

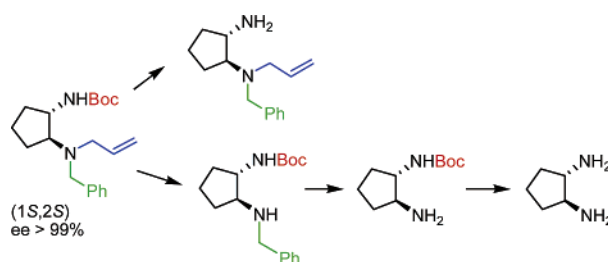
A Biocatalytic Approach to Synthesizing Optically Active Orthogonally Protected *trans*-Cyclopentane-1,2-Diamine Derivatives

Javier González-Sabín, Vicente Gotor,* and Francisca Rebolledo*

Departamento de Química Orgánica e Inorgánica, Facultad de Química, Universidad de Oviedo, 33071-Oviedo, Spain

vgs@fq.uniovi.es; frv@fq.uniovi.es

Received October 24, 2006



A straightforward chemoenzymatic synthesis of optically active *trans*-*N,N*-dialkylcyclopentane-1,2-diamines has been efficiently developed starting out from their analogous (\pm)-*trans*-2-(*N,N*-dialkylamino)-cyclopentanol. The route involves the one-pot stereospecific transformation of the racemic amino alcohols into racemic diamines and a subsequent kinetic resolution by means of lipase-B from *Candida antarctica*-catalyzed acylation reactions. The careful selection of both the alkyl substituents present in the diamine and the derivatization strategy applied to the enzymatic reaction enabled the easy preparation of other synthetically valuable optically active *trans*-cyclopentane-1,2-diamines derivatives.

Introduction

The 1,2-diamino moiety is present in the structure of a great variety of natural products such as biotin (vitamin H),¹ the alkaloid slaframine,² or balanol,³ an inhibitor of the protein kinase C. Furthermore, the therapeutic properties of many synthetic optically active 1,2-diamines have been explored in different areas of medicinal chemistry. Among these, we may

cite platinum 1,2-diamino complexes as anticancer drugs⁴ and some cyclohexane-1,2-diamine derivatives as highly selective κ -opioid agonists.⁵ Moreover, vicinal diamines have also shown great utility in other areas such as coordination chemistry or asymmetric catalysis.⁶ For all these reasons, it is easy to understand the intensive efforts that chemists have devoted to the development of new and efficient methods to prepare these compounds.

The commercially available enantiopure *trans*-cyclohexane-1,2-diamine has perhaps been the most used diamine for the synthesis of ligands and receptors.⁷ It is thus common to find this diamine as the structural key of many catalysts in a wide range of asymmetric process applications; for instance, addition of organozinc compounds to aldehydes and ketones,⁸ hydroge-

(1) (a) Eisenberg, M. A. In *Escherichia coli and Salmonella typhimurium: Cellular and Molecular Biology*; Neidhardt, F. C., Ed.; American Society for Microbiology: Washington, DC, 1987; Vol. 1, pp 544–550. (b) Marquet, A. *Pure Appl. Chem.* **1993**, *65*, 1249–1252.

(2) Gardiner, R. A.; Rinehart, K. L., Jr.; Snyder, J. J.; Broquist, H. P. *J. Am. Chem. Soc.* **1968**, *90*, 5639–5640.

(3) Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. P.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452–6453.

(4) (a) Brunner, H.; Hankofer, P.; Holzinger, U.; Treitinger, B.; Schönenberger, H. *Eur. J. Med. Chem.* **1990**, *25*, 35–44. (b) Brunner, H.; Hankofer, P.; Holzinger, U.; Treitinger, B. *Chem. Ber.* **1990**, *123*, 1029–1038. (c) Gust, R.; Burgemeister, T.; Mannschreck, A.; Schönenberger, H. *J. Med. Chem.* **1990**, *33*, 2535–2544. (d) Kelland, L. R.; Abel, G.; McKeage, M. J.; Jones, M.; Goddard, P. M.; Valenti, M.; Murrer, B. A.; Harrap, K. R. *Cancer Res.* **1993**, *5*, 2581–2586. (e) Kim, D.-K.; Kim, Y.-W.; Kim, H.-T.; Kim, K. H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 643–646. (f) Khokhar, A. R.; Al-Baker, S.; Shamsuddin, S.; Siddik, Z. H. *J. Med. Chem.* **1997**, *40*, 112–116. (g) Reedijk, J. *Chem. Commun.* **1996**, 801–806.

