

Biocatalytic Approaches toward the Synthesis of Both Enantiomers of *trans*-Cyclopentane-1,2-diamine

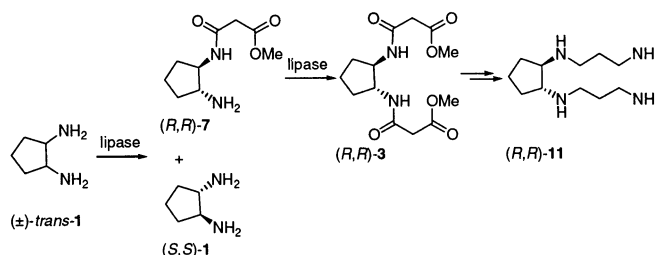
Amparo Luna, Ignacio Alfonso, and Vicente Gotor*

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

vgs@sauron.quimica.uniovi.es

Received July 22, 2002

ABSTRACT



A lipase-catalyzed double monoaminolysis of dimethyl malonate by (\pm)-*trans*-cyclopentane-1,2-diamine allows the sequential resolution of the latter compound, affording an enantiopure bis(amidoester), which is subsequently transformed into an optically active polyamine. As an alternative, both enantiomers of the diamine can be obtained from enantiopure (+)- or (–)-2-aminocyclopentanol, prepared by enzymatic resolution.

Many biologically valuable products contain a 1,2-diamino moiety.¹ In recent years, chiral synthetic diamine derivatives have been employed as medicinal agents, in particular in chemotherapy.² Their use in organic synthesis has also increased considerably, especially in the field of catalytic asymmetric induction.³ The easy availability of both enantiomers of the target compound in very high ee is one of the

limitations for the use of some optically active diamines. Related to this, nonracemic *trans*-cyclopentane-1,2-diamine (**1**) has been synthesized through a multistep sequence, and high ees are obtained only after several recrystallization steps, which lead to a low overall yield.⁴ It is, therefore, of considerable interest to develop an efficient method for preparing optically active *trans*-cyclopentane-1,2-diamine (**1**) that minimizes the number of synthetic steps and maximizes the yield and ee of this important compound. Lipase-catalyzed kinetic resolution of racemates is one of the most frequently used strategies for the preparation of optically active compounds.⁵ Moreover, when the substrate structure allows the coupling of two sequential kinetic resolutions, the second step can improve the enantiomeric purity of the product.⁶ Racemic diamines are very interesting bifunctional substrates that can undergo a sequential biocatalytic resolu-

(1) (a) Otsuka, M.; Masuda, T.; Haupt, A.; Ohno, M.; Shiraki, T.; Sugiura, Y.; Maeda, K. *J. Am. Chem. Soc.* **1990**, *112*, 838. (b) Stubbe, J.; Kozarich, J. W. *Chem. Rev.* **1987**, *87*, 1107. (c) Kulanthaivel, P.; Hallock, Y. F.; Boros, C.; Hamilton, S. M.; Janzen, W. P.; Ballas, L. M.; Loomis, C. R.; Jiang, J. B.; Katz, B.; Steiner, J. R.; Clardy, J. *J. Am. Chem. Soc.* **1993**, *115*, 6452. (d) Rosenberg, B.; VanCamp, L.; Trosko, J. E.; Masour, V. H. *Nature* **1969**, *222*, 385.

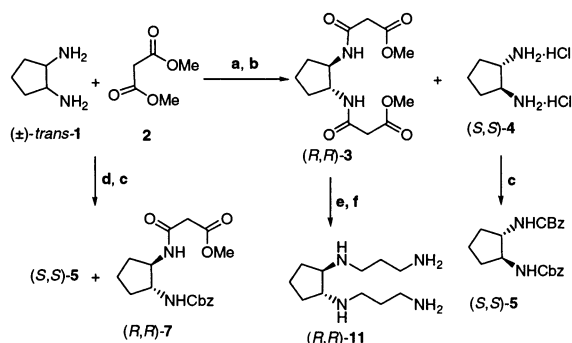
(2) (a) Gust, R.; Burgemeister, A.; Mannschreck, A.; Schönenberger, H. *J. Med. Chem.* **1990**, *33*, 2535. (b) Kelland, L. R.; Abel, G.; McKeage, M. J.; Jones, M.; Goddard, P. M.; Valenti, M.; Murrer, B. A.; Harrap, K. R. *Cancer Res.* **1993**, *53*, 2581. (c) Khokhar, A. R.; Al-Baker, S.; Shamsuddin, S.; Siddik, Z. H. *Bioorg. Med. Chem. Lett.* **1997**, *40*, 112. (d) Reedijk, J. *Chem. Commun.* **1996**, 801.

