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A Concise and Efficient Synthesis of Substituted Morpholines

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Contents:

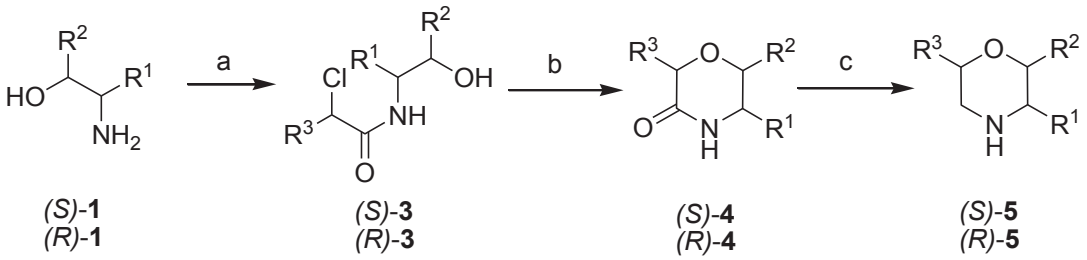
General information

Methods and Materials:

Unless otherwise noted, commercial available materials were used without further purification. Air sensitive reactions were carried out under nitrogen atmosphere. Anhydrous solvents were obtained from Sigma Aldrich. NMR spectra were recorded on a Bruker 300 MHz spectrometer. Chemical shifts (δ) are quoted in Parts per million (ppm) relative to internal solvent reference. Coupling constants are given in Hz and chemical shifts are reported in δ values in ppm. Data are reported as followed: chemical shift, multiplicity (s = singlet, s br = broad singlet, d = doublet, t = triplet, dd = double doublet, dt = double triplet, ddd = double double doublet, m = multiplet), coupling constants (Hz), and integration.

General Procedure

Scheme 1:- Three step synthesis of substituted morpholines



(S)-**1** *(R)*-**1** *(S)*-**3** *(R)*-**3** *(S)*-**4** *(R)*-**4** *(S)*-**5** *(R)*-**5**

Reagents and conditions: (a) α-Chloroacid chloride, K_2CO_3, THF, H_2O, -10°C; (b) $KOBu^t$, IPA, DCM, RT; (c) LAH, THF, 0°C to RT.

General Procedure for synthesis of 3: To a solution of **1** (1 equiv.) in THF (50 mL) was added a solution of K_2CO_3 (3 equiv.) in water (50 mL) at -10°C. To the resulting solution at -10°C was added slowly via syringe α-Chloroacid chloride **2** (1.1 equiv.) with vigorous stirring, and the reaction mixture was stirred at same temperature for 1 h. The mixture was poured in water (50 mL) and extracted with CH_2Cl_2 (2 X 100 mL), and the organic layer was dried (Na_2SO_4), filtered and concentrated to afford **3** as a colorless oil.

General Procedure for synthesis of 4: To a solution of **3** (1 equiv.) in CH_2Cl_2 (100 mL) was dropwise added $KOBu^t$ (4 equiv.) in IPA (100 mL) at 0°C. The resulting solution was stirred at RT for 1h. 2N HCl was added to adjust the pH 7 of reaction mixture. The solvent was removed under reduced pressure to obtain white precipitate. The precipitates were taken in ethyl acetate (100 mL) and washed with H_2O, The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain **4** as colorless oil.

General Procedure for synthesis of 5: LAH (2 equiv.) in THF (100 mL) was cooled to 0°C in an ice bath under nitrogen. A solution of **4** (1 equiv.) in THF (20 mL) was added dropwise, and

the resulting solution was stirred at RT for 16 hrs. The reaction mixture was cooled to 0°C and carefully quenched with water (2 mL), 2 N NaOH (2 mL) and water (8 mL). The resulting slurry was stirred at RT for 1 h and filtered through Celite. The filter cake was washed with ethyl acetate and discarded. The filtrate was dried (Na_2SO_4), separated and concentrated to afford **5** as a colorless oil.

Experimental Procedure

(S)-2-chloro-N-(1-hydroxypropan-2-yl)acetamide(3a):- To a solution of 2-(S)-amino-propan-1-ol (1.0 g, 13.33 mmol) in THF (50 mL) was added a solution of K_2CO_3 (5.52 g, 39.99 mmol) in water (50 mL) at -10°C. To the resulting solution at -10°C was added slowly via syringe α-Chloroacetylchloride **2** (1.16 mL, 14.66 mmol) with vigorous stirring, and the reaction mixture was stirred at same temperature for 1 h. The mixture was poured in water (50 mL) and extracted with CH_2Cl_2 (2 X 100 mL), and the organic layer was dried (Na_2SO_4), filtered and concentrated to afford titled compound **3a** as a colorless oil (1.71 g, 85%).^{1}H NMR (300 MHz, $CDCl_3$): δ 6.73 (br, 1H), 4.1 (m, 1H), 4.05(s, 2H), 3.70 (m, 1H), 3.57 (m, 1H), 2.57 (br, 1H), 1.22 (d, J= 6.0 Hz, 3H); MS *m/z* = 152 [M+1].

