Synthetic Applications of 1-Aminoalkyl Chloromethyl Ketones. Synthesis of Enantiopure 3-Azetidinols and Aminoalkyl Epoxides

José Barluenga,* Beatriz Baragaña, and José M. Concellón*

Instituto Universitario de Química Organometálica "Enrique Moles", Universidad de Oviedo, Julián Clavería s/n, 33071 Oviedo, Spain

Received January 10, 1997[⊗]

Addition of several organocerium compounds to chiral 1-aminoalkyl chloromethyl ketones **1** affords, after deprotection, enantiomerically pure 3-azetidinols **5**. The synthesis of enantiopure amino epoxides **8** is also described by successive treatment of chiral α-amino ketones **1** with organocerium compounds and methyllithium.

Introduction

Azetidines are of widespread interest because of their reactivity[1] and biological activity.[2] However, the chiral azetidine skeleton has been one of the most difficult amines to synthesize because of its ring strain,[1a,3] and development of effective general methods for the synthesis of enantiomerically pure azetidines is of significant value.[4] Thus, chiral 3-azetidinols can be obtained from the reduction of *β*-lactams,[5] cyclization of 3-amino-1,2-diols,[6] and nitrogen nucleophilic substitution of L-threitol.[7] Despite these methods, a simpler and more direct entry to enantiomerically pure 3-azetidinols[8] by cyclization of chiral 3-amino-1-chloroalkan-2-ols would be desirable.

Recently, we have reported the direct preparation of chiral 1-aminoalkyl chloromethyl ketones[9] and their reduction to *threo* α-aminoalkyl epoxides with high diastereoselectivity (94−98%).[10] These results prompted us to investigate the previously unreported reaction of chiral α-amino ketones with organometallic compounds. This reaction would afford the suitable chiral *γ*-chloro amines that could be easily transformed into chiral azetidinols, since their cyclization would be favored by the presence of the hydroxyl and alkyl groups at C2 and by the bulky groups on the nitrogen.[11] Thus, in this paper, we report the preparation of enantiomerically pure 3-azetidinols in an efficient synthesis starting from 1-aminoalkyl chloromethyl ketones. We also report the generalization of the synthesis of α-amino epoxides, because of their synthetic usefulness,[12] through the addition of organometallic compounds to 1-aminoalkyl chloromethyl ketones. In both cases, the addition of the organometallic compounds to the ketones takes place with high diastereoselectivity and full retention of the stereochemistry at the α-carbon of the starting α-amino ketone.

Results and Discussion

The reaction of 1-aminoalkyl chloromethyl ketones **1** with different organocerium compounds at −60 °C gave, after hydrolysis, the corresponding chlorohydrins **3** in high yield. Compounds **3** were stable in tetrahydrofuran solution.[13] When the solvents were completely evaporated to dryness at room temperature, heterocyclization of compound **3** gave the corresponding azetidinium salt **4** with high diastereoselectivity (see Experimental Section and Scheme 1).

Organocerium reagents were prepared by treatment of anhydrous cerium trichloride with organolithium[14] or organomagnesium[15] compounds in THF at −60 °C. Compounds **1** were synthesized in enantiomerically pure form starting from α-amino acids.[9] Dibenzylated ketones **1** were used as starting compounds instead of other

[⊗] Abstract published in *Advance ACS Abstracts,* August 1, 1997.

(1) Review: (a) Davies, D. E.; Storr, R. C. In *Comprenhensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon: Oxford, 1984; Vol. 7, pp 238−284. Other recent synthetic applications of azetidines: (b) Jung, M. E.; Choi, Y. M. *J. Org. Chem.* **1991**, *56*, 6729. (c) Viallon, L.; Reinand, O.; Capdevielle, P.; Maumy, M. *Tetrahedron Lett.* **1995**, *36*, 4787.

(2) (a) Testa, E.; Wittigens, A.; Meffii, G.; Bianchi, G. In *Research Progress in Organic, Biological and Medical Chemistry*; Gallo, U., Santamaria, L., Eds.; North-Holland Publishing Co.: Amsterdam, 1964; Vol. 1, pp 477−583. (b) Okutani, T.; Kaneko, T.; Masuda, K. *Chem. Pharm. Bull.* **1974**, *22*, 1490. (c) Kobayashi, J.; Cheng, J.; Ishibashi, M.; Wälchli, M. P.; Yamamura, S.; Ohizumi, Y. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1135. (d) Frigola, J.; Torrens, A.; Castrillo, J. A.; Mas, J.; Vañó, D.; Berrocal, J. M.; Calvet, C.; Salgado, L.; Redondo, J.; García-Granda, S.; Valentí, E.; Quintana, J. R. *J. Med. Chem.* **1994**, *37*, 4195.

(3) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331.

(4) Recently a synthesis of enantiomerically pure polysubstituted azetidines from 1,3-amino alcohols has been described: Barluenga, J.; Fernández-Marí, F.; Viado, A. L.; Aguilar, E.; Olano, B. *J. Org. Chem.* **1996**, *61*, 5659.

