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ASYMMETRIC 1,3-DIPOLAR CYCLOADDITION OF CHIRAL SULPHINYLETHENES WITH 1-METHYL-3-OXIDO-PYRIDINIUM AND SOME NITRONES

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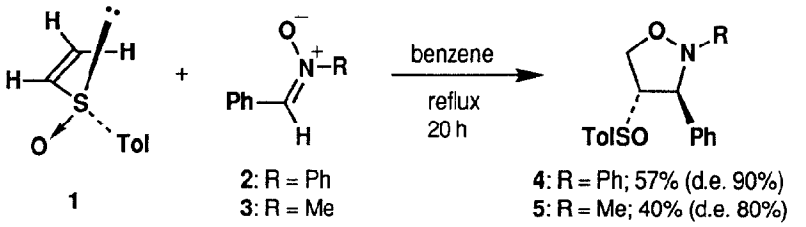
Abstract: 1,3-Dipolar cycloaddition of (*R*)-(+)-*p*-tolyl vinyl sulphoxide **1** with 1-methyl-3-oxidopyridinium **6** proceeded in a diastereoselective manner to afford the *exo* and *endo* cycloadducts **11a,b** and **12a** in 36%, 7% and 29% yield, respectively. The absolute configuration of **11a** was determined by its transformation to (1*S*)-(-)-2α-tropanol (-)-**15**. Attempts to the cycloaddition of the sulphinylethenes **17-19** with the pyridinium **6** were unsuccessful under several conditions. The reaction of the sulphoxide **20** with pyrroline 1-oxide **21** gave an inseparable mixture of products. The cycloaddition of **20** with 3,4,5,6-tetrahydropyridine 1-oxide **22** afforded a mixture of four adducts in ca. 90% yield. High level of diastereoselectivity was achieved for the *endo* cycloaddition affording the adduct **23** in 33% isolated yield. The absolute configuration of **23** was confirmed by a single-crystal X-ray diffraction study. The stereochemical course of the reaction was discussed based on the absolute configuration of the products.

Introduction

We have studied on the asymmetric Diels-Alder (D-A) reaction of the optically active sulphinylethenes.[1] High levels of reactivity and diastereofacial selectivity have been achieved in this reaction with the aid of molecular design of the sulphinylethenes. The reasons for the observed high diastereoselectivity have been elucidated as follows[2]: (1) the ground state conformation (*s-cis* or *s-trans*) of sulphinylethenes varies dramatically depending on the substituents at α or β position; (2) the most stable conformer dictates the product distributions (diastereoselectivity); (3) the dienes attack preferentially on the less hindered lone-pair side. In sharp contrast, there is little information on the 1,3-dipolar cycloaddition of chiral sulphinylethenes. (*R*)-(+)-*p*-Tolyl vinyl sulphoxide **1** has been demonstrated to react with 1,2-

diphenylnitrone **2** and 1-methyl-2-phenylnitrone **3** to give the (3*S*)-*trans*-4-isoxazolines **4** and **5** diastereoselectively (Scheme 1).[1a,3] The reaction mechanisms remain open because the chemical yield of the products was not high enough and the acyclic nitrones **2** and **3** alternate between *syn* and *anti* forms. In this research setting, we attempted an asymmetric 1,3-dipolar cycloaddition of chiral sulphinylethenes **1** and **17-20** with *cyclic* dipoles **6**, **21** and **22** (*vide infra*). The vinyl sulphoxide **1** is known to react preferentially from *s-trans* conformation in the D-A reaction, though it exhibits low diastereoselectivity.[1,2] As for the sulphoxides **17-20** which show high reactivity in the D-A reaction, *s-cis* conformation is found to be predominant without a Lewis acid.[1,2] We thus expected that the reaction of the vinyl sulphoxides **1** and **17-20** with the *cyclic* dipoles **6**, **21** and **22** might provide insight into the stereochemical course of the asymmetric 1,3-dipolar cycloaddition of the chiral sulphinylethenes. We report here the results along this line and discuss the steric course of the reaction in terms of the reactivity of the sulphinylethenes and the cyclic dipoles.

Scheme 1



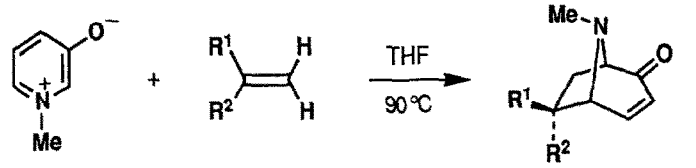
Results and Discussions

In the preliminary experiments, we undertook the reaction of 1-methyl-3-oxidopyridinium **6**[4] with phenyl vinyl sulphones **7** and **8**[5] to examine reactivity of **6** and regio- and stereoselectivity of the cycloaddition (Scheme 2). The reaction of the pyridinium **6** with the sulphones **7** and **8** proceeded with complete regio- and stereoselectivity in tetrahydrofuran (THF) at 90 °C for 13 h and 7 days, respectively, to afford single *exo* cycloadducts **9** and **10** in 84 and 97% yield.[6] *Exo* configuration of the sulphonyl group of the products **9** and **10** was determined by comparing their ^{1}H NMR spectra with that of 6β-cyano-8-azabicyclo[3.2.1]octo-3-en-2-one.[4] Being encouraged by the result that the reaction of the pyridinium **6** with the relatively inactive sulphone **8** gave the cycloadduct **10** exclusively in quantitative yield, we examined the diastereoselective cycloaddition of the chiral sulphoxide **1** using the pyridinium **6.**

