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Generation and Cycloadditions of 2-(N-Acylamino)-1-Thia-1,3-Dienes Part III[1]: Control of Diastereoselectivity Using Homochiral Auxiliaries

Andrew S. Bell[b], Colin W. G. Fishwick[a*] and Jessica E. Reed.[a†]

[a] School of Chemistry, University of Leeds, Leeds, LS2 9JT, UK.

[b] Discovery Chemistry, Pfizer Central Research, Sandwich, Kent, CT13 9NJ, UK.

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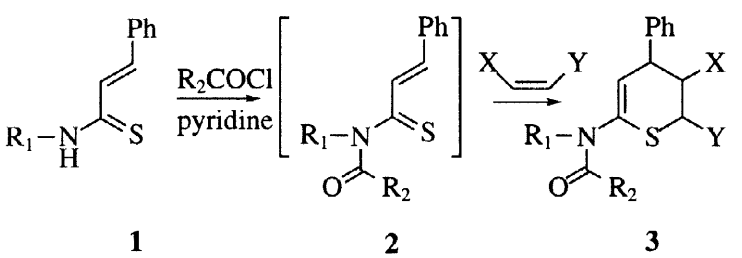
Abstract: Activated 2-(N-acylamino)-1-thia-1,3-dienes undergo efficient diastereoselective Diels-Alder cycloadditions giving access to thiopyrans of high optical purity. By variation of the position and nature of the chiral auxiliaries we have been able to induce a high degree of facial selectivity in *endo* selective cycloadditions and induce total facial control in *exo* selective cycloadditions.

The Diels-Alder reaction is amongst the most powerful and versatile of synthetic methods and continues to attract considerable attention.[2] In particular, great effort has been directed towards understanding the factors governing facial selectivity and absolute stereochemical control. Stereoselectivity has been achieved using optically active butadienes,[3] dienophiles,[4] and Lewis acid catalysts[5] with varying degrees of success. In contrast, despite their tremendous synthetic potential, stereoselective hetero Diels-Alder reactions,[6] have received much less attention. Oxygen and nitrogen based hetero Diels-Alder reactions have, in turn, been investigated more thoroughly than the sulphur based counterparts.[7] Of the few asymmetric routes to thiopyrans, most focus on the use of homochiral dienophiles[8] and to our knowledge only our previous reports[9] of the use of homochiral 1-thia-1,3-dienes have appeared. This is somewhat surprising as the rich chemistry available at, and around the sulphur atom,[10] coupled with the established regio and stereochemical advantages of concerted cycloadditions renders the hetero Diels-Alder approach to thiopyrans extremely attractive. We now wish to present a full account of our work utilising homochiral auxiliaries attached to 1-thia-1,3-dienes and their use in controlling the facial and *endo : exo* selectivity of the hetero Diels-Alder reaction.

Recently, we have described[1] the development of extremely simple, efficient and versatile methods for the generation and cycloaddition of reactive 2-N-acylamino-1-thiadienes **2**. Derived *via* acylation of thioamides **1** these dienes give access to a range of thiopyran systems **3** with good degrees of regioselectivity and *endo* : *exo* stereocontrol, **Scheme 1.** At the start of the present studies, we wished to explore the potential of homochiral auxiliaries located at R_1 and R_2 respectively (**2**, **Scheme 1**) in controlling the facial as well as the *endo : exo* selectivity of the associated Diels-Alder reactions.



1 **2** **3**

Scheme 1.

Despite the fact that substituents at positions R_1 and R_2 on diene **2** would appear to be located some distance away from the primary reacting centres, our initial observations of the spatial location of substituents at

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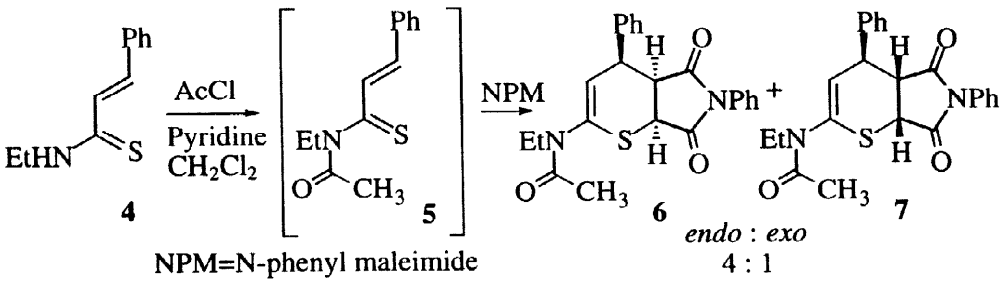
these positions within adducts derived from simple, achiral versions of diene **2**, had fueled our excitement concerning the possibility of good diastereofacial control resulting from the presence of chiral substituents at these positions.

Acylation of N-ethyl thiocinnamamide **4** gave a reactive diene, **5**, which was trapped with N-phenyl maleimide in dichloromethane at room temperature to give racemic products **6** : **7** in the ratio 4 : 1 in 92% yield, **Scheme 2**. The minor *exo* cycloadduct **7** was highly crystalline and was analysed by single crystal X-ray crystallography .



Scheme 2.

The X-ray structure of the minor *exo* component, **Figure 1**, revealed that the ethyl and acyl groups corresponding to the R_1 and R_2 positions, respectively of diene **5**, are located on opposite faces of the molecule.

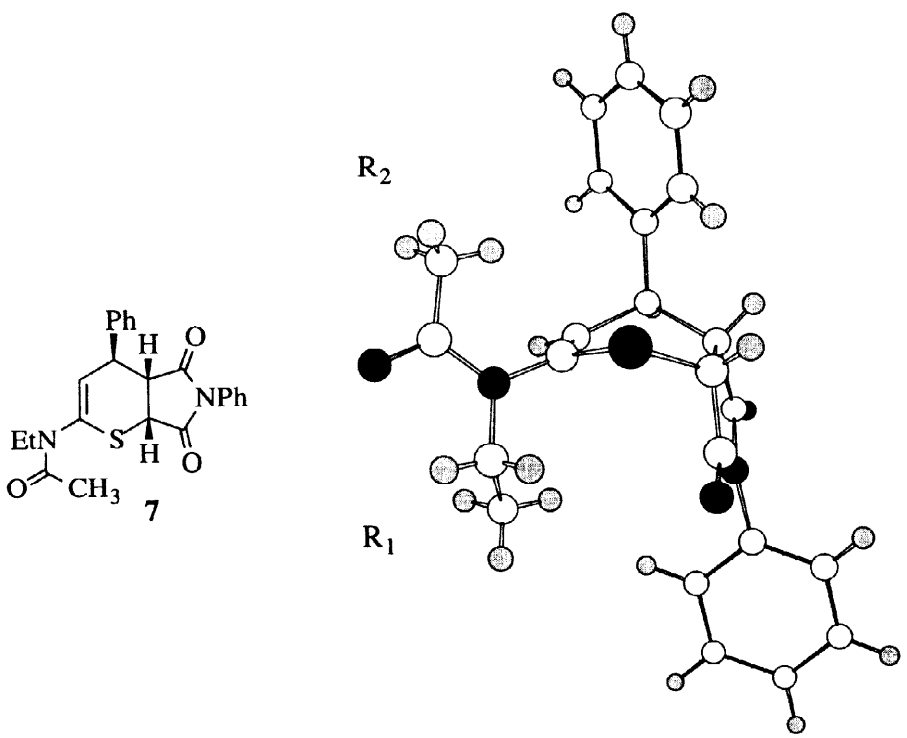


Figure 1 X-ray of *exo* cycloadduct **7**.

