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Synthesis of *NH*-3-phenylsulfanyl- and *NH*-3-benzylsulfanyl-azetidinones from 1-phenylsulfanyl- or 1-benzylsulfanyl-3-aza-1,3-dienes

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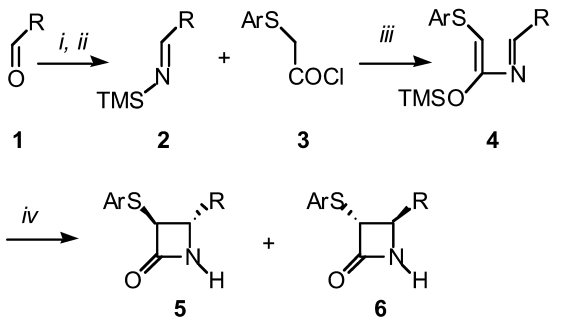
Abstract—The syntheses of *NH*-3-phenylsulfanyl- and *NH*-3-benzylsulfanyl-azetidinones, starting from 1-phenylsulfanyl- or 1-benzylsulfanyl-2-trimethylsilyloxy-3-aza-1,3-dienes are reported.

1. Introduction

The development of synthetic routes to monocyclic 2-azetidinones (β-lactams) was stimulated by the observation of antibacterial activity in monobactams and norcardicins.[1] While the interest in these materials as antibiotics has waned, 2-azetidinones have served as important intermediates in many other applications. They are precursors to β-amino alcohols and β-amino acids, which are useful building blocks for peptides containing non-protein amino acids.[2–4] 2-Azetidinones have been used to introduce the C-13 side-chain of the anticancer compound paclitaxel (taxol) and related analogues.[5] 2-Azetidinones have served as precursors to δ-lactones in the total synthesis of the macrolide antitumor antibiotic Lankacidin C.[6] More recently, certain C-3 heteroatom-substituted azetidinones have displayed potent cholesterol absorption inhibitor activity[7] and human Cytomegalo virus protease inhibitor activity.[8]

2. Results and discussion

The synthetic approaches to 2-azetidinones are almost countless, but the Staudinger approach from ketenes and imines remains the most useful despite its venerable age.[9–11] Recently we have reported a new one-pot, two step variant of this reaction via a 4π-conrotatory electrocyclization of neutral 2-trimethylsilyloxy-3-aza-1,3-dienes variably substituted in positions 1 and 3. The intermediates



Scheme 1. *Reagents and conditions*. (i) Hexane, LiHMD SA, 1 h, 25°C; (ii) TMSCl, 1 h, rt; (iii) TEA, 0°C then rt; (iv) toluene at reflux, 10 h.

can be considered stable forms of the zwitterionic intermediates invoked in the classical Staudinger reaction.[12–16] In this paper we report a further application of this strategy to the synthesis of 3-phenylsulfanyl- and 3-benzylsulfanyl-azetidinones.[17–21] In detail, the synthesis involves the preparation of an azadiene **4**,[22,23] from a *N*-trimethylsilylimine **2**[24] and the corresponding phenylsulfanyl- or benzylsulfanyl-ketene, formed in situ from the corresponding phenylsulfanyl- or benzylsulfanyl-acetyl chloride **3** and triethylamine (Scheme 1),[25] followed by its ring closure to **5** and **6** by refluxing overnight in dry toluene. The configuration of the azadiene has been assigned by Noe

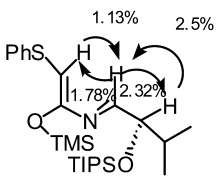


Figure 1.

