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Synthesis of asymmetrized 2-benzyl-1,3-diaminopropane by a chemoenzymatic route: a tool for combinatorially developing peptidomimetics

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Abstract

Both enantiomers of monoacetamide **5**, together with 'dipeptides' **30a**,**b** and monocarbamates **24**, (*R*)-**43** and (*S*)-**43**, all derived from 2-benzyl-1,3-diaminopropane **4**, were synthesized by a chemoenzymatic route starting from the known monoacetate **12**. The behaviour of **4** and of the bis(acylated) derivatives **8**–**11** with respect to hydrolytic enzymes is also presented, together with an extensive study on the configurational stability of monoacylated derivatives of **4**.

1. Introduction

The 1,3-diaminopropane unit is incorporated in many biologically active compounds, including fluorinated phospholipid precursors of liposomes,[1] enkephalin (opioid peptides) analogues,[2,3] drug carriers[4] and, most of all, enzyme inhibitors.[5–8] Among the enzyme inhibitors, many compounds bearing a 1,3-diaminopropane moiety have been synthesized and tested against HIV protease (aspartyl protease)[5–7] and plasmepsin II (malarial aspartyl protease).[8]

In many cases the 1,3-diaminopropane unit is substituted on C2 and/or C1 and C3. Moreover, the two amine functionalities are often alkylated or acylated with different moieties, including amino acids[2] or oligopeptides.[3] In addition, the presence of a stereogenic centre in position 2 of many of the above-mentioned compounds, makes the availability of the 1,3-diamino precursor in optically active form a crucial step in the whole sequence.

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A possible application of asymmetrized 1,3-diamino derivatives is in the field of peptidomimetics, one of the most important classes of enzyme inhibitors.[5,9] For this purpose the amine functions most likely have to be transformed into peptidic derivatives, by acylation with a suitable *N*-protected amino acid.

As a first goal we needed to prepare simple asymmetrized 2-substituted 1,3-diaminopropanes. One of the most attractive strategies for the synthesis of small enantiopure molecules is undoubtedly using enzymes to introduce chirality, particularly if they are employed to asymmetrize prochiral or *meso* substrates. Asymmetrization of diols or of the corresponding diacetates catalyzed by lipases is a well-known and useful procedure, and successfully applied by our group;[10] thus, an extension of this protocol to diamines should be very interesting.

The acylation of primary amino groups in organic solvent has been extensively investigated on α-amino acids[11] or on amines, using lipases,[12–37] proteases,[38–40] acylases[41–45] and aminopeptidases;[46] however, only seldom were these reactions performed on diamines. Apart from penicillin G acylase,[43–45] the most used enzymes are lipases.[12–37] Among the studies with these enzymes, several of them concern the resolution of racemic amines with achiral[14,16,19–25,27–30,32,33,35,36] or chiral[13,17,23,26,32,34,37] acylating agents. Only a few examples of lipase-catalyzed acylation of diamines are known,[12,18,24,27,31] but they involved simple[18,24] or double[27] resolution reactions of chiral substrates. To the best of our knowledge the only asymmetrization reactions performed on achiral diamines or diamides did not utilize lipases: actually, Prinzbach's group asymmetrized cyclic bis(phenylacet)amides using penicillin G acylase,[44] while Wong's group asymmetrized a diamine using subtilisin.[40]

2. Results and discussion

Having in mind the preparation of asymmetrized 1,3-diamines, we first focused our attention on the synthesis of a suitable substrate to be submitted to enzyme-catalyzed acylation. We chose as the first diamine compound **4** (Scheme 1). A synthesis of **4** by reduction of the corresponding dinitrile has already been reported.[47] However, this reduction gave **4** in about 40% yield, better than that reported, but still low; this is most likely due to the difficulty of obtaining crude diamine after work up and to the extensive decomposition during the purification by distillation.[‡] We then optimized the synthesis of **4** through a completely different route. Diol **1**, readily obtained by reduction of diethyl benzylmalonate,[48] was converted into the bis(mesylate) **2**, which was submitted to double nucleophilic substitution to give bis(azide) **3**. Crude bis(azide)[§] was immediately submitted to a Staudinger reaction[50] in order to obtain **4**. The diamine was never isolated as such, but the crude reaction mixture, after selective extraction of excess PPh_3 and of its oxide, was directly acylated under Schotten–Baumann conditions to give bisamides **8** and **11** and carbamates **9**[¶] and **10**. Finally, **4** was obtained on a multigram scale and nearly quantitatively by hydrogenolysis of both carbamate functionalities.

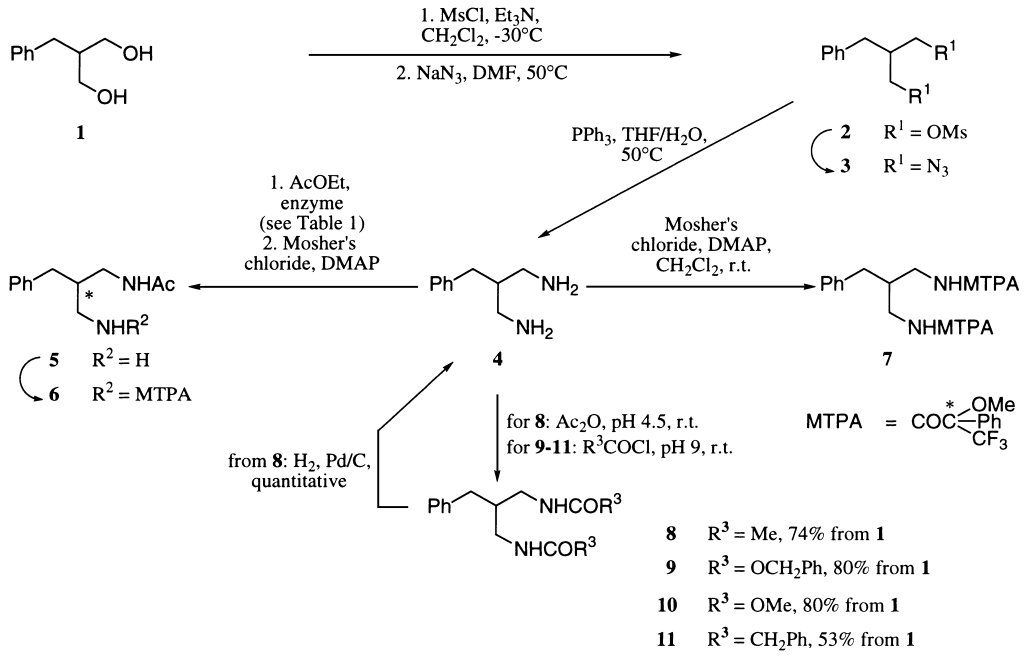
With diamine **4**, we planned to investigate the asymmetrization by acylation in organic solvent using lipases as catalysts. After a literature survey[12–37] we chose lipase from *Candida antarctica* as the first enzyme and vinyl acetate as the irreversible acylating agent.[||] The acylation was very fast and not selective to give mixtures of **5** and **8**. Moreover, after we found an $[\alpha]_D$ value $\cong 0$ for **5**, we showed that vinyl acetate also readily reacts with **4** in the absence of enzyme. This fact was already reported in

[‡] Considerable and variable amounts of product derived from elimination of ammonia were always obtained.

[§] Due to the potentially explosive properties of **3**, the solvent used for the extraction was not completely evaporated.[49]

[¶] Compound **9** could be stored indefinitely as a readily accessible source of **4**.

[||] In our experience vinyl acetate was always the best acylating agent for alcohols.



Scheme 1.

the literature,[15] although vinyl acetate has been successfully used in the resolution of a primary amine with moderate enantiomeric excess.[35] We avoided the uncatalyzed acylation using ethyl acetate and we tried different reaction conditions and enzymes.

As summarized in Table 1 the enzymatic direct acylation of **4** showed to be an inadequate procedure for many reasons: (a) the reaction was always sluggish; (b) it was impossible to quantitatively recover the unreacted diamine, since it probably tends to bind irreversibly to the enzyme; and (c) the enantiomeric excess of **5** was absolutely unsatisfactory. Using papain, a thiol protease that can act as an acylase, which was successfully used by Wong in the synthesis of peptide isosteres,[39] we did not observe any reaction at all. Also diallyl carbonate[40] as acylating agent, with CAL as enzyme, did not give any reaction.

Table 1
Acetylation of **4** catalyzed by lipases

Entry	*Enzyme*	*Solvent*	*Enz. (mg/mmol)*	*Temp. (°C)*	*Time (min)*	*Conversion[a,b] (%)*	*Yield (**5**) (%)*	*E.e.[b,c] (%)*	*Absolute config.[d]*
1	CAL[e]	THF	100	10	236	39	23	13	*S*
2	CAL[e]	THF	100	0	388	16	16	9.2	*S*
3	SPPL[e]	CH_2Cl_2/AcOEt	300	25	1440	22	39	2.5	*S*
4	Amano P[e]	CH_2Cl_2/AcOEt	301	25	1713	26	24	23	*R*
5	CCL[e]	CH_2Cl_2/AcOEt	33	25	1325	only traces of **5** were obtained			

Notes:
a) defined as the ratio (mmols of acetylated NH_2)/(initial mmols of NH_2); this value was determined approximately, due to the difficulty to recover unreacted diamine after the reaction was stopped;
b) conversion and e.e. were determined by GLC with an RSL 150 column, after acylation with Mosher's chloride (see experimental);
c) this is only an indicative value (see text for a more exhaustive explanation);
d) determined by correlation with **(*R*)-** and **(*S*)-5** derived from **12**;
e) CAL = lipase from *Candida antarctica*, SPPL = lipase from porcine pancreas supported on celite (ref. 51), Amano P = lipase from *Pseudomonas cepacia*, CCL = lipase from *Candida cylindracea*.

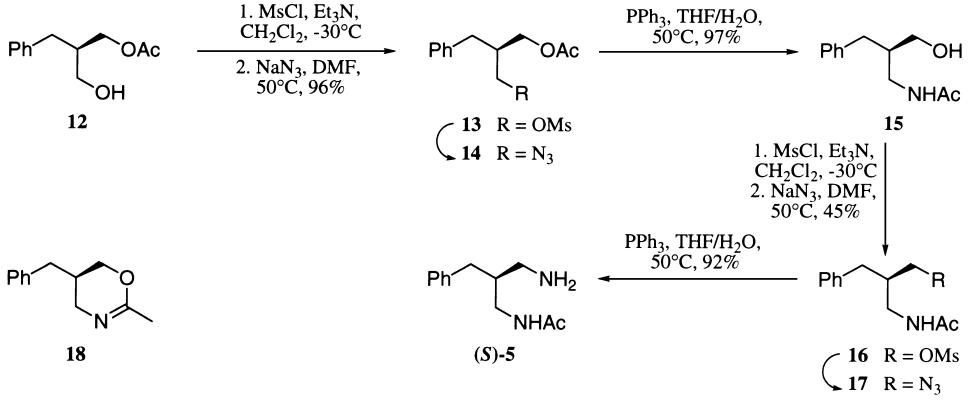
From these preliminary and unsuccessful results we concluded that **4** was not a good substrate for

enzymes, and so we turned our attention to the reverse reaction, that is the transformation of a bisamide or a biscarbamate into an analogue of **5**. In a recent paper Prinzbach[44] reported the successful hydrolysis of cyclic *meso*-bis(phenylacet)amides catalyzed by penicillin acylase from *E. coli* (EC 3.5.1.11).

We tried the same protocol on **11**, but no reaction at all was observed, even when working under conditions known to make the reaction faster. Biscarbamate **10** was reacted with pig liver esterase, hoping to obtain the monocarbamate amine through decomposition of the intermediate monocarbamic acid, but without success. Eventually, reaction of acylase from *Aspergillus melleus* was tried on bis(acet)amide **8**, but again no hydrolysis was observed. Probably diamine **4** and their derivatives are not able to enter the catalytic site of enzymes; this fact is most likely due to the relative positions of the two -NHCOR or -NH_2 groups, as it is known that cyclic diamines or bisamides prove to be reactive in the presence of enzymes.[27,40,44]

Since we were in any case interested in the preparation of **5** or of similar compounds, we decided to use monoacetate **12** as a homochiral precursor and to elaborate it via azido derivative **14**. The synthesis of **12** by lipase-catalyzed acylation of the corresponding diol **1** has already been reported;[48,52] however, we optimized its preparation using a 9:1 mixture of *i*Pr_2O/vinyl acetate both as solvent and acylating system and lipase Amano P (from *Pseudomonas cepacia*) supported on Celite as previously reported.[51,53] Following this procedure monoacetate **12** was obtained on a multigram scale as the *R* enantiomer in 95.9% enantiomeric excess.††

The transformation into azide **14** followed the above reported protocol (Scheme 2). However, treatment of **14** with triphenylphosphine gave, instead of the desired primary amine, acetamide **15** in a nearly quantitative yield. This is most likely due to the intramolecular acyl transfer during hydrolysis of the iminophosphorane intermediate resulting from PPh_3 attack on the azido group.



