

A Case of Remote Asymmetric Induction in the Peptide-Catalyzed Desymmetrization of a Bis(phenol)

Chad A. Lewis,[†] Jeffrey L. Gustafson,[†] Anna Chiu,[‡] Jaume Balsells,[‡] David Pollard,[‡]
Jerry Murry,[‡] Robert A. Reamer,[‡] Karl B. Hansen^{**} and Scott J. Miller^{*†}

[†]Department of Chemistry, Yale University, New Haven, Connecticut, 06520; [‡]Merck Research Laboratories, Rahway, New Jersey, 07065

Supplementary Materials

General Procedures. Proton NMR spectra were recorded on either a Bruker 400 or 500 MHz spectrometer or a Varian 500 or 600 MHz spectrometer. Proton chemical shifts are reported in ppm (δ) relative to internal tetramethylsilane (δ 0.0) or solvent peak (CDCl_3 or CD_3OD , 7.26 or 3.30 ppm respectively). Data are reported as follows: chemical shift (multiplicity [singlet (s), doublet (d), triplet (t), quartet (q) and multiplet (m)], coupling constants [Hz], integration). NMR data were collected at 25 °C. Infrared spectra were obtained on a ThermoNicolet Avatar 210 spectrometer. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 Å F-254 precoated plates (0.25 mm thickness). Visualization was accomplished after staining with cerium ammonium molybdenate (CAM) solution. Flash column chromatography was performed using Silica Gel 60 Å (32-63 μm). Optical rotations were recorded on a Rudolf Research Analytical Autopol IV Automatic Polarimeter at the sodium D line (path length 50 mm, corrected to 20.0 °C). High-resolution mass spectra were obtained at either the Proteomics and Mass Spectrometry Resource of the Keck Laboratory at Yale University or the Mass Spectrometry Facility at the University of Illinois Urbana-Champaign. The method of ionization is given in parentheses.

Analytical and preparative reverse phase HPLC were run on a Rainin SD-200 chromatograph equipped with a single wavelength UV detector (214 nm). Analytical reverse phase HPLC was performed on a Hewlett-Packard 1100 Series chromatograph equipped with a diode array detector. All reactions were carried out under a nitrogen atmosphere employing oven or flame-dried glassware. All solvents were either distilled or obtained from passing through activated alumina.

Peptide Synthesis and Screens

Peptides were synthesized on solid support using commercially available Wang polystyrene resin preloaded with Fmoc protected amino acid. Couplings were performed using 5 equiv. amino acid derivative, 5 equiv. HBTU, and 10 equiv. Hünig's base in DMF, for 3 h. Deprotections were performed using 20% piperidine in DMF for 20 min. (to minimize diketopiperazine formation; dipeptides were deprotected using 50% piperidine in DMF for 5 min.). Peptides were cleaved from solid support using a mixture of $\text{MeOH}:\text{DMF}:\text{NEt}_3$ (9:1:1) for 5 days. The peptides were characterized by electrospray mass spectrometry and used in parallel reaction screens without further purification. Peptides of interest were purified by reverse phase chromatography on a Biotage SP4 using C18 silica gel. The peptides were purified by a gradient of 40% methanol/water and increasing to 80% methanol/water over 35 column volumes.

Table 1: Peptide Catalysts Screened and Subsequent % ee for **3**

Peptide	Sequence	Library	Temp (°C)	% ee
1A	Boc-Pmh-Asp(OBut)-Trp-Aib-Tyr(Bn)-Phe-OMe	1	4	3
1B	Boc-Pmh-Asp(OBut)-Asn(Trt)-Aib-Phe-Phe-OMe	1	4	17
1C	Boc-Pmh-Pro-Trp-Arg(Boc) ₂ -Tyr(OH)-Phe-OMe	1	4	0
1D	Boc-Pmh-Tyr-Phe-His(Trt)-Tyr(<i>t</i> Bu)-Phe-OMe	1	4	12
1E	Boc-Pmh-Pro-Asn(Trt)-His(Trt)-Tyr(OH)-Phe-OMe	1	4	6
1F	Boc-Pmh-Phe-Gly-Leu-Phe-Phe-OMe	1	4	29
1G	Boc-Pmh-Asn(Trt)-Leu-Val-D-Phe-Phe-OMe	1	4	40
1H	Boc-Pmh-Asp(OBut)-Tyr(Bn)-Aib-Met-Phe-OMe	1	4	7
1I	Boc-Pmh-Leu-Tyr(<i>t</i> Bu)-Arg(Boc) ₂ -Lys(Boc)-Phe-OMe	1	4	4
1J	Boc-Pmh-Ile-Val-Asn-Thr(<i>t</i> Bu)-Phe-OMe	1	4	19
1K	Boc-Pmh-Glu-Val-Phe-Ala-Phe-OMe	1	4	9
1L	Boc-Pmh-Trp(Boc)-His(Trt)-Gly-Phe-Phe-OMe	1	4	4
1M	Boc-Pmh-Phe-Gly-D-Val-D-Ala-Phe-OMe	1	4	7
1N	Boc-Pmh-Aib-Pro-Phe-D-Val-Phe-OMe	1	4	3
1O	Boc-Pmh-Pro-Aib-Pro-Tyr(Bn)-Phe-OMe	1	4	4
1P	Boc-Pmh-D-Phe-Pro-Asn(Trt)-Val-Phe-OMe	1	4	7
1Q	Boc-Pmh-Phe-D-Phe-Pro-Phe-Phe-OMe	1	4	17
1R	Boc-Pmh-Phe-Gly-Pro-Phe-Phe-OMe	1	4	21
1S	Boc-Pmh-Thr(<i>t</i> Bu)-D-Val-His(Trt)-D-Phe-Phe-OMe	1	4	0
1T	Boc-Pmh-Ser(<i>t</i> Bu)-D-Ala-D-Phe-His(Trt)-Phe-OMe	1	4	13
1U	Boc-Pmh-Tyr(<i>t</i> Bu)-D-Phe-D-His(Trt)-Tyr(<i>t</i> Bu)-Phe-OMe	1	4	25
1V	Boc-Pmh-Val-Glu(<i>t</i> Bu)-Asp(OBut)-D-Phe-Phe-OMe	1	4	7
1W	Boc-Pmh-D-Leu-Tyr(<i>t</i> Bu)-Arg(Boc) ₂ -Lys(Boc)-Phe-OMe	1	4	2
1X	Boc-Pmh-D-Ile-D-Val-Asn(Trt)-Thr(<i>t</i> Bu)-Phe-OMe	1	4	58
1Y	Boc-Pmh-Pro-His(Trt)-Phe-D-Val-Phe-OMe	1	4	14
1Z	Boc-Pmh-Thr(<i>t</i> Bu)-D-Pro-Ser(<i>t</i> Bu)-Phe-Phe-OMe	1	4	21
2A	Boc-Pmh-Leu-Aib-Phe-D-Val-Phe-OMe	1	4	23
2B	Boc-Pmh-Asp(OBut)-Asn(Trt)-Arg(Boc) ₂ -Tyr(OH)-Phe-OMe	1	4	9
2C	Boc-Pmh-Asp(OBut)-Asn(Trt)-Asn(Trt)-Tyr(<i>t</i> Bu)-Phe-OMe	1	4	14
2D	Boc-Pmh-Asp(OBut)-Asn(Trt)-His(Trt)-Tyr(Bn)-Phe-OMe	1	4	5
2E	Boc-Pmh-Asp(OBut)-Asn-Met-Tyr(OH)-Phe-OMe	1	4	8

2F	Boc-Pmh-Thr(<i>t</i> Bu)-Asn(Trt)-Arg(Boc) ₂ -Tyr(Bn)-Phe-OMe	1	4	3
2G	Boc-Pmh-Ser(<i>t</i> bu)-Asn(Trt)-Arg(Boc) ₂ -Tyr(Bn)-Phe-OMe	1	4	0
2H	Boc-Pmh-Dbg-D-Phe-D-Pro-Val-Leu-OMe	1	4	28
2I	Boc-Pmh-Dbg-Phe-Pro-D-Val-Leu-OMe	1	4	14
2J	Boc-Pmh-Ala-His(Trt)-Tyr(Bn)-Leu-Ile-OMe	1	4	12
2K	Boc-Pmh-Ile-Phe-Leu-Phe-Ile-OMe	1	4	9
2L	Boc-Pmh-Hyp(OBut)-Thr(<i>t</i> Bu)-D-Ala-Val-Ile-OMe	1	4	8
2M	Boc-Pmh-Phe-Gly-Tyr(<i>t</i> bu)-Phe-Ile-OMe	1	4	4
2N	Boc-Pmh-Tyr(<i>t</i> Bu)-Val-Cha-D-Phe-Ile-OMe	1	4	16
2O	Boc-Pmh-Asp(OBut)-Asn(Trt)-Lys(Boc)-Tyr(OH)-Ile-OMe	1	4	19
2P	Boc-Pmh-Asn(Trt)-Leu-Val-Phe-D-Phe-OMe	2	4	9
2Q	Boc-Pmh-Asn(Trt)-Leu-Val-D-Phe-D-Phe-OMe	2	4	38
2R	Boc-Pmh-Asn(Trt)-Ile-Val-D-Phe-Phe-OMe	2	4	12
2S	Boc-Pmh-Asn(Trt)-Ala-Val-D-Phe-Phe-OMe	2	4	32
2T	Boc-Pmh-Asn(Trt)-D-Ala-Val-D-Phe-Phe-OMe	2	4	7
2U	Boc-Pmh-Asn(Trt)-Val-Val-D-Phe-Phe-OMe	2	4	10
2V	Boc-Pmh-Asn(Trt)-D-Val-Val-D-Phe-Phe-OMe	2	4	18
2W	Boc-Pmh-Asn(Trt)-Leu-Ile-D-Phe-Phe-OMe	2	4	22
2X	Boc-Pmh-Asn(Trt)-Leu-Ala-D-Phe-Phe-OMe	2	4	43
2X	Boc-Pmh-Asn(Trt)-Leu-Ala-D-Phe-Phe-OMe	2	-20	59
2Y	Boc-Pmh-Asn(Trt)-Leu-D-Ala-D-Phe-Phe-OMe	2	4	15
2Z	Boc-Pmh-Asn(Trt)-Leu-D-Val-D-Phe-Phe-OMe	2	4	64
2Z	Boc-Pmh-Asn(Trt)-Leu-D-Val-D-Phe-Phe-OMe	2	-20	10
3A	Boc-Pmh-Asn(Trt)-Ile-Val-D-Phe-Phe-OMe	2	4	26
3B	Boc-Pmh-Asn(Trt)-Dbg-Val-D-Phe-Phe-OMe	2	4	39
3C	Boc-Pmh-Asn(Trt)-Gly-Val-D-Phe-Phe-OMe	2	4	11
3D	Boc-Pmh-Asn(Trt)-Leu-Dbg-D-Phe-Phe-OMe	2	4	7
3E	Boc-Pmh-Asn(Trt)-Leu-Gly-D-Phe-Phe-OMe	2	4	15
3F	Boc-Pmh-Asn(Trt)-Aib-Val-D-Phe-Phe-OMe	2	4	41
3F	Boc-Pmh-Asn(Trt)-Aib-Val-D-Phe-Phe-OMe	2	-20	63
3G	Boc-Pmh-Asn(Trt)-Leu-Aib-D-Phe-Phe-OMe	2	4	34
3H	Boc-Pmh-D-Asn(Trt)-Leu-Val-D-Phe-Phe-OMe	2	4	10
3I	Boc-Pmh-Asn(Trt)-Leu-Val-D-Tyr(Bn)-Phe-OMe	2	4	32
3J	Boc-Pmh-Asn(Trt)-Ser(<i>t</i> Bu)-Val-D-Phe-Phe-OMe	2	4	28
3K	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	2	4	47
3K	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	2	-20	67
3L	Boc-Pmh-Asn(Trt)-Leu-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	2	4	49
3L	Boc-Pmh-Asn(Trt)-Leu-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	2	-20	58
3M	Boc-Pmh-Asn(Trt)-Thr(<i>t</i> Bu)-Val-D-Phe-Phe-OMe	2	4	29
3N	Boc-Pmh-Asp(OBut)-Leu-Val-D-Phe-Phe-OMe	3	4	31
3O	Boc-Pmh-Asp(OBn)-Leu-Val-D-Phe-Phe-OMe	3	4	40

3P	Boc-Pmh-D-Asp(OBut)-Leu-Val-D-Phe-Phe-OMe	3	4	32
3Q	Boc-Pmh-Asp(OBut)-D-Leu-Val-D-Phe-Phe-OMe	3	4	15
3R	Boc-Pmh-Asp(OBn)-D-Leu-Val-D-Phe-Phe-OMe	3	4	5
3S	Boc-Pmh-D-Asp(OBut)-D-Leu-Val-D-Phe-Phe-OMe	3	4	10
3T	Boc-Pmh-Asp(OBut)-Leu-D-Val-D-Phe-Phe-OMe	3	4	17
3U	Boc-Pmh-Asp(OBn)-Leu-D-Val-D-Phe-Phe-OMe	3	4	27
3V	Boc-Pmh-D-Asp(OBut)-Leu-D-Val-D-Phe-Phe-OMe	3	4	30
3W	Boc-Pmh-Asn(Trt)-D-Leu-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	3	4	21
3X	Boc-Pmh-Asn(Trt)-D-Leu-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	3	4	28
3Y	Boc-Pmh-Asn(Trt)-Leu-Tle-D-Phe-Phe-OMe	3	4	36
3Z	Boc-Pmh-Asn(Trt)-Leu-D-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	3	4	24
4A	Boc-Pmh-D-Asp(OBut)-Leu-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	3	4	42
4B	Boc-Pmh-D-Asp(OBut)-Leu-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	3	4	42
4C	Boc-Pmh-Asn(Trt)-Leu-D-Phe-D-Phe-Phe-OMe	3	4	26
4D	Boc-Pmh-D-Asp(OBut)-Val-Tle-D-Phe-Phe-OMe	3	4	12
4E	Boc-Pmh-Asn(Trt)-Phe-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	3	4	30
4F	Boc-Pmh-Asn(Trt)-D-Phe-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	3	4	23
4G	Boc-Pmh-Asn(Trt)-Met-Val-D-Phe-Phe-OMe	3	4	28
4H	Boc-Pmh-Trp(Boc)-Leu-Val-D-Phe-Phe-OMe	3	4	15
4I	Boc-Pmh-Asn(Trt)-Leu-Val-D-Val-Phe-OMe	3	4	34
4J	Boc-D-Pmh-Asn(Trt)-Leu-D-Val-D-Phe-Phe-OMe	3	4	14
4K	Boc-D-Pmh-Asn(Trt)-Leu-Val-D-Phe-Phe-OMe	3	4	0
4L	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	52
4L	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	-20	77
4M	Boc-Pmh-Asn(Trt)-Deg-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	27
4N	Boc-Pmh-Asn(Trt)-Tle-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	30
4O	Boc-Pmh-Asn(Trt)-Gly-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	18
4P	Boc-Pmh-His(Trt)-Leu-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	25
4Q	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	51
4Q	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	-20	68
4R	Boc-Pmh-His(Trt)-Val-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	29
4S	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	4	4	50
4S	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	4	-20	78
4T	Boc-Pmh-Ser(Trt)-Leu-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	24
4U	Boc-Pmh-Asn(Trt)-Aib-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	32

4U	Boc-Pmh-Asn(Trt)-Aib-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	-20	26
4V	Boc-Pmh-Asn(Trt)-Deg-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	28
4W	Boc-Pmh-Asn(Trt)-Tle-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	44
4X	Boc-Pmh-Asn(Trt)-Gly-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	26
4Y	Boc-Pmh-His(Trt)-Leu-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	28
4Z	Boc-Pmh-His(Trt)-Aib-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	44
4Z	Boc-Pmh-His(Trt)-Aib-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	-20	66
5A	Boc-Pmh-His(Trt)-Val-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	23
5B	Boc-Pmh-Asn(Trt)-Leu-Thr(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	4	4	51
5B	Boc-Pmh-Asn(Trt)-Leu-Thr(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	4	-20	68
5C	Boc-Pmh-Thr(Trt)-Leu-Thr(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	27
5D	Boc-Pmh-Asn(Trt)-Leu-Ser(Trt)-D-Phe-Phe-OMe	4	4	41
5E	Boc-Pmh-Asn(Trt)-Leu-Thr(Trt)-D-Phe-Phe-OMe	4	4	36
5F	Boc-Pmh-Asn(Trt)-Aib-Ser(Trt)-D-Phe-Phe-OMe	4	4	38
5F	Boc-Pmh-Asn(Trt)-Aib-Ser(Trt)-D-Phe-Phe-OMe	4	-20	58
5G	Boc-Pmh-Asn(Trt)-Aib-Thr(Trt)-D-Phe-Phe-OMe	4	4	35
5H	Boc-Pmh-Asn(Trt)-Ala-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	4	4	45
5I	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	4	4	56
5I	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	4	-20	79
5J	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Ala-OMe	5	4	43
5J	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Ala-OMe	5	-20	78
5K	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Ile-OMe	5	4	19
5K	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Ile-OMe	5	-20	72
5L	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phg-OMe	5	4	32
5L	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phg-OMe	5	-20	80
5M	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Val-OMe	5	4	0
5N	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Ala-OMe	5	4	36
5O	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Ile-OMe	5	4	0
5P	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phg-OMe	5	4	30
5P	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phg-OMe	5	-20	81

5Q	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Val-OMe	5	4	0
5R	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Ala-OMe	5	4	35
5S	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Ile-OMe	5	4	0
5T	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phg-OMe	5	4	34
5U	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Val-OMe	5	4	0
5V	Boc-Pmh-Asn(Trt)-Sp5-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	5	4	11
5V	Boc-Pmh-Asn(Trt)-Sp5-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	5	-20	60
5W	Boc-Pmh-Asn(Trt)-Sp6-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	5	4	11
5W	Boc-Pmh-Asn(Trt)-Sp6-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	5	-20	42
5X	Boc-Pmh-His(Trt)-Sp5-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	5	4	23
5Y	Boc-Pmh-His(Trt)-Sp6-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	5	4	0
5Z	Boc-Pmh-Asn(Trt)-Sp5-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	5	4	20
5Z	Boc-Pmh-Asn(Trt)-Sp5-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	5	-20	59
6A	Boc-Pmh-Asn(Trt)-Sp6-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	5	4	0
6A	Boc-Pmh-Asn(Trt)-Sp6-Ser(<i>t</i> Bu)-D-Phe-Phe-OMe	5	-20	34
6B	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-Ala-OMe	5	4	42
6C	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-Ile-OMe	5	4	0
6D	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-Phg-OMe	5	4	38
6E	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-Val-OMe	5	4	0
6F	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Leu-Phe-OMe	5	4	47
6F	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Leu-Phe-OMe	5	-20	81
6G	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Leu-Phe-OMe	5	4	45
6G	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Leu-Phe-OMe	5	-20	80
6H	Boc-Pmh-Asn(Trt)-D-Ala-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	22
6I	Boc-Pmh-Asn(Trt)-Gly-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	13
6J	Boc-Pmh-Asn(Trt)-Ser(<i>t</i> Bu)-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	31
6K	Boc-Pmh-Asn(Trt)-Val-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	26
6L	Boc-Pmh-Asn(Trt)-D-Val-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	15
6M	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-	6	4	55

	Trp(Boc)-OMe			
6N	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe(4-NO ₂)-Phe-OMe	6	4	49
6O	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-OMe	6	4	58
6P	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-D-Phe-OMe	6	4	61
6Q	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Leu-D-Phe-OMe	6	4	65
6Q	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Leu-D-Phe-OMe	6	-20	79
6R	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Phe-D-Phe-OMe	6	4	59
6S	Boc-Pmh-Tyr(<i>t</i> Bu)-D-Phe-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	20
6T	Boc-Pmh-Leu-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	18
6U	Boc-Pmh-Ile-D-Val-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	22
6V	Boc-Pmh-Asn(Trt)-Leu-Ser(<i>t</i> Bu)-D-Phe-D-Phe-OMe	6	4	47
6W	Boc-Pmh-Asn(Trt)-Aib-Aib-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	8
6X	Boc-Pmh-Asn(Trt)-Ser(<i>t</i> Bu)-Aib-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	7
6Y	Boc-Pmh-His(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-D-Phe-OMe	6	4	60
6Z	Boc-Pmh-Nap-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	25
7A	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Nap-Phe-OMe	6	4	55
7B	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Nap-OMe	6	4	55
7C	Boc-Pmh-Asn(Trt)-Aib-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-D-Nap-OMe	6	4	60
7D	Boc-Pmh-Asn(Trt)-Aib-Pro-His(Trt)-Phe-OMe	6	4	31
7E	Boc-Pmh-Val-Trp(Boc)-Ser(<i>t</i> Bu)-D-Tyr(<i>t</i> Bu)-Phe-OMe	6	4	23

Preparation and Characterization of Compounds

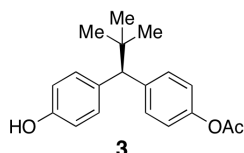
Preparation of Bis(phenol) (1). Bis(phenol) **1** was prepared as described in the literature. Rogers, E. F.; Brown, H. D.; Rasmussen, I. M.; Heal, R. E. *J. Am. Chem. Soc.* **1953**, *75*, 2991-2999.

Preparation of Mono(acetate) **3** and Bis(acetate) **5**

To a solution of bis(phenol) **1** (90.0 mg, 351.6 μmol) in 15.0 mL of CHCl₃ at -30 °C was added catalyst **4** (21.0 mg, 17.5 μmol), followed by freshly distilled acetic anhydride (70.0 μL , 740.5 μmol). The solution was stirred for 20 hours and quenched by

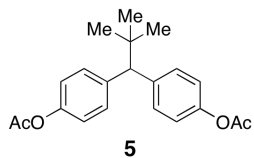
the addition of 2 mL of MeOH. Upon warming to room temperature, EtOAc and water was added. The biphasic solution was separated and the aqueous solution was extracted with EtOAc (2 x 10 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (EtOAc/hexanes 1/4 v/v) to afford 84.0 mg (281.5 μmol, 80%) of mono(acetate) **3** and 25.0 mg (73.5 μmol, 20%) of bis(acetate) **5**.

