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SYNTHESIS OF NOVEL FUNCTIONALIZED MONOCYCLIC 2-AZETIDINONES FROM *N,N'*-DIARYL-α-DIIMINES AND LITHIUM ESTER ENOLATES

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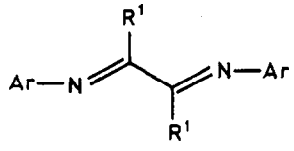
Abstract. Reaction of the glyoxal diimine **1a** with lithium ester enolates **2a-b** gave 4-imino-2-azetidinones **3a-c** in excellent yields. The biacetyl diimine **1b** only reacted with the enolate **2a** to yield the 4-imino-2-azetidinone **3d** and the 5-methylene-2-pyrrolinone **8** depending on the experimental conditions. In addition, various reactions of compounds **3** and of some derivatives, including two new examples of intramolecular β-lactam ring-opening, are described and discussed.

INTRODUCTION

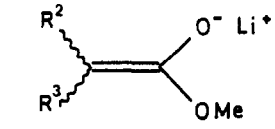
Functionalized monocyclic 2-azetidinones are an important class of compounds not only for their importance in β-lactam antibiotic synthesis,[1] but also for their conversion into various types of heterocycles.[2] Among numerous methods for the construction of the functionalized azetidinone ring, the condensation reactions of imines with ester enolates have proved to be a useful procedure for the synthesis of appropriately substituted β-lactams.[3] Most of these studies have dealt with the synthesis of thienamycin intermediates by reacting the dianion of (S)-ethyl-3-hydroxybutanoate with *N*-(p-anisyl)- or *N*-trialkylsilylimines derived from cinnamaldehyde (1-aza-1,3-butadienes), followed by oxidative cleavage of the 4-styryl moiety and further elaboration of the resulting 4-formyl-β-lactam. In addition, M. Komatsu *et al.* have described the synthesis of pyridone derivatives by the reaction of some *N*-alkyl-1-aza-1,3-butadienes with lithium enolates of substituted acetates,[4] and also the synthesis of *N*-styryl-2-azetidinones, and *N*-alkylidenamino-2-azetidinones and 1,1'-bi-(2-azetidinone)s, respectively, by the reaction of 2-aza- and 2,3-diaza-1,3-butadienes (azines) with methyl lithioisobutyrate.[5] However, to the best of our knowledge, no data have been reported on the reactivity of 1,4-diaza-1,3-butadienes (α-diimines) toward lithium ester enolates.

Within the framework of our study on the reaction of iminoketones and related bifunctional electrophiles with ester enolates,[6] we have investigated the reaction of *N,N'*-diaryl-α-diimines **1** with α-lithiated esters **2** which has allowed the obtainment of some novel substituted 4-imino-2-azetidinones **3**. Among different compounds **3** prepared, compounds **3a-c** are of particular interest due to their potential 4-formyl group, which can be easily

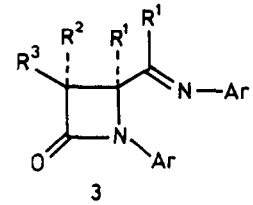
obtained by simple hydrolysis of the corresponding 4-imino group. Thus, the synthesis of some substituted 4-formyl-β-lactams **4a–c** is a particularly significant feature of this work. Substituted 3-amino-4-formylazetidinone derivatives have proven to be versatile synthons for the synthesis of both monobactams and isocepham antibiotics.[7] In addition, some manipulations of the anisyl and 4-formyl groups in **4a** are described.



1	R^1	Ar
a	H	p-MeOC$_6$H$_4$
b	Me	Ph
c	Ph	Ph



2	R^2	R^3
a	Me	Me
b	Me	LiNBz
c	H	H
d	Me	H



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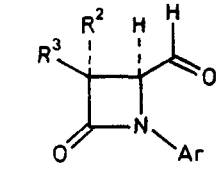

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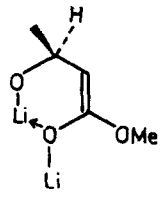
	R^1	R^2	R^3	Ar
a	H	Me	Me	p-MeOC$_6$H$_4$
b	H	Me	NHBz	p-MeOC$_6$H$_4$
c	H	NHBz	Me	p-MeOC$_6$H$_4$
d	Me	Me	Me	Ph

RESULTS AND DISCUSSION

We began by examining the reaction between the glyoxal dianil **1a** and the lithium enolate of methyl isobutyrate **2a**. Treatment of a tetrahydrofuran solution of enolate **2a** (two equivalents)[8] with the α-diimine **1a** followed by an aqueous workup (see experimental) gave β-lactam **3a** (90% in pure product). Even in the presence of a larger excess of enolate **2a**, none of the expected bis-β-lactam derivative arising from double condensation to the two imino groups could be detected. On the other hand, enediolate **2b** reacted with **1a** in a similar fashion to give a 55:45 mixture of β-lactams **3b** and **3c**, respectively, in a nearly quantitative yield in crude product (by ^{1}H-NMR).[9] Finally, β-lactams **3b** and **3c** were obtained

as pure products after chromatography over silica gel and crystallisation, in 44% and 36% yields, respectively. The relative stereochemistry at C-3 and C-4 stereocentres was based on NOE experiments. Thus, irradiation of the C-3 methyl group in **3b** and **3c** gave 14% and 4% enhancement of the C_4-H signals, respectively.

