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Development of a chemoenzymatic strategy for the synthesis of optically active and orthogonally protected polyamines

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ABSTRACT

The chemical preparation and stereoselective enzymatic desymmetrization of a series of prochiral 2-substituted-1,3-propanediamines have been carried out using *Pseudomonas cepacia* lipase as biocatalyst. Syntheses of novel optically active orthogonally protected di- or triamines have been achieved for the first time with different grade of enantiodiscrimination depending on the C-2 substitution of the propane-1,3-diamine fragment. Final monoselective deprotection reactions of (*S*)-3-allyl-2-*tert*-butyl-1-(9-fluorenylmethyl)propane-1,2,3-triyltriscarbamate have allowed us to obtain a panel of novel enantiomerically enriched disubstituted triamines, compounds of difficult access by conventional synthetic methods.

1. Introduction

Nowadays, preparation of optically pure products is a highly demanding task, which provides practical solutions for many necessities in the industrial sector.[1] In particular, enantiomerically pure amines are a class of organic compounds with attractive synthetic possibilities, having important applications as chiral ligands and building blocks for the preparation of agrochemicals, drugs and fine chemicals in an stereoselective manner.[2] A few chemical strategies have been satisfactorily developed for the production of this group of nitrogenated compounds[3] such as reductive amination of ketones,[4] catalytic hydrogenation of imines[5] or enamines,[6] hydrosilylation of imines or oximes,[7] alkylation of imines[8] or amino hydroxylation processes,[9] but also in recent years enzymatic environmentally friendly approaches have offered adequate methodologies for the access to optically active amines starting from racemic amines, ketones or imines by using lipases,[10] transaminases[11] or amino oxidases.[12]

1,2-Diamino and 1,3-diamino compounds play an important role in medicinal chemistry,[13] and can act as precursors in the synthesis of polyamines, macrocycles and bifunctional chelating agents.[14] Use of different protecting groups is a common strategy for the preparation of polyfunctional organic compounds such as peptides or carbohydrates, specially when similar motifs are present in a determined molecule. For example, many carbamates have been used as protecting groups, preventing the corresponding amines from air-sensitive oxidations and allowing easy work-up procedures of the protected compounds.[15]

In the challenging search for the synthesis of optically active diamines,[16] we have recently developed a chemoenzymatic strategy for the production of optically active aminocarbamates based on the enzymatic desymmetrization of 2-substituted-1,3-propanediamines in 1,4-dioxane,[17] being found *Pseudomonas cepacia* lipase (PCL)[18] as an ideal stereoselective biocatalyst for the alkoxycarbonylation of these prochiral compounds. Here we wish to report the advances achieved in the asymmetric preparation of novel optically active diamines and orthogonally protected triamines.

2. Results and discussion

We focused our initial studies in the synthesis of new optically active organic compounds comparing the reactivity of a set of diamines in the enantioselective desymmetrization reaction catalyzed by *P. cepacia* lipase. These substrates differ in the C-2 substitution present in the 1,3-diamine fragment, and we have paid attention to the influence of the heteroatom present in the C-2 position and its corresponding substitution (Scheme 1).

Previous results have demonstrated the versatility of PCL in the stereoselective alkoxycarbonylation of diamines, showing an excellent enantiopreference towards the *pro-R* orientation of prochiral 2-substituted-propane-1,3-diamines, specially when phenyl

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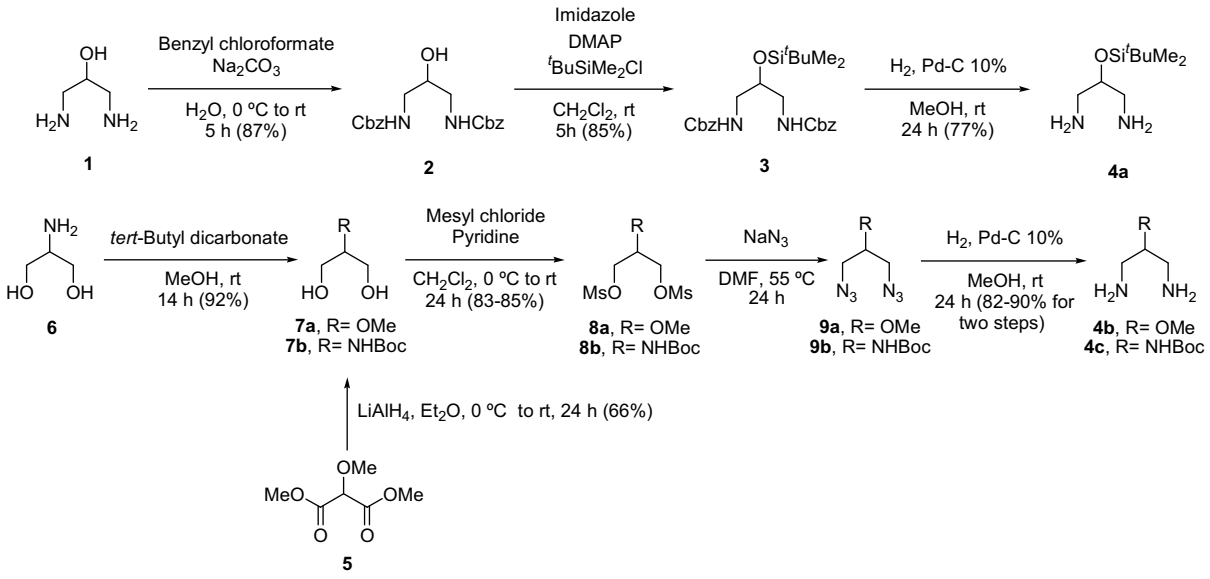


Scheme 1. Chemical synthesis of diamines **4a–c**.

rings were considered in the C-2 position. For that reason we decided to study the enzymatic desymmetrization of diamines with heteroatoms in the C-2 position such as oxygen or nitrogen, which are protected as the corresponding silyl ether (OSi^tBuMe_2), or present as a methoxy group (OMe) or a *N-tert*-butoxycarbonyl substitution (NHBoc). Then we started the synthesis of the aimed diamines and our first choice was 2-(*tert*-butyldimethylsilyloxy)-propane-1,3-diamine (**4a**) that can be easily accessible in good overall yield from 2-hydroxy-1,3-diaminopropane (**1**) by selective N-protection with benzyl chloroformate,[19] next O-protection using *tert*-butyldimethylsilyl chloride ($^tBuMe_2SiCl$) and final removal of the benzyloxycarbonyl (Cbz) group in hydrogenolysis conditions catalyzed by Pd–C (Scheme 1).

It has to be pointed out that the selective O-protection was directly attempted from **1** but the resulting diamine **4a** could not be isolated in high purity from the reaction mixture. Therefore we decided to carry out the synthesis through the three mentioned steps. This issue is critical because diamines present usually serious drawbacks at the purification step by flash chromatography or extraction protocols, so we must afford the desired diamino compound after a clean reaction before running out the enzymatic processes. A hydrogenation process is an ideal manner as the diamine can be nicely purified by a simple filtration using Celite®, allowing an easy and rapid handling of the diamine.

Next the preparations of prochiral **4b–c** were undertaken, compounds that differ from diamine **4a** in the substitution present in the oxygen atom (OMe instead of $O^tBuSiMe_2$) or in the heteroatom directly bounded to the C-2 position of the 1,3-propanediamine fragment (NHBoc). In this manner for the chemical synthesis of **4b** we selected 2-methoxydimethylmalonate (**5**) as starting material, which was reduced using lithium aluminium hydride ($LiAlH_4$) leading in to the diol **7a** in 66% yield and improving the 54% isolated yield previously reported by Krushinski Jr. and co-workers.[20] Next diprotection with mesyl chloride in the presence of triethylamine (Et_3N), nucleophilic substitution of both methanesulphonyl groups by sodium azide (NaN_3) in DMF at 55 °C and final hydrogenation using Pd–C 10% allowed the recovery of diamine **4b** in good overall yield. For **4c** we followed a similar protocol to the one described by Benoist and co-workers,[21] using serinol (**6**) as initial compound for the synthesis. Thus, serinol was *N*-Boc-monoprotected forming **7b** that was subjected to an identical reaction sequence than **7a**: Protection with mesyl chloride, nucleophilic substitution and catalytic hydrogenation, affording diamine **4c** in good overall yield.

