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Synthesis and characterization of potential impurities of Vigabatrin-An anti epileptic drug

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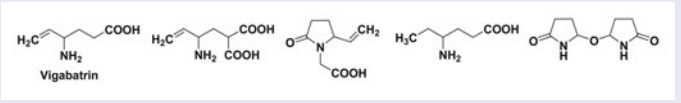
ABSTRACT

The present work describes the synthesis and characterization of four potential impurities of Vigabatrin **(1)** namely 2-(2-aminobut-3-enyl)-malonic acid **(2)** (Vigabatrin USP impurity-E), 2-(2-oxo-5-vinylpyrrolidin-1-yl)acetic acid **(3)** (USP Tablets impurity), 4-aminohexanoic acid **(4)** and 2,2′-oxo-5,5′-bispyrrolidinyl ether **(5)**. Compound **4** is a possible process related impurity of **1** where as compound **5** is a process related impurity of 5-ethoxy-2-pyrrolinone **(16)**. All these impurities have a significant impact on the quality of the drug product. This work is extremely useful for generic pharmaceutical industry.

GRAPHICAL ABSTRACT



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KEYWORDS
Vigabatrin; USP impurity-E; Tablets Impurity; Impurities; Synthesis and characterization

Introduction

Vigabatrin [γ-vinyl GABA or 4-amino-5-hexenoic acid] (1) is a synthetic analogue of GABA (γ-aminobutyric acid) is a highly selective enzyme-activated inhibitor of GABA-T in mammalian brain. Inhibition of GABA-T by γ-vinyl GABA, which replaces GABA as a substrate for GABA-T, increases the level of GABA in the central nervous system (CNS). Thus, Vigabatrin is useful for the treatment of disorders associated with depletion of GABA levels in the CNS such as tardive dyskinesia, schizopherenia and epilepsy.[1] Vigabatrin is marketed under the brand name Sabril®.

The major challenge for the organic chemist is to produce a quality, safe, reproducible synthetic schemes within the developmental space. Furthermore, it is extremely challenging to identify the impurities or related substances which are important components arise in smaller amounts during the synthesis/manufacturing of a drug substance. Besides, the presence of impurities in an active pharmaceutical ingredient (API) has a

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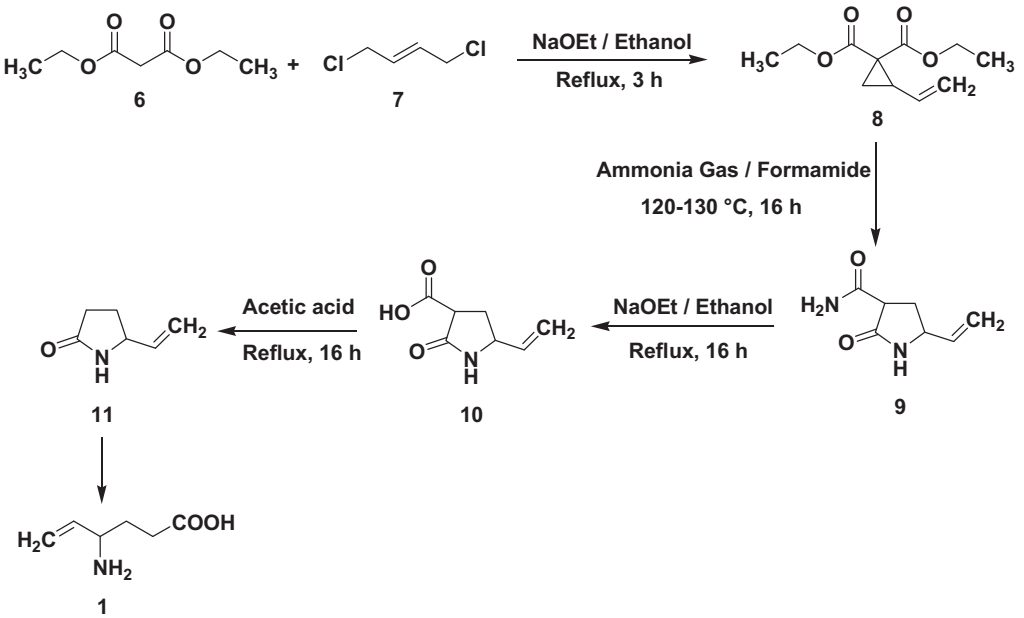
significant impact on the quality and safety of the drug. Therefore, assessment and control of the related substances is mandatory to obtain various regulatory approvals.

