Total Synthesis of the Chlorinated Marine Natural Product Dysamide B

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SUPPORTING INFORMATION

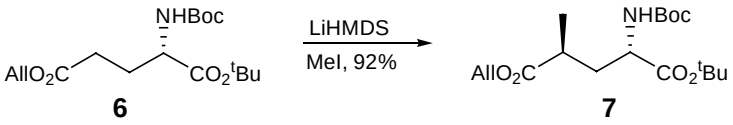
General Experimental Details

All commercially available compounds were used without further purification except where stated. All moisture or air sensitive reactions were carried out in oven-dried glassware under a positive pressure of nitrogen using standard syringe/septa techniques. Anhydrous solvents were obtained by passing through a modified Grubbs system of alumina columns, manufactured by Anhydrous Engineering. Petroleum ether is of the 40-60 ^{o}C boiling point range. Routine monitoring of reactions was performed using precoated Merck-Keiselgel 60 F_{254} aluminium backed TLC plates. The spots were visualised by UV_{254} light, or potassium permanganate. Flash column chromatography[1] was performed using silica gel (obtained from Fluorochem Ltd.) as the adsorbent.

Melting points were determined on an electrothermal apparatus and are uncorrected. Optical rotations were recorded using with the sodium D line (λ = 589 nm) on a Bellingham and Stanley ADP220 polarimeter and the $[\alpha]_D$ values are quoted in units 10^{-1} deg cm^2 g^{-1}. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR spectrometer in the solid or liquid state. ^{1}H and ^{13}C NMR spectra were recorded at using either a Jeol Delta/GX 400 MHz or a Jeol Eclipse 400 MHz spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (*J*) are in Hertz (Hz). Tetramethylsilane was used as the internal reference for proton and carbon chemical shifts. DEPT 135, COSY, HBQC and HMBC NMR spectra were routinely used to definitively assign the signals of ^{1}H and ^{13}C NMR spectra. Electron impact (EI) and chemical ionisation (CI) mass spectra were recorded on a VG Analytical Autospec mass spectrometer. Electrospray (ESI) mass spectra were recorded on a Micromass LCT mass spectrometer or a VG Quattro mass spectrometer. Methane was the ionisation gas used for chemical ionisation.

Experimental Procedures

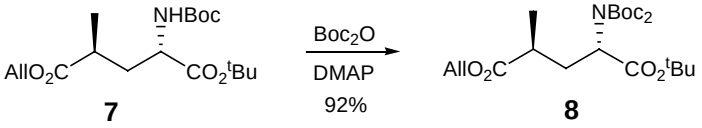
(2*S*,4*S*)-2-*tert*-Butoxycarbonylamino-4-methylpentane-1,5-dioic acid 1-*tert*butyl 5-allyl diester 7



6 **7**

n-Butyl lithium (2.5 eq, 34.5 mmol, 13.8 ml) was added dropwise to hexamethyldisilazane (2.5 eq, 34.5 mmol, 7.23 ml) in deoxygenated THF (80 ml) at 0 °C. The reaction mixture was stirred at 0 °C for 0.5 h before cooling to - 78 °C. Diester **6** (4.75 g, 13.8 mmol) in THF (80 ml) was added dropwise and the reaction mixture was stirred at - 78 °C for 0.5 h before adding MeI (1.3 eq, 17.94 mmol, 1.13 ml). The reaction was monitored by TLC and after 4.5 h had reached completion. The reaction mixture was quenched with HCl (10%, 50 ml) and the aqueous layer extracted with DCM (3 x 70 ml). The combined organic layers were washed with water (2 x 30 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography (10-15% EtOAc/petrol) gave the alkylated *diester* **7** as a yellow oil (4.56 g, 92%); $[\alpha]_D$ - 7.2 (*c* 1.04, EtOH); δ_H (400 MHz) 1.25 (3H, d, *J* 7, CH_3), 1.43 and 1.48 (each 9H, s, $C(CH_3)_3$), 1.85 (1H, m, 3-*H*H), 1.98 (1H, ddd, *J* 14, 10, 7, 3-H*H*), 2.58 (1H, m, 4-H), 4.21 (1H, m, 2-H), 4.56 and 4.61 (each 1H, each dd, *J* 13, 6, 1'-H_2), 4.9 (1H, br d, *J* 8, N-H), 5.24 (1H, dd, *J* 10, 2, 3'-*H*H), 5.32 (1H, dd, *J* 17, 2, 3'-H*H*), 5.91 (1H, ddt, *J* 17, 10, 6, 2'-H); δ_C (75 MHz) 17.2 (CH_3), 28 and 28.3 ($C(CH_3)_3$), 36.2 (C-3), 36.6 (C-4), 52.6 (C-2), 65.3 (C-1'), 81.9 and 82.4 (Cq), 118.2 (C-3'), 132.2 (C-2'), 153.3, 171.7 and 175.6 (CO); ν_{max}/cm^{-1} 3320, 2979, 1731, 1706 and 1645; *m/z* (CI) 358 (MH^+, 2%), 202 (MH^+ - Boc - ^{t}Bu + 1, 100), 156 (40) and 98 (15); Found C 60.44, H 9.09 and N 3.94, $C_{18}N_{31}NO_6$ requires C 60.59, H 8.72 and N 3.91.

(2*S*,4*S*)-2-Di*tert*-butoxycarbonylamino-4-methylpentane-1,5-dioic acid 5-allyl ester 1-*tert*butyl ester 8

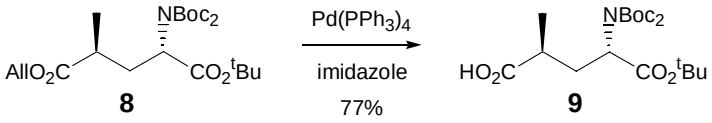


7 **8**

Allyl ester **7** (4.5 g, 12.6 mmol) was dissolved in MeCN (180 ml) and cooled to 0 °C. Di-*tert*-butyldicarbonate (3 eq, 37,8 mmol, 8.2 g) in MeCN (10 ml) was added followed by DMAP (0.2 eq, 2.52 mmol, 0.3 g) and the reaction mixture stirred at 0 °C for 2 h before warming to r.t and stirring overnight. After 2 days, further di-*tert*-butyldicarbonate (1.5 eq) and DMAP (0.2 eq) were added and the reaction mixture stirred for a further day. After this time the reaction had reached completion by TLC and the solvent was removed *in vacuo*. Purification by column chromatography (20% EtOAc/petrol) gave the diboc protected *diester* **8** as an orange oil (5.31 g, 92%); $[\alpha]_D$ - 10.5 (*c* 1, $CHCl_3$); δ_H (400 MHz) 1.21 (3H, d, *J* 7, CH_3), 1.44 (9H, s, $C(CH_3)_3$), 1.50 (18H, s, 2 x $C(CH_3)_3$), 2.12 (1H, ddd *J* 14, 8, 5, 3-*H*H), 2.32 (1H, ddd, *J* 14, 10, 4, 3-H*H*), 2.55 (1H, m, 4-H), 4.57 (2H, m, 1'-H_2), 4.81

(1H, dd, *J* 10, 5, 2-H), 5.21 (1H, dd, *J* 10, 1, 3'-*H*H), 5.29 (1H, dd, *J* 17, 1, 3'-H*H*), 5.91 (1H, ddt, *J* 17, 10, 6, 2'H); δ_C (75 MHz) 16.8 (CH_3), 27.9 and 28.1 (C(CH_3)$_3$), 33.2 (C-3), 37.1 (C-4), 57.1 (C-2), 65.1 (C-1'), 81.4 and 82.9 (Cq), 117.9 (C-3'), 132.5 (C-2'), 152.3, 169.6 and 175.7 (CO); ν_{max}/cm^{-1} 2979, 2937, 1735, 1701 and 1653; *m/z* (EI) 356 (M^+ - Boc –1, 34%), 256 (10), 200 (30) and 156 (80); Found C 60.71, H 8.89 and N 3.17, $C_{23}H_{39}NO_8$ requires C 60.37, H 8.59 and N 3.06.

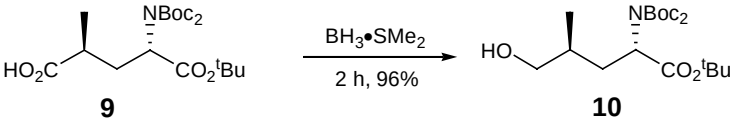
(2*S*,4*S*)-2-Di*tert*-butoxycarbonylamino-4-methylpentane-1,5-dioic acid 1-*tert*butyl ester 9



8 **9**

$Pd(PPh_3)_4$ (0.02 eq, 0.143 g, 0.129 g) was added to diester **8** (2.85 g, 6.43 mmol) in THF (40 ml). After 5 minutes $NaBH_4$ (1.5 eq, 9.64 mmol, 0.365 g) was added and the reaction mixture was left overnight. The reaction was quenched with HCl (10%) and the aqueous layer extracted with Et_2O (3 x 50 ml). The combined organic layers were washed with water (2 x 15 ml) and brine (15 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo.* Purification by column chromatography (10-20% EtOAc/petrol) gave *acid* **9** as a yellow solid (2.08 g, 77%) m.p 93-95 °C; $[\alpha]_D$ –5.6 (*c* 1.08, $CHCl_3$); δ_H (400 MHz) 1.23 (3H, d, *J* 7, CH_3), 1.44 (9H, s, C(CH_3)$_3$), 1.5 (18H, s, C(CH_3)$_3$), 2.13 (1H, ddd, *J* 14, 8, 5, 3-*H*H), 2.36 (1H, ddd, *J* 14, 10, 6, 3-H*H*), 2.51 (1H, m, 4-H), 4.83 (1H, dd, *J* 10, 5, 2-H). δ_C (75 MHz) 16.8 (CH_3), 27.9 and 28.02 (C(CH_3)$_3$), 32.9 (C-3), 37 (C-4), 57.2 (C-2), 81.5 and 82.9 (Cq), 152.3, 169.5 and 175.5 (CO); ν_{max}/cm^{-1} 3080, 2979, 1759 and 1736; *m/z* (CI) 362 (MH^+ - ^{t}Bu, 3%), 262 (15), 216 (10), 162 (23) and 57 (100); Found C 57.54, H 8.45, N 3.35, $C_{20}H_{35}O_8N$ requires C 57.62, H 8.57, N 3.35.