However, all attempts to generate a β-lactam from α-diimine **1a** and either methyl α-lithioacetate (**2c**) or methyl α-lithiopropionate (**2d**) resulted in recovered α-diimine plus other incompletely characterized products. Since the addition of ester enolates to α-diimines occurs only after the reaction temperature is raised above -78°C, these failures may be due to a lack of stability of the enolate under the reaction conditions. In order to test the possibility to prepare β-lactam **6** with an hydroxyethyl side chain on C-3 the reaction of the dianion **5**, derived from methyl β-hydroxybutyrate, with the α-diimine **1a** was also investigated. Unfortunately, **1a** did not react with **5** to form 4-imino-β-lactam **6** but resulted in the partial recovery of the starting material together with some unidentified products. This functionalized β-lactam **6** would have been a suitable precursor for the preparation of 4-formyl-β-lactam **7**, a key intermediate for the synthesis of thienamycin and related carbapenems[10] as well as of some deoxyaminohexoses, such as acosamine and daunosamine.[11]



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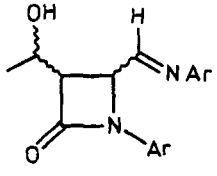

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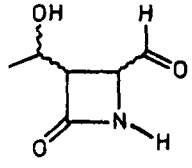

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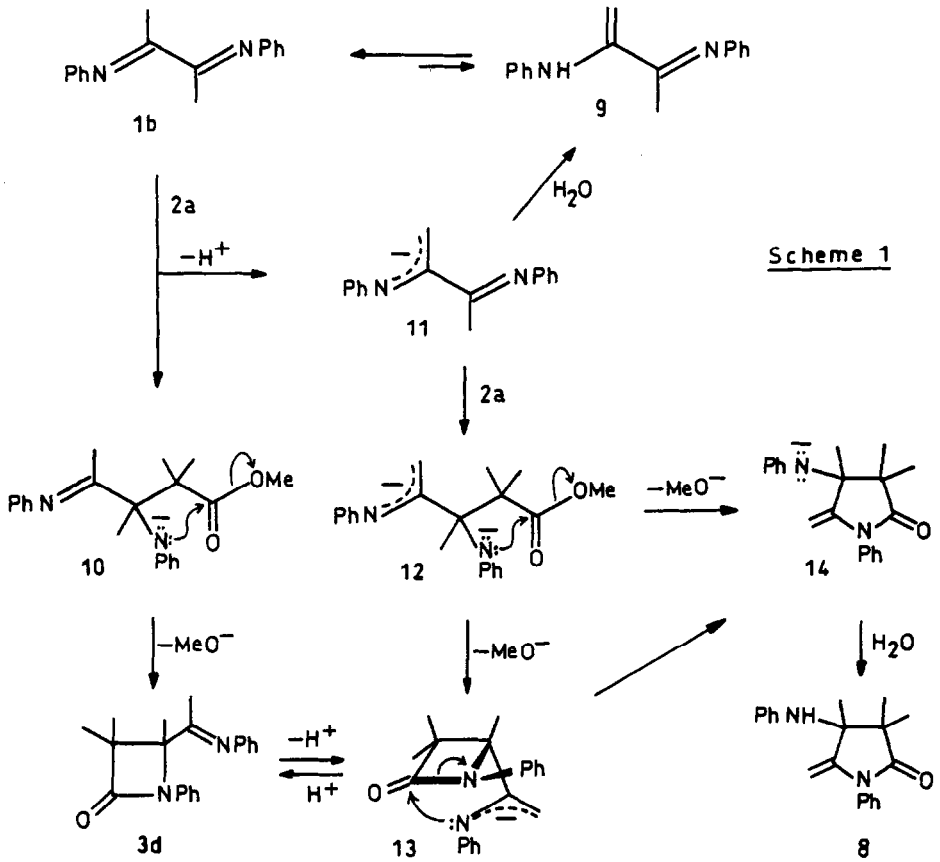
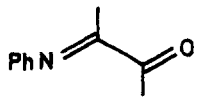
Reactions of α-diimines **1b** and **1c** with enolates **2a-d** were also investigated. Of the various experiments performed, only **2a** reacted with **1b** to give the 4-imino-β-lactam **3d** and/or the γ-methylene-γ-lactam **8** according to the reaction conditions. The best results were obtained at room temperature[12] in the presence of four equivalents of the enolate after 45 min and 5 h, respectively, for compounds **3d** and **8**. In some cases, when the reaction was performed with excess of enolate and at short reaction times, 2-amino-1-azadiene **9** was detected in the reaction mixture (by ^{1}H-NMR) along with compounds **3d**, **8** and unreacted **1b**.

The overall reaction of **1b** with excess of **2a** may be rationalized as shown in Scheme 1. Thus, initial addition of the enolate to an imino group of **1b** gives the amide **10** which immediately cyclizes to imino-β-lactam **3d**. Formation of γ-methylene-γ-lactam **8** from β-lactam **3d** can be accounted for by deprotonation and subsequent rearrangement of the resulting anion **13**. Alternatively, deprotonation of **1b** by the enolate (acting as base) could give the anion

11 which, besides yielding 9 (α-enamine-imine tautomer of the starting α-diimine 1b), can also form the dianion 12, by addition of a molecule of enolate to the remaining imino group. This dianion 12 could give anion 13 by β-lactam cyclization and/or anion 14 by γ-lactam cyclization, which would finally yield compounds 3d and 8, respectively, after quenching. In a separate experiment, it was observed that the reaction of 3d with two equivalents of LDA in THF at -15°C leads to compound 8 in quantitative yield. This clearly indicates that β-lactam anion 13 is an intermediate in its formation. Compound 8 is closely related with



compound 16 which can be obtained by the reaction of α-iminoketone 15 with an excess of enolate 2a at room temperature.[6a] Both compounds 8 and 16 are structurally related to some enamides used as intermediates in corrin synthesis.[13] Furthermore, treatment of α-diimine 1b with LDA (1.2 equivalents) gives 9 quantitatively after quenching. This product, which can



