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Highly efficient chemoenzymatic syntheses of *trans*-2-aminocyclopentanol derivatives

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ABSTRACT

A novel and efficient chemoenzymatic protocol for the preparation of both enantiomers of *trans*-2-aminocyclopentanol is described. The key steps of this strategy are the synthesis and subsequent *Burkholderia cepacia* lipase-catalyzed resolution of the racemic precursor *trans*-2-(diallylamino)cyclopentanol. In addition, a variety of diversely substituted derivatives are prepared from the enantiopure compounds isolated in the biotransformation by means of simple protection–deprotection reactions.

1. Introduction

The importance of cyclic β-amino alcohols as synthetic intermediates together with their biological significance is widespread. These compounds have also found extensive application as chiral ligands and auxiliaries in asymmetric synthesis [1]. In particular, *trans*-2-aminocyclopentanol is a valuable precursor of pharmacologically active compounds such as phosphodiesterase inhibitors [2] and alkaloids [3].

Methods to obtain optically active *trans*-2-aminocyclopentanol include the ring opening of cyclopentene oxide by a chiral amine [4], the asymmetric ring opening (ARO) of the meso epoxide by an appropriate nucleophile mediated by a chiral catalyst [5], and resolution processes. In this sense, *trans*-2-aminocyclopentanol was obtained by the classical resolution of its *N*-benzyl derivative with di-*O*-benzoyltartaric [6] or mandelic acids [7]. Concerning to the enzymatic resolution processes, our attempts to achieve the direct enzymatic acylation of (±)-*trans*-2-aminocyclopentanol failed some years ago, leading to disappointing enantioselectivities [8]. Better results were obtained when several derivatives such as benzyl *N*-(2-hydroxycyclopentyl)carbamate [8] or some precursors as *trans*-2-azido-, *trans*-2-nitro- and *trans*-2-cyanocyclopentanol were tested, especially with (±)-*trans*-2-azidocyclopentanol or its butyric ester derivative [9]. Bearing in mind the importance of this compound and the above commented reports, the search for more straightforward and safer alternatives avoiding the use of potentially dangerous reagents is fully warranted, specially for a hypothetical large-scale process. Herein, we wish to report an attractive and practical alternative for the synthesis of enantiopure *trans*-2-aminocyclopentanol based on the preparation and further enzymatic resolution of its racemic precursor *trans*-2-(diallylamino)cyclopentanol (*rac*-**1**). In addition, the versatility and easy cleavage of the allyl groups [10] also enable the preparation of *N*-, *O*-orthogonally protected derivatives with notable interest for the synthesis of chiral ligands and pharmaceuticals.

2. Materials and methods

2.1. General remarks

Immobilized lipase from *Pseudomonas cepacia* (PSL-C, 783 U/g), recently classified as *Burkholderia cepacia* lipase was purchased from Amano Pharmaceutical Co. For the enzymatic reactions, commercially available vinyl acetate and anhydrous *tert*-butyl methyl ether were used. Thin-layer chromatography was performed on precoated TLC plates of Merck silica gel $60F_{254}$, using potassium permanganate as developing reagent. For column chromatography, Merck silica gel 60 (particle size, 40–63 μm) was used. Melting points were taken on samples in open capillary tubes and are uncorrected. Optical rotations were measured using a PerkinElmer 343 polarimeter. Mass spectra were recorded on a Hewlett-Packard 1100 HPLC/MS (electrospray) instrument. ^{1}H NMR and proton-decoupled ^{13}C NMR spectra ($CDCl_3$ solutions) were obtained using AC-300 or DPX-300 (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz)

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spectrometers using the δ scale (ppm) for chemical shifts; calibration was made on the $CDCl_3$ (^{13}C; 76.95 ppm) or the residual $CHCl_3$ (^1H; 7.26 ppm) signals. GC analyses were performed on a Hewlett-Packard 5890 instrument with a Chirasil-DEX CB (Chrompack) chiral phase capillary column (25 m × 0.25 mm i.d. × 0.25 μm).

