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C-3 β-lactam carbocation equivalents: versatile synthons for C-3 substituted β-lactams

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Abstract—An efficient and operationally simple strategy for the synthesis of differently C-3 monosubstituted (**9**) and disubstituted (**10**) monocyclic β-lactams is described. This involves reaction of β-lactam carbocation equivalents (**8**) with an active aromatic, aliphatic and heterocyclic substrates in the presence of a Lewis acid.

1. Introduction

The unique structural features and chemotherapeutic properties of β-lactam antibiotics continue to attract the attention of the synthetic organic chemists as they present a variety of synthetic challenges. β-Lactams are well-acknowledged structural elements of the widely used penicillins, cephalosporins, thienamycin and other monocyclic β-lactam antibiotics[1] such as monobactams. In recent years, various natural and unnatural monocyclic β-lactams have been shown to exhibit high biological activity, suggesting that a suitably substituted monocyclic 2-azetidinone ring is the minimum requirement for biological activity. The discoveries of new monocyclic biologically active β-lactams such as **1** and **2** as cholesterol acyl transferase inhibitors,[2,3] thrombin inhibitor[4] and human cytomegalovirus protease inhibitor,[5] have renewed the interest in the synthesis of these differently substituted 3-alkyl/aryl azetidin-2-ones (Fig. 1).

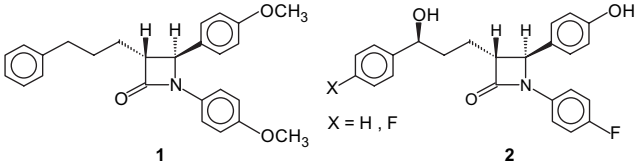

Figure 1. Cholesterol absorption inhibitors.

Cholesterol acyl transferase[6] is considered mainly responsible for atherosclerotic coronary heart disease and recently, C-3 aryl substituted monocyclic β-lactams has been shown to be potential inhibitors of this enzyme. Therefore, the development of convenient approaches for the synthesis of monocyclic azetidin-2-ones, bearing a varied array of appendages at C-3 and C-4, continues to be an area of active research. Thus, new and practical synthetic routes to α-aryl/substituted aryl-β-lactams are of particular importance. These β-lactams are not so easily accessible via the classical Staudinger reaction, the ketene–imine cycloaddition. However, synthesis of these C-3 substituted β-lactams is brought about via transformation at C-3 involving either cationic or anionic β-lactams **3** and **4**, respectively (Fig. 2). The potential of anionic β-lactam **4** has been explored by many groups[7] for the preparation of different β-lactam synthons. However, the chemistry involving cationic β-lactam **3** has not been fully explored.

In continuation to our earlier studies published in a preliminary communication,[8] we wish to report here the details of a general and operationally simple strategy for the preparation of a variety of C-3 substituted β-lactams. It has been observed that *trans*-3-chloro-3-phenylthio-β-lactams provide an easy access to 3,3-disubstituted azetidin-2-ones. Whereas, *trans*-3-chloro-3-benzylthio-β-lactams provide mainly C-3 monosubstituted β-lactams. The strategy involves the reaction of β-lactam carbocation equivalents of type **8** with active

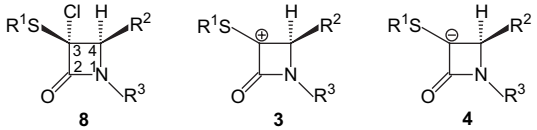

Figure 2. Cationic and anionic β-lactam equivalents.

Keywords: β-Lactam; Lewis acid; Nucleophiles; Disubstituted β-lactams; Monosubstituted β-lactams.
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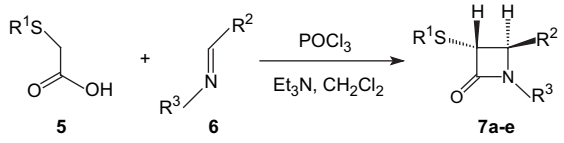
an aromatic, aliphatic and heterocyclic nucleophiles in the presence of a Lewis acid such as $TiCl_4$ or $SnCl_4$ to afford various C-3 monosubstituted and disubstituted β-lactams in excellent yields.

2. Results and discussion

We have successfully employed *trans*-3-chloro-3-phenyl/benzylthio-β-lactams (**8a–e**) as the most appropriate β-lactam carbocation equivalents for the synthesis of C-3 monosubstituted as well as disubstituted β-lactams, which may be prepared by reacting an acid chloride or an acid derivative with an imine in the presence of a base,[9] followed by stereospecific chlorination at C-3. These β-lactams **8a–e** are capable of functioning as a C-3 β-lactam carbocation in the presence of a Lewis acid[10] and have been observed to react with variety of active aromatic, aliphatic and heterocyclic substrates (nucleophiles).

The starting substrates, **7a–e** required for this study, were prepared from appropriate Schiff's bases **6** and 2-phenyl/benzylthioethanoic acid (**5**) in presence of triethylamine as the base and phosphorus oxychloride ($POCl_3$) as the condensing reagent according to reported procedure,[11] in good yields (Scheme 1, Table 1). The structures of these azetidin-2-ones **7a–e** were established on the basis of their spectral data such as IR, ^1H and ^{13}C NMR. All these cycloaddition reactions were found to be stereoselective and only *trans*-β-lactam (J=2.1–2.3 Hz, C3-H and C4-H) formation was observed.



Scheme 1. Synthesis of azetidin-2-ones **7a–e**.

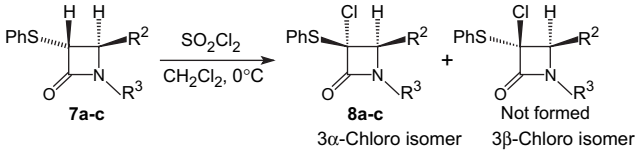
Table 1. Azetidin-2-ones **7a–e**

Entry	7	R^1	R^2	R^3	Yield[a] (%)
1	**a**	C_6H_5	C_6H_5	C_6H_4(OMe)(4)	55
2	**b**	C_6H_5	C_6H_4(OMe)(4)	C_6H_4(OMe)(4)	53
3	**c**	C_6H_5	C_6H_5	$CH_2C_6H_5$	52
4	**d**	$CH_2C_6H_5$	C_6H_5	C_6H_4(OMe)(4)	43
5	**e**	$CH_2C_6H_5$	C_6H_4(OMe)(4)	C_6H_4(OMe)(4)	44

[a] Isolated yield.

The β-lactam carbocation equivalents **8a–c**, were prepared from their corresponding azetidin-2-ones **7a–c** by α-chlorination with sulfuryl chloride (SO_2Cl_2)[12] in dichloromethane. In this reaction, although the formation of two stereoisomers (α- and β-chloro) is possible, only α-chloro isomer, i.e., *trans*-3-chloro-3-phenylthioazetidin-2-one (**8a–c**) was obtained in quantitative yields, which was evident from the ^1H NMR spectral analysis. In addition, the stereochemistry of **8a** at C-3 was established from single crystal X-ray crystallographic studies (Scheme 2).[13]

Chlorination using sulfuryl chloride (SO_2Cl_2) did not afford clean product. However, **7d–e** were transformed to corresponding **8d–e** in nearly quantitative yields using *N*-chlorosuccinimide (NCS) with catalytic amount of AIBN in carbon tetrachloride. No chlorination at the benzylic carbon was observed by ^1H NMR spectroscopy. However, the stereochemistry in this case was tentatively assigned to it keeping in view the stereochemistry of **8a** (Scheme 3, Table 2).



Scheme 2. Synthesis of *trans*-3-chloroazetidin-2-ones **8a–c**.

Scheme 3. Synthesis of *trans*-3-chloroazetidin-2-ones **8d–e**.

Table 2. *trans*-3-Chloroazetidin-2-ones **8a–e**

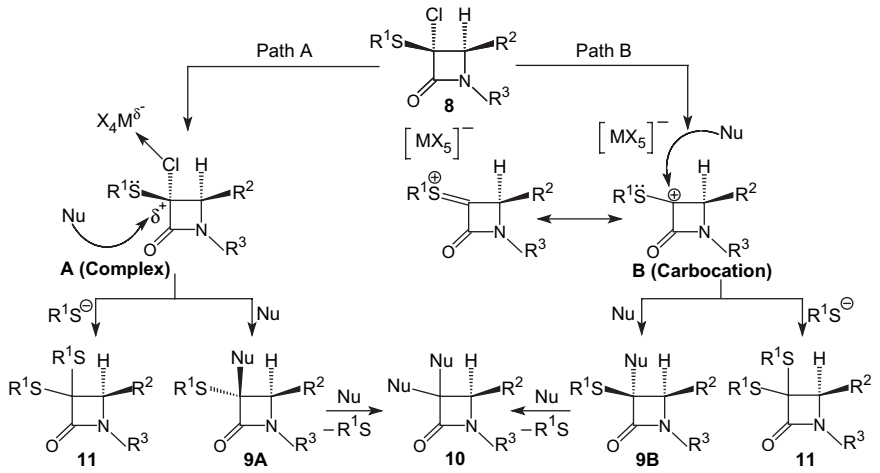
Entry	8	R^1	R^2	R^3	Yield[a] (%)
1	**a**	C_6H_5	C_6H_5	C_6H_4(OMe)(4)	95
2	**b**	C_6H_5	C_6H_4(OMe)(4)	C_6H_4(OMe)(4)	94
3	**c**	C_6H_5	C_6H_5	$CH_2C_6H_5$	94
4	**d**	$CH_2C_6H_5$	C_6H_5	C_6H_4(OMe)(4)	63
5	**e**	$CH_2C_6H_5$	C_6H_4(OMe)(4)	C_6H_4(OMe)(4)	44

[a] Isolated yield.

