Unexpected synthesis of aziridines under Cu(I) catalyzed Kinugasa conditions assisted by microwaves irradiation

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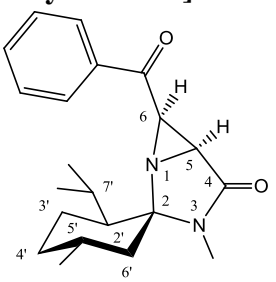
Experimental Section

General methods: Thin-layer chromatography (TLC) was carried out on aluminum sheets coated with silica gel 60 F_{254} (Merck). ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX400 spectrometer with the residual solvent as the internal standard. The chemical shifts are expressed on the δ scale in parts per million (ppm). The following abbreviations are used to explain the observed multiplicities: s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; t, triplet; m, multiplet; br, broad. NMR solvents were purchased from Eurisotop (Saint Aubin, France). MS (ESI) data were recorded in the positive mode using a Bruker MicrOTOF-Q II spectrometer. Structure elucidation was deduced from 1D and 2D NMR spectroscopy which allowed signal assignments based on COSY and HSQC correlations and by X-ray diffraction analysis.

General Procedure: Reaction of nitrone 1 with alkynes.
In a Biotage Initiator 5-mL vial, CuI (100 mg) was suspended in anhydrous DMF (1 mL). The vial was flushed with argon and Et_3N (3 eq, 1.26 mmol, 127 mg), then alkyne (4eq, 1.68 mmol) was added. The solution was stirred for 10 min at 0°C and nitrone **1** (1 eq, 0.42 mmol, 100 mg) in anhydrous DMF (1 mL) was added. The vial was sealed with a septum cap and was irradiated by microwaves at 100°C. TLC monitoring (EtOAc/PE 5/5) showed full conversion after 2 h. The crude mixture was dissolved in biphasic mixture (EtOAc/H_2O, 50 mL, 1/1). The aqueous layer was separated and then extracted with EtOAc (3×10 mL). The organic layers were combined and washed with brine (2×30 mL), dried (Na_2SO_4), filtered, concentrated and purified by flash silica gel column chromatography (EtOAc/PE 1/3) to provide aziridines **3-4**.

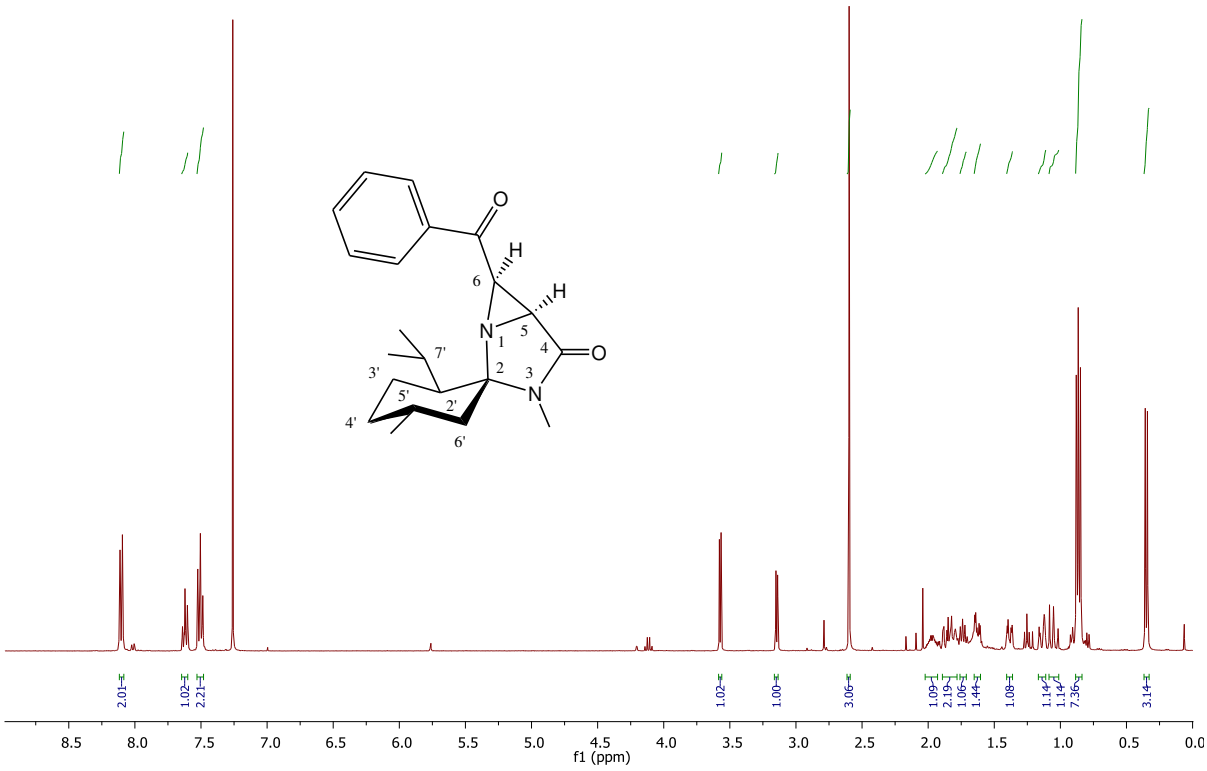
(1'R,2'S,5S,5'R,6R)-6-benzoyl-2'-isopropyl-3,5'-dimethyl-1,3-diazaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexan]-4-one (4a)

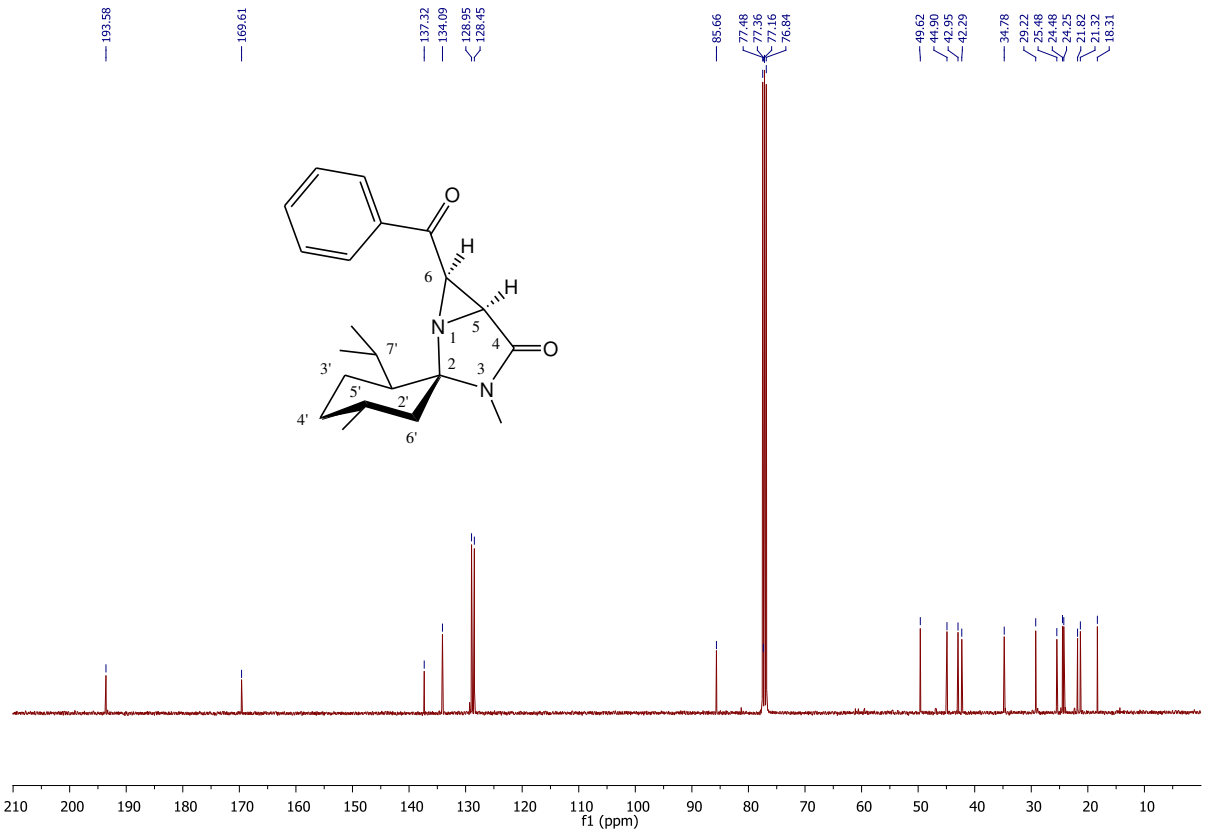


Obtained as a white solid (75 mg, 52%) following general procedure: alkyne **2a** (171 mg).

