Angewandte Chemie
Eine Zeitschrift der Gesellschaft Deutscher Chemiker

Supporting Information

69451 Weinheim, Germany

Enantioselective α-Arylation of Cyclohexanones with Diaryl Iodonium Salts; Application to the Synthesis of (-)-Epibatidine.

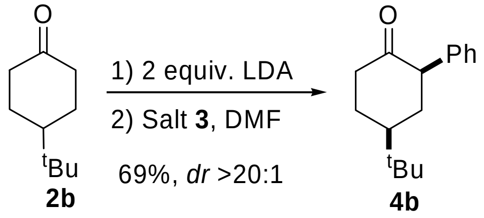
Prof. Varinder K. Aggarwal* and Dr. Berit Olofsson

29 pages

Contents:

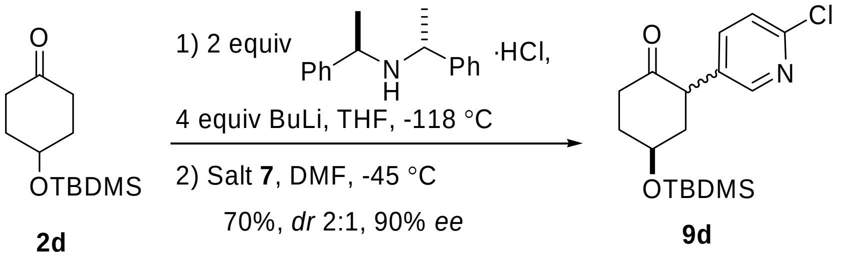
1. Representative coupling procedures & analytical data

1.1 Iodonium coupling reaction with LDA. Synthesis of *cis*-4-*tert*-butyl-2-phenylcyclohexanone (4b).



LDA was prepared by mixing dist. ${}^{i}Pr_2NH$ (46 μL, 0.32 mmol, 2 equiv.) with BuLi (1.6 M/hexane, 203 μL, 0.32 mmol, 2 equiv.) in anhydrous THF (1.8 mL) at -78 °C. After 15 min at rt, the LDA solution was cooled to -78 °C before addition of **2b** (25 mg, 0.16 mmol, 1 equiv.) in THF (0.2 mL). The enolization was allowed 50 min, after which salt **3** (66 mg, 0.16 mmol, 1 equiv.) in anhydrous DMF (6.5 mL) was added via cannula. The coupling reaction was stirred at -45 °C (CH_3CN/dry ice bath) for 3.5 h and quenched by addition of sat. NH_4Cl (1 mL). The mixture was extracted with Et_2O*3, washed with H_2O*2, dried ($MgSO_4$) and concd to give a yellow crude product. Flash chromatography (pentane → pentane: EtOAc 4:1) yielded **4b** as a white solid (25.5 mg, 69%).[1] ${}^{1}H$ NMR (300 MHz, $CDCl_3$): δ = 7.34 (m, 2H), 7.27 (m, 1H), 7.13 (m, 2H), 3.60 (m, 1H), 2.61-2.42 (m, 2H), 2.33-2.14 (m, 2H), 1.85-1.69 (m, 2H), 1.69-1.58 (m, 1H), 0.94 (s, 9H); ${}^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 210.4, 139.1, 128.7, 128.3, 126.9, 57.0, 47.5, 41.7, 26.9, 32.6, 28.5, 27.6; IR (neat): 2955, 2868, 1716 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{16}H_{23}O$ (M+H): 231.1749. Found: 231.1747. Asymmetric coupling to **(2*R*,4*S*)-4b**: Performed as described in section 1.2. The *ee* was measured to 90% on ChiralCel OD, hexane: ${}^{i}PrOH$ 98:2, 1 mL/min; retention times 8.8 min (2*S*,4*R*) and 11.1 min (2*R*,4*S*).

1.2 Iodonium coupling reaction with Simpkins' base. Synthesis of 4-(*tert*-Butyl-dimethyl-silanyloxy)-2-(6-chloro-pyridin-3-yl)cyclohexanone (9d).



Simpkins' base was prepared by mixing [*R*-(*R**,*R**)]-(+)-bis(α-methylbenzyl)amine hydrochloride (410 mg, 1.57 mmol, 2.1 equiv.) with BuLi (1.6 M/hexane, 1.96 mL, 3.13 mmol, 4.2 equiv.) in anhydrous THF (9.6 mL) at -60 °C. The mixture was stirred for 50

---

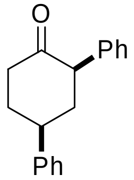
[1] Wagner, P. J., Stratton, T. J. *Tetrahedron* **1981**, *37*, 3317-3322; contains mp, IR and UV data.

min at -60 °C → rt, the salt slowly dissolved to give a yellow solution. The base solution was cooled to -118 °C (Et_2O/N_2 bath) with vigorous stirring to avoid freezing of the recation, after which **2d** (170 mg, 0.74 mmol, 1 equiv.) was slowly added in THF (1 mL). The enolization was allowed 1 h 45 min, the reaction froze a few times, and slowly turned pink. Salt **7** (318 mg, 0.82 mmol, 1.1 equiv.) in anhydrous DMF (35 mL) was slowly added via cannula, which caused a color change to yellow. The coupling reaction was stirred at -45 °C (CH_3CN/dry ice bath) for 4 h and quenched by addition of sat. NH_4Cl (1 mL) *at -95 ℃* (less byproducts are formed when the quench is performed at low temerature). The mixture was extracted with Et_2O*3, washed with aq. HCl (pH 1)*3 (to remove the amine) and brine, dried ($MgSO_4$) and concd to give a yellow crude product. Flash chromatography (pentane: EtOAc 20:1 → 1:1) yielded *cis*-**9d** (47%) and *trans*-**9d** (23%) as colorless oils. See section 4.1 for eqilibration of *cis*-**9d** to *trans*-**9d**.

***Trans*-(2*S*,4*S*)-9d:**[2] Low-melting opaque solid; the *ee* was measured to 90% on ChiralPak AD, hexane:^{i}PrOH 98.5:1.5, 1 mL/min; retention times 21.4 min (2*S*,4*S*) and 23.8 min (2*R*,4R*S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J*= 2.5 Hz, 1H), 7.45 (dd, *J*= 8.2, 2.5 Hz, 1H), 7.30 (d, *J*= 8.2 Hz, 1H), 4.31 (m, 1H), 4.18 (dd, *J*= 13.2, 5.4 Hz, 1H), 2.96 (td, *J*= 13.9, 6.2 Hz, 1H), 2.39 (ddd, *J*= 13.9, 4.5, 2.3 Hz, 1H), 2.27-2.13 (m, 2H), 2.09 (td, *J*= 13.2, 1.9 Hz, 1H), 1.99 (tdd, *J*= 13.9, 4.5, 2.3 Hz, 1H), 0.96 (s, 9H), 0.14 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.7, 149.9, 149.7, 139.3, 132.8, 123.8, 65.3, 48.0, 42.5, 36.7, 34.7, 25.7, 18.0, -5.0; $[\alpha]_D^{20}$: -17.8 (*c* 1.56, CH_2Cl_2); IR (neat): 2953, 2857, 1716, 1462, 1085 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{17}H_{27}ClNO_2Si$ (M+H): 340.1499. Found: 340.1494.

***Cis-(2R,4S)*-9d:** Low-melting opaque solid; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (d, *J*= 2.5 Hz, 1H), 7.45 (dd, *J*= 8.2, 2.5 Hz, 1H), 7.31 (d, *J*= 8.2 Hz, 1H), 4.26 (tt, *J*= 10.1, 4.1 Hz, 1H), 3.68 (dd, *J*= 13.65, 5.6 Hz, 1H), 2.54 (m, 2H), 2.33 (m, 1H), 2.25 (m, 1H), 2.02 (td, *J*= 13.0, 10.1 Hz, 1H), 1.89 (m, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.3, 150.2, 149.7, 139.1, 132.5, 124.0, 68.9, 50.6, 42.8, 38.6, 35.4, 25.7, 18.0, -4.7; $[\alpha]_D$: +12.3 (*c* 1.52, CH_2Cl_2); IR (neat): 2931, 2857, 1721, 1463, 1103 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{17}H_{27}ClNO_2Si$ (M+H): 340.1499. Found: 340.1495.

1.3 Analytical data of 4c-f and 9a,b,e.



***Cis*-2,4-Diphenylcyclohexanone (4c):**[3] White solid, mp 74-75 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34 (m, 4H), 7.27 (m, 4H), 7.17 (d, *J*= 7.9 Hz, 2H), 3.83 (dd, *J*= 13.3, 5.3 Hz, 1H), 3.30 (tt, *J*= 12.1, 3.4, 1H), 2.77-2.63 (m, 2H), 2.55-2.42 (m, 1H), 2.36 (ddd, *J*= 13.3, 5.3, 3.3 Hz, 1H), 2.26 (q, *J*= 13.3 Hz, 1H), 2.12 (qd, *J*= 13.3, 5.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.3, 144.3, 138.3, 128.7, 128.6, 128.3, 127.0, 126.7, 126.6, 57.0, 43.6, 42.6, 41.9, 34.6; IR (neat):

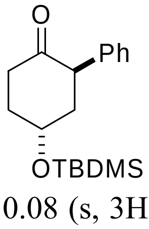
---

[2] Known as a mixture of diastereomers; see Barros, M. T., Maycock, C. D., Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166-173.

[3] Known as a mixture of diastereomers, see Lowe, J. A. III. PCT Int. Appl. 1993, WO 9315059.

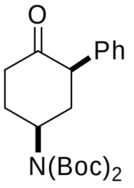
3028, 2931, 1717, 1137 cm^{-1};. HRMS (CI+) Exact mass calcd for $C_{18}H_{19}O$ (M+H): 251.1436. Found: 251.1433.

***Trans*-isomer:** White solid, mp 63-64 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ =. 7.42-7.25 (m, 10H), 3.87 (t, *J*= 4.9 Hz, 1H), 3.31 (tt, *J*= 10.1, 4.3, 1H), 2.72 (m, 1H), 2.61 (ddd, *J*= 14.5, 11.2, 6.4 Hz, 1H), 2.52-2.37 (m, 2H), 2.23-2.12 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 211.4, 144.2, 137.6, 128.9, 128.7, 127.2, 127.0, 126.7, 126.6, 53.6, 39.1, 37.7, 37.3, 33.7; IR (neat): 3027, 2932, 1710 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{18}H_{19}O$ (M+H): 251.1436. Found: 251.1432.

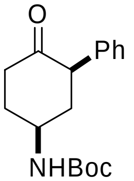


***Trans*-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-phenylcyclohexanone (4d):** Yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.21 (m, 1H), 7.08 (m, 2H), 4.25 (m, 1H), 4.09 (dd, *J*= 12.7, 5.4 Hz, 1H), 2.88 (td, *J*= 13.7, 6.1 Hz, 1H), 2.62 (ddd, *J*= 17.3, 11.3, 6.1 Hz, 1H), 2.31 (ddd, *J*= 13.7, 4.5, 2.6 Hz, 1H), 2.19 (m, 1H), 2.09 (m, 1H), 1.94 (m, 1H), 0.91 (s, 9H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 210.2, 138.5, 128.8, 128.3, 126.9, 65.7, 51.3, 42.5, 36.9, 34.9, 25.8, 18.1, -4.9; IR (neat): 2953, 2857, 1718, 1253 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{18}H_{29}O_2Si$ (M+H): 305.1937. Found: 305.1935.

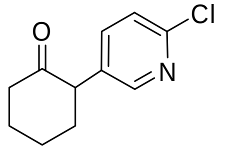
***Cis*-isomer** (not isolated)**:** ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.29 (m, 2H), 7.21 (m, 1H), 7.08 (m, 2H), 4.20 (m, 1H), 3.59 (tt, *J*= 10.3, 4.4 Hz, 1H), 3.59 (dd, *J*= 13.7, 5.4 Hz, 1H), 2.47 (m, 2H), 2.25-2.02 (m, 2H), 1.83 (m, 1H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 211.7, 138.5, 128.8, 128.6, 127.1, 69.3, 53.9, 42.9, 38.8, 35.5, 25.9, 18.1, -4.9.



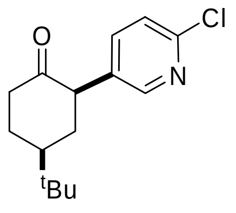
***Cis*-4-(*N,N*-BisBoc)-amino-2-phenylcyclohexanone (4e):** Colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32 (m, 2H), 7.26 (m, 1H), 7.12 (m, 2H), 4.72 (tt, *J*= 11.8, 3.6 Hz, 1H), 3.67 (dd, *J*= 13.7, 5.5 Hz, 1H), 2.71 (app. q, *J*= 12.7 Hz, 1H), 2.61-2.33 (m, 3H), 2.27 (m, 1H), 2.15 (m, 1H), 1.50 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 207.9, 153.0, 137.5, 128.7, 128.3, 127.1, 82.6, 55.8, 54.4, 40.4, 37.5, 29.5, 28.4, 28.0; HRMS (CI+) Exact mass calcd for $C_{17}H_{23}NO_3$ (M+H-Boc): 289.1678. Found: 289.1677.



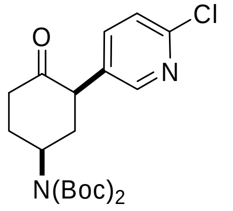
***Cis*-4-(*N*-Boc)-amino-2-phenylcyclohexanone (4f):** White solid, mp 153-154 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33 (t, *J*= 7.2 Hz, 2H), 7.26 (t, *J*= 7.2 Hz, 1H), 7.09 (d, *J*= 7.2 Hz, 2H), 4.49 (br s, 1H), 4.14 (m, 1H), 3.72 (dd, *J*= 13.9, 5.0, 1H), 2.60 (td, *J*= 13.9, 6.0, 1H), 2.55 (m, 2H), 2.39 (ddt, *J*= 12.6, 6.0, 3.2 Hz, 1H), 1.87 (app. q, *J*= 12.6 Hz, 1H), 1.72 (app. qd, *J*= 12.6, 5.3 Hz, 1H), 1.45 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.0, 155.0, 137.5, 128.5, 128.4, 127.1, 79.7, 54.8, 48.5, 40.9, 39.9, 33.3, 29.6, 28.3; IR (neat): 3361, 2974, 2931, 1708, 1518, 1169 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{17}H_{24}NO_3$ (M+H): 290.1756. Found: 290.1751.



2-(6-Chloro-pyridin-3-yl)cyclohexanone (9a):[1] Yellow solid, mp 72-74 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J*= 2.5 Hz, 1H), 7.46 (dd, *J*= 8.3, 2.5 Hz, 1H), 7.30 (d, *J*= 8.3 Hz, 1H), 3.63 (dd, *J*= 12.3, 5.2 Hz, 1H), 2,56 (m, 1H), 2.49 (m, 1H), 2.28 (m, 1H), 2.21 (m, 1H), 1.97-1.75 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 208.7, 150.0, 149.6, 139.2, 133.2, 123.9, 54.2, 42.2, 35.5, 27.7, 25.4; IR (neat): 2938, 2864, 1709, 1462, 1104 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{11}H_{13}ClNO$ (M+H): 210.0686. Found: 210.0677.



(2*R*,4*S*)-4-*tert*-Butyl-2-(6-chloro-pyridin-3-yl)cyclohexanone (9b): White solid, mp 117-118 °C; the *ee* was measured to 90% on ChiralCel OD-H, ^{i}Hex: ^{i}PrOH 95:5, 1 to 0.5 mL/min; retention times 16.2 min (2*S*,4*R*) and 20.4 min (2*R*,4*S*). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.14 (d, *J*= 2.5 Hz, 1H), 7.46 (dd, *J*= 8.3, 2.5 Hz, 1H), 7.31 (d, *J*= 8.3 Hz, 1H), 3.63 (dd, *J*= 13.2, 5.0 Hz, 1H), 2,58 (ddd, *J*= 14.0, 5.0, 3.0 Hz, 1H), 2.52 (qd, *J*= 14.0, 5.7 Hz, 1H), 2.24 (m, 2H), 1.80-1.56 (m, 3H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.0, 150.0, 149.7, 139.2, 133.4, 123.9, 53.5, 47.4, 41.5, 36.9, 32.5, 28.6, 27.6; $[\alpha]_D^{20}$: +2.2 (*c* 0.44, CH_2Cl_2); IR (neat): 2960, 2870, 1716, 1462, 1104 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{15}H_{21}ClNO$ (M+H): 266.1312. Found: 266.1309.