(S)-5-methylmorpholin-3-one (4a):- To a solution of (S)-2-chloro-N-(1-hydroxypropan-2-yl)acetamide **3a** (1.50 g, 9.93 mmol) in CH_2Cl_2 (100 mL) was dropwise added $KOBu^t$ (4.45 g, 39.72 mmol) in IPA (100 mL) at 0°C. The resulting solution was stirred at RT for 1h. 2N HCl was added to adjust the pH 7 of reaction mixture. The solvent was removed under reduced pressure to obtain white precipitate. The precipitates were taken in ethyl acetate (100 mL) and washed with H_2O, The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain titled compound **4a** as colorless oil (0.92 g, 80%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.75 (br, 1H), 4.21-4.06 (m, 2H), 3.91-3.86 (m, 1H), 3.71 (m, 1H), 3.35 (m, 1H), 1.19 (d, J= 6.0 Hz, 3H); MS *m/z* = 116 [M+1].

(S)-3-methylmorpholine (5a): LAH (0.892 g, 23.47 mmol) in THF (100 mL) was cooled to 0°C in an ice bath under nitrogen. A solution of (S)-5-methylmorpholin-3-one (0.90 g, 7.82 mmol) in THF (20 mL) was added dropwise and the resulting solution was stirred at RT for 16 hrs. The reaction mixture was cooled to 0°C and carefully quenched with water (2 mL), 2 N NaOH (4 mL) and water (6 mL). The resulting slurry was stirred at RT for 1 h and filtered through Celite. The filter cake was washed with ethyl acetate and discarded. The filtrate was dried (Na_2SO_4), separated and concentrated to afford titled compound **5a** as a colorless oil (0.56 g, 71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.75 (m, 2H), 3.45 (m, 1H), 3.07(m, 1H), 3.01-2.81 (m, 3H), 0.95 (d, J = 6.3 Hz, 3H); MS *m/z* = 102 [M+1].

Multi gram (100g) procedure for (S)-3-methylmorpholine (5a)

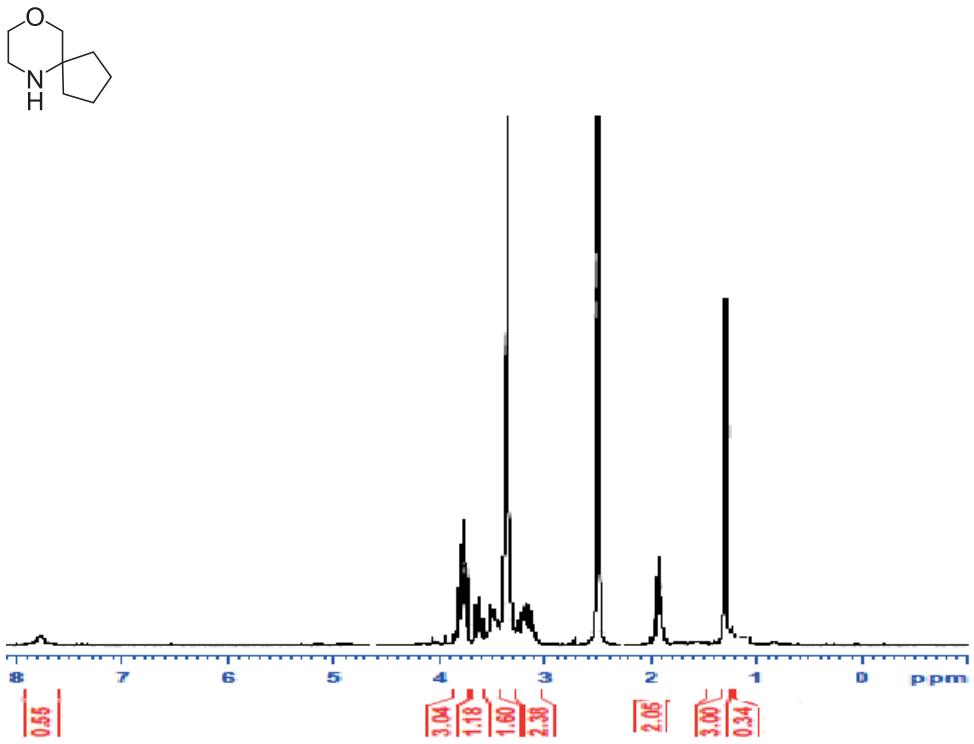
2-Amino-1-propanol (1a): In three necked 5 Liter RBF, 1.5 liter dry THF was taken and cooled to 0^{o}C. LAH (59 g, 1.5 mol) was added to it very carefully with temperature maintained at 0^{o}C. L-Alanine (70 g, 0.78 mol) was added portion wise at same temperature over 45 min. Reaction mixture was slowly allowed to warm to room temperature and heated to refluxed for 24 hrs. After completion, reaction mixture was cooled to 0^{o}C and quenched with saturated K_2CO_3 solution and stirred for 1 hrs. Added 5% MeOH/DCM solution (2 Liter) and stirred for additional 1 hrs. Crude mixture was filtered on celite pad and dried over anhydrous Na_2SO_4 and finally concentrated under reduced pressure to get product (55g, 85%) as colorless oil.

