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Simple access to novel azetidine-containing conformationally restricted amino acids by chemoselective reduction of β-lactams

Guillermo Gerona-Navarro,[a] Mª Angeles Bonache,[a] Miriam Alías,[b] Mª Jesús Pérez de Vega,[a] Mª Teresa García-López,[a] Pilar López,[b] Carlos Cativiela[b,*] and Rosario González-Muñiz[a,*]

[a]*Instituto de Química Médica (CSIC), Juan de la Cierva 3, 28006 Madrid, Spain*
[b]*Departamento de Química Orgánica, ICMA, Universidad de Zaragoza-CSIC, 50009 Zaragoza, Spain*

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Abstract—Reduction with diphenylsilane and catalytic amounts of tris(triphenylphosphine)rhodium(I) carbonyl hydride resulted in an efficient, chemoselective method for the transformation of amino-acid-derived β-lactams into the corresponding azetidines, which after removal of the *p*-methoxybenzyl group, afforded a new family of conformationally restricted amino acids. Phe-derived compounds were obtained in enantiopure form by combining HPLC resolution of the β-lactam precursor and the above-mentioned procedure.

Incorporation into peptides of amino acids with restricted ϕ dihedral angles is a general strategy to induce reverse turn conformations. This kind of constraint could be achieved through N^{α}-C^{α}-cyclizations but, with the exception of some α-alkylprolines, scarce attention has been paid to these kinds of restricted amino acid derivatives.[1,2] In this context, the four-membered ring of azetidines **2** fixes the ϕ torsion angle in values of approximately 70° or −70°, depending on the relative configuration at the C_2 stereogenic center. These values are very close to those described for the corner amino acids in standard β- and γ-turns.[3] To the best of our knowledge, only three references in the literature deal with the synthesis of α-substituted azetidine-α-carboxylic acids, related to **2**. Thus, the Seebach group reported the stereoselective synthesis of compounds **2** [$R^1 = CH(OH)R$] by hydroxyalkylation of enantiopure azetidine-2-carboxylic acid derivatives.[4] Alternatively, azetidines **2** ($R^1 = Et$, $R^2 = R^3 = H$, and $R^1 = Bzl$, $R^2 = Et$, $R^3 = Boc$) have been prepared by Seebach and Kawabata groups following $C^{\alpha} \rightarrow N^{\alpha}$- and $N^{\alpha} \rightarrow C^{\alpha}$-cyclizations of chiral halo amino acid derivatives, respectively.[5,6]

Recently, we have described a simple method for the preparation of β-lactams **1**,[7] with a suitable substitution pattern that make them attractive precursors of the corresponding azetidines **2**, just by reduction of the β-lactam ring carbonyl group (Chart 1). However, most of the methods described for the reduction of β-lactams to azetidines, $LiAlH_4$, $NaBH_4$–$AlCl_3$ DIBAL-H, $AlClH_2$, and $AlCl_2H$,[8] are not compatible with the presence of ester groups. In this paper we describe a straightforward procedure for the chemoselective reduction of compounds **1** to the corresponding azetidine-containing restricted amino acids **2**. A combination of chiral HPLC resolution of the racemic β-lactam and the application of the reduction procedure here reported allowed us to prepare pure *R* and *S* enantiomers of a Phe-derived azetidine.

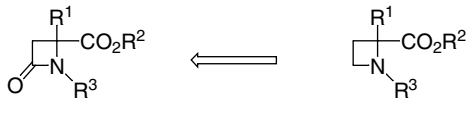

Chart 1.

Keywords: β-Lactams; Azetidines; Chemoselective reduction; Restricted amino acids; Chiral HPLC; Resolution.

* Corresponding authors. Tel./fax: +34-976-761210 (C.C.), tel.: +34-91-562-2900; fax: +34-91-5644853 (R.G.); e-mail addresses: cativiel@posta.unizar.es; iqmg313@iqm.csic.es

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The search for appropriate reduction conditions was performed using the Trp derivative **1a** as model compound. All attempts to reduce **1a** with diborane[9] resulted in complex mixtures of compounds from which, in the best case, the expected azetidine **2a** was obtained in only 34% yield. Although it has been claimed that the reduction of tertiary lactams with 9-BBN proceeds chemoselectively in the presence of esters,[10] the application of this procedure to compound **1a** resulted in the simultaneous reduction of the β-lactam carbonyl group and the 4-methyl ester, to give azetidine **4** as the major product (Chart 2).

