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A New Synthetic Approach to Novel Spiro-β-lactams

Aman Bhalla,[a] Paloth Venugopalan,[a][‡] and Shamsher S. Bari*[a]

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An operationally simple and efficient approach for the synthesis of novel spiro-β-lactams is described. The key reaction is a halogen-mediated intrasulfenyl cyclization of a *cis*-3-benzylthio-3-(prop-2-ynyloxy/-enyloxy)-β-lactam procured through a Lewis acid-mediated C-3-alkylation of the *trans*-3-benzylthio-3-chloro-β-lactam carbocation equivalent.
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Introduction

After the discovery of clinically highly useful β-lactam antibiotics such as penicillins, cephalosporins and monobactams,[1] the past few decades have witnessed a remarkable growth in the field of β-lactam chemistry. Apart from being antibacterial agents, these compounds have been found to be useful synthons for the preparation of a variety of molecules of biological and medicinal interest.[2] Very recently, β-lactam antibiotics have been shown to offer neuroprotection by increasing expression of glutamate transporters through gene activation,[3] whilst in addition, the discoveries of new biologically active β-lactams such as cholesterol acyl transferase inhibitors,[4] thrombin inhibitors,[5] human cytomegalovirus protease inhibitors,[6] matrix-metalloprotease inhibitors,[7] human leukocyte elastase,[8] cysteine protease[9] and apoptosis inductors[10] have provided motivation for the development of new β-lactam systems. In particular, spirocyclic β-lactams have become centres of attraction as they behave as β-turn mimetics[11] and precursors of α,α-disubstituted β-amino acids.[12] In addition, the spiranic β-lactam moiety is also present in the chartellins, a family of marine natural products.[13] Among more specific examples of spiro-β-lactams, **I** has been found to be an inhibitor of both poliovirus and human rhinovirus 3C-proteinases,[14] **II** exhibits cholesterol absorption inhibiting activity,[15] whereas the proline-derived spiro-β-lactam **III** serves as an efficient β-turn nucleator (Figure 1).[16]

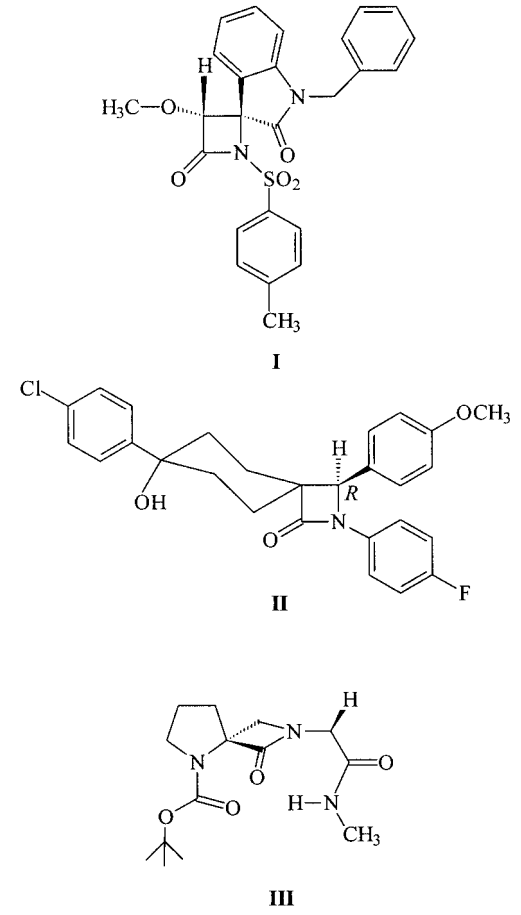

Figure 1. Biologically active spiro-β-lactams.

Several syntheses of spiro-β-lactams have been described in the literature,[17] and many researchers have in recent years accomplished the synthesis of spiro-β-lactams through cycloaddition reactions employing different ketenes and imines.[18] Recently, Alcaide et al.[19] have developed a metal-assisted synthesis of enantiopure spirocyclic

[a] Department of Chemistry, Panjab University, Chandigarh 160014, U.T., India
Fax: +91-172-2545074
E-mail: ssbari@pu.ac.in
[‡] Present address: Laboratorium für Chem. und Min. Kristallographie, Universität Bern, Freiestrasse 3, 3012 Bern, Switzerland
E-mail: venu@krist.unibe.ch
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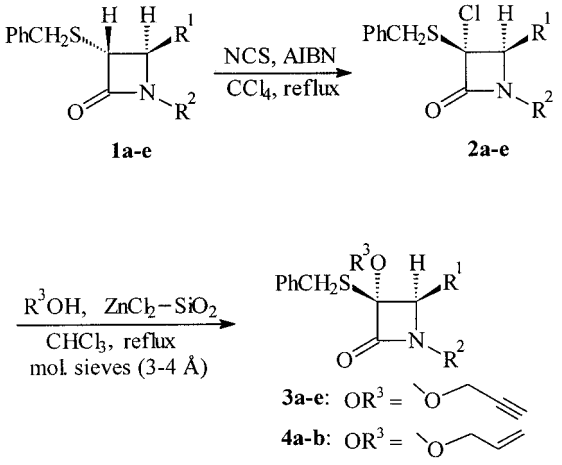
β-lactams from azetidin-2-ones. In view of the ever growing applications of spiro-β-lactams, ranging from their biological activity to their utility as synthetic intermediates in organic synthesis, we envisaged syntheses of novel spiro-β-lactams through halogen-mediated intrasulfenyl additions to alkynes/alkenes through the use of *cis*-3-(prop-2-ynyloxy/-enyloxy)-β-lactams (**3**, **4**; Scheme 1). Such spiro-β-lactams are not easily accessible by the classical ketene-imine cycloaddition, the Staudinger reaction, whilst it is well known that intramolecular addition of a heteronucleophile to a carbon–carbon double or triple bond in the presence of an electrophilic reagent is one of the most fundamental methods for construction of heterocyclic rings.[20] Thus, in continuation to our efforts relating to the C-3 functionalization of β-lactams through the use of β-lactam carbocation equivalents of type **2**,[21–26] we report here a novel, operationally simple and efficient approach for the synthesis of spiro-β-lactams.



