Supporting Information

Enantioselective Synthesis of *(R)*-Tolterodine via CuH-Catalyzed Asymmetric Conjugate Reduction

*Kihyun Yoo, Hyohyun Kim, and Jaesook Yun**

Department of Chemistry and Institute of Basic Science, Sungkyunkwan University

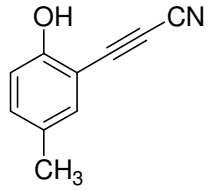
Suwon 440-746, Korea

E-mail: jaesook@skku.edu

Table of Contents

General Information. THF and toluene were distilled from sodium benzophenone ketyl under nitrogen. Tetrakis(triphenylphosphine)palladium(0), copper(I) iodide, copper(II) acetate and other commercial substrates were purchased and used as received. 2-Iodo-4-methylphenol and 3-phenylpropiolonitrile were prepared according to the literature procedure.[1,2] All reduction procedures were carried out with standard schlenk tube techniques under a nitrogen atmosphere..

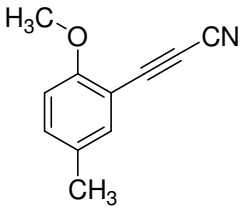
Experimental Section



3a

3-(2-hydroxy-5-methylphenyl)propiolonitrile. The title compound was synthesized according to the literature procedure.[2,3] 2-Iodo-4-methylphenol (3.6 mg, 15 mmol), tetrakis(triphenylphosphine)palladium(0) (347 mg, 0.3 mmol), and copper(I) iodide (171 mg, 0.9 mmol) were dissolved in freshly distilled toluene (50 mL) under nitrogen at room temperature. Piperidine (3.0 mL, 30 mmol) was added, followed by slow addition of propargyl alcohol (1.1 mL, 18 mmol) via syringe (Caution: exothermic reaction, when propargyl alcohol was added). The resulting dark brown reaction mixture was stirred at 50 ℃ for 3 h under nitrogen and allowed to reach room temperature. The dark brown crude product filtered over a pad of silica gel and the solvent was removed under reduced pressure. To a solution of crude product in THF (20 mL), placed in a 100 mL round-bottom flask, were added a 2 M solution of ammonia in 2-propanol (26 mL, 52 mmol) and anhydrous magnesium sulfate (12 g, 100 mmol). Then, activated manganese dioxide (17 g, 195 mmol) was added to the solution. The resulting mixture was stirred at room temperature for 2 h and then diluted with ethyl acetate (20 mL). The reaction mixture was filtered through celite and washed well with dichloromethane, and the combined filtrates concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc 5:1) to give 2.04 g of product as a pale yellow solid (87%) for two steps: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31–7.45 (m, 3H), 2.46 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.2, 134.3, 130.0, 127.1, 125.6,

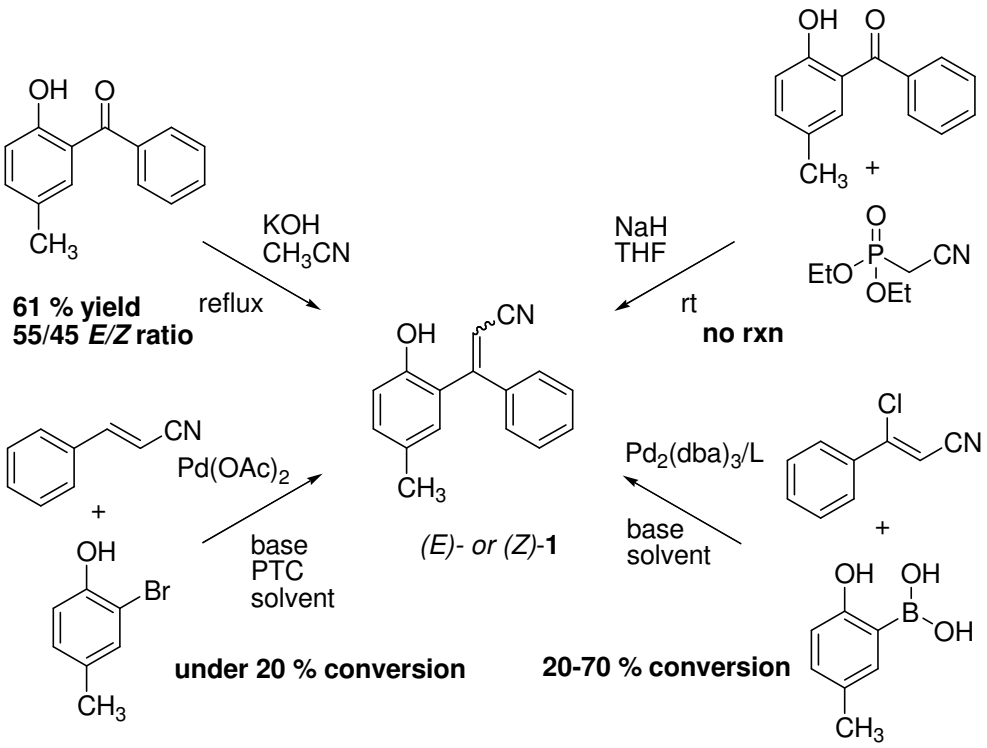
122.0, 118.3, 112.0, 111.5, 21.2; IR (neat) 2262 cm^{-1}; Anal. calcd for $C_{10}H_7NO$: C 76.42; H 4.49; N 8.91. found C 76.50; H 4.50; N 8.88.



3b

3-(2-methoxy-5-methylphenyl)propiolonitrile. Using the same procedure of **3a**, 1.79 g of product was isolated as a yellow oil (70%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.31 (s, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 6.82 (d, *J* = 8.4 Hz, 1H), 3.87 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.8, 134.9, 134.2, 129.9, 110.7, 105.8, 105.6, 80.7, 65.9, 55.5, 19.7; IR (neat) 2262 cm^{-1}; Anal. calcd for $C_{11}H_9NO$: C 77.17; H 5.30; N 8.18. found C 77.20; H 5.40; N 8.18.

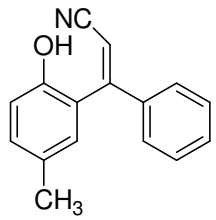
Scheme 1. Reactions which failed to efficiently give the stereoselective unsaturated nitriles



We attempted various kinds of the literature procedure such as a Heck,[4] a Suzuki-Miyaura cross coupling,[5] an Aldol-type condensation,[6] and a HWE olefination reaction[7] for the stereoselective

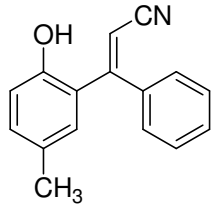
preparation of unsaturated nitriles. But the reactions resulted in low conversion and production of a inseparable mixture of *(E)*- and *(Z)*-isomers.

General Procedure for Copper-Catalyzed Stereoselective Hydroarylation:[8] To a solution of alkynenitrile **3** (5 mmol) and arylboronic acid (10 mmol) in methanol (10 mL) was added CuOAc (30.5 mg, 0.25 mmol). The reaction mixture stirred at room temperature under a nitrogen atmosphere for 6 h. After filtration of the reaction mixture through a pad of celite to remove insoluble materials, the filtrate was concentrated in vacuo. The residue was purified by flash column chromatography (SiO_2, hexane/EtOAc = 20:1).



(Z)-**1a**

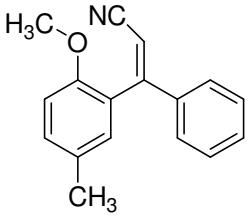
***(Z)*-3-(2-hydroxy-5-methylphenyl)-3-phenylacrylonitrile.** Using the hydroarylation procedure, **3a** (786 mg, 5mmol) and phenylboronic acid (1.2 g, 10 mmol) were employed to afford 830 mg of product as a pale yellow solid (71%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.55–7.53 (m, 3H), 7.48–7.43 (m, 2H), 7.38–7.32 (m, 2H), 7.25 (s, 1H), 6.35 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 161.1, 155.8, 152.4, 135.4, 134.0, 133.0, 129.7, 129.0, 128.5, 126.8, 118.8, 117.2, 115.3, 21.1; IR (neat) 2211 cm^{-1}; Anal. calcd for $C_{16}H_{13}NO$: C 81.68; H 5.57. found C 81.42; H 5.58; HRMS (EI) calcd for $C_{16}H_{13}NO$ 235.0997, found 235.0988.



