Three- and Four-Membered Rings from Cycloadditions of 1,3-Thiazolium-4-olates and Aldehydes

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Abstract: 2-Aminothioisomünchnones, a well-known family of masked dipoles, react with aromatic aldehydes in a domino cascade reaction that produces episulfides (thiiranes) or β-lactams (2-azetidinones). This sequence is initiated by a [3+2] dipolar cycloaddition followed by ring opening of cycloadducts and intramolecular rearrangement to afford these unusual ring contractions. The nature of the reaction products depends on the structural characteristics of the starting dipole and the experimental conditions. Episulfides are obtained selectively as *cis* isomers with respect to both aryl groups, whereas β-lactams are produced as *cis*/*trans* mixtures. These structural features were determined unequivocally by X-ray crystallographic analysis. The β-lactams still possessed a flexible acyclic chain containing sulfur, a salient lead modification of the bioactive cyclic penems and cephems. The preferential production of *exo* transition structures was rationalized with the aid of computational calculations at the B3LYP/6-31G* level.

Keywords: cycloaddition · domino reactions · episulfides · lactams · mesoionic heterocycles

Introduction

1,3-Dipolar cycloadditions constitute the most important theoretical approach to the construction of five-membered rings.[1] Reactivity in dipolar cycloadditions varies considerably from system to system, and explanations of reactivity and stereochemical issues based on perturbational molecular orbital arguments have to be substantiated by semiempirical or ab initio calculations of ground states and saddle points.[2] Nevertheless, the formation of rings other than five-membered systems by means of the typical allyl- and propargyl-type dipoles remains relatively unexplored. A plausible strategy could be the use of masked dipoles whose resulting cycloadducts may undergo cascade transformations involving ring opening, fragment extrusion, or rearrangement. Mesoionic dipoles could fulfil this requirement, as induced or spontaneous fragmentations of their cycloadducts are easily achieved, providing five- or six-membered rings as major products.[3]

Depending on the nature of heteroatoms and the electronic contribution of each atom to the π system, mesoionic 1,3-dipoles belong to one of two general types, **A** and **B** (Scheme 1). Only those of type **A** may be represented by

Scheme 1. The two classes of mesoionic dipoles. The numbers denote the electronic contribution of each atom to the aromaticity of the five-membered ring.

canonical structures resembling allyl-type dipoles and therefore participate readily in cycloadditions, whereas **B**-type dipoles tend to be equilibrated with their valence tautomers, which may well be the reactive species formed by protonation and ring opening.[4]

We have already reported the synthesis of ring-fused polyheterocycles based on a domino process of cycloaddition and ring opening, followed by a further cyclization.[5] These types of reaction provide an opportunity for linking two

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Supporting information for this article (X-ray crystallographic analysis and an ORTEP diagram of **11**) is available on the WWW under http://www.wiley-vch.de/home/chemistry or from the author.

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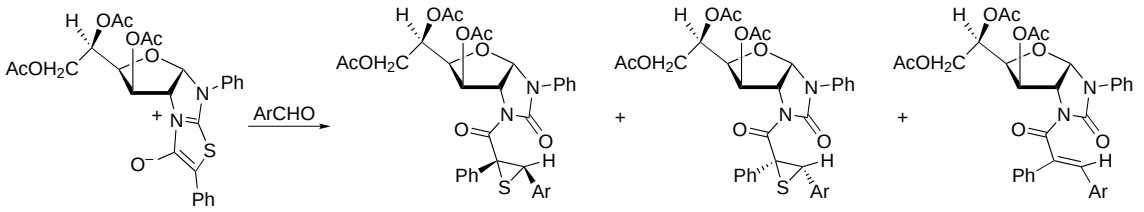
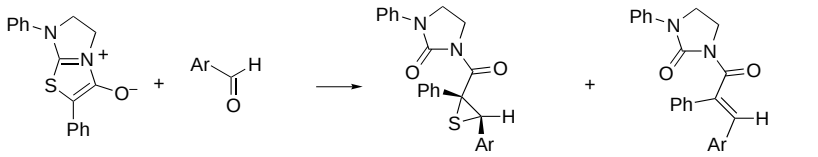


(1)

disparate ring-forming reactions sequentially. Such a protocol would also provide one-pot access to highly complex target molecules. Its modification to the formation of smaller, strained rings is still a challenge, however. Here we focus on our recent efforts in this area, describing in detail the unequivocal and unprecedented transformation of mesoionic dipoles into two important small heterocycles: episulfides and β-lactams.



(2)

1 **2a** Ar = 4-$NO_2C_6H_4$; **2b** Ar = Ph; **2c** Ar = 4-$MeOC_6H_4$; **2d** Ar = 4-$Me_2NC_6H_4$

3b Ar = Ph; **3c** Ar = 4-$MeOC_6H_4$; **3d** Ar = 4-$Me_2NC_6H_4$

4a Ar = 4-$NO_2C_6H_4$; **4d** Ar = 4-$Me_2NC_6H_4$

Results and Discussion

2-Aminothioisomünchnone cycloaddition strategy: It occurred to us that we could utilize a series of 2-amino-substituted 1,3-thiazolium-4-olates, rather than the highly stable aryl-substituted 1,3-thiazolium-4-olates which have long been employed, for the critical [3+2] cycloaddition step. Such an *N*,*N*-dialkylamino group has now been used to induce alternative cycloadduct fragmentations and to trigger a ring contraction.

We had previously detected ring contraction of a mesoionic-based cycloadduct to a three-membered ring. When a thiazolium-4-olate system embedded in a chiral tricyclic heterocycle reacted with an aromatic aldehyde, a mixture of two diastereomeric episulfides, along with an *E* olefin, were obtained [Eq. (1)].[6] The latter could also be obtained stereospecifically by thermal desulfurization of an equimolar mixture of both episulfides.

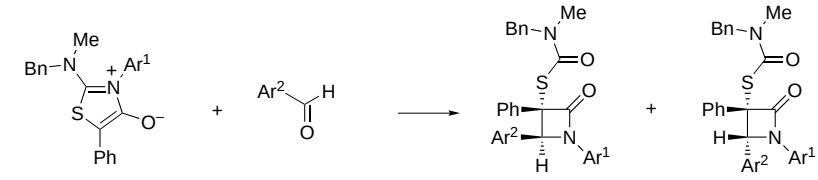
To investigate the influence of the carbohydrate moiety on the steric course of the reaction, the cycloadditions of the reduced model **1** with aromatic aldehydes **2** were studied. This substrate exhibited an analogous behavior leading regiospecifically and stereoselectively in toluene solution to episulfides **3** (as racemic mixtures), occasionally together with an *E* olefin **4** [Eq. (2), Table 1] (in general, crude samples were too complex to be evaluated by NMR spectroscopy and values therefore refer to yields of isolated products).

Whereas stereoselection was complete in the cycloadditions with benzaldehyde and 4-methoxybenzaldehyde affording episulfides, the condensation with 4-nitrobenzaldehyde resulted in a modest yield of the olefin **4a**. With 4-dimethylaminobenzaldehyde a mixture of episulfide and olefin could be detected, although the latter was the exclusive product after prolonged reaction times.

Table 1. Reaction of **1** with aromatic aldehydes in toluene solution.

Aldehyde	T [°C]	t [h]	Episulfide [%]	Olefin [%]
2a	25	24	–	**4a** (5)
2a	110	1.5	–	**4a** (28)
2b	25	1.5	**3b** (65)	–
2b	110	0.5	**3b** (20)	–
2c	110	1	**3c** (50)	–
2c	110	20	**3c** (35)	–
2d	110	1.5	**3d** (17)	**4d** (18)
2d	110	20	–	**4d** (32)

For the simple thioisomünchnones **5**–**7** in which an *N*,*N*-dialkylamino group replaced the imidazolidine ring in the bicyclic system **1**, clean reactions were obtained in refluxing benzene. NMR data of the resulting products deviated surprisingly from the pattern observed in the above-mentioned episulfides. Further analysis by X-ray diffractometry of suitable crystals of the major isomer **8f** evidenced the formation of a β-lactam ring.[7] Similar β-lactams were likewise obtained as mixtures of *cis* and *trans* diastereomers with respect to the relative orientation of the two aromatic substituents at C3 and C4 [Eq. (3), Table 2]. The isomeric



(3)

5 Ar^1 = 4-$NO_2C_6H_4$; **6** Ar^1 = Ph; **7** Ar^1 = 4-$MeOC_6H_4$

2a Ar^2 = 4-$NO_2C_6H_4$; **2b** Ar^2 = Ph; **2c** Ar^2 = 4-$MeOC_6H_4$

8a + **9a** $Ar^1 = Ar^2$ = 4-$NO_2C_6H_4$; **8b** + **9b** Ar^1 = 4-$NO_2C_6H_4$, Ar^2 = Ph; **8c** + **9c** Ar^1 = 4-$NO_2C_6H_4$, Ar^2 = 4-$MeOC_6H_4$; **8d** + **9d** Ar^1 = Ph, Ar^2 = 4-$NO_2C_6H_4$; **8e** + **9e** $Ar^1 = Ar^2$ = Ph; **8f** + **9f** Ar^1 = Ph, Ar^2 = 4-$MeOC_6H_4$

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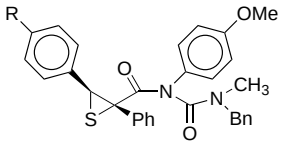
Table 2. Preparation of *cis*- and *trans*-β-lactams.

