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An improved chemoenzymatic synthesis of both enantiomers of *trans*-cyclopentane-1,2-diamine

Carmen Peña,[a] Javier González-Sabín,[b] Francisca Rebolledo[a,*] and Vicente Gotor[a,*]

[a]*Departamento de Química Orgánica e Inorgánica, Universidad de Oviedo, 33071 Oviedo, Spain*
[b]*Entrechem, SL, Edificio Científico-Tecnológico, Campus de El Cristo, 33006 Oviedo, Spain*

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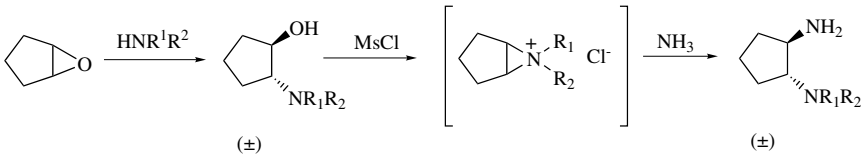
Abstract—An improved chemoenzymatic protocol for the synthesis of both enantiomers of *trans*-cyclopentane-1,2-diamine is described. The key part of the strategy relies on the synthesis and subsequent enzymatic resolution of its racemic precursor *trans*-*N*,*N*-diallylcyclopentane-1,2-diamine in which the primary amino group is masked as a tertiary diallylamine. Lipase B from *Candida antarctica* (CAL-B) catalyzes the N-acylation of this diamine with excellent enantioselectivity ($E > 200$). Further deallylation and derivatization of the enantioenriched compounds (ee $\geqslant$ 97%) obtained in the biotransformation gave access to diversely substituted derivatives.

1. Introduction

Vicinal diamines have found extensive applications as synthetic intermediates, chiral ligands and auxiliaries in asymmetric synthesis.[1] Furthermore, the therapeutic properties of many synthetic, optically active 1,2-diamines have been explored in different areas of medicinal chemistry.[2] In particular, *trans*-cyclopentane-1,2-diamine has been recently used as a modified backbone unit for novel peptide nucleic acids (PNAs) with improved properties.[3] However, in spite of the promising results obtained with *trans*-cyclopentane-1,2-diamine in some areas,[4] today its applications remain almost unexplored. Perhaps, the non-commercial availability, extreme instability and complexity of the classical reported syntheses have produced far less interest among chemists than its homologue *trans*-cyclohexane-1,2-diamine.[5] Thus, since the pioneering work of Toftlund and Pedersen,[6] only a few approaches have appeared with regard to the synthesis of the optically active diamine and, in general, they involve multistep sequences with low overall yields.[7]

Recently, we reported a chemoenzymatic protocol for the synthesis of *trans*-cyclopentane-1,2-diamine derivatives starting from cyclopentene oxide (Scheme 1).[8] In our strategy, the accurate choice of the secondary amine was crucial to ensure the success of the process: on the one hand, the resulting tertiary amino group of the amino alcohol plays a key role in its stereospecific transformation into the racemic *trans*-diamine, while on the other, the enantioselectivity of the enzymatic step is highly dependent on the size and shape of the tertiary amino group. In addition, an extra advantage of the presence of alkyl substituents on the nitrogen was the easy handling and isolation of these compounds, since the free cyclopentane-1,2-diamine degraded upon use, even under a nitrogen atmosphere. Among the substrates previously investigated, the *trans*-*N*-allyl-*N*-benzylcyclopentane-1,2-diamine (see Scheme 1,



Scheme 1. Synthesis of racemic N,N-disubstituted *trans*-cyclopentane-1,2-diamines.