(E)-**1a**

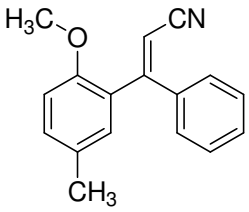
***(E)*-3-(2-hydroxy-5-methylphenyl)-3-phenylacrylonitrile.** Using the hydroarylation procedure, 3-phenyl-propiolonitrile (423 mg, 3 mmol) and 5-methyl-2-(trimethylsilyloxy)phenylboronic acid (1.33 g, 6 mmol) were employed to afford 702 mg of *(E)*-3-(5-methyl-2-(trimethylsilyloxy)phenyl)-3-phenyl-acrylonitrile (76%). To a solution of the TMS protected-adduct in THF (5 mL) was added a 1 M solution of TBAF in THF (4.5 mL, 4.5 mmol) and stirred at room temperature for 3 h. The reaction was quenched with water and the reaction mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by flash column

chromatography (SiO_2, hexane/EtOAc 3:1) to give 496 mg of product as a yellow oil (92%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.47–7.42 (m, 5H), 7.28–7.24 (m, 2H), 7.10–7.07 (m, 1H), 5.72 (s, 1H), 2.34 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 163.6, 139.2, 138.7, 137.4, 131.5, 130.2, 129.8, 129.2, 128.8, 128.7, 126.0, 118.3, 94.9, 21.6; IR (neat) 2211 cm^{-1}; Anal. calcd for $C_{16}H_{13}NO$: C 81.68; H 5.57; N 5.95. found C 81.73; H 5.68; N 5.63.



(Z)-**1b**

***(Z)*-3-(2-methoxy-5-methylphenyl)-3-phenylacrylonitrile.** Using the hydroarylation procedure, **3b** (855 mg, 5 mmol) and phenylboronic acid (1.2 g, 10 mmol) were employed to afford 990 mg of product as a white solid (80%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.40–7.29 (m, 5H), 7.22 (d, *J* = 8.4 Hz, 1H), 7.01 (s, 1H), 6.90 (d, *J* = 8.4 Hz, 1H), 5.88 (s, 1H), 3.69 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.5, 155.5, 138.4, 131.9, 131.6, 130.0, 129.6, 128.7, 128.4, 128.2, 118.3, 111.8, 97.5, 55.9, 20.5; IR (neat) 2217 cm^{-1}; Anal. calcd for $C_{17}H_{15}NO$: C 81.90; H 6.06; N 5.62. found C 81.82; H 6.21; N 5.59.



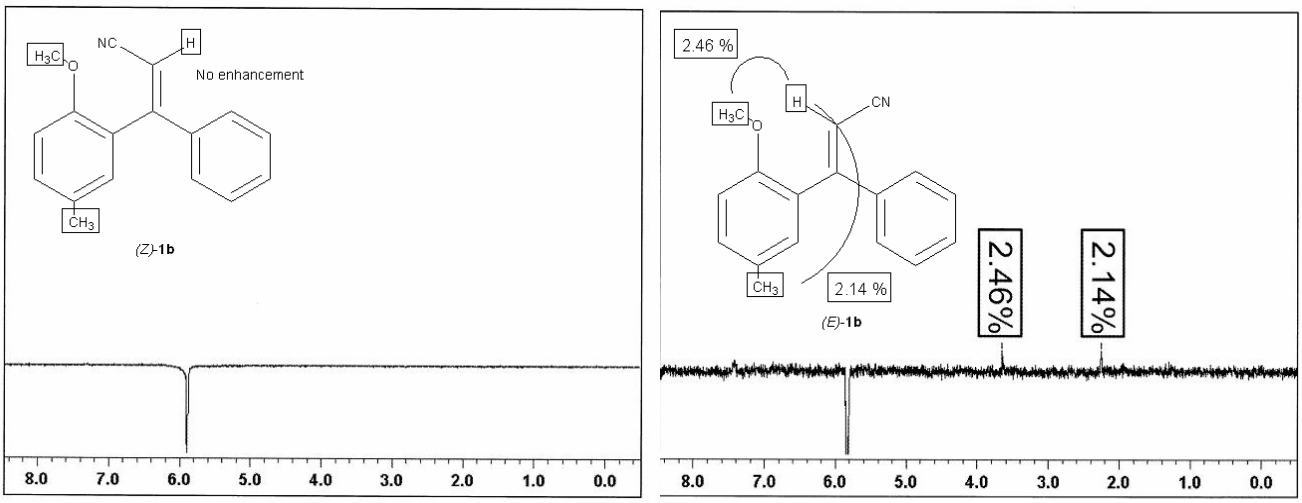
(E)-**1b**

***(E)*-3-(2-methoxy-5-methylphenyl)-3-phenylacrylonitrile.** Using the hydroarylation procedure, 3-phenyl-propiolonitrile (423 mg, 3 mmol) and 2-methoxy-5-methylphenylboronic acid (996 mg, 6 mmol) were employed to afford 450 mg of product as a white solid (60%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.44–7.40 (m, 5H), 7.16 (d, *J* = 8.4 Hz, 1H), 6.88 (s, 1H), 6.83 (d, *J* = 8.4 Hz, 1H), 5.82 (s, 1H), 3.65 (s, 3H), 2.25 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 160.3, 154.9, 138.4, 131.5, 131.2, 130.2, 130.1, 128.7, 127.3, 126.0, 117.8, 111.7, 96.6, 55.8, 20.5; IR (neat) 2217 cm^{-1}; Anal. calcd for $C_{17}H_{15}NO$: C 81.90; H 6.06; N 5.62. found C 81.83; H 6.22; N 5.47.

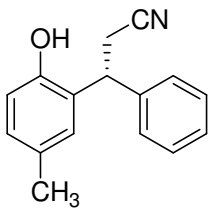
The stereochemical assignments of *(Z)*-**1b** and *(E)*-**1b** were determined by NOE experiments. In the case of *(Z)*-isomer, irradiation of the vinyl proton at δ 5.88 gave no enhancement. On the other hand, in the case of *(E)*-isomer, irradiation of the vinyl proton at δ 5.82 gave 2.46 % enhancement of the methoxy

hydrogens and 2.14 % enhancement of the methyl hydrogens. The stereochemistry of **1a** was determined by comparing ^{1}H NMR of the methylation products of **1a** with those of authentic (*Z*)- and (*E*)-**1b**.

Figure 1. NOE spectra of *(Z)*-**1b** and *(E)*-**1b**



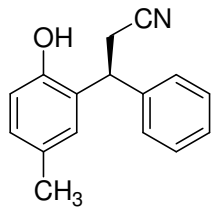
General Procedure for Copper-Catalyzed Enantioselective Reduction: $Cu(OAc)_2$ (1.82 mg, 0.010 mmol) and Josiphos ligand (6.41 mg, 0.010 mmol, ethanol adduct) were placed in an oven-dried Schlenk tube. Toluene (0.5 mL) was added under a nitrogen atmosphere and the reaction mixture was stirred for 10 min at room temperature. PMHS (75 µL, 1.25 mmol) was added to the reaction mixture and stirred for 5 min for catalyst activation. The unsaturated nitrile (0.5 mmol) and toluene (0.5 mL) were added, followed by *t*-BuOH (191 µL, 2.0 mmol). The reaction was sealed, and stirred until the starting material was completely consumed as judged by TLC. The reaction mixture was quenched with water and transferred to a round-bottomed flask with an aid of EtOAc (10 mL), and NaOH (2.5 M, 1.2 mL) was added. The biphasic mixture was stirred vigorously for 0.5 h. The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The product was purified by chromatography.



