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# Chemoenzymatic preparation of optically active *trans*- and *cis*-cyclohex-4-ene-1,2-diamine and *trans*-6-aminocyclohex-3-enol derivatives

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## ABSTRACT

Lipase from *Burkholderia cepacia* (PSL-C) effectively catalyzed the kinetic resolution of both racemic *trans*-*N,N*-diallylcyclohex-4-ene-1,2-diamine ( $\pm$ )-**6** and its precursor *trans*-6-(diallylamino)cyclohex-3-enol ( $\pm$ )-**5**. The resulting optically active vicinal diamine and  $\beta$ -amino alcohol were converted into a precursor of oseltamivir and a *cis*-cyclohex-4-ene-1,2-diamine derivative, respectively.

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## 1. Introduction

Oseltamivir phosphate (**1**, Tamiflu), a carbocyclic analogue of sialic acid, is the most widely used antiviral drug for the treatment and prevention of influenzas. This compound acts by blocking the active site of neuraminidase, a glycoprotein expressed by both influenza A and B viruses.<sup>1</sup> Between the variety of synthetic approaches to oseltamivir,<sup>2</sup> those described by Shibasaki and Kanai et al. start from epoxide **4**, which is converted into the optically active diamine derivative **2**<sup>3</sup> or into another non-symmetrical diprotected *trans*-cyclohex-4-ene-1,2-diamine.<sup>4</sup> In both cases, eight steps were necessary to access to the corresponding (1*S*,2*S*)-diamine derivative, the key step being the catalytic asymmetric ring-opening of the *meso*-*N*-3,5-dinitrobenzoylaziridine **3** with TMSN<sub>3</sub> (Fig. 1).

On the other hand, we have developed in the last years an interesting chemoenzymatic method to obtain enantioenriched *trans*-cycloalkane-1,2-diamines starting from the corresponding epoxide.<sup>5</sup> The good results attained, in both optical and chemical yields, encouraged us to apply this methodology to the synthesis of optically active *trans*-cyclohex-4-ene-1,2-diamine derivatives. Thus, we report herein an alternative chemoenzymatic preparation of the diamine precursor of oseltamivir. Moreover, taking into account the wide interest of  $\beta$ -amino alcohols and vicinal diamines in different chemical areas (medicinal, synthetic or supramolecular),<sup>6,7</sup> we also

have carried out the enzymatic resolution of  $\beta$ -amino alcohol **5**, as well as its subsequent conversion into an optically active *cis*-cyclohex-4-ene-1,2-diamine derivative.

## 2. Results and discussion

2.1. Chemoenzymatic preparation of optically active *trans*-cyclohex-4-ene-1,2-diamine derivatives

Epoxide **4** was obtained from 1,4-cyclohexadiene as described by Albeck et al.<sup>8</sup> Ring-opening of **4** with diallylamine yielded racemic *trans*-6-(diallylamino)cyclohex-3-enol ( $\pm$ )-**5**, which was one-pot converted into the *trans*-diamine ( $\pm$ )-**6** by the successive treatment with mesyl chloride and aqueous ammonia. In this process an aziridinium intermediate is formed as a consequence of the S<sub>N</sub>2 intramolecular displacement of the mesylate group by the vicinal tertiary amine. The subsequent attack of ammonia to the

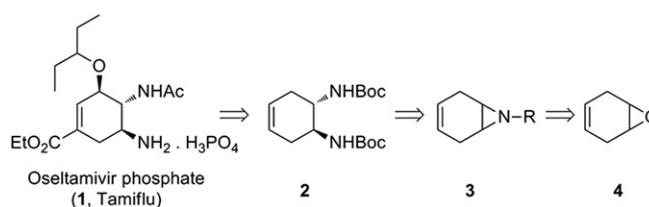
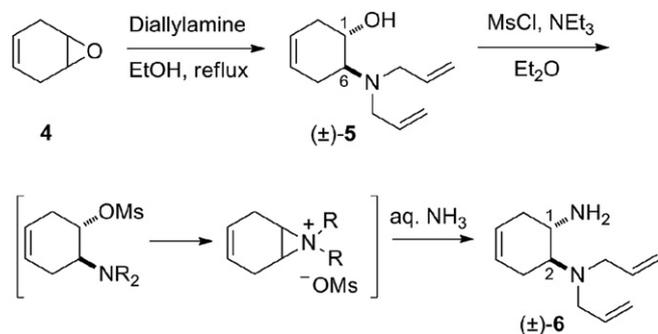


Fig. 1. Diamine derivative **2** as a precursor in the synthesis of oseltamivir (Ref. 3).

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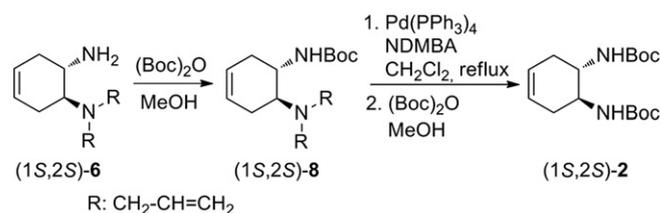
*meso*-aziridinium cation ensures the *trans* configuration of the resulting diamine **6** (Scheme 1).



Scheme 1. Synthesis of racemic *trans*-diamine (±)-6.

