Stereospecific cyclization of β-hydroxy aryl amides to β-lactams[1]

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This paper is dedicated to Professor Peter Yates on the occasion of his 60th birthday

AJAY K. BOSE, M. S. MANHAS, D. P. SAHU, and V. R. HEGDE. Can. J. Chem. **62**, 2498 (1984).

N-Aryl-β-lactams can be prepared conveniently by an intramolecular reaction of β-hydroxyarylamides under the influence of diethyl azodicarboxylate (DEAD) and triphenylphosphine (TPP). Optically active 3-amino-2-azetidinone derivatives can be prepared by this method starting with a suitably protected α-amino-β-hydroxy carboxylic acid amide. This cyclization involves the retention of configuration at C2 and complete inversion at C3 of the starting acid. In some cases diamides of azodicarboxylic acid have been used by replacing TPP with the more reactive tributyl phosphine. Other phosphorus reagents such as phosphite esters and hexamethyl phosphorus triamide could also be used.

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Grâce à une réaction intramoléculaire des β-hydroxyarylamides, qui se produit sous l'influence de l'azodicarboxylate de diéthyle (DEAD) et de la triphénylphosphine (TPP), on peut facilement préparer des *N*-aryl β-lactames. Utilisant cette méthode, on peut préparer des dérivés optiquement actifs de l'amino-3 azètidone-2 en partant de l'amide d'un acide α-amino β-hydroxy carboxylique convenablement protégé. Cette cyclisation implique une rétention de configuration en C2 et une inversion complète en C3 de l'acide de départ. Dans quelques cas, on a utilisé les diamides de l'acide azodicarboxylique en remplacant la TPP par la tributyl phosphine qui est plus réactive. On pourrait aussi utiliser d'autres réactifs phosphorés comme les esters de phosphites et le HMPT (hexaméthyl phosphore triamide).

[Traduit par le journal]

In recent years monocyclic β-lactams have become a center of attention in many laboratories. This type of heterocycle has been found in nature (2); also, suitably substituted moncyclic β-lactams can be converted to bicyclic (or polycyclic) β-lactams including naturally occurring penicillins, cephalosporins, cephamycins, and their analogs (3). In a preliminary communication (4) we have reported some aspects of our studies on the conversion of α-amino-β-hydroxy acid derivatives to optically active β-lactams by an intramolecular Mitsunobu type reaction (5). We present here details of these studies as well as new observations made by us.

Characteristics of the Mitsunobu reaction

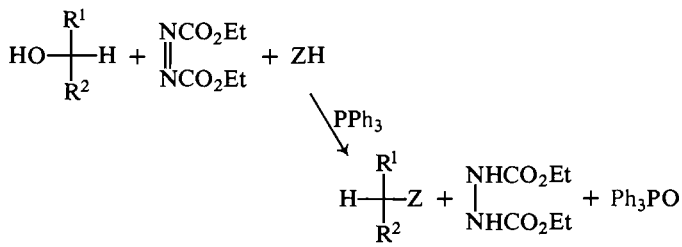
In essence the Mitsunobu reaction (5) is the replacement of a hydroxyl group by an anion under the influence of triphenylphosphine (TPP) and diethyl azodicarboxylate (DEAD) (6); the elements of water are removed by combining hydrogen with DEAD to form the hydrazine derivative and by converting TPP to its oxide (Scheme 1). The replacement of the hydroxyl group is stereospecific and occurs with complete inversion.

Even such weak acids as active methylene compounds can undergo reactions with alcohols under the influence of DEAD/TPP. For example, ethyl cyanoacetate and propyl alcohol have been reported to produce mono- and dipropylcyanoacetate (6*c*).

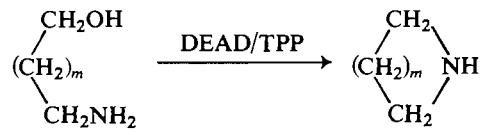
Carlock and Mack (7) have shown that intramolecular dehydration of diols to cyclic ethers (8) and amino alcohols to cyclic amines takes place under the conditions of the Mitsunobu reaction (Scheme 2).

Synthesis of 1-aryl-3-carbamato-2-azetidinones

In the light of the successful synthesis by Carlock and Mack of azacyclic compounds by an internal Mitsunobu reaction, and of our earlier work (9), we attempted the cyclization of the *p*-toluidide **1** of N-Cbz serine (Scheme 3). Under the influence of DEAD/TPP at room temperature, **1** was converted in 53% yield to the desired β-lactam **2** (4). The clearest indication of



SCHEME 1



SCHEME 2

β-lactam formation was the infrared absorption of **2** at 1770 cm^{-1} and the ^1H nmr spectrum.

While this research was in progress, Miller and co-workers (10,11) reported the synthesis of β-lactams **4** from β-hydroxyhydroxamic acids **3** under the Mitsunobu reaction conditions (Scheme 3). According to these authors, the key to their success in cyclization was the acidity ($pK_a \sim 6-10$) of the —CO—NH— bond of the hydroxamic acid.