2.2. Synthesis of racemic trans-2-(diallylamino)cyclopentanol (rac-**1**)

Diallylamine (60 mmol) was added to a sealed tube with a solution of cyclopentene oxide (20 mmol) in deoxygenated ethanol (40 mL). After 24 h at 100 °C, solvent and excess of diallylamine were evaporated under reduced pressure and the racemic amino alcohol *rac*-**1** was isolated pure in quantitative yield. Orange oil; ^1H NMR: δ = 1.23–2.02 (m, 6H), 2.35 (bs, 1H), 2.90 (dt, J = 7.4 and 9.6 Hz, 1H), 3.05 (dd, J = 7.1 and 14.0 Hz, 2H), 3.24 (ddt, J = 1.4, 5.6 and 14.0 Hz, 2H), 4.0 (q, J = 6.9 Hz, 1H), 5.18 (m, 4H), 5.85 (dddd, J = 5.8, 7.2, 10.2 and 17.3 Hz, 2H); ^{13}C NMR: δ = 20.55 (CH_2), 24.51 (CH_2), 32.47 (CH_2), 53.68 (CH_2), 69.98 (CH), 74.33 (CH), 117.09 (CH_2), 135.96 (CH); MS (ESI), m/z (%) = 182 [(M+H)$^+$, 100]; anal. calcd. for $C_{11}H_{19}NO$ (181.3): C 72.88, H 10.56, N 7.73; found: C 72.77, H 10.68, N 7.61.

2.3. Enzymatic acetylation of racemic trans-2-(diallylamino)cyclopentanol (rac-**1**)

To a mixture of amino alcohol rac-**1** (8.0 mmol), PSL-C (800 mg) and powdered 4 Å molecular sieves (200 mg) under nitrogen atmosphere, anhydrous *tert*-butyl methyl ether (TBME, 48 mL) and vinyl acetate (24.0 mmol) were added. The resulting mixture was circularly shaken at 28 °C and 200 rpm for 3 h. The enzyme was filtered off through a 2 cm pad of celite, washed with TBME and the solvent was evaporated under reduced pressure. The crude reaction mixture was purified by flash column chromatography (hexane:ethyl acetate mixtures) to obtain successively the corresponding enantioenriched amino ester (1*R*,2*R*)-**3** and amino alcohol (1*S*,2*S*)-**1**.

2.3.1. (1R,2R)-2-(Diallylamino)cyclopentyl acetate (**3**)

Yield: 47%; orange oil; $[\alpha]_D^{20} = -24.2$ (c 0.8, AcOEt); ee > 99%; ^1H NMR: δ = 1.41–1.70 (m, 4H), 1.80–1.95 (m + s, 5H), 3.13 (d, J = 6.4 Hz, 4H), 3.26 (m, 1H), 5.01–5.20 (m, 5H), 5.85 (ddt, J = 6.4, 10.2 and 17.3 Hz, 2H); ^{13}C NMR: δ = 21.32 (CH_3), 22.04 (CH_2), 27.39 (CH_2), 31.88 (CH_2), 53.61 (CH_2), 66.17 (CH), 76.79 (CH), 116.43 (CH_2), 135.20 (CH), 170.59 (C); MS (ESI), m/z (%) = 224 [(M+H)$^+$, 100]; anal. calcd. for $C_{13}H_{21}NO_2$ (223.3): C 69.92, H 9.48, N 6.27; found: C 70.07, H 9.71, N 6.40.

2.3.2. (1S,2S)-2-(Diallylamino)cyclopentanol (**1**)

Yield: 45%; $[\alpha]_D^{20} = +41.3$ (c 0.8, AcOEt); ee > 99%.