Ar^1	Ar^2	*t* [h]	*cis*/*trans*[a]
4-$NO_2C_6H_4$	4-$NO_2C_6H_4$	1	58:42
4-$NO_2C_6H_4$	Ph	1	57:43
4-$NO_2C_6H_4$	4-$MeOC_6H_4$	6	60:40
Ph	4-$NO_2C_6H_4$	3	60:40
Ph	Ph	4	65:35
Ph	4-$MeOC_6H_4$	10	70:30

[a] Determined by integration of ^{1}H NMR spectra ($CDCl_3$).

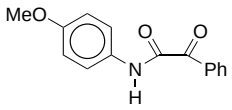
ratios were determined by NMR analysis of the crude samples. Separation of these *cis* and *trans* β-lactams by fractional crystallization or preparative chromatography facilitated their structural assignment.

No side products could be detected in the cycloadditions of **5** and **6** with aryl aldehydes, but the corresponding reactions with thioisomünchnone **7** were messy. The reaction of **7** with 4-nitrobenzaldehyde gave a complex reaction mixture, although we were able to isolate a small amount (7%) of β-lactam after 10 h at reflux. In contrast, no β-lactams could be observed in the reactions of **7** with benzaldehyde or 4-methoxybenzaldehyde after more than 50 h in refluxing benzene. We then studied these reaction mixtures systematically. From the condensation of **7** and 4-nitrobenzaldehyde under milder conditions (dry CH_2Cl_2, RT, 24 h), we isolated the episulfide **10** in 63% yield after crystallization from diethyl ether. Under



10 R = NO_2

11 R = H



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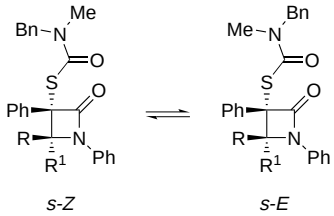
similar reaction conditions the [3+2] cycloaddition with benzaldehyde proceeded slowly (RT, 44 h) to give **11** in 15% yield after chromatographic purification and crystallization. Prolonged reaction times (RT, 96 h) yielded ketoamide **12** (10%) and crystalline sulfur (6%). From cycloaddition of **7** with 4-methoxybenzaldehyde, ketoamide **12** was the sole product (14%), although the complete conversion of the starting materials could not be observed (NMR monitoring).

The structure of **11** was further confirmed by X-ray analysis (see Supporting Information for details). The solid-state structure also reveals the relative *cis* disposition of the two phenyl groups, in agreement with the data previously obtained by our research group.[6] In addition to their unequivocal characterization by X-ray diffraction analysis, the β-lactam and episulfide derivatives exhibited notable, diagnostically valuable differences in their ^{1}H and ^{13}C NMR spectra. Thus, the only proton present in the heterocyclic moiety (H4 for β-lactams and H3 for episulfides) does appear more deshielded ($\Delta\delta \approx 1$, 5.81–6.04 versus 4.83–4.90) in the case of the four-membered rings. Moreover, H4 for the *cis* β-lactams is also more deshielded than for their *trans* isomers. Accordingly, H4 resonances of the *r*-4-aryl-3*c*-phenyl diastereomers[8] are shifted remarkably downfield relative to the *r*-4-aryl-3*t*-phenyl counterparts. Likewise, as with β-lactams, a comparison of the ^{13}C NMR data allowed us to identify diastereomeric pairs. Thus, the C3 signals for *trans* isomers (*r*-4-aryl-3*t*-phenyl) are shifted upfield relative to those of *r*-4-aryl-3*c*-phenyl diastereomers, and the resonances for C4 exhibited NMR deshielding in *trans* isomers. Moreover, carbon resonances of the episulfide moiety were shifted notably upfield ($\delta_C \approx 46-55$) compared with those of β-lactams ($\delta_C \approx 67-70$).

The ^{1}H NMR resonance signals of *N*-methyl and methylene groups appear as very broad signals. We attribute this apparent duplication of such signals at room temperature to a restricted rotation of the *N*,*N*-dialkylamino group around the (SC=O)–N bond. Accordingly, both *cis* and *trans* β-lactams should indeed exist as a mixture of *s*-*Z* and *s*-*E* rotamers [Eq. (4)].



(4)

8e R = Ph, R^1 = H

9e R = H, R^1 = Ph

The coalescence temperature (T_c) of **8e** and **9e** has been measured by variable-temperature NMR experiments. The barrier to rotation $\Delta G^{\ddagger}$ [cal mol^{-1}] can be estimated from T_c by Equation (5), derived from the Eyring equation.[9]

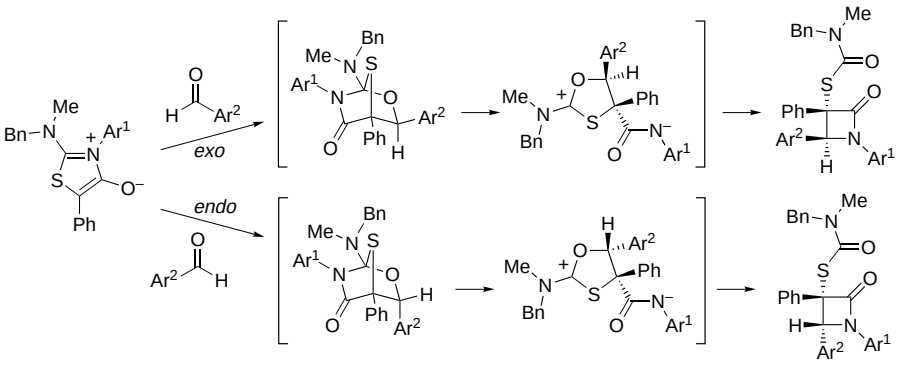
$$\Delta G^{\ddagger} = 1.987 T_c [22.62 + \ln T_c/\Delta\tilde{\nu}] \quad (5)$$

Strictly, Equation (5) should be applied only to equally populated conformational states at equilibrium, although in most cases approximate, acceptable values within the experimental error are obtained.[10] Data in Table 3 indicate a similar energy barrier for both diastereomers (approximately 15 kcal mol^{-1}), comparable with values obtained previously for twisted amides.[11]

Table 3. Barriers to rotation $\Delta G^{\ddagger}$ from ^{1}H NMR data at 400 MHz.

	Signal	$\Delta\delta$ [Hz]	T_c [K]	$\Delta G^{\ddagger}$ [kcal mol^{-1}]
8e	NCH_3	18.02	292	14.7
	H5	10.10	289	14.9
9e	N–CH_2	44.96	295	14.4
	H5	12.95	283	14.5

Mechanistic aspects: The overall transformation of thioisomünchnones and aromatic aldehydes to β-lactams (Scheme 2)



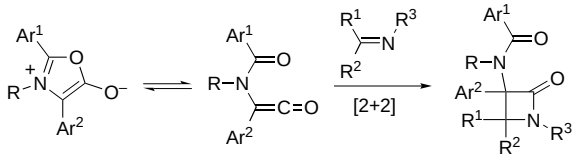
Scheme 2. Mechanism for the transformation of thiomüchnones and aromatic aldehydes to β-lactams.

is a triple cascade sequence consisting of an initial [3+2] dipolar cycloaddition to afford a cycloadduct which undergoes spontaneous cleavage of the C–N bond, followed by further rearrangement of the zwitterionic intermediate.