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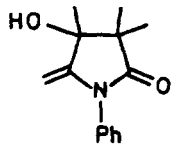

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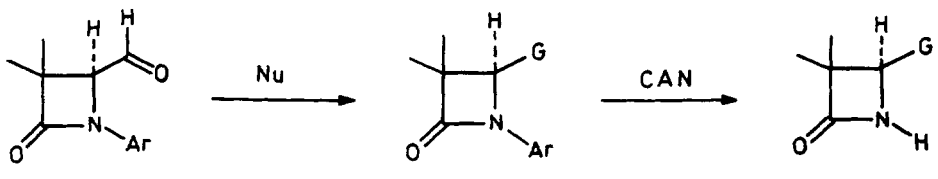
be stored for days under nitrogen at -20°C, isomerizes slowly and completely to the more stable α-diimine tautomer at room temperature.

We also examined the use of some of the imino-β-lactams 3 in the synthesis of other substituted β-lactams. Thus, hydrolysis of compound **3a-c** with diluted hydrochloric acid in chloroform gave the 4-formyl-β-lactams **4a-c** in nearly quantitative yield.[14] On the other hand, reaction of 4-formyl-β-lactam **4a** with different nucleophiles has allowed the obtainment of β-lactams **17-21**, in excellent yields (Scheme 2). Furthermore, while attempting to dehydrate β-lactam **21** with p-toluenesulfonic acid in refluxing xylene, in order to obtain



4a

	G	
17		24
18	$-C\equiv N$	25
19	$-CH=CH_2$	26
20	$-CH=CH-CO_2Me$	27
21	$-CH_2OH$	

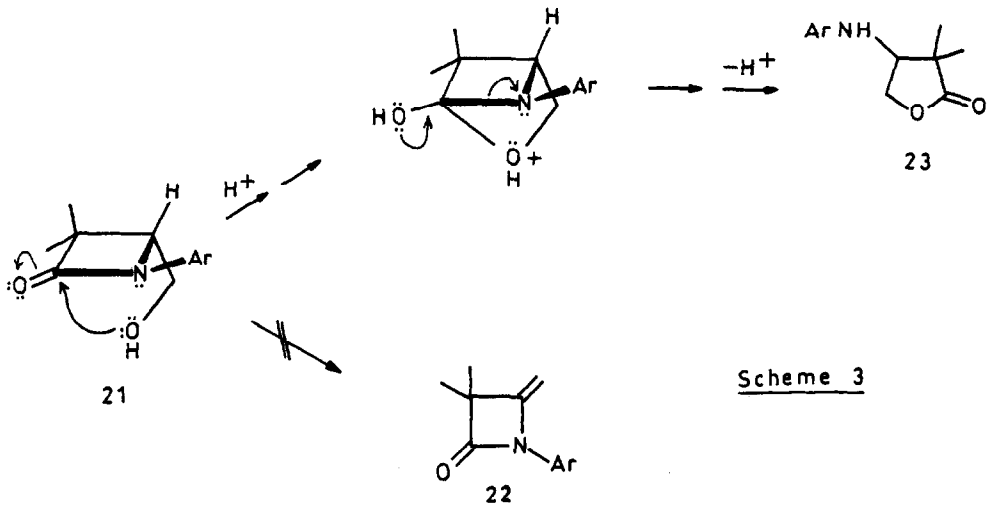
Scheme 2

4-methylene-β-lactam **22**,[15] we noted its slow and progressive conversion to amino-γ-lactone **23**. This transformation appears to take place by the process shown in Scheme 3, in which the hydroxyl group takes part in an intramolecular nucleophilic attack on the carbonyl group of the β-lactam leading to the displacement of the arylamino group. Along with the above

isomerization of imino-β-lactam **3d** into γ-methylene-γ-lactam **8**, this rearrangement constitutes a new example of intramolecular nucleophilic β-lactam ring-opening in which the nucleophile is on the C-4 substituent. Further examples of related rearrangements can be found, among others, in the studies of Bose[16] and Wasserman[17].

Recently, the oxidative removal of *N*-(*p*-methoxyphenyl) group by cerium (IV) ammonium nitrate (CAN) has been described.[18] The application of this approach to β-lactams **17-20** prepared by us led to the *N*-unsubstituted β-lactams **24-27** in excellent yields. Of the various reactions carried out, only β-lactam **21** failed to give the corresponding *N*-unsubstituted-β-lactam.

In summary, some β-lactams with potentially useful substituents at C-3, C-4 and nitrogen, can be prepared from α-diimines (1,4-diaza-1,3-butadienes) in a simple manner.



Scheme 3

EXPERIMENTAL

General. Melting points were determined in open capillaries on a Buchi 512 apparatus, and are uncorrected. IR spectra were recorded with a Perkin-Elmer 781 grating spectrophotometer. ^{1}H-NMR were recorded with a Varian T-60A (60 MHz), or with a Varian XL-400 (300 MHz), using tetramethylsilane as internal standard. ^{13}C-NMR spectra were recorded with a Varian FT-80 (20.15 MHz). ^{1}H-NMR and ^{13}C-NMR chemical shifts are reported in δ units downfield from tetramethylsilane. Mass spectra were determined with a Varian MAT 711 and a HP-5890A. Elemental analyses were performed at the Instituto de Química Bio-Orgánica, *C.S.I.C.*, Barcelona. Column chromatography was performed using Merck silica gel 230-400 mesh (flash chromatography) or 70-230 mesh. Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl and freshly distilled before use. Diisopropylamine was distilled from calcium hydride and stored over molecular sieves (4Å). Standardized (1.6 M) n-butyllithium in hexane was *obtained from Aldrich Chemical Co.*. Methyl acetate, methyl propionate and methyl isobutyrate were available through commercial sources and were distilled from sodium carbonate prior use. All reactions requiring anhydrous conditions were performed under a positive atmosphere

of nitrogen in oven-dried glassware.

