Exceptional stereoselectivity in the synthesis of 1,3,4-trisubstituted 4-carboxy β-lactam derivatives from amino acids

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Experimental Section

All reagents were of commercial quality. Solvents were dried and purified by standard methods. ^{1}H NMR spectra were recorded on 300 MHz in $CDCl_3$, using TMS as internal standard. ^{13}C NMR spectra were registered on 75 MHz. Electrospray mass spectra (positive mode) were also recorded. Analytical TLC was performed on aluminium sheets with a 0.2 mm layer of silica gel F254. Silica gel 60 (230-400 mesh) was used for column chromatography. Analytical HPLC was performed on a Novapak C_{18} (3.9 × 150 mm, 0.004mm) or on a Deltapak C_{18} (3.9 × 150 mm, 0.004mm) column, with a flow rate of 1mL/min, using a tuneable UV detector set at 214nm. Mixtures of MeCN (solvent A) and 0.05% TFA in H_2O (solvent B) were used in the mobile phase. Chiral HPLC was performed with a Chiralpak IA (4.6 × 150 mm) column, with a flow rate of 1mL/min, using a tuneable UV detector set at 214nm. The solvent mixtures are specified in each case. *N*-(*p*-Methoxy)benzyl amino acid derivatives **1a**, **1b**, **6-8** were prepared as previously described (Gerona-Navarro, G.; Bonache, M. A.; Herranz, R.; García-López, M. T.; González-Muñiz, R. *J. Org. Chem*. **2001**, *66*, 3538).

Synthesis of *N*-(*p*-methoxy)benzyl-*N*-chloropropionyl amino acid derivatives

Method A: A solution of the corresponding *N*-(*p*-methoxy)benzyl amino acid methyl ester derivative (5.78 mmol) in dry THF (28 mL) was treated with propylene oxide (87 mmol) and 2(*R,S*)-chloropropionyl chloride (8.7 mmol). The reaction was then stirred at room temperature for 2 h. The solvent was evaporated to dryness, and the residue was purified on a silica gel column as specified in each case.

Method B: To a solution of the corresponding *N*-(*p*-methoxy)benzyl amino acid methyl ester (6.67mmol) in dry DCM (10mL) was added (*R*)- or (*S*)-chloroproponic acid (13.34 mmol). Then, a solution of PyBrop (13.34mmol) and DIEA (12.01 mmol) in dry DCM (10mL) was added. The reaction was stirred overnight. The solvent was evaporated to dryness and the resulting syrup was extracted with EtOAc and washed with citric acid (10%), $HNaCO_3$ (10%) and brine. The organic layer was dried over Na_2SO_4 and after evaporation of the solvent the residue was purified on a silica gel column as specified in each case.

***N*-(*p*-Methoxy)benzyl-*N*-(2*S*)-chloropropionyl-L-Phe-OMe (3a).**

Eluent: EtOAc:hexane (1:9 to 1:6). Syrup. Yield: 48 % (Method A, from **1a**). $[\alpha]_D$ -93.7 (c = 0.94, $CHCl_3$). HPLC (Novapak): t_R = 11.85 min (A:B = 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ main rotamer 1.67 (d, 3H, *J* = 6.5, 3-H), 3.20 (dd, 1H, *J* = 14.0, 9.1, β-H), 3.35 (dd,1H, *J* = 14.0, 6.2, β-H), 3.61 (s, 3H, CH_3O), 3.79 (s, 3H, CH_3O), 3.98 (d, 1H, *J* = 16.1, CH_2-N), 4.39 (dd, 1H, *J* = 9.1, 6.2, α-H), 4.45 – 4.53 (m, 2H, 2-H and CH_2-N) 6.80 (d, 2H, *J* = 8.7, C_6H_4), 7.00 (d, 2H, *J* = 8.6, C_6H_4), 7.08–7.11 (m, 2H, C_6H_5), 7.20–7.27 (m, 3H C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.96 (3-C), 34.92 (β-C), 49.75 (2-C), 51.23 (N-CH_2), 52.03 (OMe), 55.18 (OMe), 60.19 (α-C). 113.98, 126.66, 127.07, 128.47, 128.73, 129,21, 137.58, and 159.20 (Ar), 169.40, and 170.21 (CO). EM (ES positive mode): 390.1 $(M+1)^+$, 412.1

$(M+Na)^+$. Anal Calc. for $C_{21}H_{24}ClNO_4$: C 64.69, H 6.20, N 3.59. Found: C 64.53, H 6.45, N 3.31.

_N_-(_p_-Methoxybenzyl)- _N_-(2_R_)-Chloropropionyl-L-Phe-OMe (3b).
Eluent: EtOAc:hexane (1:9 to 1:6). Syrup. Yield: 42% (Method A, from **1a**). $[\alpha]_D$ = +118.3 (c = 0.35, $CHCl_3$). HPLC (Novapak): t_R = 13.26 min (A:B = 40:60). ^1H NMR (300 MHz, $CDCl_3$): main rotamer δ 1.61 (d, 3H, *J* = 6.5, 3-H), 3.30 (dd, 1H, *J* = 13.9, 9.9 β-H), 3.38 (dd,1H, *J* = 13.9, 5.1, β-H), 3.56 (d, 1H, *J* = 16.3, CH_2-N), 3.71 (s, 3H, CH_3O), 3.78 (s, 3H, CH_3O), 4.07 (dd, 1H, *J* = 9.9, 5.1, α-H), 4.42 (q, 1H, *J*= 6.5, 2-H), 4.52 (d, 1H, *J* = 16.3, CH_2-N) 6.82 (d, 2H, *J* = 8.7, C_6H_4), 7.05 (d,2H, *J* = 8.7, C_6H_4), 7.19-7.27 (m, 5H C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.81 (3-C), 34.78 (β-C), 49.69 (2-C), 52.25 (N-CH_2), 52.43 (OMe), 55.24 (OMe), 62.40 (α-C). 114.08, 126.74, 127.46, 128.56, 128.91, 129,57, 137.78, and 159.21 (12C Ar), 169.30 and 170.15 (CO). EM (ES positive mode): 390.1 $(M+1)^+$, 412.1 $(M+Na)^+$. Anal Calc. for $C_{21}H_{24}ClNO_4$: C 64.69, H 6.20, N 3.59. Found: C 64.62, H 6.38, N 3.48.

_N_-(_p_-Methoxybenzyl)- _N_-(2_S_)-Chloropropionyl-D-Phe-OMe (3c).
Eluent: EtOAc:hexane (1:9 to 1:6). Syrup. Yield: 40% (Method A, from **1b**). $[\alpha]_D$ = -120.2 (c = 1.04, $CHCl_3$). HPLC (Novapak): t_R = 13.20 min (A:B = 40:60). Anal Calc. for $C_{21}H_{24}ClNO_4$: C 64.69, H 6.20, N 3.59. Found: C 64.51, H 6.11, N 3.33.

_N_-(_p_-Methoxybenzyl)- _N_-(2_R_)-chloropropionyl-D-Phe-OMe (3d).
Eluent: EtOAc:hexane (1:9 to 1:6). Syrup. Yield: 52 % (Method A, from **1b**). $[\alpha]_D$ +98.5 (c = 1, $CHCl_3$). HPLC (Novapak): t_R = 11.82 min (A:B = 40:60). Anal Calc. for $C_{21}H_{24}ClNO_4$: C 64.69, H 6.20, N 3.59. Found: C 64.72, H 6.13, N 3.29.

***N*-(*p*-Methoxy)benzyl-*N*-(2*S*)-chloropropionyl-L-Ala-OMe (9a)**
Eluent: Hexane: EtOAc (9:1 to 2:1). Syrup. Yield: 53%. (Method B, from **6**). $[\alpha]_D$= -46.2 (c = 0.52, $CHCl_3$). HPLC (Novapak): t_R = 12.03 min (A:B = 35:65). ^1H NMR (300MHz, $CDCl_3$): δ 1.38 (d, 3H, *J* = 6.9, β-H), 1.66 (d, 3H, *J*=6.6, 3-H), 3.65 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.43-4.58 (m, 3H, CH_2-N α-H, 2-H), 4.72 (d, 1H, *J* = 17.1, CH_2-N), 6.90 (d, 2H, *J* = 8.7, C_6H_4), 7.21 (d, 2H, *J* = 8.7, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.60 (3-C), 21.00 (β-C), 50.60 (CH_2-N), 50.35 (2-C), 52.24 (α-C), 54.91 (OMe), 55.26 (OMe), 114.35, 127.89, 128.06, and 159.25 (Ar), 169.63, and 171.57 (CO). EM (ES positive mode): 314.1 $(M+1)^+$, 336.0$(M+Na)^+$. Anal Calc. for $C_{15}H_{20}ClNO_4$: C 57.42, H 6.42, N 4.46. Found: C 57.65, H 6.30, N 4.09.

