

Supporting Information for

‘Flexible access to conformationally-locked bicyclic morpholines’

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1. General Information

All reagents were obtained from commercial suppliers and used without further purification unless otherwise stated. All reactions were carried out under an inert, dry, nitrogen atmosphere unless otherwise stated. All glassware was flame-dried and cooled under a blanket of nitrogen.

- Dichloromethane, THF, diethyl ether, and toluene were obtained from an Innovatic Technology, Pure Solv, SPS-400-5 Solvent Purification System.
- Methanol was heated to reflux over calcium hydride and then distilled under nitrogen before use.
- Benzaldehyde was distilled under nitrogen before use.

- Petrol refers to petroleum ether boiling point range 40-60 °C.
- KHMDS was purchased as a 0.5 M solution in toluene and was standardised before use using salicylaldehyde phenylhydrazone as indicator.ⁱ

Thin layer chromatography was carried out using silica gel 60 F₂₅₄ plates and were analysed using a Mineralight UVG-25 lamp or developed using vanillin solution.

Flash chromatography was carried out using Zeo Chem silica gel (40-63 µm).

IR spectra were recorded on a Perkin Elmer Spectrometer 1 machine.

High resolution mass spectra were recorded on a Finnigan MAT 90XLT instrument at the EPSRC UK National Mass Spectrometry Facility at Swansea University.

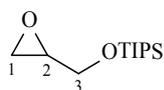
¹H and ¹³C spectra were recorded on a Bruker DPX 400 Spectrometer at 400 MHz and 100 MHz, respectively or a Bruker 500 Spectrometer at 500 MHz and 125 MHz, respectively. Analysis for compounds **25** and **27**, as well as all NOESY spectra, were recorded on a Bruker DPX 600 Spectrometer at 600 MHz.

Chemical shifts are reported in ppm and coupling constants are reported in Hz and refer to ³J_{H-H} interactions unless otherwise specified. Note: CDCl₃ is referenced at δ7.26 (¹H NMR) and 77.16 (¹³C NMR) ppm.

It should be noted that the ¹H NMR spectra of compounds **12-17**, **20-23**, **26**, and **27** give the appearance of a mixture of two isomers. Based on our published work with similar compounds, which included the use of variable temperature studies, we believe that this is, in fact, due to restricted rotation between stable conformations of the carbamate.ⁱⁱ

2. Synthetic Procedures and Analysis

Triisopropyl(oxiran-2-ylmethoxy)silane, **7**ⁱⁱⁱ



Imidazole (8.3 g, 122 mmol) was added to a stirred solution of glycidol (8.2 g, 111 mmol) in dry THF (200 mL). Triisopropylsilyl chloride (26.1 mL, 122 mmol) was then added during which time a white precipitate formed. The reaction mixture was stirred at ambient temperature overnight. The precipitate was filtered through a bed of celite and washed with diethyl ether. The filtrate was concentrated *in vacuo* and purified by column chromatography (0-5% diethyl ether in petrol) to yield **7** as a colourless oil (24.1 g, 97%).

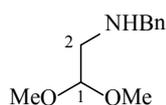
FTIR (CH₂Cl₂): 1260, 1266, 3050, 3061 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.06-1.13 (m, 21H, Si(CH(CH₃)₂)₃), 2.69 (dd, ²*J* = 5.2 Hz, *J* = 2.8 Hz, 1H, H1), 2.80 (dd, ²*J* = 5.3 Hz, *J* = 4.2 Hz, 1H, H1), 3.12-3.15 (m, 1H, H2), 3.78 (dd, ²*J* = 11.7 Hz, *J* = 4.6 Hz, 1H, H3), 3.93 ppm (dd, ²*J* = 11.6 Hz, *J* = 3.3 Hz, 1H, H3).

¹³C NMR (100 MHz, CDCl₃): 11.5, 17.4, 44.0, 52.1, 63.4 ppm.

HRMS *m/z* (ESI) calc for C₁₂H₂₇O₂Si (M⁺+H): 231.1775. Found: 231.1777.

N-Benzyl-2,2-dimethoxyethanamine, **4**^{iv}



Benzaldehyde (23.4 mL, 0.23 mol) was added to a stirred solution of 2,2-dimethoxyethanamine (25 mL, 0.23 mol) in methanol (480 mL) at ambient temperature and the resulting mixture stirred for 16 h. The mixture was then cooled to 0 °C and sodium borohydride (13.0 g, 0.34 mol) was added portionwise. After stirring the mixture for 16 h at ambient temperature, the resultant solution was acidified to pH~9 with 2 M HCl. The methanol was then removed *in vacuo* and water (400 mL) was added. The pH was corrected again to pH~9 and the product was then extracted with ethyl acetate (x 3). The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated *in vacuo* to yield **4** as a colourless oil (41.1 g, 91%).

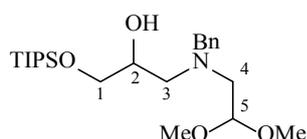
FTIR (CH₂Cl₂): 2837, 3030 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 2.77 (d, *J* = 5.5 Hz, 2H, H₂), 3.39 (s, 6H, OCH₃), 3.83 (s, 2H, benzylic CH₂), 4.51 (t, *J* = 5.5 Hz, 1H, H₁), 7.28-7.35 ppm (m, 5H, ArH).

¹³C NMR (100 MHz, CDCl₃): 50.6, 53.9, 54.0, 104.0, 127.0, 128.1, 128.4, 140.1 ppm.

HRMS *m/z* (ESI) calc for C₁₁H₁₈NO₂ (M⁺+H): 196.1332. Found: 196.1327.

5-Benzyl-10,10-diisopropyl-3-methoxy-11-methyl-2,9-dioxa-5-aza-10-siladodecan-7-ol



Epoxide **7** (24.1 g, 105 mmol) was added to a stirred solution of amine **4** (20.4 g, 105 mmol) in ethanol (500 mL) at ambient temperature. The mixture was heated to reflux and stirred at this temperature for 16 h. The mixture was then cooled and concentrated *in vacuo* to yield the title compound as a colourless oil (44.5, 100%).

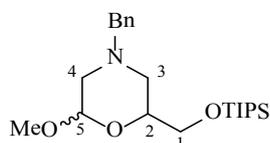
FTIR (CH₂Cl₂): 1267, 2867, 3031, 3452 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.04-1.10 (m, 21H, Si(CH(CH₃)₂)₃), 2.60-2.70 (m, 2H, H₃, H₄), 2.73-2.81 (m, 2H, H₃, H₄), 3.29 (s, 3H, OCH₃), 3.33 (s, 3H, OCH₃), 3.48 (s, 1H, OH), 3.64-3.78 (m, 4H, H₁, benzylic CH₂), 3.80-3.86 (m, 1H, H₂), 4.38 (t, *J* = 5.5 Hz, 1H, H₅), 7.31-7.36 ppm (m, 5H, ArH).

¹³C NMR (100 MHz, CDCl₃): 11.4, 17.5, 52.7, 53.4, 55.6, 57.8, 60.0, 65.3, 68.7, 102.9, 126.7, 127.8, 128.6, 138.4 ppm.

HRMS *m/z* (ESI) calc for C₂₃H₄₄NO₄Si (M⁺+H): 426.3034. Found: 426.3033.

4-Benzyl-2-methoxy-6-(((triisopropylsilyl)oxy)methyl)morpholine, **8**



5-Benzyl-10,10-diisopropyl-3-methoxy-11-methyl-2,9-dioxa-5-aza-10-siladodecan-7-ol

(44.5 g, 105 mmol) was added to a one-necked round bottom flask and *p*-toluenesulfonic acid (8.0 g, 41.8 mmol) was added. A plug of cotton wool was placed in the neck of the flask and the flask was placed into an oil bath which had been pre-heated to 115 °C. The reaction mixture was left to stir at this temperature for 16 h. The mixture was then diluted with CH₂Cl₂ and quenched with a saturated aqueous solution of sodium bicarbonate. The organic

layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (0-20% diethyl ether in petrol) to yield **8** as a mixture of diastereomers (35.8 g, 87%).

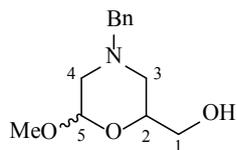
FTIR (CH₂Cl₂): 1270, 2867 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.02-1.09 (m, 21H, Si(CH(CH₃)₂)₃), 1.87-2.01 (m, 1.6H, H3, H4), 2.23 (dd, ²*J* = 11.7 Hz, *J* = 2.8 Hz, 0.4H, H4), 2.84-2.97 (m, 2H, H3, H4), 3.42 (s, 1.2H, OCH₃), 3.50 (s, 1.8H, OCH₃), 3.53-3.90 (m, 4.6H, H1, H2, benzylic CH₂), 4.05-4.12 (m, 0.4H, H2), 4.51 (dd, *J* = 8.5 Hz, *J* = 2.5 Hz, 0.6H, H5), 4.68 (bd, *J* = 2.4 Hz, 0.4H, H5), 7.29-7.39 ppm (m, 5H, ArH).