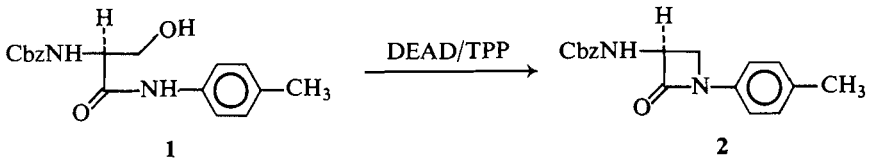
In a later publication Townsend and Nguyen (12) have reported the formation of the *N*-alkyl-β-lactam **6** from the dipeptide **5**, the —CO—NH bond of which is not expected to be particularly acidic (Scheme 4).

Our detailed studies on the internal Mitsunobu reaction of arylamides of β-hydroxy-α-amino acids disclosed that the acidity of the —CO—NH— bond is but one of several factors that affect the course of the reaction. Our findings are discussed below.

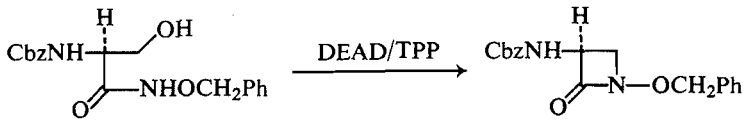
Steric course of β-lactam formation

The reaction of the *p*-toluidide **7***c* of phenylserine with DEAD and TPP led to two products, in about equal amounts,

[1] Studies on lactams, Part 70. For part 69, see ref. 1.

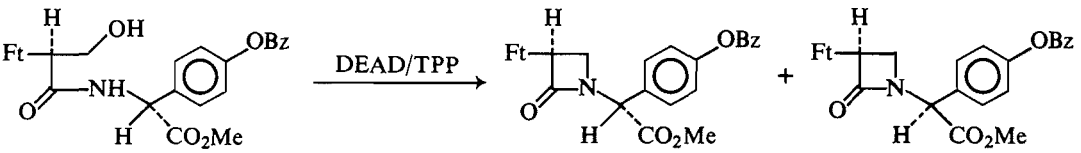


1 2



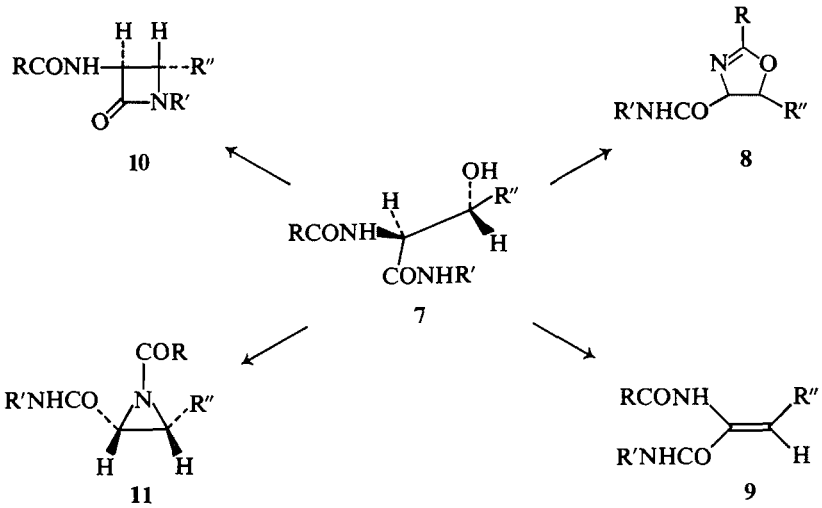
3 4

SCHEME 3



5 6

SCHEME 4



	R	R′	R″
a	OCH_2Ph	$C_6H_4CH_3(p)$	H
b	OCH_2Ph	$C_6H_4CH_3(p)$	CH_3
c	OCH_2Ph	$C_6H_4CH_3(p)$	C_6H_5
d	OCH_2Ph	$C_6H_3(OCH_3)_2$,2:4	H
e	OC_4H_9'	$C_6H_4OCH_3(p)$	H
f	OC_4H_9'	$C_6H_4CH_3(p)$	H
g	OC_4H_9'	$C_6H_4CH_3(p)$	CH_3
h	OC_4H_9'	$C_6H_4CH_3(p)$	C_6H_5

SCHEME 5

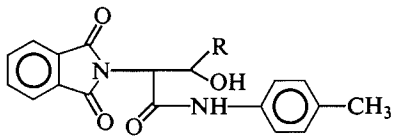
which could be separated by chromatography. Loss of the elements of water from **7***c* could possibly lead to four different types of compounds (Scheme 5). The ^1H nmr spectra of the two products obtained were incompatible with the oxazoline (**8***c*) and the eneamide (**9**) structures, but these spectra were in agreement with the four-membered and three-membered ring structures **10** and **11**, respectively.

Of the two products, one showed infrared absorption peaks at 1740, 1730, 1620 cm^{-1} and the other at 1730, 1665, 1600 cm^{-1}. Clearly, the former is the β-lactam **10***c* and the latter the aziridine **11***c*. The ^1H nmr spectrum of **10***c* showed signals δ ($CDCl_3$): 7.4–6.9 (m, 14H), 6.1 (bd, J = 9 Hz, 1H), 5.03 (s, 2H), 4.9 (bs, 1H), 4.45 (bd, J = 8 Hz, 1H), 2.2 (s, 3H). The broad singlet at δ 4.9 could be resolved into a doublet (J = 2 Hz) by adding the shift reagent $Eu(fod)_3$ to the nmr sample.