Ring opening of the initial cycloadducts, which are not isolated, alleviates their ring strain. The positive charge on the dipolar intermediate should largely be stabilized by the lone pairs of electrons on the adjacent heteroatoms, while an electron-withdrawing substituent on the aromatic group can stabilize the negative charge. It should therefore be expected that electron-donating aryl groups on the thioisomünchnone precursor (for example, **7**), will disfavor C–N bond breaking of the thia-bridged cycloadducts formed initially.

At this stage, the further rearrangement of the transient dipole is no more than an intramolecular nucleophilic attack of the amide nitrogen on the endocyclic carbon atom as a suitable leaving group. Such a displacement also causes the configurational inversion at C5 of the five-membered ring. Accordingly, *exo* and *endo* approaches of the aromatic aldehyde in the initiating cycloaddition will dictate the diastereomeric course leading to *r*-4-aryl-3*c*-phenyl and *r*-4-aryl-3*t*-phenyl β-lactams, respectively.

Early studies showed that 1,3-oxazolium-5-olates (münchnones) can provide β-lactams by reaction with imines.[12] This type of mesoionic ylide corresponds to the cyclic equivalent of an azomethine ylide and is found to undergo [3+2] cycloaddition readily with suitable dipolarophiles.[4a, 13] This condensation with imines is still underestimated as a route to the important family of four-membered lactams. The transformation was once believed to follow the pathway outlined in Scheme 3. Münchnones would be in equilibrium with their

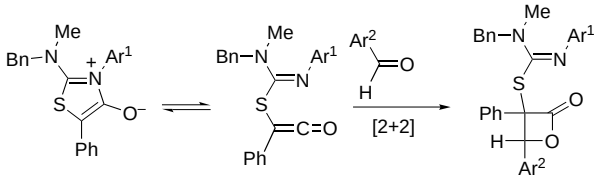


Scheme 3. Condensation of münchnones with imines as a route to four-membered lactams

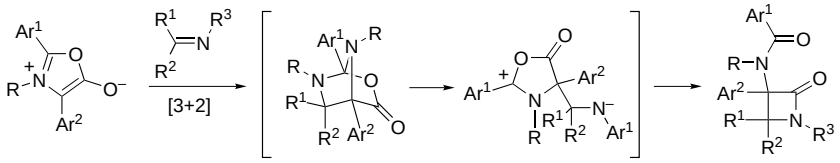
ketene-type valence tautomers, which could then be intercepted by imines through a [2+2] cycloaddition.

There is no spectroscopic evidence to support the intermediacy of such hypothetical valence tautomers, although this could simply reflect their short lifetime. Their generation from thioisomünchnones should now be reexamined, since they would afford β-lactones through a [2+2] cycloaddition with aldehydes (Scheme 4).

In the light of our results, a stepwise reaction could satisfactorily explain the formation of β-lactams from münchnones and imines (Scheme 5). Again, the [3+2] cyclo-



Scheme 4. [2+2] cycloaddition reaction of thiomünchnones with aldehydes to give β-lactones.



Scheme 5. Stepwise reaction as a possible explanation for the formation of β-lactams from münchnones and imines.

addition gives rise to an aza-bridged cycloadduct. Ring opening followed by rearrangement of the resulting zwitterionic intermediate furnishes highly substituted β-lactams.

It is striking that the ring contraction of thioisomünchnones to β-lactams occurs without the menacing extrusion of elemental sulfur.[14] This leads to monocyclic 2-azetidinones (monobactams) bearing a sulfur-containing side chain, the structural motif encountered in the well-screened cephem, penem, and penam nuclei.[15] Such β-lactam derivatives irreversibly inactivate three important classes of serine proteases[16] that specifically recognize and cleave the cyclic amide bond of these four-membered rings: D,D-transpeptidases, β-lactamases, and elastases.[15–17] In addition, renewed interest in β-lactam antibiotics is emerging from recent assays of monobactams as thrombin[18] and cholesterol acyltransferase inhibitors.[19]

Although the preparation and reactivity of thiiranes (episulfides) and thiirenes are well documented,[20] there are fewer naturally occurring thiiranes.[21] Synthetic derivatives are utilized as drugs, thermoplastic polymers or rubber plasticizers, and mild herbicides.[22]

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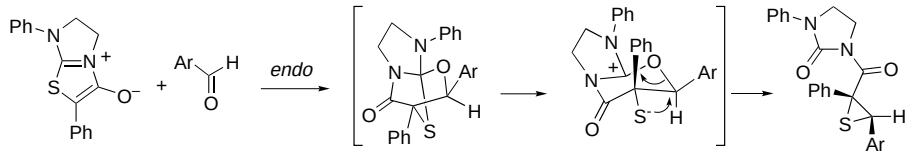
The formation of *r*-3-aryl-2*c*-phenyl episulfides [see Eq. (2)] can equally be explained by assuming a preferential *endo* [3+2] cycloaddition of the aldehyde to thioisomünchnone **1** followed by ring opening of the resulting cycloadduct, which is in this case initiated by fragmentation of the C–S bond and a subsequent intramolecular sulfur atom transfer (Scheme 6). The rigid framework provided by the bicyclic tetrahydroimidazole does effectively impede the formation of a β-lactam ring, even though the lone pair of electrons on the contiguous nitrogen may assist the alternative C–N bond cleavage.



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Scheme 6. Mechanism to explain the formation of *r*-3-aryl-2*c*-phenyl episulfides.

Computational studies: To probe more deeply the mechanistic pathway leading to the formation of β-lactams, we undertook a theoretical study capable of providing a plausible rationale. Standard molecular orbital calculations of the cycloadditions involving compounds **5**–**7** with aldehydes **2a**–**2c** were carried out using the Gaussian 94 package of programs.[23] Molecular geometries were optimized initially at the PM3 level[24] and a selection of the corresponding energies were then recalculated with the B3LYP density functional method[25] and the 6-31G* basis set. All these structures were characterized as local minima by numerical normal-mode analyses, and transition structures by the existence of one imaginary frequency in each case.

Table 4 shows the energies and coefficients of the frontier orbitals (FMOs) of the reactants with full optimization of geometries at a semiempirical (PM3) level. All these cycloadditions reactions are $HOMO_{dipole}$-controlled processes as evidenced by the smaller $HOMO_{dipole}-LUMO_{dipolarophile}$ energy gap with respect to its $HOMO_{dipolarophile}-LUMO_{dipole}$ counterpart.

According to the FMO postulates,[26] once the HOMO/LUMO pair that is closer in energy is identified, the relative sizes of the coefficients of the atomic orbitals will predict the regioselectivity. Taking the cycloaddition between the 1,3-thiazolium-4-olate system **6** and benzaldehyde (**2b**) as a reaction model, Figure 1 represents the four possible approaches facing the greater HOMO and LUMO. Unfortunately, the similarity found in the LUMO coefficients of the dipolarophile impedes prediction of the regioselectivity based solely on primary interactions.

Table 4. Coefficients and energies of FMOs for **5**–**7** and **2a**–**2c**.

	Orbital	Energy [eV]	c_1	c_2	c_3	c_4	c_5
5	HOMO	−7.85	−0.19	−0.28	0.15	0.14	0.51
	LUMO	−1.81	−0.36	0.58	−0.30	−0.01	0.29
6	HOMO	−7.50	−0.18	−0.26	0.15	0.14	0.51
	LUMO	−1.39	−0.40	0.63	−0.37	−0.02	0.29
7	HOMO	−7.47	−0.21	−0.26	0.15	0.14	0.53
	LUMO	−1.81	−0.39	0.64	−0.38	−0.02	0.30
2a	HOMO	−10.83	0.02	0.00	−0.05	–	–
	LUMO	−1.69	−0.27	0.23	0.51	–	–
2b	HOMO	−10.05	0.15	0.02	−0.34	–	–
	LUMO	−0.48	−0.37	0.36	0.50	–	–
2c	HOMO	−9.42	0.21	0.01	−0.50	–	–
	LUMO	−0.41	−0.36	0.36	0.48	–	–

The consideration of secondary orbital interactions[27] now makes it possible to assign the correct regiochemistry. Thus, Figure 2 depicts such interactions emerging from an *endo* orientation of the reactants. This approach places the oxygen atom of benzaldehyde in close contact with the C2 position of the cyclic core, which stabilizes the transition state. In the alternative approach to C5, the HOMO and the LUMO of the reactants are always of opposite signs.

