Synthesis of Novel 4-(2-Oxoethylidene)azetidin-2-ones by a Lewis Acid Mediated Reaction of Acyldiazo Compounds

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We report the synthesis of a class of 4-(2-oxoethylidene)azetidin-2-ones by a novel Lewis acid mediated reaction of acyldiazo compounds with 4-acetoxyazetidin-2-ones. Using this approach, C-3-and C-4-substituted 4-alkylideneazetidin-2-ones were obtained depending on the choice of starting azetidinone and α-diazocarbonyl compound. The products reveal excellent *Z* diastereoselection of the C-4 double bond. Variable amounts of *E* isomers are obtained depending on the nature of the C-3 side chain, the Lewis acid, and the β-lactam protection. VT NMR spectroscopic experiments and X-ray structural analysis of crystalline derivatives demonstrate the presence of an intramolecular hydrogen bond in *Z* isomers, which drives the stereochemical outcome of the reaction. A possible mechanism for this novel reaction is proposed.

Introduction

Because of the unique properties of the azetidinone ring, which is particularly strained and activated towards nucleophilic acyl substitution, the β-lactam structure is a fundamental and versatile building block in the design and synthesis of several biologically active compounds. It has been widely used to obtain fundamental antibacterial products (β-lactam antibiotics),[1] unusual peptide derivatives,[2] and, recently, enzymatic inhibitors of different serine proteases.[3] Indeed, in the last ten years several derivatized cephalosporins, penicillins, penems, and non-conventional monocyclic and bicyclic β-lactam derivatives have proved to be efficient inhibitors of HLE (Human Leukocyte Elastase),[4] HCMV (Human Cytomegalovirus Protease),[5] PSA (prostate-specific antigen),[6] and cholesterol absorption.[7]

Some structural requirements have been recognized in order for monocyclic β-lactam derivatives to gain inhibitory activity,[8] but the possibility of activating the azetidinone ring through unsaturated systems directly linked to the β-lactam ring has been poorly investigated. Notwithstanding the fact that thousands of different β-lactam compounds have been synthesized, very few examples of alkylideneazetidin-2-ones have been reported in the literature, which were studied in the 1980s by only a few authors who found little antibacterial activity.[9] For example, Bachi[10] reported the synthesis of some 4-alkylidene-β-lactams starting from 4-thioxo-2-azetidinones and disubstituted diazo compounds using rhodium catalysis followed by a reductive elimination step. Some years ago we reported the synthesis of 4-alkylideneazetidin-2-ones starting from an ester-enolate and ketenimine.[11] Many efforts have also been devoted to accomplishing the synthesis of 3-alkylidene-β-lactams[12] and, recently, 7-alkylidene-cephalosporin esters[13] and other β-lactam antibiotics with exo methylene double bonds have been reported as inhibitors of Human Leukocyte Elastase.[14]

As an extension of our continuing studies in the field of β-lactams,[15] here we report the synthesis of a class of 4-(2-oxoethylidene)azetidin-2-ones by a novel Lewis acid mediated reaction of acyldiazo compounds with 4-acetoxy-azetidin-2-ones.[16] 4-Acetoxy-β-lactam derivatives are important, frequently used intermediates in the synthesis of penicillins, cephalosporins, and carbapenems,[17] with the presence of the good leaving group at the C-4 position allowing different functionalizations.[18] In particular, compound **1** is the industrial intermediate[19] for the synthesis of thienamycin, imipenem, and derivatives, and some years ago we accomplished a simple stereocontrolled synthesis of it starting from methyl (*R*)-3-hydroxybutyrate and hexahydrotriazine.[20] Diazo compounds, ranging from simple diazoalkanes to highly substituted diazocarbonyl compounds, play an important role in modern organic synthesis.[21] In the chemistry of β-lactams, diazo compounds have been largely used as a carbene precursor to perform insertion into the N−H bond, of which the most powerful application is represented by the ring closure step in the Merck synthesis of carbapenems.[22] The reactions of 4-acetoxyazetidin-2-ones with diazomalonate in the presence of a catalytic amount of rhodium(II) acetate are also reported to furnish poor yields of *N*-substituted β-lactams through a carbene NH insertion.[23] To the best of our knowledge, no reaction is known between 4-acetoxyazetidin-2-one derivatives and a diazo-functionalized species involving the C-4 position.

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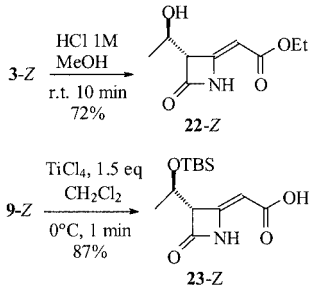
In our approach to 4-alkylidene-β-lactam derivatives, we obtain C-3- and C-4-substituted 4-alkylideneazetidin-2-ones, depending on the choice of starting azetidinone and α-diazocarbonyl compound. Moreover, the products are obtained with variable *Z*/*E* ratios, depending on the nature of the C-3 side chain, the Lewis acid, and the β-lactam protection at nitrogen.

Results and Discussion

To obtain 4-(2-oxoethylidene)azetidin-2-ones, we reacted different 3-substituted 4-acetoxy-β-lactams − in particular, 3-(1-hydroxy-1-ethyl), 3-chloro, 3-bromo, and 3-H derivatives − with several diazo compounds: diazo esters, diazo ketones, and diazomethane derivatives.

The study was initiated by analyzing the reaction of **1** with commercial ethyl diazoacetate (EDA) and different Lewis acids, for which the results are summarized in Table 1.

No reaction occurred when **1a** was treated with one equivalent of EDA (**2**) in CH_2Cl_2 in the absence of a Lewis acid (entry 1). By reacting **1a** and **2** in the presence of a catalytic amount of either $TiCl_4$, $Rh_2(OAc)_4$, or $Cu(OTf)_2$, we obtained traces of the 4-alkylidene compound **3** only when using $TiCl_4$. When we investigated the coupling of *N*-trimethylsilyl derivative **1b** with catalytic $TiCl_4$ and $Cu(OTf)_2$ (entries 6 and 7), we obtained moderate yields of two diastereoisomeric products **3**-*Z* and **3**-*E* that were easily separated by chromatography (see Exp. Sect.). Treatment of the major isomer with HCl in methanol produced a deprotected crystalline derivative **22** whose X-ray diffraction analysis established the *Z* configuration of the C=C bond (Scheme 1 and Figure 2).