At this point, the enzymatic desymmetrizations of prochiral diamines **4a–c** were performed using diallyl carbonate, PCL and 1,4-dioxane at 30 °C, best alkoxycarbonylating agent, biocatalyst and solvent found for the enantioselective preparation of related 2-substituted-propane-1,3-diamine structures by enzymatic processes (Scheme 2).[17] The resulting optically active monocarbamates **11a–c** were conveniently derivatized yielding the amidocarbamates **12a–c**, which were injected in the HPLC for the measurement of the enantiomeric excesses.

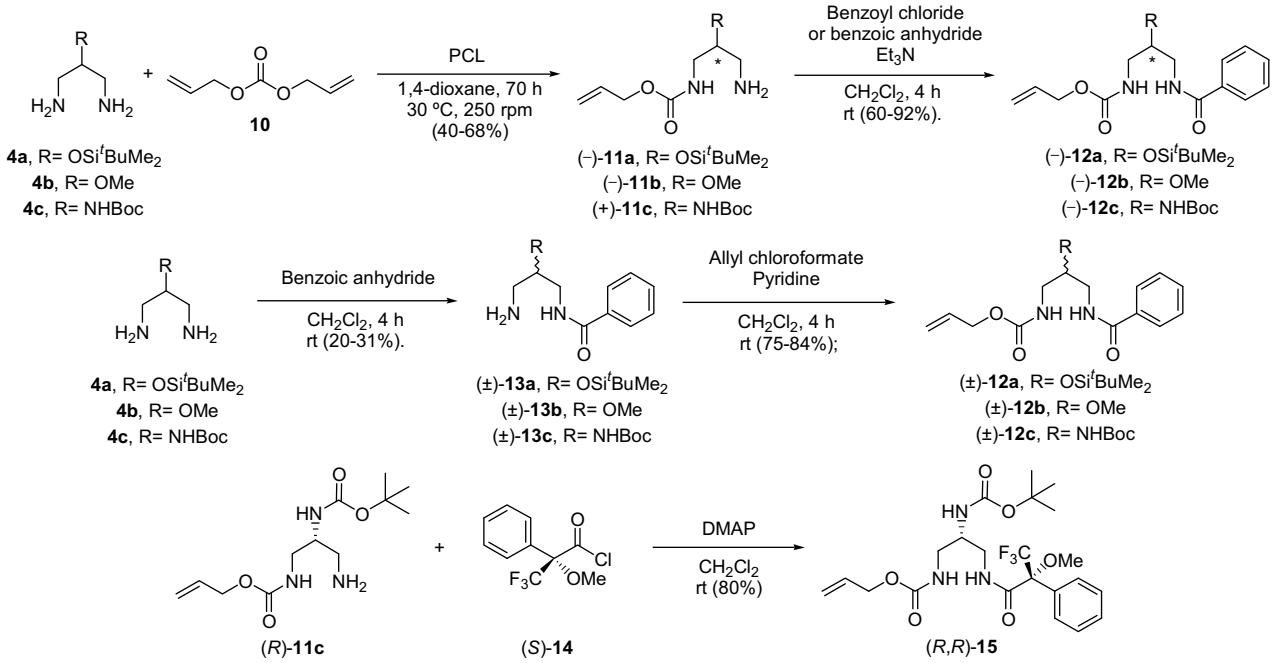
Previously, the racemic compounds **12a–c** were prepared in a two-steps sequence based on the chemical monoacylation of the prochiral diamines obtaining racemic monoamides **13a–c**,[22] which were subsequently transformed into (±)-**12a–c** by reaction with allyl chloroformate in dry dichloromethane.

Lipase-catalyzed desymmetrization reactions gave very different results depending on the C-2 substitution present in the 1,3-propanediamine fragment and the results are summarized in Table 1.

For all tested substitutions monocarbamates were isolated in moderate to good yields after a flash chromatography purification step (40–68%), however PCL displayed absolutely different enantiodiscrimination values, observing the best result when the nitrogen atom was directly connected to the C-2 atom of the 1,3-propanediamine core (entry 3, 91% ee), meanwhile both substrates with oxygen substitutions reached the corresponding monocarbamates in 8% and 40% ee for **11a** and **11b**, respectively.

Previously we found that higher ee were achieved when a sp^2 carbon atom was adjacent to the stereogenic centre, observing a loss of selectivity if an extra methylene group was located between the aromatic ring and the chiral carbon.[17b] Thus, the 2-*N-tert*-butoxycarbonyl substitution (nitrogen atom adopting a planar trigonal conformation) led to (+)-**11c** in very high enantiomeric excess in contrast to the low or moderate enantiopreferences observed with the 2-oxygenated derivatives where the oxygen atom adopt a tetrahedrical diposition in an sp^3 hybridization.

The absolute configuration of (+)-**11c** was assigned by an X-ray diffraction analysis of the corresponding Mosher amide (*R,R*)-**15** prepared by reaction of the mentioned compound with (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid chloride (**14**) and later purification by a crystallization process (Scheme 2). As can be



Scheme 2. Enzymatic enantioselective desymmetrization of diamines **4a–c**, chemical synthesis of racemic amidocarbamates **12a–c**, and preparation of Mosher derivative (*R,R*)-**15** from optically active (*R*)-**11c**.

Table 1
Enzymatic desymmetrization of diamines **4a–c** using PCL, diallyl carbonate and 1,4-dioxane at 30 °C

Entry	R	ee (%)[a]	Isolated Yield (%)[b]
1	OSi^tBuMe_2 (**4a**)	8	62
2	OMe (**4b**)	40	40
3	NHBoc (**4c**)	91	68

[a] Determined by HPLC after convenient derivatization.
[b] Isolated yield by *flash* chromatography.

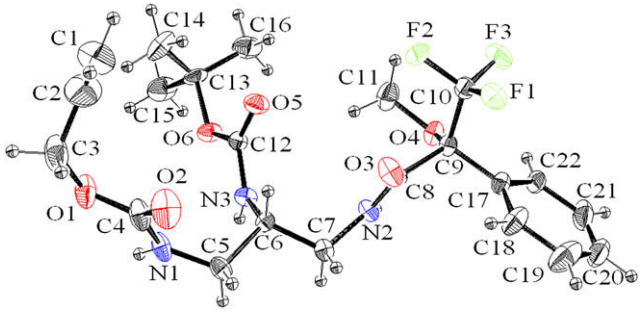


Figure 1. X-ray structure obtained for (*R,R*)-**15** obtained from optically active (*R*)-**11c** by reaction with (*S*)-(+)-**14**.

seen in Figure 1, both stereogenic centres from the acid residue and the 2-position of the diamine fragment present a (*R*)-configuration.[23]

Establishing conditions for cleavage of protecting groups are critical for the production of important polyfunctionalized scaffolds, key components for many areas in organic chemistry. Orthogonally protected triamines have been less investigated than diamines although they present potential applications in medicinal, supramolecular and combinatorial chemistry.[24] Therefore, we decided to prepare the orthogonally protected triamine (*S*)-**16** by protecting the free amino group of (*R*)-**11c** using 9-fluorenylmethyl chloroformate in the presence of sodium bicarbonate ($NaHCO_3$) at room temperature (Scheme 3).