(S)-2-chloro-N-(1-hydroxypropan-2-yl)acetamide(a):- To a solution of 2-(S)-amino-propan-1-ol (55 g, 0.73 mol) in THF (1 Liter) was added a solution of K_2CO_3 (303.5 g, 2.19 mol) in water (600 mL) at -10^{o}C. To the resulting solution at -10^{o}C was added slowly via droping funnel α-Chloroacetylchloride (65 mL, 0.80 mol) with vigorous stirring, and the reaction mixture was stirred at same temperature for 1 h. The mixture was poured in water (50 mL) and extracted with CH_2Cl_2 (3 X 500 mL), and the organic layer was dried (Na_2SO_4), filtered and concentrated to afford titled compound **3a** as a colorless oil (95 g, 85%).

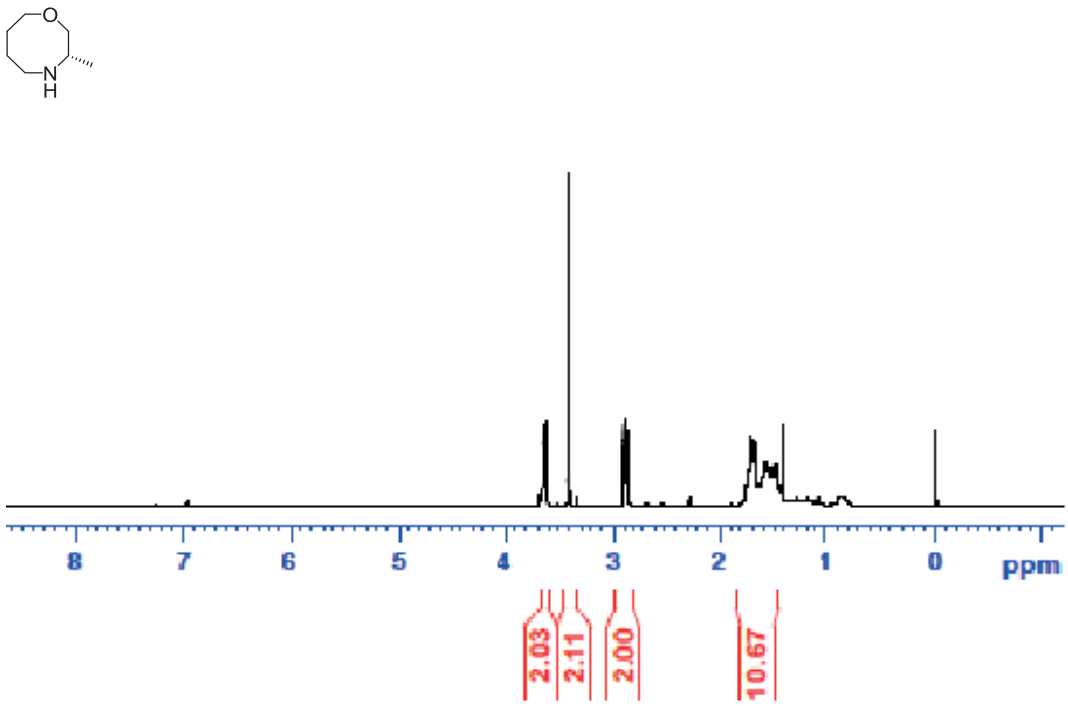
(S)-5-methylmorpholin-3-one (4a):- To a solution of (S)-2-chloro-N-(1-hydroxypropan-2-yl)acetamide (95 g, 0.62 mol) in CH_2Cl_2 (1 Liter) was dropwise added KOBu^{t} (307 g, 2.51 mol) in IPA (1 Liter) at 0^{o}C. The resulting solution was stirred at RT for 1h. 2N HCl was added to adjust the pH 7 of reaction mixture. The solvent was removed under reduced pressure to obtain white precipitate. The precipitates were taken in ethyl acetate (3 X 500 mL) and washed with H_2O, The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to obtain titled compound **4a** as colorless oil (60 g, 83%).

(S)-3-methylmorpholine (5a)[1]: LAH (59.32 g, 1.51 mol) in THF (1 Liter) was cooled to 0^{o}C in an ice bath. A solution of (S)-5-methylmorpholin-3-one (60 g, 0.52 mol) in THF (500 mL) was added dropwise and the resulting solution was stirred at RT for 16 hrs. The reaction mixture was cooled to 0^{o}C and carefully quenched with water (2 mL), 2 N NaOH (35 mL) and water (70 mL). The resulting slurry was stirred at RT for 1 h and filtered through Celite. The filter cake was washed with ethyl acetate and discarded. The filtrate was dried (Na_2SO_4), separated and concentrated to afford titled compound **5a** as a colorless oil (45 g, 86%).

