Reversal of facial selectivity in a thia-Claisen rearrangement by incorporation of a vinylic bromine substituent†

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Thia-Claisen rearrangements have been carried out using *N*-benzylpyrrolidine-2-thione and chiral allylic bromides derived from D-mannitol. Introduction of a bromine atom onto the double bond of the allylic bromide reverses the sense of diastereoselectivity in the [3,3]-sigmatropic rearrangement. Density functional theory calculations lead us to rationalise the observed selectivity in terms of a Cíeplak effect.

Introduction

The Claisen rearrangement of allyl vinyl ethers and related [3,3]-sigmatropic rearrangements have been extensively studied and widely utilised in synthesis.[1] In these reactions, a new carbon–carbon bond is formed, and one or two new stereogenic centres may be created.

As a consequence of the ordered transition state of such rearrangements, it is possible to use existing stereogenic centres to direct the formation of new ones.[2] Most of the examples of stereoselective rearrangement reported in the literature involve 1,3-chirality transfer from a stereogenic centre within the six atoms of the allyl vinyl ether system. Examples of asymmetric induction from an external stereogenic centre are less common; in particular, there are very few cases in which such a stereogenic centre on the "allyl" portion of the molecule has proven effective in inducing high levels of asymmetry in the rearrangement step.[3,4]

Several [3,3]-sigmatropic rearrangements of *E*-alkenes bearing an electronegative substituent in the allylic position are depicted in Scheme 1; the sense of asymmetric induction is the same in all cases, although its magnitude varies. For example, Ireland–Claisen rearrangement of ester **1** gives **2** as the major product with a diastereomeric ratio of 1.4 : 1,[5,6]

while rearrangement of the related ketene dithioacetal **3** occurs at room temperature to give **4** as the major component of a 1.9 : 1 mixture.[7] Johnson–Claisen rearrangement of allylic alcohol **5**, bearing a sulfur substituent at the allylic stereogenic centre, gives ester **6** as the major component of a 1.5 : 1 mixture of stereoisomers.[8] Reformatskii–Claisen rearrangement of allylic ester **7** gives **8** as the major compound in an 8.7 : 3.4 : 1.8 : 1 mixture of diastereomers.[9]

A higher level of asymmetric induction is observed in the Ireland–Claisen rearrangement of amino acid-derived esters such as **9**, with **10** being the only product stereoisomer obtained.[3] Similarly, a stereoselective zwitterionic [3,3]-rearrangement takes place on treatment of **11** with dichloroketene, leading to **12** as a single stereoisomer.[4a]

As part of a programme directed towards the synthesis of the sarain alkaloids, we have utilised a thia-Claisen rearrangement[10] to establish the two stereogenic centres in thiolactam intermediate **14** (Scheme 2). Following *S*-alkylation of *N*-benzylpyrrolidine-2-thione (**13**) with the appropriate allylic bromide, deprotonation with triethylamine afforded directly the rearranged product **14** with >40 : 1 diastereoselectivity.[11]

Herein we report our efforts to modify this diastereoselective reaction to give products such as **14** in enantiomerically enriched form. Our hope at the outset was that replacement of the achiral allylic bromide in Scheme 2 with chiral analogues such as **15** would lead to a preponderance of one of the diastereomeric products **16** and **17** (Scheme 3). Following separation of these compounds, cleavage of the protected diol unit could potentially lead to compound **14** as a single enantiomer.[12]
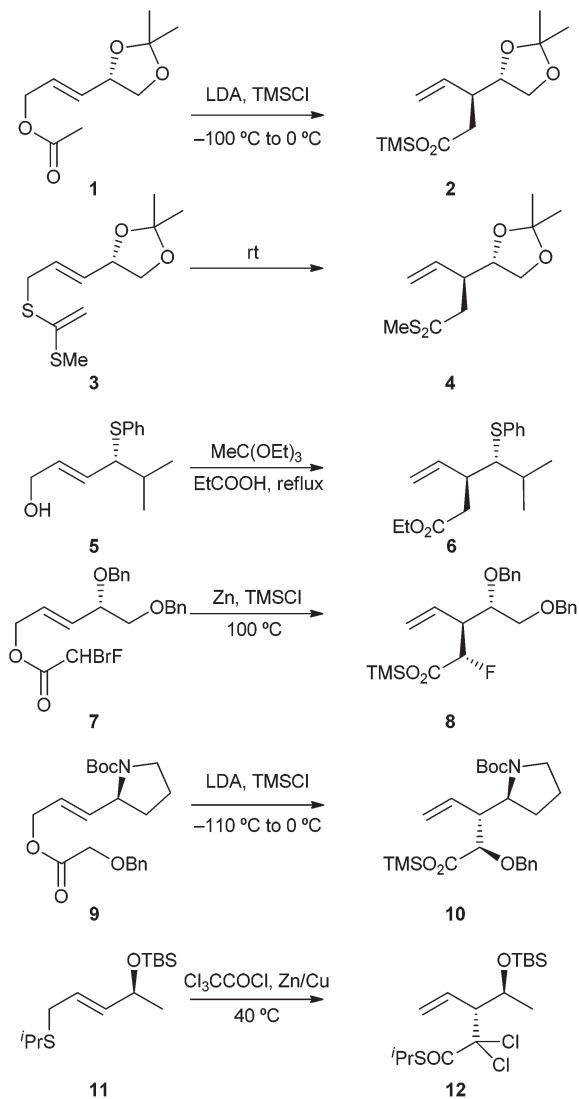
Six allylic bromides were investigated (Fig. 1): *E*-disubstituted alkenes **18a** and **19a** and *Z*-alkene **20a**, together with the analogous compounds **18b–20b** in which the double bond carries an additional bromine substituent.

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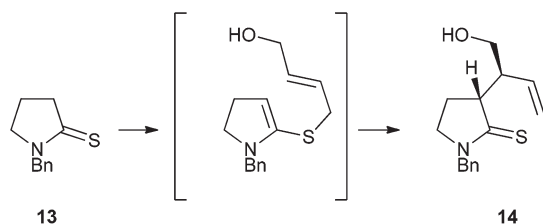[b]*Unilever Centre for Molecular Science Informatics, Department of Chemistry, Lensfield Road, Cambridge, CB2 1EW, UK*
†Electronic supplementary information (ESI) available: Details of the synthesis of allylic bromides **18a–20b** and of stereochemical assignments of thia-Claisen products; NMR spectra for all new compounds synthesised. Details of computational studies, with Cartesian coordinates and energies of transition states **Ia–IIc** and **Ia*–IIc*** for substrates **27a** and **27b**. See DOI: 10.1039/c3ob41580e

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Scheme 1 Previously reported diastereoselective Claisen rearrangements.

Scheme 2 Thia-Claisen reaction. *Reagents and conditions*: (E)-HOCH₂CH=
CHCH₂Br, MeCN then Et₃N, 40 °C, 67%.

Results and discussion

Preparation of allylic bromides

Allylic bromides **18a–20b** were all synthesised by standard methods from 1,2 : 5,6-diisopropylidene-D-mannitol. Details of
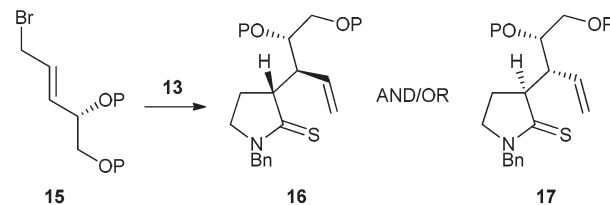
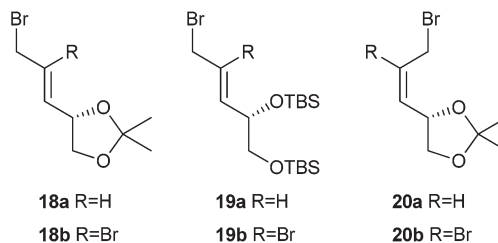**Scheme 3** Proposed diastereoselective thia-Claisen rearrangement.