Keywords: azetidinones; cyclisation; dienes; silicon and compounds; stereochemistry.
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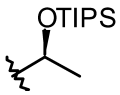
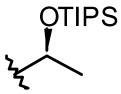
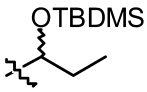
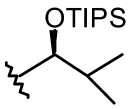
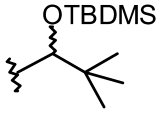
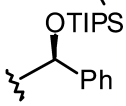
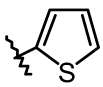
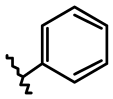
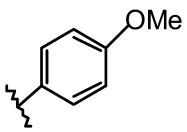
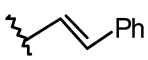
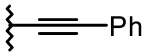
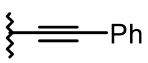
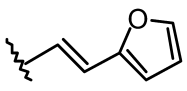
experiments (in Figure 1 the Noe values and the structure of compound **4d** are reported as an example). By this protocol a diastereomeric mixture of NH-β-lactams has been obtained after usual work-up and silica gel flash chromatography in varying yields and diastereomeric ratios depending on the substituents of the azadiene. The results are reported in Table 1. The yields of azetidinones are based on the starting aldehydes (Scheme 1) and are calculated on the pure isolated compounds. Table 1 warrants some comments: although the yields are not high, they have not been optimized and should be considered satisfactory since it must be taken into account that reactions are performed in a one-pot, three-step fashion (preparation of the imine, reaction with acyl chloride and ring closure to the β-lactam ring). The data reported show that the reaction, in term of simple diastereoselectivity, is highly stereo-controlled since only *trans* azetidinones, characterized by coupling constants H^3-H^4 of 2.0–2.5 Hz at ^1H NMR spectra, are obtained. Unfortunately no significant facial-diastereoselectivity is present in all the experiments performed and under the experimental conditions used except for the example of entry 5, Table 1. The absolute configuration of the products **5a**, **6a**, **5b**, **6b**, **5d**, **6d**, **5f**, **6f** and the relative configuration of the racemic compounds **5c**, **6c**, **5e**, **6e** have been determined from the ^1H NMR coupling constants $H^4-H^{4'}$ on the basis of the following observations and arguments. (1) In this paper as well as in related papers on the syntheses of β-lactams, carrying a silyloxy-alkyl side chain at position 4,[12–16] it has been found, from ^1H NMR data, that the two *trans* diastereoisomers obtained can be assembled in two main groups, irrespective of the exact nature of the substituents in position 3: a group A presenting a coupling constant for $H^4-H^{4'}$ within 1–3 Hz and a group B presenting a coupling constant within 5–7 Hz. (2) The compound $\mathbf{A}^1$, belonging to group A and compound $\mathbf{B}^1$, belonging to group B (Scheme 2), have been elaborated to the same enantiomeric pure compound (*epc*) **C** and, subsequently, to Aztreonam of known configuration and optical activity.[26,13] By this way, and taking into account that the parent compound of $\mathbf{A}^1$ was the (*S*)-lactaldehyde, the parent compound of $\mathbf{B}^1$ was the (*R*)-lactaldehyde and that the *trans* relationship between H^3 and H^4 is not in discussion (J=2.5 Hz), the absolute configuration of $\mathbf{A}^1$ and $\mathbf{B}^1$ is so far established. Since the coupling constants for $H^4-H^{4'}$ of the members of group A are of the same magnitude of that of $\mathbf{A}^1$, the coupling constants for $H^4-H^{4'}$ of the members of group B are of the same magnitude of that of $\mathbf{B}^1$, and that the relationship H^3-H^4 is *trans*, according the values of their coupling constants, we feel that we are allowed to attribute the relative configuration of $H^3-H^4-H^{4'}$ for all compounds of Table 1 above mentioned. (3) A further confirmation of the correct stereochemical attributions comes out from a full AM1 analysis[27] on the two model compounds $\mathbf{A}^m$ and $\mathbf{B}^m$ (Chart 1): the analysis shows that $\mathbf{A}^m$ is best described by a conformation in which the two hydrogens $H^4-H^{4'}$ are in a *gauche* relationship, whilst $\mathbf{B}^m$ is best described by two conformations in which the two hydrogens $H^4-H^{4'}$ are in *gauche* and in *anti* relationship. Due to the larger presence of *anti* conformers, to $\mathbf{B}^m$ a larger coupling constant then to $\mathbf{A}^m$ must be assigned. These theoretical calculations match perfectly with the experimental results above reported.

Table 1. Synthesis of azetidinones **5** and **6**

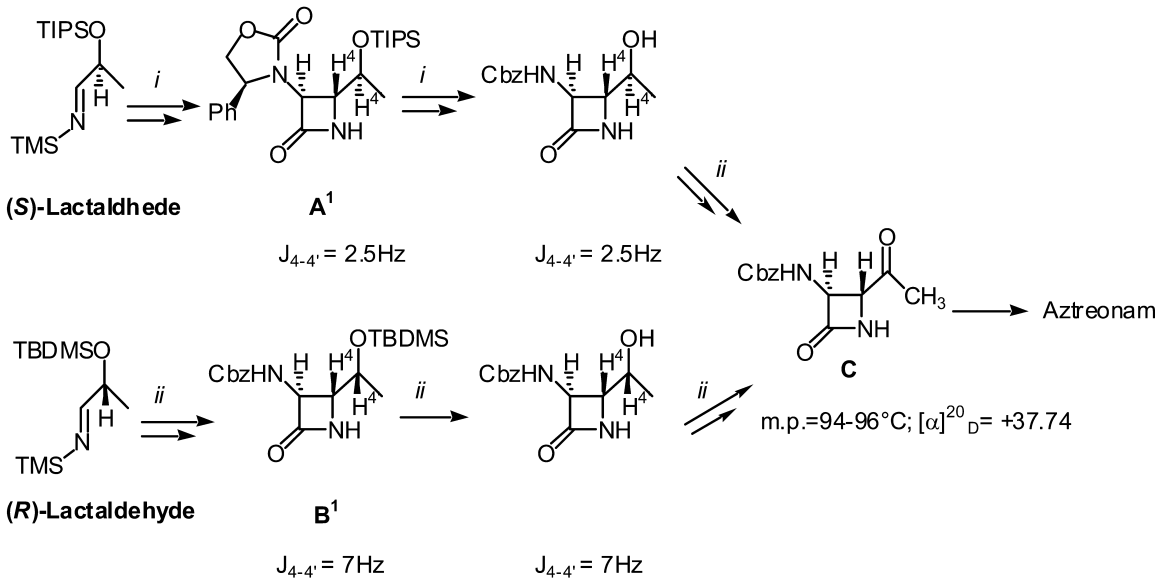
Entry	R	Ar	Products[a] (ratio 5/6)	Y %
1		PhS–	**5a/6a** (65/35)	50
2		$PhCH_2S$–	**5b/6b** (66/34)	40
3		PhS–	**5c/6c** (58/42)	31
4		PhS–	**5d/6d** (57/43)	35
5		PhS–	**5e/6e** (98/2)	40
6		PhS–	**5f/6f** (55/45)	44
7		PhS–	**5g**	25
8		PhS–	**5h**	18
9		PhS–	**5i**	15
10		PhS–	**5j**	0
11		PhS–	**5k**	25
12		$PhCH_2S$–	**5l**	25
13		PhS–	**5m**	20

[a] All products gave analytical data (^1H and ^{13}C NMR, IR, Mass spectra) consistent with the structures reported.[15]

Using as imine that derived from cinnamaldehyde (**2j**) a mixture of the adducts **7a** and **7b** in 4/1 ratio and 20% overall yield was obtained (Scheme 3). The formation of compounds **7a** and **7b** from **4j**, whose structure has been confirmed by Noe experiments, presumably involves, under the thermal conditions used, an electrocyclic disrotatory ring closure with predominant formation of the *cis*-disubstituted adduct **7a**.[28,29] Phenylpropargilic- and 3-furan-2-yl-propenyl imines, in contrast, gave rise only to the expected β-lactams (entries 11,12,13 Table 1).