Scheme 1. Synthesis of *cis*-3-benzylthio-3-(prop-2-ynyloxy/-enyloxy)azetidin-2-ones **3** and **4**.

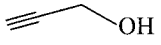
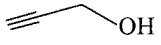
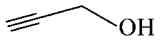
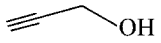
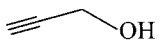
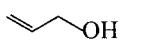
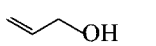
Results and Discussion

The β-lactams **1a**–**e** required for this study were prepared from benzylthioethanoic acid and the appropriate Schiff's bases by the reported procedure.[24,27] Furthermore, the *trans*-3-benzylthio-3-chloroazetidin-2-ones **2a**–**e**, the appropriate β-lactam carbocation equivalents, were obtained by stereospecific chlorination of **1a**–**e** by treatment with *N*-chlorosuccinimide (NCS) in the presence of catalytic amounts of AIBN by the reported procedure.[24–25] On treatment[25,27] with propargyl alcohol or allyl alcohol in the presence of $ZnCl_2/SiO_2$ in chloroform at reflux, these β-lactam carbocation equivalents **2a**–**e** afforded the *cis*-3-benzylthio-3-(prop-2-ynyloxy/-enyloxy)azetidin-2-ones **3a**–**e** and **4a**–**b**, considered potentially capable of undergoing halogen-mediated intrasulfenyl cyclization reactions (Scheme 1, Table 1).

The structures of the *cis*-3-(prop-2-ynyloxy/-enyloxy)-β-lactams **3a**–**e** and **4a**–**b** were established spectroscopically, by IR, ^{1}H NMR, ^{13}C NMR, and DEPT 135 ^{13}C NMR techniques. However, the stereochemistry of **3** and **4** at C-3 was tentatively assigned as *cis*, in view of the structure assignment of *cis*-3-benzylthio-3-methoxyazetidin-2-ones in single-crystal X-ray crystallographic studies.[25]

The initial studies of halogen-mediated intrasulfenyl addition reactions were carried out by treatment of *cis*-3-(prop-2-ynyloxy)-β-lactam (**3a**) with one equiv. of iodine in dichloromethane at room temperature. The reaction resulted in the exclusive formation of the five-membered ring, affording a spiro product 7-iodomethylene-2-(4-methoxyphenyl)-3-phenyl-5-oxa-8-thia-2-azaspiro[3.4]octan-1-one (**5a**). To investigate the role of halogen and selectivity in product formation, this reaction was performed with replacement of the iodine with bromine, resulting in a similar product profile, although it was observed that with bromine

Table 1. *cis*-3-Benzylthio-3-(prop-2-ynyloxy/-enyloxy)azetidin-2-ones **3a**–**e** and **4a**–**b**.

Entry	Substrate **2**	R^3OH	R^1	R^2	Product	% Yield[a]
1	**2a**		Ph	4-MeO-C_6H_4	**3a**	76
2	**2b**		4-MeO-C_6H_4	4-MeO-C_6H_4	**3b**	57
3	**2c**		Ph	Ph	**3c**	74
4	**2d**		Ph	4-Cl-C_6H_4	**3d**	71
5	**2e**		4-Cl-C_6H_4	4-Me-C_6H_4	**3e**	54
6	**2a**		Ph	4-MeO-C_6H_4	**4a**	84
7	**2b**		4-MeO-C_6H_4	4-MeO-C_6H_4	**4b**	62

[a] Yields quoted are for the isolated products characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy.

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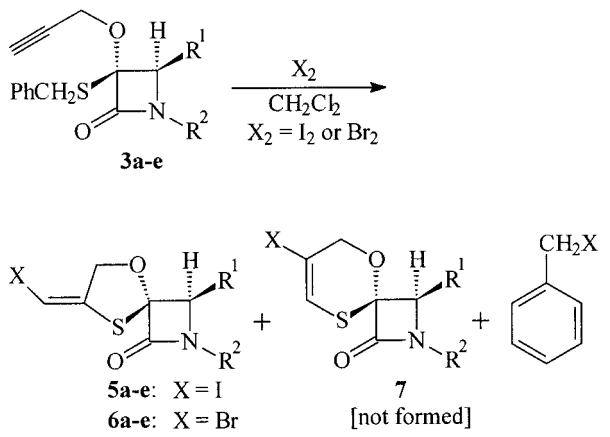
the reaction proceeded more slowly, giving a lower yield of product than had been obtained in the reaction using iodine. The reaction was found to be general with several substrates (Scheme 2), and the results are summarized in Table 2.



Scheme 2. Synthesis of spiro-β-lactams **5a**–**e** and **6a**–**e**.

Table 2. Spiroazetidin-2-ones **5a**–**e** and **6a**–**e**.

Entry	Substrate			Product (% yield)[a]	
	3	R^1	R^2	**5** (X = I)	**6** (X = Br)
1	**3a**	Ph	4-MeO-C_6H_4	**5a** (81)	**6a** (74)
2	**3b**	4-MeO-C_6H_4	4-MeO-C_6H_4	**5b** (65)	**6b** (54)
3	**3c**	Ph	Ph	**5c** (69)	**6c** (61)
4	**3d**	Ph	4-Cl-C_6H_4	**5d** (70)	**6d** (69)
5	**3e**	4-Cl-C_6H_4	4-Me-C_6H_4	**5e** (61)	**6e** (46)

[a] Yields quoted are for the isolated products characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

The structures of spiro-β-lactams **5a**–**e** and **6a**–**e** were established by spectroscopic means such as IR, ^{1}H NMR, MS, ^{13}C NMR, DEPT 135 ^{13}C NMR, proton-proton COSY (^{1}H,^{1}H COSY), and proton-carbon COSY (^{1}H,^{13}C COSY). Finally, the exclusive formation of the five-membered ring cycloadducts and the stereochemistry at the C-3 spiro junctions in **5a**–**e** and **6a**–**e** were established through single-crystal X-ray crystallographic analysis of **6d** (Figure 2).