Cycloaddition of (*R*)-(+)-*p*-tolyl vinyl sulphoxide **1**[7] and the pyridinium **6** proceeded at 90 °C for 4 days to give a mixture of both *exo* and *endo* cycloadducts (60:40) with complete regioselectivity (Scheme 3).[8] Separation of the reaction mixture on a column of silica gel gave the *exo* cycloadducts **11a,b** and the

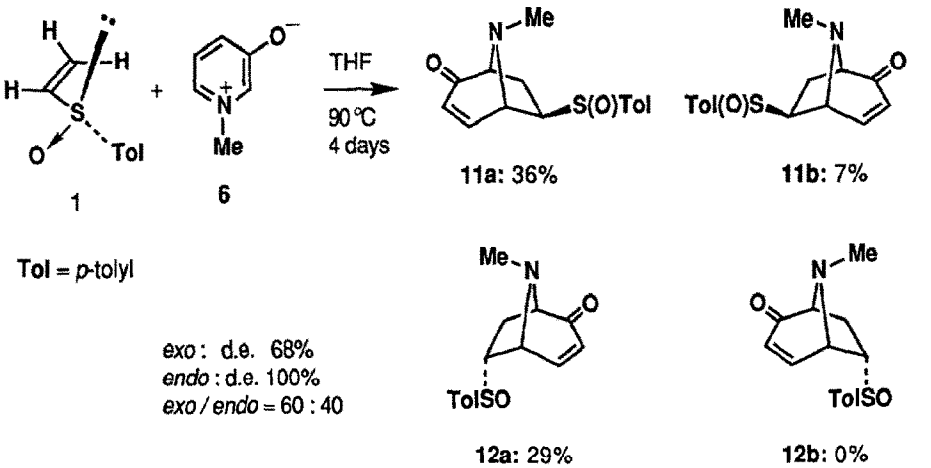
endo adduct **12a** in 36%, 7% and 29% yield, respectively (total yield 72%). The diastereoselectivities (d.e.'s) were 68% and 100% for the *exo* and *endo* cycloadducts **11** and **12**, respectively.

Scheme 2



6 **7**: $R^1 = SO_2Ph$, $R^2 = H$ **9**: $R^1 = SO_2Ph$, $R^2 = H$ (84%)
8: $R^1 = SO_2Ph$, $R^2 = F$ **10**: $R^1 = SO_2Ph$, $R^2 = F$ (97%)

Scheme 3



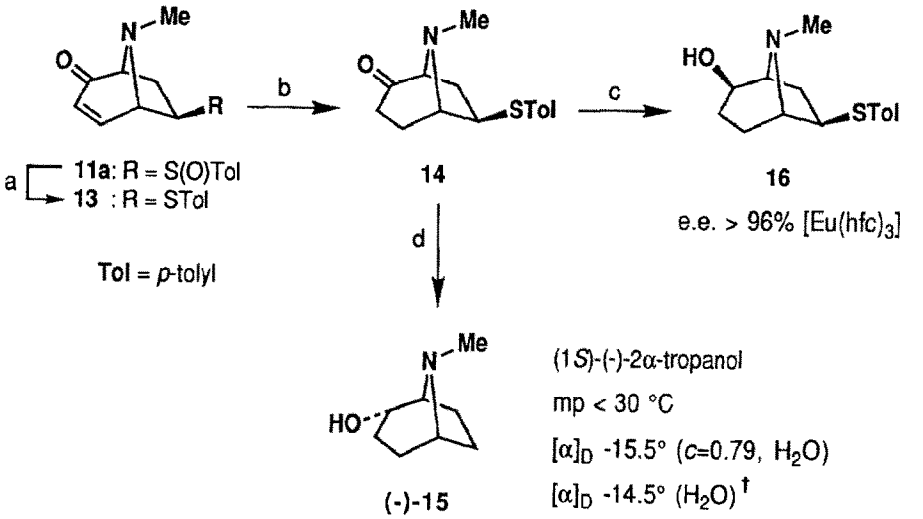
1 **6** **11a**: 36% **11b**: 7%

12a: 29% **12b**: 0%

The major *exo* cycloadduct **11a** was converted to (1*S*)-(-)-2α-tropanol (-)-**15** to determine the absolute configuration (Scheme 4). Thus, the sulphoxide **11a** was reduced with phosphorus tribromide to afford the sulphide **13**. Catalytic hydrogenation of **13** in the presence of palladium-black gave the saturated ketone **14**. The enantiomeric excess of **14** was measured after its transformation with sodium borohydride into the sulphenyl alcohol **16** and shown to be no less than 96% by 270 MHz ^{1}H NMR spectroscopy with a chiral shift reagent Eu(hfc)$_3$.[9] Desulphurisation of **14** with Raney-nickel (W-4) afforded (-)-**15**, mp < 30 °C, $[\alpha]_D$ -15.5 (*c* 0.79, H_2O), lit.[10] $[\alpha]_D$ -14.5 (H_2O), in 76% yield. The spectral data (IR and ^{1}H NMR) of the

synthetic specimen (-)-**15** were consistent with those of (+)-**15**.[11] In the result, the absolute configuration of the cycloadduct **11a** was determined as shown in Scheme 3.