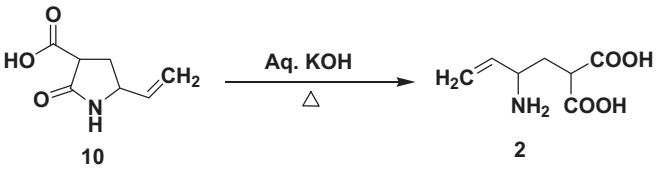
As per the monograph of US pharmacopeia (USP-40), the threshold limit of specified or un-specified impurity of **1** should be <0.10%. ICH (International Conference on Harmonization) recommended that any impurity at a level greater than the identification threshold in any batch manufactured by the proposed commercial process should be identified, based on the fact that unidentified impurities may cause health hazards by making the API (Active Pharmaceutical Ingredient) inferior in quality.[2] To have a better understanding of impurity profile, these impurities have to be identified, synthesized and controlled in the manufacturing process. In addition, these impurities in a pure form have a crucial importance in determining the analytical parameters such as accuracy, specificity, linearity, limit of detection (LOD), limit of quantification (LOQ) and relative retention factor.[3] So it is necessary to synthesize and characterize all of the related substances or impurities due to the crucial importance in the purity of a drug substance in the pharmaceutical industry. Based on the above facts and their importance, the synthesis and characterization of these potential impurities (**2**, **3**, **4** and **5**) is reported.

Discussion

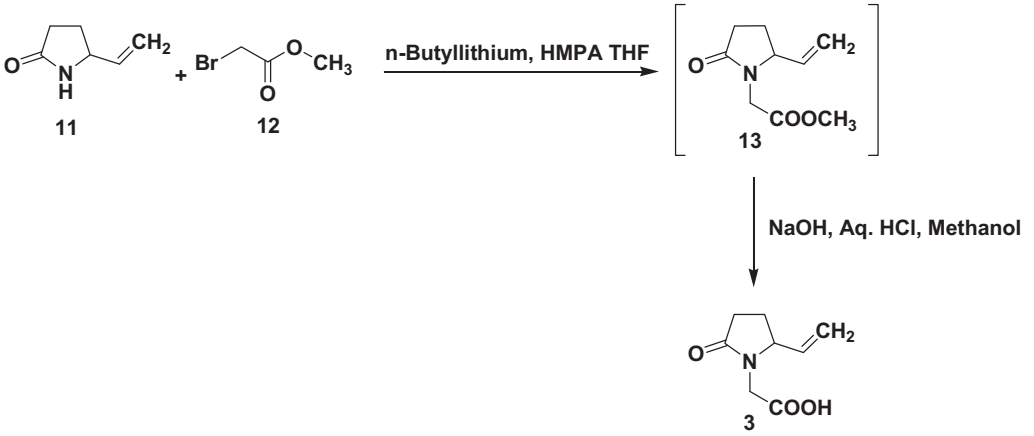
Various synthetic routes were available in literature for the preparation of **1**. Gittos et al.[4] describes the preparation of Vigabatrin involves (Scheme 1) the condensation of two commercially available raw materials diethylmalonate (**6**) and 1,4-dichloro-2-butene (**7**) to afford 1,1-bis-ethoxycarbonyl-2-vinylcyclopropane (**8**). Compound **8** is treated with ammonia gas in formamide at 120 °C to afford diethyl-2-vinylcyclopropane-1,1-dicarboxylate (**9**). Compound **9** is hydrolyzed with sodium ethoxide in ethanol and decarboxylated



Scheme 1. Reported preparation of Vigabatrin (1).



Scheme 2. Preparation of 2-(2-aminobut-3-enyl)malonic acid (2).