(R)-4-(1-(4-Hydroxyphenyl)-2,2-tert-butyl)phenyl mono(acetate) (3)



M.p.: 129 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.37 (d, *J* = 8.4 Hz, 2H), 7.20 (d, *J* = 8.4 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 6.66 (d, *J* = 8.4 Hz, 2H), 5.83 (br s, 1H), 3.62 (s, 1H), 2.23 (s, 3H), 0.96 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 170.1, 153.9, 148.6, 141.1, 134.8, 130.7, 130.5, 120.7, 114.8, 62.9, 35.2, 29.4, 21.4; **IR** (film, cm⁻¹) 3402, 2967, 2911, 2873, 1740, 1614, 1520, 1369, 1206, 1111, 1016, 908, 853, 733, 563; **TLC** R_f = 0.67 (Hexanes/EtOAc 1/1 v/v); **HPLC** 95% ee, Chiral HPLC utilized a Chiralpak AD (Daicel, 0.46 cm x 15 cm, 20 °C) eluting at 0.75 mL/min with 75% hexane/isopropanol. Retention times: R_{T(S)} = 5.5 min; R_{T(R)} = 6.2 min; **HRMS** (EI⁺) *m/z* Calc'd for C₁₉H₂₂O₃ [M] 298.1569, found 298.1574.

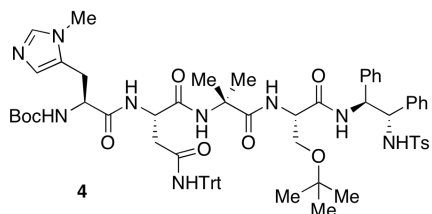
4,4'-(2,2-dimethylpropane-1,1-diyl)bis(4,1-phenylene) bis(acetate) (5)



M.p.: 131-132 °C; ¹H NMR (CDCl₃, 400 MHz) δ 7.39 (dd, *J*₁ = 6.8 Hz, *J*₂ = 1.6 Hz, 4H), 6.99 (dd, *J*₁ = 6.8 Hz, *J*₂ = 1.6 Hz, 4H), 3.72 (s, 1H), 2.22 (s, 6H), 1.00 (s, 9H); ¹³C NMR (CDCl₃, 100 MHz) δ 169.1, 148.8, 140.2, 130.5, 120.8, 63.1, 35.2, 29.3, 21.3; **IR** (film, cm⁻¹) 2967, 2911, 2873, 1759, 1520, 1381, 1211, 1016, 916, 859, 739, 570; **TLC** R_f = 0.74 (Hexanes/EtOAc 1/1 v/v); **HPLC** Chiral HPLC utilized a Chiralpak AD (Daicel, 0.46 cm x 15 cm, 20 °C) eluting at 0.75 mL/min with 75% hexane/isopropanol. Retention time: 4.0 min; **HRMS** (EI⁺) *m/z* Calc'd for C₂₁H₂₄O₄ [M] 340.1675, found 340.1681.

Preparation of Boc-Pmh-Asn(Trt)-Aib-Ser(*t*Bu)-DPDA (4)

To a solution of tetrapeptide acid (Boc-Pmh-Asn(Trt)-Aib-Ser(*t*Bu)-OH, 2.60 g, 3.04 mmol) in 86.0 mL of THF at 0 °C was added (1*S*, 2*S*)-(+)-*N*-p-Tosyl-1,2-diphenylethylenediamine (1.10 g, 3.00 mmol), HOBt (580 mg, 4.29 mmol), and EDCI (700 mg, 3.65 mmol). The solution was stirred for 3 hours and diluted with water. The biphasic solution was separated and the aqueous solution was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography (3% MeOH/CH₂Cl₂) to afford 3.50 g (2.91 mmol, 97%) of tetrapeptide amide **4** as a white solid.

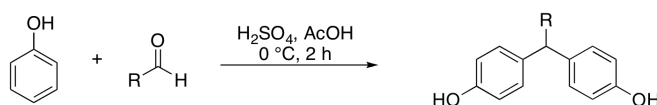


[α]^{20.0} : +5.2 (*c* 1.0, CHCl₃); ¹H NMR (CDCl₃, 600 MHz) δ 8.20 (d, *J* = 6.2 Hz, 1H), 8.09 (d, *J* = 10.1 Hz, 1H), 8.05 (s, 1H), 7.69 (s, 1H), 7.61 (s, 1H), 7.49 (m, 3H), 7.27 (m, 2H), 7.23-7.17 (m, 9H), 7.13-7.07 (m, 15H), 6.92 (s, 1H), 6.68 (d, *J* = 8.0 Hz, 2H), 5.42 (dd, *J*₁ = 10.2 Hz, *J*₂ = 3.6 Hz, 1H), 5.12-5.11 (m,

2H), 4.47 (m, 1H), 4.37 (dd, $J_1 = 6.0$ Hz, $J_2 = 3.0$ Hz, 1H), 3.87 (dd, $J_1 = 7.6$ Hz, $J_2 = 1.0$ Hz, 1H), 3.61 (s, 3H), 3.36 (dd, $J_1 = 9.0$ Hz, $J_2 = 3.6$ Hz, 1H), 3.17 (dd, $J_1 = 15.6$ Hz, $J_2 = 4.2$ Hz, 1H), 3.13 (dd, $J_1 = 15.6$ Hz, $J_2 = 6.6$ Hz, 1H), 2.86 (dd, $J_1 = 15.6$ Hz, $J_2 = 10.2$ Hz, 1H), 2.65 (dd, $J_1 = 15.6$ Hz, $J_2 = 3.6$ Hz, 1H), 2.18 (s, 3H), 1.66 (s, 3H), 1.54 (s, 3H), 1.32 (s, 9H), 1.13 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.2, 171.1, 170.2, 170.0, 156.5, 144.4, 142.1, 139.2, 139.0, 137.9, 137.1, 128.8, 128.7, 128.4, 128.3, 127.9, 127.7, 127.3, 127.0, 126.9, 126.8, 126.3, 126.1, 81.8, 75.5, 70.8, 61.7, 61.1, 57.9, 57.1, 54.8, 53.8, 51.4, 36.1, 31.4, 28.1, 27.2, 26.9, 26.1, 26.0, 23.3, 21.3; HRMS (ESI) calcd. for $\text{C}_{67}\text{H}_{79}\text{N}_9\text{O}_{10}\text{S}$ [$\text{M}+\text{H}^+$] 1202.5748, found 1202.5741.

General Procedure A: Preparation of 4,4'-(1,1-diyl)diphenols (15a-15d).

The preparation of **15a-d** was adapted from the synthesis of **1**.



To a Schlenk flask under nitrogen containing 50 mL acetic acid and 50 mL concentrated sulfuric acid at 0 °C was charged the appropriate aldehyde (40 mmol) via syringe. Phenol (7.50 g, 80 mmol) was then added in four parts over five minutes. The solution was then stirred for 2 hours at 0 °C. The crude mixture was neutralized with saturated NaHCO_3 , extracted into ethyl acetate (3 x 150 mL), washed with brine (2 x 150 mL), dried with sodium sulfate and concentrated. Silica gel chromatography was then used ($\text{CHCl}_3/\text{MeOH}$ 10/1 v/v) to purify the product. Compounds **15a**, **15b**, and **15d** were prepared by this method, **15c** was commercially available.

4,4'-(2-methylpropane-1,1-diyl)diphenol (15a)
 (155 mg, 5% yield); ^1H NMR (CD_3OD , 500 MHz) δ 7.07 (d, $J = 8.5$ Hz, 4H), 6.67 (d, $J = 8.5$ Hz, 4H), 3.23 (d, $J = 11.0$ Hz, 1H), 2.38-2.34, (m, 1H), 0.82 (d, $J = 6.0$ Hz, 6H); ^{13}C NMR (CD_3OD , 125 MHz) δ 156.7, 138.5, 130.3, 116.4, 61.1, 33.8, 22.8; IR (film, cm^{-1}) 3248, 2945, 2909, 2827; TLC $R_f = 0.38$ ($\text{CHCl}_3/\text{MeOH}$ 9/1 v/v); HRMS (ESI) m/z calc'd for $\text{C}_{16}\text{H}_{18}\text{O}_2\text{Na}$ [$\text{M}+\text{Na}^+$] 265.1204, found 265.1217.

4,4'-(propane-1,1-diyl)diphenol (15b)
 (150 mg, 4% yield); ^1H NMR (CD_3OD , 500 MHz) δ 7.02 (d, $J = 8.5$ Hz, 4H), 6.67 (d, $J = 8.5$ Hz, 4H), 3.59 (t, $J = 8.0$ Hz, 1H), 1.95 (quintet, $J = 7.5$ Hz, 2H), 0.84 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (CD_3OD , 125 MHz) δ 156.5, 138.4, 129.9, 116.1, 53.1, 30.3, 13.3; IR (film, cm^{-1}) 3305, 2943, 2909, 2827; TLC $R_f = 0.32$ ($\text{CHCl}_3/\text{MeOH}$ 9/1 v/v); HRMS (ESI) m/z calc'd for $\text{C}_{15}\text{H}_{16}\text{O}_2\text{Na}$ [$\text{M}+\text{Na}^+$] 251.1048, found 251.1057.

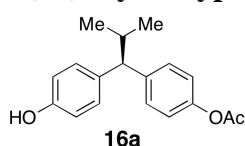
4,4'-(phenylmethylene)diphenol (15d)
 (600 mg, 10% yield); ^1H NMR (CD_3OD , 500 MHz) δ 7.22 (t, $J = 7.5$ Hz, 2H), 7.14 (t, $J = 7.5$ Hz, 1H), 7.05 (d, $J = 7.5$ Hz, 2H), 6.87 (d, $J = 8.5$, 4H), 6.68 (d, $J = 8.5$ Hz, 4H), 5.35 (s, 1H); ^{13}C NMR

(CD₃OD, 125 MHz) δ 157.2, 147.1, 137.5, 131.9, 130.9, 129.7, 127.5, 116.5, 57.1; **IR** (film, cm⁻¹) 3313, 3023, 2909, 2827; **TLC** R_f = 0.36 (CHCl₃/MeOH 10/1 v/v); **HRMS** (ESI) *m/z* calc'd for C₁₉H₁₆O₂Na [M+Na⁺] 299.1048, found 299.1072.

General Procedure for the Acylation of Substrates 15a-d

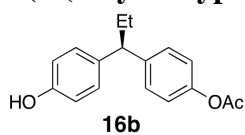
To a flame dried flask was charged the bis(phenol) (**15a-d**, 0.160 mmol) and peptide **4** (4.7 mg, 3.93 μ mol). The flask was then charged with 4.76 mL of CHCl₃ along with 20 μ L of THF. This solution was then cooled to -40 °C over 30 minutes. Freshly distilled acetic anhydride (28.5 μ L, 0.301 mmol) was then added via syringe. The solution was stirred for 18 h at -40 °C and then quenched with 0.2 ml methanol while still cold. Silica gel chromatography (Hex/EtOAc 3/1 v/v) was used to purify the products.

4-(1-(4-hydroxyphenyl)-2-methylpropyl)phenyl acetate (**16a**)



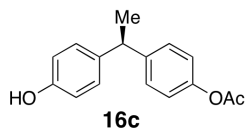
(36.0 mg, 62% yield); **¹H NMR** (CDCl₃, 400 MHz) δ 7.24 (d, *J* = 8.6 Hz, 2H), 7.10 (d, *J* = 8.5 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.71 (d, *J* = 9.0 Hz, 2H), 4.92 (s, 1H), 3.33 (d, *J* = 6.8 Hz, 1H), 2.36 (m, 1H), 2.27 (s, 3H), 0.86 (dd, *J*₁ = 6.8 Hz, *J*₂ = 2.8 Hz, 6H); **¹³C NMR** (CDCl₃, 125 MHz) δ 169.7, 153.7, 148.6, 142.8, 136.8, 129.0, 128.7, 121.2, 115.2, 59.2, 32.1, 21.8, 21.1; **IR** (film, cm⁻¹) 3404, 2967, 2868, 1742; **TLC** R_f = 0.40 (CHCl₃/MeOH 9/1 v/v); [α]^{20.0} = +1.66 (*c* = 1.0, CHCl₃); **HPLC**: 73% ee, chiral HPLC utilized 2 Chiralcel AD connected in series (Daicel, 0.46 cm x 20 cm, 10 μ M, 20 °C), eluting at 0.3 mL/min with 90% hexanes/isopropanol. Retention times: R_{T(S)} = 91.3 min, R_{T(R)} = 81.6 min; **HRMS** (ESI) *m/z* calc'd for C₁₈H₂₀O₃ [M] 284.1413, found 284.1414.

4-(1-(4-hydroxyphenyl)propyl)phenyl acetate (**16b**)



(26.0 mg, 60% yield); **¹H NMR** (CDCl₃, 500 MHz) δ 7.20 (d, *J* = 8.6 Hz, 2H), 7.06 (d, *J* = 8.0 Hz, 2H), 6.98 (d, *J* = 9.1 Hz, 2H), 6.73 (d, *J* = 8.6 Hz, 2H), 4.94 (s, 1H), 3.72 (t, *J* = 7.5 Hz, 1H), 2.27 (s, 3H), 2.00 (quintet, *J* = 7.5 Hz, 2H), 0.88 (t, *J* = 7.5 Hz, 3H); **¹³C NMR** (CDCl₃, 125 MHz) δ 169.8, 153.8, 148.7, 144.3, 137.0, 129.0, 128.7, 121.2, 115.2, 51.76, 28.8, 21.2, 12.7; **IR** (film, cm⁻¹) 3410, 2961, 2861, 1730; **TLC** R_f = 0.66 (CHCl₃/MeOH 9/1 v/v); [α]^{20.0} = +1.26 (*c* = 1.0, CHCl₃); **HPLC**: 63% ee, chiral HPLC utilized 2 Chiralcel OD columns connected in series (Daicel, 0.46 cm x 20 cm, 10 μ M, 20 °C), eluting at 0.3 mL/min with 90% hexanes/isopropanol. Retention times: R_{T(R)} = 78.7 min, R_{T(S)} = 83.9 min; **HRMS** (ESI) *m/z* calc'd for C₁₇H₁₉O₃ [M+H⁺] 271.1334, found 271.1346.

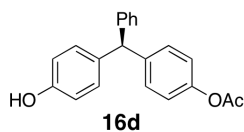
4-(1-(4-hydroxyphenyl)ethyl)phenyl acetate (**16c**)



(26.0 mg, 42% yield); **¹H NMR** (CDCl₃, 500 MHz) δ 7.18 (d, *J* = 8.8 Hz, 2H), 7.06 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.3 Hz, 2H), 6.74 (d, *J* = 8.3 Hz, 2H), 4.74 (s, 1H), 4.08 (q, *J* = 7.5 Hz, 1H), 2.28 (s, 3H), 1.59 (d, *J* = 7.5 Hz, 3H); **¹³C NMR** (CDCl₃, 125 MHz) δ 169.8, 153.8, 148.7, 144.3, 138.3, 128.7, 128.5, 121.3, 115.8, 43.4, 22.1, 21.1; **IR** (film, cm⁻¹) 3410, 2973, 1736; **TLC** R_f = 0.55 (CHCl₃/MeOH 9/1 v/v);

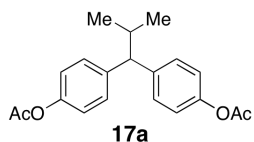
$[\alpha]^{20.0} = +0.88$ ($c = 1.0$, CHCl_3); **HPLC**: 52% ee, chiral HPLC utilized a Chiralpak AD connected in series to a Chiralcel OJ (Daicel, 0.46 cm x 20 cm, 10 μM , 20 $^\circ\text{C}$), eluting at 1 mL/min with 90% hexanes/isopropanol. Retention times: $R_{\text{T(S)}} = 98.1$ min, $R_{\text{T(R)}} = 77.2$ min. **HRMS** (ESI) m/z calc'd for $\text{C}_{16}\text{H}_{17}\text{O}_3$ $[\text{M}+\text{H}^+]$ 257.1178, found 257.1189.

4-((4-hydroxyphenyl)(phenyl)methyl)phenyl acetate (16d)



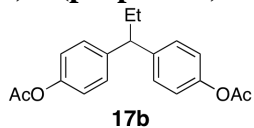
(23.0 mg, 40% yield); **$^1\text{H NMR}$** (CDCl_3 , 500 MHz) δ 7.28 (t, $J = 7.5$ Hz, 2H), 7.21 (t, $J = 7.5$ Hz, 1H), 7.09 (d, $J = 8.5$ Hz, 4H), 6.99 (d, $J = 8.5$ Hz, 2H), 6.95 (d, $J = 8.5$ Hz, 2H), 6.74 (d, $J = 8.5$ Hz, 2H), 5.47 (s, 1H), 4.87 (s, 1H), 2.28 (s, 3H); **$^{13}\text{C NMR}$** (CDCl_3 , 125 MHz) δ 169.6, 154.0, 149.0, 143.9, 141.7, 135.9, 130.5, 130.3, 129.3, 128.2, 126.3, 121.2, 115.2, 55.4, 21.1; **IR** (film, cm^{-1}) 3410, 3023, 2909, 1736; **TLC** $R_f = 0.63$ ($\text{CHCl}_3/\text{MeOH}$ 9/1 v/v); $[\alpha]^{20.0} = +1.88$ ($c = 1.0$, CHCl_3); **HPLC**: 50% ee, chiral HPLC utilized a Chiralcel AD (Daicel, 0.46 cm x 20 cm, 10 μM , 20 $^\circ\text{C}$), eluting at 0.5 mL/min with 75% hexanes/isopropanol. Retention times: $R_{\text{T(S)}} = 11.3$ min, $R_{\text{T(R)}} = 13.0$ min; **HRMS** (ESI) m/z calc'd for $\text{C}_{21}\text{H}_{19}\text{O}_3$ $[\text{M}+\text{H}^+]$ 319.1334, found 319.1346.

4,4'-(2-methylpropane-1,1-diyl)bis(4,1-phenylene) diacetate (17a)



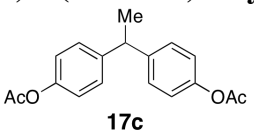
(6.0 mg, 7% yield); **$^1\text{H NMR}$** (CDCl_3 , 500 MHz) δ 7.25 (d, $J = 8.5$ Hz, 4H), 6.99 (d, $J = 8.5$ Hz, 4H), 3.42 (d, $J = 10.5$ Hz, 1H), 2.40-2.45 (m, 1H), 2.27 (s, 6H), 0.87 (d, $J = 6.5$ Hz, 6H); **$^{13}\text{C NMR}$** (CDCl_3 , 125 MHz) δ 169.4, 148.9, 142.0, 128.8, 121.4, 59.5, 32.1, 21.8, 21.1; **IR** (film, cm^{-1}) 2955, 2866, 1765, 1502, 1205; **TLC** $R_f = 0.87$ ($\text{CHCl}_3/\text{MeOH}$ 10/1 v/v); **HRMS** (ESI) m/z calc'd for $\text{C}_{20}\text{H}_{23}\text{O}_4$ $[\text{M}+\text{H}^+]$ 327.1596, found 327.1608.

4,4'-(propane-1,1-diyl)bis(4,1-phenylene) diacetate (17b)



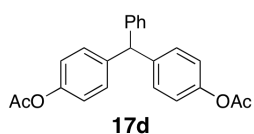
(3.0 mg, 10% yield); **$^1\text{H NMR}$** (CDCl_3 , 500 MHz) δ 7.20 (d, $J = 8.5$ Hz, 4H), 6.98 (d, $J = 8.5$ Hz, 4H), 3.78 (t, $J = 7.5$ Hz, 1H), 2.26 (s, 6H), 2.03 (quintet, $J = 7.5$ Hz, 2H), 0.88 (t, $J = 7.5$ Hz, 3H); **$^{13}\text{C NMR}$** (CDCl_3 , 125 MHz) δ 169.5, 149.0, 142.3, 128.8, 121.4, 52.1, 28.8, 21.1, 12.7; **IR** (film, cm^{-1}) 3037, 2961, 1753, 1508, 1205.2; **TLC** $R_f = 0.88$ ($\text{CHCl}_3/\text{MeOH}$ 9/1 v/v); **HRMS** (ESI) m/z calc'd for $\text{C}_{19}\text{H}_{21}\text{O}_4$ $[\text{M}+\text{H}^+]$ 313.1440, found 313.1446.

4,4'-(ethane-1,1-diyl)bis(4,1-phenylene) diacetate (17c)



(3.0 mg, 7% yield); **$^1\text{H NMR}$** (CDCl_3 , 500 MHz) δ 7.20 (d, $J = 8.2$ Hz, 4H), 7.00 (d, $J = 8.2$ Hz, 4H), 4.15 (q, $J = 7.5$ Hz, 1H), 2.28 (s, 6H), 1.61 (d, $J = 7.5$ Hz, 3H); **$^{13}\text{C NMR}$** (CDCl_3 , 125 MHz) δ 169.6, 148.9, 143.5, 128.6, 121.4, 43.7, 22.0, 21.1; **IR** (film, cm^{-1}) 3037, 2914, 1759, 1508, 1181; **TLC** $R_f = 0.88$ ($\text{CHCl}_3/\text{MeOH}$ 10/1 v/v); **HRMS** (ESI) m/z calc'd for $\text{C}_{18}\text{H}_{19}\text{O}_4$ $[\text{M}+\text{H}^+]$ 299.1283, found 299.1290.

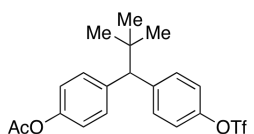
4,4'-(phenylmethylene)bis(4,1-phenylene) diacetate (**17d**)



(5.0 mg, 11% yield); $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.29 (t, $J = 7.5$ Hz, 2H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.09-7.11 (m, 6H), 7.01 (d, $J = 8.5$ Hz, 4H), 5.54 (s, 1H), 2.28 (s, 6H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 169.5, 149.1, 143.4, 141.2, 130.3, 129.4, 128.4, 126.6, 121.4, 55.7, 21.2; **IR** (film, cm^{-1}) 3023, 2909, 1736; **TLC** $R_f = 0.93$ ($\text{CHCl}_3/\text{MeOH}$ 9/1 v/v); **HRMS** (ESI) m/z calc'd for $\text{C}_{23}\text{H}_{20}\text{O}_4\text{Na}$ [$\text{M}+\text{Na}^+$] 383.1259, found 383.1257.

Preparation of 4-(2,2-dimethyl-1-phenylpropyl)phenol (**18a**)

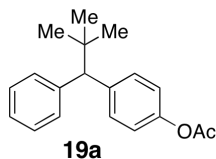
Mono(acetate) **3** (10.0 mg, 0.0335 mmol) was dissolved in dichloromethane (1 mL) and triethylamine (4.7 μL , 0.0335 mmol) was added. Triflic anhydride (10.4 μL , 0.0618 mmol) was added slowly. The reaction was checked by TLC after 10 minutes and was found to be complete. The mixture was purified by silica gel chromatography ($\text{CHCl}_3/\text{MeOH}$ 95/5 v/v) to afford the intermediate as a colorless oil 13.5 mg, 93% yield.