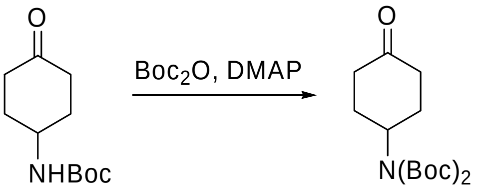
(2*R*,4*S*)-4-(*N*,*N*-BisBoc)-amino-2-(6-chloro-pyridin-3-yl)-cyclohexanone (**9e**): White solid, mp 131-132 °C; the *ee* was measured to 87% on ChiralCel OD-H, ^{i}Hex: ^{i}PrOH 95:5, 1 mL/min; retention times 23.6 min (2*R*,4*S*) and 32.9 min (2*S*,4*R*). Recrystallization of the purified product in EtOAc:pentane increased the *ee* to 94%. White crystals; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.12 (d, *J*= 2.5 Hz, 1H), 7.45 (dd, *J*= 8.2, 2.5 Hz, 1H), 7.29 (d, *J*= 8.2 Hz, 1H), 4.72 (tt, *J*= 11.8, 3.6 Hz, 1H), 3.70 (dd, *J*= 13.5, 5.3 Hz, 1H), 2.67 (app. q, *J*= 12.7 Hz, 1H), 2.58 (m, 2H), 2.50 (ddd, *J*= 17.2, 11.0, 5.9 Hz, 1H), 2.25 (m, 1H), 2.16 (m, 1H), 1.49 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.5, 152.9, 150.2, 149.7, 139.3, 132.3, 123.9, 82.9, 54.2, 52.4, 40.2, 37.4, 29.4; $[\alpha]_D^{20}$: +22.5 (*c* 1.43, CH_2Cl_2); IR (neat): 2980, 2936, 1738, 1699, 1349, 1139 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{21}H_{30}ClN_2O_5$ (M+H): 425.1843. Found: 425.1851.

2. Synthesis of 2e & analytical data of 5.

2.1 Synthesis of 4-(*N*,*N*-BisBoc)-aminocyclohexanone (2e).

---

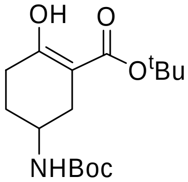
[1] Known compound, but no analysis data is published.



2f **2e**

Carbamate **2f** (1.70 g, 8.0 mmol), Boc_2O (5.50 g, 25 mmol, 3 equiv) and DMAP (3.10 g, 25 mmol, 3 equiv) were refluxed in anhydrous THF (180 mL) for 2 h to give an orange solution. H_2O (10 mL) was added, then most of the THF was removed *in vacuo*. The remaining mixture was diluted with Et_2O and H_2O and acidified to pH 5 by careful addition of HCl, followed by extraction with Et_2O*3. The organic phase was washed with brine, dried ($MgSO_4$) and concd to give a yellow solid that was pushed through a silica plug with pentane: EtOAc 4:1 to give **2e** as an offwhite solid (2.52 g, 100%). mp 72-73 °C; ^1H NMR (400 MHz, $CDCl_3$): δ = 4.48 (tt, *J*= 11.3, 4.0 Hz, 1H), 2.42 (m, 4H), 2.34 (m, 2H), 2.05 (m, 2H), 1.50 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 209.7, 153.0, 82.6, 54.2, 40.1, 28.9, 28.0; IR (neat): 2977, 1739, 1699, 1120 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{16}H_{28}NO_5$ (M+H): 314.1967. Found: 314.1962.

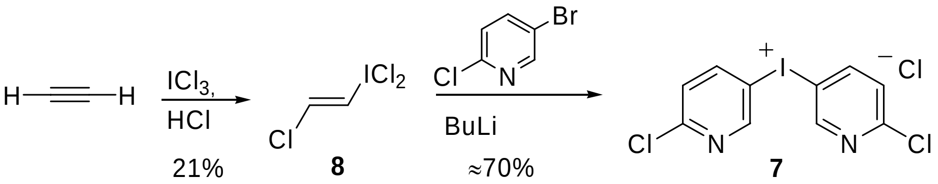
2.2 Analytical data of Boc-transfer product 5.



5-(*N*-Boc)-amino-2-hydroxy-cyclohex-1-enecarboxylic acid tert-butyl ester (5): *pH-dependent equilibrium with β-ketoester.* White solid, mp 135-136 °C; ^1H NMR (300 MHz, $CDCl_3$): δ = 12.36 (s, 1H), 4.61 (br d, *J*= 6.9 Hz, 1H), 3.71 (m, 1H), 2.51 (dd, *J*= 16.0, 4.8 Hz, 1H), 2.30 (m, 2H), 1.96 (dd, *J*= 15.7, 7.9 Hz, 1H), 1.87 (m, 1H), 1.60 (m, 1H), 1.44 (s, 9H), 1.40 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.0, 170.3, 155.2, 96.3, 81.1, 55.6, 45.5, 29.4, 28.3, 28.1, 27.1; IR (neat): 3356, 3979, 1714, 1686, 1167 cm^{-1}; MS (MALDI TOF) Exact mass calcd for $C_{16}H_{27}NO_5K$ (M+K): 352.1526. Found: 352.1523.

β-ketoester *(not isolated):* ^1H NMR (300 MHz, $CDCl_3$): δ = 4.79 (br d, *J*= 7.9 Hz, 1H), 3.95 (m, 1H), 3.34 (dd, *J*= 12.1, 5.8 Hz, 1H), 2.42 (dd, *J*= 8.7, 4.8 Hz, 1H), 2.30 (m, 2H), 1.96 (dd, *J*= 15.7, 7.9 Hz, 1H), 1.87 (m, 1H), 1.60 (m, 1H), 1.42 (s, 9H), 1.42 (s, 9H);

3. Synthesis of iodonium salt 7.



3.1 Synthesis of chlorovinyliodoso dichloride (8): [1,2]

---

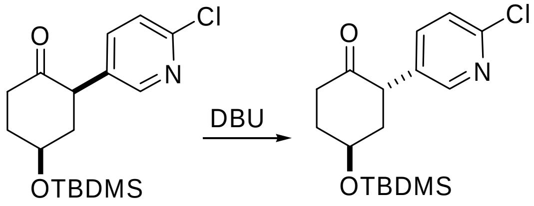
[2] Beringer, N.; Nathan, R. A. *J. Org. Chem.* **1969**, *34*, 685-689.

ICl_3 (10 g, 4.3 mmol) was dissolved in ice-water (30 mL). The solution was cooled to 0 °C before addition of conc. HCl (15 mL). Acetylene gas was bubbled through at 0 °C for 10 min, then at rt for 1.5 h. A yellow solid precipitated and was collected by suction filtration on a glass filter funnel. The solid was washed with cold H_2O (3*10 mL) and dried on the filter with suction for 10 min, which resulted in a yellow solid (2.37 g, 21%). ***NB!*** This compound is extremely unstable and decomposes autocatalytically (within seconds when it starts). It should not be handled with metal spatulaes, also avoid long reaction times, extensive drying, vacuum and N_2 flow. It can, however, be stored for weeks in the freezer when isolated as described above.
^{1}H NMR (270 MHz, $CDCl_3$): δ = 7.36 (d, *J*= 12.4 Hz, 1H), 7.28 (d, *J*= 12.4 Hz, 1H).

3.2 Synthesis of bis(6-chloro-pyridin-3-yl)iodonium chloride (7): Modified literature procedure.[2,3] 2-Chloro-5-bromopyridine[4] (1.42 g, 7.4 mmol, 2 equiv) was dissolved in anhydrous Et_2O (36 mL) and cooled to -78 °C. BuLi (1.6 M/hexane, 4.60 mL, 7.4 mmol, 2 equiv) was added, which resulted in a yellow slurry that slowly turned orange. After 40 min at -78 °C compound **8** (1.00 g, 3.8 mmol) was added in one portion to give a milky yellow suspension. The reaction was stirred at -78 °C for a further hour, then allowed to reach rt over 3h. The solid was collected by filtration, washed with Et_2O*3 and stirred with THF (10 mL) for 10 min to remove LiCl. The remaining solid was dried under vacuum to give **7** as a white solid (744 mg, 52%). The THF filtrate was concd, the solid was recrystallized from CH_2Cl_2 (dissolves poorly) to give a second crop of product (271 mg, 19%). The product might still contain some LiCl. mp 225 °C (decomposed); ^{1}H NMR (300 MHz, DMSO): δ = 9.05 (d, *J*= 2.0 Hz, 1H), 8.60 (dd, *J*= 8.5, 2.0 Hz, 1H), 7.62 (d, *J*= 8.5 Hz, 1H); ^{13}C NMR (75 MHz, DMSO): δ = 154.1, 152.2, 145.2, 127.0, 120.8; HRMS (CI+) Exact mass calcd for $C_{10}H_6Cl_2IN_2$ (M-Cl$^-$): 350.8953. Found: 350.8949.

4. Synthetic routes to Epibatidine (1).

4.1 Equilibration of *cis*-9d to *trans*-9d:



cis-**9d** *trans*-**9d**

Cis-**9d** (80 mg, 0.24 mmol) and DBU (7 μL, 0.05 mmol, 0.2 equiv) were dissolved in anhydrous THF (0.5 mL) and stirred at rt for 16 h. Bright yellow solution, turned red-brown. H_2O and Et_2O were added, the pH was adjusted to slightly acidic by careful addition of HCl. The mixture was eluted through an Extrelut® tube and concd to give a

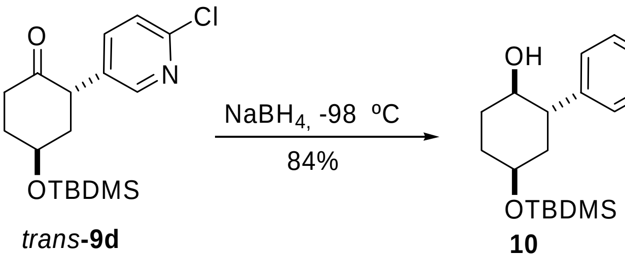
---

[3] Stang, P. J., Olenyuk, B., Chen, K. *Synthesis* **1995**, 937-938.

[4] Purchased from Aldrich and purified with flash chromatography prior to use.

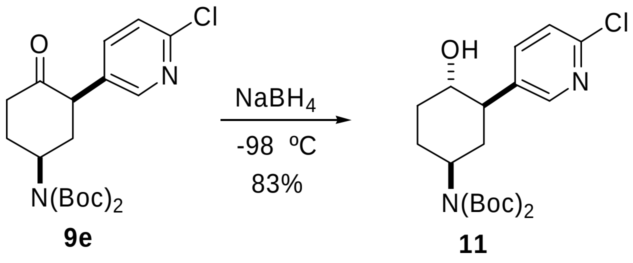
yellow oil. *Trans*-**9d** was isolated by column chromatography (pentane:EtOAc 6:1) in 70% yield (56 mg). The remaining *cis*-**9d** (14 mg, 18%) was equilibrated again, to give a 83% total yield of *trans*-**9d** (66 mg). Total yield from *cis:trans* mixture **9d**, calculating with the amount of separated *trans*-**9d** before quilibration: 88%. For analytical data, see section 1.2.

4.2 Reduction of *trans*-9d to (1*R*,2*S*,4*S*)-4-(*tert*-Butyl-dimethyl-silanyloxy)-2-(6-chloro-pyridin-3-yl)cyclohexanol (10):



Trans-**9d** (20.0 mg, 59 μmol) was dissolved in anhydrous MeOH (1 mL) and cooled to -98 °C (MeOH/N_2 bath). $NaBH_4$ (22 mg, 0.59 mmol, 10 equiv.) in MeOH (0.2 mL) was added. The reaction was stirred for 1.5 h at -98 °C and allowed to reach - 60 °C over 1 h. The reaction was quenched with sat. NH_4Cl, allowed to reach rt and most of the MeOH was removed *in vacuo*. The mixture was dissolved in CH_2Cl_2, eluted through an Extrelut® tube and concd to give a yellow oil. Crude ^{1}H NMR suggested a diastereomeric ratio of 10:1. Flash chromatography (pentane: EtOAc 8:1 → 1:1) yielded **10** (16.9 mg, 84%) as a colorless oil. Analytical data were in agreement with literature[5] apart from the optical rotation, which differed in magnitude but had the same sign. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.26 (m, 1H), 7.55 (dd, *J*= 8.2, 2.4 Hz, 1H), 7.28 (d, *J*= 8.2 Hz, 1H), 4.01 (m, 1H), 3.66 (td, *J*= 10.4, 4.8 Hz, 1H), 3.04 (dt, *J*= 10.4, 3.2 Hz, 1H), 1.98-1.77 (m, 5H), 1.61 (m, 2H), 0.92 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.6, 149.5, 138.3, 137.9, 124.1, 73.8, 65.5, 43.2, 40.1, 32.1, 29.1, 25.8, 18.0, -4.9, -5.0; $[\alpha]_D^{20}$ –7.2 (*c* 0.32, CH_2Cl_2), lit (ref 6) $[\alpha]_D^{20}$ –10.6 (*c* 0.32, CH_2Cl_2).

4.3 Reduction of 9e to (1*S*,2*R*,4*S*)-4-(*N*,*N*-BisBoc)-amino-2-(6-chloro-pyridin-3-yl)cyclohexanol (11):



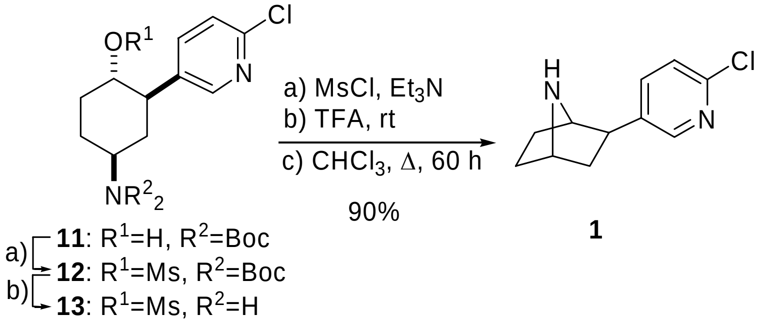
---

[5] Barros, M. T., Maycock, C. D.,Ventura, M. R. *J. Chem. Soc., Perkin Trans. 1* **2001**, 166-173.

Performed as described in section 4.2. Crude ^{1}H NMR suggested a diastereomeric ratio of 7:1 (eq:axial). Flash chromatography (pentane: EtOAc 8:1 → 1:1) yielded **11** as a white, low-melting solid (83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.23 (d, *J*= 2.5 Hz, 1H), 7.36 (dd, *J*= 8.4, 2.5 Hz, 1H), 7.26 (d, *J*= 8.4 Hz, 1H), 4.18 (tt, *J*= 12.2, 3.9 Hz, 1H), 3.68 (td, *J*= 10.3, 3.9 Hz, 1H), 2.61 (td, *J*= 10.3, 3.4 Hz, 1H), 2.28 (q, *J*= 12.4 Hz, 1H), 2.21-2.05 (m, 2H), 1.88 (m, 2H), 1.59 (m, 1H), 1.49 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 149.7, 149.5, 138.1, 136.9, 124.2, 82.4, 73.0, 55.3, 48.7, 25.4, 34.1, 28.0, 27.7; $[\alpha]_D^{20}$: +5.4 (*c* 3.28, CH_2Cl_2); IR (neat): 3420, 2979, 2935, 1698, 1344, 1197 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{21}H_{32}ClN_2O_5$ (M+H): 427.1999. Found: 427.1994.

Axial isomer: White solid, mp 58-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.29 (d, *J*= 2.5 Hz, 1H), 7.64 (dd, *J*= 8.3, 2.5 Hz, 1H), 7.26 (d, *J*= 8.3 Hz, 1H), 4.18 (tt, *J*= 11.9, 3.6 Hz, 1H), 3.94 (m, 1H), 2.80 (dt, *J*= 13.4, 2.6 Hz, 1H), 2.71 (app. q, *J*= 12.7 Hz, 1H), 2.34 (qd, *J*= 12.7, 4.0 Hz, 1H), 2.03 (dq, *J*= 14.1, 3.4 Hz, 1H), 1.77 (ddd, *J*= 14.1, 4.4, 2.3 Hz, 1H), 1.74-1.61 (m, 2H), 1.52 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 149.6, 149.3, 138.6, 137.3, 123.8, 82.3, 68.4, 55.5, 45.1, 32.8, 28.9, 28.0, 22.6; $[\alpha]_D^{20}$: -25.7 (*c* 1.10, CH_2Cl_2); IR (neat): 3500, 2980, 2934, 1739, 1345 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{21}H_{32}ClN_2O_5$ (M+H): 427.1999. Found: 427.1996.