(R)-**2a**

***(R)*-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanenitrile.** Using the general procedure for the enantioselective reduction, *(Z)*-**1a** (118 mg, 0.5 mmol) were

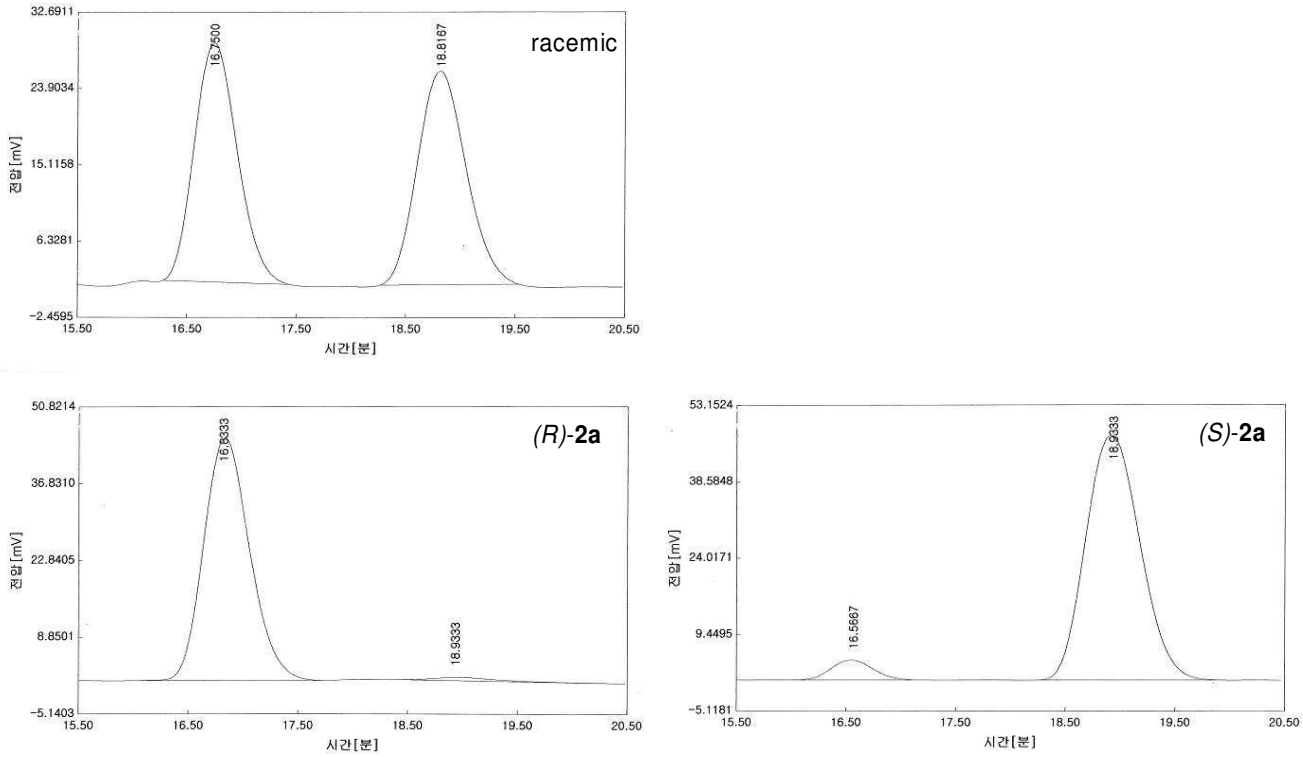
employed to afford 102 mg of product as a pale yellow oil (86%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.37–7.25 (m, 3H), 7.17–7.03 (m, 4H) 6.78 (s, 1H), 4.29 (t, *J* = 6.7 Hz, 1H), 3.02 (sept, *J* = 7.5 Hz, 2H), 2.25 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 154.6, 141.0, 129.9, 129.4, 128.8, 128.6, 127.8, 127.0, 119.0, 110.9, 55.5, 40.9, 22.7, 20.7; IR (neat) 2245 cm^{-1}; Anal. calcd for $C_{16}H_{15}NO$: C 80.98; H 6.37; N 5.90. found C 80.84; H 6.69; N 5.78. The ee (96% ee) was measured by chiral HPLC on an OD-H column (*i*-PrOH/hexane 10:90, 0.5 mL/min); *(R)*-isomer t_r = 16.8 min and *(S)*-isomer t_r = 18.9 min.

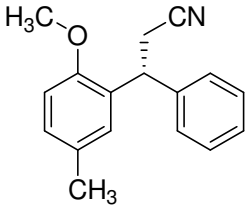


(S)-**2a**

***(S)*-3-(2-hydroxy-5-methylphenyl)-3-phenylpropanenitrile.** Using the general procedure for the enantioselective reduction, *(E)*-**1a** (118 mg, 0.5 mmol) were employed to afford 108 mg of product as a pale yellow oil (91%); The ee (86% ee) was measured by chiral HPLC on an OD-H column (*i*-PrOH/hexane 10:90, 0.5 mL/min): *(R)*-isomer t_r = 16.6 min and *(S)*-isomer t_r = 18.9 min.

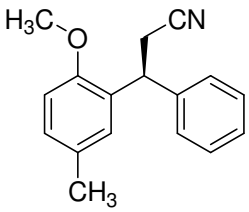
Figure 2. HPLC spectra of **2a**





(R)-**2b**

***(R)*-3-(2-methoxy-5-methylphenyl)-3-phenylpropanenitrile.** Using the general procedure for the enantioselective reduction, *(Z)*-**1b** (125 mg, 0.5 mmol) were employed to afford 109 mg of product as a white oil (87%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61–7.22 (m, 5H), 7.02 (br d, *J* = 7.5 Hz, 1H), 6.85 (s, 1H), 6.77 (d, *J* = 8.1 Hz, 1H), 4.74 (t, *J* = 7.5 Hz, 1H), 3.77 (s, 3H), 3.08 (dd, *J* = 16.5, 6.9 Hz, 1H), 2.98 (dd, *J* = 16.8, 8.4 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 141.6, 141.4, 138.8, 129.1, 129.0, 128.6, 128.4, 127.8, 127.6, 124.7, 118.8, 47.4, 31.9, 24.5, 21.7; IR (neat) 2250 cm^{-1}; Anal. calcd for $C_{17}H_{17}NO$: C 81.24; H 6.82; N 5.57. found C 81.21; H 6.83; N 5.65. The ee (92% ee) was measured by chiral HPLC on an OD-H column (*i*-PrOH/hexane 10:90, 0.5 mL/min): *(R)*-isomer t_r = 18.9 min and *(S)*-isomer t_r = 21.4 min.

