Domino 1,3-Dipolar Cycloadditions of *N*-Alkyl-α-Amino Esters with Paraformaldehyde: A Direct Access to α-Hydroxymethyl α-Amino Acids

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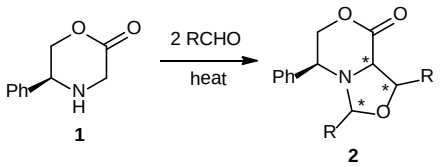
Abstract: *N*-Alkyl-α-amino esters undergo a domino reaction, based on the iminium cation generation, with paraformaldehyde, followed by a 1,3-dipolar cycloaddition of the stabilized azomethine ylide with another equivalent of formaldehyde. The resulting products are oxazolidines, which can be transformed after hydrolysis into α-hydroxymethyl α-amino acid or its derivatives. The diastereoselective 1,3-dipolar cycloaddition was performed using sarcosine (-)-menthyl or (-)-8-phenylmenthyl esters affording the cyclic product with moderate enantiomeric ratio.

Key words: cycloaddition, azomethine ylides, paraformaldehyde, serine

Serine and serine derivatives belong to a family of polar α-amino acids bearing a hydroxymethyl group at the α-position. This arrangement allows serine residues to play an important role in the catalytic function of many enzymes, for example, in the active site of acetylcholine esterase.[1] In proteins, this residue can undergo phosphorylation by kinases,[2] direct *O*-linked glycosylation,[3] or even can act as linker in modified biopharmaceuticals.[4] D-Serine itself has been one of the most extensively studied "unnatural amino acid".[5] This brain-enriched transmitter-like molecule plays a pivotal role in the human central nervous system by modulating the activity of *N*-methyl-D-aspartate (NMDA) receptors, serving as both a neurotransmitter and a gliotransmitter. This amino acid is employed for the treatment of neurological disorders such as schizophrenia, Alzheimer's disease and amyotrophic lateral sclerosis.[6] In addition, α-substituted serine structures are often observed as a subunit of many biologically active natural products, such as conagenin,[7] myriocin,[8] mycestericins,[9] among others.

One of the most employed strategies to synthesize α-amino acids consists on the introduction of the α-side chain, in this case the hydroxymethyl group.[10] Particularly, an aldol type reaction from enolates generated from glycine or other α-substituted α-amino acid templates and formaldehyde is very useful. In addition, formaldehyde can be incorporated at the α-position *via* 1,3-dipolar cycloaddition (1,3-DC)[11] employing stabilized azomethine ylides in a straightforward manner.

Formaldehyde has been employed in these 1,3-DCs with *N*-alkyl-substituted amino acids or esters, for the generation of the 1,3-dipole through the iminium route. Immediately, this reactive ylide is trapped by a dipolarophile.[12,13] The generation of chiral azomethine ylides by reaction of (5*R*)-5-phenyl-morpholin-2-one **1** with long chain aldehydes and further reaction with a second equiv. of the aldehyde was reported in a very high diastereoselective manner (Scheme 1).[14]

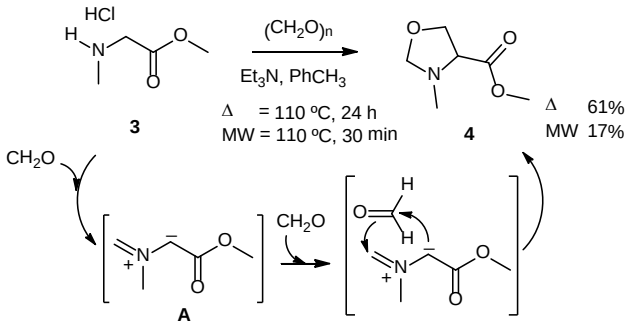


Scheme 1

To the best of our knowledge, the azomethine ylide generated from formaldehyde never was captured by formaldehyde itself.[15] So, in this work the thermal domino reaction of *N*-alkyl-α-amino esters and two equivalents of formaldehyde, focused on the preparation of α-hydroxymethyl-α-amino acids, is studied.