(5) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K.; Yamashita, M.; Abe, R. *J. Org. Chem.* **1991**, *56*, 5263 and references cited therein.

(6) (a) Poch, M.; Verdaguer, X.; Moyano, A.; Pericás, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6935. (b) Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **1995**, *36*, 4841. (c) Takikawa, H.; Maeda, T.; Mori, K. *Tetrahedron Lett.* **1995**, *36*, 7689.

(7) Wells, J. N. ; Tarwater, O. R. *J. Pharm. Bull.* **1974**, *22*, 1490.

(8) 3-Azetidinols as racemic mixture have been prepared from 1-(alkylamino)-3-chloro-2-alkanols: (a) Gaertner, V. R. *J. Org. Chem.* **1967**, *32*, 2972. (b) Higgins, R. H.; Eaton, Q. L.; Worth, L. Jr.; Peterson, M. V. *J. Heterocycl. Chem.* **1987**, *24*, 255.

(9) Barluenga, J.; Baragaña, B.; Alonso, A.; Concellón, J. M. *J. Chem. Soc., Chem. Commun.* **1994**, 969.

(10) Barluenga, J.; Baragaña, B.; Concellón, J. M. *J. Org. Chem.* **1995**, *60*, 6696.

(11) Moore, J. A.; Ayers, R. S. In *The Chemistry of Heterocyclic Compounds. Small Ring Heterocycles*; Hassner, A., Ed.; J. Wiley and Son.: New York, 1983; vol. 42, Part 2, p 11.

(12) Amino epoxides are used in synthesis of several important compounds. See, for instance: amino sugars: (a) McGarvey, G. J.; Kimura, M.; Oh, T.; Williams, J. M. *J. Carbohydr. Chem.* **1984**, *3*, 125. (b) Hauser, F. M.; Ellenberger, S. R. *J. Org. Chem.* **1986**, *51*, 50 and references cited therein. Polyoxygenated amino acids: (c) Hua, D. Y.; Miao, S. W.; Chen, J. S.; Iguchi, S. *J. Org. Chem.* **1991**, *56*, 4. Hydroxyethylene dipeptide isosteres: (d) Thompson, W. J.; Fitzgerald, P. M. D.; Holloway, M. K.; Emini, E. A.; Darke, P. L.; Mckeever, B. M.; Schleif, W. A.; Quintero, J. C.; Zugay, J. A.; Tucker, T. J.; Schwering, J. E.; Homnick, C. F.; Numberg, J.; Springer, J. P.; Huff, J. R. *J. Med. Chem.* **1992**, *35*, 1685. (e) Askin, D.; Wallace, M. A.; Vacca, J. P.; Reamer, R. A.; Volante, R. P.; Shinkai, I. *J. Org. Chem.* **1992**, *57*, 2771. Peptidyl epoxides: (f) Albeck, A.; Fluss, S.; Persky. R. *J. Am. Chem. Soc.* **1996**, *118*, 3591.

(13) Compound **3b** with 30% of THF was characterized by ^{13}C NMR *δ* 5.7, 13.3, 22.4, 25.0, 35.0, 50.9, 54.8, 55.1, 75.7, 126.4, 127.6, 128.4, 139.2.

(14) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, T.; Mita, Y.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.

(15) Imamoto, T.; Takiyama, N.; Nakamura, K.; Hatajima, T.; Kamiya, Y. *J. Am. Chem. Soc.* **1989**, *111*, 4392.

S0022-3263(97)00058-3 CCC: $14.00

Scheme 1

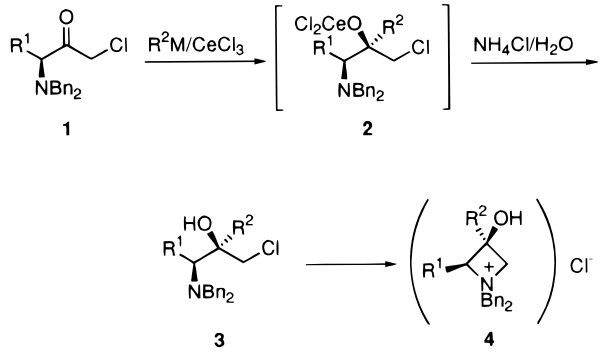
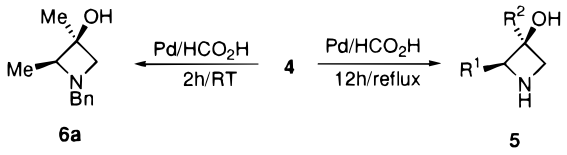


Table 1. Synthesis of Azetidinium Salts 4

product	R^1	R^2	M	yield (%)[a]	de[b]
4a	Me	Me	Li	84	94
4b	Me	Bu	Li	84	>95
4c	Me	allyl	Mg	80	>95
4d	*i*-Bu	Me	Li	76	90
4e	Bn	Me	Li	75	90
4f	Bn	Bu	Li	74	90

[a] Isolated yield based on the starting ketone **1**. [b] Diastereoisomeric excess determined by 300 MHz ^{1}H NMR analysis of the crude products **4**.

