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Oxidative Coupling of Phenols

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Abstract
Nature makes extensive use of oxidative reactions to generate bonds between carbons, particularly in the coupling of phenols, which is a striking feature in many biosynthetic pathways. The coupled phenols may exhibit the phenomenon called axial "chirality" or handedness. The Kozlowski group uses the atom economical oxidant O_2 and metal-based catalysts which, developed in-house, mimic the active sites of the enzymes to bring about these transformations. Vanadium catalysts have been extensively applied to the coupling of phenols and carbazoles with great efficiency and results. Here, this method is applied to the synthesis of bismurrayaquinone-A, an antitumor compound that occurs naturally in the roots of the curryleaf tree, *Murraya koenigii*. In this report, the routes for synthesis of the coupled phenol and carbazoles are highlighted. In the scaleup synthesis, 515 mg of the coupled carbazole was synthesized with an overall of 68% yield and 91% ee. A key oxidative coupling intermediate in the synthesis of bismurrayaquinone-A was afforded in 51% ee.

Keywords
oxidative coupling, phenols, hydroxycarbazoles, bismurrayaquinone-A, axial chirality, atropisomers, atropisomerism

Disciplines
Chemistry | Organic Chemistry

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Abstract approved:

Nature makes extensive use of oxidative reactions to generate bonds between carbons, particularly in the coupling of phenols, which is a striking feature in many biosynthetic pathways. The coupled phenols may exhibit the phenomenon called axial “chirality” or handedness. The Kozlowski group uses the atom economical oxidant O_2 and metal-based catalysts which, developed in-house, mimic the active sites of the enzymes to bring about these transformations. Vanadium catalysts have been extensively applied to the coupling of phenols and carbazoles with great efficiency and results. Here, this method is applied to the synthesis of bismurrayaquinone-A, an antitumor compound that occurs naturally in the roots of the curryleaf tree, *Murraya koenigii.* In this report, the routes for synthesis of the coupled phenol and carbazoles are highlighted. In the scaleup synthesis, 515 mg of the coupled carbazole was synthesized with an overall of 68% yield and 91% ee. A key oxidative coupling intermediate in the synthesis of bismurrayaquinone-A was afforded in 51% ee.

Oxidative coupling of Phenols

by

Prasanna Sreevatsan

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APPROVED:

Marisa Kozlowski

Marisa C Kozlowski, representing Organic Chemistry

I understand that my Capstone Report will become part of the permanent collection of the University of Pennsylvania Master of Chemical Sciences Program. My signature below authorizes release of my final report to any reader upon request.

Prasanna

Prasanna Sreevatsan, Author

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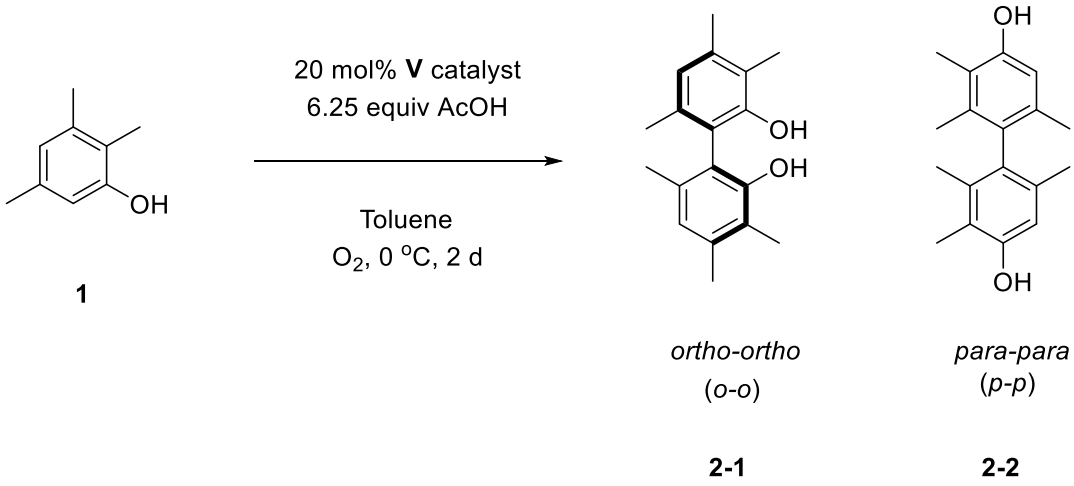
Introduction

The chiral bis-phenolic moiety is a common structural core in many natural products like knipholone and enantiomerically pure biaryls, such as (2,2'-bis(diphenylphosphino)-1,1'-binaphthyl) or commonly referred to as BINAP (**Figure 1**) which are excellent ligands in asymmetric catalysis.[1,2] The bis-phenolic moiety is not flat and exhibits axial chirality due to hindered rotation about the biaryl bond.[3] Some of these natural products that contain a stereogenic axis are biosynthetically produced by enantioselective oxidative addition.[4] Yet, current syntheses of such natural products are performed by methods specific to each architecture, which include: kinetic resolution of biaryl lactones through the addition of chiral nucleophiles[3] and diastereoselective Ullmann coupling which requires halogenation of the phenolic monomer.[5]

Scheme 1. **Oxidative coupling reaction of phenols.**[7]



The **scope** of this project is to explore syntheses of chiral bis-phenol moieties by employing a single step oxidative homocoupling of 2,3,5-trimethylphenol **(Scheme 1)** and 2-hydroxycarbazole (**Figure 1**). The oxidative coupling methodology would also be applied the asymmetric synthesis of bismurrayaquinone-A (**Figure 1**), a natural product that occurs in the roots of the curryleaf tree (*Murraya koenigii*) and is a potent anti-cancer agent (minimum inhibitory concentration IC_{50}: 125 nM), preventing angiogenesis and tumor formation.[6]

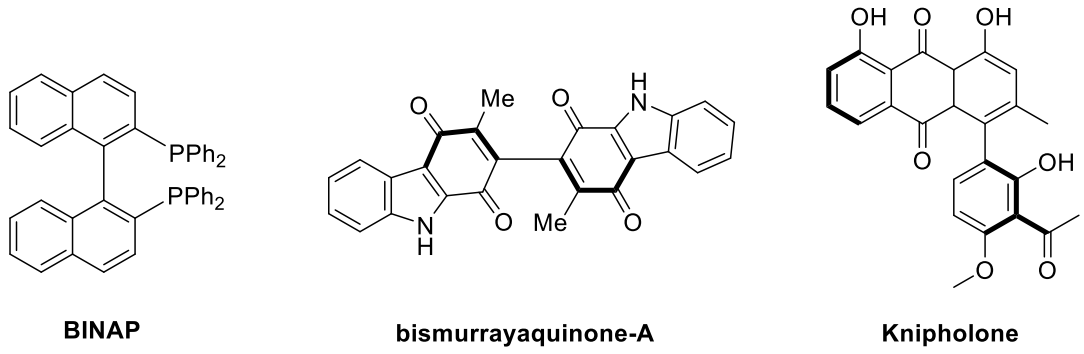


Figure 1. The ubiquitous biaryl structural motifs in ligands, natural products.[8]

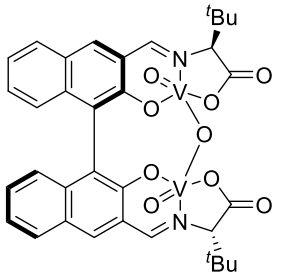
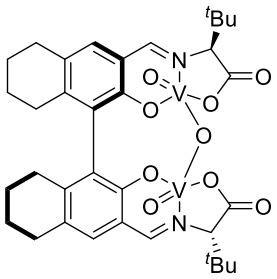
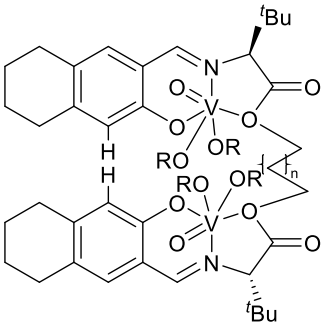
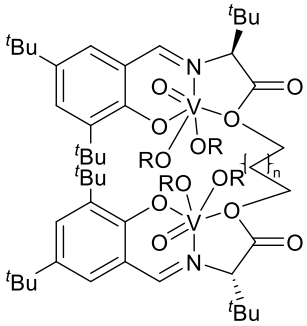
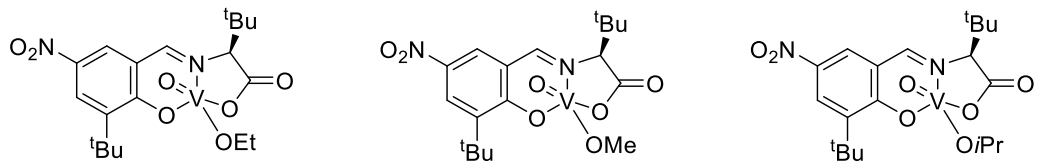
		SM : *o-o* : *p-p*	ee *o-o* (%)	*o-o* yield (%)
V1 + 6.25 equiv AcOH		9:76:15	60	75
V2 + 6.25 equiv AcOH		0:87:13	77	87
V3		56:34:10	0	ND
V4		63::31:6	67	ND

Figure 2. Development of dimeric vanadium catalysts.[7]

The Kozlowski group had already developed catalysts for asymmetric syntheses of 1,1'-bi-2-naphthols (BINOL) using Cu(I)-1,5-diaza-cis-decalin complexes.[9,10] The oxidant used in these reactions is the atom economical oxidant O_2. Their attention turned towards milder vanadium catalysts for oxidizable phenols, due to the presence of other competing reacting pathways (e.g. formation of quinones).[11] Additionally, $VO(acac)_2$ was shown to be an effective racemic catalyst for phenolic coupling with yields of 62-66% after 48-120

hours.[12] The group started with the development of generations of dimeric vanadium catalysts (**V1** through **V4**), as shown in **Figure 2**, based on the enantiomeric excess (ee), the amount of starting material (SM) remaining and the yield of the ortho-ortho coupled product **2-1** and the para-para coupled regioisomeric product **2-2**, obtained for the reaction as depicted in **Scheme 1**.[7] It was found that the additive acetic acid improved the ee for the **V1** catalyst from 37% to 60%. Changing the linker position in **V3** dramatically reduced the ee due to the loss of a sterically large group adjacent to the ligand phenoxide.[7]



V5 **V6** **V7**

Figure 3. Monomeric Vanadium catalysts.[7]

The Kozlowski group also found that the **V5** catalyst (**Figure 3**) gave similar results in terms of stereoselectivity for the reaction in **Scheme 1**. The dimeric backbone in the catalysts (**V1-V4**) was subsequently discarded for the monomeric scaffold as the latter was more amenable to modifications.[7] This scaffold was then subjected to a structure-activity relationship by modification of each of the positions of the **V5** catalyst. They developed the **V6** catalyst (**Figure 3**)**,** which allowed the reaction to proceed under milder conditions including lower loading of the catalyst (20 mol%), with a shorter reaction time of (2 days) and was regiospecific with no *para-para* coupling product **2-2** being observed.

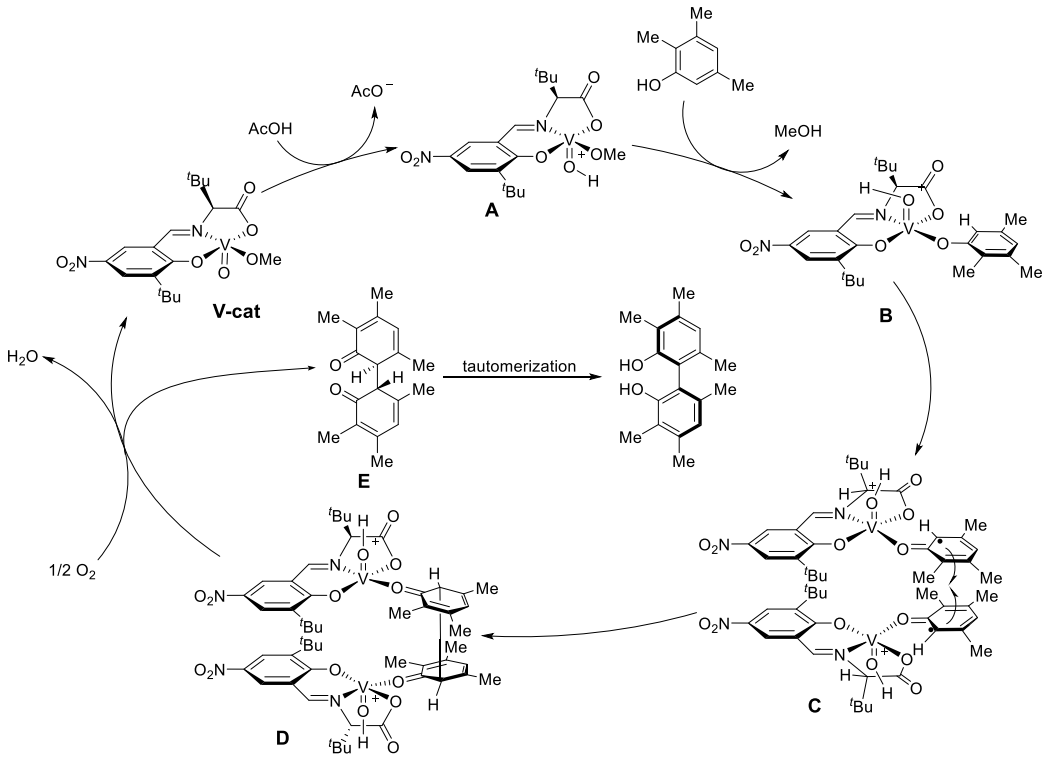
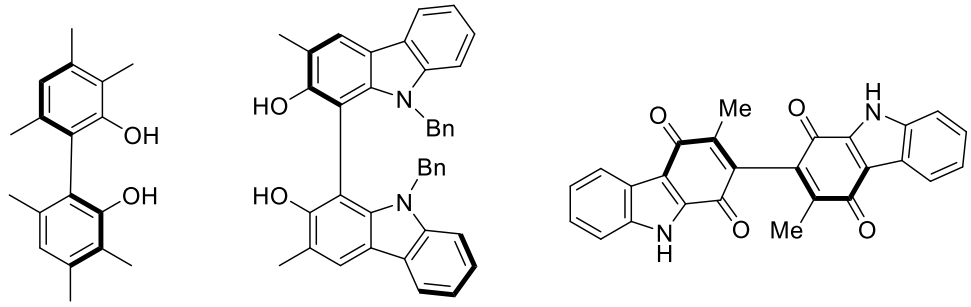


Figure 4. The proposed catalytic cycle.[14]

The studies of oxidative coupling of hydroxycarbazoles had already been performed, on a 100 mg (or lesser) scale, in the Kozlowski lab using the monomeric **V5-V7** catalysts, in **Figure 3**, to obtain ortho-ortho coupled dimers with ee ranging from 74% to 96% respectively.[13] **Figure 4** depicts the proposed mechanism, for this transformation, based on control experiments with radical inhibitors, removal of O_2 from the reaction mixture.[7] It was found that using the radical inhibitors led to precipitous drop in conversion of starting material. The absence of O_2 from the reaction mixture resulted in poor reaction yields of 9%. The catalytic cycle begins with the protonation (Bronsted acid or Lewis acid) of the oxo group on V to make it susceptible to attack by the phenol which replaces the methoxy group on the original catalyst to give **B**. The phenol is subsequently oxidized to give the keto radical intermediate as in **C**. The radicals couple to give the intermediate **D** from which the coupled moiety is released before it tautomerizes to form the product. The vanadium catalyst is re-oxidized by the oxidant O_2 to close the catalytic cycle.

The **goal** of this capstone project is to apply oxidative coupling methodology to large scale (500 mg) syntheses of the coupled homodimers **3, 4** and to synthesize **5** (**Figure 5**). The monomers of **4** and **5** would be synthesized as in **Schemes 2** and **7**. The monomer of **3** is the commercially available 2,3,5-trimethylphenol,**1.** The catalyst would be prepared as in **Scheme 3**. Using the conditions in **Scheme 1**, target molecules to be synthesized include selective *ortho-ortho* coupled dimers **3** and **4** with minimum yields and ee of 70% and 90%, respectively and at least 70% yield and 80% ee for **5**.

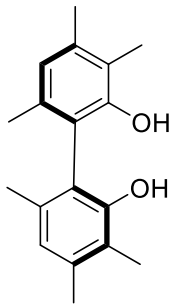


3 **4** **5**

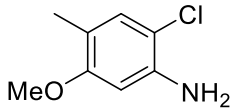
Figure 5. Target dimers to be synthesized by oxidative coupling.

Materials and Methods

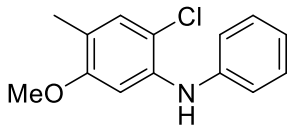
General Considerations: Unless otherwise noted, all non-aqueous reactions were carried out under an atmosphere of dry N_2 in dried glassware. When necessary, solvents and reagents were dried prior to use. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Dichloromethane, 1,2 dichloroethane, and toluene were distilled from CaH_2. Analytical thin layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica-gel 254-F plates. Visualization was accomplished with UV light. Chromatography was performed using a forced flow of the indicated solvent system on EM Reagents Silica Gel 60 (230-400 mesh). When necessary, the column was pre-washed with 1% Et_3N in the eluent system. ^1H NMR spectra were recorded on a 500 MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane (0 ppm) or from the solvent resonance ($CDCl_3$ 7.26 ppm, DMSO-d_6 3.58 ppm, acetone-d_6 2.05 ppm, DMF-d_7 2.50 ppm, CD_3CN 1.94 ppm, CD_2Cl_2 5.32 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), number of protons and coupling constants. Decoupled ^{13}C NMR spectra were recorded at 125 MHz. IR spectra were taken on an FT-IR spectrometer using a thin film on NaCl plate. Accurate mass measurement analyses were conducted via time-of-flight mass analyzer GCMS with electron ionization (EI) or via time-of-flight mass analyzer LCMS with electrospray ionization (ESI). The signals were measured against an internal reference of perfluorotributylamine for EI-GCMS and leucine enkephalin for ESI-LCMS. The instrument was calibrated, and measurements were made using neutral atomic masses; the mass of the electron removed or added to create the charged species is not taken into account. Enantiomeric excesses were determined using analytical HPLC with UV detection at 254 nm. Analytical Chiralpak columns (4.6 mm x 250 mm, 5 µm) from Daicel were used.



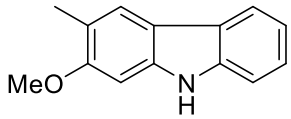
Stereoenriched (*S*)-3,3',4,4',6,6'-Hexamethyl-[1,1'-biphenyl]-2,2'-diol 3. To a flame dried microwave vial equipped with a stirbar was added **1** (30 mg, 0.22 mmol), **14** (20 mg, 0.044 mmol), acetic acid (0.08 mL), toluene (0.44 mL). The vial was evacuated and backfilled with oxygen. This process was repeated for two more times after which the vial was sealed and stirred stir at 0 ^oC for 2 d. The reaction mixture was chromatographed (5% ethyl acetate/hexanes) to afford a white solid **3** (14.7 mg, 50% yield) with 85% ee. ^1H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 2H), 4.73 (s, 2H), 2.28 (s, 6H), 2.17 (s, 6H), 1.92 (s, 6H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 151.9, 138.7, 135.2, 123.9, 120.5, 117.1, 20.2, 19.4, 11.9. Spectra is in accordance with previously reported data.[7] Chiral HPLC: Chiralpak IA column (2% isopropanol/hexanes, 1 mL/min) $t_R(1)$ = 4.40 minutes, $t_R(2)$ = 5.41 minutes.