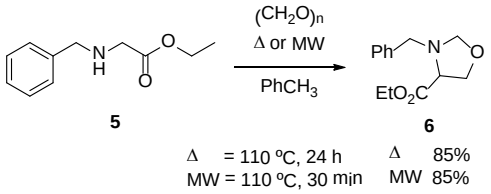
Sarcosine methyl ester hydrochloride **3** was allowed to react with paraformaldehyde in the presence of one equiv. of triethylamine in toluene at 110 ºC. Conventional heating and microwave-assisted reactions were evaluated finding a better yield (61%, Scheme 2) when the reaction was refluxed for 24 h. The employment of formalin (37%) or other different solvents such as 1,4-dioxane, chloroform, and xylene, furnished very low conversions. Despite the high efficiency of microwave-assisted 1,3-DC,[16] only a 17% yield of oxazolidine **4** was achieved after 30 min at 110 ºC.

The domino process was triggered by the generation of the free *N*-substituted α-amino ester (sarcosine methyl ester in this example) which formed the iminium salt with one equivalent of formaldehyde. The resulting transient azomethine ylide **A**, was captured by the reaction of another equivalent of formaldehyde yielding the expected oxazolidine **4** (Scheme 2).



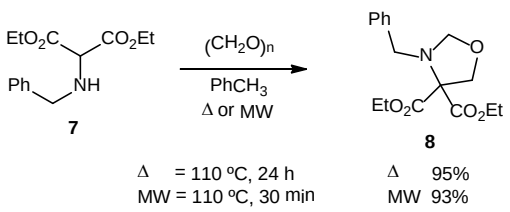
Scheme 2

In the case of using ethyl *N*-benzylglycinate **5**, a less water soluble oxazolidine **6** was isolated in 85% yield employing both conventional and microwave-assisted heating (Scheme 3). Here, triethylamine was not used because the starting amino ester **5** could be isolated as a free secondary amine.



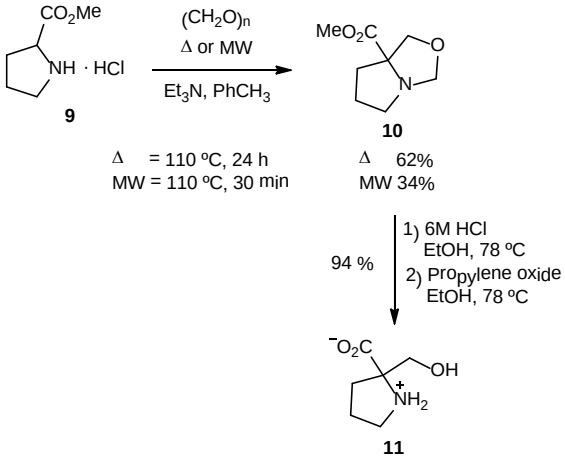
Scheme 3

N-Benzylaminomalonate **7**, prepared from diethyl α-aminomalonate and benzyl bromide, underwent almost quantitative domino 1,3-DC with paraformaldehyde independently of the heating mode (95 and 93%, respectively) (Scheme 4). Oxazolidine **8** was easily generated because of the aid of the geminally substituted α-position and also by the high stabilization of the dipole once the iminum salt was generated. The employment of the free amino ester **7** avoided the addition of Et_3N to the reaction media.



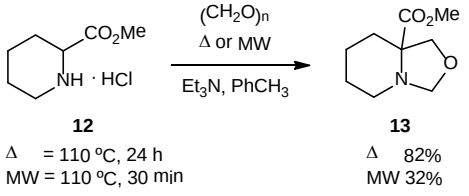
Scheme 4

Quaternary α-amino acid surrogates are known as key building blocks of proteins to obtain useful information on their bioactive conformations and to achieve beneficial physiological effects.[17] Proline methyl ester hydrochloride **9** was an appropriate substrate to run the thermal 1,3-DC affording bicyclic compund **10** in 62% isolated yield (Scheme 5). In this example microwave irradiation did not give the expected improvement of the chemical yield. Perhydropyrrolooxazole **10** was next transformed in the new quaternary α-hydroxymethylproline **11** by hydrolysis in a refluxing 1:1 6M HCl:EtOH mixture. The zwitterionic amino acid could be isolated by treatment with propylene oxide and final recrystallization. The chemical yield of the hydrolysis process was 94% whilst 58% was the overall yield calculated from proline methyl ester hydrochloride **9** (Scheme 5).



