (but not for absorption), 1660 independent reflections exceeded the significance level $|F|/\sigma(|F|) > 4.0$ The structure was solved by direct methods and refined by full matrix least squares methods. Hydrogen atoms were included in calculated positions and refined in riding mode. Refinement converged at a final *R* = 0.0418 (*wR*2 = 0.1117, for all 2031 unique data 199 parameters, mean and maximum δ/σ 0.000, 0.000), with allowance for the thermal anisotropy of all non-hydrogen atoms. Minimum and maximum final electron density −0.332 and 0.262 e Å^{-3}. A weighting scheme $w = 1/[s^2(F_o^2) + (0.0559P)^2 + 0.6583P]$ where $P = (F_o^2 + 2 * F_c^2)/3$ was used in the latter stages of refinement. Complex scattering factors were taken from the program package SHELXL93 as implemented on the Viglen 486dx computer.

(1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′-6]-8-(4-methoxybenzyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (13) and (1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′-7]-8-(4-methoxybenzyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (14). *Cycloadducts* **13** and **14** were synthesised in an analogous fashion to **11** and **12**. Flash chromatography with

30% acetone–EtOAc gave the *title compounds* as an inseparable 2.3 : 1 mixture (475 mg 78%). R_f 0.4 (50% acetone–EtOAc); ν_{max} (thin film)/cm^{-1} 3029 and 2839 (C–H), 1691 (C=O), 1613 (C=C), 1586 and 1513 (Ar), 1043 (S=O); peaks assigned to **13**: δ_H (250 MHz; $CDCl_3$) 2.22 (1H, dd, *J* 15.6 and 7.6, 7-H$_{exo}$), 2.56 (1H, d, *J* 15.6, 7-H$_{endo}$), 3.36–3.96 (10H, m, 1-H, CH_2Ar, OCH_3, and 4 × C*H*S(O)), 4.19 (1H, d, *J* 4.9, 5-H), 6.37 (1H, dd, *J* 9.8 and 1.7, 3-H), 6.80–6.88 (2H, m, Ar–H), 6.97 (1H, dd, *J* 9.8 and 4.9, 4-H), 7.15–7.23 (2H, m, Ar–H); peaks assigned to **14**: δ_H (250 MHz; $CDCl_3$) 2.43 (1H, dd, *J* 14.3 and 6.4, 6-H$_{exo}$), 2.71 (1H, d, *J* 14.3, 6-H$_{endo}$), 3.32–4.00 (10H, m, 5-H, CH_2Ar, OCH_3 and 4 × C*H*S(O)), 4.14 (1H, br s, 1-H), 6.27 (1H, dd, *J* 9.8 and 1.4, 3-H), 6.80–6.88 (2H, m, Ar–H), 7.10 (1H, dd, *J* 9.8 and 5.2, 4-H), 7.15–7.23 (2H, m, Ar–H); *m*/*z* (EI) (mixture) 366 (M$^+$, 27%), 348 (25), 336 (18), 216 (33), 151 (58), 121 (73), 59 (100); (Found: M$^+$, 366.0835. $C_{17}H_{20}NO_4S_2$ requires *m*/*z*, 366.0834). Although the *title compounds* could not be separated using flash chromatography reduction of the enone double bond using the procedure of Mahoney *et al.*[20] gave two ketones **25** and **26** that could be readily separated. This led to the unambiguous assignment of **13** and **14**.

(1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′-6]-8-allyl-8-azabicyclo[3.2.1]oct-3-en-2-one (15) and (1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′-7]-8-allyl-8-azabicyclo[3.2.1]oct-3-en-2-one (16). Cycloadducts **15** and **16** were synthesised in an analogous fashion to **11** and **12**. Flash chromatography on silica with 50% EtOAc–acetone gave the *title compounds* as an inseparable 2.3 : 1 mixture (3.3 g, 85%). R_f (acetone) 0.61, mp 145–147 °C; ν_{max} (thin film)/cm^{-1} (mixture) 2978, 2928 and 2828 (C–H), 1686 (C=O), 1643 (C=C), 1039 (S=O); peaks assigned to 6-regioisomer **15**: δ_H (250 MHz; $CDCl_3$) 2.24 (1H, dd, *J* 15.3 and 7.6, 7-H$_{exo}$), 2.56 (1H, d, *J* 15.3, 7-H$_{endo}$), 3.26–3.34 (2H, m, CH_2CH=CH_2), 3.41 (1H, td, *J* 13.7 and 4.3, C*H*S(O)), 3.54–3.66 (2H, m, 2 × C*H*S(O)), 3.83 (1H, br d, *J* 7.6, 1-H), 3.95 (1H, td, *J* 13.9 and 4.3, C*H*S(O)), 4.28 (1H, d, *J* 5.0, 5-H), 5.12–5.24 (2H, m, CH=CH_2), 5.71–5.88 (1H, m, C*H*=CH_2), 6.32 (1H, dd, *J* 9.8 and 1.7, 3-H), 6.97 (1H, dd, *J* 9.8 and 5.0, 4-H); peaks assigned to 7-regioisomer **16**: δ_H (250 MHz; $CDCl_3$) 2.42 (1H, dd, *J* 14.3 and 6.3, 6-H$_{exo}$), 2.72 (1H, d, *J* 14.3, 6-H$_{endo}$), 3.25–4.16 (8H, m, 1-H, 5-H, CH_2CH=CH_2, 4 × C*H*S(O)), 5.12–5.24 (2H, m, CH=CH_2), 5.71–5.88 (1H, m, C*H*=CH_2), 6.21 (1H, dd, *J* 9.8 and 1.4, 3-H), 7.13 (1H, dd, *J* 9.8 and 5.6, 4-H); δ_C (63 MHz; $CDCl_3$) (mixture) 26.8 (t), 31.7 (t), 48.3 (t), 49.8 (t), 50.4 (t), 51.5 (t), 52.2 (2 × t), 56.2 (d), 58.0 (d), 67.5 (d), 68.8 (d), 93.8 (s), 99.8 (s), 118.5 (2 × t), 128.3 (d), 130.6 (d), 133.6 (d), 133.7 (d), 143.2 (d), 149.6 (d), 193.8 (s), 196.4 (s); *m*/*z* (EI) (mixture) 285 (M$^+$, 22%), 268 (16), 160 (20), 150 (9), 101 (24), 86 (100), 58 (71); (Found: M$^+$, 285.0498. $C_{12}H_{15}NO_3S_2$ requires *m*/*z*, 285.0493). Although the *title compounds* could not be separated using flash chromatography reduction of the bis-sulfoxide moiety using the procedure of Drabowicz and Oae.[21] led to two bis-sulfides **21** and **22** that could be readily separated. This led to the unambiguous assignment of **15** and **16**.

