Diastereospecific Synthesis of Enantiomerically Pure Polysubstituted Azetidines from 1,3-Amino Alcohols with Three Chiral Centers

José Barluenga,* Félix Fernández-Marí, Argimiro L. Viado, Enrique Aguilar, and Bernardo Olano

Instituto Universitario de Química Organometálica "Enrique Moles", Unidad Asociada al C.S.I.C., Universidad de Oviedo, C/ Julián Clavería, 8, 33071 Oviedo, Spain

Received March 13, 1996

Introduction

Azetidines are an interesting class of four-membered heterocyclic compounds with remarkable biological activity,[1] which makes them important synthetic targets.[2] Accordingly, development of effective general methods for the synthesis of azetidines, especially in enantiomerically pure form, is of significant value. In this context, the preparation of optically active azetidines has mainly relied on classical resolutions.[3] However, some direct entries to enantiomerically pure azetidines have been described by reaction of 1,3-dihalo compounds or related derivatives with primary amines,[4] cyclization of 1,3-amino alcohols,[5] or reduction of azetidinones.[6]

On the other hand, 1,3-amino alcohols with three chiral centers have been in the focus of our efforts in the last decade. Thus, we have described a diastereoselective synthesis of these compounds by reduction of 4-amino-1-azadienes and related systems.[7] A diastereo- and enantioselective preparation of 1,3-amino alcohols **5** was carried out from 4-amino-1-azadienes **1** via the corresponding dihydro- and tetrahydropyrimidines **2** and **3** using an aldehyde as chiral auxiliary (Scheme 1); *β*-amino ketones **4** obtained from tetrahydropyrimidines **3** by hydrolysis were submitted to reduction with complex metal hydrides leading to **5**.[8] More recently, we reported the synthesis of all isomers of the *N*-terminal amino acid of the antibiotics nikkomycin B and B_x following the synthetic plan outlined here.[9]

Scheme 1

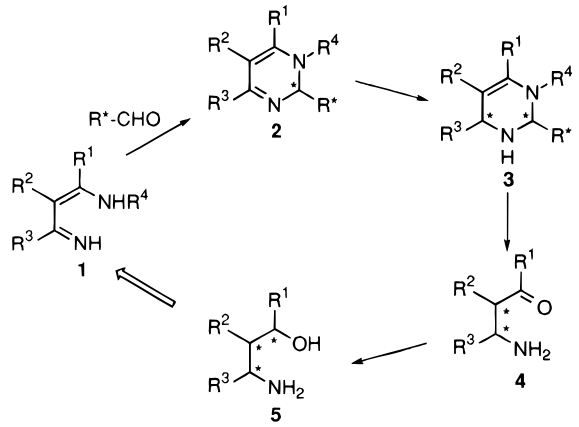


Table 1. 1,3-Amino Alcohols 5 Prepared from *β*-Amino Ketones 4

4	R^1	R^3	**5**	yield (%)[a]	mp (°C)
(±)-*anti*-**4a**	Ph	*p*-tolyl	(±)-*syn*,*anti*-**5a**	88[b]	106−7[b]
anti-**4b**	Ph	Ph	*syn*,*anti*-**5b**	93	99−100
anti-**4c**	*p*-anisyl	Ph	*syn*,*anti*-**5c**	91	62−4
anti-**4d**	*p*-anisyl	2-furyl	*syn*,*anti*-**5d**	91[c]	85−6[c]
anti-**4b**	Ph	Ph	*anti*,*anti*-**5b**	35	91−3
syn-**4b**	Ph	Ph	*syn*,*syn*-**5b**	72	100−3
syn-**4d**	*p*-anisyl	2-furyl	*syn*,*syn*-**5d**	87[c]	syrup[c]
syn-**4b**	Ph	Ph	*anti*,*syn*-**5b**	46	101−2 dec

[a] Isolated yield. [b] Reference 7a. [c] Reference 9.

As part of our continuing interest in the chemistry of 1,3-amino alcohols we now report the synthesis of optically active 2,3,4-substituted azetidines from 1,3-amino alcohols containing three chiral centers.