(**4a**) White solid ; M.p. 182–183°C (Et_2O); R_f = 0.46 (EtOAc/PE, 5/5); $[\alpha]_D^{20}$ = -85.7 (c = 0.2,CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.34 (d,3H, J = 6.6 Hz, CH_3), 0.85 (d, 3H, J = 5.84 Hz, CH_3), 0.86 (d, 3H, J = 5.92 Hz, CH_3), 0.89-0.92 (m, 1H), 1.05 (t, 1H, J_{gem} = 12.1 Hz), 1.11-1.16 (m, 1H), 1.38 (ddd, 1H, J = 9.0 Hz, J = 3.4 Hz, J = 1.1 Hz), 1.62 (dq, 1H, J = 10.2, J = 7.8, J = 4.7 Hz), 1.69-1.73 (m, 1H), 1.78-1.79 (m, 1H), 1.85-1.89 (m, 1H), 1.91-2.02 (m, 1H), 2.59 (s, 3H, NCH_3), 3.14 (d, 1H, J = 5.1 Hz), 3.57 (d, 1H, J = 5.1 Hz), 7.47-7.52 (m, 2H, Harom), 7.62 (tt, 1H, J = 6.1 Hz, J = 4.2 Hz, J = 1.3 Hz, Harom), 8.07-8.15 (m, 2H, Harom); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 18.3, 21.3, 21.8, 24.2, 24.5, 25.5 (NCH_3), 29.2,

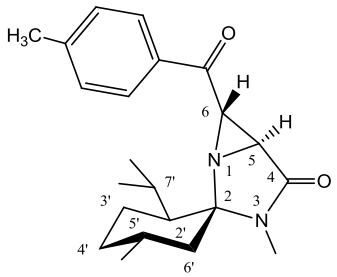
34.8, 42.3, 42.9, 44.9, 49.6, 85.7, 128.4, 128.9, 134.1, 137.3, 169.6 (C=O), 193.6(C=O); HRMS (ESI): *m/z* calcd for $C_{21}H_{29}N_2O_2[M+H]^+$ 341.2224; found 341.2228.



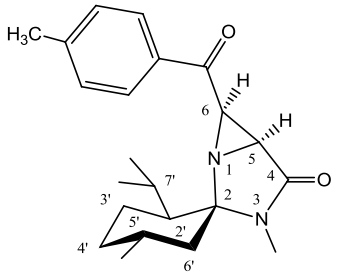


(1'R,2'S,5S,5'R,6S)-2'-isopropyl-3,5'-dimethyl-6-(4-methylbenzoyl)-1,3-diazaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexan]-4-one (3b) and (1'R,2'S,5S,5'R,6R)-2'-isopropyl-3,5'-dimethyl-6-(4-methylbenzoyl)-1,3-diazaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexan]-4-one (4b)

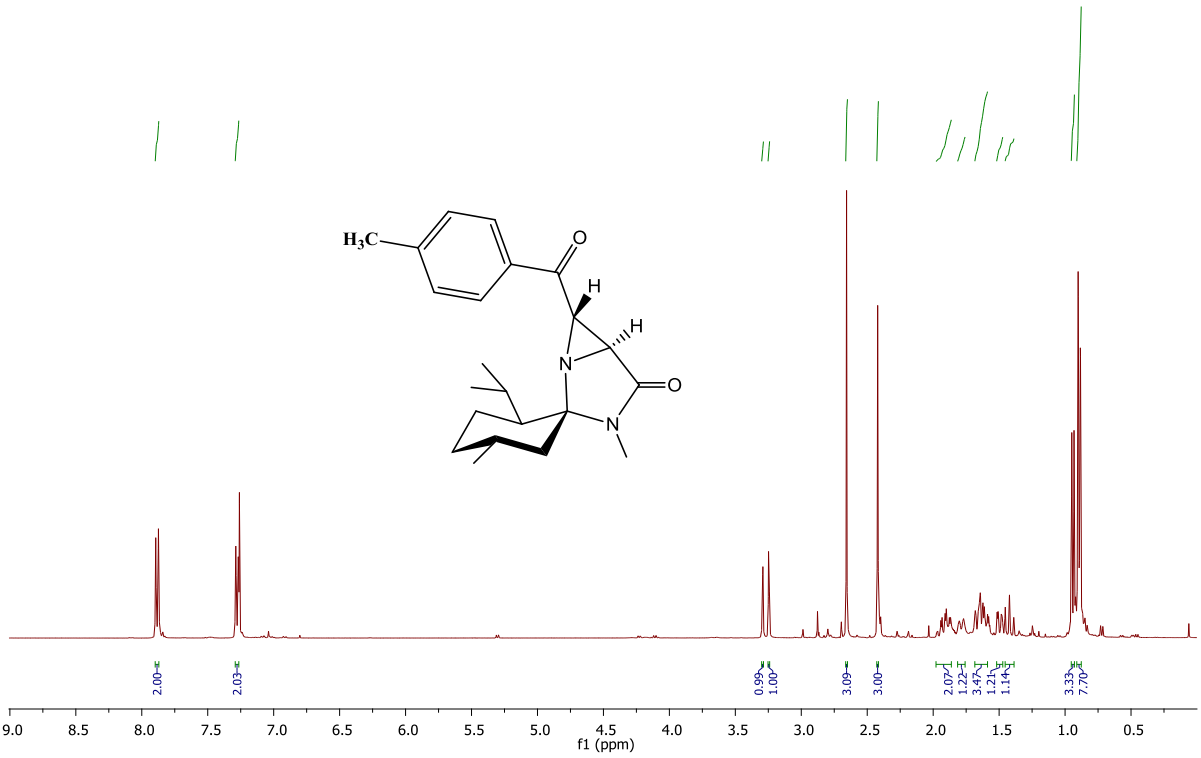
Compounds **3b** (47 mg, 13%) and **4b** (190 mg, 53%) were obtained following general procedure: alkyne **2b** (194 mg).



(3b) Yellow amorphous solid; R_f = 0.56 (EtOAc/PE, 5/5); $[\alpha]_D^{20}$ = +100.0 (c = 0.2, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (d,6H, J = 6.7 Hz, 2CH_3), 0.93 (d, 3H, J = 6.8 Hz, CH_3), 0.94-0.96 (m, 1H), 1.05 (t, 1H, J_{gem} = 12.8 Hz), 1.48-1.52 (m, 1H), 1.61-1.66 (m, 3H), 1.77-1.80 (m, 1H), 1.89-1.92 (m, 2H), 2.42 (s, 3H, CH_3), 2.65 (s, 3H, NCH_3), 3.24 (d, 1H, J = 2.0 Hz), 3.30 (d, 1H, J = 1.7 Hz), 7.27 (d, 2H, J = 8.0 Hz, Harom), 7.88 (d, 2H, J = 8.2 Hz, Harom);^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 21.3, 21.9, 22.3, 24.1, 24.6, 25.5 (NCH_3), 28.7, 34.7, 39.8, 43.2, 45.5, 48.1, 85.7, 128.6, 129.6, 134.0, 145.0, 170.8 (C=O), 192.7 (C=O); HRMS (ESI): *m/z* calcd for $C_{22}H_{31}N_2O_2[M+H]^+$ 355.2380; found 355.2378.



