β-Amino-α-hydroxy Esters by Asymmetric Hydroxylation of *homo*-β-Amino Acid Esters

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Dedicated to Prof. L. Mangoni on the occasion of his 70th birthday

Keywords: Amino acids / Asymmetric synthesis / Hydroxylation

The asymmetric α-hydroxylation of *N*,*N*-diprotected *homo*-β-amino acid methyl esters is reported. The starting compounds are readily available, being prepared from simple α-amino acids by a procedure that we have already reported. α-Hydroxylation proceeded smoothly at –78 °C with high yields and good diastereomeric ratios. In comparison with other asymmetric α-hydroxylation procedures, (a) this method does not need the use of costly chiral reagents and/or chiral auxiliaries and (b) it represents the first example of a procedure affording β-amino-α-hydroxy acids with full, orthogonal protection.

Introduction

β-Amino-α-hydroxy acids are of great biological interest since they represent substructures of more complex bioactive compounds possessing either anti-cancer or enzyme-inhibiting activity. In this context, a prominent place is held by drugs such as kynostatins,[1] conformationally constrained tripeptides, and highly potent HIV protease inhibitors containing allophenylnorstatine [(2*S*,3*S*)-3-amino-2-hydroxy-4-phenylbutyric acid]. β-Amino-α-hydroxy acids are also present, although with different configurations, in drugs such as taxol[2] and bestatin;[3] it is also noteworthy that some taxol analogues with the same stereochemistry as allophenylnorstatine have fairly recently been reported[4] to be even more active than taxol itself.

In view of both the importance and the economic significance of such compounds, it is not surprising that a great deal of work to achieve optically pure β-amino-α-hydroxy acids by various approaches has been carried out. *N*-Protected α-amino aldehydes, originating from the reduction of the corresponding carboxylic acids, have been treated with trimethylsilyl cyanide[5] to afford intermediate cyanohydrins, subsequent hydrolysis of which has provided the α-hydroxy acids. Unfortunately, such an approach is not easily applicable to gram-scale preparations, mainly due to the poor stability of the starting aldehydes themselves. These have also been treated with nitromethane[6] in the presence of a lanthanum *tert*-butoxide catalyst, but the results achieved after the acidic hydrolysis of the coupling products were still quite unsatisfactory in spite of the catalyst's extra cost.

Other, more efficient, methods for the preparation of β-amino-α-hydroxy acids include (a) the treatment of α,β-unsaturated esters with chiral lithium amides,[7–9] (b) the hydrolysis of chiral oxazoline-5-carboxylates,[10,11] and (c) the opening of α-hydroxy-β-lactams.[12]

Results and Discussion

As a part of our current interest in the chemistry of *homo*-β-amino acids,[13] we report here a practical and efficient asymmetric hydroxylation of such substrates. If the procedure for the preparation of the *homo*-β-amino acids is included, this constitutes a formal synthesis of β-amino-α-hydroxy acids from simple α-amino acids. Under the conditions that we have devised, 4-methoxybenzyl *N*,*N*-diprotected *homo*-β-amino acid methyl esters, prepared from their corresponding α-amino acids, were treated with potassium hexamethyldisilazanide (KHMDS),[14,15] and the resulting enolates were in turn allowed to react with racemic 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine[16] to afford their α-hydroxy derivatives.

The use of the more readily available lithium hexamethyldisilazanide (LHMDS) was also considered, but had to be discarded since the yields of the final products were significantly poorer.[17] This was due both to slower enolate production (monitored by quenching the reactions with D_2O

