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A case study of the MAC (masked acyl cyanide) oxyhomologation of *N*,*N*-dibenzyl-L-phenylalaninal with *anti* diastereoselectivity: preparation of (2*S*,3*S*)-allophenylnorstatin esters†

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The three-component reaction between a protected α-amino aldehyde, an alcohol and an α-silyloxymalononitrile provides an expedient access to protected α-hydroxy-β-amino acid derivatives. The prototypical process, performed on *N*-Cbz-phenylalaninal, is known to proceed with *syn* diastereoselectivity. The present study demonstrates that the diastereoselectivity of the reaction can be inverted, using the rationale of a Felkin-Anh interaction model. Reactions performed on *N*,*N*-dibenzyl-L-phenylalaninal proceed with a high *anti* diastereoselectivity, providing a panel of synthetically useful ester derivatives of (2*S*,3*S*)-allophenylnorstatin. The procedure is exploited to accomplish one of the most efficient syntheses of the title compound to date, in 3 steps (66% yield) from *N*,*N*-dibenzyl-L-phenylalaninal.

Introduction

Since its first advocacy several decades ago,[1] the umpolung concept has fructified to provide powerful tools for conducting organic synthesis.[2] Particular attention has been paid to the development and application of acyl anion equivalents, such as 1,3-dithianes,[3] dialkylhydrazones,[4] cyanohydrins[5] and α-aminonitriles.[6] A significant family of umpolung reagents are constituted by *O*-functionalized α-hydroxymalononitriles, known as masked acyl cyanide (MAC) reagents, first introduced by Yamamoto and Nemoto.[7] The deprotonated form of a MAC reagent is nucleophilic and it reacts with an electrophile; subsequent unmasking reveals an acyl cyanide which can be further transformed into a carboxylic acid derivative by reaction with a nucleophile. This reactivity profile has been widely exploited in multi-step syntheses of biologically active molecules[8] and in other synthetic applications.[9]

When the electrophilic partner is a chiral α-amino aldehyde and the MAC reagent is a silyl ether—hereafter referred to generically as H-MAC-[Si]—the one-pot reaction constitutes an oxyhomologation, presumably proceeding *via* a [1,4]-silyl transfer mechanism, to provide access to an α-hydroxy-β-amino acid derivative in which the alcohol function is protected as a silyl ether (Fig. 1). Despite the importance of α-hydroxy-β-amino acids,[10] few applications of MAC methodology have been made thereto and they have, for the most part, been characterized by a *syn* diastereoselectivity (*syn* : *anti* ratio around 4 : 1).[11] Recently, however, we discovered that when Garner's aldehyde is used as the electrophilic partner the oxyhomologation gives the corresponding MAC reaction product with an *anti* diastereoselectivity.[12]

One of the appealing features of MAC methodology is that the mild reaction conditions ensure that no erosion of the inherent enantiomeric composition of a chiral substrate is observed;[7m,8c] this means that the oxyhomologation of a single

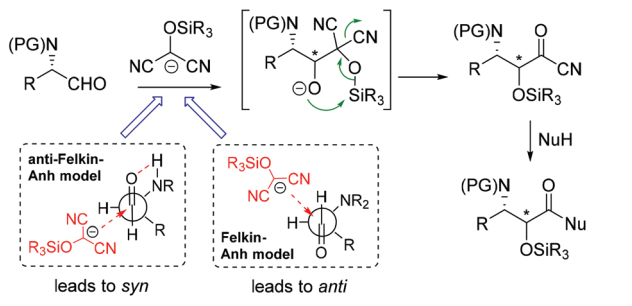

Fig. 1 The proposed mechanism for the reaction of an H-MAC-[Si] reagent with a protected chiral α-amino aldehyde, highlighting two models that may govern the diastereoselectivity in the first step. Once unmasked, the acyl cyanide intermediate reacts with a nucleophile.

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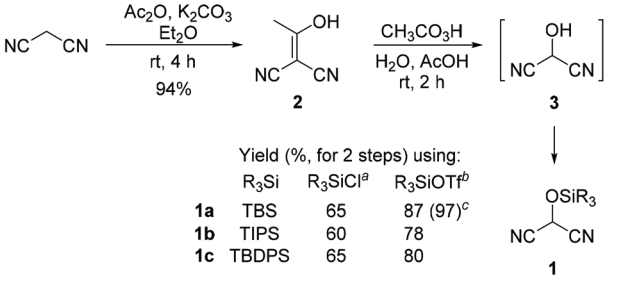
enantiomer of an α-amino aldehyde substrate will furnish the oxyhomologation product as a single enantiomer.

While the mechanism of the MAC reaction has not been studied in detail, it seems plausible that the *syn* selectivity observed with unrestricted α-amino aldehydes might arise *via* an anti-Felkin–Anh model implicating a hydrogen bond between the carbamate-protected amine and the aldehyde during the first step, whereas Garner's aldehyde, devoid of an NH motif, reacts *via* a Felkin–Anh model (Fig. 1). If this reasoning is valid, it should be possible to perform an *anti* stereoselective MAC oxyhomologation reaction on an unrestricted α-amino aldehyde on the condition that the protecting group suite does not contain an NH motif. To probe this hypothesis, an *N*,*N*-dibenzyl-protected amino aldehyde appeared to us to be an appropriate substrate, since compounds of this type are known to react with nucleophiles[13,14] with good Felkin–Anh selectivity and without loss of enantiomeric enrichment. In order to provide direct comparison with Nemoto's reference work using *N*-Cbz-phenylalaninal,[7m] the present study focuses on the MAC reaction of *N*,*N*-dibenzyl-L-phenylalaninal with alcohols. We describe herein the successful *anti* oxyhomologation of this substrate to prepare ester derivatives of the 2*S*,3*S* stereoisomer of allophenylnorstatin.[15]

Results and discussion

We began this study with a consideration of H-MAC-[Si] reagents. Almost all of the work described previously in the literature has employed 2-(*tert*-butyldimethylsilyloxy)malononitrile **1a** (H-MAC-TBS);[7j–r,8c–g,9a–d] the related triisopropylsilyl and *tert*-butyldiphenylsilyl derivatives **1b** (H-MAC-TIPS)[7m] and **1c** (H-MAC-TBDPS)[12] have each been alluded to on only one occasion. All three of these reagents are appealing since they possess significant steric bulk, which might have an advantageous impact on the diastereoselectivity of the oxyhomologation reaction. However, an important factor for the synthetic utility of any H-MAC-[Si] reagent is a convenient and reliable access to the reagent itself. No syntheses of the derivatives **1b** and **1c** have been described to date. The earliest synthesis of **1a** required a rather inefficient five-step sequence starting from diethyl 2-bromomalonate.[7a] Subsequently, a three-step procedure was proposed starting from malononitrile, requiring acetylation, oxidative cleavage, then silyl ether formation;[16] this is the basis of the approach that we have adopted for our preparative procedures (Scheme 1).

Acetylation of malononitrile[17] proceeded smoothly to provide **2** essentially in its enol tautomer form in 94% yield. Oxidative cleavage was performed using peracetic acid and, in our experience, the quality of the resulting 2-hydroxymalononitrile **3** was critical; its use immediately after preparation led to the best yields in the subsequent silylation step. For this latter, we compared the efficacy of silyl triflates with that of silyl chlorides on a 4.6 mmol scale. In all three cases the silylation was noticeably more efficient and reproducible with the triflate (yields 78–87%) than with the corresponding chloride (yields

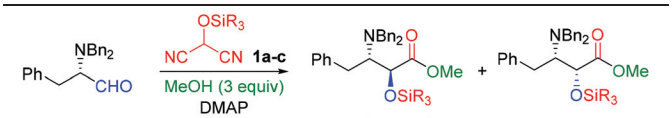


Scheme 1 Reaction conditions. Reactions carried out on 4.6 mmol scale unless stated. *a*: R_3SiCl (1.5 equiv.), imidazole (2 equiv.), DMF; R_3Si = TBS or TBDPS, 30 min at 0 °C then 30 min at rt; R_3Si = TIPS, 16 h, 0 °C slowly to rt. *b*: R_3SiOTf (1.5 equiv.), 2,6-lutidine (2 equiv.), CH_2Cl_2; R_3Si = TBS, 30 min at 0 °C then 30 min at rt; R_3Si = TIPS or TBDPS, 16 h, 0 °C slowly to rt. *c*: Conducted on 20 mmol scale.

60–65%) (Scheme 1). Using this adaptation and extension of the original procedure, the three MAC reagents **1a-c** were prepared conveniently on around gram scale. Gratifyingly, when the H-MAC-TBS **1a** synthesis was conducted at a preparative 20 mmol scale, the isolated yield of **1a** from **2** improved to 97%.

Each H-MAC-[Si] reagent **1a–c** was evaluated in the oxyhomologation of *N*,*N*-dibenzyl-L-phenylalaninal using methanol as the standard alcohol component. On the basis of previous work, DMAP was used as the mild base and reactions were run overnight in ether at 0 °C. The number of equivalents of MAC reagent and base were screened, invariably in the presence of a sufficient excess of methanol. Results are presented in Table 1.

Table 1 Investigation of the reaction conditions[a]



entry	H-MAC-[Si]	(equiv.)	DMAP (equiv.)	Yield[b] **4**/**4′** (%)	dr (*anti* : *syn*)[c]
1	**1a**	1.2	1	68	94 : 6
2	**1a**	1.2	2	77	92 : 8
3	**1a**	2.4	1	80	92 : 8
4	**1a**	**2.4**	**2**	**83**	**92 : 8**
5[d]	**1a**	2.4	2	78	91 : 9
6	**1b**	1.2	1	56	93 : 7
7	**1b**	1.2	2	65	93 : 7
8	**1b**	2.4	1	71	94 : 6
9	**1b**	**2.4**	**2**	**80**	**91 : 9**
10[d]	**1b**	2.4	2	70	91 : 9
11	**1c**	1.2	1	51	92 : 8
12	**1c**	1.2	2	51	92 : 8
13	**1c**	2.4	1	71	93 : 7
14	**1c**	**2.4**	**2**	**74**	**93 : 7**
15[d]	**1c**	2.4	2	74	91 : 9

[a] Reaction conditions: *N*,*N*-dibenzyl-L-phenylalaninal (0.5 mmol; 1 equiv.), stated amounts of H-MAC-[Si] and DMAP, methanol (3 equiv.) in Et_2O (5 mL), 16 h, 0 °C, under argon. [b] Isolated yields are given. [c] Determined by ^1H NMR; see text for details. [d] Reaction run at room temperature.

For H-MAC-TBS **1a**, use of a slight excess of the reagent gave good yields of products **4a**/**4a′** (entries 1 and 2), and this improved when a larger excess of the reagent was employed (entries 3 and 4), reaching 83% in the presence of 2 equivalents of base. Running the reaction at room temperature (entry 5) was slightly deleterious to the yield. For H-MAC-TIPS **1b**, a very similar reactivity profile was observed. With one equivalent of reagent and base the yield of **4b**/**4b′** was moderate 56% (entry 6) but improved when the quantity of either the reagent or the base was increased (entries 7 and 8) and reached a satisfying 80% in the presence of two equivalents of each (entry 9). Running the reaction at room temperature had a marginally negative effect on the yield (entry 10). For H-MAC-TBDPS **1c**, a comparable reactivity profile was once again observed, with yields of **4c**/**4c′** ranging from 51 to 74% depending on the number of reagent equivalents (entries 11–14). Running the reaction at room temperature had no perceptible effect on the yield (entry 15).