(2*S*,4*S*)-2-Di*tert*butoxycarbonylamino-5-hydroxy-4-methyl-pentanoic acid *tert*butyl ester 10[2]

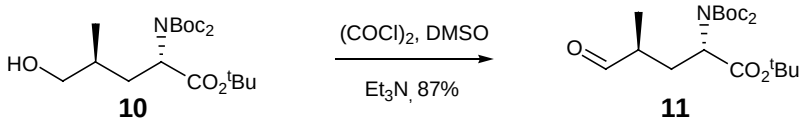


9 **10**

BMS•SMe_2 (1 eq, 4.98 mmol, 2 M sol. in THF, 2.49 ml) was added dropwise to acid **9** (2.08 g, 4.98 mmol) in Et_2O (15 ml). After 2 h the reaction had reached completion by TLC. The solvent was removed *in vacuo* and the crude product purified by column chromatography (20% EtOAc/petrol) to yield alcohol **10** as a colourless oil (1.92 g, 96%). m.p. 55-58 °C; $[\alpha]_D$ - 28.2 (*c* 2.1, $CHCl_3$); δ_H (400 MHz) 0.95 (3H, d, *J* 7, CH_3), 1.44 (9H, s, C(CH_3)$_3$), 1.5 (18 H, s, 2 x C(CH_3)$_3$), 1.7 (1H, m, 4-H), 1.93 (1H, m, 3-*H*H), 1.95 (1H, ddd, *J* 13, 9, 5, 3-H*H*), 3.44 (1H, dd, *J* 11, 5, 5-*H*H), 3.48 (1H, dd, *J* 11, 7, 5-H*H*), 4.83 (1H, dd, *J* 9, 6, 2-H); δ_C (75 MHz) 16.2 (CH_3), 28 and 28.07 (C(CH_3)$_3$), 33.2 (C-3), 56.2 (C-2), 68.1 (C-5), 81.5 and 82.9 (Cq), 152.6 and 170.2 (CO); ν_{max}/cm^{-1} 3204, 2978, 2935, 1785 and 1737; *m/z* (CI) 348 (M^+ - ^{t}Bu, 2%), 304 (3), 248 (5), 148 (40) and 57 (100); Found C 59.65, H 9.67, and N 3.32, $C_{20}H_{37}O_7N$ requires C 59.53, H 9.24, N 3.47.

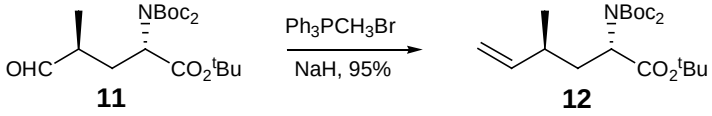
(Data not previously reported[2])

(2*S*,4*S*)-2-Di*tert*butoxycarbonylamino-4-methyl-5-oxopentanoic *tert*butyl ester 11[3]



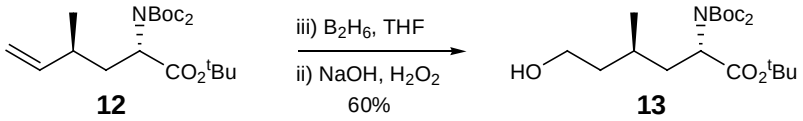
Oxalyl chloride (2 eq, 20.27 mmol, 1.77 ml) in DCM (20 ml) was added slowly to DMSO (4 eq, 40.54 mmol, 2.87 ml) in DCM (70 ml) at - 78 °C, followed by the dropwise addition of alcohol **10** (4.09 g, 10.14 mmol) in DCM (20 ml). After 45 mins Et_3N (8 eq, 81.09 mmol, 11.3 ml) was added and the temperature increased to - 45 °C. After stirring at this temperature for 1 h 45 mins aqueous NH_4Cl (30 ml) was added. The aqueous layer was extracted with DCM (3 x 40 ml), the combined organic layers were washed with water (2 x 20 ml) and brine (20 ml), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. Purification by column chromatography (20% EtOAc/petrol) gave aldehyde **11** as a yellow oily solid (3.55 g, 87%); m.p. 56-58 °C (previously reported as an oil[3]); $[\alpha]_D$ - 25 (*c* 2, $CHCl_3$); δ_H (400 MHz) 1.15 (3H, d, *J* 7, CH_3), 1.45 (9H, s, $C(CH_3)_3$), 1.51 (18H, s, 2 x $C(CH_3)_3$), 1.97 (1H, ddd, *J* 16, 11, 6, 3-*H*H), 2.34-2.44 (2H, m, 3-H*H* and 4-H), 4.82 (1H, dd, *J* 11, 5, 2-H), 9.6 (1H, d, *J* 2, 5-H); δ_C (75 MHz) 13.3 (CH_3), 27.9 and 28.1 ($C(CH_3)_3$), 30.1 (C-3), 43.9 (C-4), 56.8 (C-2), 81.7 and 83.14 (Cq), 152.5, 170 and 203.8 (CO); ν_{max}/cm^{-1} 2978, 2936, 1735 and 1697; *m/z* (CI) 402 (MH^+, 16%), 346 (58), 302 (8) and 128 (100); Found C 60.09, H 8.47, N 3.25, $C_{20}H_{35}O_7N$, requires C 59.81, H 8.79, N 3.49.

(2*S*,4*S*)-2-Di*tert*butoxycarbonylamino-4-methylhex-5-enoic acid *tert*butyl ester 12



Sodium hydride (12 eq, 74.8 mmol, 2.9 g) was added to $MePh_3PBr$ (12 eq, 74.8, 26.7 g) in THF (80 ml) and the mixture warmed slightly with a heat gun until a green tinge persisted. The reaction mixture was left stirring overnight before allowing to stand and adding to the dry aldehyde **11** (2.5 g, 6.23 mmol). After stirring overnight the reaction had reached completion. The solvent was removed *in vacuo* and the crude material was purified by column chromatography (5-20% EtOAc/petrol) to give *alkene* **12** as a pale yellow oil (2.37 g, 95%); $[\alpha]_D$ - 10.2 (*c* 1, $CHCl_3$); δ_H (400 MHz) 1.02 (3H, d, *J* 7, CH_3), 1.43 (9H, s, $C(CH_3)_3$), 1.52 (18H, s, $C(CH_3)_3$), 1.82 (1H, ddd, *J* 14, 8, 6, 3-*H*H), 2.04 (1H, ddd, *J* 14, 10, 6, 3-H*H*), 2.25 (1H, m, 4-H), 4.79 (1H, dd, *J* 8, 6, 2-H), 4.92 (1H, dd, *J* 10, 1, 6-*H*H), 4.98 (1H, dd, *J* 17, 1, 6-H*H*), 5.69 (1H, ddd, *J* 17, 10, 7, 5-H); δ_c (100 MHz) 19.8 (CH_3), 28.02 and 28.1 ($C(CH_3)_3$), 35.2 (C-4), 36.2 (C-3), 57.5 (C-2), 81 and 82.4 (Cq), 112.7 (C-6), 144 (C-5), 152.4 and 170 (CO); ν_{max}/cm^{-1} 2978, 1760, 1735, 1701 and 1641; *m/z* (CI) 400 (MH^+, 20%), 300 (15), 344 (100), 288 (75) and 188 (77); Found C 63.56, H 9.85, N 3.31, $C_{21}H_{37}NO_6$ requires C 63.31, H 9.33, N 3.51.