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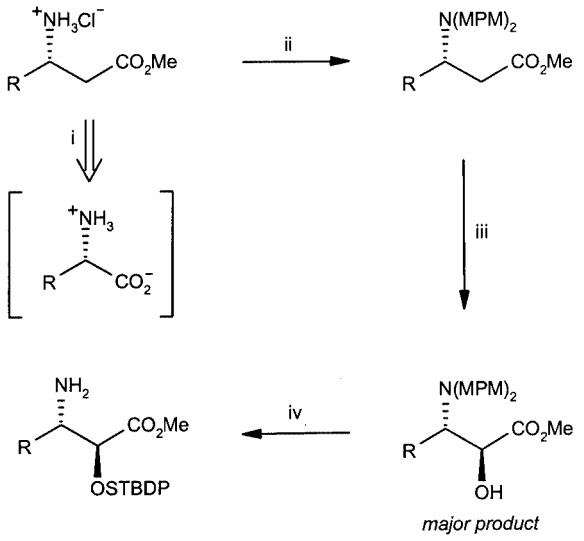
at different times) and faster formation of an enolate-consuming[18] by-product in the subsequent coupling with the oxaziridine reagent.



Scheme 1. Conversion of α-amino acids into β-amino-α-hydroxy esters: i. ref.[10]; ii. MPMCl, DIPEA, toluene, reflux; iii. KHMDS, 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine, dry THF, −78 °C; iv. a) TBDPSCl, ImH, dry THF, DMAP, 25 °C; b) CAN, CH_3CN/H_2O, 25 °C

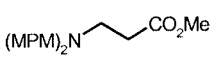
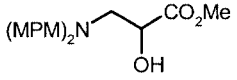
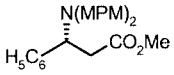
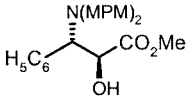
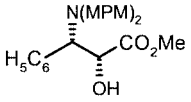
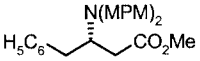
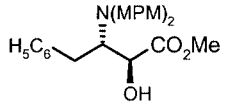
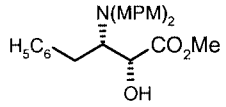
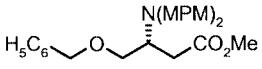
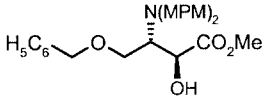
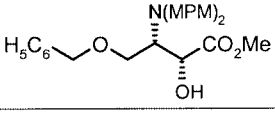
The course of the reaction is outlined in Scheme 1, and the results obtained[19] by α-hydroxylation of various fully protected *homo*-β-amino acids − namely *homo*-β-glycine (**1**), *homo*-β-phenylglycine (**2**), *homo*-β-phenylalanine (**3**), and finally *homo*-β-serine (**4**) − are reported in Table 1.

The protection of the amino group in the starting amino acid esters represented a crucial step in the overall procedure. Firstly, both the hydrogen atoms in the amino group had to be protected in order to avoid the abstraction of the residual amino hydrogen atom by the base used in the hydroxylation step. That meant that the common protecting groups, such as Boc, Cbz, etc., could not be effectively used under the hydroxylation conditions, and only benzyl protection was found to be suitable for this purpose. In view of the much greater flexibility of conditions suitable for removal of the 4-methoxybenzyl group in comparison to those required for the simple benzyl group, the former was definitely to be preferred.

Such a choice was indeed expedient to overcome the protection problems, but at the same time represented a way to introduce into the substrate molecule a very bulky substituent, capable of controlling the stereochemical outcome[20] of the subsequent coupling of the oxaziridine reagent.

Indeed, the strong point of our procedure in comparison with most other reported α-hydroxylation procedures rests in the fact that neither chiral reagents nor chiral auxiliaries,

Table 1. α-Hydroxylation of *N*,*N*-diprotected homo-β-amino acid methyl esters

	Starting compound	Yield (%)		Product(s)	$[\alpha]_D^{25}$[a]	*de* (%)
1		94	**5**		–	–
2		92	**6**		+72.4 (2.14)	82[b]
			7		+84.1 (1.63)	
3		89	**8**		+31.7 (0.30)	94[c]
			9		+1.6 (1.11)	
4		95	**10**		+41.9 (2.97)	92[c]
			11		n.d.	

