JOC Article

1,3-Dipolar Cycloaddition of 2-Dialkylaminothioisomünchnones with Aliphatic Aldehydes: Synthesis of β-Lactams and Thiiranes, Structure Elucidation, and Rationale for Chemoselective Fragmentation of Cycloadducts†

Martin Avalos, Reyes Babiano, Pedro Cintas, Fernando R. Clemente, Ruth Gordillo, José L. Jiménez,* and Juan C. Palacios

Departamento de Química Orgánica, Facultad de Ciencias, Universidad de Extremadura, E-06071 Badajoz, Spain

requejo@unex.es

Received February 11, 2003

A series of highly funtionalized β-lactams and thiiranes can be generated on treatment of 1,3-thiazolium-4-olates (thioisomünchnones) with aliphatic aldehydes. Although in some cases a variety of products have been obtained, the present paper now provides a mechanistic rationale to explain the product distribution based on stereoelectronic effects. Thus, ring fragmentation of the initial [3+2] cycloadduct is essentially dictated by the electronic character of the aryl substituent on the nitrogen atom of the parent thioisomünchnone. However, further evolution of such cycloadducts into β-lactams or thiiranes is governed by steric effects to a large extent. Evidence for such interactions has been obtained by computing PM3-optimized diastereomeric transition structures in the reaction of a thioisomünchnone with a chiral aliphatic aldehyde.

Introduction

The performance of mesoionic dipoles as substrates for 1,3-dipolar cycloadditions was well-established more than two decades ago.[1] Still, a few classes of mesoionics—such as isomünchnones and thioisomünchnones—have been incorporated into the common repertory of synthetic protocols owing to their versatility for the expeditious construction of heterocyclic systems.[2] However, most cycloadditions lead to stable cycloadducts which may undergo subsequent ring cleavage to yield a rather narrow range of five- and six-membered heterocycles.

In the early nineties, we came to cycloaddition chemistry of thioisomünchnones (the common and worldwide accepted jargon for anhydro-4-hydroxy-1,3-thiazolium hydroxides). *N*,*N*-Dialkylamino-substituted thioisomünchnones, which can easily be generated from *N*,*N*-dialkylthioureas, not only exhibited an enhanced reactivity with respect to similar masked dipoles, but also afforded products hitherto unknown in these 1,3-dipolar cycloadditions.[3−5] It was especially notable the results obtained by reaction of mesoionics **1a**−**c** with aromatic aldehydes (**2a**−**c**) (Scheme 1).

In these reactions we were gratifyingly amazed by the fact that thioisomünchnones **1a** and **1b** led to β-lactams (**4**),[6] whereas **1c** gave rise to thiiranes (**5**) under the same reaction conditions, no matter which aldehyde **2** one chooses as the reaction partner. This transformation represented a novel and stoichiometric entry[7] to this important family of constrained amides. Such findings would suggest that the cleavage of the nonisolated intermediate cycloadduct (**3**) and its further evolution could be governed by electronic factors. Our group then recognized that an analysis of the stereoelectronic effects controlling this rather capricious behavior was required. In addition, single-point energy calculations at the B3LYP/6-31G* level also confirmed the preferential exo route to β-lactams.[8]

Our next target involved the preparation of optically active β-lactams by reaction of mesoionics **1a**−**c** with a chiral building aldehyde (**6**) from D-arabinose. In stark contrast with the preceding results, no β-lactams could be detected at all, but thiiranes **8a**−**c** were detected in modest to low yields. Sometimes and depending on the reaction conditions, alkenes **9a**−**c**, arising from thiiranes

* Corresponding author. Phone: +34-924-289380. Fax: +34-924-271149.

† In loving memory of Prof. Francisco J. Higes: a good scientist, but most of all a close friend.

(1) (a) Newton, C. G.; Ramsden, C. A. *Tetrahedron* **1982**, *38*, 2965−3011. (b) Potts, K. T. In *1,3-Dipolar Cycloaddition Chemistry*; Padwa, A., Ed.; Wiley-Interscience: New York, 1984; Vol. 2, pp 1−82.

(2) (a) Osterhout, M. H.; Nadler, W. R.; Padwa, A. *Synthesis* **1994**, 123−141. (b) Padwa, A. *Top. Curr. Chem.* **1997**, *189*, 121−158.

(3) Areces, P.; Avalos, M.; Babiano, R.; Cintas, P.; González, L.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C.; Silvero, G. *Eur. J. Org. Chem.* **2001**, 2135−2144.

(4) Arévalo, M. J.; Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C. *Tetrahedron Lett.* **1999**, *40*, 8675−8678.

(5) Areces, P.; Avalos, M.; Babiano, R.; González, L.; Jiménez, J. L.; Méndez, M. M.; Palacios, J. C. *Tetrahedron Lett.* **1993**, *34*, 2999−3002.

(6) Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C. *Chem. Commun.* **1999**, 1589−1590.

(7) A series of catalytic approaches to the preparation of β-lactams has been recently envisaged. For a brief and timely revision see: Magriotis, P. A. *Angew. Chem.* **2001**, *113*, 4507−4509; *Angew. Chem., Int. Ed.* **2001**, *40*, 4377−4379.

(8) Avalos, M.; Babiano, R.; Cintas, P.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; López, I.; Palacios, J. C.; Silvero, G. *Chem. Eur. J.* **2001**, *7*, 3033−3042.

10.1021/jo034188r CCC: $25.00
Published on Web 07/12/2003

SCHEME 1

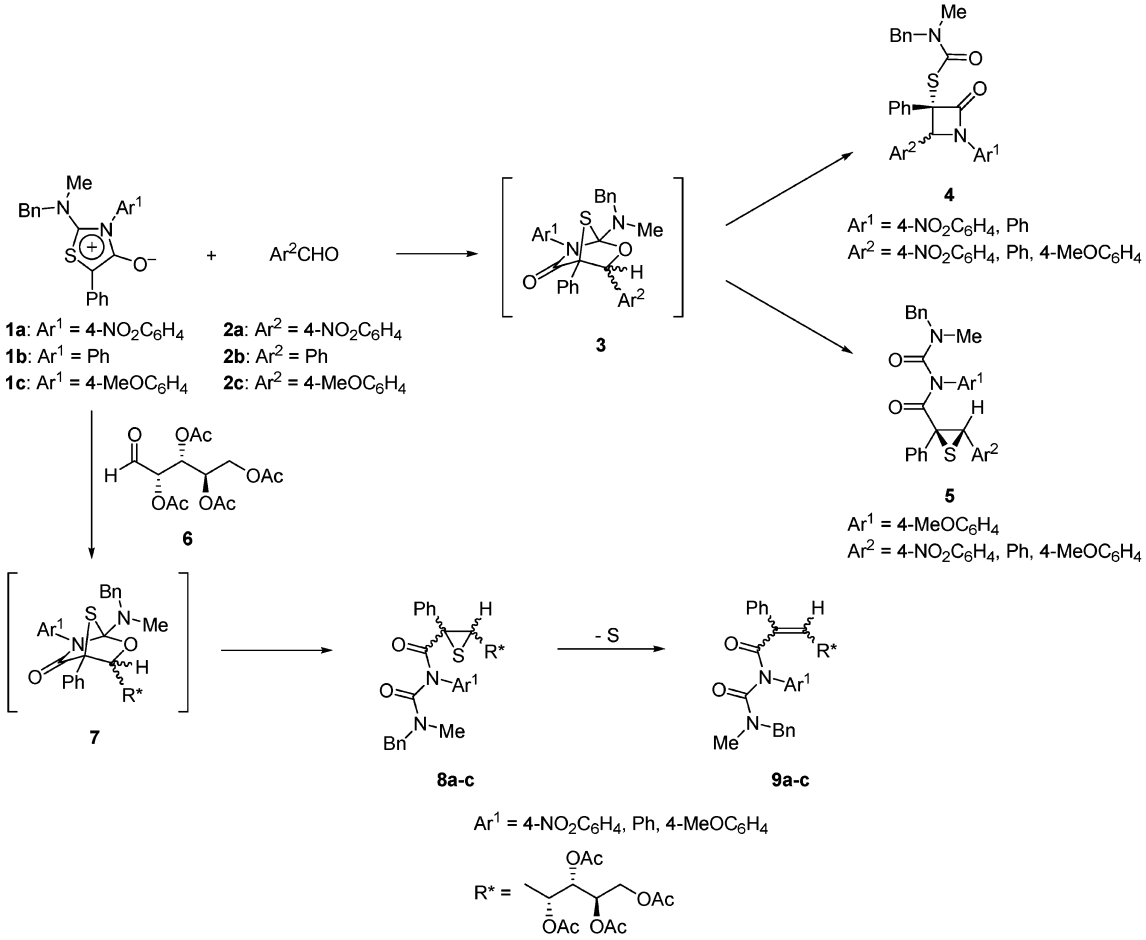
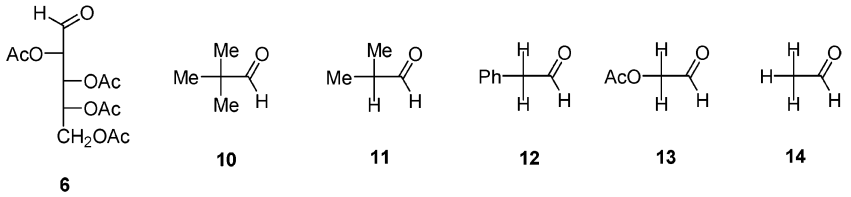


CHART 1. Aliphatic Aldehydes Used in the Cycloaddition Reactions



8 by sulfur extrusion, could also be isolated. One could then conclude that cycloadduct **7**, structurally related to **3**, evolves into three-membered rings owing to steric, rather than electronic, factors and this surmise has recently been the subject of a preliminary communication.[9]

Described below is a full account of our logical extension to diversely substituted aliphatic compounds (Chart 1), including the chiral sugar aldehyde **6**. The synthetic procedure is presented together with a mechanistic analysis that satisfactorily accounts for the full set of experimental data.

Results

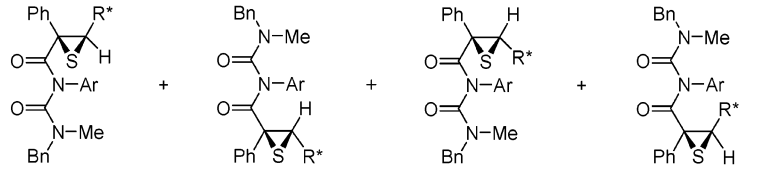
Syntheses and Structure. Reactions of mesoionics **1a**−**c**[10] with aldehyde **6** were conducted in benzene or dichloromethane at reflux. Similar results were obtained in both solvents, although the starting mesoionic was less prone to decomposition in benzene (reactions proceeded faster). Nevertheless, alkenes are often formed in this hydrocarbon solvent. Reactions of **1a**−**c** with aldehydes **10**, **12**, and **13** were run in refluxing benzene, whereas isobutyraldehyde itself (**11**, bp = 63 °C) served as the medium in its cycloaddition reactions. Reactions based on acetaldehyde (**14**, bp = 21 °C) were accomplished in CH_2Cl_2 at room temperature. Although these transformations were monitored by thin-layer chromatography, the end point could easily be determined by color discharge because the absence of the typical orange color of mesoionic species was clearly visible to the naked eye.