¹³C NMR (125 MHz, CDCl₃): 11.9, 17.9, 55.0, 55.1, 55.2, 55.7, 56.2, 56.8, 62.8, 63.4, 64.7, 65.0, 74.5, 97.3, 100.4, 127.2, 128.2, 129.2, 129.5, 136.7, 137.5 ppm.

HRMS *m/z* (ESI) calc for C₂₂H₄₀NO₃Si (M⁺+H): 394.2772. Found: 394.2771.

(4-Benzyl-6-methoxymorpholin-2-yl)methanol, **9**



Tetrabutylammonium fluoride (91 mL, 90.9 mmol, 1M in THF) was added to a stirred solution of **8** (35.8 g, 90.9 mmol) in dry THF (600 mL) at 0 °C. The solution was then allowed to stir at 0 °C for a further 2 h. The reaction mixture was quenched with a saturated aqueous solution of sodium bicarbonate and the organic layer was separated. The organic layer was dried over Na₂SO₄, and concentrated *in vacuo*. The alcohol was then purified by column chromatography (80% diethyl ether in petrol) to yield **9** as a colourless oil (19.3 g, 90%).

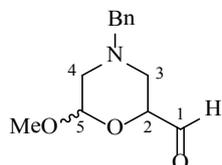
FTIR (CH₂Cl₂): 2883, 3031, 3598 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.93-2.03 (m, 1.6H, H3, H4), 2.27 (dd, ²*J* = 11.7 Hz, *J* = 2.9 Hz, 0.4H, H4), 2.72-2.74 (m, 0.6H, H3), 2.75-2.77 (m, 0.4H, H3), 2.85-2.92 (m, 1H, H4), 3.44 (s, 1.2H, OCH₃), 3.49-3.75 (m, 5.8H, OCH₃, H1, benzylic CH₂), 3.76-3.83 (m, 0.6H, H2), 4.06-4.14 (m, 0.4H, H2), 4.57 (dd, *J* = 8.4 Hz, *J* = 2.4 Hz, 0.6H, H5), 4.74 (bs, 0.4H, H5), 7.28-7.35 ppm (m, 5H, ArH).

^{13}C NMR (125 MHz, CDCl_3): 53.4, 53.6, 55.2, 55.7, 56.5, 56.7, 62.7, 63.3, 63.8, 64.2, 69.0, 74.3, 97.4, 100.6, 127.3, 128.3, 128.4, 129.2, 129.5, 136.7, 137.4 ppm.

HRMS m/z (ESI) calc for $\text{C}_{13}\text{H}_{20}\text{NO}_3$ (M^+H): 238.1438. Found: 238.1440.

4-Benzyl-6-methoxymorpholine-2-carbaldehyde, **10**



DMSO (13.3 mL, 187.1 mmol) was added slowly to a stirred solution of oxalyl chloride (9.0 mL, 105.7 mmol) in dry CH_2Cl_2 (180 mL) at $-60\text{ }^\circ\text{C}$. The mixture was stirred at this temperature for 10 minutes and then **9** (19.3 g, 81.3 mmol), as a solution in dry CH_2Cl_2 (60 mL), was slowly added. The reaction mixture was stirred for a further 15 min before triethylamine (57 mL, 406.7 mmol) was added. The mixture was then warmed to $0\text{ }^\circ\text{C}$ and toluene (15 mL) was added. The slurry was concentrated *in vacuo* to remove only the CH_2Cl_2 . The slurry was purified by column chromatography (80% diethyl ether in petrol) to yield **10** as a pale yellow oil (18.8 g, 98%).

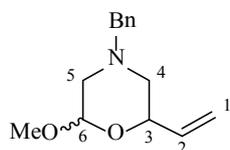
FTIR (CH_2Cl_2): 1737 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): 2.18-2.33 (m, 1.5H, H3, H4), 2.40 (dd, $^2J = 11.7\text{ Hz}$, $J = 3.1\text{ Hz}$, 0.5H, H4), 2.76-2.83 (m, 1.5H, H3, H4), 2.93-2.98 (m, 0.5H, H4), 3.47-3.60 (m, 5H, OCH_3 , benzylic CH_2), 4.09 (dd, $J = 8.7\text{ Hz}$, $J = 3.3\text{ Hz}$, 0.5H, H2), 4.47 (dd, $J = 9.7\text{ Hz}$, $J = 3.2\text{ Hz}$, 0.5H, H2), 4.64 (dd, $J = 6.8\text{ Hz}$, $J = 2.5\text{ Hz}$, 0.5H, H5), 4.82 (apparent t, $J = 2.5\text{ Hz}$, 0.5H, H5), 7.26-7.37 (m, 5H, ArH), 9.65 (s, 0.5H, H1), 9.74 ppm (s, 0.5, H1).

^{13}C NMR (125 MHz, CDCl_3): 51.0, 51.1, 55.1, 55.2, 55.9, 56.1, 62.1, 62.4, 73.7, 77.5, 97.1, 99.6, 127.0, 127.9, 128.6, 128.8, 135.8, 136.3, 199.8, 200.2 ppm.

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

4-Benzyl-2-methoxy-6-vinylmorpholine, **11**



KHMDS (39 mL, 19.6 mmol, 0.5 M in toluene) was slowly added to a stirred mixture of aldehyde **10** (4.2 g, 17.9 mmol) and methyltriphenylphosphonium bromide (7.0 g, 19.6 mmol) in dry THF (200 mL) at -78 °C. The resultant mixture was then warmed to -50 °C and stirred at this temperature for 50 min during which time the reaction mixture turned bright yellow in colour. The reaction mixture was then warmed to ambient temperature and quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-30% diethyl ether in petrol) to yield **11** (2.5 g, 59%) as a pale yellow oil.

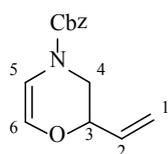
FTIR (CH₂Cl₂): 1649 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.89-2.04 (m, 1.6H, H4, H5), 2.26 (dd, ²J = 11.6 Hz, J = 2.8, 0.4H, H5), 2.70-2.93 (m, 2H, H4, H5), 3.43 (s, 1.2H, OCH₃), 3.53-3.56 (m, 3.8H, OCH₃, benzylic CH₂), 4.12-4.18 (m, 0.6H, H3), 4.46-4.52 (m, 0.4H, H3), 4.52 (dd, J = 8.5 Hz, J = 2.4, 0.6H, H6), 4.73 (bd, J = 2.4 Hz, 0.4H, H6), 5.16-5.21 (m, 1H, H1), 5.30-5.38 (m, 0.4H, H1), 5.61 (dt, J = 7.3 Hz, ⁴J = 1.5 Hz, 0.6H, H1), 5.76-5.91 (m, 1H, H2), 7.28-7.36 ppm (m, 5H, ArH).

¹³C NMR (100 MHz, CDCl₃): 54.6, 54.9, 55.9, 56.0, 56.6, 56.8, 62.1, 62.7, 74.0, 96.9, 99.9, 115.9, 116.2, 126.7, 126.8, 127.7, 127.8, 128.7, 128.9, 135.1, 135.7, 136.3, 136.9 ppm.

HRMS *m/z* (ESI) calc for C₁₄H₂₀NO₂ (M⁺+H): 234.1489. Found: 234.1483.

Benzyl 2-vinyl-2H-1,4-oxazine-4(3H)-carboxylate, **12**



Benzylchloroformate (2.4 mL, 17.2 mmol) was added to a stirred solution of **11** (2.5 g, 10.7 mmol) in CH₂Cl₂ (70 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene (200 mL) and *p*-toluenesulfonic acid (814 mg, 4.3 mmol) was added the mixture. The mixture was then stirred at reflux for 2 h using Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The oil was then

purified by column chromatography (0-40% diethyl ether in petrol) to yield **12** (1.8 g, 67%) as a pale yellow oil.

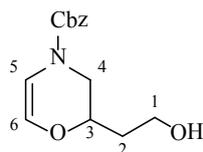
FTIR (CH₂Cl₂): 1701, 1662 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 3.20-3.33 (m, 1H, H4), 3.97-4.02 (m, 0.4H, H4), 4.08-4.13 (m, 0.6H, H4), 4.35-4.45 (m, 1H, H3), 5.22 (s, 2H, benzylic CH₂), 5.30-5.36 (m, 1H, H1), 5.40-5.47 (m, 1H, H1), 5.82-5.94 (m, 1H, H2), 5.97 (d, *J* = 5.0 Hz, 0.6H, H5), 6.10 (d, *J* = 5.0 Hz, 0.4H, H5), 6.24 (d, *J* = 5.0 Hz, 0.6H, H6), 6.37 (d, *J* = 5.0 Hz, 0.4H, H6), 7.32-7.45 ppm (m, 5H ArH).

¹³C NMR (100 MHz, CDCl₃): 45.8, 45.5, 67.2, 71.4, 73.1, 73.6, 104.8, 105.3, 117.7, 117.9, 127.5, 127.6, 127.7, 127.8, 128.1, 128.2, 129.1, 129.3, 133.1, 135.6 ppm.