* Corresponding authors. Tel./fax: +34 985103448 (V.G.); e-mail addresses: frv@fq.uniovi.es; vgs@fq.uniovi.es

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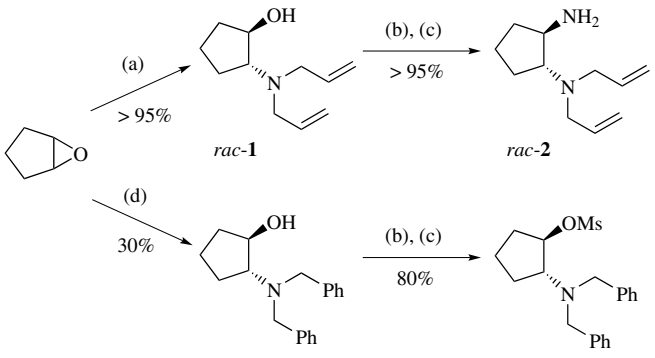
R^1: CH_2–CH=CH_2; R^2: CH_2–Ph) turned out to be the most versatile and allowed us to access several optically active N-monosubstituted derivatives. However, several steps were required for both the synthesis of the racemic compound and the further cleavage of the two protecting groups.

Herein, we report an improved version of the chemoenzymatic approach to the enantiomers of *trans*-cyclopentane-1,2-diamine taking advantage of a novel precursor of the amino group. After considering some factors, the diallylamine was selected as the source of the amino group, the unmasking of the amino function being easily achieved after the enzymatic pathway by means of a palladium-catalyzed deallylation.[9]

2. Results and discussion

After detailed revision, we considered optimizing our previous strategy by starting from a different secondary amine. In fact, the synthesis of *trans*-2-(*N*-allyl-*N*-benzylamino)cyclopentanol and *trans*-*N*-allyl-*N*-benzylcyclopentane-1,2-diamine suffered from two major drawbacks: first, *N*-allylbenzylamine was not commercially available and must be previously prepared by reductive amination of allylamine with benzaldehyde; second, the unmasking of the amino group involved two steps (in the following order: deallylation and catalytic hydrogenation). Thus, we envisaged that by employing the commercially available diallylamine or dibenzylamine both problems could be circumvented since these inexpensive amines bear two identical substituents, which can be simultaneously removed.

The synthesis of racemic *trans*-*N*,*N*-diallylcyclopentane-1,2-diamine *rac*-**2** was efficiently accomplished in a two-step fashion according to Scheme 2. First, the reaction of cyclopentene oxide with diallylamine led directly to racemic *trans*-2-(diallylamino)cyclopentanol *rac*-**1** in quantitative yield. The excess of the volatile diallylamine was easily removed by a vacuum pump and the β-amino alcohol *rac*-**1** was stereospecifically transformed into the corresponding *trans*-1,2-diamine *rac*-**2** by successive treatment with mesyl chloride and aqueous ammonia according to



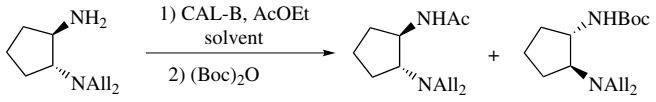
Scheme 2. Stereoselective synthesis of diamine *rac*-**2**. Reagents and conditions: (a) $(Allyl)_2NH$, EtOH, reflux; (b) MsCl, Et_3N, Et_2O, 0 °C to rt; (c) aq NH_3; (d) $(Bn)_2NH$, EtOH, reflux.

our previous reports.[8,10] It is noteworthy that the diamine was isolated in a state of purity with excellent yield, it not being necessary to perform a purification step. By contrast, the process gave unsatisfactory results starting from dibenzylamine; the ring opening step proceeded very slowly and the corresponding *trans*-2-(dibenzylamino)cyclopentanol was obtained in low yield after purification by flash chromatography. Furthermore, in this case, the mesyl ester derivative was the only isolated product after successive treatment of the amino alcohol with mesyl chloride and aqueous ammonia. This means that the presence of the two benzyl groups on the nitrogen inhibits the intramolecular attack (see Scheme 1), the aziridinium ion not being formed. Consequently, the diallyl group was selected as the protecting group and the dibenzyl group finally ruled out.