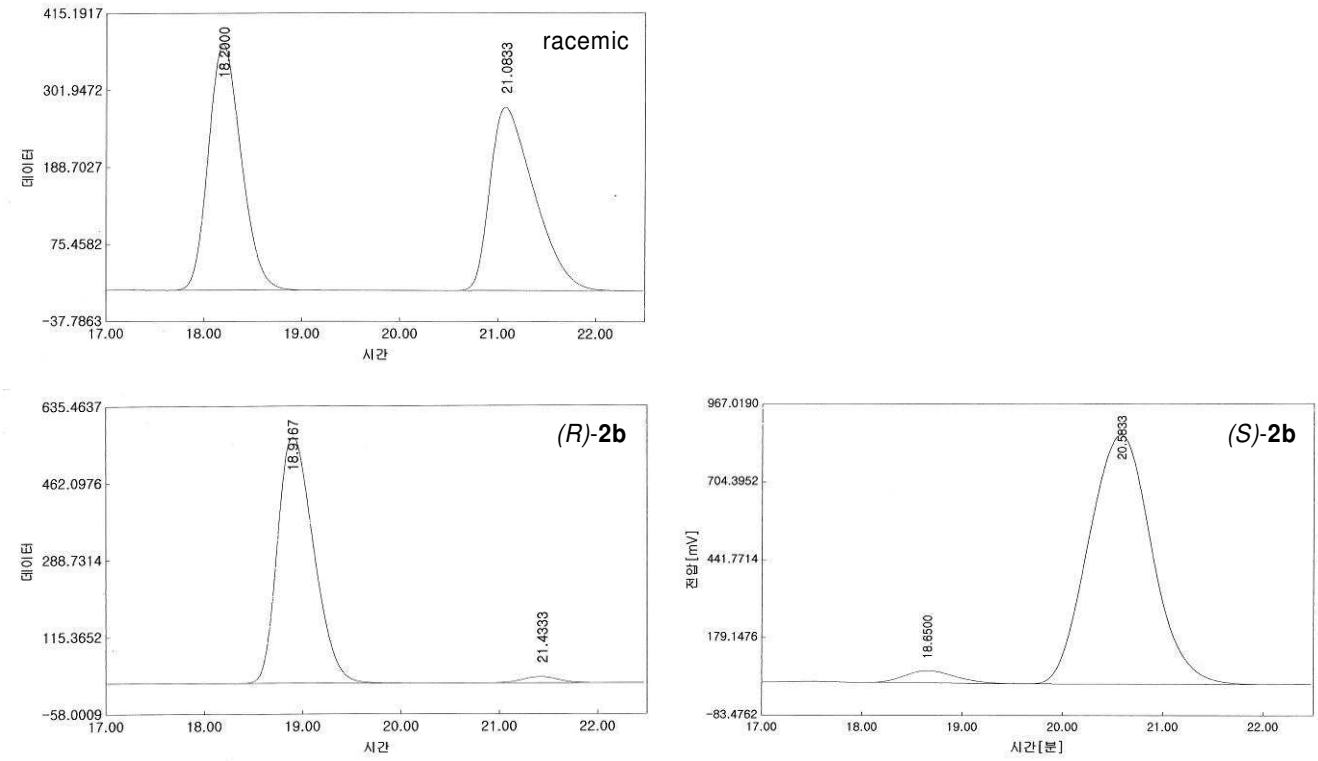


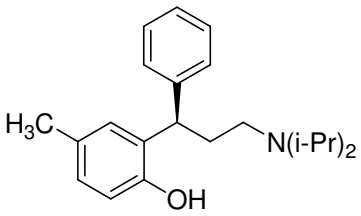
(S)-**2b**

***(S)*-3-(2-methoxy-5-methylphenyl)-3-phenylpropanenitrile.** Using the general procedure for the copper catalyzed enantioselective reduction, *(E)*-**1b** (125 mg, 0.5 mmol) were employed to afford 106 mg of product as a white oil (85%); The ee (90% ee) was measured by chiral HPLC on an OD-H column (*i*-PrOH/hexane 10:90, 0.5 mL/min): *(R)*-isomer t_r = 18.7 min and *(S)*-isomer t_r = 20.6 min.

The absolute configuration of *(R)*- and *(S)*-**2b** was determined by comparison with HPLC data of the compounds obtained by methylation of **2a** whose stereochemistry was already known.

Figure 3. HPLC spectra of **2b**





***(R)*-Tolterodine.**[9] To a solution of *(R)*-**2a** (100 mg, 0.42 mmol) in anhydrous toluene (3 mL) was added dropwise a solution of 1 M DIBAL-H in toluene (500 μL, 0.5 mmol) at 0 ℃ under a nitrogen atmosphere. The reaction was quenched after 5 h with EtOAc, a solution of sulfuric acid was added, and then the solution was stirred at room temperature overnight. The aqueous phase was extracted with EtOAc (3 x 20 mL), the organic phases were dried over Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. To a solution of the crude product in 1,2-dichloroethane (3 mL) were added diisopropylamine (280 μL, 2 mmol) and sodium triacetoxyborohydride (59.4 mg, 2 mmol), and the reaction mixture was stirred at room temperature for 16 h. Aqueous $NaHCO_3$ was added and the mixture was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Flash chromatography (SiO_2, hexane/EtOAc = 9:10) afforded 86 mg of product as a colorless oil (63 %): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.32–7.29 (m, 4H),

7.24–7.20 (m, 1H), 6.84 (dd, J = 8.2, 2.0 Hz, 1H), 6.80 (d, J = 8.1 Hz, 1H), 6.54 (s, 1H), 4.48 (dd, J = 11.1, 3.8 Hz, 1H), 3.21 (sept, J = 6.7 Hz, 2H), 2.72–2.69 (m, 1H), 2.40–2.30 (m, 2H), 2.11 (s, 3H), 2.11–2.04 (m, 1H), 1.12 (d, J = 6.7 Hz, 6H), 1.06 (d, J = 6.7 Hz, 6H); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 153.0, 144.7, 132.3, 129.1, 128.5, 128.3, 128.2, 127.6, 125.9, 117.8, 47.9, 42.2, 39.5, 33.5, 20.6, 19.9, 19.5; $[\alpha]_D^{23}$ +19.6 (c 0.5, MeOH) [lit. value : $[\alpha]_D^{20}$ +22.0 (c 0.32, MeOH) for *(R)*-tolterodine].

References

(1) Edgar, K. J.; Falling, S. N. *J. Org. Chem.* **1990**, *55*, 5287–5291.

(2) Kwong, F. Y.; Lee, H. W.; Lam, W. H.; Qiu, L.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2006***, 17*, 1238–1252.

(3) McAllister, G. D.; Wilfred, C. D.; Taylor, R. J. K. *Synlett* **2002**, 1291–1292.

(4) (a) Moreno-Mañas, M.; Pleixats, R.; Roglans, A. *Synlett* **1997**, 1157–1158. (b) Masllorens, J.; Moreno-Mañas, M.; Pla-Quintana, A.; Pleixats, R.; Roglans, A. *Synthesis* **2002**, 1903–1911.

(5) Taylor, S. J.; Netherton, M. R. *J. Org. Chem*. **2006**, *71*, 397–400.

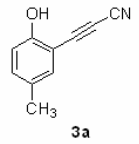
(6) Dibiase, S. A.; Lipisko, B. A.; Hagg, A.; Wolak, R. A.; Gokel, G. W. *J. Org. Chem.* **1979**, *44*, 4640–4649.

(7) Lee, D.; Yang, Y.; Yun, J. *Org. Lett*. **2007**, *9*, 2749–2751.

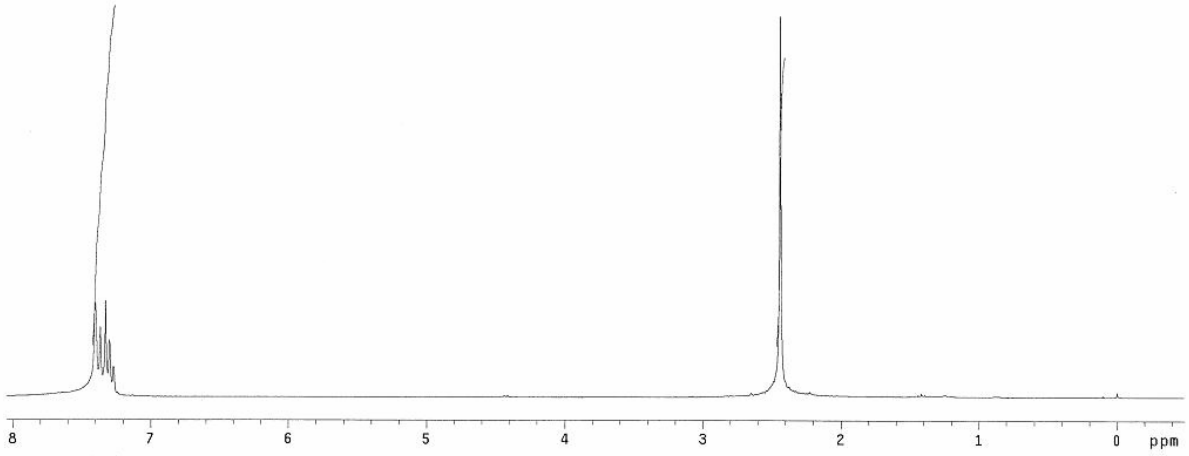
(8) (a) Yamamoto, Y.; Kirai, N.; Harada, Y. *Chem. Commun.* **2008**, 2010–2012. (b) Yamamoto, Y.; Kirai, N. *Org. Lett.* **2008**, *10,* 5513–5516.

