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## Facile Palladium Catalysed Functionalisation of 1,2-Isothiazoline-3-ones and the Highly Diastereoselective Diels-Alder Reactions of 4-vinyl-1,2-isothiazoline-3-one-1-oxides.

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Abstract: A rapid and convenient palladium catalysed method for the regioselective synthesis of a range of usefully functionalised, homochiral 4-substituted 1,2-isothiazoline-3-ones is reported. The totally diastereoselective Diels-Alder reactivity of semi-cyclic sulfoxide containing dienes, 4-vinyl-1,2-isothiazoline-3-one-1-oxides is discussed. © 1999 Elsevier Science Ltd. All rights reserved.

The use of heterocyclic systems as masked forms of organic functionality has long been a rich source of novel chemistry. During the course of work directed towards the use of chirality at sulphur to induce facial selectivity, we identified the 1,2-isothiazoline system 1 as an interesting and highly functionalised heterocyclic nucleus. Particularly attractive was the demonstrated ease of oxidation at sulphur to yield 1-(S)-oxides coupled with the known Diels-Alder reactivity of the 4,5 double bond.<sup>1,2</sup> When homochiral isothiazoline 1-S-oxides were used as dienophiles a high degree of diastereofacial selectivity was observed.<sup>2</sup> Our aims were to develop chemistry leading to homochiral dienes (2) and to establish the degree of diastereoselectivity present in the subsequent Diels-Alder reactions of these novel dienes. Reductive cleavage of the sulphur nitrogen bond<sup>2</sup> in the predicted Diels-Alder adduct 3 would lead to homochiral cyclohexene derivatives, (Scheme 1).



#### Scheme 1

There have been several reports concerning the preparation of simple N-substituted derivatives of the parent heterocycle  $1^3$  but few methods have been reported concerning the synthesis of more functionalised systems. Since our eventual requirement was for optically pure sulphoxide derivatives of these heterocycles, we chose to develop our chemistry on 2-(S)- $\alpha$ -methylbenzyl derivatives, a readily available source of chirality, as we felt the diastereomeric sulphoxides would be readily separable. We further reasoned that a rapid entry to 4-functionalised derivatives would be *via* Stille<sup>4</sup> type coupling onto the corresponding bromo-heterocycle.

In order to obtain large quantities of  $2-(S)-\alpha$ -methylbenzyl-4-bromo-1,2-isothiazoline-3-one (6) we streamlined the previously reported two step synthesis<sup>3</sup> and developed a one-pot procedure which gave 6 in 73% yield from the amide 4 as shown in Scheme 2.<sup>5</sup> The 2-ethyl derivative 7 was also prepared by this route.

Having developed a viable route to 4-bromo 1,2-isothiazoline-3-ones 6 and 7, we began to consider functionalisation at the 4-position. The bromides 6 and 7 were found to be excellent substrates for Stille<sup>4</sup> based functionalisation and underwent efficient palladium catalysed coupling to a range of stannanes as summarised in

Table 1.<sup>5</sup> The choice of a suitable catalyst is fundamental to the Stille reaction<sup>6-8</sup> (optimisation of the catalytic coupling conditions for synthesis of 8, 10 and 11 were reported previously)<sup>5</sup>.



#### Scheme 2

Entry	Product	Catalytic system	Catalyst mol. eq.	stannane mol. eq.	Temp / C <sup>a</sup>	Time /h.	Yield
1		[Pd(PPh3)4]	0.05	1.5	110	4	80
	9 R = Et	Pd(OAc) <sub>2</sub> + 2 PPh <sub>3</sub>	0.1	1.1	110	2	76
2		[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	0.1	1.1	110	4 <sup>6</sup>	69°
3		[Pd(PPh <sub>3</sub> ) <sub>4</sub> ]	0.1	1.2	110	4 <sup>6</sup>	69 <sup>d</sup>
4	Ph 12 NR	Pd(OAc) <sub>2</sub> + 2 PPh <sub>3</sub>	0.1	1.2	90	4	75
5	N 13 S <sup>NR</sup>	Pd(OAc) <sub>2</sub> + 2 PPh <sub>3</sub>	0.1°	1.2	110	24	69
6	O 14 S.NR	Pd(OAc) <sub>2</sub> + 2 PPh <sub>3</sub>	0.1	1.2 <sup>f</sup>	90	4	63 <sup>8</sup>

#### Table 1. Functionalised Isothiazolines

 $R = (S) -\alpha$ -Methylbenzyl, unless otherwise stated. \* Solvent = toluene. <sup>b</sup> Reagent added over 1 h. ° Purified using alumina chromatography. <sup>d</sup>Purified using silica gel chromatography. \* 2-Pyridyltributyltin was prepared according to the literature. <sup>9 f</sup> Tributyl stannanes used except for phenyltrimethyltin. \* 70% conversion, 90% yield.

#### **REACTIVITY OF 1,2-ISOTHIAZOLINE-3-ONE BASED 1,3-BUTADIENES**

Diels-Alder cycloadditions were attempted using the sulfide dienes 8, 9 and 10 respectively with a range of dienophiles. They were however in the main part unreactive under a range of reaction conditions, including activation with Lewis acids. (S)- $\alpha$ -Methylbenzyl-4-vinyl-1,2-isothiazoline-3-one (8) was unstable to Lewis acids or prolonged heating and decomposed under most cycloaddition conditions.

Having developed a route to the functionalised isothiazolines, preparation of the semicyclic sulfoxide containing dienes was investigated. Isolation of either diastereomeric sulfoxide containing diene species via oxidation of the (S)- $\alpha$ -methylbenzyl sulfide diene **8** proved unsuccessful, (Scheme 3).



Scheme 3

The next strategy was to synthesise the dienes via Stille coupling methodology utilising 4-brominated sulfoxide 16, (Scheme 4).



Scheme 4

#### **PREPARATION OF 1,2-ISOTHIAZOLINE-3-ONE-1-OXIDES**

To this end, oxidation of isothiazoline 6 with mCPBA formed two diastereoisomeric sulfoxides in the ratio 2.2:1 (Scheme 5). Waldner has reported X-ray data confirming the (S) chirality of the major isomer for the non-brominated system.<sup>2</sup> Therefore we reasoned that the absolute stereochemistry at sulphur of the major isomer was also (S).<sup>10</sup>



Oxidation of isothiazoline 7 using mCPBA gave the 4-bromo ethyl isothiazoline-1-oxide 18 (53% unoptimised) in racemic form, (Scheme 6).



#### UNEXPECTED DIMER FORMATION

Whereas isothiazoline 8 was unreactive as a Diels-Alder diene, coupling of the major diastereomeric derivative 16 with vinyltributyltin yielded a single product in 33% yield. Mass spectral- and NMR analysis indicated this to be dimer 19. Further analysis by NMR (ROESY) revealed that H5 is on one face of the cyclohexene ring and H9 and the vinyl substituent are on the opposite face indicating that the product is one of two possible *exo* diastereoisomers 19a or 19b. Unfortunately it was not possible to obtain crystals of X-ray quality to determine the absolute stereochemistry. However, the product must result from a diastereoselective Diels-Alder dimerisation of the initially formed diene 15 via the *exo* transition state, (Scheme 7).