Up to four compounds may be obtained on treatment of 2,3,4,5-tetra-*O*-acetyl-D-arabinose (**6**) with mesoionic heterocycles **1a**−**c** (Chart 2). In each case, such substances could be separated by flash chromatography and

(9) Preliminary communication: Avalos, M.; Babiano, R.; Cintas, P.; Clemente, F. R.; Gordillo, R.; Hursthouse, M. B.; Jiménez, J. L.; Light, M. E.; Palacios, J. C. *Tetrahedron*: *Asymmetry* **2001**, *12*, 2265−2268.

(10) Avalos, M.; Babiano, R.; Cabanillas, A.; Cintas, P.; Higes, F. J.; Jiménez, J. L.; Palacios, J. C. *J. Org. Chem.* **1996**, *61*, 3738−3748.

CHART 2



15 Ar = 4-$NO_2C_6H_4$ **18** Ar = 4-$NO_2C_6H_4$ **21** Ar = 4-$NO_2C_6H_4$ **24** Ar = 4-$NO_2C_6H_4$
16 Ar = Ph **19** Ar = Ph **22** Ar = Ph **25** Ar = Ph
17 Ar = 4-$MeOC_6H_4$ **20** Ar = 4-$MeOC_6H_4$ **23** Ar = 4-$MeOC_6H_4$ **26** Ar = 4-$MeOC_6H_4$

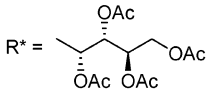
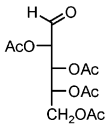


TABLE 1. Product Distributions in the Reactions of 1a−c with 6 and 11−14

	 **6**	 **11**	 **12**	 **13**	 **14**
1a	Thiirane **15** Thiirane **18** Thiirane **21** Thiirane **24**	β-lactam **27**	β-lactam **28**	β-lactam **29**	β-lactam **30**[a] β-lactam **36**[a] Alkene **45**[a]
1b	Thiirane **16** Thiirane **19** Thiirane **22** Thiirane **25**[a]	β-lactam **31** Thiirane **37**	β-lactam **32** Alkene **46**	β-lactam **33** Alkene **47** Alkene **51**	β-lactam **34**[a] Thiiranes **38**[a] + **42**[a] Alkenes **48**[a] + **52**[a]
1c	Thiirane **17** Thiirane **20** Thiirane **23** Thiirane **26**	Thiirane **39** Thiirane **43**	β-lactam **35** Thiirane **40** Alkene **49**	Alkene **50** Alkene **53**	Thiirane **41** Thiirane **44**

[a] Not isolated, detected by NMR spectroscopy.

identified as chiral thiiranes **15**−**26**. ^{1}H NMR spectra of crude mixtures recorded at 400 MHz allowed us to determine the complete product distribution (Table 1).

Suspecting that the bulky, though flexible, chiral chain of **6** might have exerted a major effect on the steric course, we embarked on an exploration of aldehyde **10**. Results were disappointing as only decomposition of the starting thioisomünchnones was observed after longer reaction times.

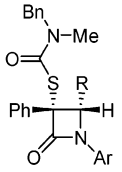
Table 1 sumarizes clearly the product of each reaction and their structures are collectively grouped in Charts 2 and 3.

Previous ambiguities as to the actual structure of the three-membered heterocycles could be ruled out by a full analysis of the X-ray crystallographic data of compounds **17** and **22**.[9] NMR data of these substances were used to correlate such structures with those of the chiral thiiranes formed on treatment of **6** with thioisomünchnones **1a**−**c**.

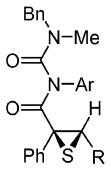
Assignments were also facilitated by the fact that the heterocyclic moieties of **15**−**17** and **18**−**20** (and likewise **21**−**23** and **24**−**26**) bear an enantiomeric relationship. This conclusion was immediately supported by the formation of alkene **55** after heating an equimolar mixture of **17** and **20** in DMSO at 100 °C. Similarly, a mixture of thiiranes **23** and **26** led to the same alkene **56** after sulfur elimination (Chart 4). Compound **54** could be isolated from the reaction mixture of **1a** and **6** and, in addition, the ^{1}H NMR spectrum (400 MHz) of a diastereomeric mixture of **15** and **18** registered in DMSO-d_6 at 87 °C revealed the formation of the (*E*)-alkene **54**.

NMR data also reveal that the H-3 resonance of (*Z*)-thiiranes is invariably more shielded than that of their (*E*)-configured counterparts. A similar trend for that signal may be observed between (*Z*)- and (*E*)-alkenes. Furthermore, most of the chemical shifts attributed to C-2 are observed at a lower field than the signals for the C-3 atoms. Likewise, the C-2 resonances for the (*Z*)-

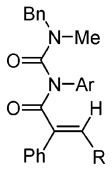
CHART 3. Structures of the Products Obtained in the Reactions of Mesoionic Heterocycles 1a−c with Achiral Aldehydes 11−14



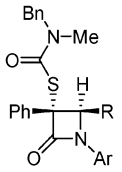
27 R = $CHMe_2$; Ar = 4-$NO_2C_6H_4$
28 R = CH_2Ph; Ar = 4-$NO_2C_6H_4$
29 R = CH_2OAc; Ar = 4-$NO_2C_6H_4$
30 R = Me; Ar = 4-$NO_2C_6H_4$
31 R = $CHMe_2$; Ar = Ph
32 R = CH_2Ph; Ar = Ph
33 R = CH_2OAc; Ar = Ph
34 R = Me; Ar = Ph
35 R = CH_2Ph; Ar = 4-$MeOC_6H_4$



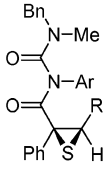
37 R = $CHMe_2$; Ar = Ph
38 R = Me; Ar = Ph
39 R = $CHMe_2$; Ar = 4-$MeOC_6H_4$
40 R = CH_2Ph; Ar = 4-$MeOC_6H_4$
41 R = Me; Ar = 4-$MeOC_6H_4$



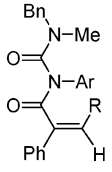
45 R = Me; Ar = 4-$NO_2C_6H_4$
46 R = CH_2Ph; Ar = Ph
47 R = CH_2OAc; Ar = Ph
48 R = Me; Ar = Ph
49 R = CH_2Ph; Ar = 4-$MeOC_6H_4$
50 R = CH_2OAc; Ar = 4-$MeOC_6H_4$



36 R = Me; Ar = 4-$NO_2C_6H_4$

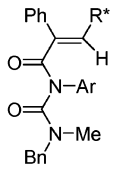


42 R = Me; Ar = Ph
43 R = $CHMe_2$; Ar = 4-$MeOC_6H_4$
44 R = Me; Ar = 4-$MeOC_6H_4$

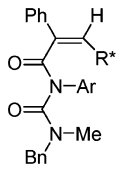


51 R = CH_2OAc; Ar = Ph
52 R = Me; Ar = Ph
53 R = CH_2OAc; Ar = 4-$MeOC_6H_4$

CHART 4



54 Ar = 4-$NO_2C_6H_4$
55 Ar = 4-$MeOC_6H_4$



56 Ar = 4-$MeOC_6H_4$

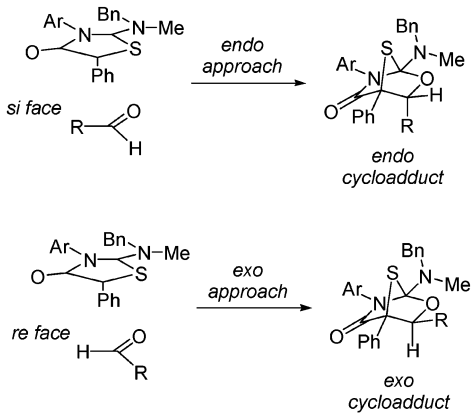
thiiranes were found to be more deshielded than those for the alternative (*E*)-configured structures.

Since the formation of only one *β*-lactam could be detected, except for the reaction of heterocycle **1a** with acetaldehyde (**14**), it was not possible to establish an unequivocal configuration for compounds **27**−**36** by means of their NMR data. Nevertheless, spectroscopic data of (*Z*)-*β*-lactams **27**−**35** are very similar, and the H4 proton appears in the range *δ* 4.93−5.49. This signal is much more deshielded than the H3 signal in thiiranes **15**−**26** and **37**−**44** (*δ* 2.49−4.40) and, in addition, more deshielded than the H4 signal in (*E*)-*β*-lactam **36** (*δ* 4.56). Moreover, both analytical and spectroscopic data for the *β*-lactams **27**−**36** are equally consistent with those of analogous systems described previously.[8] All these experimental data, together with the known tendency of aldehydes to react with thioisomünchnones adopting an endo disposition,[8] allowed us to assign a *Z* configuration to *β*-lactams **27**−**35** and an *E* configuration to *β*-lactam **36**.

Discussion

Having established that the cycloaddition reaction of 1,3-thiazolium-4-olates with aldehydes proceeds with complete regioselectivity,[8] the critical issue of stereoselection may be rationalized in terms of the endo and exo approaches (respective of the aldehyde substituent) to any enantiotopic face of the heterocyclic dipole. Such orientations involve either the *Re* or *Si* faces of the prochiral aldehydes (Scheme 2).