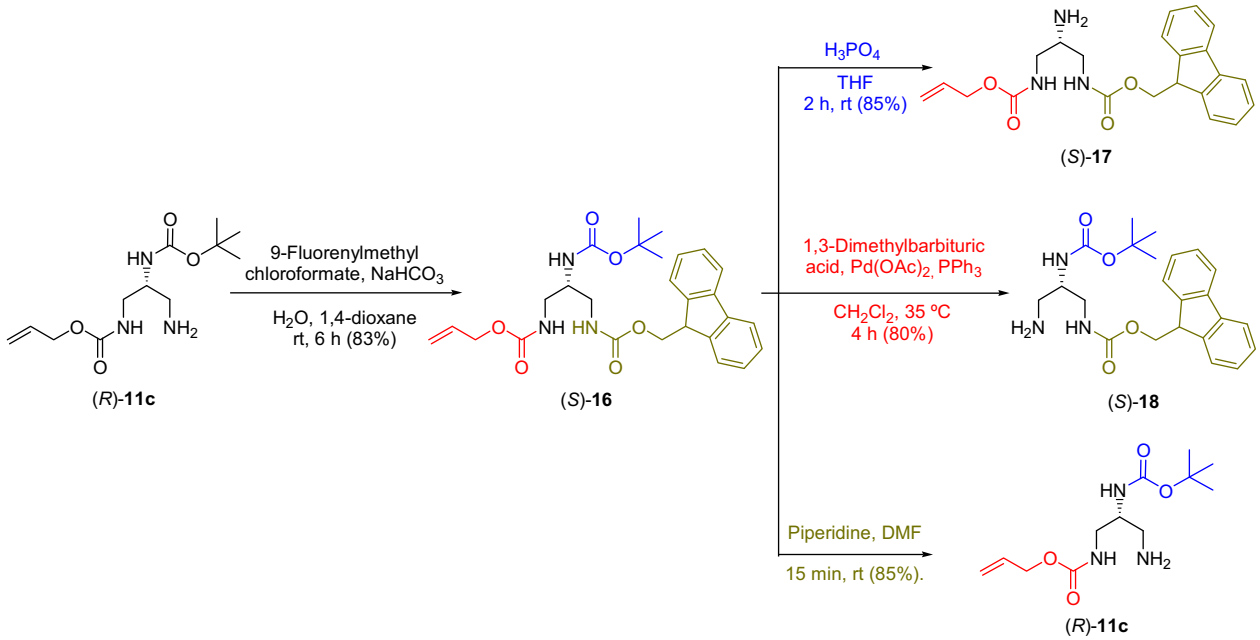
As far as we know, this is the first synthetic example of an optically active triamine orthogonally protected with different rests in its three amino groups. Some other researchers have prepared optically active triamines although there are non-examples of three different protecting groups at the same time.[25] With this orthogonally protected triamine in hand, we explored the possibility of monoselectively release each of the three carbamate functionalities. Deprotection in mild reaction conditions is mandatory for the survival of sensitive functionalities.

For instance, by simply treating (*S*)-**16** with phosphoric acid (H_3PO_4) in THF after 2 h at room temperature, the *tert*-butoxycarbonyl group was released and (*S*)-**17** isolated in 85% yield.[26] Alternatively the allyloxycarbonyl group (Aloc) was cleavaged by reaction with 1,3-dimethylbarbituric acid in the presence of palladium (II) acetate and triphenylphosphine (PPh_3) at 35 °C obtaining (*S*)-**18** in 80% yield.[27] Finally smooth deprotection of the 9-fluorenylmethyloxycarbonyl (Fmoc) group of triamine (*S*)-**16** was achieved by using a 20% solution of piperidine in DMF isolating the already described (*R*)-**11c** in 85% yield.

This synthetic approach allowed us to recover enantiomerically enriched diprotected triamines (*N*-Fmoc, *N*-Boc, *N*-Fmoc, *N*-Aloc or *N*-Aloc, *N*-Boc derivatives), which evidence the versatility and potential of this chemoenzymatic route as nitrogen atoms can be functionalized at wish by means of a protection–deprotection strategy.

3. Conclusions

In summary, a chemoenzymatic approach has been described for the synthesis of optically active carbamates. A great influence in the lipase-mediated desymmetrization has been observed depending on the substitution present in the C-2 position of the 1,3-propanediamine fragment. Therefore, we have accomplished the synthesis of a fully orthogonally protected triamine, which later has been monoselectively deprotected under mild reaction conditions obtaining three optically active amino compounds. This strategy leads for the first time to optically active compounds, which are very difficult to obtain by conventional stereoselective



Scheme 3. Chemical synthesis of triamine (*S*)-**16** and monoselective deprotection reactions.

synthetic methods and suitable for performing additional modifications in the triamine core.

4. Experimental section

4.1. General

P. cepacia lipase immobilized over ceramics (PCL or also PSL-C I, 1638 U/g) was used for the desymmetrization procedures. All other reagents were purchased from different commercial sources and used without further purification. Solvents were distilled over an adequate desiccant under nitrogen. Flash chromatographies were performed using silica gel 60 (230–240 mesh). Melting points were taken on samples in open capillary tubes and are uncorrected. IR spectra were recorded on using NaCl plates or KBr pellets. ^{1}H, ^{13}C NMR, DEPT were obtained using a Brüker NAV-300 spectrometer (^{1}H, 300.13 MHz and ^{13}C, 75.5 MHz) or a Brüker NAV-400 spectrometer (^{1}H, 400.13 MHz and ^{13}C, 100.6 MHz). The chemical shifts are given in delta (δ) values and the coupling constants (J) in Hertz (Hz). ESI^{+}, EI^{+}, APCI^{+} or APCI^{-} experiments using a liquid chromatograph mass detector were performed to record mass spectra (MS). High resolution mass spectra (HRMS) experiments were measured by ESI^{+}. Measurement of the optical rotation was done in a Perkin–Elmer 241 polarimeter. High performance liquid chromatography (HPLC) analyses were carried out in a liquid chromatograph UV detector at 210 nm using a CHIRALCEL OD or a CHIRALPAK AS column (25 cm×4.6 mm I.D.), conditions and retention times are given in the Supplementary data.

4.2. Benzyl 2-hydroxypropane-1,3-diyldicarbamate (2)

Over a solution of 2-hydroxy-1,3-diaminopropane (**1**, 1.00 g, 11.1 mmol) and Na_2CO_3 (2.82 g, 26.64 mmol) in H_2O (19 mL) at 0 °C was added benzyl chloroformate (3.25 mL, 26.64 mmol). The solution was stirred for 5 h at room temperature, after this time it was extracted with CH_2Cl_2 (3×20 mL), the organic phases were combined, dried over Na_2SO_4 and the solvent was removed by distillation at reduced pressure obtaining a crude that was purified by flash chromatography (50% EtOAc/hexane) affording **2** as a white solid (3.46 g, 87%). R_f (50% EtOAc/hexane): 0.23; mp: 125–127 °C; IR (KBr): ν_{max}/cm^{-1} 3359, 1701, 1545, 1324, 1256 and 1175; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 3.25–3.38 (m, 4H), 3.62 (br s, 1H), 3.76–3.81 (m, 1H), 5.09 (s, 4H), 5.53–5.55 (br s, 2H), 7.29–7.38 (m, 10H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 43.6 ($2CH_2$), 66.9 ($2CH_2$), 70.3 (CH), 128.0 (4CH), 128.1 (2CH), 128.5 (4CH), 136.1 (2C), 157.5 (2C); MS (ESI^{+}, m/z): 359 [(M+H)$^{+}$, 100%]; HRMS (ESI^{+}) calcd for $C_{19}H_{22}NaN_2O_5$ (M+Na)$^{+}$: 381.1433; found: 381.1421.