Scheme 2



N-protected ketones due to their stability and high diastereoselectivity showed in their reduction reaction.[10]

The diastereoisomeric excess (de) of azetidinium salts **4** (ranging between 90% and >95%) was determinated by 300 MHz ^{1}H NMR analysis. The degree of stereoselectivity was only moderately affected by the size of R^2 in the organometallic compound and R^1 at the stereogenic center in the α-amino ketone (see Table 1). Configurational assignments of product **4** were made by NOE experiments of compound **4a**. Saturation of the methyl hydrogens at C-3 produced positive NOE in H-2 proton, confirming the *cis* relationship of these protons and the *trans* relative stereochemistry for both methyl groups.

The addition of organocerium reagent to ketone **1** takes place under nonchelation control, in agreement with the previously reported addition of organometallic compounds to dibenzylated amino aldehydes[16] or reduction of amino ketones.[10,17]

We have studied the deprotection of azetidinium salts **4**. When compounds **4b** and **4d** were treated with HCO_2H in the presence of palladium in refluxing methanol for 12 h,[18] the expected 3-azetidinols **5b** and **5d** were isolated respectively (90% yield). *N*-Benzylazetidinol can be also obtained; **6a** was prepared by reaction of **4a** with HCO_2H/Pd in methanol at room temperature for 2 h (95% yield) (see Scheme 2).

Scheme 3

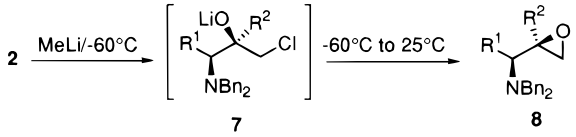


Table 2. Synthesis of Amino Epoxides 8

product	R^1	R^2	yield (%)[a]	de[b]
8a	Me	Me	75	94
8b	Me	Bu	84	>95
8c	Me	allyl	70	>95
8d	*i*-Bu	Me	75	90
8e	Bn	Me	70	90[c]
8f	Bn	Bu	60	90[d]
8g	Me	Ph	80	>95

[a] Isolated yield based on the starting ketone **1**. [b] Diastereoisomeric excess determined by 300 MHz ^{1}H NMR analysis of the crude products **8**. [c] ee > 99% HPLC (Chiracel OD-H; UV detector: **8e**, 220 nm; 0.8 mL/min; 50:1 hexane/2-propanol; t_R: **8e**, 13.58 min). [d] ee > 99% HPLC (Chiracel OD-H; UV detector: **8f,** 210 nm; 0.8 mL/min; 30:1 hexane/2-propanol; t_R: **8f**, 20.25 min).

Treatment of intermediate **2** with methyllithium at −60 °C, gave the corresponding lithium alcoholate **7**. When the reaction mixture was allowed to warm to room temperature, the epoxide **8** was isolated, as shown in Scheme 3.[19] Yields and diastereoisomeric excess are summarized in Table 2.

The racemization of *N*-protected carbonyl compounds derived from phenylalanine has been carefully documentated.[20] Under the described reaction conditions the addition of organocerium reagents to the ketone **1** derived from phenylalanine took place with no detectable racemization. The enantiomeric purity of product **8e** and **8f** was determinated by chiral HPLC (Chiracel OD-H) analysis, showing an enantiomeric excess (ee) >99% in both cases; racemic mixtures of **8e** and **8f** were prepared to exclude the possibility of comigration of both enantiomers in HPLC.

In conclusion, we have demonstrated the synthetic utility of the reaction of chiral 1-aminoalkyl chloromethyl ketones with organometallic compounds affording enantiomerically pure 3-azetidinols and α-amino epoxides with high yield and diastereoselectivity. This method is general and simple, and the starting materials are easily available.

Experimental Section

General. Analytical TLC was conducted in precoated silica gel 60 F-254 on aluminum sheets; compounds were visualized with UV light or iodine. ^{1}H NMR spectra were recorded at 300 or 200 MHz. ^{13}C NMR spectra were recorded at 75 or 50 MHz. Chemical shifts are reported in ppm relative to TMS in $CDCl_3$. Only the molecular ions and/or base peaks in MS are given. The enantiomeric purity was determined by chiral HPLC analysis using a Chiracel OD-H (0.46 × 25 cm, Diacel) column.

Methyllithium, butyllithium, lithium bromide, formic acid, allylmagnesium bromide, cerium chloride, and palladium black were purchased from Aldrich and were used without further purification. All the reactions were conducted in oven-dried glasswere under dry nitrogen. All solvents were purified before use. THF was distilled from sodium benzophenone ketyl; methanol was distilled from magnesium turnings.