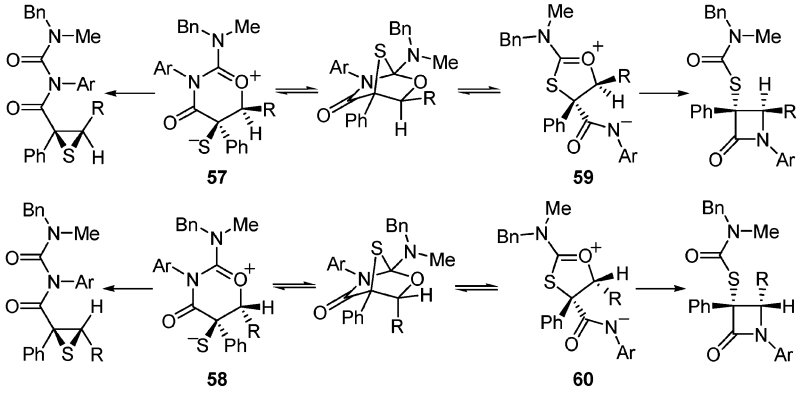
SCHEME 2



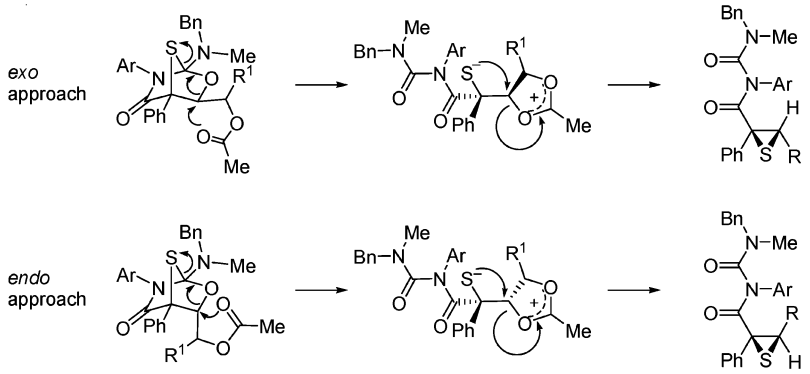
The ease with which these cycloadducts undergo ring cleavage should be ascribed to the existence of several heteroatoms capable of stabilizing, to a great extent, complete or partial charges after heterolytic scission of their bonds. Moreover, fragmentation to five- or six-membered monocyclic structures having arisen from C−N or C−S bond scission, respectively, relieves the strain. In both cases, the resulting zwitterionic structures contain a powerful nucleophile (S^- or ArN^-) and a still better leaving group (an oxonium ion).[12] A facile intramolecular nucleophilic substitution yields either *β*-lactams or thiiranes (Scheme 3).

(11) Potts, K. T.; Chen, S. J.; Kane, J.; Marshall, J. L. *J. Org. Chem.* **1977**, *42*, 1633−1638.

SCHEME 3



SCHEME 4



The observed stereospecificity of this ring opening is consistent with a concerted S_N2-like mechanism. Thus, exo cycloadducts only give rise to (*E*)-*β*-lactams and/or (*Z*)-thiiranes, while, conversely, endo isomers give (*Z*)-*β*-lactams and/or (*E*)-thiiranes.

We may then ask which factors are involved in the preferential formation of *β*-lactams or thiiranes. As to this question, the electronic effect of substituents on the *N*-aryl group should largely affect the chemical outcome. Electron-withdrawing substituents decrease the energy of the transition state by spreading the negative charge, thereby facilitating C−N bond breaking that leads to *β*-lactams. On the contrary, electron-donating groups concentrate the charge making less stable the zwitterionic intermediates **59** and **60**, while favoring the formation of 1,3-oxazinium-5-thiolate ions (**57** and **58**).

The electronic effect alone, however, does not account for the rest of the experimental evidence and an additional effect on the reactivity should almost certainly be steric at any stage of the synthesis. Thus, the thioisomünchnone **1a** reacts with aldehydes **11** and **12** to give exclusively a *β*-lactam (**27** and **28**, respectively), whereas the chiral aldehyde **6** leads to the four possible thiiranes with no trace of *β*-lactam formation. Inspection of molecular models reveals the origin of this abnormal behavior. The intramolecular attack by ArN at the first stereogenic center of the sugar chain is about as sterically hindered as attack at the analogous carbon atom of isobutyraldehyde. Accordingly, the absence of *β*-lactams in the case of **6** does not correlate with the ability of the *N*-aryl group to effect the intramolecular displacement. Severe steric strain caused by the polyacetylated side chain takes place in the initial conformation change going from cycloadducts to zwitterionic intermediates, and crowding is especially relevant in the case of **60** in which the sugar adopts an endo orientation in the cycloadduct.

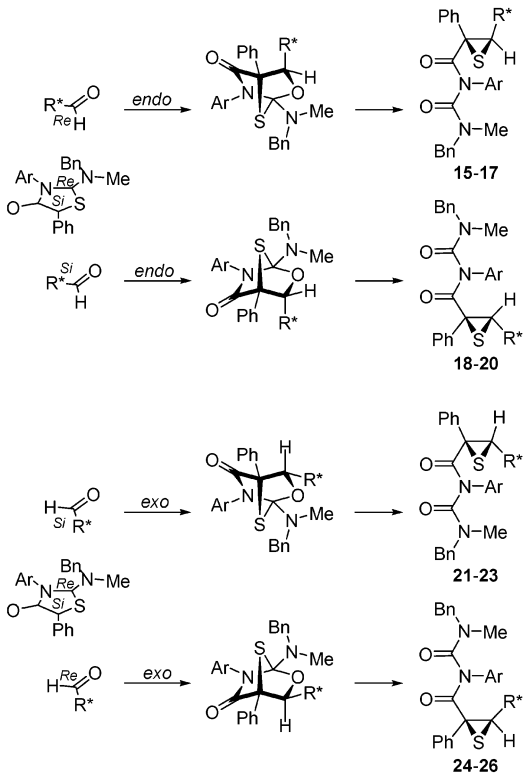
The exclusive formation of thiiranes could also be explained by the reaction mechanism outlined in Scheme 4. This pathway involves the participation of the vicinal acetyl group in the initial cycloadduct cleavage. In fact, to test this hypothesis the aldehyde **13** was also evaluated. Nevertheless, isolation of *β*-lactams **30** and **33** from cycloaddition reactions of aldehyde **13** with thioisomünchnones **1a** and **1b** allowed us to discard this reaction pathway, and therefore the influence of steric hindrance produced by the polyacetylated moiety in the nature of the final compound was fully confirmed.

The lack of reactivity exhibited by aldehyde **10** should reasonably be attributed to the steric congestion of the bimolecular transition state, irrespective of whether sulfur or nitrogen nucleophiles are involved.

Another key feature of these [3+2] cycloadditions, evidenced after conducting the synthesis with chiral aldehydes, is the absence of facial selectivity exhibited by **6**. The full sets of diastereomeric thiiranes (**15**−**17**, **18**−**20**, **21**−**23**, and **24**−**26**) were formed in essentially the same proportion. The stereochemical outcome shown in Scheme 5 indicates that (*E*)-configured thiiranes (**15**−**17** as well as **18**−**20**) stem from endo approach of **6** to both faces of the heterocyclic dipole, while exo approaches of reactants lead to (*Z*)-thiiranes.

(12) (a) Perst, H. *Oxonium Ions in Organic Chemistry*; Verlag Chemie: Deerfield Beach, FL, 1971; p 100. (b) Perst, H. In *Carbonium Ions*; Olah, G., Schleyer, P. v. R., Eds.; Wiley: New York, 1976; Vol. 5, p 1961.

SCHEME 5



The loss of facial diastereoselection with respect of the chiral aldehyde **6** is somewhat surprising assuming that the first stereocenter of its acyclic chain is adjacent to one of the reaction sites. Furthermore, the similar distribution of (*E*)- and (*Z*)-thiiranes clearly suggests that, although the bulkiness of the carbohydrate moiety should not be underestimated, it does not govern the approximation of reactants.

We have sought to identify why this chiral version proceeds with little or no face selectivity. Reasoning that the answer might lie in the nature of the transition states, we have located such structures leading to cycloadducts which, after cleavage, form the cyclized products **16**, **19**, **22**, and **25** (Figure 1). Given the large number of heavy atoms involved, the computational cost could be reduced by using semiempirical PM3 calculations[13] implemented on the Gaussian98 package.[14]

In agreement with experimental results, the gas-phase energies found for structures **TS16**, **TS19**, **TS22**, and **TS25** (Table 2) suggest that there should be no preference for a particular set of diastereomers. A further analysis of geometries reveals that the main reason for the absence of diastereoselectivity is likely to be associated with the high degree of pyramidalization of the carbonyl carbon in all the transition structures. Because that carbon is near-sp^3 hybridized, the steric factor caused by crowding of substituents, and otherwise responsible for facial discrimination, is considerably alleviated when the transition state is reached. This is why the approach to the less hindered *Si* face of the aldehyde, which would produce the preferential formation of thiiranes **18**−**23**, has not been observed.

Conclusions

This study provides a foundation for understanding the synthetic processes to form either β-lactams or thiiranes by means of thioisomünchnone−aldehyde cycloadditions. Syntheses may also be tailored to efficiently generate three- or four-membered rings with a particular configuration. We have identified the structural motifs and stereoelectronic factors that determine cycloadduct opening. Manipulation of these influences will allow a higher degree of selectivity to be achieved.

Experimental Section

General Methods. Melting points were determined on a capillary apparatus and are uncorrected. Optical rotations were measured at the sodium line at 18 ± 2 °C. Analytical and preparative TLC were performed on silica gel with monitoring by means of UV light at 254 and 360 nm and iodine vapors. Flash chromatography[15] was performed with silica gel (400−230 mesh). IR spectra were recorded in a MIDAC Corporation FTIR spectrometer on KBr pellets or as a thin film on NaCl. Nuclear magnetic resonance spectra were recorded at 400 MHz for ^{1}H and 100 MHz for ^{13}C nuclei with toluene-d_8 or DMSO-d_6. Chemical shifts are reported in ppm (δ) with Me_4Si as internal standard. High-resolution mass spectra (HRMS/CI$^+$) were obtained by the Servicio de Espectrometría de Masas at the Universidad de Córdoba, Spain. Microanalyses were obtained in a LECO CHNS-932 microanalyzer. Compounds **5**,[16] **9**,[17] and **11**−**13**[10] were prepared according to literature procedures.

General Procedure for the Synthesis of (2*R*,3*R*)-, (2*S*,3*S*)-, (2*R*,3*S*)-, and (2*S*,3*R*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-2-[4-benzyl-2-(4-nitrophenyl)-1,3-dioxo-2,4-diazapentyl]-2-phenylthiiranes (15, 18, 21, and 24) and (*E*)-*N*-(*N*′-Benzyl-*N*′-methylcarbamoyl)-*N*-(4-nitrophenyl)-2,3-dideoxy-2-phenyl-4,5,6,7-tetra-*O*-acetyl-D-*arabino*-hept-2-enamide (54). To a suspension of **1a** (0.52 g, 1.3 mmol) in benzene (20 mL) was added **6** (0.40 g, 1.3 mmol). The reaction mixture was refluxed until observance of decolorization of the solution (30 min). TLC analysis (diethyl ether−*n*-hexane, 5:1) revealed the appearance of four new compounds (R_f 0.4, 0.3, 0.2, and 0.1) which could be separated by column flash cromatography (diethyl ether−*n*-hexane, 5:1) and further purification by preparative TLC (acetonitrile−benzene, 1:10). The ^{1}H NMR spectrum of a compound having R_f 0.4 revealed the existence of a diastereomeric mixture of compounds **21** and **24** (ratio 6.4:1) (0.12 g, 12%). Compounds **15** (R_f 0.3) (0.05 g, 5%), **18** (R_f 0.2) (0.02 g, 2%), and **54** (R_f 0.1) (0.02 g, 2%) could be obtained diastereomerically pure and crystallized from diethyl ether−*n*-hexane as colorless solids.