[a] $CHCl_3$ solutions. Concentrations are given in brackets. [b] Diastereomeric ratio determined by 400 MHz ^1H NMR. [c] Diastereomeric ratio determined by GC-MS.

which are generally costly, were needed to perform the asymmetric hydroxylation; the asymmetric induction was in fact exerted by the chiral center of the starting amino acid, the contribution of which was probably amplified by the presence of the cumbersome amine protection. As a matter of fact, PM3 calculations carried out for the enolate ion produced from the starting compound **2** showed that its more favored conformation was the one with the enolate group between the hydrogen atom and the protected amino group (Figure 1). Its energy was 23.5 kJ mol^{-1} lower and, since the attack at the oxaziridine reagent took place from the lower part of the enolate moiety (opposite to the bulky substituted nitrogen group), it provided an excess of the *anti* diastereomer. Accordingly, in the case of the enolate from **3**, the same conformation had a much smaller energy advantage (9.6 kJ mol^{-1}), and this may account for the lower diastereomeric excess achieved in its hydroxylation.

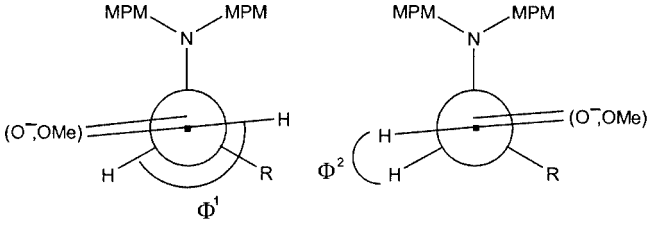


Figure 1. Conformations of the enolate anions from *homo*-β-phenylalanine (**3**) and *homo*-β-phenylglycine (**2**)

To the best of our knowledge, this procedure is presently the only one that enables the preparation of fully protected β-amino-α-hydroxy acids with three orthogonal protecting groups. In fact, the hydroxy group can easily be converted into its *O*-*tert*-butyldiphenylsilyl ether by treatment with *tert*-butyldiphenylsilyl chloride (TBDPSCl), and the amino group can in turn be deprotected by CAN and the methyl ester can be hydrolyzed in the usual ways. This may prove to be very convenient for the insertion of such units into complex bioactive molecules. Successful work aimed at the synthesis of more complex β-amino-α-hydroxy acids from α-amino acids through their β-homologues is already in progress.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra ($CDCl_3$): Bruker DRX 400 spectrometer, chemical shifts in ppm (δ), TMS internal standard. GC/MS analyses: Hewlett−Packard 6890 GC/5973N MS. Optical rotations ($CHCl_3$): Jasco P-1010 (1.0-dm cell). Combustion analyses: Perkin−Elmer Series II 2400, CHNS analyzer. TLC analyses: Merck 60 F_{254} silica gel plates (layer thickness 0.2 mm). Column chromatography: Merck 60 Kieselgel (70−230 mesh). Dry solvents were distilled immediately before use. Chemical names are accompanied by an abbreviation consisting of the three-letter code of the natural α-amino acids followed by the symbol ψ[ ], which denotes the replacement of the amino acid carboxyl group by the substructure included between the brackets.[13]