The enzymatic resolution of *rac*-**2** was performed by means of an enzymatic acetylation catalyzed by the lipase B from *Candida antarctica* (CAL-B). This enzyme has proven to be the most effective biocatalyst for the aminolysis reaction in organic solvent.[11] At first, the simplest reaction conditions were tested, that is, employing ethyl acetate as acyl donor and solvent. However, the enzyme displayed only moderate enantioselectivity (Table 1, entry 1), with the E[12] value being similar to those previously reported for other *trans*-cyclopentane-1,2-diamine derivatives.[8] In an effort to optimize the efficacy of the process, the reaction was tested using a sixfold excess of ethyl acetate as acyl donor and several solvents (Table 1, entries 2–4). Gratifyingly, excellent results were achieved when 1,4-dioxane and THF were used, the enantioselectivity being enhanced to an optimal level (E >200) in the first case (Table 1, entry 4). To facilitate the isolation of both compounds of the enzymatic reaction [the diamine (1*S*,2*S*)-**2** and the produced amino amide (1*R*,2*R*)-**3**], after the enzyme was filtered then, the resulting crude was treated with di-*tert*-butyl dicarbonate. Hence, the remaining diamine (1*S*,2*S*)-**2** was transformed into its Boc derivative (1*S*,2*S*)-**4** and the new mixture formed by the amino carbamate **4** and the unaltered amino amide **3** easily separated by flash chromatography. The assignment of the (1*S*,2*S*)-configuration for the remaining diamine **2** was established after deallylation of its Boc-derivative **4** (see Scheme 3) and comparison of the sign of the specific rotation of the resulting carbamate **7** with the reported value.[8] This means that CAL-B preferentially catalyzes the acetylation of the (1*R*,2*R*)-enantiomer of the amine, according to Kazlauskas' rule.

The optically active compounds obtained in the aminolysis reaction were also employed to prepare monofunctionalized *trans*-cyclopentane-1,2-diamines (Scheme 3). These compounds are especially interesting not only as chiral scaffolds for PNAs but also as precursors of unsymmetrical and hybrid ligands.[13] We would like to emphasize the versatility of the monoprotected cyclopentane-1,2-diamine **2** based on the orthogonality of the allyl groups with many others. Thus, both enantiomers of *trans*-*N*,*N*-diallylcyclopentane-1,2-diamine **2** could be recovered in excellent yields from acetamide (1*R*,2*R*)-**3** and carbamate (1*S*,2*S*)-**4** by acid treatments. On the other hand, (1*R*,2*R*)-**3** and (1*S*,2*S*)-**4** were easily deallylated in the presence of a Pd^0

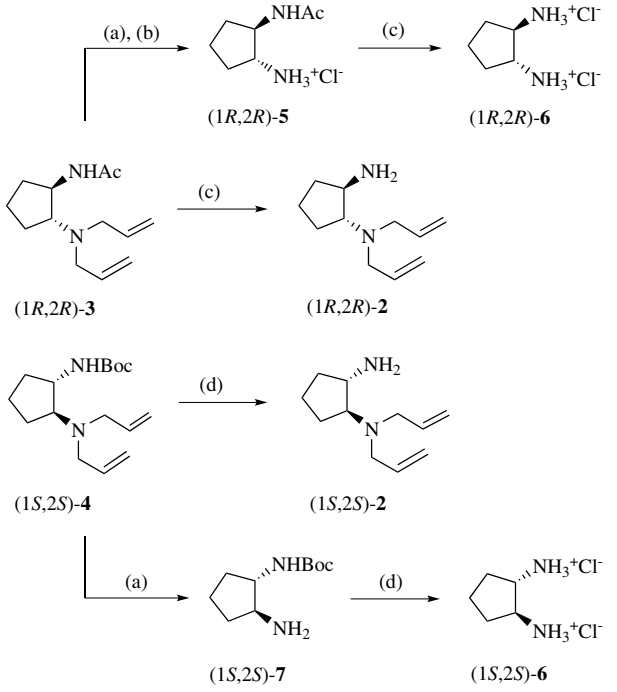
Table 1. Enzymatic resolution of (±)-*trans*-*N*,*N*-diallylcyclopentane-1,2-diamine *rac*-**2**[a]



rac-**2** (1*R*,2*R*)-**3** (1*S*,2*S*)-**4**

Entry	Solvent	Time (h)	(1*S*,2*S*)-**4**		(1*R*,2*R*)-**3**		c[c] (%)	E[d] (%)
			Yield[b] (%)	ee_s (%)	Yield[b] (%)	ee_p (%)		
1	AcOEt	7	44	90	48	79	53	26
2	TBME	24	46	77	48	95	52	78
3	THF	24	45	95	46	95	50	146
4	1,4-Dioxane	24	45	>99	47	97	51	>200

[a] All the reactions were carried out at 28 °C and 200 rpm with a 1:6 molar ratio amine/acyl donor.
[b] Isolated yields after flash chromatography.
[c] Conversion degree: $c = ee_s/(ee_s + ee_p)$.
[d] Determined from ee of the remaining substrate (ee_s) and ee of the product (ee_p) as in Ref. 12.