Fig. 1 Allylic bromides used in the study.

these syntheses, including full spectroscopic data, can be found in the ESI.†
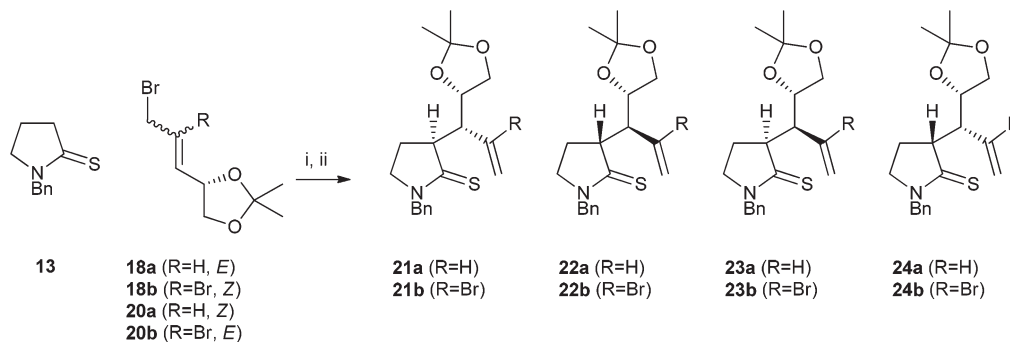
Thia-Claisen rearrangements

Initial attempts at the key thia-Claisen rearrangement were carried out using bromide **18a** under the conditions which we had previously developed.[11] Thus N-benzylpyrrolidine-2-thione (**13**) was alkylated with allylic bromide **18a** in acetonitrile. Addition of 4 Å molecular sieves was found to be helpful in suppressing undesired side reactions. Following dilution with further acetonitrile, the mixture was warmed to 40 °C and tri-ethylamine was added. The thia-Claisen rearrangement took place to give a mixture of three stereoisomeric thiolactam products, **21a**, **22a** and **23a** in a ratio of 69 : 28 : 3 (Scheme 4 and Table 1, entry 1). The two predominant products were those expected if the rearrangement proceeds through a chair transition state (see ESI† for details of the assignment of stereochemistry).

We anticipated that the use of trisubstituted alkene substrate **18b** would give **21b** with an enhanced level of asymmetric induction. Surprisingly, use of **18b** instead led to a *reversal* in the stereochemical preference of the reaction, and products **21b**, **22b** and **23b** were formed in a 7 : 88 : 5 ratio (Table 1, entry 2).

The two geometrically isomeric allylic bromides **20a** and **20b** were also subjected to the thia-Claisen sequence; with these substrates, diastereoselectivities were modest and, as expected, the major stereoisomer **23** from these rearrangements was one which had been a minor component in the previous reactions (Table 1, entries 3 and 4), consistent with a chair-like transition state. The same stereoisomer was the major product for both substrates.

Use of the bis-silyl ether **19a** in place of the acetonide **18a** gave a markedly higher ratio of thia-Claisen products

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Scheme 4   Thia-Claisen rearrangement of acetonide-containing substrates. *Reagents and conditions*: (i) MeCN, rt, 4 Å molecular sieves; (ii) Et$_3$N, 40 °C.

Table 1   Products of thia-Claisen rearrangements

Entry	Bromide	Ratio 21 : 22 : 23 : 24[a]	Yield 21[b]/%	Yield 22[b]/%	Yield 23[b]/%	Yield 24[b]/%
1	18a	69 : 28 : 3 : 0	38	10	1	—
2	18b	7 : 88 : 5 : 0	2	52	2	—
3	20a	25 : 25 : 50 : 0	10	11	18	—
4	20b	5 : 17 : 61 : 17	1	6	39	9

[a] Ratios determined from the ^{1}H NMR spectra of the crude reaction mixtures. [b] Isolated yields following column chromatography.
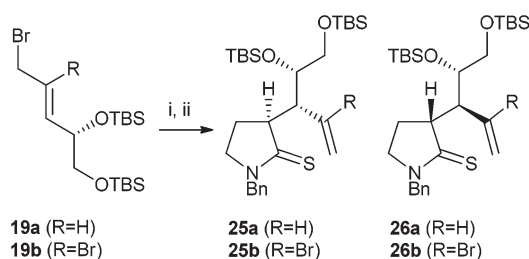
Scheme 5   Thia-Claisen rearrangement of silyl ether-containing substrates. *Reagents and conditions*: (i) 13, MeCN, rt, 4 Å molecular sieves; (ii) Et$_3$N, 40 °C.

Fig. 2   Facial selectivity in the *N,S*-ketene acetal intermediates derived from **18** and **19**.

Table 2   Products of thia-Claisen rearrangements

Entry	Bromide	Ratio 25 : 26[a]	Yield 25[b]/%	Yield 26[b]/%
1	19a	>97 : 3	41	1
2	19b	—[c]	—	—

[a] Ratio determined from the ^{1}H NMR spectrum of the crude reaction mixture; the reaction of **19a** also generated some unidentified by-products. [b] Isolated yields following column chromatography. [c] No thia-Claisen rearrangement product was obtained from this reaction.

(Scheme 5, Table 2, entry 1); in this case only two stereo-isomers, **25a** and **26a**, were observed. Attempts to use bis-silyl ether **19b** in thia-Claisen reactions were completely unsuccessful, yielding none of the expected products **25b** and **26b**.

Discussion

The diastereoselectivity of the thia-Claisen rearrangements ranged from poor (in the case of **18a** and **20a**) to excellent (**18b**

and **19a**). The choice of protecting groups was seen to have a significant effect: bis-silyl ether **19a** (entry 1, Table 2) gave a much more diastereomerically enriched mixture of products than acetonide **18a**.

Installation of a bromine atom on the double bond had a profound effect on stereoselectivity, with the sense of asymmetric induction reversed between acetonides **18a** and **18b** (entries 1 and 2, Table 1).

In each of the rearrangement reactions, the relative configuration of the two newly-formed stereogenic centres in the major product is consistent with a chair-like transition state, while their absolute configuration is determined by any facial selectivity imparted by the pre-existing stereogenic centre. Analysis of the stereochemical course of the reaction indicates that the non-brominated substrates **18a** and **19a** show a tendency for reaction through the conformation **I** (*Re*-face selectivity at the *N,S*-ketene acetal, Fig. 2) while vinyl bromide **18b** reacts primarily through conformation **II** (*Si*-face selectivity).