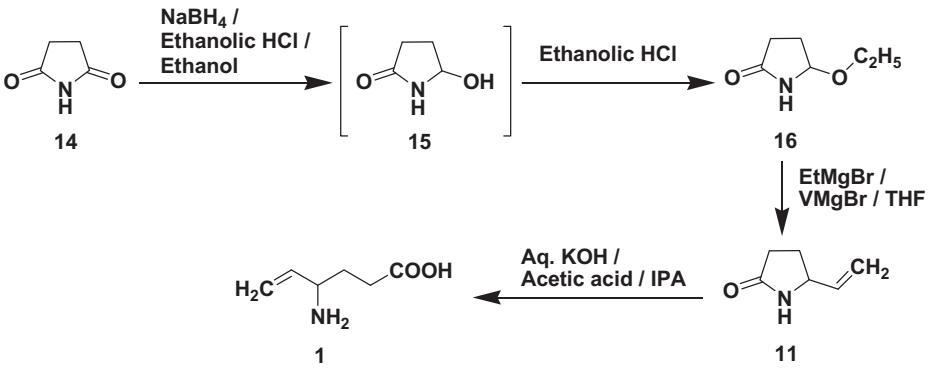


Scheme 3. Preparation of 2-(2-oxo-5-vinylpyrrolidin-1-yl)acetic acid (3).

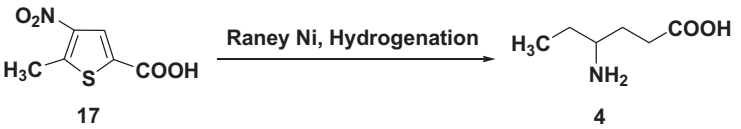
with acetic acid to afford 5-vinyl-2-pyrrolidinone **(11)**. Compound **11** is further hydrolyzed in the presence of aq. HCl and purified to afford Vigabatrin (1).

2-(2-Aminobut-3-enyl)malonic acid (2) (Vigabatrin USP impurity-E) was extremely crucial among all other related substances listed in US pharmacopeia (USP 40) for Vigabatrin. Any unknown impurities were determined against **2** in the purity method described in USP. Compound **2** may be originated by the ring cleavage of **10** during the hydrolysis of **10** to form **11**. Thus, compound **2** was prepared by the hydrolysis (Scheme 2) of **10** in the presence of KOH and isolated from a mixture of aqueous methanol after acidification with aqueous HCl. The biggest challenge was encountered during the isolation of **2** because of the presence of large amount of inorganic salt which was very difficult to eliminate completely. Furthermore, both the salts and compound **2** were soluble in water. Due to the significance of the impurity, it was required to isolate compound **2** in salt free form. To remove salts, ion exchange chromatography was employed. But the attempt was unsuccessful due to degradation of the product. Later, the residue was added minimum water and kept stationary for few days. The product was precipitated but yield was less. Finally, compound **2** was isolated from a mixture of water and methanol system.

2-(2-Oxo-5-vinylpyrrolidin-1-yl)acetic acid (3) was a USP tablets impurity, may be originated during manufacturing of Vigabatrin tablet. It was believed that, the impurity was formed due to degradation during the tablet preparation. Initially, an attempt to prepare **3** using 2-bromoacetic acid instead of methyl-2-bromoacetate **(12)** was unsuccessful. Thus, it was prepared by the condensation of **12** and **11** in the presence of n-butyllithium to afford 2-(2-oxo-5-vinylpyrrolidin-1-yl)aceticacidmethylester **(13)** which



Scheme 4. Reported preparation of Vigabatrin **1.**



Scheme 5. Reported preparation of 4-aminohexanoic acid (4).

was further hydrolyzed insitu in the presence of a base at lower temperature to afford **3** (Scheme 3).