(1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane 1′,3′-dioxide-2′-6]-8-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one (17) and (1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide-2′-7]-8-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one (18). 3-Hydroxy-1-methylpyridinium iodide (2.8 g, 11 mmol) and *N*,*N*-diisopropylethylamine (2.1 ml, 11 mmol) were added to a solution of alkene **5** (1.5 g, 10 mmol) in dry dichloromethane (20 ml), under an inert atmosphere. The reaction was stirred at room temperature for 18 hours then purified by flash chromatography on silica (acetone). The *title compounds* were isolated as an inseparable 2.3 : 1 mixture. R_f 0.4 (acetone); ν_{max} (thin film)/cm^{-1} (mixture) 2946 and 2803 (C–H), 1683 (C=O), 1038 (S=O); peaks assigned to **17**: δ_H (250 MHz: $CDCl_3$) 2.25 (1H, dd, *J* 15.6 and 7.6, 7-H$_{exo}$), 2.50 (3H, s, CH_3), 2.54 (1H, d, *J* 15.6, 7-H$_{endo}$), 3.42 (1H, td, *J* 13.9 and 4.6, C*H*S(O)), 3.54–3.60 (2H, m, 2 × C*H*S(O)), 3.73 (1H, dd, *J* 7.6 and 1.0, 1-H), 3.86–4.02 (1H, m, C*H*S(O)), 4.16 (1H, d, *J* 4.9, 5-H), 6.32 (1H, dd, *J* 9.8 and 1.0, 3-H), 6.96 (1H, dd, *J* 9.8 and 4.9, 4-H); peaks assigned to **18**: 2.16 (3H, s, CH_3), 2.45 (1H, dd, *J* 14.0 and 6.4, 6-H$_{exo}$), 2.71 (1H, d, *J* 14.0, 6-H$_{endo}$), 3.44–4.22 (6H, m, 1-H, 5-H, and 4 × C*H*S(O)), 6.20 (1H, dd, *J* 9.8 and 1.2, 3-H), 7.14 (1H, dd, *J* 9.8 and 4.9, 4-H); δ_C (63 MHz; $CDCl_3$) (mixture) 27.2 (t), 27.8 (t), 34.6 (2 × q), 48.3 (t), 49.8 (t), 52.0 (t), 52.7 (t), 58.5 (d), 60.4 (d), 69.4 (d), 70.4 (d), 98.2 (s), 100.1 (s), 130.2 (2 × d), 142.8 (2 × d), 196.0 (s), 196.7 (s); *m*/*z* (EI) (mixture) 259 (M$^+$, 17%), 242 (7), 184 (29), 134 (100), 109 (27), 81 (43), 58 (41); (Found: M$^+$, 259.0330. $C_{10}H_{13}NO_3S_2$ requires *m*/*z*, 259.0336). Although the *title compounds* could not be separated using flash chromatography reduction of the bis-sulfoxide moiety led to two bis-sulfides **23** and **24** that could be readily separated. This led to the unambiguous assignment of **17** and **18**.

(1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane)-2′,6]-8-benzyl-8-azabicyclo[3.2.1]oct-3-en-2-one (19) and (1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane)-2′,7]-8-benzyl-8-azabicyclo[3.2.1]oct-3-en-2-one (20). A 2.3 : 1 mixture of cycloadducts **11** and **12** (86.9 mg, 0.26 mmol) was dissolved in dry dichloromethane (2.6 cm^3) under nitrogen and the temperature reduced to 0 °C in an ice bath. Phosphorus tribromide (0.123 cm^3, 1.29 mmol) was added dropwise to the solution and stirring continued at 0 °C for two hours, after which time no starting material was observed by TLC analysis on mini-workup. The reaction was quenched by careful dropwise addition of cold saturated sodium bicarbonate solution and brought to alkaline pH by further addition of sodium bicarbonate solution. The aqueous phase was extracted three times with dichloromethane and the combined organic phase dried over $MgSO_4$. After filtration and evaporation of the solvent, the residue was columned on silica gel, eluting with ethyl acetate–40–60 pet ether (1 : 9 ratio) to afford the *title compounds*.