(4b) White solid; M.p. 177–178°C (Et_2O); R_f = 0.42 (EtOAc/PE, 5/5); $[\alpha]_D^{20}$ = -9.8 (c = 0.7,CH_2Cl_2); ^{1}H NMR(400 MHz, $CDCl_3$): δ = 0.36 (d,3H, J = 6.6 Hz, CH_3), 0.85 (d, 3H, J = 6.6 Hz, CH_3), 0.87 (d, 3H, J = 6.3 Hz, CH_3), 0.90-0.96 (m, 1H), 1.03 (t, 1H, J_{gem} = 13.4 Hz), 1.14-1.19 (m, 1H), 1.38 (ddd, 1H, J = 9.1 Hz, J = 3.4 Hz, J = 1.1 Hz), 1.59-1.65 (m, 1H), 1.68-1.75 (m, 1H), 1.79-1.85 (m, 2H), 1.93-2.00 (m, 1H), 2.42 (s, 3H, CH_3), 2.59 (s, 3H, NCH_3), 3.14 (d, 1H, J = 5.1 Hz), 3.56 (d, 1H, J = 5.1 Hz), 7.27-7.30 (m, 2H, Harom), 7.98-8.00 (m, 2H, Harom); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 21.4 (CH_3), 21.8, 21.9, 24.2, 24.5, 25.5 (NCH_3), 29.2, 34.8, 42.2, 43.0, 44.9, 49.6, 85.6, 128.6, 129.6, 135.0, 145.1, 169.7 (C=O), 193.2 (C=O); HRMS (ESI): *m/z* calcd for $C_{22}H_{31}N_2O_2[M+H]^+$ 355.2380; found 355.2371.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O
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1.00
3.09
3.00
2.07
1.22
3.47
1.21
1.14
3.33
7.70
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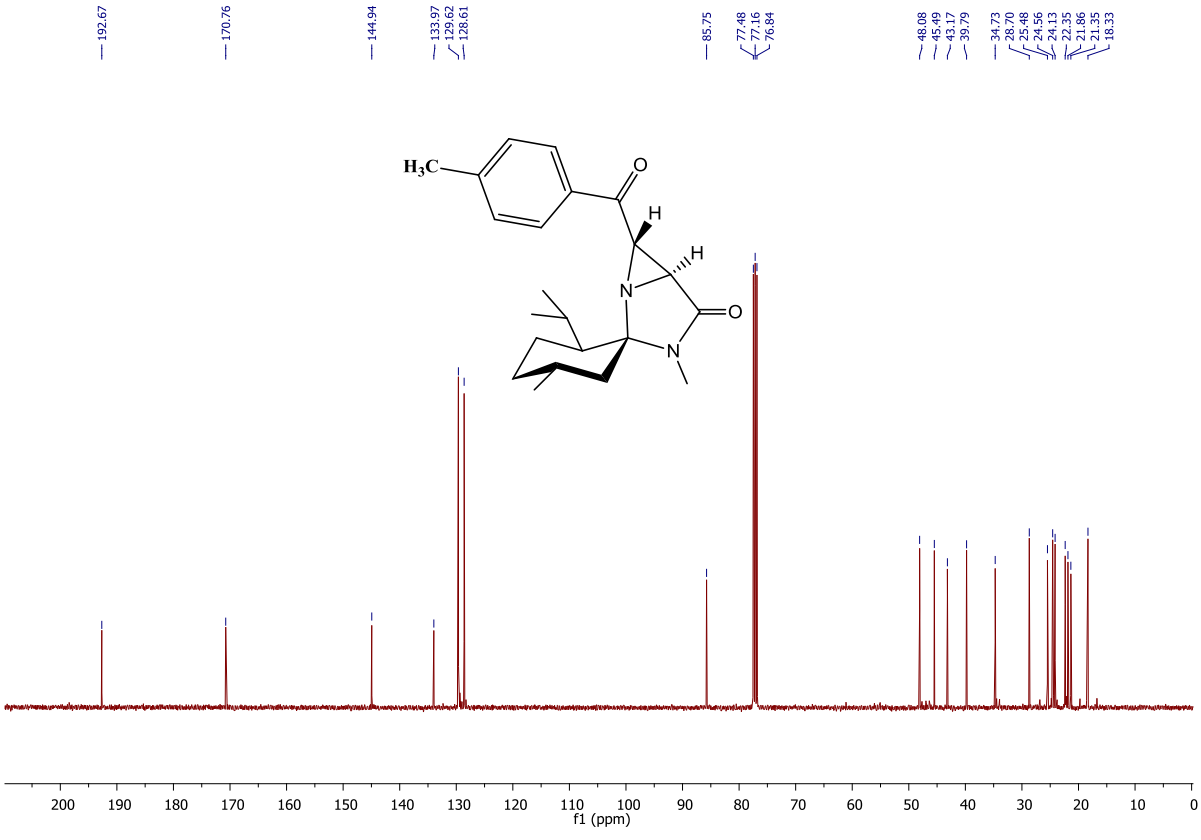
f1 (ppm)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77.48
77.16
76.84
48.08
45.49
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39.79
34.73
28.70
25.48
24.56
24.13
22.35
21.86
21.35
18.33
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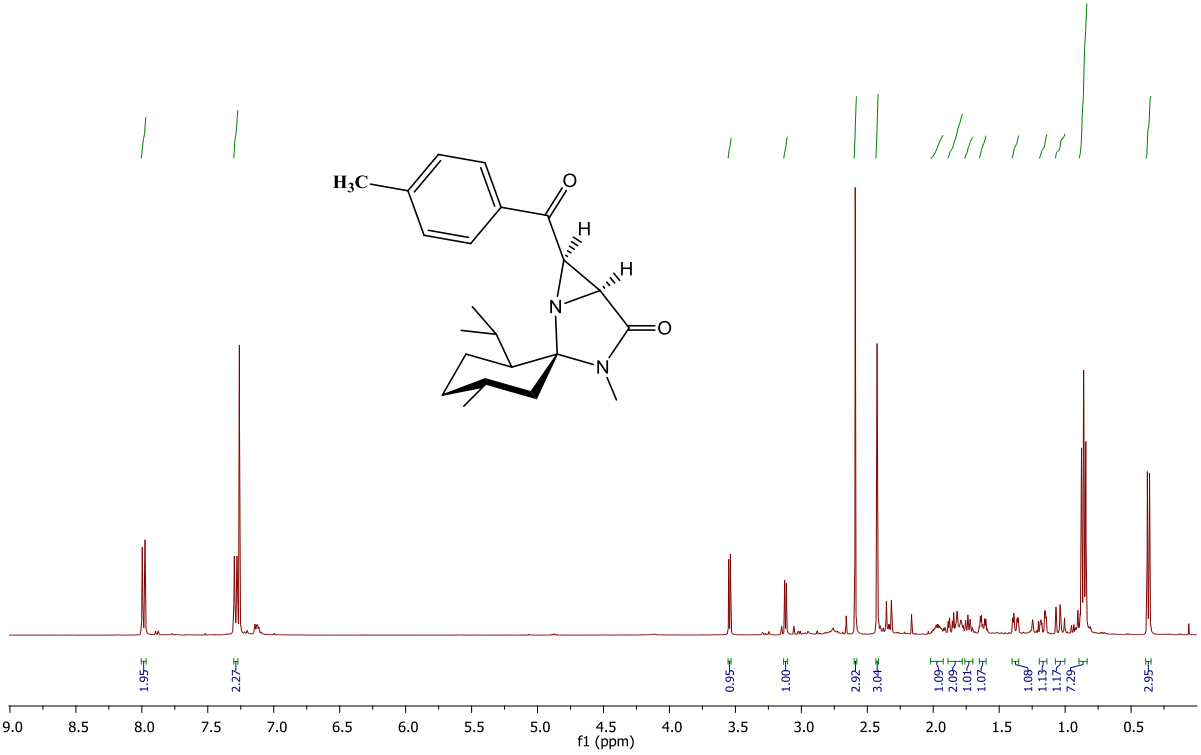
H
H
N
O
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)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H
H
N
O
N
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1.00
2.92
3.04
1.09
2.09
1.01
1.07
1.08
1.13
1.17
7.29
2.95
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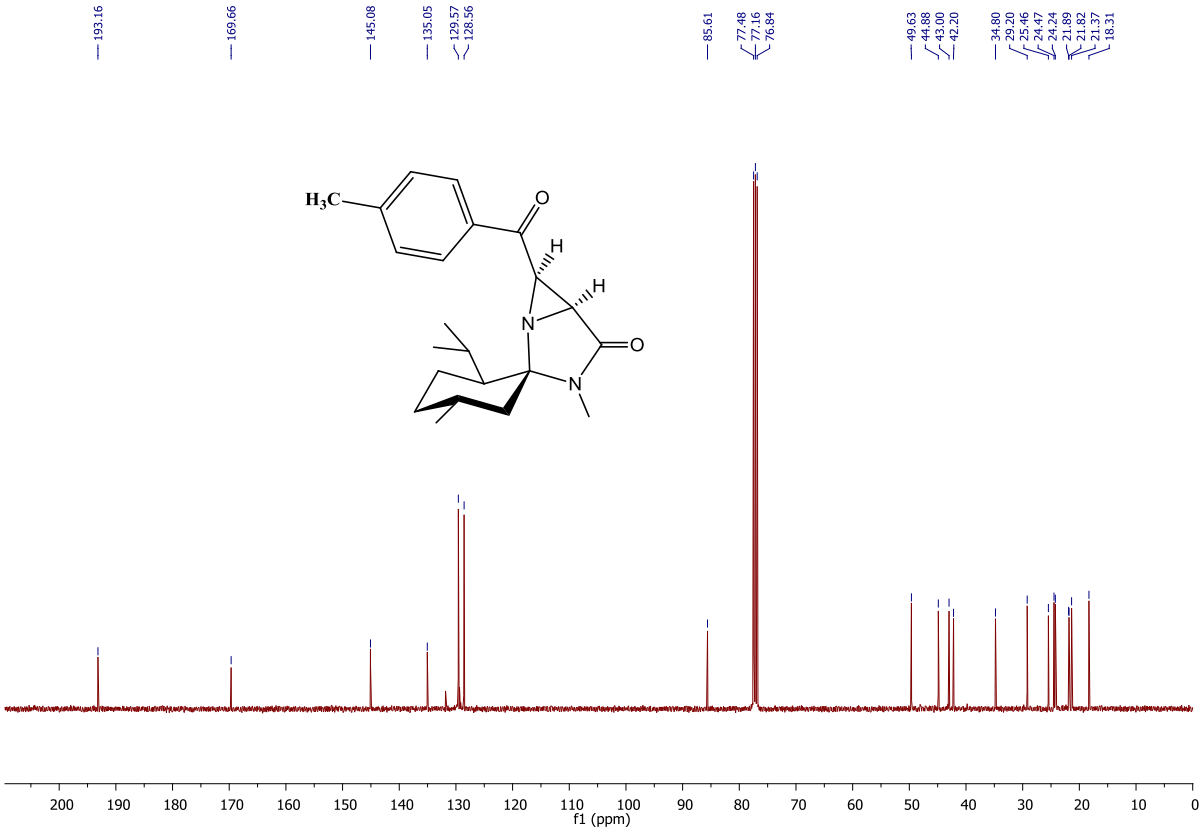
f1 (ppm)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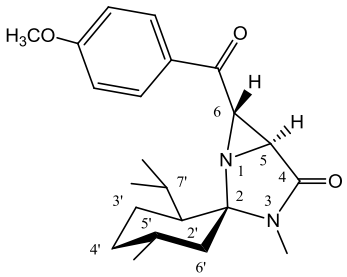
77.16
76.84
49.63
44.88
43.00
42.20
34.80
29.20
25.46
24.47
24.24
21.89
21.82
21.37
18.31
H3C
O
H
H
N
O
N
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