2.4. General procedure for deallylation of N,N-diallylamino derivatives

To a solution of $Pd(PPh_3)_4$ (0.04 mmol) in anhydrous CH_2Cl_2 (16 mL) was added, under a nitrogen atmosphere, a solution of the corresponding *N*,*N*-diallylamino derivative (2.0 mmol) in anhydrous CH_2Cl_2 (16 mL) and 1,3-dimethylbarbituric acid (NDMBA, 936 mg, 6.0 mmol). The reaction mixture was stirred and heated at 35 °C for 7 h. After cooling, the solution was extracted twice with saturated aqueous Na_2CO_3 to remove the unreacted NDMBA and its mono-*C*-allyl derivative. The organic phase was concentrated in vacuo and the crude purified by flash chromatography.

2.5. (1S,2S)-2-Benzyloxycyclopentanamine (**4**)

To a solution of (1*S*,2*S*)-**1** (364 mg, 2.0 mmol) and benzyl chloride (280 mg, 2.2 mmol) in toluene (20 mL) was added finely powdered KOH (480 mg). The resulting mixture was vigorously stirred at room temperature for 12 h. After this time, the mixture was extracted with water to remove the excess of KOH, the organic phase dried over Na_2SO_4 and concentrated in vacuo. The resulting crude *N*,*N*-diallyl-2-benzyloxycyclopentanamine was directly submitted to deallylation (*vide supra*). Yield: 80% (two steps); b.p.: 80–82 °C (0.5 Torr); $[\alpha]_D^{20} = +69.5$ (c 0.8, $CHCl_3$); ee > 99%; ^1H NMR: δ = 1.05–1.20 (m, 3H), 1.45–1.65 (m, 3H), 1.75–1.95 (m, 2H), 3.13 (q, J = 6.8 Hz, 1H), 3.40 (q, J = 6.8 Hz, 1H), AB system (δ_A 4.35, δ_B 4.44, J_{AB} = 11.9 Hz, *CH*$_2$–Ph), 7.10–7.25 (m, 5H, Ph); ^{13}C NMR: δ = 20.29 (CH_2), 29.30 (CH_2), 32.09 (CH_2), 57.55 (CH), 71.03 (CH_2), 87.63 (CH), 127.13 (CH), 127.25 (CH), 127.98 (CH), 138.46 (C); MS (ESI), m/z (%) = 192 [(M+H)$^+$, 100]; anal. calcd. for $C_{12}H_{17}NO$ (191.3): C 75.35, H 8.96, N 7.32; found: C 75.22, H 8.77, N 7.41.

2.6. (1S,2S)-2-Aminocyclopentanol hydrochloride (**5**)

A solution of (1*S*,2*S*)-**4** (1.0 mmol) in 3N aqueous HCl (25 mL) was refluxed during 7 h. After this time, the solution was cooled, washed with diethyl ether (2× 15 mL) and evaporated to yield clean the hydrochloride salt. Yield >95%. Spectroscopical data are in good agreement with those previously reported [4]. $[\alpha]_D^{20} = +29.3$ (c 2.0, EtOH); ee > 99%. Ref. [4]: $[\alpha]_D^{26} = +29.7$ (c 1.95, EtOH) for ee > 99%.

2.7. tert-Butyl (1S,2S)-N-[2-(benzyloxy)cyclopentyl]carbamate (**6**)

A solution of (1*S*,2*S*)-**4** (1.0 mmol) in dichloromethane (15 mL) was cooled to 0 °C and treated with di-*tert*-butyl dicarbonate (1.1 mmol). The mixture was stirred for 7 h and then evaporated to dryness. The resulting crude was recrystallized from hexane to yield pure (1*S*,2*S*)-**6**. Yield >95%; white solid; m.p.: 77.5–79 °C; $[\alpha]_D^{20} = -2.3$ (c 1.0, $CHCl_3$); ee > 99%; ^1H NMR: δ = 1.30–1.50 (m + s, 10H. Singlet corresponds to *tert*-butyl), 1.55–1.85 (m, 4H), 1.95–2.05 (m, 1H), 3.79 (m, 1H), 4.00 (m, 1H), 4.55–4.70 (m, 3H), 7.20–7.40 (m, 5H, Ph); ^{13}C NMR: δ = 21.58 (CH_2), 28.46 (CH_3), 30.35 (CH_2), 30.77 (CH_2), 56.70 (CH), 70.95 (CH_2), 79.21 (C), 84.96 (CH), 127.42 (CH), 127.66 (CH), 128.31 (CH), 138.74 (C), 155.34 (C); MS (ESI), m/z (%) = 292 [(M+H)$^+$, 5], 192 (10), 192 (100); anal. calcd. for $C_{17}H_{25}NO_3$ (291.4): C 70.07, H 8.65, N 4.81; found: C 70.25, H 8.48, N 4.90.

