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SUPPORTING INFORMATION

Title: Cathodic Cyclisation of *N*-(Oxoalkyl)pyridinium Salts – Formation of Tricyclic Indolizidine and Quinolizidine Derivatives in Aqueous Medium

Author(s): Jens Heimann, Hans J. Schäfer,* Roland Fröhlich, Birgit Wibbeling

Ref. No.: O03180

Contents: Additional procedures and data
NOE **33a**
Calculation results
^{13}C-NMR spectra

Additional procedures and data

2-(Hydroxymethyl)cyclopentanone (23), procedure ref. [31]

To a mixture of cyclopentanone (350 ml, 333 g, 3.95 mol), a formaldehyde solution (37 % in water, 75 ml, 81.2 g, 1.00 mol) and a spatula tip of bromothymol blue indicator was added dropwise a sodium hydroxide solution (4 % in water) until the colour changed from yellow to blue with vigorous stirring. The mixture was heated to 35 °C for 3 h. Hydroquinone (5.00 g, 45.0 mmol) was added and the temperature was maintained for another 30 min.. Brine (100 ml) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 100 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated. The residue was distilled through a vigreux column (20 cm) to give two fractions: 1) 30 °C, 30 mbar, cyclopentanone (216 g, 2.57 mol) and 2) 58 °C, 0.04 mbar, **23** (35.92 g (31.5 mmol, 32 %)) as colourless oil. IR (film): $\tilde{n}$ (cm^{-1}) = 3435 (m), 2963 (s), 2879 (m), 1730 (s), 1454 (w), 1405 (m), 1329 (w), 1272 (w), 1155 (m), 1100 (w), 1056 (m), 1002 (m), 966 (w), 926 (w), 814 (w). ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ (ppm) = 1.68 - 2.40 (m, 7H), 2.57 (s, 1H, OH), 3.72 (dd, 1H, ^2J = 11.0 Hz, ^3J = 6.2 Hz, CH_AOH), 3.81 (dd, 1H, ^2J = 11.0 Hz, ^3J = 5.3 Hz, CH_BOH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 20.7 (t), 26.1 (t), 38.4 (t), 50.7 (d), 61.8 (t, CH_2OH), 221.8 (s, C=O). MS (GC-MS): *m*/*z* (%) = 114 (42) [M^+], 96 (38) [M^+ - H_2O], 83 (18) [M^+ - CH_2OH], 73 (15), 68 (52) [M^+ - H_2O - C_2H_4], 60 (61), 57 (51), 55 (100) [M^+ - C_3H_7O], 41 (30), 39 (23). $C_6H_{10}O_2$ (114.14): calcd. C 63.14, H 8.83; found C 62.84, H 9.22. The spectral data are in good agreement with those published (^{13}C-NMR, MS): L.-L. Gundersen, T. Benneche, *Acta Chem. Scand.* **1991**, *45*, 975-977.

2-(Hydroxymethyl)cyclohexanone (24)[31]

To a mixture of cyclohexanone (415 ml, 393 g, 4.00 mol), a formaldehyde solution (37 % in water, 75 ml, 81.2 g, 1.00 mol) and a spatula tip of bromothymol blue indicator was added dropwise a sodium hydroxide solution (4 % in water) until the colour changed from yellow to blue with vigorous stirring. The mixture was heated to 35 °C for 3 h. Hydroquinone (5.00 g, 45.0 mmol) was added and the temperature was maintained for another 30 min.. Brine (100 ml) was added and the layers were separated. The aqueous layer was extracted with diethyl ether (2 × 100 ml). The combined organics were dried ($MgSO_4$), filtered and concentrated. The residue was distilled through a vigreux column (20 cm) to give two fractions: 1) 40 °C, 15 mbar, cyclohexanone (257 g, 2.62 mol) and 2) 92 °C, 8 mbar, **24** (60.72 g (474 mmol, 47 %)) as colourless oil. IR (film): $\tilde{n}$ (cm^{-1}) = 3429 (m), 2940 (s), 2864 (m), 1711 (s, C=O), 1449 (m), 1385 (w), 1313 (w), 1227 (w), 1180 (m), 1131 (m), 1094 (m), 1079 (m), 1040 (m), 1026 (m), 966 (w). ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ (ppm) = 1.40 - 2.15 (m, 6H), 2.20 - 2.60 (m, 3H), 2.91 (s, 1H, OH), 3.58 (ddd, 1H, ^2J = 11.4 Hz, J = 4.3 Hz, J = 1.4 Hz, CH_AOH), 3.74 (ddd, 1H, ^2J = 11.4 Hz, J = 6.9 Hz, J = 0.9 Hz, CH_BOH). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 24.4 (t), 27.2 (t), 29.9 (t), 41.8 (t), 52.1 (d), 62.1 (t, CH_2OH), 213.9 (s, C=O). MS (GC-MS*): m/z (%) = 128 (60) [M^+], 110 (10) [M^+ - H_2O], 109 (22), 95 (8), 81 (30), 67 (55), 55 (35), 41 (48), 39 (100). $C_7H_{12}O_2$ (128.17): calcd. C 65.60, H 9.44; found C 65.25, H 9.75. The spectral data are in good agreement with those published (IR, ^{13}C-NMR), but differ in principle for the ^{1}H-NMR.[33] The ^{1}H-NMR data agrees with: S. Kobayashi, I. Hachiya, *J. Org. Chem.* **1994**, *59*, 3590-3596 and A. Lubineau, E. Meyer, *Tetrahedron* **1988**, *44*, 6065-6070.

