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1,2-Asymmetric induction in the ketene Claisen rearrangement of (2*S*,3*E*)-5-(isopropylsulfanyl)-3-pentenes

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Abstract—The ketene Claisen rearrangement of chiral (2*S*,3*E*)-5-(isopropylsulfanyl)-3-penten-2-amines has been investigated by the semi-empirical AM1 method. The observed efficient direction of the 1,2-asymmetric induction in the ketene Claisen rearrangement has been modelled from comparison of the energies of the four possible transition states arising from two chair-like and two boat-like structures. The resulting trends of relative transition state energy are in reasonable agreement with experimental observations.

1. Introduction

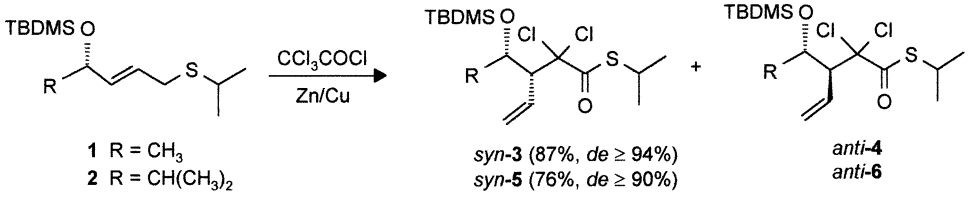
The Claisen rearrangement has become one of the most powerful tools for stereoselective carbon–carbon bond formation.[1] Much of its current popularity is due to the subsequent development of a series of new variants of this (3,3)-sigmatropic rearrangement. In 1978, we reported[2] a ketene version of the Claisen rearrangement. Treatment of allyl ethers with in situ prepared dichloroketene provided rearrangement products in good yield.[3] We showed that the ketene Claisen rearrangement of allyl thioethers **1** and **2** proceeds diastereoselectively with a high preference for *syn*-**3** (de≥94%) and *syn*-**5** (de≥90%) derivatives[4] (Scheme 1).

Here we report on the 1,2-asymmetric induction in the ketene Claisen rearrangement of chiral (2*S*,3*E*)-5-(isopropylsulfanyl)-3-penten-2-amines **13** and **14** and the possible transition states of this reaction at semi-empirical AM1 SCF-MO level.

2. Results and discussion

The methyl ester of *N*-benzyl-L-alanine[5] after reaction with di-*tert*-butyl dicarbonate and reduction with diisobutylaluminium hydride (DIBAL-H) afforded alcohol **9**.[6] A Swern oxidation, and chain elongation via Wittig olefination ($Ph_3PCHCOOCH_3$) led to ester **10**.[7] The second DIBAL-H reduction led to allyl alcohol **11**, the corresponding Mosher ester[8] of which was used to determine its optical purity (de≥95%).

Subsequently **11** was converted into thioacetate **12** by reaction with thioacetic acid under Mitsunobu conditions. Saponification and in situ alkylation with 2-bromopropane afforded thioether **13**. Thioether **14** was easily prepared by hydrolysis of **13** (with trifluoroacetic acid) and reaction of the amine with *p*-toluenesulfonyl chloride (Scheme 2). Dichloroketene, generated in situ by reductive elimination of chlorine from trichloroacetyl chloride upon treatment with activated zinc,[3] was allowed to react with allyl



Scheme 1.

Keywords: rearrangements; semi-empirical; transition state; asymmetric induction.
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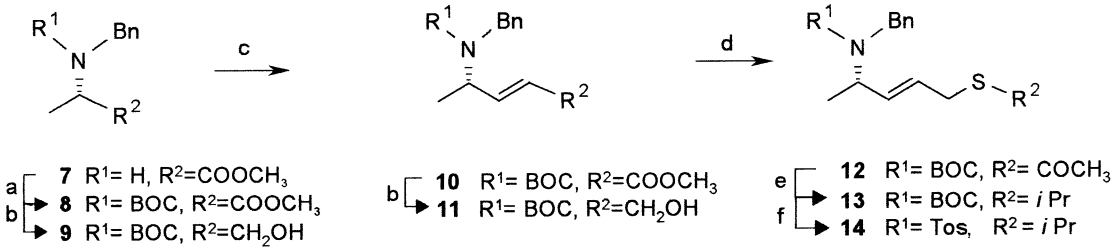
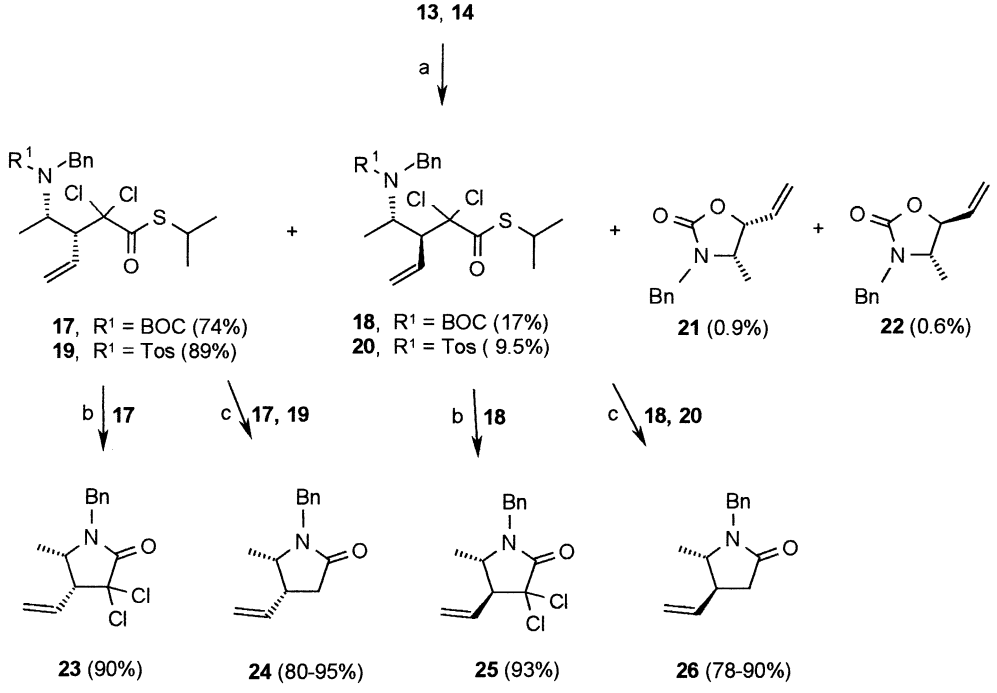


