

Supporting Information For

Iron-catalysed cross-coupling of halohydrins with arylaluminium reagents: A protecting-group-free strategy attaining remarkable rate enhancement and diastereinduction

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General. All the reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel under the positive pressure of argon gas. The air- and moisture-sensitive liquids and solutions were transferred via a syringe. Analytical thin-layer chromatography (TLC) was performed on glass plates coated with 0.25 mm 230–400 mesh silica gel containing a fluorescent indicator (Merck, #1.05715.0009). The TLC plates were visualized by exposure to ultraviolet light (254 nm) and/or by immersion in an acidic staining solution of *p*-anisaldehyde, followed by heating on a hot plate. The organic solutions were concentrated using rotary evaporation at *ca.* 20 mmHg. Flash column chromatography was performed on Merck silica gel 60 (spherical, neutral, 35–70 μm), according to the procedure described by Still *et al.*¹

Instrumentation. The proton nuclear magnetic resonance (¹H NMR) and carbon NMR (¹³C NMR), were recorded on a JEOL ECS-400NR (391.8 MHz) NMR spectrometer. The proton chemical shift values are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane, and are referenced to the residual proton signal of CDCl₃ (δ 7.26). The ¹³C NMR spectra were recorded at 98.5 MHz. The chemical shifts of the carbon atoms are reported in parts per million (ppm, δ scale) downfield from tetramethylsilane, and are referenced to the carbon resonance of CDCl₃ (δ 77.36). The data are presented as: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, sext = sextet, sept = septet, m = multiplet and/or multiplet resonances, and br = broad), coupling constant in hertz (Hz), signal area integration in natural numbers, and assignment (in *italics*).

Solvent. The anhydrous tetrahydrofuran (THF) used was purchased from Wako Pure Chemical Industries, Ltd. (Wako) and distilled from benzophenone ketyl under argon (at atmospheric pressure)

(1) W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* 1978, **43**, 2923–2925.

immediately before use. The water content of the solvent was determined using a Karl-Fischer moisture titrator (MCU-610, Kyoto Electronics Company) and found to be < 10 ppm.

Materials. The chemical reagents used were purchased from Wako Pure Chemical Industries, Ltd. (Wako), Tokyo Chemical Industry (TCI) Co. Ltd., Sigma-Aldrich Inc., and other commercial suppliers. The Florisil[®] (100–200 mesh) used was purchased from Nacalai Tesque Inc. The anhydrous FeCl₃ (powder, 99.99%) used was purchased from Sigma-Aldrich Inc., and dissolved in THF at 0 °C prior to use. Anhydrous AlCl₃ (powder, 99.99%) was purchased from Sigma-Aldrich Inc. The arylmagnesium bromides (ArMgBr) used were prepared from the corresponding aryl bromides and magnesium turnings using a standard method, and titrated before use. All the arylmagnesium chlorides were prepared from the corresponding arylchlorides and magnesium turnings activated by a catalytic amount of 1,2-dibromoethane.

GC-MS analysis. The ratio of diastereomers was determined for the crude product using GC-MS analysis on a JEOL GCmate[™] II GC-MS Double-Focusing Mass Spectrometer with a capillary column, ZB-1MS (10 m × 0.1 mm i.d., film thickness = 0.1 μm).

Investigation of a dummy ligand on aryl aluminium reagents (§c)

Despite our best efforts, an efficient dummy ligand on aryl aluminate has still not been found. The result of the reaction of phenyl aluminates that have ethyl group and *tert*-butyl groups on them was described in Scheme S1 and Table S1.

Scheme S1. Investigation of dummy ligand on phenyl aluminate

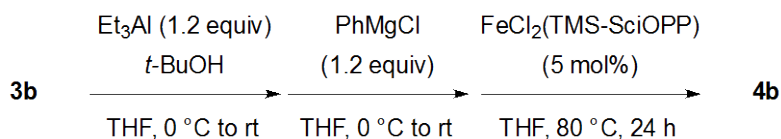


Table S1. The reaction of phenyl aluminates possessing a phenyl group and ethyl and *tert*-butoxy groups

entry ^a	amount of <i>t</i> -BuOH	yield (%) ^b			RSM (%) ^b
		4b	alkene	alkane	
1	1.2 equiv	13	2	52	29
2	2.4 equiv	0	0	0	>99
3	3.6 equiv	0	0	0	>99

^aReactions were performed on the 0.5 mmol scale. ^bThe yields were determined by ¹H NMR analysis and confirmed by GLC analysis.

Iron-catalysed cross-coupling reaction of protected halohydrins with various phenylmetal reagents (§d)

To investigate the characteristic nature of aryl aluminate in the reaction of primary alkyl chloride, various phenylmetal reagents were reacted with alkyl chloride (**3b**) in the presence of a catalytic amount of **2** (Table S2). The reaction system did not work efficiently in the reaction of **3b** regardless of the phenylmetal reagents used because of the low reactivity of the primary alkyl chloride.

Table S2. The reaction of primary alkyl chloride with various phenyl metal reagents

$$\begin{array}{c}
 \text{Ph}_n\text{M} \\
 \text{cat. 2} \\
 \text{3b} \xrightarrow{\hspace{1cm}} \text{4b} + \begin{array}{c} \text{alkene} \\ \text{alkane} \end{array} + \begin{array}{c} \text{alkene} \\ \text{alkane} \end{array} \\
 \text{(R = Si}^t\text{-BuMe}_2\text{)}
 \end{array}$$

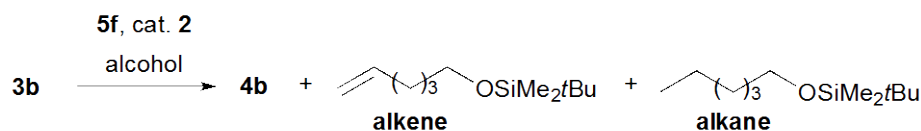
entry ^a	Ph _n M (equiv)	yield (%) ^b			RSM (%) ^b
		4b	alkene	alkane	
1	PhMgBr (5a) (2.0)	12	10	37	41
2	Ph ₂ Zn·2 MgCl ₂ (5b) (1.0)	0	0	6	93
3 ^c	Ph ₂ B(pin)·Li (5d) (1.0)	40	3	30	23
4	Ph ₃ Al·3 MgCl ₂ (5e) (1.0)	43	2	1	53
5	Ph ₄ Al·MgCl (5f) (1.0)	20	1	20	52

^aReactions were performed at 80 °C for 12 h. ^bThe yields were determined by ¹H NMR analysis and confirmed by GLC analysis. ^c20 mol% MgBr₂ was added as a co-catalyst.

Effect of alcohols in the iron-catalysed cross-coupling reaction of protected chlorohydrin with phenyl aluminate (†e)

To study the influence of aluminum alkoxide in the reaction, a series of alcohols were added to the iron-catalysed cross-coupling reaction of the primary alkyl chloride **3b** with phenyl aluminate **5f** (Table S3). Although the reactions of alkyl chlorides with phenyl aluminate in the absence of alcohol did not lead to the desired products in satisfactory yield, the reactions of phenyl aluminate in the presence of alcohols proceeded smoothly to give the product in high yield with almost the same reaction rates regardless of the structure of alcohols used as an additive (Figure S1).

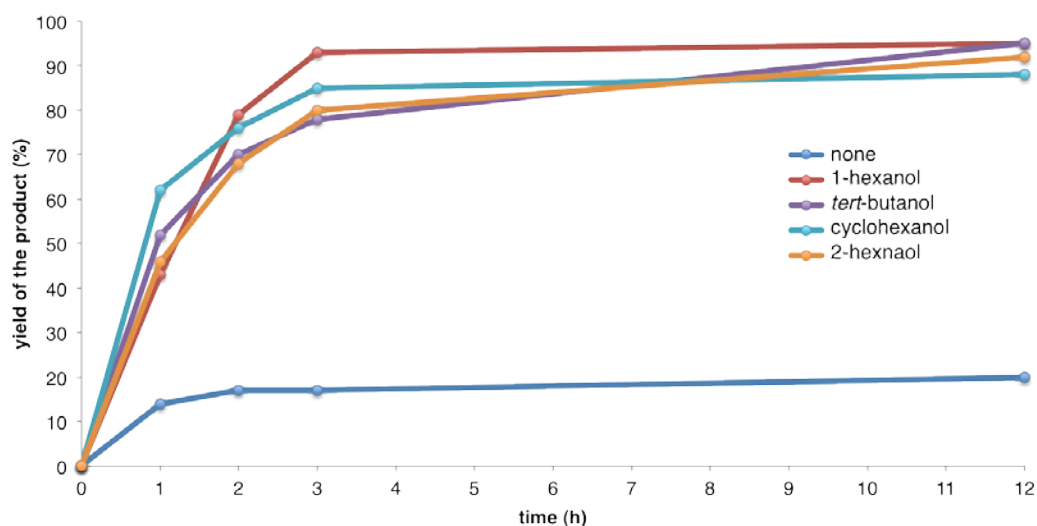
Table S3. Rate enhancement by *in situ* generated aluminum alkoxide



entry ^a	alcohol	yield (%) ^b			RSM (%) ^b
		4b	alkene	alkane	
1	none	20	1	20	52
2	1-hexanol (1.0 equiv)	95	0	5	0
3	2-hexanol (1.0 equiv)	92	0	7	0
4	<i>tert</i> -butanol (1.0 equiv)	95	0	5	0
5	1-hexanol (20 mol%)	77	0	12	11

^aReactions were performed at 80 °C for 12 h. ^bThe yields were determined by ¹H NMR analysis and confirmed by GLC analysis.

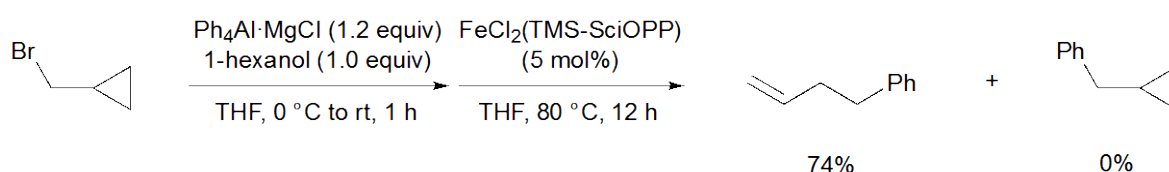
Figure S1. Reaction rates of the reaction in the presence of various alcohols



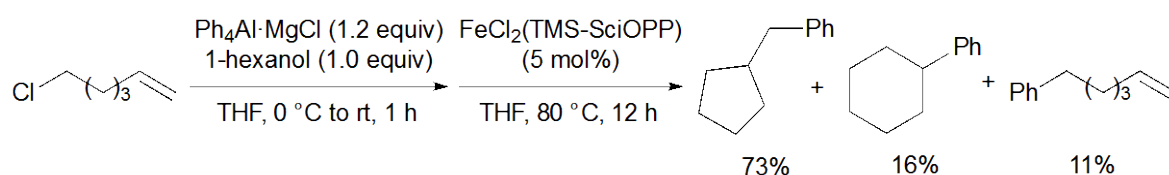
Radical clock experiment to confirm the alkyl radical formation in the catalytic cycle (†g)

Iron-catalysed cross-coupling reaction of alkyl halides is known to usually proceed through alkyl radical formation.² The alkyl radical formation in the reaction was confirmed by the use of cyclopropylmethyl bromide³ and 6-chloro-1-hexene⁴ (Scheme S2 and S3). A radical clock substrate, cyclopropylmethyl bromide lead a ring opening product in 74% yield,[†] and (cyclopropylmethyl)benzene was not obtained at all. In addition, 6-chloro-1-hexene gave the cyclized products in 89% combined yield.[†] These results prove the alkyl radical generation in the reaction.

Scheme S2. Radical clock experiment



Scheme S3. Radical probe by using 6-chloro-1-hexene



[†] The yield was determined by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

(2) For selected paper, see: D. Noda, Y. Sunada, T. Hatakeyama, M. Nakamura, and H. Nagashima, *J. Am. Chem. Soc.*, 2009, **131**, 6078.

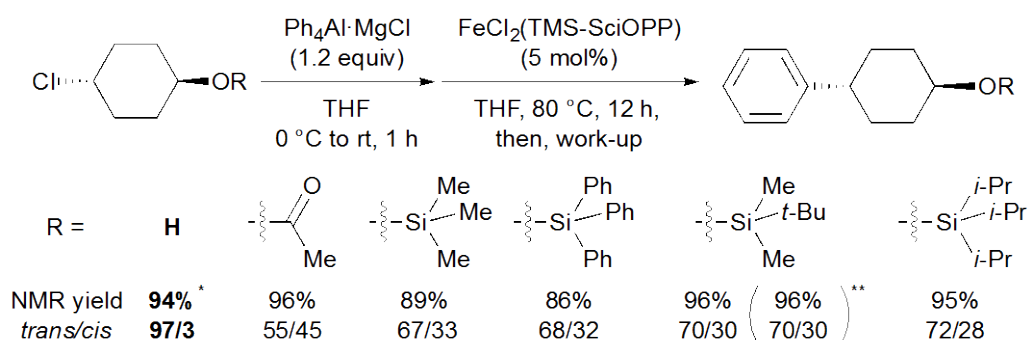
(3) Hollis, R.; Hughes, L.; Bowry, V. W.; Ingold, K. U. *J. Org. Chem.* **1992**, *57*, 4284-4287.

(4) D. Lal, D. Griller, S. Husband, and K. U. Ingold, *J. Am. Chem. Soc.*, 1974, **96**, 6355.

Effect of bulkiness of silyl groups toward the diastereoselection in the iron-catalysed cross-coupling reaction of protected cyclic chlorohydrin with phenyl aluminat (†h)

Influence of steric bulkiness of the protecting groups on the diastereoselectivity was studied in the reaction of protected *trans*-4-chlorocyclohexanol by using various silyl protected chlorocyclohexanols (Figure S2). Although the bulkiness of silyl protecting groups affected the diastereoselectivity slightly, high-level diastereoselection as such for the non-protected halohydrin (R = H), was not observed. Addition of an alcohol to the reaction did not affect the diastereoselectivity.

Figure S2. Effect of bulkiness of silyl group and alcohol as the additive to the diastereoselectivity in the reaction

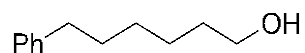


^{*} Almost all starting material was recovered in the absence of the catalyst.

