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Highly diastereoselective preparation of *anti*-α,β-dialkyl β-amino acids containing natural α-amino acid side chains

Stefania Capone,[b] Silvana Pedatella,[a,*] Annalisa Guaragna,[a] Mauro De Nisco[a] and Giovanni Palumbo[a]

[a]*Dipartimento di Chimica Organica e Biochimica, Università di Napoli Federico II, via Cynthia 4, I-80126 Napoli, Italy*
[b]*Laboratorium für Organische Chemie, ETH Zürich, HCI Hönggerberg, Wolfgang-Pauli-Strasse 10, CH-8093 Zürich, Switzerland*

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Abstract—An efficient synthesis of *anti*-2-alkyl β^3-amino acids was developed starting from the fully protected β^3-amino acids. The strategy allows the introduction of the side chain of natural α-amino acids such as Ala, Phe and Ser at the C-2 position, with high diastereoselectivity. The preparation of 2-methyliden-β^3-amino acids is also reported. This methodology does not need the use of expensive chiral reagents and/or chiral auxiliaries, and leads to compounds with orthogonal protecting groups.

1. Introduction

In recent years, the understanding of biological functions and pharmacological restrictions of proteins and natural peptides have increased the interest in the preparation of analogues by means of the incorporation of unnatural or rare amino acids into the original frameworks. Recent studies have shown that β-peptides, composed of β-amino acids, have attracted much attention mainly because, despite containing amide bonds capable of forming stabilizing intramolecular hydrogen bonds, they exhibit a great resistance to enzymatic degradation.[1] As a consequence, the development of new synthetic approaches to β-amino acids[2] is a rapidly growing field and in particular, C^2,C^3-disubstituted amino acids represent a fascinating goal because of their effects on the local conformation.[3] In addition, they have also successfully been used as intermediates for the synthesis of substituted β-lactams.[4]

Asymmetric routes to $\beta^{2,3}$-amino acids have been developed by (a) conjugate addition of chiral lithium amides on methyl and *tert*-butyl crotonates and cinnamate esters,[5] (b) chiral Lewis acid mediated conjugate addition of amines on imides and oxazolidinones[6] and (c) 1,3-dipolar cycloadditions of oximes and chiral allylic alcohols.[7]

When the starting materials used were natural α-amino acids, the construction of the second stereogenic centre was achieved by hydroboration of *N*-tosylated allyl amine intermediates.[8] Otherwise, the alkylation of β^3-amino acids, readily obtained from α-amino acids via Arndt–Eistert homologation, was investigated by Seebach as a means to obtain 2,3-dialkyl β-amino acids.[9] Furthermore alkylation of cyclic β^3-amino acids was also reported.[10] L-Aspartic acid was used to prepare *syn*- and *anti*-$\beta^{2,3}$-amino acids, via cyclic β-amino acid synthetic equivalents.[11] Finally, *tert*-butanesulfinyl imines have been employed with titanium enolates.[12] Although a large part of these synthetic methodologies have the advantage of being highly diastereo- or enantioselective, most of them are often limited by low yields or by a high number of synthetic steps. Recently, new strategies have been developed involving both homogeneous and heterogeneous catalysts of specific β-amino acid precursors.[13] However, these approaches require expensive chiral auxiliaries.

Recently, we have carried out a convenient synthesis[14] of optically active 2-hydroxy- and 2-amino-β^3-amino acids. As a part of our research interest on β-amino acids[15] we report, in this paper, an extension of this efficient methodology to the synthesis of optically active *anti*-2-alkyl β^3-amino acids starting from natural and commercially available α-amino acids. We considered it of interest to disclose this approach to synthesize dipeptides, containing aspartic acid residue linked to $\beta^{2,3}$-disubstituted amino acids, in connection with our current interest in the study of a new class of conformationally restricted aspartame analogues.

2. Results and discussion

The synthetic strategy we developed exploits the reactivity of β^3-amino esters to perform stereoselective coupling reactions using different electrophile carbon atom sources such

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* Corresponding author. Tel.: +39 081 674 118; fax: +39 081 674 119; e-mail: pedatell@unina.it

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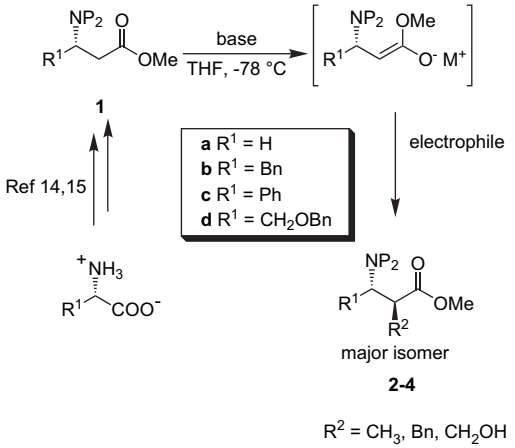
as methyl iodide, benzyl bromide and formaldehyde, in order to introduce the same side chains present in natural α-amino acids at the C-2 position.