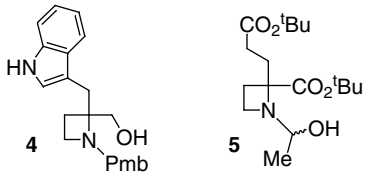
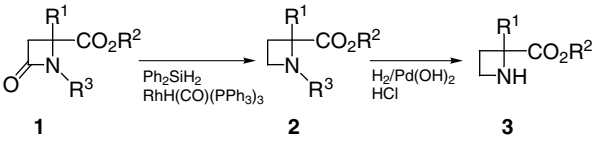


Chart 2.



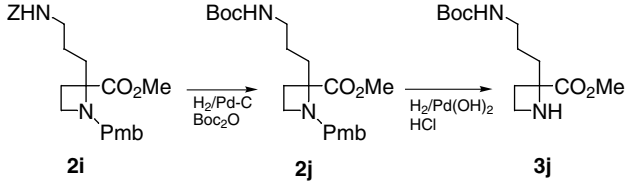
a: $R^1 = CH_2In$, $R^2 = Me$, $R^3 = Pmb$
b: $R^1 = CH_2In$, $R^2 = {}^tBu$, $R^3 = Bzl$
c: $R^1 = CH_2In(Boc)$, $R^2 = {}^tBu$, $R^3 = Pmb$
d: $R^1 = CH_2Ph$, $R^2 = Me$, $R^3 = Pmb$
e: $R^1 = CH_2Ph$, $R^2 = {}^tBu$, $R^3 = Pmb$
f: $R^1 = CH_3$, $R^2 = Me$, $R^3 = Bzl$
g: $R^1 = CH_2CH(CH_3)_2$, $R^2 = {}^tBu$, $R^3 = Pmb$
h: $R^1 = (CH_2)_2CO_2{}^tBu$, $R^2 = {}^tBu$, $R^3 = Pmb$
i: $R^1 = (CH_2)_3NHZ$, $R^2 = Me$, $R^3 = Pmb$
j: $R^1 = (CH_2)_3NHBoc$, $R^2 = Me$, $R^3 = Pmb$
(Pmb = *p*-methoxybenzyl)

Scheme 1.

Fortunately, much better results were found following the method described by Ito and co-workers for the reduction of tertiary amides with diphenylsilane and rhodium catalysts.[11] Following this procedure, azetidines **2a**–**c**, and **2h** were obtained in 51–64% yield from the corresponding Trp- and Glu-derived β-lactams **1a**–**c**, and **1h**, respectively (Scheme 1, Table 1). Improved yields were obtained in the reduction of 2-azetidinones derived from Phe, Ala, Leu, and Orn. In general, this reducing method is chemoselective with respect to carboxylic esters (Me, ^{t}Bu) and to urethane moieties (Boc, *Z*).[12,13]

Removal of the 1-Pmb group by catalytic hydrogenation in the presence of $Pd(OH)_2$ as catalyst gave the 1-unsubstituted azetidines **3** (Scheme 1, Table 1).[14,15] Compound **3h** was obtained along with a 13% of the 1-(1′-hydroxy)ethyl derivative **5** (Chart 2), probably resulting from the addition of **3h** to the acetaldehyde stabilizing the MeOH used as solvent. Due to the reaction conditions needed for the removal of the Pmb group in derivative **2i** are not compatible with the presence of the benzyloxycarbonyl moiety, this *Z*-protected Orn derivative was transformed into the corresponding Boc analogue **2j** (H_2/Pd–C/Boc_2O, 80%), prior to the transformation to the corresponding 1-unsubstituted azetidine **3j** (Scheme 2).

