Supporting Information

Water promoted cascade synthesis of α-aryl aldehydes from arylalkenes using N-halosuccinimides: An avenue for asymmetric oxidation using cinchona organocatalysis

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Experimental Section:

Materials

β-asarone was obtained from natural Acorus calamus oil following our earlier reported procedure.[1] The naphthyl and stilbene derivatives were prepared through a previously reported Grignard -dehydration[2a] or decarboxylation approach[2b] respectively. All the above alkenes were fully characterized by ^{1}H and ^{13}C NMR before further use. The rest of the aryl alkenes were reagent grade (purchased from Merck and Aldrich). NBS was freshly recrystallized from hot water (95^{o}C) before use. NIS and NCS were reagent grade (Merck) and used as such. The solvents used for isolation/purification of compounds were obtained from commercial sources (Merck) and used without further purification. Column chromatography was performed using silica gel (Merck, 60-120 mesh size). (8S,9R)-(-)-N-Benzylcinchonidinium chloride (97%), Europium (III) tris[3-(heptaflouropropylhydroxymethylene)-(+)-camphorate [(+)-(98%)-Eu(hfc)$_3$] and L-valine methyl ester hydrochloride (99%) were purchased from Aldrich chemical company and used as supplied.

Apparatus:

^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Chiral HPLC analysis was carried out on a Waters 600E system equipped with a photodiode array detector (Waters 2996) using a Daicel Chiracell OD-H (250 x 4.6 mm, 5µm) column at 20^{o}C. HRMS-ESI spectra were determined using micromass Q-TOF ultima spectrometer. GC-MS analysis was carried out on Shimadzu MS-QP-2010 system equipped with a BP-20 capillary column (SGE international).

Optical rotations were measured using a cell with 10 mm path length on a Horiba Sepa**-**300 high sensitive polarimeter and are reported as follows: $[\alpha]^{rt}D$ (*c* in g/mL solvent). CEM Discover© focused microwave (2450 MHz, 300W) was used wherever mentioned. The temperature of reactions in microwave heating experiments was measured by an inbuilt infrared temperature probe that determined the temperature on the surface of reaction flask. The sensor is attached in a feedback loop with an on-board microprocessor to control the temperature rise rate. In the case of conventional heating in oil bath, the temperature of reaction mixture was monitored by an inner thermometer.

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1 A. K. Sinha, R. Acharya and B. P. Joshi, *J. Nat. Prod.* 2002, **65**, 764.

2 (*a*) R. Kumar, A. Sharma, N. Sharma, V. Kumar and A. K. Sinha, *Eur. J. Org. Chem*. 2008, **2008,** 5577; (*b*) A. Sharma, R. Kumar, N. Sharma, V. Kumar and A. K. Sinha, *Adv. Synth. Catal.* 2008, **350**, 2910.

General

The optical purity (*ee*) of 2-(3,4-dimethoxyphenyl) propionaldehyde (11b) synthesized using achiral and chiral PTC (Cetyltrimethyl ammonium bromide (CTAB) and (8S,9R)-(-)-N-Benzylcinchonidinium chloride (97%) was determined by an ^{1}H NMR assay using L-valine methyl ester HCL as a chiral derivatizing agent. The above determined *ee* was confirmed by HPLC analysis of 2-(3,4-dioxymethylenephenyl)propionaldehydetosylhydrazone. The absolute configuration of **11b** was determined by measuring its optical rotation and comparing it with that of similar compounds reported in literature.[3]

Detailed Optimization data for oxidation of 2,4,5-(trimethoxyphenyl)propene (1a) into α-(2,4,5-trimethoxyphenyl)propionaldehyde (1b) using NBS under microwave irradiation:

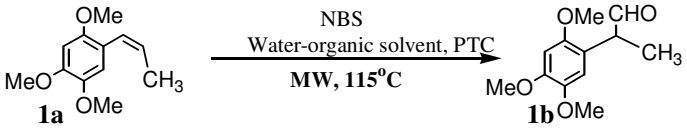
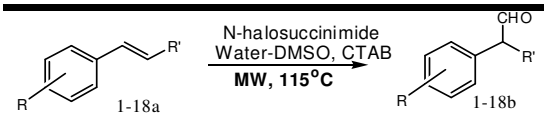


Table: Effect of different solvents and PTC on the yield of 1b under microwave irradiation[a]

Entry	Organic Solvent	Ratio (Water-organic solvent)	PTC	yield [b]
1	Dimethyl sulphoxide	1:3	–	45
2	Dioxane	1:3	–	42
3	Polyethylene glycol	1:3	–	nd[c]
4	Acetone	1:3	–	traces
5	Dimethyl sulphoxide	1:1	CTAB	50
6	Dimethyl sulphoxide	2:1	CTAB	62
7	Dimethyl sulphoxide	3:1	CTAB	70
8	Dimethyl sulphoxide	4:1	CTAB	61
9	Dimethyl sulphoxide	1:0 (neat water)	CTAB	42
10	Dimethyl sulphoxide	3:1	TBAB	nd[c]
11	Dimethyl sulphoxide	3:1	β-Cyclodextrin	37
12	Dimethyl sulphoxide	3:1	SDS	35
13	Dimethyl sulphoxide	3:1	18-Crown-6	29

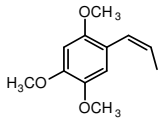
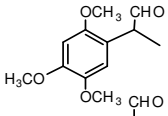
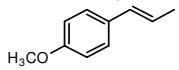
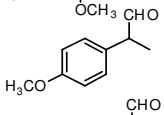
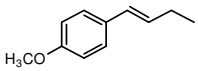
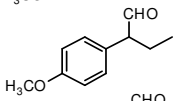
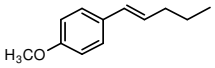
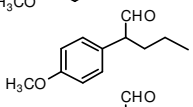
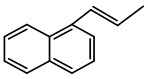
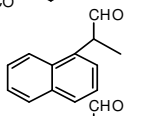
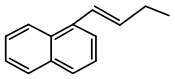
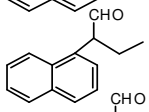
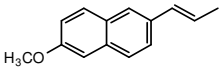
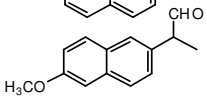
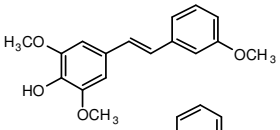
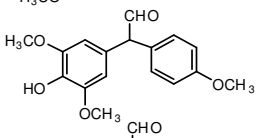
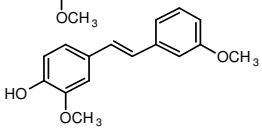
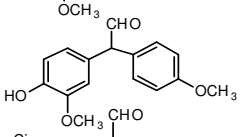
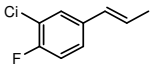
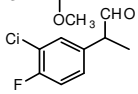
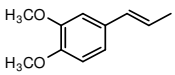
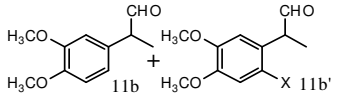
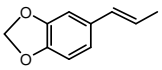
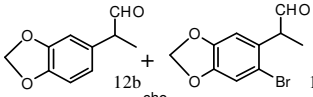
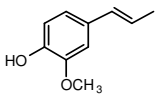
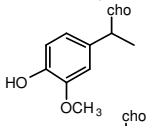
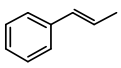
[a]CEM Monomode microwave. General conditions: Substrate (0.96 mmol), N-bromosuccinimide (1.25 mmol), PTC (0.19 mmol) under MW for 15 min (250W, 115°C). [b]Isolated yields. [c] Not detected

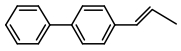
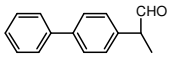
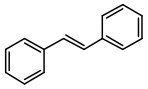
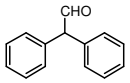
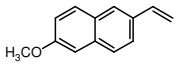
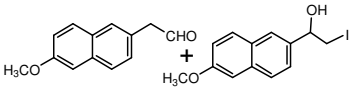
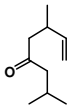
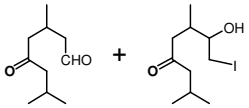
3. J. K. Stille and G. Parrinello, WO Patent 1988/8808835, EP Patent 314759, 1989.



R = H, OMe, OH, Br, (CH=CH-CH=CH) etc.
R' = H, CH_3, CH_2-CH_3, C_6H_5 etc.

Table 1 Metal-free, single step synthesis of α-aryl aldehydes from arylalkenes using N-halosuccinimides and CTAB under focused microwave.[a]

Entry[b]	Substrate (a)	Reaction Time (min)	Product (b)	Yield[c] (%) NBS	Yield[c] (%) NIS
1		15		70	74
2		15		76	78
3		15		81	86
4		15		57	63
5		15		63	74
6		45[d],15		29	83
7		15		31	68
8		15		54	58
9		15		38	49
10		40		nd[e,f]	nd[e,f]
11		15	 11b + 11b'	59+20[f,g]	65+23[f,g]
12		15	 12b + 12b'	49+33[f,g]	56+37[f,g]
13		15		nd[e,l]	24[f]
14		20		nd[e,f]	16[f]

Sr. No	Substrate (a)	Reaction Time (min)	Product (b)	Yield[b] (%) NBS	Yield[b] (%) NIS
15		15		nd[e,f]	22[f]
16		30		n[e,f]	12[f]
17		30		n[e,f]	nd[e,f]
18		40		nd[e,f]	21[f]

[a] CEM Monomode microwave. [b] Entry also denotes compound number. [c] Yield of pure isolated product (single run). [d] Reaction time with use of NBS. [e] Not detected. [f] Based on GC-MS analysis. [g] Mixture of α-arylaldehyde (11b/12b) and its ortho halogenated counterpart (11b'/12b', Scheme 1). General conditions: Substrate (Entries 1-18, 0.96 mmol), CTAB (20 mol %) with (i) NBS (1.25 mmol), water (11 ml), DMSO (3.7 ml) under MW for 15-45 min (250 W, 115°C); or ii) N-iodosuccinimide (1.25 mmol) in dioxane (11 ml), Water (3.7 ml) under MW for 15-40 min (250 W, 105°C); The structure of all the novel compounds was confirmed by NMR (1H, 13C) and HRMS analysis (See supporting information for details).

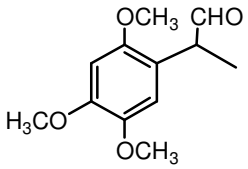
General procedure:

Representative procedure for water promoted oxidative rearrangement of aryl alkenes using NBS or NIS under Microwave

Synthesis of α-(2,4,5-trimethoxyphenyl)propionaldehyde (1b):

To a stirred mixture of 2,4,5-(trimethoxyphenyl)propene (1a, 0.2 g, 0.96 mmol) and DMSO (3.7 ml), water (11ml), CTAB (0.07g, 0.19 mmol) and NBS (0.22g, 1.25 mmol) were added and the reaction mixture allowed to stir for 5 min at room temperature. Thereafter, the flask was irradiated under focused microwave system in parts (250W, 115^{o}C) for 15 min. The reaction mixture was cooled, washed with saturated aq. $Na_2S_2O_3$ solution (1x10 ml) and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with brine (1x10 ml), dried over Na_2SO_4 and vacuum evaporated. The residue was subsequently purified by column chromatography on Silicagel (60-120 mesh size) using hexane-ethylacetate (19:1) to give α-(2,4,5-trimethoxyphenyl)propionaldehyde **1b** (0.15g, 70% yield) as a colorless viscous liquid.[4] In the case of reactions with NIS, dioxane (11 ml) and water (3.7 ml) were found to be optimum and used in place of DMSO (3.7 ml) and water (11 ml) at 250W, 105^{o}C while rest of the conditions were same. It has also been observed that the use of NIS particularly improved the performance of polyaromatic arylalkenes due to enhanced solubility in dioxane:water (3:1).

2-(2,4,5-trimethoxyphenyl)propionaldehyde (1b, Table 1)



IR (KBr, cm^{-1}) $\upsilon_{c=o}$ = 1728. Colorless viscous liquid, R_f 0.73 (hexane:ethylacetate:: 7:3), ^{1}H NMR δ_H ($CDCl_3$, 300MHz), 9.67 (1H, s), 6.66 (1H, s), 6.59 (1H, s), 3.93 (3H, s), 3.86 (3H, s), 3.84-3.83 (4H, m), 1.41 (3H, d, *J*=6.86 Hz); ^{13}C NMR δ (75.4MHz, $CDCl_3$), 202.1, 151.7, 149.3, 143.5, 118.2, 113.3, 97.9, 56.9, 56.5, 56.3, 47.0 and 13.7. HRMS-ESI: m/z $[M+H]^+$ for $C_{12}H_{16}O_4$, calculated 225.2645; observed 225.2642.

The above procedure was also followed for the synthesis of other α-arylaldehydes (Table 1; 2b-9b, 13b-16b, 18b).

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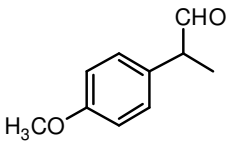
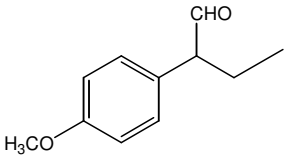
4. It has been observed that the various α-arylaldehydes are prone to decomposition upon exposure to air at room temperature. Therefore, they should be preferably stored under refrigeration after purging with nitrogen.

2-(4-methoxy phenyl) propionaldehyde (2b, Table 1):



Colorless viscous liquid,[5] R_f 0.88 (hexane:ethylacetate:: 7:3), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.54 (1H, s), 7.05 (2H, d, *J*=8.6 Hz), 6.84 (2H, d, *J*=8.6 Hz), 3.70 (3H, s), 3.50 (1H, q, *J*=7.14 Hz), 1.32 (3H, d, *J*=7.14 Hz); ^{13}C NMR δ (75.4 MHz, $CDCl_3$), 201.2, 159.1, 129.6, 129.4, 114.6, 55.3, 52.2 and 14.7.

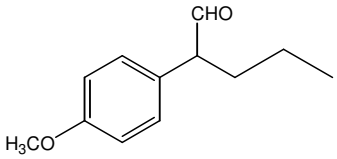
2-(4-methoxy phenyl) butaraldehyde (3b, Table 1):



Colorless viscous liquid, R_f 0.78 (hexane:ethylacetate:: 9:1), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.65 (1H, s), 7.13 (2H, d, *J*=8.6 Hz), 6.94 (2H, d, *J*=8.6 Hz), 3.82 (3H, s), 3.40 (1H, q, *J*=7.5 Hz), 2.18 (1H, m), 1.78 (1H, m), 0.91 (3H, t, *J*=7.3 Hz);

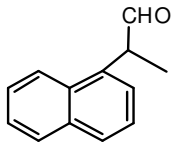
^{13}C NMR δ (75.4 MHz, $CDCl_3$), 201.2, 159.2, 129.9, 128.3, 114.6, 60.1, 55.4, 23.0 and 11.8. HRMS-ESI: m/z $[M+H]^+$for $C_{11}H_{14}O_2$, calculated 179.2433; observed 179.2433.

2-(4-methoxy phenyl) valeraldehyde (4b, Table 1):



Colorless viscous liquid,[6] R_f 0.79 (hexane:ethylacetate:: 9:1), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.65 (1H, s), 7.14 (2H, d, *J*=8.6 Hz), 6.94 (2H, d, *J*=8.6 Hz), 3.82 (3H, s), 3.50 (1H, q, *J*=7.5 Hz), 2.04 (1H, m), 1.73 (1H, m), 1.34 (2H, m), 0.95 (3H, t, *J*=7.3 Hz); ^{13}C NMR δ (75.4 MHz, $CDCl_3$), 201.3, 159.2, 130.0, 128.5, 114.7, 58.3, 55.6, 31.9, 20.4 and 14.1. HRMS-ESI: m/z $[M+H]^+$for $C_{12}H_{16}O_2$, calculated 193.2705; observed 193.2705.

2-(1-naphthyl)propionaldehyde (5b , Table 1):

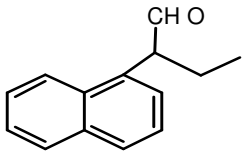


Colorless viscous liquid, [5] R_f 0.47 (hexane), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.74 (1H, s), 8.01 (1H, d, *J*=7.87 Hz), 7.90 (1H,

5. Y. Yan and X. Zhang, *J. Am. Chem. Soc.* 2006, **128**, 7198.
6. L. Lezhen, C. Peijie, G. Qingxiang and X. Song, *J. Org. Chem*, 2008, **73**, 3516.

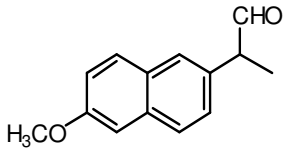
d, *J*=7.87 Hz), 7.82 (1H, d, *J*=8.05 Hz), 7.55-7.47 (3H, m), 7.29 (1H, d, *J*=7.14 Hz), 4.39 (1H, q, *J*=6.95 Hz), 1.58 (3H, d, *J*=7.14 Hz); ^{13}C NMR δ (75.4MHz, $CDC1_3$), 201.3, 134.3, 131.9, 129.3, 128.6, 126.8, 126.1, 125.8, 125.7, 125.0, 123.1, 48.9 and 14.7, HRMS-ESI: m/z $[M+H]^+$for $C_{13}H_{12}O$, calculated 185.2455; observed 185.2453.

2-(1-naphthyl)butyraldehyde (6b, Table 1):



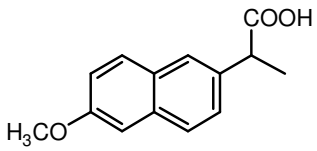
Colorless viscous liquid, R_f 0.53 (hexane), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.68 (1H, d, *J*=1.83 Hz), 8.03 (1H, d, *J*=8.05 Hz), 7.88 (1H, d, *J*=6.4 Hz), 7.81 (1H, d, *J*=8.42 Hz), 7.53-7.43 (3H, m), 7.29 (1H, d, *J*=7.14 Hz), 4.16-4.15 (1H, m), 2.30-2.25 (1H, m), 1.93-1.88 (1H, m), 0.97-0.92 (3H, m); ^{13}C NMR δ (75.4MHz, $CDC1_3$), 200.9, 134.3, 132.7, 132.3, 129.2, 128.3, 126.7, 126.2, 126.0, 125.6, 123.2, 56.3, 22.9 and 12.1. HRMS-ESI: m/z $[M+H]^+$ for $C_{14}H_{14}O$, calculated 199.2729; observed 199.2726.

2-(6-methoxy(2-naphthyl))propionaldehyde (7b, Table 1):



White solid, m.p. 40-42°C (lit. m.p. 57-74°C),[7] R_f 0.83 (hexane:ethylacetate:: 8:2), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.83 (1H, s), 7.85-7.79 (2H, t, *J*=9.77 Hz) 7.68 (1H, s), 7.38-7.35 (1H, m) 7.28-7.22 (2H, m), 3.99 (3H, s), 3.85 (1H, q, *J*=6.86 Hz), 1.62 (3H d, *J*=7.14 Hz); ^{13}C NMR δ (75.4 MHz, $CDCl_3$), 201.2, 158.0, 134.0, 132.8, 129.3, 127.8, 127.1, 126.8, 126.5, 119.4, 105.7, 55.4, 53.0 and 14.7. HRMS-ESI: m/z $[M+H]^+$ for $C_{14}H_{14}O_2$, calculated 215.2717; observed 215.2779.

2-(6-methoxy-2-naphthyl)propionic acid (7c, Table 1):



White solid, m.p. 153-155°C (lit. m.p. 154-155°C),[8] ^{1}H NMR (MeOD, 300MHz), 7.65-7.59(3H, m), 7.31(1H, d, *J*=8.78 Hz), 7.11(1H, s), 7.04(1H, d, *J*=8.78 Hz), 3.79(3H, s), 3.77-3.72(1H, m), 1.46(3H, d, *J*=7.14 Hz); ^{13}C NMR δ_C (75.4MHz, $CDC1_3$), 178.4, 159.1, 137.4, 135.2, 130.4, 130.2, 128.1, 127.2, 126.8, 119.9, 106.6, 55.7, 46.2 and 19.0.

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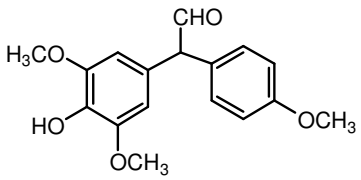
7. B. A. Barner, and J. J. Kurland, US Patent 5739385, 1998.

8. British Pharmacopoeia 1973, A66.

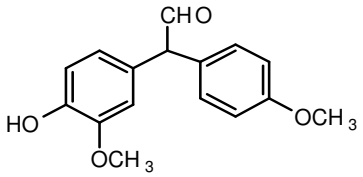
2-(4-hydroxy-3,5-dimethoxyphenyl)-2-(4'methoxyphenyl)acetaldehyde (8b, Table 1):



Light yellow viscous liquid, R_f 0.56 (hexane:ethylacetate:: 6:4), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.87 (1H, s), 7.28 (2H, d, *J*=8.96 Hz), 6.94 (2H, d, *J*=8.96 Hz), 6.58 (2H, s), 5.63 (1H, s), 4.33 (1H, s), 3.83 (6H, s), 3.82 (3H, s); ^{13}C NMR δ (75.4 MHz, $CDCl_3$), 197.6, 159.8, 147.3, 139.0, 131.5, 130.2, 129.1, 114.3, 104.6, 83.2, 56.5 and 55.6.

The structure of above compound was further confirmed by treatment with acetic anhydride (2 eq.), pyridine (2 eq.), DMAP (10 mol%) in dry dichloromethane to provide the corresponding acetoxylated derivative 2-(4-acetoxy-3,5-dimethoxyphenyl)-2-(4'methoxyphenyl)acetaldehyde HRMS-ESI: m/z $[M+H]^+$ for $C_{19}H_{20}O_6$, calculated 345.3796; observed 345.3797.

2-(4-hydroxy-3-methoxyphenyl)-2-(4'-methoxyphenyl)acetaldehyde (9b, Table 1):



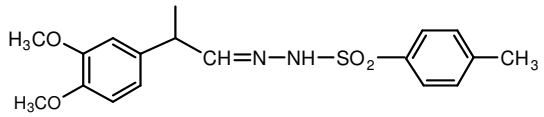
Colorless viscous liquid, R_f 0.80 (hexane:ethylacetate:: 6:4), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.79 (1H, s), 7.21 (2H, d, *J*=8.51 Hz), 6.86-6.70 (5H, m), 5.70 (1H, s), 4.30 (1H, s), 3.77 (3H, s), 3.75 (3H, s); ^{13}C NMR δ (75.4 MHz, $CDCl_3$), 198.4, 159.6, 146.9, 145.8, 131.4, 131.1, 128.8, 120.7, 114.3, 114.2, 110.9, 82.9, 56.0 and 55.3. HRMS-ESI: m/z $[M+H]^+$ for $C_{16}H_{16}O_4$, calculated 273.3085; observed 273.3086.