***N*-(*p*-methoxy)benzyl-*N*-(2*R*)-chloropropionyl-L-Ala-OMe (9b)**
Eluent: Hexane: EtOAc (20:1). Syrup. Yield: 50% (Method B, from **6**). $[\alpha]_D$= +14.5 (c = 0.45, $CHCl_3$). HPLC (Novapak): t_R = 14.48 min (A:B = 35:65). ^1H NMR (300MHz, $CDCl_3$): δ 1.39 (d, 3H, *J* = 6.9, β-H), 1.61 (d, 3H, *J* = 6.6, 3-H), 3.72 (s, 3H, OMe), 3.81 (s, 3H, OMe), 4.41-4.68 (m, 3H, CH_2-N, α-H, 2-H), 4.83 (d, 1H, *J* = 17.3, CH_2-N), 6.90 (d, 2H, *J* = 8.6, C_6H_4), 7.20 (d, 2H, *J* = 8.6, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.06 (3-C), 20.73 (β-C), 49.95 (2-C), 50.05 (CH_2-N), 52.06 (α-C), 54.77 (OMe), 55.08 (OMe), 114.17, 127.26, 128.41, and 159.06 (Ar), 169.50, and 171.39 (CO). EM (ES positive mode): 314.0 $(M+1)^+$, 336.0 $(M+Na)^+$. Anal Calc. for $C_{15}H_{20}ClNO_4$: C 57.42, H 6.42, N 4.46. Found: C 57.34, H 6.19, N 4.37.

Table 1. Evaluation of different coupling agents and bases for the preparation of compound **9a** from Pmb-L-Ala-OMe (**6**) and 2S-chloroprpopionic acid (method B).

Coupling agent	Base	diastereoisomeric excess (%)[a]	conversion[b] (%)
BOP	TEA	95	34
	DIEA	97	45
	Collidine	97	25
	2,6-Lutidine	98	22
PyBroP	DIEA	94	76
	Collidine	95	58
	2,6-Lutidine	95	46
BroP	DIEA	93	48
HATU		96	31
PyAOP		95	27
BTC		67	8
TFFH		94	46
PyBOP/HOAt		87	11

[a] The **9a**:**9b** ratio was measured by HPLC (A:B = 35:65).
[b] From HPLC crude mixtures after 48 h of reaction.

***N*-(*p*-Methoxy)benzyl-*N*-(2*S*)-chloropropionyl-L-Lys(Boc)-OMe (10a)**
Eluent: EtOAc:hexane (1:9 to 1:4). Syrup. Yield: 70% (Method B, from **7**). $[\alpha]_D$ = -17.62 (c = 0.61, $CHCl_3$). HPLC (Deltapak): t_R = 16.40 min, (A:B = 45:55). Chiral HPLC: t_R = 10.75 min (EtOH:hexane = 7:93). ^1H NMR (300 MHz, $CDCl_3$): 1.31 (m, 2H, γ-H), 1.38 (m, 2H, δ-H), 1.44 (s, 9H, CH_3 ^tBu), 1.63 (d, 3H, *J* = 6.5, 3-H), 1.81 (m, 1H, β-H), 1.99 (m, 1H, β-H), 3.06 (m, 2H, ε-H), 3.52 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.48 (m, 2H, 2-H and ε-NH), 4.49 (d, *J*=16.8, 1H, CH_2-N), 4.71 (d, 1H, *J*=16.8, CH_2-N), 4.86 (dd, *J*=8.5, 6.5, 1H, α-H), 6.88 (d, 2H, *J*=8.5, C_6H_4), 7.14 (d, 2H, *J*=8.5, C_6H_4). ^{13}C NMR

(75 MHz, $CDCl_3$): 20.8 (CH_3), 23.1 (γ-C), 28.4 (CH_3 ^tBu), 29.0 (β-C), 29.5 (δ-C), 40.2 (ε-C), 48.7 (CH_2-N), 50.1 (2-C), 51.9 (OMe), 55.3 (OMe), 57.2 (α-C), 79.0 (C ^tBu), 114.2, 127.8, 128.1, 155.9 (Ar); 159.2, 170.4, and 171.1 (CO). MS (ES positive mode): 493.1 $(M+Na)^+$. Anal Calc. for $C_{23}H_{35}ClN_2O_6$: C 58.65, H 7.49, N 5.95. Found: C 58.57, H 7.52, N 5.82.

***N*-(*p*-methoxy)benzyl-*N*-(2*R*)-chloropropionyl-L-Lys(Boc)-OMe (10b)**

Eluent: EtOAc:hexane (1:9 to 1:4). Syrup. Yield: 52% (Method B, from **7**). $[\alpha]_D$ = -34.33 (c = 0.92, $CHCl_3$). HPLC (Deltapak): t_R = 18.56 min, (A:B = 45:55). Chiral HPLC: t_R = 8.37 min (EtOH:hexane = 7:93). ^1H NMR (300 MHz, $CDCl_3$): 1.33 (m, 2H, γ-H), 1.39 (m, 2H, δ-H), 1.44 (s, 9H, CH_3 ^tBu), 1.63 (d, 3H, *J*=6.6, 3-H), 1.85 (m, 1H, β-H), 2.03 (m, 1H, β-H), 3.04 (m, 2H, ε-H), 3.69 (s, 3H, OMe), 3.82 (s, 3H, OMe), 4.28 (dd, 1H, *J*=7.8, 6.6, α-H), 4.44 (d, 1H, *J*=17.1, CH_2-N), 4.52 (m, 2H, 2-H and ε-NH), 4.83 (d, 1H, *J*=17.1, CH_2-N), 6.90 (d, 2H, *J*=8.8, C_6H_4), 7.23 (d, 2H, *J*=8.8, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): 20.7 (CH_3), 23.9 (γ-C), 28.4 (CH_3 ^tBu), 28.6 (β-C), 29.7 (δ-C), 40.1 (ε-C), 49.9 (2-C), 51.1 (CH_2-N), 52.2 (OMe), 55.3 (OMe), 59.7 (α-C), 78.8 (C ^tBu), 114.3, 127.9, 129.3, and 155.9 (Ar), 159.3, 169.9, and 171.0 (CO). MS (ES positive mode): 493.1 $(M+Na)^+$. Anal Calc. for $C_{23}H_{35}ClN_2O_6$: C 58.65, H 7.49, N 5.95. Found: C 58.68, H 7.46, N 5.98.

***N*-(*p*-Methoxy)benzyl-*N*-(2*S*)-chloropropionyl-L-Glu(O^{t}Bu)-O^{t}Bu (11a)**

Eluent: EtOAc:CH_2Cl_2 (1:30). Syrup. Yield: 52% (Method B, from **8**). HPLC (Novapak): t_R = 5.81 min, (A:B = 40:60). Chiral HPLC: t_R = 10.66 min, (EtOH/Hexane, 1:99). $[\alpha]_D$ = -37.02 (c = 0.74, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 1.37 (s, 9H, CH_3 ^tBu), 1.41 (s, 9H, CH_3 ^tBu), 1.63 (d, 3H, *J*=6.5, 3-H), 1.95 (m, 1H, β-H), 2.25 (m, 2H, γ-H), 2.31 (m, 1H, β-H), 3.80 (s, 3H, OMe), 4.28 (t, 1H, *J*=6.8, α-H), 4.53 (q, 1H, *J*=6.5, 2-H), 4.61 (s, 2H, CH_2-N), 6.88 (d, 2H, *J*=8.6, C_6H_4), 7.21 (d, 2H, *J*=8.6, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): 20.9 (3-C), 24.8 (β-C), 27.7 (CH_3 ^tBu) , 27.9 (CH_3 ^tBu), 32.0 (γ-C), 49.9 (2-C), 50.2 (CH_2-N), 55.2 (OMe), 58.7 (α-C), 80.3 (C ^tBu), 81.7 (C ^tBu), 114.1, 127.9, 128.4, and 159.2 (Ar), 169.0, 169.5, and 172.2 (CO). MS (ES positive mode): 470.13 $(M+1)^+$. Anal Calc. For $C_{24}H_{36}ClNO_6$: C 61.33, H 7.72, N 2.98. Found: C 61.35, H 7.5o, N 3.01.

***N*-(*p*-methoxy)benzyl-*N*-(2*R*)-chloropropionyl-L-Glu(O^{t}Bu)-O^{t}Bu (11b)**

Eluent: EtOAc:CH_2Cl_2 (1:30). Syrup. Yield: 65% (Method B, from **8**). HPLC (Novapak): t_R = 5.99 min, (A:B = 40:60). Chiral HPLC: t_R = 7.23 min, (EtOH/Hexane 1:99). $[\alpha]_D$ = -62.34 (c = 1.08, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): 1.41 (s, 9H, CH_3 ^tBu), 1.44 (s, 9H, CH_3 ^tBu), 1.59 (d, 3H, *J*=6.6, 3-H), 1.97 (m, 1H, β-H), 2.04 (m, 1H, β-H), 2.32 (m, 2H, γ-H), 3.80 (s, 3H, OMe), 4.17 (t, 1H, *J*=6.1, α-H), 4.38 (d, 1H, *J*=17.1, CH_2-N), 4.44 (q, 1H, *J*=6.5, 2-H), 4.87 (d, 1H, *J*=17.1, CH_2-N), 6.88 (d, 2H, *J*=8.7, C_6H_4), 7.25 (d, 2H, *J*=8.7, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): 20.7 (3-C), 24.3 (β-C), 27.9 (CH_3 ^tBu) , 28.0 (CH_3 ^tBu), 32.0 (γ-C), 49.7 (2-C), 50.9 (CH_2-N), 55.2 (OMe), 59.9 (α-C), 80.4 (C ^tBu), 81.6 (C ^tBu), 114.2, 127.8, 129.3, and 159.1 (Ar), 168.9, 169.4, and 172.3 (CO). MS (ES positive mode): 470.26 $(M+1)^+$. Anal Calc. For $C_{24}H_{36}ClNO_6$: C 61.33, H 7.72, N 2.98, Cl 7.54 Found: C 61.14, H 7.74, N 2.67, Cl 7.51.