The diastereomeric ratios (dr) were established by inspecting the ^{1}H NMR spectra of the product mixtures and integrating the signals for protons whose chemical shifts were most conveniently differentiated between diastereomer pairs. In the event, this turned out to be the TBS methyl groups signals for **4a**/**4a′**, the C*H*OTIPS signals for **4b**/**4b′** and the methyl ester signals for **4c**/**4c′**. Within the precision limits of this method, the dr was uniformly high in all three cases, regardless of the reaction conditions involved, and was always greater than 10 : 1. The major diastereomer **4c** crystallized and an X-ray diffraction study revealed that it had the 2*S*,3*S* configuration (Fig. 2),[18] which confirmed that the MAC reaction had indeed proceeded with the desired *anti* diastereoselectivity. Intuitively we felt that the major diastereomers **4a** and **4b** should also be *anti*, and this was confirmed by subjecting each of the three samples **4a**/**4a′**, **4b**/**4b′** and **4c**/**4c′** to selective desilylation using TBAF in THF to provide, in good yield after chromatography, a single product **5** (Scheme 2), whose spectroscopic and optical rotation data were the same as those published for the *anti* 2*S*,3*S* stereoisomer.[15f] In these transformations, the ^{1}H NMR spectra of the crude reaction products indicated the presence of the minor *syn* diastereomers in silylated form, suggesting that the deprotection process may be diastereoselective, although we did not pursue this matter further.

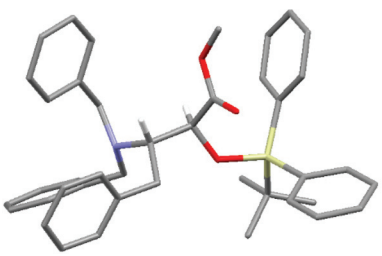
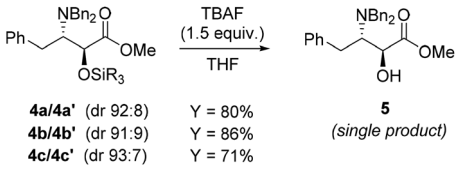


Fig. 2 X-ray diffraction structure of compound **4c** showing the 2*S*,3*S* configuration. For clarity, hydrogen atoms have been removed, with the exception of those at the stereogenic centres.



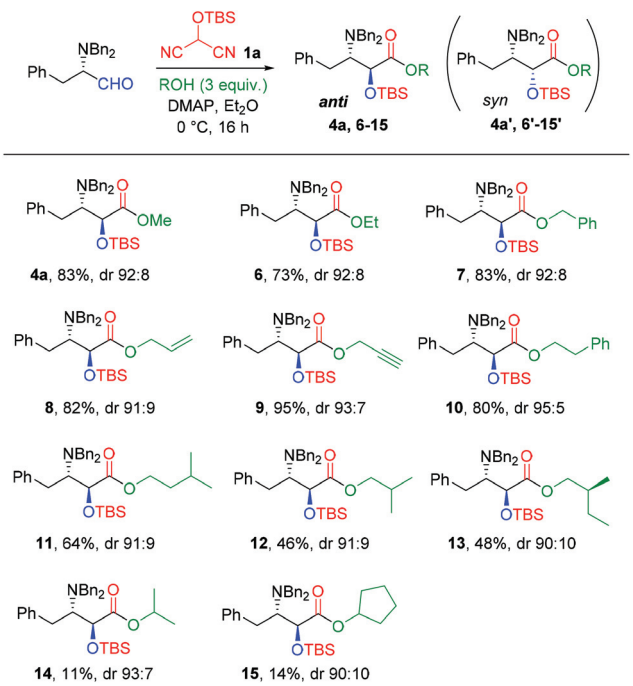
4a/4a' (dr 92:8) Y = 80%
4b/4b' (dr 91:9) Y = 86%
4c/4c' (dr 93:7) Y = 71%

5 *(single product)*

Scheme 2 Reaction conditions. For **4a**/**4a′** and **4b**/**4b′**: 1 h, 0 °C. For **4c**/**4c′**: 16 h, rt.

The results collected in Table 1 show that all three H-MAC-[Si] reagents performed in a satisfactory manner, with all products **4a**/**4a′**–**4c**/**4c′** being obtained with high *anti* diastereoselectivity. Comparison of best yields (entries 4, 9 and 14) gave a marginal advantage to **1a** over **1b** which was in turn better than **1c** (83%, 80% and 74% yields, respectively). As mentioned above, H-MAC-TBS is the most studied reagent so far and its synthesis was the most efficient in our hands so we continued our studies with this reagent and retained the conditions of entry 4 as standard.

The scope of the MAC oxyhomologation of *N*,*N*-dibenzyl-L-phenylalaninal was evaluated using a panel of alcohols. Results are presented in Scheme 3. As before, dr values were determined by integration of the ^{1}H NMR signals of the TBS methyl groups and we considered it plausible that the *anti* diastereomer predominated in each case. Support for this contention was provided by the ^{1}H NMR data, which invariably showed the diagnostic TBS methyl groups signals at lower field

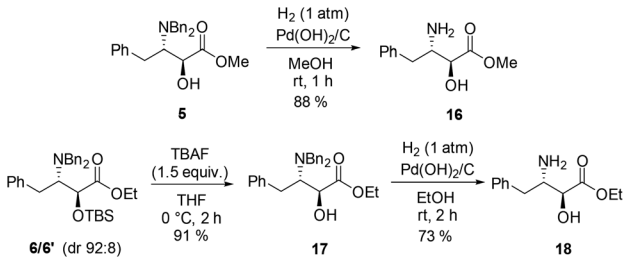


Scheme 3 Reaction conditions. *N*,*N*-dibenzyl-L-phenylalaninal (0.5 mmol; 1 equiv.), **1a** (2.4 equiv.), DMAP (2 equiv.) and ROH (3 equiv.) in Et_2O (5 mL), 16 h, 0 °C, under argon. Isolated yields are indicated. The dr was determined by ^{1}H NMR; see text for details. Only the major *anti* diastereomer is illustrated.

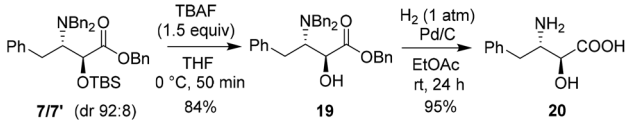
for the major *anti* isomer than for the minor *syn* isomer (see ESI†).

Ethanol and benzyl alcohol gave good yields of products **6**/**6′** and **7**/**7′** with high diastereoselectivity. With three other uncongested primary alcohols—allyl alcohol, propargyl alcohol and phenylethanol—the products (**8**/**8′**–**10**/**10′** respectively) were likewise obtained in very good yields and high dr, reaching 95 : 5 for compound **10**/**10′**. When the reaction was carried out with branched chain primary alcohols—isoamyl alcohol, isobutanol and (*S*)-2-methylbutanol—the yield of the oxyhomologation products (**11**/**11′**–**13**/**13′** respectively) was more modest (46–64%), although the dr values remained consistently high. The presence of the chiral center in 2-methylbutanol had no perceptible effect on the dr value. With two representative secondary alcohols—isopropanol and cyclopentanol—the reactions were much less efficient; the desired products **14**/**14′** and **15**/**15′** were isolated only in low yields (11% and 14%, respectively), although the dr values were still just as high as those observed for primary alcohol substrates. Notwithstanding the limitations arising from the steric bulk of the alcohol, these oxyhomologation reactions provided rapid access to a selection of ester derivatives of *N,O*-protected (2*S*,3*S*)-allophenylnorstatin, some of which (*e.g.* allyl and propargyl) appear amenable to subsequent functionalization.

The methyl ester of (2*S*,3*S*)-allophenylnorstatin, itself a LTA_4 hydrolase inhibitor,[19] has been used as a building block for the preparation of BACE1 inhibitors,[20] photobiological switches,[21] and symmetrical peptidomimetic scaffolds;[22] it has also served as an intermediate for the preparation of a variety of other biologically active compounds,[23] as has the corresponding ethyl ester.[24] These two ester derivatives were prepared readily as follows (Scheme 4). Catalytic hydrogenolysis of the single stereoisomer **5** (obtained *via* Scheme 2) gave the methyl ester **16** in high yield (88%). In a similar fashion, compound **17** was first obtained as a single *anti* isomer in 91% yield by selective desilylation of **6**/**6′** (dr 92 : 8) using TBAF in THF; taking the diastereomeric composition of the substrate into account, this equates to a near quantitative yield of the available *anti* component. Compound **17** was subjected to catalytic hydrogenolysis to provide ethyl ester **18** in good yield (73%). These procedures provide a convenient access to esters **16** and **18** as an alternative to the classical approach involving acid-mediated esterification of the parent amino acid.



Scheme 4 Preparation of (2*S*,3*S*)-allophenylnorstatin esters.



Scheme 5 Preparation of (2*S*,3*S*)-allophenylnorstatin.

To complete this study we prepared (2*S*,3*S*)-allophenylnorstatin in its free amino acid form (Scheme 5). The benzyl ester derivative **7**/**7′** (dr 92 : 8) was desilylated using TBAF to furnish exclusively the *anti* derivative **19** in 84% yield; on the basis of the diastereomeric composition of the substrate, this equates to a 91% yield of the available *anti* component. For the final step, catalytic hydrogenolysis of all three benzyl groups was envisaged in the presence of a palladium catalyst. Initial experiments carried out in methanol were hampered by the formation of mixtures of products resulting from partial *N*-debenzylation and the unwanted formation of *N*- and/or *O*-methylated derivatives.[25] To circumvent this problem we performed the hydrogenation in ethyl acetate; *mutatits mutandis*, complete debenzylation was achieved cleanly to provide the target hydroxy amino acid **20** in 95% yield. Spectroscopic and optical rotation data were in full agreement with the literature data for the (2*S*,3*S*) stereoisomer. This 3-step synthesis of (2*S*,3*S*)-allophenylnorstatin in 66% overall yield from *N*,*N*-dibenzyl-L-phenylalaninal is one of the shortest and most efficient to date.[26]

Conclusions

This study reveals that MAC reactions between *N*,*N*-dibenzyl-L-phenylalaninal and alcohols proceed with high *anti* diastereoselectivity. These results contrast significantly with Nemoto's work on MAC reactions involving *N*-Cbz-phenylalaninal, which gave products with *syn* diastereoselectivity.[7m] The combined observations provide the first example of the MAC oxyhomologation of an α-amino aldehyde in a *directed* diastereoselective manner, through judicious choice of the amine protecting group suite. Using the new *anti*-directed formulation, a panel of ester derivatives of orthogonally *N,O*-protected (2*S*,3*S*)-allophenylnorstatins has been prepared. While the reactions were sensitive to the steric bulk of the alcohol, a number of synthetically useful esters were prepared in this way and an expedient new synthesis of the title amino acid in single-enantiomer form was achieved in only 3 steps.