2.8. tert-Butyl (1S,2S)-N-[2-(hydroxy)cyclopentyl]carbamate (**7**)

A suspension of (1*S*,2*S*)-**6** (0.80 mmol) and Pd-C (10%, 160 mg) in deoxygenated methanol (20 mL) was stirred for 5 h under a hydrogen atmosphere. The reaction mixture was filtered through Celite®, and the filtrate evaporated to dryness. The resulting crude was recrystallized from hexane to yield pure (1*S*,2*S*)-**7**. Yield >95%; white solid; m.p.: 82–83 °C; $[\alpha]_D^{20} = -22.5$ (c 0.8, $CHCl_3$); ee > 99%; ^1H NMR: δ = 1.25–1.50 (m + s, 10H. Singlet corresponds to *tert*-butyl), 1.55–1.80 (m, 3H), 1.90–2.15 (m, 2H), 3.63 (tt, J = 5.4 and 8.2 Hz, 1H), 3.97 (q, J = 5.9 Hz, 1H), 4.11 (bs, 1H), 4.77 (bs, 1H); ^{13}C NMR: δ = 20.93 (CH_2), 28.35 (CH_3), 30.38 (CH_2), 32.34 (CH_2), 60.43 (CH), 79.59 (C), 79.94 (CH), 157.21 (C); MS (ESI), m/z (%) = 202 [(M+H)$^+$, 100]; anal. calcd. for $C_{10}H_{19}NO_3$ (201.3): C 59.68, H 9.52, N 6.96; found: C 59.81, H 9.40, N 6.83.

2.9. Determination of enantiomeric excesses

Enantiomeric excess of amino ester (1*R*,2*R*)-**3** was determined by chiral GC. To determine the ee of the amino alcohol (1*S*,2*S*)-**1**, it was previously transformed into its corresponding acetate (1*S*,2*S*)-**3** (1.2 equiv. of acetyl chloride in anhydrous dichloromethane, r.t.). GC conditions: Chirasil-DEX CB column (25 m × 0.25 mm) and N_2 as carrier gas were used. Gradient temperature program: 70 °C (3 min)

to 200 °C (5 min) at 3 °C min^{-1} gradient. The injector and detector temperatures were maintained at 225 °C and 250 °C, respectively; t_R = 24.33 (*S*,*S*) and 24.66 (*R*,*R*) min.

Enantiomeric excesses of amino alcohols (1*R*,2*R*)-**4** and (1*S*,2*S*)-**4** were determined by chiral HPLC after transformation into their *N*-Boc derivatives (1*R*,2*R*)-**6** and (1*S*,2*S*)-**6** (see Section 2.7). HPLC conditions: Chiralpak AS column (25 cm × 4.6 mm i.d.), hexane/isopropyl alcohol (H/*i*PA) 95:5; 0.8 mL/min; *T* = 20 °C; t_R = 6.6 (*R*,*R*) and 7.4 (*S*,*S*) min; R_s = 4.7.