Synthesis of 2-azetidinone derivatives

A solution of the corresponding *N*-(*p*-methoxybenzyl)-N-chloropropionyl derivative (1 mmol) in dry MeCN (12 mL) was treated with $CsCO_3$ (2 mmol) or BTPP (1.5 mmol) and stirred at room temperature until dissapearance of the starting material. The solvent was then evaporated to dryness, and the residue was partioned between EtOAc and H_2O. The organic layer was dried over Na_2SO_4 and after evaporation the residue was purified on a silica gel column as specified in each case.

(3*S*,4*S*)-4-Benzyl-1-(*p*-methoxy)benzyl-4-methoycarbonyl-3-methyl-2-azetidinone (5a)

Eluent: Hexane: EtOAc (5:1 to 3:1). Syrup. Yield: 70% (from **3a** and **3c**). HPLC (Novapak): t_R = 10.72 min (A:B = 40:60). Chiral HPLC: t_R = 12.49 min (EtOH/hexane, 5:95). $[\alpha]_D$= -6.6 (c = 1, $CHCl_3$). ^1H NMR (300MHz, $CDCl_3$): δ 1.14 (d, 3H, *J* = 7.6, 3-CH_3), 3.10 (d, 1H, *J* = 14.7, 4-CH_2), 3.15 (q, 1H, *J* = 7.6, 3-H), 3.33 (d, 1H, *J* = 14.4, 4-CH_2), 3.71 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.13 (d, 1H, *J* = 15.3, 1-CH_2), 4.40 (d, 1H, *J* = 15.3, 1-CH_2), 6.83 (d, 2H, *J* = 8.6, C_6H_4), 6.93-6.96 (m, 2H, C_6H_5), 7.14 (d, 2H, *J* = 8.6, C_6H_4), 7.19-7.22 (m, 3H, C_6H_5). ^{13}C NMR (75 MHz, $CDCl_3$): δ 10.02 (3-CH_3), 40.36 (4-CH_2), 45.43 (CH_2-N), 51.16 (3-C), 53.48 (OMe), 55.21 (OMe), 68.96 (4-C), 113.70, 127.13, 128.44, 128.87, 129.38, 129.89, 135.03, and 158.82 (Ar), 169.58, and 171.69 (CO). EM (ES positive mode): 354.1 $(M+1)^+$. Anal Calc. for $C_{21}H_{23}NO_4$: C 71.37, H 6.56, N 3.96. Found: C 70.95, H 6.44, N 4.01.

(3*R*,4*R*)-4-Benzyl-1-(*p*-methoxy)benzyl-4-methoycarbonyl-3-methyl-2-azetidinone (5b)

Eluent: Hexane: EtOAc (5:1 to 3:1). Syrup. Yield: 66% and 69% (from **3b** and **3d**, respectively). Chiral HPLC: t_R = 11.44 min (EtOH/hexane, 5:95). $[\alpha]_D$= +6.7 (c = 1, $CHCl_3$). Anal Calc. for $C_{21}H_{23}NO_4$: C 71.37, H 6.56, N 3.96. Found: C 71.17, H 6.38, N 4.00.

(3*S*,4*S*)-1-(*p*-methoxy)benzyl-3,4-dimethyl-4-methoxycarbonyl-2-azetidinone (12a)

Eluent: Hexane: EtOAc (3:1 to 2:1). Syrup. Yield: 66% (from **6**). HPLC (Novapak): t_R = 5.87 min (A:B = 35:65). $[\alpha]_D$ = -49.6 (c = 0.51, $CHCl_3$). ^1H NMR (300MHz, $CDCl_3$): δ 1.16 (d, 3H, *J* = 7.5, 3-CH_3), 1.29 (s, 3H, 4-CH_3), 3.04 (q, 1H, *J* = 7.5, 3-H), 3.73 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.12 (d, 1H, *J* = 15.0, 1-CH_2), 4.71 (d, 1H, *J* = 15.0, 1-CH_2), 6.84 (d, 2H, *J* = 8.7, C_6H_4), 7.22 (d, 2H, *J* = 8.7, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): δ 9.72 (3-CH_3), 21.24 (4-CH_3), 43.89 (CH_2-N), 51.82 (3-C), 54.95 (OMe), 56.21 (OMe), 64.53 (4-C), 113.68, 127.98,

129.73, and 158.87 (Ar), 168.49, and 171.85 (CO). EM (ES positive mode): 278.0 $(M+1)^+$. Anal Calc. for $C_{15}H_{19}NO_4$: C 64.97, H 6.91, N 5.05. Found: C 65.83, H 6.73, N 4.90.

(3*R*,4*R*)-1-(*p*-methoxy)benzyl-3,4-dimethyl-4-methoxycarbonyl-2-azetidinone (12b)

Eluent: Hexane: EtOAc (3:1 to 2:1). Syrup. Yield: 54% (from **6**). HPLC (Novapak): t_R = 5.80 min (A:B = 35:65). $[\alpha]_D$ = +48.8 (c = 0.49, $CHCl_3$). Anal Calc. for $C_{15}H_{19}NO_4$: C 64.97, H 6.91, N 5.05. Found: C 65.70, H 6.98, N 5.14.

(3*S*,4*S*)-1-(*p*-methoxy)benzyl-4-[4'-(*tert*-butoxycarbonyl)amino]butyl-3-methyl-4-methoxycarbonyl-2-azetidinone (13a)

Eluent: EtOAc:hexane (1:4 to 1:3). Syrup. Yield: 67% (from **10a**). $[\alpha]_D$ = -17.4 (c = 1.18, $CHCl_3$). Chiral HPLC: t_R = 12.30 min, (EtOH/Hexane, 7:93). ^{1}H NMR (300 MHz, $CDCl_3$): 0.99 (m, 1H, 2'-H), 1.11 (m, 3H, 2'-H and 3'-H), 1.16 (d, 3H, J=7.5, 3-CH_3), 1.44 (s, 9H, CH_3 Boc), 1.72 (m, 2H, 1'-H), 2.88 (m, 2H, 4'-H), 3.14 (q, 1H, *J*=7.5, 3-H), 3.46 (s, 3H, OMe), 3.79 (s, 3H, OMe), 4.11 (d, 1H, *J*=15.4, 1-CH_2), 4.31 (brs, 1H, 4'-NH), 4.77 (d, 1H, *J*=15.4, 1-CH_2), 6.86 (d, 2H, *J*=8.7, C_6H_4), 7.22 (d, 2H, *J*=8.7, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): 10.1 (3-CH_3), 21.3 (2'-C), 28.4 (CH_3 ^{t}Bu), 29.9 (3'-C), 34.1 (1'-C), 39.9 (4'-C), 44.5 (1-CH_2), 52.0 (OMe), 52.9 (3-C), 55.2 (OMe), 68.6 (4-C), 79.1 (C ^{t}Bu), 113.9, 128.8, 129.7, and 155.8 (Ar), 159.1, 169.3, and 171.8 (CO). EM (ES positive mode): 457.1 $(M+Na)^+$. Anal Calc. For $C_{23}H_{34}N_2O_6$: C 63.57, H 7.89, N 6.45. Found: C 63.45, H 7.86, N 6.48.

(3*R*,4*R*)-1-(*p*-methoxy)benzyl-4-[4'-(*tert*-butoxycarbonyl)amino]butyl-3-methyl-4-methoxycarbonyl-2-azetidinone (13b)

Eluent: EtOAc:hexane (1:4 to 1:3). Syrup. Yield: 77% (from **10b**) Chiral HPLC: t_R = 16.22 min, (EtOH/Hexane, 7:93). $[\alpha]_D$ = +15.2 (c = 1.17, $CHCl_3$). EM (ES positive mode): 457.1 $(M+Na)^+$. Anal Calc. For $C_{23}H_{34}N_2O_6$: C 63.57, H 7.89, N 6.45, Found: C 63.42, H 7.69, N 6.41.

(3*S*,4*S*)-1-(*p*-methoxy)benzyl-4-*tert*-butoxycarbonyl-4-(2-*tert*-butoxycarbonyl)ethyl-3-methyl-2-azetidinone (14a)

Eluent: EtOAc:hexane (1:9 to 1:5). Syrup. Yield: 48% (from **11a**). HPLC (Novapak): t_R = 6.01 min, (A:B = 40:60). Chiral HPLC: t_R = 11.39 min, (EtOH/Hexane 2:98). $[\alpha]_D$ = -23.70 (c = 0.945, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 1.22 (d, 3H, *J*=7.6, 3-CH_3), 1.35 (s, 9H, CH_3 ^{t}Bu), 1.49 (s, 9H, CH_3 ^{t}Bu), 1.96 (m, 4H, 1'-H and 2'-H), 3.08 (c, 1H, *J*=7.6, 3-H), 3.78 (s, 3H, OMe), 4.09 (d, 1H, *J*=15.4, 1-CH_2), 4.87 (d, 1H, *J*=15.4, 1-CH_2), 6.84 (d, 2H, *J*=8.8, C_6H_4), 7.24 (d, 2H, *J*=8.8, C_6H_4). ^{13}C NMR (75 MHz, $CDCl_3$): 10.4 (3-CH_3), 27.9 (CH_3 ^{t}Bu) , 28.1 (CH_3 ^{t}Bu), 29.5, and 29.9 (β-C and γ-C), 44.3 (1-CH_2), 52.7 (3-C), 55.1 (OMe), 67.7 (α-C), 80.4, and 82.9 (C ^{t}Bu), 113.9, 128.5, 129.7, 159.0 (Ar), 169.3, 169.9, and 171.5 (CO). MS (ES positive mode): 434.13 $(M+1)^+$. Anal Calc. For $C_{24}H_{35}NO_6$: C 66.49, H 8.14, N 3.23. Found: C 66.25, H 8.27, N 3.05.