(13) Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209−220.

(14) Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Gonzalez, C.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. *Gaussian 98*, Revision A.7; Gaussian, Inc.: Pittsburgh, PA, 1998.

(15) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923−2925.

(16) Wolfrom, M. L.; Weisblat, D. I.; Zophy, W. H.; Waisbrot, S. W. *J. Am. Chem. Soc.* **1941**, *63*, 201−203 and references therein.

(17) Shiao, M. J.; Yang, C. Y.; Lee, S. H.; Wu, T. C. *Synth. Commun.* **1988**, *18*, 359−366.

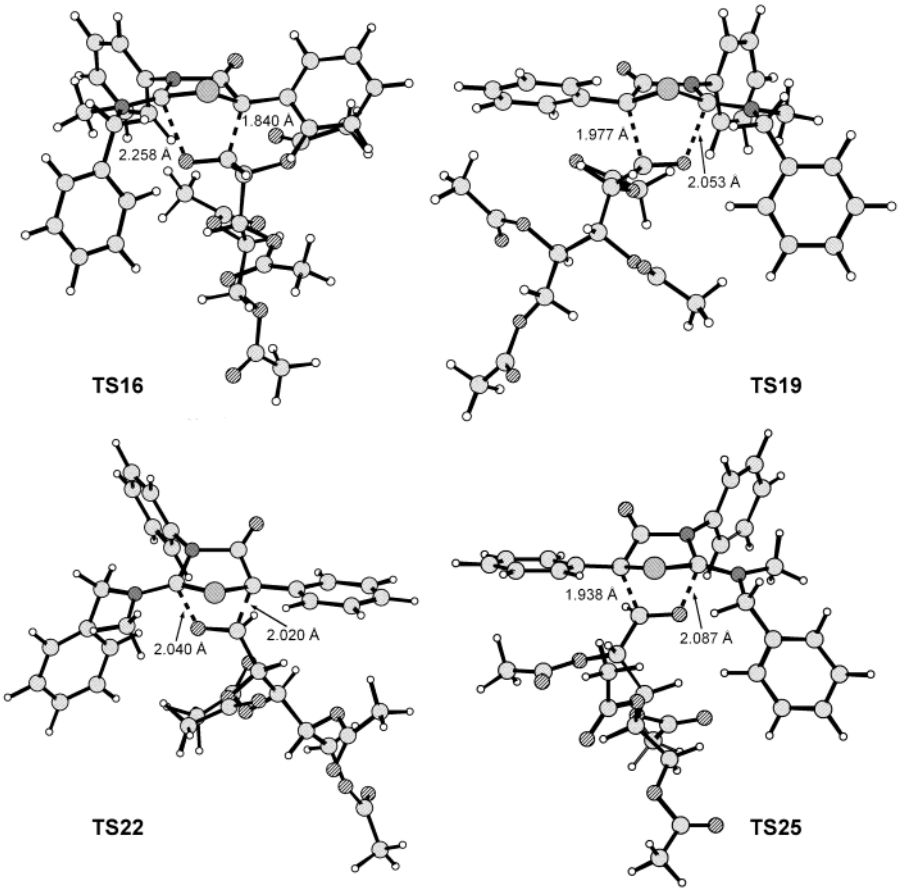


FIGURE 1. PM3-optimized diastereomeric transition structures for the 1,3-dipolar cycloaddition of **3** with **5**.

TABLE 2. Calculated Energies (in kcal/mol, PM3 level) for Structures TS16, TS29, TS22, and TS25 (Figure 1)

	energy
TS16	−237.3
TS19	−235.7
TS22	−236.7
TS25	−236.1

Procedure b for the Synthesis of 15, 18, 21, and 24. A solution of **1a** (0.29 g, 0.9 mmol) and **6** (0.38 g, 0.9 mmol) in CH_2Cl_2 (20 mL) was refluxed until observance of decolorization of the solution (3 h). TLC analysis (diethyl ether−*n*-hexane, 5:1) of the reaction mixture revealed the formation of three new compounds (R_f 0.4, 0.3, and 0.2) which could be separated by preparative TLC (diethyl ether−*n*-hexane, 5:1). The ^{1}H NMR spectrum of a compound having R_f 0.4 revealed the existence of a diastereomeric mixture of compounds **21** and **24** (ratio 4.6:1) (0.13 g, 19%). Compounds **15** (R_f 0.3) (0.22 g, 33%) and **18** (R_f 0.2) (0.04 g, 6%) could be obtained diastereomerically pure and crystallized from diethyl ether−*n*-hexane as colorless solids.

Compound 15: mp 85 °C; $[\alpha]_D$ +165.6 (*c* 0.4, $CHCl_3$); IR (KBr) 1745, 1670, 1665 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 350 K) δ 7.57 (m, 4H), 7.08−6.85 (m, 10H), 5.15 (dd, J = 9.2, 1.9 Hz, 1H), 5.01 (m, 1H), 4.63 (dd, J = 9.6, 1.9 Hz, 1H), 4.36 (d, J = 9.6 Hz, 1H), 4.13 (m, 2H), 3.97 (m, 1H), 3.92 (dd, J = 12.5, 4.9 Hz, 1H), 2.30 (br s, 3H), 1.99 (s, 3H), 1.77 (s, 3H), 1.73 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.4, 170.0, 169.6, 169.5, 161.0, 155.3, 147.7, 144.1, 136.9, 133.2, 131.1, 129.5, 129.1, 128.8, 128.6, 124.6, 71.7, 70.5, 69.3, 62.7, 54.1, 53.5, 44.5, 35.5, 20.8, 20.7. Anal. Calcd for $C_{36}H_{37}N_3O_{12}S$: C, 58.77; H, 5.07; N, 5.71; S, 4.36. Found: C, 58.60; H, 4.89; N, 5.83; S, 4.05.

Compound 18: mp 85 °C; $[\alpha]_D$ −170.6 (*c* 0.8, $CHCl_3$); IR (KBr) 1745, 1690, 1680 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 350 K) δ 7.60 (d, J = 8.8 Hz, 2H), 7.19−6.91 (m, 12H), 5.58 (dd, J = 8.2, 3.0 Hz, 1H), 5.08 (m, 1H), 4.47 (dd, J = 9.4, 2.9 Hz, 1H), 4.35 (d, J = 9.4 Hz, 1H), 4.29 (dd, J = 12.3, 2.3 Hz, 1H), 4.12 (m, 3H), 2.34 (s, 3H), 1.76 (s, 3H), 1.74 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.7, 170.0, 168.5, 155.8, 148.3, 141.3, 136.9, 133.3, 130.5, 129.9, 129.7, 129.4, 128.9, 124.7, 73.0, 71.9, 70.4, 62.7, 54.3, 54.2, 43.5, 35.5, 21.0, 20.8, 20.7. Anal. Calcd for $C_{36}H_{37}N_3O_{12}S$: C, 58.77; H, 5.07; N, 5.71; S, 4.36. Found: C, 58.70; H, 5.37; N, 5.62; S, 4.04.

Diastereomeric mixture of 21 and 24: ^{1}H NMR (400 MHz, toluene-d_8, 350 K) δ 7.85−6.94 (m, 28H), 6.35 (d, J = 8.1 Hz, 2H), 5.81 (m, 2H), 5.43 (m, 2H), 5.31 (m, 1H), 4.49−4.13 (m, 8H), 3.46 (d, J = 9.6 Hz, 1H), 3.20 (d, J = 8.1 Hz, 1H), 2.56 (br s, 3H), 2.47 (s, 3H), 2.04 (s, 3H), 1.84−1.61 (m, 21H).

Compound 54: mp 71 °C, $[\alpha]_D$ −18.5 (*c* 0.1, $CHCl_3$); IR (KBr) 1750, 1740, 1730, 1695, 1680 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 350 K) δ 7.73 (d, J = 8.8 Hz, 2H), 7.57 (d, J = 7.3 Hz, 2H), 7.08−6.89 (m, 10H), 6.45 (d, J = 8.4 Hz, 1H), 5.80 (dd, J = 8.4, 3.5 Hz, 1H), 5.38 (dd, J = 7.8, 3.7 Hz, 1H), 5.26 (m, 1H), 4.18 (m, 2H), 4.07 (m, 2H), 2.27 (br s, 3H), 1.88 (s, 3H), 1.71 (s, 3H), 1.69 (s, 3H), 1.67 (s, 3H); ^{1}H NMR (400 MHz, DMSO-d_6, 360 K) δ 8.15 (d, J = 9.1 Hz, 2H), 7.37−7.14 (m, 12H), 6.25 (d, J = 8.3 Hz, 1H), 5.49 (dd, J = 8.5, 3.7 Hz, 1H), 5.13 (dd, J = 7.0, 3.9 Hz, 1H), 5.03 (m, 1H), 4.39 (s, 2H), 4.11 (dd, J = 12.3, 3.1 Hz, 1H), 4.03 (dd, J = 12.3, 5.9 Hz, 1H), 2.63 (s, 3H), 2.08 (s, 3H), 1.96 (s, 3H), 1.89 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.3, 169.9, 160.8, 156.3, 148.0, 147.0, 135.1, 134.2, 130.7, 130.0, 129.7, 129.4, 129.3, 127.5, 125.2, 72.5, 70.3, 70.1, 62.9, 54.4, 35.7, 20.8.

Anal. Calcd for $C_{36}H_{37}N_3O_{12}$: C, 61.45; H, 5.30; N, 5.97. Found: C, 61.19; H, 5.23; N, 5.79.

Synthesis of (2*R*,3*R*)-, (2*S*,3*S*)-, and (2*R*,3*S*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-2-[4-benzyl-1,3-dioxo-2-phenyl-2,4-diazapentyl]-2-phenylthiiranes (16, 19, and 22). These substances were obtained from **1b** (0.47 g, 1.3 mmol) and **6** (0.40 g, 1.3 mmol) according to the general procedure b described above. The reaction mixture was refluxed until observance of decolorization of the solution (1 h): **22** (R_f 0.4.), **16** (R_f 0.3), and **19** (R_f 0.2). Purification by preparative TLC (diethyl ether−*n*-hexane, 5:1) gave **16** (0.24 g, 28%) and **19** (0.06 g, 7%) and as colorless solids.