Scheme 2.

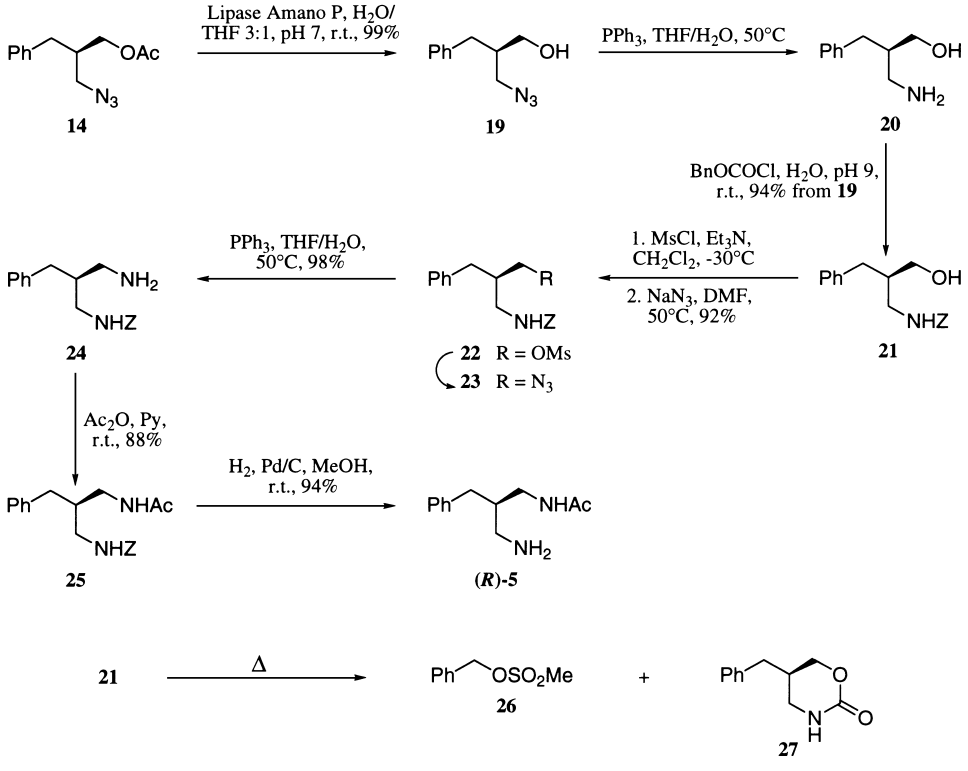
Acetamide **15** was then converted as usual into azide **17** but, in contrast to all other cases reported later in this paper, **17** was obtained only in moderate yield (never more than 45%). We attributed this fact to the competitive formation of dihydro-1,3-oxazine **18**. Although we never succeeded in isolating **18**, we detected the formation of considerable amounts of a compound with the same molecular weight by GC–MS.‡‡ After chromatography we isolated, together with **17**, substantial amounts of alcohol **15**, although it was absent in the starting crude mesylate **16**. Thus it is likely that intermediate dihydro-

†† In some experiments we obtained up to 98% enantiomeric excess for **12**, depending on the degree of conversion.

‡‡ Also, mesylate **16** (MW 249) gave the same result in GC–MS, that is a peak at an unusually low R_t (5.70) with respect to the corresponding azide (R_t 7.82, MW 232); this can be explained with the thermal decomposition of **16** to give **18** (MW 189).

1,3-oxazine **18** is converted back to **15** upon chromatography. It was also observed that, keeping a sample of crude **17** in solution for a few days, containing **18** (by GC–MS), the latter underwent gradual and complete hydrolysis to give **15**. Finally, azide **17** was reduced and (*S*)-**5** was obtained in nearly quantitative yield.

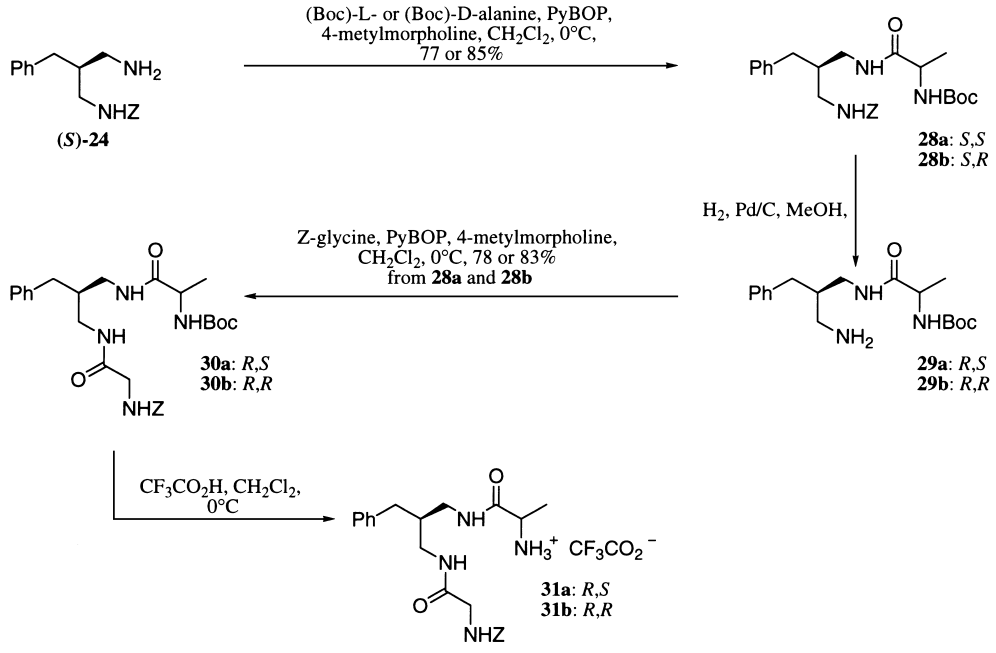
For the synthesis of (*R*)-**5** we had to transform the acetate group of **12** into the acetamide. Starting from the common intermediate **14**, we hydrolyzed in nearly quantitative yield the ester function using Amano P lipase as catalyst in a mixture of THF/H_2O at pH 7. Azide reduction gave amino alcohol **20**, which was never isolated but directly acylated under Schotten–Baumann conditions to give **21**.[§§] Following the usual protocol we readily obtained amine **24**, which, after conventional acetylation and hydrogenolysis of the benzyl carbamate, gave the desired (*R*)-**5** (Scheme 3).



Scheme 3.

Having in mind the preparation of new peptidomimetics, we then focused our attention on the preparation of analogues of **5**, with one or both amine functionalities acylated with different natural *N*-protected amino acids (Scheme 4). For this purpose, we synthesized the two diastereomeric 'dipeptides', **30a**,**b**, starting from (*S*)-benzyl carbamate **24**, which was acylated with L- and D-*t*-butoxycarbonylalanine, respectively, using (benzotriazolyl-1-oxy)tripyrrolidinophosphonium hexafluorophosphate as coupling agent, to give diastereomeric **28a** and **28b**. After removal of the Z group, followed by acylation of the amines **29a**,**b** with Z-glycine, compounds **30a** and **30b** were obtained in good overall yield.

[§§] Alcohol **21** and mesylate **22** were indistinguishable by TLC, so we followed the mesylation by GC–MS analysis, which proved the thermal instability of **22**. In fact, **22** was quantitatively transformed into an equimolecular mixture of **26** and **27**.



Scheme 4.

After having set up a simple and efficient preparation of differently mono- and bisacylated compounds derived from 1,3-diaminopropane, we had to check the enantiomeric excess of the obtained compounds, knowing the enantiomeric excess of starting chiral building block **12**.

First we determined the enantiomeric excesses of both enantiomers of **5**, obtained by different elaborations of **12**, by GLC analysis of the corresponding Mosher's amides **6**. We were disappointed when we noticed an appreciable racemization of about 20%, with respect to the starting enantiomeric excess of **12** (95.9%). In order to establish the step responsible for such behaviour, we analyzed the enantiomeric excess of some intermediates, by converting **15**, **19** and **21** into the corresponding Mosher's ester and analyzing their ^{1}H NMR spectra (Scheme 5). In all cases we observed the maintenance of the original enantiomeric excess, so we concluded that racemization had occurred in one of the steps following the formation of azides **17** and **23**, respectively.

32 R^1 = NHAc
33 R^1 = N_3
34 R^1 = NHZ
35 R^1 = NHBoc

36 R^2 = NHZ
37 R^2 = NHBoc

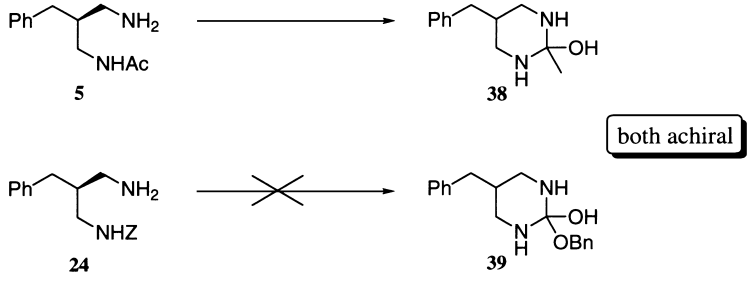
Scheme 5.

To exclude the responsibility of the Staudinger reaction, different methods for transforming the azide into the amine were explored, that is treatment of **23** with: (a) triethylphosphite, followed by anhydrous HCl to give the hydrochloride of **24**, which was acetylated with acetic anhydride in aqueous medium at pH 4.5 to give **25**;[54] (b) $SnCl_2$ in the presence of thiophenol and triethylamine, followed by conventional acetylation;[55] and (c) thiolacetic acid to give directly **25**.[56] In all cases we observed the same extent of racemization on **5**, so we could not establish if this step was responsible for the extensive racemization we observed.

We then turned our attention towards the behaviour of **5** and we found some factors which affect the degree of racemization: (a) the chromatographic eluent, when it contains a small percent of triethylamine; (b) the use of silica gel as the stationary phase for chromatography; (c) the experimental conditions used for hydrogenolysis of the benzyl carbamate; and (d) the use of 4-dimethylaminopyridine to catalyze the acylation with Mosher's chloride.[¶¶] Moreover, we found that **5** itself is configurationally unstable, even when stored at −20°C in the dry state: the effect of the presence of acidic or basic media, as described above, makes the racemization much faster.

At this point we also had to check the enantiomeric excess of benzyl carbamate **24**: once again we analyzed the ^{1}H NMR spectrum of the corresponding Mosher's amides **36** and in this case we did not detect any appreciable racemization.

Concerning the racemization of **5**, this could take place following two different pathways: (a) abstraction of the proton bonded to the stereogenic centre, followed by random reprotonation; and (b) intramolecular acyl transfer from one nitrogen to the other. The acyl transfer in **5** should probably involve an achiral intermediate such as **38** or **39** (Scheme 6). This process is more favourable in the case of **5**, giving **38**, than in the case of **24**, giving **39**, most likely for electronic reasons. The lower tendency of benzyl carbamate to migrate with respect to acetamide was confirmed by preparing both enantiomers of *tert*-butoxycarbonyl carbamate **43**.



Scheme 6.

Actually, **24** was easily transformed into (*R*)-**43**, that is a carbamate which, although not being the enantiomer, had the opposite configuration (Scheme 7). On the other hand, the preparation of (*S*)-**43** was realized starting from the above prepared aminoalcohol **20**. This compound, after transformation into Boc derivative **30**, was elaborated to give (*S*)-**43**, following the same protocol described for the Z derivative.

As expected, for both enantiomers of **43** we confirmed that no racemization had occurred during the whole synthesis, by analysis of the Mosher's amides.

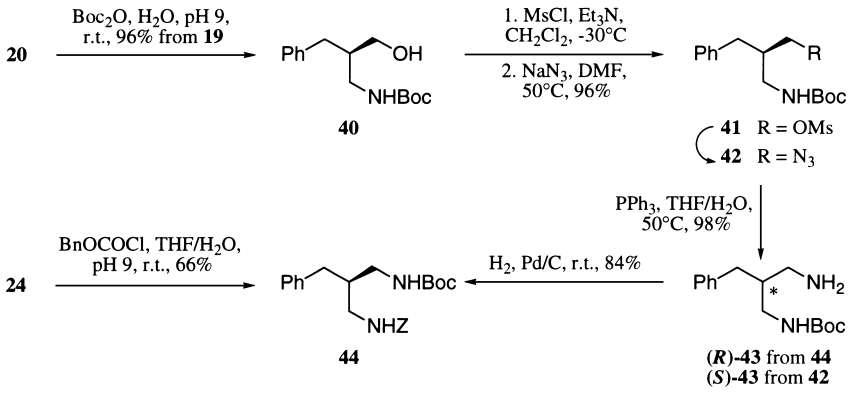
Disappointed by the relatively low configurational stability of **5**, we decided anyway to check the diastereomeric ratio of 'dipetides' **30a**,**b**, a problem that was not trivial. Probably, due to the symmetry of these compounds, the differences in spectroscopic properties are very low, while they display opposite signs in optical rotation. Moreover, even HPLC, either in direct or in reverse phase, did not allow any separation. Surprisingly, after removal of the Boc protecting group with trifluoroacetic acid, we found a

[¶¶] Acylation in pyridine without catalyst (see experimental) proved to be less racemizing.