Under our conditions (Scheme 1), the fully protected β^3-amino methylester was allowed to react with a suitable base, at −78 °C in anhydrous THF, to ensure the formation of the corresponding enolate. It was in turn treated with an electrophile, at −78 °C under nitrogen atmosphere, to afford the α-alkyl derivatives.



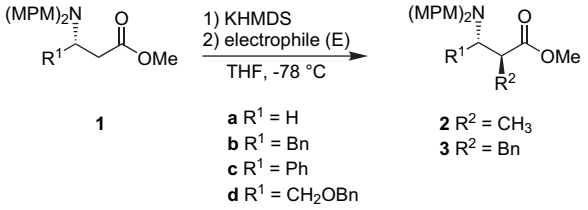
Scheme 1. Synthetic path.

The stereochemical outcome of the reaction as well as the yields was optimized taking into account different experimental conditions. Having considered the properties of Li^+ and K^+ as coordinating ions, we chose potassium hexamethyldisilazide (KHMDS). As already reported,[14,16] lithium hexamethyldisilazide (LHMDS) gave poorer yield. Furthermore, the protection of the amino group was also a crucial point. As previously reported,[14] a double protection avoids side reactions in the presence of the strong base used and represents, at the same time, a very bulky nitrogen substituent, suitable for the efficient diastereocontrol in the subsequent coupling reaction with electrophiles. We preferred 4-methoxybenzyl group (MPM) as protection of the amino function in order to have all orthogonal protecting groups on the β^3-amino esters (e.g., *O*-benzyl protected β^3-serine **1d**).

The results are summarized in Table 1. The stoichiometric ratio of β^3-amino ester, base and electrophile was important for reaction yields. With regards to the amount of the base in respect of the substrate the results are consistent with those of the corresponding α-amino functionalizations.[14a] By using a 1:2 substrate/base ratio the yields were excellent in all cases (61–97%). Conversely, it was found that the efficiency of the process increased on increasing the amount of electrophile (entry 5 vs 6), except for *N*,*N*-diprotected β-alanine **1a** (entry 1 vs 2 and 3 vs 4). In the case of the latter, the lack of the substituent at the C-3 position probably led to an easier attack at the less hindered C-2 position of the monoalkylated derivative, affording a significant amount (35%) of 2,2′-dialkylated amino acids.

Furthermore, the synthetic utility of the protocol here described was investigated to introduce the Ser side chain as

Table 1. α-Alkylation of β^3-amino esters **1a–d**[a]

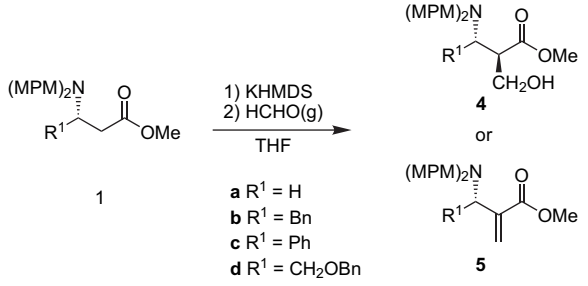


Entry	1	E	Time (h)	Product	Yield[b] (%)	*anti*:*syn*[c]
1	**a**	CH_3I	2.5	**2a**	40[d]	—
2			2.5	**2a**	61[e] (22)	—
3		BnBr	3.5	**3a**	40[d]	—
4			3.5	**3a**	65[e] (25)	—
5	**b**	CH_3I	3	**2b**	54[e] (35)	93:7 (2*S*,3*S*)
6			3	**2b**	97	93:7 (2*S*,3*S*)
7		BnBr	3.5	**3b**	90	97:3 (2*S*,3*S*)
8	**c**	CH_3I	5	**2c**	80	90:10 (2*S*,3*R*)
9		BnBr	4	**3c**	75	92:8 (2*S*,3*R*)
10	**d**	CH_3I	5	**2d**	89	94:6 (2*S*,3*R*)
11		BnBr	4	**3d**	78	96:4 (2*S*,3*R*)

[a] The reaction was performed by procedure B (**1**/KHMDS/electrophile ratio of 1:2:2.2).
[b] Concerning **b–d** series, yields are referred to the diastereomeric mixture; yields in brackets are referred to the recovered starting materials.
[c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy.
[d] 2,2′-Dialkylated product was also observed.
[e] The reaction was performed by procedure A (**1**/KHMDS/electrophile ratio of 1:2:1.1).

well as a methylidene group at C-2 position of the β^3-amino esters (Table 2). The preparation of the 2-hydroxymethyl-β^3-amino esters **4a–d** was performed using formaldehyde, obtained by cracking of paraformaldehyde, on the enolate generated in situ at −78 °C under the already reported conditions. An interesting finding was that the reaction performed at −20 °C afforded the α-methyliden-β^3-amino esters **5a**,**b**,**d** in high yields.