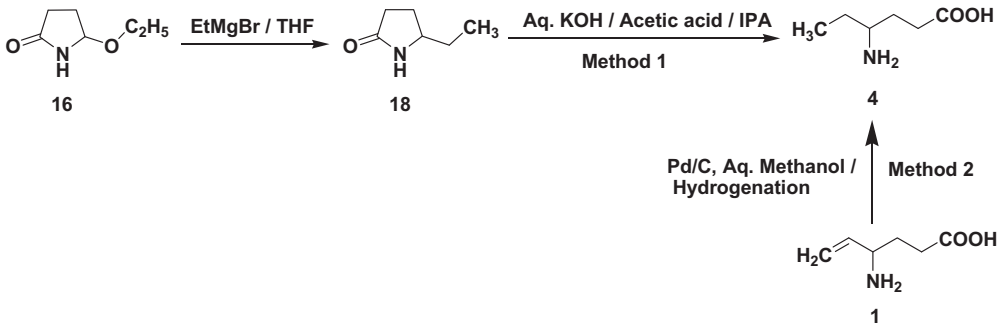
In another report for the synthesis of **1**[5] (Scheme 4) involves by the reduction of succinimide **(14)** in the presence of $NaBH_4$ to form 5-hydroxy-2-pyrrolidinone **(15)** in ethanol which upon treating with ethanolic HCl insitu to afford 5-ethoxy-2-pyrrolidinone **(16).** Compound **16** is treated in a mixture of EtMgBr (Ethyl Magnesium Bromide) and VMgBr (Vinyl Magnesium Bromide) in THF to afford **11**. Further, compound **11** is hydrolyzed in the presence of KOH to afford **1**.

4-Aminohexanoic acid (4) was a process related impurity, may be originated during the preparation of **11** from **16** in a mixture of EtMgBr (Ethyl Magnesium Bromide) and VMgBr (Vinyl Magnesium Bromide) in THF. It may be due to usage of excess moles of EtMgBr which may lead to form 5-ethyl-2-pyrrolidinone **(18).** Further, compound **18** was carried forwarded and hydrolyzed to form **4** in the next step.

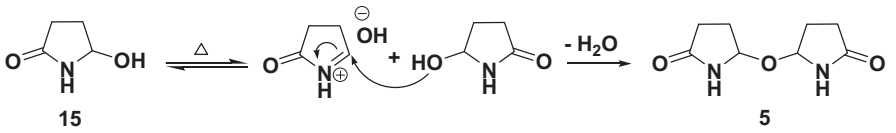
A single reported process of **4**[6] was in the milligram quantities by Raney nickel catalyzed reduction of 5-methyl-4-nitrothiophene-2-carboxylic acid **(17)** (Scheme 5). However, there was no proper synthetic procedure and characterization described.

In our approach, compound **16** was treated with EtMgBr to afford 5-ethyl-2-pyrrolidinone **(18)** which was further hydrolyzed in the presence of KOH to afford **4**. In another approach, compound **4** was prepared by Pd/C catalyzed reduction of **1** in aqueous methanol (Scheme 6).

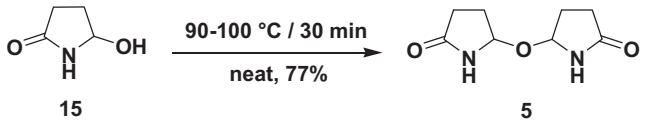
2,2′-Oxo-5,5′-bispyrrolidinyl ether (5) was observed as a key impurity during the manufacturing of 5-ethoxy-2-pyrrolidinone **(16)** via 5-hydroxy-2-pyrrolidinone **(15)** from succinimide **(14)**. It is believed that, the impurity was originated by the self condensation of compound **15** under thermal condition. The plausible mechanism for compound **5** was stated in Scheme 7.



Scheme 6. Preparation of 4-aminohexanoic acid (4).



Scheme 7. Plausible mechanism of 2,2′-oxo-5,5′-bispyrrolidinyl ether (5).



Scheme 8. Preparation of 2,2′-oxo-5,5′-bispyrrolidinyl ether (5).

The sole reported synthesis of **5**[7] involves by treating compound **16** in large volume of water under reflux condition to afford **5** with 54% yield where as in less volume of water to afford **15**. The above process was attempted to prepare **5** but obtained product was **15** instead of **5**. The desired compound formation was not observed. Furthermore, it was described that there was no molecular ion was observed for **5** in MASS analysis.[7]

However, it was required to prepare compound **5** in a pure form to meet the requirement. Hence, a simple and reproducible methodology was developed under solvent free condition with 77% of yield and good quality. In our approach, compound **15**[7] was allowed for self-condensation at 90–100 °C under neat conditions to afford **5** (Scheme 8).