The juxtaposition of chlorine and sulfur atoms attached to the same carbon produce functionality with several attractive features in chemical synthesis. The potential of these α-chlorosulfides as reactive intermediates has been explored recently. These are useful and reactive electrophiles for many of sulfur-mediated alkylation reactions of aromatic substrates,[14] alkenes[15] and trimethylsilylenol ethers[16] etc.

Initial studies were carried out by reacting **8a** with anisole as the aromatic substrate in the presence of $SnCl_4$ at −78 °C. Instead of leading to the formation of the expected monosubstituted product of type **9** (Scheme 4), a mixture of two compounds was formed. These products, after chromatographic purification, were identified as **10a** and **11a** on the basis of their spectroscopic data and X-ray crystallographic analysis.[17,18] (Fig. 3). The reaction proceeds well with one equivalent of $SnCl_4$ in CH_2Cl_2 at −78 °C. However, $TiCl_4$ was not the Lewis acid of choice for this reaction since it produced invariably a mixture of nonseparable products.

The reaction was found to be general for several active aromatic substrates and the results are summarized in Table 3. Most of the activated aromatic substrates on reaction with **8a–c** produced mainly 3,3-disubstituted azetidin-2-ones of type **10**, along with the varying amount of 3,3-bis(alkylthio)azetidin-2-ones of the type **11**. However, in case of β-lactams **8a** and **8c** (Table 3, entries 3, 8 and 9) monosubstituted products of the type **9** were also formed along with disubstituted products (Scheme 4). Benzene and toluene failed to give the anticipated products.



Scheme 4. Synthesis of C-3 substituted β-lactams.

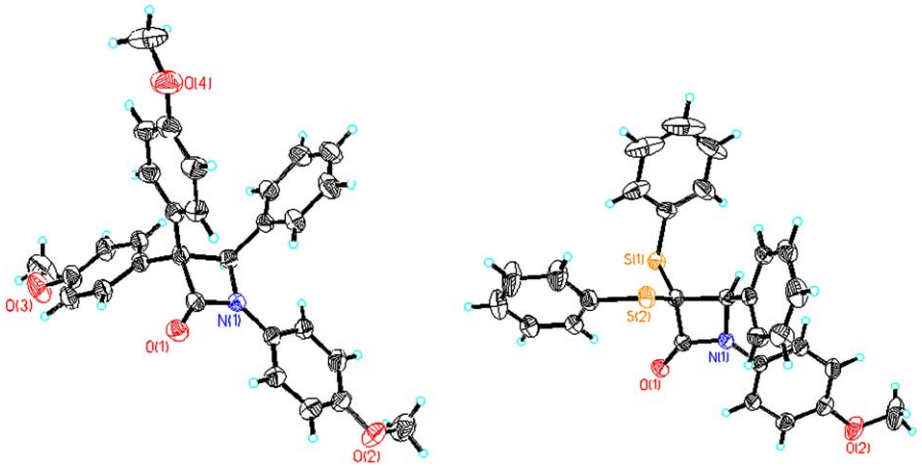
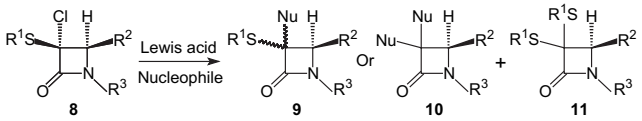


Figure 3. ORTEP diagrams for compounds **10a** and **11a**.

Table 3. Reaction of **8a–c** with various active aromatic substrates using $SnCl_4$ as the Lewis acid



Entry	8	Substrates (Nu)	Products[a] of type (% yield)[b]		
			9	10	11
1	**8a**	C_6H_5OMe	—	**10a** (47)	**11a** (42)
2	**8b**	C_6H_5OMe	—	**10b** (42)	**11b** (39)
3	**8c**	C_6H_5OMe	**9c** (45)	**10c** (35)	**11c** (16)
4	**8a**	1,3-$C_6H_4(OMe)_2$	—	**10f** (43)	**11a** (35)
5	**8b**	1,3-$C_6H_4(OMe)_2$	—	**10g** (39)	**11b** (32)
6	**8a**	1,4-$C_6H_4(OMe)_2$	—	**10h** (38)	**11a** (43)
7	**8b**	C_6H_5OH	—	**10i** (36)	**11b** (26)
8	**8a**	$C_{10}H_7(OMe)(2)$	**9j** (48)	—	**11a** (29)
9	**8c**	$C_{10}H_7(OMe)(2)$	**9k** (42)	—	**11c** (20)

[a] All new compounds gave satisfactory CHN analysis.
[b] Yields quoted are for the isolated products characterized by IR, ^1H NMR, ^{13}C NMR and MS.

2.1. C-3 monosubstituted β-lactams

Since C-3 monosubstituted azetidin-2-ones are also very important synthons from the biological point of view, this methodology has also been successfully employed for the synthesis of C-3 monosubstituted azetidin-2-ones. It was envisaged that replacement of good leaving and resonance stabilized PhS-group by a poor leaving and less stable group such as benzylthio ($PhCH_2S$–) would allow monosubstitution. Thus, studies were carried out by treating **8d** with aromatic substrates such as 1,4-dimethoxybenzene in the presence of one equivalent of $SnCl_4$ at 0 °C. This reaction surprisingly resulted in the formation of only monosubstituted product, **9d**, in excellent yield. No formation of 3,3-disubstituted product was observed by ^1H NMR spectroscopy. $TiCl_4$ also promoted the formation of only monosubstituted product.

Various reactions were carried out successfully with different active substrates and the results are summarized in Table 4. Interestingly, all the active substrates react to give C-3 monosubstituted products. However, in some cases varying amounts of 3,3-bis(arylthio)azetidin-2-ones were also formed along with 3,3-disubstituted azetidin-2-ones (Table 4, entries 2 and 4). Here, again, benzene was found to be unreactive under given set of conditions. However, toluene did afford a C-3 monosubstituted product.

In continuation to our studies with cationic β-lactam equivalents, reactions were carried out, by treating **8a–b**,**d** with

Table 4. Reaction of **8d** with various active aromatic substrates using $SnCl_4$ or $TiCl_4$ as Lewis acid

Entry	Substrates (Nu)	Products[a] of type (% yield)[b]		
		9	**10**	**11**
1	1,4-$C_6H_4(OMe)_2$	**9d** (67)	—	—
2	C_6H_5OMe	**9l** (60)	**10a** (21)	**11d** (17)
3	$C_{10}H_7(OMe)(2)$	**9m** (61)	—	**11d** (21)
4	1,3-$C_6H_4(OMe)_2$	**9n** (51)	**10f** (23)	**11d** (33)
5	C_6H_5Me	**9o** (58)	—	—
6	C_6H_5OH	**9p** (26)	—	**11d** (42)

[a] All new compounds gave satisfactory CHN analysis.
[b] Yields quoted are for the isolated products characterized by IR, ^1H and ^{13}C NMR.

various active aliphatic and heterocyclic substrates and the results are summarized in Table 5. Initially, allyltrimethylsilane and 1-cyclohexenyltrimethylsilyl ether, as the alkyl reactive substrates, were treated with **8a**,**d** and **8b**, respectively, in the presence of one equivalent of $SnCl_4$ or $TiCl_4$ at 0 °C and this resulted in the formation of only monosubstituted product of type **9** (Table 5, entries 1, 2 and 3). To extend these studies further, the reaction of cationic equivalents **8a**,**d** with heterocyclic substrates was examined. The heterocyclic substrates such as furan, pyrrole and indole react with **8a**,**d** under these conditions and the results are summarized in Table 5. Quite interestingly pyrrole reacts with cationic β-lactam equivalents, **8a**,**d**, to give only 3,3-disubstituted products along with varying amount of 3,3-bis(arylthio)azetidin-2-ones of the type **11**.

The spatial relationship of the C-4 hydrogen and new substituent at C-3 in **9j** was assigned the trans configuration on the basis of its transformation to the *cis*-β-lactam (J=6.2 Hz, C3-H and C4-H) on stereospecific[19] Raney-nickel desulfurization was further confirmed by X-ray crystallographic analysis[20] of **9j** (Fig. 4). It is interesting to note that approach of the nucleophile to more hindered face of the β-lactams forms the monosubstituted products. A possible explanation is that the Lewis acid first forms a complex (A) with β-lactam (Scheme 4), which being bulkier in size thus prevents the approach of the incoming nucleophiles from its side. Thus the reaction probably follows *Path A* and proceeds via an S_N2 mechanism.