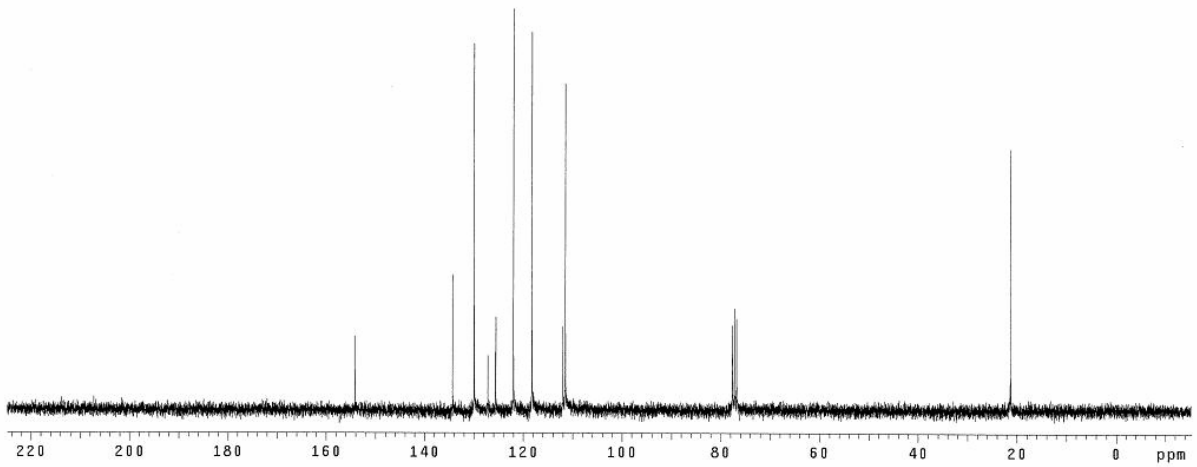
(9) Sörgel, S.; Tokunaga, N.; Sasaki, K.; Okamoto, K.; Hayashi, T. *Org. Lett.* **2008**, *10*, 589–592.

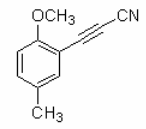
Spectra (^{1}H, ^{13}C NMR)