Thioacetal **19** was obtained as a yellow oil which solidified to a yellow solid in the freezer (53 mg, 67%). R_f 0.3 (10% EtOAc–40–60 pet ether), mp 82–84 °C. (Found: C, 63.2; H, 5.6; N, 4.5; S, 20.9. $C_{16}H_{17}S_2ON$ requires C, 63.3; H, 5.65; N, 4.6; S, 21.1%); ν_{max} (thin film)/cm^{-1} 3061 and 3029 (unsaturated C–H), 2955, 2924, 2870 and 2840 (saturated C–H), 1735 (C=O), 1690 (C=C) and 1602, 1572 and 1495 (Ar); δ_H (400 MHz; $CDCl_3$) 2.39 (1H, dd, *J* 15 and 1, 7-H$_{endo}$), 3.13 (1H, dd, *J* 15 and 8, 7-H$_{exo}$), 3.14–3.26 (2H, m, 4′-H and 5′-H), 3.31–3.41 (2H, m, 4′-H and 5′-H), 3.59 (1H, ddt, *J* 8, 2 and 1, 1, 1-H), 3.70 (1H, br d, *J* 5, 5-H), 3.78 (1H, d, *J* 8.5, 9-H$_a$), 3.88 (1H, d, *J* 8.5, 9-H$_b$), 6.15 (1H, dd, *J* 10 and 1.5, 3-H), 6.90 (1H, dd, *J* 10 and 5, 4-H), 7.22–7.36 (5H, m, Ar–H); δ_C (63 MHz, $CDCl_3$) 40.2 and 40.5 (4′-C and 5′-C), 45.3 (7-C), 52.5 (9-C), 68.0 (1-C), 69.1 (5-C), 71.0 (6-C), 127.4, 127.5, 128.4, 128.5 (Ar–CH and 3-C), 137.7 (Ar–C), 146.9 (4-C), 198.7 (2-C); *m*/*z* (EI) 303 (M$^+$, 28%), 214 (35), 185 (39) and 91 (100).

Thioacetal **20** was obtained as a yellow oil (6.5 mg, 8%). R_f 0.1 (10% EtOAc–40–60 pet ether); ν_{max} (thin film)/cm^{-1} 3059, 3027 (unsaturated C–H), 2924, 2847 (saturated C–H), 1683 (C=O), 1602 and 1494 (Ar); δ_H (250 MHz; $CDCl_3$) 2.44 (1H, d, *J* 13.5, 6-H$_{endo}$), 2.98 (1H, dd, *J* 13.5 and 6.5, 6-H$_{exo}$), 3.06–3.49 (4H, m, 4′-H and 5′-H), 3.66 (1H, t, *J* 1, 1-H), 3.75 (1H, br t, *J* 5.5, 5-H), 3.87 (2H, s, 9-H), 6.09 (1H, dd, *J* 10 and 1.5, 3-H), 6.92 (1H, dd, *J* 10 and 5, 4-H), 7.21–7.38 (5H, m, Ar–H); δ_C (63 MHz, $CDCl_3$) 38.8 and 41.0 (4′-C and 5′-C), 45.8 (6-C), 53.1 (9-C), 57.6 (5-C), 65.5 (7-C), 84.0 (1-C), 127.4, 127.7, 128.4 and 128.5 (Ar–CH and 3-C), 137.7 (Ar–C), 148.5 (4-C), 195.6 (2-C); *m*/*z* (EI) 303 (M$^+$, 57%), 214 (75), 185 (45) and 91 (100) (Found: M$^+$, 303.0755. $C_{16}H_{17}S_2ON$ requires *m*/*z*, 303.0752).

(1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane)-2′-6]-8-allyl-8-azabicyclo[3.2.1]oct-3-en-2-one (21) and (1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane)-2′-7]-8-allyl-8-azabicyclo[3.2.1]oct-3-en-2-one (22). To the mixture of cycloadducts **15** and **16** (700 mg, 2.5 mmol) in

dry acetonitrile (50 ml) at 0 °C, sodium iodide (2.9 g, 19.6 mmol) was added. The mixture was stirred for 5 minutes then trifluoroacetic anhydride (2.8 ml, 19.6 mmol) was added dropwise. A brown coloration immediately formed signalling the production of iodine. The reaction mixture was stirred at 0 °C for a further 2 hours, after which time, the iodine was removed with a saturated aqueous solution of sodium thiosulfate. The pH of the aqueous layer was adjusted to pH 10 by the addition of 2 M NaOH (aq), and the mixture partitioned into dichloromethane (40 ml). The organic layer was separated and the aqueous layer further extracted with dichloromethane (3 × 30 ml). The organic layers were combined, washed with brine (100 ml) and dried over $MgSO_4$. The solvent was removed *in vacuo* to yield a yellow oil. Purification by flash chromatography on silica (20% EtOAc–pet ether) gave the *two sulfide cycloadducts.*

The *6-regio-sulfide* **21** eluted first and was obtained as a yellow oil which solidified in the freezer (360 mg, 83%). R_f 0.3 (20% EtOAc–pet ether), mp 47–49 °C. (Found: C, 56.8; H, 6.0; N, 5.55; S, 25.2. $C_{12}H_{15}NOS_2$ requires C, 56.9; H, 6.0; N, 5.5; S, 25.3%); ν_{max} (thin film/cm^{-1}) 2943, 2923 and 2824 (C–H), 1691 (C=O), 1643 (C=C); δ_H (250 MHz; $CDCl_3$) 2.39 (1H, d, *J* 14.8, 7-H$_{endo}$), 3.11 (1H, dd, *J* 14.8 and 8.1, 7-H$_{exo}$), 3.19–3.47 (6H, m, 4 × C*H*S(O) and C*H*$_2$CH=CH$_2$), 3.60 (1H, br d, *J* 8.1, 1-H), 3.82 (1H, d, *J* 4.9, 5-H), 5.12–5.26 (2H, m, CH=C*H*$_2$), 5.76–5.92 (1H, m, C*H*=CH$_2$), 6.11 (1H, dd, *J* 9.9 and 1.6, 3-H), 6.94 (1H, dd, *J* 9.9 and 4.9, 4-H); δ_C (63 MHz; $CDCl_3$) 40.3 (t), 40.5 (t), 45.2 (t), 51.3 (t), 67.9 (d), 69.3 (d), 70.9 (s), 117.8 (t), 127.5 (d), 134.5 (d), 147.0 (d), 198.5 (s); *m*/*z* (EI) 253 (M$^+$, 1%), 136 (95), 135 (100), 106 (13) 41(16); (Found: M$^+$, 253.0595. $C_{12}H_{15}NOS_2$ requires *m*/*z*, 253.0595).

