

Electronic Supporting Information

Asymmetric synthesis of synthetic alkaloids by a biocatalysis/Ugi/Pictet-Spengler sequence

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| Item | Page |
|--|------|
| General information | S2 |
| Experimental procedures | S2 |
| References | S12 |
| Copies of ¹ H and ¹³ C NMR spectra | S13 |
| Crystallographic data | S35 |

General Information

Starting materials and solvents were purchased from ABCR and Sigma-Aldrich and were used without treatment. 3-Azabicyclo[3,3,0]octane hydrochloride was purchased from AK Scientific. (1*R*,2*S*,6*R*,7*S*)-4-methyl-4-azatricyclo[5.2.1.0^{2,6}]dec-8-ene was prepared according to literature procedure.¹ Column chromatography was performed on silica gel. ¹H and ¹³C NMR spectra were recorded on a Bruker Avance 400 (400.13 MHz for ¹H and 100.61 MHz for ¹³C) or Bruker Avance 500 (500.23 MHz for ¹H and 125.78 MHz for ¹³C) in CDCl₃. Chemical shifts are reported in δ values (ppm) downfield from tetramethylsilane.

Electrospray Ionisation (ESI) mass spectrometry was carried out using a Bruker micrOTOF-Q instrument in positive ion mode (capillary potential of 4500 V).

Infrared (IR) spectra were recorded neat, and wavenumbers are reported in cm⁻¹. Optical rotations were measured with a sodium lamp and are reported as follows: $[\alpha]_D^{20}$ (c = g/100 mL, solvent).

2-(2-isocyanoethyl)-1*H*-indole **17**, 4-(isocyanomethyl)-1,2-dimethoxybenzene **13** and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene **8** were synthesized according to literature procedures.²

General Procedure 1: Preparation of optically active imines (3*S*,7*R*)-**11** and azabicyclo-[3,3,0]oct-2-ene

Unless stated otherwise: imines were synthesized according to literature procedure³ with minor adjustments. 0.7 g of freeze-dried MAO-N D5 *E. coli* were rehydrated for 30 min. in 20 ml of KPO₄ buffer (100 mM, pH = 8,0) at 37 °C. Subsequently 1 mmol amine ((3*S*,7*R*)-**11** or azabicyclo-[3,3,0]oct-2-ene) in 30 ml of KPO₄ buffer (100 mM, pH = 8,0) was prepared. The pH of the solution was adjusted to 8.0 by addition of NaOH and then added to the rehydrated cells. After 16-17 h the reaction was stopped (conversions were > 95 %) and worked up. For workup the reaction mixture was centrifuged at 4000 rpm and 4 °C until the supernatant had clarified (40 – 60 minutes). The pH of the supernatant was then adjusted to 10-11 by addition of aq. NaOH and the supernatant was subsequently extracted with *t*-butyl methyl ether or dichloromethane (4 × 70 mL). The combined organic phases were dried with Na₂SO₄ and concentrated at the rotary evaporator.

General procedure 2: Preparation of optically active Ugi derivatives 14a-d, 18a-c and 20-22

Unless stated otherwise: Ugi derivatives were synthesised according to literature procedure.⁴

Imine (0.70 mmol) was dissolved in 2 ml of CH₂Cl₂ followed by the addition of carboxylic acid (0.93 mmol) and isocyanide (0.93 mmol). The reaction mixture was stirred for 24 h at RT. CH₂Cl₂ (8 mL) was added and the resulting mixture was washed with Na₂CO₃ (2 × 10 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Subsequently the crude product was subjected to column chromatography (SiO₂, EtOAc (1): cyclohexane (1)). After concentration *in vacuo*, the pure oily compound was

dissolved in a CH₂Cl₂/hexane mixture and concentrated to give the product as a solid.
Note: Rotamer formation and traces of hexane might be observed in the NMR data.

General procedure 3: Preparation of DKP derivatives 15a-b, 16, 19a-c and 23-25 via a Pictet-Spengler cyclization

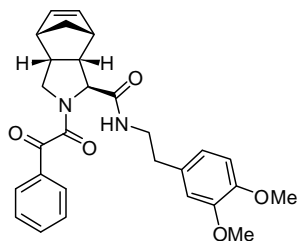
Unless stated otherwise: A dry 500 ml flask with activated 4 Å molecular sieves was prepared. Ugi derivative (0.25 mmol) was dissolved in 300 ml dry CH₂Cl₂ and cooled down to -10°C. 1.3 eq. (0.325 mmol) of TMSOTf was dissolved in 5 ml dry CH₂Cl₂ and dropwise added in 5 h to the mixture while stirring the flask. After complete addition of the TMSOTf the mixture was allowed to warm up to room temperature. The reaction mixture was stirred for another 11 h. The resulting mixture was filtered and washed with NaHCO₃ (2 × 20 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Subsequently the crude product was subjected to column chromatography (SiO₂, EtOAc (1): cyclohexane (1)). After concentration *in vacuo*, the pure oily compound was dissolved in a CH₂Cl₂/hexane mixture and concentrated to give the product as a solid.

Note: Traces of hexane might be observed in the NMR data.

General procedure 4: Preparation of DKP derivatives 15c and 16 via a Pictet-Spengler cyclization

Unless stated otherwise: A dry 50 ml flask with activated 4 Å molecular sieves was prepared. Ugi derivative (0.25 mmol) was dissolved in 10 ml dry CH₂Cl₂ and 10 ml TFA. 1.0 eq. (0.25 mmol) of trifluoroacetic anhydride was added in and subsequently stirred for 16 h. The resulting mixture was filtered and washed with NaHCO₃ (2 × 20 mL), dried (MgSO₄), filtered, and concentrated *in vacuo*. Subsequently the crude product was subjected to column chromatography (SiO₂, EtOAc (1): cyclohexane (1)). After concentration *in vacuo*, the pure oily compound was dissolved in a CH₂Cl₂/hexane mixture and concentrated to give the product as a solid.

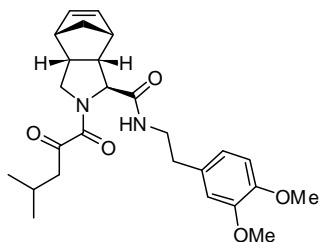
Note: Traces of hexane might be observed in the NMR data.



Compound 14a: General procedure 2 was followed using imine (94.4 mg, 0.709 mmol), phenylglyoxylic acid (138.6 mg, 0.923 mmol) and 4-(2-isocyanoethyl)-1,2-dimethoxybenzene (160.9 mg, 0.842 mmol) giving **14a** as a pale yellow solid, yield 72%.

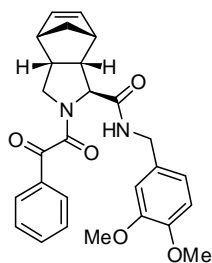
$[\alpha]_D^{20} = -18.2$ (c = 0.440, MeCN). ¹H NMR (500.23 MHz, CDCl₃), δ 7.91 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.67-7.64 (m, 1H), 7.53-7.49 (m, 2H), 6.80 (d, *J* = 8.3 Hz, 1H), 6.75 (d, *J* = 1.9 Hz, 1H), 6.72-6.69 (m, 1H), 6.64 (bs, 1H), 6.25 (dd, *J* = 5.7, 3.0 Hz, 1H), 6.00 (dd, *J* = 5.7, 3.0 Hz, 1H), 4.32 (d, *J* = 2.1 Hz, 1H), 3.86 (s, 3H), δ 3.83 (s, 3H), 3.81-3.80 (m, 1H), 3.54-3.40 (m, 3H), 3.10 (m, 2H), 2.94-2.89 (m, 1H), 2.87-2.83 (m, 1H), 2.77 (t, *J* = 7.2 Hz, 2H), 1.53-1.51 (m, 1H), 1.43-1.40 (m, 1H); ¹³C NMR (125.78 MHz, CDCl₃), δ = 191.0, 170.2, 164.8, 149.0, 147.7, 135.4, 134.9, 134.7, 132.5, 131.2, 129.9, 129.1, 120.7, 111.9, 111.4, 64.5, 62.2, 55.9, 55.8, 51.7, 49.8, 47.2, 46.6, 45.0, 41.2,

35.0; IR (neat): ν_{\max} (cm^{-1}) = 3320 (w), 2930 (w), 1676 (m), 1628 (s), 1514 (m), 1443 (m), 1260 (s), 1234 (s), 1140 (m), 1026 (s), 714 (s), 665 (s); HRMS (ESI+) calcd for $\text{C}_{28}\text{H}_{31}\text{N}_2\text{O}_5$ ($[\text{M}+\text{H}]^+$) 475.2155, found 475.2213.



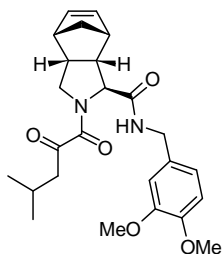
Compound 14b: General procedure 2 was followed using imine (70.5 mg, 0.529 mmol), 4-methyl-2-oxopentanoic acid (89.6 mg, 85 μL , 0.688 mmol) and 4-(2-isocianoethyl)-1,2-dimethoxybenzene (140.6 mg, 0.735 mmol) giving **14b** as a yellow wax, yield 77%.

^1H NMR (500.23 MHz, CDCl_3), δ 6.78 (d, $J = 7.9$ Hz, 1H), 6.72-6.67 (m, 2H), 6.46 (bs, 1H), 6.12 (dd, $J = 5.6, 3.0$ Hz, 1H), 6.08 (dd, $J = 5.6, 2.7$ Hz, 1H), 4.16 (d, $J = 1.9$ Hz, 1H), δ 3.87 (s, 3H), δ 3.85 (s, 3H), 3.49-3.41 (m, 3H), 3.35 (m, 2H), 3.03-2.98 (m, 1H), 2.95-2.90 (m, 2H), 2.72-2.54 (m, 4H), 2.14 (sep, $J = 6.7$ Hz, 1H), δ 1.52-1.49 (m, 1H), δ 1.43-1.40 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.94 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 200.1, 170.2, 163.8, 148.9, 147.6, 134.8, 134.7, 131.2, 120.6, 111.8, 111.2, 62.8, 55.9, 55.8, 51.7, 49.8, 48.0, 47.0, 46.6, 45.7, 45.3, 40.9, 35.2, 23.9, 22.6, 22.4$; IR (neat): ν_{\max} (cm^{-1}) = 3310 (w), 2957 (w), 1624 (s), 1530 (m), 1454 (m), 1341 (m), 1221 (m), 739 (s); HRMS (ESI+) calcd for $\text{C}_{26}\text{H}_{35}\text{N}_2\text{O}_5$ ($[\text{M}+\text{H}]^+$) 455.2468, found 455.2537.



Compound 14c: General procedure 2 was followed using imine (133.0 mg, 1.0 mmol), phenylglyoxylic acid (195 mg, 1.3 mmol) and 4-(2-isocyanomethyl)-1,2-dimethoxybenzene (230 mg, 1.3 mmol) giving **14c** as a yellow solid, yield 79%.

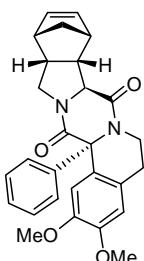
$[\alpha]_{\text{D}}^{20} = +16.5$ ($c = 0.121$, MeCN). ^1H NMR (500.23 MHz, CDCl_3), δ 7.86-7.84 (m, 1H), 7.65-7.62 (m, 1H), 7.51-7.45 (m, 3H), 7.00 (bs, 1H), 6.83-6.79 (m, 3H), 6.27 (dd, $J = 5.7, 2.9$ Hz, 1H), 6.04 (dd, $J = 5.5, 2.9$ Hz, 1H), 4.45 (dd, $J = 14.7, 6.0$ Hz, 1H), 4.36 (dd, $J = 14.7, 5.6$ Hz, 1H), 4.40 (d, $J = 1.7$ Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.52-3.47 (m, 1H), 3.12 (dd, $J = 11.9, 1.9$ Hz, 1H), 3.09-3.06 (m, 1H), 3.01-2.94 (m, 2H), 2.89-2.86 (m, 1H), 1.54-1.51 (m, 1H), 1.46-1.43 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3), δ 190.7, 170.0, 165.3, 149.1, 148.3, 135.4, 134.9, 134.7, 132.4, 130.6, 129.9, 129.0, 119.8, 111.2, 110.8, 62.3, 55.9, 55.9, 51.7, 49.8, 47.0, 46.6, 46.1, 45.2, 43.5, ; IR (neat): ν_{\max} (cm^{-1}) = 3306 (w), 2940 (w), 1632 (s), 1512 (s), 1443 (s), 1234 (s) 1138 (s), 1022 (s), 718 (s), 667 (m), 459 (m); HRMS (ESI+) calcd for $\text{C}_{27}\text{H}_{29}\text{N}_2\text{O}_5$ ($[\text{M}+\text{H}]^+$) 461.2076, found 461.2067.



Compound 14d: General procedure 2 was followed using imine (70.7 mg, 0.531 mmol), 4-methyl-2-oxopentanoic acid (89.8 mg, 85 μL , 0.690 mmol) and 4-(isocyanomethyl)-1,2-dimethoxybenzene (122.2 mg, 0.690 mmol) giving **14d** as yellow solid, yield 44%.

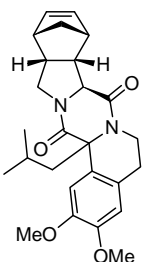
^1H NMR (500.23 MHz, CDCl_3): 6.84-6.75 (m, 3H), 6.13 (dd, $J = 5.7, 3.0$ Hz, 1H), 6.11 (dd, $J = 5.5, 2.8$ Hz, 1H), 4.34 (d, $J = 5.8$ Hz, 2H),

4.25 (d, $J = 1.9$ Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.55 (dd, $J = 12.5, 8.8$ Hz, 1H), 3.42-3.30 (m, 2H), 3.02-2.93 (m, 3H), 2.71-2.52 (m, 2H), 2.13-2.09 (m, 1H), 1.53-1.51 (m, 1H), 1.45-1.39 (m, 1H), 0.94 (d, $J = 6.9$ Hz, 3H), 0.92 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 200.0, 170.1, 163.9, 149.1, 148.3, 134.9, 134.8, 130.6, 119.6, 111.1, 110.7, 62.9, 55.9, 55.8, 51.7, 51.7, 49.9, 48.1, 47.0, 46.6, 45.6, 45.4, 43.3, 23.9, 22.6, 22.5$; IR (neat): ν_{max} (cm^{-1}) = 3308 (w), 2959 (w), 2928 (w), 1711 (w), 1630 (s), 1451 (m), 1358 (m), 1261 (s), 1234 (s), 1138 (s), 1026 (s), 729 (m); HRMS (ESI+) calcd for $\text{C}_{25}\text{H}_{33}\text{N}_2\text{O}_5$ ($[\text{M}+\text{H}]^+$) 441.2311, found 441.2387.



Compound 15a: General procedure 3 was followed using **14a** (138.3 mg, 0.292 mmol) and TMSOTf (71.3 mg, 58 μL , 0.321 mmol) giving **15a** as a white solid, yield 72%.

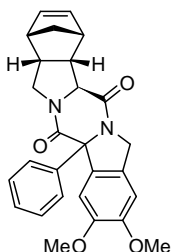
$[\alpha]_{\text{D}}^{20} = +292.0$ ($c = 0.210$, MeCN). ^1H NMR (500.23 MHz, CDCl_3), δ 7.36-7.26 (m, 5H), 6.61 (s, 1H), 6.59 (s, 1H), 6.23 (dd, $J = 5.7, 3.0$ Hz, 1H), 5.90 (dd, $J = 5.7, 3.0$ Hz, 1H), 4.96 (ddd, $J = 12.9, 2.5, 2.3$ Hz, 1H), 3.86-3.82 (m, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 3.53-3.49 (m, 1H), 3.32 (ddd, $J = 25.1, 12.5, 3.3$ Hz, 1H), 3.10-3.07 (m, 1H), δ 3.05-3.03 (m, 2H), δ 3.01-2.96 (m, 2H), δ 2.87-2.83 (m, 1H), δ 2.79-2.73 (m, 1H), δ 1.70-1.67 (m, 1H), 1.61-1.58 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 169.5, 165.7, 148.3, 146.8, 141.6, 136.9, 136.7, 128.9, 128.3, 127.2, 126.3, 125.4, 115.1, 110.3, 69.6, 61.5, 55.9, 55.8, 52.6, 50.0, 48.7, 45.7, 45.6, 43.8, 40.2, 29.0$; IR (neat): ν_{max} (cm^{-1}) = (w), 1665 (s), 1542 (m), 1398 (s), 1261 (s), 1219 (m), 743 (s), 706 (m); HRMS (ESI+) calcd for $\text{C}_{28}\text{H}_{29}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$) 457.2049, found 457.2107.



Compound 15b: General procedure 3 was followed using **14b** (109.6 mg, 0.241 mmol) and TMSOTf (70.1 mg, 57 μL , 0.315 mmol) giving **15b** as a white solid, yield 86%.

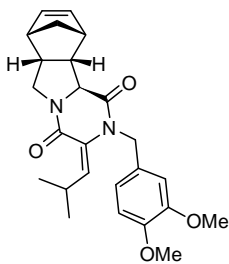
(Note: Minor diastereomer is given in *italic*). ^1H NMR (400.13 MHz, CDCl_3), δ 7.44 (s, 1H), 6.47 (s, 1H), 6.18 (dd, $J = 5.7, 3.2$ Hz, 1H), 6.13 (dd, $J = 5.1, 2.7$ Hz, 1H), 4.74 (ddd, $J = 20.4, 13.3, 7.2$ Hz, 1H), 4.13 (dd, $J = 12.3, 9.0$ Hz, 1H), 3.78 (s, 3H), 3.76 (s, 3H), 3.43 (d, $J = 8.2$ Hz, 1H), 3.18-3.10 (m, 1H), 3.08-2.98 (m, 3H), 2.91-2.82 (m, 2H), 2.57-2.46 (m, 3H), 1.86 (dd, $J = 14.8, 4.9$ Hz, 1H), 1.76-1.74 (m, 1H), 1.62-1.60 (m, 1H), 1.50 (sep, $J = 6.4$ Hz, 1H), 0.82 (d, $J = 6.7$ Hz, 3H), 0.78 (d, $J = 6.6$ Hz, 3H); ^1H NMR (400.13 MHz, CDCl_3): δ 7.53 (s, 1H), 6.45 (s, 1H), 6.27 (dd, $J = 5.7, 3.0$ Hz, 1H), 6.22 (dd, $J = 4.8, 2.0$ Hz, 1H), 4.85-4.81 (m, 1H), 3.91-3.86 (m, 1H), 3.84 (s, 3H), 3.77 (s, 3H), 3.62 (d, $J = 7.6$ Hz, 1H), 3.25-3.21 (m, 1H), 3.10-3.06 (m, 1H), 2.87-2.79 (m, 4H), 2.65 (dd, $J = 12.3, 7.0$ Hz, 1H), 2.56-2.50 (m, 1H), 2.11 (dd, $J = 14.8, 6.3$ Hz, 1H), 2.00-1.94 (m, 1H), 1.77-1.72 (m, 1H), 1.62-1.53 (m, 2H), 0.84 (d, $J = 6.7$ Hz, 3H), 0.74 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (100.61 MHz, CDCl_3), $\delta = 167.5, 154.0, 147.3, 137.5, 137.2, 129.8, 124.9, 111.9, 108.8, 66.5, 60.0, 55.9, 55.8, 53.5, 53.4, 49.4, 45.8, 45.3, 44.5, 43.2, 36.9, 27.2, 25.2, 23.6, 21.8$; ^{13}C NMR (100.61 MHz, CDCl_3), $\delta = 166.9, 166.2, 148.2, 146.8, 137.6, 137.3, 127.7, 127.3$,

113.1, 110.9, 67.0, 60.4, 56.1, 55.8, 53.4, 52.6, 49.3, 48.3, 45.3, 44.8, 43.3, 37.8, 29.0, 24.8, 24.3, 23.7; IR (neat): ν_{\max} (cm^{-1}) = 2953 (w), 1651 (s), 1514 (m), 1408 (s), 1256 (s), 1219 (s), 1096 (m), 737 (m); HRMS (ESI+) calcd for $\text{C}_{26}\text{H}_{33}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$) 437.2362, found 437.2419.