Scheme 4



Reagents and conditions: a, PBr_3, DMF, 0 °C; b, H_2, Pd-C, AcOEt, 3 atm; c, $NaBH_4$, EtOH; d, Raney-Ni (W-4), EtOH, reflux.

† reference 10.

Having satisfactory chemical yield of the cycloadducts and the absolute configuration of the major adduct **11a** in hand, we proposed the stereochemical course of the 1,3-dipolar cycloaddition of the sulphinylethene **1** with the pyridinium **6** as shown in Scheme 5. The conformational equilibrium of the sulphinylethene **1** is imposed to *s-trans* resulting in the preferential *exo* attack of a pyridinium on the less hindered lone-pair side to give the major *exo* cycloadduct **11a**. The minor *exo* cycloadduct **11b** may be derived from the minor *s-cis* conformation. Similar to the *exo* cycloadduct **11a**, the *endo* diastreoisomer **12a** may be formed from the *s-trans* conformer. Accordingly, the absolute configurations of **11b** and **12a** were deduced as shown in Scheme 3.

Next, we undertook the cycloaddition of more reactive sulphinylethenes **17**-**19**[12,13] with the pyridinium **6** (Figure 1). However, any expected products were not obtained under several reaction conditions (temperature, time, solvents, etc.). Small amounts of the desulphenylated cycloadducts and some unidentified compounds, which were derived from the sulphinylethenes, were detected in the reaction

Scheme 5

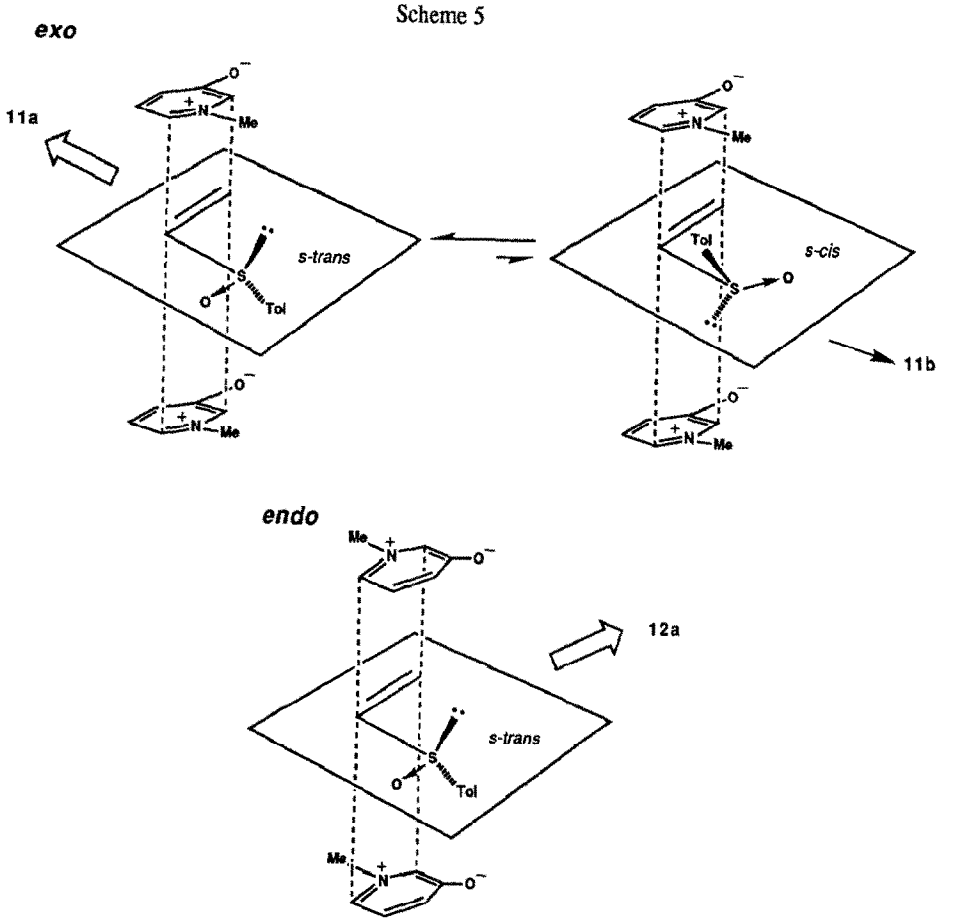
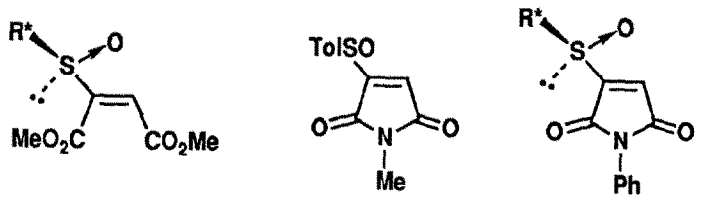
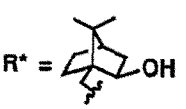