The *7-regio-sulfide* **22** eluted second and was obtained as a yellow oil (153 mg, 81%). R_f 0.2 (20% EtOAc–pet ether); ν_{max} (thin film/cm^{-1}) 2943, 2928 and 2826 (C–H), 1687 (C=O), 1643 (C=C); δ_H (250 MHz; $CDCl_3$) 2.44 (1H, d, *J* 13.6, 6-H$_{endo}$), 2.93 (1H, dd, *J* 13.6 and 6.5, 6-H$_{exo}$), 3.10–3.48 (6H, m, 4 × C*H*S(O) and C*H*$_2$CH=CH$_2$), 3.68 (1H, br s, 1-H), 3.82 (1H, dd, *J* 6.5 and 5.0, 5-H), 5.13–5.24 (2H, m, CH=C*H*$_2$), 5.76–5.89 (1H, m, C*H*=CH$_2$), 6.03 (1H, dd, *J* 9.8 and 1.4, 3-H), 6.93 (1H, dd, *J* 9.8 and 5.0, 4-H); δ_C (63 MHz; $CDCl_3$) 38.9 (t), 40.5 (t), 45.2 (t), 52.1 (t), 58.0 (d), 65.3 (s), 83.8 (d), 118.1 (t), 127.6 (d), 134.5 (d), 148.4 (d), 195.4 (s); *m*/*z* (EI) 136 (M–C$_4$H$_5$S$_2$, 100%), 135 (96), 106 (29), 41(86); No M$^+$.

(1*S*, 5*S*)-[Spiro-(1′,3′-dithiolane)-2′-6]-8-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one (23) and (1*S*, 5*S*)-[spiro-(1′,3′-dithiolane)-2′-7]-8-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one (24). Cycloadducts **17** and **18** were reduced to give two bis-sulfides **23** and **24** using an analogous procedure to that used for the reduction of **15** and **16**. The resultant residue was purified by flash chromatography on silica (25% EtOAc–pet ether).

The *6-regio-sulfide* **23** was isolated first as a yellow solid (1.5 g, 71%). R_f 0.3 (25% EtOAc–pet ether), mp 92–93 °C; ν_{max} (thin film)/cm^{-1} 2945 and 2800 (C–H), 1682 (C=O), 1437 (C=C); δ_H (250 MHz; $CDCl_3$) 2.38 (1H, dd, *J* 14.7 and 0.9, 7-H$_{endo}$), 2.51 (3H, s, C*H*$_3$), 3.09 (1H, dd, *J* 14.7 and 8.1, 7-H$_{exo}$), 3.17–3.48 (4H, m, 4 × C*H*S), 3.51 (1H, ddt, *J* 8.1, 1.5 and 0.9, 1-H), 3.71 (1H, d, *J* 4.8, 5-H), 6.09 (1H, dd, *J* 9.8 and 1.5, 3-H), 6.92 (1H, dd, *J* 9.8 and 4.8, 4-H); δ_C (63 MHz; $CDCl_3$) 35.0 (q), 40.3 (t), 40.6 (t), 45.5 (t), 69.5 (d), 71.2 (s), 72.0 (d), 127.0 (d), 146.6, (d), 198.8 (s); *m*/*z* (EI) 227 (M$^+$, 13%), 214 (11), 171(5), 110 (100), 81(41); (Found: M$^+$, 227.0446. $C_{10}H_{13}NOS_2$ requires *m*/*z*, 227.0439).

The *7-regio-sulfide* **24** was isolated second as a yellow solid (539 mg, 58%). R_f 0.1 (25% EtOAc–pet ether), mp 126–128 °C; ν_{max} (thin film)/cm^{-1} 3028, 2970, 2930, 2885 and 2852 (C–H), 1683 (C=O), 1602 (C=C); δ_H (250 MHz; $CDCl_3$) 2.42 (1H, d, *J* 13.7, 6-H$_{endo}$), 2.50 (3H, s, C*H*$_3$), 2.92 (1H, dd, *J* 13.7 and 6.1, 6-H$_{exo}$), 3.05–3.45 (4H, m, 4 × C*H*S), 3.52 (1H, br s, 1-H), 3.71 (1H, dd, *J* 6.1 and 5.2, 5-H), 5.99 (1H, dd, *J* 9.8 and 1.6, 3-H), 6.87 (1H, dd, *J* 9.8 and 5.2, 4-H); δ_C (63 MHz; $CDCl_3$) 36.3 (q), 38.9 (t), 41.0 (t), 46.0 (t), 60.0 (d), 65.5 (s), 85.9 (d), 127.2 (d), 148.0 (d), 195.6 (s); *m*/*z* (EI) 227 (M$^+$, 17%), 110 (100), 81 (32); (Found: M$^+$, 227.0438. $C_{10}H_{13}NOS_2$ requires *m*/*z*, 227.0439).