It was possible however, that the relative positions of these substituents was being dictated by packing requirements within the crystal, and did not reflect the spatial relationship of these substituents in the reactive diene **5**, or more importantly, within the reaction transition state. However, we were encouraged by the fact that calculations of the structure of diene **5**, predicted similar relative positions for the acyl and ethyl substituents to

that observed in the X-ray structure of *exo* adduct, **7**. We therefore embarked upon a study of the effect of chiral auxiliaries located at R_1 and R_2 on the facial selectivity of the corresponding hetero Diels-Alder cycloadditions, **Figure 2.**

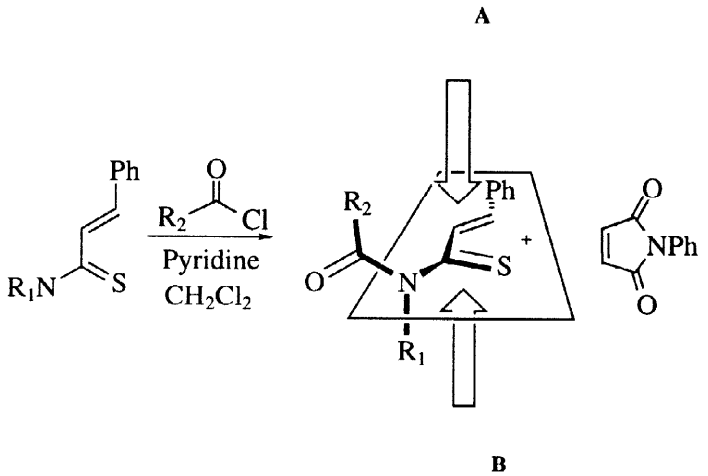
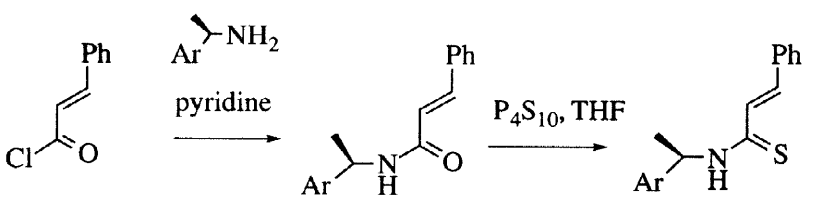


Figure 2.

Effects of Homochiral Auxiliaries at the Amino Position R_1.

We chose to study dienes based on cinnamyl derivatives because of their known reactivity, stability and the crystalline properties of the diene precursors.[1] In our first approach, we focused on optically active amines containing bulky substituents near to the amine group. The commercially-available (R)-α-methylbenzylamine and the more sterically encumbered (R)-1-(1-naphthyl)ethylamine were used to prepare the cinnamamides **9** and **10** in good yields, **Scheme 3**. The homochiral thioamides **11** and **12** were prepared using P_4S_{10} by vigorous stirring overnight in THF. The yields were not optimised.



8

9 Ar = phenyl, 95%

10 Ar = 1-naphthyl, 94%

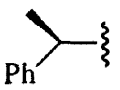
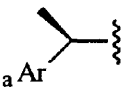
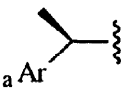
11 Ar = phenyl, 52%

12 Ar = 1-naphthyl, 54%

Scheme 3.

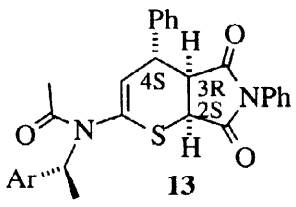
In order to investigate the effects of these chiral substituents at the position R_1, N-phenyl maleimide, was chosen as the dienophilic trap due to its high yielding cycloadditions and its *endo* preference, as seen for the achiral diene, R_1 = Et, **Table 1**, **Entry 1.** When activated with acetyl chloride and trapped *in situ* with N-phenyl maleimide the (R)-α-methylbenzylamine based diene, **11**, **Entry 2**, gave a mixture of four diastereomeric cycloadducts in 95% yield in the ratio 59 : 30 : 10 : 1, as established by chiral HPLC analysis. Although the cycloaddition itself was clearly proceeding in excellent yield, the diastereoselectivity was disappointing.

Table 1 The effects of homochiral auxiliaries at R_1 on cycloaddition products.

Entry	R_1	dienophile	Temp.	Yield (%)	ratio of products[b]
1	CH_2CH_3	NPM	r.t.	92	40 : 40 : 10 : 10 *endo exo* 4 : 1
2		NPM	r.t.	95	59: 30 : 10 : 1
3		NPM	r.t.	92	72[c] : 28 : < 1: < 1
4		NPM	-15 °C	95	72[c] : 28 : <1: <1

[a] Ar = 1-naphthyl. [b]relative stereochemistry not determined unless indicated. [c]*exo* cycloadduct.

Reaction of the more sterically encumbered (R)-1-(1-naphthyl)ethylamine based diene, **12**, with N-phenyl maleimide at room temperature gave an excellent yield of two diastereomeric cycloadducts (92%) in the ratio 72 : 28 as determined by chiral HPLC, **Entry 3**. When the cycloaddition reaction was repeated at -15 °C, **Entry 4**, the yield of the cycloaddition was increased to 95% but the product ratio remained unchanged. The major component, **13**, was found to be an *exo* cycloadduct by single crystal X-ray analysis, **Figure 3**. This was intriguing as our previous work using a simple achiral diene, R_1 = Et, had revealed a preference for *endo* cycloadducts with this dienophile.



Ar = 1-naphthyl

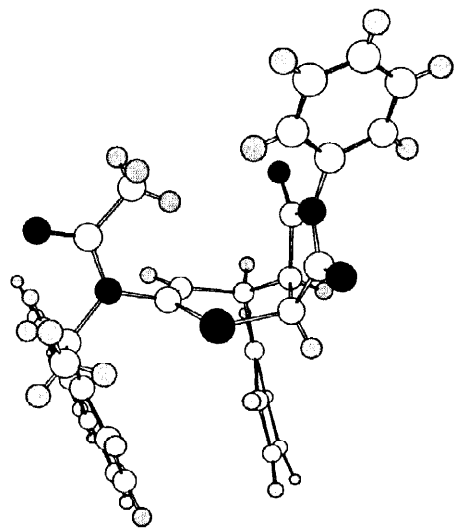


Figure 3. X-ray structure of **13**.

In order to gain insight into this abnormal *exo* selectivity and to attempt to rationalize the facial preference of the cycloaddition reactions, the lowest energy conformation of the reactive diene **14** was calculated using a molecular modeling approach.[11] According to these calculations, the structure predicted to have the lowest energy, **14**, possesses a number of interesting features, **Figure 4**, (the model is shown looking along the plane of the diene from sulphur). In particular, the 4-phenyl substituent is located in close proximity to the naphthyl unit with its edge to the plane of the naphthyl ring. The existence of this edge-to-face motif results in a twisting of the 4-phenyl group relative to the plane of the diene system. This π interaction leads to a conformationally locked diene in which both orbitally preferred *endo* approaches appear to be sterically hindered accounting for

the departure from the usual *endo* selectivity. This twisting also appears to sterically hinder the approach of the dienophile from the "acyl-face" but allows *exo* approach from the more accessible "napthyl-face". The more efficient π interaction of the naphthyl group of diene **14** compared with that of a phenyl group in the acyl derivative of diene **11** may account for its improved facial selectivity.

Given the observed *exo* preference of cycloadditions of diene **14**, with NPM it was desirable to investigate trapping of the diene with cyclopentene. Our previously reported examples involving achiral diene **5**, **Scheme 2**, where R_1 = ethyl, gave the racemic *exo* product exclusively with cyclopentene as the dienophile.[1]

The naphthyl based diene **12** was acylated to generate the reactive diene species **14** which underwent rapid cycloaddition with cyclopentene at room temperature in dichloromethane furnishing one diastereomeric *exo* cycloadduct **15** exclusively in 95% yield, **Scheme 4**.

