An unprecedented cleavage of the β-lactam ring: a novel synthesis of acyclic *N,O*- and *N,S*-acetals

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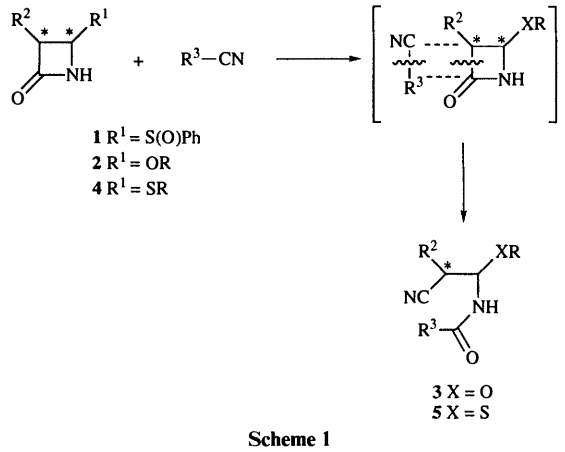
A new synthesis of acyclic *N,O*-acetals 3 and *N,S*-acetals 5 has been devised by way of a trimethylsilyl trifluoromethanesulfonate promoted formal 2,3-bond fragmentation of 4-heteroatom substituted azetidinones 1 and 4, respectively. This reaction proceeds by nucleophilic attack of a nitrile group of the solvent on the cation intermediate A. However, when there is a second nucleophile such as azidotrimethylsilane in the reaction system, no solvent attack occurs but, rather, the second nucleophile attacks the intermediate to form novel α-azido sulfides 6.

Introduction

Very recently, we briefly communicated a novel ring cleavage, where 4-sulfinyl- and/or 4-alkoxy-azetidinones undergo a formal 2,3-bond fission leading to α-cyano-*N,O*-acetals.[1] In this paper, we report the generality of this type of cleavage of β-lactams in detail.



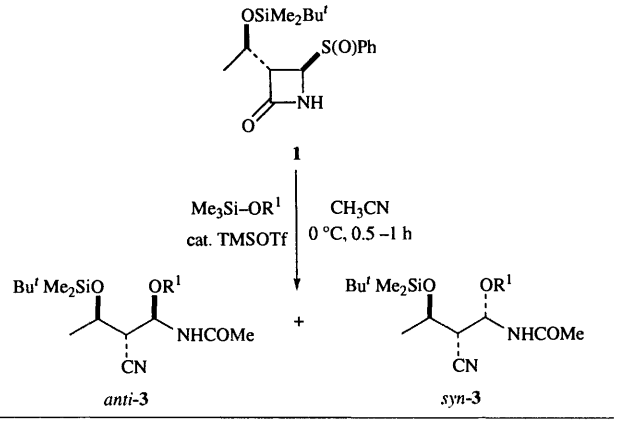
Scheme 1

Fragmentation of 4-sulfinylazetidin-2-one 1

Recently, we reported a novel alkoxylation of **1** with various tributyltin alkoxides (Bu_3SnOR) in the presence of a catalytic amount of ZnI_2 in benzene to give 4-alkoxyazetidin-2-ones **2** in good yields.[2] The reactions also proceeded in the presence of a catalytic amount of trimethylsilyl trifluoromethanesulfonate (TMSOTf) in acetonitrile (MeCN). In contrast, the use of **1** with trimethylsilyl alkoxide (Me_3SiOR) instead of Bu_3SnOR in the presence of a catalytic amount of TMSOTf in MeCN failed to give the expected compound **2** but, rather, a novel and unexpected compound, α-cyano-*N,O*-acetal **3** was obtained instead in good yield (Table 1).

The above-described unexpected and unprecedented reaction was thought to proceed *via* **2**, since the reaction of **1** in the absence of trimethylsilyl alkoxide failed to give any cleavage product. In fact, cleavage proceeded equally well with a variety of separately prepared 4-alkoxyazetidin-2-ones **2a–e** in the presence of a catalytic amount of TMSOTf in acetonitrile to give the corresponding α-cyano-*N,O*-acetals **3a,e,n**. Furthermore, the reaction occurs not only in acetonitrile but also in other cyano group-containing solvents such as propionitrile, butyronitrile, and benzonitrile (Table 2). All the reactions proceeded smoothly and stereoselectively.

Table 1 β-Lactam fragmentation of 4-sulfinylazetidin-2-one **1**



Run	R^1	Product 3	Yield (%)[a]	Ratio of *anti*:*syn*[b]
1	Me	**3a**	62	1.4:1[c]
2	Bn	**3b**	82	7:1
3	Pr	**3c**	52	2.2:1
4	Cyclohexyl	**3d**	58	13:1

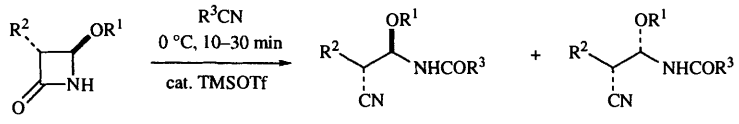
[a] After silica gel column chromatography. [b] Determined from ^1H NMR data. [c] The low selectivity was observed in run 1 due to the over-reaction of **3** with the excess of Me_3SiOR^1.

The structure of **3** was determined from ^1H and ^{13}C NMR and IR data. An X-ray crystallographic structure of **3a** shows that the major isomer has an *anti* configuration (Fig. 1).†

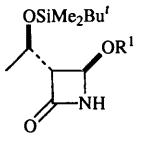
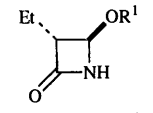
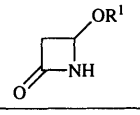
A mechanistic rationale for the reaction is presented in Scheme 2. Substitution at the 4-position of **1** with alkoxysilanes affords the corresponding 4-alkoxyazetidin-2-ones **2** which may yield the oxocarbenium intermediate **A** with TMSOTf by way of 1,4-bond cleavage.[3] **A** is then attacked by the solvent (R^3CN) to give the *N,O*-acetals **3** *via* cyclic intermediate **B**.

† Compound **3a** was prepared from two different starting materials, **1** and **2a** in a ratio 1.4:1 and 13:1 (*anti*:*syn*), respectively (see Experimental section). The pure sample of **3a** for X-ray crystallographic analysis was obtained by the recrystallization of the latter sample (*anti*:*syn* = 13:1) from hexane.

Table 2 β-Lactam fragmentation of 4-alkoxyazetidin-2-ones **2a–e**



2 *anti*-**3** *syn*-**3**

Run		β-Lactam **2**	R^1	R^3	Product **3**	Yield (%)[a]	Ratio of *anti*:*syn*[b]
1	**2a**		Me	Me	**3a**	71	13:1
2	**2a**		Me	Et	**3e**	70	8:1
3	**2a**		Me	Pr	**3f**	90	5.7:1
4	**2a**		Me	Ph	**3g**	81	15:1
5	**2b**		Allyl	Me	**3h**	81	4.6:1
6	**2b**		Allyl	Pr	**3i**	66	14:1
7	**2c**		Me	Me	**3j**	82	1.2:1 (or 1:1.2)
8	**2c**		Me	Pr	**3k**	71	1.3:1 (or 1:1.3)
9	**2c**		Me	Ph	**3l**	61	1.2:1 (or 1:1.2)
10	**2d**		Allyl	Me	**3m**	61	1.3:1 (or 1:1.3)
11	**2e**[c]		Me	Me	**3n**	69	—

[a] After silica gel column chromatography. [b] Determined from ^{1}H NMR data. [c] Racemic **2e** was used.

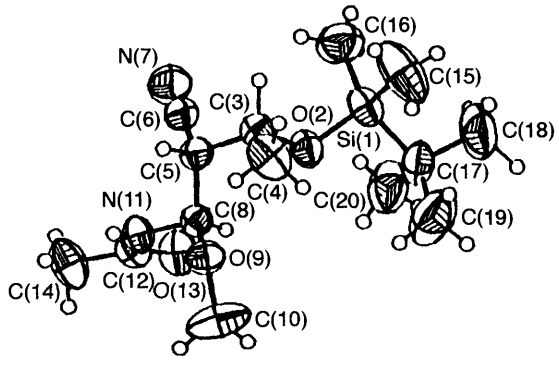
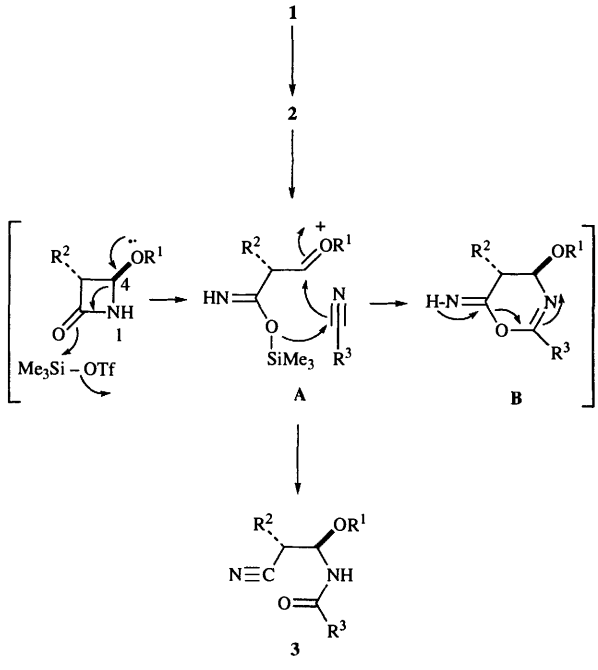


Fig. 1 X-Ray crystallographic structure of *anti*-**3a**



Scheme 2

Although there have been several reports of the synthesis of cyanides by way of β-lactam cleavage,[4] most of the methods were inapplicable to the synthesis of α-chiral cyanides since α,β-unsaturated compounds would be formed. Our stereoselective fragmentation selectively gives α-chiral cyanides under mild conditions in good yields.

Fragmentation of 4-alkylthioazetidin-2-ones 4

A previously described mechanism of fragmentation of **1** and **2** showed that 4-heterofunction-substituted azetidin-2-ones may cause a similar type of cleavage.[5] Application of this novel cleavage reaction to 4-alkylthioazetidin-2-ones **4**, as sulfur analogues of **2**, gave acyclic α-cyano-*N*,*S*-acetals.

The reaction of various substituted compounds **4** in the presence of a catalytic amount of TMSOTf in acetonitrile and other cyano group-containing solvents proceeded similarly well and yielded the corresponding α-cyano-*N*,*S*-acetals **5** (Table 3).

The fragmentation mechanism of **4** is presumably similar to that of **2**, and, therefore, the major isomer of **5** has an *anti* configuration. Although the reason for the difference in selectivity remains unclear, it seems to arise from differences in oxocarbenium and thionium reaction intermediates.

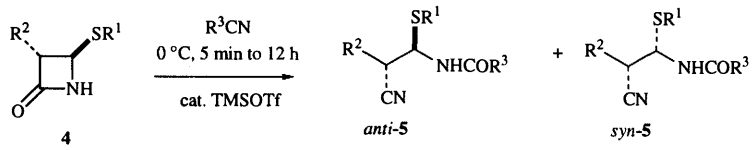
In general, it was supposed to be difficult to synthesize acyclic *N*,*S*-acetals[6] because of their instability. Although several methods have appeared for syntheses of acyclic *N*,*S*-acetals, for instance, an addition to an imine intermediate with an thia-nucleophile[7] and an addition to a thionium intermediate with an aza-nucleophile,[8] most of the methods had several problems in terms of low yield and vigorous reaction conditions. Our novel fragmentation of **4** proceeded under mild conditions and was expected to be a novel synthesis of various acyclic *N*,*S*-acetals.

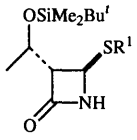
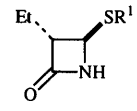
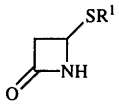
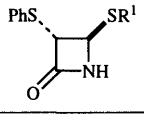
A novel synthesis of α-azido sulfides from 4-alkylthioazetidin-2-ones 4

Finally, we examined what happened when an azido nucleophile was introduced instead of a nitrile to the thionium intermediate generated in the cleavage of **4**.