2-Chloro-5-methoxy-4-methylaniline 7. To a 100 mL round bottom flask equipped with a stirbar was added 4-amino-5-chloro-2-methoxybenzoic acid **6** (5.00 g, 24.8 mmol) and chlorobenzene (49.5 mL). The flask was cooled to 0 °C. Neat $BH_3{\cdot}SMe_2$ (7.1 mL, 74.4 mmol) was added with vigorous stirring. When effervescence ceased, the flask was equipped with a reflux condenser under argon and the reaction mixture was placed in a preheated oil bath at 80 °C and heated for 3 h and then 130 °C for 18 h until all of **6** was consumed as judged by TLC. The reaction mixture was then quenched by addition of saturated Na_2CO_3 aqueous solution (1 M, 82 mL). The mixture was then extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed (10% ethyl acetate in hexanes) to afford a yellow solid **7** (2.30 g, 56% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.97 (s, 1H), 6.26 (s, 1H), 3.91 (s, 2H), 3.76 (s, 3H), 2.08 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 157.3, 141.4, 130.6, 117.9, 110.2, 99.0, 55.6, 15.3. Spectra is in accordance with previously reported data. [14]

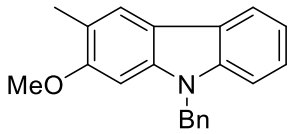


2-Chloro-5-methoxy-4-methyl-*N*-phenylaniline 9. To a 100 mL round bottom flask equipped with a stirbar in an inert atmosphere glovebox was added **7** (1.00 g, 5.81 mmol), $Pd(OAc)_2$ (52.4 mg, 0.233 mmol), *t*Bu_3PHBF_4 (84.6 mg, 0.29 mmol), and NaO*t*Bu (1.68 g, 17.5 mmol). The flask was sealed with a septum and removed from the glovebox. Toluene (23 mL) and **8** (0.65 mL, 5.93 mmol) were added, under argon, and the mixture was stirred. The flask was equipped with a reflux condenser, under argon, and placed in a preheated oil bath at 120 °C to ensure reflux of the reaction mixture. After 16 h, the starting material was consumed, as judged by TLC. The reaction mixture was then cooled to room temperature and quenched by addition of 2 M HCl (aq). The mixture was extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed (5% ethyl acetate in hexanes) to afford a brown oil **9** (0.85 g, 59% yield). Spectra is in accordance with previously reported data.[14]

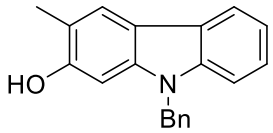


2-Methoxy-3-methyl-9*H*-carbazole 10. To a 250 mL round bottom flask equipped with a stirbar in an inert atmosphere glovebox was added **9** (5.35 g, 21.57 mmol), $Pd(OAc)_2$ (242.2 mg, 1.09 mmol), *t*Bu_3PHBF_4 (661 mg, 2.27 mmol), K_2CO_3 (8.93 g, 64.7 mmol). The flask was sealed with a septum and removed from the glovebox. N,N'-Dimethylacetamide (86 mL) was added under an argon atmosphere and the mixture was stirred. The flask was equipped with a reflux condenser, under argon, and placed in a preheated oil bath at 130 °C. After 20 h, the starting material was consumed as judged by TLC. The reaction mixture was then cooled to room temperature and quenched by addition of 2 M HCl (aq). The mixture was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed (10% ethyl acetate/hexanes) to afford a solid **10** (3.14 g, 69% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 7.95 (d, 1H, J = 8.0 Hz), 7.80 (s, 1H), 7.41 (d, 1H, J = 8.0 Hz), 7.25 (t, 1H, J= 7.5 Hz,

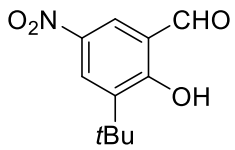
8.0 Hz), 7.10 (t, 1H, J= 7.5 Hz, 8.0 Hz), 7.01 (s, 1H), 3.88 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (500 MHz, acetone-d_6) δ 158.7, 141.33, 141.30, 130.8, 124.7, 122.4, 120.3, 119.9, 119.5, 117.3, 111.8, 93.9, 56.2, 17.3. Spectra are in accordance with previously reported data.[14]



9-Benzyl-2-methoxy-3-methyl-9H-carbazole 11. To a 250 mL two-neck round bottom flask equipped with a stirbar was added **10** (3.42 g, 16.2 mmol), N,N'-dimethylformamide (40.5 mL), and tetrahydrofuran (81 mL) under an argon atmosphere. The flask was placed in an ice bath and cooled to 0 °C. NaH (973 mg, 40.5 mmol) was added in portions with vigorous stirring. Benzyl chloride (1 M in THF, 17.8 mL, 17.8 mmol) was added after the reaction mixture had stirred for 30 minutes at ambient temperature. The reaction mixture was then stirred until the starting material was consumed as judged by TLC. The reaction was quenched with ice cold water, saturated $NaHCO_3$ (aq) solution and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (5% ethyl acetate/hexanes) to afford a solid **11** (4.20 g, 87% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.01 (d, 1H, J = 7.5 Hz), 7.87 (s, 1H), 7.42 (d, 1H, J = 8.5 Hz), 7.30-7.25 (m, 3H), 7.22-7.19 (m, 3H), 7.16-7.13 (m, 2H), 5.61 (s, 2H), 3.88 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (500 MHz, acetone-d_6) δ 159.2, 142.2, 139.5, 130.0, 128.6, 128.1, 125.4, 124.7, 122.8, 120.5, 120.4, 119.9, 117.1, 110.4, 92.8, 56.5, 47.4, 17.3. Spectra are in accord with previously reported data.[14]

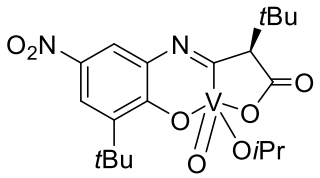


9-Benzyl-3-methyl-9H-carbazol-2-ol 12. To a flame dried 50 mL round bottom flask equipped with a stirbar was added **11** (600 mg, 1.99 mmol) and dichloromethane (19.93 mL) under an argon atmosphere. The flask was cooled to -78 °C using a dry ice-acetone bath. BBr_3 (1 M in CH_2Cl_2, 1.99 mL, 1.99 mmol) was added dropwise and slowly into the flask with vigorous stirring. After 30 min, the flask was moved to a water-ice bath at 0 °C. After 5 h, the starting material was consumed as judged by TLC. The reaction was quenched with ice cold water and saturated $NaHCO_3$ (aq) solution. After extraction with ethyl acetate (3 x 50 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (15% ethyl acetate/hexanes) to afford a yellow solid **12** (390 mg, 68% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.26 (br s, 1H), 7.99 (d, 1H, J = 8.0 Hz), 7.84 (s, 1H), 7.43 (d, 1H, J = 8.0 Hz), 7.29-7.19 (m, 4H), 7.18-7.11 (m, 3H), 6.89 (s, 1H), 5.50 (s, 2H), 2.34 (s, 3H). Spectra are in accordance with previously reported data.[14]

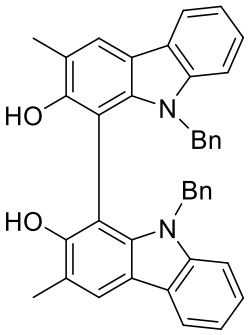


3-(*tert*-Butyl)-2-hydroxy-5-nitrobenzaldehyde 14. To a flame dried 250 mL round bottom flask equipped with a stirbar was added 3-(*tert*-butyl)-2-hydroxy-benzaldehyde **13** (6.0 mL, 35 mmol), acetic acid (106 mL) and the flask was cooled to 0 °C by placing it in

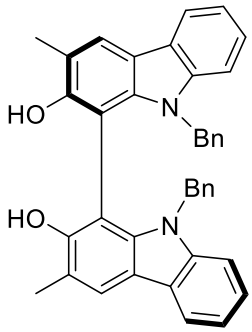
an ice-water bath. Nitric acid (37.3 mL) was added slowly dropwise until the color changed to bright orange. The cooling bath was removed, and the mixture was stirred 1 h further at ambient temperature. The reaction was quenched by pouring into a beaker of ice cold water causing a yellow solid to precipitate out, which was collected by vacuum filtration to afford a pale yellow solid **14** (6.5 g, 84% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 12.42 (s, 1H), 9.96 (s, 1H), 8.40 (s, 2H), 1.45 (s, 9H). Spectra are in accordance with previously reported data.[14]



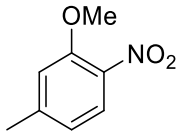
(*S*)-Vanadium Catalyst 16. To a flame dried 250 mL round bottom flask equipped with a stirbar was added **14** (3g, 13.45 mmol), L-*tert*-leucine (2.29 g, 17.5 mmol) and a 1:1 mixture of methanol and CH_2Cl_2 (40 mL each). The flask was fitted with a reflux condenser under Argon, was placed in a preheated oil bath at 45 °C and refluxed for 2 h. The mixture was cooled to room temperature after which the solvent was removed. Freshly distilled CH_2Cl_2 (68 mL) was added under an argon atmosphere and $VO(OiPr)_3$ (2.88 mL, 13.5 mmol) was introduced. After stirring 3 h at ambient temperature, the solvent was removed to afford a dark red-brown solid **16** (6.1 g, 98% yield). Spectra are in accordance with previously reported data.[14]



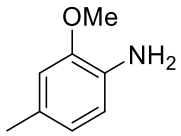
Racemic 9,9'-Dibenzyl-3,3'-dimethyl-9H,9'H-[1,1'-bicarbazole]-2,2'-diol 4. To a flame dried microwave vial equipped with a stirbar was added **12** (30 mg, 0.10 mmol), $VO(acac)_2$ (7 mg, 0.05 mmol), toluene (0.48 mL). The vial was evacuated and backfilled with oxygen. This process was repeated two more times after which the vial was sealed and set to stir at ambient temperature for 2 d. The reaction mixture was chromatographed (5% ethyl acetate/hexanes) to afford a yellow solid **4** (17 mg, 57% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.05 (d, 2H, J = 8.0 Hz), 7.94 (s, 2H), 7.23 (t, 2H, J = 7.5 Hz), 7.17 (t, 2H, J = 8.0 Hz), 7.08 (d, 2H, J = 8.0 Hz), 6.83 (d, 8H, J = 3.5 Hz), 6.44 (d, 4H, J = 4.0 Hz), 4.82 (d, 2H, J = 17.5 Hz), 4.69 (d, 2H, J = 17.5 Hz), 2.20 (s, 6H). Spectra are in accordance with previously reported data.[14] Chiral HPLC: Chiralpak IA column (10% isopropanol/hexanes, 1 mL/min) $t_R(1)$ =7.63 min , $t_R(2)$ = 10.95 min.



Enantioenriched 9,9'-Dibenzyl-3,3'-dimethyl-9H,9'H-[1,1'-bicarbazole]-2,2'-diol 4. To a flame dried 25 mL round bottom flask equipped with a stirbar was added **12** (640 mg, 2.23 mmol), **14** (205 mg, 0.45 mmol), acetic acid (0.82 mL), chlorobenzene (4.46 mL). The flask was evacuated and backfilled with oxygen. This process was repeated two more times after which the flask was sealed with a parafilm on top of the septum and an O_2 balloon was inserted into the septum. After stirring 2 d at 0 ^oC, the reaction mixture was chromatographed (5% ethyl acetate/hexanes) to afford a yellow solid **4** (520 mg, 82% yield). Chiral HPLC indicated an enantiomeric excess of 85%. The solid was triturated with diethyl ether and the filtrate was concentrated to afford a solid **4** (425 mg, 68%) of 91.0% ee. ^1H NMR (500 MHz, acetone-d_6) δ 8.05 (d, 2H, J = 8Hz), 7.94 (s, 2H), 7.23 (t, 2H, J = 7.5 Hz), 7.17 (t, 2H, J = 8.0 Hz), 7.08 (d, 2H, J = 8.0 Hz), 6.83 (d, 8H, J = 3.5 Hz), 6.44 (d, 4H, J = 4.0 Hz), 4.82 (d, 2H, J = 17.5 Hz), 4.69 (d, 2H, J = 17.5 Hz), 2.20 (s, 6H). Spectra are in accordance with previously reported data.[14] Chiral HPLC: Chiralpak IA column (10% isopropanol in hexanes, 1 mL/min) $t_R(1)$ =7.63 minutes, $t_R(2)$ = 10.95 minutes.

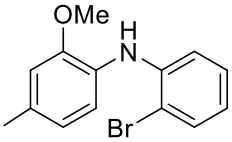


5-Methyl-2-nitroanisole 18. To an oven dried 100 mL round bottom flask with a stirbar, was added 5-nitro-*m*-cresol **17** (5.2 g, 34.0 mmol), K_2CO_3 (9.39 g, 67.9 mmol), acetone (85 mL). After stirring at ambient temperature for 15 min, dimethylsulfate (4.83 mL, 50.9 mmol) was added slowly dropwise to the stirring flask. Once complete the flask was fitted with a reflux condenser under Argon and placed in a preheated oil bath at 75 ^oC. It was heated to reflux for 3 h or until the starting material was consumed as determined by TLC. The flask was cooled, and the reaction mixture was filtered and the solid was washed with ethyl acetate. The filtrate was transferred to a separatory funnel and diluted with water. The organic layer was washed repeatedly with water, dried over Na_2SO_4, and concentrated to afford a yellow solid **18** (5.2 g, 92% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, 1H, J = 8 Hz), 6.87 (s, 1H), 6.81 (d, 1H, J = 8 Hz), 3.94 (s, 3H), 2.42 (s, 3H). Spectra are in accordance with previously reported data.[15]

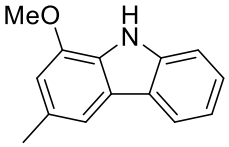


2-Methoxy-4-methylaniline 19. To an oven dried 250 mL round bottom flask equipped with a stirbar, was added 5-methyl-2-nitroanisole **18** (1.5 g, 9.0 mmol), $SnCl_2{\cdot}2H_2O$ (10.1 g, 44.9 mmol), and methanol (60 mL). The flask was fitted with a reflux condenser under argon and placed in a preheated oil bath at 75 ^oC. The mixture was heated at reflux for 3 h until the starting material was consumed as judged by TLC. The flask was cooled to

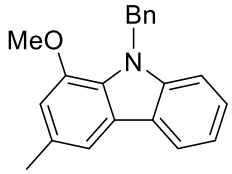
ambient temperature and the solvent removed. The residue was solubilized in 50 mL ethyl acetate and diluted with 50 mL water. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and the solvent removed to afford a red viscous oil **19** (1.1 g, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63-6.59 (m, 3H), 3.83 (s, 3H), 3.65 (s, 2H), 2.22 (s, 3H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 147.5, 133.6, 128.2, 121.3, 115.2, 111.7, 55.6, 21.1. Spectra are in accordance with previously reported data.[16]



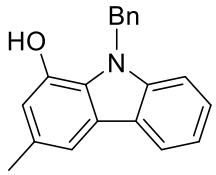
N-(2-Bromophenyl)-2-methoxy-4-methylaniline 21. To a 100 mL round bottom flask equipped with a stirbar was added **19** (1.55 g, 11.3 mmol). In an inert atmosphere glovebox, $PdCl_2$·DPPF (in CH_2Cl_2) (460 mg, 0.57 mmol), and NaO*t*Bu (2.17 g, 22.6 mmol) were added and the flask was sealed with a septum. Toluene (23 mL) and **20** (1.45 mL, 11.3 mmol) were added under an argon atmosphere and the mixture was stirred. The flask was fitted with a reflux condenser under argon, placed in a preheated oil bath at 120 °C and heated to reflux. After 16 h, the starting material was consumed as judged by TLC. The reaction mixture was cooled to room temperature and quenched by addition of 2 M HCl (aq). The mixture was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed (5% ethyl acetate/hexanes) to afford a brown oil **21** (2.1 g, 63% yield). ^{1}H NMR (500 MHz, acetone-*d*$_6$) δ 7.29-7.26 (m, 2H), 7.16-7.14 (m, 3H), 6.91-6.90 (m, 2H), 6.82 (s, 1H), 3.73 (s, 3H), 2.10 (s, 3H).



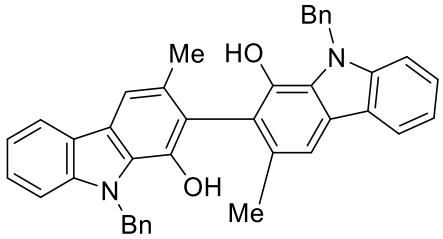
1-Methoxy-3-methyl-9*H*-carbazole 22. To a 250 mL round bottom flask equipped with a stirbar was added **21** (1.90 g, 6.50 mmol). In an inert atmosphere glovebox, $Pd(OAc)_2$ (73.0 mg, 0.32 mmol), *t*Bu_3PHBF_4 (199 mg, 0.68 mmol), and K_2CO_3 (2.69 g, 19.5 mmol) were added and the flask which was sealed with a septum. N,N'-Dimethylacetamide (26 mL) was added under an argon atmosphere and the mixture was stirred. The flask was fitted with a reflux condenser under argon, placed in a preheated oil bath at 130 °C. After 20 h, the starting material was consumed as judged by TLC. The reaction mixture was then cooled to room temperature and quenched by addition of 2 M HCl (aq). The mixture was then extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was chromatographed (10% ethyl acetate/hexanes) to afford a solid **22** (1.20 g, 87.4% yield). ^{1}H NMR (500 MHz, acetone-*d*$_6$) δ 10.13 (br s, 1H), 8.02 (d, 1H, J = 7.5 Hz), 7.54 (d, 1H, J = 8.0 Hz), 7.48 (s, 1H), 7.35 (t, 1H, J = 7.5 Hz, 7.5 Hz), 7.13 (t, 1H, J = 7.5 Hz, 7.5 Hz), 6.80 (s, 1H), 3.96 (s, 3H), 2.48 (s, 3H). Spectra are in accord with previously reported data.[17]



9-Benzyl-1-methoxy-3-methyl-9H-carbazole 23. To a 250 mL two-neck round bottom flask equipped with a stirbar was added **22** (0.94 g, 4.43 mmol), N,N'-dimethylformamide (4.4 mL), and tetrahydrofuran (17.7 mL) under an argon atmosphere. The flask was placed in an ice bath and cooled to 0 ^{o}C. NaH (266 mg, 11.1 mmol) was added in portions with vigorous stirring. After 30 min at ambient temperature, benzyl chloride (1 M in THF, 4.87 mL, 4.87 mmol) was added. After stirring until the starting material was consumed as judged by TLC, the reaction was quenched with ice cold water and saturated $NaHCO_3$ (aq) solution. The reaction mixture was washed well with water (3 x 40 mL) to remove the DMF. The aqueous layer was extracted with ethyl acetate (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (10% ethyl acetate/hexanes) to afford a solid **23** (1.19 g, 89% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.06 (d, 1H, J = 8.0 Hz), 7.51 (s, 1H), 7.43 (d, 1H, J = 8.0 Hz), 7.34-7.31 (m, 1H), 7.20-7.11 (m, 6H), 6.84 (s, 1H), 5.88 (s, 2H), 3.89 (s, 3H), 2.45 (s, 3H). Spectra are in accordance with previously reported data.[18]

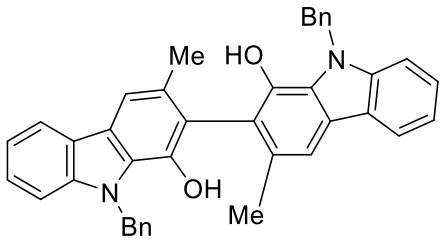


9-Benzyl-3-methyl-9H-carbazol-1-ol 24. To a flame dried 25 mL round bottom flask equipped with a stirbar was added **23** (180 mg, 0.59 mmol), CH_2Cl_2 (6.0 mL) under an argon atmosphere. The flask was cooled to -78 ^{o}C by means of a dry ice-acetone bath. BBr_3 (1 M in CH_2Cl_2, 0.60 mL, 0.60 mmol) was added slowly dropwise with vigorous stirring. After 30 min, the flask was moved to an ice-water bath. After an additional 5 h, the starting material was consumed as judged by TLC. The reaction was quenched with ice cold water and saturated $NaHCO_3$ (aq) solution. After extraction with ethyl acetate (3 x 50 mL), the combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. The residue was chromatographed (15% ethyl acetate/hexanes) to afford a red-brown solid **24** (147 mg, 86% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.65 (s, 1H), 8.01 (d, 1H, J = 8.0 Hz), 7.42 (t, 2H, J = 8.5 Hz), 7.34-7.30 (m, 1H), 7.22-7.15 (m, 5H), 7.13-7.10 (m, 1H), 6.78 (s, 1H), 5.93 (s, 2H), 2.39 (s, 3H). Spectra are in accordance with previously reported data.[18]

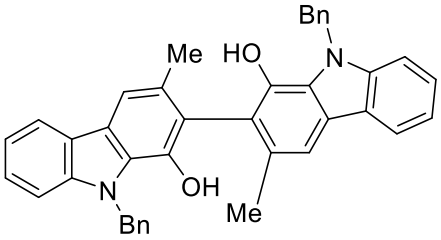


Racemic 9,9'-Dibenzyl-3,3'-dimethyl-9H,9'H-[1,1'-bicarbazole]-2,2'-diol 25. To a flame dried microwave vial equipped with a stirbar was added **24** (34 mg, 0.12 mmol), $VO(acac)_2$ (8.0 mg, 0.059 mmol), and toluene (0.54 mL). The vial was evacuated and backfilled with oxygen. This process was repeated two more times after which the vial was sealed and

set to stir at ambient temperature for 2 d. The residue was chromatographed (15% ethyl acetate/hexanes) to afford an orange gummy substance **25** (15 mg, 45% yield). ^{1}H NMR (500 MHz, acetone-d_6) δ 8.27 (d, 2H, J = 8.0 Hz), 7.78- 7.65 (m, 3H), 7.49-7.38 (m, 5H), 7.27-7.19 (m, 10H), 5.98 (d, 2H, J = 16.0 Hz), 5.91 (d, 2H, J = 16.0 Hz), 4.03 (s, 2H, J = 6.5 Hz), 2.71 (s, 6H). Chiral HPLC: Chiralpak IA column (15% isopropanol/hexanes, 1 mL/min) t_R(1) = 20.3 minutes , t_R(2) = 28.4 minutes.