(5) (a) Szmuszkovicz, J.; Von Voigtlander, P. F. *J. Med. Chem.* **1982**, *25*, 1125–1126. (b) Szmuszkovicz, J. Eur. Pat. Appl. EP 126612, 1984; *Chem. Abstr.* **1985**, *102*, 184969b. (c) Clark, C. R.; Halfpenny, P. R.; Hill, R. G.; Horwell, D. C.; Hughes, J.; Jarvis, T. C.; Rees, D. C.; Schofield, D. *J. Med. Chem.* **1988**, *31*, 831–836. (d) Costello, G. F.; James, R.; Shaw, J. S.; Slater, A. M.; Stutchbury, N. C. *J. Med. Chem.* **1991**, *34*, 181–189. (e) Barlow, J. J.; Blackburn, T. P.; Costello, G. F.; James, R.; Le Count, D. J.; Main, B. G.; Pearce, R. J.; Russell, K.; Shaw, J. S. *J. Med. Chem.* **1991**, *34*, 3149–3158.

(6) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580–2627.

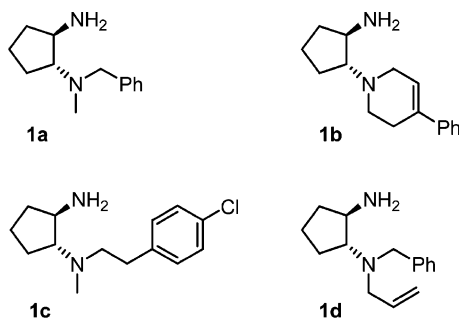


FIGURE 1. Selected *trans*-*N,N*-dialkylcyclopentane-1,2-diamines.

nation of prochiral ketones,⁹ or epoxidation and cyclopropanation of olefins.¹⁰ In contrast, applications of nonracemic *trans*-cyclopentane-1,2-diamine still remain almost unexplored due to the complexity of the reported syntheses and their poor yields. Since the pioneering work of Toftlund and Pedersen,¹¹ only a few approaches have appeared for this compound, and in general, the enantiopure diamine is only obtained after multistep sequences with low overall yields.¹²

Continuing with our interest in the synthesis of optically active 1,2-diamines, and encouraged both by the scarcity of reported syntheses of cyclopentane-1,2-diamine and by the promising utility of some of its derivatives as chiral ligands¹³ and precursors of improved peptide nucleic acids (PNAs),¹⁴ we focused our research on the development of efficient routes for preparing optically active *N,N*-disubstituted *trans*-cyclopentane-1,2-diamines. The strategy described in this article combines

(7) For an excellent review, see: (a) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, 97, 3161–3196. For some recent examples of the utility of *trans*-cyclohexane-1,2-diamine derivatives in asymmetric catalysis, see: (b) Huang, H.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, 128, 7170–7171. (c) Fuerst, D. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, 127, 8964–8965. (d) Evans, D. A.; Seidel, D. *J. Am. Chem. Soc.* **2005**, 127, 9958–9959. (e) Aoyama, H.; Tokunaga, M.; Kiyosu, J.; Iwasawa, T.; Obora, Y.; Tsuji, Y. *J. Am. Chem. Soc.* **2005**, 127, 10474–10475. For some examples of macrocyclic receptors containing the *trans*-cyclohexane-1,2-diamine unit, see: (f) Pan, Z.; Still, W. C. *Tetrahedron Lett.* **1996**, 37, 8699–8702. (g) Alfonso, I.; Rebollo, F.; Gotor, V. *Chem.—Eur. J.* **2000**, 6, 3331–3338. (h) Alfonso, I.; Dietrich, B.; Rebollo, F.; Gotor, V.; Lehn, J.-M. *Helv. Chim. Acta.* **2001**, 84, 280–295. (i) Lee, K. H.; Lee, D. H.; Hwang, S.; Lee, O. S.; Chung, D. S.; Hong, J.-I. *Org. Lett.* **2003**, 5, 1431–1433.

(8) (a) García, C.; Walsh, P. J. *Org. Lett.* **2003**, 5, 3641–3644. (b) Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2004**, 126, 6538–6539.

(9) Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, 10, 2045–2061.

(10) McGarrigle, E. M.; Gilheany, D. G. *Chem. Rev.* **2005**, 105, 1563–1602.

(11) Optically active *trans*-cyclopentane-1,2-diamine was prepared for the first time by applying the classical recrystallization with tartaric acid. However, high enantiomeric excesses were obtained only after several recrystallization cycles, which led to a low overall yield: Toftlund, H.; Pedersen, E. *Acta Chem. Scand.* **1972**, 26, 4019–4030.

(12) (a) Onger, S.; Aitken, D. J.; Husson, H.-P. *Synth. Commun.* **2000**, 30, 2593–2597. (b) Luna, A.; Alfonso, I.; Gotor, V. *Org. Lett.* **2002**, 4, 3627–3629. (c) de Parrodi, C. A.; Walsh, P. J. *Synlett* **2004**, 13, 2417–2420. (d) Myers, M. C.; Witschi, M. A.; Larionova, N. V.; Franck, J. M.; Haynes, R. D.; Hara, T.; Grajkowski, A.; Appella, D. H. *Org. Lett.* **2003**, 5, 2695–2698.