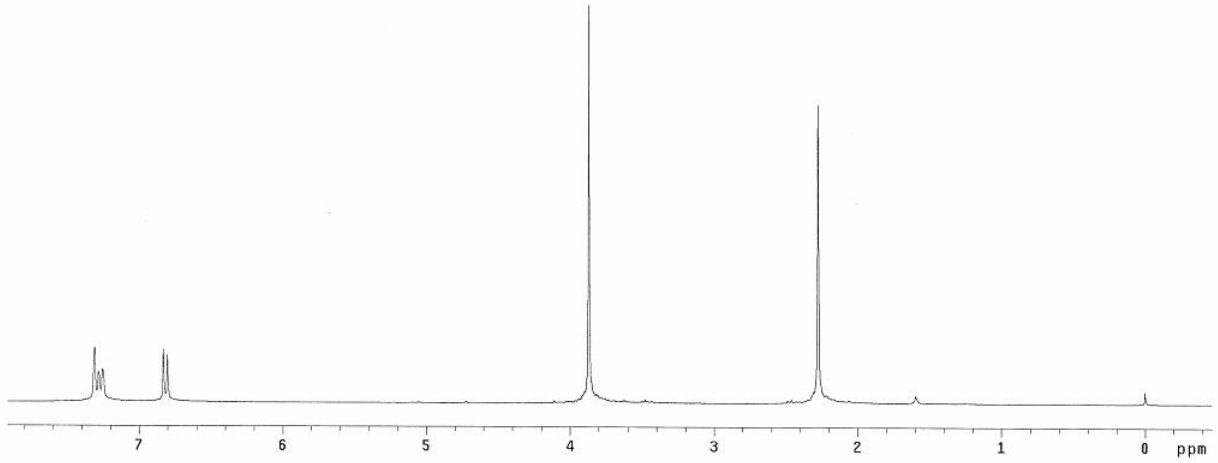
3a

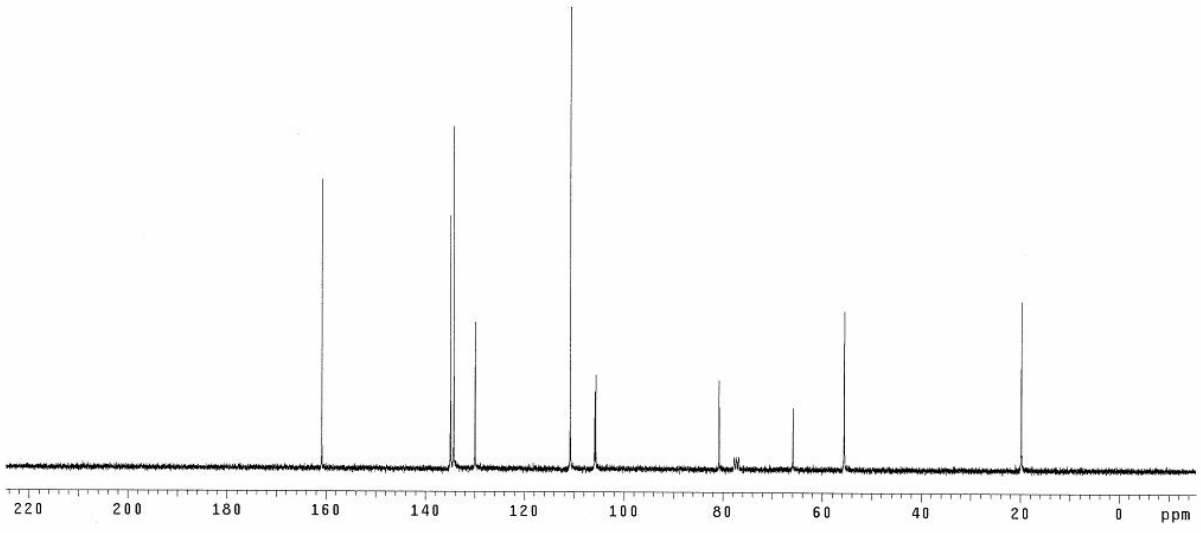


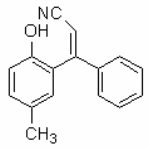



OCH3
CN
CH3

3b

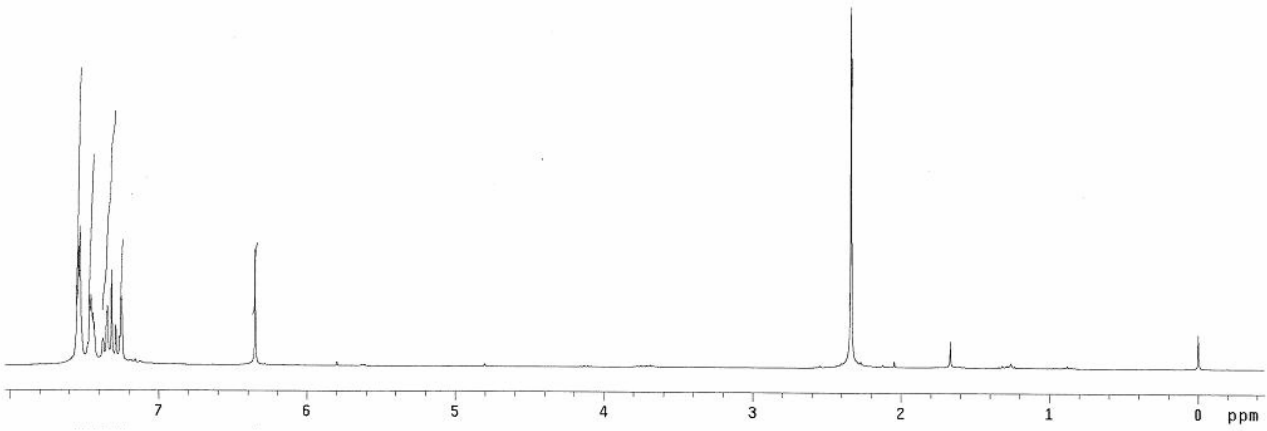

7
6
5
4
3
2
1
0
ppm


220
200
180
160
140
120
100
80
60
40
20
0
ppm

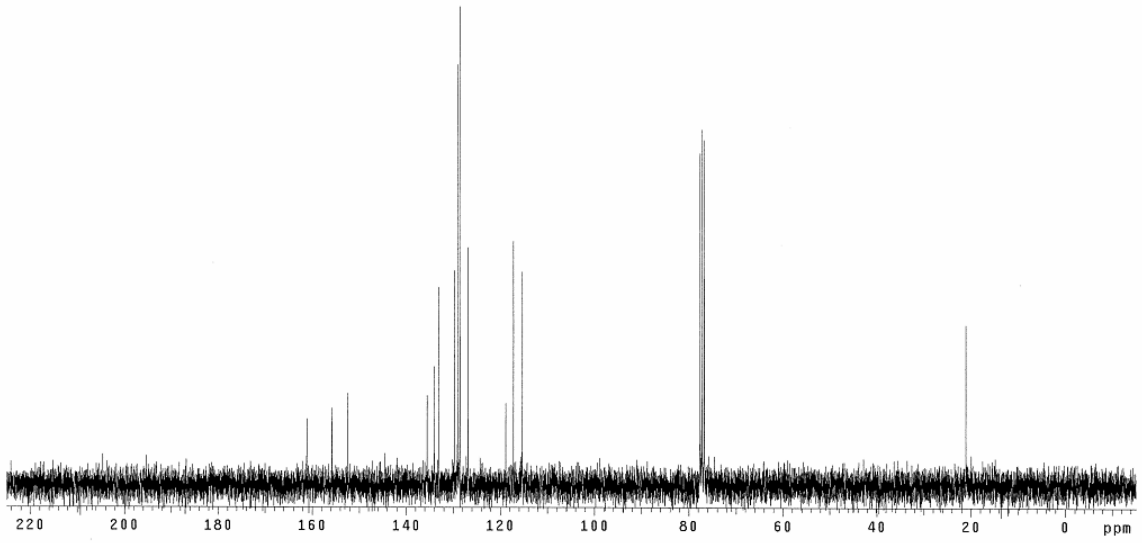


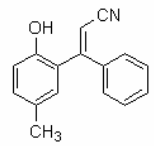
(Z)-1a

INDEX	FREQUENCY	PPM	HEIGHT
1	700.584	2.336	71.5

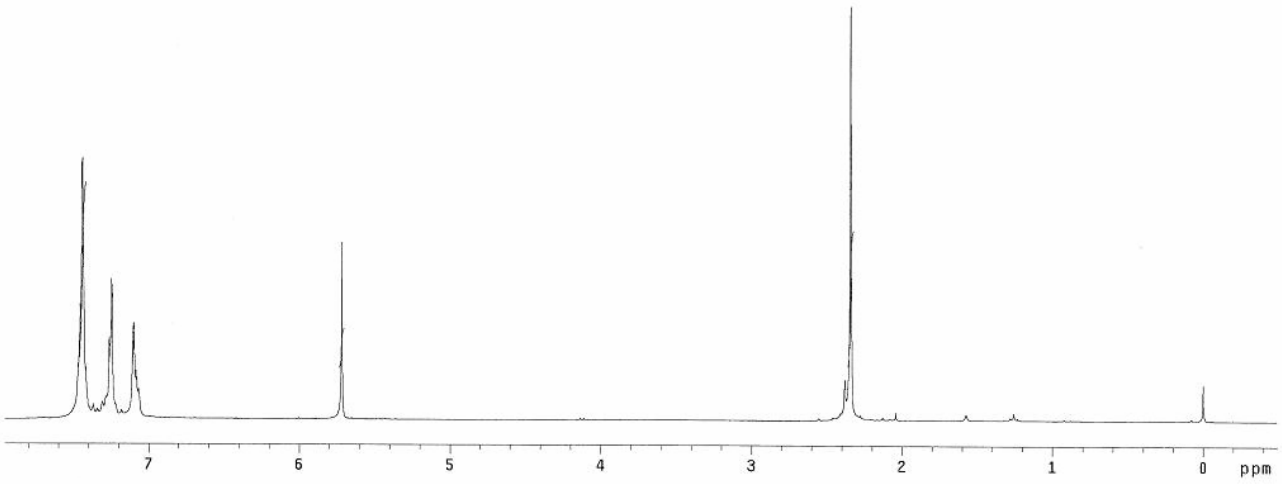


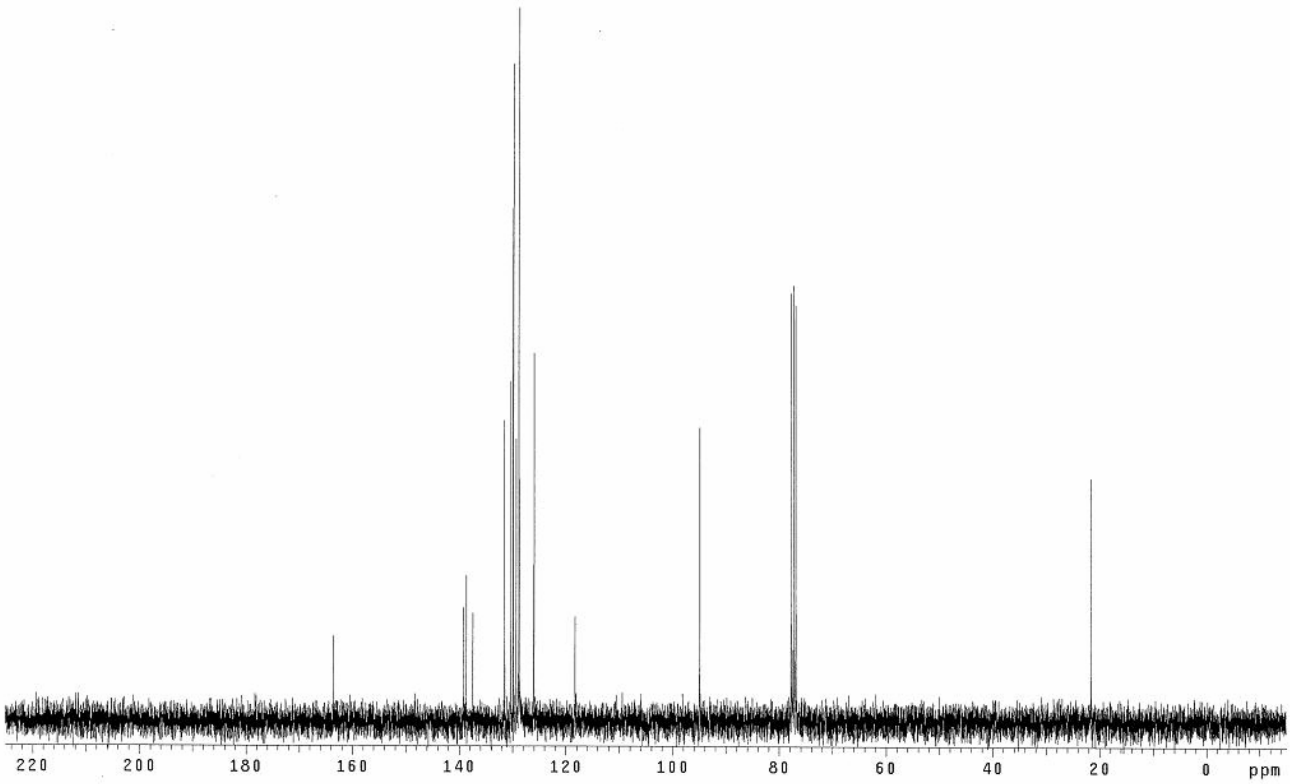
INDEX	FREQUENCY	PPM	HEIGHT
1	12149.518	161.109	14.7
2	11745.381	155.750	17.1
3	11494.385	152.421	20.4
4	10216.185	135.472	19.9
5	10105.061	133.998	26.3
6	10033.190	133.045	43.7
7	9781.641	129.710	47.5
8	9726.356	128.976	93.0
9	9693.185	128.537	105.9
10	9563.264	126.814	52.5
11	8957.335	118.779	18.2
12	8835.707	117.166	53.8
13	8693.623	115.282	47.1
14	5850.292	77.578	73.5
15	5818.779	77.160	78.7
16	5786.713	76.735	76.4
17	1587.782	21.055	35.6