Initially, reaction of **4** with azidotrimethylsilane (Me_3SiN_3) in the presence of a catalytic amount of TMSOTf in methylene dichloride was examined; the reaction gave only acrylamide

Table 3 β-Lactam fragmentation of 4-alkylthioazetidin-2-ones **4a–h**



Run		β-Lactam **4**	R^1	R^3	Product **5**	Yield (%)[a]	Ratio of diastereoisomer[b]
1	**4a**		Bn	Me	**5a**	50	2.8:1
2	**4b**		*p*-MeOBn	Me	**5b**	47	2.9:1
3	**4c**		Allyl	Me	**5c**	45	2:1
4	**4d**		Pr^i	Me	**5d**	64	2:1
5	**4e**		Cyclohexyl	Me	**5e**	84	1.8:1
6	**4f**		Bu^t	Me	**5f**	89	1:1
7	**4f**		Bu^t	Pr	**5g**	63	1.1:1
8	**4f**		Bu^t	Ph	**5h**	46	1.3:1
9	**4g**		Bu^t	Me	**5i**	91	1.2:1
10	**4g**		Bu^t	Pr	**5j**	77	1.4:1
11	**4g**		Bu^t	Ph	**5k**	53	1:1
12	**4h**[c]		Bu^t	Me	**5l**	65	—
13	**4i**[c]		Bu^t	Me	**5m**	54	1:1

[a] After silica gel chromatography. [b] Determined from ^{1}H NMR data. [c] Racemic **4** was used.

derivatives by way of 1,4-bond cleavage. Following an examination of a variety of reaction conditions, we found that the best conditions to give azido nucleophile adducts were as follows. Reaction of **4** with Me_3SiN_3 in the presence of BF_3·OEt_2 (1–2 equiv.) in methylene dichloride gave the corresponding β-amido-α-azido sulfide **6** in good yield (Table 4).

α-Azido sulfides have potential for the synthesis of various types of acyclic *N,S*-acetals, since the azido moiety can be changed to other azasubstituents through the use of triphenylphosphine, *etc.*[9]

Experimental

All melting points are uncorrected. IR absorption spectra were recorded on a JASCO HPIR-102 and Shimadzu FTIR-8100 spectrophotometers with $CHCl_3$ as a solvent. ^{1}H NMR spectra were measured on JEOL JNM-EX270 (270 MHz) and JEOL JNM-GX500 (500 MHz) spectrometers with $CDCl_3$ as a solvent with tetramethylsilane as an internal standard unless otherwise noted. *J* Values are given in Hz. Mass spectra (MS) and high-resolution MS were obtained by ESCO EMD-05A and JEOL JMS-D300 mass spectrometers. Optical rotations were measured in 1 dm cells of 1 ml capacity with a Perkin-Elmer 241 instrument; values are quoted in units of 10^{-1} deg cm^2 g^{-1}. E. Merck silica gel 60 (70–230 mesh ASTM) for column chromatography and E. Merck silica gel 60 (230–400 mesh ASTM) for flash chromatography were used. E. Merck pre-coated TLC plates and silica gel F_{254} for preparative thin layer chromatography (prep. TLC) were used. Organic layers were dried with anhydrous Na_2SO_4.

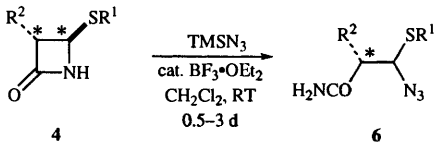
General procedure for the reaction of 4-sulfinylazetidin-2-one 1 with alkoxytrimethylsilanes

To a stirred solution of (3*R*,4*R*)-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)ethyl]-4-phenylsulfinylazetidin-2-one[10] **1** (0.100 mmol) and alkoxytrimethylsilane ($ROSiMe_3$) (0.3–0.5 mmol) in dry MeCN (1 ml) was added TMSOTf (0.01 mmol) under nitrogen at 0 °C. After being stirred for 0.5–1 h, the reaction mixture was poured into saturated aq. sodium hydrogen carbonate and repeatedly extracted with methylene dichloride. The organic layer was washed with brine, dried, and evaporated. The residue was purified by preparative TLC to give the corresponding α-cyano-*N,O*-acetals **3** in good yield.

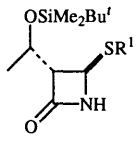
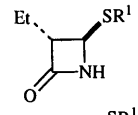
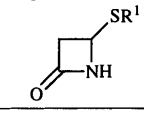
(2*R*,3*R*)-1-Acetamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-methoxybutane 3a. Compound **1** (51.5 mg, 0.146 mmol), $MeOSiMe_3$ (75.9 mg, 0.730 mmol), TMSOTf (3.2 mg, 0.0146 mmol), MeCN (1 ml); **3a** (27.0 mg, 62%) a colourless oil, *anti*:*syn* = 1.4:1 (Found: C, 55.9; H, 9.2; N, 9.4. $C_{14}H_{28}N_2O_3Si$ requires C, 55.95; H, 9.4; N, 9.3%); ν_{max}/cm^{-1} 3310 (NH), 2249 (CN) and 1670 (C=O); δ_H(270 MHz) 0.092 (6 H, s, $SiMe_2$), 0.90 (9 H, s, SiBu^t), 1.33 (1.4/2.4 × 3 H, d, *J* 5.9, MeCH), 1.35 (1/2.4 × 3 H, d, *J* 5.9, MeCH), 2.05 (3 H, s, MeCON), 2.72 (1/2.4 × 1 H, dd, *J* 3, 8.6, CHCN), 2.92 (1.4/2.4 × 1 H, dd, *J* 3.6, 7.3, CHCN), 3.35 (3 H, s, OMe), 4.11 (1 H, br quint, *J* 5.9, CHMe), 5.41 (1.4/2.4 × 1 H, dd, *J* 3.6, 10, CHOMe), 5.50 (1/2.4 × 1 H, dd, *J* 3, 10, CHOMe), 6.09 (1/2.4 × 1 H, d, *J* 10, NH) and 6.31 (1.4/2.4 × 1 H, d, *J* 10, NH); *m/z* 243 (M^+ − Bu^t) (Found: M^+ − Bu^t, 243.1155. $C_{10}H_{19}N_2O_3Si$ requires *M*, 243.1163).

(2*R*,3*R*)-1-Acetamido-1-benzyloxy-3-*tert*-butyldimethylsiloxy-2-cyanobutane 3b. Compound **1** (30.0 mg, 0.085 mmol), $PhCH_2OSiMe_3$ (45.9 mg, 0.255 mmol), TMSOTf (1.5 mg, 0.0085 mmol), MeCN (1 ml); **3b** (26.2 mg, 82%) a colourless oil, *anti*:*syn* = 7:1 (Found: C, 64.0; H, 8.75; N, 7.0; $C_{20}H_{32}N_2O_3Si$ requires C, 63.8; H, 8.6; N, 7.45%); $[\alpha]_D^{25}$ +52.8 (*c* 0.708, EtOH); ν_{max}/cm^{-1} 3400 (NH), 2250 (CN) and 1680 (C=O); δ_H(250 MHz) 0.058, 0.066 (total 6 H, each s, $SiMe_2$), 0.87 (7/8 × 9 H, s, Bu^t), 0.90 (1/8 × 9 H, s, SiBu^t), 1.28

Table 4 α-Azido sulfide formation from 4-alkylthioazetidin-2-ones



4 6

Run		β-Lactam **4**	R^1	Product **6**	Yield (%)[a]	Ratio of diastereoisomer[b]
1	**4d**		Pr^i	**6a**	80	1:1
2	**4e**		Cyclohexyl	**6b**	81	1.2:1
3	**4f**		Bu^t	**6c**	77	1.3:1
4	**4g**[c]		Bu^t	**6d**	91	1:1
5	**4i**[c]		Bu^t	**6e**	97	—

[a] After silica gel column chromatography. [b] Determined from ^{1}H NMR data. [c] Racemic **4** was used.

(7/8 × 3 H, d, *J* 6, MeCH), 1.37 (1/8 × 3 H, d, *J* 6, MeCH), 1.94 (1/8 × 3 H, s, MeCON), 2.02 (7/8 × 3 H, s, MeCON), 2.78 (1/8 × 1 H, dd, *J* 3.3, 7.8, CHCN), 2.93 (7/8 × 1 H, dd, *J* 3.8, 5.6, CHCN), 4.10 (7/8 × 1 H, quint, *J* 6, CHMe), 4.16 (1/8 × 1 H, m, CHMe), 4.55, 4.64 (7/8 × 2 H, ABq, *J* 12, CH_2Ph), 4.57, 4.64 (1/8 × 2 H, ABq, *J* 12, CH_2Ph), 5.61 (7/8 × 1 H, dd, *J* 3.8, 10, CHN), 5.74 (1/8 × 1 H, dd, *J* 3.3, 10, CHN), 6.05 (1/8 × 1 H, d, *J* 10, NH), 6.30 (7/8 × 1 H, d, *J* 10, NH) and 7.33 (5 H, br s, Ph); *m/z* 319 ($M^+ - Bu^t$) (Found: $M^+ - Bu^t$, 319.1475. $C_{16}H_{23}N_2O_3Si$ requires *M*, 319.1467).

(2*R*,3*R*)-1-Acetamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-propoxybutane 3c. Compound **1** (51.8 mg, 0.176 mmol), $PrOSiMe_3$ (58.2 mg, 0.441 mmol), TMSOTf (3.3 mg, 0.0147 mmol), MeCN (1 ml); **3c** (24.9 mg, 52%) a colourless oil, *anti*:*syn* = 2.2:1 (Found: C, 58.4; H, 9.7; N, 8.3. $C_{16}H_{32}N_2O_3Si$ requires C, 58.5; H, 9.8; N, 8.55%); $[\alpha]_D^{24}$ +25.7 (*c* 0.894, MeOH); ν_{max}/cm^{-1} 3422 (NH), 2249 (CN) and 1690 (C=O); δ_H(270 MHz) 0.091, 0.095, 0.100 (total 6 H, each s, $SiMe_2$), 0.899 (1/3.2 × 9 H, s, $SiBu^t$), 0.903 (2.2/3.2 × 9 H + 3 H, s, $SiBu^t$, $MeCH_2$), 1.34 (2.2/3.2 × 3 H, d, *J* 6, MeCH), 1.36 (1/3.2 × 3 H, d, *J* 6, MeCH), 1.57 (br sextet, 2 H, *J* 6.9, CH_2Me), 2.03 (s, 2.2/3.2 × 3 H, MeCON), 2.04 (1/3.2 × 3 H, s, MeCON), 2.75 (1/3.2 × 1 H, dd, *J* 3.3, 8.3, CHCN), 2.89 (2.2/3.2 × 1 H, dd, *J* 4, 7.6, CHCN), 3.39 (1/3.2 × 1 H, ddd, OC*H*H), 3.43, 3.52, 3.55 (total 1 H + 2.2/3.2 × 1 H, each t, OCH_2), 4.14 (1 H, br dq, *J* 6, 7.6, CHMe), 5.49 (2.2/3.2 × 1 H, dd, *J* 4, 10, CHOMe), 5.55 (1/3.2 × 1 H, dd, *J* 3, 10, CHOMe), 6.06 (1/3.2 × 1 H, d, *J* 10, NH) and 6.31 (2.2/3.2 × 1 H, d, *J* 10, NH); *m/z* 271 ($M^+ - Bu^t$) (Found: $M^+ - Bu^t$, 271.1476. $C_{12}H_{23}N_2O_3Si$ requires *M*, 271.1476).

(2*R*,3*R*)-1-Acetamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-cyclohexyloxybutane 3d. Compound **1** (50.0 mg, 0.14 mmol), c-$C_6H_{11}OSiMe_3$ (73.1 mg, 0.42 mmol), TMSOTf (3.1 mg, 0.014 mmol), MeCN (1 ml); **3d** (30.0 mg, 58%) a colourless oil, *anti*:*syn* = 13:1 (Found: C, 62.05; H, 9.7; N, 7.25. $C_{19}H_{36}N_2O_3Si$ requires C, 61.9; H, 9.85; N, 7.6%); $[\alpha]_D^{25}$ +47.3 (*c* 0.766, EtOH); *m/z* 368 (M^+) (Found: M^+, 368.2515. $C_{19}H_{36}N_2O_3Si$ requires *M*, 368.2495); *m/z* 369 (M^+ + H) (Found: M^+ + H, 369.2603. $C_{19}H_{37}N_2O_3Si$ requires *M*, 369.2573); ν_{max}/cm^{-1} 3420 (NH), 2250 (CN) and 1690 (C=O); δ_H(270 MHz) 0.10 (1/14 × 6 H, s, $SiMe_2$), 0.11, 0.12 (total 13/14 × 6 H, each s, $SiMe_2$), 0.90 (1/14 × 9 H, s, $SiBu^t$), 0.91 (13/14 × 9 H, s, $SiBu^t$), 1.00–1.99 [10 H, br m, $(CH_2)_5$], 1.35 (3 H, d, *J* 6.3, MeCH), 2.82 (1/14 × 1 H, dd, *J* 4, 7.6, CHCN), 2.84 (13/14 × 1 H, dd, *J* 3.6, 7.6, CHCN), 3.52 (13/14 × 1 H, m, OCH<), 3.62 (1/14 × 1 H, m, OCH<), 4.03 (1/14 × 1 H, br quint, *J* 6.3, CHMe), 4.16 (13/14 × 1 H, dq, *J* 6.3, 7.6, CHMe), 5.61 (1/14 × 1 H, dd, *J* 4, 10, CHOMe), 5.64 (dd, 13/14 × 1 H, *J* 3.6, 10, CHOMe), 5.96 (1/14 × 1 H, br d, *J* 10, NH) and 6.32 (13/14 × 1 H, d, *J* 10, NH).