Results and Discussion

Preparation of 1,3-Amino Alcohols 5 from *β*-Amino Ketones 4. 1,3-Amino alcohols **5** (R^2 = Me) were synthesized by diastereoselective reduction of enantiomerically pure *β*-amino ketones **4** (R^2 = Me) which can be obtained as indicated in Scheme 1 by using (*R*)-*O*-benzyllactic aldehyde as chiral auxiliary. Reduction of *anti*-**4** and *syn*-**4** with Red-Al and DIBALH/$ZnCl_2$ led to *syn*,*anti*-**5** and *syn*,*syn*-**5**, respectively, as the only diastereoisomers (Scheme 2) according to reduction of the carbonyl group through a rigid cyclic model.[7a,d] On the other hand, reduction of *anti*-**4** and *syn*-**4** with N- and K-selectride, respectively, took place mainly through an open chain model[7a] to give *anti*,*anti*-**5** and *anti*,*syn*-**5** as major components mixed with their respective epimers. Compounds **5** used in the synthesis of azetidines were obtained in diastereomerically pure form in moderate to good yields following the procedure previously developed[7d,9] (Table 1).

Synthesis of 2,3,4-Substituted Azetidines 6. Although preparation of azetidines from 1,3-amino alcohols is well documented, as indicated in the introduction, synthesis of 2,3,4-substituted examples has been gener-

(1) (a) Testa, E.; Wittigens, A.; Maffii, G.; Bianchi, G. in *Research Progress in Organic, Biological and Medicinal Chemistry*; Gallo, U., Santamaria, L., Eds.; North-Holland Publishing Co.; Amsterdam, 1964; Vol 1, p 477. (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 and references cited therein.

(2) For reviews see: (a) Cromwell, N. H.; Phillips, B. *Chem. Rev.* **1979**, *79*, 331. (b) Moore, J. A.; Ayers, R. S. In *Small Ring Heterocycles*; Hassner, A., Ed.; Wiley; New York, 1983; Part 2, p 1. (c) Davies, D. E.; Storr, R. C. In *Comprehensive Heterocyclic Chemistry*; Lwowski, W., Ed.; Pergamon; Oxford, 1984; Vol 7, p 237.

(3) (a) Rama Rao, A. V.; Gurjar, M. K.; Kaiwar, V. *Tetrahedron: Asymmetry* **1992**, *3*, 859. (b) Kozikowski, A. P.; Tückmantel, W.; Liao, Y.; Manev, H.; Ikonomovic, S.; Wroblewski, J. T. *J. Med. Chem.* **1993**, *36*, 2706. (c) Guanti, G.; Riva, R. *Tetrahedron: Asymmetry* **1995**, *6*, 2921.

(4) (a) Duréault, A.; Portal, M.; Carreaux, F.; Depezay, J. C. *Tetrahedron* **1993**, *49*, 4201. (b) Hoshino, J.; Hiraoka, J.; Hata, Y.; Sawada, S.; Yamamoto, Y. *J. Chem. Soc., Perkin Trans. 1* **1995**, 693.

(5) (a) Poch, M.; Verdaguer, X.; Moyano, A.; Pericàs, M. A.; Riera, A. *Tetrahedron Lett.* **1991**, *32*, 6935. (b) Hiraki, T.; Yamagiwa, Y.; Kamikawa, T. *Tetrahedron Lett.* **1995**, *36*, 4841.

(6) (a) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339. (b) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K. *J. Org. Chem.* **1991**, *56*, 5263. (c) Shustov, G. V.; Rauk, A. *J. Am. Chem. Soc.* **1995**, *117*, 928.