Enantioenriched 9,9'-Dibenzyl-3,3'-dimethyl-9H,9'H-[1,1'-bicarbazole]-2,2'-diol 4. To a flame dried microwave vial equipped with a stirbar was added **24** (20 mg, 0.069 mmol), **14** (6.4 mg, 0.013 mmol), acetic acid (0.02 mL, 0.43 mmol), and chlorobenzene (0.14 mL). The vial was evacuated and backfilled with oxygen. This process was repeated two more times after which the vial was sealed and set to stir at 0 ^{o}C for 2 d. The reaction mixture was chromatographed (15% ethyl acetate/hexanes) to afford an orange gummy substance **25** (9.0 mg, 45% yield) with 20% ee. Spectra are in accordance with previously reported data for the racemic **25**. Chiral HPLC: Chiralpak IA column (15% isopropanol/hexanes, 1 mL/min) t_R(1) = 20.3 minutes , t_R(2) = 28.4 minutes.



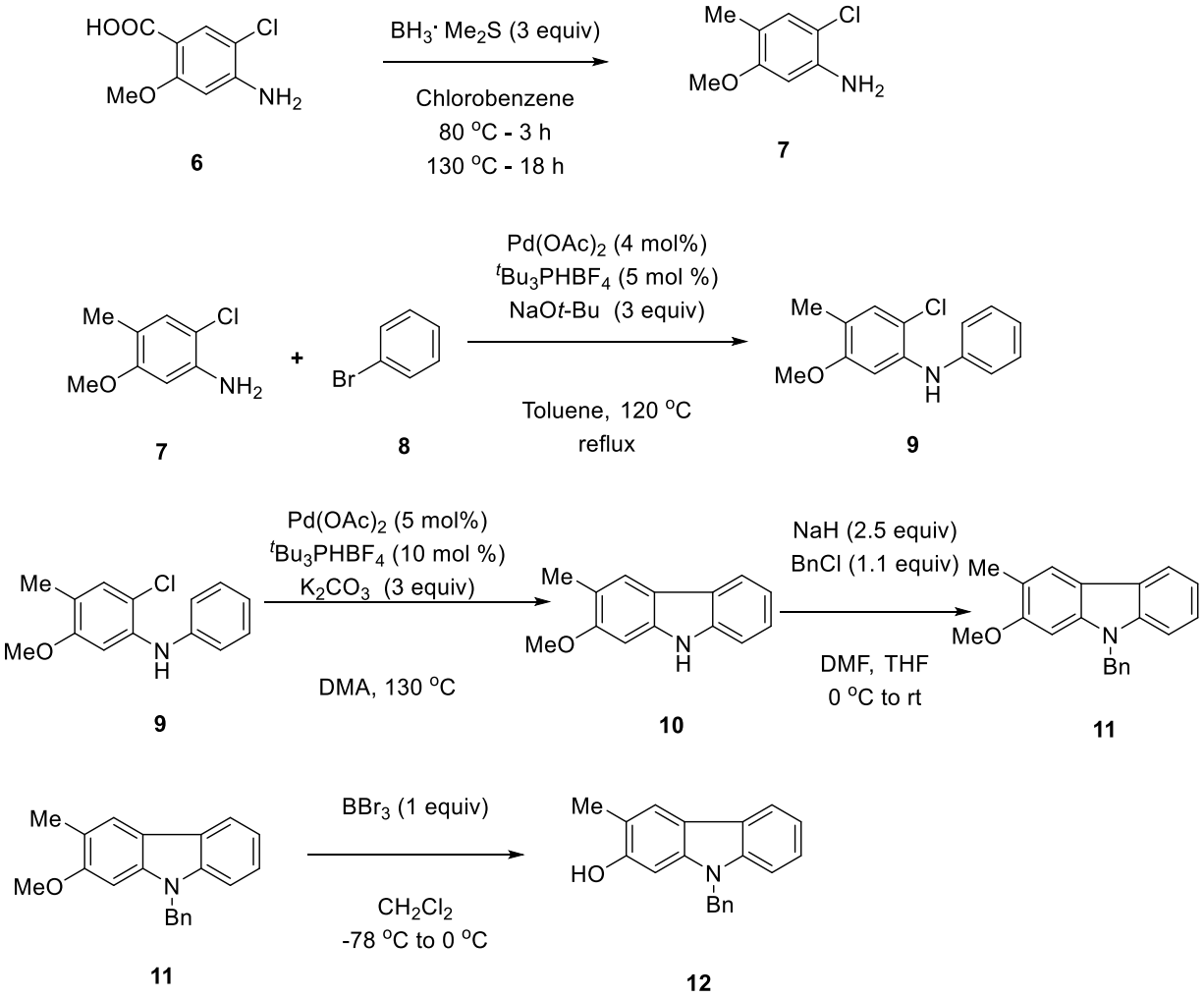
Enantioenriched 9,9'-Dibenzyl-3,3'-dimethyl-9H,9'H-[1,1'-bicarbazole]-2,2'-diol 4. To a flame dried microwave vial equipped with a stirbar was added **24** (20 mg, 0.069 mmol), **14** (6.4 mg, 0.013 mmol), lithium chloride (2.95 mg, 0.069 mmol), and chlorobenzene (0.14 mL). The vial was evacuated and backfilled with oxygen. This process was repeated two more times after which the vial was sealed and set to stir at 0 ^{o}C for 2 d. The reaction mixture was chromatographed (15% ethyl acetate/hexanes) to afford an orange gummy substance **25** (9.0 mg, 45% yield) with 51% ee. Spectra are in accordance with previously reported data for the racemic **25**. Chiral HPLC: Chiralpak IA column (15% isopropanol/hexanes, 1 mL/min) t_R(1) = 20.3 minutes , t_R(2) = 28.4 minutes.

Results and Discussions

Large scale synthesis (500 mg) of compounds 3 and 4

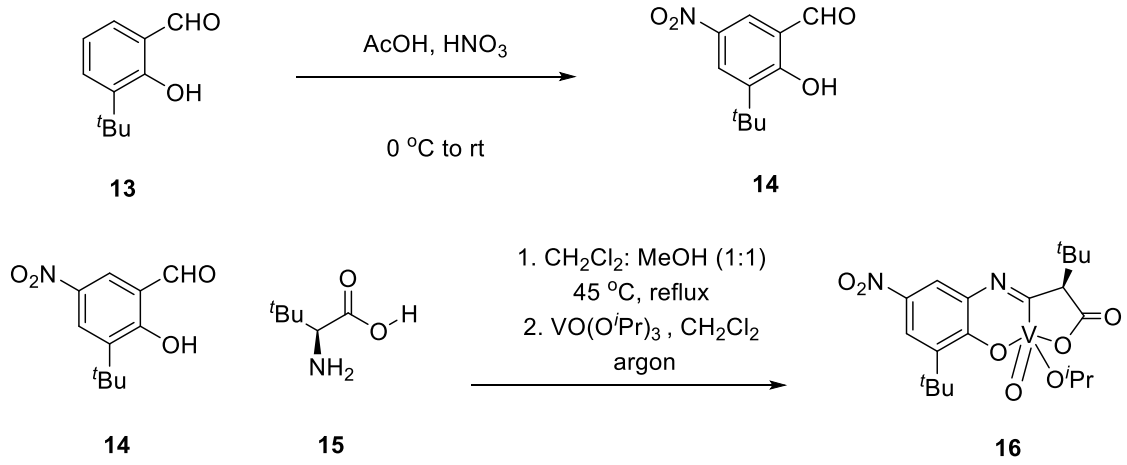
The synthesis of the monomer **12** starts with the reduction of the carboxylic acid group in the commercially available **6** (**Scheme 2**). $BH_3 \cdot Me_2S$ dimethyl sulfide was used to form the reduced compound **7** in 45% yield. This material was then coupled with bromobenzene **8** by Buchwald-Hartwig coupling to form the monoarylated product **9** along with a small amount of the diarylated impurity. The monoaryl product is difficult to separate from the diaryl impurity as they have similar R_f values. Thus, unpurified **9** was subjected to cyclization to form the carbazole **10.** At this point, the cyclized product and the diaryl impurity have greatly different R_f values and were readily separated. Initially, this cyclization reaction failed (only SM remained), and the catalyst was determined to have decomposed because the reaction mixture turned black even under argon. The reaction was repeated with a new batch of catalyst, but it formed the cyclized product in minimal

Scheme 2. **Synthesis of the monomer 12.**[14]



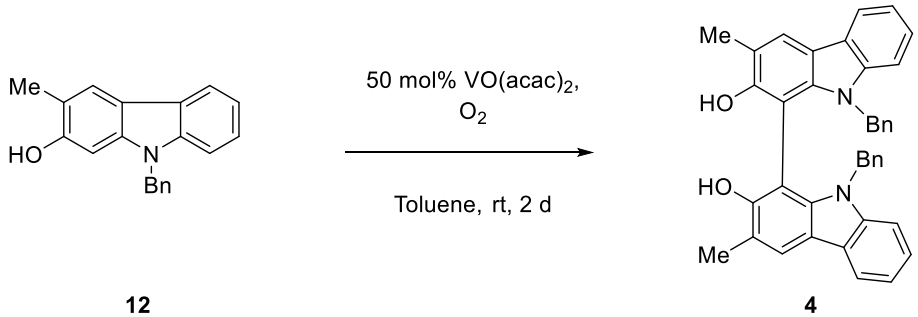
yields with much unreacted starting material. It was seen on the TLC that the cyclization reaction was not going to completion as the diarylated impurity was formed in a larger amount compared to the monoarylated product. The problem was finally traced to the earlier step to form **9** where the bromobenzene had been incorrectly syringed out. The slightly excess bromobenzene in the reaction caused the diarylated impurity to form more than the monoarylated product. With the corrected volume of bromobenzene used, another reaction was set up in which **9** was formed as a major product. The cyclization reaction now went to completion. The TLC clearly showed two spots: the polar product **10** and the non-polar diarylated impurity at the bottom and top of the plate respectively. The amine nitrogen was then benzylated, to form **11,** to prevent the nitrogen from interfering with the catalyst during the oxidative coupling process. Compound **11** was subjected to demethylation to afford the starting material, the hydroxycarbazole **12**. [14]

Scheme 3. **Synthesis of the Vanadium catalyst V7.**[14,19]



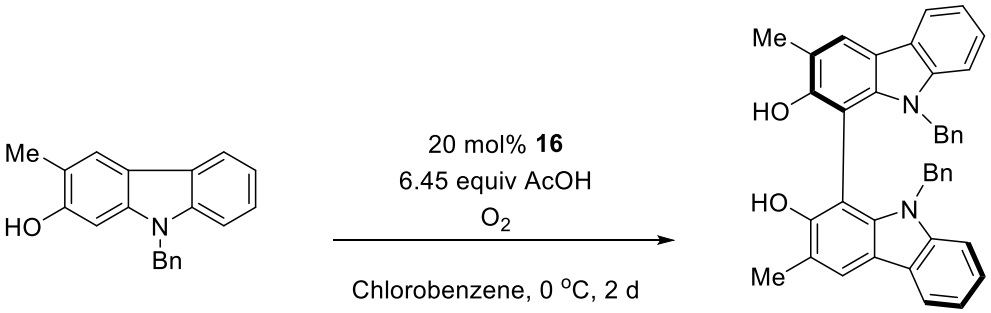
The catalyst **16** is prepared by synthesizing the Schiff's base ligand and then combining with a vanadium oxide (**Scheme 3**). Commercially available **13** is nitrated using acetic acid. Since nitric acid is a strong oxidizing agent and can easily oxidize the aldehyde group on the aromatic ring, the temperature is lowered to 0 °C and the nitric acid is added slowly and dropwise. Once the addition is done, the reaction mixture is warmed slowly to ambient temperature. Nitration occurs within an hour giving **14** which is combined with L-t*ert*-Leucine **15** to form the Schiff's base ligand. The Schiff's base ligand is not isolated but is combined with a vanadium oxide [in this case $VO(O^iPr)_3$] under an argon atmosphere for 3 hours at ambient temperature to give a dark reddish-brown catalyst.

Scheme 4. **Synthesis of racemic dimer 4.**[14]



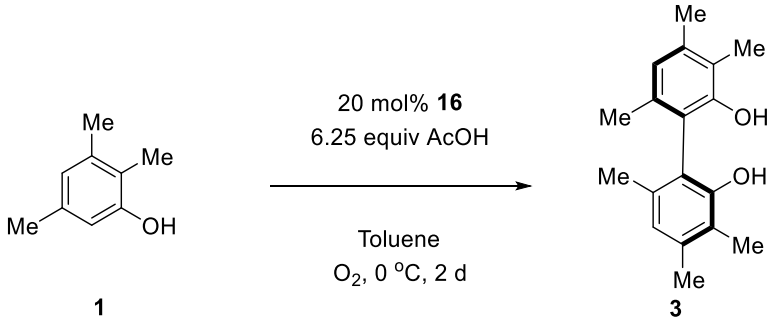
Uang found that 2-naphthols and phenols can be oxidatively coupled using $VO(acac)_2$ as the catalyst and under aerobic conditions to give the *ortho-ortho* coupled product.[12] Using these conditions, the carbazole substrate **12** was dimerized to give racemic homo-dimer (**Scheme 4**). The isolated product is solubilized in dichloromethane and HPLC grade *n*-hexanes for injection onto a chiral HPLC IA™ column to separate and resolve the enantiomers comprising the racemic mixture. The retention times and the area under the curve for each stereoisomer is used to judge the efficiency and efficacy of the asymmetric coupling for the catalyst**.**

Scheme 5. **Stereoselective synthesis of oxidatively coupled 4.**[14]



The carbazole **12** is subjected to enantioselective oxidative homocoupling using the catalyst **16**, protic acid additive (acetic acid), and the solvent chlorobenzene (**Scheme 5**). The temperature of the reaction is lowered to 0 °C to improve the stereoselectivty. The isolated product is assessed by chiral HPLC IA column to determine the efficiency of the catalyst. Once the efficiency of the catalyst has been deemed satisfactory (greater than 85% ee), the reaction is performed on a larger scale. The isolated product is triturated with diethyl ether to achieve further enrichment (as verified by chiral HPLC analysis) since the racemate and single atropisomer have different solubility properties.

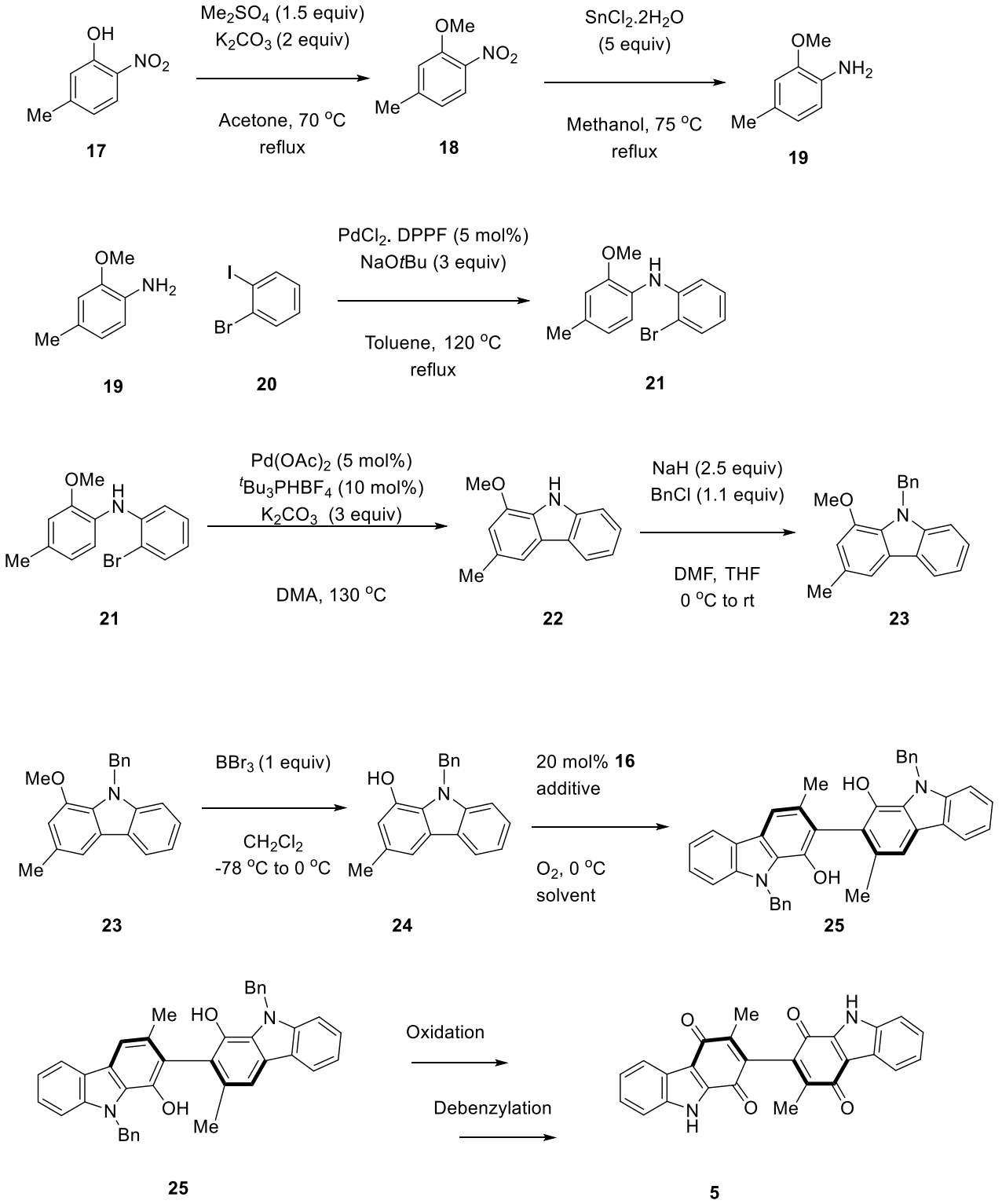
Scheme 6. **Synthesis of compound 3 by oxidative dimerization.**[14]



The oxidatively coupled compound **3** was synthesized from the commercially available 2,3,5-trimethylphenol **1** using the synthesized vanadium catalyst **16** as shown in **Scheme 6**. The reaction was performed at 0 °C to increase the ee to 87%, despite the reaction not going to completion. The purified product is further enantio-enriched by repeated trituration with *n*-heptane or *n*-hexane.

