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REGIOCONTROLLED NUCLEOPHILIC ADDITION TO THE CARBONYL AND IMINO GROUPS IN THE REACTION OF 2-ARYLAMINO-2-METHOXY-1-PHENYLETHANONES WITH SIMPLE LITHIUM ESTER ENOLATES[1]

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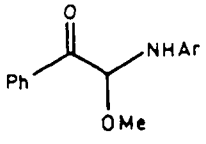
Abstract. The nucleophilic addition of lithium ester enolates **3** to 2-arylamino-2-methoxy-1-phenylethanones **1** (synthetic equivalents of the related phenylglyoxal anils **2**) is reported. While enolates derived from α,α-dialkyl methyl esters, **3a** and **3b**, give addition products by attack at either the carbonyl (kinetic products) or the imino groups through a thermally controlled process, those derived from methyl dimethoxyacetate, methyl acetate and methyl propionate, **3c**, **3d**, and **3e**, respectively, only lead to addition products to the carbonyl group. On the basis of the isolation of all these compounds as stable products and of some transformations and crossover experiments a reasonable mechanism is proposed for the whole process. In all cases, addition products at the imino groups can also be obtained by the SiO_2-catalyzed rearrangement of the corresponding kinetic addition compounds. The synthesis of some substituted 4-benzoyl-β-lactams **8a-g** is a particularly significant feature of this work.

INTRODUCTION

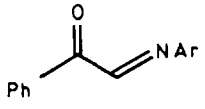
The reactions of α-lithiated esters with simple carbonyl compounds and imines have been the subject of extensive studies. Thus, the addition of lithium ester enolates to aldehydes and ketones provides a simple alternative to the original Reformatsky reaction.[2] The condensation reactions of various types of imines with lithiated esters have proved to be useful procedures for the synthesis of appropriately substituted β-lactams.[3] Several years ago we became interested in the reaction of imino ketones and related bifunctional electrophiles with ester enolates as potential methodology for the obtention of synthetically useful, simple polyfunctional compounds. Previously, we have described the reaction of simple lithium ester enolates with α-imino and β-imino ketones[4] which undergo exclusive addition to their carbonyl groups.

In a preliminary communication[1] we have reported the first example of nucleophilic addition of an ester enolate at either the carbonyl or the imino groups in a masked α-imino ketone through a regiocontrolled process, demostrating the importance of experimental parameters in partitioning both modes of addition with stabilized carbanions.[5] We wish to report now our findings concerning the reaction of lithium ester enolates **3** with **1** which has allowed for the synthesis of various types of polyfunctional

compounds **4–8** in a simple and regiospecific fashion. Compounds **4–6** are addition products to the carbonyl group while compounds **7** and **8** represent the formal addition products to the masked imino group of **1**.[6] Among the different compounds prepared, structures **5**, **7**, and **8** are of particular potential interest. Compounds **5** are both β-hydroxy esters and α-hydroxy imines, while **7** are both α-amino ketones and β-amino esters. These structures have aroused interest from both the synthetic and the theoretical standpoint.[7–10] On the other hand, compounds **8** are the first 4-acyl β-lactams obtained under standard enolate-imine reaction conditions from compounds bearing a ketonic carbonyl group at the imine carbon atom.[11] This procedure becomes an alternative route to the synthesis of 4-benzoyl β-lactams by (2+2) cycloaddition of phenylglyoxal anils with an acyl chloride in the presence of triethylamine.[12,13]



1



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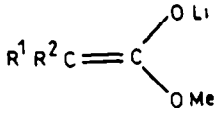


3

a: Ar = 4-$MeOC_6H_4$
b: Ar = 4-MeC_6H_4
c: Ar = C_6H_5
d: Ar = 4-BrC_6H_4
e: Ar = 4-$NO_2C_6H_4$

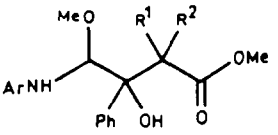
a: $R^1 = R^2$ = Me
b: R^1, R^2 = $-(CH_2)_5-$
c: $R^1 = R^2$ = OMe
d: $R^1 = R^2$ = H
e: R^1 = Me, R^2 = H

RESULTS AND DISCUSSION

The synthesis of methanol adducts **1** and of their corresponding anils **2** has already been described by us.[14] While free anils **2** are notably more difficult to isolate and handle due to their highly hygroscopic nature, adducts **1** can be easily synthesized and purified. However, since adducts **1** are easily transformed into the anils **2** in the presence of base as well as in some other ways, they can be conveniently used as synthetic equivalents of the related anils.

By reacting compounds **1** with an excess of ester enolates **3** (2.2 equivalents)[15] generated *in situ* from the corresponding carboxylic esters and lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at -78°C, we have regiospecifically obtained in good to excellent yields, β-hydroxy-γ-amino-γ-methoxy esters **4**, β-hydroxy-γ-imino esters **5**, β-hydroxy-γ-methoxy γ-lactams **6**, β-amino-γ-keto esters **7**, and β-benzoyl-β-lactams **8**, depending on the nature of both the enolate and the aryl group, and/or the experimental conditions, mainly the temperature (see Experimental Section).

We began this investigation by examining the reaction between the lithium enolate of methyl isobutyrate, **3a**, and a series of representative *para*-substituted *N*-(α-methoxyphenacyl)anilines **1a–e**. Treatment of a THF solution of enolate **3a** with phenacylanilines **1** gave compounds **4–8** depending on the temperature and on the nature of



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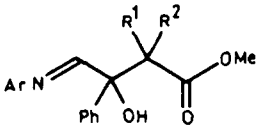

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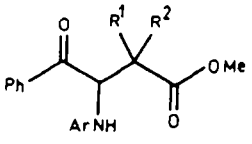

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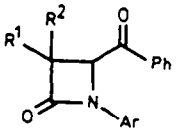
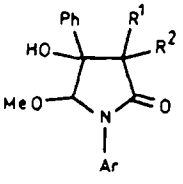


8

4,5,7,8	X	R^1	R^2
a	OMe	Me	Me
b	Me	Me	Me
c	H	Me	Me
d	Br	Me	Me
e	OMe	$-(CH_2)_5-$	
f	Br	$-(CH_2)_5-$	
g	OMe	OMe	OMe
h	Br	OMe	OMe
i	OMe	H	H
j	Me	H	H
k	H	H	H
l	Br	H	H
m	OMe	Me	H
n	H	Me	H
o	Br	Me	H



6

6	X	R^1	R^2
a	NO_2	Me	Me
b	NO_2	Me	H

(Ar = 4-X-C_6H_4)

the *para*-substituent. Thus, when the reactions were carried out at -78°C for 5 min and then quenched with water at that temperature, compounds **4a–d** were obtained in nearly quantitative yields in crude products from the corresponding adducts **1a–d**. Furthermore, when the reaction mixture obtained initially at -78°C was successively warmed to -35°C, -15°C, and room temperature for the times indicated in the Tables before quenching with water at those temperatures, products **5**, **7**, and **8** were obtained, respectively. From adduct **1e**, however, compound **6a** was the only isolated product in the above conditions, the best

result being obtained after 5 min at -78°C. Compounds **4** and **6** derived from enolate **3a** were obtained as mixtures of diastereoisomers in the relative proportions 5:1 in all cases in which analysis of the crude reaction mixtures by ^{1}H-NMR could be achieved (all except **4a**). On the other hand, the lithium enolate of methyl cyclohexanecarboxylate (**3b**) reacted with adducts **1a** and **1d** in a similar fashion to give the corresponding compounds **4** (as a 7:3 mixture of diastereoisomers), **5**, **7**, and **8**. In addition, anil **2d** reacted with enolate **3a** at -78°C for 5 min yielding the related compound **5d** in 75% as a pure product (procedure D, see Experimental Section). Also, from **2d** β-lactam **8d** was obtained by using similar experimental conditions to those used for **1d**, the yield being also similar.

The reactions of some compounds **1** with methyl α-lithiodimethoxyacetate (**3c**), methyl α-lithioacetate (**3d**), and methyl α-lithiopropionate (**3e**) were also investigated. Of the various experiments performed at the same reaction temperatures to those used before for enolates **3a** and **3b**, only addition products to the carbonyl group were obtained when the reactions were carried out at -78°C. When the reaction temperature was raised above -78°C only intractable crude reaction mixtures were obtained from enolates **3d** and **3e**. Therefore, from these enolates it was not possible to obtain and not even to detect addition products to the imino group (types **7** and **8**) in the crude mixture.

Thus, starting with enolate **3c**, its reaction with **1a** and **1d** at -78°C produced mixtures of the corresponding products **4** and **6** in variable ratios depending of the experiment. The latter was the main product when the reaction mixture was allowed to warm up to room temperature. Therefore, in this case it is necessary to start from iminoketone **2** in order to obtain the corresponding iminoesters **5** (**5g** and **5h**) free from γ-lactams **6** and in good yied (procedure D, see Experimental Section). The reaction between enolate **3d** and phenacylanilines **1a–e** afforded only the corresponding products **4**. Compounds **4** and **6** arising from enolates **3c** and **3d** were obtained as a single diastereoisomer in both cases. In the reaction of enolate **3e** with **1a**, **1c**, and **1d**, the corresponding products **4** were obtained as mixtures of two diastereomers in a 7:3 relative ratio, while from the reaction with **1e** a mixture of diastereoisomerically pure compounds **4** and **6**, was obtained in a 3:7 relative ratio.

Compounds **4** lose methanol easily in either chloroform or methanol solution, giving the related compounds **5** in excellent yields (procedures B and C, see Experimental Section).[16] The only exceptions are compounds **4**, with Ar = p-$NO_2C_6H_4$, which do not lose methanol even after prolongued reaction times in different solvents.[17] The observed rate of demethanolation depends upon the nature of the *para*-substituent on the aryl group attached to the nitrogen atom (MeO > Me > H > Br). In every case, the major isomer, which could be isolated sometimes by crystallization from hexanes or methanol, loses methanol much more rapidly than the minor one.

When compounds **4** derived from enolate **3e**, as diastereomeric mixtures in a 7:3 ratio, were demethanolized, the corresponding hydroxy-imino esters **5a–o** were obtained as diastereomeric mixtures in the same relative ratio as the starting adducts. Furthermore, when the starting material in the reaction with enolate **3e** was the corresponding anil **2**,

in which that chiral center does not exist, the same 7:3 mixture of diastereoisomers was obtained.