$^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.46 (d, $J = 8.8$ Hz, 2H), 7.38 (d, $J = 8.6$ Hz, 2H), 7.17 (d, $J = 8.8$ Hz, 2H), 7.01 (d, $J = 8.6$ Hz, 2H), 3.76 (s, 1H), 2.26 (s, 3H), 1.00 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 169.5, 149.4, 148.1, 143.5, 139.7, 131.5, 130.7, 122.7, 121.3, 120.8, 120.1, 117.6, 115.0, 63.2, 35.3, 29.2, 21.2; **IR** (film, cm^{-1}) 2962, 2909, 2864, 1764, 1503, 1426, 1368, 1213, 1148, 1021, 890; **TLC** $R_f = 0.50$ (hexanes/EtOAc 4/1 v/v); **HRMS** (ES^+) m/z Calc'd for $\text{C}_{20}\text{H}_{21}\text{F}_3\text{O}_5\text{S}$ [$\text{M} + \text{H}^+$] 431.1134, found 431.1114.

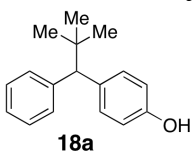
Monoacetate monotriflate (28.3 mg, 0.658 mmol) was dissolved in absolute ethanol (1.5 mL) and degassed with nitrogen. *N,N*-Diisopropylethylamine (22.9 μL , 0.0658 mmol) was then added. The solution was then charged with Pd/C (10%, 3.0 mg) and a hydrogen balloon added. After one hour, the reaction was deemed complete by TLC ($R_f = 0.57$, hexanes/EtOAc 4/1 v/v) and was passed through a short length of silica gel (hexanes/EtOAc 4/1 v/v) providing **19a**. The product was then concentrated to a colorless oil. Potassium carbonate (10.0 mg, 0.0724 mmol) in methanol (4 mL) was then added to the oil and the reaction monitored. After 10 minutes, the cleavage of the acetate was complete and the reaction filtered. The resulting solution was concentrated and then purified by silica gel chromatography ($\text{CHCl}_3/\text{MeOH}$ 95/5 v/v) to afford **18a**, 14.3 mg, 91%, two steps.

4-(2,2-dimethyl-1-phenylpropyl)phenyl acetate (**19a**)



$^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.40 (t, $J = 8.7$ Hz, 4H), 7.25 (t, $J = 7.6$ Hz, 2H), 7.18 (t, $J = 7.7$ Hz, 1H), 6.98 (d, $J = 8.1$ Hz, 2H), 3.71 (s, 1H), 2.24 (s, 3H), 1.01 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 169.5, 149.1, 143.0, 140.8, 130.8, 129.9, 128.1, 126.2, 120.9, 63.9, 35.2, 29.4, 21.3; **IR** (film, cm^{-1}) 2953, 2904, 2872, 1761, 1507, 1368, 1201, 1172, 1013; **TLC** $R_f = 0.57$ (hexanes/EtOAc 4/1 v/v); **HRMS** (ES^+) m/z Calc'd for $\text{C}_{19}\text{H}_{22}\text{NaO}_2$ [$\text{M}+\text{Na}^+$] 305.1512, found 305.1497.

4-(2,2-dimethyl-1-phenylpropyl)phenol (**18a**)



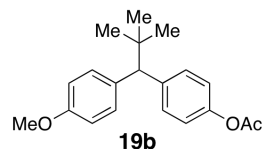
$^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.39 (d, $J = 7.2$ Hz, 2H), 7.27 (d, $J = 8.6$ Hz, 2H), 7.24 (d, $J = 6.9$ Hz, 2H), 7.16 (t, $J = 7.3$ Hz, 1H), 6.71 (d, $J = 8.7$ Hz, 2H), 4.75 (s, 1H), 3.64 (s, 1H), 0.99 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 153.8, 143.6, 135.7, 131.0, 129.9, 128.1, 126.0, 114.9, 63.7, 35.2, 29.4; **IR** (film, cm^{-1}) 3354, 2949, 2901, 2872, 1511, 1364, 1221;

TLC $R_f = 0.55$ ($\text{CHCl}_3/\text{MeOH}$ 9/1 v/v); **HRMS** (ES^+) m/z Calc'd for $\text{C}_{17}\text{H}_{20}\text{ONa}$ [$\text{M}+\text{Na}^+$] 263.1412, found 263.1412.

For the structure proof, **HPLC** 90%ee, Chiralcel AD, 85:15 hexanes:iPrOH, 0.5 mL/min, 215 nm, $R_{\text{T(R)}} = 10.0$ min, $R_{\text{T(S)}} = 12.2$ min. $[\alpha]^{20.0} -5.3^\circ$ (c 0.2, CHCl_3).

Preparation of 4-(1-(4-methoxyphenyl)-2,2-dimethylpropyl)phenol (**18b**)

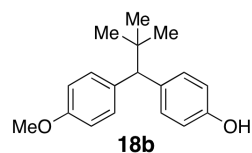
4-(1-(4-methoxyphenyl)-2,2-dimethylpropyl)phenyl acetate (**19b**)



Mono(acetate) **3** (203.0 mg, 0.700 mmol) in THF (5 mL) was slowly added via syringe to a flame dried flask under N_2 at 0°C containing NaH (36 mg, 1.4 mmol) in 15 mL THF and let stir for 0.5 hours upon which time iodomethane (0.10 mL, 1.61 mmol) was added dropwise. The reaction mixture was allowed to warm

to room temperature and stir for 10 hours. The mixture was then cooled to 0°C , quenched with acetic acid, then washed with Na_2CO_3 (1 X 20 mL) and extracted into DCM (3 X 20 mL). The organic layers were dried with MgSO_4 and concentrated down to yield an oil which was purified by flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 98/2 v/v) to yield 90.0 mg (41% yield) of **19b**; $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.40 (d, $J = 8.5$ Hz, 2H), 7.32 (d, $J = 8.7$ Hz, 2H), 6.99 (d, $J = 8.5$ Hz, 2H), 6.81 (d, $J = 8.7$ Hz, 2H), 3.78 (s, 3H), 3.62 (s, 1H), 2.28 (s, 3H), 1.01 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 169.4, 157.9, 148.9, 141.0, 135.1, 130.7, 130.6, 120.8, 113.4, 62.9, 55.2, 35.1, 29.2, 21.2; **IR** (film, cm^{-1}) 2955, 2903, 2874, 1760, 1508, 1205; **TLC** $R_f = 0.44$ (Hex/EtOAc 4/1 v/v); **HRMS** (ESI) m/z calc'd for $\text{C}_{20}\text{H}_{25}\text{O}_3$ [$\text{M}+\text{H}^+$] 313.1804, found 313.1799.

4-(1-(4-methoxyphenyl)-2,2-dimethylpropyl)phenol (**18b**)

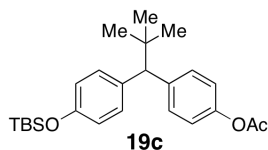


To a round bottom flask with stir bar was charged **19b** (90 mg, 0.284 mmol) which was then dissolved in 10 mL methanol. K_2CO_3 (150 mg, 1.5 mmol) was then added and the mixture was allowed to stir for 2 hours upon which time the mixture was extracted into DCM (3 X 20 mL), washed with brine (2 X 20 mL), dried with

MgSO_4 and concentrated to yield an oil which was purified by flash chromatography ($\text{CHCl}_3/\text{MeOH}$ 98/2 v/v) to yield 50.0 mg (67% yield) **18b**. $^1\text{H NMR}$ (CDCl_3 , 500 MHz) δ 7.32 (d, $J = 8.5$ Hz, 2H), 7.27 (d, $J = 8.5$ Hz, 2H), 6.82 (d, $J = 8.7$ Hz, 2H), 6.73 (d, $J = 8.5$ Hz, 2H), 4.82 (br s, 1H), 3.78 (s, 3H), 3.62 (s, 1H), 1.00 (s, 9H); $^{13}\text{C NMR}$ (CDCl_3 , 125 MHz) δ 158.1, 154.1, 136.3, 136.2, 131.2, 131.0, 115.1, 113.7, 63.0, 55.6, 35.5, 29.6; **IR** (film, cm^{-1}) 3399, 2943, 2897, 2868, 1601, 1495, 1230; **TLC** $R_f = 0.27$ ($\text{CHCl}_3/\text{MeOH}$ 98/2 v/v); **HRMS** (ESI) m/z calc'd for $\text{C}_{18}\text{H}_{18}\text{O}_2\text{Na}$ [$\text{M}+\text{Na}^+$] 293.1517, found 293.1518.

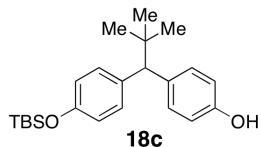
Preparation of 4-(1-(4-(*tert*-butyldimethylsilyloxy)phenyl)-2,2-dimethylpropyl)phenol (18c)

4-(1-(4-(*tert*-butyldimethylsilyloxy)phenyl)-2,2-dimethylpropyl)phenyl acetate (19c)



To a flame dried round bottom flask with a stir bar was charged with mono(acetate) **3** (120.0 mg, 0.41 mmol) which was dissolved in DCM (10 mL) and cooled to 0 °C. TBSCl (125.0 mg, 0.83 mmol), DMAP (1.5 mg, 0.04 mmol), and triethylamine (0.173 mL, 1.23 mmol) were added and the reaction mixture was stirred for 12 hours upon which time water was added and the reaction was extracted into DCM (2 X 10 mL). The organic layers were combined and washed with brine (2 X 10 mL), dried with MgSO₄, and concentrated to yield an oil which was purified by flash chromatography (CHCl₃/MeOH 98/2 v/v) to yield 105.0 mg (62% yield) of product **19c**. ¹H NMR (CDCl₃, 500 MHz) δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.24 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.7 Hz, 2H), 6.73 (d, *J* = 8.5 Hz, 2H), 3.65 (s, 1H), 2.27 (s, 3H), 0.99 (s, 9H), 0.98 (s, 9H), 0.18 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 169.4, 153.8, 148.8, 141.0, 135.6, 130.6, 120.7, 120.4, 63.0, 35.1, 29.1, 25.7, 25.6, 21.1, 18.1, -4.5; IR (film, cm⁻¹) 2944, 2920, 2862, 1760, 1491, 1252, 1194, 1164; TLC R_f = 0.75 (CHCl₃/MeOH 98/2 v/v); HRMS (ESI) *m/z* calc'd for C₂₅H₃₇O₃ [M+H⁺] 413.2512, found 413.2493.

4-(1-(4-(*tert*-butyldimethylsilyloxy)phenyl)-2,2-dimethylpropyl)phenol (18c)



To a round bottom flask with stir bar was charged **19c** (105.0 mg, 0.254 mmol) which was dissolved in methanol (10 mL). K₂CO₃ (150.0 mg, 1.5 mmol) was then added and the mixture was stirred for 2 hours upon which time the mixture was extracted into DCM (3 X 20 mL), washed with brine (2 X 20 mL), dried with MgSO₄ and concentrated to yield an oil which was purified by flash chromatography (CHCl₃/MeOH 98/2 v/v) to yield 90.0 mg (97% yield) of **18c**. ¹H NMR (CDCl₃, 500 MHz) δ 7.28 (d, *J* = 8.7 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 6.73-6.75 (m, 4H), 4.69 (br s, 1H), 3.59 (s, 1H), 0.98 (s, 18H), 0.18 (s, 6H); ¹³C NMR (CDCl₃, 125 MHz) δ 154.1, 154.0, 136.6, 136.4, 131.3, 131.0, 119.7, 115.0, 63.1, 35.5, 29.6, 26.1, 18.6, -4.0; IR (film, cm⁻¹) 3364, 2955, 2903, 2856, 1603, 1497, 1246; TLC R_f = 0.36 (hexanes/EtOAc 4/1 v/v); HRMS (ESI) *m/z* calc'd for C₂₃H₃₅O₂ [M+H⁺] 371.2406, found 371.2393.

Kinetic Resolution of Racemic **18a**, **18b**, **18c**, **3**

To a flame dried flask was charged the monophenol (**18a**, **18b**, **18c**, or **3**, 0.085 mmol) and peptide **4** (2.5 mg, 2.1 μmol). This was then dissolved in 3.5 mL of CHCl₃ along with 20 μL THF. This solution was then cooled to -40 °C over 30 minutes. Freshly distilled acetic anhydride (16.0 μL, 0.17 mmol) was then added via syringe. This was left to stir for 18 h at -40 °C at which time it was quenched with 0.2 mL methanol while still cold. Flash chromatography (CHCl₃/MeOH 98/2 v/v) yielded the products (**19a**, **19b**, **19c**, **5**) and recovered starting material (**18a**, **18b**, **18c**, **3**) in their respective yields. For analysis of enantiomeric excess for the acylated products (**19a**, **19b**, **19c**), the acetate was hydrolyzed to the monophenol using standard conditions.

Compound 3: 52% yield, 11% ee; **Compound 5:** 48% yield, Chiralcel AD, 70:30 hexanes:iPrOH, 0.5 ml/min, 215 nm, $R_{T(R)} = 10.5$ min, $R_{T(S)} = 11.3$ min.

Compound 18a: 52% yield, 16% ee; **Compound 19a** (after hydrolysis): 46% yield, 22% ee, Chiralcel AD, 85:15 hexanes:iPrOH, 0.5 ml/min, 215 nm, $R_{T(R)} = 10.0$ min, $R_{T(S)}$ (minor) = 12.2 min.

Compound 18b: 55% yield, 5% ee; **Compound 19b** (after hydrolysis): 44% yield, 13% ee, Chiralcel AD, 70:30 hexanes:iPrOH, 0.5 ml/min, 254 nm, $R_{T(R)} = 13.5$ min, $R_{T(S)} = 9.7$ min.

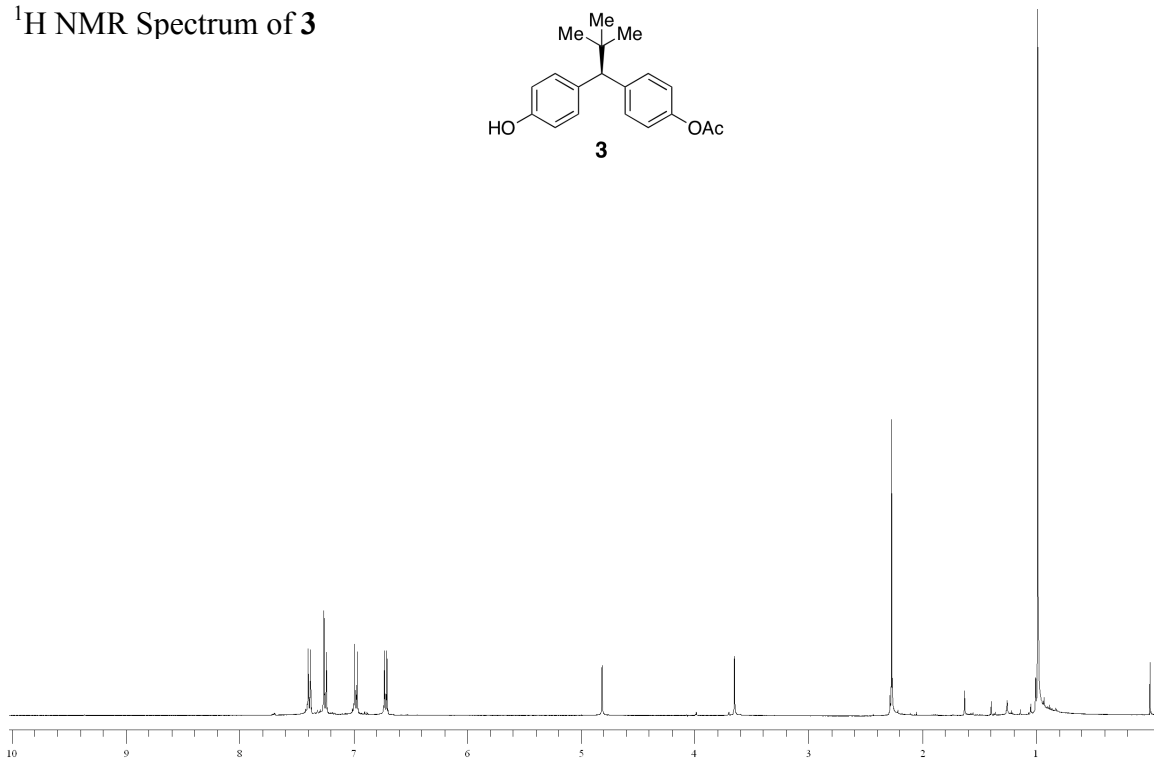
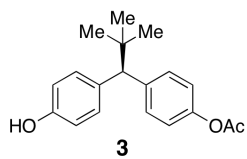
Compound 18c: 62% yield, 5% ee; **Compound 19c** (after hydrolysis): 38% yield, 5% ee, Chiralcel AD, 95:5 hexanes:iPrOH, 0.5 ml/min, 254 nm, $R_{T(R)} = 17.2$ min, $R_{T(S)} = 14.7$ min.

NMR Studies of Peptide-Substrate Complex

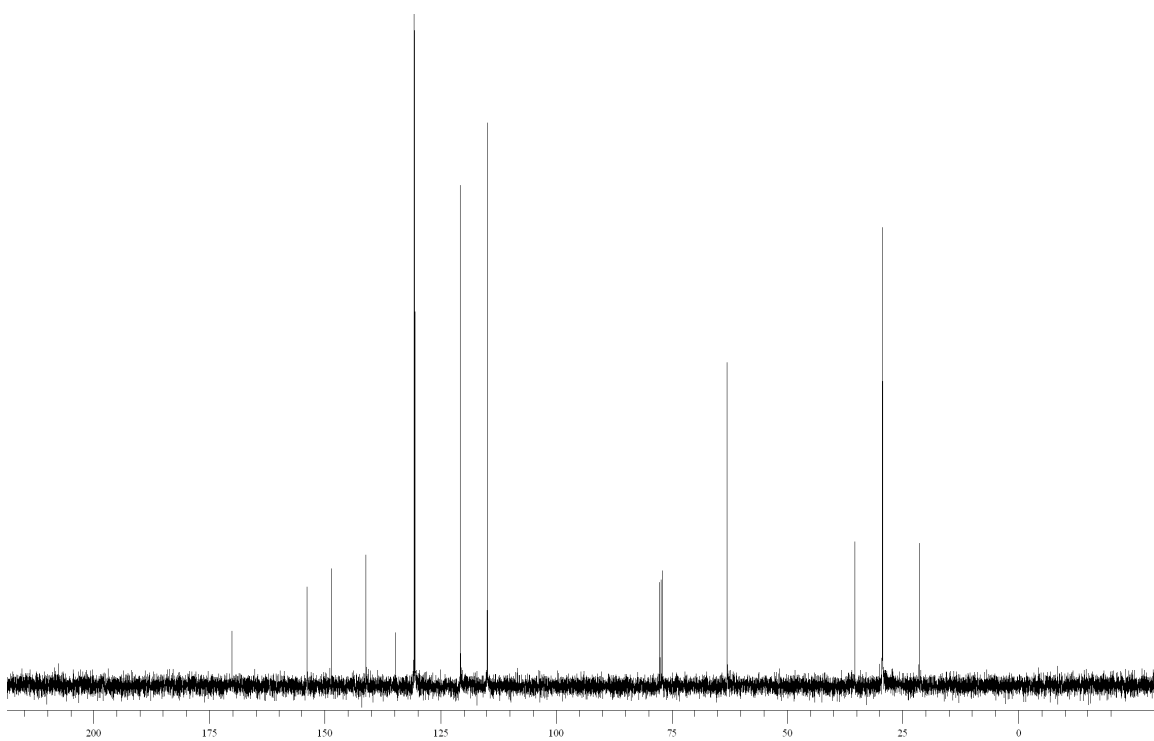
^1H NMR Studies. The bisphenol **1** (4.3 mg, 16.6 μmol) and peptide **4** (20.0 mg, 16.6 μmol), was dissolved in 600 μL of CDCl_3 and the spectra recorded on a Bruker 500 MHz spectrometer in CDCl_3 at ambient temperature.

^{13}C NMR Studies. ^{13}C labeled Bisphenol **1** (4.3 mg, 16.6 μmol), was co-mixed with the catalysts (20.0 mg **4**; 1.33 μL NMI; 12.1 mg, Table 3, entry 10; 18.1 mg, Table 3, entry 8; 14.4 mg, Table 3, entry 9; 16.6 μmol) in 600 μL of CDCl_3 and cooled to -30 $^\circ\text{C}$ in the NMR spectrometer (Bruker 500 MHz). The spectra were recorded after 10 minutes of exposure to the -30 $^\circ\text{C}$ sample chamber.

