# *Bio-based building blocks from 5-hydroxymethylfurfural via 1-hydroxyhexane-2,5-dione as intermediate*

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*Martyna*, przyszłość maluje się w jasnych barwach.

# *Abstract*

This PhD thesis describes the utilization of the biomass-derived platform chemical 5-hydroxymethylfurfural (5-HMF), which can be obtained by dehydration of fructose, for the production of a wide range of useful chemicals *via* 1-hydroxyhexane-2,5-dione (HHD) as an intermediate. For this reason, an efficient procedure for the synthesis of HHD was established *via* hydrogenation of 5-HMF under hydrolytic conditions, using half-sandwich iridium complexes as catalysts. Moreover, a large-scale synthesis of HHD was performed and the target product was isolated and fully characterized including X-ray analysis.

The potential of HHD as a useful starting material for industrially-relevant chemical synthesis was tested in the base-promoted intramolecular aldol condensation. This resulted in the formation of 2-hydroxy-3-methylcyclopent-2-enone (MCP), which was further transformed into valuable cyclopentanone derivatives. In addition, an attractive approach to produce numerous *N*-substituted pyrroles *via* the Paal-Knorr synthesis in the absence of catalyst was demonstrated. Noteworthy, the high efficiency of this reaction under moderate conditions qualifies it as a *Click Reaction.*

Furthermore, an elegant protocol for the deoxydehydration of renewable triols (including those obtained from 5-HMF) was described. For this purpose, the readily accessible and cheapest rhenium source – rhenium(VII) oxide was successfully applied as catalyst under solvent-free and aerobic conditions affording the corresponding unsaturated alcohols in good to excellent yields.

# *Zusammenfassung*

Diese Dissertation beschreibt die Verwertung der biobasierten Plattformchemikalie 5-Hydroxymethylfurfural (5-HMF), die über die Dehydrierung der Fruktose zugänglich ist, für die Herstellung eines breiten Spektrums an nützlichen Chemikalien. Die Syntheseroute führt dabei über 1-Hydroxyhexan-2,5-dion (HHD) als wichtiges Intermediat. Daher wurde für die Synthese des HHD ein effizientes Hydrierungsverfahren unter hydrolytischen Bedingungen entwickelt, das durch Halbsandwich-Iridium-Komplexe katalysiert wird. Darüber hinaus wurde die Herstellung des HHD im Großmaßstab durchgeführt, das Produkt erfolgreich isoliert und vollständig inklusive Röntgenstrukturanalytik charakterisiert.

Das Potential des HHD als nützliches Startmaterial für industrierelevante chemische Synthesen wurde in der basischen intramolekularen Aldol-Kondensation getestet. Dies führte zur Bildung des 2-Hydroxy-3-methylcyclopent-2-enon (MCP), welches weiter in wertvolle Cyclopentanon-Derivate umgewandelt wurde. Daneben wurden verschiedene *N*-substituierte Pyrrole durch die Paal-Knorr-Synthese unter Abwesenheit eines Katalysators hergestellt. Die hohe Effizienz dieser Reaktion bei gleichzeitig milden Bedingungen qualifiziert sie als *Click-Reaktion*.

Außerdem wurde ein eleganter Weg für die Deoxyhydrierung biobasierter Triole (einschließlich der aus 5-HMF erhaltenen) beschrieben. Zu diesem Zweck wurde kommerziell erhältliches und preisgünstigstes Rhenium(VII)-oxid erfolgreich als Katalysator unter lösungsmittelfreien und aerobischen Bedingungen eingesetzt. Dabei konnten die korrespondierenden ungesättigten Alkohole in guten bis exzellenten Ausbeuten erhalten werden.

# *Table of Contents*

# *Abbreviations*

| | |
|---|---|
| Ac | acetyl |
| $Ac_2O$ | acetic anhydride |
| AcOH | acetic acid |
| Bu | butyl |
| Cat. | catalyst |
| Conc. | concentration |
| Conv. | conversion |
| Cp | cyclopentadienyl |
| Cy | cyclohexyl |
| DMF | dimethylformamide |
| DMSO | dimethylsulfoxide |
| Et | ethyl |
| *et al.* | lat. *et alia* – eng. and others |
| Eq. | equivalent |
| GC-MS | gas chromatography coupled with mass spectrometry |
| HR-MS | high-resolution mass spectrometry |
| $^{i}Pr$ | isopropyl |
| Isol. | isolated |
| $KO^{t}Bu$ | potassium *tert*-butoxide |
| M | mol/L |
| Me | methyl |
| MeCN | acetonitrile |
| MeOH | methanol |
| MIBK | methyl isobutyl ketone |
| MOF | metal-organic framework |
| NMR | nuclear magnetic resonance |
| $NNS^{Et}$ | 2-(Ethylthio)-*N*-((pyridin-2-yl)methyl)ethan-1-amine |
| PET | polyethylene terephthalate |
| Ph | phenyl |
| Pr | propyl |
| PTSA | *para*-toluenesulfonic acid |
| Red. | reductant |
| Ref. | reference |
| RT | room temperature |
| Subs. | substrate |
| $^{t}Bu$ | *tert*-butyl |
| TEAB | tetraethylammonium bromide |
| Temp. | temperature |
| THF | tetrahydrofuran |
| wt | weight |
| w/w | weight by weight |
| Xantphos | 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene |

# *List of Figures*



# *List of Schemes*

# *List of Tables*

# 1. 5-hydroxymethylfurfural, a Prominent Platform Chemical Obtained from Biomass

Extensive utilization of fossil fuel reserves and as a consequence of this the global warming issues are currently the major challenges our modern society needs to face.[1-3] Considering the fact that more than 90% of chemicals our lives depend upon, such as polymers, pharmaceuticals, detergents or food additives are currently derived from crude oil,[4] development of new sustainable technologies with the aim to produce chemicals from renewable resources is crucial. Biomass is the most attractive, low-cost feedstock produced by Nature and therefore readily available around the world.[5-9] Unlike other renewable sources like solar, wind, hydroelectric and geothermal energy, biomass contains organic carbon and has a great potential to substitute oil and coal in the production of fuels and chemicals. Lignocellulosic biomass is one of the most abundant feedstock widely available in the form of nonedible forestry or agro waste.[10] Depending on the class and origin of the plant, polymeric lignocellulose is comprised of three basic materials in various ratios i) 30-50 wt% cellulose, ii) 20-40 wt% hemicellulose and iii) 10-20% lignin.[11] Special attention has been given to the conversion of lignocellulose or its constituents to widely applicable so-called *Platform Chemicals* of high industrial potential (Figure 1).[8] Platform chemical is an intermediate molecule, which is produced from biomass at a competitive cost and can be transformed to a number of valuable intermediates, preferably in a large scale process.

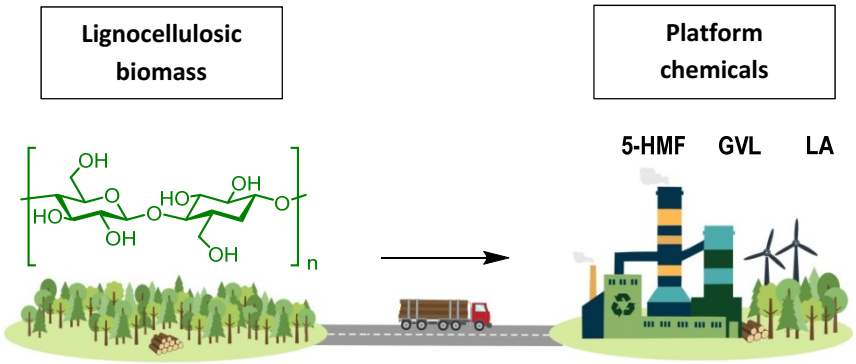



**Figure 1**. Conversion of lignocellulose to valuable platform chemicals.

5-Hydroxymethylfurfural (5-HMF) is one of the most valuable platform chemical included in the "Top 10" list of chemicals obtained from biomass in the report made for the U.S. Department of Energy.[12] It can be obtained in relatively high yields from fructose or in lower yields from glucose or even cellulose.[19] 5-HMF is a furan-type compound which has retained all six carbons from the hexose and contains two functional groups: an aldehyde

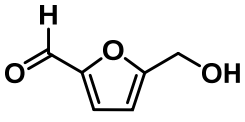
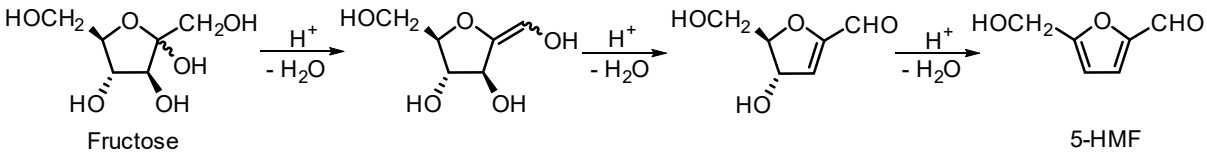



**Figure 2**. Chemical structure of 5-hydroxymethylfurfural (5-HMF).

and a hydroxymethyl group (Figure 2). 5-HMF is a natural compound, which is present on a daily basis in the human diet with an approximately intake of 30-150 mg per person.[13] In particular, high concentrations of 5-HMF (exceeding 1g/1kg) were found in dried fruits, caramel products and coffee. 5-HMF is formed during thermal treatment of food containing carbohydrates including caramelization[14] and Maillard reactions.[15] Human exposure to 5-HMF has initiated a serious debate of its potential health hazard. However, according to the opinion of the German Federal Institute for Risk Assessment (Bundesinstitut für Risikobewertung, BfR), 5-HMF does not possess toxic properties and was determined to be safe for the human body.[16] On the contrary, 5-HMF has been indicated as a substance with positive effects on health, aiding in the prevention of alcohol-related liver damage[17] and neurodegenerative diseases.[18]




**Scheme 1**. Cyclic pathway of fructose dehydration to 5-HMF.

In general, there are three possible mechanisms of 5-HMF formation from hexoses; however no conclusive mechanistic proof has been reported yet. The first and most common route is an acid-catalyzed dehydration, in which three water molecules are removed from the corresponding sugar molecule e.g. fructose (Scheme 1). The second one describes production of 5-HMF from hexoses *via* a Maillard reaction in the presence of amino acids and amines. The third mechanism involves $C_3$ sugar degradation products (pyruvaldehyde and glyceraldehyde) in the formation of 5-HMF *via* aldol condensation. Mechanistic aspects of formation of 5-HMF from sugars have been reviewed in details by several groups and therefore will not be the subject of this work.[19-22]

The first reports on 5-HMF synthesis by Güll[23] and Kiermayer[24] can be dated back to 1895. Since then, a significant growth in interest on 5-HMF formation and applicability resulted in

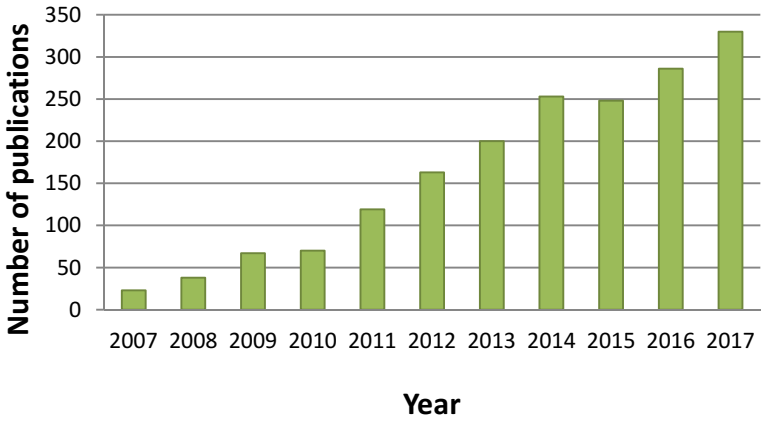



**Figure 3**. Number of publications on 5-HMF from 2007 to 2017. Source: Web of Science (keyword: 5-hydroxymethylfurfural).

an enormous number of publications with an evident peak in the last years (Figure 3). As a consequence of this, recent advances in the synthesis and utilization of 5-HMF were reviewed by several groups.[19-22, 25-27]

In particular fructose is a highly efficient carbohydrate feedstock for the selective formation of 5-HMF in good to excellent yields (up to 99%). However, in most cases, the reported yields were calculated based on GC-MS while no product isolation was performed. Therefore, a summary of reported 5-HMF syntheses including isolated yields seems to give a more realistic impression. In addition, two additional criteria have been taken into account: i) availability of the catalyst, ii) reactions conducted on at least one-gram scale. Conversion of fructose to 5-HMF using different catalytic systems is presented in Table 1. The catalytic strategies utilized until the 1990s focused mainly on the use of mineral acids in water such as hydrochloric and sulfuric acids.[28-30] However, the reported 5-HMF yields were usually low (around 30%), mainly due to its rehydration resulting in the formation of levulinic acid and formic acid. Another major byproduct is a brown, insoluble polymeric material usually referred to as humins. These humins are formed by aldol addition/condensation of 5-HMF with itself and with sugars.[31] Van Bekkum and co-workers reported by far the highest isolated yield of 5-HMF in water, in which case a yield of 48% at 72% conversion was obtained by reacting 4.5 wt% fructose in water with 320 mol% HCl at 90 $^{o}$C for 7 h. In general the yield of 5-HMF is higher and the amount of humin lower if the fructose concentration is

**Table 1**. Dehydration of fructose to 5-HMF.

| Fructose (wt%) | Catalyst | Cat. loading | Solvent | Temp. ($^{o}$C) | Time | Conv. (%) | Isol. yield (%) | Ref. |
|---|---|---|---|---|---|---|---|---|
| 4.5 | HCl | 320 mol% | $H_2O$ | 90 | 7 h | 72 | 48 | 32 |
| 9 | $FeCl_3/Et_4NBr$ | 10 mol%/18 mol% | NMP | 90 | 2 h | 100 | 78 | 34 |
| 4 | HBr/silica | 100 mol% | THF | 30 | 24 h | na | 95 | 35 |
| 5 | Amberlyst-15/$Et_3NHCl$ | 10 wt%/10 mol% | MeCN | 100 | 2.5 h | na | 69 | 36 |
| 30 | HCl | 0.25 M | $H_2O$/DMSO MIBK/2-BuOH | 180 | 2.5-3 min | 87 | 71 | 37 |
| 9 | Amberlyst-15 | 10 wt% | $Et_4NBr$:$H_2O$ | 100 | 15 min | na | 91 | 38 |
| 5.5 | $BF_3O(Et)_2$ | 10 mol% | DMC:$Et_4NBr$ | 90 | 5 h | 100 | 76 | 39 |
| 10 | $WCl_6$ | 10 mol% | [bmim]Cl/THF | 50 | 42 h | na | 55 | 40 |

na- not available

kept low. However, these low concentrations lead to uneconomic productivities. In the last 30 years further investigations revealed significant improvements in the formation of 5-HMF from hexoses by changing reaction media. Based on this, catalytic systems can be divided into three categories: i) traditional single-phase systems including organic solvents, ii) biphasic systems, iii) systems utilizing ionic liquids as solvents. Especially DMSO has been

extensively studied as a solvent in single-phase systems for fructose dehydration. For example, Ishida and co-workers reported 95% yield of 5-HMF in the presence of 2.5 mol% $LaCl_3$ at 100 $^oC$ after 4 hours.[33] However, due to the high boiling point of DMSO, the isolation of 5-HMF from the reaction mixture has not been reported in the literature. Tong *et al*. performed the $FeCl_3/Et_4NBr$ catalyzed dehydration of fructose in *N*-methylpyrrolidine (NMP) and found an 5-HMF yield of 78% at full conversion of the starting material after 2 hours.[34] The pure product was isolated after removing the solvent by distillation under reduced pressure, extraction of the remaining mixture with ethyl acetate, washing the extracts with water followed by another distillation of the organic phase. The dehydrations performed in different solvents such as DMF and DMSO showed lower 5-HMF yields of 62% and 53% respectively. Vairaprahash and co-workers examined fructose dehydration in THF.[35] A typical experiment was performed at 30 $^oC$ with both fructose and HBr loaded on the silica at 1:1 ratio. The authors claimed an isolated 5-HMF yield of 95% after 24 h in a three-cycle process (reaction medium was exchanged with fresh solvent in an interval of 8 h). The authors attributed such a high 5-HMF yield to the reduction of intermolecular interactions between fructose and intermediates, thus inhibiting humins formation after fructose loading on the solid support. On the other hand, this approach suffers from requiring stoichiometric amounts of HBr and the use of catalytic systems is more desired. Work by Brown *et al*. on fructose dehydration in acetonitrile at 100 $^oC$ using a combination of Amberlyst-15 and $Et_3NHCl$ as the catalysts revealed 69% yield of 5-HMF after 2.5 h.[36] Interestingly, when DMSO was used as a solvent, quantitative yields of 5-HMF were achieved as estimated by $^1H$ NMR; however, separation of 5-HMF from DMSO proved to be impossible. An important breakthrough in terms of reaction times came with the use of biphasic systems. The group of Dumesic has developed the HCl catalyzed dehydration of fructose in a two phases four solvents system and obtained 5-HMF in 71% yield after 3 minutes.[37] Extensive studies revealed the best results when 5-HMF was continuously extracted from the aqueous medium consisting of 8:2 (w/w) water/DMSO by an organic phase mixture of 7:3 (w/w) MIBK/2-BuOH and isolating 5-HMF by solvent evaporation. Recently, some additional work was published on fructose degradation using easily crystallized and low-volatility solids as an efficient reaction media. This approach allowed processing with solids such as tetrapropylamonium bromide ($Pr_4NBr$) or tetraethylammonium bromide ($Et_4NBr$) by melting them at the prevailing reaction conditions. Furthermore, the reaction media crystallize by cooling and 5-HMF can be easily isolated by extraction and solvent evaporation. Following this protocol, Simeonov *et al*. reported an efficient method for 5-HMF production from fructose by applying $Et_4NBr$ as a reaction media in the presence of 10 wt% of Amberlyst-15.[38] 5-HMF yields of up to 91% were attained after 15 minutes at 100 $^oC$. The experiments revealed that the addition of 10 wt% water to the reaction medium was crucial to accomplish a clean transformation. The group of Aricò investigated the conversion of fructose in dimethyl carbonate (DMC) using TEAB as a cosolvent.[39] The experiments were carried out at 90 $^oC$ with 10 mol% borontrifluoride diethyl etherate resulting in an isolated 5-HMF yield of 76% after 5 h. Slightly lower yield (70%) was achieved by applying 10 wt% Amberlyst-15 under the same

conditions. It is noteworthy that in the last 10 years, several efforts were made to improve the sugars dehydration by the use of ionic liquids. However, development of an efficient method for the isolation of 5-HMF from ionic liquids and their further reusability still remains a great challenge. To overcome this, Zhang and co-workers demonstrated the production of 5-HMF in biphasic system consisting of THF and 1-butyl-3-methylimidazolium chloride ([bmim]Cl).[40] Several metal chloride catalysts were tested for fructose dehydration at low temperatures (RT to 50 °C), where the best results (72% selectivity towards 5-HMF) were achieved with 10 mol% $WCl_6$ at 50 °C after 4 h. Similar results were achieved in the presence of solid acid additives such as zeolites (H-Y). In addition, a large scale experiment was performed starting from 10 g of fructose in order to isolate pure 5-HMF (Figure 4). It is important to emphasize that 5-HMF was extracted into the THF phase and the solvent was continuously removed, while fresh THF was constantly added (4 L per 6 h). 5-HMF was isolated simply by evaporation of the solvent which was reused, whereas a new portion of fructose (10 g) was added every 6 hours. In total, 26.7 g of 5-HMF (55% yield) was obtained after 7 cycles.

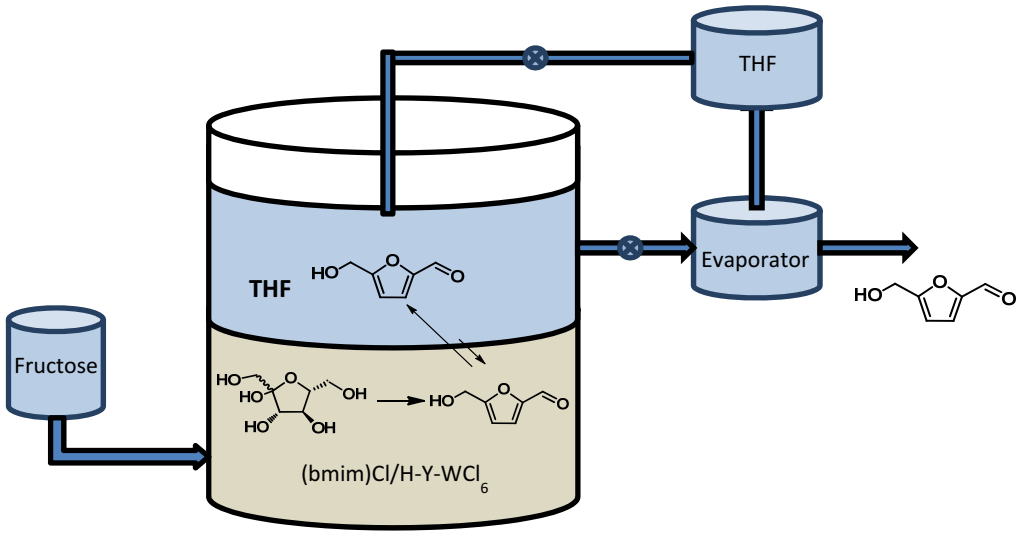



**Figure 4**. Continuous batch process for the conversion of fructose to 5-HMF. Adapted from ref. 40.

Besides the application of fructose in 5-HMF synthesis, other hexoses as well as di- and polysaccharides have been extensively investigated. Especially, glucose was found to be an attractive starting material due to its lower cost and its availability from lignocellulosic biomass. However, typically lower yields of 5-HMF are obtained from glucose due to the necessity of its isomerization to fructose in the first step. Moreover, only a limited number of studies report the isolation of 5-HMF using glucose as a starting material as shown in Table 2. Going back as far as the last half-century, it was proposed that the combination of catalytic amounts of weak acid and weak base provides higher 5-HMF yields compared to reactions with acid alone. Mednick was the first to report the conversion of glucose to 5-HMF followed by the isolation of the target product.[41] He was able to obtain a 46% 5-HMF yield after 20 min (with 33 min additional warm-up time), by using pyridine-phosphoric acid system in $H_2O$: dioxane (1:1 v/v) at the temperature range of 200-230 °C. The intensive

research activities on the transformation of glucose have led to the identification that Lewis acids promote isomerization step and provide higher 5-HMF yields particularly in ionic liquids. Zhang and co-workers reported high 5-HMF yields of 68-70% by using 10 mol% of $CrCl_2$ and 1-ethyl-3-methylimidazolium chloride as a solvent.[42] Further improvements in the conversion of glucose to 5-HMF were reported by Binder *et al*. using *N,N*-dimethylacetamide (DMA) as a solvent.[43] An outstanding 80% 5-HMF yield was reached with 6 mol% $CrCl_2$ in a DMA solution of sodium bromide at 100 $^{o}$C after 5 h. However, the use of toxic chromium salts and difficulties in the separation and isolation of 5-HMF stimulated researches to find alternative processes. In 2012, Dumesic and co-workers made an important advance in the synthesis and isolation of 5-HMF from glucose.[44] The authors demonstrated that the combination of Lewis acid/Bronsted acid ($AlCl_3$/HCl) in a biphasic system provides better selectivity towards 5-HMF. The reported isolated yield was 60% when water and 2-sec-butylphenol were applied as solvents. It was shown that 97% of the produced 5-HMF was extracted to the organic layer, whereas acid catalysts remain in the aqueous phase. The reusability of the catalytic system was also tested and no significant decreases in activity

**Table 2**. Dehydration of glucose, sucrose and inulin to 5-HMF.

| Subs. | Subs. conc. (wt%) | Catalyst | Cat. loading | Solvent | Temp. ($^{o}$C) | Time | Conv. | Isol. yield (%) | Ref. |
|---|---|---|---|---|---|---|---|---|---|
| glucose | 20 | Pyridine/$H_3PO_4$ | 0.3 M/0.2 M | $H_2O$: dioxane | 200-230 | 20 min | na | 46 | 41 |
| glucose | 5 | $AlCl_3$, HCl | 1.5 mol% | $H_2O$ : SBP | 170 | 40 min | 91 | 60 | 44 |
| sucrose | 9 | $FeCl_3$/$Et_4NBr$ | 10 mol%/18 mol% | NMP | 90 | 4 h | na | 40 | 34 |
| inulin | 16 | Amberlyst-15 | 10 wt% | $Et_4NBr$ : $H_2O$ | 100 | 15 min | na | 55 | 38 |

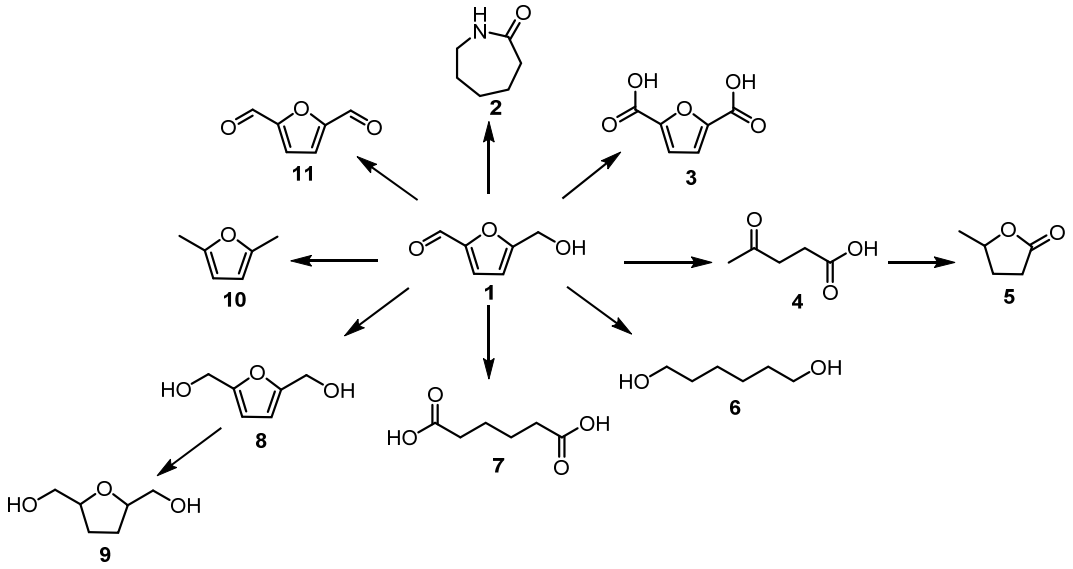
na- not available

were observed after four consecutive runs. Some catalytic systems reported for the dehydration of fructose have been successfully adapted to sucrose and inulin. In the same system as applied for fructose (i.e. $FeCl_3$-$Et_4NBr$ catalyst in NMP, 90 $^{o}$C), Tong *et al*. performed reactions with sucrose, reporting 40% 5-HMF yield after 3 hours.[34] This result was expected, since around 80% 5-HMF was obtained from fructose and only 3% was achieved from glucose. Afonso and co-workers used an established catalytic strategy for 5-HMF synthesis from fructose in the dehydration of the polysaccharide inulin.[38] After extraction, filtration and evaporation of the solvent, the isolated 5-HMF yield was 55% with a purity of 98%.