4.3. Benzyl 2-(*tert*-butyldimethylsilyloxy)propane-1,3-diyldicarbamate (3)

Over a solution of **2** (1.00 g, 2.77 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added imidazol (566 mg, 8.33 mmol), DMAP (67 mg, 0.27 mmol) and *tert*-butyldimethylsilyl chloride (666 mg, 5.55 mmol). The solution was stirred for 5 h at room temperature, after this time the solvent was removed by distillation at reduced pressure obtaining a crude that was purified by flash chromatography (10–30% EtOAc/hexane) affording **3** as a white solid (1.11 g, 85%). R_f (20% EtOAc/hexane): 0.21; mp: 87–89 °C; IR (KBr): ν_{max}/cm^{-1} 3367, 1697, 1532, 1291 and 1192; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 0.11 (s, 6H), 0.91 (s, 9H), 2.97–3.07 (m, 2H), 3.41–3.52 (m, 2H), 3.87–3.92 (m, 1H), 5.12 (AB system, J_{AB}=12.4 Hz, 4H), 5.31 (br s, 2H), 7.31–7.39 (m, 10H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): −5.2 ($2CH_3$), 17.7 (C), 25.4 ($3CH_3$), 43.0 ($2CH_2$), 66.5 ($2CH_2$), 69.2 (CH), 127.7 (4CH), 127.8 (2CH), 128.2 (4CH), 136.1 (2C), 156.6 (2C); MS (ESI^{+}, m/z): 473 [(M+H)$^{+}$, 100%].

4.4. 2-(*tert*-Butyldimethylsilyloxy)propane-1,3-diamine (4a)

To a suspension containing dicarbamate **3** (800 mg, 1.69 mmol) and Pd–C 10% (120 mg) in a 100 mL round-bottom flask a H_2 balloon was connected and deoxygenated MeOH (8.0 mL) was carefully added. The resulting suspension was stirred at room temperature during 24 h and after this time the reaction was stopped filtering the mixture through Celite®. The solvent was evaporated under reduced pressure affording **4a** as a colourless oil (266 mg, 77%). R_f (2% NH_3/MeOH): 0.21; δ_H (300.13 MHz, CD_3OD,

Me_4Si): 0.31 (s, 6H), 1.12 (s, 9H), 2.81–2.95 (m, 4H), 3.83–4.95 (m 1H); δ_C (75.5 MHz, CD_3OD, Me_4Si): δ −3.1 ($2CH_3$), 20.2 (CH), 28.7 ($3CH_3$), 46.9 ($2CH_2$), 76.4 (CH).

4.5. 2-Methoxypropane-1,3-diol (7a)

A solution of 2-methoxydimethylmalonate (**5**, 387 μL, 2.8 mmol) in dry Et_2O (11 mL) was cooled to 0 °C and $LiAlH_4$ (425 mg, 11.2 mmol) was carefully added during 15 min. The resulting solution was stirred for 24 h at room temperature and then the reaction was stopped adding H_2O (1.5 mL) at 0 °C. Salts were filtered off through Celite, and the filtrate was washed with Et_2O (6×10 mL). Organic phases were combined, dried over Na_2SO_4 and the solvent evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (20% MeOH/EtOAc), affording **7a** as a colourless oil (196 mg, 66%). R_f (20% MeOH/EtOAc): 0.33; IR (NaCl): ν_{max}/cm^{-1} 3383, 2940, 1124 and 1069; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 2.06–2.10 (t, $^3J_{HH}$=5.9 Hz, 2H), 3.36–3.43 (q, $^3J_{HH}$=6.3 Hz, 1H), 3.50 (s, 3H), 3.68–3.86 (m, 4H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 57.3 ($2CH_2$), 61.2 (CH_3), 81.2 (CH); MS (ESI^+, m/z): 107 [$(M+H)^+$, 100%].

4.6. *tert*-Butyl 1,3-dihydroxypropan-2-yl carbamate (7b)[19]

To a solution of serinol (**6**, 1.00 g, 11.0 mmol) in MeOH (50 mL) was added *tert*-butyl dicarbonate (2.63 g, 12.1 mmol) and this solution was stirred for 14 h at room temperature. After this time the solvent was removed by distillation at reduced pressure obtaining a crude that was purified by flash chromatography, affording **7b** as a white solid (1.92 g, 92%). R_f (5% MeOH/CH_2Cl_2): 0.29; mp: 84–85 °C; IR (NaCl): ν_{max}/cm^{-1} 3410, 1686, 1531, 1250 and 1168; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.42 (s, 9H), 3.30 (br s, 2H), 3.41–3.74 (m, 5H), 5.31 (br s, 1H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): δ 28.4 ($3CH_3$), 53.2 (CH), 63.0 ($2CH_2$), 79.9 (C), 156.5 (C); MS (ESI^+, m/z): 192 [$(M+H)^+$, 100%].

4.7. 2-Methoxypropane-1,3-diyl dimethyl bissulfate (8a)

To a solution of diol **7a** (250 mg, 2.35 mmol) in dry CH_2Cl_2 (15 mL) was added pyridine (733 μL, 9.35 mmol), and the mixture was cooled at 0 °C. Then mesyl chloride (716 μL, 9.35 mmol) was added and the resulting solution was stirred at room temperature for 24 h after complete disappearance of the starting material. The solvent was evaporated by distillation at reduced pressure, obtaining a reaction crude that was purified by flash chromatography (50% EtOAc/hexane), yielding **8a** as a colourless oil (523 mg, 85%). R_f (50% EtOAc/hexane): 0.17; IR (NaCl): ν_{max}/cm^{-1} 3431, 1630, 1335 and 1166; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 2.99 (s, 6H), 3.39 (s, 3H), 3.61–3.69 (m, 1H), 4.16–4.30 (m, 4H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 36.9 ($2CH_3$), 57.7 (CH_3), 66.9 ($2CH_2$), 75.9 (CH); MS (ESI^+, m/z): 263 [$(M+H)^+$, 100%].

4.8. 2-(*tert*-Butoxycarbonylamino)propane-1,3-diyl dimethanesulfonate (8b)

To a solution of diol **7b** (1.64 g, 8.60 mmol) in dry CH_2Cl_2 (50 mL) pyridine (4.3 mL, 34.23 mmol) was added and the mixture was cooled at 0 °C. Then mesyl chloride (4.4 mL, 34.23 mmol) was added and the resulting solution was stirred at room temperature for 24 h after complete disappearance of the starting material. The solvent was evaporated by distillation at reduced pressure, obtaining a reaction crude that was purified by flash chromatography (2% MeOH/CH_2Cl_2), yielding **8b** as a white solid (2.45 g, 83%). R_f (5% MeOH/CH_2Cl_2): 0.29; mp: 99–100 °C; IR (KBr): ν_{max}/cm^{-1} 1694, 1526, 1534 and 1175; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.47 (s, 9H), 3.09 (s, 6H), 4.22–4.39 (m, 5H), 5.02 (br s, 1H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 28.2 ($3CH_3$), 37.5 ($2CH_3$), 48.4 (CH), 66.8 ($2CH_2$), 80.9 (C), 154.8 (C); MS (ESI^+, m/z): 348 [$(M+H)^+$, 40%], 248 [$(M-NHBoc)^+$, 100%].

4.9. 2-Methoxypropane-1,3-diazide (9a)

To a solution under nitrogen atmosphere of compound **8a** (392 mg, 1.50 mmol) in dry DMF (7.5 mL) was added sodium azide (1.26 g, 19.32 mmol), and the resulting suspension was stirred at 55 °C during 24 h. After this time the reaction was quenched with H_2O (50 mL) and the residue was extracted with Et_2O (3×50 mL). The organic phases were combined and dried over Na_2SO_4, the solvent evaporated under reduced pressure affording a crude that was purified by flash chromatography (5% EtOAc/hexane). The azide fractions were carefully evaporated under reduced pressure avoiding complete dryness and the hydrogenation step was performed at this stage without further manipulation of this unstable compound. R_f (5% EtOAc/hexane): 0.16; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 3.37 (d, $^3J_{HH}$=6.7 Hz, 4H), 3.48–3.53 (m, 4H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): δ 50.8 ($2CH_2$), 58.4 (CH_3), 78.8 (CH).