In trying to elucidate the reasons for this divergent stereoselectivity, it is necessary to consider six reactive conformations of the diene, corresponding to three rotamers about the bond linking the alkene to the stereogenic centre for each of the conformations **I** and **II**. These conformations are depicted in Fig. 3: in conformations **Ia** and **IIa**, the new C–C
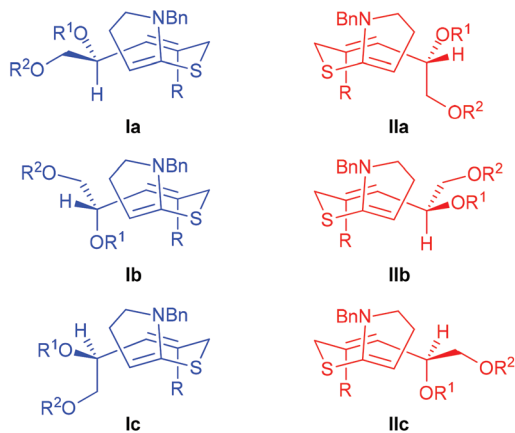
Fig. 3 Possible reactive conformations of the *N,S*-ketene acetal intermediates derived from **18** and **19**.

bond is formed antiperiplanar to the allylic C–O bond; in conformations **Ib** and **IIb**, it is formed antiperiplanar to the allylic C–C bond; while in conformations **Ic** and **IIc**, it is formed antiperiplanar to the allylic C–H.‡

The selectivity observed for the non-brominated substrates **18a** and **19a** is consistent with that shown by all the related literature examples (Scheme 1); such selectivity has previously been rationalised in terms of a reactive conformation corresponding to **Ia**. The electron-rich character of the *N,S*-ketene acetal component means that the rearrangement is expected to occur through a polarised transition state, with a "nucleophilic" ketene acetal fragment and an "electrophilic" allyl component.[13] Attack on the electrophilic component is assumed to take place antiperiplanar to the allylic C–O bond, as this allows stabilization of the newly forming σ-bond by interaction with the low-lying σ*-orbital of the C–O bond;[13,14] hence reaction should take place through either conformation **Ia** or **IIa**. The preference for the former conformation can be understood as **Ia** will suffer less allylic ($A^{1,3}$) strain[15] than **IIa**.

The stereochemical preferences of vinyl bromide substrate **18b** are contrary to all previously reported [3,3]-sigmatropic rearrangement substrates with an electronegative allylic substituent, and this behaviour is harder to explain. Our *a priori* expectation had been that the increased allylic ($A^{1,3}$) strain in conformation **IIa** when R ≠ H would lead to a stronger preference for reactive conformation **Ia** and hence an *enhanced* level of stereoselectivity in favour of product **21b**. The experimental observation, conversely, was that **22b** is the major product in the reaction of bromide **18b**.

It seems unlikely that the reaction of bromide **18b** proceeds through conformation **IIa**, in which allylic strain will be more severe than in conformer **Ia**, and so the other possible conformations must be considered. Conformations **Ib** or **Ic** would lead to product **21b**, while **IIb** or **IIc** would lead to the observed major

‡The structures in Fig. 3 are depicted for clarity with a substituent at the allylic stereocentre eclipsing the vinylic substituent R; the conformations in which the new σ-bond is formed antiperiplanar to an existing substituent are obtained by a rotation of 30° about the C(sp²)–C(sp³) bond.

product **22b**. As there was no obvious explanation for the change in stereochemical preference on bromination of the double bond, we carried out a computational study to gain further insight into the stereochemical course of these reactions.[16]

Computational studies

Initial attempts to locate transition states for compounds containing a dioxolane ring indicated a complicated potential energy surface on which multiple transition states, differing only in the conformation of the dioxolane, could be identified. In order to simplify the computational problem, while retaining the salient features of substrates **18** and **19**, we chose to carry out the computational study on the rearrangement of allylic methyl ethers **27a** and **27b** (Fig. 4).

A detailed search for chair-like transition state geometries was undertaken using density functional theory: for each of the two substrates **27a** and **27b**, we considered (i) *Re* and *Si*-face reaction of the *N,S*-ketene acetal (*i.e.* **I** and **II**, Fig. 2); (ii) three rotamers about the bond linking the alkene to the stereogenic centre (*i.e.* **a**, **b** and **c**, Fig. 3); and (iii) three staggered rotamers about the MeO–C bond, giving a total of 18 possible transition state structures for each compound. For each of the two compounds **27a** and **27b**, transition states were located for 17 of the 18 possible conformations – the missing conformation in each case being one of type **IIb** in which the *O*-methyl group would be directed into the pyrroline ring.

For all six conformer types **Ia–IIc** for both substrates, the rotamer in which the O–CH₃ bond lay antiperiplanar to the alkene portion of the molecule was markedly lower in energy than the other two rotamers around the C–OCH₃ bond, and so only these rotamers were considered for the remainder of the study.

Having identified transition states corresponding to the conformers **Ia–IIc**, it was noted that two different conformations of the pyrroline ring, differing in the direction of pyramidalisation of the nitrogen atom, were present among the transition states identified. Further searching was therefore carried out to locate transition states for *both* pyrroline conformers in every case.

This exhaustive search resulted in twelve transition state structures for each of the two substrates, corresponding to the six conformations **Ia–IIc** each with two different pyrroline conformations. Fig. 5 shows twelve of these 24 transition state structures[17] – in each case, the structure depicted is the lower-
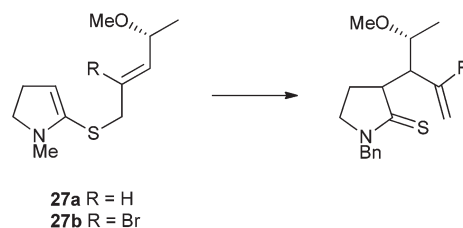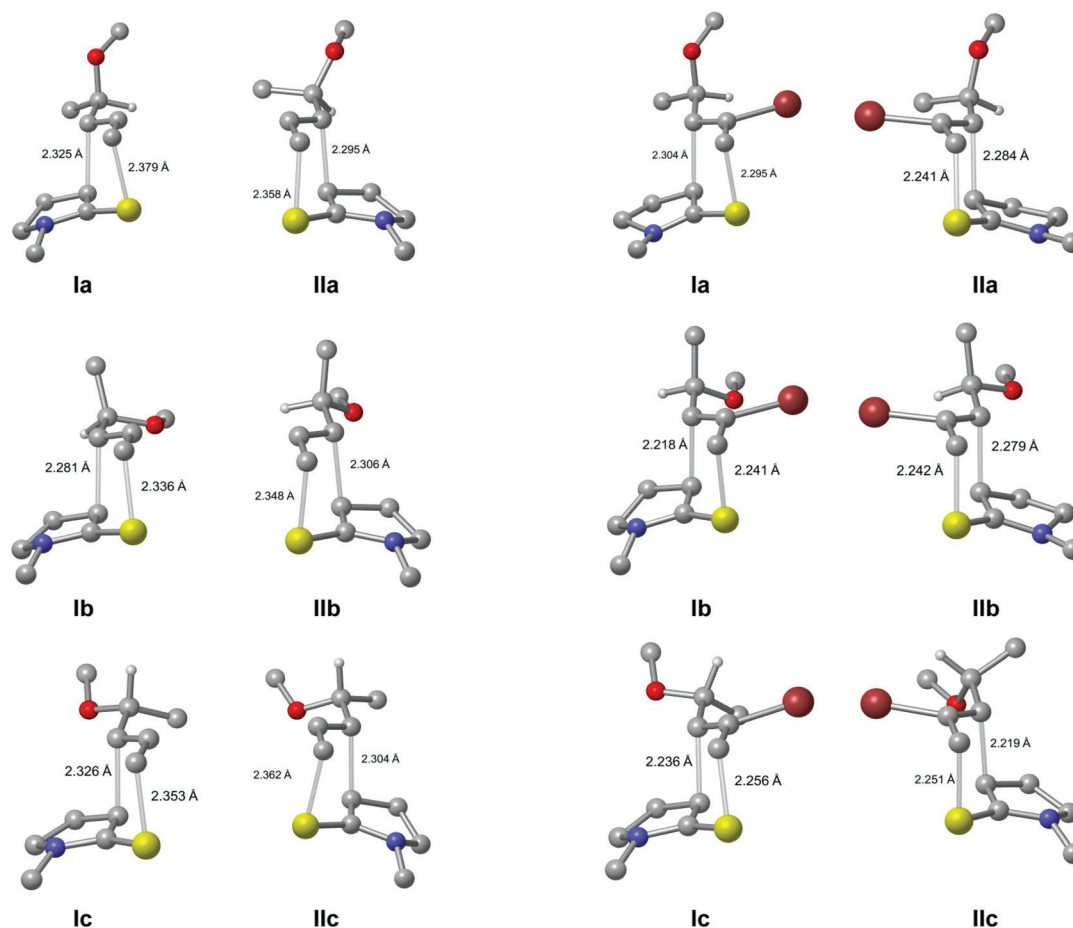
Fig. 4 Simplified structures for computational studies.