The stereochemical course of the formation, under the same experimental conditions, of γ-lactams **6** must be similar to the formation of open-chain compounds **4**. Since through the intramolecular aminolysis process the stereochemistry of the chiral centers created in the initial stage of addition of the enolate to the carbonyl group of phenacylanilines **1** is not affected, the relative stereochemistry of both diastereoisomers in each one of compounds **4** can be correlated with the corresponding diastereomeric γ-lactams, **6**. Analysis by X-ray diffraction of the major isomer of γ-lactam **6a**, derived from enolate **3a**, and of γ-lactam **6b**, obtained from enolate **3e**, has established their relative stereochemistry as $4R^*5R^*$ and $3R^*4R^*5S^*$, respectively (Figure 1). These results allow for the assigment of a $3R^*4R^*$ stereochemistry to the major stereoisomers of compounds **4** derived from enolate **3a** (and, presumably, also for the corresponding isomer derived from **3b**, and $3R^*4S^*$ for those derived from the other achiral enolates **3c-d**), and a $2R^*3R^*4S^*$ stereochemistry for the major isomers of compounds **4**, derived from enolate **3e**.

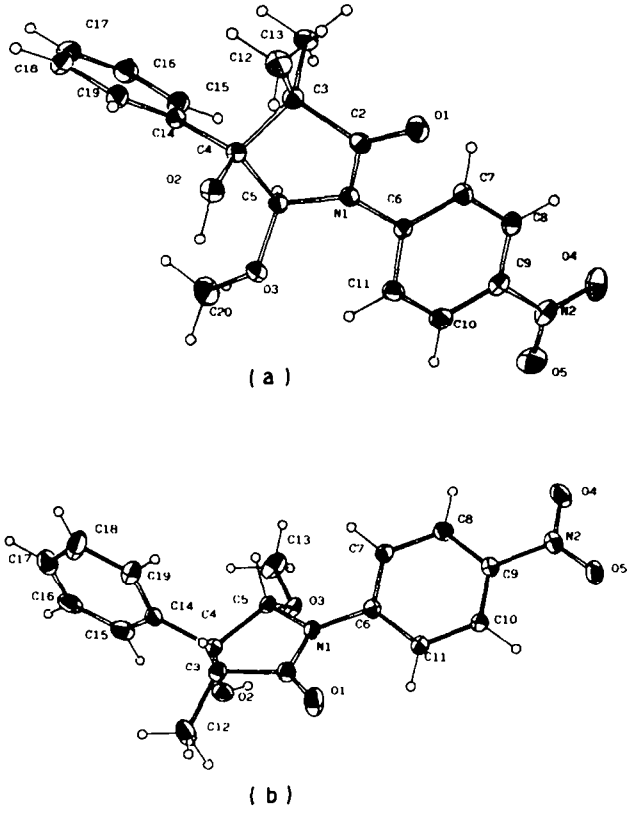
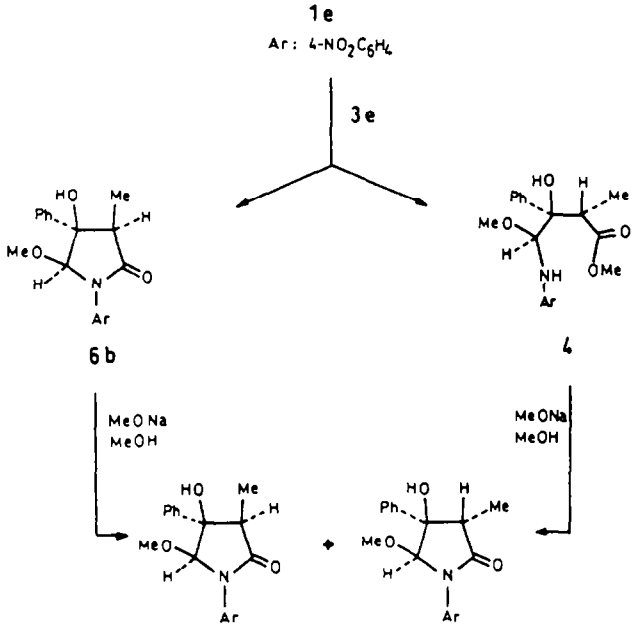


Figure 1. ORTEP drawing of compounds **6a** (a) and **6b** (b).[26]

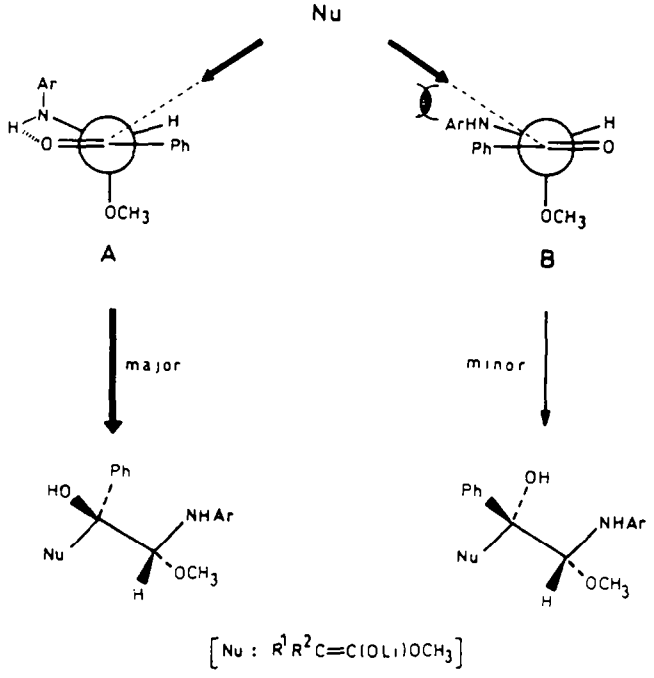
On the other hand, both γ-lactam **6b** and ester **4**, produced in the reaction between **1e** and enolate **3e**, led to the same mixture of isomeric γ-lactams in an equimolecular ratio by reaction with methanolic sodium methoxide; from these data, it may be deduced that both substrates have the same relative configuration in the fragment -NCH(OMe)-C(Ph)(OH)-, while they differ just in the configuration of the other chiral atom (C-2 in **4** and C-3 in **6b**) (Scheme I). Based on this evidence, they must be, therefore, epimeric in this chiral center, the carbon atom α respect to the C=O, which is the only center capable of undergoing epimerization under such conditions. Additional evidence is provided by the fact that the mixture of isomeric γ-lactams **6a**, which do not possess the aforementioned chiral center, is not altered under the same experimental conditions. Therefore, the minor diastereoisomers of compounds **4** derived from enolate **3e** must have a relative configuration $2S^*3R^*4S^*$. This allows for the assignment of a $2R^*3R^*$ and $2S^*3R^*$ configuration, respectively, to the major (α) and minor (β) diastereoisomers of hydroxy-imino esters **5m-o**.



Scheme I

The stereoselectivity observed upon formation of the carbinolic chiral center in the reaction of the different enolates considered may be accounted for by application of Felkin's model for asymmetric induction, by assuming the methoxy group to be the "large" substituent.[18] According to Felkin's model refined by Anh and Eisenstein[19] and considering the Dunitz-Bürgi trajectory for carbonyl addition,[20] the major and minor products from the reaction of lithium ester enolates with *N*-(α-methoxyphenacyl)anilines **1** are those

predicted from attack as illustrated in conformations A and B (Scheme II). While the transition state implied in conformation A will be the most stable since it may also benefit from a certain degree of intramolecular hydrogen bond stabilization between carbonyl and amino groups,[21] B will be very unstable due to the large interaction $(Ph\text{-}NHAr)_{1,2}$[e]. Moreover, NHAr ↔ Nu transition state steric effects also favor transition state A over B. However, it is difficult to explain with the available data the difference in stercoselectivity observed in the reactions of enolates 3a and 3b with regard to the other enolates tested. On the other hand, the stereoselectivity observed in the reaction of enolate 3e with compounds 1 is difficult to rationalize, if we consider that the stereochemical result is identical when anils 2 are utilized, and, furthermore, it is independent of the use of co-solvents such as hexamethylphosphoric triamide (HMPA) and N,N,N',N'-tetramethylenediamine (TMEDA) through the generation of the enolate.[22] Although it is possible to develop models which are consistent with the observed stereoselectivity, we defer all speculation until more information is available about the study with other related enolates and solvents.



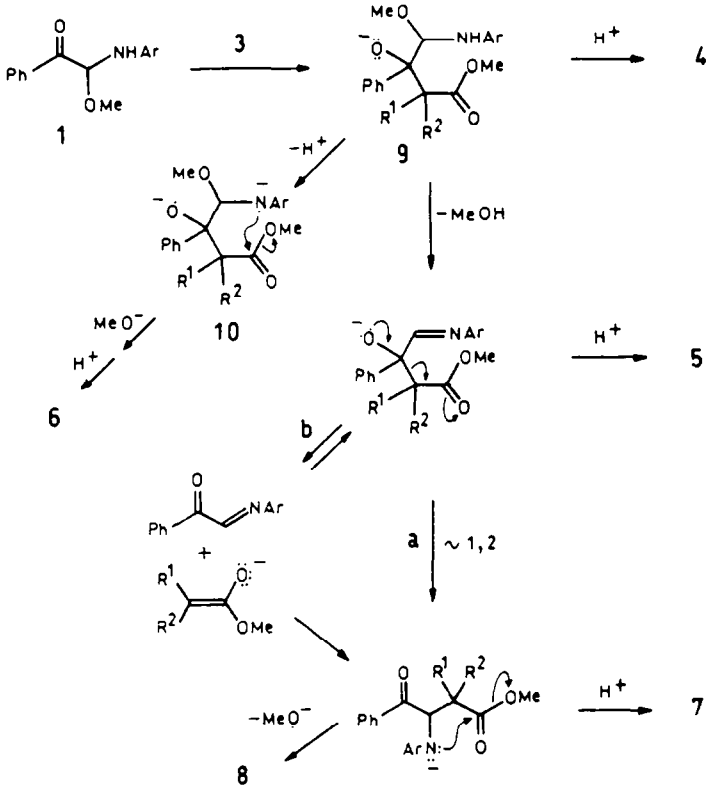
[Nu : $R^1R^2C{=}C(OLi)OCH_3$]

Scheme II

We have previously proposed the reaction course shown in Scheme III, where $R^1 = R^2 =$ Me, to account for the formation of different types of compounds 4-8 from enolate 3a,[1] the rearrangement of compounds 5 to 7 being the key step in the process, which may take place either through a process related to the α-ketol rearrangement in the α-hydroxy imine

moiety,[23] or by reversion to the corresponding α-imino ketone and further addition of enolate to its imino group.