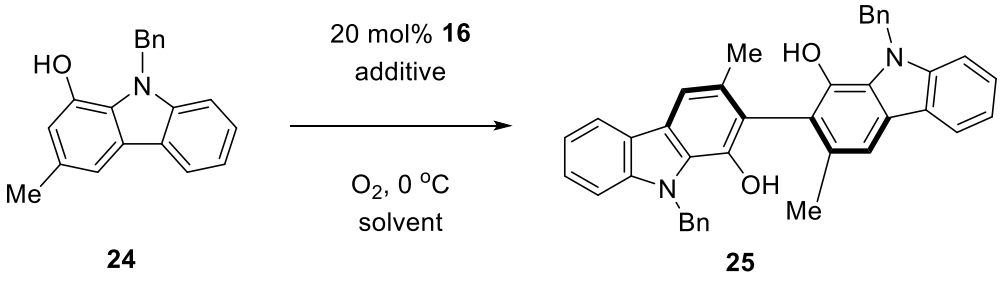
Synthesis of the natural product, *bismurrayaquinone-A*

Scheme 7. Proposed Synthesis of bismurrayaquinone-A.[14]



The synthesis of **5** starts with synthesizing the monomer **24** (**Scheme 7**)**.** The commercially available **17** is subjected to methylation, reduction**,** the Buchwlad-Hartwig amination, the cyclization (intramolecular C-H activation), switching the protecting groups (**Scheme 7**)**.** The phenolic hydroxyl group in the commercially available compound **17** was protected using dimethyl sulfate to form **18** in 93% yield. The compound 1**8** was reduced using tin(II) chloride dihydrate to form **19** in 88% yield. Coupling of compound **19** with 1,2-dibromobenzene was attempted using a Buchwald-Hartwig amination with various phosphine ligands (BrettPhos, tri-*tert*-butylphosphine) but did not give desired product in high yields (many byproducts were obtained).[14] It was then coupled with 2-bromo-1-iodobenzene **20** successfully using modified conditions.[20] The reaction is selective towards the more reactive iodide relative to the bromide. Compound **21** (along with the diarylated impurity) was cyclized to form compound **22**, the amine group of which was protected using benzyl chloride to form **23**. Subsequently, demethylation afforded compound **24** which was oxidatively coupled twice: first to generate a racemic mixture standard and then to investigate the efficiency of the chiral catalyst. To complete bismurrayaquinone synthesis, future work would entail oxidation of the dimeric product **25** to form the quinone, followed by deprotection of the carbazole nitrogens. Compound **25** was synthesized from **24** as in **Scheme 5**. Using the additive acetic acid with the solvent chlorobenzene gave a modest yield of 45% and a poor ee of 20%. The lower selectively relative to **Scheme 5** likely arises from oxidation of the 2-position vs the 1-position of the carbazole. This change in position causes the oxidation site to be less activated (only one donor group ortho vs two groups with **12**. In addition, the large N-Bn group adjacent to the metal binding site (the phenol) may be problematic.

Table 1. Optimization of the oxidative coupling reaction of **24**



24 **25**

Entry	Additive	Solvent	ee (%)
1	Acetic Acid	chlorobenzene	20
2	LiCl	chlorobenzene	51
3	LiCl	toluene	In progress

The additive seemed to directly impact the ee of the reaction as seen in **Table 1**. 1 equiv of LiCl, as the additive, improved the ee to 50% from the 20% ee observed with acetic acid. The optimization of conditions and substrates to enhance the stereoselectivity of this reaction is in progress.

Summary and Future work

Oxidative coupling of phenols using the atom economical oxidant is an attractive method to build complex atropisomers in high selectivities. The basic motivation for this work is to mimic how this process occurs in nature to produce the structural motifs seen in natural products of biological/ medicinal importance. The methods developed by the Kozlowski group generates the atropisomers intrinsically as a result of the designed catalyst as opposed to relying on other strategies of dynamic kinetic resolution or pre-functionalizing the molecule.[3] These methods have been successfully applied to the oxidative homodimerization of 2,3,5-trimethylphenol, a hydroxycarbazole with high enantioselectivity. Syntheses of bismurrayaquinone-A, a potent anti-tumor compound, in a stereoselective form are sparse in literature.[21,22] The stereoselectivity is generated by kinetic resolution or much earlier in the synthetic route. The method from the Kozlowski group can generate both the atropisomers almost exclusively and is hence, a unique approach for the synthesis of range of important natural products. Compound **25** has been synthesized with yield of 45% and an ee of 20%. This was subsequently improved to 50% ee providing a promising starting point for use of this method in this context. In the future, the conditions for the oxidative homocoupling to produce the natural product will be optimized (solvent, additives, catalyst, chiral ligands, protecting groups) to increase the outcome to 90% ee or greater. Once the e.e has been optimized, the other isomer of **25** would be produced by using D-*tert*-Leucine to make the catalyst and to complete the synthesis.

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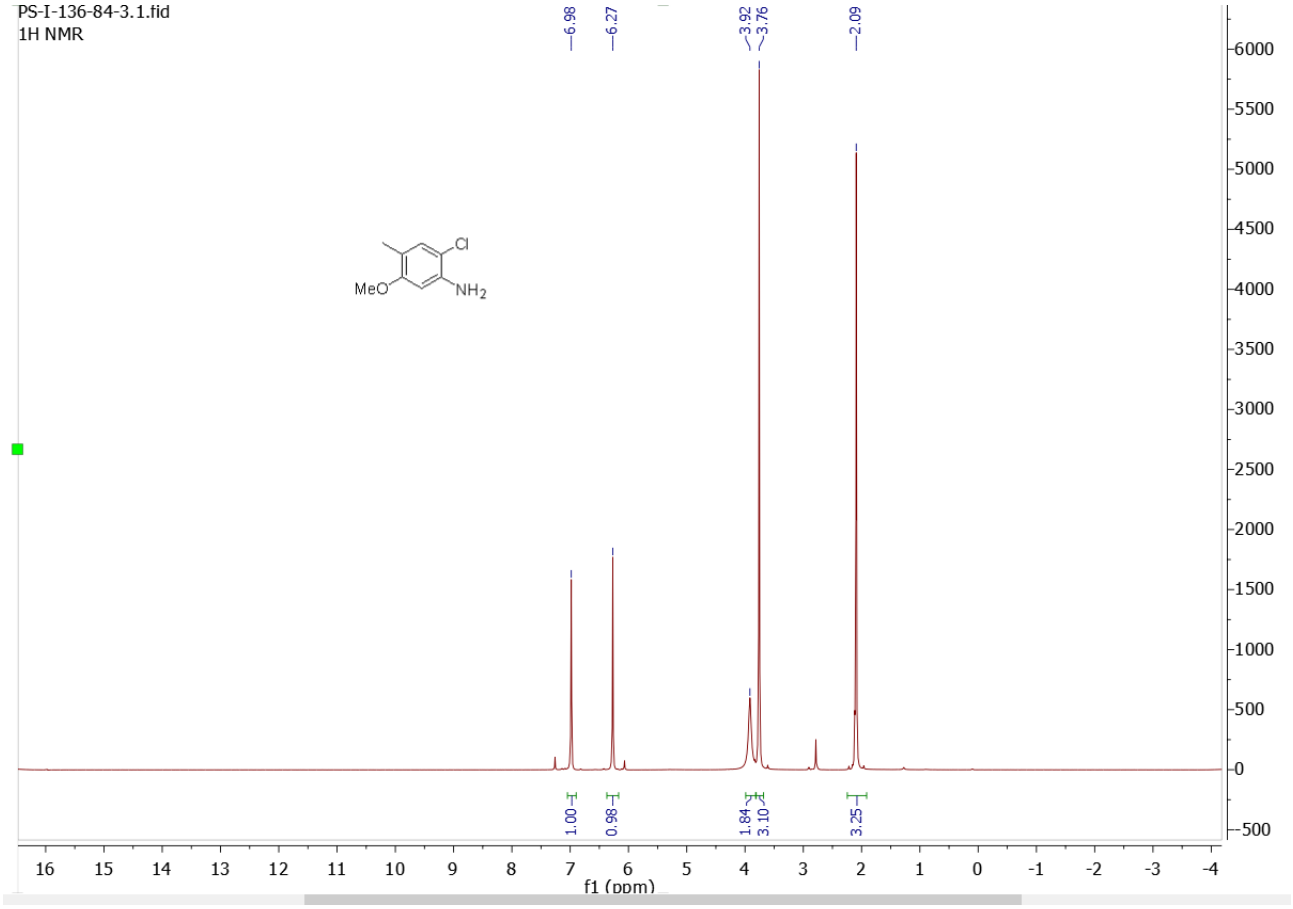
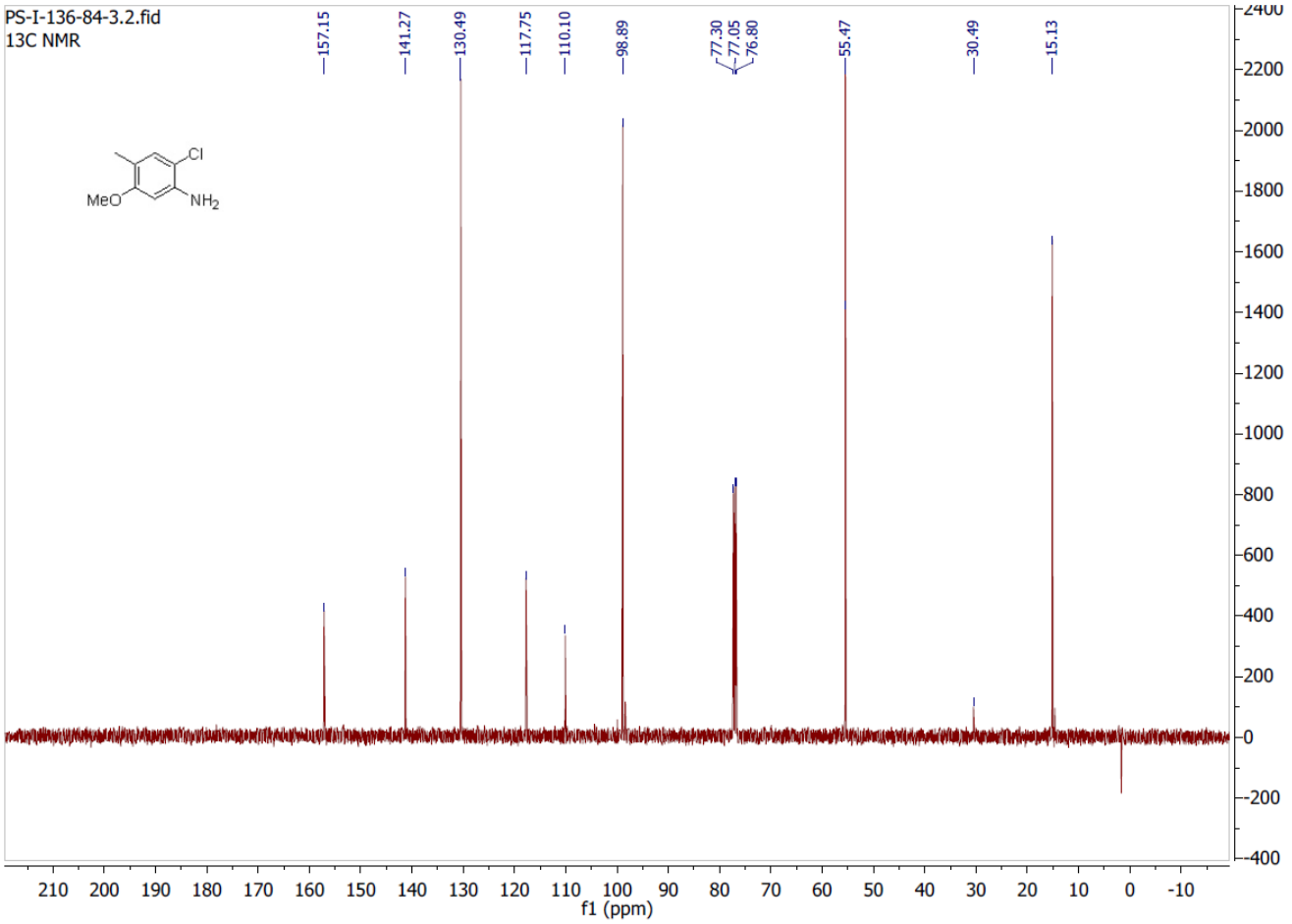
Appendices