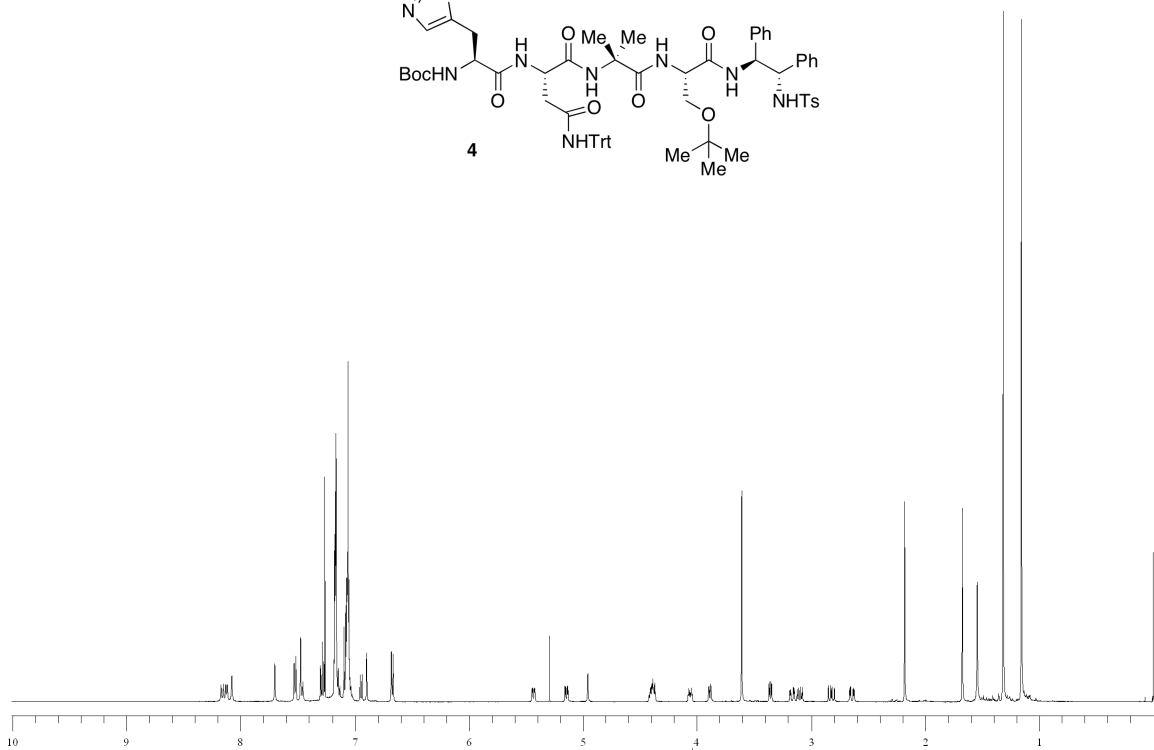
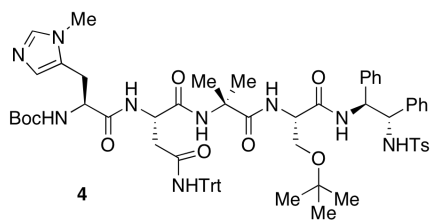
¹H NMR Spectrum of **3**



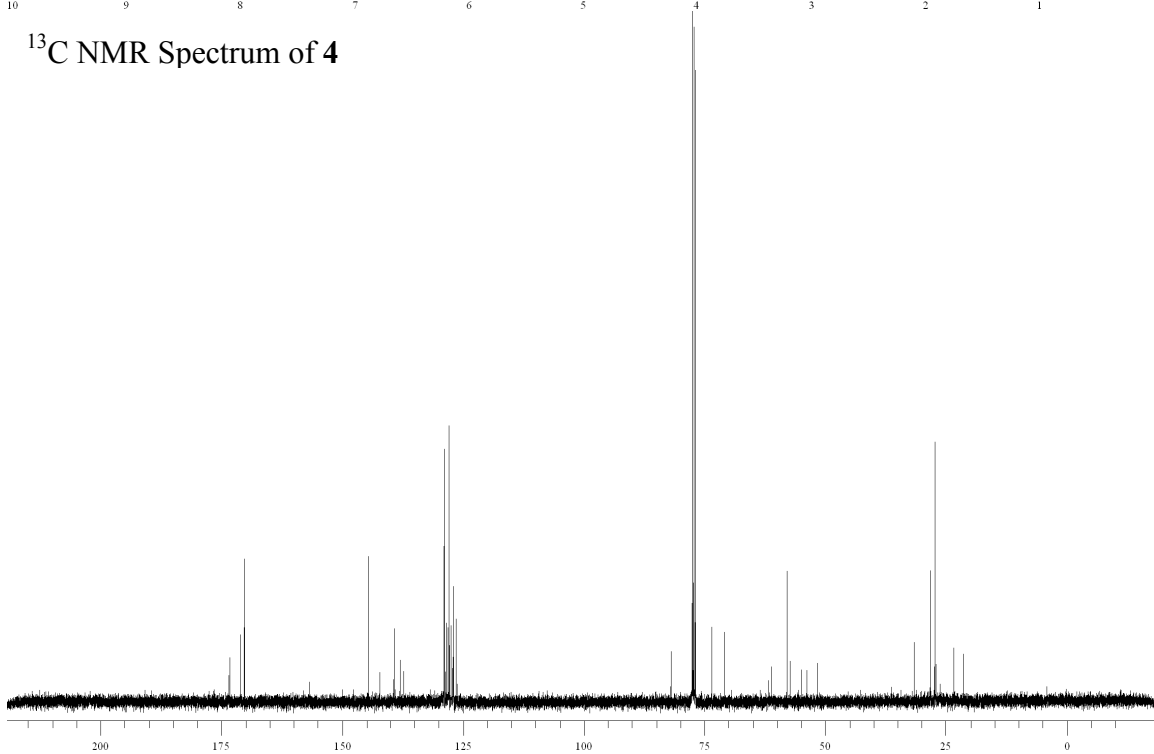
¹³C NMR Spectrum of **3**



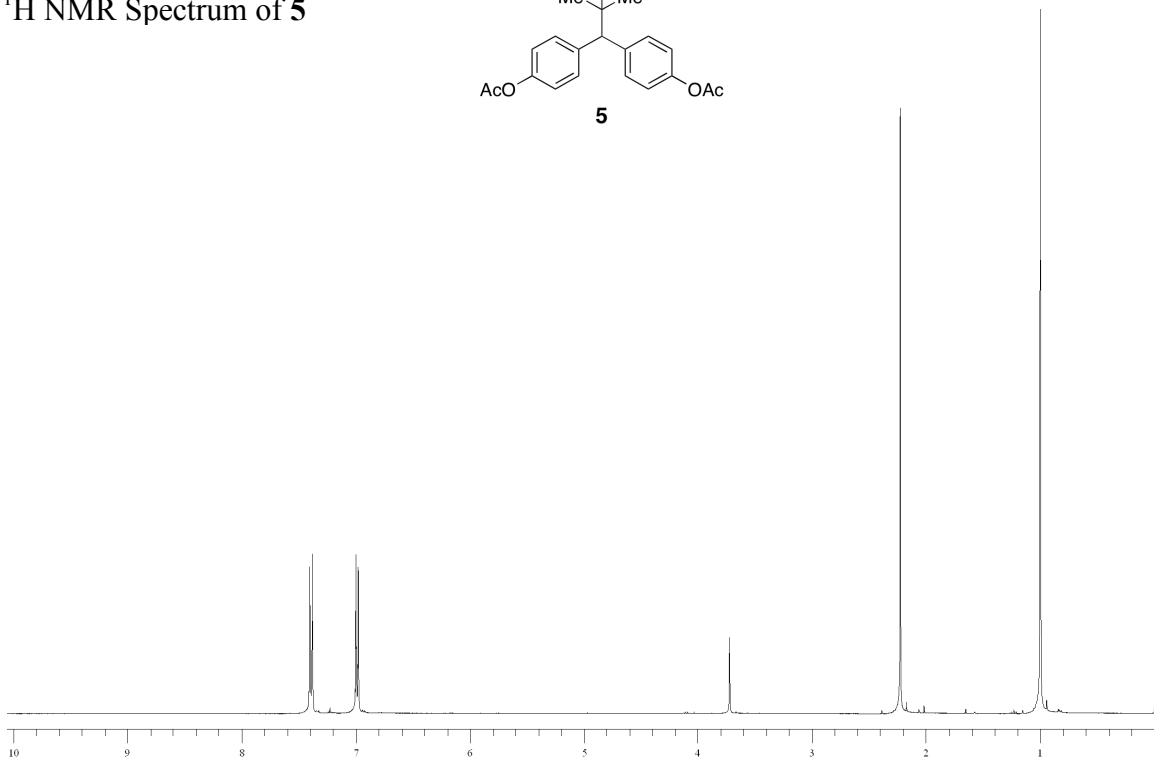
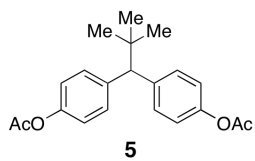
¹H NMR Spectrum of 4



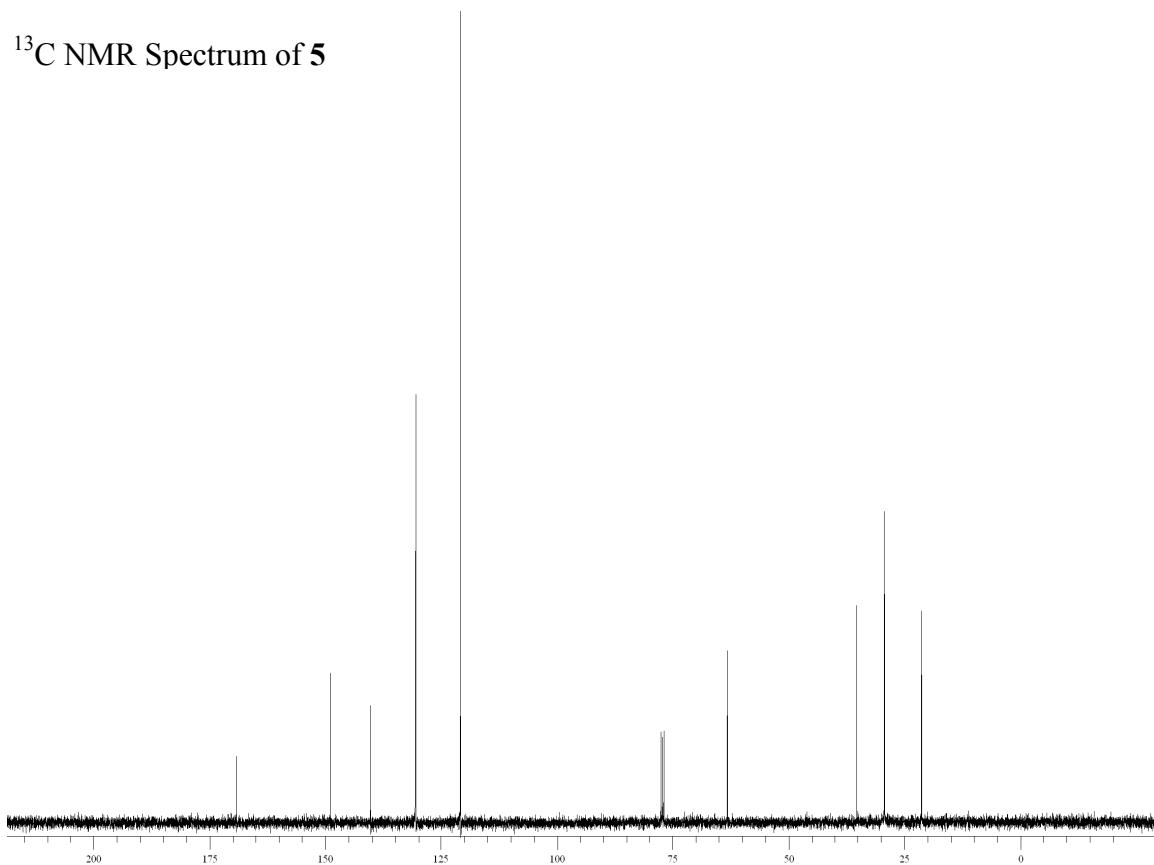
¹³C NMR Spectrum of 4



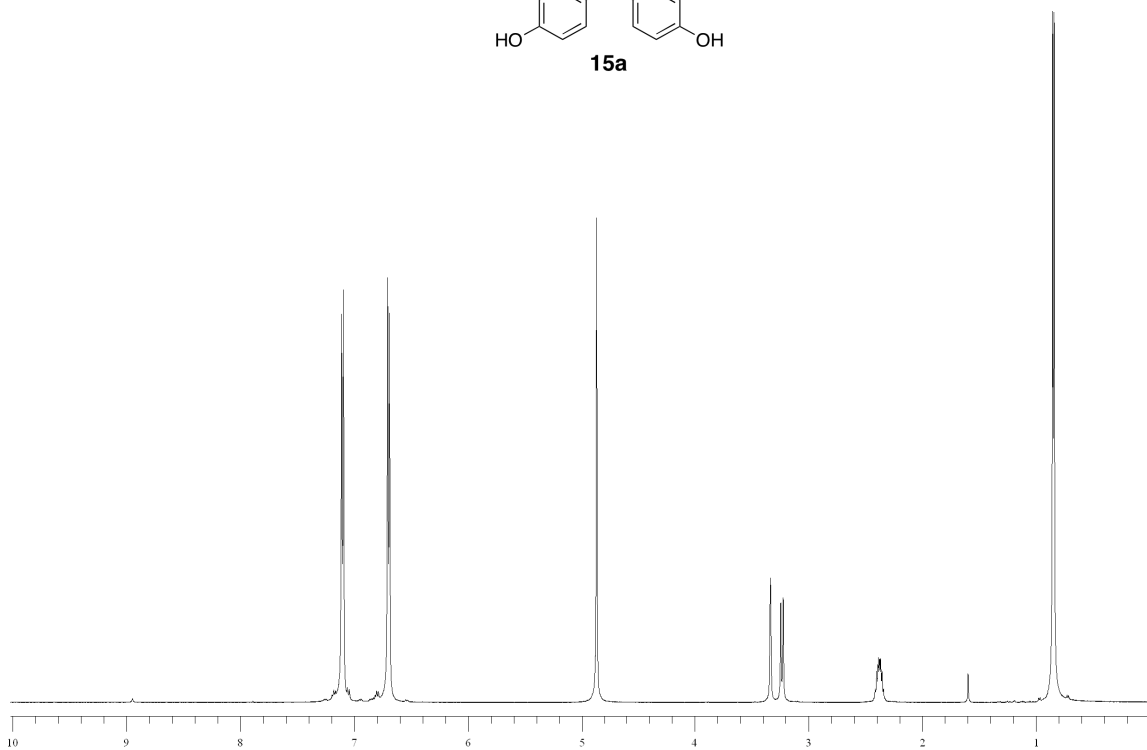
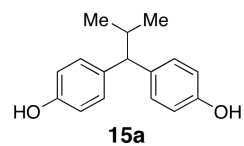
^1H NMR Spectrum of **5**



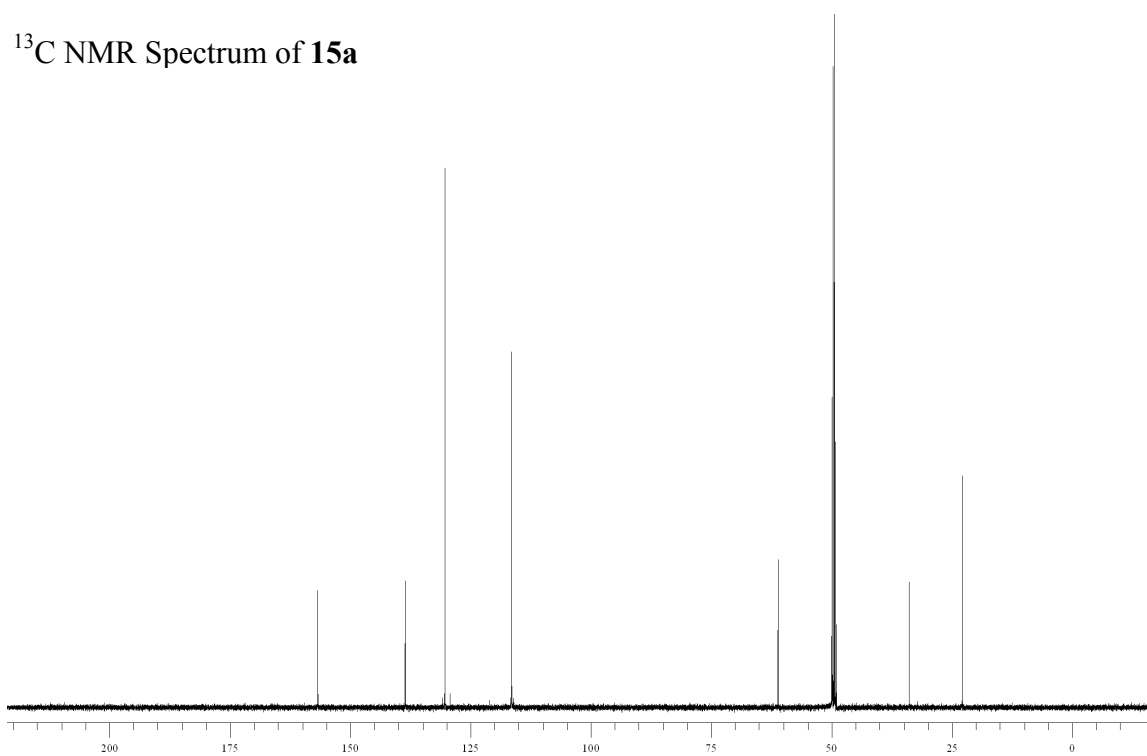
^{13}C NMR Spectrum of **5**



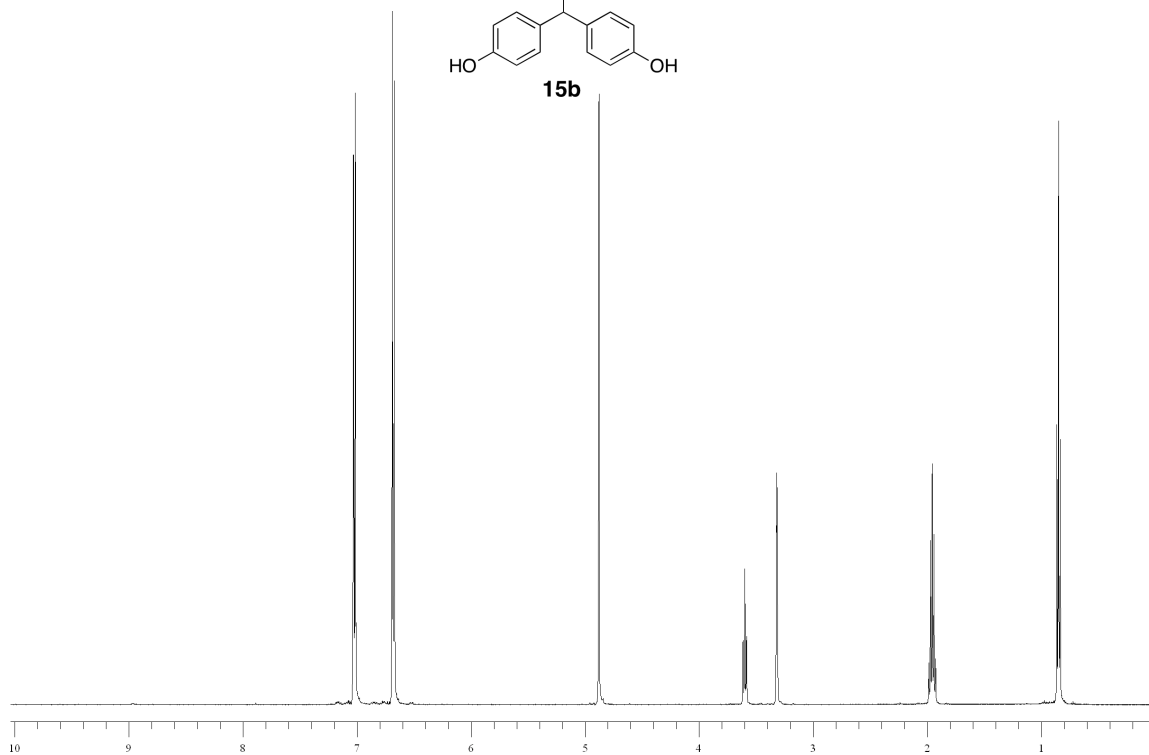
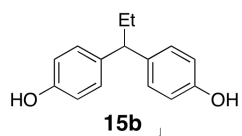
^1H NMR Spectrum of **15a**



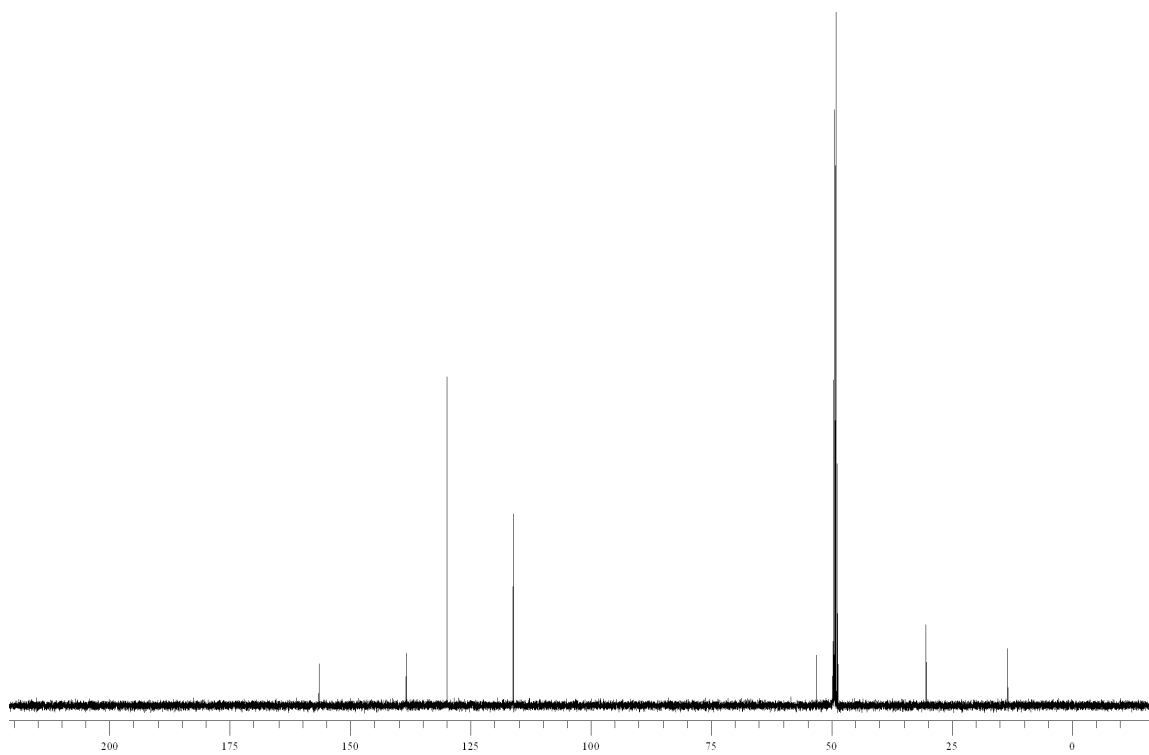
^{13}C NMR Spectrum of **15a**



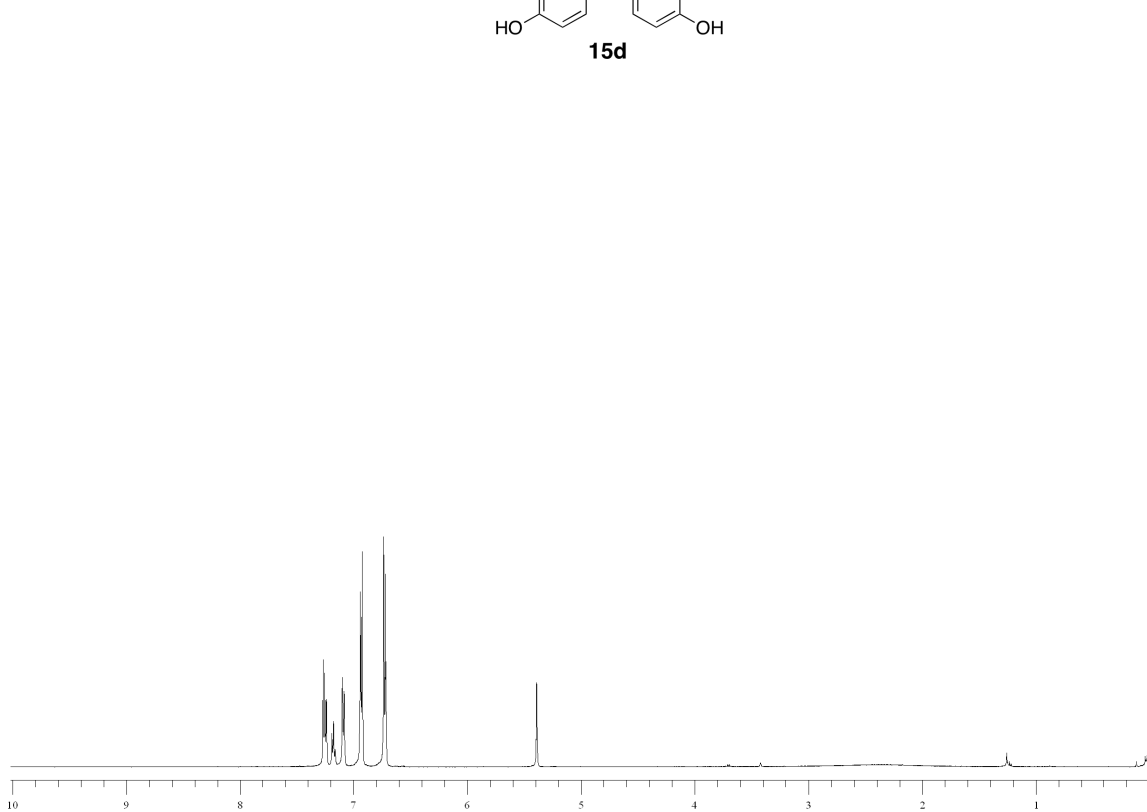
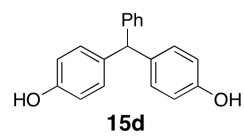
¹H NMR Spectrum of **15b**