Compound 16: mp 72 °C; $[\alpha]_D$ +140.9 (*c* 0.5, $CHCl_3$); IR (KBr) 1749, 1689 cm^{-1}; ^1H NMR (400 MHz, toluene-d_8, 350 K) δ 7.5 (br s, 2H), 7.09−6.85 (m, 13H), 5.16 (d, J = 8.9 Hz, 1H), 5.03 (m, 1H), 4.65 (d, J = 9.7 Hz, 1H), 4.37 (dd, J = 9.8, 1.5 Hz, 1H), 4.16 (m, 3H), 3.90 (dd, J = 12.4, 4.9 Hz, 1H), 2.48 (br s, 3H), 2.00 (s, 3H), 1.76 (s, 3H), 1.73 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.4, 170.2, 169.8, 169.6, 156.4, 139.1, 137.6, 133.9, 131.0, 129.9, 129.5, 129.1, 128.4, 72.1, 70.7, 69.6, 62.9, 54.2, 53.9, 44.7, 35.5, 21.0. Anal. Calcd for $C_{36}H_{38}N_2O_{10}S$: C, 62.60; H, 5.54; N, 4.05; S, 4.64. Found: C, 62.20; H, 5.43; N, 4.31; S, 4.73.

Compound 19: mp 74 °C; $[\alpha]_D$ −162.4 (*c* 0.2, $CHCl_3$); IR (KBr) 1751, 1689 cm^{-1}; ^1H NMR (400 MHz, toluene-d_8, 350 K) δ 7.21 (br s, 2H), 7.10−6.72 (m, 13H), 5.62 (d, J = 8.1, 2.2 Hz, 1H), 5.07 (m, 1H), 4.47 (dd, J = 9.3, 2.7 Hz, 1H), 4.32 (m, 3H), 4.15 (m, 2H), 2.50 (s, 3H), 1.76 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.4, 170.0, 168.3, 155.5, 138.9, 137.5, 130.4, 130.0, 129.6, 129.3, 129.2, 129.0, 128.5, 73.0, 72.1, 70.4, 62.8, 54.2, 43.4, 35.3, 21.1, 20.8, 20.7. Anal. Calcd for $C_{36}H_{38}N_2O_{10}S$: C, 62.60; H, 5.54; N, 4.05; S, 4.64. Found: C, 62.43; H, 5.64; N, 4.21; S, 4.68.

Compound 22: mp 161 °C; $[\alpha]_D$ −176.3 (*c* 1.0, $CHCl_3$); IR (KBr) 1751, 1692, 1655 cm^{-1}; ^1H NMR (400 MHz, toluene-d_8, 350 K) δ 7.85 (d, J = 7.2 Hz, 2H), 7.35 (d, J = 7.5 Hz, 2H), 7.13−6.91 (m, 11H), 5.83 (dd, J = 7.4, 2.1 Hz, 1H), 5.49 (dd, J = 9.5, 2.2 Hz, 1H), 5.31 (m, 1H), 4.44 (m, 2H), 4.26 (m, 2H), 3.42 (d, J = 9.5 Hz, 1H), 2.59 (s, 3H), 2.02 (s, 3H), 1.82 (s, 3H), 1.73 (s, 3H), 1.68 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.5, 170.4, 170.1, 169.9, 169.3, 157.5, 140.0, 139.5, 137.4, 130.7, 129.8, 129.5, 129.4, 128.9, 128.6, 128.2, 74.1, 73.1, 71.2, 62.8, 56.5, 54.5, 46.5, 35.8, 21.4, 21.2, 20.8, 20.6. Anal. Calcd for $C_{36}H_{38}N_2O_{10}S$: C, 62.60; H, 5.54; N, 4.05; S, 4.64. Found: C, 62.20; H, 5.61; N, 4.19; S, 4.88.

Synthesis of (2*R*,3*R*)-, (2*S*,3*S*)-, (2*R*,3*S*)-, and (2*S*,3*R*)-3-(1′,2′,3′,4′-Tetra-*O*-acetyl-D-*arabino*-tetritol-1′-yl)-2-[4-benzyl-2-(4-methoxyphenyl)-1,3-dioxo-2,4-diazapentyl]-2-phenylthiiranes (17, 20, 23, and 26). These substances were obtained from **1c** (0.51 g, 1.3 mmol) and **6** (0.40 g, 1.3 mmol) according to the general procedure b described above. The reaction mixture was refluxed until observance of decolorization of the solution (1 h): diastereomeric mixture of **23** and **26** (R_f 0.4), **17** (R_f 0.3), and **20** (R_f 0.2). Purification by preparative TLC (diethyl ether−*n*-hexane 5:1) gave **17** (R_f 0.3) (0.39 g, 43%), **20** (R_f 0.2) (0.08 g, 8%), and a diastereomeric mixture of **23** and **26** (ratio 1:1.3) (0.13 g, 15%).

Compound 17: mp 140 °C; $[\alpha]_D$ +110.1 (*c* 1.2, $CHCl_3$); IR (KBr) 2940, 1740, 1670 cm^{-1}; ^1H NMR (400 MHz, toluene-d_8, 350 K) δ 7.48 (br s, 2H), 7.12−6.95 (m, 10H), 6.44 (d, J = 8.5 Hz, 2H), 5.19 (dd, J = 8.9, 1.7 Hz, 1H), 5.08 (m, 1H), 4.69 (dd, J = 9.5, 1.8 Hz, 1H), 4.40 (d, J = 9.7 Hz, 1H), 4.32 (br s, 2H), 4.17 (dd, J = 12.4, 2.3 Hz, 1H), 3.93 (dd, J = 12.4, 5.1 Hz, 1H), 3.32 (s, 3H), 2.63 (br s, 3H), 2.05 (s, 3H), 1.79 (s, 3H), 1.75 (s, 3H), 1.61 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.4, 170.2, 169.8, 169.6, 160.4, 156.7, 137.7, 134.0, 131.5, 130.7, 129.9, 129.5, 129.2, 129.1, 129.0, 128.4, 115.0, 72.2, 70.6, 69.5, 62.9, 55.8, 54.2, 54.0, 44.8, 35.4, 21.0, 20.9. Anal. Calcd for $C_{37}H_{40}N_2O_{11}S$: C, 61.65; H, 5.59; N, 3.88; S, 4.44. Found: C, 61.79; H, 5.34; N, 3.66; S, 4.19.

Compound 20: mp 69 °C; $[\alpha]_D$ −88.3 (*c* 0.4, $CHCl_3$); IR (KBr) 1740, 1680 cm^{-1}; ^1H NMR (400 MHz, toluene-d_8, 350 K) δ 7.20−6.93 (m, 12H), 6.46 (d, J = 8.6 Hz, 2H), 5.59 (dd, J = 8.1, 2.6 Hz, 1H), 5.07 (m, 1H), 4.47 (dd, J = 9.5, 2.4 Hz, 1H), 4.32 (m, 4H), 4.13 (dd, J = 12.4, 5.0 Hz, 1H), 3.35 (s, 3H), 2.62 (s, 3H), 1.78 (s, 3H), 1.74 (s, 3H), 1.68 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) δ 170.4, 170.2, 170.0, 168.3, 160.5, 155.2, 137.7, 133.8, 131.5, 130.1, 129.6, 129.3, 129.1, 128.9, 128.4, 115.1, 72.9, 72.1, 70.4, 62.7, 55.9, 54.3, 54.1, 43.4, 35.3, 21.1, 20.8, 20.7. Anal. Calcd for $C_{37}H_{40}N_2O_{11}S$: C, 61.65; H, 5.59; N, 3.88; S, 4.44. Found: C, 61.20; H, 5.35; N, 3.40; S, 4.30.

Diastereomeric mixture of 23 and 26: ^1H NMR (400 MHz, toluene-d_8, 350 K) δ 7.81 (d, J = 7.6 Hz, 2H), 7.64 (br s, 2H), 7.24 (d, J = 8.8 Hz, 2H), 7.10−6.98 (m, 18H), 6.62 (d, J = 9.0 Hz, 2H), 6.55 (d, J = 8.5 Hz, 2H), 6.42 (dd, J = 8.1, 4.0 Hz, 1H), 5.82 (m, 2H), 5.48 (dd, J = 9.5, 2.5 Hz, 1H), 5.41 (m, 1H), 5.31 (m, 1H), 4.47 (dd, J = 12.4, 2.7 Hz, 1H), 4.38 (m, 5H), 4.26 (dd, J = 12.6, 5.2 Hz, 1H), 4.18 (dd, J = 12.3, 5.8 Hz, 1H), 3.37 (d, J = 9.5 Hz, 1H), 3.30 (br s, 6H), 3.10 (d, J = 8.8 Hz, 1H), 2.78 (br s, 3H), 2.64 (s, 3H), 2.02 (s, 3H), 1.85−1.59 (m, 21H); ^{13}C NMR (100 MHz, toluene-d_8, 350 K) 170.7, 170.5, 170.4, 170.3, 170.1, 169.9, 169.4, 160.6, 160.3, 157.9, 157.2, 140.0, 138.3, 137.5, 132.1, 131.7, 130.9, 130.6, 130.0, 129.7, 129.5, 129.3, 129.1, 129.0, 128.5, 128.4, 115.4, 115.2, 74.1, 73.3, 73.0, 71.2, 70.7, 63.4, 62.8, 56.6, 56.2, 55.8, 54.5, 46.5, 45.5, 35.9, 21.5, 21.4, 21.3, 21.2, 21.0, 20.9, 20.6. Anal. Calcd for $C_{37}H_{40}N_2O_{11}S$: C, 61.65; H, 5.59; N, 3.88; S, 4.44. Found: C, 61.44; H, 5.62; N, 3.51; S, 4.01.

Synthesis of (*E*)-*N*-(*N*′-Benzyl-*N*′-methylcarbamoyl)-*N*-(4-methoxyphenyl)-2,3-dideoxy-2-phenyl-4,5,6,7-tetra-*O*-acetyl-D-*arabino*-hept-2-enamide (55) from 17 and 20. A solution of a diastereomeric mixture of **17** and **20** (0.10 g, 0.1 mmol) in DMSO (1 mL) was heated for 1 h at 100 °C. Following workup, the solution was diluted with 5 mL of distilled water and extracted with diethyl ether to remove DMSO, the combined ethereal layers were dried with anhydrous magnesium sulfate, and the solvent was evaporated. TLC analysis (diethyl ether−*n*-hexane, 5:1) revealed the complete disappearance of **17** and the appearance of **55** (R_f 0.1), which crystallized form diethyl ether−*n*-hexane as a colorless solid (0.03 g, 37%).

Compound 55: mp 55.8 °C, $[\alpha]_D$ +11.2 (*c* 0.3, $CHCl_3$); IR (KBr) 1749, 1683 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 360 K) δ 7.34−7.25 (m, 6H), 7.14 (m, 4H), 6.97 (d, J = 6.9 Hz, 2H), 6.85 (d, J = 8.8 Hz, 2H), 6.09 (d, J = 8.7 Hz, 1H), 5.45 (dd, J = 8.7, 3.8 Hz, 1H), 5.11 (dd, J = 6.9, 4.0 Hz, 1H), 5.01 (m, 1H), 4.42 (s, 2H), 4.08 (dd, J = 12.3, 3.3 Hz, 1H), 4.03 (dd, J = 12.3, 5.9 Hz, 1H), 3.76 (s, 3H), 2.70 (s, 3H), 2.06 (s, 3H), 1.95 (s, 3H), 1.89 (s, 3H), 1.87 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 360 K) δ 169.3, 168.8, 168.2, 158.3, 155.5, 141.2, 136.0, 133.3, 130.6, 129.6, 128.2, 128.0, 127.8, 127.6, 127.3, 127.0, 114.2, 70.7, 68.4, 67.6, 61.2, 55.2, 52.2, 34.6, 19.8. Anal. Calcd for $C_{37}H_{40}N_2O_{11}$: C, 64.52; H, 5.85; N, 4.07. Found: C, 64.13; H, 6.16; N, 4.05.