Methyl 3-[Bis(4-methoxybenzyl)amino]propanoate, *N*,*N*-(MPM)-Glyψ[CH_2CO_2Me] (1); Typical Procedure for the Full Protection of the Amino Group: A magnetically stirred suspension of *homo*-β-glycine hydrochloride methyl ester (0.39 g; 2.84 mmol) and diisopropylethylamine (DIPEA, 25 mL; 0.14 mmol) in toluene (10 mL) was gently warmed until a clear solution was obtained. 4-Methoxybenzyl chloride (2.3 mL; 17 mmol) was then added in one portion, and the resulting solution was heated under reflux until the starting *homo*-β-glycine, and also the intermediate *N*-monosubstituted derivative, were completely consumed (ca. 5 h, TLC monitoring). The reaction mixture was then cooled in an ice bath, diluted with ethyl acetate (0.2 L), and extracted with 10% aq. NH_4Cl. The organic layer was washed with brine and dried (Na_2SO_4), and the solvents were evaporated under reduced pressure to afford a crude reaction product, chromatography of which on silica gel (petroleum ether/Et_2O, 8:2) gave the pure, oily title compound **1** (0.37 g; 85%). ^{1}H NMR: δ = 2.50 (t, $J_{2,3}$ = 7.3 Hz, 2 H, 2-H), 2.78 (t, $J_{3,2}$ = 7.3 Hz, 2 H, 3-H), 3.52 (s, 4 H, 2 × MPM-CH_2), 3.62 (s, 3 H, OMe), 3.80 (s, 6 H, 2 × MPM-OMe), 6.85 (d, J = 8.7 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.24 (d, J = 8.7 Hz, 4 H, 2 × MPM-2-H and 6-H) ppm. ^{13}C NMR: δ = 32.5 (C-2), 48.7 (C-3), 51.5 (OMe), 55.2 (OMe-MPM), 57.1 (CH_2-MPM), 113.6, and 129.9, and 131.0, and 158.6 (C, aromatic), 173.1 (C=O) ppm. $C_{20}H_{25}NO_4$ (343.43): calcd. C 69.95, H 7.34; found C 70.20, H 7.30. Under the same conditions, the following *N*-protected esters were also obtained.

Methyl (*R*)-3-[Bis(4-methoxybenzyl)amino]-3-phenylpropanoate, *N*,*N*-(MPM)-Phgψ[CH_2CO_2Me] (2): Oil (83%). ^{1}H NMR: δ = 2.71 (dd, $J_{2a,3}$ = 7.2 Hz, $J_{2a,2b}$ = 14.5 Hz, 1 H, 2-H_a), 3.09 (d, $J_{a,b}$ = 13.6 Hz, 2 H, 2 × MPM-CH_aH_b), 3.07−3.18 (m, 1 H, 2-H_b), 3.64 (s, 3 H, OMe), 3.69 (d, $J_{b,a}$ = 13.6 Hz, 2 H, 2 × MPM-CH_aH_b), 3.79 (s, 6 H, 2 × MPM-OMe), 4.29 (dd, $J_{3,2a}$ = 7.2, $J_{3,2b}$ = 8.7 Hz, 1 H, 3-H), 6.85 (d, J = 8.7 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.23−7.41 (m, 9 H, 5 × Ph-H, 2 × MPM-2-H and 6-H) ppm. ^{13}C NMR: δ = 36.4 (C-2), 51.4 (OMe), 52.6 (CH_2-MPM), 55.1 (OMe-MPM), 58.5 (C-3), 113.5, and 127.3, and 128.0, and 128.5, and 129.8, and 131.6, and 137.6, and 158.6 (C, aromatic), 172.0 (C=O) ppm. $C_{26}H_{29}NO_4$ (419.53): calcd. C 74.44, H 6.97; found C 74.79, H 6.93.