Scheme 3. Selective deprotection of optically active *trans*-cyclopentane-1,2-diamine derivatives. Reagents and conditions: (a) $Pd(PPh_3)_4$, NDMBA, PhMe; (b) 3 M HCl in MeOH, rt; (c) 6 M aq HCl, reflux; (d) 3 M HCl in MeOH, reflux.

catalyst and *N*,*N*′-dimethylbarbituric acid (NDMBA) as allyl group scavenger[14] affording the corresponding acetamide (1*R*,2*R*)-**5** and carbamate (1*S*,2*S*)-**7**[15] in high yields. Finally, from the acid treatment of **5** and **7**,[8] both enantiomers of *trans*-cyclopentane-1,2-diamine were isolated as their dihydrochloride salts **6** in 95% and 97% yields, respectively.

Lastly, it should be noted that the strategy herein presented for the synthesis of *trans*-cyclopentane-1,2-diamine represents a significant improvement with respect to the existing methods (including our preliminary report). Thus, the overall yields from cyclopentene oxide were 38% for (1*R*,2*R*)-**6** and 40% for (1*S*,2*S*)-**6** (78% if both enantiomers are considered together), that is, 20% higher than those previously reported by us for the same compounds. In addition, all the starting materials and reagents are commercially available and a reduced number of purification and deprotection steps are required. Hence, based on its simplicity and efficacy, we find this strategy especially suitable for the large-scale preparation of optically active *trans*-cyclopentane-1,2-diamine.

3. Conclusion

In conclusion, we have developed an improved chemoenzymatic protocol for the synthesis of both enantiomers of *trans*-cyclopentane-1,2-diamine by rational introduction of a protecting diallyl group over the nitrogen atom. The easy cleavage of the diallyl group allowed us to prepare, by conventional chemical transformations, some diversely substituted derivatives. Additionally, we have synthesized (1*S*,2*S*)-**7**, a valuable precursor of modified PNAs.

4. Experimental

4.1. General

C. antarctica lipase B (Novozyme 435, available immobilized on polyacrylamide, 7300 PLU/g) was gifted by Novo Nordisk Co. For the enzymatic reactions, ethyl acetate of spectrophotometric grade (stored with 4 Å molecular sieves) and the commercially available anhydrous *tert*-butyl methyl ether, 1,4-dioxane and tetrahydrofurane were used. Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded on an Infrared FT spectrophotometer using KBr pellets (for solids) or neat (for liquids). ^1H NMR and proton-decoupled ^{13}C NMR spectra ($CDCl_3$ solutions) were obtained using AC-300 or DPX-300 (^1H, 300.13 MHz and ^{13}C, 75.5 MHz) 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.