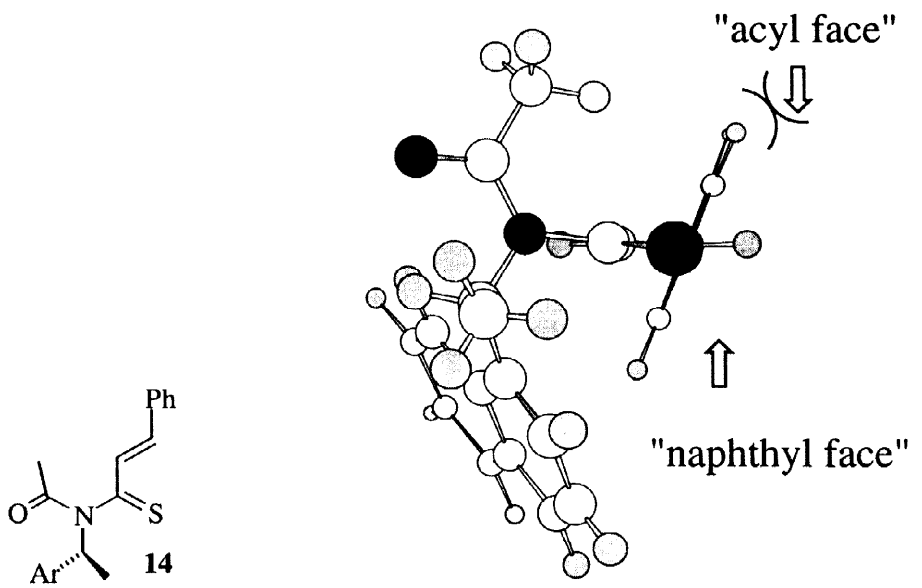
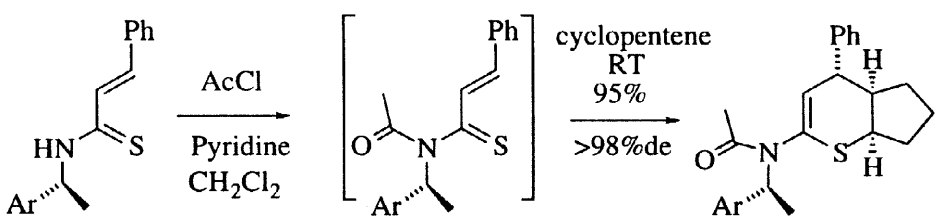


Figure 4. Energy minimised diene **14**.



12 **14** **15**

Ar = 1-naphthyl

Scheme 4.

In terms of the facial selectivity of the cycloaddition, a similar argument to that presented above would predict that this dienophile would also approach from the *exo* "naphthyl-face" of diene **14**. In order to quantify this effect, we used a semi-empirical approach[11] to calculate the energies of the transition states for *exo* addition of cyclopentene to both faces respectively of diene **14** whilst in its lowest energy conformation. These calculations re-enforce the qualitative arguments presented above and indicate a striking preference for *exo* addition from the same face of the molecule as that containing the naphthyl auxiliary, **Figure 5**.

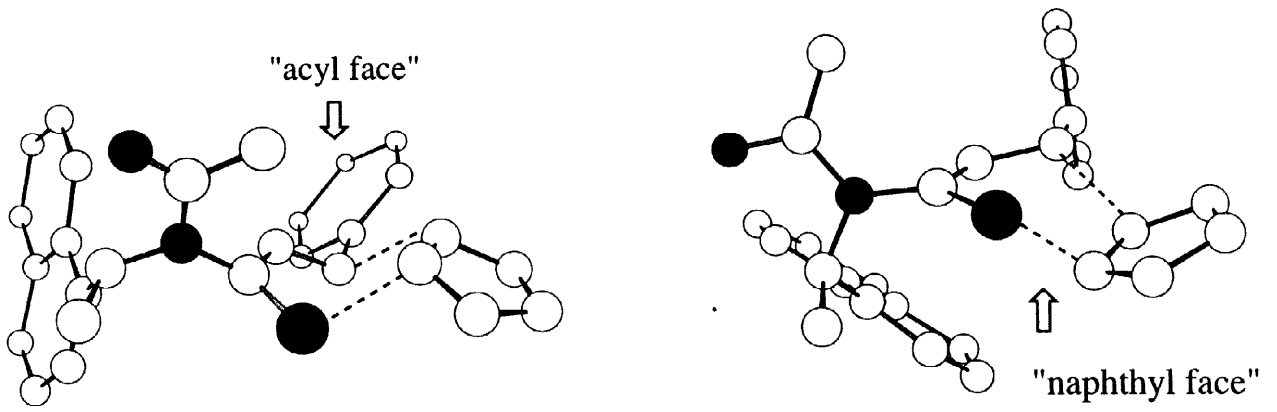
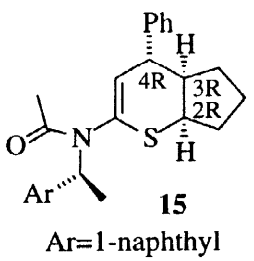


Figure 5. Transition state structures of 1-naphthyl based diene **14** with cyclopentene.

It may be the case that the improved selectivity seen with cyclopentene is due to the stronger *exo* preference of cyclopentene as dienophile and its more discriminate nature compared with the more reactive NPM.



15

Ar=1-naphthyl

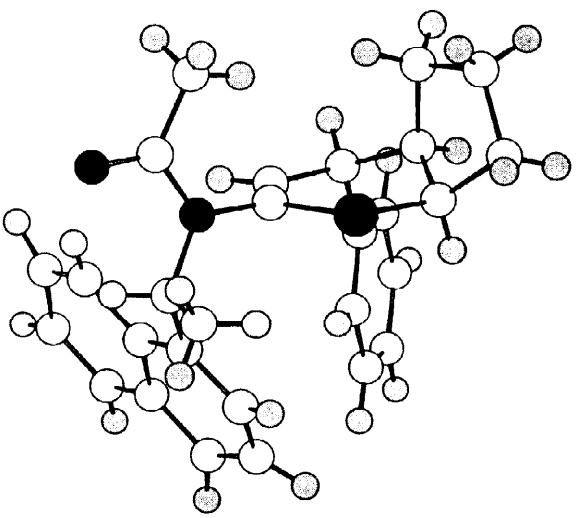


Figure 6. X-ray structure of **15**.

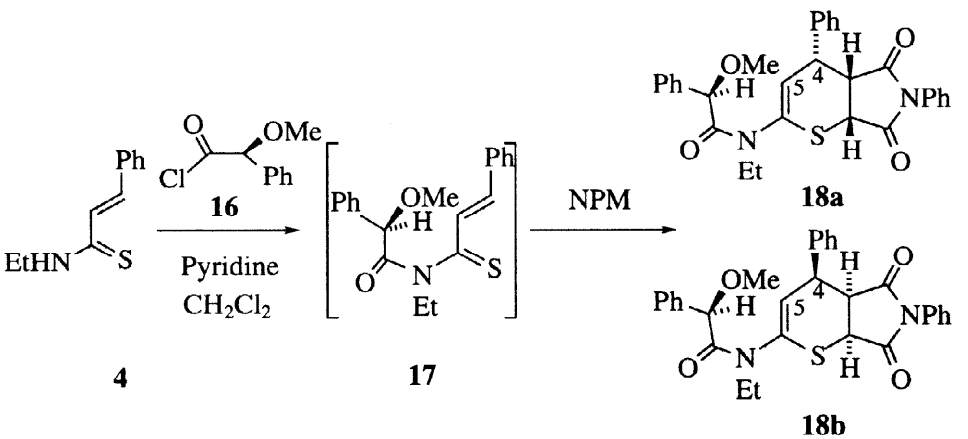
The X-ray structure of the cyclopentadiene cycloadduct **15** clearly shows that the naphthyl- and the 4-phenyl substituent are almost perpendicular to each other and this face-to-edge interaction may have a substantial role in dictating the diastereoselectivity of the cycloadditions.

Effects of chiral auxiliaries at R_2

In the light of the totally *exo* selective cycloadditions observed for the diene **14**, containing a chiral centre directly connected to the nitrogen atom, at the R_1 position, we were keen to explore the effect of chiral moieties located at the R_2 position, **Figure 2**. Indeed, inspection of simple models had suggested that a substituent located at this position may not be able to interact with the 4-phenyl moiety of the diene and thus, while still inducing good face selectivity, a chiral substituent located at the R_2 position may allow a return to the *endo* cycloaddition mode preferred by electron deficient dienophiles. A number of reactions involving different optically active acid chlorides[12] with N-phenyl maleimide as the dienophile were examined as summarised in **Table 2**.

Table 2, Entry 1 corresponds to **Scheme 2**. Cycloaddition of a diene possessing an (S)-α-methylbenzyl substituent at the R_2 position, **Entry 2**, was less diastereoselective than the corresponding reaction of diene **11**, having this chiral moiety located at position R_1.[9] The compound isolated in 41% yield was found to posses *endo* geometry by nuclear Overhauser effect difference spectroscopy (nOe). Surprisingly, use of the bulky camphanyl substituent, **Entry 3**, induced even less selectivity.

