

Concise General Synthesis of α,γ -Disubstituted β -Amino Ketones from β -Lactams

Claudio Palomo,* Jesús M. Aizpurua, Jesús M. García, Miren Iturburu, and José M. Odriozola

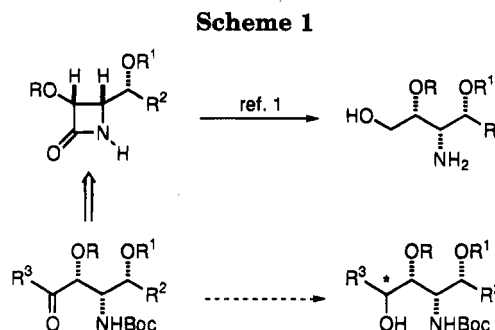
Departamento de Química Orgánica, Facultad de Química, Universidad del País Vasco, Apdo 1072, 20080 San Sebastián, Spain

Received March 30, 1994[®]

α,γ -Disubstituted β -amino ketones were obtained by ring opening of 3,4-disubstituted *N*-Boc- β -lactams, promoted by Grignard and organocuprate reagents.

A recent report from this laboratory documented the cycloaddition reaction of alkoxyketenes to O-protected α -hydroxy aldehyde-derived imines as a method of choice for the production of masked forms of both α,γ -dialkoxy β -amino esters and 1,3-amino polyols.¹ Interest in acyclic amino polyols has recently increased not only because of their physiological activities but also due to their use as building blocks of polyhydroxylated nitrogen heterocycles and polyhydroxyamino acids.² As a logical extension of our work, more elaborated aminopolyols, which carry additional stereogenic centers (Scheme 1), should be readily obtainable from α,γ -dialkoxy- β -amino ketones, owing to the ample precedence for stereocontrolled reductions of α -(alkoxycarbonyl) compounds.³ However, while the literature pertaining to the N_1 - C_2 β -lactam cleavage by means of heteronucleophiles is abundant,⁴ the reaction promoted by carbon nucleophiles, which would give the required β -amino ketones, has been the subject of very few investigations.⁵ We report here the results of our approach to the synthesis of α,γ -disubstituted β -amino ketones.⁶

By analogy with the ring-opening reaction of *N*-Boc- γ -lactams with carbon nucleophiles,⁷ we selected for our study (Scheme 2) the *N*-Boc- β -lactam **4** as a masked form of hydroxylated β -amino ketones. The starting material was easily prepared in two steps from the Bose–Manhas β -lactam **1**.⁸ Thus, *N*-dearylation of the 3-(benzyloxy) β -lactam **1**, under standard conditions,⁹ furnished the *N*-unsubstituted β -lactam **3** in 90% yield. Subsequent



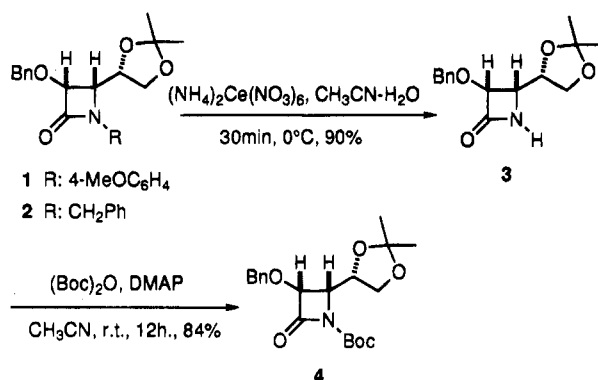
exposure of **3** to (Boc)₂O in the presence of 4-(dimethylamino)pyridine (DMAP) in acetonitrile¹⁰ gave **4** in 84% yield. We have found (Scheme 2) that this β -lactam compound, upon treatment with aryl Grignard reagents at low temperature (-40 °C) in THF as solvent, affords β -amino ketones **5** in excellent yields. In no case was overaddition observed under these conditions, even when an excess of the reagent was present in the reaction medium. However, when the reaction was performed at room temperature instead of at -40 °C, only tertiary alcohols were obtained. Results are listed in Table 1 and illustrate the effectiveness of this β -lactam ring opening. For example, the reaction of **4** with a slightly excess of phenylmagnesium bromide at -40 °C led to the formation of **5a** in 90% isolated yield as the only product. Similarly, compounds **5b**, **5c**, and **5d** were obtained in 95%, 94%, and 96% yields, respectively. On the other hand, when **4** was allowed to react with a 4-fold excess of phenylmagnesium bromide, beginning at -78 °C and warming to room temperature, the corresponding carbinol **6a** was produced in 86% yield. Under these conditions, carbinols **6e** and **6f** were also obtained from **4** and the respective Grignard reagents in yields of 83% and 64%.

