Preparation of α-Methylene and α-Ethylidene β-Lactams via the Ester Enolate–Imine Condensation Using β-(Dialkylamino) Esters as Starting Materials: Scope and Synthetic Applications

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A new, simple procedure for the preparation of appropriately substituted α-methylene and α-ethylidene β-lactams via the ester enolate–imine condensation is described. The method is based on the use of lithium 3-(dialkylamino) ester enolates as synthetic equivalents of the corresponding acrylate α-anions. Thus, the reaction of lithium enolates of 3-(dialkylamino) esters with imines produced α-[(dialkylamino)alkyl] β-lactams stereoselectively and in high yield. Upon dehydroamination the latter furnished a variety of α-alkylidene β-lactams. The synthesis of 3-alkylidene-4-formyl-2-azetidinones is a particularly significant feature of this work. Preparation of functionalized α-keto β-lactams and β-lactam–furan hybrids through a dihydroxylation–oxidation process starting from different α-alkylidene derivatives is also described. In addition, reduction of various 4-functionalized (*Z*)- and (*E*)-3-ethylidene-2-azetidinones yielded the corresponding 3-ethylideneazetidines as advanced precursors of polyoximic acids.

Introduction

Although considerable synthetic progress has been made in the area of mono and bicyclic β-lactam antibiotics in recent years,[1] the discovery and development of new antibacterial agents with enhanced activity and greater stability toward β-lactamases still remains an important endeavor for medicinal chemists. Also, the widespread incidence of antibacterial resistence to the β-lactam antibiotics caused by β-lactamase formation has provoked a growing interest in the development of effective β-lactamase inhibitors. Since the discovery of the first clinically important β-lactamase inhibitor clavulanic acid,[2] various extremely active compounds have been reported in the literature. Included among these compounds are the "ene-type" β-lactam antibiotics which possess an α-alkylidene side chain on the β-lactam nucleus. Some specific examples are the asparenomycins,[3] Ro15-1903,[4] 6-[(*Z*)-methoxymethylidene]penicillanic acid,[5] and other closely related compounds.[6] In addition, α-alkylidene β-lactams are valuable synthetic intermediates which can serve not only for the introduction of the side chains common to the carbapenems,[7] but also for the preparation of other useful synthetic targets such as α-keto β-lactams.[8,9]

Because of the importance of α-alkylidene β-lactams, different methods have been described for the synthesis of both mono- and bicyclic compounds. Most of the strategies that have been developed can be classified according to two general approaches: (i) α-alkylidenation on preformed β-lactams[5b,10] and (ii) α-alkylidenation reactions on acyclic substrates with concomitant β-lactam ring formation. Of these two strategies, the latter is inherently the most attractive because of the greater degree of convergency associated with this approach.

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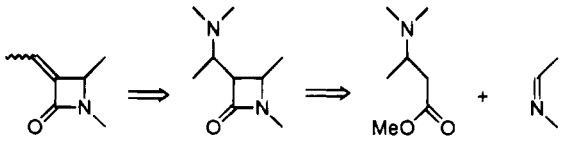
Scheme 1



Typical procedures using this methodology include the Pd-catalyzed carbonylation of amine derivatives[11] and related metal-mediated proccesses,[12] the addition of chlorosulfonyl isocyanate to functionalized allenes,[7,13] and those that employ masked[14] or unmasked[15] acrylic acid derivatives. Often, many of these methods either involve multistep synthesis and low yields or are limited in scope regarding the nature of substituents on N_1, C_4, and the alkylidene chain.

The condensation of metal ester enolates with imines has become one of the major routes for the construction of the functionalized β-lactam ring.[16] Surprisingly, this method has not been used in the synthesis of α-alkylidene β-lactams. In this paper we report in full[17] a convenient, simple method for the synthesis of various α-methylene and α-ethylidene β-lactams based upon the condensation of lithium enolates of 3-(dialkylamino) esters with imines followed by straightforward dehydroamination of the resulting 3-(1-aminoalkyl)-2-azetidinones (Scheme 1). This novel approach involves the use of β-amino ester enolates as synthetic equivalents of acrylate α-anions. In addition, some transformations of different α-alkylidene derivatives are also described. These include preparation of functionalized α-keto β-lactams and β-lactam–furan hybrids through a dihydroxylation–oxidation process, as well as the reduction of various 4-functionalized (*Z*)- and (*E*)-3-ethylidene-2-azetidinones to the corresponding 3-ethylideneazetidines, advanced precursors of polyoximic acids.

Results and Discussion

It has been described that β-amino ester enolates efficiently react with both alkyl halides and aldehydes to give, after elimination of the amino group, α-alkylated enoates in a simple stereoselective manner.[18] Consequently, we thought that we could utilize this methodology for preparing valuable monocyclic α-alkylidene β-lactams using imines as the alkylating reagents (Scheme 1). For our study we examined the behavior of imines **1** toward several lithium enolates derived from β-amino esters **2**. Imines derived from functionalized aldehydes having *N*-4-methoxyphenyl (PMP) or N-trimethylsilyl (TMS) groups are excellent choices, since these groups can be removed later under mild conditions,[19] and groups on C_4 in the final β-lactams are suitable for an easy functionalization, particularly those derived from glyoxal diimine **1a**.[20] With the exception of methyl 3-(dimethylamino)propionate (**2a**) which is commercially available, the β-amino esters **2** were easily prepared by conjugated addition of the corresponding lithium amides to α,β-unsaturated esters following a standard protocol.[21] Then we investigated reactions of the lithium enolate derived from **2a** with imines **1**. In fact reaction between an excess of this enolate (2.2 equiv) with these imines **1** in THF as solvent, under standard conditions,[22] furnished the desired β-lactams **3** as mixtures of *cis* and *trans* isomers in yields ranging from 54% to nearly quantitative (Scheme 2). The relative stereochemistry at C_3 and C_4 was assigned on the basis of coupling constants of the corresponding ^{1}H-NMR spectra. Results of these reactions are summarized in Table 1 (entries 1–5).

Chart 1

1

1a: R^1 = CH=NPMP, R^2 = PMP
1b: R^1 = CH=CHPh, R^2 = PMP
1c: R^1 = 2-furyl, R^2 = PMP
1d: R^1 = 2-furyl, R^2 = TMS
1e: R^1 = Ph, R^2 = PMP

2

2a: R^3 = H, R^4 = R^5 = Me
2b: R^3 = Me, R^4 = R^5 = *i*-Pr
2c: R^3 = Ph, R^4 = R^5 = Bn
2d: R^3 = Me, R^4 = Bn, R^5 = (*R*)-Ph(Me)CH

Next, we turned our attention to the lithium enolate derived from **2b** as a precursor for α-ethylidene β-lactams. In this case, the starting enolate was obtained either by treatment of the β-amino ester **2b** with LDA under the usual conditions for the generation of enolates from simple esters (method A) or by the conjugate addition of LDA to methyl crotonate[21] at −78 °C (method B). When this enolate was allowed to react with imines **1**, mixtures of *cis*- and *trans*-[3-[α-(diisopropylamino)-ethyl] β-lactams] **4** were obtained in good to excellent yields (Scheme 2). Of the various reactions carried out, only that of imine **1b** failed to give the corresponding β-lactam either by method A or B. This is in clear contrast with the facile reaction of glyoxal diimine **1a**. Both imines may be considered as synthetic equivalents of the unknown *N*-(*p*-anisyl)-α-formylmethanimine (the

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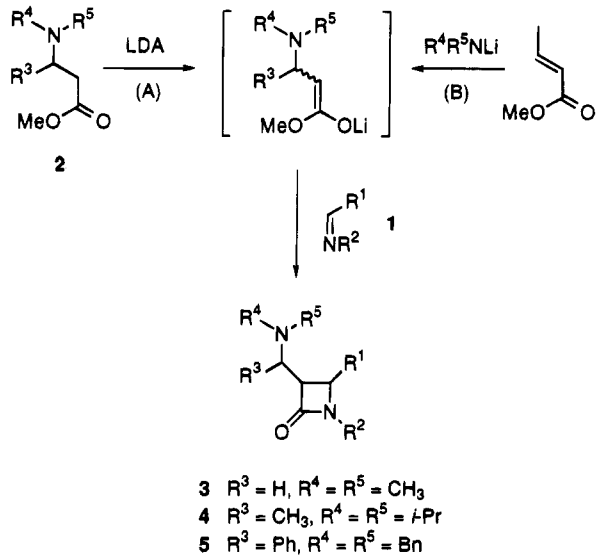
Scheme 2



3 R^3 = H, R^4 = R^5 = CH_3
4 R^3 = CH_3, R^4 = R^5 = *i*-Pr
5 R^3 = Ph, R^4 = R^5 = Bn

formal precursor for the synthesis of 4-formyl-2-azetidinones). Whenever possible, isomers were isolated and purified by column chromatography and/or crystallization. The results, summarized in Table 1 (entries 6–12), indicate that both the *anti*/*syn*-diastereoselection and the *cis*/*trans*-selectivity in the condensation of enolate derived from **2b** with imines **1** are greatly influenced by both the substituents on the starting imine and the method (A or B) for the generation of the enolate.