(16) (a) Reetz, M. T.; Drewes, M. W.; Schmitz, A. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1141. (b) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1531.

(17) Reetz, M. T.; Drewes, M. W.; Lennick, K.; Schmitz, A.; Holdgrün, X. *Tetrahedron: Asymmetry* **1990**, *1*, 375.

(18) ElAmin, B.; Anantharamaiah, G. M.; Royer, G. P.; Means, G. E. *J. Org. Chem.* **1979**, *44*, 3442.

(19) When intermediates **2** were hydrolyzed at room temperature, compounds **4** were isolated instead of epoxides **8**.

(20) Rittle, K. E.; Homnick, C. F.; Ponciello, G. S.; Evans, B. E. *J. Org. Chem.* **1982**, *47*, 3016.

Azetidinium Salts 4. A suspension of anhydrous $CeCl_3$ (1.97 g; 8 mmol) in THF (30 mL) was stirred overnight at room temperature. Organolithium or allylmagnesium bromide (8 mmol) was added to this suspension at −60 °C, and the mixture was stirred at this temperature for 1 h . Ketone **1** (4 mmol) was added, and after stirring for 2 h at −60 °C the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was recrystallized from CH_2Cl_2−EtOAc to give **4** as white crystalline powder.

(2*S*,3*S*)-1,1-Dibenzyl-3-hydroxy-2,3-dimethylazetidinium Chloride (4a) (84% yield): $[\alpha]^{25}_D$ +26.6 (*c* 0.36, $CHCl_3$); ^{1}H NMR δ 1.20 (s, 3 H), 1.60 (d, J = 6.9 Hz, 3 H), 3.94 (d, J = 11.2 Hz, 1 H), 4.30 (d, J = 13.1 Hz, 1 H), 4.57 (d, J = 11.2 Hz, 1 H), 4.70 (q, J = 6.9 Hz, 1 H), 4.80 (d, J = 12.5 Hz, 1 H), 5.06 (d, J = 13.1 Hz, 1 H), 5.28 (d, J = 12.5 Hz, 1 H), 6.88 (s, 1 H), 7.31−7.53 (m, 8 H), 7.79−7.81 (m, 2 H); ^{13}C NMR δ 8.1, 24.4, 58.9, 61.1, 66.4, 69.8, 77.4, 127.7, 128.1, 129.1, 130.0, 130.3, 132.6, 133.0; MS (FAB) *m*/*z* (rel intensity) 317 (M^+, >1), 282 (M^+ − Cl, 100). Anal. Calcd for $C_{19}H_{24}ClNO$: C, 71.80; H, 7.61; N, 4.41. Found: C, 71.52; H, 7.58; N, 4.39.

(2*S*,3*S*)-1,1-Dibenzyl-3-butyl-3-hydroxy-2-methylazetidinium Chloride (4b) (84% yield): $[\alpha]^{25}_D$ +7.3 (*c* 0.95, $CHCl_3$); ^{1}H NMR δ 0.56−0.60 (m, 3 H), 0.81−0.96 (m, 4H), 1.16−1.21 (m, 2H), 1.67 (d, J = 6.9 Hz, 3 H), 3.74 (d, J = 11.6 Hz, 1 H), 3.93 (d, J = 12.9 Hz, 1 H), 4.51−4.63 (m, 2 H), 4.85 (d, J = 12.5 Hz, 1 H), 5.17 (d, J = 12.9 Hz, 1 H), 5.33 (d, J = 12.5 Hz, 1 H), 6.77 (s, 1 H), 7.24−7.40 (m, 8 H), 7.81−7.84 (m, 2 H); ^{13}C NMR δ 8.7, 13.5, 22.1, 25.0, 37.3, 59.9, 60.9, 64.0, 71.5, 75.5, 127.7, 128.1, 128.9, 129.8, 130.2, 132.8, 133.1; MS (FAB) *m*/*z* (rel intensity) 358 (M^+, >1), 324 (100). Anal. Calcd for $C_{22}H_{29}ClNO$: C, 73.62; H, 8.14; N, 3.90. Found: C, 73.70; H, 8.02; N, 3.81.

(2*S*,3*S*)-3-Allyl-1,1-dibenzyl-3-hydroxy-2-methylazetidinium Chloride (4c) (80% yield): $[\alpha]^{25}_D$ +14.8 (*c* 0.52, $CHCl_3$); ^{1}H NMR δ 1.69 (d, J = 7.0 Hz, 3 H), 2.08−2.23 (m, 2 H), 3.86 (d, J = 11.7 Hz, 1 H), 4.05 (d, J = 13.2 Hz, 1 H), 4.59 (d, J = 11.7 Hz, 1 H), 4.65 (q, J = 7.0 Hz, 1 H), 4.73−4.78 (m, 2 H), 4.88 (d, J = 12.4 Hz, 1 H), 5.13 (d, J = 13.2 Hz, 1 H), 5.24−5.35 (m, 2 H), 6.30 (s, 1 H), 7.40−7.51 (m, 8 H), 7.82−7.85 (m, 2 H); ^{13}C NMR δ 8.9, 42.3, 60.3, 61.2, 63.6, 71.7, 74.8, 119.4, 127.7, 128.0, 129.2, 129.3, 130.3, 130.6, 131.1, 133.1, 133.3; MS (FAB) *m*/*z* (rel intensity) 344 (M^+ + 1, 2), 308 (M^+ − Cl, 33), 133 (100). Anal. Calcd for $C_{21}H_{26}ClNO$: C, 73.35; H, 7.62; N, 4.07. Found: C, 73.31; H, 7.71; N, 3.99.