Methyl (*S*)-3-[Bis(4-methoxybenzyl)amino]-4-phenylbutanoate, *N*,*N*-(MPM)-Pheψ[CH_2CO_2Me] (3): Oil (88%). ^{1}H NMR: δ = 2.31 (dd, $J_{2a,3}$ = 6.1 Hz, $J_{2a,2b}$ = 14.1 Hz, 1 H, 2-H_a), 2.53 (dd, $J_{4a,3}$ = 8.8, $J_{4a,4b}$ = 13.5 Hz, 1 H, 4-H_a), 2.63 (dd, $J_{2a,3}$ = 8.6, $J_{2b,2a}$ = 14.1 Hz, 1 H, 2-H_b), 3.08 (dd, $J_{4b,3}$ = 5.7, $J_{4b,4a}$ = 13.5 Hz, 1 H, 4-H_b), 3.46 (m, 1 H, 3-H), 3.52 (d, $J_{a,b}$ = 13.4 Hz, 2 H, 2 × MPM-CH_aH_b), 3.56 (s, 3 H, OMe), 3.66 (d, $J_{b,a}$ = 13.4 Hz, 2 H, 2 × MPM-CH_aH_b), 3.80 (s, 6 H, 2 × MPM-OMe), 6.83 (d, J = 8.7 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.06−7.26 (m, 9 H, 5 × Bzl-H, 2 × MPM-2-H and 6-H) ppm. ^{13}C NMR: δ = 35.5, 36.0 (C-2, C-4), 51.2 (OMe), 52.4 (CH_2-MPM), 55.1 (OMe-MPM), 57.1 (C-3), 113.4, and 125.9, and 128.2, and 129.1, and 129.8, and 131.5, and 139.4, and 158.5 (C, aromatic), 172.7 (C=O) ppm. $C_{27}H_{31}NO_4$ (433.55): calcd. C 74.80, H 7.21; found C 74.69, H 7.23.

Methyl (*R*)-4-(Benzyloxy)-3-[bis(4-methoxybenzyl)amino]butanoate, *N*,*N*-(MPM)-*O*-(Bzl)-Serψ[CH_2CO_2Me] (4): Oil (85%). ^{1}H NMR: δ = 2.51 (dd, $J_{2a,3}$ = 6.3 Hz, $J_{2a,2b}$ = 14.2 Hz, 1 H, 2-H_a), 2.64 (dd, $J_{2b,3}$ = 7.7, $J_{2b,2a}$ = 14.2 Hz, 1 H, 2-H_b), 3.43−3.51 (m, 1 H, 3-H), 3.53 (dd, $J_{4a,3}$ = 6.1, $J_{4a,4b}$ = 9.5 Hz, 1 H, 4-H_a), 3.55 (d,

$J_{a,b}$ = 13.6 Hz, 2 H, 2 × MPM-CH_aH_b), 3.58 (s, 3 H, OMe), 3.64 (d, $J_{b,a}$ = 13.6 Hz, 2 H, 2 × MPM-CH$_a$$H_b$), 3.79 (s, 6 H, 2 × MPM-OMe), 4.48 (s, 2 H, Bzl-CH$_2$), 6.83 (d, J = 8.7 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.21 (d, J = 8.7 Hz, 4 H, 2 × MPM-2-H and 6-H), 7.30−7.36 (m, 5 H, Bzl-H) ppm. ^{13}C NMR: δ = 34.5 (C-2), 51.4 (OMe), 53.4 (CH$_2$-MPM), 54.7 (C-3), 55.2 (OMe-MPM), 70.2 (C-4), 73.1 (CH$_2$-Bzl), 113.5, and 127.5, and 128.3, and 129.9, and 132.0, and 138.3, and 158.6 (C, aromatic), 172.8 (C=O) ppm. $C_{20}H_{25}NO_4$ (463.58): calcd. C 72.55, H 7.18; found C 72.31, H 7.22.