In order to shed some light on this problem, we have carried out some crossover experiments with different β-hydroxy-γ-imino esters **5** and enolates **3**. If compounds **5** followed an intramolecular pathway (route **a**), only the normal rearrangement products would be expected. On the other hand, an intermolecular reaction course (route **b**) would also lead to the mixed isomerization products. From the reaction of hydroxy-imino ester **5f** with an excess of enolate **3a** exclusively β-lactam **8f** (92% yield after purification) was formed as deduced by the ^{1}H-NMR (300 MHz) analysis of the reaction mixture. Also, in the reaction of **5d** with enolate **3b** β-lactam **8d** was the only product obtained (90% yield in pure product). These and other similar crossover experiments with different compounds **5** suggest a mechanism implying a 1,2 intramolecular nucleophilic rearrangement (α-ketol-type basic isomerization), and rule out the alternative reaction course involving an intermolecular addition of enolate to the imino group.



Scheme III

In conclusion, it may be stated that the reaction between phenacylanilines **1** or the

corresponding anils **2** with enolates from α,α-dialkyl esters gives addition products by attack at either the carbonyl (kinetic products) or the imino groups through a thermally controlled process (Scheme III). On the contrary, enolates bearing additional α-hydrogen or withdrawing groups only lead to addition products to the carbonyl group. It is very significant that such a marked difference of reactivities was observed among various enolates studied in their reactions with **1** or **2**. Although this finding could be accounted for in terms of the enolization and migratory aptitud of the different groups introduced by the enolates, it is difficult at present to rationalize satisfactorily the dependence of the reaction pattern on the nature of the enolate.

Finally, two aspects of the reaction between phenacylaniline **1e** with enolates **3a**, **3d**, and **3e**, at -78°C, must be considered: **i)** for a given enolate, for example **3a**, the difference in behaviour between **1e** and the remainder phenacylanilines, and **ii)** the difference in behaviour observed in the reaction of **1e** with the above enolates, **3a**, **3d**, and **3e**. The former aspect may be justified as a consequence of the increase of acidity of the amine hydrogen of alkoxide **9** when Ar = p-$NO_2C_6H_4$ ($pk_a \simeq 18$),[24] which permits its capture by a second enolate molecule, acting as a base, to render amide **10** which cyclizes rapidly to **6**. In the other cases this process cannot take place due to the considerably diminished acidity of the amine proton [pk_a(aniline) ≃ 25],[24] evolving differently as shown in Scheme III. Regarding the latter aspect, this could be explained as a function of the relative ease of kinetic enolization of alkoxides **9**, which would prevent or disfavor the cyclization under the conditions of kinetic control in which the reactions were carried out.

We have also investigated some reactions of several β-hydroxy-γ-iminoesters **5**, particularly the rearrangement to β-amino-γ-keto esters **7** or to β-benzoyl β-lactams **8** in different media and reaction conditions. The crossover experiments of some compounds **5**, such as **5d** and **5f**, derived from α,α-dialkylsubstituted esters with enolates **3a** and **3b**, have already been discussed. These experiments are examples of reactions of basic rearrangements which lead to compounds **7** or **8** depending upon the time and rection temperature. Compounds **5a-f** are remarkable for their readiness to undergo rearrangement under the influence of bases (LDA, enolates, etc.), acids, and thermally by either direct heating or under reflux in a variety of solvents.

Similar experiments with other compounds **5** derived from enolates **3c-e**, compounds **5i-o**, in different basic media such as LDA, ester enolates, alkoxides, etc., under different experimental conditions were fruitless; complex mixtures of products of undetermined nature and composition were obtained. Attempts towards the thermal rearrangement of some of these compounds failed too although in solvents such as dimethyl sulfoxide, partial transformations into aminoketo esters along with other uncharacterized products were obtained. However, the use of acidic catalysts such as benzoic acid and p-toluenesulfonic acid resulted in good yields of rearrangement products. The best results, quantitative in many cases, were obtained with silica gel as catalyst in

refluxing toluene. Thus, silica gel is an acidic reagent highly effective to carry out cleanly the isomerization of any α-hydroxy-γ-imino ester 5 into its corresponding β-amino-γ-keto ester 7 (procedure B, see Experimental Section).

The reaction of hydroxy-imino ester **5m(α)** with SiO_2 produced exclusively one diastereomer, **7m**, in almost quantitative yield. Starting with **5o(α)**, a 85:15 (measured by ^{1}H-NMR) mixture of isomers was obtained, from which the major isomer, **7o**, could be isolated in 70% yield. In this case, other experiments carried out at shorter reaction times indicate that the reaction is, as before, totally stereoselective but since the α-hydroxy-imine/α-aminoketone rearrangement is slower, partial epimerization of the major isomer in the reaction medium takes place. In a separate experiment the major isomer **7o**, subjected to the same reaction conditions, was transformed into the same 85:15 mixture of isomers. X-Ray difraction analysis of compound **7m** has established its relative stereochemistry as $2R^*3R^*$ (Figure 2). The fact that the reaction is totally

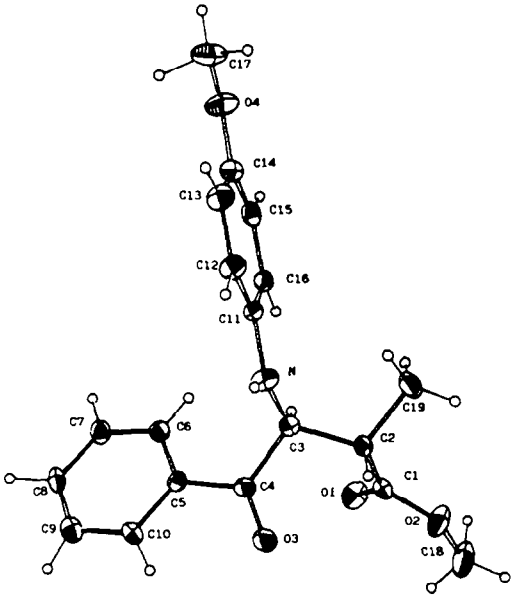
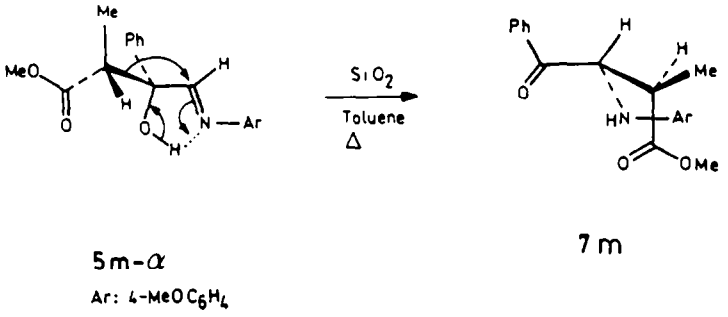


Figure 2. ORTEP drawing of compound **7m**.[26]

stereoselective suggests a cyclic intramolecular mechanism similar to the one proposed by Stevens and co-workers[8] for the thermal isomerization of α-hydroxy-imines to α-aminoketones, which requires a S-cis arrangement of the OH and C=N functionalities, as indicated in Scheme IV.

On the other hand, treatment of compound **7g** with LDA in THF produced β-lactam **8g** in excellent yield. This interesting β-lactam, potentially susceptible to undergo useful further transformations, could be obtained from anil **2a** through a three step sequence,



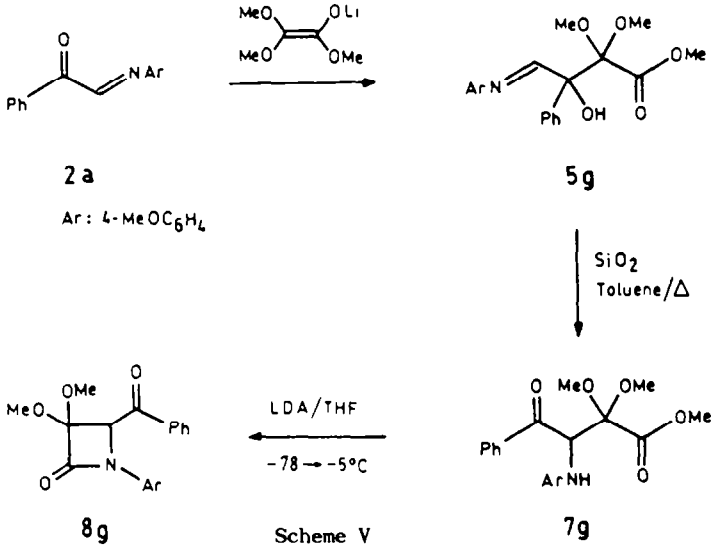
5m-α

Ar: 4-MeOC$_6$H$_4$

7m

Scheme IV

with the key step being the hydroxy-imino ester/aminoketo ester rearrangement catalyzed by SiO_2, in 50% overall yield in pure product (Scheme V).



2a

Ar: 4-MeOC$_6$H$_4$

5g

8g

Scheme V

7g

Experimental Section

Melting points were determined in open capillaries on a Büchi 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 VXR 300S (300 MHz), using tetramethylsilane as internal standard. ^{13}C-NMR spectra were recorded with a Varian FT-80 (20.15 MHz), or with a Varian VXR 300S (75.4 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 instrument. Elemental analyses were performed at the Instituto de Química Bio-Orgánica, C.S.I.C., Barcelona. Column chromatography was performed using Merck silica gel (70-230 mesh). Tetrahydrofuran (THF) was dried over sodium-benzophenone ketyl and freshly distilled before use. Diisopropyl-amine was distilled from calcium hydride and stored over molecular sieves (4Å). Standardized (1.6 M)

n-butyllithium in hexanes was obtained from Aldrich Chemical Co.. Esters were available through commercial sources and were distilled prior to use. All reactions requiring anhydrous conditions were performed under a positive pressure of nitrogen in oven-dried glassware.

The starting 2-arylamino-2-methoxy-1-phenylethanones were obtained by reaction of phenylglyoxal hydrate[26] with anilines in refluxing methanol as reported in Ref. 14.

Preparation of γ-amino-β-hydroxy-γ-methoxy esters, 4. Lithium diisopropylamide (11 mmol) was prepared from diisopropylamine (1.54 ml, 11 mmol) and n-butyllithium (6.87 ml, 1.6 M in hexanes) in dry THF (11 ml). To this solution cooled to -78°C was added the appropriate ester (11 mmol) in THF (3 ml) keeping the temperature below -70°C and the mixture was stirred for 15 min followed by the addition of 1 (5 mmol) in THF (12 ml). The resulting solution was stirred at -78°C for 5 min, diluted with 100 ml of diethyl ether and washed successively with water (2 x 20 ml) and brine (20 ml). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was used as such without further purification.