4.10. *tert*-Butyl 1,3-diazidopropan-2-yl carbamate (9b)

To a solution of compound **8b** (750 mg, 2.25 mmol) in dry DMF (11.0 mL) sodium azide (871 mg, 13.56 mmol) was added under nitrogen atmosphere, and the resulting suspension was stirred at 55 °C during 24 h. After this time the reaction was quenched with H_2O (25 mL) and the residue was extracted with Et_2O (3×25 mL). The organic phases were combined and dried over Na_2SO_4, the solvent evaporated under reduced pressure, affording a crude that was purified by flash chromatography (5% EtOAc/hexane). The azide fractions were carefully evaporated under reduced pressure avoiding complete dryness, and the hydrogenation step was performed at this stage without further manipulation of this unstable compound. R_f (5% EtOAc/hexane): 0.23; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.48 (s, 9H), 3.41–3.53 (m, 4H), 3.78–3.89 (m, 1H), 4.81 (br s, 1H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 27.9 ($3CH_3$), 49.1 (CH), 51.3 ($2CH_2$), 79.9 (C), 154.6 (C).

4.11. 2-Methoxypropane-1,3-diamine (4b)

To a suspension containing azide **9a** (1.65 mmol) and Pd–C 10% (130 mg) in a 100 mL round-bottom flask, was connected a H_2 balloon and deoxygenated MeOH was carefully added (6.5 mL). The resulting suspension was stirred at room temperature during 24 h and after this time the reaction was stopped filtering the mixture through Celite®. The solvent was evaporated under reduced pressure affording **4b** as a colourless oil (257 mg, 82% for two steps). R_f (5% NH_3/MeOH): 0.21; δ_H (300.13 MHz, CD_3OD, Me_4Si): 2.80–2.97 (m, 4H), 3.32–3.41 (m, 1H), 3.64 (s, 3H); δ_C (75.5 MHz, CD_3OD, Me_4Si): 44.2 ($2CH_2$), 59.0 (CH_3), 85.2 (CH).

4.12. *tert*-Butyl 1,3-diaminopropan-2-ylcarbamate (4c)

To a suspension containing azide **9b** (1.51 mmol) and Pd–C 10% (115 mg) in a 100 mL round-bottom flask a H_2 balloon was connected and deoxygenated MeOH (6.0 mL) was also carefully added. The resulting suspension was stirred at room temperature during 24 h and after this time the reaction was stopped filtering the mixture through Celite®. The solvent was evaporated under reduced pressure affording **4c** as a colourless oil (232 mg, 90% for two steps). R_f (5% NH_3/MeOH): 0.22; δ_H (400.13 MHz, CD_3OD, Me_4Si): 1.61 (s, 9H), 2.72–2.87 (m, 4H), 3.62–3.68 (m, 1H); δ_C (100.6 MHz, CD_3OD, Me_4Si): 30.0 ($3CH_3$), 45.5 ($2CH_2$), 57.8 (CH), 81.3 (C), 159.7 (C).

4.13. (−)-Allyl (3-amino-2-(*tert*-butyldimethylsilyloxy)-propyl)carbamate [(−)-11a]

To a suspension of diamine **4a** (146 mg, 0.71 mmol) and PCL (213 mg) in dry 1,4-dioxane (7.1 mL), diallyl carbonate (100 μL, 0.71 mmol) was added under nitrogen atmosphere and the mixture was shaken at 30 °C and 250 rpm, following the progress of the reaction by TLC analysis. The reaction was stopped after 70 h, the enzyme was filtered off and washed with MeOH (3×10 mL). The solvent was evaporated under reduced pressure and the resulting crude was purified by flash chromatography (60% MeOH/EtOAc), affording monoamine (−)-**11a** as a colourless oil (126 mg, 62% isolated yield, 8% ee). R_f (60% MeOH/EtOAc): 0.24; IR (NaCl): ν_{max}/cm^{-1} 3435, 1715, 1545, 1399 and 1253; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 0.07 (s, 6H), 0.89 (s, 9H), 1.55 (br s, 2H), 2.64–2.78 (m, 2H), 3.18–3.35 (m, 2H), 3.71–3.75 (m, 1H), 4.55 (d, $^3J_{HH}$=5.0 Hz, 2H), 5.21–5.32 (m, 3H), 5.86–5.98 (m, 1H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): −4.7 ($2CH_3$), 18.0 (C), 25.8 ($3CH_3$), 44.1 (CH_2), 45.2 (CH_2), 65.3 (CH_2), 72.2 (CH_2), 117.6 (CH_2), 132.9 (CH), 156.5 (C); MS (ESI^+, *m*/*z*): 288 [$(M+H)^+$, 100%]; $[\alpha]_D^{20}$=−1.5 (*c* 1.0, $CHCl_3$) for 8% ee.

4.14. (−)-Allyl (3-amino-2-methoxypropyl)-carbamate [(−)-11b]

To a suspension of diamine **4b** (52 mg, 0.50 mmol) and PCL (150 mg) in dry 1,4-dioxane (5.0 mL) was added diallyl carbonate (70 μL, 0.50 mmol) under nitrogen atmosphere, and the mixture was shaken at 30 °C and 250 rpm, following the progress of the reaction by TLC analysis. The reaction was stopped after 70 h, the enzyme was filtered off and washed with MeOH (3×5 mL). The solvent was evaporated under reduced pressure and the resulting crude was purified by flash chromatography (70% MeOH/EtOAc), affording monoamine (−)-**11b** (38 mg, 40% isolated yield, 40% ee). R_f (70% MeOH/EtOAc): 0.15; IR (NaCl): ν_{max}/cm^{-1} 3325, 2943, 1075, 1616, 1525, 1234 and 1021; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.51 (br s, 2H), 2.73–2.87 (m, 2H), 3.23–3.50 (m, 6H), 4.53 (d, $^3J_{HH}$=5.3 Hz, 2H), 5.15–5.33 (m, 3H), 5.87–5.99 (m, 1H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 41.3 (CH_2), 42.4 (CH_2), 57.2 (CH_3), 65.5 (CH_2), 80.5 (CH), 117.6 (CH_2), 132.8 (CH), 156.5 (CH); MS (ESI^+, *m*/*z*): 189 [$(M+H)^+$, 100%]; MS (ESI^+, *m*/*z*): 263 [$(M+H)^+$, 100%]; $[\alpha]_D^{20}$=−1.5 (*c* 1.0, $CHCl_3$) for 40% ee.