With a suitable method for the preparation of the azetidine-containing amino acids, the next issue we addressed was the possibility of preparing these compounds in enantiomerically pure form. For that purpose, the HPLC analytical resolution of Phe derivatives



Scheme 2.

Table 1. Transformation of β-lactams **1** to azetidines

Entry	Starting compound	Reduction method	**2** (%)[a]	**3** (%)[a]
1	**1a**	B_2H_6/THF/65 °C	34	—
2	**1a**	9-BBN/THF/65 °C	—[b]	—
3	**1a**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	51	70[c]
4	**1b**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	58	—
5	**1c**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	64	—
6	**1d**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	94	93
7	**1e**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	90	78
8	**1f**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	85	—
9	**1g**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	90	—
10	**1h**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	62	55[d]
11	**1i**	Ph_2SiH_2/RhH(CO)$(PPh_3)_3$/THF/Ar/rt	89	95[e]

[a] Yield of isolated compound.
[b] 2-Hydroxymethyl azetidine derivative **4** (24%) was obtained as the major compound.
[c] Hydrogenation performed with Pd black.[7a]
[d] Compound **5** (13%) was also isolated.
[e] Compound **3j** obtained from Boc-derivative **2j**.

1d, **2d**, and **3d** was tested on four different silica-bonded chiral phases.[16] Compound **1d** could be separated into their corresponding enantiomers on CSP-**1** and CSP-**3**, and **2d** could be resolved on CSP-**2**. The best resolution was achieved for β-lactam **1d** using the CSP-**1**, derived of mixed 10-undecenoate/3,5-dimethylphenyl-carbamate of cellulose (Fig. 1A). Therefore, compound **1d** was selected as the most appropriate candidate to carry out the preparative chromatography. Working in an overload mode with the analytical column, the conditions established at this level were scaled up to preparative chromatography.[17] Thus, enantioseparation of a quasi racemic mixture of (*R*)- and (*S*)-**1d**[18] was achieved by successive injections, using the peak shaving technique. In this way, enriched mixtures of each enantiomer of **1d** were obtained (85% and 92% enantiomeric purity of first and last eluted enantiomers, respectively). Optically pure compounds were finally obtained by crystallization of the above-mentioned mixtures[19] (Scheme 3, Fig. 1B and C). The absolute configuration of enantiomerically pure β-lactams **6d** has been previously established.[20] Saponification of optically pure enantiomers of **1d** to obtain both enantiomers of **6d** and comparison of the sign of their optical rotation with the values reported in

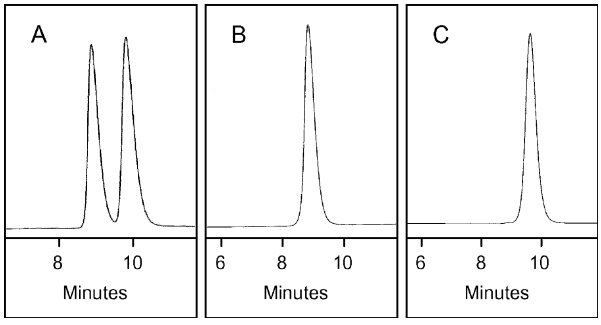
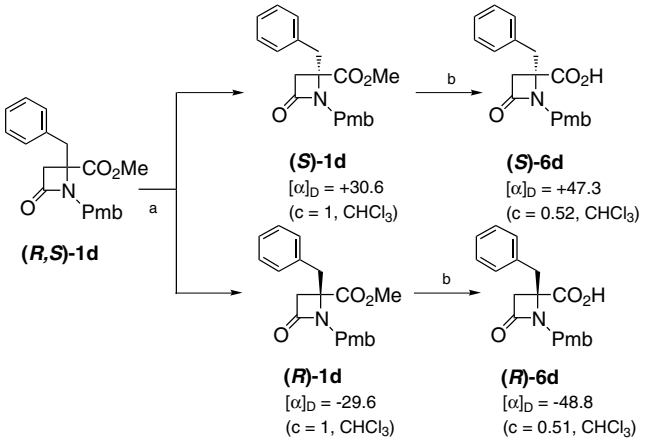
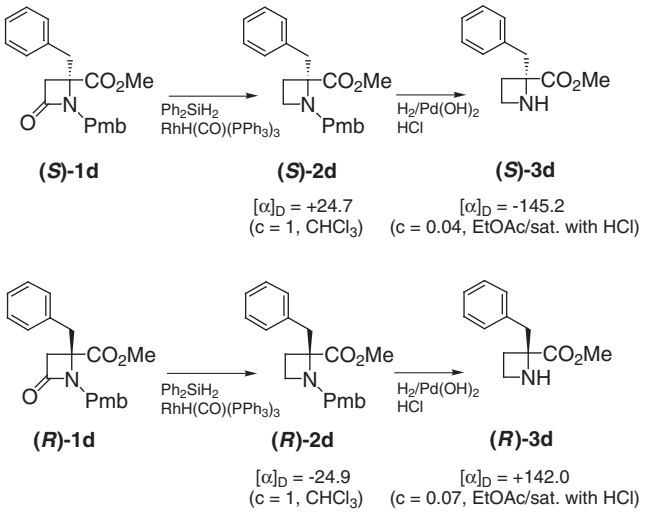