Representative procedure for conversion of inseparable mixture of α-arylaldehydes (11b+11b') into easily separable hydrazone derivatives followed by their structural elucidation of 11b and 11b':

The mixture of inseparable α-arylaldehydes **(11b + 11b')** was obtained by reaction of 3, 4-dimethoxyphenylpropene (0.17g, 0.96 mmol) with NBS 0.22 g, 1.24 mmol) as given in procedure-1. The individual amounts of respective α-arylaldehydes **(11b + 11b')** in the above mixture was calculated on GCMS basis (0.128 + 0.061 g, 0.659 mmol + 0.223 mmol).

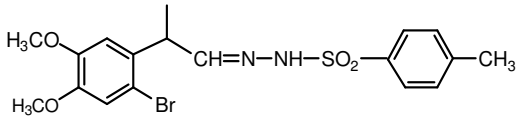
Consequently, the above mixture, *p*-toluenesulphonyl hydrazide (0.165 g, 0.88 mmol) and methanol (10 ml) were taken in a 50 ml round bottom flask and allowed to stir at room temperature for 2h. After completion of reaction (TLC basis), methanol was vacuum evaporated to obtain a viscous liquid which was found to be easily separable by column chromatography on Silicagel (60-120 mesh size) using hexane-ethylacetate (19:1) to give 2-(3,4-dimethoxyphenyl) propionaldehyde tosyl hydrazone (40% yield, 0.095 g) and 2-(2-bromo-3,4-dimethoxyphenyl) propionaldehyde tosyl hydrazone (62 % yield, 0.06 g).

2-(3,4-dimethoxyphenyl)propionaldehydetosylhydrazone(11c, Scheme-1a):



Colorless viscous liquid, R_f 0.72 (hexane:ethylacetate:: 7:3) ^{1}H NMR δ ($CDCl_3$, 300MHz), 8.06 (1H, s), 7.82 (2H, d), 7.31 2H, d), 7.21-7.18 (1H, m), 6.74 (1H, d), 6.62 (1H, d), 6.60 (1H, s), 3.87 (3H, s), 3.73 (3H, s), 3.61 (1H, q), 2.44 (3H, s),1.37 (3H, d); ^{13}C NMR δ (75.4MHz, $CDCl_3$), 154.9, 149.1, 148.0, 144.1, ,134.1, 133.1, 129.6, 126.5, 119.4, 111.4, 110.9, 56.0, 55.8, 42.5, 21.7 and 18.3. HRMS-ESI: m/z $[M+H]^+$ for $C_{18}H_{22}N_2O_4S$, calculated 393.4915; observed 393.4915.

(2-bromo-4,5-dimethoxyphenyl)propionaldehydetosylhydrazone(11c',Scheme-1a):

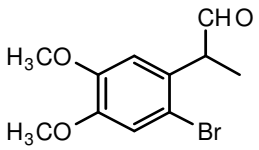


White solid, m.p. 140-142°C, R_f 0.52 (hexane:ethylacetate :: 7:3), ^{1}H NMR δ ($CDCl_3$, 300MHz), 8.26 (1H, s), 7.81 (2H, d, *J*=8.96 Hz), 7.28-7.20 (3H, d, *J*=8.23 Hz), 6.95 (1H, s), 6.44 (1H, s), 4.02 (1H, q, *J*=7.14 Hz), 3.80 (3H, s), 3.65 (3H, s), 2.41 (3H, s), 1.19 (3H, d, *J*=7.14 Hz); ^{13}C NMR δ (75.4MHz, $CDCl_3$), 153.2, 149.2, 149.0, 144.2, ,135.3, 132.8, 129.5, 128.1, 115.7, 114.1, 111.1, 56.2, 55.9, 41.5, 21.7 and 15.3. HRMS-ESI: m/z $[M+H]^+$ for $C_{18}H_{21}BrN_2O_4S$, calculated 442.3530; observed 442.3505.

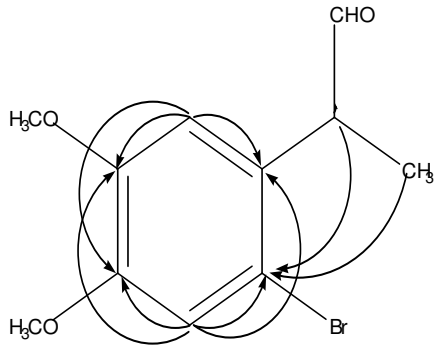
Synthesis of 2-(2-bromo-4, 5-dimethoxyphenyl) propionaldehyde (11b', Table 2):

To a stirred mixture of 3,4-dimethoxyphenylpropene (11a, 0.17 g, 0.96 mmol) and DMSO (3.7 ml), water (11ml), CTAB (0.07 g, 0.19 mmol) and NBS (0.68 g, 3.82 mmol) were added and the reaction mixture allowed to stir for 5 min at room temperature. Thereafter, the flask was irradiated under focused microwave system in parts (250W, 115°C) for 15 min. The reaction mixture was cooled, washed with saturated aq. $Na_2S_2O_3$ solution (1x10 ml) and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with brine (1x10 ml), dried over Na_2SO_4 and vacuum evaporated. The residue was subsequently purified by column chromatography on Silicagel (60-120 mesh size) using hexane-ethylacetate (19:1) to give 2-(2-bromo-4,5-dimethoxyphenyl) propionaldehyde (11b', 0.177 g, 68% yield) as a colorless viscous liquid.

2-(2-bromo-4,5-dimethoxyphenyl)propionaldehyde (11b'):



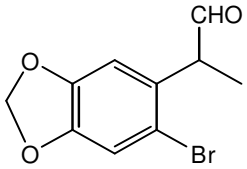
Colorless viscous liquid, R_f 0.82 (hexane:ethylacetate:: 7:3), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.70 (1H, s), 7.09 (1H, s), 6.55 (1H, s), 4.11 (1H, q, *J*=6.95 Hz), 3.88 (3H, s), 3.84 (3H, s), 1.41 (3H, d, *J*=7.14 Hz); ^{13}C NMR δ (75.4MHz, $CDCl_3$), 200.5, 149.1, 129.5, 116.1, 115.2, 111.6, 56.2, 51.8 and 14.1. HRMS-ESI: m/z $[M+2]^+$ for $C_{11}H_{13}BrO_3$, calculated 275.14208; observed 275.1421.



Selected HMBC correlations (from H to C) of (11b') establishing the relative position of bromo group.

The above procedure was also followed for the synthesis of 12b' (Table 2)

2-(2-bromo-4,5-dioxymethylenephenyl)propionaldehyde (12b'):



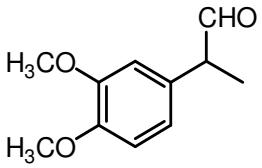
Colorless viscous liquid, R_f 0.87 (hexane:ethylacetate:: 7:3), ^{1}H NMR δ ($CDCl_3$ 300MHz), 9.70 (1H, s), 7.11 (1H, s), 6.62 (1H, s), 6.02 (2H, s), 4.16 (1H, q, *J*=7.14 Hz), 1.40 (3H, d, *J*=7.14 Hz); ^{13}C NMR δ (75.4MHz, $CDCl_3$), 200.5, 148.2, 147.9, 130.7, 115.6, 113.3, 108.8, 102.1, 51.9 and 14.2. HRMS-ESI: m/z $[M+H]^+$ for $C_{10}H_9$ BrO_3 , calculated 257.993; observed 257.993.

Synthesis of 2-(3,4-dimethoxyphenyl) propionaldehyde (11b, Table 2):

To a stirred mixture of 3,4-dimethoxyphenylpropene (11a, 0.17 g, 0.96 mmol) DMSO (3.7 ml), water (11ml), CTAB (0.07 g, 0.13 mmol) and NBS (0.17 g, 0.96 mmol) were added and the reaction mixture allowed to stir for 5 min at room temperature. Thereafter, the flask was irradiated under focused microwave system in parts (250W, 115^{o}C) for 15 min. The reaction mixture was cooled, washed with saturated aq. $Na_2S_2O_3$ solution (1x10 ml) and extracted with ethyl acetate (3x20

ml). The combined organic layer was washed with brine (1x10 ml), dried over Na_2SO_4 and vacuum evaporated. The residue was subsequently purified by column chromatography on Silicagel (60-120 mesh size) using hexane-ethylacetate (19:1) to give 2-(3,4-dimethoxyphenyl) propionaldehyde (11b', 0.11 g, 60% yield) as a colorless viscous liquid.

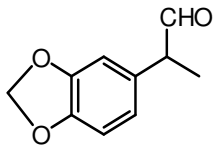
2-(3,4-dimethoxyphenyl)propionaldehyde (11b):



Colorless viscous liquid, R_f 0.82 (hexane:ethylacetate:: 7:3), ^{1}H NMR δ ($CDCl_3$, 300MHz), 9.65 (1H, s), 6.89 (1H, d, *J*=8.23 Hz), 6.78 (1H, d, *J*=8.05 Hz), 6.69 (1H, s), 3.88 (6H, s), 3.6 (1H, q, *J*=7.14 Hz), 1.43 (3H, d, *J*=7.14 Hz): ^{13}C NMR δ (75.4MHz, $CDCl_3$), 201.0, 149.5, 148.6, 130.1, 120.5, 111.7, 111.4, 56.0, 52.6 and 14.7.

The above procedure was also followed for the synthesis of 12b (Table 2)

2-(3,4-dioxymethylenephenyl)propionaldehyde (12b):



Colorless viscous liquid,[9] R_f 0.87 (hexane:ethylacetate:: 7:3), ^{1}H NMR δ ($CDCl_3$ 300MHz), 9.62 (1H, s), 6.82 (1H, d, *J*=7.87 Hz), 6.67 (1H, s), 6.65 (1H, d, *J*=8.78 Hz), 5.95 (2H, s), 3.58 (1H, q, *J*=7.14 Hz), 1.41 (3H, d, *J*=7.14 Hz); ^{13}C NMR δ (75.4MHz, $CDCl_3$), 200.9, 148.4, 147.1, 131.4, 121.7, 108.9, 108.7, 101.3, 52.7 and 14.8.

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9. T. Hamori, S. Solyom, P. Berzsenyi, F. Andrasi and I. Tarnawa, *Bioorg. Med. Chem. Lett*. 2000, **10**, 899.

Representative procedure for enantioselective synthesis of (S)-2-(3,4-dimethoxyphenyl) propionaldehyde (11b) from 3,4-dimethoxyphenylpropene using cinchona phase transfer organocatalyst (Scheme 2):

To a stirred mixture of 3,4-dimethoxyphenylpropene (0.2 g, 1.12 mmol) and DMSO (3.7 ml), water (11ml), N-benzylcinchonidinium chloride (0.19 g, 0.45 mmol) and N-bromosuccinimide (0.26 g, 1.46 mmol) were added and the reaction mixture allowed to stir for 5 min at room temperature. Thereafter, the flask was irradiated under focused microwave system in parts (250W, 115^{o}C) till the completion of reaction (monitored by TLC). The reaction mixture was cooled, washed with saturated aq. $Na_2S_2O_3$ solution (1x10 ml) and extracted with ethyl acetate (3x20 ml). The combined organic layer was washed with brine (1x10 ml), dried over Na_2SO_4 and vacuum evaporated.

The residue was subsequently purified by column chromatography on Silicagel (60-120 mesh size) using hexane-ethylacetate (19:1) to give (S)-2-(3,4-dimethoxyphenyl) propionaldehyde (11b, 0.104 g, 48% yield) as a colorless viscous liquid. The enantiomeric excess was determined as explained below by ^{1}H NMR (300 MHz, $CDCl_3$, 20°C) ee assay of imines formed after in situ reaction with L-valine methyl ester HCl in $CDCl_3$: major diastereoisomer δ = 7.55-7.61 (br), minor diastereoisomer δ = 7.61-7.68 (d, *J* = 8.6 Hz), (minor area : major area = 1.0 : 1.87); $[\alpha]_D^{20}$ = +15.416 (c = 0.015g/ml, $CHCl_3$, 30% ee, 19.4^{o}C).

Determination of *ee* via ^{1}H NMR assay

Our initial attempts to ascertain the enantiomeric excess of **11b** obtained by above organocatalytic approach proved futile as the above product (11b) proved to be non-resolvable[10] under both chiral GC as well as chiral HPLC conditions which was further corroborated by a couple of earlier literature precedents.[11] Unfortunately, the use of chiral NMR shift agents like $Eu(tfc)_3$ (0.1 -0.5 eq.) also proved to be of no avail as it lead to considerable line broadening with no apparent splitting of any NMR peak of aldehyde.

Subsequently, the ^{1}H NMR assay based methodology developed by Gellman et al[12] proved useful. This assay involves the formation of diastereomeric imines by the addition of L-valine methyl ester HCl to the aldehyde dissolved in a suitable NMR solvent. Although, the above report utilized L-valine methyl ester, but in our case we found that use of L- valine methyl ester HCl provided comparatively better resolution of desired peaks.

In the above mentioned typical example, **11b** was dissolved in 0.5 ml of $CDCl_3$ in an NMR tube and L- valine methyl ester HCl (2 eq.) was added. The resulting mixture was shaken for 30-40 seconds and ^{1}H NMR spectrum was taken immediately. The *ee* of **11b** was determined by integration of the signals corresponding to the imine proton and it was found to be 30%

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10. Both chiral HPLC and chiral GC analysis were similarly unable to resolve various other structurally different arylaldehydes.
11. Y. Yan, and X. Zhang, *J. Am. Chem. Soc.* 2006, **128**, 7198.
12. Y. Chi, T. J. Peelen and S. H. Gellman, *Org. Lett*. 2005**, 7**, 3469-3472.

with N-benzylcinchonidinium chloride (See page S71). In order to further enhance the accuracy of our ^{1}H NMR assay,[15] it was felt necessary to further enhance the base line separation of resonances of imine protons. In this context, we were prompted to screen different NMR solvents for above assay as peak resolution has been known to be influenced by the NMR solvent. Consequently, the above experiment was repeated by using various solvents like DMSO-d6), MeOD in place of $CDCl_3$ while rest of the conditions were the same. Interestingly, the use of MeOD provided a much improved base line separation of imine ^{1}H NMR signals as the *ee* of **11b** was found to be 32% (See page S72). In addition, the above investigation further confirmed the reproducibility of using such an NMR assay based methodology. It would also be worthwhile to mention that the arylaldehydes prepared using various other phase transfer catalysts like CTAB, cyclodextrin under similar conditions provided **11b** in comparatively lower ee (4-5%) thereby emphasizing the beneficial role of N-benzylcinchonidinium chloride.

As per the suggestion of reviewers, the conversion of aldehyde into more easily resolvable corresponding alcohol or carboxylic acid derivatives was taken up in order to further confirm the *ee* determination by chiral HPLC/GC analysis. However, it proved difficult to maintain the enantiopurity of α-arylated substrates (11b) in such transformations due to their widely known tendency towards racemization and side reactions.[13] Thus, the treatment of **11b** with sodium chlorite, $KMnO_4$ or $LiAlH_4$ led to the formation of a number of side products, while the use of PDC or Oxone provided unexpected products like 3,4-dimethoxyacetophenone[14a] or 3,4-dimethoxyphenylacetate[14b] respectively. On the other hand, in situ treatment of **11b** (obtained by using CTAB or chiral PTC; N-benzylcinchonidinium chloride) with $NaBH_4$[14c] and subsequent chiral HPLC analysis confirmed that the racemic aldehyde provided corresponding alcohol in 0.8% ee (see page S73) while alcohol with an ee of 6.8 % (see page S74) was obtained from reduction of chiral α-aryl aldehyde (11b) thereby indicating considerable racemisation during above reduction. Similarly, the Ag_2O[14d] promoted oxidation of comparatively more stable 2-(6-methoxy(2-naphthyl)propionaldehyde (solid, m.p 42^{o}C) also led to formation of corresponding acid derivative (2-(6-methoxy-2-naphthyl)propionic acid in racemized form (see page S56-57).

Confirmation of involvement of bromohydrin intermediate in cascade synthesis of arylaldehydes[15]:
In order to confirm the involvement of a bromohydrin intermediate during cascade synthesis of aryl aldehydes from arylalkenes (Fig. 1), a two steps methodology was conducted. Thus, 3,4-dimethoxyphenylpropene (11a) was initially stirred with NBS in DMSO:water mixture at room temperature which after purification by column chromatography provided the corresponding bromohydrin derivative whose spectral data is given as follow:

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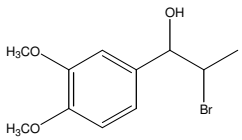
13. (*a*) C. Botuha, M. Haddad and M. Larchevêque, *Tetrahedron: Asymmetry*, 1998, **9***,* 1929; (*b*) A. G. Myers, B. Zhong, D. W. Kung, M. Movassaghi, B. A. Lanman, and S. Kwon, *Org. Lett.,* 2000, **2**, 3337; (*c*) S. Kobayashi, H. Miyamura, R. Akiyama, and T. Ishida, *J. Am. Chem. Soc.* 2005, **127**, 9251.

14 (*a*) C. H. Heathcock, S. D. Young J. P. Hagen, R. Pilli and U. Badertscher, *J. Org. Chem.*, 1984, **50**, 2095; (*b*) B. R. Travis, M. Sivakumar, G. O. Hollist and B. Borhan, *Org. Lett.,* 2003, **5**, 1031; (c) M. Prashad, D. Har, H. Y. Kim and O. Repic, *Tet. Lett*. 1998, **39**. 7067; (*d*) P. Coutrot, C. Grison, C. Bômont, *J. Organometallic Chem*. 1999, **586**, 208.

15. We thank the reviewers for their insightful remarks and suggestions regarding these aspects.

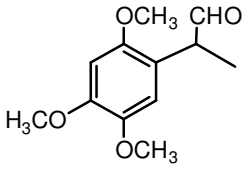
1-(3,4-dimethoxyphenyl)-1-(2-bromopropanol)



Colorless viscous liquid, ^{1}H NMR δ ($CDCl_3$, 300MHz), 6.95-6.84 (3H, m), 4.96 (1H, d), 4.44-4.32 (1H, m), 3.90 (3H, s), 3.89(3H, s), 2.5(1H, s), 1.58(3H, d); ^{13}C NMR δ (75.4MHz, $CDC1_3$), 149.3, 149.2, 132.7, 119.8, 111.4, 110.0, 77.5, 56.6, 56.3, 19.3.

Subsequently, the above bromohydrin derivative was subjected to microwave irradiation which provided the corresponding 2-(3,4-dimethoxyphenyl) propionaldehyde (11b) whose NMR spectra matched with that obtained earlier (page S12) NMR. The above result clearly highlights the role of bromohydrin intermediate which undergoes a thermal rearrangement into corresponding aryaldehyde under microwave irradiation.

Table 1/ 1b, ^{1}H NMR (in $CDCl_3$)



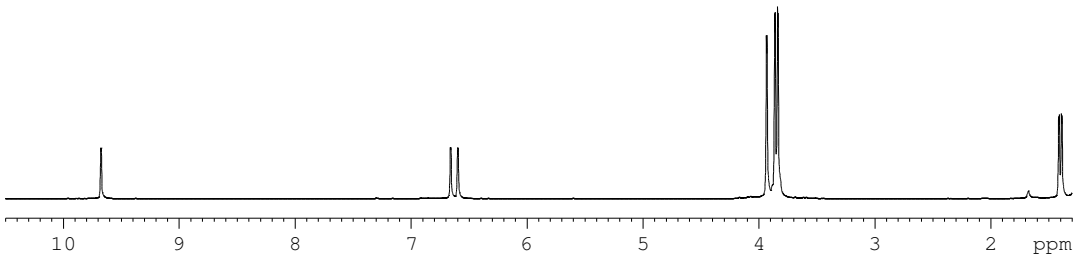
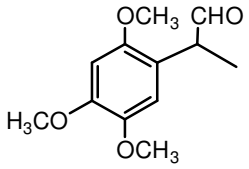


Table 1/ 1b, ^{13}C NMR (in $CDCl_3$)



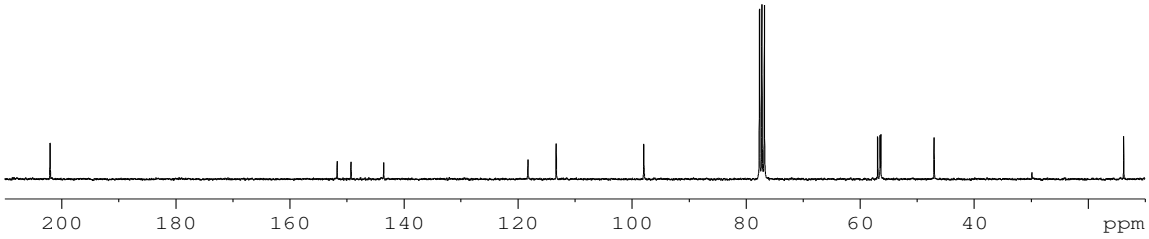
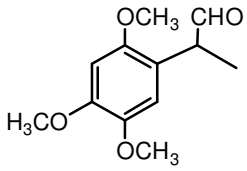


Table 1/ 1b, HMBC (in $CDCl_3$)



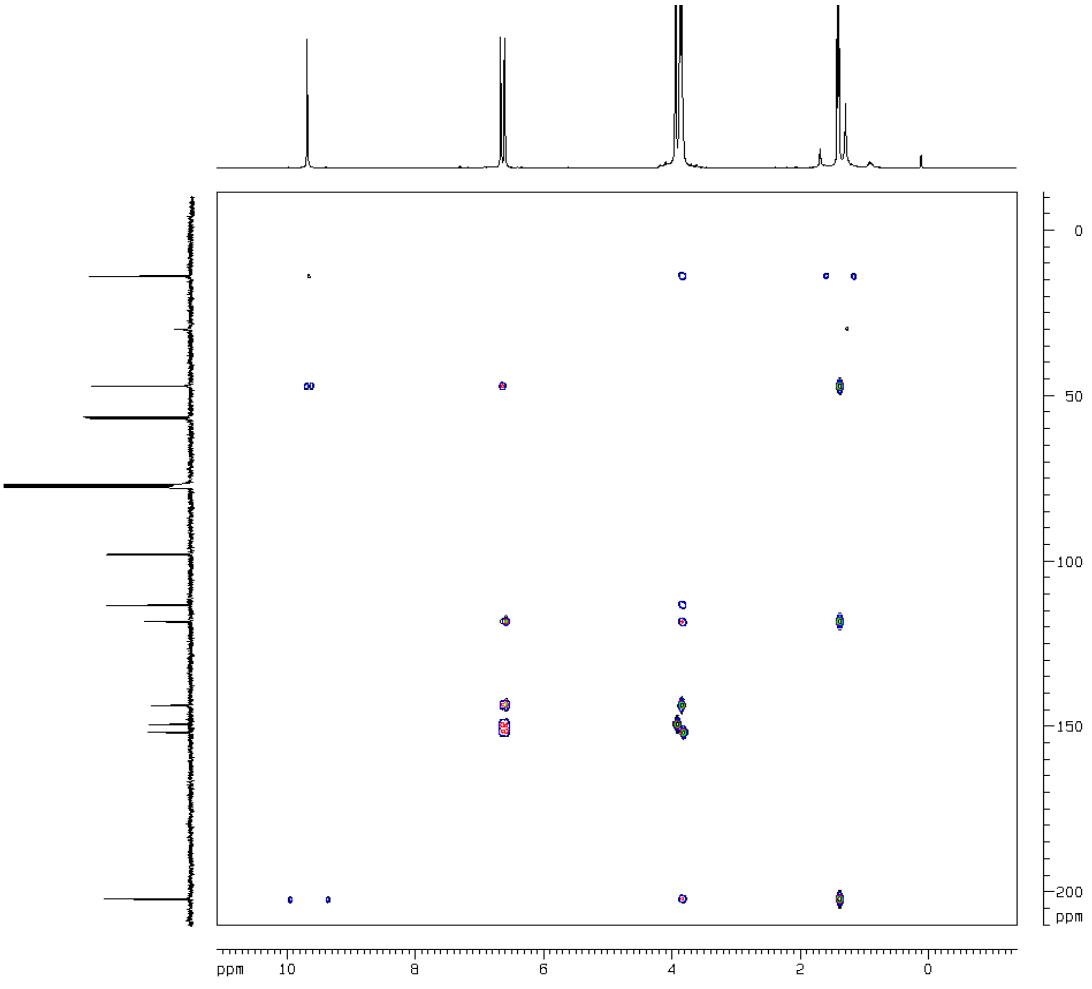
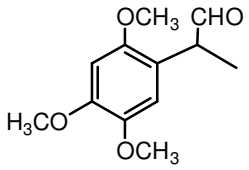