Table 2. Reaction of β^3-amino esters with formaldehyde[a]



Entry	1	Time (h)	Yield[b] (%)	Product	*anti*:*syn*[c]
1	**a**	2.5	85	**4a**	—
2		3	90	**5a**[d]	—
3	**b**	2	65	**4b**	99:1 (2*R*,3*S*)
4		2.5	80	**5b**[d]	—
5	**c**	2	88	**4c**	97:3 (2*R*,3*R*)
6	**d**	2	78	**4d**	95:5 (2*R*,3*R*)
7		2.5	87	**5d**[d]	—

[a] The reaction was performed at −78 °C with a **1**/KHMDS/formaldehyde ratio of 1:2:8.
[b] Concerning the products **4b–d**, yields are referred to the diastereomeric mixture.
[c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy.
[d] The reaction was performed at −20 °C.

It is noteworthy that, under our conditions, all the products shown in Tables 1 and 2 (**2b–d**, **3b–d** and **4b–d**) are generated with a very high *anti*-diastereoselectivity.

The diastereoselectivity could be envisioned by the formation of the *Z*-enolate,[17] which led to the most stable conformation due to stereoelectronic factors. Thus, the attack by the alkylating agent occurs at the less hindered face of the lower energy conformation[14b] of the enolate to give the *anti* product, in excellent diastereomeric ratio. These results, combined with data of α-hydroxylation and α-amination reactions,[14] suggest that the nature of the electrophile does not have a significant influence on the stereoselectivity.

In conclusion this procedure enables the diastereoselective preparation of *anti*-2-alkyl β^3-amino acids featuring by the orthogonal protecting groups, starting from inexpensive natural α-amino acids. The stereoselectivity of the key alkylation step is extremely sensitive to steric effects due to the doubly protected amino group. Work is in progress to utilize these 2-alkyl β^3-amino acids as non-proteinogenic amino acid scaffolds for the preparation of peptidomimetic compounds.

3. Experimental

3.1. General

IR spectra were recorded in $CHCl_3$ on a Nicolet 5700 FTIR spectrometer. NMR spectra were recorded on Varian Inova 500 MHz, Varian Gemini 200 MHz, Varian Gemini 300 MHz, Bruker DRX 400 MHz spectrometers; chemical shifts are in parts per million (δ) and *J* coupling constants in hertz; solvent $CDCl_3$. Elemental analyses were performed on a Perkin–Elmer Series II 2400, CHNS analyzer. TLC was carried out on silica gel Merck 60 F_{254} plates (0.2 mm layer) and column chromatographies on Merck Kieselgel 60 (70–230 mesh). Anhydrous solvents were distilled immediately before use.

3.2. Synthesis

3.2.1. α-Alkylation: procedure A.

3.2.1.1. Methyl 3-[bis(4-methoxybenzyl)amino]-2-methyl propanoate (2a). To a magnetically stirred solution of **1a** (0.15 g, 0.44 mmol) in anhydrous THF (8 mL), 0.5 M KHMDS in the same solvent (1.77 mL, 0.88 mmol) was added dropwise, at −78 °C under nitrogen stream. After 1 h, CH_3I (0.03 mL, 0.48 mmol) was added to the solution in one portion, and the reaction mixture was kept at −78 °C with stirring. Within 1.5 h, the reaction was quenched by the addition of 10% aq NH_4Cl (20 mL) and extracted with ethyl acetate. The organic layer was washed with brine until neutral and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue, purified by chromatography on silica gel (hexane/ethyl acetate, 9:1), afforded the pure yellow oily title compound **2a** (0.09 g, 61% yield). FTIR: ν_{max} 1730, 1602, 1205 cm^{-1}. ^1H NMR (500 MHz): δ 1.08 (d, *J*=6.5, 3H, CH_3), 2.32–2.42 (m, 1H, H-2), 2.70–2.80 (m, 2H, H-3), 3.41 (d, *J*=13.5, 2H, 2×CH_aMPM), 3.54 (d, *J*=13.5, 2H, 2×CH_bMPM), 3.64 (s, 3H, COOMe), 3.80 (s, 6H, 2×OMe), 6.84 (d, *J*=8.5, 4H, 4×H_{meta}), 7.21 (d, *J*=8.5, 4H, 4×H_{ortho}). ^{13}C NMR (125 MHz): δ 15.2, 38.6, 51.4, 55.2, 57.0, 57.5, 113.4, 129.9, 131.3, 158.5, 176.2. Anal. Calcd for $C_{21}H_{27}NO_4$: C 70.56, H 7.61, N 3.92. Found: C 70.38, H 7.59, N 3.90.