(2*S*,3*S*)-1,1-Dibenzyl-3-hydroxy-3-methyl-2-(2-methylpropyl)azetidinium Chloride (4d) (76% yield): $[\alpha]^{25}_D$ +33.4 (*c* 0.53, $CHCl_3$); ^{1}H NMR δ 0.79 (d, J = 5.6 Hz, 3 H), 0.84 (d, J = 5.6 Hz, 3 H), 1.18 (s, 3 H), 1.54−1.57 (m, 2 H), 2.21−2.31 (m, 1 H), 3.80 (d, J = 11.1 Hz, 1 H), 4.17 (d, J = 13.0 Hz, 1 H), 4.43−4.57 (m, 2 H), 4.71 (d, J = 12.5 Hz, 1 H), 4.99 (d, J = 13.0 Hz, 1 H), 5.22 (d, J = 12.5 Hz, 1 H), 6.92 (s, 1 H), 7.27−7.44 (m, 8 H), 7.75−7.80 (m, 2 H); ^{13}C NMR δ 20.9, 23.8, 24.3, 25.9, 30.8, 59.5, 61.2, 65.8, 69.8, 78.6, 127.7, 128.1, 129.0, 129.9, 130.4, 132.7, 133.2; MS (FAB) *m*/*z* (rel intensity) 358 (M^+ − 1, <1), 324 (100). Anal. Calcd for $C_{22}H_{30}ClNO$: C, 73.41; H, 8.40; N, 3.89. Found: C, 73.19; H, 8.27; N, 3.87.

(2*S*,3*S*)-1,1,2-Tribenzyl-3-hydroxy-3-methylazetidinium Chloride (4e) (75% yield): $[\alpha]^{25}_D$ +35.0 (*c* 0.70, $CHCl_3$); ^{1}H NMR δ 0.84 (s, 3 H), 2.06 (s, 1 H), 3.52−3.63 (m, 2 H), 3.75 (d, J = 11.6 Hz, 1 H), 4.08 (d, J = 13.3 Hz, 1 H), 4.39 (dd, J = 4.3, 10.3 Hz, 1 H), 4.72 (d, J = 11.6 Hz, 1 H), 5.07 (d, J = 12.5 Hz, 1 H), 5.20 (d, J = 13.3 Hz, 1 H), 5.55 (d, J = 12.5 Hz, 1 H), 7.14−7.48 (m, 13 H), 7.86−7.88 (m, 2 H); ^{13}C NMR δ 25.7, 28.7, 60.5, 61.1, 65.2, 69.8, 79.5 126.8, 127.7, 128.2, 128.4, 129.07, 129.14, 129.4, 129.6, 130.1, 130.5, 132.8, 133.2, 133.3, 133.5, 134.5; MS (FAB) *m*/*z* (rel intensity) 393 (M^+, 1), 358 (M^+ − Cl, 100). Anal. Calcd for $C_{25}H_{28}ClNO$: C, 76.22; H, 7.16; N, 3.56. Found: C, 76.01; H, 7.27; N, 3.48.

(2*S*,3*S*)-1,1,2-Tribenzyl-3-butyl-3-hydroxyazetidinium Chloride (4f) (74% yield): $[\alpha]^{25}_D$ +32.9 (*c* 1.36, $CHCl_3$); ^{1}H NMR δ 0.01−0.44 (m, 5 H), 0.71−0.78 (m, 3 H), 1.04−1.13 (m, 1 H), 2.56 (br s, 1 H), 3.56−3.71 (m, 2 H), 3.87 (d, J = 13.1 Hz, 1 H), 3.98 (d, J = 11.6 Hz, 1 H), 4.48 (d, J = 11.6 Hz, 1 H), 4.74 (d, J = 11.2 Hz, 1 H), 5.19 (d, J = 12.0 Hz, 1 H), 5.47 (d, J = 13.1 Hz, 1 H), 5.63 (d, J = 12.0 Hz, 1 H), 7.11−7.48 (m, 13 H), 8.01−7.99 (m, 2 H); ^{13}C NMR δ 12.9, 21.5, 24.7, 28.4, 37.5, 60.8, 60.9, 61.8, 71.9, 76.8, 126.4, 127.6, 128.0, 128.6, 128.7, 129.4, 129.6, 130.1, 132.8, 133.2, 134.6; MS (FAB) *m*/*z* (rel intensity) 400 (M^+ − Cl, 100). Anal. Calcd for $C_{28}H_{34}ClNO$: C, 77.13; H, 7.86; N, 3.21. Found: C, 76.89; H, 7.69; N, 3.12.