^{**} The reaction was performed in the presence of 1.0 equiv of 1-hexanol.

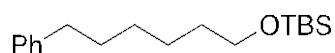
Experimental Section

Reaction of 6-chlorohexan-1-ol with various phenylmetal reagents (Table 1, entry1-6)



6-Chlorohexan-1-ol **3a** (67.3 mg, 0.50 mmol) was added to a THF solution of phenylmetal reagents⁵ (0.5 mmol) prepared by transmetalation between metal salts (1.0 M, 0.6 mL, 0.6 mmol) and phenylmagnesium chloride (0.94 M) at 0 °C, and then the reaction mixture was stirred at room temperature for 1 h. A THF solution of FeCl₂(TMS-SciOPP) (0.10 M, 250 μL, 0.03 mmol) was added to the resulting solution at room temperature. The coupling reaction was carried out at 80 °C for 12 h. After cooling the mixture to 0 °C, aqueous HCl (3 N, 2 mL) were added and stirred at room temperature for 3 h. The aqueous layer was extracted with ethyl acetate three times (2 mL × 3). The combined organic extracts were filtered using a pad of Florisil[®] (100–200 mesh, Nacalai Tesque Inc.). After removal of the solvent *in vacuo*, the yield of the cross-coupling product was estimated by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard, and diastereomer ratio was determined by GC-MS analysis.

Reaction of *tert*-butyldimethyl((6-phenylhexyl)oxy)silane with various phenylmetal reagents (Table 1, entry7)



tert-Butyldimethyl((6-chlorohexyl)oxy)silane **3b** (146.3 mg, 0.50 mmol) and a THF solution of FeCl₂(TMS-SciOPP) (0.10 M, 250 μL, 0.03 mmol) were added to a THF solution of phenylmetal reagent (0.6 mmol) prepared by transmetalation between metal salts (1.0 M, 0.6 mL, 0.6 mmol) and phenylmagnesium chloride (0.94 M). The coupling reaction was carried out at 80 °C for 12 h. After cooling the mixture to 0 °C, saturated Rochelle salt solution (3 mL) were added. The aqueous layer was extracted with ethyl acetate three times (2 mL × 3). The combined organic extracts were filtered using a pad of Florisil[®] (100–200 mesh, Nacalai Tesque Inc.). After removal of the solvent *in vacuo*, the yield of the cross-coupling product was estimated by ¹H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard, and diastereomer ratio was determined by GC-MS analysis.

Typical procedure (A) for the reaction shown in Table 2

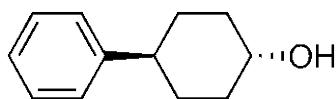
(5) Phenylmetal reagents were prepared according to the literatures: phenylzinc reagents; M. Nakamura, S. Ito, K. Matsuo, and E. Nakamura, *Synlett*, 2005, **11**, 1794. phenylaluminum reagents; S. Kawamura, K. Ishizuka, H. Takaya, and M. Nakamura, *Chem Commun.*, 2010, **46**, 6054. phenylpinacoleborate; T. Hatakeyama, T. Hashimoto, Y. Kondo, Y. Fujiwara, H. Seike, H. Takaya, Y. Tamada, T. Ono and M. Nakamura, *J. Am. Chem. Soc.*, 2010, **132**, 10674.

A THF solution of arylmagnesium bromide (4.80 mmol) was added to a solution of AlCl₃ (160 mg, 1.20 mmol) in 1.20 mL of THF at 0 °C. The reaction mixture was stirred at room temperature for 30 min, and then halohydrin (1.00 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 1 h. A THF solution of FeCl₂(TMS–SciOPP) (0.10 M, 500 μL, 0.05 mmol) was added to the resulting solution at room temperature. The coupling reaction was carried out at 80 °C for 12–24 h. After adding aqueous HCl (3 N, 4 mL) at 0 °C, the mixture was stirred at room temperature for 3 h. The aqueous layer was extracted with ethyl acetate three times (3 mL × 3). The combined organic extracts were filtered using a pad of Florisil[®] (100–200 mesh, Nacalai Tesque Inc.), and concentrated *in vacuo*. The crude product was finally purified by chromatography over silica gel (230–400 mesh).

Typical procedure (B) for the reaction of protected cyclic chlorohydrins shown in Table 2

A THF solution of phenylmagnesium chloride (4.75 mL, 1.01 M, 4.8 mmol) was added to a solution of AlCl₃ (160.0 mg, 1.2 mmol) in 1.2 mL of THF at 0 °C. The reaction mixture was stirred at room temperature for 30 min, and then protected cyclic chlorohydrin (1.00 mmol) was added to the reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 1 h. A THF solution of FeCl₂(TMS–SciOPP) (0.10 M, 500 μL, 0.05 mmol) was added to the resulting solution at room temperature. The coupling reaction was carried out at 80 °C for 12 h. After cooling the mixture to 0 °C, Rochelle salt solution (4 mL) were added and stirred at room temperature for 3h. The aqueous layer was extracted with ethyl acetate three times (3 mL × 3). The combined organic extracts were filtered using a pad of Florisil[®] (100–200 mesh, Nacalai Tesque Inc.), and concentrated *in vacuo*. The crude product was finally purified by chromatography over silica gel (230–400 mesh).

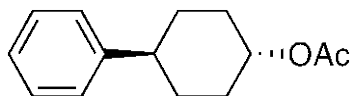
Synthesis of 4-phenylcyclohexanol (1)



The reaction was carried out according to the typical procedure (A) for 12 h by using a THF solution of phenylmagnesium chloride (4.75 mL, 1.01 M, 4.80 mmol) and 4-chlorocyclohexanol (134 mg, 1.00 mmol). The title compound (165 mg, 94% yield, >99% pure on GC analysis) was obtained as a colourless solid after silica gel column chromatography (40% AcOEt in hexane). IR (neat) 3398, 3029, 2921, 2877, 1600, 1493, 1451, 1344, 1312, 1225, 1116, 1028, 967, 888, 755; ¹H NMR (391.8 MHz, CDCl₃, δ): *trans-isomer*; 1.49 (m, 4H), 1.92 (m, 2H), 2.12 (m, 2H), 2.50 (tt, *J* = 11.8, 3.6 Hz, 1H), 3.69 (tt, *J* = 11.8, 4.0 Hz, 1H), 7.30 (m, 5H). *cis-isomer*; 1.52 (s, 1H), 1.69 (m, 4H), 1.86 (m, 4H), 2.57 (tt, *J* = 11.7, 3.3 Hz, 1H), 4.14 (br, 1H), 7.27 (m, 5H); ¹³C NMR (98.5 MHz, CDCl₃, δ):

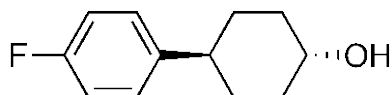
diastereo mixture; 27.7, 32.4, 33.0, 35.9, 65.6, 70.6, 125.9, 126.0, 126.7, 126.8, 128.3, 146.5. Anal. calcd for C₁₂H₁₆O, C, 81.77; H, 9.15. found C, 81.59; H, 9.24.

Synthesis of 4-phenylcyclohexyl acetate (2)



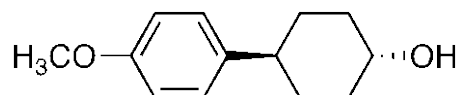
The reaction was carried out according to the typical procedure (B) for 12 hours by using a THF solution of phenylmagnesium chloride (4.75 mL, 1.01 M, 4.80 mmol) and 4-chlorocyclohexyl acetate (177 mg, 1.00 mmol). The title compound (210 mg, 96% yield, >99% pure on GC analysis) was obtained as a colourless oil after silica gel column chromatography (10% AcOEt in hexane). IR (neat) 3023, 2970, 2874, 1760, 1605, 1487, 1430, 1378, 1239, 1200, 1160, 1120, 1040, 890, 750; ¹H NMR (391.8 MHz, CDCl₃, δ): *trans-isomer*; 1.52 (m, 2H), 1.62 (m, 2H), 1.94 (m, 2H), 2.07 (s, 3H), 2.12 (m, 2H), 2.52 (tt, *J* = 11.8, 3.9 Hz, 1H) 4.78 (tt, *J* = 11.5, 3.5 Hz, 1H), 7.13-7.33 (m, 5H), *cis-isomer*; 1.70 (m, 4H), 1.79 (m, 4H), 2.57 (tt, *J* = 11.5, 3.4 Hz, 1H), 5.10 (m, *J* = 3.3 Hz, 1H), 7.13-7.33 (m, 5H), ¹³C NMR (98.5 MHz, CDCl₃, δ): diastereomer mixture; 21.5, 28.3, 30.2, 32.0, 32.2, 43.3, 43.4, 69.0, 73.0, 126.0, 126.2, 126.7, 126.8, 128.4, 146.2, 147.1, 170.7. Anal. calcd for C₁₄H₁₈O₂, C, 77.03; H, 8.31. found C, 76.73; H, 8.26

Synthesis of 4-(4-fluorophenyl)cyclohexanol (4)



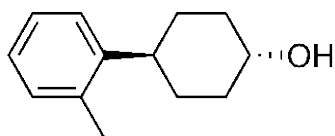
The reaction was carried out according to the typical procedure (A) for 12 hours by using a THF solution of (4-fluorophenyl)magnesium bromide (4.32 mL, 1.11 M, 4.80 mmol) and *trans*-4-chlorocyclohexanol (134 mg, 1.00 mmol). The title compound (143 mg, 75% yield, >99% pure on GC analysis) was obtained as a colourless solid after silica gel column chromatography (40% AcOEt in hexane). IR (neat) 3411, 3019, 2923, 2855, 1599, 1500, 1483, 1342, 1219, 1159, 1061, 967, 825, 718; ¹H NMR (391.8 MHz, CDCl₃, δ): *trans-isomer*; 1.45-1.51 (m, 4H), 1.89-1.92 (m, 2H), 2.08-2.11 (m, 2H), 2.49 (tt, *J* = 11.6, 3.6 Hz, 1H), 3.68 (tt, *J* = 11.8, 3.3 Hz, 1H), 6.94-7.01 (m, 2H), 7.12-7.21 (m, 2H), *cis-isomer*; 1.63-1.70 (m, 4H), 1.81-1.84 (m, 4H), 2.52 (tt, *J* = 11.6, 3.5 Hz, 1H), 4.14 (br, 1H), 6.94-7.01 (m, 2H), 7.12-7.21 (m, 2H); ¹³C NMR (98.5 MHz, CDCl₃, δ): diastereomer mixture; 27.9, 32.6, 33.0, 35.9, 70.6, 114.9, 115.1, 115.2, 142.1, 162.0, 162.5. HRMS-EI: (m/z): [M]⁺ calcd. for C₁₂H₁₅FO, 194.1107; found, 194.1111

Synthesis of 4-(4-methoxyphenyl)cyclohexanol (5)



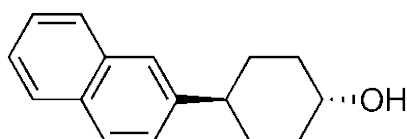
The reaction was carried out according to the typical procedure (A) for 12 hours by using a THF solution of (4-methoxyphenyl)magnesium bromide (4.57 mL, 1.05 M, 4.80 mmol) and *trans*-4-chlorocyclohexanol (134 mg, 1.00 mmol). The title compound (192 mg, 93% yield, >99% pure on GC analysis) was obtained as a colourless solid after silica gel column chromatography (40% AcOEt in hexane). IR (neat) 3442, 3030, 2921, 2852, 1730, 1610, 1512, 1453, 1246, 1176, 1056, 1030, 961, 813, 762; ^1H NMR (391.8 MHz, CDCl_3 , δ): *trans-isomer*; 1.36-1.59 (m, 4H), 1.87-1.92 (m, 2H), 2.07-2.10 (m, 2H), 2.45 (tt, $J = 11.6$, 3.4 Hz, 1H), 3.68 (tt, $J = 11.8$, 3.3 Hz, 1H), 3.79 (s, 3H), 6.82-6.87 (m, 2H), 7.10-7.13 (m, 2H), *cis-isomer*; 1.63-1.70 (m, 4H), 1.81-1.84 (m, 4H), 2.48 (tt, $J = 11.8$, 3.3 Hz, 1H), 3.79 (s, 3H), 4.12 (br, 1H), 6.82-6.87 (m, 2H), 7.15-7.17 (m, 2H), ^{13}C NMR (98.5 MHz, CDCl_3 , δ): diastereomer mixture; 28.0, 32.7, 33.1, 36.0, 42.5, 42.9, 55.2, 65.7, 70.7, 113.7, 127.6, 127.7, 138.7, 139.6, 157.8, 156.9. Anal. calcd for $\text{C}_{13}\text{H}_{18}\text{O}_2$, C, 75.69; H, 8.80. found C, 75.44; H, 8.86.