(1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′-6]-8-(4-methoxybenzyl)-8-azabicyclo[3.2.1]octan-2-one (25) and (1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′-7]-8-(4-methoxybenzyl)-8-azabicyclo[3.2.1]-octan-2-one (26). A 2.3 : 1 mixture of regioisomers **13** and **14** (1.3 g, 3.5 mmol) was dissolved in dry, de-oxygenated toluene (84 ml) under an inert atmosphere. Distilled water (84 µl), which had been degassed by bubbling argon for 20 minutes in a sonicator, was added, followed by triphenylphosphine copper(I) hydride hexamer (2.4 g, 1.2 mmol). The progress of the reaction could not be followed using TLC and was therefore monitored using ^{1}H NMR. After 18 hours at room temperature the reaction mixture was opened to the atmosphere and stirred for 2 hours to precipitate the copper salts. These were removed by filtration through Celite, which was further washed with toluene (100 ml). The solvent was removed under reduced pressure and the residue purified by flash chromatography (silica gel, 20% acetone–EtOAc).

The *ketone* **26** eluted first and was obtained as white solid (290 mg, 74%). R_f 0.3 (10% acetone–EtOAc), mp 165–167 °C; ν_{max} (thin film)/cm^{-1}) 2937 and 2836 (C–H), 1714 (C=O), 1612, 1586 and 1513 (Ar); δ_H (400 MHz; $CDCl_3$) 1.86–1.94 (1H, m, 4-H$_a$), 2.15 (1H, dd, *J* 15.2 and 7.2, 6-H$_{exo}$), 2.38–2.47 (1H, m, 4-H$_b$), 2.57–2.60 (2H, m, 3-H), 2.65 (1H, d, *J* 15.2, 6-H$_{endo}$), 3.45 (1H, td, *J* 14.0 and 4.4, C*H*S(O)), 3.53 (1H, m, C*H*S(O)), 3.55–3.58 (1H, m, C*H*S(O)), 3.61–3.65 (1H, m, 5-H), 3.78 (3H, s, OC*H*$_3$), 3.78–3.87 (4-H, m, 1-H, C*H*$_2$Ar and C*H*S(O)), 6.82–6.88 (2H, m, Ar–H), 7.21–7.32 (2H, m, Ar–H); δ_C (63 MHz; $CDCl_3$) 28.0 (t), 29.2 (t), 35.1 (t), 48.6 (t), 51.6 (t), 51.7 (t), 55.3 (d), 55.5 (d), 68.3 (q), 95.8 (s), 113.9 (d), 128.4 (s), 129.7 (d), 159.2 (s), 204.9 (s); *m*/*z* (EI) 367 (M$^+$, 26%), 350 (88), 339 (50), 322 (43), 311 (13), 121 (100); (Found: M$^+$ 367.09113. $C_{17}H_{21}NO_4S_2$ requires *m*/*z*, 367.09112).

The *ketone* **25** eluted second and was obtained as a white solid (646 mg, 72%). R_f 0.2 (10% acetone–EtOAc), mp 172–174 °C; ν_{max} (thin film)/cm^{-1} 2933 and 2834 (C–H), 1719 (C=O), 1611, 1585 and 1512 (Ar), 1036 (S=O); δ_H (400 MHz; $CDCl_3$) 1.98 (1H, dd, *J* 15.6 and 7.5, 7-H$_{exo}$), 2.34–2.50 (2H, m, 3-H$_a$ and 4-H$_a$), 2.58–2.70 (2H, m, 3-H$_b$ and 4-H$_b$), 2.75 (1H, d, *J* 15.6, 7-H$_{endo}$), 3.43–3.60 (4H, m, 1-H and 3 × C*H*S(O)), 3.78 (3H, s, OC*H*$_3$), 3.79 (1H, d, *J* 13.1, C*H*Ar), 3.84 (1H, d, *J* 13.1, C*H*Ar), 3.90 (1H br d, *J* 3.1, 5-H), 3.88–4.05 (1H, m, C*H*S(O)), 6.83–6.86 (2H, m, Ar–H), 7.21–7.25 (2H, m, Ar–H); δ_C (100 MHz; $CDCl_3$) 26.0 (t), 27.9 (t), 33.5 (t), 48.1 (t), 51.3 (t), 51.7 (t), 55.4 (q), 56.2 (d), 66.9 (d), 96.2 (s), 113.9 (d), 128.4 (s), 129.7 (d), 159.1 (s), 208.0 (s); *m*/*z* (EI) 367 (M$^+$, 6%), 350 (13), 322 (7), 311 (22), 121 (100); (Found: M$^+$ 367.09110. $C_{17}H_{21}NO_4S_2$ requires *m*/*z*, 367.09112).

(1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′,6]-8-benzyl-1-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one (30). *Cycloadduct* **30** was synthesised in an analogous fashion to **11** and **12**, although the reaction was left for only 5 hours. After purification by flash chromatography on silica (50% acetone–EtOAc) a mixture of *cycloadducts* was isolated, which contained the *title compound* as the single major product, in an 8 : 1 ratio as judged by ^{1}H NMR (29 mg, 25%). R_f (50% acetone–EtOAc) 0.5, mp 161–162 °C; ν_{max} (thin film)/cm^{-1} 3030, 2978 and 2850 (C–H), 1694 (C=O), 1603 (C=C), 1496 (Ar), 1044 (S=O); δ_H (250 MHz; $CDCl_3$) 1.36 (3H, br s C*H*$_3$), 1.83 (1H, d, *J* 15.7, 7-H$_{exo}$), 2.78 (1H, d, *J* 15.7, 7-H$_{endo}$), 3.38 (1H, td, *J* 13.7 and 4.6, C*H*S(O)), 3.47–3.60 (2H, m, 2 × C*H*S(O)), 3.52 (1H, d, *J* 13.4, C*H*Ph), 3.80–3.95 (1H, m, C*H*S(O)), 3.88 (1H, d, *J* 13.4, C*H*Ph), 4.07 (1H, d, *J* 4.9, 5-H), 6.36 (1H, d, *J* 9.6, 3-H), 6.89 (1H, dd, *J* 9.6 and 4.9, 4-H), 7.19–7.37 (5H, m, Ar–H); δ_C (63 MHz; $CDCl_3$) 18.0 (q), 34.5 (t), 48.2 (t), 48.9 (t), 51.9 (t), 56.8

(d), 70.2 (s), 97.9 (s), 127.7 (d), 128.3 (d), 128.5 (d), 130.8 (d), 137.2 (s), 143.0 (d), 198.1 (s); *m*/*z* (EI) 349 (M^+, 20%), 332 (11), 224 (77), 91 (100); (Found: M^+, 349.0802. $C_{17}H_{19}NO_3S_2$ requires *m*/*z*, 349.0806).