3-Azetidinols 5. A solution of the azetidinium salt **4** (0.3 g) in 5% formic acid−methanol (30 mL) containing palladium black catalyst (0.3 g) was stirred at reflux temperature overnight. Then, the reaction mixture is filtrated through Celite and evaporated to dryness. The residue was extracted into CH_2Cl_2 (10mL) and washed with saturated K_2CO_3. The organic layer was dried (Na_2SO_4), and the solvents were removed in vacuo to provide 3-azetinols **5**.

(2*S*,3*S*)-3-Butyl-2-methyl-3-azetidinol (5b) (90% yield): $[\alpha]^{25}_D$ −3.8 (*c* 1.43, CH_2Cl_2); ^{1}H NMR δ 0.83−0.90 (m, 3 H), 1.18 (d, J = 6.7 Hz, 3 H), 1.26−1.34 (m, 4 H), 1.56−1.61 (m, 2 H), 3.26 (d, J = 8.8 Hz, 1 H), 3.49 (d, J = 8.8 Hz, 1 H), 3.59 (br s, 2H), 3.72 (q, J = 6.7 Hz, 1 H); ^{13}C NMR δ 13.9, 16.0, 22.9, 25.3, 39.0, 57.1, 63.4, 76.0; MS (EI) *m*/*z* (rel intensity) 144 (M^+ + 1, 5), 58 (100). Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 66.82; H, 11.83; N, 9.64.

(2*S*,3*S*)-3-Methyl-2-(2-methylpropyl)-3-azetidinol (5d) (90% yield): $[\alpha]^{25}_D$ +2.5 (*c* 0.47, $CHCl_3$); ^{1}H NMR δ 0.88−0.94 (m, 6 H), 1.37 (s, 3 H), 1.49−1.68 (m, 3 H), 3.37 (d, J = 8.8 Hz, 1 H), 3.60 (d, J = 8.8 Hz, 1 H), 3.76−3.80 (m, 1H), 4.18 (br s, 2 H); ^{13}C NMR δ 22.6, 22.9, 24.7, 25.8, 38.6, 57.8, 67.5, 74.0, 77.1; MS (EI) *m*/*z* (rel intensity) 128 (M^+ − CH_3, <1), 100 (M^+ − C_3H_7, 7), 86 (M^+ − C_4H_9, 100). Anal. Calcd for $C_8H_{17}NO$: C, 67.09; H, 11.96; N, 9.78. Found: C, 67.22; H, 11.91; N, 9.69.

(2*S*,3*S*)-1-Benzyl-2,3-dimethyl-3-azetidinol (6a). A solution of the azetidinium salt **4a** (0.3 g) in 5% formic acid−methanol (30 mL) containing palladium black catalyst (0.3 g) was stirred at room temperature for 2 h. Then, the reaction mixture is filtered through Celite and evaporated to dryness. The residue was extracted with CH_2Cl_2 (10mL) and washed with saturated K_2CO_3. The organic layer was dried (Na_2SO_4), and the solvents were removed in vacuo to provide 1-benzyl-3-azetinol **6a** (90% yield): $[\alpha]^{25}_D$ +55.8 (*c* 0.45, $CHCl_3$); ^{1}H NMR δ 1.03 (d, J = 6.4 Hz, 3 H), 1.25 (s, 3 H), 2.84 (d, J = 8.6 Hz, 1 H), 3.07−3.14 (m, 2 H), 3.48 (d, J = 12.2 Hz, 1 H), 3.70 (d, J = 12.2 Hz, 1 H), 4.32 (br s, 1 H), 7.27−7.32 (m, 5 H); ^{13}C NMR δ 12.7, 24.8, 61.5, 65.1, 71.1, 71.2, 127.0, 127.9, 129.3, 137.0; MS (EI) *m*/*z* (rel intensity) 191 (M^+, 2), 91 (100).

Amino Epoxides 8. A suspension of anhydrous $CeCl_3$ (1.97 g; 8 mmol) in THF (30 mL) was stirred overnight at room temperature. Organolithium or allylmagnesium bromide (8 mmol) was added to this suspension at −60 °C, and the mixture was stirred at this temperature for 1 h. Ketone **1** (4 mmol) was added, and after stirring for 2 h at −60 °C, methyllithium (3.2 mL of 1.5 M solution in diethyl ether; 4.8 mmol) was added and the mixture was allowed to warm to room temperature. Stirring was continued for 1 h, and the reaction was hydrolyzed with aqueous NH_4Cl (10 mL) and extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried (Na_2SO_4), and the solvents were removed in vacuo. The epoxides **6** were examined by ^{1}H NMR to give the diasteromeric excess reported in Table 2. Column flash chromatography over silica gel (15/1 *n*-hexane/ethyl acetate) provided pure amino epoxides **6**.