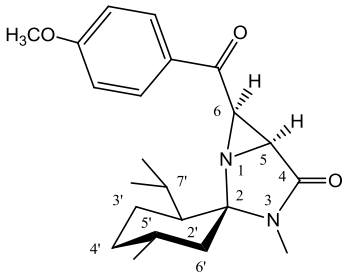
(1'R,2'S,5S,5'R,6S)-2'-isopropyl-6-(4-methoxybenzoyl)-3,5'-dimethyl-1,3-diazaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexan]-4-one (3c) and (1'R,2'S,5S,5'R,6R)-2'-isopropyl-6-(4-methoxybenzoyl)-3,5'-dimethyl-1,3-diazaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexan]-4-one (4c)

Compounds **3c** (80 mg, 21%) and **4c** (194 mg, 52%) were obtained following general procedure: alkyne **2c** (221 mg).

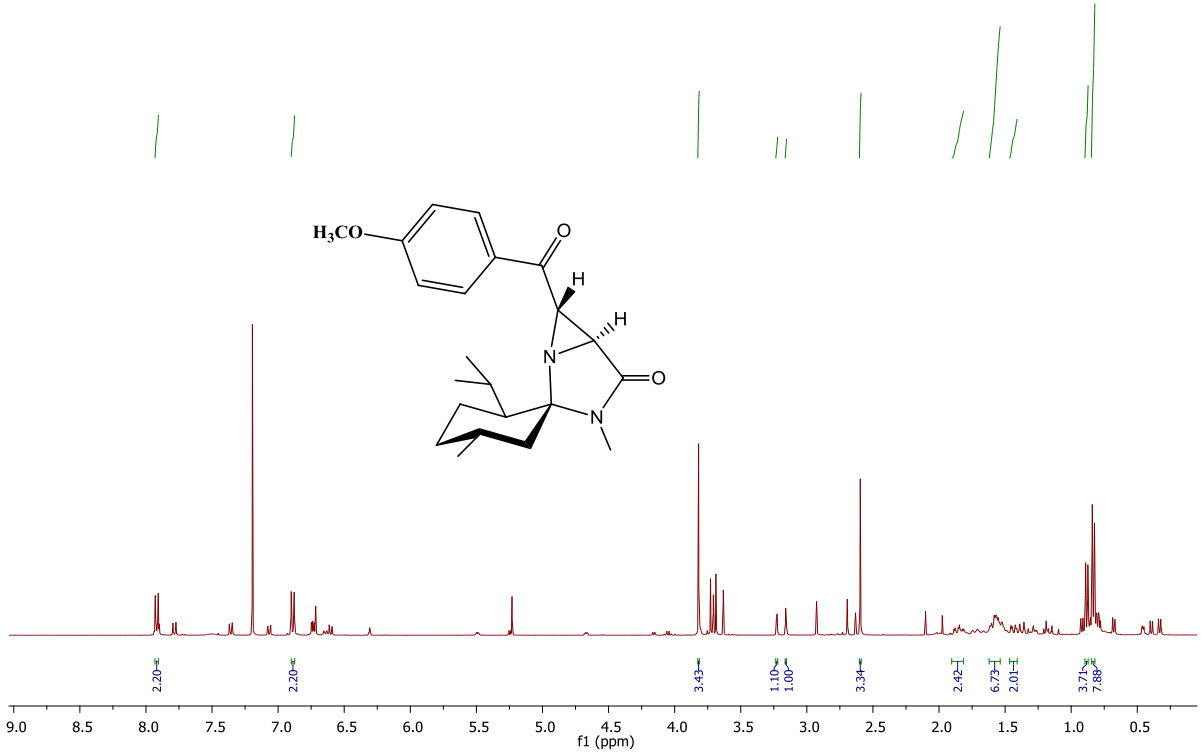


(3c)* Yellow amorphous solid; R_f = 0.38 (EtOAc/PE, 5/5); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d, 6H, J = 6.7 Hz, $2CH_3$), 0.94 (d, 3H, J = 6.8 Hz, CH_3), 0.96-0.99 (m, 1H), 1.21-1.27 (m, 1H), 1.50 (ddd, 1H, J = 8.8 Hz, J = 3.5 Hz, J = 1.1 Hz), 1.59-1.65 (m, 3H), 1.76-1.79 (m, 3H), 2.66 (s, 3H, NCH_3), 3.22 (d, 1H, J = 2.0 Hz), 3.29 (d, 1H, J = 1.8 Hz), 3.88 (s, 3H, OCH_3), 6.95 (dt, 2H, J = 8.9 Hz, J = 2.8 Hz, H-arom), 7.98 (dt, 2H, J = 8.9Hz, J = 3.2 Hz, H-arom).^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 21.4,22.4, 24.2, 24.6, 25.5 (NCH_3), 28.7, 34.8, 39.8, 43.2, 45.4, 48.1, 55.7 (OCH_3), 85.7, 114.1, 130.7, 131.0, 164.1, 170.7 (C=O), 191.3 (C=O); HRMS (ESI): *m/z* calcd for $C_{22}H_{31}N_2O_3[M+H]^+$ 371.2320; found 371.2317.

* Compound **3c** is contaminated by unknown products.