Preparation of β-hydroxy-γ-imino esters, 5: *Procedure A.* All operations were identical to the procedure outlined for 4 except that the resulting solution was stirred at -78°C for 5 min and allowed to warm to -35°C followed by stirring for the indicated period of time. The residue was purified by recrystallization or chromatography over silica gel (eluted with an appropriate ethyl acetate-hexanes mixture).

Procedure B. The crude product 4 (5 mmol) was disolved in 18 ml of commercial chloroform and heated under reflux for the indicated time period. The residue was purified by recrystallization or chromatography over silica gel (eluted with an appropriate ethyl acetate-hexanes mixture).

Procedure C was identical with procedure B except the mixture was stirred at room temperature.

Procedure D. All operations were identical with the procedure outlined for 4 except α-imino ketone 2 was used instead of N-(α-methoxyphenacyl)-aniline 1. The residue was purified by recrystallization.

Methyl 3-Hydroxy-2,2-dimethyl-4-(p-methoxyphenyl)imino-3-phenylbutanoate (5a). Proc. C: 2 h, 79%. White solid, m.p. 74-76°C (ethanol). IR (KBr): ν 3310 (OH), 1725 (C=O), 1630 (CH=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.22 [s, 6H, $(CH_3)_2C$], 3.65 (s, 3H, CO_2CH_3), 3.80 (s, 3H, Ar-OCH_3), 5.54 (s, 1H, OH), 6.87-7.55 (m, 9H, arom.), 8.70 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 176.9 ($\underline{C}O_2Me$), 163.5 (CH=N), 158.4, 141.9, 140.6, 127.7, 127.2, 126.4, 122.3, 114.2, 77.8 (C-OH), 55.4 (Ar-OCH_3), 51.8 (OCH_3 ester and $\underline{C}Me_2$), 21.8 (CH_3), 20.4 (CH_3). Analysis found: C 70.35, H 6.84, N 4.15%; $C_{20}H_{23}NO_4$ requires C 70.36, H 6.79, N 4.10%.

Methyl 3-Hydroxy-2,2-dimethyl-4-(p-methylphenyl)imino-3-phenylbutanoate (5b). Proc. A: 1 h 15 min, 60%. White solid, m.p. 53-55°C (ethanol). IR (KBr): ν 3360 (OH), 1730 (C=O), 1640 (CH=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.23 [s, 6H, $(CH_3)_2C$], 2.33 (s, 3H, Ar-CH_3), 3.63 (s, 3H, CO_2CH_3), 5.43 (s, 1H, OH), 7.00-7.60 (m, 9H, arom.), 8.67 (s, 1H, CH=N). Analysis found: C 73.90, H 7.09, N 4.31%; $C_{20}H_{23}NO_3$ requires C 73.82, H 7.12, N 4.30%.

Methyl 3-hydroxy-2,2-dimethyl-3-phenyl-4-phenyliminobutanoate (5c). Proc. A: 1 h 30 min, 60%. Proc. B: 5 h 30 min, 80%. White solid, m.p. 56-58°C (ethanol). IR (KBr): ν 3380 (OH), 1710 (C=O), 1645 (CH=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.27 (s, 6H, $(CH_3)_2C$), 3.67 (s, 3H, CO_2CH_3), 5.43 (s, 1H, OH), 7.10-7.60 (m, 10H, arom.), 8.70 (s, 1H, CH=N). Analysis found: C 73.35, H 6.75, N 4.46%; $C_{19}H_{21}NO_3$ requires C 73.29, H 6.80, N 4.50%.

Methyl 4-(p-Bromophenyl)imino-3-hydroxy-2,2-dimethyl-3-phenylbutanoate (5d). Proc. A: 1 h 45 min, 50%. Proc. B: 2 h, 73%. Proc. D: 75%. White solid, m.p. 73-74°C (ethanol). IR (KBr): ν 3360 (OH), 1725 (C=O), 1640 (CH=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.27 [s, 6H, $(CH_3)_2C$], 3.67 (s, 3H, CO_2CH_3), 5.30 (s, 1H, OH), 6.87-7.50 (m, 9H, arom.), 8.63 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 177.0 ($\underline{C}O_2Me$), 166.9 (CH=N), 148.5, 140.4, 132.2, 128.0, 127.7, 126.7, 122.8, 119.9, 78.3 (C-OH), 52.2 ($CO_2\underline{C}H_3$ y $\underline{C}Me_2$), 22.0 (CH_3), 20.7 (CH_3). Analysis found: C 58.50, H 5.30, N 3.45, Br 20.20%; $C_{19}H_{20}NO_3Br$ requires C 58.50, H 5.15, N 3.60, Br 20.45%.

Methyl 1-[1'-hydroxy-2'-(N-p-methoxyphenyl)imino-1'-phenyl]cyclohexanecarboxylate (5e). Proc. B: 10 min, 73%. White solid, m.p. 88-89°C (methanol). IR (KBr): ν 3360 (OH), 1710 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.00-2.20 (m, 10H, C_6H_{10}), 3.63 (s, 3H, CO_2CH_3), 3.81 (s, 3H, Ar-OCH_3), 5.54 (s, 1H, OH), 6.87-7.47 (m, 9H, arom.), 8.70 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 175.0 (C=O), 163.4 (CH=N), 158.5, 141.7, 140.7, 127.5, 127.2, 126.5, 122.4, 114.2, 77.4 (C-OH), 57.8 ($C_6H_{10}\underline{C}$), 55.4 (Ar-OCH_3), 51.4 (OCH_3 ester), 29.7, 27.5, 25.2, 23.4, 23.4 (5xCH_2). Analysis found: C 72.52, H 7.24, N 3.67%; $C_{23}H_{27}NO_4$ requires C 72.42, H 7.13, N 3.67%.

Methyl 1-[2'-(N-p-Bromophenyl)imino-1'-hydroxy-1'-phenyl]cyclohexanecarboxylate (5f). Proc. B: 30 min, 85%. White solid, m.p. 120-122°C (methanol). IR (KBr): ν 3350 (OH), 1710 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.09-2.12 (m, 10H, C_6H_{10}), 3.64 (s, 3H, CO_2CH_3), 5.30 (s, 1H, OH), 7.01-7.48 (m, 9H, arom.), 8.70 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 175.0 ($\underline{C}O_2Me$), 166.5 (CH=N), 148.0, 140.2, 132.1, 127.6, 127.4, 126.5, 122.7, 119.9, 77.6 (C-OH), 57.8 ($C_6H_{10}\underline{C}$), 51.4 (OCH_3), 29.7, 27.5, 25.2, 23.4, 23.3 (5xCH_2). Analysis found: C 61.36, H 5.55, N 3.30, Br 18.69%; $C_{22}H_{24}NO_3Br$ requires C 61.40, H 5.62, N 3.25, Br 18.57%.

Methyl 3-hydroxy-2,2-dimethoxy-4-(p-methoxyphenyl)imino-3-phenylbutanoate (5g). Proc. D: 66%. White solid, m.p. 98-100°C (ethyl acetate/hexane). IR (KBr): ν 3330 (OH), 1725 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.13 (s, 3H, OCH_3), 3.41 (s, 3H, OCH_3), 3.68 (s, 3H, OCH_3 ester), 3.79 (Ar-OCH_3), 5.61 (s 1H, OH), 6.85-7.83 (m, 9H, arom.), 8.50 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 168.0 (C=O), 161.6 (CH=N), 158.4, 141.6, 139.1, 128.0, 127.7, 126.9, 122.4, 114.1, 105.4 [$(MeO)_2\underline{C}$], 78.7 (C-OH), 55.4 (Ar-OCH_3), 52.5, 52.4 and 52.3 (OCH_3 ester and 2xOCH_3). Analysis found: C 64.25, H 6.23, N 3.72%; $C_{20}H_{23}NO_6$ requires C 64.33, H 6.21, N 3.75%.

Methyl 4-(p-Bromophenyl)imino-3-hydroxy-2,2-dimethoxy-3-phenylbutanoate (5h). Proc. D: 75%. White solid, m.p. 132-134°C (ethyl acetate/hexane). IR (KBr): ν 3340 (OH), 1725 (C=O), 1645 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.11 (s, 3H, OCH_3), 3.42 (s, 3H, OCH_3), 3.71 (s, 3H, CO_2CH_3), 5.38 (s, 1H, OH), 6.95-7.82 (m, 9H, arom.), 8.50 (s, 1H, CH=N). ^{13}C-RMN ($CDCl_3$): δ 168.0 (C=O), 164.5 (CH=N), 147.9, 138.5, 132.0, 128.1, 127.9, 126.9, 122.7, 119.8, 105.3 [$(MeO)_2\underline{C}$], 78.9 (C-OH), 52.6, 52.4, and 52.3 (OCH_3 ester and 2xOCH_3). MS m/z (%): 423 (M+2, <1), 421 (M^+, <1), 208 (13), 184 (8), 182 (7), 176 (5), 157 (4), 155 (4), 133 (100), 105 (17), 77 (8), 75 (5), 59 (7). Analysis found: C 54.24, H 4.78, N 3.31, Br 18.93%; $C_{19}H_{20}NO_6Br$ requires C 54.04, H 4.77, N 3.32, Br 18.92%.

Methyl 3-hydroxy-4-(p-methoxyphenyl)imino-3-phenylbutanoate (5i). Proc. B: 1 h, 85%. White solid, m.p. 81-83°C (ethyl acetate/hexane). IR (KBr): ν 3490 (OH), 1700 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.99 and 3.28 (dd, 2H, J = 16 Hz, CH_2), 3.67 (s, 3H, CO_2CH_3), 3.77 (s, 3H, Ar-OCH_3), 5.40 (broad s, 1H, OH), 6.57-7.70 (m, 9H, arom.), 7.97 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 171.9 (C=O), 162.7 (CH=N), 158.3, 142.2, 141.4, 128.4, 127.4, 125.0, 122.0, 114.0, 75.6 (C-OH), 55.1 (Ar-$O\underline{C}H_3$), 51.5 (OCH_3 ester), 44.0 (CH_2). Analysis found: C 69.15, H 6.79, N 4.23%; $C_{18}H_{19}NO_4$ requires C 68.99, H 6.11, N 4.47%.