As a consequence of these results the analysis of enzymatic reactions (see Table 1) can only give definite data on the enzyme ability of catalyzing acylation of **4** to give **5**; the reported enantiomeric excesses for **5** are, on the other hand, indicative, since Mosher's amides were prepared using DMAP as catalyst and we showed that the latter reagent can cause racemization of **5**.

Racemization in the presence of triethylamine should support the first hypothesis, while effect of DMAP should support the second one.

After we had nearly completed our project an analogous transformation on similar compounds was reported.[57]



Scheme 7.

small, but meaningful difference in the chemical shift of the methyl derived from alanine (the signal was differentiated when the spectrum was recorded on an equimolar mixture of **31a**,**b**). From these spectra we could exclude any racemization higher than 5% in the whole synthesis. A possible explanation for this different behaviour with respect to acetamide **5** can be given in terms of steric hindrance: passing from an unsubstituted to a substituted acyl group decreases the propensity of acyl migration from one amino group to the other. This steric inhibition should be enhanced by using more sterically encumbered amino acids than alanine (that is, most other proteinogenic amino acids) or bulkier *N*-protecting groups. In fact, it is likely that the protection of the amine functionality plays an important role in preventing (or minimizing) the racemization of monoacylated amines.

3. Conclusions

In this paper we have demonstrated that asymmetrized 2-substituted-1,3-propanediamines, despite their simple structure, are not easy to obtain and, most of all, their prochiral precursors are not substrates for enzymes usually able to form or cleave amide bonds. The configurational stability of these compounds is ensured provided that a carbamate moiety or an acyl derived from an amino acid is present in the molecule. Although carbamates **24**, (*R*)-**43** and (*S*)-**43** could not be obtained by direct enzyme-catalyzed manipulation of **4**, they were, anyway, accessible by a simple synthetic sequence, characterized by excellent yields in every step, starting from **12**. In these compounds the two amino groups are differentiated and could be elaborated independently. Moreover, since both benzyl and *tert*-butoxycarbonyl carbamates (that is, protecting groups with orthogonal properties) are available, a huge variety of differently *N*-protected amino acids can be used in the acylation step.

This fact enables the synthesis of compounds like **30** in high enantiomeric excess. The structure of these compounds, together with the nature of the reactions performed, makes the preparation of bisacylated amines very attractive from a combinatorial point of view, either in solution or in the solid phase. In this case, analogues of **24** or **43** had to be employed, most of all for the solid phase approach: a hydroxy or a 4-hydroxyphenyl group in position 2 with respect to the amino groups seem to be the most promising for bonding our intermediates to a polymer through a linker. Studies in this field are in progress and will be presented in due course.

4. Experimental

4.1. General

NMR spectra were taken in $CDCl_3$, at 200 MHz (^1H), and 50 MHz (^{13}C), using TMS as an internal standard. Chemical shifts are reported in ppm (δ scale), and coupling constants are reported in hertz. Peak assignment in ^1H NMR spectra was also made with the aid of double resonance experiments. In ABX systems, the proton A is considered downfield and B upfield. Peak assignment in ^{13}C spectra was made with the aid of DEPT experiments. GC–MS was carried out on an HP-5971A instrument, using an HP-1 column (12 m long, 0.2 mm wide), electron impact at 70 eV, and a mass temperature of about 170°C. Unless otherwise indicated analyses were performed with a constant He flow of 0.9 ml/min, init. temp. 100°C, init. time 2 min, rate 20°C/min, final temp. 260°C, final time 4 min, inj. temp. 250°C, det. temp. 280°C. IR spectra were measured with a Perkin–Elmer 881 instrument as $CHCl_3$ solutions. Values of $[\alpha]_D$ were determined on a Jasco DIP 181 polarimeter, in $CHCl_3$ (containing 0.75–1% EtOH) solution. Enantiomeric excesses of **5** as diastereomeric ratios of **7** were determined on the corresponding Mosher's amides using a Carlo Erba Fractovap gas chromatograph equipped with an RSL-150 column (25 m long, 0.25 mm wide). Melting points were determined on a Büchi 535 apparatus and are uncorrected. TLC analyses were carried out on silica gel plates which were developed by these detection methods: (**A**) UV; (**B**) dipping into a solution of $(NH_4)_4MoO_4 \cdot 4H_2O$ (21 g) and $Ce(SO_4)_2 \cdot 4H_2O$ (1 g) in H_2SO_4 (31 ml) and H_2O (469 ml) and warming; (**C**) dipping into 48% aqueous HBr, warming and then dipping into a solution of ninhydrin [900 mg into *n*-butanol (300 ml) and acetic acid (9 ml)], followed by warming again; and (**D**) dipping into a 2% aqueous $KMnO_4$ solution and warming. R_f was measured after an elution of 7–9 cm. Chromatographies were carried out on 220–400 mesh silica gel (if not otherwise specified) using the 'flash' methodology. Petroleum ether (40–60°C) is abbreviated as PE. In extractive work-up, aqueous solutions were always re-extracted three times with the appropriate organic solvent. Organic extracts were washed with brine, dried over Na_2SO_4 and filtered, before evaporation of the solvent under reduced pressure. All reactions employing dry solvents were carried out under a nitrogen atmosphere. The purity of all compounds was established by TLC, ^1H NMR, GC–MS. Lipase from recombinant *Candida antarctica* was a kind gift from Novo Nordisk. Lipase Amano P and acylase from *Aspergillus melleus* were kindly donated by Amano. Penicillin G acylase was kindly given by Recordati. Lipase from *Candida cylindracea*, PPL and papain were purchased from Sigma, while PLE was purchased from Fluka.

4.2. 2-Benzyl-1,3-propanediol *1*

This known compound[48] was prepared by an improved procedure, as reported by us for similar compounds in 94% yield.[51]

4.3. General procedure for the synthesis of mesylates *2*, *13*, *16*, *22* and *41*

The appropriate diol **1** or alcohols **12**, **15**, **21** and **40** (10 mmol) were dissolved in dry CH_2Cl_2 (25 ml) and cooled to −30°C. Triethylamine was added (25 mmol for **1**, 13 mmol in all other cases), followed by methanesulfonyl chloride (23 mmol for **1**, 12 mmol in all other cases). After stirring at the same temperature for 2–2.5 h the reaction was quenched by adding saturated aqueous NH_4Cl. Extraction with Et_2O and solvent evaporation gave crude mesylates, used as such in the next reaction. Their identity was proven by GC–MS (when feasible) or ^1H NMR or both.

*4.3.1. 2-Benzyl-1,3-bis(methanesulfonyloxy)propane **2***

R_f 0.44 (Et_2O, **A**, **B**). GC–MS: R_t 9.54; *m/z*: 226 ($M^+-CH_3SO_3H$, 6.9), 185 (22), 131 (117), 130 (100), 129 (36), 117 (24), 116 (5.2), 115 (22), 107 (6.2), 104 (7.3), 92 (6.3), 91 (62), 79 (20), 65 (9.8). ^{1}H NMR (on crude **2**): 2.42–2.55 (1H, m, >C*H*($CH_2OMs)_2$), 2.76 (2H, d, -CH_2Ph, J=7.7), 3.03 (6H, s, -SO_2CH_3), 4.19 and 4.28 (4H, AB part of ABX system, -CH_2OMs, J_{AB}=10.0, J_{AX} and J_{BX}=4.2, 6.2), 7.17–7.38 (5H, m, aromatics).

*4.3.2. (S)-1-Acetoxy-2-benzyl-3-(methanesulfonyloxy)propane **13***

R_f 0.52 (PE:AcOEt 4:6, **A**, **B**). GC–MS: R_t 8.20; *m/z*: 226 ($M^+-CH_3CO_2H$, 2.8), 190 (17), 185 (15), 149 (7.2), 131 (14), 130 (100), 129 (40), 117 (30), 116 (5.5), 115 (22), 107 (8.0), 104 (11), 92 (5.6), 91 (46), 79 (7.6), 65 (6.6), 43 (39).

*4.3.3. (R)-(N-Acetyl)-2-benzyl-3-(methanesulfonyloxy)propanamine **16***

R_f 0.48 (AcOEt+2% MeOH, **A**, **B**). GC–MS: R_t 5.70 (this most likely represents compound **18**, formed by thermal decomposition of **16**); *m/z*: 189 ($M^+-CH_3CO_2H$, 5.3), 130 (5.7), 119 (5.5), 118 (63), 117 (100), 115 (12), 98 (47), 92 (7.0), 91 (25), 72 (14), 65 (9.3), 56 (13), 51 (5.1), 43 (24), 42 (6.6), 39 (8.4). ^{1}H NMR (on crude **16**): 1.97 (3H, s, -COCH_3), 2.25–2.41 (1H, m, >C*H*CH_2OMs), 2.58–2.80 (2H, m, -CH_2Ph), 3.02 (3H, s, -SO_2CH_3), 3.14–3.53 (2H, m, -CH_2NHAc), 4.03 and 4.24 (2H, AB part of ABX system, -C$H_2OSO_2CH_3$, J_{AB}=10.2, J_{AX} and J_{BX}=3.9, 4.4), 5.93 (1H, br s, -N*H*Ac), 7.11–7.35 (5H, m, aromatics).

*4.3.4. (R)-2-Benzyl-[N-(benzyloxycarbonyl)]-3-(methanesulfonyloxy)propanamine **22***

R_f 0.41 (PE:Et_2O 3:7, **A**, **B**). GC–MS: **21** is not thermally stable and was quantitatively transformed into **26** (R_t 4.98 min) and **27** (R_t 8.31 min). ^{1}H NMR (on crude **21**): 2.20–2.38 (1H, m, >C*H*CH_2OMs), 2.65 and 2.72 (2H, AB part of ABX system, -CH_2Ph, J_{AB}=13.2, J_{AX} and J_{BX}=5.4, 9.1), 2.97 (3H, s, -SO_2CH_3), 3.14–3.45 (2H, m, -CH_2NHZ), 4.05 and 4.23 (2H, AB part of ABX system, -C$H_2OSO_2CH_3$, J_{AB}=10.1, J_{AX} and J_{BX}=3.9, 4.7), 5.02–5.20 (1H, m, -N*H*Z), 5.08 and 5.11 (2H, AB system, -OCH_2Ph, J=12.3), 5.11 (1H, broad s, -N*H*Z), 7.16–7.35 (10H, m, aromatics).

*4.3.5. (R)-2-Benzyl-3-[(tert-butoxycarbonyl)amino]propanol **41***

R_f 0.43 (PE:Et_2O 3:7, **A**, **B**). GC–MS: **41** is not thermally stable and was quantitatively transformed into **27** (R_t 8.31 min). ^{1}H NMR (on crude **41**): 1.44 (9H, s, -C($CH_3)_3$), 2.16–2.34 (1H, m, >C*H*CH_2OMs), 2.64 and 2.72 (2H, AB part of ABX system, -CH_2Ph, J_{AB}=13.6, J_{AX} and J_{BX}=6.5, 8.3), 3.00 (3H, s, -SO_2CH_3), 3.06–3.44 (2H, m, -CH_2NHBoc), 4.06 and 4.23 (2H, AB part of ABX system, -C$H_2OSO_2CH_3$, J_{AB}=10.0, J_{AX} and J_{BX}=4.0, 4.5), 4.82 (1H, br t, -N*H*Boc, J=5.6), 7.17–7.36 (5H, m, aromatics).

*4.4. General procedure for the synthesis of azides **3**, **14**, **17**, **23** and **42***

The appropriate crude bis(mesylate) **2** or mesylates **13**, **16**, **22** and **41** (10 mmol) were dissolved in dry DMF (30–40 ml) and treated with sodium azide (30 mmol for **2**, 20 mmol in all other cases, based on starting alcohol). The resulting suspension was heated at 50°C until reaction was judged complete by TLC (usually 15–20 h). The crude mixture was then diluted with water and extracted with ether. Compound **3**, due to its potential explosive properties,[11] was concentrated carefully, without removing all the solvent and immediately reduced to diamine **4**. Differently, all other azides were purified and identified as reported.

*4.4.1. 2-Benzyl-1,3-diazidopropane **3***

R_f 0.55 (PE:Et_2O 3:7, **A**, **B**). GC–MS: R_t 6.22; *m/z*: 188 (M^+-N_2, 0.74), 159 (9.0), 146 (26), 133 (6.0), 132 (28), 131 (13), 130 (53), 119 (5.3), 118 (15), 117 (50), 116 (6.3), 115 (23), 105 (20), 104 (45), 103 (25), 102 (5.0), 92 (12), 91 (100), 89 (8.2), 80 (5.3), 79 (22), 78 (30), 77 (49), 76 (5.0), 69 (5.5), 65 (45), 64 (5.2), 63 (15), 56 (9.2), 54 (8.8), 52 (13), 51 (43), 50 (16), 42 (20), 41 (43), 40 (6.7), 39 (42), 38 (5.6).