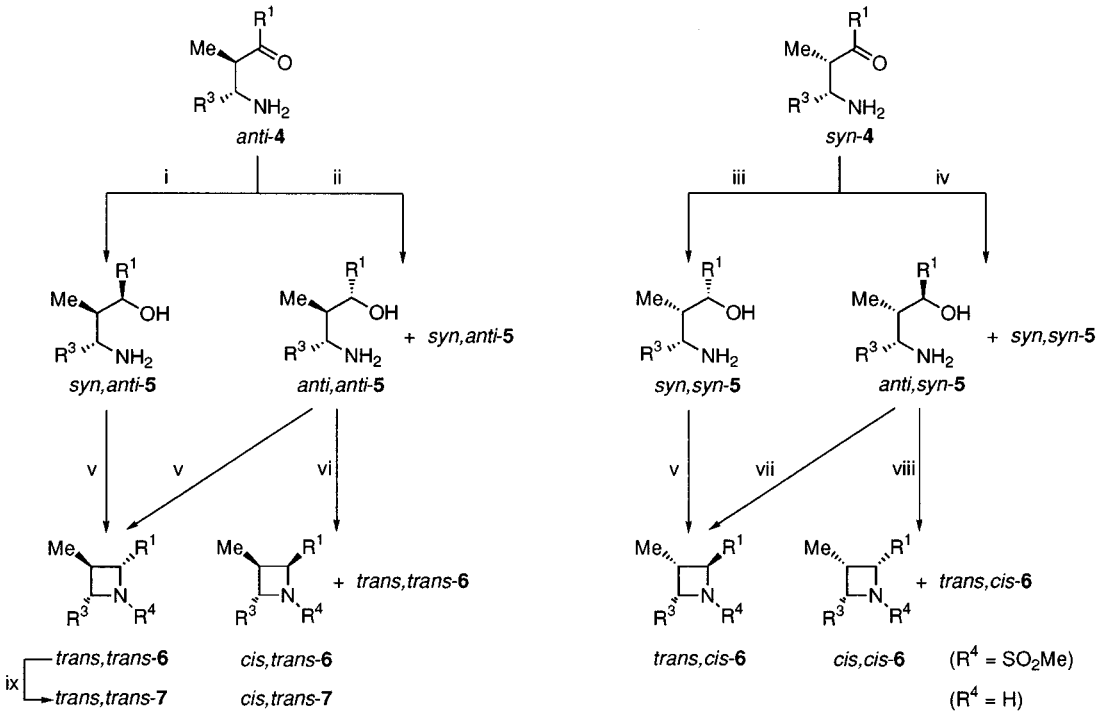
(7) (a) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1985**, *50*, 4052. (b) Barluenga, J.; Joglar, J.; González, F. J.; Fustero, S. *Tetrahedron Lett.* **1989**, *30*, 2001. (c) Barluenga, J.; Aguilar, E.; Olano, B.; Fustero, S. *Synlett* **1990**, 463. (d) Barluenga, J.; Aguilar, E.; Fustero, S.; Olano, B.; Viado, A. L. *J. Org. Chem.* **1992**, *57*, 1219.

(8) Barluenga, J.; Olano, B.; Fustero, S.; Foces-Foces, M. C.; Cano, F. H. *J. Chem. Soc., Chem. Commun.* **1988**, 410.

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

S0022-3263(96)00494-X CCC: $12.00

Scheme 2 [a]



[a] **Reagents**: (i) $NaAlH_2(OCH_2CH_2OCH_3)_2$/ toluene/ -78°C. (ii) $NaBH(s\text{-}Bu)_3$/ THF/ -78°C to rt. (iii) DIBALH/ $ZnCl_2$/ -78°C. (iv) $KBH(s\text{-}Bu)_3$/ THF/ -78°C to rt. (v) $MeSO_2Cl$ (excess)/ Et_3N/ CH_2Cl_2/ 40 °C. (vi) $MeSO_2Cl$ (excess)/ Et_3N/ hexane:toluene (10:1)/ rt. (vii) $MeSO_2Cl$ (excess)/ Et_3N/ MeCN/ reflux. (viii) $MeSO_2Cl$ (excess)/ Et_3N/ MeCN/ rt. (ix) $NaAlH_2(OCH_2CH_2OCH_3)_2$/ benzene/ reflux.

Table 2. Azetidines 6 and 7 Obtained from 1,3-Amino Alcohols 5

entry	5	6	yield (%)[a]	mp (°C)[b]	7	yield (%)[c]
1	(±)-*syn,anti*-**5a**	(±)-*trans,trans*-**6a**	53	syrup	(±)-*trans,trans*-**7a**	65
2	*syn,anti*-**5b**	*trans,trans*-**6b**	59 (54)[d] (47)[e]	137−9	*trans,trans*-**7b**	56
3	*syn,anti*-**5c**	*trans,trans*-**6c**	55	92−4	*trans,trans*-**7c**	72
4	*syn,anti*-**5d**	*trans,trans*-**6d**	33	syrup		
5	*anti,anti*-**5b**	*trans,trans*-**6b**	41			
6	*anti,anti*-**5b**	*cis,trans*-**6b**	39[f]	140−2	*cis,trans*-**7b**	76
7	*syn,syn*-**5b**	*trans,cis*-**6b**	59			
8	*syn,syn*-**5d**	*trans,cis*-**6d**	10	syrup		
9	*anti,syn*-**5b**	*trans,cis*-**6b**	35			
10	*anti,syn*-**5b**	*cis,cis*-**6b**	13[g] (9)[h]	syrup		

[a] Isolated yield under the conditions indicated in Scheme 2. [b] Recrystallized from hexane/$CHCl_3$ (3:1). [c] Isolated yield from **6**. [d] Reaction carried out in refluxing benzene. [e] Reaction carried out in refluxing THF. [f] A *cis,trans*-**6b**/*trans,trans*-**6b** mixture (ratio 96/4, ^{1}H NMR 300 MHz) was observed in the crude product. [g] *trans,cis*-**6b** was also isolated in 29% yield. [h] Reaction performed in DMF at rt; *trans,cis*-**6b** also isolated in 42% yield.