Scheme 7

In an attempt to predict which diastereoisomer had been formed, semi-empirical calculations were performed to model the transition states leading to 19a and 19b, respectively, (Figure 1).<sup>11</sup>





Transition State exo-syn  $H_f = 53.50$  kcal mol<sup>-1</sup> Transition State exo -anti  $H_f = 59.15$  kcal mol<sup>-1</sup>

Figure 1. Transition structures leading to 19a exo-syn and 19b exo-anti.

The results of these calculations summarised in Figure 1, predict a striking preference for transition state *exo-syn* which is  $ca \ 6 \ kcal \ mol^{-1}$  lower in energy than the transition state leading to the adduct 19b. This energy difference could account for the observed total diastereoselectivity.

Jones et al.<sup>12</sup> found the facial selectivity of sulfoxide-containing dienes reacting in the presence of Lewis acids to be syn. The preferred endo-syn transition state was rationalised in terms of Lewis acid co-ordination between the sulfoxide oxygen and the ester carbonyl of the dienophile. A recent review discusses the selectivity of sulfinyl dienes further.<sup>13</sup>

As the dimerisation occurs *in situ* and in the presence of both tin and palladium, the observed selectivity could be explained *via* a stabilising metal chelation to the sulfoxide oxygens of both addends. Interestingly the distance between the sulfoxide oxygens in the *exo-anti* transition state is 5.38Å which is too great to allow such a stabilising metal chelation.<sup>14,15</sup>

However, in the exo-syn transition state either metal can comfortably chelate to the sulfoxides with an optimal bond length, 14,15 accommodating the required transition state geometry and with favourable alignment of the S-O electronic dipoles, (Figure 2).

Thus, in addition to dipole alignment, metal chelation may also greatly affect the diastereoselectivity. This may also explain the departure from the normal endo selectivity where a stabilising metal chelation with the same regiochemistry is not possible.

The transition states for the 2-methyl-1,2-isothiazoline-3-one analogues were also modelled using semiempirical calculations<sup>11</sup> to determine if the predicted exo syn selectivity was a function of the bulky 2-(S)- $\alpha$ methylbenzyl substituent.



M = Sn or Pd

Figure 2. Possible metal chelation in TS (exo-syn).

Although in this case the energy difference is less-pronounced, the models again predict a preference for the exo-syn cycloadduct, (Figure 3).



TS exo-syn  $H_f = 3.77 \text{ kcal mol}^{-1}$ 



TS exo-anti  $H_f = 4.22$  kcal mol<sup>-1</sup>

Figure 3. Transition state models of dimerisation of 2-methyl-4-vinyl-1,2-isothiazoline-3-one-1-oxides.

To elucidate the true selectivity and the validity of the predicted models the 2-ethyl-isothiazoline-3-one analogue was investigated. Vinylation of 18 resulted in the formation of a single cycloadduct 21, (Scheme 8). The stereochemistry shown below is relative as the system is racemic. To our delight, the reaction appears to be completely diastereoselective.<sup>10</sup> The dimeric product was highly crystalline and was found to have structure 21 by single crystal X-ray analysis, (Figure 4).

This result closely fits the predicted models for these systems and results exclusively from an exo-syn transition state.<sup>10</sup>



Scheme 8

The preference for dimerisation to involve the endocyclic double bond as dienophile can be explained in terms of a HOMO diene-LUMO dienophile interaction and thus constitutes a normal electron demand Diels-Alder reaction, (Figure 5). Calculation of the dienophile LUMO orbital coefficients reveals that the endocyclic double bond has larger orbital coefficients than the corresponding coefficients in the exocyclic double bond and would thus allow better orbital overlap with the coefficients from diene HOMO. This is similar to the findings discussed by Vogel.<sup>16</sup>



Figure 5 Calculated orbital coefficients for diene 20

It was still an important aim to develop a route to the monomeric diene species. As isolation of the diene species via an oxidative or coupling route had not proved possible, in situ trapping of the diene via oxidation of the 2-ethyl 1,2-isothiazoline species was attempted.

#### **OXIDATIVE ROUTE TO DIENES**



Using the Stille methodology, the reactive dienes are formed under conditions conducive to dimerisation. To avoid this, our aim was to generate the diene at much lower temperatures. Oxidation of 9 with mCPBA at 0°C gave a new product (tlc analysis) which was observed to undergo further reaction upon warming to room temperature. Following chromatography, a dimeric product was isolated in low yield which was found to be the endo dimer 22. This contrasts with the formation of the exo-syn dimer obtained from cycloaddition under Stille coupling conditions. We have yet to determine whether this dimerisation occurs in a syn or anti mode, (Scheme 9).

The stereochemistry of cycloadduct 22 was determined using nOe spectroscopy. Irradiation of the signal corresponding to H15 gives enhancements to signals H9 and H5 indicating that these hydrogens are on the same face of the molecule and thus confirming that the dimer is indeed *endo* (see experimental section).

Thus it seems likely that the intermediate system detected at 0°C is diene 20, although attempts to isolate and characterise this species were unsuccessful. However, *in situ* trapping of diene 20 with N-phenyl maleimide was successful. This cycloaddition appeared to be completely diastereoselective and a single diastereomeric cycloaddition product, 23 was obtained in 49% yield.

A theoretical investigation of the Diels-Alder trapping of diene 20 reveals some interesting points. The cycloaddition behaviour of diene 20 was modelled using the hypothetical cycloaddition of this diene with maleic anhydride *in vacuo*, and all four transition states corresponding to all possible combinations of *exo*, *endo*, *syn* and anti modes were located.<sup>11</sup> These calculations predict that the transition state leading to the *exo-syn* product is clearly favoured *in vacuo*, (Figure 6).



Figure 6 Calculated transition states for reaction of diene 20 with maleic anhydride

Inspection of the orbital coefficients in the energetically favoured diene-HOMO(E = -9.57 eV)/dieneophile-LUMO(E = -1.62 eV) combination reveals the presence of a large antibonding secondary-orbital interaction between a maleic anhydride carbonyl and the isothiazolone nitrogen, (Figure 7).

Thus although the expected favourable *endo* secondary-orbital interaction of the anhydride carbonyl groups and C4 and C8 of the diene respectively are present, the additional large antibonding combination may be enough to render the *endo* geometry unfavourable under these conditions.

It was also apparent that the endo transition states posses markedly greater dipole moments compared to

those of the *exo* structures and it was reasoned that the *endo* cycloaddition mode should be favoured by increasing solvent dielectric. Thus, the calculations were repeated in the presence of a simulated uniform electric field to mimick the presence of solvent and thus should more closely mimick the actual reaction conditions. These calculations now reveal that the *endo-anti* transition state is energetically favoured (Figure 6). Thus it would appear that the actual stereochemical outcome of cycloadditions involving dienes of type 20 may be considerably influenced by the nature of the solvent in which the cycloaddition takes place.



Figure 7 Secondary orbital interactions

The stereochemistry of the cycloadduct resulting from the reaction of diene 20 with N-phenyl maleimide was determined using nuclear Overhauser experiments. Irradiation of the signal corresponding to H7a gives enhancement of the signals corresponding to H9, H8 and H5 indicating they are on the same face of the molecule. Similar irradiation of H7b shows no enhancements of these signals indicating it is on the opposite face (see experimental section). This indicates the cycloadduct formed is from *endo* addition, 23 in complete agreement with that predicted by calculations which included simulation of the presence of solvent, (Scheme 10).