*4.4.2. (*R*)-1-Acetoxy-3-azido-2-benzylpropane **14***

Chromatography with PE:Et_2O 9:1→7:3 gave **14** as a pale yellow oil with 96% overall yield from **12**. R_f 0.44 (PE:Et_2O 8:2, **A**, **B**). $[\alpha]_D$=−9.36 (*c* 1.66). IR: ν_{max} 2997, 2937, 2862, 2111, 1728, 1602, 1492, 1450, 1389, 1368, 1192, 1037. GC–MS: R_t 6.53; *m/z*: 205 (M^+-N_2, 2.2), 146 (30), 145 (6.0), 144 (24), 134 (6.1), 133 (5.7), 132 (15), 130 (10), 118 (8.3), 117 (39), 116 (8.3), 115 (19), 105 (11), 104 (11), 92 (9.9), 91 (48), 78 (7.8), 77 (9.2), 65 (13), 51 (6.6), 43 (100), 41 (7.9), 39 (7.2). ^{1}H NMR: 2.08 (3H, s, -CH_3), 2.21 (1H, centre of m, >C*H*CH_2OAc), 2.68 (2H, d, -CH_2Ph, *J*=7.4), 3.32 and 3.37 (2H, AB part of ABX system, -CH_2N_3, J_{AB}=12.3, J_{AX} and J_{BX}=5.3, 5.8), 4.01 and 4.09 (2H, AB part of ABX system, -CH_2OCOCH_3, J_{AB}=11.2, J_{AX} and J_{BX}=5.0, 6.7), 7.15–7.36 (5H, m, aromatics). ^{13}C NMR: 20.71 (-*C*H_3), 35.14 (-*C*H_2Ph), 39.88 (>*C*HCH_2OAc), 51.86 (-*C*H_2N_3), 64.23 (-*C*H_2OAc), 126.49 (>*C*H- *para* to -CH_2-), 128.59 (2C, >*C*H- *meta* to -CH_2-), 128.98 (2C, >*C*H- *ortho* to -CH_2-), 138.52 (>*C*<, *ipso*), 170.65 (2C, >*C*=O).

*4.4.3. (*R*)-(*N*-Acetyl)-3-azido-2-benzylpropanamine **17***

Chromatography with PE:AcOEt 3:7→2:8 gave **17** as a yellow oil in 45% overall yield from **15**. R_f 0.27 (PE:AcOEt 3:7, **A**, **B**). $[\alpha]_D$=+6.97 (*c* 1.58). IR: ν_{max} 3446, 2997, 2930, 2861, 2102, 1668, 1603, 1495, 1450, 1266. GC–MS: R_t 7.82; *m/z*: 204 (M^+-N_2, 2.7), 146 (8.7), 145 (12), 144 (31), 133 (29), 132 (100), 131 (7.2), 130 (16), 129 (5.5), 128 (5.4), 118 (23), 117 (77), 116 (24), 115 (27), 106 (5.6), 105 (5.7), 104 (7.7), 103 (5.2), 98 (13), 92 (5.4), 91 (50), 84 (22), 77 (8.2), 73 (25), 72 (16), 71 (6.0), 65 (9.1), 60 (10), 57 (5.3), 56 (8.6), 43 (31). ^{1}H NMR: 1.95 (3H, s, -CH_3), 2.11 (1H, centre of m, >C*H*CH_2N_3), 2.65 (2H, d, -CH_2Ph, *J*=7.5), 3.22–3.40 (4H, m, -CH_2N_3 and -CH_2NHAc), 5.77 (1H, broad s, -N*H*-), 7.14–7.36 (5H, m, aromatics). ^{13}C NMR: 23.15 (-*C*H_3), 36.46 (-*C*H_2Ph), 40.44 (>*C*HCH_2N_3), 41.65 (-*C*H_2N_3), 53.03 (-*C*H_2NHAc), 126.45 (>*C*H- *para* to-CH_2-), 128.62 (2C, >*C*H- *meta* to -CH_2-), 128.97 (2C, >*C*H- *ortho* to -CH_2-), 138.94 (>*C*<, *ipso*), 170.26 (>*C*=O).

*4.4.4. (*R*)-3-Azido-2-benzyl-[*N*-(benzyloxycarbonyl)]propanamine **23***

Chromatography with PE:Et_2O 6:4→1:1 gave **23** as a pale yellow oil in 92% overall yield from **21**. R_f 0.56 (PE:Et_2O 1:1, **A**, **B**). $[\alpha]_D$=+3.21 (*c* 4.90). IR: ν_{max} 3447, 3004, 2931, 2101, 1718, 1603, 1501, 1452, 1192. GC–MS: R_t 10.67; *m/z*: 296 (M^+-N_2, 0.6), 205 (7.88), 144 (9.3), 133 (8.6), 132 (35), 117 (24), 115 (5.4), 108 (6.1), 92 (9.3), 91 (100), 79 (6.1), 77 (6.5), 74 (7.6), 65 (11). ^{1}H NMR: 2.09 (1H, centre of m, >C*H*CH_2N_3), 2.61 and 2.66 (2H, AB part of ABX system, -CH_2Ph, J_{AB}=13.9, J_{AX} and J_{BX}=6.9, 7.9), 3.12–3.40 (4H, m, -CH_2N_3+-CH_2NHZ), 4.92 (1H, broad s, -N*H*-), 5.10 (2H, s, -CO_2CH_2Ph), 7.14–7.38 (10H, m, aromatics). ^{13}C NMR: 36.08 (-*C*H_2Ph), 40.75 (>*C*HCH_2N_3), 42.94 (-*C*H_2NHZ), 52.60 (-*C*H_2N_3), 66.86 (-CO_2*C*H_2Ph), 126.46 (>*C*H- *para* to -CH_2CH<), 128.08 (2C, >*C*H- *ortho* to -CH_2O-), 128.13 (>*C*H- *para* to -CH_2O-), 128.52 (2C, >*C*H- *meta* to -CH_2O-), 128.62 (2C, >*C*H- *meta* to -CH_2CH<), 128.99 (2C, >*C*H- *ortho* to -CH_2CH<), 136.53 (>*C*<, *ipso* of -CO_2CH_2Ph), 138.84 (>*C*<, *ipso* of -CH_2Ph), 156.53 (>*C*=O).

*4.4.5. (*R*)-3-Azido-2-benzyl-[*N*-(*tert*-butoxycarbonyl)]propanamine **42***

Chromatography with PE:Et_2O 9:1→100% Et_2O gave **42** as a white solid in 91% overall yield from **30**. It was crystallized from PE. Mp=56.0–56.3°C (PE). R_f 0.41 (PE:Et_2O 7:3, **A**, **C**). $[\alpha]_D$=+5.80 (*c* 3.84). IR: ν_{max} 3451, 2968, 2926, 2098, 1705, 1604, 1491, 1448, 1390, 1197, 1162, 850. GC–MS: R_t 8.45; *m/z*: 262 (M^+-N_2, 0.23), 146 (6.3), 144 (5.6), 133 (8.5), 132 (45), 130 (6.5), 118 (8.5), 117 (15), 116 (22), 115 (7.1), 105 (5.5), 102 (12), 91 (24), 74 (7.0), 65 (5.2), 59 (9.8), 58 (6.4), 57 (100), 41 (22), 39 (6.3). ^{1}H NMR: 1.44 (9H, s, -C(C*H*$_3$)$_3$), 1.96–2.17 (1H, m, >C*H*CH$_2$N$_3$), 2.61 and 2.66 (2H, AB part of ABX system, -C*H*$_2$Ph, J_{AB}=13.9, J_{AX} and J_{BX}=6.6, 8.2), 3.04–3.27 (2H, m, -C*H*$_2$NHBoc), 3.27 and 3.34 (2H, AB part of ABX system, -C*H*$_2$N$_3$, J_{AB}=12.6, J_{AX} and J_{BX}=5.7, 5.7), 4.68 (1H, broad s, -N*H*-), 7.13–7.35 (5H, m, aromatics). ^{13}C NMR: 28.35 (3C, -C(*C*H$_3$)$_3$), 36.01 (-*C*H$_2$Ph), 40.79 (>*C*HCH$_2$N$_3$), 42.34 (-*C*H$_2$NHBoc), 52.44 (-*C*H$_2$N$_3$), 79.42 (-*C*(CH$_3$)$_3$), 126.34 (>*C*H- *para* to -CH$_2$-), 128.55 (2C, >*C*H- *meta* to -CH$_2$-), 129.00 (2C, >*C*H- *ortho* to -CH$_2$-), 138.98 (>*C*<, *ipso*), 156.01 (>*C*=O).

*4.5. 2-Benzyl-1,3-propanediamine **4***

(a) From bis(azide) **3**: The above prepared solution of **3** in ether (about 20 ml) was diluted with THF (34 ml) and treated with water (2 ml) and triphenylphosphine (7.87 g, 30.0 mmol) at room temperature. After the development of nitrogen ceased (a few minutes required) the solution was stirred at 50°C for about 20 h. After cooling to room temperature, the pH was adjusted to 1 by careful addition of 1N HCl. Non-basic organic compounds were extracted with CH_2Cl_2; since **4** has a great affinity for water it was not possible to quantitatively extract the diamine from aqueous solution. Solutions of **4** as bis(hydrochloride) were then directly used for bisacylation reactions, leading to **8**, **9**, **10** and **11**, as described later.

(b) From bis(benzyloxycarbonyl) derivative **9**: Compound **9** (1.00 g, 2.31 mmol) was dissolved in methanol (15 ml), treated with Pd/C (10%, 150 mg) and hydrogenated at 1 atm for 30 min. The catalyst was filtered and the solvent was removed in vacuo. The resulting diamine, obtained in quantitative yield as a pale yellow oil, was very pure and was used without further purification. R_f≈0.15 (MeOH:Et_3N 9:1, elongated spot, **A**, **C**). IR: ν_{max} 3386, 3319, 2926, 2864, 1601, 1492, 1453. GC–MS: R_t 5.28; *m/z*: 164 (M^+, 0.026), 118 (14), 117 (27), 91 (14), 65 (5.1), 56 (100). ^{1}H NMR: 1.75 (1H, centre of m, -C*H*(CH$_2$NH$_2$)$_2$), 2.61 (2H, d, -C*H*$_2$Ph, *J*=7.3), 2.67–2.80 (4H, m, -C*H*$_2$NH$_2$), 7.16–7.32 (5H, m, aromatics). ^{13}C NMR: 36.67 (-*C*H$_2$Ph), 43.30 (2C, -*C*H$_2$NH$_2$), 44.91 (>*C*HCH$_2$Ph), 125.90 (>*C*H-, *para* to -CH$_2$), 128.31 (2C, >*C*H-, *meta* to -CH$_2$), 128.96 (2C, >*C*H-, *ortho* to -CH$_2$), 140.33 (>*C*<, *ipso*).

*4.6. (*N*-Acetyl)-2-benzyl-1,3-propanediamine **5***

(a) (*R*)-**5** and (*S*)-**5** by enzyme-catalyzed acylation: Diamine **4** (100 mg, 609 μmol) was dissolved in 5 ml of the suitable solvent (see Table 1) and stirred at room temperature for 15 min in the presence of 15 mg of powdered 3 Å molecular sieves. The mixture was cooled to the desired reaction temperature and, if not used as cosolvent, the acylating agent was added, followed by the enzyme. After stirring for the desired time, the enzyme was filtered and the solution concentrated in vacuo. Chromatography (for this compound 70–230 mesh silica was used) with AcOEt:MeOH 1:1→AcOEt:MeOH 1:1+10% Et_3N gave pure **5** slightly enriched in the (*R*)- or (*S*)-enantiomer as a pale yellow oil.

(b) (*S*)-**5** from **17**: Compound **17** (737 mg, 3.17 mmol) was dissolved in THF (16 ml) and treated with water (1.2 ml) and triphenylphosphine (1.25 g, 4.77 mmol). After the development of nitrogen ceased (some minutes required) the solution was stirred at 50°C for about 6 h. The pH was adjusted to 10 by addition of 1N NaOH and the extraction was performed with AcOEt. The crude product was purified by chromatography and 600 mg of (*S*)-**5** were obtained (92% yield). Due to the configurational instability

of **5** no $[\alpha]_D$ was reported, although it is possible to say that the (*R*)-enantiomer is dextrorotatory, while the (*S*)-enantiomer is levorotatory.

(c) (*R*)-**5** from **25**: Compound **25** (102 mg, 300 μmol) was hydrogenated as described above for preparation of **4** from **9**. After chromatography, 58 mg of pure (*R*)-**5** were obtained in 94% yield.