ally achieved by several methods with only low yields.[5b,10] In this context, conversion of amino alcohols **5** to the corresponding azetidines would constitute the systematic synthesis of all possible diastereomers of the related 2,3,4-substituted azetidines. Transformation of **5** into azetidines **6** was carried out with an excess of $MsCl/Et_3N$ in different solvents overnight. When the reaction was performed on amino alcohols with syn relative stereochemistry at the carbinolic center, *syn,anti*-**5** or *syn,syn*-**5**, azetidines **6** with trans relative sterochemistry at this carbon were obtained as the only diastereoisomers independent of the solvent used in the reaction. The best yields were obtained with CH_2Cl_2 (Table 2, entries 1−4, 7, and 8). However, when the reaction was carried out with *anti,anti*-**5b**, *trans,trans*-**6b** was obtained as the only diastereoisomer in CH_2Cl_2 (Table 2, entry 5), whereas *cis,trans*-**6b** was obtained as the major diastereoisomer mixed with its epimer in hexane/toluene (10:1) at room temperature (Table 2, entry 6). On the other hand, no azetidines were detected in CH_2Cl_2 starting from *anti,syn*-**5b**; by contrast, *trans,cis*-**6b** (equal to *cis,trans*-**6b**) was formed as the only product in refluxing MeCN and as the main product—together with *cis,cis*-**6b**—in MeCN at room temperature (Table 2, entries 9 and 10).

These results can be understood by taking into account that although cyclization of 1,3-amino alcohols to azetidines is basically a S_N2 process, a S_N1 mechanism does usually compete and becomes even more favorable when the leaving group is on a secondary carbon atom.[11] Moreover, in our case the carbon bearing the leaving group is benzylic; thus, whereas ring formation from *syn*-3-aminopropanols takes place with inversion of configu-

(10) (a) Stevens, M. F.; Cromwell, N. H. *J. Heterocyc. Chem.* **1971**, *8*, 253. (b) Kurteva, V. B.; Lyapova, M. J.; Pojarlieff, I. G. *J. Chem. Res. (S)* **1993**, 270.

(11) For mechanistic considerations, see: Vaughan, W. R.; Klonowski, R. S.; McElhinney, R. S.; Millward, B. B. *J. Org. Chem.* **1961**, *26*, 138.

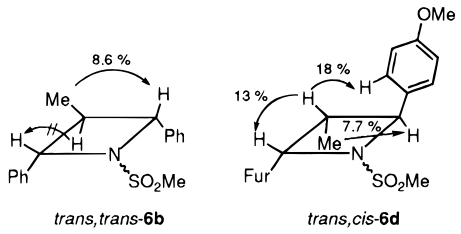


Figure 1.

ration to give *trans*-azetidines, the anti epimers, *anti*,*anti*-**5b** and *anti*,*syn*-**5b**, strongly tend to give also *trans*-azetidines in a presumably S_N1 process[12] which occurs with retention of configuration, leading through the most accessible transition state to the most stable diastereoisomer. In this regard, formation of *cis*,*trans*-**6b** from *anti*,*anti*-**5b** is favored by the use of a less polar solvent and is presumably the result of a S_N2 process,[13] whereas *cis*,*cis*-**6b** seems to be the most inaccessible azetidine due perhaps to its hindered structure. Taking this into account, it is not surprising that yields of azetidines **6** listed on Table 2 are low to moderate. Thus, although it is quite common to find yields ≥70% in the synthesis of azetidines from 1,3-amino alcohols with a primary carbinolic carbon,[5a,14] rather lower yields are often obtained from amino alcohols containing secondary carbinolic carbons.[5b,10b]

The configurational assignment of azetidines **6** was made from ^{1}H NMR data on the basis of the coupling constants $J_{\text{trans H/H}}$ and $J_{\text{cis H/H}}$ of the heterocycle which are in the range of 5.8−7.9 and 8.4−8.9 Hz, respectively (see Experimental Section), as expected for the azetidine ring.[15] The relative configuration was further confirmed by NOE experiments as shown in Figure 1 for the structures of *trans*,*trans*-**6b** and *trans*,*cis*-**6d**.