Scheme 5

Pipecolic acid methyl ester hydrochloride **12** was a suitable substrate to run the optimized domino process with paraformaldehyde (Scheme 6). Under conventional heating conditions the chemical yield was higher (82%) than the described for the transformation involving proline methyl ester **9**. This homoproline derivative **13** has not been described previously and a promising biological activity can be envisaged.

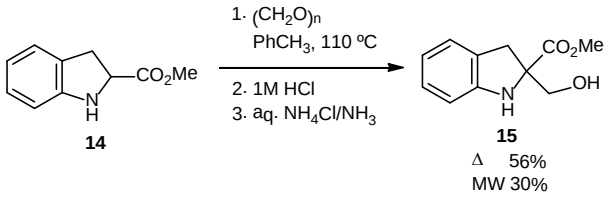


Scheme 6

During our study of the diastereoselective process, (2*S*,4*R*)-4-hydroxyproline methyl ester hydrochloride and its *O*-TBDMS protected derivative were tested as enantiomerically enriched starting materials. Disappointingly, (2*S*,4*R*)-4-hydroxyproline gave a complex reaction mixture with multiple signals in crude ^{1}H NMR spectra originated by polymeric substances formed in the process. On the other side,

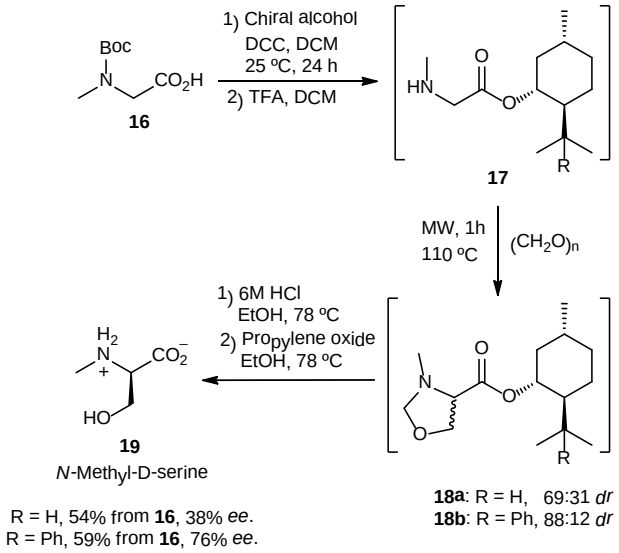
the enantiopure silyl ether decomposed under both thermal reaction conditions.

2,3-Dihydro-1*H*-indole-2-carboxylic acid methyl ester **13** was submitted to the standard reaction conditions using conventional heating and microwave assisted one obtaining, after acidic hydrolysis, the hydroxymethyl derivative **14** in 56% and 30% yield, respectively (Scheme 7).



Scheme 7

Next, we decided to use a chiral auxiliary incorporated into the α-imino ester in order to obtain *in situ* the chiral enantiopure azomethine ylide and analyze the diastereoselection of the thermal process. In this way, *N*-Boc-sarcosine **16** was treated with DCC, DMAP, and L-menthol [(1*R*,2*S*,5*R*)(−)-menthol][18] or (−)-8-phenylmenthol[19] in CH_2Cl_2 under mild conditions to give the corresponding esters. Without previous purification, the removal of the Boc group took place with TFA giving the free amines **17a** and **17b** in quantitative yield (Scheme 8). The microwave-assisted 1,3-DC of **17a** with paraformaldehyde (in 1 h) furnished a 63:31 *dr* of **18a** determined by ^{1}H NMR of the crude product.[20] The crude reaction mixture was very pure and the conversion was almost complete. Moreover, a 88:12 *dr* was isolated for **18b**[21] when the 1,3-DC was carried out under the same reaction conditions using the 8-phenylmenthol derived ester.[15b] However, the conventional heating did not give a good conversion and small signals of unidentified impurities were recorded by ^{1}H-NMR spectra in both diastereoselective transformations. Immediately, the generation of *N*-methyl-D-serine **19** as major enantiomer (38% *ee*) was achieved after hydrolysis of **18a** with 6M HCl/EtOH and further treatment with propylene oxide. *N*-Methyl-D-serine **19** was obtained in 76% *ee* once the hydrolysis was completed. The absolute configuration of α-methyl-α-amino acid **19** was established according to its specific optical rotation.[22] Compound **19** was isolated in 54, and 59% overall yield from *N*-Boc-sarcosine **16** (Scheme 7).