Starting material for synthesis. The known dianils **1a**,[19] **1b**[20,21] and **1c**[21] were prepared easily by condensation of the corresponding α-dicarbonyl compounds with an excess of the appropriate aniline. *Dianil* **1a** was prepared using Kliegman's method.[19] *Dianil* **1b** was obtained by reaction of biacetyl with 2 equivalents of aniline without solvent at room temperature for one day, as a pale yellow crystalline solid, m.p. 136-137°C (ethanol) (yield: 52%). *Dianil* **1c** was prepared by reaction of benzil with 2 equivalents of aniline in xylene at reflux temperature (3 days) using a Dean-Stark device for azeotropic distillation of water, as a pale crystalline solid, m.p. 139-141°C (ethanol) (yield: 54%). *Methyl 2-(benzoylamino)propionate* was prepared from *rac*-alanine by *N*-benzoylation and subsequent esterification with MeOH-HCl.[22,23] All known compounds gave satisfactory physical and spectral data consistent with their structures.

1-(p-Anisyl)-4-[N-(p-anisyl)-azomethinyl]-3,3-dimethyl-2-azetidinone (3a). Lithium diisopropylamide (23.5 mmol) was prepared from diisopropylamine (3.30 ml, 23.5 mmol) and n-butyllithium (14.69 ml of a 1.6 M solution in hexane, 23.5 mmol) in dry THF (23.5 ml). To this solution cooled to -78°C, methyl isobutyrate (2.55 ml, 22.4 mmol) in THF (5 ml) was added keeping the temperature below -70°C, and the mixture was stirred for 15 min followed by the addition of the diimine **1a** (3 g, 11.2 mmol) in THF (11 ml). Then, the cold bath was removed and the mixture was allowed to warm to room temperature followed by stirring for 45 min. Finally, the reaction was worked up by diluting the reaction mixture with diethyl ether (150 ml) and washing successively with portions of water (3x30 ml) and brine (30 ml). The organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo* to yield after treatment with ethyl acetate/hexane 3.4 g (90%) of **3a** as a white solid, m.p. 91-92°C (ethyl acetate/hexane). IR (KBr) ν: 1740 (C=O), 1640 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.42 (d, 1H, J = 7 Hz, NC-H), 6.70-7.47 (m, 8H, H arom.), 7.88 (d, 1H, J = 7 Hz, N=CH). ^{13}C-NMR ($CDCl_3$) δ: 17.4 (CH_3) 22.9 (CH_3), 55.0 and 55.4 (2xOCH_3 and C-3), 64.9 (C-4), 114.0, 117.5, 121.7, 131.4, 143.0, 155.7, 158.4, 159.6, 169.6 (C-2). MS m/z (%): 338 (M^+, 75), 323 (100), 295 (8), 267 (17), 253 (15), 237 (11), 189 (21), 174 (15), 149 (8), 135 (21), 134 (17).

(3R*,4R*)- and (3R*,4S*)-1-(p-Anisyl)-4-[N-(p-anisyl)-azomethinyl]-3-(benzoylamino)-3-methyl-2-azetidinone (3b and 3c). The dilithium enediolate **2b** (3.73 mmol) was generated by addition of methyl 2-(benzoylamino)propionate (722 mg, 3.73 mmol) in THF (4 ml) to a solution of LDA (7.65 mmol) cooled to -78°C, then, reaction mixture was warmed to -20°C for 30 min, stirred for 1 h at this temperature and recooled to -78°C before addition of the diimine **1a** (0.5 g, 1.87 mmol). The resulting mixture was stirred at -78°C for 1 h and the dry ice/acetone bath was allowed to expire (about 2.5-3 h). The reaction was stirred for an additional 13 h at room temperature. Finally, the reaction was worked up as above to yield, in sequence, after flash chromatography (hexane:ethyl acetate, 1:1) 300 mg (36%) of the minor isomer **3c** and 365 mg (44%) of the major isomer **3b**.

Physical and spectral properties of **3b**: white solid, m.p. 109-111°C (decomp.) (ethyl acetate/hexane). IR (KBr) ν: 3210 (NH), 1755 (NC=O), 1650 (PhC=O and C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.85 (s, 3H, CH_3), 3.73 (s, 3H, OCH_3), 3.78 (s, 3H, OCH_3), 4.72 (d, 1H, J = 5.1 Hz, NC-H), 6.72-7.75 (m, 14H, H arom. and NH), 8.13 (d, 1H, J = 5.1 Hz, N=CH). ^{13}C-NMR ($CDCl_3$) δ: 21.2 (CH_3), 55.1 (OCH_3), 55.3 (OCH_3), 67.8 and 68.1 (C-3 and C-4), 114.0, 114.3, 118.1, 121.9, 127.1, 128.3, 131.1, 131.8, 132.7, 143.3, 156.2, 158.3, 158.6, 165.4 and 167.2 (PhCO and C-2). MS m/z (%): 309 (52), 103 (72), 61 (22), 45 (28), 43 (100). Analysis found: C 70.35%, H 5.76%, N 9.49%; $C_{26}H_{25}N_3O_4$ requires C 70.41%, H 5.68%, N 9.47%.