(3*R*,4*R*)-1-(*p*-methoxy)benzyl-4-*tert*-butoxycarbonyl-4-(2-*tert*-butoxycarbonyl)-ethyl-3-methyl-2-azetidinone (14b)

Eluent: EtOAc:hexane (1:9 to 1:5). Syrup. Yield: 54% (from **11b**) HPLC (Novapak): t_R = 6.01 min, (A:B = 40:60). Chiral HPLC: t_R = 21.65 min, (EtOH/Hexane 2:98). $[\alpha]_D$ = +19.79 (c = 1.01, $CHCl_3$). MS (ES positive mode): 434.13 $(M+1)^+$. Anal Calc. For $C_{24}H_{35}NO_6$: C 66.49, H 8.14, N 3.23. Found: C 66.20, H 8.02, N 3.24.

Synthesis of dipeptide derivatives

General procedure: A solution of the corresponding 2-azetidinone (0.82 mmol) in MeOH (10 mL) was treated with 2M NaOH (2 mmol), and stirred overnight at room temperature. The solvent was evaporated and the residue was dissolved in H_2O (8 mL) and acidified with 1M HCl to pH=3. The aqueous layer was extracted with EtOAc, the phases were separated and the organic layer was dried over Na_2SO_4 and the solvent evaporated. A portion of the carboxylic acid obtained (0.175mmol) was dissolved in dry THF (2 mL), and then treated with H-L-Xaa-OMe.HCl (0.35 mmol), BOP (0.35mmol) and TEA (0.70mmol) in this order. The solution was stirred for 48 h at room temperature. The solvent was evaporated and the residue was extracted with EtOAc, and washed with citric acid (10%), $HNaCO_3$ (10%) and brine. The organic layer was dried over Na_2SO_4 and, after evaporation of the solvent, the residue was purified on a silica gel column as specified in each case.

(3*S*,4*S*,1'*S*)-4-Benzyl-1-(p-methoxy)benzyl-4-[*N*-(1'-(methoxycarbonyl)ethyl]carbamoyl-3-methyl-2-azetidinone (15a)

Eluent: Hexane: EtOAc (3:1 to 2:1). Syrup. Yield: 66% (from **5a**). HPLC (Novapak): t_R = 13.34 min (A:B = 40:60). ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84 (d, 3H, *J* = 7.3, 2'-H), 1.08 (d, 3H, *J* = 7.5, 3-CH_3), 3.08 – 3.24 (m, 2H, 3-H, 4-CH_2), 3.63 (s, 3H, OMe), 3.70 (m, 2H, 4-CH_2, CH_2-N), 3.72 (s, 1H, OMe), 4.24 (m, 1H, 1'-H), 4.61 (d, 1H, *J* = 15.4, CH_2-N), 5.62 (d, 1H, *J* = 7.1, 1'-NH), 6.75 (d, 2H, *J* = 8.6, C_6H_4), 7.05 (d, 2H, *J* = 8.6, C_6H_4), 7.15 – 7.32 (m, 5H, C_6H_5). Anal Calc. for $C_{24}H_{28}N_2O_5$: C 67.91, H 6.65, N 6.60. Found: C, 67.49, H 6.32, N 6.38.

(3*R*,4*R*,1'*S*)-4-Benzyl-1-(p-methoxy)benzyl-4-[*N*-(1'-(methoxycarbonyl)ethyl]carbamoyl-3-methyl-2-azetidinone (15b).

Eluent: Hexane: EtOAc (3:1 to 2:1). Syrup.Yield: 70% (from **5b**). HPLC (Novapak): t_R = 15.02 min (A:B = 40:60^{1}H NMR (300 MHz, $CDCl_3$): δ 0.71 (d, 3H, *J* = 7.1, 2'-H), 1.13 (d, 3H, *J* = 7.6, 3-CH_3), 3.05 – 3.12 (m, 2H, 3-H, 4-CH_2), 3.56 (s, 3H, OMe), 3.63 (d, 1H, *J* = 15.1, CH_2-N), 3.68 (s, 1H, OMe), 3.75 (d, 1H, *J* = 14.4, 4-CH_2), 4.29 (m, 1H, 1'-H), 4.70 (d, 1H, *J* = 15.1, CH_2-N),

5.84 (d, 1H, *J* = 7.5, 1'-NH), 6.73 (d, 2H, *J* = 8.5, C_6H_4), 6.90 (d, 2H, *J* = 8.5, C_6H_4), 7.17 – 7.29 (m, 5H, C_6H_5). Anal Calc. for $C_{24}H_{28}N_2O_5$: C 67.91, H 6.65, N 6.60. Found: C 67.55, H 6.90, N 6.57.

(3*S*,4*S*,1'*S*)-1-(*p*-Methoxy)benzyl-4-[*N*-(1'-(methoxycarbonyl-2'-phenyl)ethyl]carbamoyl-3,4-dimethyl-2-azetidinone (16a)

Eluent: Hexane: EtOAc (1:1 to 1:2). Syrup. Yield: 69% (from **12a**). HPLC (Novapak): t_R = 13.20 min (A:B = 35:65). ^{1}H NMR (300MHz, $CDCl_3$): δ 0.73 (d, 3H, *J* = 7.5, 3-CH_3), 1.46 (s, 3H, 4-CH_3), 2.50 (dd, 1H, *J* = 9.6, 12.6, 2'-H), 2.94 (q, 1H, *J* = 7.8, 3-H), 3.04 (dd, 1H, *J*= 5.1, 13.8, 2'-H), 3.72 (s, 3H, OMe), 3.80 (s, 3H, OMe), 4.11 (d, 1H, *J* = 15.0, 1-CH_2), 4.42 (d, 1H, *J* = 15.0, 1-CH_2), 4.59-4.66 (m, 1H, 1'-H), 5.94 (d, 1H, *J* = 8.1, 1'-NH), 6.89 (d, 2H, *J*=8.1, C_6H_4), 6.95 (m, 2H, C_6H_5), 7.21-7.31 (m, 3H, C_6H_5), 7.33 (d, 2H, J=8.4, C_6H_4). EM (ES positive mode): 425.2 $(M+1)^+$, 447.3 $(M+Na)^+$. Anal Calc. for $C_{24}H_{28}N_2O_5$: C 67.91, H 6.65, N 6.60. Found: C 68.06, H 6.79, N 6.25.

(3*R*,4*R*,1'*S*)-1-(*p*-Methoxy)benzyl-4-[*N*-(1'-(methoxycarbonyl-2'-phenyl)ethyl]carbamoyl-3,4-dimethyl-2-azetidinone (16b)

Eluent: Hexane: EtOAc (2:1). Yield: 45% (from **12b)**. HPLC (Novapak): t_R = 15.25 min (A:B = 35:65). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.16 (d, 3H, J = 7.5, 3-CH_3), 1.37 (s, 3H, 4-CH_3), 2.70 (dd, 1H, J = 14.1, 7.5, 2'-H), 2.96-3.05 (m, 2H, 2'-H, 3-H), 3.67 (s, 3H, OMe), 3.78 (s, 3H, OMe), 3.96 (d, 1H, J = 15.2, 1-CH_2), 4.19 (d, 1H, J = 15.2, 1-CH_2), 4.74 (m, 1H, 1'-H), 6.20 (d, 1H, J = 7.5, 1'-NH), 6.84 (d, 2H, J = 8.4, C_6H_4), 7.07 (m, 2H, C_6H_5), 7.11 (d, 2H, J = 8.4, C_6H_4) 7.24-7.35 (m, 3H, C_6H_5). EM (ES positive mode): 425.2 $(M+1)^+$. Anal Calc. for $C_{24}H_{28}N_2O_5$: C 67.91, H 6.65, N 6.60. Found: C 67.89, H 6.31, N 6.44.