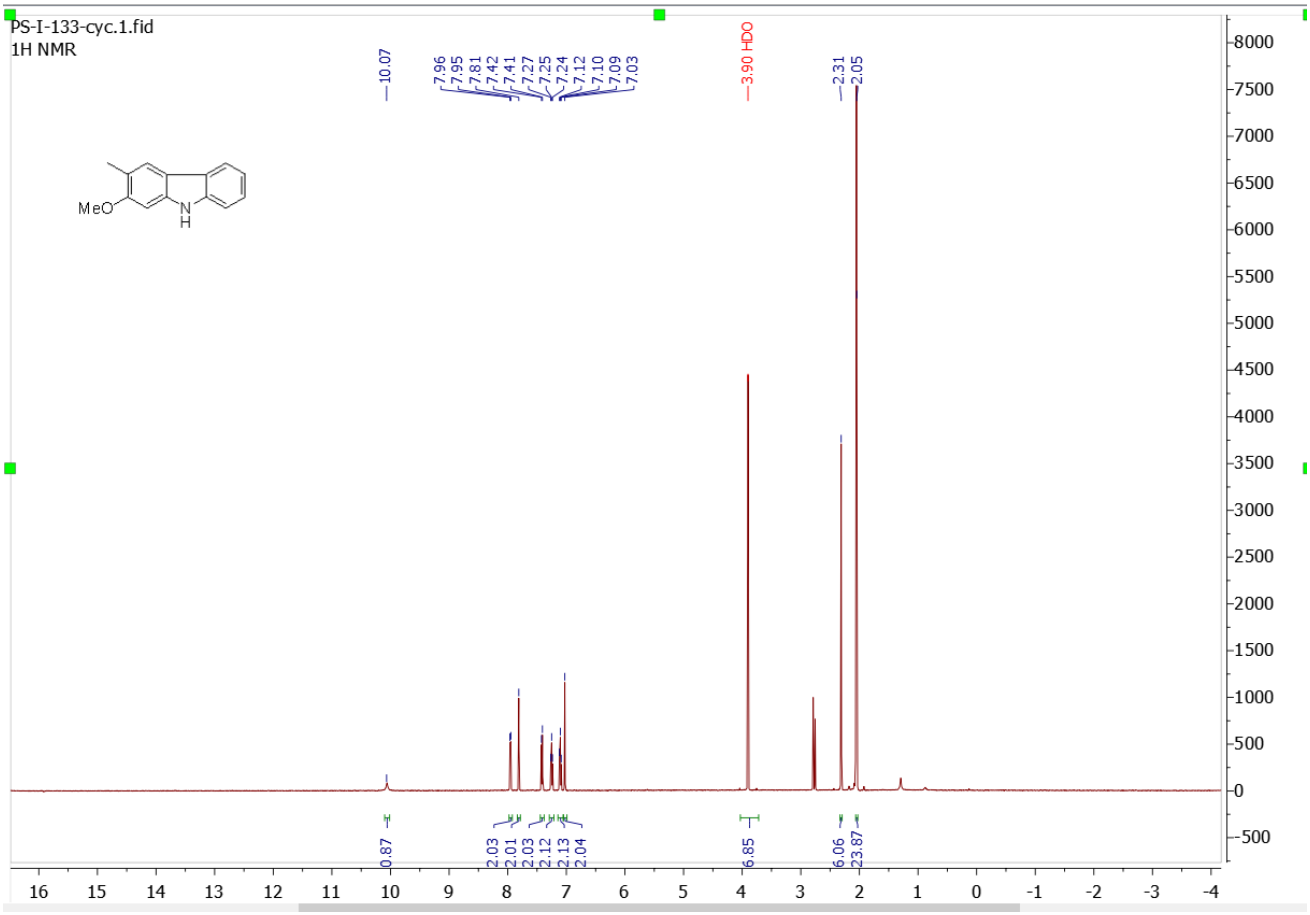
Appendix 1. ^{1}H NMR spectrum of 7



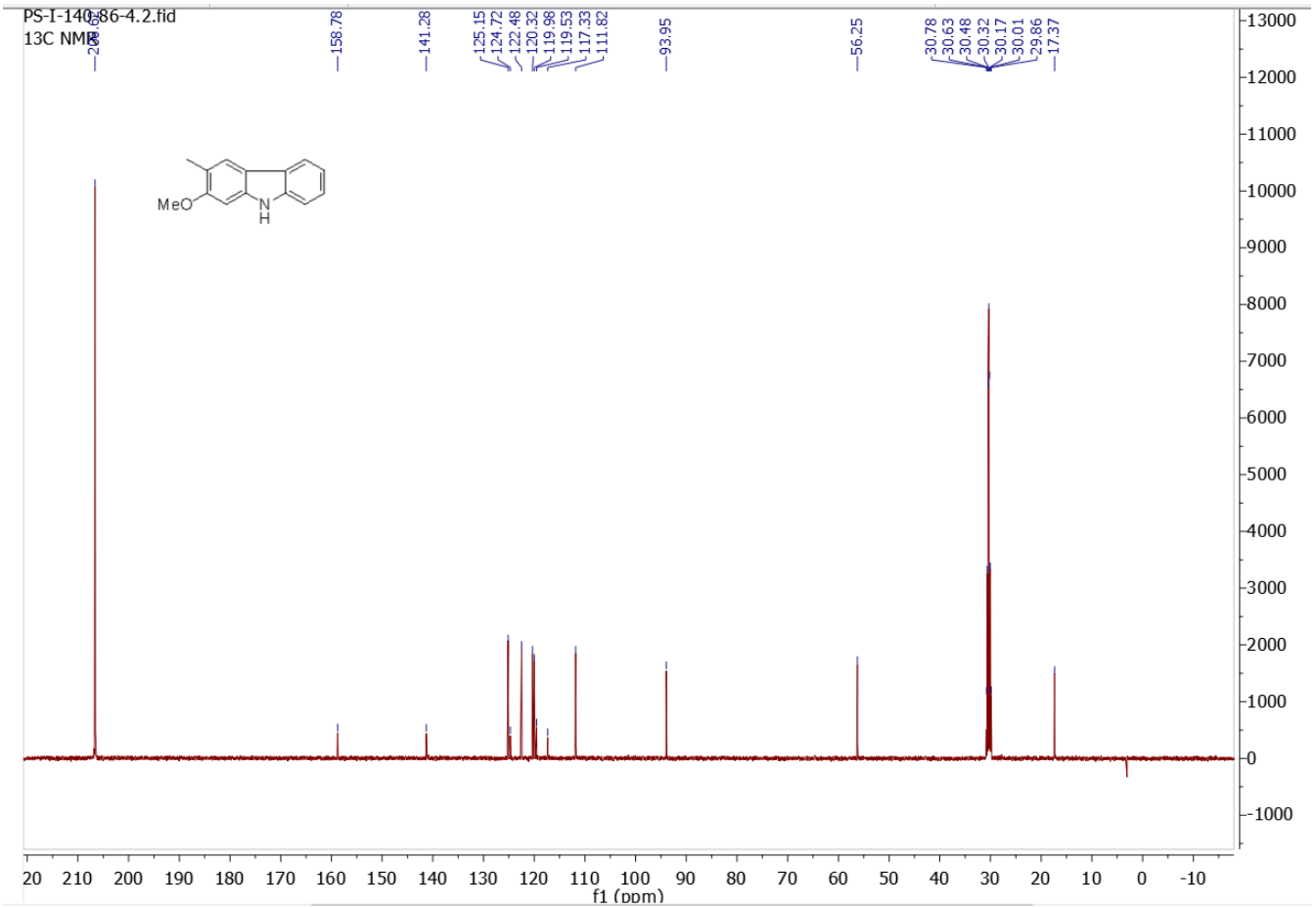
Appendix 2. ^{13}C NMR spectrum of 7



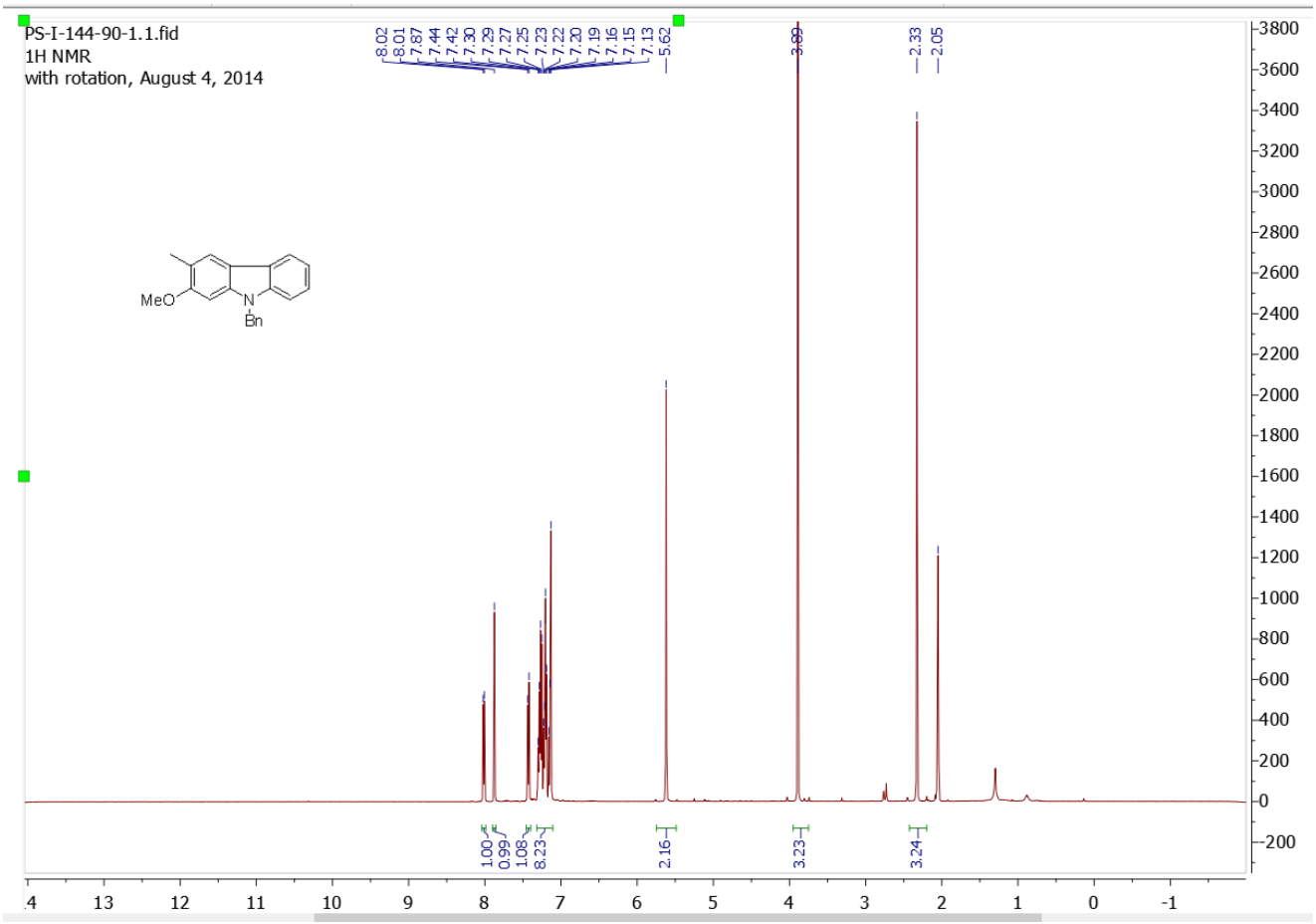
Appendix 3. ^{1}H NMR spectrum of 10



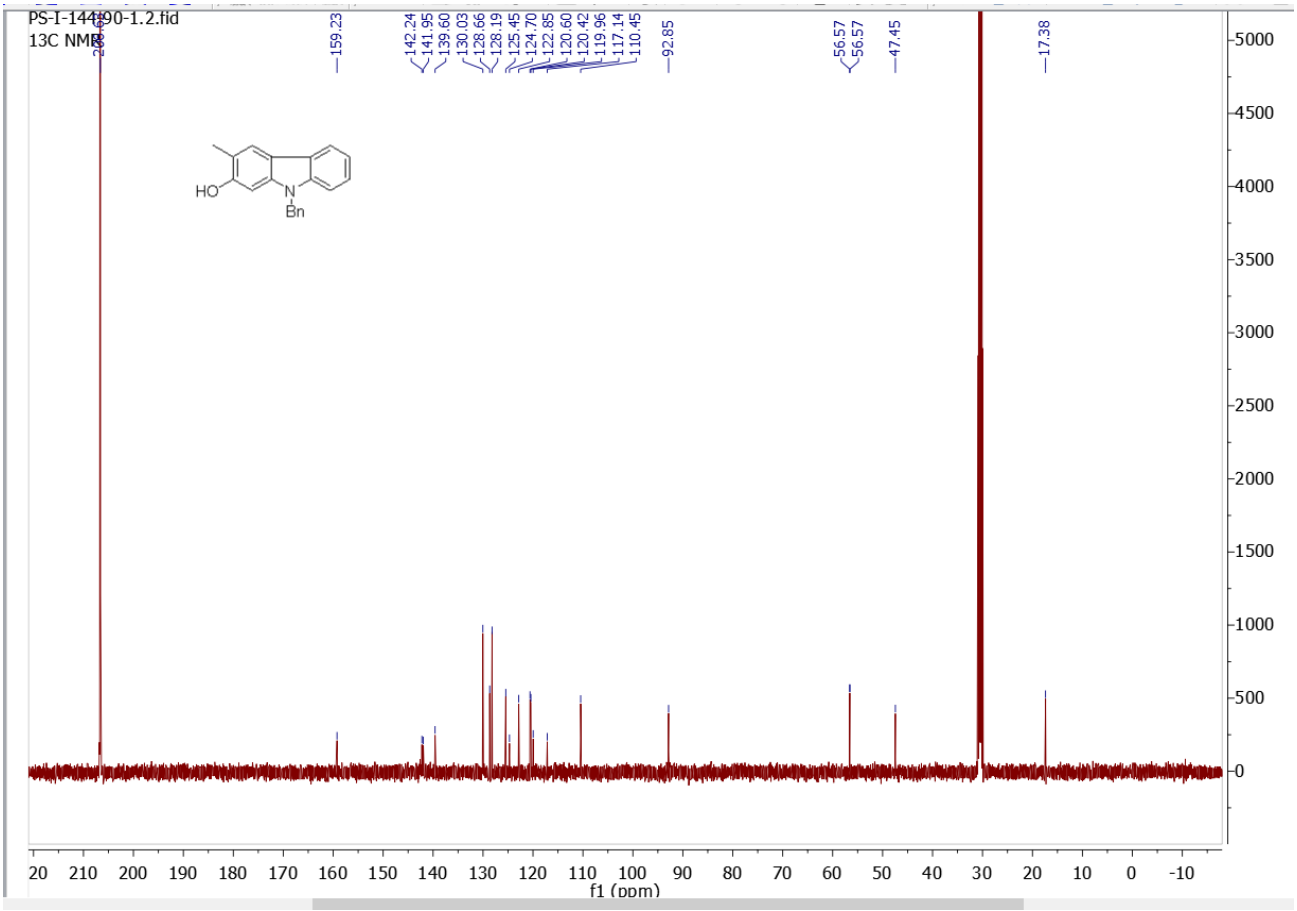
Appendix 4. ^{13}C NMR spectrum of 10



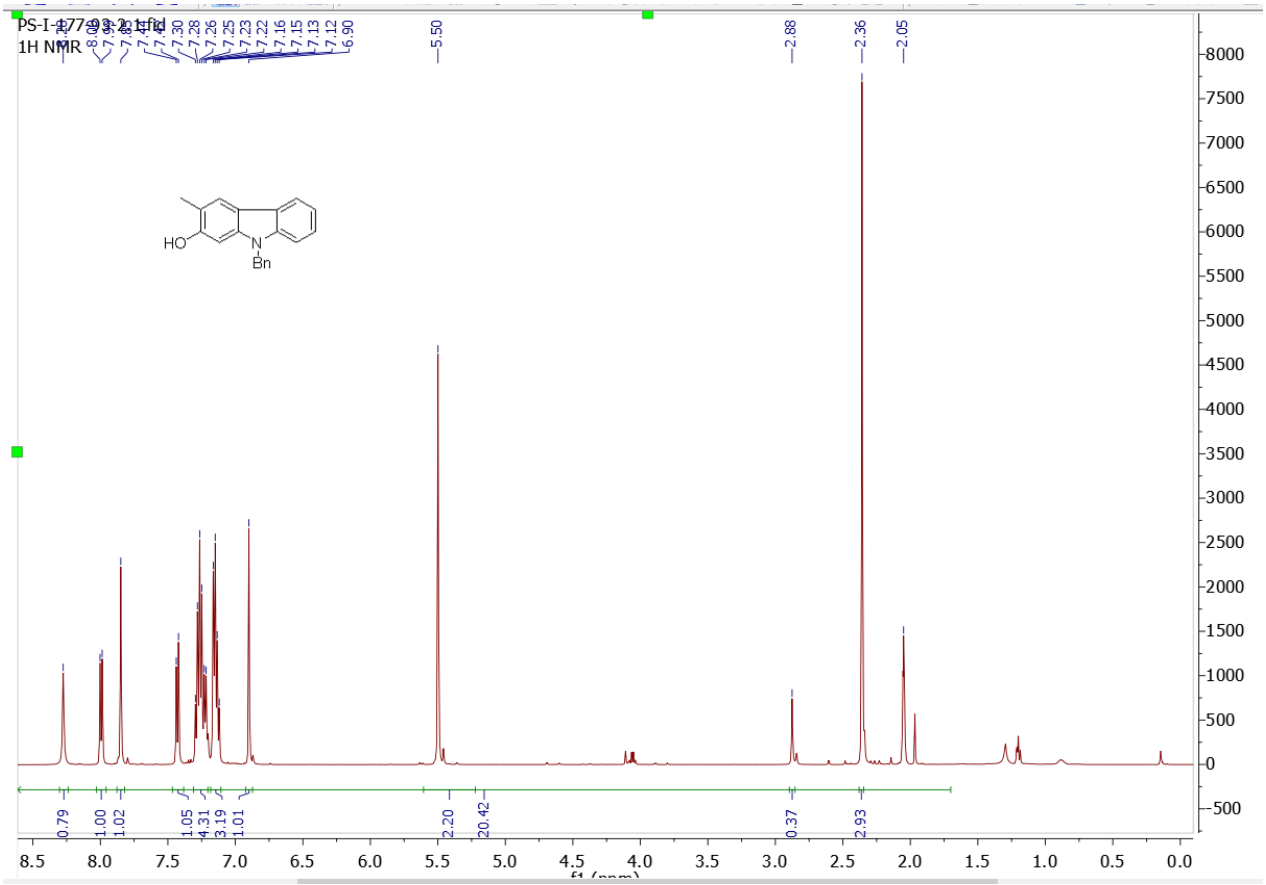
Appendix 5. ^{1}H NMR spectrum of 11



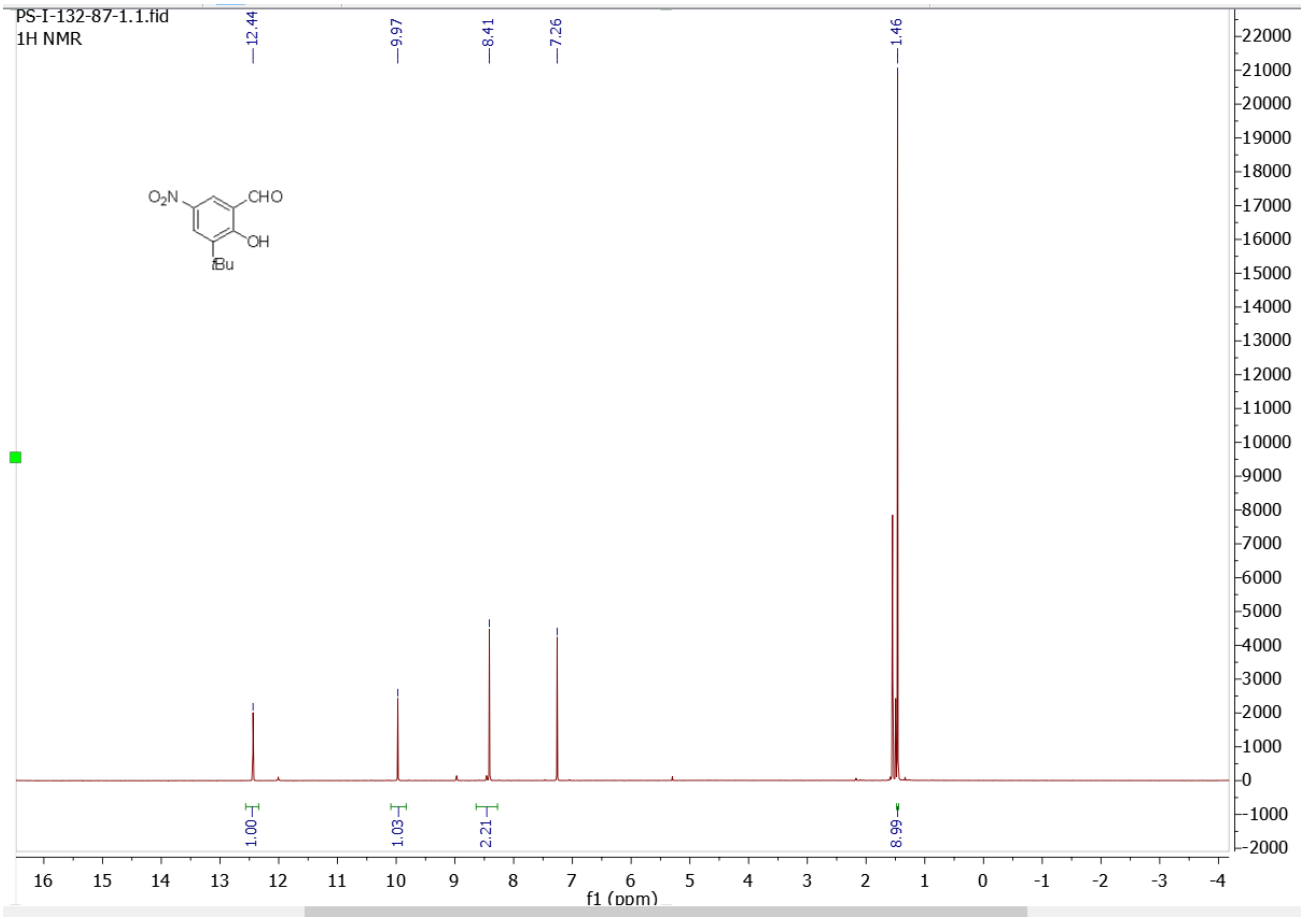
Appendix 6. ^{13}C NMR spectrum of 11