Table 1/ 1b, HMQC (in $CDCl_3$)



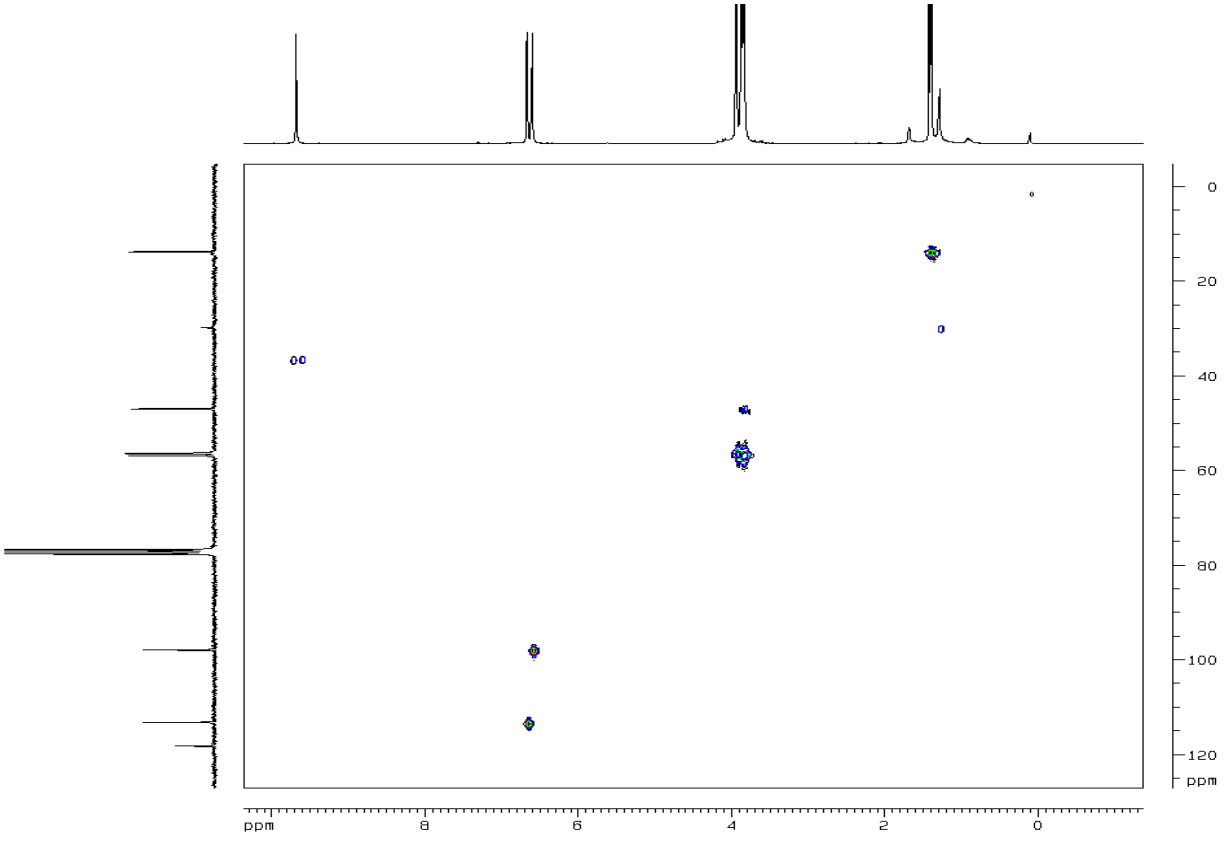
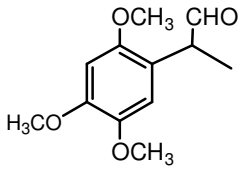


Table 1/ 1b, HRMS Spectrum



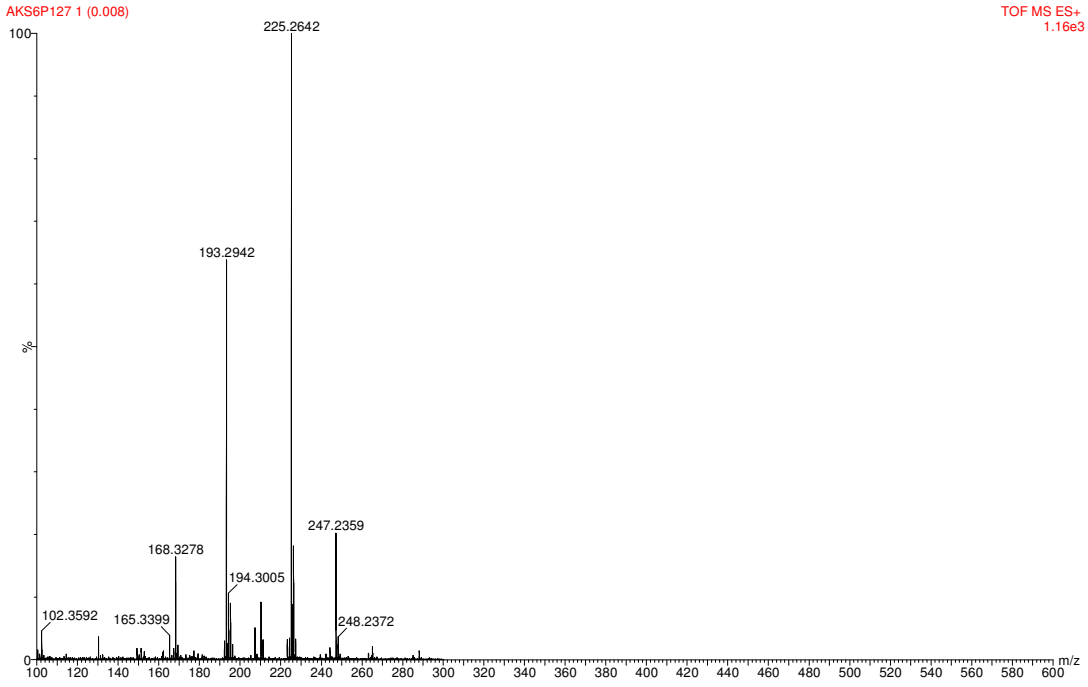


Table 1/ 2b, ^{1}H NMR (in $CDCl_3$)

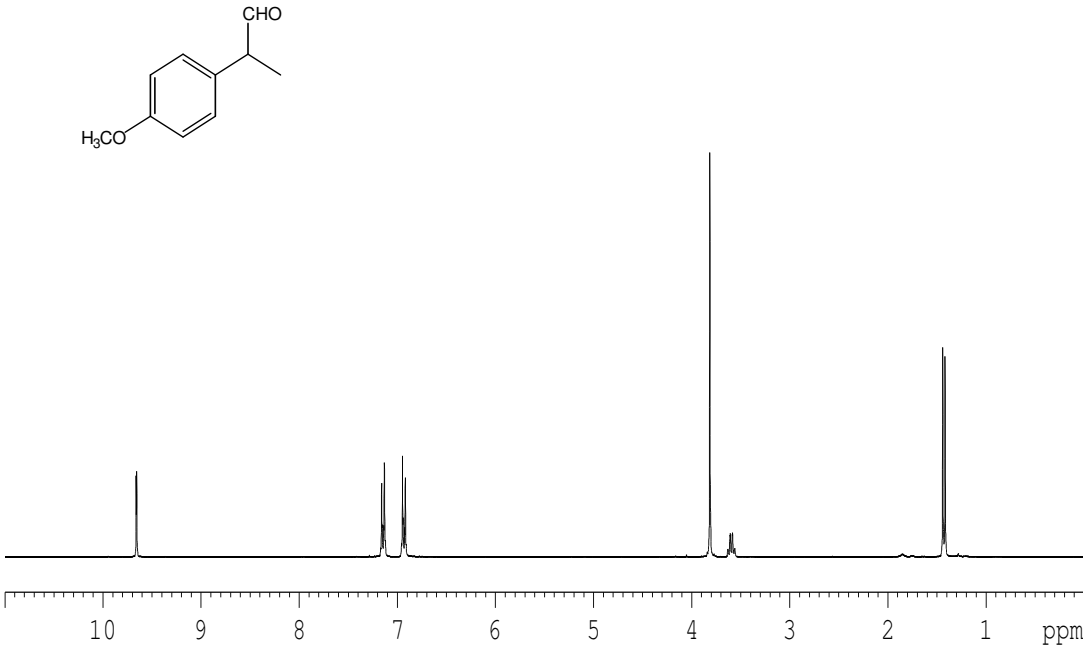
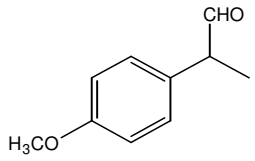


Table 1/ 2b, ^{13}C NMR (in $CDCl_3$)



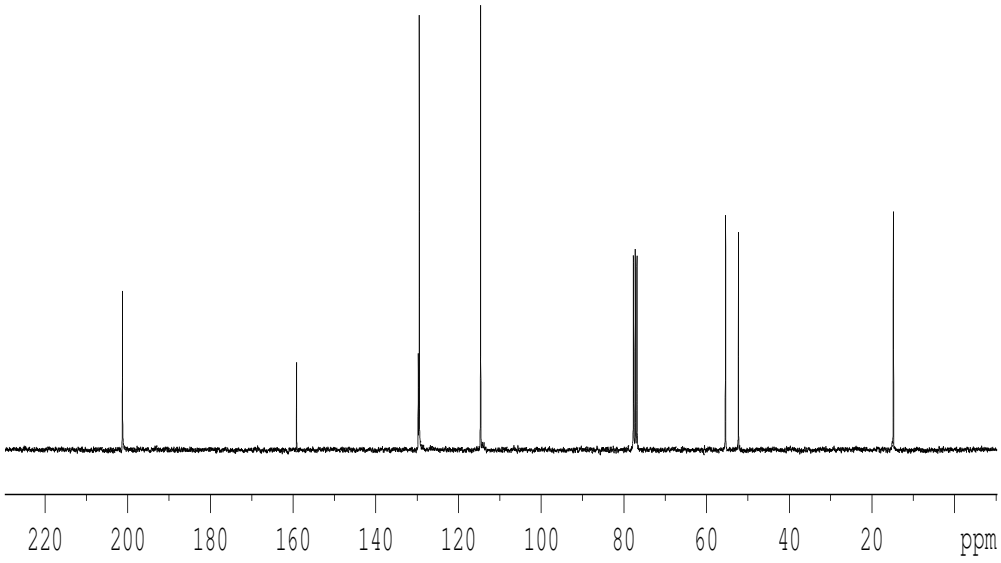
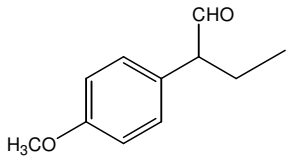


Table 1/ 3b, ^{1}H NMR (in $CDCl_3$)



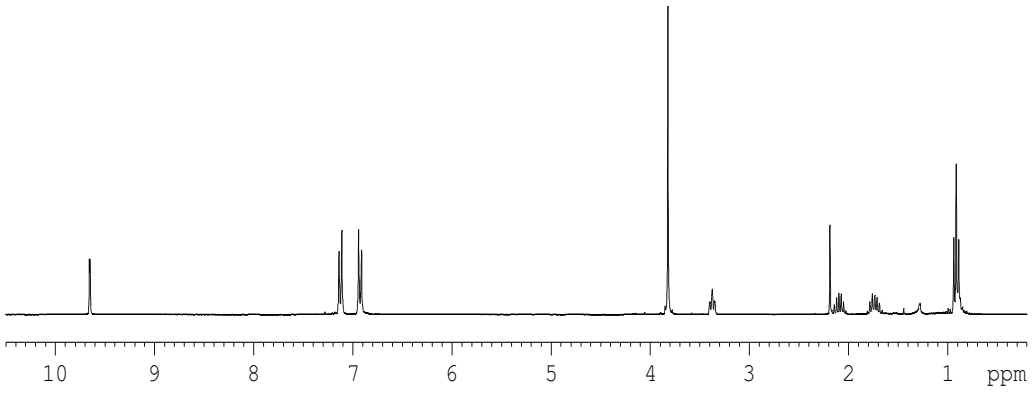
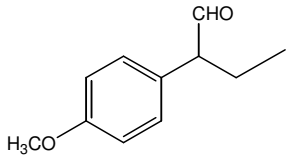


Table 1/ 3b, ^{13}C NMR (in $CDCl_3$)



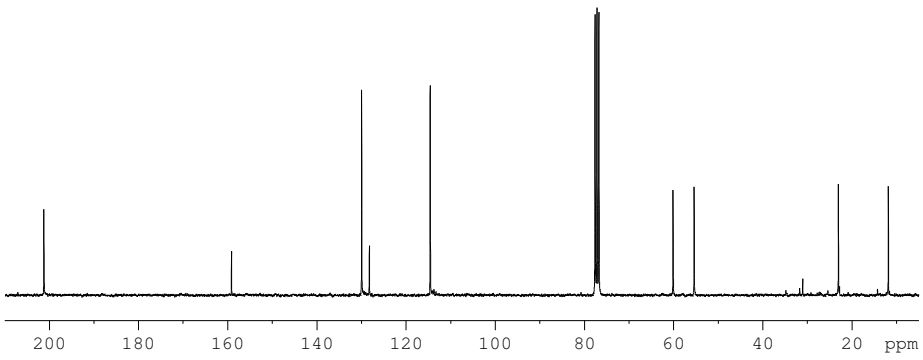
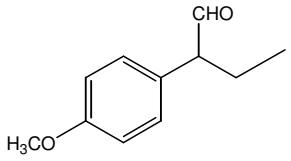


Table 1/ 3b, HRMS Spectrum



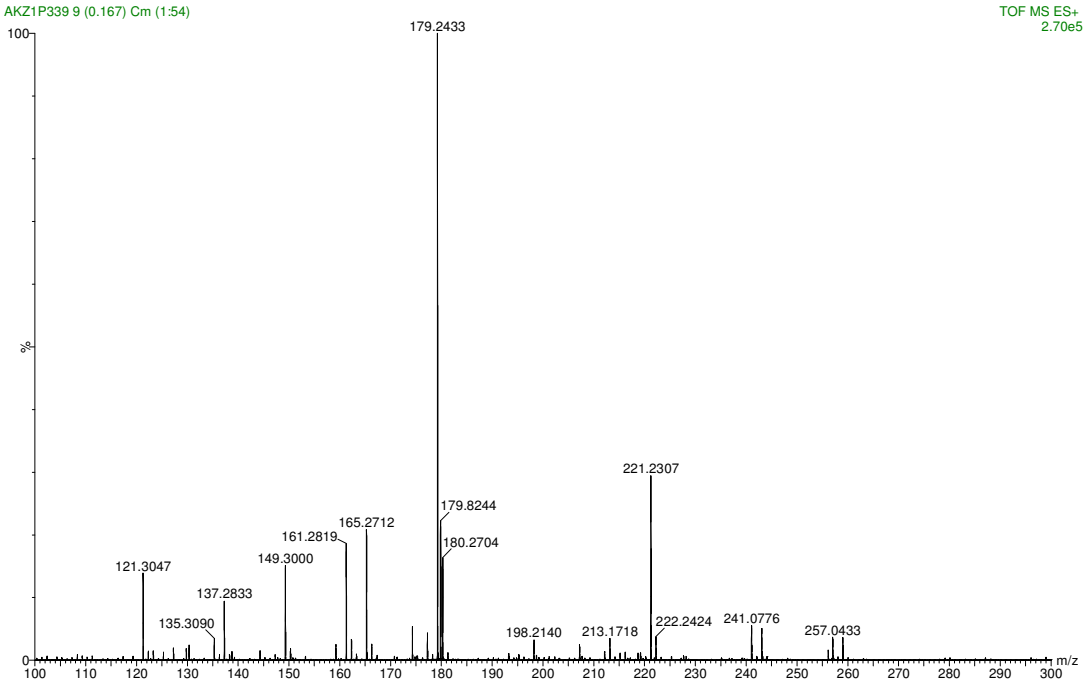
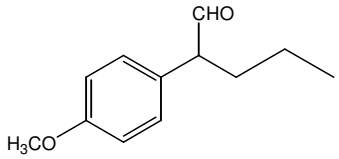


Table 1/ 4b, ^{1}H NMR (in $CDCl_3$)



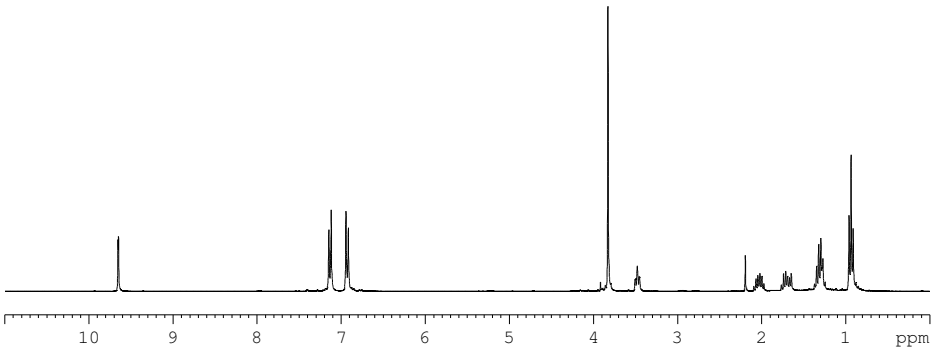
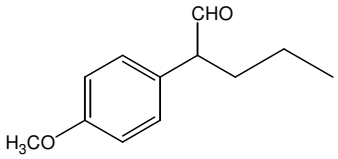


Table 1/ 4b, ^{13}C NMR (in $CDCl_3$)



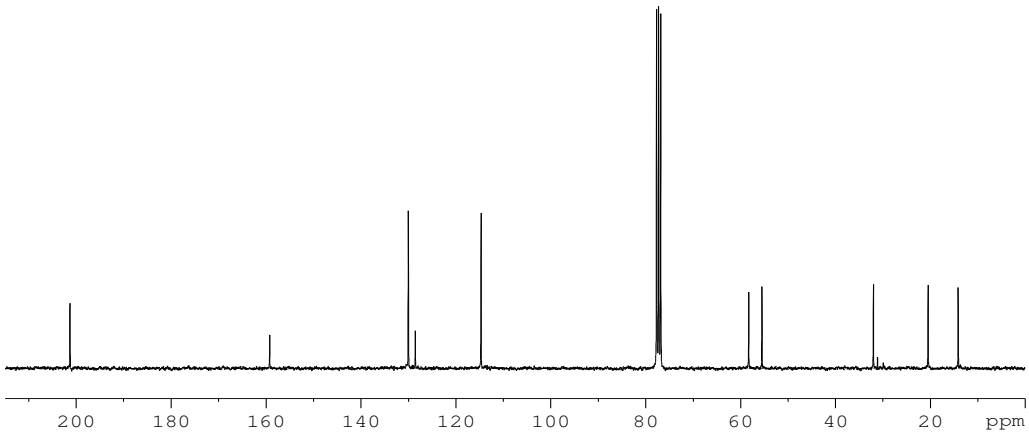
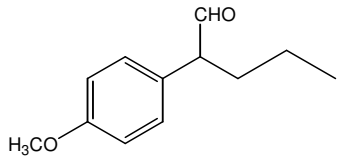


Table 1/ 4b, HRMS Spectrum



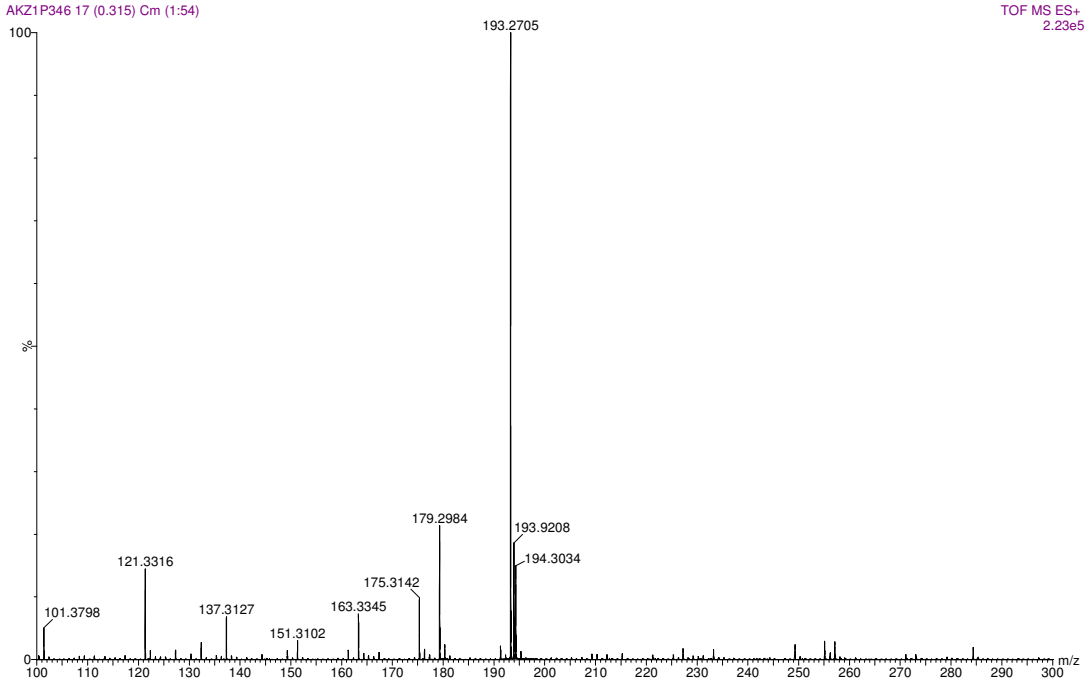


Table 1/ 5b, ^{1}H NMR (in $CDCl_3$)