4.4 Mesylation, deprotection and ring-closure to (–)-Epibatidine (1):[6]



*As mesylates **12** and **13** are unstable, much higher overall yield was obtained when they were not isolated but used as crude products (52% over three steps with isolation).*

Mesylation of 11 to (1*S*,2*R*,4*S*)-methanesulfonic acid 4-(*N*,*N*-BisBoc)-amino-2-(6-chloro-pyridin-3-yl)cyclohexyl ester (12):

Alcohol **11** (49 mg, 115 μmol) was dissolved in anhydrous CH_2Cl_2 (2 mL) and MsCl (32 μL, 0.46 mmol, 4 equiv.) and dist. Et_3N (32 μL, 0.23 mmol, 2 equiv.) were added. The reaction was stirred for 4 h at rt and quenched by addition of sat. $NaHCO_3$. The mixture was eluted through an Extrelut® tube with CH_2Cl_2 and concd to give a yellow oil that was directly used in the following reaction. A small portion was purified with column chromatography (pentane:EtOAc 6:1 → 1:1) for analytical purposes to yield **12** as colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J*= 2.6 Hz, 1H), 7.60 (dd, *J*= 8.3, 2.6 Hz, 1H), 7.32 (d, *J*= 8.3 Hz, 1H), 4.63 (td, *J*= 10.9, 4.6 Hz, 1H), 4.20 (tt, *J*= 12.2, 3.8

---

[6] The conversion of alcohol **11** to epibatidine follows the sequence described for the corresponding NHBoc compound, see Trost, B. M.,Cook, G. R. *Tetrahedron Lett.* **1996**, *37*, 7485-7488.

Hz, 1H), 2.89 (ddd, *J*= 12.9, 10.9, 3.6 Hz, 1H), 2.48 (s, 3H), 2.46 (m, 1H), 2.42 (q, *J*= 12.7 Hz, 1H), 2.21 (qd, *J*= 12.8, 3.8 Hz, 1H), 1.98 (dq, *J*= 12.8, 3.7 Hz, 1H), 1.91 (m, 1H), 1.83 (m, 1H), 1.49 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.0, 150.5, 149.6, 137.7, 135.4, 124.3, 82.8, 82.7, 54.4, 45.9, 38.2, 35.5, 32.7, 28.0, 27.1; $[\alpha]_D^{20}$: +20.2 (*c* 0.63, CH_2Cl_2); IR (neat): 2980, 2936, 1699, 1461, 1346, 1176, 1145 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{22}H_{34}ClN_2O_7S$ (M+H):505.1775. Found: 505.1772.

Deprotection of 12 to (1*S*,2*R*,4*S*)-methanesulfonic acid 4-amino-2-(6-chloro-pyridin-3-yl)cyclohexyl ester (13): [1,7]

The crude mesylate **12** was dissolved in anhydrous CH_2Cl_2 (1 mL) and treated with TFA (134 µL, 1.74 mmol, 20 equiv.). The yellow mixture was stirred at rt for for 15 h and quenched by addition of sat. K_2CO_3. The mixture was eluted through an Extrelut® tube with CH_2Cl_2 and concd to give a yellow oil that was directly used in the following reaction (section 4.5). A small portion was purified with flash chromatography (EtOAc → EtOAc:MeOH 4:1 with NH_4OH) for analytical purposes; amino mesylate **13** was isolated as a yellow oil together with a small amount of cyclized material (**1**). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J*= 2.5 Hz, 1H), 7.58 (dd, *J*= 8.2, 2.5 Hz, 1H), 7.34 (d, *J*= 8.2 Hz, 1H), 4.61 (td, *J*= 11.0, 4.7 Hz, 1H), 2.97 (tt, *J*= 11.0, 3.9 Hz, 1H), 2.89 (td, *J*= 11.0, 3.5 Hz, 1H), 2.50 (s, 3H), 2.42 (dq, *J*= 12.8, 4.3 Hz, 1H), 2.04 (m, 2H), 1.90 (br s, 2H), 1.82 (m, 1H), 1.55 (m, 1H), 1.41 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.5, 149.6, 137.6, 135.6, 124.3, 83.5, 49.3, 45.0, 41.8, 38.2, 33.9, 32.1; $[\alpha]_D^{20}$: +25.7 (*c* 1.18, CH_2Cl_2); IR (neat): 3351, 2939, 3874, 1460, 1351, 1175 cm^{-1}; HRMS (CI+) Exact mass calcd for $C_{12}H_{18}ClN_2O_3S$ (M+H):305.0727. Found: 305.0731.

Ring-closure of 13 to (–)-epibatidine (1):

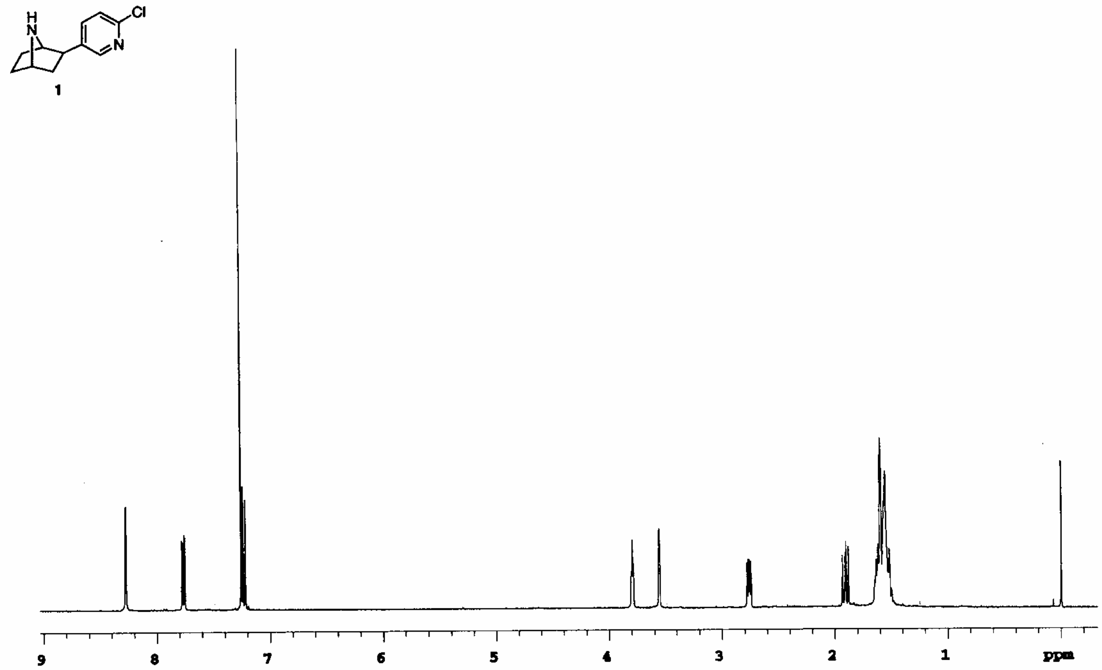
Crude amine **13** was dissolved in anhydrous $CHCl_3$ (9 mL) and heated to reflux in a sealed flask for 48 h. To improve the conversion, the formed MsOH was removed by workup with sat. Na_2CO_3/CH_2Cl_2, Na_2SO_4 and concd. The reaction was then continued for another 12 h, and worked up as described above again. The crude product was pushed through a silica plug (EtOAc → EtOAc:MeOH 10:1 with NH_4OH) to give **1** (26.5 mg, 90% over three steps). Analytical data were in agreement with the literature.[8] ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.28 (d, *J*= 2.5 Hz, 1H), 7.77 (dd, *J*= 8.3, 2.5 Hz, 1H), 7.23 (d, *J*= 8.3 Hz, 1H), 3.80 (app. t, *J*= 4.4 Hz, 1H), 3.56 (d, *J*= 2.0 Hz, 1H), 2.76 (d, *J*= 9.0, 4.9 Hz, 1H), 1.91 (dd, *J*= 12.2, 9.0 Hz, 1H), 1.65-1.49 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 148.9, 148.8, 141.0, 137.7, 123.9, 62.8, 56.4, 44.5, 40.3, 31.3, 30.1; $[\alpha]_D^{20}$: -6.2 (*c* 0.21, CH_2Cl_2); lit (ref 11) $[\alpha]_D^{25}$ D: -6.7 (*c* 0.21, CH_2Cl_2).

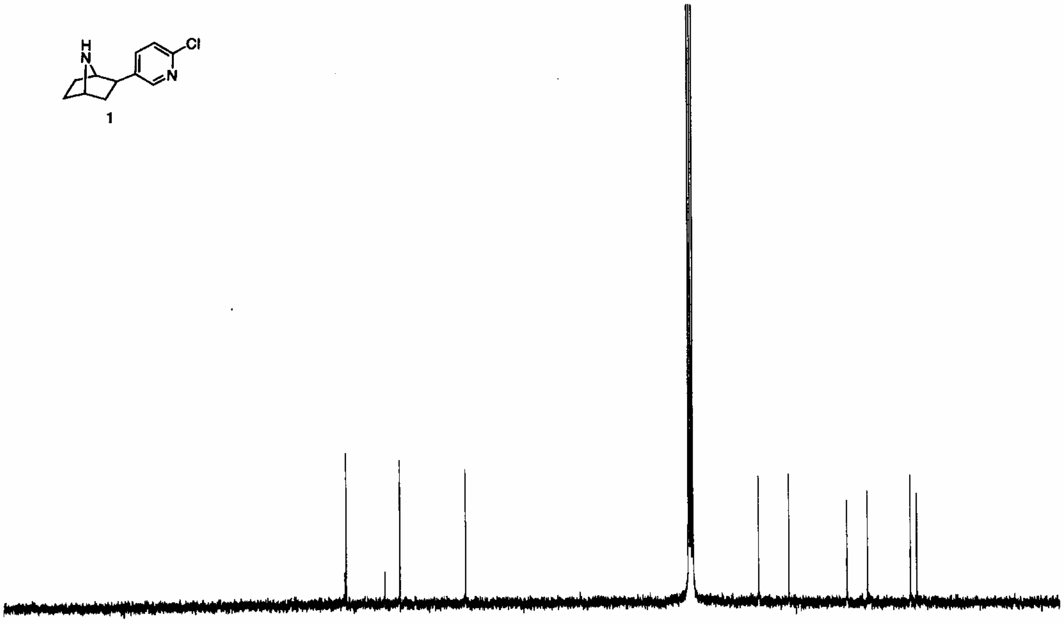
5. NMR spectra of compounds 1, 2e, 4b-f, 5, 7, 8, 9a,b, 10-12.

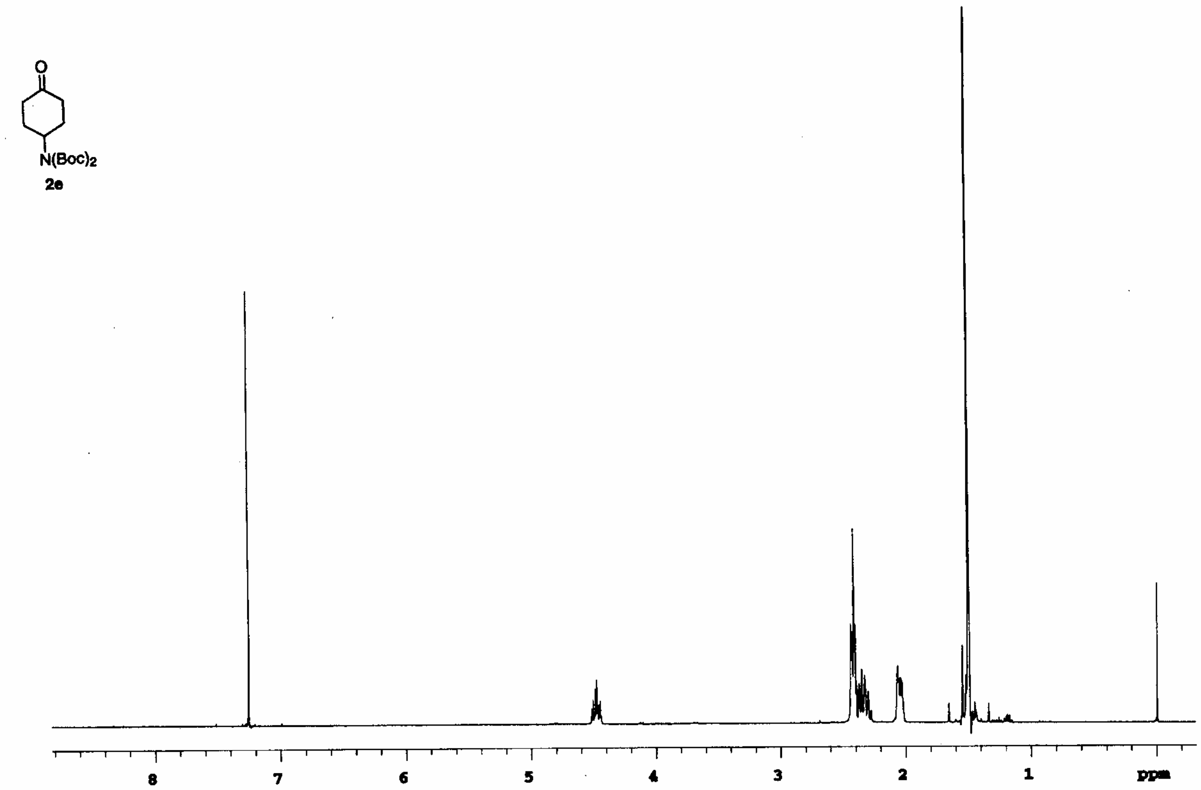
---

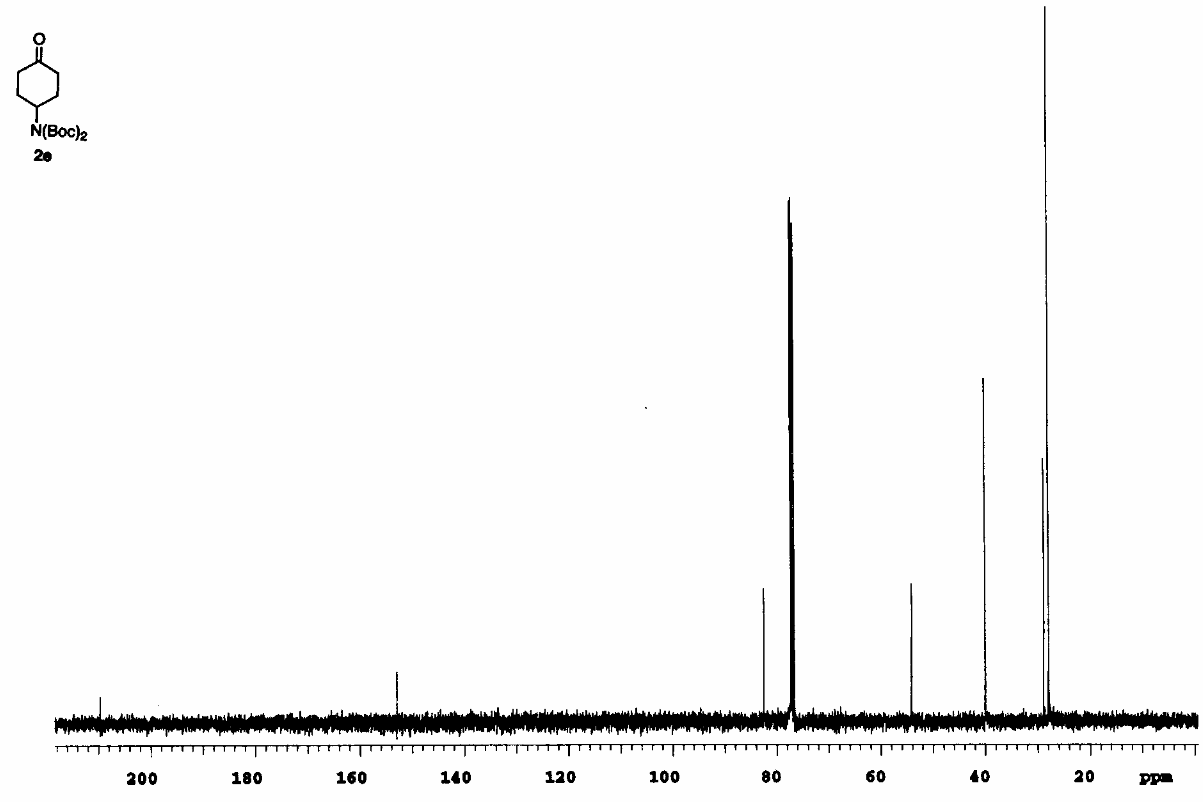
[7] Ko, S. Y.; Lerpiniere, J.; Linney, I. D.; Wrigglesworth, R. *J. Chem. Soc., Chem. Commun.* **1994**, 1775-1776; Broka, Chris A. *Tetrahedron Lett.* **1994**, *34*, 3251-3254.