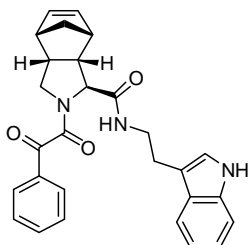
Compound 15c: General procedure 4 was followed using **14c** (110.0 mg, 0.255 mmol) and trifluoroacetic anhydride (33.7 mg, 21 μL , 0.255 mmol) giving **15c** as a white solid, 60% yield.

$[\alpha]_{\text{D}}^{20} = +247.6$ ($c = 0.210$, MeCN). ^1H NMR (500.23 MHz, CDCl_3), δ 7.36-7.32 (m, 5H), 7.22 (s, 1H), 6.76 (s, 1H), 6.23 (dd, $J = 7.1, 3.0$ Hz, 1H), 5.94 (dd, $J = 5.0, 2.6$ Hz, 1H), 4.97 (d, $J = 15.0$ Hz, 1H), 4.80 (d, $J = 15.0$ Hz, 1H), 3.86 (s, 3H), 3.85 (s, 3H), 3.85-3.82 (m, 1H), 3.58-3.54 (m, 1H), 3.28 (d, $J = 5.9$ Hz, 1H), 3.09-3.03 (m, 1H), 3.00-2.97 (m, 1H), 2.94-2.91 (m, 1H), 2.87 (dd, $J = 6.1, 12.5$ Hz, 1H), 1.72-1.68 (m, 1H), 1.63-1.58 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3), δ 167.7, 165.9, 150.0, 149.3, 139.8, 137.2, 136.6, 132.0, 129.2, 128.3, 125.9, 124.6, 108.3, 104.8, 75.5, 61.7, 56.1, 56.1, 52.8, 50.9, 49.1, 48.3, 45.7, 45.5, 44.3; ; IR (neat): ν_{\max} (cm^{-1}) = 2924 (w), 2855 (w), 1667 (s), 1408 (s), 1327 (m), 849 (m), 741 (s), 702 (m), 606 (m), 467 (w); HRMS (ESI+) calcd for $\text{C}_{27}\text{H}_{27}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$) 443.1971, found 443.1972.



Compound 16: General procedure 4 was followed using **14d** (69.9 mg, 0.159 mmol) and trifluoroacetic anhydride (34.4 mg, 21 μL , 0.260 mmol) giving **15c** as a pale yellow solid, 60% yield.

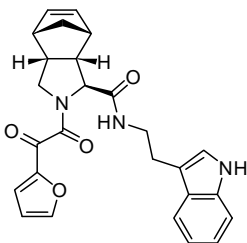
$[\alpha]_{\text{D}}^{20} = -126.8$ ($c = 0.205$, MeCN). ^1H NMR (500.23MHz, CDCl_3): δ = 6.80-6.70 (m, 3H), 6.31-6.28 (m, 2H), 5.42 (d, $J = 10.0$ Hz, 1H), 4.90 (d, $J = 15.4$, 1H), 4.74 (d, $J = 15.4$, 1H), 3.90 (dd, $J = 9.6, 12.6$ Hz, 1H), 3.67 (d, $J = 6.5$ Hz, 1H), 3.52-3.45 (m, 1H), 3.12- 3.09 (m, 1H), 3.08-3.02 (m, 1), 2.98-2.94 (m, 1H), 2.84 (dd, $J = 6.5, 12.7$ Hz, 1H), 1.79-1.77 (m, 1H), 1.68- 1.66 (m, 1H), 0.98 (d, $J = 6.6, 3\text{H}$), 0.90 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (125.78 MHz, CDCl_3), δ = 167.0, 159.2, 149.1, 148.3, 137.6, 137.0, 134.7, 129.6, 129.1, 119.4, 111.2, 110.6, 60.8, 55.9, 55.9, 53.1, 50.7, 47.7, 47.7, 45.5, 45.4, 43.8, 26.7, 23.2, 23.0; IR (neat): ν_{\max} (cm^{-1}) = 2963 (w), 1674 (s), 1624 (s), 1516 (s), 1452 (m), 1393 (s), 1258 (s), 1138 (s), 1026 (s), 733 (s); HRMS (ESI+) calcd for $\text{C}_{25}\text{H}_{31}\text{N}_2\text{O}_4$ ($[\text{M}+\text{H}]^+$) 423.2206, found 423.2269.



Compound 18a: General procedure 2 was followed using imine (66.8 mg, 0.501 mmol), phenylglyoxylic acid (98.0 mg, 0.653 mmol) and 2-(2-isocyanoethyl)-1H-indole (110.8 mg, 0.651 mmol) giving **18a** as a pale yellow solid, yield 77%.

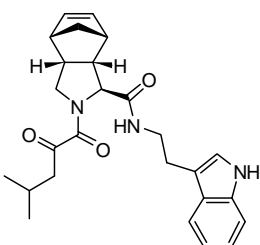
$[\alpha]_{\text{D}}^{20} = -18.00$ ($c = 0.445$, MeCN). ^1H NMR (500. 23MHz, CDCl_3), δ 8.05 (bs, 1H), 7.89 (dd, $J = 1.3, 8.3$ Hz, 2H), 7.65-7.08 (m, 7H),

6.60 (bs, 1H), 6.23 (dd, $J = 5.7, 3.0$ Hz, 1H), 5.99 (dd, $J = 5.7, 3.0$ Hz, 1H), 4.31 (d, $J = 2.1$ Hz, 1H), 3.64-3.56 (m, 2H), 3.43-3.38 (m, 2H), 3.01-2.98 (m, 3H), 2.96-2.87 (m, 3H), 2.85-2.82 (m, 1H), 2.80-2.78 (m, 1H), 1.51-1.48 (m, 1H), 1.41-1.39 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 191.0, 170.1, 165.2, 136.4, 135.3, 134.9, 134.7, 132.4, 129.9, 129.0, 127.2, 122.5, 122.1, 119.5, 118.7, 112.6, 111.2, 64.5, 62.2, 51.7, 49.8, 47.0, 46.6, 46.5, 45.0, 39.8, 25.2$; IR (neat): ν_{max} (cm^{-1}) = 3312 (w), 2930 (w), 1624 (s), 1530 (m), 1447 (m), 1343 (m), 1215 (s), 739 (s), 714 (s), 667 (s); HRMS (ESI+) calcd for $\text{C}_{28}\text{H}_{28}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$) 454.2052, found 454.2121.



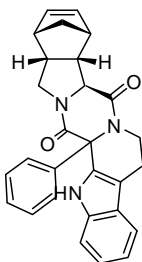
Compound 18b: General procedure 3 was followed using imine (70.2 mg, 0.527 mmol), 2-(furan-2-yl)-2-oxoacetic acid (96.0 mg, 0.685 mmol) and 2-(2-isocyanoethyl)-1H-indole (116.6 mg, 0.685 mmol) giving **18b** as a yellow solid, yield 71%.

$[\alpha]_{\text{D}}^{20} = -12.5$ ($c = 0.320$, MeCN). ^1H NMR (500.23 MHz, CDCl_3): δ 8.04 (bs, 1H), 7.64 (d, $J = 1.0$ Hz, 1H), 7.61 (d, $J = 7.9$ Hz, 1H), 7.34 (d, $J = 8.1$ Hz, 1H), 7.24 (dd, $J = 0.5, 3.7$ Hz, 1H), 7.19 (t, $J = 7.0$ Hz, 1H), 7.14-7.10 (m, 1H), 7.06 (d, $J = 2.2$ Hz, 1H), 6.53 (dd, $J = 1.7, 3.7$ Hz, 1H), 6.46 (bs, 1H), 6.17 (dd, $J = 3.0, 5.7$ Hz, 1H), 6.02 (dd, $J = 2.6, 5.7$ Hz, 1H), 4.29 (d, $J = 2.1$ Hz, 1H), 3.60-3.53 (m, 2H), 3.44-3.35 (m, 2H), 3.24 (dd, $J = 1.3, 11.9$ Hz, 2H), 3.19-3.15 (m, 1H), 3.03-2.93 (m, 3H), 2.88-2.85 (m, 2H), 1.49 (m, 1H), 1.41 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 177.6, 169.9, 163.5, 149.6, 149.1, 136.4, 135.0, 134.6, 127.2, 122.5, 122.1, 119.4, 118.6, 113.0, 112.6, 111.3, 62.5, 51.6, 49.9, 47.0, 46.7, 46.2, 45.0, 39.6, 25.1$; IR (neat): ν_{max} (cm^{-1}) = 3314 (w), 2924 (w), 1628 (s), 1535 (w), 1452 (s), 1389 (m), 1011 (m), 741 (s), 590 (m); HRMS (ESI+) calcd for $\text{C}_{26}\text{H}_{26}\text{N}_3\text{O}_4$ ($[\text{M}+\text{H}]^+$) 444.1845, found 444.1897.



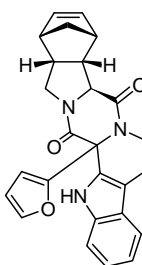
Compound 18c: General procedure 3 was followed using imine (74.1 mg, 0.556 mmol), 4-methyl-2-oxopentanoic acid (94.1 mg, 89 μL , 0.723 mmol) and 2-(2-isocyanoethyl)-1H-indole (124.0 mg, 0.729 mmol) giving **18c** as a yellow solid, yield 48%.

$[\alpha]_{\text{D}}^{20} = -21.3$ ($c = 0.470$, MeCN). ^1H NMR (500.23 MHz, CDCl_3): δ 8.04 (bs, 1H), 7.59 (d, $J = 9.7$ Hz, 1H), 7.35 (d, $J = 9.8$ Hz, 1H), 7.22-7.10 (m, 2H), 7.01 (d, $J = 2.3$ Hz, 1H), 6.42 (bs, 1H), 6.11-6.08 (m, 2H), 4.16 (d, $J = 1.9$ Hz, 1H), 3.59-3.51 (m, 2H), 3.46-3.43 (m, 1H), 3.33-3.29 (m, 2H), 3.00-2.89 (m, 4H), 2.63-2.49 (m, 2H), 2.16-2.06 (m, 1H), 1.51-1.48 (m, 1H), 1.41-1.39 (m, 1H), 0.95 (d, $J = 6.7$ Hz, 3H), 0.94 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 200.2, 170.1, 163.8, 136.3, 134.8, 127.2, 122.2, 122.1, 119.4, 118.7, 112.7, 111.2, 62.8, 51.7, 49.8, 48.0, 47.0, 46.6, 45.8, 45.2, 39.7, 25.1, 23.8, 22.6, 22.4$; IR (neat): HRMS (ESI+) calcd for $\text{C}_{26}\text{H}_{32}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$) 434.2365, found 434.2438.



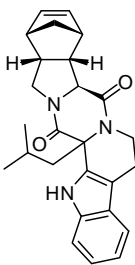
Compound 19a: General procedure 4 was followed using **18a** (137.8 mg, 0.304 mmol) and TMSOTf (92.3 mg, 75 μ L, 0.415 mmol) giving **19a** as a pale yellow solid, yield 92%.

(Note: Minor diastereomer is given in *italic*). ^1H NMR (500.23 MHz, CDCl_3): δ 9.28 (bs, 1H), 7.51-7.08 (m, 9H), 6.32-6.28 (m, 1H), 6.24 (dd, $J = 5.7, 3.0$ Hz, 1H), δ 4.79 (dd, $J = 12.5, 5.8$ Hz, 1H), 4.14-4.02 (m, 1H), 3.75 (d, $J = 8.9$ Hz, 1H), 3.39-3.34 (m, 1H), 3.23-3.20 (m, 1H), 3.04-2.87 (m, 3H), 2.80-2.58 (m, 3H), 1.89-1.86 (m, 1H), 1.76-1.73 (m, 1H); ^1H NMR (500.23 MHz, CDCl_3): δ 9.70 (bs, 1H), 7.51-7.08 (m, 9H), 6.34 (dd, $J = 5.7, 3.0$ Hz, 1H), 6.32-6.28 (m, 1H), δ 4.89 (dd, $J = 12.6, 5.6$ Hz, 1H), 4.14-4.02 (m, 1H), 3.86 (d, $J = 7.9$ Hz, 1H), 3.39-3.34 (m, 1H), 3.18-3.15 (m, 1H), 3.04-2.87 (m, 4H), 2.80-2.58 (m, 2H), 1.84-1.81 (m, 1H), 1.68-1.65 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 164.5, 163.4, 142.5, 137.7, 137.3, 126.6, 126.4, 126.2, 122.7, 119.8, 118.6, 111.4, 110.3, 60.9, 53.5, 53.1, 47.4, 45.0, 44.3, 44.0, 37.2, 20.7$; ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 165.6, 164.0, 143.3, 137.6, 137.4, 126.4, 126.2, 126.0, 122.7, 119.6, 118.5, 111.6, 111.0, 60.6, 53.4, 53.0, 48.0, 45.3, 44.7, 43.3, 37.5, 20.6$; IR (neat): ν_{max} (cm^{-1}) = 3318 (w), 2928 (w), 1651 (s), 1422 (s), 1300 (m), 1233 (m), 733 (s), 505 (s); HRMS (ESI+) calcd for $\text{C}_{28}\text{H}_{26}\text{N}_3\text{O}_2$ ($[\text{M}+\text{H}]^+$) 436.1947, found 436.2005.



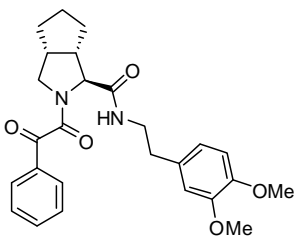
Compound 19b: General procedure 4 was followed using **18b** (137.8 mg, 0.304 mmol) and TMSOTf (92.3 mg, 75 μ L, 0.415 mmol) giving **19b** as a white solid, yield 92%.

(Note: Minor diastereomer is given in *italic*). ^1H NMR (500.23 MHz, CDCl_3): δ 9.57, 7.54-7.12 (m, 5H), 6.36-6.33 (m, 1H), 6.27-6.24 (m, 2H), 6.08 (dd, $J = 3.3, 0.72$ Hz, 1H), 4.84-4.81 (m, 1H), 4.27 (dd, $J = 12.2, 9.0$ Hz, 1H), 3.75 (d, $J = 9.0$ Hz, 1H), 3.40-3.33 (m, 1H), 3.21-3.19 (m, 1H), 3.10-2.75 (m, 3H), 2.61 (dd, $J = 12.2, 8.3$ Hz, 1H), 1.91-1.89 (m, 1H), 1.77-1.75 (m, 1H); ^1H NMR (500.23 MHz, CDCl_3): δ 9.28, 7.54-7.12 (m, 5H), 6.39 (dd, $J = 5.8, 3.1$ Hz, 1H), 6.36-6.33 (m, 1H), 6.27-6.24 (m, 1H), 5.99 (dd, $J = 3.3, 0.72$ Hz, 1H), 4.97-4.92 (m, 1H), 4.02-3.97 (m, 2H), 3.40-3.33 (m, 1H), 3.21-3.19 (m, 1H), 3.10-2.75 (m, 4H), 1.86-1.84 (m, 1H), 1.71-1.69 (m, 1H); ^{13}C NMR (125.78 MHz, CDCl_3): $\delta = 164.7, 161.4, 152.5, 142.9, 137.7, 137.1, 135.817, 127.8, 126.3, 122.8, 119.7, 118.6, 111.6, 111.3, 110.5, 110.3, 61.2, 53.6, 52.7, 47.6, 44.8, 44.2, 44.2, 36.8, 29.7, 20.6$; ^{13}C NMR (125.78 MHz, CDCl_3), $\delta = 166.9, 162.4, 151.7, 143.3, 137.6, 137.4, 136.4, 128.3, 125.9, 122.8, 119.5, 118.6, 111.7, 111.4, 110.9, 110.4, 60.6, 53.4, 52.5, 48.2, 45.4, 44.9, 43.4, 37.2, 31.6, 22.7$; IR (neat): ν_{max} (cm^{-1}) = 3318 (w), 2928 (w), 1651 (s), 1422 (s), 1300 (m), 1233 (m), 733 (s), 505 (s); HRMS (ESI+) calcd for $\text{C}_{26}\text{H}_{24}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$) 427.1739, found 427.1904.



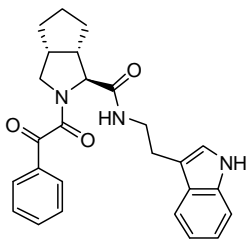
Compound 19c: General procedure 4 was followed using **18c** (110.0 mg, 0.254 mmol) and TMSOTf (73.4 mg, 60 μ L, 0.330 mmol) giving **19c** as a white solid, yield 90%.