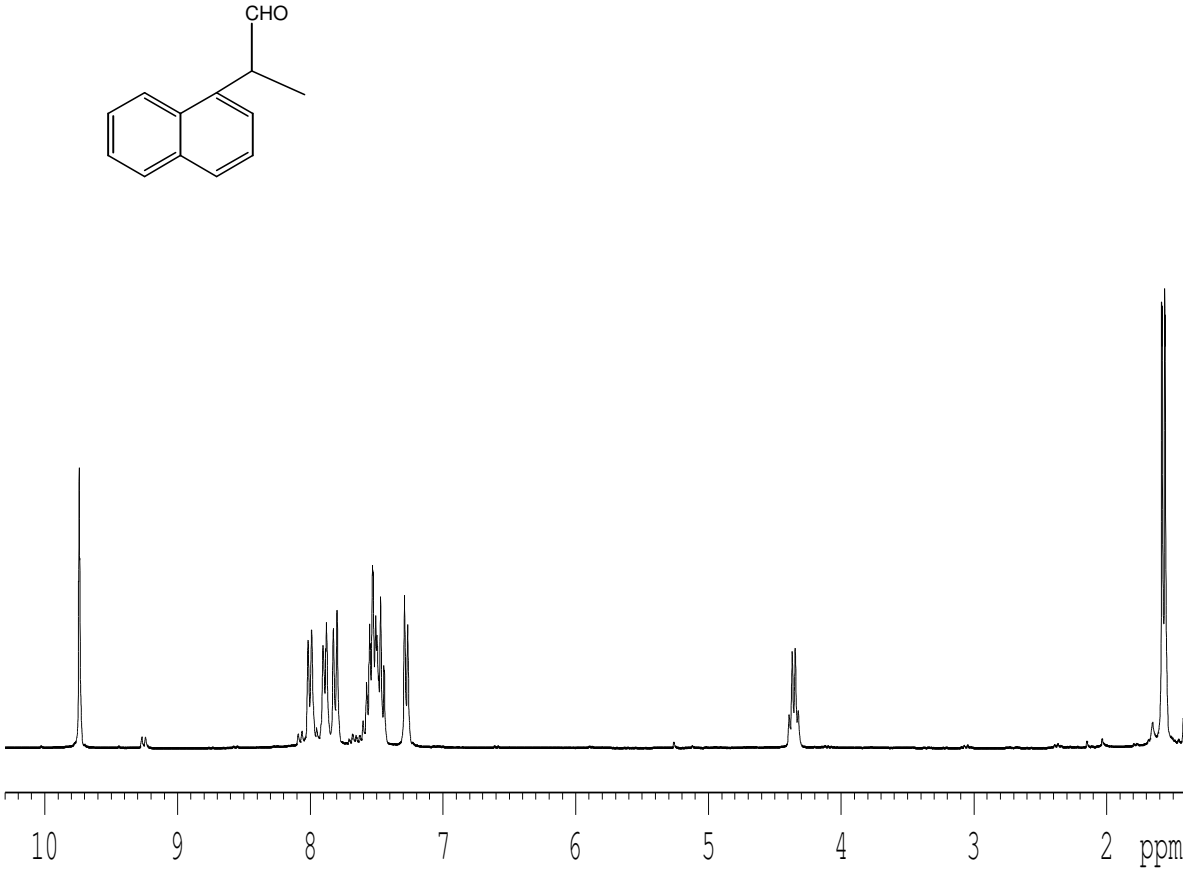


Table 1/ 5b, ^{13}C NMR (in $CDCl_3$)

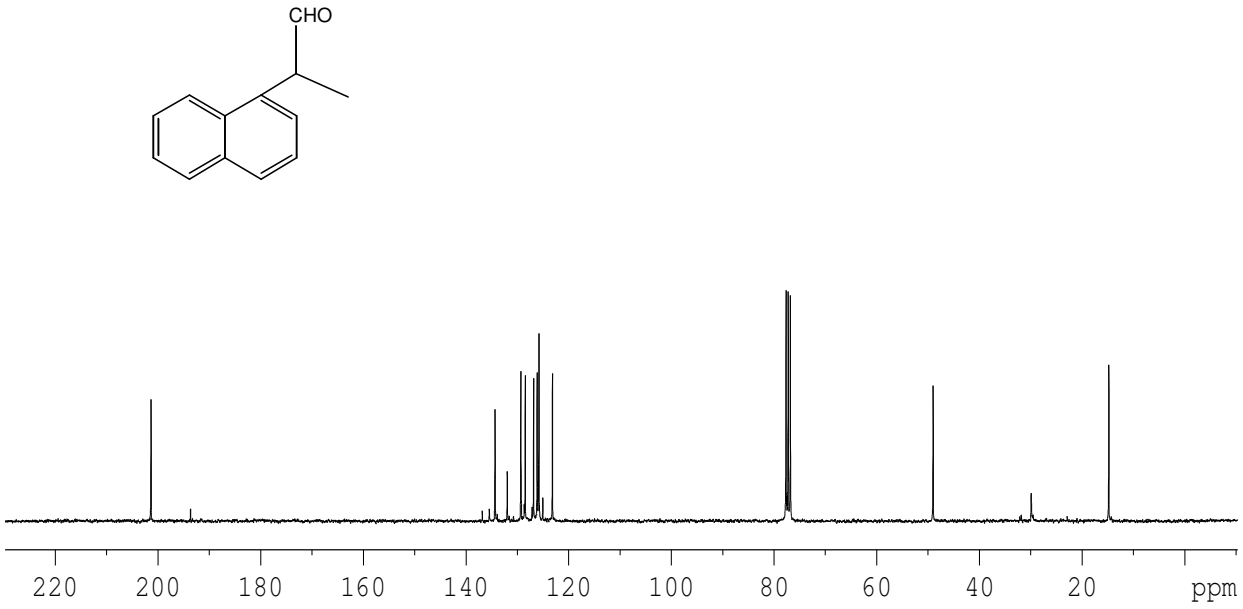
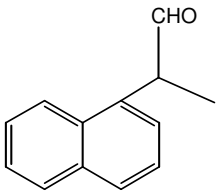


Table 1/ 5b, HRMS SPECTRUM



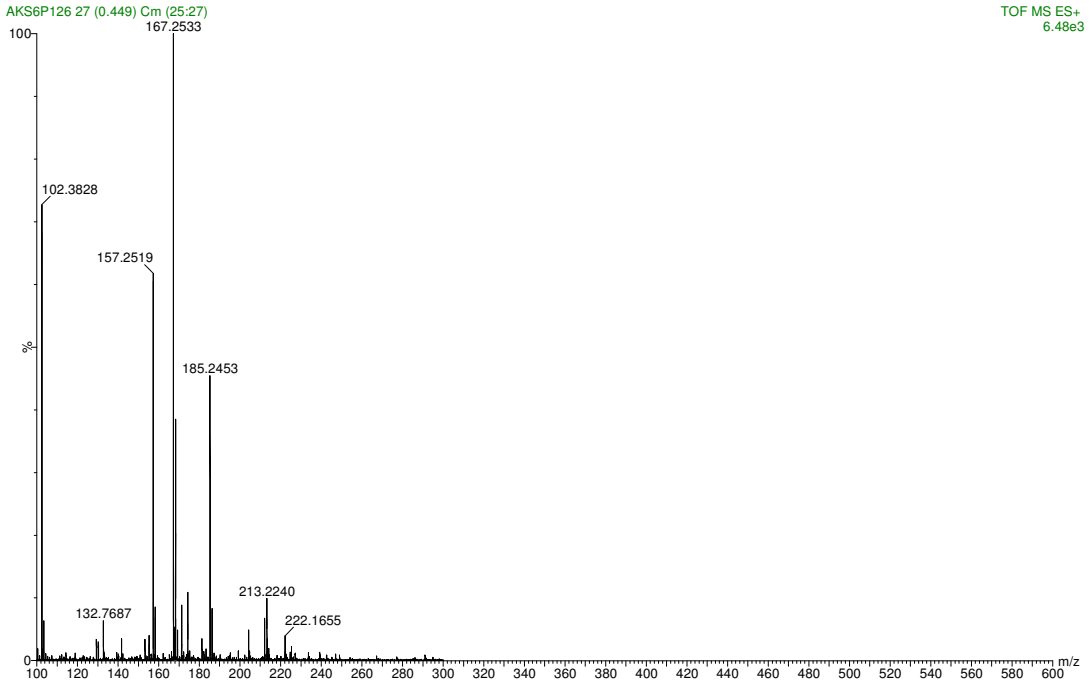
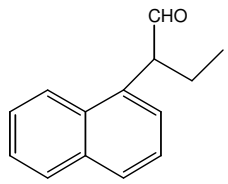


Table 1/ 6b, ^{1}H NMR (in $CDCl_3$)



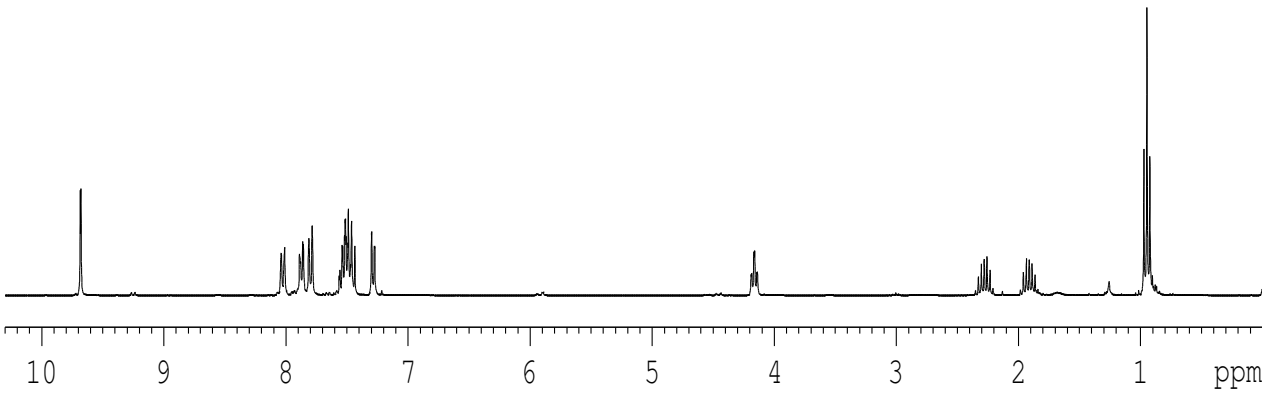


Table 1/ 6b, ^{13}C NMR (in $CDCl_3$)

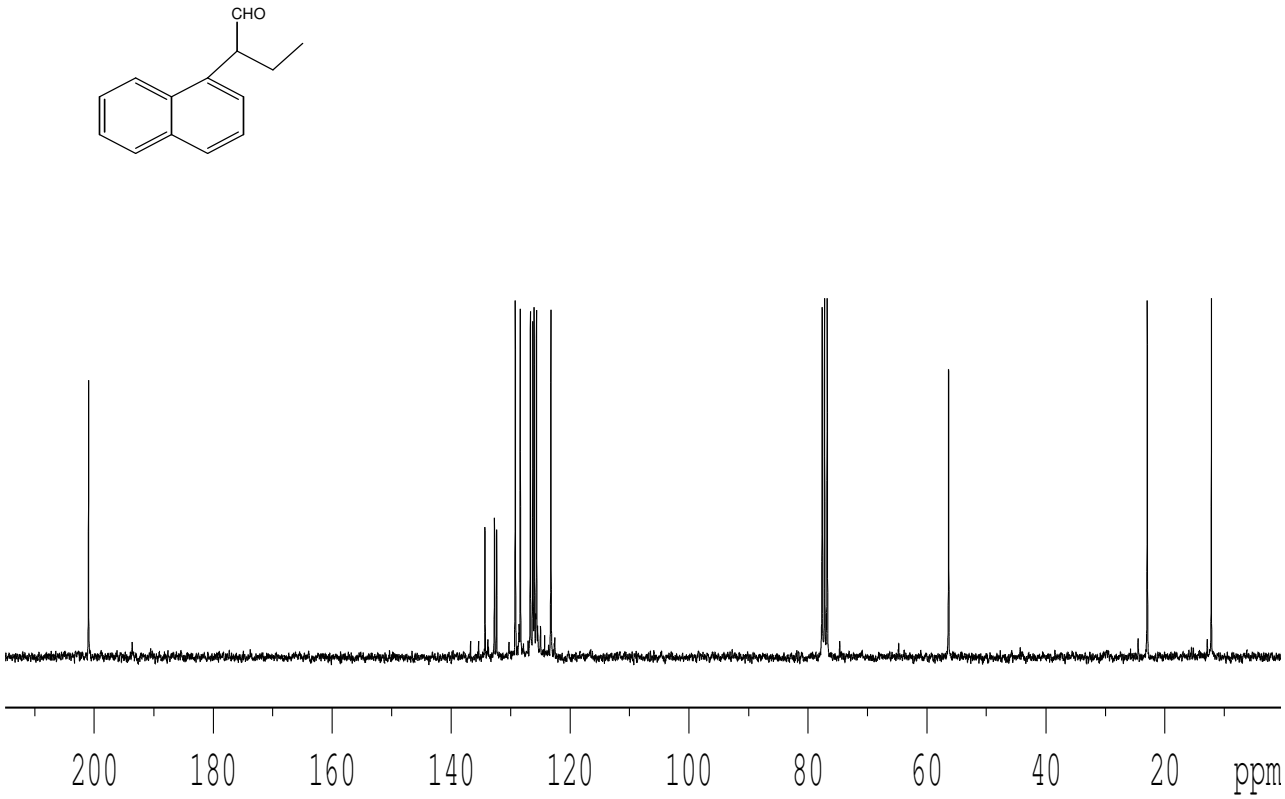
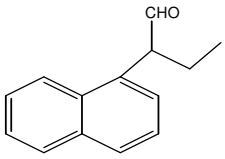


Table 1/ 6b, HRMS SPECTRUM



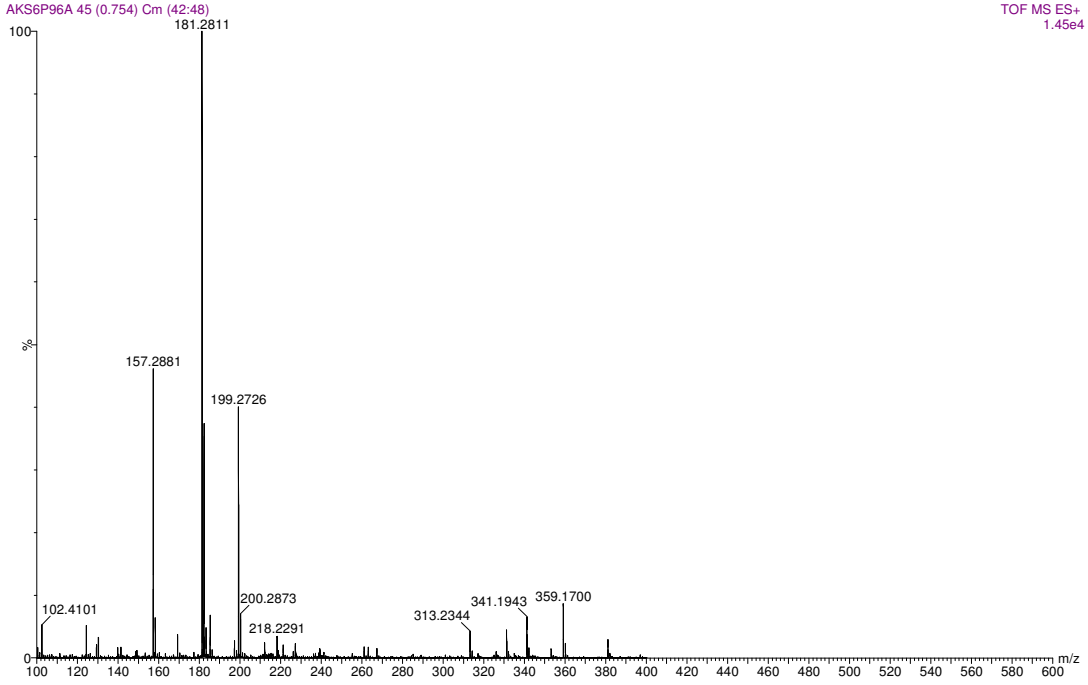


Table 1/ 7b, ^{1}H NMR (in $CDCl_3$)

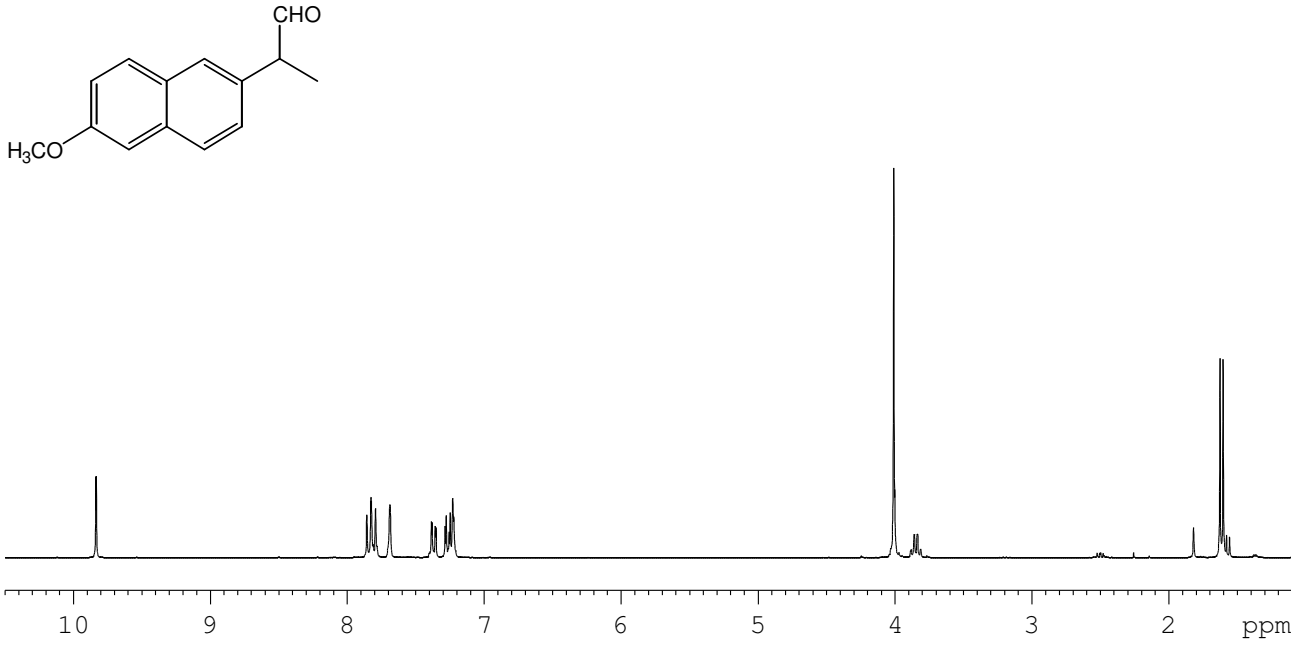
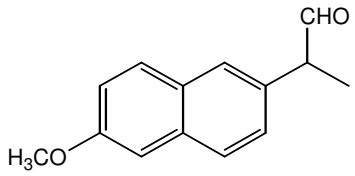


Table 1/ 7b, ^{13}C NMR (in $CDCl_3$)



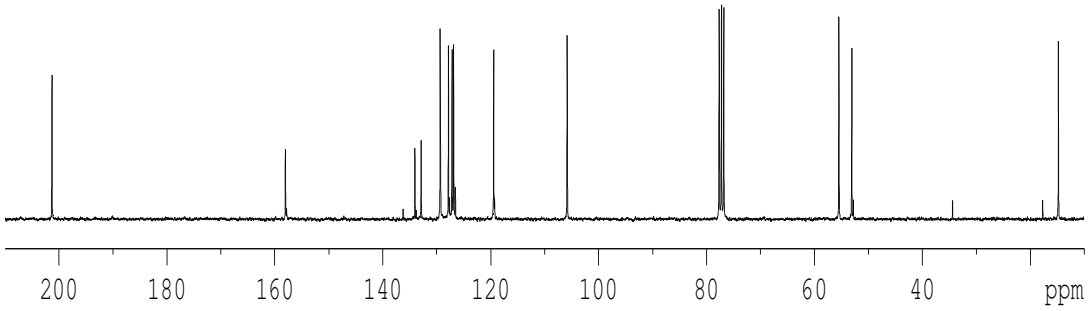
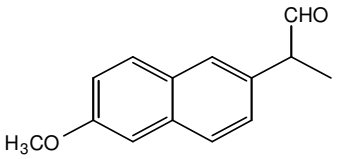


Table 1/ 7b, HRMS SPECTRUM



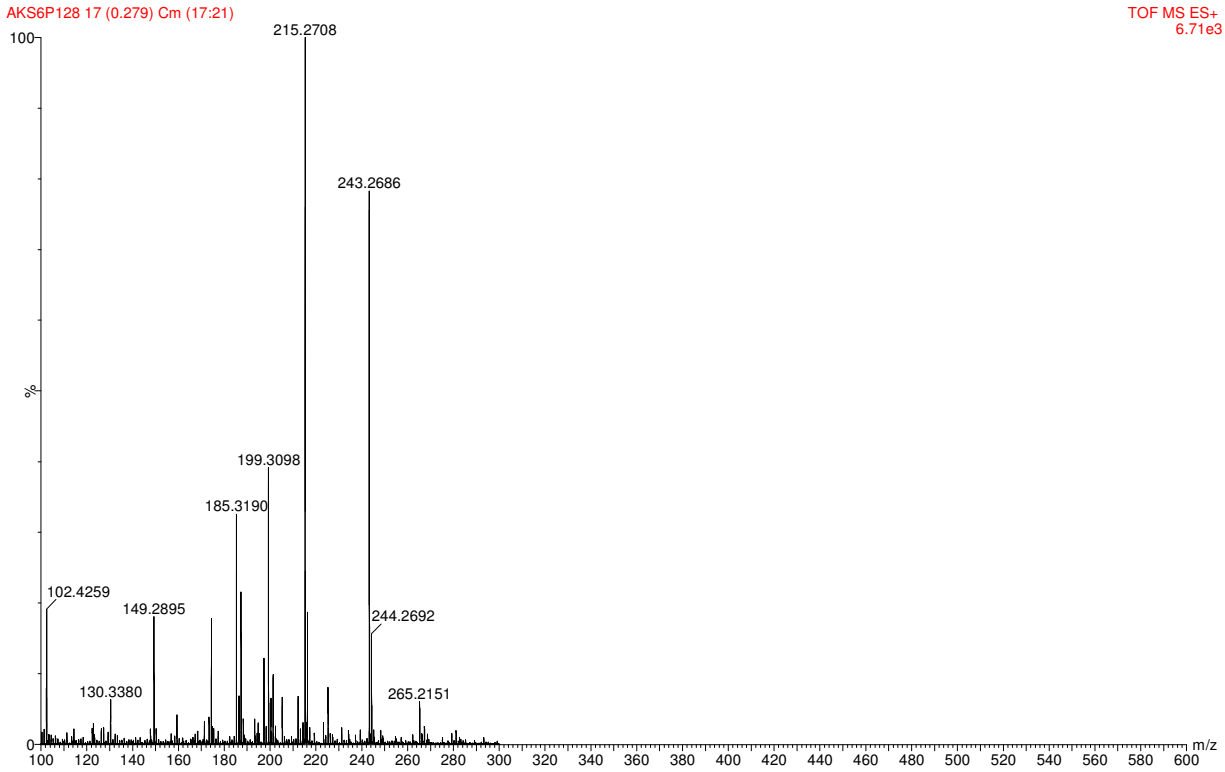


Table 1/ 7c, ^{1}H NMR (in MeOD)