Thus, the *cis*/*trans*-selectivity in β-lactams obtained by method A was excellent in almost all cases ranging from *trans* for diimine **1a** (entry 6) to *cis* for the remaining imines studied (**1c–e**; entries 8, 10, and 14). However, *trans* β-lactams were the only or predominant isomers produced by using method B. It is worth noting the complete change in the selectivity (*cis* to *trans*) observed for imine **1d** depending on the method for the generation of the enolate (entries 10 and 11). With regard to the *anti*/*syn*-diastereoselection, method B seems to favor *anti* isomers (entries 7, 9 and 11), while method A gives *anti* or *syn* isomers depending on the nature of the imine (entries 6, 8, 10, and 12).

The *trans* and *cis* isomers were easily distinguished by the value of $J_{3,4}$, the *cis* value (5.1–6.0 Hz) always being larger than the *trans* (1.7–2.4 Hz) in such compounds. In general, signals corresponding to both H_3 and H_4 protons in a *cis* isomer appear at lower fields than the corresponding signals in the respective *trans* isomer. On the other hand, the relative stereochemistry of diastereomeric β-lactams, *anti* and *syn*, respectively, according to the nomenclature used by Georg[23] (Figure 1), was determined by X-ray diffraction analysis of two selected isomers, i.e. *cis,anti*-β-lactam **4b**-α and *trans,anti*-β-lactam **4c**-γ (major isomers for their respective reactions; see Table 1, entries 8 and 11), and also by comparison of their corresponding $J_{1',3}$ values and chemical shifts with those observed for the remaining isomers.[30] From the data compiled in Table 2 it might be deduced that in each case the lower field H_3 and H_4 protons correspond to the *cis* or *trans anti*-**4** isomers having the smaller $J_{1',3}$ values (4.6–7.5 Hz). On the other hand, the higher field H_3 and H_4 protons could be assigned to the *cis* or *trans syn*-**4** isomers with the larger $J_{1',3}$ values (10.8–11.4 Hz).

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In addition, we considered the reactions of the enolate derived from β-amino ester **2c** with imines **1a** and **1e**. The results shown in Table 1 (entries 13 and 14) indicate that an increase in the bulkiness of the amine moiety has little effect on the *cis/trans* ratio, but leads to a moderate to excellent increase in the *anti/syn* ratio for either *cis* and *trans* isomers. Only the *trans,syn*-isomer **5a** was produced in the reaction of imine **1a**. Reactions of the enolate derived from chiral β-amino ester **2d** (methods A and B) with imine **1a** were also investigated. Unfortunately, **1a** did not react with the enolate to form the expected β-lactam; some unidentified products as well as starting material were recovered.

At this stage we examined the elimination of the amino group in 3-[1′-(dialkylamino)alkyl] β-lactams **3–5** to produce the desired α-alkylidene β-lactams. Dehydroamination was accomplished in different ways depending on the nature of R^4 (R^5) (Scheme 3). When R^4 = *i*-Pr, elimination was performed by heating under reflux in toluene with silica gel.[24] The dimethylamino group was better removed by quaternization with methyl iodide followed by DBU-induced elimination under different conditions.[18] Results are summarized in Table 3. In all cases, α-alkylidene β-lactams **6** and **7** were obtained from *cis/trans* mixtures of β-lactams **3** and **4**, respectively. For the synthesis of α-methylene β-lactams **6**, method B gave better results. Otherwise, of the various substrates assayed only **3d** failed to give the corresponding elimination product. In this case a complex reaction mixture, in which no desired β-lactam could be detected, was formed. Due to the failure of methods B and C, α-ethylidene β-lactams **7** were exclusively produced by method A, as mixtures of *E*/*Z* isomers in a ratio ranging from 60/40 to 43/57. The ratio of *E*/*Z* isomers produced for a given β-lactam was independent of the *cis/trans* ratio of the starting amine. Thus, starting from **4b** as a 46/54 or 18/85 mixture of α/β isomers, β-lactam **7b** was obtained as a 50/50 mixture of *E*/*Z* isomers. The same yield and composition for **7b** was produced from a 65/35 mixture of γ/δ isomers. Moreover, as it can be deduced from experiments at different reaction times, *cis* β-lactams **3** or **4** react faster than the corresponding *trans* isomers. However, all attempts to dehydroaminate β-lactams **5a** and **5b**, suitable precursors for the preparation of α-benzylidene β-lactams, were unfruitful, and the starting compounds were recovered unchanged. With the exception of **7a**, the remaining compounds **7** were easily separated into their *E* and *Z* isomers by column chromatography on silica gel. The *E*/*Z* stereochemistry of the double bond in these compounds was determined by NMR spectroscopy through the chemical shift of the vinylic proton, which resonates at higher field for the *Z* isomer (5.47–5.87 ppm) than that for the *E* isomer (6.26–6.44 ppm), according to the assignment made on related compounds.[7e] Additionally, compounds **7a–c** were prepared in one-pot fashion with similar or higher yields (see Table 3) starting from the corresponding β-amino ester and imine, without previous purification of the intermediate 3-(aminoalkyl)-2-azetidinones **4a–c** (see Table 1, entries 6, 8, and 10, and Table 3, entries 9–11). This is particularly significant in the cases of compounds **7b** and **7c**. Compare, for example, the 62 and 42% yields, respectively, for compounds **7b** and **7c** in the two-step synthesis with the 92 and 70% yields in the one-pot

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Table 1. Preparation of 3-[1'-(Dialkylamino)alkyl]-2-azetidinones 3, 4, and 5 from Ester Enolates 2a–c and Imines 1

								ratio isomers[e]			
								cis		*trans*	
entry	compd[a]	R^1[b]	R^2[b]	R^3	R^4, R^5	method[c]	yield, %[d]	*anti* (α)	*syn* (β)	*anti* (γ)	*syn* (δ)
1	**3a**	CH=N-PMP	PMP	H	Me	A	100	30		70	
2	**3b**	CH=CHPh	PMP	H	Me	A	54	75		25	
3	**3c**	2-furyl	PMP	H	Me	A	77	50		50	
4	**3d**[f]	2-furyl	TMS/H	H	Me	A	70	50		50	
5	**3e**	Ph	PMP	H	Me	A	63	94		6	
6	**4a**	CH=N-PMP	PMP	Me	*i*-Pr	A	100	–	–	30	70
7						B	95	–	–	70	30
8	**4b**	2-furyl	PMP	Me	*i*-Pr	A	65	83	12	2	3
9						B	60	19	25	40	16
10	**4c**[f]	2-furyl	TMS/H[g]	Me	*i*-Pr	A	61	33	67	–	–
11						B	74	–	–	65	35
12	**4d**	Ph	PMP	Me	*i*-Pr	A	82	54	30	8	8
13	**5a**	CH=N-PMP	PMP	Ph	Bn	A	80	–	–	–	100
14	**5b**	Ph	PMP	Ph	Bn	A	60	63	37	–	–

[a] All compounds are racemic. [b] In all cases PMP = 4-$MeOC_6H_4$. [c] A = imine/β-amino ester/LDA; B = imine/methyl crotonate/LDA. [d] Yields based on weight of isolated material by column chromatography, except for **3a** (determined by ^{1}H-NMR). [e] All percentages refer to diastereomeric ratios, determined by integration of the characteristic ^{1}H NMR signals of the crude reaction mixtures. [f] Imine **1d** was prepared *in situ* in THF and was directly added to a solution containing the enolate. [g] Upon hydrolysis the TMS group is replaced by a hydrogen.