In addition to allowing the variation of solvent, this oxidative route will allow investigation of the cycloaddition under a range of conditions and their effects on the selectivity. For instance, it has been reported

that Lewis acids can alter the observed facial selectivity of sulfoxide containing dienes.<sup>12,13</sup> Co-ordination of the Lewis acid between the sulfoxide oxygen and the dienophile may lead to stabilisation of the *endo syn* transition state as reported by Jones *et. al.*<sup>12</sup> and thus lead to a reversal of facial selectivity to that predicted in the absence of Lewis acids.

#### CONCLUSIONS

This work has led to a facile palladium catalysed entry into a range of 4-substituted 1,2-isothiazoline-3ones. We have also developed a palladium catalysed route to reactive sulfoxide containing dienes which undergo highly diastereoselective Diels-Alder dimerisations via a proposed *exo-sym* transition state stabilised by possible metal chelation. An oxidative route to reactive diene species has also been developed leading to diastereoselective cycloadditions when trapped *in situ*. In addition, calculations modelling the reactivity of the dienes indicate that the stereochemistry of the cycloadditions may be altered by variation of the reaction solvent, the observed stereochemisty being due to an interplay of FMO and electronic effects.

The methods of preparation of the diene species allow for considerable variation in thier substitution pattern- particularly at the 2-position. Additionally, the development of effective asymmetric oxidation of a racemic diene system will lead to an oxidative route to simple, homochiral dienes of type 20.

#### EXPERIMENTAL

All reagents were used as obtained from commercial sources unless otherwise stated and in these cases were purified by standard procedures. All solvents were dried and distilled prior to use. Apparatus for reactions involving moisture and/or air sensitive reagents were routinely assembled hot after drying in an oven or were flame dried as assembled. All such reactions were performed under a steady flow of anhydrous argon. Melting points were measured on a Kofler hot stage microscope and are uncorrected. Optical rotation measurements were made using a Optical Activity AA1000 auto ranging polarimeter, at wavelength 589nm (sodium D-line) in a 0.25 decimetre cell. Infra-Red spectra were recorded on a Phillips PU 9706 infra-red spectrometer, and are reported as  $v_{max}$  in cm<sup>-1</sup>. <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded using GE QE-300MHz and Bruker WP4W 400MHz spectrometers. Nuclear Overhauser Effect Spectroscopy experiments were performed at Pfizer, Sandwich, on a Varian Unity 500MHz spectrometer. Mass spectra and accurate mass measurements were obtained on a 70 eV VG Autospec mass spectrometer. Elemental analyses (CHN) were determined using a Carlo Erba Elemental Analyser MOD 1106. Merck Flash Silica gel 60 (230-400 mesh) was used in chromatographic purifications.

#### Preparation of N,N-di-(S)- $\alpha$ -methylbenzyl-3, 3-dithiodipropionamide (4).

(S)- $\alpha$ -Methylbenzylamine (100 g, 0.83 mol) was diluted with dichloromethane (50 ml) and pyridine (67 ml, 0.83 mol) was added. The reaction mixture was cooled to below 0 °C using an ice/salt water bath and 3,3dithiodipropionyl chloride (102 g, 0.41 mol) was added dropwise. The reaction mixture was then allowed to warm to room temperature and was stirred for 3 h. The reaction mixture was diluted with dichloromethane (2 l) and washed with dilute aqueous hydrochloric acid (0.1 M, 500 ml), followed by brine (500 ml), dried (MgSO4) and the solvent removed *in vacuo*. The resulting oil slowly solidified and was recrystallised from dichloromethane to give the title compound as colourless needles (130 g, 76%). m.p.131-133 °C.  $\upsilon_{max}$  (Nujol) 3400 (N-H), 1660 (C=O), 1550, 1480, 1400, 1220 cm<sup>-1</sup>.  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 7.31 (10H, m, 2 x PhCHCH<sub>3</sub>), 6.36 (2H, d, J=6Hz CHNHCO), 5.10 (2H, dq, J=6, 7Hz, 2 x CH<sub>3</sub>PhCHNH), 2.96 (4H, m, 2 x CH<sub>2</sub>CH<sub>2</sub>S), 2.52 (4H, m, 2 x CH<sub>2</sub>CH<sub>2</sub>S), 1.46 (6H, d, J=7Hz 2 x CH<sub>3</sub>CHPh). m/z (EI) 416 M<sup>+</sup>(3), 209 (37), 176 (12), 120 (21), 105 (CHCH<sub>3</sub>Ph<sup>+</sup>) (100), 77 (13), 55 (8%). Found: C, 63.5; H, 6.75; N, 6.80; S, 15.25. C<sub>22</sub>H<sub>28</sub>N<sub>2</sub>O<sub>2</sub>S<sub>2</sub> requires C, 63.44; H, 6.76; N, 6.72; S, 15.37%.

#### Preparation of N-ethyl-3, 3-dithiodipropionamide (5)

3,3-Dithiodipropionyl chloride (112.9 g, 0.476 mol) was diluted with dichloromethane (50 ml) and added dropwise to a solution of ethylamine (60 ml, 0.915 mol) stirred at 0 °C in dichloromethane (200 ml), with pyridine (74 ml, 0.92 mol). After the addition was complete the reaction mixture was allowed to reach room temperature and stirred overnight. The reaction mixture was diluted with dichloromethane (21) washed with dilute aqueous hydrochloric acid 0.1M (500 ml), followed by brine (500 ml) then dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The resulting product was air dried overnight and then oven dried overnight to give the title compound as a cream coloured powder (126 g, 99%). m.p. 128 - 130 °C.  $\upsilon_{max}$  (Nujol) 3290 (N-H), 1640 (C=O), 1540 cm<sup>-1</sup>.  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 5.92 (1H, bs, CH<sub>3</sub>CH<sub>2</sub>NH), 3.25-3.34 (2H, m, CH<sub>3</sub>CH<sub>2</sub>NH), 3.00 (2H, t, J=7Hz, CH<sub>2</sub>CH<sub>2</sub>S), 2.55 (2H, t, J=7Hz, CH<sub>2</sub>CH<sub>2</sub>S), 1.80, (3H, t, J=7Hz, CH<sub>3</sub>CH<sub>2</sub>NH). *m/z* (EI) 264 (M<sup>+</sup>), 264 (10), 132 (65), 100 (100%). Found: C, 49.5; H, 5.40; N, 8.35; S, 18.55. C<sub>10</sub>H<sub>20</sub>N<sub>2</sub>O<sub>2</sub>S requires C, 49.21; H, 5.30; N, 8.19; S, 18.70%.

## Preparation of 2-(S)- $\alpha$ -methylbenzyl-4-bromo-1,2-isothiazoline-3-one (6) and 2-(S)- $\alpha$ -methylbenzyl-4-bromo-5-chloro-1,2-isothiazoline-3-one.