1H NMR spectrum of 5g



1H NMR Spectrum of 5K



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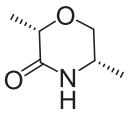

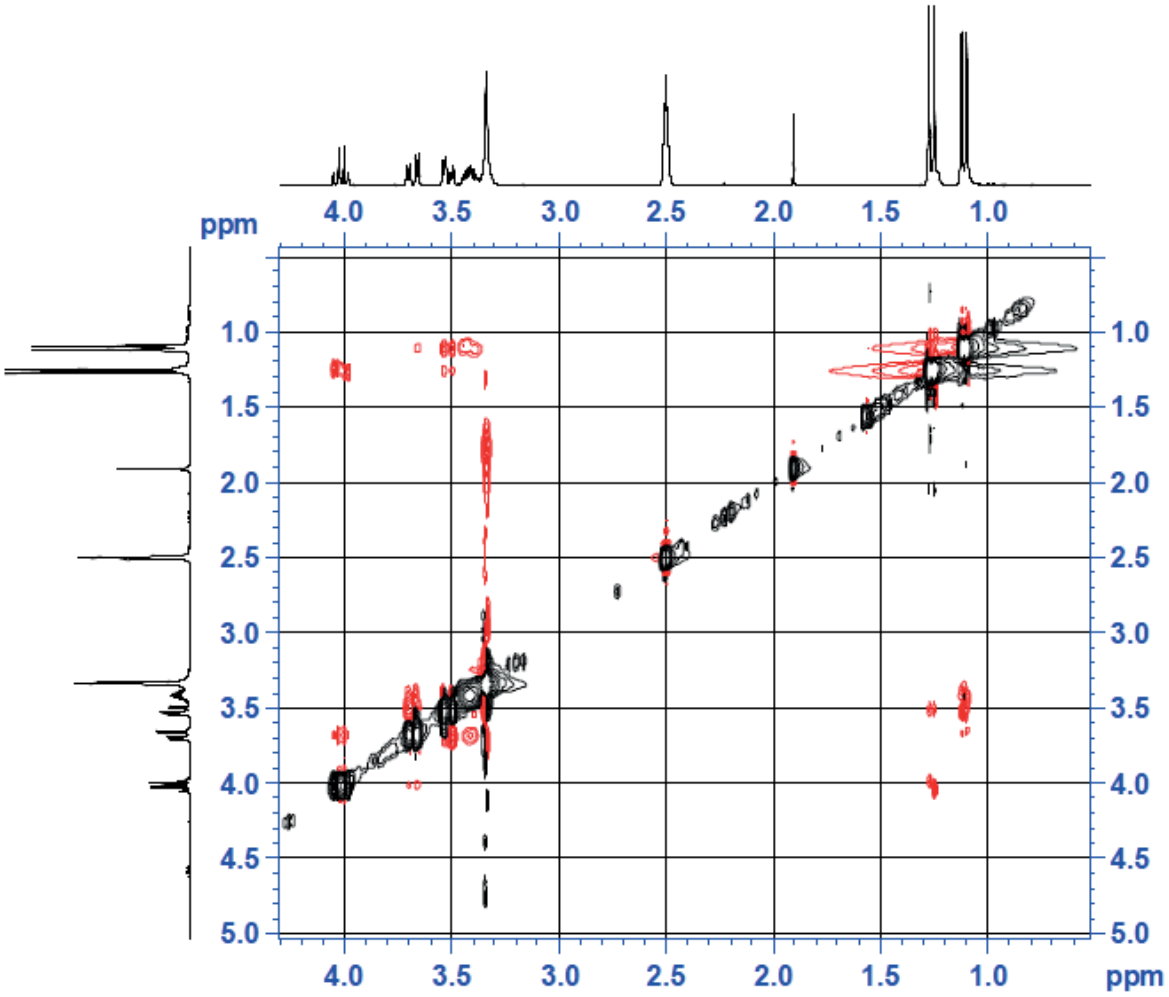

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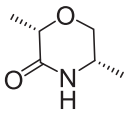