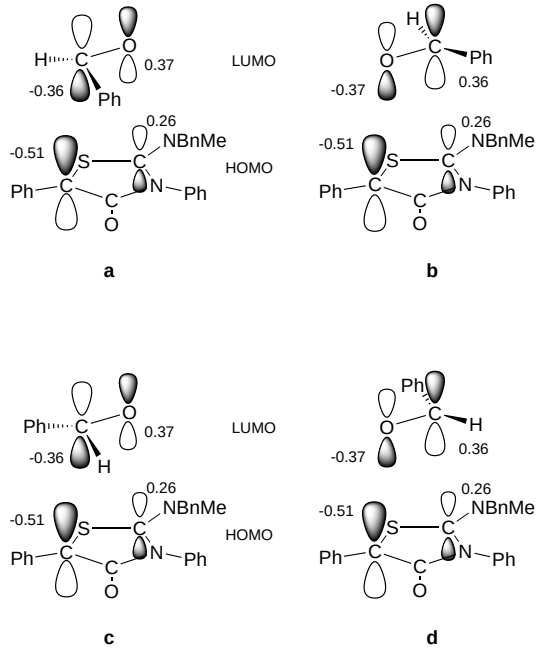

Figure 1. The four possible *exo* and *endo* approaches of benzaldehyde to the mesoionic dipole.

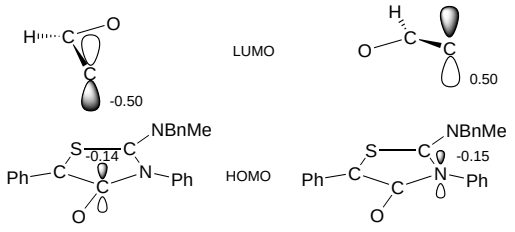

Figure 2. Secondary orbital interactions in the *endo* approach of benzaldehyde to thioisomünchnone **6**.

Although the secondary interactions should constitute the dominant regiochemical controller, we find that the PM3 procedure is not suitable for reliably predicting the stereo-

chemical outcome because there is a slight preference for the *endo* transition states, in disagreement with the experimental observations. This can be appreciated by examining the PM3 transition structures arising from cycloadditions of thioisomünchnones **5**–**7** with benzaldehyde (**2b**), as well as the transition structures resulting from the reactions of **6** with the aldehydes **2a** and **2c** (Table 5, Figure 3) (orientations **a**–**d** refer to the notation indicated in Figure 1).

Approaches **a** and **c**, which also exhibit the regiochemical outcome observed experimentally, appear to be more stabilized that the orientations with the opposite regiochemistry. Moreover, structures **a** and **c** suggest concerted and more synchronous processes, bringing about shorter interatomic distance differences representing the bonds being formed; this is one important difference from approaches **b** and **d**.

Although a small energy difference is found, at the PM3 level, between the more stabilized transition structures **a** and **c**, **a** is favored slightly, in agreement with the FMO theory predicting the formation of *endo* cycloadducts which would otherwise lead to *trans* β-lactams.

We have also studied *endo* and *exo* approaches of the three possible aldehydes **2a**–**2c** to the simpler thioisomünchnone **6**, and calculated improved energies at the B3LYP/6-31G* level (Table 6).

The most relevant discovery is the inverted stability of transition structures **a** (*endo*) and **c** (*exo*) with respect to the corresponding results from semiempirical calculations. The *exo* approach corresponds to a lower activation energy and after cycloadduct cleavage the favored isomer should be a β-lactam with a relative *cis* stereochemistry, in full agreement

Table 5. Computed energies [kcal mol^{-1}] and bond lengths [Å] for transition structures.

	Approach	$\Delta E^{\neq}$ (PM3)	C2–O	C5–C	C2–C	C5–O
5 + **2b**	**a** (*endo*)	38.58	2.00	2.08	–	–
	b (*endo*)	52.40	–	–	2.24	1.92
	c (*exo*)	40.22	2.00	2.09	–	–
	d (*exo*)	51.85	–	–	2.21	1.97
6 + **2a**	**a** (*endo*)	36.15	2.07	1.99	–	–
	b (*endo*)	54.03	–	–	2.35	1.87
	c (*exo*)	37.62	2.08	2.00	–	–
	d (*exo*)	50.37	–	–	2.22	1.96
6 + **2b**	**a** (*endo*)	38.69	2.01	2.06	–	–
	b (*endo*)	57.45	–	–	2.30	1.89
	c (*exo*)	40.31	2.01	2.07	–	–
	d (*exo*)	52.10	–	–	2.22	1.96
6 + **2c**	**a** (*endo*)	39.15	2.00	2.07	–	–
	b (*endo*)	56.02	–	–	2.30	1.90
	c (*exo*)	40.52	2.00	2.08	–	–
	d (*exo*)	52.54	–	–	2.22	1.96
7 + **2b**	**a** (*endo*)	38.93	2.01	2.06	–	–
	b (*endo*)	57.60	–	–	2.30	1.89
	c (*exo*)	40.52	2.01	2.07	–	–
	d (*exo*)	52.30	–	–	2.22	1.96

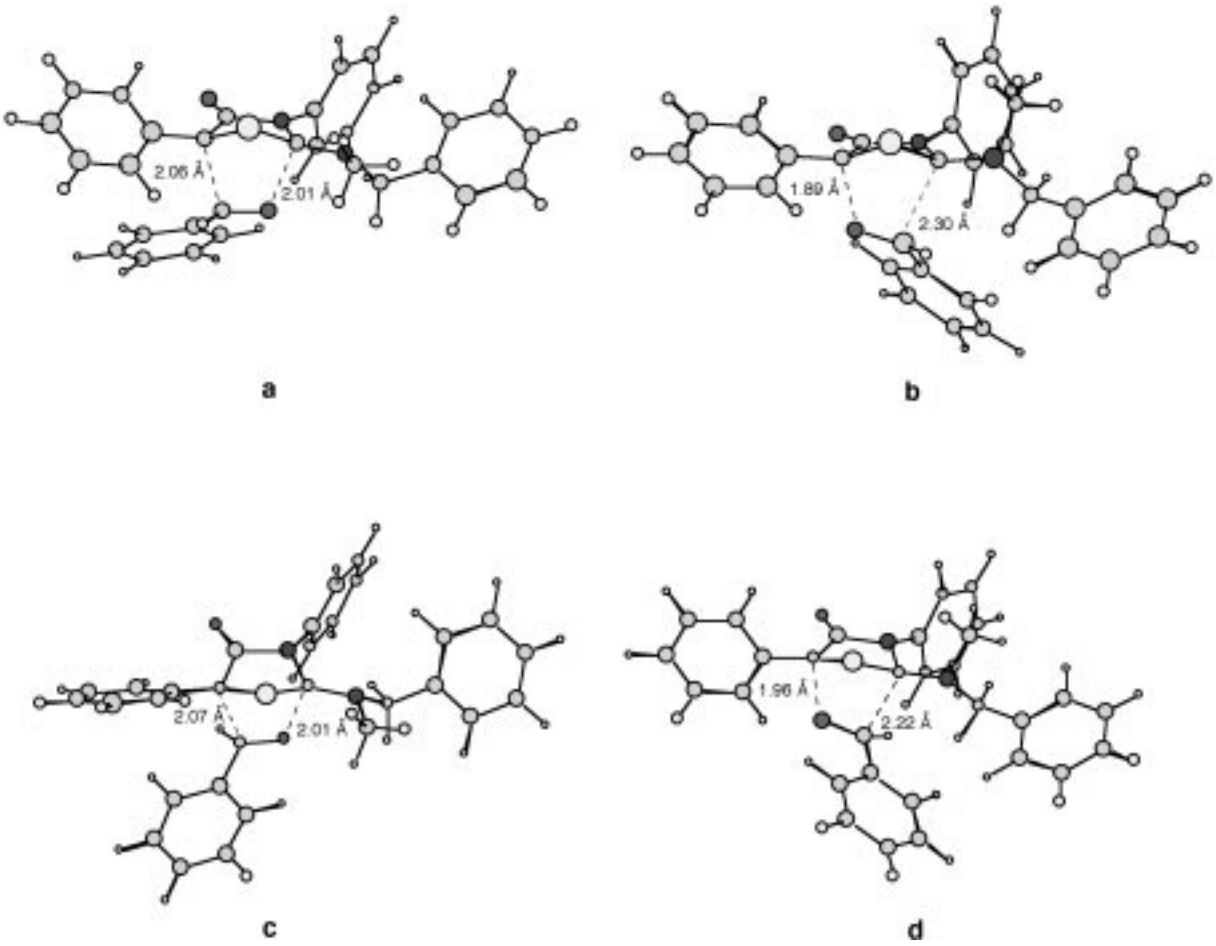

Figure 3. Transition structures from cycloadditions of **6** with benzaldehyde.