27a R = H
27b R = Br

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Fig. 5 Transition state structures for thia-Claisen rearrangement of **27a** (left) and **27b** (right). Hydrogen atoms, other than the one at the stereogenic centre, are omitted for clarity.

Table 3 Properties of the thia-Claisen transition states

Transition structure	Facial orientation[a]	Antiperiplanar atom[b]	27a $\Delta\Delta G^{\ddagger}$/kJ mol^{-1} [M06-2X/B3LYP][c,d]	27b $\Delta\Delta G^{\ddagger}$/kJ mol^{-1} [M06-2X/B3LYP][c,d]
Ia	*Re*	O	21.1 (17.5)	10.4 (8.2)
IIa	*Si*	O	9.9 (7.2)	27.4 (21.7)
Ib	*Re*	C	0.0 (0.0)	11.3 (9.9*)
IIb	*Si*	C	3.7 (5.6*)	0.0 (0.0)
Ic	*Re*	H	8.3 (10.3*)	6.0 (8.1)
IIc	*Si*	H	22.1 (21.0)	7.3 (8.6*)

[a] Face selectivity as defined by reaction of the *N*,*S*-ketene acetal moiety. [b] Atom bonded to the stereogenic centre which is most nearly antiperiplanar to the forming C–C bond. [c] Gibbs energy of transition states relative to the lowest in energy for that set. Figures in parentheses indicate solution (THF) phase energies calculated for the gas-phase optimised structures. An asterisk denotes the Gibbs energy of a structure differing in the pyrroline conformation from that depicted. [d] Gibbs energy calculated by a single-point energy calculation with the M06-2X functional on the B3LYP gas-phase optimised structure, followed by a free energy correction from the B3LYP values.[17]

energy of the two pyrroline conformations. The relative Gibbs energies of these transition states are collected in Table 3.[18] In four cases, the energetic ordering of the two pyrroline conformations was reversed between gas-phase and solution-phase calculations; these cases are marked with an asterisk.

Contrary to our expectation, the lowest-energy transition states for the reaction of **27a** did not place the C–O bond of the stereogenic centre antiperiplanar to the newly-forming C–C bond. Rather the most favourable transition states are those in which the allylic C–C bond occupies the antiperiplanar position (*i.e.* **Ib** and **IIb**), with structure **Ib** (corresponding to the observed major product) having the lowest energy of all the transition states. Only a small Gibbs energy difference was found between structures **Ib** and **IIb** (3.7 kJ mol^{-1} in the gas phase, 5.6 kJ mol^{-1} in solution). This corresponds qualitatively to the low stereoselectivity observed in the reaction.

In the case of brominated substrate **27b**, the lowest energy transition state is again one in which the newly forming C–C bond is situated antiperiplanar to the C–C bond at the stereogenic centre; for this compound however, structure **IIb** is markedly lower in energy than structure **Ib**, as would be expected from the greater degree of $A^{1,3}$-strain in **Ib**. Indeed, while **IIb** is the lowest-energy transition state structure for this substrate, the next-lowest is **Ic**, in which a hydrogen atom occupies the antiperiplanar position. The Gibbs energy difference between transition states **IIb** and **Ic** was found to be 6.0 kJ mol^{-1}, rising to 8.1 kJ mol^{-1} when solvation effects were included. These increased energy differences, compared to those found for substrate **27a**, again agree qualitatively with the experimental observation that substrate **18b** reacts with reversed and higher levels of stereoselectivity compared to substrate **18a**.

The indication from these computational studies is thus that there is an intrinsic preference for reaction to take place *anti-* to the carbon substituent at the stereogenic centre and not *anti-* to the oxygen substituent as has been suggested for related systems.[3b,4a,b,5,6e,7,8,13] Intriguingly, an AM1 study of the zwitterionic Claisen reaction of **11** to give **12** (Scheme 1) also appears to show a preference for reaction *anti-* to the carbon substituent but no comment is made by the authors on the conformation of the transition states located.[4c]

A possible explanation for the preferred reactive conformation is that stabilisation of the transition state occurs most effectively not through interaction of the newly forming σ-bond with a low-lying σ* orbital but rather through a Cíeplak effect[19] in which a σ-bonding orbital at the stereogenic centre interacts with the low-lying antibonding orbital of the incipient σ-bond. While the C–H bond is likely to be the best σ-donor, the conformations in which this bond is antiperiplanar to the newly forming σ-bond (**Ic** and **IIc**) are also likely to be the most sterically hindered; reaction *anti-* to the C–C bond is thus a compromise between σ-donor ability and steric hindrance.

For non-brominated substrate **27a**, the energy of transition state **Ib** is slightly lower than that of **IIb** – possibly due to the steric interactions between the pyrroline ring and the allylic methoxy substituent in conformer **IIb**.

In the case of brominated substrate **27b**, however, transition state **Ib** is greatly destabilised by the increased $A^{1,3}$-strain resulting from introduction of the bromine atom; this leaves **IIb** as the lowest energy transition state structure.

If *Z*-allylic bromide **20a** and its vinyl bromide congener **20b** also react with Cíeplak diastereoselection, the corresponding chair conformations should be **III** and **IV**, depicted in Fig. 6. In conformation **III**, $A^{1,3}$-strain is minimised and this should thus represent the dominant reaction pathway regardless of the identity of R. Indeed, the major product observed for both substrates is **23**, corresponding to reaction through conformation **III**.

It is clear from inspection of structures **III** and **IV** that significant destabilising interactions could exist between the allylic substituents and the pyrroline ring; these interactions would be removed in the boat conformations **V** and **VI**. Of the two possible boat conformations, we would expect **V** to be
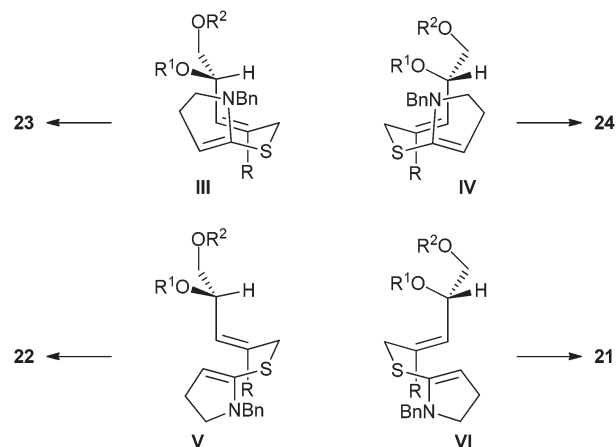

Fig. 6 Possible chair (top) and boat (bottom) conformations of the *N,S*-ketene acetal intermediates derived from **20**.

favoured over **VI** due to the minimisation of allylic strain and hence product **22** should be favoured over **21**.
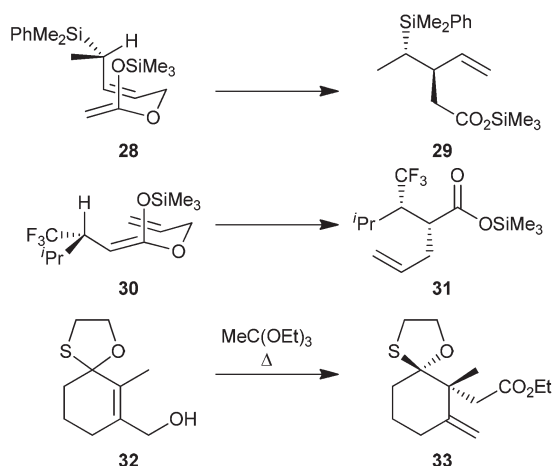
Experimentally, significant amounts of products arising from boat transition states are seen for both substrates. For compound **20b**, as expected, product **22b** predominates over **21b** while for compound **20a**, the products **21a** and **22a** are formed in equal amounts. The reasons for this lack of selectivity between the competing boat transition states when R = H are unclear.