HRMS *m/z* (ESI) calc for C₁₄H₁₉N₂O₃ (M⁺+NH₄): 246.1125. Found: 246.1128.

Benzyl 2-(2-hydroxyethyl)-2H-1,4-oxazine-4(3H)-carboxylate, 13



9-BBN (4.2 mL, 2.1 mmol, 0.5 M in THF) was added to a stirred solution of **12** (340 mg, 1.4 mmol) in dry THF (14 mL) and the resultant solution was stirred at ambient temperature for 16 h. The reaction mixture was then cooled to 0 °C and water (1.4 mL), followed by 3 M NaOH (3.7 mL) and 30% aqueous hydrogen peroxide (2.7 mL) were added. The reaction mixture was then stirred for a further 1 h at 0 °C before being diluted with diethyl ether and the organics separated. The aqueous phase was extracted (x 2) with diethyl ether, the extracts were combined, and a saturated aqueous solution of sodium metabisulfite was added. After stirring the mixture vigorously for 10 min, the organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (40-80% diethyl ether in petrol) to yield **13** (365 mg, 68%) as a colourless oil.

FTIR (CH₂Cl₂): 1662, 1697, 3414 cm⁻¹.

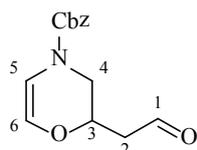
¹H NMR (400 MHz, CDCl₃): 1.81-1.92 (m, 3H, H2, OH), 3.18 (dd, ²*J* = 12.8 Hz, *J* = 8.3 Hz, 0.6H, H4), 3.26 (dd, ²*J* = 13.1 Hz, *J* = 8.4 Hz, 0.4H, H4), 3.80-3.87 (m, 2H, H1) 4.05-4.16 (m, 2H, H3, H4), 5.20 (s, 2H, benzylic CH₂), 5.88 (d, *J* = 5.0 Hz, 0.6H, H5), 6.02 (d, *J* = 5.0

Hz, 0.4H, H5), 6.23 (d, $J = 5.0$ Hz, 0.6H, H6), 6.36 (d, $J = 5.0$ Hz, 0.4H, H6), 7.31-7.43 ppm (m, 5H, ArH).

^{13}C NMR (125 MHz, CDCl_3): 34.6, 34.7, 45.6, 46.3, 59.4, 67.7, 67.7, 71.7, 72.3, 105.5, 106.0, 128.1, 128.3, 128.6, 129.3, 136.1, 151.9, 152.2 ppm.

HRMS m/z (ESI) calc for $\text{C}_{14}\text{H}_{18}\text{NO}_4$ (M^+H): 264.1230. Found: 264.1223.

Benzyl 2-(2-oxoethyl)-2H-1,4-oxazine-4(3H)-carboxylate, **14**



DMP (1.89 g, 4.43 mmol) was added to a stirred solution of alcohol **13** (1.06 g, 4.03 mmol) in dry CH_2Cl_2 (25 mL). The reaction mixture was stirred at ambient temperature for 30 min during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and CH_2Cl_2 was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% aqueous solution of sodium thiosulfate and saturated aqueous solution of sodium bicarbonate (300 mL) was added. The organic layer was separated, washed with brine, dried over sodium thiosulfite, and concentrated *in vacuo*. The resultant oil was purified by column chromatography, (60% diethyl ether in petrol) to yield **14** (751 mg, 75%) as a colourless oil.

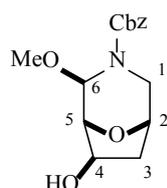
FTIR (CH_2Cl_2): 1662, 1697 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): 2.67-2.75 (m, 1H, H2), 2.77 (dd, $^2J = 7.7$ Hz, $J = 2.0$ Hz, 0.6H, H2), 2.79 (dd, $^2J = 7.8$ Hz, $J = 2.1$ Hz, 0.4H, H2), 3.26 (dd, $^2J = 13.0$ Hz, $J = 7.8$ Hz, 0.6H, H4), 3.34 (dd, $^2J = 13.3$ Hz, $J = 8.1$ Hz, 0.4H, H4), 3.96-4.07 (m, 1H, H4), 4.43-4.52 (m, 1H, H3), 5.17-5.23 (m, 2H, benzylic CH_2), 5.88 (d, $J = 5.2$ Hz, 0.6H, H5), 6.01 (d, $J = 5.2$ Hz, 0.4H, H5), 6.25 (d, $J = 5.2$ Hz, 0.6H, H6), 6.37 (d, $J = 5.2$ Hz, 0.4H, H6), 7.32-7.43 (m, 5H, ArH), 9.79-9.82 ppm (m, 1H, H1).

^{13}C NMR (125 MHz, CDCl_3): 44.9, 45.6, 45.7, 67.8, 67.9, 68.2, 68.7, 105.6, 106.1, 128.0, 128.1, 128.2, 128.4, 128.6, 129.1, 135.9, 136.0, 151.9, 152.2, 198.5, 198.7 ppm.

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

Benzyl 7-hydroxy-2-methoxy-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, **15**



Methanol (36 μ L, 0.89 mmol) followed by *p*-toluenesulfonic acid (9 mg, 0.045 mmol) were added to a stirred solution of **14** (117 mg, 0.45 mmol) in acetonitrile (4.3 mL) at ambient temperature. The reaction mixture was stirred for 16 h before being quenched with a saturated aqueous solution of sodium bicarbonate. The solution was diluted with diethyl ether and the organics were separated. The aqueous was extracted with diethyl ether (x 2) and the combined organics were dried over Na_2SO_4 and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (100% diethyl ether) to yield **15** (93 mg, 71%) as a colourless oil.

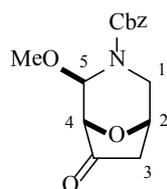
FTIR (CH_2Cl_2): 1697, 3449 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): 1.62 (bs, 1H, OH), 1.86 (dd, $^2J = 7.5$ Hz, $J = 2.7$ Hz, 0.5H, H3), 1.89 (dd, $^2J = 7.1$ Hz, $J = 2.2$ Hz, 0.5H, H3), 2.19, (dd, $^2J = 13.3$ Hz, $J = 7.4$ Hz, 0.5H, H3), 2.26 (dd, $^2J = 13.9$ Hz, $J = 7.7$ Hz, 0.5H, H3), 3.29-3.60 (m, 5H, H1, OCH_3), 4.15 (bs, 0.5H, H5), 4.23 (bs, 0.5H, H5), 4.29 (dd, $^2J = 7.5$ Hz, $J = 2.6$ Hz, 0.5H, H4), 4.36 (dd, $^2J = 7.5$ Hz, $J = 2.5$ Hz, 0.5H, H4), 4.57 (d, $J = 7.3$ Hz, 0.5H, H2), 4.61 (d, $J = 7.3$ Hz, 0.5H, H2), 4.97 (d, $J = 1.4$ Hz, 0.5H, H6), 5.10 (d, $J = 1.6$ Hz, 0.5H, H6), 5.14-5.26 (m, 2H, benzylic CH_2), 7.28-7.50 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, CDCl_3): 38.4, 38.5, 44.6, 45.3, 54.8, 55.3, 67.2, 67.4, 72.1, 72.3, 74.2, 74.7, 80.9, 81.3, 82.8, 83.2, 127.4, 127.7, 127.9, 128.0, 128.1, 128.2, 128.3, 128.6 135.5, 151.3, 151.8 ppm.

HRMS m/z (ESI) calc for $\text{C}_{15}\text{H}_{19}\text{NO}_5\text{Na}$ ($\text{M}^+ + \text{Na}$): 316.1155. Found: 316.1159.

Benzyl 2-methoxy-7-oxo-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, **16**



DMSO (176 μ L, 2.27 mmol) was slowly added to a stirred solution of oxalyl chloride (110 μ L, 1.28 mmol) in dry CH_2Cl_2 (1.9 mL) at -60 $^\circ\text{C}$. The mixture was stirred at this

temperature for 10 minutes and **15** (289 mg, 0.99 mmol), as a solution in dry CH₂Cl₂ (0.9 mL), was added. The reaction mixture was stirred for a further 15 minutes before triethylamine (689 μL, 4.93 mmol) was slowly added. The mixture was then warmed to ambient temperature and stirred for a further 1 h before being quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated. The organic layer was washed with water (x 2) and brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (40% diethyl ether in petrol) to yield **16** as a colourless oil (137 mg, 48%).

FTIR (CH₂Cl₂): 1707, 1765 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 2.20-2.34 (m, 1H, H3), 2.63-2.73 (m, 1H, H3), 3.30 (s, 1.8H, OCH₃), 3.45 (s, 1.2H, OCH₃), 3.63-3.45 (m, 2H, H1), 4.07 (bs, 0.6H, H4), 4.14 (bs, 0.4H, H4), 4.74 (d, *J* = 7.3 Hz, 0.4H, H2), 4.82 (d, *J* = 7.3 Hz, 0.6H, H2), 5.04-5.27 (m, 3H, H5, benzylic CH₂), 7.31-7.42 ppm (m, 5H, ArH).