Data of 1,4-dioxaspiro[4.5]dec-6-ylmethanol (16)

IR (film): $\tilde{n}$ (cm^{-1}) = 3448 (s), 2939 (s), 2886 (s), 1447 (m), 1352 (m), 1336 (m), 1279 (m), 1250 (m), 1211 (m), 1159 (s), 1141 (s), 1089 (s), 1056 (s), 1033 (s), 1007 (s), 974 (m), 949 (m), 925 (m), 891 (w), 864 (m), 829 (w), 801 (w). ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ (ppm) = 1.20 - 1.95 (m, 9H), 2.80 (s, 1H, OH), 3.53 (dd, 1H, ^2J = 11.0 Hz, ^3J = 3.8 Hz, CH_AOH), 3.75 (dd, 1H, ^2J = 11.0 Hz, ^3J = 7.2 Hz, CH_BOH), 3.95 - 4.05 (m, 4H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 23.5 (t), 24.3 (t), 26.9 (t), 34.0 (t), 45.7 (d), 63.4 (t), 64.0 (t), 64.4 (t), 111.5 (s). MS (GC-MS*): m/z (%) = 171 (10) [M^+ - H], 154 (3) [M^+ - H_2O], 140 (12) [M^+ - CH_3OH], 129 (17), 128 (50) [M^+ - OC_2H_4], 113 (20), 99 (100) [M^+ - C_4H_8OH], 86 (12), 67 (8), 55 (25), 41 (18). $C_9H_{16}O_3$ (172.22): calcd. C 62.77, H 9.36; found C 62.49, H 9.47. The spectral data are in good agreement with those published.[31]

Ethyl 1,4-dioxaspiro[4.4]nonane-6-carboxylate (26), procedure ref. [35]

A solution of ethyl 2-oxocyclopentanecarboxylate (**14**, 23.43 g, 150 mmol), ethylene glycol (12.41 g, 200 mmol) and 4-methylbenzenesulfonic acid monohydrate (390 mg, 2.05 mmol) in dichloromethane (300 ml) was heated to reflux for 4 days. Azeotropic water was collected in a pressure equalising dropping funnel. The reaction mixture was allowed to cool to room temperature, was washed with saturated sodium hydrogencarbonate solution (2 × 150 ml) and brine (2 × 150 ml), dried ($MgSO_4$), filtered and concentrated. The residue was purified in portions by flash chromatography (light petroleum : diethyl ether = 1 : 1, R_f = 0.43). Combined yield: 16.91 g (84.4 mmol, 56 %) **26** as colourless oil. IR (film): $\tilde{n}$ (cm^{-1}) = 2977 (s), 2890 (m), 1732 (s, C=O), 1468 (w), 1449 (w), 1371 (m), 1343 (m), 1313 (m), 1258 (m), 1213 (s), 1161 (s), 1038 (m), 1039 (m), 950 (w), 853 (w). ^{1}H-NMR (300.1 MHz, C_6D_6): δ (ppm) = 1.04 (q, 3H, CH_3), 1.50 - 1.90 (m, 4H), 2.00 - 2.10 (m, 2H), 2.20 - 2.31 (m, 1H), 3.50 - 3.75 (m, 4H), 4.05 (q, 2H, $C\mathit{H}_2CH_3$). ^{13}C-NMR (75.5 MHz, C_6D_6): δ (ppm) = 14.3 (q, CH_3), 22.4 (t), 27.3 (t), 37.1 (t), 52.7 (d), 60.1 (t $\mathit{C}H_2CH_3$), 64.4 (t), 65.2 (t), 118.8 (s), 171.8 (s, C=O). MS (GC-MS*): m/z (%) = 199 (3) [M^+ - H], 171 (7) [M^+ - C_2H_5], 155 (16) [M^+ - C_2H_5O], 127 (3) [M^+ - C_2H_5O - CO], 113 (11), 99 (100) [M^+ - C_2H_5O - CO

- C_2H_4], 83 (4), 55 (22), 39 (10). $C_{10}H_{16}O_4$ (200.23): calcd. C 59.98, H 8.05; found C 60.11, H 8.06. The ^{1}H-NMR spectrum agrees with the data published: H. Paulsen, U. Maaß, *Chem. Ber.* **1981**, *114*, 346-358.

1,4-Dioxaspiro[4.4]non-6-ylmethanol (25), procedure ref. [35]

The reaction was carried out under an atmosphere of argon in dried glassware. To a suspension of lithium aluminium hydride (1.60 g, 42.2 mmol) in dry THF (20 ml) was added a solution of ethyl 1,4-dioxaspiro[4.4]nonane-6-carboxylate (**26**, 6.41 g, 32.0 mmol) at a rate to maintain a gentle reflux. The reaction mixture was then heated to reflux for 3 h. Wet THF, followed by brine was added dropwise until the evolution of hydrogen ceased. The hydrolised mixture was heated at reflux so that a flaky precipitate formed. The mixture was filtered, dried ($MgSO_4$) and concentrated. The residue was purified by flash chromatography (diethyl ether, R_f = 0.30). Yield: 3.71 g (23.5 mmol, 73 %) **25** as colourless oil. IR (film): $\tilde{n}$ (cm^{-1}) = 3425 (m), 2961 (s), 2880 (s), 1472 (w), 1436 (w), 1407 (w), 1322 (m), 1204 (m), 1105 (m), 1023 (s), 949 (m), 833 (w). ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ (ppm) = 1.50 - 1.90 (m, 6H), 2.10 - 2.20 (m, 1H), 2.45 (s, 1H, OH), 3.50 - 3.65 (m, 2H, CH_2OH), 3.80 - 4.00 (m, 4H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.3 (t), 25.7 (t), 35.7 (t), 47.1 (d), 62.6 (t), 64.0 (t), 64.5 (t), 119.1 (s, C-5). MS (GC-MS): *m*/*z* (%) = 158 (24) [M^+], 141 (8), 129 (34) [M^+ - C_2H_5], 115 (11), 113 (7), 100 (26), 99 (100) [M^+ - C_3H_7O], 85 (11), 67 (7), 55 (35) [M^+ - OC_2H_4 - C_3H_7O], 43 (8), 41 (15), 39 (7). $C_8H_{14}O_3$ (158.20): calcd. C 60.74, H 8.92; found C 60.48, H 9.13. The ^{1}H-NMR spectrum agrees with the data published: H. Paulsen, U. Maaß, *Chem. Ber.* **1981**, *114*, 346-358 and S. Nagumo, A. Matsukuma, H. Suemune, K. Sakai, *Tetrahedron* **1993**, *49*, 10501-10510 (also MS).