Scheme 2. (a) BOC_2O, DMPA, 87%; (b) DIBAH, hexane, −78°C (68–75%); (c) (i) $(COCl)_2$, DMSO, Net_3, −78°C, (ii) $Ph_3P{=}CHCOOCH_3$, THF, CH_2Cl_2, −78°C→20°C (64%); (d) AcSH, Ph_3P, diethyl azodicarboxylate (DEAD), THF, 0°C (71%); (e) NaOEt, EtOH, 20°C, 1 h then *i*-PrBr, 12 h (99%); (f) (i) TFA, K_2CO_3, (ii) TsCl, K_2CO_3 (80%).

thioethers **13** and **14**. Compound **13** afforded diastereoisomers **17** and **18** in a ratio of 80:20 (de=60%) and oxazolidones **21** and **22** as byproducts. Thioether **14** afforded **19** and **20** as a mixture of diastereoisomers, 90:10 (de=80%). Examination of the configuration in thioesters **17**, **18** and **19**, **20** was carried out using ^1H NMR spectroscopy of the corresponding cyclised products **24** and **26**, which were obtained by reductive cyclization with Zn/AcOH (Scheme 3). Irradiation of the methyl protons in lactone **24** resulted in a 9% NOE on the vinyl CH signal, indicating a *cis* relationship between these two substituents which supports a *threo* configuration and *syn* selectivity in the formation of **17** and **19**. Irradiation of the methyl protons in **26** led to 0% NOE on the vinyl CH, indicating a *trans* relationship between these substituents and thus the *erythro* configuration of **18** and **20**. Under non-reducing conditions, thioesters **17** and **18** afforded chlorolactones **23** and **25** (Scheme 3).

It is worth noting that while high 1,2-stereoinduction occurred upon dichloroketene addition to **1** and **2** (with 94 and 90%, respectively), reactions of **13** and **14** in the same conditions led to only 60 and 80% de. This fact prompted us to investigate the models corresponding to this rearrangement. Theoretical calculations were carried out at the semi-empirical RHF AM1 SCF-MO level, as implemented in the MOPAC 6.0 program.[9–11] We obtained optimized geometries for all molecules in the reactions using the BFGS optimization method with AM1 parameters. The energetics reported are based upon the lowest energy reactant and product conformations. We explored the conformation space of reactant and product using a grid calculation implemented in MOPAC.[9] The resultant low-energy structures were fully optimized at the AM1 level. The transition states for the ketene Claisen rearrangement of compounds **1**, **2** and **13** were located using the SADDLE routine[12] implemented in MOPAC and performing a grid calculation with bond distance search on the active $S–C_5$ and $C_2–C_3$ bonds (Fig. 1, Table 1). Further refinements of these approximate transition-state geometries were carried out by minimizing the energy[12] using the eigenvector-following (EF) method. The resulting geometries have one and only one negative vibration freqency[12] and verification using intrinsic reaction coordinate calculations for modes 1 and −1 led to the reactants and products of the reactions.

For the reaction of **1** with ketene to give *syn*-**3** and *anti*-**4**,



Scheme 3. (a) CCl_3COCl, Et_2O, Zn/Cu, 40°C, 3–6 h; (b) TFA, $NaHCO_3$, 2 h; (c) AcOH, Zn, 110°C (**17**, **18** 3 h; **19**, **20** 24 h).