The J value of 2 Hz for the coupling of C3 and C4 protons in **10***c* is evidence for the *trans* stereochemistry of the β-lactam. Since the starting compound **7***c* had the *erythro* or (2*SR*,3*RS*) configuration, the internal Mitsunobu-type reaction must proceed with inversion at C3 of **7***c*. The *cis* or *trans* configuration of the β-lactam, therefore, can be controlled by selecting a *threo*- or *erythro*-β-hydroxy-α-amino acid as the

starting material.

The second product, **11***c*, which is isomeric with **10***c*, is best described by the aziridine structure **11**. The two ring protons of **11***c* which resonate at 3.6 and 4.0 ppm show a coupling constant of 7 Hz and are therefore *cis* to each other. During cyclization to the 3-membered ring, inversion must have occurred at C3 of the starting material **7***c*.



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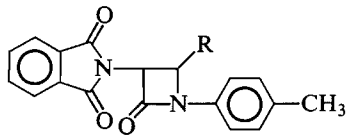
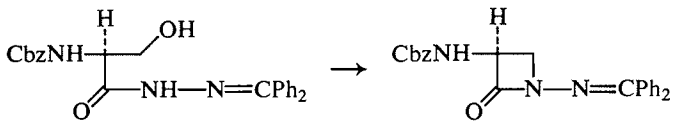


13

a = H
b = CH_3
c = Ph

A simple way of preventing the formation of aziridine is to use the *N*-phthaloyl derivative of a β-hydroxy-α-amino acid. Thus, the phthalimido derivative **12** was smoothly converted to the β-lactam **13** under the DEAD/TPP reaction conditions.

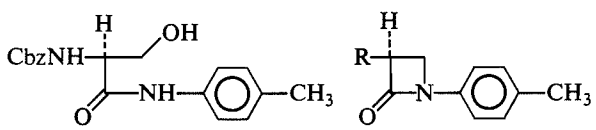
Previously we (4) have reported that the acyl hydrazide **14** can be cyclized to the β-lactam **15** – although in low yield – under the influence of DEAD/TPP at room temperature. It should be possible to prepare an *N*-unsubstituted β-lactam by taking advantage of N—N bond scission under dissolving metal reduction conditions.



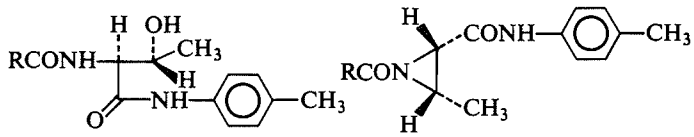
14 **15**

Chiral synthesis

The chiral nature of the synthesis described here was established by converting the *p*-toluidide **7***a* of *N*-carbobenzyloxy-L-serine to the β-lactam **10***a*. Attempts to determine the optical purity of **10***a* by using the chiral shift reagent Eu(tfac)$_3$ for nmr spectral studies were unsuccessful. To induce stronger binding with the shift reagent, the β-lactam **14** containing a free amino group was then generated by catalytic hydrogenation of **10***a*. The shift in the signal for the 4H proton *trans* to the 3H proton (shown by J = 1.5 Hz) in the ^{1}H nmr spectrum of **10***a* was studied. The quartet pattern for this proton in DL-**10***a* derived from DL-serine was shifted to form two sets of quartets of equal area. Under the same conditions **10***a* from L-serine showed only the quartet at lower field. Hence, in the course of β-lactam formation there was retention of the chirality of the α-amino acid.



7*a* **10***a* R = CbzNH
16 R = NH_2



7 **11**

R = OCH_2Ph
R = $OC_4H_9^t$

Influence of various parameters

The L-threonine amides **7***b* and **7***g* on DEAD/TPP reaction gave no β-lactam; the aziridine derivatives **11***b* and **11***g* were formed instead. This indicates the importance of the group attached to the carbinol carbon in directing the course of the reaction. The *cis*-stereochemistry of the C2 and C3 protons in **11***b* and **11***g* was as expected.

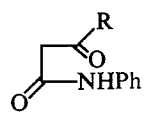
2′,4′-Dimethoxybenzamide of carbobenzyloxyserine failed to undergo any reaction with DEAD/TPP under similar conditions. The nature of the group attached to the amide nitrogen also appears to play a significant role in this reaction. Thus, the 2′,4′-dimethoxylbenzamide **7***d* and the *p*-methoxybenzamide **7***b* produced only dehydration products of the type **9** under the influence of DEAD and tributylphosphine or triethyl phosphite.

We have studied the effect of changing the nature of the phosphorus and the hydrazine compounds used in our β-lactam synthesis. Table 1 shows the conversion of **7***a* to **10***a* using various phosphorus compounds and diethyl azodicarboxylate. Triphenylphosphite failed to produce any β-lactam in 2 h at room temperature. In the light of later work (11, 12), that 2 h appears to have been inadequate reaction time. Morrison and Miller (11) have shown that β-lactam formation using triphenylphosphite and DEAD requires several days at room temperature.