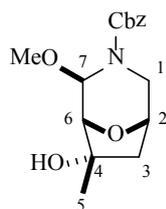
¹³C NMR (125 MHz, CDCl₃): 39.4, 44.0, 44.8, 55.9, 56.3, 65.8, 68.0, 68.1, 72.8, 73.3, 77.4, 80.7, 81.1, 128.0, 128.1, 128.4, 128.5, 128.6, 135.6, 135.7, 155.5, 155.9, 209.6, 210.3 ppm.

HRMS *m/z* (ESI) calc for C₁₅H₁₇NO₅Na (M⁺+Na): 314.0999. Found: 314.1001.

HRMS *m/z* (ESI) calc for C₁₅H₂₁N₂O₅ (M⁺+NH₄): 309.1445. Found: 309.1451.

Benzyl 7-hydroxy-2-methoxy-7-methyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate,

17



Lithium chloride (26 mg, 0.61 mmol) was placed in a three-necked round bottom flask which was flame dried under vacuum and allowed to cool under a blanket of nitrogen. Methylmagnesium chloride (3 M in THF, 204 μL, 0.61 mmol) was added and the resultant mixture was cooled to 0 °C. Ketone **16** (137 mg, 0.47 mmol), as a dry THF (2 mL) solution, was slowly added and the mixture was stirred at 0 °C for a further 2 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The resultant alcohol

was purified by column chromatography (60-80% diethyl ether in petrol) to yield **17** (105 mg, 72%) as a colourless oil.

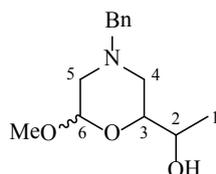
FTIR (CH₂Cl₂): 1688, 3447 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.42-1.49 (2 x overlapping s, 3H, H5), 1.77 (m, 1H, H3), 2.11 (m, 1H, H3), 3.29-3.83 (m, 6H, OCH₃, H1, H6), 4.28 (d, *J* = 7.4 Hz, 0.5H, H2), 4.35 (d, *J* = 7.4 Hz, 0.5H, H2), 5.14-5.23 (m, 2H, benzylic CH₂), 5.29 (s, 0.5H, H7), 5.36 (s, 0.5H, H7), 7.27-7.43 ppm (m, 5H, ArH).

¹³C NMR (100 MHz, CDCl₃): 30.0, 30.1, 42.5, 42.6, 45.1, 45.7, 55.0, 55.4, 67.1, 67.2, 73.8, 74.2, 77.1, 80.4, 80.7, 81.8, 82.3, 127.3, 127.4, 127.7, 128.0, 128.1, 135.7, 155.8, 156.0 ppm.

HRMS *m/z* (ESI) calc for C₁₆H₂₁NO₅Na (M⁺+Na): 330.1312. Found: 330.1314.

1-(4-Benzyl-6-methoxymorpholin-2-yl)ethanol, **18**



Lithium chloride (3.4 g, 80.8 mmol) was placed in a three-necked round bottom flask which was flame-dried under vacuum and allowed to cool under a blanket of nitrogen. Methylmagnesium chloride (3 M in THF, 27 mL, 80.8 mmol) was added and the resultant mixture was cooled to 0 °C. Aldehyde **10** (9.5 g, 40.4 mmol), as a dry THF (100 mL) solution, was slowly added and the mixture was stirred at 0 °C for a further 2 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The resultant alcohol (present as a mixture of diastereomers) was purified by column chromatography (60-80% diethyl ether in petrol) to yield **18** (9.4 g, 93%) as a colourless oil.

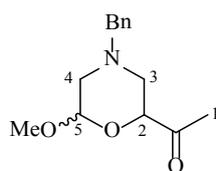
FTIR (CH₂Cl₂): 3032, 3599 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.17-1.24 (m, 3H, H1), 1.86-2.31 (m, 2H, H4, H5), 2.75-2.91 (m, 2H, H4, H5), 3.40-3.63 (m, 6H, benzylic CH₂, H2, OCH₃), 3.84-3.97 (m, 1H, H3), 4.52-4.57 (m, 0.5H, H6), 4.70-4.77 (m, 0.5H, H6), 7.30-7.37 ppm (m, 5H, ArH).

¹³C NMR (125 MHz, CDCl₃): 18.4, 18.5, 52.2, 55.1, 55.6, 56.4, 56.7, 62.9, 63.4, 68.4, 68.5, 71.9, 97.5, 100.6, 127.3, 128.3, 129.2, 129.5, 136.7, 137.5 ppm.

HRMS *m/z* (ESI) calc for C₁₄H₂₂NO₃ (M⁺+H): 252.1594. Found: 252.1595.

1-(4-Benzyl-6-methoxymorpholin-2-yl)ethanone, **19**



DMSO (6.1 mL, 86.0 mmol) was added slowly to a stirred solution of oxalyl chloride (4.2 mL, 48.6 mmol) in dry CH₂Cl₂ (83 mL) at -60 °C. The mixture was stirred at this temperature for 10 minutes and then **18** (9.4 g, 37.4 mmol), as a solution in dry CH₂Cl₂ (28 mL), was slowly added. The reaction mixture was stirred for a further 15 minutes before triethylamine (26 mL, 187.0 mmol) was added. The mixture was warmed to ambient temperature and allowed to stir for 1 h. The reaction mixture was quenched with saturated aqueous solution of ammonium chloride, and the organic layer was separated. After washing with water (x 2) and brine, the organic layer was dried over Na₂SO₄, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-50% diethyl ether in petrol) to yield **19** (7.0 g, 75%) as a pale yellow oil.

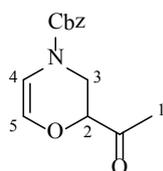
FTIR (CH₂Cl₂): 1718, 2828, 3031 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.91-2.04 (m, 1.5H, H3, H4), 2.08-2.15 (m, 0.5H, H4), 2.22 (s, 1H, H1), 2.29 (s, 2H, H1), 2.83-2.92 (m, 1H, H3), 3.00-3.14 (m, 1H, H4), 3.48 (s, 1.2H, OCH₃), 3.50-3.62 (m, 3.8H, benzylic CH₂, OCH₃), 4.09 (dd, *J* = 10.5 Hz, *J* = 2.9 Hz, 0.5H, H2), 4.45 (dd, *J* = 10.4 Hz, *J* = 2.9 Hz, 0.5H, H2), 4.56 (dd, *J* = 8.5 Hz, *J* = 2.4 Hz, 0.5H, H5), 4.80 (bs, 0.5H, H5), 7.29-7.56 ppm (m, 5H, ArH).

¹³C NMR (125 MHz, CDCl₃): 26.3, 53.0, 53.1, 55.3, 55.5, 56.2, 56.5, 62.5, 63.0, 74.3, 79.2, 97.5, 100.7, 127.4, 128.3, 128.4, 129.1, 129.4, 136.4, 137.0, 207.1, 207.2 ppm.

HRMS *m/z* (ESI) calc for C₁₄H₂₀NO₃ (M⁺+H): 250.1438. Found: 250.1440.

Benzyl 2-acetyl-2H-1,4-oxazine-4(3H)-carboxylate, **20**



Benzylchloroformate (6.4 mL, 44.7 mmol) was added to a stirred solution of **19** (7.0 g, 28.1 mmol) in CH₂Cl₂ (185 mL). The mixture was stirred at ambient temperature for 16 h before being concentrated *in vacuo*. The resultant oil was then dissolved in toluene (530 mL) and *p*-

toluenesulfonic acid (2.1 g, 11.2 mmol) was added the mixture. The mixture was then stirred at reflux for 2 h using Dean-Stark apparatus. The solution was then cooled to ambient temperature and quenched with a saturated aqueous solution of sodium bicarbonate. The organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The oil was then purified by column chromatography (0-40% diethyl ether in petrol) to yield **20** (4.1 g, 56%) as a pale yellow oil.

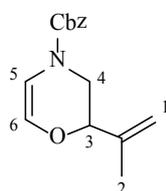
FTIR (CH₂Cl₂): 1666, 1710 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 2.30 (s, 3H, H1), 3.71 (dd, ²J = 13.2 Hz, J = 6.5 Hz, 0.5H, H3), 3.80 (dd, ²J = 13.4 Hz, J = 6.3 Hz, 0.5H, H3), 3.95 (bd, ²J = 13.4 Hz, 0.5H, H3), 4.05 (bd, ²J = 13.0 Hz, 0.5H, H3), 4.37-4.43 (m, 1H, H2), 5.17-5.26 (m, 2H, benzylic CH₂), 6.01 (d, J = 4.8 Hz, 0.5H, H4), 6.13 (d, J = 4.8 Hz, 0.5H, H4), 6.29 (d, J = 4.8 Hz, 0.5H, H5), 6.43 (d, J = 4.8 Hz, 0.5H, H5), 7.30-7.46 ppm (m, 5H, ArH).