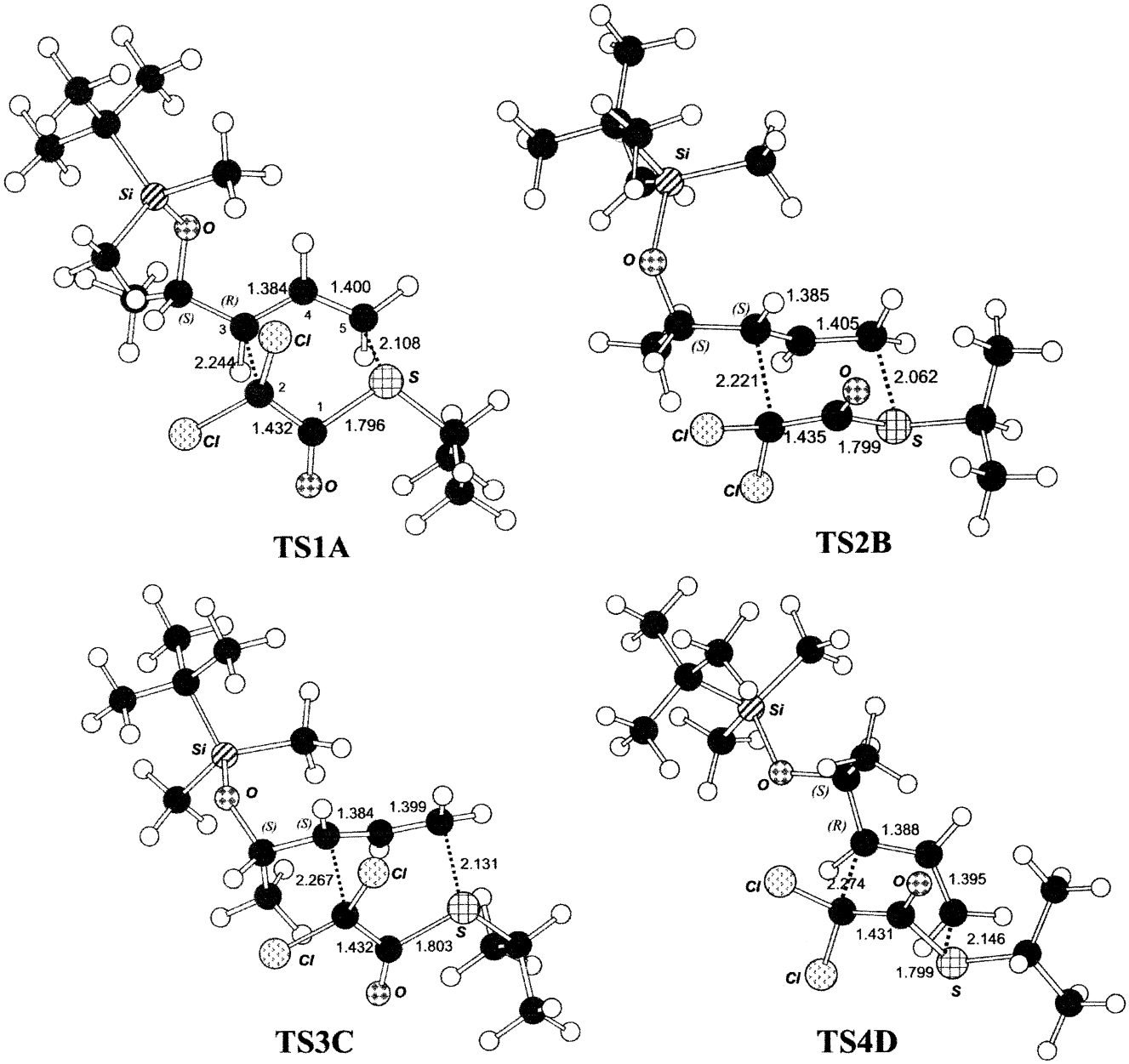


Figure 1. The transition structures of reaction of **1** with ketene (AM1 geometry; distances in angstroms).

Table 1. Heat of formation ΔH_f (298 K) and some geometrical parameters for localized stationary structures

	1	**TS1A**	**TS2B**	**TS3C**	**TS4D**	*syn*-**3**	*anti*-**4**
ΔH_f (kJ/mol)	−501.24 (0.00)[a]	−470.28 (17.15)	−453.12 (20.37)	−449.90 (23.84)	−446.43	−634.96	−623.49
S–C5[b]		2.108	2.062	2.131	2.146		
C2–C3		2.244	2.221	2.267	2.274		
	2	**TS1E**	**TS2F**	**TS3G**	**TS4H**	*syn*-**5**	*anti*-**6**
ΔH_f (kJ/mol)	−537.76 (0.00)	−509.15 (25.43)	−483.71 (28.66)	−477.17 (29.28)	−479.86	−671.23	−650.52
S–C5		2.107	2.062	2.148	2.132		
C2–C3		2.249	2.227	2.275	2.267		
	13	**TS1I**	**TS2J**	**TS3K**	**TS4L**	*syn*-**17**	*anti*-**18**
ΔH_f (kJ/mol)	−276.60	−240.49 (0.00)	−238.99 (1.50)	−239.40 (1.08)	−227.48 (13.01)	−406.22	−401.49
S–C5		2.107	2.086	2.157	2.185		
C2–C3		2.239	2.228	2.279	2.287		

[a] Value in parentheses are relative energies in kJ/mol.
[b] Distances are in angstroms.

two *chair-like* transition states **TS1A** and **TS2B** with $\Delta H_f = -470.28$ and -453.12 kJ/mol and two *boat-like* transition structures **TS3C** and **TS4D** with $\Delta H_f = -449.90$ and -446.43 kJ/mol, respectively, were found (Table 1). The calculated energy difference in favor of diastereoisomer *syn*-**3** (formed via **TS1A**) is 17.15 kJ/mol in comparison to the *anti*-**4** (via **TS2B**) and predicts exclusive formation of this product (calculated diastereoselectivity, de≥99.9%). In the reaction of **2** with ketene to *syn*-**5** and *anti*-**6**, the diastereomeric chair-like **TS1E**, which leads to *syn*-**5**, is preferred by 25.43 kJ/mol in comparison to the chair-like **TS2F** (which led to *anti*-**6**) (Table 1). These results are in good agreement with experimentally[4] determined high (94 and 90%) *syn* selectivity. For the reaction of **13** with ketene to give products *syn*-**17** and *anti*-**18**, two chair-like transition states **TS1I** and **TS2J** with $\Delta H_f = -240.49$ and -238.99 kJ/mol and two boat-like transition structures **TS3K** and **TS4L** with $\Delta H_f = -239.40$ and -227.48 kJ/mol, respectively, were found (Table 1). The transition state **TS1I**, which led to *syn*-**17**, is favored by only 1.08 kJ/mol in comparison with **TS3K** and the calculated diastereoselectivity, de=20%, is in resonable agreement with the de=60% observed. This is indicative of more complex electronic and steric interaction in transitions states of the reaction.