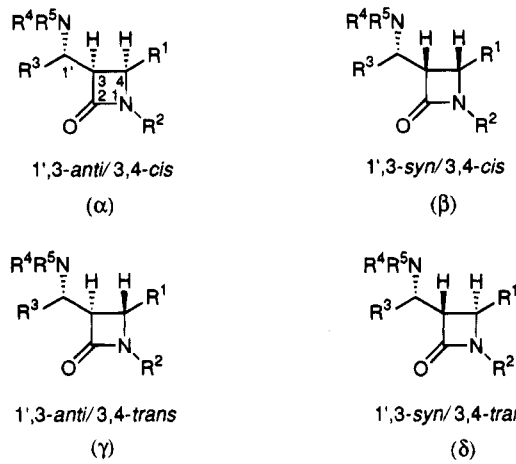


Figure 1. Diastereoisomers of 3-[(1'-dialkylamino)alkyl]-2-azetidinones.

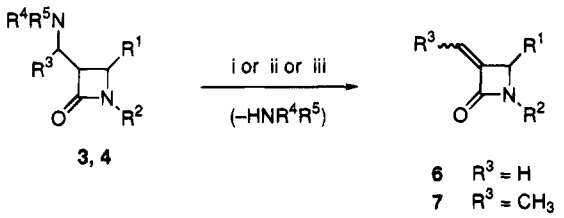
Table 2. Selected ^{1}H NMR Data of β-Lactams 4 and 5[a]

	δ (ppm)[b]			*J* (Hz)	
compd	H_3	H_4	$H_{1'}$	$J_{3,4}$	$J_{1',3}$
anti,trans-**4a**	3.27	4.76	3.45	2.1	4.6
syn,trans-**4a**	3.28	4.50	3.35	1.7	10.8
anti,cis-**4b**	3.74	5.10	3.19	5.7	7.5
syn,cis-**4b**	3.56	5.05	3.25	5.7	11.4
anti,trans-**4b**	3.10–3.40[c]	5.08	3.10–3.40[c]	2.4	
syn,trans-**4b**	2.98–3.45[c]	4.73	2.98–3.45[c]	2.4	
anti,cis-**4c**	3.48	4.76	3.02–3.23[c]	5.1	6.6
syn,cis-**4c**	3.44	4.75	3.02–3.23[c]	5.1	11.1
anti,trans-**4c**	3.30	4.72	3.10–3.32[c]	2.1	5.4
syn,trans-**4c**	3.10–3.32[c]	4.41	2.95–3.38[c]	2.4	
anti,cis-**4d**	3.81	5.12	2.90	6.0	6.3
syn,cis-**4d**	3.57	5.03	3.00	5.4	11.4
anti,trans-**4d**		5.03		2.1	
syn,trans-**4d**	2.96–3.36[c]	4.66	2.96–3.36[c]	2.4	
syn,trans-**5a**	4.14[c]	4.66	4.14	1.8	11.4
anti,cis-**5b**	4.27	5.01	3.88	6.0	7.2
syn,cis-**5b**	4.49	4.92	3.81	5.7	12.6

[a] Determined by 300 MHz ^{1}H NMR spectroscopy in $CDCl_3$ solution. [b] Chemical shifts downfield relative to internal TMS. [c] As complex multiplet.

procedure. This experimental simplification provides an added value to the strategy, in terms of synthetic efficiency.

Scheme 3



[a] Key: (i) silica gel, toluene, Δ (method A). (ii) MeI, MeOH, rt, and then DBU, acetone, rt (method B). (iii) MeI, MeOH, rt, and then DBU, benzene, Δ (method C).

Among the different compounds **6** and **7** prepared, compounds **6a** and **7a** are of particular interest due to their potential formyl group on C_4, which can be easily obtained by simple hydrolysis of the corresponding imino group (Scheme 4).[20] Thus, treatment of β-lactams **6a** and **7a** (*E*/*Z*: 60/40) with dilute hydrochloric acid in chloroform gave the 4-formyl-2-azetidinones **8** and **9** (*E*/*Z*: 60/40) in good to excellent yield. Major isomer (*E*)-**9** was easily obtained in 46% yield by crystallization of the crude reaction mixture. However, attempts to separate both *E*/*Z* isomers by chromatography were unsuccessful, decomposition to complex mixtures being observed. In order to test the feasibility of the use of both *E* and *Z* isomers for the synthesis of other more elaborated compounds, we prepared different formyl derivatives for which the isomers could be readily separated, making possible their independent utilization (Scheme 4). Thus, reduction of *(E,Z)*-**9** with $NaBH_4$ in methanol gave alcohols **10**, and acetals **11** and **12** were prepared following standard methodology. All these compounds **10**–**12** obtained in excellent yields, were easily separated by column chromatography into their respective *E* and *Z* isomers.

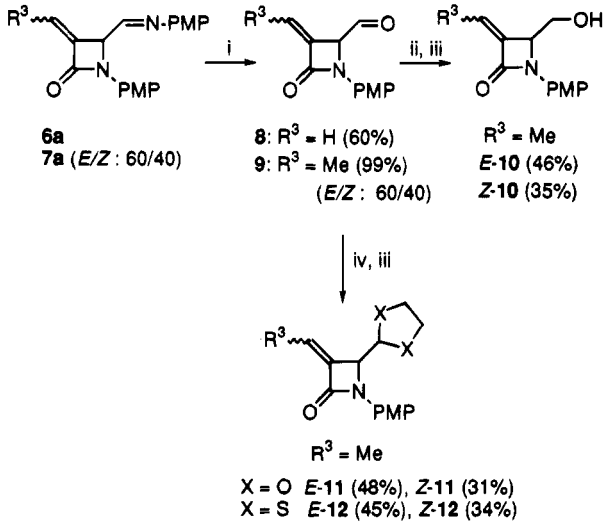
In addition, some aspects of the chemistry of compounds **6** and **7** were investigated. First, the synthesis of α-keto β-lactams by osmylation–oxidative cleavage of the olefinic moiety was addressed. There is only one example, reported by Ban, of the application of this procedure to the synthesis of an α-keto β-lactam; in his case a 4-unsubstituted-3-oxo-2-azetidinone was synthesized from an α-methylene β-lactam.[9b] In order to check the generality of this procedure for the synthesis of

Table 3. Preparation of α-Methylene and α-Ethylidene β-Lactams 6 and 7[a]

entry	compound	R^1	R^2	R^3	method[b]	t (h)	yield (%)[c]	E/Z ratio[d]	mp, °C[e]
1	**6a**	CH=N-PMP	PMP	H	B	4	40		syrup
2					C	4	61		
3	**6b**	CH=CHPh	PMP	H	A	48	37	–	102–104
4					B	6	80	–	
5	**6c**	2′-furyl	PMP	H	A	48	35	–	102–103
6					B	6	57	–	
7	**6d**	Ph	PMP	H	A	62	75	–	127–129
8					B	4	85	–	
9	**7a**	CH=N-PMP	PMP	Me	A	48	74 (73)	60/40	
10	**7b**	2′-furyl	PMP	Me	A	15	95 (92)	50/50	167–169 (*E*) 142–144 (*Z*)
11	**7c**	2′-furyl	H	Me	A	6	70 (70)	55/45	131–132 (*E*) 104–106 (*Z*)
12	**7d**	Ph	PMP	Me	A	7	98	43/57	163–165 (*E*)

[a] All compounds are racemic. In all cases PMP = 4-$MeOC_6H_4$. [b] A = silica gel/toluene/Δ; B = (1) MeI excess/MeOH, (2) DBU/acetone/rt; C = (1) MeI excess/MeOH, (2) DBU/benzene/Δ. [c] As isolated product by column chromatography, mixture of *E*/*Z* isomers. Yields without parentheses refer to isolated products starting from their corresponding 3-aminoalkyl β-lactams **3** or **4**. Those within parentheses are overall yields for isolated products starting from their corresponding imines and β-amino esters without purification of the intermediates products **3** or **4**. [d] Determined from integration of the characteristic signals in the ^{1}H-NMR (300 MHz) of the crude reaction mixtures. [e] In all cases, crystallized from AcOEt/hexanes.