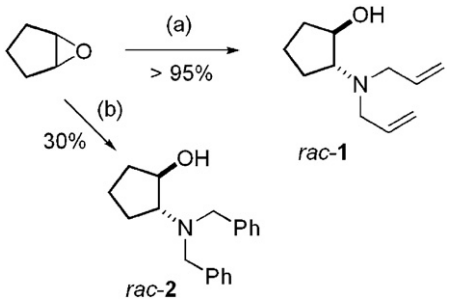
Enantiomeric excesses of (1*R*,2*R*)-**7** and (1*S*,2*S*)-**7** were determined by chiral HPLC after transformation into (1*R*,2*R*)-**5** and (1*S*,2*S*)-**5**, respectively, by simple acid hydrolysis (reaction conditions identical to those reported in Section 2.6) and further derivatization with Sanger's reagent (see experimental section of Ref. [5]). HPLC conditions of the 2,4-dinitroaniline derivative: Chiralcel OD column (25 cm × 4.6 mm i.d.), hexane/isopropyl alcohol (H/*i*PA) 80:20; 0.8 mL/min; *T* = 35 °C; t_R = 13.6 (*S*,*S*) and 14.8 (*R*,*R*) min; R_s = 3.3.

3. Results and discussion

3.1. Selection of the precursor of trans-2-aminocyclopentanol

In recent reports we described a chemoenzymatic protocol for the synthesis of optically active *trans*-2-(*N*,*N*-dialkylamino) cycloalkanols starting from the corresponding meso epoxide [11]. Although the enantioselectivities were excellent in all cases, our selection of substrates was restricted to a narrow spectrum of amino alcohols suitable for further derivatizations. In fact, in the case of 2-aminocyclopentanols only *trans*-2-(*N*-allyl-*N*-benzylamino)cyclopentanol allowed us to obtain the free amino alcohol by means of sequential deprotection steps. Although this route could be an interesting alternative to obtain enantiopure 2-aminocyclopentanol, the synthesis of the racemic precursor suffered from several drawbacks: first, the ring opening reaction of cyclopentene oxide with the non-commercially available *N*-allylbenzylamine proceeded very slowly and with poor yield (<30%) [12], even though employing some catalysts such as lithium perchlorate or lithium bromide; second, an alternative high-yield synthesis involved two steps (ring opening reaction of cyclopente oxide with allylamine and subsequent benzylation of the resulting amino alcohol) and a flash chromatography purification of the final product. On the other hand, the unmasking of the amino group after the enzymatic pathway involved also two steps in the following order: deallylation and catalytic hydrogenation. Taking in mind this facts, we envisaged a more straightforward and robust chemoenzymatic protocol in which the above commented drawbacks could be circumvented just by changing *N*-allylbenzylamine by diallylamine or dibenzylamine as the source of the amino group. Thus, both of these amines are commercially available, inexpensive and bearer of two identical substituents which could be simultaneously removed in one single step.

The synthesis of racemic *trans*-2-(diallylamino)cyclopentanol (*rac*-**1**) was efficiently accomplished by means of the stereospecific ring opening reaction of cyclopentene oxide with diallylamine (Scheme 1). After elimination of the volatile diallylamine in the vacuum pump, the β-amino alcohol *rac*-**1** was quantitatively isolated in state of purity and employed in the subsequent biotransformation without further purification. By contrast, the process gave unsatisfactory results starting from dibenzylamine. Similarly to the case of the *N*-allylbenzylamine, the ring opening reaction proceeded very slowly and the corresponding *trans*-2-(dibenzylamino)cyclopentanol (*rac*-**2**) was obtained in low yield after purification by flash chromatography. Consequently, diallylamine was selected as the source of the amino group and dibenzylamine finally ruled out.



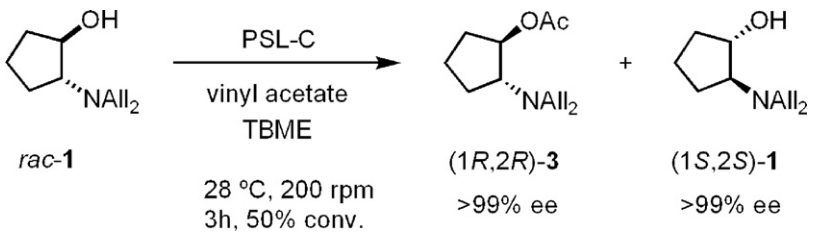
Scheme 1. Synthesis of racemic *trans*-2-dialkylaminocyclopentanols. Reagents: (a) $(Allyl)_2NH$, EtOH, reflux, 24 h and (b) $(Bn)_2NH$, EtOH, reflux, 5 days.