When (R)-α-methoxyphenyl acetyl chloride, **16**, was used to generate the reactive diene species the diastereoselectivity improved with the major cycloaddition product, **18**, being formed in 72% yield. This product was isolated using column chromatography and was found to be an *endo* product by nOe, **Scheme 5**.



Scheme 5

Table 2 The effects of homochiral auxiliaries at R_2 on cycloaddition products.

Entry	R_1	R_2	Acid chloride	Temp.	Yield (%)	ratio of products
1	Et	CH_3	Acetyl chloride	r.t.	84	*endo* 4 : 1 *exo*
2	Et	(S)-CH_3, Ph	2-(S)-Phenyl propionyl chloride	r.t.	93	45 : 41[a]: 10 : 4[b]
3	Et	(S), O, O	(S)-Camphanyl chloride	r.t.	86	39 : 36 : 18 : 11[b]
4	Et	(R)-OCH_3, Ph	(R) - methoxy phenyl acetyl chloride	r.t.	65	72.2[a] : 27.4: 0.2 : 0.2[b]

[a] *endo* cycloadducts. [b]relative stereochemistry not determined unless indicated.

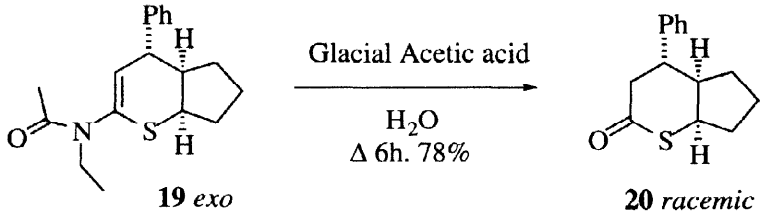
NOe's were observed between the α-proton on the homochiral R_2 substituent CHOMePh and the signals corresponding to signals H4 and H5 and may provide a clue to the high diastereoselectivities observed. In the cycloadduct this group appears to be in close proximity to these protons and may lie on one face of the diene, in the corresponding *endo* transition state blocking one face of the diene and inducing diastereoselectivity. The improved selectivity may also be due to an electronic repulsion between the methoxy group on one face of the diene and the carbonyl of the approaching dienophile leading to an increased preference for addition to the less repulsive and less hindered face. The high *endo* preference is intriguing and strongly contrasts with the

preference for *exo* cycloadducts displayed by optically active diene **14**. In the case of diene **17**, cycloaddition from the sterically accessible face opposite to that containing the methoxy group of the chiral auxiliary can now proceed in an FMO-promoted *endo* fashion due to the absence of any serious steric repulsions derived from the N-ethyl substituent present on diene **17**. Unfortunately we have been unable to grow a crystal of X-ray quality and the absolute stereochemistry of the major product, either **18a** or **18b** has yet to be determined.

Thus by altering the positions of chiral auxiliaries relative to the diene framework, dramatic reversal of cycloaddition stereochemistry can occur and it has been possible to induce a considerable degree of facial selectivity in an *endo* selective cycloaddition and induce total facial control in *exo* selective cycloadditions.[9]

Synthetic Manipulation of Cycloadducts

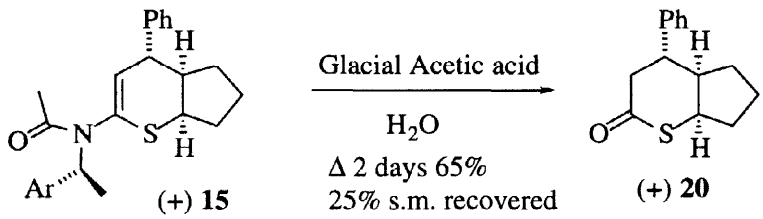
Clearly it is important from a synthetic point of view to be able to remove the homochiral auxiliaries and obtain thiopyrans enriched in one enantiomer. Hydrolysis of the racemic cycloadduct, **19**, using glacial acetic acid gave the racemic thiolactone **20** in good yield **Scheme 6**.



19 *exo* **20** *racemic*

Scheme 6

Hydrolysis of the 1-naphthyl substituted *exo* cycloadduct (+)**15** resulted in a more sluggish reaction but (+)**20** was obtained in good yield, **Scheme 7**.



Ar=1-naphthyl

Scheme 7

Conclusions:

The use of homochiral auxiliaries to control the facial selectivity of 1-thia-dienes has led to a viable and flexible route to optically active thiopyrans. Use of a homochiral 1-naphthyl derived auxiliary at the R_1 position has led to high yielding *exo* cycloadditions and complete diastereofacial control. The cycloadditions occur at room temperature with both electron rich and electron deficient dienophiles and the cycloadducts obtained are highly crystalline leading to easy purification.[9] It has also been possible to induce high levels of diastereofacial control in *endo* cycloadditions through the use of a homochiral auxiliary at R_2. Hydrolysis of the cycloadducts gives a viable route to a range of optically active thiolactones in good yield.

The dienes reported are highly tunable, in terms of how different substituents in different positions influence their facial selectivity, their *endo : exo* selectivity and their reactivity. The cycloadducts produced are open to further synthetic manipulation through chemistry at sulphur or the amide functionality. In addition, use of these reactive homochiral 1-thia-1,3-dienes could lead to the stereocontrolled synthesis of interesting heterocycles through the use of heterodienophiles.

Acknowledgments.

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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 υ_{max} in cm^{-1}. ^{1}H and ^{13}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 endo, 6-(N-acetyl, N-ethylamino)-3,4-dihydro-4β-phenyl-N-(8)-phenylpyrrolo-[3,4-b]-2H-thiopyran-7,9-dione, **6**, *and exo, 6-(N-acetyl, N-ethylamino)-3,4-dihydro-4β-phenyl-N-(8)-phenylpyrrolo-[3,4-b]-2H-thiopyran-7,9-dione,* **7**.

N-Ethyl thiocinnamamide **4**[13] (2.00 g, 10.47 mmol) and N-phenyl maleimide (2.72 g, 15.7 mmol) were dissolved in pyridine (1.27 cm^3, 15.7 mmol) and dichloromethane (50 cm^3). A solution of acetyl chloride (1.11 cm^3, 15.7 mol) in dichloromethane (10 cm^3) was added dropwise and the reaction mixture stirred at room temperature for 2 days. The reaction mixture was diluted with dichloromethane (50 cm^3) and washed successively with dilute acid, 10% w/v potassium carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual orange oil was purified by column chromatography (ethyl acetate : hexane 1:1) to give a 4 : 1 mixture of *endo : exo* isomers, by NMR, as a colourless foam (3.92 g, 92%). The individual isomers were separated using column chromatography (ethyl acetate : hexane 1:4). The first fraction was recrystallised from dichloromethane / hexane to give the minor *exo* product **7** as colourless prisms. m.p. 186.5 - 188 °C. δ_H (300 MHz; $CDCl_3$) 7.25-7.55 (10H, Ph), 6.26 (1H, d, J=6Hz, H5), 4.50 (1H, dd, J=6Hz, 3Hz, H4), 4.35 (1H, d, J=9Hz, H2), 3.79 (1H, dd, J=9Hz, 3Hz, H3), 3.70 (1H, m, J=7Hz $CH_3CH_x\underline{H}_y$), 3.47 (1H, m, J=7Hz, $CH_3C\underline{H}_xH_y$), 2.0 (3H, s, $C\underline{H}_3CO$), 1.12 (3H, t, J=7Hz, $C\underline{H}_3CH_2$). *m/z* (EI) 407 (MH^+)(27.59), 406 (M^+)(100), 364 (41), 363 (26), 335 (33), 331 (30), 321 (11), 233 (21), 190 (48), 173 (21), 161 (22), 158 (43), 147 (45), 130 (35), 103 (26), 77 (23). Found: C, 67.75; H, 5.35; N, 6.90; S, 8.0. $C_{23}H_{22}N_2O_3S$ requires C, 67.9; H, 5.46; N, 6.89; S, 7.88%.