4.15. (*R*)-(+)-Allyl *tert*-butyl (3-aminopropane-1,2-diyl)biscarbamate [(*R*)-(+)-11c]

To a suspension of diamine **4c** (307 mg, 1.71 mmol) and PCL (513 mg) in dry 1,4-dioxane (17.1 mL), diallyl carbonate (245 μL, 1.71 mmol) was added under nitrogen atmosphere and the mixture was shaken at 30 °C and 250 rpm, following the progress of the reaction by TLC analysis. The reaction was stopped after 70 h, the enzyme was filtered off and washed with MeOH (3×25 mL). The solvent was evaporated under reduced pressure and the resulting crude was purified by flash chromatography (60% MeOH/EtOAc), affording monoamine (*R*)-(+)-**11c** as a colourless oil (317 mg, 68% isolated yield, 91% ee). R_f (60% MeOH/EtOAc): 0.24; IR (NaCl): ν_{max}/cm^{-1} 3335, 2978, 1699, 1531, 1456, 1367, 1253 and 1170; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.41 (s, 9H), 2.10 (br s, 2H), 2.69–2.78 (m, 2H), 3.20–3.44 (m, 2H), 3.54–3.60 (m, 1H), 4.55 (d, $^3J_{HH}$=5.0 Hz, 2H), 5.16–5.29 (m, 3H), 5.48 (m, 1H), 5.83–5.93 (m, 1H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 28.2 ($3CH_3$), 42.6 ($2CH_2$), 52.5 (CH), 65.5 (CH_2), 79.3 (C), 117.5 (CH_2), 132.7 (CH), 156.1 (C), 156.9 (C); MS ($APCI^+$, *m*/*z*): 274 [$(M+H)^+$, 100%]; HRMS (ESI^+) calcd for $C_{12}H_{23}NaN_3O_4$ $(M+Na)^+$: 296.1581; found: 296.1574; $[\alpha]_D^{20}$=+5.0 (*c* 1.0, EtOH) for 91% ee.

4.16. (−)-Allyl [3-(benzoylamino)-2-(*tert*-butyldimethylsilyloxy)propyl]carbamate [(−)-12a]

To a solution of compound (−)-**11a** (60 mg, 0.20 mmol) in dry CH_2Cl_2 (2.0 mL) under nitrogen atmosphere NEt_3 (54 μL, 0.40 mmol) and benzoyl chloride (28 μL, 0.24 mmol) were successively added. The mixture was stirred for 4 h at room temperature and after this time the solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (30% EtOAc/hexane) affording amidocarbamate (−)-**12a** as a white solid (65 mg, 83%). R_f (30% EtOAc/hexane): 0.23; mp: 121–123 °C; IR (NaCl): ν_{max}/cm^{-1} 3435, 1734, 1545, 1324 and 1211; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 0.14 (s, 6H), 0.93 (s, 9H), 2.97–3.10 (m, 2H), 3.52–3.59 (m, 1H), 3.88–3.97 (m, 2H), 4.58–4.61 (m, 2H), 5.21–5.42 (m, 3H), 5.87–6.00 (m, 1H), 7.05 (br s, 1H), 7.40–7.51 (m, 3H), 7.83 (d, $^3J_{HH}$=7.2 Hz, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): −4.4 ($2CH_3$), 18.4 (C), 26.2 ($2CH_3$), 42.1 (CH_2), 44.0 (CH_2), 66.2 (CH_2), 69.0 (CH), 118.2 (CH_2), 127.4 (2CH), 129.0 (2CH), 132.0 (CH), 133.1 (CH), 134.5 (C), 157.6 (C), 168.0 (C); MS (ESI^+, *m*/*z*): 392 [$(M+H)^+$, 100%]; $[\alpha]_D^{20}$=−1.3 (*c* 1.0, CH_2Cl_2) for 8% ee.

4.17. (−)-Allyl [3-(benzoylamino)-2-methoxypropyl]-carbamate [(−)-12b]

To a solution of compound (*R*)-(−)-**11b** (22 mg, 0.12 mmol) in dry CH_2Cl_2 (1.0 mL) under nitrogen atmosphere were successively added NEt_3 (13 μL, 0.14 mmol) and benzoyl chloride (16 μL, 0.14 mmol). The mixture was stirred for 4 h at room temperature and after this time the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (60% EtOAc/hexane) affording monoamide (−)-**12b** as a colourless oil (30 mg, 84%). R_f (60% EtOAc/hexane): 0.21; IR (NaCl): ν_{max}/cm^{-1} 3320, 1701, 1635, 1522 and 1236; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 3.17–3.31 (m, 2H), 3.45 (s, 3H), 3.47–3.53 (m, 2H), 3.90–3.99 (m, 1H), 4.62 (d, $^3J_{HH}$=5.3 Hz, 2H), 5.23–5.37 (m, 2H), 5.45 (br s, 1H), 5.88–5.99 (m, 1H), 7.05 (br s, 1H), 7.44–7.53 (m, 3H), 7.85 (d, $^3J_{HH}$=5.3 Hz, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 36.7 (CH_2), 40.3 (CH_2), 57.2 (CH_3), 65.7 (CH_2), 77.7 (CH), 117.7 (CH_2), 126.9 (2CH), 128.5 (2CH), 131.5 (CH), 133.1 (CH), 134.0 (C), 157.1 (C), 167.7 (C); MS (ESI^+, *m*/*z*): 293 [$(M+H)^+$, 100%]; $[\alpha]_D^{20}$=−1.9 (*c* 1.0, $CHCl_3$) for 40% ee.

4.18. (*R*)-(−)-Allyl [3-(benzoylamino)-2-(*tert*-butoxycarbonylamino)propyl]carbamate [(*R*)-(−)-12c]

To a solution of compound (*R*)-(+)-**11c** (40 mg, 0.15 mmol) in dry CH_2Cl_2 (2.0 mL) under nitrogen atmosphere NEt_3 (26 μL, 0.18 mmol) and benzoic anhydride (42 mg, 0.18 mmol) were successively added. The mixture was stirred for 4 h at room temperature and after this time the solvent was evaporated under reduced pressure, obtaining a reaction crude that was purified by flash chromatography (50% EtOAc/hexane) affording amidocarbamate (*R*)-(−)-**12c** as a colourless oil (52 mg, 92%). R_f (50% EtOAc/hexane): 0.21; IR (NaCl): ν_{max}/cm^{-1} 3341, 1682, 1539 and 1266; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.49 (s, 9H), 3.28–3.51 (m, 3H), 3.71–3.84 (m, 2H), 4.60 (d, $^3J_{HH}$=5.0 Hz, 2H), 5.18–5.38 (m, 2H), 5.69–5.75 (br s, 2H), 5.90–6.00 (m, 1H), 7.40–7.61 (m, 3H), 7.65 (br s, 1H), 7.85 (d, $^3J_{HH}$=7.1 Hz, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 28.3 ($3CH_3$), 41.0 (CH_2), 41.5 (CH_2), 52.3 (CH), 65.9 (CH_2), 79.8 (C), 117.8 (CH_2), 128.5 (2CH), 128.8 (2CH), 131.6 (C), 132.5 (CH), 133.7 (CH), 156.3 (C), 157.7 (C), 168.4 (C); MS (ESI^+, *m*/*z*): 378 [$(M+H)^+$, 100%]; HRMS (ESI^+) calcd for $C_{19}H_{27}NaN_3O_5$ $(M+Na)^+$: 400.1843; found: 400.1854. $[\alpha]_D^{20}$=−2.7 (*c* 1.0, CH_2Cl_2) for 91% ee.

4.19. (±)-*N*-(3-Amino-2-*tert*-butyldimethylsilyloxy)-propylbenzamide (13a)

To a solution of compound **4a** (108 mg, 0.53 mmol) in dry CH_2Cl_2 (2.0 mL) under nitrogen atmosphere was added Bz_2O (120 mg, 0.53 mmol) in portions, and the mixture was stirred for 4 h at room temperature. After this time the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (20% MeOH/EtOAc) affording racemic amino amide **13a** as a colourless oil (47 mg, 29%). R_f (20% MeOH/EtOAc): 0.18; IR (NaCl): ν_{max}/cm^{-1} 3211, 1710, 1644, 1445, 1320 and 1253; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 0.08 (s, 6H), 0.91 (s, 9H), 1.68 (br s, 2H), 2.81 (m, 2H), 3.42–3.72 (m, 2H), 3.83–3.91 (m, 1H), 7.18 (br s, 1H), 7.37–7.57 (m, 3H), 7.76 (d, $^3J_{HH}$=7.2 Hz, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): −4.3 ($2CH_3$), 18.4 (C), 26.2 ($3CH_3$), 44.0 (CH_2), 46.0 (CH_2), 71.8 (CH), 127.8 (2CH), 129.0 (2CH), 131.8 (CH), 134.9 (C), 168.0 (C); MS (APCI$^+$, *m*/*z*): 309 [(M+H)$^+$, 100%].