(3*S*,4*S*,1'*S*)-1-(p-Methoxy)benzyl-4-[4'-(*tert*-butoxycarbonyl)amino]butyl-4-[*N*-(1'-(methoxycarbonyl-2''-phenyl)ethyl]carbamoyl-3-methyl-2-azetidinone (17a)

Eluent: EtOAc:hexane (1:4 to 1:2). Syrup. Yield: 63% (from **13a**) HPLC (Novapak): t_R = 7.93 min, (A:B = 45:55). $[\alpha]_D$ = -28.71 (c = 0.89, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 0.63 (d, *J*=7.6, 3H, 3-CH_3), 1.11 (m, 1H, 3'-H), 1.28 (m, 3H, 2'-H and 3'-H), 1.36 (s, 9H, CH_3 ^{t}Bu), 1.85 (m, 2H, 2'-H), 2.36 (m, 1H, 2''-H), 2.94 (m, 4H, H3, 2''-H, 4'-H), 3.65 (s, 3H, OMe), 3.72 (s, 3H, OMe), 4.05 (d, 1H, *J*=15.1, 1-CH_2), 4.39 (d, 1H, *J*=15.1, 1-CH_2), 4.45 (brs, 1H, 4'-NH), 4.57 (m, 1H, 1''-H), 5.88 (d, 1H, *J*=8.3, 1''-NH), 7.29-6.80 (m, 9H, Ar), ^{13}C NMR (75 MHz, $CDCl_3$): 9.3 (3-CH_3), 21.0 (2'-C), 28.3 (CH_3 ^{t}Bu), 30.0 (3'-C), 32.8 (1'-C), 37.0 (2''-C), 39.9 (4'-C), 44.4 (1-CH_2), 52.3 (OMe), 52.8 (3-C), 53.1 (1''-C), 55.3 (OMe), 69.5 (4-C), 79.1 (C ^{t}Bu), 114.3, 127.2, 128.6, 130.5, 135.8, 155.9 (Ar), 159.5, 170.5, 170.9, 171.4 (CO). EM (ES positive mode): 604.2 $(M+Na)^+$. Anal Calc. For $C_{32}H_{43}N_3O_7$: C 66.07, H 7.45, N 7.22. Found: C 65.98, H 7.47, N 7.26.

(3*R*,4*R*,1'*S*)-1-(p-Methoxy)benzyl-4-[4'-(*tert*-butoxycarbonyl)amino]butyl-4-[*N*-(1'-(methoxycarbonyl-2''-phenyl)ethyl]carbamoyl-3-methyl-2-azetidinone (17b).

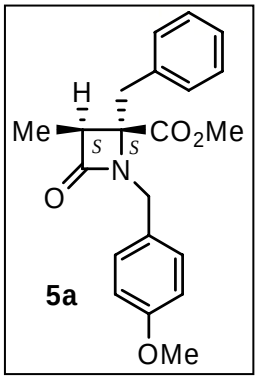
Eluent: EtOAc:hexane (1:4 to 1:2). Syrup. Yield: 63% (from **13b**). HPLC (Novapak): t_R = 8.35 min, (A:B = 45:55). $[\alpha]_D$ = -48.39 (c =1.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): 0.89 (m, 1H, 3'-H), 1.07 (d, *J*=7.6, 3H, 3-CH_3), 1.12 (m, 3H, 2'-H, 3'-H), 1.37 (s, 9H, CH_3 ^{t}Bu), 1.70 (m, 2H, 1'-H), 2.63 (m, 1H, 2''-H), 2.87 (m, 2H, 4'-H), 3.01 (m, 2H, H-3, 2''-H), 3.61 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.89 (d, 1H, *J*=15.4, 1-CH_2), 4.19 (d, 1H, *J*=15.4, 1-CH_2), 4.41 (brs, 1H, 4'-NH), 4.75 (m, 1H, 1''-H), 6.21(d, 1H, *J*=8.1, 1''-NH), 7.27-6.79 (m, 9H, Ar), ^{13}C NMR (75 MHz, $CDCl_3$): 9.6 (CH_3), 21.1 (2'-C), 28.2 (CH_3 ^{t}Bu), 29.6 (3'-C), 33.2 (1'-C), 37.2 (2''-C), 39.6 (4'-C), 43.9 (1-CH_2), 52.1 (OMe), 52.4 (1''-C), 53.4 (3-C), 55.1 (OMe), 69.3 (4-C), 78.8 (C ^{t}Bu), 114.1, 126.9, 128.4, 128.6, 129.25, 135.7, and 155.6 (Ar), 159.1, 169.8, 170.9, and 171.2 (CO). EM (ES positive mode): 604.3 $(M+Na)^+$. Anal Calc. For $C_{32}H_{43}N_3O_7$: C 66.07, H 7.45, N 7.22. Found: C 66.11, H 7.48, N 7.18.

Synthesis of 4-Benzyl-1-(*p*-methoxy)benzyl-4-hydroxymethyl-3-methyl-2-azetidinone (18a)

Compound **5a** (70.5 mg, 0.20mmol) was dissolved in MeOH (2.4mL), and treated with NaOH (0.3mL, 0.60mmol), then left stirring for 24 h. The solvent was evaporated and the residue dissolved in H_2O (4mL) and acidified with 1M HCl to pH=3. The aqueous layer was extracted with EtOAc, the phases were separated and the organic layer was dried over Na_2SO_4 and the solvent was evaporated to yield 56 mg (84%) of the corresponding free carboxylic acid. HPLC (Novapak): t_R = min 9.04 (A:B = 35:65). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.24 (d, 3H, *J* = 7.8, 3-CH_3), 3.11 (d, 1H, *J* = 14.4, 4-CH_2), 3.21 (q, 1H, *J* = 7.5, 3-H), 3.32 (d, 1H, *J* = 14.4, 4-CH_2), 3.80 (s, 3H, OMe), 4.08 (d, 1H, *J* = 15.3, 1-CH_2), 4.56 (d, 1H, *J* = 15.3, 1-CH_2), 6.84 (d, 2H, *J* = 8.5, C_6H_4), 6.94 (d, 2H, *J*=8.5, C_6H_4), 7.16-7.26 (m, 5H, C_6H_5). EM (ES positive mode): 340.1 $(M+1)^+$.

A solution of this compound (45 mg, 0.13mmol) in dry THF (1mL) was cooled to −15°C. Then, NMM (14µl, 0.13mmol) and isobutyl chloroformate (68.6µl, 0.13mmol) were added and the solution was stirred for 10 min. The *N*-methylmorpholine hydrochloride precipitate formed was removed by filtration and washed with THF. The filtrate was then cooled to -15°C and a solution of $NaBH_4$ (7.18mg, 0.19mmol) in H_2O (2.33mL) was added. After 1 h the solvents were evaporated to dryness and the remaining residue was separated between H_2O and EtOAc. The organic layer was washed with citric acid (10%), $HNaCO_3$ (10%) and brine, dried over Na_2SO_4 and, after evaporation, the residue was purified on a silica gel column using Hexane: EtOAc (5:1 to 3:1) as eluent. The title compound 33.4 mg (79%) was obtained as a

syrup. HPLC (Novapak): t_R = 8.75 min (A:B = 35:65). ^{1}H NMR (300MHz, $CDCl_3$): δ 1.00 (d, 3H, *J* = 7.6, 3-CH_3), 2.70 (d, 1H, *J* = 13.4, 4-CH_2), 3.06-3.41 (m, 2H, 3-H, 4-CH_2), 3.41 (s, 2H, C*H*$_2$-OH), 3.73 (s, 3H, OMe), 4.03 (d, 1H, *J* = 15.1, 1-CH_2), 4.63 (d, 1H, *J* = 15.1, 1-CH_2), 6.81 (d, 2H, *J* = 8.6, C_6H_4), 7.10-7.25 (m, 7H, C_6H_4, C_6H_5). EM (ES positive mode): 326.3 $(M+1)^+$. Anal Calc. for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30. Found: C 73.47, H 7.46, N 4.06.



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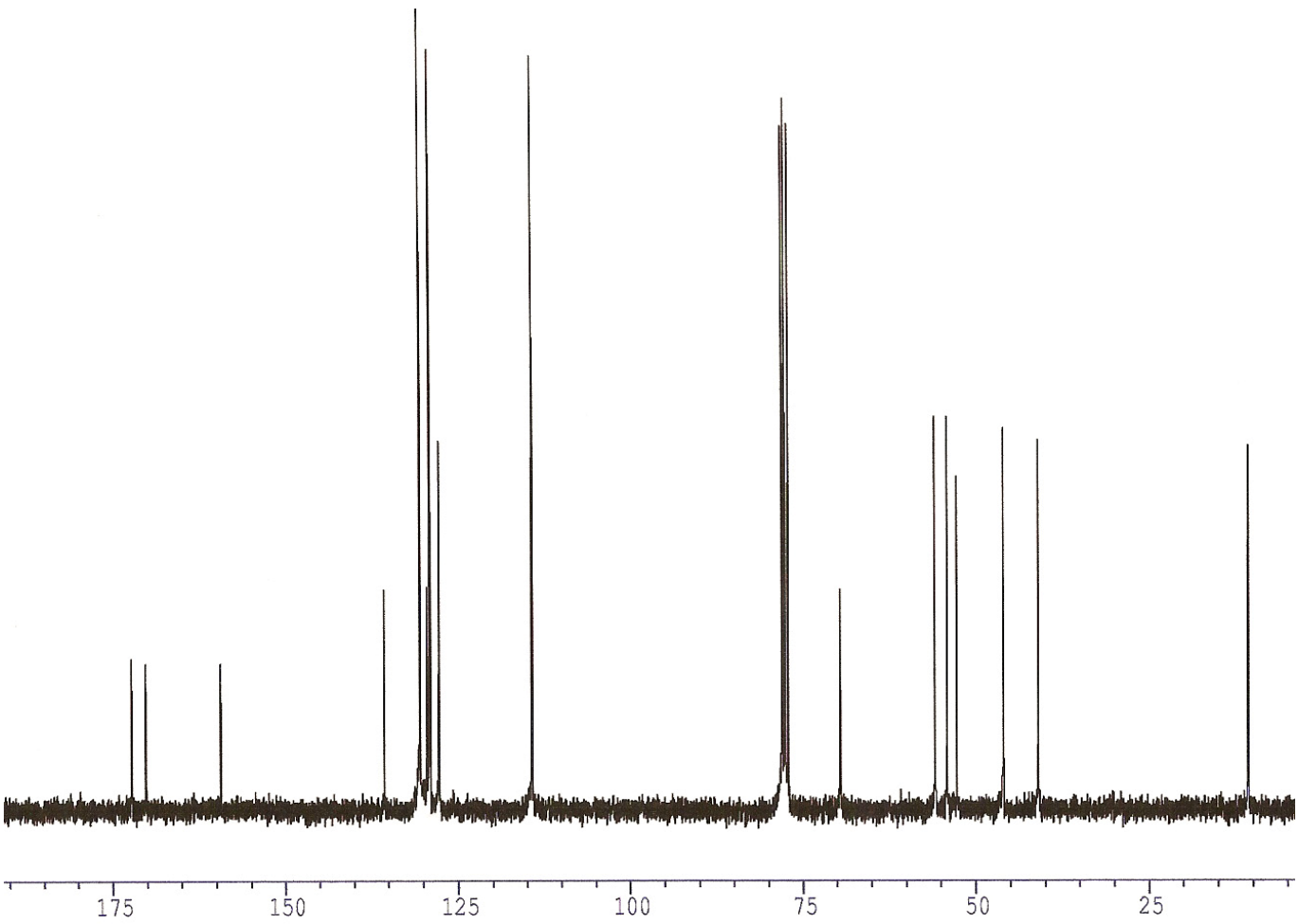