3.2. Enzymatic resolution of racemic trans-2-(diallylamino)cyclopentanol, rac-1

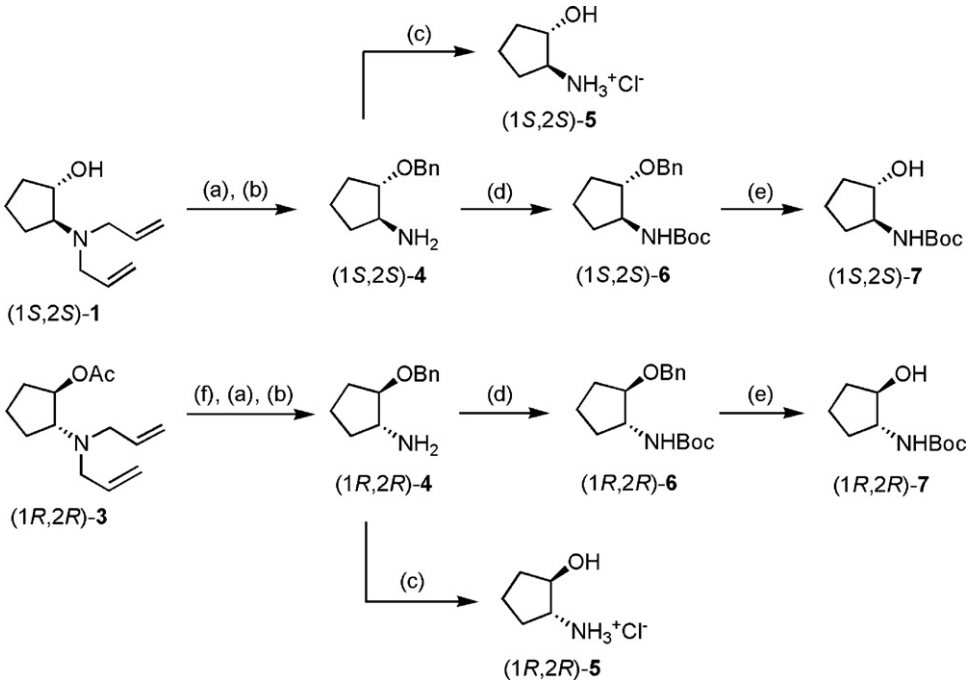
Based on our experience with other 2-aminocycloalkanols [11], we initially planned the resolution of the amino alcohol *rac*-**1** by transesterification reaction catalyzed by *Burkholderia cepacia* lipase (PSL-C) using vinyl acetate as the acyl donor and *tert*-butyl methyl ether (TBME) as the solvent. The acyl donor was employed in a three-fold molar excess with respect to the substrate and 4 Å molecular sieves was added to ensure a low water activity in the reaction medium [13]. As can be seen in Scheme 2, the biotransformation was highly efficient; the *O*-acylation of the (*R*,*R*)-enantiomer took place quickly and the optimal degree of conversion (50%) was reached in only 3 h of reaction [14]. Moreover, both substrate and product were isolated, after separation by flash chromatography, in enantiomerically pure form with excellent yields. Configuration (1*S*,2*S*) for the remaining amino alcohol **1** was established after its transformation into *trans*-2-aminocyclopentanol hydrochloride **5** (Scheme 3) and further comparison of the sign of its specific rotation with the reported value for (1*S*,2*S*)-**5** [4]. This means that PSL-C follows Kazlauskas' rule [15], showing stereopreference toward the (1*R*,2*R*)-enantiomer of the racemic amino alcohol. In addition, the process was also successfully carried out at the 100 gram-scale with a drastic decrease of the amount of lipase. In these conditions, and despite a slower rate of reaction, the process happened with the same enantioselectivity which allowed us to obtain both the remaining substrate and product in enantiomerically pure form.