The biggest challenge still to overcome in the large-scale production of 5-HMF is the use of readily available feedstocks such as cellulose, starch or preferably lignocellulose. Currently, 5-HMF is only produced on a scale of a few hundred tons per year by Ava-Biochem as a side product of sugar carbonization and hence relatively expensive (www.ava-biochem.com). Therefore, the development of sustainable technologies converting lignocellulosic biomass is necessary to reach a cost price of 5-HMF of around $1-2/kg.

Recently, many attempts were performed to convert 5-HMF in situ to more stable derivatives. In 2010, Avantium Chemicals from the Netherlands began with the pilot project called "YXY" for production of furan-based compounds from bio-based feedstock. The patented catalytic system is able to convert carbohydrates to stable 5-HMF ether derivatives.[45] Further catalytic oxidation of 5-HMF ether compounds leads to the formation of 2,5-furan-dicarboxylic acid dimethyl ester, a promising precursor for the production of bio-based polymers.[46,47] Interestingly, extensive studies on the furan-based biopolymer PEF (Polyethylene 2,5-furandicarboxylate) revealed similar properties to its petrochemical analogue PET and therefore became the desired substitute for many industrial companies like Coca-Cola or Danone. Avantium and BASF have started a joint-venture aiming to build a large scale production plant for FDCA and PEF in Antwerp. Mascal and co-workers developed the production of 5-chloromethyl-furfural (CMF), another interesting molecule that is more stable than 5-HMF.[48] What makes this production more important is the direct conversion of cellulose to CMF in isolated yields higher than 80%. The experiments were carried out in apparatus for continuous extraction containing water-1,2-dichloroethane biphasic system. The HCl-catalyzed conversion of carbohydrates occurs in 30 h at 65 $^{o}$C in the presence of 5 wt% LiCl. Furthermore, CMF can be easily converted to 5-HMF in 86% yield by hydrolysis in a boiling water for 30 second.[49]

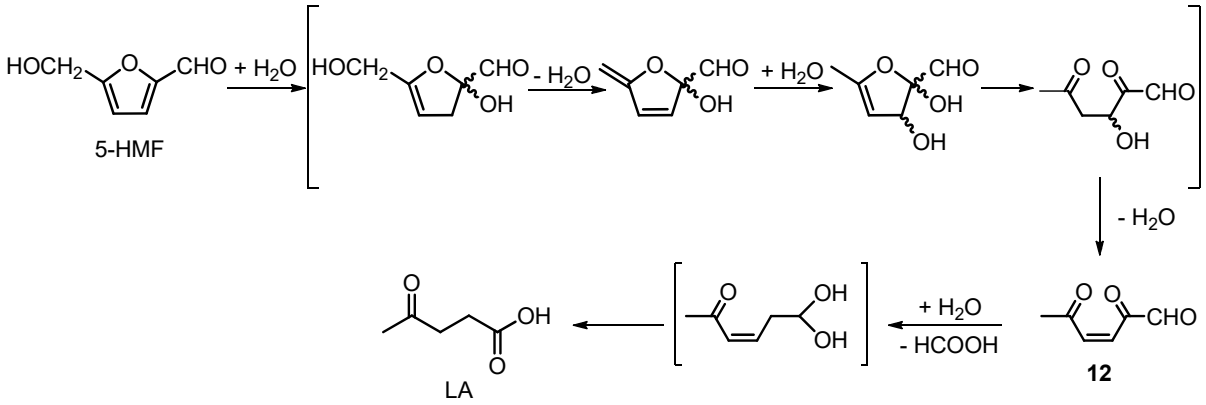
These efforts aimed at the development of a sustainable process for the production of 5-HMF, raises the question: "Why is 5-HMF such an important chemical?". As was already mentioned above, 5-HMF was qualified as a relevant platform chemical, which means it is a very valuable building block with a wide range of applications. Within this section the focus will be on the conversion of 5-HMF to the most beneficial follow-up products and their importance in the substitution of non-renewable analogues (Scheme 2). In 2011, de Vries, Heeres and co-workers reported an excellent work on the conversion of 5-HMF to caprolactam (CA, **2**), a monomer for Nylon-6 production.[50] Starting from 5-HMF, different pathways were investigated using various heterogeneous catalysts to produce 1,6-hexanediol (HDO, **6**) as an intermediate product. The diol was converted to caprolactone in quantitative yield by a double Oppenauer oxidation using a catalyst formed in situ from [{Ru(cymene)$Cl_2$}$_2$] and 1,1'-bis(diphenylphosphino)ferrocene (DPPF). In the last step, caprolactam is obtained from caprolactone by well-established ammonia treatment widely used on industrial-scale. Overall caprolactone was synthesized from 5-HMF in four steps with 86% selectivity. Therefore, this approach opens a new direction for the production of bio-based polymers of high industrial potential. There is also a growing interest in the



**Scheme 2**. Conversion of 5-HMF to valuable chemicals.

synthesis and applications of bio-derived 2,5-furandicarboxylicacid (FDCA, **3**), as discussed before. Detailed studies on the bio-based PET analogues revealed superior barrier properties and higher glass transition temperatures compared to the traditional PET polymer.[51] Moreover, FDCA was highlighted in the list of "Top Value Added Chemicals from Biomass" reported by the U.S. Department of Energy as an important platform chemical, which can be utilized for the production of valuable products such as succinic acid.[5] Therefore, efficient strategies for the conversion of 5-HMF to FDCA have been intensively investigated. Initially, 5-HMF was converted to FDCA with the use of stoichiometric amounts of strong oxidants (e.g. $N_2O_5$, $KMnO_4$, $HNO_3$).[52] However, molecular oxygen has been identified as the most efficient stoichiometric oxidant. Recently, Shen *et al*. published the work on the synthesis of FDCA under base-free conditions catalyzed by platinum nanoparticles deposited on Ni/AC (AC- active carbon).[53] The FDCA yield of 98% was achieved after 15 hours at 100 $^{o}$C in water under 10 bar of oxygen pressure. A near quantitative yield of FDCA (99%) was reported by Pingkai and co-workers under similar conditions, but at 4 bar of $O_2$ in the presence of $Pt/ZrO_2$ heterogeneous catalyst.[54] However, in both cases given yields were based on the direct analysis of reaction mixture and isolated yields were not reported. It should be noted that oxidation reactions under ambient air have also been reported, however to achieve excellent yields high pressures of air are required.[55,56] Levulinic acid (LA, **4**) is the most important non-furanic $C_5$ compound obtained from 5-HMF, which was also included in the list of "TOP 12 Chemicals".[5] However, LA can be more economically produced by direct treatment of lignocellulosic biomass with dilute sulfuric acid at 200 °C. LA was found to be an important building block for the synthesis of value-added chemicals such as pharmaceuticals, pesticides, cosmetics and food additives.[57] Moreover, some LA derivatives like γ-valerolactone, ethyl levulinate or methyltetrahydrofuran have been reported as good candidates for fuel applications.[58] The formation of LA from sucrose in the presence of mineral acids was discovered in the middle of the 19th century by German scientist Mulder.[59] However, a strong growth in the interest toward the synthesis and applications of

**4** appeared in the 21th century. Several mechanisms have been proposed for the formation of LA from 5-HMF, but no definitive proof has been published.[60-62] The mechanism proposed by Šunjić describes the production of LA from 5-HMF in the rehydration process consisting of the addition of a water molecule to the C2-C3 furanic double bond followed by a dehydration/hydration sequence to form unstable tricarbonyl intermediate **12**, which decomposes to give LA and formic acid in equimolar amounts (Scheme 3).[60] Flannely *et al*. reported an LA yield of 71% using fructose as a starting material by applying 2 wt% $H_2SO_4$ in water at 150 °C for 2 h.[63] Doherty and co-workers performed research on the degradation of glucose with 0.1 M $H_2SO_4$ at 200 °C.[64] The highest LA yield of 45% was obtained after 30

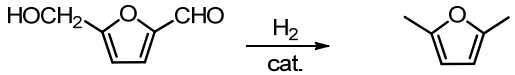



**Scheme 3**. Formation of LA from 5-HMF proposed by Šunjić.

minutes. It should be noted that the formation of humins (major byproduct) is unavoidable under aqueous acidic conditions, as already mentioned above. Obviously, the most attractive route concerns the direct conversion of $C_6$ sugars as well as lignocellulosic biomass to LA. An industrial process was developed by the company Biofine; it provides over 60% yield of LA from lignocellulosic biomass by using $H_2SO_4$ as the catalyst.[65] One of the most valuable platform chemical obtained from LA is γ-valerolactone (GVL, **5**). Conversion of LA to GVL could proceed *via* two different routes: i) hydrogenation of LA (or its esters); ii) dehydration to angelica lactones followed by hydrogenation. In practice only the first route is used. Catalytic systems for the production of GVL were recently reviewed.[66-68] Besides the application of HDO (**6**) in the synthesis of caprolactone, it has been also extensively utilized in the production of adhesives, coatings and polyesters.[69] 5-HMF has been converted to HDO in two-steps by de Vries, Heeres and co-workers in 86% overall yield.[70] Direct formation of HDO from 5-HMF requires harsh conditions and usually lower yields are obtained. Tuteja *et al*. reported 43% yield of HDO from 5-HMF in one-step by applying reusable Pd/ZrP catalyst and HCOOH as hydrogen source at 140 °C for 21 h under atmospheric pressure.[71] Another important molecule that can be obtained from 5-HMF *via* FDCA (**3**) is adipic acid (**7**), one of the two monomers for the production of Nylon 66. Rennovia patented an efficient protocol to obtain adipic acid from FDCA *via* two steps: i) $Pd/SiO_2$ catalyzed hydrogenation of FDCA at 140 °C for 3 h in acetic acid resulting in the formation of 2,5-tetrahydrofuran-dicarboxylic acid in 88% yield; ii) subsequent ring-opening catalyzed by $Pd/SiO_2$ in acetic acid under hydrogen pressure at 160 °C in the presence of

halogen source (0.2 M of HI) forming adipic acid in quantitative yield.[72] 2,5-Bishydroxymethylfuran (BHMF, **8**) represents furan-containing derivative with many potential applications in polymerization or cycloaddition chemistry. For example, BHMF was used as a monomer for the synthesis of poly(2,5-furandimethylene succinate) (PFS) by the reaction of **8** with succinic acid.[73] Depending on the type of the reaction, BHMF can serve as a valuable intermediate in oxidation or reduction processes. There are many reports on the hydrogenation of 5-HMF to BHMF using homogeneous and heterogeneous catalysts.[74] Recently, Puylaert *et al*. performed hydrogenation of 5-HMF by using 0.5 mol% $Ru(NNS^{Et})(PPh_3)Cl_2$ complex in the presence of 5 mol% KO$^t$Bu under relatively mild reaction conditions. The experiments were carried out at 80 $^oC$ and 30 bar of $H_2$ resulting in an isolated BHMF yield of 93% after 1 hour.[75] Harsher hydrogenation conditions including higher pressures (over 50 bar $H_2$) and the use of supported metal catalysts lead to complete hydrogenation of the furanic ring to produce tetrahydro-2,5-furandimethanol (THFDM, **9**). Near quantitative yields of THFDMF were reported in the reactions catalyzed by Raney-Ni[49] or Pd/C.[76] Furthermore, THFDM can be converted into 1,6-hexanediol[50] or utilized as a solvent or monomer for the synthesis of polyesters.[77] Recently, direct synthesis of 2,5-dimethylfuran (2,5-DMF, **10**) from 5-HMF has received more attention. Intensive studies on 2,5-DMF properties revealed superior energy density and octane number comparable to the ones obtained from bioethanol.[78] Moreover, higher boiling point and immiscibility with water favor 2,5-DMF in the considerations as a modern liquid biofuel for transportation.

**Table 3**. Reduction of 5-HMF to 2,5-DMF.




5-HMF 2,5-DMF

| Reductant | Catalyst | Conditions | Yield (%) | Ref. |
|---|---|---|---|---|
| Hydrogen | Cu-Co/$Al_2O_3$ | 30 bar, 220 $^oC$, THF, 8 h | 78 | 79 |
| Hydrogen | Pd-Au/graphite | 10 bar, 150 $^oC$, THF, 4 h | 82 | 80 |
| Hydrogen | Pd-Zr MOF | 10 bar, 160 $^oC$, THF, 3 h | 99 | 81 |
| Hydrogen | Ni/C | 6 bar, 150 $^oC$, EtOH, 15 h | 90 | 82 |
| Methanol | $Cu_3Al$-A | 10 bar, 240 $^oC$, MeOH, 1.5 h | 97 | 83 |
| Isopropanol | Ru on N-doped carbon | 20 bar, 160 $^oC$, $^i$PrOH, 8 h | 55 | 84 |
| Cyclohexanol | Ni-Cu alloy | 240 $^oC$, 1,4-dioxane | 98 | 85 |

Recent advances in catalytic reduction of 5-HMF to 2,5-DMF are summarized in Table 3. In general, the use of heterogeneous systems at high temperatures (>150 $^oC$) are required for this transformation. For example, Kim and co-workers demonstrated that Pd-Zr MOF deposited on sulfonated graphene oxide reduces 5-HMF into 2,5-DMF in 99% yield after 3 h at 160 $^oC$ and 10 bar of hydrogen in THF.[81] In addition, the direct conversion of fructose and

glucose led to the formation of 2,5-DMF in a 71% and 45% yield respectively. Recently, much research activity has been addressed to the selective oxidation of 5-HMF resulting in the formation of 2,5-diformylfuran (DFF, **11**), an interesting building block with a variety of applications. DFF was found to be an excellent starting material for the synthesis of polymers, pharmaceuticals, ligands and fungicides.[86,87] Similarly to the synthesis of FDCA, the most efficient oxidant for the conversion of 5-HMF to DFF is molecular oxygen. Other methods involved the utilization of enzymes[88] or photocatalytic systems.[89] Recently, the group of Dibenedetto performed extensive research on $Mg/CeO_2$ catalyzed oxidation of 5-HMF.[90] The experiments were carried out in water at 100 $^{o}$C by using 9 bar of $O_2$ and showed high selectivity (96%) toward DFF at 98% conversion of 5-HMF after 15 hours. It should be noted that the oxidation of 5-HMF under the same conditions but at 130 $^{o}$C led to 90% selectivity towards 2-formyl-5-furancarboxylic acid (FFCA).

The chemistry of 5-HMF is an area of a great potential for the substitution of fossil resources. The development of sustainable production of 5-HMF and its derivatives from biomass is crucial to fulfill future generation's needs. Intensified research in both academic and industrial sectors gives hope that in forthcoming years the production of everyday products such as plastics, solvents, cosmetics, paints and pharmaceuticals will be possible from renewable sources.

# 2. Synthesis of 1-Hydroxyhexane-2,5-dione

Among various useful chemicals obtained from 5-HMF, 1-hydroxyhexane-2,5-dione (HHD) has become the focus of interest for our group. HHD is a ring-opening product, which has retained all six carbons that were present in 5-HMF (Figure 5). Moreover, the presence of two carbonyl groups and one hydroxyl group in the alkyl chain makes it an appropriate precursor for the synthesis of valuable follow-up products.

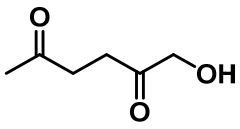
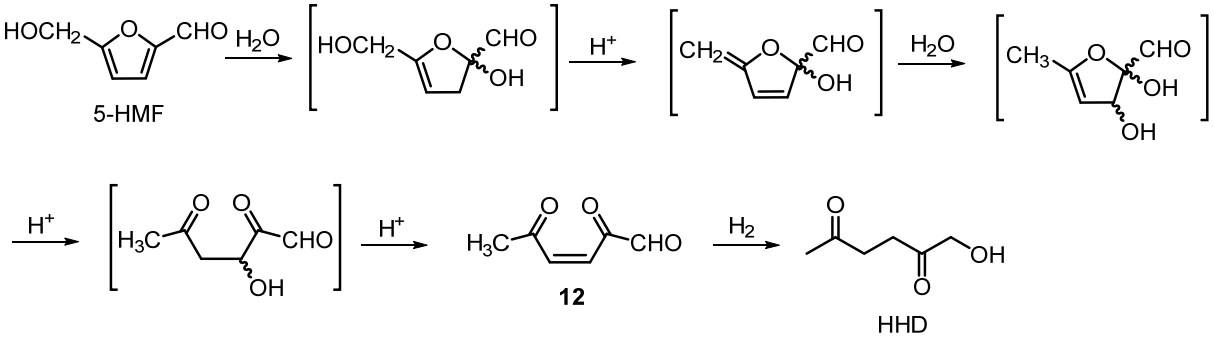



**Figure 5**. Chemical structure of 1-hydroxyhexane-2,5-dione (HHD).

It is possible to convert 5-HMF into HHD by hydrogenation/hydrolytic ring opening reaction in aqueous phase using various heterogeneous and homogeneous catalysts.[91-103] However, reports on isolation and purification of HHD are hardly available. In this chapter, different catalytic strategies for the synthesis of HHD from 5-HMF as well as mechanistic aspects of this transformation will be discussed.

## *2.1 Hydrogenation/Hydrolytic Ring Opening of 5-HMF Catalyzed by Heterogeneous Catalysts*

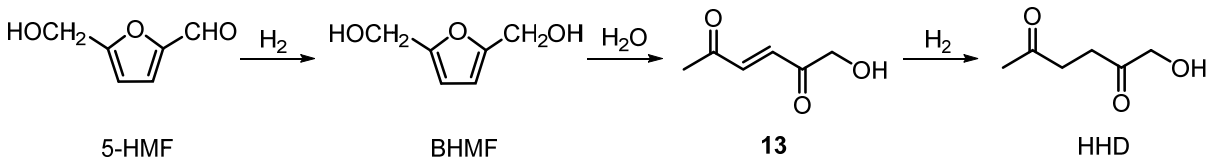
The first publication regarding HHD synthesis dates back to 1991.[91] Descotes and co-workers reported the Pt/C catalyzed formation of HHD in water containing 15 wt% of oxalic acid. The reaction was carried out at 140 °C under 30 bar of $H_2$ for 3 h resulting in 60% of HHD. When 70 bar $H_2$ was applied, a decrease in HHD yield was observed (to 51%). A separate experiment under the same conditions, but in the presence of 75 wt% oxalic acid in water afforded only 31% of HHD. In addition to these experiments a possible mechanism for the conversion of 5-HMF to HHD was proposed (Scheme 4). Under acidic conditions 5-HMF undergoes rehydration followed by ring-opening to form the stable intermediate **12,** which was confirmed by $^{13}C$ NMR. In a subsequent step, the double bond and aldehyde functionalities are hydrogenated selectively in the presence of the ketone groups leading to the the formation of HHD. The group of Bekkum investigated hydrogenolysis of 5-HMF in




**Scheme 4**. Proposed pathway for HHD synthesis by Descotes.

water using 10% Pd/C under mild reaction conditions (1 bar $H_2$, 60 °C).[92] The experiments showed that adding small amounts of concentrated HCl was necessary to obtain HHD. The reported HHD yield after 410 min was 28%, at 98% conversion of 5-HMF. The main product obtained under these conditions was BHMF (47%). Interestingly, when the reaction was performed in a biphasic solvent system, consisting of water and toluene in a 2:1 ratio, considerable HHD yield improvement of up to 68% was revealed. Heeres, de Vries and co-workers reported the use of a bimetallic Rh-Re system supported on silica for the hydrogenation of 5-HMF to HHD.[49] Initially, the reaction was carried out at 120 °C using 10 mol% of the catalyst in water at 10 bar $H_2$ for 1 hour. After this time, the pressure was raised to 80 bar of $H_2$ and the reaction was stirred for 17 hours resulting in 81% selectivity toward HHD at full conversion of the starting material. HDO, at a yield of 6%, was mentioned as one of the byproducts. Ohyama *et al*. reported a gold nanoparticles catalyzed hydrogenation of 5-HMF in aqueous solutions.[93] Depending on the metal oxide that was used as a support, BHMF and/or HHD were obtained by applying 38 bar of $H_2$ at 140 °C. The best result of 57% HHD yield was achieved using 1 wt% $Au/TiO_2$ combined with 4 wt% of $SO_3$, which acted as a Brønsted acid. A later publication by the same group reported a 60% yield of HHD at 81% 5-HMF conversion in the reaction catalyzed by gold nanoparticles supported on $Nb_2O_5$.[94] For

this purpose, higher pressures (80 bar of $H_2$) and addition of catalytic amounts of $H_3PO_4$ were required. In addition, the authors suggested an alternative route for HHD formation (Scheme 5). In the first step, 5-HMF is hydrogenated to BHMF followed by the hydrolytic ring-opening to 1-hydroxyhex-3-en-2,5-dione (**13**) in the second step and the reduction of **13** to HHD in the last step. In 2014, the group of Jerôme came to the same conclusions concerning the




**Scheme 5**. Conversion of 5-HMF to HHD, as proposed by Satsuma.

mechanism.[95] They were able to convert BHMF to HHD in 60% yield in a reaction catalyzed by 2 wt% Pd/C in water at 120 °C under 10 bar of $H_2$ and 30 bar of $CO_2$. The addition of $CO_2$ appears to be necessary to obtain HHD through the formation of carbonic acid, which provides acidic conditions. Further investigations revealed an increase in HHD yield to 77% when the experiment was performed in the presence of 7.5 wt% Pd/C and 5-HMF was used as a starting material. It should be noted that different $H_2/CO_2$ ratios and higher catalyst loadings showed no significant improvement. The authors also examined direct conversion of fructose and inulin to HHD for the first time. In the first step, carbohydrates are converted to 5-HMF by heating in water at 150 °C under 40 bar of $CO_2$ followed by hydrogenation/hydrolytic ring open of 5-HMF after addition of Pd/C (7.5 wt%) and applying 10 bar of $H_2$. The overall HHD yields were 36% and 15% from fructose and inulin respectively. In an extended work by the same group, the combination of both solid catalysts Amberlyst-15 and Pd/C was evaluated for the synthesis of HHD.[96] Compared to the method described earlier, reactions were carried out in THF at 80 °C. It must be noted though, that wet reagents were used and the water content of the reaction media reached 3.8 wt% based on Karl Fischer analysis. After the optimization, 77% HHD yield was achieved after 15 hours by the use of 5.5 wt% Pd/C, 20 wt% Amberlyst-15 at 50 bar of $H_2$. Again, this catalytic system was demonstrated to be efficient for the conversion of fructose and inulin towards HHD in 55% and 27% yields respectively. In 2017, Duan *et al*. applied palladium supported on acidic $Nb_2O_5$ calcinated at 400 °C for the hydrogenation of 5-HMF in water.[97] Various reaction parameters were tested. The highest selectivity towards HHD was 73% at 97% conversion after 6 hours at 140 °C and 40 bar of $H_2$. In addition, heterogeneous Pd/$Ni_2O_5$-400 catalyst could be recycled up to 4 times without apparent loss in the activity.