(1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′,6]-8-benzyl-5-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one (35) and (1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′,7]-8-benzyl-5-methyl-8-azabicyclo[3.2.1]oct-3-en-2-one (36) and (1′*RS*, 3′*RS*, 1*SR*, 5*SR*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′,6]-8-benzyl-5-methyl-8-azabicyclo-[3.2.1]oct-3-en-2-one (39). *Cycloadducts* **35**, **36** and **39** were synthesised in an analogous fashion to **11** and **12**. Purification by flash chromatography on silica (acetone) gave a mixture of *cycloadducts*, which consisted of three products in a 5.5 : 4.4 : 1 ratio (**35** : **39** : **36**), as judged by ^{1}H NMR (77 mg, 33%). On standing in deuterated chloroform for one week **35** completely disappeared to leave a *mixture* of **39** and **36** (3.5 : 1 ratio). R_f (acetone) 0.4; ν_{max} (thin film)/cm^{-1} (mixture) 3030–2676 (C–H), 1685 (C=O), 1495, 1034 (S=O); peaks assigned to **35**: δ_H (250 MHz; $CDCl_3$) 1.67 (1H, dd, *J* 15.2 and 8.1), 1.75 (3H, s), 2.54 (1H, dd, *J* 15.2 and 0.9), 3.31–4.06 (6H, m, 1-H), 4.23 (1H, ddd, *J* 13.7, 12.8 and 5.8), 6.22 (1H, dd, *J* 9.8 and 1.8), 6.73 (1H, d, *J* 9.8), 7.19–7.35 (5H, m); peaks assigned to **36**: δ_H (250 MHz; $CDCl_3$) 1.47 (3H, s), 2.11 (1H, d, *J* 14.3), 2.93 (1H, d, *J* 14.3), 3.26–4.12 (7H, m, 1-H), 6.23 (1H, dd, *J* 9.8 and 1.2), 6.93 (1H, d, *J* 9.8), 7.19–7.35 (5H, m,); peaks assigned to **39**: δ_H (250 MHz; $CDCl_3$) 1.54 (1H, d, *J* 15.0), 1.63 (3H, s), 3.14 (1H, dd, *J* 15.0 and 8.6), 3.26–3.48 (1H, m), 3.48 (1H, d, *J* 13.7), 3.51–3.68 (3H, m, 1-H), 3.87–4.07 (1H, m), 3.93 (1H, d, *J* 13.7), 6.27 (1H, dd, *J* 9.8 and 1.8), 7.03 (1H, d, *J* 9.8), 7.19–7.35 (5H, m); δ_C (63 MHz; $CDCl_3$) (mixture **39** and **36**) 18.7 (q), 18.9 (q), 24.7 (t), 24.8 (t), 47.8 (t), 49.1 (t), 49.3 (t), 50.6 (t), 51.3 (t), 52.3 (t), 61.4 (s), 66.4 (d), 67.8 (d), 68.3 (s), 100.6 (2 × s), 126.9 (d), 127.6 (d), 128.6 (d), 128.7 (d), 129.2 (d), 129.6 (d), 129.7 (d), 132.7 (s), 135.9 (d), 136.9 (s), 148.9 (d), 153.2 (d), 197.6 (2 × s); ^{13}C NMR data was not obtained for **35** due to its thermodynamic instability; *m*/*z* (EI) (mixture) 349 (M^+, 15%), 332 (8), 224 (9), 150 (16), 108 (29), 101 (38), 91 (25), 86 (100), 58 (59); (Found: M^+, 349.0795. $C_{17}H_{19}NO_3S_2$ requires *m*/*z*, 349.0806).

1-Benzyl-3-hydroxy-2-methylpyridinium bromide (37). 2-Methyl-3-hydroxypyridine (0.5 g, 4.6 mmol) and benzyl bromide (0.6 ml, 4.6 mmol) were heated at 160 °C for 18 hours. The mixture was allowed to cool to room temperature and the resulting sticky solid recrystallised (acetone–ether) to give the *title compound* as a light brown solid (0.8 g, 65%). Mp 164–165 °C (acetone–ether). (Found: C, 55.3; H, 4.9; N, 5.0; Br, 28.4. $C_{13}H_{14}NOBr$ requires C, 55.7; H, 5.0; N, 5.0; Br, 28.5%); ν_{max} (KBr)/cm^{-1} 3447 (O–H), 3017 (C–H), 1623, 1584, 1560, 1528, 1507 and 1498 (Ar); δ_H (250 MHz; DMSO) 2.52 (3H, s, CH_3), 5.91 (2H, br s, CH_2), 7.16–7.24 (2H, m, Ar–H), 7.32–7.46 (3H, m, Ar–H), 7.86 (1H, dd, *J* 8.5 and 5.8, 5-H), 7.96 (1H, dd, *J* 8.5 and 0.9, 4-H), 8.64 (1H, dd, *J* 5.8 and 0.9, 6-H); δ_C (63 MHz; D_2O) 12.8 (q), 61.5 (t), 125.4 (d), 127.3 (d), 129.1 (d), 129.4 (d), 129.5 (d), 132.6 (s), 136.3 (d), 145.5 (s), 155.7 (s); *m*/*z* (EI) 199 ((M − 1)$^+$ 16%), 109 (71), 91 (100), 80 (68).