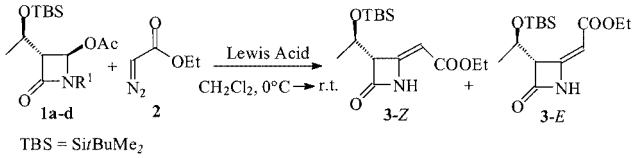


Scheme 1

Critical to the success of the reaction was the use of a stoichiometric amount of $TiCl_4$ and a requirement for tri-

Table 1. Reaction of **1a**−**d** with **2** (EDA) using different Lewis acids

Entry	Substrate	R^1	Equiv. of EDA	Lewis acid (equiv.)	Yields (%)[a]	*Z*/*E* (%)
1	**1a**	H	1	−	−	−
2	**1a**	H	1	$Rh_2(OAc)_4$ (0.01)	−	−
3	**1a**	H	1	$Cu(OTf)_2$ (0.1)	−	−
4	**1a**	H	1	$TiCl_4$ (0.1)	traces	−
6	**1b**	$SiMe_3$	1	$TiCl_4$ (0.1)	38	86:14
7	**1b**	$SiMe_3$	1	$Cu(OTf)_2$ (0.1)	24	25:75
8	**1a**	H	1	$TiCl_4$ (1)	23	> 99:1
9	**1b**	$SiMe_3$	1	$TiCl_4$ (1)	60	85:15
10	**1a**	H	4	$TiCl_4$ (1)	77	> 99:1
11	**1b**	$SiMe_3$	4	$TiCl_4$ (1)	91	80:20
12	**1b**	$SiMe_3$	1	Me_3SiCl (1)	−	−
13	**1a**	H	4	Me_3SiCl (2) /$TiCl_4$ (0.1)	49	> 99:1
14	**1b**	$SiMe_3$	4	Me_3SiCl (2) /$TiCl_4$ (0.1)	81	60:40
15	**1a**	H	4	$Cu(OTf)_2$ (1)	−	−
16	**1b**	$SiMe_3$	4	$Cu(OTf)_2$ (1)	−	−
17	**1b**	$SiMe_3$	4	TiF_4 (1)	72	58:42
18	**1b**	$SiMe_3$	4	$InBr_3$ (1)	−	−
19	**1a**	H	4	$SnCl_4$ (1)	58	> 99:1
20	**1b**	$SiMe_3$	4	$SnCl_4$ (1)	35	> 99:1
21	**1a**	H	4	$AlCl_3$ (1)	45	50:50
22	**1b**	$SiMe_3$	4	$AlCl_3$ (1)	73	53:47
23	**1b**	$SiMe_3$	4	Et_2AlCl (1)	59	50:50
24	**1b**	$SiMe_3$	4	$BF_3{\cdot}Et_2O$ (1)	18	< 1:99
25	**1b**	$SiMe_3$	4	$ZnCl_2$ (1)	16	> 99:1
26	**1c**	$SiMe_2tBu$	4	$TiCl_4$ (1)	−	−
27	**1d**	$COCH_3$	4	$TiCl_4$ (1)	−	−



[a] Isolated yields after flash chromatography.

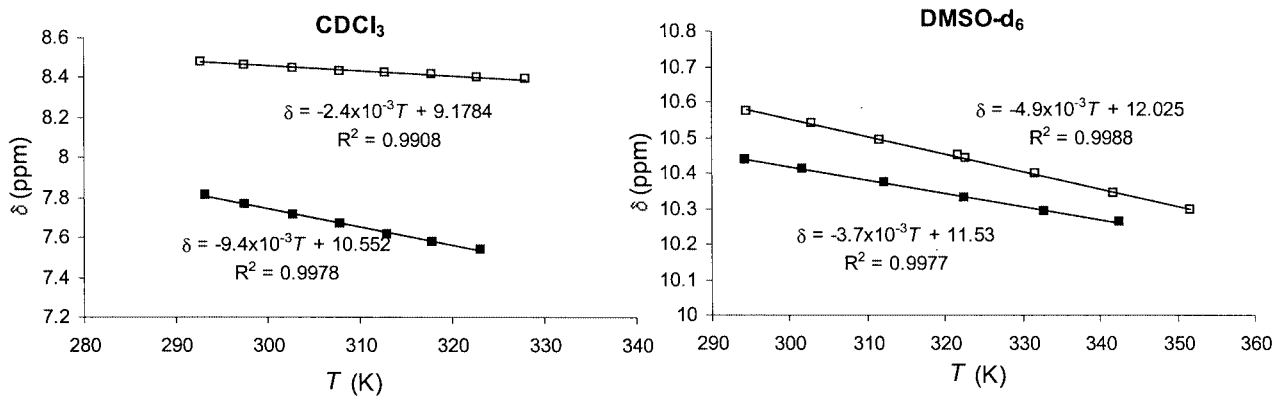


Figure 1. Temperature dependence of ^{1}H NMR chemical shifts for the amido protons of **3**-*Z* (□) and **3**-*E* (■) in $CDCl_3$ and [D_6]DMSO

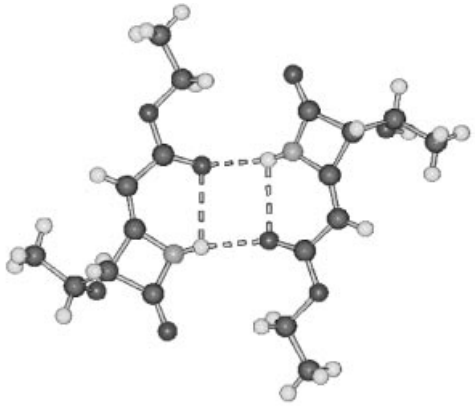


Figure 2. A view of the molecular compound **22**; the hydrogen bonds are shown as dotted lines

methylsilyl protection of the β-lactam nitrogen atom (Table 1, entry 9). Four equivalents of ethyl diazoacetate, together with one equivalent of $TiCl_4$, improved the reaction yield from 38 to 91% (Table 1, entry 11).

Among the Lewis acids we tested, $ZnCl_2$ and $BF_3.OEt_2$ promoted the reaction with excellent, and complementary, stereoselectivities, but the yields were not satisfactory (Table 1, entries 24 and 25). TiF_4, $AlCl_3$, and Et_2AlCl were good catalysts for this reaction, furnishing **3** in almost equimolar *Z*/*E* mixtures (Table 1, entries 17, 22 and 23). $SnCl_4$ effectively catalyzed the addition of EDA to **1a** and **1b**, with the formation of **3**-*Z* as the sole isomeric product (Table 1, entries 19 and 20). Me_3SiCl did not promote the reaction (Table 1, entry 12), but a combination of two equivalents of TMSCl and 10% of $TiCl_4$ provided a catalytic version of the reaction (Table 1, entries 13 and 14) with complete stereoselectivity for **3**-*Z* starting from **1a**. Interestingly, at least when $TiCl_4$ was used as a catalyst, complete stereochemical control in favor of the *Z* isomer was achieved with the free-amine starting material **1a**, whereas the *N*-$SiMe_3$ derivative **1b** gave *Z*/*E* mixtures.

Protecting the β-lactam nitrogen atom with less-labile and more-hindered groups, such as Si*t*$BuMe_2$ or acetyl (Table 1, entries 26 and 27), resulted in no product formation.

The compounds **3**-*Z* and **3**-*E* were evaluated as inhibitors of Human Leucocyte Elastase (HLE)[24] and compared with the corresponding product saturated at the C-4 position.[25] Preliminary results indicate that, at a concentration of 100 μM, **3**-*Z* and **3**-*E* inhibited HLE by 57.6 and 66.2%, respectively, and the saturated compound was inactive. This result is consistent with the concept that a C-4-unsaturated system is able to activate monocyclic β-lactams towards serine proteases, such as HLE.

To extend the scope of this new reaction, we analyzed the reactivity of **1a/b** toward different diazo compounds. The results are reported in Table 2.