3. Conclusion

The results presented in this paper may be considered a new



Scheme 2. (i) Ref. 13; (ii) Ref. 26.

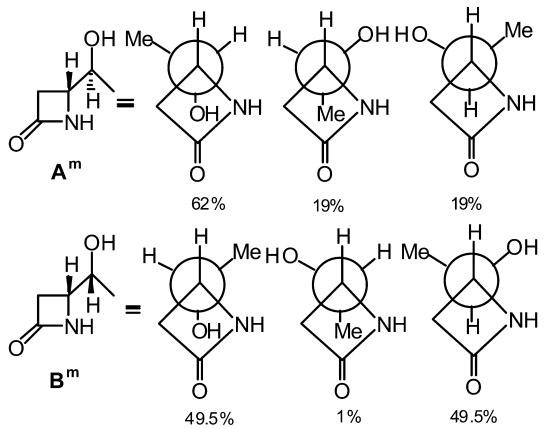
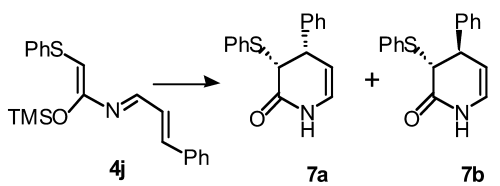


Chart 1.



Scheme 3.

contribution to the synthesis of β-lactams via a two step Staudinger reaction and demonstrate that this approach may be used for the synthesis of variably 3-substituted azetidinones. Work is in progress to extend these results to the synthesis of more valuable compounds known to present biological activity.

4. Experimental

4.1. General

Melting points were taken on a Mel-Temp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on Varian Gemini-200, Varian INOVA 300 MHz or Varian-Mercury 400 MHz. Chemical shifts are reported in δ scale and coupling constants (J) are reported in Hz. In brackets are reported the values of diagnostic protons and carbons. Infrared spectra were recorded as nujol mulls on a Nicolet 205 FT-IR spectrophotometer. Optical rotation measurements were carried out on a Perkin–Elmer 343 Polarimeter and specific rotation $[\alpha]_D^{20}$ was reported in deg per dm at the specified temperature and with the concentration [c] given in g per 100 mL in $CHCl_3$. THF, toluene, and heptane were distilled from benzophenone ketyl. Mass spectra were recorded on Finningam-Mat. Lithium bis(trimethylsilyl)amide (LiHMSDA) (1 M solution in hexane) was purchased from Lancaster.

4.2. Materials

N-Trialkylsilylimines were prepared according to reported procedures[25] starting from the parent aldehydes. Triethylamine was dried over KOH. Other solvents and reagents were obtained commercially and were used as received. All reactions were performed under nitrogen, and the yields are referred to the whole process starting from the aldehyde used in the preparation of imine.

4.3. Preparation of the (5*S*)-1-phenylsulfanyl-2-trimethylsilyloxy-3-aza-5-trisopropylsilyoxy-6-methylhepta-1,3-diene (4d) as typical procedure

To a hexane solution of 1 mmol of [3-methyl-2-(*S*)-(triisopropyl-silanyloxy)-butylidene]-(trimethyl-silanyl)-amine (**2d**),[26] prepared according to a literature procedure,[24] were added, dropwise, at 0°C, under efficient stirring, TEA (2 mmol, 280 μL)) followed by a hexane solution of commercially available phenylsulfanylacetyl chloride (**3**) (1 mmol, 148 μL). The solution was stirred at 0°C for 40 min and then for 1 h at rt. During this time a copious precipitate occurred. The mixture was filtered under a stream of nitrogen on Celite and from the filtrate the low-boiling materials were removed under vacuum. An aliquot of the yellow crude material was analyzed by IR, ^{1}H and ^{13}C NMR.

4.3.1. (5*S*)-1-Phenylsulfanyl-2-trimethylsilyloxy-3-aza-5-triisopropylsilyloxy-6-methyl-hepta-1,3-diene (4d). IR (film): 1678 cm^{-1}; δ_H (400 MHz $CDCl_3$) ppm: 7.66 (d, *J*=6.2 Hz, 1H, N=C*H*), 7.36–7.17 (m, 5H, Ph), 5.84 (s, 1H, PhSC*H*), 4.17 (dd, J_1=4.8 Hz, J_2=6.2 Hz, 1H, C*H*OTIPS), 1.96 (m, 1H, CH(OTIPS)C*H*Me_2), 1.05 (s, 21H, OSi*iPr*$_3$), 0.97 (d, *J*=6.4 Hz, 6H, CH(OTIPS)CH*Me*$_2$), 0.31 (s, 9H, OSi*Me*$_3$); δ_C (100 MHz $CDCl_3$) ppm: 161.6, 152.5, 136.5, 128.9, 127.9, 126.9, 102.5, 78.9, 34.4, 18.0, 17.9, 17.8, 17.7, 17.6, 12.3, 0.61).