A plausible mechanism for the formation of the five-membered ring spiro-β-lactams is presented in Scheme 3, with the substrate **3** cyclizing to give exclusively the five-membered ring cycloadduct by a 5-*exo* ring-closure process, rather than 6-*endo* ring-closure. The 5-*exo*-*dig* cyclizations appear to be kinetically controlled and are believed to proceed through the addition of a nucleophilic sulfur to electrophilically activated triple/double bonds.[28] The reaction first involves the coordination by halogen to the triple bond of β-lactam **3** to produce a π complex (**A**). Subsequently, nucleophilic addition of the sulfide centre to the halogen-olefin complex gives the cyclic sulfonium ion (**C**), which undergoes further dealkylation by halide ion to produce benzyl halide and the five-membered ring spiro[3.4]-β-lactams **5** and **6**. The faster rate of ring-closure for the 5-*exo*-*dig* pathway than for the 6-*endo*-*dig* mode may, in part, be

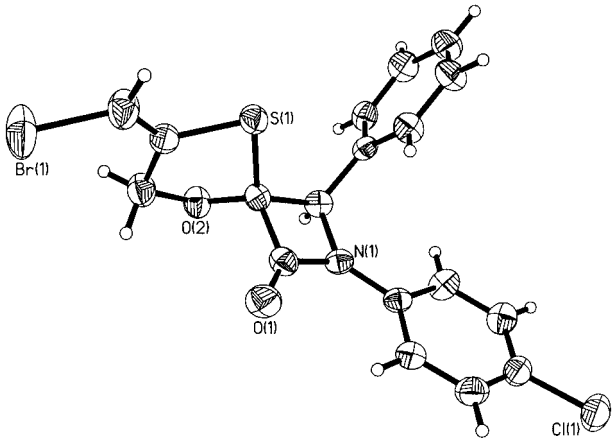


Figure 2. An ORTEP view of compound **6d**.

due to the internal *p*-lobe of the acetylene-X_2 π complex (**B**) having a more favourable alignment with the lone pair of the incoming sulfur nucleophile. No six-membered ring regioadducts are formed in these halogen-mediated intrasulfenyl reactions of alkynyloxy substrates **3a**–**e**, which is reasonable to accept, since equilibrium between five- and six-membered ring isomers (**5**, **6** and **7**) would necessarily proceed through an unsaturated episulfonium intermediate (**D**), which is quite unlikely to be formed (Scheme 3).

In continuation of this study, we further examined the behaviour of the *cis*-3-benzylthio-3-(prop-2-enyloxy)azetidin-2-ones **4a**–**b** under the same conditions as described above (Scheme 4). Initially, **4a** was treated with one equiv. of bromine in dichloromethane at room temperature, resulting in the formation of a mixture of two diastereomeric five-membered ring spiro-β-lactams **8a** and **9a** as the major products, along with a single isomer of the six-membered ring spiro-β-lactam **10a** as a minor one.

Furthermore, the major isomeric cyclized five-membered ring adducts **8a** and **9a** were formed in 1:1 ratio, as was evident from ^{1}H NMR spectroscopy. One of the isomers – **8a** – crystallized in pure form from dichloromethane/hexanes and was identified as 7α-bromomethyl-2-(4-methoxyphenyl)-3-phenyl-5-oxa-8-thia-2-azaspiro[3.4]octan-1-one, whereas the other isomer **9a** remained as a liquid product and was identified as 7β-bromomethyl-2-(4-methoxyphenyl)-3-phenyl-5-oxa-8-thia-2-azaspiro[3.4]octan-1-one. Similar results were obtained with iodine as the halogenating reagent, although the reaction proceeded very slowly relative to the bromination reaction. The reaction was also found to give the same profile of products with the other substrate **4b** and results are summarized in Table 3.

The isomeric spiro-β-lactams **8** and **11** were separated by crystallization, whereas the other isomeric spiro-β-lactams **9** and **12** remained as liquids. The six-membered spiro-β-lactams **10** and **13** were easily separated by chromatography and the structures of the spiro-β-lactams **8**–**13**(**a**–**b**) were established by spectroscopic techniques such as IR, ^{1}H NMR, MS, ^{13}C NMR, DEPT 90 ^{13}C NMR, DEPT 135 ^{13}C NMR, proton–proton COSY (^{1}H,^{1}H COSY) and heteronuclear single quantum correlation (HSQC). In addition,

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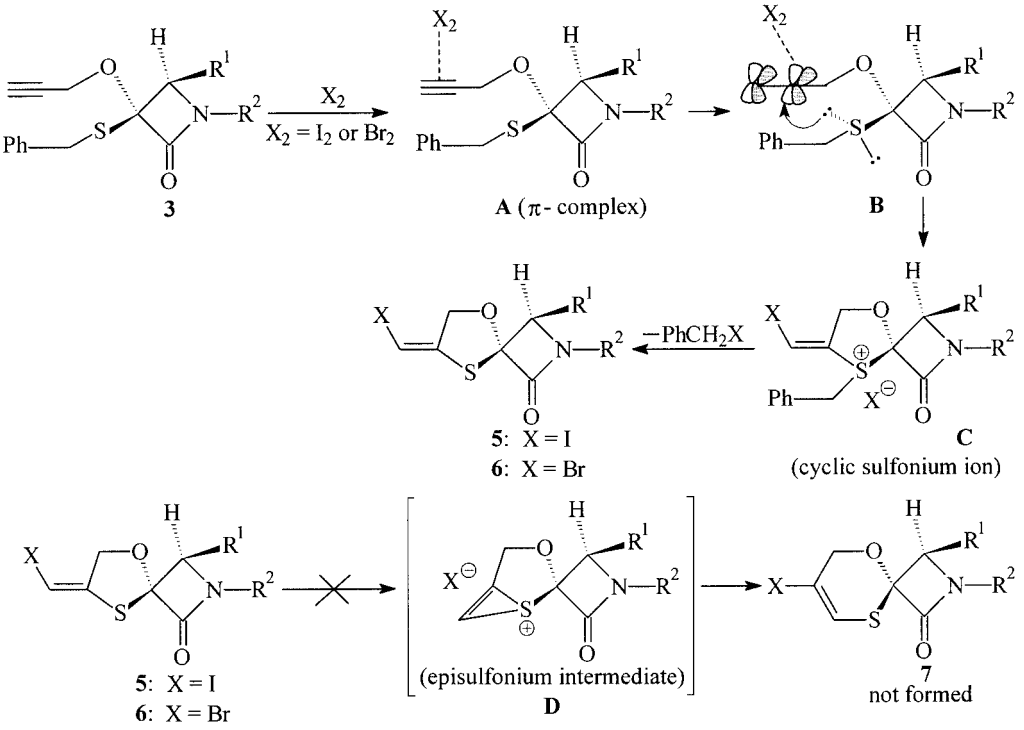
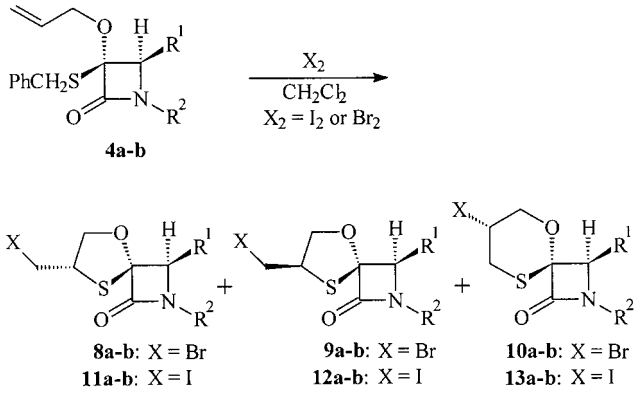