Resolution of (±)-**6** was accomplished by enzymatic aminolysis using ethyl acetate as the acyl donor and the solvent. At first, we tried the resolution of (±)-**6** using lipase B from *Candida antarctica* (CAL-B) as catalyst. This lipase had shown both great activity and high enantioselectivity in the resolution of racemic *trans*-*N,N*-diallylcyclohexane-1,2-diamine, a saturated analogue of (±)-**6**.<sup>5c</sup> However, its reaction with (±)-**6** was very slow (Table 1, entry 1), the acetylation of the diamine taking place with a very low enantioselectivity ( $E=3$ ).<sup>9</sup> Other combinations of acylating agent and solvent were assayed, but in no case was the reaction of practical utility (entries 2–4), the best result being obtained with (±)-1-phenylethyl acetate and *tert*-butyl methyl ether (TBME).<sup>10</sup> Fortunately, a remarkable improvement was achieved when CAL-B was replaced by the lipase from *Burkholderia cepacia* (PSL-C).<sup>11</sup> This lipase transformed the substrate with total enantioselectivity, the remaining diamine (1*S*,2*S*)-**6** and the produced acetamide (1*R*,2*R*)-**7** being obtained in enantiopure form after 48 h of reaction (Table 1, entry 5). In this process, both compounds were isolated in very high yields. The absolute configuration (1*S*,2*S*) of the remaining substrate **6** was established after its transformation into (1*S*,2*S*)-**2** (see Scheme 2). This means that the enzyme shows preference for the enantiomer (1*R*,2*R*) of the amine, thus following the Kazlauskas' rule.<sup>12</sup>

Since the allyl groups on the tertiary nitrogen can be easily and selectively removed in the presence of other protecting groups, the method developed here could be applied to the synthesis of a variety of *trans*-cyclohex-4-ene-1,2-diamine derivatives in the two enantiomeric forms. As a proof, (1*S*,2*S*)-**6** was converted into (1*S*,2*S*)-**2**, precursor of the oseltamivir (Scheme 2). Thus, treatment



Scheme 2. Transformation of (1*S*,2*S*)-**6** into (1*S*,2*S*)-**2**.

of (1*S*,2*S*)-**6** with di-*tert*-butyl pyrocarbonate yielded carbamate (1*S*,2*S*)-**8**, which was submitted to reaction with *N,N'*-dimethylbarbituric acid (NDMBA) as the allyl group scavenger and Pd(0) as catalyst.<sup>13</sup> In these conditions, removal of both allyl groups took place. The resulting crude mono-Boc diamine derivative was next treated with di-*tert*-butyl pyrocarbonate to give (1*S*,2*S*)-**2** in very high yield (92%, calculated from **6**). The sign of the optical rotation of the thus obtained di-carbamate **2** matched the described value for (1*S*,2*S*)-**2** (see Experimental section).

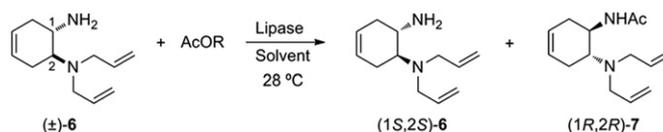
## 2.2. Enzymatic resolution of β-amino alcohol (±)-5. Synthesis of an optically active *cis*-cyclohex-4-ene-1,2-diamine derivative

Enzymatic resolution of racemic *trans*-6-(diallylamino)cyclohex-3-enol (±)-**5** was carried out by transesterification reaction using PSL-C as catalyst,<sup>14</sup> vinyl acetate as the acyl donor and TBME as the solvent (Scheme 3). Similarly to the preceding aminolysis process, the enzyme showed a great efficacy, catalyzing the acetylation of the (1*R*,6*R*) enantiomer of the amino alcohol **5**. Thus, after 48 h of reaction (28 °C), the remaining substrate (1*S*,6*S*)-**5** and the produced acetate (1*R*,6*R*)-**9** were obtained with very high enantiomeric excesses and yields.

The (1*R*,6*R*) enantiopreference of the lipase was demonstrated by the chemical correlation of the remaining substrate (1*S*,6*S*)-**5** with the configurationally known derivative (1*S*,2*S*)-**12** (Scheme 4). At first, allyl groups were removed as indicated in Scheme 2. The resulting free (1*S*,6*S*)-6-aminocyclohex-3-enol [(1*S*,6*S*)-**10**] was converted into the *tert*-butyl carbamate (1*S*,6*S*)-**11**. Catalytic hydrogenation of **11** yielded the *tert*-butyl carbamate **12**. Comparison of the sign of the optical rotation of **12** with that published for (1*S*,2*S*)-**12** ( $[\alpha]_D^{20} +19.19$ ;  $c$  0.50, MeOH)<sup>15</sup> establishes the (1*S*,2*S*) configuration for the remaining substrate of the enzymatic transesterification.

Moreover, in order to show the synthetic utility of the enzymatically prepared compounds, the optically active *cis*-diamine derivative (1*S*,2*R*)-**15** was prepared from the *tert*-butyl carbamate

Table 1  
Lipase-catalyzed resolution of diamine (±)-**6**



Entry	Enzyme	Acyl donor (AcOR)	Solvent	Time (days)	Remaining substrate (1 <i>S</i> ,2 <i>S</i> )- <b>6</b> , ee <sub>S</sub> (%)	Product (1 <i>R</i> ,2 <i>R</i> )- <b>7</b> ee <sub>P</sub> (%)	$c^a$ (%)	$E^b$
1	CAL-B	AcOEt	AcOEt	5	11	41	21	3
2	CAL-B	AcOEt <sup>c</sup>	TBME	7	4	85	4	12
3	CAL-B	AcOCH(Ph)CH <sub>3</sub> <sup>d</sup>	TBME	5	12	93	11	31
4	CAL-B	AcOCH(Ph)CH <sub>3</sub> <sup>d</sup>	THF	7	6	83	7	11
5	PSL-C	AcOEt	AcOEt	2	>99 <sup>e</sup>	>99 <sup>e</sup>	50	>200

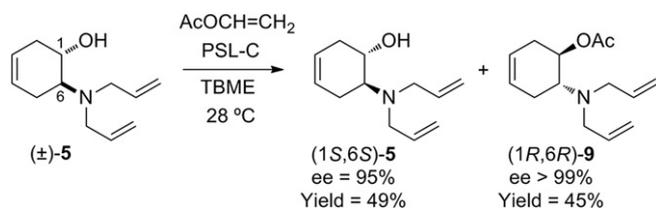
<sup>a</sup> Conversion degree:  $c = ee_S / (ee_S + ee_P)$ .