¹³C NMR (125 MHz, CDCl₃): 26.2, 41.7, 42.2, 67.9, 78.1, 78.5, 106.5, 107.1, 127.6, 128.2, 128.4, 128.6, 135.7, 135.9, 148.0, 206.4 ppm.

HRMS *m/z* (ESI) calc for C₁₄H₁₆NO₄ (M⁺+H): 262.1074. Found: 262.1079.

Benzyl 2-(prop-1-en-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, 21



Potassium *tert*-butoxide (1.7 g, 15.4 mmol) was added portionwise to a stirred slurry of methyltriphenylphosphonium bromide (5.5 g, 15.4 mmol) in dry THF (100 mL) at 0 °C. The resultant yellow slurry was stirred at this temperature for 30 minutes. A solution of **20** (3.1 g, 11.9 mmol) in dry THF (20 mL) was added dropwise and the resultant slurry was stirred at 0 °C for a further 45 minutes. The mixture was then warmed to ambient temperature before being quenched with a saturated aqueous solution of ammonium chloride and extracted with diethyl ether. The organic layer was separated, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The resultant oil was purified by column chromatography (0-20% diethyl ether in petrol) to yield **21** (2.7 g, 87%) as a pale yellow oil.

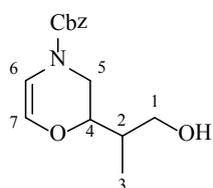
FTIR (CH₂Cl₂): 1665, 1703 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 1.79-1.82 (m, 3H, H2), 3.17 (dd, ²J = 13.0 Hz, J = 8.7 Hz, 0.6H, H4), 3.27 (dd, ²J = 12.8 Hz, J = 8.7 Hz, 0.4H, H4), 4.08 (bd, ²J = 12.3 Hz, 0.4H, H4), 4.18-4.28 (m, 1.6H, H3, H4), 5.04 (bs, 1H, H1), 5.09 (d, ²J = 5.6 Hz, 1H, H1), 5.18-5.27 (m, 2H, benzylic CH₂), 6.10 (d, J = 5.0 Hz, 0.6H, H5), 6.12 (d, J = 5.0 Hz, 0.4H, H5), 6.25 (d, J = 4.8 Hz, 0.6H, H6), 6.37 (d, J = 4.8 Hz, 0.4H, H6), 7.32-7.49 ppm (m, 5H, ArH).

¹³C NMR (100 MHz, CDCl₃): 18.2, 18.3, 44.3, 44.9, 67.2, 75.7, 76.1, 104.7, 105.2, 112.9, 113.2, 127.6, 127.7, 127.8, 128.1, 128.5, 129.6, 135.6, 140.5, 151.4, 151.7 ppm.

HRMS *m/z* (ESI) calc for C₁₅H₁₈NO₃ (M⁺+H): 260.1281. Found: 260.1286.

Benzyl 2-(1-hydroxypropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, **22**



9-BBN (14.4 mL, 7.2 mmol, 0.5 M in THF) was added to a stirred solution of **21** (1.1 g, 4.24 mmol) in dry THF (42 mL) and the resultant solution was stirred at ambient temperature for 16 h. The reaction mixture was then cooled to 0 °C and water (4.2 mL), followed by 3 M NaOH (12 mL) and 30% aqueous hydrogen peroxide (8.3 mL) were added. The reaction mixture was then stirred for a further 1 h at 0 °C before being diluted with diethyl ether and the organics separated. The aqueous phase was extracted (x 2) with diethyl ether, the extracts were combined, and a saturated aqueous solution of sodium metabisulfite was added. After stirring the mixture vigorously for 10 min, the organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The oil resultant was then purified by column chromatography (40-80% ether in petrol) to yield **22** (964 mg, 82%) as a colourless oil.

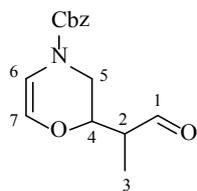
FTIR (CH₂Cl₂): 1665, 1694, 3477 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): 0.99-1.04 (m, 3H, H3), 1.89-2.01 (m, 2H, H2, OH), 3.22 (dd, ²J = 13.1 Hz, J = 8.7 Hz, 0.7H, H5), 3.35 (dd, ²J = 12.7 Hz, J = 8.7 Hz, 0.3H, H5), 3.69-3.76 (m, 2H, H1), 3.81-3.88 (m, 1H, H4), 3.97-4.06 (m, 0.3H, H5), 4.13-4.20 (m, 0.7H, H5), 5.16-5.27 (s, 2H, benzylic CH₂), 5.92-5.95 (m, 0.7H, H6), 6.04-6.06 (m, 0.3H, H6), 6.24-6.26 (m, 0.7H, H7), 6.36-6.38 (m, 0.3H, H7), 7.31-7.45 ppm (m, 5H, ArH).

¹³C NMR (125 MHz, CDCl₃): 13.2, 13.3, 37.2, 37.5, 44.0, 44.5, 65.5, 67.7, 67.8, 76.7, 105.7, 106.2, 128.1, 128.3, 128.6, 128.9, 129.3, 136.1, 152.2 ppm.

HRMS *m/z* (ESI) calc for C₁₅H₁₉NO₄Na (M⁺+Na): 300.1206. Found: 300.1211.

Benzyl 2-(1-oxopropan-2-yl)-2H-1,4-oxazine-4(3H)-carboxylate, **23**



DMP (471 mg, 1.11 mmol) was added to a stirred solution of alcohol **22** (280 mg, 1.01 mmol) in dry CH_2Cl_2 (6.3 mL). The reaction mixture was stirred at ambient temperature for 30 min during which time a white precipitate formed. The reaction mixture was diluted with diethyl ether and CH_2Cl_2 was removed *in vacuo*. The mixture was further diluted with diethyl ether and a 1:1 mixture of 10% sodium thiosulfite and saturated aqueous solution of sodium bicarbonate (100 mL) was added. The organic layer was separated, washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The resultant oil was purified by column chromatography (60% ether in petrol) to yield **23** (222 mg, 80%) as a colourless oil.

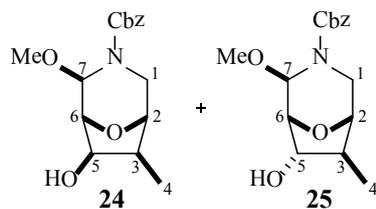
FTIR (CH_2Cl_2): 1662, 1699 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): 1.14-1.26 (m, 3H, H3), 2.60-2.72 (m, 1H, H2), 3.34 (dd, $^2J = 12.7$ Hz, $J = 7.7$ Hz, 0.6H, H5), 3.42 (dd, $^2J = 13.0$ Hz, $J = 7.9$ Hz, 0.4H, H5), 3.95-4.20 (m, 2H, H4, H5), 5.22 (s, 2H, benzylic CH_2), 5.91 (d, $J = 5$ Hz, 0.6H, H6), 6.05 (d, $J = 4.8$ Hz, 0.4H, H6), 6.27 (d, $J = 5.0$ Hz, 0.6H, H7), 6.39 (d, $J = 4.9$ Hz, 0.4H, H7), 7.33-7.44 (m, 5H, ArH), 9.71-9.80 ppm (m, 1H, H1).

^{13}C NMR (100 MHz, CDCl_3): 9.68, 42.7, 43.2, 47.1, 47.3, 67.4, 73.2, 73.7, 105.2, 105.8, 127.6, 127.7, 127.8, 127.9, 128.1, 128.8, 135.4, 201.4, 201.6 ppm.

Due to the sensitive nature of this product accurate mass spectral details could not be obtained.

**Benzyl 7-hydroxy-2-methoxy-6-methyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate,
24/25**



Methanol (65 μ L, 1.61 mmol) followed by *p*-toluenesulfonic acid (15 mg, 0.08 mmol) were added to a stirred solution of **23** (222 mg, 0.81 mmol) in acetonitrile (8 mL) at ambient temperature. The reaction mixture was stirred for 16 h before being quenched with a saturated aqueous solution of sodium bicarbonate. The solution was diluted with ether and the organics were separated. The aqueous layer was extracted with ether (x 2) and the combined organic extracts were dried over Na₂SO₄ and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (100% diethyl ether) to yield **24/25** (166 mg, 67%, 7:3 *dr*) as a colourless oil.

FTIR (CH₂Cl₂): 1679, 3488 cm⁻¹.

24/25 Mixture

¹H NMR (400 MHz, CDCl₃): 1.10-1.27 (m, 3H, H4), 1.82-2.13 (m, 1.3H, OH, H3), 2.12-2.37 (m, 0.7H, H3), 3.27-4.30 (m, 8H, H1, H2, H5, H6, OCH₃), 4.96-5.27 (m, 3H, H7, benzylic CH₂), 7.30-7.45 ppm (m, 5H, ArH).