Under the same conditions (using BnBr as electrophile) the α-benzyl-β^3-amino acid **3a** was also obtained.

3.2.1.2. Methyl 2-benzyl-3-[bis(4-methoxybenzyl)-amino] propanoate (3a). Oil (65%). FTIR: ν_{max} 1735, 1605, 1209 cm^{-1}. ^1H NMR (500 MHz): δ 2.49 (dd, *J*=6.2, 12.7, 1H, CH_aPh), 2.74–2.82 (m, 3H, H-3, CH_bPh), 2.94–3.05 (m, 1H, H-2), 3.37 (d, *J*=13.7, 2H, 2×CH_aMPM), 3.57 (s, 3H, COOMe), 3.58 (d, *J*=13.7, 2H, 2×CH_bMPM), 3.80 (s, 6H, 2×OMe), 6.84 (d, *J*=8.3, 4H, 4×H_{meta}MPM), 7.08 (d, *J*=7.8, 2H, 2×H_{ortho}Ph), 7.13 (d, *J*=8.3, 4H, 4×H_{ortho}MPM), 7.22–7.31 (m, 3H, 3×HPh). ^{13}C NMR (125 MHz): δ 36.7, 47.2, 55.4, 55.5, 57.8, 57.9, 113.7, 128.9, 130.2, 130.4, 131.3, 139.5, 158.8, 175.2. Anal. Calcd for $C_{27}H_{31}NO_4$: C 74.80, H 7.21, N 3.23. Found: C 75.01, H 7.19, N 3.24.

3.2.2. α-Alkylation: procedure B.

3.2.2.1. Methyl (2*S*,3*S*)-3-[bis(4-methoxybenzyl)-amino]-2-methyl-4-phenylbutanoate (2b). To a magnetically stirred solution of **1b** (0.19 g, 0.44 mmol) in anhydrous THF (8 mL), 0.5 M KHMDS in the same solvent (1.77 mL, 0.88 mmol) was added dropwise, at −78 °C under nitrogen stream. After 1 h, CH_3I (0.06 mL, 0.97 mmol) was added to the solution in one portion, and the reaction mixture was kept at −78 °C with stirring. Within 2 h, the work up described above afforded the pure oily title compound **2b** (0.19 g, 97% yield). FTIR: ν_{max} 1739, 1610, 1215 cm^{-1}. ^1H NMR (400 MHz): δ 1.03 (d, *J*=6.9, 3H, CH_3), 2.74 (dd, *J*=7.1, 14.2, 1H, H-4_a), 2.80–2.88 (m, 1H, H-2), 3.10 (dd, *J*=6.1, 14.2, 1H, H-4_b), 3.24–3.27 (m, 1H, H-3), 3.41 (d, *J*=13.4, 2H, 2×CH_aMPM), 3.63 (s, 3H, COOMe), 3.71 (d, *J*=13.4, 2H, 2×CH_bMPM), 3.81 (s, 6H, 2×OMe), 6.84 (d, *J*=8.6, 4H, 4×H_{meta}MPM), 7.15 (d, *J*=8.6, 4H, 4×H_{ortho}-MPM), 7.17–7.35 (m, 5H, 5×HPh). ^{13}C NMR (100 MHz): δ 15.4, 33.1, 42.7, 51.3, 53.2, 55.1, 61.9, 113.2, 125.8, 128.7, 129.2, 129.8, 130.0, 131.6, 140.9, 158.4, 175.7. Anal. Calcd for $C_{28}H_{33}NO_4$: C 75.44, H 7.43, N 3.13. Found: C 75.27, H 7.45, N 3.15.

Under the same conditions we obtained the following compounds.