Synthesis of 4-(2-methylphenyl)cyclohexanol (6)



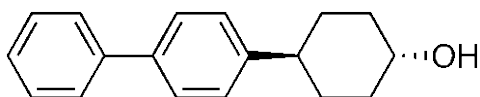
The reaction was carried out according to the typical procedure (A) for 12 hours by using a THF solution of *o*-tolylmagnesium bromide (4.80 mL, 1.00 M, 4.80 mmol) and *trans*-4-chlorocyclohexanol (134 mg, 1.00 mmol). The title compound (161 mg, 85% yield, >99% pure on GC analysis) was obtained as a colourless oil after silica gel column chromatography (40% AcOEt in hexane). IR (neat) 3332, 3019, 2927, 2854, 1603, 1450, 1360, 1277, 1123, 1061, 1047, 998, 723; ^1H NMR (391.8 MHz, CDCl_3 , δ): *trans-isomer*; 1.39-1.58 (m, 4H), 1.85-1.87 (m, 2H), 2.10-2.14 (m, 2H), 2.38 (s, 3H), 2.70 (tt, $J = 11.8$, 3.3 Hz, 1H), 3.71 (tt, $J = 10.9$, 4.6 Hz), 7.09-7.20 (m, 4H), *cis-isomer*; 1.65-1.73 (m, 4H), 1.89-1.95 (m, 4H), 2.73 (tt, $J = 12.0$, 3.3 Hz), 4.16 (tt, $J = 2.7$, 2.8 Hz), 7.09-7.20 (m, 4H), ^{13}C NMR (98.5 MHz, CDCl_3 , δ): diastereomer mixture; 19.4, 26.9, 31.6, 33.3, 36.2, 38.9, 39.6, 65.6, 70.8, 125.1, 125.5, 125.6, 125.8, 126.1, 126.2, 130.2, 130.3, 135.0, 135.3, 144.4, 145.3. HRMS-EI: (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{13}\text{H}_{18}\text{O}$, 190.1358; found, 190.1369

Synthesis of 4-(naphthalen-2-yl)cyclohexanol (7)



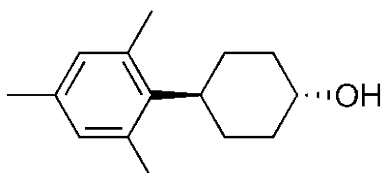
The reaction was carried out according to the typical procedure (A) for 12 hours by using a THF solution of naphthalen-2-ylphenylmagnesium bromide (5.57 mL, 0.86 M, 4.80 mmol) and *trans*-4-chlorocyclohexanol (134 mg, 1.00 mmol). The title compound (210 mg, 93% yield, >99% pure on GC analysis) was obtained as a colourless solid after silica gel column chromatography (40% AcOEt in hexane). IR (neat) 3456, 3035, 2925, 2864, 1604, 1470, 1430, 1110, 1070, 960, 823, 750; ¹H NMR (391.8 MHz, CDCl₃, δ): *trans-isomer*; 1.73-1.82 (m, 4H), 1.92-2.03 (m, 4H), 2.71 (tt, *J* = 3.0, 11.8 Hz, 1H), 4.18 (br, 1H), 7.39-7.46 (m, 3H), 7.62(m, 1H), 7.77-7.81 (m, 3H), *cis-isomer*; 1.69-1.71 (m, 4H), 2.06 (m, 4H), 2.82 (tt, *J* = 7.9 Hz, 1H), 3.69 (tt, *J* = 6.4 Hz, 1H), 7.39-7.81 (m, 5H); ¹³C NMR (98.5 MHz, CDCl₃, δ): diastereomer mixture; 27.7, 33.1, 43.9, 65.7, 124.5, 125.1, 125.8, 126.1, 127.5, 127.6, 127.8, 133.6, 144.8. HRMS-EI: (m/z): [M]⁺ calcd. for C₁₆H₁₈O, 226.1358; found, 226.1365

Synthesis of 4-([1,1'-biphenyl]-4-yl)cyclohexanol (8)



The reaction was carried out according to the typical procedure (A) for 24 hours by using a THF solution of [1,1'-biphenyl]-4-ylmagnesium bromide (4.52 mL, 1.06 M, 4.80 mmol) and *trans*-4-chlorocyclohexanol (134 mg, 1.00 mmol). The title compound (238 mg, 94% yield, >99% pure on GC analysis) was obtained as a colourless solid after silica gel column chromatography (40% AcOEt in hexane). IR (neat) 3429, 3028, 2924, 2855, 1598, 1484, 1445, 1117, 1065, 960, 826, 762, 735; ¹H NMR (391.8 MHz, CDCl₃, δ): *trans-isomer*; 1.40-1.50 (m, 4H), 1.95-1.98 (m, 2H), 2.10-2.13 (m, 2H), 2.54 (tt, *J* = 3.4, 12.1 Hz, 1H), 1.45 (br, 1H), 7.25-7.58 (m, 9H), *cis-isomer*; 1.70-1.73 (m, 4H), 1.91-1.92 (m, 4H), 2.61 (br, 1H), 4.15 (br, 1H), 7.25-7.58 (m, 9H), ¹³C NMR (98.5 MHz, CDCl₃, δ): diastereomer mixture; 27.7, 32.4, 33.0, 35.9, 43.1, 43.5, 65.6, 70.6, 127.0, 127.1, 127.2, 127.3, 128.7, 128.8, 138.9, 139.0, 141.0, 141.1, 145.7, 146.4. Anal. calcd for C₁₈H₂₀O, C, 85.67; H, 7.99. found C, 85.54; H, 8.02

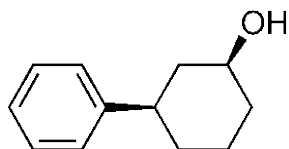
Synthesis of 4-mesitylcyclohexanol (9)



The reaction was carried out according to the typical procedure (A) for 24 hours by using a THF solution of mesitylmagnesium bromide (4.57 mL, 1.05 M, 4.80 mmol) and *trans*-4-chlorocyclohexanol (134 mg, 1.00 mmol). The title compound (36 mg, 16% yield, 98% pure on GC analysis) was obtained as a colourless oil after silica gel column chromatography (40% AcOEt in

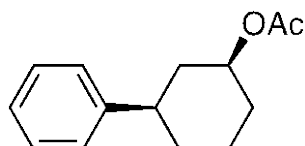
hexane). IR (neat) 3450, 3021, 2994, 2850, 1601, 1483, 1410, 1130, 1065, 945, 823, 750; ^1H NMR (391.8 MHz, CDCl_3 , δ): 1.19-1.54 (m, 3H), 1.70-2.13 (m, 5H), 2.93 (tt, $J = 3.5, 12.7$ Hz, 1H), 3.70 (tt, $J = 4.1, 10.9$ Hz, 1H), 6.81 (br. 2H); ^{13}C NMR (98.5 MHz, CDCl_3 , δ): 20.6, 28.3, 70.9, 135.1, 136.2, 138.7. HRMS-EI: (m/z): $[\text{M}]^+$ calcd. for $\text{C}_{15}\text{H}_{22}\text{O}$, 218.1671; found, 218.1683

Synthesis of 3-phenylcyclohexanol (11)



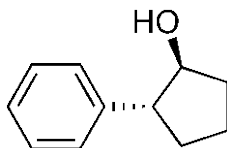
The reaction was carried out according to the typical procedure (A) for 12 hours by using a THF solution of phenylmagnesium chloride (4.75 mL, 1.01 M, 4.80 mmol) and 3-chlorocyclohexanol (134 mg, 1.00 mmol). The title compound (145 mg, 83% yield, >99% pure on GC analysis) was obtained as a colourless solid after silica gel column chromatography (40% AcOEt in hexane). IR (neat) 3379, 3029, 2923, 2869, 1598, 1491, 1449, 1225, 1198, 1141, 1101, 1084, 1042, 860, 741; ^1H NMR (391.8 MHz, CDCl_3 , δ): *trans-isomer*, 1.26-2.18 (m, 8H), 2.58 (tt, $J = 3.2, 12.2$ Hz, 1H), 3.72 (tt, $J = 4.3, 10.8$, 1H), 7.16-7.33 (m, 5H), *cis-isomer*, 1.26-2.18 (m, 8H), 3.01 (tt, $J = 3.2, 12.3$ Hz, 1H), 4.23 (br, 1H), 7.16-7.33 (m, 5H), ^{13}C NMR (98.5 MHz, CDCl_3 , δ): diastereomer mixture; 20.4, 24.5, 32.4, 33.4, 33.8, 35.4, 37.5, 40.5, 42.8, 43.2, 66.8, 71.0, 76.7, 125.9, 126.1, 126.9, 128.4, 128.4, 146.2, 147.1. Anal. calcd for $\text{C}_{12}\text{H}_{16}\text{O}$, C, 81.77; H, 9.15. found C, 81.52; H, 9.18

Synthesis of 3-phenylcyclohexyl acetate (12)



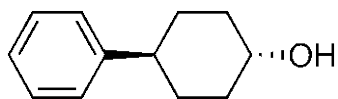
The reaction was carried out according to the typical procedure (B) for 12 hours by using a THF solution of phenylmagnesium chloride (4.75 mL, 1.01 M, 4.80 mmol) and 3-chlorocyclohexyl acetate (177 mg, 1.00 mmol). The title compound (193 mg, 88% yield, >99% pure on GC analysis) was obtained as a pale yellow oil after silica gel column chromatography (10% AcOEt in hexane). IR (neat) 3024, 2936, 2861, 1731, 1602, 1494, 1450, 1363, 1239, 1146, 1028, 964, 895, 855, 755, 658; ^1H NMR (391.8 MHz, CDCl_3 , δ): *trans-isomer*, 1.38-1.96 (m, 8H), 2.03 (s, 3H), 2.65 (tt, $J = 3.3, 12.5$, 1H), 4.84 (tt, $J = 4.4, 11.0$ Hz, 1H), 7.18-7.32 (m, 5H), *cis-isomer*, 1.38-1.96 (m, 8H), 2.11 (s, 3H), 2.91 (tt, $J = 3.2, 12.0$ Hz, 1H), 5.20 (br, 1H), 7.18-7.32 (m, 5H), ^{13}C NMR (98.5 MHz, CDCl_3 , δ): diastereo mixture; 21.1, 21.4, 21.5, 24.3, 29.5, 31.5, 33.2, 33.6, 37.3, 38.2, 39.3, 42.6, 70.1, 73.2, 76.7, 126.1, 126.2, 126.8, 126.8, 128.4, 145.8, 170.6. Anal. calcd for $\text{C}_{14}\text{H}_{18}\text{O}_2$, C, 77.03; H, 8.31. found C, 76.94; H, 8.41

Synthesis of 2-phenylcyclopentanol (13)