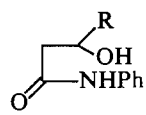
The effect of changing the azo reagent was also studied. Several azo reagents were prepared by heating diethyl azodicarboxylate with secondary amines in ether (13). These reagents were tested for the cyclization of **7***a* to **10***a* (Table 2). It was found that **17**, **18**, and **19** failed to produce **10***a* when triphenylphosphine was used as the phosphorus compound. However, these compounds reacted with **7***a* in the presence of tri-n-butyl phosphine. Table 2 shows the yields of β-lactam **10***a* obtained with these reagents.

3-Unsubstituted-2-azetidinones

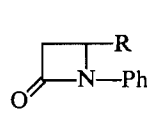
We have found that an α-carbamato or α-phthlimido group is not necessary for cyclization to β-lactams. Thus, benzoylacetanilide (**20**) was reduced with sodium borohydride in methanol to the corresponding β-hydroxy derivative (**21**) which on treatment with DEAD/TPP gave the β-lactam **22** (15) in 61% yield. The structure of this compound was established



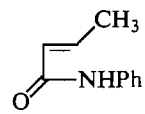
20 R = Ph
23 R = CH_3



21 R = Ph
24 R = CH_3



22 R = Ph
25 R = CH_3



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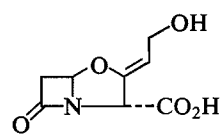

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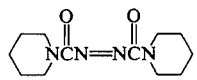
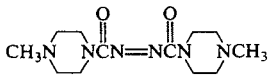
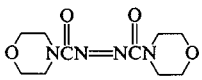
TABLE 1. Cyclization of **7***a* to **10***a*

Phosphorus reagent	Yield* of **10***a* (%)
$P(C_6H_5)_3$	74
$P(n\text{-}Bu)_3$	68
$P(OEt)_3$	79
$P[N(CH_3)_2]_3$	67
$P(OPh)_3$	0

*The yields were not optimized.

TABLE 2. Cyclization of **7***a* to **10***a* using n-Bu_3P

Azo reagent		Yield of **10***a* (%)
	(**17**)	57
	(**18**)	57
	(**19**)	47

through its spectral analysis. Acetoacetanilide **23**, under similar conditions, gave a mixture of the expected β-lactam **25** and crotonanilide **26**. The β-lactams obtained are unsubstituted on C3 and are thus similar in structure to a series of naturally occurring β-lactams, a representative example of which is clavulanic acid **27**.

Conclusions

The reaction of a phosphine and an azo compound with an arylamide of a β-hydroxycarboxylic acid constitutes a convenient synthesis of substituted β-lactams under mild conditions. This method involves the retention of the configuration at C2 and total inversion of the configuration at C3 of the β-hydroxy-α-amino acid starting material. Therefore, knowledge about the steric disposition of the starting compound permits one to predict the absolute and relative configuration of the β-lactam formed. Extension of the scope of this reaction is possible (16); further studies are in progress in our laboratory.

Experimental

The melting points are uncorrected. The ^1H nmr spectra were recorded on a Varian EM-390 nmr spectrometer. Chemical shifts are reported in parts per million from tetramethylsilane as internal standard, with the downfield direction taken as positive. Mass spectra were taken with a Hitachi RMU-7 mass spectrometer and a CIMS-Biospec instrument. The infrared spectra were recorded on a Perkin–Elmer 1310 infrared spectrophotomer. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Inc., Woodside, N.Y.

Formation of amides from protected amino acids

To a mixture of carbobenzyloxyamino acid (0.05 *M*) and dicyclohexylcarbodiimide (0.055 *M*) in 100 mL of chloroform, was added *p*-toluidine (0.05 *M*) and the solution was stirred at room temperature for about 5 h. The cooled solution was filtered to remove precipitated dicyclohexylurea. The filtrate was washed successively with 0.5 *N* hydrochloric acid, 5% sodium bicarbonate, and water. The solution was then dried ($MgSO_4$). Removal of the solvent under reduced pressure gave the crude amide as a gummy solid which on crystallization from chloroform and petroleum ether afforded the pure product. The compounds listed in Table 3 were synthesized by using this procedure.

Preparation of diazenecarboxamides

To a solution of 2 g of diethyl azodicarboxylate in 20 mL of dry ether at 0°C was added dropwise with stirring 2 g of the secondary amine in 20 mL dry ether. After 2 h at 0°C the crystallized product was filtered, dried, and recrystallized from ether and petroleum ether to obtain pure diazenecarboxamide. Compounds **17** and **19** were prepared by this method (13).

Cyclization of β-hydroxy-α-amino acid amides

To a mixture of carbobenzyloxyamino acid amide (0.003 *M*) and triaryl (or trialkyl) phosphine (0.004 *M*) in 30 mL of dry tetrahydrofuran, was added diethyl azodicarboxylate (or diazenecarboxamide) in 15 mL of tetrahydrofuran, dropwise with stirring, over a period of 30 min. The course of the reaction was monitored with thin-layer chromatography. The reaction mixture was stirred at room temperature for 2 h. Removal of the solvent afforded a gummy mass which on passing through silica gel column gave the pure product. The compounds shown in Table 4 were obtained by this method.