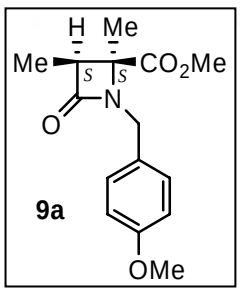
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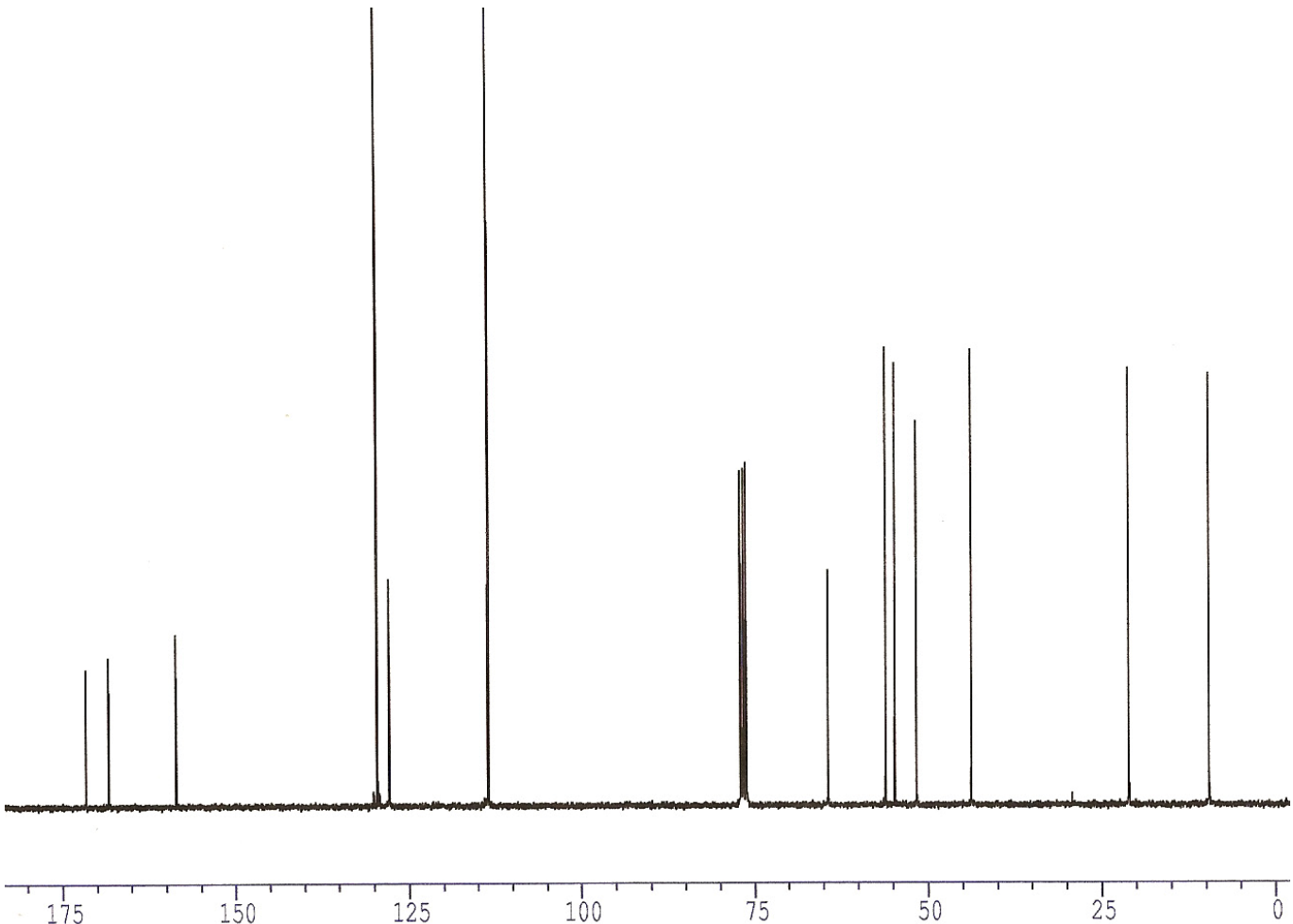
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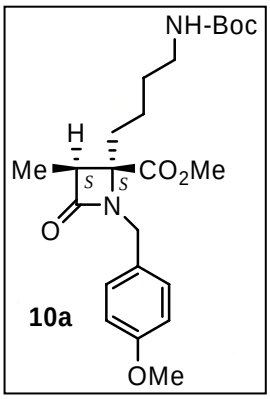
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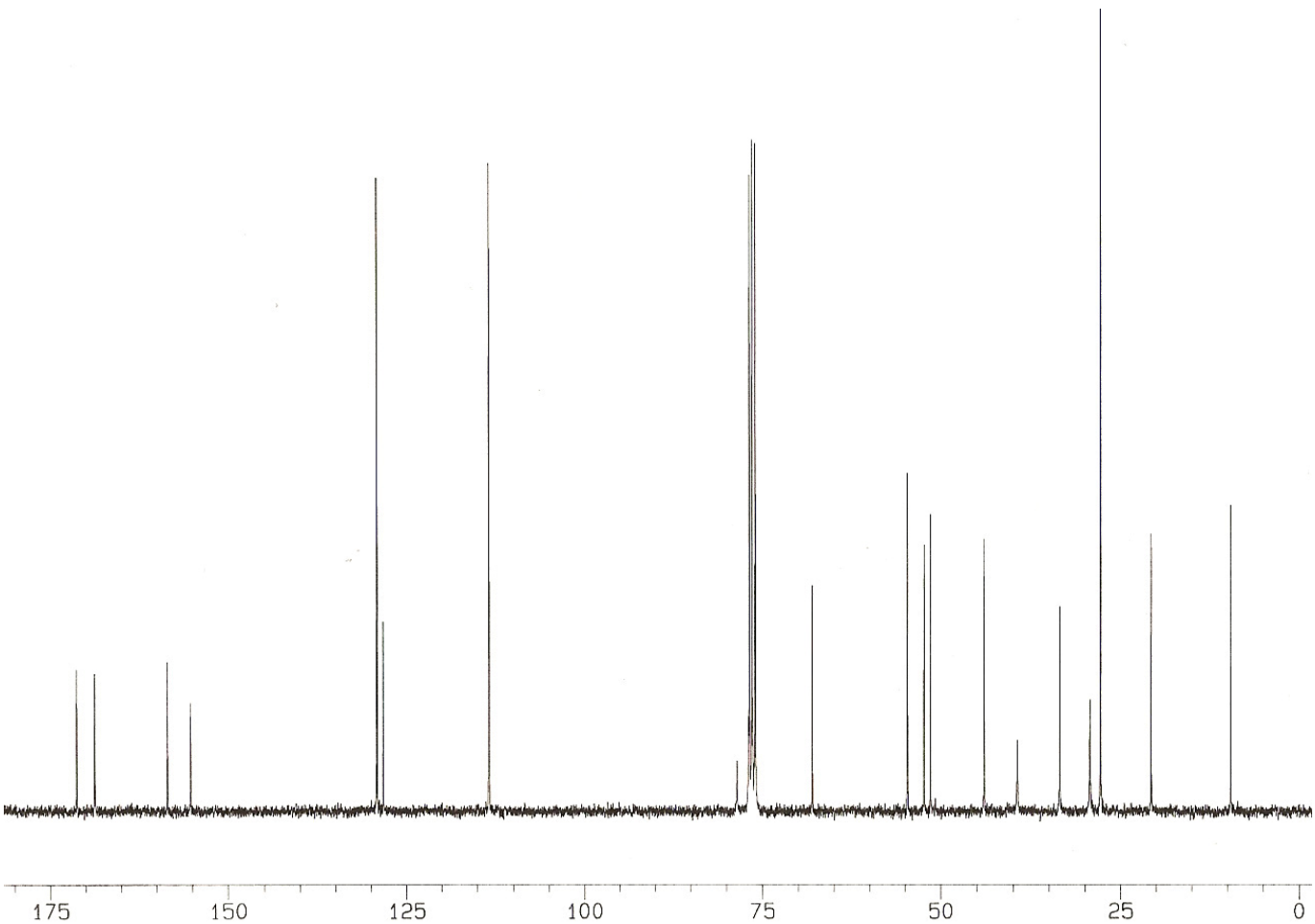
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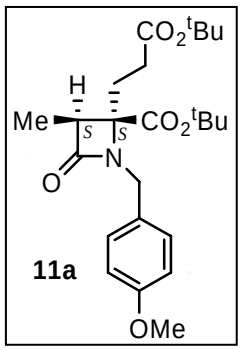
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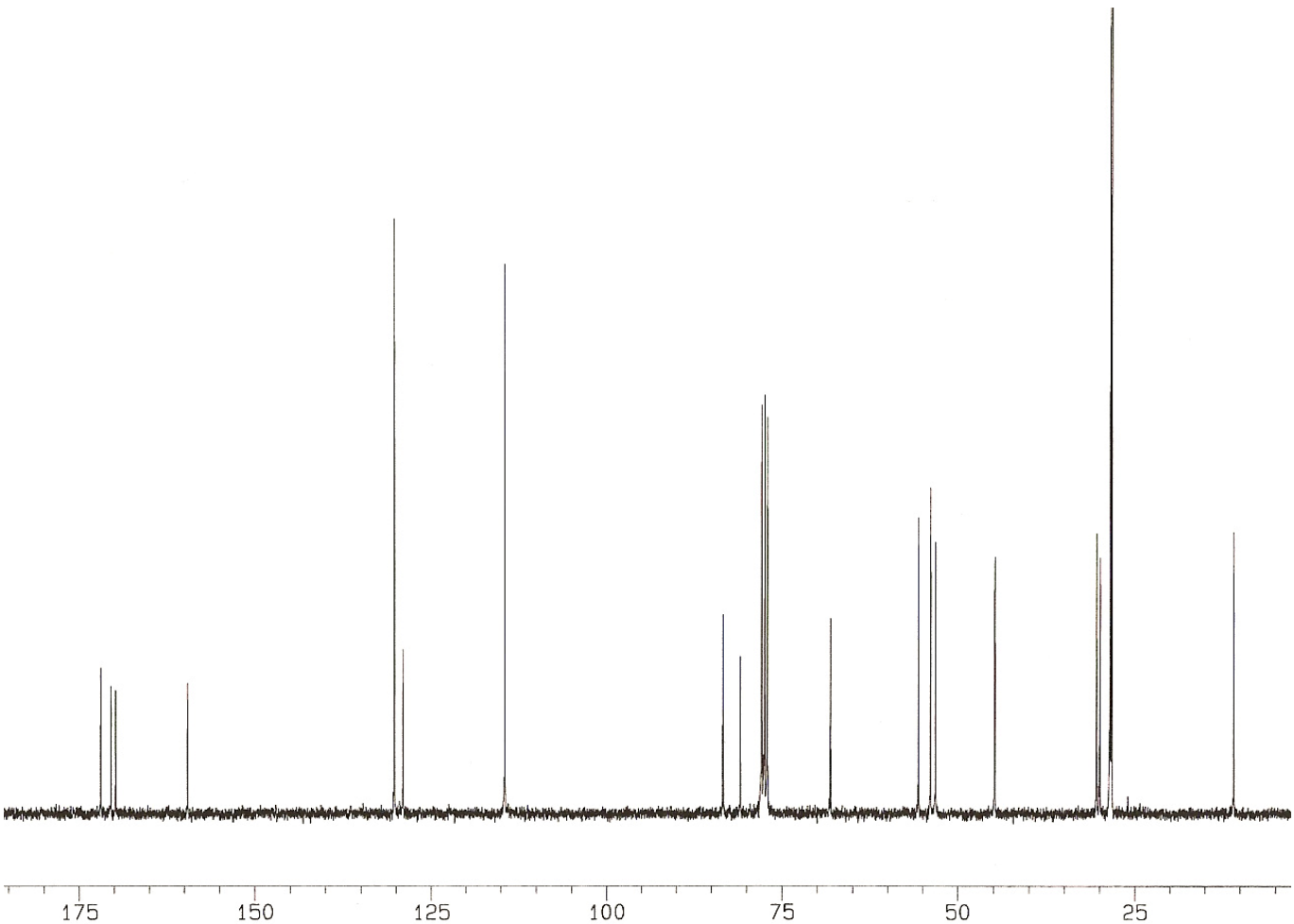