Scheme 4

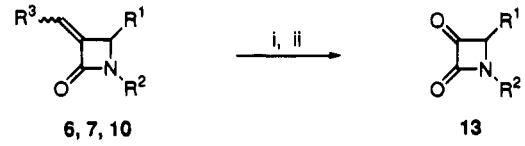


[a] Key: (i) 5% aqueous HCl, $HCCl_3$, rt, 1.5 h. (ii) $NaBH_4$, MeOH, rt; (iii) flash chromatography (SiO_2, hexane/AcOEt); (iv) for **11**: 1,2-ethanediol, *p*-toluenesulfonic acid, toluene, Δ (Dean–Stark); for **12**: 1,2-ethanedithiol, BF_3·Et_2O, CH_2Cl_2, rt, 3 h, and then 5% aqueous NaOH, 10 min.

different 4-substituted 2-azetidinones, we applied this one-pot oxidation sequence to some α-alkylidene β-lactams **6** and **7**. The presence of different substituents and functionalities on C_4 could have some influence either on the reaction course or on the nature of the resulting produts. On the other hand, this could be a good alternative to the cleavage by ozonolysis, which cannot be considered as a general mode of access to these compounds due to the observed ozonide fragmentation to α-amino acid-*N*-carboxy anhydrides in some instances.[25] Thus, different α-alkylidene β-lactams **6**, **7**, and **10** were oxidized with a catalytic amount of osmium tetroxide in the presence of trimethylamine *N*-oxide (TMNO) followed by cleavage of the resulting diol derivative with sodium metaperiodate to give α-oxo β-lactams **13** in good yields (Scheme 5, Table 4). Yield is independent of the olefinic moiety, as can be observed in the

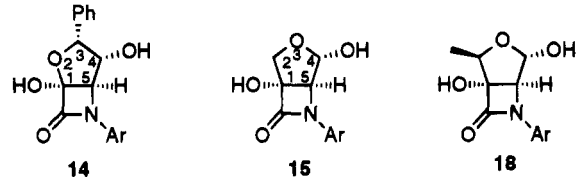
(25) (a) Bateson, J. H.; Kaura, A. C.; Southgate, R. *Tetrahedron Lett.* **1991**, *32*, 2065. (b) Bateson, J. H.; Fell, S. C. M.; Kaura, A. C.; Southgate, R. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1577.

Scheme 5



[a] Key: (i) OsO_4 cat., TMNO, acetone–water, rt, and then 40% $NaHSO_3$; (ii) $NaIO_4$, methanol–water, rt.

reactions of compounds **6c** and **7b** (Table 4, entries 1 and 2). The reaction of 3-methylene-4-styryl-2-azetidinone **6b** deserves some additional comments. Depending on the experimental conditions (mainly reaction time both for hydroxylation and for oxidative cleavage), along with 3-oxo β-lactam **13c**, bicyclic β-lactams **14** and **15** were



obtained in a selective fashion (Table 5). Thus, compound **13c** was the only product formed at shorter hydroxylation time (t_1) (entry 1). At longer times (t_1), the proportion of this compound decreases in favor of bicyclic hemiacetals **14** and **15** (entries 1–3). These two compounds were the only observed products at very prolonged reaction times (entries 4 and 5). From these results the following conclusions can be deduced: (i) the methylene group in **6b** is hydroxylated faster than the styryl group. This fact makes possible the preparation of α-oxo β-lactam **13c**; (ii) the dihydroxylation of both olefinic groups can be achieved in large part at longer hydroxylation time (entry 4); (iii) cleavage of the diol moiety derived from the styryl group on C_4 is faster than that from the methylene group on C_3 as it can be deduced from the preferential formation of compound **15** over **14** (entries 2–4). At longer cleavage time (t_2) (entry 5) hemiacetal **14** was the only isolable product. This fact clearly indicates that compound **15** decomposes with time to other unidentified, unisolated products, probably by degradation through the corresponding 4-formyl-3-oxo-2-azetidinone.

The relative stereochemistry of the bicyclic β-lactams **14** and **15** was established on the basis of their ^{1}H-NMR

Table 4. Preparation of α-Oxo β-Lactams 13 from α-Alkylidene β-Lactams 6, 7, and 10[a]

entry	substrate	R^1	R^{2a}	R^3	product	t_1[b]	t_2[c]	yield (%)[d]	mp, °C[e]
1	**6c**	2′-furyl	PMP	H	**13a**	18	48	80	90–92
2	**7b**[f]	2′-furyl	PMP	Me	**13a**	18	48	76	
3	**6d**	Ph	PMP	H	**13b**	18	5.5	80	130–131[e]
4	**6b**	CH=CHPh	PMP	H	**13c**	2	1	61	108–110
5	**10**[f]	CH_2OH	PMP	Me	**13d**	5	6	62	148–150

[a]All compounds are racemic. In all cases PMP = 4-$MeOC_6H_4$. [b]Reaction time for osmylation (hours). [c]Reaction time for oxidative cleavage (hours). [d]In pure, isolated product with correct analytical data. [e]Crystallized from AcOEt/hexanes, except for **13d** from AcOEt. [f]As *E*/*Z* mixture.

Table 5. Results of Osmylation–Oxidative Cleavage from 3-Methylene-4-styryl-2-azetidinone 6b[a]

entry	t_1[b]	t_2[c]	product[d]	yield, %[e]
1	1	60	**13c**	61
2	2	60	**13c**	40
			14	5
			15	30
3	5	30	**13c**	20
			14	18
			15	33
4	45	25	**14**	25
			15	50
5	45	90	**14**	30

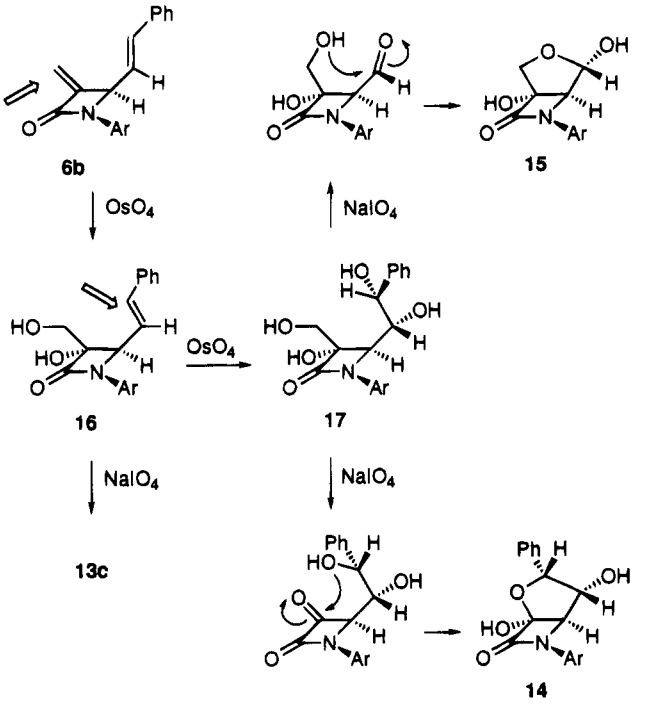
[a] Reactions were conducted until complete disappearance of the starting β-lactam **6b**. [b]Reaction time for osmylation (h). [c]Reaction time for oxidative cleavage (min). [d]All compounds are racemic. [e]Yields are for pure, isolated product by column chromatography.