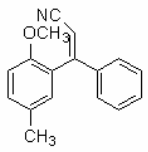



OH
CN
CH3

(E)-1 a

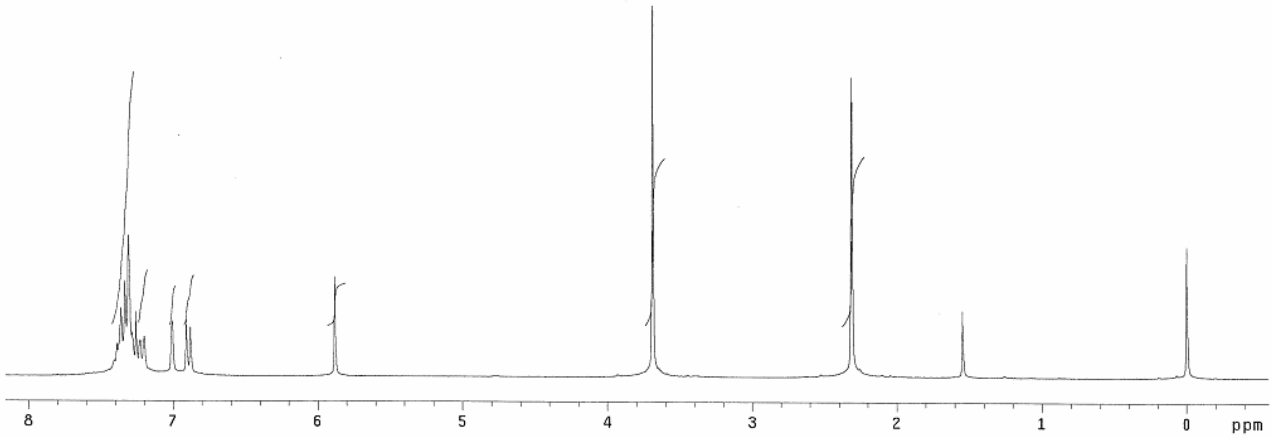

7
6
5
4
3
2
1
0
ppm

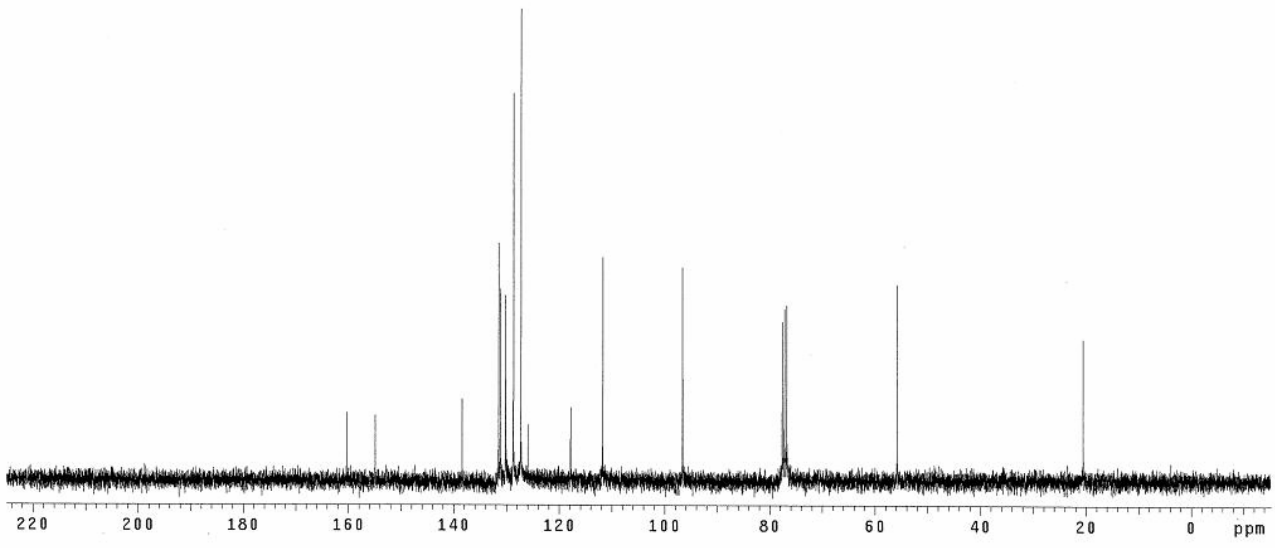

220
200
180
160
140
120
100
80
60
40
20
0
ppm

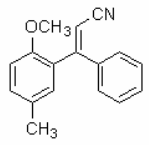


(Z)-1b

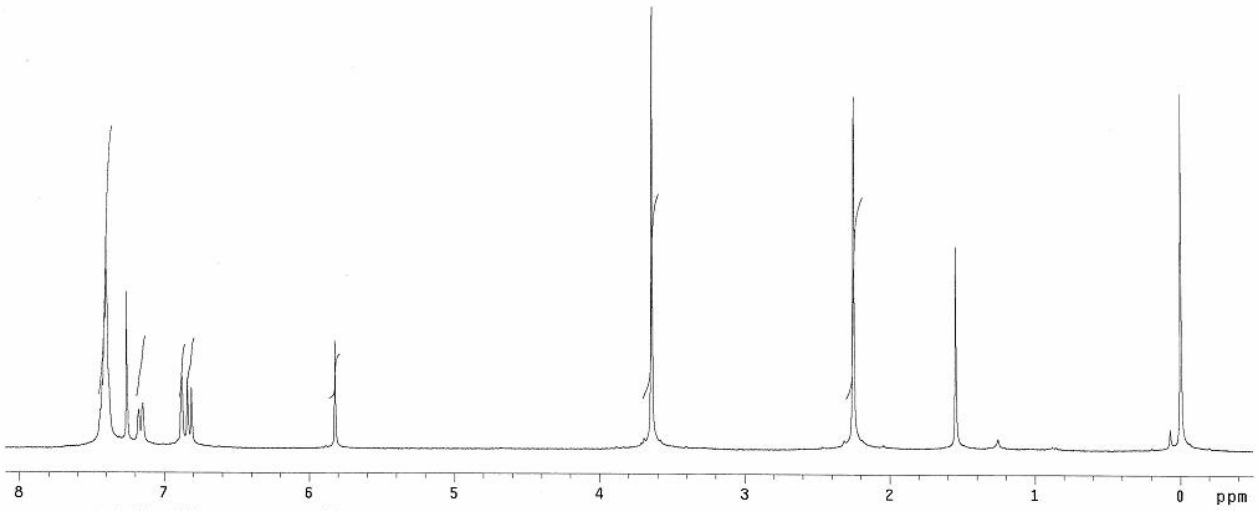
INDEX	FREQUENCY	PPM	HEIGHT
1	2220.301	7.403	3.1
2	2216.339	7.390	6.4
3	2212.671	7.378	6.3
4	2209.883	7.369	10.1
5	2207.683	7.361	13.5
6	2199.907	7.335	18.8
7	2192.277	7.310	27.7
8	2184.941	7.285	8.7
9	2177.018	7.259	12.7
10	2168.069	7.229	7.1
11	2159.706	7.201	7.8
12	2101.311	7.007	10.9
13	2072.261	6.910	11.2
14	2063.898	6.882	9.7
15	1764.738	5.884	19.7
16	1107.583	3.693	73.3
17	694.275	2.315	59.1
18	464.073	1.547	13.2
19	-0.000	-0.000	25.8