Sodium borohydride reduction of β-keto acid anilides

To a cold (5°C) solution of β-keto acid anilide (0.01 *M*) in methanol was added sodium borohydride (0.015 *M*) in small portions with stirring. After 2 h of stirring, methanol was removed under reduced pressure. To the resulting solid were added ethyl acetate and water and the mixture was well shaken. The contents (ethyl acetate and water layers) were slowly neutralized with dilute hydrochloric acid. The ethyl acetate layer was separated, dried, and solvent evaporated to get a white solid which was further crystallized from ethyl acetate and hexane to obtain the β-hydroxyanilides. Compounds **21** and **24** were prepared by this method.

Cyclization of β-hydroxy acid anilides

Cyclizations of β-hydroxy acid anilides were effected using the DEAD/TPP reaction. The method is similar to the one explained in the case of cyclization of β-hydroxy-α-amino acid amides. Compounds **22**, **25**, and the amide **26** were obtained by using this procedure.

cis-*1-Carbobenzyloxy-2-methyl-3-(*N-p-*tolyl)amidoaziridine* (**11***b*) was obtained as an oily liquid in 66% yield; ir (neat): 3300, 1715, 1660 cm^{-1}; nmr ($CDCl_3$) δ: 1.26 (d, 3H, J = 6 Hz), 2.3 (s, 3H), 2.83 (quintet, 1H, J = 6 Hz), 3.30 (d, 1H, J = 6 Hz), 5.26 (s, 2H), 7.08 (d, 2H, J = 9 Hz), 7.28 (s, 5H), 7.52 (d, 2H, J = 9 Hz), 9.11 (b, 1H).

cis-*1-*tert-*butoxycarbonyl-2-methyl-3-(*N-p-*tolyl)amidoaziridine* (**11***g*) was obtained as a viscous liquid in 54% yield; ir (neat): 3300, 1715, 1635 cm^{-1}; nmr ($CDCl_3$) δ: 1.30 (d, 3H, J = 6 Hz), 1.52 (s, 9H), 2.26 (s, 3H), 2.28 (quintet, 1H, J = 6 Hz), 3.16 (d, 1H, J = 6 Hz), 7.15 (d, 2H, J = 9 Hz), 7.45 (d, 2H, J = 9 Hz), 8.20 (s, H).

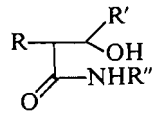
cis-*1-Carbobenzyloxy-2-phenyl-3-(*N-p-*tolyl)amidoaziridine* (**11***h*) was isolated in 39% yield, mp 107°C; ir (Nujol): 1730, 1665, 1600 cm^{-1}; nmr ($CDCl_3$) δ: 2.2 (s, 3H), 3.6 (d, 1H, J = 7 Hz), 4.0 (d, 1H, J = 7 Hz), 5.2 (s, 2H), 6.9–7.5 (m, 14H), 7.64 (b, 1H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 387 ($M^+ + 1$). *Anal.* calcd. for $C_{24}H_{22}N_2O_3$: C 74.59, H 5.74, N 7.25%; found: C 74.57, H 5.74, N 7.31%.

α-*Carbobenzyloxyamino-*N-*(2,4-dimethoxyphenyl)acrylamide* (**9***d*) was isolated as a white crystalline solid in 48% yield, mp 101°C; ir (Nujol); 3300, 1710, 1660 cm^{-1}; nmr (DMSO-d_6) δ: 3.66 (s, 6H), 4.98 (s, 2H), 5.40 (s, 1H), 5.55 (s, 1H), 6.42 (m, 2H), 7.20 (s, 5H), 7.42 (m, 1H) 8.60 (b, 1H), 8.96 (b, 1H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 357 ($M^+ + 1$). *Anal.* calcd. for $C_{19}H_{20}N_2O_5$: C 64.04, H 5.61, N 7.86%; found: C 65.03, H 5.71, N 7.87%.

α-tert-*Butoxycarbonylamino-*N-*(*p-*anisyl)acrylamide* (**9***e*) was obtained in 55% yield, mp 153–155°C; nmr ($CDCl_3$) δ: 1.50 (s, 9H), 3.47 (s, 3H), 5.2 (b, 1H), 6.06 (b, 1H), 6.90 (d, 2H, J = 9 Hz), 7.30 (b, 1H), 7.40 (d, 2H, J = 9 Hz), 7.90 (b, 1H). *Anal.* calcd. for $C_{15}H_{20}N_2O_4$: C 61.64, H 7.53, N 9.58%; found: C 61.62, H 7.46, N 9.53%.