Table 5. Reaction of **8a–b**,**d** with various active aliphatic and heterocyclic substrates using $SnCl_4$ or $TiCl_4$ as Lewis acid

Entry	**8**	Substrates (Nu)	Products[a] of type (% yield)[b]		
			9	**10**	**11**
1	**8d**	$CH_2{=}CHCH_2Si(Me)_3$	**9q** (90)	—	—
2	**8a**	$CH_2{=}CHCH_2Si(Me)_3$	**9r** (86)	—	—
3	**8b**	$C_6H_9OSi(Me)_3$	**9s** (44)	—	—
4	**8d**	C_4H_4O	**9t** (78)	—	—
5	**8d**	C_8H_6NH	**9u** (17)	—	**11d** (58)
6	**8a**	C_8H_6NH	—	**10v** (36)	**11a** (42)
7	**8d**	C_4H_4NH	—	**10w** (57)	**11d** (22)
8	**8a**	C_4H_4NH	—	**10w** (46)	**11a** (31)

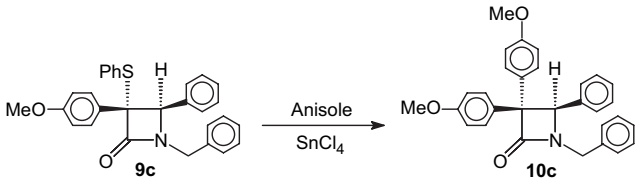
[a] All new compounds gave satisfactory CHN analysis.
[b] Yields quoted are for the isolated products characterized by IR, ^1H NMR, ^{13}C NMR and MS.

However, the spatial juxtaposition of the C-4 hydrogen and new substituent at C-3 in case of **9r**[21] and **9s** was assigned cis on the basis of single crystal X-ray crystallography[22] (Fig. 4). Here, the reaction most likely follows *Path B* involving the intermediate formation of carbocation at C-3 (Scheme 4). The silylenol ether approaches the carbocation from the side of hydrogen atom at C-4, which is less hindered.

The possible role of **9** as an intermediate in the formation of disubstituted products **10** was supported by transformation of monosubstituted β-lactam **9c** into the disubstituted β-lactam **10c** on treatment with anisole, in the presence of $SnCl_4$ (Scheme 5). The formation of **11** was totally unexpected. The ambiphilic behaviour of –SPh and $–SCH_2Ph$ as the leaving group (leading to **10**) and at the same time acting as nucleophiles (leading to **11**) is remarkable.

Raney-nickel desulfurization of **9c** and **9k** led to the formation of *cis*-β-lactam **12** and *cis*-β-lactam **13** (J=5.6 Hz, C3-H and C4-H), respectively (Scheme 6).

The trans stereochemistry of monosubstituted β-lactams **9d** and **9t** was also established on the basis of their stereospecific desulfurization with Raney-nickel leading to the formation of *cis*-β-lactams **14** and **15** (J=6 Hz, C3-H and C4-H), respectively (Scheme 7).



Scheme 5. Transformation of monosubstituted β-lactam **9c** into disubstituted β-lactam **10c**.

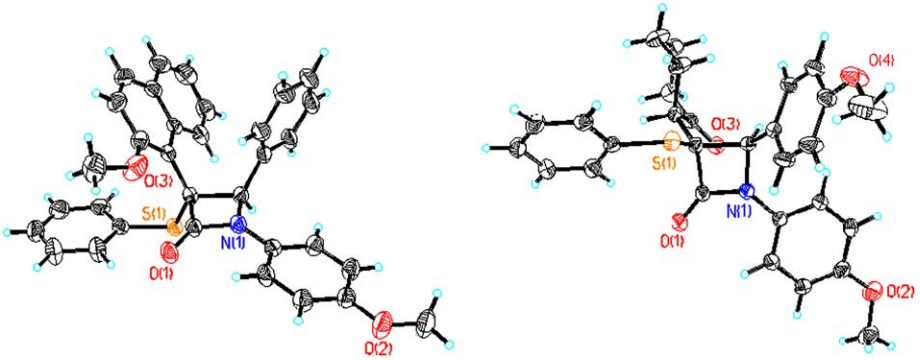
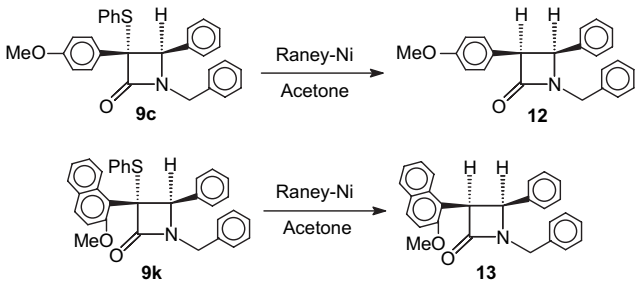
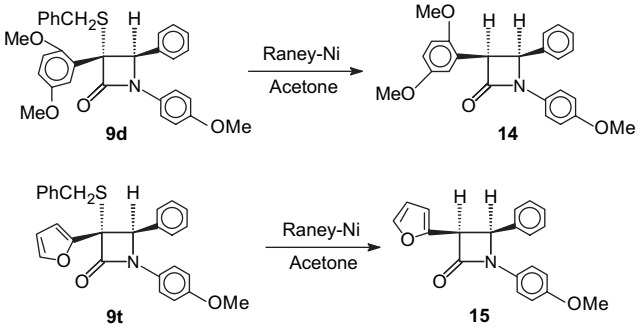


Figure 4. ORTEP diagrams for compounds **9j** and **9s**.



Scheme 6. Raney-nickel desulfurization of 3-phenylthio-β-lactams (**9c**, **9k**).



Scheme 7. Raney-nickel desulfurization of 3-benzylthio-β-lactams (**9d**, **9t**).

3. Conclusion

In conclusion, we have shown that the reactions of *trans*-3-chloro-3-benzylthio-β-lactams with an active aromatic, aliphatic and heterocyclic substrates provide an easy access to novel C-3 monosubstituted β-lactams and *trans*-3-chloro-3-phenylthio-β-lactams allows the formation of bis(arylthio)-β-lactams and 3,3-disubstituted β-lactams fairly efficiently.

4. Experimental

4.1. General

^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, in $CDCl_3$ solution using BRUKER or JEOL 300 MHz NMR spectrometers. Chemical shifts are given in parts per million relative to tetramethylsilane as an internal standard (δ=0 ppm) for ^{1}H NMR and $CDCl_3$ (δ=77.0 ppm) for ^{13}C NMR spectra. IR spectra were taken on a FTIR spectrophotometer and are reported in cm^{-1}. Mass spectra were recorded at 70 eV using VG ANALYTICAL 11-250-J 70S spectrometer. The elemental analysis (C, H, N) was carried out using a PERKIN–ELMER 2400 elemental analyzer. Column chromatography was performed using Merck Silica Gel (100–200 mesh). Thin-layer chromatography (TLC) was performed using Merck Silica Gel G. For visualization, TLC plates were stained with iodine vapours. Melting points are uncorrected. All commercially available compounds/reagents were used without further purification. Dichloromethane and carbon tetrachloride distilled over P_2O_5 were redistilled over CaH_2 before use. Crystallographic data (excluding structure factors) of compounds **9j**,[20] **9s**,[22] **10a**[17] and **11a**[18] in CIF format have been deposited with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (internet.) +44 1223/336 033; e-mail: deposit@ccdc.cam.ac.uk]. All other relevant information regarding the data and supplementary publication CCDC number is presented in respective references.

4.2. General procedure for synthesis of *trans*-3-phenyl/benzylthio-β-lactams (7a–e)

Compounds **7a**–**c**[11] were prepared by the procedure described in the cited reference. The spectroscopic data of compound **7a**[11] were reported in the cited reference.

4.2.1. *trans*-1-(4′-Methoxyphenyl)-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (7b). Yellow crystalline solid; yield 53%; mp 94–96 °C; [Found: C, 73.27; H, 5.22; N, 3.41. $C_{23}H_{21}NO_3S$ requires C, 73.57; H, 5.40; N, 3.58%]; IR (cm^{-1}, $CHCl_3$): 1747 (C=O); δ_H (300 MHz, $CDCl_3$) 7.60–6.70 (13H, m, Ph), 4.70 (1H, d, *J* 2.2 Hz, C4-*H*), 4.20 (1H, d, *J* 2.2 Hz, C3-*H*), 3.74 (3H, s, OCH_3), 3.70 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 162.3, 160.0, 156.2, 132.5, 131.9, 130.7, 129.1, 128.1, 127.8, 127.4, 118.7, 114.6, 114.3, 63.0, 61.4, 55.4, 55.3.