(*Note: Minor diastereomer is given in italic.*) $^1\text{H NMR}$ (400.13 MHz, CDCl_3), δ 9.33 (bs, 1H), 7.46 (d, $J = 7.6$ Hz, 1H), 7.33 (d, $J = 8.1$ Hz, 1H), 7.08 (t, $J = 7.17$ Hz, 1H), 7.06 (t, $J = 7.8$ Hz, 1H), 6.35 (dd, $J = 5.7, 3.0$ Hz, 1H), 6.31-6.29 (m, 1H), 5.03 (dd, $J = 13.0, 4.5$ Hz, 1H), 4.04 (dd, $J = 12.4, 9.0$ Hz, 1H), 3.72 (d, $J = 8.0$ Hz, 1H), 3.28-3.21 (m, 1H), 3.19-3.15 (m, 2H), 2.92-2.88 (3H), 2.80-2.70 (m, 2H), 2.34 (dd, $J = 14.8, 6.2$ Hz, 1H), δ 2.10 (dd, $J = 14.7, 5.6$ Hz, 1H), 1.85-1.83 (m, 1H), 1.73-1.66 (m, 2H); $^1\text{H NMR}$ (400.13 MHz, CDCl_3), δ 8.91 (bs, 1H), 7.46-7.08 (m, 1H), 6.35 (dd, $J = 5.7, 3.0$ Hz, 1H), 6.21 (dd, $J = 5.6, 2.8$ Hz, 1H), 5.03 (dd, $J = 13.0, 4.5$ Hz, 1H), 4.21 (dd, $J = 12.3, 9.0$ Hz, 1H), 3.65 (d, $J = 8.5$ Hz, 1H), 3.28-3.21 (m, 1H), 3.19-3.15 (m, 2H), 2.92-2.88 (3H), 2.80-2.70 (m, 2H), 2.59 (dd, $J = 12.3, 8.1$ Hz, 1H), δ 2.49 (dd, $J = 14.7, 6.5$ Hz, 1H), 1.85-1.83 (m, 1H), 1.73-1.66 (m, 2H); $^{13}\text{C NMR}$ (100.61 MHz, CDCl_3), $\delta = 165.8, 165.3, 137.6, 137.5, 136.1, 133.5, 126.3, 122.4, 119.5, 118.3, 111.5, 108.6, 65.2, 60.4, 53.5, 52.9, 48.8, 47.9, 45.2, 44.7, 43.3, 37.0, 25.0, 23.9, 23.5, 20.6$; (ESI+) calcd for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_2$ (MH $^+$) 416.2360, found 416.2313. $^{13}\text{C NMR}$ (100.61 MHz, CDCl_3), $\delta = 165.6, 163.9, 137.7, 137.1, 135.6, 133.1, 126.6, 122.4, 119.6, 118.3, 111.3, 107.3, 64.5, 60.8, 53.5, 53.1, 48.8, 47.2, 45.0, 44.3, 43.9, 36.8, 25.1, 23.6, 22.8, 20.6$; IR (neat): ν_{max} (cm^{-1}) = 3329 (w), 2953 (w), 1649 (s), 1416 (s), 1300 (m), 1233 (m), 733 (s); HRMS (ESI+) calcd for $\text{C}_{26}\text{H}_{30}\text{N}_3\text{O}_2$ ([M+H] $^+$) 416.2360, found 416.2313.



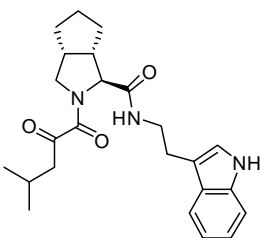
Compound 20: General procedure 2 was followed using imine (54.4 mg, 0.498 mmol), phenylglyoxylic acid (123.9 mg, 0.648 mmol) and 4-(2-isocianoethyl)-1,2-dimethoxybenzene (97.3 mg, 0.648 mmol) giving **20** as a white solid, yield 75%.

$[\alpha]_{\text{D}}^{20} = +25.0$ ($c = 0.240$, MeCN). $^1\text{H NMR}$ (500.23 MHz, CDCl_3), δ 7.96 (d, $J = 7.4$ Hz, 2H), δ 7.64 (t, $J = 7.0$ Hz, 1H), δ 7.51 (t, $J = 7.6$ Hz, 2H), δ 6.78-6.67 (m, 3H), δ 6.59-6.55 (m, 1H), δ 4.44 (s, 1H), δ 3.85 (s, 3H), δ 3.83 (s, 3H), δ 3.65-3.51 (m, 3H), δ 3.26 (dd, $J = 2.7, 11.0$ Hz, 2H), δ 3.02-2.96 (m, 1H), δ 2.81-2.71 (m, 3H), δ 2.01-1.88 (m, 1H), 1.87-1.77 (m, 1H), 1.76-1.65 (m, 1H), 1.63-1.45 (m, 2H), 1.36-1.27 (m, 1H); $^{13}\text{C NMR}$ (125.78 MHz, CDCl_3), $\delta = 190.9, 170.2, 165.9, 148.9, 147.6, 134.9, 132.6, 131.2, 129.8, 129.1, 120.7, 111.9, 111.3, 66.1, 55.8, 55.8, 53.5, 45.7, 42.8, 41.1, 40.7, 35.3, 32.8, 32.1, 25.8$; IR (neat): ν_{max} (cm^{-1}) = 3312 (w), 2930 (w), 1676 (m), 1632 (s), 1514 (s), 1443 (s), 1260 (s), 1234 (s), 1140 (s), 1024 (s), 802 (m), 718 (s); HRMS (ESI+) calcd for $\text{C}_{26}\text{H}_{31}\text{N}_2\text{O}_5$ ([M+H] $^+$) 451.2155, found 451.2217.



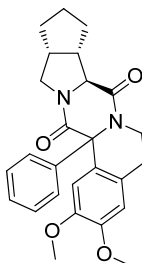
Compound 21: General procedure 2 was followed using imine (54.2 mg, 0.496 mmol), phenylglyoxylic acid (97.2 mg, 0.647 mmol) and 2-(2-isocyanoethyl)-1H-indole (110.3 mg, 0.648 mmol) giving **22** as a yellow solid, yield 75%.

$[\alpha]_D^{20} = -9.3$ ($c = 0.215$, MeCN). $^1\text{H NMR}$ (500.23 MHz, CDCl_3), δ 8.07 (bs, 1H), 7.96-7.93 (m, 2H), 7.65-7.62 (m, 2H), 7.48-7.45 (m, 2H), 7.38-7.35 (m, 1H), 7.22-7.12 (m, 3H), 6.49 (bs, 1H), 4.44 (d, $J = 2.6$ Hz, 1H), 3.78-3.58 (m, 3H), 3.25 (dd, $J = 11.2, 3.6$ Hz, 1H), 3.05-3.01 (m, 2H), 2.88-2.84 (m, 1H), 2.77-2.74 (m, 1H), 1.99-1.23 (m, 6H); $^{13}\text{C NMR}$ (125.78 MHz, CDCl_3), $\delta = 191.1, 170.2, 166.0, 136.4, 134.9, 132.7, 129.8, 129.1, 127.3, 122.6, 122.1, 119.4, 118.7, 112.6, 111.3, 66.2, 53.5, 45.7, 42.8, 39.9, 32.9, 32.2, 25.9, 25.2$; IR (neat): ν_{max} (cm^{-1}) = 3304 (w), 2945 (w), 1670 (m), 1628 (s), 1530 (m), 1447 (s), 1227 (s), 741 (s), 718 (s), 665 (s); HRMS (ESI+) calcd for $\text{C}_{26}\text{H}_{28}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$) 430.2052, found 430.2116.



Compound 22: General procedure 3 was followed using imine (74.7 mg, 0.684 mmol), 4-methyl-2-oxopentanoic acid (115.8 mg, 110 μL , 0.890 mmol) and 2-(2-isocyanoethyl)-1H-indole (151.4 mg, 0.890 mmol) giving **23** as an orange solid, yield 56%.

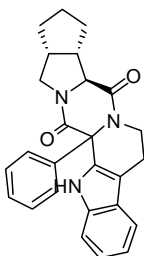
$[\alpha]_D^{20} = -19.7$ ($c = 0.305$, MeCN). $^1\text{H NMR}$ (500.23 MHz, CDCl_3): $\delta = 8.10$ (t, $J = 21.7$ Hz, 1H), 7.60 (d, $J = 7.8$ Hz, 1H), 7.34 (q, $J = 8.0$ Hz, 1H), 7.19 (p, $J = 7.7$ Hz, 1H), 7.12 (q, $J = 7.3$ Hz, 1H), 7.06-7.04 (m, 1H), 6.43-6.33 (m, 1H), 4.31 (d, $J = 2.2$ Hz, 1H), 3.76-3.68 (m, 1H), 3.62-3.49 (m, 2H), 3.47-3.44 (m, 1H), 3.01-2.93 (m, 3H), 2.81-2.73 (m, 1H), 2.64-2.58 (m, 2H), 2.20-1.29 (m, 7H), 0.97-0.90 (m, 6H); $^{13}\text{C NMR}$ (125.78 MHz, CDCl_3), $\delta = 199.6, 169.2, 163.3, 135.3, 126.3, 121.2, 121.1, 118.4, 117.7, 111.7, 110.2, 65.9, 52.8, 48.4, 47.1, 43.9, 42.0, 38.7, 31.7, 31.3, 24.8, 24.1, 23.0, 21.6, 21.4$. IR (neat): ν_{max} (cm^{-1}) = 3314 (w), 2955 (w), 1624 (s), 1532 (w), 1454 (m), 1358 (m), 1227 (m), 741 (s), 424 (s); HRMS (ESI+) calcd for $\text{C}_{24}\text{H}_{32}\text{N}_3\text{O}_3$ ($[\text{M}+\text{H}]^+$) 410.2438, found 410.2431.



Compound 23: General procedure 2 was followed using **20** (90.0 mg, 0.200 mmol) and TMSOTf (57.8 mg, 47 μL , 0.260 mmol) giving **24** as a yellow solid, yield 62%.

(Note: Minor diastereomer is given in *italic*). $[\alpha]_D^{20} = -186.7$ ($c = 0.225$, MeCN). $^1\text{H NMR}$ (500.23 MHz, CDCl_3), δ 7.30-7.20 (m, 5H), 6.73 (s, 1H), 6.53 (s, 1H), 4.88 (dq, $J = 2.4$ Hz, 1H), 4.01 (dd, $J = 8.6, 12.4$ Hz, 1H), 3.78 (s, 3H), 3.63 (s, 3H), 3.24 (td, $J = 3.3, 12.3$ Hz, 1H), 3.19 (d, $J = 7.7$ Hz), 3.13 (dd, $J = 5.2$ Hz, 1H), 3.04-2.98 (m, 1H), 2.87-2.80 (m, 1H), 2.69 (dt, $J = 2.7, 15.6$ Hz, 1H), 2.64-2.57 (m, 1H), 1.85-1.71 (m, 2H), 1.63-1.49 (m, 2H), 1.36-1.28 (m, 1H), 1.25-1.16 (m, 1H); $^1\text{H NMR}$ (500.23 MHz, CDCl_3), δ 7.55 (s, 1H), 7.31-7.26 (m, 3H), 7.06-7.03 (m, 2H), 6.65 (s, 1H), 4.48 (ddd, $J = 2.0, 7.3, 20.5$ Hz, 1H), 4.42 (dd, $J = 9.0, 12.3$ Hz, 1H), 3.89 (s, 3H), 3.88 (s, 3H), 3.65 (d, $J = 9.0$ Hz, 1H), 3.15-3.07 (m, 1H), 3.07-3.00 (m, 1H), 2.83 (dd, $J = 6.9, 12.4$ Hz, 1H), 2.80-2.72 (m, 2H), 2.47 (ddd, $J = 1.7, 5.5, 16.5$ Hz, 1H), 2.03-1.97 (m, 1H), 1.91-1.82 (m, 1H), 1.79-1.71 (m, 2H), 1.69-1.59 (m,

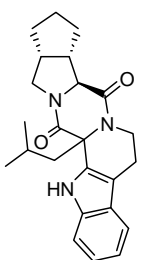
1H), 1.53-1.46 (m, 1H); ¹³C NMR (125.78 MHz, CDCl₃), δ = 169.2, 165.4, 148.4, 146.8, 142.0, 129.0, 128.3, 127.4, 126.3, 125.5, 115.0, 110.4, 69.5, 64.0, 55.9, 55.8, 51.6, 47.5, 40.5, 40.0, 32.1, 31.4, 29.0, 25.0; ¹³C NMR (125.78 MHz, CDCl₃), δ = 167.2, 163.8, 148.9, 146.9, 143.2, 128.4, 127.9, 127.3, 127.2, 125.8, 112.1, 110.4, 70.2, 62.6, 56.1, 55.9, 51.4, 49.9, 39.9, 37.9, 32.1, 31.5, 31.0, 26.7, 24.7; IR (neat): ν_{max} (cm⁻¹) = 2934 (w), 1655 (s), 1512 (m), 1400 (s), 1258 (s), 1221 (s), 1028 (m), 750 (m), 714 (m), 698 (m); HRMS (ESI+) calcd for C₂₆H₂₉N₂O₄ ([M+H]⁺) 433.2049, found 433.2109



Compound 24: General procedure 3 was followed using **22** (75.0 mg, 0.175 mmol) and TMSOTf (50.5 mg, 41 μL, 0.227 mmol) giving **26** as a white solid, yield 83%.

(Note: Minor diastereomer is given in *italic*). ¹H NMR (500.23 MHz, CDCl₃): δ 9.32 (bs, 1H), δ 7.54-7.12 (m, 9H), 4.82 (dd, *J* = 12.6, 6.0 Hz, 1H), 4.40 (dd, *J* = 12.2, 9.1 Hz, 2H), 3.80 (d, *J* = 6.7 Hz, 1H), 3.11-2.65 (m, 6H), δ 2.16-1.50 (m, 6H); ¹H NMR (500.23 MHz, CDCl₃): δ 9.74 (bs, 1H), 7.54-7.12 (m, 9H), 4.92 (dd, *J* = 13.1, 5.1 Hz, 1H), 4.31 (dd, *J* = 12.7, 9.3

Hz, 1H), 3.97 (d, *J* = 8.9 Hz, 1H), 3.11-2.65 (m, 6H), δ 2.16-1.50 (m, 6H). ¹³C NMR (125.78 MHz, CDCl₃), δ = 164.4, 163.4, 142.3, 135.7, 129.4, 128.7, 126.6, 126.3, 122.8, 119.8, 118.6, 111.5, 110.3, 67.1, 62.9, 50.8, 49.9, 40.5, 37.2, 31.8, 31.2, 24.6, 20.7; ¹³C NMR (125.78 MHz, CDCl₃), δ = 165.4, 163.9, 140.6, 136.2, 130.3, 129.0, 128.6, 126.4, 126.2, 119.7, 118.6, 111.6, 111.1, 67.1, 63.1, 51.4, 49.4, 39.8, 37.4, 32.2, 31.6, 24.9, 20.6; IR (neat): ν_{max} (cm⁻¹) = 3331 (w), 2922 (w), 1649 (s), 1422 (s), 1298 (m), 1234 (m), 739 (s), 694 (s), 577 (m), 509 (m); HRMS (ESI+) calcd for C₂₆H₂₆N₃O₂ ([M+H]⁺) 412.1947, found 412.2008.



Compound 25: General procedure 4 was followed using **23** (96.8 mg, 0.236 mmol) and TMSOTf (68.3 mg, 56 μL, 0.307 mmol) giving **27** as a white solid, yield 83%.

(Note: Minor diastereomer is given in *italic*). ¹H NMR (500.23 MHz, CDCl₃), δ 9.35 (bs, 1H), 7.48-7.09 (m, 4H), δ 5.06 (dd, *J* = 13.1, 4.7 Hz, 1H), 4.27 (dd, *J* = 9.3, 12.5 Hz, 1H), 3.76 (d, *J* = 9.0 Hz, 1H), 3.21-3.12 (m, 1H), 3.00-2.60 (m, 4H), 2.50 (dd, *J* = 14.7, 6.2, 1H), 2.38 (dd, *J* = 14.8, 6.1 Hz, 1H), 2.13 (dd, *J* = 14.8, 5.7 Hz, 1H), 2.00-1.48 (m, 6H), 0.94 (d, *J* = 4.7

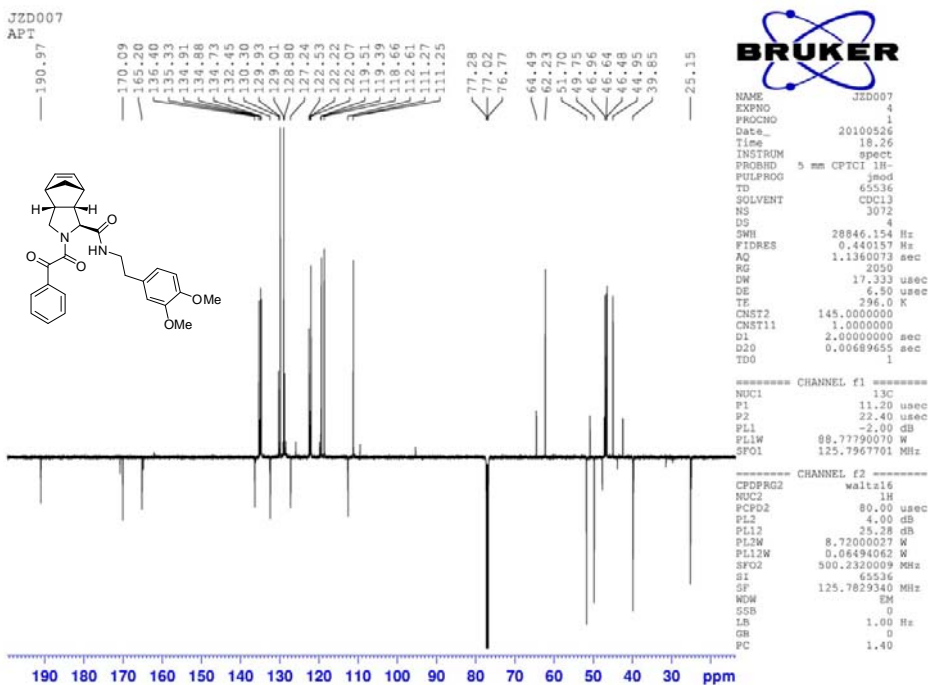
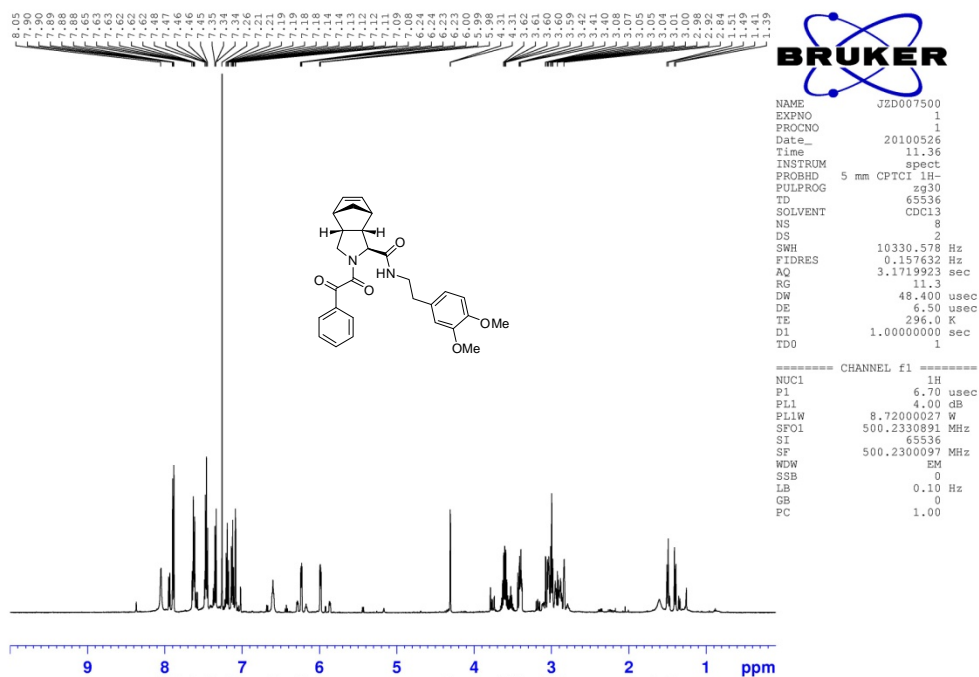
Hz, 3H), 0.93 (d, *J* = 4.7 Hz, 3H); ¹H NMR (500.23 MHz, CDCl₃), δ 8.97 (bs, 1H), 7.48-7.09 (m, 4H), 5.06 (dd, *J* = 13.1, 4.7 Hz, 1H), 4.46 (dd, *J* = 12.0, 8.8 Hz, 1H), 3.67 (d, *J* = 9.6 Hz, 1H), 3.21-3.12 (m, 1H), 3.00-2.60 (m, 4H), 2.50 (dd, *J* = 14.7, 6.2, 1H), 2.08 (dd, *J* = 14.7, 5.7 Hz, 1H), 2.00-1.48 (m, 6H), 0.91 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 3.6 Hz, 3H); ¹³C NMR (125.78 MHz, CDCl₃), δ = 165.6, 165.0, 136.0, 134.0, 126.2, 122.4, 119.5, 118.3, 111.4, 108.5, 65.1, 62.8, 51.2, 49.3, 48.8, 39.6, 36.9, 32.2, 31.5, 25.0, 24.8, 23.9, 23.6, 20.6; ¹³C NMR (125.78 MHz, CDCl₃), δ = 165.4, 163.8, 135.6, 133.1, 126.6, 122.4, 119.6, 118.3, 111.3, 107.4, 64.5, 62.7, 50.6, 49.6, 48.6, 40.4, 36.7, 31.8, 31.2, 25.0, 24.6, 23.6, 23.0, 20.6; IR (neat): ν_{max} (cm⁻¹) = 3349 (w), 2953 (w), 1651 (s), 1418 (s),

1298 (m), 1235 (m), 737 (s), 511 (m); HRMS (ESI+) calcd for C₂₄H₃₀N₃O₂ ([M+H]⁺) 392.2260, found 392.2327.