(13) (a) Dominguez, B.; Hodnett, N. S.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2001**, 40, 4289–4291. (b) Gouin, S. G.; Gestin, J.-F.; Joly, K.; Loussouarn, A.; Reliquet, A.; Meslin, J. C.; Deniaud, D. *Tetrahedron* **2002**, 58, 1131–1136. (c) Hoffmann, R. W.; Klute, W.; Dress, R. K.; Wenzel, A. *J. Chem. Soc., Perkin Trans. 2* **1995**, 1721–1726. (d) Daly, A. M.; Gilheany, D. G. *Tetrahedron: Asymmetry* **2003**, 14, 127–137.

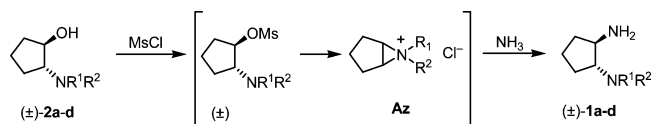
(14) (a) Pokorski, J. K.; Witschi, M. A.; Purnell, B. L.; Appella, D. H. *J. Am. Chem. Soc.* **2004**, 126, 15067–15073. (b) Pokorski, J. K.; Nam, J.-M.; Vega, R. A.; Mirkin, C. A.; Appella, D. H. *Chem. Commun.* **2005**, 2055–2056.

biocatalytic and nonenzymatic processes: the stereospecific transformation of (\pm)-*trans*-2-(*N,N*-dialkylamino)cyclopentanol into (\pm)-*trans*-cyclopentane-1,2-diamines and the subsequent enzymatic resolution are the key steps. Some of the diamines (Figure 1) were also chosen for their pharmacological properties; **1b** is an analogue of the anticholinergic vesamicol,¹⁵ and **1c** is precursor of CCR-3 chemokine receptor antagonists.¹⁶ In addition, diamines **1a** and **1d** bear easily removable substituents, which allowed us to differ both amino groups for the modular synthesis of a novel set of derivatives with potential synthetic utility.

Results and Discussion

Synthesis of Racemic Diamines 1a–d. Diamines (\pm)-**1a–d** (Scheme 1) were prepared from the analogous (\pm)-*trans*-2-(*N,N*-dialkylamino)cyclopentanol (**2a–d**)¹⁷ following the strategy developed for the synthesis of racemic *N,N*-disubstituted cyclohexane-1,2-diamines.¹⁸ Thus, the one-pot treatment of (\pm)-**2a–d** with mesyl chloride and subsequently with aqueous ammonia afforded *trans*-diamines (\pm)-**1a–d** as the only product, in very good yields (>85%). We expected this reaction to proceed via an aziridinium intermediate as in the case of the cyclohexane-1,2-diamines. Once the mesylation of alcohol takes place, the resulting mesyl derivative would experience an intramolecular S_N2 reaction with the formation of the *meso*-aziridinium ion (**Az**), which would be attacked by the ammonia leading to the final *trans*-diamine (Scheme 1).

SCHEME 1. Preparation of Racemic Diamines 1a–d



As the configuration of cyclopentane derivatives cannot be assigned from values of coupling constants, the *trans* configuration of these diamines **1a–d** was assigned by comparison with the configurationally known *trans*-amino alcohols **2a–d**.¹⁷ Accordingly, we carried out NOE measures on the *trans*-amino alcohol **2a** and the acetamide **3a**, obtained by acetylation of **1a** (with unknown relative configuration).¹⁹ Two signals, OH (or NH) and H-2, were irradiated for both compounds, and the NOE enhancements of the other two depicted signals (Figure 2) were

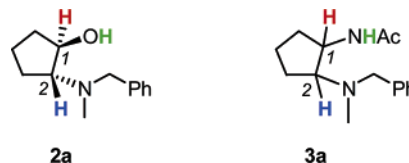


FIGURE 2. Selected signals of **2a** and **3a** for NOE experiments.

compared in each case. Irradiation of the H-2 signal of **2a** causes a strong NOE on the OH signal, which increased much more than that of H-1, as expected due to the *trans* configuration. The same effect was observed when we irradiated the H-2 signal of the acetamide **3a**. Moreover, the NOE enhancement of both

(15) Marshall, I. G.; Parsons, S. M. *Trends Neurosci.* **1987**, 10, 174–177.

(16) Du, B.; Daisy, J. J. *PCT Int. Appl.* **2003**, WO 2003022799 A1; *Chem. Abstr.* **2003**, 138, 254963.