R_f 0.39 (elongated spot, AcOEt:MeOH 1:1+8% Et_3N, **A**, **C**). IR: ν_{max} 3605, 3449, 2993, 2922, 1660, 1601, 1511, 1452, 1370, 1217. GC–MS: R_t 7.43; *m/z*: 206 (M^+, 4.8), 177 (23), 134 (35), 132 (5.4), 130 (9.7), 129 (5.3), 118 (49), 117 (100), 116 (8.6), 115 (40), 98 (12), 92 (5.0), 91 (42), 86 (5.1), 77 (5.1), 73 (99), 72 (8.4), 65 (12), 60 (30), 56 (70), 44 (12), 43 (42), 42 (5.0), 39 (6.4). ^{1}H NMR: 1.83–2.00 (1H, m, >C*H*CH_2NH_2), 1.93 (3H, s, -C*H*$_3$), 2.59 (2H, d, -C*H*$_2$Ph, *J*=7.4), 2.62 and 2.82 (2H, AB part of ABX system, -C*H*$_2NH_2$, J_{AB}=12.8, J_{AX} and J_{BX}=4.1, 7.4), 3.15–3.48 (2H, m, -C*H*$_2$NHAc, became AB part of ABX system after irradiating at 1.93; δ: ν_A 3.23 and ν_B 3.42, J_{AB}=13.7, J_{AX} and J_{BX}=5.3, 6.0), 6.66 (1H, broad s, -N*H*-), 7.15–7.34 (5H, m, aromatics). ^{13}C NMR: 23.08 (-*C*H_3), 36.98 (-*C*H_2Ph), 41.04 (>*C*HCH_2Ph), 41.36 (-*C*H_2NH_2), 42.78 (-*C*H_2NHAc), 126.31 (>*C*H-, *para* to -CH_2-), 128.52 (2C, >*C*H-, *meta* to -CH_2-), 128.92 (2C, >*C*H-, *ortho* to -CH_2-), 139.33 (>*C*<, *ipso*), 171.22 (>*C*=O).

*4.7. Acylation of crude enzymatic reaction mixture by Mosher's chloride to give **6**, **7** and **8***

Crude **5** (about 10 mg), in a mixture with diacetamide **8** and unreacted diamine **4**, as derived from enzymatic reactions, was dissolved in dry CH_2Cl_2 (1 ml) and treated with 4-dimethylaminopyridine (14 mg, 121 μmol) and (*R*)- or (*S*)-Mosher's chloride (23 μl, 121 μmol). After 1.5 h the mixture was concentrated and rapidly purified, without separation of the components, by filtration over silica gel, using AcOEt:MeOH 9:1 as eluent. The mixture was then analyzed by GLC (He pressure: 1.7 kg/cm^2; split ratio: 41:1; inj. 250°C; det. 250°C; init. temp.: 200°C for 40 min and then raising the temperature by 10°C/min until 290°C; final time 10 min), giving the following: R_t: 6.12 min for **8**; 38.92 min for **6** (*R*,*R*- or *S*,*S*-diastereoisomers) and 40.42 for **6** (*R*,*S*- or *S*,*R*-diastereoisomers) and 51.90 min for **7**.

*4.8. 2-Benzyl-(*N,N′*-diacetyl)-1,3-propanediamine **8***

An acidic aqueous solution of **4** (3.00 mmol based on starting diol **1**), obtained from **3** after work-up, was treated with 6N NaOH until pH 5 and mixed with $AcONa\cdot 3H_2O$ (6.81 g, 50.0 mmol), in order to maintain pH ≅4.5. After cooling to 0°C acetic anhydride (850 μl, 9.01 mmol) was added and, after 5 min, the reaction was allowed to stir at room temperature. Since the reaction was slow, two further portions of acetic anhydride (850 μl each) were added, and finally the pH was adjusted to 7 by addition of 6N NaOH and the mixture stirred again overnight. Extraction was performed with AcOEt and the crude product was purified by chromatography using AcOEt:MeOH 98:2→9:1 as eluent. In this way, 551 mg of **8** were obtained as a colourless oil in 74% overall yield from **1**. R_f 0.46 (AcOEt:MeOH 8:2, **A**). IR: ν_{max} 3446, 2994, 2931, 1659, 1515, 1437, 1369, 1281. GC–MS: R_t 8.87; *m/z*: 248 (M^+, 8.9), 177 (6.7), 176 (49), 157 (15), 146 (8.0), 134 (8.1), 132 (5.1), 130 (6.1), 118 (25), 117 (100), 116 (5.8), 115 (13), 98 (28), 91 (32), 73 (47), 72 (34), 65 (7.1), 60 (19), 56 (36), 44 (8.3), 43 (56). ^{1}H NMR: 1.97–2.04 (1H, m, -C*H*$(CH_2NHAc)_2$), 2.00 (6H, s, -C*H*$_3$), 2.56 (2H, d, -C*H*$_2$Ph, *J*=7.5), 2.97–3.41 (4H, m, -C*H*$_2$NHAc, became AB part of ABX system after irradiating at 6.38; δ: ν_A 3.04 and ν_B 3.34, J_{AB}=14.0, J_{AX} and J_{BX}=4.1, 7.1), 6.38 (2H, broad t, -N*H*Ac, *J*=4.9), 7.14–7.35 (5H, m, aromatics). ^{13}C NMR: 23.07 (2C, -*C*H_3), 39.76 (2C, -*C*H_2NHAc), 36.82 (-*C*H_2Ph), 39.76 (2C, -*C*H_2NHAc), 41.04 (-*C*H$(CH_2NHAc)_2$), 126.22 (>*C*H- *para* to -CH_2-), 128.46 (2C, >*C*H- *meta* to -CH_2-), 128.78 (2C, >*C*H- *ortho* to -CH_2-), 139.40 (>*C*< *ipso*), 171.02 (2C, >*C*=O).

4.9. Acylation of **4** under Schotten–Baumann conditions to give **9**, **10** and **11**

An acidic aqueous solution of **4** (3.00 mmol based on starting diol **1**), obtained from **3** after work-up, was treated with 6N NaOH until pH ≅9. After cooling to 0°C the appropriate acylating agent was added (benzyl chloroformate to obtain **9**, methyl chloroformate to obtain **10**, phenylacetyl chloride to obtain **11**, 7.5 mmol), and after 10 min the reaction was allowed to stir at room temperature, while pH was maintained at 9 by occasional addition of 1N NaOH. The reaction was usually complete in 2–6 h. After saturation with solid NaCl, the organic compounds were extracted with AcOEt.

4.9.1. 2-Benzyl-[N,N′-bis(benzyloxycarbonyl)]-1,3-propanediamine **9**

Chromatography with PE:Et_2O 65:35→1:1 gave pure **9** (80% overall yield from **1**), which was crystallized from Et_2O/ETP to give a pale yellow solid. Mp=87.9–88.4°C (PE/Et_2O). R_f 0.54 (PE:Et_2O 4:6, **A**, **B**). IR: ν_{max} 3448, 2998, 2940, 1713, 1503, 1453, 1248. GC–MS: **9** decomposes in the chromatographic column. ^{1}H NMR: 1.95–2.09 (1H, m, -C*H*($CH_2NHZ)_2$), 2.55 (2H, d, -C*H*$_2$Ph, *J*=7.6), 2.92–3.39 (4H, m, -C*H*$_2$NHZ, became AB part of ABX system after irradiating at 5.35; δ: ν_A 2.99 and ν_B 3.32, J_{AB}=14.4, J_{AX} and J_{BX}=4.0, 7.0), 5.10 (4H, s, 2 -CO_2C*H*$_2$Ph), 5.35 (2H, broad t, -N*H*-, *J*=5.9), 7.13–7.35 (15H, m, aromatics). ^{13}C NMR: 36.22 (-*C*H$_2$Ph), 41.25 (2C, -*C*H$_2$NHZ), 41.35 (-*C*H($CH_2NHZ)_2$), 66.74 (2C, -O*C*H$_2$Ph), 126.27 (>*C*H- *para* to -CH_2C*H*<), 127.97 (4C, >*C*H- *ortho* to -CH_2O-), 128.02 (2C, >*C*H- *para* to -CH_2O-), 128.44 (4C, >*C*H- *meta* to -CH_2O-), 128.55 (2C, >*C*H- *meta* to -CH_2C*H*<), 128.81 (2C, >*C*H- *ortho* to -CH_2C*H*<), 136.58 (2C, >*C*< *ipso* of -CO_2CH_2Ph), 139.31 (>*C*< *ipso* of -CH_2Ph), 157.07 (2C, >*C*=O).

4.9.2. 2-Benzyl-[N,N′-bis(methoxycarbonyl)]-1,3-propanediamine **10**

Chromatography with PE:Et_2O 2:8→Et_2O gave pure **10** (80% overall yield from **1**), which was crystallized from CH_2Cl_2/Et_2O to give a white solid. Mp=100.0–100.4°C (CH_2Cl_2/Et_2O). R_f 0.60 (Et_2O, **A**, **C**, **D**). IR: ν_{max} 3450, 2953, 1711, 1601, 1510, 1450, 1193, 906. GC–MS: R_t 8.87; *m/z*: 280 (M^+, 6.3), 205 (5.7), 192 (7.2), 160 (30), 131 (6.1), 130 (34), 129 (6.4), 118 (41), 117 (47), 116 (7.6), 115 (16), 114 (44), 104 (5.1), 102 (6.7), 92 (6.9), 91 (42), 89 (12), 88 (100), 76 (18), 74 (5.4), 65 (8.6), 59 (22), 56 (5.3), 44 (33), 42 (5.1). ^{1}H NMR: 1.93–2.07 (1H, m, -C*H*($CO_2CH_3)_2$), 2.56 (2H, d, -C*H*$_2$Ph, *J*=7.6), 2.93–3.36 (2H, m, -C*H*$_2$$CO_2CH_3$, became AB part of ABX system after irradiating at 5.33; δ: ν_A 3.00 and ν_B 3.29, J_{AB}=14.4, J_{AX} and J_{BX}=3.8, 7.1), 3.67 (6H, s, 2 -C*H*$_3$), 5.33 (2H, broad t, -N*H*-, *J*=5.1), 7.14–7.32 (5H, m, aromatics). ^{13}C NMR: 36.18 (-*C*H$_2$Ph), 41.08 (2C, -*C*H$_2$NHCO_2CH_3), 41.40 (-*C*H($CH_2NHCO_2CH_3)_2$), 52.06 (2C, -*C*H$_3$), 126.22 (>*C*H- *para* to -CH_2C*H*<), 128.49 (2C, >*C*H- *meta* to -CH_2C*H*<), 128.79 (2C, >*C*H- *ortho* to -CH_2C*H*<), 139.34 (>*C*< *ipso* of -CH_2Ph), 157.75 (2C, >*C*=O).

4.9.3. 2-Benzyl-[N,N′-bis(phenylacetyl)]-1,3-propanediamine **11**

Crude **11** was directly crystallized from AcOEt/Et_2O, giving a white solid (53% overall yield from **1**). Mp=137.3–138.1°C (AcOEt/Et_2O). R_f 0.34 (PE:AcOEt 3:7, **A**, **D**). IR: ν_{max} 3423, 2996, 2942, 1658, 1602, 1507, 1436, 1191, 1014. GC–MS: R_t 14.69 (usual conditions but with a final temp. of 290°C and final time of 4 min); *m/z*: 400 (M^+, 6.7), 309 (12), 252 (15), 191 (27), 174 (6.3), 149 (7.4), 148 (6.4), 146 (5.7), 118 (9.8), 117 (23), 115 (5.9), 92 (12), 91 (100), 65 (9.1), 56 (17), 44 (8.2). ^{1}H NMR: 1.84–2.01 (1H, m, -C*H*($CH_2NHCOCH_2Ph)_2$), 2.32 (2H, d, -C*H*$_2$Ph, *J*=7.7), 2.75–3.31 (4H, m, -C*H*$_2$NH-), 3.56 (4H, s, -COC*H*$_2$Ph), 6.19 (2H, broad t, -N*H*-, *J*=6.1), 6.84–7.42 (15H, m, aromatics). ^{13}C NMR: 36.40 (-*C*H$_2$Ph), 39.52 (2C, -*C*H$_2$NHCOCH$_2$Ph), 40.84 (-CH(*C*H$_2$NHCOCH$_2$Ph)$_2$), 43.82 (2C, -CO*C*H$_2$Ph), 126.19 (>*C*H- *para* to -CH_2C*H*<), 127.12 (>*C*H- *para* to -CH_2CO-), 128.48 (2C,

>*C*H- *meta* to -CH_2CH<), 128.61 (2C, >*C*H- *ortho* to -CH_2CH<), 128.82 (2C, >*C*H- *meta* to-CH_2CO-), 129.16 (2C, >*C*H- *ortho* to -CH_2CO-), 135.14 (>*C*< *ipso* of -CH_2CO-), 139.12 (>*C*< *ipso* of -CH_2Ph), 171.80 (2C, >*C*=O).