3. Conclusion

Calculated transition states for the ketene Claisen rearrangements of chiral (2*S*,3*E*)-5-(isopropylsulfanyl)-3-pentenes at a semiempirical AM1 level are concerted but asynchronous. Chair-like and boat-like structures are typical[13] for (3,3)-sigmatropic rearrangements. The simple AM1 model presented for the ketene Claisen rearrangement of allyl thioethers demonstrates that the diastereoselectivities observed are entirely consistent with the energy difference between such diastereomeric transition states.

4. Experimental

The reagents and solvents: purchased from Fluka AG in the highest obtainable purity. $CHCl_3$ and $CDCl_3$ were passed throgh basic alumina (Woelm, act. 1) immediately before use. Optical rotations: Perkin–Elmer 241 MC. TLC: DC Alufolien Kieselgel 60_{F254} (Merck), detection UV (254 nm) and/or $KMnO_4$ spray. Chromatography: Kieselgel 0.032–0.060 mesh (Merck). IR spectra (2–3%) in $CHCl_3$: Perkin–Elmer 599 IR spectrometer; absorptions in cm^{-1}. NMR spectra: δ in ppm relative to internal Me_4Si (=0 ppm) in $CDCl_3$ at rt, Bruckner WM 360 (360.13, 90.56 MHz). All reactions were run under argon using flame-dried glassware.

4.1. Data for compounds

4.1.1. *tert*-Butyl *N*-benzyl-*N*-[(1*S*,2*E*)-4-hydroxy-1-methyl-2-butenyl]carbamate (11). To a stirred solution of **10** (1.27 g, 4 mmol) in THF (50 mL) was added dropwise DIBAL-H (1 M in toluene, 8.1 mL, 8.1 mmol) at 0°C. The mixture was stirred for an additional 30 min and quenched with H_2O and diluted with AcOEt (100 mL). The organic layer was washed with brine (60 mL), dried ($MgSO_4$) and concentrated in vacuo. Purification of the residue by column chromatograpy on silica gel using hexane/AcOEt (7:3) as an eluent afforded **11** (0.87 g, 75%) as a colourless oil. $[\alpha]_D^{21} = -17.42$ (*c* 0.79, $CHCl_3$). IR: 3600, 3450, 3030, 2980, 2930, 2827, 1730, 1680, 1600, 1490, 1450 1405, 1365, 1340, 1240, 1165, 1100, 1030, 1000, 980, 865. ^{1}H NMR: 1.21 (3H, d, *J*=7.2 Hz, C*H*$_3$CH), 1.37 (9H, b s, (C*H*$_3$)$_3$C), 3.66 (1H, b s, O*H*), 4.02 (2H, d, *J*=4.7 Hz, C*H*$_2$OH), 4.33–4.42 (1H, m, C*H*CH$_3$), 4.50 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.59 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.65–5.71 (1H, m, C*H*=CHCH$_2$), 5.95–6.01 (1H, m, CH=C*H*CH$_2$), 7.11–7.35 (5H, m, Ph). ^{13}C NMR: 19.2, 24.4, 43.8, 46.5, 61.6, 80.1, 123.5, 123.6, 124.2, 126.3, 140.2, 153.3. Anal. calcd for $C_{17}H_{25}NO_3$: C 70.07, H 8.65, N 4.81; found: C 70.12, H 8.62, N 4.78.

4.1.2. (*E*,4*S*)-4-[Benzyl(*tert*-butoxycarbonyl)amino]-2-pentenyl ethanethioate (12). To a stirred solution of triphenylphosphine (3.25 g, 12.4 mmol) in THF was added dropwise diethylazodicarboxylate (2.15 g, 12.3 mmol) at 0°C. the solution of **11** (2.39 g, 8.2 mmol) in THF (15 mL) was added at the same temperature. To the mixture was added thioacetic acid (0.94 g, 12.3 mmol) in THF (15 mL) and stirring was continued at 0°C for 1 h. The mixture was allowed to warm to rt over 2 h and then quenched with 0.5 mL H_2O and 100 mL *n*-pentane. The precipitate was collected by filtration. The organic layer was concentrated in vacuo. Purification of the residue by column chromatography on silica gel using hexane/AcOEt (95:5) as an eluent afforded **12** (2.03 g, 71%) as a colourless oil. $[\alpha]_D^{21} = -39.29$ (*c* 0.84, $CHCl_3$). IR: 2970, 2930, 1685, 1492, 1450, 1400, 1365, 1340, 1240, 1165, 1135, 1112, 1020, 960. ^{1}H NMR: 1.16 (3H, d, *J*=6.91 Hz, C*H*$_3$CH), 1.44 (9H, s, (C*H*$_3$)$_3$C), 2.31 (3H, s, C*H*$_3$CO), 3.03 (2H, d, *J*=6.7 Hz, C*H*$_2$S), 3.50–3.61 (1H, m, C*H*CH$_3$), 4.25 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.34 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.48–5.53 (1H, m, C*H*=CHCH$_2$), 5.65–5.72 (1H, m, CH=C*H*CH$_2$), 7.19–7.32 (5H, m, Ph). ^{13}C NMR: 17.9, 28.3, 30.8, 33.3, 47.1, 52.3, 79.6, 126.5, 126.8, 128.1, 128.2, 134.4, 139.3, 155.5, 194.5. Anal. calcd for $C_{19}H_{27}NO_3S$: C 65.33, 7.79, N 4.01, S 9.17; found: C 65.29, H 7.83, N 3.98, S 9.16.