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Table 6. Single-point energies $\Delta E+$ at the B3LYP/6-31G*//PM3 level.

	Approach	ΔE^{+} [kcal mol^{-1}]
6 + **2a**	**a** (*endo*)	15.53
	b (*endo*)	34.08
	c (*exo*)	11.52
	d (*exo*)	34.74
6 + **2b**	**a** (*endo*)	20.02
	b (*endo*)	36.67
	c (*exo*)	15.74
	d (*exo*)	37.95
6 + **2c**	**a** (*endo*)	23.63
	b (*endo*)	38.87
	c (*exo*)	17.07
	d (*exo*)	41.68

with experiment. This simple analysis reinforces the importance, suggested widely in modern computational chemistry, of utilizing theoretical methods involving any kind of electronic correlation (ab initio or DFT).[28]

Conclusion

We have shown that two important classes of heterocyclic rings (episulfides and β-lactams) can be accessed readily by a triple domino cascade involving the dipolar cycloaddition of a mesoionic thioisomünchnone to an aromatic aldehyde, fragmentation of an amino-substituted [3+2] cycloadduct, and further rearrangement of a zwitterionic intermediate. The ease of cycloaddition, the rapid accumulation of polyfunctionality in a small molecular framework, the stereochemical control of the 1,3-dipolar cycloaddition, and the predictability of its regiochemical pattern make this sequential transformation valuable. In the realm of synthesis, where selectivity is rated highly, the structural characteristics of the starting thioisomünchnone strongly direct the course of the cycloaddition. Episulfides are obtained selectively with ring-fused heterocycles [Eqs. (1) and (2)] in which C–S bond cleavage will be the preferred mode of rearrangement. A major cornerstone of synthetic chemistry has been the development of an efficient preparation of epoxides of high optical purity (for example, by the Sharpless epoxidation); synthetic protocols to access homochiral episulfides would be equally desirable. Optically active derivatives have been obtained by resolution of racemates.[29] Very recently, we have used the methodology described here for a diastereoselective synthesis of optically active episulfides, whose chirality is imprinted by a chiral carbohydrate aldehyde and whose structure has been confirmed by X-ray analyses.[30]

The formation of β-lactams occurs smoothly from neutral or electronically deactivated thioisomünchnones in good overall yields, although the selectivity (in terms of *cis*/*trans* ratios) is rather modest. A key feature of these molecules is that they bear a sulfur-containing acyclic chain, a structural motif also found in bioactive ring-fused β-lactams such as penicillins and cephalosporins. We find that the stereochemical outcome cannot be inferred from the postulates of the FMO theory, but a higher level of theory (B3LYP/6-31G*) does predict the favored *exo* transition pathway.

We hope that the remarkable features of these cycloadditions will fuel attempts to synthesize polyfunctional small molecules and will stimulate continuing interest in other synthetic targets.

Experimental Section

General methods: Melting points were determined on a capillary melting point apparatus and are uncorrected. Yields refer to analytically pure compounds. All solvents were dried and stored over molecular sieves. TLC was performed with Merck $60GF_{254}$ silica gel plates, and column chromatography by standard techniques on silica gel. IR spectra were obtained with KBr pellets in Perkin-Elmer 399 and FT-Midac spectrophotometers. Microanalyses were carried out by the Servei de Microanàlisi/Centre d'Investigació i Desenvolupament (Barcelona), by the Instituto de Investigaciones Químicas, CSIC (Sevilla), and by the analytical laboratory of our institute (Lecco CHNS 932 microanalyzer). The ^{1}H; ^{13}C, DEPT and variable-temperature NMR spectra were recorded on Bruker AC-200 and AM-400 spectrometers. The NMR spectra were referenced to the TMS line as internal standard at $\delta = 0.00$. The X-ray diffraction was measured with an Enraf Nonius diffractometer at the University of Southampton.

2,7-Diphenyl-5*H*,6*H*,7*H*-imidazole[2,1-*b*]-1,4-thiazolium-3-thiolate (1): Triethylamine (1.8 mL, 12.5 mmol) was added dropwise to a solution of 1-phenylimidazolidine-2-thione (2.20 g, 12.5 mmol) and α-bromophenylacetic acid (2.70 g, 12.5 mmol) in benzene (100 mL). The reaction mixture was stirred at room temperature for 17 h. The white solid precipitate was filtered and washed with cold water (yield 1.37 g, 36%). This substance, 2-phenyl-2-[1-phenyl-(2-imidazolin-2-ylthio)acetic acid (1.00 g, 4.25 mmol), was then dissolved in acetic anhydride (16 mL) and treated with triethylamine (6 mL) to afford a yellowish solid (0.28 g, 30%) after 5 min, m.p. 121–123 °C. The latter was filtered, washed with diethyl ether, and used without further purification.

(2′*R*,3′*R*)- and (2′*S*,3′*S*)-1-(2′,3′-epithio-2′,3′-diphenyl)propanoyl-3-phenyltetrahydroimidazol-2-one (3b)

Procedure a: Benzaldehyde (0.11 g, 1.0 mmol) was added to a suspension of **1** (0.30 g, 1.0 mmol) in toluene (5 mL) and the mixture was stirred at room temperature for 90 min. The solvent was evaporated under reduced pressure and the resulting crude was treated with ethanol, crystallizing **3b** (0.26 g, 65%). M.p. 169–171 °C (ethanol); IR (KBr): $\tilde{\nu} = 1737$, 1668, 1289, 695 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.44$–7.02 (m, 15H; Ar), 4.90 (s, 1H; CH), 3.98–3.68 (m, 4H; $2 \times CH_2$); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 169.55$ (C1′), 150.63 (C2), 138.51, 134.30, 132.52, 129.97, 128.90, 128.79, 127.50, 127.43, 127.29, 127.08, 124.28, 119.03 (Ar), 54.57 (C2′), 46.63(C3′), 41.63 (CH_2), 39.78 (CH_2); elemental analysis calcd (%) for $C_{24}H_{20}N_2O_2S$ (400.49): C 71.98, H 5.03, N 6.99; found: C 71.70, H 4.97, N 6.96.

Procedure b: Benzaldehyde (0.07 g, 0.7 mmol) was added to a suspension of **1** (0.20 g, 0.7 mmol) in toluene (5 mL) and the reaction mixture was refluxed for 10 min. The solvent was evaporated under reduced pressure and the residue was treated with ethanol, crystallizing **3b** (0.05 g, 20%).

(2′*R*,3′*R*)- and (2′*S*,3′*S*)-1-[2′,3′-epithio-3′-(4-methoxyphenyl)-2′-phenyl]-propanoyl-3-phenyltetrahydroimidazol-2-one (3c)

Procedure a: 4-Methoxybenzaldehyde (0.23 g, 1.7 mmol) was added to a suspension of **1** (0.50 g, 1.7 mmol) in toluene (20 mL) and the mixture was refluxed for 40 min. After solvent evaporation under reduced pressure, the resulting crude was treated with ethanol, crystallizing **3c** (0.28 g, 50%). M.p. 152–154 °C; IR (KBr): $\tilde{\nu} = 1730$, 1660, 1290, 695 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 7.47$–6.57 (m, 14H; Ar), 4.85 (s, 1H; CH), 4.02–3.74 (m, 4H; $2 \times CH_2$), 3.66 (s, 3H; CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta =$ 169.65 (C1′), 158.62 (Ar), 150.64 (C2), 138.53, 132.66, 130.06, 129.93, 128.90, 127.51, 127.33, 126.38, 124.27, 119.02, 112.88 (Ar), 55.01 (CH_3), 54.50 (C2′), 46.47(C3′), 41.62 (CH_2), 39.79 (CH_2); elemental analysis calcd (%) for $C_{25}H_{22}N_2O_3S$ (430.52): C 69.75, H 5.15, N 6.51; found: C 69.60, H 5.16, N 6.55.

Procedure b: 4-Methoxybenzaldehyde (0.10 g, 0.7 mmol) was added to a suspension of **1** (0.20 g, 0.7 mmol) in toluene (3 mL) and the reaction mixture was refluxed for 20 h. After solvent evaporation under reduced

pressure, the resulting crude was treated with ethanol to give crystals of **3c** (0.10 g, 35%).