spectral data, in particular the coupling constants $J_{3,4}$ and $J_{4,5}$ which are in good agreement with those reported for related systems.[26] The assignments are also in agreement with the expected course of the reactions. Thus, for compound **14** the proton at C_3 shows as a doublet at 5.14 ppm ($J_{3,4}$ = 4.8 Hz) indicative of a *cis* position with respect to the proton on C_4. Moreover, the C_5-H proton appears as a singlet at 4.25 ppm as expected for a *trans* disposition to the hydroxylic proton on this carbon atom (J = 3.6 Hz). In the case of compound **15** the proton at C_4 (5.23 ppm) was only coupled with the hydroxylic proton (J = 3.9 Hz), the proton at C_5 being a singlet at 4.09 ppm. The exclusive formation of the above stereoisomers for compounds **14** and **15** clearly shows that both the mono and the dihydroxylation on **6b** occur in a totally stereoselective fashion. As shown in Scheme 6 attack of OsO_4 on the methylene group at the less hindered side of the double bond gives the intermediate diol derivative **16**. It is possible that this diol functionality directs hydroxylation of the styryl group in a later stage to form stereoselectively the tetraol derivative **17**. After cleavage of one of these diol groups in **17**, the corresponding hemiacetal could be formed by intramolecular attack of the γ-hydroxyl group on the aldehyde function.

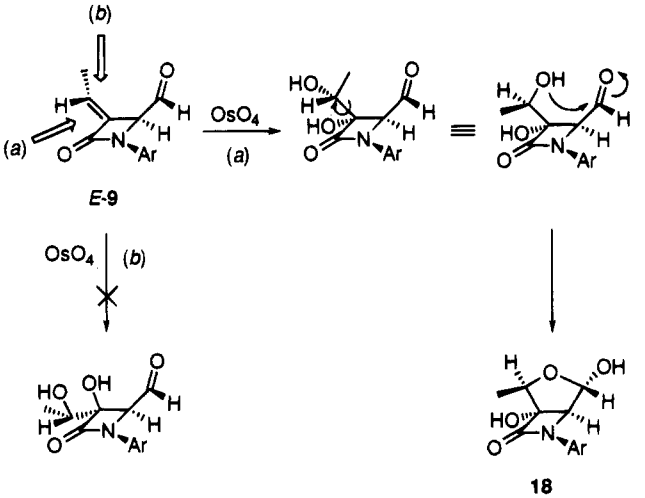
Next, the above catalytic osmylation–oxidative cleavage sequence was tested on 4-formyl-3-(*E*)-ethylidene-2-azetidinone **9**. In view of the results from compound **6b**, especially regarding the formation of bicyclic β-lactams **14** and **15**, a similar β-lactam–furan hybrid would be expected through a stereoselective route. Thus, compound (*E*)-**9** gave the corresponding bicyclic compound **18** as only one stereoisomer in 65% yield. Exclusive formation of isomer **18** can be accounted for by OsO_4 attack on the less hindered side (a in Scheme 7) followed by cyclization of the resulting diol derivative to the final bicyclic compound. Attack on the other side (b in Scheme 7) would yield a diol with less likelihood to cyclize. The reaction of **9** stopped at the stage of hemiacetal **18** which remained unaltered in the presence of sodium metaperiodate at longer reaction times.

Finally, we considered the synthesis of 2-functionalized-3-ethylideneazetidines **19** from 3-ethylidene-4-formyl-2-azetidinones **9** and derivatives **11** and **12**. Azetidines **19** are closely related to the polyoximic acid [(2*S*,*Z*)-3-ethylideneazetidine-2-carboxylic acid][27] constituent of tripeptidyl polyoxins, nucleoside antibiotics with fungicidal properties (Figure 2).[28] The transformation of the

Scheme 6



Scheme 7



(26) Galluci, J. C.; Ha, D.-C.; Hart, D. J. *Tetrahedron* **1989**, *45*, 1283.

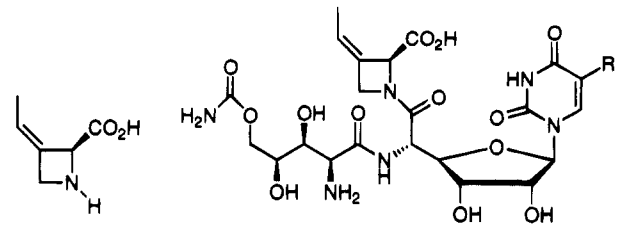
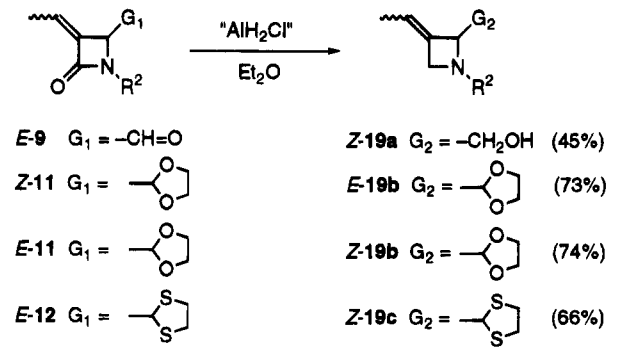


Figure 2.

Scheme 8



β-lactam nucleus into the azetidine ring was carried out through reduction of the lactamic carbonyl with chlorodihydroalane (AlH_2Cl) following the procedure reported by Ojima for related β-lactams.[29] Although this method has been applied successfully for a variety of both monocyclic and bicyclic β-lactams, its use has not been reported for this particular type of β-lactam having a conjugated olefinic double bond on α-position. Thus, reduction of isomerically pure 3-ethylidene β-lactams **9**, **11**, and **12** with excess AlH_2Cl generated *in situ* from equimolar amounts of $LiAlH_4$ and $AlCl_3$ led to the corresponding 3-ethylideneazetidines **19a–c** in moderate to good yields (Scheme 8). As expected, in compound (*E*)-**9** reduction of the lactamic carbonyl was concurrent with that of the formyl group on C_4, the 2-(hydroxymethyl)azetidine **19a** being obtained. Otherwise, starting from **9** as a mixture of *E*/*Z* isomers, a mixture of azetidines in the same relative proportion was produced. These data show that reduction occurs without change in both the integrity and the stereochemistry of the ethylenic double bond.

The relative *E*/*Z* stereochemistry was deduced by comparison of the chemical shifts for the olefinic proton and the methyl group in the spectra of both the *E* and *Z* isomers for compounds **19a** and **19b** with the corresponding chemical shifts for (*E*)- and (*Z*)-polyoximic acid.[27] Thus, in each case the lower field olefinic protons (C_3=C*H*) and higher field methyl protons could be assigned to the (*E*)-**19** isomers, as in the related polyoximic acids. Since the *p*-methoxyphenyl group can be removed under mild conditions by the Krönenthal method,[19] this simple β-lactam approach may be considered as a simple, direct entry into some interesting polyoximic acid derivatives.

In conclusion, the ester enolate–imine condensation using β-(dialkylamino) esters as starting materials seems to be of general utility for the preparation of a variety of both α-methylene and α-ethylidene β-lactams since a variety of structurally different imines could be used. The β-lactams prepared may be easily transformed to other products some retaining the β-lactam structure (as shown for the preparation of either 3-oxo-2-azetidinones and β-lactam–furan hybrids) as well as selected fuctionalized 3-ethylideneazetidines.

Experimental Section

General experimental conditions have been previously reported.[20c,22b] Silylimine **1d** was prepared immediately before use according to literature procedure.[19b] β-Amino esters **2b–d** were prepared by conjugated addition of the corresponding lithium amides to methyl crotonate or methyl cinnamate following standard methodology. Compounds **8** and **9** were prepared by acid hydrolysis of **6a** and **7a**, respectively. Compounds **10–12** were prepared by standard methodology. See supplementary material for full experimental procedure and spectroscopic data.