1,4-Dioxaspiro[4.5]dec-6-ylmethyl 4-methylbenzenesulfonate (17)

To a solution of alcohol **16** (4.00 g, 23.2 mmol) in dry pyridine (15 ml) 4-methylbenzenesulfonyl chloride (4.77 g, 25.0 mmol) was added in small portions. After 24 h of stirring at room temperature, diethyl ether (100 ml) and saturated sodium hydrogen carbonate solution (100 ml) were added. The organic layer was separated, washed with brine (100 ml), dried ($NaSO_4$), filtered and concentrated. The residue was purified by flash chromatography (light petroleum : diethyl ether = 1 : 1, R_f = 0.38). Yield: 6.03 g (18.5 mmol, 80 %) **17** as viscous, colourless oil, which was kept at -20 °C. IR (film): $\tilde{n}$ (cm^{-1}) = 2939 (s), 2887 (m), 2864 (m), 1598 (m), 1448 (m), 1361 (s), 1307 (w), 1238 (w), 1252 (w), 1221 (w), 1177 (s), 1098 (s), 1058 (m), 1018 (m), 960 (s), 843 (s), 815 (s), 768 (w). ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ (ppm) = 1.15 - 2.05 (m, 9H), 2.45 (s, 3H, CH_3), 3.71 - 4.00 (m, 5H), 4.27 (dd, 1H, *J* = 9.5 Hz, *J* = 4.1 Hz, CH_BO), 7.33 (dd, 2H, ^3J = 8.1 Hz, ^4J = 0.7 Hz), 7.78 (dd, 2H, ^3J = 8.1 Hz, ^4J = 1.9 Hz). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 21.5 (q, CH_3), 23.4 (t), 23.8 (t), 26.9 (t), 34.3 (t), 43.8 (d), 64.4 (2t), 70.2 (t), 109.0 (s), 127.8 (d), 129.7 (d), 133.3 (s), 144.5 (s). MS (GC-MS*): *m*/*z* (%) = 283 (5), 203 (6), 171 (100) [M^+ - $SO_2C_6H_4CH_3$], 155 (95) [M^+ - $SO_3C_6H_4CH_3$ / $SO_2C_6H_4CH_3^+$], 139 (5) [$SOC_6H_4CH_3^+$], 113 (25), 99 (58), 91 (35) [$C_6H_4CH_3^+$], 65 (24), 55 (50), 41 (28), 39 (33). $C_{16}H_{22}O_5S$ (326.41): calcd. C 58.88, H 6.79; found C 58.93, H 6.78.

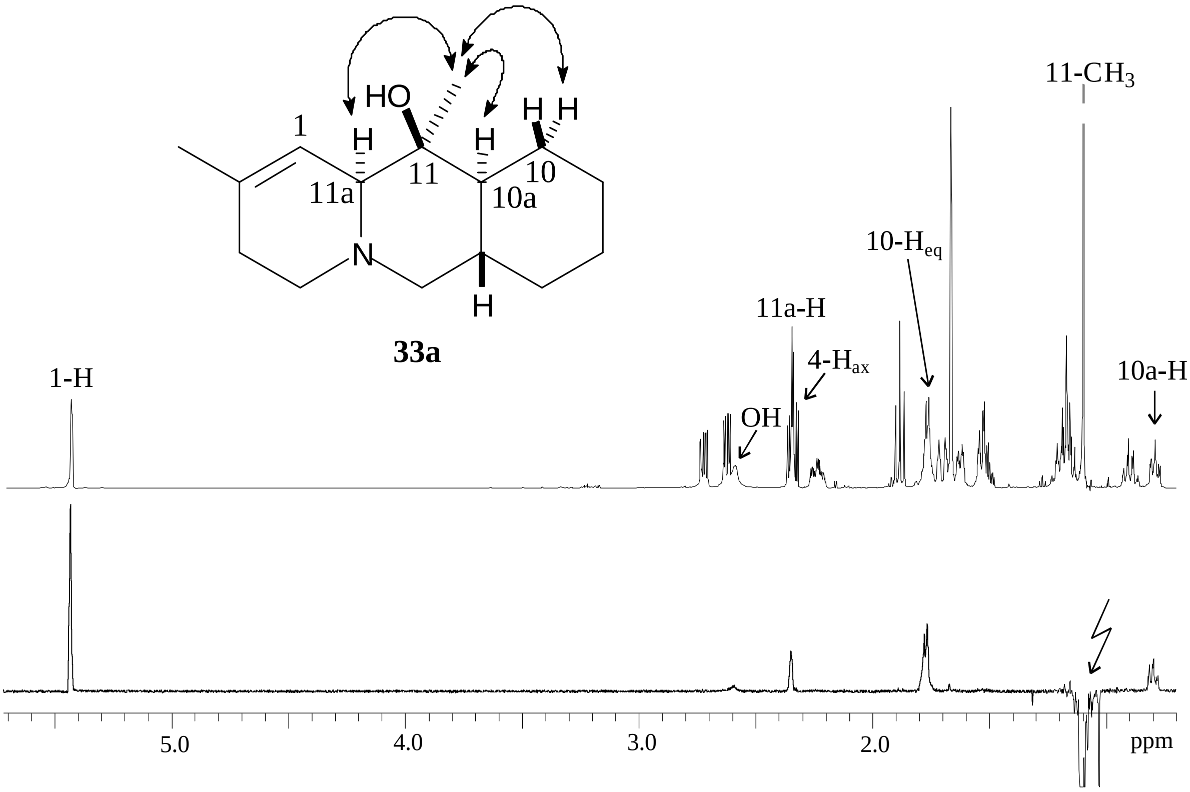
1,4-Dioxaspiro[4.5]dec-6-ylmethyl methanesulfonate (18)