4.2.2. *trans*-1-Benzyl-3-phenylthio-4-phenylazetidin-2-one (7c). Colourless crystalline solid; yield 52%; mp 124–126 °C; [Found: C, 76.34; H, 5.43; N, 4.01. $C_{22}H_{19}NOS$ requires C, 76.49; H, 5.54; N, 4.05%]; IR (cm^{-1}, KBr): 1755 (C=O); δ_H (300 MHz, $CDCl_3$) 7.52–6.73 (15H, m, Ph), 4.70 (1H, d, *J* 15.1 Hz, CH_aH$_b$Ph), 4.20 (1H, d, *J* 2.2 Hz, C4-*H*), 4.14 (1H, d, *J* 2.2 Hz, C3-*H*), 3.60 (1H, d, *J* 15.1 Hz, CH$_a$$H_b$Ph); δ_C (75 MHz, $CDCl_3$) 165.8, 135.9, 134.5, 133.6, 133.2, 131.2, 129.2, 129.1, 128.9, 128.6, 128.3, 127.5, 61.9, 61.6, 44.5.

4.2.3. *trans*-1-(4′-Methoxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (7d). This compound was prepared by using the same method as for **7a**–**c**, starting from 2-benzylthioethanoic acid. Colourless crystalline solid; yield 43%; mp 95–97 °C; [Found: C, 73.46; H, 5.52; N, 3.64. $C_{23}H_{21}NO_2S$ requires C, 73.58; H, 5.63; N, 3.70%]; IR (cm^{-1}, KBr): 1739 (C=O); δ_H (300 MHz, $CDCl_3$) 7.35–6.71 (14H, m, Ph), 4.80 (1H, d, *J* 2.2 Hz, C4-*H*), 3.97 (2H, d, *J* 4.8 Hz, CH_2S), 3.88 (1H, d, *J* 2.4 Hz, C3-*H*), 3.73 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 162.3, 156.2, 137.7, 137.0, 131.1, 129.2, 128.7, 128.6, 127.3, 125.9, 118.5, 114.3, 63.2, 59.1, 55.2, 35.3.

4.2.4. *trans*-1-(4′-Methoxyphenyl)-3-benzylthio-4-(4′-methoxyphenyl)azetidin-2-one (7e). This compound was prepared by using the same method as for **7a**–**c**, starting from 2-benzylthioethanoic acid. White solid; yield 44%; mp 108–111 °C; [Found: C, 71.01; H, 5.62; N, 3.37. $C_{24}H_{23}NO_3S$ requires C, 71.09; H, 5.71; N, 3.45%]; IR (cm^{-1}, KBr): 1731 (C=O); δ_H (300 MHz, $CDCl_3$) 7.35–6.70 (13H, m, Ph), 4.51 (1H, d, *J* 2.2 Hz, C4-*H*), 3.95 (2H, d, *J* 4.8 Hz, CH_2S), 3.85 (1H, d, *J* 2.2 Hz, C3-*H*), 3.78 (3H, s, OCH_3), 3.74 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 162.4, 156.9, 156.1, 137.7, 131.1, 129.2, 128.7, 128.5, 127.3, 127.2, 118.5, 114.5, 114.2, 62.8, 59.0, 55.1, 55.0, 35.2.

4.3. General procedure for synthesis of *trans*-3-chloro-3-phenylthio-β-lactams (8a–c)

Compounds **8a–c**[11] were prepared by the procedure as described in the cited reference. The spectroscopic data of compound **8a**[11] were reported in the cited reference.

4.3.1. *trans*-1-(4′-Methoxyphenyl)-3-chloro-3-phenylthio-4-(4′-methoxyphenyl)azetidin-2-one (8b). Colourless crystalline solid; yield 94%; mp 75–76 °C; [Found: C, 64.56; H, 4.61; N, 3.14. $C_{23}H_{20}NO_3ClS$ requires C, 64.24; H, 4.73; N, 3.28%]; IR (cm^{-1}, KBr): 1764 (C=O); δ_H (300 MHz, $CDCl_3$) 7.50–6.81 (13H, m, Ph), 5.39 (1H, s, C4-*H*), 3.80 (3H, s, OCH_3), 3.70 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 160.6, 160.2, 156.7, 135.3, 129.8, 129.6, 129.3, 128.7, 128.4, 123.4, 119.2, 114.4, 114.0, 80.3, 71.5, 55.4, 55.3.

4.3.2. *trans*-1-Benzyl-3-chloro-3-phenylthio-4-phenylazetidin-2-one (8c). Colourless crystalline solid; yield 94%; mp 90–92 °C; [Found: C, 69.47; H, 4.71; N, 3.63. $C_{22}H_{18}NOClS$ requires C, 69.55; H, 4.78; N, 3.68%]; IR (cm^{-1}, KBr): 1776 (C=O); δ_H (300 MHz, $CDCl_3$) 7.45–7.15 (15H, m, Ph), 5.05 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 4.82 (1H, s, C4-*H*), 3.90 (1H, d, *J* 15.1 Hz, CH$_a$$H_b$Ph); δ_C (75 MHz, $CDCl_3$) 163.9, 135.1, 134.1, 131.8, 129.7, 129.1, 129.0, 128.6, 128.5, 128.3, 128.2, 80.9, 71.1, 44.6.

4.4. General procedure for synthesis of *trans*-3-chloro-3-benzylthio-β-lactams (8d–e)

To a solution of **7d/7e** (1 mmol) in 80 mL dry carbon tetrachloride were added *N*-chlorosuccinimide (NCS) (1.2 mmol) and catalytic amount of AIBN. The reaction mixture was refluxed and progress of the reaction was monitored by TLC. After the completion of reaction, the reaction mixture was filtered and the filtrate was evaporated in vacuo. This crude product was purified by silica gel column chromatography (10% EtOAc/hexane).

4.4.1. *trans*-1-(4′-Methoxyphenyl)-3-chloro-3-benzylthio-4-phenylazetidin-2-one (8d). Colourless crystalline solid; yield 63%; mp 135–137 °C; [Found: C, 67.29; H, 4.84; N, 3.36. $C_{23}H_{20}NO_2ClS$ requires C, 67.39; H, 4.91; N, 3.42%]; IR (cm^{-1}, KBr): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.38–6.75 (14H, m, Ph), 5.38 (1H, s, C4-*H*), 4.28 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.98 (1H, d, *J* 11.7 Hz, CH$_a$$H_b$S), 3.74 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 159.9, 156.7, 135.4, 135.3, 131.4, 131.5, 129.7, 129.6, 129.4, 128.6, 128.5, 127.9, 127.4, 119.1, 114.4, 80.7, 71.5, 55.3, 34.7, 25.1.

4.4.2. *trans*-1-(4′-Methoxyphenyl)-3-chloro-3-benzylthio-4-(4′-methoxyphenyl)azetidin-2-one (8e). Yellow oil; yield 44%; [Found: C, 65.47; H, 4.97; N, 3.11. $C_{23}H_{20}NO_3ClS$ requires C, 65.52; H, 5.04; N, 3.18%]; IR (cm^{-1}, $CHCl_3$): 1750 (C=O); δ_H (300 MHz, $CDCl_3$) 7.32–6.71 (14H, m, Ph), 5.30 (1H, s, C4-*H*), 4.29 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 4.00 (1H, d, *J* 11.7 Hz, CH$_a$$H_b$S), 3.77 (3H, s, OC$H_3$), 3.76 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 160.5, 159.7, 156.6, 135.7, 130.1, 129.5, 129.3, 128.7, 128.5, 127.4, 123.3, 119.0, 114.4, 114.0, 81.1, 71.2, 55.1, 55.0, 34.8, 25.2, 23.6.

4.5. General procedure for synthesis of C-3 substituted azetidin-2-ones

To a well stirred solution of **8a–e** (1 mmol) in 10 mL dry methylene chloride was added substrates (nucleophile) (1.1 mmol) followed by stannic chloride (1.2 mmol) via a syringe, under inert atmosphere, at −78 °C for **8a–c** and at 0 °C for **8d–e**. The reaction mixture was stirred for 1 h at the same temperature. The progress of the reaction was checked by TLC, which showed the appearance of spots different from the starting compound. The reaction mixture was quenched with water, extracted with methylene chloride (4×10 mL), washed with 5% $NaHCO_3$ solution and then dried (anhydrous Na_2SO_4). The residue after solvent evaporation in vacuo, was purified by silica gel column chromatography (10% EtOAc/hexane).

4.5.1. *cis*-1-Benzyl-3-(4′-methoxyphenyl)-3-phenylthio-4-phenylazetidin-2-one (9c). Colourless oil; yield 45%; [Found: C, 77.28; H, 5.52; N, 3.04. $C_{29}H_{25}NO_2S$ requires C, 77.34; H, 5.58; N, 3.10%]; R_f (10% EtOAc/hexane) 0.42; IR (cm^{-1}, $CHCl_3$): 1756 (C=O); δ_H (300 MHz, $CDCl_3$) 7.65–6.53 (19H, m, Ph), 4.75 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 4.59 (1H, s, C4-*H*), 3.70 (1H, d, *J* 14.9 Hz, CH$_a$$H_b$Ph), 3.63 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 167.9, 158.8, 136.5, 134.3, 134.0, 130.6, 130.0, 129.4, 129.0, 128.5, 128.3, 128.1, 127.4, 125.9, 113.2, 72.2, 66.8, 55.1, 44.0.