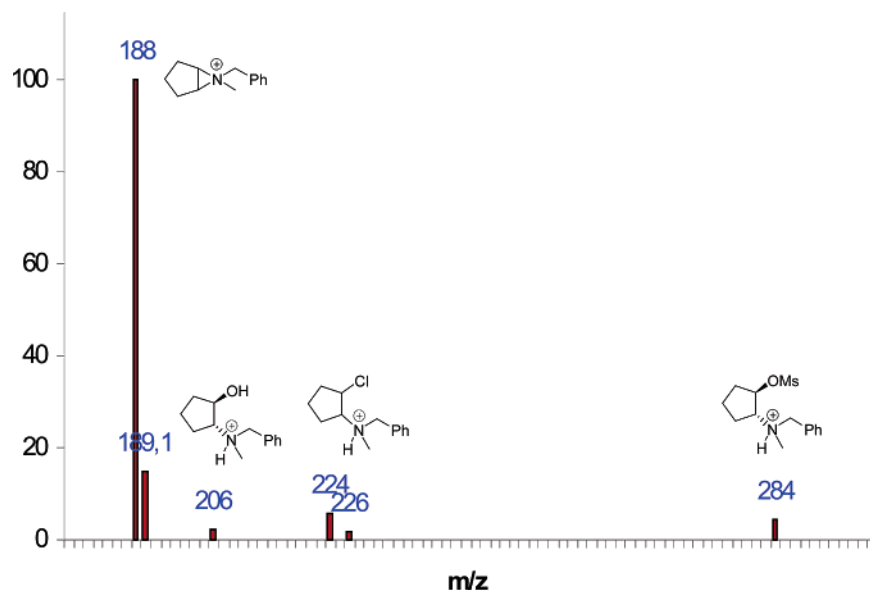


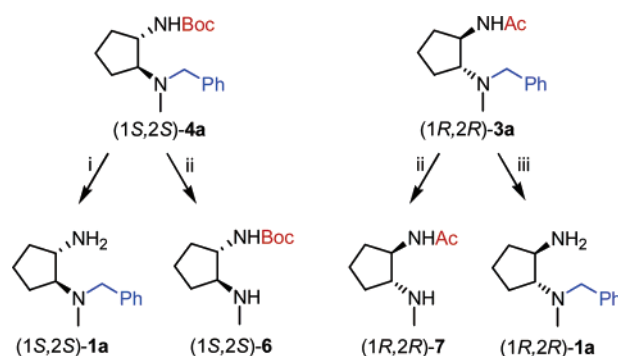
FIGURE 3. ESI-MS spectrum of the reaction mixture of (±)-**2a** and mesyl chloride.

H-1 signals was similar (see details of these experiments in the Supporting Information). We likewise observed strong NOE in the H-2 signals of both the amino alcohol and the acetamide after irradiation of the corresponding OH or NH signal. From these results, we can deduce that compounds **2a** and **3a**, and by extension **1a**, have the same *trans* configuration.

This *trans* configuration supports the notion that the reaction proceeds through the *meso*-aziridinium ion²⁰ intermediate (**Az**, Scheme 1). Analysis of the ESI-MS spectrum of the reaction mixture obtained just a few minutes after mixing the amino alcohol **2a** and mesyl chloride allowed us to detect the *meso*-aziridinium ion ($m/z = 188$) as the base peak (Figure 3), in addition to other species such as the starting protonated amino alcohol ($m/z = 206$), and their mesyl ($m/z = 284$) and chloride ($m/z = 224$) derivatives. This last species could have *trans* configuration if formed by ring opening of the aziridinium ion (**Az**), or *cis* configuration if generated by the S_N2 attack of the chloride anion on the mesylated amino alcohol. These results indicate that, although the mediation of the aziridinium ion in the process is clear, the *trans*-diamine may also proceed non-exclusively from this intermediate, as well as from a hypothetical chlorine byproduct of *cis* configuration. The involvement of either *trans*-mesyl and *trans*-chlorine derivatives is ruled out because both intermediates should lead to the *cis*-diastereomer.

An additional proof supports the premise that *trans*-diamines are only formed through the *meso*-aziridinium: when enantiopure amino alcohol (1*R*,2*R*)-**2a**¹⁷ was submitted to the same

SCHEME 2^a



^a Reagents and conditions: (i) 3 N aq HCl; (ii) H₂, Pd-C 10%; (iii) 6 N aq HCl, reflux.

reaction conditions, a complete loss of optical activity took place and racemic *trans*-diamine (±)-**1a** was isolated.

Enzymatic Resolution of Racemic Diamines 1a–d. Following the excellent results obtained with *N,N*-disubstituted cyclohexane-1,2-diamines,¹⁸ we designed the CAL-B-catalyzed resolution of diamines (±)-**1a–d** by aminolysis processes under the simplest reaction conditions (i.e., employing ethyl acetate as acyl donor and solvent). Thus far, CAL-B (Novozyme SP-435) has proven to be the most effective catalyst for the aminolysis reaction in organic solvent.²¹ The results presented in Table 1 show that lipase displayed good enantioselectivities with diamines **1a**, **1b**, and **1d** ($E^{22} > 65$) and only moderate enantioselectivity with **1c** ($E = 20$). In the enzymatic reaction of (±)-**1b**, the resulting mixture formed by the acetamide **3b** and the diamine **1b** was easily separated by flash chromatography. In the other cases, the isolation of both the diamine and acetamide was facilitated by derivatization of the reaction

(17) Synthesized by ring opening of cyclopentene oxide with the corresponding secondary amine: González-Sabín, J.; Rebollo, F.; Gotor, V. *Biotechnol. J.* **2006**, *1*, 835–841.