Using one equivalent of *tert*-butyl diazoacetate **4** and $TiCl_4$, we obtained β-lactam **9** in 42% yield with complete *Z* diastereoselectivity (Table 2, entry 1). Hydrolysis of the *tert*-butyl ester **9** using $TiCl_4$ in CH_2Cl_2 at 0 °C produced the carboxylic acid derivative **23** (Scheme 1) whose single-crystal X-ray diffraction analysis indicated the structure reported in Figure 3.

Even diazo ketones **5** and **6** furnished the corresponding 4-alkylideneazetidin-2-ones **10** and **11** (complete *Z* diastereoselectivity) with $TiCl_4$ catalysis (Table 2, entries 2 and 4). Diazo compound **7** (ethyl 4-diazoacetoacetate) did not yield the β-lactam product when using either $TiCl_4$ or $AlCl_3$ (Table 2, entries 5, 6). Diazo compound **8** (2,4-bis(diazo)-acetoacetate, entry 7) gave the expected product **12** in 20% yield (*Z* isomer only).

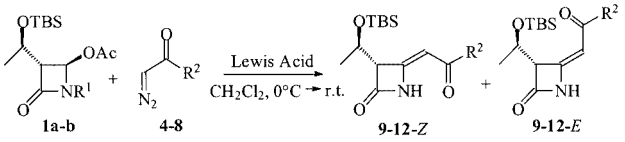
We found that there was no reaction with diazomethane derivatives (i.e., diazomethane, trimethylsylildiazomethane, and diphenyldiazomethane) under $TiCl_4$ catalysis. In addition, no product was observed, using *tert*-butyl α-diazoacetoacetate.

To obtain 3-substituted 4-alkylidene derivatives, we investigated the reactivity of diazo compounds **2**, **5**, and **6** toward several 4-acetoxy-β-lactams. The results are summarized in Table 3.

Phenylacetamido-4-acetoxyazetidin-2-one **13** failed to give the desired product under a variety of conditions (Table 3, entry 1). 4-Acetoxyazetidin-2-one **14** furnished products **17** in good yields and with different diastereoselectivities depending on the substitution of the β-lactam nitrogen atom. 4-Alkylidene-β-lactams **18** and **19** were obtained

Table 2. Reaction of **1a/b** with different diazo compounds and Lewis acids

Entry	Substrate	R^1	R^2	Diazo compound (equiv.)	Lewis acid (equiv.)	Product	Yields (%)[a]	*Z*/*E* (%)
1	**1b**	$SiMe_3$	O*t*Bu	**4** (1)	$TiCl_4$ (1)	**9**	42	> 99:1
2	**1b**	$SiMe_3$	Ph	**5** (4)	$TiCl_4$ (1)	**10**	55	> 99:1
3	**1a**	H	Ph	**5** (2)	$TiCl_4$ (1)	**10**	20	> 99:1
4	**1b**	$SiMe_3$	CH=CHPh	**6** (4)	$TiCl_4$ (1)	**11**	22	> 99:1
5	**1b**	$SiMe_3$	CH_2COOEt	**7** (4)	$TiCl_4$ (1)	–	–	–
6	**1b**	$SiMe_3$	CH_2COOEt	**7** (3)	$AlCl_3$ (1)	–	–	–
7	**1b**	$SiMe_3$	$C(N_2)COOEt$	**8** (2)	$TiCl_4$ (1)	**12**	20	> 99:1



[a] Isolated yields after flash chromatography.

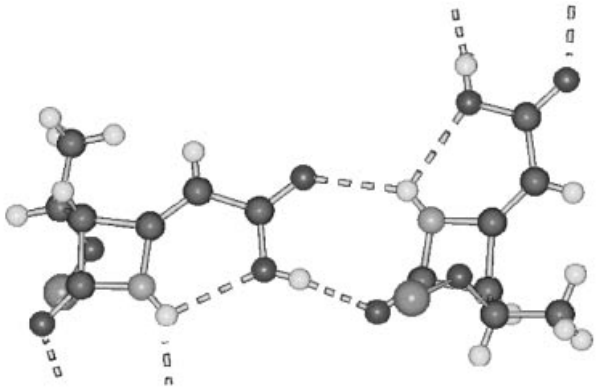


Figure 3. A view of the molecular compound **23**; for the sake of clarity, the alkyl substituents of the silicon atom (wider atom) are omitted; the hydrogen bonds are shown as dotted lines

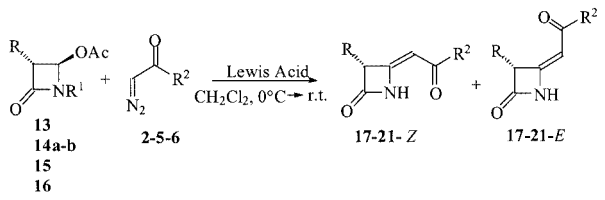
from diazo ketones **5** and **6** in moderate to poor yields, but with complete *Z* diastereoselectivity (entries 4 and 5). Unexpectedly, 3-chloro- and 3-bromo-4-acetoxyazetidin-2-one **15** and **16** furnished products **20** and **21** in poor yields only (entries 8−11).

In each case (Table 1, 2, and 3) when the reaction did not proceed or the yields were poor, we never isolated β-lactam intermediates or byproducts containing the β-lactam ring.

All derivatives obtained show a peculiar IR absorption of the β-lactam carbonyl group at 1820 cm^{-1}, indicative of a strong activation towards nucleophilic acylation. Very high frequencies have previously been observed in 4-alkylidene derivatives (see refs.[9−11]). Furthermore, the more-deshielded NH resonances in the ^1H NMR spectra in $CDCl_3$ of the *Z* isomers, compared to those of the *E* isomers, are quite interesting, for they suggest the existence of intramol-

Table 3. Reaction of 4-acetoxyazetidin-2-ones with different diazo compounds and Lewis acids

Entry	Substrate	R	R^1	R^2	Diazo compound (4 equiv.)	Lewis acid (equiv.)	Product	Yields (%)[a]	*Z*/*E* (%)
1	**13**	BnCONH	$SiMe_3$	OEt	**2**	$TiCl_4$ (1)	–	–	–
2	**14a**	H	H	OEt	**2**	$TiCl_4$ (1)	**17**	54	83:17
3	**14b**	H	$SiMe_3$	OEt	**2**	$TiCl_4$ (1)	**17**	79	33:67
4	**14b**	H	$SiMe_3$	Ph	**5**	$TiCl_4$ (1)	**18**	30	> 99:1
5	**14b**	H	$SiMe_3$	CH=CHPh	**6**	$TiCl_4$ (1)	**19**	10	–
6	**15**	Cl (*trans*)	$SiMe_3$	OEt	**2**	$TiCl_4$ (1)	**20**	20	86:14
7	**15**	Cl (*cis*)	H	OEt	**2**	$TiCl_4$ (1)	**20**	14	> 99:1
8	**15**	Cl (*cis*)	$SiMe_3$	OEt	**2**	$TiCl_4$ (1)	**20**	26	> 99:1
9	**15**	Cl (*cis*)	$SiMe_3$	OEt	**2**	$AlCl_3$ (1)	**20**	10	> 99:1
10	**16**	Br (*trans*)	$SiMe_3$	OEt	**2**	$TiCl_4$ (1)	**21**	10	> 99:1
11	**16**	Br (*cis*)	$SiMe_3$	OEt	**2**	$TiCl_4$ (1)	**21**	10	> 99:1



[a] Isolated yields after flash chromatography.