*4.10. (*R*)-3-Acetoxy-2-benzyl-1-propanol **12***

A slightly different procedure was followed with respect to a literature report in order to prepare the known **12**.[51] A suspension of crystallized diol **1** (5.10 g, 30.7 mmol) in a mixture of isopropyl ether (117 ml) and vinyl acetate (8 ml) was treated with powdered 3 Å molecular sieves (520 mg) and stirred at 25°C for 15 min. Then lipase Amano P supported on Celite (5.10 g), following our reported protocol for PPL,[51] was added and the mixture stirred at the same temperature for 5.7 h. The enzyme was filtered, washed with CH_2Cl_2 and the organic solution was concentrated in vacuo. Chromatography with PE:Et_2O 4:6→Et_2O gave **12** as a pale yellow oil (6.05 g, 95% yield) with 95.9% enantiomeric excess.

*4.11. (*R*)-3-(*N*-Acetylamino)-2-benzyl-1-propanol **15***

Azide **14** was transformed into **15** following the same procedure used for diazide **3**, using in this case 1.5 mmol of PPh_3/mmol of **14**. After 6 h at 50°C the product was extracted with AcOEt and purified by chromatography with AcOEt→AcOEt:MeOH 9:1 to give **15** in 97% overall yield from **12**. This compound was crystallized from CH_2Cl_2/Et_2O to give a pale yellow solid. Mp=75.6–76.9°C (CH_2Cl_2/Et_2O). R_f 0.33 (AcOEt+3% MeOH, **A**, **B**). $[\alpha]_D$=−24.21 (*c* 1.59). IR: ν_{max} 3450, 2995, 2933, 2992, 1657, 1603, 1510, 1439, 1273, 1044, 992. GC–MS: R_t 7.55; *m/z*: 207 (M^+, 1.7), 189 (33), 132 (5.1), 131 (7.8), 130 (61), 129 (13), 118 (27), 117 (82), 116 (10), 115 (18), 104 (8.1), 98 (46), 92 (12), 91 (59), 85 (24), 78 (6.7), 77 (9.6), 74 (12), 73 (100), 72 (40), 65 (17), 60 (22), 57 (6.3), 56 (32), 51 (7.9), 45 (9.6), 44 (10), 43 (73), 42 (6.3), 41 (5.3), 39 (9.0). ^{1}H NMR: 1.83–1.99 (1H, m, >C*H*(CH_2OH)), 2.01 (3H, s, -CH_3), 2.53 and 2.67 (2H, AB part of ABX system, -CH_2Ph, J_{AB}=13.6, J_{AX} and J_{BX}=7.3, 7.8), 3.17–3.38 (2H, m, -CH_2NHAc), 3.39 and 3.56 (2H, AB part of ABX system, -CH_2OH, J_{AB}=12.3, J_{AX} and J_{BX}=3.6, 6.7), 3.80 (1H, broad s, -O*H*), 5.87 (1H, broad s, -N*H*-), 7.15–7.35 (5H, m, aromatics). ^{13}C NMR: 22.87 (-*C*H_3), 35.63 (-*C*H_2Ph), 40.32 (-*C*H_2NH-), 42.91 (>*C*H(CH_2OH)), 62.16 (-*C*H_2OH), 126.09 (>*C*H- *para* to -CH_2CH<), 128.40 (2C, >*C*H- *meta* to -CH_2CH<), 128.86 (2C, >*C*H *-ortho* to -CH_2CH<), 139.78 (>*C*< *ipso*), 171.80 (>*C*=O).

*4.12. (*R*)-3-Azido-2-benzyl-1-propanol **19***

Azide **14** (4.40 mg, 18.9 mmol) was dissolved in THF (45 ml); then 135 ml of 0.067 M pH 7 buffer solution were added, followed by unsupported lipase Amano P (1.51 g). The resulting biphasic system was stirred at room temperature for about 22 h, while the pH was adjusted to 7, when necessary, by addition of 1N NaOH. The enzyme was filtered over a Celite pad, and an extraction with Et_2O was performed. The crude compound was then purified by chromatography, using PE:Et_2O 8:2→Et_2O as eluent to give **19** as a yellow oil (3.58 g, 99% yield). R_f 0.27 (PE:Et_2O 6:4, **A**, **B**). $[\alpha]_D$=−35.16 (*c* 1.06). IR: ν_{max} 3622, 3007, 2930, 2100, 1602, 1492, 1450, 1285, 1029. GC–MS: R_t 5.96; *m/z*: 163 (M^+−N_2, 3.9), 162 (8.5), 146 (9.7), 144 (7.9), 133 (5.8), 132 (25), 130 (6.4), 118 (7.6), 117 (21), 115 (14), 106 (10), 105 (28), 104 (19), 103 (7), 92 (29), 91 (100), 79 (10), 78 (18), 77 (17), 65 (22), 63 (5.2), 51 (11), 41 (5.3), 39 (9.1). ^{1}H NMR: 2.06 (1H, centre of m, >C*H*CH_2OH), 2.65 and 2.71 (2H, AB part of ABX system, -CH_2Ph, J_{AB}=13.8, J_{AX} and J_{BX}=7.46, 7.50), 3.37 and 3.44 (2H, AB part of ABX system, -CH_2N_3, J_{AB}=12.3, J_{AX} and J_{BX}=5.1, 6.5), 3.60 and 3.68 (2H, AB part of ABX system, -CH_2OH, J_{AB}=10.8,

J_{AX} and J_{BX}=4.5, 6.3, determined after exchange with D_2O), 7.15–7.36 (5H, m, aromatics). ^{13}C NMR: 34.98 (-*C*H_2Ph), 42.58 (>*C*HCH$_2$OH), 52.16 (-*C*H_2N_3), 62.86 (-*C*H_2OH), 126.29 (>CH- *para* to -CH_2), 128.50 (2C, >CH- *meta* to -CH_2), 129.00 (2C, >CH- *ortho* to -CH_2), 139.20 (>C< *ipso*).

4.13. (R)-3-Amino-2-benzyl-1-propanol **20**

The same procedure described above for compound **15** was followed. At the end of the reaction, the pH was adjusted to 1 by addition of 1N HCl and the non-basic products were extracted with CH_2Cl_2. It was not possible to extract **20** from the basic aqueous solution and so it was used as such for the next reaction. R_f 0.33 (elongated spot, MeOH:Et_3N 9:1, **A**).

4.14. Acylation of **20** under Schotten–Baumann conditions to give **21** and **40**

The same procedure reported above for compounds **9**, **10** and **11** was followed, using, respectively, benzyl chloroformate to obtain **21** and di-*tert*-butyl dicarbonate to obtain **40**.

4.14.1. (R)-2-Benzyl-3-[N-(benzyloxycarbonyl)amino]-1-propanol **21**

Chromatography with PE:Et_2O 6:4→2:8 gave **21** as a pale yellow oil (94% overall yield from **19**). R_f 0.41 (PE:Et_2O 3:7, **A**, **B**). $[\alpha]_D$=−23.51 (*c* 1.83). IR: ν_{max} 3449, 3000, 2928, 1702, 1602, 1505, 1452, 1195, 1028. GC–MS: R_t 10.54; *m/z*: 299 (M^+, 0.097), 190 (10), 178 (9.0), 129 (7.8), 118 (9.5), 117 (67), 108 (14), 107 (9.8), 100 (6.3), 92 (19), 91 (100), 79 (15), 77 (11), 74 (13), 65 (12), 51 (5.8), 39 (6.0). ^1H NMR: 1.86–2.03 (1H, m, >C*H*CH$_2$OH), 2.52 and 2.65 (2H, AB part of ABX system, -C*H*$_2$Ph, J_{AB}=13.7, J_{AX} and J_{BX}=7.6, 7.7), 3.11–3.39 (2H, m, -C*H*$_2$NHZ), 3.42 and 3.59 (2H, AB part of ABX system, -C*H*$_2$OH, J_{AB}=11.8, J_{AX} and J_{BX}=3.6, 6.2, determined after exchange with D_2O), 5.03 (1H, broad dt, -N*H*-, *J*=2.2, 6.4), 5.11 (2H, s, -CO$_2$C*H*$_2$Ph), 7.14–7.35 (10H, m, aromatics). ^{13}C NMR: 35.42 (-*C*H_2Ph), 41.49 (-*C*H_2NHZ), 43.33 (>*C*HCH$_2$OH), 62.50 (-*C*H_2OH), 67.09 (-CO$_2$*C*H_2Ph), 126.24 (>*C*H- *para* to -CH_2CH<), 128.12 (2C, >*C*H- *ortho* to -CH_2O-), 128.22 (>*C*H- *para* to -CH_2O-), 128.58 (4C, >*C*H- *meta* to -CH_2CH< and *meta* to -CH_2O-), 128.97 (2C, >*C*H- *ortho* to -CH_2CH<), 136.48 (>*C*< *ipso* of -CO$_2$CH$_2$Ph), 139.77 (>*C*< *ipso* of -CH_2Ph), 157.72 (>*C*=O).

4.14.2. (R)-2-Benzyl-3-[N-(tert-butoxycarbonyl)amino]-1-propanol **40**

Chromatography with PE:Et_2O 6:4→3:7 gave **40** (96% overall yield from **19**), which was crystallized from *i*-Pr_2O/PE to give a white solid. Mp=70.4–70.7°C (*i*-Pr_2O/PE). R_f 0.58 (PE:Et_2O 3:7, **A**, **C**). $[\alpha]_D$=−26.24 (*c* 2.22). IR: ν_{max} 3453, 3039, 2931, 1686, 1602, 1494, 1444, 1367, 1157. GC–MS: R_t 8.20; *m/z*: 265 (M^+, 0.059), 209 (5.2), 192 (8.7), 191 (38), 131 (16), 130 (100), 118 (29), 117 (33), 115 (5.2), 104 (6.2), 100 (6.5), 92 (11), 91 (36), 74 (15), 65 (5.7), 59 (19), 58 (5.0), 57 (99), 56 (6.8), 41 (22), 39 (6.6). ^1H NMR: 1.45 (9H, s, -C(C*H*$_3$)$_3$), 1.84–1.98 (1H, m, >C*H*CH$_2$OH), 2.51 and 2.64 (2H, AB part of ABX system, -C*H*$_2$Ph, J_{AB}=13.7, J_{AX} and J_{BX}=7.5, 8.0), 3.02–3.32 (2H, m, -C*H*$_2$NHBoc), 3.40 and 3.58 (2H, AB part of ABX system, -C*H*$_2$OH, J_{AB}=11.9, J_{AX} and J_{BX}=3.8, 6.3, determined after exchange with D_2O), 4.79 (1H, broad t, -N*H*-, *J*=6.6), 7.15–7.34 (5H, m, aromatics). ^{13}C NMR: 28.34 (3C, -C(*C*H$_3$)$_3$), 35.35 (-*C*H_2Ph), 40.31 (-*C*H_2NHBoc), 43.58 (>*C*HCH$_2$OH), 61.99 (-*C*H_2OH), 79.94 (-*C*(CH$_3$)$_3$), 126.13 (>*C*H- *para* to -CH_2CH<), 128.49 (2C, >*C*H- *meta* to -CH_2CH<), 128.95 (2C, >*C*H- *ortho* to -CH_2CH<), 139.92 (>*C*< *ipso* of -CH_2Ph), 157.60 (>*C*=O).

4.15. (S)-2-Benzyl-[N-(benzyloxycarbonyl)]-1,3-propanediamine **24**

The same procedure described above for compound **15** was followed. In this case non-basic products could not be extracted selectively, probably due to the low basicity of **24**. The crude reaction mixture was then directly extracted with AcOEt. Chromatography (70–230 mesh silica was used) with AcOEt, AcOEt:MeOH 1:1→AcOEt:MeOH 1:1+2% Et_3N gave pure **24** as a pale yellow oil (98% yield). R_f 0.40 (AcOEt:MeOH 1:1+2% Et_3N, **A**, **B**). $[\alpha]_D$=−15.78 (*c* 1.56). IR: ν_{max} 3448, 3312, 3029, 2929, 1712, 1600, 1497, 1453, 1372, 1245. GC–MS: R_t 10.45 (usual conditions but with a final temp. of 290°C and a final time of 4 min); *m/z*: 298 (M^+, 3.8), 207 (5.4), 190 (9.5), 178 (8.6), 146 (11), 134 (10), 118 (9.5), 117 (37), 116 (5.6), 115 (5.5), 108 (9.3), 107 (6.8), 99 (8.2), 92 (12), 91 (100), 79 (11), 77 (8.3), 74 (19), 65 (11), 56 (17). ^{1}H NMR: 1.82–1.99 (1H, m, >C*H*CH_2NH_2), 2.58 (2H, d, -C*H*$_2$Ph, *J*=7.4), 2.63–2.91 (2H, m, -C*H*$_2NH_2$), 3.10–3.42 (2H, m, -C*H*$_2$NHZ), 5.09 (2H, s, -CO_2C*H*$_2$Ph), 5.60 (1H, broad t, -N*H*-, *J*=5.4), 7.13–7.35 (10H, m, aromatics). ^{13}C NMR: 36.77 (-*C*H$_2$Ph), 42.71 (>*C*HCH_2NH_2), 43.18 and 43.57 (2C, -*C*H_2NH_2 and -*C*H_2NHZ), 66.65 (-CO_2*C*H_2Ph), 126.18 (>*C*H- *para* to -CH_2CH<), 128.01, 128.48 and 128.92 (9C, >*C*H- aromatics), 136.75 (>*C*< *ipso* of -CO_2CH_2Ph), 139.78 (>*C*< *ipso* of -CH_2Ph), 156.78 (2C, >*C*=O).