(2′*R*,3′*R*)- and (2′*S*,3′*S*)-1-{2′,3′-epithio-3′-[4-(*N*,*N*-dimethylamino)]phenyl-2′-phenyl}propanoyl-3-phenyltetrahydroimidazol-2-one (3d) and (*E*)-1-{3′-[4-(*N*,*N*-dimethylamino)phenyl]-2′-phenylacryloyl}-3-phenyltetrahydroimidazol-2-one (4d)

Procedure a: 4-(*N*,*N*′-Dimethylamino)benzaldehyde (0.05 g, 0.35 mmol) was added to a suspension of **1** (0.10 g, 0.35 mmol) in toluene (2.5 mL) and the mixture was refluxed for 80 min. The solvent was evaporated under reduced pressure and the resulting crude was purified by silica gel column chromatography (benzene – acetonitrile, 20:1 v/v), to afford first **3d** (0.03 g, 17%) and then **4d** (0.03 g, 18%) after a further elution. Compound **3d** was recrystallized from ethanol. M.p. 183 – 185 °C; IR (KBr): $\tilde{\nu}$ = 1730, 1650, 1290, 690 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.51 – 6.40 (m, 14H; Ar), 4.83 (s, 1H; CH), 4.03 – 3.81 (m, 4H; 2 × CH_2), 2.82 (s, 6H; 2 × CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.83 (C1′), 150.61 (C2), 149.51, 138.57, 132.95, 130.42, 129.56, 128.85, 127.40, 127.27, 124.16, 121.81, 118.95, 111.47 (Ar), 54.42 (C2′), 46.08 (C3′), 41.57 (CH_2), 40.31 (2 × CH_3), 39.77 (CH_2); elemental analysis calcd (%) for $C_{26}H_{25}N_3O_2S$ (443.57): C 70.40, H 5.68, N 9.47; found: C 70.05, H 5.57, N 9.35.

Compound **4d** was recrystallized from diethyl ether. M.p. 211 – 213 °C; IR (KBr): $\tilde{\nu}$ = 1730, 1650, 1590, 1280, 680 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.52 – 6.60 (m, 14H; Ar), 6.93 (s, 1H; CH), 4.08 – 3.78 (m, 4H; 2 × CH_2), 2.94 (s, 6H; 2 × CH_3); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 170.34 (C1′), 150.56 (C2), 150.04, 138.63, 137.56, 132.66, 129.43, 129.28, 128.79, 128.52, 127.31, 125.97, 124.07, 118.75, 112.02 (Ar and C=C), 41.65 (CH_2), 40.22 (2 × CH_3), 39.16 (CH_2); elemental analysis calcd (%) for $C_{26}H_{25}N_3O_2$ (411.50): C 75.89, H 6.12, N 10.21; found: C 75.75, H 6.09, N 10.26.

Procedure b: 4-(*N*,*N*′-Dimethyamino)benzaldehyde (0.05 g, 0.3 mmol) was added to a suspension of **1** (0.10 g, 0.3 mmol) in toluene (2.5 mL) and the mixture was refluxed for 20 h. The solvent was evaporated under reduced pressure and the resulting crude was treated with diethyl ether to yield **4d** (0.04 g, 32%).

(*E*)-1-[-3′-(4-nitrophenyl)-2′-phenylacryloyl]-3-phenyltetrahydroimidazol-2-one (4a): 4-Nitrobenzaldehyde (0.26 g, 1.7 mmol) was added to a suspension of **1** (0.50 g, 1.7 mmol) in toluene (10 mL) and the mixture was refluxed for 80 min. After solvent evaporation under reduced pressure, the resulting crude was treated with diethyl ether to produce crystals of **4a** (0.21 g, 28%). Compound **4** was recrystallized from diethyl ether. M.p. 262 – 264 °C; IR (KBr): $\tilde{\nu}$ = 1730, 1640, 1590, 1340, 1280, 680 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 8.19 – 7.08 (m, 14H; Ar), 7.01 (s, 1H; CH), 4.14 – 3.82 (m, 4H; 2 × CH_2); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 168.38 (C1′), 146.94 (C2), 142.70, 140.88, 138.12, 136.03, 128.99, 128.88, 128.83, 128.72, 126.51, 126.32, 124.66, 123.86, 118.90 (Ar and C=C), 41.72 (CH_2), 38.91 (CH_2); elemental analysis calcd (%) for $C_{24}H_{19}N_3O_4$ (413.43): C 69.72, H 4.63, N 10.16; found: C 69.65, H 4.71, N 10.14.

(3*R*,4*S*)- and (3*S*,4*R*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-1,4-bis(4-nitrophenyl)-3-phenylazetidin-2-one (8a) and (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-benzyl-*N*-methylcarbamoylthio)-1,4-bis(4-nitrophenyl)-3-phenylazetidin-2-one (9a): 4-Nitrobenzaldehyde (0.23 g, 1.5 mmol) was added to a suspension of **5** (0.63 g, 1.5 mmol) in dry benzene (7.5 mL) and the mixture was refluxed with stirring for 1 h, then evaporated to dryness under reduced pressure. Ethanol was added, crystallizing a mixture of diastereomers **8a** and **9a**. These compounds were further separated by preparative TLC (benzene – acetonitrile, 40:1 v/v). The product with higher R_f, **8a**, was crystallized from ethanol (0.36 g, 42%). M.p. 124 – 126 °C; IR (KBr): $\tilde{\nu}$ = 1770, 1650, 1330, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.17 (d, 2H; Ar), 8.02 (d, 2H; Ar), 7.46 – 7.14 (m, 14H; Ar), 6.04 (s, 1H; H4), 4.54 (m, 2H; CH_2), 2.91 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 165.93 (C5), 165.05 (C2), 147.95, 143.79, 142.43, 141.19, 135.71, 134.86, 131.66, 131.45, 128.96, 128.71, 128.14, 127.94, 127.19, 125.35, 123.71, 117.43 (Ar), 70.61 (C3), 67.82 (C4), 53.98 and 52.14 (C7), 34.45 (C6); elemental analysis calcd (%) for $C_{30}H_{24}N_4O_6S$ (568.61): C 63.37, H 4.25, N 9.85; found: C 63.22, H 4.16, N 9.78.

Compound **9a** was crystallized from ethanol (0.21 g, 25%). M.p. 169 – 171 °C; IR (KBr): $\tilde{\nu}$ = 1760, 1660, 1340, 740, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.22 (m, 4H; Ar), 7.84 (d, 2H; Ar), 7.71 (d, 2H; Ar), 7.50 – 7.39 (m, 5H; Ar), 7.22 (m, 3H; Ar), 6.78 (m, 2H; Ar), 5.95 (s, 1H; H4), 4.19 (m, 2H; CH_2), 2.61 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.75 (C2), 163.31 (C5), 147.95, 143.79, 141.83, 140.17, 135.92, 135.57, 129.99, 128.98, 128.62, 127.99, 127.47, 126.58, 125.37, 123.13, 117.24 (Ar), 70.82 (C3), 66.75 (C4), 53.54 and 52.06 (C7), 34.56 and 30.93 (C6); elemental analysis calcd (%) for $C_{30}H_{24}N_4O_6S$ (568.61): C 63.37, H 4.25, N 9.85; found: C 63.07, H 4.33, N 9.83.

(3*R*,4*S*)- and (3*S*,4*R*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-1-(4-nitrophenyl)-3,4-diphenylazetidin-2-one (8b) and (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-benzyl-*N*-methylcarbamoylthio)-1-(4-nitrophenyl)-3,4-diphenylazetidin-2-one (9b): Benzaldehyde (0.21 g, 2.0 mmol) was added to a suspension of **5** (0.84 g, 2.0 mmol) in dry benzene (10 mL) and the mixture was stirred under reflux for 1 h. The solvent was evaporated in vacuo, then the residue was treated with methanol and diethyl ether, crystallizing a mixture of two diastereomers, **8b** and **9b**, which were separated by preparative TLC (benzene). The compound with higher R_f, **8b**, was crystallized from ethanol (0.37 g, 35%). M.p. 116 – 118 °C; IR (KBr): $\tilde{\nu}$ = 1760, 1650, 1330, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, 2H; Ar), 7.50 (d, 2H; Ar), 7.35 – 7.11 (m, 15H; Ar), 5.92 (s, 1H; H4), 4.53 (m, 2H; CH_2), 2.89 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.18 (C2), 165.70 (C5), 143.43, 143.00, 135.91, 135.06, 133.51, 132.17, 130.38, 128.85, 128.56, 128.40, 128.36, 128.29, 128.14, 127.96, 127.80, 127.32, 127.22, 125.18, 124.90, 119.18, 117.55 (Ar), 69.84 (C3), 68.94 (C4), 53.92 and 52.00 (C7), 34.35 (C6); elemental analysis calcd (%) for $C_{30}H_{25}N_3O_4S$ (523.61): C 68.82, H 4.81, N 8.03, S 6.12; found: C 68.93, H 4.83, N 7.96, S 5.87.