3.2.2.2. Methyl (2*S*,3*R*)-3-[bis(4-methoxybenzy1)-amino]-2-methyl-3-phenylpropanoate (2c). Oil (80%). FTIR: ν_{max} 1732, 1608, 1210 cm^{-1}. ^1H NMR (500 MHz): δ 1.46 (d, *J*=6.8, 3H, CH_3), 2.92 (d, *J*=13.7, 2H, 2×CH_aMPM), 3.30 (s, 3H, COOMe), 3.31–3.37 (m, 1H, H-2), 3.78 (d, *J*=13.7, 2H, 2×CH_bMPM), 3.79–3.85 (m, 7H, H-3, 2×OMe), 6.88 (d, *J*=8.7, 4H, 4×H_{meta}MPM), 7.18 (d, *J*=8.3, H_{ortho}Ph), 7.29 (d, *J*=8.7, 4H, 4×H_{ortho}MPM), 7.30–7.32 (t, *J*=8.3, 2H, 2×H_{meta}Ph), 7.37 (t, *J*=8.3, 1H, H_{para}Ph). ^{13}C NMR (125 MHz): δ 16.5, 42.1, 51.5, 53.1, 55.5, 64.2, 114.0, 127.5, 128.0, 129.6, 130.1, 131.9, 135.8, 158.8, 175.9. Anal. Calcd for $C_{27}H_{31}NO_4$: C 74.80, H 7.21, N 3.23. Found: C 74.95, H 7.24, N 3.25.

3.2.2.3. Methyl (2*S*,3*R*)-4-(benzyloxy)-3-[bis(4-methoxybenzyl)amino]-2-methylbutanoate (2d). Oil (89%). FTIR: ν_{max} 1735, 1608, 1202 cm^{-1}. ^{1}H NMR (400 MHz): δ 1.10 (d, J=6.0, 3H, CH_3), 3.05–3.10 (m, 1H, H-2), 3.39 (d, J=l3.6, 2H, 2×CH_aMPM), 3.58–3.64 (m, 4H, COOMe, H-4$_a$), 3.78 (dd, J=2.5, 10.2, 1H, H-4$_b$), 3.81 (s, 6H, 2×OMe), 3.88 (d, J=13.6, 2×CH_bMPM), 4.50 (d, J=12.0, 1H, OCH_aPh), 4.58 (d, J=12.0, 1H, OCH_bPh), 6.85 (d, J=8.6, 4H, 4×H_{meta}MPM), 7.15 (d, J=8.6, 4H, 4×H_{ortho}-MPM), 7.30–7.42 (m, 5H, HPh). ^{13}C NMR (100 MHz): δ 14.6, 40.6, 50.9, 53.7, 54.9, 59.5, 65.9, 73.0, 113.1, 127.2, 127.6, 128.0, 128.8, 131.7, 138.1, 158.2, 175.6. Anal. Calcd for $C_{29}H_{35}NO_5$: C 72.93, H 7.39, N 2.93. Found: C 73.15, H 7.41, N 2.96.

Under the same conditions of the procedure B (using BnBr as electrophile) the α-benzyl-β^3-amino acids **3b**, **3c** and **3d** were also obtained.

3.2.2.4. Methyl (2*S*,3*S*)-2-benzyl-3-[bis(4-methoxybenzyl)amino]-4-phenylbutanoate (3b). Oil (90%). FTIR: ν_{max} 1731, 1601, 1207 cm^{-1}. ^{1}H NMR (400 MHz): δ 2.62 (dd, J=4.6, 13.7, 1H, CH_aPh), 2.72 (dd, J=10.7, 13.7, 1H, CH_bPh), 2.85 (dd, J=7.7, 14.2, 1H, H-4$_a$), 3.04–3.10 (m, 1H, H-2), 3.25 (dd, J=5.7, 14.2, 1H, H-4$_b$), 3.34–3.40 (m, 1H, H-3), 3.42 (d, J=13.3, 2H, 2×CH_aMPM), 3.50 (s, 3H, COOMe), 3.76 (d, J=13.3, 2H, 2×CH_bMPM), 3.82 (s, 6H, 2×OMe), 6.85 (d, J=8.7, 4H, 4×H_{meta}-MPM), 7.08 (d, J=8.3, 2H, 2×HPh), 7.10–7.38 (m, 12H, 8×HPh, 4×H_{ortho}MPM). ^{13}C NMR (125 MHz): δ 29.6, 33.5, 36.3, 51.5, 53.3, 55.1, 61.2, 113.6, 126.0, 128.1, 128.4, 128.5, 129.1, 129.3, 129.9, 130.3, 131.4, 139.4, 158.5, 174.0. Anal. Calcd for $C_{34}H_{37}NO_4$: C 77.98, H 7.12, N 2.67. Found: C 78.15, H 7.15, N 2.69.