4.4. Preparation of the (3*S*,4*S*)- and (3*R*,4*R*)-3-phenylsulfanyl-4-[(1*S*)-1-triisopropylsilanyloxy-2-methylpropyl]-azetidin-2-one (5d) and 6d as typical procedure

The crude azadiene **4d**, prepared as reported above, was dissolved in anhydrous toluene and refluxed overnight under nitrogen. The mixture was poured in saturated ammonium chloride solution and extracted with ethyl acetate (3×10 mL). The organic layers were dried over Na_2SO_4, the solvent removed. Flash chromatography (CH_2Cl_2/acetone 97/3) of the residue yielded the title compounds **5d** and **6d** as pale yellow oils in 50% yield (calculated on the basis of the starting aldehyde) and 50/50 diastereomeric ratio.

4.4.1. (3*S*,4*S*)-3-Phenylsulfanyl-4-[(1*S*)-1-triisopropylsilanyloxy-2-methyl-propyl]-azetidin-2-one (5d). Pale yellow oil, Y=20%, [Found: C 65.01, H 9.09. $C_{22}H_{37}NO_2SSi$ requires C 64.81, H 9.15]. R_f (CH_2Cl_2/acetone 97/3) 0.38; $[\alpha]_D^{20}$=−24 (*c*=1, $CHCl_3$); IR ($CHCl_3$): 1760 cm^{-1}; δ_H (400 MHz $CDCl_3$) ppm: 7.60 (m, 2H, Ph), 7.35 (m, 3H, Ph), 5.58 (bs, 1H, NH), 4.35 (dd, J_1=2.1 Hz, J_2=1.2 Hz, 1H, PhSC*H*), 3.90 (dd, J_1=1.5 Hz, J_2=4.0 Hz, 1H, C*H*OTIPS), 3.45 (dd, J_1=1.5 Hz, J_2=2.1 Hz, 1H, C*H*NH), 1.92 (m, 1H, CH(OTIPS)C*H*Me_2), 1.05 (s, 21H, OSi*iPr*$_3$), 1.00 (d, *J*=7.2 Hz, 3H, CH(OTIPS)CH*Me*$_2$), 0.93 (d, *J*=7.2 Hz, 3H, CH(OTIPS)CH*Me*$_2$); δ_C (100 MHz $CDCl_3$) ppm: 167.7, 133.5, 131.7, 129.1, 128.2, 75.5, 56.0, 53.2, 33.4, 19.0, 18.2, 16.6, 12.9; Ms (*m*/*z*): 407, 364, 321, 214.

4.4.2. (3*R*,4*R*)-3-Phenylsulfanyl-4-[(1*S*)-1-triisopropylsilanyloxy-2-methyl-propyl]-azetidin-2-one (6d). Pale yellow oil, Y=15%, [Found: C; 64.95, H 9.08. $C_{22}H_{37}NO_2SSi$ requires C 64.81, H 9.15]. R_f (CH_2Cl_2/acetone 97/3) 0.45; $[\alpha]_D^{20}$=58 (*c*=0.2, $CHCl_3$); IR ($CHCl_3$): 3424, 1765 cm^{-1}; δ_H (400 MHz $CDCl_3$) ppm: 7.60 (m, 2H, Ph), 7.30 (m, 3H, Ph), 5.73 (bs, 1H, NH), 3.93 (dd, J_1=2.6 Hz, J_2=1.0 Hz, 1H, PhSC*H*), 3.75 (dd, J_1=3.0 Hz, J_2=7.2 Hz, 1H, C*H*OTIPS), 3.45 (dd, J_1=2.6 Hz, J_2=7.2 Hz, 1H, C*H*NH), 1.92 (m, 1H, CH(OTIPS)C*H*Me_2), 1.05 (s, 27H, CH(OTIPS)CH*Me*$_2$+OSi*iPr*$_3$); δ_C (100 MHz $CDCl_3$) ppm: 167.8, 133.4, 131.5, 129.2, 128.3, 78.6, 56.6, 55.8, 33.1, 18.2, 18.1, 17.2, 13.0; Ms (*m*/*z*): 407, 364, 321, 214.

Following the general procedure reported above for azadiene **4d** and azetidinones **5d** and **6d**, the compounds **5a**–**5m** and **6a**–**6f** were obtained.

4.4.3. (3*S*,4*S*)-3-Phenylsulfanyl-4-[(1*S*)-1-triisopropylsilanyloxy-ethyl]-azetidin-2-one (5a). Pale yellow oil, Y=33%, [Found: C 63.42, H 8.80. $C_{20}H_{33}NO_2SSi$ requires C 63.28, H 8.76]. R_f (CH_2Cl_2/acetone 97/3) 0.47; $[\alpha]_D^{20}$=−37 (*c*=1, $CHCl_3$); IR ($CHCl_3$): 3420, 1768 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.59 (m, 2H, Ph), 7.30 (m,3H, Ph), 5.70 (bs, 1H, NH), 4.26 (dd, J_1=2.5 Hz, J_2=1.2 Hz, 1H, C*H*SPh), 4.12 (dq, J_1=6.2 Hz, J_2=2.5 Hz, 1H, C*H*OTIPS), 3.42 (pt, *J*=2.5 Hz, 1H, C*H*NH), 1.25 (d, *J*=6.2 Hz, 3H, CH(OTIPS)*Me*), 1.01 (s, 21H, OSi*iPr*$_3$); δ_C (50 MHz $CDCl_3$) ppm: 166.9, 153.7, 133.2, 129.1, 128.1, 67.3, 61.0, 53.4, 19.9, 18.1, 12.5; Ms (*m*/*z*): 380, 293, 227, 186, 149.