<sup>b</sup> Determined from ee<sub>S</sub> and ee<sub>P</sub> as in Ref. 9.

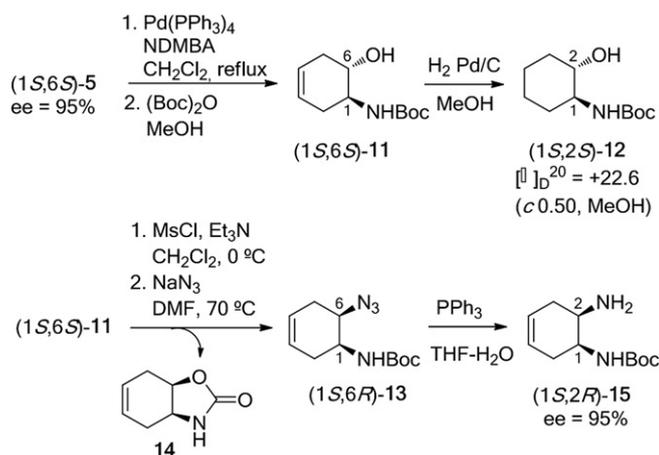
<sup>c</sup> A molar ratio ester/diamine of 6:1 was used.

<sup>d</sup> A molar ratio ester/diamine of 3:1 was used.

<sup>e</sup> Isolated yields after flash chromatography were 42% and 47% for (1*S*,2*S*)-**6** and (1*R*,2*R*)-**7**, respectively.



Scheme 3. Enzymatic resolution of (±)-5.

Scheme 4. Assignment of the absolute configuration of the enzymatically prepared **5** and its transformation into the *cis*-diamine (1S,2R)-**15**.

(1S,6S)-**11**. Thus, treatment of **11** with mesyl chloride gave the mesylate derivative, which was subsequently treated with sodium azide in DMF at 70 °C. In this reaction, beside the *cis*-azido carbamate (1S,6R)-**13**, the oxazolidinone **14** was also isolated as a minor product (see experimental section). This bicyclic compound is the result of an intramolecular S<sub>N</sub>2 displacement of the mesylate group by the carbonyl oxygen of the Boc group.<sup>16</sup> To minimize the formation of **14**, the reaction with sodium azide was also tried at a lower temperature (50 °C) but under these reaction conditions, compound **13** was not formed. Finally, the Staudinger reduction of the azide function of (1S,6R)-**13** yielded the *cis*-amino carbamate (1S,2R)-**15**. In all the synthetic approaches no racemization took place as confirmed by chiral-HPLC analysis of **15**.

### 3. Conclusions

Efficient chemoenzymatic approaches to optically active *trans*-cyclohex-4-ene-1,2-diamine and *trans*-6-aminocyclohex-3-enol derivatives have been developed, in both cases the key step being the kinetic resolution of the corresponding racemic compound catalyzed by PSL-C. Moreover, the preparation of a precursor of oseltamivir as well as an optically active *cis*-cyclohex-4-ene-1,2-diamine derivative have also been carried out.

## 4. Experimental section

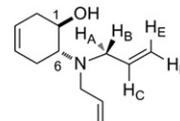
### 4.1. General

Lipase B from *C. antarctica* (Novozyme 435, available immobilized on polyacrylamide, 7300 PLU/g) was gifted by Novo Nordisk Co. Immobilized lipase from *Burkholderia cepacia* (PSL-C, 783 U/g) was purchased from Amano Pharmaceutical Co. For the enzymatic reactions, ethyl acetate of spectrophotometric grade (stored with 4 Å molecular sieves), anhydrous TBME or THF and (±)-1-phenylethyl acetate were used. Melting points were taken on

samples in open capillary tubes and are uncorrected. <sup>1</sup>H NMR and proton-decoupled <sup>13</sup>C NMR spectra (CDCl<sub>3</sub> solutions) were obtained using AC-300 or DPX-300 (<sup>1</sup>H, 300.13 MHz and <sup>13</sup>C, 75.5 MHz) and AV-400 MHz (<sup>1</sup>H, 400.13 MHz and <sup>13</sup>C, 100.63 MHz) spectrometers using the δ scale (parts per million) for chemical shifts; calibration was made on the CDCl<sub>3</sub> (<sup>13</sup>C; 76.95 ppm) or the residual CHCl<sub>3</sub> (<sup>1</sup>H; 7.26 ppm) signals.