(3) (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580. (b) Blazis, V. J.; Koeller, K. J.; Spilling, C. D. *Tetrahedron: Asymmetry* **1994**, *5*, 499. (c) Conlon, D. A.; Yasuda, N. *Adv. Synth. Catal.* **2001**, *1*, 343. (d) Togni, A.; Venanzi, L. M. *Angew. Chem., Int. Ed.* **1994**, *33*, 497.

(4) Toftlund, H.; Pedersen, E. *Acta Chem. Scand.* **1972**, *26*, 4019.

(5) (a) Faber, K. *Biotransformations in Organic Chemistry*, 4th ed.; Springer: Heidelberg, 2000. (b) Theil, F. *Chem. Rev.* **1995**, *95*, 2203.

(6) Guo, Z.-W.; Wu, S.-H.; Chen, C.-S.; Girdaukas, G.; Sih, C. J. *J. Am. Chem. Soc.* **1990**, *112*, 4942.

Scheme 1^a

^a Reaction conditions: (a) 1:1 molar ratio of (±)-*trans*-1/2, CALB, 1,4-dioxane, 30 °C; (b) 2 N HCl; (c) CbzCl, Na₂CO₃, H₂O; (d) 2:1 molar ratio of (±)-*trans*-1:2, CALB, 1,4-dioxane, 30 °C, 1 h; (e) NH₃, MeOH; (f) BH₃·THF, 6 N HCl, 4 N NaOH.

tion. This strategy has been successfully used for the preparation of optically active *trans*-cyclohexane-1,2-diamine.⁷ With a suitable acyl donor, the appropriate enzyme can catalyze the enantioselective monoacylation of the diamine and subsequent enantioselective acylation of the resulting optically enriched monoamide, thus affording an enantiomerically pure diamide. The potential importance of *trans*-cyclopentane-1,2-diamine (**1**) led us to explore the resolution of this diamine⁸ by means of two sequential aminolysis reactions, using dimethyl malonate (**2**) as the acyl donor and *Candida antarctica* lipase (CALB) as the catalyst. The selection of the acyl donor is associated to the synthetic utility of the resulting products for the preparation of optically active polyamines and macrocycles.⁹ It is remarkable that, although (±)-*trans*-cyclohexane-1,2-diamine is commercially available, the (±)-*trans*-cyclopentane-1,2-diamine is not. Therefore, it has been scarcely studied, and it would be of great interest to find an efficient procedure for obtaining enantiopure *trans*-cyclopentane-1,2-diamine.

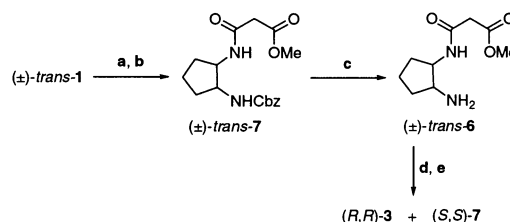
Commercially available (±)-*trans*-cyclopentane-1,2-diol was transformed into (±)-*trans*-cyclopentane-1,2-diamine (**1**) using a procedure described in the literature.¹⁰

A one-pot double-acylation reaction (Scheme 1) using an equimolecular mixture of (±)-*trans*-1 and **2** with CALB¹¹ in 1,4-dioxane (9 h) afforded enantiopure bis(amidoester) (*R,R*)-**3**. The unreacted (*S,S*)-**1** was isolated as its diammonium salt, (*S,S*)-**4**, formed by treatment of the reaction mixture with 2 N HCl. To determine the optical purity of (*S,S*)-**1**, its salt (*S,S*)-**4** was converted into the *N,N'*-bis-

(benzyloxycarbonyl) derivative (*S,S*)-**5**, whose chiral HPLC analysis showed an 87% ee. In this case, we obtained a very high apparent enantioselectivity ($E > 200$)¹² calculated from both ee values.