N,N-Di- $\alpha$ -methylbenzyl-3,3-dithiodipropionamide (4) (5.0 g, 1.2 mmol) was dissolved in dichloromethane (5 ml) under nitrogen. Sulphuryl chloride (3.7 ml, 1.0 M solution in dichloromethane, 3.7 mmol) was added dropwise over 15 min. to the reaction which was heated at reflux for 1h. Bromine (0.29 ml, 3.7 mmol) was subsequently added dropwise over 15 min. and the reaction mixture heated at reflux for a further 14 h. The solvent was removed *in vacuo* and the residue adsorbed onto silica gel and purified by column chromatography (gradient elution with ethyl acetate/petrol (40-60)). The first fraction gave a yellow solid which was recrystallised from toluene to give 2-(S)- $\alpha$ -methylbenzyl-4-bromo-1,2-isothiazoline-3-one (6) as pale yellow prisms (0.49 g, 72%). m.p. 102 - 104 °C. ( $\alpha$ )<sub>D</sub><sup>25</sup> -218 (c = 0.99 methanol). $\upsilon_{max}$  (Nujol) 1660-1620 (C=O), 1480-1450, 1200, 825 cm<sup>-1</sup>.  $\delta_{H}$  (300 MHz; CDCl<sub>3</sub>) 8.12 (1H, s, H5), 7.33 (5H, m, Ph), 5.82 (1H, q, J=7Hz, CH<sub>3</sub>CHPh), 1.75 (3H, d, J=7Hz, PhCHCH<sub>3</sub>).<sup>13</sup>C (300MHz, CDCl<sub>3</sub>)  $\delta$ 163.67 (C3), 139.98 (Ph *ipso*), 134.78 (C5), 128.48 (Ph *ortho*), 128.23 (Ph *para*), 126.99 (Ph *meta*), 101.79 (C4), 53.73 (CH<sub>3</sub>CHPh), 18.90 (CH<sub>3</sub>CHPh). *m/z* (EI) 285 (M<sup>+</sup>) (3), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100), 77 (20), 55 (8%). Found: C, 46.5; H, 3.5; N, 4.9; S, 11.05; Br, 27.9. C<sub>11</sub>H<sub>10</sub>NOSBr requires C, 46.49; H, 3.55; N, 4.93; S, 11.26; Br 28.15%.

The second fraction gave a pale yellow solid which was recrystallised from toluene to give 2-(S)- $\alpha$ -methylbenzyl-4-bromo-5-chloro-1,2-isothiazoline-3-one as opaque needles (0.10 g, 12%). m.p. 107 - 109 °C.  $\upsilon_{max}$  (Nujol) 3000-2890 (C-H), 1690-1670 (C=O), 1490-1470, 1320-1300 (C=C), 1140 cm<sup>-1</sup>.  $\delta_{H}$  (300 MHz; CDCl<sub>3</sub>) 7.33 (5H, m, Ph), 5.92 (1H, q, J=7Hz, CH<sub>3</sub>C<u>H</u>Ph,), 1.75 (3H, d, 7Hz, PhCHC<u>H<sub>3</sub></u>). *m/z* (EI) 363 (M<sup>+</sup>), 319 (M<sup>+</sup>) (42), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100%). Found M<sup>+</sup> 318.9246 C<sub>11</sub>H<sub>9</sub>NOS<sup>37</sup>Cl<sup>79</sup>Br requires M<sup>+</sup> 318.9247. Found M<sup>+</sup>316.9268 C<sub>11</sub>H<sub>9</sub>NOS<sup>35</sup>Cl<sup>79</sup>Br requires M<sup>+</sup> 316.9277.

#### Preparation of 2-ethyl-4-bromo-1,2-isothiazoline-3-one (7)

Sulphuryl chloride (7.60 ml, 94.6 mmol) was added dropwise to a solution of N-ethyl 3,3dithiopropionylamide, (5) (10 g, 37.8 mmol) in dichloromethane (50 ml) at reflux. After the addition was complete bromine (4.87 ml 113 mmol) was added dropwise and the reaction mixture was heated at reflux and stirred overnight. The solvent and excess sulphuryl chloride were removed *in vacuo*. The residual oil and salts were partitioned between dichloromethane (50 ml) and a saturated solution of sodium bicarbonate (50 ml). The organic layer was separated and washed with a saturated solution of sodium thiosulphate (50 ml) followed by brine (50 ml) then dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The product was purified by column chromatography (ethyl acetate : hexane 1:2). The resultant pale yellow solid was recrystallised from dichloromethane/hexane to give the title compound as pale yellow plates (8.77g, 56%). m.p. 64 - 66 °C.  $v_{max}$ (Nujol) 1690-1630 (C=O), 1410, 1260, 1130-110, 870, 850 cm<sup>-1</sup>.  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 8.07 (1H, s, H5), 3.88 (2H, q, J=7Hz, CH<sub>3</sub>CH<sub>2</sub>), 1.32 (3H, t, J=7Hz, CH<sub>3</sub>CH<sub>2</sub>).  $\delta_{\rm C}$  (100MHz; CDCl<sub>3</sub>) 164.07 (C3), 134.66 (C5), 102.24 (C4), 40.51 (CH<sub>3</sub>CH<sub>2</sub>), 14.73 (CH<sub>3</sub>CH<sub>2</sub>). *m/z* (EI) 209 (M<sup>+</sup>) (51), 207 (50), 181 (100), 165 (12), 100 (59), 72 (38), 57 (52), 53 (32), 44 (45%). Found C, 29.05; H, 2.85; N, 6.70; S, 15.4; Br, 38.65. C<sub>5</sub>H<sub>6</sub>NOSBr requires C, 28.86; H, 2.90; N, 6.73; S, 15.47; Br, 38.44%.

#### Preparation of 2-(S)-a-methylbenzyl-4-vinyl-1,2-isothiazoline-3-one (8)

2-(S)- $\alpha$ -Methylbenzyl-4-bromo-1,2-isothiazoline-3-one (6) (0.2 g, 7.0 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (0.05 mol eq.) were dissolved in toluene (5 ml). Vinyltributyltin (0.3 ml, 1.0 mmol) was added and the reaction mixture stirred at 110 °C for 4h. under argon and then allowed to cool to room temperature. The solvent was removed *in vacuo* and the residue purified by column chromatography (ethyl acetate : hexane 1:1). The resulting pale yellow gum crystallised from hexane to give the title compound as pale yellow needles (0.13 g, 80%). m.p. 53 - 55 °C. ( $\alpha$ )<sub>D</sub><sup>25</sup> -302.2 (c= 0.10 %, methanol).  $\upsilon_{max}$  (Nujol) 1670-1620 (C=O), 1480, 1400, 1270, 940, 880cm<sup>-1</sup>.  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 7.85 (1H, s, H5), 7.33 (5H, m, Ph), 6.55 (1H, dd, J=18Hz *trans*, 12Hz, *cis*, CH=CH<sub>2</sub>), 6.22 (1H, dd, J=18Hz *trans*, 1Hz *gem* CH=CH<sub>2</sub>), 5.88 (1H, q, J=7Hz CH<sub>3</sub>CHPh), 5.35 (1H, dd, J=12Hz *cis*, 1Hz *gem* CH=CH<sub>2</sub>), 1.75 (3H, d, J=7Hz, PhCHCH<sub>3</sub>).  $\delta_{\rm C}$  (100MHz; CDCl<sub>3</sub>) 166.42 (C3), 140.21 (Ph *ipso*), 132.99 (C5), 128.69 (*ortho* Ph), 128.16 (*para* Ph), 127.37 (CH=CH<sub>2</sub>), 127.16 (*meta* Ph), 123.64 (C4), 116.62 (CH=CH<sub>2</sub>), 52.52 (PhCHCH<sub>3</sub>), 19.80 (PhCHCH<sub>3</sub>). *m*/z (EI) 231 (M<sup>+</sup>) (15), 127 (30), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100), 77 (23), 55 (10%). Found: C, 67.7; H, 5.65; N, 5.95; S, 14.0. C<sub>13</sub>H<sub>13</sub>NOS requires C, 67.52; H, 5.67; N, 6.05; S, 13.84%.