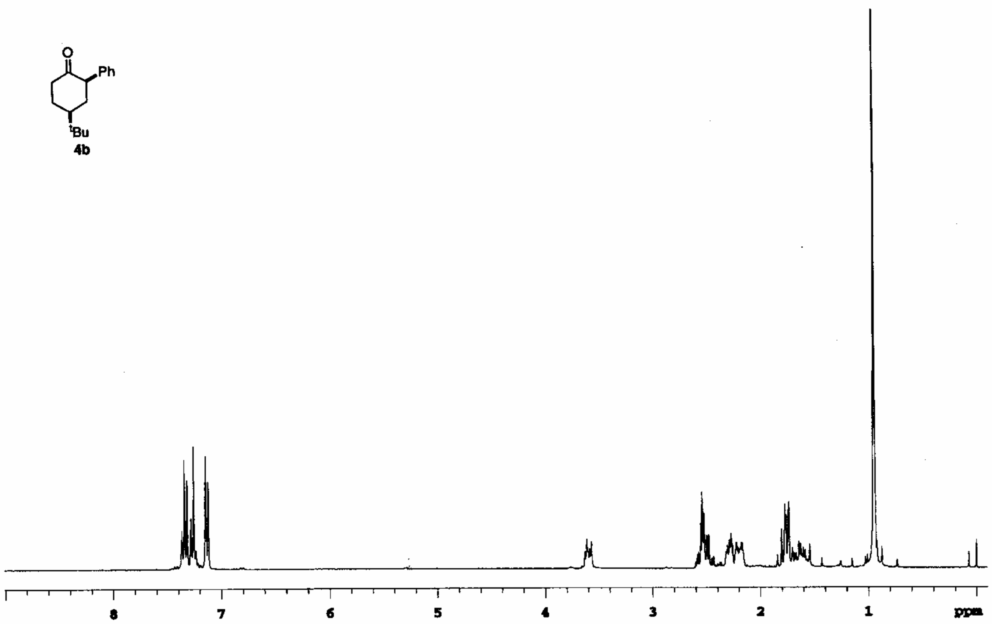
[8] Evans, D. A., Scheidt, K. A.,Downey, C. W. *Org. Lett.* **2001**, *3*, 3009-3012 and references cited therein.