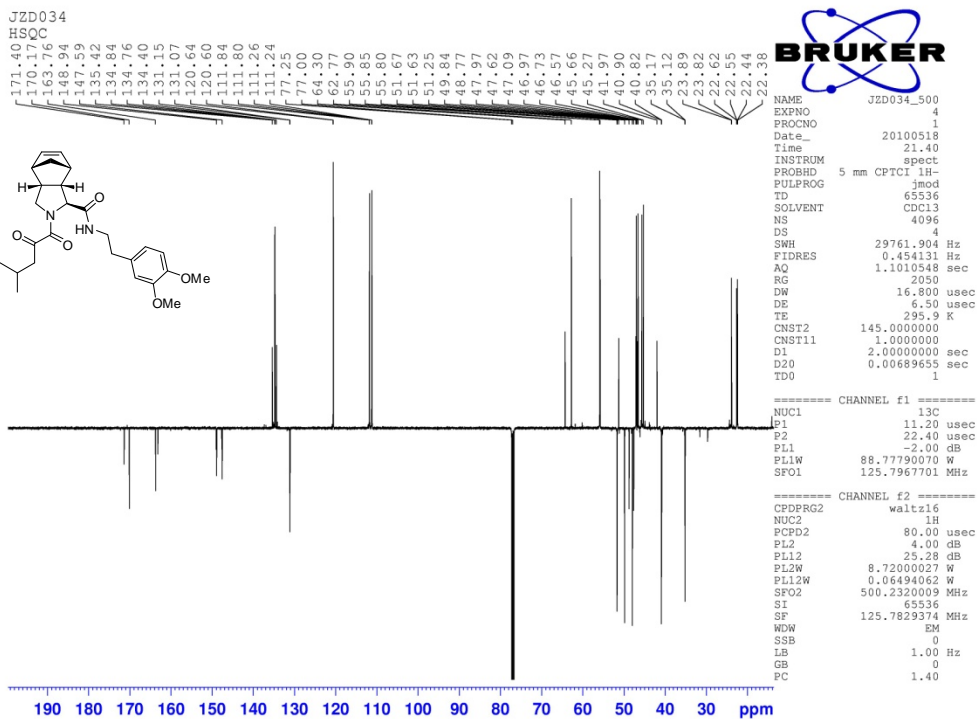
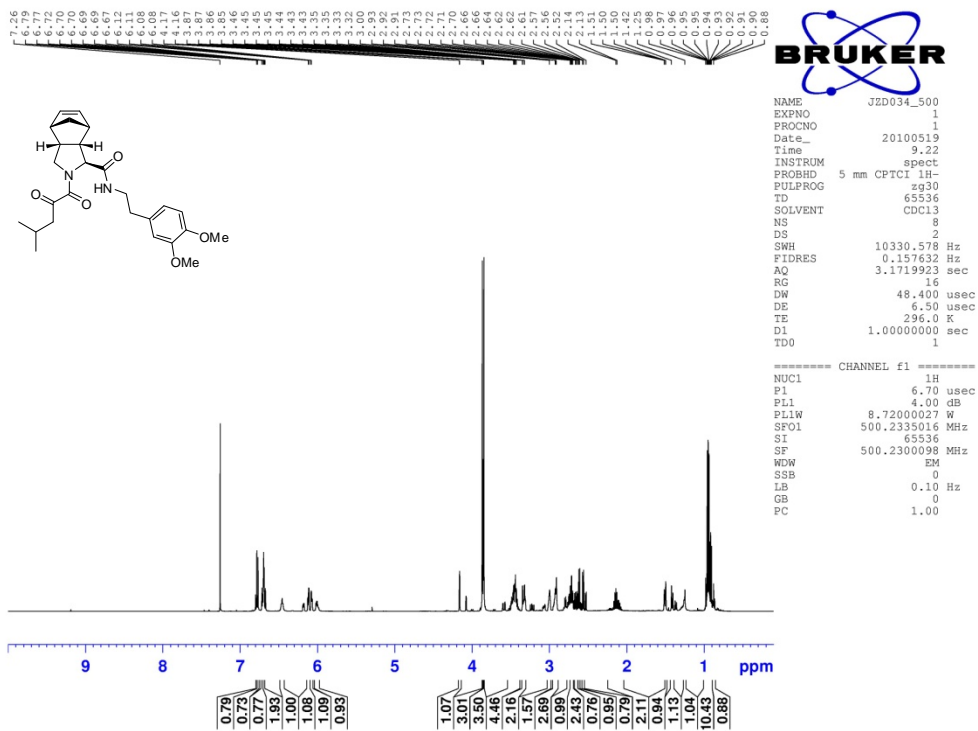
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1. S. Michaelis and S. Blechert, *Chem. Eur. J.* 2007, **13**, 2358.
2. N. Elders, E. Ruijter, F. J. J. de Kanter, E. Janssen, M. Lutz, A. L. Spek and R. V. A. Orru, *Chem. Eur. J.* 2009, 6096.
3. V. Köhler, K. R. Bailey, A. Znabet, J. Raftery, M. Helliwell and N. J. Turner, *Angew. Chem. Int. Ed.* 2010, **49**, 2182.
4. A. Znabet, E. Ruijter, F. J. J. de Kanter, V. Köhler, M. Helliwell, N. J. Turner and R. V. A. Orru, *Angew. Chem. Int. Ed.* 2010, **49**, 5289.

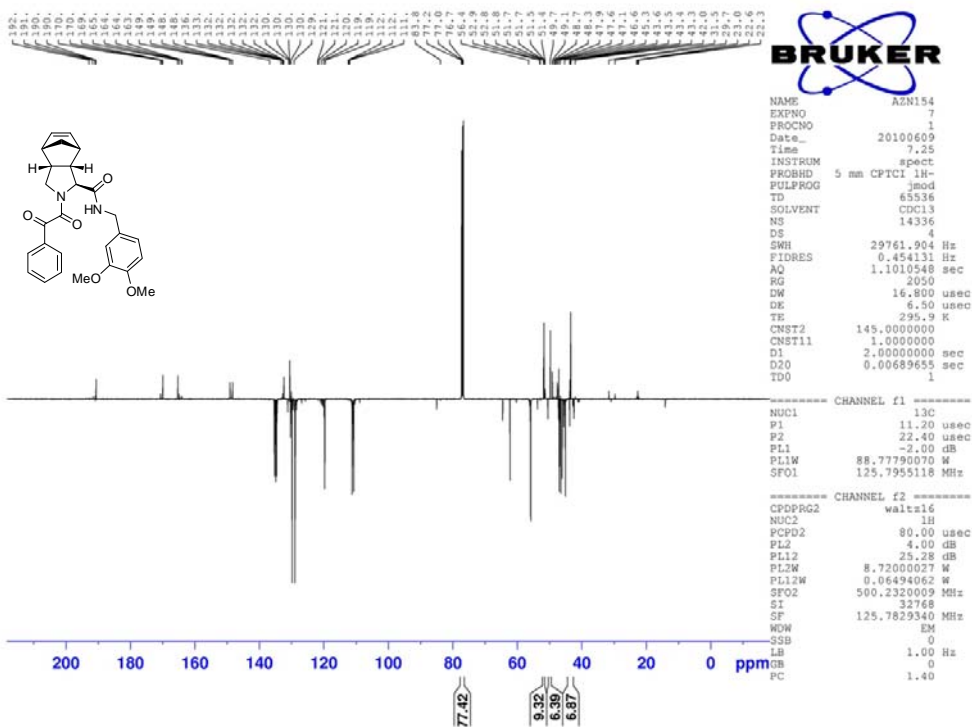
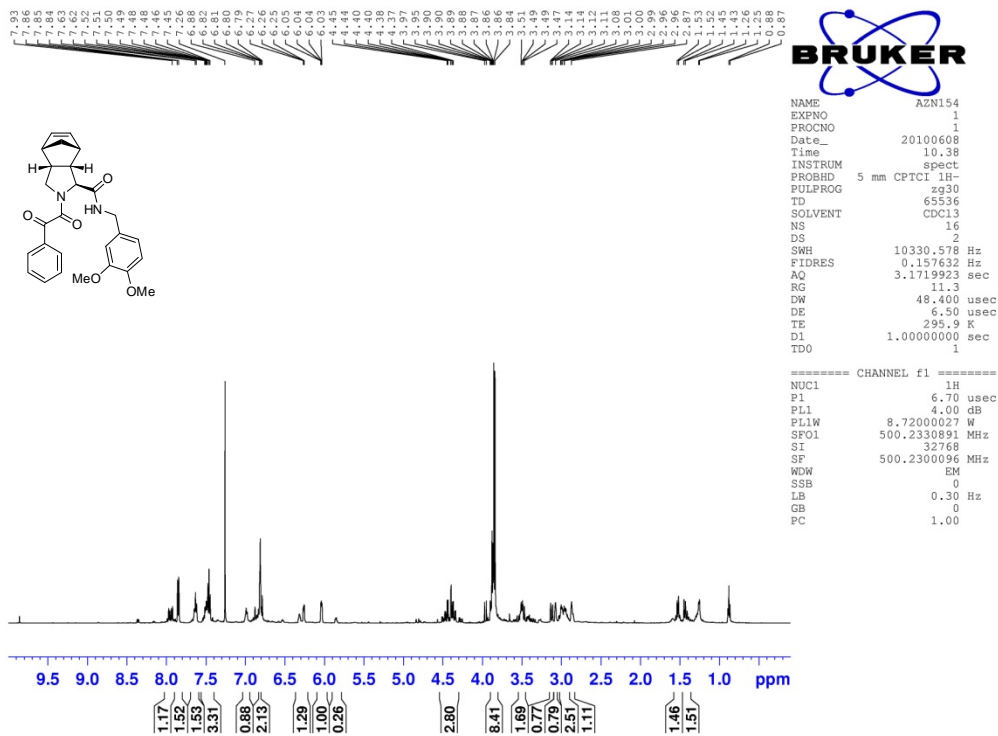
Compound 14a



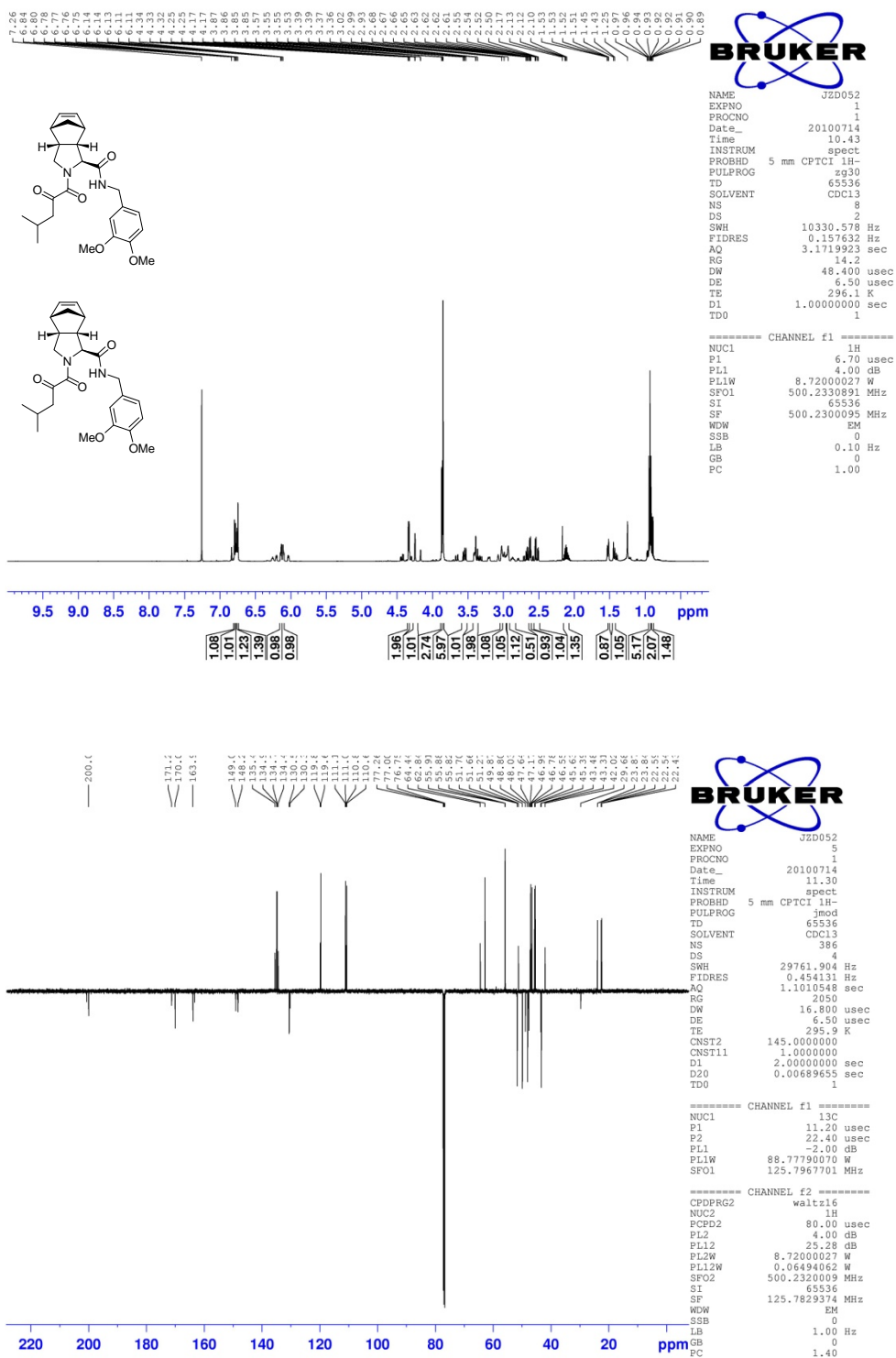
Compound 14b



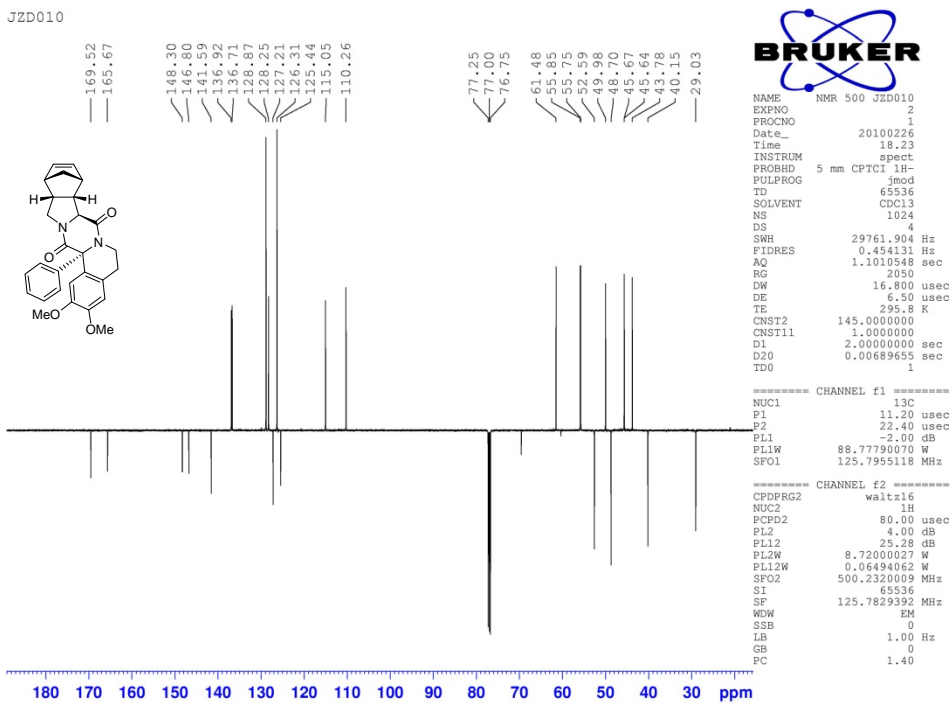
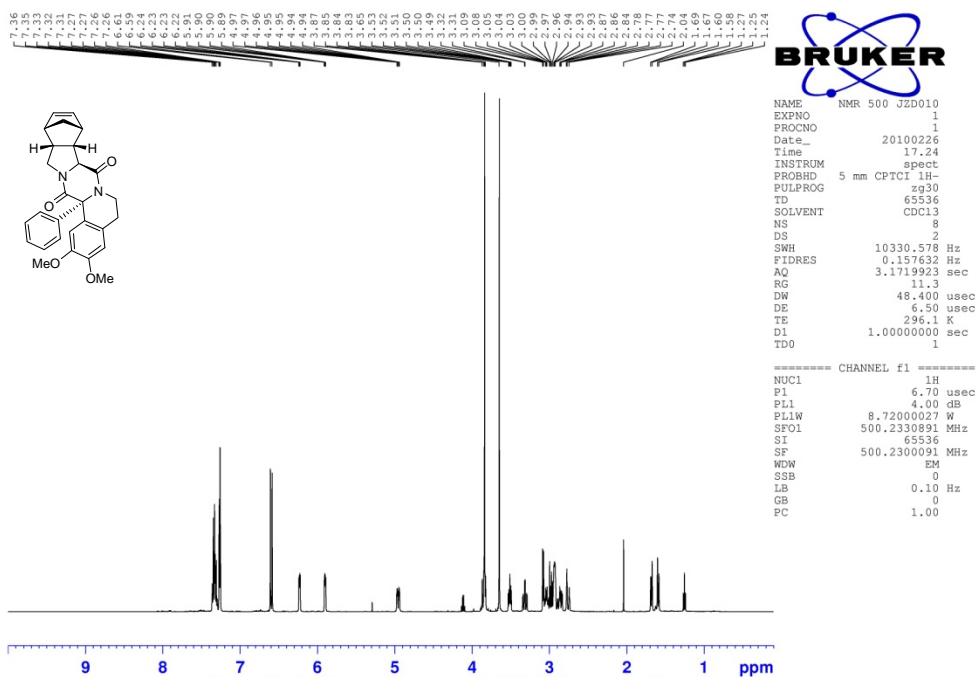
Compound 14c