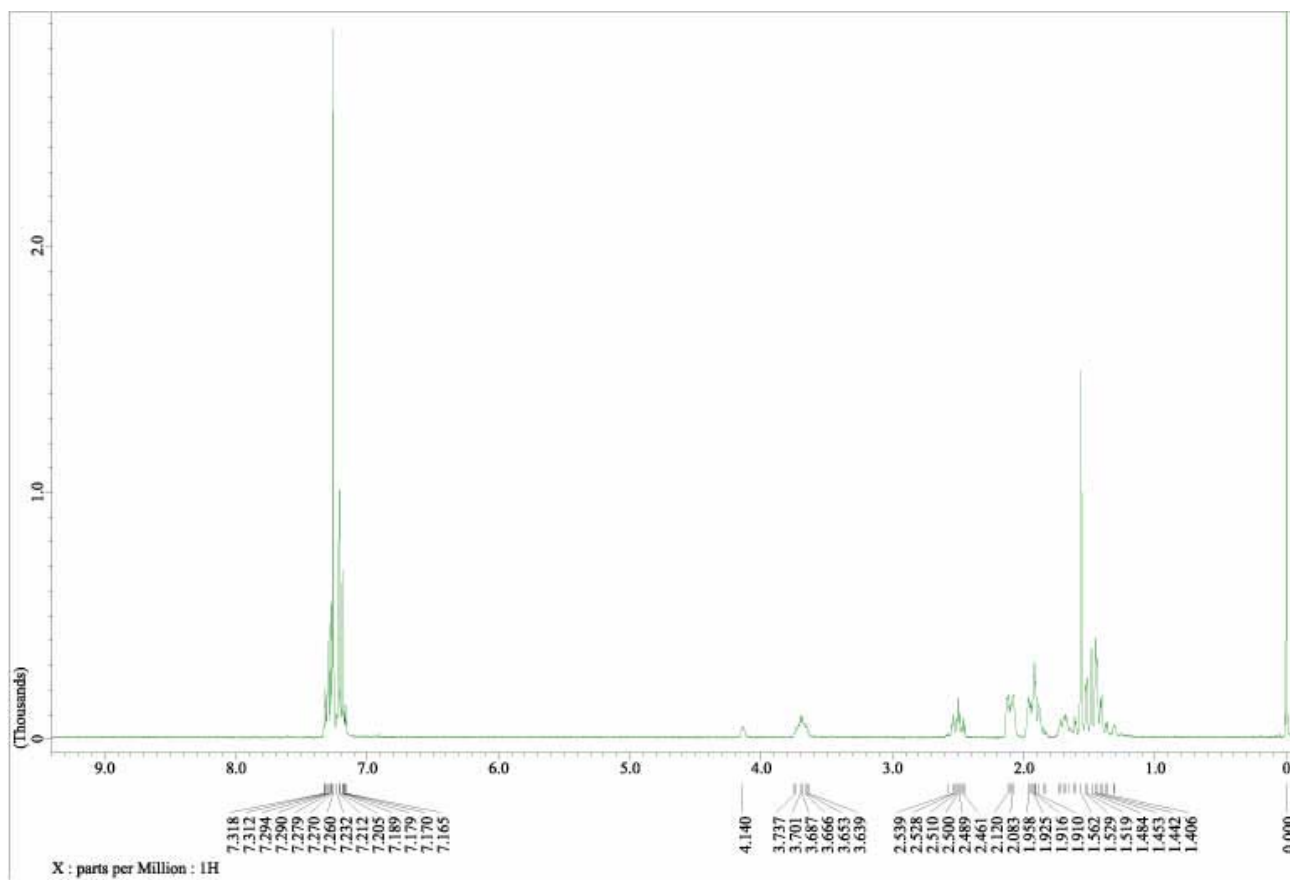


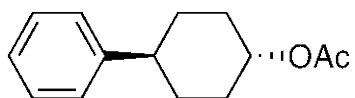
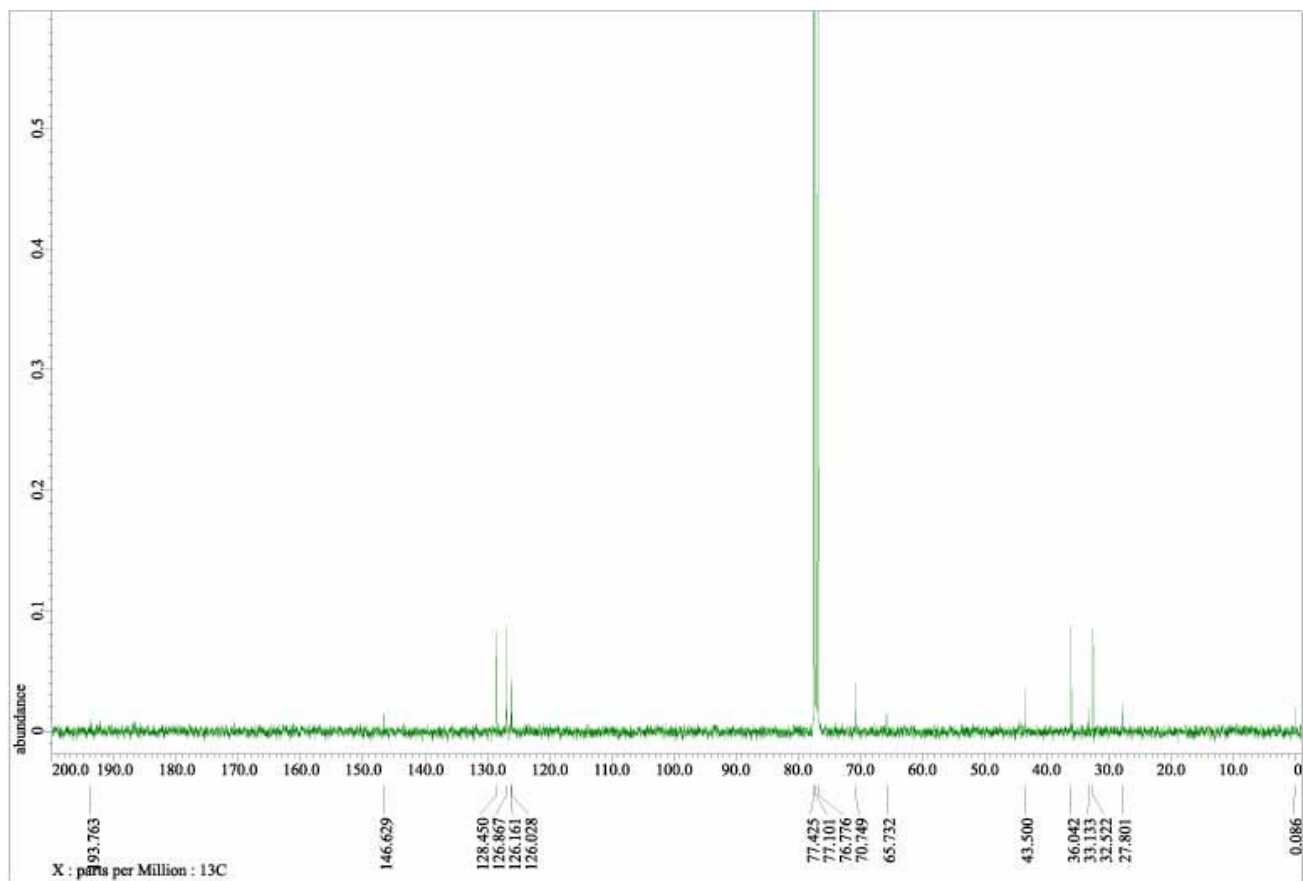
The reaction was carried out according to the typical procedure (A) for 12 hours by using a THF solution of phenylmagnesium bromide (4.75 mL, 1.01 M, 4.80 mmol) and *trans*-2-chlorocyclopentanol (120 mg, 1.00 mmol). The title compound (109 mg, 67% yield, >99% pure on GC analysis) was obtained as a colourless oil after silica gel column chromatography (40% AcOEt in hexane). IR (neat) 3390, 3026, 2932, 2870, 1600, 1488, 1451, 1340, 1220, 1202, 1150, 1056, 1011, 957, 884, 760; ¹H NMR (391.8 MHz, CDCl₃, δ): *trans-isomer*; 1.12 (s, 1H), 1.69-2.12 (m, 6H), 3.03-3.09 (m, 1H), 4.31 (br, 1H), 7.19-7.36 (m, 5H), *cis-isomer*; 1.69-2.12 (m, 8H), 3.03-3.09 (m, 1H), 4.31(m, 1H), 7.19-7.36 (m, 5H). Anal. calcd for C₁₁H₁₄O, C, 81.44; H, 8.70. found C, 81.16; H, 8.55

^1H and ^{13}C NMR spectra of the compounds

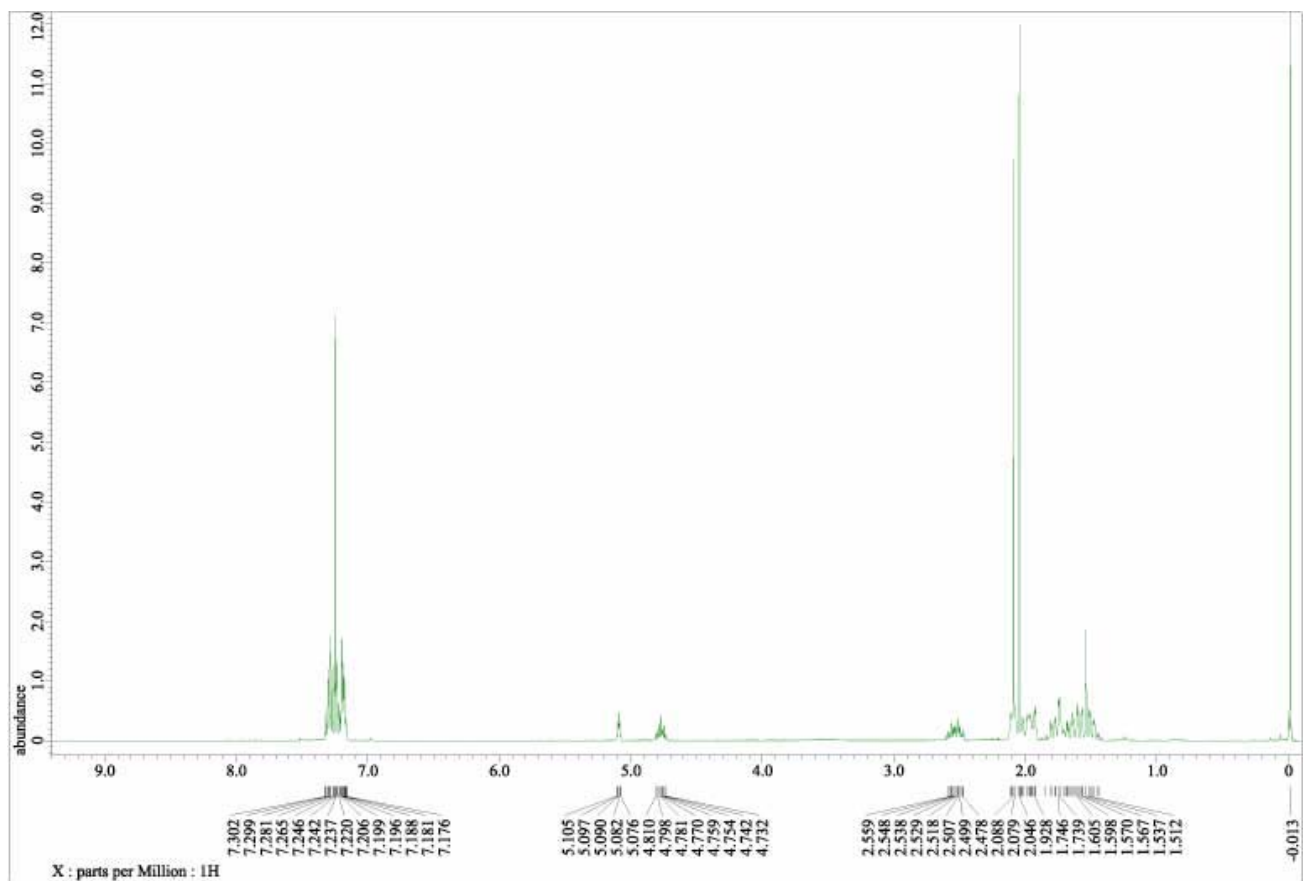


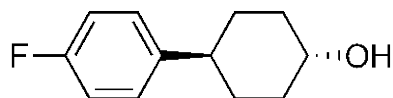
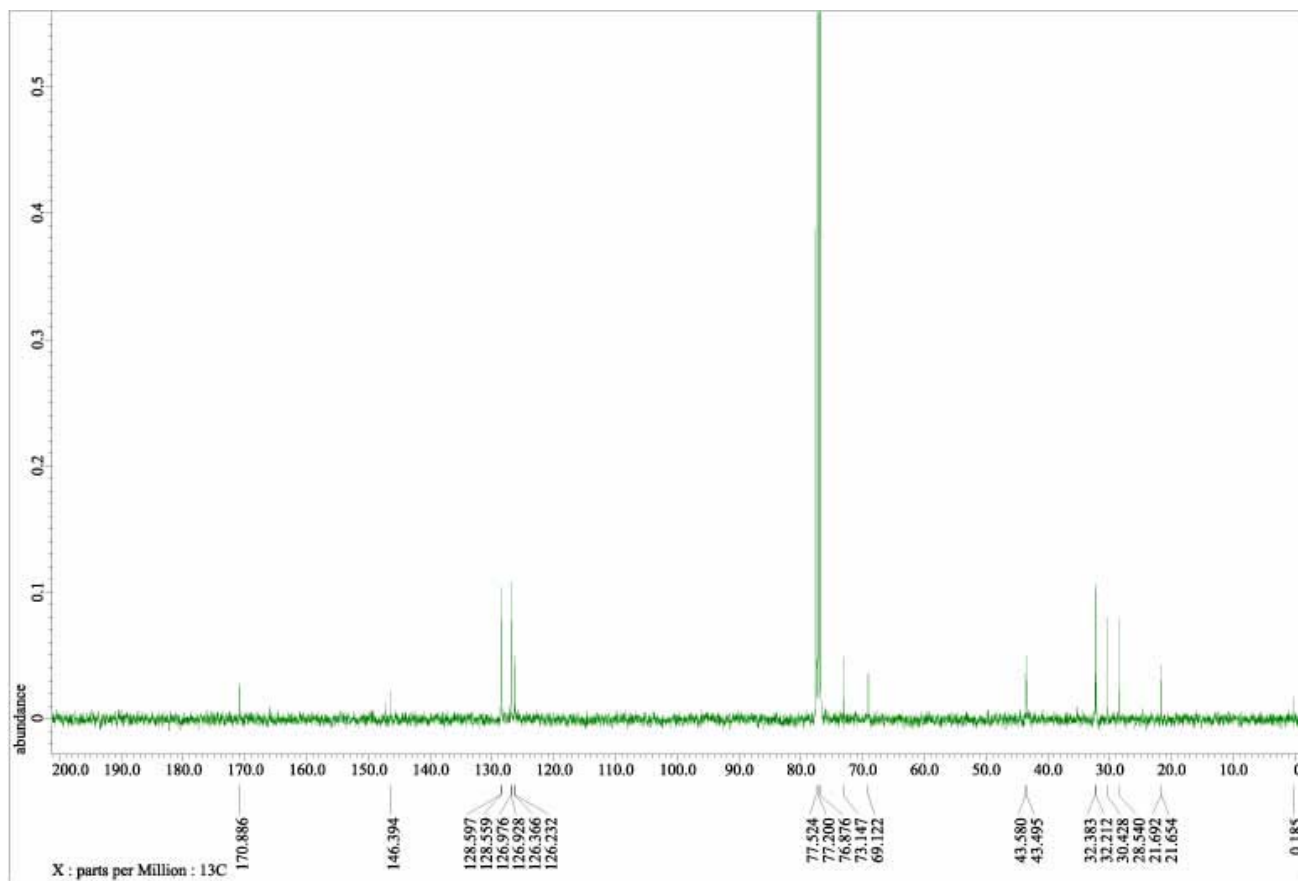
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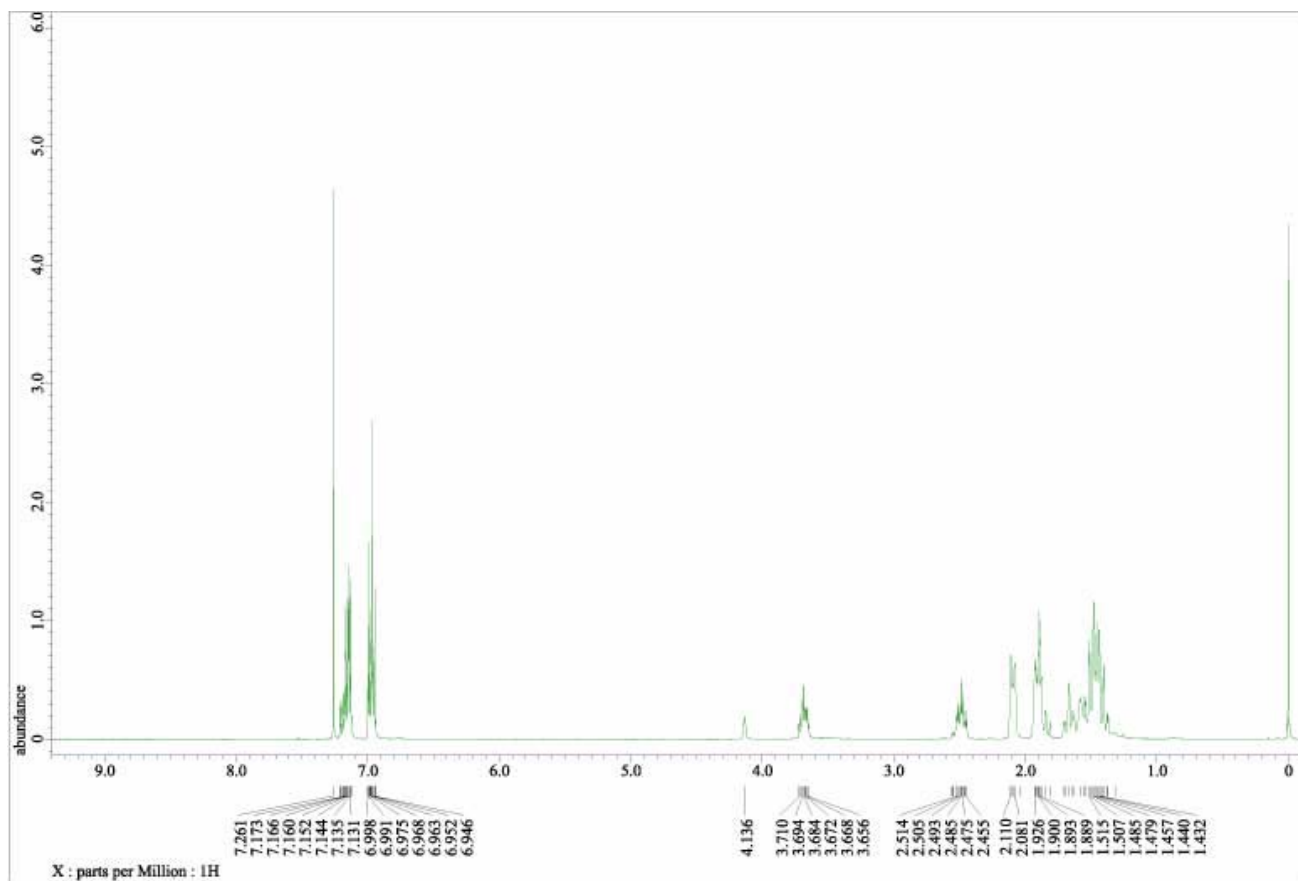