(4c) White solid; M.p. 165–166°C (Et_2O); R_f = 0.28 (EtOAc/PE, 5/5); $[\alpha]_D^{20}$ = -6.1 (c = 0.8, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.39 (d,3H, J = 6.6 Hz, CH_3), 0.85 (d, 3H, J = 6.7 Hz, CH_3), 0.86 (d, 3H, J = 6.2 Hz, CH_3), 0.89-0.92 (m, 1H), 1.03 (t, 1H, J_{gem} = 13.3 Hz), 1.18-1.23 (m, 1H), 1.37 (ddd, 1H, J = 9.0 Hz, J = 3.4 Hz, J = 1.1 Hz), 1.59-1.64 (m, 1H), 1.70-1.77 (m, 1H), 1.81-1.85 (m, 2H), 1.91-2.01 (m, 1H), 2.58 (s, 3H, NCH_3), 3.11 (d, 1H, J = 5.1 Hz), 3.52 (d, 1H, J = 5.2 Hz), 3.88 (s, 3H, OCH_3), 6.95 (dt, 2H, J = 9 Hz, J = 2.7 Hz, Harom), 8.07 (dt, 2H, J = 9 Hz, J = 2.9 Hz, Harom); ^{13}C NMR (100 MHz, $CDCl_3$): δ= 18.3, 21.5, 21.8, 24.2, 24.5, 25.5 (NCH_3), 29.2, 34.8, 42.1, 43.0, 44.8, 49.6, 55.7 (OCH_3), 85.6, 114.1, 130.7,130.8, 164.2,169.7 (C=O), 191.9 (C=O); HRMS (ESI): *m/z* calcd for $C_{22}H_{30}N_2NaO_3[M+Na]^+$ 393.2149; found 393.2140.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H
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2.01
3.71
7.88
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
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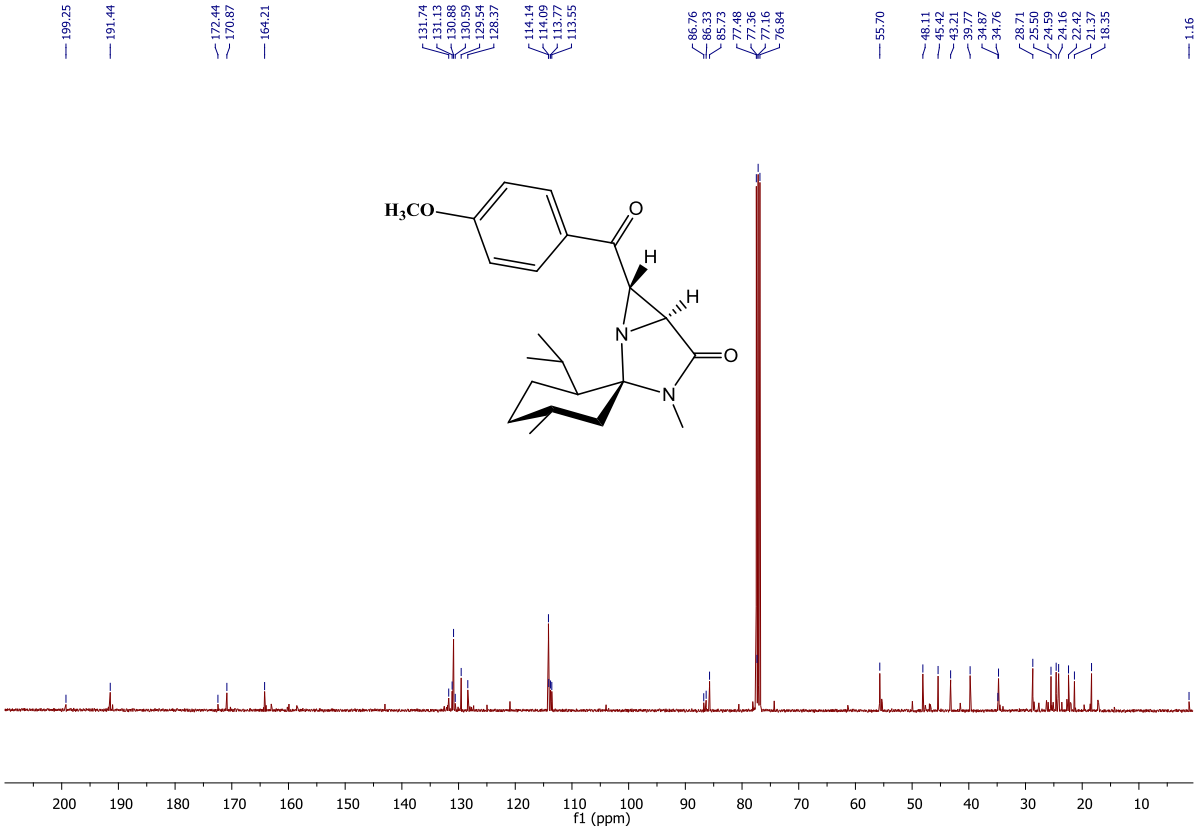
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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131.74
131.13
130.88
130.59
129.54
128.37
114.14
114.09
113.77
113.55
86.76
86.33
85.73
77.48
77.36
77.16
76.84
55.70
48.11
45.42
43.21
39.77
34.87
34.76
28.71
25.50
24.59
24.16
22.42
21.37
18.35
1.16
H3CO
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H
H
N
O
N
200
190
180
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140
130
120
110
100
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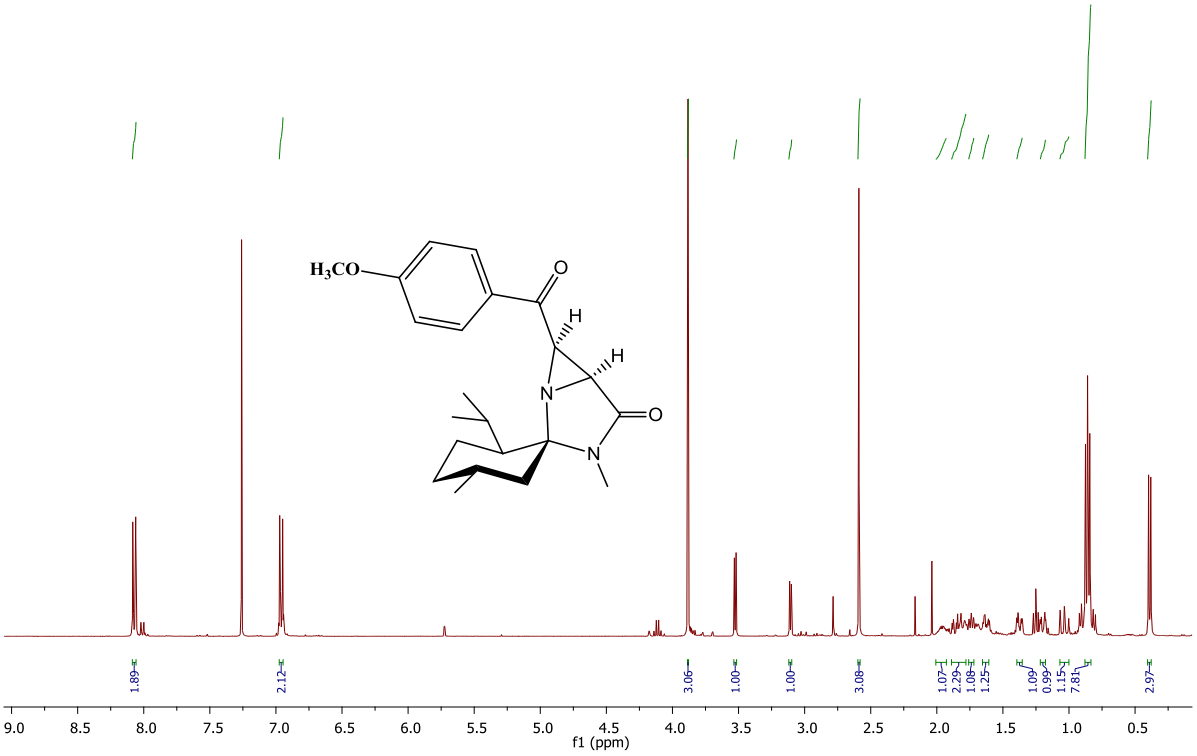
60
50
40
30
20
10
f1 (ppm)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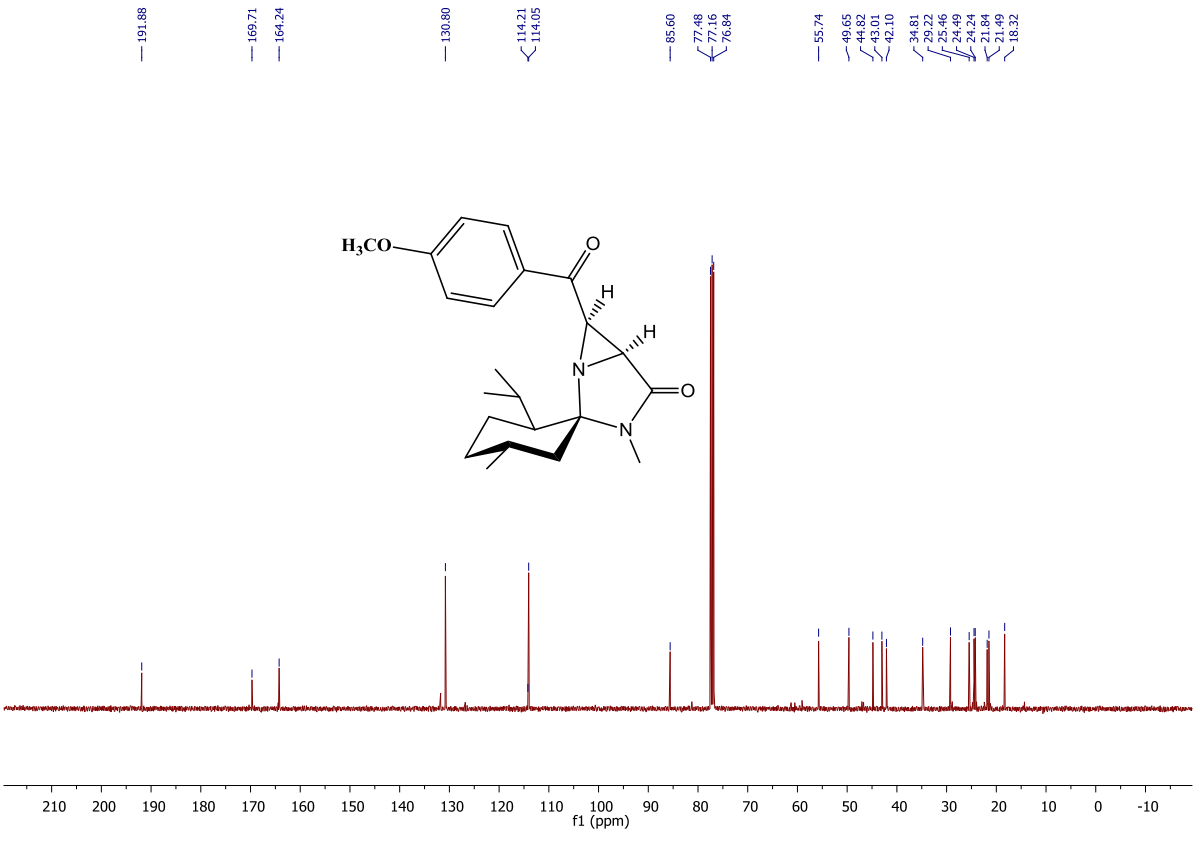
1.00
3.08
1.07
2.29
1.08
1.25
1.09
0.99
1.15
7.81
2.97
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)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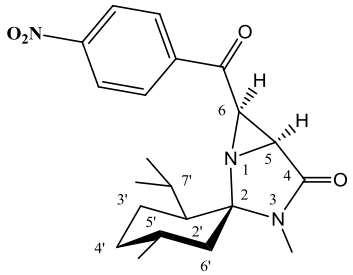
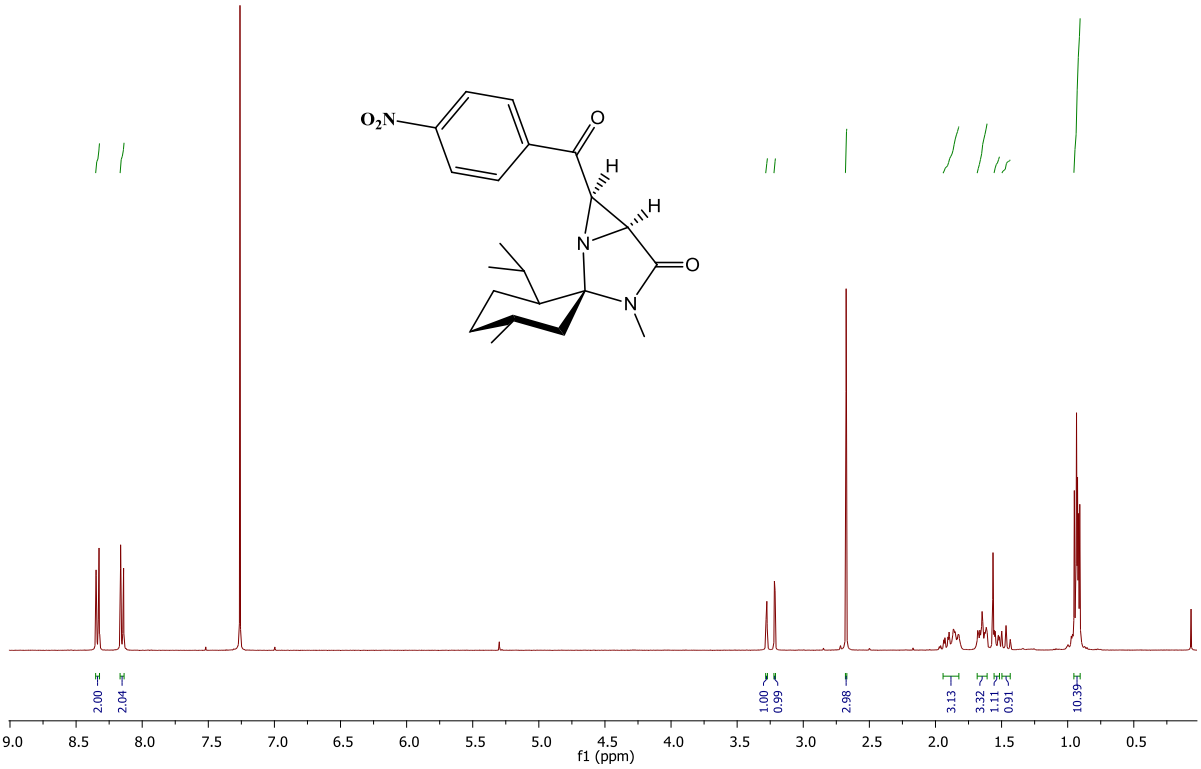
130.80
114.21
114.05
85.60
77.48
77.16
76.84
55.74
49.65
44.82
43.01
42.10
34.81
29.22
25.46
24.49
24.24
21.84
21.49
18.32
H3CO
O
H
H
N
O
N
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