Methyl 3-hydroxy-4-(p-methylphenyl)imino-3-phenylbutanoate (5j). Proc. B: 1 h 15 min, 83%. White solid, m.p. 71-73°C (ethyl acetate/hexane). IR (KBr): ν 3460 (OH), 1695 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.30 (s, 3H, Ar-CH_3), 2.95 and 3.29 (dd, 2H, J = 16 Hz, CH_2), 3.67 (s, 3H, CO_2CH_3), 5.37 (broad s, 1H, OH), 6.77-7.77 (m, 9H, arom.), 7.93 (s, 1H, CH=N). Analysis found: C 72.83, H 7.24, N 4.35%; $C_{18}H_{19}NO_3$ requires C 72.71, H 6.44, N 4.71%.

Methyl 3-hydroxy-3-phenyl-4-phenyliminobutanoate (5k). Proc. B: 2 h, 80%. White solid, m.p. 84-85°C (ethyl acetate/hexane). IR (KBr): ν 3480 (OH), 1700 (C=O), 1635 (CH=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.98 and 3.32 (dd, 2H, J = 16 Hz, CH_2), 3.67 (s, 3H, CO_2CH_3), 5.33 (s, 1H, OH), 6.90-7.67 (m, 10H, arom.), 7.93 (s, 1H, CH=N). Analysis found: C 72.13, H 6.00, N 4.90%; $C_{17}H_{17}NO_3$ requires C 72.07, H 6.05, N 4.94%.

Methyl 4-(p-Bromophenyl)imino-3-hydroxy-3-phenylbutanoate (5l). Proc. B: 4 h, 81%. White solid, m.p. 79-80°C (ethyl acetate/hexane). IR (KBr): ν 3480 (OH), 1690 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.98 and 3.32 (dd, 2H, J = 16 Hz, CH_2), 3.67 (s, 3H, CO_2CH_3), 5.27

(s, 1H, OH), 6.73-7.63 (m, 9H, arom.), 7.93 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 172.0 (CO_2Me), 165.7 (CH=N), 148.6, 140.8, 131.8, 128.4, 127.6, 125.0, 122.3, 119.4, 75.7 (C-OH), 51.6 (OCH_3), 43.7 (CH_2). Analysis found: C 56.22, H 4.33, N 3.81, Br 22.00%; $C_{17}H_{16}NO_3Br$ requires C 56.37, H 4.45, N 3.87, Br 22.56%.

Methyl 3-hydroxy-4-(p-methoxyphenyl)imino-2-methyl-3-phenylbutanoate (**5m**). Proc. B: 2 h. Chromatography of crude product (hexane:ethyl acetate, 8:2) gave, in sequence, the major isomer in 40% yield and the minor isomer in 12% yield.

Major isomer ($2R^*,3R^*$). White solid, m.p. 73-75°C (methanol). IR (KBr): ν 3480 (OH), 1700 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.06 (d, 3H, J = 7 Hz, CH_3), 3.37 (q, 1H, J = 7 Hz, CH), 3.67 (s, 3H, CO_2CH_3), 3.79 (s, 3H, Ar-OCH_3), 5.20 (s, 1H, OH), 6.84-7.54 (m, 9H, arom.), 8.09 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 176.1 (C=O), 163.8 (CH=N), 158.3, 142.4, 140.1, 128.4, 127.4, 125.6, 122.1, 114.2, 78.2 (C-OH), 55.4 (Ar-OCH_3), 51.7 (OCH_3 ester), 47.1 (CH), 11.3 (CH_3). Analysis found: C 69.44, H 6.69, N 4.13%; $C_{19}H_{21}NO_4$ requires C 69.71, H 6.47, N 4.28%.

Minor isomer ($2S^*,3R^*$). Colourless oil. IR (CCl_4): ν 3480 (OH), 1730 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.28 (d, 3H, J = 7 Hz, CH_3), 3.40 (q, 1H, J = 7 Hz, CH), 3.47 (s, 3H, CO_2CH_3), 3.77 (s, 3H, Ar-OCH_3), 5.06 (s, 1H, OH), 6.73-7.70 (m, 9H, arom.), 8.13 (s, 1H, CH=N). Analysis found: C 69.52, H 6.60, N 4.25%; $C_{19}H_{21}NO_4$ requires C 69.71, H 6.47, N 4.28%.

Methyl 3-hydroxy-2-methyl-3-phenyl-4-phenyliminobutanoate (**5n**). Proc. B: 6 h. Chromatography of crude product (hexane:ethyl acetate, 8:2) gave, in sequence, the major isomer in 50% yield and the minor isomer in 18% yield.

Major isomer ($2R^*,3R^*$). White solid, m.p. 92-94°C (ethyl acetate/hexane). IR (KBr): ν 3460 (OH), 1695 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.07 (d, 3H, J = 7 Hz, CH_3), 3.40 (q, 1H, J = 7 Hz, CH), 3.70 (s, 3H, CO_2CH_3), 5.13 (s, 1H, OH), 6.87-7.67 (m, 10H, arom.), 8.03 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 175.8 (C=O), 166.0 (CH=N), 149.5, 139.6, 128.7, 128.2, 127.2, 125.9, 125.4, 120.5, 78.1 (C-OH), 51.4 (OCH_3), 46.7 (CH), 11.0 (CH_3). Analysis found: C 72.72, H 6.35, N 4.58%; $C_{18}H_{19}NO_3$ requires C 72.71, H 6.44, N 4.71%.

Minor isomer ($2S^*,3R^*$). White solid, m.p. 68-70°C (ethyl acetate/hexane). IR (KBr): ν 3330 (OH), 1730 and 1720 (C=O), 1640 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.30 (d, 3H, J = 7 Hz, CH_3), 3.43 (q, 1H, J = 7 Hz, CH), 3.50 (s, 3H, CO_2CH_3), 4.97 (s, 1H, OH), 6.93-7.67 (m, 10H, arom.), 8.10 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 174.6 (C=O), 164.6 (CH=N), 149.5, 141.6, 129.0, 128.3, 127.5, 126.3, 125.7, 120.7, 77.7 (C-OH), 51.6 (OCH_3), 48.1 (CH), 12.5 (CH_3). Analysis found: C 72.66, H 6.65, N 4.47%; $C_{18}H_{19}NO_3$ requires C 72.71, H 6.44, N 4.71%.

Methyl 4-(p-Bromophenyl)imino-3-hydroxy-2-methyl-3-phenylbutanoate (**5o**). Proc. B: 8 h. Chromatography of crude product (hexane:ethyl acetate, 8:2) gave, in sequence, the major isomer in 40% yield and an analytical sample of pure minor isomer.

Major isomer ($2R^*,3R^*$). White solid, m.p. 91-92°C (ethanol). IR (KBr): ν 3470 (OH), 1700 (C=O), 1645 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.07 (d, 3H, J = 7 Hz, CH_3), 3.40 (q, 1H, J = 7 Hz, CH), 3.70 (s, 3H, CO_2CH_3), 5.10 (s, 1H, OH), 6.73-7.67 (m, 9H, arom.), 7.97 (s, 1H, CH=N). ^{13}C-NMR ($CDCl_3$): δ 176.0 (C=O), 166.8 (CH=N), 148.6, 139.3, 131.8, 128.4, 127.4, 125.4, 122.3, 119.4, 78.2 (C-OH), 51.6 (OCH_3), 46.7 (CH), 11.1 (CH_3). MS m/z (%): 377 (M+2, <3), 375 (M^+, <3), 216 (4), 214 (4), 193 (42), 184 (13), 182 (13), 161 (16), 157 (12), 155 (12), 105 (100), 88 (33), 77 (54), 51 (13). Analysis found: C 57.55, H 4.76, N 3.71, Br 21.04%; $C_{18}H_{18}NO_3Br$ requires C 57.46, H 4.82, N 3.72, Br 21.24%.

Minor isomer ($2S^*,3R^*$). Colourless oil. IR ($CHCl_3$): ν 3430 (OH), 1730 (C=O), 1645 (C=N) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.30 (d, 3H, J = 7 Hz, CH_3), 3.43 (q, 1H, J = 7 Hz, CH), 3.50 (s, 3H, CO_2CH_3), 4.80 (broad s, 1H, OH), 6.80-7.60 (m, 9H, arom.), 8.03 (s, 1H, CH=N). Analysis found: C 57.33, H 4.72, N 3.67%; $C_{18}H_{18}NO_3Br$ requires C 57.46, H 4.82, N 3.72, Br 21.24%.

Preparation of β-amino-γ-keto esters, 7: *Procedure* A. All operations were identical with the procedure outlined for 4 except that the resulting solution was stirred at -78°C for 5 min and allowed to warm to -15°C followed by stirring for the indicated period of time. The residue was purified by recrystallization or chromatography over silica gel

(eluted with an appropriate ethyl acetate-hexanes mixture).

Procedure B. A solution of β-hydroxy-γ-imino ester **5** (1 mmol) in toluene (20 ml) with silica gel (100% w/w) was heated under reflux for the indicated time period. The silica gel was filtered off, washed with diethyl ether and the combined organic layers were removed *in vacuo*. The residue was purified by recrystallization or chromatography over silica gel (eluted with an appropriate ethyl acetate-hexanes mixture).

Methyl 3-(p-methoxyphenyl)amino-2,2-dimethyl-4-oxo-4-phenylbutanoate (**7a**). Proc. A: 4 h, 72%. Proc. B: 30 min, 100%. Yellow oil. IR (net): ν 3380 (NH), 1730 (C=O ester), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.20 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.53 (s, 3H, CO_2CH_3), 3.68 (s, 3H, Ar-OCH_3), 4.47 (s, 1H, NH), 5.20 (s, 1H, CH), 6.70 (s, 4H, C_6H_4), 7.10-7.92 (m, 5H, C_6H_5). Analysis found: C 70.08, H 6.65, N 4.20%; $C_{20}H_{23}NO_4$ requires C 70.36, H 6.79, N 4.10%.