### 4.2. Procedures and characterization of products

#### 4.2.1. (±)-*trans*-6-(Diallylamino)cyclohex-3-en-1-ol [(±)-**5**].



Diallylamine (10.3 mL, 84.0 mmol) was added to a solution of epoxide **4** (3.80 g, 40.0 mmol) in deoxygenated ethanol (80 mL). After refluxing under a nitrogen atmosphere for 48 h, the solvent and the excess amine were evaporated in vacuo to give the crude product, which was purified by distillation to reduced pressure to give the title compound (±)-**5** (bp=54 °C, 0.01 Torr; 5.00 g, 66%) as a colourless oil; [found: C, 74.8; H, 10.2; N 7.5. C<sub>12</sub>H<sub>19</sub>NO requires C, 74.57; H, 9.91; N, 7.25%]; R<sub>f</sub> (hexane/AcOEt 10:1) 0.21; ν<sub>max</sub>(CH<sub>2</sub>Cl<sub>2</sub>) 3412, 1630, 1527, 1120 cm<sup>-1</sup>; δ<sub>H</sub> (400 MHz CDCl<sub>3</sub>) 5.80 (dddd, 2H, <sup>3</sup>J<sub>C,A</sub> 4.4 Hz, <sup>3</sup>J<sub>C,B</sub> 8.0 Hz, <sup>3</sup>J<sub>C,D</sub> 10.2 Hz, <sup>3</sup>J<sub>C,E</sub> 14.9 Hz, H<sub>C</sub>), 5.63–5.50 (m, 2H, H-3 and H-4), 5.22–5.08 (m, 4H, H<sub>D</sub> and H<sub>E</sub>), 3.69 (ddd, 1H, <sup>3</sup>J 6.1, 9.5, 10.8 Hz, H-1), 3.33 (ddt, 2H, <sup>4</sup>J<sub>A,D</sub>=<sup>4</sup>J<sub>A,E</sub>=1.7 Hz, <sup>3</sup>J<sub>A,C</sub> 4.4 Hz, <sup>2</sup>J<sub>A,B</sub> 14.2 Hz, H<sub>A</sub>), 2.95 (dd, 2H, <sup>3</sup>J<sub>B,C</sub> 8.0 Hz, <sup>2</sup>J<sub>B,A</sub> 14.2 Hz, H<sub>B</sub>), 2.83 (dt, 1H, <sup>3</sup>J 5.6 (d), 10.8 (t) Hz, H-6), 2.58–2.50 (m, 1H), 2.21–2.12 (m, 1H), 2.09–1.97 (m, 2H); δ<sub>C</sub> (75.5 MHz CDCl<sub>3</sub>) 136.3 (CH=CH<sub>2</sub>), 125.1 (C-3 or C-4), 124.5 (C-4 or C-3), 117.3 (CH=CH<sub>2</sub>), 65.7 (CH), 61.1 (CH), 52.4 (N-CH<sub>2</sub>), 33.8 (CH<sub>2</sub>), 22.7 (CH<sub>2</sub>); m/z (ESI<sup>+</sup>) 194 (100, MH<sup>+</sup>).

4.2.2. (±)-*trans*-N,N-Diallylcyclohex-4-ene-1,2-diamine [(±)-**6**]. To a cooled (0 °C) solution of (±)-**5** (1.50 g, 7.70 mmol) in anhydrous diethyl ether (17 mL), triethylamine (1.7 mL, 12.4 mmol) and mesyl chloride (0.720 mL, 9.30 mmol) were added. The stirred mixture was allowed to warm to room temperature and, after 30 min, triethylamine (2.2 mL, 15.5 mmol) and concentrated aqueous NH<sub>3</sub> (20 mL) were added. The resulting two-phase reaction mixture was vigorously stirred for 12 h. The layers were separated, and the aqueous layer was extracted with diethyl ether (420 mL). All the organic layers were combined and successively washed with aqueous 3 M NaOH (20 mL) and brine (20 mL). After removal of the organic solvents under reduced pressure, the obtained crude product was purified by flash chromatography (a gradient of AcOEt to AcOEt/methanol 4:1 was used as eluent) to give the title compound (±)-**6** (78%) as a colourless oil; [found: C, 74.8; H, 10.7; N 14.3. C<sub>12</sub>H<sub>20</sub>N<sub>2</sub> requires C, 74.95; H, 10.48; N, 14.57%]; R<sub>f</sub> (hexane/AcOEt 1:1) 0.17; ν<sub>max</sub>(CH<sub>2</sub>Cl<sub>2</sub>) 3420, 3347, 2980, 1634 cm<sup>-1</sup>; δ<sub>H</sub> (300 MHz CDCl<sub>3</sub>) 5.81 (dddd, 2H, <sup>3</sup>J 4.5, 7.8, 10.2, 14.7 Hz, CH=CH<sub>2</sub>), 5.67–5.57 (m, 2H, CH=CH), 5.22–5.03 (m, 4H, CH=CH<sub>2</sub>), 3.34–3.20 (m, 2H, N-CHH), 2.99–2.85 (m, 3H, N-CHH+H-1), 2.64 [dt, 1H, <sup>3</sup>J 5.4 (d), 10.8 (t) Hz, H-2], 2.50–2.38 (m, 1H), 2.20–2.08 (m, 1H), 2.19–1.77 [m+s, 4H. Singlet corresponds to NH<sub>2</sub> (1.80 ppm)]; δ<sub>C</sub> (75.5 MHz CDCl<sub>3</sub>) 136.8 (CH=CH<sub>2</sub>), 125.2 (CH=CH), 124.5 (CH=CH), 115.9 (CH=CH<sub>2</sub>), 60.8 (CH), 52.0 (N-CH<sub>2</sub>), 47.6 (CH), 35.0 (CH<sub>2</sub>), 22.3 (CH<sub>2</sub>); m/z (ESI<sup>+</sup>) 193 (100, MH<sup>+</sup>).

4.2.3. Enzymatic kinetic resolution of amino alcohol (±)-**5**. To a mixture of (±)-**5** (1.00 g, 5.10 mmol), PSL-C (520 mg) and 4 Å

molecular sieves (50 mg), under a nitrogen atmosphere, anhydrous *tert*-butyl methyl ether (30 mL) and vinyl acetate (1.40 mL, 15.6 mmol) were added. The mixture was stirred for 48 h at 28 °C and 200 rpm. After this time, the enzyme was filtered through a pad of Celite® and the solid was washed with methanol. The solution was concentrated to reduced pressure and the resulting crude, which was formed by the optically active (1*S*,6*S*)-**5** and the ester (1*R*,6*R*)-**9**, was submitted to flash chromatography (hexane/AcOEt 30:1).