Figure 1. HPLC analytical resolution of racemate **1d** (A), and resolved enantiomers (*S*)-**1d** (B) and (*R*)-**1d** (C). Column: 150×4.6 mm ID containing 3,5-dimethylphenylcarbamate of cellulose (CSP-**1**). Eluent: *n*-hexane/2-propanol 96:4. Flow rate: 0.8 mL/min. UV detection: 210 nm. Chromatographic parameters: $k'_1 = 2.43$; $\alpha = 1.18$; $R_S = 1.52$.



Scheme 3. (a): (i) HPLC resolution, (ii) crystallization; (b): (i) 2 N NaOH, (ii) HCl (pH = 3).



Scheme 4.

Ref. 20 permitted assignment of the (*S*)-configuration to the less retained enantiomer and the (*R*) stereochemistry to the more retained enantiomer.[21]

Once the enantiomerically pure precursors (*S*)-**1d** and (*R*)-**1d** were available, they were subjected to the previously established reducing method, affording 1-Pmb derivatives (*S*)-**2d** and (*R*)-**2d**. Finally, removal of Pmb group in these latter compounds allowed the preparation of the desired optically pure Phe-derived conformationally constrained amino esters hydrochlorides (*S*)-**3d** and (*R*)-**3d** (Scheme 4).

In summary, we have demonstrated that the use of diphenylsilane, in the presence of tris(triphenylphosphine)-rhodium(I) carbonyl hydride as catalyst, is an efficient and versatile method for the chemoselective reduction of β-lactams to azetidines. This procedure was compatible with the presence of commonly used carboxylic acid and amino protecting groups. In the case of a Phe derivative, HPLC resolution of the racemic β-lactam precursor, using a noncommercial cellulose-derived stationary phase, has allowed the preparation of both enantiomers of the azetidine restricted amino ester **3d** in optically pure form. The ability of these constrained amino acids to induce folded conformations upon incorporation into peptides is now under investigation, and will be published in due course.

References and notes

1. Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2000**, *11*, 645–732.
2. (a) Thaisrivongs, S.; Pals, D. T.; Lawson, J. A.; Turner, S. R.; Harris, D. W. *J. Med. Chem.* **1987**, *30*, 536–541; (b) Hinds, M. G.; Welsh, J. H.; Brennand, D. M.; Fischer, J.; Glennie, M. J.; Richards, N. G. J.; Turner, D. L.; Robinson, J. A. *J. Med. Chem.* **1991**, *34*, 1177–1189; (c) Fincham, C. I.; Horwell, D. C.; Ratcliffe, G. S.; Rees, D. C. *Bioorg. Med. Chem. Lett.* **1992**, *2*, 403–406; (d) Bisang, C.; Weber, C.; Inglis, J.; Schiffer, C. A.; van Gunsteren, W.