#### Preparation of 2-ethyl-4-vinyl-1,2-isothiazoline-3-one (9)

N-Ethyl-4-bromo-1,2-isothiazoline-3-one (7) (600 mg, 2.88 mmol), palladium acetate (65 mg, 0.28 mmol) and triphenylphosphine (151 mg, 0.57 mmol) were dissolved in toluene (15 ml) and stirred under argon at 110 °C for 5 min. Vinyltributyltin (0.93 ml, 3.17 mmol) was added and the reaction mixture stirred at 110 °C for 2h. The solvent was removed *in vacuo* and the residual oil purified using column chromatography (ethyl acetate : hexane 1:5) to give the title compound as a pale yellow oil (337 mg, 76%).  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 7.95 (1H, s, H5), 6.56 (1H, dd, J=20Hz *trans*, 10Hz *cis*, CH=CH<sub>2</sub>), 6.25, (1H, d, J=20Hz *trans*, CH=CH<sub>2</sub>), 5.32 (1H, d, J=10Hz *cis*, CH=CH<sub>2</sub>), 2.90 (1H, q, J=7Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.37 (3H, t, J=7Hz, CH<sub>2</sub>CH<sub>3</sub>). *m/z* (EI) 155 (M<sup>+</sup>) (100), 140 (13), 127 (47), 99 (26), 84 (38), 58 (20), 53 (11%). Found M<sup>+</sup> 155.0406. C<sub>7</sub>H<sub>9</sub>NOS requires M<sup>+</sup> 155.0405.

#### Preparation of 2-(S)-a-methylbenzyl-4-ethoxyvinyl-1, 2-isothiazoline-3-one (10)

2-(S)- $\alpha$ -Methylbenzyl-4-bromo-1,2-isothiazoline-3-one (6) (0.2 g, 0.70 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (80 mg, 0.07 mmol) were dissolved in toluene (5 ml) and heated at reflux under argon. 1-Ethoxyvinyltributyltin (0.26 ml, 1.0 mmol) was added over 1 hour (4 x 65  $\mu$ l every 15min). The mixture was heated at reflux for a further 3 h. under argon and the solvent removed *in vacuo*. The residue was purified using column chromatography (neutral alumina, hexane : diethyl ether 1:1) to give the title compound as an off-white solid (0.13 g, 69%). During attempts at recrystallisation the vinyl ether hydrolysed to the more stable ketone, 2-(S)- $\alpha$ -methylbenzyl-4-acetyl-1,2-isothiazoline-3-one 11.  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 8.20 (1H, s, H5), 7.33 (5H, m, Ph), 5.88 (1H, q, J=7Hz, CH<sub>3</sub>C<u>H</u>Ph), 5.74 (1H, s, vinylic C<u>H</u>), 4.40 (1H, s, vinylic C<u>H</u>), 3.88 (2H, q, J=7Hz, CH<sub>3</sub>CH<sub>2</sub>O), 1.72 (3H, d, J=7Hz, PhCHC<u>H<sub>3</sub></u>), 1.35 (3H, t, J=7Hz, CH<sub>3</sub>CH<sub>2</sub>O). m/z (EI) 275 (M<sup>+</sup>) (10), 170 (20), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100), 77 (35%). Found: M<sup>+</sup> 275.0968. C<sub>15</sub>H<sub>17</sub>NO<sub>2</sub>S requires M<sup>+</sup> 275.0980.

#### Preparation of 2-(S)-a-methylbenzyl-4-acetyl-1,2-isothiazoline-3-one (11)

2-(S)- $\alpha$ -Methylbenzyl-4-bromo-1,2-isothiazoline-3-one (6) (0.2 g, 0.70 mmol) and Pd(PPh<sub>3</sub>)<sub>4</sub> (80 mg, 0.07 mmol) were dissolved in toluene (5 ml) and heated at reflux under an argon atmosphere. 1-Ethoxyvinyltributyltin (0.26 ml, 1.0 mmol) was added over 1 hour (4 x 65  $\mu$ l every 15min). The mixture was heated at reflux for a further 3 h. under argon and the solvent removed *in vacuo*. The residue was purified using column chromatography (ethyl acetate : hexane 1:1). The resulting yellow solid was recrystallised from ethyl acetate / hexane to give the title compound as pale yellow needles (0.120 mg, 69%). m.p. 80 - 81.5 °C.  $[\alpha]_D^{25}$  -269 (c= 0.10, methanol).  $\upsilon_{max}$  (Nujol) 1670 -1640(C=O), 1620 - 1590 (C=O) 1500, 1340, 1300, 1180, 840 cm<sup>-1</sup>.  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 8.90 (1H, s, H5), 7.35 (5H, m, Ph), 5.85 (1H, q, J=7Hz CH<sub>3</sub>CHPh), 2.62 (3H, s, CH<sub>3</sub>CO), 1.78 (3H, d, J=7Hz, PhCHCH<sub>3</sub>). *m/z* (EI) 247 (M<sup>+</sup>) (24), 230 (9),105 (PhCHCH<sub>3</sub><sup>+</sup>)(100), 77(35), 51(11), 43(CH<sub>3</sub>CO<sup>+</sup>) (25%). Found: C, 62.9; H, 5.45; N, 5.95; S, 12.75. C<sub>13</sub>H<sub>13</sub>NO<sub>2</sub>S requires C, 63.16; H, 5.30; N, 5.66; S, 12.95%.

#### General procedure for preparation of 12,13 and 14 (Table 1)

 $2-(S)-\alpha$ -Methylbenzyl-4-bromo-1,2-isothiazoline-3-one (6) (0.2 g, 0.7 mmol), triphenylphosphine (37 mg, 0.14 mmol) and Pd(OAc)<sub>2</sub> (16 mg, 0.07 mmol) were dissolved in toluene (5 ml). The reaction mixture was heated at reflux under argon and and the stannane (0.7 mmol) was added. The mixture was heated at the reaction temperature for the reaction time and the solvent was removed *in vacuo*. The residue was purified using column chromatography.

#### Preparation of 2-(S)-a-methylbenzyl-4-phenylethynyl-1,2-isothiazoline-3-one (12)

The residue was purified using column chromatography (ethyl acetate : hexane 1:10 - 1:1). The resulting solid was recrystallised from ethyl acetate / hexane to give the title compound as pale yellow needles (0.164 g, 75%). m.p. 90 - 92 °C.  $\upsilon_{max}$  (Nujol) 1670 -1620 (C=O) 1400, 1310, 1210, 1120, 840 cm<sup>-1</sup>.  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 8.02 (1H, s, H5), 7.1-7.5 (10H, m, Ph), 5.85 (1H, q, J=7Hz CH<sub>3</sub>CHPh), 1.75 (3H, d, J=7Hz, PhCHCH<sub>3</sub>). *m/z* (EI) 306 (MH<sup>+</sup>), 305 (M<sup>+</sup>) (25), 201 (76), 114 (15), 105 (PhCHCH3<sup>+</sup>) (100), 77 (24), 51 (10%). Found: M<sup>+</sup> 305.0877. C<sub>19</sub>H<sub>15</sub>NOS requires *M*<sup>+</sup> 305.0874.