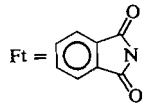
Crotonanilide (**28**) was formed in 21% yield from **24**, mp 112°C;

TABLE 3. β-Hydroxyamides



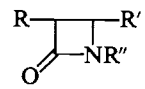
Entry	R	R′	R″	Melting point (°C)	Yield (%)	Molecular formula
7*a*	CbzNH	H	$C_6H_4CH_3(p)$	163–165	86	$C_{18}H_{20}N_2O_4$
7*b*	CbzNH	CH_3	$C_6H_4CH_3(p)$	155–156	92	$C_{19}H_{22}N_2O_4$
7*c*	CbzNH	C_6H_5	$C_6H_4CH_3(p)$	172	57	$C_{24}H_{24}N_2O_4$
7*d*	CbzNH	H	$C_6H_3(OCH_3)$ (2,4)	123–125	85	$C_{19}H_{22}N_2O_6$
7*e*	*t*-BocNH	H	$C_6H_4OCH_3$	98–99	98	$C_{15}H_{22}N_2O_5$
7*f*	*t*-BocNH	H	$C_6H_4CH_3$	165–167	64	$C_{15}H_{22}N_2O_4$
7*g*	*t*-BocNH	CH_3	$C_6H_4CH_3(p)$	153–155	89	$C_{16}H_{24}N_2O_4$
7*h*	*t*-BocNH	PH	$C_6H_4CH_3(p)$	153–154	58	$C_{21}H_{26}N_2O_4$
12*a*	Ft	H	$C_6H_4CH_3(p)$	Semi-solid	50	$C_{18}H_{16}N_2O_4$
12*b*	Ft	CH_3	$C_6H_4CH_3(p)$	138–140	86	$C_{19}H_{18}N_2O_4$
12*c*	Ft	Ph	$C_6H_4OCH_3(p)$	219–220	95	$C_{24}H_{20}N_2O_5$
14	CbzNH	H	$-N{=}CPh_2$	146–148	25	$C_{24}H_{23}N_3O_4$
24	H	CH_3	Ph	109	81	$C_{10}H_{13}NO_2$

* Values in parentheses refer to calculated values.