4.2.3.1. (1*S*,6*S*)-6-(Diallylamino)cyclohex-3-en-1-ol [(1*S*,6*S*)-**5**]. Yield 49%;  $[\alpha]_{\text{D}}^{20} +43.5$  (c 1.0, CHCl<sub>3</sub>), ee 95%.

4.2.3.2. (1*R*,6*R*)-6-(Diallylamino)cyclohex-3-enyl acetate [(1*R*,6*R*)-**9**]. Colourless oil; yield 45%; [found: C, 71.7; H, 8.7; N 6.2. C<sub>14</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub> requires C, 71.46; H, 8.99; N, 5.95%]; *R*<sub>f</sub> (hexane/AcOEt 10:1) 0.42;  $[\alpha]_{\text{D}}^{20} -2.6$  (c 1.0, CHCl<sub>3</sub>), ee >99%;  $\nu_{\text{max}}$ (CH<sub>2</sub>Cl<sub>2</sub>) 1728, 1634, 1503, 1210 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz CDCl<sub>3</sub>) 5.72 (dddd, 2H, <sup>3</sup>J 5.4, 6.9, 10.3, 12.0 Hz, CH=CH<sub>2</sub>), 5.61–5.55 (m, 1H, CH=CH), 5.47–5.42 (m, 1H, CH=CH), 5.15 [dq, 2H, *J* 1.7 (q), 12.0 (d) Hz, CH=CHH], 5.20–5.00 (m, 1H, H-1), 5.05 [dq, 2H, *J* 1.7 (q), 10.3 (d) Hz, CH=CHH], 3.22 (ddt, 2H, <sup>4</sup>*J* 1.4 (t) Hz, <sup>3</sup>*J* 5.0 Hz, <sup>2</sup>*J* 14.4 Hz, N-CHH), 3.10–2.94 (m, 3H, N-CHH+H-6), 2.52–2.42 (m, 1H), 2.24–2.02 [m+s, 6H. Singlet corresponds to CH<sub>3</sub> (2.07 ppm)];  $\delta_{\text{C}}$  (75.5 MHz CDCl<sub>3</sub>) 170.2 (C=O), 137.4 (CH=CH<sub>2</sub>), 125.8 (CH=CH), 123.4 (CH=CH), 115.9 (CH=CH<sub>2</sub>), 69.8 (CH), 57.6 (CH), 52.8 (N-CH<sub>2</sub>), 31.9 (CH<sub>2</sub>), 25.8 (CH<sub>2</sub>), 21.2 (CH<sub>3</sub>); *m/z* (EI<sup>+</sup>): 235 (15, M<sup>+</sup>), 194 [18 (M-CH<sub>2</sub>-CH=CH<sub>2</sub>)<sup>+</sup>], 149 (100).

4.2.4. Enzymatic kinetic resolution of diamine (±)-**6**. Ethyl acetate (24 mL) was added to a mixture of racemic diamine (±)-**6** (0.750 g, 3.90 mmol) and PSL-C (0.390 g) under a nitrogen atmosphere. The new mixture was stirred at 28 °C and 200 rpm during 48 h. Then, the reaction mixture was filtered through a pad of Celite® and the solid was washed with methanol. Organic solvents were evaporated under reduced pressure and the resulting crude, which consisted of a mixture of diamine (1*S*,2*S*)-**6** and monoamide (1*R*,2*R*)-**7**, was subjected to flash chromatography (a gradient of hexane/AcOEt 1:1 to AcOEt/methanol 4:1 was used as eluent).

4.2.4.1. (1*S*,2*S*)-*N,N*-Diallylcyclohex-4-ene-1,2-diamine [(1*S*,2*S*)-**6**]. Yield 42%;  $[\alpha]_{\text{D}}^{20} +67.3$  (c 1.0, CHCl<sub>3</sub>), ee >99%.

4.2.4.2. (1*R*,2*R*)-*N*-Acetyl-*N',N'*-diallylcyclohex-4-ene-1,2-diamine [(1*R*,2*R*)-**7**]. Yield 47%; mp 98–100 °C; [found: C, 71.9; H, 9.6; N 12.2. C<sub>14</sub>H<sub>22</sub>N<sub>2</sub>O requires C, 71.76; H, 9.46; N, 11.95%]; *R*<sub>f</sub> (hexane/AcOEt 5:1) 0.41;  $[\alpha]_{\text{D}}^{20} -5.4$  (c 1.0, CHCl<sub>3</sub>), ee >99%;  $\nu_{\text{max}}$ (CH<sub>2</sub>Cl<sub>2</sub>) 3261, 3095, 1634, 1579 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz CDCl<sub>3</sub>) 6.39 (br s, 1H, NH), 5.72 (dddd, 2H, <sup>3</sup>*J* 4.6, 8.0, 10.2, 12.6 Hz, CH=CH<sub>2</sub>), 5.64–5.48 (m, 2H, CH=CH), 5.21–5.05 (m, 4H, CH=CH<sub>2</sub>), 3.79–3.65 (m, 1H, H-1), 3.31–3.19 (m, 2H, N-CHH), 3.02–2.80 (m, 4H, N-CHH+H-2+CHH), 2.28–2.12 (m, 1H, CHH), 2.12–1.77 [m+s, 5H. Singlet corresponds to CH<sub>3</sub> (1.95 ppm)];  $\delta_{\text{C}}$  (75.5 MHz CDCl<sub>3</sub>) 170.4 (C=O), 136.5 (CH=CH<sub>2</sub>), 125.1 (CH=CH), 124.9 (CH=CH), 116.8 (CH=CH<sub>2</sub>), 57.5 (CH), 52.0 (N-CH<sub>2</sub>), 47.8 (CH), 33.3 (CH<sub>2</sub>), 23.4 (CH<sub>3</sub>), 23.0 (CH<sub>2</sub>); *m/z* (EI<sup>+</sup>): 193 [70, (M-CH<sub>2</sub>-CH=CH<sub>2</sub>)<sup>+</sup>], 162 (100).