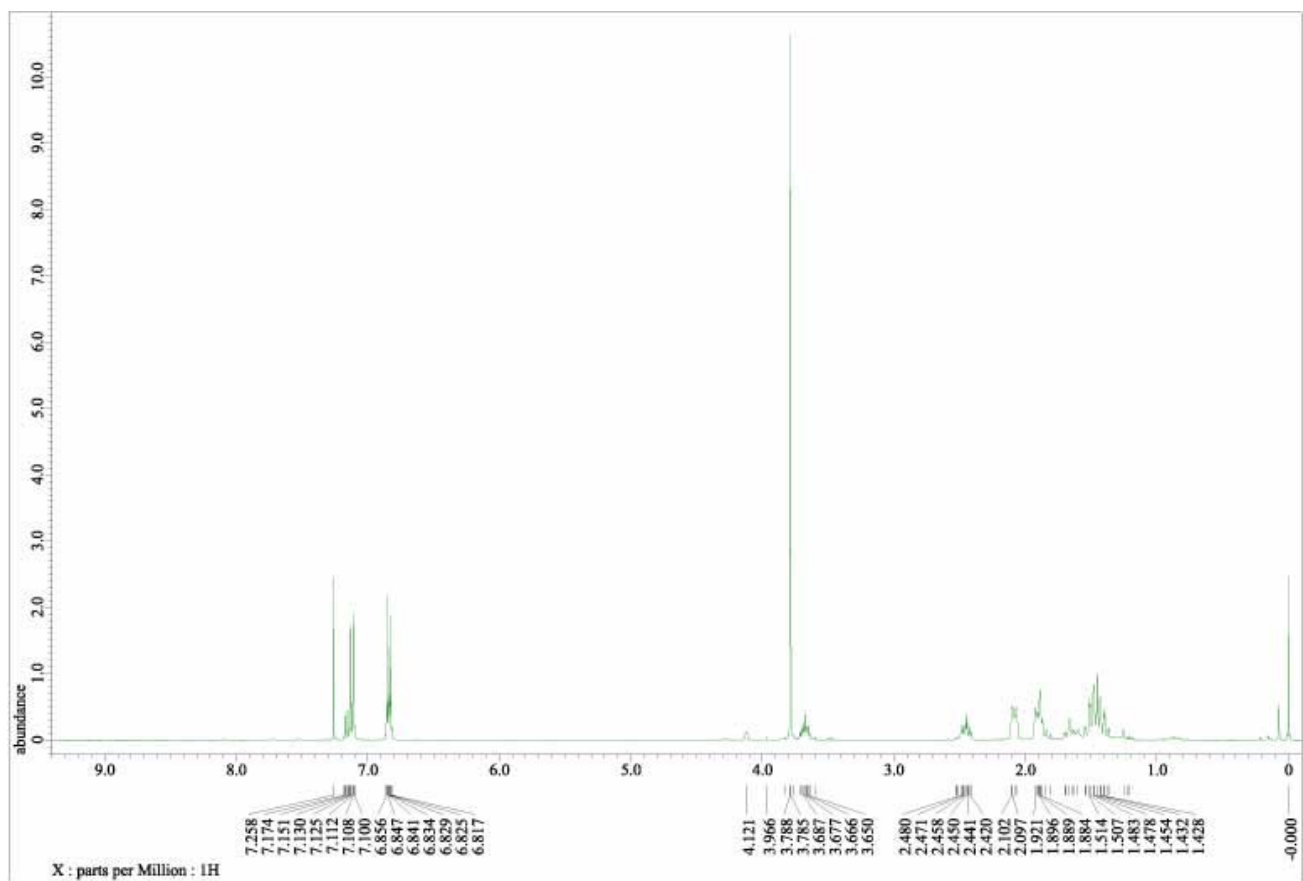
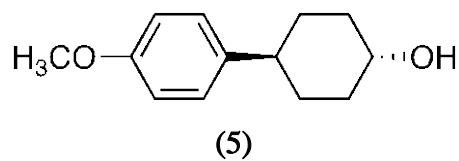
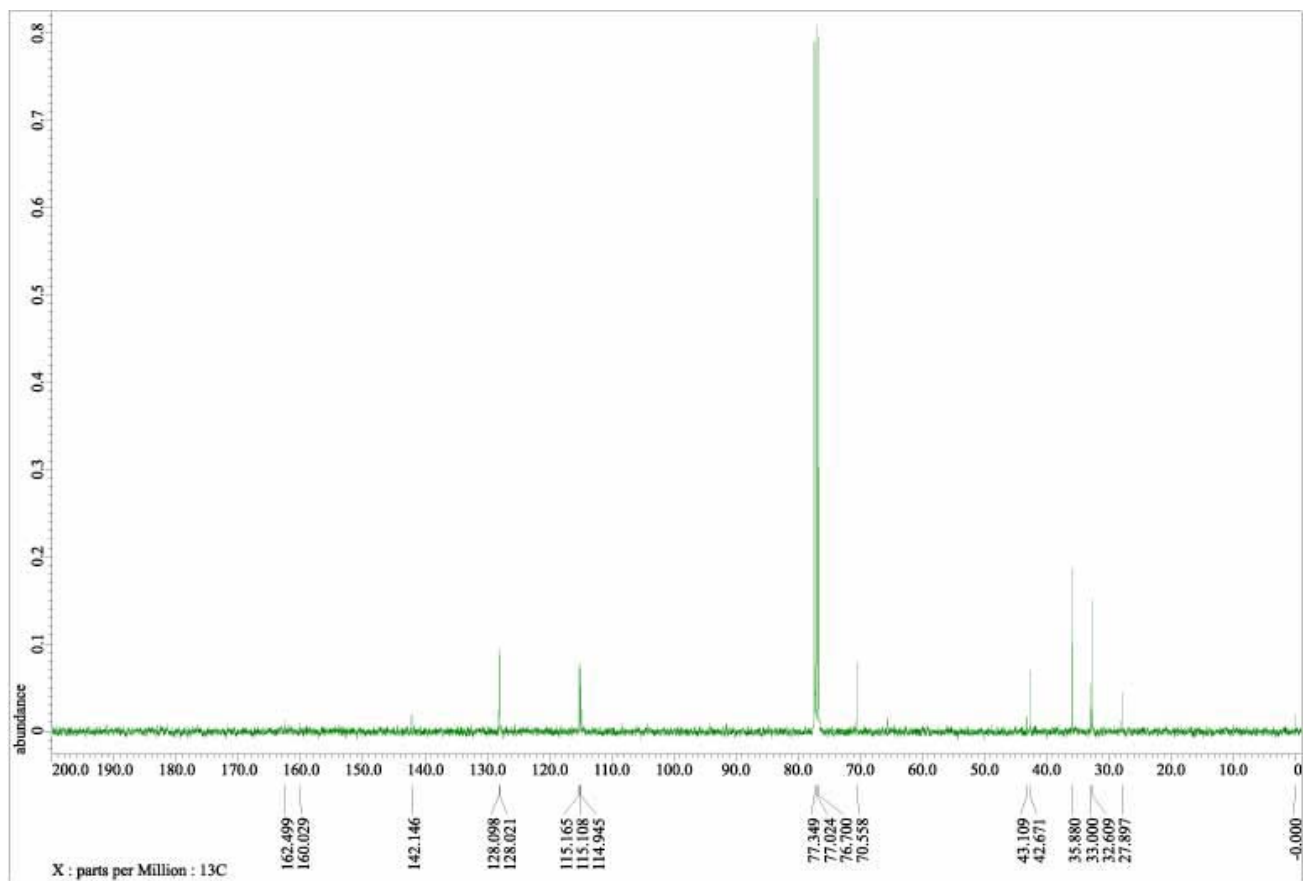
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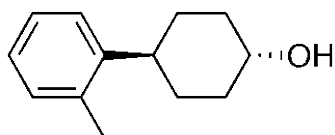
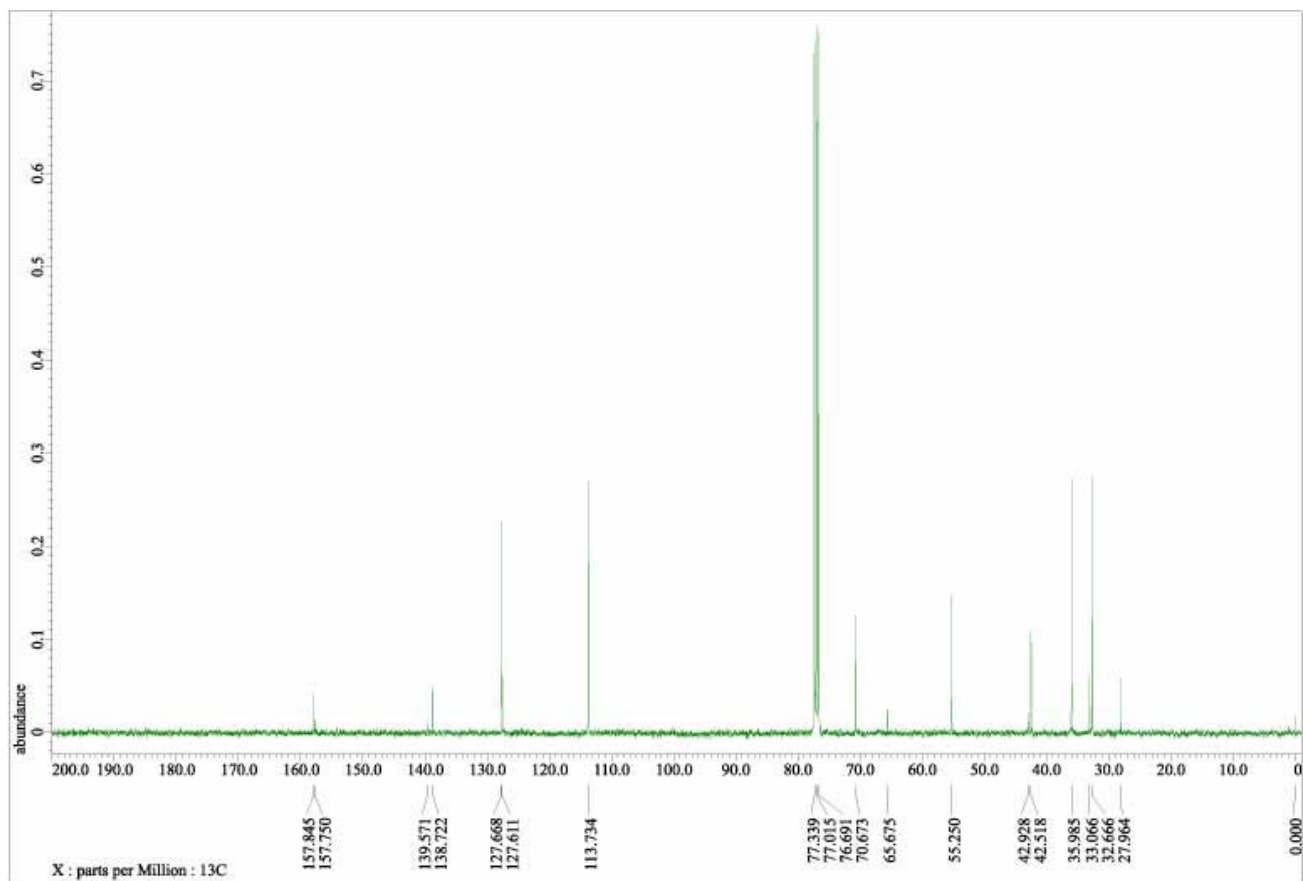