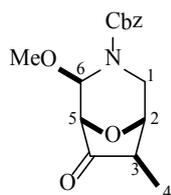
¹³C NMR (100 MHz, CDCl₃): 12.6, 12.7, 14.8, 19.1, 19.2, 29.8, 39.2, 39.4, 43.4, 44.6, 45.2, 45.3, 53.0, 54.8, 55.0, 55.5, 65.4, 67.1, 67.4, 73.2, 73.5, 77.5, 78.0, 79.0, 79.8, 80.0, 80.1, 80.5, 81.1, 81.5, 82.0, 83.8, 84.2, 127.4, 127.5, 127.6, 127.7, 127.8, 128.0, 128.1, 128.2, 135.4, 135.5, 155.3, 155.8 ppm.

Compound 25 (minor diastereomer)

¹H NMR (600 MHz, CDCl₃): 1.19-1.23 (m, 3H, H4), 1.80-1.85 (m, 0.4H, H3), 1.87-1.92 (m, 0.6H, H3), 3.30 (s, 1.2H, OCH₃), 3.39-3.42 (m, 2.4H, OCH₃, H1), 3.47-3.51 (0.4H, H1), 3.63-3.67 (m, 0.4H, H1), 3.74-3.76 (m, 1H, H1, H2), 3.83 (bs, 0.6H, H2), 3.94-3.98 (m, 1H, H5), 4.15-4.18 (m, 0.6H, H6), 4.23-4.26 (m, 0.4H, H6), 5.14-5.21 (m, 2H, benzylic CH₂), 5.21 (bs, 0.6H, H7), 5.29 (bs, 0.4H, H7), 7.29-7.38 ppm (m, 5H, ArH).

HRMS *m/z* (ESI) calc for C₁₆H₂₁NO₅Na (M⁺+Na): 330.1312. Found: 330.1316.

Benzyl 2-methoxy-6-methyl-7-oxo-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, **26**



DMSO (60 μL , 0.83 mmol) was slowly added to a stirred solution of oxalyl chloride (40 μL , 0.47 mmol) in dry CH_2Cl_2 (1 mL) at -60°C . The mixture was stirred at this temperature for 10 minutes and a mixture of **24** and **25** (7:3, 111 mg, 0.36 mmol), as a solution in dry CH_2Cl_2 (0.5 mL), was added. The reaction mixture was stirred for a further 15 minutes before triethylamine (252 μL , 1.81 mmol) was slowly added. The mixture was then warmed to ambient temperature, quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated. The organic layer was washed with water (x 2) and brine, dried over Na_2SO_4 , and concentrated *in vacuo*. The resultant oil was then purified by column chromatography (40% diethyl ether in petrol) to yield **26** as a colourless oil (81 mg, 74%).

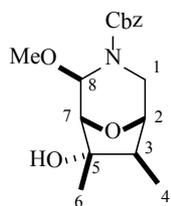
FTIR (CH_2Cl_2): 1701, 1769 cm^{-1} .

^1H NMR (400 MHz, CDCl_3): 1.24-1.42 (m, 3H, H4), 2.24-2.45 (m, 1H, H3), 3.31 (s, 1.8H, OCH_3), 3.47 (s, 1.2H, OCH_3), 3.62-3.89 (m, 2H, H1), 4.10-4.48 (m, 2H, H2, H5), 5.03-5.33 (m, 3H, benzylic CH_2 , H6), 7.30-7.53 ppm (m, 5H, ArH).

^{13}C NMR (100 MHz, CDCl_3): 14.3, 14.4, 43.2, 43.6, 44.3, 55.2, 55.9, 67.5, 67.6, 77.2, 77.5, 78.7, 79.2, 80.2, 80.6, 127.6, 127.9, 128.1, 131.2, 132.2, 135.1, 135.2, 141.3, 154.2, 155.4 ppm.

HRMS m/z (ESI) calc for $\text{C}_{16}\text{H}_{23}\text{N}_2\text{O}_5$ ($\text{M}^+ + \text{NH}_4$): 323.1601. Found: 323.1608.

Benzyl 7-hydroxy-2-methoxy-6,7-dimethyl-8-oxa-3-azabicyclo[3.2.1]octane-3-carboxylate, **27**



Lithium chloride (15 mg, 0.35 mmol) was placed in a three-necked round bottom flask which was flame-dried under vacuum and allowed to cool under a blanket of nitrogen. Methylmagnesium chloride (3 M in THF, 117 μL , 0.35 mmol) was added and the resultant

mixture was cooled to 0 °C. Ketone **26** (62 mg, 0.20 mmol), as a dry THF (1 mL) solution, was slowly added and the mixture was stirred at 0 °C for a further 3 h. The reaction mixture was then quenched with a saturated aqueous solution of ammonium chloride and the organic layer was separated, dried over Na₂SO₄, and concentrated *in vacuo*. The resultant alcohol was purified by column chromatography (60-80% diethyl ether in petrol) to yield **27** (46 mg, 70%) as a colourless oil.

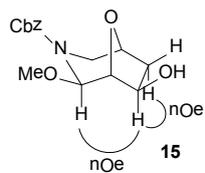
FTIR (CH₂Cl₂): 1688, 3466 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): 1.09-1.16 (m, 3H, H4), 1.30-1.32 (2 x overlapping s, 3H, H6), 1.96-2.12 (m, 1H, H3), 3.28 (s, 1.2H, OCH₃), 3.38-3.41 (m, 2.2H, OCH₃, H1), 3.46-3.49 (m, 0.6H, H1), 3.62-3.65 (m, 0.4H, H1), 3.69-3.71 (m, 0.6H, H7), 3.72-3.75 (m, 0.6H, H1), 3.75-3.78 (m, 0.8H, H2, H7), 3.83-3.85 (m, 0.6H, H2), 5.14-5.21 (m, 2H, benzylic CH₂), 5.27 (bs, 0.6H, H8), 5.34 (bs, 0.4H, H8), 7.28-7.37 ppm (m, 5H, ArH).

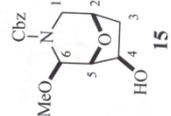
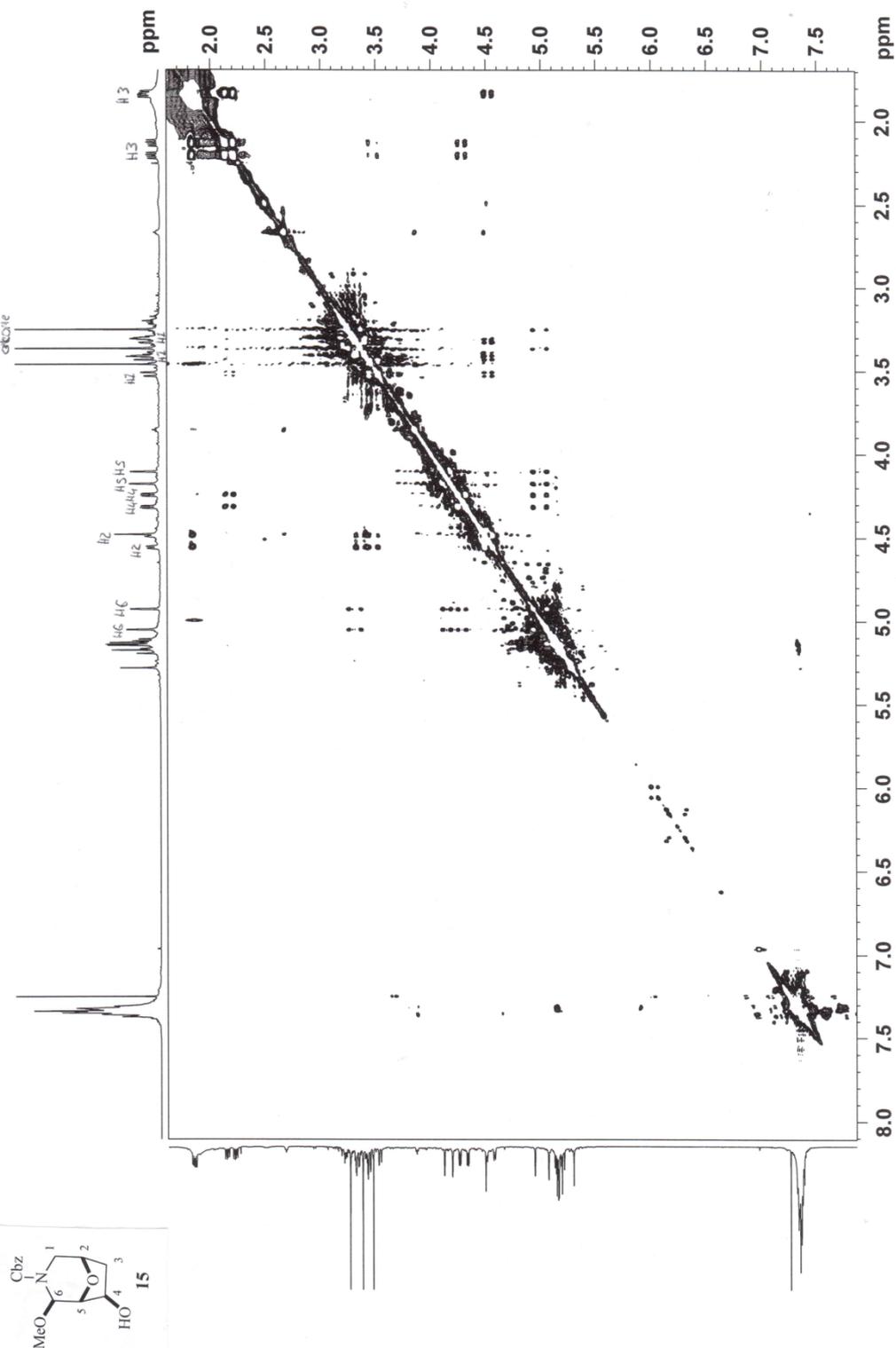
¹³C NMR (100 MHz, CDCl₃): 14.6, 14.7, 24.2, 24.3, 44.9, 45.6, 45.9, 55.0, 55.5, 67.1, 67.2, 79.2, 80.2, 80.5, 81.2, 81.6, 83.5, 84.0, 127.4, 127.5, 127.7, 127.8, 128.1, 135.7, 155.7, 155.9 ppm.