#### Preparation of 2-(S)-a-methylbenzyl-4-(2-pyridyl)-1,2-isothiazoline-3-one (13)

The residue was purified using column chromatography (ethyl acetate : hexane 1:4) and the resulting solid was recrystallised from ethyl acetate / hexane to give the title compound as pale yellow prisms (0.136 g, 69%). m.p. 105.5 - 107 °C.  $[\alpha]_D^{18}$  - 274 (c= 1.0, methanol).  $\upsilon_{max}$  (Nujol) 1600 (C=O), 1260, 1180, 870, 830cm<sup>-1</sup>.  $\delta_H$  (300 MHz; CDCl<sub>3</sub>) 8.92 (1H, s, H5), 8.59 (1H, d, J=7hz), 8.56 (1H, d, J=6Hz), 7.72 (1H, t, J=7Hz), 7.30 - 7.40 (5H, m, Ph), 7.18 (1H, t, J=6Hz), 5.94 (1H, q, J=7Hz CH<sub>3</sub>C<u>H</u>Ph), 1.78 (3H, d, J=7Hz, PhCHC<u>H<sub>3</sub></u>). *m/z* (EI) 283 (MH<sup>+</sup>), 282 (M<sup>+</sup>) (26), 178 (63), 135 (10), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100), 78 (23), 77 (22), 51(13%). Found: C, 68.0; H, 5.2; N, 9.85; S, 11.4. C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>OS requires C, 68.1; H, 5.0; N, 9.92; S, 11.34%.

#### Preparation of 2-(S)-a-methylbenzyl-4-phenyl-1,2-isothiazoline-3-one (14)

The residue was purified using column chromatography (ethyl acetate : hexane 1:5). The resulting solid was recrystallised from ethyl acetate / hexane to give pale yellow plates (0.123 g 63%). m.p. 128 - 129.5 °C. Starting material was also recovered (61 mg, 30%).  $\upsilon_{max}$  (Nujol) 1610-1630 (C=O), 1590-1600 (C=C), 1240, 1200, 835, 825 cm<sup>-1</sup>.  $\delta_{H}$  (300 MHz; CDCl<sub>3</sub>) 8.11 (1H, s, H5), 7.87 (2H, d, J=7Hz, Ph *ortho*), 7.24-7.44 (5H, m, Ph), 5.94 (1H, q, J=7Hz CH<sub>3</sub>CHPh), 1.77 (3H, d, J=7Hz, PhCHCH<sub>3</sub>). *m*/z (EI) 282 (MH<sup>+</sup>) (4.14), 281 (M<sup>+</sup>) (21), 178 (13), 177 (82), 133 (14), 110 (13), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100), 78 (23), 77 (30), 51 (16%). Found: C, 72.55; H, 5.45; N, 4.90; S, 11.5. C<sub>17</sub>H<sub>15</sub>NOS requires C, 72.58; H, 5.37; N, 4.98; S, 11.38%.

#### Preparation of 2-(S)-a-methylbenzyl-4-bromo-1,2-isothiazoline-3-one-1-oxides (S)-16 and (R)-17

 $2-(S)-\alpha$ -Methylbenzyl-4-bromo-1,2-isothiazoline-3-one (6) (0.2 g, 0.7 mmol) was dissolved in dichloromethane (5 ml) and *m*CPBA (0.17 g, (75% *m*CPBA) 0.71 mmol) was added. The reaction mixture was stirred at room temperature for 2.5 h. The reaction mixture was then added to saturated sodium hydrogen carbonate solution (10 ml) and extracted with dichloromethane (3 x 10 ml). The combined extracts were dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The crude reaction mixture was analysed by NMR and found to be a 2.2 : 1 mixture of diastereomers. The mixture was purified by column chromatography (2-methyl propan-2-ol: hexane 1: 5). The first and major fraction gave an opaque gum which crystallised from hexane to afford 2-(S)- $\alpha$ -methylbenzyl-4-bromo-1,2-isothiazoline-3-one-1-(S)-oxide (16) as colourless needles (125 mg, 60%). m.p. 50.5 - 52 °C.

 $u_{max}$  (Nujol) 1680-1710 (C=O), 1570, 1275, 1175, 1080-1110 (S=O), 830 cm<sup>-1</sup>.  $\delta_{H}$  (300 MHz; CDCl<sub>3</sub>) 7.62 (1H, s, H5), 7.5-7.3 (5H, m, Ph), 5.58 (1H, q, J=7Hz, CH<sub>3</sub>C<u>H</u>Ph), 1.90 (3H, d, J=7Hz, PhCHC<u>H<sub>3</sub></u>). *m/z* (EI) 300 (M<sup>+</sup>), 284 (6), 220 (13), 202 (12), 119 (33), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100), 77 (36), 51 (15%). Found: C, 44.0; H, 3.55; N, 4.61. (M<sup>+</sup> 298.9612). C<sub>11</sub>H<sub>10</sub>NO<sub>2</sub>BrS requires C, 44.07; H, 3.36; N, 4.66%. (*M*<sup>+</sup> 298.9616). The second fraction afforded 2-(S)- $\alpha$ -methylbenzyl-4-bromo-1,2-isothiazoline-3-one-1-(R)-oxide (17) as an

opaque gum (62 mg, 28%).  $\upsilon_{max}$  (film) 1680-1720 (C=O), 1570, 1270, 1175, 1070-1120 (S=O), 820 cm<sup>-1</sup>.  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>), 7.68 (1H, s, H5), 7.15-7.5 (5H, m, Ph), 5.32 (1H, q, J=7Hz CH<sub>3</sub>C<u>H</u>Ph), 1.90 (3H, d, J=7Hz, PhCHC<u>H<sub>3</sub></u>). *m/z* (EI) 300 (M<sup>+</sup>), 284 (4), 220 (15), 202 (14), 119 (43), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100), 77 (33), 51 (13%). Found: M<sup>+</sup>-CH<sub>3</sub> 298.9610. C<sub>10</sub>H<sub>7</sub>NO<sub>2</sub>BrS requires *M*<sup>+</sup>-CH<sub>3</sub> 298.9616.