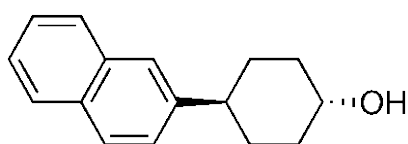
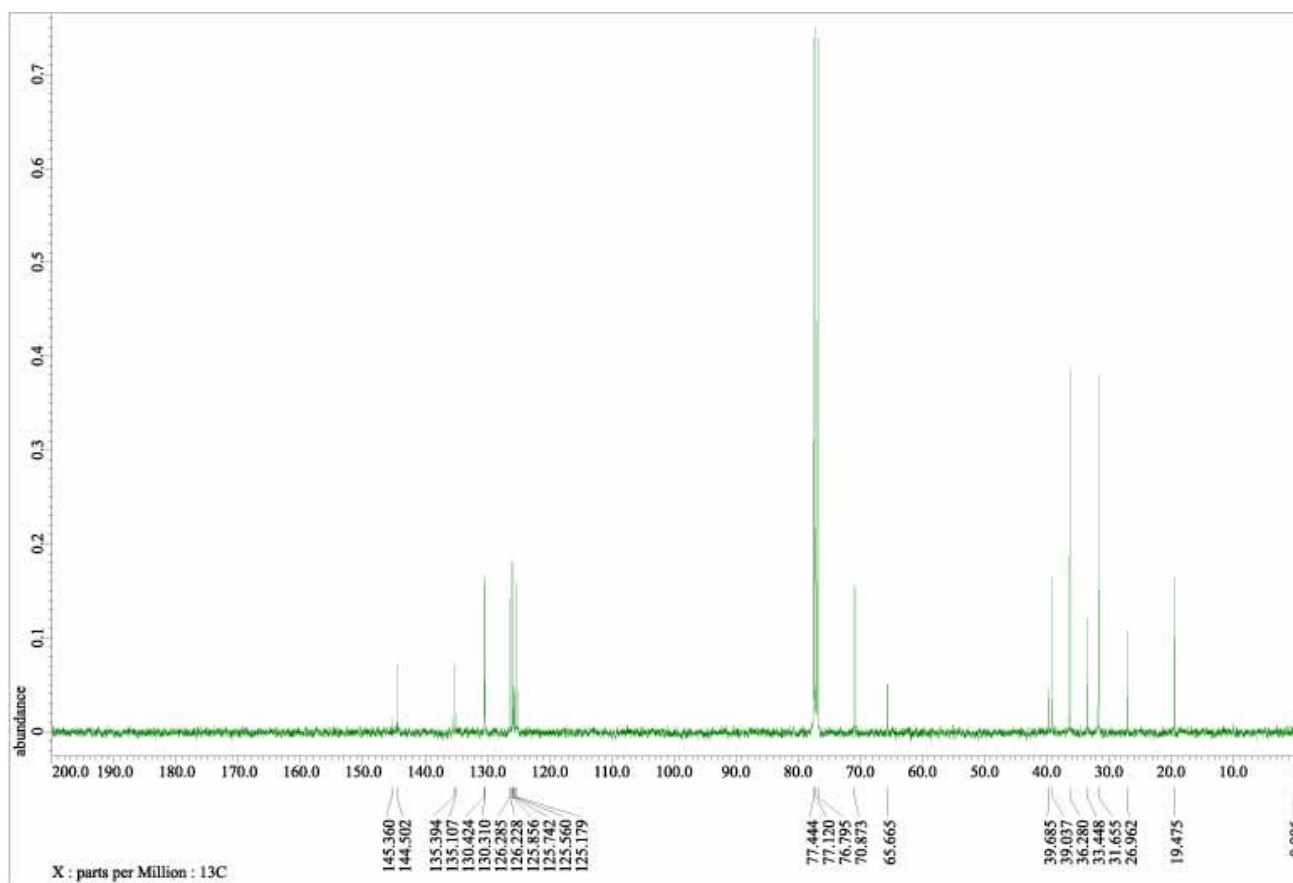
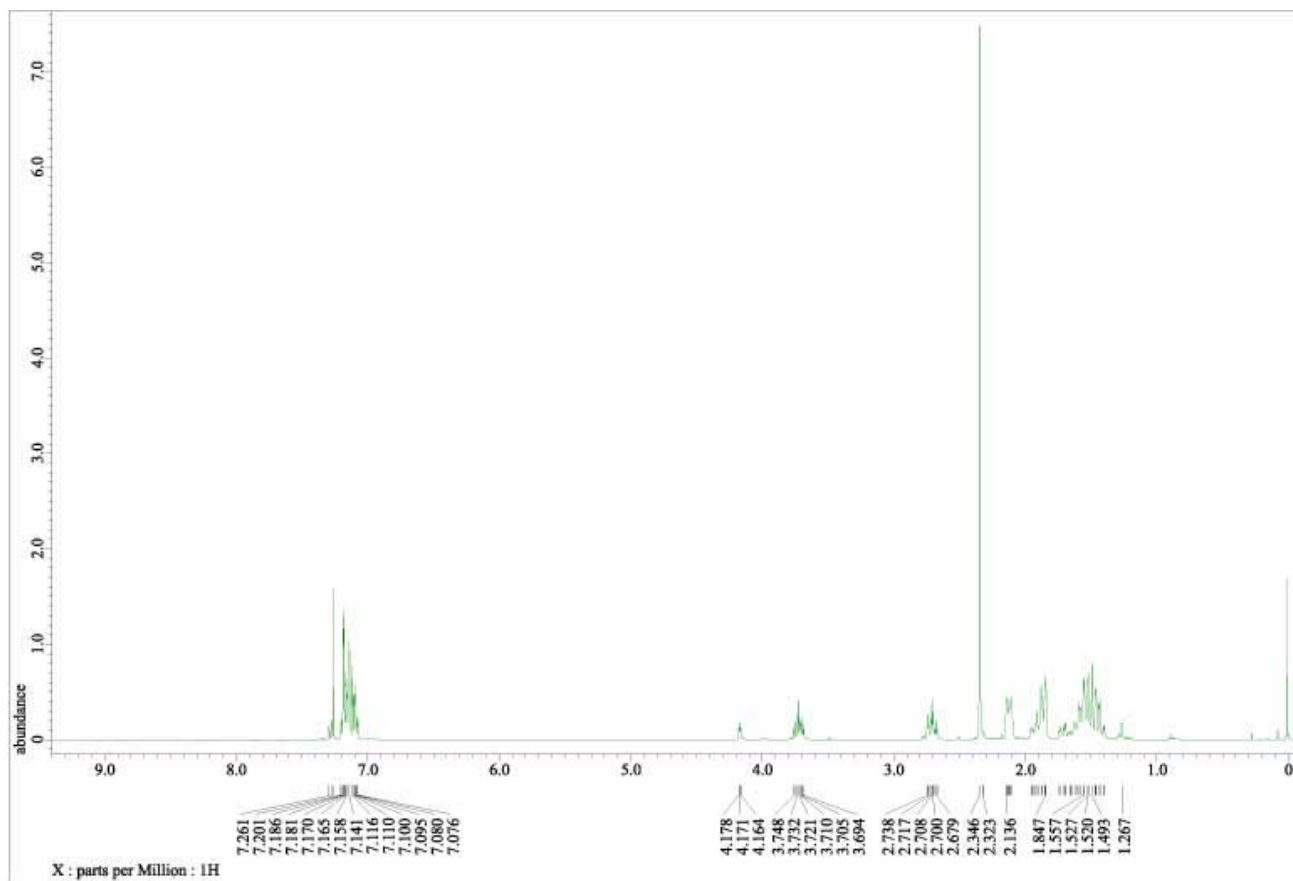
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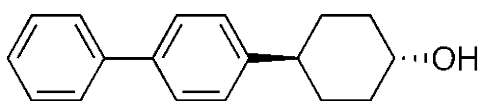
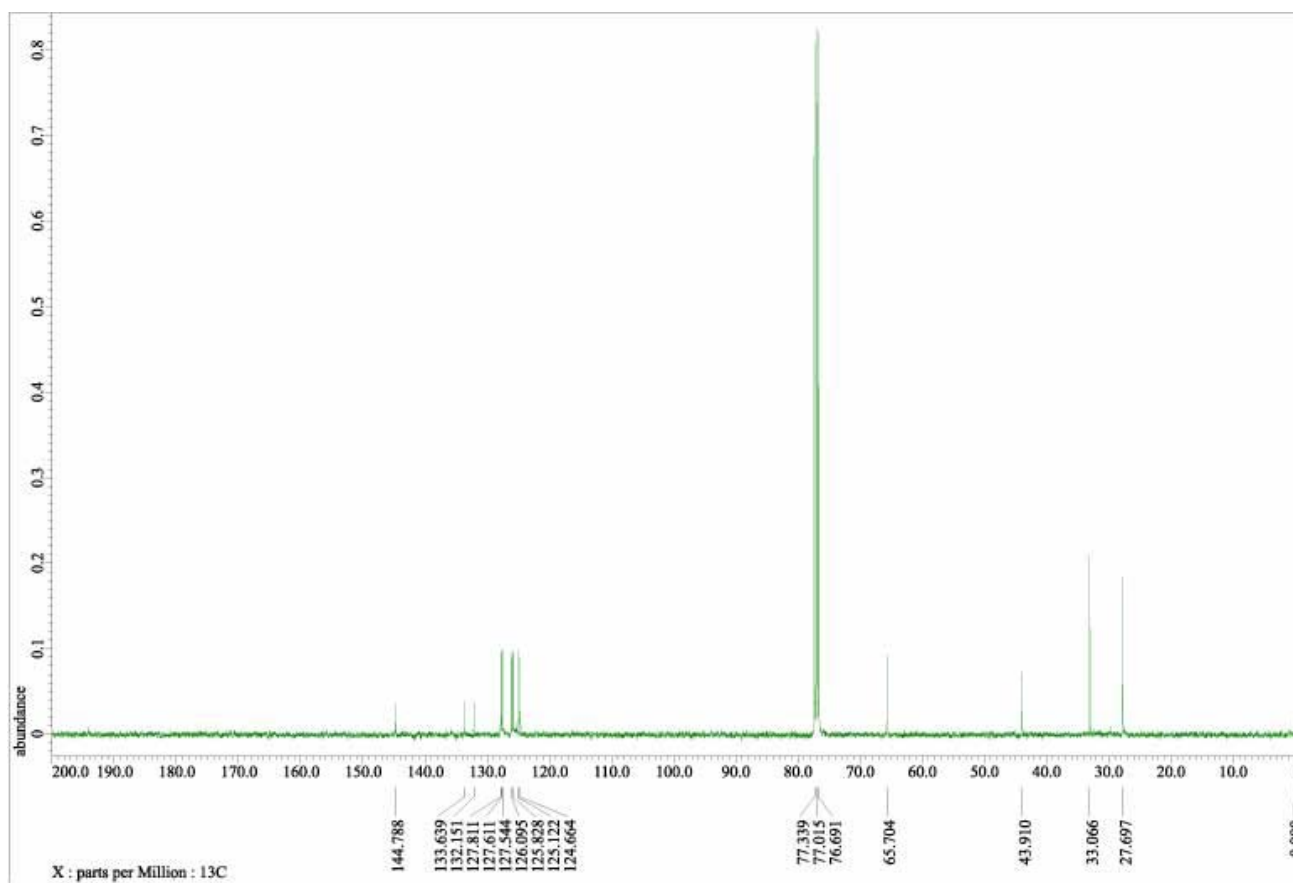
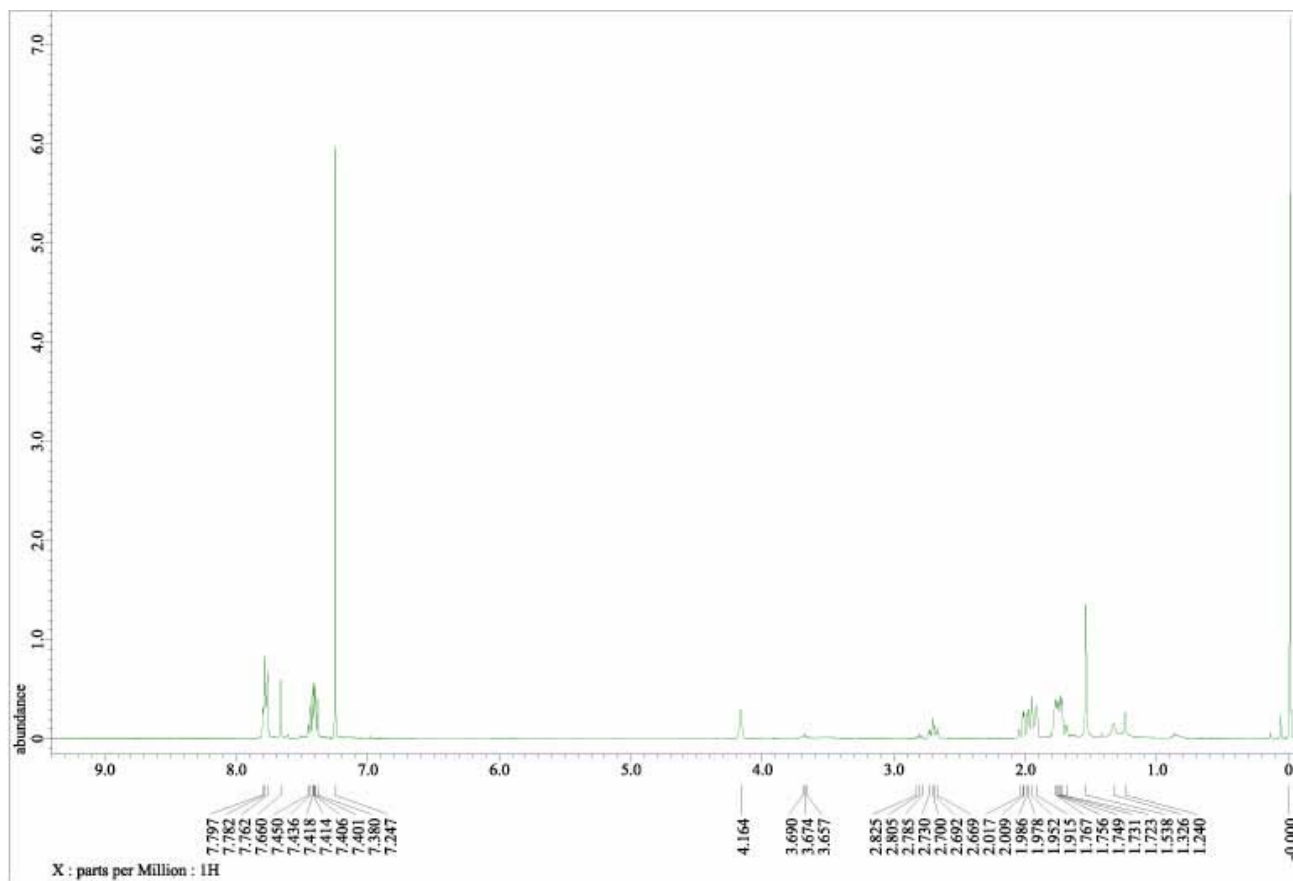