In contrast to the above observations, reaction of **4** with primary alkylmagnesium bromides as well as alkylolithi-

[®] Abstract published in *Advance ACS Abstracts*, August 1, 1994.
 (1) Palomo, C.; Aizpurua, J. M.; Urchegui, R.; Garcia, J. M. *J. Org. Chem.* **1993**, *58*, 1646.
 (2) (a) Golebiowski, A.; Jurczak, J. *Synlett* **1993**, 241. (b) Ohfuné, Y. *Acc. Chem. Res.* **1992**, *25*, 360. (c) Cintas, P. *Tetrahedron* **1991**, *47*, 6079. For an extensive list of references, see: (d) Jäger, V.; Hümmer, W.; Stahl, U.; Gracza, T. *Synthesis* **1991**, 769. (e) Jäger, V.; Stahl, U.; Hümmer, W. *Synthesis* **1991**, 776. (f) Dondoni, A.; Merino, P.; Perrone, D. *Tetrahedron* **1993**, *49*, 2939.
 (3) For recent reviews, see: (a) Ager, D. J.; East, M. B. *Tetrahedron* **1992**, *48*, 2803. (b) Greeves, N. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: New York, 1991; Vol. 8, p 1. For a review on amino alcohols from amino carbonyl compounds, see: (c) Tramontini, M. *Synthesis* **1992**, 605.
 (4) For reviews see: (a) Mukerjee, A. K.; Singh, A. K. *Synthesis* **1975**, 547. (b) Mukerjee, A. K.; Singh, A. K. *Tetrahedron* **1978**, *34*, 1731. (c) Manhas, M. S.; Wagle, D. R.; Chiang, J.; Bose, A. K. *Heterocycles* **1988**, *27*, 1755.
 (5) While our work was in progress the synthesis of α -unsubstituted β -amino ketones from an aspartic acid-derived β -lactam opening was reported; see: Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R. A.; Gollins, D. W.; Smith, M. L.; Russel, A. T. *Synlett* **1993**, 51. (b) Baldwin, J. E.; Adlington, R. M.; Godfrey, C. R.; Gollins, D. W.; Vaughan, J. G. *J. Chem. Soc., Chem. Commun.* **1993**, 1434. For a preliminary account from this laboratory, see: (c) Palomo, C.; Aizpurua, J. M. *Trends in Organic Chemistry*, CSRI: India, 1994; in press. For related works on this subject, see: (d) Kano, S.; Ebata, T.; Shibuya, S. *Chem. Pharm. Bull.* **1979**, *27*, 2450. (e) Shiozaki, M.; Ishida, N.; Sato, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3950. (f) Galluci, J. G.; Ha, D.-C.; Hart, D. J. *Tetrahedron* **1989**, *45*, 1283.

(6) (a) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1983**, *48*, 2255. (b) Barluenga, J.; Olano, B.; Fustero, S.; Foces-Foces, M. C.; Cano, F. H. *J. Chem. Soc., Chem. Commun.* **1988**, 410. (c) Barluenga, J.; Aguilar, E.; Olano, B.; Fustero, S. *Synlett* **1990**, 463.
 (7) (a) Ohta, T.; Hasoi, A.; Kumura, T.; Nozoe, S. *Chem. Lett.* **1987**, 2091. (b) Ohta, T.; Kimura, T.; Sato, N.; Nozoe, S. *Tetrahedron Lett.* **1988**, *29*, 4303. (c) Woo, K.-C.; Jones, K. *Tetrahedron Lett.* **1991**, *32*, 6949. (d) Ezquerro, J.; Mendoza, J.; Pedregal, C.; Ramirez, C. *Tetrahedron Lett.* **1992**, *33*, 5589.
 (8) Wagle, D. R.; Garai, G.; Chiang, J.; Monteleone, M. G.; Kurys, B. E.; Strohmeier, T. W.; Hedge, V. R.; Manhas, M. S.; Bose, A. K. *J. Org. Chem.* **1988**, *53*, 4227.
 (9) Kronenthal, D. R.; Han, C. Y.; Taylor, M. K. *J. Org. Chem.* **1982**, *47*, 2765.
 (10) Baldwin, J. E.; Adlington, R. M.; Gollins, D. W.; Schofield, C. J. *Tetrahedron* **1990**, *46*, 4733.

Scheme 2

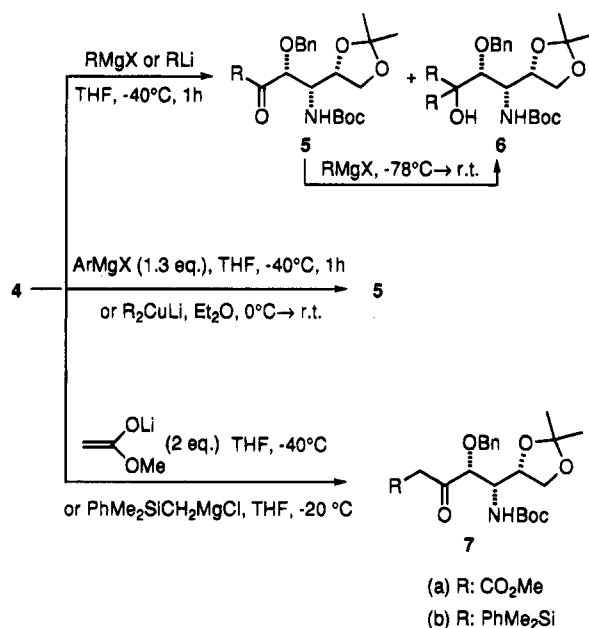
Table 1. Ring-Opening Reaction of the *N*-Boc- β -lactam 4 with Grignard Reagents^a