4.2.5. (1*S*,2*S*)-*N*-(*tert*-Butoxycarbonyl)-*N',N'*-diallylcyclohex-4-ene-1,2-diamine [(1*S*,2*S*)-**8**]. Di-*tert*-butyl pyrocarbonate (0.419 g, 1.90 mmol) was added to a solution of (1*S*,2*S*)-**6** (0.336 g, 1.75 mmol) in methanol (10 mL). After 1 h of reaction at room temperature, solvents were evaporated and the residue was purified by flash chromatography (hexane/AcOEt 15:1 as eluent) to yield the title compound (1*S*,2*S*)-**8** (98%) as a white solid; mp 45–46 °C; *R*<sub>f</sub> (hexane/AcOEt 5:1) 0.52;  $[\alpha]_{\text{D}}^{20} +49.7$  (c 1.0, CHCl<sub>3</sub>), ee 98%;  $\nu_{\text{max}}$ (CH<sub>2</sub>Cl<sub>2</sub>) 3381, 2977, 1715, 1648 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz CDCl<sub>3</sub>) 5.77 (dddd, 2H, <sup>3</sup>*J* 4.8, 8.0, 10.2, 12.7 Hz, CH=CH<sub>2</sub>), 5.62–5.50 (m, 2H, CH=CH), 5.42 (br s, 1H, NH), 5.20–5.04 (m, 4H,

CH=CH<sub>2</sub>), 3.57–3.43 (m, 1H, H-1), 3.32–3.18 (m, 2H, N-CHH), 2.91–2.76 (m, 4H, N-CHH+H-2+CHH), 2.26–2.12 (m, 1H, CHH), 2.08–1.83 (m, 2H, 2× CHH), 1.44 (s, 9H, <sup>t</sup>Bu);  $\delta_{\text{C}}$  (75.5 MHz CDCl<sub>3</sub>) 156.0 (C=O), 136.6 (CH=CH<sub>2</sub>), 124.9 (CH=CH), 124.8 (CH=CH), 116.6 (CH=CH<sub>2</sub>), 78.5 (C), 57.6 (CH), 52.0 (N-CH<sub>2</sub>), 48.3 (CH), 33.8 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>), 23.0 (CH<sub>2</sub>); *m/z* (ESI<sup>+</sup>) 293 (50, MH<sup>+</sup>), 237 (100); HRMS (ESI<sup>+</sup>): MH<sup>+</sup>, found 293.2230. C<sub>17</sub>H<sub>29</sub>N<sub>2</sub>O<sub>2</sub> requires 293.2224.

4.2.6. (1*S*,2*S*)-*N,N'*-Di(*tert*-butoxycarbonyl)cyclohex-4-ene-1,2-diamine [(1*S*,2*S*)-**2**]. Obtained from (1*S*,2*S*)-**8** (0.58 mmol). The allyl groups were removed following the method described by an analogous *N,N*-diallylcyclopentane-1,2-diamine.<sup>17</sup> The resulting crude mono-Boc diamine was subsequently dissolved in methanol (4 mL) and treated with di-*tert*-butyl pyrocarbonate (0.140 g, 0.64 mmol). After 5 h of reaction at room temperature, solvents were eliminated and the residue was subjected to flash chromatography (hexane/Et<sub>2</sub>O 7:3 as eluent) to yield the title compound (1*S*,2*S*)-**2** (94%). Spectroscopic data are in good agreement with those previously reported.<sup>3</sup>  $[\alpha]_{\text{D}}^{20} -30.1$  (c 1.0, CHCl<sub>3</sub>). Ref. 3:  $[\alpha]_{\text{D}}^{21} -34.5$  (c 1.100, CHCl<sub>3</sub>), ee 99%.

4.2.7. (1*S*,6*S*)-6-Aminocyclohex-3-en-1-ol [(1*S*,6*S*)-**10**]. It was obtained from (1*S*,6*S*)-**5** (0.400 g, 2.07 mmol) following the method described for the removal of allyl groups.<sup>17</sup> White solid; yield 82%; mp 106–107 °C; *R*<sub>f</sub> (methanol) 0.18;  $[\alpha]_{\text{D}}^{20} +141.9$  (c 1.0, CHCl<sub>3</sub>), ee 95%;  $\nu_{\text{max}}$ (CH<sub>2</sub>Cl<sub>2</sub>) 3410, 3368, 3320, 1693, 1535 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (400 MHz CDCl<sub>3</sub>) 5.58–5.48 (m, 2H, CH=CH), 3.47 (dt, 1H, *J* 5.9 (d), 9.6 (t) Hz, H-1), 2.77 (q, 1H, <sup>3</sup>*J* 9.6 Hz, H-6), 2.43–2.18 (m, 5H, 2× CHH+OH+NH<sub>2</sub>), 2.09–1.97 (m, 1H, CHH), 1.93–1.81 (m, 1H, CHH);  $\delta_{\text{C}}$  (100 MHz CDCl<sub>3</sub>) 125.0 (CH=CH), 71.9 (CH), 53.0 (CH), 34.9 (CH<sub>2</sub>), 33.6 (CH<sub>2</sub>); *m/z* (ESI<sup>+</sup>) 114 (100, MH<sup>+</sup>); HRMS (ESI<sup>+</sup>): MH<sup>+</sup>, found 114.0919. C<sub>6</sub>H<sub>12</sub>NO requires 114.0913.