1-Benzyl-5-hydroxy-2-methylpyridinium bromide (38). Benzyl bromide (0.7 ml, 5.5 mmol) was added to a suspension of 5-hydroxy-2-methylpyridine (500 mg, 4.6 mmol) in toluene (5.0 ml). The mixture was heated at reflux for 16 hours, then evaporated to dryness. The crude residue was recrystallised (EtOH–ether) to give the *title compound* as white crystals (1.1 g, 82%). Mp 189–190 °C (EtOH–ether). (Found: C, 55.7; H, 5.2; N, 4.8; S, 28.5. $C_{13}H_{14}NOBr$ requires C, 55.7; H, 5.0; N, 5.0; Br, 28.5%); ν_{max} (KBr)/cm^{-1} 3445 (O–H), 2975 and 2946 (C–H), 1640, 1579, 1562, 1533, 1496; δ_H (250 MHz; DMSO) 2.61 (3H, s, CH_3), 5.85 (2H, s, CH_2), 7.28–7.32 (2H, m, Ar–H), 7.46–7.57 (3H, m, Ar–H), 7.90 (1H, d, *J* 8.9, 3-H), 8.01 (1H, dd, *J* 8.9 and 2.4, 4-H), 8.66 (1H, d, *J* 2.4, 6-H); δ_C (63 MHz; D_2O) 19.3 (q), 60.8 (t), 128.0 (d), 129.3 (d), 129.7 (d), 131.2 (d), 133.2 (d), 133.7 (s), 133.8 (d), 146.3 (s), 155.6 (s); *m*/*z* (CI) 200 (M^+, 18%), 110 (100), 91 (34), 80 (7); (Found: M^+, 200.1077. $C_{13}H_{14}NO$ requires *m*/*z*, 200.1075).

(1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[Spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′,7]-8-oxabicyclo[3.2.1]oct-3-en-2-one (42) and (1′*RS*, 3′*RS*, 1*RS*, 5*RS*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′,6]-8-oxabicyclo[3.2.1]oct-3-en-2-one (43) and (1′*RS*, 3′*RS*, 1*SR*, 5*SR*)-[spiro-(1′,3′-dithiolane 1′,3′-dioxide)-2′,6]-8-oxabicyclo-[3.2.1]oct-3-en-2-one (44). DIPEA (58 μl, 0.33 mmol) was added to a solution of acetoxypyrone **40** (52 mg, 0.33 mmol) and alkene **5** (50 mg, 0.33 mmol) in dry dichloromethane (0.7 ml), under nitrogen. After stirring for 18 hours the reaction mixture was purified by flash chromatography on silica (50% acetone–EtOAc). The remaining pyrone **40** and material resulting from its dimerisation were isolated (combined yield 29 mg, 56%), followed by a mixture of *cycloadducts* that consisted of three products in a 5.8 : 2.5 : 1 ratio (**43** : **44** : **42**) as judged by ^{1}H NMR (36 mg, 44%). R_f (50% acetone–EtOAc) 0.4; ν_{max} (thin film)/cm^{-1} (mixture) 2990 (C–H), 1693 (C=O), 1644 (C=C), 1030 (S=O); peaks assigned to **42**: δ_H (250 MHz; $CDCl_3$) 2.43 (1H, dd, *J* 14.0 and 6.7, 6-H$_{exo}$), 2.75 (1H, d, *J* 14.0, 6-H$_{endo}$), 3.30–4.19 (4H, m, 4 × C*H*S(O)), 5.01 (1H, br s, 1-H), 5.06 (1H, dd, *J* 6.7 and 4.6, 5-H), 6.17 (1H, dd, *J* 9.9 and 1.1, 3-H), 7.36 (1H, dd, *J* 9.9 and 4.6, 4-H); peaks assigned to **43**: δ_H (250 MHz; $CDCl_3$) 2.25 (1H, dd, *J* 15.3 and 8.2, 7-H$_{exo}$), 2.59 (1H, dd, *J* 15.3 and 1.4, 7-H$_{endo}$), 3.37–4.19 (4H, m, 4 × C*H*S(O)), 4.80 (1H, dt, *J* 8.2 and 1.4, 1-H), 5.27 (1H, d, *J* 4.9, 5-H), 6.27 (1H, dd, *J* 9.8 and 1.4, 3-H), 7.34 (1H, dd, *J* 9.8 and 4.9, 4-H); peaks assigned to **44**: δ_H (250 MHz; $CDCl_3$) 1.83 (1H, dd, *J* 14.8 and 1.4, 7-H$_{endo}$), 3.15 (1H, dd, *J* 14.8 and 8.7, 7-H$_{exo}$), 3.30–4.19 (4H, m, 4 × C*H*S(O)), 4.77 (1H, dt, *J* 8.7 and 1.4, 1-H), 5.02 (1H, d, *J* 4.6, 5-H), 6.22 (1H, dd, *J* 9.9 and 1.4, 3-H), 7.55 (1H, dd, *J* 9.9 and 4.6, 4-H); δ_C (63 MHz; $CDCl_3$) (mixture) 25.3 (t), 27.4 (t), 32.1 (t), 49.9 (t), 50.5 (t), 51.3 (t), 52.1 (2 × t), 52.5 (t), 72.0 (d), 76.6 (d), 77.2 (d), 80.5 (d), 81.8 (d), 82.6 (d), 99.5 (2 × s), 100.8 (s), 127.0 (d), 127.9 (d), 129.0 (d), 147.7 (d), 148.4 (d), 152.3 (d), 193.5 (2 × s), 194.2 (s); *m*/*z* (EI) (mixture) 246 (M^+, 84%), 182 (22), 121 (100), 108 (78), 97 (84); (Found: M^+, 246.0011. $C_9H_{10}O_4S_2$ requires *m*/*z*, 246.0020).