compd	R	X	product ratio ^b 4:5:6	yield, ^c % of compd 5	mp, ^e °C	[α] _D ²⁵ , ^f deg
a	C ₆ H ₅	Br	—:100:—	90	116–118	+14.2
b	4-FC ₆ H ₄	Br	—:100:—	95	68–70	+14.9
c	4-MeC ₆ H ₄	Br	—:100:—	94	94–96	+24.5
d	4-MeOC ₆ H ₄	Br	—:100:—	96	110–112	+33.3
e	Me	Br	13:45:42	40 (55) ^d	46–49	+1.7
f	Et	Br	12:67:21	60	66–68	+3.8
g	<i>n</i> -Bu	Cl	—:90:10	80(67) ^d	42–44	+4.1
h	<i>n</i> -Hex	Br	8:84:8	82	oil	+2.1
	<i>n</i> -Hex	Cl	—:89:11	85		
i	CH ₃ (CH ₂) ₁₁	Br	19:69:12	58	oil	+3.2
j	(CH ₃) ₂ CH	Cl	—:100:—	75	oil	–21.7
k	<i>c</i> -C ₆ H ₁₁	Br	—:100:—	83	oil	–14.3

^a Reactions conducted on a 1 mmol scale. ^b Determined by ¹H NMR 300-MHz spectroscopy. ^c Isolated yield of pure compounds. ^d Yields in brackets refer to reactions carried out with the corresponding cuprates. ^e Solids crystallized from hexane. Oils purified by preparative HPLC (ethyl acetate/hexane 1:3; 15 mL/min). ^f (*c* = 1, CH₂Cl₂).

ums at –40 °C invariably led to a mixture of the corresponding β -amino ketones **5** and β -amino carbinols **6** along with the starting β -lactam **4**. It should be noted that the use of the less reactive alkylmagnesium chlorides instead of the respective bromides (entries **g**, **h**) leads to a virtually complete conversion of the starting material, thus increasing the amount of the β -amino ketone without diminishing the formation of **6**. In each case the proportion of products, as shown in Table 1, was easily determined by ¹H-NMR analysis of the corresponding crude reaction mixture. In general, this could be effected by integrating one geminal benzylic proton of the resulting β -amino ketone at 4.5 ppm and the methinic proton, at δ 3.5 ppm, adjacent to the benzyloxy group in carbinols **6**. After examining various reaction conditions to optimize the above results,¹¹ we found that the use of Gilman cuprates afforded the best results in terms of chemoselectivity, although the yields were only moderate. For instance, reaction of **4** with lithium dimethyl cuprate in a ratio of 1:2 gave **5e** in 55% yield as the only reaction product. Similarly, lithium di-*n*-butylcuprate furnished **5g** in 67% isolated yield without traces of the correspond-

Scheme 3

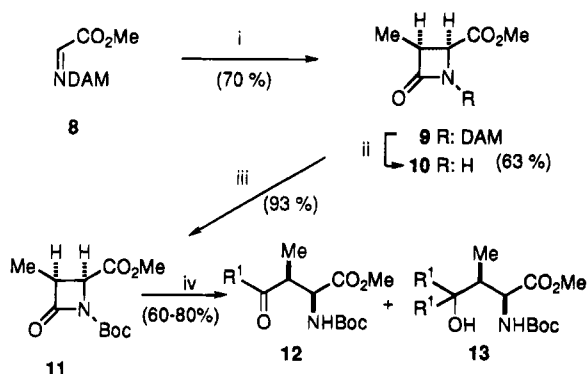


ing **6g**. We also examined the behavior of secondary alkylmagnesium halides in such a β -lactam ring opening and in both cases tested (entries **j**, **k**) the reaction proceeded as aryl Grignard did.

As shown in Scheme 3, β -amino ketones carrying additional functionality could also be prepared by this method. Reaction of **4** with the lithium enolate of methyl acetate led to the formation of **7a** in 73% yield without traces of hydroxy compounds derived from attack at the resulting carbonyl groups. Compound **7b**, which incorporates a silyl moiety amenable to further transformation,¹² could also be obtained as a sole reaction product albeit in modest yield (45%). After the optimum conditions to perform this azetidin-2-one cleavage were established, the effect of other substituents on the β -lactam nitrogen atom was evaluated. In our hands, compound **3**, upon treatment with a 4-fold excess of either [(dimethylphenylsilyl)methyl]magnesium chloride or phenylmagnesium bromide under the above reaction conditions, did not react to afford the expected open product, and the starting material was recovered unchanged.

(11) For instance, reaction of **4** with ethylmagnesium bromide (molar ratio 1:1.3) in THF at –78 °C for 2.5 h led to a mixture of **5f**, **6f**, and the starting **4** in a ratio of 68:16:16. When the reaction was carried out in toluene as solvent, under the same conditions as above, the ratio of products was 66:7:27, respectively. In the latter case, increasing the amount of Grignard reagent from 1.3 to 2.6 equiv did not improve the product ratio. The use of the corresponding organomanganese reagent, prepared by addition of MnCl₂ and LiCl to ethylmagnesium bromide in THF at –10 °C led to product decomposition.

(12) The silyl moiety in **7b** could be transformed into the hydroxy group following Fleming's protocol, and subsequent cyclization should render hydroxylated pyrrolidines, an important class of glycosidase inhibitors. (a) Fleming, I.; Sanderson, P. E. J. *Tetrahedron Lett.* **1987**, 28, 4229. (b) Fleming, I. *Pure Appl. Chem.* **1988**, 60, 71.