H
N
Cl
N
1
9
8
7
6
5
4
3
2
1
ppm

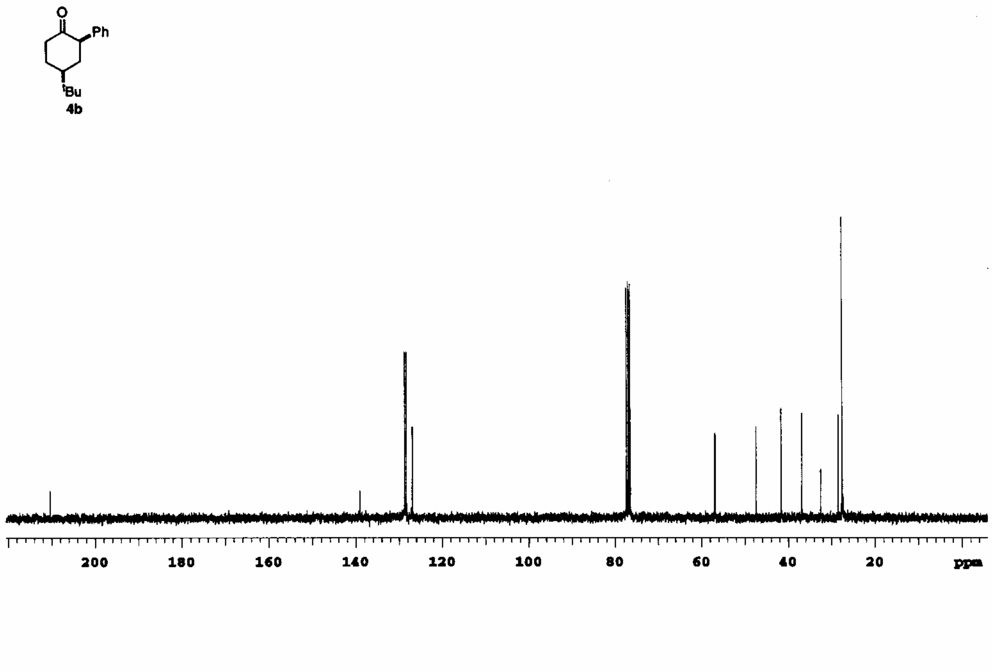

H
N
Cl
N
1
200
180
160
140
120
100
80
60
40
20
ppm


O
N(Boc)2
2e
8
7
6
5
4
3
2
1
ppm

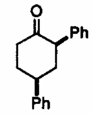

O
N(Boc)2
2e
200
180
160
140
120
100
80
60
40
20
ppm


Ph
tBu
8
7
6
5
4
3
2
1
ppm

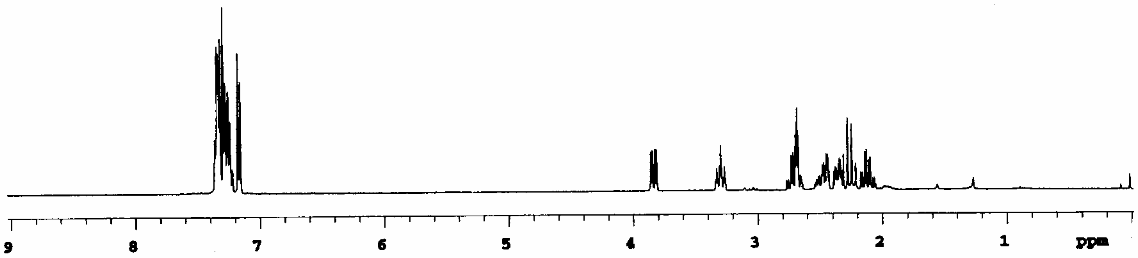
4b

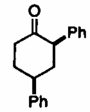

Ph
tBu
200
180
160
140
120
100
80
60
40
20
ppm

4b

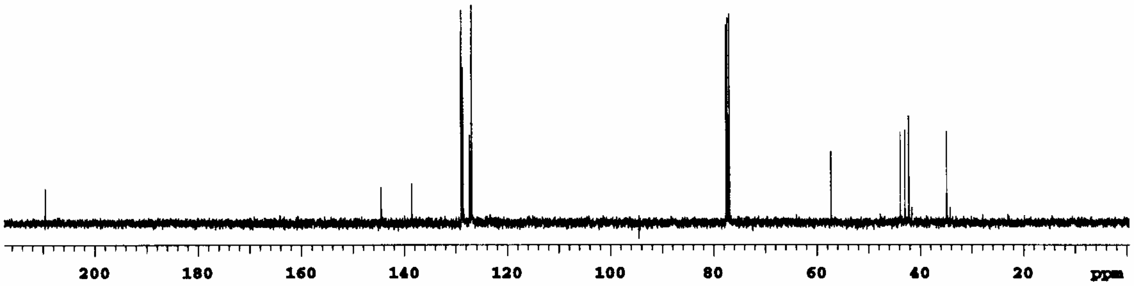

O
Ph
Ph

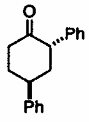
cis-**4c**


9
8
7
6
5
4
3
2
1
ppm

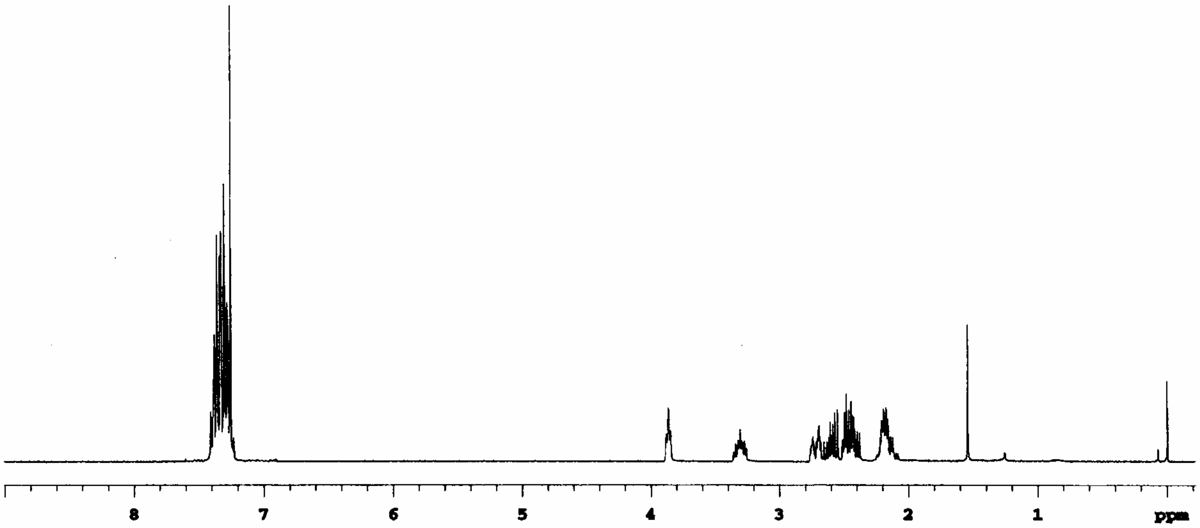

O
Ph
Ph

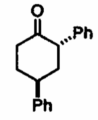
cis-**4c**


200
180
160
140
120
100
80
60
40
20
ppm

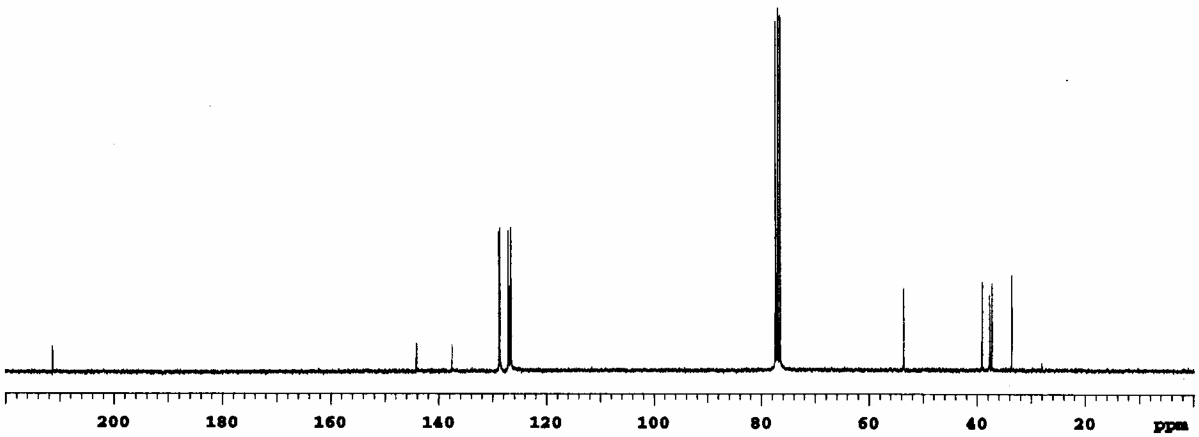


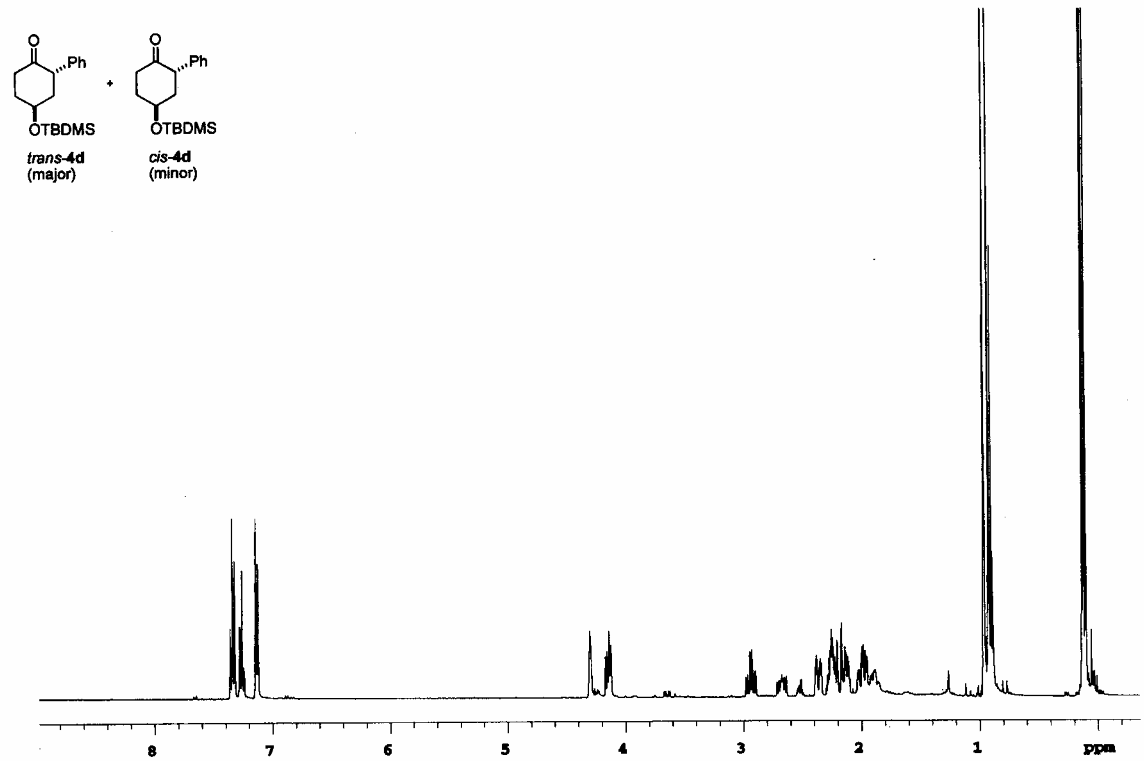
trans-**4c**

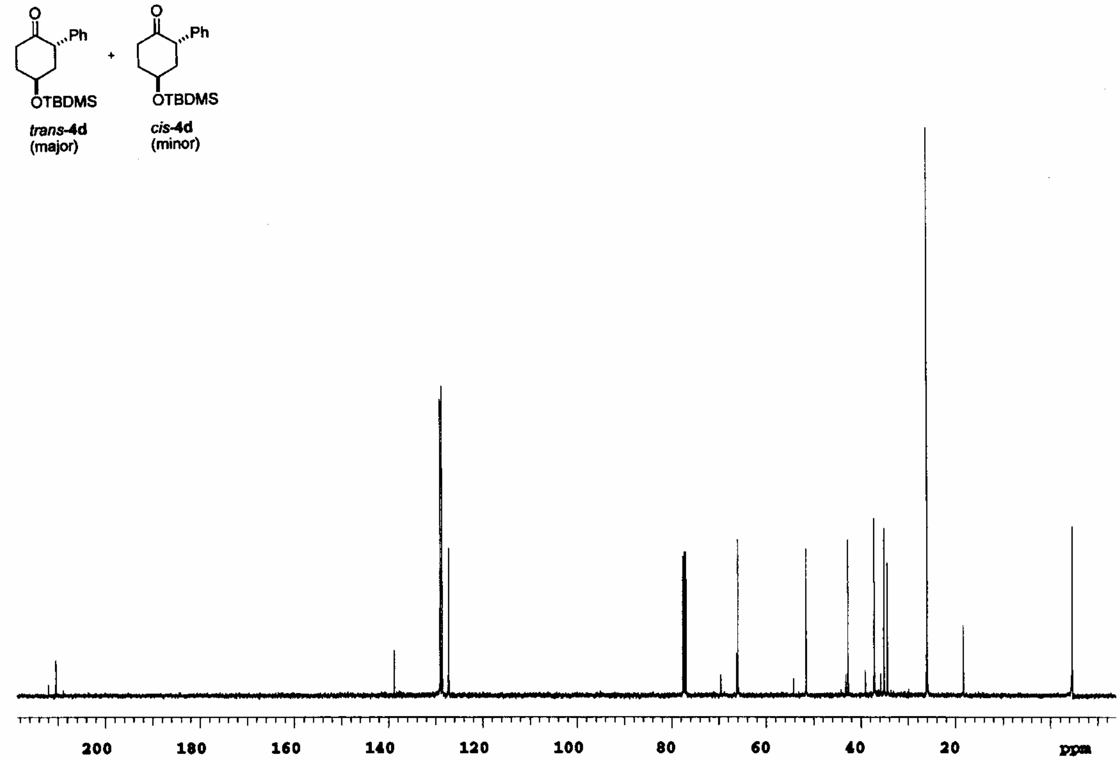


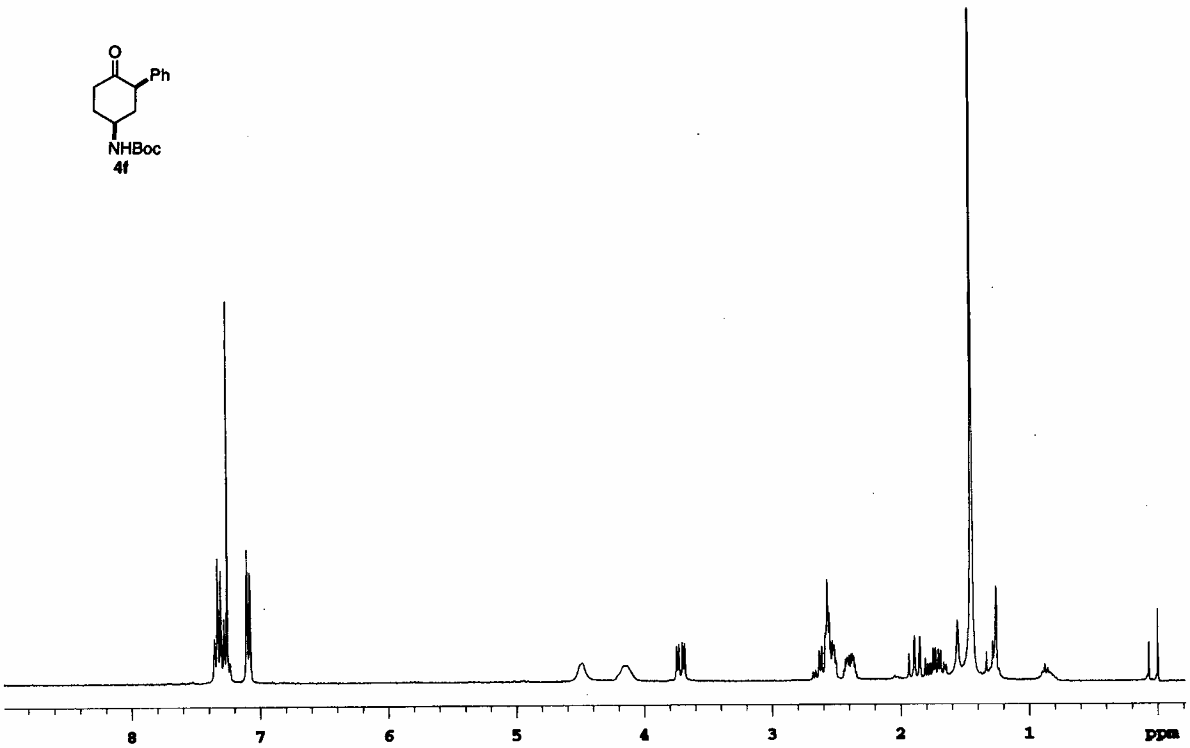


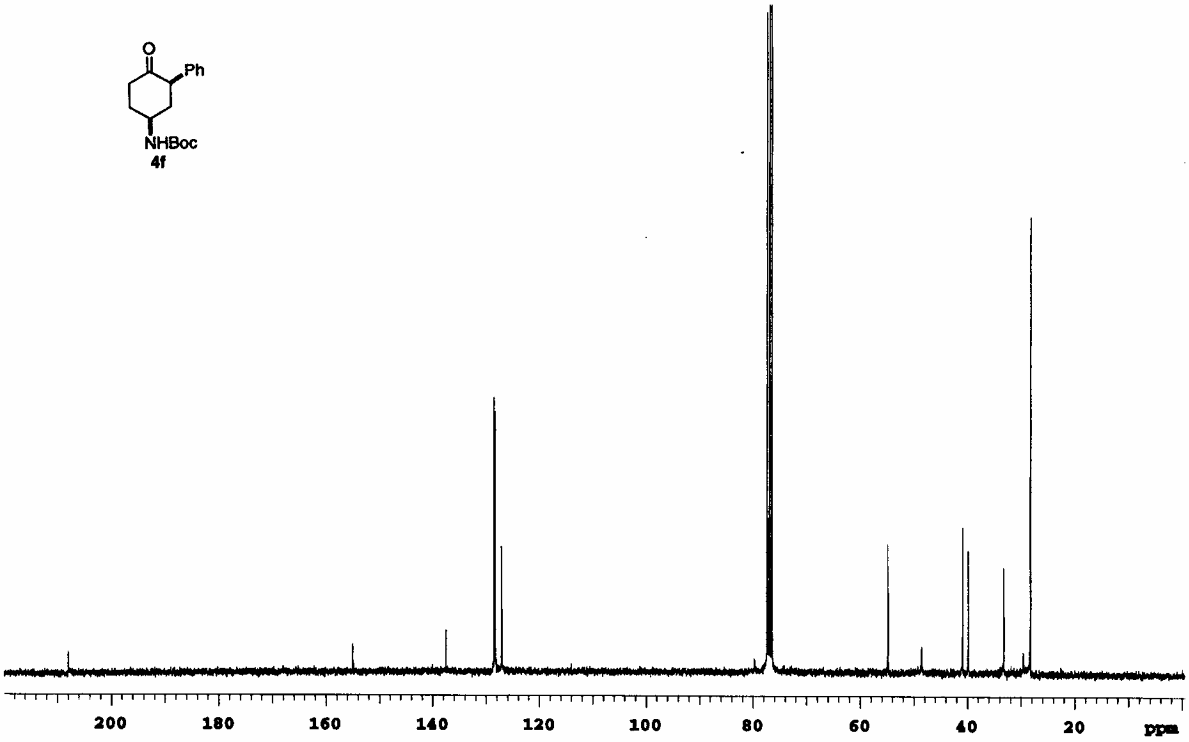
trans-**4c**

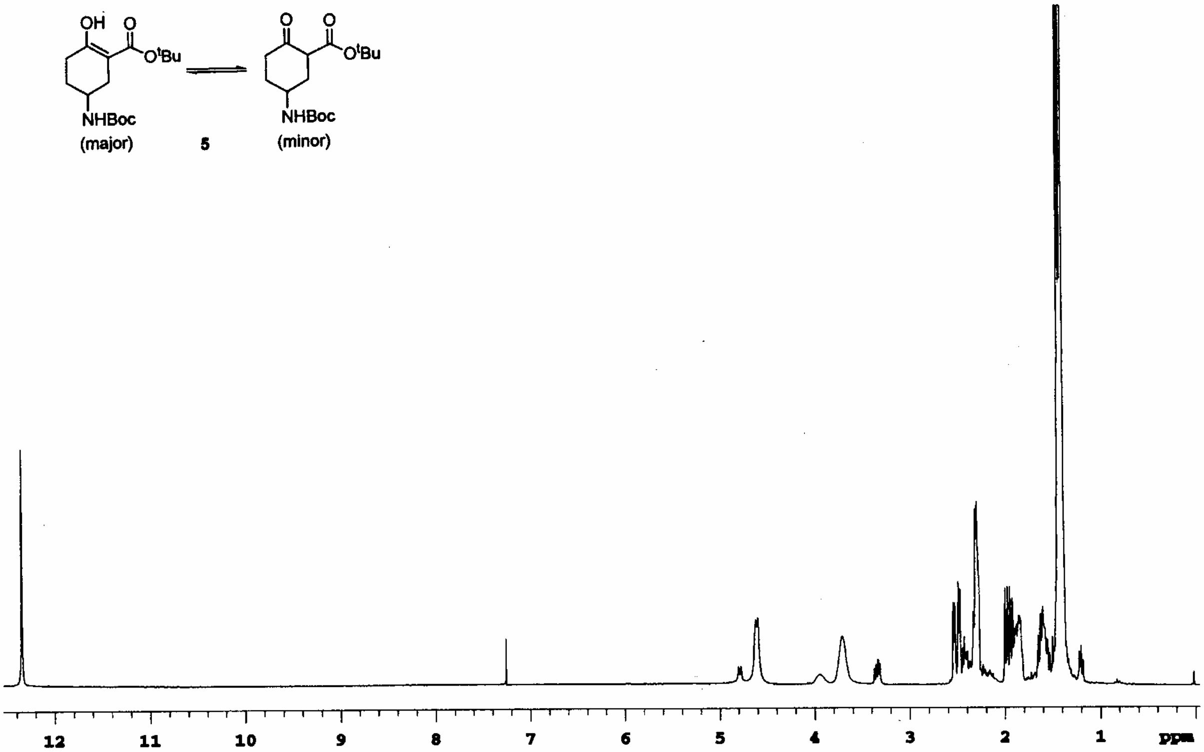


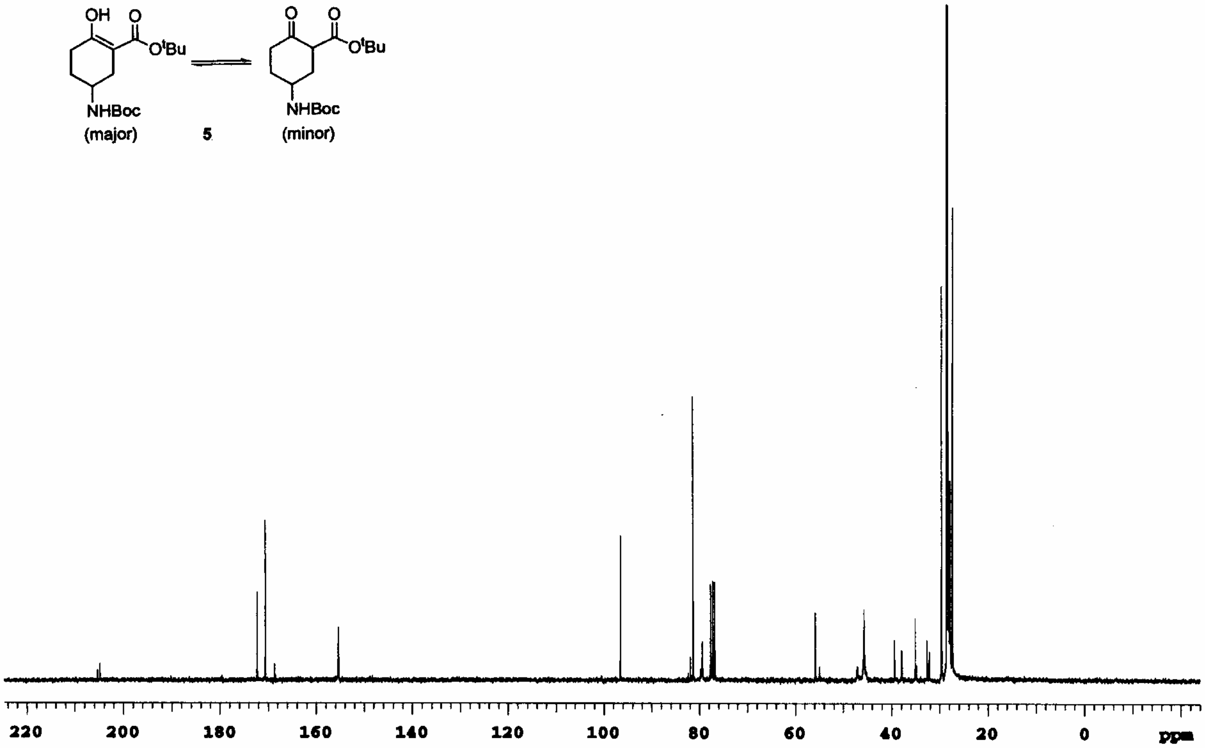

O
Ph
+
OTBDMS
trans-4d
(major)
cis-4d
(minor)
8
7
6
5
4
3
2
1
ppm

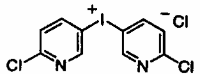

O
Ph
+
OTBDMS
trans-4d
(major)
cis-4d
(minor)
200
180
160
140
120
100
80
60
40
20
ppm


O
Ph
NHBoc
4f
8
7
6
5
4
3
2
1
ppm

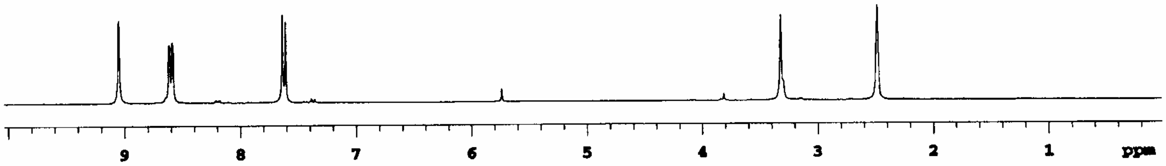

O
Ph
NHBoc
4f
200
180
160
140
120
100
80
60
40
20
ppm

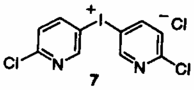

OH
O
O^{t}Bu
NHBoc
(major)
5
O
O
O^{t}Bu
NHBoc
(minor)
12
11
10
9
8
7
6
5
4
3
2
1
ppm


OH
O
O^{t}Bu
NHBoc
(major)
5
O
O
O^{t}Bu
NHBoc
(minor)
220
200
180
160
140
120
100
80
60
40
20
0
ppm