General Procedures for the Synthesis of 3-[(Dimethylamino)methyl]azetidin-2-ones (3) and 3-[1′-(Dialkylamino)alkyl]azetidin-2-ones (4). Method A. The corresponding 3-(dialkylamino) ester (2.2 mmol) dissolved in anhydrous THF (2 mL) was added dropwise to a stirred solution of LDA (2.2 mmol) in THF (10 mL) cooled to −78 °C under argon. After 15 min at this temperature, a solution of the corresponding imine (1 mmol) in THF (10 mL) was added. The mixture was allowed to warm to room temperature followed by stirring for the indicated period of time. The reaction was quenched with H_2O and diluted with Et_2O (two or three times its original volume). The organic layer was successively washed with H_2O (×2), brine, and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude products were analyzed by ^{1}H-NMR to determine the ratio of isomers. Purification was performed by flash chromatography (hexanes/EtOAc mixtures, except otherwise stated) and/or crystallization (except **3a** which was used as such in the next stage without further purification).

Method B. All operations were identical with method A except the appropriate α,β-unsaturated ester was used instead of a 3-(dialkylamino) ester.

1-(*p*-Anisyl)-4-(2′-furyl)-3-[(dimethylamino)methyl]azetidin-2-one (3c). Method A. 2.5 h. Obtained as a 50/50 mixture of *cis*:*trans* isomers. Flash chromatography of crude product yielded a pure mixture of both isomers. Yield: 77%. When the resulting oil was treated with EtOAc/hexanes, the pure *trans* isomer precipitated (30%). A new chromatography of the mother liquors gave the pure *cis* isomer (35%).

***Cis*-Isomer.** Colorless oil. ^{1}H-NMR: δ 2.13 (s, 6H), 2.45 (dd, 1H, J_1 = 7.8 Hz, J_2 = 13.2 Hz), 2.65 (dd, 1H, J_1 = 5.4 Hz, J_2 = 13.2 Hz), 3.77 (m, 4H), 5.20 (d, 1H, J = 5.7 Hz), 6.33–7.43 (m, 7H). ^{13}C-NMR: δ 165.5, 155.7, 148.8, 142.9, 130.9, 118.0, 114.1, 110.5, 110.1, 55.3, 54.4, 53.9, 52.4, 45.4.

***Trans*-Isomer.** White crystalline solid. Mp: 114–116 °C (EtOAc/hexanes). ^{1}H-NMR: δ 2.25 (s, 6H), 2.76 (dd, 1H, J_1 = 9.3 Hz, J_2 = 14.2 Hz), 2.87 (dd, 1H, J_1 = 4.8 Hz, J_2 = 14.2 Hz), 3.62 (m, 1H), 3.73 (s, 3H), 4.84 (d, 1H, J = 2.7 Hz), 6.33–7.39 (m, 7H). ^{13}C-NMR: δ 165.4, 155.9, 150.1, 142.9, 131.0, 117.9, 114.0, 110.4, 109.1, 57.4, 55.8, 55.2, 53.7, 45.2. IR (KBr): ν 1760. MS: *m*/*e* 300 ($M^{+\cdot}$), 59 (parent). Anal. Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.85; H, 6.76; N, 9.41.

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(30) The author has deposited atomic coordinates for these structures with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

1-(*p*-Anisyl)-4-[[*N*-(*p*-Anisyl)imino]methyl]-3-[1′-(diisopropylamino)ethyl]azetidin-2-one (4a). Method A. 0.5 h. Obtained as a 30/70 mixture of γ/δ isomers (*trans*). Yield: 100%. **Method B.** 0.5 h. Obtained as a 70/30 mixture of γ/δ isomers (*trans*). Yield: 95%. The excess of β-amino ester was eliminated by heating the crude product at 120 °C/0.1 mmHg for 1 h. When the resulting oil was treated with EtOH, the pure δ isomer precipitated. Chromatography of the mother liquors (hexanes/Et_2O 3:2) gave the pure γ isomer.

γ-Isomer. Pale yellow oil. ^{1}H-NMR: δ 1.05 (d, 6H, J = 6.7 Hz), 1.06 (d, 6H, J = 6.7 Hz), 1.31 (d, 3H, J = 6.1 Hz), 3.17 (m, 2H, J = 6.7 Hz), 3.27 (dd, 1H, J_1 = 2.1 Hz, J_2 = 4.6 Hz), 3.45 (dq, 1H, J_1 = 4.6 Hz, J_2 = 6.7 Hz), 3.78 (s, 3H), 3.79 (s, 3H), 4.76 (dd, 1H, J_1 = 2.1 Hz, J_2 = 7.2 Hz), 6.80−7.21 (m, 8H), 7.90 (d, 1H, J = 7.2 Hz). ^{13}C-NMR: δ 165.9, 160.7, 158.6, 155.9, 143.3, 131.8, 121.9, 117.6, 114.3, 114.2, 61.6, 57.5, 55.4, 55.3, 47.6, 45.2, 23.4, 21.9, 17.48. IR (KBr): ν 1755, 1660.

δ-Isomer. White solid. Mp: 139−141 °C (EtOH). ^{1}H-NMR: δ 1.05 (d, 6H, J = 6.7 Hz), 1.06 (d, 6H, J = 6.7 Hz), 1.33 (d, 3H, J = 6.1 Hz), 3.13 (m, 2H, J = 6.7 Hz), 3.28 (dd, 1H, J_1 = 1.7 Hz, J_2 = 10.8 Hz), 3.35 (dq, 1H, J_1 = 6.1 Hz, J_2 = 10.8 Hz), 3.77 (s, 3H), 3.80 (s, 3H), 4.50 (dd, 1H, J_1 = 1.7 Hz, J_2 = 7.3 Hz), 6.81−7.44 (m, 8H), 7.81 (d, 1H, J = 7.1 Hz). ^{13}C-NMR: δ 166.3, 160.3, 158.5, 155.9, 143.6, 131.9, 121.8, 117.6, 114.2, 60.1, 59.5, 55.4, 55.3, 49.5, 44.4, 23.8, 21.9, 19.3. IR (KBr): ν 1740, 1645. MS: m/e 437 ($M^{\bullet+}$), 128 (parent). Anal. Calcd for $C_{26}H_{35}N_3O_3$: C, 71.37; H, 8.06; N, 9.60. Found: C, 71.29; H, 8.09; N, 9.58.

1-(*p*-Anisyl)-3-[1′-(diisopropylamino)ethyl]-4-(2′-furyl)-azetidin-2-one (4b). Method A. 15 h. Obtained as a mixture of four diastereoisomers in the ratio α/β/γ/δ, 83:12:2:3 (*cis*/*trans* 95:5). When the crude product was treated with cold EtOAc/hexanes, the pure α isomer precipitated (32%). Flash chromatography of the mother liquors (hexanes/Et_2O 4:1) gave, in sequence, a mixture of the two *trans* isomers, and a mixture of the two *cis* isomers. Total yield: 65%. **Method B.** 1.5 h. Obtained as a mixture of four diastereoisomers in the ratio α/β/γ/δ 19:25:40:16 (*cis*/*trans* 44:56). When the crude product was treated with cold EtOAc/hexanes, an analytical amount of α isomer precipitated. Flash chromatography of the mother liquors (hexanes/Et_2O 4:1) gave, in sequence, a mixture of the two *trans* isomers, and a mixture of the two *cis* isomers. Total yield: 60%.

α-Isomer. White crystalline solid. Mp: 150−152 °C (EtOAc/hexanes). ^{1}H-NMR: δ 0.81 (d, 6H, J = 6.6 Hz), 0.95 (d, 6H, J = 6.6 Hz), 1.22 (d, 3H, J = 6.6 Hz), 3.07−3.17 (m, 2H), 3.19 (dq, 1H, J_1 = 6.6 Hz, J_2 = 7.5 Hz), 3.73 (s, 3H), 3.74 (dd, 1H, J_1 = 5.7 Hz, J_2 = 7.5 Hz), 5.10 (d, 1H, J = 5.7 Hz), 6.27−7.41 (m, 7H). ^{13}C-NMR: δ 166.4, 155.7, 149.5, 142.6, 131.2, 117.9, 114.1, 110.1, 109.9, 60.8, 55.3, 52.5, 47.3, 45.0, 23.4, 22.5, 18.6. IR (KBr): ν 1745. MS: m/e 370 ($M^{\bullet+}$), 128 (parent). Anal. Calcd for $C_{22}H_{30}N_2O_3$: C, 71.32; H, 8.16; N, 7.56. Found: C, 71.13; H, 8.04; N, 7.71.