Scheme 4^a

a R¹: Me
 b R¹: C₆H₅
 c R¹: 4-MeOC₆H₄

DAM: CH(C₆H₄OMe-4)₂

^a Reagents and Conditions: (i) MeCH₂COCl, Et₃N, C₆H₆, reflux, 16 h; (ii) (NH₄)₂Ce(NO₃)₆, CH₃CN-H₂O, 0–5 °C, 30 min; (iii) (Boc)₂O, DMAP cat., CH₃CN, rt, 12 h; (iv) R¹MgBr, THF –40 °C.

When the same reaction was carried out on the *N*-benzyl- β -lactam **2**, only partial transformation was observed, and any attempt to improve this result was unfruitful.¹³

To extend the scope of this procedure, the reaction of some representative Grignard reagents with the racemic form of the β -lactam **11**, Scheme 4, was also tested. In particular, we speculated that reaction of **11** with aryl Grignard reagents should provide a straightforward route to immediate precursors of important γ -hydroxy- α -amino acids commonly found in natural products.¹⁴ The β -lactam **11** needed for the study was easily prepared by cycloaddition of methylketene, generated from propanoyl chloride and triethylamine, with the imine **8** in refluxing benzene.¹⁵ The resulting β -lactam **9** was then *N*-dearylated¹⁶ and the intermediate **10** subsequently *N*-Boc-protected to give the required compound **11** in 41% overall yield from **8**. Remarkably, Grignard reagents, on treatment with the β -lactam **11** under the same conditions as above, react selectively with the imide function to exclusively afford products **12** and **13**. For instance, methylmagnesium bromide reacted with **11** at –40 °C in THF as solvent to give a mixture of **12a**, **13a**, and the starting product **11** in a ratio of 70:10:20, respectively, without affecting the methoxycarbonyl group. In the case of aryl Grignard reagents, only β -amino ketones **12b** and **12c** were produced and in yields of 80% and 72%, respectively.

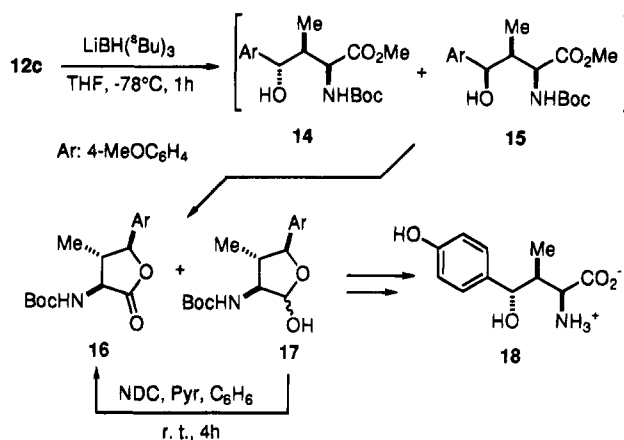
(13) For example, reaction of **2** with 4 equiv of phenylmagnesium bromide in THF or Et₂O at –40 °C to room temperature led to a mixture of the starting material and the corresponding opened product. When more Grignard reagent was added to the mixture any progress was observed.

(14) For some representative examples see: Nikkomycins or neopolyoxins: (a) Dähn, U.; Hagenmaier, H.; Höhne, H.; König, W. A.; Wolf, G.; Zähler, H. *Arch. Microbiol.* **1976**, *107*, 249. (b) Kobinata, K.; Uramoto, M.; Nishii, M.; Kusakabe, H.; Nokamura, G.; Isono, K. *Agric. Biol. Chem.* **1980**, *44*, 1709. (c) Isono, K.; Suzuki, S. *Heterocycles* **1979**, *13*, 333. Amino acids from mushrooms: (d) Hatanaka, S.-I. In *Progress in the Chemistry of Organic Natural Products*; Herz, W., Kirby, G. W., Moore, R. E., Steglich, W., Tamm, Ch., Eds.; Springer Verlag: New York, 1992; p 1.

(15) Palomo, C.; Aizpurua, J. M.; Ontoria, J. M.; Iturburu, M. *Tetrahedron Lett.* **1992**, *33*, 4823.

(16) Kobayashi, Y.; Ito, Y.; Terashima, S. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 3041.

Scheme 5



Finally, on the basis of previous findings by Barluenga and co-workers^{6,17} we expected that stereoselective reduction of the keto group in **12c** would provide, as shown in Scheme 5, the carbinol (4*S**)-**14** as the protected form of the α -amino acid fragment found in nikkomycins.^{14a–c} Actually, when **12c** was subjected to treatment with L-Selectride (Aldrich) at –78 °C, only the amino lactone **16** and the hemiacetal **17** were obtained in a ratio of 62:38, respectively. Under these conditions we did not detect the formation of either the corresponding epimeric lactone of **16** or the epimeric hemiacetal of **17**, which should arise from the minor (4*R**)-**15** alcohol.¹⁸ Although the relative stereochemistry of all of the stereogenic centers of the hemiacetal **17** was not determined, it was assumed as such on the basis of its conversion into the lactone **16** by a mild oxidation of the free hydroxy group using the mixed nicotinic–chromic anhydride (NDC) developed in our laboratory.¹⁹ By that means, the overall yield of the amino lactone **16** was 73%. This compound can be opened under suitable conditions²⁰ to give the nikkomycin-derived α -amino acid **18**, albeit in its racemic form.²¹

From the above results it is clear that the approach developed provides a general route for the preparation of a wide variety of α,γ -disubstituted β -amino ketones, which might be employed as precursors of α -amino acids and polyhydroxylated nitrogen-containing compounds. Further work on this subject is currently underway in our laboratory.