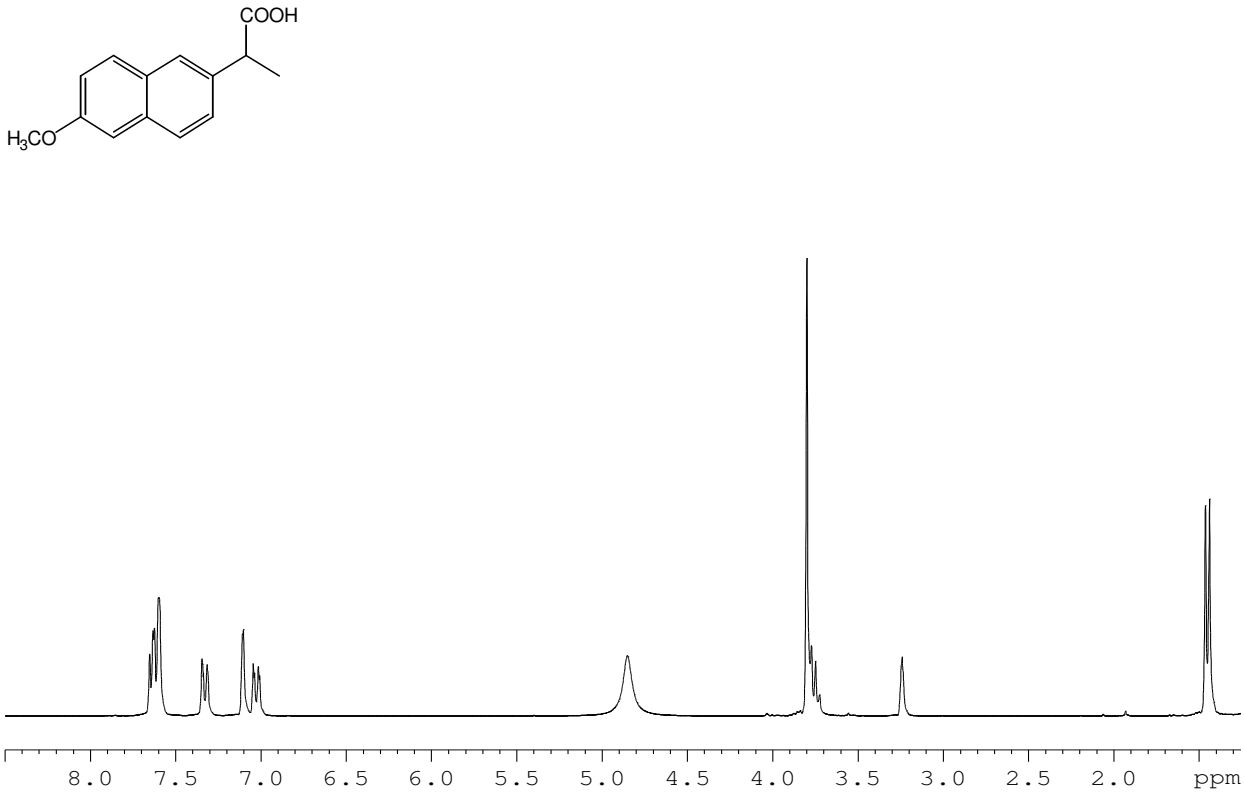


Table 1/ 7c, ^{13}C NMR (in MeOD)

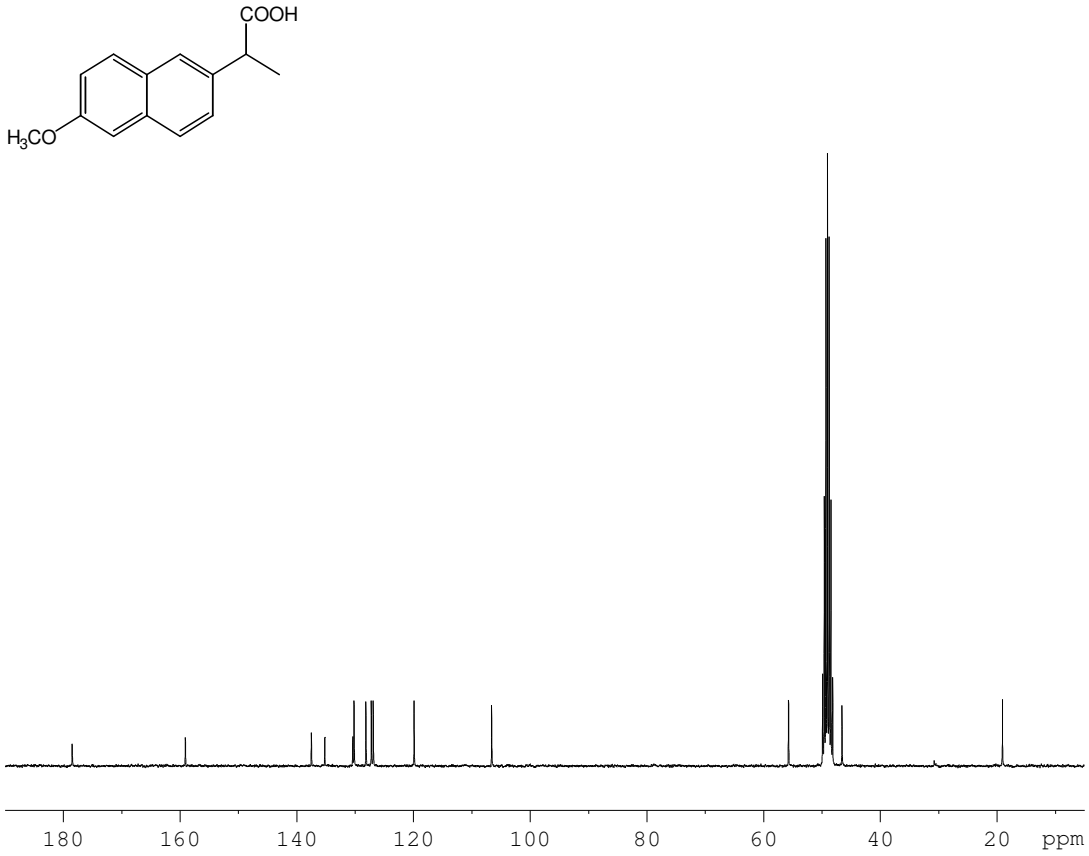
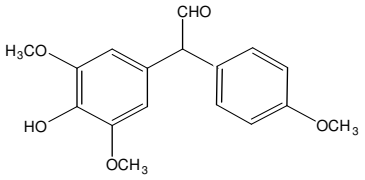


Table 1/ 8b, ^{1}H NMR (in $CDCl_3$)



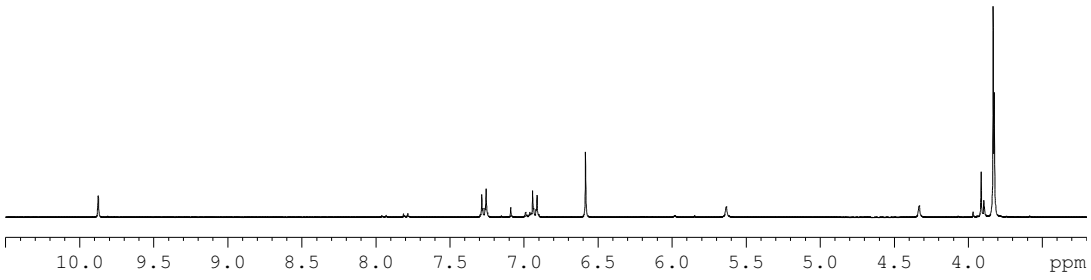


Table 1/ 8b, ^{13}C NMR (in $CDCl_3$)

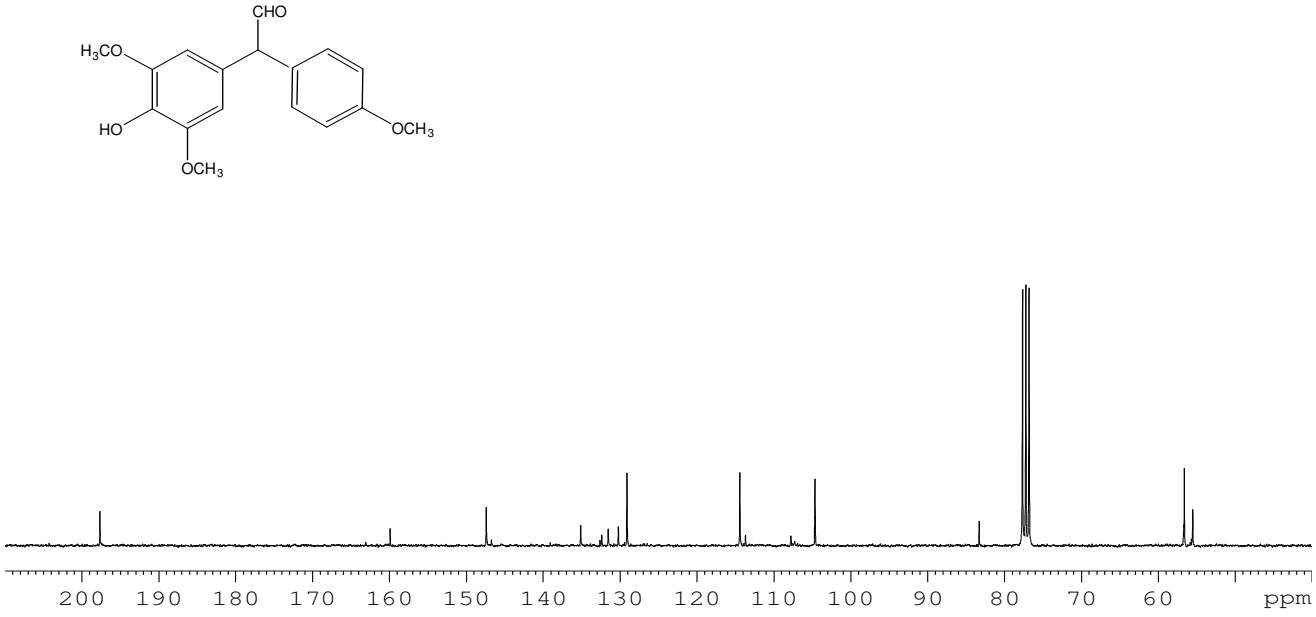
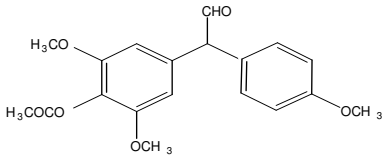


Table 1/ 8b, HRMS SPECTRUM



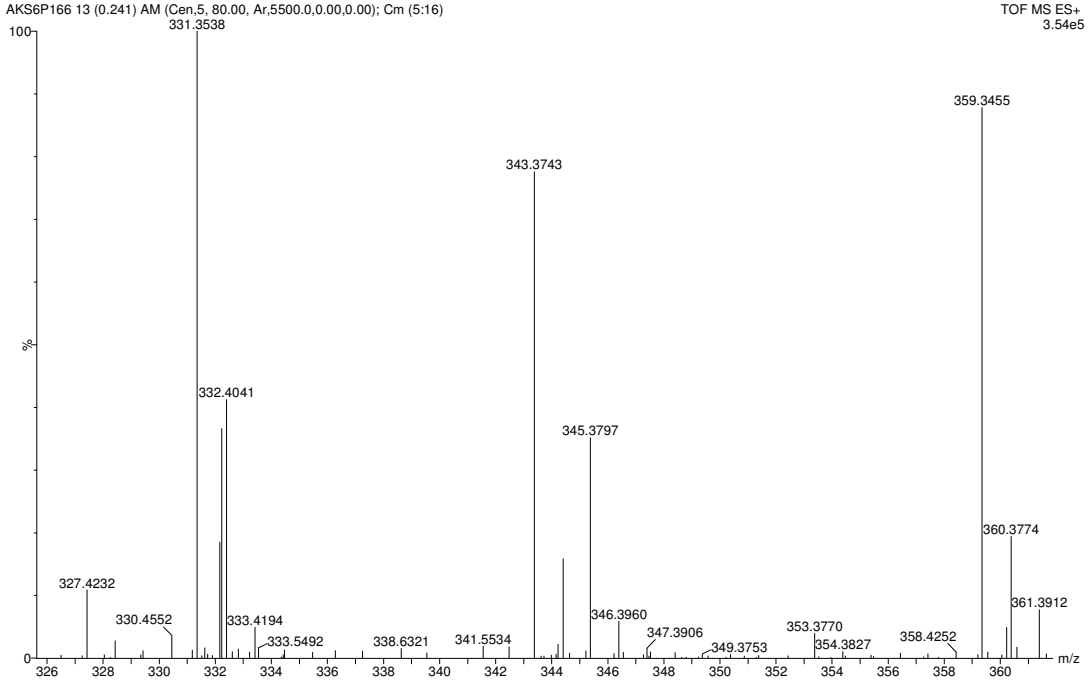


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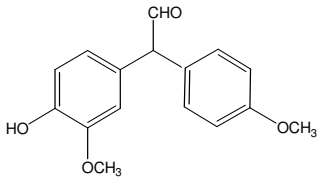
Table 1/ 9b, ^{1}H NMR (in $CDCl_3$)



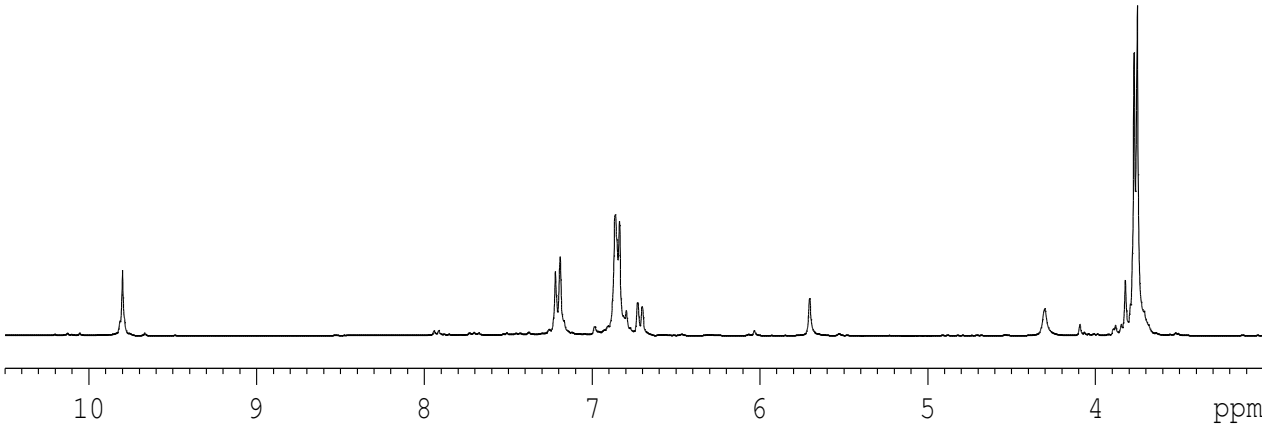
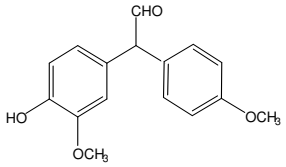


Table 1/ 9b, ^{13}C NMR (in $CDCl_3$)



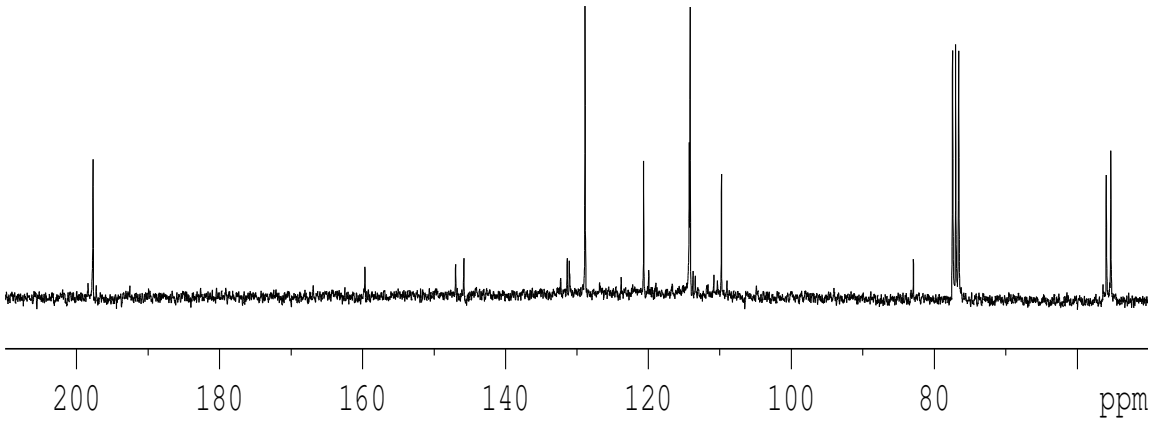
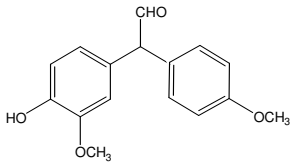


Table 1/ 9b, HRMS SPECTRUM



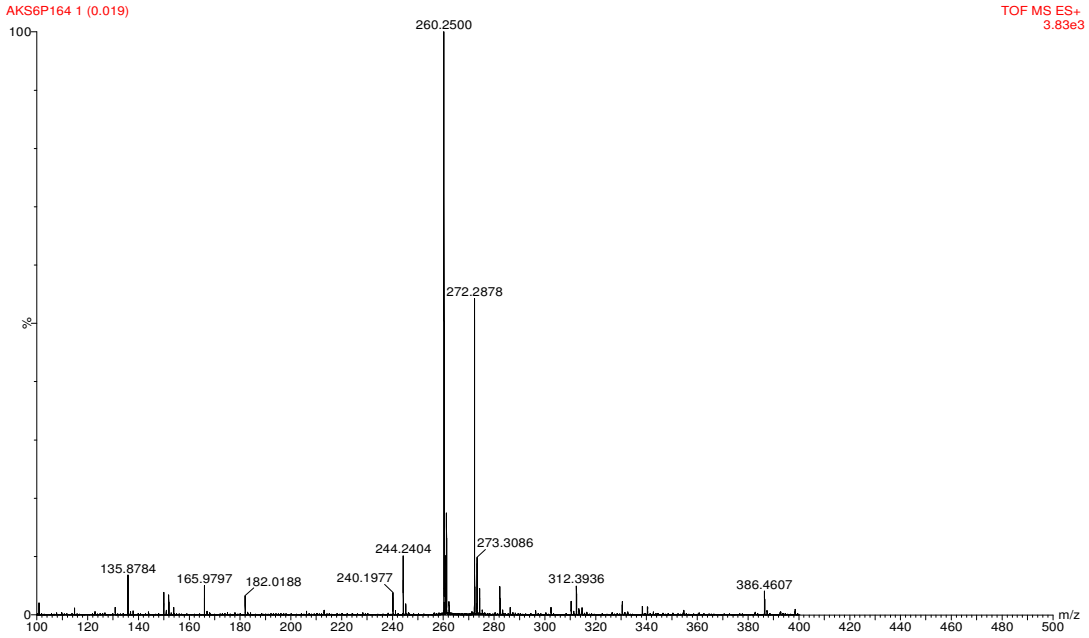
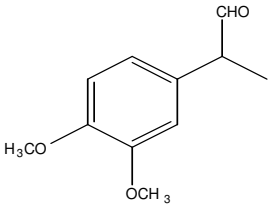


Table 1/ 11b, ^{1}H NMR (in $CDCl_3$)



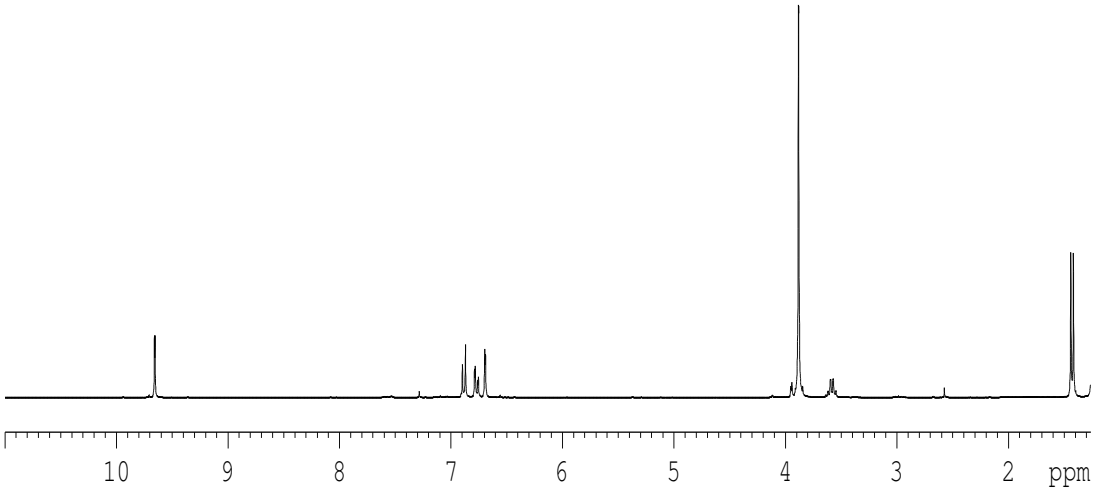
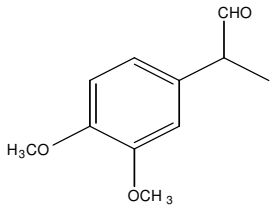


Table 1/ 11b, ^{13}C NMR (in $CDCl_3$)



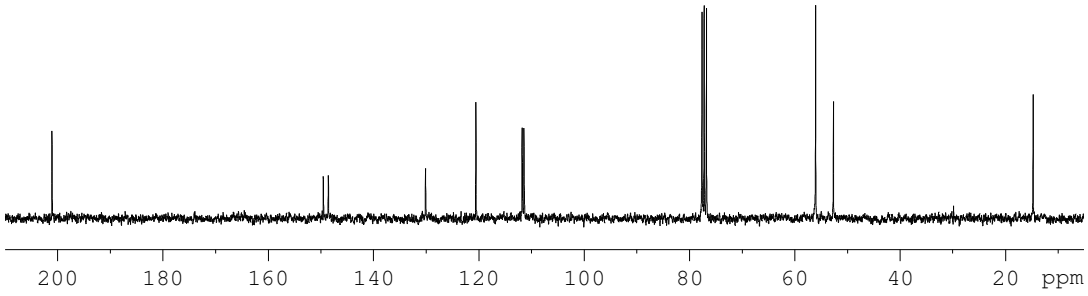
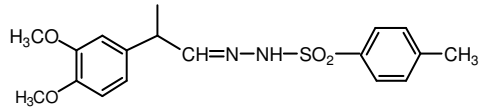