(2*R*,1′*S*)-2-[1′-(Dibenzylamino)ethyl]-2-methyloxirane (8a) (75% yield): R_f 0.35 (10/1 *n*-hexane/ethyl acetate); $[\alpha]^{25}_D$ +18.9 (*c* 0.75, $CHCl_3$); ^{1}H NMR δ 0.92 (d, J = 6.9 Hz, 3 H), 1.40 (s, 3 H), 2.51 (d, J = 4.7 Hz, 1 H), 2.85 (d, J = 4.7 Hz, 1 H), 2.99 (q, J = 6.9 Hz, 1 H), 3.44 (d, J = 13.8 Hz, 2 H), 3.78 (d, J = 13.8 Hz, 2 H), 7.19−7.39 (m, 10 H); ^{13}C NMR δ 6.3, 20.5, 50.3, 54.2, 56.3, 58.3, 126.7, 128.1, 128.5, 139.7; MS (EI) *m*/*z* (rel intensity) 281 (M^+, <1), 224 (M^+ − C_3H_5O, 98), 91 (100). HRMS calcd for $C_{19}H_{23}NO$ 281.1780, found 281.1779.

(2*R*,1′*S*)-2-[1′-(Dibenzylamino)ethyl]-2-butyloxirane (8b) (84% yield): R_f 0.42 (10/1 *n*-hexane/ethyl acetate); $[\alpha]^{25}_D$ +6.5 (*c* 0.37, $CHCl_3$); ^{1}H NMR δ 0.79 (t, J = 7.1 Hz, 3 H), 0.86−1.10 (m ,5 H), 1.25−1.13 (m, 2 H), 1.34−1.44 (m, 1 H), 2.08-1.98 (m, 1 H), 2.52 (d, J = 4.7 Hz, 1 H), 2.89 (d, J = 4.7 Hz, 1 H), 3.16 (q, J = 6.7 Hz, 1 H), 3.36 (d, J = 13.3 Hz, 2 H), 3.78

(d, J = 13.3 Hz, 2 H), 7.20−7.37 (m, 10 H); ^{13}C NMR δ 5.0, 13.9, 22.9, 25.7, 32.6, 49.6, 52.9, 54.2, 60.5, 126.8, 128.1, 128.8, 139.8; MS (EI) m/z (rel intensity) 323 (M^+, <1), 224 ($M^+ - C_6H_{11}O$, 100). HRMS calcd for $C_{22}H_{29}NO$ 323.2249, found 323.2239.

(2*R*,1′*S*)-2-[1′-(Dibenzylamino)ethyl]-2-allyloxirane (8c) (70% yield): R_f 0.20 (20/1 *n*-hexane/ethyl acetate); $[\alpha]^{25}_D$ +5.5 (*c* 0.60, $CHCl_3$); ^{1}H NMR δ 0.86 (d, J = 6.9 Hz, 3 H), 2.39 (dd, J = 7.7, 14.6 Hz, 1 H), 2.49 (d, J = 4.7 Hz, 1 H), 2.57 (dd, J = 6.4, 14.6 Hz, 1 H), 2.78 (d, J = 4.7 Hz, 1 H), 3.07 (q, J = 6.9 Hz, 1 H), 3.33 (d, J = 13.8 Hz, 2 H), 3.72 (d, J = 13.8 Hz, 2 H), 4.84−4.90 (m, 2 H), 5.38−5.51 (m, 1 H), 7.14−7.31 (m, 10 H); ^{13}C NMR 5.4, 36.8, 48.2, 54.3, 54.5, 60.0, 117.9, 126.9, 128.2, 128.7, 132.9, 139.7; MS (EI) m/z (rel intensity) 307 (M^+, 6), 225 ($M^+ + 1 - C_5H_7O$, 100), 224 (M^+-C_5H_7O, 96). HRMS calcd for $C_{21}H_{25}NO$ 307.1936, found 307.1931.

(2*R*,1′*S*)-2-[1′-(Dibenzylamino)-3′-methylbutyl]-2-methyloxirane (8d) (75% yield): R_f 0.45 (10/1 *n*-hexane/ethyl acetate); $[\alpha]^{25}_D$ +0.6 (*c* 0.64, CH_2Cl_2); ^{1}H NMR δ 0.67 (d, J = 6.4 Hz, 3 H), 084 (d, J = 6.4 Hz, 3 H), 0.90−1.10 (m, 1 H), 1.42 (s, 3 H), 1.52−1.45 (m, 1 H), 1.68−1.79 (m, 1 H), 2.46 (d, J = 4.7 Hz, 1 H, AB system), 2.65 (d, J = 4.7 Hz, 1 H, AB system), 2.70−2.74 (m, 1 H), 3.69 (d, J = 13.7 Hz, 2 H, AB system), 3.83 (d, J = 13.7 Hz, 1 H, AB system), 7.21−7.37 (m, 10 H); ^{13}C NMR δ 21.2, 22.4, 23.1, 25.2, 35.5, 51.2, 54.5, 58.6, 58.7, 126.7, 128.0, 128.8, 140.2; MS (EI) m/z (rel intensity) 323 (M^+, >1), 266 ($M^+ - C_3H_5O$, 100). HRMS calcd for $C_{22}H_{29}NO$ 323.2249, found 323.2240.