(17) Barluenga, J.; Viado, A. L.; Aguilar, E.; Fustero, S.; Olano, B. *J. Org. Chem.* **1993**, *58*, 5972.

(18) These results seem to indicate that the stereochemical outcome for the reduction step is consistent with a nonchelate Felkin–Anh model giving rise to the corresponding 4*S** alcohol, which spontaneously would cyclize to the lactone **16**. Nonetheless, it is also possible that the undetected (4*R**)-lactone, as pointed out by Barluenga¹⁷, epimerizes to the most stable (4*S**)-lactone. Attempts to use less than 2 equiv of L-Selectride to avoid overreduction resulted in incomplete conversion and recovering of the starting ketone **12c**.

(19) Cossio, F. P.; Lopez, M. C.; Palomo, C. *Tetrahedron* **1987**, *43*, 3963.

(20) (a) Jäger, V.; Grund, H.; Buss, V.; Schwab, W.; Müller, I.; Schohe, R.; Franz, R.; Ehrlé, R. *Bull. Soc. Chim. Belg.* **1983**, *92*, 1039. (b) Zimmermann, G.; Hass, N.; Faasch, H.; Schmalte, H.; König, W. A. *Liebigs Ann. Chem.* **1985**, 2165. (c) Barrett, A. G. M.; Lebold, S. A. *J. Org. Chem.* **1991**, *56*, 4875.

(21) The asymmetric synthesis of 3-alkyl-4-(alkoxycarbonyl) β -lactams, which would allow the synthesis of α -amino acids in their enantiomerically pure forms, is under development in our laboratory. For comprehensive reviews on α -amino acid synthesis, see: (a) Williams, R. M. *Synthesis of Optically Active α -Amino Acids*; Pergamon: Oxford, 1989. (b) Duthaler, R. O. *Tetrahedron* **1994**, *50*, 1539.

Experimental Section

Melting points were determined on a Büchi SMP-20 instrument and are uncorrected. Proton nuclear magnetic resonance spectra and ^{13}C spectra were recorded on a Varian VXR 300 spectrometer. All chemical shifts are reported as δ values (ppm) relative to internal tetramethylsilane. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrometer. Mass spectra were obtained using a Shimadzu GCMS QP-200 spectrometer operated at 70 eV. HPLC analysis were performed on a Shimadzu apparatus, using a SPD-6AV UV detector and Lichrosorb Si 60 (7 μm) preparative 25-cm column (Merck). Microanalytical data were obtained on a Perkin-Elmer 240-C instrument. Commercially available compounds were used in this work without further purification or were prepared following literature procedures. Acetonitrile and hexane were dried and purified by distillation. Tetrahydrofuran was distilled over sodium and benzophenone (indicator). Methylene chloride was shaken with concentrated sulfuric acid, dried over potassium carbonate, and distilled.

(3*R*,4*S*)-3-(Benzyloxy)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (3). A solution of $(\text{NH}_4)_2\text{Ce}(\text{NO}_3)_6$ (16.4 g, 30 mmol) in water (120 mL) was added dropwise to a solution of the (3*R*,4*S*)-3-(benzyloxy)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]-1-(4-methoxyphenyl)azetididin-2-one (3.83 g, 10 mmol) in acetonitrile (125 mL) at 0 °C. The mixture was stirred at this temperature for 30 min. Then, water (400 mL) was added, and this mixture was extracted with EtOAc (3 \times 150 mL) and washed with a saturated solution of NaHCO_3 (350 mL). The aqueous layer of NaHCO_3 was extracted again with EtOAc (60 mL), and all organic layers were washed with NaHSO_3 (40%) (4 \times 300 mL) and saturated solutions of NaHCO_3 (70 mL) and NaCl (70 mL). The organic layer was dried over MgSO_4 , and the solvents were removed in vacuo. The title β -lactam was purified by column chromatography (silica gel, hexane/EtOAc 3:1) and crystallized from hexane/Et₂O; yield 2.49 g (90%); mp 87–89 °C (hexane/Et₂O); IR (KBr) ν 3168 cm^{-1} (NH); 1749 cm^{-1} , 1718 cm^{-1} (C=O); $[\alpha]_D^{25} = +64.4$ ($c = 1.0$, CH_2Cl_2); $^1\text{H NMR}$ (CDCl_3) δ 7.39–7.30 (m, 5H, arom), 6.35 (s, 1H, NH), 4.92 (d, 1H, $J = -11.7$ Hz, HCH), 4.69 (dd, 1H, $J = 2.3$ Hz, $J' = 5.2$ Hz, CH), 4.65 (d, 1H, $J = -11.7$ Hz, HCH), 4.35–4.28 (m, 1H, CH), 4.14 (dd, 1H, $J = 6.6$ Hz, $J' = -8.8$ Hz, HCH), 3.69 (dd, 1H, $J = 5.2$ Hz, $J = 8.9$ Hz, CH), 3.64 (dd, 1H, $J = 5.8$ Hz, $J' = -8.8$ Hz, HCH), 1.42 (s, 3H, Me), 1.35 (s, 3H, Me). $^{13}\text{C NMR}$ (CDCl_3) δ 168.3, 136.7, 128.5, 128.2, 127.8, 109.5, 81.6, 76.9, 72.9, 66.6, 56.9, 26.8, 25.1. Anal. Calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.15; H, 6.85; N, 5.09.