### *2.2 Hydrogenation/Hydrolytic Ring Opening of 5-HMF Catalyzed by Homogeneous Catalysts*

Only a limited number of studies is available on the conversion of 5-HMF to HHD using homogeneous catalysts. The significant advantage of the homogeneous systems arise from higher HHD yields, shorter reaction times and milder conditions (temperature, pressure) compared to heterogeneous systems. Especially, iridium and ruthenium-based metal

complexes were found to be efficient in 5-HMF hydrogenation/transfer hydrogenation (Figure 6). Concerning the use of homogeneous catalyst for the synthesis of HHD, limitations appear to be mainly in the requirements of water solubility and stability under acidic conditions. Zhang and co-workers were the first to apply a homogeneous catalyst in HHD synthesis.[98] Hydrogenation/hydrolytic ring opening of 5-HMF was performed in aqueous solution using bipyridine coordinated Cp*-Ir complexes (Cp*= pentamethylcyclopentadiene) (Fig. 6) at different temperatures (110-130 °C) and hydrogen pressures (5-20 bar $H_2$). The highest HHD yield of 86% at full conversion was obtained with 0.26 mol% **[Ir]-1** at 120 °C

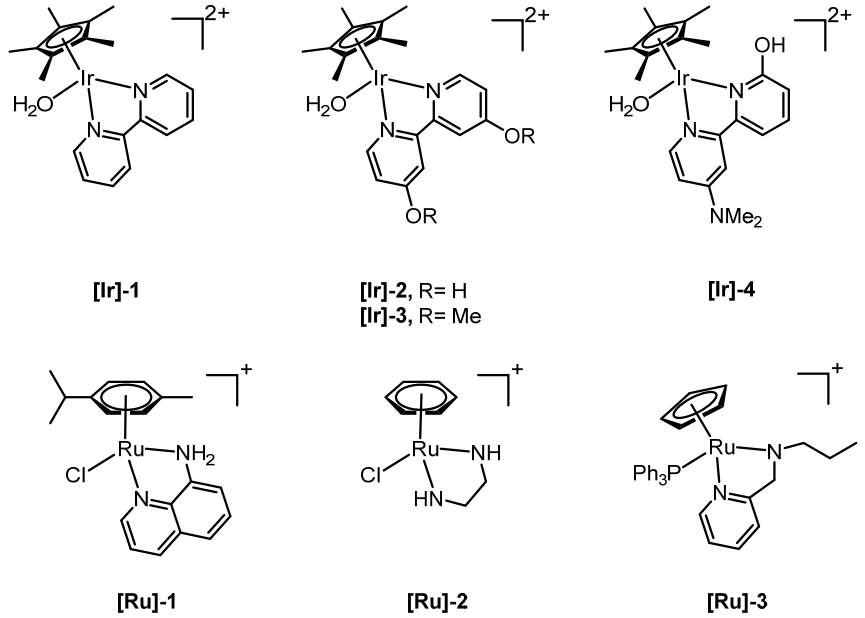
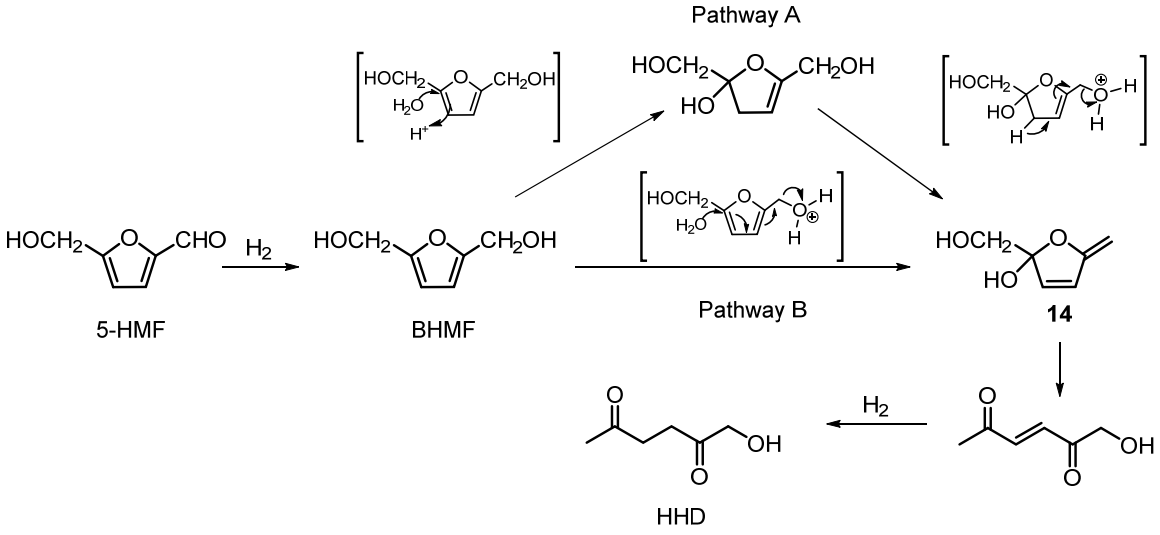


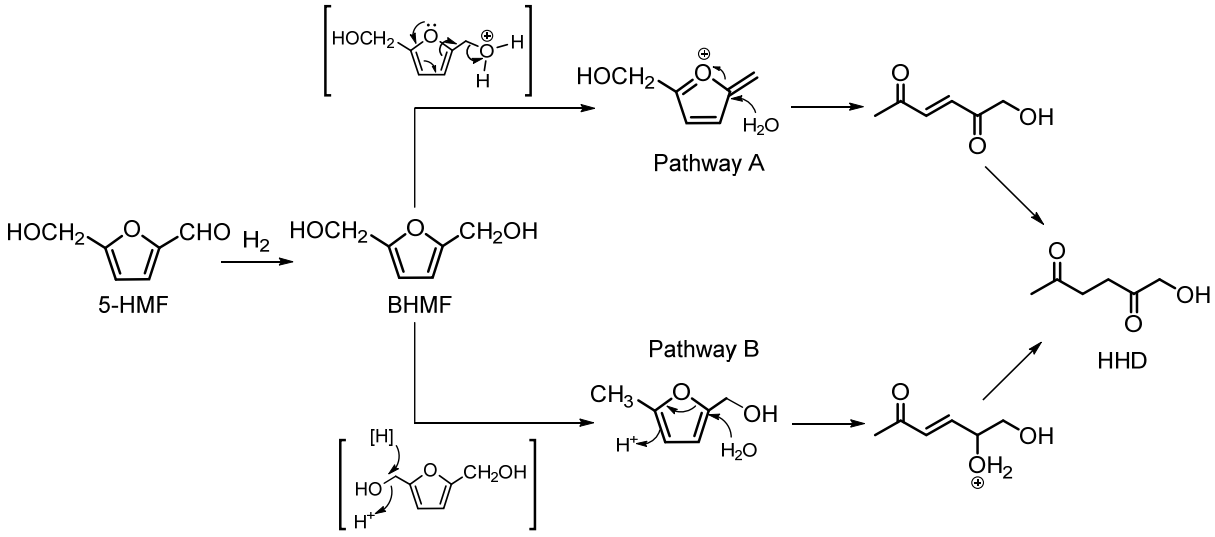

**Figure 6**. Iridium- and ruthenium-based complexes for the synthesis of HHD.

after 2 hours by introducing 7 bar of $H_2$. Moreover, detailed mechanistic studies were performed by the use of quantitative isotope marked GC-MS analysis. Two possible mechanistic pathways were proposed through key intermediate **14** as described in Scheme




**Scheme 6**. Proposed pathways for HHD synthesis by Zhang.

6. Pathway A assumes a two-steps reaction to generate **14** from BHMF with an initial water addition followed by H- and OH-elimination, whereas pathway B proceeds through one-step hydrolysis process. In the next step, intermediate **14** is hydrolyzed to α,β-unsaturated carbonyl compound, which then undergoes hydrogenation to form HHD. Hydrogenation of BHMF in $D_2O$ catalyzed by **[Ir]-1** leads to the conclusion that pathway B is more plausible based on the composition of deuterated HHD ion fragment (GC-MS analysis) and statistical calculations. Gupta *et al*. reported water soluble 8-aminoquinoline coordinated arene-ruthenium(II) complexes for the conversion of biomass-derived furans.[99] Moreover, formic acid was successfully applied as a hydrogen source. By the use of 12 eq. of formic acid in the presence of 1 mol% **[Ru]-1**, a moderate selectivity to HHD of 52% was obtained from 5-HMF at 80 °C after 48 hours. Apart from HHD, other products were also formed: levulinic acid and 3-hydroxy-2,5-hexanedione with 21% and 27% selectivity respectively. A later publication by the same group reported the use of arene-Ru(II) complexes containing ethylenediamine-based ligands for the synthesis of diketones.[100] Nevertheless, lower HHD selectivity (44%) was obtained after 8 hours in the reaction catalyzed by 5 mol% of **[Ru]-2** at 100 °C in the presence of formic acid. In addition, the direct conversion of fructose to valuable products was investigated. The optimized system gave 27% HHD and 51% LA selectivity. However, longer reaction time (16 h) led to a significantly higher HHD selectivity of 87%. In 2016, Fu and co-workers made an important advance in the synthesis of HHD from 5-HMF.[101] They evaluated a series of Cp*Ir(III) complexes bearing bipyridine ligand with both electron-donating and electron-withdrawing groups at different positions. An extended work revealed that the combined influence of temperature and pH is the most relevant factor for the formation of HHD in high yields. Catalyst screening showed relatively high HHD selectivities of around 70% with **[Ir]-2** and **[Ir]-3** complexes in aqueous formate buffer solution (FBS, pH= 2.5) at 120 °C in 2 hours. Interestingly, an increase in temperature to 130 °C led to remarkably higher HHD selectivity of up to 95%. Moreover, a large-scale experiment was performed with the aim to isolate HHD and test the recyclability of the



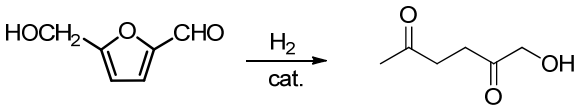

**Scheme 7**. Proposed pathways for HHD synthesis by Fu.

catalysts. The authors claimed an isolated HHD yield of 85% (92% GC yield) after the first cycle under the optimized conditions. Nevertheless, further details on the isolation procedure are lacking in their paper. In a recycling experiment a decrease in activity of the catalyst was observed and HHD was produced in 70% yield. Additionally, another insight in the mechanism of HHD formation was proposed as depicted in Scheme 7. In the first step, 5-HMF is hydrogenated to BHMF as postulated previously. In the next step, two alternative routes were assessed for the conversion of BHMF to HHD. The formation of 5-methylfurfuryl alcohol as an intermediate revealed an important distinction between the two catalytic routes. However, when 5-methylfurfuryl alcohol was used as a starting material under the same experimental conditions, the only product obtained was 2,5-hexanedione. On the basis of this result, pathway A was indicated to be the more likely one. In another publication by Zhang and co-workers, a new series of half-sandwich Cp*-Ir(III) complexes were tested for the synthesis of HHD from 5-HMF.[102] Promising results were achieved using **[Ir]-4** complex bearing a bipyridine ligand containing both *o*-hydroxyl and *p*-*N*-dimethylamino groups. The effect of the catalyst loading, pH and pressure was investigated. At low **[Ir]-4** catalyst loading of 0.0008 mol% hydrogenation resulted in 67% selectivity towards HHD at 88% conversion after 6 hours in water (pH= 3.4) at 120 $^{o}$C under 35 bar of $H_2$. Based on this experiment, TOF (31 560 $h^{-1}$) and TON (70 800) were calculated. The same catalyst was tested for the transfer hydrogenation of 5-HMF using 2 eq. of formic acid at 120 $^{o}$C. This catalytic system provided 60% HHD yield in the presence of 0.005 mol% of **[Ir]-4** after 2 hours. Recently, Dwivedi *et al*. examined cationic cyclopentadienyl-ruthenium(II)-pyridylamine complexes for the conversion of 5-HMF to HHD.[103] The reactions were carried out in water in the presence of formic acid (12 eq.) at 120 $^{o}$C. The $\eta^5$-Cp−Ru(II) complex bearing *N*-(pyridin-2-ylmethyl)propan-1-amine as ligand (**[Ru]-3**) was found to be the most efficient; 69% selectivity to HHD was achieved after 12 hours with 5 mol% of the catalyst. In addition, the authors obtained purified product in 42% yield after column chromatography. Direct conversion of fructose under the same conditions resulted in 65% selectivity towards HHD after 6 hours.

### *2.3 Conclusions on Conversion of 5-HMF to HHD*

Over the last 20 years, the conversion of 5-HMF to HHD has been studied by several groups. An overview of catalytic systems applied for the production of HHD is summarized in Table 4. In general, the utilization of half-sandwich Cp*Ir complexes provides highest selectivities to HHD at lowest catalyst loadings. However, an efficient isolation procedure still needs to be developed.

**Table 4**. Catalytic systems reported for the synthesis of HHD.




5-HMF HHD

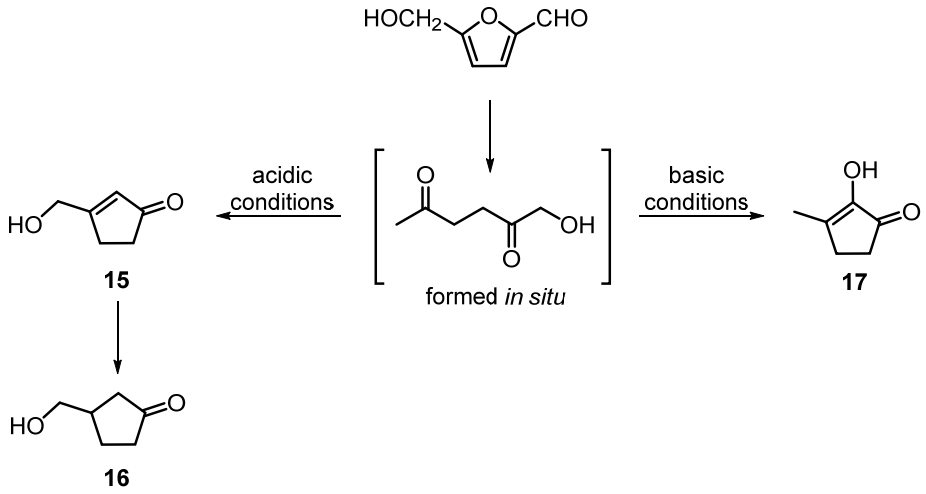
| Catalyst (cat. loading) | Conditions | Conversion (%) | HHD Yield (%) | Ref. |
|---|---|---|---|---|
| Pt/C (0.5 wt%) | 15 mol% $C_2H_2O_4$, 140 °C, $H_2O$, 30 bar $H_2$, 3 h, | na | 60 | 91 |
| Pd/C (50 wt%) | 12.5 mol% HCl, 60 °C, $H_2O$:toluene (2:1), 1 bar $H_2$, 4 h | 97 | 68 | 92 |
| Rh-Re/$SiO_2$ (10 mol%) | 120 °C, $H_2O$, 10 bar $H_2$ for 1h, then 80 bar $H_2$ for 17 h | 100 | 81 | 50 |
| Au/$TiO_2$ (1 wt%) | 4 wt% $SO_3$, 140 °C, $H_2O$, 38 bar $H_2$, 4 h | 84 | 57 | 93 |
| Au/$Ni_2O_5$ (1 wt%) | 8.5 mM $H_3PO_4$, 140 °C, $H_2O$, 80 bar $H_2$, 12 h | 81 | 60 | 94 |
| Pd/C (7.5 wt%) | 120 °C, $H_2O$, 10 bar $H_2$, 30 bar $CO_2$, 15 h, | 100 | 77 | 95 |
| Pd/C (5.5 wt%) | 20 wt% Amberlyst-15, 80 °C, THF (containing 3.8 wt% $H_2O$), 50 bar $H_2$, 15 h, | 100 | 77 | 96 |
| Pd/$Nb_2O_5$ (2 wt%) | 140 °C, $H_2O$, 40 bar $H_2$, 6 h | 93 | 73 | 97 |
| **[Ir]-1** (0.26 mol%) | 120 °C, $H_2O$, 7 bar $H_2$, 2 h | 100 | 86 | 98 |
| **[Ru]-1** (1 mol%) | 80 °C, $H_2O$, 12 eq. HCOOH, 48 h | 100 | 52 | 99 |
| **[Ru]-2** (5 mol%) | 100 °C, $H_2O$, 12 eq. HCOOH, 8 h | 100 | 44 | 100 |
| **[Ir]-2** (0.01 mol%) | 130 °C, FBS (pH=2.5), 2 h | 100 | 92 (85)[a] | 101 |
| **[Ir]-4** (0.0008 mol%) | 120 °C, $H_2O$ (pH= 3.4), 35 bar $H_2$, 6 h | 88 | 67 | 102 |
| **[Ru]-3** (5 mol%) | 120 °C, $H_2O$, 12 eq. HCOOH, 12 h | 96 | 69 (42)[a] | 103 |

[a] Isolated yield; na- not available

# 3. Applications of 1-Hydroxyhexane-2,5-dione

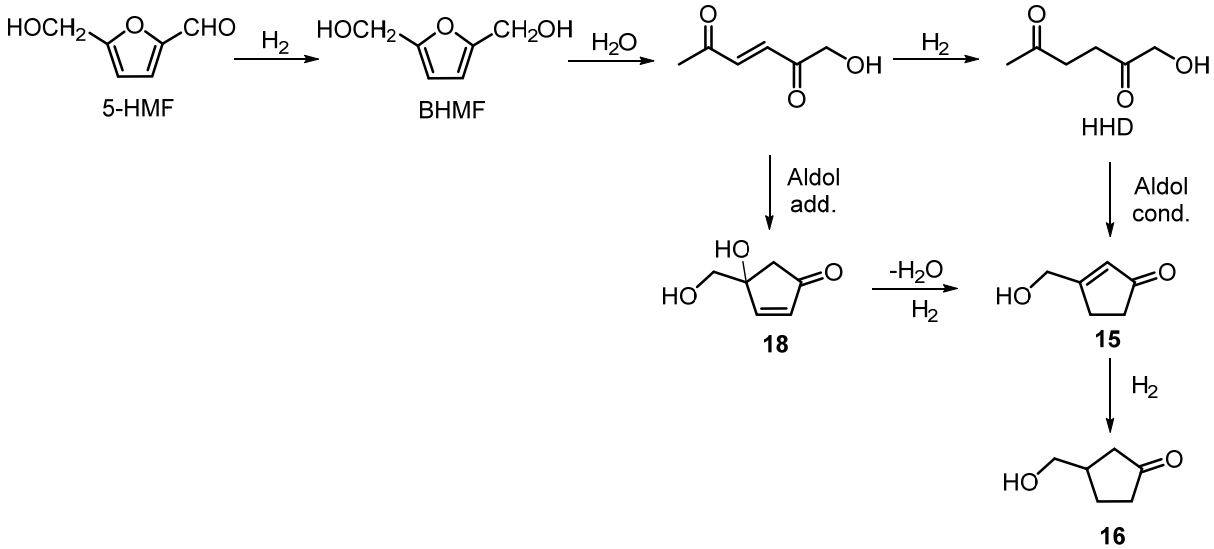
The utilization of HHD for the synthesis of useful follow-up products is still in its infancy. Moreover, in most cases, further transformations of HHD formed *in situ* have been reported, due to the limited number of reports on isolation and purification of HHD. The intramolecular aldol condensation of HHD, leads to the formation of interesting five-membered ring compounds. Aldol condensation of HHD can occur *via* two different routes depending on the reaction conditions as described in Scheme 8. The group of Satsuma

performed extensive research on the conversion of 5-HMF to 3-hydroxycyclopentanone (HCPN, **16**) under acidic conditions and $H_2$ pressure.[94,104,105] HCPN is an important chemical intermediate in the synthesis of polymers, pharmaceuticals and fuels.[106,107]. The first approach to the conversion of 5-HMF to HCPN *via* HHD was based on the use of supported




**Scheme 8**. Aldol condensation products starting from HHD.

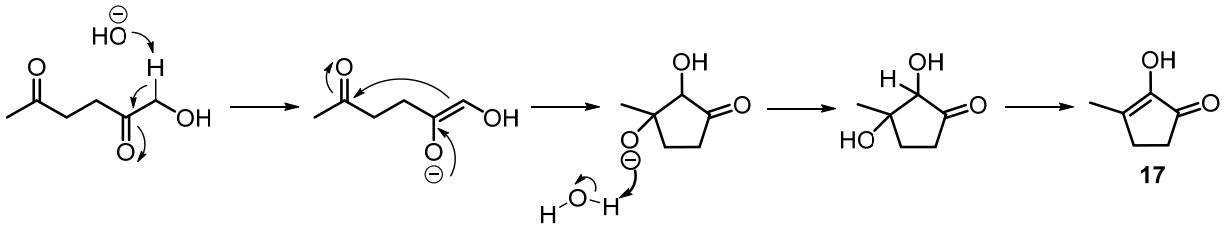
gold nanoparticles.[94] Various metal oxides were examined as support under 80 bar of $H_2$; they acted as a Lewis acids and promoted ring rearrangement of 5-HMF. The highest reported selectivity towards HCPN was 86% after 12 hours using 1 wt% Au supported on niobium oxide at 140 $^{o}$C. Moreover, the activity of the catalyst did not decrease significantly after the second cycle (84% selectivity). Following the reaction over time revealed formation of HHD in 20% yield, which after 6 hours decreased and HCPN was produced exclusively. Based on this result, a plausible mechanism was proposed for the conversion of 5-HMF to HCPN (Scheme 9). Hydrogenation/hydrolytic ring opening of 5-HMF leads to the formation of HHD, which is consistent with the generally proposed mechanism. Furthermore, intramolecular aldol condensation of HHD occurs under acidic conditions resulting in the




**Scheme 9**. Plausible mechanism for the conversion of 5-HMF to HCPN *via* HHD.

formation of 3-(hydroxymethyl)cyclopent-2-en-1-one (HCPEN, **15**), which is subsequently hydrogenated to **16**. The same group investigated the effect of acid–base catalysis on the ring rearrangement of 5-HMF by using a combination of a hydrogenation catalyst ($Pt/SiO_2$) with acidic and basic metal oxides.[104] The results of the experiments showed that basic metal oxides such as $La_2O_3$ and $CeO_2$ produce HCPN in low yields (<25% yield), however addition of acidic metal oxides (e.g. $Ta_2O_5$, $ZrO_2$, $Nb_2O_5$) enhanced the yield of HCPN to around 80%. The best catalytic performance was observed by using 1 wt% $Pt/SiO_2$ together with $Ta_2O_5$ in water at 140 °C under 30 bar of $H_2$ resulting in 82% yield of HCPN after 12 hours. The formation of HCPN *via* HHD was also proposed by Perret *et al.*[108] To avoid the use of noble metal complexes, the catalytic activity of nickel supported on alumina was tested. A comparable yield of HCPN (81%) was produced after 6 hours at 140 °C and 20 bar of $H_2$. Further research on the selective conversion of 5-HMF to cyclopentanone derivatives was performed using $Cu/Al_2O_3$ and $Co/Al_2O_3$ catalysts.[109] When using 26 wt% of $Cu/Al_2O_3$ as a catalyst at 180 °C and 20 bar of $H_2$, the HCPN yield was 86% at full conversion after 6 hours. However, hydrogenative ring-rearrangement of 5-HMF catalyzed by 9 wt% $Co/Al_2O_3$ revealed the formation of 3-hydroxymethylcyclopentanol (HCPL), a hydrogenation product of HCPN. The highest HCPL yield of 94% was achieved at 140 °C and 20 bar of $H_2$ after 48 hours. Ohyama *et al.* also reported work on a direct conversion of 5-HMF to HCPL using a combination of $Pt/SiO_2$ and lanthanide oxides.[105] High product yields (ca. 88%) were obtained by applying 5 wt% $Pt/Nd_2O_3$ in water at 140 °C and 30 bar of $H_2$ after 30 h.

Compared with acidic systems, intramolecular aldol condensation of HHD under basic conditions has been investigated to a lesser extent. Yang and co-workers examined the conversion of HHD to 2-hydroxy-3-methylcyclopent-2-enone (MCP, **17**) in the presence of




**Scheme 10**. Base-promoted intramolecular aldol condensation of HHD.

different bases.[97] The addition of solid base Ca-Al (200 mg) to a refluxing aqueous solution of HHD (0.1 M) led to 88% selectivity toward MCP after 6 hours. Other solvents such as n-butanol, ethanol and MIBK were also tested but did not show any improvements in MCP selectivities. A reaction mechanism was proposed as described in Scheme 10. In addition, direct synthesis of MCP from 5-HMF under optimized conditions was reported. The product was isolated in 58% yield.

In summary, only a limited number of catalytic systems have been reported for the conversion of HHD to useful chemicals. Key to the success of HHD will be the development of an efficient isolation method at larger (commercial) scale. This should provide a growing

interest in the chemistry of HHD, which has a great potential to become a new generation of *Platform Chemicals*.

# 4. Formation and Utilization of Pyrroles

Pyrroles are a highly important class of heterocycles. They occur naturally in many biologically active compounds like vitamin B, bilirubin, biliverdin, as well as heme and chlorophyll in the form of porphyrin rings.[110,111] The simplest pyrrole is a five-membered heterocyclic compound with a molecular formula $C_4H_4NH$. The first evidence of existence of pyrroles was reported by Runge, who detected them in coal tar back in 1834.[112] He named it from the Greek *phyrros* (πυρρός, "reddish"), from the observation of reddening wood (dipped in coal tar) after reacting it with HCl. It should be emphasized that in addition to its occurrence in natural products, pyrrole derivatives are present in many pharmaceutically active compounds.[113-116] Figure 7 presents selected examples of drugs containing the

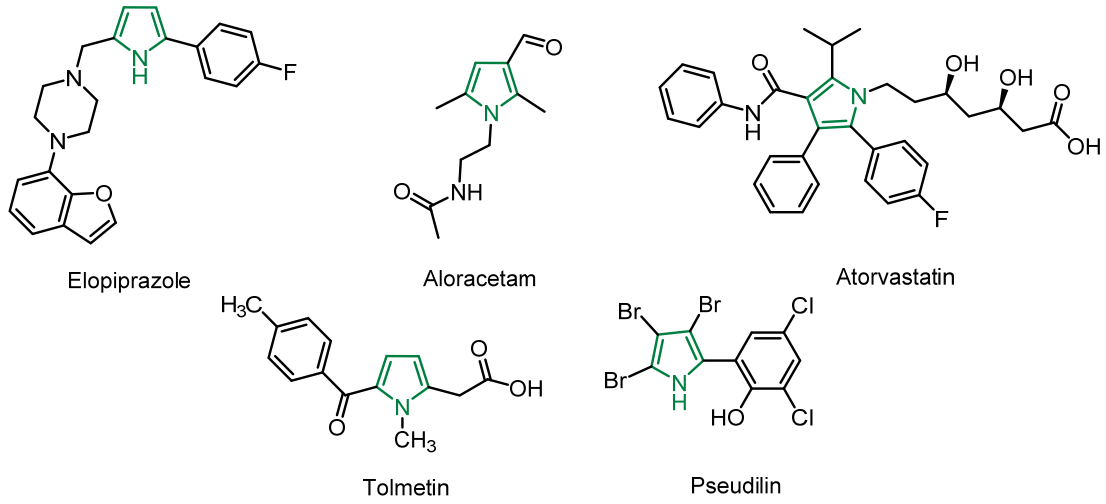
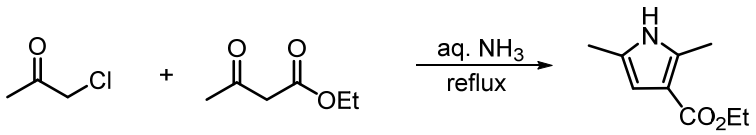



**Figure 7**. Structures of pharmaceutically active compounds containing pyrrole moiety.

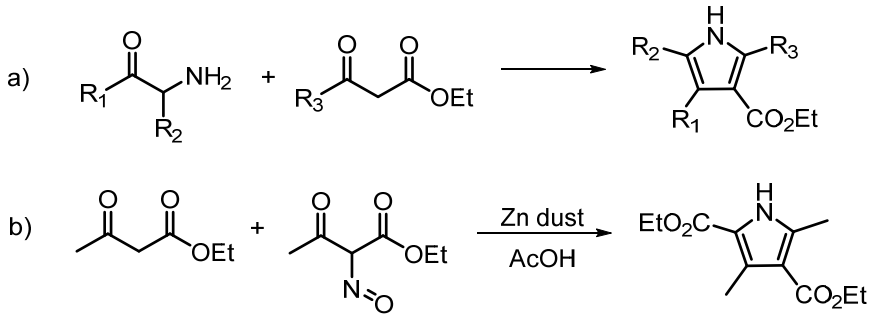
pyrrole skeleton with useful applications in medicine. Pyrroles have received increased attention due to their antitumor, anti-inflammatory, antibacterial, antioxidant and antifungal properties.[117,118] Moreover, atorvastatin, a lipid-lowering drug became the world's best-selling medicament (from 1996 to 2012) under the trade name Lipitor.[119] Pyrroles are an important class of compounds that are used in the preparation of agrochemicals, flavors, dyes and functionalized materials.[120-124] The simplest pyrrole ($C_4H_4NH$) is prepared on industrial scale by treatment of furan with ammonia in the presence of a solid acid catalyst ($SiO_2$, $Al_2O_3$) or by dehydrogenation of pyrrolidine.[125] A variety of methods have been developed for the synthesis of substituted pyrroles including transition metal catalyzed couplings,[116] cycloaddition reactions,[126] cycloisomerization reactions of Morita-Baylis-Hillman (MBH)[127] and oxidative aromatization.[128] However, the use of conventional methods for the preparation of pyrrole derivatives such as the Hantzsch reaction and the Paal-Knorr synthesis is still highly relevant. Hantzsch demonstrated in 1890 the reaction

between chloroacetone and acetoacetic ester in stoichiometric amounts under reflux in concentrated ammonia resulting in the formation of a new product, correctly assigned as a pyrrole derivative (Scheme 11).[129] Interestingly, this work has been identified as a high-potential multicomponent reaction many years later and this transformation has attracted more attention recently.[116]




**Scheme 11**. Hantzsch reaction for the production of pyrroles.

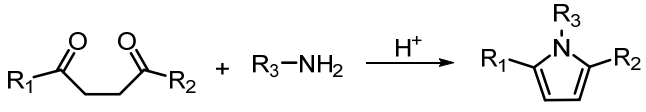
Another classical transformation regarding the production of pyrroles is the Knorr synthesis.[130] The proposed method involved reaction of α-aminoketones and compound containing electron-withdrawing groups (e.g. ester) in α-position to a carbonyl group (Scheme 12, equation a). However, due to high instability of α-aminoketones, the original




**Scheme 12**. Synthesis of pyrroles proposed by Knorr.

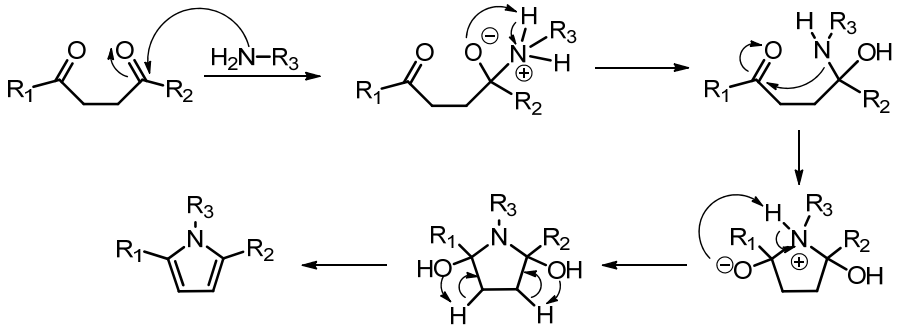
protocol described the use of two equivalents of ethylacetoacetate, one of which was converted to ethyl 2-oximinoacetoacetate *via* reaction with acetic acid and sodium nitrite (Scheme 12, equation b). Next, the oxime group was reduced with zinc and the pyrrole ring was formed.