Synthesis of (*Z*)-*N*-(*N*′-Benzyl-*N*′-methylcarbamoyl)-*N*-(4-methoxyphenyl)-2,3-dideoxy-2-phenyl-4,5,6,7-tetra-*O*-acetyl-D-*arabino*-hept-2-enamide (56) from 23 and 26. A solution of a diastereomeric mixture of **23** and **26** (0.10 g, 0.1 mmol) in DMSO (1 mL) was heated for 1 h at 100 °C. Following workup, the solution was diluted with 5 mL of distilled water and extracted with diethyl ether to remove DMSO, the combined ethereal layers were dried with anhydrous magnesium sulfate, and the solvent was evaporated. TLC analysis (diethyl ether−*n*-hexane, 5:1) revealed the complete disappearance of **23** and **26** and the appearance of **56** (R_f 0.3), which crystallized form diethyl ether−*n*-hexane as a colorless solid (0.04 g, 37%).

Compound 56: mp 61 °C, $[\alpha]_D$ −167.6 (*c* 0.3, $CHCl_3$); IR (KBr) 1749, 1693 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 360 K) δ 7.31−7.14 (m, 10H), 7.01 (d, J = 8.5 Hz, 2H), 6.74 (d, J = 8.3 Hz, 2H), 6.01 (dd, J = 8.7, 3.9 Hz, 1H), 5.87 (d, J = 8.8 Hz,

1H), 5.9 (dd, J = 6.6, 4.0 Hz, 1H), 5.20 (m, 1H), 4.43 (br s, 2H), 4.31 (dd, J = 12.3, 3.0 Hz, 1H), 4.16 (dd, J = 12.1, 6.1 Hz, 1H), 3.71 (s, 3H), 2.77 (br s, 3H), 2.08 (s, 3H), 2.06 (s, 3H), 1.99 (s, 3H), 1.94 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6, 360 K) δ 169.5, 169.0, 168.9, 166.9, 158.4, 154.8, 140.9, 135.8, 135.4, 129.5, 128.0, 127.7, 127.2, 126.9, 125.9, 113.9, 71.4, 68.6, 68.3, 61.4, 55.2, 52.2, 34.4, 20.2, 19.9. Anal. Calcd for $C_{37}H_{40}N_2O_{11}$: C, 64.52; H, 5.85; N, 4.07. Found: C, 64.48; H, 5.89; N, 4.03.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-4-isopropyl-1-(4-nitrophenyl)-3-phenylazetidin-2-one (27). A suspension of **1a** (0.50 g, 1.2 mmol) in 5 mL of redistilled isobutyraldehyde (**11**) was refluxed under Argon atmosphere and decolorization of the solution was instantaneouly observed. TLC analysis (diethyl ether−*n*-hexane, 1:1) revealed the appearance of a new product **27** (R_f 0.3). Purification by flash chromatography (diethyl ether−*n*-hexane, 1:1) gave **27** (0.44 g, 76%) as a yellow pale solid.

Compound 27: mp 63 °C; IR (KBr) 2965, 2922, 1767, 1657, 1593, 1516, 1497 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.88 (d, J = 9.0 Hz, 2H), 7.77 (m, 2H), 7.40 (d, J = 9.1 Hz, 2H), 7.09 (m, 8H), 4.95 (d, J = 4.8 Hz, 1H), 4.15 (m, 2H), 2.48 (s, 3H), 2.07 (m, 1H), 0.90 (d, J = 6.9 Hz, 3H), 0.55 (d, J = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 400 K) δ 167.7, 166.6, 145.3, 145.1, 137.2, 136.2, 129.9, 129.7, 129.2, 128.6, 125.6, 125.4, 120.2, 119.9, 72.6, 68.9, 53.8, 34.9, 30.7, 22.3, 19.2. HRMS (CI$^+$) calcd for $C_{27}H_{27}N_3O_4S$ + H$^+$ 490.1801, found 490.1814.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-4-isopropyl-1,3-diphenylazetidin-2-one (31) and (2*R*,3*R*)- and (2*S*,3*S*)-2-(4-Benzyl-1,3-dioxo-2-phenyl-2,4-diazapentyl)-3-isopropyl-2-phenylthiirane (37). A suspension of **1b** (0.50 g, 1.3 mmol) in 5 mL of redistilled isobutyraldehyde (**11**) was refluxed under Argon atmosphere until observance of decolorization of the solution (10 min). TLC analysis (diethyl ether−*n*-hexane, 1:1) revealed the appearance of two new compounds **37** (R_f 0.5) and **31** (R_f 0.4). Purification by preparative TLC (diethyl ether−*n*-hexane, 1:1) gave **31** (0.06 g, 10%) as a colorless oil and **37** (0.04 g, 7%) as a colorless solid.

Compound 31: IR (NaCl) 2965, 1757, 1659, 1599, 1495 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.54 (d, J = 8.2 Hz, 2H), 7.16−6.86 (m, 11H), 5.04 (d, J = 4.5 Hz, 1H), 4.17 (m, 2H), 2.45 (s, 3H), 2.17 (m, 1H), 0.95 (dd, J = 7.0, 0.7 Hz, 3H), 0.58 (dd, J = 7.0, 0.8 Hz, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 400 K) δ 167.2, 165.6, 140.2, 137.7, 129.8, 129.6, 129.4, 129.2, 128.7, 128.5, 125.6, 121.4, 72.2, 68.3, 53.8, 34.9, 30.8, 22.7, 18.8. HRMS (CI$^+$) calcd for $C_{27}H_{28}N_2O_2S$ + H$^+$ 445.1950, found 445.1975.

Compound 37: mp 51 °C; IR (KBr) 3069, 3034, 2961, 2922, 2870, 1686, 1593, 1491, 1452 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.25−6.84 (m, 15H), 4.30 (m, 2H), 3.79 (d, J = 8.9 Hz, 1H), 2.59 (s, 3H), 0.89 (d, J = 5.9 Hz, 3H), 0.78 (m, 4H); ^{13}C NMR (100 MHz, toluene-d_8, 400 K) δ 170.5, 156.6, 137.6, 135.2, 130.6, 129.5, 129.3, 128.9, 128.7, 128.3, 55.6, 54.3, 54.1, 35.2, 31.3, 24.0, 20.8. HRMS (CI$^+$) calcd for $C_{27}H_{28}N_2O_2$-S + H$^+$ 445.1950, found 445.1963.

Synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-2-[4-Benzyl-2-(4-methoxyphenyl)-1,3-dioxo-2,4-diazapentyl]-3-isopropyl-2-phenylthiirane (39) and (2*R*,3*S*)- and (2*S*,3*R*)-2-[4-Benzyl-2-(4-methoxyphenyl)-1,3-dioxo-2,4-diazapentyl]-3-isopropyl-2-phenylthiirane (43). A suspension of **1c** (0.50 g, 1.22 mmol) in 5 mL of redistilled isobutyraldehyde (**11**) was refluxed under Argon atmosphere until observance of decolorization of the solution (20 min). TLC analysis (diethyl ether−*n*-hexane, 1:1) revealed the appearance of two new compounds **43** (R_f 0.5) and **39** (R_f 0.4). Purification by preparative TLC (diethyl ether−*n*-hexane 1:1) gave **39** (0.35 g, 59%) and **43** (0.01 g, 2%) as colorless solids.

Compound 39: mp 55 °C; IR (KBr) 2963, 1696, 1605, 1593, 1495 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.21−6.87 (m, 12H), 6.38 (d, J = 8.8 Hz, 2H), 4.41 (d, J = 13.2 Hz, 1H), 4.26 (d, J = 15.0 Hz, 1H), 3.75 (d, J = 9.2 Hz, 1H), 3.25 (s, 3H), 2.64 (s, 3H), 0.85 (d, J = 6.2 Hz, 3H), 0.74 (m, 4H); ^{13}C NMR (100 MHz, toluene-d_8, 400 K) δ 170.8, 156.9, 137.8, 135.3, 131.8, 130.4, 129.5, 128.9, 128.7, 128.5, 128.3, 114.8, 55.8, 55.7, 54.4, 54.1, 35.3, 31.3, 24.0, 20.8. Anal. Calcd for $C_{28}H_{30}N_2O_3S$: C, 70.86; H, 6.37; N, 5.90; S, 6.75. Found: C, 70.55; H, 6.62; N, 5.75; S, 6.39.

Compound 43: mp 123 °C; IR (KBr) 3046, 2955, 1676, 1605, 1508 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.70 (d, J = 7.1 Hz, 2H), 7.11−6.98 (m, 10H), 6.53 (d, J = 9.0 Hz, 2H), 4.37 (s, 2H), 3.28 (s, 3H), 2.61 (s, 3H), 2.49 (d, J = 9.8 Hz, 1H), 1.95 (m, 1H), 1.37 (d, J = 6.4 Hz, 3H), 1.06 (d, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 400 K) δ 170.2, 160.2, 157.5, 140.6, 137.7, 132.2, 130.4, 129.9, 129.7, 129.5, 129.2, 129.0, 128.5, 115.2, 58.7, 57.1, 55.7, 54.3, 35.5, 34.3, 24.3, 22.1. HRMS (CI$^+$) calcd for $C_{28}H_{30}N_2O_3S$ + H$^+$ 475.2055, found 475.2032.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-4-Benzyl-3-(*N*-benzyl-*N*-methylcarbamoylthio)-3-phenyl-1-(4-nitrophenyl)-azetidin-2-one (28). To a suspension of **1a** (0.50 g, 1.2 mmol) in benzene (5 mL) was added 0.2 mL (1.7 mmol) of phenylacetaldehyde (**12**). The reaction mixture was refluxed and instantaneous decolorization of the solution was observed. TLC analysis (diethyl ether−*n*-hexane, 1:1) revealed the appearance of a new compound **28** (R_f 0.3). Purification by flash chromatography (diethyl ether−*n*-hexane, 1:1) gave **28** (0.48 g, 74%) as a yellow pale solid.