3.3. Synthesis of optically active trans-2-aminocyclopentanol and some of its derivatives

In order to demonstrate the synthetic utility of our methodology, we carried out a sequence of protection–deprotection steps with the optically active (*1R*,2*R*)-**3** and (1*S*,2*S*)-**1**, providing a set of *N*- and *O*-protected derivatives of both enantiomers of *trans*-2-aminocyclopentanol (Scheme 3). First, amino alcohol (1*S*,2*S*)-**1** was quantitatively benzylated with benzyl chloride and potassium hydroxide. After that, the resulting benzylic ether was easily deallylated in the presence of a Pd^0 catalyst and *N*,*N*′-dimethylbarbituric acid (NDMBA) as the allyl group scavenger [16], thus affording the *O*-protected amino alcohol (1*S*,2*S*)-**4** with very high yield. This intermediate gave quantitative access to the hydrochloride salt of *trans*-2-aminocyclopentanol (1*S*,2*S*)-**5** by a simple hydrolysis with refluxing 3N aqueous HCl. In addition, the *N*-Boc derivative (1*S*,2*S*)-**7** was obtained by treatment of (1*S*,2*S*)-**4** with di-*tert*-butyl dicarbonate and further Pd^0 catalysed hydrogenolysis. Similarly, the same set of selective deprotections were carried out with the (1*R*,2*R*) enantiomer, after previous saponification of the amino ester (1*R*,2*R*)-**3** obtained in the enzymatic reaction. It must be pointed out that when the deallylation was directly performed with the amino ester (1*R*,2*R*)-**3** or amino alcohol (1*S*,2*S*)-**1** the yields dramatically



Scheme 2. Enzymatic resolution of racemic *trans*-2-(diallylamino)cyclopentanol.



Scheme 3. Synthesis of optically active *trans*-2-aminocyclopentanol and derivatives. Reagents: (a) BnCl, KOH powder, PhMe; (b) $Pd(PPh_3)_4$, NDMBA, PhMe; (c) 3N aqueous HCl, reflux.; (d) $(Boc)_2O$, CH_2Cl_2; (e) H_2, Pd-C 10%, MeOH; (f) 1N NaOH in MeOH.

dropped due to the high water-solubility of the deallylated products during the basic extraction required in the work-up. Thus, in this synthetic strategy, the benzylation step has a double function: facilitate the removal of the allyl groups and allow the preparation of the orthogonally protected 2-aminocyclopentanol **6**, a versatile intermediate whose synthesis is a challenging task from the hydrochloride salt of the amino alcohol **5**. Moreover, optically active *O*-benzylderivative **4** is precursor of pharmaceuticals for treating of hypertension [17] and Alzheimer's disease [18].

4. Conclusions

We have developed a highly efficient chemoenzymatic synthesis of both enantiomers of *trans*-2-aminocyclopentanol by means of the kinetic resolution and further deprotection of *trans*-2-(diallylamino)cyclopentanol. Respect to our previous report using *trans*-2-(*N*-allyl-*N*-benzylamino)cyclopentanol as the precursor, the process described here is more straightforward and presents significant improvements: first, the synthesis of the racemic amino alcohol is quantitative, free of flash chromatography purification and employs only commercially available materials. Second, the enantioselectivity of the enzymatic resolution is notably higher and both the substrate and product are isolated in enantiomerically pure form. Finally, the deprotection steps towards *trans*-2-aminocyclopentanol have been shortened since both allyl groups can be simultaneously removed in one step.

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[13] In our previous report dealing about enzymatic resolution of β-aminocyclohexanols (see Ref. 11.a) and despite the use of anhydrous solvent and molecular sieves, partial lipase-catalyzed hydrolysis of vinyl acetate was detected with the amino group being partially protonated by the released acetic acid. However, the influence of this side reaction on the enantioselectivity and rate was demonstrated to be no significant.
[14] This result represents a significant improvement respect to our previous strategy using the *N*-benzyloxycarbonyl derivative of *trans*-2-aminocyclopentanol (see Ref. 8) for which a reaction time of five days was necessary to achieve a conversion value of 50%.
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