4.5.2. *cis*-1-(4′-Methoxyphenyl)-3-(2′,5′-dimethoxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (9d). White semisolid; yield 67%; [Found: C, 72.75; H, 5.63; N, 2.69. $C_{31}H_{29}NO_4S$ requires C, 72.78; H, 5.71; N, 2.74%]; IR (cm^{-1}, $CHCl_3$): 1741 (C=O); δ_H (300 MHz, $CDCl_3$) 7.44–6.40 (17H, m, Ph), 5.19 (1H, s, C4-*H*), 3.96 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.73 (3H, s, OCH_3), 3.70 (3H, s, OCH_3), 3.62 (3H, s, OCH_3), 3.38 (1H, d, *J* 11.7 Hz, CH$_a$$H_b$S); δ_C (75 MHz, $CDCl_3$) 165.0, 156.0, 153.6, 151.2, 137.2, 133.8, 131.2, 129.2, 128.6, 128.1, 127.8, 127.6, 126.7, 118.7, 114.7, 114.4, 114.2, 113.2, 66.9, 65.2, 56.0, 55.5, 55.1, 34.5; δ_C (DEPT-135) (75 MHz, $CDCl_3$) 129.3 (+), 129.2 (+), 128.6 (+), 128.1 (+), 127.8 (+), 126.7 (+), 118.7 (+), 114.7 (+), 114.4 (+), 114.2 (+), 113.2 (+), 66.9 (+), 56.0 (+), 55.5 (+), 55.2 (+), 34.5 (−).

4.5.3. *cis*-1-(4′-Methoxyphenyl)-3-(2′-methoxynaphthyl)-3-phenylthio-4-phenylazetidin-2-one (9j). Colourless crystalline solid; yield 45%; mp 190–192 °C; [Found: C, 76.48; H, 5.22; N, 2.64. $C_{33}H_{27}NO_3S$ requires C, 76.57; H, 5.27; N, 2.70%]; R_f (10% EtOAc/hexane) 0.40; IR (cm^{-1}, KBr): 1720 (C=O); δ_H (300 MHz, $CDCl_3$) 8.50–6.60 (20H, m, Ph), 5.24 (1H, s, C4-*H*), 3.68 (3H, s, OCH_3), 3.56 (3H, s, OCH_3) (for one isomer) and 9.40–6.60 (20H, m, Ph), 5.32 (1H, s, C4-*H*), 3.82 (3H, s, OCH_3), 3.71 (3H, s, OCH_3) (for other isomer); *m/z*: 306 (M^+); the ^{1}H NMR spectrum showed it to be a mixture of two rotamers as evident from the appearance of two signals for C4-H and a downfield appearance of an aromatic proton.

4.5.4. *cis*-1-Benzyl-3-(2′-methoxynaphthyl)-3-phenylthio-4-phenylazetidin-2-one (9k). Yellow oil; yield 42%; [Found: C, 78.96; H, 5.38; N, 2.73. $C_{33}H_{27}NO_2S$ requires C, 79.02; H, 5.42; N, 2.79%]; R_f (10% EtOAc/hexane)

0.35; IR (cm^{-1}, $CHCl_3$): 1725 (C=O); δ_H (300 MHz, $CDCl_3$) 9.35–6.65 (21H, m, Ph), 4.74 (1H, s, C4-*H*), 4.56 (1H, d, *J* 15.1 Hz, CH_aH$_b$Ph), 3.70 (1H, d, *J* 15.0 Hz, CH$_a$$H_b$Ph), 3.32 (3H, s, OC$H_3$) (for one isomer) and 8.20–6.63 (21H, m, Ph), 4.78 (1H, s, C4-*H*), 4.75 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 3.79 (3H, s, OCH_3), 3.75 (1H, d, *J* 14.9 Hz, CH$_a$$H_b$Ph), (for other isomer); the ^{1}H NMR spectrum showed it to be a mixture of two rotamers as evident from the appearance of two signals for C4-H and a downfield appearance of an aromatic proton.

4.5.5. *cis*-1-(4′-Methoxyphenyl)-3-(4′-methoxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (9l). Colourless oil; yield 60%; [Found: C, 74.73; H, 5.56; N, 2.87. $C_{30}H_{27}NO_3S$ requires C, 74.82; H, 5.65; N, 2.91%]; R_f (10% EtOAc/hexane) 0.31; IR (cm^{-1}, $CHCl_3$): 1751 (C=O); δ_H (300 MHz, $CDCl_3$) 7.59–6.66 (18H, m, Ph), 5.10 (1H, s, C4-*H*), 3.85 (1H, d, *J* 11.4 Hz, CH_aH$_b$S), 3.76 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 3.22 (1H, d, *J* 11.1 Hz, CH$_a$$H_b$S); δ_C (75 MHz, $CDCl_3$) 165.3, 159.4, 156.2, 136.8, 135.7, 133.1, 130.8, 130.5, 130.3, 129.2, 129.6, 128.3, 128.1, 128.1, 128.0, 126.9, 126.8, 118.8, 118.7, 114.3, 114.2, 102.4, 67.9, 67.5, 56.0, 55.2, 54.5, 34.4.

4.5.6. *cis*-1-(4′-Methoxyphenyl)-3-(2′-methoxynaphthyl)-3-benzylthio-4-phenylazetidin-2-one (9m). Yellow oil; yield 61%; [Found: C, 76.73; H, 5.44; N, 2.58. $C_{34}H_{29}NO_3S$ requires C, 76.81; H, 5.49; N, 2.63%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, $CHCl_3$): 1745 (C=O); δ_H (300 MHz, $CDCl_3$) 8.00–6.68 (20H, m, Ph), 5.21 (1H, s, C4-*H*), 4.14 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.70 (3H, s, OCH_3), 3.64 (3H, s, OCH_3), 3.22 (1H, d, *J* 11.7 Hz, CH$_a$$H_b$S) (for one isomer) and 8.20–6.72 (20H, m, Ph), 5.26 (1H, s, C4-*H*), 4.29 (1H, d, *J* 12.3 Hz, CH_aH$_b$S), 3.93 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.58 (1H, d, *J* 12.3 Hz, CH$_a$$H_b$S) (for other isomer); the ^{1}H NMR spectrum showed it to be a mixture of two rotamers as evident from the appearance of two signals for C4-H and a downfield appearance of an aromatic proton.

4.5.7. *cis*-1-(4′-Methoxyphenyl)-3-(2′,4′-dimethoxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (9n). Brown oil; yield 51%; [Found: C, 72.73; H, 5.65; N, 2.67. $C_{31}H_{29}NO_4S$ requires C, 72.78; H, 5.71; N, 2.74%]; R_f (10% EtOAc/hexane) 0.30; IR (cm^{-1}, $CHCl_3$): 1745 (C=O); δ_H (300 MHz, $CDCl_3$) 7.79–6.37 (17H, m, Ph), 5.18 (1H, s, C4-*H*), 3.95 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.79 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.65 (3H, s, OCH_3), 3.35 (1H, d, *J* 12.0 Hz, CH$_a$$H_b$S); δ_C (75 MHz, $CDCl_3$) 161.0, 158.1, 156.0, 137.3, 133.8, 131.1, 129.7, 129.2, 129.1, 128.6, 128.1, 127.8, 126.6, 118.7, 114.2, 103.6, 99.9, 68.1, 67.0, 65.8, 65.0, 55.3, 55.2, 34.5.

4.5.8. *cis*-1-(4′-Methoxyphenyl)-3-(4′-methylphenyl)-3-benzylthio-4-phenylazetidin-2-one (9o). White semisolid; yield 58%; [Found: C, 77.32; H, 5.80; N, 2.94. $C_{30}H_{27}NO_2S$ requires C, 77.39; H, 5.84; N, 3.01%]; IR (cm^{-1}, $CHCl_3$): 1751 (C=O); δ_H (300 MHz, $CDCl_3$) 7.59–6.67 (18H, m, Ph), 5.10 (1H, s, C4-*H*), 3.92 (1H, d, *J* 11.4 Hz, CH_aH$_b$S), 3.70 (3H, s, OCH_3), 3.25 (1H, d, *J* 11.4 Hz, CH$_a$$H_b$S), 2.30 (3H, s, C$H_3$); δ_C (75 MHz, $CDCl_3$) 156.2, 137.5, 136.9, 136.3, 134.4, 130.9, 129.5, 129.4, 128.9, 128.6, 128.3, 128.2, 127.7, 127.3, 126.8, 118.8, 118.6, 114.3, 114.2, 68.9, 68.1, 55.1, 34.4, 21.2.