(1'R,2'S,5S,5'R,6R)-2'-isopropyl-3,5'-dimethyl-6-(4-nitrobenzoyl)-1,3-diazaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexan]-4-one (4d)

Obtained as a yellow solid (157 mg, 64%) following general procedure: alkyne **2d** (277 mg).



(4d) Yellow solid; M.p. 188–189°C (Et_2O); R_f = 0.56 (EtOAc/PE, 5/5); $[\alpha]_D^{20}$ = +50.0 (c = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.91 (d,3H, J = 4.1 Hz, CH_3), 0.92 (d,3H, J = 3 Hz, CH_3), 0.94 (d, 3H, J = 6.6 Hz, CH_3), 0.96-1.00 (m, 1H), 1.46 (t, 1H, J_{gem} = 12.9 Hz), 1.53 (ddd, 1H, J = 9.0 Hz, J = 3.4 Hz, J = 1.2 Hz), 1.62-1.67 (m, 3H), 1.82-1.96 (m, 3H), 2.67 (s, 3H, NCH_3), 3.21 (d, 1H, J = 2.0 Hz), 3.28 (d, 1H, J = 1.7 Hz), 8.15 (dt, 2H, J = 9.0Hz, J = 2.2 Hz, Harom), 8.34 (dt, 2H, J = 8.9 Hz, J = 2.2 Hz, Harom); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 21.5, 22.4, 24.1, 24.5, 25.6 (NCH_3), 28.9, 34.7, 40.7, 43.1, 46.0, 48.1, 85.9, 124.1, 129.6, 140.7, 150.7, 169.9 (C=O), 192.3 (C=O); HRMS (ESI): *m/z* calcd for $C_{21}H_{28}N_3O_4[M+H]^+$ 386.2074; found 386.2074.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O
H
H
N
O
N
2.00
2.04
1.00
0.99
2.98
3.13
3.32
1.11
0.91
10.39
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
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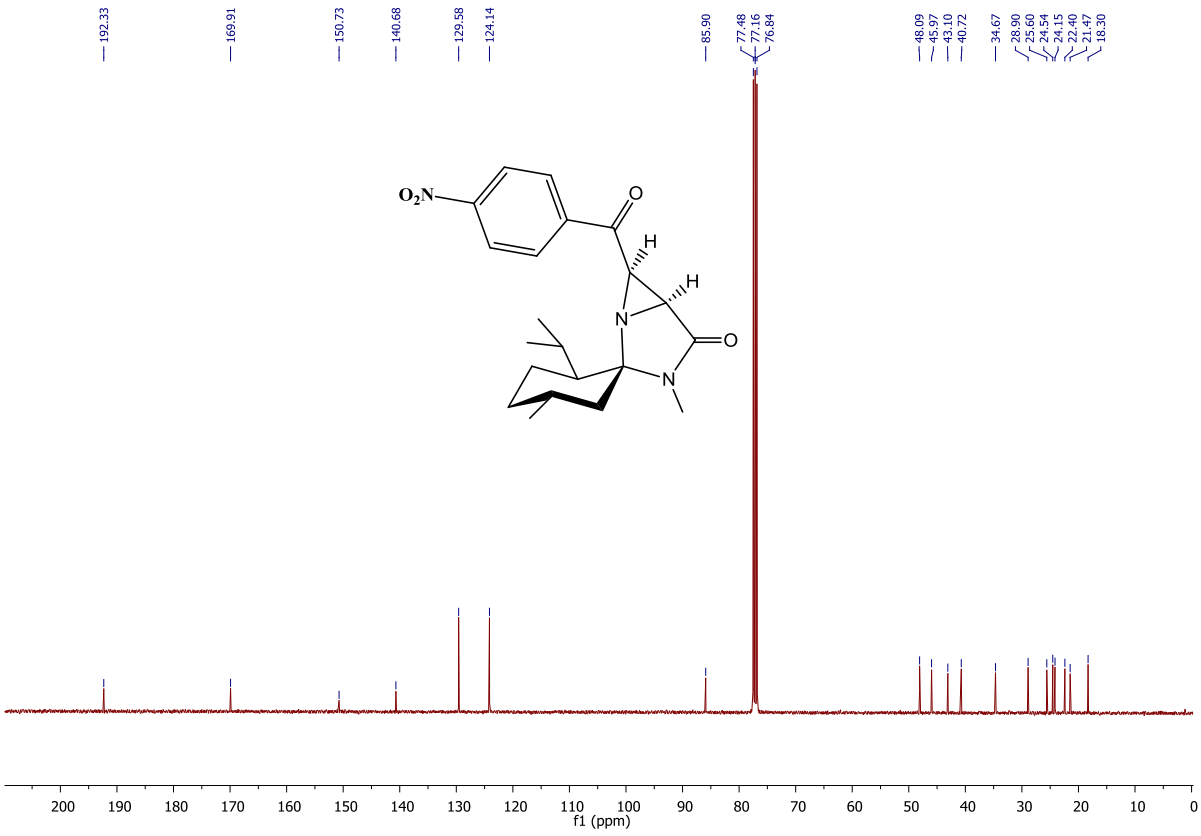
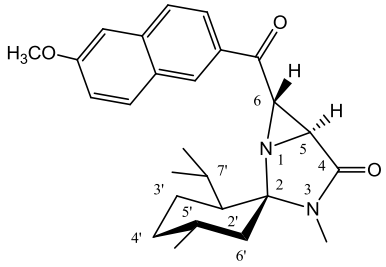
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

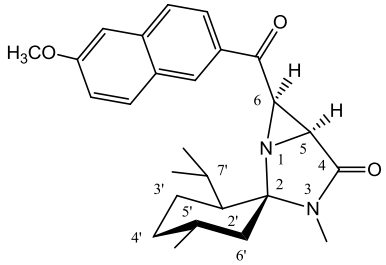

192.33
169.91
150.73
140.68
129.58
124.14
85.90
77.48
77.16
76.84
48.09
45.97
43.10
40.72
34.67
28.90
25.60
24.54
24.15
22.40
21.47
18.30
O2N
O
H
H
N
O
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

(1'R,2'S,5S,5'R,6S)-2'-isopropyl-6-(6-methoxy-2-naphthoyl)-3,5'-dimethyl-1,3-diazaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexan]-4-one (3e) and (1'R,2'S,5S,5'R,6R)-2'-isopropyl-6-(6-methoxy-2-naphthoyl)-3,5'-dimethyl-1,3-diazaspiro[bicyclo[3.1.0]hexane-2,1'-cyclohexan]-4-one (4e)