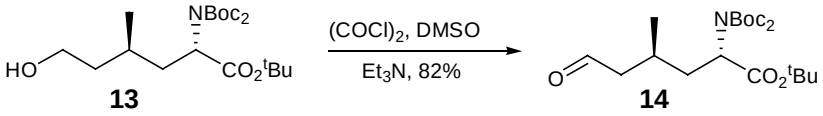
(2*S*,4*S*)-2-Di*tert*butoxycarbonylamino-6-hydroxy- 4-methylhexanoic acid *tert*butyl ester 13



12 **13**

Borane - THF complex (1.3 eq, 1 M sol. in THF, 7.6 mmol, 7.6 ml) was added to alkene **12** (2.34 g, 5.86 mmol) in THF (30 ml) at 0 °C before allowing to warm to room temperature. The reaction was monitored by TLC and after 4.5 h had reached completion. Aqueous NaOH (1.5 eq, 8.79 mmol, 8.79 ml) and H_2O_2 (35%, 11 eq, 64.4 mmol, 7.3 ml) were added and the mixture stirred for 0.5 h. After this time, brine (5 ml) and water (10 ml) were added. The aqueous layer was extracted with EtOAc (3 x 60 ml). The combined organic layers were washed with water (2 x 20 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography gave the *alcohol* **13** as a white solid (1.44 g, 60%). m.p 45-47 °C; $[\alpha]_D$ -32.4 (*c* 1.9, $CHCl_3$); δ_H (400 MHz) 0.89 (3H, d, *J* 6, CH_3), 1.36 (9H, s, $C(CH_3)_3$), 1.44 (18H, s, $C(CH_3)_3$), 1.56-1.7 (3H, m, 5-H_2, 4-H), 1.77 (1H, ddd, *J* 14, 10, 5, 3-*H*H), 2.0 (1H, ddd, *J* 14, 10, 4, 3-H*H*), 3.66 (2H, ddd, *J* 17, 10, 6, 6-H_2), 4.81 (1H, dd, *J* 10, 5, 2-H); δ_C (75 MHz) 19.3 (CH_3), 26.7 (C-4), 27.9 and 28.1 ($C(CH_3)_3$), 35.9 (C-3), 40.3 (C-5), 57.1 (C-2), 60.9 (C-6), 81.2 and 82.7 (Cq), 152.7 and 170 (CO); ν_{max}/cm^{-1} 3457, 2978, 2934, 1736 and 1699; *m/z* (CI) 262 (M^+-Boc-^{t}Bu, 0.5%), 162 (63) and 57 (100); Found: C 60.31, H 9.33, N 3.23, $C_{21}H_{39}NO_7$ requires C 60.41, H 9.41, N 3.35.

(2*S*,4*S*)-2-Di*tert*butyloxycarbonylamino-4-methyl-6-oxohexanoic acid *tert*butyl ester 14

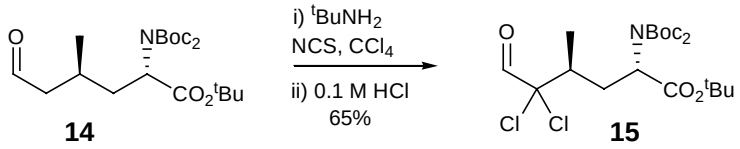


13 **14**

A solution of oxalyl chloride (2 eq, 9.77 mmol, 0.85 ml) in DCM (10 ml) was added dropwise to a solution of DMSO (4 eq, 19.6 mmol, 1.39 ml) in DCM (40 ml) at - 78 °C under N_2. This was followed by the dropwise addition of the alcohol **13** (1 eq, 2.04 g, 4.89 mmol) in DCM. After 45 minutes Et_3N was added (8 eq, 39.12 mmol, 5.45 ml) and the temperature increased to - 45 °C. The reaction was monitored by TLC and after 4.5 h had reached completion. Saturated aqueous NH_4Cl (30 ml) was added. The aqueous phase was extracted with DCM (3 x 30 ml), the combined organic layers were washed with water (20 ml) and brine (20 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography (20% EtOAc/petrol) gave *aldehyde* **14** as a pale yellow solid (1.8 g, 82%); m.p 49-52 °C; $[\alpha]_D$ -26.2 (*c* 1.2, $CHCl_3$); δ_H (400 MHz) 1.01 (3H, d, *J* 6, CH_3), 1.44 (9 H, s, $C(CH_3)_3$), 1.51 (18 H, s, 2 x $C(CH_3)_3$), 1.85 - 2 (2H, m, 3-H_2), 2.1 (1H, m, 4-H), 2.3 (1H, ddd, *J* 17, 8, 2, 5-H*H*), 2.4 (1H, ddd, *J* 17, 6, 2, 5-*H*H), 4.8 (1H, dd, *J* 8, 6, 2-H), 9.7 (1H, t, *J* 2, 6-H); δ_C (100 MHz), 19.4 (CH_3), 25.5 (C-4), 28.0 (3 x $C(CH_3)_3$), 36.0 (C-3), 51.2 (C-5),

57 (C-2), 81.1 and 82.9 (Cq), 152.1, 170 and 211 (CO); ν_{max}/cm^{-1} 2979, 1750 and 1730; *m/z* (CI) 432 (M^+, 6%), 360 (11), 232 (14) and 57 (100); Found C 60.70, H 8.98, N 3.37, $C_{21}H_{37}NO_7$ requires C 60.61, H 9.39, N 3.18.

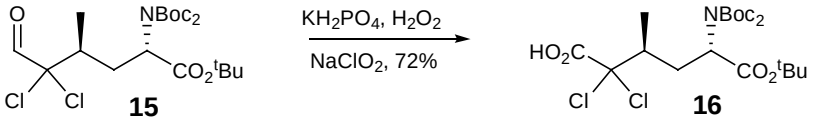
(2*S*,4*S*)-2-Di*tert*butyloxycarbonylamino-5,5-dichloro-4-methyl-6-oxohexanoic acid *tert*butyl ester 15



14 **15**

tert-Butyl amine (1 eq, 5.87 mmol, 0.62 ml) was added to a rapidly stirring solution of the aldehyde **14** (1 eq, 2.44 g, 5.87 mmol) in CCl_4 (20 ml) at room temperature under N_2. The solution was stirred for 1 h in the presence of molecular sieves (4 Å) after which time further CCl_4 (10 ml) and $MgSO_4$ (5 g) were added and the suspension filtered. *N*-Chlorosuccinimide (2.2 eq, 12.9 mmol, 1.73 g) was added in one portion and the suspension was stirred overnight. The succinimide was removed by filtration and the filtrate evaporated *in vacuo*. The product was hydrolysed by stirring in HCl (0.1M, 53 ml) overnight. After this time Et_2O (70 ml) was added to the reaction mixture and layers were separated. The aqueous layer was extracted with Et_2O (3 x 30 ml), the combined organic layers were washed with water (2 x 18 ml) dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give the dichlorinated aldehyde **15** as yellow oil (1.86 g, 65%); $[\alpha]_D$ - 29.5 (*c* 1.5, $CHCl_3$); δ_H (400 MHz) 1.2 (3H, d, *J* 7, CH_3), 1.45 (9 H, s, C(C*H*$_3$)$_3$), 1.52 (18 H, s, 2 x C(C*H*$_3$)$_3$), 2.0 (1H, ddd, *J* 15, 11, 4, 3-*H*H), 2.38 (2H, m, 3-H*H* and 4-H), 4.80 (1H, dd, *J* 8, 4, 2-H), 9.21 (1H, s, 6-H); δ_C (100 MHz), 14.6 (CH_3), 27.9 and 28 (C(*C*H$_3$)$_3$), 31.1 (C-3), 39.5 (C-4), 56.6 (C-2), 81.7 and 83 (Cq), 93.9 (C-5), 152.5 (CO), 169.3 (CO), 185 (C-6); ν_{max}/cm^{-1} 2976, 2930 and 1734; *m/z* (EI) 281 (1), 270 (2), 186 (3), 184 (13), 182 (21), 164 (7), 57 (100); $C_6H_{10}O_2Cl_2NO^+$ requires 182.0139, found 182.0137

(2*S*,4*S*)-2-Di*tert*butyloxycarbonylamino-5,5-dichloro-4-methylhexane-1,6-dioic acid 1-*tert*butyl ester 16

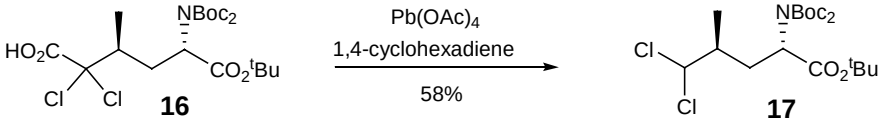


15 **16**

An aqueous KH_2PO_4 solution (pH 4, 0.4 ml) was added to dichlorinated aldehyde **15** (1 eq, 0.226 g, 0.466 mmol) in MeCN (3 ml) at 0 °C. This was followed by the addition of H_2O_2 (3.5 eq, 30%, 1.6 mmol, 0.047 ml) and $NaClO_2$ (2.2 eq, 1.03 mmol, 0.093 g) in water (4.5 ml). The reaction was monitored by TLC and after 2 h had reached completion. Na_2SO_3 (0.05 g) was added to destroy any excess $NaClO_2$ and the mixture was stirred for a further 1 h. The reaction mixture was acidified to pH 3 with HCl (10%, 1.3 ml). The aqueous phase was extracted with EtOAc (3 x 15 ml). The combined organic layers were washed with water (2 x 8 ml), dried over anhydrous magnesium sulfate and the solvent removed *in vacuo* to give acid **16** as a white solid (0.168 g, 72%). (0.14g,

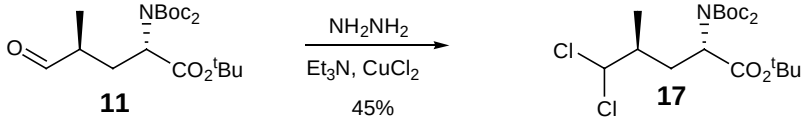
56%); m.p. 155-157 °C; $[\alpha]_D$ - 27.3 (c 1.2, $CHCl_3$); δ_H (400 MHz) 1.23 (3H, d, *J* 6, CH_3), 1.45 (9 H, s, $C(CH_3)_3$), 1.51 (18 H, s, 2 x $C(CH_3)_3$), 2.03 (1H, ddd, *J* 15, 11, 3, 3-*H*H), 2.35-2.45 (1H, m, 4-H), 2.53 (1H, ddd, *J* 15, 7, 3, 3-H*H*), 4.83 (1H, dd, *J* 11, 3, 2-H); δ_C (100 MHz) 14.9 (CH_3), 28.0 ($C(CH_3)_3$), 31.6 (C-3), 42.1 (C-4), 57.0 (C-2), 82.0 and 83.8 (Cq), 113.6 (C-5), 152.3, 169.0 and 170.0 (CO); ν_{max}/cm^{-1} 3150, 2977, 1780 and 1726; *m/z* (EI) 402 (0.1) 400 (0.3), 398 (0.4), 302 (0.35), 300 (2.6), 298 (0.35), 202 (2), 200 (8), 202 (14); $C_{11}H_{18}Cl_2NO_4$ requires 298.0613, found 298.0619.