Experimental

General experimental methods

N,*N*-Dibenzyl-L-phenylalaninal {$[\alpha]_D^{24}$ = −91.2 (*c* 1.0, $CHCl_3$), lit.[27] $[\alpha]_D^{20}$ = −90.0 (*c* 1.0, $CHCl_3$)} was prepared from commercial (*S*)-phenylalaninol according to literature procedure.[28] Peracetic acid solution (35 wt% in acetic acid) was purchased from Acros. Solvents and reagents were purified under argon

as follows: Et_2O and THF were distilled from Na/benzophenone; DMF and 2,6-lutidine were distilled from CaH_2; CH_2Cl_2 was passed through an activated alumina column immediately before use; methanol and ethanol were distilled from Mg/I_2; benzyl alcohol, isopropanol, isobutanol, isoamyl alcohol and (*S*)-2-methylbutan-1-ol were distilled from CaO; allyl alcohol, propargyl alcohol and phenylethyl alcohol were dried over $CaSO_4$, K_2CO_3 and Na_2SO_4 respectively, followed by distillation. All other reagents were obtained commercially and were used directly as supplied. Preparative flash chromatography was performed using columns packed with SDS (35–70 μm) or Macherey–Nagel (40–63 μm) silica gel. Analytical thin-layer chromatography, used to monitor preparative flash chromatography and to provide characteristic retention factors (R_f), was performed on 0.25 mm commercial silica gel plates (Merck 60F-254); plates were visualized by UV fluorescence at 254 nm and then revealed by heating after dipping in a ninhydrin solution (1.5% in *n*-BuOH) or a potassium permanganate solution (7.5% in water). ^{1}H and ^{13}C NMR spectra were recorded on Bruker DPX250 (250 and 62.9 MHz, respectively), Bruker AV300 (300 and 75.5 MHz, respectively), Bruker AV360 (360 and 90.6 MHz, respectively), Bruker Avance I 400 and Bruker Avance III 400 spectrometers (400 and 100.6 MHz, respectively). Chemical shifts (δ) are given in parts per million, using solvent signals as internal standards ($CDCl_3$: δ_H = 7.26 ppm, δ_C = 77.0 ppm; DMSO-d_6: δ_H = 2.50 ppm, δ_C = 39.5 ppm; CD_3OD: δ_H = 3.31 ppm, δ_C = 49.0 ppm; D_2O: δ_H = 4.79 ppm). Assignments were aided by JMOD pulse sequences and 2D experiments (HSQC, HMBC, COSY). Splitting patterns for ^{1}H signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), br s (broad singlet), or m (multiplet). Coupling constants (*J*) are reported in Hz. Positive and negative electrospray (ES^+, ES^-) high resolution mass spectra (HRMS) were recorded with a Bruker Daltonics micrOTOF-Q instrument. Infrared spectroscopy (IR) analyses were recorded on a FT-IR PerkinElmer Spectrum Two spectrophotometer using an ATR diamond accessory; maximum absorbances (ν) are given in cm^{-1}. Elemental analyses were performed by the Microanalysis Service of the I.C.S.N. (Gif-sur-Yvette, France). Melting points (Mp) were determined with a Büchi M-560 apparatus in open capillary tubes and are uncorrected. Optical rotations were measured on a Jasco P-1010 polarimeter using a 10 cm quartz cell; values for $[\alpha]_D^T$ were obtained with the D-line of sodium at the indicated temperature *T*, using solutions of concentration (*c*) in units of g 100 mL^{-1}.

Preparation of MAC reagents: H-MAC-[Si]

2-(1-Hydroxyethylidene)malononitrile (2). Malononitrile (3.00 g, 45.4 mmol) was dissolved in ether (50 mL). Potassium carbonate (7.50 g, 54.3 mmol) was added in one portion and the reaction mixture was stirred vigorously for 1 h at room temperature under argon. After cooling at 0 °C, acetic anhydride (6.9 mL, 73.0 mmol) diluted in Et_2O (25 mL) was added dropwise over 20 min and the reaction mixture was stirred for 4 h at room temperature. Water (30 mL) was introduced and the mixture was acidified at 0 °C with concentrated HCl until pH ~1. The aqueous phase was extracted with Et_2O (3 × 20 mL) and the combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **2** (4.60 g, 94%) as a yellow-orange solid. Mp 141 °C. Crude 2-(1-hydroxyethylidene)malononitrile obtained in this way showed a very satisfactory ^{1}H NMR spectrum and could be used in the subsequent reaction without further purification. An analytically pure sample was obtained by recrystallization from Et_2O/*n*-hexane to furnish **2** (4.22 g, 86%) as a light yellow-orange solid. Mp 141 °C (lit.[17] 140.5 °C). R_f 0.25 (EtOAc/MeOH, 9 : 1). IR (ATR): ν 3045, 2610, 2238, 2225, 1600, 1574, 1507, 1402, 1359, 1227 cm^{-1}. HRMS (ES^-): calcd for $C_5H_3N_2O$ $[M - H]^-$ 107.0251; found 107.0250. ^{1}H NMR (360 MHz, DMSO-d_6), δ 2.21 (s, 3H, =C–CH_3), 12.1 (br s, 1H, =C–OH). ^{13}C NMR (62.9 MHz, DMSO-d_6), δ 21.2 (=C–CH_3), 59.2 ($C(CN)_2$), 113.8 (C(CN)CN), 115.7 (C(CN)CN), 189.3 (=C–OH). Anal. calcd for $C_5H_4N_2O$: C, 55.56; H, 3.73; N, 25.91. Found: C, 55.54; H, 3.53; N, 25.97.

2-Hydroxymalononitrile (3). To a solution of crude 2-(1-hydroxyethylidene)malononitrile **2** (1.00 g, 9.26 mmol) in water (24 mL) was added dropwise over 10 min at 0 °C a peracetic acid solution (35 wt% in acetic acid, 6.2 mL, 32.3 mmol) diluted with glacial acetic acid (20 mL). After complete addition, the resulting clear yellow solution was stirred at room temperature for 2 h. The reaction mixture was gradually concentrated on a rotary evaporator (water bath below 35 °C) until 10 mbar and traces of acetic acid were removed by three co-evaporations with water. (NOTE: Although we have never observed any complications, a Plexiglas protective shield around the rotary evaporator was used during concentration of peracetic acid). The residual yellowish oil was dried under high vacuum (10^{-2} mbar) until no more traces of water or acetic acid were observed by ^{1}H NMR (around 2 h). Unstable 2-hydroxymalononitrile **3** (~760 mg, 9.26 mmol, quant.), isolated as a milky yellowish oil, was quickly analyzed by NMR. It was then engaged directly in the next reaction without any purification. ^{1}H NMR (300 MHz, DMSO-d_6), δ 6.08 (s, 1H, CH($CN)_2$), 8.22 (br s, 1H, OH). ^{13}C NMR (62.9 MHz, DMSO-d_6), δ 49.9 (CH$(CN)_2$), 114.6 (CH($CN)_2$).

General procedure for 2-hydroxymalononitrile silylation

Method A (using a silyl chloride). Crude 2-hydroxymalononitrile **3** (4.63 mmol, 1 equiv.) was dissolved in DMF (10 mL) under argon and the solution was cooled at 0 °C. Silyl chloride reagent (1.5 equiv.) was added in one portion, followed by imidazole (630 mg, 9.26 mmol, 2.0 equiv.) in several portions. The reaction mixture was then stirred for the specified time and at the indicated temperature (see below). After addition of a saturated aqueous Na_2CO_3 solution (10 mL), the aqueous phase was extracted with Et_2O (6 × 10 mL). The combined organic layers were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator (water bath at 40 °C) until the appropriate pressure depending of the nature of the H-MAC-[Si]. The crude residue was then purified by flash chromatography to afford pure *O*-silylated hydroxymalononitrile.

Method B (using a silyl triflate). To an ice-cooled mixture of crude 2-hydroxymalononitrile **3** (4.63 mmol, 1 equiv.) in CH_2Cl_2 (5 mL) under argon was added the silyl triflate reagent (1.5 equiv.) in a single portion followed by dropwise addition of 2,6-lutidine (1.08 mL, 9.26 mmol, 2.0 equiv.) and the reaction mixture was then stirred for the specified time and at the indicated temperature (see below). After addition of a saturated aqueous Na_2CO_3 solution (10 mL), the aqueous layer was extracted with Et_2O (6 × 10 mL) and the combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator (water bath at 40 °C) until the appropriate pressure depending of the nature of the H-MAC-[Si]. The crude residue was then purified by flash chromatography to afford pure *O*-silylated hydroxymalononitrile.

2-(*tert*-Butyldimethylsilyloxy)malononitrile, H-MAC-TBS (1a). *According to method A*: silylation of 2-hydroxymalononitrile **3** (380 mg, 4.63 mmol) was performed with *tert*-butyldimethylsilyl chloride (1.05 g, 7.00 mmol) and imidazole in DMF for 30 min at 0 °C followed by 30 min at room temperature. After work-up and concentration under reduced pressure (until 450 mbar), the brown liquid residue was purified by flash chromatography (pentane then pentane/Et_2O, 20 : 1; then concentration of fractions on a rotary evaporator with a water bath at 40 °C until 450 mbar) to give H-MAC-TBS **1a** (583 mg, 65% over 2 steps) as a colorless liquid. *According to method B*: silylation of 2-hydroxymalononitrile **3** (380 mg, 4.63 mmol) was carried out with *tert*-butyldimethylsilyl triflate (1.6 mL, 6.97 mmol) and 2,6-lutidine in CH_2Cl_2 for 30 min at 0 °C followed by 30 min at room temperature. After work-up and concentration under reduced pressure (until 450 mbar), the pale brown liquid residue was purified by flash chromatography (pentane then pentane/Et_2O, 20 : 1; then concentration of fractions on a rotary evaporator with a water bath at 40 °C until 450 mbar) to furnish compound **1a** (790 mg, 87% over 2 steps) as a colorless liquid. H-MAC-TBS **1a** can be stored under argon for several months at −18 °C. R_f 0.18 (pentane/Et_2O, 20 : 1). IR (ATR): ν 2957, 2934, 2862, 2252, 1473, 1259, 1115 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.28 (s, 6H, $Si(CH_3)_2$), 0.94 (s, 9H, $SiC(CH_3)_3$), 5.33 (s, 1H, $CH(CN)_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ −5.5 ($Si(CH_3)_2$), 17.9 ($SiC(CH_3)_3$), 25.0 ($SiC(CH_3)_3$), 50.8 ($CH(CN)_2$), 112.3 ($CH(CN)_2$). Anal. calcd for $C_9H_{16}N_2OSi$: C, 55.06; H, 8.21; N, 14.27. Found: C, 54.81; H, 8.12; N, 14.13. ^1H and ^{13}C NMR data were in agreement with those described in literature.[7a]

Larger scale synthesis of H-MAC-TBS (1a). To a solution of crude 2-(1-hydroxyethylidene)malononitrile **2** (2.15 g, 19.9 mmol) in water (25 mL) was added dropwise over 20 min at 0 °C a peracetic acid solution (35 wt% in acetic acid, 13.4 mL, 69.8 mmol) diluted with glacial acetic acid (42 mL). After complete addition, the resulting clear yellow solution was stirred at room temperature for 2 h. The reaction mixture was gradually concentrated on a rotary evaporator (water bath below 35 °C) until 10 mbar and traces of acetic acid were removed by three co-evaporations with water. (NOTE: Although we have never observed any complications, a Plexiglas protective shield around the rotary evaporator was used during concentration of peracetic acid). The residual yellowish oil was dried under high vacuum (10^{-2} mbar) until no more trace of water and acetic acid was observed by ^1H NMR (around 2 h). To the crude 2-hydroxymalononitrile **3** (1.66 g, 19.91 mmol) in solution in CH_2Cl_2 (8 mL), were slowly introduced *tert*-butyldimethylsilyl triflate (7.1 mL, 31.0 mmol), followed by 2,6-lutidine (4.8 mL, 41.5 mmol). The resulting solution was stirred for 30 min at 0 °C and for an additional 30 min at room temperature. After addition of a saturated aqueous Na_2CO_3 solution (40 mL), the aqueous layer was extracted with Et_2O (6 × 20 mL) and the combined organic phases were washed with 1 M HCl (100 mL), brine (100 mL), dried over Na_2SO_4 and concentrated on a rotary evaporator (water bath at 40 °C) until 450 mbar. The crude residue was then purified by flash chromatography (pentane then pentane/Et_2O, 20 : 1; then concentration of fractions on a rotary evaporator with a water bath at 40 °C until 450 mbar) to furnish compound **1a** (3.79 g, 97% over 2 steps) as a colorless liquid.