(18) González-Sabín, J.; Rebollo, F.; Gotor, V. *Chem.–Eur. J.* **2004**, *10*, 5788–5794.

(19) We chose acetamide **3a** instead of diamine **1a** due to the clearer ¹H NMR spectrum.

(20) For some applications of aziridinium ions in synthesis, see: (a) Couturier, M.; Tucker, J. L.; Andresen, B. M.; DeVries, K. M.; Vanderplas, B. C.; Ito, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3517–3523. (b) Piotrowska, D. G.; Wróblewski, A. E. *Tetrahedron* **2003**, *59*, 8405–8410. (c) Andrews, D. R.; Dahanukar, V. H.; Eckert, J. M.; Gala, D.; Lucas, B. S.; Schumacher, D. P.; Zavialov, I. A. *Tetrahedron Lett.* **2002**, *43*, 6121–6125. (d) Chuang, T. H.; Sharpless, K. B. *Org. Lett.* **2000**, *2*, 3555–3557.

(21) For some recent reviews, see: (a) Gotor-Fernández, V.; Busto, E.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 797–812. (b) Van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **2004**, *60*, 501–519. (c) Alfonso, I.; Gotor, V. *Chem. Soc. Rev.* **2004**, *33*, 201–209.

(22) Chen, C. S.; Fujimoto, Y.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1982**, *104*, 7294–7299.

TABLE 1. Enzymatic Resolution of Racemic Diamines (\pm)-**1a–d**^a

Diamine	NR ¹ R ²	t (h)	c ^b (%)	Remaining Substrate (1 <i>S</i> ,2 <i>S</i>)			Product (1 <i>R</i> ,2 <i>R</i>)			<i>E</i> ^c
				diamine or carbamate	yield (%)	ee (%)	amide	yield (%)	ee (%)	
(\pm)- 1a		3	47	4a	45	84	3a	46	94	86
(\pm)- 1b		13	51	1b	43	93	3b	47	90	65
(\pm)- 1c		6	55	5c	43	89	3c	48	74	20
(\pm)- 1d		5	42	4d	48	68	3d	40	95	72

^a All the reactions were carried out at 28 °C and 200 rpm. ^b Conversion: $c = ee_s/(ee_s + ee_p)$. ^c Enantiomeric ratio calculated according to ref 22.

mixtures with benzyl chloroformate (in the case of **1c**) or di-*tert*-butyl dicarbonate (for **1a** and **1d**). Hence, the remaining (1*S*,2*S*)-diamines were transformed into the corresponding Cbz or Boc derivatives, the resulting mixtures of carbamate and acetamide also being separated by flash chromatography. In all the processes, both the remaining substrate and product were obtained in high yields (>40%), bearing in mind the limiting yield of 50% allowed in a kinetic resolution. Moreover, free diamines (1*S*,2*S*)-**1a**, **1c**, and **1d** were quantitatively recovered after removal of the benzyloxycarbonyl (H₂, 10% Pd–C) or *tert*-butoxycarbonyl (HCl 3 N) groups.

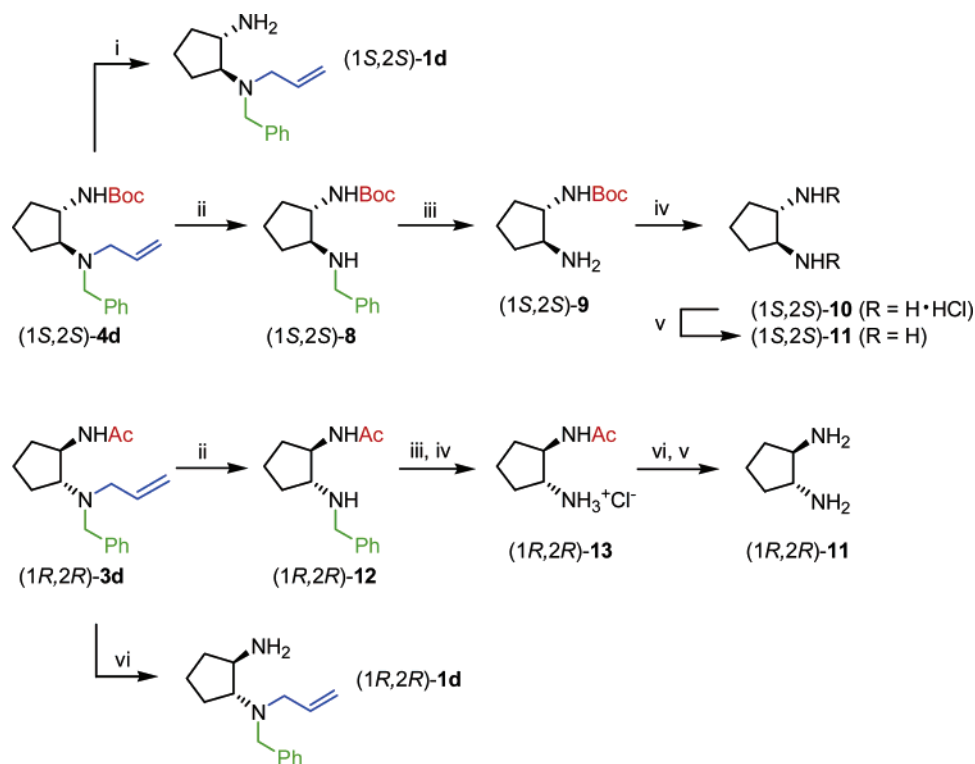
To improve the enantioselectivity of these processes, some changes in the reaction conditions were accomplished using compound **1a** as a model substrate. Thus, *tert*-butyl methyl ether (TBME) was tested as solvent and methyl methoxyacetate or α -methylbenzyl acetate as acyl donors.²³ The reaction with methyl methoxyacetate was very fast, and enantiopure carbamate (1*S*,2*S*)-**4a** was isolated after only 3 h ($c = 55\%$, $E = 89$). The corresponding aminolysis of α -methylbenzyl acetate proceeded