Methyl (±)-3-[Bis(4-methoxybenzyl)amino]-2-hydroxypropanoate, *N,N*-(MPM)-Glyψ[CH(OH)CO$_2$Me] (5); Typical Procedure for the α-Hydroxylation: KHDMS in THF (0.5 M, 11.6 mL, 5.8 mmol) was added dropwise, at −78 °C and under dry argon, to a magnetically stirred solution of **1** (1.0 g; 2.9 mmol) in dry THF (27 mL). After 1 h, solid 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine (1.4 g; 5.2 mmol) was added to the solution in one portion, and the reaction mixture was kept at −78 °C whilst stirring. Within 30 min, the reaction was quenched by addition of 10% aq NH_4Cl (10 mL) and extracted with ethyl acetate. The organic layer was washed with brine until neutral and dried (Na_2SO_4), and the solvents were evaporated in vacuo. The residue was dissolved in CCl_4 (10 mL) and the resulting precipitate was filtered off. Evaporation of the solvent under reduced pressure gave an oil, chromatography of which on silica gel (hexane/ethyl acetate, 8:2) afforded the pure, oily title compound **5** (0.94 g; 94%). ^{1}H NMR: δ = 1.4−1.9 (br s, 1 H, OH), 2.75−2.92 (m, 2 H, 3-H), 3.45 (d, $J_{a,b}$ = 13.3 Hz, 2 H, 2 × MPM-CH_aH_b), 3.68 (s, 3 H, OMe), 3.69 (d, $J_{b,a}$ = 13.3, 2 H, 2 × MPM-CH$_a$$H_b$), 3.80 (s, 6 H, 2 × MPM-OMe), 4.21 (dd, $J_{2,3a}$ = 4.9, $J_{2,3b}$ = 6.6 Hz, 1 H, 2-H), 6.85 (d, J = 8.7 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.20 (d, J = 8.7 Hz, 4 H, 2 × MPM-2-H and 6-H) ppm. ^{13}C NMR: δ = 52.0 (OMe), 55.1 (OMe-MPM), 55.7 (C-3), 57.8 (CH$_2$-MPM), 68.9 (C-2), 113.6, and 130.1, and 130.2, and 158.7 (C, aromatic), 173.8 (C=O) ppm. $C_{20}H_{25}NO_5$ (359.43): calcd. C 66.84, H 7.01; found C 66.60, H 6.98. Under the same conditions, the other α-hydroxy compounds listed in Table 1 were also obtained.

Methyl (2*S*,3*S*)-3-[Bis(4-methoxybenzyl)amino]-2-hydroxy-3-phenylpropanoate, *anti-N,N*-(MPM)-Phgψ[(*S*)-CH(OH)CO$_2$Me] (6): Oil (84%). ^{1}H NMR: δ = 3.17 (d, $J_{a,b}$ = 13.6 Hz, 2 H, 2 × MPM-CH_aH_b), 3.75 (s, 3 H, OMe), 3.80 (s, 6 H, 2 × MPM-OMe), 3.86 (d, $J_{b,a}$ = 13.6 Hz, 2 H, 2 × MPM-CH$_a$$H_b$), 4.06 (d, $J_{2,3}$ = 7.7 Hz, 1 H, 2-H), 4.90 (d, $J_{3,2}$ = 7.7 Hz, 1 H, 3-H), 6.88 (d, J = 8.0 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.25 (d, J = 8.0 Hz, 4 H, 2 × MPM-2-H and 6-H), 7.33−7.43 (m, 5 H, Ph-aromatic H) ppm. ^{13}C NMR: δ = 52.1 (OMe), 53.6 (CH$_2$-MPM), 55.1 (OMe-MPM), 65.5 (C-3), 72.0 (C-2), 113.6, and 127.8, and 128.2, and 129.7, and 129.9, and 131.2, and 134.5, and 158.6 (C, aromatic), 173.6 (C=O) ppm. $C_{26}H_{29}NO_5$ (435.52): calcd. C 71.70, H 6.71; found C 71.35, H 6.73.