4.1.3. *tert*-Butyl *N*-benzyl-*N*-[(1*S*,2*E*)-4-(isopropylsulfanyl)-1-methyl-2-butenyl]carbamate (13). Compound **12** (3.5 g, 10 mmol) in 5 mL of ethanol was added to 7 mmol of freshly prepared NaOEt in 1 mL of ethanol. After stirring at rt for 1 h, the mixture was treated with 1.22 g (10 mmol) of 2-bromopropane. After 12 h, the mixture was diluted with 50 mL of Et_2O and washed with H_2O (2×15 mL), brine (10 mL), dried ($MgSO_4$), and concentrated in vacuo. The purification of the residue by column chromatography on silica gel using hexane/AcOEt (7:3) as an eluent afforded **13** (3.40 g, 99%) as a colourless oil. $[\alpha]_D^{21} = -12.29$ (*c* 0.84, $CHCl_3$). IR: 2972, 2930, 1680, 1490, 1455, 1410, 1360, 1343, 1242, 1170, 1140, 1110, 1022, 963. ^{1}H NMR: 1.16 (3H, d, *J*=6.91 Hz, C*H*$_3$CHN), 1.19 (6H, d, *J*=6.7 Hz, (C*H*$_3$)$_2$CHS), 1.45 (9H, b s, (C*H*$_3$)$_3$C), 2.60–2.71 (1H, m, C*H*S), 3.03 (2H, d, *J*=6.6 Hz, C*H*$_2$S), 3.50 (1H, m, C*H*N), 4.25 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.33 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.44–5.49 (1H, m, C*H*=CHCH$_2$), 5.62–5.71 (1H, m,

CH═C*H*CH$_2$), 7.19–7.32 (5H, m, Ph). ^{13}C NMR: 17.8, 28.5, 28.3, 32.1, 45.1, 53.2, 78.9, 126.4, 126.5, 128.5, 128.5, 134.5, 139.6, 155.6, 194.8. Anal. calcd for $C_{20}H_{31}NO_2S$: C 68.73, H 8.94, N 4.01, S 9.17; found: C 68.67, H 8.86, N 4.01, S 9.16.

4.1.4. Ketene Claisen rearrangement of allylthioether 13. Allyl thioether **13** (0.501 g, 1.5 mmol) and about 15 mmol Zn/Cu alloy were placed in 15 mL of vigorously stirred diethylether under argon and the mixture was heated to reflux. A solution of 0.55 g (3 mmol) of freshly distilled trichloroacetylchloride in 5 mL of ether was added dropwise to the solution over 4 h by means of a syringe pump. After cooling, the reaction solution was decanted from the residue. Chromatographic separation on silica gel (hexane/AcOEt, 9:1) yield, **17** (0.52 g, 74%), **18** (0.12 g, 17%), **21** (0.003 g, 0.9%) and **22** (0.002 g, 0.6%).

4.1.5. Isopropyl (3*R*)-3-((1*S*)-1-benzyl(*tert*-butoxycarbonyl)amino)ethyl)-2,2-dichloropent-4-enethioate (17). Colourless oil. $[\alpha]_D^{21}$=+7.09 (*c* 0.76, $CHCl_3$). IR: 2980, 2930, 2870, 1770, 1500, 1470, 1452, 1405, 1395, 1368, 1345, 1310, 1240, 1170, 1060, 1030, 1000, 940, 910, 800, 700, 650, 620. ^{1}H NMR: 1.18 (d, 3H, *J*=6.2 Hz, C*H*$_3$CH), 1.31 (6H, d, *J*=7.2 Hz, (C*H*$_3$)$_2$CH), 1.40 (9H, s, (C*H*$_3$)$_3$C), 3.50–3.58 (1H, m, C*H*S), 3.64–3.70 (m, 1H, C*H*CH═CH$_2$), 4.11–4.20 (m, 1H, C*H*N), 4.25 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.38 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.15–5.20 (1H, m, C*H*$_a$H$_b$═CH), 5.23–5.25 (1H, m, CH$_a$*H*$_b$═CH), 5.67 (1H, m, C*H*═CH$_2$), 7.20–7.35 (m, 5H, Ph). ^{13}C NMR: 18.4, 19.5, 23.0, 29.1, 51.8, 53.8, 58.2, 81.0, 92.8, 122.8, 127.5, 127.6, 128.0, 132.6, 140.0, 155.8, 194.0. Anal. calcd for $C_{22}H_{31}Cl_2NO_3S$: C 57.39, H 6.79, N 3.04, S 6.96; found: C 57.43, H 6.84, N 3.08, S 7.00.