ecular hydrogen bonds in the *Z* isomers. The details of the hydrogen bonding patterns in **3**-*Z* and **3**-*E* were further substantiated by variable-temperature ^{1}H NMR experiments.[26] Figure 1 shows the temperature dependence of the chemical shifts of the amide protons in *Z* and *E* isomers. In a [D$_6$]DMSO solution over a range 294−342 K, the ^{1}H NMR chemical shifts of the amide NH resonance in **3**-*Z* and **3**-*E* show a linear relationship for δ vs. *T*, with a slight temperature dependence (4.9 and 3.7 × 10^{-3} ppm K^{-1}, respectively). In a non-competitive solvent, such as $CDCl_3$, the value of $-d\delta/dT$ of the NH unit in the *Z* isomer is small (2.4 × 10^{-3} ppm K^{-1}), whereas that of the *E* isomer shows a greater temperature dependence (9.4 × 10^{-3} ppm K^{-1}). Such a low value of $-d\delta/dT$ (≤ 6 × 10^{-3} ppm K^{-1}) has generally been attributed to intramolecularly hydrogen-bonded amido groups, and indicates that the NH unit is hydrogen bonded with the COOEt group, and shielded from the solvent, in the *Z* isomer.[27]

Because of its intramolecular hydrogen bond, the *Z* isomer is likely to be the more stable of the two, a suggestion that was supported experimentally by the observed spontaneous slow conversion of the isolated *E* isomer into its *Z* isomer.

The conformations adopted by compounds **22** and **23** in the crystalline state are depicted in Figure 2 and Figure 3, respectively.

In both compounds the β-lactam ring and the unsaturated chain in the C-4 position are coplanar. Even the ester group in compound **22** lies almost within this plane, with its displacement being only 0.09 Å. The voluminous TBS group in the C-3 position of **23** completely shields one side of the azetidinone ring (Figure 4). The endocyclic angles at the C-4 positions appear to be unusual (89° and 91° for the carboxylic acid and ester, respectively) in that they are wider than those found in the literature for analogous β-lactams having *sp*^{3} hybridization at that position (86° for the C-4-saturated carboxylic acid).[28] The main difference between the structures of the two compounds in the crystalline state is in the network of hydrogen bonds (Figure 2 and 3). Carboxylic acid **23** shows an intramolecular hydrogen bond and four intermolecular contacts that extend throughout the crystal, whereas in the ester **22** only hydrogen-bonded dimers exist.

On the basis of our experimental results and the structures of the products, a possible mechanism for this novel reaction is proposed.

It has been stated that 4-acetoxy-β-lactams undergo reactions with nucleophiles in the presence of Lewis acids through an iminium ion intermediate.[29] It is possible that in the case studied here, the main role of the Lewis acid is to activate the displacement of the acetoxy group to form an intermediate iminium ion of type **A** (Scheme 2). It is important to note that the preliminary activation of the β-lactam is a basic requirement for the reaction, because no product was isolated with an inverse addition of reagents (i.e., $TiCl_4$ as the last added reagent after EDA).

Under our reaction conditions, it is highly probable that the diazo compounds do not react as carbenes, but as nucleophiles. This hypothesis is drawn from three pieces of evidence: i) only stabilized α-diazocarbonyl compounds gave products; ii) $Rh_2(OAc)_4$ is not a catalyst for the reaction; and iii) no product was derived from carbene insertion. The tendency of diazoesters to react as nucleophiles has been described both in base-promoted reactions with carbonyl compounds to form diazoketols[30] and in Lewis acid catalyzed addition to give β-dicarbonyls.[31]

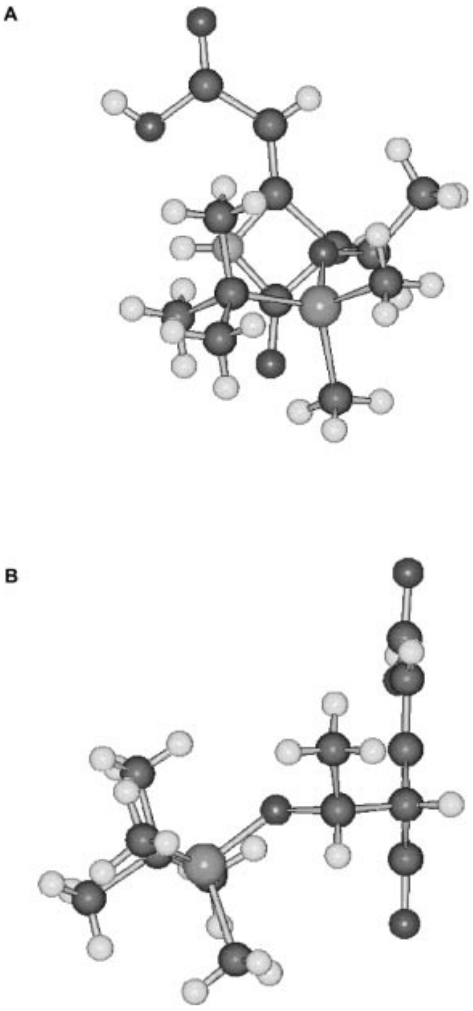
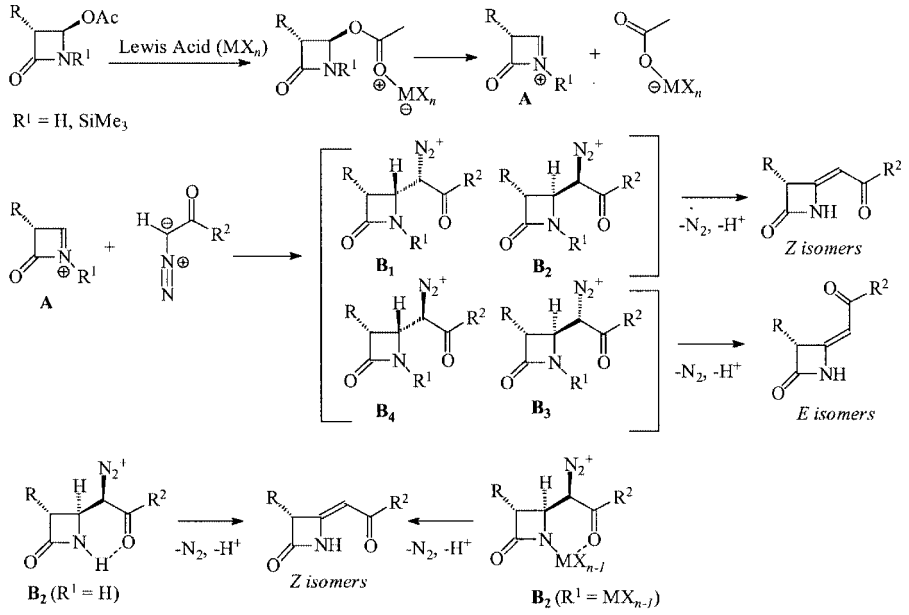


Figure 4. Two views of the molecular compound **23** showing the TBS protecting group; in A, the plane of the β-lactam ring is perpendicular to the view direction; in B, it is parallel

That higher yields were obtained for the addition of diazo compound to the iminium species when 4 equivalents of EDA were used could indicate a slow reaction rate. This rate may even account for the lower yields obtained when using 3-chloro- and 3-bromo-azetidinones. In these cases, the corresponding iminium ion intermediates might be too short-lived to undergo the slow addition to the diazocarbonyl compound, and so instead they decompose.[32]

Addition of a diazo compound to an iminium ion intermediate leads to four possible diazo derivatives (**B$_1$**, **B$_2$**, **B$_3$**, and **B$_4$**) obtained by attack on the two faces of the iminium ion.[33] In particular, *trans* intermediates **B$_2$** and **B$_3$** would be greatly favored in the case of a bulky R substituent on



Scheme 2

the β-lactam. This preference is supported by the crystal structure of **23**, in which the TBS group completely shields one face of the β-lactam ring (Figure 4).