Preparation of 4-alkoxyazetidin-2-ones 2

4-Alkoxyazetidin-2-ones **2a**, **2b** and **2e** were prepared by our previously reported method.[2]

(3*R*,4*R*)-3-Ethyl-4-methoxyazetidin-2-one 2c. To a stirred solution of (3*S*,4*R*)-4-acetoxy-3-ethylazetidin-2-one[11] (202 mg, 1.29 mmol) in dry MeOH (10 ml) was added sodium methoxide (174 mg, 3.23 mmol) at 0 °C for 30 min under nitrogen. The mixture was stirred at room temperature for 30 min and then poured into water and repeatedly extracted with AcOEt. The combined extracts were washed with brine, dried, and evaporated. The residue was purified by flash chromatography, eluting with 20% AcOEt in hexane to give **2c** (153 mg, 92%) as a colourless oil; *m/z* 129 (M^+) (Found: M^+, 129.078. $C_6H_{11}NO_2$ requires *M*, 129.0787); $[\alpha]_D^{26}$ +14.4 (*c* 1.53, $CHCl_3$); ν_{max}/cm^{-1} 3430 (NH) and 1760 (C=O); δ_H(270 MHz) 1.05 (3 H, t, *J* 7.6, $MeCH_2$), 1.68, 1.78 (total 2 H, each d quint, *J* 6.3, 7.6, CH_2Me), 3.00 (1 H, ddd, *J* 1.1, 6.3, 7.6, 3-H), 3.32 (3 H, s, OMe), 4.70 (1 H, d, *J* 1.1, 4-H) and 6.54 (1 H, br s, NH).

(3*R*,4*R*)-4-Allyloxy-3-ethylazetidin-2-one 2d. To a solution of (3*R*,4*R*)-4-acetoxy-3-ethylazetidin-2-one (310 mg, 1.97 mmol) in dry benzene (10 ml) was added allyl alcohol (2 ml, 29.6 mmol) and zinc acetate (721 mg, 3.94 mmol) in one portion. The resulting mixture was refluxed with a Dean–Stark trap (MS4A) for 12 h after which it was poured into water and repeatedly extracted with AcOEt. The combined extracts were washed with brine, dried, and evaporated. The residue was purified by flash chromatography, eluting with 20% AcOEt in hexane to give **2d** (238 mg, 78%) as a colourless oil; *m/z* 155 (M^+) (Found: M^+, 155.0935. $C_8H_{13}NO_2$ requires *M*, 155.0945); $[\alpha]_D^{26}$ +42.4 (*c* 1.97, $CHCl_3$); ν_{max}/cm^{-1} 3400 (NH) and 1760 (C=O); δ_H(270 MHz) 0.96 (3 H, t, *J* 7.4, $MeCH_2$), 1.64 (2 H, m, CH_2Me), 2.94 (1 H, dt, *J* 1.3, 7.4, 3-H), 3.97 (2 H, dt, *J* 5.5, 1.0, OCH_2), 4.71 (1 H, d, *J* 1.3, 4-H), 5.16 (1 H, ddd, *J* 1.0, 2.5, 11, C*H*H=CH), 5.24 (1 H, ddd, *J* 1.0, 2.5, 17, C*H*H=CH), 5.84 (1 H, ddt, *J* 5.5, 11, 17, C*H*=CH_2) and 6.52 (1 H, br s, NH).

General procedure for the synthesis of α-cyano-*N*,*O*-acetals 3 from 4-alkoxyazetidin-2-ones 2

To a stirred solution of 4-alkoxyazetidin-2-one **2** (0.100 mmol) in dry RCN (1 ml) was added dropwise TMSOTf (0.01 mmol) at 0 °C for 10–30 min under nitrogen. The mixture was then poured into saturated aq. sodium hydrogen carbonate and repeatedly extracted with CH_2Cl_2. The combined extracts were washed with brine, dried, and evaporated. The residue was purified by preparative TLC to give the corresponding α-cyano-*N*,*O*-acetals **3** in considerable yield.

(2*R*,3*R*)-1-Acetamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-methoxybutane 3a. Compound **2a** (208 mg, 0.803 mmol), TMSOTf (17.8 mg, 0.0803 mmol), MeCN (2 ml); **3a** (171 mg, 71%), *anti*:*syn* = 13:1. Pure *anti*-**3a** colourless crystals, mp 107–112 °C (hexane); $[\alpha]_D^{23}$ +47.8 (*c* 1.39, MeOH); δ_H(270 MHz) 0.09 (6 H, s, $SiMe_2$), 0.09 (9 H, s, SiBu^t), 1.33 (3 H, d, *J* 5.9, MeCH), 2.05 (3 H, s, CH_3CONH), 2.91 (1 H, dd, *J* 4.0, 7.3, CHCN), 3.34 (3 H, s, OMe), 4.11 (1 H, qd, *J* 5.9, 7.3, $CHCH_3$), 5.41 (1 H, dd, *J* 4.0, 10.0, $CHOCH_3$), 6.34 (1 H, br d, *J* 10.0, NH); δ_C(270 MHz, $CDCl_3$) 170.7 (CO), 117.5 (CN), 77.6 (1-CH), 66.0 (2-CH), 55.8 (O-CH_3), 46.2 (3-CH), 25.9 [SiC(CH_3)$_3$], 23.0 (4-CH_3), 21.4 (NHCOCH_3), 17.7 (SiCMe_3) and −4.56 ($SiCH_3$ × 2).

(2*R*,3*R*)-3-*tert*-Butyldimethylsiloxy-2-cyano-1-methoxy-1-propanamidobutane 3e. Compound **2a** (46.7 mg, 0.180 mmol), TMSOTf (4.0 mg, 0.018 mmol), EtCN (1 ml); **3e** (38.8 mg, 70%), a colourless oil, *anti*:*syn* = 8:1; $[\alpha]_D^{25}$ +41.0 (*c* 0.612, EtOH); ν_{max}/cm^{-1} 3400 (NH), 2240 (CN) and 1680 (C=O); δ_H(270 MHz) 0.089 (6 H, s, $SiMe_2$), 0.900 (9 H, s, Bu^t), 1.18 (3 H, t, *J* 7.6, $MeCH_2$), 1.33 (3 H, d, *J* 5.9, >CHMe), 2.27 (2 H, q, *J* 7.6, CH_2Me), 2.73 (1/9 × 1 H, dd, *J* 3, 8.6, CHCN), 2.91 (8/9 × 1 H, dd, *J* 4, 7.6, CHCN), 3.39 (3 H, s, OMe), 4.10 (1 H, dq, *J* 5.9, 7.6, CHMe), 5.44 (8/9 × 1 H, dd, *J* 4, 10, CHOMe), 5.53 (1/9 × 1 H, dd, *J* 3, 10, CHOMe), 5.99 (1/9 × 1 H, d, *J* 10, NH) and 6.21 (8/9 × 1 H, d, *J* 10, NH); *m*/*z* 257 (M^+ − Bu^t) (Found: M^+ − Bu^t, 257.1311. $C_{11}H_{21}N_2O_3Si$ requires *M*, 257.1318).

(2*R*,3*R*)-1-Butanamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-methoxybutane 3f. Compound **2a** (52.2 mg, 0.202 mmol), TMSOTf (4.5 mg, 0.0202 mmol), PrCN (1 ml); **3f** (59.4 mg, 90%), a colourless oil, *anti*:*syn* = 5.7:1 (Found: C, 58.1; H, 9.85; N, 8.45. $C_{16}H_{32}N_2O_3Si$ requires C, 58.5; H, 9.8; N, 8.55%); $[\alpha]_D^{23}$ +36.5 (*c* 2.29, MeOH); ν_{max}/cm^{-1} 3420 (NH), 2249 (CN) and 1692 (C=O); δ_H(270 MHz) 0.091 (6 H, s, $SiMe_2$), 0.90 (9 H, s, SiBu^t), 0.96 (3 H, t, *J* 7.3, $MeCH_2$), 1.33 (5.7/6.7 × 3 H, d, *J* 5.9, >CHMe), 1.35 (1/6.7 × 3 H, d, *J* 5.6, >CHMe), 1.70 (2 H, sextet, *J* 7.3, CH_2Me), 2.22 (5.7/6.7 × 1 H, t, *J* 7.3, CH_2CON), 2.23 (1/6.7 × 1 H, t, *J* 7.3, CH_2CON), 2.73 (1/6.7 × 1 H, dd, *J* 3, 8.6, CHCN), 2.91 (5.7/6.7 × 1 H, dd, *J* 4, 7.6, CHCN), 3.34 (3 H, s, OMe), 4.09 (1 H, quint, *J* 7.3, CHMe), 5.44 (5.7/6.7 × 1 H, dd, *J* 4, 10, CHOMe), 5.53 (1/6.7 × 1 H, dd, *J* 3, 10, CHOMe), 5.98 (1/6.7 × 1 H, d, *J* 10, NH) and 6.21 (5.7/6.7 × 1 H, d, *J* 10, NH); *m*/*z* 271 (M^+ − Bu^t) (Found: M^+ − Bu^t, 271.1480. $C_{12}H_{23}N_2O_3Si$ requires *M*, 271.1478).

(2*R*,3*R*)-1-Benzamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-methoxybutane 3g. Compound **2a** (50.0 mg, 0.193 mmol), TMSOTf (3.7 mg, 0.0193 mmol), PhCN (0.5 ml); **3g** (56.8 mg, 81%), colourless crystals, mp 62–65 °C (hexane), *anti*:*syn* = 15:1; $[\alpha]_D^{25}$ +15.1 (*c* 2.60, $CHCl_3$); ν_{max}/cm^{-1} 3310 (NH), 2249 (CN) and 1670 (C=O); δ_H(270 MHz) 0.076, 0.086 (total 15/16 × 6 H, each s, $SiMe_2$), 0.12, 0.13 (total 1/16 × 6 H, each s, $SiMe_2$), 0.88 (15/16 × 9 H, s, SiBu^t), 0.89 (1/16 × 9 H, s, SiBu^t), 1.36 (15/16 × 3 H, d, *J* 6.3, MeCH), 1.39 (1/16 × 3 H, d, *J* 6.3, MeCH), 2.88 (1/16 × 1 H, dd, *J* 3, 8.6, CHCN), 3.05 (15/16 × 1 H, dd, *J* 4, 7.3, CHCN), 3.42 (3 H, s, OMe), 4.16 (1 H, dq, *J* 7.3, 6.3, CHMe), 5.65 (15/16 × 1 H, dd, *J* 4, 9.9, CHOMe), 5.73 (1/16 × 1 H, dd, *J* 3, 9.6, CHOMe), 6.64 (1/16 × 1 H, d, *J* 9.6, NH) and 6.85 (15/16 × 1 H, d, *J* 9.9, NH); *m*/*z* 305 (M^+ − Bu^t) (Found: M^+ − Bu^t, 305.1293. $C_{15}H_{21}N_2O_3Si$ requires *M*, 305.1319).

(2*R*,3*R*)-1-Acetamido-1-allyloxy-3-*tert*-butyldimethylsiloxy-2-cyanobutane 3h. Compound **2a** (52.0 mg, 0.182 mmol), TMSOTf (4.0 mg, 0.0182 mmol), MeCN (1 ml); **3h** (47.9 mg, 81%), colourless crystals, mp 52–58 °C (hexane), *anti*:*syn* = 4.6:1 (Found: C, 58.75; H, 9.25; N, 8.45. $C_{16}H_{30}N_2O_3Si$ requires C, 58.55; H, 9.25; N, 8.6%); $[\alpha]_D^{24}$ +34.6 (*c* 2.11, EtOH); ν_{max}/cm^{-1} 3420 (NH), 2249 (CN) and 1694 (C=O); δ_H(270 MHz) 0.081, 0.084 (total 6 H, each s, $SiMe_2$), 0.89 (9 H, s, SiBu^t), 1.32 (4.6/5.6 × 3 H, d, *J* 6.3, MeCH), 1.35 (1/5.6 × 3 H, d, *J* 6.3, MeCH), 2.03 (3 H, s, MeCON), 2.75 (1/5.6 × 1 H, dd, *J* 3, 8.3, CHCN), 2.92 (4.6/5.6 × 1 H, dd, *J* 3.6, 7.3, CHCN), 3.92–4.16 (3 H, m, CH_2O, CHMe), 5.15 (1/5.6 × 1 H, ddd, *J* 1.3, 3, 10, C*H*H=CH), 5.18 (4.6/5.6 × 1 H, ddd, *J* 1.3, 3, 10, C*H*H=CH), 5.28 (1 H, ddd, *J* 1.3, 1.7, 17, CH*H*=CH), 5.53 (4.6/5.6 × 1 H, dd, *J* 4, 10, CHOMe), 5.59 (1/5.6 × 1 H, dd, *J* 3, 10, CHOMe), 5.78–5.94 (1 H, m, C*H*=CH_2) and 6.28 (1/5.6 × 1 H, br d, *J* 10, CHOMe); *m*/*z* 269 (M^+ − Bu^t) (Found: M^+ − Bu^t, 269.1338. $C_{12}H_{21}N_2O_3Si$ requires *M*, 269.1322).