Figure 1



17 18 19

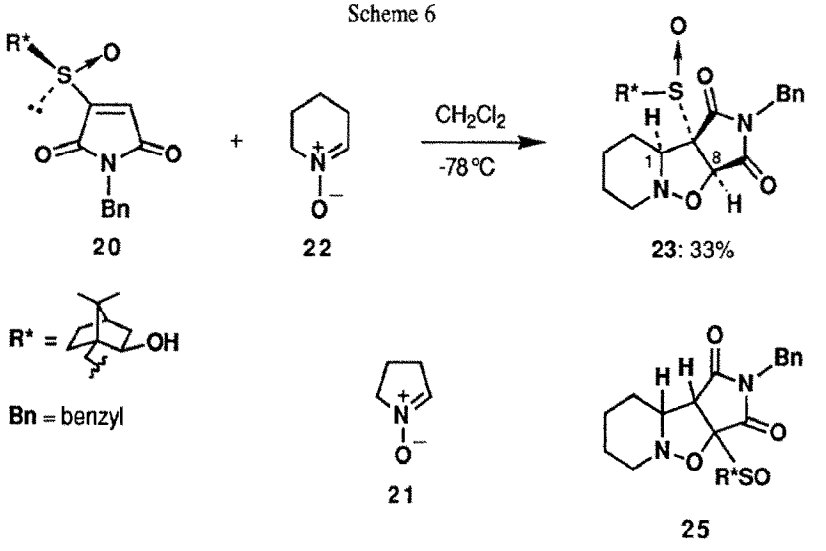


Tol = *p*-tolyl

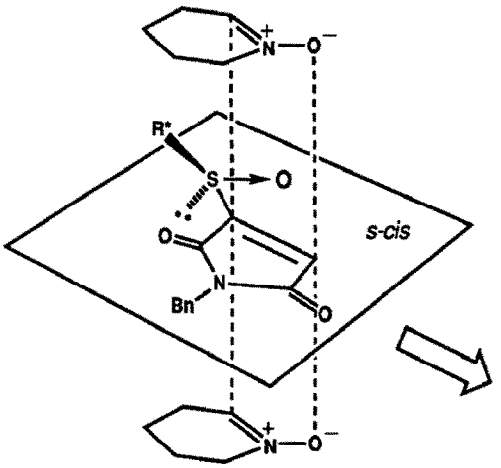
mixture. We considered that the sulphinylethenes and/or the cycloadducts decomposed under the reaction conditions.

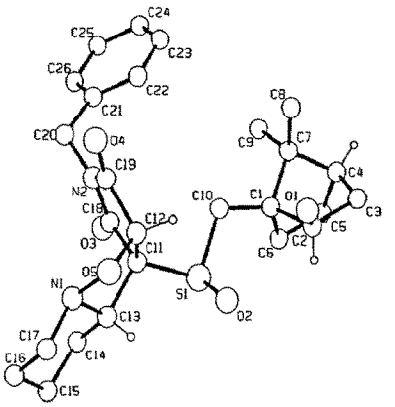
Then, we examined the cycloaddition of one of the most reactive dipolarophiles **20**[13] with more reactive 1,3-dipoles, the cyclic nitrones **21**[14] and **22**[14] at low temperature (Scheme 6). The reaction of the sulphinylethene **20** with pyrroline 1-oxide **21** in CH_2Cl_2 at -20 °C gave an inseparable mixture of products. Cycloaddition of the sulphoxide **20** and 3,4,5,6-tetrahydropyridine 1-oxide **22** proceeded in CH_2Cl_2 at -78 °C to afford four products (**23**, **24**, **25**, and **26**) in a ratio of 64:20:10:6 (by ^1H NMR spectrum and HPLC) in ca. 90% yield. The major adduct **23** was isolated in pure form by crystallisation of the reaction mixture in 33% yield. The absolute configuration of **23** was determined as depicted in Scheme 6 by a single-crystal X-ray diffraction study (Scheme 7). It was very hard to separate the adducts **24**-**26** even with the aid of HPLC. Among them, however, only a trace amount of the adduct **25** was isolated and assigned as the regioisomer of **23** by comparing its spectral data with those of **23**.[15] A careful examination of the ^1H NMR spectrum of the crude reaction mixture (4.9-5.3 ppm region corresponding to the singlet H-8 of diastereomers of **23**) indicated the presence of diastereomers other than **23** in no more than 5%, suggesting the highly diastereoselective formation of the *endo* cycloadduct **23**. From the absolute configuration of the adduct **23**, the steric course for the formation of **23** was suggested as follows: by analogy with the asymmetric D-A reaction,[1] the conformational equilibrium of the sulphinylethene **20** may be imposed to *s-cis* resulting in preferential *endo* attack of the nitrone **22** on the less hindered lone-pair side to give the *endo* adduct **23** (Scheme 7).