In 1884, the two German chemists, Paal and Knorr developed independently a synthetic procedure for the production of furans from 1,4-diketones, which was further extended to the synthesis of pyrroles and thiophenes.[131,132] Since then, there has been a continued and growing interest in the Paal-Knorr synthesis leading to the production of a wide variety of important compounds, especially pyrroles.[133-135] In general, pyrrole derivatives are formed by the reaction between 1,4-diketones and primary amines in the presence of an acid catalyst (Scheme 13). Although a lot of attempts have been made to understand the mechanism of the Paal-Knorr synthesis, consensus on the actual mechanism has not been




**Scheme 13**. The Paal-Knorr synthesis of pyrroles.

reached till the 1990s. Amarnath *et al.* suggested that one of the carbonyl groups reacts with the amino group to form a hemiaminal, which further attacks the other carbonyl group resulting in a 2,5-dihydroxytetrahydropyrrole derivative (Scheme 14).[136] Next, dehydration of the cyclic product leads to the formation of final product – the corresponding substituted pyrrole. In the original procedures by Paal and Knorr it was concluded that the use of weak mineral acid catalysts is crucial for the formation of heterocyclic compounds *via* elimination of two water molecules. This catalytic system was later improved by application of zeolites,[137] p-TSA,[138] $Al_2O_3$,[139] $Ti(O^iPr)_4$,[140] layered zirconium phosphate and zirconium sulfophenyl phosphonate,[141] as well as the use of microwave irradiation.[142]

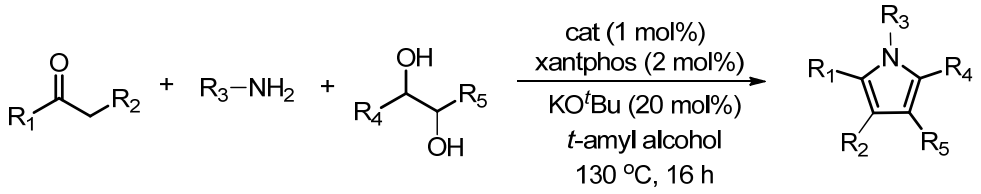


**Scheme 14**. The proposed mechanism of Paal-Knorr synthesis.

Danks reported the microwave-assisted Paal-Knorr synthesis using 2,5-hexandione and aniline derivatives as substrates.[141] Irradiation at 200 watts for 0.5-2 min under neat conditions resulted in the formation of *N*-substituted pyrroles in good yields (75-90%). Several catalysts such as copper iodide on activated carbon,[143] glutathione bearing nanoferrites[144] or polystyrenesulfonate (PSS) were also tested.[145] In the latter reaction, an aqueous solution of PSS in ethanol was utilized for the synthesis of *N*-polyaromatic substituted pyrroles. A typical experiment was performed at room temperature and isolated yields varied between 81% and 96% at reaction times of 10-22 hours. *N*-polyaromatic pyrroles were classified as biologically active compounds and were tested against various cancer cells *in vitro*. Recently, Török and co-workers reported the synthesis of *N*-substituted 2,5-dimethyl pyrroles in the absence of catalyst.[146] All reactions were conducted under solvent-free conditions at room temperature. Using 2,5-hexanedione as a model substrate, various aliphatic and aromatic amines were tested in the reaction. In general, the synthesis of *N*-alkyl substituted pyrroles resulted in shorter reaction times (up to 10 minutes) compared to the *N*-aryl substituted analogues (24 hours). In addition, 2,5-dimethylpyrrole was formed in the reaction of the diketone with aqueous $NH_4OH$ after a prolonged reaction time (120 hours) using an $NH_4OH$/diketone ratio value of 2.5. The same experiment with a 10-fold excess of aqueous $NH_4OH$ resulted in quantitative formation of this compound after 3 hours.

Recently, the group of Beller developed a regioselective synthesis of pyrroles *via* a ruthenium catalyzed multicomponent reaction.[147] They studied combinations of ketones, amines and vicinal diols in the presence of $[RuCl_2(p\text{-cymene})]_2$/Xantphos/$KO^tBu$ catalyst

system (Scheme 15). In general, polysubstituted pyrroles were produced in reasonable to excellent yield by using *t*-amyl alcohol as a solvent at 130 °C. Wang and co-workers described four-component synthesis of 2-acylpyrroles by using 2 equivalents of 2-bromoacetophenones, primary amines and ethyl glyoxylate.[148] The experiments were carried out in acetonitrile in the presence of pyridine as a base catalyst under reflux conditions. Substituted pyrroles were obtained in moderate to good yields (28-70%).



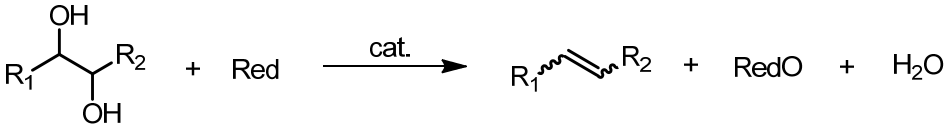

**Scheme 15**. Three- component synthesis of pyrroles developed by Beller.

To summarize, various catalytic methods were reported in the literature for the synthesis of *N*-substituted pyrroles. These heterocyclic compounds have gained growing interest from the pharmaceutical industry because of their anti-inflammatory, antioxidant and other useful properties. However, most of the described protocols involve the use of toxic organic solvents in the presence of excessive amounts of the catalyst and there are only a few studies focusing on the formation of pyrrole derivatives in agreement with the green chemistry principles.[143-145] This encouraged us to use a biomass-derived diketone for the synthesis of a range of *N*-substituted pyrroles under mild conditions, which is summarized in section 6.3.

# 5. Rhenium Catalyzed Deoxydehydration of Diols and Polyols

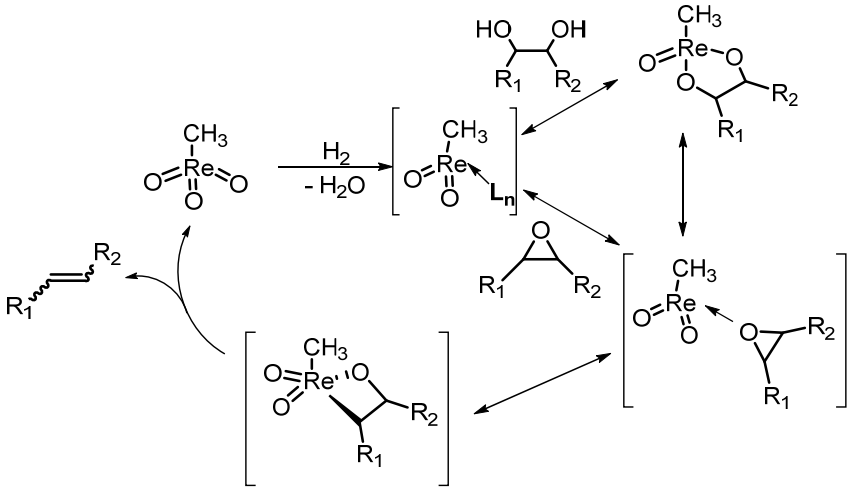
As was already discussed above, the direct replacement of petroleum resources with biomass-derived feedstocks is highly desirable. However, compared to fossil fuels, which consist of carbon and hydrogen exclusively, biomass based raw materials may contain up to 50 wt% of oxygen.[149] Therefore, researchers' attention has been directed to develop selective methods for lowering the oxygen content in carbohydrates in order to produce valuable chemicals.[150,151] Several processes have been reported on the conversion of biomass with the simultaneous reduction of oxygen content including dehydration,[152,153] decarbonylation,[154] decarboxylation,[155] hydrogenolysis/hydrogenation/ hydrodeoxygenation.[156,157] However, in most cases severe reaction conditions (high temperatures and pressures) were required. Among many different methods, deoxydehydration (DODH) of diols and polyols has been identified as a highly efficient way to lower the oxygen content in biomass-derived chemicals without losing any carbon atoms.[158] The DODH approach eliminates two adjacent hydroxyl group from vicinal diols in the presence of a reductant and a catalyst resulting in the formation of the corresponding

olefins with high selectivity (Scheme 16). Usually, transition metal catalysts are used for such a transformation; however there are processes where the latter is not required.[158,159] Ellman and co-workers performed DODH of biomass-derived polyols using formic acid as both the source of hydrogen and the catalyst.[160] All reactions were carried out at 230-240 °C affording the corresponding unsaturated products in good to excellent yields (56-96%). On the other hand, a number of metal complexes have been reported for this transformation such as molybdenum[161,162] and vanadium[163,164] complexes, especially rhenium based catalysts showed outstanding catalytic performance.[165,166] The first publication on catalytic DODH dates from 1996, by Cook and Andrews, in which it was




**Scheme 16**. Catalytic DODH of vicinal diols to the corresponding alkenes.

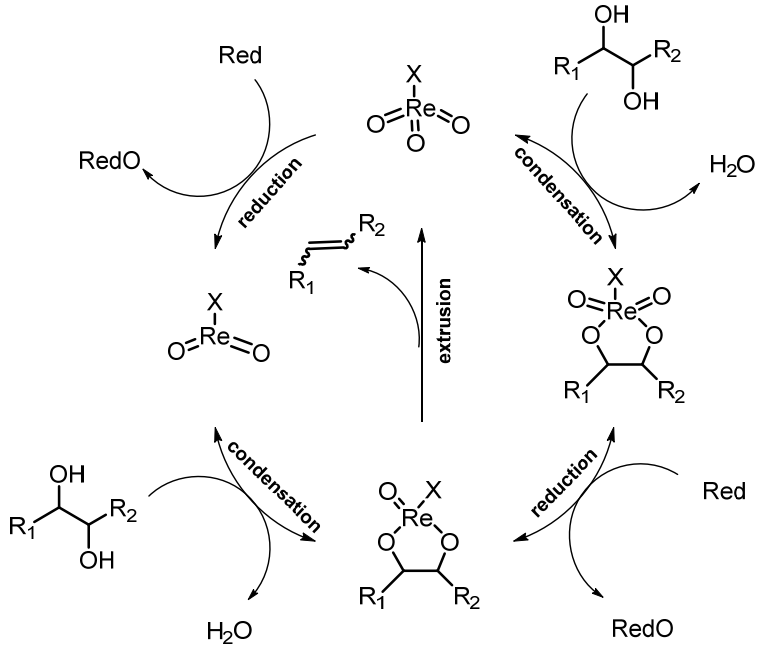
demonstrated that catalytic amounts of $Cp^*ReO_3$ (2 mol%) were able to quantitatively convert phenyl-1,2-ethanediol (styrenediol) to styrene by treatment with stoichiometric amounts of triphenylphosphine ($PPh_3$) in chlorobenzene at 90 °C.[167] Under the same conditions but at higher temperatures (135 °C) an 80% yield of butadiene was obtained from erythritol. In 2009, the group of Abu-Omar developed the deoxygenation of epoxides and diols using hydrogen gas (5-20 bar) as the reductant.[168] The experiments were carried out




**Scheme 17**. Proposed mechanism of deoxygenation of epoxides and diols by Abu-Omar. L= solvent molecule (THF or water, n= 1 or 2).

at 150 °C in THF with methyltrioxorhenium (MTO) as the catalyst. The system showed good performance for the conversion of *cis*-1,2-cyclohexanediol (60% of cyclohexene was obtained) but *trans*-1,2-cyclohexanediol did not form any of the corresponding alkene. This was explained by the deoxydehydration mechanism, which they propose proceeds through the *cis*-epoxide as an intermediate (Scheme 17). The main drawbacks of this procedure are the formation of alkanes as an over-hydrogenated products and limited substrate scope due

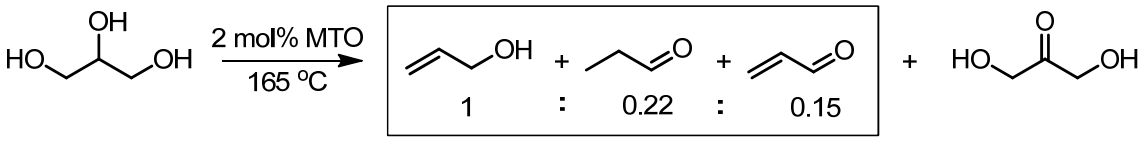
to the decomposition of biomass-derived starting materials under the applied reaction conditions. Further research on the rhenium catalyzed deoxydehydration was done by Nicholas and co-workers.[169,170] They evaluated the use of sulfite and bisulfite salts as a low-cost reductants with strong reducing potentials and low toxicity. The effect of different solvents (benzene, chlorobenzene, THF, ACN) and various rhenium sources (MTO, $Bu_4NReO_4$, $NH_4ReO_4$, $NaReO_4$) was investigated. In general, moderate to good yields of alkenes (34-80%) were obtained by using 1-1.5 eq. of $Na_2SO_3$ and MTO (up to 10 mol%) in benzene at 150 °C. In some cases higher yields were reported in the presence of $Bu_4NReO_4$, however longer reaction times were necessary. For example, MTO-catalyzed deoxydehydration of styrenediol led to 59% yield of styrene after 4 hours, whereas when $Bu_4NReO_4$ was used as the catalyst, 71% yield of the product was achieved after 59 hours. In addition, the authors postulated two possible reaction mechanisms as described in Scheme 18. The first pathway




**Scheme 18**. Two possible mechanisms for catalytic deoxydehydration proposed by Nicholas.

assumes the reduction of rhenium(VII) to rhenium(V) followed by condensation of the diol and oxorhenium(V) complex resulting in the Re(V)-diolate, which is regenerated to oxorhenium(VII) after extrusion of alkene. The second pathway differs in the sequence of the condensation and reduction but leads to the same intermediate (Re(V)-diolate). Depending on the nature of the reductant, *O*-transfer from an oxo-metal species to the reductant is favored in the first step or after condensation with the diol. Detailed mechanistic studies of the individual steps accompanied by DFT calculations revealed that extrusion of alkene was the rate-limiting step. Arceo *et al.* looked into a number of secondary alcohols as reductants for rhenium catalyzed DODH of vicinal diols to alkenes.[171] The catalytic system was developed for the conversion of 1,2-tetradecanediol at 180 °C under solvent-free aerobic conditions in the presence of 2.5 mol% $Re_2(CO)_{10}$. It was found that 3-octanol (13 eq.) is the most efficient reductant for the synthesis of 1-tetradecene

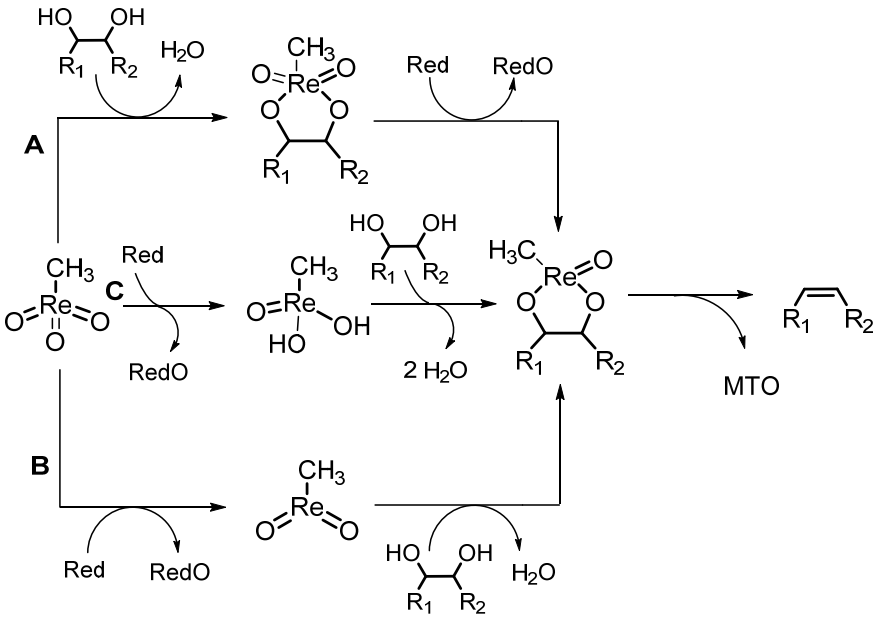
providing 84% yield after 4 hours. Interestingly, the same experiment under nitrogen atmosphere showed no conversion of diol suggesting that higher oxidation states of rhenium were involved in the catalytic transformation. The same protocol was successfully applied for the conversion of internal diols (e.g. decane-3,4-diol afforded the corresponding alkene in 82% yield after 2 hours). The authors demonstrated that addition of catalytic quantities of *p*-toluenesulfonic acid allowed the production of the desired alkene at lower temperatures and lower catalyst loading. In addition, DODH of octane-4,5-diol in the absence of the reducing agent showed full conversion after 3.5 hours and the formation of the corresponding alkene in 50% yield together with vicinal diketone as the byproduct, which decomposed over the time. This indicates that vicinal diols might undergo a disproportionation reaction and can be used as a substrates as well as reductants. A similar strategy was adopted by Abu-Omar and co-workers for the DODH of glycerol under neat conditions.[172] Using 2 mol% of MTO at 165 °C glycerol was converted to the mixture of




**Scheme 19**. Rhenium catalyzed DODH of glycerol in the absence of reductant.

volatile products in 74% yield, where allyl alcohol, propanal and acrolein were obtained in the ratio of 1 : 0.22 : 0.15 (Scheme 19). As expected, the only byproduct formed was non-volatile dihydroxyacetone. This catalytic system was later improved by application of $NaReO_4$ (2 mol%) as the catalyst in the presence of $NH_4Cl$ (1.5 mol%) as the additive resulting in 96% yield of volatile products. However, when 2 mol% of $NH_4ReO_4$ was used with 2 mol% of NaCl only 42% yield of volatile products was achieved. The influence of the cation was not explained by the authors. In addition, another insight in the mechanism of MTO-catalyzed DODH was reported (Scheme 20, pathway **A**). The proposed mechanism involves the following steps: a) condensation of vicinal diol to Re(VII) MTO catalyst; b) reduction o Re(VII) diolate complex to Re(V) diolate; c) extrusion of the olefin and regeneration of the catalyst.

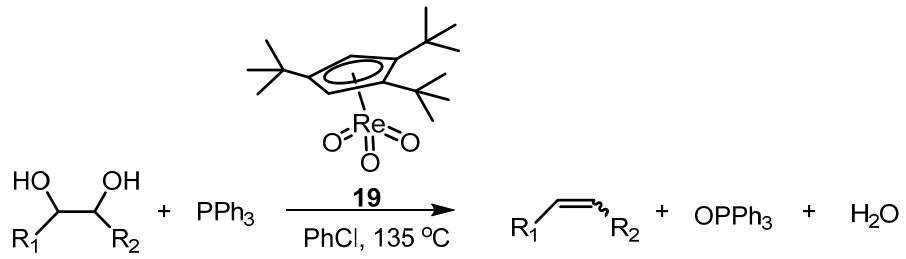
In 2012, a publication by Schiramizu and Toste marked a breakthrough in the sugars and sugar alcohols deoxydehydration.[173] Initially, a number of rhenium catalysts were tested for the alcohol-driven DODH of 1,4-anhydroerythritol to 2,5-dihydrofuran. The highest yields were obtained with 2.5 mol% MTO at 170 °C driven by the oxidation of 3-pentanol or 3-octanol resulting in 95% and 92% yield of the desired product respectively. On the basis of these results, the same approach was examined for the conversion of glycerol to allylic alcohol (90% yield) and erythritol to butadiene (89% yield) using 3-octanol as the reducing agent. Furthermore, the system with 3-pentanol as both the reducing agent and the solvent led to the efficient conversions of sorbitol and mannitol to 1,3,5-hexanetriene (54% yield). Also three pentitols, such as xylitol, arabinitol and ribitol were converted to 2,4-pentadiene-1-ol (61%, 43%, and 33% yield respectively). It should be emphasized that alcohol-driven DODH of hexoses yielded mixtures of 2-vinylfuran and furan. The best result of 40% NMR




**Scheme 20**. Different mechanisms proposed for DODH of vicinal diols.

yield with the ratio of 1 : 2.1 was achieved from D-allose at 155 °C after 3 hours. The mechanistic studies gave plausible mechanism involving the same steps as reported by Abu-Omar (Scheme 20, pathway **A**) although in reverse order (Scheme 20, pathway **B**). However, extensive research on the mechanism of MTO-catalyzed DODH performed by Wang and co-workers revealed the more favorable pathway based on the computational study.[174] According to the mechanism **C** (Scheme 20), MTO is reduced in the first step to dihydroxy(oxo)rhenate, both kinetically and thermodynamically more favorable intermediate. All subsequent steps follow the pathways described above.

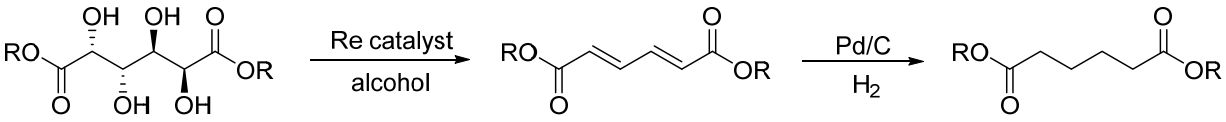
Klein Gebbink and co-workers studied the deoxydehydration of vicinal diols by using bulky Cp-based trioxorhenium complex **19** at relatively low temperature for this reaction (135 °C,




**Scheme 21**. Deoxydehydration of vicinal diols into olefins catalyzed by **19.**

Scheme 21).[175] Reaction conditions were optimized by testing a range of reductants and solvents for the transformation of 1,2-octanediol to 1-octene. At optimum conditions using 2 mol% of the catalyst and 1.1 eq. of $PPh_3$ in chlorobenzene, a selectivity of 90% to 1-octene was achieved after 15 hours. Noteworthy, the formation of isomerized products (*trans*-2-octene and *cis*-2-octene) was also observed (up to 10%). After the optimization of the reaction conditions a variety of vicinal diols, both internal and terminal was tested, showing good to excellent yields at prolonged reaction times (40 h). In another publication by

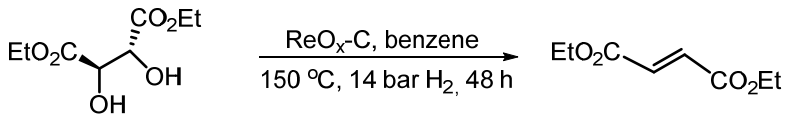
Schiramizu and Toste, oxorhenium catalysts such as MTO were applied not only for the DODH of vicinal diols (1,2-DODH) but also for the conversion of 2-ene-1,4-diols (1,4-DODH) and 2,4-diene-1,6-diols (1,6-DODH).[176] This was attributed to the their ability to catalyze the [1,3]-OH shift of an allylic alcohol.[177] This work was extended to the one-pot synthesis of the




**Scheme 22**. One-pot synthesis of diester of adipic acid from mucic acid diester.

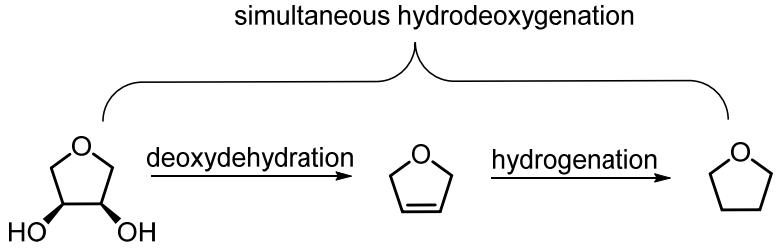
diester of adipic acid from mucic acid using $HReO_4$ as the catalyst.[176] Initially, mucic acid was converted to *trans*,-*trans*-di-butyl muconate using n-butanol as the reductant at 170 °C for 15 hours followed by a Pd/C-catalyzed hydrogenation under 7 bar of $H_2$ at room temperature to form the diester of the acid in 62% yield (Scheme 22). Further improvements to the conversion of mucic acid to adipic acid esters were introduced by Li *et al*.[178] A near quantitative yield of the product was obtained in a two step one-pot route by applying MTO as the catalyst, lowering the temperature to 120 °C and by using 3-pentanol as the reducing agent. McClain *et al*. demonstrated that common elements like Fe, Zn, C, Mn proved to be practical reductants for the DODH of vicinal diols catalyzed by $NH_4ReO_4$.[179] However, high catalyst loading (10 mol%) and prolonged reaction times (24 h) were necessary to obtain the corresponding alkenes in moderate to good yields (46-85%). Recently Love and co-workers showed that pyridinium perrhenate salts were able to catalyze the DODH of vicinal diols and polyols to alkenes at significantly lower temperatures (90 °C) than other oxorhenium complexes.[180] The 2,6-lutidinium perrhenate catalyst (5 mol%) was found to be the most active in combination with $PPh_3$ as the reductant in chloroform. On the basis of DFT calculations a mechanism was proposed, in which the Re(VII) complex is reduced to Re(V) in the first step, followed by diol condensation and elimination of the alkene. Interestingly, reduction of the rhenium source was indicated as the rate determining step, which is in contrast to the findings by Andrews[167] and Nicholas.[170,181]

Only limited attention has been paid to the DODH of vicinal diols and polyols over heterogeneous catalysts.[182-184] Denning *et al*. reported DODH reactions catalyzed by $ReO_x$ supported on carbon by applying both $H_2$ and hydrogen-transfer reductants.[182] A typical experiment was performed in benzene at 150 °C. For the DODH of (+)-diethyl tartrate the highest diethyl fumarate yield of 95% (NMR yield) was found under 14 bar of $H_2$ after 48 hours with no detectable reduction or hydrolysis of the carboxyl groups (Scheme 23). When benzyl alcohol was used as the reductant in the $ReO_x$-C catalyzed DODH of 1,2-




**Scheme 23**. Conversion of (+)-diethyl tartate to *trans*-diethyl fumarate catalyzed by $ReO_x$-C.

tetradecanediol, a 52% yield of the corresponding alkene was obtained after 70 hours along with benzaldehyde. Noteworthy, leaching of rhenium into the solvent was observed after hot filtration, which suggests that catalysis is performed partially by soluble rhenium species. Recently, the group of Palkovits reported the application of a stable heterogeneous catalyst based on $ReO_x$ supported on porous anatase titania for the DODH of polyols.[183] Among many different rhenium sources, $NH_4ReO_4$ was selected as the most promising metal precursor for impregnation and reduction to lower oxidation state rhenium oxide (ReOx) under $H_2$ atmosphere at 300 $^oC$. Although the transformation of glycerol to allyl alcohol afforded a moderate yield of 48% in the first run, the ReOx-$TiO_2$ catalytic system showed no loss of activity for seven consecutive catalytic experiments (54% yield in the seventh run). A heterogeneous ReOx-Pd/$CeO_2$ catalyst was investigated by Oma *et al*. in the simultaneous hydrodeoxygenation of vicinal diols.[184] This reaction consisted of a deoxydehydration in the first step followed by hydrogenation of the double bond to give alkanes (Scheme 24). For




**Scheme 24**. Simultaneous hydrodeoxygenation of 1,4 anhydroerythritol.

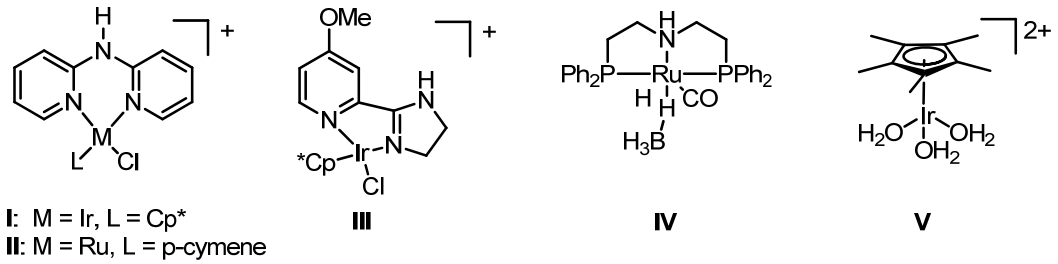
example, 1,4-anhydroerythritol was converted to THF in near quantitative yield by using 1,4-dioxane as the solvent at 140 $^oC$ under 80 bar $H_2$ after 60 hours. The same concept was applied for the synthesis of diols and mono-ols from sugar alcohols such as erythritol, xylitol and sorbitol.