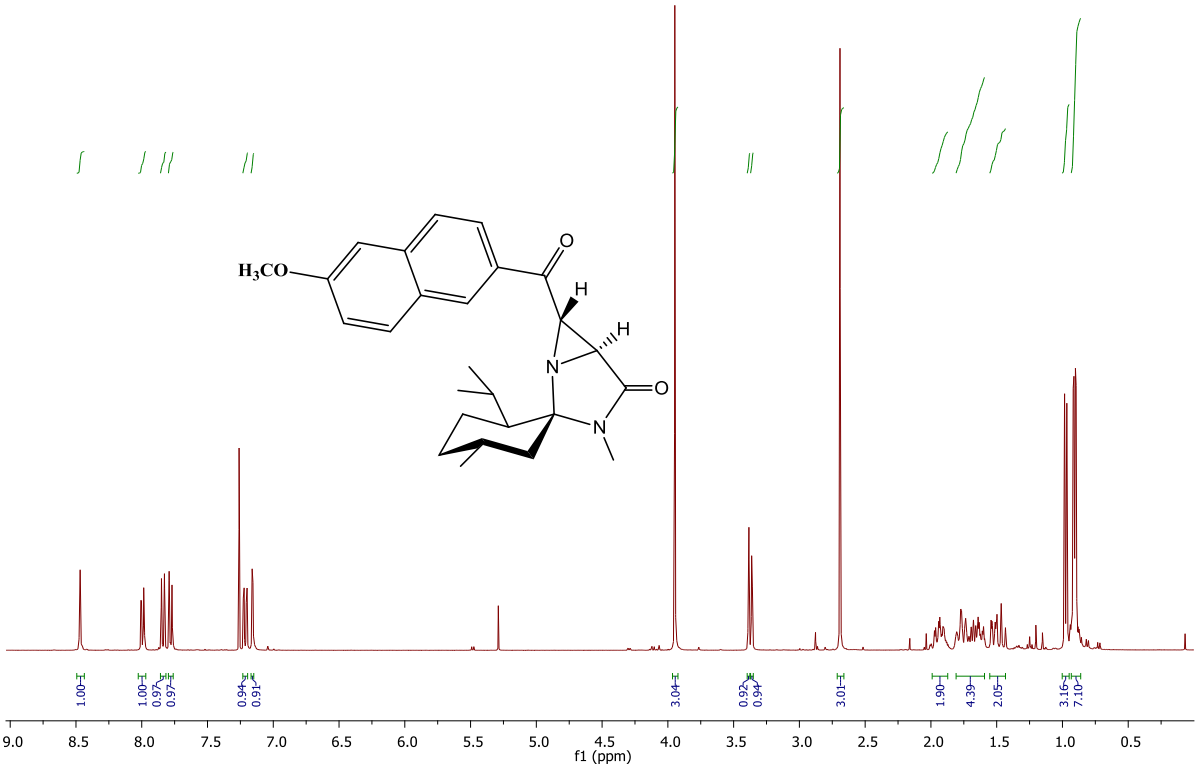
Compounds **3e** (50 mg, 12%) and **4e** (215 mg, 51%) were obtained following general procedure: alkyne **2e** (305 mg).



(3e) Yellow amorphous solid; R_f = 0.54 (EtOAc/PE, 5/5); $[\alpha]_D^{20}$ = +17,1 (c = 1.4,CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (d,3H, J =2.0 Hz, CH_3), 0.91 (d, 3H, J =2.4 Hz, CH_3), 0.93-0.95 (m, 1H), 0.97 (d,3H, J = 6.9 Hz, CH_3),1.46 (t, 1H, J_{gem} = 12.9 Hz), 1.50-1.54 (ddd, 1H, J = 9.0 Hz, J = 3.5 Hz, J = 1.3 Hz),1.59-1.65 (m, 1H),1.76-1.80 (m, 1H), 1.73-1.80 (m, 2H), 1.86-2.00 (m, 2H), 2.69 (s, 3H, NCH_3), 3.35 (d, 1H, J = 1.8 Hz), 3.38 (d, 1H, J = 2.0 Hz), 3.94 (s, 3H, OCH_3), 7.16 (d, 1H, J = 2.4 Hz, Harom), 7.19-7.22 (dd, 1H, J = 8.9 Hz, J = 2.5 Hz, Harom), 7.76-7.79 (d, 1H, J = 8.7 Hz,Harom), 7.83 (d, 1H, J = 8.9 Hz, Harom),7.99 (dd, 1H, J = 8.6 Hz, J = 1.8 Hz, Harom), 8.46 (d, 1H, J = 1.3 Hz, Harom); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.4, 21.4, 22.5, 24.1, 24.6, 25.5 (NCH_3), 28.7, 34.7, 40.0, 43.2, 45.6, 48.1, 55.6 (OCH_3), 85.8, 106.0, 120.2, 124.7, 127.6, 127.8, 130.3, 131.3, 131.9, 137.7, 160.3, 170.8 (C=O), 192.6 (C=O); HRMS (ESI): *m/z* calcd for $C_{26}H_{33}N_2O_3[M+H]^+$ 421.2486; found 421.2484.