4.4.4. (3*R*,4*R*)-3-Phenylsulfanyl-4-[(1*S*)-1-triisopropylsilanyloxy-ethyl]-azetidin-2-one (6a). Pale yellow oil, Y=17%, [Found: C 63.50, H 8.81. $C_{20}H_{33}NO_2SSi$ requires C 63.28, H 8.76]. R_f (CH_2Cl_2/acetone 97/3) 0.51; $[\alpha]_D^{20}$=+54.8 (*c*=0.7, $CHCl_3$); IR ($CHCl_3$): 3415, 1767 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.58 (m, 2H, Ph), 7.30 (m, 3H, Ph), 5.88 (bs, 1H, NH), 3.92 (m, 2H, PhSC*H*+C*H*OTIPS), 3.35 (dd, J_1=2.6 Hz, J_2=6.8 Hz, 1H, NHC*H*), 1.15 (d, *J*=6.2 Hz, 3H, C*H*(OTIPS)*Me*), 1.01 (m, 21H, OSi*iPr*$_3$); δ_C (50 MHz $CDCl_3$) ppm: 167.4, 153.4, 133.0, 129.1, 127.9, 69.9, 61.6, 55.0, 20.1, 18.1, 12.6; Ms (*m*/*z*): 380, 293, 227, 186, 149.

4.4.5. (3*S*,4*S*)-3-Benzylsulfanyl-4-[(1*S*)-1-triisopropylsilanyloxy-ethyl]-azetidin-2-one (5b). Pale yellow oil, Y=26%, [Found: C 64.30, H 9.01. $C_{21}H_{35}NO_2SSi$ requires C 64.07, H 8.96]. R_f (cyclohexane/ethyl acetate 75/25) 0.45; $[\alpha]_D^{20}$=−77 (*c*=1, $CHCl_3$); IR ($CHCl_3$): 3415, 1764 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.35–7.25 (m, 5H, Ph), 5.67 (bs, 1H, NH), 4.02 (d, *J*=13.2 Hz, 1H, CH_2SPh), 4.00 (dd, J_1=2.9 Hz, J_2=6.2 Hz 1H, C*H*OTIPS), 3.90 (dd, J_1=2.3 Hz, J_2=1.5 Hz, 1H, C*H*SPh), 3.85 (d, *J*=13.2 Hz, 1H, CH_2SPh), 3.36 (dd, J_1=2.3 Hz, J_2=2.9 Hz, 1H, NHC*H*), 1.08 (d, *J*=6.2 Hz, 3H, CH(OTIPS)*Me*), 1.00 (m, 21H, OSi*iPr*$_3$; δ_C (75 MHz $CDCl_3$) ppm: 167.5, 137.5, 129.1, 128.5, 127.2, 67.5, 61.5, 49.9, 35.1, 19.7, 18.1, 12.5; Ms (*m*/*z*): 394, 307, 259, 227, 186, 143, 91.

4.4.6. (3*R*,4*R*)-3-Benzylsulfanyl-4-[(1*S*)-1-triisopropylsilanyloxy-ethyl]-azetidin-2-one (6b). Pale yellow oil, Y=14%, [Found: C 64.32, H 9.00. $C_{21}H_{35}NO_2SSi$ requires C 64.07, H 8.96]. R_f (cyclohexane/ethyl acetate 75/25) 0.38; $[\alpha]_D^{20}$=+110 (*c*=0.9, $CHCl_3$); IR ($CHCl_3$): 3241, 1759 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.36–7.25 (m, 5H, Ph), 6.29 (bs, 1H, NH), 4.03 (d, *J*=13.1 Hz, 1H, CH_2SPh), 3.91 (m, 1H, C*H*OTIPS), 3.83 (d, *J*=13.1 Hz, 1H, CH_2SPh), 3.67 (dd, J_1=2.3 Hz, J_2=1.5 Hz, 1H, BzSC*H*), 3.32 (dd, J_1=2.3 Hz, J_2=6.0 Hz, 1H, C*H*NH), 1.11 (d, *J*=6.3 Hz, 3H, CH(OTIPS)*Me*), 1.01 (m, 21H, OSi*iPr*$_3$); δ_C (75 MHz $CDCl_3$) ppm: 167.1, 137.2, 129.1, 128.5, 127.3, 69.8, 61.8, 50.8, 34.8, 20.1, 18.1, 12.5; Ms (*m*/*z*): 394, 307, 259, 227, 186, 143, 91.

4.4.7. (3*S,4*S**)-3-Phenylsulfanyl-4-[(1*S**)-1-tert-butyldimethyl-silanyloxy-propyl]-azetidin-2-one (5c).** Pale yellow solid mp: 100°C. Y=18%, [Found: C 61.37, H 8.28. $C_{18}H_{29}NO_2SSi$ requires C 61.49, H 8.31]. R_f (cyclohexane/ethyl acetate 75/25) 0.60; IR ($CHCl_3$): 3415, 1769 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.65–7.27 (m, 5H, Ph), 5.79 (bs, 1H, NH), 4.28 (dd, J_1=2.4 Hz, J_2=1.0 Hz, 1H, PhSC*H*), 3.74 (dt, J_1=2.4 Hz, J_2=6.0 Hz, 1H, C*H*OTBDMS), 3.40 (t, *J*=2.4 Hz, 1H, C*H*NH), 1.50 (m, 2H, CH_2CH_3), 0.91 (t, *J*=7.32 Hz, 3H, CH_2CH_3), 0.85 (s, 9H, OSiMe$_2$*tBu*) 0.04 (s, 3H, OSi*Me*$_2$*t*Bu), 0.02 (s, 3H,

OSi*Me*$_2$*t*Bu); δ_C (75 MHz $CDCl_3$) ppm: 167.1, 133.3, 132.2, 129.3, 128.0, 72.1, 58.8, 53.2, 27.6, 25.8, 18.1, 9.6, −4.5, −4.6; Ms (*m*/*z*): 352, 317,279, 251, 199, 144.