Physical and spectral properties of **3c**: white solid, m.p. 167-169°C (decomp.) (ethyl acetate/hexane). IR (KBr) ν: 3300 (NH), 1755 (NC=O), 1640 (PhC=O and C=N). ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.66 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 5.16 (d, 1H, J = 5.5 Hz, NC-H), 6.84-7.83 (m, 14H, H arom. and NH), 8.10 (d, 1H, J = 5.5 Hz, N=CH). ^{13}C-NMR ($CDCl_3$) δ: 17.1 (CH_3), 55.3 (2xOCH_3), 64.4 and 68.3 (C-4 and C-3), 114.2, 118.6, 121.9, 127.1, 128.3, 131.2, 131.8, 132.7, 143.2, 156.3, 158.1, 158.7, 165.7 and 167.0 (PhCO and C-2). MS m/z (%): 433 (M^+, 22), 322 (100), 269 (31), 121 (31), 105 (33), 77 (28). Analysis found: C 70.29%, H 5.80%, N 9.48%; $C_{26}H_{25}N_3O_4$ requires C 70.41%, H 5.68%, N 9.47%.

3,3-Dimethyl-1-phenyl-4-[N-(phenyl)-(1'-methyl)-azomethinyl]-2-azetidinone (3d). To a solution of enolate **2a** (33.9 mmol), prepared as before, cooled to -78°C, diimine **1b** (2 g, 8.47 mmol) in THF (20 ml) was added. The cold bath was removed and the mixture was allowed to warm to room temperature followed by stirring for 45 min. The reaction was worked up as before after which the crude mixture was heated in hexane to separate unreacted diimine and other minor soluble by-products, and 1.28 g of insoluble β-lactam **3d** (50%) was collected on a filter as a white solid, m.p. 158-159°C (ethanol). IR (KBr) υ: 1740 (C=O), 1660 (C=N). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (s, 3H, CH_3), 1.43 (s, 3H, CH_3), 1.83 (s, 6H, CH_3C=N and CH_3C-N), 6.53-7.63 (m, 10H, H arom.). ^{13}C-NMR ($CDCl_3$) δ: 17.6, 18.0, 18.2 and 18.3 (4xCH_3), 56.6 (C-3), 70.0 (C-4), 117.3, 118.1, 122.9, 128.3, 128.5, 137.3, 150.2, 170.3 and 170.5 (CH=N and C-2). Analysis found: C 78.46%, H 7.45%, N 9.31%; $C_{20}H_{22}N_2O$ requires C 78.40%, H 7.24%, N 9.14%.

3,3,4-Trimethyl-5-methylene-1-phenyl-4-(phenylamino)-2-pyrrolinone (8). *Procedure A.-* This procedure was identical to the one followed for the synthesis of β-lactam **3d**, with the exception that the mixture was stirred for 5 h at room temperature. Treatment of the reaction mixture with hexane precipitated a solid which was crystallized from hexane to give 0.77 g (30%) of **8** as a white solid, m.p. 95-96°C. IR (KBr) υ: 3410 (NH), 1715 (C=O), 1650 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.30, 1.33 and 1.60 (s, s and s, 9H, 3xCH_3), 3.73 (broad s, 1H, NH), 4.32 and 4.39 (dd, 2H, J = 2 Hz, CH_2=C), 6.63-7.60 (m, 10H, H arom.). ^{13}C-NMR ($CDCl_3$) δ: 18.8 (CH_3), 20.5 (CH_3), 20.8 (CH_3), 48.8 (C-3), 63.8 (C-4), 88.2 (=CH_2), 119.5, 119.9, 126.8, 127.4, 128.5, 129.0, 135.1, 145.2, 153.8 (C-5), 178.2 (C-2). Analysis found: C 78.46%, H 7.22%, N 9.08%; $C_{20}H_{22}N_2O$ requires C 78.40%, H 7.24%, N 9.14%.

Procedure B: By reaction of the β-lactam **3d** *with LDA.-* To a stirred solution of LDA (1.64 mmol) in dry THF (2 ml), under nitrogen, at -78°C, a solution of 250 mg (0.82 mmol) of **3d** in THF (2 ml) was added dropwise. The cold bath was removed and the mixture was allowed to warm to -15°C and stirred for 30 min at this temperature. Work-up as before led finally to the purified compound **8** (250 mg, cuantitative).

General procedure for the hydrolysis of 4-imino-2-azetidinones 3a-c. Synthesis of 4-formyl-2-azetidinones 4. To a solution of 1 equivalent of the imino-β-lactam in chloroform (20 ml/mmol of imino β-lactam), HCl 5% (10 ml/mmol of β-lactam) was added, and the mixture was stirred vigorously at room temperature for 1 h. Then, the mixture was diluted with $CHCl_3$ (30 ml/mmol β-lactam), the organic layer washed successively with HCl 5% (2x10 ml/mmol imino β-lactam), water (10 ml/mmol imino β-lactam) and brine (10 ml/mmol imino β-lactam), dried over anhydrous $MgSO_4$ and the solvent was removed *in vacuo*. The residue was purified by flash chromatography (hexane:ethyl acetate, 1:1).

1-(p-Anisyl)-4-formyl-3,3-dimethyl-2-azetidinone **(4a).** From 500 mg (1.48 mmol) of **3a**, 330 mg (90%) of **4a** was obtained as a crystalline white solid, m.p. 110-111°C (ethyl acetate/hexane). IR (KBr) υ: 1725 (NC=O and HC=O). ^{1}H-NMR ($CDCl_3$) δ: 1.30 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.13 (d, 1H, J = 3.5 Hz, NC-H), 6.70-7.27 (m, 4H, H arom.), 9.74 (d, 1H, J = 3.5 Hz, HC=O). ^{13}C-NMR ($CDCl_3$) δ: 17.6 (CH_3), 22.6 (CH_3), 55.3 and 56.0 (OCH_3 and C-3), 67.4 (C-4), 114.4, 117.6, 131.1, 156.4, 169.1 (C-2), 199.9 (HC=O). MS m/z (%): 233 (M^+, 100), 176 (41), 163 (22), 149 (80), 134 (59). Analysis found: C 67.04%, H 6.72%, N 5.93%; $C_{13}H_{15}NO_3$ requires C 66.94%, H 6.48%, N 6.00%.