4.16. (S)-(N-Acetyl)-2-benzyl-[N′-(benzyloxycarbonyl)]-1,3-propanediamine **25**

A solution of **24** (207 mg, 751 μmol) in dry pyridine (2 ml) was treated with acetic anhydride (106 μl, 1.13 mmol) and stirred at room temperature for 1.5 h. The solution was diluted with water and extracted with ether. The combined organic layers were washed with 0.7 M H_2SO_4 solution to remove pyridine and then with 5% aqueous $NH_4H_2PO_4$ and brine. The crude product was purified by chromatography with PE:AcOEt 7:3→AcOEt to give **25** (207 mg, 88%). Crystallization from CH_2Cl_2 gave a pale yellow solid. Mp=115.7–116.5°C (CH_2Cl_2/Et_2O). R_f 0.39 (AcOEt:ETP 8:2, **A**, **B**). $[\alpha]_D$=+4.49 (*c* 2.08). IR: ν_{max} 3447, 3001, 2935, 1710, 1664, 1601, 1507, 1244. GC–MS: R_t 12.42 (**12** tends to decompose in the GC column); *m/z*: 340 (M^+, 3.2), 249 (8.8), 178 (6.4), 176 (22), 160 (12), 146 (28), 130 (5.0), 129 (23), 118 (12), 117 (49), 116 (5.3), 115 (7.4), 108 (6.3), 107 (5.2), 92 (9.6), 91 (100), 79 (7.1), 77 (6.7), 74 (12), 73 (21), 72 (30), 65 (12), 60 (8.2), 56 (6.6), 43 (18). ^{1}H NMR: 1.92–2.09 (1H, m, >C*H*CH_2NHAc), 1.98 (3H, s, -C*H*$_3$), 2.52 and 2.59 (2H, AB part of ABX system, -C*H*$_2$Ph, J_{AB}=13.9, J_{AX} and J_{BX}=7.4, 7.8), 2.92–3.46 (4H, m, -C*H*$_2$NHZ and -C*H*$_2$NHAc), 5.11 (2H, s, -CO_2C*H*$_2$Ph), 5.37 (1H, broad t, -N*H*Z, *J*=6.4), 6.27 (1H, broad s, -N*H*Ac), 7.14–7.36 (10H, m, aromatics). ^{13}C NMR: 23.04 (-*C*H$_3$), 36.47 (-*C*H$_2$Ph), 39.84 (-*C*H_2NHAc), 41.13 (2C, >*C*HCH_2NHAc and -*C*H_2NHZ), 66.64 (-CO_2*C*H_2Ph), 126.20 (>*C*H- *para* to -CH_2CH<), 127.82 (2C, >*C*H- *ortho* to -CH_2O-), 127.97 (>*C*H- *para* to -CH_2O-), 128.39 (2C, >*C*H- *meta* to -CH_2O-), 128.46 (2C, >*C*H- *meta* to -CH_2CH<), 128.77 (2C, >*C*H- *ortho* to -CH_2CH<), 136.49 (>*C*<, *ipso* of -CO_2CH_2Ph), 139.36 (>*C*<, *ipso* of -CH_2Ph), 157.26 (-*C*O_2CH_2Ph), 170.81 (-*C*OCH_3).

4.17. General procedure for the acylation of monoprotected 2-benzyl-1,3-propanediamines with N-protected amino acids to give **28a**,**b** and **30a**,**b**

A solution of amine **24**, **29a** or **29b** (amines **29a** and **29b** were obtained from **28a**,**b** by hydrogenolysis of the *N*-benzyloxycarbonyl group, as described above for compound **4** from **9**; they were used as such for the following coupling reaction) (459 μmol) was dissolved in dry CH_2Cl_2 (10 ml) and cooled to 0°C. The desired amino acid (*N*-*tert*-butoxycarbonyl-L-alanine for the synthesis of **28a**, *N*-*tert*-butoxycarbonyl-D-alanine for the synthesis of **28b**, *N*-benzyloxycarbonylglycine for the synthesis of **30a**,**b**, 689 μmol)

was added, followed by (benzotriazolyl-1-oxy)tripyrrolidinophosphonium hexafluorophosphate (PyBOP, 287 mg, 551 μmol) and 4-methylmorpholine (73 μl, 661 μmol). The resulting solution was stirred at the same temperature until complete (3–12 h). After dilution with water, the mixture was extracted with ethyl acetate. Combined organic layers were washed with a diluted solution of H_2SO_4 (pH 2–3), then with a diluted solution of Na_2CO_3 (pH 10) and, finally with brine. After solvent removal, crude products were obtained.

*4.17.1. (*S*)-2-Benzyl-[*N*-(benzyloxycarbonyl)]-[*N′*-(*tert*-butoxycarbonyl)-*L*-alanyl]-1,3-propanediamine* ***28a***

Chromatography with PE:AcOEt 7:3→2:8 gave **28a** as a white solid (77% yield), which was triturated with ether. Mp=144.4–145.2°C (Et_2O). R_f 0.42 (PE:AcOEt 1:1, **A**, **C**). $[\alpha]_D$=−33.26 (*c* 1.08). IR: ν_{max} 3435, 2970, 2929, 1707, 1488, 1445, 1368, 1194, 1158. GC–MS: this compound decomposes in the GC column. ^{1}H NMR (DMSO-d_6, temp. 100°C): 1.22 (3H, d, C*H*$_3$CH(NHBoc)-, *J*=7.1), 1.40 (9H, s, -C(C*H*$_3$)$_3$), 1.98 (1H, quintuplet, >C*H*CH$_2$NHZ, *J*=6.3), 2.55 (2H, d, -C*H*$_2$Ph, *J*=7.0), 2.89–3.11 (4H, m, -C*H*$_2$NHZ and -C*H*$_2$NHAla), 3.97 (1H, quintuplet, CH$_3$C*H*(NHBoc)-, *J*=7.2), 5.04 (2H, apparent s, -CO$_2$C*H*$_2$Ph), 6.38 (1H, broad s (broad d at 6.94, *J*=7.0, temp. 22°C), -N*H*Boc), 6.83 (1H, broad s, -N*H*Z), 7.12–7.38 (10H, m, aromatics), 7.47 (1H, broad s (broad t at 7.78, *J*=5.5, temp. 22°C), -N*H*Ala). ^{13}C NMR (DMSO-d_6, temp. 22°C): 18.01 (*C*H$_3$CH(NHBoc)-), 28.09 (3C, -C(*C*H$_3$)$_3$), 35.30 (-*C*H$_2$Ph), 39.42 (-*C*H$_2$NHAla), 40.78 (-*C*HCH$_2$NHZ), 41.11 (-*C*H$_2$NHZ), 49.89 (CH$_3$*C*H(NHBoc)-), 65.17 (-CO$_2$*C*H$_2$Ph), 77.91 (-*C*(CH$_3$)$_3$), 125.74 (>*C*H- *para* to -CH$_2$*C*H<), 127.61, 127.68, 128.08, 128.27, 128.98 (9C, >*C*H-, aromatics), 137.15 (>*C*<, *ipso* of -CO$_2$CH$_2$*C*$_6$H$_5$), 140.01 (>*C*<, *ipso* of -CH$_2$*C*$_6$H$_5$), 155.02 (-*C*O$_2$*t*Bu), 156.29 (-*C*O$_2$CH$_2$*C*$_6$H$_5$), 173.11 (-*C*OCH(CH$_3$)-).

*4.17.2. (*S*)-2-Benzyl-[*N*-(benzyloxycarbonyl)]-[*N′*-(*tert*-butoxycarbonyl)-*D*-alanyl]-1,3-propanediamine* ***28b***

Chromatography with PE:AcOEt 6:4→1:9 gave **28b** as a white foam (85% yield). R_f 0.38 (PE:AcOEt 1:1, **A**, **C**). $[\alpha]_D$=+24.52 (*c* 0.52). IR: ν_{max} 3432, 2972, 2929, 1704, 1490, 1444, 1367, 1201, 1162. GC–MS: this compound decomposes in the GC column. ^{1}H NMR (DMSO-d_6, temp. 100°C): 1.23 (3H, d, C*H*$_3$CH(NHBoc)-, *J*=7.3), 1.41 (9H, s, -C(C*H*$_3$)$_3$), 2.00 (1H, quintuplet, >C*H*CH$_2$NHZ, *J*=6.4), 2.56 (2H, d, -C*H*$_2$Ph, *J*=7.0), 2.92–3.17 (4H, m, -C*H*$_2$NHZ and -C*H*$_2$NHAla), 3.98 (1H, centre of m, CH$_3$C*H*(NHBoc)-), 5.05 (2H, apparent s, -CO$_2$C*H*$_2$Ph), 6.38 (1H, broad s (broad d at 6.98, *J*=7.0, temp. 22°C), -N*H*Boc), 6.83 (1H, broad s, -N*H*Z), 7.14–7.37 (10H, m, aromatics), 7.48 (1H, broad t (broad t at 7.83, *J*=5.5, temp. 22°C), -N*H*Ala, *J*=4.8). ^{13}C NMR (DMSO-d_6, temp. 22°C): 18.00 (*C*H$_3$CH(NHBoc)-), 28.09 (3C, -C(*C*H$_3$)$_3$), 35.29 (-*C*H$_2$Ph), 39.45 (-*C*H$_2$NHAla), 40.66 (-*C*HCH$_2$NHZ), 40.94 (-*C*H$_2$NHZ), 49.94 (CH$_3$*C*H(NHBoc)-), 65.18 (-CO$_2$*C*H$_2$Ph), 77.91 (-*C*(CH$_3$)$_3$), 125.74 (>*C*H- *para* to -CH$_2$*C*H<), 127.61, 127.69, 128.07, 128.27, 128.98 (9C, >*C*H-, aromatics), 137.15 (>*C*<, *ipso* of -CO$_2$CH$_2$*C*$_6$H$_5$), 140.03 (>*C*<, *ipso* of -CH$_2$*C*$_6$H$_5$), 155.04 (-*C*O$_2$*t*Bu), 156.34 (-*C*O$_2$CH$_2$*C*$_6$H$_5$), 173.13 (-*C*OCH(CH$_3$)-).

*4.17.3. (*R*)-2-Benzyl-[*N*-(benzyloxycarbonyl)glycyl]-[*N′*-(*tert*-butoxycarbonyl)-*L*-alanyl]-1,3-propanediamine* ***30a***

Chromatography with AcOEt:CH_2Cl_2 8:2→AcOEt:CH_2Cl_2 8:2+2% MeOH gave **30a** as a thick colourless oil (78% yield). R_f 0.45 (AcOEt:CH_2Cl_2 8:2+2% MeOH, **A**, **C**). $[\alpha]_D$=−11.54 (*c* 1.78). IR: ν_{max} 3433, 2967, 2920, 1705, 1662, 1486, 1445, 1367, 1158. GC–MS: this compound decomposes in the GC column. ^{1}H NMR (DMSO-d_6, temp. 100°C): 1.23 (3H, d, C*H*$_3$CH(NHBoc)-, *J*=7.2), 1.40 (9H, s, -C(C*H*$_3$)$_3$), 1.97 (1H, quintuplet, >C*H*CH$_2$NHAla, *J*=6.4), 2.54 (2H, d, -C*H*$_2$Ph, *J*=7.0), 3.04–3.10 (4H,

m, 2 -CH_2NHCO-), 3.65 (2H, d, -CH_2CO$_2$CH$_2$Ph, J=6.0), 3.98 (1H, centre of m, CH$_3$CH(NHBoc)-), 5.04 (2H, apparent s, -CO$_2$CH_2Ph), 6.37 (1H, broad d (broad d at 6.97, J=6.9, temp. 22°C), -NHBoc, J=6.5), 6.98 (1H, broad s, (broad t at 7.51, J=5.0, temp. 22°C) -NHZ), 7.12–7.38 (10H, m, aromatics), 7.50 (2H, centre of m (2 broad t at 7.82, J=6.6 and 7.89, J=6.6, temp. 22°C), 2 -CH$_2$NHCO-). ^{13}C NMR (DMSO-d_6, temp. 22°C): 18.01 (*C*H$_3$CH(NHBoc)-), 28.10 (3C, -C(*C*H$_3$)$_3$), 35.40 (-*C*H$_2$Ph), 39.10 (-*C*H$_2$NHAla), 40.70 (-*C*HCH$_2$NHZ), 43.61 (-*C*H$_2$NHGly), 49.95 (CH$_3$*C*H(NHBoc)-), 65.43 (-CO$_2$*C*H$_2$Ph), 77.93 (-*C*(CH$_3$)$_3$), 125.74 (>*C*H- *para* to -CH$_2$*C*H<), 127.64, 128.08, 128.24, 128.98 (9C, >*C*H-, aromatics), 136.93 (>*C*<, *ipso* of -CO$_2$CH$_2$*C*H$_2$Ph), 140.05 (>*C*<, *ipso* of -CH$_2$*C*H$_2$Ph), 155.03 (-*C*O$_2$*t*Bu), 156.41 (-*C*O$_2$CH$_2$Ph), 169.26 (-*C*OCH$_2$NHZ), 173.12 (-*C*OCH(CH$_3$)-).