HRMS *m/z* (ESI) calc for C₁₇H₂₃NO₅Na (M⁺+Na): 344.1468. Found: 344.1467.

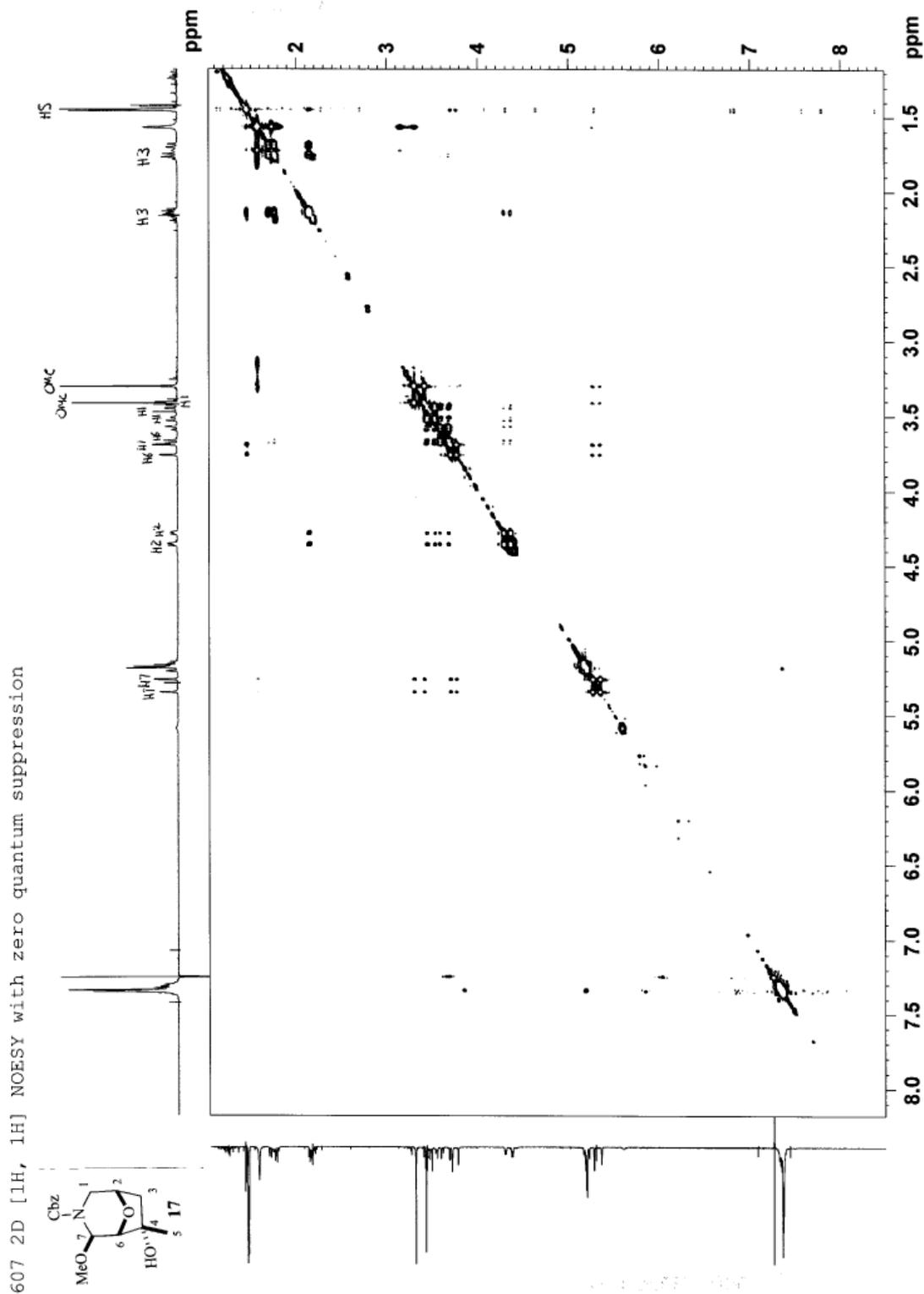
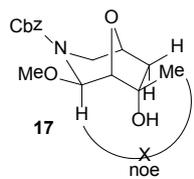
3. NOESY Spectrum for Compound 15



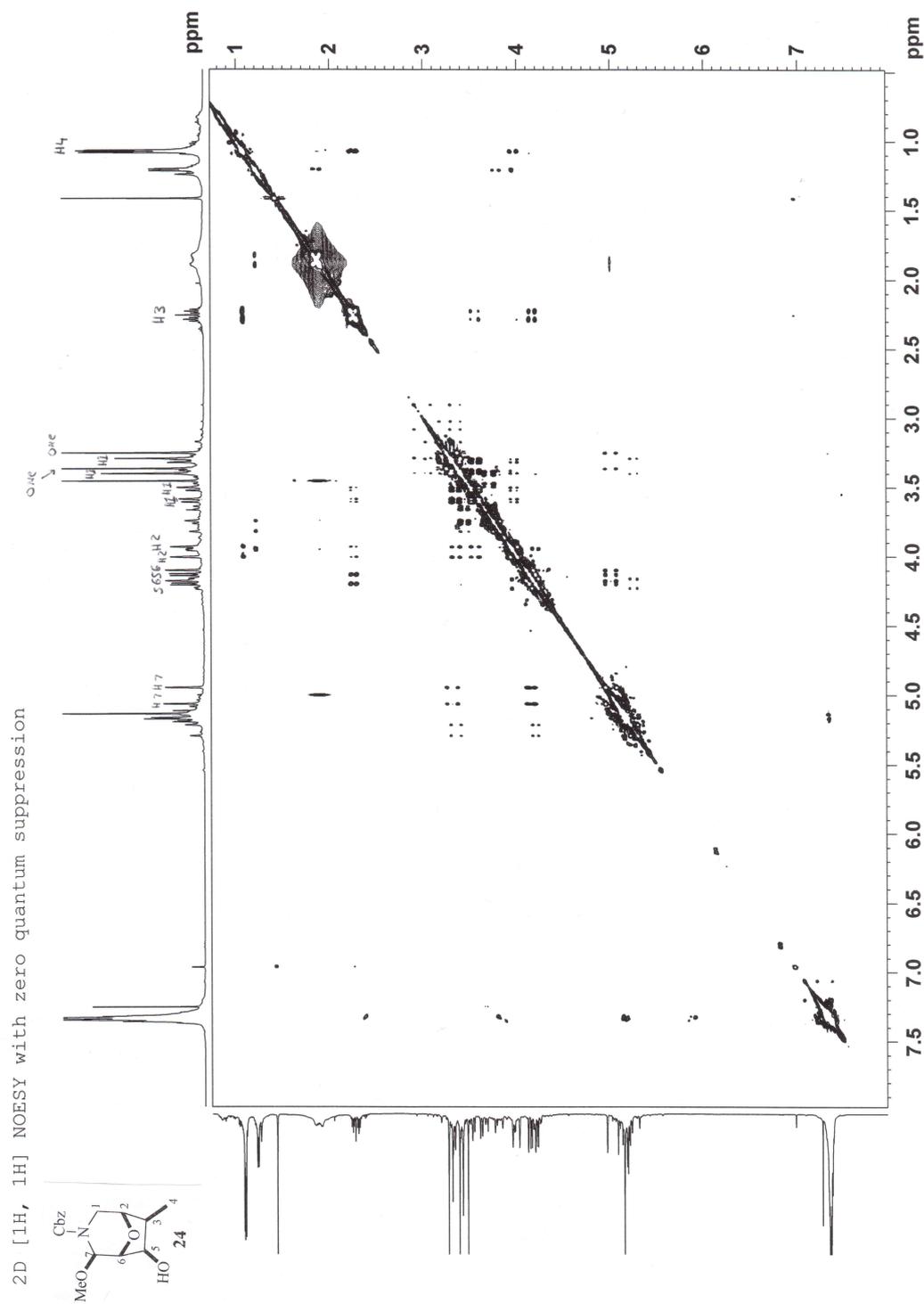
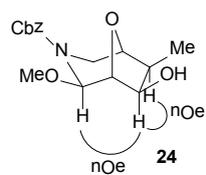
2D [¹H, ¹H] NOESY with zero quantum suppression