Methyl 2,2-dimethyl-3-(p-methylphenyl)amino-4-oxo-4-phenylbutanoate (**7b**). Proc. A: 4 h, 72%. Colourless solid, m.p. 84-86°C (ethanol). IR (KBr): ν 3350 (NH), 1710 (C=O ester), 1670 (PHC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.12 (s, 3H, CH_3), 1.22 (s, 3H, CH_3), 2.13 (s, 3H, Ar-CH_3), 3.46 (s, 3H, CO_2CH_3), 4.56 (d, 1H, J = 10 Hz, NH), 5.17 (d, 1H, J = 10 Hz, CH), 6.61-7.83 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 200.0 (Ph<u>C</u>=O), 176.6 (C=O ester), 144.8, 137.0, 133.2, 129.7, 128.5, 128.2, 127.8, 114.2, 63.1 (CHN), 51.8 (OCH_3), 46.3 (<u>C</u>Me_2), 22.6 (CH_3), 22.1 (CH_3). Analysis found: C 73.70, H 7.25, N 4.20%; $C_{20}H_{23}NO_3$ requires C 73.82, H 7.12, N 4.30%.

Methyl 2,2-dimethyl-4-oxo-4-phenyl-3-phenylaminobutanoate (**7c**). Proc. A: 4 h, 70%. Colourless solid, m.p. 78-79°C (ethanol). IR (KBr): ν 3400 (NH), 1730 (C=O ester), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.23 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.57 (s, 3H, CO_2CH_3), 4.73 (d, 1H, J = 10 Hz, NH), 5.27 (d, 1H, J = 10 Hz, CH), 6.67-7.97 (m, 10H, arom.). Analysis found: C 73.21, H 6.89, N 4.52%; $C_{19}H_{21}NO_3$ requires C 73.29, H 6.80, N 4.50%.

Methyl 3-(p-Bromophenyl)amino-2,2-dimethyl-4-oxo-4-phenylbutanoate (**7d**). Proc. A: 1 h 45 min, 70%. Proc. B: 30 min, 100%. Colourless solid, m.p. 81-82°C (ethanol). IR (KBr): ν 3360 (NH), 1725 (C=O ester), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.23 (s, 3H, CH_3), 1.33 (s, 3H, CH_3), 3.57 (s, 3H, CO_2CH_3), 4.77 (d, 1H, J = 10 Hz, NH), 5.23 (d, 1H, J = 10 Hz, CH), 6.50-7.97 (m, 9H, arom.). Analysis found: C 58.59, H 5.01, N 3.73 Br 20.26%; $C_{19}H_{20}NO_3Br$ requires C 58.50, H 5.15, N 3.60 Br 20.45%.

Methyl 1-[1'-(p-methoxyphenyl)amino-2'-oxo-2'-phenyl]cyclohexanecarboxylate (**7e**). Proc. B: 20 min, 100%. Yellow crystals, m.p. 120-122°C (ethanol). IR (KBr): ν 3370 (NH), 1720 (C=O ester), 1675 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.25-2.20 (m, 10H, 5xCH_2) 3.41 and 3.70 (s and s, 6H, CO_2CH_3 and Ar-OCH_3), 4.58 (d, 1H, J = 10 Hz, NH), 5.02 (d, 1H, J = 10 Hz, CH), 6.72 (s, 4H, p-MeO-C_6<u>H_4</u>), 7.44-7.88 (m, 5H, arom.). ^{13}C-NMR ($CDCl_3$): δ 200.8 (Ph<u>C</u>O), 174.8 (C=O ester), 152.8, 141.5, 137.4, 133.3, 128.5, 128.2, 115.9, 114.7, 65.1 (CHN), 55.5 (Ar-OCH_3), 52.0 and 51.5 (OCH_3 ester and C_6H_{10}<u>C</u>), 31.1, 30.7, 25.3, 23.2, 23.0 (5xCH_2). Analysis found: C 72.44, H 7.14, N 3.89%; $C_{23}H_{27}NO_4$ requires C 72.42, H 7.13, N 3.67%.

Methyl 1-[1'-(p-Bromophenyl)amino-2'-oxo-2'-phenyl]cyclohexanecarboxylate (**7f**). Proc. B: 20 min, 100%. White crystals, m.p. 140-142°C (ethanol). IR (KBr): ν 3370 (NH), 1715 (C=O, ester), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.11-2.15 (m, 10H, 5xCH_2) 3.42 (s, 3H, CO_2CH_3), 4.90 (d, 1H, J = 10 Hz, NH), 5.08 (d, 1H, J = 10 Hz, CH), 6.60-7.90 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 199.7 (Ph<u>C</u>O), 174.7 (C=O ester), 146.3, 137.0, 133.6, 131.9, 128.6, 128.2, 115.4, 109.9, 63.4 (CHN), 51.9 and 51.6 (OCH_3 and C_6H_{10}<u>C</u>), 31.3, 30.9, 25.2, 23.1, 22.9 (5xCH_2). Analysis found: C 61.27, H 5.62, N 3.20, Br 18.28%; $C_{22}H_{24}NO_3Br$ requires C 61.40, H 5.62, N 3.25, Br 18.57%.

Methyl 2,2-dimethoxy-3-(p-methoxyphenyl)amino-4-oxo-4-phenylbutanoate (**7g**). Proc. B: 30 min, 92%. Colourless solid, m.p. 95-97°C (methanol). IR (KBr): ν 3370 (NH), 1745 (C=O ester), 1685 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.33 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.68 (s, 3H, Ar-OCH_3), 3.80 (s, 3H, CO_2CH_3), 4.66 (d, 1H, J = 10 Hz, NH), 5.44 (d, 1H, J = 10 Hz, CH), 6.59-8.07 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 198.9 (Ph<u>C</u>O), 167.8 (C=O ester), 152.9, 140.2, 137.1, 133.2, 128.8, 128.3, 115.7, 114.6, 102.3 [$(MeO)_2$<u>C</u>], 62.2 (CHN), 55.4

($Ar-OCH_3$), 52.7, 51.3 and 51.1 ($2xOCH_3$ and CO_2CH_3). Analysis found: C 64.32, H 6.20, N 3.74%; $C_{20}H_{23}NO_6$ requires C 64.33, H 6.21, N 3.75%.

Methyl 3-(p-Bromophenyl)amino-2,2-dimethoxy-4-oxo-4-phenylbutanoate (7h). Proc. B: 30 min, 100%. Colourless solid, m.p. 136-137°C (ethanol). IR (KBr): υ 3340 (NH), 1755 (C=O ester), 1690 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.34 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 3.79 (s, 3H, CO_2CH_3), 4.93 (d, 1H, J = 10 Hz, NH), 5.47 (d, 1H, J = 10 Hz, CH), 6.50 (d, 2H, J = 9 Hz, arom.), 7.18 (d, 2H, J = 9 Hz, arom.), 7.46-7.64 (m, 3H, arom.), 8.05 (d, 2H, J = 9 Hz, arom.). ^{13}C-NMR ($CDCl_3$): δ 198.1 (PhCO), 167.7 (C=O ester), 145.2, 136.8, 133.5, 131.9, 128.8, 128.4, 115.5, 110.4, 102.0 [$C(OMe)_2$], 60.8 (CHN), 52.8, 51.4 and 51.1 ($2xOCH_3$ and CO_2CH_3). MS m/z (%): 423 (M+2, 3), 421 (M^+, 3), 305 (4), 303 (4), 290 (3), 288 (3), 286 (3), 284 (3), 254 (4), 252 (4), 226 (3), 224 (3), 184 (5), 182 (6), 157 (3), 155 (3), 133 (100), 105 (18), 77 (11), 75 (8). Analysis found: C 53.56, H 4.71, N 3.59, Br 18.31%; $C_{19}H_{20}NO_6Br$ requires C 54.04, H 4.77, N 3.32, Br 18.92%.

Methyl 3-(p-methoxyphenyl)amino-4-oxo-4-phenylbutanoate (7i). Proc. B: 2 h 30 min, 66%. Yellow oil. IR (CCl_4): υ 3360 (NH), 1730 (C=O ester), 1685 (PhC=O). ^{1}H-NMR ($CDCl_3$): δ 2.70-2.83 (m, 2H, CH_2), 3.60 and 3.67 (s and s, 6H, $Ar-OCH_3$ and CO_2CH_3), 4.13 (broad s, 1H, NH), 5.30 (t, 1H, J = 6 Hz, CH), 6.67 (s, 4H, C_6H_4), 7.20-7.97 (m, 5H, C_6H_5). ^{13}C-NMR ($CDCl_3$): δ 198.6 (PhCO), 171.2 (C=O ester), 152.8, 140.1, 134.6, 133.3, 128.5, 128.3, 115.7, 114.6, 56.2 (CHN), 55.3 ($Ar-OCH_3$), 51.6 (CO_2CH_3), 36.8 (CH_2). Analysis found: C 68.88, H 6.13, N 4.46%; $C_{18}H_{19}NO_4$ requires C 68.99, H 6.11, N 4.47%.

Methyl 3-(p-Bromophenyl)amino-4-oxo-4-phenylbutanoate (7l). Proc. B: 2 h 30 min, 55%. Colourless oil. IR (CCl_4): υ 3360 (NH), 1730 (C=O ester), 1685 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 2.71, 2.90 (dd, dd, 2H, J = 6.6 Hz, J = 5.4 Hz, J = 15.9 Hz, CH_2), 3.65 (s, 3H, CO_2CH_3), 4.60 (broad s, 1H, NH), 5.38 (t, 1H, J = 6 Hz, CH), 6.62-8.00 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 198.0 (PhCO), 171.1 (C=O ester), 145.1, 134.0, 133.8, 132.1, 128.8, 128.5, 115.6, 110.5, 55.0 (CHN), 52.0 (OCH_3), 37.1 (CH_2). Analysis found: C 56.20, H 4.34, N 3.93, Br 22.69%; $C_{17}H_{16}NO_3Br$ requires C 56.37, H 4.45, N 3.87, Br 22.56%.

(2R,3R*)-3-(p-methoxyphenyl)amino-2-methyl-4-oxo-4-phenylbutanoate (7m)*. Proc. B: 1 h 10 min [from the major isomer **5m(α)**], 93%. Yellow solid, m.p. 115-117°C (methanol). IR (KBr): υ 3400 (NH), 1720 (C=O ester), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.13 (d, 3H, J = 7 Hz, CH_3), 2.98-3.06 (m, 1H, CH-CH_3), 3.70 and 3.71 (s and s, 6H, CO_2CH_3 and $Ar-OCH_3$), 4.32 (broad s, 1H, NH), 5.42 (m, 1H, CH-NH), 6.74 (s, 4H, arom.), 7.44-8.01 (m, 5H, arom.). Upon addition of D_2O, a doblet was observed (J = 4 Hz) at 5.42 ppm. ^{13}C-NMR ($CDCl_3$): δ 199.1 (PhCO), 174.1 (C=O ester), 153.1, 141.1, 134.8, 133.7, 128.9, 128.5, 116.5, 114.8, 61.8 (CHN), 55.6 ($Ar-OCH_3$), 52.2 (CO_2CH_3), 42.0 (CH-CO_2Me), 10.9 (CH_3). Analysis found: C 69.91, H 6.50, N 4.26%; $C_{19}H_{21}NO_4$ requires C 69.71, H 6.47, N 4.28%.