2-(Triisopropylsilyloxy)malononitrile, H-MAC-TIPS (1b). *According to method A*: silylation of 2-hydroxymalononitrile **3** (380 mg, 4.63 mmol) was performed with triisopropylsilyl chloride (1.5 mL, 7.01 mmol) and imidazole in DMF overnight from 0 °C to room temperature. After work-up and concentration under reduced pressure, the brown liquid residue was purified by two successive flash chromatographies (pentane then pentane/Et_2O, 50 : 1; pentane then pentane/Et_2O, 20 : 1) to separate H-MAC-TIPS from triisopropylsilanol. H-MAC-TIPS **1b** (665 mg, 60% over 2 steps) was isolated as a colorless viscous liquid. *According to method B*: silylation of 2-hydroxymalononitrile **3** (380 mg, 4.63 mmol) was carried out with triisopropylsilyl triflate (1.9 mL, 7.05 mmol) and 2,6-lutidine in CH_2Cl_2 overnight from 0 °C to room temperature. After work-up and concentration under reduced pressure, the brown liquid residue was purified by two successive flash chromatographies (pentane then pentane/Et_2O, 50 : 1; pentane then pentane/Et_2O, 20 : 1) to separate H-MAC-TIPS from triisopropylsilanol. H-MAC-TIPS **1b** (862 mg, 78% over 2 steps) was obtained as a colorless liquid. H-MAC-TIPS **1b** can be stored under argon for several months at −18 °C. R_f 0.23 (pentane/Et_2O, 20 : 1). IR (ATR): ν 2948, 2870, 2252, 1463, 1114 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 1.07–1.14 (m, 18H, $SiCH(CH_3)_2$), 1.16–1.24 (m, 3H, $SiCH(CH_3)_2$), 5.40 (s, 1H, $CH(CN)_2$). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 11.5 ($SiCH(CH_3)_2$), 17.3 ($SiCH(CH_3)_2$), 51.3 ($CH(CN)_2$), 112.3 ($CH(CN)_2$). Anal. Calcd for $C_{12}H_{22}N_2OSi$: C, 60.46; H, 9.30; N, 11.75. Found: C, 60.20; H, 9.08; N, 11.67.

2-(*tert*-Butyldiphenylsilyloxy)malononitrile, H-MAC-TBDPS (1c). *According to method A*: silylation of 2-hydroxymalononitrile **3** (380 mg, 4.63 mmol) was performed with *tert*-butyldiphenylsilyl chloride (1.8 mL, 7.03 mmol) and imidazole in DMF for 30 min at 0 °C followed by 30 min at room temperature. After work-up and concentration under reduced pressure, the orange viscous oil was purified by flash chromatography (pentane/Et_2O, 9 : 1) to give H-MAC-TBDPS **1c** (965 mg, 65% over 2 steps) as a colorless viscous oil, which crystallized as a

white solid after standing for 24 h at −18 °C. *According to method B*: silylation of 2-hydroxymalononitrile **3** (380 mg, 4.63 mmol) was carried out with *tert*-butyldiphenylsilyl triflate[29] (1.43 M in $CHCl_3$, 5.0 mL, 7.15 mmol) and 2,6-lutidine in CH_2Cl_2 overnight from 0 °C to room temperature. After work-up and concentration under reduced pressure, the brown liquid residue was purified by flash chromatography (pentane then pentane/Et_2O: 20 : 1) to furnish H-MAC-TBDPS **1c** (1.18 g, 80% over 2 steps) as a colorless viscous oil, which crystallized as a white solid after standing for 16 h under high vacuum (10^{-2} mbar). H-MAC-TBDPS **1c** can be stored under argon for several months at −18 °C. Mp 48 °C. R_f 0.25 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3074, 2962, 2933, 2890, 2860, 2253, 1590, 1472, 1428, 1112 cm^{-1}. HRMS (ES^+): calcd for $C_{19}H_{20}N_2NaOSi$ $[M + Na]^+$ 343.1237; found 343.1228. ^1H NMR (300 MHz, $CDCl_3$), δ 1.15 (s, 9H, $SiC(CH_3)_3$), 5.08 (s, 1H, $CH(CN)_2$), 7.46–7.59 (m, 6H, SiPh), 7.69–7.73 (m, 4H, SiPh). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 19.3 ($SiC(CH_3)_3$), 26.3 ($SiC(CH_3)_3$), 51.5 ($CH(CN)_2$), 111.9 ($CH(CN)_2$), 128.5 (CH_{Ph}), 129.3 (C_{Ph}), 131.2 (CH_{Ph}), 135.5 (CH_{Ph}). Anal. calcd for $C_{19}H_{20}N_2OSi$: C, 71.21; H, 6.29; N, 8.74. Found: C, 71.22; H, 6.33; N, 8.55.

MAC reactions with alcohols as nucleophiles

General procedure for MAC reactions. To freshly prepared *N*,*N*-dibenzyl-L-phenylalaninal (*c*. 0.5 mmol, 1 equiv.) and H-MAC-[Si] **1a–c** (2.4 equiv.) under argon, were added dry Et_2O (5 mL) followed by the alcohol (3 equiv.). After cooling at 0 °C, DMAP (2 equiv.) was added in one portion and the reaction mixture was stirred overnight under argon at this temperature. A saturated aqueous Na_2CO_3 solution (10 mL) was introduced at 0 °C. After addition of water (10 mL) to dissolve the salts, the aqueous phase was extracted with Et_2O (6 × 10 mL). The combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude residue was purified by flash chromatography (pentane/Et_2O, 20 : 1) to give the corresponding ester MAC reaction products.

The diastereoisomeric ratio (dr) was determined by ^1H NMR analysis ($CDCl_3$ at 293 K) on crude products either before or (in the cases of **14**/**14′**, **15**/**15′**, **4b**/**4b′** and **4c**/**4c′**) after chromatography. For product samples obtained from H-MAC-TBS, dr was determined by integration of the TBS methyl groups signals. For product samples obtained from H-MAC-TIPS, dr was determined by integration of the C*H*OTIPS signals. For product samples obtained from H-MAC-TBDPS, dr was determined by integration of the OMe signals.

Methyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (4a). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (155 mg, 0.47 mmol), H-MAC-TBS **1a** (223 mg, 1.14 mmol), methanol (58 μL, 1.43 mmol) and DMAP (115 mg, 0.94 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **4a**/**4a′** (dr 92 : 8, 196 mg, 83%), as a colorless oil. R_f 0.39 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3022, 2951, 2925, 2858, 1752, 1738, 1605, 1494, 1454, 1250, 1125 cm^{-1}. HRMS (ES^+): calcd for $C_{31}H_{42}NO_3Si$ $[M + H]^+$ 504.2928; found 504.2904. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**4a**): ^1H NMR (360 MHz, $CDCl_3$), δ 0.08 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.96 (s, 9H, $SiC(CH_3)_3$), 2.91–3.05 (m, 2H, $PhCH_2CH$), 3.37–3.44 (m, 1H, CHN), 3.53 (s, 3H, OCH_3), 3.61 (d, J = 13.9 Hz, 2H) and 3.78 (d, J = 13.9 Hz, 2H) (AB syst., $N(CH_2Ph)_2$), 4.60 (d, J = 4.3 Hz, 1H, C*H*OTBS), 7.08–7.14 (m, 6H, Ph), 7.17–7.31 (m, 9H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.8 ($Si(CH_3)_2$), 18.2 ($SiC(CH_3)_3$), 25.8 ($SiC(CH_3)_3$), 32.6 ($PhCH_2CH$), 51.5 (OCH_3), 54.4 ($N(CH_2Ph)_2$), 62.7 (CHN), 71.9 (*C*HOTBS), 125.8 (CH_{Ph}), 126.7 (CH_{Ph}), 127.9 (CH_{Ph}), 128.0 (CH_{Ph}), 128.7 (CH_{Ph}), 129.6 (CH_{Ph}), 139.5 (C_{Ph}), 140.3 (C_{Ph}), 173.4 ($COOCH_3$).

Methyl (2*S*,3*S*)-3-(dibenzylamino)-2-(triisopropylsilyloxy)-4-phenylbutanoate (4b). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (164 mg, 0.50 mmol), H-MAC-TIPS **1b** (290 mg, 1.22 mmol), methanol (62 μL, 1.53 mmol) and DMAP (122 mg, 1.00 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **4b**/**4b′** (dr 91 : 9, 217 mg, 80%), as a colorless oil. R_f 0.36 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3028, 2946, 2864, 2804, 1755, 1738, 1604, 1495, 1455, 1256, 1122 cm^{-1}. HRMS (ES^+): calcd for $C_{34}H_{48}NO_3Si$ $[M + H]^+$ 546.3398; found 546.3375. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**4b**): ^1H NMR (250 MHz, $CDCl_3$), δ 0.96–1.10 (m, 21H, $Si(CH(CH_3)_2)_3$), 2.99 (dd, J = 14.8, 9.5 Hz, 1H) and 3.08 (dd, J = 14.8, 5.0 Hz, 1H) (AB part of ABX syst., $PhCH_2CH$), 3.35–3.44 (m, 1H, CHN), 3.55 (s, 3H, OCH_3), 3.60 (d, J = 13.8 Hz, 2H) and 3.69 (d, J = 13.8 Hz, 2H) (AB syst., $N(CH_2Ph)_2$), 4.62 (d, J = 5.8 Hz, 1H, C*H*OTIPS), 7.04–7.10 (m, 4H, Ph), 7.14–7.29 (m, 11H, Ph). ^{13}C NMR (62.9 MHz, $CDCl_3$), δ 12.7 ($Si(CH(CH_3)_2)_3$), 18.1 ($Si(CH(CH_3)_2)_3$), 32.8 ($PhCH_2CH$), 51.4 (OCH_3), 54.6 ($N(CH_2Ph)_2$), 63.8 (CHN), 73.2 (*C*HOTIPS), 125.9 (CH_{Ph}), 126.7 (CH_{Ph}), 127.9 (CH_{Ph}), 128.1 (CH_{Ph}), 128.9 (CH_{Ph}), 129.6 (CH_{Ph}), 139.5 (C_{Ph}), 140.8 (C_{Ph}), 173.4 ($COOCH_3$).