4.5.9. *cis*-1-(4′-Methoxyphenyl)-3-(4′-hydroxyphenyl)-3-benzylthio-4-phenylazetidin-2-one (9p). Brownish-yellow oil; yield 26%; [Found: C, 74.56; H, 5.31; N, 2.96. $C_{29}H_{25}NO_4$ requires C, 74.50; H, 5.38; N, 2.99%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, $CHCl_3$): 1729 (C=O), 3374 (OH); δ_H (300 MHz, $CDCl_3$) 7.46–6.39 (18H, m, Ph), 5.20 (1H, s, C4-*H*), 3.77 (1H, d, *J* 11.4 Hz, CH_aH$_b$S), 3.66 (3H, s, OCH_3), 3.19 (1H, d, *J* 11.4 Hz, CH$_a$$H_b$S).

4.5.10. *trans*-1-(4′-Methoxyphenyl)-3-allyl-3-phenylthio-4-phenylazetidin-2-one (9q). Colourless crystalline solid; yield 86%; mp 130–132 °C; [Found: C, 74.64; H, 5.66; N, 3.39. $C_{25}H_{23}NO_2S$ requires C, 74.78; H, 5.77; N, 3.48%]; IR (cm^{-1}, KBr): 1745 (C=O), 1510 (C=C); δ_H (300 MHz, $CDCl_3$) 7.62–6.83 (14H, m, Ph), 6.01 (1H, m, C*H*=CH$_2$), 5.30 (1H, br s, CH=CH_aH$_b$), 5.26 (1H, m, CH=CH$_a$$H_b$), 5.15 (1H, s, C4-*H*), 3.78 (3H, s, OCH_3), 2.68 (2H, d, *J* 7.3 Hz, CH_2CH=); δ_C (75 MHz, $CDCl_3$) 165.7, 156.2, 135.2, 133.6, 132.8, 130.9, 130.7, 128.6, 128.2, 128.0, 126.3, 119.4, 118.5, 114.3, 65.9, 63.5, 55.1, 38.0; *m/z*: 401 (M^+).

4.5.11. *trans*-1-(4′-Methoxyphenyl)-3-allyl-3-benzylthio-4-phenylazetidin-2-one (9r). Colourless crystalline solid; yield 90%; mp 143–144 °C; [Found: C, 77.11; H, 6.02; N, 3.34. $C_{26}H_{25}NO_2S$ requires C, 77.16; H, 6.06; N, 3.37%]; IR (cm^{-1}, KBr): 1750 (C=O), 1515 (C=C); δ_H (300 MHz, $CDCl_3$) 7.22–6.63 (14H, m, Ph), 5.88 (1H, m, C*H*=CH$_2$), 5.26 (1H, br s, CH=CH_aH$_b$), 5.22 (1H, m, CH=CH$_a$$H_b$), 4.88 (1H, s, C4-*H*), 3.63 (2H, d, *J* 11.4 Hz, CH_2S), 3.61 (3H, s, OCH_3), 2.73 (2H, d, *J* 7.3 Hz, CH_2CH=); δ_C (75 MHz, $CDCl_3$) 165.1, 156.1, 137.1, 133.8, 132.8, 131.0, 129.2, 128.7, 128.4, 128.3, 128.1, 127.8, 127.2, 127.0, 119.4, 118.4, 114.3, 114.2, 65.3, 64.4, 55.1, 39.1, 33.6; δ_C (DEPT-135) (75 MHz, $CDCl_3$) 132.8 (+), 129.2 (+), 128.4 (+), 128.3 (+), 128.1 (+), 127.8 (+), 127.0 (+), 119.4 (−), 118.4 (+), 114.3 (+), 114.2 (+), 64.4 (+), 55.1 (+), 39.1 (−), 33.6 (−).

4.5.12. *trans*-1-(4′-Methoxyphenyl)-3-(2′-oxocyclohexanyl)-3-phenylthio-4-phenylazetidin-2-one (9s). Colourless crystalline solid; yield 44%; mp 179–181 °C; [Found: C, 71.49; H, 5.96; N, 2.83. $C_{29}H_{29}NO_4S$ requires C, 71.43; H, 6.01; N, 2.87%]; IR (cm^{-1}, KBr): 1755 (lactam C=O), 1720 (C=O); δ_H (300 MHz, $CDCl_3$) 7.68–6.79 (13H, m, Ph), 5.21 (1H, s, C4-*H*), 3.61 (3H, s, OCH_3), 2.76 (2H, m, $C_5H_7H_{h-i}$C=O), 2.37 (1H, m, $C_5H_8H_a$C=O), 2.27 (1H, m, $C_5H_8H_f$C=O), 2.08 (2H, m, $C_5H_7H_{b-c}$C=O), 1.82 (2H, m, $C_5H_7H_{d,g}$C=O), 1.49 (1H, m, $C_5H_8H_e$C=O); δ_C (75 MHz, $CDCl_3$) 210.2, 167.5, 159.9, 156.1, 135.6, 131.8, 130.3, 129.6, 128.9, 125.7, 118.8, 114.4, 113.7, 66.6, 62.3, 55.5, 55.3, 50.0, 42.5, 29.9, 27.9, 25.3.

4.5.13. *cis*-1-(4′-Methoxyphenyl)-3-(2′-furanyl)-3-benzylthio-4-phenylazetidin-2-one 9t. White solid; yield 78%; mp 148–150 °C; [Found: C, 73.46; H, 5.21; N, 3.11. $C_{27}H_{23}NO_3S$ requires C, 73.45; H, 5.25; N, 3.17%]; IR (cm^{-1}, KBr): 1744 (C=O); δ_H (300 MHz, $CDCl_3$) 7.50 (1H, dd, *J* 0.9, 0.9 Hz, $C_4H_aH_bH_c$O), 7.39–6.75 (14H, m, Ph), 6.61 (1H, dd, *J* 0.9, 0.9 Hz, $C_4H_aH_bH_c$O), 6.38 (1H, dd, *J* 1.8, 1.8 Hz, $C_4H_aH_bH_c$O), 5.33 (1H, s, C4-*H*), 3.94 (1H, d, *J* 11.4 Hz, CH_aH$_b$S), 3.74 (3H, s, OCH_3), 3.47 (1H,

d, *J* 11.4 Hz, CH_aH_bS); δ_C (75 MHz, $CDCl_3$) 156.4, 149.6, 143.3, 136.7, 132.8, 131.0, 129.3, 128.9, 128.4, 128.3, 128.1, 127.0, 118.8, 114.4, 110.7, 109.6, 65.3, 63.1, 55.2, 34.6; δ_C (DEPT-135) (75 MHz, $CDCl_3$) 143.3 (+), 129.3 (+), 128.9 (+), 128.3 (+), 128.1 (+), 127.0 (+), 118.8 (+), 114.4 (+), 110.7 (+), 109.6 (+), 65.3 (+), 55.2 (+), 34.6 (−).

4.5.14. *cis*-1-(4′-Methoxyphenyl)-3-(3′-indolyl)-3-benzylthio-4-phenylazetidin-2-one (9u). Reddish-brown oil; yield 17%; [Found: C, 75.84; H, 5.31; N, 5.67. $C_{31}H_{26}N_2O_2S$ requires C, 75.89; H, 5.34; N, 5.71%]; R_f (10% EtOAc/hexane) 0.43; IR (cm^{-1}, $CHCl_3$): 1764 (C═O); δ_H (300 MHz, $CDCl_3$) 8.12 (1H, br s, N*H*, D_2O exchangeable), 7.82–6.67 (19H, m, Ph), 5.10 (1H, s, C4-*H*), 3.87 (1H, d, *J* 11.4 Hz, CH_aH_bS), 3.66 (3H, s, OCH_3), 3.24 (1H, d, *J* 11.4 Hz, CH_aH_bS).

4.5.15. 1-(4′-Methoxyphenyl)-3,3-bis(4′-methoxyphenyl)-4-phenylazetidin-2-one (10a). Colourless crystalline solid; yield 47%; mp 135–137 °C; [Found: C, 77.47; H, 5.81; N, 2.96. $C_{30}H_{27}NO_4$ requires C, 77.39; H, 5.86; N, 3.01%]; R_f (10% EtOAc/hexane) 0.39; IR (cm^{-1}, KBr): 1735 (C═O); δ_H (300 MHz, $CDCl_3$) 7.54–6.53 (17H, m, Ph), 5.67 (1H, s, C4-*H*), 3.79 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.65 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.0, 158.8, 158.1, 156.1, 135.1, 133.3, 131.1, 129.7, 129.5, 128.4, 128.3, 128.1, 127.6, 118.7, 114.2, 114.1, 113.2, 71.2, 67.5, 55.3, 55.3, 55.0; *m*/*z*: 465 (M^+).

4.5.16. 1-(4′-Methoxyphenyl)-3,3-bis(4′-methoxyphenyl)-4-(4′-methoxyphenyl)azetidin-2-one (10b). Yellow oil; yield 42%; [Found: C, 75.21; H, 5.81; N, 2.76. $C_{31}H_{29}NO_5$ requires C, 75.14; H, 5.89; N, 2.83%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, $CHCl_3$): 1739 (C═O); δ_H (300 MHz, $CDCl_3$) 7.48–6.53 (16H, m, Ph), 5.58 (1H, s, C4-*H*), 3.77 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 3.67 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.2, 159.4, 158.7, 158.1, 156.1, 133.6, 131.2, 129.8, 129.6, 128.9, 128.4, 127.1, 118.8, 114.3, 114.1, 113.8, 113.3, 71.1, 67.5, 55.4, 55.2.