Conclusions

Moderate to high levels of diastereoselectivity can be obtained in the thia-Claisen rearrangement of allyl vinyl sulfides derived from chiral allylic bromides and *N*-benzylpyrrolidine-2-thione. By installing an additional bromine atom on the alkene of the allylic bromide, the stereochemical preference of the reaction may be reversed. These results are summarised in the upper part of Scheme 7: the major isomers obtained from the reaction of bromides **18a** and **18b** have different relative stereochemistry, while those from the reactions of **20a** and **20b** have the same stereochemistry.

Density functional theory calculations suggest that the preferred reactive conformation positions a C–C bond at the existing stereogenic centre antiperiplanar to the newly forming C–C bond, consistent with the operation of a Cíeplak effect. Cíeplak-type diastereoselection in [3,3]-sigmatropic rearrangements has been reported previously. Betson and Fleming[20] found that Ireland–Claisen rearrangement of silyl ketene acetal **28** proceeded through the conformation shown (reaction antiperiplanar to the electropositive silyl substituent) to give **29** in a 93 : 7 diastereomeric ratio (Scheme 6). Similarly, Yamazaki *et al.*[21] showed that Ireland–Claisen rearrangement of **30** proceeded with bond formation antiperiplanar to the isopropyl rather than the trifluoromethyl substituent, while Yadav *et al.*[22] found that Johnson–Claisen rearrangement of allylic alcohol **32** occurred solely on the alkene face which is *anti-* to

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Scheme 6 Cíeplak diastereoselection in [3,3]-sigmatropic rearrangements.[20–22]

the sulfur of the oxathiolane ring, yielding **33**. The preference for this orientation of reaction, together with considerations of allylic strain and other steric interactions, allow us to rationalise the observed stereoselectivities, as shown schematically in the lower part of Scheme 7. In the absence of a vinylic bromide substituent, the intermediate arising from compound **18a**

reacts preferentially through the conformation shown, with the allylic C–O bond approximately eclipsing the alkene and the allylic C–H bond projecting towards the pyrroline portion of the molecule. When a vinylic substituent is present that is *syn*- to the allylic stereocentre, allylic strain becomes the dominant factor. Hence the diene intermediate derived from vinylic bromide substrate **18b** adopts the reactive conformation shown, in which the allylic C–H bond eclipses the alkene such that $A^{1,3}$-strain is minimised. A similar effect is seen in the reactions of allylic bromides **20a** and **20b**; here, the steric interaction is with the allylic methylene group rather than the bromine atom and so both bromides react with the same sense of stereoinduction.

Experimental section

For general experimental procedures, see the ESI.†

Thia-Claisen rearrangement: general procedure

A mixture of thioamide **13** (116 mg, 0.61 mmol), allylic bromide (0.67 mmol), MeCN (1 mL) and 4 Å molecular sieves (250 mg) was stirred under an argon atmosphere for
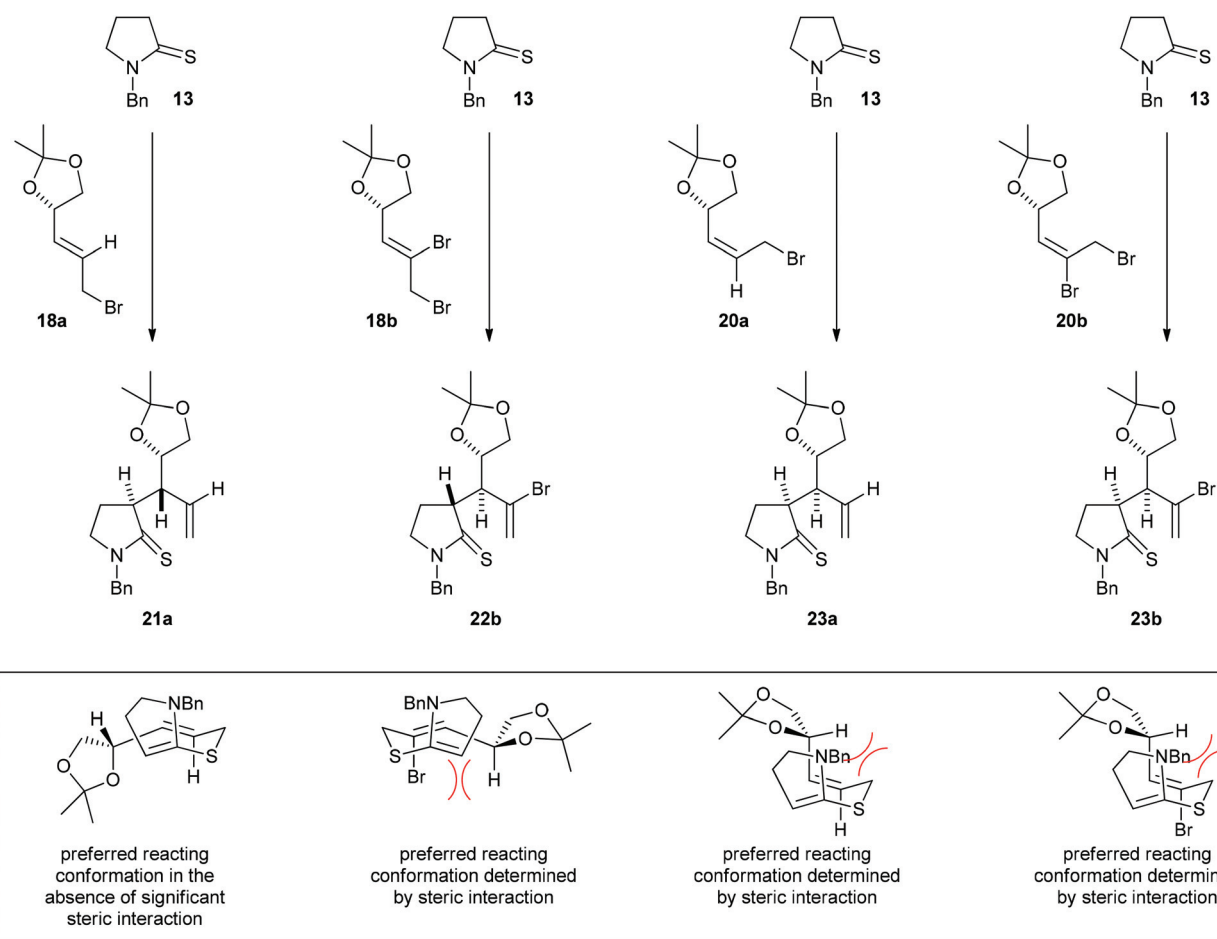
Scheme 7 Summary of major products and reactive conformations.