β-Isomer. ^{1}H-NMR (from the mixture of *cis* isomers): δ 0.68 (d, 3H, J = 6.6 Hz), 0.96 (d, 6H, J = 6.6 Hz), 1.12 (d, 6H, J = 6.6 Hz), 3.01−3.23 (m, 2H), 3.25 (dq, 1H, J_1 = 6.6 Hz, J_2 = 11.4 Hz), 3.56 (dd, 1H, J_1 = 5.7 Hz, J_2 = 11.4 Hz), 3.72 (s, 3H), 5.05 (d, 1H, J = 5.7 Hz), 6.35−7.45 (m, 7H).

γ-Isomer. ^{1}H-NMR (from the mixture of *trans* isomers): δ 0.91 (d, 6H, J = 6.6 Hz), 1.00 (d, 6H, J = 6.6 Hz), 1.31 (d, 3H, J = 6.6 Hz), 3.10−3.40 (m, 4H), 3.74 (s, 3H), 5.08 (d, 1H, J = 2.4 Hz), 6.3−7.4 (m, 7H).

δ-Isomer. ^{1}H-NMR (from the mixture of *trans* isomers): δ 0.88 (d, 6H, J = 6.6 Hz), 1.02 (d, 6H, J = 6.6 Hz), 1.30 (d, 3H, J = 6.3 Hz), 2.98−3.45 (m, 4H), 3.74 (s, 3H), 4.73 (d, 1H, J = 2.4 Hz), 6.3−7.4 (m, 7H).

3-[1′-(Diisopropylamino)ethyl]-4-(2′-furyl)azetidin-2-one (4c). Method A. 3 h. Obtained as a 33/67 mixture of α/β isomers (*cis*). Yield: 61%. **Method B.** 1 h. Obtained as a 65/35 mixture of γ/δ isomers (*trans*). Yield: 74%.

α-Isomer. ^{1}H-NMR (from the mixture of *cis* isomers): δ 0.79 (d, 6H, J = 6.9 Hz), 0.92 (d, 6H, J = 6.6 Hz), 1.11 (d, 3H, J = 6.9 Hz), 3.02−3.23 (m, 3H), 3.48 (ddd, 1H, J_1 = 0.6 Hz, J_2 = 5.1 Hz, J_3 = 6.6 Hz), 4.76 (d, 1H, J = 5.1 Hz), 5.96 (br s, 1H), 6.32−6.39 (m, 2H), 7.40 (m, 1H).

β-Isomer. ^{1}H-NMR (from the mixture of *cis* isomers): δ 0.63 (d, 3H, J = 6.6 Hz), 0.93 (d, 6H, J = 6.6 Hz), 1.08 (d, 6H, J = 6.6 Hz), 3.02−3.23 (m, 3H), 3.44 (ddd, 1H, J_1 = 2.1 Hz, J_2 = 5.4 Hz, J_3 = 11.1 Hz), 4.75 (d, 1H, J = 5.1 Hz), 5.90 (br s, 1H), 6.35−6.40 (m, 2H), 7.43 (m, 1H). IR (KBr) (mixture of *cis* isomers): ν 3250, 1750.

γ-Isomer. Isolated by crystallization of pure mixture of *trans*-isomers. White solid. Mp: 86−88 °C (EtAcO/hexanes). ^{1}H-NMR: δ 0.98 (d, 6H, J = 7.2 Hz), 1.01 (d, 6H, J = 6.6 Hz), 1.26 (d, 3H, J = 6.6 Hz), 3.19 (m, 2H), 3.10−3.32 (m, 2H), 4.72 (d, 1H, J = 2.1 Hz), 6.18 (s, 1H), 6.25 (m, 1H), 6.32 (m, 1H), 7.36 (m, 1H). ^{13}C-NMR: δ 170.8, 152.8, 142.4, 110.3, 107.3, 64.8, 47.3, 47.2, 45.1, 23.5, 21.7, 17.4. IR (KBr): ν 3220, 1755. MS: m/e 264 ($M^{\bullet+}$), 28 (parent). Anal. Calcd for $C_{15}H_{24}N_2O_2$: C, 68.15; H, 9.15; N, 10.59. Found: C, 67.96; H, 8.96; N, 10.76.

δ-Isomer. ^{1}H-NMR (from the mixture of *trans* isomers): δ 0.87 (d, 6H, J = 6.6 Hz), 1.02 (d, 6H, J = 6.6 Hz), 1.24 (d, 3H, J = 6.6 Hz), 3.01 (m, 2H), 2.95−3.38 (m, 2H), 4.41 (d, 1H, J = 2.4 Hz), 6.25−6.37 (m, 3H), 7.34 (m, 1H).

General Procedures for the Synthesis of 3-Alkylideneazetidin-2-ones (6, 7). Method A. A stirred solution of 3-[(dialkylamino)alkyl]azetidin-2-one (1 mmol) in toluene (5 mL) with silica gel (200% w/w) was heated under reflux for the indicated period of time. After cooling at room temperature, the mixture was diluted with Et_2O (20 mL) and the silica gel was filtered off. The organic layer was successively washed with saturated NH_4Cl, brine, and dried ($MgSO_4$). After filtration and evaporation of the solvent under reduced pressure, the crude products were purified by flash chromatography (hexanes/EtOAc 4:1), except **6e** which was used in the next step without purification.

Method B. Methyl iodide (20 mmol) was added neat to a solution of the corresponding 3-[(dimethylamino)methyl]azetidin-2-one (1 mmol) in absolute MeOH (20 mL). After stirring at room temperature for 12 h, the solvent was evaporated and the residue suspended in acetone (20 mL). DBU (1.1 mmol) was then added and the mixture stirred for the indicated period of time. The acetone was evaporated, EtOAc added, and the insoluble salt filtered off. Finally, the EtOAc layer was concentrated and the crude product purified by flash chromatography (hexanes/EtOAc 4:1), except **6a** which was used in the next step without purification.

Method C. All operations were identical with method B except the reaction with DBU was carried out in refluxing benzene (20 mL) under argon.

1-(*p*-Anisyl)-3-methylene-4-(*trans*-styryl)azetidin-2-one (6b). Method A. 48 h; yield: 37%. **Method B.** 6 h; yield: 80%. White crystalline solid. Mp: 102−104°C (EtOAc/hexanes). ^{1}H-NMR: δ 3.76 (s, 3H), 5.03 (d, 1H, J = 9.0 Hz), 5.27 (t, 1H, J = 1.5 Hz), 5.83 (t, 1H, J = 1.5 Hz), 6.22 (dd, 1H, J_1 = 9.0 Hz, J_2 = 16.0 Hz), 6.83−7.39 (m, 10H). ^{13}C-NMR: δ 159.8, 156.1, 148.3, 135.2, 131.6, 128.6, 126.6, 118.1, 114.3, 110.6, 110.5, 62.9, 55.3. IR (KBr): ν 1750. MS: m/e 291 ($M^{\bullet+}$, parent). Anal. Calcd for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.39; H, 5.77; N, 4.69.

1-(*p*-Anisyl)-3-ethylidene-4-(2′-furyl)azetidin-2-one (7b). Method A. 15 h. Obtained as a 50/50 mixture of *E*:*Z* isomers (from mixtures of either *cis* or *trans* **4b**, in different ratios, as starting material). Flash chromatography of crude product gave, in sequence, the pure *Z* isomer (49%) and the pure *E* isomer (46%).