Scheme 6

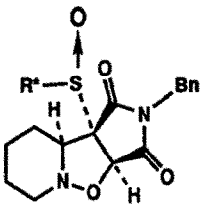


Scheme 7





Perspective structure of **23**



23

In conclusion, satisfactory chemical yield and diastereoselectivity were achieved in this 1,3-dipolar cycloaddition when the reactivities of both dipolarophile and dipole were matched each other: both low (such as **1** and **6**) or high (such as **20** and **22**). We isolated the major cycloadducts **11a** and **23**, respectively, and determined their absolute configurations. Similar to the D-A reaction, the steric course of this reaction may most likely affected by the ground state conformations. The most stable conformers of **1** (*s-trans*) and **20** (*s-cis*) in this reaction were consistent with those in the D-A reaction, respectively. The obseved difference of the diastereoselectivity in each D-A reaction[1] and 1,3-dipolar cycloaddition might be a reflection of the inherent dipolarophilic-reactivities of both *s-trans* and *s-cis* conformers, of which estimation should be a subject of future investigation. Moreover, an exploitation of matched sulphinylethene-dipole pair is now in progress successfully and an application to the chiral synthesis of *N*-heterocycles will be reported elsewhere.

Acknowledgement

We are grateful to Drs. M. R. Bell and R. L. Clarke of the Sterling-Winthrop Research Institute, Rensseler, New York, 12144, for supply of (1*R*)-2α-tropanyl benzilate hydrochloride.

Experimental Section

Melting points were measured with a Yanaco micro melting point apparatus and are uncorrected. Microanalyses were performed by Microanalysis Centre of Toyama Medical & Pharmaceutical University. Spectroscopic measurements were carried out with the following instruments: IR, JASCO A-102 and Perkin-Elmer 1600 Series FTIR; ^{1}H NMR, JEOL JNM-GX 270 (270 MHz) for solutions in $CDCl_3$ with Me_4Si as internal standard unless otherwise stated; mass (MS) and high resolution mass spectra (HRMS), JEOL JMS D-200; optical rotations, JASCO DIP-140 digital polarimeter. *J* values are given in Hz. Column chromatography and preparative TLC (PLC) were performed on Kieselgel 60 (Merck, Art. 9385 and Art. 7748, respectively).

1,3-Dipolar cycloaddition of phenyl vinyl sulphone (7) with 1-methyl-3-oxidopyridinium (6).

Phenyl vinyl sulphone **7** (3.042 g, 18.1 mmol) and the pyridinium **6**[4] (2.56 g, 23.5 mmol) were dissolved into dry THF (20 ml). The reaction mixture was heated in a sealed tube at 90 °C for 13 h. After evaporation of the solvent, the residue was purified by column chromatography [hexane-AcOEt (1:1)] followed by recrystallisation from hexane-AcOEt to afford *N*-methyl-6β-(phenylsulphonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one **9** (4.21 g, 84%) as yellow needles; mp 124-127 °C; IR (KBr) 1675, 1595, 1290 cm^{-1}; ^{1}H NMR δ 1.92 (dd, *J* 9, 14, 1H), 2.38 (s, 3H), 2.77 (ddd, *J* 4, 8, 14, 1H), 3.54 (br d, *J* 8, 1H), 3.57 (dd, *J* 4, 9, 1H), 4.23 (br d *J* 5, 1H), 6.06 (dd, *J* 2, 10, 1H), 6.93 (dd, *J* 5, 10, 1H), 7.58 (m, 2H), 7.67 (m, 1H), 7.92 (m, 2H); MS *m/z* 277 (M^+), 138 (M^+-SO_2Ph); Anal. calcd for $C_{14}H_{15}NO_3S$: C 60.65, H 5.42, N 5.05 %. Found: C 60.82, H 5.42, N 4.89 %.

1,3-Dipolar cycloaddition of 1-(benzenesulphonyl)-1-fluoroethene (8) with 1-methyl-3-oxidopyridinium (6).

A similar procedure to above was followed with the fluoro vinyl sulphone **8**[5] (60.7 mg, 0.33 mmol) and the pyridinium **6** (0.14 g, 1.3 mmol) in dry THF (3 ml) at 90 °C for 7 days. *N*-Methyl-6α-fluoro-6β-(phenylsulphonyl)-8-azabicyclo[3.2.1]oct-3-en-2-one **10** (92 mg, 97%) was obtained as yellow needles after PLC [hexane-AcOEt (2:1)] and recrystallisation from hexane-AcOEt; mp 118-121 °C; IR (KBr) 1685, 1325 cm^{-1}; ^{1}H NMR δ 1.84 (dd, *J* 15, 24, 1H), 2.50 (s, 3H), 3.21 (ddd, *J* 8, 15, 15, 1H), 3.60 (br d, *J* 8, 1H), 4.43 (br d, *J* 5, 1H), 6.26 (dt, *J* 1.5, 10, 1H), 6.74 (ddd, *J* 1.5, 5, 10, 1H), 7.63 (m, 2H), 7.75 (m, 1H), 8.00 (m, 2H); MS *m/z* 295 (M^+), 155 (M^+-SO_2Ph); Anal. calcd for $C_{14}H_{14}FNO_3S$: C 56.95, H 4.75, N 4.7 5%. Found: C 56.99, H 4.86, N 4.91 %.

1,3-Dipolar cycloaddition of (+)-(*R*)-*p*-tolyl vinyl sulphoxide (1) with 1-methyl-3-oxidopyridinium (6).