In conclusion, the rhenium catalyzed DODH of diols- and polyols-derived from biomass is the most commonly used strategy for the efficient production of olefins. However, so far relatively large amounts of catalysts were used, often in combination with toxic solvents such as benzene. Therefore, we focused mainly on the improvement of current methods and the development of cheaper catalytic protocol, which aims to convert biomass-derived triols (including those obtained from 5-HMF) to valuable unsaturated alcohols as described in Section 6.4.

# 6. Objectives of This Work

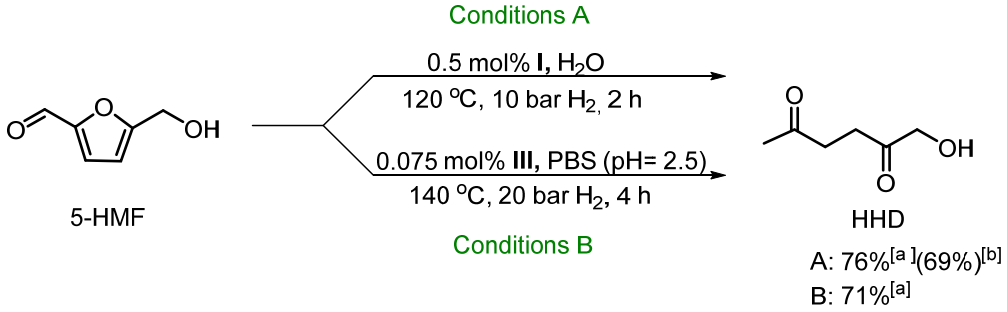
## *6.1 Synthesis and Isolation of HHD from 5-HMF*

As described in sections 1 and 2, the synthesis of new biomass-derived chemicals and the development of innovative bio-based routes to existing chemicals are crucial to support the society's needs. However, the utilization of biomass is associated with a number of important issues. One of the challenges regarding applicability of biomass-derived products is the lack of reports on isolation procedures. Most publications in this area report only GC yields of the products. We have become interested in the catalytic conversion of 5-hydroxymethylfurfural (5-HMF), derived from carbohydrates, into known or new chemicals. The main focus was on the transformation of 5-HMF to the ring-opened product – 1-hydroxyhexane-2,5-dione (HHD). Therefore, a series of air- and moisture-stable iridium and ruthenium complexes was investigated for the hydrogenation/hydrolytic ring opening of 5-HMF (Scheme 25). Catalyst screening revealed promising results in terms of HHD yields,




**Scheme 25**. Iridium and ruthenium complexes used for the conversion of 5-HMF to HHD.

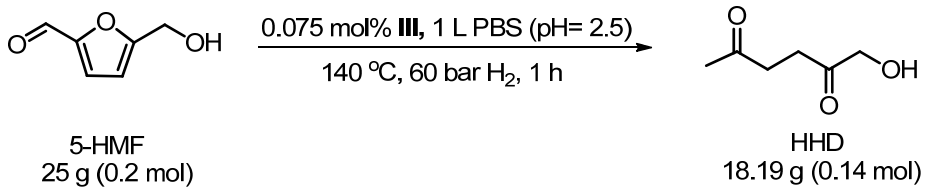
particularly in reactions catalyzed by the half-sandwich iridium complexes **I** and **III**. After the optimization of the reaction conditions, HHD was isolated in 69% yield (76% selectivity) when reacting 5-HMF in water with 0.5 mol% catalyst **I** at 120 °C under 10 bar $H_2$ for 2 h (Scheme 26, conditions A). Interestingly, the utilization of phosphate buffer solution (PBS, pH= 2.5) as the reaction medium allowed processing at lower catalyst loading (0.075 mol%) without significant losses in selectivity towards HHD; 71% HHD was obtained in the presence of Cp*Ir catalyst **III** (Scheme 26, conditions B). It should be noted that the major byproduct formed under these conditions was an insoluble brown polymeric material which we assume




**Scheme 26**. Conversion of 5-HMF to HHD under various reaction conditions; [a] Determined by $^1$H NMR spectroscopy with $(CH_3)_4NBF_4$ as an internal standard; [b] Isolated yield.

are humins, which is in agreement with the observations of other groups.[95,101]

In addition, we aimed to perform a large-scale synthesis of HHD under the optimized conditions in PBS (Scheme 27). However, to reduce the formation of humins we felt it could be useful to reduce the reaction time. Thus, the reaction was conducted under 60 bar of $H_2$ resulting in the full conversion of 5-HMF after 1 hour. The isolation process consisted of the




**Scheme 27**. Large-scale synthesis of HHD from 5-HMF.

concentration of the resulting mixture under vacuum, extraction with DCM and purification of the product by flash column chromatography. HHD was isolated in 71% yield, which corresponds to 18.19 g. Moreover, the full characterization of HHD was reported including its crystal structure, obtained by X-Ray diffraction analysis for the first time (Figure 8).

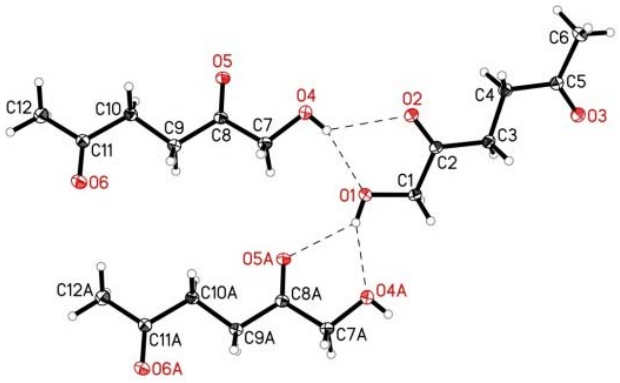



**Figure 8.** ORTEP representation of HHD showing intermolecular O–H···O hydrogen bonds. Displacement ellipsoids correspond to 30% probability.

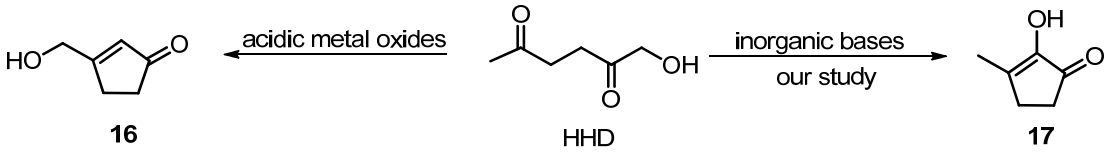
In summary, we have developed a new catalytic process for the hydrogenation/hydrolytic ring opening of 5-HMF resulting in the formation of HHD in good yields. Furthermore, the large-scale synthesis allowed the isolation of HHD in pure form, which was confirmed by detailed analysis (X-Ray diffraction, elemental analysis, HR-MS).

*The published article concerning this work is included in section 7.1 and 7.2*

## *6.2 Conversion of HHD into Valuable Cyclopentanone Derivatives*

With reasonable amounts of pure compound in hand, further research focused on the synthesis of useful follow-up products from HHD. The first approach involved the investigation of the base-promoted intramolecular aldol condensation of HHD. To our delight, 2-hydroxy-3-methylcyclopent-2-enone (MCP, **17**) was found to be the major product formed during the reaction, together with some insoluble polymeric solid as the only

byproduct. It should be emphasized that the formation of 3-(hydroxymethyl)cyclopent-2-en-1-one (HCPN, **16**) was not observed. Formation of this product was reported as product from the intramolecular aldol condensation of HHD under acidic conditions (Scheme 28).[94,104]

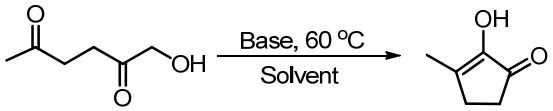



16 HHD 17

**Scheme 28**. Intramolecular aldol condensation products starting from HHD.

MCP is a known naturally occurring flavor ingredient in roasted coffee[185] and maple syrup.[186] On the basis of these properties it has found commercial use in the food industry as a flavoring agent. Apart from its natural occurrence, MCP is commonly produced from adipic acid in a multistep reaction; however the use of toxic reagents such as $Cl_2$ is required for this process.[187] Therefore, the development of a bio-based route to MCP is highly desirable. We initiated our studies by examining the role of the base in the aldol condensation reaction of HHD at 60 °C. Without base or in the presence of small amounts of KOH, no conversion of HHD was observed. A significant improvement in the reactivity of HHD was achieved by increasing the HHD/KOH ratio to 1.5; full conversion was obtained

**Table 5**. Solvent and base screening for the synthesis of MCP from HHD.[a]



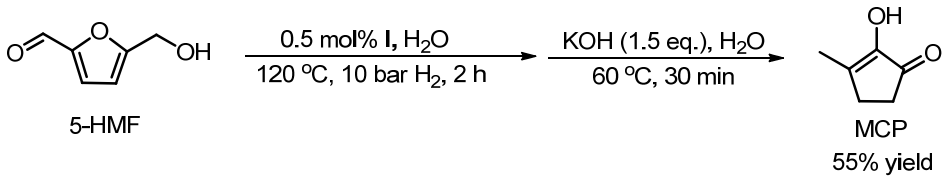

HHD MCP

| Entry | Base (1.5 eq.) | Solvent | Time | Conv. (%)[b] | Isolated yield (%) |
|---|---|---|---|---|---|
| 1 | NaOH | $H_2O$ | 15 min | >99 | 70 |
| 2 | KOH | $H_2O$ | 15 min | >99 | 72 |
| 3 | $CsCO_3$ | $H_2O$ | 20 h | >99 | 62 |
| 4 | $K_3PO_4$ | $H_2O$ | 2 h | >99 | 71 |
| 5 | KOH | EtOH | 15 min | >99 | 61 |
| 6 | KOH | MeOH | 15 min | >99 | 57 |
| 7 | KOH | ACN | 24 h | - | - |
| 8 | KOH | THF | 22 h | >99 | 60 |
| 9 | KO$^t$Bu | THF | 5 min | >99 | **80** |

[a] Reaction conditions: HHD (0.4 mmol), base (0.6 mmol), solvent (2 mL); [b] Determined by thin-layer chromatography.

within 15 min affording MCP in 72% isolated yield. A similar experiment performed at room temperature led to the formation of MCP in 70% yield after 1.5 h. Next, the effects of a solvent and a base on the selectivity of the reaction were investigated (Table 5). In general, the utilization of simple inorganic bases such as alkaline hydroxides promotes fast conversion of HHD to MCP with an average isolated yield of 65% in aqueous and alcoholic solutions (Table 5, entries 1-2 and 5-6). However, the highest isolated MCP yield of 80% at full conversion of the starting material was obtained after 5 min by applying KO$^t$Bu as a base in THF (Table 5, entry 9).

Another elegant approach was the application of the optimized conditions for both HHD and MCP syntheses for a novel one-pot reaction for the production of MCP directly from 5-HMF *via* HHD as an intermediate (Scheme 29). As a consequence of this, hydrogenation/hydrolytic




**Scheme 29**. A one-pot synthesis of MCP from 5-HMF.

ring opening of 5-HMF followed by intramolecular aldol condensation afforded 55% isolated yield of MCP. In addition, crystals were grown from DCM/pentane mixtures at -30 °C and the structure was determined by X-Ray diffraction analysis (Figure 9).

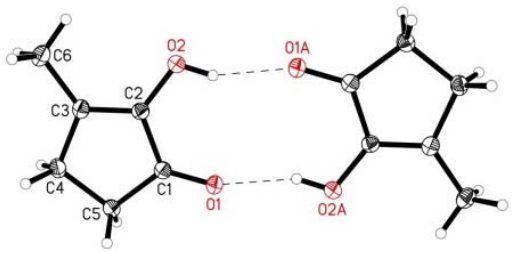
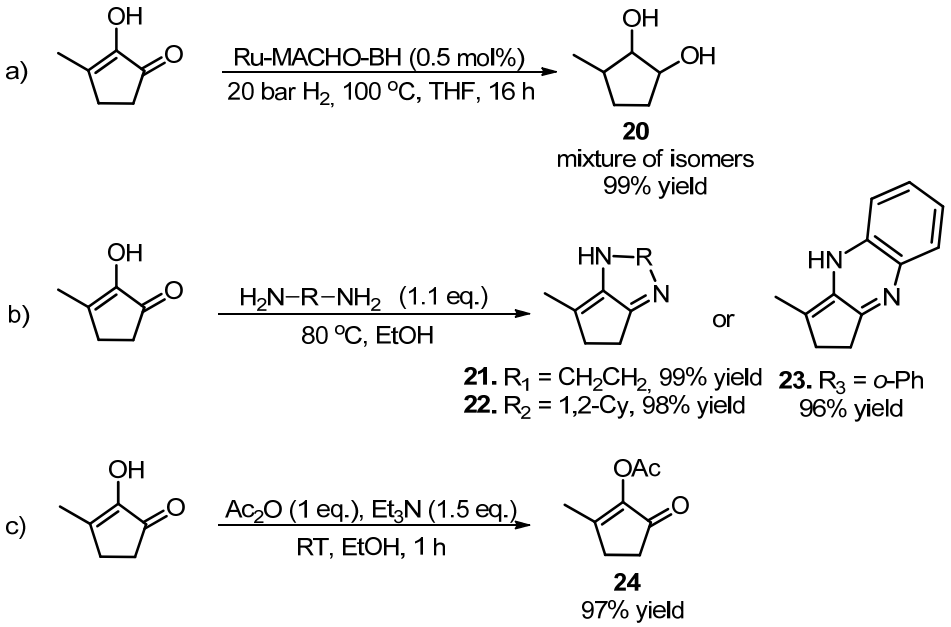



**Figure 9**. ORTEP representation of MCP showing intermolecular O–H···O hydrogen bonds. Displacement ellipsoids correspond to 30% probability.

Furthermore, MCP was converted to a number of valuable products as described in Scheme 30. For example, the fully hydrogenated form of MCP, 3-methyl-1,2-cyclopentanediol (**20**) was obtained in near quantitative yield as a mixture of isomers by using the commercially available Ru-MACHO-BH catalyst (Scheme 30, equation a). The oxidative carbonylation of diol **20** has been reported to lead to the formation of the cyclic carbonate.[188] Cyclic carbonates are important intermediates in the synthesis of pharmaceuticals, polymers and agrochemicals. The application of aliphatic and aromatic diamines in the reaction with MCP revealed excellent yields of the corresponding α,β-unsaturated heterocyclic imines and a quinoxaline derivate (Scheme 30, equation b, **21-23**). Quinoxalines are known intermediates for the manufacturing of pharmaceuticals due to their antiviral, anticancer and antidepressant properties.[189] Another possible useful synthetic approach is the

transformation of MCP to the corresponding enol acetate (**24**, Scheme 30, equation c), which is a starting material for the synthesis of dihydrojasmone, a fragrance used in perfumes.[190]



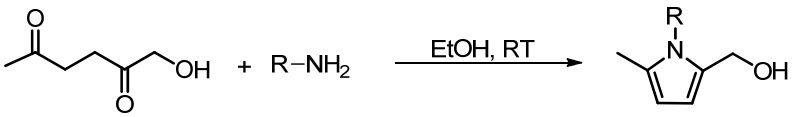

**Scheme 30**. Conversion of MCP into valuable biomass-based products.

The applicability of the HHD was demonstrated by the synthesis of MCP *via* base-promoted intramolecular aldol condensation. This approach has been extended to the synthesis of MCP directly from 5-HMF, which represents a novel biomass-based route for the production of this compound. Additionally, MCP proved to be an interesting starting material for the synthesis of useful building blocks in excellent yields.

*The published article concerning this work is included in section 7.1*

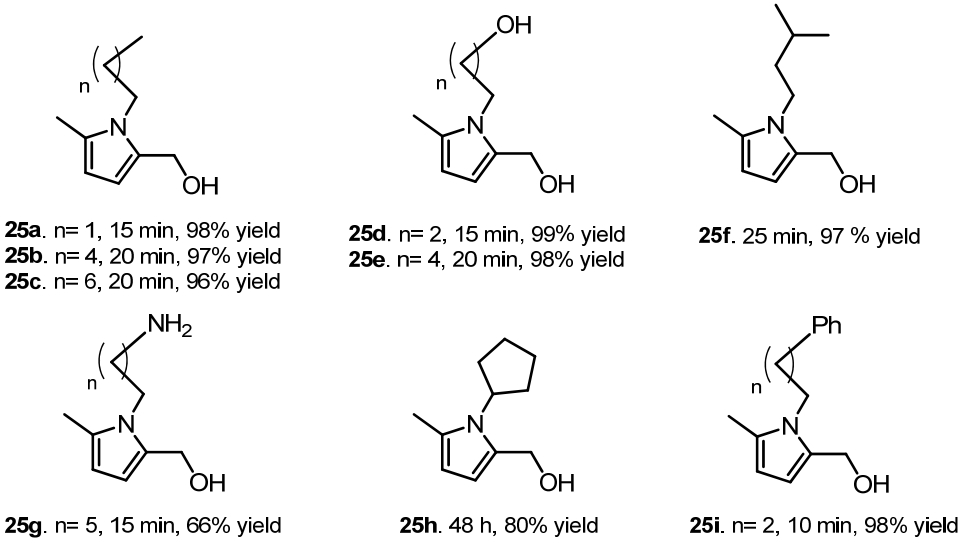
## *6.3 Synthesis of N-Substituted Pyrroles via Click Reaction*

In order to access new HHD-derived products, our focus was on the utilization of the diketone moiety of HHD. As mentioned in section 4, it is possible to convert 1,4-diketones to the *N*-substituted pyrroles in the Paal-Knorr synthesis, which is typically an acid-catalyzed reaction. Following the *Principles of Green Chemistry*[191] we performed the synthesis of *N*-substituted 2-hydroxymethyl-5-methyl-pyrroles at room temperature in ethanol as a solvent in the absence of catalyst starting from HHD and a variety of primary amines (Scheme 31). To assess the potential of HHD in Paal-Knorr synthesis, first a range of alkylamines was tested. In general, most of the *N*-alkyl substituted pyrroles were obtained in excellent




**Scheme 31**. The Paal-Knorr synthesis of *N*-substituted pyrroles starting from HHD.

isolated yields (96-99%) in short reaction times (up to 25 min) by simply evaporating the solvent and drying the product *in vacuo* (Figure 10). A prolonged reaction time (48 h) was required to achieve full conversion of HHD for the preparation of product **25h** (Figure 10). The most likely reason for this slow reaction is the steric hindrance of the cyclopentyl ring.




**25a**. n= 1, 15 min, 98% yield
**25b**. n= 4, 20 min, 97% yield
**25c**. n= 6, 20 min, 96% yield

**25d**. n= 2, 15 min, 99% yield
**25e**. n= 4, 20 min, 98% yield

**25f**. 25 min, 97 % yield

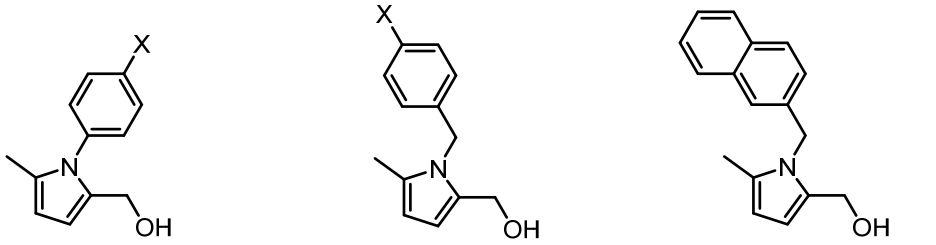
**25g**. n= 5, 15 min, 66% yield

**25h**. 48 h, 80% yield

**25i**. n= 2, 10 min, 98% yield

**Figure 10**. *N*-alkylsubstituted pyrroles derived from HHD.

The decrease in reaction rates and yields of isolated products was also observed for the synthesis of *N*-substituted pyrroles from HHD and aniline derivatives (Figure 11). For example, the reaction of HHD with aniline resulted in the formation of the *N*-phenyl-2-hydroxymethyl-5-methylpyrrole (**26a**, Figure 11) with 76% yield after 48 hours. However,




**26a**. X= H, 48 h, 76% yield
**26b**. X= F, 48 h, 74% yield
**26c**. X= $NH_2$, 10 h, 82% yield
**26d**. X= $SCH_3$, 48 h, 78% yield
**26e**. X= OEt, 20 h, 88% yield

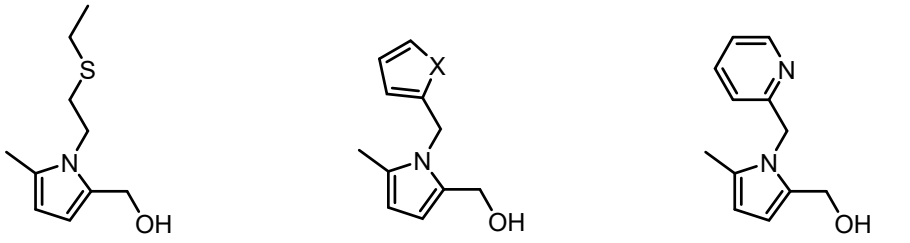
**27a**. X= H, 25 min, 97% yield
**27b**. X= Cl, 20 min, 99% yield
**27c**. X= OMe, 10 min, 99% yield
**27d**. X= $CF_3$, 1 h, 96% yield

**27e**. 30 min, 88% yield

**Figure 11**. *N*-aryl and -benzylamine substituted products of Paal-Knorr synthesis from HHD.

aniline derivatives containing electron donating groups were converted to the corresponding *N*-substituted pyrroles (**26c**, **26e**, Figure 11) with higher isolated yields and shorter reaction times (10 h and 20 h respectively). As expected, the utilization of benzylamines under the same experimental conditions showed good performance towards pyrroles, due to the much lower steric hindrance of the nitrogen atom in comparison to the anilines (**27a**-**27d**, Figure 11). Moreover, the substituent effect was also investigated by reacting HHD with 4-methoxybenzylamine and 4-(trifluoromethyl)benzylamine. The corresponding *N*-substituted

pyrroles **27c** and **27d** were obtained in near quantitative yields in 10 minutes and 1 hour respectively. In addition, a series of pyrroles containing heteroatoms such as sulfur (**28a**, **28c**), oxygen (**28b**) and nitrogen (**28d**) was synthesized in up to 99% isolated yields (Figure 12). Furthermore, the alcohol functionality of these products provides a handle to introduce a further ligating group (e.g. phosphinite) and synthesize a new class of biomass-derived ligands or ligand precursors. On the basis of these results, the described Paal-Knorr synthesis meets the *Click Reaction*[192] requirements as it provides the products in near quantitative yields in very short reaction times and proceeds under mild conditions in a benign solvent. Moreover, in most cases, the only byproduct of the reaction is water and the pure product was simply isolated by evaporation of the solvent.




**28a**. 30 min, 99% yield

**28b**. X= O, 1h, 96% yield
**28c**. X= S, 1h, 99% yield

**28d**. 10 min, 98% yield

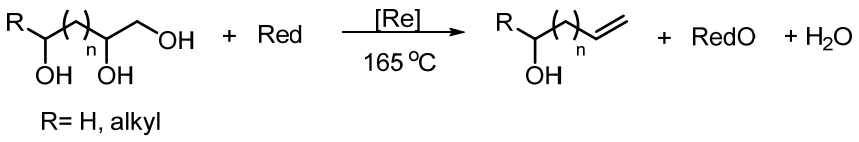
**Figure 12**. The potential biomass-derived ligand precursors.