(2*R*,3*R*)-1-Allyloxy-1-butanamido-3-*tert*-butyldimethylsiloxy-2-cyanobutane 3i. Compound **2a** (50.9 mg, 0.179 mmol), TMSOTf (4 mg, 0.0179 mmol), PrCN (1 ml); **3i** (42 mg, 66%), a colourless oil, *anti*:*syn* = 14:1 (Found: C, 60.75; H, 9.7; N, 7.8. $C_{18}H_{34}N_2O_3Si$ requires C, 60.95; H, 9.65; N, 7.9%); $[\alpha]_D^{24}$ +38.0 (*c* 1.85, MeOH); ν_{max}/cm^{-1} 3420 (NH), 2249 (CN) and 1694 (C=O); δ_H(270 MHz) 0.086 (6 H, s, $SiMe_2$), 0.89 (9 H, s, SiBu^t), 0.96 (3 H, t, *J* 7.3, $MeCH_2$), 1.33 (14/15 × 3 H, d, *J* 6.3, MeCH), 1.36 (1/15 × 3 H, d, *J* 6.3, MeCH), 2.20 (3 H, t, *J* 7.3, CH_2CON), 2.75 (1/15 × 1 H, dd, *J* 3.3, 8.3, CHCN), 2.92 (14/15 × 1 H, dd, *J* 4, 7.3, CHCN), 3.98 (14/15 × 1 H, dddd, *J* 1.3, 3, 5.6, 19, C*H*HO), 4.06–4.16 (2 H + 1/14 × 1 H, m, CH_2O, CHMe), 5.18 (14/15 × 1 H, ddd, *J* 1.3, 3, 11, CH*H*=CH), 5.28 (ddd, 14/15 × 1 H, *J* 1.3, 3, 17, CH*H*=CH), 5.56 (dd, 14/15 × 1 H, *J* 4, 10, CHOMe), 5.62 (dd, 1/15 × 1 H, *J* 3.3, 10, CHOMe), 5.84 (ddt, 1 H, *J* 5.6, 11, 17, C*H*=CH_2), 6.03 (br d, 1/15 × 1 H, *J* 10, NH) and 6.26 (br d, 14/15 × 1 H, *J* 10, NH). Other signals could not be assigned; *m*/*z* 297 (M^+ − Bu^t) (Found: M^+ − Bu^t, 297.1631. $C_{14}H_{25}N_2O_3Si$ requires *M*, 297.1632).

(2*S*)-1-Acetamido-2-cyano-1-methoxybutane 3j. Compound **2c** (22.0 mg, 0.171 mmol), TMSOTf (3.8 mg, 0.0171 mmol), MeCN (1 ml); **3j** (23.7 mg, 82%), a colourless oil, *anti*:*syn* = 1.2:1 (or 1:1.2); $[\alpha]_D^{24}$ +8.9 (*c* 0.923, $CHCl_3$); *m*/*z* 170 (M^+) (Found: M^+, 170.1062. $C_8H_{14}N_2O_2$ requires *M*, 170.1056); ν_{max}/cm^{-1} 3422 (NH), 2247 (CN) and 1686 (C=O); δ_H(270 MHz) 1.10 (t, 3 H, *J* 7.6, $MeCH_2$), 1.57–1.86 (2 H, m, CH_2Me), 2.07 (1.2/2.2 × 3 H, s, MeCON), 2.10 (1/2.2 × 3 H, s, MeCON), 2.71 (1.2/2.2 × 1 H, ddd, *J* 4.3, 6, 10, CHCN), 2.87 (1/2.2 × 1 H, ddd, *J* 4.3, 6, 10, CHCN), 3.36 (1/2.2 × 3 H, s, OMe), 3.40 (1.2/2.2 × 3 H, s, OMe), 5.21 (1.2/2.2 × 1 H, dd, *J* 4.3, 10, CHOMe), 5.27 (1/2.2 × 1 H, dd, *J* 4.3, 10, CHOMe) and 6.20 (1 H, br s, NH).

(2*S*)-2-Cyano-1-butanamido-1-methoxybutane 3k. Compound **2c** (23.1 mg, 0.179 mmol), TMSOTf (4.0 mg, 0.0179 mmol), PrCN (1 ml); **3k** (25.0 mg, 71%), a colourless oil, *anti*:*syn* = 1.3:1 (or 1:1.3); $[\alpha]_D^{27}$ +15.6 (*c* 0.917, $CHCl_3$); *m*/*z* 198 (M^+) (Found: M^+, 198.1369. $C_{10}H_{18}N_2O_2$ requires *M*, 198.1386); *m*/*z* 199 (M^+ + H) (Found: 199.1469. $C_{10}H_{19}N_2O_2$ requires *M*, 199.1446); ν_{max}/cm^{-1} 3428 (NH), 2247 (CN) and 1676 (C=O); δ_H(270 MHz) 0.978 (1/2.3 × 3 H, t, *J* 7.3, $MeCH_2CH_2$), 0.984 (1.3/2.3 × 3 H, t, *J* 7.3, $MeCH_2CH_2$), 1.10 (3 H, t, *J* 7.6, $MeCH_2CH$), 1.71 (m, 4 H, CH_2Me × 2), 2.25, 2.27 (each t, total 2 H, *J* 7.6, CH_2CO), 2.71 (1/2.3 × 1 H, ddd, *J* 4.3, 5.9, 9.2, CHCN), 2.87 (1.3/2.3 × 1 H, ddd, *J* 4.3, 5.9, 9.2, CHCN), 3.36 (1.3/2.3 × 3 H, s, OMe), 3.39 (1/2.3 × 3 H, s, OMe), 5.23 (1/2.3 × 1 H, dd, *J* 4.3, 9.9, CHOMe), 5.29 (1.3/2.3 × 1 H, dd, *J* 4.3, 9.9, CHOMe), 6.11 (1.3/2.3 × 1 H, d, *J* 9.9, NH) and 6.18 (1/2.3 × 1 H, d, *J* 9.9, NH).

(2*S*)-1-Benzamido-2-cyano-1-methoxybutane 3l. Compound

2c (36.7 mg, 0.284 mmol), TMSOTf (6.3 mg, 0.0284 mmol), PhCN (0.5 ml); **3l** (40.3 mg, 61%), colourless crystals, mp 128–129 °C (hexane–CH_2Cl_2); *anti*:*syn* = 1.2:1 (or 1:1.2) (Found: C, 67.2; H, 6.95; N, 11.95. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.95; N, 12.05%); $[\alpha]_D^{25}$ +11.2 (*c* 0.491, EtOH); ν_{max}/cm^{-1} 3428 (NH), 2247 (CN) and 1676 (C=O); δ_H(270 MHz) 1.13 (1.3/2.3 × 3 H, t, *J* 7.3, $MeCH_2$), 1.14 (1/2.3 × 3 H, t, *J* 7.3, $MeCH_2$), 1.64–1.92 (2 H, m, CH_2Me), 2.85 (1/2.3 × 1 H, ddd, *J* 4.3, 5.9, 9.2, CHCN), 2.98 (1.3/2.3 × 1 H, ddd, *J* 4.3, 5.9, 9.6, CHCN), 3.43 (1.3/2.3 × 3 H, s, OMe), 3.47 (1/2.3 × 3 H, s, OMe), 5.44 (1/2.3 × 1 H, dd, *J* 4.3, 10, CHOMe), 5.51 (1.3/2.3 × 1 H, dd, *J* 4.3, 10, CHOMe), 6.55 (1.3/2.3 × 1 H, br d, *J* 10, NH), 6.59 (1/2.3 × 1 H, br d, *J* 10, NH) and 7.45–7.86 (5 H, m, Ph); *m*/*z* 232 (Found: M^+, 232.1198. $C_{13}H_{16}N_2O_2$ requires *M*, 232.1209); *m*/*z* 217 (M^+ – Me) (Found: M^+ – Me, 217.0986. $C_{12}H_{13}N_2O_2$ requires *M*, 217.0978).

(2*S*)-1-Acetamido-1-allyloxy-2-cyanobutane 3m. Compound **2d** (25.0 mg, 0.161 mmol), TMSOTf (3.6 mg, 0.0161 mmol), MeCN (1 ml); **3m** (19.1 mg, 61%), a colourless oil, *anti*:*syn* = 1.3:1 (or 1:1.3); $[\alpha]_D^{25}$ +8.6 (*c* 0.790, $CHCl_3$); *m*/*z* 196 (M^+) (Found: M^+, 196.1213. $C_{10}H_{16}N_2O_2$ requires *M*, 196.1212); *m*/*z* 197 (M^+ + H) (Found: M^+ + H, 197.1261. $C_{10}H_{17}N_2O_2$ requires *M*, 197.1287); ν_{max}/cm^{-1} 3422 (NH), 2245 (CN) and 1688 (C=O); δ_H(270 MHz) 1.10 (3 H, t, *J* 7.6, $MeCH_2$), 1.58–1.86 (2 H, m, CH_2Me), 2.06 (1.2/2.2 × 3 H, s, MeCON), 2.08 (1/2.2 × 3 H, s, MeCON), 2.72 (1.2/2.2 × 1 H, ddd, *J* 4.3, 6, 10, CHCN), 2.88 (1/2.2 × 1 H, ddd, *J* 4.3, 6, 10, CHCN), 3.98 (1 H, dd, *J* 6.3, 10, OC*H*H), 4.11 (1.2/2.2 × 1 H, ddd, *J* 1.3, 5.3, 10, OCH*H*), 4.16 (1/2.2 × 1 H, ddd, *J* 1.3, 5.3, 10, OCH*H*), 5.18–5.37 (1.2/2.2 × 1 H + 2 H, m, C*H*OMe, CH_2=CH), 5.40 1/2.2 × 1 H, dd, *J* 4.3, 10, CHOMe), 5.88 (1 H, ddt, *J* 5.9, 12, 18, C*H*=CH_2) and 6.17 (1 H, br s, NH).

3-Acetamido-3-methoxypropionitrile 3n. Compound **2e** (104 mg, 1.05 mmol), TMSOTf (20 mg, 0.0901 mmol), MeCN (5 ml); **3n** (91.3 mg, 69%), a colourless oil; ν_{max}/cm^{-1} 3420 (NH), 2240 (CN) and 1680 (C=O); δ_H(270 MHz) 2.04 (3 H, s, MeCON), 2.68 (1 H, dd, *J* 5, 9.6, C*H*HCN), 2.75 (1 H, dd, *J* 5, 9.6, CH*H*CN), 3.36 (3 H, s, OMe), 5.36 (1 H, dt, *J* 8.6, 9.6, CHOMe) and 6.69 (1 H, d, *J* 8.6, NH); *m*/*z* 127 (M^+ – Me) (Found: M^+ – Me, 127.0532. $C_5H_7N_2O_2$ requires *M*, 127.0508).

Preparation of 4-alkylthioazetidin-2-ones 4

4-Alkylthioazetidin-2-one **4a** was prepared by our previously reported method,[10] and **4b–f**, **h** were prepared by a method similar to that used to prepare **4a**.

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-(4-methoxyphenylmethyl)thioazetidin-2-one 4b. Compound **1** (102.0 mg, 0.289 mmol), $MeOC_6H_4CH_2SSiMe_3$ (196 mg, 0.867 mmol), ZnI_2 (9.2 mg, 0.0289 mmol); **4b** (90.3 mg, 82%), *m*/*z* 324 (M^+ – Bu^t) (Found: M^+ – Bu^t, 324.1091. $C_{15}H_{22}NO_3SSi$ requires *M*, 324.1090); colourless crystals, mp 76–79 °C (hexane); $[\alpha]_D^{20}$ +12.8 (*c* 0.810, $CHCl_3$); ν_{max}/cm^{-1} 3409 (NH) and 1763 (C=O); δ_H(250 MHz) 0.024 (3 H, s, $SiMe_2$), 0.048 (3 H, s, $SiMe_2$), 0.85 (9 H, s, SiBu^t), 1.16 (3 H, d, *J* 6.3, MeCH), 3.03 (1 H, m, 3-H), 3.80 (3 H, s, MeO), 3.81 (2 H, s, SCH_2), 4.18 (1 H, dq, *J* 3.5, 6.3, OCHMe), 4.76 (1 H, d, *J* 2.3, 4-H), 5.38 (1 H, br s, NH) and 6.83–7.26 (4 H, m, ArH).