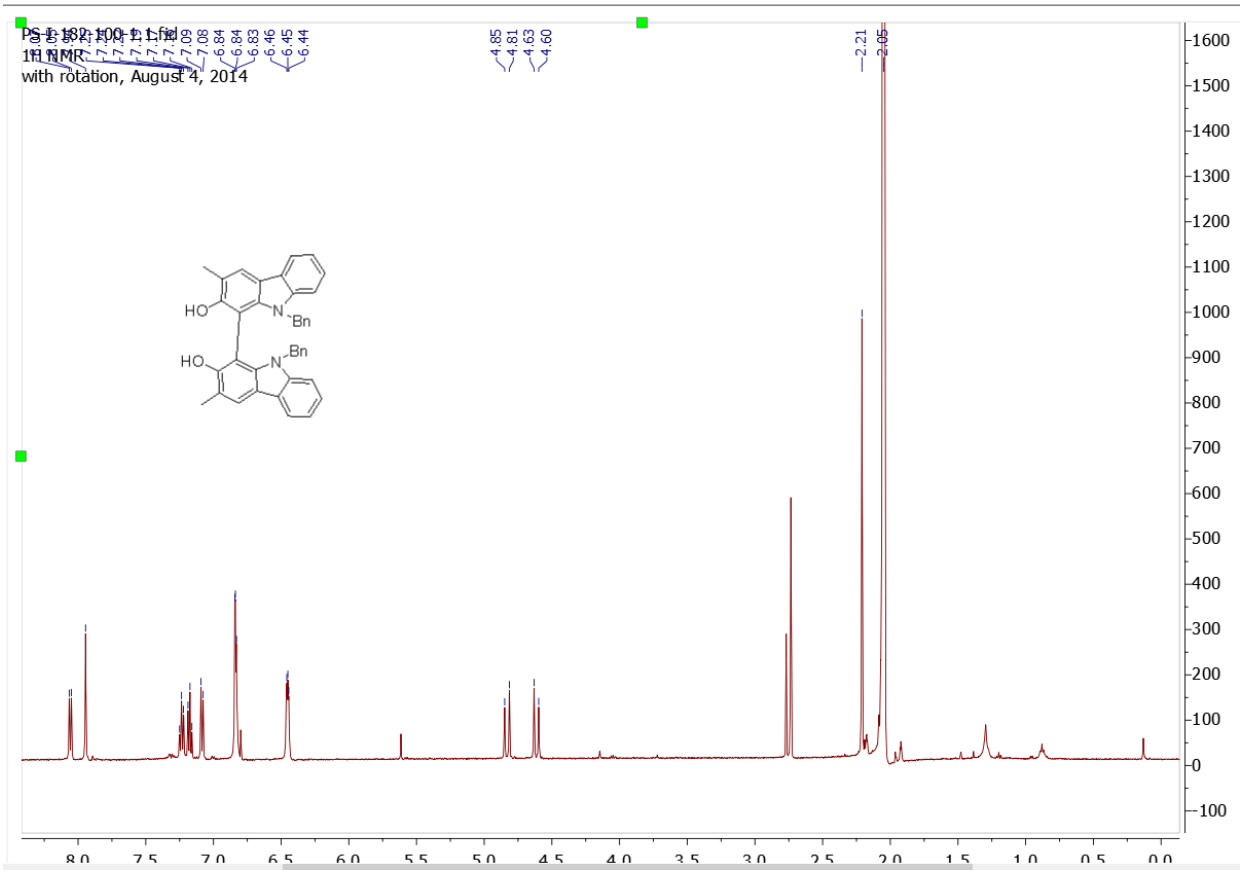
Appendix 7. ^{1}H NMR spectrum of 12



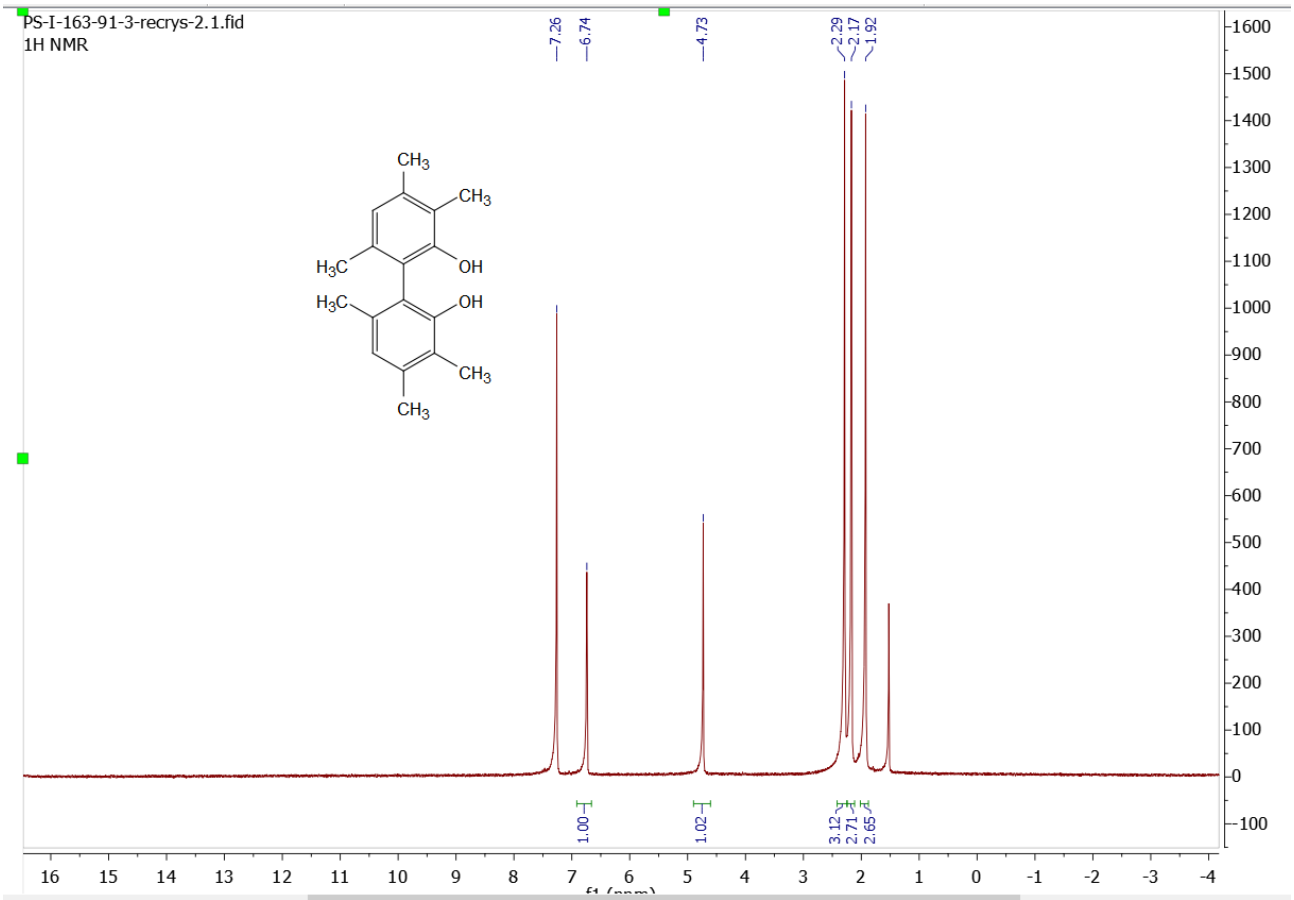
Appendix 8. ^{1}H NMR spectrum of 14



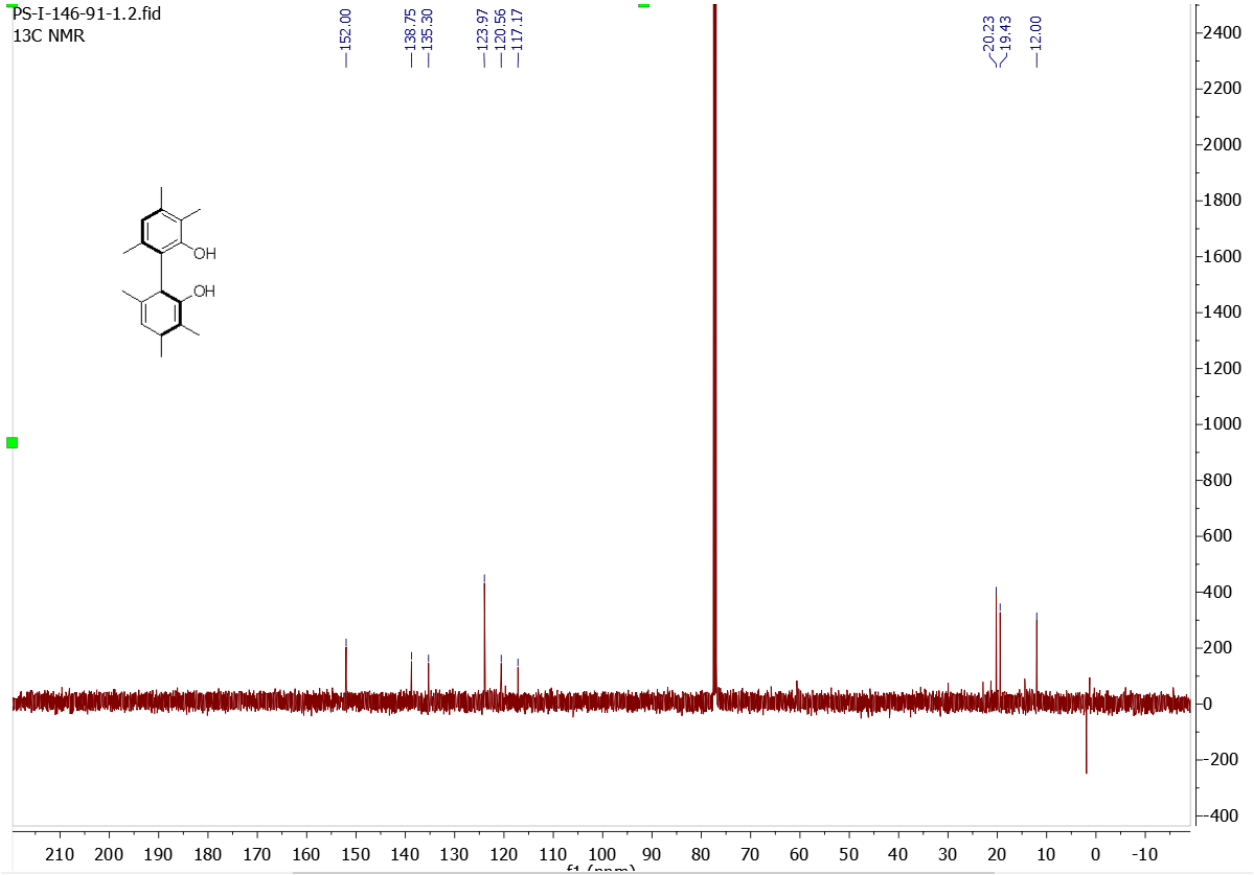
Appendix 9. ^{1}H NMR spectrum of 4



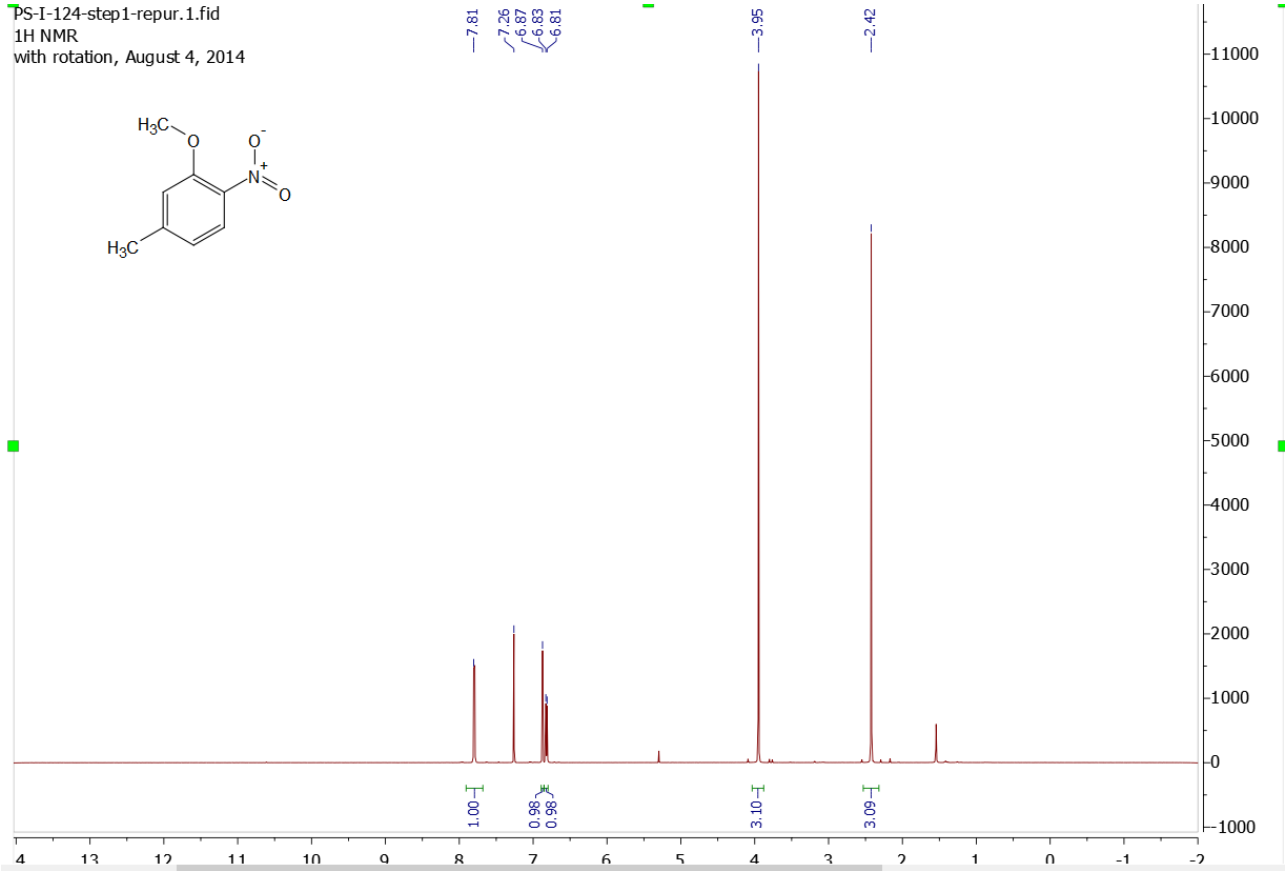
Appendix 10. ^{1}H NMR spectrum of 3



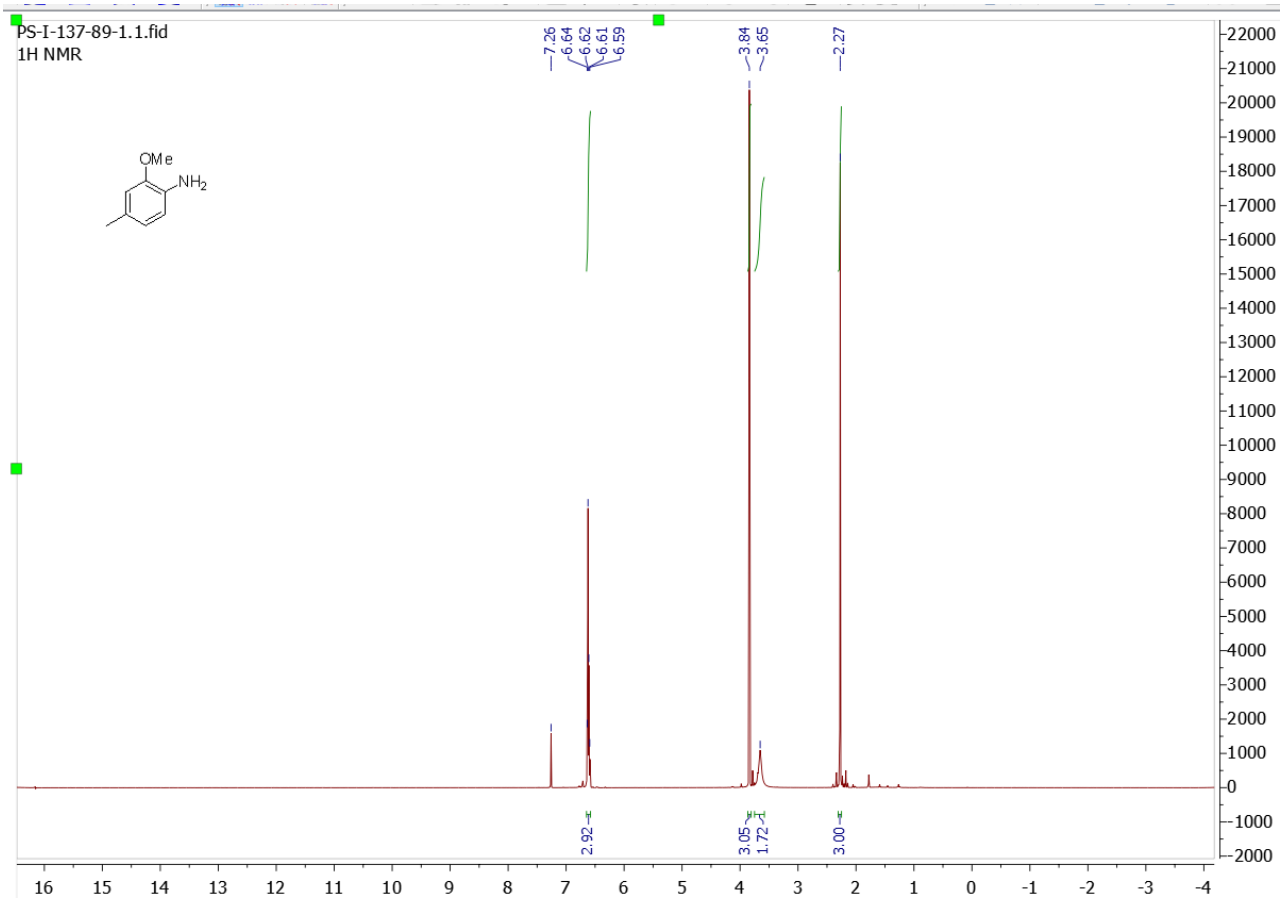
Appendix 11. ^{13}C NMR spectrum of 3



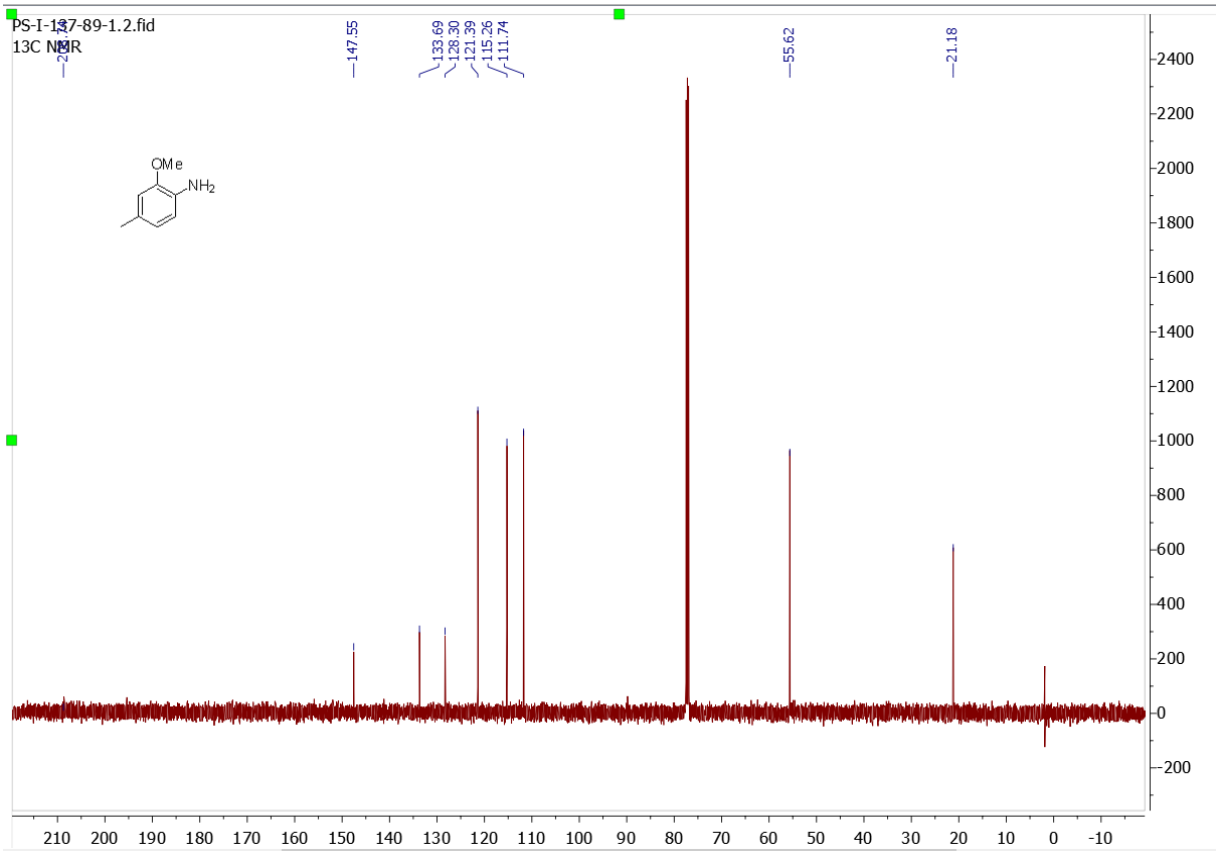
Appendix 12. ^{1}H NMR spectrum of 18



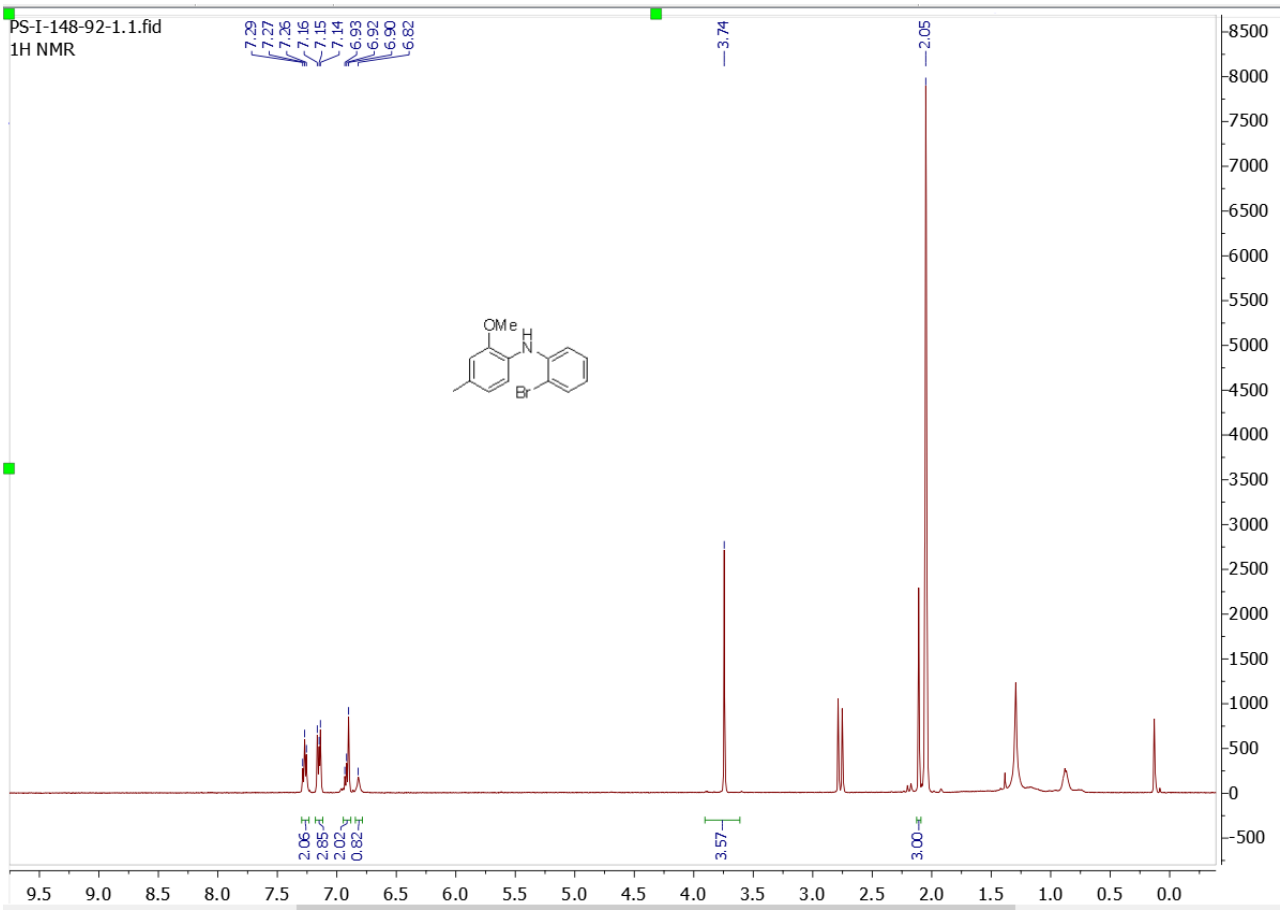