The elimination of molecular nitrogen and a proton, leading to 4-alkylidene products, could, in principle, follow an E1 or an E2 mechanism. Because of the occurrence of an intramolecular rearrangement, E1 elimination (carbocation formation) has been proposed by Wang et al.[34] to occur in the reaction of *N*-tosyl diazoketamines catalyzed by $Rh_2(OAc)_4$ or TsOH. In the present study, however, the lack of rearranged products, which should generate more-stable γ-lactams, and the instability of the α-carboxy cation strongly suggest that an E2 elimination occurs. Thus, the stereochemical outcome of the reaction probably occurs through an anti-periplanar elimination from the four diazo derivatives **B_1**, **B_2**, **B_3**, and **B_4**; in particular, **B_1** and **B_2** will lead to *Z* isomers and **B_3** and **B_4** to *E* isomers.

VT ^{1}H NMR spectroscopy and X-ray structures have demonstrated that an intramolecular hydrogen bond has a stabilizing effect in the *Z* diastereoisomer. It seems quite reasonable that, whenever the reaction was performed on the NH-containing β-lactam, a hydrogen bond should already be present in the diazo intermediates (Scheme 2). It follows that only **B_1** and **B_2** (R^1 = H) present the correct anti-periplanar arrangement for the E_2 elimination, thus leading to the *Z* isomer, whereas **B_3** and **B_4** must first release the hydrogen bond and then undergo rotation around the C−C bond in order to undergo elimination to furnish the *E* isomer. Thus, the preferential formation of the *Z* isomers is dictated by the stabilizing effect of the intramolecular hydrogen bond and by the more-favorable kinetics resulting from the stereochemical requirements of the elimination step.

This model also accounts for the appearance of a significant amount of the *E* isomer whenever the starting β-lactam has been silylated. Indeed, in this case there is no stabilization by an intramolecular hydrogen bond and so all of the diazo intermediates **B** are active and result in the formation of the *Z*/*E* mixtures.

Our results demonstrate that the nature of the Lewis acid also governs the *Z*/*E* ratio of the products, indicating that it plays a further role. The evidence that 4-acetoxyazetidinones with less-labile *N*-protecting groups (such as *N*-Si*t*-$BuMe_2$ or *N*-$COCH_3$) did not produce 4-alkylidene derivatives, and that, in the case of *N*-$SiMe_3$, we failed to find *N*-$SiMe_3$-4-alkylidene derivatives in the reaction mixture, could indicate a possible ligand-exchange process that irreversibly bonds the metal cation of the Lewis acid to the β-lactam nitrogen atom leading to a *N*-metallated iminium species. This process could also account for the requirement of a full equivalent of the Lewis acid being necessary for obtaining good yields of reaction. Then diazo intermediates **B_1** and **B_2** (R^1 = MX_{n-1}) should favor the stereochemical predominance of the *Z* isomer by means of chelation of the metal (e.g., from $TiCl_4$ or $SnCl_4$) to the carboxyethyl chain. It follows from this hypothesis that whenever the Lewis acid is not a part of chelation and/or of a ligand exchange (e.g., for TiF_4, $AlCl_3$, $Cu(OTf)_2$, and $BF_3{\cdot}OEt_2$), the result is a variable *Z*/*E* ratio or a predominance of the *E* isomer.[35]

Conclusion

The synthesis of a class of 4-(2-oxoethylidene)azetidin-2-ones was carried out efficiently by novel Lewis acid mediated reactions of 4-acetoxy-azetidin-2-ones with α-diazocarbonyl compounds. All the starting materials are widely used and readily accessible compounds, which allow for the preparation of several different products. In particular, the reaction could be performed using differently 3-substituted

4-acetoxy-β-lactams with diazoesters and diazo ketones. The products have been obtained with an excellent *Z* diastereoselectivity at the C-4 double bond. Variable amounts of *E* isomers can be obtained depending on the nature of the C-3 side chain, the Lewis acid, and the degree of β-lactam protection. VT NMR spectroscopic experiments and X-ray structure determination of crystalline derivatives demonstrate the presence of an intramolecular hydrogen bond in *Z* isomers that drives the stereochemical result.

Preliminary biological results provide a basis for the development of more-potent 4-alkylidene-β-lactam-based inhibitors of serine enzymes.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were recorded using a 5-mm probe. All chemical shifts are quoted relative to deuterated solvent signals, δ in ppm, *J* in Hz. FT-IR spectra were measured as films between NaCl plates and reported in cm^{-1}. GC-MS: HP5980, capillary column HP-1 or HP-5 connected to HP5970 (70 eV). HRMS: VG7070E, positive-ion mode. Elemental analysis was performed at the Istituto di Biologia Marina, CNR, Bologna, Italy. Single-crystal X-ray diffraction data collection was performed at room temperature on a Bruker SMART2000 (CCD detector, compound **22**) and Nonius CAD4 (counter, compound **23**) diffractometers equipped with a graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). In both cases the data handling was performed using the SMART software package. 9161 (**22**) and 2921 (**23**) independent reflections were collected, 3140 (**22**) and 1212 (**23**) observed for $I > 2\sigma(I)$. Data were corrected for Lorentz-polarization effects and for absorption using an empirical method (SADABS program). The structure was solved by direct methods (SHELXTL program) and refined by full-matrix least-squares calculations. Hydrogen atoms were placed in calculated positions and refined isotropically. Anisotropic thermal parameters were used for all the non-hydrogen atoms. The final *R* factors obtained are $R_1 = 0.056$ (**22**) and $R_1 = 0.054$ (**23**). Both molecules crystallize in the monoclinic $P2_1$ space group. The unit cell parameters are $a = 5.3090(6)$, $b = 9.7675(11)$, $c = 19.872(2)$ Å, β = 91.485(3)° for **22**, and $a = 7.7935(16)$, $b = 11.744(2)$, $c = 8.9742(18)$ Å, β = 93.18(3)° for **23**. CCDC-163737 for compound **22** and CCDC-163974 for compound **23** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44−1223/336−033; E-mail: deposit@ccdc.cam.ac.uk].

Starting Materials: Azetidin-2-ones **1** and **14** and ethyl diazoacetate **2** are commercial products, β-lactams **13**, **15**, and **16** were synthesized by degradation of penicillin G.[36] Diazo compounds **4**, **5**, and **6** where synthesized according to a known procedure.[37]

Diazo compounds **7** and **8** were known,[38] but were prepared according to an improved procedure: **7** was prepared in 72% yield by reacting commercial ethyl malonyl chloride with diazomethane (5 equiv.) in Et_2O and converted into **8** by diazo transfer using *p*-acetamidobenzenesulfonyl azide (1 equiv.) and Et_3N (1 equiv.) in CH_3CN (88% yield).