To a solution of alcohol **16** (10.0 g, 58.1 mmol) in dry pyridine (20 ml) was slowly added dropwise (2 h) methanesulfonyl chloride (4.49 ml, 6.65 g, 58.1 mmol) at 0°C. After stirring at 0 °C for 1 h and at room temperature for 3 h, diethyl ether (100 ml) and saturated sodium hydrogen carbonate solution (100 ml) were added. The layers were separated, the organic layer dried ($MgSO_4$), filtered and evaporated. The residue was recrystallised from diethyl ether by the addition of light petroleum at -20 °C. The product was kept at -20 °C. Yield: 13.1 g (52.3 mmol, 90 %) **18** as white crystalline solid. M. p.: 61 °C, R_f = 0.48 (diethyl ether). IR (KBr): $\tilde{n}$ (cm^{-1}) = 2938 (s), 2893 (m), 2854 (m), 1444 (w), 1346 (s), 1282 (m), 1250 (w), 1219 (m), 1170 (s), 1105 (s), 1058 (m), 1019 (m), 983 (s), 950 (s), 898 (m), 858 (s), 800 (w), 775 (w), 756 (m). ^{1}H-NMR (300.1 MHz, C_6D_6): δ (ppm) = 1.00 - 1.36 (m, 2H), 1.45 - 1.65 (m, 5H), 1.90 - 2.15 (m, 2H), 2.41 (s, 3H, CH_3), 3.45 - 3.62 (m, 4H), 4.14 (dd, 1H, ^2J = 9.5 Hz, ^3J = 9.5 Hz, CH_AOS), 4.58 (dd, 1H, ^2J = 9.5 Hz, ^3J = 4.1 Hz, CH_BOS). ^{13}C-NMR (75.5 MHz, C_6D_6): δ (ppm) = 23.7 (t), 24.2 (t), 27.3 (t), 34.7 (t), 36.6 (q, CH_3), 44.5 (d), 64.5 (2t), 69.7 (t), 109.2 (s). MS (GC-MS): *m/z* (%) = 250 (5) [M^+], 207 (44), 171 (62) [M^+ - SO_2CH_3], 155 (100) [M^+ - SO_3CH_3], 113 (10), 99 (50), 55 (20), 41 (10). $C_{10}H_{18}O_5S$ (250.32): calcd. C 47.98, H 7.25; found C 47.69, H 7.18. The ^{1}H-NMR spectrum agrees with the data reported.[30b]

1-Acetylbicyclo[4.1.0]heptane (36)

The reaction was carried out under an atmosphere of argon in dried glassware. To a mixture of trimethyloxosulfonium iodide (26.41 g, 120 mmol) and sodium hydride (75 % suspension in mineral oil, 3.84 g, 120 mmol) was added dropwise dimethylsulfoxide (100 ml, dried over molecular sieves 3 Å) with cooling in a water bath over a period of 1 h. After stirring at room temperature for additional 30 min., a solution of 1-acetyl-1-cyclohexene (**37**, 12.4 g, 100 mmol) in dimethylsulfoxide (10 ml) was added dropwise over a period of 30 min.. The resulting suspension was then stirred at room temperature for additional 2 h, then 1 h at 50 °C. The reaction mixture was poured into a mixture of ice and water (150 ml) and extracted with diethyl ether (1 × 200 ml, then 3 × 100 ml). The combined extracts were dried ($MgSO_4$), filtered and concentrated. The crude product was purified by flash chromatography (light petroleum : diethyl ether = 2 : 1, R_f = 0.44). Yield: 5.84 g (42.3 mmol, 42 %) **36** as colourless oil. IR (film): $\tilde{n}$ (cm^{-1}) = 3074 (w, C-H cyclopropyl), 3001 (w), 2933 (s), 2861 (m), 1682 (s), 1452 (m), 1428 (w), 1385 (w), 1352 (m), 1275 (w), 1252 (w), 1167 (m), 1130 (w), 1031 (w), 977 (w), 925 (w), 834 (w). ^{1}H-NMR (300.1 MHz, $CDCl_3$): δ (ppm) = 0.72 (dd, 1H, J = 6.9 Hz, J = 4.3 Hz, 2-H_A), 1.15 - 1.39 (m, 4H, dd, 1H, 2-H_B), 1.55 - 1.78 (m, 3H), 1.82 - 1.98 (m, 1H), 2.04 (s, 3H, CH_3), 2.45 - 2.56 (m, 1H). ^{13}C-NMR (75.5 MHz, $CDCl_3$): δ (ppm) = 20.4, 21.2, 21.6, 22.5, 23.2, 24.4, 25.2, 31.3 (s, C-1), 209.4 (s, C=O). MS (GC-MS*): *m/z* (%) = 138 (5) [M^+], 137 (14) [M^+ - H], 123 (14) [M^+ - CH_3], 109 (28), 95 (65) [M^+ - CH_3CO], 81 (17), 80 (17), 79 (18), 67 (55), 55 (14), 53 (13), 43 (100) [$C_2H_3O^+$], 41 (21), 39 (50). $C_9H_{14}O$ (138.21): calcd. C 78.21, H 10.21; found C 78.16, H 10.45. The spectral data (^{1}H-NMR and IR) are in good agreement with those published: M. Bertrand, P. Archier, C. Santelli-Rouvier, *C. R. Seances Acad. Sci., Ser. C* **1970**, *271*, 385-388.

NOE 33a



Calculation results

MOPAC 93 was used for the calculations, starting geometries were optimised with PC Model V 7.5 (MMX). In all cases of the transition states **TS** and the cyclised intermediates **I** the data of the conformer lowest in energy is given (rotation of the hydroxyl group, conformation of the rings.
Keywords for cyclised intermediates **I**: AM1 UHF DOUBLET CHARGE=1 EF GNORM=0.01.
Keywords for transition states **TS**: AM1 UHF DOUBLET CHARGE=1 TS RECALC=10 GNORM=0.01. The length of the new bond was set to 2.0 Å in the starting geometries.