4.4.8. (3*R* *,4*R* *)-3-Phenylsulfanyl-4-[(1*S* *)-1-*t*-butyl-dimethyllsilylanoxy-propyl]-azetidin-2-one (6c). Pale yellow oil, Y=13%, [Found: C 61.61, H 8.34. $C_{18}H_{29}NO_2$ SSi requires C 61.49, H 8.31]. R_f (cyclohexane/ethyl acetate 75/25) 0.42; IR ($CHCl_3$): 3424, 1768 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.65–7.27(m, 5H, Ph), 5.73 (bs, 1H, NH), 3.93 (dd, J_1=2.5 Hz, J_2=1.2 Hz, 1H, PhSC*H*), 3.60 (m, 1H, C*H*OTBDMS), 3.40 (dd, J_1=2.5 Hz, J_2=7.0 Hz, 1H, NHC*H*), 1.50 (m, 2H, CH_2CH_3), 0.90 (t, *J*=6.8 Hz, 3H, CH_2CH_3), 0.85 (s, 9H, OSi*t*BuMe_2), 0.05 (s, 3H, OSi*t*Bu*Me*$_2$), 0.02 (s, 3H, OSi*t*Bu*Me*$_2$); δ_C (75 MHz $CDCl_3$) ppm: 166.4, 153.7, 133.3, 129.3, 128.3, 74.9, 59.1, 55.4, 27.3, 25.8, 15.0, 9.0, 4.2, 4.4; Ms (*m*/*z*): 352, 306,279, 251, 199, 145.

4.4.9. (3*S* *,4*S* *)-3-Phenylsulfanyl-4-[(1*S* *)-1-*tert*-butyl-dimethylsilanyloxy-2,2-dimethyl-propyl]-azetidin-2-one (5e). Pale yellow solid mp: 139–140°C. Y=39%, [Found: C 63.46, H 8.72. $C_{20}H_{33}NO_2SSi$ requires C 63.28, H 8.76]. R_f (CH_2Cl_2) 0.55; IR ($CHCl_3$): 1766 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.60 (m, 2H, Ph), 7.30 (m, 3H, Ph), 5.68 (bs, 1H, NH), 4.28 (d, *J*=2.2 Hz, 1H, PhSC*H*), 3.58 (dd, J_1=2.2 Hz, J_2=0.8 Hz, 1H, C*H*NH), 3.46 (bs, 1H, C*H**t*Bu), 0.96 (s, 9H, CH(OTBDMS)*tBu*), 0.92 (s, 9H, OSiMe$_2$*tBu*), 0.05 (s, 6H, OSi*Me*$_2$*t*Bu); δ_C (75 MHz $CDCl_3$) ppm: 168.0, 133.3, 132.0, 129.1, 128.1, 78.8, 56.0, 53.0, 35.3, 26.8, 26.2, 18.5, 3.3, 4.2; Ms (*m*/*z*): 380, 340, 279, 201, 172.

4.4.10. (3*R* *,4*R* *)-3-Phenylsulfanyl-4-[(1*S* *)-1-*tert*-butyl-dimethyl-silanyloxy-2,2-dimethyl-propyl]-azetidin-2-one (6e). Pale yellow oil, Y=1%, [Found: C 63.50, H 8.70. $C_{20}H_{33}NO_2SSi$ requires C 63.28, H 8.76]. R_f (CH_2Cl_2) 0.76; IR ($CHCl_3$): 3412, 1766 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.60 (m, 2H, Ph), 7.30 (m, 3H, Ph), 5.62 (bs, 1H, NH), 3.87 (dd, J_1=1.3 Hz, J_2=2.2 Hz, 1H, PhSC*H*), 3.43 (dd, J_1=2.2 Hz, J_2=7.6 Hz, 1H, C*H*NH), 3.35 (d, *J*=7.6 Hz, 1H, CHOTBDMS), 1.1 (s, 9H, CH(OTBDMS)*tBu*), 0.98 (s, 9H, OSiMe$_2$*tBu*), 0.16 (s, 6H, OSi*Me*$_2$*t*Bu); δ_C (75 MHz $CDCl_3$) ppm: 169.4, 133.1, 132.3, 129.1, 127.2, 81.8, 81.4, 73.0, 35.3, 26.8, 26.2, 18.5, 3.3, 4.2; Ms (*m*/*z*): 380, 340, 279, 201, 172.

4.4.11. (3*S*,4*S*)-3-Phenylsulfanyl-4-[(1*S*)-tri-isopropyl-silanyloxy-phenyl]-azetidin-2-one (5f). Pale yellow oil, Y=24%, [Found: C 68.25, H 8.02. $C_{25}H_{35}NO_2SSi$ requires C 67.98, H 7.99]. R_f (CH_2Cl_2) 0.38; $[\alpha]_D^{20}$=−15.45 (*c*=1.65, $CHCl_3$); IR ($CHCl_3$): 3413, 2946, 1767 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.47 (m, 2H, Ph), 7.28 (m, 8H, Ph), 5.62 (bs, 1H, NH), 4.85 (d, *J*=4.5 Hz, 1H, C*H*OTIPS), 4.07 (dd, J_1=2.4 Hz, J_2=1.1 Hz, 1H, PhSC*H*), 3.60 (dd, J_1=2.4 Hz, J_2=4.5 Hz, 1H, C*H*NH), 0.98–0.92 (m, 21H, OSi*iPr*); δ_C (50 MHz $CDCl_3$) ppm: 166.5, 140.1, 133.6, 131.9, 129.0, 128.4, 128.3, 128.2, 126.5, 75.1, 61.0, 54.6, 17.8, 12.3; Ms (*m*/*z*): 442, 398, 355, 289, 248, 115.