#### Preparation of 2-ethyl-4-bromo-1,2-isothiazoline-3-one-1-oxide (18)

N-Ethyl-4-bromo-1,2-isothiazoline-3-one (7) (3.0 g, 14.4 mmol) was dissolved in dichloromethane (50 ml). Sodium hydrogen carbonate (2.42 g, 28.8 mmol) was added and the reaction mixture cooled to 0  $^{\circ}$ C.

mCPBA (4.95 g, 15.1 mmol) was added and the reaction mixture stirred for 20 min. The reaction mixture was allowed to reach room temperature and washed with saturated sodium carbonate solution (30 ml). The organic layer was dried (MgSO<sub>4</sub>) and the solvent removed *in vacuo*. The residual oil was purified by column chromatography (neutral alumina, ethyl acetate : hexane 1:4). The resulting solid was recrystallised from ethyl acetate/hexane to give the title compound as a colourless solid (1.7g, 53%). m.p. 55 - 56.5 °C.  $v_{max}$  (Nujol) 1720-1700 (C=O), 1580, 1350, 1320, 1220, 1110-1100, 1085, 1010, 970, 850 cm<sup>-1</sup>.  $\delta_{\rm H}$  (300 MHz; CDCl<sub>3</sub>) 7.74 (1H, s, H5), 3.87 (1H, q, J=7Hz, CH<sub>3</sub>CH<sub>x</sub>Hy), 3.75 (1H, q, J=7Hz, CH<sub>3</sub>CH<sub>x</sub>Hy), 1.30 (3H, t, J=7Hz, CH<sub>3</sub>CH<sub>2</sub>).  $\delta_{\rm C}$  (100MHz; CDCl<sub>3</sub>) 161.16 (C3), 144.11 (C5), 127.86 (C4), 37.61 (CH<sub>3</sub>CH<sub>2</sub>) 14.49 (CH<sub>3</sub>CH<sub>2</sub>). *m/z* (EI) 225 (M<sup>+</sup>) (4), 223 (4), 182 (11), 180 (10), 75 (100), 72 (18), 53 (46), 47 (13), 45 (24%). Found: C, 27.1; H, 2.40; N, 6.25; S, 14.4; Br, 35.75 C<sub>5</sub>H<sub>6</sub>NO<sub>2</sub>SBr requires C, 26.8; H, 2.7; N, 6.25; S, 14.29; Br, 35.7%.

Preparation of the Diels-Alder dimer resulting from vinylation of  $2-(S)-\alpha$ -methylbenzyl-4-vinyl-1,2isothiazoline -3-one-1-(S)-oxide (19)

 $2-(S)-\alpha$ -methylbenzyl-4-bromo-1,2-isothiazoline-3-one-(S)-1-oxide (16) (0.53 g, 1.75 mmol) was dissolved in toluene (10 ml) and stirred under argon. Pd(PPh<sub>3</sub>)<sub>4</sub> (0.2 g, 0.175 mmol) was added followed by vinyltributyltin (0.51 ml, 1.75 mmol). The reaction mixture was heated at 110° for 4 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (ethyl acetate : hexane 1:10). The residual solid was recrystallised from methanol to give the title compound (19) as fine pale yellow needles (142 mg, 33%). m.p. 108 - 110 °C.

 $\upsilon_{max}$  (Nujol) 1680 -1710 (C=O), 1370, 1330, 1270-1240, 1100-1060 cm<sup>-1</sup>.  $\delta_{H}$  (400 MHz; CDCl<sub>3</sub>) 7.30 - 7.42 (10H, m, Ph), 7.10 - 7.20 (1H, m, H6), 5.82 (1H, dd, J=18Hz *trans*, 9Hz *cis* H21), 5.58 (1H, q, J=7Hz, PhC<u>H</u>CH<sub>3</sub>), 5.50 (1H, q, J=7Hz, PhC<u>H</u>CH<sub>3</sub>), 5.20 (2H, m, H22a, H22b), 4.13 - 4.10 (1H, m, H5), 3.95 - 3.90 (1H, bd, H9), 2.82 (1H, m, H7b), 2.70 (1H, m, H7a), 1.82 (6H, d, J=7Hz, CHC<u>H<sub>3</sub>Ph</u>).  $\delta_{C}$  (100MHz; CDCl<sub>3</sub>) 174.49 (C3), 165.40 (C12), 139.53,138.28 (2 *ipso* Ph), 137.28 (C21), 136.95 (C6) (128.87, 128.66, 128.40, 128.20, 127.67, 127.39 (Ph)), 126.65 (C4), 118.10 (C22), 55.19 (C9), 54.34, 53.83 (2 C<u>H</u>CH<sub>3</sub>Ph), 51.17 (C7), 50.94 (C5), 33.76 (C8), 19.92, 19.64 (2 x CH<u>C</u>H<sub>3</sub>Ph). *m/z* (EI) 495 (MH<sup>+</sup>), 494(M<sup>+</sup>)(9), 390 (10), 299 (8), 243 (10), 195 (23), 131 (22), 105 (PhCHCH<sub>3</sub><sup>+</sup>) (100), 77 (24), 51 (7%). Found: C, 63.1; H, 5.45; N, 5.55; S, 12.8. C<sub>26</sub>H<sub>26</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> requires C, 63.15; H, 5.30; N, 5.66; S, 12.95%.



500MHz (ROESY) was used to further elucidate the structure of 19. Cross peaks between H9 and H7a to the vinylic protons H21, H22a and H22b show these protons are on the same face of the ring. Cross peaks between H5, H7b and H6 show these protons are on the other face of the same ring. The absence of cross peaks

between H5 and H21, H22a and H22b indicate that they are on opposite faces indicating that 19 is an exo adduct.

### Preparation of the Diels-Alder dimer 21 generated under Stille coupling conditions

2-Ethyl-4-bromo-1,2-isothiazoline-3-one-1-oxide (18) (200 mg, 0.89 mmol) triphenyl phosphine (51 mg, 0.19 mmol) and palladium acetate (22 mg, 0.09 mmol) were dissolved in toluene (5 ml) and heated to 100 °C. Vinyltributyltin (287  $\mu$ l, 0.98 mmol) was added and the reaction mixture heated at 100 °C for 4 h. The solvent was removed *in vacuo* and the residue adsorbed on to silica and purified using column chromatography (ethyl acetate : hexane 2:1). The resultant solid was recrystallised from dichloromethane/hexane to give the title compound 21 as opaque prisms (51mg, 33%). m.p. 148 - 150 °C. Product identified as 21b by x-ray analysis.



 $u_{max}$  (Nujol) 1720-1690(C=O), 1530, 1380, 1350, 1300, 1130-1110, 1030, 1010, 950 cm<sup>-1</sup>. δ<sub>H</sub> (400 MHz; CDCl<sub>3</sub>) 7.14 (1H, m, H6), 5.86 (1H, dd, J=18Hz *trans*, 9Hz *cis*, H15), 5.22 (1H, d, J=9Hz *cis*, H16b), 5.21 (1H, d, J=18Hz *trans*, H16a), 4.25 (1H, m, H5), 4.18 (1H, d, J=8Hz, H9), 3.6 - 3.9 (4H, m, 2 x CH<sub>2</sub>CH<sub>3</sub>), 2.85 (1H, ddd, J=18Hz, 3Hz, 3Hz, H7a), 2.75 (1H, ddd, J=18Hz, 1.2Hz, 6.2Hz, H7b), 1.38 (6H, t, J=7Hz, 2 x CH<sub>2</sub>CH<sub>3</sub>). δ<sub>C</sub> (100MHz CDCl<sub>3</sub>) 173.94 (Cl<sub>2</sub>), 165.61 (C<sub>3</sub>), 137.39 (Cl<sub>5</sub>), 136.77 (C6), 125.75 (C4), 117.87 (C16), 55.72 (C5), 51.13 (C8), 50.56, (C9) 37.99, 37.41 (2 x CH<sub>2</sub>CH<sub>3</sub>), 33.65 (C7), 13.97, 14.61 (2 x CH<sub>2</sub>CH<sub>3</sub>). *m*/z (EI) 342 (M<sup>+</sup>) (8), 250 (13), 223 (19), 205 (29), 190 (11), 177 (21) 162 (18), 135 (13), 137 (100), 104 (18), 91 (13), 77(15%). Found: C, 45.4; H, 7.8; N, 10.5; S, 24.0. C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> requires C, 45.4; H, 7.63; N, 10.6; S, 24.2%.