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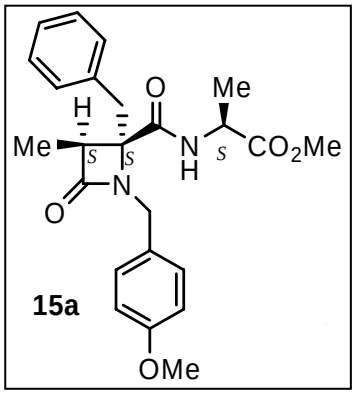
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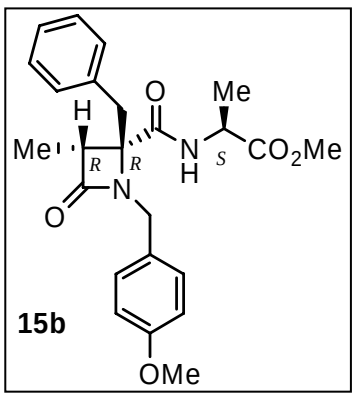
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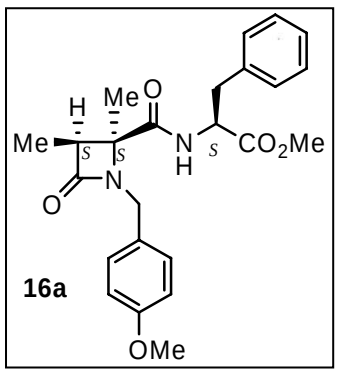
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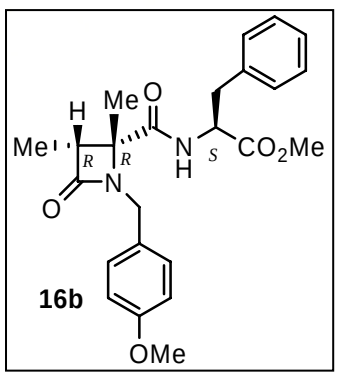
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O
N
OMe