(3R,4R*)-1-(p-Anisyl)-3-benzoylamino-4-formyl-3-methyl-2-azetidinone* **(4b).** From 300 mg (0.68 mmol) of **3b**, 210 mg (92%) of **4b** was obtained as a crystalline white solid, m.p. 156-158°C (decomp.) (ethyl acetate/hexane). IR (KBr) υ: 3300 (NH), 1750 (NC=O), 1720 (HC=O), 1660 (PhC=O). ^{1}H-NMR ($CDCl_3$) δ: 1.70 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.20 (d, 1H, J = 1.5 Hz, NC-H), 6.73-7.73 (m, 10H, H arom. and NH), 9.73 (d, 1H, J = 1.5 Hz, HC=O). ^{13}C-NMR ($CDCl_3$) δ: 21.1 (CH_3), 55.4 (OCH_3), 67.9 and 69.8 (C-3 and C-4), 114.5, 118.0, 127.1, 128.4, 130.7, 132.2, 156.6, 165.2 and 167.6 (PhCO and C-2), 195.6 (CH=O). Analysis found: C 67.50%, H 5.26%, N 8.28%; $C_{19}H_{18}N_2O_4$ requires C 67.44%, H 5.36%, N 8.28%.

(3R,4S*)-1-(p-Anisyl)-3-benzoylamino-4-formyl-3-methyl-2-azetidinone* **(4c).** From 300 mg (0.68 mmol) of **3c**, 220 mg (96%) of **4c** was obtained as a white solid, m.p. 188-190°C (decomp.) (ethyl acetate). IR (KBr) υ: 3260 (NH), 1770 (NC=O), 1720 (HC=O), 1630 (PhC=O).

^{1}H-NMR ($CDCl_3$) δ: 1.63 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.97 (d, 1H, J = 1.5 Hz, NC-H), 6.70-7.83 (m, 10H, H arom. and NH), 9.93 (d, 1H, J = 1.5 Hz, HC=O). ^{13}C-NMR (DMSO-d_6) δ: 17.1 (CH_3), 55.4 (OCH_3), 66.8 and 67.8 (C-3 and C-4), 114.3, 118.4, 127.8, 128.4, 131.6, 132.0, 132.9, 155.9, 166.2, and 166.9 (PhCO and C-2), 200.3 (CH=O). Analysis found: C 67.58%, H 5.25%, N 8.24%; $C_{19}H_{18}N_2O_4$ requires C 67.44%, H 5.36%, N 8.28%.

1-(p-Anisyl)-4-(2'-dioxolanyl)-3,3-dimethyl-2-azetidinone (17). In a flask equipped with a Dean-Stark device for azeotropic distillation of water, a reflux condenser and a pressure equalizing addition funnel, the β-lactam **3a** (740 mg, 3.18 mmol) was dissolved in anhydrous benzene (30 ml) and a trace of p-toluenesulphonic acid was added. The above solution was heated at reflux and a solution of ethyleneglycol (394 mg, 6.35 mmol) in 15 ml of dry benzene was added dropwise from the addition funnel. After the addition was completed, the reaction mixture was stirred under reflux for an additional 1h 30 min. The mixture was worked up by diluting with 40 ml of benzene and washing successively with $NaHCO_3$ 5%, water and brine. The organic layer was dried over anhydrous Na_2SO_4 and evaporated. Finally, the residue was recrystallized from ethyl acetate/hexane to yield 710 mg (81%) of **17** as a white solid, m.p. 89-91°C. IR (KBr): υ 1735 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.37 (s, 6H, 2xCH_3), 3.70 (d, 1H, J = 6 Hz, OCHO), 3.73 (s, 3H, OCH_3), 3.90 (broad s, 4H, 2xCH_2), 5.00 (d, 1H, J = 6Hz, NC-H), 6.78 (d, 2H, J = 9 Hz, H arom.), 7.48 (d, 2H, J = 9 Hz, H arom.). Analysis found: C 65.25%, H 6.99%, N 5.05%. $C_{15}H_{19}NO_4$ requires C 64.97%, H 6.91%, N 5.05%.

1-(p-Anisyl)-4-cyano-3,3-dimethyl-2-azetidinone (18). A previously described method[24] was used to convert **4a** (1 g, 429 mmol) in **18**. The residue was recrystallized from methanol: 730 mg (74%) of **18** as a white solid, m.p. 83-85°C. IR (KBr) υ: 2240 (CN), 1740 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.32 (s, 1H, NCH), 6.84 (d, 2H, J = 9 Hz, H arom.), 7.32 (d, 2H, J = 9 Hz, H arom.). ^{13}C-NMR ($CDCl_3$) δ: 19.3 (CH_3), 21.1 (CH_3), 51.2 (C-4), 55.3 and 55.9(OCH_3 and C-3), 114.5, 115.1 (C$\equiv$N), 117.9, 129.8, 156.8, 167.5 (C-2). MS m/z (%): 230 (M^+, 32), 160 (57), 149 (100), 145 (21), 134 (38), 106 (16), 90 (16), 70 (15), 41 (16). Analysis found: C 68.03%, H 6.25%, N 11.92%. $C_{13}H_{14}N_2O_2$ requires C 67.81%, H 6.13%, N 12.17%.