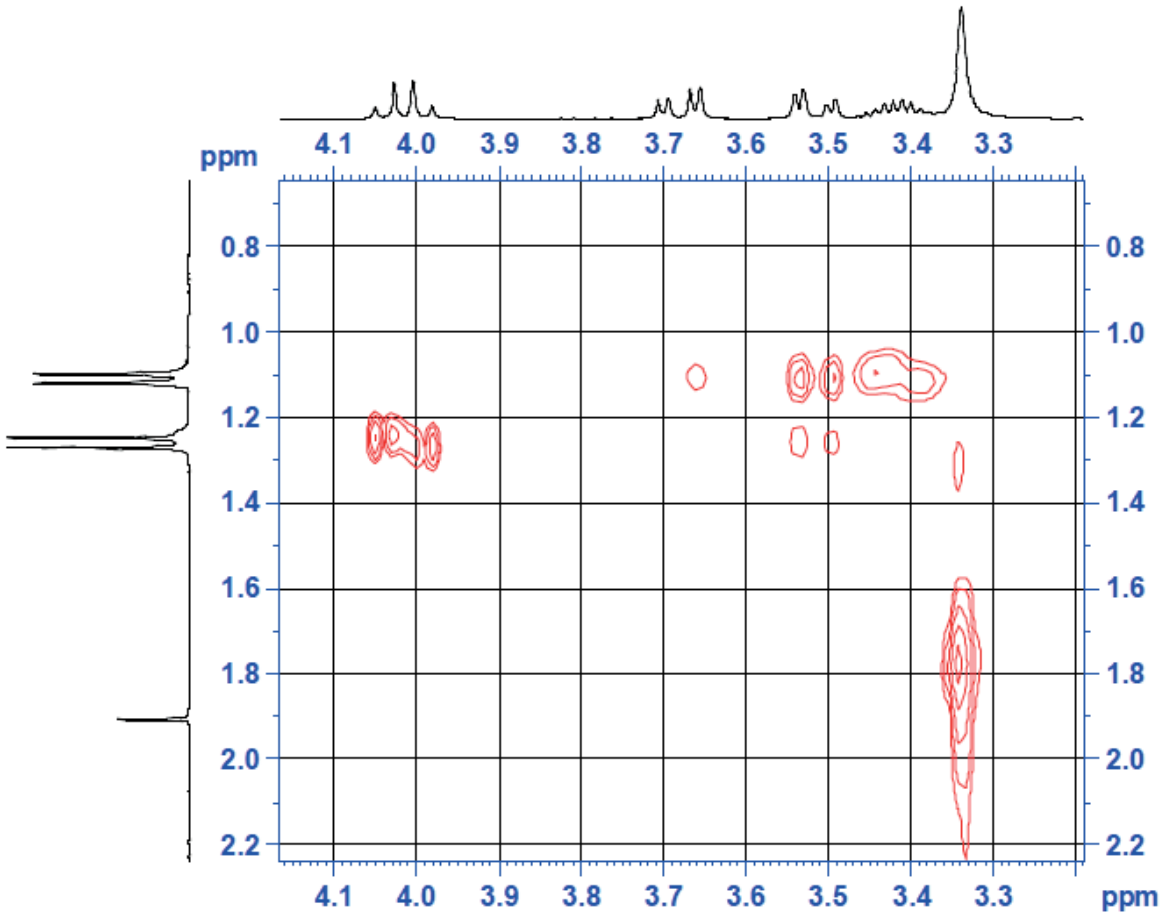

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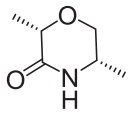

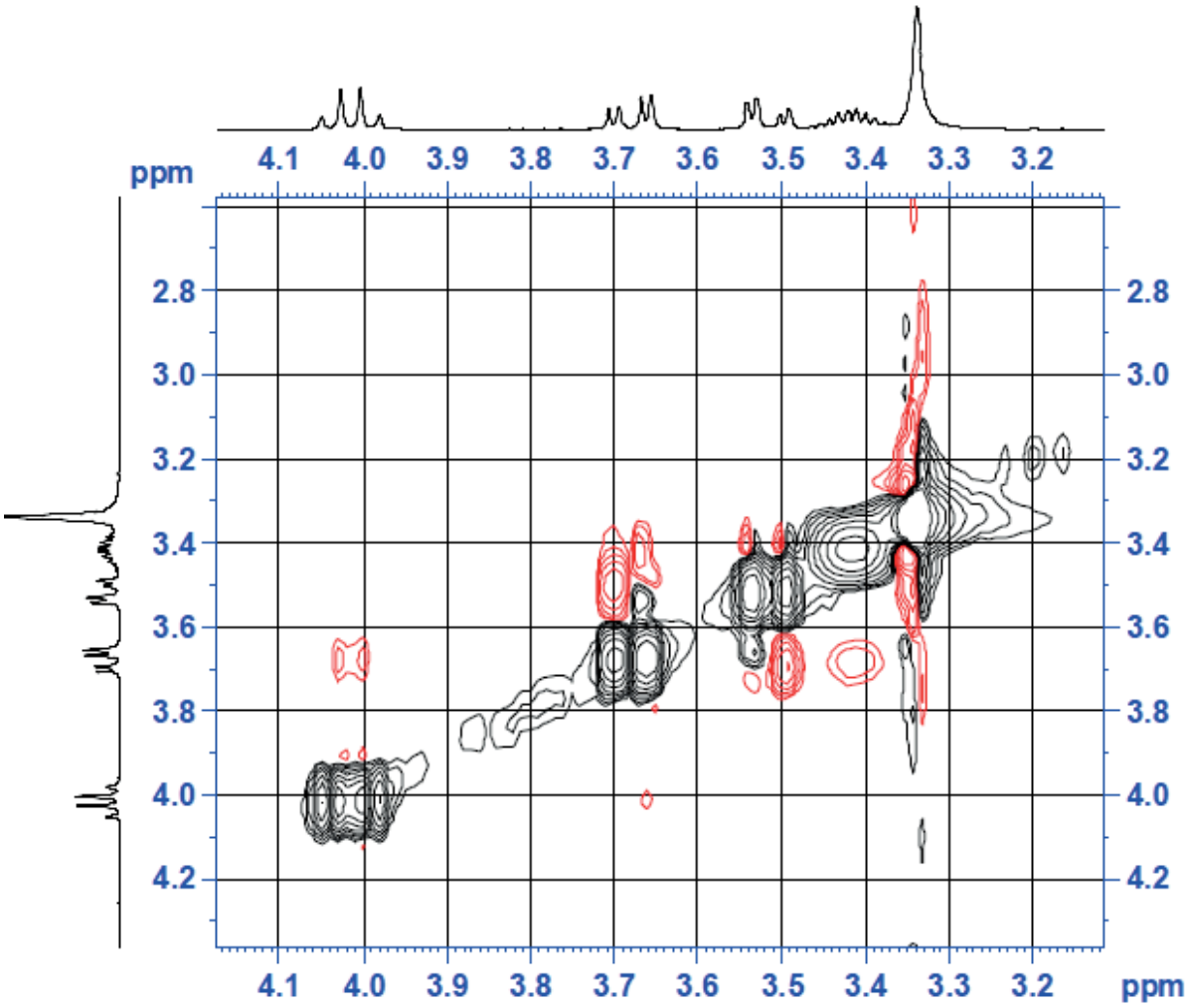

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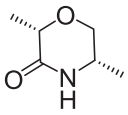