Spectral data	Analysis		
	C	H	N
Infrared (Nujol): 3280, 1700, 1660 cm^{-1}; nmr ($CDCl_3$) δ: 2.33 (s, 3H), 3.68 (b, 1H, exchangeable with D_2O), 4.18 (m, 1H), 4.30 (m, 2H), 5.33 (s, 2H), 5.88 (b, 1H), 7.18 (d, 2H, J = 9 Hz), 7.34 (m, 2H), 7.40 (s, 5H), 8.66 (b, 1H); mass spectrum (PC1, NH_3 reagent gas) m/z: 329 (M^+ + 1), 346 (M^+ + 18)	65.22 (65.85)*	6.18 (6.14)	8.44 8.53
Infrared (Nujol): 3330, 1689, 1644 cm^{-1}; nmr ($CDCl_3$) δ: 1.14 (d, 3H J = 6 Hz), 2.33 (s, 3H), 3.54 (b, 1H, exchangeable with D_2O), 4.18 (m, 1H), 4.60 (m, 1H), 5.14 (s, 2H), 5.93 (b, 1H), 7.18 (d, 2H, J = 9 Hz), 7.36 (m, 2H), 7.46 (s, 5H), 8.83 (b, 1H); mass spectrum (PC1, NH_3 reagent gas) m/z: 343 (M^+ + 1), 360 (M^+ + 18)	66.66 (66.65)	6.43 (6.48)	8.18 (8.18)
Infrared (Nujol): 3450, 3360, 1730, 1640, 1600 cm^{-1}; nmr ($CDCl_3$) δ: 2.3 (s, 3H), 2.55 (dd, 1H, J = 5 Hz), 5.0 (s, 2H), 5.3 (m, 1H), 5.4 (d, 1H, J = 5 Hz), 6.3 (d, 1H, J = 9 Hz), 7.0–7.5 (m, 14H), 9.12 (b, 1H)	71.38 (71.27)	6.49 (5.98)	7.12 6.93
Infrared (Nujol): 3300, 1710, 1640 cm^{-1}; nmr ($CDCl_3$) δ: 3.42 (b, 1H, exchangeable with D_2O), 3.50 (m, 1H), 3.78 (s, 6H), 4.10 (m, 1H), 4.36 (m, 1H), 5.13 (s, 2H), 5.92 (b, 1H), 6.16 (d, 1H, J = 7.5 Hz), 6.46 (m, 2H), 7.36 (s, 5H), 8.13 (m, 1H), 8.66 (b, 1H); mass spectrum (PC1, NH_3 reagent gas) m/z: 375 (M^+ + 1), 357 ($M^+ - H_2O$ + 1)			
Infrared (Nujol): 3300, 1700, 1635 cm^{-1}; nmr ($CDCl_3$) δ: 3.40 (s, 9H), 3.70 (s, 3H), 3.73 (b, 1H, exchangeable with D_2O), 4.33 (m, 1H)			
Infrared (Nujol): 3500, 3300, 1708, 1680 cm^{-1}; nmr ($CDCl_3$ + DMSO-d_6) δ: 1.48 (s, 9H), 2.25 (s, 3H), 3.78 (m, 2H, 1H exchangeable with D_2O), 4.23 (m, 1H), 4.74 (m, 1H), 6.10 (bd, 1H), 7.06 (d, 2H, J = 9 Hz), 7.40 (d, 2H, J = 9 Hz), 9.28 (b, 1H)	60.80 (61.21)	7.74 (7.53)	9.58 (9.52)
Infrared (Nujol): 3300, 1695, 1645 cm^{-1}; nmr ($CDCl_3$) δ: 1.13 (d, 3H, J = 6 Hz), 1.44 (s, 9H), 2.33 (s, 3H), 3.40 (b, 1H, exchangeable with D_2O), 4.18 (dd, 1H, J = 1.5 Hz and J = 6.0 Hz), 4.40 (m, 1H), 5.56 (d, 1H, J = 6 Hz), 7.03 (d, 2H, J = 9 Hz) 7.20 (d, 2H, J = 9 Hz), 8.53 (b, 1H)	62.10 (62.32)	7.99 (7.84)	9.13 (9.09)
Infrared (Nujol): 3350, 1705, 1680 cm^{-1}; nmr ($CDCl_3$) δ: 1.38 (s, 9H), 2.28 (s, 3H), 3.80 (b, 1H, exchangeable with D_2O), 4.52 (m, 1H), 5.08 (m, 1H), 5.20 (m, 1H), 7.08 (d, 2H, J = 9 Hz), 7.28 (s, 5H), 7.36 (d, 2H, J = 9 Hz), 8.40 (b, 1H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 371 (M^+ + 1), 388 (M^+ + 18)			
Infrared (Nujol): 3300, 1740, 1710, 1650 cm^{-1}; nmr ($CDCl_3$) δ: 1.4 (s, 3H), 3.70 (b, 1H, exchangeable with D_2O), 4.13 (m, 2H), 5.03 (m, 1H), 7.03 (d, 2H, J = 9 Hz), 7.36 (d, 2H, J = 9 Hz); mass spectrum (CIMS, NH_3 reagent gas) m/z: 325 (M^+ + 1), 342 (M^+ + 18)			
Infrared (Nujol): 3250, 1745, 1715, 1648 cm^{-1}; nmr ($CDCl_3$) δ: 1.6 (d, 3H, J = 6 Hz), 2.66 (s, 3H), 3.70 (b, 1H, exchangeable with D_2O), 4.68 (m, 1H), 4.90 (d, 1H, J = 6 Hz), 7.06 (d, 2H, J = 9 Hz), 7.36 (d, 2H, J = 9 Hz), 7.80 (m, 4H), 8.93 (bs, 1H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 339 (M^+ +1), 356 (M^+ + 18)			
Infrared (Nujol): 1730, 1694, 1666 cm^{-1}; nmr (DMSO-d_6) δ: 3.70 (s, 3H), 4.60 (b, 1H, exchangeable with D_2O), 5.10 (d, 1H, J = 7 Hz), 5.72 (d, 1H, J = 7 Hz), 6.80 (d, 2H, J = 9 Hz), 7.38 (m, 6H), 7.92 (s, 5H), 9.40 (b, 1H).	69.09 (69.23)	4.94 (4.84)	6.65 (6.73)
Infrared (Nujol): 3300, 1695, 1640 cm^{-1}; nmr ($CDCl_3$ + DMSO-d_6) δ: 3.60 (b, 1H, exchangeable with D_2O), 4.1 (m, 2H), 5.10 (s, 2H), 5.20 (m, 1H), 6.43 (b, 1H), 7.43 (s, 10H), 7.63 (m, 5H), 8,53 (b, 1H); mass spectrum (NCl, NH_3 + NH_4Cl) m/z: 416 $(M - 1)^-$, 452 $(M + 35)^-$			
Infrared (Nujol): 3150, 1660, 1600 cm^{-1}; nmr ($CDCl_3$) δ: 1.23 (d, 3H, J = 9 Hz), 2.48 (d, 2H, J = 9 Hz), 3.65 (b, 1H), 4.23 (m, 1H), 6.9–7.6 (m, 5H), 8.27 (b, 1H)	67.29 (67.02)	7.57 (7.31)	7.84 (7.82)