Cyclised intermediates I

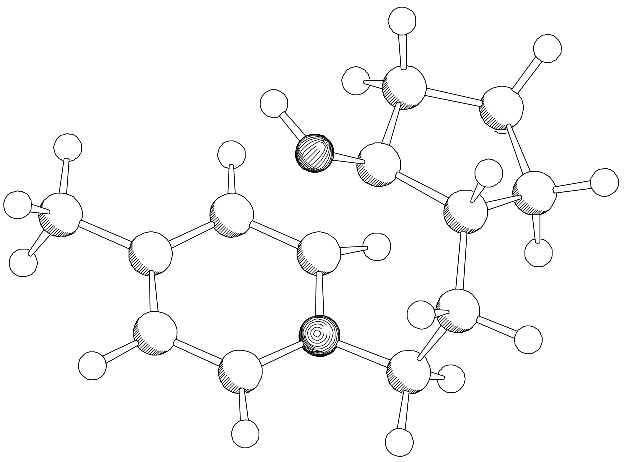
	I-1a	**I-1b**	**I-1c**	**I-1d**	**I-2a**	**I-2b**	**I-2c**	**I-2d**
$\Delta_f H$ / $kJmol^{-1}$	510.9	511.5	523.8	535.8	474.0	471.1	468.5	484.6
$\Delta\Delta_f H$ / $kJmol^{-1}$	0	0.6	12.9	24.9	5.5	5.6	0	16.1

	I-3a	**I-3b**	**I-3c**	**I-3d**	**I-4a**	**I-4b**	**I-4c**	**I-4d**
$\Delta_f H$ / $kJmol^{-1}$	549.0	549.9	629.5	646.5	521.3	523.6	540.3	554.7
$\Delta\Delta_f H$ / $kJmol^{-1}$	0	0.9	80.5	97.5	0	2.3	19.0	33.4

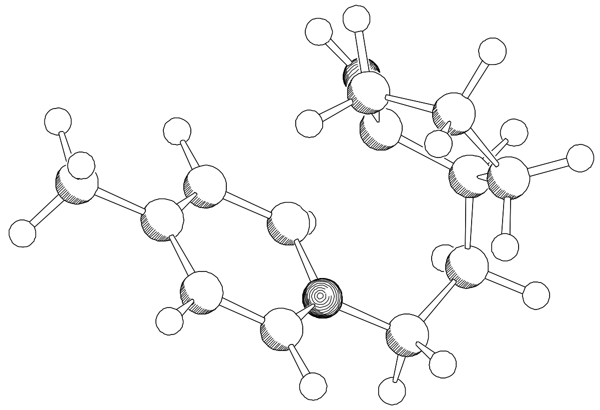
Transition states TS

	TS-1a	**TS-1b**	**TS-1c**	**TS-1d**	**TS-2a**	**TS-2b**	**TS-2c**	**TS-2d**
$\Delta_f H$ / kJmol^{-1}	566.5	571.1	594.5	611.3	524.9	531.5	523.6	542.3
$\Delta\Delta_f H$ / kJmol^{-1}	0	4.6	28.0	44.8	1.3	7.9	0	18.7
distance reaction centres / Å	2.012	2.011	2.015	2.021	2.009	2.015	2.023	2.020
force constant / cm^{-1}	-598.4	-597.5	-591.1	-604.6	-603.1	-549.0	-545.3	-568.2

Graphics of TS-1



TS-1a



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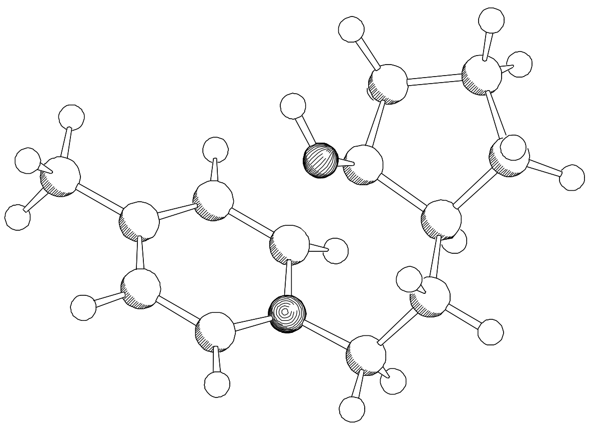

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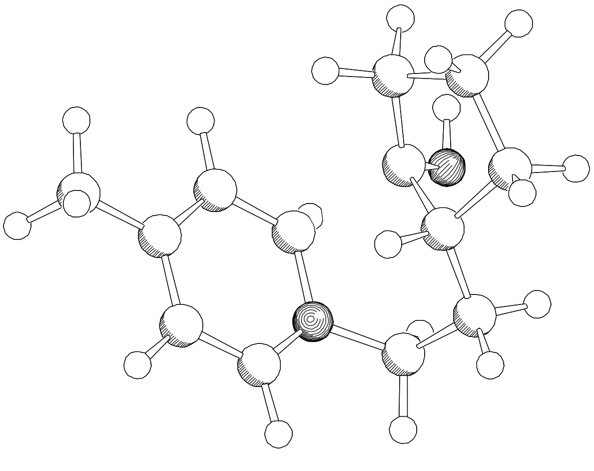
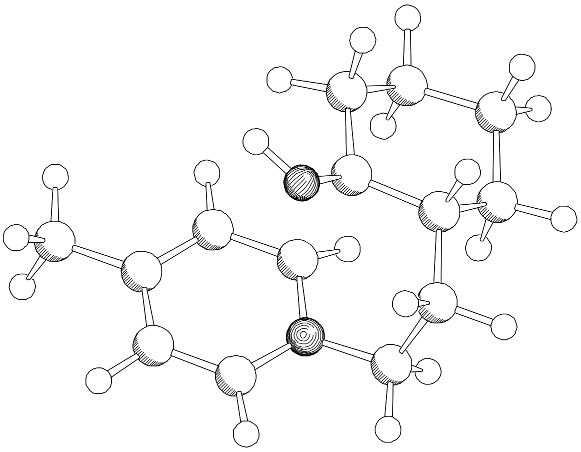


TS-1d

Graphics of TS-2



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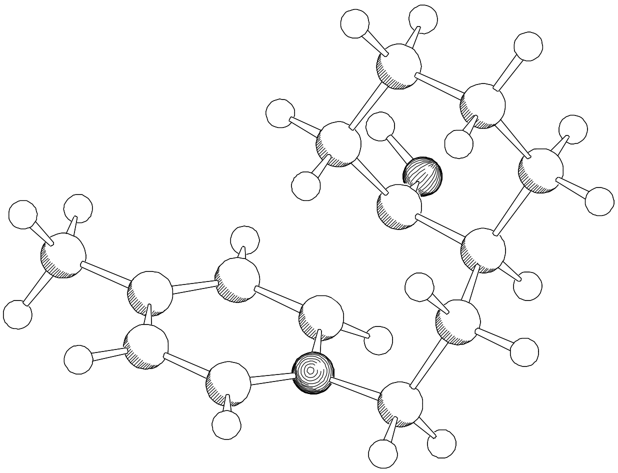