not only slightly slower but also with less enantioselectivity ($E = 47$). Finally, when we applied the best reaction conditions (methyl methoxyacetate and TBME) to the resolution of **1c**, the process took place with poor enantioselectivity ($E = 10$).

For our further synthetic goals regarding diamines **1a** and **1d**, it would be desirable to obtain these compounds and their acetamide derivatives with high optical purity. To do so, an accurate control of the percentage of conversion in the enzymatic process is required. Despite the slightly higher enantioselectivity when using TBME and methyl methoxyacetate, we chose the first conditions employing only ethyl acetate due to the simplicity and lower cost of this methodology. Thus, remaining amines (1*S*,2*S*)-**1a** and (1*S*,2*S*)-**1d**, isolated as the corresponding carbamates (1*S*,2*S*)-**4a** and (1*S*,2*S*)-**4d**, were obtained in enantiomerically pure form after 10 and 21 h of reaction, respectively ($c = 55\%$). Acetamides (1*R*,2*R*)-**3a** and (1*R*,2*R*)-**3d** of 95% ee were likewise obtained after only 2.5 and 5 h, respectively ($c = 42\%$).

In all cases, enantiomeric excesses were determined by HPLC using a chiral column. Configuration (1*S*,2*S*) for the remaining diamine **1d** was established after transformation of its carbamoyl

(23) González-Sabín, J.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **2004**, 15, 481–488.

SCHEME 3^a

^a Reagents and conditions: (i) 3 N aq HCl; (ii) Pd(dba)₂, dppb, mercaptobenzoic acid; (iii) H₂, Pd-C 10%; (iv) 3 N HCl in MeOH; (v) solid NaOH, extraction with CH₂Cl₂; (vi) 6 N aq HCl, reflux.

derivative **4d** into *trans*-cyclopentane-1,2-diamine **11** (Scheme 3) and comparison of the sign of its specific rotation with the reported value for (1*S*,2*S*)-(-)-**11**.¹¹ This means that CAL-B follows Kazlauskas' rule,²⁴ showing stereopreference toward the (1*R*,2*R*)-enantiomer of the racemic diamine. Taking into account this result, the structural resemblance between diamines reported here, and the stereopreference shown for CAL-B with the analogous cyclohexane-1,2-diamines, we have tentatively assigned the (1*S*,2*S*) configuration to the other remaining diamines **1a–c** and the (1*R*,2*R*) configuration to the corresponding acetamides **3a–c**.

Selective Cleavage of Protecting Groups of the Optically Active Compounds 1a and 1d. Diamines **1a** and **1d**, bearing the easily removable benzyl and allyl groups within their structures, were deliberately chosen with the aim of preparing some orthogonally protected *trans*-cyclopentane-1,2-diamine derivatives. This was why their enzymatic crude products were derivatized with di-*tert*-butyl dicarbonate. Thus, both compounds isolated from the enzymatic reactions of **1a**, the aminocarbamate (1*S*,2*S*)-**4a** (ee > 99%) and the aminoacetamide (1*R*,2*R*)-**3a** (ee = 95%), contain orthogonal protective groups: Boc and benzyl in the case of **4a**, and acetamide and benzyl in the case of **3a** (Scheme 2). Effectively, the selective removal of these groups led to very high yields of both enantiomers of *trans*-*N*-benzyl-*N*-methylcyclopentane-1,2-diamine [(1*S*,2*S*)-**1a** and (1*R*,2*R*)-**1a**], as well as the derivatives (1*S*,2*S*)-**6** and (1*R*,2*R*)-**7**, which are precursors of the monosubstituted *N*-methylcyclopentane-1,2-diamine.