Methyl (2*R*,3*S*)-3-[Bis(4-methoxybenzyl)amino]-2-hydroxy-3-phenylpropanoate, *syn-N,N*-(MPM)-Phgψ[(*R*)-CH(OH)CO$_2$Me] (7): Oil (8%). ^{1}H NMR: δ = 3.03 (d, $J_{a,b}$ = 13.3 Hz, 2 H, 2 × MPM-CH_aH_b), 3.46 (s, 3 H, OMe), 3.80 (s, 6 H, 2 × MPM-OMe), 3.92 (d, $J_{b,a}$ = 13.3 Hz, 2 H, 2 × MPM-CH$_a$$H_b$), 3.98 (d, $J_{2,3}$ = 7.9 Hz, 1 H, 2-H), 4.65 (d, $J_{3,2}$ = 7.9 Hz, 1 H, 3-H), 6.88 (d, J = 8.5 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.21 (d, J = 8.5 Hz, 4 H, 2 × MPM-2-H and 6-H), 7.36−7.42 (m, 5 H, Ph-aromatic H) ppm. ^{13}C NMR: δ = 52.0 (OMe), 53.4 (CH$_2$-MPM), 55.1 (OMe-MPM), 63.7 (C-3), 71.2 (C-2), 113.8, and 127.9, and 130.0, and 130.5, and 133.5, and 158.6 (C, aromatic), 172.7 (C=O) ppm. $C_{26}H_{29}NO_5$ (435.52): calcd. C 71.70, H 6.71; found C 71.37, H 6.72.

Methyl (2*S*,3*S*)-3-[Bis(4-methoxybenzyl)amino]-2-hydroxy-4-phenylbutanoate, *anti-N,N*-(MPM)-Pheψ[(*S*)-CH(OH)CO$_2$Me] (8): Oil (86%). ^{1}H NMR: δ = 2.85 (dd, $J_{4,3}$ = 7.8, $J_{4a,4b}$ = 13.8 Hz, 1 H, 4-H$_a$), 3.02 (dd, $J_{4,3}$ = 7.3, $J_{4b,4a}$ = 13.8 Hz, 1 H, 4-H$_b$), 3.44 (dt, $J_{3,2}$ = 2.6, $J_{3,4}$ = 7.3 Hz, 1 H, 3-H), 3.57−3.61 (m, 5 H, OMe and 2 × MPM-CH_aH_b), 3.73 (d, J = 13.7 Hz, 2 H, 2 × MPM-CH$_a$$H_b$), 3.80 (s, 6 H, 2 × MPM-OMe), 4.46 (d, $J_{2,3}$ = 2.6 Hz, 1 H, 2-H), 6.83 (d, J = 8.6 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.09−7.26 (m, 9 H, 5 × Bzl-aromatic H, and 2 × MPM-2-H and 6-H) ppm. ^{13}C NMR: δ = 31.8 (C-4), 52.1 (OMe), 53.6 (CH$_2$-MPM), 55.0 (OMe-MPM), 61.8 (C-3), 69.4 (C-2), 113.4, and 125.9, and 128.0, and 129.4, and 129.8, and 131.5, and 139.0, and 158.4 (C, aromatic), 174.8 (C=O) ppm. $C_{27}H_{31}NO_5$ (449.55): calcd. C 72.14, H 6.95; found C 72.31, H 6.92.

Methyl (2*R*,3*S*)-3-[Bis(4-methoxybenzyl)amino]-2-hydroxy-4-phenylbutanoate, *syn-N,N*-(MPM)-Pheψ[(*R*)-CH(OH)CO$_2$Me] (9): Oil (3%). ^{1}H NMR: δ = 3.02−3.24 (m, 4 H, 2 × 4-H, and 3-H, and OH), 3.36 (d, $J_{a,b}$ = 13.3 Hz, 2 H, 2 × MPM-CH_aH_b), 3.43 (s, 3 H, OMe), 3.79 (s, 6 H, 2 × MPM-OMe), 3.99−4.06 (m, 3 H, 2-H, and 2 × MPM-CH$_a$$H_b$), 6.84 (d, J = 8.7 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.15−7.50 (m, 9 H, 5 × Bzl-aromatic H, and 2 × MPM-2-H and 6-H). $C_{27}H_{31}NO_5$ (449.55): calcd. C 72.14, H 6.95; found C 72.28, H 6.93.