Methyl (2*S*,3*S*)-2-(*tert*-butyldiphenylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (4c). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (146 mg, 0.44 mmol), H-MAC-TBDPS **1c** (340 mg, 1.06 mmol), methanol (54 μL, 1.33 mmol) and DMAP (108 mg, 0.88 mmol) in Et_2O. The resulting reaction mixture was concentrated under reduced pressure to destroy excess of H-MAC-TBDPS and purified directly. Flash chromatography gave inseparable MAC reaction products **4c**/**4c′** (dr 93 : 7, 203 mg, 74%), as a colorless oil. R_f 0.20 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3027, 2950, 2929, 2855, 2800, 1748, 1601, 1496, 1451, 1428, 1360, 1257, 1106 cm^{-1}. HRMS (ES^+): calcd for $C_{41}H_{46}NO_3Si$ $[M + H]^+$ 628.3241; found 628.3210. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**4c**): ^1H NMR (360 MHz, $CDCl_3$), δ 1.09 (s, 9H, $SiC(CH_3)_3$), 2.98 (dd, J = 14.8, 9.7 Hz, 1H) and 3.14 (dd, J = 14.8, 4.0 Hz, 1H) (AB part of ABX syst., $PhCH_2CH$), 3.19 (s, 3H, OCH_3), 3.38–3.44 (m, 1H, CHN), 3.45 (d, J = 13.7 Hz, 2H) and 3.62 (d, J = 13.7 Hz, 2H) (AB syst., $N(CH_2Ph)_2$), 4.54 (d, J = 5.4 Hz, 1H, C*H*OTBDPS), 6.96–7.02 (m, 4H, Ph), 7.11–7.17 (m, 7H, Ph), 7.20–7.27 (m, 4H, Ph), 7.32–7.43 (m, 6H, Ph), 7.62–7.67 (m, 4H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ 19.5 ($SiC(CH_3)_3$), 27.1 ($SiC(CH_3)_3$),

33.1 (Ph*C*H$_2$CH), 51.1 (OCH$_3$), 54.4 (N(*C*H$_2$Ph)$_2$), 63.4 (CHN), 73.2 (*C*HOTBDPS), 125.9 (CH$_{Ph}$), 126.6 (CH$_{Ph}$), 127.4 (CH$_{Ph}$), 127.6 (CH$_{Ph}$), 127.8 (CH$_{Ph}$), 128.1 (CH$_{Ph}$), 128.8 (CH$_{Ph}$), 129.6 (CH$_{Ph}$), 129.7 (CH$_{Ph}$), 129.8 (CH$_{Ph}$), 132.9 (C$_{Ph}$), 133.0 (C$_{Ph}$), 136.0 (CH$_{Ph}$), 136.1 (CH$_{Ph}$), 139.4 (C$_{Ph}$), 140.6 (C$_{Ph}$), 172.5 (*C*OOCH$_3$).

Methyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate (5). *From **4a**/**4a**′*: To a stirred solution of methyl (2*SR*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **4a**/**4a**′ (dr 92 : 8; 161 mg, 0.32 mmol) in dry THF (10 mL) at 0 °C under argon, was added dropwise tetrabutylammonium fluoride (1 M in THF, 480 µL, 0.48 mmol). After stirring for 1 h at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/EtOAc, 5 : 1) to furnish the *anti* alcohol **5** (100 mg, 80%), as a colorless oil. *From **4b**/**4b**′*: Following the above procedure using (2*SR*,3*S*)-3-(dibenzylamino)-2-(triisopropylsilyloxy)-4-phenylbutanoate **4b**/**4b**′ (dr 91 : 9; 169 mg, 0.31 mmol), *anti* alcohol **5** (104 mg, 86%) was obtained after flash chromatography (pentane/EtOAc, 3 : 1). *From **4c**/**4c**′*: Following a minor modification of the above procedure (reaction performed at rt for 16 h) using methyl (2*SR*,3*S*)-2-(*tert*-butyldiphenylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **4c**/**4c**′ (dr 93 : 7; 200 mg, 0.32 mmol), *anti* alcohol **5** (88 mg, 71%) was obtained after flash chromatography (pentane/EtOAc, 5 : 1). R_f 0.20 (pentane/EtOAc, 5 : 1). $[\alpha]_D^{22}$ = +35.9 (*c* 1.0, $CHCl_3$) [lit.[14e] $[\alpha]_D^{20}$ = + 35.8 (*c* 1.0, $CHCl_3$)]. IR (ATR): ν 3513, 3062, 3026, 2952, 2803, 1729, 1602, 1494, 1453, 1252, 1220, 1105 cm^{-1}. HRMS (ES$^+$): calcd for $C_{25}H_{28}NO_3$ $[M + H]^+$ 390.2064; found 390.2051. ^{1}H NMR (360 MHz, $CDCl_3$), δ 2.82 (dd, *J* = 14.0, 7.6 Hz, 1H) and 3.04 (dd, *J* = 14.0, 7.2 Hz, 1H) (AB part of ABX syst., PhC*H*$_2$CH), 3.14 (br s, 1H, CHO*H*), 3.43 (ddd, *J* = 7.6, 7.2, 1.8 Hz, 1H, CHN), 3.53 (s, 3H, OCH$_3$), 3.67 (d, *J* = 13.7 Hz, 2H) and 3.83 (d, *J* = 13.7 Hz, 2H) (AB syst., N(C*H*$_2$Ph)$_2$), 4.50 (br s, 1H, C*H*OH), 7.04–7.10 (m, 2H, Ph), 7.19–7.32 (m, 13H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ 31.9 (Ph*C*H$_2$CH), 52.3 (OCH$_3$), 54.5 (N(*C*H$_2$Ph)$_2$), 62.1 (CHN), 69.6 (CHOH), 126.1 (CH$_{Ph}$), 126.9 (CH$_{Ph}$), 128.0 (CH$_{Ph}$), 128.1 (CH$_{Ph}$), 128.8 (CH$_{Ph}$), 129.5 (CH$_{Ph}$), 139.0 (C$_{Ph}$), 139.5 (C$_{Ph}$), 174.9 (*C*OOCH$_3$).

Ethyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (6). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (151 mg, 0.46 mmol), H-MAC-TBS **1a** (215 mg, 1.10 mmol), ethanol (82 µL, 1.40 mmol) and DMAP (112 mg, 0.92 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **6**/**6**′ (dr 91 : 9, 174 mg, 73%), as a viscous colorless oil. R_f 0.29 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3027, 2956, 2929, 2854, 2796, 1747, 1730, 1601, 1494, 1454, 1365, 1254, 1130 cm^{-1}. HRMS (ES$^+$): calcd for $C_{32}H_{44}NO_3Si$ $[M + H]^+$ 518.3085; found 518.3062. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**6**): ^{1}H NMR (360 MHz, $CDCl_3$), δ 0.09 (s, 3H, SiCH$_3$), 0.13 (s, 3H, SiCH$_3$), 0.96 (s, 9H, SiC(CH$_3$)$_3$), 1.10 (t, *J* = 7.0 Hz, 3H, OCH$_2$C*H*$_3$), 2.90 (dd, *J* = 14.4, 5.0 Hz, 1H) and 2.98 (dd, *J* = 14.4, 8.8 Hz, 1H) (AB part of ABX syst., PhC*H*$_2$CH), 3.34–3.41 (m, 1H, CHN), 3.57 (d, *J* = 13.7 Hz, 2H) and 3.83 (d, *J* = 13.7 Hz, 2H) (AB syst., N(C*H*$_2$Ph)$_2$), 3.87–4.05 (m, 2H, OC*H*$_2$CH$_3$), 4.62 (d, *J* = 3.6 Hz, 1H, C*H*OTBS), 7.02–7.07 (m, 2H, Ph), 7.08–7.13 (m, 4H, Ph), 7.15–7.23 (m, 9H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.7 (SiCH$_3$), −4.6 (SiCH$_3$), 14.0 (OCH$_2$*C*H$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 32.6 (Ph*C*H$_2$CH), 54.4 (N(*C*H$_2$Ph)$_2$), 60.6 (O*C*H$_2$CH$_3$), 62.7 (CHN), 71.4 (*C*HOTBS), 125.7 (CH$_{Ph}$), 126.7 (CH$_{Ph}$), 127.9 (CH$_{Ph}$), 128.8 (CH$_{Ph}$), 129.6 (CH$_{Ph}$), 139.6 (C$_{Ph}$), 140.2 (C$_{Ph}$), 173.1 (*C*OOEt).

Benzyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (7). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (147 mg, 0.45 mmol), H-MAC-TBS **1a** (212 mg, 1.08 mmol), benzyl alcohol (140 µL, 1.35 mmol) and DMAP (110 mg, 0.90 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **7**/**7**′ (dr 92 : 8, 215 mg, 83%), as a colorless oil. R_f 0.34 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3031, 2956, 2929, 2858, 2801, 1752, 1730, 1601, 1494, 1454, 1363, 1253, 1123 cm^{-1}. HRMS (ES$^+$): calcd for $C_{37}H_{46}NO_3Si$ $[M + H]^+$ 580.3241; found 580.3217. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**7**): ^{1}H NMR (360 MHz, $CDCl_3$), δ 0.05 (s, 3H, SiCH$_3$), 0.13 (s, 3H, SiCH$_3$), 0.95 (s, 9H, SiC(CH$_3$)$_3$), 2.80 (dd, *J* = 14.4, 4.3 Hz, 1H) and 2.95 (dd, *J* = 14.4, 9.7 Hz, 1H) (AB part of ABX syst., PhC*H*$_2$CH), 3.31–3.38 (m, 1H, CHN), 3.55 (d, *J* = 14.6 Hz, 2H) and 3.87 (d, *J* = 14.6 Hz, 2H) (AB syst., N(C*H*$_2$Ph)$_2$), 4.71 (d, *J* = 2.9 Hz, 1H, C*H*OTBS), 4.85 (d, *J* = 12.2 Hz, 1H) and 5.03 (d, *J* = 12.2 Hz, 1H) (AB syst., OC*H*$_2$Ph), 6.82–6.91 (m, 2H, Ph), 7.03–7.11 (m, 6H, Ph), 7.12–7.19 (m, 9H, Ph), 7.27–7.31 (m, 3H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.7 (SiCH$_3$), −4.6 (SiCH$_3$), 18.2 (Si*C*(CH$_3$)$_3$), 25.8 (SiC(*C*H$_3$)$_3$), 32.4 (Ph*C*H$_2$CH), 54.4 (N(*C*H$_2$Ph)$_2$), 62.6 (CHN), 66.3 (O*C*H$_2$Ph), 70.9 (*C*HOTBS), 125.7 (CH$_{Ph}$), 126.6 (CH$_{Ph}$), 127.8 (CH$_{Ph}$), 128.0 (CH$_{Ph}$), 128.1 (CH$_{Ph}$), 128.4 (CH$_{Ph}$), 128.6 (CH$_{Ph}$), 129.7 (CH$_{Ph}$), 135.4 (C$_{Ph}$), 139.6 (C$_{Ph}$), 140.1 (C$_{Ph}$), 172.9 (*C*OOBn).

Allyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (8). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (143 mg, 0.43 mmol), H-MAC-TBS **1a** (203 mg, 1.03 mmol), allyl alcohol (88 µL, 1.29 mmol) and DMAP (105 mg, 0.86 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **8**/**8**′ (dr 91 : 9, 188 mg, 82%), as a colorless oil. R_f 0.35 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3027, 2956, 2929, 2858, 2800, 1751, 1730, 1602, 1494 1453, 1362, 1252, 1126 cm^{-1}. HRMS (ES$^+$): calcd for $C_{33}H_{44}NO_3Si$ $[M + H]^+$ 530.3085; found 530.3060. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**8**): ^{1}H NMR (360 MHz, $CDCl_3$), δ 0.08 (s, 3H, SiCH$_3$), 0.13 (s, 3H, SiCH$_3$), 0.96 (s, 9H, SiC(CH$_3$)$_3$), 2.91 (dd, *J* = 14.4, 5.0 Hz, 1H) and 2.99 (dd, *J* = 14.4, 9.0 Hz, 1H) (AB part of ABX syst., PhC*H*$_2$CH), 3.37–3.45 (m, 1H, CHN), 3.58 (d, *J* = 14.0 Hz, 2H) and 3.83 (d, *J* = 14.0 Hz, 2H) (AB syst., N(C*H*$_2$Ph)$_2$), 4.35 (ddt, *J* = 13.0, 5.8, 1.1 Hz, 1H) and 4.43 (ddt, *J* = 13.0, 6.1, 1.1 Hz, 1H) (AB part of ABXM syst.,

OCH_2CH=CH_2), 4.66 (d, J = 3.6 Hz, 1H, CHOTBS), 5.11–5.21 (m, 2H, OCH$_2$CH=CH_2), 5.74 (dddd, J = 16.9, 10.4, 6.1, 5.8 Hz, 1H, OCH$_2$CH=CH$_2$), 7.01–7.08 (m, 2H, Ph), 7.08–7.13 (m, 4H, Ph), 7.15–7.23 (m, 9H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.7 ($SiCH_3$), −4.6 ($SiCH_3$), 18.2 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 32.5 (PhCH$_2$CH), 54.5 (N(CH$_2$Ph)$_2$), 62.7 (CHN), 65.3 (OCH$_2$CH=CH$_2$), 71.4 (CHOTBS), 118.6 (OCH$_2$CH=CH$_2$), 125.8 (CH_{Ph}), 126.7 (CH_{Ph}), 127.9 (CH_{Ph}), 128.0 (CH_{Ph}), 128.7 (CH_{Ph}), 129.7 (CH_{Ph}), 131.7 (OCH$_2$$C$H=CH$_2$), 139.5 ($C_{Ph}$), 140.1 ($C_{Ph}$), 172.7 ($C$OOAll).

Propargyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (9). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (143 mg, 0.43 mmol), H-MAC-TBS **1a** (202 mg, 1.03 mmol), propargyl alcohol (80 μL, 1.29 mmol) and DMAP (105 mg, 0.86 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **9**/**9′** (dr 93 : 7, 217 mg, 95%), as a colorless oil. R_f 0.15 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3311, 3027, 2951, 2929, 2856, 2802, 2134, 1757, 1740, 1602, 1493, 1452, 1363, 1250, 1124 cm^{-1}. HRMS (ES$^+$): calcd for $C_{33}H_{42}NO_3Si$ [M + H]$^+$ 528.2928; found 528.2906. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**9**): ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.09 (s, 3H, $SiCH_3$), 0.13 (s, 3H, $SiCH_3$), 0.95 (s, 9H, SiC(CH$_3$)$_3$), 2.42 (t, J = 2.7 Hz, 1H, OCH$_2$C≡CH), 2.89–3.03 (m, 2H, PhCH_2CH), 3.36–3.45 (m, 1H, CHN), 3.58 (d, J = 14.0 Hz, 2H) and 3.79 (d, J = 14.0 Hz, 2H) (AB syst., N(CH_2Ph)$_2$), 4.40 (dd, J = 15.6, 2.7 Hz, 1H) and 4.56 (dd, J = 15.6, 2.7 Hz, 1H) (AB syst., OCH_2C≡CH), 4.63 (d, J = 3.9 Hz, 1H, CHOTBS), 7.05–7.13 (m, 6H, Ph), 7.16–7.25 (m, 9H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.8 ($SiCH_3$), −4.7 ($SiCH_3$), 18.1 (SiC(CH$_3$)$_3$), 25.8 (SiC(CH$_3$)$_3$), 32.6 (PhCH$_2$CH), 51.9 (OCH$_2$C≡CH), 54.4 (N(CH$_2$Ph)$_2$), 62.6 (CHN), 71.5 (CHOTBS), 75.0 (OCH$_2$C≡CH), 77.3 (OCH$_2$$C$≡CH), 125.8 ($CH_{Ph}$), 126.7 ($CH_{Ph}$), 128.0 ($CH_{Ph}$), 128.8 ($CH_{Ph}$), 129.6 ($CH_{Ph}$), 139.4 ($C_{Ph}$), 140.1 ($C_{Ph}$), 172.2 ($C$OOCH$_2$C≡CH).

2-Phenylethyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (10). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (145 mg, 0.44 mmol), H-MAC-TBS **1a** (208 mg, 1.06 mmol), 2-phényléthanol (160 μL, 1.33 mmol) and DMAP (108 mg, 0.88 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **10**/**10′** (dr 95 : 5, 210 mg, 80%), as a colorless oil. R_f 0.05 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3027, 2953, 2929, 2857, 2801, 1751, 1729, 1601, 1495, 1453, 1361, 1254, 1130 cm^{-1}. HRMS (ES$^+$): calcd for $C_{38}H_{48}NO_3Si$ [M + H]$^+$ 594.3398; found 594.3372. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**10**): ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.05 (s, 3H, $SiCH_3$), 0.11 (s, 3H, $SiCH_3$), 0.95 (s, 9H, SiC(CH$_3$)$_3$), 2.75 (t, J = 7.2 Hz, 2H, OCH$_2$CH_2Ph), 2.84 (dd, J = 14.4, 4.8 Hz, 1H) and 2.98 (dd, J = 14.4, 9.0 Hz, 1H) (AB part of ABX syst., PhCH_2CH), 3.32–3.43 (m, 1H, CHN), 3.57 (d, J = 14.2 Hz, 2H) and 3.83 (d, J = 14.2 Hz, 2H) (AB syst., N(CH_2Ph)$_2$), 4.12 (t, J = 7.2 Hz, 2H, OCH_2CH$_2$Ph), 4.63 (d, J = 3.3 Hz, 1H, CHOTBS), 6.97–7.04 (m, 2H, Ph), 7.06–7.13 (m, 6H, Ph), 7.16–7.35 (m, 12H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.8 ($SiCH_3$), −4.6 ($SiCH_3$), 18.2 (SiC(CH$_3$)$_3$), 25.9 (SiC(CH$_3$)$_3$), 32.5 (PhCH$_2$CH), 34.8 (OCH$_2$$CH_2$Ph), 54.4 (N($CH_2$Ph)$_2$), 62.5 (CHN), 65.1 (O$CH_2CH_2$Ph), 71.3 (C$H$OTBS), 125.7 ($CH_{Ph}$), 126.5 ($CH_{Ph}$), 126.7 ($CH_{Ph}$), 127.9 ($CH_{Ph}$), 128.0 ($CH_{Ph}$), 128.4 ($CH_{Ph}$), 128.6 ($CH_{Ph}$), 128.7 ($CH_{Ph}$), 129.7 ($CH_{Ph}$), 137.4 ($C_{Ph}$), 139.6 ($C_{Ph}$), 140.0 ($C_{Ph}$), 173.0 ($C$OOCH$_2CH_2$Ph).

3-Methylbutyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (11). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (141 mg, 0.43 mmol), H-MAC-TBS **1a** (202 mg, 1.03 mmol), isoamyl alcohol (140 μL, 1.29 mmol) and DMAP (105 mg, 0.86 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **11**/**11′** (dr 91 : 9, 154 mg, 64%), as a colorless oil. R_f 0.44 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3031, 2956, 2928, 2857, 2801, 1750, 1726, 1603, 1494, 1455, 1362, 1253, 1126 cm^{-1}. HRMS (ES$^+$): calcd for $C_{35}H_{50}NO_3Si$ [M + H]$^+$ 560.3554; found 560.3531. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**11**): ^{1}H NMR (400 MHz, $CDCl_3$), δ 0.10 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.83 (d, J = 6.8 Hz, 6H, OCH$_2$CH$_2$CH(CH_3)$_2$), 0.97 (s, 9H, SiC(CH$_3$)$_3$), 1.34 (q, J = 6.8 Hz, 2H, OCH$_2$CH_2CH(CH$_3$)$_2$), 1.44–1.52 (m, 1H, OCH$_2$CH$_2$CH(CH$_3$)$_2$), 2.88 (dd, J = 14.8, 4.8 Hz, 1H) and 3.00 (dd, J = 14.8, 9.2 Hz, 1H) (AB part of ABX syst., PhCH_2CH), 3.34–3.41 (m, 1H, CHN), 3.57 (d, J = 13.6 Hz, 2H) and 3.87 (d, J = 13.6 Hz, 2H) (AB syst., N(CH_2Ph)$_2$), 3.90–4.02 (m, 2H, OCH_2CH$_2$CH(CH$_3$)$_2$), 4.66 (d, J = 2.8 Hz, 1H, CHOTBS), 7.01–7.05 (m, 2H, Ph), 7.06–7.11 (m, 4H, Ph), 7.14–7.23 (m, 9H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ −4.6 ($SiCH_3$), −4.5 ($SiCH_3$), 18.2 (SiC(CH$_3$)$_3$), 22.3 (OCH$_2$CH$_2$CHCH$_3$), 22.4 (OCH$_2$CH$_2$CHCH$_3$), 24.7 (OCH$_2$CH$_2$$C$H(CH$_3$)$_2$), 25.9 (SiC($CH_3$)$_3$), 32.5 (Ph$CH_2$CH), 37.1 (OCH$_2$$CH_2$CH(CH$_3$)$_2$), 54.4 (N($CH_2$Ph)$_2$), 62.6 (CHN), 63.2 (O$CH_2CH_2$CH(CH$_3$)$_2$), 71.1 (C$H$OTBS), 125.8 ($CH_{Ph}$), 126.7 ($CH_{Ph}$), 127.9 ($CH_{Ph}$), 128.0 ($CH_{Ph}$), 128.7 ($CH_{Ph}$), 129.7 ($CH_{Ph}$), 139.6 ($C_{Ph}$), 140.1 ($C_{Ph}$), 173.2 ($C$OOCH$_2$).

Isobutyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (12). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (138 mg, 0.42 mmol), H-MAC-TBS **1a** (196 mg, 1.00 mmol), isobutanol (118 μL, 1.27 mmol) and DMAP (103 mg, 0.84 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **12**/**12′** (dr 91 : 9, 105 mg, 46%), as a colorless oil. R_f 0.39 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3026, 2957, 2931, 2857, 2800, 1750, 1730, 1603, 1495, 1453, 1363, 1251, 1129 cm^{-1}. HRMS (ES$^+$): calcd for $C_{34}H_{48}NO_3Si$ [M + H]$^+$ 546.3398; found 546.3375. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**12**): ^{1}H NMR (250 MHz, $CDCl_3$), δ 0.10 (s, 3H, $SiCH_3$), 0.15 (s, 3H, $SiCH_3$), 0.76 (d, J = 6.7 Hz, 3H, OCH$_2$CHCH_3), 0.79 (d, J = 6.7 Hz, 3H, OCH$_2$CHCH_3), 0.98 (s, 9H, SiC(CH$_3$)$_3$), 1.73 (nonuplet, J = 6.7 Hz, 1H, OCH$_2$CH(CH$_3$)$_2$), 2.87 (dd, J = 14.5, 5.0 Hz, 1H) and 3.01 (dd, J = 14.5, 9.0 Hz, 1H) (AB part of ABX syst., PhCH_2CH), 3.34–3.44 (m, 1H, CHN), 3.57 (d, J = 14.0 Hz, 2H) and 3.89 (d, J = 14.0 Hz, 2H) (AB syst., N(CH_2Ph)$_2$), 3.65 (dd, J = 10.5, 6.7 Hz, 1H) and 3.70 (dd, J = 10.5, 6.7 Hz, 1H) (AB part of ABX syst., OCH_2CH(CH$_3$)$_2$), 4.70 (d, J = 2.8 Hz, 1H, CHOTBS),

6.97–7.06 (m, 2H, Ph), 7.06–7.12 (m, 4H, Ph), 7.14–7.24 (m, 9H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.6 ($SiCH_3$), −4.5 ($SiCH_3$), 18.2 ($SiC(CH_3)_3$), 19.1 ($OCH_2CH(CH_3)_2$), 25.9 ($SiC(CH_3)_3$), 27.5 ($OCH_2CH(CH_3)_2$), 32.4 ($PhCH_2CH$), 54.4 ($N(CH_2Ph)_2$), 62.5 (CHN), 70.9 ($OCH_2CH(CH_3)_2$), 71.0 (CHOTBS), 125.8 (CH_{Ph}), 126.7 (CH_{Ph}), 127.9 (CH_{Ph}), 128.0 (CH_{Ph}), 128.6 (CH_{Ph}), 129.7 (CH_{Ph}), 139.6 (C_{Ph}), 140.0 (C_{Ph}), 173.2 (COOi-Bu).