(2*S*,4*S*)-2-Di*tert*butyloxycarbonylamino-5,5-dichloro-4-methylpentanoic acid *tert*butyl ester 17[3]



Lead tetraacetate (1 eq, 1.10 mmol, 0.486 g) was added in one portion to acid **16** (1 eq, 0.58 g, 1.10 mmol) in benzene (15 ml) under N_2. This was followed by the addition of 1,4-cyclohexadiene (1.2 eq, 1.32 mmol, 0.12 ml) and the reaction heated under gentle refluxing conditions at 60 °C for 2 h. Further $Pb(OAc)_4$ (1 eq) and 1,4-cyclohexadiene (1.2 eq) were added and the reaction was heated under refluxing conditions for another 1 h. The mixture was diluted with Et_2O (20 ml) and washed with perchloric acid (7%, 2 x 15 ml). The aqueous layer was extracted with Et_2O (3 x 15 ml). The combined organic layers were washed with sat. aqueous $NaHCO_3$ solution (3 x 10 ml). Again the aqueous layer was extracted with Et_2O (1 x 10 ml). The combined organic layers were washed with water (2 x 18 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. The crude material was purified by column chromatography (0 - 5% EtOAc/petrol) to give dichlorinated protected amino acid **17** as a white solid (0.29 g, 58%). The $NaHCO_3$ extracts were acidified and extracted with ethyl acetate, dried and concentrated *in vacuo* however no starting acid was recovered; m.p. 54-56 °C (previously reported as an oil[3]); $[\alpha]_D$ - 23 (*c* 1.1. in CH_2Cl_2), (lit.[3] - 25.5 (*c* 0.95, CH_2Cl_2)); δ_H (400 MHz) 1.28 (3H, d, *J* 6, CH_3), 1.45 (9 H, s, $C(CH_3)_3$), 1.51 (18 H, s, 2 x $C(CH_3)_3$), 2.03 (1H, ddd, *J* 14, 10, 4, 3-*H*H), 2.13 (1H, m, 4-H), 2.3 (1H, ddd, *J* 14, 11, 3, 3-H*H*), 4.78 (1H, dd, *J* 11, 4, 2-H), 5.78 (1H, d, *J* 3, 5-H); δ_C (100 MHz), 15.0 (CH_3), 28.0 and 28.1 ($C(CH_3)_3$), 31.5 (C-3), 41.5 (C-4), 56.8 (C-2), 78.8 and 81.6 (Cq), 83.1 (C-5), 152.5 (CO), and 169.6 (CO); ν_{max}/cm^{-1} 2980, 1735 and 1710; *m/z* (CI) 456 (MH^+, 1%), 400 (12), 344 (30), 288 (36), and 57 (100); Found C 52.84, H 7.73, N 2.83, Cl 15.39, $C_{20}H_{35}NO_6C_{l2}$, requires C 52.63, H 7.56, N 3.07, Cl 15.54.

(2*S*,4*S*)-2-Di*tert*butyloxycarbonylamino-5,5-dichloro-4-methylpentanoic acid *tert*butyl ester 17[3]



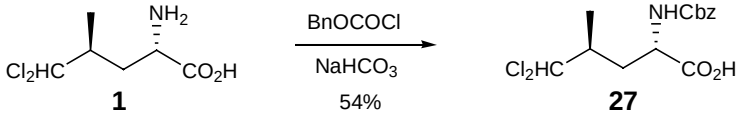
Aldehyde **11** (3g, 7.47 mmol) in MeOH (20 ml) was added dropwise to hydrazine hydrate (20 eq, 149 mmol, 7.26 ml) in MeOH (20 ml). The reaction was stirred for 2 h before adding further hydrazine hydrate (10 eq) and

stirring for an additional 1 h. The reaction mixture was concentrated *in vacuo*. Meanwhile Et_3N (3 eq, 22.42 mmol, 3.12 ml) was added to a solution of $CuCl_2$ (6 eq, 44.8 mmol, 6.03 g) in MeOH (30ml) and stirred for 10 minutes. The crude hydrazone was added dropwise to the pre-stirred solution of Et_3N and $CuCl_2$ and the reaction mixture stirred for 3 h before adding an aqueous solution of NH_3 (3.5%, 30 ml). The reaction mixture was extracted with Et_2O (3 x 40 ml) and the combined organic layers were washed with water (2 x 20 ml) and brine (20 ml) before drying over anhydrous magnesium sulfate and the solvent removed *in vacuo*. Purification by column chromatography (0-10% EtOAc/petrol) gave the dichloride **17** as a white solid (1.54 g, 45%). *Spectral data as above.*

(2*S*,4*S*)-5,5-Dichloroleucine 1[3]

Dichloride **17** (2.7 g, 5.85 mmol) was dissolved in TFA (10 ml) and stirred for 1 h. The mixture was concentrated *in vacuo* to give a white solid. Purification by Dowex column eluting with pyridine (0.1 M) gave 2*S*,4*S*-dichloroleucine **1** as a white solid (1.4 g, 100%); mp 222-223 °C (previously reported as an oil[3]); $[\alpha]_D$ -38 (*c* 1.0, H_2O), (lit.[3] - 23 (*c* 0.16, HCl 1 N)); δ_H (400 MHz, D_2O) 1.20 (3H, d, *J* 7, CH_3), 2.01 (1H, ddd, *J* 15, 10, 5, 3-*H*H), 2.16 (1H, ddd, *J* 15, 9, 4, 3-H*H*), 2.40 (1H, m, 4-H), 3.92 (1H, dd, *J* 9, 5, 2-H), 6.12 (1H, d, *J* 3, 5-H); δ_C (100 MHz; D_2O), 17.0 (CH_3), 36.0 (C-3), 42.6 (C-4), 57.1 (C-2), 81.5 (C-5), 177.4 (C-1); *m/z* (ESI) 204 (12), 202 (67), 200 (MH^+, 100%); $C_6H_{12}O_2NCl_2$ requires 200.0240, found 200.0245.

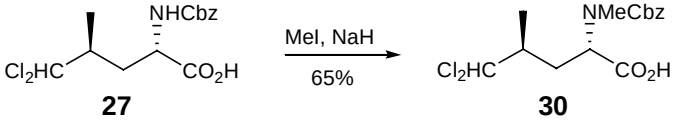
(2*S*,4*S*)-2-Benzyloxycarbonylamino-5,5-dichloro-4-methylpentanoic acid 27



(2*S*, 4*S*)-Dichloroleucine **1** (5 g, 25.0 mmol) was dissolved in water (95 ml) and dioxane (39 ml) at 0 °C. $NaHCO_3$ (1 eq, 38.12 mmol, 3.2 g) was added followed by benzyl chloroformate (1.1 eq, 41.9 mmol, 5.98 ml) in dioxane (52 ml). The reaction mixture was stirred at 0 °C for 2 h then warmed to room temperature and stirred overnight. The reaction mixture was washed with Et_2O (3 x 30 ml) and the combined aqueous layers acidified to pH 2 (HCl, 1N) and extracted with EtOAc (3 x 50 ml). The combined organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed in *vacuo* to give *Cbz dichloroleucine* **27** as a colourless oil (8.35g, 54%); $[\alpha]_D$ - 8.8 (*c* 1.4, CH_2Cl_2); δ_H (400 MHz, major rotamer) 1.21 (3H, d, *J* 7, CH_3), 1.8-2.0 (2H, m, 3-H_2), 2.3 (1H, m, 4-H), 4.47 (1H, m, 2-H), 5.13 (2H, br s, CH_2), 5.78 (1H, d, *J* 3, 5-H), 7.2-7.4 (5H, m, Ph-H), 7.7 (1H, br s, CO_2H); δ_C (100 MHz) 14.9 (CH_3), 35.07 (C-3), 40.8 (C-4), 51.78 (C-2), 67.5 (CH_2), 78.4 (C-5), 128.1-128.6 (Ph),

136 (ipso), 156.6 (C-1); ν_{max}/cm^{-1} 3314, 2971, 1694, 1523 and 1217; *m/z* (CI) 334 (MH^+, 2%), 308 (6), 226 (11), 218 (15) and 91 (100); $C_{14}H_{18}Cl_2NO_4$ requires 334.0607, found 334.0612.