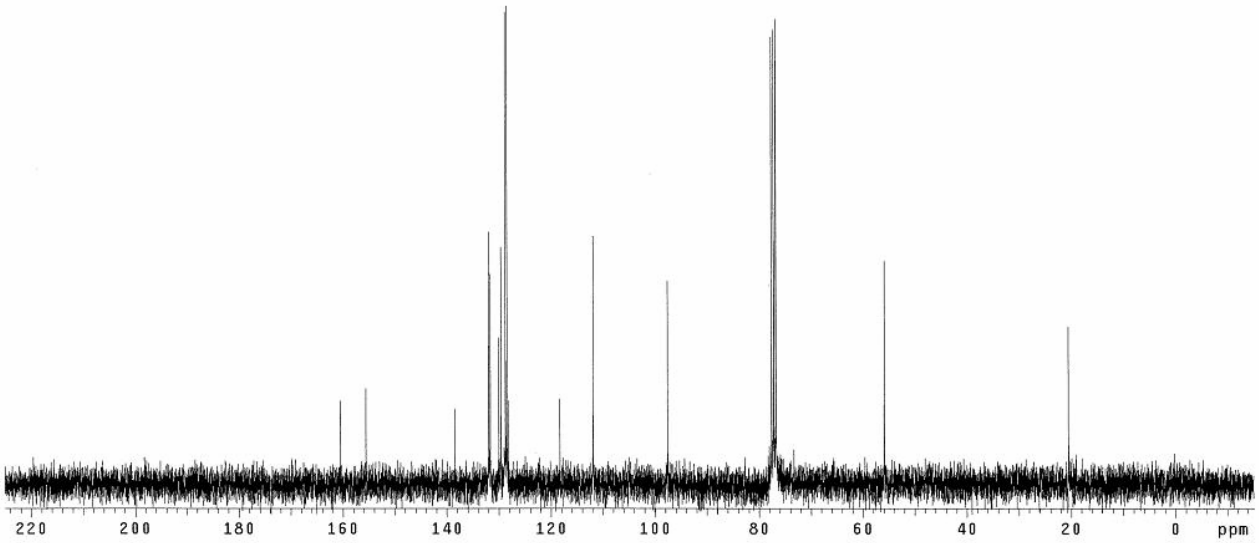


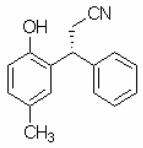



OCH3
CN
CH3

(E)-**1b**

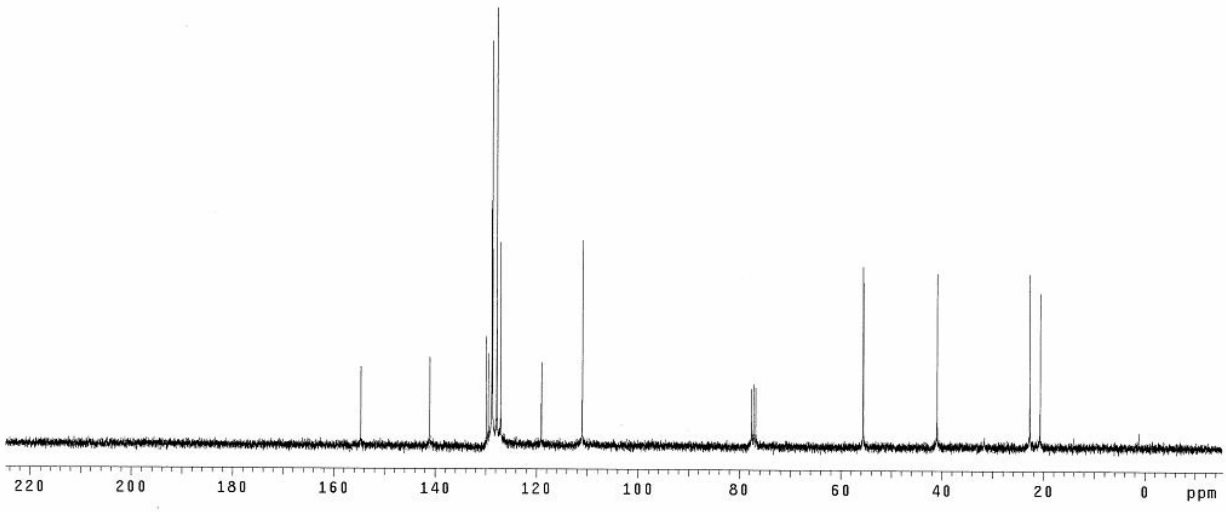

8
7
6
5
4
3
2
1
0
ppm

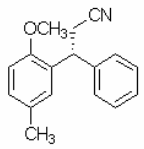

220
200
180
160
140
120
100
80
60
40
20
0
ppm


OH
CN
CH3

(R)-**2a**

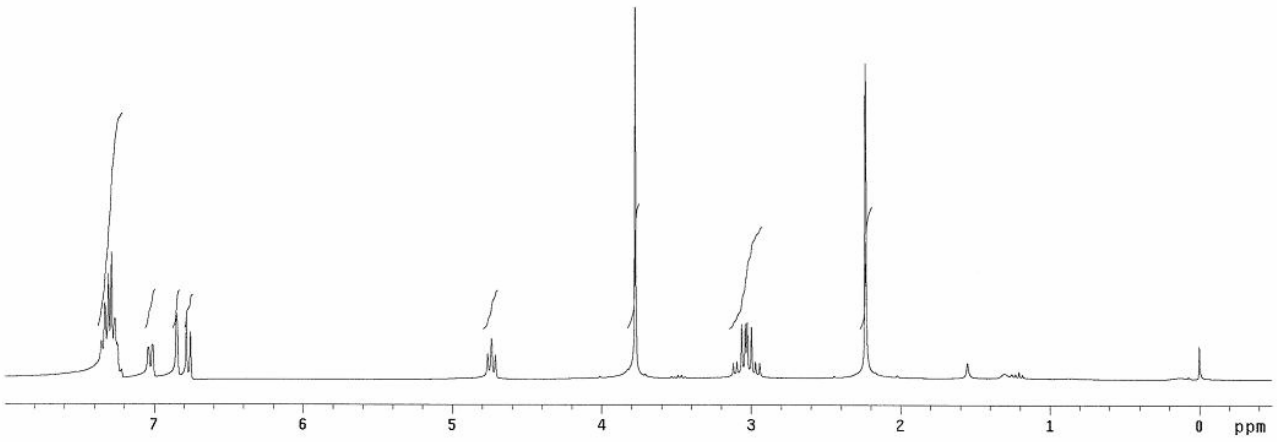
INDEX FREQUENCY PPM HEIGHT
1 674.908 2.250 83.2
7
6
5
4
3
2
1
0
ppm

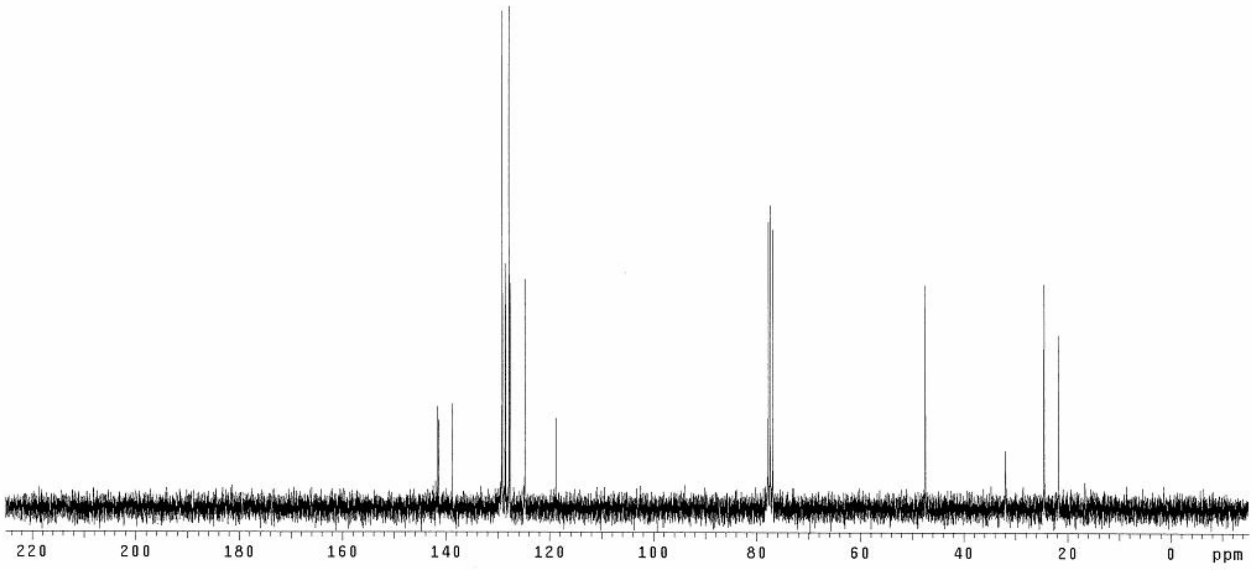

220
200
180
160
140
120
100
80
60
40
20
0
ppm

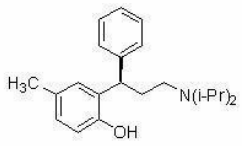


(*R*)-**2b**

INDEX FREQUENCY PPM HEIGHT
1 1131.938 3.774 73.4







(R)-**Tolterodine**