(*S*)-2-Methylbutyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (13). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (131 mg, 0.40 mmol), H-MAC-TBS **1a** (188 mg, 0.96 mmol), (*S*)-2-methylbutan-1-ol (135 μL, 1.20 mmol) and DMAP (98 mg, 0.80 mmol) in Et_2O. Flash chromatography gave inseparable MAC reaction products **13**/**13′** (dr 90 : 10, 107 mg, 48%), as a colorless oil. R_f 0.27 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3027, 2957, 2929, 2858, 2800, 1747, 1726, 1603, 1496, 1453, 1361, 1254, 1128 cm^{-1}. HRMS (ES$^+$): calcd for $C_{35}H_{50}NO_3Si$ $[M + H]^+$ 560.3554; found 560.3534. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**13**): ^{1}H NMR (400 MHz, $CDCl_3$), δ 0.10 (s, 3H, $SiCH_3$), 0.14 (s, 3H, $SiCH_3$), 0.74 (d, J = 6.8 Hz, 3H, $OCH_2CH(CH_3)CH_2CH_3$), 0.81 (t, J = 7.4 Hz, 3H, $OCH_2CH(CH_3)CH_2CH_3$), 0.97 (s, 9H, $SiC(CH_3)_3$), 1.18–1.28 (m, 2H, $OCH_2CH(CH_3)CH_2CH_3$), 1.46–1.56 (m, 1H, $OCH_2CH(CH_3)CH_2CH_3$), 2.86 (dd, J = 14.6, 4.8 Hz, 1H) and 3.01 (dd, J = 14.6, 9.6 Hz, 1H) (AB part of ABX syst., $PhCH_2CH$), 3.35–3.42 (m, 1H, CHN), 3.57 (d, J = 14.0 Hz, 2H) and 3.90 (d, J = 14.0 Hz, 2H) (AB syst., $N(CH_2Ph)_2$), 3.69 (dd, J = 10.6, 6.6 Hz, 1H) and 3.78 (dd, J = 10.6, 6.2 Hz, 1H) (AB part of ABX syst., $OCH_2CH(CH_3)CH_2CH_3$), 4.69 (d, J = 2.4 Hz, 1H, CHOTBS), 7.00–7.04 (m, 2H, Ph), 7.06–7.11 (m, 4H, Ph), 7.13–7.24 (m, 9H, Ph). ^{13}C NMR (100.6 MHz, $CDCl_3$), δ −4.6 ($SiCH_3$), −4.5 ($SiCH_3$), 11.1 ($OCH_2CH(CH_3)CH_2CH_3$), 16.2 ($OCH_2CH(CH_3)CH_2CH_3$), 18.2 ($SiC(CH_3)_3$), 25.8 ($OCH_2CH(CH_3)CH_2CH_3$), 25.9 ($SiC(CH_3)_3$), 32.4 ($PhCH_2CH$), 33.9 ($OCH_2CH(CH_3)CH_2CH_3$), 54.4 ($N(CH_2Ph)_2$), 62.5 (CHN), 69.4 ($OCH_2CH(CH_3)CH_2CH_3$), 70.9 (CHOTBS), 125.8 (CH_{Ph}), 126.7 (CH_{Ph}), 127.9 (CH_{Ph}), 128.0 (CH_{Ph}), 128.6 (CH_{Ph}), 129.7 (CH_{Ph}), 139.6 (C_{Ph}), 140.0 (C_{Ph}), 173.3 ($COOCH_2$).

Isopropyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (14). According to the general procedure, the MAC reaction was performed with *N*,*N*-dibenzyl-L-phenylalaninal (121 mg, 0.37 mmol), H-MAC-TBS **1a** (175 mg, 0.89 mmol), isopropanol (85 μL, 1.11 mmol) and DMAP (90 mg, 0.74 mmol) in Et_2O (4 mL). Flash chromatography gave inseparable MAC reaction products **14**/**14′** (dr 93 : 7, 21 mg, 11%), as a colorless oil. R_f 0.40 (pentane/Et_2O, 20 : 1). IR (ATR): ν 3028, 2952, 2930, 2855, 2800, 1749, 1721, 1604, 1495, 1454, 1373, 1258, 1141, 1105 cm^{-1}. HRMS (ES$^+$): calcd for $C_{33}H_{46}NO_3Si$ $[M + H]^+$ 532.3241; found 532.3217. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**14**): ^{1}H NMR (360 MHz, $CDCl_3$), δ 0.12 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$), 0.99 (s, 9H, $SiC(CH_3)_3$), 1.03 (d, J = 6.3 Hz, 3H, $OCHCH_3$), 1.18 (d, J = 6.3 Hz, 3H, $OCHCH_3$), 2.82 (dd, J = 14.8, 4.7 Hz, 1H) and 2.98 (dd, J = 14.8, 9.7 Hz, 1H) (AB part of ABX syst., $PhCH_2CH$), 3.32 (ddd, J = 6.8, 4.7, 2.5 Hz, 1H, CHN), 3.52 (d, J = 14.0 Hz, 2H) and 3.93 (d, J = 14.0 Hz, 2H) (AB syst., $N(CH_2Ph)_2$), 4.68 (d, J = 2.5 Hz, 1H, CHOTBS), 4.86 (septuplet, J = 6.3 Hz, 1H, $OCH(CH_3)_2$), 6.94–7.02 (m, 2H, Ph), 7.05–7.12 (m, 4H, Ph), 7.15–7.23 (m, 9H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.6 ($SiCH_3$), −4.4 ($SiCH_3$), 18.2 ($SiC(CH_3)_3$), 21.5 ($OCHCH_3$), 21.8 ($OCHCH_3$), 25.9 ($SiC(CH_3)_3$), 32.4 ($PhCH_2CH$), 54.3 ($N(CH_2Ph)_2$), 62.4 (CHN), 68.2 ($OCH(CH_3)_2$), 70.4 (CHOTBS), 125.7 (CH_{Ph}), 126.7 (CH_{Ph}), 127.8 (CH_{Ph}), 127.9 (CH_{Ph}), 128.7 (CH_{Ph}), 129.7 (CH_{Ph}), 139.6 (C_{Ph}), 140.1 (C_{Ph}), 172.9 (COOi-Pr).

Cyclopentyl (2*S*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate (15). A minor adaptation of the general procedure was used. To freshly prepared *N*,*N*-dibenzyl-L-phenylalaninal (161 mg, 0.49 mmol) and H-MAC-TBS **1a** (231 mg, 1.18 mmol) under argon, was added dry Et_2O (5 mL). After cooling at 0 °C, DMAP (120 mg, 0.98 mmol) was introduced and the reaction mixture was stirred for 10 min at 0 °C then cyclopentanol (95 μL, 1.47 mmol) was added. The reaction mixture was stirred overnight under argon at 0 °C. A saturated aqueous Na_2CO_3 solution (10 mL) was introduced at 0 °C. After addition of water (10 mL) to dissolve the salts, the aqueous phase was extracted with Et_2O (6 × 10 mL). Followed by the addition of water (10 mL) to dissolve the salts. The combined organic phases were washed with 1 M HCl (50 mL), brine (50 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography (pentane/Et_2O, 30 : 1) gave inseparable MAC reaction products **15**/**15′** (dr 90 : 10, 38 mg, 14%), as a viscous colorless oil. R_f 0.43 (pentane/Et_2O, 10 : 1). IR (ATR): ν 3025, 2956, 2929, 2860, 2800, 1758, 1728, 1604, 1494, 1462, 1379, 1268, 1121 cm^{-1}. HRMS (ES$^+$): calcd for $C_{35}H_{48}NO_3Si$ $[M + H]^+$ 558.3398; found 558.3371. Spectroscopic data for the major *anti* (*2S,3S*)-diastereomer (**15**): ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.13 (s, 3H, $SiCH_3$), 0.16 (s, 3H, $SiCH_3$), 1.00 (s, 9H, $SiC(CH_3)_3$), 1.39–1.53 (m, 4H, $OCH(CH_2CH_2)_2$), 1.56–1.71 (m, 4H, $OCH(CH_2CH_2)_2$), 2.84 (dd, J = 14.7, 4.8 Hz, 1H) and 3.00 (dd, J = 14.7, 9.3 Hz, 1H) (AB part of ABX syst., $PhCH_2CH$), 3.35 (ddd, J = 9.3, 4.8, 2.4 Hz, 1H, CHN), 3.55 (d, J = 14.0 Hz, 2H) and 3.93 (d, J = 14.0 Hz, 2H) (AB syst., $N(CH_2Ph)_2$), 4.68 (d, J = 2.4 Hz, 1H, CHOTBS), 4.96–5.03 (m, 1H, $OCH(CH_2CH_2)_2$), 6.95–7.03 (m, 2H, Ph), 7.07–7.13 (m, 4H, Ph), 7.15–7.25 (m, 9H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ −4.6 ($SiCH_3$), −4.4 ($SiCH_3$), 18.2 ($SiC(CH_3)_3$), 23.5 ($OCHCH_2CH_2$), 23.6 ($OCHCH_2CH_2$), 25.9 ($SiC(CH_3)_3$), 32.3 ($PhCH_2CH$), 32.5 ($OCH(CH_2CH_2)_2$), 54.4 ($N(CH_2Ph)_2$), 62.4 (CHN), 70.6 (CHOTBS), 77.6 ($OCH(CH_2CH_2)_2$), 125.7 (CH_{Ph}), 126.7 (CH_{Ph}), 127.9 (CH_{Ph}), 128.0 (CH_{Ph}), 128.6 (CH_{Ph}), 129.7 (CH_{Ph}), 139.7 (C_{Ph}), 140.0 (C_{Ph}), 173.1 (COOCH).