(3*R*,4*S*)-3-(Benzyloxy)-1-(*tert*-butoxycarbonyl)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (4). Boc_2O (4.32 g, 20 mmol) and DMAP (0.12 g, 1 mmol) were added to a solution of the (3*R*,4*S*)-3-(benzyloxy)-4-[(*S*)-2,2-dimethyl-1,3-dioxolan-4-yl]azetididin-2-one (2.77 g, 10 mmol) in acetonitrile (24 mL) at 0 °C, and the mixture was stirred at room temperature overnight. Then, methylene chloride (25 mL) was added, and the mixture was washed with 1 M NaHSO_3 (2 \times 25 mL), a saturated solution of NaHCO_3 (25 mL), and a saturated solution of NaCl (25 mL). The organic layer was dried over MgSO_4 , and the solvent was removed in vacuo. Purification by column chromatography (silica gel, hexane/EtOAc 10:1) and crystallization from hexane/Et₂O furnished the title β -lactam: yield 3.17 g (84%); mp 104–105 °C (hexane/Et₂O); IR (KBr) ν 1810 cm^{-1} , 1794 cm^{-1} (C=O); 1705 cm^{-1} (C=O); $[\alpha]_D^{25} = +72.8$ ($c = 1.0$, CH_2Cl_2); $^1\text{H NMR}$ (CDCl_3) δ 7.35 (m, 5H, arom.), 4.92 (d, 1H, $J = -11.9$ Hz, HCH), 4.69 (d, 1H, $J = -11.9$ Hz, HCH), 4.66 (d, 1H, $J = 6.3$ Hz, CH), 4.38–4.29 (m, 1H, CH), 4.17–4.08 (m, 2H, CH, HCH), 3.92 (dd, 1H, $J = 5.7$, -8.6 Hz, HCH), 1.51 (s, 9H, Me₃), 1.45 (s, 3H, Me), 1.36 (s, 3H, Me); $^{13}\text{C NMR}$ (CDCl_3) δ 165.2, 147.8, 136.3, 128.4, 127.9, 109.7, 83.3, 79.4, 74.5, 73.3, 66.6, 59.5, 27.8, 26.2, 25.0. Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_8$: C, 63.64; H, 7.21; N, 3.71. Found: C, 63.37; H, 7.32; N, 3.68.

(3*S,4*S**)-*N*-(*Di-p*-anisylmethyl)-4-(methoxycarbonyl)-3-methylazetididin-2-one (9).**¹⁵ A solution of propionyl chloride (5.2 mL, 60 mmol) in benzene (25 mL) was added dropwise to a solution of (methoxycarbonyl)-*N*-(*di-p*-anisylmethyl)imine

(15.65 g, 50 mmol) and triethylamine (16.55 mL, 120 mmol) in benzene (150 mL) with molecular sieves (4 Å) (10 g) at room temperature. The resulting mixture was stirred magnetically, refluxed overnight, and then cooled to room temperature, filtered through Celite, and diluted with CH_2Cl_2 (100 mL). The resulting solution was washed with water (100 mL), 1 N HCl (100 mL), and NaHCO_3 (100 mL, saturated solution). The organic layer was separated and dried (MgSO_4). Evaporation of the solvents at reduced pressure gave the crude β -lactam, which was purified by column chromatography (silica gel 70–230 mesh, EtOAc/hexane 1:10 as eluent): yield 12.92 g (70%); oil; IR (film) ν , 1745 cm^{-1} (C=O); 1733 cm^{-1} (C=O); $^1\text{H NMR}$ (CDCl_3) δ 7.26 (d, 2H, $J = 8.5$ Hz, arom), 7.13 (d, 2H, $J = 8.4$ Hz, arom), 6.86 (d, 2H, $J = 8.8$ Hz, arom), 6.83 (d, 2H, $J = 8.8$ Hz, arom), 5.76 (s, 1H, CHC_6H_4), 4.09 (d, 1H, $J = 5.9$ Hz, CHCO_2Me), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 3.59 (s, 3H, OCH_3), 3.47 (m, 1H, CHCH_3), 1.20 (d, 3H, $J = 7.5$ Hz, CH_3CH); $^{13}\text{C NMR}$ (CDCl_3) δ 170.2, 169.4, 158.9, 132.2, 129.4, 129.3, 113.7, 60.9, 55.2, 51.9, 47.0, 9.7; MS (m/z) 369.

(3*S,4*S**)-4-(Methoxycarbonyl)-3-methylazetididin-2-one (10).** The same procedure for the preparation of **3** was used: yield 0.90 g (63%); oil; IR (film) ν 3237 cm^{-1} (NH); 1742 cm^{-1} (C=O); 1734 cm^{-1} (C=O); $^1\text{H NMR}$ (CDCl_3) δ 6.29 (s, 1H, NH), 4.29 (d, 1H, $J = 5.9$ Hz, CHN), 3.79 (s, 3H, OCH_3), 3.60 (m, 1H, CHCO), 1.20 (d, 3H, $J = 7.6$ Hz, CH_3CH); $^{13}\text{C NMR}$ (CDCl_3) δ 170.6, 170.2, 52.7, 52.3, 50.1, 10.1; MS (m/z) 144 ($M + 1$).