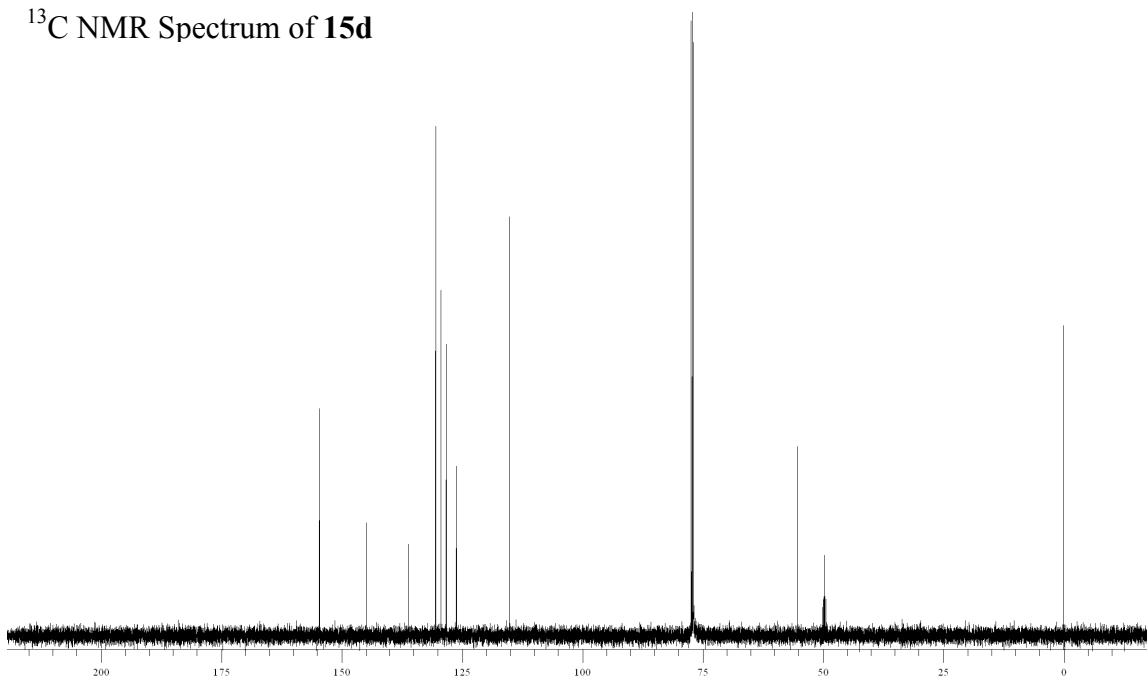
¹³C NMR Spectrum of **15b**



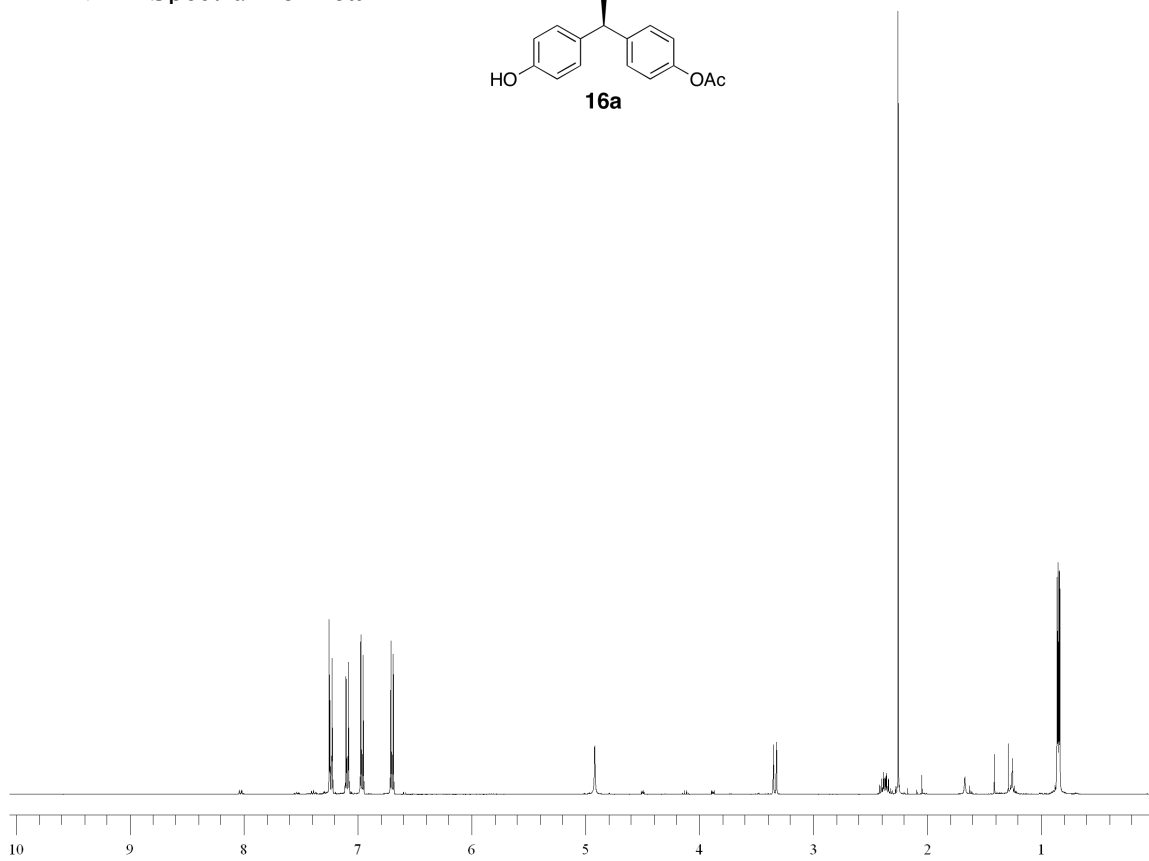
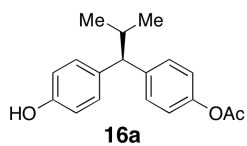
¹H NMR Spectrum of **15d**



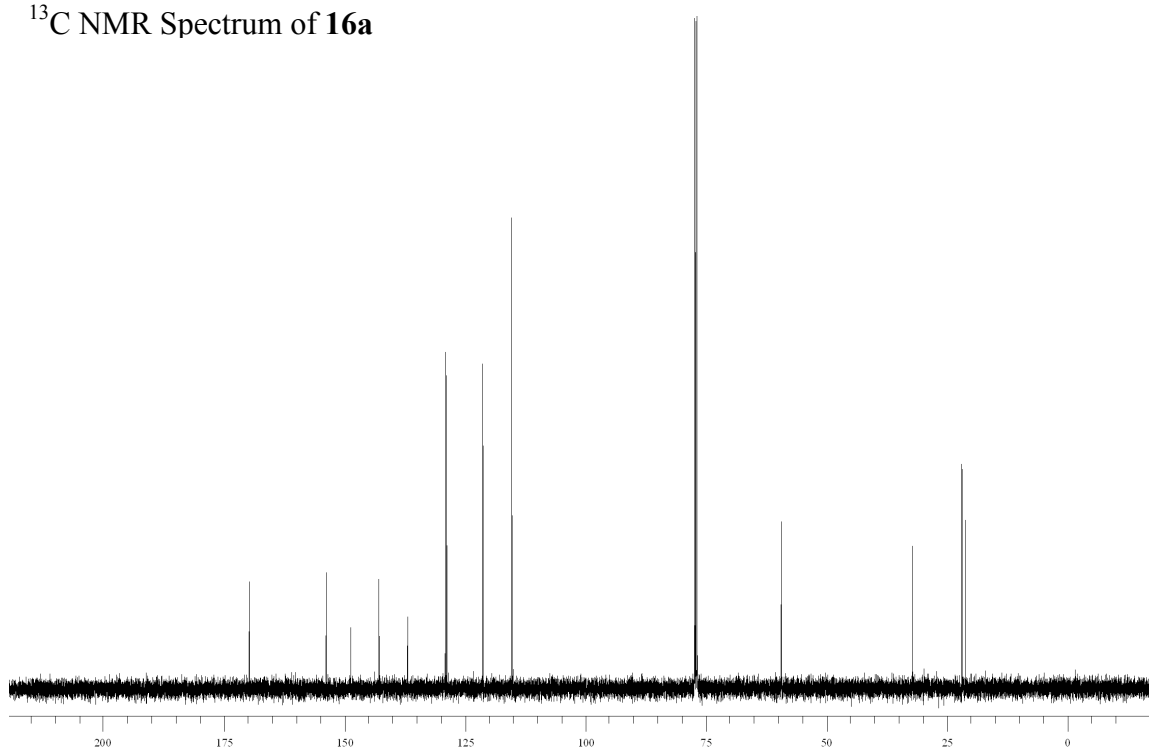
¹³C NMR Spectrum of **15d**



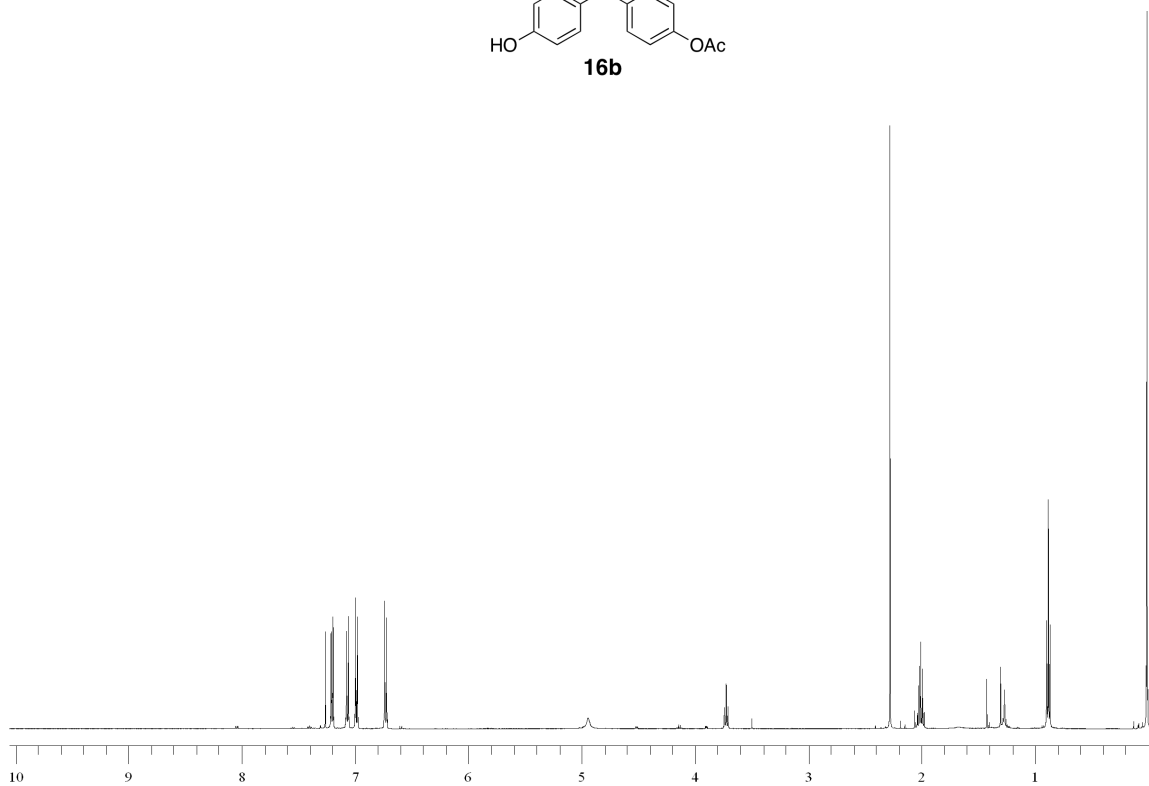
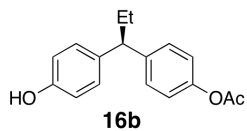
¹H NMR Spectrum of **16a**



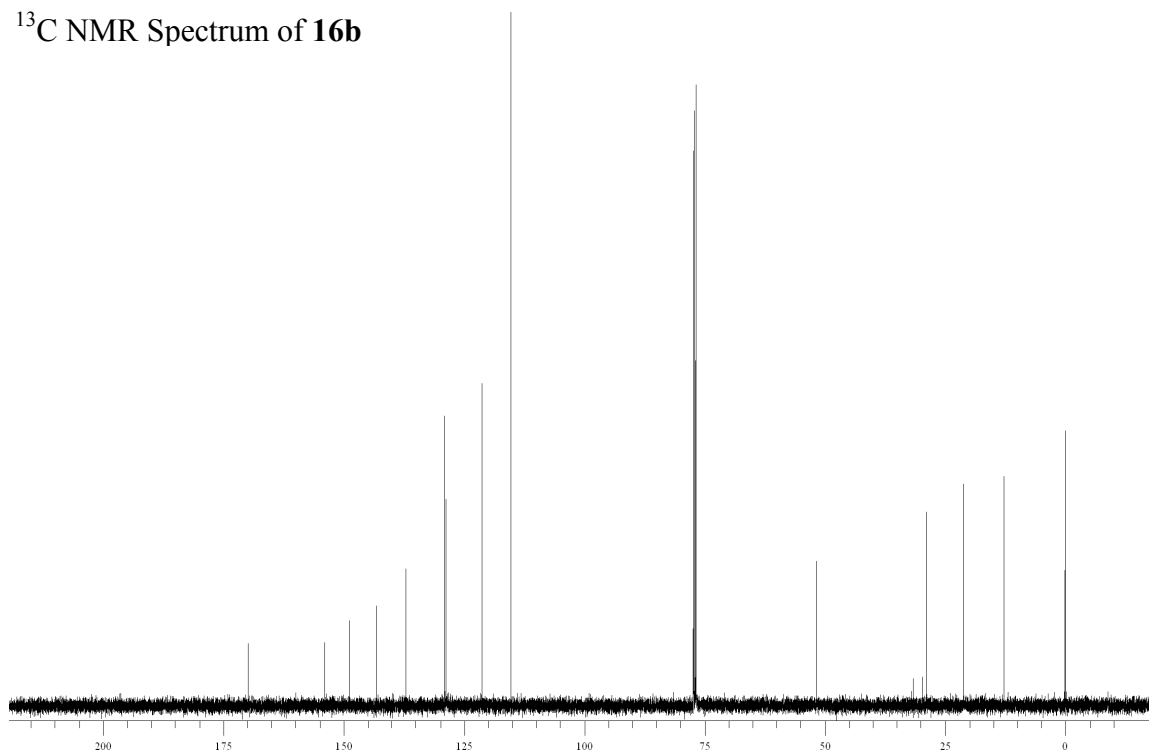
¹³C NMR Spectrum of **16a**



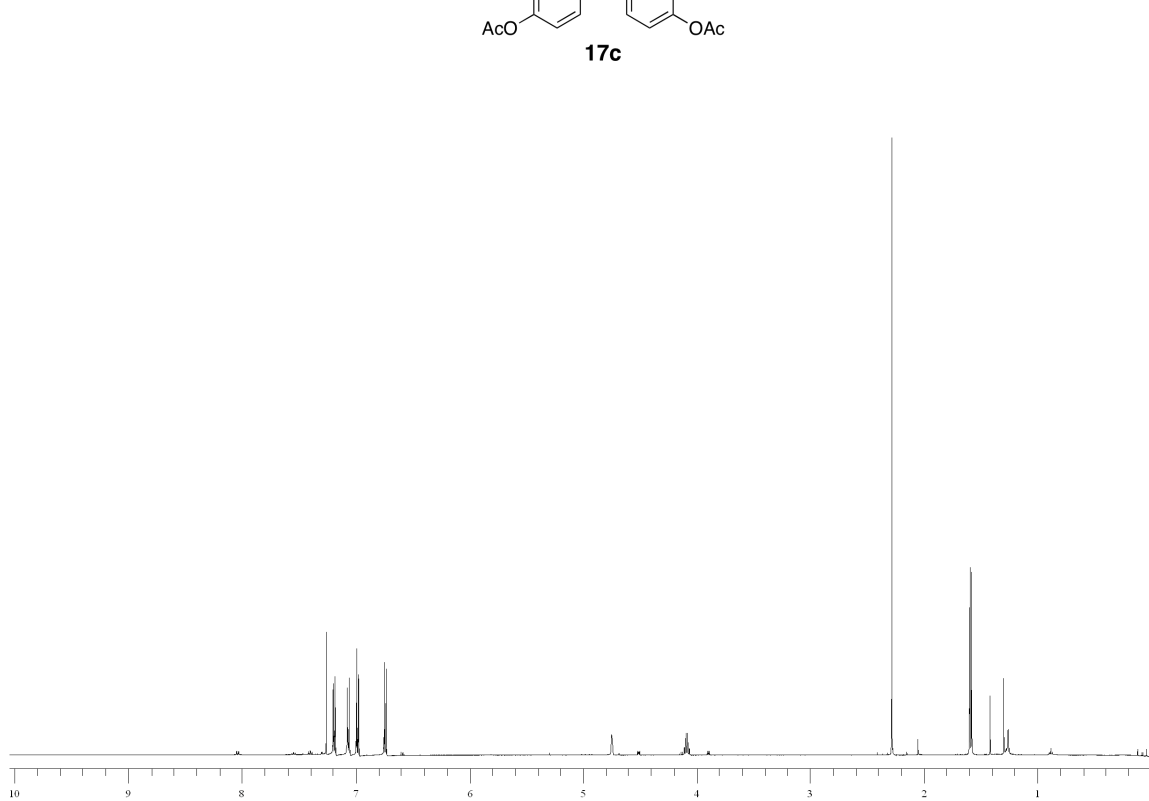
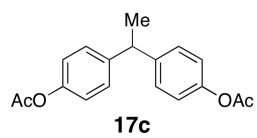
¹H NMR Spectrum of **16b**