# Preparation of the endo dimer 22 of 4-vinyl-1,2-isothiazoline-3-one-1-oxide generated under oxidation conditions.

2-Ethyl-4-vinyl-1,2-isothiazoline-3-one (9) (248 mg, 1.6 mmol) was dissolved in dichloromethane (10 ml). Distilled water (5 ml) followed by sodium hydrogen carbonate (403 mg, 4.8 mmol) was added and the reaction mixture cooled to 0 °C using an ice/water bath. mCPBA (552 mg, 1.6 mmol) was added and the reaction mixture stirred vigorously for 30 min. The reaction mixture was poured into saturated sodium carbonate solution (20 ml) and extracted with dichloromethane (3 x 20 ml). The organic layer was washed with brine (20 ml), dried with MgSO4 and the solvent reduced in vacuo to a volume of ca. 5ml, and stirred at 30 °C for 1h. The solvent was removed in vacuo and the residue analysed by NMR. This revealed a mixture of products and contained none of the previously isolated exo dimer 21. A different dimer product 22 was isolated from the reaction mixture using column chromatography (ethyl acetate : hexane 1:1). The title compound was obtained as a pale yellow solid (32 mg, 11%). m.p. 156 -158 °C.



 $δ_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 6.78 - 6.81 (1H, m, H6), 6.32 (1H, dd, J=18Hz trans, 11Hz cis, H15), 5.67 (1H, d, J=18Hz trans, H16a), 5.63 (1H, d, J=11Hz cis, H16b), 3.86 - 3.94 (1H, m, CH<sub>x</sub>CH<sub>y</sub>CH<sub>3</sub>), 3.66 - 3.85 (1H, m, CH<sub>x</sub>CH<sub>y</sub>CH<sub>3</sub>), 3.52 - 3.66 (3H, m, CH<sub>x</sub>CH<sub>y</sub>CH<sub>3</sub>, H5), 3.44 - 3.45 (1H, m, H9), 2.78 - 2.88 (2H, m, H7), 1.35 (3H, t, J=7Hz, CH<sub>2</sub>CH<sub>3</sub>), 1.19 (3H, t, J=7Hz, CH<sub>2</sub>CH<sub>3</sub>).  $δ_{\rm C}$  (100MHz; CDCl<sub>3</sub>) 173.98 (C12), 163.87 (C3), 134.65 (C15), 130.55 (C6), 128.58 (C4), 120.61 (C16), 70.67 (C5), 63.40 (C9), 54.42, (C8), 38.53 (CH<sub>2</sub>CH<sub>3</sub>), 37.42 (CH<sub>2</sub>CH<sub>3</sub>), 23.58 (C7), 14.38, 13.92 2 x (CH<sub>2</sub>CH<sub>3</sub>). m/z (EI) 342 (M<sup>+</sup>), 251 (6), 180 (9), 159 (7), 131 (100), 104 (24), 77 (12%). Found M<sup>+</sup> 342.0705 C<sub>14</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S<sub>2</sub> requires M<sup>+</sup> 342.0708. 400 MHz Noe spectroscopy revealed that H15, H16a, H16b and H5 and H9 are on the same face of the molecule indicating the product is from *endo* addition. Irradiation of the signal corresponding to H15 gave a 3% enhancement of the overlapping signals corresponding to H16a and H16b, a 7% enhancement of the signal corresponding to H5 and a 7% enhancement of the signal corresponding to H9.

#### Preparation of cycloadduct 23

2-Ethyl-4-vinyl-1,2-isothiazoline-3-one (9) (392 mg, 2.52 mmol) was dissolved in dichloromethane (10 ml). Distilled water (5 ml) followed by sodium hydrogen carbonate (847 mg, 10.1 mmol) was added and the reaction mixture cooled to 0 °C using an ice/water bath. *m*CPBA (873 mg, 2.52 mmol) was added and the reaction mixture stirred vigorously for 30 min. The reaction mixture was poured into saturated sodium carbonate solution (20 ml) and extracted with dichloromethane (3 x 20 ml). The organic layer was washed with brine (20 ml), dried with MgSO<sub>4</sub> and the solvent reduced *in vacuo* to a volume of *ca*. 20 ml. N-phenyl maleimide (523 mg, 3.02mmol) was subsequently added and the reaction stirred at 30 °C for 2 h. The solvent was then removed *in vacuo* and the residue purified by column chromatography (ethyl acetate : hexane 1:1) The resulting solid was recrystallised from ethyl acetate to give the title compound as colourless prisms (426 mg, 49%). m.p. 222 -224 °C



23 endo cycloadduct

 $\delta_{\rm H}$  (400 MHz; CDCl<sub>3</sub>) 7.49 - 7.59 (3H, m, Ar), 7.15 (1H, m, H6), 7.18-7.21 (2H, m, Ar), 4.62 (1H, dd, J = 6Hz, 9Hz, H5), 3.91 - 3.94 (1H, m, H9), 3.79 - 3.88 (1H, m, CH<sub>x</sub>CH<sub>y</sub>CH<sub>3</sub>) 3.64 - 3.72 (2H, m, H8, CH<sub>x</sub>CH<sub>y</sub>CH<sub>3</sub>), 2.69 - 2.77 (1H, m, H7a), 2.61 - 2.63 (1H, m, H7b), 1.27 (3H, t, J = 8Hz, CH<sub>2</sub>CH<sub>3</sub>).

 $\delta_{C}$  (100MHz; CDCl<sub>3</sub>) 181.61 (C12), 179.49 (C10), 168.23 (C3), 139.08 (C6) 135.63 (C4), 134.02 (*ipso* Ph) 132.88, 132.50, 130.45, (CH Ar), 67.24 (C5), 45.50 (C6), 45.40 (C7), 40.58 (<u>CH<sub>2</sub>CH<sub>3</sub></u>), 29.94 (C7), 17.94, (CH<sub>2</sub>CH<sub>3</sub>). *m/z* (EI) 344 (M<sup>+</sup>) (21), 253 (51), 225 (42), 119 (9), 105 (59), 78 (100%).

Found M<sup>+</sup>344.0848  $C_{17}H_{16}N_2O_4S$  requires  $M^+$  344.0831. 400 MHz NOe spectroscopy revealed that H5, H7a, H8 and H9 are on the same face of the molecule and on the opposite face of the molecule to H7b indicating the product is from *endo* addition. Irradiation of the signal corresponding to H5 gave a 14% enhancement of H9 and a 3% enhancement of H7a. Irradiation of the signal corresponding to H7b gave a 24.5% enhancement of H7b and a 22% enhancement of the signal corresponding to H6. Irradiation of the signal corresponding to H7a gave a 17% enhancement of H7b, a 26% enhancement of H8, a 21.5% enhancement of H5 and a -1.8% enhancement of the signal corresponding to H9.

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