(3*S,4*S**)-4-(Methoxycarbonyl)-3-methyl-*N*-(*tert*-butoxycarbonyl)azetididin-2-one (11).** The same procedure for the preparation of **4** was used: yield 2.11 g (93%); oil; IR (film) ν 1810 cm^{-1} (C=O); 1743 cm^{-1} (C=O); 1723 cm^{-1} (C=O); $^1\text{H NMR}$ (CDCl_3) δ 4.50 (d, 1H, $J = 6.8$ Hz, CHN), 3.80 (s, 3H, OCH_3), 3.54 (m, 1H, CHCH_3), 1.50 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.20 (d, 3H, $J = 7.6$ Hz, CH_3CH); $^{13}\text{C NMR}$ (CDCl_3) δ 168.3, 165.9, 128.6, 54.7, 52.3, 47.3, 27.8, 9.0; MS (m/z) 187 ($M^+ - 56$).

General Procedure for the Coupling of β -Lactams with Grignard Reagents. **Method A.** The aryl- or alkyl-magnesium bromide (3.0 M in Et₂O) (0.43 mL, 1.3 mmol) was added to a solution of the β -lactam (0.38 g, 1 mmol) in THF (3 mL) at -78 °C. The reaction mixture was stirred at -40 °C (acetonitrile–CO₂ bath) for 1 h. A saturated solution of NH_4Cl (5 mL) was poured into the mixture and then extracted with methylene chloride (2 \times 10 mL). The organic layer was dried over MgSO_4 , and the solvent was removed in vacuo yielding the product. Purification by column chromatography on silica gel with hexane–ethyl acetate (10:1, 5:1) gave the β -amino ketone as an oil or a white solid, which was crystallized from hexane. **Method B.** The Grignard reagent (phenyl-, ethyl-, or methylmagnesium bromide) (3.0 M in Et₂O) (1.33 mL, 4 mmol) was added to a solution of the β -lactam (0.38 g, 1 mmol) in THF (3 mL) at -78 °C. The reaction mixture was warmed slowly at room temperature and stirred overnight. The usual workup and the purification by column chromatography on silica gel with hexane–ethyl acetate (10:1, 5:1) yielded the carbinol as an oil or a white solid, which was crystallized from hexane.

General Procedure for the Addition of Cuprate Reagents to *N*-Boc- β -lactams. To an ice-cooled suspension of CuI (0.19 g, 1 mmol) in Et₂O (4 mL) was added a 1.6 M solution of RLi (1.25 mL, 2 mmol) in Et₂O, and the mixture was stirred at 0 °C for 20 min. Then a solution of the β -lactam (0.19 g, 0.5 mmol) in Et₂O (2 mL) was added, and the resulting suspension was stirred at 0 °C for 1.5 h and then at room temperature overnight. The reaction was quenched with a saturated solution of NH_4Cl (5 mL), stirred for 15 min, and extracted with methylene chloride (2 \times 10 mL). The organic layer was dried over MgSO_4 , and the solvent was removed in vacuo. Purification by column chromatography on silica gel with hexane–ethyl acetate (10:1, 5:1) gave the β -amino ketone as a white solid.

Compound 7a. To a solution of lithium diisopropylamide (LDA) at -78 °C, prepared from diisopropylamine (0.49 mL, 3.5 mmol) and *n*-butyllithium (2.19 mL, 3.15 mmol) in THF (15 mL) under nitrogen atmosphere, was added methyl acetate (0.25 mL, 3.15 mmol) dropwise. The mixture was stirred at -78 °C for 30 min, and then a solution of β -lactam **4** (0.38 g,

1 mmol) in THF (5 mL) was added dropwise at the same temperature. The resulting mixture was kept at $-78\text{ }^{\circ}\text{C}$ for 30 min and quenched with a solution of ammonium chloride (1.5 g) in water (25 mL). The mixture was allowed to warm room temperature and extracted with methylene chloride ($2 \times 25\text{ mL}$). The organic layer was washed with 0.1 N HCl (25 mL), NaHCO_3 (25 mL, saturated solution), water (25 mL), and dried over Na_2SO_4 . The solvent was removed in vacuo, yielding an oil which was purified by column chromatography (AcOEt/hexane 1:10) to give a solid which was crystallized from hexane: yield 0.33 g (73%); mp $80\text{--}81\text{ }^{\circ}\text{C}$ (hexane); IR (KBr) ν 3404 cm^{-1} ; 1730 cm^{-1} (C=O); 1695 cm^{-1} (C=O); $[\alpha]_{\text{D}}^{25} = -3.2$ ($c = 1.0$, CH_2Cl_2); $^1\text{H NMR}$ (CDCl_3) δ 7.35–7.31 (m, 5H, arom), 5.17 (d, 1H, $J = 8.8\text{ Hz}$, NH), 4.63 (d, 1H, $J = -11.6\text{ Hz}$, HCH), 4.56 (d, 1H, $J = -11.6\text{ Hz}$, HCH), 4.40–4.32 (m, 1H, CH), 4.12–4.02 (m, 2H, CH, CH), 3.91 (dd, 1H, $J = 6.8\text{ Hz}$, $J' = -8.4\text{ Hz}$, HCH), 3.77–3.64 (m, 3H, HCH, HCH), 3.66 (s, 9H, OCH_3), 1.44 (s, 9H, Me_3), 1.35 (s, 3H, Me), 1.30 (s, 3H, Me); $^{13}\text{C NMR}$ (CDCl_3) δ 204.0, 167.8, 155.7, 136.7, 128.5, 128.4, 128.2, 128.1, 128.0, 109.5, 82.8, 79.9, 73.6, 73.0, 65.8, 52.1, 51.6, 45.9, 28.2, 26.0, 25.0. Anal. Calcd for $\text{C}_{23}\text{H}_{33}\text{NO}_3$: C, 61.18; H, 7.37; N, 3.10. Found: C, 61.06; H, 7.31; N, 3.15.