Scheme 3. Plausible mechanism for the formation of spiro-β-lactams **5a–e** and **6a–e**.



Scheme 4. Synthesis of spiroazetidin-2-ones **8a–b** to **13a–b**.

double irradiation studies and NOE measurements confirmed the assignments made. The formation of five-membered ring spiro-β-lactams and the stereochemical assignments at the C-7 and C-3 spiro junctions in **8** and **11** were established by single-crystal X-ray crystallographic analysis of **8a** (Figure 3). The geometries of the **9** and **12** epimers were tentatively assigned by comparison of their data with those relating to **8** and **11**, respectively, whilst the steric arrangements of the six-membered ring spiro-β-lactams **10** and **13** were tentatively assigned on the basis of various NMR spectral studies.

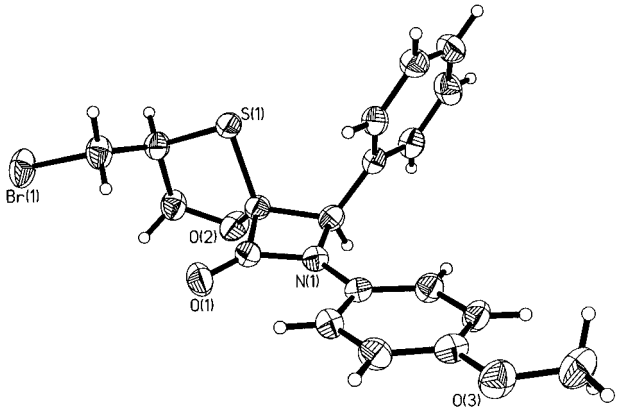


Figure 3. An ORTEP view of compound **8a**.

The formation of five- and six-membered ring spiro-β-lactams in this case can be explained by the plausible

Table 3. Synthesis of spiroazetidin-2-ones **8a–b** to **13a–b**.

Entry	Substrate **4**	X_2	R^1	R^2	Five-membered ring cycloadduct α-isomer (% yield)[a]	β-isomer (% yield)[a]	Six-membered ring cycloadduct α-isomer (% yield)[a]
1	**4a**	Br_2	Ph	4-MeO-C_6H_4	**8a** (35)	**9a** (32)	**10a** (16)
2	**4b**	Br_2	4-MeO-C_6H_4	4-MeO-C_6H_4	**8b** (27)	**9b** (25)	**10b** (12)
3	**4a**	I_2	Ph	4-MeO-C_6H_4	**11a** (31)	**12a** (29)	**13a** (13)
4	**4b**	I_2	4-MeO-C_6H_4	4-MeO-C_6H_4	**11b** (24)	**12b** (21)	**13b** (10)

[a] Yields quoted are for the isolated products characterized by IR, ^{1}H NMR, ^{13}C NMR and MS.

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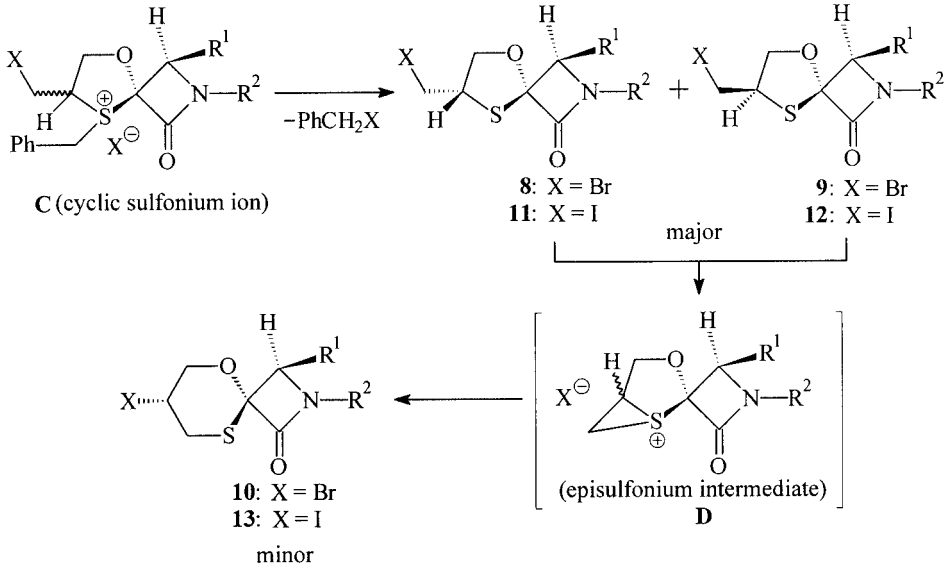

Scheme 5. Plausible reaction pathway for the formation of spiro-β-lactams **8a**–**b** to **13a**–**b**.

mechanism presented in Scheme 5. The reaction is believed to proceed by a similar pathway as for the spiro-β-lactams **5** and **6**.