F.; Jelesarov, I.; Bosshard, H. R.; Robinson, J. A. *J. Am. Chem. Soc.* **1995**, *117*, 7904–7915.
3. Rose, G. D.; Gierasch, L. M.; Smith, J. A. *Adv. Protein Chem.* **1985**, *37*, 1–109.
4. Seebach, D.; Vettiger, T.; Müller, H.-M.; Plattner, D. A.; Petter, W. *Liebigs Ann. Chem.* **1990**, 687–695.
5. Seebach, D.; Dziadulewicz, E.; Behrendt, L.; Cantoreggi, S.; Fitzi, R. *Liebigs Ann. Chem.* **1989**, 1215–1232.
6. While preparing this manuscript, a four-step synthesis of the Phe-derived azetidine **2** ($R^1 = Bzl$, $R^2 = Et$, $R^3 = Boc$) was published, but the configuration of the main obtained isomer was not reported: Kawabata, T.; Kawakami, S.; Majumdar, S. *J. Am. Chem. Soc.* **2003**, *125*, 13012–13013.
7. (a) Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *Synlett* **2000**, 1249–1252; (b) Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem.* **2001**, *66*, 3538–3547.
8. (a) Verkoyen, C.; Rademacher, P. *Chem. Ber.* **1984**, *117*, 1659–1670; (b) Yamashita, M.; Ojima, I. *J. Am. Chem. Soc.* **1983**, *105*, 6339; (c) Ojima, I.; Yamato, T.; Nakahashi, K. *Tetrahedron Lett.* **1985**, *26*, 2035–2038; (d) Ojima, I.; Zhao, M.; Yamato, T.; Nakahashi, K. *J. Org. Chem.* **1991**, *56*, 5263–5277; (e) Sudo, A.; Iitaka, Y.; Endo, T. *J. Polym. Sci. Part A: Polym. Chem.* **2002**, *40*, 1912–1917.
9. (a) Brown, H.; Heim, P. *J. Org. Chem.* **1973**, *38*, 912–916; (b) Adachi, K.; Tsuru, E.; Banjyo, E.; Doe, M.; Shibata, K.; Yamashita, T. *Synthesis* **1998**, 1623–1626.
10. Collins, C. J.; Lanz, M.; Singaram, B. *Tetrahedron Lett.* **1999**, *40*, 3673–3676.
11. Kuwano, R.; Takahashi, M.; Ito, Y. *Tetrahedron Lett.* **1998**, *39*, 1017–1020.
12. General procedure for the β-lactam reduction: To a solution of the corresponding azetidinone (5.01 mmol) in dry THF (5 mL) was added, under Ar atmosphere, tris(triphenyl-phosphine)rhodium(I) carbonyl hydride (46 mg, 1%) and diphenylsilane (2.3 mL, 12.5 mmol). After 15 h of reaction at room temperature, the solvent was evaporated to give a residue that was dissolved in Et_2O and washed twice with 1 M HCl. The aqueous layer was treated with 2 N NaOH to pH 10 and extracted with EtOAc. The organic layer was washed with brine and dried over Na_2SO_4. Evaporation to dryness afforded the corresponding 1-Pmb-azetidine that usually did not required further purification.
13. Selected spectroscopic data for compound **2d**: ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 and 6.80 (m, 9H, Ar-*H*), 3.72 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.67 (d, 1H, 1-CH_2, $J = 12.7$ Hz), 3.50 (d, 1H, 1-CH_2, $J = 12.7$ Hz), 3.21 (d, 1H, 2-CH_2, $J = 13.3$ Hz), 3.10 (m, 2H, 4-H), 3.09 (d, 1H, 2-CH_2, $J = 13.3$ Hz), 2.41 (m, 1H, 3-H), 2.12 (m, 1H, 3-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.06 (COO), 158.52, 136.50, 130.23, 129.75, 129.55, 128.06, 126.37, 113.55 (Ar), 72.86 (2-C), 55.28 (1-CH_2), 55.06 (OMe), 51.17 (OMe), 49.48 (4-C), 40.98 (2-CH_2), 25.74 (3-C). ES-MS: 326.4 $(M+1)^+$.
14. General method for the removal of 1-Pmb group: To a solution of the corresponding 1-(*p*-methoxy)benzylazetidine (3.86 mmol) in MeOH (75 mL) was successively added HCl 12 M (0.34 mL, 3.86 mmol) and $Pd(OH)_2$ (20% w/w). The obtained suspension was hydrogenated at 50 °C and 40 psi of pressure for 15 h. After filtration of the catalyst, the solvent was evaporated and the final azetidine hydrochloride was precipitated with Et_2O. Purification by column chromatography was required in some instances.