Appendix 13. ^{1}H NMR spectrum of 19



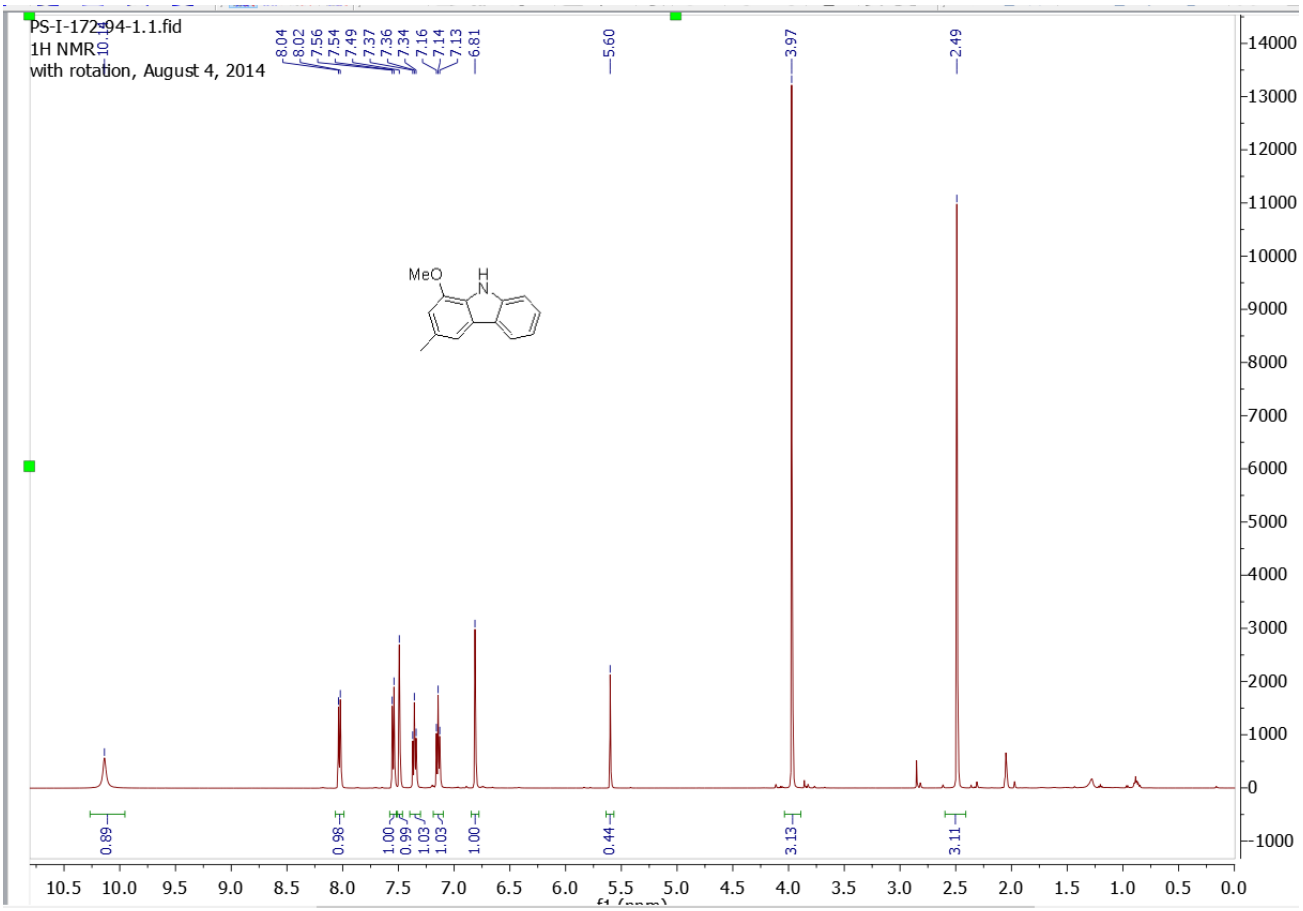
Appendix 14. ^{13}C NMR spectrum of 19



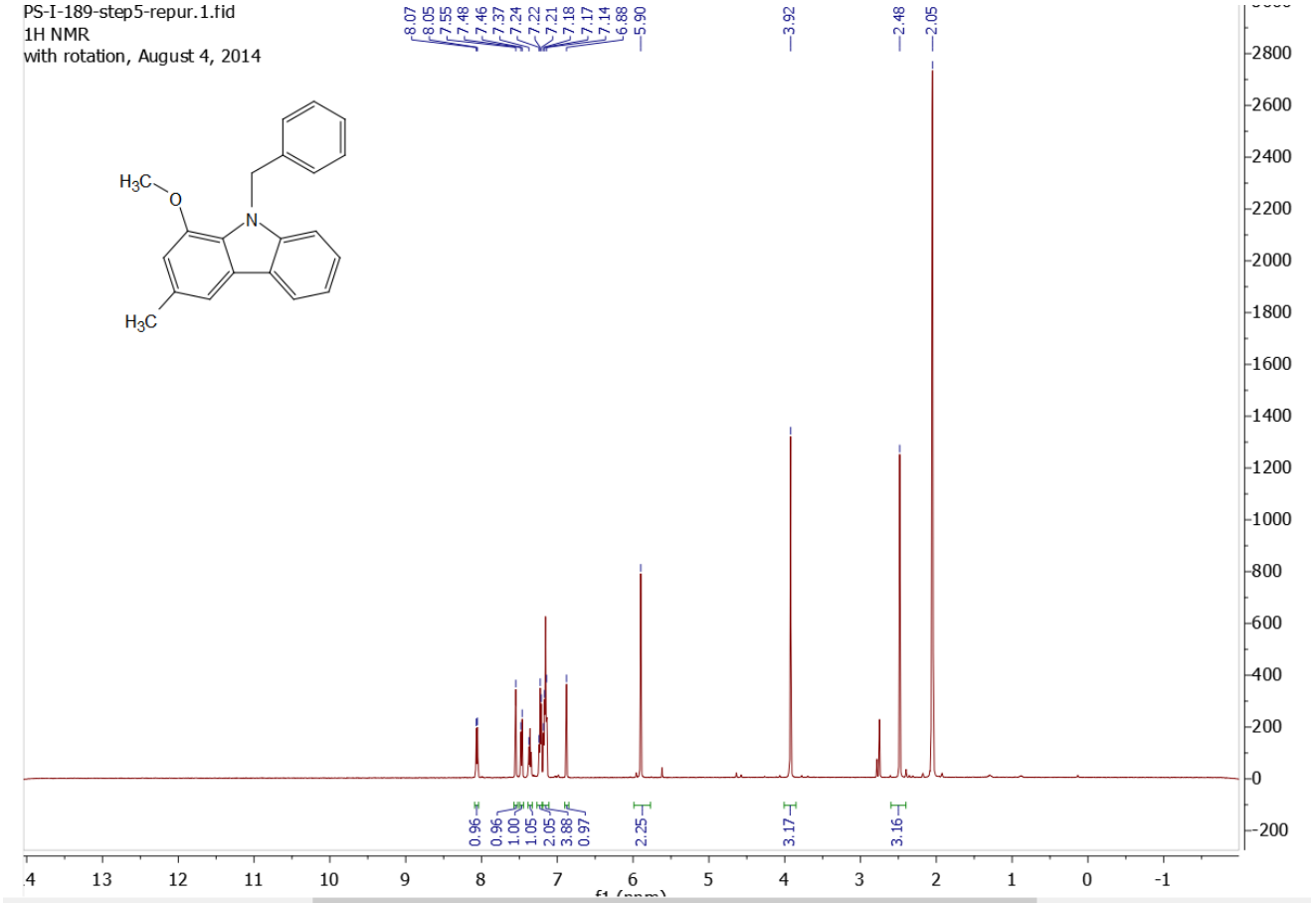
Appendix 15. ^{1}H NMR spectrum of 21



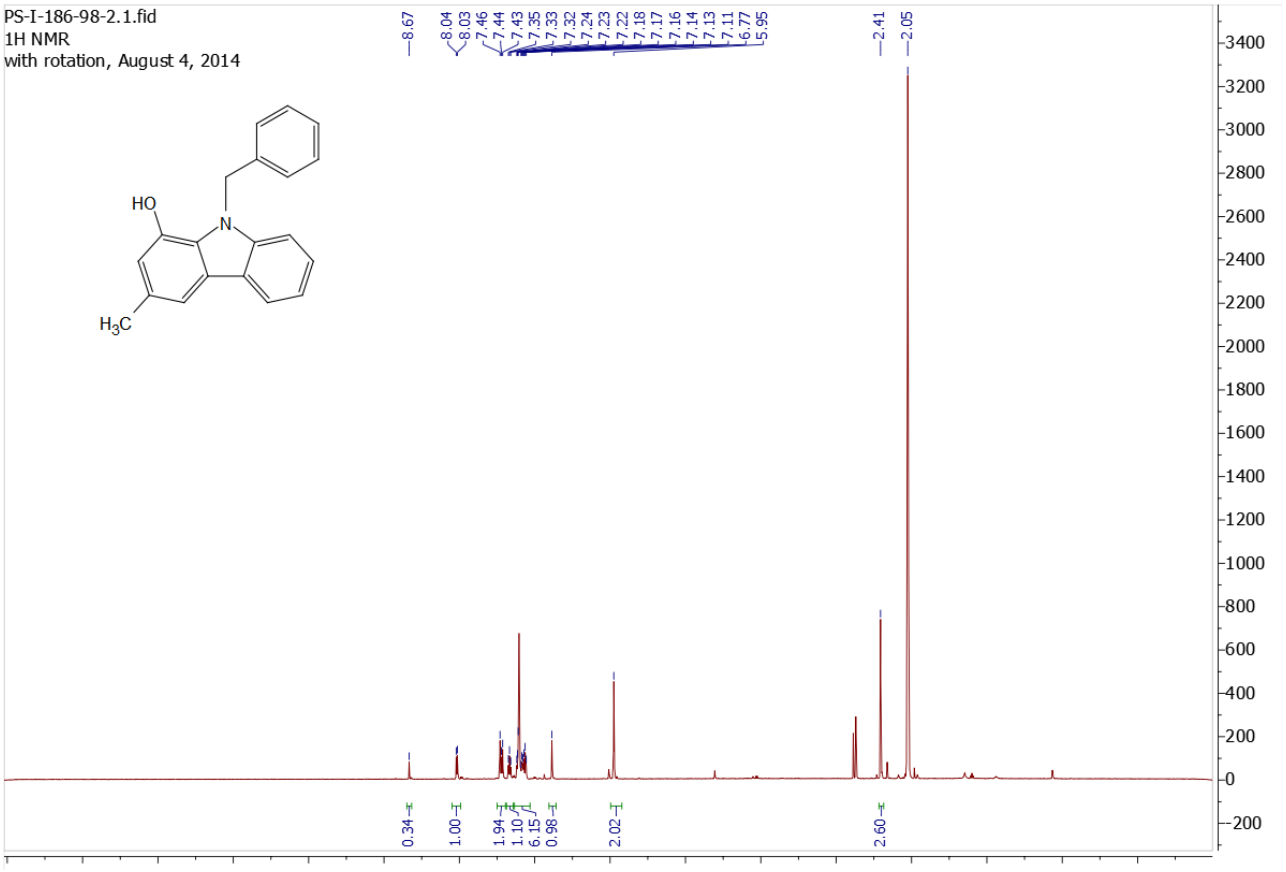
Appendix 16. ^{1}H NMR spectrum of 22



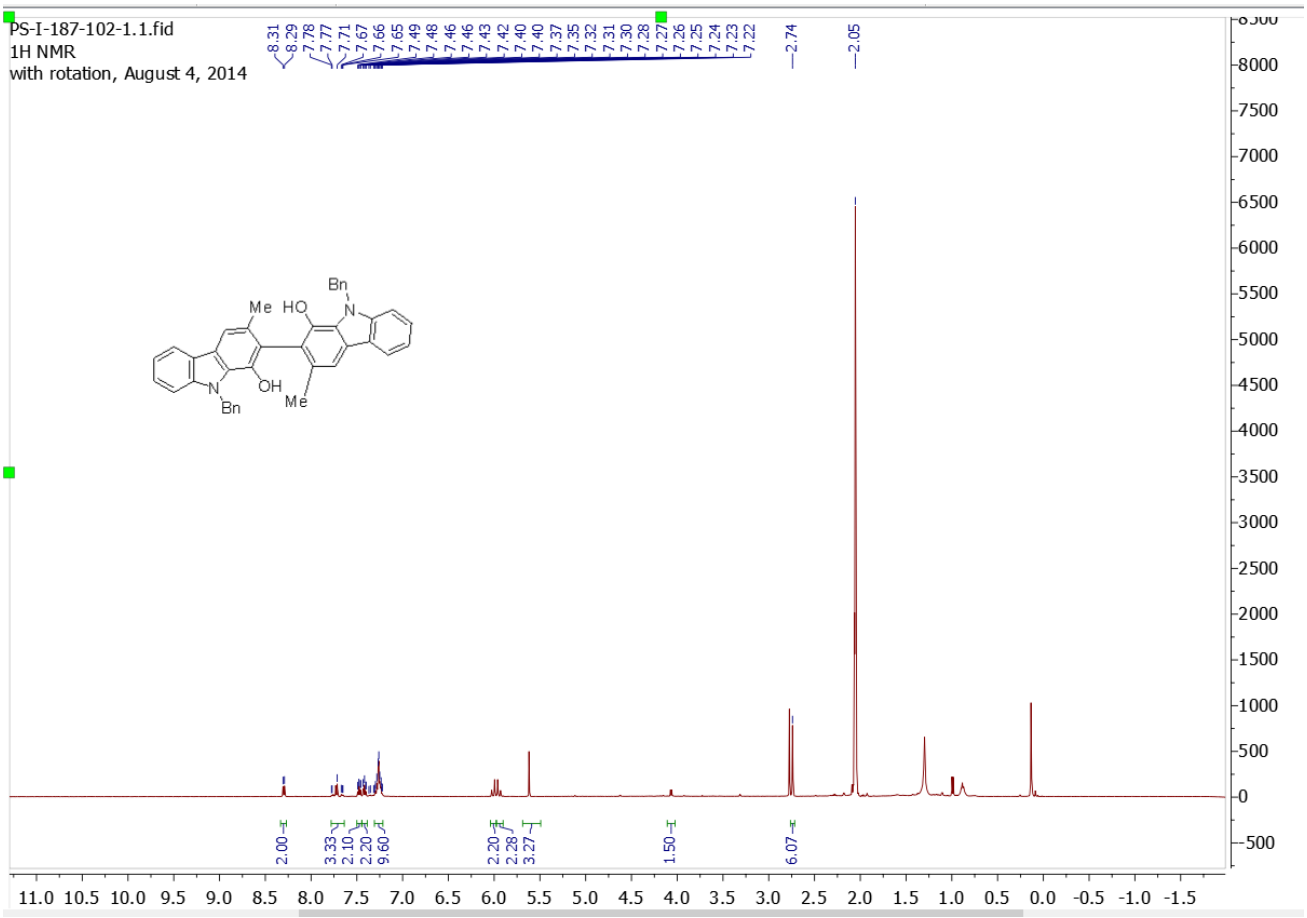
Appendix 17. ^{1}H NMR spectrum of 23



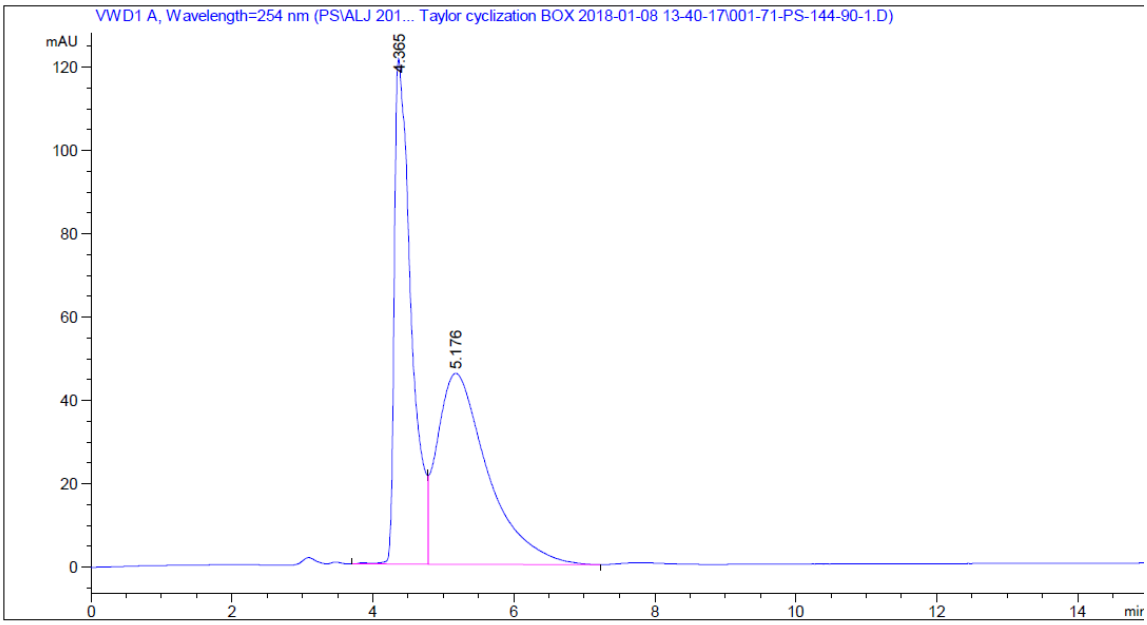
Appendix 18. ^{1}H NMR spectrum of 24



Appendix 19. ^{1}H NMR spectrum of 25 (racemic)