***E*-Isomer.** White solid. Mp: 167−169 °C (EtOAc/hexanes). ^{1}H-NMR: δ 1.68 (d, 3H, J = 6.9 Hz), 3.75 (s, 3H), 5.47 (s, 1H), 6.33 (dq, 1H, J_1 = 0.9 Hz, J_2 = 6.9 Hz), 6.37−6.44 (m, 2H), 6.82 (m, 2H), 7.34−7.41 (m, 3H). ^{13}C-NMR: δ 160.5, 155.8, 149.8, 143.0, 139.5, 131.3, 123.6, 117.8, 114.2, 110.6, 109.3, 55.5, 55.3, 13.5. IR (KBr): ν 1730, 1710. Anal. Calcd for $C_{16}H_{15}NO_3$: C, 71.35; H, 5.61; N, 5.20. Found: C, 71.28; H, 5.60; N, 5.39.

***Z*-Isomer.** White crystalline solid. Mp: 142−144 °C (EtOAc/hexanes). ^{1}H-NMR: δ 2.11 (d, 3H, J = 6.9 Hz), 3.74 (s, 3H), 5.34 (s, 1H), 5.75 (dq, 1H, J_1 = 0.9 Hz, J_2 = 6.9 Hz), 6.33−7.39 (m, 7H). ^{13}C-NMR: δ 161.0, 155.9, 150.4, 143.1, 138.7, 131.4, 126.9, 117.7, 114.2, 110.5, 109.2, 55.8, 55.3, 14.6. IR (KBr): ν 1740, 1725. MS: m/e 269 ($M^{\bullet+}$, parent). Anal.

Calcd for $C_{16}H_{15}NO_3$: C, 71.35; H, 5.61; N, 5.20. Found: C, 71.44; H, 5.69; N, 5.31.

General Procedure for Synthesis of 3-Oxoazetidin-2-ones (13) and β-Lactam-Furan Hybrids (14, 15, 18). A solution of the corresponding α-alkylidene-β-lactam (0.5 mmol) in acetone/water, 8:1 (36 mL), trimethylamine *N*-oxide (1 mmol, except 2 mmol for **13c**), and OsO_4 (0.025 mmol, except 0.05 mmol for **13c**) was stirred at room temperature until complete disappearance of starting material (TLC). $NaHSO_3$ (40% aqueous solution) was then added, and after stirring for 30 min, the reaction mixture was extracted with EtAcO (×3). The organic layer was washed with brine and dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude product was used in the next step without further purification (except for **18** which was directly purified).

The viscous oil obtained before was dissolved in MeOH/water, 4:1 (10 mL), and $NaIO_4$ (1 mmol) was added. The mixture was stirred at room temperature until complete disappearance of starting material (TLC). MeOH was evaporated, EtAcO was added, and it was filtered through a Celite pad. The organic layer was decanted, washed with brine, and dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude products were purified by flash chromatography (EtAcO/hexanes 4:1).

1-(*p*-Anisyl)-4-furylazetidine-2,3-dione (13a). Osmylation: 18 h. Oxidative cleavage: 48 h. White crystalline solid. Yield: 80%. Mp: 90−92 °C (EtAcO/hexanes). ^{1}H-NMR: δ 3.70 (s, 3H), 5.53 (s, 1H), 6.33 (m, 1H), 6.48 (d, 2H, J = 9.0 Hz), 7.33 (m, 1H), 7.41 (d, 2H, J = 9.0 Hz). ^{13}C-NMR: δ 189.4, 159.7, 157.9, 145.1, 144.3, 129.8, 119.2, 114.5, 111.7, 110.9, 68.0, 55.4. IR (KBr): ν 1825, 1810, 1750. MS: *m/e* 257 ($M^{\bullet+}$), 202 (parent). Anal. Calcd for $C_{14}H_{11}NO_4$: C, 65.42; H, 4.28; N, 5.45. Found: C, 65.47; H, 4.31; N, 5.40.

(1*R,2*R**,4*S**,5*S**)-6-(*p*-Anisyl)-1,4-dihydroxy-2-methyl-3-oxo-6-azabicyclo[3.2.0]heptan-7-one (18).** Osmylation: 26 h. White crystalline solid. Yield: 65%. Mp: 116−118 °C (CH_2Cl_2). ^{1}H-NMR (DMSO-d_6): δ 1.21 (d, 3H, J = 6.3 Hz), 3.70 (s, 3H), 4.02 (q, 1H, J = 6.3 Hz), 4.06 (s, 1H), 5.18 (d, 1H, J = 3.6 Hz), 6.74 (d, 1H, J = 3.6 Hz), 6.87 (s, 1H), 6.93 (d, 2H, J = 9.0 Hz), 7.29 (d, 2H, J = 9.0 Hz). ^{13}C-NMR (DMSO-d_6): δ 164.8, 155.8, 130.3, 117.8, 114.3, 93.6, 92.1, 73.3, 68.1, 55.3, 14.6. IR (KBr): ν 3330, 1730. MS: *m/e* 265 ($M^{\bullet+}$, parent). Anal. Calcd for $C_{13}H_{15}NO_5$: C, 58.85; H, 5.66; N, 5.28. Found: C, 58.91; H, 5.68; N, 5.18.

General Procedure for the Synthesis of 3-Ethylideneazetidines 19. To a suspension of LAH (3 mmol) in anhydrous ether (5 mL) was added, *via* cannula, a solution of $AlCl_3$ (3 mmol) in ether (5 mL). The mixture was heated under reflux for 30 min. The AlH_2Cl suspension prepared was added, *via* cannula, to a suspension of the corresponding β-lactam (1 mmol) in ether (10 mL). The mixture was heated under reflux, with vigorous stirring, for the indicated period of time. After cooling, water (50 mL) was added, and it was extracted with ether. The organic layer was washed with brine and dried ($MgSO_4$). After filtration and evaporation of the solvent, the crude product was purified by flash chromatography.

(*Z*)-1-(*p*-Anisyl)-2-(1,3-dioxolan-2-yl)-3-ethylideneazetidine ((*Z*)-19b). Reaction time: 35 min. Flash chromatography (hexanes/EtAcO 5:1). Colorless oil. Yield: 74%. ^{1}H-NMR: δ 1.67 (dd, 3H, J_1 = 1.8 Hz, J_2 = 7.2 Hz), 3.75 (s, 3H), 3.89−4.16 (m, 5H), 4.52−4.58 (m, 1H), 4.65 (m, 1H), 5.31 (d, 1H, J = 3.0 Hz), 5.38 (m, 1H), 6.67 (d, 2H, J = 9.0 Hz), 6.82 (d, 2H, J = 9.0 Hz). ^{13}C-NMR: δ 152.4, 145.6, 130.0, 117.5, 114.4, 113.8, 105.0, 73.5, 65.3, 65.1, 59.2, 55.7, 13.5. IR ($CDCl_3$): ν 1620, 1230.

(*E*)-1-(*p*-Anisyl)-2-(1,3-dioxolan-2-yl)-3-ethylideneazetidine ((*E*)-19b). Reaction time: 25 min. Flash chromatography (hexanes/EtAcO 4:1). Colorless oil. Yield: 73%. ^{1}H-NMR: δ 1.51 (dd, 3H, J_1 = 1.5 Hz, J_2 = 6.9 Hz), 3.68 (s, 3H), 3.81−4.10 (m, 5H), 4.32 (m, 1H), 4.49−4.53 (m, 1H), 5.01 (d, 1H, J = 4.8 Hz), 5.44 (m, 1H), 6.64 (d, 2H, J = 9.0 Hz), 6.74 (d, 2H, J = 9.0 Hz). ^{13}C-NMR: δ 152.4, 146.0, 130.0, 117.4, 114.3, 113.8, 105.0, 73.3, 65.3, 65.1, 59.2, 55.6, 13.5. IR ($CDCl_3$): ν 1620, 1230.

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Supplementary Material Available: Additional procedures; compound characterization data; X-ray data for **4b**-α and **4c**-γ; ^{1}H-NMR and ^{13}C-NMR spectra of compounds *cis*-**3c**, **4a**-γ, (*Z*)-**19b**, and (*E*)-**19b**; and ^{1}H-NMR spectra of mixtures of compounds **4b**-α and **4b**-β, **4b**-γ and **4b**-δ, **4c**-α and **4c**-β, **4c**-γ and **4c**-δ (28 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.