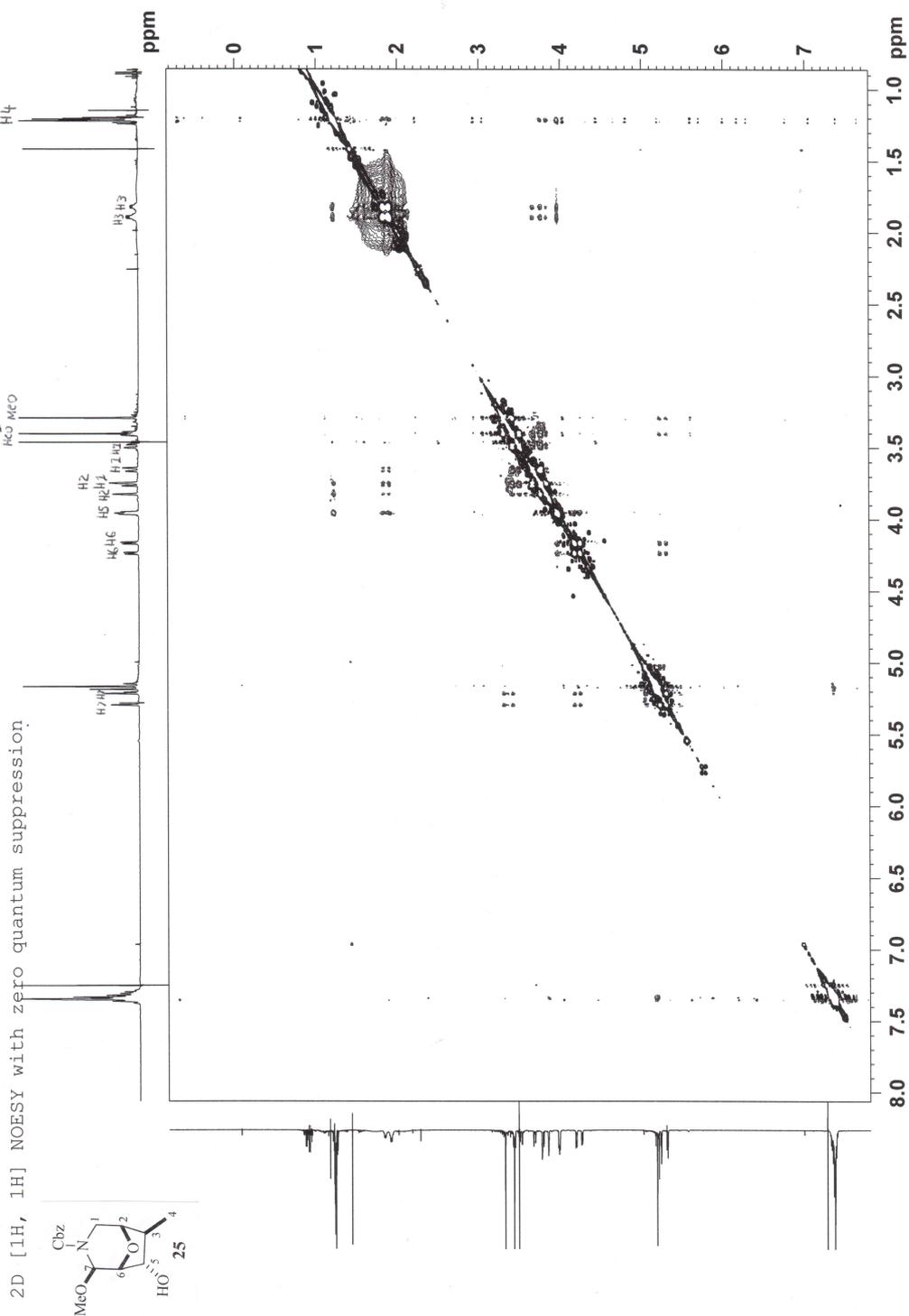
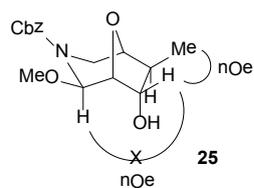
4. NOESY Spectrum for Compound 17



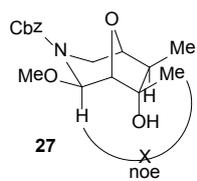
5. NOESY Spectrum for Compound 24



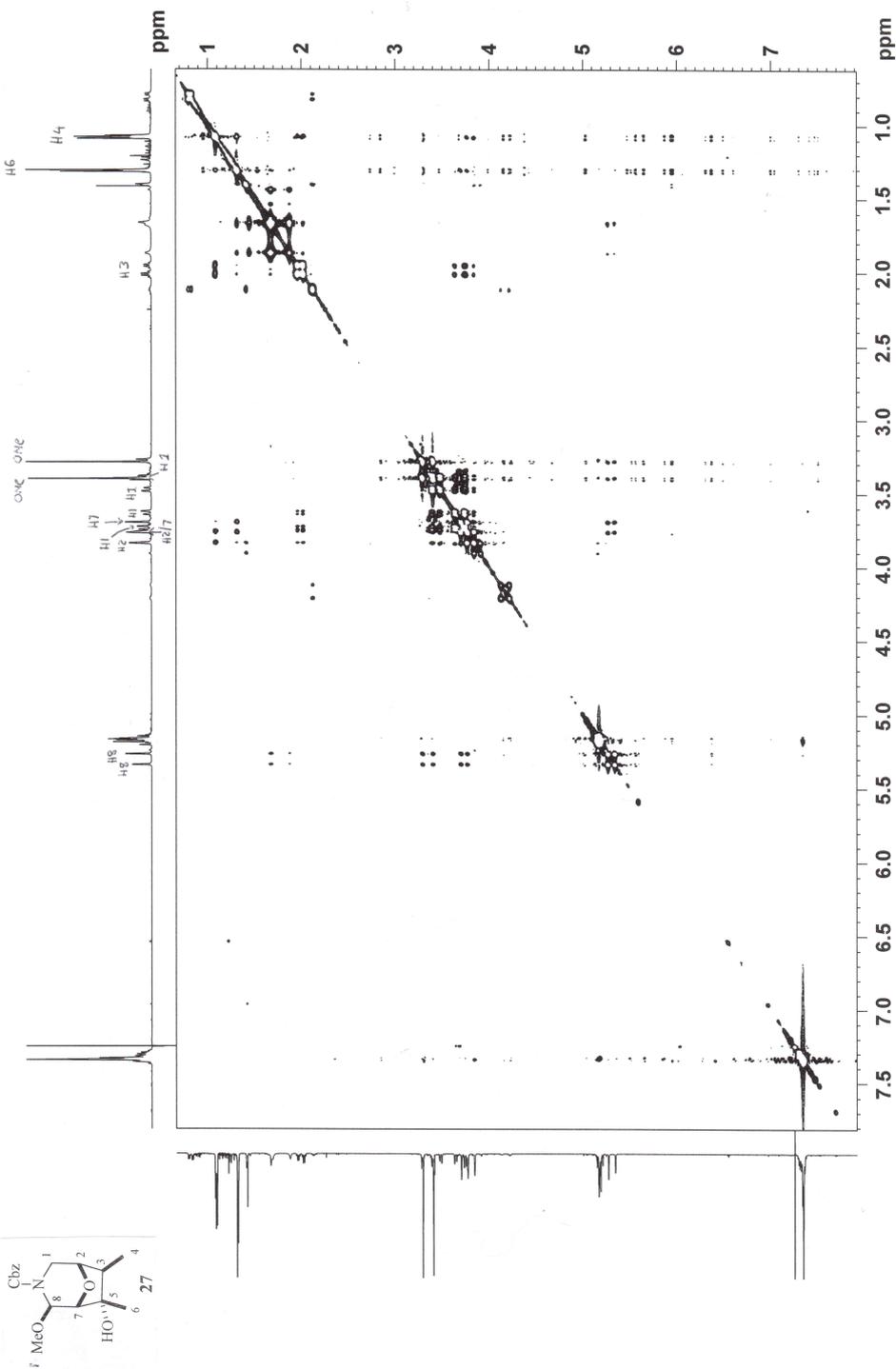
6. NOESY Spectrum for Compound 25



7. NOESY Spectrum for Compound 27



607 2D [1H, 1H] NOESY with zero quantum suppression



8. References

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- ii. H. Brice, D. M. Gill, L. Goldie, P. S. Keegan, W. J. Kerr and P. H. Svensson, *Chem. Commun.*, 2012, **48**, 4836.
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- iv. M. Boisbrum, L. Jeannin, L. Toupet and J.-V. Laronze, *Eur. J. Org. Chem.*, 2000, 3051.