Compound 12c: yield 0.25 g (72%); oil, IR (film) ν 3335 cm^{-1} (NH); 1735 cm^{-1} (C=O); 1708 cm^{-1} (C=O); 1670 cm^{-1} (C=O); $^1\text{H NMR}$ (CDCl_3) δ 7.96 (d, 2H, $J = 9.0\text{ Hz}$, arom), 6.95 (d, 2H, $J = 9.0\text{ Hz}$, arom), 5.31 (d, 1H, $J = 8.1\text{ Hz}$, NH), 4.59 (dd, 1H, $J = 5.9\text{ Hz}$, $J' = 8.3\text{ Hz}$, CHNH), 4.07 (m, 1H, CHCH_3), 3.87 (s, 3H, OCH_3), 3.74 (s, 3H, OCH_3), 1.42 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.28 (d, 3H, $J = 7.3\text{ Hz}$, CH_3CH); $^{13}\text{C NMR}$ (CDCl_3) δ 199.3, 171.7, 163.6, 155.2, 130.6, 113.8, 79.9, 55.6, 55.4, 52.3, 42.7, 28.1, 13.8.

Reduction of 12c with L-Selectride. Preparation of 16. To a dry ice-cooled ($-78\text{ }^{\circ}\text{C}$) solution of **12c** (0.35g, 1.0 mmol) in anhydrous THF (6 mL) was added a 1 M solution of L-Selectride (2.0 mL, 2.0 mmol) in the same solvent, and the mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h. Then, the reaction mixture was quenched with a saturated solution of NH_4Cl (6 mL), extracted with Et_2O (15 mL), and filtered through Celite to give an organic solution which was dried (MgSO_4) and evaporated in vacuo to afford a 62:38 mixture of **16** and **17** as

a colorless oil. Separation by column chromatography on silica gel with hexane–ethyl acetate (10:1, then 5:1) gave compounds **16** and **17**. Compound **16:** yield 0.16 g (50%); oil; IR (film) ν 3340 cm^{-1} (NH); 1781 cm^{-1} (C=O); 1707 cm^{-1} (C=O); $^1\text{H NMR}$ (CDCl_3) δ 7.28 (d, 2H, arom), 6.92 (d, 2H, arom), 5.10 (d, 1H, $J = 7.6\text{ Hz}$, NH), 4.83 (d, 1H, $J = 10.3\text{ Hz}$, CHO), 4.26 (dd, 1H, $J = 11.5\text{ Hz}$, $J' = 7.6\text{ Hz}$, CHNH), 3.82 (s, 3H, OMe), 1.47 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.17 (d, 3H, $J = 6.4\text{ Hz}$, CH_3CH); $^{13}\text{C NMR}$ (CDCl_3) δ 174.2, 160.2, 155.5, 136.0, 128.1, 114.1, 84.7, 80.5, 57.9, 55.3, 46.8, 28.2, 13.6. Compound **17:** yield 0.09 g (28%); oil; IR (film) ν 3386 cm^{-1} (OH); 3374 cm^{-1} (NH); 1709 cm^{-1} (C=O); $^1\text{H NMR}$ (CDCl_3) δ 7.30 (d, 2H, arom), 6.86 (d, 2H, arom), 5.34 (d, 1H, $J = 4.3\text{ Hz}$, NH), 5.06 (dd, 1H, $J = 9.3\text{ Hz}$, CHO), 4.43 (d, 1H, $J = 9.3\text{ Hz}$, CHN), 4.33 (s, 1H, OH), 3.78 (s, 3H, OCH_3), 2.04 (m, 1H, CHCH_3), 1.45 (s, 9H, $\text{C}(\text{CH}_3)_3$), 1.02 (d, 3H, $J = 6.4\text{ Hz}$, CH_3CH). This compound (0.09 g, 0.28 mmol) in benzene (0.5 mL) was added to a suspension of NDC (0.32 g, 0.70 mmol) and pyridine (0.45 mL, 5.57 mmol) in the same solvent (1 mL), and the mixture was stirred at room temperature for 4 h. Afterwards, the suspension was filtered through a pad of silica gel, and the organic solution was washed with 6 N HCl (1 mL) and NaHCO_3 (1 mL), dried over MgSO_4 , and evaporated to give 0.074 g of **16** as a viscous oil (83%). Overall yield of **16** 0.234 g (73%).

Acknowledgment. Financial support of this work by the Universidad del País Vasco (Project UPV 170.215-EA172/93) and in part by Gobierno Vasco (Project PI9386) as well as a grant from the Ministerio de Educación y Ciencia to M. I. and a grant from Gobierno Vasco to J. M. G. are gratefully acknowledged.

Supplementary Material Available: Spectral and analytical data ($^1\text{H NMR}$, $^{13}\text{C NMR}$, IR, MS) are provided for compounds **5**, **6**, **7b**, and **12a,b** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.