4.1.6. Isopropyl (3*S*)-3-((1*S*)-1-benzyl(*tert*-butoxycarbonyl)amino)ethyl)-2,2-dichloropent-4-enethioate (18). Colourless oil. $[\alpha]_D^{21}$=−2.91 (*c* 1.04 $CHCl_3$). IR: 2978, 2930, 2860, 1685, 1495, 1465, 1450, 1405, 1390, 1340, 1240, 1160, 1120, 1080, 1060, 1030, 995, 930, 910, 860. ^{1}H NMR: 1.09 (d, 3H, *J*=6.3 Hz, C*H*$_3$CH), 1.34 (6H, d, *J*=7.2 Hz, (C*H*$_3$)$_2$CH), 1.43 (9H, s, (C*H*$_3$)$_3$C), 3.62–3.71 (m, 1H, C*H*CH═CH$_2$), 3.72–3.83 (1H, m, C*H*S), 4.13–4.20 (m, 1H, C*H*N), 4.29 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.43 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.21–5.22 (1H, m, C*H*$_a$H$_b$═CH), 5.26–5.33 (1H, m, CH$_a$*H*$_b$═CH), 5.73 (1H, m, C*H*═CH$_2$), 7.19–7.33 (m, 5H, Ph). ^{13}C NMR: 19.3, 20.3, 22.8, 28.8, 36.9, 54.0, 58.4, 80.3, 80.4, 92.0, 121.4, 121.5, 127.0, 129.0, 133.8, 133.9, 139.9, 156.0, 195.0. Anal. calcd for $C_{22}H_{31}Cl_2NO_3S$: C 57.39, H 6.79, N 3.04, S 6.96; found: C 57.41, H 6.82, N 3.09, S 7.01.

4.1.7. (4*S*,5*R*)-3-Benzyl-4-methyl-5-vinyl-1,3-oxazolan-2-one (21). Colourless oil. $[\alpha]_D^{21}$=−9.4 (*c* 1.08 $CHCl_3$). IR: 3080, 3060, 3020, 2870, 2820, 1740, 1490, 1410, 1480, 1460, 1420, 1235, 1200, 1175, 1100, 1060, 1025, 990, 955, 760, 700. ^{1}H NMR: 1.08 (3H, d, *J*=7.1 Hz, CH$_3$), 3.70–3.76 (1H, m, C*H*N), 4.04 (1H, d, *J*=9.2 Hz, C*H*$_a$H$_b$Ph), 4.84 (1H, d, *J*=9.2 Hz, CH$_a$*H*$_b$Ph), 4.85–4.88 (1H, m, C*H*O), 5.36 (1H, m, C*H*$_a$H$_b$═CH), 5.42–5.46 (1H, m, CH$_a$*H*$_b$═CH), 5.85 (1H, m, C–*H*═CH$_2$), 7.23–7.40 (5H, m, Ph). ^{13}C NMR: 13.7, 45.8, 53.2, 78.1, 120.0, 127.9, 128.1, 28.8, 131.2, 136.1, 157.6. Anal. calcd for $C_{13}H_{15}NO_2$: C 71.87, H 6.96, N 6.45; found: C 71.85, H 6.99, N 6.43.

4.1.8. (4*S*,5S)-3-Benzyl-4-methyl-5-vinyl-1,3-oxazolan-2-one (22). Colourless oil. $[\alpha]_D^{21}$=+4.6 (*c* 0.96 $CHCl_3$). IR: 3080, 3060, 3020, 2970, 2920, 1740, 1492, 1410, 1380, 1360, 1320, 1325, 1200, 1175, 1100, 1020, 1025, 985, 955, 940, 760, 700. ^{1}H NMR: 1.10 (3H, d, *J*=6.0 Hz, CH$_3$), 3.53–3.61 (1H, m, C*H*N), 4.11 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.80 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 4.78–4.82 (1H, m, C*H*O), 5.24 (1H, m, C*H*$_a$H$_b$═CH), 5.43–5.47 (1H, m, CH$_a$*H*$_b$═CH), 5.79–5.83 (1H, m, C*H*═CH$_2$), 7.22–7.39 (5H, m, Ph). ^{13}C NMR: 17.0, 45.9, 55.9, 81.9, 119.5, 127.9, 128.1, 128.8, 133.6, 135.9, 157.8. Anal. calcd for $C_{13}H_{15}NO_2$: C 71.87, H 6.96, N 6.45; found: C 71.84, H 6.95, N 6.41.

4.1.9. (4*R*,5*S*)-1-Benzyl-3,3-dichloro-5-methyl-4-vinyltetrahydro-1*H*-pyrrol-2-one (23). Thioester **17** (0.456 g, 1 mmol) in 69 mL CH_3CN was treated slowly with 4 mL of 48% HF in CH_3CN with stirring at rt. After 2.5 h, the mixture was poured on ice/solid $NaHCO_3$ and extracted with CH_2Cl_2 (5×25 mL). The organic layer was dried ($MgSO_4$) and concentrated to give a yellow oil. Rapid chromatography on silica gel (ether/petroleum ether, 2:8) yielded **23** (0.257 g, 90%) as a colourless oil. $[\alpha]_D^{21}$=−5.18 (*c* 0.89 $CHCl_3$). IR: 3080, 3020, 2970, 2920, 2860, 1715, 1490, 1410, 1380, 1350, 1310, 1275, 1230, 1200, 850, 740, 695. ^{1}H NMR: 1.22 (3H, d, *J*=6.6 Hz, CH$_3$), 3.23–3.27 (1H, m, C*H*N), 3.58–3.63 (1H, m, C*H*CCl$_2$), 4.06 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 5.08 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.28–5.34 (1H, m, C*H*$_a$H$_b$═CH), 5.41–5.45 (1H, m, CH$_a$*H*$_b$═CH), 5.93–6.04 (1H, m, C*H*═CH$_2$), 7.19–7.33 (5H, m, Ph). ^{13}C NMR: 13.6, 45.4, 53.8, 57.7, 84.9, 123.0, 128.2, 129.0, 129.7, 135.1, 166.4. Anal. calcd for $C_{14}H_{15}Cl_2NO$: C 59.17, H 5.32, N 4.93; found: C 59.15, H 5.29, N 4.89.