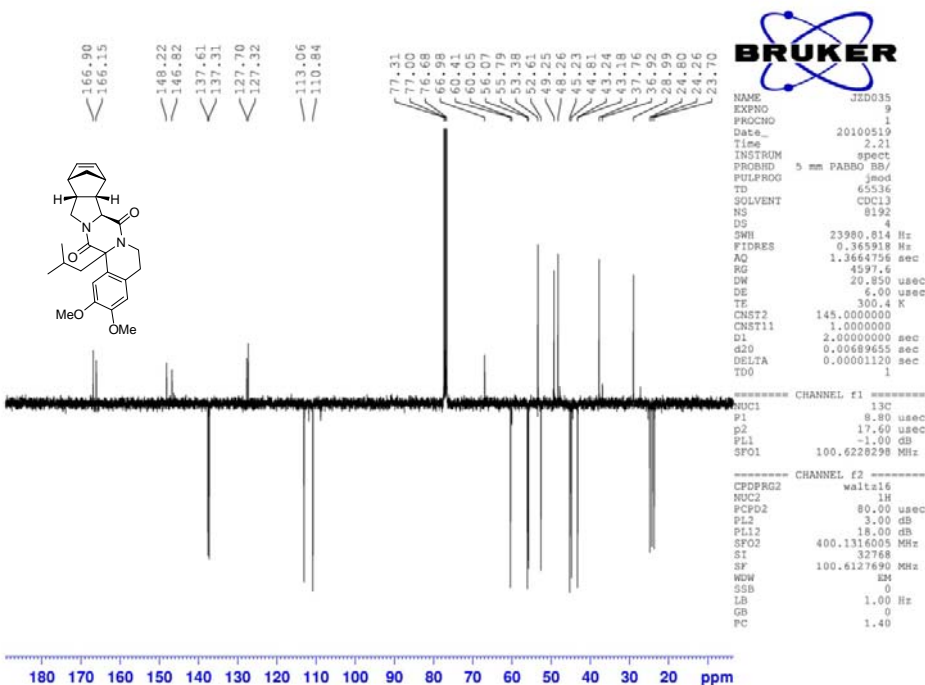
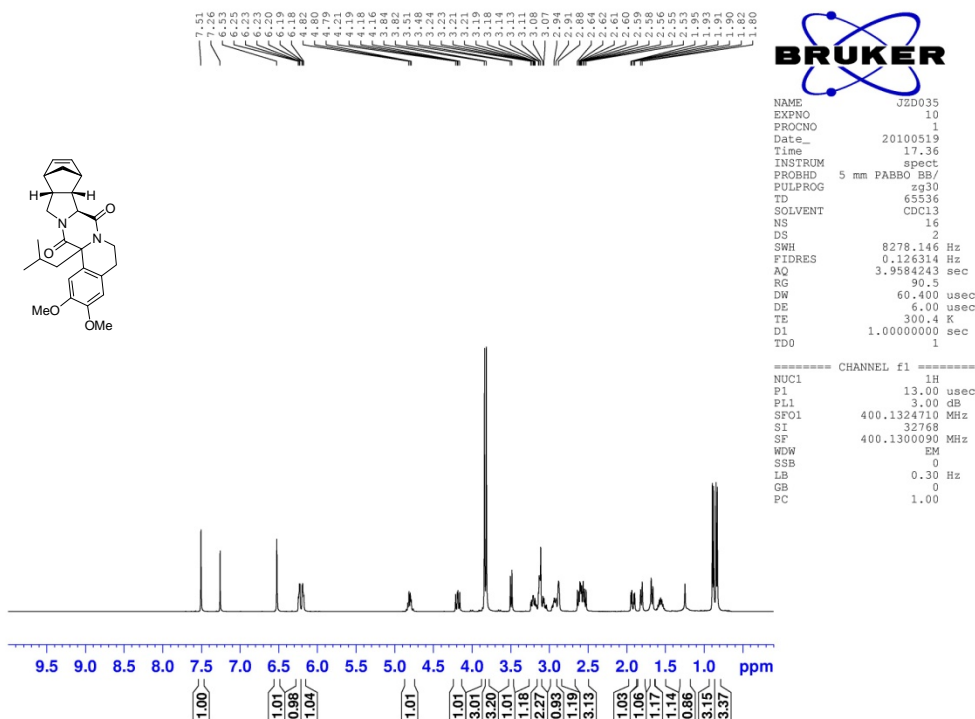
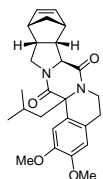
Compound 14d



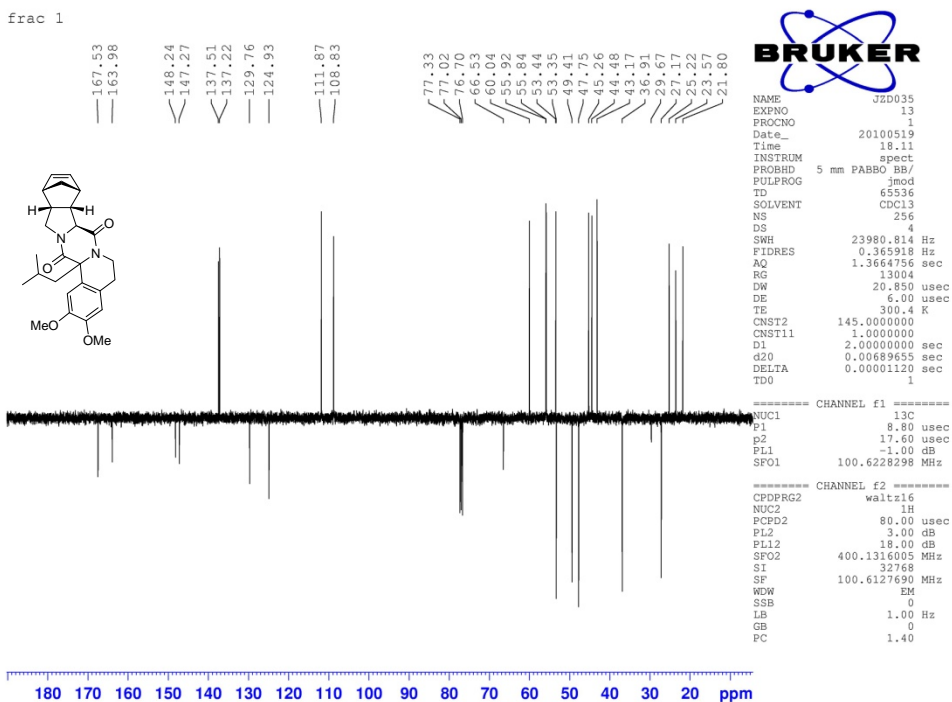
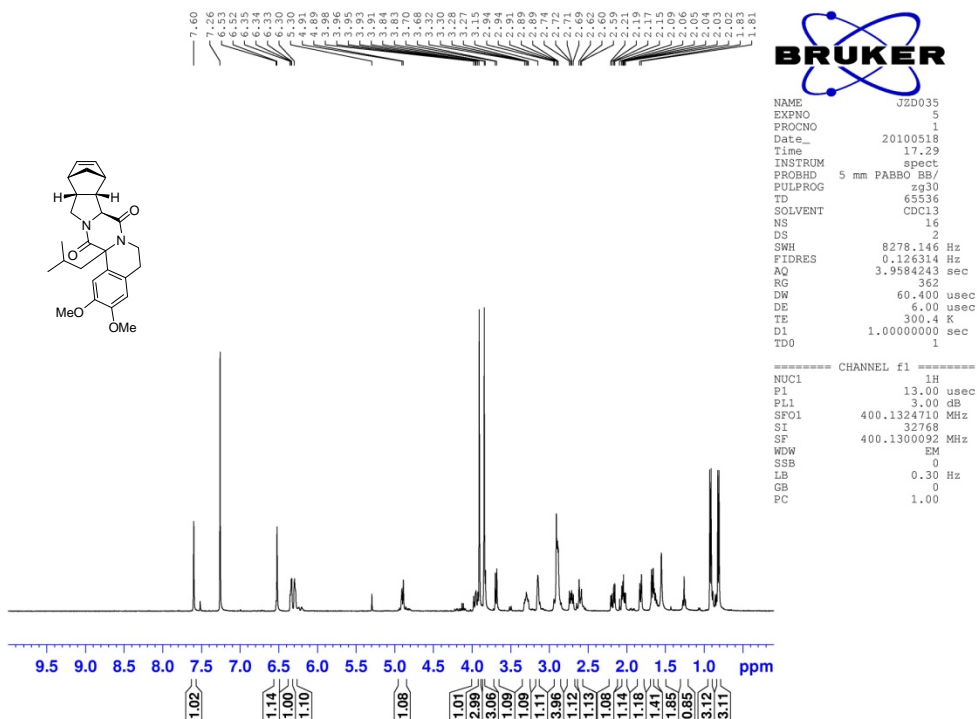
Compound 15a



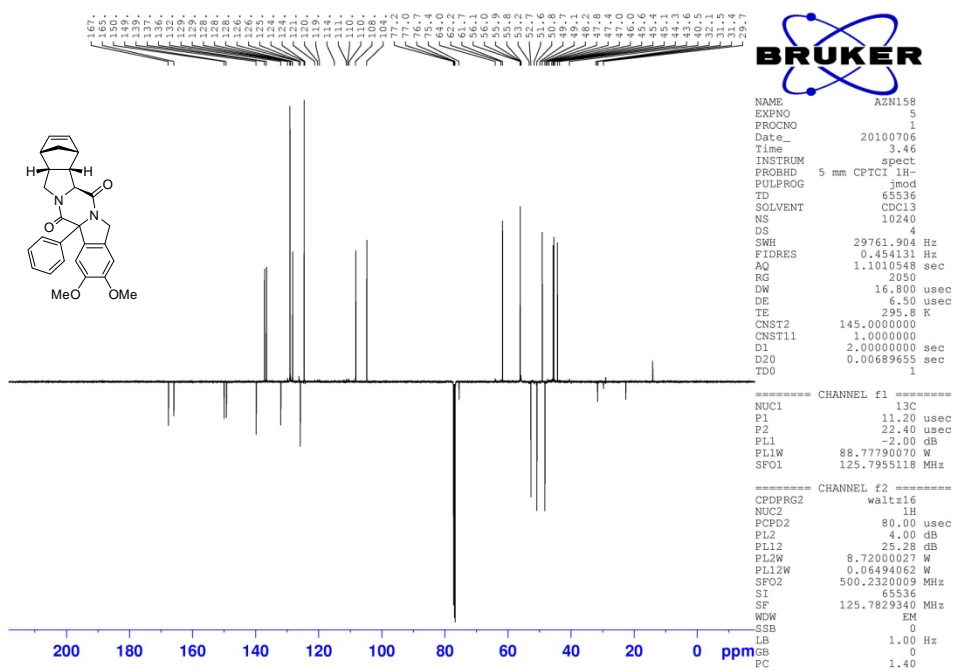
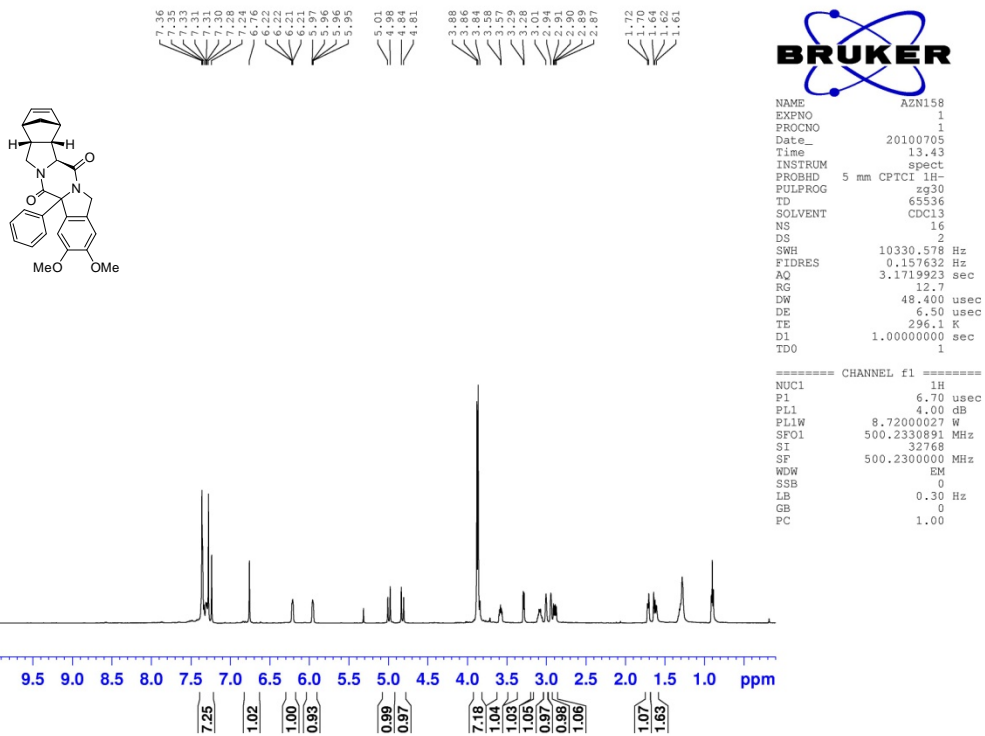
Compound 15b (major diastereomer)



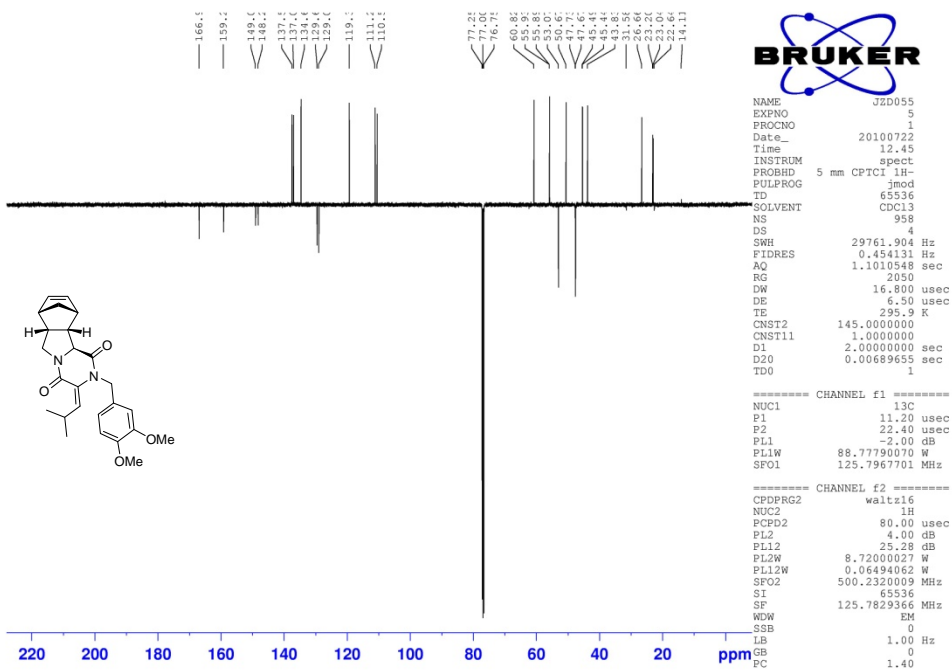
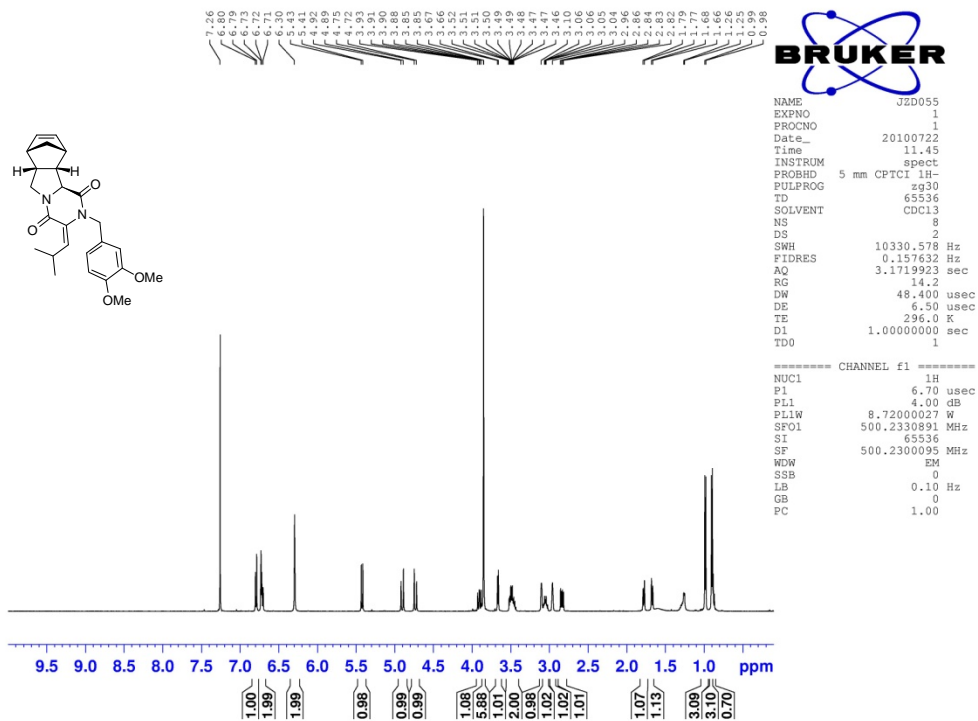
Compound 15b (minor diastereomer)