A similar procedure to above was followed with the sulphoxide **1**[7] (200 mg, 1.20 mmol) and the pyridinium **6** (384 mg, 3.02 mmol) in dry THF (5 ml) at 90 °C for 4 days. Separation of the residue by PLC (AcOEt) gave *N*-methyl-(1*S*,5*S*,6*R*,R_S)-6-(*p*-tolylsulphinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one **11a** (118 mg, 36%), *N*-methyl-(1*R*,5*R*,6*S*,R_S)-6-(*p*-tolylsulphinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one **11b** (24 mg, 7%) and

N-methyl-(1*R*,5*R*,6*R*,R_S)-6-(*p*-tolylsulphinyl)-8-azabicyclo[3.2.1]oct-3-en-2-one **12a** (96 mg, 29%). The *exo* adducts **11a,b** were recrystallised from hexane-AcOEt to afford yellow needles, respectively.

For **11a**: mp 121-122 °C; $[\alpha]_D^{23}$ -184.7 (*c* 0.86, $CHCl_3$); IR (KBr) 1680, 1590, 1040 cm^{-1}; ^1H NMR δ 1.55 (dd, *J* 8.5, 14.7, 1H), 2.09 (ddd, *J* 3.4, 7.8, 14.7, 1H), 2.42 (s, 3H), 2.54 (s, 3H), 3.25 (dd, *J* 3.4, 8.5, 1H), 3.58 (d, *J* 7.9, 1H), 4.35 (d, *J* 4.9, 1H), 6.09 (dd, *J* 1.5, 9.8, 1H), 6.98 (dd, *J* 4.9, 9.8, 1H), 7.33 (d, *J* 8.1, 2H), 7.65 (d, *J* 8.1, 1H); MS *m/z* 275 (M^+); Anal. calcd for $C_{15}H_{17}NO_2S$: C 65.44, H 6.22, N 5.09 %. Found: C 65.80, H 6.55, N 4.88 %.

For **11b**: mp 132-134 °C; $[\alpha]_D^{23}$ +386.9 (*c* 0.65, $CHCl_3$); IR (KBr) 1690, 1035 cm^{-1}; ^1H NMR δ 1.84 (dd, *J* 8.8, 14.8, 1H), 2.43 (s, 3H), 2.45 (s, 3H), 3.01 (ddd, *J* 3.0, 7.9, 14.8, 1H), 3.16 (dd, *J* 3.0, 8.8, 1H), 3.64 (d, *J* 7.9, 1H), 3.70 (d, *J* 5.0, 1H), 6.02 (dd, *J* 1.5, 10.0, 1H), 6.74 (dd, *J* 5.0, 10.0, 1H), 7.35 (d, *J* 8.3, 2H), 7.58 (d, *J* 8.3 2H); MS *m/z* 275 (M^+); Anal. calcd for $C_{15}H_{17}NO_2S$: C 65.44, H 6.22, N 5.09 %. Found: C 65.25, H 6.26, N 4.84 %.

For **12a**: oil; $[\alpha]_D^{23}$ +183.5 (*c* 1.04, $CHCl_3$); IR (neat) 1685, 1030 cm^{-1}; ^1H NMR δ 1.42 (dd, *J* 6.2, 14.3, 1H), 2.15 (ddd, *J* 7.4, 10.0, 14.3, 1H), 2.42 (s, 6H), 3.51 (d, *J* 7.4, 1H), 3.89 (ddd, *J* 5.9, 6.2, 10.0, 1H), 4.14 (dd, *J* 5.0, 5.9, 1H), 6.33 (dd, *J* 1.5, 10.0, 1H), 7.33 (d, *J* 8.0, 2H), 7.38 (dd, *J* 5.0, 10.0, 1H), 7.59 (d, *J* 8.0, 2H); MS *m/z* 275 (M^+); HRMS calcd for $C_{15}H_{17}NO_2S$ 275.0979. found 275.0953.

_N_-Methyl-(1*S*,5*S*,6*R*)-6-(*p*-tolylsulphenyl)-8-azabicyclo[3.2.1]oct-3-en-2-one (13).

Phosphorus tribromide (0.56 ml, 5.9 mmol) was added to a solution of the sulphoxide **11a** (272 mg, 0.989 mmol) in dry DMF (10 ml) under argon at 0 °C. After being stirred at 0 °C for 1 h, the solvent was removed. The residue was treated with cold, saturated aqueous $NaHCO_3$ at 0 °C and the pH was brought to 7. The aqueous layer was extracted with CH_2Cl_2 (4 x 20 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and the solvent was evaporated. The residue was purified by column chromatography [hexane-AcOEt (1:1)] and subsequent recrystallisation from ether-hexane to give the sulphide **13** (199 mg, 78%) as yellow needles; mp 59-60 °C; $[\alpha]_D^{23}$ -249.7 (*c* 0.71, $CHCl_3$); IR ($CHCl_3$) 1680 cm^{-1}; ^1H NMR δ 2.16 (dd, *J* 8.6, 14.2, 1H), 2.34 (ddd, *J* 3.7, 7.7, 14.2, 1H), 2.53 (s, 3H), 3.58-3.65 (m, 2H), 3.62 (dd, *J* 3.7, 8.6, 1H), 6.03 (dd, *J* 1.5, 9.8, 1H), 6.84 (dd, *J* 5.0, 9.8, 1H), 7.14 (d, *J* 7.8, 2H), 7.30 (d, *J* 7.8, 2H); MS *m/z* 259 (M^+); Anal. calcd for $C_{15}H_{17}NOS$: C 69.48, H 6.61, N 5.40 %. Found: C 69.56, H 6.45, N 5.35 %.