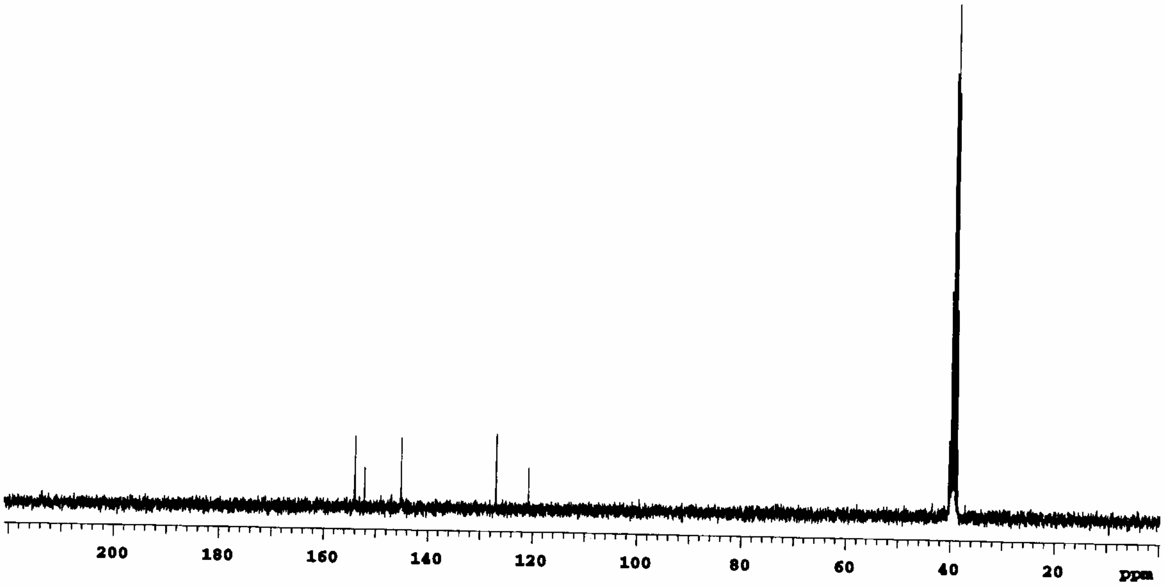


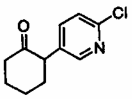
7



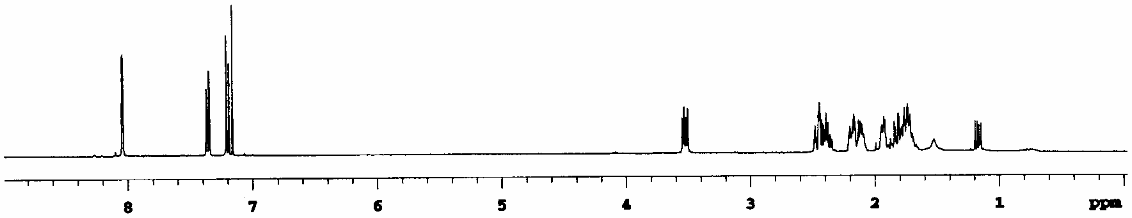


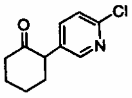
7



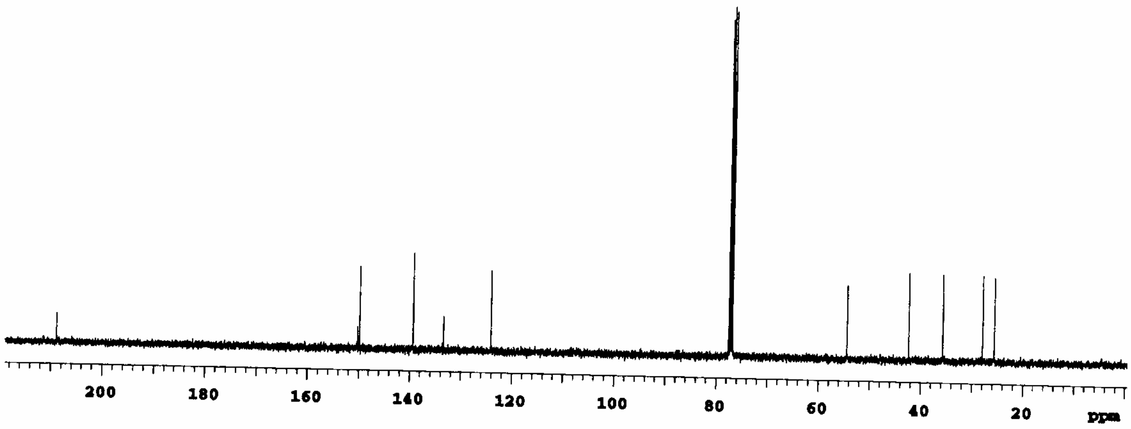


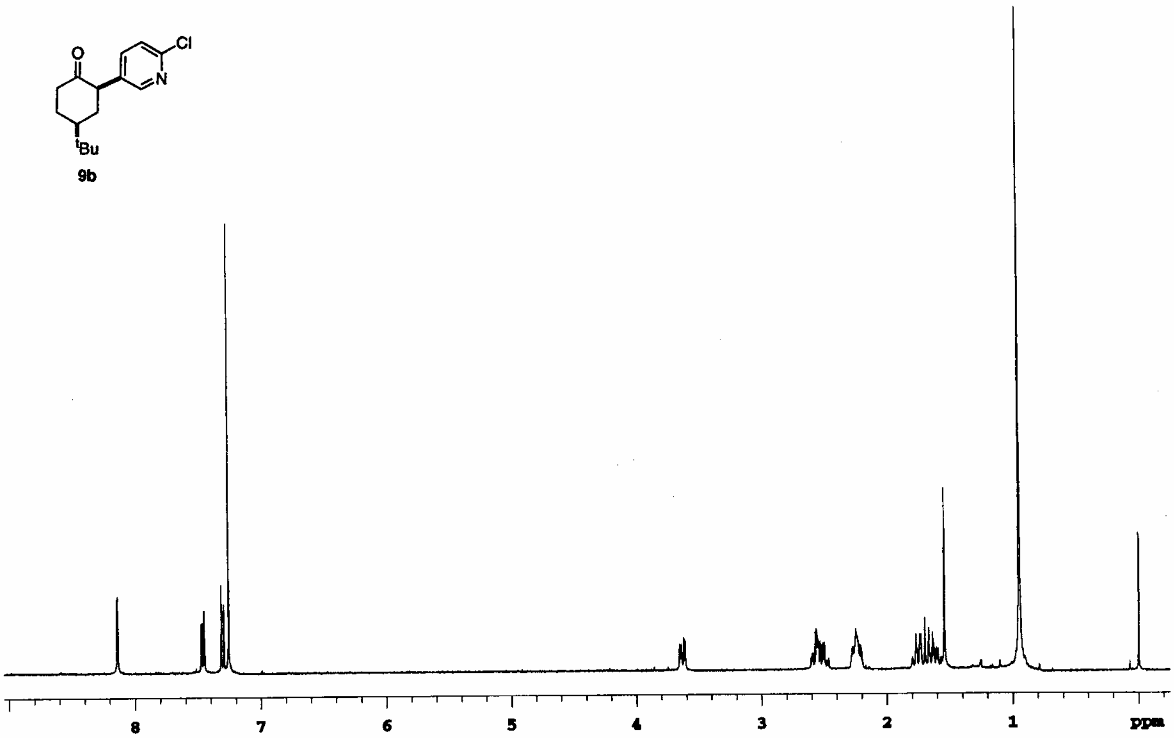
9a

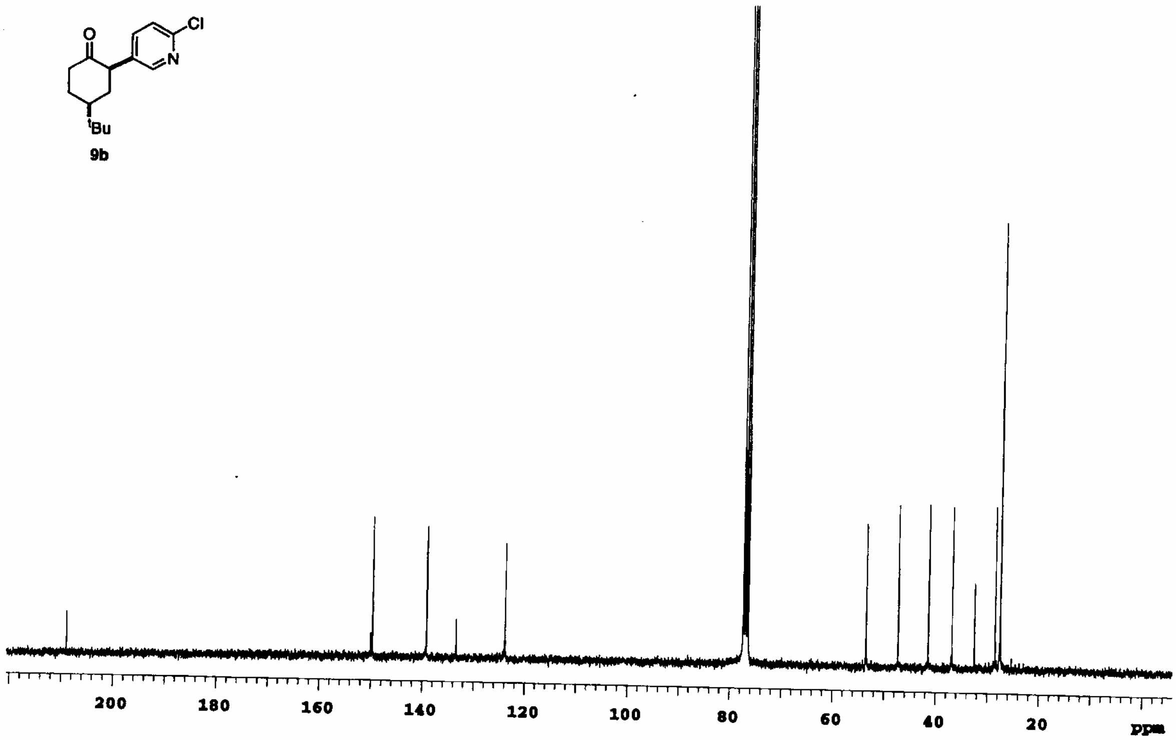


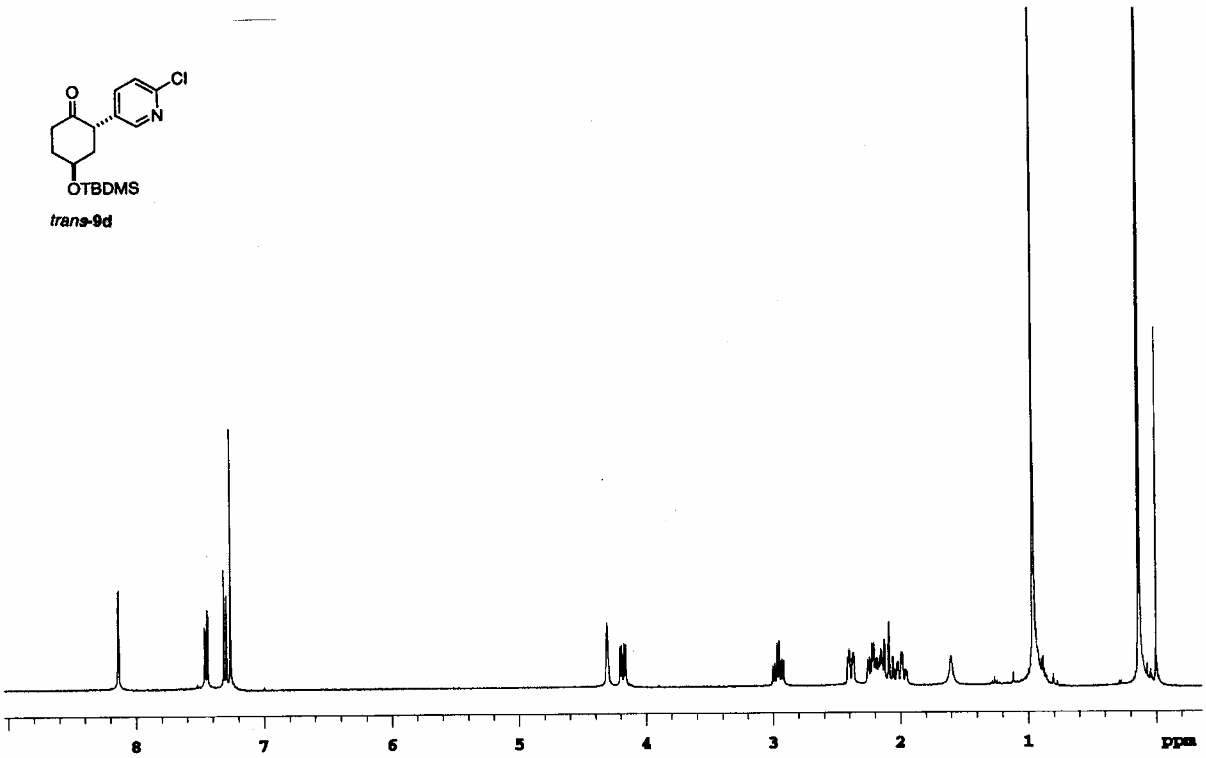


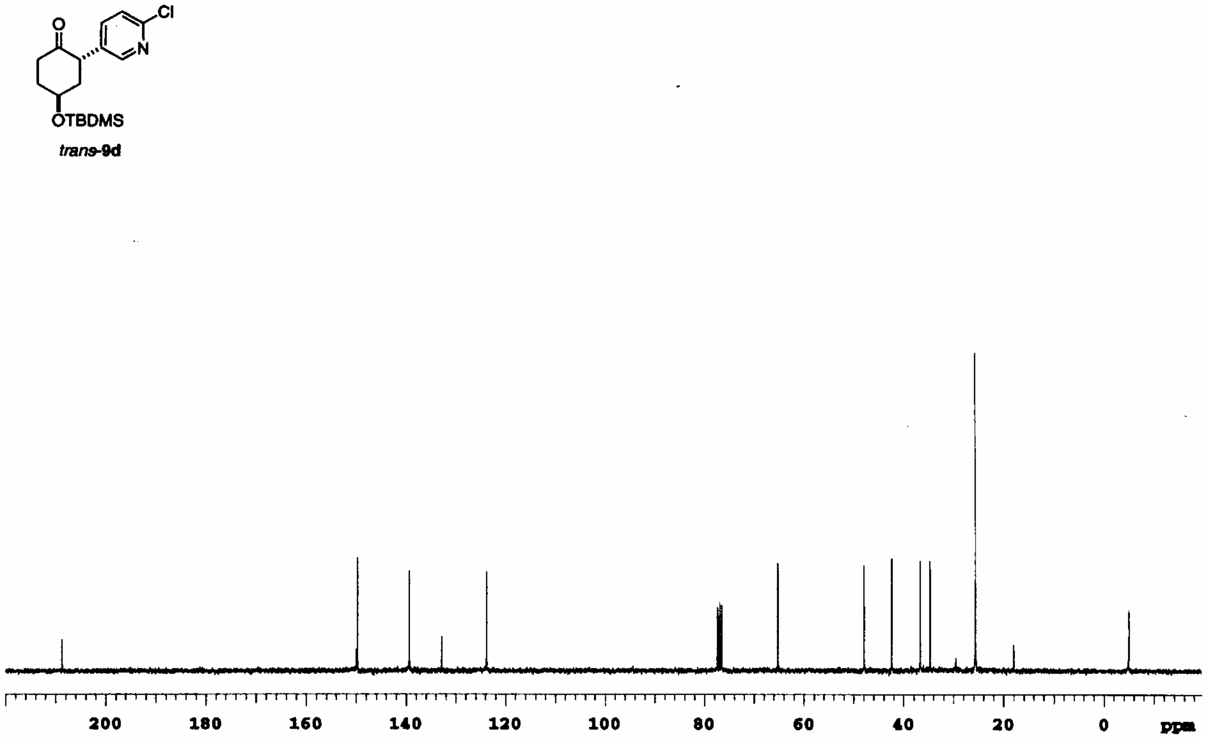
9a

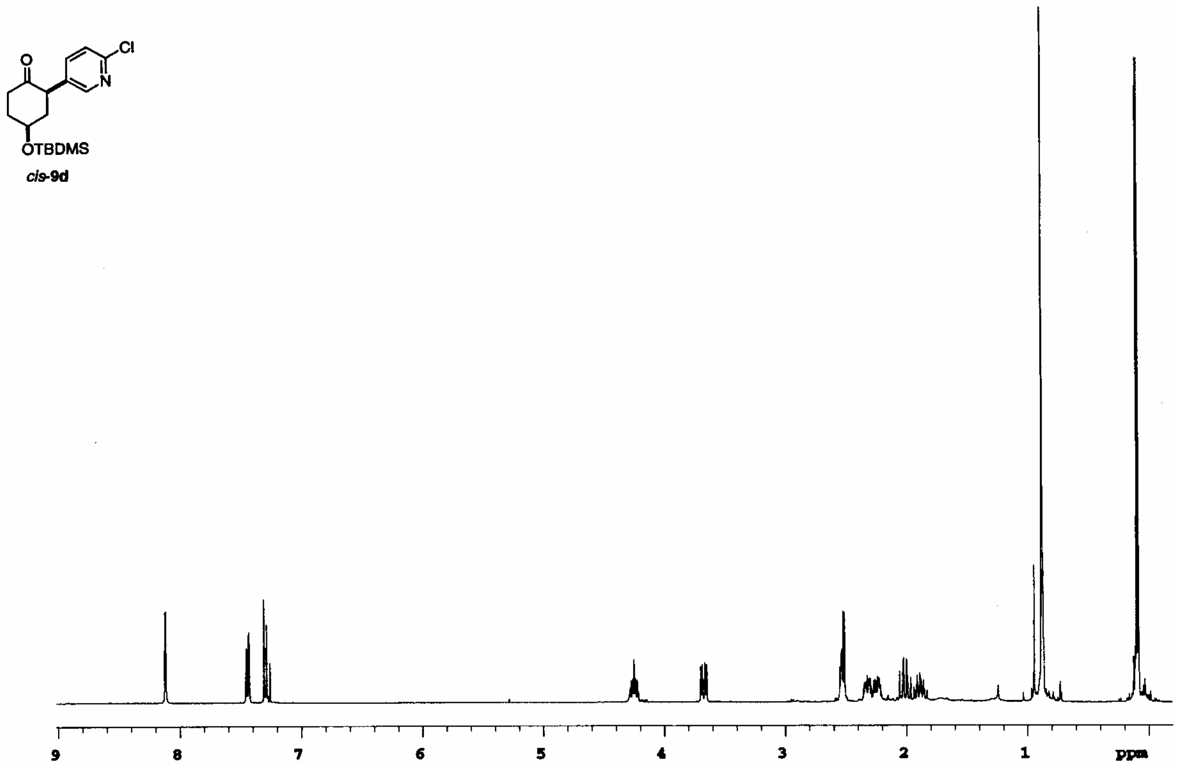



O
Cl
N
tBu
9b
8
7
6
5
4
3
2
1
ppm

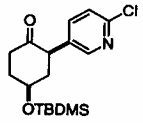

O
Cl
N
tBu
9b
200
180
160
140
120
100
80
60
40
20
ppm


O
Cl
N
OTBDMS
trans-9d
8
7
6
5
4
3
2
1