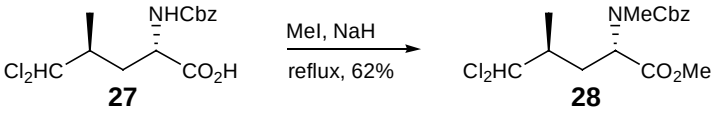
(2*S*,4*S*)-2-(*N*-Benzyloxycarbonyl-*N*-methyl-amino)-5,5-dichloro-4-methylpentanoic acid 30



27 **30**

N-Cbz dichlorinated leucine **27** (0.43 g, 1.29 mmol) was dissolved in MeCN (10 ml) at 0 °C. MeI (8 eq, 10.3 mmol, 0.7 ml) was added followed by NaH (3.87 mmol 0.15 g) before allowing the reaction mixture to warm to room temperature and stirring for 24 h. Ethyl acetate (20 ml) was added followed by water (5 ml) before removing the solvent *in vacuo*. The crude material was dissolved in Et_2O (10 ml) and water (10 ml) and the separated aqueous layer washed with Et_2O (3 x 10 ml). The combined organic layers were washed with a sat aqueous solution of $NaHCO_3$ (2 x 5 ml). The combined aqueous layers were acidified to pH 2 with HCl (1 M), extracted with EtOAc (3 x 10 ml), washed with water (10 ml), sodium thiosulfate (2 x 5 ml) then further washed with water (5 ml). The combined organic layers were dried over anhydrous magnesium sulfate and the solvent removed *in vacuo*. Purification by column chromatography (0-20% EtOAc/petrol) gave *N-Me dichloride* **30** as an oil (0.29 g, 65%); $[\alpha]_D$ - 8.5 (*c* 0.94, CH_2Cl_2); δ_H (400 MHz, major rotamer) 1.19 (3H, d, *J* 6, CH_3), 1.85 - 2.1 (2H, m, 3-H_2), 2.25 (1H, m, 4-H), 2.9 (3H, s, N-CH_3), 4.8 (1H, dd, *J* 12, 4, 2-H), 5.1 - 5.2 (2H, m, CH_2), 5.8 (1H, d, *J* 3, 5-H), 7.3-7.4 (5H, m, Ph-H); δ_C (100 MHz) 15.4 (CH_3), 30.3 (C-3), 30.6 (N-CH_3), 40.8 (C-4), 53.5 (C-2), 67.8 (CH_2), 78.2 (C-5), 1282-128.6 (Ph), 134 (ipso), 157.2 and 160 (CO); ν_{max}/cm^{-1} 3150, 2926, 1719, 1705 and 1264; *m/z* (CI) 348 (MH^+, 6%), 304 (26), 268 (24) and 91 (100); $C_{15}H_{20}Cl_2NO_4$ requires 348.0765, found 348.0769.

(2*S*,4*S*)-2-(*N*-Benzyloxycarbonyl-*N*-methylamino)-5,5-dichloro-4-methylpentanoic acid methyl ester 28

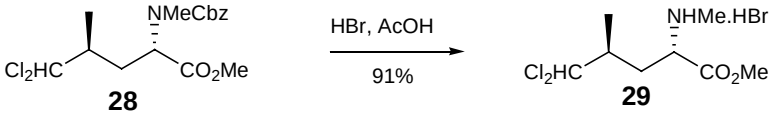


27 **28**

Methyl iodide (0.44 ml, 6.72 mmol) was added to a solution of *N*-Cbz dichlorinated leucine **27** (0.28 g, 0.84 mmol) in THF/DMF (10:1, 2 ml) followed by the addition of NaH (0.1 g, 2.52 mmol). The reaction mixture was heated at reflux for 24 h, before cooling to room temperature and removing the solvent *in vacuo*. The crude material was dissolved in Et_2O (5 ml) and washed with water (2x 5 ml), sodium thiosulfate (2 x 5 ml) and further water (5 ml). The organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed

in vacuo. Purification by column chromatography (20% EtOAc/petrol) gave *N-Me methyl ester* **28** as an oil (0.19 g, 62%); $[\alpha]_D$ - 13.3 (*c* 3.4, CH_2Cl_2); δ_H (400 MHz, major rotamer) 1.18 (3H, d, *J* 6, CH_3), 1.8 - 2 (2H, m, 3-H_2), 2.17 (1H, m, 4-H), 2.8 (3H, s, N-CH_3), 3.7 (3H, s, O-CH_3), 4.74 (1H, dd, *J* 12, 4, 2-H), 5.17 (2H, d, *J* 3, CH_2), 5.78 (1H, d, *J* 3, 5-H), 7.3 - 7.4 (5H, m, Ph-H); δ_C (100 MHz) 15.3 (CH_3), 30.1 (C-3), 30.3 (N-CH_3), 40.9 (C-4), 52.4 (O-CH_3), 56.2 (C-2), 67.7 (CH_2), 78.7 (C-5), 127.7 - 128.6 (Ph), 136 (ipso), 157 and 171 (CO); ν_{max}/cm^{-1} 2953, 1742 and 1698; *m/z* (CI) 362 (MH^+, 64%), 326 (48), 318 (82), 258 (92) and 91 (100); $C_{16}H_{22}Cl_2NO_4$ requires 362.0928, found 362.0925.

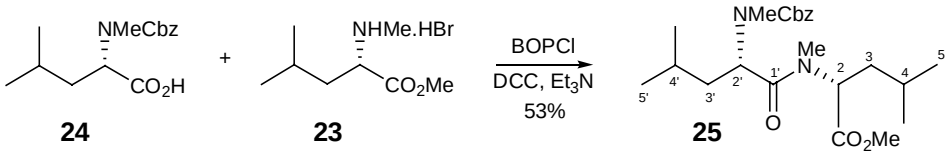
(2*S*,4*S*)-2-Methylamino-5,5-dichloro-4-methylpentanoic acid methyl ester hydrobromide salt 29



28 **29**

Hydrobromic acid (37%, 1.5 ml) was added to *N*-methyl protected dichloroleucine **28** (0.206 g, 0.57 mmol) and stirred for 2 h. The solvent was removed *in vacuo* and water (10 ml) was added. The aqueous layer was washed with Et_2O (2 x 10 ml) before removing the solvent *in vacuo* to give the hydrobromide **29** as a yellow oil (0.16 g, 91%); $[\alpha]_D$ + 8 (*c* 1.5, MeOH); δ_H (400 MHz, D_2O) 1.12 (3H, d, *J* 7, CH_3), 1.95 (1H, ddd, *J* 15, 7, 4, 3-*H*H), 2.17 (1H, ddd, *J* 15, 7, 5, 3-H*H*), 2.36 (1H, m, 4-H), 2.68 (3H, s, N-CH_3), 3.7 (3H, s, O-CH_3), 4.12 (1H, t, *J* 7, 2-H), 6.07 (1H, d, *J* 3, 5-H); δ_C (100 MHz) 15.1 (CH_3), 31.7 (C-3), 31.9 (N-CH_3), 40.1 (C-4), 54.2 (O-CH_3), 58.9 (C-2), 77.8 (C-5), 170 (C-1); ν_{max}/cm^{-1} 3353, 2948 and 1735; *m/z* (CI) 228 (MH^+ -HBr, 92%), 192 (84), 168 (100), 156 (50) and 102 (89). $C_8H_{16}NO_2Cl_2$ requires 228.0558, found 228.0558.

***N*-[2-*N*-[(Benzyloxycarbonyl)-methyl-amino)-L-leucinyl]-methyl-L-leucine methyl ester 25**

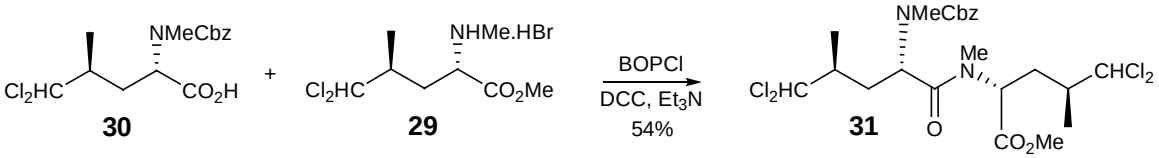


24 **23** **25**

N-Methyl amino acid **24** (0.35 g, 1.26 mmol) and hydrobromide salt **23** (1 eq, 1.26 mmol, 0.302 g) were dissolved in DCM (15 ml) at 0 °C. Et_3N (2 eq, 2.5 mmol, 0.35 ml) and BOPCl (1.1 eq, 1.38 mol, 0.35 g) were then added and the reaction mixture stirred overnight. The reaction mixture was quenched with HCl (1M, 10 ml) and the aqueous layer extracted with EtOAc. The combined organic layers were washed with a sat aqueous solution of $NaHCO_3$ (2 x 8 ml) and water (10 ml), dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purification by column chromatography (0-10% EtOAc/petrol) gave *dipeptide* **25** as a white solid (0.28 g, 53%). m.p. 103-105 °C; $[\alpha]_D$ - 132 (*c* 1.3, CH_2Cl_2); δ_H (400 MHz) 0.87 and 0.92 (each 3H, d,