4 d. Further MeCN (2 mL) was added and the mixture warmed to 40 °C. Et$_3$N (94 µL, 0.67 mmol) was added and the resulting solution stirred at 35 °C for 7 h. The mixture was cooled to room temperature, diluted with CH$_2$Cl$_2$ (30 mL) and washed with 2% citric acid (2 × 50 mL). The combined aqueous washings were extracted with CH$_2$Cl$_2$ (50 mL), and the combined organic layers dried (MgSO$_4$) and concentrated *in vacuo* to give the crude product. Individual components were isolated by flash chromatography (SiO$_2$; petrol–EtOAc 19 : 1).

(3*S*,1′*R*,4″*S*)-1-Benzyl-3-[1-(2,2-dimethyl-1,3-dioxolan-4-yl)-allyl]pyrrolidine-2-thione (21a). Pale yellow oil: R_f = 0.82 (petrol–EtOAc 7 : 3); $[\alpha]_D^{17}$ −5.6 (*c* 0.68, CHCl$_3$); ν_{max}/cm^{-1} (film) 3067, 2931 (CH), 1638 (C=C), 1605, 1585; ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.21 (3H, s) and 1.34 (3H, s, C(CH$_3$)$_2$), 2.13 (1H, dtd, *J* 13.0, 9.2, 5.5 Hz) and 2.30 (1H, ddt, *J* 13.0, 9.0, 6.5 Hz, NCH$_2$CH$_2$), 3.05 (1H, dt, *J* 9.2, 3.3 Hz, CH$_2$=CHCH), 3.15 (1H, ddd, *J* 9.7, 6.5, 3.8 Hz, C=SCH), 3.47 (1H, ddd, *J* 11.0, 8.9, 6.3 Hz) and 3.62 (1H, m, NCH$_2$CH$_2$), 3.64 (1H, t, *J* 7.9 Hz) and 4.05 (1H, dd, *J* 8.0, 6.4 Hz, OCH$_2$), 4.29 (1H, ddd, *J* 7.8, 6.4, 2.8 Hz, OCH), 4.83 (1H, d, *J* 14.2 Hz, NCHHPh), 5.21–5.28 (3H, m, CH$_2$=CH and NCHHPh), 5.96 (1H, ddd, *J* 17.3, 10.2, 9.2 Hz, CH$_2$=CH), 7.30–7.36 (5H, m, ArH); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 22.4 (NCH$_2$CH$_2$), 25.4 and 26.3 (C(CH$_3$)$_2$), 47.7 (CH$_2$=CHCH), 51.8 (NCH$_2$Ph), 52.9 (NCH$_2$CH$_2$), 58.0 (C=SCH), 68.0 (OCH$_2$), 74.5 (OCH), 109.1 (CMe$_2$), 118.7 (CH$_2$=CH), 128.0, 128.3 and 128.8 (aromatic CH), 135.0 (aromatic C), 135.1 (CH$_2$=CH), 205.4 (C=S); *m/z* (CI$^+$) 332 (MH$^+$, 31%), 316 (24), 275 (37), 230 (80), 191 (100), 91 (40); HRMS found 332.1677, C$_{19}$H$_{26}$NO$_2$S (MH$^+$) requires 332.1684.

(3*R*,1′*S*,4″*S*)-1-Benzyl-3-[1-(2,2-dimethyl-1,3-dioxolan-4-yl)-allyl]pyrrolidine-2-thione (22a). Pale yellow oil: R_f = 0.76 (petrol–EtOAc 7 : 3); $[\alpha]_D^{22}$ +82.2 (*c* 0.60, CHCl$_3$); ν_{max}/cm^{-1} (CHCl$_3$ cast) 2983, 2931, 2873 (CH), 1637 (C=C), 1503, 1452 (C=S); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.38 (3H, s) and 1.42 (3H, s, C(CH$_3$)$_2$), 1.89 (1H, ddt, *J* 12.8, 8.8, 6.3 Hz) and 2.21 (1H, dtd, *J* 12.8, 9.1, 5.9 Hz, NCH$_2$CH$_2$), 2.62 (1H, m, CH$_2$=CHCH), 3.43 (1H, ddd, *J* 10.7, 9.0, 6.1 Hz, C=SCH), 3.50–3.55 (2H, m, NCH$_2$CH$_2$), 3.60 (1H, dd, *J* 8.2, 6.6 Hz) and 3.98 (1H, dd, *J* 8.2, 6.1 Hz, OCH$_2$), 4.94 (1H, d, *J* 14.4 Hz, NCHHPh), 5.00 (1H, m, OCH), 5.05 (1H, d, *J* 14.4 Hz, NCHHPh), 5.09 (1H, dd, *J* 10.2, 1.6 Hz) and 5.19 (1H, dd, *J* 17.2, 1.0 Hz, CH$_2$=CH), 5.79 (1H, dt, *J* 17.2, 9.9 Hz, CH$_2$=CH), 7.29–7.35 (5H, m, ArH); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 24.4 (NCH$_2$CH$_2$), 25.7 and 27.0 (C(CH$_3$)$_2$), 51.5 (NCH$_2$Ph), 52.5 (C=SCH), 53.0 (CH$_2$=CHCH), 54.1 (NCH$_2$CH$_2$), 68.6 (OCH$_2$), 75.0 (OCH), 109.2 (C(Me)$_2$), 119.1 (CH$_2$=CH), 127.9, 128.3 and 128.7 (aromatic CH), 134.9 (CH$_2$=CH), 135.2 (aromatic C), 202.6 (C=S); *m/z* (CI$^+$) 332 (MH$^+$, 22%), 274 (100); HRMS found 332.1676, C$_{19}$H$_{26}$NO$_2$S (MH$^+$) requires 332.1684.

(3*S*,1′*S*,4″*S*)-1-Benzyl-3-[1-(2,2-dimethyl-1,3-dioxolan-4-yl)allyl]-pyrrolidine-2-thione (23a). Pale yellow oil: R_f = 0.62 (petrol–EtOAc 7 : 3); $[\alpha]_D^{22}$ −27.7 (*c* 1.35, CHCl$_3$); ν_{max}/cm^{-1} (CDCl$_3$ cast) 2981, 2920 (CH), 1644 (C=C); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.36 (3H, s) and 1.48 (3H, s, C(CH$_3$)$_2$), 1.97 (1H, ddt, *J* 13.2, 8.5, 7.5 Hz) and 2.17 (1H, dddd, *J* 13.2, 9.3, 7.8, 5.6 Hz, NCH$_2$CH$_2$), 3.35 (1H, td, *J* 8.9, 3.0 Hz, CH$_2$=CHCH), 3.45–3.54

(3H, m, C=SCH and NCH$_2$CH$_2$), 3.75 (1H, dd, *J* 7.9, 5.7 Hz) and 4.06 (1H, dd, *J* 7.9, 6.0 Hz, OCH$_2$), 4.07 (1H, dt, *J* 9.6, 6.0 Hz, OCH), 4.90 (1H, d, *J* 14.3 Hz) and 5.11 (1H, d, *J* 14.3 Hz, NCH$_2$Ph), 5.13 (1H, dd, *J* 10.5, 1.4 Hz) and 5.24 (1H, ddd, *J* 17.3, 1.7, 1.0 Hz, CH$_2$=CH), 5.57 (1H, ddd, *J* 17.3, 10.5, 8.4 Hz, CH$_2$=CH), 7.28–7.34 (5H, m, ArH); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 20.4 (NCH$_2$CH$_2$), 25.7 and 27.0 (C(CH$_3$)$_2$), 49.5 (CH$_2$=CHCH), 51.7 (NCH$_2$Ph), 52.7 (NCH$_2$CH$_2$), 54.6 (C=SCH), 68.6 (OCH$_2$), 75.7 (OCH), 109.4 (C(Me)$_2$), 120.1 (CH$_2$=CH), 127.9, 128.3 and 128.7 (aromatic CH), 132.9 (CH$_2$=CH), 135.1 (aromatic C), 203.9 (C=S); *m/z* (EI) 331 (M$^+$, 16%), 316 (14), 91 (12), 65 (19), 55 (21), 51 (100); HRMS found 331.1605, C$_{19}$H$_{25}$NO$_2$S (M$^+$) requires 331.1601.