ppm

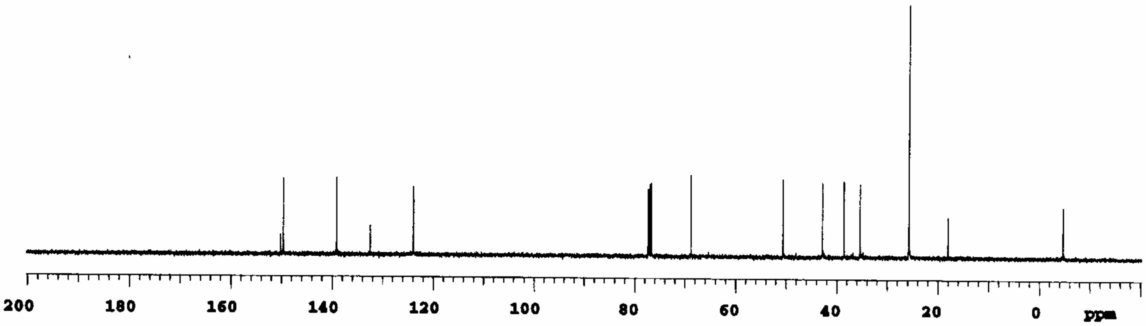

O
Cl
N
OTBDMS
trans-9d
200
180
160
140
120
100
80
60
40
20
0
ppm

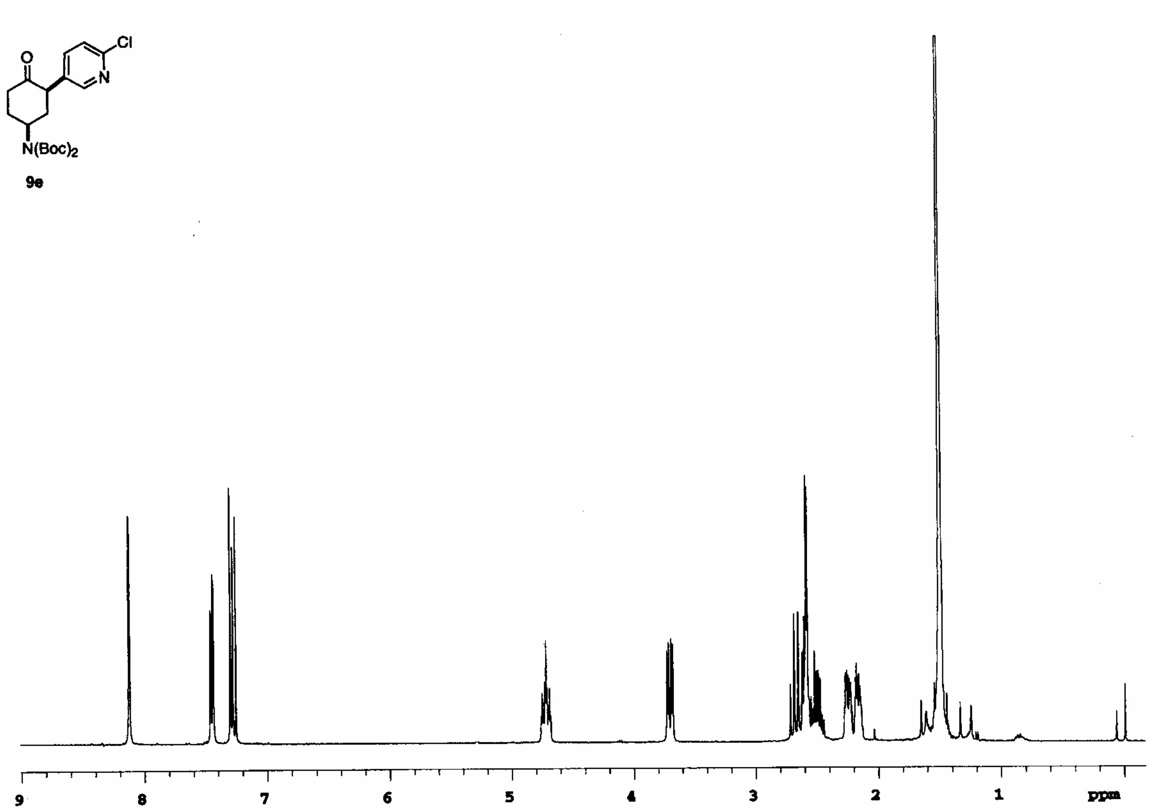


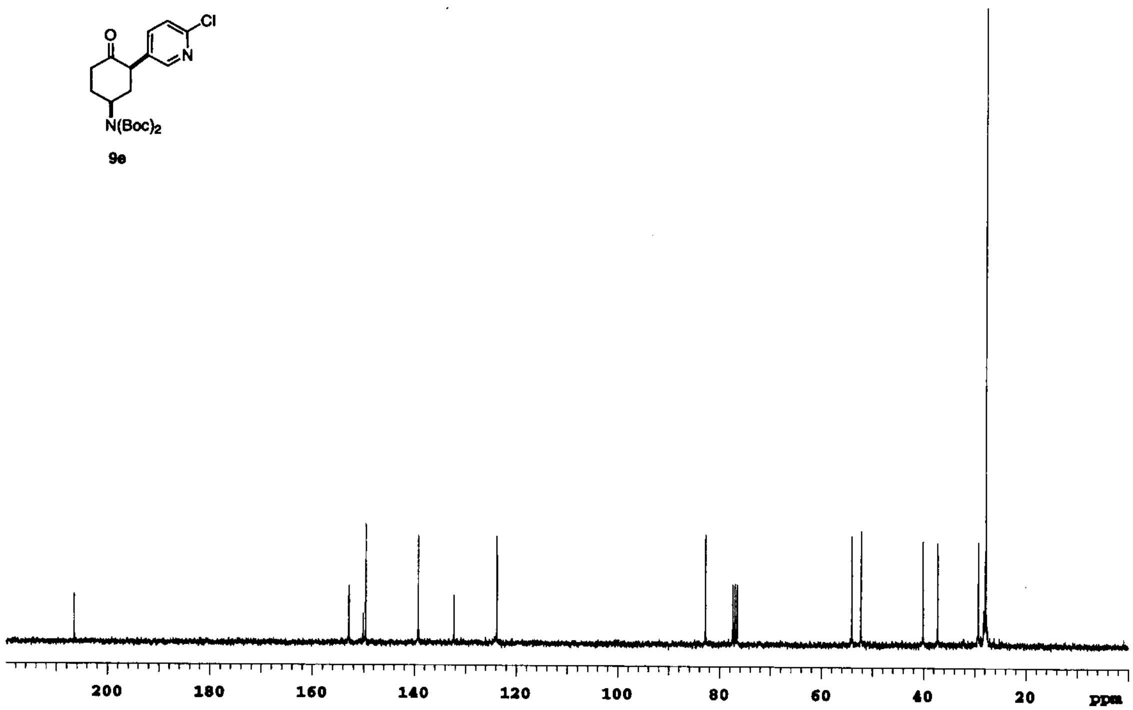
cis-**9d**

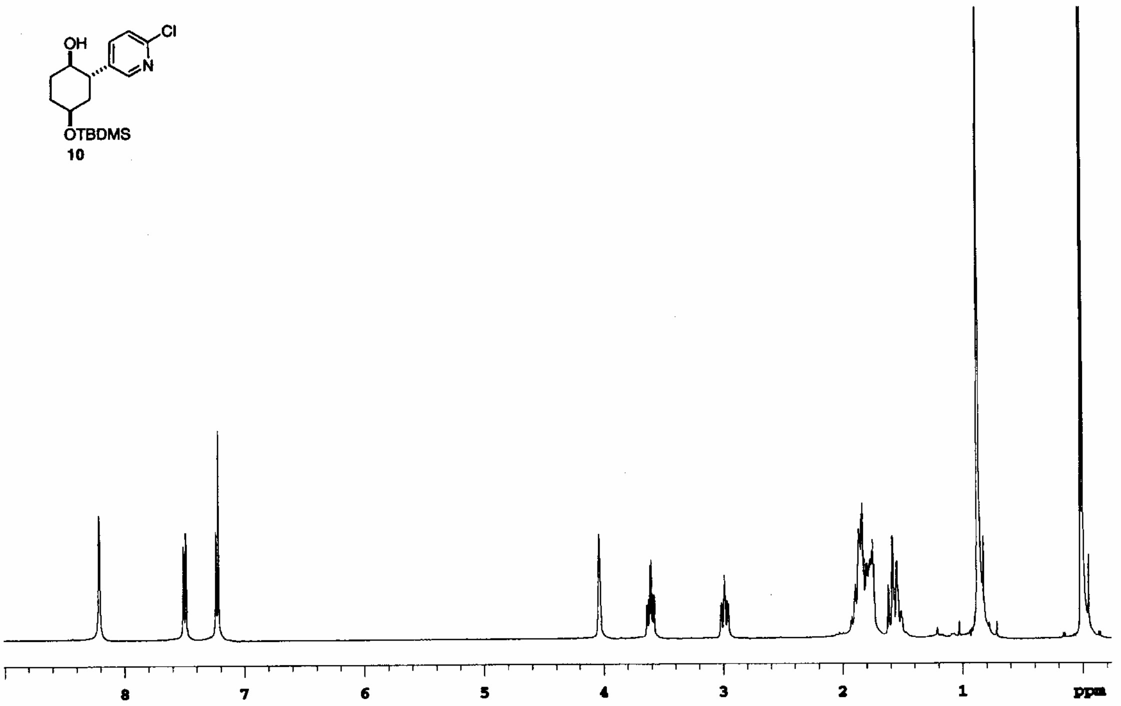


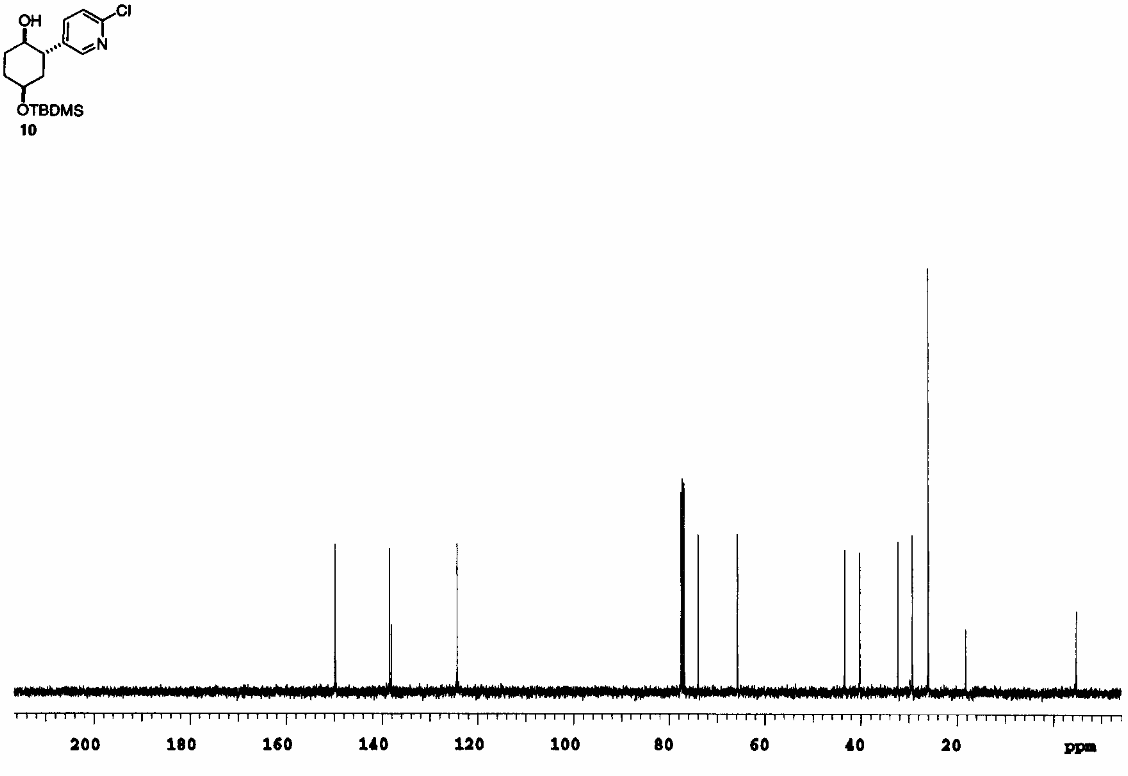
cis-**9d**

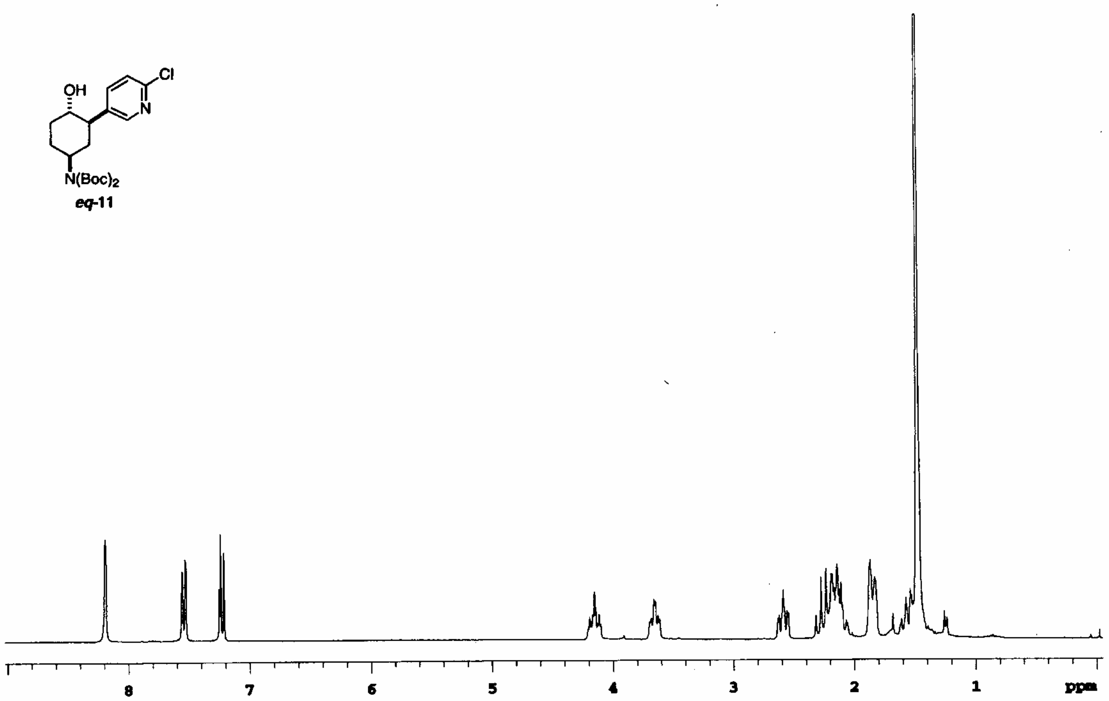



O
Cl
N
N(Boc)$_2$
9e
9
8
7
6
5
4
3
2
1
ppm

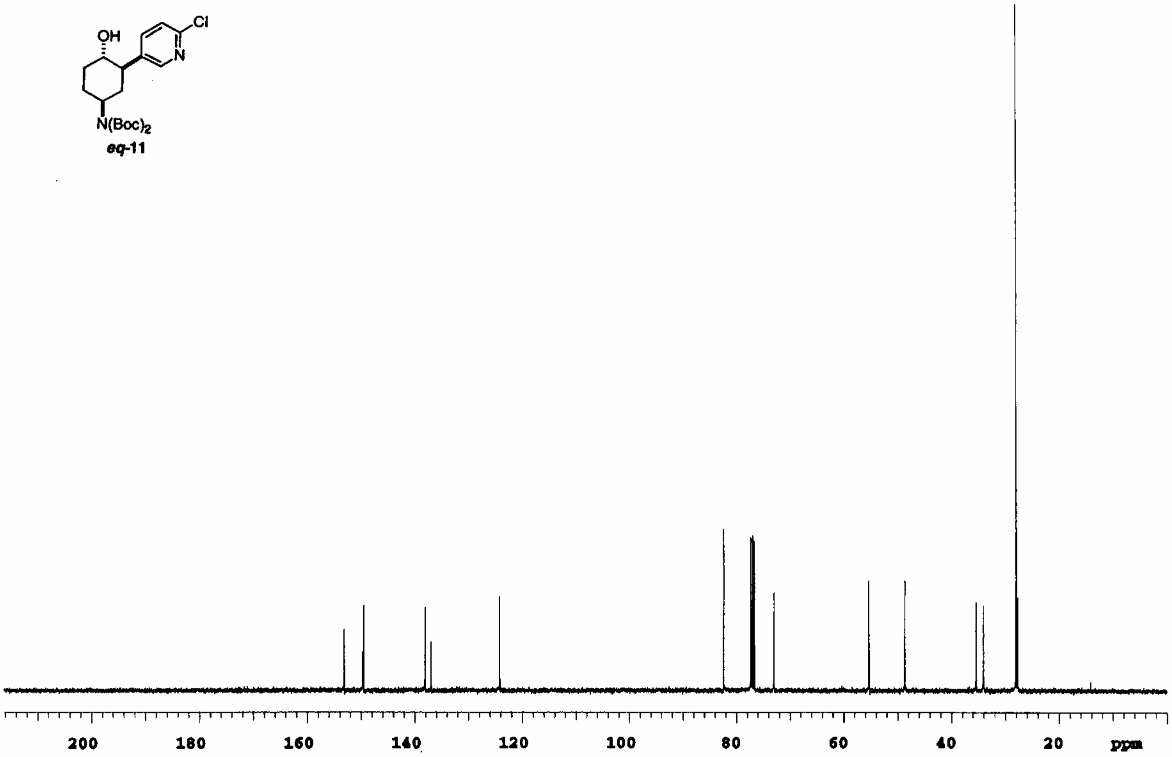

O
Cl
N
N(Boc)$_2$
9e
200
180
160
140
120
100
80
60
40
20
ppm


OH
Cl
N
OTBDMS
10
8
7
6
5
4
3
2
1
ppm

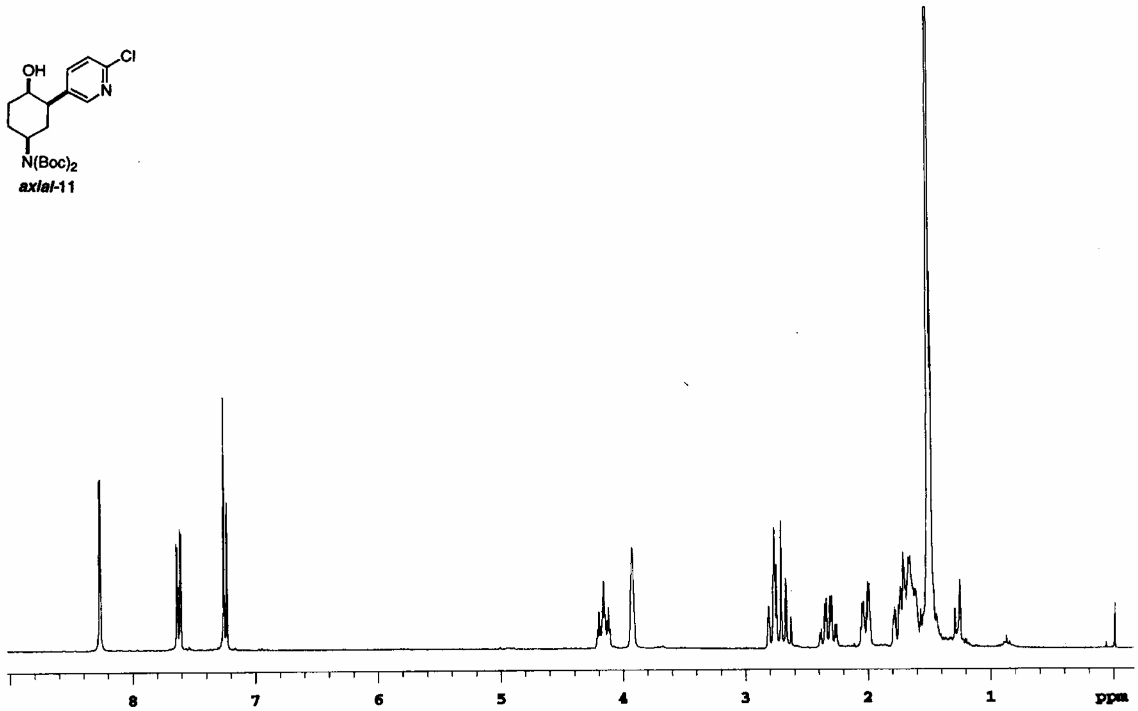

OH
Cl
N
OTBDMS
10
200
180
160
140