Scheme 8

By using this diastereoselective approach the synthesis of enantiomerically enriched α-(hydroxymethyl)proline was attempted. Unexpectedly, no reaction was observed between the corresponding (−)-8-phenylmenthol proline ester and paraformaldehyde despite testing several reaction conditions.

As summary, the introduction of formaldehyde as dipolarophile was achieved from *N*-alkylamino esters and following the generation of the stabilized azomethine ylide through the iminium route. This strategy represents a straightforward way to access to interesting quaternized α-(hydroxymethyl)amino acids. The major diastereoselection was achieved when (−)-8-phenylmenthol was employed as chiral auxiliary in the formation of the corresponding chiral *N*-methyl-D-serine.

Experimental section

Microwave experiments were performed in a CEM Discover Synthesis Unit (CEM Corp., Matthews, NC) with a continuous focused microwave power delivery system in glass vessels (10 ml) sealed with a septum under magnetic stirring. Melting points were determined with a Reichert Thermovar hot plate apparatus and are uncorrected. Only the structurally most important peaks of the IR spectra (recorded on a Nicolet 510 P-FT) are listed. For solid samples ATR device was employed. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained on a Bruker AC-300 using $CDCl_3$ as solvent and TMS as internal standard, unless otherwise stated. Optical rotations were measured on a Perkin Elmer 341 polarimeter. Low-resolution electron impact (EI) mass spectra were obtained at 70eV on a Shimadzu QP-5000 and high-resolution mass spectra were obtained on a Finnigan VG Platform. HRMS (EI) were recorded on a Finnigan MAT 95S. Microanalyses were performed on a Perkin Elmer 2400 and a Carlo Erba EA1108. Analytical TLC was performed on Schleicher & Schuell

F1400/LS silica gel plates and the spots were visualized under UV light (λ = 254 nm). For flash chromatography we employed Merck silica gel 60 (0.040-0.063 mm).

*Synthesis of oxazolidines **4**, **6**, **8**, **10**, **13** and **15**. General Procedure.* To a solution of the corresponding aminoester hydrochloride (0.43 mmol) in toluene (2 mL), Et_3N or not (1.5 equiv., 90 μL, 0.645 mmol, see text) and paraformaldehyde (15 equiv, 306 mg, 6.45 mmol) were added. The resulting mixture was refluxed at 111 ºC for 24 h or irradiated with microwaves (111 ºC, 30 min). Ethyl acetate (5 mL) and water (5 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated obtaining the pure heterocycle in good chemical yields (see text).

*Methyl 3-methyloxazolidine-4-carboxylate **4**.*[23] 38 mg, 61%; Colorless oil; IR (neat) ν_{max}: 1746, 1705 cm^{-1}; ^{1}H-NMR δ_H: 2.53 (s, 3H, NC*H*$_3$), 3.49-3.55 (dd, *J* = 7.7, 5.8 Hz, 1H, CH_2CH_2O), 3.77 (s, 3H, OC*H*$_3$), 3.85-3.91 (dd, *J* = 7.7, 6.1, 1H, CH_2CH_2O), 4.18 (t, *J* = 8.2 Hz, 1H, C*H*), 4.27 (d, *J* = 4.8 Hz, 1H, NC*H*$_2$), 4.47 (d, *J* = 4.8 Hz 1H, NC*H*$_2$); ^{13}C-NMR δ_c: 41.7 (N*C*H$_3$), 52.4 (O*C*H$_3$), 66.6 (*C*H), 67.3 (O*C*H$_2$CH), 88.8 (N*C*H$_2$), 172.1 (*C*O). ME (EI) *m/z* (%): 145 (M^+, 2), 100 (11), 86 (100), 56 (13), 42.0 (23). HRMS required for $C_6H_{11}NO_3$: 145.0739; found: 145.0730.