4.1.10. (4*S*,5*S*)-1-Benzyl-3,3-dichloro-5-methyl-4-vinyltetrahydro-1*H*-pyrrol-2-one (25). Following the procedure described for the preparation of **23**, **18** (0.456 g, 1 mmol) gave, after chromatography on silica gel (ether/petroleum ether, 2:8), 25 (0.263 g, 93%) as a colourless oil. $[\alpha]_D^{21}$=+5.25 (*c* 1.13, $CHCl_3$). IR: 3030, 2970, 2920, 2860, 1710, 1440, 1420, 1380, 1350, 1250, 1150, 1110, 1070, 1040, 940, 890, 850. ^{1}H NMR: 1.20 (3H, d, *J*=6.0 Hz, CH$_3$), 3.26–3.29 (1H, m, C*H*N), 3.55–3.61 (1H, m, C*H*CCl$_2$), 4.02 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 5.16 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.35–5.40 (1H, m, C*H*$_a$H$_b$═CH), 5.46–5.51 (1H, m, CH$_a$*H*$_b$═CH), 5.87–5.92 (1H, m, C*H*═CH$_2$), 7.20–7.34 (5H, m, Ph). ^{13}C NMR: 15.9, 44.6, 53.5, 62.2, 85.1, 123.5, 127.9, 128.0, 128.9, 129.5, 135.1, 167.0. Anal. calcd for $C_{14}H_{15}Cl_2NO$: C 59.17, H 5.32, N 4.93; found: C 59.18, H 5.28, N 4.90.

4.1.11. *N*-(Benzyl(4-toluenesulfonyl)-(2*S*,3*E*)-5-isopropylthio)pent-3-en-2-amine (14). To a trifluoroacetic acid (10 mL) was added **13** (3.50 g, 10 mmol) at 0°C and stirring was continued for 2 h. The reaction mixture was evaporated in vacuo and residue was triturated with sat. Na_2CO_3 (40 mL). After addition of tosylchloride (1.90 g, 10 mmol) in CH_2Cl_2 (15 mL) was reaction mixture stirred additional 12 h at rt. The organic layer was washed with 0.5 M HCl

(50 mL), dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed on silica gel (hexane/AcOEt), 7:3) to yield **14** (3.2 g, 80 %) as a oil. $[\alpha]_D^{21}=-12.9$ (*c* 1.02 $CHCl_3$). IR: 3070, 3040, 2930, 2870, 1600, 1500, 1450, 1380, 1360, 1340, 1300, 1200, 1160, 1100, 1010, 980, 920, 860. ^{1}H NMR: 1.08 (3H, d, *J*=7.2 Hz, C*H*$_3$CHN), 1.19 (6H, d, *J*=6.7 Hz, (C*H*$_3$)$_2$CH), 2.20 (3H, s, CH_3Ph), 2.66 (1H, m, C*H*(CH$_3$)$_2$), 2.95 (2H, d, *J*=6.6 Hz, CH_2S), 4.22 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.40 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 4.42–4.46 (1H, m, C*H*N), 5.20–5.26 (1H, m, C*H*=CHCH$_2$), 5.41–5.44 (1H, m, CH=C*H*CH$_2$), 7.18–7.32 (5H, m, Ph), 7.87–7.94 (4H, m, Ph). ^{13}C NMR: 19.8, 21.9, 24.1, 32.4, 34.2, 48.0, 55.2, 127.8, 128.2, 128.3, 130.0, 131.8, 127.9, 130.8, 143.6. Anal. calcd for $C_{22}H_{29}NO_2S_2$: C 65.47, H 7.24, N 3.47, S 15.89; found: C 65.45, H 7.22, N 3.40, S 15.86.

4.1.12. Ketene Claisen rearrangement of allyl thioether 14. Folowing the procedure described for the rearrangement of **13**, thioether **14** (0.4 g, 1 mmol) gave, after chromatography on silica gel (ether/petroleum ether, 2:9) **19** (0.458 g, 89%) and **20** (0.048 g, 9.5%).

4.1.13. Isopropyl (3*R*)-3-((1*S*)-1-benzyl((4-methylphenyl)-sulfonyl)amino)ethyl)-2,2-dichloropent-4-enethioate (19). Colourless oil. $[\alpha]_D^{21}=+3.2$ (*c* 0.77 $CHCl_3$). IR: 2960, 2920, 2860, 1680, 1595, 1495, 1450, 1340, 1300, 1160, 1090, 1055, 1000, 940, 920, 860, 810, 800, 760, 650. ^{1}H NMR: 1.21 (3H, d, *J*=6.3 Hz, C*H*$_3$CH), 1.32 (6H, d, *J*=6.7 Hz, (C*H*$_3$)$_2$CH), 2.42 (3H, s, C*H*$_3$Ph), 3.31–3.35 (1H, m, C*H*S), 3.85–3.91 (1H, m, C*H*CCl$_2$), 4.14 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.32–4.38 (1H, m, C*H*N), 4.45 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 4.63–4.68 (1H, m, C*H*$_a$H$_b$=CH), 5.13–5.21 (1H, m, CH$_a$*H*$_b$=CH), 5.65–5.78 (1H, m, CH$_2$=C*H*), 7.19–7.32 (5H, m, Ph), 7.71–7.78 (4H, m, Ph). ^{13}C NMR: 18.8, 22.1, 37.0, 48.4, 56.9, 57.5, 92.0, 123.2, 127.5, 128.1, 128.2, 128.3, 128.7, 130.0, 131.2, 133.5. Anal. calcd for $C_{24}H_{29}Cl_2NO_3S_2$: C 56.02, H 5.68, N 2.72, S 12.46; found: C 56.05, H 5.71, N 2.75, S 12.43.