The second fraction was recrystallised from dichloromethane / hexane to afford **6** as colourless needles. m.p. 89.5 - 91.5 °C. υ_{max} (nujol) 2990 - 2810 (C-H), 1720 - 1690, 1660 - 1620, (C=O), 1490, 1450, 1400 - 1350, 1280, 1190, 1160 cm^{-1}. δ_H (300 MHz; $CDCl_3$) 7.25 - 7.55 (8H, m, Ph), 7.06 (2H, m, Ph), 6.46 (1H, d, J=5.31Hz, H5), 4.42 (1H, d, J=8.8Hz, 3Hz, H2), 3.96 (1H, m, J=5.31Hz, H4), 3.91 (1H, dd, J=8.8Hz, 3Hz, H3), 3.84 (1H, m, J=6.6Hz, $CH_3CH_x\underline{H}_y$), 3.34 (1H, m, J=6.6Hz, $CH_3C\underline{H}_xH_y$), 2.05 (3H, s, $C\underline{H}_3CO$), 1.10 (3H, t, J=6.6Hz, $C\underline{H}_3CH_2$). δ_C (100MHz; $CDCl_3$) 173.55 (C=O), 173.28 (C=O), 169.56 (C=O), 138.73 (Ph ipso C), 137.22 (C6), 131.05 (NPh ipso C) 129.05, 128.88, 128.77, 128.64, 127.74, 125.81 (Ar $\underline{C}H$) 53.39 (C4), 49.42, 49.40 (C3, C2), 45.06 (C5), 41.33 ($\underline{C}H_xH_yCH_3$), 22.01 ($COCH_3$), 13.26 ($CH_xH_y\underline{C}H_3$). *m/z* (EI) 407 (MH^+ 5), 406 (M^+ 18), 233 (64), 190 (95), 161 (17), 147 (85), 130 (40),

115 (21), 103 (14), 84 (76), 51 (36), 49 (100%). Found: C, 67.85; H, 5.35; N, 6.85; S, 7.85. $C_{23}H_{22}N_2O_3S$ requires C, 67.9; H, 5.46; N, 6.89; S, 7.88%.

Preparation of N-(S)-α-methylbenzyl cinnamamide, **9**.

A solution of *trans* cinnamoyl chloride **8** (20.00 g, 0.12 mol) in anhydrous ether (50 cm^3) was added dropwise to (S)-α-methylbenzylamine (30.95 cm^3, 0.24 mol) with continuous stirring at 0° using ice / water bath. The reaction mixture was stirred overnight. The reaction mixture was neutralised using dilute HCl and extracted with ether. The ether layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude amide. This was recrystallised from ethanol to give **9**, as colourless needles (28.63g, 95%). m.p. 168 - 170 °C. υ_{max} (nujol) 3240 (N-H), 1600 (C=O), 1525 (C=C), 1340, 1210, 1110, 980 cm^{-1}. δ_H (300 MHz; $CDCl_3$) 7.65 (1H, d, J=16Hz, COC<u>H</u>=CHPh), 7.28 - 7.45 (5H, m, Ph), 6.40 (1H, d, J=16Hz trans, COCH=C<u>H</u>Ph), 5.90 (1H, bd, J=7Hz, N<u>H</u>CHPhCH$_3$), 5.29 (1H, quintet, J=7Hz NHC<u>H</u>PhCH$_3$), 1.58 (3H, d, J=7Hz, NHCHPhC<u>H</u>$_3$). *m/z* (EI) 252 (MH^+ 10), 251(M^+ 57), 132 (57), 132 (21), 131 (100), 121 (6) 120 (43), 103 (44), 91 (20), 77 (42), 51 (16%). Found: C, 81.15; H, 6.7; N, 5.35. $C_{17}H_{17}NO$ requires C, 81.25; H, 6.82; N, 5.57%.

Preparation of N-(R)-1-(1-naphthyl)ethyl cinnamamide **10**

Compound **10** was prepared as described for compound **9**. The crude amide obtained as a colourless solid was recrystallised from ethanol to give the title compound as colourless needles (8.25 g, 94%). m.p. 189 - 190 °C. υ_{max} (nujol) 3250 (N-H) 1630 (C=O), 1595 (C=C), 1510, 1200, 1100, 960, 850 cm^{-1}. δ_H (300 MHz; $CDCl_3$) 8.15-7.82 (2H, m, Nap), 7.65 (1H, d, J=14Hz, COC<u>H</u>=CHPh) 7.25-7.60 (5H, m, Nap), 6.32 (1H, d, J=14Hz trans, COCH=C<u>H</u>Ph), 6.08 (1H, q, J=7Hz, NHC<u>H</u>NapCH$_3$), 5.90 (1H, bd, J=7Hz, N<u>H</u>CHNapCH$_3$), 1.72 (3H, d, J=7Hz, NHCHNapC<u>H</u>$_3$). δ_C (100MHz; $CDCl_3$) 164.776 (C=O), 414.142,138.027, 134.646, 133.792, 125.089, 123.369, 122.572, 120.489, 112.988, 44.675 (NH<u>C</u>HNapCH$_3$), 20.479 (NHCHNap<u>C</u>H$_3$). *m/z* (EI) 302 (MH^+ 12), 301 (M^+ 52), 170 (74), 154 (29),131 (100), 127 (18), 103 (53), 77 (45), 51 (19%). Found: C, 83.45; H, 6.25; N, 4.5. $C_{21}H_{19}NO$ requires C, 83.6; H, 6.35; N, 4.64%.

Preparation of N-(S)-α-methylbenzyl thiocinnamamide, **11**.

N-(S)-α-Methylbenzylcinnamamide **9** (1.00 g, 3.98 mmol) was dissolved in THF (50cm^3) and phosphorus pentasulphide (0.884 g, 1.99 mmol) was added portion wise at room temperature. Once the addition was complete the mixture was irradiated with ultrasound for 8 h. The reaction mixture was filtered through celite and the solvent removed *in vacuo*. The reaction mixture was redissolved in ether, dried ($MgSO_4$) and the solvent removed *in vacuo* to give the crude thioamide. This was purified by column chromatography (ethyl acetate : hexane 1:10). The resulting product was recrystallised from ethanol to give **11** as golden needles (0.549g, 52%). m.p. 90 - 92 °C. υ_{max} (nujol) 3285 (N-H str.) 1700 (C=O), 1590 (C=C), 1510, 1410, 1210, 830 cm^{-1}. δ_H (300 MHz; $CDCl_3$) 7.80 (1H, d, J=16Hz, CSC<u>H</u>=CHPh), 7.22 - 7.55 (5H, m, Ph), 6.81 (1H, d, J=16Hz trans, CSCH=C<u>H</u>Ph), 5.95 (1H, q, J=7Hz, NHC<u>H</u>PhCH$_3$), 1.65 (3H, d, J=7Hz, NHCHPhC<u>H</u>$_3$). *m/z* (EI) 268 (MH^+ 21), 234 (M^+ 6), 162 (12), 147 (22),130 (16), 120 (44), 115 (33), 111 (10), 105 (50), 77 (35), 55 (27%). Found: C, 76.6; H, 6.65; N, 5.35; S, 11.90. $C_{17}H_{17}NS$ requires C, 76.39; H, 6.41; N, 5.24; S, 11.98 %.

Preparation of N-(R)-1-(1-naphthyl)ethyl thiocinnamamide **12**

Compound **12** was prepared as described for **11**. The resulting yellow solid was recrystallised from ethanol to give the title compound as golden needles (2.95 g, 56%). m.p. 130 - 131 °C. $[\alpha]_D^{18}$ + 63 ° (c=0.99 %, methanol). υ_{max} (nujol) 2980 - 2810 (C-H), 1620 (w), 1500, 1470 - 1440, 1400 - 1370, 1170 cm^{-1} δ_H (300 MHz; $CDCl_3$) 8.11-7.92 (2H, m, Nap), 7.80 (1H, d, J=16Hz, CSC<u>H</u>=CHPh)) 7.25 - 7.60 (5H, m, Nap), 6.77 (1H, d, J=16Hz trans, CSCH=C<u>H</u>Ph), 6.55 (1H, bquintet, J=7Hz, NHC<u>H</u>NapCH$_3$), 1.86 (3H, d, J=7Hz, NHCHNapC<u>H</u>$_3$). δ_C (100MHz; $CDCl_3$) 164.776 (C=O), 141.809, 129.508, 128.722, 128.496, 127.642, 127.136, 126.746, 125.846, 124.823, 123.270, 122.982, 112.654, 50.229 (NH<u>C</u>HNapCH$_3$), 17.685 (NHCHNap<u>C</u>H$_3$). *m/z* (EI) 318 (MH^+) (21), 317 (M^+) (76), 284 (74), 170 (37), 168 (22), 160 (16),

155 (100), 147 (26), 128 (32), 115 (38), 103 (14), 91(13), 77 (22%). Found: C, 79.2; H, 5.95; N, 4.4; S, 10.0. $C_{21}H_{19}NS$ requires C, 79.4; H, 6.03; N, 4.41; S, 10.09%.