TABLE 4. β-Lactams



Entry	R	R′	R″	Melting point (°C)	Yield (%)	Molecular formula	Analysis C	Analysis H	Analysis N	Spectral data
10*a*	CbzNH	H	$C_6H_4CH_3(p)$	181–183	53	$C_{18}H_{18}N_2O_3$	69.80 (69.66)	5.94 (5.85)	8.97 (9.03)	Infrared (Nujol): 3300, 1770, 1700 cm^{-1}; nmr ($CDCl_3$) δ: 2.34 (s, 3H), 3.60 (dd, 1H, J = 3 Hz), 3.92 (t, 1H), 4.90 (m, 1H), 5.12 (s, 2H), 5.36 (b, 1H), 7.33 (m, 9H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 311 ($M^+ + 1$)
10*c*	CbzNH	Ph	$C_6H_4CH_3(p)$	136	42	$C_{24}H_{22}N_2O_3$	74.17 (74.59)	5.76 (5.74)	7.16 (7.25)	Infrared (Nujol): 1740, 1730, 1620 cm^{-1}; nmr ($CDCl_3$) δ: 2.2 (s, 3H), 4.45 (d, 1H, J = 8 Hz), 4.9 (bs, 1H, d with $Eu(fod)_3$, J = 2 Hz), 5.03 (s, 2H), 6.1 (bd, 1H, J = 8 Hz), 6.9–7.4 (m, 14H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 387 ($M^+ + 1$)
10*f*	*t*-BocNH	H	$C_6H_4CH_3(p)$	228–229	64	$C_{15}H_{22}N_2O_3$				Infrared (Nujol): 3450, 1778, 1708 cm^{-1}; nmr ($CDCl_3$) δ: 1.40 (s, 9H), 2.30 (s, 3H), 3.58 (dd, 1H, J = 3 Hz and J = 6 Hz), 3.98 (t, 1H, J = 6 Hz), 4.83 (m, 1H), 5.13 (m, 1H), 7.10 (d, 2H, J = 9 Hz), 7.20 (m, 2H, J = 9 Hz)
10*h*	*t*-BocNH	Ph	$C_6H_4CH_3(p)$	190–191	83	$C_{21}H_{24}N_2O_3$				Infrared (Nujol): 3380, 1760, 1718 cm^{-1}; nmr ($CDCl_3$) δ: 1.43 (s, 9H), 2.36 (s, 3H), 4.32 (m, 1H), 4.96 (d, 1H, J = 2.5 Hz), 5.0 (m, 1H), 7.0 (d, 2H, J = 9 Hz), 7.22 (d, 2H, J = 9 Hz), 7.33 (s, 5H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 353 ($M^+ + 1$) 370 ($M^+ + 18$)
12*a*	Ft	H	$C_6H_4CH_3(p)$	208–210	78	$C_{18}H_{14}N_2O_3$	70.45 (70.58)	4.66 (4.61)	9.21 (9.15)	Infrared (Nujol): 1775, 1738, 1712 cm^{-1}; nmr ($CDCl_3$) δ: 2.33 (s, 3H), 4.0 (d, 2H, J = 4 Hz), 5.55 (t, 1H, J = 4.5 Hz), 7.16 (d, 2H, J = 9 Hz), 7.30 (d, 2H, J = 9 Hz), 7.83 (m, 4H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 307 ($M^+ + 1$), 324 ($M^+ + 18$)
12*b*	Ft	CH_3	$C_6H_4CH_3(p)$	198–200	41	$C_{19}H_{16}N_2O_3$	70.95 (71.25)	5.66 (5.03)	8.91 (8.75)	Infrared (Nujol): 1772, 1740, 1715 cm^{-1}; nmr ($CDCl_3$) δ: 1.6 (d, 3H, J = 6 Hz), 2.32 (s, 3H), 4.50 (dd, 1H, J = 3 Hz and J = 6 Hz), 5.05 (d, 1H, J = 3 Hz), 7.15 (d, 2H, J = 9 Hz), 7.23 (d, 2H, J = 9 Hz), 7.8 (m, 4H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 321 ($M^+ + 1$), 338 ($M^+ + 18$)
12*c*	Ft	Ph	$C_6H_4OCH_3(p)$	188–190	58	$C_{24}H_{18}N_2O_4$	72.61 (72.35)	4.61 (4.55)	6.93 (7.03)	Infrared (Nujol): 1769, 1709, 1666 cm^{-1}; nmr ($CDCl_3$) δ: 3.73 (s, 3H), 5.34 (d, 1H, J = 1.5 Hz), 5.36 (d, 1H, J = 1.5 Hz), 6.88 (d, 2H), 7.37 (d, 2H), 7.45 (s, 5H), 7.88 (s, 4H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 399 ($M^+ + 1$)
15	CbzNH	H	N=CPh_2	104–106	30	$C_{24}H_{21}N_3O_3$	71.89 (72.18)	5.54 (5.26)	10.37 (10.52)	Infrared (Nujol): 3290, 1770, 1680 cm^{-1}; nmr ($CDCl_3$) δ: 2.86 (dd, 1H, J = 3 Hz), 3.17 (t, 1H, J = 6 Hz), 4.62 (b, 1H), 5.04 (s, 2H), 5.4 (m, 1H), 7.45 (m, 15H); mass spectrum (CIMS, NH_3 reagent gas) m/z: 410 ($M^+ + 1$)
22	H	CH_3	Ph	Oily liquid	41	$C_{10}H_{11}NO$				Infrared (neat): 1770 cm^{-1}; nmr ($CDCl_3$) δ: 1.5 (d, 3H, J = 6 Hz), 2.6 (dd, 1H, J = 6 Hz and J = 9 Hz), 4.13 (m, 1H), 6.9–7.3 (m, 5H)
25	H	Ph	Ph	153	61	$C_{15}H_{13}NO$				Infrared (Nujol): 1760 cm^{-1}; nmr ($CDCl_3$) δ: 1.9 (dd, 1H, J = 3 Hz and J = 9 Hz), 3.53 (dd, 1H, J = 6 Hz and J = 9 Hz), 5.0 (dd, 1H, J = 3 Hz and J = 3 Hz), 6.9–7.4 (m, 10H)

ir (Nujol): 1660 cm^{-1}; nmr ($CDCl_3$) δ: 1.8 (dd, 3H, J = 2 Hz and J = 6 Hz), 6.0 (dd, 1H, J = 2 Hz and J = 15 Hz), 6.67–7 (m, 6H), 8.6 (b, 1H).

Acknowledgements

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