3.2.2.5. Methyl (2*S*,3*R*)-2-benzyl-3-[bis(4-methoxybenzyl)amino]-3-phenylpropanoate (3c). Oil (75%). FTIR: ν_{max} 1730, 1610, 1204 cm^{-1}. ^{1}H NMR (500 MHz): δ 2.36 (br d, J=11.7, 1H, CH_aPh), 2.59 (br t, J=12.2, 1H, CH_bPh), 2.88 (d, J=13.2, 2H, 2×CH_aMPM), 3.56–3.62 (m, 1H, H-2), 3.60 (s, 3H, COOMe), 3.79 (s, 6H, 2×OMe), 3.90 (d, J=13.2, 2H, 2×CH_bMPM), 4.15 (d, J=11.7, 1H, H-3), 6.85 (d, J=7.3, 4H, 4×H_{meta}MPM), 6.99 (d, J=7.8, 2H, H_{ortho}Ph), 7.10–7.50 (m, 14H, 10×HPh, 4×H_{ortho}MPM). ^{13}C NMR (125 MHz): δ 29.7, 36.7, 51.3, 53.0, 55.2, 64.6, 113.5, 126.3, 127.8, 128.4, 129.6, 129.9, 131.4, 134.2, 139.3, 158.6, 174.1. Anal. Calcd for $C_{33}H_{35}NO_4$: C 77.77, H 6.92, N 2.75. Found: C 77.96, H 6.94, N 2.77.

3.2.2.6. Methyl (2*S*,3*R*)-2-benzyl-4-(benzyloxy)-3-[bis(4-methoxybenzyl)amino]butanoate (3d). Oil (78%). FTIR: ν_{max} 1738, 1601, 1205 cm^{-1}. ^{1}H NMR (400 MHz): δ 2.40 (dd, J=11.7, 13.7, 1H, CH_aPh), 2.93 (ddd, J=3.7, 11.7, 13.7, 1H, H-2), 3.13–3.17 (m, 1H, H-3), 3.34 (s, 3H, COOMe), 3.45 (dd, J=3.7, 11.7, 1H, CH_bPh), 3.53 (d, J=13.5, 2H, 2×CH_aMPM), 3.65 (dd, J=4.7, 9.9, 1H, H-4$_a$), 3.75 (dd, J=5.8, 9.9, 1H, H-4$_b$), 3.81 (s, 6H, 2×OMe), 3.88 (d, J=13.5, 2H, 2×CH_bMPM), 4.45 (d, J=11.9, 1H, OCH_aPh), 4.50 (d, J=11.9, 1H, OCH_bPh), 6.91 (d, J=8.6, 4H, 4×H_{meta}MPM), 7.10 (d, J=6.8, 2H, 2×HPh), 7.10–7.40 (m, 12H, 8×HPh, 4×H_{ortho}MPM). ^{13}C NMR (75 MHz): δ 35.7, 49.3, 53.8, 55.1, 59.1, 65.8, 73.2, 113.3, 127.4, 128.2, 128.6, 130.0, 131.7, 139.1, 139.3, 158.7, 174.1. Anal. Calcd for $C_{35}H_{39}NO_5$: C 75.92, H 7.10, N 2.53. Found: C 76.13, H 7.08, N 2.55.

3.2.3. α-Formylation: typical procedure.

3.2.3.1. Methyl 3-[bis(4-methoxybenzyl)amino]-2-(hydroxymethyl) propanoate (4a). To a magnetically stirred solution of **1a** (0.44 mmol, 0.15 g) in anhydrous THF (8.3 mL), 0.5 M KHMDS in the same solvent (1.80 mL, 0.88 mmol) was added dropwise, at −78 °C under nitrogen stream. After 1 h HCHO(g), generated by cracking of paraformaldehyde (0.11 g, 3.52 mmol) at 220 °C, is bubbled into the solution by nitrogen stream. Within 1.5 h, the reaction was quenched by the addition of 10% aq NH_4Cl (20 mL) and extracted with ethyl acetate. The organic layer was washed with brine until neutral and dried (Na_2SO_4), and the solvent was evaporated in vacuo. The residue purified by chromatography on silica gel (hexane/ethyl acetate, 7:3) afforded the pure yellow oily title compound **4a** (0.14 g, 85% yield). FTIR: ν_{max} 3441, 1733, 1603, 1211 cm^{-1}. ^{1}H NMR (500 MHz): δ 2.76 (dd, J=4.7, 12.7, 1H, H-3$_a$), 2.86 (dd, J=10.2, 12.7, 1H, H-3$_b$), 2.95–3.05 (m, 1H, H-2), 3.26 (d, J=13.2, 2H, 2×CH_aMPM), 3.65 (s, 3H, COOMe), 3.76 (d, J=13.2, 2H, 2×CH_bMPM), 3.78–3.82 (m, 7H, 2×OMe, CH_aOH), 3.84 (dd, J=4.9, 11.2, 1H, CH_bOH), 6.82 (d, J=8.4, 4H, 4×H_{meta}MPM), 7.20 (d, J=8.4, 4H, 4×H_{ortho}MPM). ^{13}C NMR (125 MHz): δ 44.3, 51.6, 53.8, 55.1, 57.8, 63.9, 113.7, 129.8, 130.1, 158.7, 172.9. Anal. Calcd for $C_{21}H_{27}NO_5$: C 67.54, H 7.29, N 3.75. Found: C 67.70, H 7.31, N 3.76.