Azetidines **6**, obtained as *N*-mesylated derivatives, could be deprotected by reaction with Red-Al (Scheme 2). The reaction was carried out with *trans*,*trans*-**6a**−**c** and *cis*,*trans*-**6b** to give the corresponding *N*-unsubstituted azetidines **7** in yields of 56−76% (Table 2, entries 1−3 and 6).

In conclusion, 1,3-amino alcohols **5**, obtained through diastereoselective reduction of *β*-amino ketones **4**, were cyclized to polysubstituted *N*-mesylazetidines **6** in low to moderate yields. The synthesis allows one to obtain all possible diastereoisomers of enantiomerically pure azetidines **6** with three chiral centers in a diastereospecific manner. Work is in progress in order to improve the yields in the preparation of azetidines **6** and to study the synthetic applications of N-unprotected azetidines **7** mainly as chiral auxiliaries.

(12) This is in accordance with the observation of elimination and fragmentation products in the reactions toward azetidines **6** described in Scheme 2, which compete with ring closure especially in *anti*,*anti*-**5b** and *anti*,*syn*-**5b**. The *p*-anisyl group in **5d** favors S_N1 processes even more and increases rupture and elimination processes so much that only 10% of *trans*,*cis*-**6d** or 33% of *trans*,*trans*-**6d** are obtained.

(13) The inversion of configuration detected in the cyclization of an anti-amino alcohol is remarkable, despite formation of a hindered cis-azetidine, which has also been observed in ref 5b. In our case, the presence of an aryl group in the hydroxylic carbon would explain the formation of a little amount of the *trans*-azetidine even in a very little polar solvent (see Table 2, entry 6 and footnote f).

(14) (a) Axenrod, T.; Watnick, C.; Yazdekhasti, H.; Dave, P. R. *Tetrahedron Lett.* **1993**, *34*, 6677. (b) Huszthy, P.; Bradshaw, J. S.; Krakowiak, K. E.; Wang, T.; Dalley, N. K. *J. Heterocyc. Chem.* **1993**, *30*, 1197.

(15) Batterham, T. J. *NMR Spectra of Simple Heterocycles*; Wiley; New York, 1973; p 144.

Experimental Section

General. Solvents were dried according to established protocols by distillation under nitrogen from an appropriate drying agent. Thus, THF and benzene were distilled from sodium/benzophenone ketyl. Dichloromethane and acetonitrile were distilled from calcium hydride. DMF was distilled from calcium hydride under reduced pressure (<20 mmHg), and triethylamine was refluxed over KOH, distilled, and stored over 3 Å molecular sieves. Mesyl chloride was distilled from P_2O_5. Solvents used in extractions were distilled prior to use.

Compounds were visualized on analytical thin-layer chromatograms (TLC) by UV light (254 nm) or by using ninhydrin or potasium permanganate staining solutions. Silica gel (60 Å) for flash chromatography was purchased from Scharlau or Merck (200−450 mesh). GC-MS and HRMS were measured at 70 eV.

Reactions requiring an inert atmosphere were conducted under dry nitrogen, and the glassware was oven dried (120 °C), evacuated, and purged with nitrogen. Temperatures are reported as bath temperatures. Melting points are reported uncorrected. Fourier transform infrared (IR) spectra were recorded on films. ^{1}H NMR spectra were recorded with a 200 or a 300 MHz instrument, with tetramethylsilane as the internal standard; ^{13}C NMR spectra and DEPT experiments were determined at 50 or 75 MHz.

Compounds (±)-*anti*-**4a**,[16] *anti*-**4d**,[9] syn-**4d**,[9] (±)-*syn*,*anti*-**5a**,[7a] *syn*,*anti*-**5d**,[9] and *syn*,*syn*-**5d**[9] have been previously reported and were prepared as described. All other reagents were commercially available and were used without any further purification.

Preparation of Azetidines 6. General Procedure. A solution of amino alcohol **5** (2 mmol) in 150 mL of the corresponding dry solvent (See Table 2, Scheme 2) was cooled to 0 °C, and Et_3N (2.25 mL, 16 mmol) and MsCl (1.25 mL, 16 mmol) were added dropwise via syringe. The resulting solution was stirred overnight at the temperatures reported in Table 2 and Scheme 2. The mixture was then cooled to 0 °C and treated with 3 N NaOH (30 mL). The organic layer was extracted with CH_2Cl_2 (2 × 25 mL), washed with saturated brine (25 mL), dried over Na_2SO_4, and filtered. Solvents were removed under reduced pressure, and the crude residue was chromatographed on SiO_2. Isolated yields of *N*-mesylazetidines **6** are reported in Table 2.