Compound 28: mp 79 °C; IR (KBr) 3077, 2924, 1767, 1555, 1514 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.33 (m, 4H), 7.18−6.93 (m, 15H), 5.42 (m, 1H), 4.17 (s, 2H), 2.98 (dd, J = 15.1, 5.3 Hz, 1H), 2.58 (dd, J = 15.1, 7.5 Hz, 1H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 400 K) δ 167.0, 166.1, 144.9, 144.15, 138.7, 137.2, 135.7, 130.3, 129.8, 128.7, 127.9, 125.4, 119.2, 69.4, 68.3, 53.9, 39.1, 35.0. Anal. Calcd for $C_{31}H_{27}N_3O_4S$: C, 69.25; H, 5.06; N, 7.82; S, 5.96. Found: C, 69.5; H, 5.10; N, 7.32; S, 5.49.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-4-Benzyl-3-(*N*-benzyl-*N*-methylcarbamoylthio)-1,3-diphenylazetidin-2-one (32) and (*E*)-*N*-(*N*′-Benzyl-*N*′-methylcarbamoyl)-*N*,2,4-triphenylenamide (46). To a suspension of **1b** (0.50 g, 1.3 mmol) in benzene (5 mL) was added 0.2 mL (1.7 mmol) of phenylacetaldehyde (**12**). The reaction mixture was refluxed until observance of decolorization of the solution (30 min). TLC analysis (diethyl ether−*n*-hexane, 1:1) revealed the appearance of two new compounds **32** (R_f 0.5) and **46** (R_f 0.4). Purification by preparative TLC (ethyl ether−*n*-hexane, 1:1) gave **32** as a colorless solid (0.13 g, 19%) and **46** (0.15 g, 28%) as a colorless oil.

Compound 32: mp 133 °C; IR (KBr) 3061, 3027, 2915, 1742, 1653, 1597, 1495, 1454 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.83 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 7.7 Hz, 2H), 7.18−6.98 (m, 15H), 6.82 (m, 1H), 5.49 (m, 1H), 4.19 (s, 2H), 3.06 (dd, J = 15.1, 5.4 Hz, 1H), 2.71 (dd, J = 15.1, 7.1 Hz), 2.48 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 167.4, 165.0, 139.5, 139.3, 137.5, 137.5, 136.9, 130.4, 130.0, 129.6, 129.5, 129.4, 128.7, 128.5, 127.4, 125.0, 120.0, 69.0, 67.8, 53.9, 39.0, 34.9. Anal. Calcd for $C_{31}H_{28}N_2O_2S$: C, 75.58; H, 5.73; N, 5.69; S, 6.51. Found: C, 75.39; H, 5.67; N, 5.78; S, 6.73.

Compound 46: IR (NaCl) 3050, 3020, 1690, 1685, 1655, 1590, 1485, 1440 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.40 (m, 2H), 7.12−6.91 (m, 18H), 6.52 (t, J = 7.7 Hz, 1H), 4.29 (s, 2H), 3.30 (d, J = 7.7 Hz, 2H), 2.38 (s, 3H); ^{1}H NMR (400 MHz, DMSO-d_6, 360 K) δ 7.37−7.03 (m, 20H), 6.44 (t, J = 7.7 Hz, 1H), 4.37 (s, 2H), 3.38 (d, J = 7.6 Hz, 2H), 2.64 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 171.4, 157.9, 140.7, 140.6, 137.7, 136.8, 136.6, 130.8, 129.9, 129.6, 129.5, 129.2, 129.0, 128.6, 128.4, 127.9, 127.6, 127.2, 54.2, 35.8, 35.5. HRMS (CI$^+$) calcd for $C_{31}H_{28}N_2O_2$ 460.2151, found 460.2151.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-4-Benzyl-3-(*N*-benzyl-*N*-methylcarbamoylthio)-1-(4-methoxyphenyl)-3-phenylazetidin-2-one (35), (2*R*,3*R*)- and (2*S*,3*S*)-3-Benzyl-2-[4-benzyl-2-(4-methoxyphenyl)-1,3-dioxo-2,4-diazapen-

tyl]-2-phenylthiirane (40), and (*E*)-*N*-(*N*′-Benzyl-*N*′-methylcarbamoyl)-*N*-(4-methoxyphenyl)-2,4-diphenylbut-2-enamide (49). To a suspension of **1c** (0.50 g, 1.2 mmol) in benzene (5 mL) was added 0.2 mL (1.7 mmol) of phenylacetaldehyde (**12**). The reaction mixture was refluxed until observance of decolorization of the solution (30 min). TLC analysis (diethyl ether−*n*-hexane, 1:1) revealed the appearance of three new compounds **40** (R_f 0.3), **35** (R_f 0.2), and **49** (R_f 0.1) which could be separated by flash chromatography (diethyl ether−*n*-hexane, 1:1) and further purification by preparative TLC (diethyl ether−*n*-hexane, 1:1). Compounds **35** (0.09 g, 14%) and **40** (0.31 g, 49%) crystallized from diethyl ether−*n*-hexane as colorless solids and **49** (0.03 g, 4%) was obtained as a colorless oil.

Compound 35: mp 57 °C; IR (KBr) 2918, 2357, 1753, 1653, 1512 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.86 (dd, J = 8.4, 1.6 Hz, 2H), 7.25−6.99 (m, 15H), 6.58 (m, 2H), 5.45 (m, 1H), 4.20 (s, 2H), 3.31 (s, 3H), 3.10 (dd, J = 15.0, 5.2 Hz, 1H), 2.69 (dd, J = 14.9, 7.2 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 167.9, 164.6, 157.9, 139.7, 137.2, 132.7, 130.5, 130.1, 130.0, 129.7, 129.5, 129.4, 129.0, 128.8, 128.6, 127.4, 121.8, 115.3, 69.0, 68.1, 55.7, 54.1, 39.2, 35.0. HRMS (CI$^+$) calcd for $C_{32}H_{30}N_2O_3S$ 522.1977, found 522.1991.

Compound 40: mp 59 °C; IR (KBr) 3043, 2953, 2948, 2835, 1685, 1603, 1508, 1496 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.22 (d, J = 6.1 Hz, 2H), 7.10−6.93 (m, 15H), 6.45 (d, J = 8.7 Hz, 2H), 4.32 (m, 3H), 3.30 (s, 3H), 2.59 (m, 4H), 2.15 (dd, J = 15.0, 8.5 Hz, 1H); ^{13}C NMR (100 MHz, toluene-d_8, 400 K) δ 170.7, 160.4, 156.9, 140.2, 137.8, 135.5, 131.8, 131.5, 130.4, 129.9, 129.5, 129.3, 128.9, 128.8, 128.6, 128.3, 127.4, 114.9, 55.8, 55.3, 54.1, 47.1, 38.9, 34.9. Anal. Calcd for $C_{32}H_{30}N_2O_3S$: C, 73.54; H, 5.79; N, 5.36; S, 6.14. Found: C, 73.38; H, 5.91; N, 5.44; S, 5.72.

Compound 49: IR (NaCl) 3059, 2926, 2852, 1680, 1510 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 5.89 (m, 2H), 7.14−6.95 (m, 15H), 6.59 (d, J = 8.8 Hz, 2H), 6.49 (t, J = 7.7 Hz, 1H), 4.26 (s, 2H), 3.39 (s, 3H), 3.29 (d, J = 7.7 Hz, 2H), 2.48 (s, 3H); ^{1}H NMR (400 MHz, DMSO-d_6, 360 K) δ 7.36−7.20 (m, 14H), 7.03 (m, 4H), 6.87 (m, 2H), 6.40 (t, J = 7.6 Hz, 1H), 4.38 (s, 2H), 3.77 (s, 3H), 3.36 (d, J = 7.7 Hz, 2H), 2.68 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 171.5, 159.9, 158.1, 140.7, 140.6, 137.9, 136.8, 136.4, 136.5, 130.7, 129.5, 129.1, 129.0, 128.6, 128.4, 127.2, 115.4, 55.8, 54.2, 35.8, 35.5. HRMS (CI$^+$) calcd for $C_{32}H_{30}N_2O_3$ 490.2256, found 490.2268.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-4-(1′-Acetoxymethyl)-3-(*N*-benzyl-*N*-methylcarbamoylthio)-1-(4-nitrophenyl)-3-phenylazetidin-2-one (29). To a suspension of **1a** (0.60 g, 1.4 mmol) in benzene (10 mL) was added 2-acetoxypropanal (**13**) (0.50 g, 4.9 mmol) dissolved in benzene (10 mL). The reaction mixture was refluxed and instantaneous decolorization of the solution was observed. TLC analysis (diethyl ether−*n*-hexane, 2:1) revealed the appearance of a new compound **29** (R_f 0.3). Purification by flash chromatography (diethyl ether−*n*-hexane, 1:1) gave **29** (0.24 g, 32%) as a yellow pale solid.

Compound 29: mp 55 °C; IR (KBr) 2930, 1771, 1655, 1593, 1516, 1449 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.91 (dd, J = 9.0, 1.8 Hz, 2H), 7.76 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 9.1 Hz, 2H), 7.18−6.96 (m, 8H), 5.18 (t, J = 4.9 Hz, 1H), 4.21−4.09 (m, 4H), 2.45 (s, 3H), 1.56 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 170.0, 166.7, 156.6, 145.3, 144.1, 137.1, 135.1, 130.0, 129.7, 129.1, 128.8, 128.7, 126.0, 118.8, 68.3, 64.8, 62.7, 53.8, 34.9, 20.7. Anal. Calcd for $C_{27}H_{25}N_3O_6S$: C, 62.41; H, 4.85; N, 8.09; S, 6.17. Found: C, 62.65; H, 5.19; N, 7.97; S, 5.78.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-4-(1′-Acetoxymethyl)-3-(*N*-benzyl-*N*-methylcarbamoylthio)-1,3-diphenylazetidin-2-one (33), (*E*)-4-Acetoxy-*N*-(*N*′-benzyl-*N*′-methylcarbamoyl)-*N*,2-diphenylbut-2-enamide (47), and (*Z*)-4-Acetoxy-*N*-(*N*′-benzyl-*N*′-methylcarbamoyl)-*N*,2-diphenylbut-2-enamide (51). To a suspension of **1b** (0.30 g, 0.8 mmol) in benzene (5 mL) was added 2-acetoxypropanal (**13**) (0.25 g, 2.5 mmol) solved in benzene (5 mL). The reaction mixture was refluxed until observance of decolorization of the solution (10 min). TLC analysis (diethyl ether−*n*-hexane, 3:2) revealed the appearance of three new compounds **33** (R_f 0.3), **51** (R_f 0.2), and **47** (R_f 0.1) which could be purified by preparative TLC (diethyl ether−*n*-hexane, 3:2). Compounds **33** (0.08 g, 20%), **47** (0.09 g, 24%), and **51** (0.06, 18%) were obtained as colorless oils.