In summary, we have described an elegant protocol for the synthesis of *N*-substituted pyrroles from HHD and a variety of amines under mild conditions without any catalyst or additives. The vast majority of the products was isolated in excellent yields, which qualifies this transformation as a new *Click Reaction*. In addition, the hydroxyl functionality creates a possibility for further modifications either to produce novel bioactive molecules or to introduce a new functional or ligating group. Thus it should be possible to click a functionalized molecule onto the amino group of lysine in enzymes.

*The published article concerning this work is included in section 7.2.*

## *6.4 Deoxydehydration of Biomass-Based Triols*

Based on our long-standing interest in the conversion of biomass-derived platform chemicals, which possess high oxygen content, we were motivated to develop a cheap and efficient method for oxygen removal without losing any carbon atoms. As a consequence, several rhenium sources were investigated for the catalytic deoxydehydration (DODH) of biomass-based triols in the presence of a reductant (Scheme 32). The catalytic reaction was

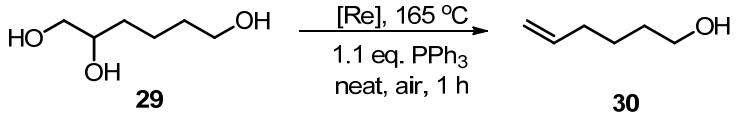



R= H, alkyl

**Scheme 32**. Rhenium catalyzed DODH of biomass-based triols.

tested for the conversion of 1,2,6-hexanetriol (1,2,6-HT, **29**), a model substrate obtained from 5-HMF[50] along with 1.1 equivalents of $PPh_3$ under neat conditions and ambient atmosphere at 165 °C (Table 6). Catalyst screening revealed outstanding 5-hexen-1-ol (**30**) yields (>95%) after 1 hour when 1 mol% of $MeReO_3$ or 0.5 mol% of $Re_2O_7$ were used as the catalysts (Table 6. entries 1, 2). Moreover, the desired product was isolated in around 90% yield simply after Kugelrohr distillation. A significant loss in activity of the catalyst was observed at lower temperatures as well as when the loadings were reduced (Table 6, entries 6-9). When substrate **29** was used as its own reductant in the presence of 1 mol% $Re_2O_7$, the cyclic product tetrahydro-2H-pyran-2-ylmethanol (2-THPM) was formed as the main product

**Table 6**. Catalytic DODH of 1,2,6-hexanetriol under aerobic and neat conditions.[a]




**29** **30**

| Entry | Catalyst | Cat. loading | Conv.[b] (%) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $MeReO_3$ | 1 mol% | >99 | 96 (90)[c] |
| 2 | $Re_2O_7$ | 0.5 mol% | >99 | 98 (91)[c] |
| 3 | $NH_4ReO_4$ | 1 mol% | 70 | 67 |
| 4 | $Re_2(CO)_{10}$ | 1 mol% | - | - |
| 5[d] | (X)$ReO_4$ | 1 mol% | 85 | 84 |
| 6 | $MeReO_3$ | 0.5 mol% | 45 | 43 |
| 7 | $Re_2O_7$ | 0.25 mol% | 79 | 77 |
| 8[e] | $Re_2O_7$ | 0.1 mol% | 55 | 53 |
| 9[f] | $Re_2O_7$ | 0.5 mol% | 17 | 15 |
| 10[g] | $Re_2O_7$ | 1 mol% | 63 | 13 |

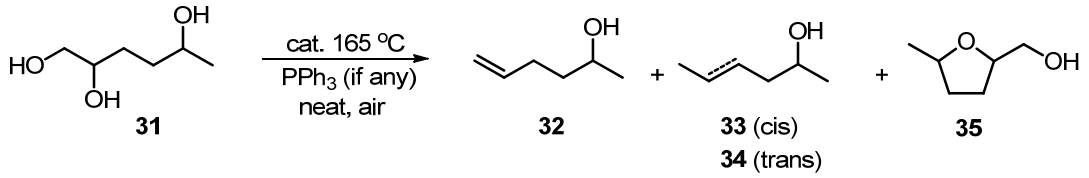
[a] Reaction conditions: 1,2,6-HT (1.0 mmol), $PPh_3$ (1.1 mmol), catalyst, aerobic conditions at 165 °C, 1 h; [b] Determined by $^1H$ NMR spectroscopy using dimethyl phthalate as an internal standard; [c] Isolated yields, 5 mmol scale; [d] X = 2,6-lutidinium cation; [e] 6 h; [f] 150 °C; [g] Without reductant; 34% of 2-THPM was formed.

along with 13% yield of **30**, while no formation of hex-5-enal was observed (Table 6, entry 10). This result could be expected based on the Lewis acidity of $Re_2O_7$. Furthermore, a number of reducing agents were tested in order to substitute $PPh_3$. However, only moderate yields were achieved when 3-octanol and 3-pentanol were applied as the reductants (51% and 13% yield of **30** respectively).

In addition, we synthesized another 5-HMF-derivative – 1,2,5-hexanetriol (1,2,5-HT, **31**), which is an analogue of 1,2,6-HT. A near quantitative isolated yield of **31** (98%) was achieved

by hydrogenation of HHD in the presence of Ru-MACHO-BH (0.5 mol%) as catalyst. Next, 1,2,5-HT was used as a starting material for DODH under the optimized reaction conditions and the results are summarized in Table 7. Only 20% conversion of **31** was achieved after 1 hour resulting in the formation of the expected 5-hexen-2-ol (**32**) as well as a mixture of *cis*-(**33**) and *trans*-2-hexen-5-ol (**34**) (Table 7, entry 1). An increase of the catalyst loading to 3 mol% afforded a mixture of **33** (39%) and **34** (25%) as the main products at full conversion after 1 hour (Table 7, entry 2). This illustrates an interesting OH-position dependence, where the isomerization of the double bond occurs dominantly in the case of 1,2,5-HT but only

**Table 7**. Catalytic transformations of 1,2,5-hexanetriol under neat and aerobic conditions.




| | | | | Yield[c] (%) | | | |
|---|---|---|---|---|---|---|---|
| Entry | Catalyst (mol%) | Time | Conv.[c] (%) | **32** | **33** | **34** | **45** |
| 1[a] | $Re_2O_7$ (0.5) | 1 h | 20 | 10 | 7 | 3 | - |
| 2[a] | $Re_2O_7$ (3) | 1 h | >99 | 3 | 39 | 25 | 10 |
| 3[b,d] | $Re_2O_7$ (0.5) | 10 min | >99 | | | | 90 |
| 4[b] | PTSA (0.5) | 10 min | 51 | | | | 38 |
| 5[b] | TFA (0.5) | 10 min | - | | | | |

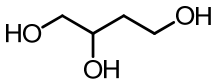
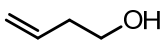
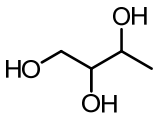
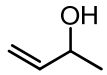
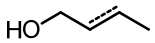
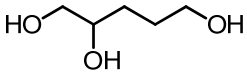
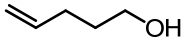
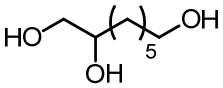
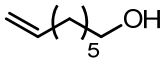
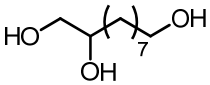
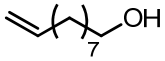
[a] Reaction conditions: 1,2,5-HT (1.0 mmol), $PPh_3$ (1.1 mmol), $Re_2O_7$, aerobic conditions at 165 °C; [b] Without $PPh_3$; [c] Determined by $^1H$ NMR spectroscopy using dimethyl phthalate as internal standard; [d] Isolated yield.

marginally for 1,2,6-HT. In addition, the $Re_2O_7$ catalyzed reaction in which 1,2,5-HT was used as a substrate as well as reductant resulted in the selective formation of the cyclic product 5-methyltetrahydrofurfuryl alcohol (5-MTHFA, **35**) (Table 7, entry 3). Tests with catalytic amounts of organic acids (e.g. PTSA) under the same reaction conditions led to considerably lower yields (Table 7, entry 4).

Next, to investigate the scope of this catalytic system, a variety of triols, mostly derived from sugars were subjected to DODH under neat and aerobic conditions (Table 8). In general, the yields and reaction rates were higher for substrates with longer alkyl chains. Therefore, higher catalyst loadings were necessary to convert the short-chain triols i.e. butanetriols (**36a** and **36b**) and pentanetriols (**36c**) to the corresponding alkenes in good yields (Table 8, entries 1-3). As expected, the $Re_2O_7$ catalyzed DODH of **36b** afforded a mixture of products – but-3-en-2-ol (**37b**) and but-2-en-1-ol (**37c**, *cis* and *trans* isomers) as described in Table 8. Moreover, 5 mol% of the catalyst was required to achieve good conversion and yield after 1 hour. Excellent catalytic performance was shown for the conversion of 1,2,8-octanetriol

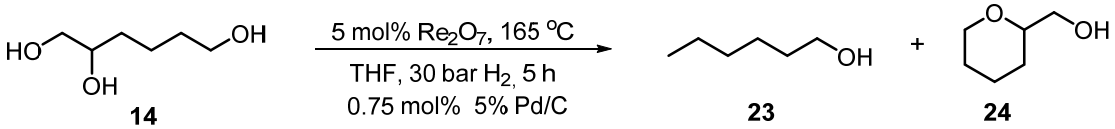
(**36d**) and 1,2,10-decanetriol (**36e**) in the presence of 1 mol% of $Re_2O_7$ (Table 8, entries 4, 5). The corresponding unsaturated alcohols were isolated in 90% yield.

**Table 8**. Substrate scope for $Re_2O_7$ catalyzed DODH of triols.[a]

| Entry | Substrate | Product(s) | $Re_2O_7$ (mol%) | Time (h) | Conv.[b] (%) | Yield[b] (%) |
|---|---|---|---|---|---|---|
| 1 |  **36a** |  **37a** | 2 | 6 | >99 | 97 (77)[c] |
| 2 |  **36b** |  **37b**  **37c** | 5 | 1 | 83 | 42 : 34 **23b** : **23c** |
| 3 |  **36c** |  **37d** | 2 | 1 | 97 | 91 (75)[c] |
| 4 |  **36d** |  **37e** | 1 | 1 | >99 | 98 (90)[c] |
| 5 |  **36e** |  **37f** | 1 | 1 | >99 | 99 (90)[c] |

[a] Reaction conditions: Triol (1.0 mmol), $PPh_3$ (1.1 mmol), $Re_2O_7$, aerobic conditions at 165 °C; [b] Determined by $^1H$ NMR spectroscopy using dimethyl phthalate as internal standard; [c] Isolated yields, 5 mmol scale.

Another reaction which may have potential for large scale application was a one-pot deoxydehydration-hydrogenation (DODH-HG) of triols in order to produce saturated alcohols. For this purpose, Pd/C was applied as a co-catalyst with $Re_2O_7$ in the DODH-HG of 1,2,6-HT in THF at 165 °C under 30 bar of $H_2$ (Scheme 33). Under these conditions, the




**14** **23** **24**

**Scheme 33**. Rhenium catalyzed DODH-HG of 1,2,6-HT to 1-hexanol

reaction was accomplished in 5 hours resulting in the formation of 1-hexanol (**23**, Scheme 33) in 68% yield. It has been reported that 1-hexanol can be dehydrated to 1-hexene,[193] a well-known co-monomer in the production of polyethylene.

In summary, we have demonstrated that $Re_2O_7$, a readily available and relatively cheap rhenium source, is able to promote the fast and highly efficient DODH of biomass-derived triols under solvent-free conditions. The vast majority of the unsaturated alcohols was isolated simply by Kugelrohr distillation from the crude reaction mixture in good to excellent yields. In addition, a one-pot DODH–HG of 1,2,6-hexanetriol was performed, producing 1-hexanol in good yields.

*The published article concerning this work is included in section 7.3.*

In conclusion, we have shown that HHD, which can be readily obtained from biomass-derived 5-HMF is a good starting material for a range of products that can be used as building blocks in various sectors of the chemical and pharmaceutical industries. Catalytic routes were derived for most of these reactions. The reaction of HHD with amines and anilines to the pyrroles proceeded uncatalyzed in very high yields.

# 7. Selected Publications

## *7.1 Cyclopentanone Derivatives from 5-Hydroxymethylfurfural via 1-Hydroxyhexane-2,5-dione as Intermediate*

B. Wozniak, A. Spannenberg, Y. Li, S. Hinze, and J.G. de Vries

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The own contribution to this work is 80%.

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CHEMSUSCHEM Communications

# Cyclopentanone Derivatives from 5-Hydroxymethylfurfural via 1-Hydroxyhexane-2,5-dione as Intermediate

Bartosz Wozniak,[a] Anke Spannenberg,[a] Yuehui Li,[b] Sandra Hinze,[a] and Johannes G. de Vries*[a]

An efficient strategy for the conversion of biomass derived 5-hydroxymethylfurfural (HMF) into 2-hydroxy-3-methylcyclopent-2-enone (MCP) by an intramolecular aldol condensation of 1-hydroxyhexane-2,5-dione (HHD) has been developed. Further transformations of MCP towards the diol, enol acetate, levulinic acid and N-heterocyclic compounds are also reported.

In view of the dwindling supply of fossil resources, new scenarios need to be developed for the manufacture of the chemicals our lives depend upon, such as pharmaceuticals or plastics, which are currently derived from crude oil. We are interested in the catalytic conversion of platform chemicals derived from renewable resources into known or new chemicals.[1] 5-Hydroxymethylfurfural (HMF; Scheme 1, **1**) is obtained from the dehydration of fructose and has become a well-known platform chemical for the production of numerous valuable chemicals, such as 2,5-furandicarboxylic acid.[2] Recently, we have become interested in the further development of 1-hydroxyhexane-2,5-dione (HHD, **2**), a product of the hydrogenation/hydrolytic ring opening of HMF (Scheme 1).

Several catalytic systems have been reported to produce HHD. Hydrogenation of HMF into HHD in acidic media catalyzed by Pt/C was reported by Descotes and co-workers in 1991.[3] Various heterogeneous catalysts were then reported for the hydrogenative ring opening of HMF, including Rh–Re/$SiO_2$,[4] Pd/C,[5,6] and Au nanoparticles on metal oxide supports.[7,8] However, these methods require high $H_2$ pressures and selectivities vary from 57% to 81%. Higher HHD selectivities are obtained in processes catalyzed by homogeneous catalysts.[9–12] In particular, $Cp^*Ir^{III}$ half-sandwich complexes have appeared to be most promising.[10–12]

Fu and co-workers increased the selectivity to 99%,[12] by using such a complex with electron-donating ligands, and adjusting the pH during the reaction. However, they only obtained high conversions and selectivities when using formic acid as the hydrogen source. None of these publications have reported an isolation procedure. The catalytic hydrogenation of HMF to HHD still needs to be improved and development of an effective HHD isolation method remains a major challenge.[10–12] Furthermore, to our knowledge, no further conversions of HHD as a starting material have been reported to date.

Herein, we present an improved protocol for the synthesis of HHD. We report the first isolation procedure, as well as the full characterization of HHD. To establish HHD as a platform chemical we show its potential as a building block, namely its transformation into 2-hydroxy-3-methylcyclopent-2-enone (MCP, **3**) and potentially useful follow-up products.

Concerning the development of new homogeneous catalysts for the conversion of HMF into HHD, limitations arise from the requirements of water solubility and stability under acidic conditions. Thus, activated base metal catalysts, which are used for hydrogenation and transfer hydrogenation reactions, did not show any selectivity towards HHD. We evaluated a series of air- and moisture-stable iridium and ruthenium complexes (Figure 1) that have not been previously used for the hydrogenation of HMF to HHD. The best results were obtained with the half-sandwich [Cp*Ir(dpa)Cl]Cl (dpa = dipyridylamine) catalyst **I** (Table 1, entry 1), which is a known catalyst for water oxidation[13] and the transfer hydrogenation of levulinic acid.[14] Poor selectivities were observed with ruthenium complexes **II**, **IV**, and **V** (Figure 1 and Table 1, entries 2, 4, and 5). After fur-

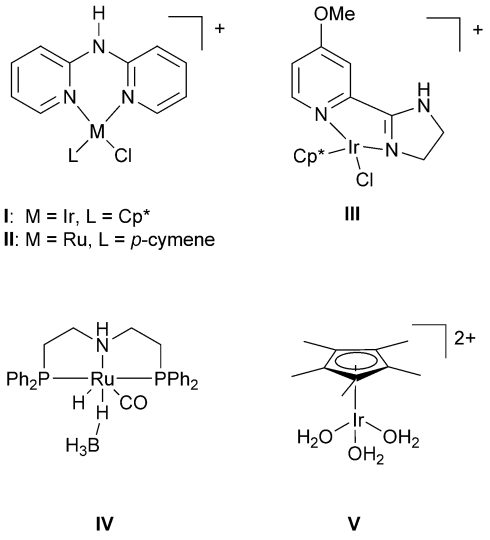


**Figure 1.** Iridium and ruthenium complexes used.

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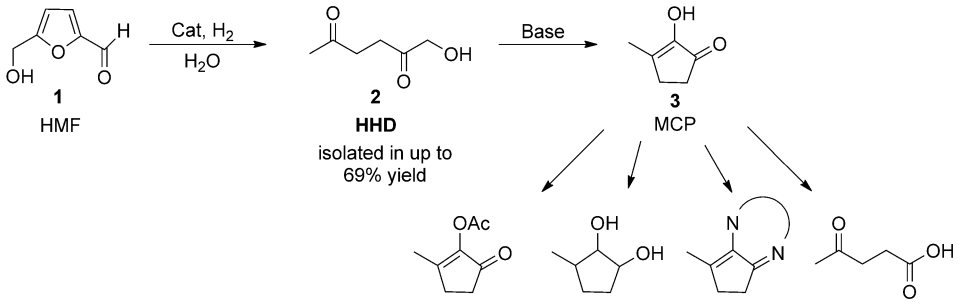
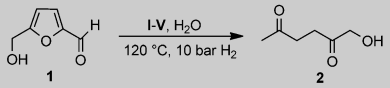



**Scheme 1.** Conversion of HMF (**1**) into MCP (**3**) via HHD (**2**) and further possible reactions.

**Table 1.** Screening of catalysts **I-V** for HHD formation in aqueous media.[a]




| Entry | Catalyst | *t* [h] | Conv. [%][b] | Yield [%][b] |
|---|---|---|---|---|
| 1 | **I** | 2 | >99 | 76 (69)[c] |
| 2 | **II** | 4 | 97 | 42 |
| 3 | **III** | 1 | >99 | 60 |
| 4 | **IV** | 2 | 93 | 5 |
| 5 | **V** | 2 | 34 | 25 |
| 6[d] | **I** | 4 | >99 | 67 |
| 7[d] | **III** | 4 | >99 | 71 |

[a] Reaction conditions (unless otherwise stated): HMF (4 mmol), water (20 mL), **I–V** (0.5 mol%), 120 °C, 10 bar $H_2$. [b] Determined by $^1$H NMR spectroscopy with $(CH_3)_4NBF_4$ as an internal standard. [c] Figure in parentheses refers to isolated product. [d] HMF (40 mmol), phosphate buffer (200 mL, 0.1 M, pH 2.5), catalyst (0.075 mol%), 140 °C, 20 bar $H_2$.

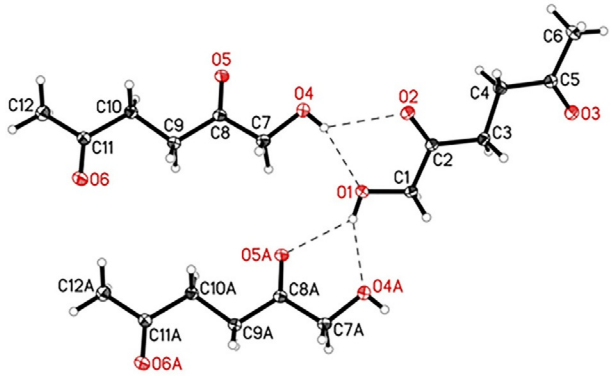


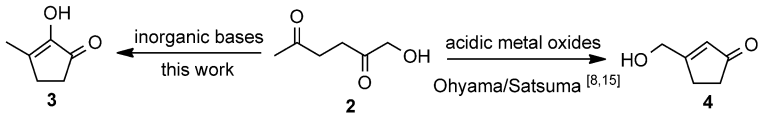

**Figure 2.** ORTEP representation of HHD showing intermolecular O–H···O hydrogen bonds (for more details, see the Supporting Information). Displacement ellipsoids correspond to 30% probability.

ther optimization, the best results were obtained with **I** (0.5 mol%) with 10 bar $H_2$ at 120 °C in water and HHD was isolated in 69% yield (Table 1, entry 1). The major byproduct was found to be an insoluble polymeric solid, presumably humins, which is consistent with the observations of other groups.[6,12] In addition, the utilization of a phosphoric acid/sodium phosphate buffer solution allowed processing with lower catalyst loading (0.075 mol%), albeit with no improvement in yield.

Single crystals were grown from a DCM/pentane mixture at −30 °C and the crystal structure was determined for the first time by X-ray diffraction analysis (Figure 2). With reasonable amounts of clean compound in hand, we started to investigate further reactions that used HHD as a starting material.

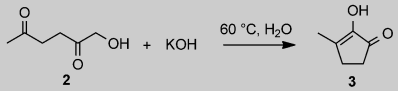
Interestingly, base-promoted aldol condensation led to 2-hydroxy-3-methylcyclopent-2-enone (MCP, **3**) instead of the expected 3-(hydroxymethyl)cyclopent-2-en-1-one (HCPEN, **4**), as shown in Scheme 2.[8,15] MCP is a known flavor ingredient in roasted coffee and maple syrup, and is widely used in the food industry. It also finds use as a precursor for the biosynthesis of antibiotics,[16] as a fragrance in perfumery,[17] and as ligand in metal complexes.[18] Several routes towards MCP have been previously reported, starting from isoprene,[19] 2-keto-glutaric acid,[20] dimethyl adipate,[21] or 1-acetoxy3-buten-2-one.[22] We report the efficient synthesis of MCP starting from biomass-derived HMF in a two-step process, involving HHD as an intermediate. We optimized the reaction by investigating the role of base in the aldol condensation reaction of HHD at 60 °C (Table 2). Without base or in the presence of small amounts of KOH, no conversion was observed even after 8 h (Table 2, entries 1–3). With an increased KOH/HHD ratio of 1.5, full conversion was achieved in 15 minutes, affording MCP in 72% yield (Table 2, entry 7). Similar results were obtained at room temperature after 1.5 h (Table 2, entry 8).

Based on these results, we carried out further optimizations by using 1.5 equivalents of base at 60 °C. The results of solvent and base screenings are shown in Table 3. Simple inorganic bases such as alkaline hydroxides promote the aldol condensa-




**Scheme 2.** Aldol condensation products starting from **2**.

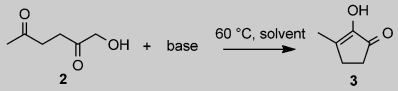
**Table 2.** Influence of the amount of base on the synthesis of MCP (**3**) from HHD (**2**).[a]




| Entry | KOH [equiv.] | *t* | Conv. [%][b] | Yield [%][c] |
|---|---|---|---|---|
| 1 | – | 8 h | – | – |
| 2 | 0.1 | 8 h | – | – |
| 3 | 0.4 | 8 h | – | – |
| 4 | 0.7 | 16 h | >99 | 47 |
| 5 | 1.0 | 1 h | >99 | 65 |
| 6 | 1.2 | 30 min | >99 | 68 |
| 7 | 1.5 | 15 min | >99 | 72 |
| 8[d] | 1.5 | 1.5 h | >99 | 70 |

[a] Reaction conditions (unless otherwise stated): HHD (0.4 mmol), KOH, water (2 mL), 60 °C. [b] Determined by thin-layer chromatography. [c] Isolated yields. [d] Reaction carried out at room temperature.

**Table 3.** Solvent and base screening in the intramolecular aldol condensation of HHD.[a]



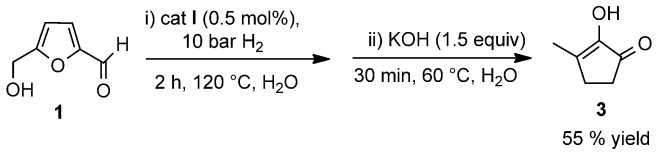

| Entry | Base | Solvent | *t* | Conv. [%][b] | Yield [%][c] |
|---|---|---|---|---|---|
| 1 | NaOH | $H_2O$ | 15 min | >99 | 70 |
| 2 | KOH | $H_2O$ | 15 min | >99 | 72 |
| 3 | $CsCO_3$ | $H_2O$ | 20 h | >99 | 62 |
| 4 | $K_3PO_4$ | $H_2O$ | 2 h | >99 | 71 |
| 5 | KOH | EtOH | 15 min | >99 | 61 |
| 6 | KOH | MeOH | 15 min | >99 | 57 |
| 7 | KOH | MeCN | 24 h | – | – |
| 8 | KOH | THF | 22 h | >99 | 60 |
| 9 | KOtBu | THF | 5 min | >99 | **80** |

[a] Reaction conditions: HHD (0.4 mmol), base (0.6 mmol), solvent (2 mL), 60 °C. [b] Determined by thin-layer chromatography. [c] Isolated yields.

tion when water and alcohols are used as solvents (Table 3, entries 1–2, 5–6). However, the utilization of potassium *tert*-butoxide in THF led to full conversion in 5 minutes and higher yield of the isolated product (Table 3, entry 9). Notably, no formation of **4** was observed. The only byproduct present was an insoluble polymeric substance, which was also reported by Ohyama, Sutsuma and co-workers.[15]

We also established a one-pot synthesis of MCP directly from HMF. Under optimized conditions, the hydrogenation/hydrolytic ring opening of HMF followed by intramolecular aldol condensation led to 55% yield of isolated MCP (Scheme 3). Crystals of MCP suitable for X-ray diffraction analysis were obtained (Figure 3).

We then turned our attention to the conversion of MCP into valuable biomass-based chemicals (Scheme 4). Hydrogenation of MCP catalyzed by Ru-MACHO-BH[23] (Figure 1, complex **IV**) gave full conversion of MCP after 16 h (Scheme 4a). 3-Methyl-1,2-cyclopentanediol (**5**) was isolated in near-quantitative yield as a mixture of 3 diastereomers (3.3:1.6:5.0). Access to **5** is limited and its synthesis usually requires harsh conditions.[24] Recently, **5** was used by Chavan and Bhanage in oxidative carbonylation reactions to form cyclic carbonates, which play an




**Scheme 3.** One-pot synthesis of MCP (**3**). Reaction conditions: i) HMF (7.9 mmol), water (40 mL), catalyst (0.5 mol%), 120 °C, 10 bar $H_2$, 2 h; ii) KOH (11.9 mmol), 60 °C, 30 min.