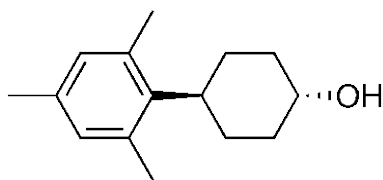
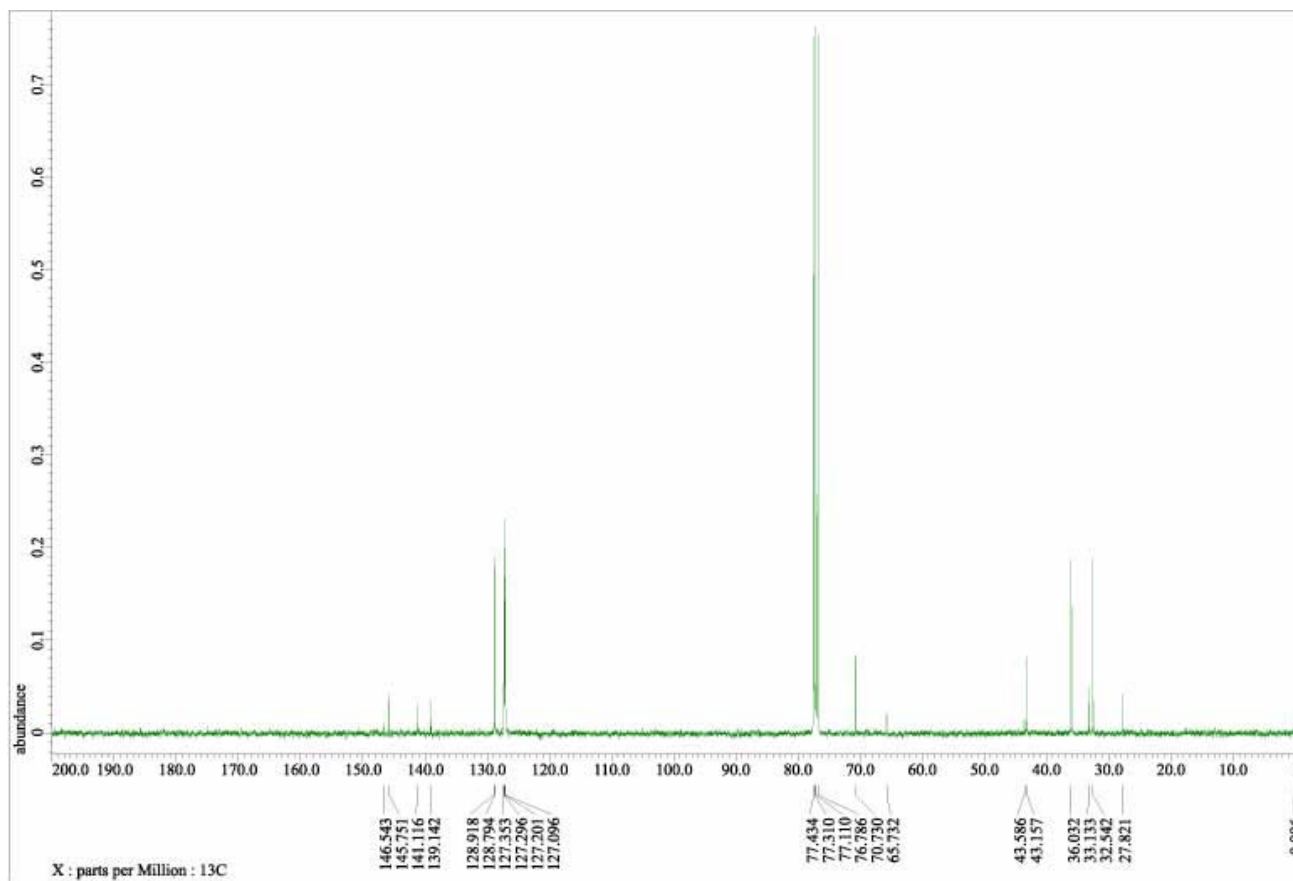
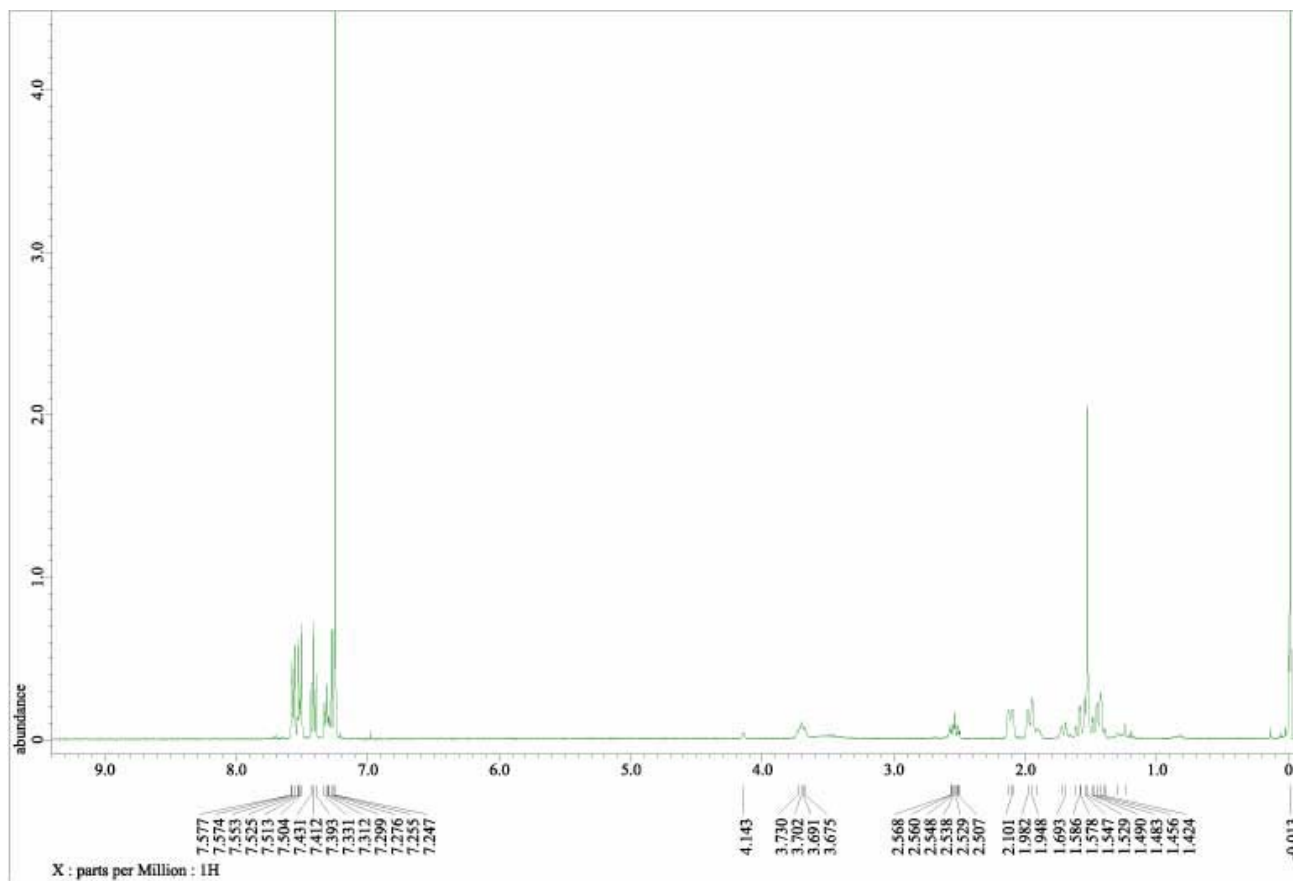
(6)



(7)

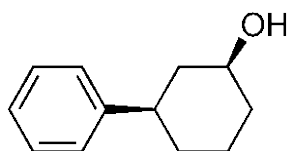
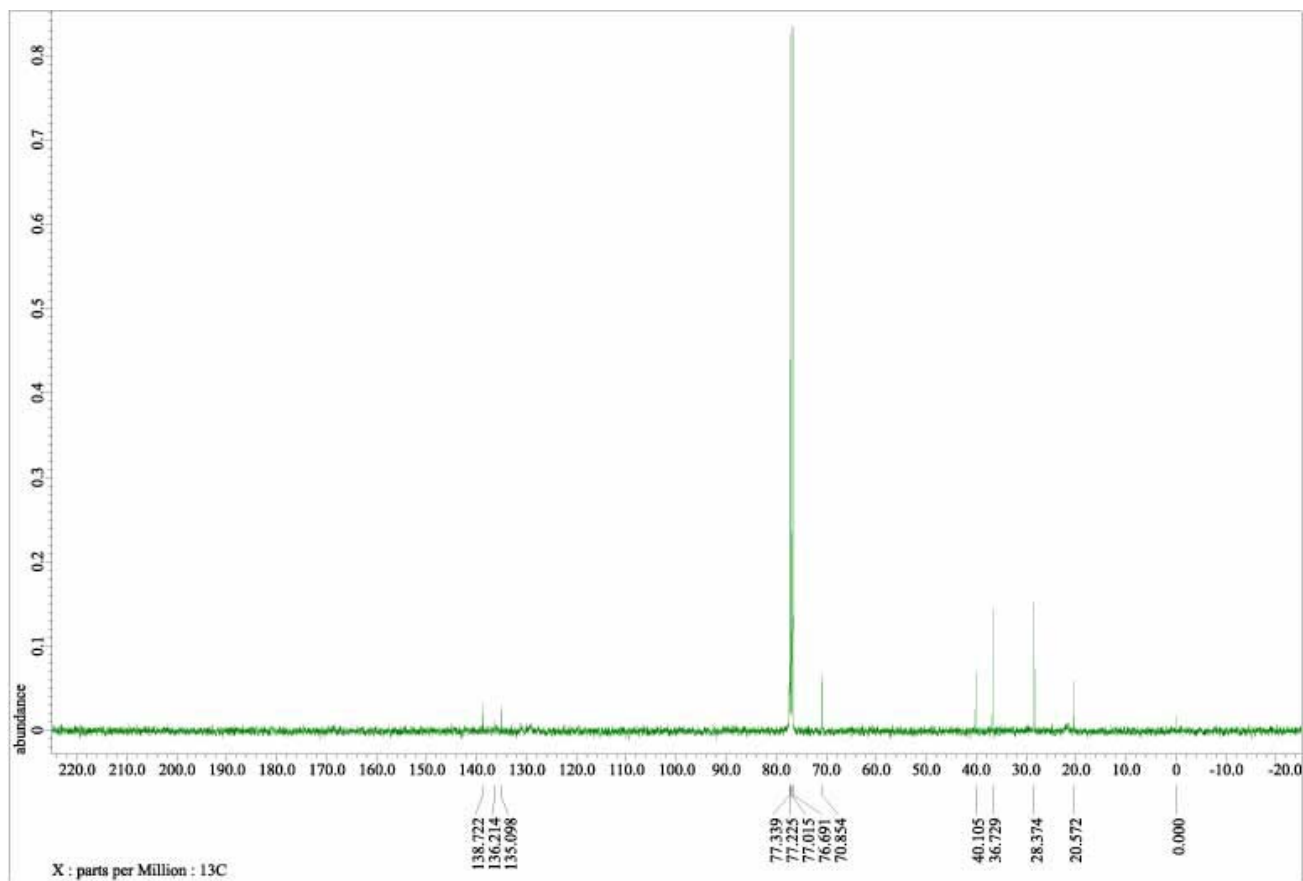
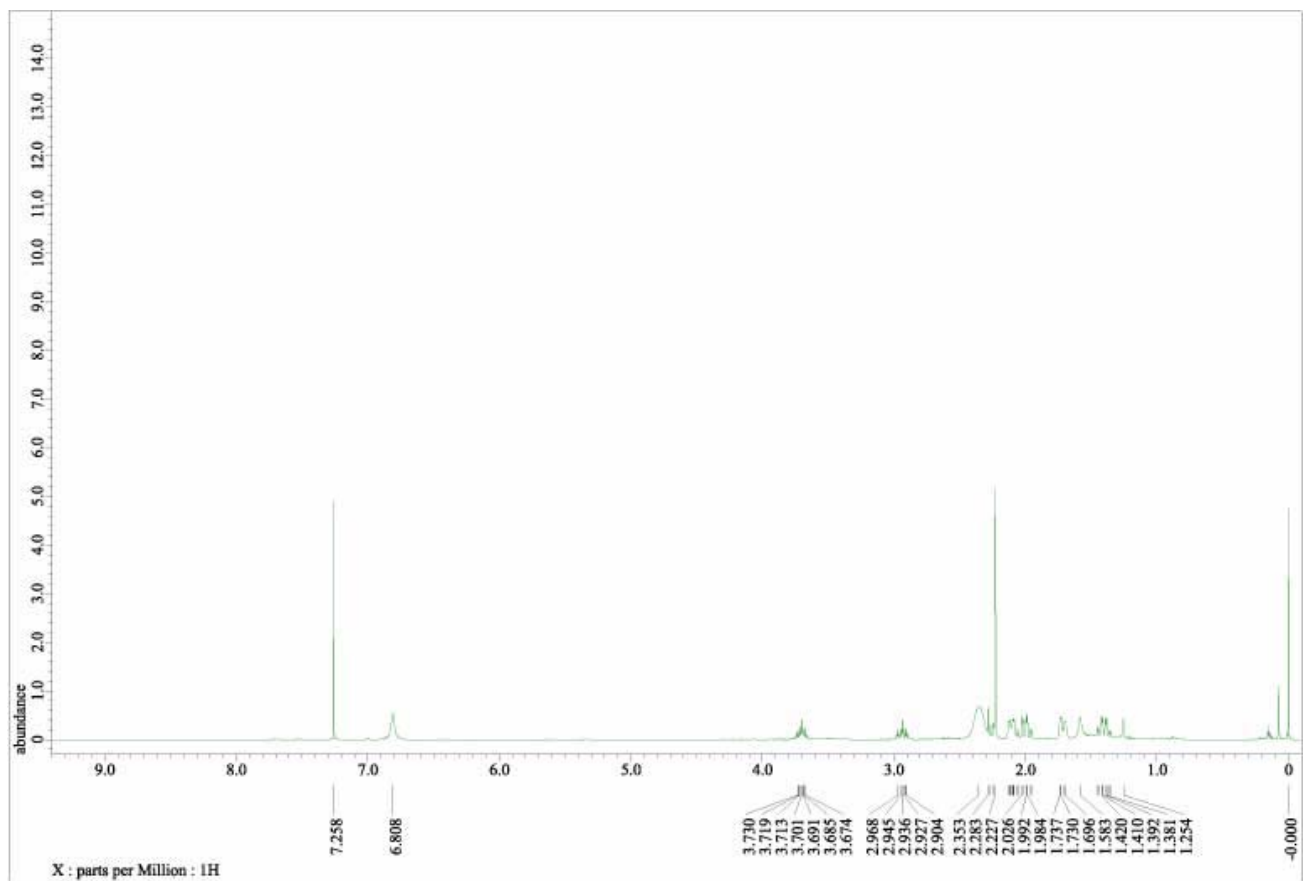