Methyl 3-(p-Bromophenyl)amino-2-methyl-4-oxo-4-phenylbutanoate (7o). Proc. B: 2 h 5 min [from the major isomer **5o(α)**]. Complete conversion of the starting material to yield two diastereoisomers (85:15) was observed by ^{1}H-NMR of the crude product. Major isomer (2R*,3R*) was isolated upon crystallization from methanol. Yield: 70%. Colourless solid, m.p. 109-111°C. IR (KBr): υ 3380 (NH), 1720 (C=O ester), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.12 (d, 3H, J = 7 Hz, CH_3), 3.03-3.10 (m, 1H, CH-CH_3), 3.69 (s, 3H, CO_2CH_3), 4.59 (d, 1H, J = 10 Hz, NH), 5.47-5.52 (dd, 1H, J = 10 Hz, J = 4 Hz, CH-NH), 6.65-8.02 (m, 9H, arom.). Upon irradiation the signal at 1.12 ppm, the multiplet at 3.03-3.10 ppm colapsed to a dd (J = 4 Hz). ^{13}C-NMR ($CDCl_3$): δ 198.0 (PhCO), 173.8 (C=O ester), 145.9, 134.3, 133.9, 132.0, 128.9, 128.4, 115.9, 110.4, 59.9 (CHN), 52.2 (OCH_3), 41.9 (CH-CO_2Me), 10.7 (CH_3). Analysis found: C 57.37, H 4.79, N 3.75, Br 21.35%; $C_{18}H_{18}NO_3Br$ requires C 57.46, H 4.82, N 3.72, Br 21.24%.

Preparation of β-benzoyl β-lactams, 8. *Procedure A.* All operations were identical with the procedure outlined for **4** except that the resulting solution was stirred at -78°C for 5 min and allowed to warm to room temperature followed by stirring for the indicated period of time. The residue was purified by recrystallization or chromatography over silica gel (eluted with an appropriate ethyl acetate-hexanes mixture).

Procedure B. To a stirred solution of lithium diisopropylamide (1.2 mmol) in THF (1.5 ml) at -78°C, a solution of 5 (1 mmol) in THF (3 ml) was added dropwise. The cold bath was removed and the mixture was allowed to warm to room temperature followed by stirring for

the indicated period of time. After work-up as before the residue was purified by recrystallization or chromatography over silica gel (eluted with an appropriate ethyl acetate-hexanes mixture).

Procedure C. To a stirred solution of lithium diisopropylamide (2.2 mmol) in THF (2.5 ml) at -78°C, a solution of 7 (1 mmol) in THF (3 ml) was added dropwise. The cold bath was removed and the mixture was allowed to warm to -5°C followed by stirring for the indicated time period. After work-up as before the residue was purified by recrystallization or chromatography over silica gel (eluted with an appropriate ethyl acetate-hexanes mixture).

4-Benzoyl-1-(p-methoxy)phenyl-3,3-dimethyl-2-azetidinone (**8a**). Proc. A: 5 h, 60%. Proc. B: 5 h, 88%. White crystals, m.p. 104-106°C (ethyl acetate/hexane). IR (KBr): ν 1740 (C=O lactam), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.08 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 3.76 (s, 3H, OCH_3), 5.21 (s, 1H, CHN), 6.81-7.98 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 193.7 (Ph$\underline{C}$O), 168.6 (N-$\underline{C}$O), 156.0, 135.3, 134.1, 131.2, 129.0, 127.9, 118.3, 114.2, 66.4 (CHN), 55.4 and 55.2 ($Me_2\underline{C}$ and $O\underline{C}H_3$), 22.0 (CH_3), 17.3 (CH_3). Analysis found: C 73.79, H 6.15, N 4.54%; $C_{19}H_{19}NO_3$ requires C 73.77, H 6.19, N 4.53%.

4-Benzoyl-3,3-dimethyl-1-(p-methyl)phenyl-2-azetidinone (**8b**). Proc. A: 4 h 30 min, 62%. White crystals, m.p. 132-134°C (ethanol). IR (KBr): ν 1750 (C=O lactam), 1685 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.07 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 2.28 (s, 3H, Ar-CH_3), 5.23 (s, 1H, CHN), 7.05-7.97 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 193.6 (Ph$\underline{C}$O), 168.8 (N-$\underline{C}$O), 135.2, 135.1, 134.1, 133.4, 129.3, 129.0, 127.8, 116.8, 66.1 and 66.0 (CHN and Ar-$\underline{C}H_3$), 55.0 ($Me_2\underline{C}$), 21.9 (CH_3), 17.2 (CH_3). Analysis found: C 77.60, H 6.80, N 4.70%; $C_{19}H_{19}NO_2$ requires C 77.80, H 6.55, N 4.75%.

4-Benzoyl-3,3-dimethyl-1-phenyl-2-azetidinone (**8c**). Proc. A: 4 h, 70%. White crystals, m.p. 124-125°C (methanol). IR (KBr): ν 1755 (C=O lactam), 1690 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.08 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 5.25 (s, 1H, CHN), 7.00-7.98 (m, 10H, arom.). ^{13}C-NMR ($CDCl_3$): δ 193.5 (Ph$\underline{C}$O), 169.0 (N-$\underline{C}$O), 137.6, 135.2, 134.2, 129.0, 128.8, 127.8, 123.8, 116.8, 66.0 (CHN), 55.1 ($Me_2\underline{C}$), 21.9 (CH_3), 17.2 (CH_3). Analysis found: C 76.70, H 6.35, N 4.90%; $C_{18}H_{17}NO_2$ requires C 77.40, H 6.15, N 5.00%.

4-Benzoyl-1-(p-bromo)phenyl-3,3-dimethyl-2-azetidinone (**8d**). Proc. A: 45 min, 70%. Proc. B: 1 h, 60%. White crystals, m.p. 146-148°C (ethanol). IR (KBr): ν 1760 (C=O lactam), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.08 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 5.22 (s, 1H, CHN), 7.15-7.97 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 193.2 (Ph$\underline{C}$O), 168.9 (N-$\underline{C}$O), 136.6, 134.9, 134.2, 131.7, 129.0, 127.7, 118.4, 116.3, 66.2 (CHN), 55.4 ($\underline{C}Me_2$), 21.8 (CH_3), 17.2 (CH_3). Analysis found: C 60.40, H 4.45, N 3.90, Br 22.10%; $C_{18}H_{16}NO_2Br$ requires C 60.35, H 4.50, N 3.90, Br 22.30%.

3-Benzoyl-2-(p-methoxy)phenyl-1-oxo-2-azaspiro[3.5]nonane (**8e**). Proc. A: 4 h, 86%. White solid, m.p. 118-120°C (ethyl acetate/hexane). IR (KBr): ν 1735 (C=O lactam), 1685 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.10-2.35 (m, 10H, 5xCH_2), 3.75 (s, 3H, OCH_3), 5.15 (s, 1H, CHN), 6.80-8.00 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 193.8 (Ph$\underline{C}$O), 168.7 (N-$\underline{C}$O), 155.9, 135.6, 134.0, 131.3, 129.0, 128.0, 118.0, 114.2, 65.3 (CHN), 60.2 ($C_2H_6\underline{C}$), 55.4 (OCH_3), 33.2, 27.8, 25.1, 23.3, 22.9 (5xCH_2). Analysis found: C 75.67, H 6.66, N 4.10%; $C_{22}H_{23}NO_3$ requires C 75.62, H 6.63, N 4.01%.

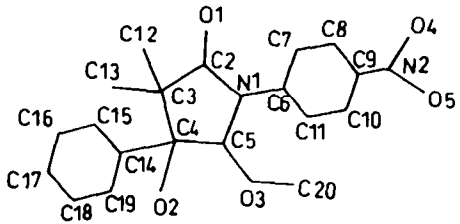
3-Benzoyl-2-(p-bromo)phenyl-1-oxo-2-azaspiro[3.5]nonane (**8f**). Proc. A: 2 h, 74%. Proc. B: 4 h, 70%. White solid, m.p. 139-141°C (methanol). IR (KBr): ν 1745 (C=O lactam), 1680 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 1.20-2.35 (m, 10H, 5xCH_2), 5.16 (s, 1H, CHN), 7.12-8.00 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 193.2 (Ph$\underline{C}$O), 169.1 (N-$\underline{C}$O), 136.6, 135.3, 134.3, 131.9, 129.1, 128.0, 118.3, 116.3, 65.3 (CHN), 60.5 ($C_5H_{10}\underline{C}$), 33.1, 27.8, 25.1, 23.3, 22.8 (5xCH_2). Analysis found: C 63.50, H 4.97, N 3.56, Br 20.14%; $C_{21}H_{20}NO_2Br$ requires C 63.33, H 5.06, N 3.52, Br 20.06%.

4-Benzoyl-3,3-dimethoxy-1-(p-methoxy)phenyl-2-azetidinone (**8g**). Proc. C: 50 min, 82%. White crystals, m.p. 93-95°C (ethyl acetate/hexane). IR (KBr): ν 1755 (C=O lactam), 1690 (PhC=O) cm^{-1}. ^{1}H-NMR ($CDCl_3$): δ 3.49, 3.65, and 3.77 (s, s, and s, 9H, 2xOCH_3 and Ar-OCH_3), 5.49 (s, 1H, CHN), 6.83-8.04 (m, 9H, arom.). ^{13}C-NMR ($CDCl_3$): δ 191.7 (Ph$\underline{C}$O), 161.5 (N-$\underline{C}$O), 156.8, 135.5, 134.0, 130.3, 128.9, 128.4, 119.0, 114.4, 109.8 [$(MeO)_2\underline{C}$],

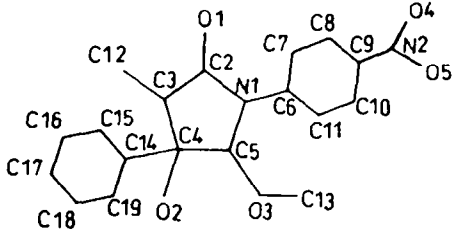
Table 1. Crystal and Refinement Data for Compounds **6a**, **6b**, and **7a**.