4.4.12. (3*R*,4*R*)-3-Phenylsulfanyl-4-[(1*S*)-triisopropyl-silanyloxy-phenyl]-azetidin-2-one (6f). Pale yellow oil, Y=20%, [Found: C 68.22, H 8.01. $C_{25}H_{35}NO_2SSi$ requires C 67.98, H 7.99]. R_f (CH_2Cl_2) 0.31; $[\alpha]_D^{20}$=+45 (*c*=1.65, $CHCl_3$); IR ($CHCl_3$): 3419, 1767 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.50 (m, 10H, Ph+Ph), 5.90 (bs, 1H, NH), 4.81 (d, *J*=6.0 Hz, 1H, C*H*OTIPS), 4.07 (dd, J_1=2.5 Hz, J_2=1.0 Hz, 1H, PhSC*H*), 3.60 (dd, J_1=2.5 Hz, J_2=6.0 Hz, 1H, C*H*NH), 0.9–1.1 (m, 21H, OSi*iPr*); δ_C (50 MHz $CDCl_3$) ppm: 166.4, 140.7, 133.2, 133.2, 131.8, 129.0, 128.6, 128.1, 126.4, 76.1, 62.0, 54.8, 17.8, 12.3; Ms (*m*/*z*): 442, 398, 355, 289, 248, 115.

4.4.13. (3*S* *,4*S* *)-3-Phenylsulfanyl-4-thiophen-azetidin-2-one (5g). Pale yellow solid mp: 86–88°C. Y=25%, [Found: C 59.60, H 4.26. $C_{13}H_{11}NOS_2$ requires C 59.74, H 4.24]. R_f (CH_2Cl_2/ethyl acetate 90/10) 0.57; IR ($CHCl_3$): 3408, 1773 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.50 (m, 2H, thiophen-2-yl), 7.30 (m, 4H, Ph), 7.0 (m, 2H, Ph+thiophen-2-yl), 6.35 (bs, 1H, NH), 4.75(d, *J*=2.2 Hz, 1H, C*H*NH), 4.29 (dd, J_1=2.2 Hz, J_2=0.94 Hz, 1H, PhSC*H*); δ_C (50 MHz $CDCl_3$) ppm: 166.2, 142.3, 132.6, 132.0, 129.2, 128.1, 127.3, 125.7, 125.4, 63.6, 55.6; Ms (*m*/*z*): 261, 218, 185, 112.

4.4.14. (3*S* *,4*S* *)-4-Phenyl-3-phenylsulfanyl-azetidin-2-one (5h). Pale yellow solid mp: 98–99°C. Y=18%, [Found: C 70.76, H 5.15. $C_{15}H_{13}NOS$ requires C 70.56, H 5.13]. R_f (CH_2Cl_2/acetone 98/2) 0.38; IR ($CHCl_3$): 1769 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.52 (m, 2H, Ph), 7.4 (m, 8H, Ph), 6.18 (bs, 1H, NH), 4.53 (d, *J*=2.4 Hz, 1H, C*H*NH), 4.18 (dd, J_1=2.4 Hz, J_2=0.84 Hz, 1H, PhSC*H*); δ_C (75 MHz $CDCl_3$) ppm: 166.6, 138.3, 132.8, 132.1, 129.2, 129.0, 128.7, 128.1, 125.7, 62.9, 59.2; Ms (*m*/*z*): 255, 212, 178, 106, 77.

4.4.15. (3*S* *,4*S* *)-3-Phenylsulfanyl-4-(4-methoxy-phenyl)-azetidin-2-one (5i). Pale yellow oil, Y=15%, [Found: C 67.14, H 5.28. $C_{16}H_{15}NO_2S$ requires C 67.34, H 5.30]. R_f (cyclohexane/ethyl acetate 60/40) 0.27; IR ($CHCl_3$): 1756 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.48 (m, 2H, *p*-MeO-Ph), 7.25 (m, 5H, Ph), 6.87 (d, 2H, *p*-MeO-Ph), 6.05 (bs, 1H, NH), 4.45 (d, *J*=2.3 Hz, 1H, C*H*NH), 4.13 (dd, J_1=2.3 Hz, J_2=0.94 Hz, 1H, PhSC*H*), 3.80 (s, 3H); δ_C (75 MHz $CDCl_3$) ppm: 166.6, 160.0, 153.6, 132.5, 130.3, 129.2, 128.0, 127.0, 114.4, 62.8, 59.1, 55.4; Ms (*m*/*z*): 285, 242, 227, 211, 197, 178, 165, 149, 136, 121, 77.