4.2.8. *tert*-Butyl (1*S*,6*S*)-*N*-[6-(hydroxy)cyclohex-3-enyl]carbamate [(1*S*,6*S*)-**11**]. Prepared by *tert*-butoxycarbonylation of (1*S*,6*S*)-**10** following the method described for (1*S*,2*S*)-**8**. The title compound was isolated as a white solid (99%); mp 95–96 °C; *R*<sub>f</sub> (hexane/AcOEt 3:1) 0.28;  $[\alpha]_{\text{D}}^{20} +30.5$  (c 1.0, CHCl<sub>3</sub>), ee 95%;  $\nu_{\text{max}}$ (CH<sub>2</sub>Cl<sub>2</sub>) 3428, 2980, 1693, 1503, 1171 cm<sup>-1</sup>;  $\delta_{\text{H}}$  (300 MHz CDCl<sub>3</sub>) 5.62–5.50 (m, 2H, CH=CH), 4.66 (br s, 1H, NH), 3.78–3.58 (m, 2H, H-1+H-6), 2.92 (br s, 1H, OH), 2.57–2.43 (m, 2H), 2.18–2.00 (m, 1H), 2.00–1.90 (m, 1H), 1.45 (s, 9H, <sup>t</sup>Bu);  $\delta_{\text{C}}$  (75.5 MHz CDCl<sub>3</sub>) 156.7 (C=O), 124.6 (CH=CH), 124.2 (CH=CH), 79.7 (C), 70.1 (CH), 52.1 (CH), 33.5 (CH<sub>2</sub>), 31.3 (CH<sub>2</sub>), 28.2 (CH<sub>3</sub>); *m/z* (ESI<sup>+</sup>) 236 (100, MNa<sup>+</sup>); HRMS (ESI<sup>+</sup>): MNa<sup>+</sup>, found 236.1266. C<sub>11</sub>H<sub>19</sub>NNaO<sub>3</sub> requires 236.1257.

4.2.9. *tert*-Butyl (1*S*,2*S*)-*N*-(2-hydroxycyclohexyl)carbamate [(1*S*,2*S*)-**12**]. To a mixture of (1*S*,6*S*)-**11** (27 mg, 0.13 mmol) and 10% Pd-C (13 mg) under a hydrogen atmosphere, methanol (1.0 mL) was added. The mixture was stirred under the hydrogen atmosphere at room temperature for 10 h. After this time, the catalyst was filtered through a pad of Celite® and washed with methanol. The filtrate was concentrated to reduced pressure to give pure the title compound (1*S*,2*S*)-**12** (99%). Spectroscopic data are in good agreement with those previously reported.<sup>15</sup>  $[\alpha]_{\text{D}}^{20} +22.6$  (c 0.50, MeOH), ee 95%. Ref. 15:  $[\alpha]_{\text{D}}^{20} +19.19$  (c 0.50, MeOH), enantiopure.

4.2.10. *tert*-Butyl (1*S*,6*R*)-*N*-[6-(azido)cyclohex-3-enyl]carbamate [(1*S*,6*R*)-**13**]. It was obtained by previous mesylation of (1*S*,6*S*)-**11** (0.115 g, 0.54 mmol) with mesyl chloride following the procedure described.<sup>18</sup> Then, the crude mesyl derivative was dissolved in anhydrous *N,N*-dimethylformamide (1.0 mL) and sodium azide (0.105 g, 1.62 mmol) was added. After heating the mixture at 70 °C during 24 h, ethyl acetate (5 mL) was added and the organic solution was repeatedly washed with water. The organic phase was dried with Na<sub>2</sub>SO<sub>4</sub>, and evaporated to reduce pressure to give

a residue, which was subjected to flash chromatography (hexane/AcOEt 30:1; hexane/AcOEt 20:1; dichloromethane were successively used as eluent).<sup>19</sup> The title compound (1*S*,6*R*)-**13** was obtained as a white solid (63%); mp 72–73 °C;  $R_f$  (hexane/AcOEt 3:1) 0.51;  $[\alpha]_D^{20}$  –60.1 (c 1.0, CHCl<sub>3</sub>), ee=95%;  $\nu_{\max}$ (CH<sub>2</sub>Cl<sub>2</sub>) 2980, 2130, 1634, 1340, 1160 cm<sup>-1</sup>;  $\delta_H$  (300 MHz CDCl<sub>3</sub>) 5.70–5.50 (m, 2H, CH=CH); 4.72 (br s, 1H, NH), 4.00–3.82 (m, 2H, H-1+H-6), 2.58–2.40 (m, 1H), 2.38–2.29 (m, 2H), 2.11–2.01 (m, 1H), 1.44 (s, 9H, <sup>t</sup>Bu);  $\delta_C$  (75.5 MHz CDCl<sub>3</sub>) 155.1 (C=O), 125.1 (CH=CH), 122.6 (CH=CH), 79.6 (C), 59.1 (CH), 48.1 (CH), 29.0 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>+CH<sub>2</sub>);  $m/z$  (ESI<sup>+</sup>) 261 (100, MNa<sup>+</sup>); HRMS (ESI<sup>+</sup>): MNa<sup>+</sup>, found 261.1318. C<sub>11</sub>H<sub>18</sub>N<sub>4</sub>NaO<sub>2</sub> requires 261.1322.