_N_-Methyl-(1*S*,5*S*,6*R*)-6-(*p*-tolylsulphenyl)-8-azabicyclo[3.2.1]octan-2-one (14).

A mixture of the unsaturated ketone **13** (512 mg, 1.98 mmol) and 5% Pd-C (500 mg) in AcOEt (25 ml) was hydrogenated (3.0 atm starting pressure of hydrogen gas) at room temperature for 1 h in a Parr hydrogenation apparatus. The catalyst was removed by filtration, washed with AcOEt and the filtrate was concentrated. Recrystallisation of the residue from AcOEt-hexane gave the saturated ketone **14** (370 mg, 72%) as yellow plates; mp 114-115 °C; $[\alpha]_D^{23}$ +47.0 (*c* 0.74, $CHCl_3$); IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR δ 1.8-1.9 (m, 1H), 2.1–2.5 (m, 5H), 2.33 (s, 3H), 2.55 (s, 3H), 3.31 (br s, 1H), 3.40 (d, *J* 7.1, 1H), 3.75 (dd, *J* 5.1, 8.5, 1H), 7.13 (d, *J* 8.0, 2H), 7.30 (d, *J* 8.0, 2H); MS *m/z* 261 (M^+); Anal. calcd for $C_{15}H_{19}NOS$: C 68.97, H 7.28, N 5.36 %. Found: C 69.03, H 7.39, N 5.26 %.

N-Methyl-(1S,2S,5R)-8-azabicyclo[3.2.1]octan-2-ol [(1S)-(-)-2α-tropanol] (-)-(15).

Raney Ni (W-4, 0.2 ml) was added to a solution of the sulphide **14** (88.2 mg, 0.34 mmol) in abs. EtOH (3 ml) and the mixture was refluxed for 1.5 h. The metal powder was filtered off and washed with EtOH-H_2O [8:2 (10 ml) + c. NH_4OH 1 drop]. The filtrate was concentrated and the residue was purified by PLC [$CHCl_3$-MeOH-c. NH_4OH (78:19:3)] to give the alcohol (-)-**15** (36.3 mg, 76%) as colourless needles; mp < 30 °C; $[\alpha]_D^{23}$ -15.5 (*c* 0.79, H_2O), {lit.[10] $[\alpha]_D$ -14.5 (H_2O)}; IR ($CHCl_3$) 3625, 3350 cm^{-1}; ^1H NMR δ 1.1-1.25 (m, 1H), 1.25-1.55 (m, 2H), 1.60-1.95 (m, 4H), 1.95-2.10 (m, 1H), 2.27 (s, 3H), 3.04 (m, 2H), 3.28 (br s, 1H), 3.84 (ddd, *J* 3.7, 5.3, 10.4, 1H); MS *m/z* 141 (M^+); HRMS calcd for $C_8H_{15}NO$ 141.1153. found 141.1184. Hydrochloride; mp 245 °C (decomp.); $[\alpha]_D^{23}$ -15.3 (*c* 0.47, H_2O); Anal. calcd for $C_8H_{15}NO$•HCl: C 54.08, H 9.08, N 7.88 %. Found: C 54.24, H 9.19, N 7.92 %.

N-Methyl-(1S,2R,5S,6R)-6-(*p*-tolylsulphenyl)-8-azabicyclo[3.2.1]octan-2-ol (16).

$NaBH_4$ (14 mg, 0.37 mmol) was added portionwise to a mixture of the ketone **14** (49.3 mg, 0.19 mmol) in EtOH (2 ml) and the mixture was stirred at room temperature for 0.5 h. H_2O (0.9 ml) was added to the reaction mixture and the aqueous layer was extracted with $CHCl_3$ (4 x 5 ml). The combined extracts were washed with brine, dried ($MgSO_4$) and evaporated. Purification of the residue by PLC [AcOEt-MeOH (2:3)] followed by recrystallisation from hexane gave the 2β-alcohol **16** (28.9 mg, 58%) as colourless needles; mp 33-34 °C; $[\alpha]_D^{23}$ +85.7 (*c* 0.77, $CHCl_3$); IR ($CHCl_3$) 3340 cm^{-1}; ^1H NMR δ 1.35-1.55 (m, 3H), 1.85-2.00 (m, 1H), 2.11 (dd, *J* 8.2, 13.8, 1H), 2.21 (dd, *J* 5.8, 13.8, 1H), 2.33 (s, 3H), 2.58 (s, 3H), 3.22 (br s, 1H), 3.27 (br, 1H), 3.54 (m, 1H), 3.58 (dd, *J* 5.8, 8.2, 1H), 7.11 (d, *J* 8.0, 2H), 7.24 (d, *J* 8.0, 2H); MS *m/z* 263 (M^+); HRMS calcd for $C_{15}H_{21}NOS$ 263.1343. found 263.1333.