In the case of diamine **1d**, the aminocarbamate (1*S*,2*S*)-**4d** (ee > 99%) and the aminoacetamide (1*R*,2*R*)-**3d** (ee = 95%)

isolated from the enzymatic reactions bear a set of three removable protecting groups: (i) Boc or Ac, (ii) *N*-allyl, and (iii) *N*-benzyl (Scheme 3). First, the acid treatment of **4d** and **3d** led to both enantiomers of **1d** in excellent yields. Next, we planned the cleavage of the two protective groups over the other nitrogen atom of (1*S*,2*S*)-**4d** and (1*R*,2*R*)-**3d**. As the allyl group reacts in the conditions used for the debenzylation, we first carried out selective deallylation, isolating the *N*-benzyl derivatives (1*S*,2*S*)-**8** and (1*R*,2*R*)-**12**.²⁵ Subsequent hydrogenolysis of these compounds afforded (1*S*,2*S*)-**9** and (1*R*,2*R*)-**13** in quantitative yields. Finally, from the acid treatment of **9** and **13**, both enantiomers of the *trans*-cyclopentane-1,2-diamine were isolated as free diamines [(1*S*,2*S*)-**11** and (1*R*,2*R*)-**11**] or as their dihydrochloride salts (**10**).

Analysis of Schemes 2 and 3 reveals the plethora of optically active cyclopentane-1,2-diamine derivatives that can be prepared following a very simple methodology. In addition to the interesting monoalkyl derivatives bearing in turn an additional transformable function (**8** and **12**), note should be taken of the easy accessibility to *N*-methylated compounds (**6** and **7**), which are difficult to prepare by conventional methods. In addition, the monoprotected diamines are common synthetic intermediates in the synthesis of PNA monomers, and the carbamate **9** is a key building block of a novel class of modified PNAs with an increased binding affinity and sequence specificity to complementary DNA.¹⁴ On the other hand, as in the case of *trans*-cyclohexane-1,2-diamine,²⁶ the *N,N'*-unsymmetrical derivatives of the cyclopentyl analogues could be highly valuable molecules in both asymmetric catalysis and medicinal chemistry.

(24) Kazlauskas, R. J.; Weissfloch, A. N. E.; Rappaport, A. T.; Cuccia, L. A. *J. Org. Chem.* **1991**, *56*, 2656–2665.

(25) Allyl group was selectively removed employing a Pd(0) catalyst and mercaptobenzoic acid as allyl group scavenger: Lemaire-Audoire, S.; Savignac, M.; Genêt, J. P. *Tetrahedron Lett.* **1995**, *36*, 1267–1270.

Conclusion

We have developed a new chemoenzymatic protocol for the preparation of optically active *trans*-*N,N*-dialkylcyclopentane-1,2-diamines starting out from the structurally analogous (\pm)-*trans*-2-(*N,N*-dialkylamino)cyclopentanol. The adequate arrangement of protecting groups attached to the nitrogen atoms allowed us to isolate orthogonally protected derivatives in high yields and ee. The synthetic value of these compounds was also demonstrated by the selective deprotection of each group on the nitrogen atoms under mild reaction conditions. Both the efficacy of the syntheses included here as well as the structural variety of the compounds make this strategy one of the most appropriate methods for preparing nonracemic *trans*-cyclopentane-1,2-diamine derivatives.

Experimental Section

General Procedure for the Preparation of Racemic Diamines 1a–d. The corresponding (\pm)-*trans*-2-(*N,N*-dialkylamino)cyclopentanol¹⁷ (**2a–d**, 25 mmol) was dissolved in anhydrous diethyl ether (45 mL), and triethylamine (39 mmol) was added. The solution was cooled to 0 °C, and mesyl chloride (29.7 mmol) was added dropwise. A white precipitate formed that made stirring difficult. After 30 min, triethylamine (49 mmol) was added. After the reaction mixture was allowed to warm to room temperature, concd aq NH₃ (50 mL) was added and the resulting two-phase reaction mixture was vigorously stirred for 16 h. The layers were separated, and the light-yellow aqueous layer was extracted with Et₂O (3 \times 30 mL). The combined organic layers were washed with brine (20 mL), dried with Na₂SO₄, and evaporated under reduced pressure to give the crude product, which was purified by distillation or flash chromatography (ethyl acetate/methanol mixtures).