4.1.14. Isopropyl (3*S*)-3-((1*S*)-1-benzyl((4-methylphenyl)-sulfonyl)amino)ethyl)-2,2-dichloropent-4-enethioate (20). Colourless oil. $[\alpha]_D^{21}=-6.1$ (*c* 0.57 $CHCl_3$). IR: 2960, 2920, 2860, 1680, 1595, 1495, 1450, 1340, 1300, 1160, 1090, 1055, 1000, 940, 920, 860, 810, 800, 760, 650. ^{1}H NMR: 1.18 (3H, d, *J*=6.3 Hz, C*H*$_3$CH), 1.36 (6H, d, *J*=6.7 Hz, (C*H*$_3$)$_2$CH), 2.37 (3H, s, C*H*$_3$Ph), 3.42–3.48 (1H, m, C*H*S), 3.75–3.88 (1H, m, C*H*CCl$_2$), 4.14 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.29–4.35 (1H, m, C*H*N), 4.42 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 4.60–4.66 (1H, m, C*H*$_a$H$_b$=CH), 5.20–5.28 (1H, m, CH$_a$*H*$_b$=CH), 5.70–5.85 (1H, m, CH$_2$=C*H*), 7.19–7.33 (5H, m, Ph), 7.72–7.77 (4H, m, Ph). ^{13}C NMR: 17.2, 23.1, 37.8, 48.8, 54.3, 59.4, 92.8, 123.9, 127.6, 128.0, 128.8, 131.2, 138.2, 142.0, 194.0. Anal. calcd for $C_{24}H_{29}Cl_2NO_3S_2$: C 56.02, H 5.68, N 2.72, S 12.46; found: C 56.06, H 5.70, N 2.73, S 12.40.

4.1.15. (4*R*,5*S*)-1-Benzyl-5-methyl-4-vinyltetrahydro-1*H*-pyrrol-2-one (24). Thioester **17** (0.46 g, 1 mmol) in 35 mL AcOH at 100–110°C was treated with 1 g Zn powder for 3 h. The mixture was cooled to rt, poured into 50 mL ice-water and 30 mL 2N NaOH, and extracted with Et_2O (5×25 mL). The combined org. layers were succesively washed with 2N NaOH (30 mL) and sat. $NaHCO_3$ (2×20 mL), dried ($MgSO_4$), and concentrated. The residue was chromatographed on silica gel (Et_2O/petroleum ether, 2:8) to yield **24** (250 mg, 95%) as a colourless oil. $[\alpha]_D^{21}=-5.8$ (*c* 0.89 $CHCl_3$). IR: 3350, 3060, 2970, 2920, 1670, 1490, 1440, 1415, 1380, 1353, 1315, 1295, 1255, 1230, 1200, 1165, 1080, 1030, 1000, 925. ^{1}H NMR: 1.03 (3H, d, *J*=6 Hz, CH_3), 2.40–2.54 (2H, m, C*H*$_2$CO), 2.94–3.02 (m, 1H, C*H*CH$_2$), 3.03–3.35 (1H, m, C*H*), 3.91 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.64–4.69 (1H, m, C*H*$_a$H$_b$=CH), 5.38 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.47–5.63 (1H, m, CH$_a$*H*$_b$=CH), 5.75–5.85 (1H, m, CH$_2$=C*H*), 7.20–7.32 (5H, m, Ph). ^{13}C NMR: 14.0, 35.2, 41.0, 44.0, 55.7, 117.3, 127.5, 128.0, 128.7, 136.0, 136.8 173.6. Anal. calcd for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51; found: C 78.13, H 7.94, N 6.48.

4.1.16. (4*S*,5*S*)-1-Benzyl-5-methyl-4-vinyltetrahydro-1*H*-pyrrol-2-one (26). Following the procedure described for the preparation **24**, compound **18** (0.46 g, 1 mmol) gave after chromatography on silica gel (ether/petroleum ether, 2:8) **26** (193 mg, 90%) as a colourless oil. $[\alpha]_D^{21}=+6.4$ (*c* 0.77 $CHCl_3$). IR: 3350, 3060, 3020, 2920, 1680, 1495, 1450, 1420, 1380, 1360, 1320, 1300, 1260, 1230, 1205, 1170, 1030, 1000, 925. ^{1}H NMR: 1.16 (3H, d, *J*=6 Hz, CH_3), 2.40–2.47 (2H, m, C*H*$_2$CO), 2.89–3.02 (m, 1H, C*H*CH$_2$), 3.15–3.31 (1H, m, C*H*), 4.12 (1H, d, *J*=9.3 Hz, C*H*$_a$H$_b$Ph), 4.61–4.65 (1H, m, C*H*$_a$H$_b$=CH), 5.25 (1H, d, *J*=9.3 Hz, CH$_a$*H*$_b$Ph), 5.59–5.64 (1H, m, CH$_a$*H*$_b$=CH), 5.73–5.81 (1H, m, CH$_2$=C*H*), 7.19–7.31 (5H, m, Ph). ^{13}C NMR: 17.8, 36.9, 44.0, 57.9, 116.7, 127.5, 128.0, 128.7, 136.7, 137.8, 173.9. Anal. calcd for $C_{14}H_{17}NO$: C 78.10, H 7.96, N 6.51; found: C 78.15, H 7.93, N 6.47.

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