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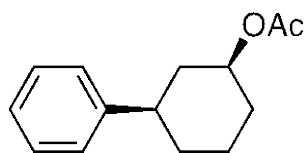
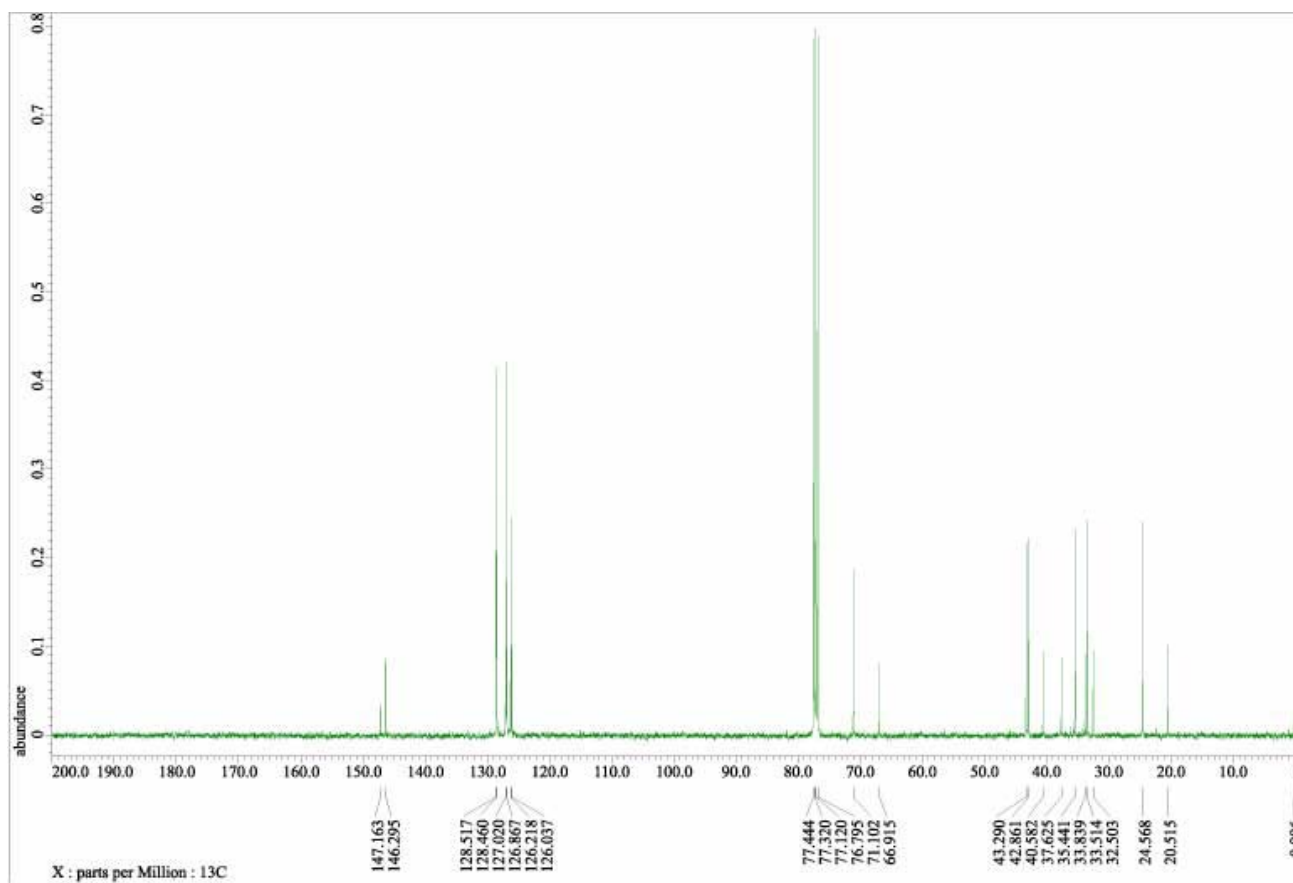
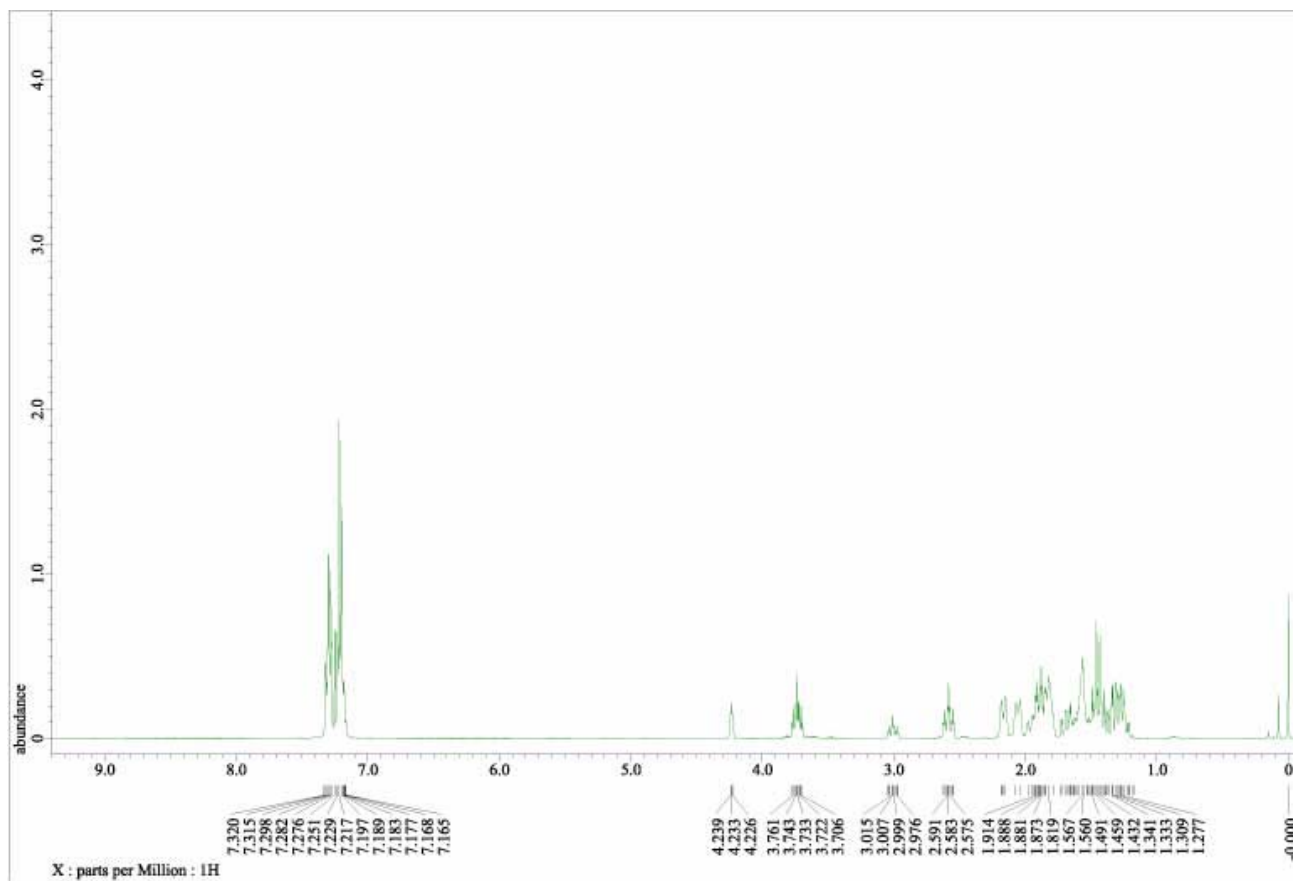


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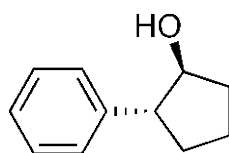
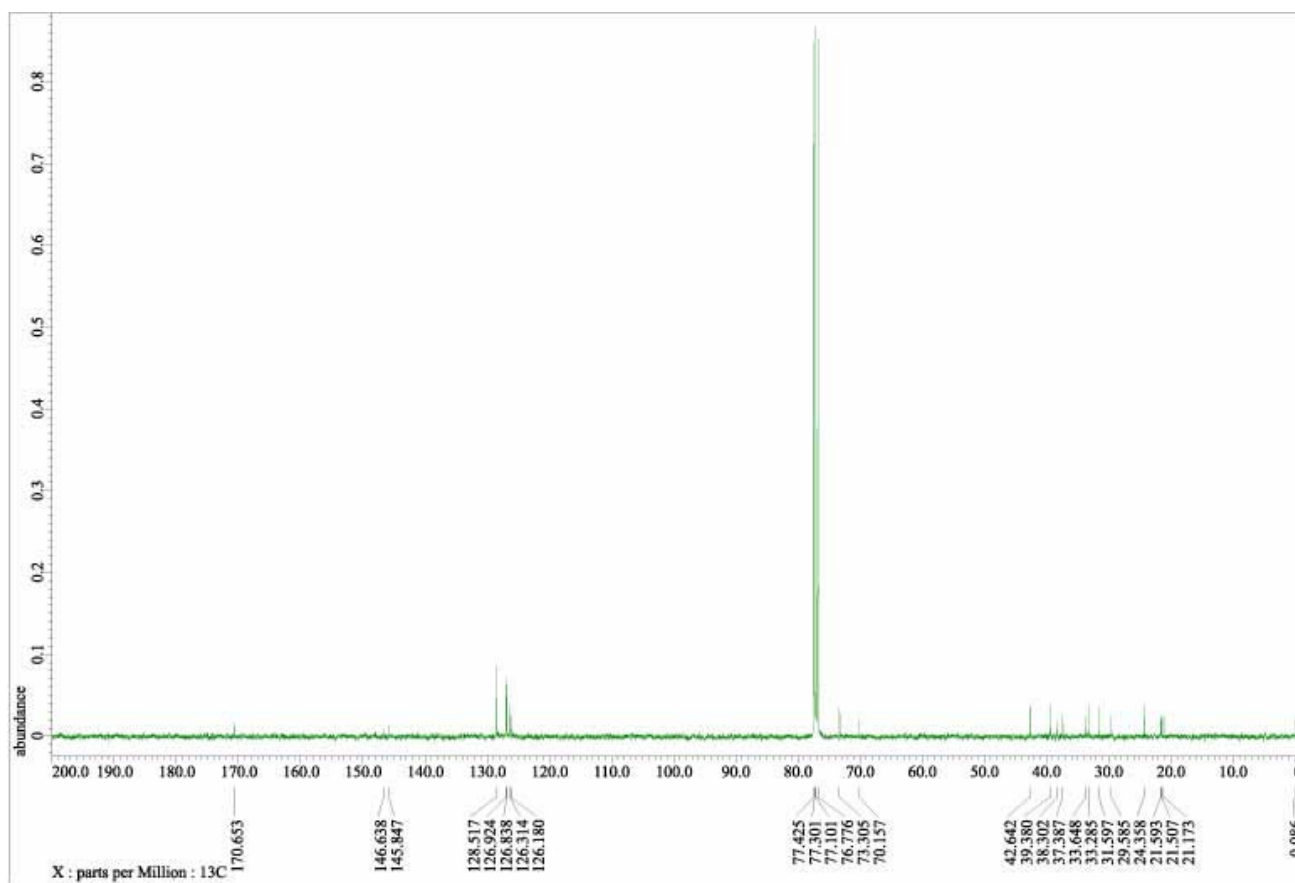
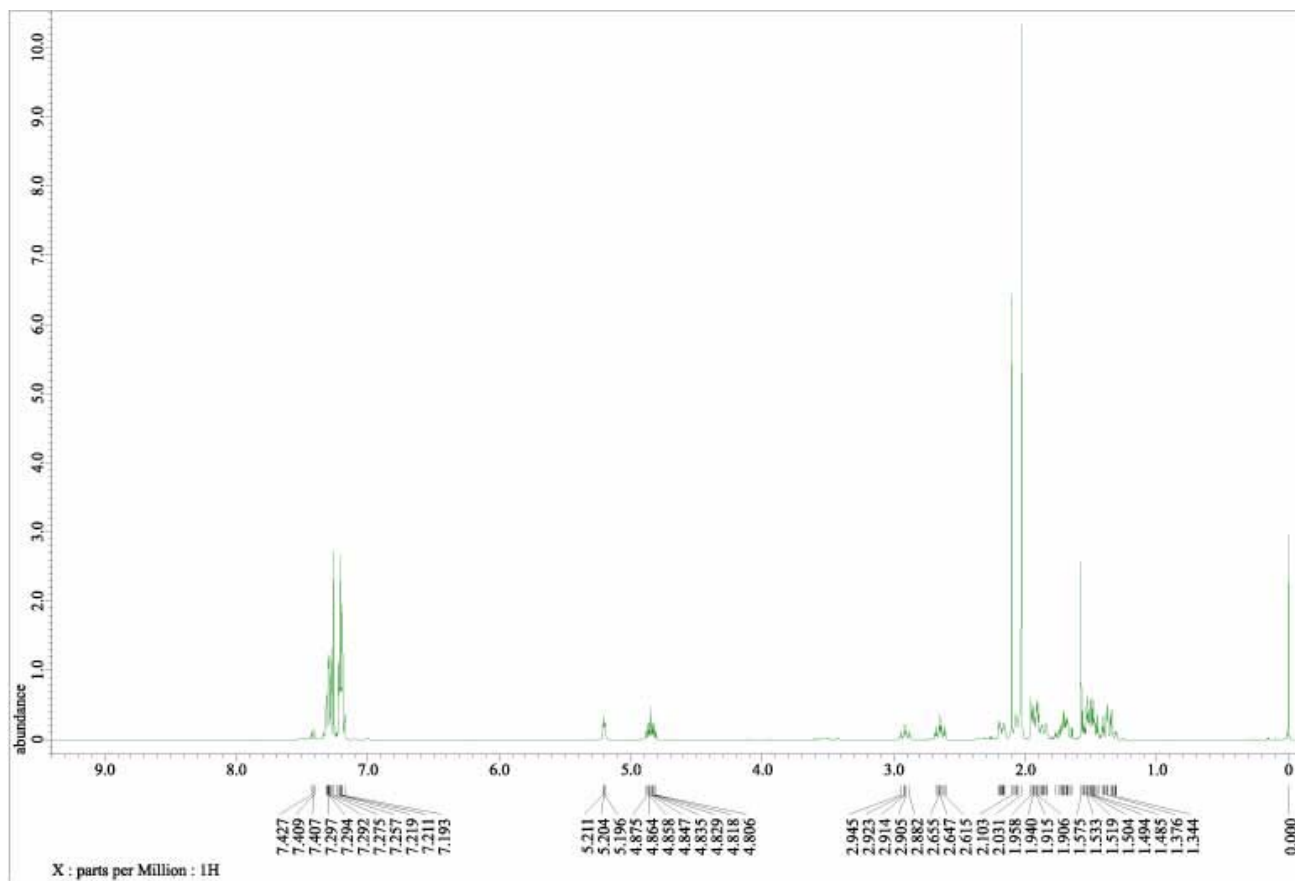
S21



(11)



(12)



(13)