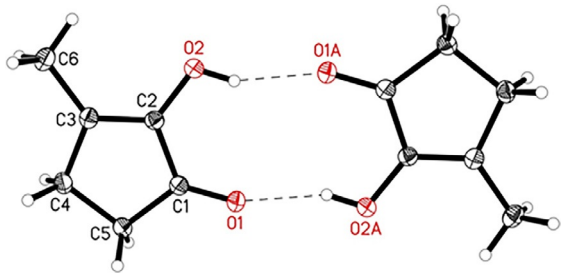
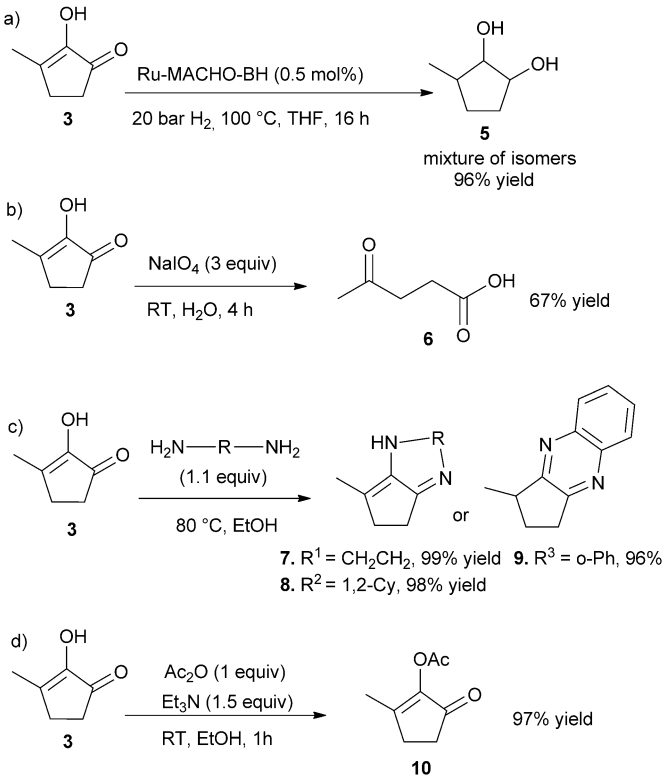



**Figure 3.** ORTEP representation of MCP showing intermolecular O–H···O hydrogen bonds (for more details, see the Supporting Information). Displacement ellipsoids correspond to 30% probability.




**Scheme 4.** Conversion of MCP into valuable biomass-based chemicals: a) MCP (2.2 mmol), Ru-MACHO-BH (0.5 mol%), THF (10 mL), 10 bar $H_2$, 100 °C, 16 h; b) MCP (2.2 mmol), $NaIO_4$ (6.6 mmol), $H_2O$ (10 mL), RT, 6 h; c) MCP (2.2 mmol), diamine (2.4 mmol), EtOH (5 mL), 80 °C; d) MCP (4.45 mmol), $Ac_2O$ (4.45 mmol), $Et_3N$ (6.79 mmol), EtOH (5 mL), RT.

important role in pharmaceuticals, polymers and agrochemicals.[25] The addition of sodium periodate to aqueous MCP solutions led to the formation of levulinic acid (**6**; Scheme 4b), a well-known precursor for a variety of compounds with a broad range of applications.[26] Naturally occurring MCP is therefore a potential alternative to HMF for the production of **6**.

Furthermore, α,β-unsaturated imines **7** and **8** and quinoxaline derivative **9** were obtained in excellent yields by addition of diamines to MCP in EtOH at 80 °C (Scheme 4c). Unsaturated imines were used in numerous studies related to C–C and C–N bond formations,[27] and quinoxalines are important pharmaceutical intermediates, based on their antiviral, anticancer and antifungal properties.[28] In another example, MCP was acetylated to give the corresponding enol acetate **10** in excellent yield (Scheme 4d). This compound is of use in the synthesis of fragrances such as dihydrojasmone.[17]

In conclusion, we have described a novel pathway for the conversion of biomass-based HMF into MCP via HHD. Aldol condensation of HHD by using inorganic bases led to MCP as sole product. Both HHD and MCP were isolated and fully characterized. We obtained MCP directly from HMF in 55% yield. Finally, we demonstrated that MCP can be further transformed into useful building blocks in excellent yields.

## Acknowledgements

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## *Conflict of interest*

*The authors declare no conflict of interest.*

**Keywords:** biomass · cycloketones · homogeneous catalysis · platform chemicals · renewable resources

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## *7.2 Efficient Synthesis of Biomass-Derived N-Substituted 2-Hydroxymethyl-5-Methyl-Pyrroles in Two Steps from 5-Hydroxymethylfurfural*

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*Eur. J. Org. Chem.* **2018**, *11*, 2009-2012

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The own contribution to this work is 80%.

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Communication

Renewable Pyrroles

# Efficient Synthesis of Biomass-Derived N-Substituted 2-Hydroxymethyl-5-Methyl-Pyrroles in Two Steps from 5-Hydroxymethylfurfural

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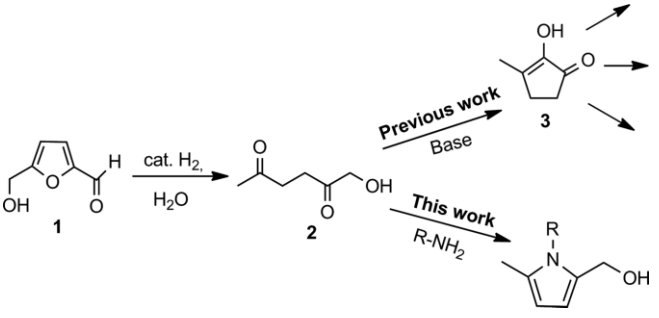
**Abstract:** An efficient two-step synthesis for the conversion of biomass-derived 5-hydroxymethyl-furfural (HMF) to a variety of N-substituted 2-hydroxymethyl-5-methylpyrroles was developed. In the first step, 1-hydroxyhexane-2,5-dione (HHD) was obtained by hydrogenation of HMF and thereafter used in a Paal–Knorr reaction with a range of amines in the absence of catalyst at room temperature. The reaction could potentially be used as a click reaction.

## Introduction

Pyrroles are amongst the most important heterocyclic aromatic compounds. They are present in many pharmaceutically active compounds[1–3] as well as in dyes, fluorescent compounds, and conductive materials, among others.[4–7] Although a variety of methods exist for the preparation of pyrroles,[8–13] one of the simplest and most widely used methods is the Paal–Knorr synthesis.[13–19] Although most of the literature examples typically use catalysis for this transformation,[13–16,18,19] it was also shown that the reaction can be performed without catalysis.[17]

In view of the dwindling supply of fossil resources and the environmental issues related to their use there is a strong drive towards new production methods based on renewable resources. 5-Hydroxymethylfurfural (HMF, **1**) is a platform chemical that can be obtained by dehydration of fructose.[20] Hydrogenation with concomitant hydrolytic ring opening of **1** leads to the formation of 1-hydroxyhexane-2,5-dione (HHD, **2**),[21] which could serve as a building block for the production of a wide range of fine chemicals. Although a few publications exist on the preparation of HHD (**2**) from 5-HMF (**1**) using homogeneous or heterogeneous catalysis, its isolation in pure form was reported only by Deng, Fu and co-workers.[21k]

Recently, we have revisited the synthesis of **2**, using a series of iridium and ruthenium catalysts, and we have reported its full characterization and isolation.[22] In addition, 2-hydroxy-3-methylcyclopent-2-enone MCP (**3**) was obtained by intermolecular aldol condensation of HHD (**2**) and was further converted into valuable biomass-derived chemicals (Scheme 1). Synthesis of **3** under the influence of base has also been reported by Yang and co-workers[23] as well as by Deng, Fu and co-workers.[24] Under acidic conditions 3-hydroxymethyl cyclopentanone (HCPN) is obtained.[21g,24]




Scheme 1. Previously reported conversion of HMF (**1**) to HHD (**2**) and further possible reactions.

Herein, we present our work on the conversion of 5-HMF (**1**) into N-substituted 2-hydroxymethyl-5-methylpyrroles via HHD (**2**) under mild conditions (Scheme 1).

## Results and Discussion

We initiated our studies by synthesizing a large amount of HHD (**2**) (Scheme 2). For this purpose, the recently optimized conditions were applied using iridium complex **I** as the catalyst of choice. It is worth noting that full conversion of 5-HMF was achieved in phosphate buffer solution (PBS, pH = 2.5) within 1 hour (as compared to the 4 hours we had previously reported;[22] see the Supporting Information for details) and HHD (**2**) was isolated in good yield (71 %). With reasonable amounts of **2** in hand, we tested a number of amines in the Paal–Knorr synthesis with the intent to produce a variety of N-substituted 2-hydroxymethyl-5-methyl pyrroles. To the best of our knowledge, this is the first study of the use of HHD (**2**) in the Paal–Knorr synthesis.

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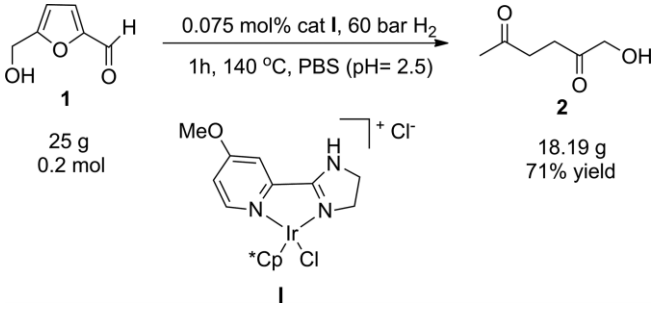
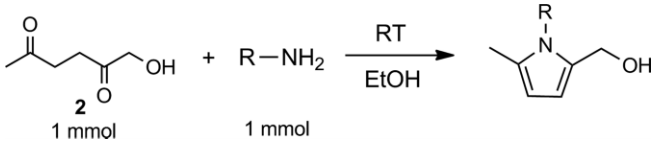



Scheme 2. Large-scale synthesis of HHD (**2**).

All reactions were carried out at room temperature using ethanol as a solvent without any catalyst at a 1:1 molar ratio of HHD (**2**) to amine (Scheme 3). These conditions are in agreement with the principles of green chemistry.[25]




Scheme 3. The Paal–Knorr synthesis of pyrroles from HHD (**2**) and primary amines.

We started our substrate screening by employing alkylamines (Figure 1). The conversion of HHD (**2**) was monitored by thin-layer chromatography. Most of the targeted N-alkyl-substituted 2-hydroxymethyl-5-methylpyrroles were obtained with excellent yields of isolated product and with full conversions after 5–25 minutes at room temperature. Product **4g** was formed after a significantly prolonged reaction time (48 hours were required to achieve full conversion of HHD). This much slower reaction is likely due to the steric hindrance of the cyclopentyl ring. For the same reason, the reaction with *tert*-butylamine did not show any conversion to product **4f** under the same conditions. A lower yield of isolated product was also obtained for product **4i** when 1,6-hexanediamine was used as a substrate. The reason is that the product consisted of a mixture of mono- and bis-pyrroles (4:1 ratio, respectively). A reaction of **2** with aqueous $NH_4OH$ to the NH pyrrole was also tested, but selectivity to the desired product was very low.

Next, the scope was extended to aniline derivatives containing both electron-donating and electron-withdrawing groups (Figure 2). In comparison to the reactions with alkylamines, synthesis of N-aryl-substituted 2-hydroxymethyl-5-methylpyrroles required prolonged reaction times (up to 48 hours). However, neither the reaction with aniline nor the reactions with anilines containing electron-withdrawing groups resulted in full conversions. Flash column chromatography was necessary to purify the products **5a**–**5c**.

On the other hand, the duration of the reactions with anilines bearing electron-donating groups was much shorter (10 h and 20 h for **5c** and **5e**, respectively) and better yields of isolated product were obtained. The substituent effect was also investigated in the Paal–Knorr synthesis of **2** with benzylamines. As expected, due to the much lower steric hindrance of the nitrogen atom in comparison to the anilines, the rates of the reactions with these arylalkylamines were much faster. Moreover, the effects exerted by the substituents attached to the aromatic ring of benzylamine are consistent with those observed in the reactions with the anilines. For example, reaction of **2** with 4-methoxybenzylamine, which forms **6c**, goes to completion after 10 minutes. On the other hand, an electron-withdrawing group (such as $CF_3$) decreases the reactivity of the amine and product **6d** was formed with full conversion in 1 hour (Figure 3).

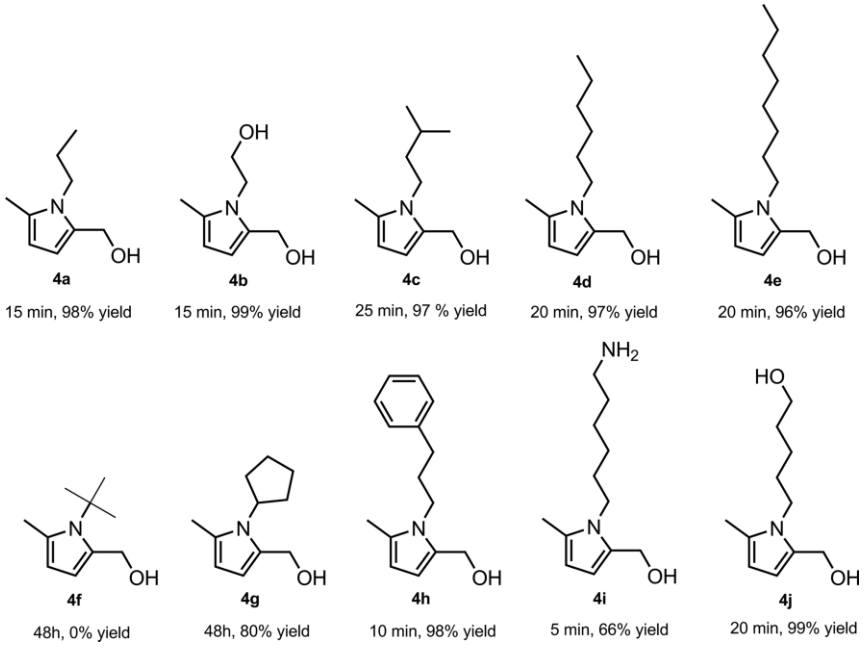



Figure 1. N-alkyl-substituted pyrroles from Paal–Knorr synthesis of HHD (**2**).

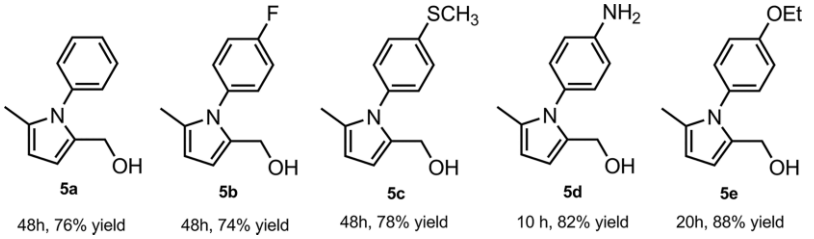



Figure 2. The N-aryl-substituted products of Paal–Knorr synthesis from HHD (**2**).

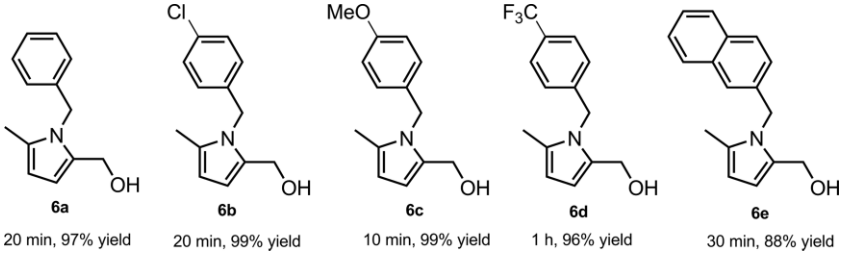



Figure 3. The N-benzylamine-substituted products of Paal–Knorr synthesis from HHD (**2**).

Finally, this synthesis opens up the possibility to introduce functional groups that could serve as ligand precursors in combination with the 2-hydroxymethyl-5-methyl-pyrrole moiety. Several groups reported monodentate[26] as well as bidentate[27] ligands based on N-substituted pyrroles. Thus, a series of pyrrole-based compounds were synthesized containing donor atoms, such as sulfur (**7a**, **7c**), oxygen (**7b**), and nitrogen (**7d**) with excellent yields (Figure 4). Purification of **7a**–**d** was not needed, and pure compounds were obtained by simply evaporating the solvent and drying the product in vacuo. The hydroxyl functionality could in principle be used for the introduction of further ligating groups, such as phosphites or phosphinites.

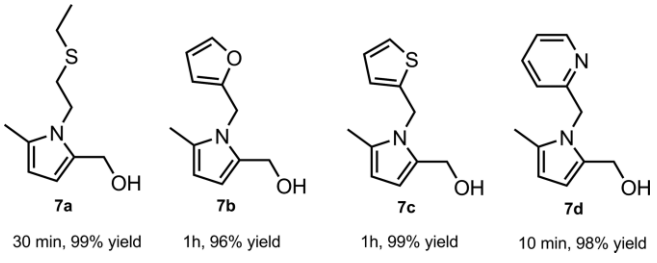



Figure 4. The potential biomass-derived candidates for ligands.

## Conclusions

In conclusion, we have described the efficient synthesis of N-substituted 2-hydroxymethyl-5-methylpyrroles in two steps from biomass-derived 5-HMF (**1**) via HHD (**2**). The reaction was performed in line with green chemistry principles, that is, without any additives at room temperature in ethanol as a solvent. A wide scope in amines was tested. Some of the products could potentially be used as biomass-derived ligands. Additionally, the alcohol functionality provides a handle for further modification either to produce novel bioactive molecules or to introduce a third ligating group. The high efficiency of this reaction under moderate conditions would qualify it as a click reaction.[28] One obvious application would be as crosslinking agent to enzymes. In this approach, a functional unit could be attached by acylation, alkylation, or silylation to the hydroxy group after which the ensemble could be clicked onto the enzyme by reaction with a lysine side chain. We are currently investigating such an approach.

## Experimental Section

**General Procedure for the Synthesis of N-Substituted 2-Hydroxymethyl-5-methylpyrroles:** Under aerobic conditions HHD (130 mg, 1.0 mmol) was dissolved in ethanol (2.0 mL) and amine (1 mmol) was added. The reaction was stirred and monitored by thin-layer chromatography until complete conversion of substrate was achieved. The solutions were filtered through celite and concentrated in vacuo. Unless otherwise stated, pure products were obtained and further purification methods were not required. In cases where this was necessary column purification was performed over silicia using cyclohexane/ethyl acetate (1:2) as eluents.

## *Acknowledgments*

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**Keywords:** Pyrroles · Paal–Knorr synthesis · Heterocycles · Cyclization · Renewable resources

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## *7.3 Rhenium-Catalyzed Deoxydehydration of Renewable Triols Derived from Sugars*

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The own contribution to this work is 85%.

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# Rhenium-catalyzed deoxydehydration of renewable triols derived from sugars†

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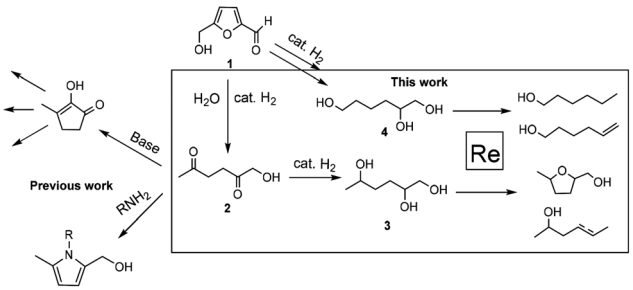
**An efficient method for the catalytic deoxydehydration of renewable triols, including those obtained from 5-HMF, is described. The corresponding unsaturated alcohols were obtained in good yields using simple rhenium(VII)oxide under neat conditions and ambient atmosphere at 165 °C.**

The dwindling supply of fossil resources as well as the side effects of their continued use, such as global warming, forces us to develop a new and sustainable access to fuels and chemicals.[1] Biomass is the most attractive, globally accessible carbon-rich feedstock that has great potential to replace non-renewable resources.[2] However, biomass-derived raw materials may contain up to 50 wt% of oxygen.[3] Deoxydehydration (DODH) of diols and polyols to the alkenes is one of the most efficient ways to lower the oxygen content of biomass and biomass-derived platform chemicals and could develop into a methodology that allows access to a wide range of valuable chemicals.[4] Several catalysts have been reported to perform this reaction including vanadium[5] and molybdenum[6] complexes. However, rhenium-based catalysts attracted the most attention in the past ten years.[7]

The most common rhenium catalysts used in DODH are $MeReO_3$,[8a] $Re_2(CO)_{10}$ [8b] and $Re_2O_7$ (or $HReO_4$),[8c] however the latter was mainly used as a supported catalyst in heterogeneous systems.[8d] Several reductants have been reported; triphenylphosphine seems to be the most effective, although good results have also been obtained with secondary alcohols. Hydrogen and CO are usually less effective.

Recently, we became interested in the synthesis and applications of 1-hydroxyhexane-2,5-dione (HHD, **2**),[9] which can be obtained in excellent yield by hydrogenation of 5-(hydroxymethyl)furfural (HMF, **1**), a prominent platform chemical derived from carbohydrates (Scheme 1).[10] Herein, we report the homogeneous hydrogenation of **2** to 1,2,5-hexanetriol (1,2,5-HT, **3**), an analogue of 5-HMF-derived 1,2,6-hexanetriol (1,2,6-HT, **4**), which has been reported in the past (Scheme 1, conversion of **2** to **3**).[11] Next, we subjected these biomass-based hexanetriols to DODH using the cheap rhenium catalyst $Re_2O_7$ under neat conditions and ambient atmosphere. The generality of this approach was then extended by also investigating various renewable triols *e.g.* butanetriols.[12] Typically, the corresponding alkenes were obtained in very good yields and short reaction times. In addition, a one-pot deoxydehydration–hydrogenation (DODH–HG) approach was investigated, leading to the isolation of 1-hexanol (**13**) from 1,2,6-hexanetriol (**4**).




**Scheme 1** Synthetic routes for the conversion of HMF (**1**) and HHD (**2**) into useful building blocks.

## Results and discussion

We initiated our studies by examining the hydrogenation of **2** to **3**, which was first described by Descotes' group in 1991.[9a] Recently, a number of studies reported **3** as the by-product,[13] as well as the main product[14] in the hydrogenation of **1** with heterogeneous ruthenium catalysts. However, efficient methods reporting quantitative yields using homogeneous catalysis are absent. We found that use of commercially available Ru-MACHO-BH (cat **I**),[15] a well-known catalyst for a variety of (de)hydrogenation reactions, was quite effective.[16] A near

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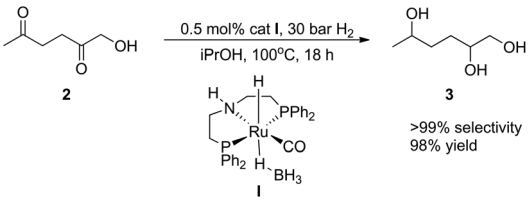
†Electronic supplementary information (ESI) available. See DOI: 10.1039/c8gc02387e

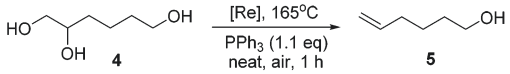



Scheme 2 Homogeneous hydrogenation of HHD (**2**).

quantitative yield of **3** was achieved after 18 hours at 100 °C with 30 bar of $H_2$ using 0.5 mol% of the catalyst and isopropanol as the solvent (Scheme 2).

We next examined the DODH of a variety of triols, especially hexanetriols **3** and **4** derived from **1**. Initial reaction optimization was carried out by testing different rhenium sources under aerobic and neat conditions using **4** as a model substrate and triphenylphosphine ($PPh_3$) as a reductant in stoichiometric amounts (Table 1). When 1 mol% of catalyst (respectively 0.5 mol% of dimeric $Re_2O_7$) was used, very good yields of 5-hexen-1-ol (**5**) (>95%) were achieved at full conversion with $MeReO_3$ and $Re_2O_7$ (Table 1, entries 1–2). A decrease in activity was found when ammonium- or 2,6-lutidinium[17] perrhenate salts were used as catalysts (Table 1, entries 3, 5). On the other hand, no conversion of **4** was observed in the presence of $Re_2(CO)_{10}$ under the same experimental conditions (Table 1, entry 4). This may have been caused by its easy sublimation. A decrease of catalyst loading resulted in a decrease in activity, however the DODH still occurs in the presence of 0.1 mol% $Re_2O_7$ (Table 1, entry 8). As $Re_2O_7$ is more active and remarkably cheaper than $MeReO_3$, it was selected as the rhenium source for further reaction optimization. The combination of $Re_2O_7$ and $PPh_3$ has been used before *e.g.* in deoxygenation of aliphatic epoxides.[18]

Table 1 Catalyst testing in DODH of 1,2,6-HT under aerobic and neat conditions[a]




| Entry | Catalyst | Cat loading | Conv.[b] (%) | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $MeReO_3$ | 1 mol% | >99 | 96 (90)[c] |
| 2 | $Re_2O_7$ | 0.5 mol% | >99 | 98 (91)[c] |
| 3 | $NH_4ReO_4$ | 1 mol% | 70 | 67 |
| 4 | $Re_2(CO)_{10}$ | 1 mol% | — | — |
| 5[d] | (X)$ReO_4$ | 1 mol% | 85 | 84 |
| 6 | $MeReO_3$ | 0.5 mol% | 45 | 43 |
| 7 | $Re_2O_7$ | 0.25 mol% | 79 | 77 |
| 8[e] | $Re_2O_7$ | 0.1 mol% | 55 | 53 |
| 9[f] | $Re_2O_7$ | 0.5 mol% | 17 | 15 |
| 10[g] | $Re_2O_7$ | 1 mol% | 63 | 13 |

[a] Reaction conditions: 1,2,6-HT (1.0 mmol), $PPh_3$ (1.1 mmol), catalyst, under air at 165 °C, 1 h. [b] Determined by $^1H$ NMR spectroscopy using dimethyl phthalate as an internal standard. [c] Isolated yields, 5 mmol scale. [d] X = 2,6-lutidinium cation. [e] 6 h. [f] 150 °C. [g] Without reductant; 34% of 2-THPM was formed.

Lowering the reaction temperature to 150 °C led to a much lower conversion after 1 hour (Table 1, entry 9).

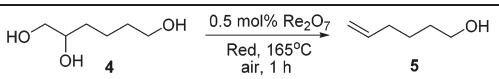
A recyclability test revealed some loss in activity (only 51% yield of **5** under otherwise similar conditions) during the second cycle when 1.1 eq. of $PPh_3$ was used as a reductant (see ESI† for details). This loss of activity might be due to excessive rhenium reduction and indeed, the formation of a black, insoluble precipitate suggests the formation of rhenium nanoparticles.[7b,17,19] Working on this premise, we used only 0.95 eq. of $PPh_3$ in the first cycle in order to retain the activity of the catalyst. Reuse of this catalyst with 1.1 eq. of $PPh_3$ in the second cycle lead to the formation of alkene (**5**) in 104% yield (5% of the remaining triol was left after first cycle). It thus appears possible to reuse the catalyst several times.