The formation of (*R,R*)-**3** involves two biocatalytic steps [diamine to mono(amidoester) to bis(amidoester)] and, therefore, the above-mentioned enantiopurity of (*R,R*)-**3** has to be clearly determined by the enantioselectivities of both steps. To study the enantioselectivity shown by the CALB in each step, we have calculated E_1 and E_2 values. The lability of **1** toward oxidation, as well as the final persistence of trace amounts of mono(amidoester) (detected in the derivatization process of **4**), made the accurate determination of the reaction conversion c difficult. For these reasons, E_1 was determined when a 2:1 molar ratio of diamine:acyl donor was used and the reaction stopped at the mono(amidoester) stage (Scheme 1). In this process, substrate **1** and product **6** were isolated as their benzyl carbamates (*S,S*)-**5** and (*R,R*)-**7**, with 83 and 66% ees, respectively. The enantioselectivity ($E_1 = 21$) and conversion ($c = 44\%$) were determined from these values.¹² This enantioselectivity value is not high enough to get the product in enantiopure form, so the second aminolysis step must also be enantioselective.

Enantioselectivity of the second step (E_2) was also determined from the single-step aminolysis reaction between racemic mono(amidoester) **6** and dimethyl malonate **2** (Scheme 2).

Scheme 2^a

^a Reaction conditions: (a) 1:0.5 molar ratio of (±)-*trans*-1/CbzCl, Na₂CO₃, CH₂Cl₂; (b) ClC(O)CH₂CO₂Me, Et₃N, CH₂Cl₂; (c) H₂, Pd-black, MeOH; (d) 2:1 molar ratio of (±)-*trans*-6/1, CALB, 1,4-dioxane, 30 °C, 3 h; (e) CbzCl, Na₂CO₃, H₂O.

Compound **6** was prepared from (±)-*trans*-1 by mono-protection with benzyloxycarbonyl group, treatment with malonyl chloride monomethyl ester, and finally removal of the Cbz group (50% yield). Enzymatic aminolysis of (±)-*trans*-**6** and **2** (molar ratio = 2:1) yielded a mixture of (*S,S*)-**6**, isolated as its carbamate (*S,S*)-**7**, and the bis(amidoester) (*R,R*)-**3** both in enantiomerically pure forms (ee > 99%). Conversion ($c = 49\%$) and enantioselectivity ($E_2 > 200$) were also determined from these values.¹²

In this biocatalytic process, CALB clearly shows the same stereochemical preference toward the (*R,R*)-enantiomer of the substrate in both steps. This fact and the strategy of the

(7) Alfonso, I.; Astorga, C.; Rebollo, F.; Gotor, V. *Chem. Commun.* **1996**, 2471.

(8) Domínguez, B.; Hodnett, N. S.; Lloyd-Jones, G. C. *Angew. Chem., Int. Ed.* **2001**, *40*, 4289.

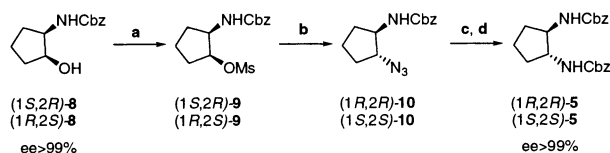
(9) (a) Alfonso, I.; Rebollo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 367. (b) Alfonso, I.; Rebollo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 2515. (c) Alfonso, I.; Dietrich, B.; Rebollo, F.; Gotor, V.; Lehn, J. M. *Helv. Chim. Acta* **2001**, *280*. (d) Alfonso, I.; Rebollo, F.; Gotor, V. *Chem. Eur. J.* **2000**, *6*, 3331.

(10) (a) Or, Y. S.; Phan, L. T.; Chan, D. T.; Spina, K. P.; Halla, R.; Elliot, R. L. WO Patent 9 717 356, 1997; *Chem. Abstr.* **1997**, *127*, 34467.

(b) Onger, S.; Aitken, D. J.; Husson, H.-P. *Synth. Commun.* **2000**, *30*, 2593.

(11) Catalyst can be reused several times.

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

Scheme 3^a

^a Reaction conditions: (a) MsCl, Et₃N, CH₂Cl₂, 0 °C; (b) NaN₃, DMF, 60 °C; (c) H₂, Pd–C, MeOH; (d) CbzCl, Na₂CO₃, H₂O.

sequential resolution are the keys to the successful preparation of enantiopure (*R,R*)-**3**. As can be deduced from the above results, enantiopure products cannot be obtained with the first aminolysis reaction (*E*₁), but the second biocatalytic process (*E*₂) is sufficiently enantioselective to produce bis-(amidoester) **3** and mono(amidoester) **7** both in enantiomerically pure forms. This conclusion is extracted after measurement of the two enantioselectivity values from the sequential aminolysis reactions.