4.20. (±)-Allyl [3-(benzoylamino)-2-(*tert*-butyldimethylsilyloxy)propyl]carbamate (12a)

Then to a solution of the racemic amino amide **13a** (45 mg, 0.14 mmol) in dry CH_2Cl_2 (2.0 mL) under nitrogen atmosphere were successively added pyridine (13 μL, 0.17 mmol) and allyl chloroformate (18 μL, 0.17 mmol). The mixture was stirred for 4 h at room temperature and after this time the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (30% EtOAc/hexane) affording racemic amidocarbamate **12a** as a white solid (45 mg, 82%).

4.21. (±)-*N*-(3-Amino-2-methoxypropyl)benzamide (13b)

To a solution of compound **4b** (48 mg, 0.46 mmol) in dry CH_2Cl_2 (4.5 mL) under nitrogen atmosphere was added benzoic anhydride (339 mg, 1.50 mmol), and the mixture was stirred for 4 h at room temperature and after this time the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (100% EtOAc to 100% MeOH) affording monoamide **13b** as a colourless oil (29 mg, 31%). R_f (1% NH_3/MeOH): 0.18; IR (NaCl): ν_{max}/cm^{-1} 3423, 1780, 1545, 1432 and 1234; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 2.00 (br s, 2H), 2.71–2.95 (m, 2H), 3.45 (s, 3H), 3.49–3.91 (m, 2H), 7.20 (br s, 1H), 7.39–7.56 (m, 3H), 7.86 (d, $^3J_{HH}$=7.7 Hz, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 40.3 (CH_2), 40.6 (CH_2), 57.4 (CH_3), 78.5 (CH), 127.0 (2CH), 128.5 (2CH), 131.2 (CH), 134.5 (C), 167.6 (C); MS (ESI$^+$, *m*/*z*): 209 [(M+H)$^+$, 100%].

4.22. (±)-Allyl [3-(benzoylylamino)-2-methoxypropyl]-carbamate (12b)

To a solution of the monoamide **13b** (29 mg, 0.14 mmol) in dry CH_2Cl_2 (1 mL) under nitrogen atmosphere were successively added pyridine (12 μL, 0.15 mmol) and allyl chloroformate (16 μL, 0.15 mmol). The mixture was stirred for 4 h at room temperature and after this time the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (60% EtOAc/hexane) affording amidocarbamate **12b** as a colourless oil (33 mg, 75%).

4.23. (±)-*tert*-Butyl 1-amino-3-benzamidopropan-2-ylcarbamate (13c)

To a solution of compound **4c** (142 mg, 0.75 mmol) in dry CH_2Cl_2 (2.0 mL) under nitrogen atmosphere was added Bz_2O (170 mg, 0.75 mmol) in portions, and the mixture was stirred for 4 h at room temperature. After this time the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (100% MeOH) affording amino amide **13c** as a colourless oil (62 mg, 30%). R_f (100%MeOH): 0.21; IR (NaCl): ν_{max}/cm^{-1} 3423, 1732, 1644, 1565, 1432, 1389, 1255 and 1146; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.47 (s, 9H), 1.56 (br s, 2H), 2.83–2.93 (m, 2H), 3.48–3.65 (m, 2H), 3.71–3.85 (m, 1H), 5.55 (br s, 1H), 7.39–7.54 (m, 4H), 7.82 (d, $^3J_{HH}$=7.3 Hz, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 28.8 ($3CH_3$), 43.7 (CH_2), 44.0 (CH_2), 52.2 (CH), 80.2 (C), 127.4 (2CH), 128.9 (2CH), 131.5 (CH), 134.0 (C), 157.4 (C), 168.4 (C); MS (APCI$^+$, *m*/*z*): 294 [(M+H)$^+$, 100%].

4.24. (±)-Allyl [3-(benzoylamino)-2-(*tert*-butoxycarbonylamino)propyl]carbamate (12c)

To a solution of the racemic amino amide **13c** (53 mg, 0.18 mmol) in dry CH_2Cl_2 (2.0 mL) under nitrogen atmosphere were successively added pyridine (15 μL, 0.20 mmol) and allyl chloroformate (21 μL, 0.20 mmol). The mixture was stirred for 4 h at room temperature and after this time the solvent was evaporated under reduced pressure obtaining a reaction crude that was purified by flash chromatography (100% EtOAc) affording amidocarbamate **12c** as a colourless oil (57 mg, 84%).

4.25. (*R*,*R*)-Allyl [3-(3′,3′,3′-trifluoromethyl-2′-methoxy-2′-phenylpropanoylamino)-2-(*tert*-butoxycarbonylamino)propyl]carbamate [(*R*,*R*)-15]

To a solution of (*R*)-(+)-**11c** (30 mg, 0.11 mmol) in dry CH_2Cl_2 (1 mL) was added DMAP (27 mg, 0.22 mmol) and (*S*)-(+)-α-methoxy-α-trifluoromethylphenyl acetic acid chloride (24 μL, 0.13 mmol). The solution was stirred at room temperature for 4 h and after this time the solvent was removed by distillation at reduced pressure obtaining a reaction crude that was purified by flash chromatography (80% EtOAc/hexane) affording amidocarbamate (*R*,*R*)-**15** as a white solid (43 mg, 80%, 91% ee). This solid was recrystallized in a CH_2Cl_2/hexane mixture obtaining colourless crystals of diastereomerically pure (*R*,*R*)-**15**, which were suitable for X-ray monocrystal analysis. δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.43 (s, 9H), 3.13–3.18 (m, 1H), 3.32–3.55 (m, 5H), 3.61–3.70 (m, 2H), 4.43–4.56 (m, 2H), 5.20–5.32 (m, 2H), 5.51 (br s, 1H), 5.58 (br s, 1H), 5.87–5.93 (m, 1H), 7.41–7.45 (m, 3H), 7.50–7.53 (m, 2H), 7.63 (br s, 1H).

4.26. (*S*)-3-Allyl-2-*tert*-butyl-1-(9-fluorenylmethyl)propane-1,2,3-triyltriscarbamate [(*S*)-(−)-16]

Over a solution of (*R*)-(+)-**11c** (300 mg, 1.10 mmol) and $NaHCO_3$ (277 mg, 3.30 mmol) in H_2O (17 mL) at 0 °C was added dropwise a solution of 9-fluorenylmethyl chloroformate (1.32 mmol, 341 mg) in 1,4-dioxane (17 mL). This solution was stirred at room temperature for 6 h, after this time it was extracted with EtOAc (3×20 mL), the organic phases were combined, dried over Na_2SO_4 obtaining a reaction crude that was purified by flash chromatography (50% EtOAc/hexane) affording (*S*)-(−)-**16** as a white solid (453 mg, 83%). R_f (50% EtOAc/hexane): 0.23; mp: 148–150; IR (KBr): ν_{max}/cm^{-1} 3338, 1699, 1527, 1251 and 1164; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.49 (s, 9H), 3.11–3.42 (m, 3H), 3.61–3.68 (m, 1H), 4.19–4.23 (m, 1H), 4.41 (d, $^3J_{HH}$=5.0 Hz, 2H), 4.51–4.54 (m, 2H), 5.17–5.31 (m, 2H), 5.45 (br s, 1H), 5.61–5.73 (br s, 2H), 5.83–5.99 (m, 1H), 7.22–7.41 (m, 4H), 7.60 (d, $^3J_{HH}$=7.2 Hz, 2H), 7.78 (d, $^3J_{HH}$=7.3 Hz, 2H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 28.8 ($3CH_3$), 42.0 (CH_2), 42.1 (CH_2), 47.6 (CH), 52.5 (CH), 66.3 (CH_2), 67.4 (CH_2), 80.2 (C), 118.2 (CH_2), 120.4 (2CH), 125.4 (2CH), 127.5 (2CH), 127.8 (2CH), 133.1 (CH), 141.7 (2C), 144.2 (2C), 156.4 (C), 157.8 (C), 157.9 (C); MS (APCI$^-$, *m*/*z*): 533 [(M+^{37}Cl)$^-$, 33%] 531 [(M+^{35}Cl)$^-$, 100%]; HRMS (ESI$^+$) calcd for $C_{27}H_{33}N_3NaO_6$ (M+Na)$^+$: 518.2267; found: 518.2286. $[\alpha]_D^{20}$=−2.3 (*c* 1.0, CH_2Cl_2) for 91% ee.