Methyl (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate (16). Palladium hydroxide (20 wt%) on activated carbon (7.2 mg) was added to a solution of methyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **5** (55 mg, 0.14 mmol) in MeOH (10 mL). The resulting mixture was stirred under H_2 (1 atm) for 1 h at room temperature and then filtered through a pad of Celite which was washed through with MeOH. The combined filtrate and washings were concentrated under reduced pressure. The residual pale yellow oil was taken up in Et_2O, fil-

tered through a PVDF membrane (0.22 μm pore size) and the filtrate was evaporated under reduced pressure to furnish (2*S*,3*S*)-allophenylnorstatin methyl ester **16** (26 mg, 88%), as a colorless oil. R_f 0.50 (MeOH). $[\alpha]_D^{22}$ = +24.1 (*c* 1.0, CH_3OH). IR (ATR): ν 3474, 3357, 3297, 3028, 2953, 2922, 2853, 1732, 1601, 1583, 1496, 1452, 1438, 1207 cm^{-1}. HRMS (ES^+): calcd for $C_{11}H_{16}NO_3$ $[M + H]^+$ 210.1125; found 210.1119. ^1H NMR (360 MHz, CD_3OD), δ 2.63 (dd, *J* = 13.7, 8.6 Hz, 1H) and 2.86 (dd, *J* = 13.7, 6.0 Hz, 1H) (AB part of ABX syst., PhCH_2CH), 3.27–3.36 (m, 1H, CHN), 3.67 (s, 3H, OCH_3), 4.14 (d, *J* = 4.0 Hz, 1H, C*H*OH), 7.18–7.25 (m, 3H, Ph), 7.26–7.33 (m, 2H, Ph). ^{13}C NMR (90.6 MHz, CD_3OD), δ 39.5 (Ph*C*H_2CH), 52.4 (OCH_3), 57.0 (CHN), 74.8 (CHOH), 127.5 (CH_{Ph}), 129.5 (CH_{Ph}), 130.5 (CH_{Ph}), 139.8 (C_{Ph}), 174.6 (*C*OOMe).

Ethyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate (17). Tetrabutylammonium fluoride (1 M in THF, 930 μL, 0.93 mmol) was added dropwise to a stirred solution of ethyl (2*SR*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenyl-butanoate **6a**/**6a′** (dr 92 : 8; 322 mg, 0.62 mmol) in dry THF (15 mL) at 0 °C. After stirring for 2 h at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution (5 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/CH_2Cl_2/Et_2O, 10 : 1 : 1 then pentane/EtOAc, 5 : 1) to furnish the *anti* alcohol **17** (229 mg, 91%), as a colorless oil. R_f 0.34 (pentane/EtOAc, 5 : 1). $[\alpha]_D^{19}$ = +70.4 (*c* 1.0, $CHCl_3$). IR (ATR): ν 3499, 3062, 3025, 2974, 2804, 1724, 1603, 1495, 1452, 1368, 1249, 1215, 1105 cm^{-1}. HRMS (ES^+): calcd for $C_{26}H_{30}NO_3$ $[M + H]^+$ 404.2220; found 404.2204. ^1H NMR (360 MHz, $CDCl_3$), δ 1.11 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 2.78 (dd, *J* = 14.0, 7.2 Hz, 1H) and 3.00 (dd, *J* = 14.0, 7.2 Hz, 1H) (AB part of ABX syst., PhCH_2CH), 3.12 (d, *J* = 6.1 Hz, 1H, CHO*H*), 3.44 (ddd, *J* = 7.2, 7.2, 2.1 Hz, 1H, CHN), 3.64 (d, *J* = 14.0 Hz, 2H) and 3.86 (d, *J* = 14.0 Hz, 2H) (AB syst., $N(CH_2Ph)_2$), 3.89–4.05 (m, 2H, OCH_2CH_3), 4.52 (dd, *J* = 6.1, 2.1 Hz, 1H, C*H*OH), 7.00–7.05 (m, 2H, Ph), 7.19–7.28 (m, 13H, Ph). ^{13}C NMR (90.6 MHz, $CDCl_3$), δ 13.8 (OCH_2CH_3), 31.9 (Ph*C*H_2CH), 54.5 ($N(CH_2Ph)_2$), 61.6 (OCH_2CH_3), 61.9 (CHN), 69.4 (CHOH), 126.0 (CH_{Ph}), 126.8 (CH_{Ph}), 128.0 (CH_{Ph}), 128.1 (CH_{Ph}), 128.8 (CH_{Ph}), 129.5 (CH_{Ph}), 139.0 (C_{Ph}), 139.6 (C_{Ph}), 174.6 (*C*OOEt).

Ethyl (2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutanoate (18). Palladium hydroxide (20 wt%) on activated carbon (4 mg) was added to a solution of ethyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **17** (37 mg, 0.09 mmol) in EtOH (10 mL). The resulting mixture was stirred under H_2 (1 atm) for 2 h at room temperature and then filtered through a pad of Celite which was washed with EtOH. The combined filtrate and washings were concentrated under reduced pressure. The residual pale yellow oil was taken up in Et_2O, filtered through a PVDF membrane (0.22 μm pore size) and the filtrate was evaporated under reduced pressure to furnish (2*S*,3*S*)-allophenylnorstatin ethyl ester **18** (15 mg, 73%), as a colorless oil. R_f 0.57 (MeOH). $[\alpha]_D^{24}$ = +20.0 (*c* 1.0, CH_3OH). IR (ATR): ν 3478, 3362, 3287, 3064, 2924, 2859, 1731, 1602, 1496, 1454, 1368, 1202 cm^{-1}. HRMS (ES^+): calcd for $C_{12}H_{18}NO_3$ $[M + H]^+$ 224.1281; found 224.1274. ^1H NMR (400 MHz, DMSO-d_6), δ 1.21 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3), 1.36 (br s, 2H, NH_2), 2.46 (dd, *J* = 13.2, 8.8 Hz, 1H) and 2.76 (dd, *J* = 13.2, 4.2 Hz, 1H) (AB part of ABX syst., PhCH_2CH), 3.01–3.10 (m, 1H, CHN), 3.85 (br d, *J* = 4.8 Hz, 1H, C*H*OH), 4.02–4.12 (m, 2H, OCH_2CH_3), 5.52 (br s, 1H, CHO*H*), 7.15–7.23 (m, 3H, Ph), 7.24–7.31 (m, 2H, Ph). ^{13}C NMR (100 MHz, DMSO-d_6), δ 14.1 (OCH_2CH_3), 38.8 (Ph*C*H_2CH), 56.0 (CHN), 59.8 (OCH_2CH_3), 74.5 (CHOH), 125.8 (CH_{Ph}), 128.0 (CH_{Ph}), 129.3 (CH_{Ph}), 139.5 (C_{Ph}), 172.7 (*C*OOEt).

Benzyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate (19). To a stirred solution of benzyl (2*SR*,3*S*)-2-(*tert*-butyldimethylsilyloxy)-3-(dibenzylamino)-4-phenylbutanoate **7**/**7′** (dr 92 : 8; 173 mg, 0.30 mmol) in dry THF (4 mL) at 0 °C under argon, was added dropwise tetrabutylammonium fluoride (1 M in THF, 450 μL, 0.45 mmol). After stirring for 50 minutes at 0 °C, the reaction mixture was quenched by addition of a saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by flash chromatography (pentane/EtOAc, 10 : 1) to furnish the *anti* alcohol **19** (117 mg, 84%), as a colorless oil. R_f 0.32 (pentane/EtOAc, 5 : 1). $[\alpha]_D^{22}$ = +28.7 (*c* 1.0, $CHCl_3$). IR (ATR): ν 3514, 3066, 3028, 2926, 2804, 1730, 1599, 1496, 1452, 1258, 1211, 1104 cm^{-1}. HRMS (ES^+): calcd for $C_{31}H_{32}NO_3$ $[M + H]^+$ 466.2376; found 466.2365. ^1H NMR (300 MHz, $CDCl_3$), δ 2.68 (dd, *J* = 14.1, 6.9 Hz, 1H) and 2.96 (dd, *J* = 14.1, 7.8 Hz, 1H) (AB part of ABX syst., PhCH_2CH), 3.09 (d, *J* = 6.0 Hz, 1H, CHO*H*), 3.44 (ddd, *J* = 7.8, 6.9, 1.8 Hz, 1H, CHN), 3.61 (d, *J* = 14.0 Hz, 2H) and 3.86 (d, *J* = 14.0 Hz, 2H) (AB syst., $N(CH_2Ph)_2$), 4.60 (dd, *J* = 6.0, 1.8 Hz, 1H, C*H*OH), 4.88 (d, *J* = 12.3 Hz, 1H) and 4.92 (d, *J* = 12.3 Hz, 1H) (AB syst., OCH_2Ph), 6.85–6.90 (m, 2H, Ph), 7.04–7.09 (m, 2H, Ph), 7.11–7.16 (m, 3H, Ph), 7.18–7.24 (m, 10H, Ph), 7.26–7.32 (m, 3H, Ph). ^{13}C NMR (75.5 MHz, $CDCl_3$), δ 31.9 (Ph*C*H_2CH), 54.5 ($N(CH_2Ph)_2$), 61.9 (CHN), 67.2 (OCH_2Ph), 69.4 (CHOH), 126.0 (CH_{Ph}), 126.8 (CH_{Ph}), 127.9 (CH_{Ph}), 128.0 (CH_{Ph}), 128.1 (CH_{Ph}), 128.3 (CH_{Ph}), 128.5 (CH_{Ph}), 128.7 (CH_{Ph}), 129.6 (CH_{Ph}), 134.8 (C_{Ph}), 138.9 (C_{Ph}), 139.6 (C_{Ph}), 174.5 (*C*OOBn).

(2*S*,3*S*)-3-Amino-2-hydroxy-4-phenylbutanoic acid, (−)-allophenylnorstatin (20). Palladium (10 wt%) on activated carbon (6 mg) was added to a solution of benzyl (2*S*,3*S*)-3-(dibenzylamino)-2-hydroxy-4-phenylbutanoate **19** (50 mg, 0.10 mmol) in EtOAc (8 mL). The resulting mixture was stirred under H_2 (1 atm pressure) for 24 h at room temperature and then filtered through a short pad of Celite which was washed through with further EtOAc. Water (3 × 5 mL) was then allowed to percolate through the solid material that remained on the Celite pad. The combined aqueous extracts were concentrated under reduced pressure and dried under high vacuum to furnish (2*S*,3*S*)-allophenylnorstatin **20** (20 mg, 95%), as a white powder. Mp 196 °C (dec.) [lit.[15p] 195 °C (dec.)]. R_f 0.53 (MeOH). $[\alpha]_D^{23}$ = −5.6 (*c* 0.1, 1 M HCl) [lit.[15m] $[\alpha]_D^{20}$ = −5.5 (*c* 0.1, 1 M HCl)]. IR (ATR): ν 3369, 3024, 1599, 1549, 1417, 1342, 1301, 1062 cm^{-1}. HRMS (ES^-): calcd for $C_{10}H_{12}NO_3$ $[M - H]^-$

194.0822; found 194.0819. ^{1}H NMR (300 MHz, D_2O), δ 2.91 (dd, J = 14.4, 10.5 Hz, 1H) and 3.02 (dd, J = 14.4, 3.9 Hz, 1H) (AB part of ABX syst., PhCH_2CH), 3.89 (ddd, J = 10.5, 3.9, 3.3 Hz, 1H, CHNH_2), 4.33 (d, J = 3.3 Hz, 1H, CHOH), 7.33–7.52 (m, 5H, Ph). ^{13}C NMR (75.5 MHz, D_2O), δ 33.1 (PhCH_2CH), 55.7 (CHNH_2), 71.4 (CHOH), 127.6 (CH_{Ph}), 129.2 (CH_{Ph}), 129.4 (CH_{Ph}), 135.4 (C_{Ph}), 176.4 (COOH). ^{1}H and ^{13}C NMR data were in agreement with those described in literature.[15m,p]

Conflicts of interest

There are no conflicts to declare.

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