120
100
80
60
40
20
ppm


OH
Cl
N
N(Boc)$_2$
8
7
6
5
4
3
2
1
ppm

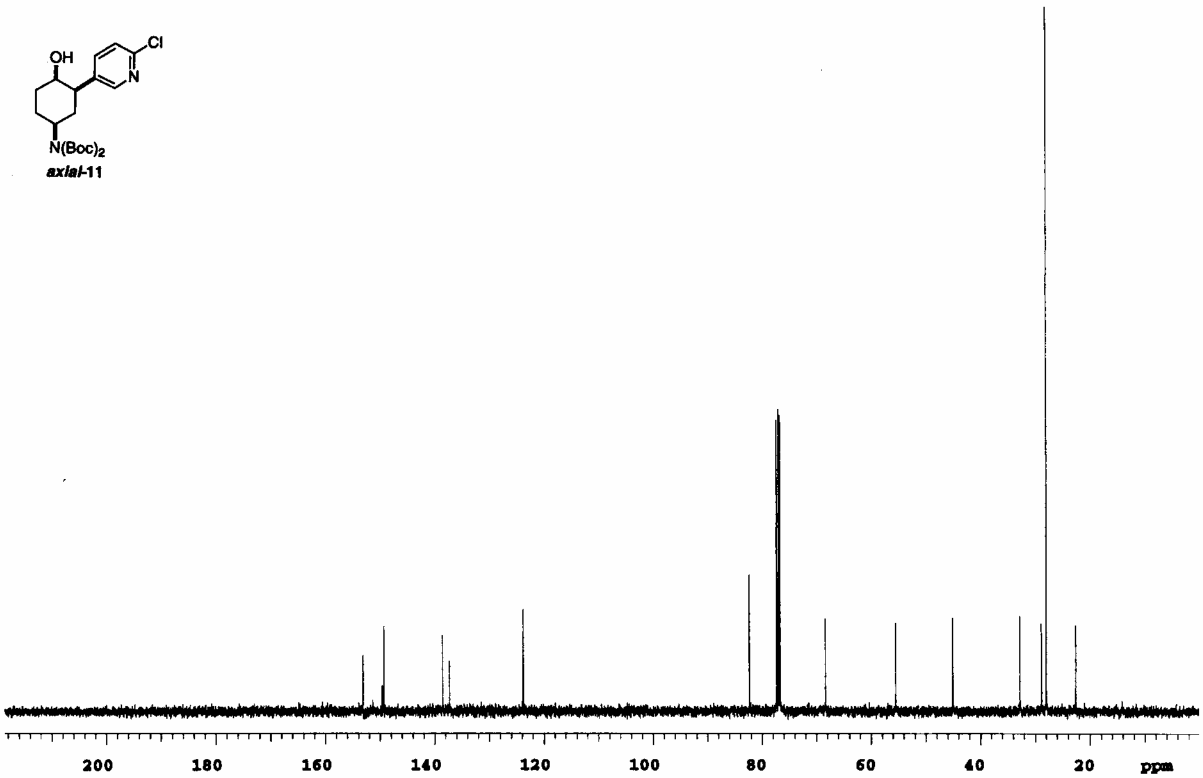
eq-11


OH
Cl
N
N(Boc)$_2$
200
180
160
140
120
100
80
60
40
20
ppm

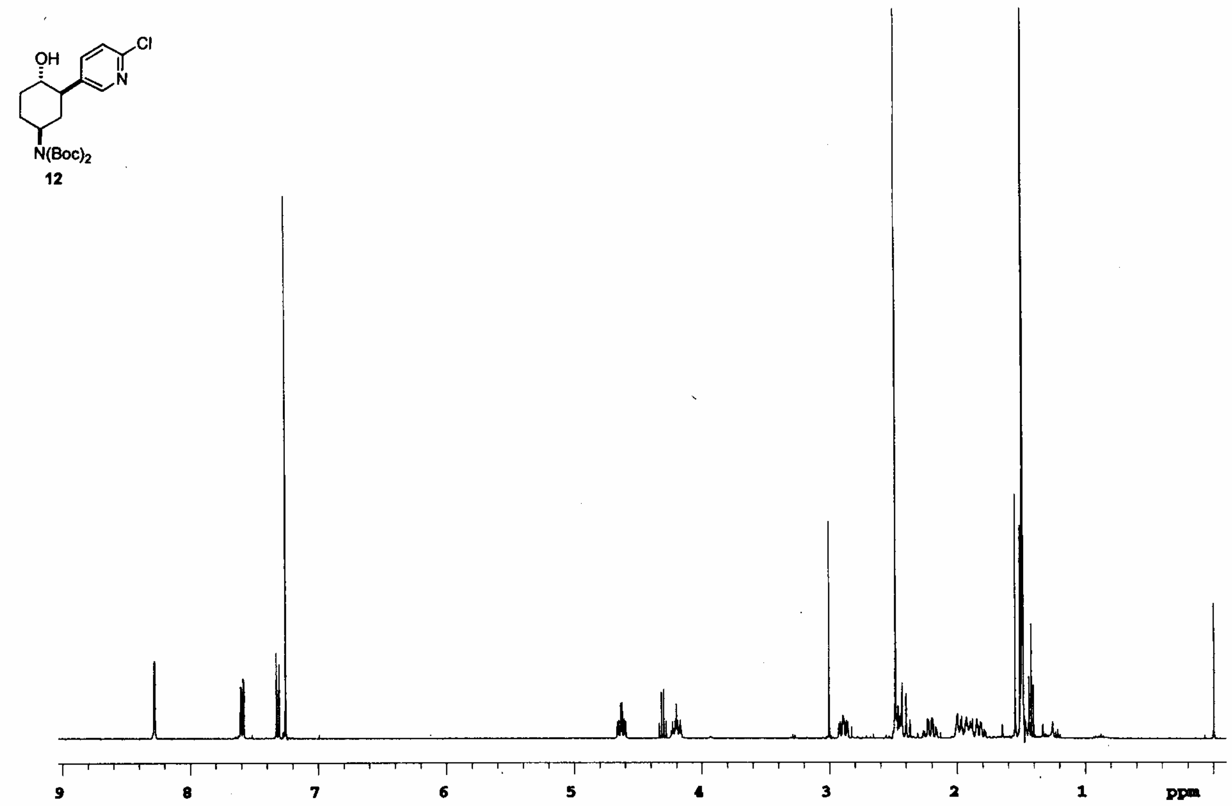
eq-11



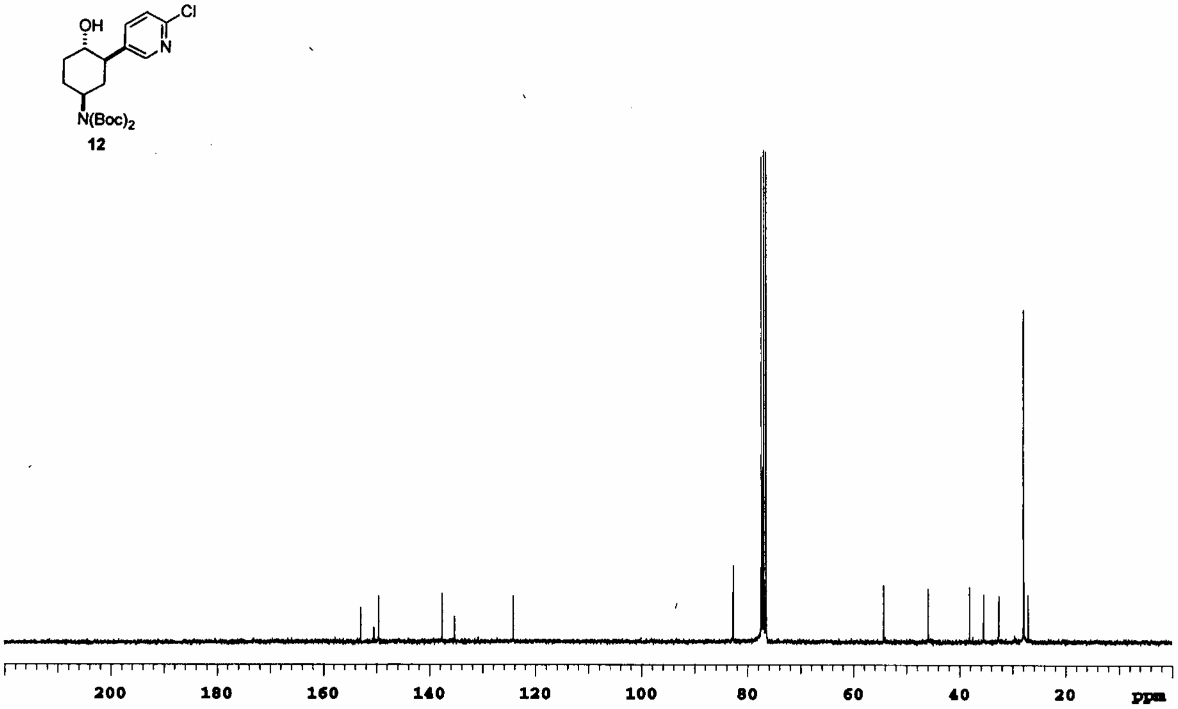
axial-11



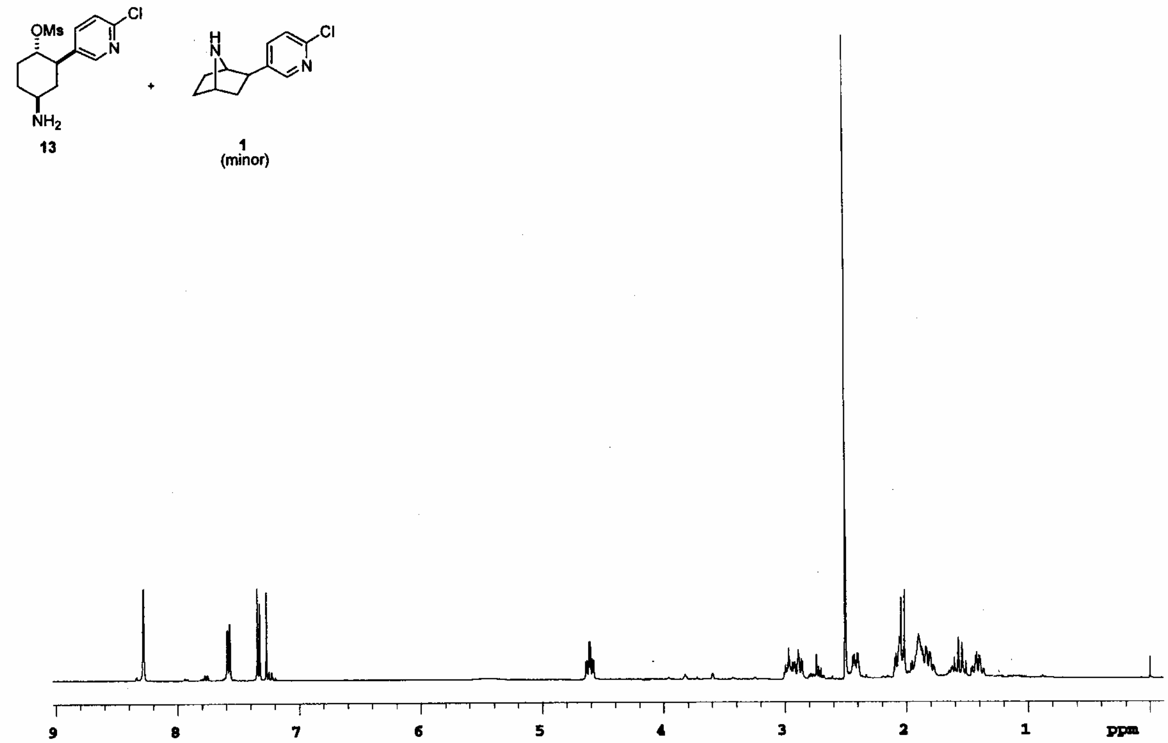
axial-11

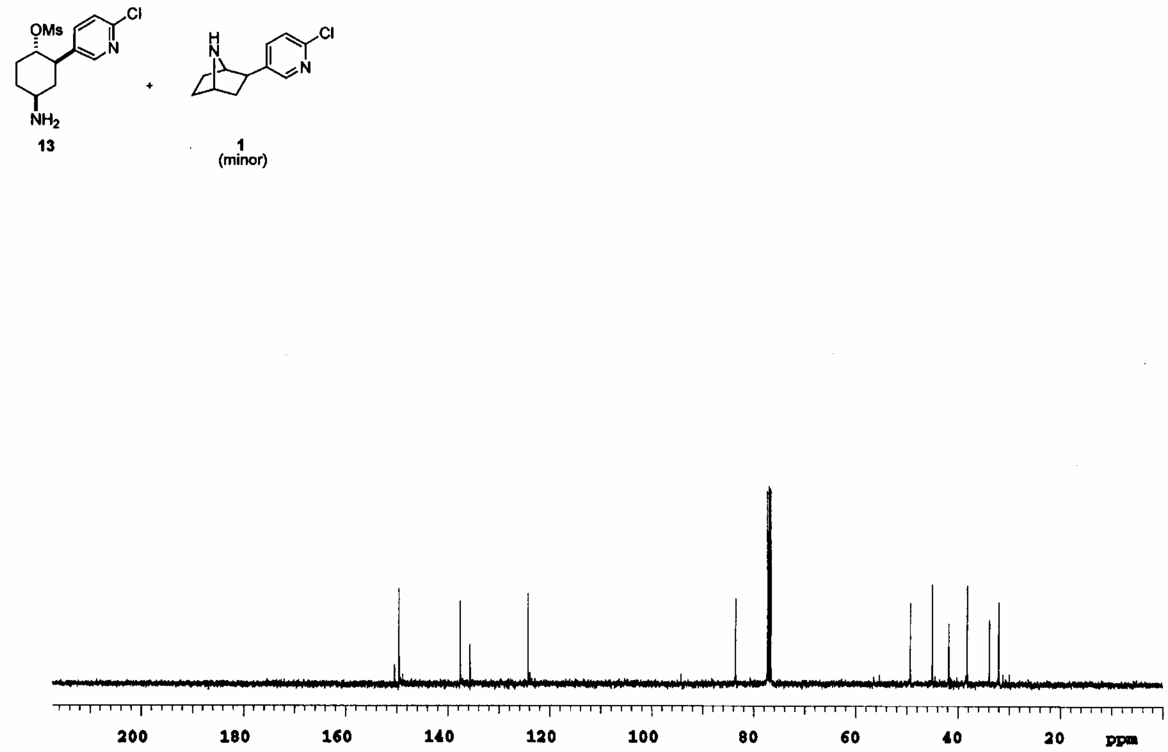

12

OH
Cl
N
N(Boc)₂
9
8
7
6
5
4
3
2
1
ppm


12

OH
Cl
N
N(Boc)₂
200
180
160
140
120
100
80
60
40
20
ppm


OMs
Cl
N
NH2
13
+
H
N
Cl
N
1
(minor)
9
8
7
6
5
4
3
2
1
ppm


OMs
Cl
N
NH2
13
+
H
N
Cl
N
1
(minor)
200
180
160
140
120
100
80
60
40
20
ppm