(3*S*,4*R*)-4-Allylthio-3-[(1*R*)-1-(*tert*-butyldimethylsiloxy)-ethyl]azetidin-2-one 4c. Compound **1** (98.4 mg, 0.279 mmol), CH_2=$CHCH_2SSiMe_3$ (122.2 mg, 0.837 mmol), ZnI_2 (8.9 mg, 0.0279 mmol); **4c** (63.0 mg, 75%), colourless crystals, mp 113–114 °C (hexane) (Found: C, 55.6; H, 9.0; N, 4.7. $C_{14}H_{27}NO_2SSi$ requires C, 55.75; H, 9.05; N, 4.65%); $[\alpha]_D^{20}$ +82.3 (*c* 1.14, $CHCl_3$); ν_{max}/cm^{-1} 3414 (NH) and 1765 (C=O); δ_H(250 MHz) 0.061 (3 H, s, $SiMe_2$), 0.072 (3 H, s, $SiMe_2$), 0.87 (9 H, s, SiBu^t), 1.22 (3 H, d, *J* 6.3, MeCH), 3.13 (1 H, m, 3-H), 3.20–3.37 (2 H, m, SCH_2), 4.24 (1 H, dq, *J* 3.4, 6.3, CHMe), 4.83 (1 H, d, *J* 2.5, 4-H), 5.11–5.26 (2 H, m, CH_2=CH), 5.80–6.00 (1 H, m, C*H*=CH_2) and 6.05 (1 H, br s, NH).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-isopropylthioazetidin-2-one 4d. Compound **1** (125.1 mg, 0.354 mmol), $Me_2CHSSiMe_3$ (156.9 mg, 1.06 mmol), ZnI_2 (11.3 mg, 0.0354 mmol); **4d** (94.5 mg, 88%), colourless crystals, mp 131–132 °C (hexane) (Found: C, 55.2; H, 9.65; N, 4.6. $C_{14}H_{29}NO_2SSi$ requires C, 55.4; H, 9.65; N, 4.6%); $[\alpha]_D^{20}$ +62.3 (*c* 0.303, $CHCl_3$); ν_{max}/cm^{-1} 3414 (NH) and 1765 (C=O); δ_H(250 MHz) 0.071 (s, 3 H, $SiMe_2$), 0.079 (s, 3 H, $SiMe_2$), 0.88 (9 H, s, SiBu^t), 1.23 (3 H, d, *J* 6.3, MeCHO), 1.33 (6 H, d, *J* 7.0, Me_2CH), 3.00–3.12 (3 H, m, C*H*Me_2, 3-H), 4.25 (1 H, dq, *J* 3.8, 6.3, OC*H*Me), 4.90 (1 H, d, *J* 2.5, 4-H) and 6.02 (1 H, br s, NH).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-cyclohexylthioazetidin-2-one 4e. Compound **1** (100.7 mg, 0.285 mmol), c-$C_6H_{11}SSiMe_3$ (160.7 mg, 0.855 mmol), ZnI_2 (9.1 mg, 0.0285 mmol); **4e** (76.3 mg, 78%), colourless crystals, mp 146–147 °C (hexane) (Found: C, 59.3; H, 9.85; N, 4.0. $C_{17}H_{33}NO_2SSi$ requires C, 59.45; H, 9.7; N, 4.1%); $[\alpha]_D^{20}$ + 64.6 (*c* 0.593, $CHCl_3$); ν_{max}/cm^{-1} 3414 (NH) and 1765 (C=O); δ_H(250 MHz) 0.069 (s, 3 H, $SiMe_2$), 0.078 (s, 3 H, $SiMe_2$), 0.88 (9 H, s, SiBu^t), 1.23 (3 H, d, *J* 6.3, MeCH), 1.25–2.10 [10 H, m, $(CH_2)_5$], 2.73–2.86 (1 H, m, SCH), 3.08 (1 H, ddd, *J* 1.0, 2.5, 3.8, 3-H), 4.25 (1 H, dq, *J* 3.8, 6.3, OC*H*Me), 4.90 (1 H, d, *J* 2.5, 4-H) and 5.98 (1 H, br s, NH).

(3*S*,4*R*)-3-[(1*R*)-1-(*tert*-Butyldimethylsiloxy)ethyl]-4-*tert*-butylthioazetidin-2-one 4f. Compound **1** (342.5 mg, 0.970 mmol), Bu^t$SSiMe_3$ (471.4 mg, 2.91 mmol), ZnI_2 (30.9 mg, 0.0970 mmol); **4f** (262.4 mg, 85%), colourless crystals, mp 160–162 °C (hexane) (Found: C, 56.45; H, 9.7; N, 4.45. $C_{15}H_{31}NO_2SSi$ requires C, 56.75; H, 9.85; N, 4.4%); $[\alpha]_D^{20}$ +86.3 (*c* 0.422, $CHCl_3$); ν_{max}/cm^{-1} 3418 (NH) and 1765 (C=O); δ_H(250 MHz) 0.074, 0.082 (total 6 H, each s, $SiMe_2$), 0.89 (9 H, s, SiBu^t), 1.21 (3 H, d, *J* 6.3, MeCH), 1.38 (9 H, s, 3-H), 4.27 (1 H, dq, *J* 3.5, 6.3, CHMe), 5.02 (1 H, d, *J* 2.8, 4-H) and 6.10 (1 H, br s, NH).

4-*tert*-Butylthioazetidin-2-one 4h. 4-Phenylsulfinylazetidin-2-one[9] (235.4 mg, 1.21 mmol), Bu^t$SSiMe_3$ (588.1 mg, 3.63 mmol), ZnI_2 (28.6 mg, 0.121 mmol); **4h** (167.5 mg, 87%), colourless crystals, mp 122–123 °C (hexane–CH_2Cl_2) (Found: C, 52.7; H, 8.0; N, 8.8; S, 20.1. $C_7H_{13}NOS$ requires C, 52.8; H, 8.25; N, 8.8; S, 20.15%); ν_{max}/cm^{-1} 3418 (NH) and 1759 (C=O); δ_H(250 MHz) 1.39 (9 H, s, SBu^t), 2.88 (1 H, ddd, *J* 1.5, 2.8, 15, C*H*HCO), 3.45 (1 H, ddd, *J* 1.8, 5.3, 15, CH*H*CO), 4.90 (1 H, dd, *J* 2.8, 5.3, 4-H) and 6.75 (1 H, br s, NH).

(3*S*,4*R*)-4-*tert*-Butylthio-3-ethylazetidin-2-one 4g. To a stirred solution of (3*R*,4*R*)-4-acetoxy-3-ethylazetidin-2-one (80.2 mg, 0.511 mmol) in isopropyl alcohol (5 ml) was added a solution of 1,1-dimethylethane-1-thiol (59.8 mg, 0.664 mmol) in isopropyl alcohol (1 ml) and a solution of sodium hydroxide (20.4 mg, 0.511 mmol) in water (1 ml) at 0 °C for 30 min. The mixture was stirred at room temperature for 1 h after which it was poured into water and repeatedly extracted with AcOEt. The organic layer was washed with brine, dried, and evaporated. The residue was purified by preparative TLC to give **4g** (90.3 mg, 94%) as colourless crystals, mp 106–109 °C (hexane–CH_2Cl_2); $[\alpha]_D^{26}$ +130 (*c* 0.383, $CHCl_3$); *m*/*z* 187 (M^+) (Found: M^+, 187.1027. $C_9H_{17}NOS$ requires *M*, 187.1028); ν_{max}/cm^{-1} 3416 (NH), 2967, 2942 and 1759 (C=O); δ_H(250 MHz) 1.06 (3 H, t, *J* 7.5, $MeCH_2$), 1.37 (9 H, s, SBu^t), 1.81 (2 H, m, CH_2Me), 3.01 (1 H, ddt, *J* 1.3, 2.5, 7.2, 3-H), 4.60 (1 H, d, *J* 2.5, 4-H) and 6.56 (1 H, br s, NH).

***trans*-4-*tert*-Butylthio-3-phenylthioazetidin-2-one 4i.** To a stirred solution of LDA, which had been prepared from diisopropylamine (89.8 mg, 0.887 mmol) and butyllithium (1.71 mol dm^{-3} solution in hexane; 0.51 ml), in dry THF (4 ml) under nitrogen was added dropwise a solution of 1-*tert*-butyldimethylsilyl-4-*tert*-butylthioazetidin-2-one (200 mg, 0.733 mmol) in dry THF (1 ml), which had prepared by *tert*-butyldimethylsilylation of **4h**, at −78 °C. After 10 min, chlorotrimethylsilane (119 mg, 1.1 mmol) was added dropwise to the solution which was then stirred for 1 h whilst being

allowed to warm to room temperature. The reaction mixture was then poured into saturated aqueous ammonium chloride and extracted with Et_2O. The extracts were washed with water and saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with Et_2O–hexane (5:95) to give the 3-trimethylsilylated intermediate (199 mg, 79%); δ_H(270 MHz) 0.17 (9 H, s, $SiMe_3$), 0.26 (6 H, s, $SiMe_2$), 0.98 (9 H, s, SiBu^t), 1.34 (9 H, s, SBu^t), 2.98 (d, 1 H, *J* 1.8, 3-H) and 4.49 (1 H, d, *J* 1.8, 4-H).

To a stirred solution of LDA, which had been prepared from diisopropylamine (66.8 mg, 0.660 mmol) and butyllithium (1.71 mol dm^{-3} solution in hexane; 0.39 ml), in dry THF (3 ml) under nitrogen was added dropwise a solution of the intermediate (199 mg, 0.627 mmol) in dry THF at −78 °C. The reaction mixture was stirred for 30 min after which then a solution of $PhSO_2SPh$ (204 mg, 0.827 mmol) in THF (1 ml) was added to it at −78 °C. After this, the reaction mixture was stirred and warmed to room temperature over 30 min and then poured into saturated aqueous ammonium chloride and extracted with Et_2O. After being washed with water and saturated brine, the extracts were dried (Na_2SO_4) and evaporated under reduced pressure. The residue was dissolved in THF (3 ml), and to this solution was added a solution of tetrabutylammonium fluoride (245 mg, 0.777 mmol) in THF (2 ml) at 0 °C. After being stirred for 5 min, the reaction mixture was diluted with AcOEt, washed with water and saturated brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by flash chromatography, eluting with hexane–AcOEt (85:15), to give **4i** (83 mg, 53%) as colourless crystals, mp 76–77 °C (CH_2Cl_2–hexane); *m/z* 267 (M^+) (Found: M^+, 267.0751. $C_{13}H_{17}NOS_2$ requires *M*, 267.0751); ν_{max}/cm^{-1} 3413 (NH) and 1774 (C=O); δ_H(270 MHz) 1.36 (9 H, s, SBu^t), 4.19 (1 H, dd, *J* 1.3, 2.5, 3-H), 4.59 (1 H, d, *J* 2.5, 4-H), 6.50 (1 H, br d, NH) and 7.30–7.60 (5 H, m, ArH).

General procedure for the synthesis of α-cyano-*N*,*S*-acetals 5 from 4-alkylthioazetidin-2-ones 4

To a stirred solution of 4-alkylthioazetidin-2-one **4** (0.100 mmol) in dry RCN (5 ml) was added dropwise TMSOTf (0.01 mmol) at 0 °C for 5 min–12 h under nitrogen, after which the mixture was poured into saturated aqueous sodium hydrogen carbonate and repeatedly extracted with CH_2Cl_2. The extract was washed with brine, dried, and evaporated. The residue was purified by preparative TLC to give the corresponding α-cyano-*N*,*S*-acetals **5** in good yield.