Compound	**6a**	**6b**	**7a**
Formula	$C_{19}H_{20}N_2O_5$	$C_{18}H_{18}N_2O_5$	$C_{19}H_{21}NO_4$
Crystal system	monoclinic	orthorhombic	monoclinic
Space group	$P2_1/n$	$Pna2_1$	$P2_1/n$
a, Å	8.012 (1)	11.323 (6)	11.981 (2)
b, Å	20.978 (7)	18.552 (2)	9.456 (4)
c, Å	10.353 (6)	8.228 (5)	15.514 (2)
β	95.50 (3)		91.50 (1)
V, Å^3	1732 (1)	1728 (1)	1757.0 (8)
Z	4	4	4
F (000)	752	720	696
ρ(calcd), g cm^{-3}	1.37	1.32	1.24
Temp, °C	21	21	21
μ, cm^{-1}	0.93	0.91	0.81
Cryst dimens, mm	0.2 x 0.3 x 0.4	0.3 x 0.2 x 0.3	0.2 x 0.2 x 0.3
Diffractometer		Enraf-Nonius CAD4	
Radiation		Graphite-monochromated Mo Kα (λ=0.71069 Å)	
Scan technique		$\Omega/2\theta$	
Data collected	(-10,0,0) to (10,26,13)	(0,0,0) to (16,27,13)	(-15,0,0) to (15,12,19)
Unique data	3761	3173	3819
Observed data	2405 (I) $\geq 2\sigma$ (I)	1083 (I) $\geq 3\sigma$ (I)	1179 (I) $\geq 1\sigma$ (I)
Std rflns	3 rflns	3 rflns	3 rflns
Solution mode		Multan 80, X-Ray 76 System	
Refinement mode		Least-squares on F s, observed reflections	
R_F, %	3.9	4.1	5.5
Rw_F, %	3.6	3.9	5.6
Average shift/error	0.001	0.03	0.01
Maximun shift/error	0.003	0.13	0.09
Atomic factors		International Tables for X-ray Crystallography	

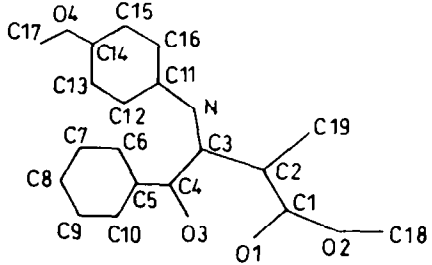
Table 2. Selected Bond Lengths (Å) and Angles (°) for Compounds 6a, 6b and 7a.



6a ($C_{19}H_{20}N_2O_5$)



6b ($C_{18}H_{18}N_2O_5$)



7a ($C_{19}H_{21}NO_4$)

Bond Lengths		Angles		Bond Lengths		Angles		Bond Lengths		Angles	
N1-C2	1.456 (3)	C5 -N1-C6	121.5 (2)	N1-C2	1.392 (8)	C2 -N1-C6	125.7 (7)	N -C3	1.43 (1)	C3 -N -C11	127.0 (6)
N1-C5	1.456 (3)	C2 -N1-C6	123.9 (2)	N1-C5	1.473 (7)	C2 -N1-C5	111.7 (3)	N -C11	1.39 (1)	C1 -02-C18	117.2 (8)
N1-C6	1.418 (3)	C2 -N1-C5	112.8 (2)	N1-C6	1.416 (7)	C5 -N1-C6	122.3 (3)	01-C1	1.20 (1)	C14-04-C17	118.3 (8)
N2-04	1.219 (3)	N1 -C2-01	124.8 (2)	01-C2	1.202 (9)	C4 -C5-N1	103.7 (4)	02-C1	1.33 (1)	01 -C1-02	121.9 (8)
N2-05	1.222 (3)	01 -C2-C3	126.3 (2)	02-C4	1.410 (7)	C4 -C5-03	111.7 (5)	02-C18	1.44 (1)	02 -C1-C2	111.4 (7)
N2-C9	1.460 (3)	N1 -C2-C3	108.7 (2)	03-C5	1.414 (9)	03 -C5-N1	105.8 (4)	03-C4	1.23 (1)	01 -C1-C2	126.7 (8)
01-C2	1.215 (2)	C2 -C3-C13	104.3 (2)	03-C13	1.438 (9)	C5 -C4-C3	102.6 (5)	04-C14	1.38 (1)	C1 -C2-C19	108.6 (7)
02-C4	1.419 (2)	C2 -C3-C12	112.3 (2)	C1-C3	1.513 (9)	C5 -C4-02	108.8 (5)	04-C17	1.39 (1)	C3 -C2-C19	111.9 (6)
03-C5	1.409 (2)	C2 -C3-C4	102.6 (2)	C1-C4	1.537 (7)	C5 -C4-C14	112.8 (5)	C1-C2	1.48 (1)	N -C3-C2	112.5 (6)
03-C20	1.422 (3)	C12-C3-C13	109.3 (2)	C2-C3	1.513 (7)	02 -C4-C3	108.1 (5)	C2-C3	1.54 (1)	C2 -C3-C4	110.2 (6)
C2-C3	1.512 (3)	C4 -C3-C13	113.5 (2)	C3-C4	1.545 (9)	02 -C4-C5	108.8 (5)	C2-C19	1.54 (1)	N -C3-C4	107.4 (6)
C3-C4	1.549 (3)	C4 -C3-C12	114.2 (2)	C4-C5	1.555 (7)	C14-C4-C3	112.9 (5)	C3-C4	1.54 (1)	03 -C4-C3	119.2 (7)
C3-C12	1.520 (3)	02 -C4-C3	106.0 (2)			C2 -C3-C12	113.7 (5)	C4-C5	1.49 (1)	C3 -C4-C5	119.2 (6)
C3-C13	1.538 (3)	C3 -C4-C14	113.5 (2)			C4 -C3-C2	103.0 (5)			03 -C4-C5	121.4 (7)
C4-C5	1.554 (3)	C3 -C4-C5	104.2 (2)			C4 -C3-C12	115.9 (6)				
C4-C14	1.524 (3)	02 -C4-C14	110.2 (2)			C3 -C2-N1	108.4 (5)				
		02 -C4-C5	108.1 (2)			C3 -C2-01	126.4 (6)				
		05 -C4-C14	114.4 (2)			N1 -C2-01	125.1 (5)				
		03 -C5-C4	110.6 (2)								
		N1 -C5-C4	104.1 (2)								
		N1 -C5-03	109.1 (2)								

68.4 (CHN), 55.5, 54.3, 53.1 (3xOCH$_3$). Analysis found: C 66.79, H 5.59, N 4.12%; $C_{19}H_{19}NO_5$ requires C 66.85, H 5.61, N 4.10%.

Preparation of β-hydroxy-γ-methoxy γ-lactams, 6. This method is the same as described for **4**. The residue was purified by recrystallization:

(4R*,5R*)-*4-Hydroxy-3,3-dimethyl-5-methoxy-1-(p-nitro)phenyl-4-phenyl-pyrrolin-2-one* (**6a**). Yield: 73%. Yellow crystals, m.p. 161-162°C (ethanol). IR (KBr): 3440 (OH), 1715 (C=O) cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ 0.83 (s, 3H, CH$_3$), 1.40 (s, 3H, CH$_3$), 3.47 (s, 1H, OH), 3.50 (s, 3H, OCH$_3$), 5.53 (s, 1H, CH), 7.10-8.30 (m, 9H, arom.). ^{13}C-NMR (DMSO-d$_6$): δ 18.6 (CH$_3$), 22.2 (CH$_3$), 49.3 (C-3), 58.1 (OCH$_3$), 78.7 (C-4), 92.1 (C-5), 122.6, 124.2, 126.2, 127.6, 128.1, 141.0, 143.6, 143.7, 177.3 (C-2). Analysis found: C 63.80, H 5.73, N 7.99%; $C_{19}H_{20}N_2O_6$ requires C 64.04, H 5.66, N, 7.86%.

(3R*,4R*,5S*)-*4-Hydroxy-3-methyl-5-methoxy-1-(p-nitro)phenyl-4-phenyl-pyrrolin-2-one* (**6b**). Yield: 54%. Colourless crystals, m.p. 168-170°C (methanol). IR (KBr): 3490 (OH), 1715, 1700 (C=O) cm^{-1}. ^{1}H-NMR (CDCl$_3$): δ 1.26 (d, 3H, J = 7 Hz, CH$_3$), 2.92 (q, 1H, J = 7 Hz, CH-Me), 3.30 (s, 3H, OCH$_3$), 3.47 (s, 1H, OH), 5.47 (s, 1H, N-CH), 7.27-7.33 (m, 7H, arom.) 8.03-8.30 (m, 2H, arom.). ^{13}C-NMR (CDCl$_3$): δ 7.9 (CH$_3$), 49.3 (C-3), 58.6 (OCH$_3$), 76.1 (C-4), 95.7 (C-5), 122.3, 124.2, 124.7, 127.9, 128.7, 141.6, 142.7, 144.3, 173.7 (C-2). MS m/z (%): 342 (26), 181 (97), 135 (18), 134 (100), 133 (42), 105 (36), 103 (30). Analysis found: C 63.55, H 5.23, N 8.14%; $C_{19}H_{18}N_2O_6$ requires C 63.15, H 5.30, N 8.18%.

Crossover experiments. *Example 1*: reaction of **5d** with enolate **3b**. To a stirred solution of enolate **3b** (2.2 mmol) in THF at -78°C, a solution of **5d** (1 mmol) in THF (3 ml) was added. Then, the reaction was carried out under the standard procedure B conditions described for **8** (75 min). The ^{1}H-NMR spectra of the crude product showed only the presence of β-lactam **8d** (90% yield after purification).

Example 2: reaction of **5f** with **3a**. The reaction was carried out as in example 1. The ^{1}H-NMR spectra of the crude product showed only the presence of β-lactam **8f** (92% yield after purification).

X-Ray analysis parameters. The main characteristics of the analysis are given in Table 1.[27-29] Selected bond lengths and angles for compounds **6a**, **6b**, and **7a** are summarized in Table 2.

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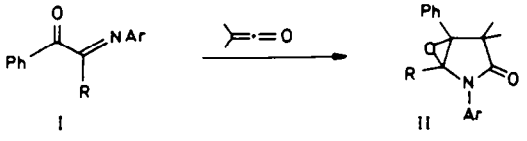

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16. These two-step one-pot procedures allow for the synthesis of compounds 5 cleanly an with better yield than the direct one-step procedure A (see Experimental Section).

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