4.27. (*S*)-Allyl 9-fluorenylmethyl (2-aminopropane-1,3-diyl)biscarbamate [(*S*)-(+)-17]

Over a solution of (*S*)-(+)-**16** (50 mg, 0.10 mmol) in THF (100 μL) was added H_3PO_4 (300 μL), the mixture was stirred for 2 h at room temperature, then the reaction was quenched adding a saturated solution of $NaHCO_3$ (10 mL). The aqueous phase was extracted with EtOAc (3×10 mL), the organic were combined and dried over Na_2SO_4, the solvent was removed by distillation at reduced pressure obtaining a reaction crude that was purified by flash chromatography (20% MeOH/EtOAc) affording (*S*)-(+)-**17** as a colourless oil (34 mg, 85%). R_f (20% MeOH/EtOAc): 0.24; IR (NaCl): ν_{max}/cm^{-1} 3355, 1687, 1539, 1435, 1342 and 1286; δ_H (400.13 MHz, CD_3OD, Me_4Si): 3.13–3.16 (m, 1H), 3.25–3.38 (m, 4H), 4.39–4.45 (m, 1H), 4.58–4.61 (m, 2H), 4.73 (d, $^3J_{HH}$=5.0 Hz, 2H), 5.35–5.51 (m, 2H), 6.07–6.16 (m, 1H), 7.48–7.59 (m, 4H), 7.83 (d, $^3J_{HH}$=7.3 Hz, 2H), 7.98 (d, $^3J_{HH}$=7.2 Hz, 1H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 45.9 ($2CH_2$), 50.0 (CH), 53.9 (CH), 67.9 (CH_2), 69.0 (CH_2), 118.9 (CH_2), 122.2 (2CH), 127.4 (2CH), 129.4 (2CH), 130.0 (2CH), 135.9 (CH), 143.9 (2C), 146.5 (2C), 160.3 (2C); MS ($APCI^+$, *m*/*z*): 396 [$(M+H)^+$, 100%]; HRMS (ESI^+) calcd for $C_{22}H_{26}N_3O_4$ $(M+H)^+$: 396.1918; found: 396.1924. $[\alpha]_D^{20}$=+2.0 (*c* 1.0, CH_2Cl_2) for 91% ee.

4.28. (*S*)-*tert*-Butyl 9-fluorenylmethyl (2-aminopropane-1,3-diyl)biscarbamate [(*S*)-(−)-18]

To a solution of $Pd(OAc)_2$ (2.5 mg, 0.01 mmol), PPh_3 (8 mg, 0.03 mmol) and 1,3-dimethylbarbituric acid (42 mg, 0.27 mmol) in dry CH_2Cl_2 (1.2 mL) (*S*)-(−)-**16** (50 mg, 0.10 mmol) was added under nitrogen atmosphere. The mixture was stirred for 4 h at 35 °C and after this time the solvent was evaporated under reduced pressure obtaining a reaction crude, which was redisolved in CH_2Cl_2 (10 mL) and washed with $NaHCO_3$ (1×10 mL). The organic phase was dried over Na_2SO_4, and the solvent was removed under reduced pressure obtaining a crude that was purified by flash chromatography (50% MeOH/EtOAc), affording amino carbamate (*S*)-(−)-**18** as a colourless oil (33 mg, 80%). R_f (50% MeOH/EtOAc): 0.22; IR (NaCl): ν_{max}/cm^{-1} 3243, 1695, 1555, 1445, 1221 and 1155; δ_H (400.13 MHz, $CDCl_3$, Me_4Si): 1.49 (s, 9H), 1.92 (br s, 2H), 2.70–2.82 (m, 2H), 3.21–3.39 (m, 2H), 3.58–3.65 (m, 1H), 4.15–4.23 (m, 1H), 4.39–4.46 (m, 2H), 5.23 (br s, 1H), 5.52 (br s, 1H), 7.28–7.42 (m, 4H), 7.61 (d, $^3J_{HH}$=7.3 Hz, 2H), 7.81 (d, $^3J_{HH}$=7.5 Hz, 2H); δ_C (100.6 MHz, $CDCl_3$, Me_4Si): 28.3 ($3CH_3$), 42.6 (CH_2), 42.8 (CH_2), 47.2 (CH), 52.2 (CH), 66.7 (CH_2), 79.6 (C), 119.6 (2CH), 125.0 (2CH), 127.0 (2CH), 127.6 (2CH), 141.0 (2C), 144.0 (2C), 156.1 (C), 157.0 (C); MS ($APCI^+$, *m*/*z*): 412 [$(M+H)^+$, 100%]; HRMS (ESI^+) calcd for $C_{23}H_{29}NaN_3O_4$ $(M+Na)^+$: 434.2050; found: 434.2067. $[\alpha]_D^{20}$=−3.7 (*c* 1.0, CH_2Cl_2) for 91% ee.

4.29. (*R*)-Allyl *tert*-butyl (3-aminopropane-1,2-diyl)biscarbamate [(*R*)-(+)-11c]

(*S*)-(−)-**16** (50 mg, 0.1 mmol) was dissolved in a 20% solution of piperidine in DMF (500 μL), the solution was stirred for 15 min, after complete disappearance of the starting material the solvent was removed by distillation at reduced pressure obtaining a crude that was purified by flash chromatography (60% MeOH/EtOAc), affording (*R*)-(+)-**11c** as a colourless oil (23 mg, 85%). R_f (60% MeOH/EtOAc): 0.24; IR (NaCl): ν_{max}/cm^{-1} 3335, 2978, 1699, 1531, 1456, 1367, 1253 and 1170; δ_H (300.13 MHz, $CDCl_3$, Me_4Si): 1.41 (s, 9H), 2.10 (br s, 2H), 2.69–2.78 (m, 2H), 3.20–3.34 (m, 2H), 3.54–3.60 (m, 1H), 4.51 (d, $^3J_{HH}$=5.0 Hz, 2H), 5.16–5.29 (m, 3H), 5.48 (m, 1H), 5.83–5.93 (m, 1H); δ_C (75.5 MHz, $CDCl_3$, Me_4Si): 28.2 ($3CH_3$), 42.6 (CH_2), 42.6 (CH_2), 52.5 (CH), 65.5 (CH_2), 79.3 (C), 117.5 (CH_2), 132.7 (CH), 156.1 (C), 156.9 (C) MS ($APCI^+$, *m*/*z*): 274 [$(M+H)^+$, 100%]; HRMS (ESI^+) calcd for $C_{12}H_{23}NaN_3O_4$ $(M+Na)^+$: 296.1581; found: 296.1574. $[\alpha]_D^{20}$=+4.7 (*c* 1.0, EtOH) for 91% ee.

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Supplementary data

Supplementary data associated with this article can be found in online version, at doi:10.1016/j.tet.2009.08.001.

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