The formation of the five-membered ring spiro[3.4]-β-lactams **8** as major products suggests that the difference in the thermodynamic stabilities of the five- and six-membered ring cycloadducts must be significantly large to force the equilibrium in the direction of the five-membered ring. It would appear that the exocyclic positioning of the halomethyl moiety on the five-membered ring is energetically more favourable than having the halo group on the six-membered ring cycloadduct. It is further believed that the attack of the halogen on the episulfonium intermediate (**D**) occurs from the less hindered side, avoiding any steric repulsion with the phenyl group on C-4, thus favouring the formation of the α-isomer of the six-membered ring spiro[3.5]-β-lactam.

These studies have revealed some interesting features of the halocyclization reactions of *cis*-3-alkoxy-β-lactams **3** and **4**. The regio- and stereochemistries of the products formed after the intramolecular addition of the heteronucleophile depend on the type of unsaturation within the substrate. Initiated by a halogen, the alkynyloxy and alkenyloxy sulfides cyclize to give the five-membered ring products by a 5-*exo*-ring closure process. The regiospecificities of these ring closures may in part be due to a kinetic preference for formation of the five-membered rings; these results are consistent with observations reported by Turos et al.[28] Moreover, the type of unsaturation in the substrate dictates which halogenating reagent should be used as the initiating agent. For alkynyloxy sulfide cyclizations, iodine generally gives better results than bromine because the iodocycloadducts are stable to the reaction conditions and can be obtained in quantitative yields. On the other hand, bromine is preferred over iodine for promoting the cyclization of alkenyloxy sulfides because the bromination reaches completion more rapidly.

Conclusion

In conclusion, a facile route to novel spiro-β-lactams through intramolecular halogen-mediated cyclization reactions of *cis*-3-benzylthio-3-(prop-2-ynyloxy/-enyloxy)azetidin-2-ones has been developed. Furthermore, the alkynyloxy sulfide ring closures result in the exclusive formation of five-membered ring spiro[3.4]-β-lactams, whereas alkenyloxy sulfide ring closures result in the formation of mixtures of five-membered ring spiro[3.4]-β-lactams as the major products along with six-membered ring spiro[3.5]-β-lactams as minor products.

Experimental Section

General: Compounds **1a**–**e**, **2a**–**e**,[24] **3a**–**e** and **4a**–**b**[25] were prepared as described previously. Spectroscopic data for compounds **1a**–**b** and **2a**–**b**[24] were reported previously. NMR spectra were recorded on Jeol 300 and Bruker Avance II 400 spectrometers. Chemical shifts are given in ppm 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 measured on a Perkin–Elmer 430 FTIR spectrometer. MS spectra were recorded on a Shimadzu GCMS-QT 5000 instrument and elemental analyses (C,H,N) were performed on a Perkin–Elmer 2400 elemental analyzer. Column chromatography was carried out on silica gel (60–120 mesh, Merck). Thin-layer chromatography (TLC) was performed on silica gel G (Merck). For visualization, TLC plates were stained with iodine vapour. Melting points are uncorrected. All commercially available compounds/reagents were used without further purification. Dichloromethane, carbon tetrachloride and chloroform, distilled over P_2O_5, were redistilled over CaH_2 before use.

***trans*-3-Benzylthio-1,4-diphenylazetidin-2-one (1c):** Yield 1.500 g (40%), white solid flakes, m.p. 136–137 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–7.00 (m, 15 H, ArH), 4.51 (d, J = 2.1 Hz, 1 H, C3-H), 3.95 (d, J = 4.8 Hz, 2 H, CH_2S), 3.85 (d, J = 2.4 Hz, 1 H, C4-H) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.1, 137.4, 136.8, 129.6, 129.3, 129.1 (2), 128.9, 128.6, 128.5, 128.3, 128.2, 128.1, 127.6, 127.2, 125.7, 123.9, 117.1, 63.0, 58.9, 35.2 ppm.

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IR (KBr): $\tilde{\nu}_{max}$ = 1739 (C=O) cm^{-1}. $C_{22}H_{19}NOS$ (345.37): calcd. C 76.49, H 5.54, N 4.05; found C 76.31, H 5.43, N 3.99.

***trans*-3-Benzylthio-3-chloro-1,4-diphenylazetidin-2-one (2c):** Yield 0.350 g (53%), white solid flakes, m.p. 147–148 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.37–7.06 (m, 15 H, ArH), 5.42 (s, 1 H, C4-H), 4.29 (d, J = 11.4 Hz, 1 H, CH_aH_bS), 3.99 (d, J = 11.2 Hz, 1 H, CH_aH_bS) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 160.3, 136.7, 135.5, 131.5 (2), 129.7, 129.5 (2), 129.3 (2), 128.6 (2), 128.5, 127.9 (2), 127.5 (2), 124.8, 117.8 (2), 113.8, 80.7, 71.5, 34.9 ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1769 (C=O) cm^{-1}. $C_{22}H_{18}ClNOS$ (379.89): calcd. C 69.56, H 4.77, N 3.69; found: C 69.45, H 4.68, N 3.62.

***cis*-3-Benzylthio-1-(4-methoxyphenyl)-4-phenyl-3-(prop-2-ynyloxy)-azetidin-2-one (3a):** Yield 0.040 g (76%), brownish-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.35–6.69 (m, 14 H, ArH), 5.34 (s, 1 H, C4-H), 4.50 (dd, J = 2.4, 2.4 Hz, 1 H, CH_aH_bO), 4.22 (dd, J = 2.7, 2.4 Hz, 1 H, CH_aH_bO), 3.87 (d, J = 12.2 Hz, 1 H, CH_aH_bS), 3.71 (s, 3 H, OCH_3), 3.69 (d, J = 12.2 Hz, 1 H, CH_aH_bS), 2.47 (t, 1 H, HC≡) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 161.2, 156.4, 137.4, 133.1, 130.5, 129.2, 128.9, 128.4, 128.1, 127.0, 119.0, 114.4, 98.2, 79.9, 75.4, 67.7, 55.1, 52.8, 32.4 ppm. ^{13}C NMR (DEPT 135) (75.5 MHz, $CDCl_3$): δ = 129.2 (+), 128.9 (+), 128.4 (+), 128.1 (+), 127.0 (+), 119.0 (+), 114.4 (+), 79.9 (+), 75.4 (+), 67.7 (+), 55.1 (+), 52.8 (–), 32.4 (–) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1760 (C=O) cm^{-1}. $C_{26}H_{23}NO_3S$ (429.51): calcd. C 72.71, H 5.39, N 3.26; found: C 72.67, H 5.33, N 3.29.