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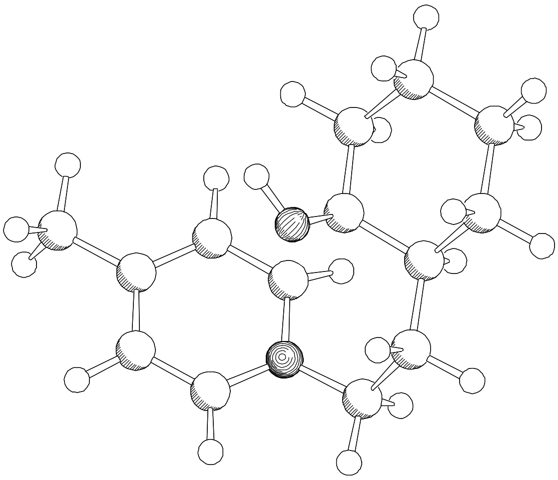

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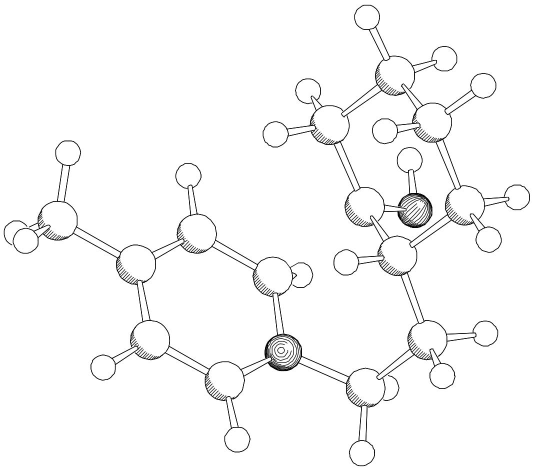
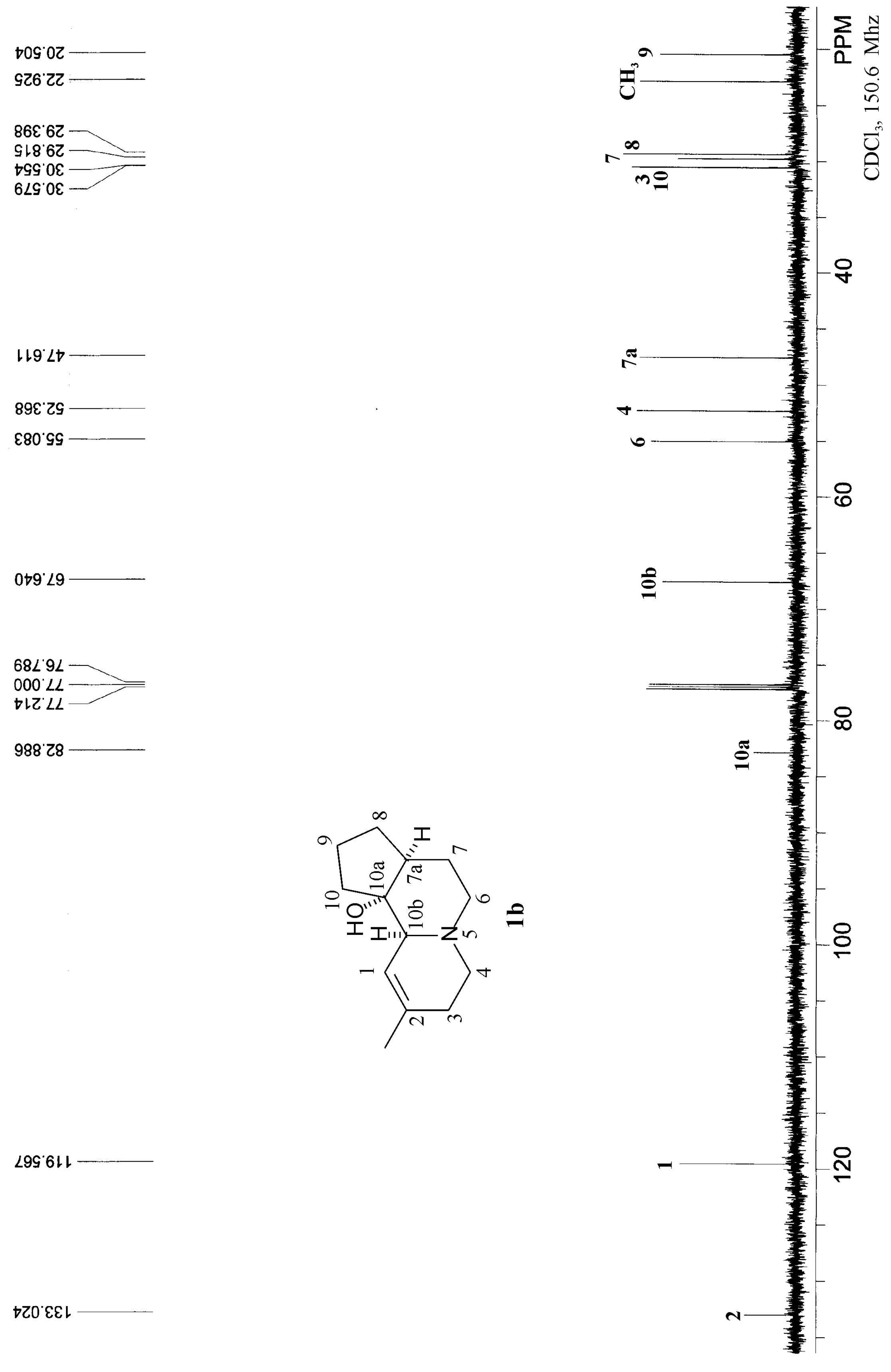