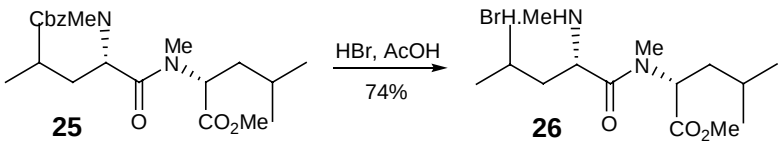
J 7, CH_3), 0.95 (6H, d, *J* 7, 2 x CH_3), 1.35-1.74 (6H, m, 2 x 4-H and 3-H_2), 2.84 and 2.94 each (3H, s, N-CH_3), 3.69 (3H, s, O-CH_3), 5.12-5.25 (2H, m, 2 x 2-H), 5.35 (2H, m, CH_2); δ_C (100 MHz) 21.3 and 22.4 (CH_3), 25 (C-4), 29.1 and 31.2 (N-CH_3), 37.3 (C-3), 52.2 (O-CH_3), 57.4 (C-2), 67.4 (CH_2), 127.7-128.6 (Ph), 136.2 (ipso), 156, 164 and 172.1 (CO); ν_{max}/cm^{-1} 2956, 1742, 1695 and 1652; *m/z* (CI) 421 (MH^+, 76%), 313 (42), 262 (44), 234 (90) and 190 (100); Found C 65.53, H 8.61 and N 6.50, $C_{23}H_{36}N_2O_5$ requires C 65.69, H 8.63 and N 6.66.

_N_-[(2_S_,4_S_,2'_S_,4'_S_)-2-_N_-[(Benzyloxycarbonyl)-methyl-amino)-5,5,dichloroleucinyl]-methyl-5,5-dichloroleucine methyl ester 31



The above method was repeated with *N*-methyl protected dichlorinated amino acid **30** (1 eq, 0.831 mmol, 0.289 g) and dichlorinated ester **29** (1 eq, 0.831 mmol, 0.257 g) to give *dipeptide* **31** as a colourless oil (0.23 g, 54%); $[\alpha]_D$ - 42.2 (*c* 1.8, CH_2Cl_2); δ_H (400 MHz) 1.12 and 1.18 (each 3H, d, *J* 6, CH_3), 1.52 - 2.3 (6H, m, 2 x 4-H and 3-H_2), 2.8 (6H, s, 2 x N-CH_3), 3.7 (3H, s, O-CH_3), 4.9 - 5.07 (2H, m, 2 x 2-H), 5.1 and 5.19 each (1H, d, *J* 9, CH_2), 5.72 and 5.76 each (1H, d, *J* 3, $CHCl_2$); δ_C (100 MHz) 15.3 (CH_3), 29.7 (N-CH_3), 30.8 (C-3), 40.5 (C-4), 52.6 (O-CH_3), 54.03 (C-2), 67.8 (CH_2), 78.6 ($CHCl_2$), 127.8-128.6 (Ph), 132 (ipso), 156 and 171.3 (CO); ν_{max}/cm^{-1} 2953, 1741, 1694 and 1650; *m/z* (CI) 557 (MH^+, 24%), 521 (60), 302 (70) and 258 (100). $C_{23}H_{33}Cl_2N_2O_5$ requires 557.1143, found 557.1129.

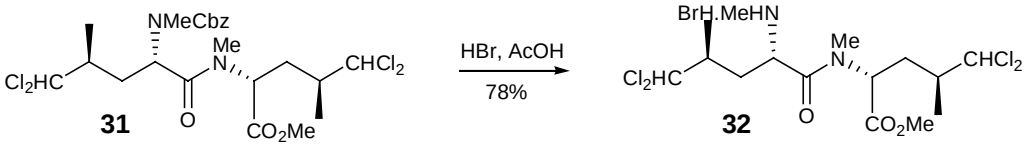
_N_-[2-_N_-[(Benzyloxycarbonyl)-methyl-amino)-L-leucinyl]-methyl-L-leucine methyl ester hydrobromic salt 26



Dipeptide **25** (0.21 g, 0.499 mmol) was treated with HBr (37%, 5 ml) and stirred for 3 h. The solvent was removed *in vacuo* and the crude material was dissolved in water and washed with Et_2O (2 x 10 ml). The solvent was removed *in vacuo* to give the *hydrobromide salt* **26** as an orange solid (0.135 g, 74%); $[\alpha]_D$ - 36 (*c* 1, MeOH); δ_H (400 MHz) 0.82 (3H, d, *J* 6, CH_3), 0.84 (3H, d, *J* 7, CH_3), 0.93 and 0.95 (each 3H, d, *J* 7, 2 x CH_3),

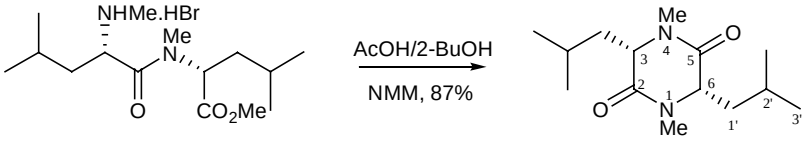
1.42 - 1.44 (1H, m, C*H*-CH_3), 1.72 - 1.75 (4H, m, 2 x CH_3), 1.87-1.89 (1H, m, CH-CH_3), 2.6 (3H, s, N-CH_3), 3.05 (3H, s, N-CH_3), 3.7 (3H, s, O-CH_3), 4.42 (1H, t, *J* 5, 2-H), 4.99 (1H, dd, *J* 11, 5, 2-H); δ_C (100 MHz) 20.09, 22.09, 23.9 and 24.5 (CH_3), 30.5 and 31.8 (N-CH_3), 36.2 (CH_2), 38.6 (CH_2), 56 (O-CH_3), 58.1 and 59 (C-2), 168.5 and 172 (CO); ν_{max}/cm^{-1} 3327, 2944, 2831, 1743 and 1653; *m/z* (CI) 288 (MH^+- HBr, 100%), 230 (10) and 101 (100); $C_{15}H_{31}BrN_2O_3$ requires 287.2329, found 287.2334.

N-[(2*S*,4*S*,2'*S*,4'*S*)-2-*N*-[(Benzyloxycarbonyl)-methyl-amino)-5,5,dichloroleucinyl]-methyl-5,5-dichloroleucine methyl ester hydrobromic salt 32



The above method was repeated using the chlorinated dipeptide **31** (0.19 g, 0.34 mmol) to give the corresponding *HBr salt* **32** as an orange oil (0.134 g, 78%); $[\alpha]_D$ - 13.3 (*c* 1.2, MeOH); δ_H (400 MHz) 1.12 and 1.23 (each 3H, d, *J* 6, CH_3), 1.8-2.3 (6H, m, 2 x 4-H and 3-H_2), 2.7 (3H, s, N-CH_3), 3.07 (3H, s, N-CH_3), 3.7 (3H, s, O-CH_3), 4.55 (1H, dd, *J* 9, 4, 2-H), 5.09 (1H, m, 2-H), 6.07 (2H, d, *J* 3, 2 x $CHCl_2$); δ_C (100 MHz) 15.04 and 15.7 (CH_3), 32.5 and 32.6 (N-CH_3), 35.5 and 35.7 (CH_2) , 40.1 and 41.9 (C-4), 53.2 (O-CH_3), 56.1 and 58.3 (C-2), 79.1 and 79.8 ($CHCl_2$), 170 and 171.7 (CO); ν_{max}/cm^{-1} 3355, 2947, 1739 and 1655; *m/z* (CI) 423 (MH^+ - HBr, 20%), 287 (44), 351 (38) and 168 (100); $C_{15}H_{27}N_2O_3Cl_4$ requires 423.0768, found 423.0775.