(3*S*,1′*R*,4″*S*)-1-Benzyl-3-[2-bromo-1-(2,2-dimethyl-1,3-dioxolan-4-yl)allyl]pyrrolidine-2-thione (21b). Colourless oil: R_f = 0.29 (petrol–EtOAc 85 : 15); $[\alpha]_D^{20}$ −33.5 (*c* 0.65, CHCl$_3$); ν_{max}/cm^{-1} (CHCl$_3$ cast) 2985, 2883 (CH), 1625 (C=C), 1507, 1452, 1311 (C=S); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.25 (3H, s) and 1.42 (3H, s, C(CH$_3$)$_2$), 2.20 (1H, dddd, *J* 13.4, 8.8, 7.6, 6.9 Hz) and 2.31 (1H, dtd, *J* 13.4, 8.9, 4.6 Hz, NCH$_2$CH$_2$), 3.37 (1H, m, CSCH), 3.49 (1H, ddd, *J* 11.1, 8.5, 6.9 Hz, NCHHCH$_2$), 3.59–3.64 (2H, m, CH$_2$=C(Br)CH and NCHHCH$_2$), 3.89 (1H, t, *J* 7.9 Hz) and 4.02 (1H, dd, *J* 8.0, 6.5 Hz, OCH$_2$), 4.43 (1H, dt, *J* 7.6, 6.1 Hz, OCH), 4.88 (1H, d, *J* 14.3 Hz) and 5.16 (1H, d, *J* 14.3 Hz, NCH$_2$Ph), 5.69 (1H, d, *J* 1.8 Hz) and 6.08 (1H, dd, *J* 1.8, 0.5 Hz, CH$_2$=CBr), 7.30–7.37 (5H, m, ArH); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 22.7 (NCH$_2$CH$_2$), 25.1 and 26.5 (C(CH$_3$)$_2$), 52.1 (NCH$_2$Ph), 52.5 (NCH$_2$CH$_2$), 52.8 (CH$_2$=C(Br)CH), 56.2 (C=SCH), 67.2 (OCH$_2$), 74.6 (OCH), 109.1 (C(Me)$_2$), 120.9 (CH$_2$=CBr), 128.1, 128.4, 128.9 (aromatic CH), 131.7 (CBr), 135.0 (aromatic C), 201.6 (C=S); *m/z* (CI$^+$) 410/412 (MH$^+$, 24/26%), 338 (79), 141 (100); HRMS found 410.0774, C$_{19}$H$_{25}$^{79}BrNO$_2$S (MH$^+$) requires 410.0789.

(3*R*,1′*S*,4″*S*)-1-Benzyl-3-[2-bromo-1-(2,2-dimethyl-1,3-dioxolan-4-yl)allyl]pyrrolidine-2-thione (22b). Pale yellow oil: R_f 0.43 (petrol–EtOAc 85 : 15); $[\alpha]_D^{20}$ +31.5 (*c* 1.08, CHCl$_3$); ν_{max}/cm^{-1} (CHCl$_3$ cast) 2983, 2934, 2874 (CH), 1625 (C=C), 1499, 1452, 1316 (C=S); ^{1}H NMR (CDCl$_3$, 600 MHz) δ 1.31 (3H, s) and 1.37 (3H, s, C(CH$_3$)$_2$), 2.31–2.41 (2H, m, NCH$_2$CH$_2$), 3.22 (1H, t, *J* 8.6 Hz, CHC=S), 3.52 (1H, ddd, *J* 10.8, 8.4, 7.1 Hz) and 3.66 (1H, ddd, *J* 10.8, 8.9, 5.2 Hz, NCH$_2$CH$_2$), 3.76 (1H, dd, *J* 8.5, 6.9 Hz, CHHO), 3.89 (1H, dd, *J* 10.1, 1.6 Hz, H$_2$C=C(Br)CH), 4.11 (1H, dd, *J* 8.5, 6.0 Hz, CHHO), 4.45 (1H, dt, *J* 10.1, 6.5 Hz, CHO), 4.82 (1H, d, *J* 14.6 Hz) and 5.19 (1H, d, *J* 14.6 Hz, PhCH$_2$), 5.54 (1H, dd, *J* 1.9, 0.5 Hz) and 5.93 (1H, d, *J* 1.9 Hz, C=CH$_2$), 7.29–7.36 (5H, m, ArH); ^{13}C NMR (CDCl$_3$, 150 MHz) δ 22.1 (NCH$_2$CH$_2$), 25.9 and 26.4 (C(CH$_3$)$_2$), 51.8 (PhCH$_2$), 52.7 (NCH$_2$CH$_2$), 55.1 (H$_2$C=C(Br)CH), 56.8 (CHC=S), 68.6 (CH$_2$O), 74.6 (CHO), 110.0 (C(CH$_3$)$_2$), 119.8 (C=CH$_2$), 127.8, 128.1 and 128.7 (aromatic CH), 133.3 (C=CH$_2$), 135.1 (aromatic C), 203.5 (C=S); *m/z* (CI$^+$, CH$_4$) 410/412 (MH$^+$, 16/14%), 352/354 ([MH − Me$_2$CO]$^+$, 46/50), 338 (63), 330 ([MH − HBr]$^+$, 100); HRMS found 410.0799, C$_{19}$H$_{25}$^{79}BrNO$_2$S (MH$^+$) requires 410.0789.

(3*S*,1′*S*,4″*S*)-1-Benzyl-3-[2-bromo-1-(2,2-dimethyl-1,3-dioxolan-4-yl)allyl]pyrrolidine-2-thione (23b). Colourless oil: R_f = 0.19 (petrol–EtOAc 8 : 2); ν_{max}/cm^{-1} (CHCl$_3$ cast) 2984, 2932, 2877

(CH), 1615 (C=C), 1507, 1453 (C=S); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 1.38 (3H, s) and 1.50 (3H, s, C(CH$_3$)$_2$), 2.19 (1H, dtd, J 13.2, 9.5, 6.0 Hz) and 2.42 (1H, ddt, J 13.2, 8.8, 6.1 Hz, NCH$_2$CH$_2$), 3.48–3.70 (4H, m, C=SCH, CH$_2$=C(Br)CH and NCH$_2$CH$_2$), 3.82 (1H, dd, J 8.6, 5.1 Hz) and 4.16 (1H, dd, J 8.6, 6.0 Hz, OCH$_2$), 4.38 (1H, dt, J 9.2, 5.6 Hz, OCH), 4.92 (1H, d, J 14.4 Hz) and 5.09 (1H, d, J 14.4 Hz, NCH$_2$Ph), 5.56 (1H, d, J 1.6 Hz) and 6.06 (1H, d, J 1.6 Hz, CH$_2$=CBr), 7.30–7.36 (5H, m, ArH); ^{13}C NMR (CDCl$_3$, 125 MHz) δ 20.5 (NCH$_2$CH$_2$), 25.5 and 27.0 (C(CH$_3$)$_2$), 51.9 (NCH$_2$Ph), 52.7 (CH$_2$=C(Br)CH), 53.0 (NCH$_2$CH$_2$), 54.9 (C=SCH), 68.0 (OCH$_2$), 76.0 (OCH), 109.9 (C(Me)$_2$), 123.5(CH$_2$=CBr), 128.0, 128.4 (aromatic CH), 128.5 (CBr), 128.7 (aromatic CH), 135.0 (aromatic C), 202.8 (C=S); m/z (CI$^+$) 410/412 (MH$^+$, 2/2%), 183 (100) 141 (17), 119 (18); HRMS found 410.0786, C$_{19}$H$_{25}$^{79}BrNO$_2$S (MH$^+$) requires 410.0789.