4.2. Synthesis of *rac-trans-N,N*-diallylcyclopentane-1,2-diamine *rac*-2

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 refluxing, 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; ^{1}H NMR: $\delta = 1.23$–2.02 (m, 6H), 2.35 (br s, 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: $\delta = 20.55$ (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). Then, *rac*-**1** (20 mmol) was dissolved in anhydrous diethyl ether (40 mL), and triethylamine (32 mmol) was added. The solution was cooled to 0 °C, and mesyl chloride (24 mmol) was added dropwise. A white precipitate was formed that made stirring difficult. After 30 min, triethylamine (40 mmol) was added. After the reaction mixture was allowed to warm to room temperature, concentrated aq NH_3 (50 mL) was added and the resulting two-phase reaction mixture was stirred vigorously for 16 h. The layers were separated, and the light-yellow aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic layers were washed with brine (25 mL), dried with Na_2SO_4, and evaporated under reduced pressure to give the crude product *rac*-**2**, which was employed in the subsequent biotransformation without further purification. Yield >95%. For an analytical sample, the crude diamine was easily purified by distillation (yield: 90%); bp: 53–55 °C (0.5 Torr); ^{1}H NMR: $\delta = 1.02$–1.83 (m, 6H), 1.85 (br s, 2H), 2.64 (q, $J = 7.8$, 1H), 2.85 (dd, $J = 7.2$ and 14.3 Hz, 2H), 2.97 (q, $J = 8.1$ Hz, 1H), 3.15 (dd, $J = 5.1$ and 14.3 Hz, 2H), 5.00 (m, 4H), 5.75 (dddd, $J = 5.1$, 7.2, 10.2 and 17.3 Hz, 2H); ^{13}C NMR: $\delta = 20.56$ (CH_2), 23.07 (CH_2), 32.70 (CH_2), 53.68 (CH_2), 54.20 (CH), 70.42 (CH), 116.28 (CH_2), 136.95 (CH); MS (ESI), m/z (%) = 181 [$(M+H)^+$, 100]; Anal. Calcd for $C_{11}H_{20}N_2$ (180.3): C, 73.28; H, 11.18; N, 15.54. Found: C, 73.17; H, 11.31; N, 15.42.

4.3. Enzymatic acetylation of *rac*-2

To a mixture of diamine *rac*-**2** (8.0 mmol) and CAL-B (800 mg) under a nitrogen atmosphere, the corresponding anhydrous solvent (Table 1) (24 mL) and ethyl acetate (48 mmol) were added. Then, the mixture was circularly shaken at 28 °C and 200 rpm. The enzyme was subsequently filtered and washed with ethyl acetate. The resulting solution was cooled to 0 °C and then treated with di-*tert*-butyl dicarbonate (1.2 equiv). After 12 h, the solvent was evaporated and the crude reaction mixture was separated by flash column chromatography (ethyl acetate/methanol mixtures) to obtain successively the corresponding enantioenriched amino carbamate (1*S*,2*S*)-**4** and the amino amide (1*R*,2*R*)-**3**.

4.3.1. *tert*-Butyl (1*S*,2*S*)-*N*-[2-(*N*′,*N*′-diallylamino)cyclopentyl]carbamate 4.

Yield: 45%; white solid; mp: 53–54 °C; $[\alpha]_D^{20} = +23.6$ (*c* 0.5, $CHCl_3$); ee >99%; ^{1}H NMR: $\delta =$ 1.28–1.83 (m, 14H), 2.06 (m, 1H), 2.90 (q, $J = 8.4$ Hz, 1H), 3.15 (dd, $J = 6.8$ and 14.3 Hz, 2H), 3.20 (dd, $J = 5.9$ and 14.3 Hz, 2H), 3.74 (m, 1H), 4.55 (br s, 1H), 5.08 (dd, $J = 1.4$ and 8.2 Hz, 2H), 5.11 (dd, $J = 4.1$ and 17.2 Hz, 2H), 5.85 (dddd, $J = 5.1$, 7.2, 10.1 and 17.2 Hz, 2H);^{13}C NMR: $\delta = 20.05$ (CH_2), 23.02 (CH_2), 30.41 (CH_3), 33.78 (CH_2), 50.96 (CH), 55.48 (CH_2), 69.27 (CH), 118.79 (CH_2), 138.66 (CH), 155.62 (C); MS (ESI), m/z (%) = 281 [$(M+H)^+$, 100]; Anal. Calcd for $C_{16}H_{28}N_2O_2$ (280.4): C, 68.53; H, 10.06; N, 9.99. Found: C, 68.41; H, 10.24; N, 9.76.

4.3.2. (1*R*,2*R*)-*N*-[2-(*N*′,*N*′-Diallylamino)cyclopentyl]acetamide 3.