Table 1/ 11c, HRMS Spectrum



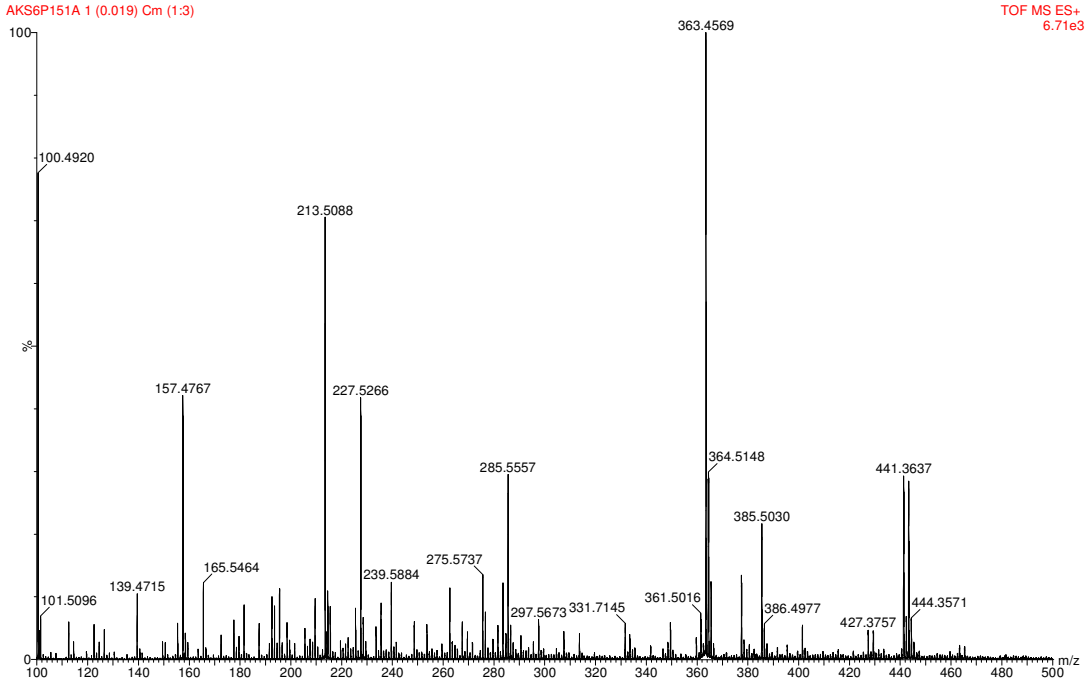
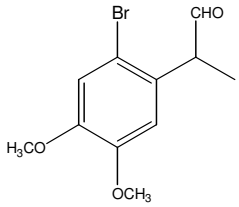


Table 1/ 11b', ^{1}H NMR (in $CDCl_3$)



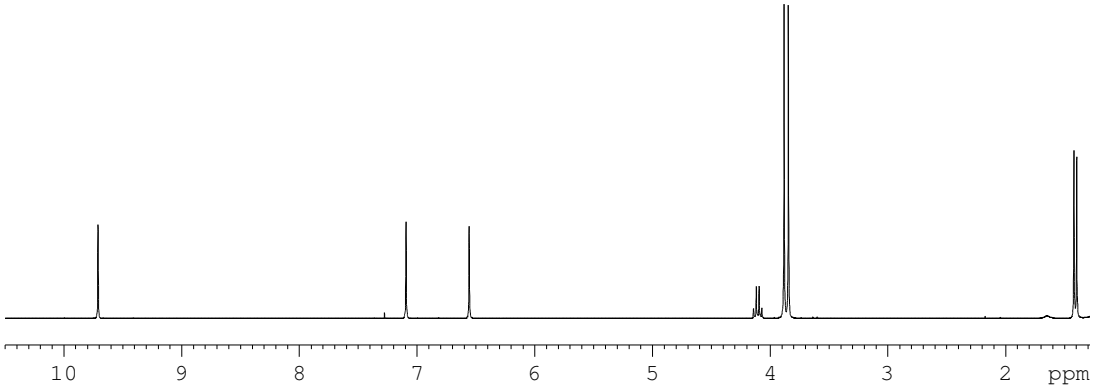
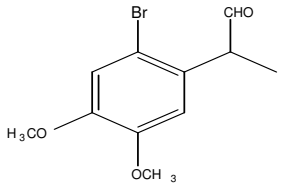


Table 1/ 11b', ^{13}C NMR (in $CDCl_3$)



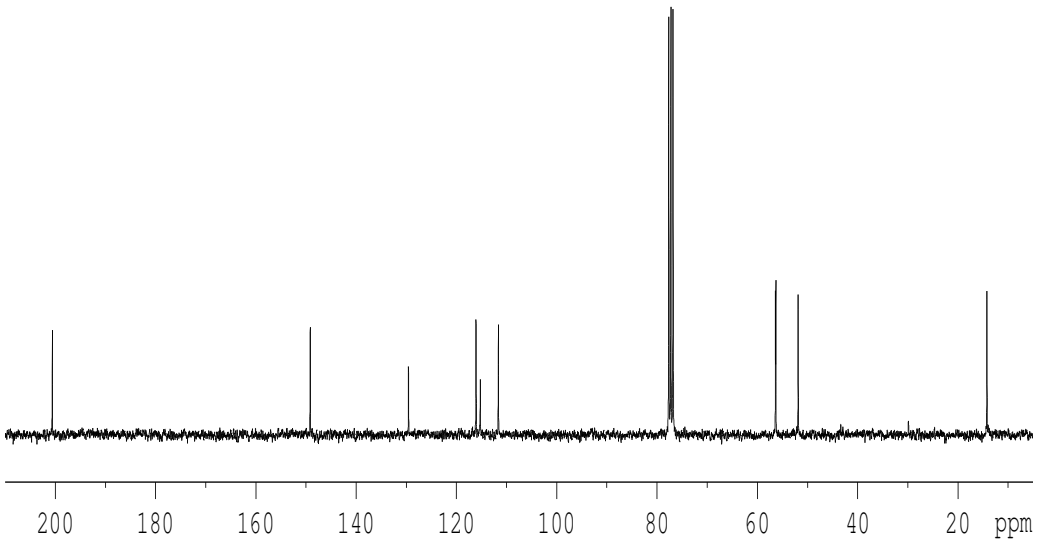


Table 1/ 11b', DEPT NMR (in $CDCl_3$)

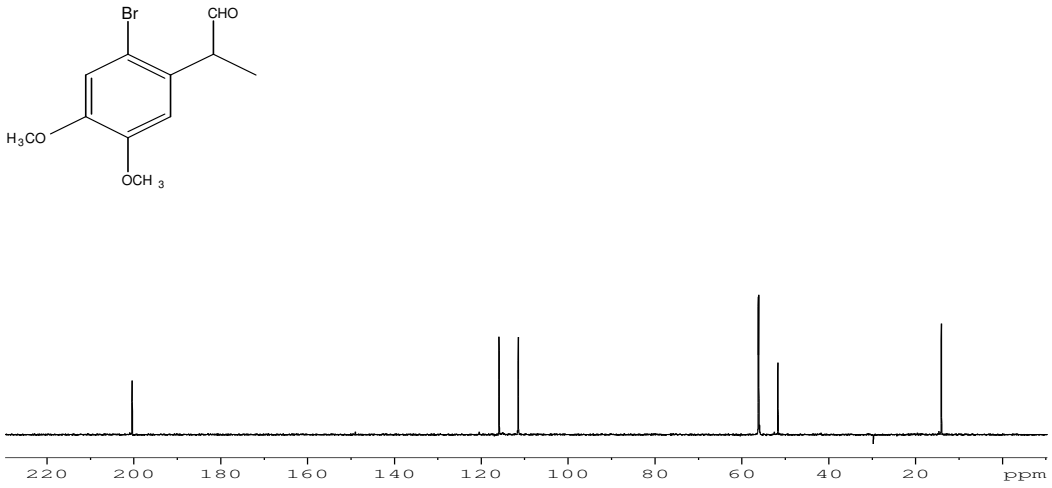
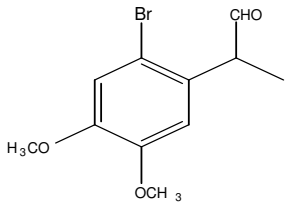


Table 1/ 11b', HMBC (in $CDCl_3$)



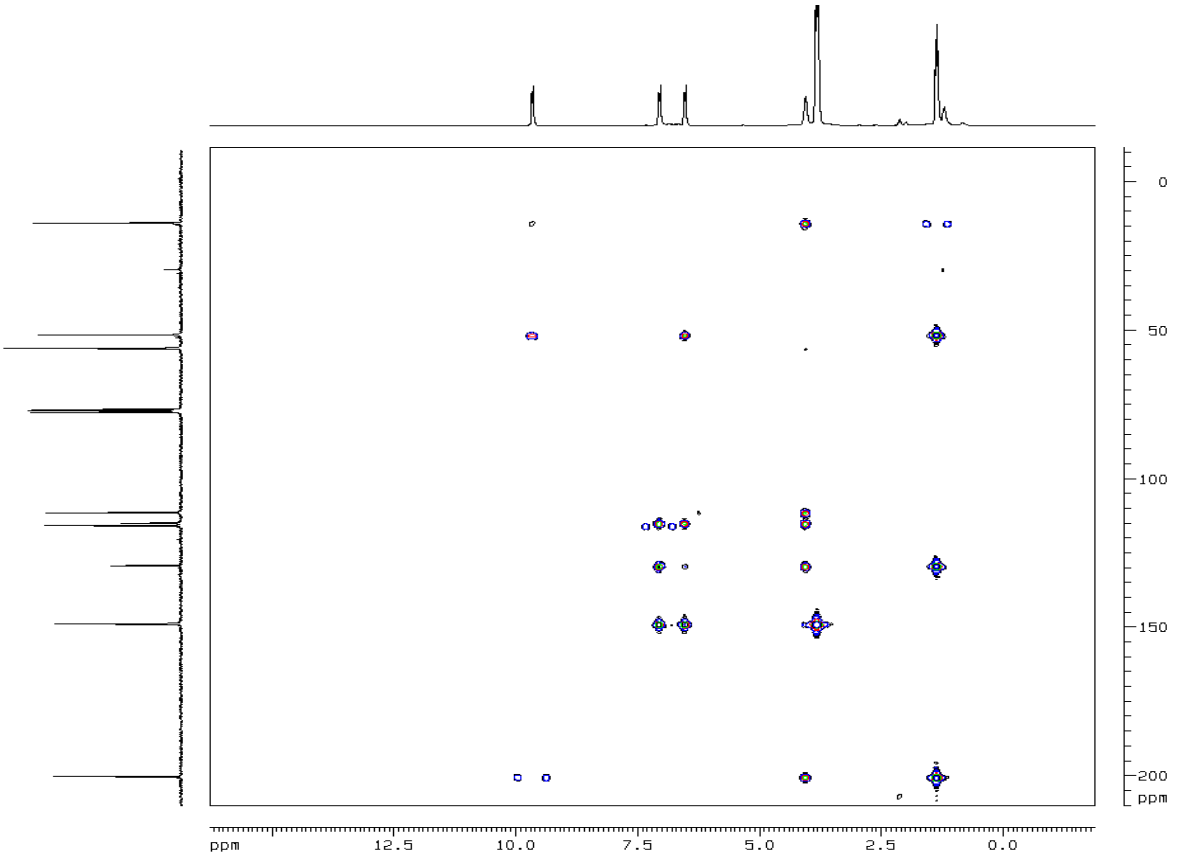


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Table 1/ 11b', HMQC (in $CDCl_3$)

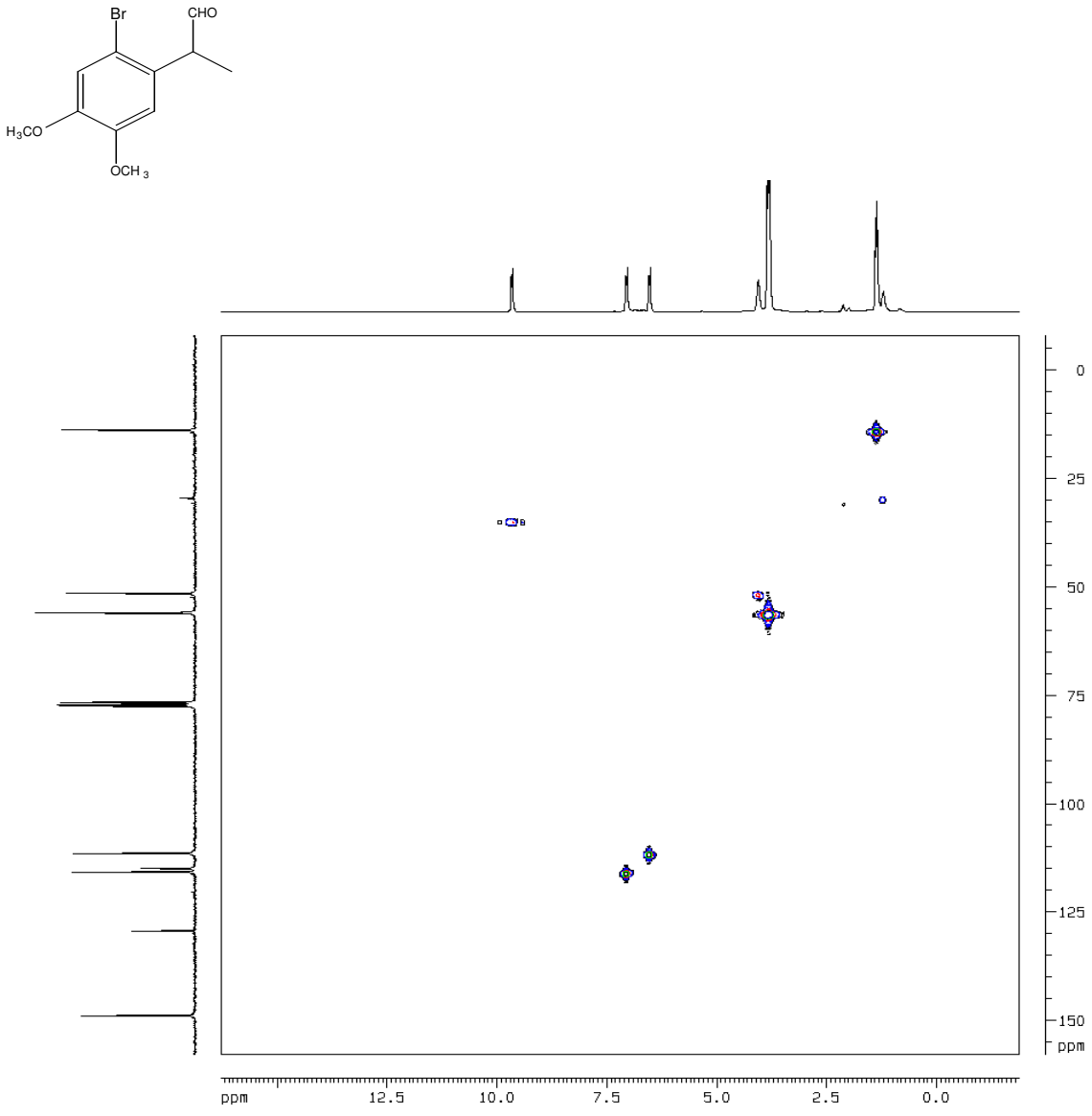
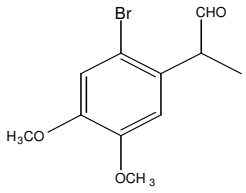


Table 1/ 11b', HRMS spectrum



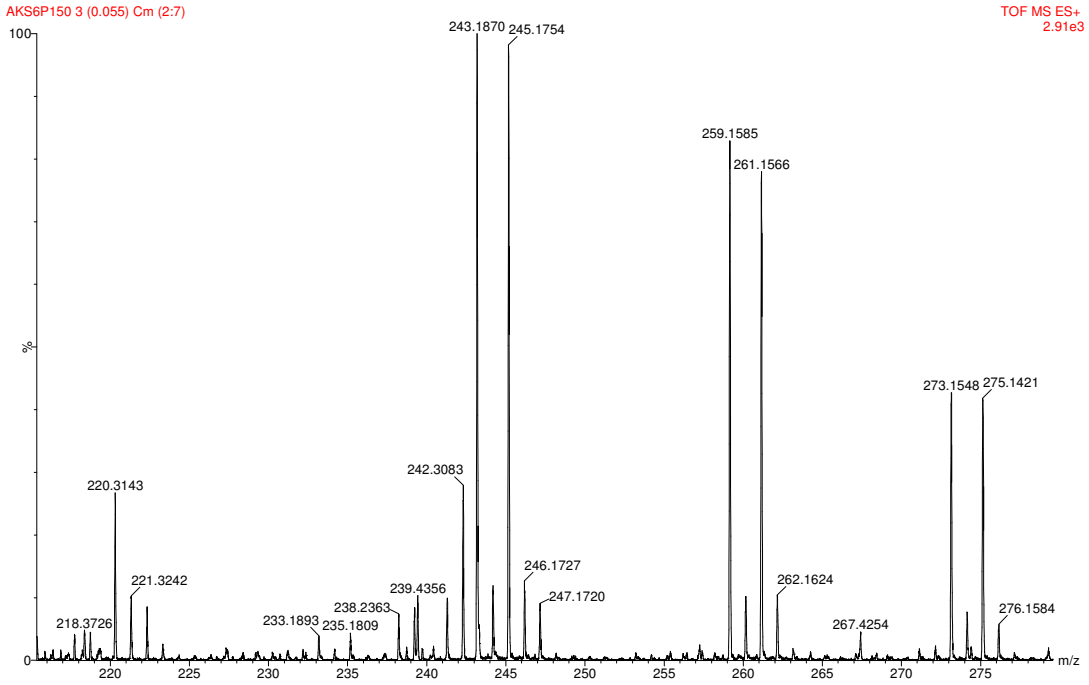
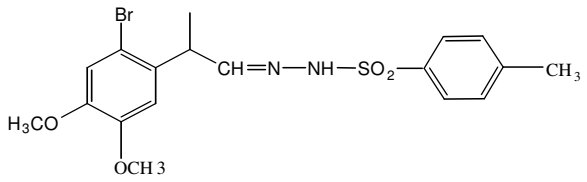


Table 1/ 11c', ^{1}H NMR (in $CDCl_3$)



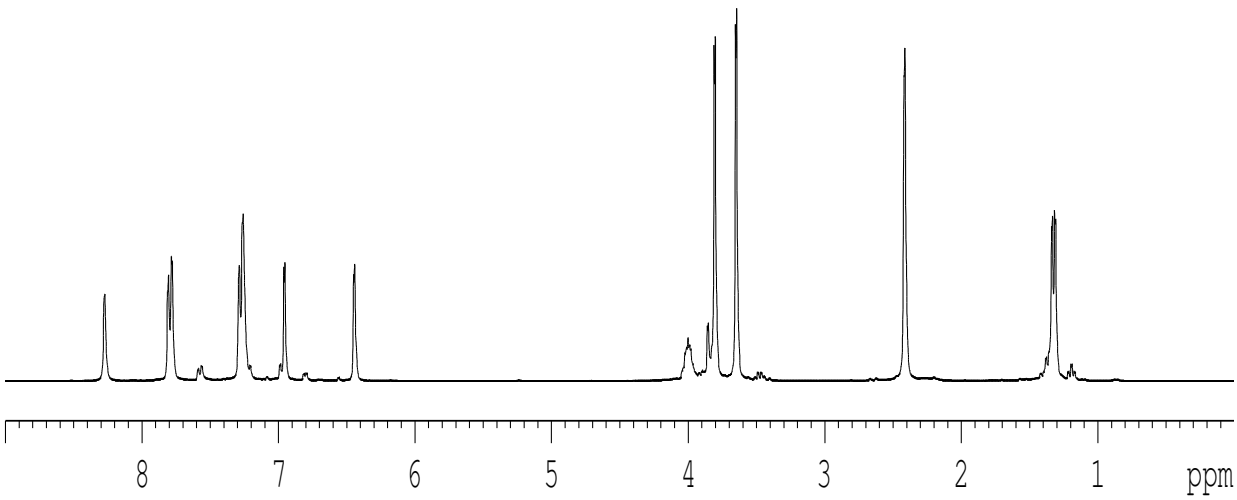
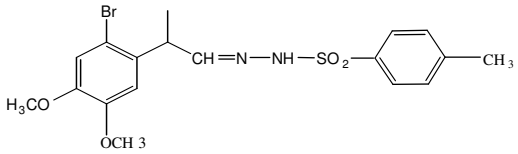


Table 1/ 11c', ^{13}C NMR (in $CDCl_3$)



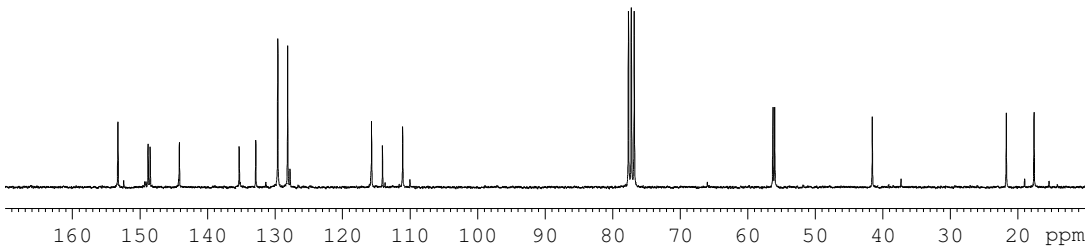
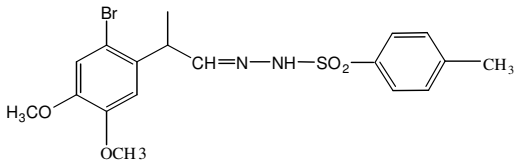