16b

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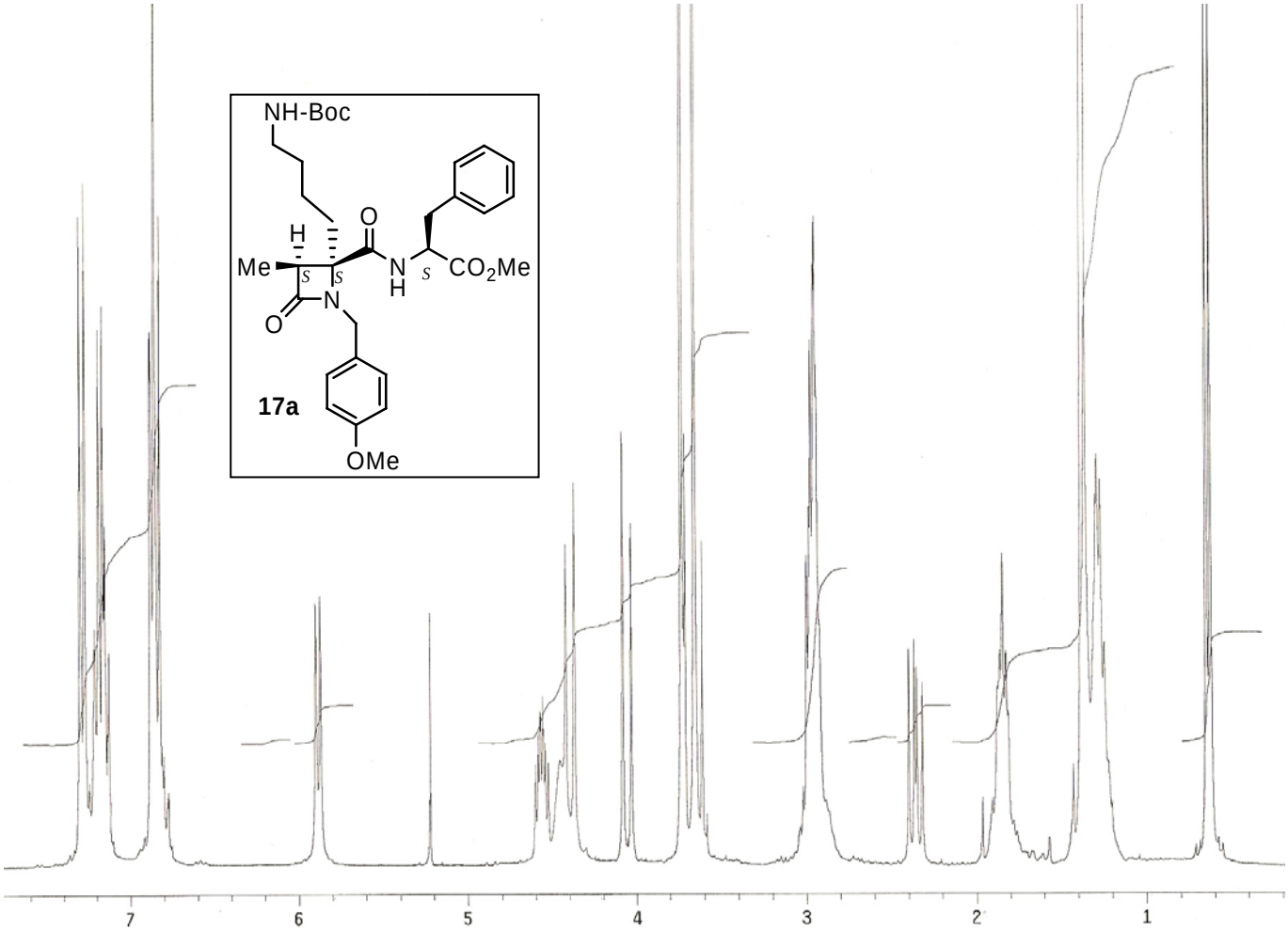
2
1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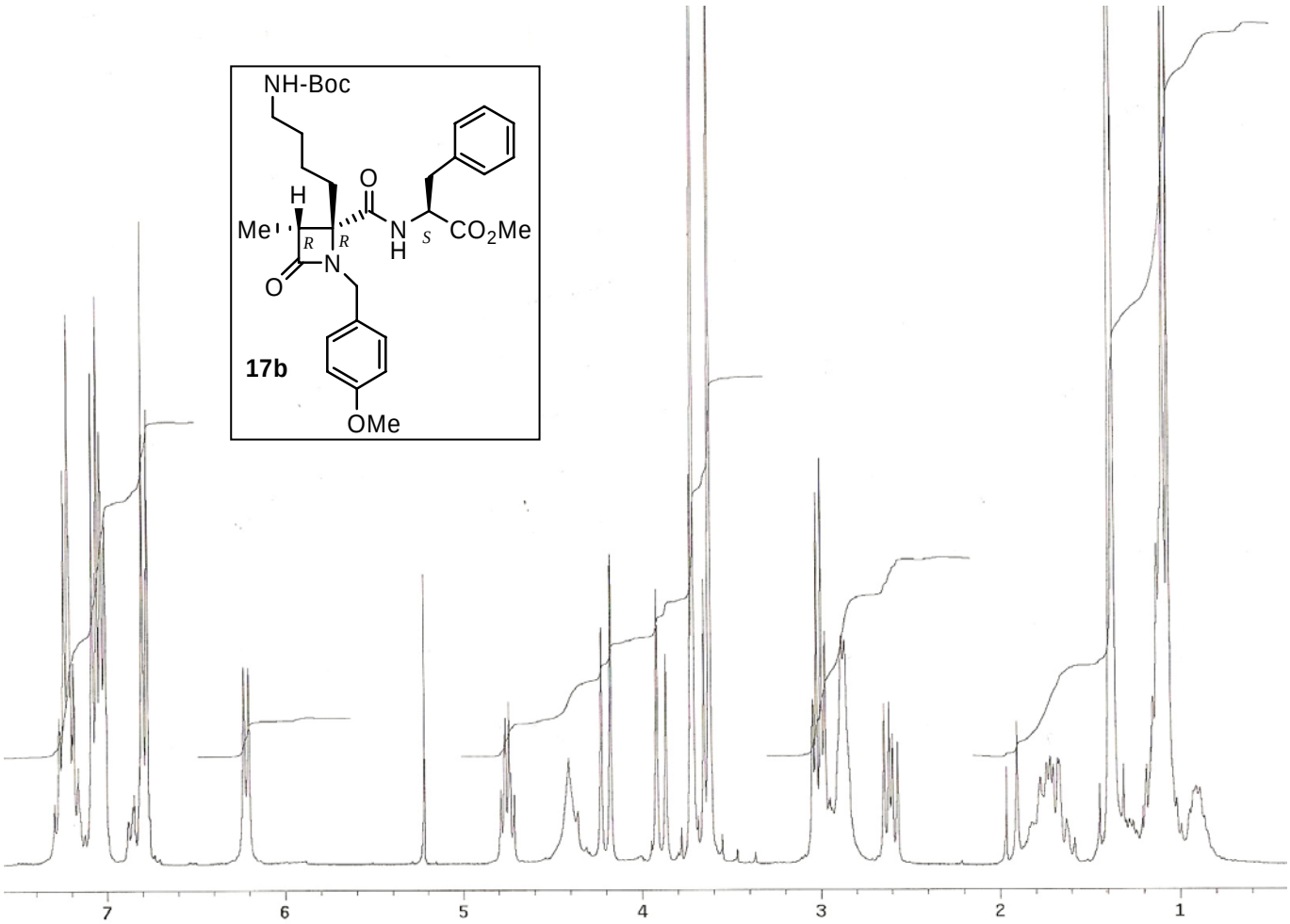
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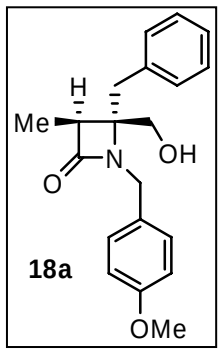
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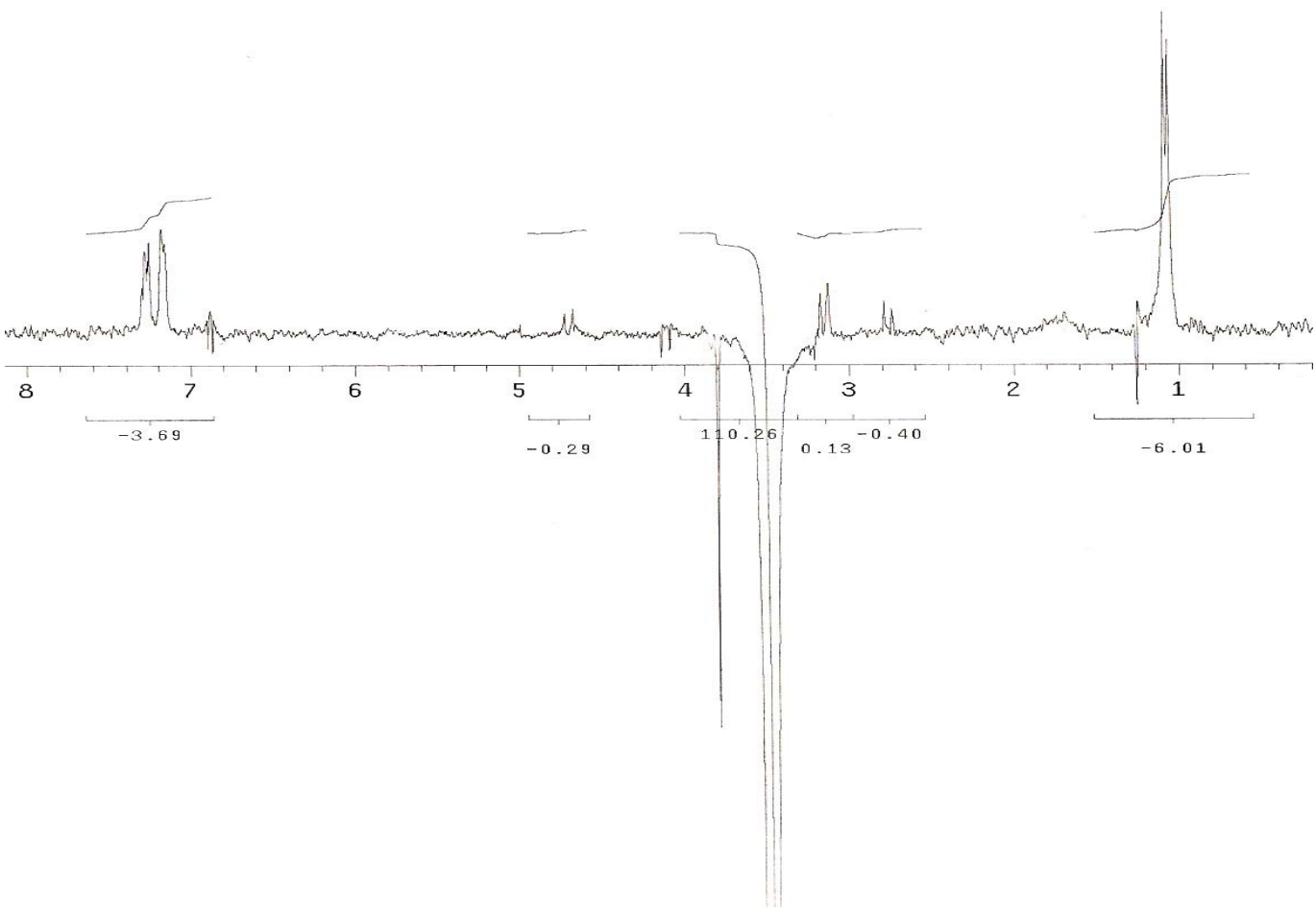
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