Experimental Section

All melting points were uncorrected and were determined using a Reichert Thermopan apparatus. ^{1}H and ^{13}C NMR spectra were recorded by a Bruker Advance 300 MHz and Varian 500 MHz spectrometer using TMS as internal standard in D_2O and DMSO-d_6. The ^{1}H chemical shift values were reported in the δ scale relative to TMS (δ 0.00) and the ^{13}C chemical shift values were given relative to D_2O, $CDCl_3$ and DMSO-d_6 as internal standards. The IR spectra were recorded as KBr pellets using Perkin Elmer

Spectrum One Fourier Transform (FT) IR spectrophotometer. High-resolution mass spectral (HRMS) analysis was performed using the electrospray ionization (ESI) method and a Xevo G2 QTOF mass spectrometer. IR spectra were obtained from Perkin-Elmer Spectrum ES version. All raw materials were purchased from commercial sources and used without purification.

Preparation of (2-aminobut-3-enyl)malonic acid (Vigabatrin USP impurity-E) (2)

Compound **10** (8 g, 0.05 mol) was added to a solution of potassium hydroxide (3.2 g, 0.05 mol) in DM water (5 mL) at ambient temperature. The reaction mass was warmed and stirred under reflux for 6 h. The reaction mass was acidified with Conc. HCl and the water in the reaction mass was distilled out completely under reduced pressure to obtain semisolid mass. Further, a mixture of DM water (4 mL) and methanol (40 mL) was added. The reaction mass was stirred for 24 h at ambient temperature. The precipitated product was collected by filtration, dried and characterized as **2** as an off-white solid. ^{1}H NMR (300 MHz, D_2O): 2.13-2.22 (m, 1H), 2.28-2.38 (m, 1H), 3.32-3.36 (m, 1H), 3.81-3.89 (m, 1H), 5.45-5.50 (m, 2H), 5.77-5.89 (m, 1H); ^{13}C NMR (300 MHz, D_2O): 31.73, 51.41, 52.99, 122.12, 132.07, 175.25, 175.45; HRMS (ESI) calculated for $C_7H_{11}NO_4$ $(M+H)^+$ 174.0766, found: 174.0768; Melting Point: Decomposed at 152 °C; IR (KBr) 3967, 3854, 3850, 3828, 3808, 3788, 3752, 3741, 2346, 2289, 2215, 1986, 1930 cm^{-1}.

Preparation of 2-(2-oxo-5-vinylpyrrolidin-1-yl)acetic acid (3)

To a solution of **11** (10 g, 0.09 mol) in THF was added n-butyllithium (57 mL, 15% in hexanes, d = 0.68, 0.09 mol) at −65 to −70 °C under nitrogen atmosphere. Compound **12** (13.8 g, 0.09 mol) was added portion wise through a dropping funnel at −65 to −70 °C. The reaction mass was warmed to 20–30 °C and was added hexamethylphosphoramide (HMPA) (5 mL). The reaction mass was stirred for 5 h at the same temperature. Aqueous ammonium chloride was added cautiously and was stirred for 30 min at same temperature. The layers were separated and the aqueous layer was extracted with ethyl acetate. Combined organic extract was washed with brine solution. The organic layer was separated and evaporated to afford 2-(2-oxo-5-vinylpyrrolidin-1-yl) aceticacid-methylester **(13)** as pale brown colour oil (14 g). The above obtained residue was dissolved in methanol (140 mL) and sodium hydroxide (3.6 g, 0.09 mol) solution in methanol (36 mL) was added portion wise for 30 min. The reaction mixture was stirred for 16 h at 20–30 °C and the methanol was distilled out completely under reduced pressure. DM water (50 mL) was added to the obtained residue and was washed with DCM (25 mL). The separated aqueous layer was acidified with conc. HCl and washed with DCM (25 mL). The separated aqueous layer was saturated with NaCl and extracted with DCM (100 mL). The separated organic layer distilled out completely under reduced pressure to afford **3** (5 g, 33%). ^{1}H NMR (300 MHz, DMSO-d_6): 1.73–1.83 (m, 1H), 2.22–2.42 (m, 3H), 3.55 (d, 1H, J = 8.7 Hz), 4.05–4.20 (m, 2H), 5.25–5.34 (m, 2H), 5.72–5.84 (m, 1H); ^{13}C NMR (300 MHz, DMSO-d_6): 24.98, 29.28, 61.09, 118.39, 138.05,

170.02, 174.343; HRMS (ESI) calculated for $C_8H_{11}NO_3$ $(M+H)^+$ 170.0817, found: 170.0818; Melting Point: 112–115 °C; IR (KBr) 3455, 3244, 2981, 2139, 1737, 1337 cm^{-1}.