4.5.17. 1-Benzyl-3,3-bis(4′-methoxyphenyl)-4-phenylazetidin-2-one (10c). Colourless crystalline solid; yield 35%; mp 145–147 °C; [Found: C, 80.21; H, 6.01; N, 3.07. $C_{30}H_{27}NO_3$ requires C, 80.15; H, 6.07; N, 3.11%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, KBr): 1741 (C═O); δ_H (300 MHz, $CDCl_3$) 7.33–6.53 (18H, m, Ph), 5.06 (1H, s, C4-*H*), 4.95 (1H, d, *J* 15.2 Hz, CH_aH_bPh), 3.90 (1H, d, *J* 14.9 Hz, CH_aH_bPh), 3.76 (3H, s, OCH_3), 3.66 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 170.2, 158.6, 158.1, 135.4, 135.1, 133.5, 129.6, 128.8, 128.6, 128.3, 128.1, 127.8, 114.0, 113.2, 72.0, 67.1, 55.3, 55.1, 44.3.

4.5.18. 1-(4′-Methoxyphenyl)-3,3-bis(2′,4′-dimethoxyphenyl)-4-phenylazetidin-2-one (10f). Colourless crystalline solid; yield 43%; mp 175–177 °C; [Found: C, 73.19; H, 5.90; N, 2.63. $C_{32}H_{31}NO_6$ requires C, 73.12; H, 5.96; N, 2.66%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, KBr): 1740 (C═O); δ_H (300 MHz, $CDCl_3$) 7.71–5.95 (15H, m, Ph), 5.75 (1H, s, C4-*H*), 3.77 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.01 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 168.2, 160.4, 159.9, 158.5, 155.9, 155.7, 136.8, 132.7, 132.3, 132.1, 130.2, 129.1, 128.7, 128.6, 127.6, 127.3, 127.0, 126.3, 119.6, 119.4, 118.8, 118.7, 117.3, 114.5, 114.1, 104.3, 103.6, 99.1, 98.4, 68.7, 66.5, 59.5, 55.4, 55.3, 54.0.

4.5.19. 1-(4′-Methoxyphenyl)-3,3-bis(2′,4′-dimethoxyphenyl)-4-(4′-methoxyphenyl)azetidin-2-one (10g). Brownish-yellow oil; yield 39%; [Found: C, 71.17; H, 5.90; N, 2.47. $C_{32}H_{31}NO_7$ requires C, 71.13; H, 5.98; N, 2.52%]; R_f (10% EtOAc/hexane) 0.30; IR (cm^{-1}, $CHCl_3$): 1736 (C═O); δ_H (300 MHz, $CDCl_3$) 7.69–6.01 (14H, m, Ph), 5.70 (1H, s, C4-*H*), 3.76 (3H, s, 2×OCH_3), 3.73 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.68 (3H, s, OCH_3), 3.07 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 168.9, 160.7, 160.2, 158.8, 155.7, 132.3, 132.1, 130.1, 129.7, 128.9, 118.9, 118.7, 117.5, 114.1, 112.5, 104.2, 103.6, 99.1, 98.5, 68.7, 66.1, 55.9, 55.4, 55.3, 55.2, 54.2.

4.5.20. 1-(4′-Methoxyphenyl)-3,3-bis(2′,5′-dimethoxyphenyl)-4-phenylazetidin-2-one (10h). Colourless crystalline solid; yield 38%; mp 268–270 °C; [Found: C, 73.02; H, 5.92; N, 2.61. $C_{32}H_{31}NO_6$ requires C, 73.12; H, 5.96; N, 2.66%]; R_f (10% EtOAc/hexane) 0.42; IR (cm^{-1}, KBr): 1742 (C═O); δ_H (300 MHz, $CDCl_3$) 7.42–6.27 (15H, m, Ph), 5.84 (1H, s, C4-*H*), 3.77 (3H, s, OCH_3), 3.73 (3H, s, OCH_3), 3.69 (3H, s, OCH_3), 3.61 (3H, s, OCH_3), 3.01 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.9, 155.8, 153.4, 152.3, 150.8, 136.5, 132.1, 128.6, 127.1, 127.0, 125.1, 118.7, 118.0, 115.8, 114.1, 113.9, 113.1, 112.5, 110.7, 69.5, 66.3, 56.5, 55.8, 55.6, 55.4, 54.3.

4.5.21. 1-(4′-Methoxyphenyl)-3,3-bis(4′-hydroxyphenyl)-4-(4′-methoxyphenyl)azetidin-2-one (10i). Yellow oil; yield 36%; [Found: C, 74.57; H, 5.35; N, 2.97. $C_{29}H_{25}NO_5$ requires C, 74.51; H, 5.39; N, 3.00%]; R_f (10% EtOAc/hexane) 0.29; IR (cm^{-1}, $CHCl_3$): 1725 (C═O), 3369 (OH), 3383 (OH); δ_H (300 MHz, $CDCl_3$) 7.32–6.43 (16H, m, Ph), 5.61 (1H, s, C4-*H*), 3.71 (3H, s, OCH_3), 3.66 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 167.9, 159.3, 156.3, 155.2, 154.5, 132.7, 130.8, 129.8, 129.2, 128.9, 128.6, 126.9, 119.0, 115.8, 114.9, 114.3, 113.8, 71.0, 67.7, 55.5, 55.2.

4.5.22. 1-(4′-Methoxyphenyl)-3,3-bis(3′-indolyl)-4-phenylazetidin-2-one (10v). Reddish-brown oil; yield 36%; [Found: C, 79.59; H, 5.16; N, 8.65. $C_{32}H_{25}N_3O$ requires C, 79.64; H, 5.20; N, 8.69%]; R_f (10% EtOAc/hexane) 0.40; IR (cm^{-1}, $CHCl_3$): 1762 (C═O); δ_H (300 MHz, $CDCl_3$) 7.35 (1H, br s, N*H*, D_2O exchangeable), 7.10 (1H, br s, N*H*, D_2O exchangeable), 7.32–6.43 (19H, m, Ph), 5.63 (1H, s, C4-*H*), 3.76 (3H, s, OCH_3).

4.5.23. 1-(4′-Methoxyphenyl)-3,3-bis(3′-pyrrolyl)-4-phenylazetidin-2-one (10w). Black oil; yield 46%; [Found: C, 75.14; H, 5.48; N, 10.91. $C_{24}H_{21}N_3O_2$ requires C, 75.18; H, 5.52; N, 10.96%]; R_f (10% EtOAc/hexane) 0.35; IR (cm^{-1}, $CHCl_3$): 1743 (C═O); δ_H (300 MHz, $CDCl_3$) 8.51 (1H, br s, N*H*, D_2O exchangeable), 7.83 (1H, br s, N*H*, D_2O exchangeable), 7.51–5.89 (15H, m, Ph), 5.58 (1H, s, C4-*H*), 3.73 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 165.1, 156.4, 134.3, 131.0, 128.7, 128.4, 127.4, 127.0, 124.8, 119.8, 118.9, 118.7, 118.4, 114.4, 108.8, 108.7, 108.3, 105.8, 67.6, 63.1, 55.5.

4.5.24. 1-(4′-Methoxyphenyl)-3,3-bis(phenylthio)-4-phenylazetidin-2-one (11a). Colourless crystalline solid;

yield 29%; mp 118–120 °C; [Found: C, 71.54; H, 4.90; N, 2.94. $C_{28}H_{23}NO_2S_2$ requires C, 71.61; H, 4.95; N, 2.98%]; R_f (10% EtOAc/hexane) 0.55; IR (cm^{-1}, KBr): 1741(C═O); δ_H (300 MHz, $CDCl_3$) 7.68–6.73 (19H, m, Ph), 5.15 (1H, s, C4-*H*), 3.73 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 162.7, 156.3, 139.6, 139.1, 135.7, 134.9, 132.5, 130.5, 130.1, 128.5, 18.3, 128.1, 118.9, 114.2, 72.5, 67.0, 55.4; *m/z*: 469 (M^+).

4.5.25. 1-(4′-Methoxyphenyl)-3,3-bis(phenylthio)-4-(4′-methoxyphenyl)azetidin-2-one (11b). Yellow oil; yield 38%; [Found: C, 69.76; H, 4.98; N, 2.74. $C_{29}H_{25}NO_3S_2$ requires C, 69.72; H, 5.04; N, 2.80%]; R_f (10% EtOAc/hexane) 0.50; IR (cm^{-1}, $CHCl_3$): 1748 (C═O); δ_H (300 MHz, $CDCl_3$) 7.78–6.71 (18H, m, Ph), 5.12 (1H, s, C4-*H*), 3.75 (3H, s, OCH_3), 3.72 (3H, s, OCH_3).