(\pm)-*trans*-*N*-Benzyl-*N*-methylcyclopentane-1,2-diamine [(\pm)-1a**].** Prepared from (\pm)-*trans*-2-(*N*-benzyl-*N*-methylamino)cyclopentanol (**2a**). Yield: 92%; bp 95–97 °C (0.5 Torr); ¹H NMR (200 MHz, CDCl₃): δ 1.25–1.45 (m, 1H), 1.50–1.80 (m, 4H), 1.85–2.00 (m, 1H), 2.15 (s, 3H, CH₃), 2.45 (brs, 2H, NH₂), 2.56 (c, 1H, *J* = 7.8 Hz), 3.12 (c, 1H, *J* = 7.8 Hz), AB system (δ_A 3.45, δ_B 3.58, *J*_{AB} = 13.3 Hz, CH₂-Ph), 7.20–7.40 (m, 5H, Ph); ¹³C NMR

(75.5 MHz, CDCl₃): δ 20.9 (CH₂), 23.0 (CH₂), 33.4 (CH₂), 38.0 (CH₃), 54.2 (CH), 59.4 (CH₂), 73.7 (CH), 126.6 (CH), 128.0 (CH), 128.5 (CH), 139.8 (C); IR (neat): ν 3362 cm⁻¹; MS (ESI⁺) *m/z* (%): 205.1 (100) [M + H]⁺, 227.1 (15) [M + Na]⁺; elemental analysis (%) calcd for C₁₃H₂₀N₂: C, 76.42; H, 9.87; N, 13.71. Found: C, 76.51; H, 9.70; N, 13.59.

General Procedure for the Enzymatic Acetylation of Racemic Diamines 1a–d. Ethyl acetate (12 mL) was added under nitrogen atmosphere to a mixture of racemic diamine **1a–d** (2.0 mmol) and CAL-B (200 mg). The resulting mixture was shaken at 28 °C and 200 rpm. The enzyme was subsequently filtered and washed with ethyl acetate. For the reactions of **1a** and **1d**, the resulting solution was cooled to 0 °C and then treated with di-*tert*-butyl dicarbonate (1.3 mmol). After 12 h, the solvent was evaporated and both the acetamide and carbamate present in the residue were separated by flash chromatography (ethyl acetate/methanol mixtures). Similarly, benzyl chloroformate was used in the derivatization process for the reaction of **1c**. For the reaction of **1b**, after filtration of the enzyme, the corresponding acetamide and the remaining diamine were separated by flash chromatography using ethyl acetate/methanol 3:1.

(1*R*,2*R*)-*N*-[2-(*N'*-Benzyl-*N'*-methylamino)cyclopentyl]acetamide [(1*R*,2*R*)-3a**].** Yield: 46%; mp 82–84 °C; [α]_D²⁰ –27.8 (c 1.0 in CHCl₃) 94% ee; ¹H NMR (300 MHz, CDCl₃): δ 1.25–1.40 (m, 1H), 1.50–1.80 (m, 4H), 1.98 (s, 3H, CH₃), 2.05–2.25 (m + s, 4H), 2.80 (c, 1H, *J* = 11.7 Hz), AB system (δ_A 3.50, δ_B 3.64, *J*_{AB} = 19.4 Hz, CH₂-Ph), 4.16 (q, 1H, *J* = 11.7 Hz), 5.68 (brd, 1H, NH, *J* = 8.2 Hz), 7.20, 7.40 (m, 5H, Ph); ¹³C NMR (75.5 MHz, CDCl₃): δ 21.1 (CH₂), 23.4 (CH₃), 23.5 (CH₂), 31.5 (CH₂), 38.0 (CH₃), 51.9 (CH), 58.9 (CH₂), 70.0 (CH), 126.9 (CH), 128.2 (CH), 128.7 (CH), 139.4 (C), 169.7 (C=O); IR (neat): ν 3307, 1636 cm⁻¹; MS (EI⁺) *m/z* (%): 246.2 (5) [M]⁺, 187.2 (70), 91.0 (100); elemental analysis (%) calcd for C₁₅H₂₂N₂O: C, 73.13; H, 9.00; N, 11.37. Found: C, 73.26; H, 8.78; N, 11.25.

Acknowledgment. This article is dedicated to Professor Víctor Riera on the occasion of his retirement. We thank Novo Nordisk Co. for the generous gift of the CALB. This work was supported by the Ministry of Education and Science (Spain; Project MEC-04-CTQ-04185).

Supporting Information Available: Additional experimental procedures and chiral HPLC analyses data for the optically active compounds, copies of ¹H and ¹³C NMR spectra, and copies of chiral HPLC chromatograms. This material is available free of charge via the Internet at <http://pubs.acs.org>.

JO062205H

(26) (a) Boyd, E.; Coumbarides, G. S.; Eames, J.; Jones, R. V. H.; Stenson, R. A.; Suggate, M. J. *Tetrahedron Lett.* **2005**, *46*, 3473–3478. (b) Bisai, A.; Bhanu Prasad, B. A.; Singh, V. K. *Tetrahedron Lett.* **2005**, *46*, 7935–7939. (c) Holbach, M.; Zheng, X.; Burd, C.; Jones, C. W.; Weck, M. J. *Org. Chem.* **2006**, *71*, 2903–2906.