Under the same conditions we obtained the following compounds.

3.2.3.2. Methyl (2*R*,3*S*)-3-[bis(4-methoxybenzyl)-amino]-2-(hydroxylmethy1)-4-phenylbutanoate (4b). Oil (65%). FTIR: ν_{max} 3435, 1735, 1608, 1215 cm^{-1}. ^{1}H NMR (500 MHz): δ 2.64–2.71 (m, 1H, H-2), 2.92 (dd, J=9.1, 13.8, 1H, H-4$_a$), 3.14 (dd, J=5.1, 13.8, 1H, H-4$_b$), 3.31–3.42 (m, 3H, H-3, 2×CH_aMPM), 3.52 (dd, J=5.0, 11.3, 1H, CH_aOH), 3.61 (dd, J=6.9, 11.3, CH_bOH), 3.71 (s, 3H, COOMe), 3.74–3.86 (m, 8H, 2×CH_bMPM, 2×OMe), 6.85 (d, J=8.3, 4H, 4×H_{meta}MPM), 7.14–7.32 (m, 9H, 5×HPh, 4×H_{ortho}MPM). ^{13}C NMR (75 MHz): δ 32.4, 49.2, 51.5, 53.8, 54.2, 59.4, 62.1, 113.6, 126.1, 128.5, 129.2, 130.2, 131.3, 140.0, 158.6, 173.0. Anal. Calcd for $C_{28}H_{33}NO_5$: C 72.55, H 7.18, N 3.02. Found: C 72.35, H 7.21, N 3.01.

3.2.3.3. Methyl (2*R*,3*R*)-3-[bis(4-methoxybenzyl)-amino]-2-(hydroxymethyl)-3-phenylpropanoate (4c). Oil (88%). FTIR: ν_{max} 3430, 1731, 1602, 1210 cm^{-1}. ^{1}H NMR (500 MHz): δ 2.89 (d, J=13.7, 2H, 2×CH_aMPM), 3.42 (dd, J=6.8, 10.7, 1H, CH_aOH), 3.45 (dd, J=3.5, 10.7, 1H, CH_bOH), 3.56 (ddd, J=3.5, 6.8, 12.2, 1H, H-2), 3.80 (s, 6H, 2×OMe), 3.84 (s, 3H, COOMe), 3.90 (d, J=13.4, 2H, 2×CH_bMPM), 4.10 (d, J=12.2, 1H, H-3), 6.88 (d, J=8.7, 4H, 4×H_{meta}MPM), 7.19–7.45 (m, 9H, 5×HPh, 4×H_{ortho}-MPM). ^{13}C NMR (125 MHz): δ 50.2, 51.7, 52.8, 55.1, 60.8, 61.9, 113.5, 127.7, 128.2, 129.2, 129.6, 129.7, 131.1, 133.6, 158.4, 174.1. Anal. Calcd for $C_{27}H_{31}NO_5$: C 72.14, H 6.95, N 3.12. Found: C 71.98, H 6.97, N 3.13.

3.2.3.4. Methyl (2*R*,3*R*)-4-(benzyloxy)-3-[bis(4-methoxybenzyl)amino]-2-(hydroxymethyl)butanoate (4d). Oil (78%). FTIR: ν_{max} 3430, 1735, 1605, 1208 cm^{-1}. ^{1}H

NMR (400 MHz): δ 3.12–3.20 (m, 1H, H-2), 3.31–3.37 (m, 1H, H-3), 3.40 (d, J=13.5, 2H, 2×CH_aMPM), 3.68 (s, 3H, COOMe), 3.69–3.72 (m, 2H, H-4$_a$, CH_aOH), 3.73–3.78 (m, 2H, H-4$_b$, CH_bOH), 3.80 (s, 6H, 2×OMe), 3.88 (d, J=13.5, 2H, 2×CH_bMPM), 4.53 (d, J=11.9, 1H, CH_aPh), 4.58 (d, J=11.9, 1H, CH_bPh), 6.88 (d, J=8.7, 4H, 4×H$_{meta}$MPM), 7.19 (d, J=8.6, 4H, 4×H$_{ortho}$MPM), 7.31–7.48 (m, 5H, 5×HPh). ^{13}C NMR (50 MHz): δ 49.0, 51.5, 53.7, 55.1, 56.3, 61.5, 66.5, 73.2, 113.4, 127.5, 127.7, 128.4, 130.0, 131.4, 137.7, 158.5, 174.2. Anal. Calcd for $C_{29}H_{35}NO_6$: C 70.57, H 7.15, N 2.84. Found: C 70.72, H 7.18, N 2.85.