Cycloaddition of N-(S)-α-methylbenzyl thiocinnamamide, **11**, *with N-phenyl maleimide*

N-(S)-α-Methylbenzyl thiocinnamamide, **11**, (0.200 g, 0.75 mmol) and N-phenyl maleimide (0.194 mg, 1.12 mmol) were dissolved in dichloromethane (3 cm^3) and pyridine (0.120 cm^3, 1.5 mmol) was added. A solution of acetyl chloride (0.110 cm^3, 1.5 mmol) in dichloromethane (2 cm^3) was added dropwise and the solution became a deep red colour. The reaction mixture was heated at reflux for 4 h until a pale yellow colour was observed. The reaction mixture was diluted with dichloromethane (15 cm^3) and washed successively with dilute acid, 10% w/v potassium carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual yellow oil was purified by column chromatography (ethyl acetate : hexane 1:10 - 1:1) to give a mixture of isomers as a colourless foam (345 mg, 95%).
Chiral HPLC was used to determine the ratio of the cycloaddition products. The solvent system used was hexane : IPA 75 : 25. The column was 25cm x 0.46cm Chiralpak AD. Four peaks were detected in the ratio 59 : 30: 10 : 1 with corresponding retention times of 42.5, 36.45, 24.32 and 19.8 min, respectively.

Preparation of exo, 6-(N-acetyl, N-(R)-1-(1-naphthyl)ethylamino)-3,4-dihydro-4β-phenyl-N-(8)-phenylpyrrolo-[3,4-b]-2H-thiopyran-7,9-dione, **13**.

Compound **13** was prepared as described above. The residual yellow oil was purified by column chromatography (ethyl acetate : hexane 1:10) to give a mixture of isomers as a colourless foam (0.610g, 92%).
Chiral HPLC was used to determine the ratio of the cycloaddition products. The solvent system used was hexane : IPA 60:40. The column was 25cm x 0.46cm Chiralpak AD. Four peaks were detected in the ratio 72 : 28: >0.1 : >0.1 with corresponding retention times of 9.5 and 18.7 min respectively. **13** was found to correspond to the component of 72 % ratio with a retention time of 9.5 min.
The mixture was purified by column chromatography (ethyl acetate : hexane 1:10) and the resulting colourless solid was recrystallised from dichloromethane hexane to give the title compound, **13** as colourless prisms. m.p. 221 - 223 °C. υ_{max} (nujol) 1795,1705 (C=O), 1675, 1560, 1515, 1455, 1440, 1395 cm^{-1}. δ_H (400 MHz; $CDCl_3$) 7.1-7.9 (17H, m, Ar), 6.57 (1H, q, J=6.6Hz, C<u>H</u>CH_3), 6.25 (2H, d, J=6.9Hz, *ortho* Ph), 5.13 (1H, d, J=4.61Hz, H5), 3.91 (1H,d, J=8.5, H2), 3.34 (1H, ddd, J=5.81, 7.89, 4.61Hz, H4), 2.44 (1H, ddd, J=7.89, 5.81, 8.46Hz, H3), 2.10 (3H, s, C<u>H</u>$_3$CO), 1.96 (3H, d, J=6.6Hz, C<u>H</u>$_3$CHNphth). δ_C (100MHz; $CDCl_3$) 173.75 (C=O), 169.67 (C=O), 139.66 (C=OCH_3), 135.03 (q), 134.034 (q), 133.50 (q), 133.01 (CH), 132.26 (q) 131.03 (q), 129.13 (q), 128.89, 128.75, 128.54, 127.71, 127.20, 127.13, 125.98, 125.90, 125.48, 124.77, 123.58, (ArCH), 50.34 (C<u>H</u>CH_3) 49.37 (CH), 44.11 (CH), 42.88 (CH), 22.63, 17.98 (CH_3). *m/z* (EI) 533 (MH^+ 4), 532 (M^+ 8), 377 (24), 173 (9), 155 (100), 129 (12), 115 (10%). Found: C, 74.3; H, 5.30; N, 5.15; S, 6.05; $C_{33}H_{28}N_2O_3S$ requires C, 74.42; H, 5.30; N, 5.26; S, 6.01%.
See appendix for X-ray data

Preparation of: 6-(N-acetyl, N-(R)-1-(1-naphthyl)ethylamino)-3,4-dihydro-4β-phenyl-2H-cyclopenta-[b]-thiopyran. **15.**

N-(R)-1-(1-Naphthyl)ethyl thiocinnamamide **12** (0.4 g, 1.26 mmol) was dissolved in pyridine, (0.152 cm^3, 1.89 mmol) and dichloromethane (6 cm^3) and cyclopentene (4 cm^3) were added. A solution of acetyl chloride (0.134 cm^3, 1.89 mmol) in dichloromethane (2 cm^3) was added dropwise. The reaction mixture developed a dark red appearance and was left stirring for 4 h until the colour faded to pale yellow. The reaction mixture was diluted with dichloromethane (25 cm^3) and successively washed with dilute hydrochloric acid, 10% w/v potassium carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual yellow oil was purified by column chromatography (ethyl acetate : hexane 1:7). The resulting colourless solid was recrystallised from dichloromethane / hexane to give **15** as colourless prisms (0.48 g, 90%). m.p. 124.5 - 126 °C. $[\alpha]_D^{18}$ + 23 ° (c=0.99 %, methanol). υ_{max} (nujol) 2950 - 2840 (C-H), 1640, 1620 (C=O), 1450, 1370, 1350, 1330, 1250, 1190, 1050 cm^{-1}. δ_H (400 MHz; $CDCl_3$) 8.0 - 6.9 (10H, m, Ph), 6.80 (1H, q, J=7Hz, C<u>H</u>CH_3), 6.12 (2H, d, J=6Hz, Ar), 4.84 (1H, d, J=4Hz, H5), 3.21 (1H, m,

H2), 2.80 (1H, m, H3), 2.15 (3H, s, $COC\underline{H}_3$), 1.92 (3H, t, J=7Hz, $CHC\underline{H}_3$), 2.03 - 1.87 (1H, m, $H\beta 7$), 1.88 - 1.77 (2H, m, $H_a 9$, $H_x 8$), 1.70 - 1.57 (1H, $H\alpha 7$), 1.55-1.36 (2H, m, $H_b 9$, $H_y 8$). *m/z* (EI) 428 (MH^+ 23), 427 (M^+ 72), 384 (100), 316 (16), 272 (60), 155 (24%). Found: C, 78.8; H, 6.7; N, 3.3; S 7.45. $C_{28}H_{29}NOS$ requires C, 78.66; H, 6.84; N, 3.27, S 7.49%. see appendix for X-ray data

General procedure for preparation of chiral acylating agents:
Example preparation : 2-phenyl propionyl chloride

Thionyl chloride (0.286 cm^3, 3.9 mmol) was added dropwise to 2-(S)-phenyl propionic acid (0.393 g, 2.62 mmol) in the presence of a catalytic amount of DMF and the reaction mixture stirred at room temperature. The reaction was monitored by tlc, and after 2 h the reaction had gone to completion. The solvent was removed *in vacuo* and the resulting acid chloride was used crude as a chiral acylating agent.