4.5.26. 1-Benzyl-3,3-bis(phenylthio)-4-phenylazetidin-2-one (11c). Colourless crystalline solid; yield 16%; mp 134–136 °C; [Found: C, 74.09; H, 5.06; N, 3.04. $C_{28}H_{23}NOS_2$ requires C, 74.14; H, 5.11; N, 3.09%]; R_f (10% EtOAc/hexane) 0.55; IR (cm^{-1}, KBr): 1763 (C═O); δ_H (300 MHz, $CDCl_3$) 7.57–6.78 (20H, m, Ph), 4.80 (1H, d, *J* 15.1 Hz, CH_aH$_b$Ph), 4.62 (1H, s, C4-*H*), 3.90 (1H, d, *J* 15.0 Hz, CH$_a$$H_b$Ph); δ_C (75 MHz, $CDCl_3$) 166.1, 136.1, 134.8, 134.2, 132.7, 130.5, 130.1, 129.5,129.2, 128.7, 128.5, 128.3, 127.7, 73.0, 66.5, 44.6.

4.5.27. 1-(4′-Methoxyphenyl)-3,3-bis(benzylthio)-4-phenylazetidin-2-one (11d). White crystalline solid; yield 17%; mp 103–104 °C; [Found: C, 74.77; H, 5.62; N, 2.88. $C_{30}H_{27}NOS_2$ requires C, 74.81; H, 5.65; N, 2.91%]; R_f (10% EtOAc/hexane) 0.50; IR (cm^{-1}, KBr): 1755 (C═O); δ_H (300 MHz, $CDCl_3$) 7.29–6.65 (19H, m, Ph), 4.84 (1H, s, C4-*H*), 4.14 (2H, m, CH_2S), 3.84 (1H, d, *J* 11.7 Hz, CH_aH$_b$S), 3.67 (3H, s, OCH_3), 3.55 (1H, d, *J* 11.4 Hz, CH$_a$$H_b$S); δ_C (75 MHz, $CDCl_3$) 162.1, 156.4, 137.2, 136.3, 132.8, 130.6, 129.4, 129.4, 129.0, 128.7, 128.4, 128.3, 128.2, 127.3, 127.2, 118.8, 114.3, 71.3, 68.9, 55.2, 35.6, 34.7.

4.6. General procedure for Raney-nickel desulfurization

To a suspension of Raney-nickel (10 mmol, 100% activated) in dry acetone (10 mL) were added **9c/9d/9k/9t** (1 mmol). The suspension was refluxed for 1 h. The progress of reaction was checked by TLC. After disappearance of spot for starting β-lactam and appearance of new spot, suspension was filtered and acetone was evaporated in vacuo, extracted with methylene chloride (3×20 mL) and then dried (anhydrous Na_2SO_4). The residue so obtained was purified by silica gel column chromatography (10% EtOAc/hexane).

4.6.1. *cis*-1-Benzyl-3-(4′-methoxyphenyl)-4-phenylazetidin-2-one (12). Yellow oil; yield 53%; [Found: C, 80.50; H, 6.13; N, 4.04. $C_{23}H_{21}NO_2$ requires C, 80.46; H, 6.16; N, 4.09%]; IR (cm^{-1}, $CHCl_3$): 1742 (C═O); δ_H (300 MHz, $CDCl_3$) 7.30–6.60 (14H, m, Ph), 5.02 (1H, d, *J* 14.9 Hz, CH_aH$_b$Ph), 4.81 (1H, d, *J* 5.5 Hz, C3-*H*), 4.76 (1H, d, *J* 5.6 Hz, C4-*H*), 3.92 (1H, d, *J* 14.8 Hz, CH$_a$$H_b$Ph), 3.66 (3H, s, OC$H_3$); δ_C (75 MHz, $CDCl_3$) 168.5, 158.4, 135.5, 134.9, 129.8, 129.1, 128.8, 127.5, 126.5, 124.8, 113.5, 60.4, 59.9, 55.1, 44.7.

4.6.2. *cis*-1-Benzyl-3-(2′-methoxynaphthyl)-4-phenylazetidin-2-one (13). Yellow oil; yield 56%; [Found: C, 82.54; H, 5.26; N, 3.67. $C_{26}H_{20}NO_2$ requires C, 82.52; H, 5.32; N, 3.70%]; IR (cm^{-1}, $CHCl_3$): 1742 (C═O); δ_H (300 MHz, $CDCl_3$) 7.84–6.92 (16H, m, Ph), 5.26 (1H, d, *J* 5.5 Hz, C3-*H*), 5.05 (1H, d, *J* 15.0 Hz, CH_aH$_b$Ph), 4.97 (1H, d, *J* 5.7 Hz, C4-*H*), 4.16 (1H, d, *J* 14.8 Hz, CH$_a$$H_b$Ph), 3.86 (3H, s, OC$H_3$).

4.6.3. *cis*-1-(4′-Methoxyphenyl)-3-(2′,5′-dimethoxyphenyl)-4-phenylazetidin-2-one (14). White solid; yield 78%; mp 122–123 °C; [Found: C, 74.05; H, 5.89; N, 3.56. $C_{24}H_{23}NO_4$ requires C, 74.02; H, 5.95; N, 3.60%]; IR (cm^{-1}, $CHCl_3$): 1735 (C═O); δ_H (300 MHz, $CDCl_3$) 7.23–6.25 (12H, m, Ph), 5.27 (1H, d, *J* 6.0 Hz, C3-*H*), 5.00 (1H, d, *J* 5.7 Hz, C4-*H*), 3.65 (3H, s, OCH_3), 3.60 (3H, s, OCH_3), 3.44 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 165.2, 155.9, 153.0, 150.7, 134.7, 131.4, 128.8, 127.5, 127.2, 126.2, 122.0, 118.4, 115.2, 114.2, 113.3, 110.0, 96.1, 61.7, 60.2, 55.9, 55.3, 55.0.

4.6.4. *cis*-1-(4′-Methoxyphenyl)-3-(2′-furanyl)-4-phenylazetidin-2-one (15). White semisolid; yield 90%; [Found: C, 75.18; H, 5.27; N, 4.36. $C_{20}H_{17}NO_3$ requires C, 75.22; H, 5.36; N, 4.39%]; IR (cm^{-1}, $CHCl_3$): 1759 (C═O); δ_H (300 MHz, $CDCl_3$) 7.25–6.67 (9H, m, Ph), 6.97 (1H, dd, *J* 11.4, 11.4 Hz, $C_4H_aH_bH_c$O), 6.07 (1H, dd, *J* 0.9, 0.9 Hz, $C_4H_aH_bH_c$O), 6.00 (1H, dd, *J* 1.8, 1.8 Hz, $C_4H_aH_bH_c$O), 5.25 (1H, d, *J* 5.7 Hz, C3-*H*), 4.88 (1H, d, *J* 5.7 Hz, C4-*H*), 3.68 (3H, s, OCH_3); δ_C (75 MHz, $CDCl_3$) 156.2, 146.2, 142.5, 131.2, 128.3, 128.2, 126.9, 118.4, 114.4, 110.1, 109.8, 96.2, 59.7, 55.3, 54.7, 29.8.

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17. Crystal data for **10a**: monoclinic, $P2_1/n$, a=11.361(1), b=11.083(1), c=19.635(1) Å, β=92.33(1)°, V=2470.2(3) Å^3, Z=4, ρ_{calcd}=1.252 mg/m^3, μ(Mo Kα)=0.083 mm^{-1}, full matrix least-square on F^2, R_1=0.0493, wR_2=0.1102 for 2339 reflections [$I>2\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure **10a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292646.
18. Crystal data for **11a**: monoclinic, $C2/c$, a=16.546(1), b=12.185(1), c=24.07(2) Å, β=93.24(1)°, V=4845.1(3) Å^3, Z=8, ρ_{calcd}=1.288 mg/m^3, μ(Mo Kα)=1.288 mm^{-1}, full matrix least-square on F^2, R_1=0.0384, wR_2=0.1011 for 3147 reflections [$I>2\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure **11a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292647.
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20. Crystal data for **9j**: monoclinic, $P2_1/c$, a=10.546(1), b=21.341(2), c=12.501(1) Å, β=108.60(1)°, V=2666.5(4) Å^3, Z=4, ρ_{calcd}=1.289 mg/m^3, μ(Mo Kα)=0.157 mm^{-1}, full matrix least-square on F^2, R_1=0.0407, wR_2=0.1115 for 3655 reflections [$I>2\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure **9j** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292645.
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22. Crystal data for **9s**: triclinic, $P1^-$, a=9.784(1), b=11.675(1), c=11.905(1) Å, β=72.69(1)°, V=1262.7(2) Å^3, Z=2, ρ_{calcd}=1.282 mg/m^3, μ(Mo Kα)=0.164 mm^{-1}, full matrix least-square on F^2, R_1=0.0344, wR_2=0.0915 for 3511 reflections [$I>2\sigma(I)$]. Crystallographic data (excluding structure factors) for the structure **9s** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 292648.