15. Selected analytical and spectroscopic data for azetidine **3d**: mp: 118–120 °C (EtOAc/hexane). ^{1}H NMR (200 MHz, $CDCl_3$): 7.36–7.26 (m, 7H, C_6H_5 and NH_2^+), 4.03 (m, 2H, 4-H), 3.78 (s, 3H, OMe), 3.77 (d, 1H, 2-CH_2, $J = 14.2$ Hz), 3.46 (d, 1H, 2-CH_2, $J = 14.2$ Hz), 2.74 (m, 2H, 3-H). Anal. Calcd For $C_{12}H_{16}ClNO_2$: C, 59.63; H, 6.67; Cl, 14.67; N, 5.79. Found: C, 59.40; H, 6.55; Cl, 14.03; N, 5.86.
16. Chiral stationary phases (CSPs) were prepared by covalent bonding of a mixed polysaccharide derivative on allyl silica gel. CSPs used in this work contained the mixed 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose (CSP-**1**), 10-undecenoate/*p*-methylbenzoate of cellulose (CSP-**2**), 10-undecenoate/phenylcarbamate of cellulose (CSP-**3**) and 10-undecenoate/3,5-dimethylphenylcarbamate of amylose (CSP-**4**) as chiral selectors: (a) Oliveros, L.; Lopez, P.; Minguillón, C.; Franco, P. *J. Liq. Chromatogr.* **1995**, *18*, 1521–1532; (b) Minguillón, C.; Franco, P.; Oliveros, L.; López, P. *J. Chromatogr. A* **1996**, *728*, 407–414.
17. Preparative resolution of **1d** was carried out on a 150×20 mm ID column containing the same CSP as analytical column, 10-undecenoate/3,5-dimethylphenylcarbamate of cellulose covalently linked to allyl silica gel. Although chloroform had led to a lower resolution factor, elution was performed in a mixture of *n*-hexane/2-propanol/chloroform 96:2:2 to increase the sample solubility and, then, the column loadability. Flow rate: 15 mL/min. UV detection: 254 nm.
18. Although compound **1d** could be obtained in an enantioselective manner due to the memory of chirality phenomenon, for the resolution process it was prepared in almost racemic form (enantiomeric ratio: 43/57) using a combination of *N*-methyl-2-pyrrolidone as solvent and BEMP as base: (a) Bonache, M. A.; Gerona-Navarro, G.; Martín-Martínez, M.; García-López, M. T.; López, P.; Cativiela, C.; González-Muñiz, R. *Synlett* **2003**, 1007–1011; (b) Bonache, M. A.; Gerona-Navarro, G.; García-Aparicio, C.; Alías, M.; Martín-Martínez, M.; García-López, M. T.; López, P.; Cativiela, C.; González-Muñiz, R. *Tetrahedron: Asymmetry* **2003**, *14*, 2161–2169.
19. Under the conditions described above, a total of 1 g of **1d** was injected in 3.3 mL of $CHCl_3$ and each run (0.2 mL) was collected into three separated fractions. The first combined fraction (245 mg) and the last one (335 mg) contained mainly one of the enantiomers (85% and 92% of enantiomeric purity, respectively). The third fraction (400 mg) was reinjected and similar enantioselectives mixtures were obtained. Crystallization of the enriched mixtures in ethanol/hexanes led to the optically pure compounds. By this procedure 275 and 285 mg of the first and second eluted enantiomers of **1d** can be obtained.
20. Gerona-Navarro, G.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem.* **2002**, *67*, 3953–3956.
21. Polarimetry data of (*S*)- and (*R*)-**6d**, prepared according to the HPLC resolution procedure described here, are higher than those reported in Ref. 20, indicating a more accurate resolution in this case.