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References

1 (*a*) J. H. Rigby and F. C. Pigge, *J. Org. Chem.*, 1995, **60**, 7392–7393; (*b*) A. S. Hernández, A. Thaler, J. Castells and H. P. Rapoport, *J. Org. Chem.*, 1996, **61**, 314–323; (*c*) D. E. Justice and J. R. Malpass, *Tetrahedron*, 1996, **52**, 11977–11994; (*d*) H. M. L. Davies, J. L. Matasi, M. Hodges, N. J. S. Huby, C. Thornley, N. Kong and J. H. Houser, *J. Org. Chem.*, 1997, **62**, 1095–1105; (*e*) M. Majewski, R. Lazny and A. Ulaczyk, *Can. J. Chem.*, 1997, **75**, 754–761; (*f*) R. Lin, J. Castells and H. P. Rapoport, *J. Org. Chem.*, 1998, **63**, 4069–4078; (*g*) J. L. Lee, K. Lee and J. K. Cha, *J. Org. Chem.*, 2000, **65**, 4773–4775; (*h*) A. Hall, P. D. Bailey, D. C. Rees, G. M. Rosair and R. H. Wightman, *J. Chem. Soc., Perkin Trans. 1*, 2000, 329–243; (*i*) S. Y. Jonsson, C. M. G. Löfström and J.-E. Bäckvall, *J. Org. Chem.*, 2000, **65**, 8454–8457; (*j*) T. Katoh, K. Kakiya, T. Nakai, S. Nakamura, K. Nishide and M. Node, *Tetrahedron: Asymmetry*, 2002, **13**, 2351–2358.

2 A. R. Katritzky and N. Dennis, *Chem. Rev.*, 1989, **89**, 827–861.

3 (*a*) T. Takahashi, K. Kitano, T. Hagi, H. Nihonmatsu and T. Koizumi, *Chem. Lett.*, 1989, 597–598; (*b*) T. Takahashi, A. Fujii, J. Sugita, T. Hagi, K. Kitano, Y. Arai, T. Koizumi and M. Shiro, *Tetrahedron: Asymmetry*, 1991, **2**, 1379–1390.

4 V. C. Pham and J. L. Charlton, *J. Org. Chem.*, 1995, **60**, 8051–8055.
5 (*a*) G. L. Araldi, K. R. C. Prakash, C. George and A. P. Kozikowski, *Chem. Commun.*, 1997, 1875–1876; (*b*) K. R. C. Prakash, M. Trzcinska, K. M. Johnson and A. P. Kozikowski, *Bioorg. Med. Chem. Lett.*, 2000, **10**, 1443–1446.
6 (*a*) V. K. Aggarwal, J. Drabowicz, R. S. Grainger, Z. Gültekin, M. Lightowler and P. L. Spargo, *J. Org. Chem.*, 1995, **60**, 4962–4963; (*b*) V. K. Aggarwal, Z. Gültekin, R. S. Grainger, H. Adams and P. L. Spargo, *J. Chem. Soc., Perkin Trans. 1*, 1998, 2771–2781.
7 V. K. Aggarwal, R. S. Grainger, H. Adams and P. L. Spargo, *J. Org. Chem.*, 1998, **63**, 3481–3485.
8 For intramolecular nitrone cycloadditions of ketene dithioacetal bis-sulfoxides see: (*a*) V. K. Aggarwal, S. J. Roseblade, J. K. Barrell and R. Alexander, *Org. Lett*, 2002, **4**, 1227–1229; (*b*) V. K. Aggarwal, S. J. Roseblade and R. Alexander, *Org. Biomol. Chem.*, 2003, **1**, 684–691.
9 A. R. Katritzky and Y. Takeuchi, *J. Chem. Soc. C*, 1971, 874–877.
10 N. Dennis, B. Ibrahim and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2307–2327.
11 F. López, L. Castedo and J. L. Mascareñas, *Chem. Eur. J.*, 2002, **8**, 884–899 and references therein.
12 N. Dennis, I. Badreldin and A. R. Katritzky, *J. Chem. Soc., Perkin Trans. 1*, 1976, 2296–2306.
13 K. V. Gothelf and K. A. Jørgensen, *J. Org. Chem.*, 1994, **59**, 5687–5691.
14 M. Hamaguchi, H. Matsuura and T. Nagai, *J. Chem. Soc., Chem. Commun.*, 1982, 262–263.
15 J. B. Hendrickson and J. S. Farina, *J. Org. Chem.*, 1980, **45**, 3359–3361.
16 O. Achmatowicz, P. Bukowski, B. Szechner, Z. Zwierzchowska and A. Zamojski, *Tetrahedron*, 1971, **27**, 1973–1996.
17 R. Laliberté, G. Médawar and Y. Lefebvre, *J. Med. Chem.*, 1973, **16**, 1084–1089.
18 M. E. Jung, L. M. Zeng, T. S. Peng, H. Y. Zeng, Y. Le and J. Y. Su, *J. Org. Chem.*, 1992, **57**, 3528–3530.
19 S. L. Shapiro, K. Weinberg and L. Freedman, *J. Am. Chem. Soc.*, 1959, **81**, 5140–5145.
20 W. S. Mahoney, D. M. Brestensky and J. M. Stryker, *J. Am. Chem. Soc.*, 1988, **110**, 291–293.
21 J. Drabowicz and S. Oae, *Synthesis*, 1977, 404–405.