Methyl (2*S*,3*S*)-4-(Benzyloxy)-3-[bis(4-methoxybenzyl)amino]-2-hydroxybutanoate, *anti-N,N*-(MPM)-Serψ[(*S*)-CH(OH)CO$_2$Me] (10): Oil (91%). ^{1}H NMR: δ = 3.18−3.34 (br s, 1 H, OH), 3.40−3.48 (m, 1 H, 3-H), 3.63 (s, 3 H, OMe), 3.64 (d, J = 13.6 Hz, 2 H, 2 × MPM-CH_aH_b), 3.68 (dd, $J_{4a,3}$ = 5.4, $J_{4a,4b}$ = 9.3 Hz, 1 H, 4-H$_a$), 3.73 (d, J = 13.6 Hz, 2 H, 2 × MPM-CH$_a$$H_b$), 3.81 (s, 6 H, 2 × MPM-OMe), 3.85 (dd, $J_{4b,3}$ = 7.8, $J_{4b,4a}$ = 9.3 Hz, 1 H, 4-H$_b$), 4.44 (d, $J_{a,b}$ = 12.3 Hz, 1 H, Bzl-H$_a$), 4.72 (d, $J_{b,a}$ = 12.3 Hz, 1 H, Bzl-H$_b$), 4.51 (br d, $J_{2,3}$ = 3.4 Hz, 1 H, 2-H), 6.86 (d, J = 8.6 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.25 (d, J = 8.6 Hz, 4 H, 2 × MPM-2-H and 6-H), 7.29−7.41 (m, 5 H, Bzl-aromatic H) ppm. ^{13}C NMR: δ = 52.3 (OMe), 54.4 (CH$_2$-MPM), 55.2 (OMe-MPM), 59.5 (C-3), 67.6 (C-2), 69.3 (C-4), 73.4 (CH$_2$Ph), 113.6, and 127.7, and 128.3, and 129.9, and 131.8, and 140.0, and 158.6 (C, aromatic), 174.8 (C=O) ppm. $C_{28}H_{33}NO_6$ (479.58): calcd. C 70.13, H 6.94; found C 69.85, H 6.91.

Methyl (2*R*,3*S*)-4-(Benzyloxy)-3-[bis(4-methoxybenzyl)amino]-2-hydroxybutanoate, *syn-N,N*-(MPM)-Serψ[(*R*)-CH(OH)CO$_2$Me] (11): Oil (4%). ^{1}H NMR: δ = 3.13−3.28 (br s, 1 H, OH), 3.40−3.46 (m, 1 H, 3-H), 3.59 (d, J = 13.7 Hz, 2 H, 2 × MPM-CH_aH_b), 3.64 (dd, $J_{4a,3}$ = 5.4, $J_{4a,4b}$ = 9.3 Hz, 1 H, 4-H$_a$), 3.72 (d, J = 13.7 Hz, 2 H, 2 × MPM-CH$_a$$H_b$), 3.79 (s, 3 H, OMe), 3.80 (s, 6 H, 2 × MPM-OMe), 3.82 (dd, $J_{4b,3}$ = 7.8, $J_{4b,4a}$ = 9.3 Hz, 1 H, 4-H$_b$), 4.40 (d, $J_{a,b}$ = 12.2 Hz, 1 H, Bzl-H$_a$), 4.43 (d, $J_{b,a}$ = 12.2 Hz, 1 H, Bzl-H$_b$), 4.47 (br d, $J_{2,3}$ = 2.9 Hz, 1 H, 2-H), 6.86 (d, J = 8.7 Hz, 4 H, 2 × MPM-3-H and 5-H), 7.25 (d, J = 8.7 Hz, 4 H, 2 × MPM-2-H and 6-H), 7.29−7.41 (m, 5 H, Bzl-aromatic H). $C_{28}H_{33}NO_6$ (479.58): calcd. C 70.13, H 6.94; found C 70.25, H 6.90.

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