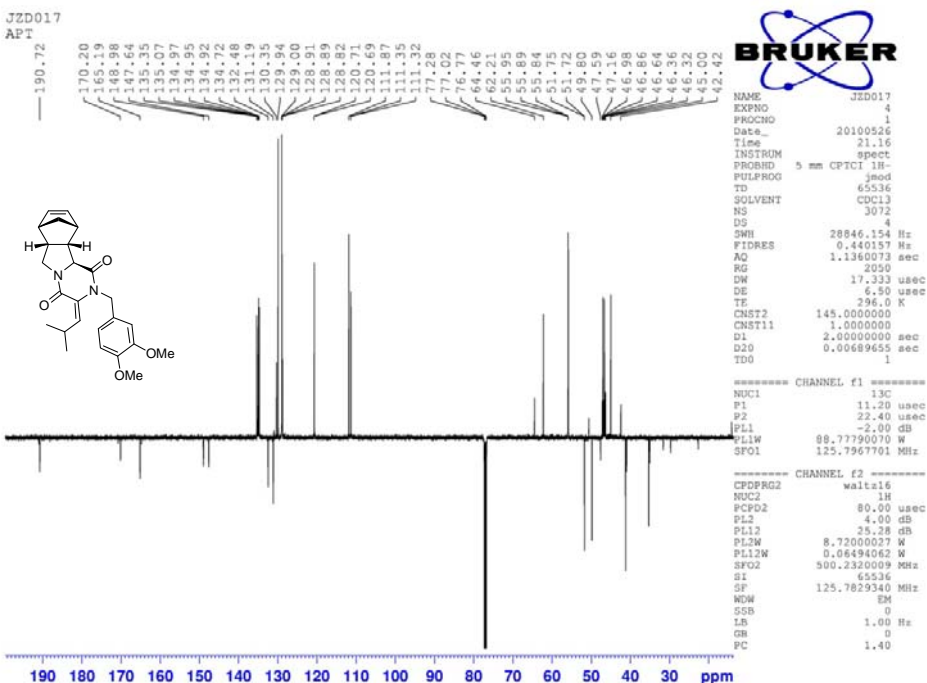
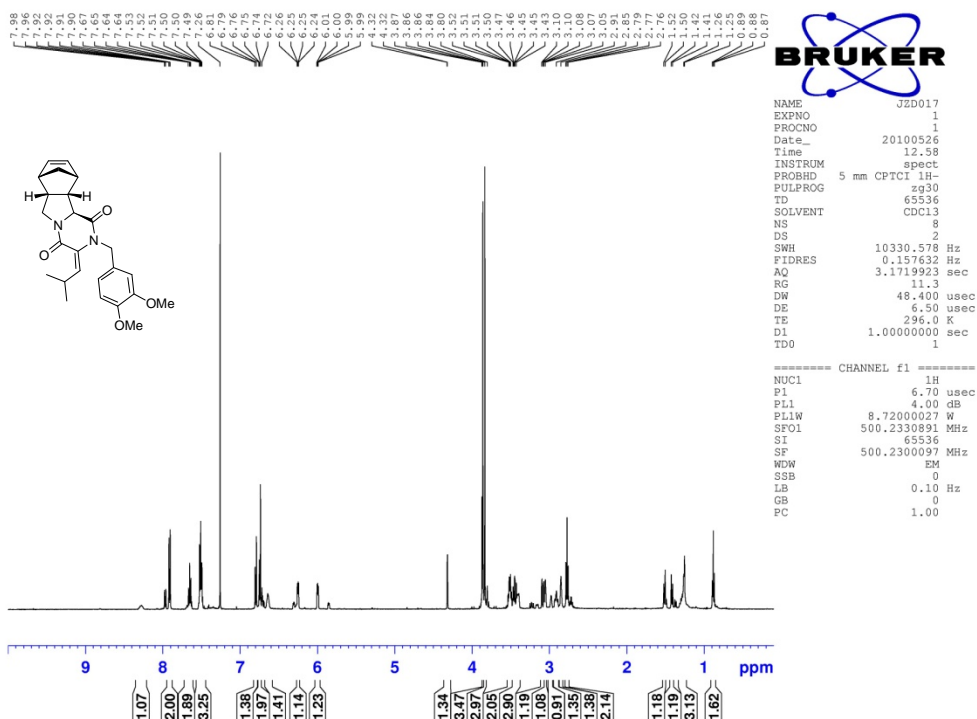
Compound 15c



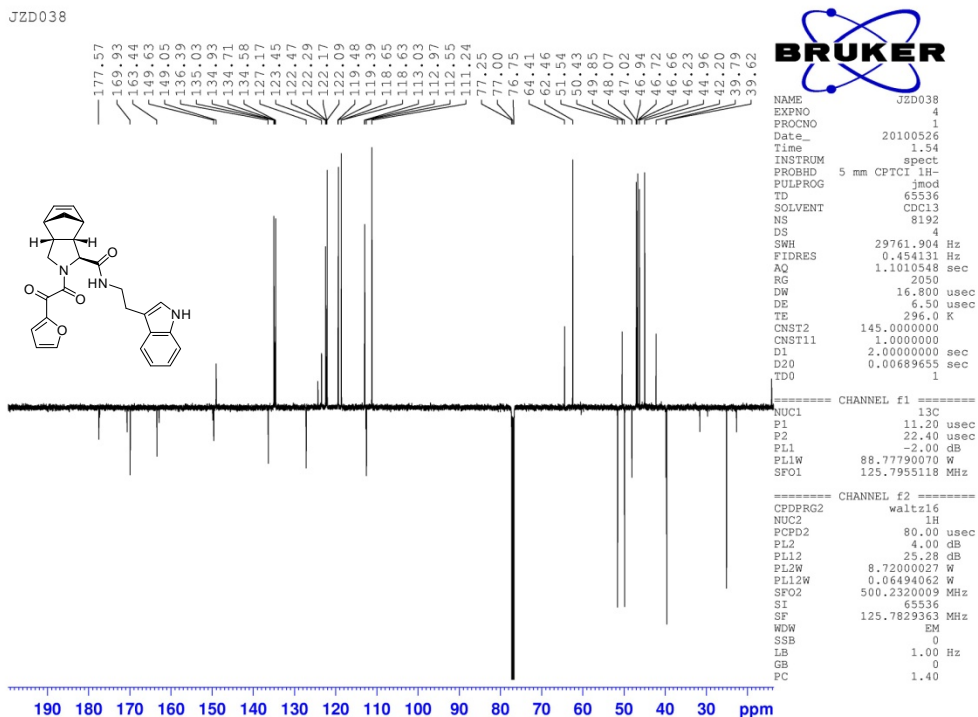
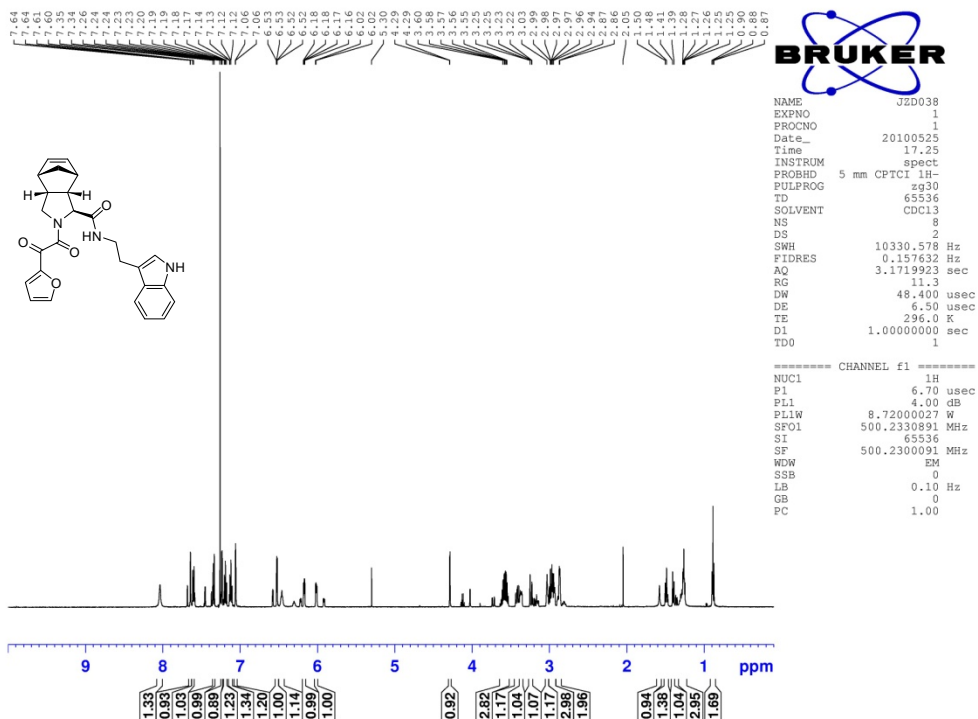
Compound 16



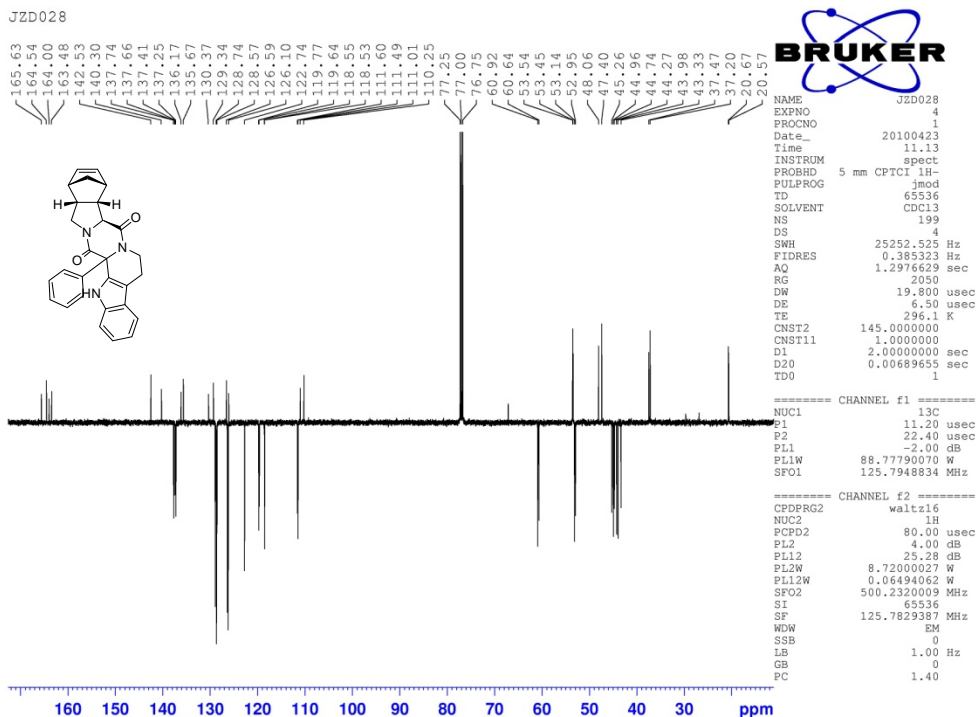
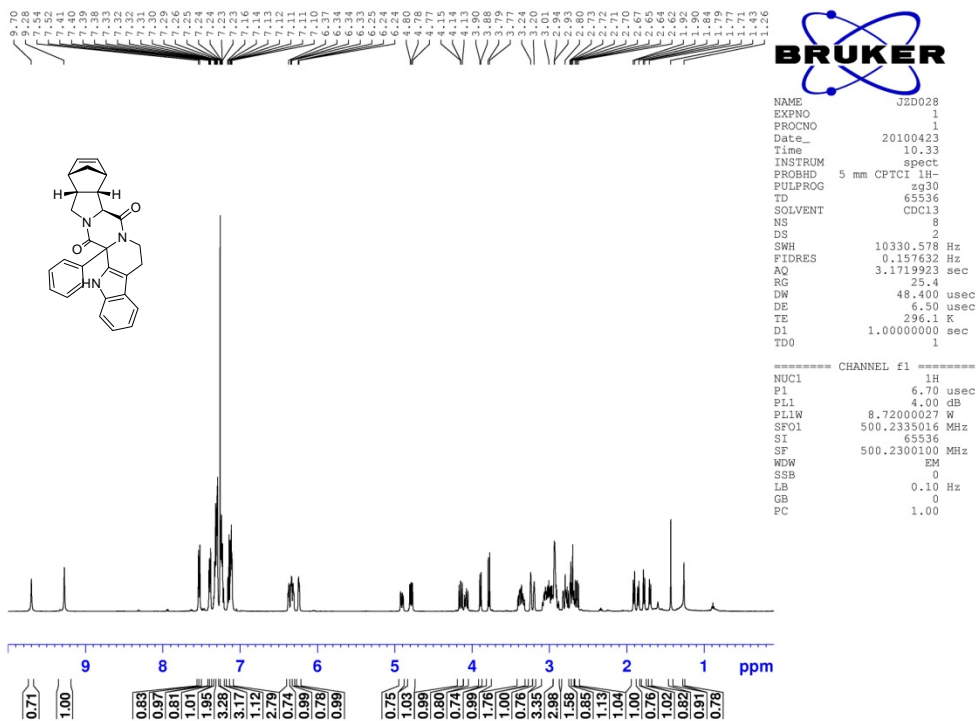
Compound 18a



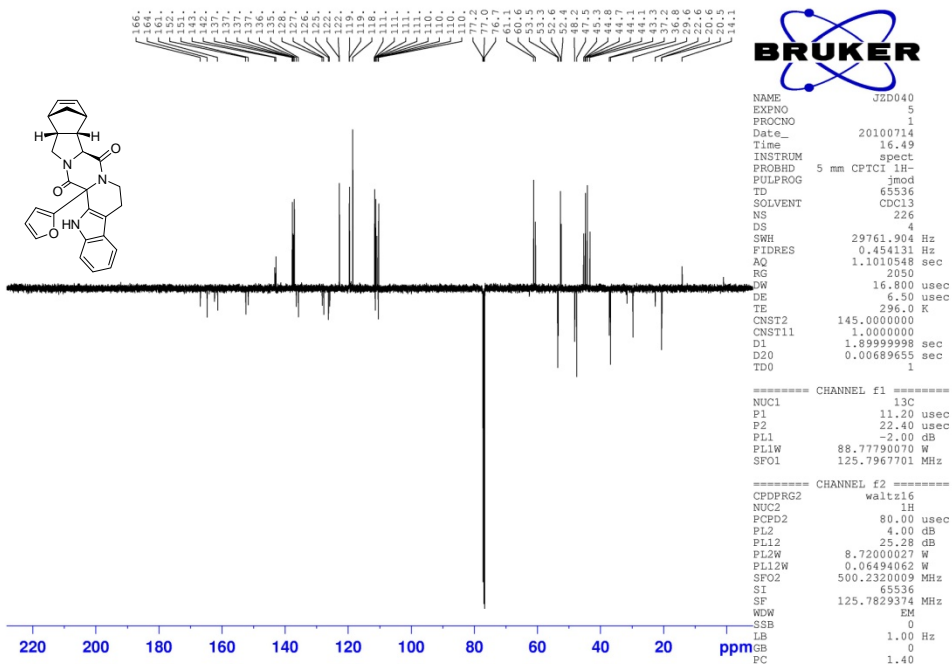
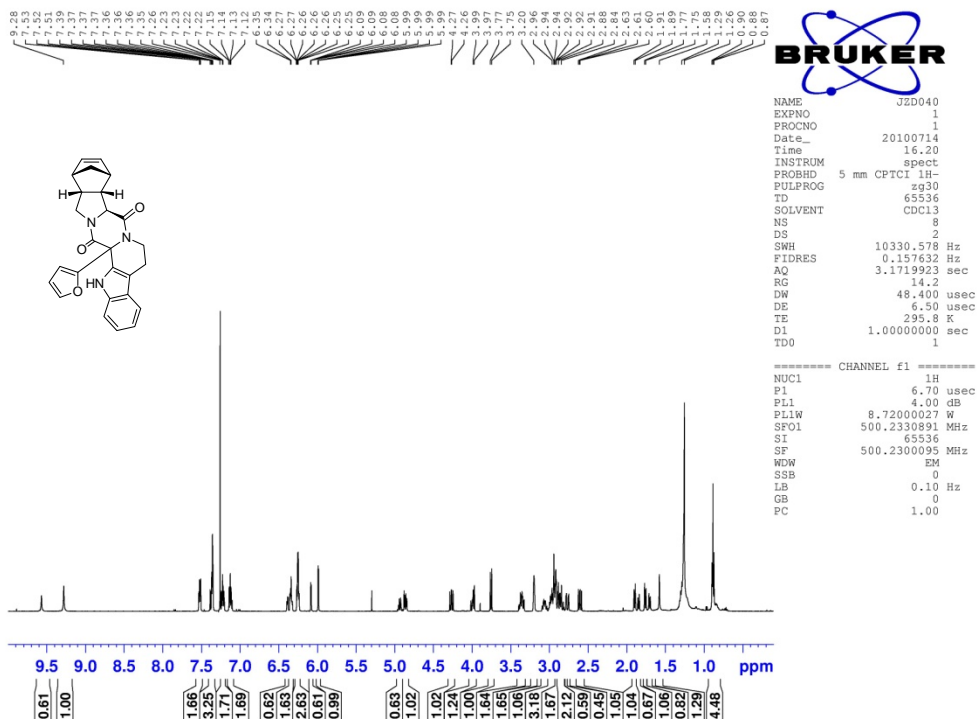
Compound 18b



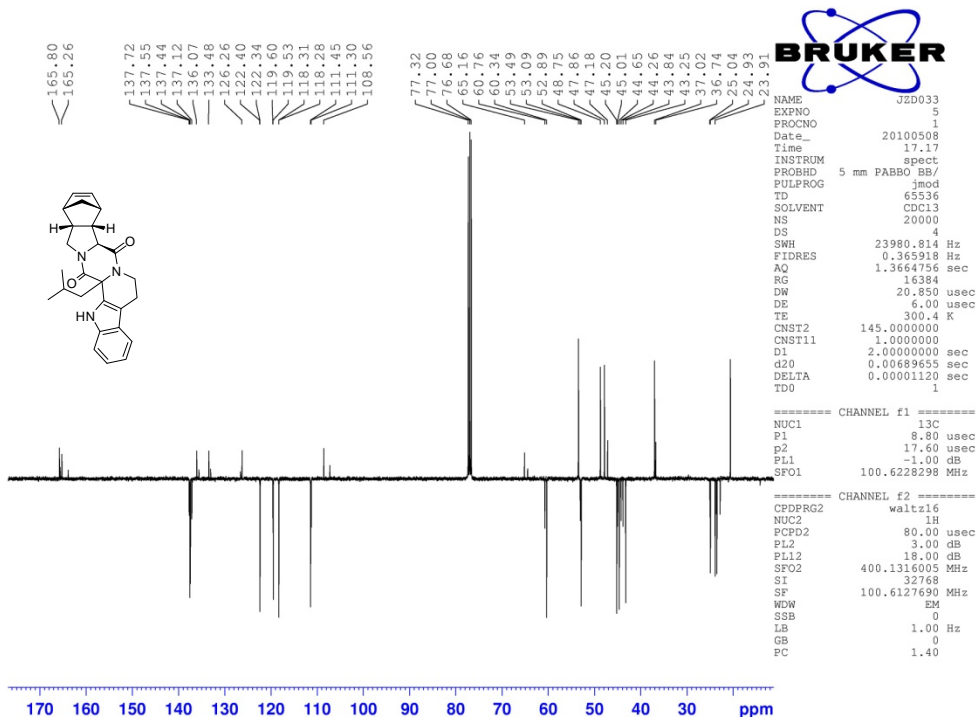
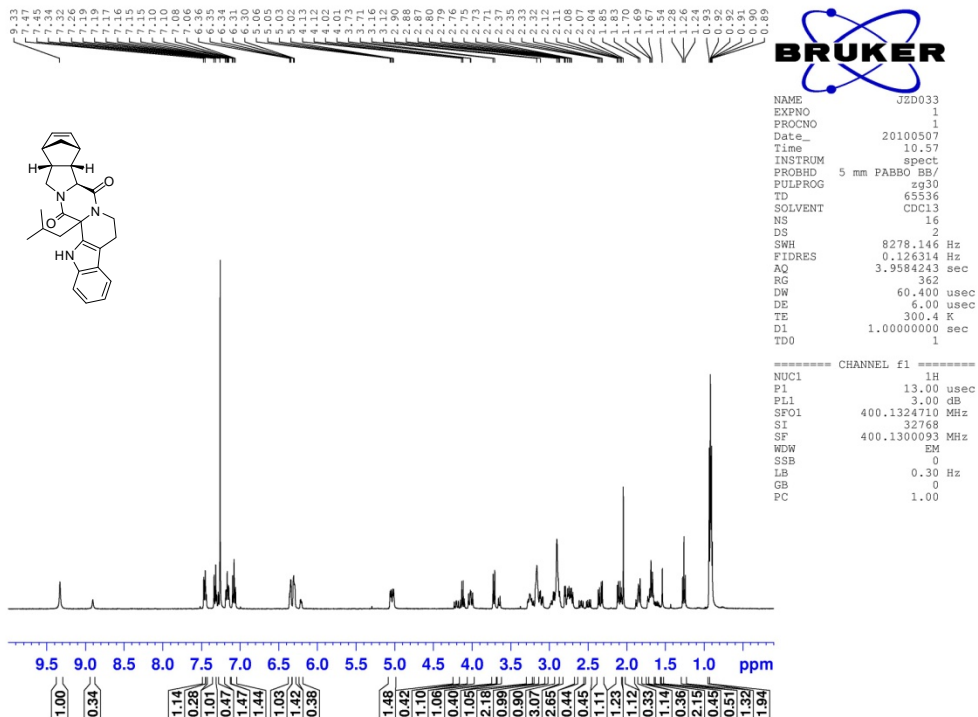
Compound 19a