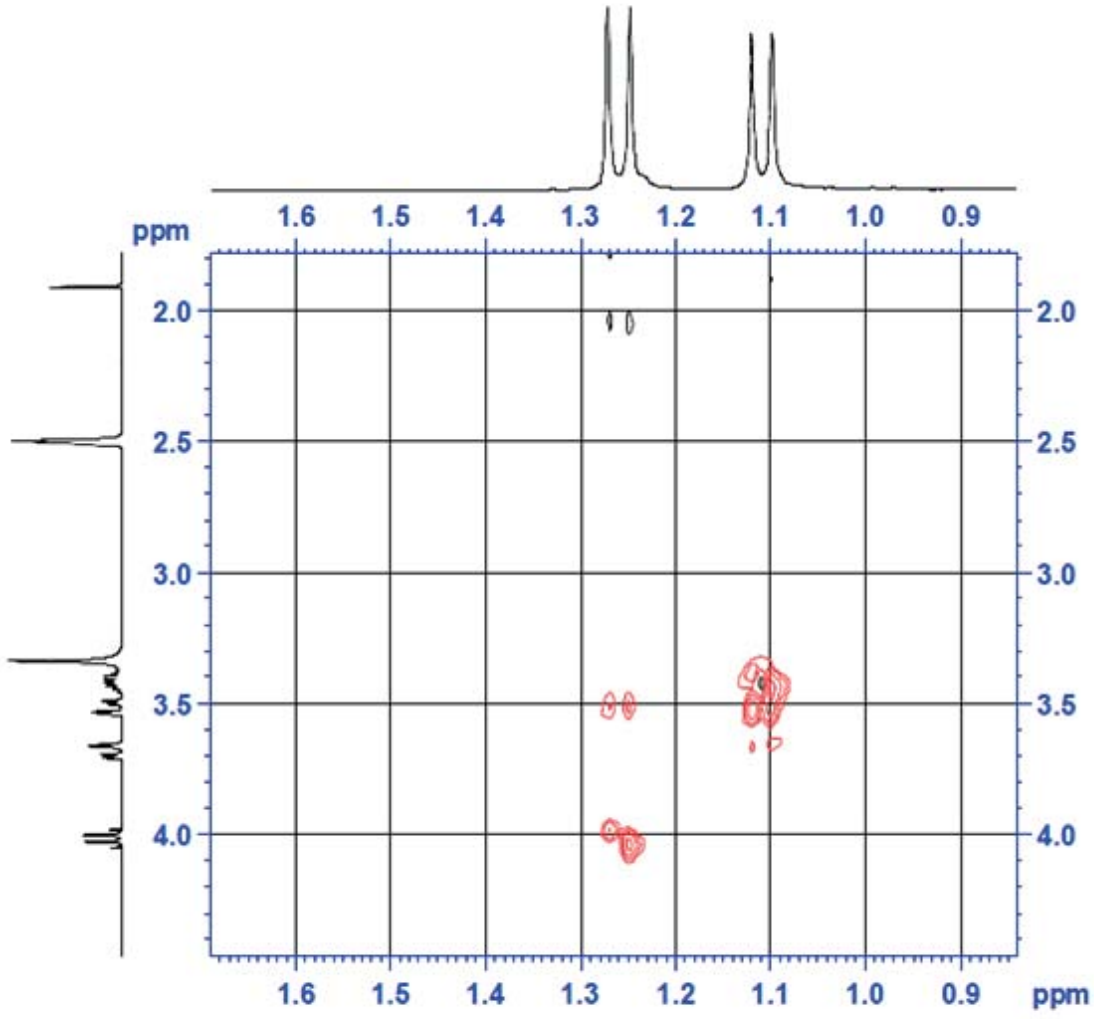

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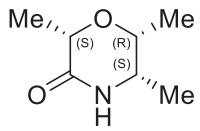