Table 1/ 11c', HRMS spectrum



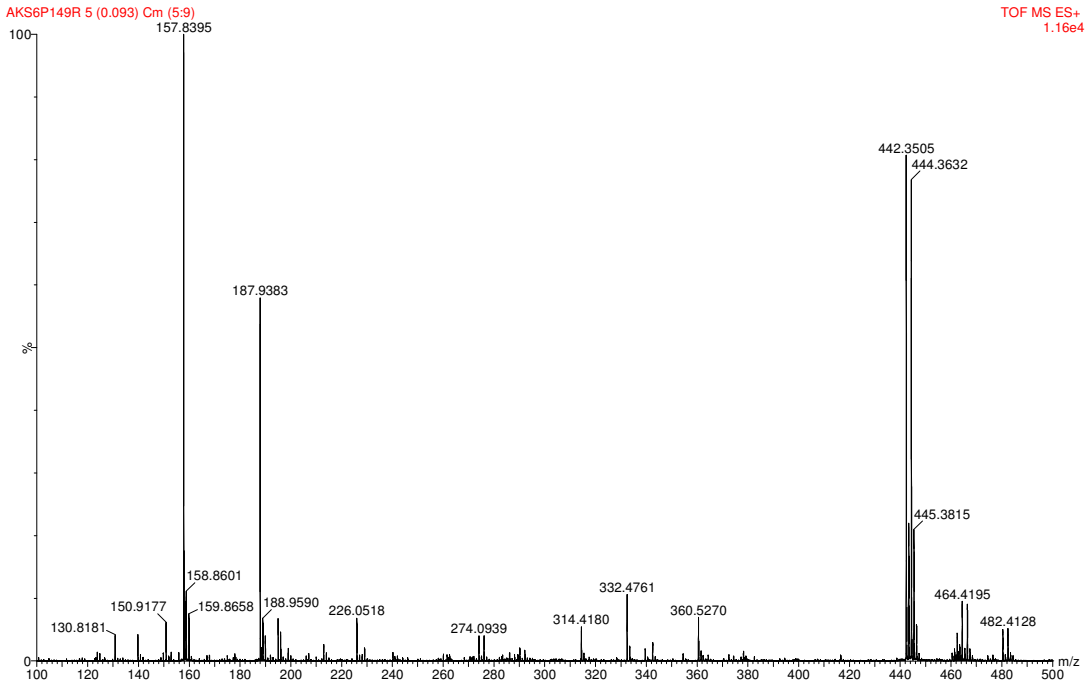
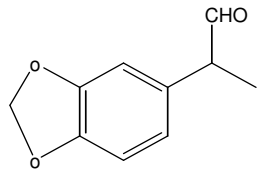


Table 1/ 12b, ^{1}H NMR (in $CDCl_3$)



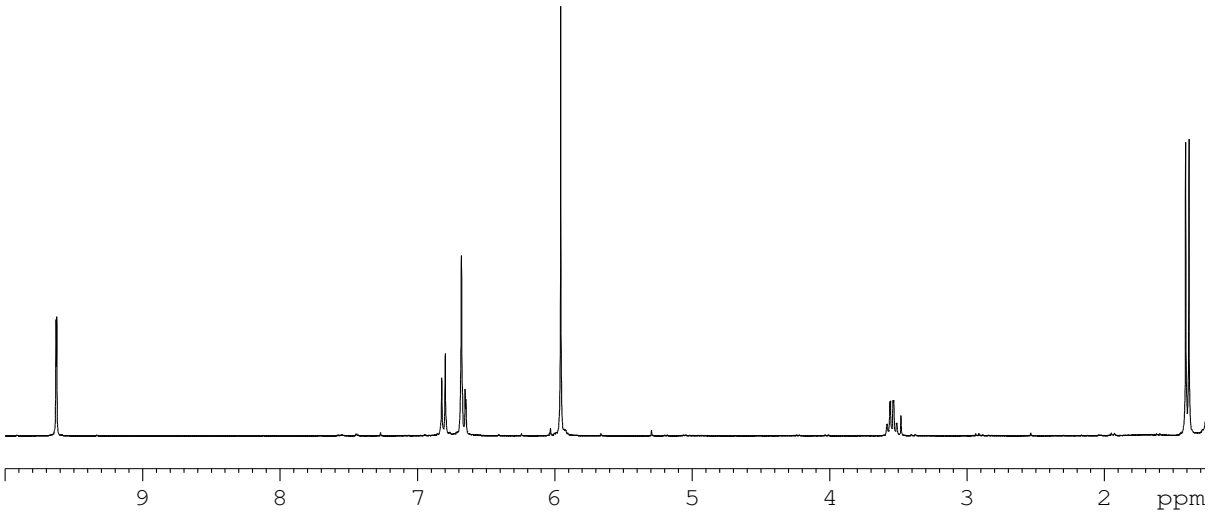
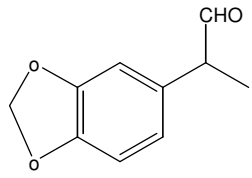


Table 1/ 12b, ^{13}C NMR (in $CDCl_3$)



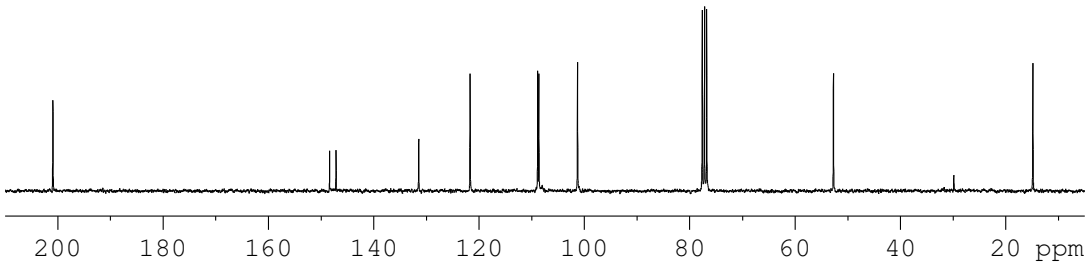
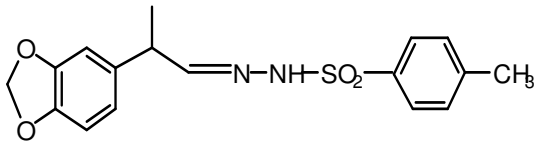


Table 1/12c, HRMS spectrum



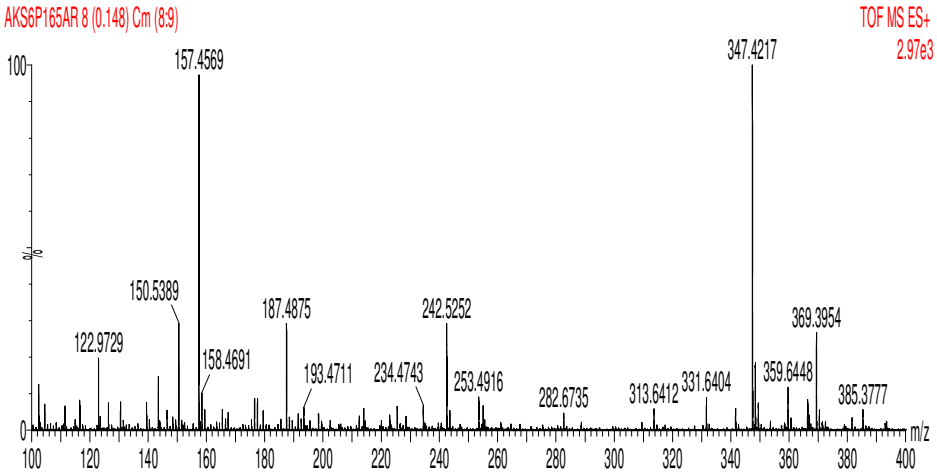
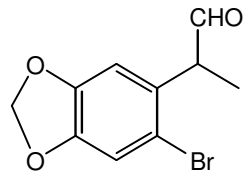


Table 1/ 12b', ^{1}H NMR (in $CDCl_3$)



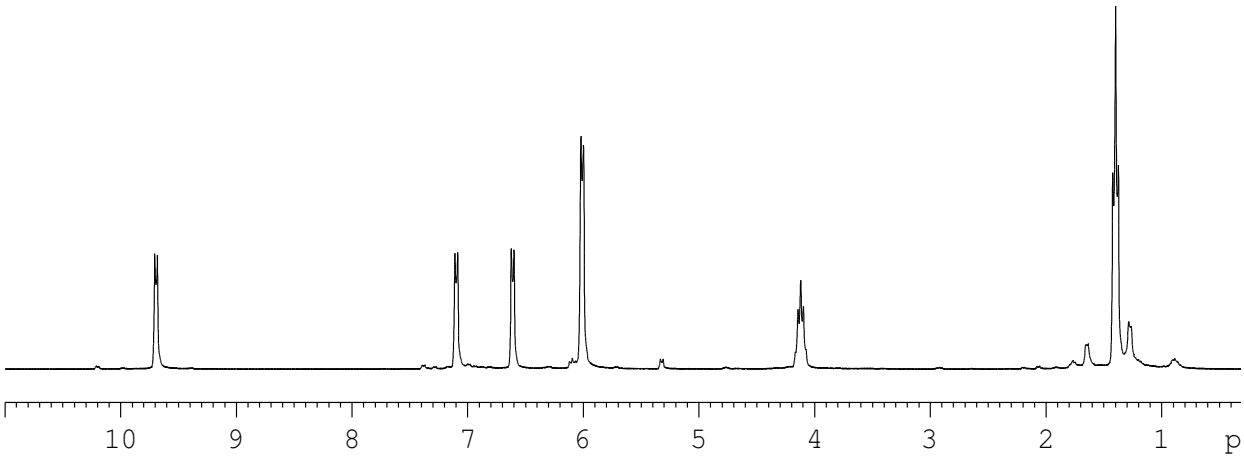
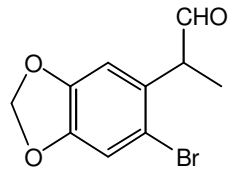


Table 1/ 12b', ^{13}C NMR (in $CDCl_3$)



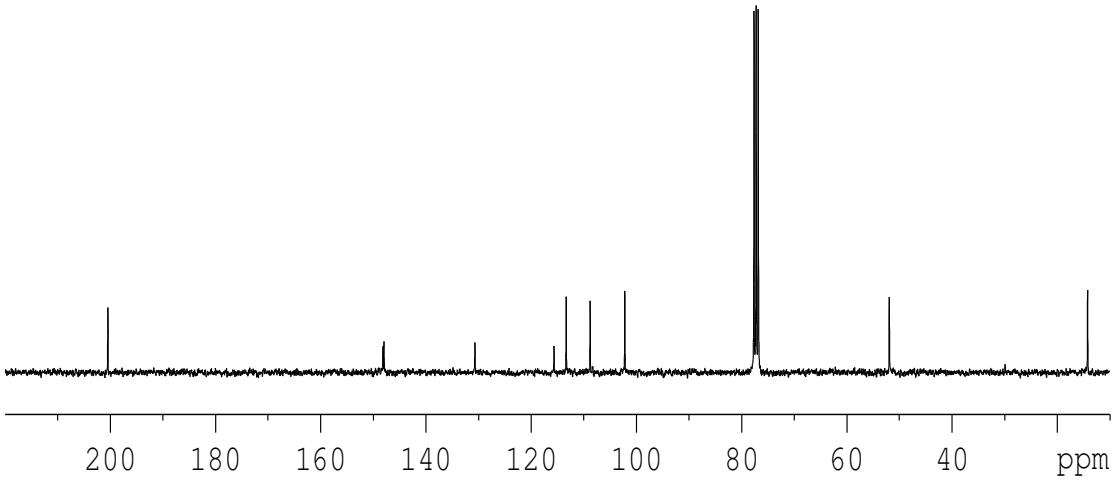
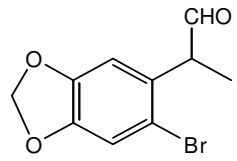


Table 1/ 12b', HMBC (in $CDCl_3$)



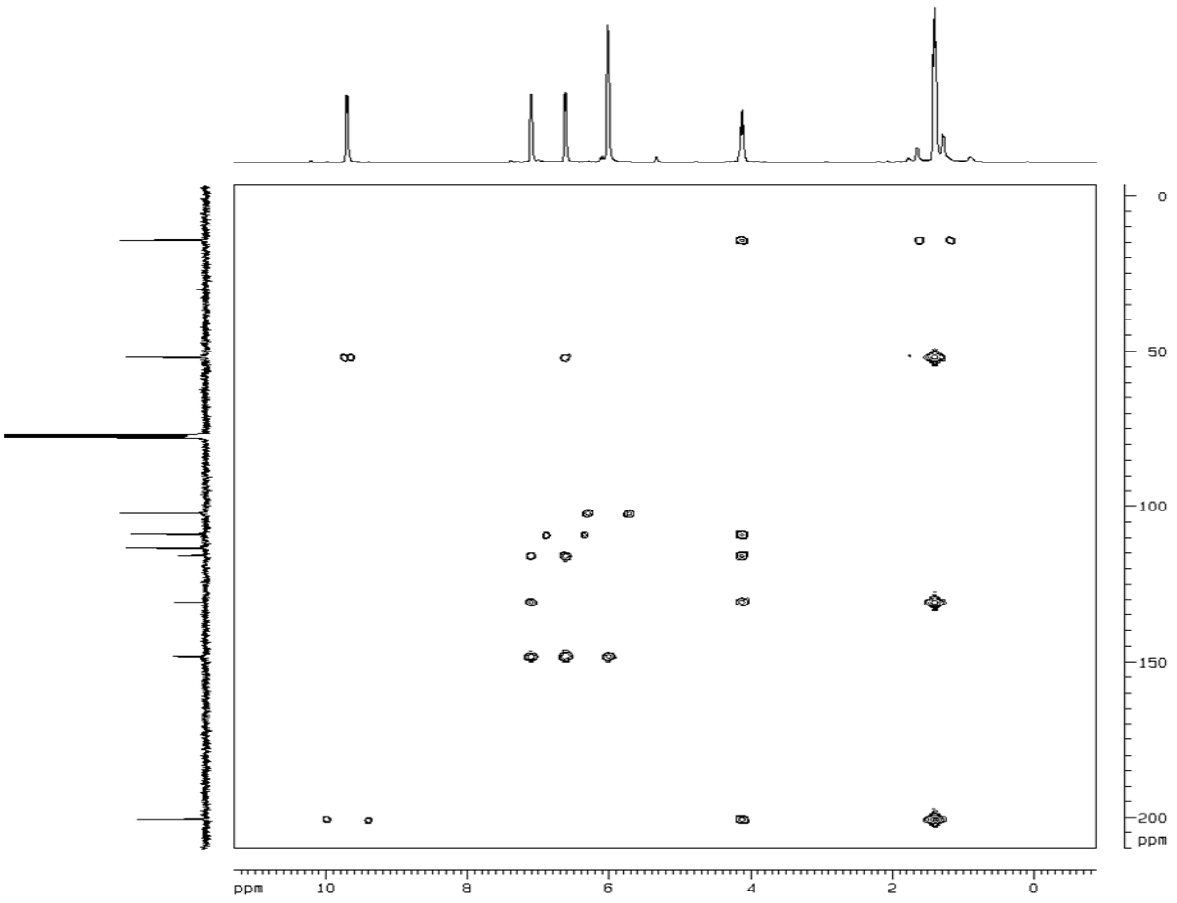
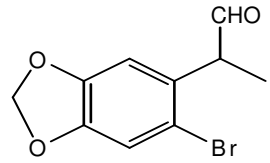


Table 1/ 12b', HMQC (in $CDCl_3$)



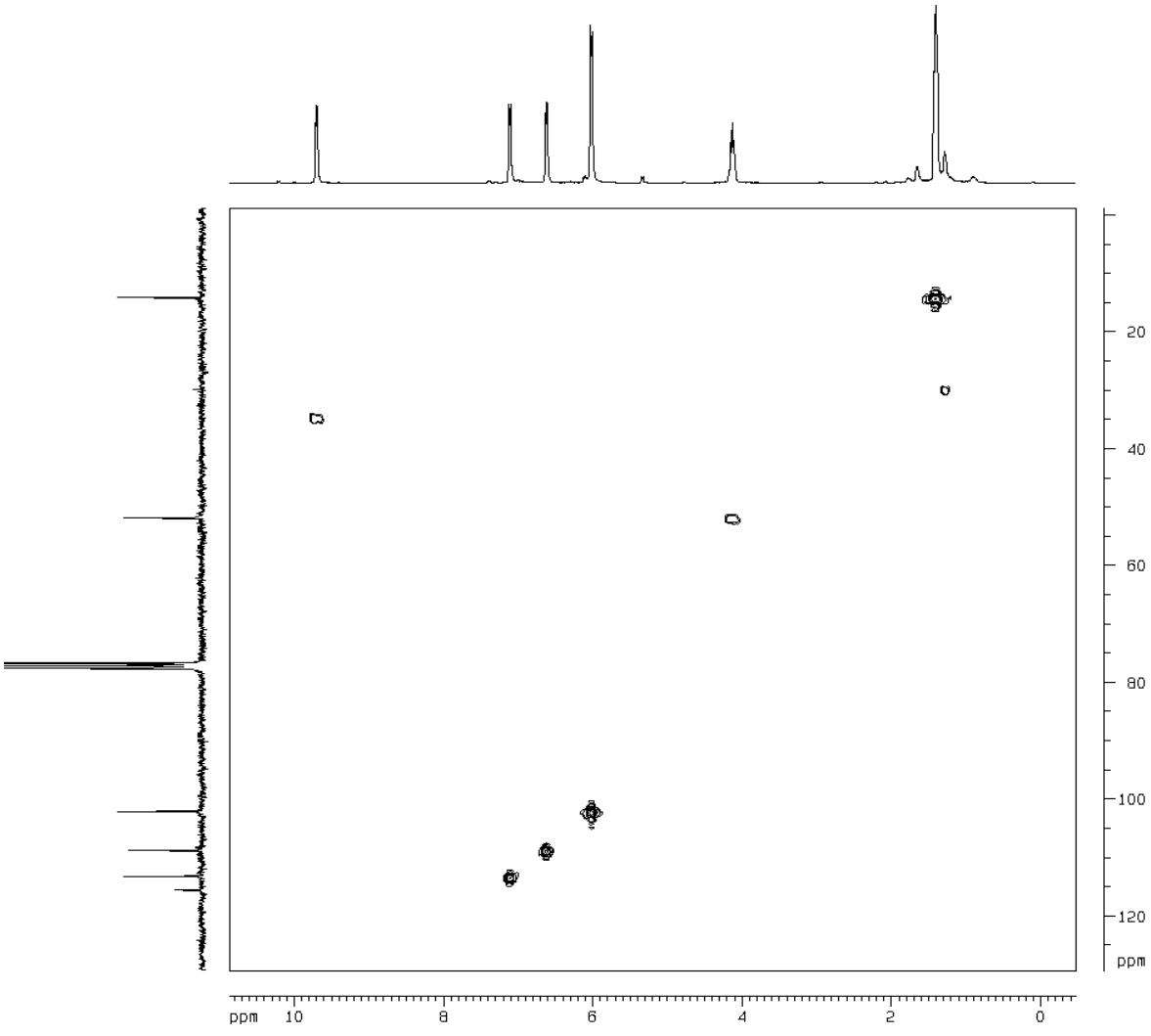
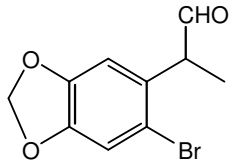


Table 1/ 12b', HRMS SPECTRUM



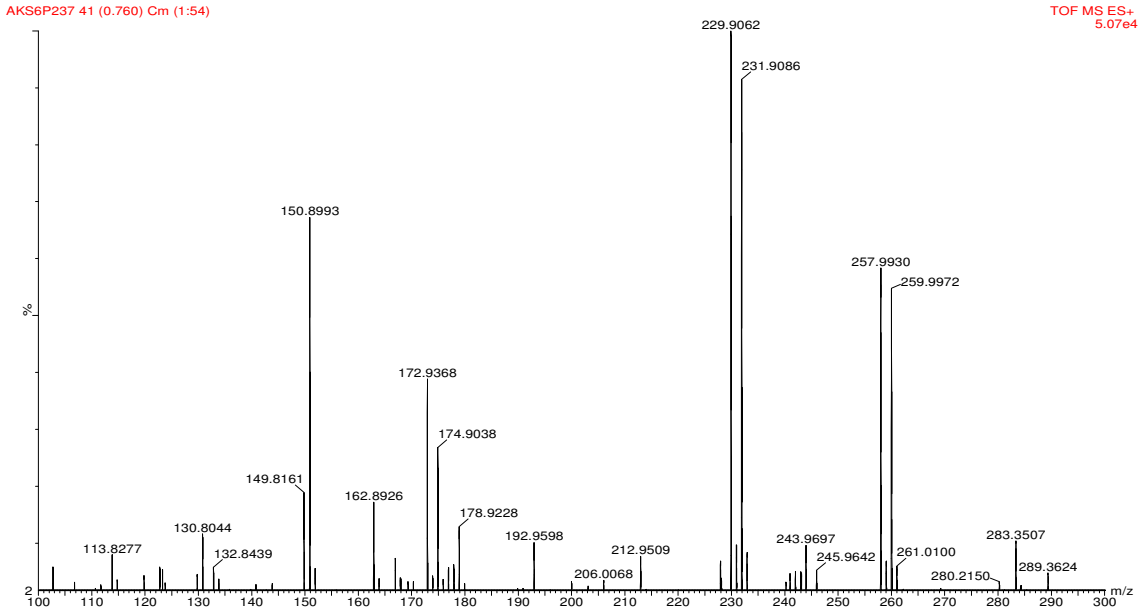
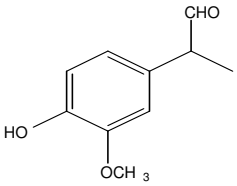


Table 1/ 13b, GCMS Spectrum



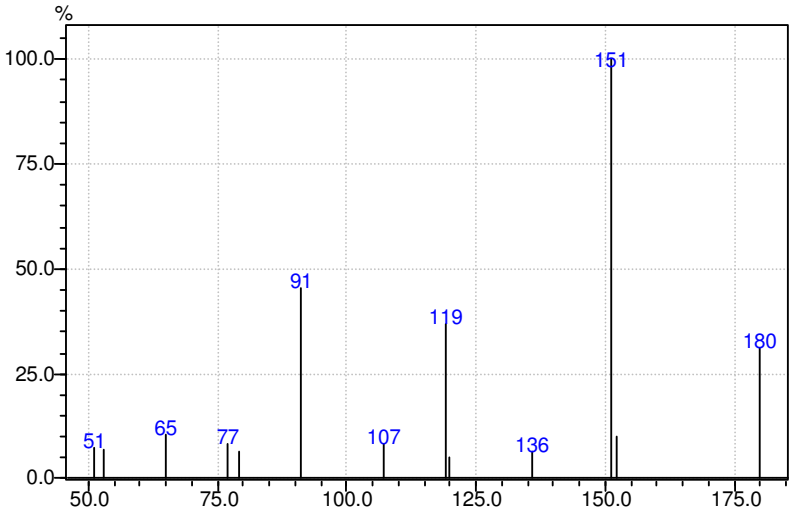
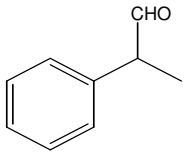


Table 1/ 14b, GC-MS SPECTRUM



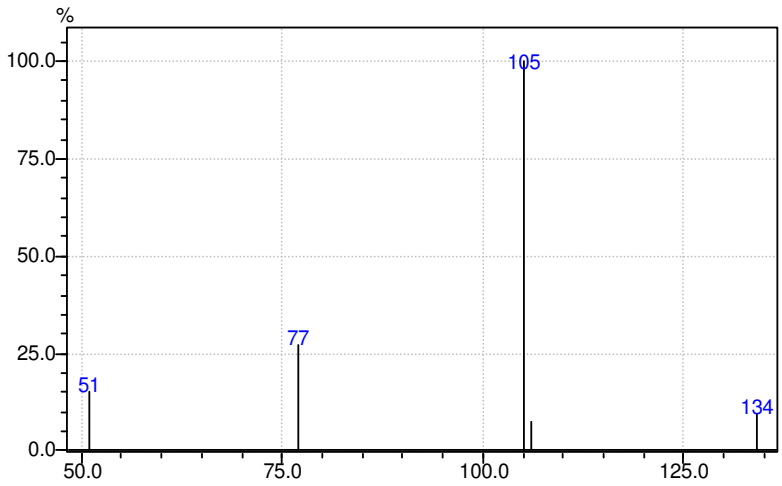
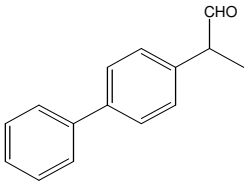