Preparation of 4-aminohexanoic acid (4) (Method 1)

Compound **18** (15 g, 0.13 mol) was added to a solution of potassium hydroxide (8.27 g, 0.13 mol) in DM water (15 mL) at ambient temperature. The reaction mass was warmed to reflux and stirred for 2 h under reflux. The reaction mass was cooled to 25–30 °C and diluted with isopropanol (135 mL). Acetic acid (8 g, 0.13 mol) was further added portion wise for 30 min. The slurry was stirred for 2 h at 20–30 °C and further 2 h at 0–5 °C. The precipitated product was collected by filtration and dried to afford **4** (13 g, 74%) as an off-white solid. ^{1}H NMR (500 MHz, D_2O): 0.97 (t, 3H, $J = 7$ Hz), 1.63–1.76 (m, 2H), 1.83–1.95 (m, 2H), 2.31–2.34 (t, 2H, $J = 7.5$ Hz), 3.19–3.24 (m, 1H); ^{13}C NMR (300 MHz, D_2O): 8.60, 24.95, 28.18, 33.46, 53.14, 181.66; HRMS (ESI) calculated for $C_6H_{13}NO_2$ $(M+H)^+$ 132.1025, found: 132.1009; Melting Point: 181–183 °C, lit.[6] 181–182 °C; IR (KBr) 2966, 2941, 2820, 2672, 2626, 2205, 1663, 1453, 1348, 1296 cm^{-1}.

Preparation of 4-Aminohexanoic acid (4) (Method 2)

Compound **1** (5 g), 10% Pd/C (0.2 g) was added to a mixture of DM water (10 mL) and methanol (50 mL) into an autoclave unit at ambient temperature. Hydrogen gas pressure of 5 Kg/cm^2 was applied and the reaction mixture was stirred by maintaining at the same pressure for 16 h at 20–30 °C. The palladium catalyst was removed by hyflo bed filtration and the solvent in the filtrate was distilled out completely under reduced pressure. Isopropanol (15 mL) was added to the obtained residue. The precipitated product was collected by filtration, dried and characterized as **4** (4.5 g, 90%) as an off-white power. The ^{1}H NMR, ^{13}C NMR and MASS spectral data were recorded and found identical (see above).

Preparation of 2,2′-oxo-5,5′-bispyrrolidinyl ether (5)

Compound **15** (10 g, 0.09 mol) was stirred at 90-100 °C under neat conditions for 30 min. The reaction mass was cooled to 30–35 °C and DCM (100 mL) was added. The reaction mass was stirred for 1 h at the same temperature. The reaction mass was further cooled to 20–30 °C. The product was collected by filtration, dried and characterized as **5** as an off-white solid (3.5 g, 77%). ^{1}H NMR (300 MHz, DMSO-d_6): 1.76–1.86 (m, 2H), 1.95–2.09 (m, 2H), 2.15–2.50 (m, 4H), 5.03 (d, 2H, $J = 3$ Hz), 8.58 (s, 2H); HRMS (ESI) calculated for $C_8H_{12}N_2O_3$ $(M+Na)^+$: 207.0746, found: 207.0762; Melting Point: 169–173 °C; IR (KBr) 3182, 3108, 2991, 2968, 2929, 2773, 1447, 1422, 1404, 1373, 1183, 1160 cm^{-1}.

Conclusion

A simple, efficient synthesis and characterization of **2**, **3**, **4** and **5**, the potential impurities of Vigabatrin have been successfully demonstrated. In addition, the possible pathways for the formation of these impurities are also described. The synthesis of these impurities not only helps in obtaining good quality of the drug substance but also helps

in establishing the impurity profile of **1** by understanding the cause of its origin. Keeping in view the regulatory importance of Vigabatrin impurities, our efforts to synthesize and characterize them effectively have proved to be beneficial.

Acknowledgement

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Supporting Information

Full experiment detail, ^{1}H NMR spectra, ^{13}C NMR spectra and HRMS. This material can be found via the "Supplementary Content" section of this article's webpage.

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