4.17.4. (R)-2-Benzyl-[N-(benzyloxycarbonyl)glycyl]-[N′-(tert-butoxycarbonyl)-D-alanyl]-1,3-propanediamine **30b**

Chromatography with AcOEt:CH_2Cl_2 7:3→AcOEt:CH_2Cl_2 8:2+1% MeOH gave **30b** as a thick colourless oil (83% yield). R_f 0.45 (AcOEt:CH_2Cl_2 8:2+2% MeOH, **A**, **C**). $[\alpha]_D$=+8.27 (*c* 0.44). IR: ν_{max} 3430, 2979, 2929, 1727, 1671, 1492, 1452, 1370, 1194. GC–MS: this compound decomposes in the GC column. ^{1}H NMR (DMSO-d_6, temp. 100°C): 1.23 (3H, d, CH_3CH(NHBoc)-, J=7.0), 1.40 (9H, s, -C(CH_3)$_3$), 1.97 (1H, centre of m, >CHCH$_2$NHAla), 2.53 (2H, d, -CH_2Ph, J=7.0), 2.84–3.21 (4H, m, 2 -CH_2NHCO-), 3.65 (2H, d, -CH_2CO$_2$CH$_2$Ph, J=6.0), 3.98 (1H, centre of m, CH$_3$CH(NHBoc)-), 5.07 (2H, apparent s, -CO$_2$CH_2Ph), 6.37 (1H, broad d (broad d at 6.98, J=7.0, temp. 22°C), -NHBoc, J=7.2), 6.97 (1H, broad s, (broad t at 7.51, J=6.0, temp. 22°C) -NHZ), 7.14–7.38 (10H, m, aromatics), 7.50 (2H, centre of m (2 broad t at 7.85, J=4.6 and 7.89, J=5.9, temp. 22°C), 2 -CH$_2$NHCO-). ^{13}C NMR (DMSO-d_6, temp. 22°C): 18.01 (*C*H$_3$CH(NHBoc)-), 28.09 (3C, -C(*C*H$_3$)$_3$), 35.40 (-*C*H$_2$Ph), 39.20 (-*C*H$_2$NHAla), 40.60 (-*C*HCH$_2$NHZ), 43.56 (-*C*H$_2$NHGly), 50.02 (CH$_3$*C*H(NHBoc)-), 65.42 (-CO$_2$*C*H$_2$Ph), 77.93 (-*C*(CH$_3$)$_3$), 125.74 (>*C*H- *para* to -CH$_2$*C*H<), 127.64, 128.07, 128.24, 128.97 (9C, >*C*H-, aromatics), 136.94 (>*C*<, *ipso* of -CO$_2$CH$_2$*C*H$_2$Ph), 140.06 (>*C*<, *ipso* of -CH$_2$*C*H$_2$Ph), 155.03 (-*C*O$_2$*t*Bu), 156.40 (-*C*O$_2$CH$_2$Ph), 169.27 (-*C*OCH$_2$NHZ), 173.12 (-*C*OCH(CH$_3$)-).

4.18. General procedure for tert-butoxycarbonyl group removal

Compound **30a**,**b** (10 mg) was dissolved in dry CH_2Cl_2 (1 ml), cooled to 0°C and treated with trifluoroacetic acid (0.5 ml). After 20 min stirring at 0°C, solvent was removed in vacuo. Traces of acid were azeotropically removed with heptane and the oily residue was kept at 8×10^{-2} mbar overnight. The crude product was directly dissolved in methanol-d_4 for ^{1}H NMR spectrum recording.

4.18.1. Characterization of **31a**

^{1}H NMR (methanol-d_4): 1.50 (3H, d, CH_3CH(NH$_3^+$)-, J=7.0), 2.08 (1H, centre of m, >CHCH$_2$NHZ), 2.48–2.69 (2H, m, -CH_2Ph), 3.07–3.58 (4H, m, 2 -CH_2NHCO-), 3.75 (2H, s, -CH_2NHZ), 3.91 (1H, q, CH$_3$CH(NH$_3^+$)-, J=7.0), 5.11 (2H, apparent s, -CO$_2$CH_2Ph), 7.18–7.42 (10H, m, aromatics).

4.18.2. Characterization of **31b**

^{1}H NMR (methanol-d_4): 1.49 (3H, d, CH_3CH(NH$_3^+$)-, J=7.1), 2.06 (1H, centre of m, >CHCH$_2$NHZ), 2.48–2.69 (2H, m, -CH_2Ph), 3.07–3.42 (4H, m, 2 -CH_2NHCO-), 3.76 (2H, s, -CH_2NHZ), 3.91 (1H, q, CH$_3$CH(NH$_3^+$)-, J=7.0), 5.11 (2H, apparent s, -CO$_2$CH_2Ph), 7.14–7.42 (10H, m, aromatics).

4.19. (R)- and (S)-2-Benzyl-[N-(tert-butoxycarbonyl)]-1,3-propanediamine **43**

(a) (*R*)-**43** from **44**: A solution of **42** (272 mg, 0.68 mmol) in methanol (10 ml) was treated with Pd/C (10%, 54 mg) and hydrogenated at room temperature and 1 atm pressure for 6 h. The catalyst was filtered off and the solvent was removed in vacuo. Chromatography (70–230 mesh) with AcOEt, AcOEt:MeOH 1:1→AcOEt:MeOH 1:1+1% Et_3N gave (*R*)-**41** (152 mg) as a pale yellow oil in 85% yield.

(b) (*S*)-**43** from **42**: The same procedure described above for compounds **15** and **24** was followed. After chromatography, pure (*S*)-**41** was obtained in 95% yield. R_f 0.30 (elongated spot, AcOEt:MeOH 1:1+1% Et_3N, **A**, **C**). $[\alpha]_D$ [(*R*)-**41**]=+19.87 (*c* 2.56); $[\alpha]_D$ [(*S*)-**41**]=−17.77 (*c* 2.05). IR: ν_{max} 3451, 3039, 2933, 1692, 1603, 1492, 1452, 1367, 1192. GC–MS: 8.17; *m/z*: 264 (M^+, 3.0), 208 (17), 191 (26), 179 (7.1), 173 (6.4), 156 (7.3), 146 (23), 134 (26), 132 (5.4), 131 (6.0), 130 (31), 119 (9.8), 118 (100), 117 (76), 116 (8.8), 115 (9.8), 100 (19), 92 (13), 91 (41), 74 (9.0), 65 (7.9), 59 (19), 58 (5.3), 57 (94), 56 (67), 44 (8.4), 43 (8.4), 41 (32), 39 (10). ^{1}H NMR: 1.43 (9H, m, -C(C*H*$_3$)$_3$), 2.19–2.31 (1H, m, >C*H*CH$_2$NH$_2$), 2.58–3.40 (4H, m, -C*H*$_2$NH$_2$ and -C*H*$_2$NHBoc), 2.59 and 2.67 (2H, AB part of ABX system, -C*H*$_2$Ph, J_{AB}=13.7, J_{AX} and J_{BX}=7.3, 7.6), 4.95 (2H, broad s, -N*H*$_2$), 5.12 (1H, broad t, -N*H*-, *J*=5.4), 7.16–7.33 (5H, m, aromatics). ^{13}C NMR: 28.28 (3C, -C(*C*H$_3$)$_3$), 36.24 (-*C*H$_2$Ph), 40.51 (>*C*HCH$_2$NH$_2$), 40.79 (-*C*H$_2$NHBoc), 41.36 (-*C*H$_2$NH$_2$), 79.61 (-*C*(CH)$_3$), 126.26 (>*C*H- *para* to -CH$_2$CH<), 128.50 (2C, >*C*H- *meta* to -CH$_2$CH<), 128.88 (2C, >*C*H- *ortho* to -CH$_2$CH<), 138.89 (>*C*< *ipso* of -CH$_2$Ph), 156.93 (>*C*=O).

4.20. (S)-2-Benzyl-[N-(benzyloxycarbonyl)]-[N′-(tert-butoxycarbonyl)]-1,3-propanediamine **44**

A solution of **24** (226 mg, 758 μmol) in THF (0.5 ml) was diluted with water (4.5 ml), then the pH was adjusted to 9 by addition of 1N NaOH. Di-*tert*-butyl dicarbonate (261 ml, 1.16 mmol) was added and the reaction was stirred at room temperature for 2.5 h. The reaction was diluted with water and extracted with Et_2O. The crude product was chromatographed with PE:Et_2O 7:3→3:7 to give a thick pale yellow oil (259 mg, 86% yield). R_f 0.40 (PE:Et_2O 1:1, **A**, **B**, **C**). $[\alpha]_D$=−0.15 (*c* 2.21). IR: ν_{max} 3450, 3024, 2930, 1703, 1603, 1494, 1443, 1189, 991. GC–MS: this compound decomposes in the GC column. ^{1}H NMR: 1.43 (9H, s, -C(C*H*$_3$)$_3$), 1.91–2.04 (1H, m, >C*H*CH$_2$NHAc), 2.54 (2H, d, -C*H*$_2$Ph, *J*=7.7), 2.84–3.38 (4H, m, -C*H*$_2$NHZ and -C*H*$_2$NHBoc), 5.00 (1H, broad t, -N*H*Z, *J*=6.5), 5.09 and 5.12 (2H, AB system, -CO$_2$C*H*$_2$Ph, *J*=12.4), 5.56 (1H, broad t, -N*H*Ac, *J*=6.1), 7.14–7.38 (10H, m, aromatics). ^{13}C NMR: 28.39 (3C, -C(*C*H$_3$)$_3$), 36.22 (-*C*H$_2$Ph), 40.55 (-*C*H$_2$NHBoc), 41.28 (-*C*H$_2$NHZ), 41.55 (-*C*HCH$_2$NHZ), 66.68 (-CO$_2$*C*H$_2$Ph), 79.43 (-*C*(CH$_3$)$_3$), 126.27 (>*C*H- *para* to -CH$_2$CH<), 128.02, 128.49, 128.59 and 128.87 (9C, >*C*H-, aromatics), 136.67 (>*C*<, *ipso* of -CO$_2$CH$_2$Ph), 139.48 (>*C*<, *ipso* of -CH$_2$Ph), 156.74 and 157.05 (2C, >*C*=O).

4.21. General method for the preparation of Mosher's esters **32**, **33**, **34** and **35**

About 15 μmol of alcohol (**15**, **19**, **21** and **40**, respectively) were dissolved in dry CH_2Cl_2 (0.5 ml) and treated with 4-dimethylaminopyridine (6 mol equivalents) and Mosher's chloride (3 mol equivalents). After 1 h crude mixture was directly purified by preparative thin layer chromatography to give the corresponding esters in 70–92% yield.

4.21.1. (R,R)- and (R,S)-Esters (from **15**) **32**

Eluent for chromatography: PE:AcOEt 1:9. R_f 0.48 (PE:AcOEt 1:9, **A**, **B**).

*4.21.2. (*R,R*)- and (*R,S*)-Esters (from **19**) **33***

Eluent for chromatography: PE:Et_2O 8:2. R_f 0.48 (PE:Et_2O 8:2, **A**, **B**).

*4.21.3. (*R,R*)- and (*R,S*)-Esters (from **21**) **34***

Eluent for chromatography: PE:Et_2O 1:1. R_f 0.32 (PE:Et_2O 6:4, **A**, **B**).

*4.21.4. (*R,R*)- and (*R,S*)-Esters (from **30**) **35***

Eluent for chromatography: PE:Et_2O 6:4 R_f 0.37 (PE:Et_2O 7:3, **A**, **C**).

*4.22. General method for the preparation of Mosher's amides **36**, **37***

About 15 μmol of amine (**24** and **43**, respectively) were dissolved in dry pyridine (0.5 ml) and treated with Mosher's chloride (3 mol equivalents). After 2–3 h the crude mixture was diluted with water and extracted with ether. After solvent evaporation residual pyridine was azeotropically removed with heptane. Purification was performed by preparative thin layer chromatography to give the corresponding amides in 66–84% yield.

*4.22.1. (*R,R*)- and (*R,S*)-Amides (from **24**) **36***

Eluent for chromatography: PE:Et_2O 1:1. R_f 0.38 (PE:Et_2O 1:1, **A**, **B**).

*4.22.2. (*R,R*)- and (*R,S*)-Amides (from **43**) **37***

Eluent for chromatography: PE:Et_2O 1:1. R_f 0.39 (PE:Et_2O 1:1, **A**, **C**).

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