Preparation of 6-(N-2-(S)-phenyl propionyl, N-ethylamino)-3,4-dihydro-4-phenyl-N-(8)-phenylpyrrolo-[3,4-b]-2H-thiopyran-7,9-dione. **Table 2, Entry 2.**

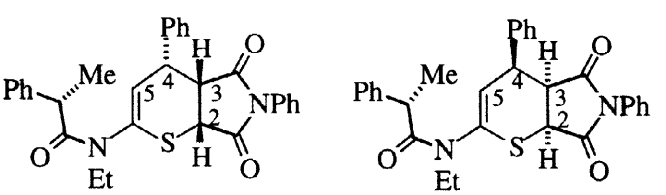
N-Ethyl thiocinnamamide **4**[13] (0.100 g, 0.524 mmol) and N-phenyl maleimide (0.180 g, 1.05 mmol) were dissolved in pyridine (0.085 cm^3, 1.05 mmol) and dichloromethane (2 cm^3). A solution of 2-(S)-phenyl propionyl chloride (0.176 g, 1.05 mmol) in dichloromethane (2 cm^3) was added dropwise. The reaction mixture developed a dark red appearance and was left stirring overnight until the colour faded to pale red. The reaction mixture was diluted with dichloromethane (5 cm^3) and washed successively with dilute acid, 10% w/v potassium carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual yellow oil was purified by column chromatography (ethyl acetate : hexane 1:5) to give a mixture of isomers as a colourless foam (0.22 g, 93%).

Chiral HPLC was used to determine the ratio of the cycloaddition products. The solvent system used was hexane : IPA 70:30, flow rate 1ml/min. 4 peaks were detected in the ratio 45:41:10:4 with corresponding retention times of 31, 21.5, 16.5, and 12.7 min, respectively.

The mixture was further purified by column chromatography (ethyl acetate : hexane 1:10) to give a colourless solid which was recrystallised from ethyl acetate / hexane to give *endo, 6-(N-(S)-2-phenyl-propionyl, N-ethylamino)-3,4-dihydro-4-phenyl-N-(8)-phenylpyrrolo-[3,4-b]-2H-thiopyran-7,9-dione,* as fine, colourless needles. m.p. 151 - 153 °C. This corresponded to 41% of the reaction products with a retention time of 21.5 min.

υ_{max} (nujol) 1700, 1650 (C=O), 1370, 1230, 1150 cm^{-1}. δ_H (400 MHz; $DMSO^{D6}$) 6.95-7.45 (15H, m, Ph), 5.80 (1H, d, J=6Hz, H5), 4.80 (1H, d, J=10Hz, H2), 4.20-4.18 (1H, m, H3), 3.95-3.85 (2H, m, H4, $CH_3CH_x\underline{H}_y$), 3.70 (1H, q, J=7Hz, $CH_3C\underline{H}Ph$), 3.25 (1H, dq, J=7Hz, $CH_3C\underline{H}_xH_y$), 1.40 (3H, d, J=7Hz, $C\underline{H}_3CHPh$), 1.09 (3H, t, J=7Hz, $C\underline{H}_3CH_2$). δ_C(75MHz; $DMSO^{D6}$) 174.0, 173.9, 172.9 ($\underline{C}$=O), 142.9, 142.8, 137.1, 131.1, 129.1, 128.8, 128.7, 128.4, 128.3, 127.5, 126.5, 125.8, 56.5, 49.9, 45.3, 45.0, 44.0 ($\underline{C}$H), 41.2 ($\underline{C}HCH_3$), 33.2 ($\underline{C}H_2$), 21.1, 13.0 ($\underline{C}H_3$). *m/z* (EI) 496 (M^+), 191 (6), 137 (7), 123 (13), 111 (11), 109 (16), 105 (100) 95 (22), 83 (25), 69 (39%). Found: C, 72.65; H, 5.7; N, 5.65; S, 6.45. $C_{30}H_{28}N_2O_3$ requires C, 72.56; H, 5.68; N, 5.64; S, 6.45%.

500MHz Nuclear Overhauser effect difference spectroscopy experiments indicate H2, H3 and H4 are on the same face of the ring and the cycloadduct is *endo*. When H5 was irradiated, a 1.8% enhancement of the signal H4 was observed. When H2 was irradiated, a 6.8% enhancement of the signal corresponding to H3 and a 0.9% enhancement of signal H4 were observed. Irradiation of H3 gave a 7% enhancement of signal H2 and a 2% enhancement of H4. Irradiation of H4 gave 3.7% enhancement of signal H3, a 1.4% enhancement of signal H2, and a 2% enhancement of signal H5.



Cycloaddition of N-ethyl thiocinnamide **4** *with N-phenyl maleimide utilising S-camphanoyl chloride as a homochiral acylating agent.* **Table 2, Entry 3**.

N-Ethyl thiocinnamamide[13] **4** (200 mg, 1.0 mmol) and N-phenyl maleimide (0.36 g, 2.09 mmol) were dissolved in pyridine (0.170 cm^3, 2.10 mmol) and dichloromethane (3 cm^3). A solution of (S)-camphanoyl-chloride (0.454g, 2.09 mmol) in dichloromethane (2 cm^3) was added dropwise. The reaction mixture developed a dark red appearance and was left stirring at room temperature for 6h until a faint orange colour was observed. The reaction mixture was diluted with dichloromethane (15 cm^3) and washed successively with dilute acid, 10% w/v potassium carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual orange oil was purified by column chromatography (ethyl acetate : hexane 1:1) to give a mixture of isomers as a pale yellow foam (0.495 g, 87%). Chiral HPLC was used to determine the ratio of the cycladdition products. The solvent system used was hexane : IPA 60:40 flow rate 1ml/min. The column was 25cm x 0.46cm Chiralpak AD. Four peaks were detected in the ratio 39 : 36 : 18 : 11 with corresponding retention times of 14.5, 17.3, 12.5, and 11.5 min, respectively.

Preparation of 6-(N-(R)-α-methoxyphenyl acetyl, N-ethylamino)-3,4-dihydro-4-phenyl-N-(8)-phenylpyrrolo-[3,4-b]-2H-thiopyran-7,9-dione, **18**.

N-Ethyl thiocinnamamide, **4**,[13] (0.200 g, 1.05 mmol) and N-phenyl maleimide (0.360 g, 2.09 mmol) were dissolved in pyridine (0.170 cm^3, 2.10 mmol) and dichloromethane (5 cm^3). A solution of (R)-α-methoxyphenyl acetyl chloride, **16**, (0.353 g, 2.10 mmol) in dichloromethane (2 cm^3) was added dropwise. The reaction mixture developed a dark red appearance and was left stirring overnight until the colour faded to a pale red. The reaction mixture was diluted with dichloromethane (15 cm^3) and washed successively with dilute acid, 10% w/v potassium carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual yellow oil was purified by column chromatography (ethyl acetate : hexane 1:1) to give a mixture of isomers as a colourless foam (0.492 g, 93%).

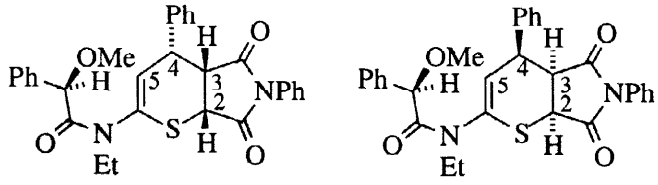
Chiral HPLC was used to determine the ratio of the cycloaddition products. The solvent system used was hexane : IPA 70:30 flow rate 1ml/min. The column was 25cm x 0.46cm Chiralpak AD.

Four peaks were detected in the ratio 72.2 : 27.4 : 0.2 : 0.2 with corresponding retention times of 9.4, 17.7, 6.9, and 6.4 min respectively. Cycloadduct **18**, was found to correspond to the component of 71.2% ratio with a retention time of 9.4 min.

The mixture was purified by column chromatography (ethyl acetate : hexane 1:6). The resulting colourless solid was recrystallised from ethyl acetate / hexane to give **18**, *endo* as fine colourless needles. m.p.182 -183.5 °C. δ_H (500 MHz; $DMSO^{D6}$) 7.06-8.0 (10H, m, Ph), 6.21 (1H, brs, H5), 4.90 (1H, s, C<u>H</u>OMePh), 4.82 (1H, d, J=10Hz, H2), 4.25-4.2 (1H, m, H3), 4.02-3.98 (1H, m, H4), 3.70 (1H, dq, J=7Hz, $CH_3C\underline{H}_xH_y$), 3.15 (1H, dq, J=7Hz, $CH_3CH_x\underline{H}_y$), 3.12 (3H, s, CH_3O), 0.98 (3H, t, J=7Hz, $C\underline{H}_3CH_xH_y$). *m/z* (EI) 513 (M^+)(8), 512 (6), 480 (4), 390 (6), 339 (29), 309 (19), 307 (24), 173 (11), 161 (19), 147 (26), 121 (100), 105 (30), 91 (24), 77 (34%).