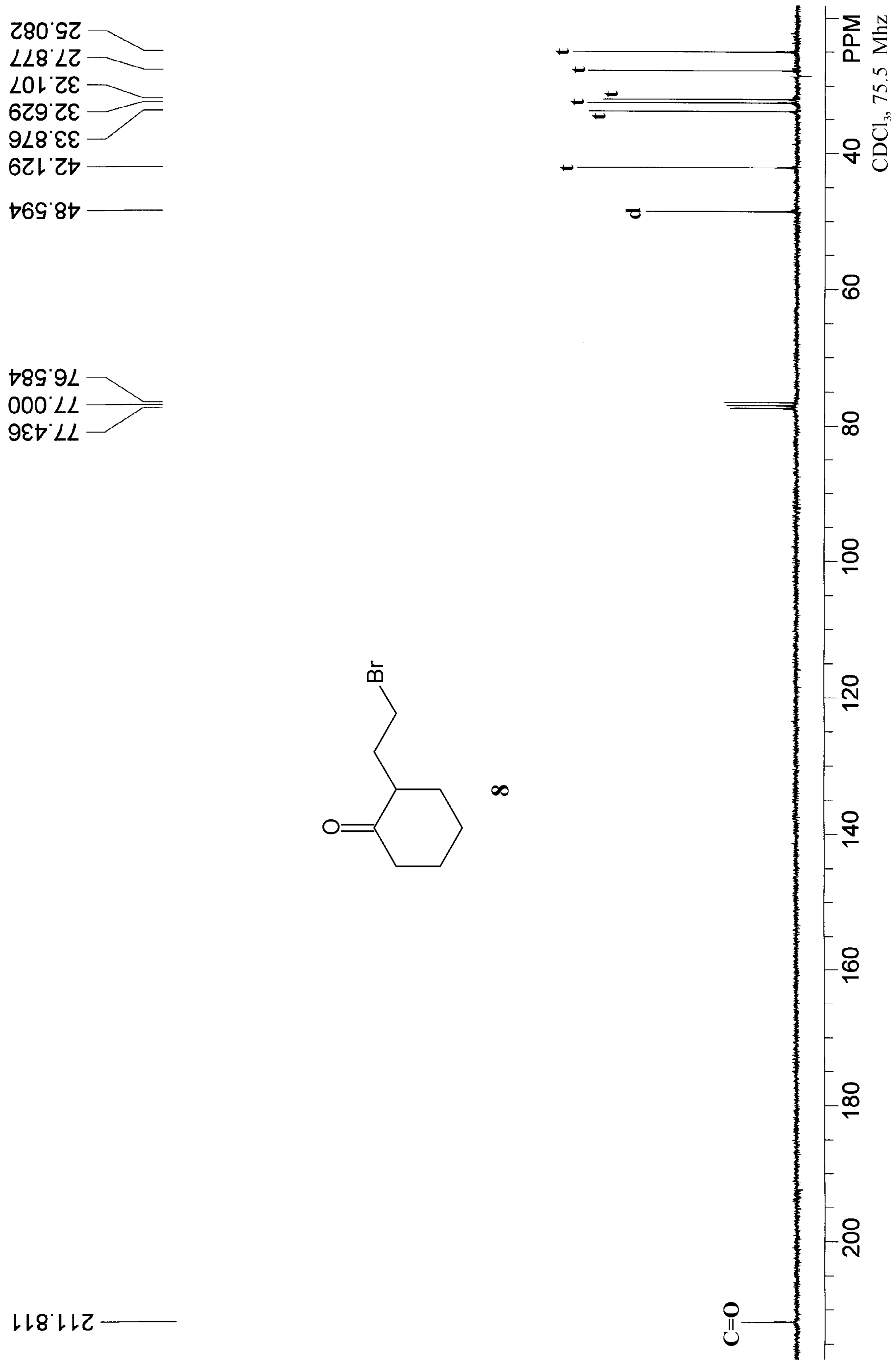
TS-2d

^{13}C-NMR spectra

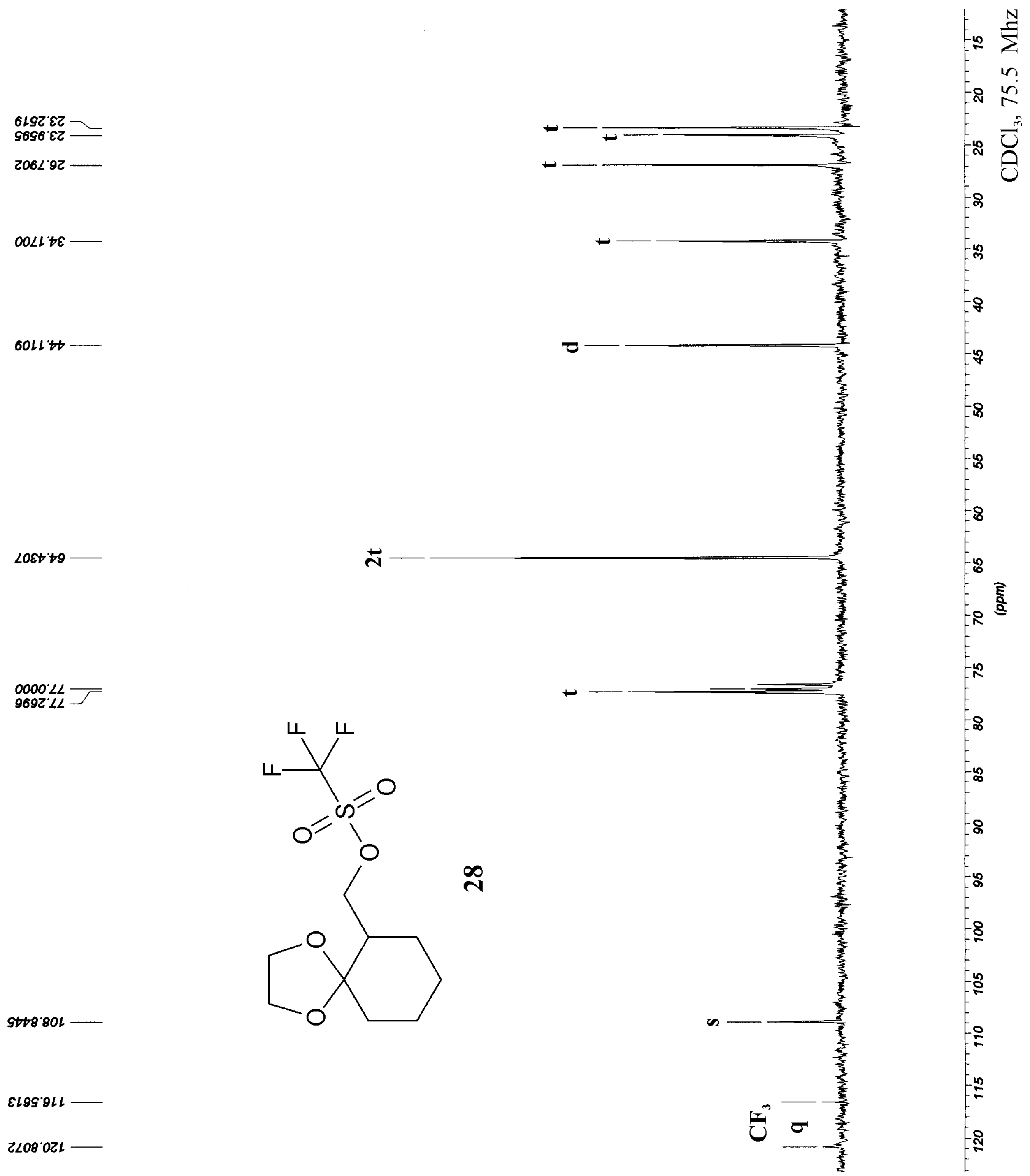
^{13}C-NMR spectrum of *rac*-(7a*S*,10a*R*,10b*S*)-2-methyl-3,4,6,7,7a,8,9,10,10a,10b-decahydroycyclopenta[*a*]chinolizine-10a-ol (1b)