4.4.16. (3,4-*cis*)-3-Phenylsulfanyl-4-phenyl-3,4-dihydro-1*H*-pyridin-2-one (7a). Pale yellow oil, Y=16%, [Found: C 72.87, H: 5.39. $C_{17}H_{15}NOS$ requires C 72.57, H 5.37]. R_f (CH_2Cl_2/ethyl acetate 90/10) 0.55; IR ($CHCl_3$): 3620, 3017, 1688, 1659 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 8.06 (bs, 1H, NH), 7.60–7.56 (m, 2H, Ph), 7.42–7.12 (m, 8H, Ph), 6.24 (dd, J_1=4.66 Hz, J_2=7.74 Hz, 1H, NHC*H*), 5.24 (m, 1H, NHCH=C*H*), 3.86 (m, 1H, PhSC*H*), 3.85 (m, 1H, PhC*H*); δ_C (75 MHz $CDCl_3$) ppm: 168.4, 140.0, 133.1, 132.9, 129.0, 128.9, 128.1, 127.5, 127.0, 125.0, 105.7, 53.7, 44.7; Ms (*m*/*z*): 281, 172, 132, 115, 105, 77.

4.4.17. (3,4-*trans*)-3-Phenylsulfanyl-4-phenyl-3,4-dihydro-1*H*-pyridin-2-one (7b). Pale yellow oil, Y=4%, [Found: C 72.80, H 5.39. $C_{17}H_{15}NOS$ requires C 72.57, H 5.37]. R_f (CH_2Cl_2/ethyl acetate 90/10) 0.44; IR ($CHCl_3$): 3620, 3018, 1656, 1521 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.52–7.05 (m, 11H, 2Ph+NH), 6.28 (m, 1H, PhC*H*), 5.39 (m, 1H, NHCH=C*H*), 4.24 (m, 1H, NHC*H*), 3.98 (d, *J*=5.7 Hz, 1H,

PhSC*H*). δ_C (75 MHz $CDCl_3$) ppm: 169.7, 138.8, 138.1, 134.8, 132.4, 129.7, 129.6, 129.0, 128.9, 128.6, 128.5, 127.5, 127.4, 125.7, 108.0, 59.7, 42.9; Ms (*m*/*z*): 281, 172, 132, 115, 105, 77.

4.4.18. (3*S,4*S**)-3-Phenylsulfanyl-4-phenylethynyl-azetidin-2-one (5k).** Pale yellow oil, Y=25%, [Found: C 72.87, H 4.68. $C_{17}H_{13}NOS$ requires C 73.09, H 4.69]. R_f (cyclohexane/ethyl acetate 80/20) 0.35; IR ($CHCl_3$): 3413, 1775 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.58–7.31 (m, 10H, 2Ph), 6.21 (bs, 1H, NH), 4.53(dd, J_1=2.4, J_2=1.4 Hz, 1H, PhSC*H*), 4.29 (d, *J*=2.4 Hz, 1H, C*H*NH); δ_C (50 MHz $CDCl_3$) ppm: 165.4, 132.7, 131.2, 131.8, 129.3, 129.1, 128.5, 128.3, 121.8, 86.9, 84.9, 62.2, 46.7; Ms (*m*/*z*): 279, 235, 202, 130, 121, 105, 77.

4.4.19. (3*S,4*S**)-3-Benzylsulfanyl-4-phenylethynyl-azetidin-2-one (5l).** Pale yellow solid mp: 109–112°C. Y=25%, [Found: C 73.80, H: 5.17. $C_{18}H_{15}NOS$ requires C 73.69, H 5.15]. R_f (cyclohexane/ethyl acetate 80/20) 0.29; IR ($CHCl_3$): 3413, 1774 cm^{-1}; δ_H (200 MHz $CDCl_3$) ppm: 7.73–7.26 (m, 10H, 2Ph), 6.42 (bs, 1H, NH), 4.23 (m, 1H, BzSC*H*), 4.16 (d, *J*=1.9 Hz, 1H, C*H*NH), 3.96 (d, *J*=13.2 Hz, 1H, PhCH_2S), 3.87 (d, *J*=13.2 Hz, 1H, PhCH_2S); δ_C (50 MHz $CDCl_3$) ppm: 165.8, 137.0, 131.6, 129.1, 128.9, 128.7, 128.4, 127.5, 121.7, 86.5, 85.0, 59.5, 47.4, 35.4; Ms (*m*/*z*): 293, 260, 247, 217, 202, 171, 158, 144, 130, 115, 92, 77.

4.4.20. (3*S,4*S**)-3-Phenylsulfanyl-4-furan-2yl-azetidin-2-one (5m).** Pale yellow oil, Y=20%, [Found: C 66.67, H 4.85. $C_{15}H_{13}NO_2S$ requires C 66.40, H 4.83]. R_f (cyclohexane/ethyl acetate 70/30) 0.28; IR ($CHCl_3$): 3422, 1766 cm^{-1}; δ_H (400 MHz $CDCl_3$) ppm: 7.75 (bs, 1H, NH), 7.57 (m, 2H, Ph+CH=C*H*O), 7.32 (m, 4H, Ph), 6.25 (dd, J_1=2.0 Hz, J_2=3.2 Hz, 1H, CH=C*H*–O), 6.20 (dd, J_1=4.8 Hz, J_1=7.6 Hz, 1H, NHCH–CH=C*H*–), 6.09 (d, *J*=3.2 Hz, 1H, C*H*=C–O), 5.21 (m, 1H, NHCH–C*H*=CH), 4.01 (m, 1H, PhSC*H*), 3.94 (dd, J_1=1.6 Hz, J_1=6 Hz, 1H, C*H*NH); δ_C (75 MHz $CDCl_3$) ppm: 169.1, 152.4, 143.5, 132.9, 132.8, 129.1, 128.1, 125.8, 110.3, 106.2, 103.0, 50.8, 38.4; Ms (*m*/*z*): 271, 239, 205, 162, 149, 122, 105.

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