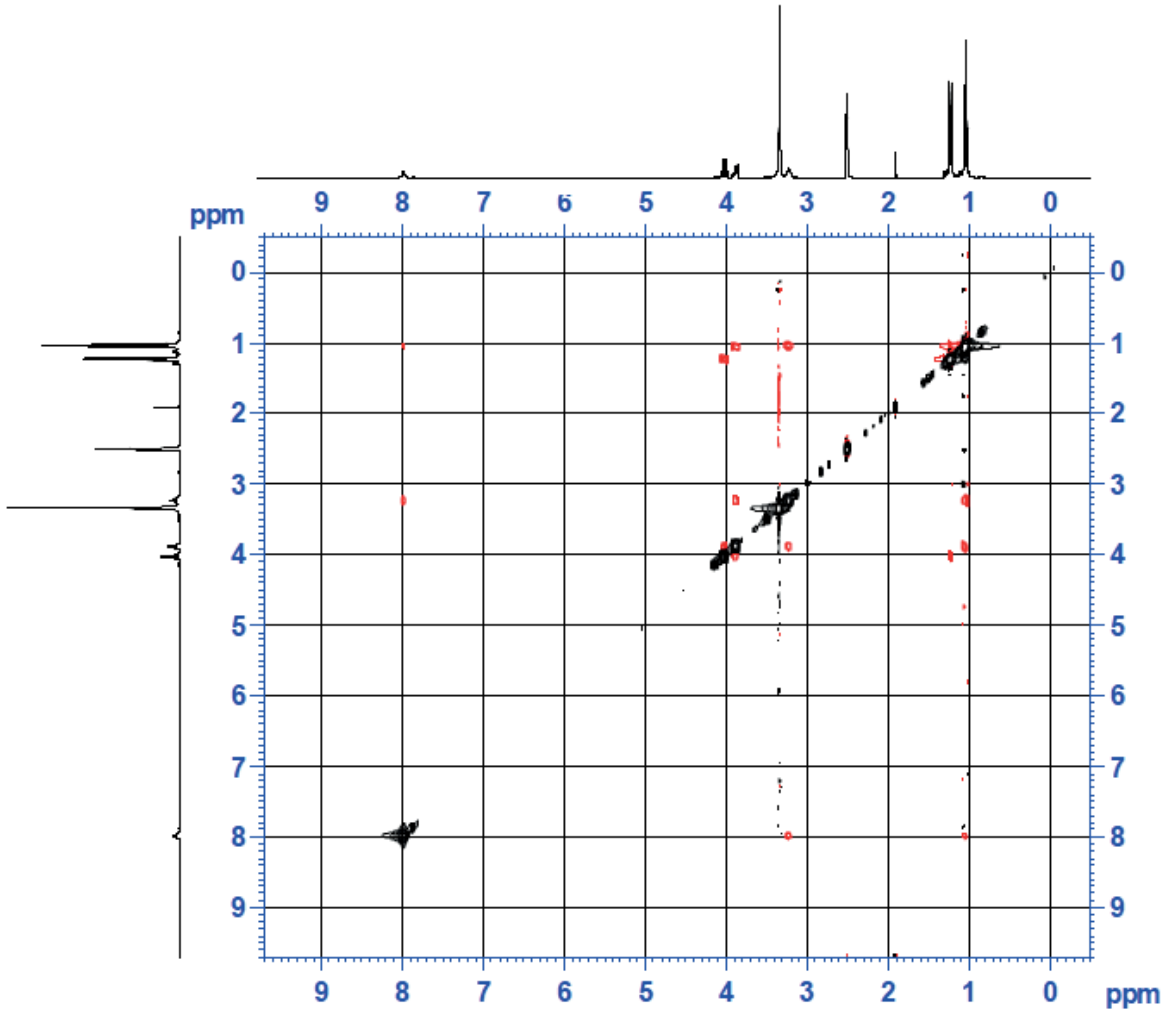

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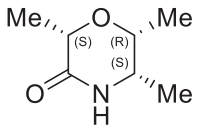