1-(p-Anisyl)-3,3-dimethyl-4-vinyl-2-azetidinone (19). A flask fitted with a magnetic stirrer, was loaded with methyltriphenylphosphonium iodide (484 mg, 1.2 mmol) and dry THF (30 ml). The above suspension was treated with n-BuLi (1.2 mmol, 1.6 M in n-hexane). The mixture was stirred for 30 min and a solution of **4a** (230 mg, 1 mmol) in 15 ml of anhydrous THF was added. After the addition was completed, the mixture was stirred for 50 min. It was then quenched with NaCl and extracted with diethyl ether (3x25 ml). The organic layer was dried ($MgSO_4$) and evaporated leaving the crude as a colourless oil. Purification was acomplished by chromatography, (hexane:ethyl acetate, 1:1) to give **19** as a colorless oil, 200 mg (88%). IR ($CHCl_3$) υ: 1740 (C=O), 1645 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.19 (s, 3H, CH_3), 1.36 (s, 3H, CH_3), 3.75 (s, 3H, OCH_3), 4.14 (d, 1H, J = 7 Hz, NCH), 5.13-6.26 (m, 3H, H olef.), 6.80 (d, 2H, J = 11 Hz, H arom.), 7.33 (d, 2H, J = 11 Hz, H arom.). ^{13}C-NMR ($CDCl_3$) δ: 17.4 (CH_3), 22.0 (CH_3), 54.1 and 55.0 (C-3 and OCH_3), 65.2 (C-4), 113.9, 117.9, 119.9 (=CH_2), 131.6, 133.7 (CH=), 155.5, 170.3 (C-2).

1-(p-Anisyl)-4E-[(2'-methoxycarbonyl)ethylidene]-3,3-dimethyl-2-azetidinone (20). In a flask equipped with a reflux condenser, the β-lactam **4a** (400 mg,1.71 mmol) was dissolved in anhydrous THF (20 ml), and methoxycarbonylmethylenetriphenylphosphorane (690 mg, 2 mmol) was added. The above solution was heated at reflux for 50 min. The solvent was removed *in vacuo* leaving the crude β-lactam as a colorless oil. Purification was acomplished by chromatography (hexane:ethyl acetate, 1:1) to give 495 mg (cuantitative) of **20** as a white solid, m.p. 116-118°C (EtOH). IR (KBr) υ: 1740 (NC=O), 1720 (OC=O), 1660 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.21 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.66 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3), 4.17 (d, 1H, J = 7 Hz, NCH), 6.03 (d, 1H, J = 15 Hz, MeO_2C-CH=), 6.70-7.30 (m, 5H, C_4-CH= and H arom.). MS m/z (%): 289 (M^+, 17), 219 (7), 204 (12), 160 (11), 149 (100), 134 (22), 125 (8), 92 (8), 81 (13), 41 (8). Analysis found: C 66.39%, H 6.72%, N 4.58%. $C_{16}H_{19}NO_4$ requires C 66.42%, H 6.62%, N 4.84%.

1-(p-Anisyl)-4-hydroxymethyl-3,3-dimethyl-2-azetidinone (21). Compound **4a** (1.42 g, 6.1 mmol) was dissolved in dry MeOH (50 ml), and $NaBH_4$ (0.90 g, 24.4 mmol) was added in portions. The mixture was stirred at room temperature for 15 min. The solvent was removed and the crude

product was then poured on water and extracted with diethyl ether (3x25 ml). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed on silica gel (30 g) with hexane:ethyl acetate 1:2 as eluent to yield 1.33 g (93%) of **21** as a white solid, m.p. 71-73°C (ethyl acetate/hexane). IR (KBr) υ: 3430 (OH), 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.27 (s, 3H, CH_3), 1.37 (s, 3H, CH_3), 3.20 (s, 1H, OH); 3.73 (s, 3H, OCH_3), 3.73-4.00 (m, 3H, CH_2 and NCH), 6.77 (d, 2H, J = 9 Hz, H arom.), 7.38 (d, 2H, J = 9 Hz, H arom.). ^{13}C-NMR ($CDCl_3$) δ: 16.1 (CH_3), 22.5 (CH_3), 51.3 (C-3), 55.0 (OCH_3), 60.1 (C-4), 63.7 (CH_2OH), 113.9, 118.6, 130.8, 155.7, 171.5 (C-2). MS m/z (%): 235 (M^+, 17), 176 (7), 165 (6), 149 (100), 134 (54), 121 (6), 106 (11), 92 (15), 77 (21), 71 (14), 41 (20), 31 (28). Analysis found: C 66.60%, H 7.35%, N 5.65%. $C_{13}H_{17}NO_3$ requires C 66.36%, H 7.28%, N 5.95%.

4-(p-Anisylamino)-3,3-dimethyl-tetrahydrofuran-2-one (23). In a flask equipped with a reflux condenser, the β-lactam **21** (500 mg, 2.1 mmol) was dissolved in xylene (20 ml) and a trace of p-toluensulphonic acid was added. Reflux was maintained for three days. The solvent was removed and the residue was chromatographed with hexane:ethyl acetate 1:1 as eluent to give 400 mg of **23** as a white solid, m.p. 87-89°C (ethyl acetate/hexane). IR (KBr) υ: 3370 (NH), 1775 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.33 (broad s, 1H, NH), 3.73 (s, 3H, OCH_3), 3.73-4.60 (m, 3H, CH-CH_2), 6.50-6.87 (m, 4H, H arom.). ^{13}C-NMR ($CDCl_3$) δ: 17.8 (CH_3), 23.4 (CH_3), 42.2 (C-3), 55.6 (OCH_3), 59.8 (C-4), 69.5 (C-5), 114.9, 115.0, 140.0, 152.9, 180.7 (C-2). MS m/z (%): 235 (M^+, 100), 177 (9), 165 (79), 134 (73), 117 (25), 92 (14), 77 (20), 41 (26). Analysis found: C 66.63%, H 7.34%, N 5.88%. $C_{13}H_{17}NO_3$ requires C 66.36%, H 7.28%, N 5.95%.