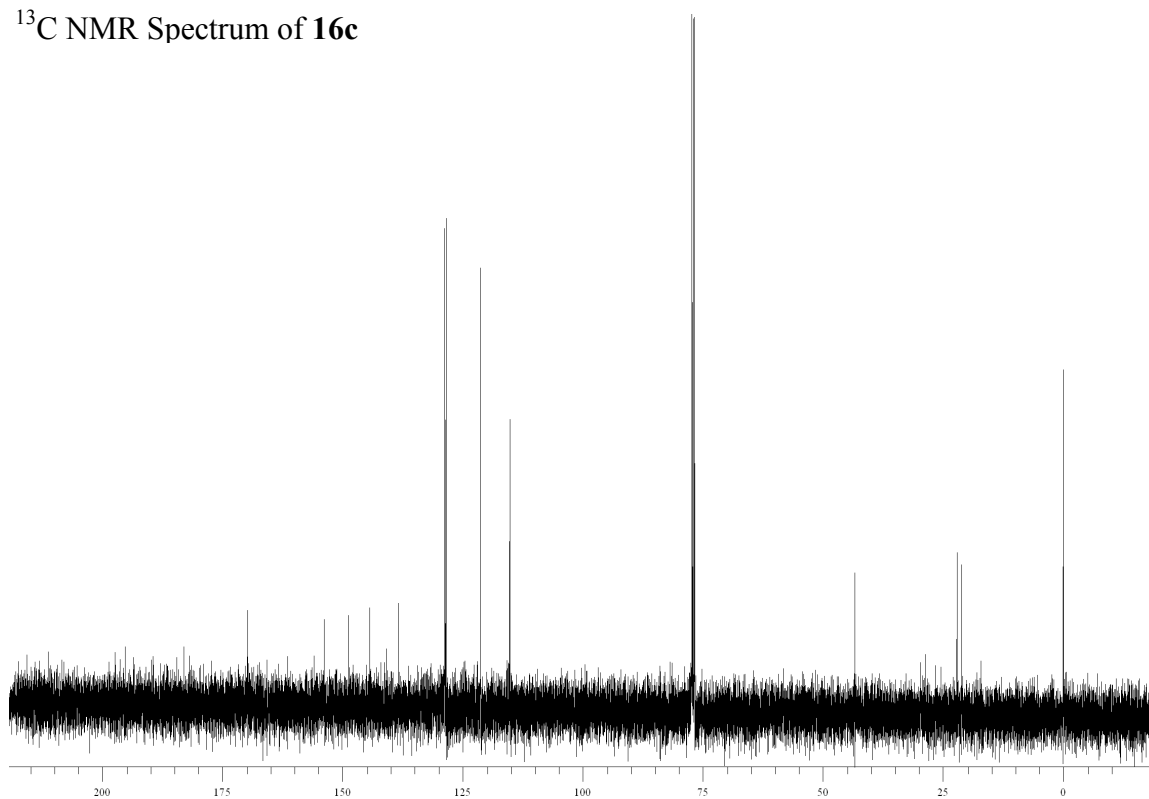
¹³C NMR Spectrum of **16b**



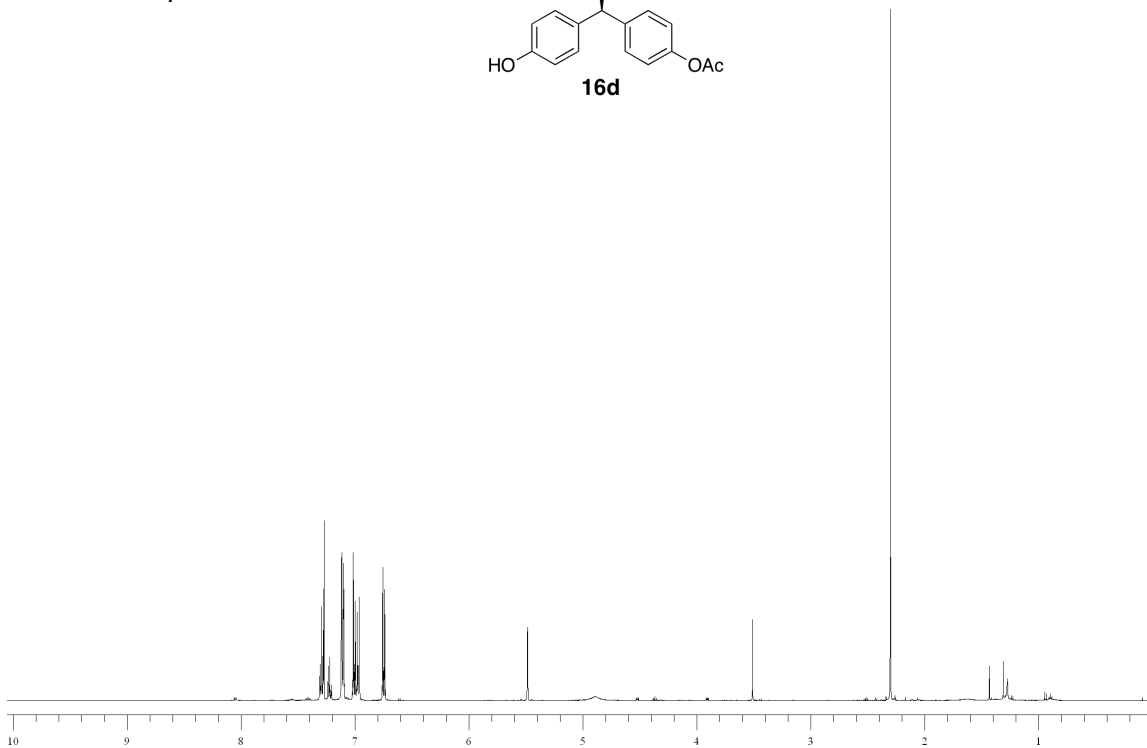
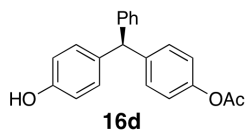
¹H NMR Spectrum of **16c**



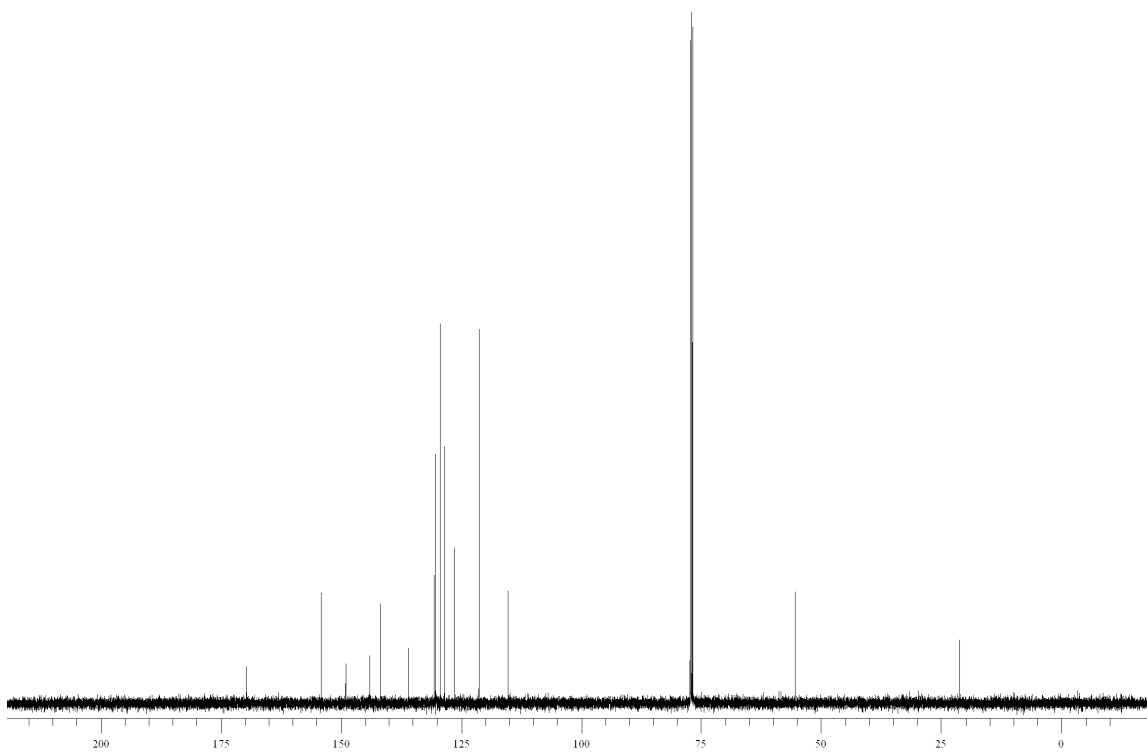
¹³C NMR Spectrum of **16c**



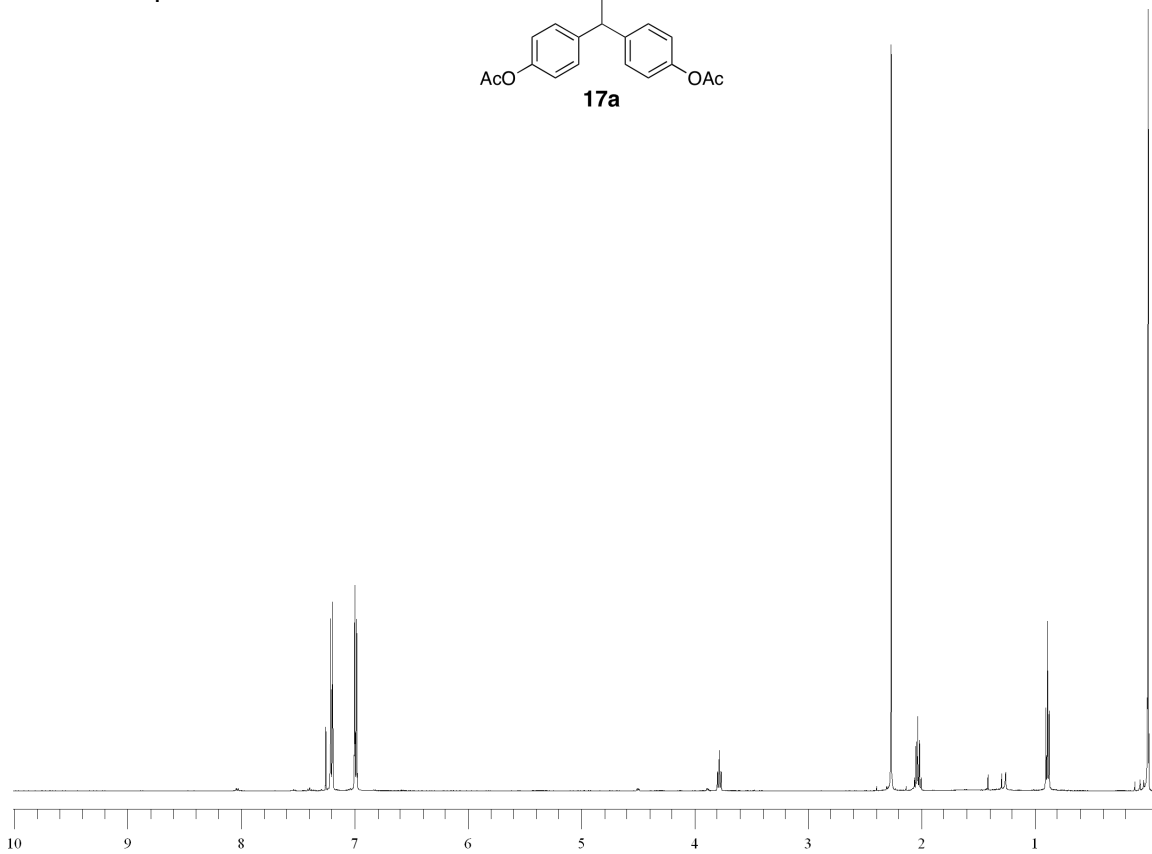
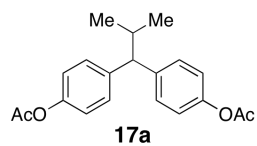
^1H NMR Spectrum of **16d**



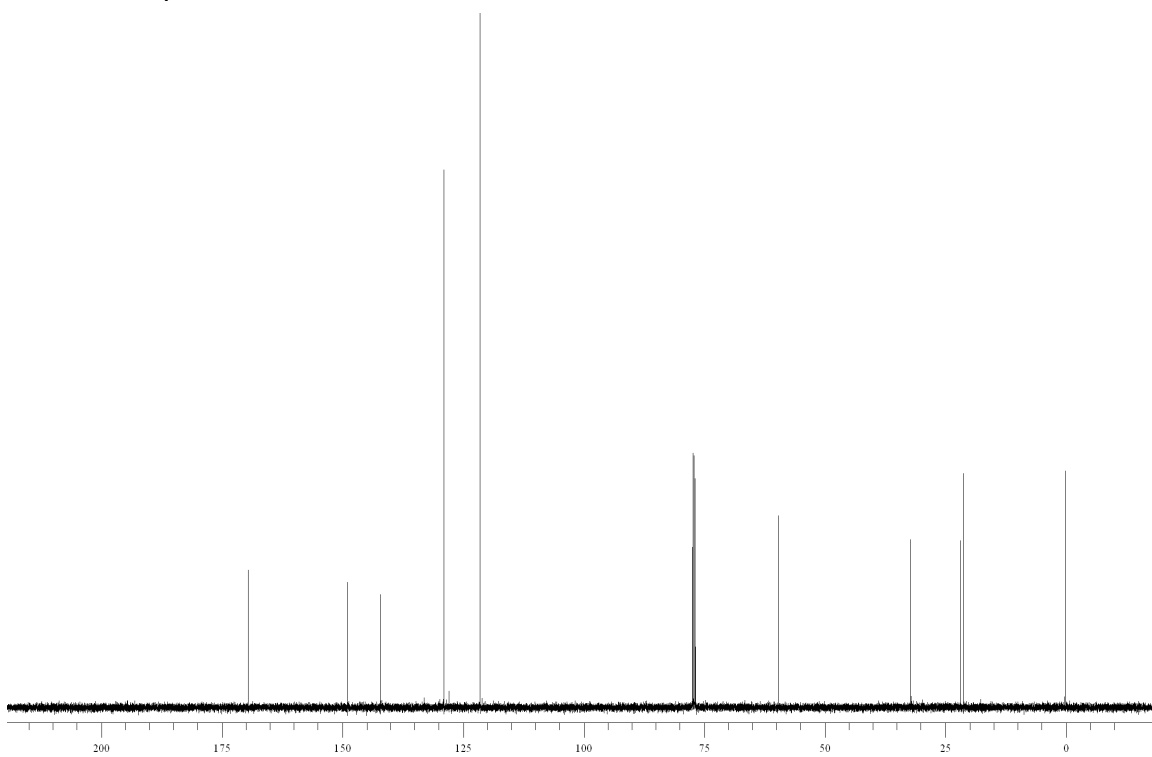
^{13}C NMR Spectrum of **16d**



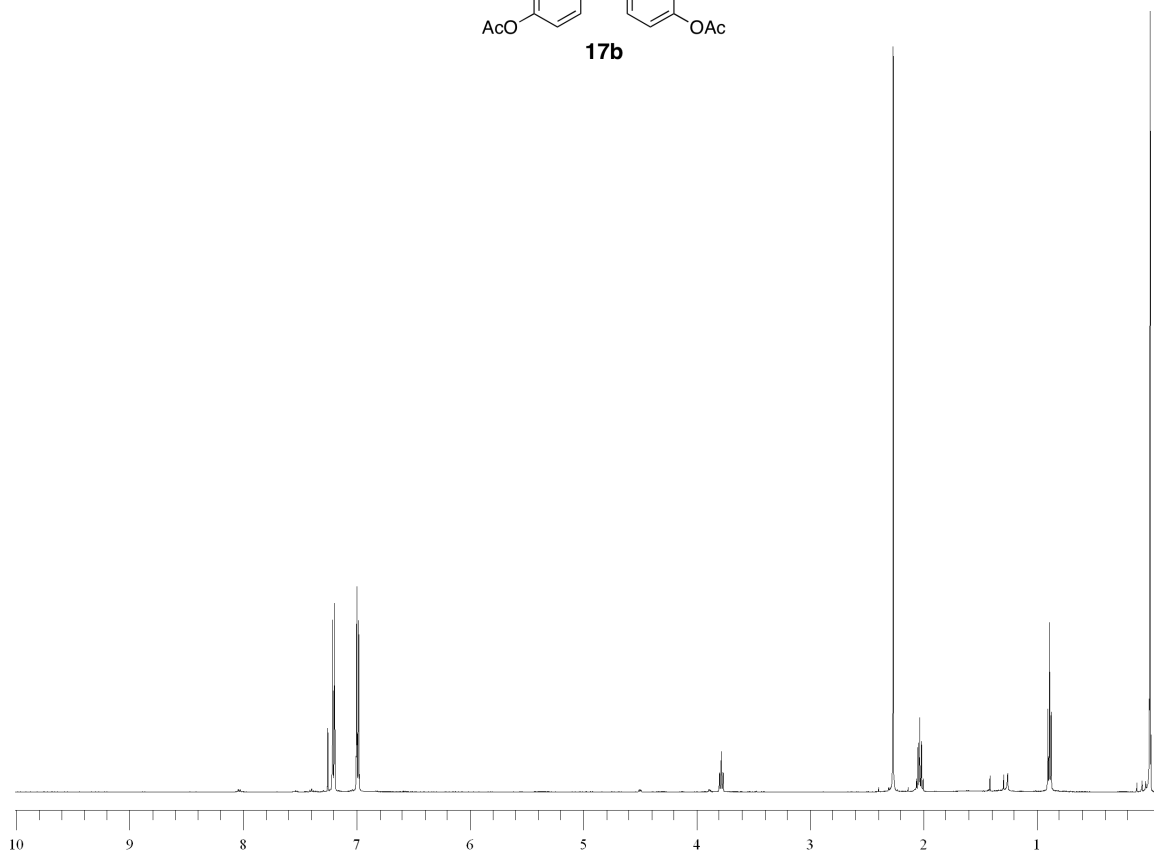
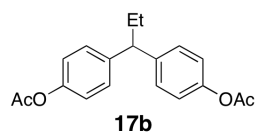
¹H NMR Spectrum of **17a**



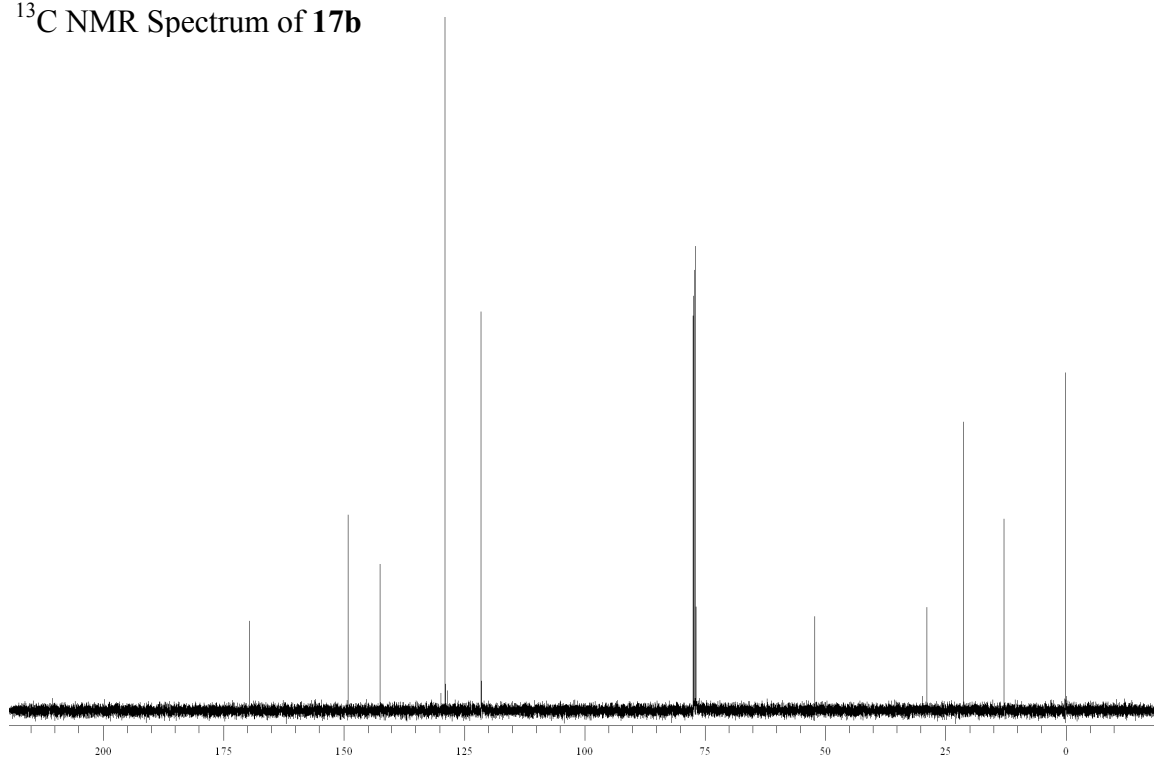
¹³C NMR Spectrum of **17a**



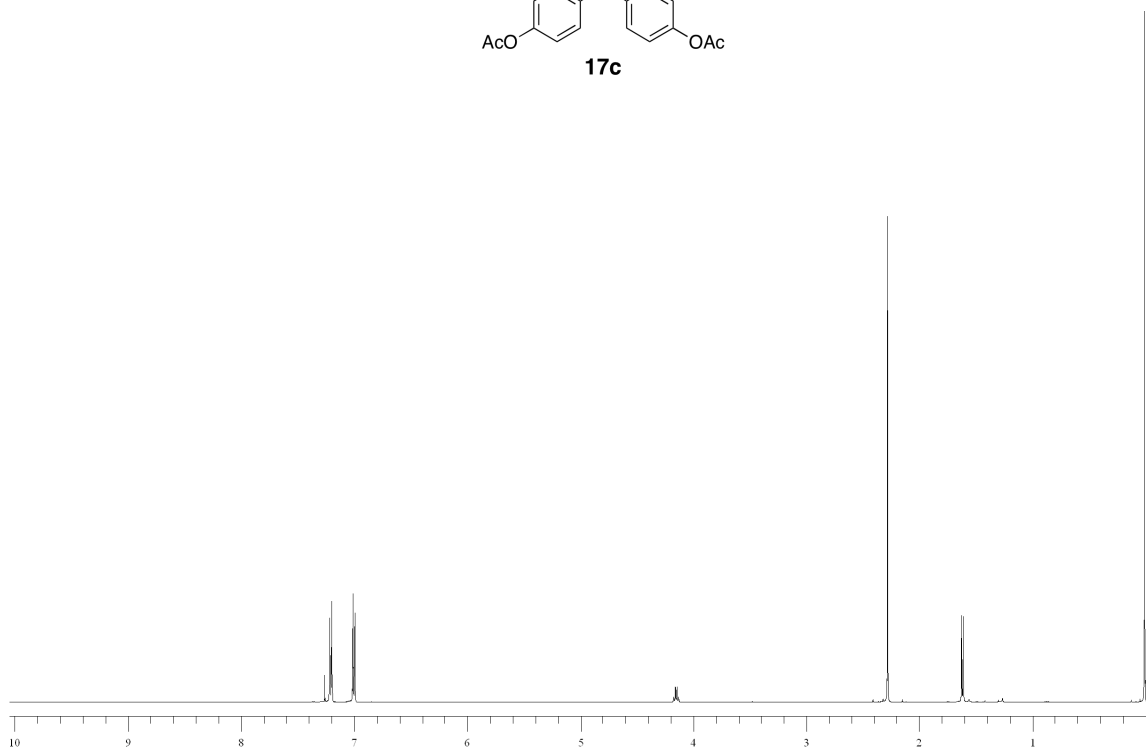
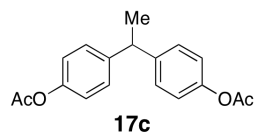
¹H NMR Spectrum of **17b**