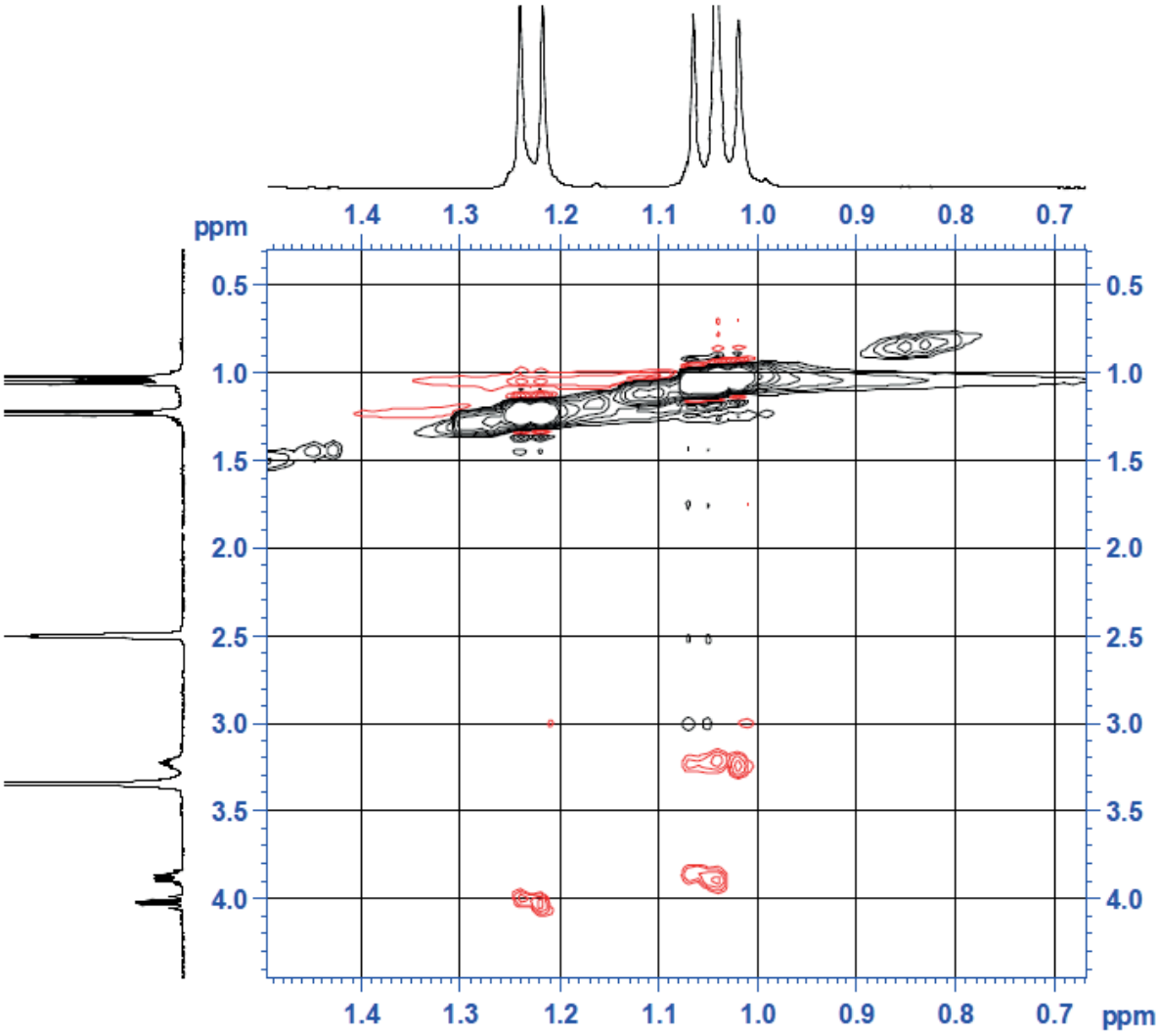

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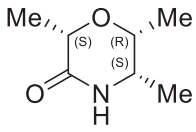

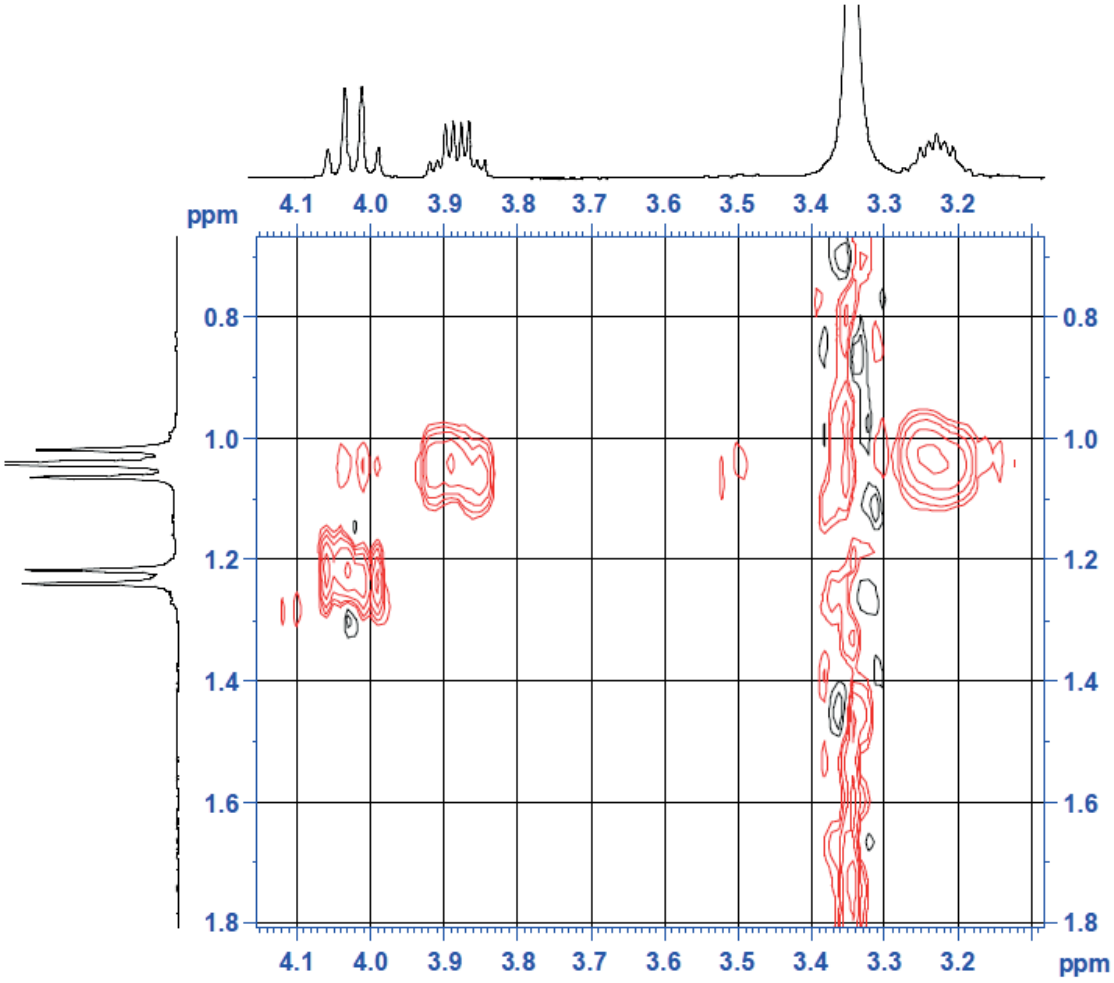

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