Table 1/ 15b, GCMS SPECTRUM



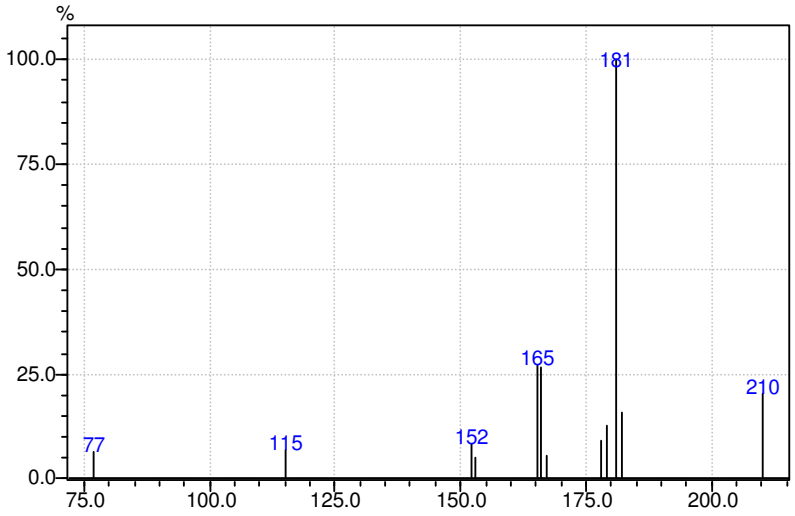
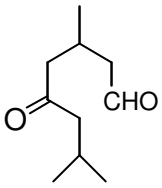
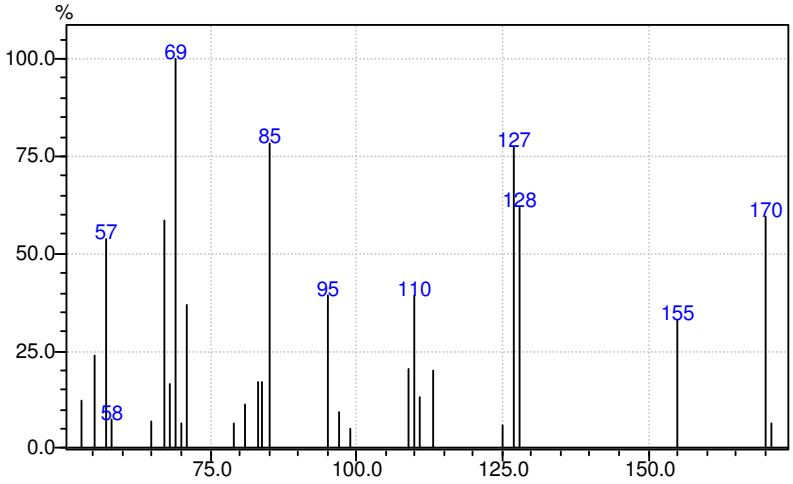
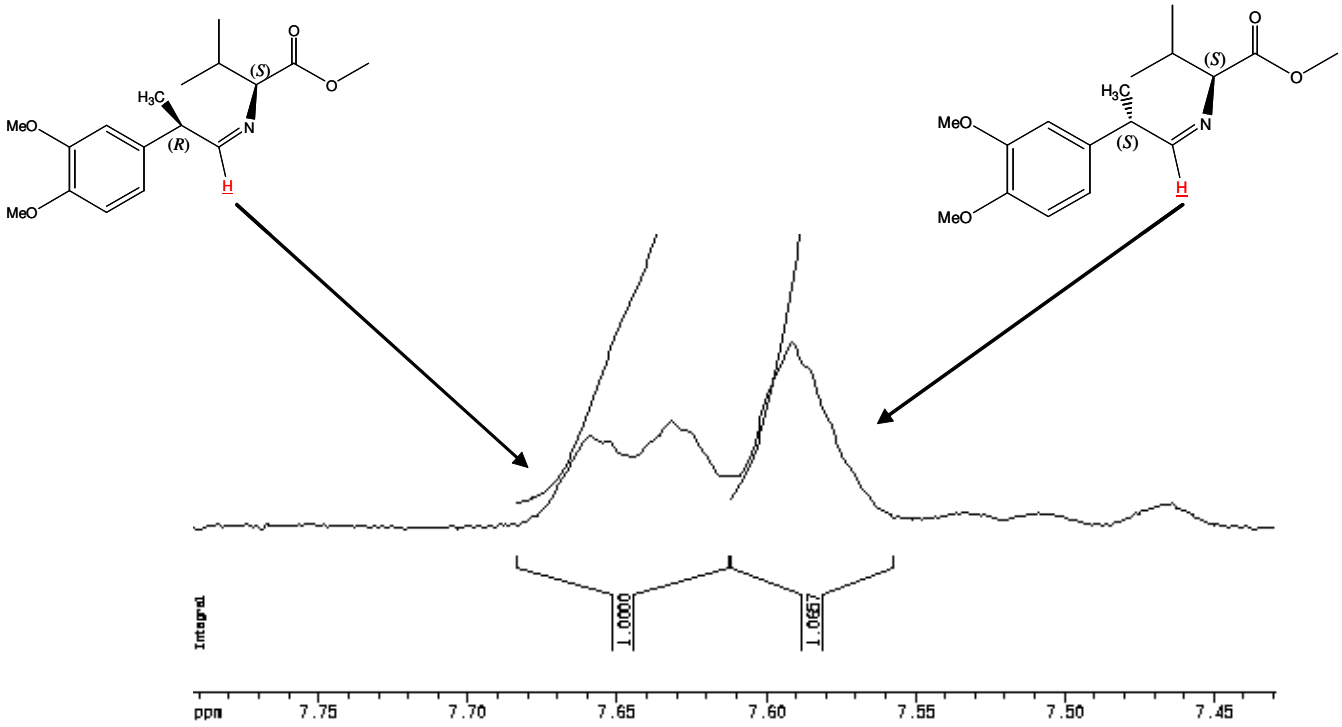


Table 1/ 18b, GC-MS SPECTRUM



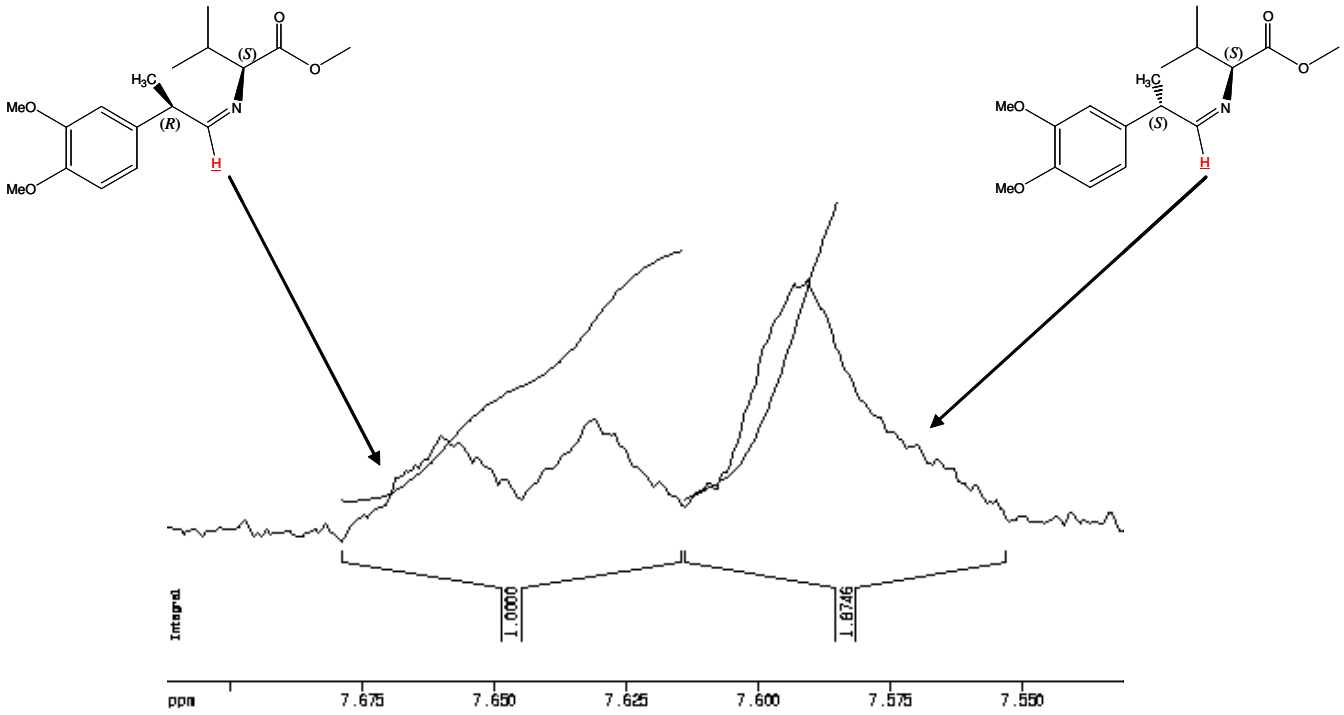


Determination of *ee* by addition of L-valine methyl ester HCl to 11b (obtained by the oxidative rearrangement using CTAB as PTC , and ^{1}H NMR analysis (300MHz, $CDCl_3$) of resulting imine proton

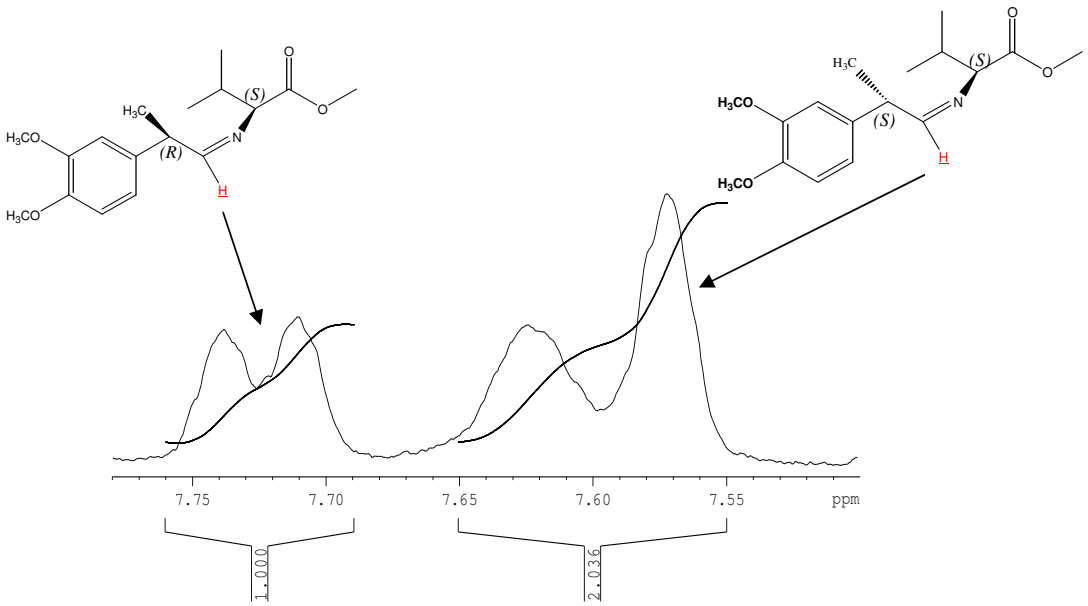


Determination of *ee* by addition of L-valine methyl ester HCl to 11b (obtained by the oxidative rearrangement using chiral (-)-N-Benzyl cinchonidinium chloride (40 mol %) as PTC, Scheme-2) and ^{1}H NMR analysis (300MHz) of resulting imine proton

a) using $CDCl_3$ as NMR solvent (ee = 30%)

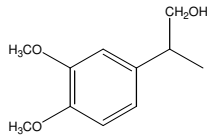


b) Using MeOD as NMR solvent (ee = 32%, a clear peak separation was observed as compared to NMR assay using $CDCl_3$)



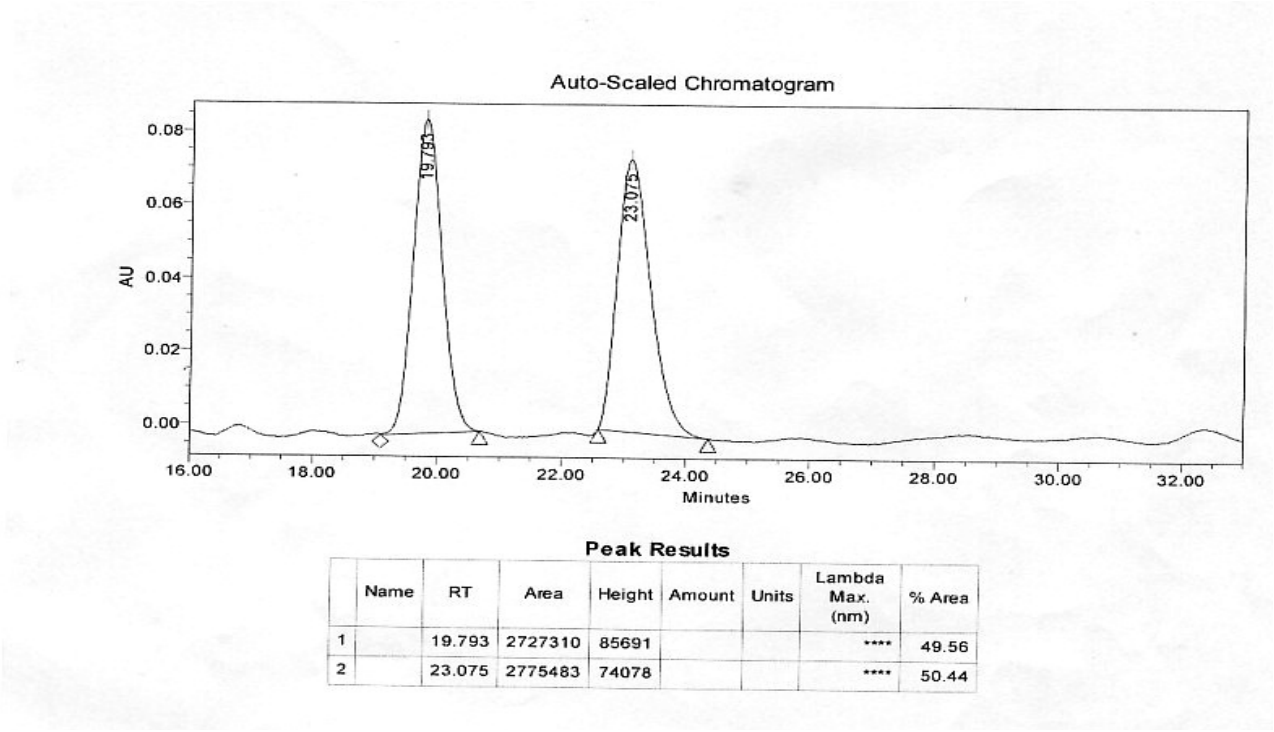
Chiral HPLC chromatogram of 2-(3,4-dimethoxy phenyl)propanol (11d)

(Daicel Chiracell OD-H (250 x 4.6 mm, 5µm) column (*n*-hexane:*i*-PrOH::95:5, 30°C) at 0.6ml/min)



(11d)

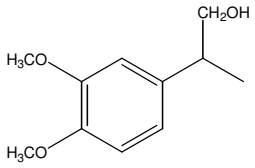
a) Racemic aldehyde (11b, obtained using CTAB as PTC) was reduced with $NaBH_4$ to obtain alcohol derivative (11d) which was subjected to chiral HPLC analysis (ee obtained = 0.8%)

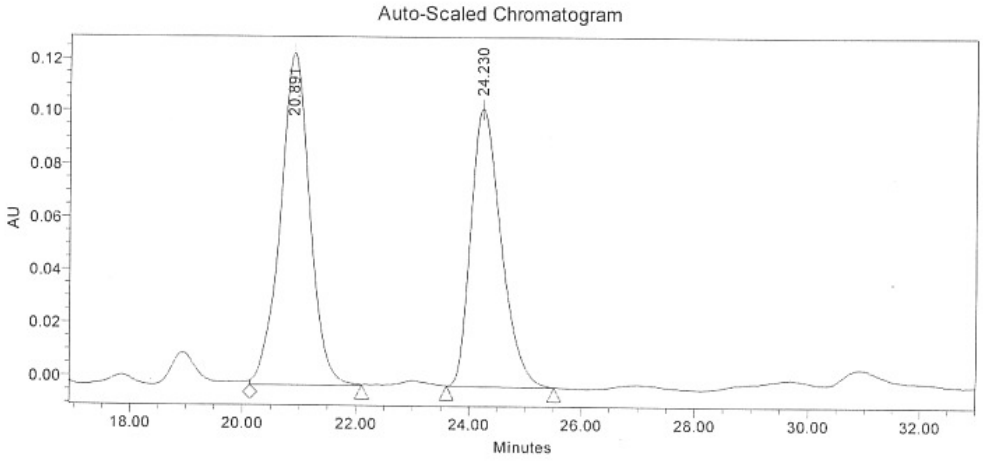


Peak Results

	Name	RT	Area	Height	Amount	Units	Lambda Max. (nm)	% Area
1		19.793	2727310	85691			****	49.56
2		23.075	2775483	74078			****	50.44

b) Chiral aldehyde (11b, obtained using (-)-N-Benzylcinchonidinium chloride (40 mol%) as PTC) was reduced with $NaBH_4$ to obtain alcohol derivative (11d) which was subjected to chiral HPLC analysis (ee obtained = 6.8%)





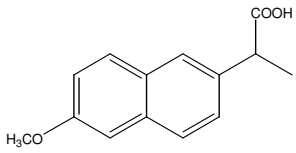
Peak Results

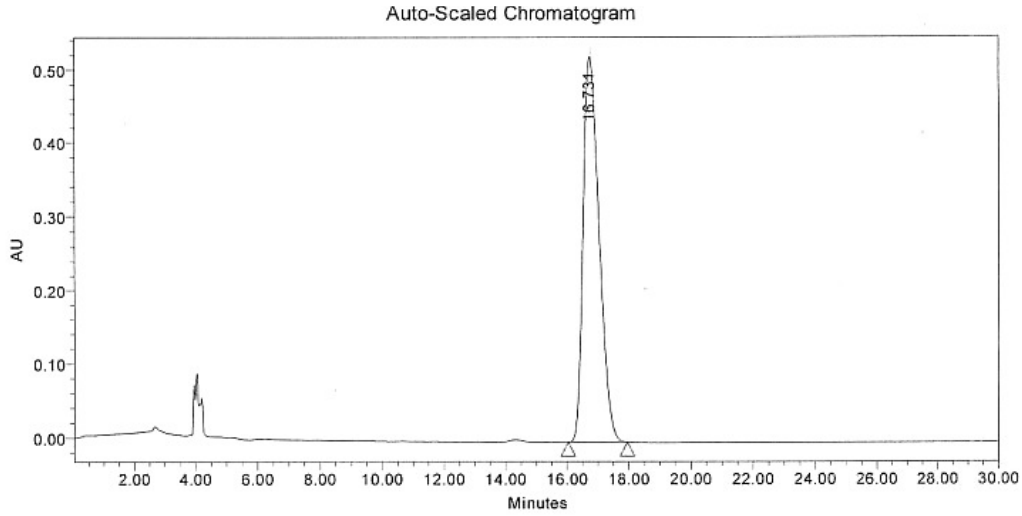
	Name	RT	Area	Height	Amount	Units	Lambda Max. (nm)	% Area
1		20.891	4497319	125649			****	53.40
2		24.230	3924052	104547			****	46.60

Chiral HPLC chromatogram of standard (*S*) (2-(6- methoxy-2-naphthyl)propionic acid

(Daicel Chiracell OD-H (250 x 4.6 mm, 5µm) column (*n*-hexane:*i*-PrOH:TFA :: 90:10:0.75, 25°C)

at 1.00 ml/min

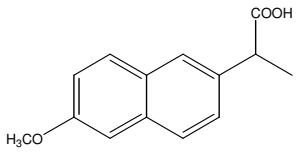




Peak Results

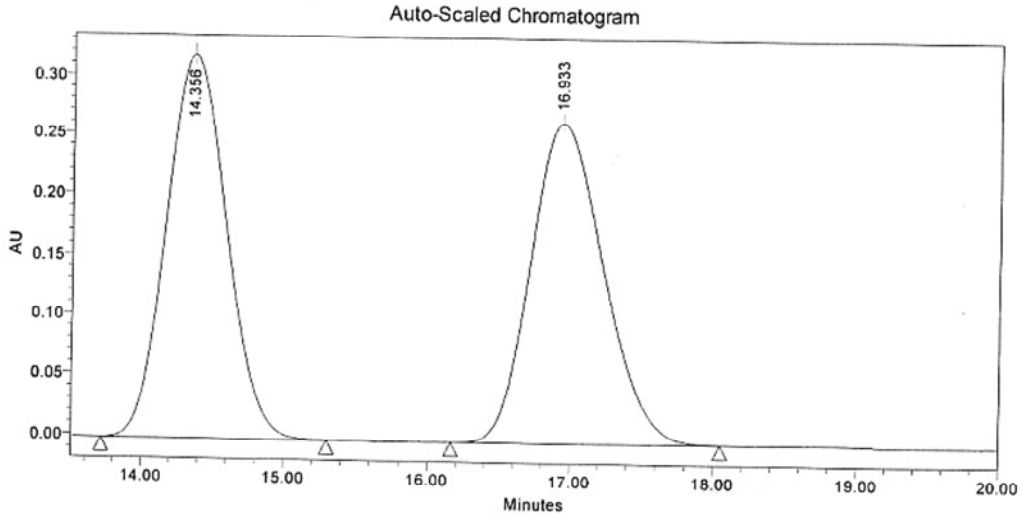
	Name	RT	Area	Height	Amount	Units	Lambda Max. (nm)	% Area
1		16.731	18788360	523343			****	100.00

Chiral HPLC chromatogram of (2-(6- methoxy-2-naphthyl)propionic acid (7c) obtained by Ag_2O assisted oxidation of 7b (Daicel Chiracell OD-H (250 x 4.6 mm, 5µm) column (*n*-hexane:*i*-PrOH:TFA :: 90:10:0.75, 25°C) at 1.00 ml/min)



(7c)

Chiral aldehyde (7b), obtained using (-)-N-Benzylcinchonidinium chloride (40 mol%) as PTC was oxidized with Ag_2O to obtain acid derivative (7c) which was subjected to chiral HPLC analysis (ee obtained = 0.2%)



Peak Results

	Name	RT	Area	Height	Amount	Units	Lambda Max. (nm)	% Area
1		14.356	9361774	319961			****	49.90
2		16.933	9398645	264820			****	50.10