On the other hand, we have previously reported a practical and efficient procedure for the resolution of (±)-*cis*-*N*-Cbz-2-aminocyclopentanol.¹³ In this case, the product and the substrate were recovered in 99% ee. We carried out an alternative synthesis using these enantiomers as starting material (Scheme 3).¹⁴ First, mesylation of hydroxycarbamate **8** led to product **9**, which was then substituted using NaN₃ in DMF for obtaining **10**, which was followed by hydrogenation with Pd/C to give the corresponding diamines (*R,R*)-**1** or (*S,S*)-**1**, both isolated as *N,N'*-bis(benzyloxycarbonyl) derivatives (91% yield).

Finally, the enantiopure (*R,R*)-**3** is easily transformed into the polyamine **11** (Scheme 1). Polyamines are polycationic compounds, which are essential for cell growth and division.¹⁵ These compounds have wide-ranging therapeutic applications in neurological diseases,¹⁶ in development of

new antidiarrheals in AIDS-related cases,¹⁷ and as anticancer agents.¹⁸ Polyamine **11** is a C6–C10-fused *N,N'*-bis(3-aminopropyl)cadaverine. This spermine analogue has been found to be formed in *Saccharomyces cerevisiae*¹⁹ and mycorrhizal and phytopathogenic fungi.²⁰ Moreover, the introduction of a chiral rigid cyclic moiety in the structure could confer novel and interesting properties to the compound.²¹ Treatment of (*R,R*)-**3** with ammonia in methanol and subsequent reduction of the resulting tetraamide with BH₃·THF afforded polyamine (*R,R*)-**11** with 80% yield, calculated from the starting bis(amidoester) (*R,R*)-**3**. Synthetic and biological applications of these compounds are currently under investigation.

Acknowledgment. Financial support of this work by the Spanish Ministerio de Ciencia y Tecnología (Project PPQ-2001-2683) and by Principado de Asturias (Project GE-EXP01-03) is gratefully acknowledged. A.L. thanks CON-ACYT (Mexico) for a predoctoral fellowship.

Supporting Information Available: Experimental procedures, ¹H and ¹³C NMR spectra, and HPLC chromatograms of all products. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL026574L

(13) Luna, A.; Astorga, C.; Fülöp, F.; Gotor, V. *Tetrahedron: Asymmetry* **1998**, *9*, 4483.

(14) Acylated product was hydrolyzed using CALB in ⁱPr₂O/EtOH

(15) (a) Campbell, D. R.; Morris, D. R.; Bartos, D.; Daves, G. D., Jr.; Bartos, F. *Advances in Polyamine Research*; Raven Press: New York, 1978. (b) Goldenburg, S. H.; Algranati, J. D. *The Biology and Chemistry of Polyamines*; JCSU Press: Oxford, 1990. (c) Kuksa, V.; Buchan, R.; Kong Thoo Lin, P. *Synthesis* **2000**, *9*, 1189.

(16) Bergeron, R. J.; Weimar, W. R.; Wu, Q.; Austin, J. K., Jr.; McManis, J. S. *J. Med. Chem.* **1995**, *38*, 425.

(17) Bergeron, R. J.; Yao, G. W.; Yao, H.; Weimar, W. R.; Sninsky, R. B.; Feng, Y.; Wu, Q.; Gao, F. *J. Med. Chem.* **1996**, *39*, 2461.

(18) (a) Casero, R. A.; Woster, P. M. *J. Med. Chem.* **2001**, *44*, 1. (b) Zou, Y.; Wu, Z.; Sirisoma, N.; Woster, P. M.; Casero, R. A., Jr.; Weiss, L. M.; Rattendi, D.; Lane, S.; Bacchi, C. J. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1613.

(19) Walters, D. R.; Cowley, T. *FEMS Microbiology Lett.* **1996**, *145* (2), 255.

(20) Zarb, J.; Walters, D. R. *Lett. Appl. Microbiol.* **1994**, *19* (4), 277.

(21) (a) Nagamani, D.; Ganesh, K. *Org. Lett.* **2001**, *3*, 103. (b) Valasinas, A.; Sarkar, A.; Reddy, V. K.; Marton, L. J.; Basu, H. S.; Frydman, B. *J. Med. Chem.* **2001**, *44*, 390. (c) Havis, N. D.; Walters, D. R. *J. Agric. Food Chem.* **1997**, *45*, 2341.