The 2α-alcohol, *N*-methyl-(1*S*,2*S*,5*S*,6*R*)-6-(*p*-tolylsulphenyl)-8-azabicyclo[3.2.1]octan-2-ol, (15.1 mg, 30%) was also obtained as a minor product: oil; IR (neat) 3350 cm^{-1}; ^1H NMR δ 1.25-1.82 (m, 4H), 2.00 (m, 1H), 2.32 (s, 3H), 2.45 (dd, *J* 8.8, 14.2, 1H), 2.62 (s, 3H), 3.17 (br s, 1H), 3.25 (m, 1H), 3.48 (dd, *J* 5.1, 8.8, 1H), 3.90 (m, 1H), 7.11 (d, *J* 7.8, 2H), 7.25 (d, *J* 7.8, 2H); MS *m/z* 263 (M^+); HRMS calcd for $C_{15}H_{21}NOS$ 263.1343. found 263.1376.

1,3-Dipolar cycloaddition of (R_S)-N-benzyl-3-({(1S,2R,4R)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl}methylsulphinyl)maleimide (20) with 3,4,5,6-tetrahydropyridine 1-oxide (22).

A solution of 3,4,5,6-tetrahydropyridine 1-oxide **22**[14] (50 mg, 0.50 mmol) in dry CH_2Cl_2 (4 ml) was added to a solution of the sulphoxide **20**[13] (50 mg, 0.13 mmol) in dry CH_2Cl_2 (4 ml) under argon at -78 °C within 5 min. After evaporation of the solvent, the crude reaction mixture was passed through a short column of silica gel [hexane-AcOEt (4:1)] to give the residue (60 mg), which contained four products **23**, **24**, **25** and **26** in a ratio of 64:20:10:6 (by ^1H NMR spectrum and HPLC). (1*S*,8*S*,9*S*,R_S)-11-Benzyl-9-({(1*S*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl}methylsulphinyl)-6,11-diaza-7-oxatricyclo-[4.3.1]dodecan-10,12-dione **23** (21 mg, 33%) was obtained as colourless needles by recrystallisation of the residue from hexane-AcOEt; mp 198-200 °C; $[\alpha]_D^{26}$ +36.6 (*c* 1.00, $CHCl_3$); IR (KBr) 3515, 1779, 1710,

1038 cm^{-1}; ^1H NMR δ 0.53 (s, 3H), 0.88 (s, 3H), 1.1-2.3 (m, 13H), 2.06 (d, *J* 12.4, 1H), 2.60 (br d, *J* 9.4, 1H), 2.75 (dd, *J* 2.5, 11.5, 1H), 3.16 (d, *J* 12.4, 1H), 3.30 (br, 1H), 3.54 (br d, *J* 9.3, 1H), 3.95 (m, 1H), 4.72 (d, *J* 14.2, 1H), 4.79 (d, *J* 14.2, 1H), 5.13 (s, 1H), 7.2-7.4 (m, 5H); MS *m/z* 487 (M^++1); Anal. calcd for $C_{26}H_{34}N_2O_5S$: C 64.18, H 7.04, N 5.76 %. Found: C 63.89, H 6.95, N 5.48 %.

(*R*s)-11-Benzyl-8-({(1*S*,2*R*,4*R*)-2-hydroxy-7,7-dimethylbicyclo[2.2.1]heptan-1-yl}methylsulphinyl)-6,11-diaza-7-oxatricyclo[4.3.1]dodecan-10,12-dione **25** (2 mg, 1%) was isolated as colourless needles by crystallisation of the mother liquor of **23** from hexane-AcOEt in a 150 mg-scale experiment; mp 187-189 °C; IR (KBr) 3470, 1777, 1709, 1040 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.68 (s, 3H), 0.97 (s, 3H), 1.1-2.3 (m, 13H), 2.40 (d, *J* 12.9, 1H), 2.61 (m, 2H), 3.32 (d, *J* 3.4, 1H), 3.54 (br s, 1H), 3.59 (d, *J* 12.9, 1H), 3.83 (d, *J* 7.1, 1H), 3.94 (m, 1H), 4.72 (d, *J* 14.4, 1H), 4.80 (d, *J* 14.4, 1H), 7.2-7.4 (m, 5H); MS *m/z* 487 (M^++1).

X-Ray Structure Determination of Compound (23).

$C_{26}H_{34}N_2O_5S$, M, 486.62, monoclinic, space group $P2_1$, a = 6.408(2), b = 17.903(3), c = 11.000(2) Å, β = 103.35(2)°, V = 1227.9(6) $Å^3$, *Z* = 2, D_c = 1.316 g cm^{-3}, μ (Cu Kα) = 14.55 cm^{-1}, Cu Kα (λ = 1.54178 Å). Single crystals (needles) were prepared by recrystallisation from hexane-AcOEt. Intensity data were collected on a Rigaku AFC-5R diffractometer. The structure was solved by direct methods and refined by full-matrix least-squares method to $R = 0.043$ for 1654 reflections with $I > 3\sigma(I)$.

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