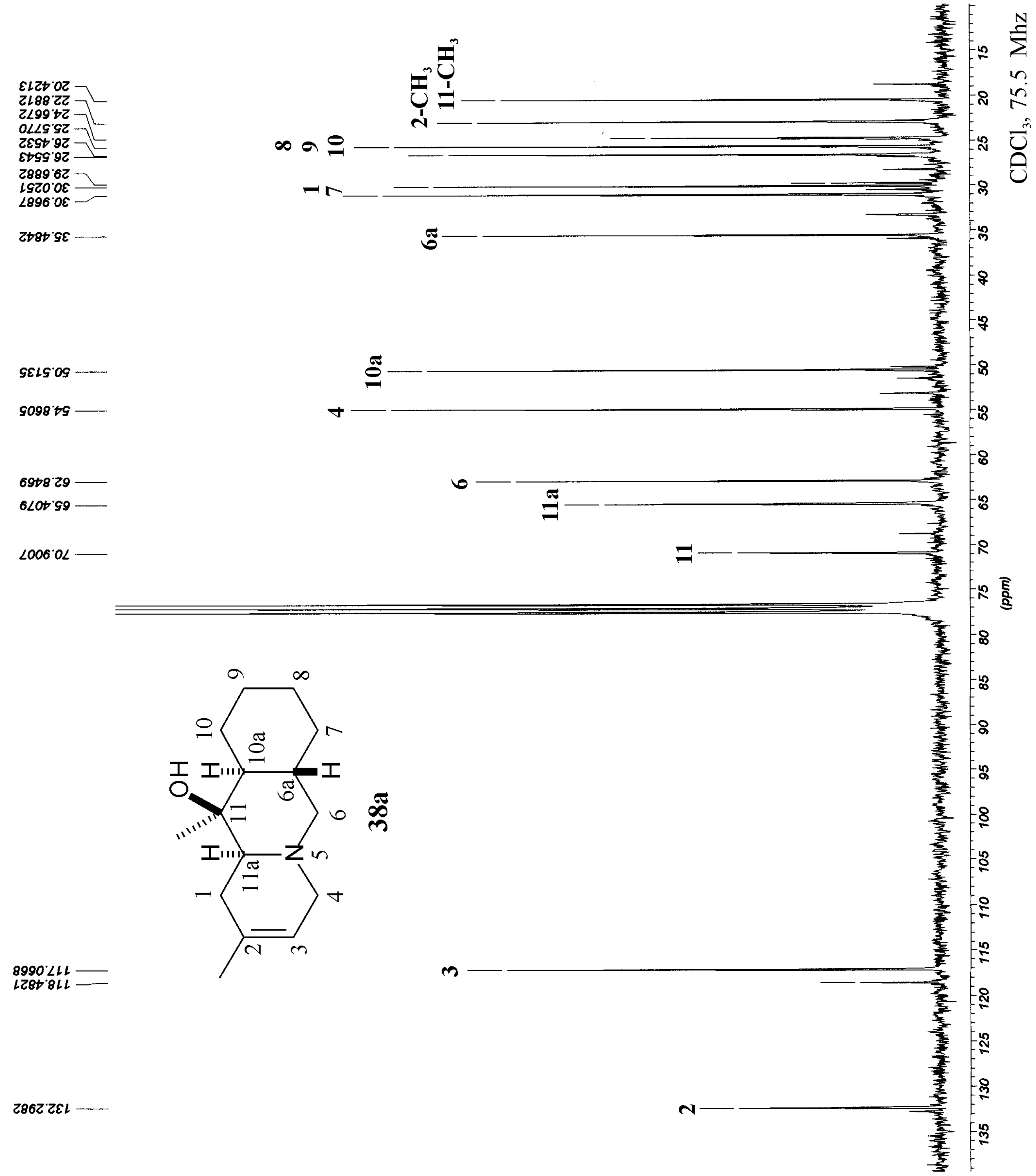
^{13}C-NMR spectrum of 2-(2-bromoethyl)cyclohexanone (8)



^{13}C-NMR spectrum of 1,4-dioxaspiro[4.5]dec-6-ylmethyl trifluoromethanesulfonate (28)



^{13}C-NMR spectrum of *rac*-(6a*S*,10a*S*,11*S*,11a*S*)-2,11-Dimethyl-1,6,6a,7,8,9,10,10a,11,11a-decahydro-4*H*-cyclohexa[*b*]quinolizine-11-ol (38a)



The sample contained traces of another isomer.