(2*R,3*S**,4*S**)-1-Mesyl-3-methyl-2-phenyl-4-(*p*-tolyl)azetidine (*trans*,*trans*-6a):** colorless syrup; R_f = 0.15 (Hex/AcOEt 5/1); ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.55−7.21 (9 H, m), 4.77 (1 H, d, *J* = 7.7 Hz), 4.75 (1 H, d, *J* = 7.7 Hz), 2.65 (3 H, s), 2.43 (1 H, ddq, *J* = 6.7, 7.7, and 7.7 Hz), 2.37 (3 H, s), 1.28 (3 H, d, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, TMS, 75 MHz) *δ* 139.9 (C), 138.2 (C), 136.7 (C), 129.4 (CH), 128.7 (CH), 128.3 (CH), 126.7 (CH), 126.6 (CH), 68.1 (CH), 68.0 (CH), 45.1 (CH), 40.9 (CH_3), 21.1 (CH_3), 16.2 (CH_3). Anal. Calcd for $C_{18}H_{21}NO_2S$: C, 68.54; H, 6.71; N, 4.44. Found: C, 68.73; H, 6.68; N, 4.40.

(2*R*,3*r*,4*S*)-1-Mesyl-3-methyl-2,4-diphenylazetidine (*trans*,*trans*-6b): IR *ν* (cm^{-1}) 1454, 1322; ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 7.59−7.32 (10 H, m), 4.83 (2 H, d, *J* = 7.6 Hz), 2.69 (3 H, s), 2.47 (1 H, tq, *J* = 6.7 and 7.6 Hz), 1.32 (3 H, d, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 139.7 (C), 128.8 (CH), 128.3 (CH), 126.6 (CH), 68.1 (CH), 45.0 (CH), 40.8 (CH_3), 16.3 (CH_3); MS (*m*/*z*) 301 (M^+), 222, 184, 118; HRMS calcd for $C_{17}H_{19}NO_2S$ 301.1137, found 301.1136

(2*R*,3*R*,4*S*)-2-(*p*-Anisyl)-1-mesyl-3-methyl-4-phenylazetidine (*trans*,*trans*-6c): IR *ν* (cm^{-1}) 1514, 1321; ^{1}H NMR ($CDCl_3$, 300 MHz) *δ* 7.56−7.33 (7 H, m), 6.96 (2 H, d, *J* = 8.5 Hz), 4.77 (1 H, d, *J* = 7.9 Hz), 4.73 (1 H, d, *J* = 8.0 Hz), 3.84 (3 H, s), 2.65 (3 H, s), 2.46 (1 H, ddq, *J* = 6.7, 7.9, and 8.0 Hz), 1.28 (3 H, d, *J* = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) *δ* 159.6 (C), 139.9 (C), 131.2 (C), 128.7 (CH), 128.2 (CH), 126.5 (CH), 114.1 (CH), 67.9 (CH), 67.8 (CH), 55.2 (CH_3), 45.1 (CH), 40.9 (CH_3), 16.1 (CH_3); MS (*m*/*z*) 331(M^+), 214, 148, 118; HRMS calcd for $C_{18}H_{21}NO_3S$ 331.1242, found 331.1246. $[\alpha]^{28}_D$ = − 3.9 (*c* 1.05, $CHCl_3$).

(2*R*,3*S*,4*S*)-2-(*p*-Anisyl)-4-(2-furyl)-1-mesyl-3-methylazetidine (*trans*,*trans*-6d): Colorless syrup; R_f = 0.20 (Hex/AcOEt, 5/1); IR *ν* (cm^{-1}) 1514, 1323; ^{1}H NMR ($CDCl_3$, 200 MHz) *δ* 7.49 (1 H, m), 7.50−6.94 (4 H, AB q, *J* = 8.8 Hz), 6.45 (1 H, m), 6.40

(16) Barluenga, J.; Olano, B.; Fustero, S. *J. Org. Chem.* **1983**, *48*, 2255.

(1 H, m), 4.78 (1 H, d, J = 7.8 Hz), 4.65 (1 H, d, J = 7.6 Hz), 3.83 (3 H, s), 2.83 (1 H, ddq, J = 6.8, 7.6, and 7.8 Hz), 2.61 (3 H, s), 1.25 (3 H, d, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$,75 MHz) δ 159.7 (C), 152.1 (C), 143.2 (CH), 132.0 (C), 128.4 (CH), 114.0 (CH), 110.5 (CH), 109.3 (CH), 67.7 (CH), 60.1 (CH), 55.2 (CH_3), 41.2 (CH), 41.1 (CH_3), 16.2 (CH_3); MS (m/z) 321 (M^+), 214, 148, 108. HRMS calcd for $C_{16}H_{19}NO_4S$ 321.1035; found: 321.1035; $[\alpha]^{22}_D$ = + 5.0 (c 1.08, $CHCl_3$).