*Ethyl 3-benzyloxazolidine-4-carboxylate **6**.* 86 mg, 85%; Colorless oil; IR (neat) ν_{max}: 1732,1186 cm^{-1}; ^{1}H-NMR δ_H: 1.24 (t, *J* = 7.1 Hz, 3H, C*H*$_3$CH$_2$CO$_2$), 3.66 (dd, *J* = 7.9, 5.3 Hz,1H, CH_2CH_2O), 3.85-3.89 (m, 3H, PhC*H*$_2$N, 1H CH_2CH_2O), 4.12-4.20 (m, 3H, $CH_3CH_2CO_2$, C*H*), 4.44 (s, 2H, NC*H*$_2$O), 7.23-7.40 (m, 5H, Ar*H*); ^{13}C-NMR δ_c: 14.1 (CH_2CH_3), 58.7 (N*C*H$_2$Ph), 61.0 (*C*H$_2$CH$_3$), 64.4 (N*C*H), 67.1 (O*C*H$_2$CH), 87.0 (N*C*H$_2$O), 127.4, 128.4, 128.7, 138.08 (Ar*C*), 171.9 (*C*O). MS (EI) *m/z* (%): 235 (M^+, 2), 234 (119), 162 (32), 91 (100). HRMS required for $C_{13}H_{17}NO_3$: 235.1208; found: 235.1201.

*Diethyl 3-benzyloxazolidine-4,4-dicarboxylate **8**.* 125 mg, 95%; Colorless oil; IR (neat) ν_{max}: 1732. 1265 cm^{-1}; ^{1}H-NMR (CD_3COCD_3) δ_H: 1.32 (t, *J* = 7.12 Hz, 6H, C*H*$_3$CH$_2$), 4.04 (s, 3H, NC*H*$_2$Ph and 1H of CC*H*$_2$O), 4.30 (q, *J* = 7.1 Hz, 5H, CH$_3$C*H*$_2$ and 1H of CC*H*$_2$O), 4.43 (s, 2H, NC*H*$_2$O), 7.23-7.40 (m, 5H, Ar*H*); ^{13}C-NMR (CD_3COCD_3) δ_c: 14.1 (2x*C*H$_3$), 51.3 (N*C*H$_2$Ph), 61.8 (2x*C*H$_2$CH$_3$), 72.7 (quat-C), 73.6 (O*C*H$_2$C), 85.7 (N*C*H$_2$O), 127.3, 128.1, 128.3, 138.5 (Ar*C*), 168.7 (2x*C*O); MS (EI) *m/z* (%): 307 (M^+, 5), 235 (17), 234 (100), 92 (19), 91 (100), 65 (13); HRMS required for $C_{16}H_{21}NO_5$: 307.1420; found: 307.1412.

*Methyl hexahydropyrrolo[1,2-c]oxazole-7a-carboxylate **10**.*[24] 46 mg, 62%; Pale yellow oil; IR (neat) ν_{max}: 2924, 1779, 1731, 1656 1051 cm^{-1}; ^{1}H-NMR δ_H: 1.80-1.90 (m, 3H, C*H*$_2$C*H*$_2$C), 2.40-2.50 (m, 1H, C*H*$_2$C), 2.82-2.91, 3.32-3.42 (2xm, 2H, NCH$_2$), 3.77 (d, *J* = 8.7 Hz, 2H, OC*H*$_2$C), 3.77 (s, 3H, OC*H*$_3$), 4.32, 4.55 (2xd, *J* = 6.5Hz, 2H, NC*H*$_2$O); ^{13}C-NMR δ_c: 26.1 ($CH_2CH_2CH_2$), 36.7 (C*C*H$_2$), 52.6 (O*C*H$_3$), 56.1 (NCH$_2$), 74.3 (O*C*H$_2$C), 77.2 (C), 88.7 (N*C*H$_2$O), 175.2 (*C*O). MS (EI) *m/z* (%): 171 (M^+, 9), 170 (16), 154 (16), 143 (60), 142 (19), 141(16), 138 (50), 128(93), 126 (17), 125 (18), 124 (100), 122 (18), 112 (24), 111 (17), 110 (33), 100 (57), 97 (25), 96 (34), 91 (45), 83 (33), 82 (23), 71 (24), 70 (21), 69 (28), 58 (36), 55 (39), 43 (40); HRMS required for $C_8H_{13}NO_3$: 171.0895; found 171.0885.