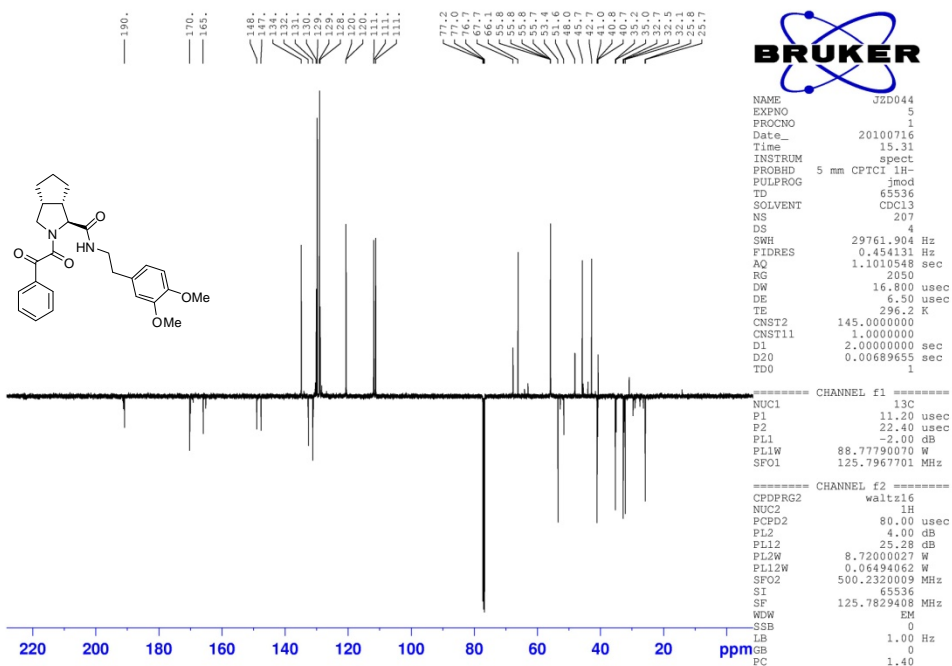
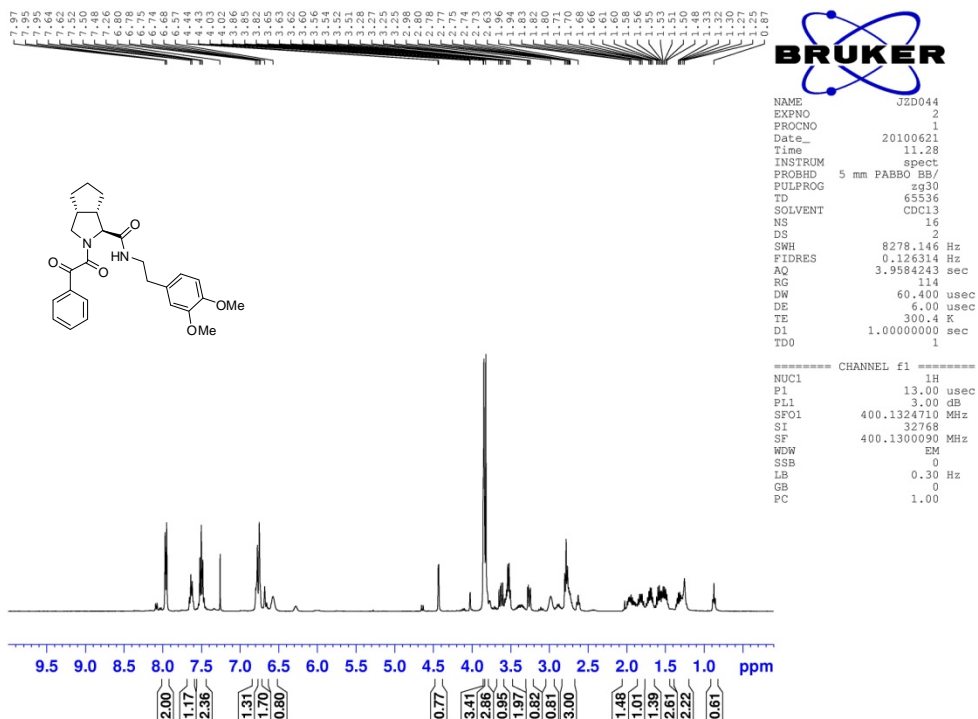
Compound 19b



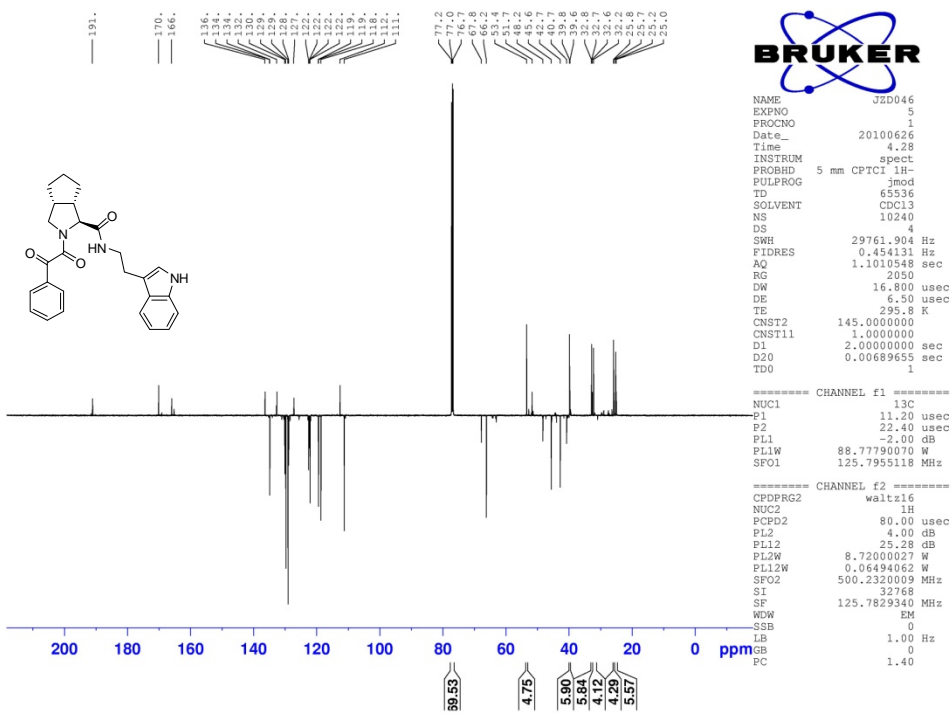
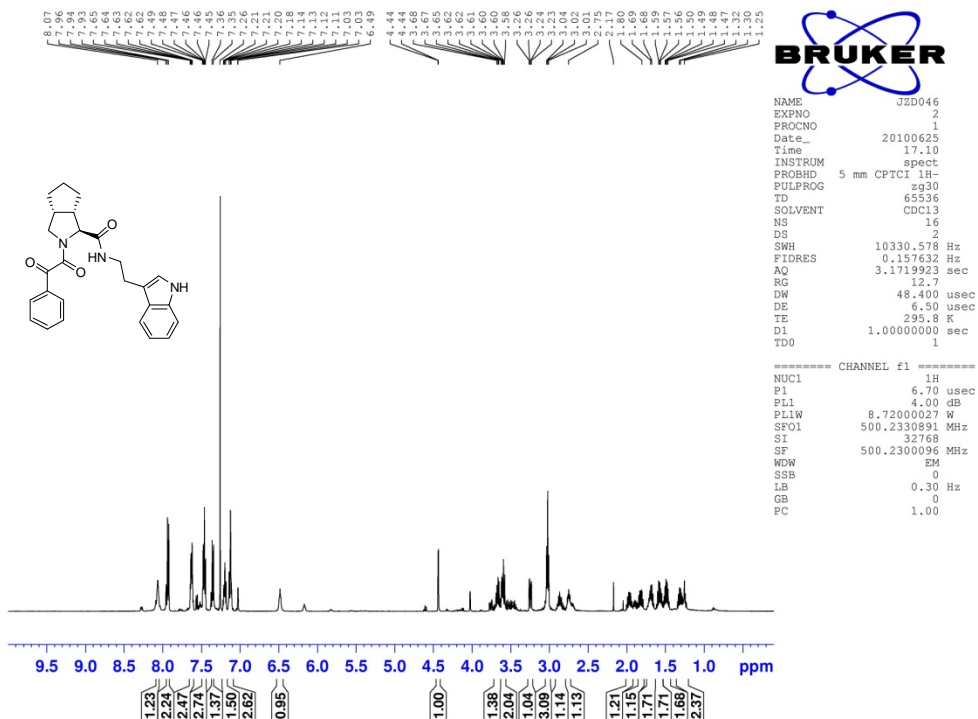
Compound 19c



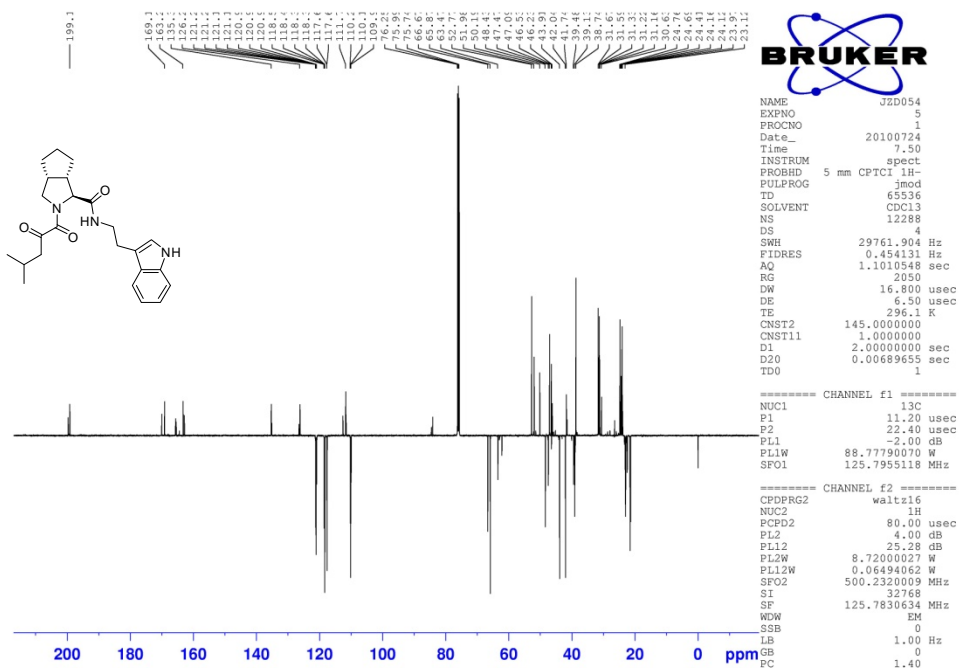
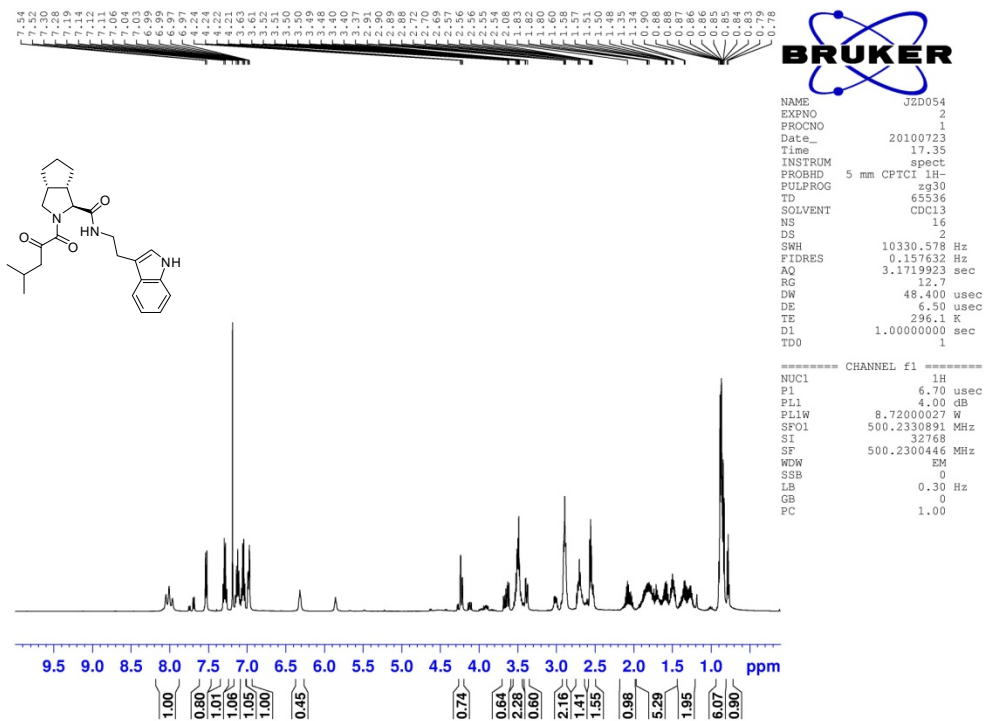
Compound 20



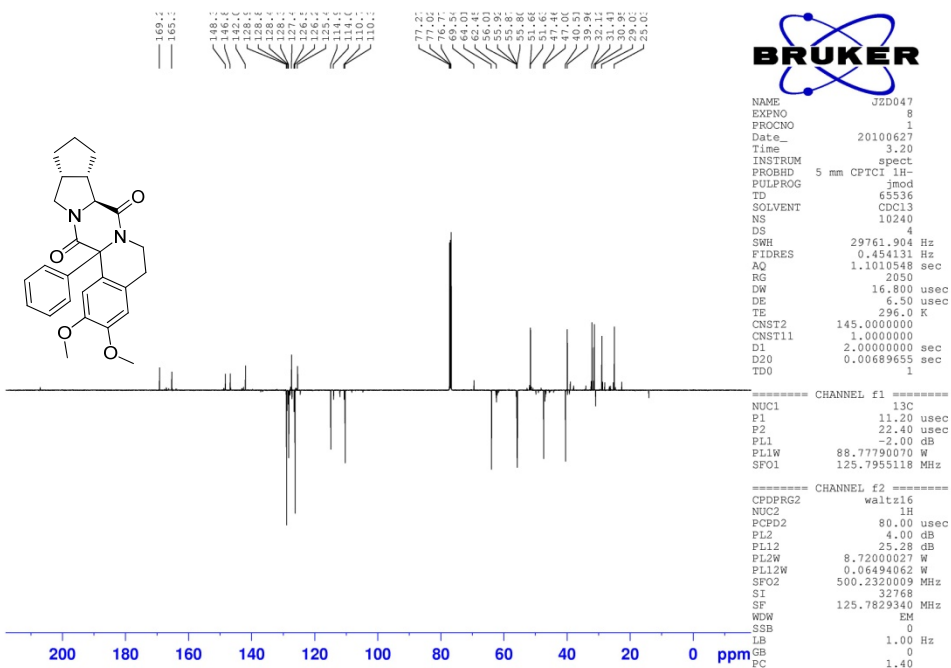
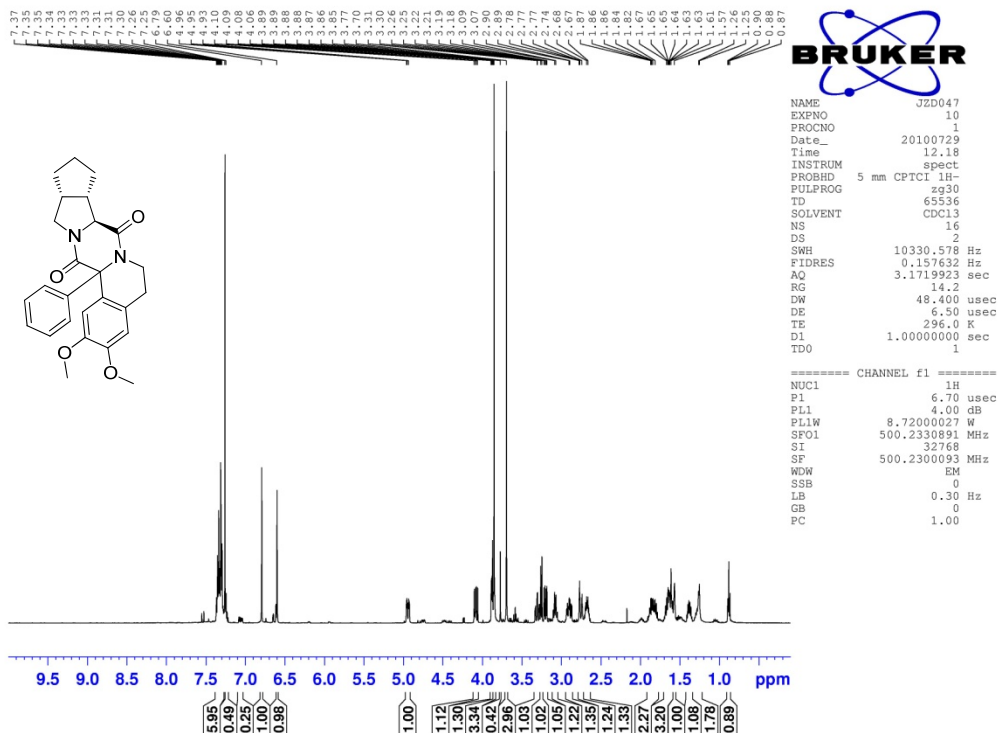
Compound 21