Compound **9b** was crystallized from ethanol (0.26 g, 25%). M.p. 109 – 111 °C; IR (KBr): $\tilde{\nu}$ = 1760, 1650, 1330, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, 2H; Ar), 7.86 (d, 2H; Ar), 7.52 – 7.22 (m, 13H; Ar), 6.80 (bs, 2H; Ar), 5.85 (s, 1H; H4), 4.21 (d, 2H; CH_2), 2.57 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.41 (C2), 164.25 (C5), 143.46, 142.41, 136.73, 132.63, 128.89, 128.81, 128.72, 128.57, 128.32, 128.14, 128.06, 127.62, 126.86, 125.17, 117.59, 117.43 (Ar), 70.45 (C3), 67.78 (C4), 53.58 (C7), 34.09 (C6); elemental analysis calcd (%) for $C_{30}H_{25}N_3O_4S$ (523.61): C 68.82, H 4.81, N 8.03, S 6.12; found: C 68.54, H 4.69, N 8.05, S 5.90.

(3*R*,4*S*)- and (3*S*,4*R*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-4-(4-methoxyphenyl)-1-(4-nitrophenyl)-3-phenylazetidin-2-one (8c) and (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-benzyl-*N*-methylcarbamoylthio)-4-(4-methoxyphenyl)-1-(4-nitrophenyl)-3-phenylazetidin-2-one (9c): 4-Methoxybenzaldehyde (0.20 g, 1.5 mmol) was added to a suspension of **5** (0.63 g, 1.5 mmol) in dry benzene (7.5 mL) and the mixture was stirred at reflux for 6 h. The solvent was evaporated in vacuo and the resulting residue was treated with ethanol and dichloromethane, crystallizing a mixture of **8c** and **9c** which were further purified by preparative TLC (benzene). Compound **8c** was crystallized from ethanol (0.24 g, 29%). M.p. 102 – 104 °C; IR (KBr): $\tilde{\nu}$ = 1760, 1650, 1330, 1250, 1030, 750, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, 2H; Ar), 7.50 (d, 2H; Ar), 7.35 – 6.69 (m, 14H; Ar), 5.87 (s, 1H; H4), 4.52 (m, 2H; CH_2), 3.73 (s, 3H; OCH_3), 2.89 (bs, 3H; NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.24 (C2), 165.82 (C5), 143.40, 143.09, 135.96, 135.14, 132.38, 129.18, 128.78, 128.53, 128.37, 127.98, 127.75, 127.25, 125.39, 125.17, 117.59, 113.98 (Ar), 69.63 (C3), 68.68 (C4), 55.20 (OCH_3), 53.95 and 52.01 (C7), 34.38 (C6); elemental analysis calcd (%) for $C_{31}H_{27}N_3O_5S$ (553.64): C 67.25, H 4.92, N 7.59; found: C 67.52, H 4.87, N 7.72.

Compound **9c** was crystallized from ethanol (0.17 g, 20%). M.p. 150 – 152 °C; IR (KBr): $\tilde{\nu}$ = 1750, 1650, 1330, 1250, 1030, 750, 740, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (d, 2H; Ar), 7.85 (d, 2H; Ar), 7.48 – 6.82 (m, 14H; Ar), 5.81 (s, 1H; H4), 4.23 (m, 2H; CH_2), 3.85 (s, 3H; OCH_3), 2.61 (s, 3H; NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.45 (C2), 164.14 (C5), 159.96, 143.40, 142.42, 136.93, 135.08, 130.19, 128.73, 128.56, 128.05, 127.68, 126.89, 125.13, 124.44, 117.47, 113.55 (Ar), 70.55 (C3), 67.38 (C4), 55.21 (OCH_3), 56.63 and 51.77 (C7), 34.26 (C6); elemental analysis calcd (%) for $C_{31}H_{27}N_3O_5S$ (553.64): C 67.25, H 4.92, N 7.59; found: C 67.44, H 4.81, N 7.63.

(3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-4-(4-nitrophenyl)-1,3-diphenylazetidin-2-one (9d): 4-Nitrobenzaldehyde (0.30 g, 2.0 mmol) was added to a suspension of **6** (0.74 g, 2.0 mmol) in dry benzene (10.0 mL) and the mixture was stirred and refluxed for 3 h. The solvent was evaporated under reduced pressure and, after the addition of diethyl ether, crystals of **9d** were obtained (0.31 g, 30%). This compound was recrystallized from ethanol – diethyl ether (1:5 v/v). M.p. 179 – 181 °C; IR (KBr): $\tilde{\nu}$ = 1750, 1650, 1360, 1200, 750, 740, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.21 (d, 2H; Ar), 7.89 (d, 2H; Ar), 7.74 (d, 2H; Ar), 7.47 – 7.07 (m, 11H; Ar), 6.73 (d, 2H; Ar), 5.95 (s, 1H; H4), 4.19 (m, 2H;

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CH_2), 2.60 (bs, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 163.78$ (C5), 162.84 (C2), 147.63, 141.42, 136.69, 135.73, 134.94, 130.27, 129.23, 128.59, 128.44, 128.21, 127.89, 127.75, 127.41, 126.62, 124.69, 122.78, 117.28 (Ar), 70.06 (C3), 65.61 (C4), 53.48 and 51.85 (C7), 34.46 and 34.21 (C6); elemental analysis calcd (%) for $C_{30}H_{25}N_3O_4S$ (523.61): C 68.82, H 4.81, N 8.03, S 6.12; found: C 68.71, H 4.78, N 8.05, S 6.16.

(3*R*,4*S*)- and (3*S*,4*R*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-1,3,4-triphenylazetidin-2-one (8e) and (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-benzyl-*N*-methylcarbamoylthio)-1,3,4-triphenylazetidin-2-one (9e): Benzaldehyde (0.21 g, 2.0 mmol) was added to a suspension of **6** (0.74 g, 2.0 mmol) in dry benzene (10.0 mL) and the mixture was stirred at reflux for 4 h. The solvent was evaporated in vacuo and the residue was treated with ethanol to give crystals of **8e** (0.40 g, 41%). M.p. 147–149 °C (ethanol); IR (KBr): $\tilde{\nu} =$ 1730, 1660, 1200, 750, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.41–7.02$ (m, 20H; Ar), 5.89 (s, 1H; H4), 4.54 (m, 2H; CH_2), 2.89 (m, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 166.30$ (C5), 164.64 (C2), 137.69, 136.16, 134.48, 133.49, 129.01, 128.72, 128.56, 128.30, 128.23, 128.02, 127.93, 127.62, 127.25, 124.14, 117.79 (Ar), 69.02 (C3), 68.29 (C4), 53.91 and 51.94 (C7), 34.34 (C6); elemental analysis calcd (%) for $C_{30}H_{26}N_2O_2S$ (478.61): C 75.29, H 5.48, N 5.85, S 6.70; found: C 75.18, H 5.51, N 5.89, S 6.65.

Compound **9e** crystallized from diethyl ether (0.33 g, 34%). M.p. 203–205 °C (dichloromethane–ethyl acetate–diethyl ether, 1:10:10 by v/v/v); IR (KBr): $\tilde{\nu} =$ 1740, 1660, 1200, 760, 740, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.91$ (d, 2H; Ar), 7.55 (d, 2H; Ar), 7.45–7.22 (m, 13H; Ar), 7.05 (t, 1H; Ar), 6.78 (t, 2H; Ar), 5.83 (s, 1H; H4), 4.13 (d, 2H; CH_2), 2.55 (s, 3H; CH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.13$ (C5), 163.48 (C2), 137.60, 137.21, 135.70, 133.68, 129.12, 128.96, 128.39, 128.26, 128.05, 127.74, 127.40, 126.93, 124.16, 117.49 (Ar), 69.72 (C3), 66.64 (C4), 52.57 (C7), 34.13 (C6); elemental analysis calcd (%) for $C_{30}H_{26}N_2O_2S$ (478.61): C 75.29, H 5.48, N 5.85, S 6.70; found: C 75.02, H 5.44, N 5.86, S 6.82.