*Synthesis of methyl hexahydro-1*H*-oxazolo[3,4-a]pyridine-8a-carboxylate **13**.* 65 mg, 82%; Pale yellow oil. IR (neat) ν_{max}: 2924, 1769, cm^{-1}; ^{1}H-NMR δ_H: 1.50-1.55 (m, 2H, NCH$_2$C*H*$_2$), 1.64-1.69 (m, 2H, NCH$_2$CH$_2$C*H*$_2$), 1.96-1.99 (dd, *J* =10.0, 4.3 Hz, 1H, CC*H*$_2$), 2.71 (ddd, *J* = 11.7, 9.4, 3.6 Hz, 1H, CC*H*$_2$), 3-02-3.13 (m, 2H, NCH$_2$), 3.67 (d, *J* = 7.7 Hz, 1H, CC*H*$_2$O), 3.76 (s, 3H, OC*H*$_3$), 4.17 (d, *J* = 7.9 Hz, 1H, CC*H*$_2$O), 4.41 and 4.47 (2xd, *J* = 4.8 Hz, 2H, NC*H*$_2$O); ^{13}C-NMR δ_c: 20.1 (NCH$_2$CH$_2$*C*H$_2$), 23.3 (NCH$_2$*C*H$_2$), 27.9 (C*C*H$_2$CH$_2$), 46.9 (N*C*H$_2$), 52.6 (*C*H$_3$), 53.4 (C), 68.5 (C*C*H$_2$O), 86.9 (N*C*H$_2$O), 174.7 (CO); MS (EI) *m/z* (%): 185 (M^+, 1), 126 (100), 98 (36); MA required for $C_9H_{15}NO_3$: C, 58.4; H, 8.2; N, 7.6%; found C, 58.5; H, 8.3; N, 7.7%.

*Methyl 2-(hydroxymethyl)indoline-2-carboxylate **15**.* Pale yellow sticky oil; IR (solid) ν_{max}: 3475, 2992, 1733 cm^{-1} ^{1}H NMR δ_H: 3.16 (d, *J* = 16.5 Hz, 1H, CH$_2$C), 3.41 (d, *J* = 10.9 Hz, 1H, C*H*$_2$C), 3.69 (d, *J* = 10.9 Hz, 1H, C*H*$_2$OH), 3.78 (s, 3H, C*H*$_3$), 3.84 (d, *J* = 10.9 Hz, 1H, CH$_2$OH), 4.75 (br, 1H, NH), 6.78 (dd, *J* = 14.0, 6.9 Hz, ArH), 7.06 (dd, *J* = 4.4, 3.1 Hz, ArH); ^{13}C-NMR δ_c: 36.4, 52.9, 66.8, 71.2, 111.1, 120.2, 124.6, 127.7, 149.3, 175.1. MS *m/z*: 207 (M^+,42%), 176 (30), 175 (73), 148 (17), 144 (35), 143 (100), 130 (31), 118 (66), 89 (40). EA required for $C_{11}H_{13}NO_3$: C 63.8, H 6.3, N 6.7%; found C 63.9, H 6.1, N 6.5%.