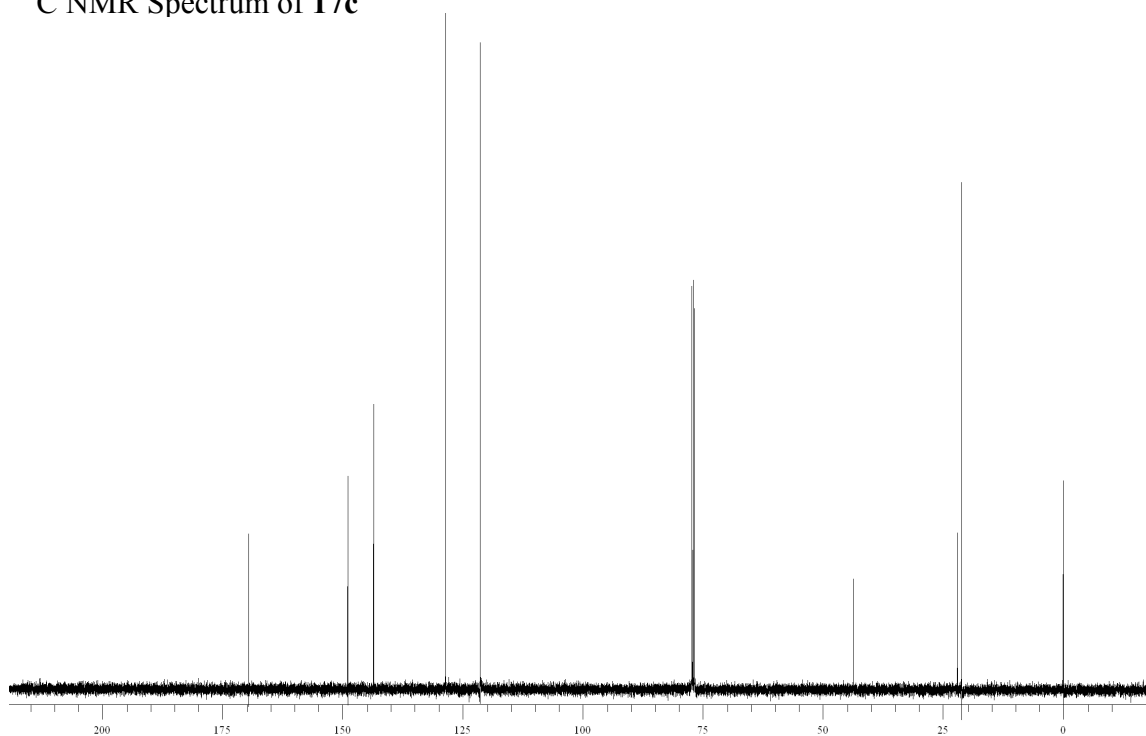
¹³C NMR Spectrum of **17b**



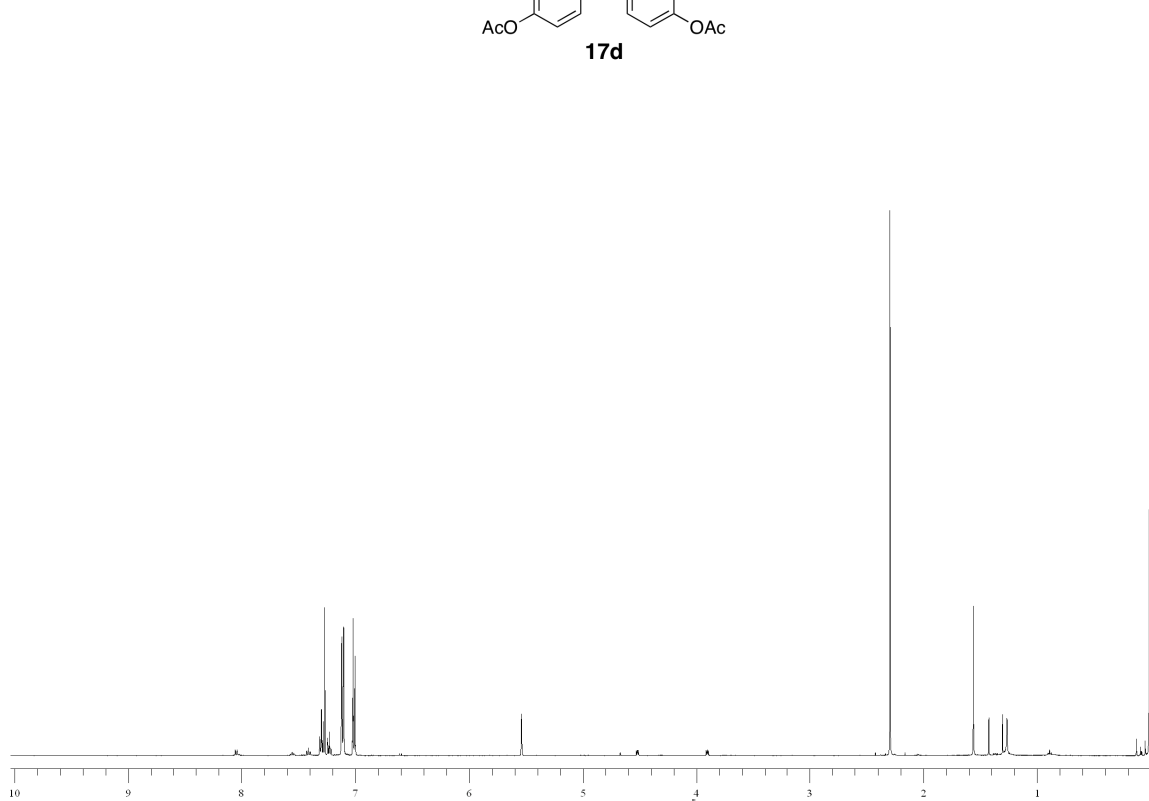
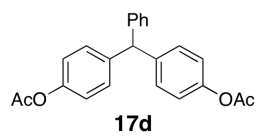
¹H NMR Spectrum of **17c**



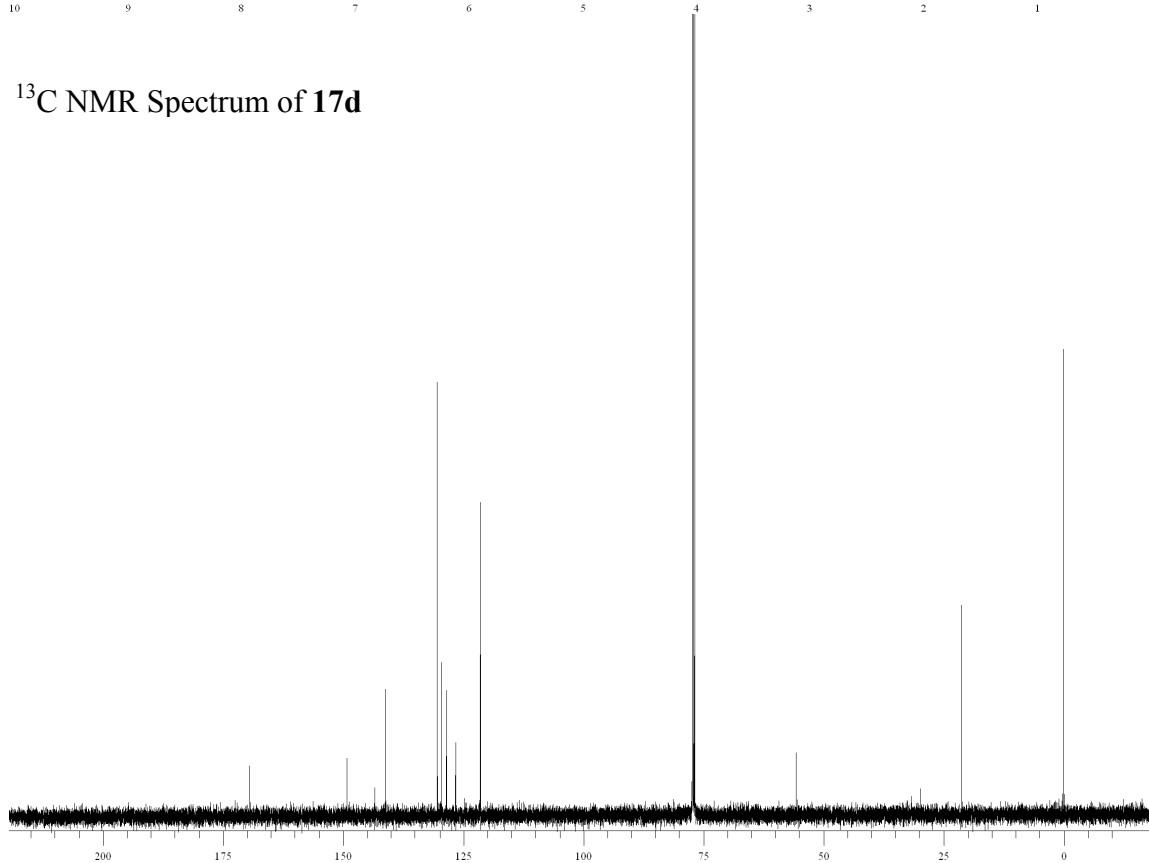
¹³C NMR Spectrum of **17c**



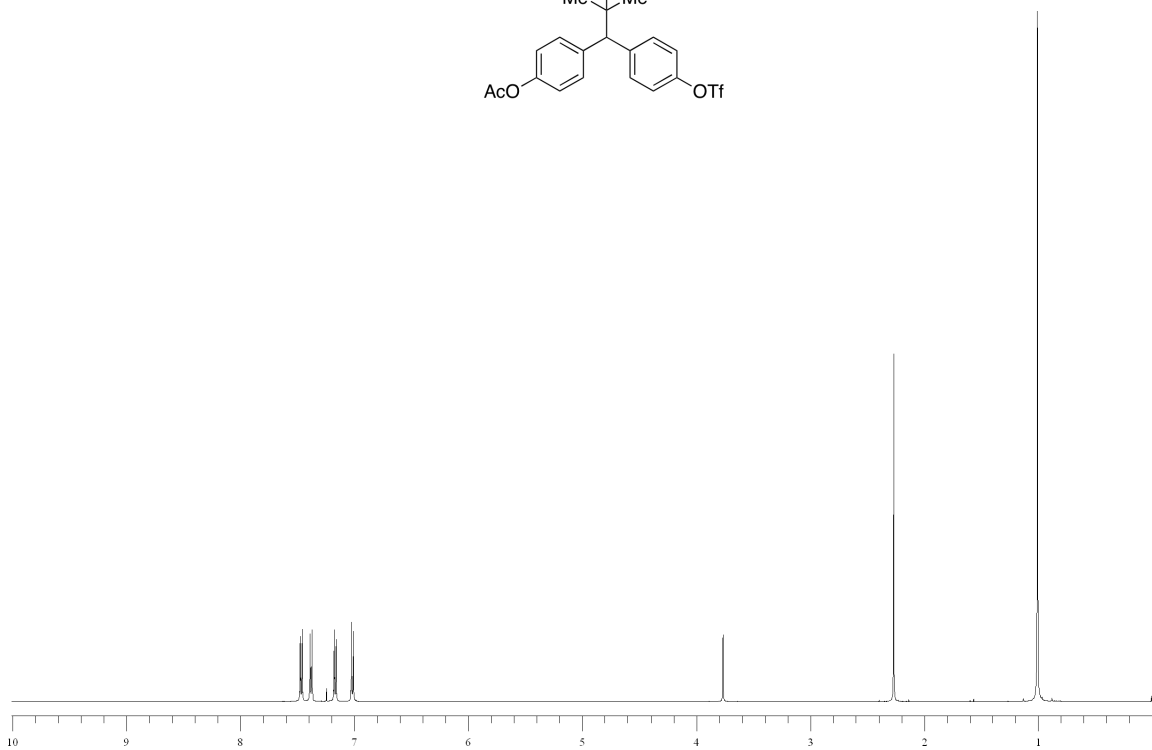
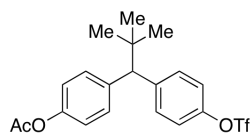
¹H NMR Spectrum of **17d**



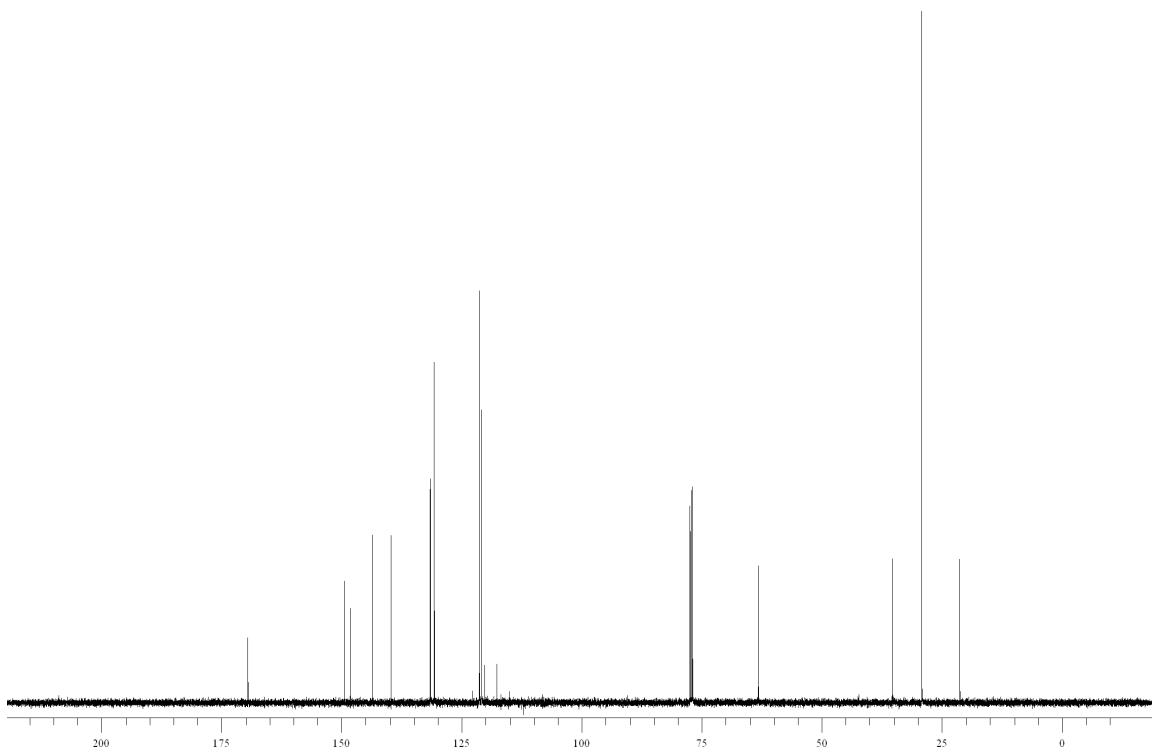
¹³C NMR Spectrum of **17d**



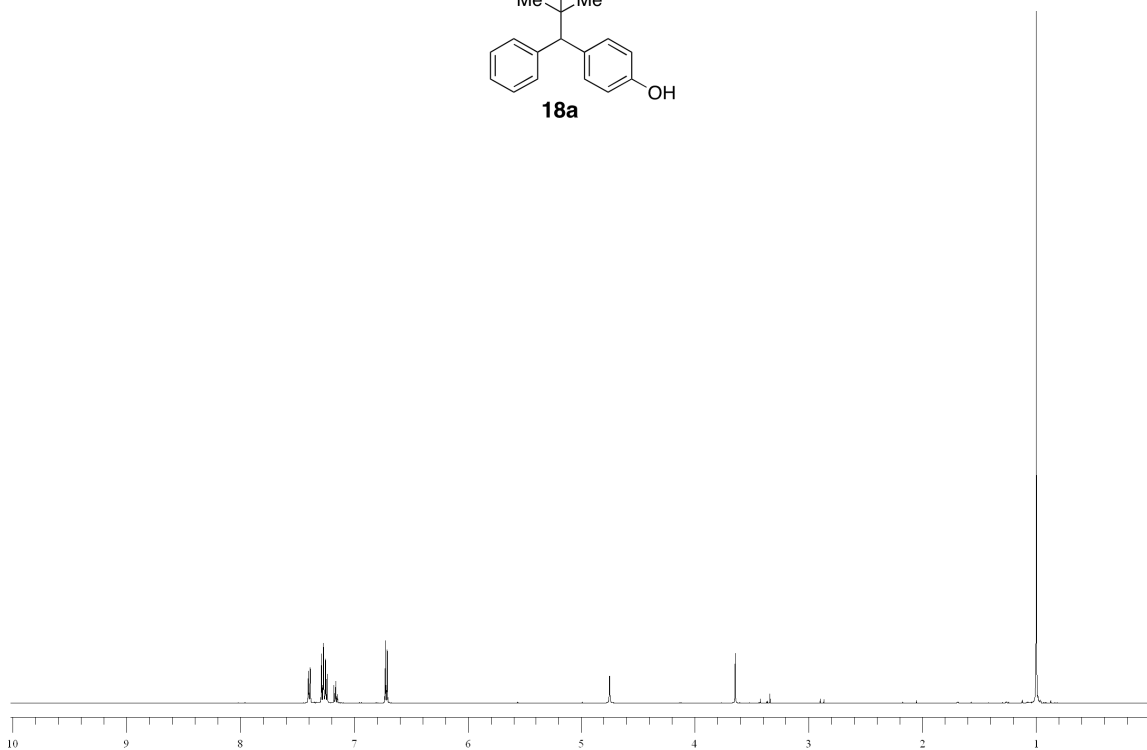
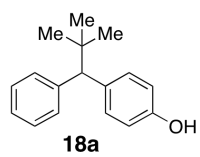
¹H NMR Spectrum of **Mono(acetate) mono(triflate)**



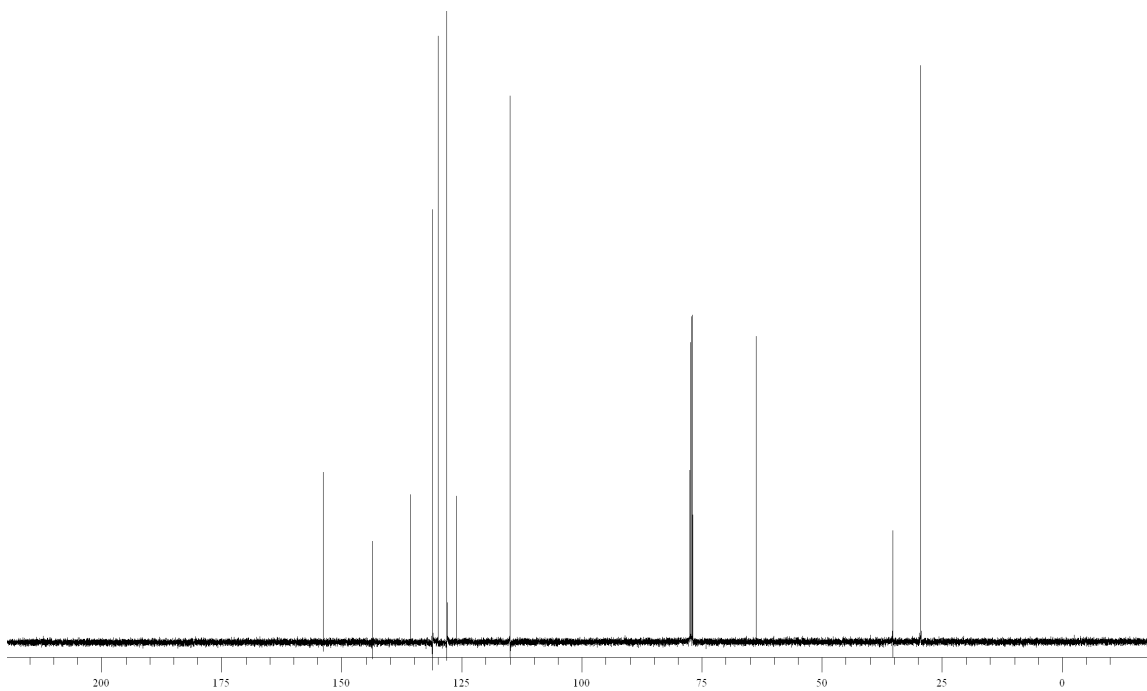
¹³C NMR Spectrum of **Mono(acetate) mono(triflate)**



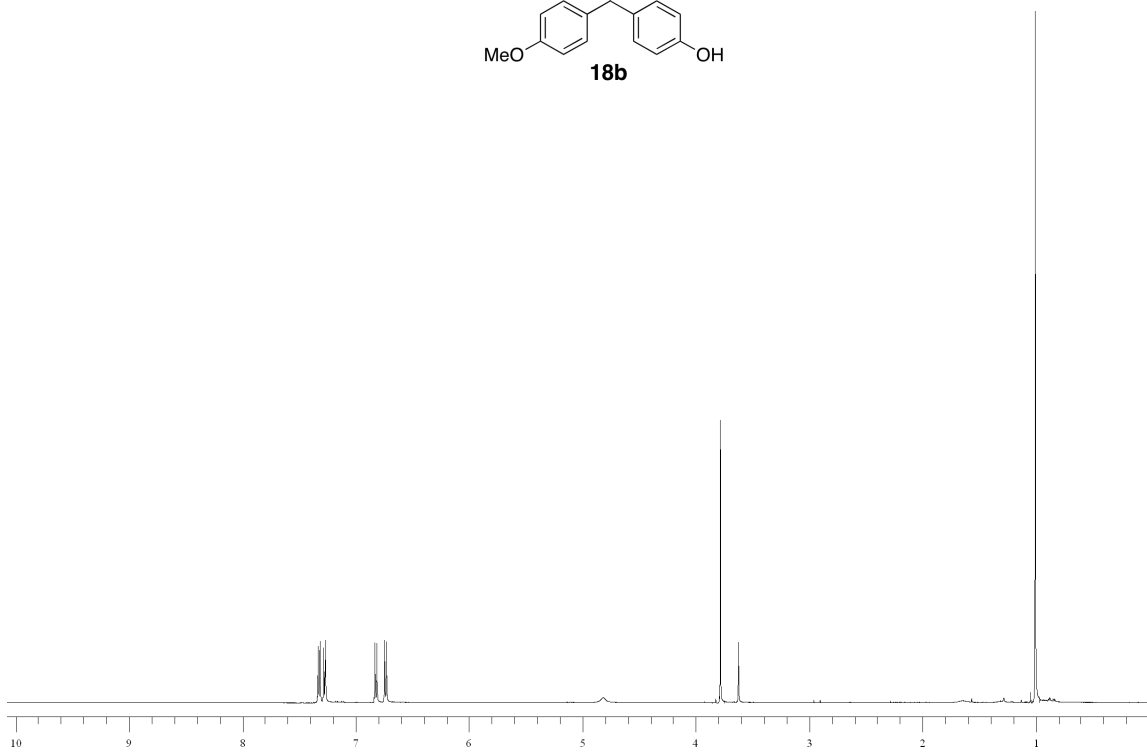
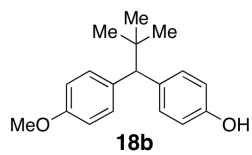
¹H NMR Spectrum of **18a**