(3*R*,4*S*)- and (3*S*,4*R*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-4-(4-methoxyphenyl)-1,3-diphenylazetidin-2-one (8f) and (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-benzyl-*N*-methylcarbamoylthio)-4-(4-methoxyphenyl)-1,3-diphenylazetidin-2-one (9f): 4-Methoxybenzaldehyde (0.27 g, 2.0 mmol) was added to a suspension of **6** (0.74 g, 2.0 mmol) in dry benzene (10.0 mL) with stirring and the mixture was refluxed for 10 h. The solvent was evaporated to dryness under reduced pressure and, after fractional crystallization from ethanol, **8f** (0.55 g, 54%) and **9f** (0.20 g, 20%) were separated. Compound **8f** was recrystallized from ethanol–ethyl acetate–dichloromethane (10:10:1 by v/v/v). M.p. 173–175 °C; IR (KBr): $\tilde{\nu} =$ 1740, 1650, 1250, 1030, 750, 730, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.40–7.02$ (m, 17H; Ar), 6.65 (d, 2H; Ar), 5.84 (s, 1H; H4), 4.61–4.53 (m, 2H; CH_2), 3.70 (s, 3H; OCH_3), 2.88 (bs, 3H; NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta =$ 166.44 (C5), 164.72 (C2), 159.56, 137.78, 136.22, 135.65, 133.80, 129.32, 128.99, 128.69, 128.11, 127.93, 127.29, 126.48, 124.10, 117.86, 113.63 (Ar), 68.83 (C3), 68.03 (C4), 55.14 (OCH_3), 52.16 and 51.96 (C7), 34.37 (C6); elemental analysis calcd (%) for $C_{31}H_{28}N_2O_3S$ (508.64): C 73.20, H 5.55, N 5.51, S 6.30; found: C 73.08, H 5.70, N 5.55, S 6.25.

Compound **9f** was recrystallized from ethanol–dichloromethane (1:5 by v/v). M.p. 150–152 °C; IR (KBr): $\tilde{\nu} =$ 1750, 1650, 1240, 1030, 750, 700, 690 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.90$ (d, 2H; Ar), 7.48–7.21 (m, 12H; Ar), 7.04 (t, 1H; Ar), 6.91 (d, 2H; Ar), 6.79 (m, 2H; Ar), 5.79 (bs, 1H; H4), 4.41–4.07 (m, 2H; CH_2), 3.82 (s, 3H; OCH_3), 2.58 (s, 3H; NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 164.19$ (C5), 163.51 (C2), 159.62, 137.76, 137.21, 136.10, 135.36, 130.36, 128.94, 128.47, 128.33, 128.26, 127.97, 127.56, 126.96, 125.60, 124.11, 117.50, 113.16 (Ar), 69.84 (C3), 66.28 (C4), 55.19 (OCH_3), 53.55 and 51.56 (C7), 34.15 (C6); elemental analysis calcd (%) for $C_{31}H_{28}N_2O_3S$ (508.64): C 73.20, H 5.55, N 5.51; found: C 73.50, H 5.41, N 5.60.

(2*R*,3*R*)- and (2*S*,3*S*)-2-[4-Benzyl-2-(4-methoxyphenyl)-1,3-dioxo-2,4-diazapentyl]-3-(4-nitrophenyl)-2-phenylthiirane (10): 4-Nitrobenzaldehyde (0.30 g, 2.0 mmol) was added to a suspension of **7** (0.81 g, 2.0 mmol) in dry dichloromethane (5 mL) and the reaction mixture was stirred at room temperature for 24 h. The solvent was evaporated under reduced pressure and **10** was crystallized by addition of diethyl ether (0.70 g, 63%), then recrystallized from diethyl ether–ethyl acetate–dichloromethane (10:10:1 by v/v/v). M.p. 164–166 °C; IR (KBr): $\tilde{\nu} =$ 1680, 1330, 1240, 1020, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.86$ (d, 2H; Ar), 7.26–6.72 (m, 16H; Ar), 5.15 (s, 1H; CH), 4.63 (bs, 2H; CH_2), 3.78 (s, 3H; OCH_3), 2.72 (bs, 3H; NCH_3); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 159.14$ (NCON), 155.72 (C1′), 146.96, 141.95, 135.67, 131.96, 129.60, 128.61, 128.06, 127.80, 127.61, 122.70, 114.13 (Ar), 55.48 (OCH_3), 55.05 (C2′), 52.80 (CH_2), 45.52 (C3′), 34.91 (NCH_3); elemental analysis calcd (%) for $C_{31}H_{27}N_3O_5S$ (553.64): C 67.25, H 4.92, N 7.59, S 5.79; found: C 67.15, H 5.00, N 7.78, S 5.62.

(2*R*,3*R*)- and (2*S*,3*S*)-2-[4-Benzyl-2-(4-methoxyphenyl)-1,3-dioxo-2,4-diazapentyl]-2,3-diphenylthiirane (11): Benzaldehyde (0.21 g, 2.0 mmol) was added to a solution of **7** (0.81 g, 2.0 mmol) in dry dichloromethane (10 mL) and the mixture was stirred at room temperature for 44 h. The solvent was evaporated under reduced pressure and the resultant crude was purified by column chromatography (benzene–acetonitrile eluent system). Compound **11** (0.16 g, 15%) crystallized from diethyl ether–petroleum ether (5:1 by v/v). M.p. 128–130 °C; IR (KBr): $\tilde{\nu} =$ 1660, 1250, 1030, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.25–6.70$ (m, 19H; Ar), 5.10 (s, 1H; CH), 4.68 (bs, 2H; CH_2), 3.77 (s, 3H; OCH_3), 2.74 (bs, 3H; NCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 159.05$ (NCON), 155.97 (C1′), 135.88, 134.03, 132.74, 130.14, 129.92, 129.54, 129.27, 129.05, 128.59, 127.71, 127.42, 114.00 (Ar), 55.45 (OCH_3), 54.65 (C2′), 52.72 (CH_2), 46.87 (C3′), 34.90 (NCH_3); elemental analysis calcd (%) for $C_{31}H_{28}N_2O_3S$ (508.64): C 73.20, H 5.55, N 5.51, S 6.30; found: C 73.16, H 5.65, N 5.48, S 6.23.

Reaction of 3-(4-methoxyphenyl)-2-(*N*-methyl)benzylamino-5-phenyl-1,3-thiazolium-4-olate (7) with benzaldehyde (2b): Benzaldehyde (0.64 g, 6.0 mmol) was added to a suspension of **7** (2.40 g, 6.0 mmol) in dry dichloromethane (15 mL) and the mixture was stirred at room temperature for four days. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography with benzene as eluent. Compound **12** could be isolated after crystallization from diethyl ether–petroleum ether (0.55 g, 10%). M.p. 93–95 °C; IR (KBr): $\tilde{\nu} =$ 3340, 1690, 1650, 1510, 1250, 1030 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 8.88$ (s, 1H; NH), 8.41 (m, 2H; Ar), 7.67–7.49 (m, 3H; Ar), 6.93 (m, 2H; Ar), 3.82 (s, 3H; OCH_3); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 187.57$ (Ph*C*O), 158.62 (CON), 157.04, 134.54, 133.17, 131.45, 129.78, 128.53, 121.47, 114.36 (Ar), 55.49 (CH_3); elemental analysis calcd (%) for $C_{15}H_{13}NO_3$ (255.27): C 70.58, H 5.13, N 5.49; found: C 70.32, H 5.44, N 5.48. Crystalline sulfur (0.01 g, 6%) could also be obtained from a different fraction of high R_f.

Reaction of 7 with 4-methoxybenzaldehyde (2c): Compound **2c** (0.34 g, 2.5 mmol) was added to a suspension of **7** (0.81 g, 2.0 mmol) in dry dichloromethane (15 mL) and the mixture was stirred at room temperature for 55 h. After solvent evaporation, the residue was first purified by column chromatography (benzene–acetonitrile, 50:1 v/v) and then by preparative TLC with benzene as eluent. Compound **12** could be isolated and crystallized from diethyl ether–petroleum ether (0.07 g, 14%). M.p. 93 °C.

X-ray acquisition data for compound 11: For data collection, a crystal with dimensions 0.10 mm × 0.05 mm × 0.05 mm was used. Cell parameters for the structure were obtained by least-squares refinement.[31] The structure was solved by direct methods using SHELXS 97[32] and refinement on F^2 was carried out by application of *SHELXL 97*.[33] The absorption correction was empirical (SORTAV).[34] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication no. CCDC-146111. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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