(4e) Amorphous solid; R_f = 0.34 (EtOAc/PE, 5/5); $[\alpha]_D^{20}$ = -40.0 (c = 0.3,CH_2Cl_2);^{1}H NMR(400 MHz, $CDCl_3$): δ = 0.18 (d,3H, J = 6.6 Hz, CH_3), 0.87 (d, 3H, J =1.8 Hz, CH_3), 0.88 (d, 3H, J = 1.6 Hz, CH_3), 0.91-0.92 (m, 1H), 1.03 (t, 1H, J_{gem} = 13.2 Hz, H-6'a), 1.20-1.23 (m, 1H), 1.39 (ddd, 1H, J = 8.9 Hz, J = 3.4 Hz, J = 1.1 Hz, H-2'), 1.62-1.67 (m, 1H, H-3'a), 1.73-1.80 (m, 2H), 1.85-1.96 (m, 1H), 1.98-2.02 (m, 1H), 2.60 (s, 3H, NCH_3), 3.16 (d, 1H, J = 5.1 Hz, H-5), 3.69 (d, 1H, J = 5.1 Hz, H-6), 3.95 (s,3H, OCH_3), 7.15 (d, 1H, J = 2.4 Hz, H-arom), 7.20-7.23 (dd, 1H, J = 8.9 Hz, J = 2.5 Hz, Harom), 7.78 (d, 1H, J = 8.7 Hz, Harom), 7.86 (d, 1H, J = 9.0 Hz, Harom), 8.05 (dd, 1H, J = 8.6 Hz, J = 1.8 Hz, Harom), 8.59 (d, 1H, J = 1.4 Hz, Harom); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 21.2, 21.9, 24.2, 24.5, 25.5 (NCH_3), 29.3, 34.8, 42.2, 43.2, 44.8, 49.7, 55.6 (OCH_3), 85.7, 106.0, 120.3, 124.4, 127.5, 127.8, 130.4, 131.4, 133.0, 137.8, 160.3, 169.7 (C=O), 193.0 (C=O); HRMS (ESI): *m/z* calcd for $C_{26}H_{32}N_2NaO_3[M+Na]^+$ 443.2305; found 443.2291.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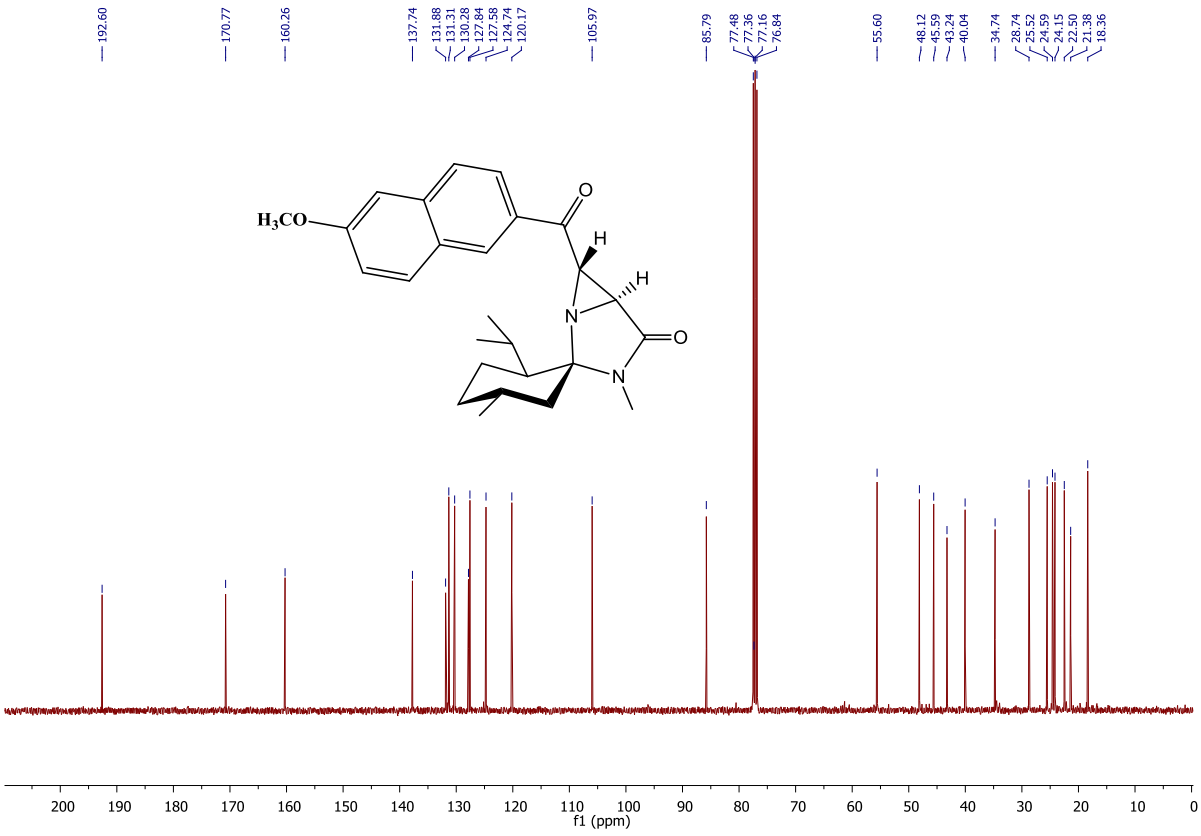
H
H
N
O
N
1.00
1.00
0.97
0.97
0.94
0.91
3.04
0.93
0.94
3.01
1.90
4.39
2.05
3.16
7.10
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)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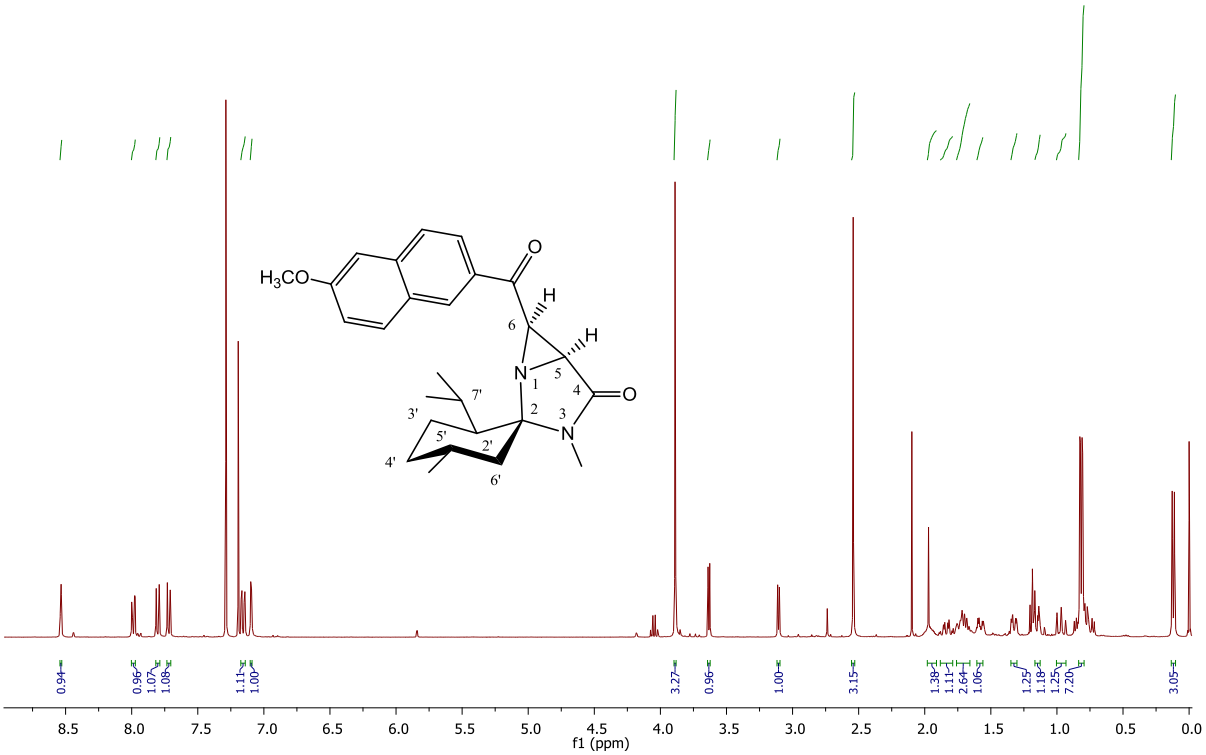
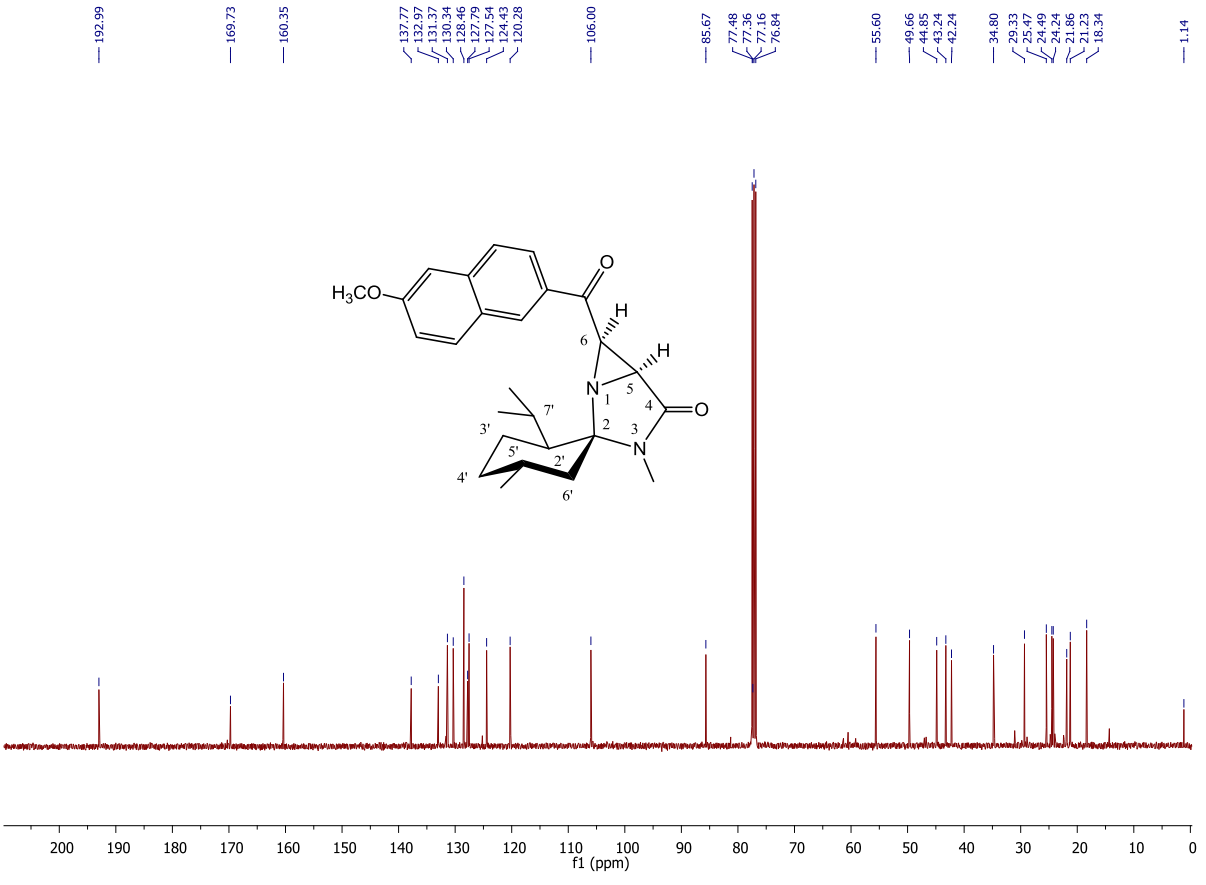
170.77
160.26
137.74
131.88
131.31
130.28
127.84
127.58
124.74
120.17
105.97
85.79
77.48
77.36
77.16
76.84
55.60
48.12
45.59
43.24
40.04
34.74
28.74
25.52
24.59
24.15
22.50
21.38
18.36
H3CO
O
H
H
N
O
N
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


H3CO
O
H
6
H
N
1
5
4
O
7'
3'
2
3
5'
2'
N
4'
6'
0.94
0.96
1.07
1.08
1.11
1.00
3.27
0.96
1.00
3.15
1.38
1.11
2.64
1.06
1.25
1.18
1.25
7.20
3.05
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


192.99
169.73
160.35
137.77
132.97
131.37
130.34
128.46
127.79
127.54
124.43
120.28
106.00
85.67
77.48
77.36
77.16
76.84
55.60
49.66
44.85
43.24
42.24
34.80
29.33
25.47
24.49
24.24
21.86
21.23
18.34
1.14
H3CO
O
H
6
H
N
1
5
4
O
7'
3'
2
3
5'
2'
N
4'
6'
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)