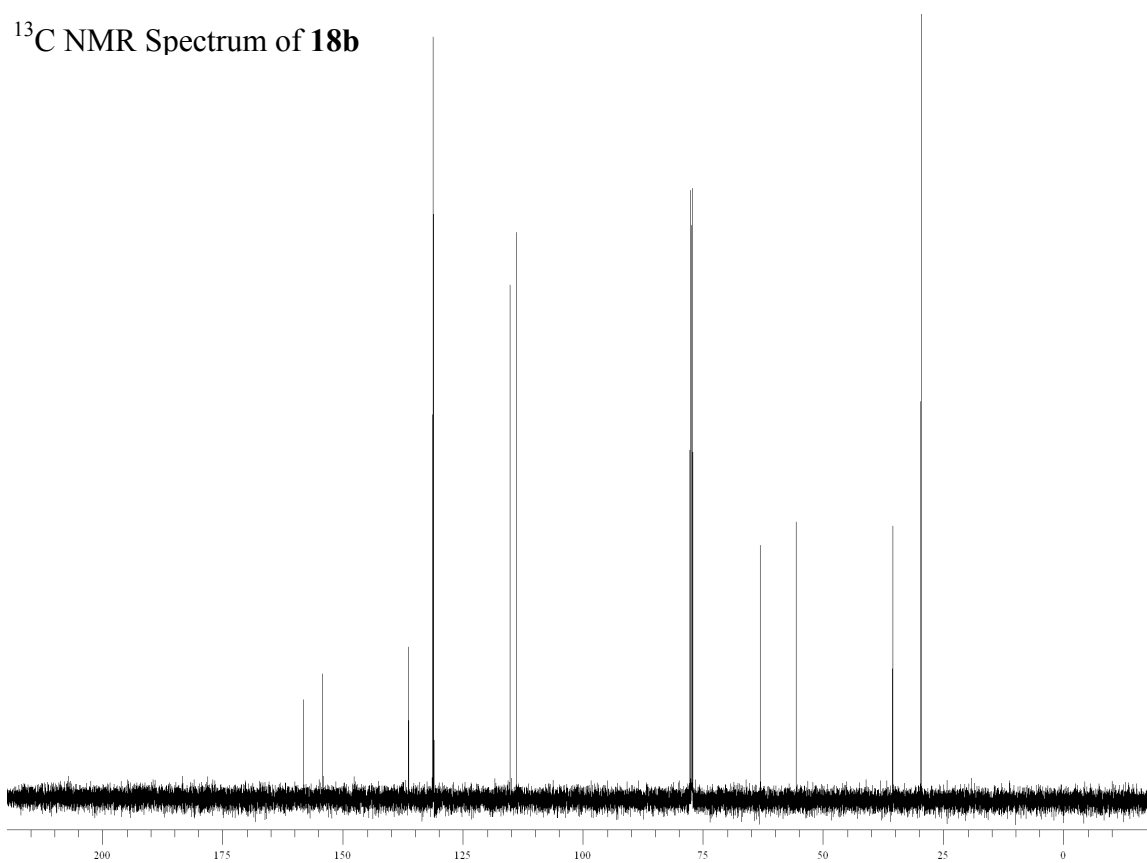
¹³C NMR Spectrum of **18a**



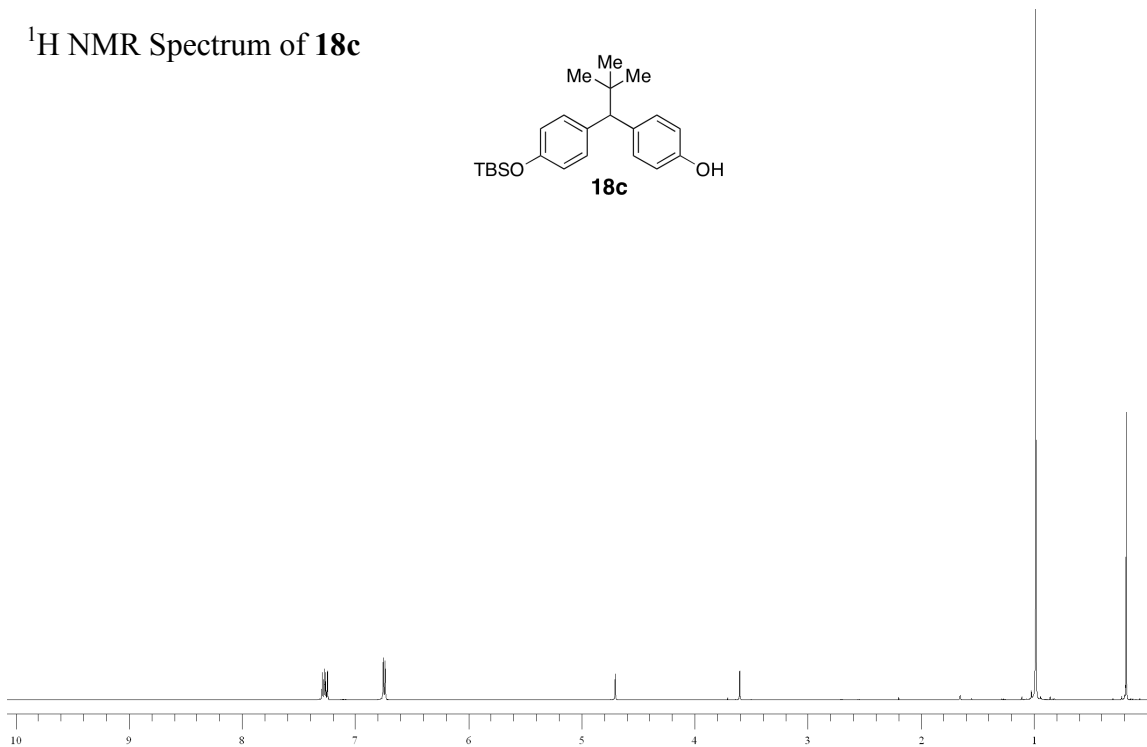
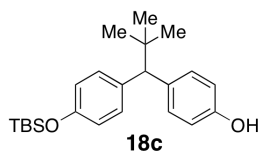
^1H NMR Spectrum of **18b**



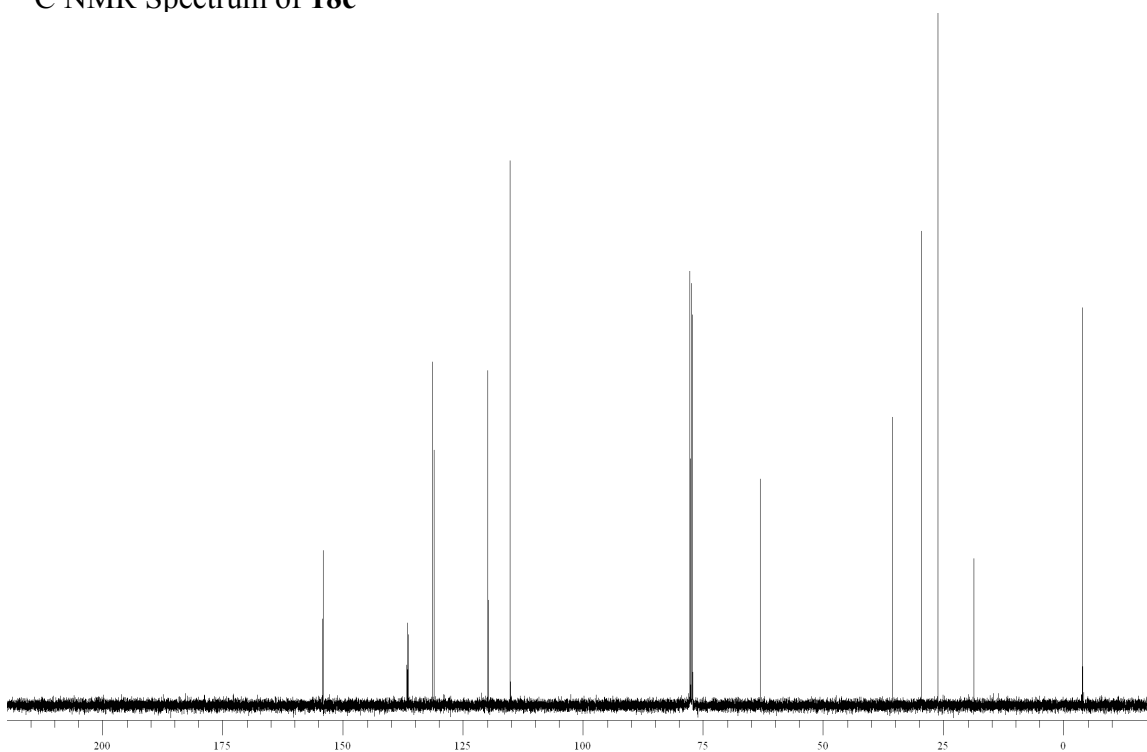
^{13}C NMR Spectrum of **18b**



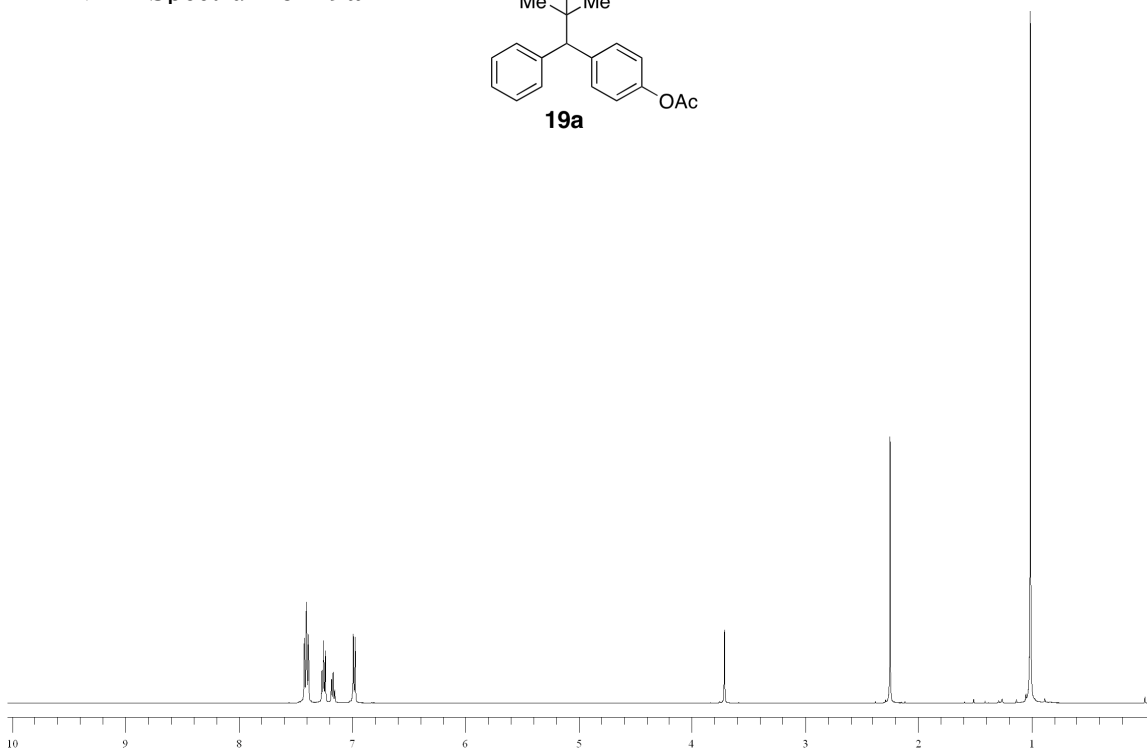
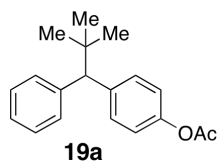
^1H NMR Spectrum of **18c**



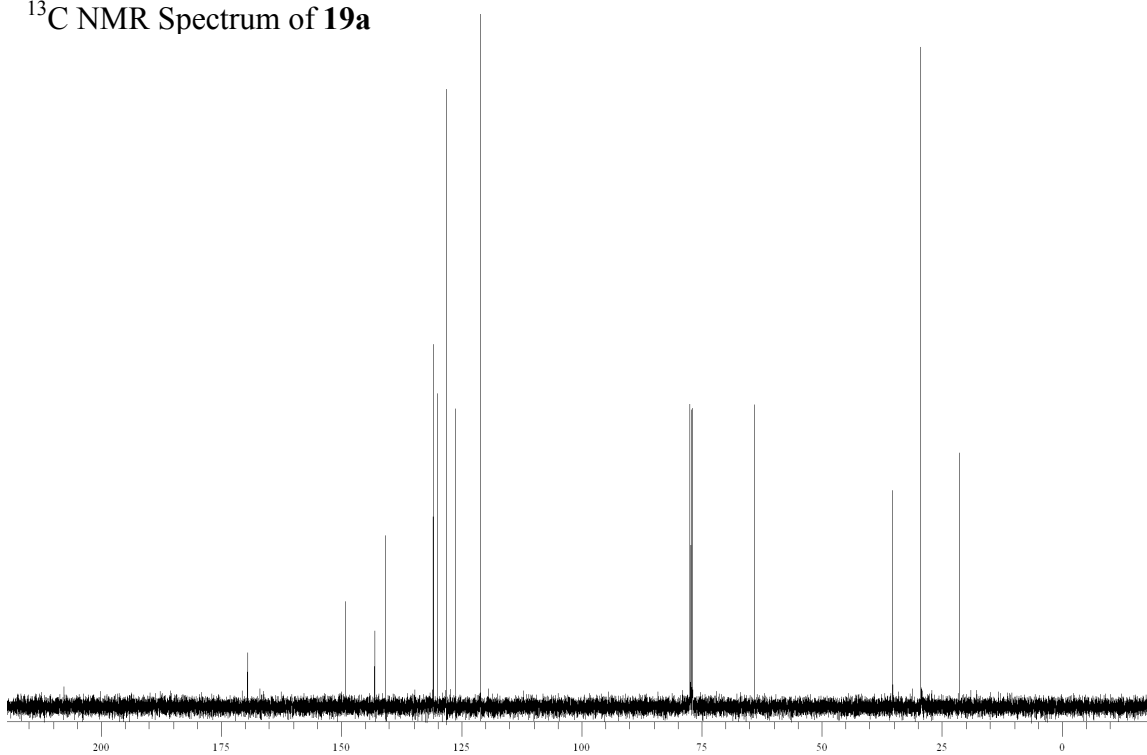
^{13}C NMR Spectrum of **18c**



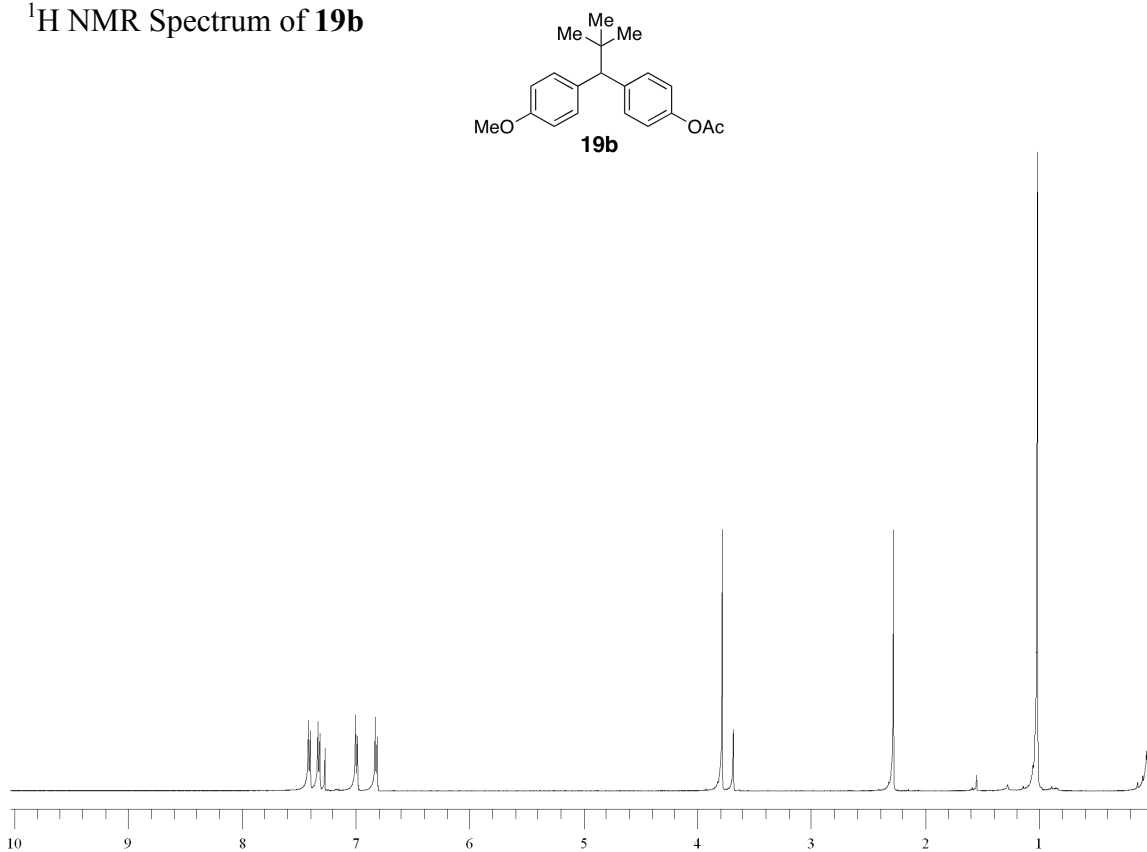
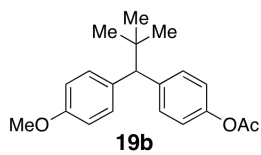
^1H NMR Spectrum of **19a**



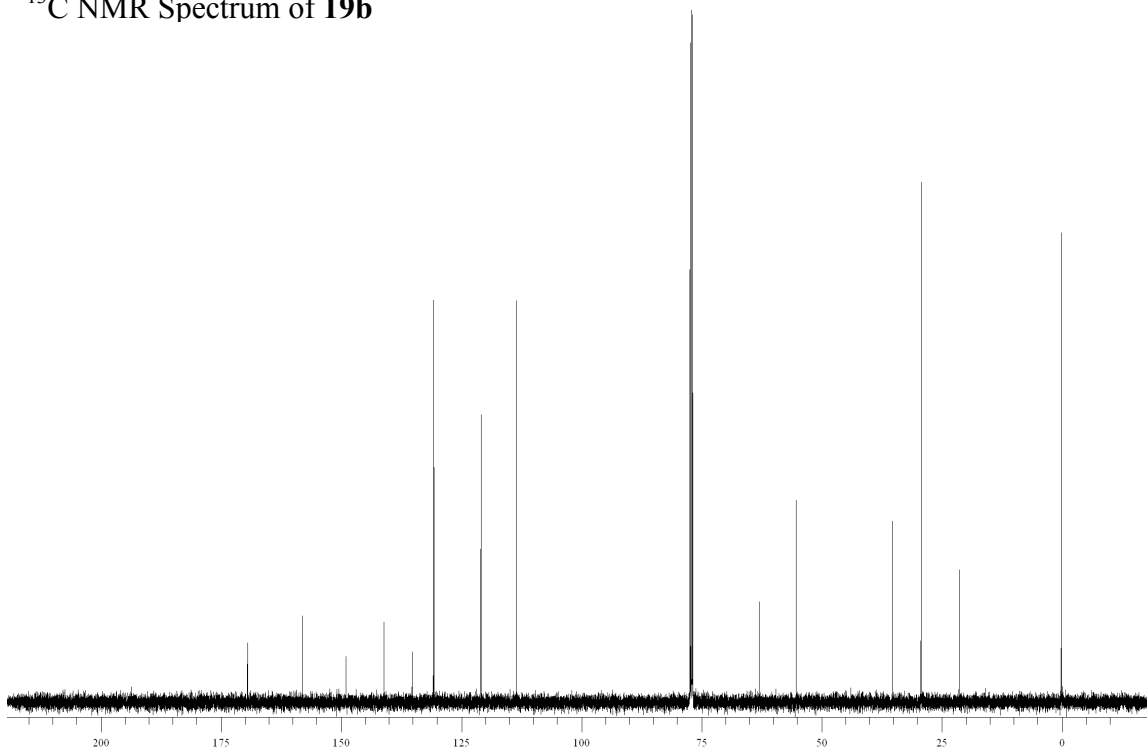
^{13}C NMR Spectrum of **19a**



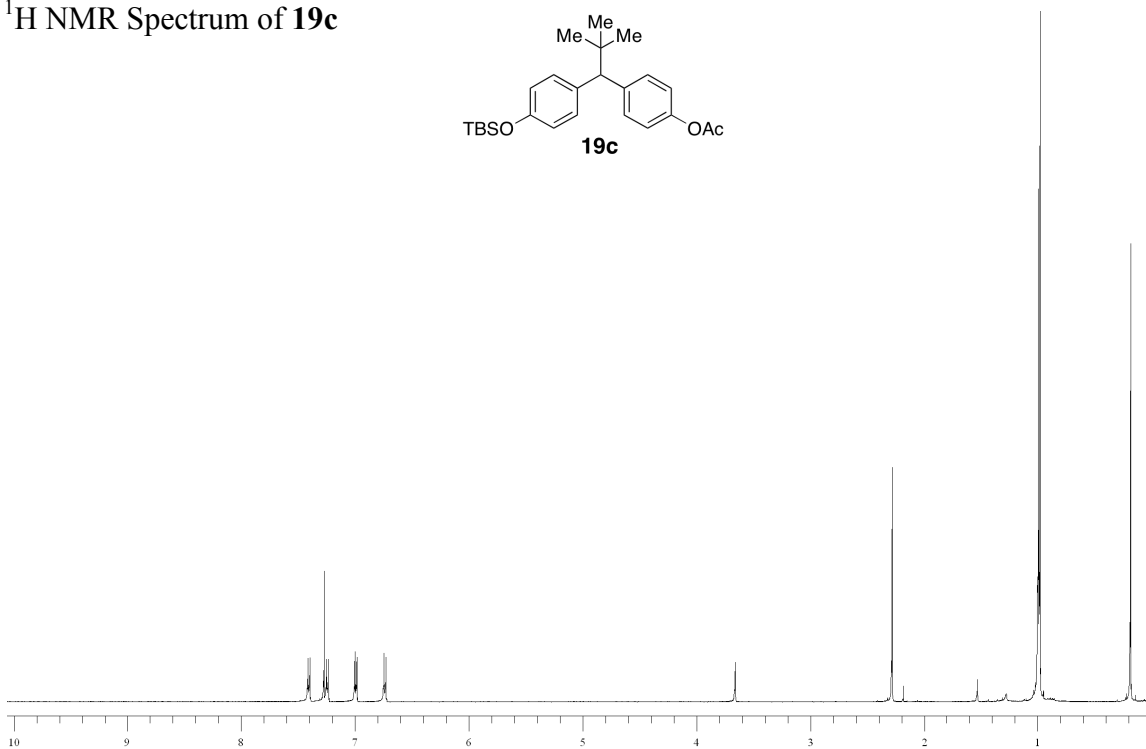
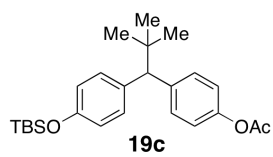
^1H NMR Spectrum of **19b**



^{13}C NMR Spectrum of **19b**



^1H NMR Spectrum of **19c**



^{13}C NMR Spectrum of **19c**