3.2.4. α-Methylidenation: typical procedure.

3.2.4.1. Methyl 2-{[bis(4-methoxybenzyl)amino]methyl}acrylate (5a). To a magnetically stirred solution of **1a** (0.15 g, 0.44 mmol) in anhydrous THF (8.3 mL), 0.5 M KHMDS in THF (1.80 mL, 0.88 mmol) was added dropwise, at −78 °C under nitrogen. After 1 h, the solution was warmed to −20 °C and HCHO(g), generated by cracking of paraformaldehyde (0.11 mg, 3.52 mmol), was bubbled into the solution by nitrogen stream. Within 2 h, the reaction was quenched by the addition of 10% aq NH_4Cl (20 mL). The usual work up afforded a residue that purified by chromatography on silica gel (hexane/ethyl acetate, 7:3) gave the pure oily title compound **5a** (0.14 g, 90% yield). FTIR: ν_{max} 1716, 1611, 1202 cm^{-1}. ^{1}H NMR (400 MHz): δ 3.27 (s, 2H, CH_2N), 3.50 (s, 4H, 2×CH_2MPM), 3.72 (s, 3H, COOMe), 3.79 (s, 6H, 2×OMe), 6.00 (s, 1H, H-3$_a$), 6.25 (s, 1H, H-3$_b$), 6.82 (d, J=8.4, 4×H$_{meta}$MPM), 7.20 (d, J=8.4, 4H, 4×H$_{ortho}$MPM). ^{13}C NMR (50 MHz): δ 51.5, 53.5, 55.1, 57.1, 113.4, 125.8, 129.5, 131.2, 138.2, 158.5, 167.4. Anal. Calcd for $C_{21}H_{25}NO_4$: C 70.96, H 7.09, N 3.94. Found: C 71.15, H 7.11, N 3.93.

Under the same conditions we obtained the following compounds.

3.2.4.2. Methyl 2-{(1*S*)-1-[bis(4-methoxybenzyl)amino]-2-phenylethyl}acrylate (5b). Oil (80%). FTIR: ν_{max} 1725, 1610, 1205 cm^{-1}. ^{1}H NMR (500 MHz): δ 2.91 (dd, J=8.8, 14.2, 1H, CH_aPh), 3.21 (dd, J=6.3, 14.2, 1H, CH_bPh), 3.49 (d, J=13.7, 2H, 2×CH_aMPM), 3.59 (d, J=13.7, 2H, 2×CH_bMPM), 3.66 (s, 3H, COOMe), 4.16 (dd, J=6.3, 8.8, 1H, CHN), 5.59 (s, 1H, H-3$_a$), 6.22 (s, 1H, H-3$_b$), 6.79 (d, J=8.3, 4H, 4×H$_{meta}$MPM), 7.10 (d, J=8.3, 4H, 4×H$_{ortho}$MPM), 7.20–7.30 (m, 5H, 5×HPh). ^{13}C NMR (50 MHz): δ 34.0, 51.8, 52.8, 55.2, 58.7, 113.4, 125.7, 125.9, 128.2, 129.2, 129.8, 131.8, 139.7, 158.4, 168.1. Anal. Calcd for $C_{28}H_{31}NO_4$: C 75.48, H 7.01, N 3.14. Found: C 75.70, H 6.99, N 3.13.

3.2.4.3. Methyl 2-{(1*R*)-2-benzyloxy-1-[bis(4-methoxybenzyl)amino]ethyl}acrylate (5d). Oil (87%). FTIR: ν_{max} 1720, 1608, 1210 cm^{-1}. ^{1}H NMR (300 MHz): δ 3.59 (s, 4H, 2×CH_2MPM), 3.68 (s, 3H, COOMe), 3.70–3.82 (m, 8H, CH_2O, 2×OMe), 4.05 (t, J=9.0, 1H, CHN), 4.49 (s, 2H, CH_2Ph), 5.65 (s, 1H, H-3$_a$), 6.29 (s, 1H, H-3$_b$), 6.82 (d, J=8.2, 4H, 4×H$_{meta}$MPM), 7.19 (d, J=8.2, 4H, 4×H$_{ortho}$MPM), 7.27–7.35 (m, 5H, 5×HPh). ^{13}C NMR (50 MHz): δ 51.0, 55.6, 57.2, 60.1, 70.5, 73.4, 113.3, 125.7, 128.1, 129.1, 129.5, 129.7, 131.6, 138.2, 158.6, 168.2. Anal. Calcd for $C_{29}H_{33}NO_5$: C 73.24, H 6.99, N 2.95. Found: C 73.08, H 7.01, N 2.94.

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