*Synthesis of α-(hydroxymethyl)proline **11**.* The bicyclic product **10** (68 mg, 0.4 mmol) was suspended in 1.1 6M HCl:EtOH mixture (2 mL) and refluxed for 24 h. The water was evaporated under vacuo and the remaining residue was dissolved in EtOH (2 mL). Propylene oxide (140 μL, 2 mmol) was added and the solution refluxed for 30 min. The mixture was cooled at 0 ºC and free amino acid was isolated as pale yellow prisms (54 mg, 95%); mp 195 ºC (dec.); IR (solid) ν_{max}: 3350, 3600-3100, 1643-1600 cm^{-1}; ^{1}H-NMR (D_2O) δ_H: 1.90-2.06 (m, 3H, CC*H*$_2$C*H*$_2$), 2.12-2.23 (m, 1H, CC*H*$_2$), 3.33 (ddd, *J* = 11.5, 7.7, 3.4 Hz, 1H, NC*H*$_2$), 3,39-3,48 (m, 1H, NC*H*$_2$), 3.73 (d, *J* = 12.1, 1H, C*H*$_2$OH), 4.03 (d, *J* = 12.1, 1H, C*H*$_2$OH); ^{13}C-NMR (D_2O) δ_c: 24.1 ($CH_2CH_2CH_2$), 32.0 (C*C*H$_2$), 46.9 (*C*H$_2$OH), 63.7 (N*C*H$_2$), 75.8 (quat-C), 175.6 (CO); MS (EI) *m/z* (%): 145 (M^+, 0.7), 128 (16), 114 (100), 100 (90), 96 (75), 86 (15), 84(21), 82 (28), 73 (19), 70 (27), 68 (42), 55 (20), 44(27), 41 (48); MA required for $C_6H_{11}NO_3$: C, 49.7; H, 7.6; N, 9.7%; found C, 49.5; H, 7.8; N, 9.7%.

Diastereoselective synthesis of N*-methyl-D-serine **19**.* To a solution of *N*-Boc-sarcosine **16** (193 mg, 1 mmol) in DCM (4 mL) was added DCC (206 mg, 1 mmol). After 10 min, (−)-menthol or (−)-8-phenylmenthol (1 mmol) was slowly added at room temperature and stirring was continued at this temperature overnight. The solvent was evaporated and the residue purified by flash chromatography (SiO_2) affording the enantiomerically enriched esters **17a** and **17b** (301 mg, 0.9 mmol, 90% and 390 mg, 0.95 mmol, 95%, respectively). These compounds were dissolved in TFA (2 mL) and the reaction was monitored by TLC. After 6 h the reaction was completed and TFA was removed giving a residue, which was treated with triethylamine (270 μL, 2 mmol) and was immediately allow to undergo the reaction with paraformaldehyde assisted by microwave irradiation (see above) affording a 69:31 *dr* of compound **18a** and a 88:12 *dr* of compound **18b**. This crude material was suspended in 1.1 6M HCl:EtOH mixture (5 mL) and the resulting solution refluxed for 24 h. The water was evaporated under vacuo and the remaining residue was dissolved in EtOH (4 mL). Propylene oxide (280 μL, 4 mmol) was added and the solution refluxed for 30 min. The mixture was cooled at 0 ºC and free amino acid **19** was isolated as colorless needles (66 mg, 54% or 72 mg, 59% from **16**).

N-*Methyl-D-serine **19**.*[20] Mp 195 ºC (dec); $[\alpha]_{21}^{D}$ -11.6° (*c* 1.0, 6*N* HCl, 38% *ee*); or $[\alpha]_{21}^{D}$ -24.2º (*c* 1.0, 6*M* HCl, 76% *ee*); $[\alpha]_{21}^{D}$ 30.5° (*c* 1.0, 6*M* HCl).[22a]

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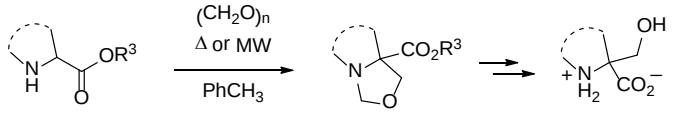

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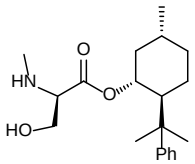

18b'

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