(2*R*,1′*S*)-2-[1′-(Dibenzylamino)-2′-phenylethyl]-2-methyloxirane (8e) (75% yield): R_f 0.52 (10/1 *n*-hexane/ethyl acetate); $[\alpha]^{25}_D$ −7.9 (*c* 1.22, $CHCl_3$); ^{1}H NMR δ 1.42 (s, 3 H), 2.41 (d, J = 4.4 Hz, 1 H), 2.57 (d, J = 4.4 Hz, 1 H), 2.62 (dd, J = 6.1, 14.0 Hz, 1 H), 2.93 (dd, J = 7.3, 14.0, 1 H), 3.06−3.13 (m, 1 H), 3.66 (d, J = 13.9 Hz, 2 H), 3.84 (d, J = 13.9 Hz, 2 H), 7.10−7.29 (m, 15 H); ^{13}C NMR δ 20.7, 32.2, 51.2, 54.6, 58.1, 63.5, 125.8, 126.7, 128.0, 128.2, 128.7, 129.2, 139.7, 140.5; MS, m/z 357 (M^+, <1), 266 ($M^+ - C_7H_7$, 66), 91 (100). HRMS calcd for $C_{18}H_{20}NO$ 266.1545, found 266.1545.

(2*R*,1′*S*)-2-[1′-(Dibenzylamino)-2′-phenylethyl]-2-butyloxirane (8f) (60% yield): R_f 0.32 (20/1 *n*-hexane/ethyl acetate); $[\alpha]^{25}_D$ −12.9 (*c* 0.59, $CHCl_3$); ^{1}H NMR δ 0.73−1.19 (m, 7 H), 1.40−1.55 (m, 1 H), 1.80−1.95 (m, 1 H), 2.56 (d, J = 6.2 Hz, 1 H), 2.68 (dd, J = 5.5, 14.3 Hz, 1 H), 2.85−2.95 (m, 2 H), 3.33−3.39 (m, 1 H), 3.53 (d, J = 13.7 Hz, 2 H), 3.81 (d, J = 13.7 Hz, 2 H), 7.17−7.33 (m, 15 H); ^{13}C NMR δ 13.9, 22.8, 25.9, 30.3, 33.0, 49.6, 54.6, 60.4, 60.6, 125.7, 126.7, 128.0, 128.2, 128.8, 129.3, 139.7, 141.3; MS, m/z 399 (M^+, <1), 308 ($M^+ - C_7H_7$, 98), 91 (100). HRMS calcd for $C_{28}H_{33}NO$ 399.2562, found 399.2555.

(2*R*,1′*S*)-2-[1′-(Dibenzylamino)ethyl]-2-phenyloxirane (8g) (80% yield): R_f 0.46 (10/1 *n*-hexane/ethyl acetate); $[\alpha]^{25}_D$ +32.0 (*c* 0.50, $CHCl_3$); ^{1}H NMR δ 1.07 (d, J = 7.0 Hz, 3 H), 2.79 (d, J = 5.5 Hz, 1 H), 3.38−3.55 (m, 4 H), 3.89 (d, J = 14.0 Hz, 2 H), 7.16−7.30 (m, 15 H); ^{13}C NMR δ 7.4, 51.3, 54.4, 54.5, 63.9, 126.7, 127.0, 127.4, 127.9, 128.1, 128.4, 139.8, 140.2; MS (EI) m/z (rel intensity) 343 (M^+, 5), 224 ($M^+ - C_8H_7O$, 28), 91 (100). HRMS calcd for $C_{24}H_{25}NO$ 343.1936, found 343.1937. Anal. Calcd for $C_{24}H_{25}NO$: C, 83.93; H, 7.34; N, 4.08. Found: C, 83.81; H, 7.36; N, 4.06.

Acknowledgment. The authors are grateful to Dr. P. Bernad (Servicio de Espectrometría de Masas, Universidad de Oviedo) for spectroscopic mass determination. This research was supported by DGICYT (Grant PB92-1005 and PB93-0330). B. Baragaña thanks II Plan Regional de Investigación del Principado de Asturias for a predoctoral fellowship.

Supporting Information Available: Copies of the ^{1}H and ^{13}C NMR spectra for all compounds (32 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 ACS; see any current masthead page for ordering information.

JO9700585