Ethyl 4-Diazo-3-oxobutyrate (7): $R_f = 0.5$ (cyclohexane/ethyl acetate, 1:1). IR (neat): ṽ = 2109, 1734, 1637 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.27 (t, *J* = 7.4 Hz, 3 H, CH_3), 3.35 (br. s, 2 H, $COCH_2CO$), 4.18 (q, *J* = 7.4 Hz, 2 H, CH_2CH_3), 5.56 (br. s, 1 H, N_2CH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.1, 47.0, 55.9, 61.6, 167.1, 186.0 ppm.

Ethyl 2,4-Bis(diazo)-3-oxobutyrate (8): $R_f = 0.6$ (cyclohexane/ethyl acetate, 7:3). IR (neat): ṽ = 2137, 2107, 1705, 1599, 1357, 1308 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.33 (t, *J* = 7.0 Hz, 3 H, CH_3), 4.29 (q, *J* = 7.0 Hz, 2 H, CH_2CH_3), 6.49 (s, 1 H, N_2CH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.4, 54.6, 61.6, 161.7, 177.3 ppm.

Typical Procedure for the Preparation of 4-(2-Oxoethylidene)azetidin-2-ones, Compounds 3, 9, 10, 11, 12, 17, 18, 19, 20, 21, 22: Et_3N (1.3 mmol, 0.172 mL) and Me_3SiCl (1.1 mmol, 0.140 mL) were added at room temperature to a solution of 4-acetoxy-β-lactam **1** or **13**, **14**, **15**, **16** (1 mmol) in CH_2Cl_2 (5 mL). After complete conversion of the starting material (GC monitoring), the solution was brought to 0 °C and a solution of $TiCl_4$ (or of the appropriate Lewis Acid) (1 M, 1 mL, 1 mmol) in CH_2Cl_2 was added. After 1 min, a solution of the chosen diazo compound (4 equiv.) in CH_2Cl_2 (2 mL) was slowly added dropwise (over 30 min) at 0 °C. The reaction mixture was stirred at room temperature and the conversion was monitored by TLC or GC. After 3 h the reaction was quenched in ice-cold water and extracted with CH_2Cl_2 (3 × 15 mL). The extracts were dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (eluent: cyclohexane/ethyl acetate) to afford separated *Z* and *E* isomers as products. Yields and isomer percentages are reported in Tables 1, 2, and 3.

Ethyl {(2*Z*,3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-ylidene}acetate (compound 3, *Z* isomer): $R_f = 0.8$ (cyclohexane/ethyl acetate, 7:3). $[\alpha]_D^{25} = -40.8$ (*c* = 0.53, $CHCl_3$). IR (neat): ṽ = 3250, 1821, 1693, 1652, 1238 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.06 (s, 3 H, $SiCH_3$), 0.07 (s, 3 H, $SiCH_3$), 0.87 (s, 9 H, Si*t*Bu), 1.29 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2), 1.31 (d, *J* = 6.3 Hz, 3 H, CH_3CHO), 3.66 (dd, *J* = 5.4, 0.9 Hz, 1 H, CHOC*H*), 4.19 (q, *J* = 7.2 Hz, 2 H, CH_3CH_2), 4.23 (m, 1 H, CHO), 5.21 (d, *J* = 0.9 Hz, 1 H, C=CH), 8.61 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = −5.0, −4.3, 14.3, 17.9, 22.3, 25.6, 60.1, 64.7, 65.1, 90.3, 153.3, 166.7, 167.2 ppm. MS (70 eV): *m*/*z* (%) = 298 (3) [$M^+ - CH_3$], 268 (5), 256 (90) [$M^+ - t$Bu], 210 (100), 184 (14), 143 (44), 75 (32), 73 (29). $C_{15}H_{27}NO_4Si$ (313.46): calcd: C 57.47, H 8.68, N 4.47; found C 57.58, H 8.63, N 4.41.

Ethyl {(2*E*,3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-ylidene}acetate (compound 3, *E* isomer): $R_f = 0.7$ (cyclohexane/ethyl acetate, 7:3) $[\alpha]_D^{25} = +106.5$ (*c* = 1.7, CH_2Cl_2). IR ($CHCl_3$): ṽ = 3257, 1819, 1706, 1666, 1268 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.11 (s, 3 H, $SiCH_3$), 0.13 (s, 3 H, $SiCH_3$), 0.91 (s, 9 H, Si*t*Bu), 1.22 (d, *J* = 6.3 Hz, 3 H, CH_3CHO), 1.28 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2), 4.10 (m, 1 H, CHOC*H*), 4.17 (q, *J* = 7.2 Hz, 2 H, CH_3CH_2), 4.65 (dq, *J* = 6.3, 3.9 Hz, 1 H, CHO), 5.31 (d, *J* = 0.6 Hz, 1 H, C=CH), 7.9 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 100 MHz): δ = −5.0, −4.7, 14.3, 18.0, 19.5, 25.7, 59.9, 64.6, 64.7, 92.5, 153.0, 166.3, 168.0 ppm. MS (70 eV): *m*/*z* (%) = 298 (2) [$M^+ - CH_3$], 268 (5), 256 (92) [$M^+ - t$Bu], 210 (20), 184 (18), 143 (11), 75 (85), 73 (100). $C_{15}H_{27}NO_4Si$ (313.46): calcd: C 57.47, H 8.68, N 4.47; found C 57.51, H 8.75, N 4.51.

***tert*-Butyl {(2*Z*,3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-ylidene}acetate (compound 9, *Z* isomer):** $R_f = 0.7$ (cyclohexane/ethyl acetate, 7:3). $[\alpha]_D^{25} = -20.1$ (*c* = 0.6, $CHCl_3$). IR (nujol): ṽ = 3251, 1819, 1699, 1660, 1235 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.06 (s, 3 H, $OSiCH_3$), 0.07 (s, 3 H, $OSiCH_3$), 0.87 (s, 9 H, OSi*t*Bu), 1.31 (d, *J* = 6.3 Hz, 3 H,

CH_3CHOSi), 1.49 (s, 9 H, O*t*Bu), 3.63 (d, J = 4.8 Hz, 1 H, SiOCHCH), 4.23 (dq, J = 4.8, 6.3 Hz, 1 H, CH_3CHOSi), 5.13 (s, 1 H, C=CH), 8.31 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.0, −4.2, 17.9, 22.3, 25.7, 28.3, 64.6, 65.0, 80.3, 92.4, 151.5, 166.0, 166.1 ppm. MS (70 eV): *m*/*z* (%) = 284 (3) [M^+ − *t*Bu], 228 (55), 210 (46), 73 (67), 57 (100), 41 (81). $C_{17}H_{31}NO_4Si$ (341.52): calcd. C 59.79, H 9.15, N 4.10; found C 59.65, H 9.12, N 4.01.