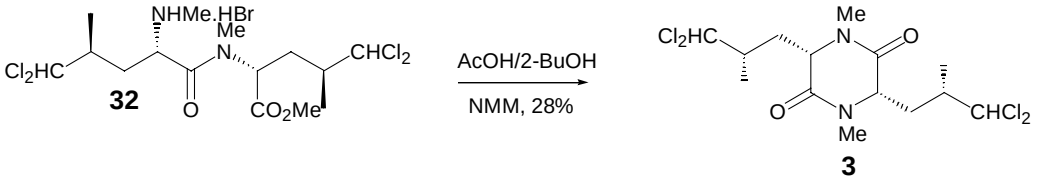
(3*S*,6*S*)-(2'-Methylpropyl)-1,4-dimethylpiperazine-2,5-dione 19



Dipeptide **26** (0.1 g, 0.2722 mmol) was dissolved in acetic acid in 2-butanol (2M, 10 ml), then treated with *N*-methyl morpholine (2 eq, 0.544 mmol, 0.06 ml) and heated at reflux for 4 h. The solvent was removed in *vacuo*, the crude material dissolved in EtOAc (15 ml), washed with water (10 ml) and brine (10 ml). The organic layers were dried over anhydrous magnesium sulfate, filtered and the solvent removed *in vacuo*. Purfication by column chromatography (0-25% EtOAc/petrol) gave diketopiperazine **19** as a white solid (0.06 g, 87%); m.p. 135-138 °C [lit. [4] see below*]; [α_D] + 32.2 (*c* 1.0, $CHCl_3$) [lit.[4] + 48.8 (*c* 1.0, $CHCl_3$)]; δ_H (400 MHz) 0.96 and 0.98 (each 6H, d, *J* 7, 4 x CH_3), 1.57 (2H, ddd, *J* 14, 9, 5, 1'-H_2), 1.70 (2H, ddd, *J* 14, 9, 5, 1'-H_2), 1.85 - 2.0 (2H, m, 2 x 2'-H), 2.9 (6H, s, 2 x N-CH_3), 3.82 (2H, dd, *J* 9, 5, 2 x 6-H); δ_C (100 MHz) 21.9 and 23 (CH_3), 25.2 (C-2'), 32.7 (N-CH_3), 43.7 (C-1'), 60.8 (C-3 and C-6) and 166.8 (CO); ν_{max}/cm^{-1} 2961, 1667, 1403; *m/z* (CI) 255 (MH^+, 100); Found C 66.21, H, 10.37, N 11.05, $C_{14}H_{26}N_2O_2$ requires C 66.10, H 10.30 and N 11.01.

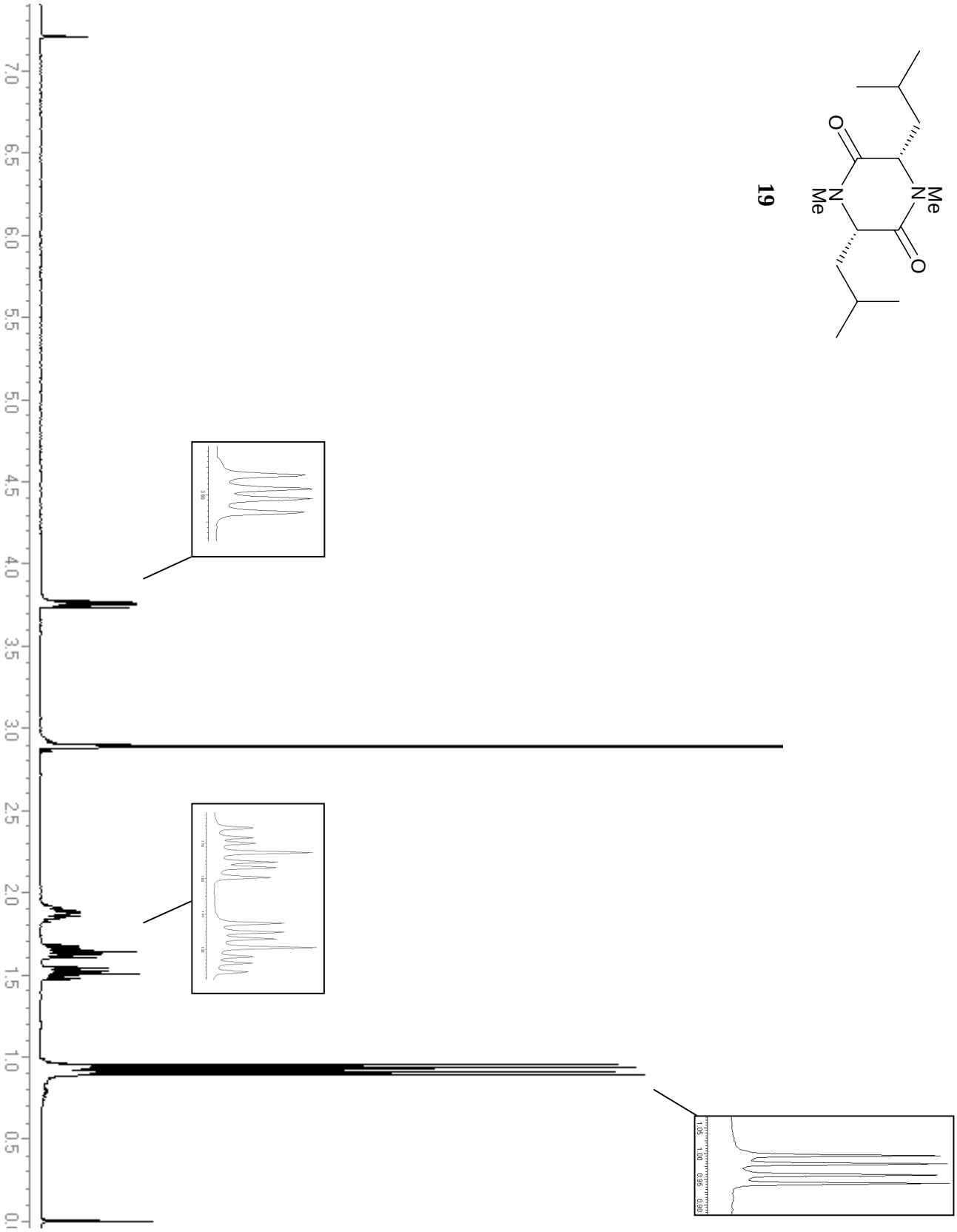
* mp. 110 °C prepared using MeI/Ag_2O; mp. 114-116 °C prepared using MeI/NaH (Scheme 4)[4]

Dysamide B 3

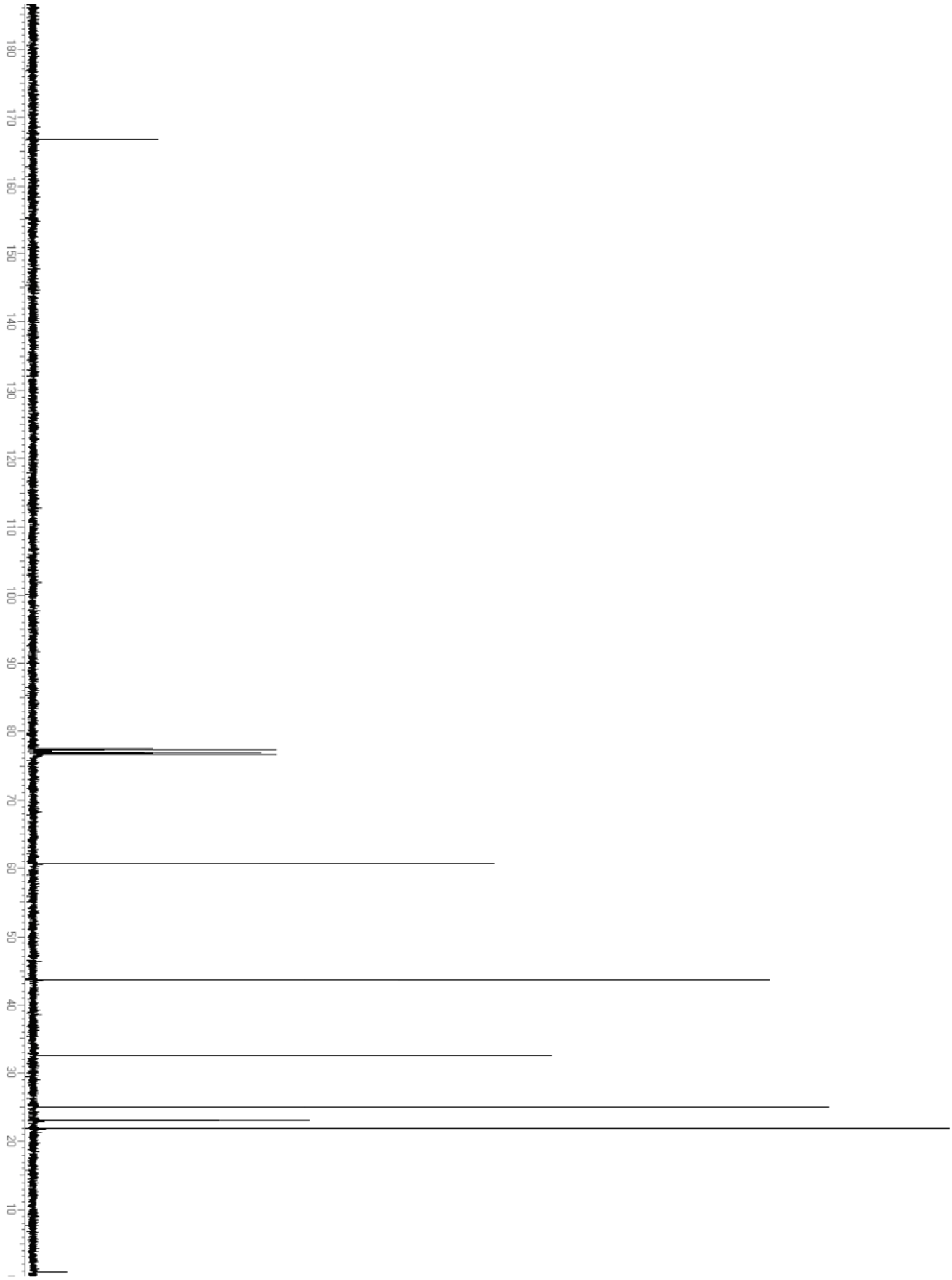


The above method was repeated with chlorinated dipeptide **32** (0.113 g, 0.224 mmol) to give dysamide B **3** as a white solid (0.024 g, 28%); m.p. 147-149 °C (lit. [5] m.p -natural product 147-149 °C $[\alpha]_D$ + 10.7 (c 1.6, MeOH) (lit.[5] –natural product + 13.7 (c 0.117, MeOH)); δ_H (400 MHz) 1.12 (6H, d, *J* 6, CH_3), 1.57 (2H, ddd, *J* 14, 10, 5, 1'-*H*H), 2.19 (2H, ddd, *J* 14, 8, 5, 1'-H*H*), 2.49 - 2.51 (2H, m, 2 x 2'-H), 2.94 (6H, s, 2 x N-CH_3), 3.79 (2H, dd, *J* 10, 5, 3-H and 6-H), 6.12 (2H, d, *J* 3, 2 x $CHCl_2$); δ_C (100 MHz) 15.6 (C-3'), 33.03 (N-CH_3), 37.7 (C-1'), 40.3 (C-2'), 60.2 (C-3 and C-6), 77.4 ($CHCl_2$), 165.8 (CO); *m/z* (CI) 393 (MH^+, 78%), 355 (100), 319 (30) and 265 (60); $C_{14}H_{23}Cl_4N_2O_2$ requires 391.0514, found 391.0513.