General procedure for the oxidative N-dearylation of 1-aryl-2-azetidinones 17-20. A previously described method[18] was used to convert the *N*-aryl-β-lactams **17-20** into the related *NH*-β-lactams. To a solution of 1 equivalent of 1-aryl-2-azetidinone in acetonitrile (10 ml/mmol of β-lactam), 3 equivalents of a solution of cerium (IV) ammonium nitrate in water (7 ml/mmol of CAN), at 0°C, were added. The reaction was stirred at 0°C for 25 minutes and diluted with water (60 ml/mmol β-lactam). The mixture was extracted with ethyl acetate (3x15 ml/mmol β-lactam) and the organic extracts were washed succesively with Na_2SO_3 10% (until the aqueous layer remained colourless), $NaHCO_3$ 5% (10 ml/mmol β-lactam) and brine (10ml/mmol β-lactam). Finally, the solution was swirled with charcoal for 30 min, dried over $MgSO_4$ and the solvent was evaporated. The residue was chromatographed.

4-(2'-Dioxolanyl)-3,3-dimethyl-2-azetidinone (**24**). From 710 mg (2.56 mmol) of **17**, 360 mg (82%) of **24** was obtained as a white solid after chromatography (hexane:ethyl acetate, 1:1), m.p. 60-62°C (ethyl acetate/hexane). IR(KBr) υ: 3150 (NH), 1760 and 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.20 (s, 3H, CH_3), 1.27 (s, 3H, CH_3), 3.12 (d, 1H, J = 7 Hz, OCHO), 3.87 (broad s, 4H, 2xCH_2), 4.81 (d, 1H, J = 7 Hz, NCH), 6.60 (s, 1H, NH). MS m/z (%): 128 (15), 127 (16), 113 (79), 83 (13), 73 (100), 45 (26).

4-Cyano-3,3-dimethyl-2-azetidinone (**25**). From 560 mg (2.43 mmol) of **18**, 240 mg (80%) of **25** was obtained as a white solid after chromatography (hexane:ethyl acetate, 1:1), m.p. 84-86°C (ethyl acetate/hexane). IR (KBr) υ: 3270 (NH), 2240 (C≡N), 1770 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.43 (s, 3H, CH_3), 1.50 (s, 3H, CH_3), 4.03 (s, 1H, CH), 6.87 (broad s, 1H, NH). ^{13}C-NMR ($CDCl_3$) δ: 19.2 (CH_3), 20.8 (CH_3), 48.0 (C-4), 58.4 (C-3), 116.5 (C≡N), 172.3 (C-2). MS m/z (%): 81 (100), 70 (34), 66 (13), 54 (36), 41 (64). Analysis found: C 58.00%, H 6.63%, N 22.60%; $C_6H_8N_2O$ requires C 58.05%, H 6.50%, N 22.57%.

3,3-Dimethyl-4-vinyl-2-azetidinone (**26**). From 150 mg (0.65 mmol) of **19**, 70 mg (86%) of **26** was obtained as a colourless oil after chromatography (hexane:ethyl acetate, 1:1). IR ($CHCl_3$) υ: 3240 (NH), 1745 (C=O), 1645 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.10 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.83 (d, 1H, J = 6 Hz, CH), 5.07-6.17 (m, 3H, H olef.), 6.43 (broad s, 1H, NH). MS m/z (%): 82 (96), 70 (30), 67 (100), 56 (31), 54 (22), 42 (49), 41 (42), 39 (47).

4E-[(2'-Methoxycarbonyl)ethylidene]-3,3-dimethyl-2-azetidinone (**27**). From 370 mg (1.28 mmol) of **20**, 210 mg of **27** (90%) was obtained as a white solid after chromatography (hexane:ethyl acetate, 1:1), m.p. 73-75°C (ethyl acetate/hexane). IR (KBr) υ: 3190 (NH), 1745 (NC=O), 1720 (OC=O), 1660 (C=C). ^{1}H-NMR ($CDCl_3$) δ: 1.13 (s, 3H, CH_3), 1.40 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.02 (dd, 1H, J = 6 Hz, J = 1.5 Hz, NCH), 6.00 (dd, 1H, J = 1.5 Hz, J = 16 Hz, MeO_2OCH=), 6.83 (broad s, 1H, NH), 6.93 (dd, 1H, J = 6 Hz, J = 16 Hz, MeO_2OCH=C<u>H</u>-). ^{13}C-NMR

($CDCl_3$) δ: 17.2 (CH_3), 21.5 (CH_3), 51.2 (OCH_3), 56.5 (C-3), 59.3 (C-4), 122.3 (MeO_2C-$\underline{C}H$=), 144.3 (MeO_2C-CH=$\underline{C}H$), 165.7 (OC=O), 174.3 (NC=O). MS m/z (%): 185 (M^+, 0.15), 140 (27), 125 (67), 114 (20), 81 (100), 70 (61), 55 (16), 42 (46), 41 (37), 39 (25). Analysis found: C 59.23%, H 7.01%, N 7.60%; $C_9H_{13}NO_3$ requires C 59.00%, H 7.15%, N 7.65%.

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