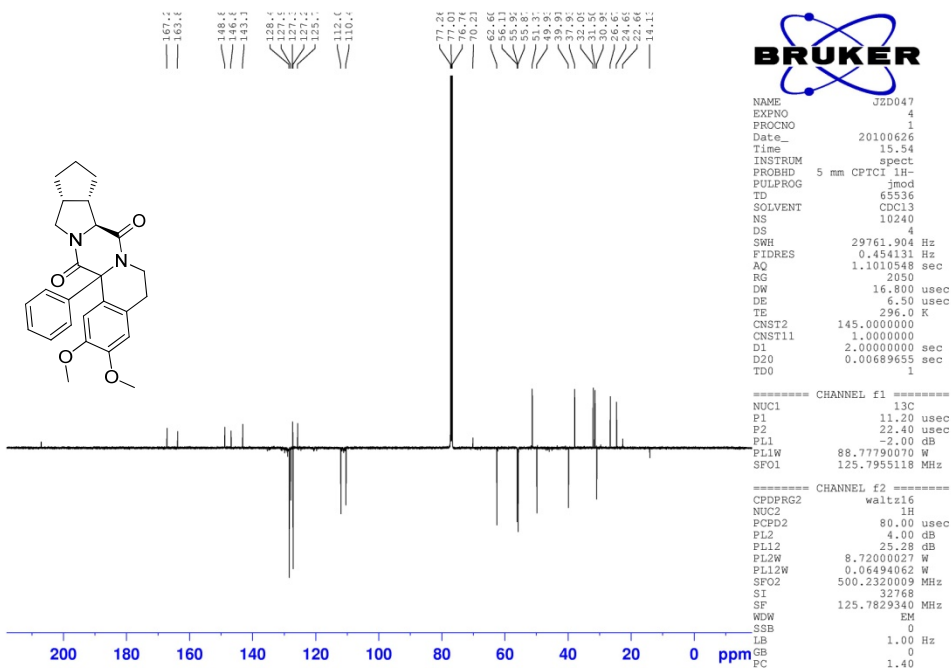
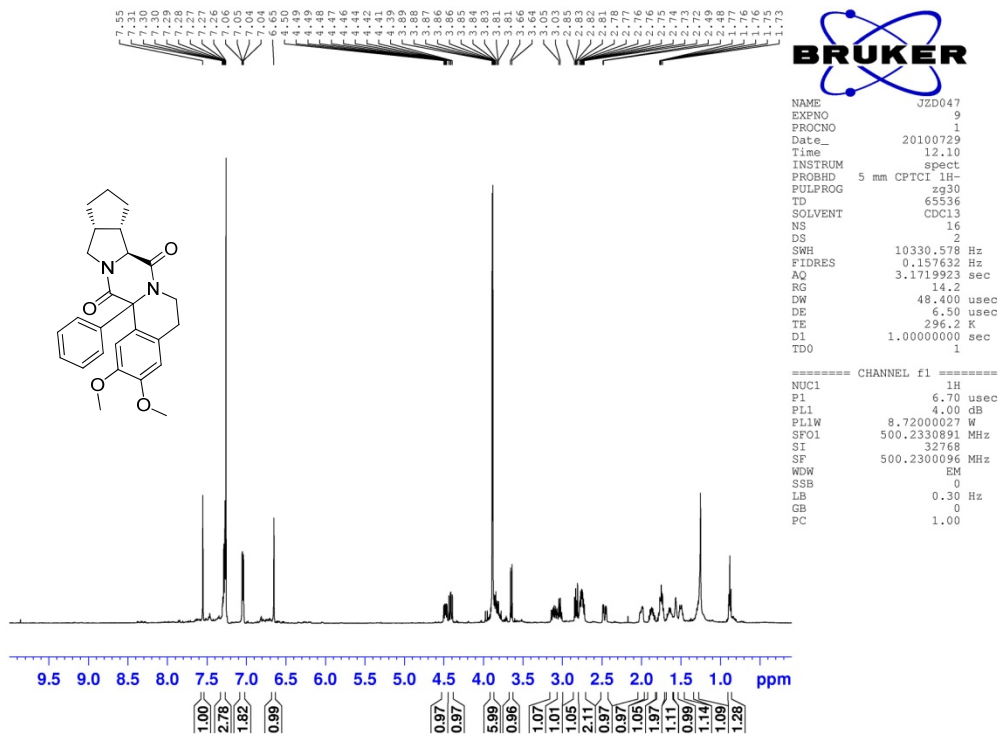
Compound 22



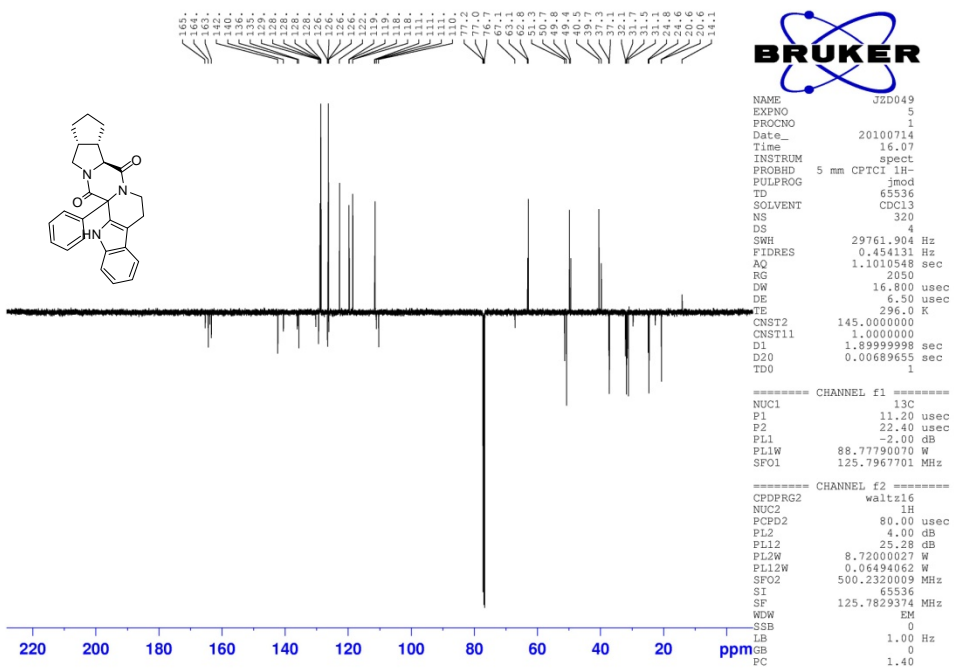
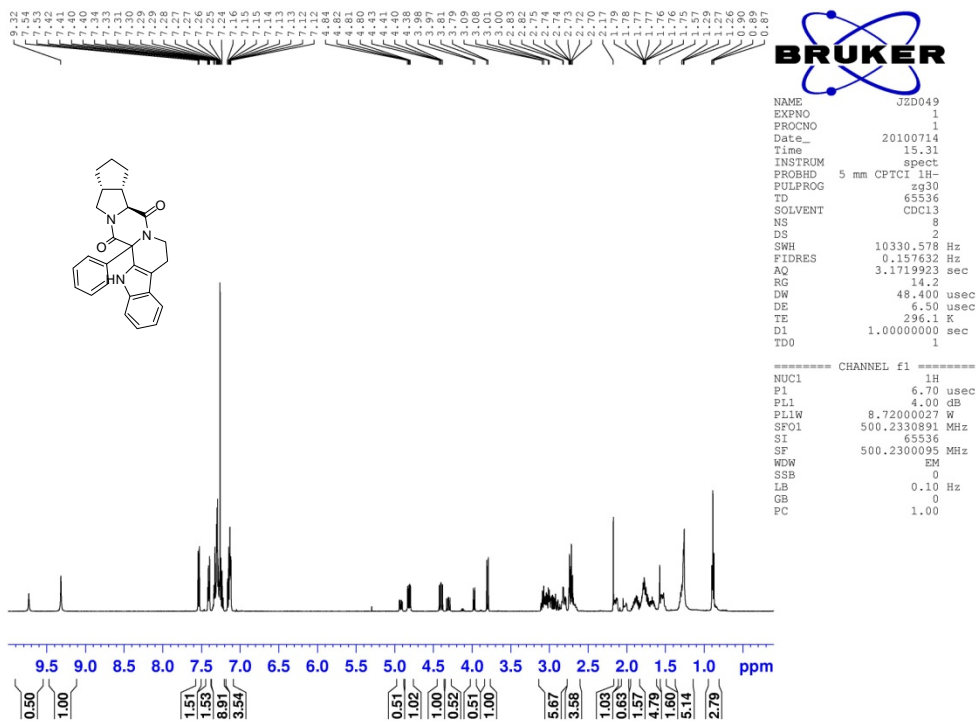
Compound 23 (major diastereomer)



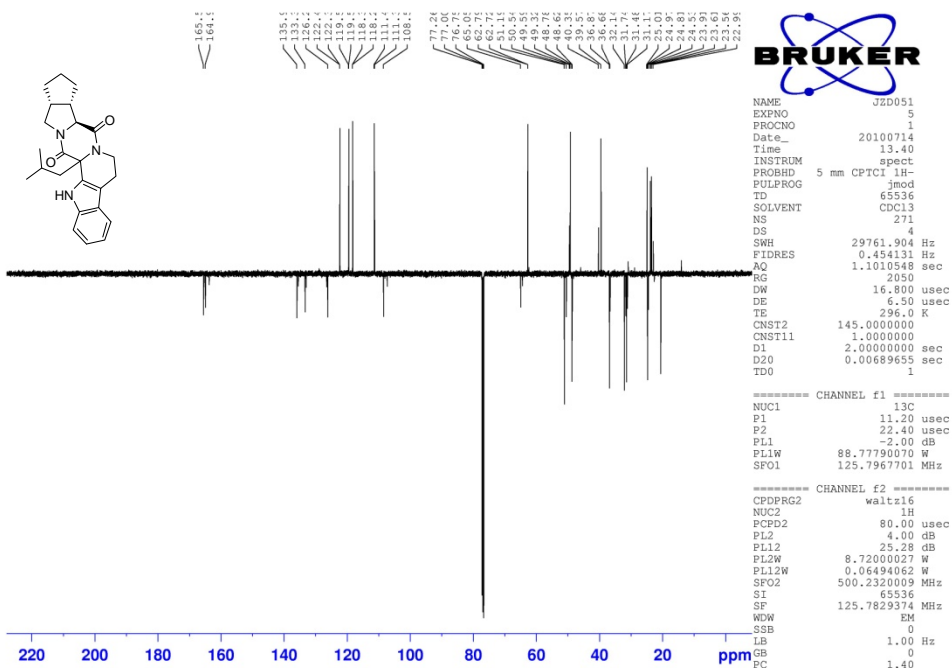
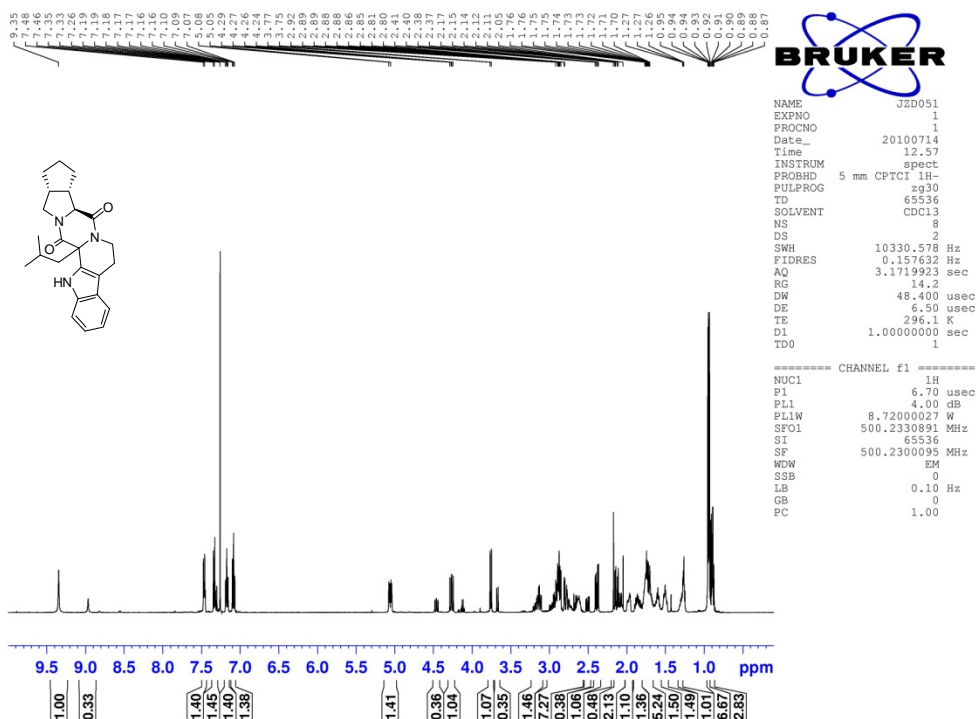
Compound 23 (minor diastereomer)



Compound 24



Compound 25



Crystallographic data

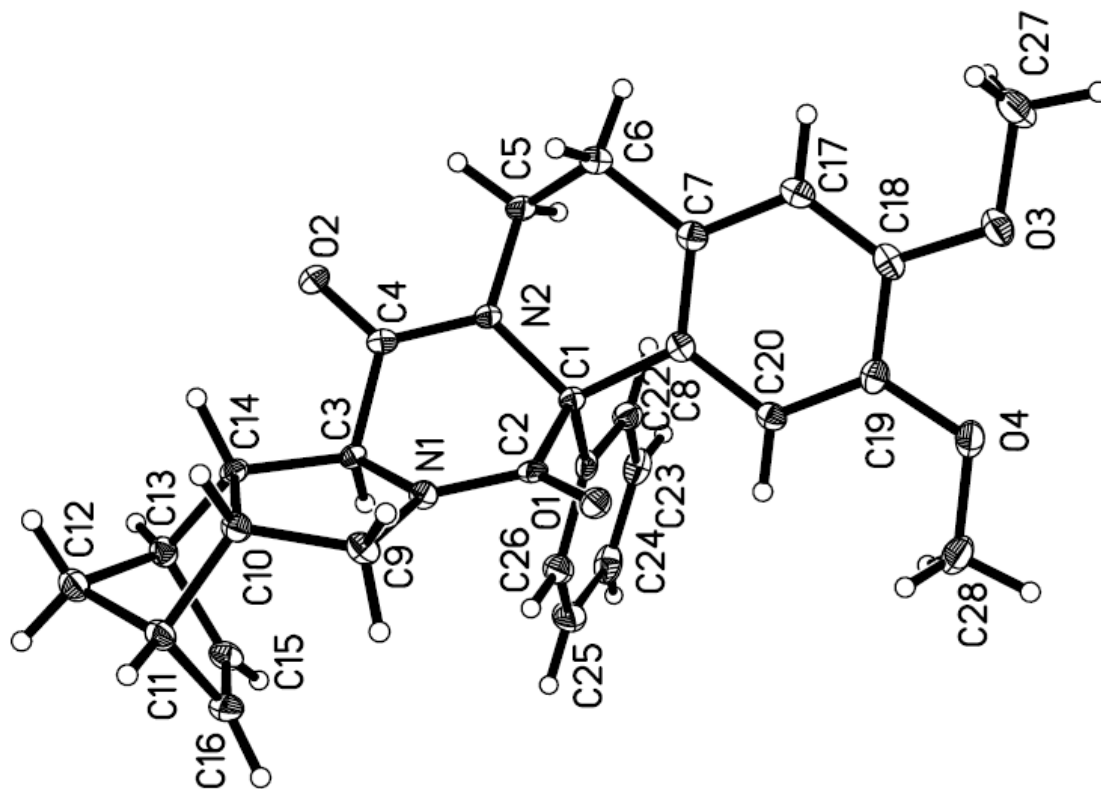


Fig. S1 X-ray crystal structure of compound **14a** with atom labels

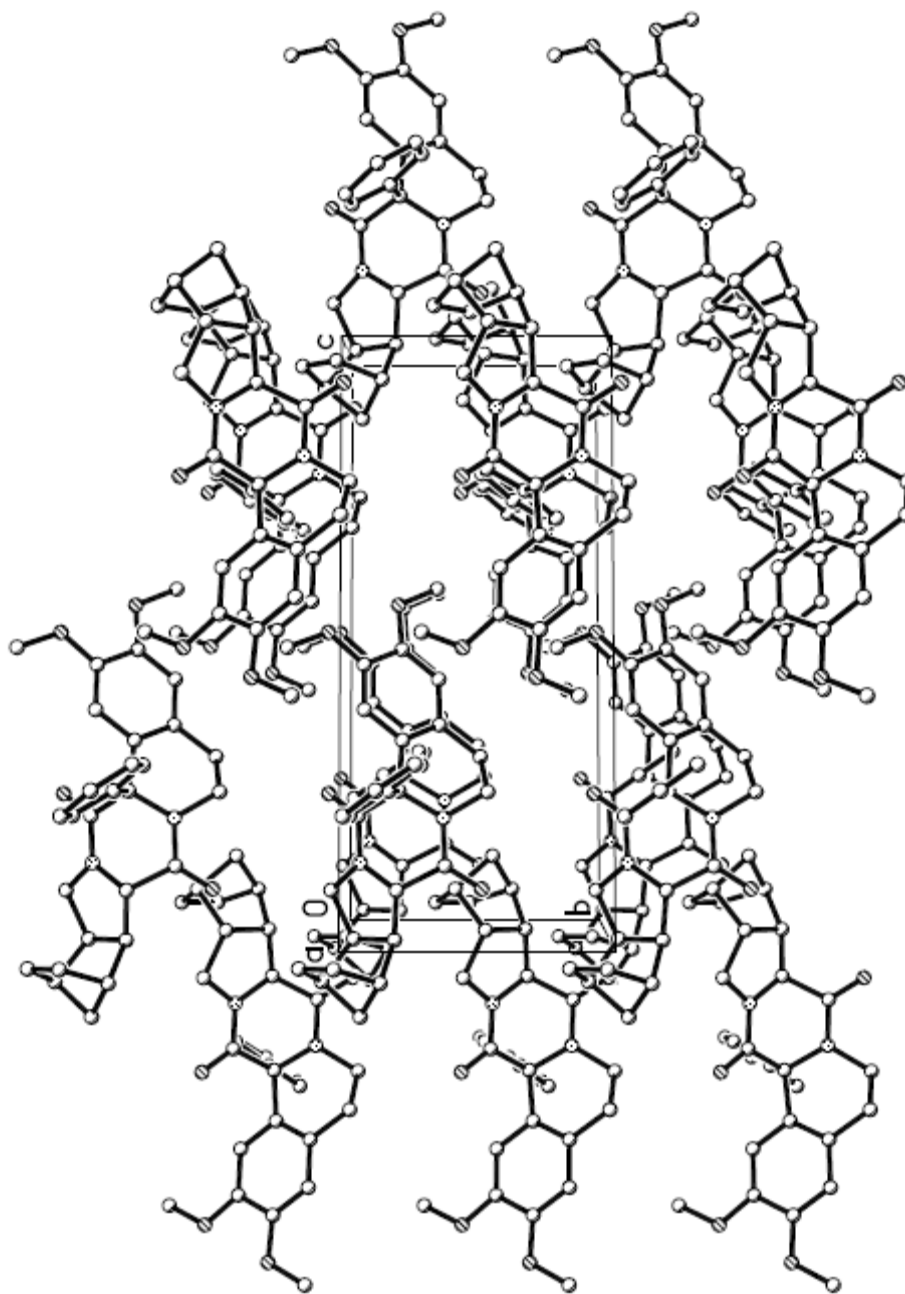


Fig. S2 X-ray crystal structure of compound **14a** with unit cell