***cis*-3-Benzylthio-1-(4′-methoxyphenyl)-4-phenyl-3-(prop-2-enyloxy)-azetidin-2-one (4a):** Yield 0.044 g (84%), yellowish-white solid, m.p. 70–71 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.31–6.70 (m, 14 H, ArH), 5.92–5.81 (m, 1 H, H_2C=C*H*–), 5.37–5.30 (m, 1 H, CH_aH_bO), 5.21–5.17 (m, 1 H, CH_aH_bO), 5.10 (s, 1 H, C4-H), 4.42–4.35 (m, 1 H, H_bH_aC=CH–), 4.26–4.19 (m, 1 H, H_bH_aC=CH–), 3.88 (d, J = 12.3 Hz, 1 H, CH_aH_bS), 3.70 (s, 3 H, OCH_3), 3.66 (d, J = 12.3 Hz, 1 H, CH_aH_bS) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 162.3, 156.3, 137.2, 133.3, 133.2, 132.6, 130.2, 129.1, 128.9, 128.4, 128.2, 127.9, 127.0, 119.0, 117.8, 114.3, 77.2, 68.0, 66.3, 55.4, 32.2, 28.0 ppm. ^{13}C NMR (DEPT 135) (75.5 MHz, $CDCl_3$): δ = 130.2 (+), 129.1 (+), 128.9 (+), 128.4 (+), 128.2 (+), 127.9 (+), 127.0 (+), 119.0 (+), 117.8 (–), 114.3 (+), 68.0 (+), 66.3 (–), 55.4 (+), 32.2 (–), 28.0 (+) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1762 (C=O) cm^{-1}. $C_{26}H_{25}NO_3S$ (431.53): calcd. C 72.36, H 5.83, N 3.24; found: C 72.27, H 5.79, N 3.21.

Preparation of Spiro-β-lactams 5-13. General Procedure: Iodine/bromine (1.2 mmol) was added at room temperature to a stirred solution of the *cis*-3-(prop-2-ynyloxy)-β-lactam **3** or the *cis*-3-(prop-2-enyloxy)-β-lactam **4** (1.0 mmol) in dry dichloromethane (10 mL). The reaction mixture was stirred for 4–7 h, the progress of the reaction being monitored by TLC. After TLC indicated complete consumption of the starting substrate, the reaction mixture was poured into aqueous 5% $Na_2S_2O_3$/5% $Na_2S_2O_5$ solution (10 mL) and stirred until the purplish coloration of iodine/reddish coloration of bromine dissipated. The aqueous mixture was extracted with dichloromethane (3 × 10 mL) and the combined organic layer was washed with brine (2 × 5 mL) and dried with anhydrous Na_2SO_4. After evaporation of the solvent under vacuum, the residue was purified by column chromatography on silica gel in hexanes/ethyl acetate (93:7).

7-Iodomethylene-2-(4-methoxyphenyl)-3-phenyl-5-oxa-8-thia-2-aza-spiro[3.4]octan-1-one (5a): Yield 0.044 g (81%), white solid flakes, m.p. 128–129 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.25–6.69 (m, 9 H, ArH), 5.74 (t, 1 H, ICH), 5.23 (s, 1 H, C3-H), 4.79 (dd, J = 2.1, 2.4 Hz, 1 H, CH_aH_bO), 4.75 (dd, J = 2.4, 2.1 Hz, 1 H, CH_aH_bO), 3.73 (s, 3 H, OCH_3) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 163.0, 156.7, 142.5, 134.0, 130.1, 129.4, 129.1, 126.5, 119.0, 114.4, 106.7, 79.5, 67.5, 58.5, 55.2 ppm. ^{13}C NMR (DEPT 135) (75.5 MHz, $CDCl_3$): δ = 129.4 (+), 129.1 (+), 126.5 (+), 119.0 (+), 114.4 (+), 79.5 (–), 67.5 (+), 58.5 (+), 55.2 (+) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1754 (C=O) cm^{-1}. MS (70eV, EI): *m*/*z*: 465 (29) $[M]^+$, 316 (100), 211 (65), 196 (55), 189 (24), 167 (26), 161 (22), 149 (9), 128 (31), 118 (68), 90 (46), 77 (24), 45 (48). $C_{19}H_{16}INO_3S$ (465.29): calcd. C 49.05, H 3.46, N 3.01; found: C 48.98, H 3.39, N 2.93.

7-Bromomethylene-2-(4-chlorophenyl)-3-phenyl-5-oxa-8-thia-2-aza-spiro[3.4]octan-1-one (6d): Yield 0.037 g (69%), colourless, crystalline solid, m.p. 142–143 °C (dec.). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.44–7.19 (m, 9 H, ArH), 5.81 (t, 1 H, BrCH), 5.27 (s, 1 H, C3-H), 4.93 (dd, J = 2.4, 2.4 Hz, 1 H, CH_aH_bO), 4.84 (dd, J = 2.7, 2.4 Hz, 1 H, CH_aH_bO) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 163.5, 138.7, 135.2, 133.6, 130.1, 129.7, 129.4, 129.3, 126.5, 118.9, 106.2, 90.6, 76.2, 67.2 ppm. ^{13}C NMR (DEPT 135) (75.5 MHz, $CDCl_3$): δ = 129.7 (+), 129.4 (+), 129.3 (+), 126.5 (+), 118.9 (+), 90.6 (+), 76.2 (–), 67.2 (+) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1771 (C=O) cm^{-1}. $C_{18}H_{13}BrClNO_2S$ (422.71): calcd. C 51.14, H 3.10, N 3.31; found: C 51.06, H 3.03, N 3.24.