Yield: 47%; yellow oil; $[\alpha]_D^{20} = -21.6$ (*c* 0.6, $CHCl_3$); ee = 97%; ^{1}H NMR: $\delta = 1.20$–1.80 (m, 4H), 1.80–2.05 (m + s, 4H), 2.07–2.20 (m, 1H), 2.88–3.13 (m, 3H), 3.22 (ddd, $J = 1.3$, 5.8 and 14.1 Hz, 2H), 4.01 (q, $J = 7.8$ Hz, 1H), 5.07 (m, 4H), 5.56 (br s, 1H), 5.85 (dddd, $J = 5.8$, 7.2, 10.1 and 17.2 Hz, 2H); ^{13}C NMR: $\delta = 20.89$ (CH_2), 23.16 (CH_3), 24.41 (CH_2), 31.30 (CH_2), 51.82 (CH), 53.21 (CH_2), 66.86 (CH), 116.74 (CH_2), 136.39 (CH), 169.67 (C); MS (ESI), m/z (%) = 223 [$(M+H)^+$, 100]; Anal. Calcd for $C_{13}H_{22}N_2O$ (222.3): C, 70.23; H, 9.97; N, 12.60. Found: C, 70.11; H, 10.02; N, 12.49.

4.4. (1*R*,2*R*)-*N*,*N*-Diallylcyclopentane-1,2-diamine 2

A solution of (1*R*,2*R*)-**3** (360 mg, 2.0 mmol) in 6 M aq HCl (25 mL) was refluxed for 12 h. After this time, the solution was cooled and basified with pellets of NaOH. Further extraction with dichloromethane (3 × 20 mL) and evaporation of the organic solvent yielded pure diamine (1*R*,2*R*)-**2**. Yield: 94%; $[\alpha]_D^{20} = -71.9$ (*c* 0.5, $CHCl_3$); ee = 97%.

4.5. (1*R*,2*R*)-2-(Acetylamino)cyclopentanamine hydrochloride 5

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 (1*R*,2*R*)-**3** (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 (ethyl acetate/methanol mixtures) to yield the amino acetamide, which was converted into its hydrochloride by treatment with 3 M methanolic HCl. Yield: 80%; Spectroscopic data are in good agreement with those previously reported.[8] $[\alpha]_D^{20} = -10.9$ (*c* 0.5, MeOH); ee = 97%. Ref. 8: $[\alpha]_D^{20} = -10.2$ (*c* 0.9, MeOH) for ee = 95%.

4.6. (1*S*,2*S*)-*N*,*N*-Diallylcyclopentane-1,2-diamine 2

A solution of (1*S*,2*S*)-**4** (444 mg, 2.0 mmol) in 6 M methanolic HCl (30 mL) was refluxed for 6 h. After this time, the solution was cooled, concentrated in vacuo, redissolved in 30 mL of water and basified with pellets of NaOH. Further extraction with dichloromethane (3 × 20 mL) and evapora-

tion of the organic solvent yielded pure diamine (1*S*,2*S*)-**2**. Yield: 92%; $[\alpha]_D^{20} = +72.8$ (*c* 0.5, $CHCl_3$); ee >99%.

4.7. *tert*-Butyl (1*S*,2*S*)-*N*-(2-aminocyclopentyl)carbamate 7

This compound was obtained from (1*S*,2*S*)-**4**, allyl groups being removed as described for the amino acetamide (1*R*,2*R*)-**5**; yield: 85%. Spectroscopical data are in good agreement with those previously reported.[8] $[\alpha]_D^{20} = +10.8$ (*c* 1.0, $CHCl_3$); ee >99%. Ref. 8: $[\alpha]_D^{20} = +10.6$ (*c* 1.0, $CHCl_3$) for ee >99%.

4.8. Determination of enantiomeric excesses

Enantiomeric excess of diamine (1*S*,2*S*)-**2** was determined by chiral HPLC after transformation into its *N*-Cbz derivative **8** (1.2 equiv of benzyl chloroformate, dichloromethane, rt). Chiral HPLC was also used to determine the ee of amino amide (1*R*,2*R*)-**3**. HPLC conditions: Chiralcel OD column (25 cm × 4.6 mm i.d.), hexane/isopropyl alcohol (H/*i*PA) mixtures, 0.8 mL/min. For (±)-**3**: H/*i*PA 96:4; $T = 40$ °C; $t_R = 11.6$ (*R*,*R*) and 12.4 (*S*,*S*) min; $R_S = 1.8$. For (±)-**8**: H/*i*PA 92:8; $T = 20$ °C; $t_R = 7.2$ (*R*,*R*) and 12.2 (*S*,*S*) min; $R_S = 7.6$.

Acknowledgements

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