(2*R*,3*R*)-1-Acetamido-1-benzylthio-3-*tert*-butyldimethylsiloxy-2-cyanobutane 5a. Compound **4a** (39.1 mg, 0.111 mmol), TMSOTf (7.4 mg, 0.0333 mmol), MeCN (5 ml); **5a** (21.9 mg, 50%), colourless crystals, mp 71–73 °C; *anti*:*syn* = 2.8:1 (Found: C, 61.35; H, 8.25; N, 6.85; S, 8.2. $C_{20}H_{32}N_2O_2SSi$ requires C, 61.2; H, 8.2; N, 7.15; S, 8.15%); $[\alpha]_D^{22}$ +42.3 (*c* 0.456, EtOH); *m/z* 392 (M^+) (Found: M^+, 392.1953. $C_{20}H_{32}N_2O_2SSi$ requires *M*, 392.1953); ν_{max}/cm^{-1} 3420 (NH), 2245 (CN) and 1682 (C=O); δ_H(270 MHz) 0.067, 0.088 (total 1/3.8 × 6 H, each s, $SiMe_2$), 0.095, 0.11 (total 2.8/3.8 × 6 H, each s, $SiMe_2$), 0.87 (1/3.8 × 9 H, s, SiBu^t), 0.92 (2.8/3.8 × 9 H, s, SiBu^t), 1.26 (1/3.8 × 3 H, d, *J* 6.3, MeCH), 1.35 (2.8/3.8 × 3 H, d, *J* 6.3, MeCH), 1.79 (s, 2.8/3.8 × 3 H, MeCON), 1.93 (s, 1/3.8 × 3 H, MeCON), 2.83 (1/3.8 × 1 H, dd, *J* 3.5, 7.4, CHCN), 3.00 (2.8/3.8 × 1 H, dd, *J* 4.2, 8.7, CHCN), 3.76–4.17 (1 H + 2 H, m, CHMe, SCH_2Ph), 5.48 (1/3.8 × 1 H, dd, *J* 3.5, 10, SCHN), 5.51 (2.8/3.8 × 1 H, dd, *J* 4.2, 9.1, SCHN), 5.71 (2.8/3.8 × 1 H, br d, *J* 9.1, NH), 5.97 (1/3.8 × 1 H, br d, *J* 10, NH) and 7.20–7.37 (5 H, m, ArH).

(2*R*,3*R*)-1-Acetamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-(4-methoxyphenylmethylthio)butane 5b. Compound **4b** (50.8 mg, 0.133 mmol), TMSOTf (8.9 mg, 0.0399 mmol), MeCN (5 ml); **5b** (26.3 mg, 47%), a colourless oil; *anti*:*syn* = 2.9:1; $[\alpha]_D^{29}$ +39.3 (*c* 0.486, EtOH); *m/z* 422 (M^+) (Found: M^+, 422.2058. $C_{21}H_{34}N_2O_3SSi$ requires *M*, 422.2058); ν_{max}/cm^{-1} 3418 (NH), 2245 (CN) and 1682 (C=O); δ_H(270 MHz) 0.070, 0.088 (total 1/3.9 × 6 H, each s, $SiMe_2$), 0.094, 0.11 (total 2.9/3.9 × 6 H, each s, $SiMe_2$), 0.87 (1/3.9 × 9 H, s, SiBu^t), 0.92 (2.9/3.9 × 9 H, s, SiBu^t), 1.26 (1/3.9 × 3 H, d, *J* 6.4, MeCH), 1.35 (2.9/3.9 × 3 H, d, *J* 6.4, MeCH), 1.85 (2.9/3.9 × 3 H, s, MeCON), 1.96 (1/3.9 × 3 H, s, MeCON), 2.84 (1/3.9 × 1 H, dd, *J* 3.7, 7.3, CHCN), 3.01 (2.9/3.9 × 1 H, dd, *J* 3.7, 8.3, CHCN), 3.79 (3 H, s, MeO), 3.76, 3.84 (2 H, ABq, *J* 14, CH_2S), 4.02 (1/3.9 × 1 H, dq, *J* 7.3, 6.4, CHMe), 4.11 (2.9/3.9 × 1 H, dq, *J* 8.3, 6.4, CHMe), 5.46 (1/3.9 × 1 H, dd, *J* 3.7, 10, SCHN), 5.48 (2.9/3.9 × 1 H, dd, *J* 3.7, 9.2, SCHN), 5.75 (2.9/3.9 × 1 H, d, *J* 9.2, NH), 5.97 (1/3.9 × 1 H, d, *J* 10, NH) and 6.83–7.21 (4 H, m, ArH). Other signals could not be assigned.

(2*R*,3*R*)-1-Acetamido-1-allylthio-3-*tert*-butyldimethylsiloxy-2-cyanobutane 5c. Compound **4c** (47.9 mg, 0.159 mmol), TMSOTf (10.6 mg, 0.0477 mmol), MeCN (5 ml); **5c** (24.7 mg, 45%), a colourless oil; *anti*:*syn* = 2:1; $[\alpha]_D^{25}$ +36.0 (*c* 0.628, EtOH); *m/z* 342 (M^+) (Found: M^+, 342.1792. $C_{16}H_{30}N_2O_2SSi$ requires *M*, 342.1795); ν_{max}/cm^{-1} 3420 (NH), 2245 (CN) and 1684 (C=O); δ_H(270 MHz) 0.10, 0.11, 0.14 (total 6 H, each s, $SiMe_2$), 0.91 (1/3 × 9 H, s, SiBu^t), 0.92 (2/3 × 9 H, s, SiBu^t), 1.35 (1/3 × 3 H, d, *J* 6.4, MeCH), 1.37 (2/3 × 3 H, d, *J* 5.5, MeCH), 2.02 (2/3 × 3 H, s, MeCON), 2.03 (1/3 × 3 H, s, MeCON), 2.92 (1/3 × 1 H, dd, *J* 3.7, 7.3, CHCN), 3.03 (2/3 × 1 H, dd, *J* 4.6, 8.3, CHCN), 3.20–3.39 (2 H, m, SCH_2), 4.06–4.16 (1 H, m, CH_2Me), 5.03–5.24 (2 H, m, CH_2=CH), 5.44 (2/3 × 1 H, dd, *J* 4.6, 9.2, SCHN), 5.47 (1/3 × 1 H, dd, *J* 3.7, 10, SCHN), 5.87 (2/3 × 1 H, br d, *J* 9.2, NH) and 6.04 (1/3 × 1 H, br d, *J* 10, NH).

(2*R*,3*R*)-1-Acetamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-isopropylthiobutane 5d. Compound **4d** (48.4 mg, 0.160 mmol), TMSOTf (7.1 mg, 0.0320 mmol), MeCN (5 ml); **5d** (34.4 mg, 63%), a colourless oil; *anti*:*syn* = 2:1 (Found: C, 56.1; H, 9.25; N, 7.9; S, 9.1. $C_{16}H_{32}N_2O_2SSi$ requires C, 55.77; H, 9.36; N, 8.13; S, 9.31%); $[\alpha]_D^{26}$ +27.9 (*c* 1.39, EtOH); *m/z* 344 (M^+) (Found: M^+, 344.1953. $C_{16}H_{32}N_2O_2SSi$ requires *M*, 344.1953); ν_{max}/cm^{-1} 3422 (NH), 2245 (CN) and 1682 (C=O); δ_H(270 MHz) 0.096, 0.11, 0.13, 0.14 (total 6 H, each s, $SiMe_2$), 0.90 (1/3 × 9 H, s, SiBu^t), 0.91 (2/3 × 9 H, s, SiBu^t), 1.25–1.31 (6 H, m, Me_2CH), 1.35 (1/3 × 3 H, d, *J* 6.4, MeCH), 1.37 (2/3 × 3 H, d, *J* 6, MeCH), 2.02 (2/3 × 3 H, s, MeCON), 2.03 (1/3 × 3 H, s, MeCON), 2.89 (1/3 × 1 H, dd, *J* 3.7, 7.3, CHCN), 3.01–3.09 (1 H + 2/3 × 1 H, m, $CHMe_2$, CHCN), 4.09 (1/3 × 1 H, dq, *J* 7.3, 6.4, CHMe), 4.12 (2/3 × 1 H, dq, *J* 8.6, 6.4, CHMe), 5.51 (2/3 × 1 H, dd, *J* 3.7, 9.2, SCHN), 5.56 (1/3 × 1 H, dd, *J* 3.7, 10, SCHN), 5.98 (2/3 × 1 H, br d, *J* 9.2, NH) and 6.04 (1/3 × 1 H, br d, *J* 10, NH).

(2*R*,3*R*)-1-Acetamido-3-*tert*-butyldimethylsiloxy-2-cyano-1-cyclohexylthiobutane 5e. Compound **4e** (46.6 mg, 0.136 mmol), TMSOTf (6.0 mg, 0.0272 mmol), MeCN (7 ml); **5e** (35.8 mg, 69%), a colourless oil; *anti*:*syn* = 1.8:1 (Found: C, 59.15; H, 9.35; N, 7.25. $C_{19}H_{36}N_2O_2SSi$ requires C, 59.33; H, 9.43; N, 7.28%); *m/z* 384 (M^+) (Found: M^+, 384.2275. $C_{19}H_{36}N_2O_2SSi$ requires *M*, 384.2267); $[\alpha]_D^{26}$ +19.4 (*c* 1.29, EtOH); ν_{max}/cm^{-1} 3422 (NH), 2245 (CN) and 1682 (C=O); δ_H(270 MHz) 0.095, 0.11, 0.12, 0.13 (total 6 H, each s, $SiMe_2$), 0.90 (1/2.8 × 9 H, s, SiBu^t), 0.91 (1.8/2.8 × 9 H, s, SiBu^t), 1.21–1.99 [10 H, m, $(CH_2)_5$], 1.35 (1/2.8 × 3 H, d, *J* 6.8, MeCH), 1.37 (1.8/2.8 × 3 H, d, *J* 6.8, MeCH), 2.01 (1.8/2.8 × 3 H, s, MeCON), 2.02 (1/2.8 × 3 H, s, MeCON), 2.81 (1 H, m, SCH), 2.89 (1/2.8 × 1 H, dd, *J* 3.3, 7.7, CHCN), 3.02 (1.8/2.8 × 1 H, dd, *J* 4.3, 8.4, CHCN), 4.01–4.18 (1 H, m, CHMe), 5.49 (1.8/2.8 × 1 H, dd, *J* 4.3, 8.9, SCHN), 5.55 (1/2.8 × 1 H, dd, *J* 3.3, 10, SCHN), 6.07 (1.8/2.8 × 1 H, br d, *J* 8.9, NH) and 6.12 (1/2.8 × 1 H, br d, *J* 10, NH).

(2*R*,3*R*)-1-Acetamido-3-*tert*-butyldimethylsiloxy-1-*tert*-butylthio-2-cyanobutane 5f. Compound **4f** (52.2 mg, 0.165 mmol), TMSOTf (11.0 mg, 0.0495 mmol), MeCN (5 ml); **5f** (52.9 mg, 89%), colourless crystals, mp 116–119.5 °C (hexane);

anti:*syn* = 1:1 (Found: C, 56.7; H, 9.4; N, 7.75; S, 8.9. $C_{17}H_{34}N_2O_2SSi$ requires C, 56.95; H, 9.55; N, 7.8; S, 8.95%); *m*/*z* 358 (M^+) (Found: M^+, 358.2104. $C_{17}H_{34}N_2O_2SSi$ requires *M*, 358.2107); $[\alpha]_D^{23}$ +41.7 (*c* 1.30, EtOH); ν_{max}/cm^{-1} 3424 (NH), 2245 (CN) and 1682 (C=O); δ_H(270 MHz) 0.103 (6 H, s, $SiMe_2$), 0.903 (1/2 × 9 H, s, SiBu^t), 0.912 (1/2 × 9 H, s, SiBu^t), 1.37 (total 12 H, m, MeCH, SBu^t), 1.99 (3 H, s, MeCON), 2.92 (1/2 × 1 H, dd, *J* 3.3, 7.9, CHCN), 3.02 (1/2 × 1 H, dd, *J* 5.0, 7.3, CHCN), 4.08 (1 H, m, CHMe), 5.41 (1/2 × 1 H, dd, *J* 5.0, 8.9, SCHN), 5.54 (1/2 × 1 H, dd, *J* 3.3, 9.9, SCHN), 6.03 (1/2 × 1 H, br d, *J* 8.9, NH) and 6.11 (1/2 × 1 H, br d, *J* 9.9, NH).

(2*R*,3*R*)-1-Butanamido-3-*tert*-butyldimethylsiloxy-1-*tert*-butylthio-2-cyanobutane 5g. Compound **4f** (44.0 mg, 0.139 mmol), TMSOTf (6.2 mg, 0.0278 mmol), PrCN (2 ml); **5g** (29.3 mg, 57%); *anti*:*syn* = 1:1 (Found: C, 59.1; H, 9.75; N, 7.1; S, 8.15. $C_{19}H_{38}N_2O_2SSi$ requires C, 59.0; H, 9.9; N, 7.25; S, 8.3%); $[\alpha]_D^{23}$ +42.5 (*c* 0.900, EtOH); ν_{max}/cm^{-1} 3424 (NH), 2245 (CN) and 1676 (C=O); δ_H(270 MHz) 0.099, 0.154 (total 6 H, each s, $SiMe_2$), 0.90 (1/2 × 9 H, s, SiBu^t), 0.91 (1/2 × 9 H, s, SiBu^t), 0.95 (3 H, t, *J* 7.3, $MeCH_2$), 1.35 (1/2 × 3 H, d, *J* 5.9, CHMe), 1.37 (9 H, s, SBu^t), 1.39 (1/2 × 3 H, d, *J* 6.3, MeCH), 1.66 (2 H, sextet, *J* 7.3, CH_2Me), 2.15 (1/2 × 2 H, t, *J* 7.3, CH_2CON), 2.16 (1/2 × 2 H, t, *J* 7.3, CH_2CON), 2.92 (1/2 × 1 H, dd, *J* 3.5, 7.8, CHCN), 3.02 (1/2 × 1 H, dd, *J* 5.3, 6.9, CHCN), 3.99–4.15 (2 H, m, CHMe), 5.40 (1/2 × 1 H, dd, *J* 5.3, 8.6, SCHN), 5.55 (1/2 × 1 H, dd, *J* 3.5, 9.9, SCHN), 5.90 (1/2 × 1 H, br d, *J* 8.6, NH) and 6.04 (1/2 × 1 H, br d, *J* 9.9, NH); *m*/*z* 329 (M^+ − Bu^t) (Found: M^+ − Bu^t, 329.1733. $C_{15}H_{29}N_2O_2SSi$ requires *M*, 329.1720).