7α-Bromomethyl-2-(4-methoxyphenyl)-3-phenyl-5-oxa-8-thia-2-aza-spiro[3.4]octan-1-one (8a): Yield 0.022 g (35%), colourless, crystalline solid, m.p. 148–149 °C (dec.). R_f (**8a**) = 0.40, R_f (**4a**) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–6.78 (m, 9 H, ArH), 5.24 (s, 1 H, C3-H), 4.52 (dd, J = 1.8, 1.5 Hz, 1 H, $CH_\alpha H_\beta O$), 4.16–4.12 (m, 1 H, $CH_\alpha H_\beta O$), 3.80–3.74 (m, 1 H, $CH_\beta S$), 3.74 (s, 3 H, OCH_3), 3.72 (dd, J = 1.8, 1.5 Hz, 1 H, $BrCH_\alpha H_\beta$), 3.54–3.52 (m, 1 H, $BrCH_\alpha H_\beta$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3, 156.6, 134.5, 130.1, 129.2, 129.1, 126.8, 119.3, 114.5, 103.5, 75.5, 70.0, 55.5, 50.8, 33.1 ppm. ^{13}C NMR (DEPT 135) (100 MHz, $CDCl_3$): δ = 129.2 (+), 129.1 (+), 126.8 (+), 119.3 (+), 114.5 (+), 75.5 (–), 70.0 (+), 55.5 (+), 50.8 (+), 33.1 (–) ppm. ^{13}C NMR (DEPT 90) (100 MHz, $CDCl_3$): δ = 129.2 (+), 129.1 (+), 126.8 (+), 119.3 (+), 114.5 (+), 70.0 (+), 50.8 (+) ppm. IR (KBr): $\tilde{\nu}_{max}$ = 1752 (C=O) cm^{-1}. MS (70eV, EI): *m*/*z*: 421 (31), 419 (20) $[M]^+$, 272 (100), 271 (97), 211 (75), 196 (57), 167 (17), 121 (28), 118 (78), 90 (25), 88 (19), 77 (21), 73 (44), 44 (33), 41 (97). $C_{19}H_{18}NO_3BrS$ (420.30): C 54.30, H 4.31, N 3.33; found: C 54.23, H 4.25, N 3.29.

7β-Bromomethyl-2-(4-methoxyphenyl)-3-phenyl-5-oxa-8-thia-2-aza-spiro[3.4]octan-1-one (9a): Yield 0.020 g (32%), yellow oil. R_f (**9a**) = 0.40, R_f (**4a**) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–6.77 (m, 9 H, ArH), 5.25 (s, 1 H, C3-H), 4.53 (dd, J = 1.8, 1.5 Hz, 1 H, $CH_\alpha H_\beta O$), 4.40–4.37 (m, 1 H, $CH_\alpha H_\beta O$), 3.83–3.81 (m, 1 H, $CH_\alpha S$), 3.75–3.74 (m, 1 H, $BrCH_\alpha H_\beta$), 3.74 (s, 3 H, OCH_3), 3.21 (dd, J = 1.8, 1.5 Hz, 1 H, $BrCH_\alpha H_\beta$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.2, 156.6, 135.1, 130.3, 129.1, 126.6, 119.1, 114.4, 104.0, 74.9, 68.2, 55.2, 49.6, 32.9 ppm. ^{13}C NMR (DEPT 135) (100 MHz, $CDCl_3$): δ = 129.1 (+), 126.6 (+), 119.1 (+), 114.4 (+), 74.9 (–), 68.2 (+), 55.2 (+), 49.6 (+), 32.9 (–) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1765 (C=O) cm^{-1}. $C_{19}H_{18}BrNO_3S$ (420.30): C 54.30, H 4.31, N 3.33; found: C 54.19, H 4.22, N 3.24.

7α-Bromo-2-(4-methoxyphenyl)-3-phenyl-5-oxa-9-thia-2-azaspiro-[3.5]nonan-1-one (10a): Yield 0.010 g (16%), white solid flakes, m.p. 146–147 °C (dec.). R_f (**10a**) = 0.50, R_f (**4a**) = 0.45. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–6.74 (m, 9 H, ArH), 4.90 (s, 1 H, C3-H), 4.61 (t, 1 H, $CH_\alpha H_\beta O$), 4.34–4.24 (m, 1 H, $BrCH_\beta$), 4.20–4.14 (m, 1 H, $CH_\alpha H_\beta O$), 3.90 (t, 1 H, $CH_\alpha H_\beta S$), 3.72 (s, 3 H, OCH_3), 2.98–2.92 (m, 1 H, $CH_\alpha H_\beta S$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 162.4, 156.5, 132.0, 130.3, 129.4, 128.6, 127.6, 118.9, 114.5, 91.4, 71.1, 67.6, 55.2, 43.0, 32.9 ppm. ^{13}C NMR (DEPT 135) (100 MHz, $CDCl_3$): δ = 129.4 (+), 128.6 (+), 127.6 (+), 118.9 (+), 114.5 (+), 71.1 (–), 67.6 (+), 55.2 (+), 43.0 (+), 32.9 (–) ppm. IR

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($CHCl_3$): $\tilde{\nu}_{max}$ = 1756 (C=O) cm^{-1}. $C_{19}H_{18}BrNO_3S$ (420.30): C 54.30, H 4.31, N 3.33; found: C 54.18, H 4.20, N 3.26.

7α-Iodomethyl-2-(4-methoxyphenyl)-3-phenyl-5-oxa-8-thia-2-azaspiro[3.4]octan-1-one (11a): Yield 0.020 g (31%), white solid flakes, m.p. 159–160 °C (dec.). R_f (**11a**) = 0.42, R_f (**4a**) = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–6.75 (m, 9 H, ArH), 5.19 (s, 1 H, C3-H), 4.83 (dd, J = 1.8, 1.5 Hz, 1 H, $CH_\alpha H_\beta O$), 4.23–4.20 (m, 1 H, $CH_\alpha H_\beta O$), 3.84–3.78 (m, 1 H, $CH_\beta S$), 3.75 (s, 3 H, OCH_3), 3.73 (dd, J = 1.8, 1.8 Hz, 1 H, $ICH_\alpha H_\beta$), 3.43–3.39 (m, 1 H, $ICH_\alpha H_\beta$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.5, 156.4, 134.7, 134.4, 130.0, 129.1, 126.6, 119.1, 114.3, 103.6, 77.4, 69.8, 55.3, 51.0, 29.1 ppm. ^{13}C NMR (DEPT 135) (75.5 MHz, $CDCl_3$): δ = 129.1 (+), 126.6 (+), 119.1 (+), 114.3 (+), 77.4 (–), 69.8 (+), 55.3 (+), 51.0 (+), 29.1 (–) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1763 (C=O) cm^{-1}. $C_{19}H_{18}NO_3IS$ (467.30): C 48.83, H 3.87, N 2.99; found: C 48.77, H 3.82, N 2.92.