Appendix 20. HPLC trace of **3 (racemic)**

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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   4.365 VV R  0.2239 2026.51819  121.36228  46.9014
   2   5.176 VB    0.7399 2294.28369   45.82774  53.0986
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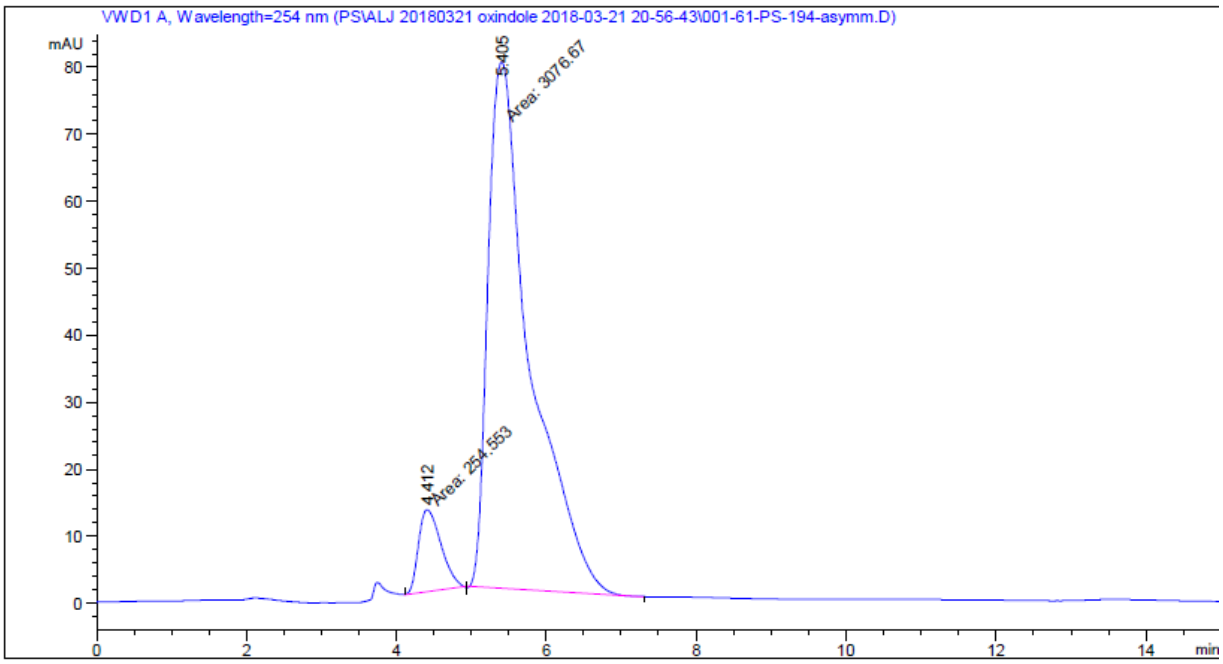
Appendix 21. HPLC trace of **3 (catalyst check)**

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   4.412 MM    0.3469  254.55330   12.22920   7.6414
   2   5.405 MM    0.6533 3076.66919   78.49374  92.3586

Totals :                  3331.22249   90.72294

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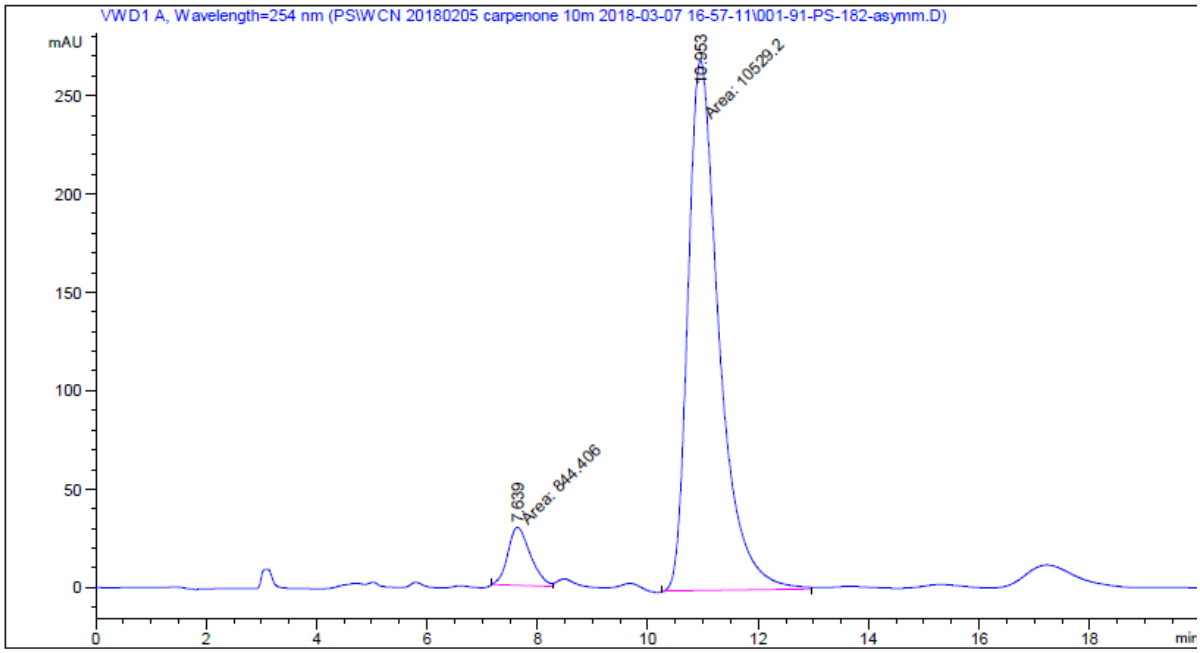
Appendix 22. HPLC trace of **4 (catalyst check)**

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   7.639 MM    0.4773  844.40582   29.48679   7.4242
   2  10.953 MM    0.6521 1.05292e4   269.10507  92.5758

Totals :                  1.13736e4   298.59187


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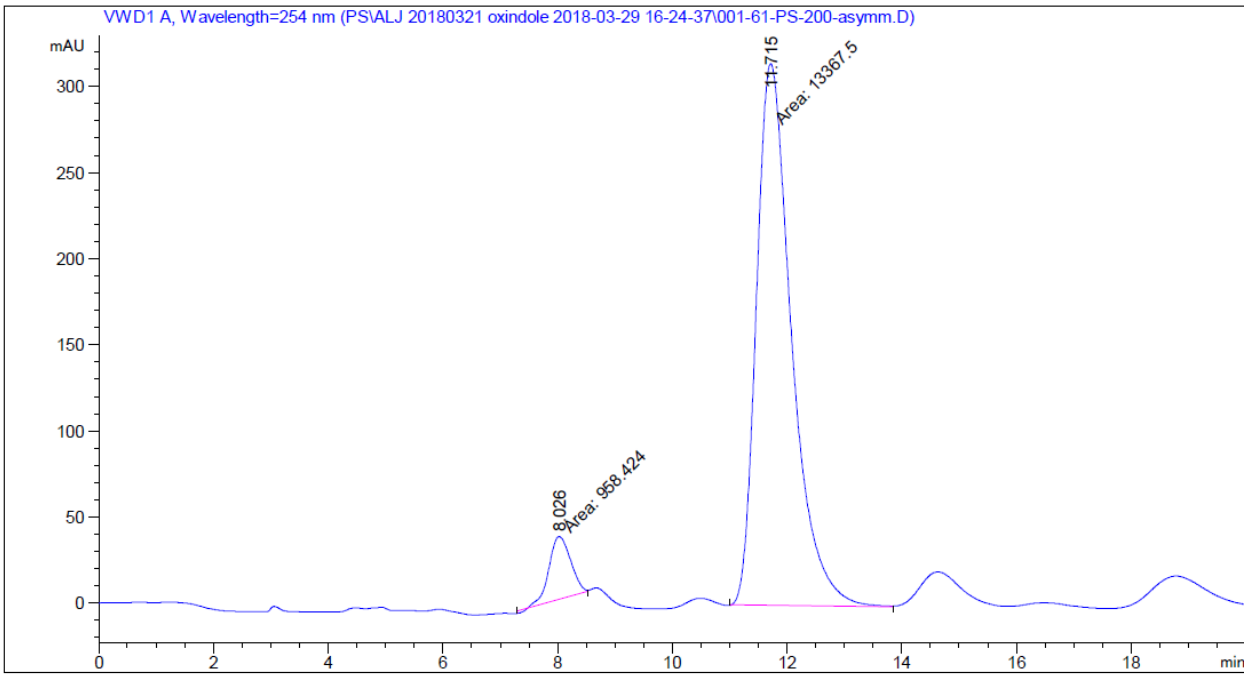
Appendix 23. HPLC trace of **4 (stereoselective): before trituration**

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
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----|-------|----|-------|----------|----------|--------|
   1   8.026 MM    0.4386  958.42352   36.42165   6.6901
   2  11.715 MM    0.7089 1.33675e4   314.27301  93.3099

Totals :                  1.43259e4   350.69466


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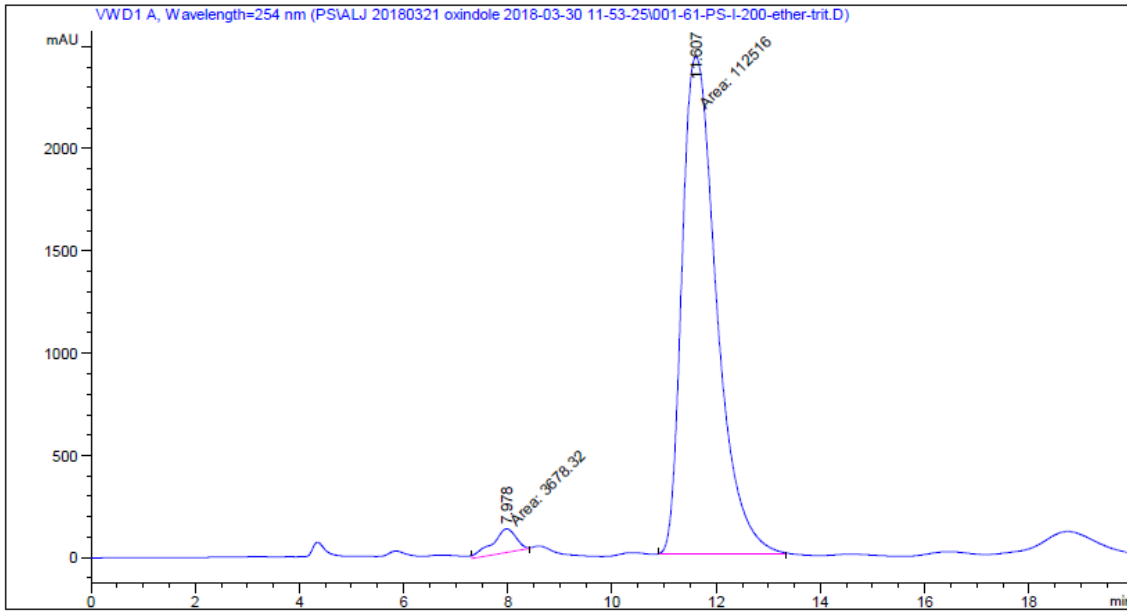
Appendix 24. HPLC trace of **4 (stereoselective): after trituration**

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1   7.978 MM    0.5339 3678.31543  114.83454   3.1657
   2  11.607 MM    0.7701 1.12516e5  2435.03442  96.8343

Totals :                  1.16194e5  2549.86897

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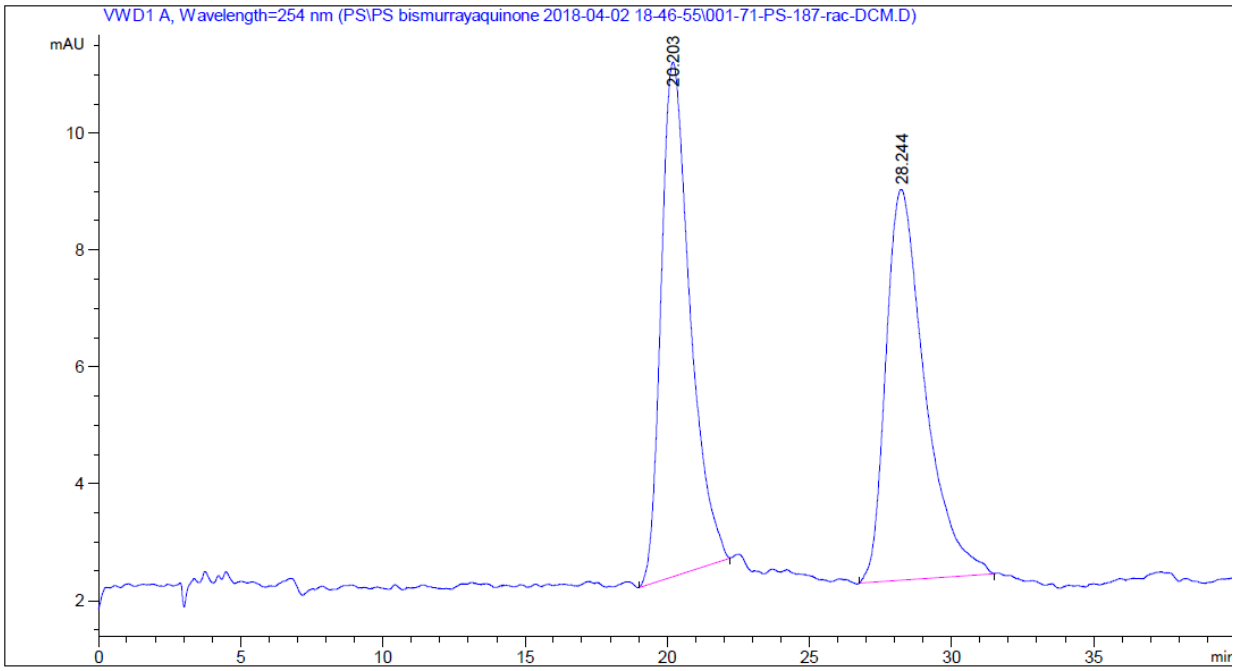
Appendix 25. HPLC trace of **25 (racemic)**

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Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

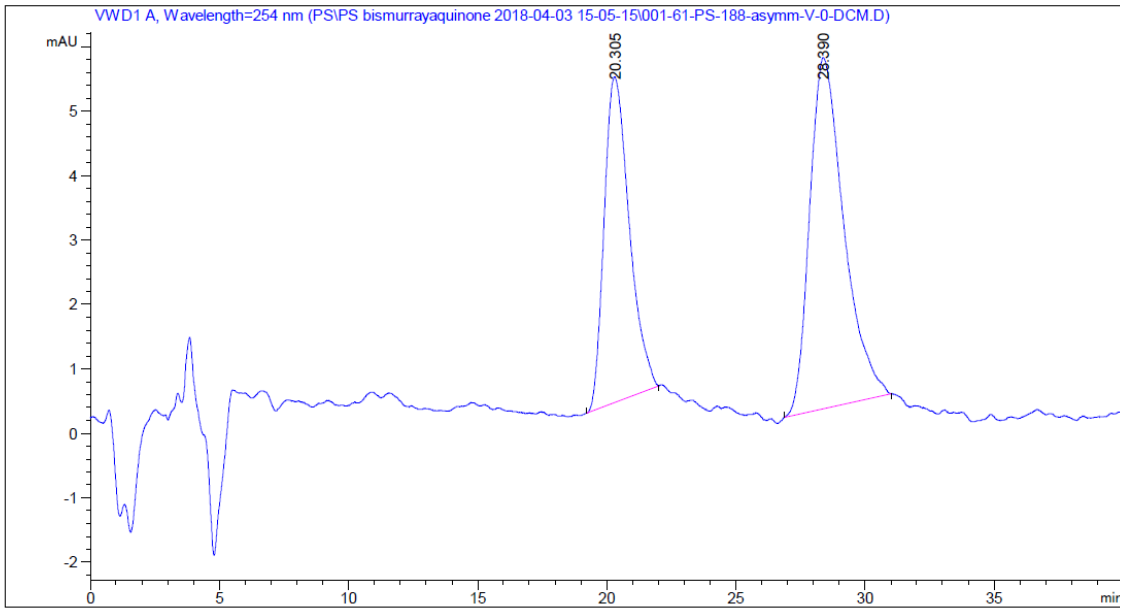

Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.203 BB    0.9904  625.02856    8.79842  49.4035
   2  28.244 BB    1.1415  640.12158    6.68751  50.5965

Totals :                  1265.15015   15.48594

==================================================================================
                            *** End of Report ***
```

Appendix 26. HPLC trace of **25 (acetic acid additive)**




```
==================================================================
                        Area Percent Report
==================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs

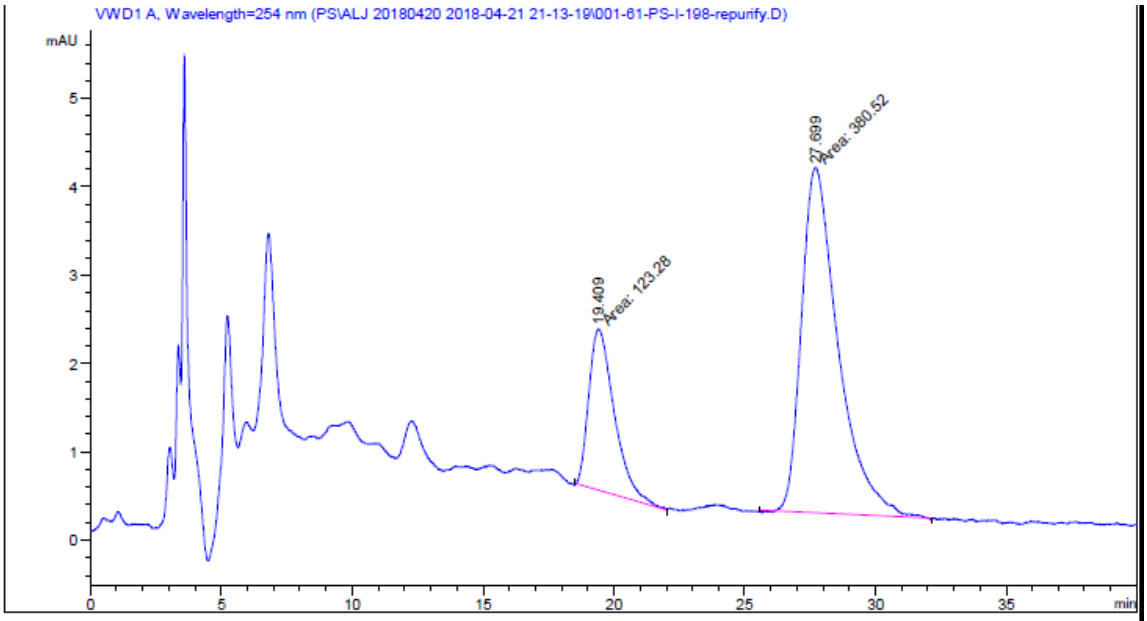

Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  20.305 BB    0.9005  342.65393    5.06151  40.6399
   2  28.390 BB    1.0861  500.49265    5.44907  59.3601

Totals :                   843.14658   10.51058


==================================================================
                        *** End of Report ***
```

Appendix 27. HPLC trace of **25 (Lithium chloride additive)**




```
=====================================================================
                        Area Percent Report
=====================================================================

Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Do not use Multiplier & Dilution Factor with ISTDs


Signal 1: VWD1 A, Wavelength=254 nm

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   1  19.409 MM    1.1241  123.27954    1.82784  24.4700
   2  27.699 MM    1.6219  380.51965    3.91021  75.5300

Totals :                   503.79919    5.73805

=====================================================================
                          *** End of Report ***
```