(3R,1$'R$,4$''S$)-1-Benzyl-3-[2-bromo-1-(2,2-dimethyl-1,3-dioxolan-4-yl)allyl]pyrrolidine-2-thione (24b). Colourless oil: R_f = 0.50 (petrol–EtOAc 7 : 3); ^{1}H NMR (CDCl$_3$, 600 MHz) δ 1.41 (3H, s) and 1.46 (3H, s, C(CH$_3$)$_2$), 2.00–2.48 (2H, m, NCH$_2$CH$_2$), 2.97 (1H, m), 3.52 (1H, m) and 3.65–3.71 (2H, m, C=SCH, CH$_2$=C(Br)CH and NCH$_2$CH$_2$), 3.87 (1H, dd, J 8.0, 7.6 Hz) and 4.14 (1H, dd, J 8.0, 5.8 Hz, OCH$_2$), 4.49 (1H, m, OCH), 4.92 (1H, d, J 14.3 Hz) and 5.08 (1H, d, J 14.3 Hz, NCH$_2$Ph), 5.61 (1H, d, J 1.4 Hz) and 5.98 (1H, d, J 1.4 Hz, CH$_2$=CH(Br)), 7.30–7.36 (5H, m, aromatic CH).

(3S,3$'R$,4$'S$)-1-Benzyl-3-[4,5-di-($tert$-butyldimethylsilanyloxy)-pent-1-en-3-yl]pyrrolidine-2-thione (25a). White solid, m.p. 51–52 °C; R_f = 0.57 (petrol–EtOAc 9 : 1); [α]$_D^{17}$ −14.0 (c 0.88, CHCl$_3$); ν_{max}/cm^{-1} (film) 2932 (CH), 1630 (C=C); ^{1}H NMR (CDCl$_3$, 500 MHz) δ −0.02 (3H, s), 0.06 (3H, s), 0.07 (3H, s) and 0.07 (3H, s, 2 × Si(CH$_3$)$_2$), 0.86 (9H, s) and 0.91 (9H, s, 2 × C(CH$_3$)$_3$), 2.05–2.19 (2H, m, NCH$_2$CH$_2$), 2.79 (1H, dt, J 9.5, 4.8 Hz, CH$_2$=CHCH), 3.30 (1H, m, C=SCH), 3.39 (1H, ddd, J 11.0, 8.6, 6.4 Hz) and 3.51 (1H, ddd, J 11.0, 8.7, 5.7 Hz, NCH$_2$CH$_2$), 3.63 (1H, dd, J 10.5, 4.8 Hz) and 3.82 (1H, dd, J 10.5, 4.3 Hz, OCH$_2$), 4.30 (1H, q, J 4.7 Hz, OCH), 4.86 (1H, d, J 14.3 Hz, NCHHPh), 5.06–5.11 (2H, m, CH$_2$=CH), 5.14 (1H, J 14.3 Hz, NCHHPh), 5.95 (1H, m, CH$_2$=CH), 7.30–7.36 (5H, m, ArH); ^{13}C NMR (CDCl$_3$, 125 MHz) δ −5.4, −5.3, −4.6 and −3.7 (2 × Si(CH$_3$)$_2$), 18.2 and 18.3 (2 × C(CH$_3$)$_3$), 24.5 (NCH$_2$CH$_2$), 26.0 (2 × C(CH$_3$)$_3$), 49.6 (CH$_2$=CHCH), 51.5 (NCH$_2$Ph), 52.2 (NCH$_2$CH$_2$), 56.0 (C=SCH), 66.0 (OCH$_2$), 72.8 (OCH), 117.8 (CH$_2$=CH), 127.9, 128.3 and 128.7 (aromatic CH), 135.3 (aromatic C), 136.8 (CH$_2$=CH), 203.3 (C=S); m/z (CI$^+$) 520 (MH$^+$, 18%), 504 (25), 462 (44), 388 (100), 330 (11), 230 (54), 191 (33), 91 (34); HRMS found 520.3115, C$_{28}$H$_{50}$NO$_2$SSi$_2$ (MH$^+$) requires 520.3101.

(3R,3$'S$,4$'S$)-1-Benzyl-3-[4,5-di-($tert$-butyldimethylsilanyloxy)-pent-1-en-3-yl]pyrrolidine-2-thione (26a). Yellow oil: R_f = 0.36 (petrol–EtOAc 19 : 1); [α]$_D^{20}$ +14.0 (c 0.3, CHCl$_3$); ν_{max}/cm^{-1} (CHCl$_3$ cast) 2928 (CH), 1624 (C=C); ^{1}H NMR (CDCl$_3$, 500 MHz) δ 0.01 (3H, s), 0.03 (3H, s), 0.18 (3H, s) and 0.23 (3H, s, 2 × Si(CH$_3$)$_2$), 0.90 (9H, s) and 0.92 (9H, s, C(CH$_3$)$_3$), 1.85 (1H, ddt, J 12.9, 8.9, 6.6 Hz) and 2.19 (1H, dtd, J 12.9, 9.1, 5.4 Hz, NCH$_2$CH$_2$), 2.43 (1H, td, J 9.9, 2.0 Hz, CH$_2$=CHCH),

3.37 (1H, ddd, J 10.9, 8.8, 6.6 Hz) and 3.45 (1H, m, NCH$_2$CH$_2$), 3.48 (1H, dd, J 10.7, 4.1 Hz, OCHH), 3.64 (1H, m, C=SCH), 3.67 (1H, dd, J 10.7, 2.6 Hz, OCHH), 4.88 (1H, m, OCH), 4.90 (1H, d, J 14.4 Hz, NCHHPh), 5.03 (1H, dd, J 10.2, 2.3 Hz, CHH=CH), 5.07 (1H, d, J 14.4 Hz, NCHHPh), 5.08 (1H, dd, J 17.2, 2.3 Hz, CHH=CH), 5.91 (1H, dt, J 17.2, 10.2 Hz, CH$_2$=CH), 7.28–7.33 (5H, m, ArH); ^{13}C NMR (CDCl$_3$, 125 MHz) δ −5.5, −5.4, −4.1 and −4.0 (2 × Si(CH$_3$)$_2$), 18.3 and 18.4 (2 × C(CH$_3$)$_3$), 25.9 and 26.0 (2 × C(CH$_3$)$_3$), 26.2 (NCH$_2$CH$_2$), 51.2 (NCH$_2$Ph), 52.1 (NCH$_2$CH$_2$), 52.3 (C=SCH), 53.1 (CH$_2$=CHCH), 66.2 (OCH$_2$), 72.8 (OCH), 118.4 (CH$_2$=CH), 127.8, 128.2 and 128.6 (aromatic CH), 135.4 (aromatic C), 135.9 (CH$_2$=CH), 202.8 (C=S); m/z (CI$^+$) 520 (MH$^+$, 100%), 504 (44), 388 (42); HRMS found 520.3110, C$_{28}$H$_{50}$NO$_2$SSi$_2$ (MH$^+$) requires 520.3101.

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