Found M^+512.1764 $C_{30}H_{28}N_2O_4S$ requires M^+ 512.1769.

500MHz Nuclear Overhauser effect difference spectroscopy experiments in $DMSOD^6$ at 30 °C revealed H2, H3 and H4 are on the same face of the ring and the cycloadduct is *endo*. Irradiation of H5, gave a 1.5% enhancement of signals C<u>H</u>OMePh and H4. Irradiation of C<u>H</u>OMePh and the close signal H2, gave a 1.3% enhancement of H5, a 2% enhancement of H3, and a 0.75% enhancement of signal H4. Irradiation of H2 and the close signal C<u>H</u>OMePh gave a 5.5% enhancement of H3 and a 0.75% enhancement of H4. Irradiation of H3 gave a 9% enhancement of H2 and a -1.5% enhancement of H4. Irradiation of H4 gave a 1.5% enhancement of H3, a 1.3% enhancement of H2, a 0.75% enhancement of C<u>H</u>OMePh and a 2% enhancement of H5.



18a **18b**

Preparation of exo, 6-(N-acetyl, N-ethylamino)-3,4-dihydro-4β-phenyl-2H-cyclopenta-[b]-thiopyran **19**.

N-Ethyl thiocinnammamide, **4** (0.2 g, 1.02 mmol) was dissolved in pyridine (0.13 cm^3, 1.57 mmol) and dichloromethane (2 cm^3) and cyclopentene (5 cm^3) were added. A solution of acetyl chloride (0.12 cm^3, 1.57 mmol) in dichloromethane (2 cm^3) was added dropwise. The reaction mixture developed a dark red appearance and was left stirring at room temperature overnight until the colour faded to a pale orange. The reaction mixture was diluted with dichloromethane (15 cm^3) and washed successively with dilute acid, 10% w/v potassium carbonate solution and brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo*. The residual yellow oil was purified by column chromatography (ethyl acetate : hexane 1:4) to give **19** as a colourless oil (0.233 g, 74%). Lit.[14] υ_{max} (nujol) 3060,1690 (C=O), 1595, 1395 cm^{-1}.
δ_H (400 MHz; $CDCl_3$) 7.23-7.17 (5H, m, Ph), 5.80 (1H, d, J=5Hz, H5), 3.65 (1H, dq, J=7Hz, $NCH_X\underline{H}_YCH_3$), 3.50 (1H, dq, J=7Hz, $NC\underline{H}_XH_YCH_3$), 3.44 (1H, t, J=5Hz, H4), 2.15 (1H, m, H-3), 2.15 (3H, s, $COC\underline{H}_3$), 1.87-2.03 (2H, m, Hβ7, H_y8), 1.55-1.83 (4H, m, H_α7,H_x8, $H_2$9), 1.14 (3H, t, J=7Hz, $NCH_2C\underline{H}_3$). δ_C (100mHz; $CDCl_3$) 169.3 (C=O), 144.0 (ipso C Ph), 136.2 (C6), 128.4, 127.5, 126.5 (Ar), 45.9 (C3), 44.5 (C4), 43.0, (C2), 40.2 ($N\underline{C}H_2CH_3$), 32.3 (C7), 29.0 (C9), 21.5 ($NCO\underline{C}H_3$) 21.2 (C8). *m/z* (EI) 301 (M^+)(61), 272 (13), 233 (56), 190 (99), 147 (100), 130 (45), 115 (25), 103 (20), 91 (30), 70 (22), 43 (39%).

Preparation of racemic thiolactone, **20**.

6-(N-Acetyl, N-ethylamino)-3,4-dihydro-4β-phenyl-2H-cyclopenta-[b]-thiopyran, **19** (0.233 g, 0.774 mmol) was dissolved in glacial acetic acid (6 cm^3) and water (4 cm^3) was added. The reaction mixture was heated at reflux for 6 h. The cooled reaction mixture was poured into water, neutralised using sodium carbonate solution and extracted with dichloromethane. The organic layer was dried ($MgSO_4$), the solvent removed *in vacuo*. The residual oil purified using column chromatography (ethyl acetate : hexane 1:6). The resulting gum was crystallised from hexane to give **20** as colourless needles (0.140 g, 78%). m.p. 58 - 59.5 °C. Lit.[14] (58 - 59.5 °C). υ_{max} (nujol) 1655, 1595, 1575, 1130, 1045 cm^{-1}. δ_H (400 MHz; $CDCl_3$) 7.1-7.9 (5H, m, Ph), 4.0 (1H, q, J=7Hz, H2), 2.91(1H, m, H4), 2.79 (1H, m, H_α5), 2.66 (1H, dd, J=2Hz, 15Hz, Hβ5), 2.55 (1H, dq, H3 J=8Hz), 2.22 (1H, m, Hβ7), 1.74-1.93 (3H, m, H_α7, H_α8, H_α9), 1.47-1.64 (2H, m, Hβ8, Hβ9). δ_C (100MHz; $CDCl_3$) 203.927 (C=O, C6), 143.255 (ipso C Ph), 128.808, 127.244, 126.947 (ArCH), 47.947 (C5), 47.142 (C4), 45.669, 45.455 (C2, 3), 33.701, 31.160, 24.615 ($\underline{C}H_2$, C7, 8, 9). *m/z* (EI) 232 (M^+)(50), 204 (100), 170 (18), 161 (11), 144 (78), 136 (56), 129 (53), 15 (29), 104 (70), 91 (43), 77 (27%). Found: C, 72.6; H, 6.9; S, 13.8. M^+232.0922 $C_{14}H_{16}OS$ requires C, 72.39; H, 6.94; S, 13.78% M^+232.0923.

Preparation of optically active thiolactone **20**

6-(N-Acetyl,N-(R)-1-(1-naphthyl)ethylamino)-3,4-dihydro-4β-phenyl-2H-cyclopenta-[b]-thiopyran, **15** (0.132 g, 0.468 mmol) was dissolved in glacial acetic acid (6 cm^3) and water (4 cm^3) was added. The reaction mixture was heated at reflux for 2 days. The cooled reaction mixture was poured into water, neutralised using sodium carbonate solution and extracted with dichloromethane. The organic layer was dried ($MgSO_4$), the solvent removed *in vacuo*. The residual oil was purified using column chromatography (ethyl acetate : hexane 1:6). The resulting solid was recrystallised from hexane to give **20** as colourless needles (71 mg, 65%). m.p. 56 - 58 °C starting material **15** was also recovered (49 mg, 25%). $[\alpha]_D^{18}$ + 106 ° (c=1.8, methanol) υ_{max} (nujol) 1655, 1595, 1130, 1045 cm^{-1}. δ_H (400 MHz; $CDCl_3$) 7.1-7.9 (5H, m, Ph), 4.0 (1H, q, J=7Hz, H2), 2.91(1H, m, H4), 2.79 (1H, m, H_α5), 2.66 (1H, dd, J=2Hz, 15Hz, Hβ5), 2.55 (1H, dq, H3 J=8Hz), 2.22

(1H, m, Hβ7), 1.74-1.93 (3H, m, Hα7,Hα8, Hα9), 1.47-1.64 (2H, m, Hβ8, Hβ9). δ_C (100MHz; $CDCl_3$) 203.927 (C=O, C6), 143.255 (ipso C Ph), 128.808, 127.244, 126.947 (ArCH), 47.947 C5, 47.142 C4, (45.669, 45.455 C2, 3), 33.701, 31.160, 24.615 ($\underline{C}H_2$, C7, 8, 9). *m/z* (EI) 232 (M^+)(49), 204 (100), 170 (18), 161 (12), 144 (77), 136 (56), 129 (52), 15 (29), 104 (70), 91 (44), 77 (28%). Found M^+ 232.0916 $C_{14}H_{16}OS$ requires M^+ 232.0922.

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† Presently at the School of Chemistry, University of Rochester, Rochester, NY 14627, USA.

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