(2*S*,4*S*)-1-Mesyl-3-methyl-2,4-diphenylazetidine (*cis,trans*-6b): IR ν (cm^{-1}) 1454, 1333; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63−7.30 (10 H, m), 5.63 (1 H, d, J = 8.7 Hz), 5.03 (1 H, d, J = 5.8 Hz), 3.17 (1 H, ddq, J = 5.8, 7.2, and 8.7 Hz), 2.43 (3 H, s), 0.85 (3 H, d, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.1 (C), 136.8 (C), 128.9 (CH), 128.8 (CH), 128.2 (CH), 127.9 (CH), 127.4 (CH), 73.2 (CH), 69.1 (CH), 41.3 (CH_3), 38.9 (CH), 14.1 (CH_3); MS (m/z) 222 (M^+ − 79), 149, 118, 44. Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.81; H, 6.36; N, 4.65. Found: C, 67.69; H, 6.40; N, 4.59; $[\alpha]^{22}_D$ = −129.3 (c 1.12, $CHCl_3$).

(2*S*,3*R*,4*S*)-2-(*p*-Anisyl)-4-(2-furyl)-1-mesyl-3-methylazetidine (*trans,cis*-6d): Colorless syrup; R_f = 0.14 (Hex/AcOEt 5/1); IR ν (cm^{-1}) 1514, 1325; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.55−7.45 (3 H, m), 6.99−6.91 (2 H, m), 6.52−6.50 (1 H, m), 6.46−6.43 (1 H, m), 5.35 (1 H, d, J = 8.4 Hz), 5.16 (1 H, d, J = 7.7 Hz), 3.83 (3 H, s), 3.10 (1 H, ddq, J = 7.0, 7.7, and 8.4 Hz), 2.46 (3 H, s), 1.06 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.8 (C), 150.5 (C), 142.7 (CH), 131.2 (C), 128.4 (CH), 114.0 (CH), 111.5 (CH), 110.8 (CH), 72.8 (CH), 61.8 (CH), 55.2 (CH_3), 41.4 (CH), 39.9 (CH_3), 12.6 (CH_3); MS (m/z) 321 (M^+), 305, 265, 121; HRMS calcd for $C_{16}H_{19}NO_4S$ 321.10345, found: 321.1033; $[\alpha]^{22}_D$ = −100.0 (c 0.27, $CHCl_3$).

(2*R*,3*s*,4*S*)-1-Mesyl-3-methyl-2,4-diphenylazetidine (*cis,cis*-6b): colorless syrup; R_f = 0.21 (Hex/AcOEt 3/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59−7.32 (10 H, m), 5.58 (2 H, d, J = 8.9 Hz), 3.22 (1 H, tq, J = 7.3 and 8.9 Hz), 2.86 (3 H, s), 0.40 (3 H, d, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 136.7 (C), 128.3 (CH), 127.7 (CH), 126.9 (CH), 63.4 (CH), 40.2 (CH_3), 34.0 (CH), 11.5 (CH_3). Anal. Calcd for $C_{17}H_{19}NO_2S$: C, 67.81; H, 6.36; N, 4.65. Found: C, 67.63; H, 6.39; N, 4.71.

Preparation of Azetidines 7. General Procedure. A solution of azetidine **6** (0.5 mmol) in dry benzene (15 mL) was treated with an excess of Red-Al (2.0 mmol, 65 + wt % in toluene) at room temperature. The resulting solution was refluxed until TLC disappearance of starting material (∼3.5 h), and then cooled to 0 °C, and 3 N NaOH (10 mL) was added dropwise. The organic layer was extracted with AcOEt (3 × 15 mL), washed with saturated brine (15 mL), dried over Na_2SO_4, and filtered. Solvents were removed under reduced pressure, and the crude residue was chromatographed on SiO_2. Isolated yields of N-unsubstituted azetidines **7** are given in Table 2.