Compound 33: IR (NaCl) 3034, 2941, 1746, 1657, 1597, 1501, 1447, 1377 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.92 (m, 2H), 7.70 (m, 2H), 7.17−6.90 (m, 11H), 5.27 (t, J = 4.8 Hz, 1H), 4.40 (dd, J = 12.5, 4.4 Hz, 1H), 4.20−4.14 (m, 3H), 2.44 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 170.0, 167.0, 164.5, 139.4, 137.4, 136.6, 130.0, 129.9, 129.7, 129.5, 129.3, 129.0, 128.7, 128.6, 125.3, 119.5, 67.7, 64.2, 62.8, 53.8, 34.0, 20.6. HRMS (CI$^+$) calcd for $C_{27}H_{26}N_2O_4S$ + H$^+$ 475.1695, found 475.1684.

Compound 47: IR (NaCl) 3055, 2930, 1742, 1682, 1595, 1493, 1396 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.28 (dd, J = 8.2, 1.4 Hz, 2H), 7.09−6.91 (m, 13H), 6.44 (t, J = 6.5 Hz, 1H), 4.53 (d, J = 6.5 Hz, 2H), 4.21 (s, 2H), 2.40 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 170.6, 170.3, 157.5, 142.7, 140.2, 137.6, 135.7, 132.0, 130.4, 129.9, 129.5, 129.2, 129.1, 129.0, 128.6, 128.5, 127.8, 127.7, 120.7, 61.9, 54.1, 35.5, 20.9. HRMS (CI$^+$) calcd for $C_{27}H_{26}N_2O_4$ 442.1893, found 442.1888.

Compound 51: IR (NaCl) 3032, 2945, 1738, 1688, 1595, 1491, 1364 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.24−7.20 (m, 4H), 7.11−6.86 (m, 11H), 5.84 (t, J = 6.5 Hz, 1H), 4.99 (d, J = 6.5 Hz, 2H), 4.22 (s, 2H), 2.49 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 170.5, 168.7 156.6, 141.7, 139.3, 138.0, 137.5, 129.9, 129.7, 129.5, 129.4, 129.0, 128.5, 128.1, 127.9, 127.8, 63.0, 54.2, 35.4, 21.0. HRMS (CI$^+$) calcd for $C_{27}H_{26}N_2O_4$ 442.1893, found 442.1889.

Synthesis of (*E*)-4-Acetoxy-*N*-(*N*′-benzyl-*N*′-methylcarbamoyl)-*N*-(4-methoxyphenyl)-2-phenylbut-2-enamide (50) and (*Z*)-4-Acetoxy-*N*-(*N*′-benzyl-*N*′-methylcarbamoyl)-*N*-(4-methoxyphenyl)-2-phenylbut-2-enamide (53). To a suspension of **1c** (0.30 g, 0.7 mmol) in benzene (5 mL) was added 2-acetoxypropanal (**13**) (0.25 g, 2.5 mmol) dissolved in benzene (5 mL). The reaction mixture was refluxed until observance of decolorization of the solution (30 min). TLC analysis (diethyl ether−*n*-hexane, 8:5) revealed the appearance of two new compounds **53** (R_f 0.2) and **50** (R_f 0.1) which could be purified by preparative TLC (diethyl ether−*n*-hexane, 3:2). Compounds **50** (0.19 g, 55%) and **53** (0.10, 28%) were obtained as colorless oils.

Compound 50: IR (NaCl) 2963, 1737, 1682, 1510, 1443, 1396 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.27 (d, J = 6.9 Hz, 2H), 7.08−6.96 (m, 10H), 6.58 (d, J = 8.8 Hz, 2H), 6.42 (t, J = 6.6 Hz, 1H), 4.53 (d, J = 6.6 Hz, 2H), 4.27 (s, 2H), 3.32 (s, 3H), 2.49 (s, 3H), 1.64 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 170.8, 170.2, 160.0, 157.7, 142.8, 137.8, 135.9, 132.9, 131.6, 130.3, 129.9, 129.6, 129.5, 129.1, 129.0, 128.9, 128.5, 126.2, 115.4, 61.9, 55.8, 54.2, 35.4, 20.9. HRMS (CI$^+$) calcd for $C_{28}H_{28}N_2O_5$ 472.1998, found 472.2002.

Compound 53: IR (NaCl) 2938, 2847, 1694, 1510, 1365 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.23−7.01 (m, 12H), 6.54 (m, 2H), 5.83 (t, J = 6.5 Hz, 1H), 5.01 (d, J = 6.5 Hz, 2H), 4.35 (s, 2H), 3.31 (s, 3H), 2.62 (s, 3H), 1.78 (s, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 170.5, 169.0 160.3, 156.9, 142.0, 138.1, 137.6, 132.0, 129.9, 129.6, 129.5, 129.4, 129.2, 129.0, 128.4, 127.7, 115.2, 63.1, 55.8, 54.2, 35.5, 21.0. HRMS (CI$^+$) calcd for $C_{28}H_{28}N_2O_5$ 472.1998, found 472.2001.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-4-methyl-1-(4-nitrophenyl)-3-phenylazetidin-2-one (30), (3*R*,4*S*)- and (3*S*,4*R*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-4-methyl-1-(4-nitrophenyl)-3-phenylazetidin-2-one (36), and (*E*)-*N*-(*N*′-Benzyl-*N*′-methylcarbamoyl)-*N*-(4-nitrophenyl)-2-phenylbut-2-enamide (45). To a solution of **1a** (0.50 g, 1.2 mmol) in CH_2Cl_2 (3 mL)

was added acetaldehyde (**14**) (0.1 mL, 1.8 mmol). The solution was stirred until observance of decolorization of the solution (20 min). ^{1}H NMR analysis of the reaction mixture revealed that compounds **30**, **36**, and **45** were formed in a 6.6:3.8:1.0 ratio.

Synthesis of (3*R*,4*R*)- and (3*S*,4*S*)-3-(*N*-Benzyl-*N*-methylcarbamoylthio)-4-methyl-1,3-diphenylazetidin-2-one (34), (2*R*,3*R*)- and (2*S*,3*S*)-2-(4-Benzyl-2-phenyl-1,3-dioxo-2,4-diazapentyl)-3-methyl-2-phenylthiirane (38), (2*R*,3*S*)- and (2*S*,3*R*)-2-(4-Benzyl-2-phenyl-1,3-dioxo-2,4-diazapentyl)-3-methyl-2-phenylthiirane (42), (*E*)-*N*-(*N*′-Benzyl-*N*′-methylcarbamoyl)-*N*,2-diphenylbut-2-enamide (48), and (*Z*)-*N*-(*N*′-Benzyl-*N*′-methylcarbamoyl)-*N*,2-diphenylbut-2-enamide (52). To a solution of **1b** (0.50 g, 1.3 mmol) in CH_2Cl_2 (3 mL) was added acetaldehyde (**14**) (0.1 mL, 1.8 mmol). The solution was stirred until observance of decolorization of the solution (40 min). ^{1}H NMR of the reaction mixture revealed that compounds **34**, **38**, **42**, **48**, and **52** were formed in a 1:3.5:3.5:10.6:2.3 ratio.

Synthesis of (2*R*,3*R*)- and (2*S*,3*S*)-2-[4-Benzyl-2-(4-methoxyphenyl)-1,3-dioxo-2,4-diazapentyl]-3-methyl-2-phenylthiirane (41) and (2*R*,3*S*)- and (2*S*,3*R*)-2-[4-Benzyl-2-(4-methoxyphenyl)-1,3-dioxo-2,4-diazapentyl]-3-methyl-2-phenylthiirane (44). To a solution of **1c** (0.50 g, 1.2 mmol) in CH_2Cl_2 (3 mL) was added acetaldehyde (**14**) (0.1 mL, 1.8 mmol). The solution was stirred until observance of decolorization of the solution (1 h). TLC analysis (diethyl ether−*n*-hexane, 1:1) revealed the appearance of two new compounds **44** (R_f 0.4) and **41** (R_f 0.3) which could be purified by preparative TLC (benzene−acetonitrile, 30:1). ^{1}H NMR of the reaction mixture revealed that compounds **41** and **44** were formed in a 2:1 ratio. Compounds **41** (0.12 g, 22%) and **44** (0.04, 7%) were obtained as colorless solids.

Compound 41: mp 52 °C; IR (KBr) 2932, 1686, 1508, 1445, 1397 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.16−6.92 (m, 12H), 6.45 (d, J = 8.8 Hz, 2H), 4.39 (d, J = 15.0 Hz, 1H), 4.30 (d, J = 15.0 Hz, 1H), 4.05 (q, J = 6.0 Hz, 1H), 3.30 (s, 3H), 2.63 (s, 3H), 0.85 (d, J = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 170.9, 159.2 157.0, 137.8, 135.6, 131.7, 130.4, 129.5, 129.4, 129.3, 128.8, 128.5, 128.4, 115.0, 55.7, 55.1, 54.1, 41.3, 35.3, 54.2, 17.9. Anal. Calcd for $C_{26}H_{26}N_2O_3S$: C, 69.9; H, 5.87; N, 6.27; S, 7.18. Found: C, 69.9; H, 6.11; N, 6.47; S, 6.84.

Compound 44: mp 110 °C; IR (KBr) 2967, 1682, 1607, 1508, 1449, 1395 cm^{-1}; ^{1}H NMR (400 MHz, toluene-d_8, 340 K) δ 7.66 (d, J = 7.4 Hz, 2H), 7.11−7.00 (m, 10H), 6.57 (m, 2H), 4.33 (s, 2H), 3.30 (s, 3H), 2.80 (c, J = 6.0 Hz, 1H), 2.55 (s, 3H), 2.63 (s, 3H), 1.72 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, toluene-d_8, 340 K) δ 169.8, 160.2 157.5, 140.6, 137.7, 132.3, 130.2, 129.9, 129.6, 129.5, 129.2, 129.0, 128.5, 115.2, 56.1, 55.7, 54.3, 45.4, 35.5, 21.0. Anal. Calcd for $C_{26}H_{26}N_2O_3S$: C, 69.9; H, 5.87; N, 6.27; S, 7.18. Found: C, 70.0; H, 6.14; N, 5.95; S, 6.66.

Acknowledgment. Financial support from the Ministry of Science and Technology (Projects PB98-0997 and BQU2000-0248) and the Junta de Extremadura-Fondo Social Europeo (Grants IPR00-C021, IPR00-C047, and IPR98-A065) is gratefully acknowledged. R.G. thanks the Junta de Extremadura for a predoctoral scholarship. We thank Professor José Luis García Ruano for helpful discussions and suggestions.

Supporting Information Available: Cartesian coordinates of transition structures **TS16**, **TS19**, **TS22**, and **TS25** with their computed total energies; ^{1}H NMR spectra of diastereomeric mixtures of compounds **21** and **24**, and **23** and **26**; ^{1}H NMR spectra of compounds **27**, **31**, **33**, **35**, **37**, **43**, **46**, **47**, **49**, **50**, **51**, and **53**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO034188R