The ^{1}H- and ^{13}C NMR spectra of diketopiperazine **19** and dysamide B **3** in $CDCl_3$ are shown below:



19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100
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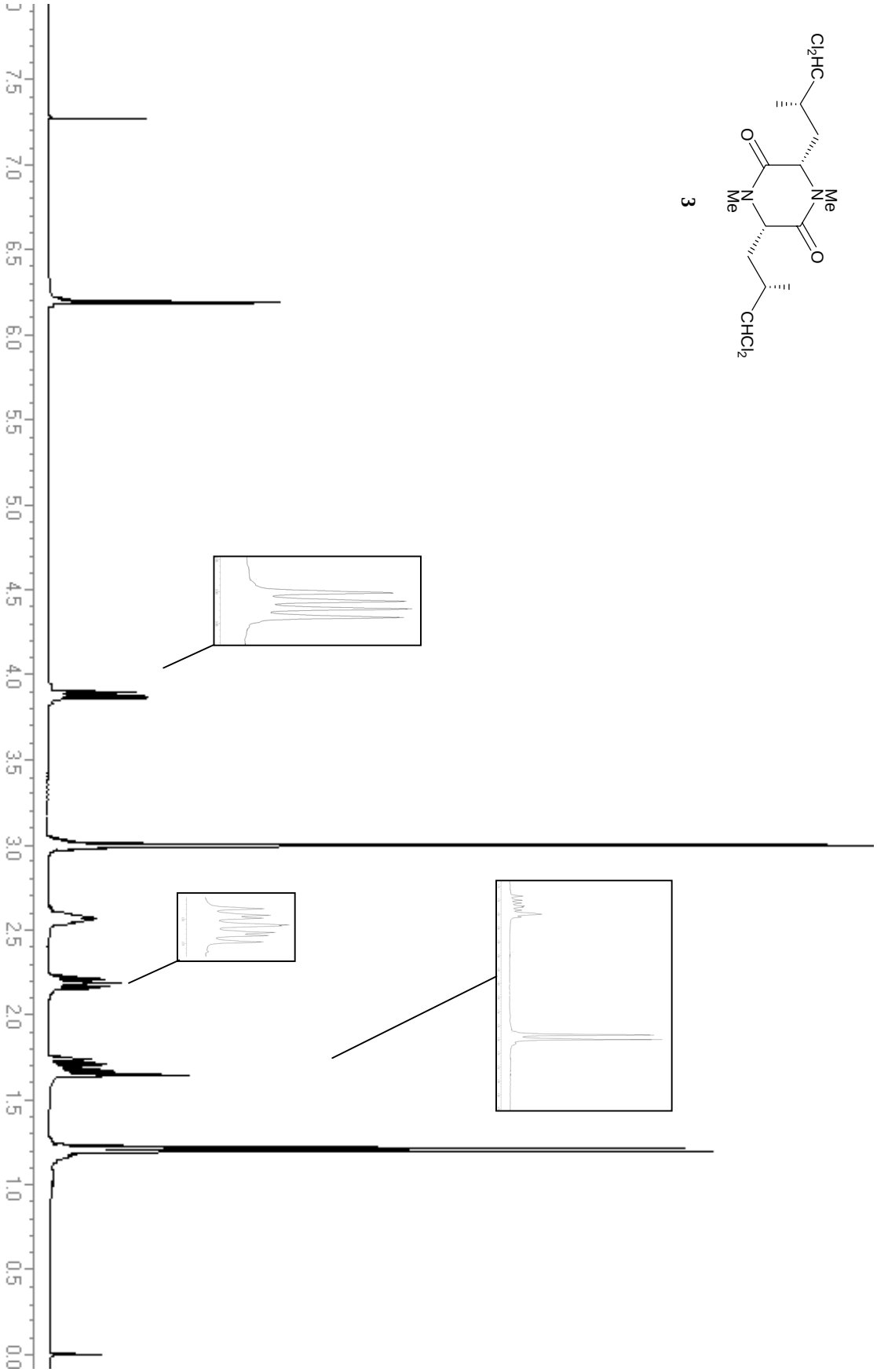
Cl2HC
O
N
Me
Me
N
O
CHCl2
3
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7.0
6.5
6.0
5.5
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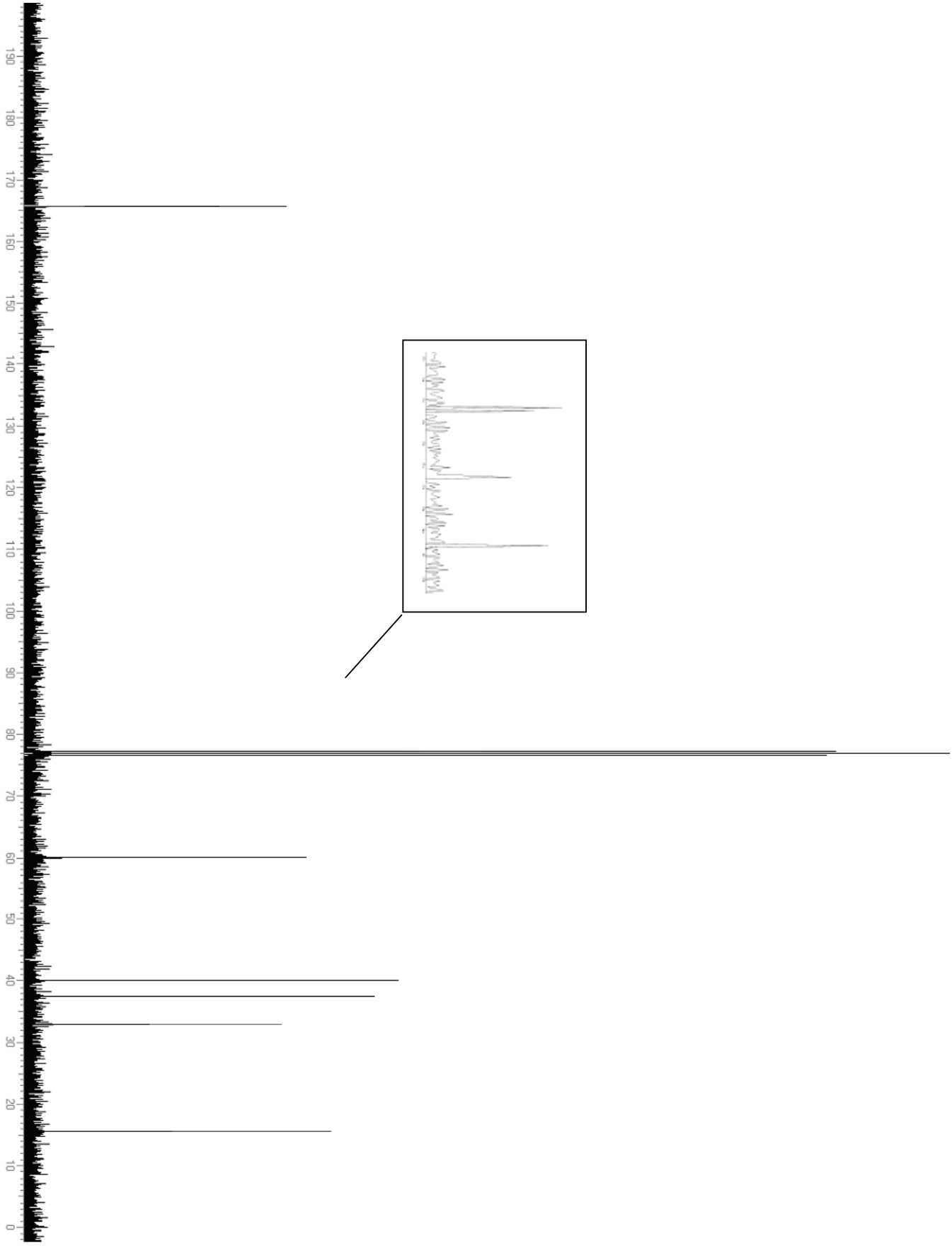
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0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0

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