7β-Iodomethyl-2-(4-methoxyphenyl)-3-phenyl-5-oxa-8-thia-2-azaspiro[3.4]octan-1-one (12a): Yield 0.018 g (29%), yellow oil. R_f (**12a**) = 0.42, R_f (**4a**) = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.41–6.75 (m, 9 H, ArH), 5.21 (s, 1 H, C3-H), 4.43 (dd, J = 1.4, 1.4 Hz, 1 H, $CH_\alpha H_\beta O$), 4.12–4.09 (m, 1 H, $CH_\alpha H_\beta O$), 3.94–3.88 (m, 1 H, $CH_\alpha S$), 3.75 (s, 3 H, OCH_3), 3.69–3.62 (m, 1 H, $ICH_\alpha H_\beta$), 3.01 (dd, J = 1.8, 1.5 Hz, 1 H, $ICH_\alpha H_\beta$) ppm. ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 164.3, 156.4, 134.8, 134.3, 130.1, 129.0, 126.6, 119.0, 114.3, 104.2, 77.1, 68.5, 55.1, 50.0, 28.9 ppm. ^{13}C NMR (DEPT 135) (75.5 MHz, $CDCl_3$): δ = 129.0 (+), 126.6 (+), 119.0 (+), 114.3 (+), 77.1 (–), 68.5 (+), 55.1 (+), 50.0 (+), 28.9 (–) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1768 (C=O) cm^{-1}. $C_{19}H_{18}INO_3S$ (467.30): C 48.83, H 3.87, N 2.99; found: C 48.71, H 3.75, N 2.86.

7α-Iodo-2-(4-methoxyphenyl)-3-phenyl-5-oxa-9-thia-2-azaspiro[3.5]-nonan-1-one (13a): Yield 0.008 g (13%), colourless oil. R_f (**13a**) = 0.55, R_f (**4a**) = 0.45. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.27–6.68 (m, 9 H, ArH), 4.81 (s, 1 H, C3-H), 4.70 (t, 1 H, $CH_\alpha H_\beta O$), 4.45–4.36 (m, 1 H, ICH_β), 4.19–4.14 (m, 1 H, $CH_\alpha H_\beta O$), 4.01 (t, 1 H, $CH_\alpha H_\beta S$), 3.68 (s, 3 H, OCH_3), 2.99-2.93 (m, 1 H, $CH_\alpha H_\beta S$) ppm. IR ($CHCl_3$): $\tilde{\nu}_{max}$ = 1757 (C=O) cm^{-1}. $C_{19}H_{18}INO_3S$ (467.30): C 48.83, H 3.87, N 2.99; found: C 48.73, H 3.79, N 2.89.

Table 4. Crystallographic data for **6d** and **8a**.

Compound	**6d**	**8a**
Empirical formula	$C_{18}H_{13}BrClNO_2S$	$C_{19}H_{18}BrNO_3S$
Formula mass	422.71	420.31
Temperature [K]	293(2)	293(2)
Crystal size [mm]	0.25×0.19×0.18	0.21×0.18×0.11
Crystal system	monoclinic	monoclinic
Space group	$P2_1/c$	$P2_1/c$
a [Å]	11.201(1)	10.8578(12)
b [Å]	16.014(2)	17.0488(19)
c [Å]	9.978(1)	9.8850(11)
α [°]	90	90
β [°]	99.37(1)	98.437(2)
γ [°]	90	90
V [Å^3]	1765.9(15)	1810.0(3)
Z	4	4
d_c [mg m^{-3}]	1.590	1.542
F(000)	848	856
μ(Mo-K_α) [mm^{-1}]	2.607	2.404
θ range [°]	1.84 to 24.00	2.24 to 25.00
Index range	$-12 \le h \le 12$, $-18 \le k \le 0$, $-11 \le l \le 0$	$-5 \le h \le 12$, $-19 \le k \le 20$, $-11 \le l \le 11$
No. of reflns. collected	2927	8721
No. of independent reflns.	2752 [R_{int} = 0.0238]	3174 [R_{int} = 0.0219]
No. of reflns. with $I > 2\sigma(I)$	1741	2805
R_1; wR_2 [$I > 2\sigma(I)$]	0.0566; 0.1312	0.0474; 0.1152
R_1; wR_2 (all data)	0.0990; 0.1535	0.0704; 0.1284
Data/restraints/parameters	2752/0/217	3174/0/226
GOF on F^2	1.014	1.034
Largest diff. peak/hole [e·Å^{-3}]	0.436/–0.665	1.313/–0.832

X-ray Structure Determination: Data were collected on diffractometers: Siemens P4 (for **6d**) and Bruker SMART 1 K CCD (for **8a**). For details see Table 4. The data were collected by φ and ω scan mode and corrected by Lorentz and polarization factors, but no absorption correction was applied. The structure was solved by direct methods by use of the SHELX-97 program (G. M. Sheldrick, University of Göttingen, Germany, 1997) and also refined on F^2 by use of the same program suite.

CCDC-606118 and -606119 (for **6d** and **8a**, respectively) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): 2D NMR spectra (^{1}H,^{1}H COSY, ^{1}H,^{13}C COSY, and HSQC) for compounds **5a**, **8a** and **10a**. Spectroscopic data for compounds **1d**–**e**, **2d**–**e**, **3b**–**e**, **4b**, **5b**–**e**, **6a**–**c**,**e**, **8b**, **9b**, **10b**, **11b**, **12b** and **13b**.

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