(3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-[(1*Z*)-2-oxo-2-phenylethylidene]azetidin-2-one (compound 10, *Z* isomer): R_f = 0.6 (cyclohexane/ethyl acetate, 7:3). $[\alpha]_D^{25}$ = +17.3 (c = 1.1, $CHCl_3$). IR (CH_2Cl_2): ν̃ = 3251, 1813, 1660, 1593, 1240 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.08 (s, 3 H, $SiCH_3$), 0.09 (s, 3 H, $SiCH_3$), 0.89 (s, 9 H, Si*t*Bu), 1.39 (d, J = 6.2 Hz, 3 H, CH_3CHOSi), 3.81 (d, J = 5.6 Hz, 1 H, SiOCHCH), 4.30 (dq, J = 5.6, 6.2 Hz, 1 H, CH_3CHOSi), 6.41 (s, 1 H, C=CH), 7.40−7.94 (m, 5 H), 9.28 (br. s, 1 H, NH). ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.9, −4.1, 18.0, 22.6, 25.7, 65.5, 65.8, 94.8, 127.8, 128.5, 132.5, 137.9, 155.3, 167.2, 189.9 ppm. MS (70 eV): *m*/*z* (%) = 330 (2) [M^+ − CH_3], 288 (100) [M^+ − *t*Bu], 244 (43), 105 (39), 77 (28), 73 (33). $C_{19}H_{27}NO_3Si$ (345.51): calcd. C 66.05, H 7.88, N 4.05; found C 65.69, H 7.80, N 4.03.

(3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-[(1*Z*,3*E*)-2-oxo-4-phenylbut-3-enylidene]azetidin-2-one (compound 11, *Z* isomer): $[\alpha]_D^{25}$ = +23.1 (c = 1.3, $CHCl_3$). IR (CH_2Cl_2): ν̃ = 3231, 1825, 1680, 1630, 1580, 1254 cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.09 (s, 6 H, $OSiCH_3$), 0.89 (s, 9 H, Si*t*Bu), 1.37 (d, J = 6.2 Hz, 3 H, CH_3CHOSi), 3.76 (d, J = 5.6 Hz, 1 H, SiOCHCH), 4.27 (dq, J = 5.6, 6.2 Hz, 1 H, CH_3CHOSi), 5.96 (s, 1 H, C=CH), 6.77 (d, J = 16.2 Hz, 1 H, CH=CHPh), 7.40−7.70 (m, 6 H, CH=CHPh + Ph), 9.09 (br. s, 1 H, NH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = −4.9, −4.1, 18.0, 22.6, 25.7, 65.5, 65.8, 98.1, 126.7, 128.2, 128.8, 130.2, 134.7, 142.3, 154.4, 167.3, 188.7 ppm. MS (70 eV): *m*/*z* (%) = 356 (2) [M^+ − CH_3], 315 (100) [M^+ − *t*Bu], 270 (33), 131 (48), 103 (42), 75 (82), 73 (67). $C_{21}H_{29}NO_3Si$ (371.55): calcd. C 67.89, H 7.87, N 3.77; found C 67.98, H 7.92, N 3.80.

Ethyl 4-{(2*Z*,3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-ylidene}-2-diazo-3-oxobutyrate (compound 12, *Z* isomer): R_f = 0.7 (cyclohexane/ethyl acetate, 7:3). $[\alpha]_D^{25}$ = −12.0 (c = 0.7, $CHCl_3$). IR (CH_2Cl_2): ν̃ = 3290, 2136, 1817, 1717, 1652, 1312 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.06 (s, 6 H, $SiCH_3$), 0.85 (s, 9 H, Si*t*Bu), 1.34 (d, J = 7.0 Hz, 3 H, CH_3CHO), 1.34 (t, J = 7.2 Hz, 3 H, CH_3CH$_2$), 3.74 (d, J = 4.4 Hz 1 H, OCHCH), 4.25 (m, 1 H, CHO), 4.31 (q, J = 7.2 Hz, 2 H, CH_3CH_2), 6.69 (s, 1 H, C=CH), 9.05 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = −5.0, −4.3, 14.4, 18.0, 22.2, 25.7, 53.4, 61.4, 64.9, 65.8, 95.6, 153.5, 161.2, 167.2, 181.3 ppm. MS (70 eV): *m*/*z* (%) = 366.5 (3) [M^+ − CH_3], 324 (48) [M^+ − *t*Bu], 223 (38), 143 (33), 73 (100). $C_{17}H_{27}N_3O_5Si$ (381.50): calcd. C 53.52, H 7.13, N 11.01; found C 53.30, H 7.10, N 10.90.

Ethyl [(2*Z*)-4-Oxoazetidin-2-ylidene]acetate (compound 17, *Z* isomer): R_f = 0.5 (cyclohexane/ethyl acetate, 1:1). IR (nujol): ν̃ = 3230, 1819, 1699, 1646, 1255 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (t, J = 7.2 Hz, 3 H, CH_3CH$_2$), 3.56 (s, 2 H, CH_2C=CH), 4.20 (q, H CH_3CH_2, J = 7.2 Hz), 5.17 (s, 1 H, C=CH), 8.47 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.4, 44.9, 60.2, 90.6, 149.7, 164.6, 167.0 ppm. MS (70 eV): *m*/*z* (%) = 155 (11) [M^+],127 (37), 99 (100), 85 (35), 67 (29), 43 (52). HRMS: calcd.for $C_7H_9NO_3$ *m*/*z* = 155.0582; found *m*/*z* = 155.0584. $C_7H_9NO_3$ (155.2): calcd. C 54.19, H 5.85, N 9.03; found C 54.12, H 5.85, N 9.02.

Ethyl [(2*E*)-4-Oxoazetidin-2-ylidene]acetate (compound 17, *E* isomer): R_f = 0.4 (cyclohexane/ethyl acetate, 1:1). IR (CH_2Cl_2): ν̃ = 3204, 1812, 1779, 1713, 1646, 1275 cm^{-1}. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.29 (t, J = 7.2 Hz, 3 H, CH_3CH$_2$), 3.80 (m, 2 H, CH_2C=CH), 4.18 (q, 2 H, CH_3CH_2, J = 7.2 Hz), 5.35 (m, 1 H, C=CH), 7.29 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.4, 46.1, 60.1, 92.4, 150.4, 165.7, 166.4 ppm. MS (70 eV): *m*/*z* (%) = 155 (30) [M^+],127 (12), 99 (100), 85 (30), 68 (78), 43 (50). HRMS: calcd.for $C_7H_9NO_3$ *m*/*z* = 155.0582; found *m*/*z* = 155.0584. $C_7H_9NO_3$ (155.2): calcd. C 54.19, H 5.85, N 9.03; found C 54.12, H 5.70, N 9.00.

4-[(1*Z*)-2-Oxo-2-phenylethylidene]azetidin-2-one (compound 18, *Z* isomer): R_f = 0.6 (cyclohexane/ethyl acetate, 1:1). IR (nujol): ν̃ = 3225, 1805, 1660, 1600, 1255 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.67 (s, 2 H), 6.36 (s, 1 H), 7.5−7.8 (m, 5 H), 9.71 (br. s, 1 H, NH) − ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.9, 94.8, 127.9, 128.6, 132.7, 17.8, 151.9, 165.6, 190.0 ppm. MS (70 eV): *m*/*z* (%) = 187 (9) [M^+], 159 (42), 105 (27), 77 (100), 51 (48). HRMS: calcd.for $C_{11}H_9NO_2$ *m*/*z* = 187.0633; found *m*/*z* = 187.0635. $C_{11}H_9NO_2$ (187.2): calcd. C 70.58, H 4.85, N 7.48; found C 70.63, H 4.84, N 7.48.