4.2.11. (3*aS*,7*aR*)-3*a*,4,7,7*a*-Tetrahydrobenzo[d]oxazol-2(3*H*)-one [(3*aS*,7*aR*)-**14**]. It was isolated after the flash chromatography of the residue obtained in the previous reaction with 27% yield. White solid; mp 53–55 °C;  $R_f$  (AcOEt) 0.37;  $[\alpha]_D^{20}$  +49.7 (c 1.0, CHCl<sub>3</sub>), ee 95%;  $\nu_{\max}$ (CH<sub>2</sub>Cl<sub>2</sub>) 2973, 1684, 1634, 1167 cm<sup>-1</sup>;  $\delta_H$  (300 MHz CDCl<sub>3</sub>) 6.12 (br s, 1H, NH), 5.91 (br s, 2H, CH=CH), 4.98–4.84 (m, 1H, O–CH), 4.16–4.04 (m, 1H, N–CH), 2.58–2.44 (m, 1H, CHH), 2.24–2.02 (m, 3H, CH<sub>2</sub>+CHH);  $\delta_C$  (75.5 MHz CDCl<sub>3</sub>) 160.1 (C=O), 126.6 (CH=CH), 125.9 (CH=CH), 75.3 (CH), 50.4 (CH), 28.4 (CH<sub>2</sub>), 27.6 (CH<sub>2</sub>);  $m/z$  (ESI<sup>+</sup>) 162 (100, MNa<sup>+</sup>), 140 (60, MH<sup>+</sup>); HRMS (ESI<sup>+</sup>): MH<sup>+</sup>, found 140.0706. C<sub>7</sub>H<sub>10</sub>NO<sub>2</sub> requires 140.0704.

4.2.12. (1*S*,2*R*)-*N*-(*tert*-Butoxycarbonyl)cyclohex-4-ene-1,2-diamine [(1*S*,2*R*)-**15**]. It was prepared by Staudinger reduction of azido-carbamate (1*S*,6*R*)-**13** following a previously described procedure.<sup>18</sup> Flash chromatography (AcOEt/methanol 10:1 as eluent) of the crude of the reaction yielded compound (1*S*,6*R*)-**15** (68%) as a colourless oil;  $R_f$  (AcOEt/MeOH 20:1) 0.17;  $[\alpha]_D^{20}$  –14.7 (c 1.0, CHCl<sub>3</sub>), ee 95%;  $\nu_{\max}$ (CH<sub>2</sub>Cl<sub>2</sub>) 3355, 3281, 2976, 1692, 1535, 1167 cm<sup>-1</sup>;  $\delta_H$  (300 MHz CDCl<sub>3</sub>) 5.52 (s, 2H, CH=CH), 5.00 (br s, 1H, NH), 3.75 (br s, 1H, H-1), 3.10–3.01 (m, 1H, H-2), 2.47–2.25 (m, 2H), 2.06–1.82 (m, 2H), 1.62–1.38 [br s+s, 11H; NH<sub>2</sub> (br s, 1.53 ppm) and <sup>t</sup>Bu (s, 1.42 ppm)];  $\delta_C$  (75.5 MHz CDCl<sub>3</sub>) 155.8 (C=O), 124.4 (CH=CH), 79.1 (C), 49.4 (CH), 48.2 (CH), 33.0 (CH<sub>2</sub>), 29.1 (CH<sub>2</sub>), 28.3 (CH<sub>3</sub>);  $m/z$  (ESI<sup>+</sup>) 213 (100, MH<sup>+</sup>); HRMS (ESI<sup>+</sup>): MH<sup>+</sup>, found 213.1592. C<sub>11</sub>H<sub>21</sub>N<sub>2</sub>O<sub>2</sub> requires 213.1598.

### 4.3. HPLC determination of the enantiomeric excesses

The ee for each compound obtained in the enzymatic resolutions as well as for the *cis*-diamine derivative **15** was determined by chiral HPLC using Chiralpack-IA column. Compounds **5** and **7** were analyzed directly. Amino ester **9** was previously converted into the amino alcohol **5** by hydrolysis with a 0.50 M methanolic solution of NaOH. *trans*-Diamine **6** was transformed into its *tert*-butyl carbamate derivative **8**. The chemoenzymatically prepared *cis*-amino carbamate **15** was treated with acetic anhydride and the resulting amido carbamate analysed. Results obtained in the analysis of racemic samples are as follows:

Amino alcohol (±)-**5**: hexane/ethanol 98:2, 0.8 mL/min, 30 °C;  $t_R$ =8.9 (1*R*,6*R*) and 11.6 (1*S*,6*S*) min;  $R_S$ =4.3.

Amino amide (±)-**7**: hexane/ethanol 95:5, 0.8 mL/min, 30 °C;  $t_R$ =10.4 (1*R*,2*R*) and 14.4 (1*S*,2*S*) min;  $R_S$ =6.0.

Amino carbamate (±)-**8**: hexane/ethanol 98:2, 0.8 mL/min, 30 °C;  $t_R$ =5.6 (1*R*,2*R*) and 6.8 (1*S*,2*S*) min;  $R_S$ =3.3.

Amido carbamate derived from (±)-**15**: hexane/propan-2-ol 90:10, 0.8 mL/min, 30 °C;  $t_R$ =17.3 (1*S*,2*R*) and 20.4 (1*R*,2*S*) min;  $R_S$ =2.6.

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- Beside the compound (1*S*,6*R*)-**13**, the bicyclic oxazolidinone **14** was also isolated in this reaction. Characterization of **14** is given in section 4.2.10.