(2*R*,3*R*)-1-Benzamido-3-*tert*-butyldimethylsiloxy-1-*tert*-butylthio-2-cyanobutane 5h. Compound **4f** (29.3 mg, 0.0924 mmol), TMSOTf (6.2 mg, 0.0277 mmol), PhCN (4 ml); **5h** (17.9 mg, 46%), a colourless oil; *anti*:*syn* = 1.3:1 (Found: C, 62.6; H, 8.65; N, 6.55. $C_{22}H_{36}N_2O_2SSi$ requires C, 62.8; H, 8.65; N, 6.65%); *m*/*z* 420 (M^+) (Found: M^+, 420.2264. $C_{22}H_{36}N_2O_2SSi$ requires *M*, 420.2264); $[\alpha]_D^{26}$ +42.6 (*c* 0.768, EtOH); ν_{max}/cm^{-1} 3431 (NH), 2245 (CN) and 1667 (C=O); δ_H(500 MHz) 0.11, 0.13 (total 1/2.3 × 6 H, each s, $SiMe_2$), 0.14, 0.19 (total 1.3/2.3 × 6 H, each s, $SiMe_2$), 0.90 (1.3/2.3 × 9 H, s, SiBu^t), 0.95 (1/2.3 × 9 H, s, SiBu^t), 1.39 (1.3/2.3 × 3 H, d, *J* 6.4, MeCH), 1.40 (1/2.3 × 9 H, s, SBu^t), 1.41 (1.3/2.3 × 9 H, s, SBu^t), 1.45 (1/2.3 × 3 H, d, *J* 6.4, MeCH), 3.05 (1.3/2.3 × 1 H, dd, *J* 3.7, 7.3, CHCN), 3.18 (1/2.3 × 1 H, dd, *J* 5.5, 7.3, CHCN), 4.13 (1.3/2.3 × 1 H, quint, *J* 6.4, CHMe), 4.20 (1/2.3 × 1 H, quint, *J* 6.4, CHMe), 5.65 (1/2.3 × 1 H, dd, *J* 5.5, 8.3, SCHN), 5.80 (1.3/2.3 × 1 H, dd, *J* 3.7, 10, SCHN), 6.50 (1/2.3 × 1 H, d, *J* 8.3, NH), 6.64 (1.3/2.3 × 1 H, d, *J* 10, NH) and 7.44–7.78 (5 H, m, ArH).

(2*S*)-1-Acetamido-1-*tert*-butylthio-2-cyanobutane 5i. Compound **4g** (20.3 mg, 0.109 mmol), TMSOTf (4.8 mg, 0.0218 mmol), MeCN (1 ml); **5i** (22.6 mg, 91%), a colourless oil; *anti*:*syn* = 1.2:1 (or 1:1.2); *m*/*z* 228 (M^+) (Found: M^+, 228.1292. $C_{11}H_{20}N_2OS$ requires *M*, 228.1294); $[\alpha]_D^{23}$ +7.6 (*c* 0.644, EtOH); ν_{max}/cm^{-1} 3428 (NH), 2244 (CN) and 1678 (C=O); δ_H(500 MHz) 1.11 (3 H, t, *J* 7.3, $MeCH_2$), 1.36 (1.2/2.2 × 9 H, s, SBu^t), 1.37 (1/2.2 × 9 H, s, SBu^t), 1.62–1.92 (2 H, m, CH_2Me), 2.01 (1.2/2.2 × 3 H, s, MeCON), 2.02 (1/2.2 × 3 H, s, MeCON), 2.87 (1/2.2 × 1 H, ddd, *J* 3.8, 5.8, 9.6, CHCN), 2.98 (1.2/2.2 × 1 H, ddd, *J* 4.6, 5.5, 9.2, CHCN), 5.01 (1.2/2.2 × 1 H, dd, *J* 4.6, 8.2, SCHN), 5.30 (1/2.2 × 1 H, dd, *J* 3.8, 9.2, SCHN), 5.96 (1/2.2 × 1 H, br d, *J* 9.2, NH) and 6.10 (1.2/2.2 × 1 H, br d, *J* 8.2, NH).

(2*S*)-1-Butanamido-1-*tert*-butylthio-2-cyanobutane 5j. Compound **4g** (21.3 mg, 0.144 mmol), TMSOTf (5.1 mg, 0.0228 mmol), PrCN (3 ml); **5j** (22.5 mg, 77%), colourless crystals, mp 65–67 °C; *anti*:*syn* = 1.4:1 (or 1:1.4) (Found: C, 60.85; H, 9.3; N, 10.8; S, 12.3. $C_{13}H_{24}N_2OS$ requires C, 60.9; H, 9.45; N, 10.95; S, 12.5%); $[\alpha]_D^{23}$ +12.3 (*c* 0.908, EtOH); ν_{max}/cm^{-1} 3428 (NH), 2244 (CN) and 1672 (C=O); δ_H(270 MHz) 0.96 (3 H, t, *J* 7.4, $MeCH_2CH_2$), 1.11 (3 H, t, *J* 7.3, $MeCH_2CH$), 1.36 (1.4/2.4 × 9 H, s, SBu^t), 1.37 (1/2.4 × 9 H, s, SBu^t), 1.60–1.95 (4 H, m, CH_2Me × 2), 2.18 (1.4/2.4 × 2 H, t, *J* 7.6, CH_2CON), 2.19 (1/2.4 × 2 H, t, *J* 7.3, CH_2CON), 2.89 (1/2.4 × 1 H, ddd, *J* 4.0, 5.3, 9.6, CHCN), 3.00 (1.4/2.4 × 1 H, ddd, *J* 4.6, 5.3, 9.6, CHCN), 5.02 (1.4/2.4 × 1 H, dd, *J* 4.6, 7.9, SCHN), 5.32 (1/2.4 × 1 H, dd, *J* 4.0, 9.2, SCHN), 5.93 (1/2.4 × 1 H, br d, *J* 9.2, NH) and 6.08 (1.4/2.4 × 1 H, br d, *J* 7.9, NH).

(2*R*)-1-Benzamido-1-*tert*-butylthio-2-cyanobutane 5k. Compound **4g** (19.1 mg, 0.102 mmol), TMSOTf (6.8 mg, 0.0306 mmol), PhCN (0.5 ml); **5k** (15.8 mg, 53%), colourless crystals, mp 90–92 °C; *anti*:*syn* = 1.1:1 (or 1:1.1) (Found: C, 66.15; H, 7.7; N, 9.5; S, 10.75. $C_{16}H_{22}N_2OS$ requires C, 66.15; H, 7.65; N, 9.65; S, 11.05%); *m*/*z* 290 (M^+) (Found: M^+, 290.1454. $C_{16}H_{22}N_2OS$ requires *M*, 290.1453); $[\alpha]_D^{23}$ +14.5 (*c* 0.497, EtOH); ν_{max}/cm^{-1} 3434 (NH), 2244 (CN) and 1662 (C=O); δ_H(270 MHz) 1.13 (1/2.1 × 3 H, t, *J* 7.3, $MeCH_2$), 1.15 (1.1/2.1 × 3 H, t, *J* 7.3, $MeCH_2$), 1.39 (9 H, s, SBu^t), 1.63–1.99 (2 H, m, CH_2Me), 3.02 (1/2.1 × 1 H, ddd, *J* 4.0, 5.6, 9.9, CHCN), 3.30 (1.1/2.1 × 1 H, ddd, *J* 4.6, 5.6, 9.9, CHCN), 5.24 (1.1/2.1 × 1 H, dd, *J* 4.6, 7.6, SCHN), 5.55 (1/2.1 × 1 H, dd, *J* 4.0, 8.9, SCHN), 6.50 (1/2.1 × 1 H, br d, *J* 8.9, NH), 6.63 (1.1/2.1 × 1 H, br d, *J* 7.6, NH) and 7.44–7.81 (5 H, m, ArH).

3-Acetamido-3-*tert*-butylthiopropionitrile 5l. Compound **4h** (37.2 mg, 0.234 mmol), TMSOTf (10.4 mg, 0.0468 mmol), MeCN (15 ml); **5l** (30.5 mg, 65%), a colourless oil (Found: C, 53.8; H, 7.85; N, 13.8. $C_9H_{16}N_2OS$ requires C, 53.95; H, 8.05; N, 13.0%); *m*/*z* 200 (M^+) (Found: M^+, 200.1002. $C_9H_{16}N_2OS$ requires *M*, 200.0984); ν_{max}/cm^{-1} 3432 (NH), 2253 (CN) and 1676 (C=O); δ_H(270 MHz) 1.38 (9 H, s, SBu^t), 2.02 (3 H, s, MeCON), 2.79 (1 H, dd, *J* 4.6, 17, C*H*HCN), 2.93 (1 H, dd, *J* 6.3, 17, CH*H*CN), 5.27 (1 H, ddd, *J* 4.6, 6.3, 11, SCHN) and 6.13 (1 H, br s, NH).

3-Acetamido-3-*tert*-butylthio-2-phenylthiopropionitrile 5m. Compound **4i** (22.8 mg, 0.0854 mmol), TMSOTf (3.8 mg, 0.0171 mmol), MeCN (5 ml); **5m** (13.9 mg, 53%), a colourless oil; *anti*:*syn* = 1.1:1 (or 1:1.1); *m*/*z* 251 (M^+ − Bu^t) (Found: M^+ − Bu^t, 251.0321. $C_{11}H_{11}N_2OS_2$ requires *M*, 251.0313); ν_{max}/cm^{-1} 3428 (NH), 2240 (CN) and 1680 (C=O); δ_H(270 MHz) 1.36 (1/2.1 × 9 H, s, SBu^t), 1.40 (1.1/2.1 × 9 H, s, SBu^t), 1.98 (1/2.1 × 3 H, s, MeCON), 2.00 (1.1/2.1 × 3 H, s, MeCON), 4.21 (1/2.1 × 1 H, d, *J* 3.6, CHCN), 4.25 (1.1/2.1 × 1 H, d, *J* 5.3, CHCN), 5.31 (1.1/2.1 × 1 H, dd, *J* 5.3, 7.8, SCHN), 5.48 (1/2.1 × 1 H, dd, *J* 3.6, 8.9, SCHN), 6.03–6.68 (1 H, br m, NH) and 7.36–7.64 (5 H, m, ArH).

General procedure for the synthesis of the β-amido-α-azido sulfide 6 from 4-alkylthioazetidin-2-ones 4 with azidotrimethylsilane

To a stirred solution of 4-alkylthioazetidin-2-one **4** (0.150 mmol) and azidotrimethylsilane (0.750 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise BF_3·OEt_2 (0.150 mmol) at 0 °C. Stirring was continued for 0.5–3 d at room temperature under nitrogen after which the mixture was poured into saturated aqueous sodium hydrogen carbonate and repeatedly extracted with AcOEt. The extract was washed with brine, dried, and evaporated. The residue was purified by preparative TLC to give the corresponding β-amido-α-azido sulfide **6** in good yield.