4-[(1*Z*,3*E*)-2-Oxo-4-phenylbut-3-enylidene]azetidin-2-one (compound 19, *Z* isomer): IR (nujol): ν̃ = 3198, 1806, 1660, 1630 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.65 (s, 2 H, CH_2CO), 5.91 (s, 1 H, C=C=CH), 6.78 (d, J = 15.9 Hz, 1 H, CH=CHPh), 7.3−7.6 (m, 6 H, CH=CHPh + Ph), 9.28 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.8, 97.9, 126.8, 128.3, 128.9, 130.4, 134.7, 142.5, 150.8, 165.3, 188.9 ppm. MS (70 eV): *m*/*z* (%) = 213 (34) [M^+], 156 (21), 115 (28), 77 (100). HRMS: calcd.for $C_{13}H_{11}NO_2$ *m*/*z* = 213.0790; found *m*/*z* = 213.0792. $C_{13}H_{11}NO_2$ (213.2) calcd. C 73.23, H 5.20, N 6.57; found C 73.20, H 5.18, N 6.54.

Ethyl [(2*Z*,3*R*)-3-Chloro-4-oxoazetidin-2-ylidene]acetate (compound 20, *Z* isomer): R_f = 0.8 (cyclohexane/ethyl acetate, 1:1). $[\alpha]_D^{25}$ = +7.3 (c = 0.84, $CHCl_3$). IR (CH_2Cl_2): ν̃ = 3260, 1830, 1705, 1660, 1250 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.32 (t, J = 7.0 Hz, 3 H, CH_3CH$_2$), 4.23 (q, 2 H, CH_3CH_2, J = 7.0 Hz), 5.23 (s, 1 H, C=CH), 5.40 (d, J = 0.8 Hz,, 1 H, ClCH), 8.80 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 14.3, 59.8, 60.8, 91.3, 150.9, 161.8, 166.7 ppm. MS (70 eV): *m*/*z* (%) = 189 (8) [M^+], 161 (31), 143 (46), 68 (100), 52 (58). HRMS: calcd.for $C_7H_8ClNO_3$ *m*/*z* = 189.0193; found *m*/*z* = 189.0194. $C_7H_8ClNO_3$ (189.6) calcd. C 44.34, H 4.25, N 7.39; found C 44.31, H 4.20, N 7.38.

Ethyl [(2*Z*,3*R*)-3-Bromo-4-oxoazetidin-2-ylidene]acetate (compound 21, *Z* isomer): R_f = 0.8 (cyclohexane/ethyl acetate, 1:1) $[\alpha]_D^{25}$ = −7.0 (c = 0.57, $CHCl_3$). IR (CH_2Cl_2): ν̃ = 3250, 1830, 1710, 1660, 1250 cm^{-1}. ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.31 (t, J = 7.4 Hz, 3 H, CH_3CH$_2$), 4.22 (q, 2 H, CH_3CH_2, J = 7.4 Hz), 5.26 (dd, J = 0.8, 2.2 Hz, 1 H, C=CH), 5.38 (d, J = 0.8 Hz, 1 H, BrCH), 8.65 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.3, 45.5, 60.8, 91.4, 151.2, 161.7, 166.8 ppm. $C_7H_8BrNO_3$ (234.05): calcd. C 35.92, H 3.45, N 5.98; found C 35.91, H 3.48, N 5.94.

Ethyl [(2*Z*,3*R*)-3-(1-Hydroxyethyl)-4-oxoazetidin-2-ylidene]acetate (compound 22, *Z* isomer): 1 N HCl (1 mL) was added to a solution of β-lactam **3**-*Z* (313 mg, 1 mmol) in CH_3OH (8 mL). The reaction was monitored by TLC and further portions of 1 N HCl (1 mL) were added until total conversion was accomplished. The reaction was quenched in ice-cold water and extracted with CH_2Cl_2 (3 × 15 mL). The extracts were dried (Na_2SO_4) and concentrated, and then the residue was purified by flash chromatography (cyclohexane/ethyl acetate, 4:6). Yield 72%. $[\alpha]_D^{25}$ = −24 (c = 0.61, $CHCl_3$).

IR (neat): $\tilde{\nu}$ = 3423, 3257, 1805, 1792, 1646 cm^{-1}. ^1H NMR ($CDCl_3$, 300 MHz): δ = 1.30 (t, *J* = 7.2 Hz, 3 H, CH_3CH_2), 1.39 (d, *J* = 6.6 Hz, 3 H, CH_3CHO), 2.1 (br. s, 1 H, OH), 3.75 (d, *J* = 5.7 Hz, 1 H, CHOC*H*), 4.21 (q, H CH_3CH_2, *J* = 7.2 Hz), 4.23 (m, 1 H, C*H*OH), 5.27 (d, *J* = 0.3 Hz, 1 H, C=CH), 8.73 (br. s, 1 H, NH) ppm. ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 14.3, 21.5, 60.3, 64.0, 64.8, 90.9, 152.2, 166.3, 166.9 ppm. MS (70 eV): *m*/*z* (%) = 199 (4) [M^+], 184 (11) [$M^+ - CH_3$], 166 (43), 155 (57), 138 (57), 99 (100), 68 (41). HRMS: calcd.for *m*/*z* = 199.0845; found *m*/*z* = 199.0848. $C_9H_{13}NO_4$ (199.2) calcd. C 54.26, H 6.58, N 7.03; found C 53.68, H 6.64, N 7.03.

{(2*Z*,3*S*)-3-[(1*R*)-1-(*tert*-Butyldimethylsilanyloxy)ethyl]-4-oxoazetidin-2-ylidene}acetic Acid (compound 23, *Z* isomer): A solution of $TiCl_4$ (3 mmol) in CH_2Cl_2 (2 mL) was added at 0 °C to a solution of **9** (341 mg, 1 mmol) in CH_2Cl_2 (5 mL). After 1 min, the reaction is controlled by TLC (cyclohexane/ethyl acetate 1:1), the reaction mixture was poured into ice-water and extracted with CH_2Cl_2 (3 × 10 mL). The extracts were dried (Na_2SO_4) and concentrated, and then the residue was purified by flash chromatography (cyclohexane/ethyl acetate, 1:1). Yield 87%. $[\alpha]_D^{25} = -22.7$ (*c* = 0.3, $CHCl_3$). IR ($CHCl_3$): $\tilde{\nu}$ = 3358, 1785, 1691, 1655, 1462, 1250 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 0.07 (s, 3 H, $SiCH_3$), 0.08 (s, 3 H, $SiCH_3$), 0.88 (s, 9 H, Si*t*Bu), 1.33 (d, *J* = 6.2 Hz, 3 H, CH_3CHOSi), 3.71 (d, *J* = 4.6 Hz, 1 H, SiOCHC*H*), 4.24 (m, 1 H, CH_3CHOSi), 5.24 (s, 1 H, C=CH), 8.40 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = −5.0, −4.2, 18.0, 22.3, 25.7, 65.0, 65.0, 90.0, 155.4, 166.4, 171.8 ppm. $C_{17}H_{31}NO_4Si$ (341.52): calcd. C 59.79, H 9.15, N 4.10; found C 59.63, H 9.14, N 4.08.

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