(2*R,3*S**,4*S**)-3-Methyl-2-phenyl-4-(*p*-tolyl)azetidine (*trans,trans*-7a):** colorless oil; R_f = 0.45 (Hex/AcOEt/Et_3N 100/1/1); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.54−7.16 (9 H, m), 4.38 (1 H, d, J = 7.3 Hz), 4.36 (1 H, d, J = 7.3 Hz), 2.50 (1 H, NH, br s), 2.35 (3 H, s), 2.33 (1 H, ddq, J = 6.6, 7.3, and 7.3 Hz), 1.25 (3 H, d, J = 6.6 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.4 (C),141.3 (C), 136.6 (C), 128,9 (CH), 128.2 (CH), 127.0 (CH), 126.3 (CH), 64.7 (CH), 64.6 (CH), 50.1 (CH), 21.1 (CH_3), 16.9 (CH_3). Anal. Calcd for $C_{17}H_{19}N$: C, 86.03; H, 8.07; N, 5.90. Found: C, 86.21; H, 8.00; N, 5.82.

(2*R*,3*r*,4*S*)-3-Methyl-2,4-diphenylazetidine (*trans,trans*-7b): Colorless oil; R_f = 0.41 (Hex/AcOEt/Et_3N 100/1/1); ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.63−7.28 (10 H, m), 4.46 (2 H, d, J = 7.8 Hz), 2.54 (1 H, br s), 2.38 (1 H, tq, J = 6.7 and 7.8 Hz), 1.33 (3 H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 144.4 (C), 128,2 (CH), 126.9 (CH), 126.3 (CH), 64.7 (CH), 50.1 (CH), 16.9 (CH_3). Anal. Calcd for $C_{16}H_{17}N$: C, 86.06; H, 7.67; N, 6.27. Found: C, 85.85; H, 7.70; N, 6.26.

(2*R*,3*R*,4*S*)-2-(*p*-Anisyl)-3-methyl-4-phenylazetidine (*trans,trans*-7c): colorless oil; R_f = 0.35 (Hex/AcOEt/Et_3N 20/1/1); IR ν (cm^{-1}) 3329, 1512, 1246. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.59−7.28 (7 H, m), 6.95 (2 H, d, J = 8.6 Hz), 4.41 (1 H, d, J = 7.3 Hz), 4.37 (1 H, d, J = 7.6 Hz), 3.85 (3 H, s), 2.54 (1 H, NH, br.s), 2.33 (1 H, ddq, J = 6.7, 7.3, and 7.6 Hz), 1.28 (3 H, d, J = 6.7 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 158.7 (C), 144.5 (C), 136.6 (C), 128,2 (CH), 127.5 (CH), 126.9 (CH), 126.2 (CH), 113.6 (CH), 64.6 (CH), 64.4 (CH), 55.2 (CH_3), 50.3 (CH), 16.8 (CH_3); MS (m/z) 253 (M^+), 148, 136, 118; HRMS calcd for $C_{17}H_{19}NO$ 253.1467. found 253.1472; $[\alpha]^{23}_D$ = + 4.8 (c 0.58, $CHCl_3$).

(2*S*,4*S*)-3-Methyl-2,4-diphenylazetidine (*cis,trans*-7b); colorless syrup. R_f = 0.23 (Hex/AcOEt 3/1); IR ν (cm^{-1}) 3443; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.63−7.29 (10 H, m), 5.03 (1 H, d, J = 8.6 Hz), 4.53 (1 H, d, J = 6.7 Hz), 3.01 (1 H, ddq, J = 6.7, 7.0, and 8.6 Hz), 2.8−2.2 (1 H, br s, NH), 0.72 (3 H, d, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.5 (C), 141.5 (C), 128.5 (CH), 128.2 (CH), 127.1 (CH), 126.8 (CH), 126.6 (CH), 125.8 (CH), 67.1 (CH), 62.0 (CH), 42.4 (CH), 15.1 (CH_3). MS (m/z) 223 (M^+); $[\alpha]^{21}_D$ = −185.0 (c 0.44, $CHCl_3$). Anal. Calcd for $C_{16}H_{17}N$: C, 80.06; H, 7.67; N, 6.27. Found: C, 79.96; H, 7.61; N, 6.22.

Acknowledgment. We are thankful for the financial support received from the Dirección General de Investigación Científica y Técnica (DGICYT, PB92-1005). A. L. Viado and F. Fernández-Marí are indebted to the Ministerio de Educación y Ciencia (Spain) for predoctoral fellowships. We are also grateful to Dr. Bernard for measurement of the mass spectra.

Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectral data, as well as other spectroscopic data for compounds *anti*-**4b,c**, *syn*-**4b**, *syn,anti*-**5b,c**, *anti,anti*-**5b**, *syn,syn*-**5b**, and *anti,syn*-**5b** (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.

JO960494B