(2*R*,3*R*)-3-*tert*-Butyldimethylsiloxy-2-[azido(isopropylthio)-methyl]butanamide 6a. Compound **4d** (43.0 mg, 0.142 mmol), $TMSN_3$ (81.7 mg, 0.710 mmol), BF_3·OEt_2 (40.3 mg, 0.284 mmol); **6a** (39.5 mg, 80%), colourless crystals, mp 140–143 °C (hexane); *anti*:*syn* = 1:1 (Found: C, 48.3; H, 8.8; N, 15.85; S, 9.0. $C_{14}H_{30}N_4O_2SSi$ requires C, 48.5; H, 8.75; N, 16.15; S, 8.25%); $[\alpha]_D^{20}$ +30.0 (*c* 1.68, $CHCl_3$); ν_{max}/cm^{-1} 3497 (NH_2), 3403 (NH_2), 2110 (CN) and 1688 (C=O); δ_H(270 MHz) 0.10, 0.11 (total 6 H, each s, $SiMe_2$), 0.89 (9 H, s, SiBu^t), 1.18 (1/2 × 3 H, d, *J* 6.8, MeCHOSi), 1.22 (1/2 × 3 H, d, *J* 6.0, MeCHOSi), 1.32–1.37 (6 H, m, Me_2CH), 2.54 (1/2 × 1 H, t, *J* 6.8,

CHCON), 2.68 (1/2 × 1 H, dd, *J* 4.3, 8.6, CHCON), 3.18 (1 H, sextet, *J* 6.8, $CHMe_2$), 4.19–4.29 (1 H, m, CHOSi), 4.77 (1/2 × 1 H, d, *J* 8.6, CHN_3), 4.84 (1/2 × 1 H, d, *J* 6.8, CHN_3) and 5.67, 5.78, 6.00, 6.04 (total 2 H, each br s, NH_2); *m/z* 289 ($M^+ - Bu^t$) (Found: M − Bu', 289.1162. $C_{10}H_{21}N_4O_2SSi$ requires *M*, 289.1154).

(2*R*,3*R*)-3-*tert*-Butyldimethylsiloxy-2-[azido(cyclohexylthio)methyl]butanamide 6b. Compound **4e** (43.2 mg, 0.126 mmol), $TMSN_3$ (72.5 mg, 0.630 mmol), $BF_3{\cdot}OEt_2$ (35.8 mg, 0.252 mmol); **6b** (39.2 mg, 81%), a colourless oil; *anti*:*syn* = 1.2:1 (or 1:1.2); $[\alpha]_D^{21}$ +30.9 (*c* 1.45, $CHCl_3$); ν_{max}/cm^{-1} 3497 (NH_2), 3405 (NH_2), 2110 (CN) and 1688 (C=O); δ_H(270 MHz) 0.094, 0.11 (total 6 H, each s, $SiMe_2$), 0.88 (9 H, s, SiBu'), 1.16 (1.2/2.2 × 3 H, d, *J* 6.3, MeCH), 1.20 (1/2.2 × 3 H, d, *J* 6.3, MeCH), 1.25–2.15 [10 H, m, $(CH_2)_5$], 2.53 (1.2/2.2 × 1 H, t, *J* 6.6, CHCON), 2.67 (1/2.2 × 1 H, dd, *J* 4.3, 8.6, CHCON), 2.82–2.94 (1 H, m, SCH), 4.15–4.30 (1 H, m, CHMe), 4.78 (1/2.2 × 1 H, d, *J* 8.6, CHN_3), 4.85 (1.2/2.2 × 1 H, d, *J* 6.6, CHN_3) and 5.72, 5.83, 5.98, 6.04 (each br s, total 2 H, NH_2); *m/z* 329 ($M^+ - Bu^t$) (Found: M − Bu', 329.1457. $C_{13}H_{25}N_4O_2SSi$ requires *M*, 329.1468).

(2*R*,3*R*)-3-*tert*-Butyldimethylsiloxy-2-[azido(*tert*-butylthio)methyl]butanamide 6c. Compound **4f** (42.3 mg, 0.133 mmol), $TMSN_3$ (76.5 mg, 0.665 mmol), $BF_3{\cdot}OEt_2$ (37.8 mg, 0.266 mmol); **6c** (36.8 mg, 77%), colourless crystals, mp 152–154 °C (hexane); *anti*:*syn* = 1.3:1 (or 1:1.3); *m/z* 360 (M^+) (Found: M^+, 360.2021. $C_{15}H_{32}N_4O_2SSi$ requires *M*, 360.2015); $[\alpha]_D^{19}$ +14.2 (*c* 1.67, $CHCl_3$); ν_{max}/cm^{-1} 3497 (NH_2), 3403 (NH_2), 2112 (CN) and 1688 (C=O); δ_H(270 MHz) 0.10, 0.11, 0.13 (total 6 H, each s, $SiMe_2$), 0.89 (1/2.3 × 9 H, s, SiBu'), 0.90 (1.3/2.3 × 9 H, s, SiBu'), 1.18 (1.3/2.3 × 3 H, d, *J* 5.9, MeCH), 1.23 (1/2.3 × 3 H, d, *J* 6.3, MeCH), 1.39 (1.3/2.3 × 9 H, s, SBu'), 1.40 (1/2.3 × 9 H, s, SBu'), 2.48 (1.3/2.3 × 1 H, dd, *J* 5.3, 7.6, CHCON), 2.68 (1/2.3 × 1 H, dd, *J* 4.0, 8.9, CHCON), 4.19 (1.3/2.3 × 1 H, dq, *J* 7.6, 5.9, CHMe), 4.26 (1/2.3 × 1 H, dq, *J* 4.0, 6.3, CHMe), 4.71 (1/2.3 × 1 H, d, *J* 8.9, CHN_3), 4.86 (1.3/2.3 × 1 H, d, *J* 5.3, CHN_3) and 5.68, 5.85, 5.96, 6.00 (total 2 H, each br s, NH_2).

2-[Azido(*tert*-butylthio)methyl]butanamide 6d. Compound (±)-**4g** (33.1 mg, 0.177 mmol), $TMSN_3$ (101.8 mg, 0.885 mmol), $BF_3{\cdot}OEt_2$ (25.1 mg, 0.177 mmol); **6d** (36.6 mg, 91%), colourless crystals, mp 82–83 °C (Et_2O–hexane); *anti*:*syn* = 1.3:1 (or 1:1.3) (Found: C, 46.9; H, 7.75; N, 24.35; S, 13.8. $C_9H_{18}N_4OS$ requires C, 46.95; H, 7.9; N, 24.3; S, 13.9%); *m/z* 230 (M^+) (Found: M^+, 230.1224. $C_9H_{18}N_4OS$ requires *M*, 230.1201); ν_{max}/cm^{-1} 3524 (NH_2), 3407 (NH_2), 2112 (N_3) and 1686 (C=O); δ_H(270 MHz) 0.96 (1.3/2.3 × 3 H, t, *J* 7.3, $MeCH_2$), 0.99 (1/2.3 × 3 H, t, *J* 7.3, $MeCH_2$), 1.39 (1/2.3 × 9 H, s, SBu'), 1.41 (1.3/2.3 × 9 H, s, SBu'), 1.63–1.95 (2 H, m, CH_2Me), 2.27–2.43 (1 H, m, CHCON), 4.45 (1/2.3 × 1 H, d, *J* 8.9, CHN_3), 4.52 (1.3/2.3 × 1 H, d, *J* 9.2, CHN_3) and 5.80, 5.91, 5.96, 6.10 (total 2 H, each br s, NH_2).

3-Azido-3-*tert*-butylthiopropanamide 6e. Compound **4h** (25.4 mg, 0.160 mmol), $TMSN_3$ (101.8 mg, 0.885 mmol), $BF_3{\cdot}OEt_2$ (25.1 mg, 0.177 mmol); **6c** (31.3 mg, 97%), a colourless oil; *m/z* 202 (M^+) (Found: M^+, 202.0915. $C_7H_{14}N_4OS$ requires *M*, 202.0888); ν_{max}/cm^{-1} 3526 (NH_2), 3411 (NH_2), 2110 (N_3) and 1690 (C=O); δ_H(500 MHz) 1.42 (9 H, s, SBu'), 2.64 (1 H, dd, *J* 6.4, 15, C*H*HCO), 2.70 (1 H, dd, *J* 7.3, 15, CH*H*CO), 4.83 (1 H, dd, *J* 6.4, 7.3, CHN_3) and 5.50, 5.62 (total 2 H, each br s, NH_2).

Crystal structure determination of *anti*-3a

Single crystals of compound *anti*-**3a** suitable for X-ray diffraction study were obtained from hexane. All measurements were carried out with a Mac Science MXC 18 four-circle automated diffractometer with graphite monochromated Cu-Kα radiation and an 18 kW rotating anode generator. Cell constants and an orientation matrix for data collection were obtained from a least-squares refinement using 20 reflections in the range $55 < 2\theta < 60$. The data were collected at 288 K using the ω–2θ scan technique to an above maximum 2θ value of 128°. Three standard reflections were measured every 100 reflections and no crystal decay was detected. All intensities were corrected for Lorentz and polarization effects. An analytical function for absorption correction was applied to the data.[11] The structure was solved by direct methods using SHELXS86[12] and refined with a full-matrix least squares refinement (number of parameters: 274). All hydrogen atoms were located by difference Fourier synthesis. The non-hydrogen atoms were refined anisotropically, while only coordinates of hydrogen atoms were refined. All calculations were performed using the CRYSTAN-G crystallographic software package from Mac Science.

Crystal data of *anti*-3a. $C_{14}H_{28}N_2O_3Si$, *M* 300.00, crystal size 0.60 × 0.50 × 0.35 mm^3, orthorhombic, space group $P2_12_12_1$, $a = 8.912(2)$, $b = 27.290(5)$, $c = 7.724(1)$ Å, $V = 1878.5(7)$ $Å^3$, $Z = 4$, $D_c = 1.06$ g cm^{-3}, λ(Cu-Kα) = 1.541 78 Å, $\mu = 10.87$ cm^{-1}, $R = 0.046$ for 1812 independent reflections.

Atomic coordinates, thermal parameters and bond lengths and angles have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Instructions for Authors, *J. Chem. Soc., Perkin Trans. 1*, 1996, Issue 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 207/43.

References

1 Y. Kita, N. Shibata, N. Yoshida, N. Kawano and K. Matsumoto, *J. Org. Chem.*, 1994, **59**, 938.
2 Y. Kita, N. Shibata, N. Yoshida and T. Tohjo, *Chem. Pharm. Bull.*, 1992, **40**, 1044.
3 F. Effenberger, P. Fischer, G. Prossel and G. Kiefer, *Chem. Ber.*, 1971, **104**, 1987.
4 (*a*) K. Hirai, H. Matsuda and Y. Kishida, *Chem. Pharm. Bull.*, 1973, **21**, 1305; (*b*) M. M. Campbell, N. I. Carruthers and S. J. Mickel, *Tetrahedron*, 1982, **38**, 2513.
5 (*a*) D. F. Sullivan, D. I. C. Scopes, A. F. Kluge and J. A. Edwards, *J. Org. Chem.*, 1976, **41**, 1112; (*b*) M. M. Campbell and G. Johnson, *J. Chem. Soc., Chem. Commun.*, 1974, 974; (*c*) M. M. Campbell and G. Johnson, *J. Chem. Soc., Perkin Trans. 1*, 1975, 1212; (*d*) S. Wolfe, S.-L. Lee, J.-B. Ducep, G. Kannengiesser and W. S. Lee, *Can. J. Chem.*, 1975, **53**, 497.
6 G. C. Barrett, *Comprehensive Organic Chemistry*, D. Barton and W. D. Ollis, Eds.; Pergamon Press, Oxford, 1979, vol. 3, pp. 55–103.
7 (*a*) C. Z. Ding and R. B. Silverman, *Synth. Commun.*, 1993, **23**, 1467; (*b*) G. Apitz and W. Steglich, *Tetrahedron Lett.*, 1991, **32**, 3163; (*c*) A. R. Katritzky, M. Szajda and S. Bayyuk, *Synthesis*, 1986, 804; (*d*) H. Sakai, K. Ito and M. Sekiya, *Chem. Pharm. Bull.*, 1973, **21**, 2257.
8 (*a*) A. F. Janzen, G. N. Lypka and R. E. Wasylishen, *J. Heterocycl. Chem.*, 1979, **16**, 415; (*b*) S. Rakhit, M. Georges and J. F. Bagli, *Can. J. Chem.*, 1979, **57**, 1153; (*c*) U. Lerch and J. G. Moffatt, *J. Org. Chem.*, 1971, **36**, 3391.
9 (*a*) E. M. Suh and Y. Kishi, *J. Am. Chem. Soc.*, 1994, **116**, 11 205; (*b*) J. W. Wilt and M. D. Tufano, *J. Org. Chem.*, 1985, **50**, 2601; (*c*) J. Garcia, F. Urpi and J. Vilarrasa, *Tetrahedron Lett.*, 1984, **25**, 4841.
10 (*a*) Y. Kita, N. Shibata, N. Yoshida and T. Tohjo, *Tetrahedron Lett.*, 1991, **32**, 2375; (*b*) Y. Kita, N. Shibata, N. Yoshida and T. Tohjo, *Chem. Pharm. Bull.*, 1992, **40**, 1733.
11 C. Katayama, *Acta Crystallogr., Sect. A*, 1986, 19.
12 G. M. Sheldrick, SHELXS 86, Program for Crystal Structure Determination, University of Göttingen, Germany, 1986.

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