We have also investigated if 1,2,6-HT **4** could be used as a substrate as well as a reductant hoping to find hex-5-enal as the product. However, the reaction of **4** without $PPh_3$ resulted in cyclic tetrahydro-2*H*-pyran-2-ylmethanol (2-THPM, **14**) as the main product and 13% yield of **5** and no hex-5-enal was obtained (Table 1, entry 10). This result could be expected based on the Lewis acidity of $Re_2O_7$. Indeed, the acid-catalyzed synthesis of **14** from **4** has already been reported,[11] and therefore no further studies were carried out on this transformation.

Next, a number of reductants were investigated in order to substitute $PPh_3$ and the results are summarized in Table 2. Unfortunately, only low and moderate yields of **5** were obtained when $H_2$ and secondary alcohols were applied as reducing agents (Table 2, entries 2–3, 8). Under solvent free conditions, $Re_2O_7$ catalyzed DODH with salts as reductants (*e.g.* sulfites or zinc dust) led to disappointing results. In view of its relatively low price, the excellent yields obtained and the simple isolation procedure by Kugelrohr distillation (see ESI† for details), $PPh_3$ was the obvious choice of reductant.

We have also investigated the influence of oxygen on the process. Notably, a separate experiment under optimized con-

Table 2 Reductant screening in DODH of 1,2,6-HT under neat and air conditions[a]




| Entry | Reductant (eq.) | Conv.[b] (%) | Yield[b] (%) |
|---|---|---|---|
| 1 | $PPh_3$ (1.1) | >99 | 98 (91)[c] |
| 2 | 3-Pentanol (2) | 42 | 13 |
| 3 | 3-Octanol (2) | >99 | 51 |
| 4 | $NaH_2PO_2$ (2) | — | — |
| 5 | Zn (2) | 2 | 1 |
| 6 | $Na_2SO_3$ (2) | — | — |
| 7 | $HCO_2NH_4$ (2) | — | — |
| 8[d] | $H_2$ | 21 | 5 |
| 9[d] | CO | — | — |

[a] Reaction conditions: 1,2,6-HT (1.0 mmol), reductant, $Re_2O_7$ (0.005 mmol), under air at 165 °C, 1 h. [b] Determined by $^1H$ NMR spectroscopy using dimethyl phthalate as internal standard. [c] Isolated yields, 5 mmol scale. [d] 7 bar.

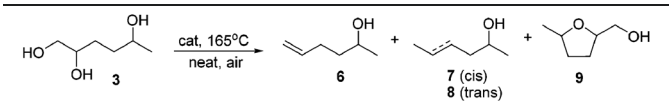
 

ditions, but under argon atmosphere instead of air gave a 65% yield of **5** (see ESI† for details), leading to the suggestion that oxygen plays a role in the catalytic process, which was also observed by Bergman *et al.*[8b]

Surprisingly, the reaction with 1,2,5-HT (**3**) under the optimized conditions proceeded only to 20% conversion after 1 hour and in addition to 5-hexen-2-ol (**6**) afforded a mixture of *cis*- (**7**) and *trans*-2-hexen-5-ol (**8**) (Table 3, entry 1). Upon increasing the catalyst loading to 3 mol%, complete conversion produced a mixture of **7** (39%) and **8** (25%) as main products. Rhenium-catalyzed isomerization of α-olefin products in DODH was reported before, although the observed amounts of isomers were small.[20] This indicates an interesting OH-position dependence, where isomerization of the double bond occurs dominantly in the case of **3**, yet only marginally for 1,2,6-HT (**4**). When substrate **3** was used as its own reductant, the cyclic product 5-methyltetrahydrofurfuryl alcohol (5-MTHFA, **9**) was obtained with high selectivity (Table 3, entry 3). Various methods exist for the preparation of 5-MTHFA from 5-methylfurfural,[21] however to the best to our knowledge, this is the first report on cyclization of 1,2,5-HT to **9**. Moreover, catalytic amounts of the organic acids TFA (trifluoroacetic acid) and PTSA (*p*-toluenesulfonic acid) were tested under the same reaction conditions, but only 38% yield of cyclic product **9** at 51% conversion could be detected in the reaction catalyzed by PTSA. Following these results, the substrate scope was investigated by using 1 mol% of $Re_2O_7$ in DODH with a variety of triols (Table 4). In general, the yields and reaction rates were higher with longer alkyl chains in the substrates. Thus, to convert the short-chain triols *i.e.* butanetriols (**10a** and **10b**) and pentanetriols (**10c**), higher catalyst loadings were necessary in order to achieve satisfactory results. For example, 1-buten-4-ol (**11a**) was obtained in a good yield using 2 mol% of the catalyst after 6 hours. As expected, when 1,2,3-butanetriol (**10b**) was used as a substrate, the mixture of alkenes **11b** and **11c** was formed. Notably, 5 mol% of $Re_2O_7$ was necessary in order to obtain good conversion and yield in 1 hour. On the contrary, the reaction of 1,2,8-octanetriol (**10d**) and 1,2,10-decanetriol (**10e**) with 1 mol% of $Re_2O_7$ led to the formation of the corresponding unsaturated alcohols in very good yields.

Finally, a one-pot deoxydehydration–hydrogenation (DODH–HG) reaction was tested for the synthesis of saturated alcohols. This transformation has been reported by several groups[22] *e.g.* for the production of deoxy sugars.[22d] We became interested in the synthesis of 1-hexanol (**13**) from **4**, which could be potentially further converted to 1-hexene,[23] a well-known co-monomer in the production of polyethylene. For this

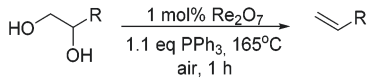
**Table 3** Catalytic conversion of 1,2,5-HT under neat and air conditions

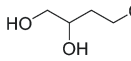
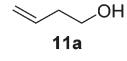
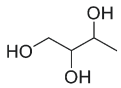
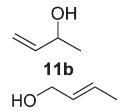
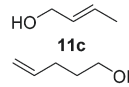
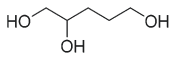
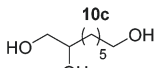
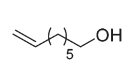
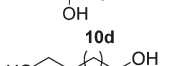
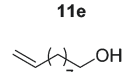



| Entry | Catalyst (mol%) | Time | Conv.[c] (%) | Yield[c] (%) 6 | 7 | 8 | 9 |
|---|---|---|---|---|---|---|---|
| 1[a] | $Re_2O_7$ (0.5) | 1 h | 20 | 10 | 7 | 3 | — |
| 2[a] | $Re_2O_7$ (3) | 1 h | >99 | 3 | 39 | 25 | 10 |
| 3[b,d] | $Re_2O_7$ (0.5) | 10 min | >99 | | | | 90 |
| 4[b] | PTSA (0.5) | 10 min | 51 | | | | 38 |
| 5[b] | TFA (0.5) | 10 min | — | | | | |

[a] Reaction conditions: 1,2,5-HT (1.0 mmol), $PPh_3$ (1.1 mmol), $Re_2O_7$ under air at 165 °C. [b] Without $PPh_3$. [c] Determined by $^1H$ NMR spectroscopy using dimethyl phthalate as internal standard. [d] Isolated yield.

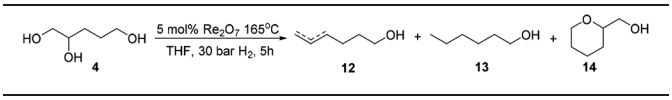
**Table 4** DODH of various triols[a]




| Entry | Substrate | Product(s) | Conv.[b] (%) | Yield[b] (%) |
|---|---|---|---|---|
| 1 |  10a |  11a | 65 | 63 |
| 2[d] | | | 98 | 97(77)[c] |
| 3 |  10b |  11b | 56 | 28 : 21, **11b : 11c** |
| 4[e] | |  11c | 83 | 42 : 34, **11b : 11c** |
| 5 |  |  11d | 92 | 89 |
| 6[f] | | | 97 | 91 (75)[c] |
| 7 |  10c |  11e | >99 | 98 (90)[c] |
| 8 |  10d |  11f | >99 | 99 (90)[c] |
| | 10e | | | |

[a] Reaction conditions: Triol (1.0 mmol), $PPh_3$ (1.1 mmol), $Re_2O_7$ (0.01 mmol), under air at 165 °C, 1 h. [b] Determined by $^1H$ NMR spectroscopy using dimethyl phthalate as internal standard. [c] Isolated yields, 5 mmol scale. [d] 2 mol% $Re_2O_7$, 6 h. [e] 5 mol% $Re_2O_7$. [f] 2 mol% $Re_2O_7$.

**Table 5** DODH–HG reaction of 1,2,6-hexanetriol[a]




| Entry | THF (mL) | Co-catal. | Conv.[b] (%) | Yield[b] (%) 12 | 13 | 14 |
|---|---|---|---|---|---|---|
| 1 | 0.5 | — | 68 | 23 | 9 | 36 |
| 2 | 2 | — | 73 | 19 | 19 | 35 |
| 3 | 10 | — | >99 | — | 40 | 27 |
| 4 | 10 | 5% Pd/C | >99 | — | 68(55)[c] | 12 |
| 5 | 10 | 5% Pt/C | >99 | — | 31 | — |
| 6 | 10 | 10% Ru/C | >99 | — | 51 | — |

[a] Reaction conditions: 1,2,6-Hexanetriol (1.0 mmol), $Re_2O_7$ (0.05 mmol), THF, 30 bar of $H_2$, 165 °C, 5 h. [b] Determined by $^1H$ NMR spectroscopy using dimethyl phthalate as internal standard. [c] Isolated yields, 5 mmol scale.

reaction (Table 2, entry 8), THF was used as a solvent and different concentrations of substrate were investigated (Table 5). When high concentrations of **4** were used, low yields of **13** were achieved and **14** was formed as the main product (Table 5, entries 1–2). Nevertheless, a mixture of 1-hexen-6-ol and 2-hexen-6-ol was still present after 5 hours. An increase of the yield of **13** was observed at high dilution, but was accompanied by significant charring (Table 5, entry 3). To suppress undesired side reactions, catalytic amounts of supported metals as co-catalysts were used. The best result of 68% yield of 1-hexanol (**13**) at full conversion of the starting material was obtained with 0.75 mol% of 5% Pd/C. The product was isolated in 55% yield after flash column chromatography.

## Conclusions

In summary, we developed a novel route for the conversion of renewable triols into the corresponding unsaturated alcohols. Employing readily available and cheapest rhenium source ($Re_2O_7$) under neat and ambient conditions at 165 °C, we were able to isolate the desired products in good to excellent yields. We have shown that the activity and selectivity of the catalyst depends on the position of a non-vicinal OH group in 5-HMF based hexanetriols. In addition, we performed a one-pot DODH–HG of 1,2,6-hexanetriols resulting in the formation of 1-hexanol. The latter is a potential precursor for 1-hexene, an important co-monomer for poly-ethylene which is currently prepared by trimerisation of ethylene or Fisher–Tropsch on a multi-ton scale. Further investigations on the isomerization mechanism are currently on-going.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

We thank the Leibniz Foundation for financial support (SAW-LIKAT-1 523).

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# 8. Thesis Summary

The research described in this thesis was aimed at the development of new bio-based routes to existing or new compounds with a wide range of useful applications. In our initial studies, we established an efficient catalytic system for the conversion of biomass-derived 5-hydroxymethylfurfural (5-HMF) to 1-hydroxyhexen-2,5-dione (HHD) *via* a hydrogenation/hydrolytic ring opening process. For this purpose, homogeneous half-sandwich iridium complexes were used as catalysts providing good selectivities towards the targeted product. Additionally, HHD was isolated and fully characterized for the first time including X-ray diffraction analysis. We identified HHD as a key biomass-derived intermediate, which can serve as a starting point for several useful building blocks (Figure 13).

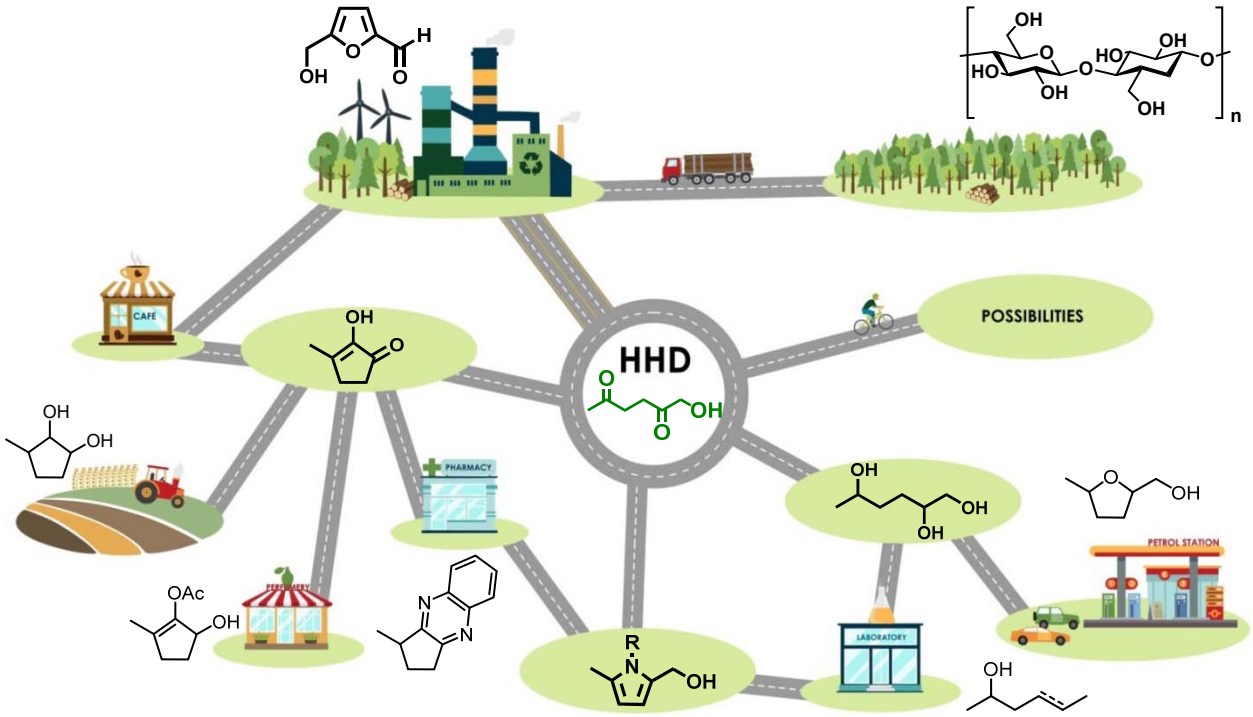


**Figure 13**. New bio-based routes to useful building blocks *via* HHD.

Studies on the base-promoted intramolecular aldol condensation of HHD revealed the formation of 2-hydroxy-3-methylcyclopent-2-enone (MCP), a well-known flavor ingredient in roasted coffee and maple syrup as the sole product. Moreover, it was possible to obtain MCP directly from 5-HMF under the optimized reaction conditions. Furthermore, MCP was transformed to a number of valuable cyclopentanone-based compounds including α,β-unsaturated imines and a quinoxaline derivative in excellent yields. (Section 7.1; *ChemSusChem* **2018**)

With the aim of exploring other applications of HHD, first its large-scale synthesis was performed resulting in 71% yield (18.2 g of the product was isolated). With reasonable

amounts of HHD in hands, a wide variety of primary amines was tested in the Paal-Knorr synthesis with the intent to produce *N*-substituted pyrroles. To our delight, most of the pyrroles were obtained in excellent yields in short reaction times at room temperature in the absence of additives. The generality of the investigated procedure was proved by applying both alkyl- and arylamines resulting in the formation of a host of *N*-substituted 2-hydroxymethyl-5-methylpyrroles. In addition, it should be emphasized that the vast majority of the products was isolated simply by evaporating the solvent, which qualifies this transformation as a *Click Reaction*. (Section 7.2; *Eur. J. Org. Chem*. **2018**)

We expanded our interest in biomass to develop efficient method for lowering the oxygen content in biomass-derived chemicals without losing any carbon atoms. Therefore, a number of rhenium sources was tested as catalyst for the deoxydehydration (DODH) of renewable triols including those obtained from 5-HMF. Notably, the best results were obtained with the cheapest rhenium precursor – rhenium(VII) oxide as catalyst, leading to the corresponding unsaturated alcohols in isolated yields of up to 91%. Furthermore, a one-pot deoxydehydration-hydrogenation was investigated for the synthesis of 1-hexanol from 1,2,6-hexanetriol, which could be potentially further converted to 1-hexene, a well-known co-monomer in the production of polyethylene. (Section 7.3; *Green Chem.* **2018**)

In conclusion, we have proven that HHD has great potential to become a new platform chemical. A broad spectrum of valuable bio-based building blocks was synthesized from it with possible applications in the production of consumer products of the chemical industry including pharmaceuticals, food additives, agrochemicals and transportation fuels.

# 9. Appendices

## *9.1 Supporting Information for section 7.1*

# Electronic Supporting Information

## Cyclopentanone derivatives from 5-hydroxymethylfurfural via 1-hydroxyhexane-2,5-dione as intermediate

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## Content

## 1.0 General remarks

All reactions were carried out in dried glassware or hastelloy autoclave vessel with magnetic stirring under argon or hydrogen atmosphere, unless otherwise stated. Reaction solvents (THF, ethanol, methanol, acetonitrile) were obtained from a solvent purification system (SPS) and stored under argon. Commercially available chemicals were purchased from Sigma, Alfa, Strem, Abcr and TCI. 5-(Hydroxymethyl)furfural was purchased from AVA-Biochem BSL AG and used without futher purification. $^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker AV 300 or 400 NMR spectrometer. All chemical shifts are related to residual solvent peaks [$CDCl_3$: 7.26 ppm (1H), 77.16 ppm ($^{13}C$)]. Electrospray ionization high resolution mass spectra were recorded on Agilent 6210 Time-of-Flight LC/MS (ESI). X-ray intensity data were collected on a Bruker Kappa APEX II Duo diffractometer. The structures were solved by direct methods (SHELXS-97: Sheldrick, G. M. *Acta Cryst.* **2008**, *A64*, 112.) and refined by full-matrix least-squares procedures on $F^2$ (SHELXL-2014: Sheldrick, G. M. *Acta Cryst.* **2015**, *C71*, 3.). XP (Bruker AXS) was used for graphical representations. CCDC 1574708-1574709 contain the supplementary crystallographic data for this paper. These data are provided free of charge by The Cambridge Crystallographic Data Centre.

## 2.0 Synthesis of catalysts

### 2.1 Synthesis of catalyst I

This catalysts was synthesized by following the reported Fischmeister[1] procedure: to a mixture of $[IrCp^*Cl_2]_2$ (0.225 g, 0.28 mmol) and 2,2'-dipyridylamine (0.095 g, 0,6 mmol) 5 mL of methanol was added and the solution was left to stir for 12 h at 50 $^{o}$C. After this time, volatiles were evaporated and the residue was washed with diethylether (3 x 10 mL) and dried under vacuum to yield 0.271 g (86% yield) of yellow solid. The $^{1}H$ and $^{13}C$ NMR data are identical to those reported.[1]

### 2.2 Synthesis of catalyst II

Using the same procedure as for synthesis of catalyst **I**: to a mixture of $[RuCl_2(p\text{-cymene})]_2$ (0,034 g, 0,2 mmol) and 2,2'-dipyridylamine (0.068 g, 0.4 mmol) 25 mL of methanol was added and the solution was stirred for 12 h at 50 $^{o}$C. After this time, volatiles were evaporated and the residue was washed with diethylether (3 x 4 mL) and dried under vacuum to yield 0.086 g (90% yield) of yellow solid. The $^{1}H$ and $^{13}C$ NMR data are identical to those reported.[1]

### 2.2 Synthesis of catalyst III

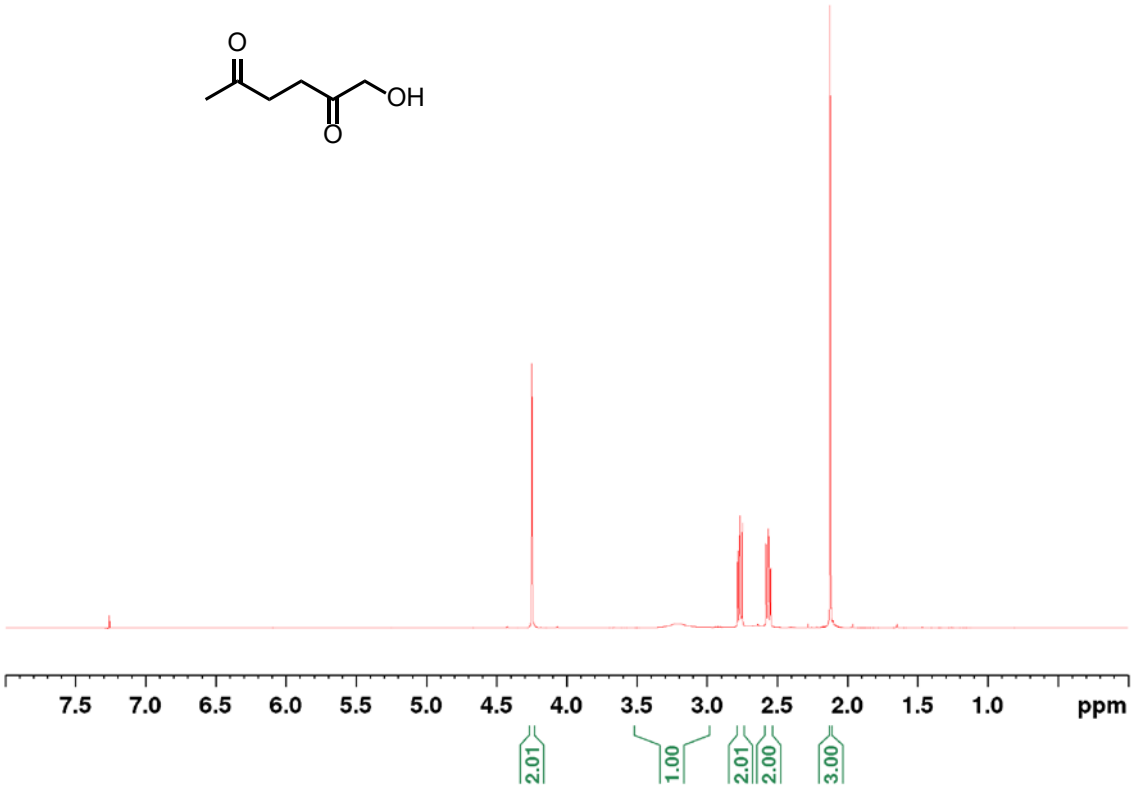
Ligand and catalyst were synthesized following a procedure described by Tang and co-workers[2]: to a mixture of $[IrCp^*Cl_2]_2$ (0.5 g, 0.62 mmol) and the corresponding ligand (0.231 g, 1.3 mmol) 6 mL of DCM was added and the solution was left to stir for 12 h at room temperature. After this time, the yellow solution was evaporated and the residue was dissolved in minimum amount of DCM, precipitated by addition of EtOAc (10 mL) and dried under vacuum to yield 0.693 g (94% yield) of yellow solid. The $^{1}H$ and $^{13}C$ NMR data are identical to those reported.[2]

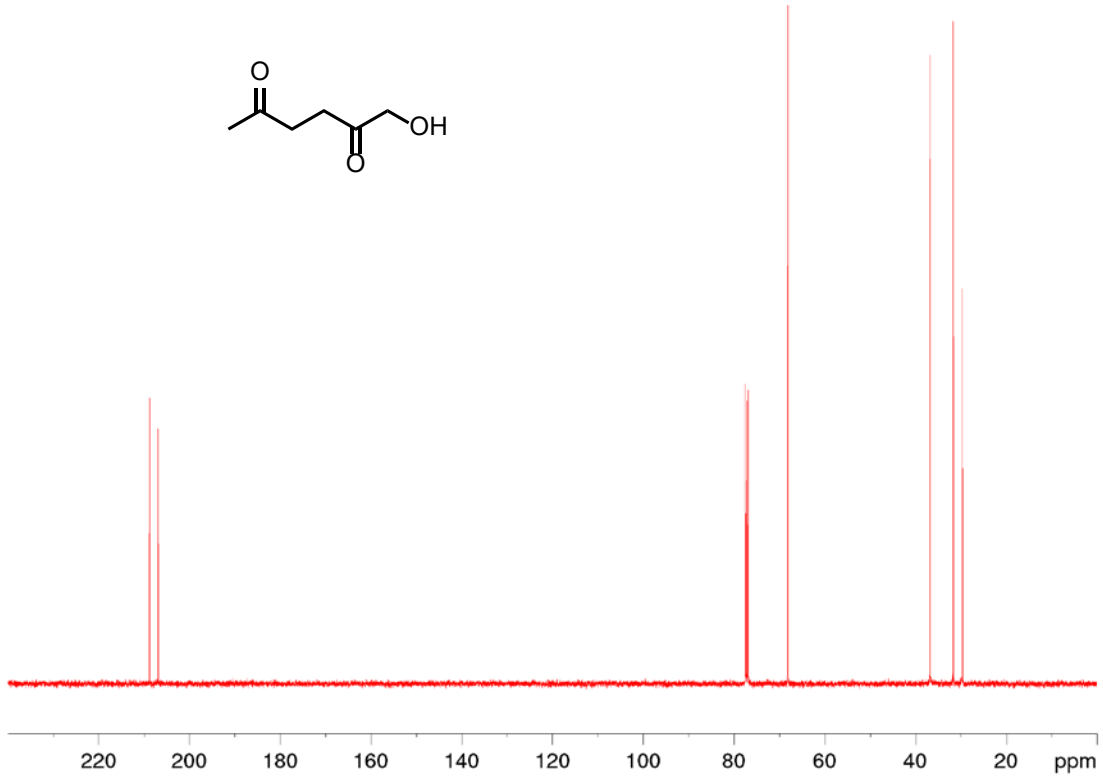
### 2.3 Synthesis of catalyst V

The catalyst was obtained following a procedure reported by Watanabe[3]: to a mixture of $[IrCp^*Cl_2]_2$ (0.480 g, 0.6 mmol) and $AgSO_4$ (0.374 g, 1.2 mmol) 5 mL of water was added and the suspension was left to stir for 12 h at room temperature. After this time, the precipitating AgCl was removed by filtration and solvent was evaporated and dried under vacuum to yield 0.553 g (97% yield) of yellow powder. The $^{1}H$ and $^{13}C$ NMR data are identical to those reported.[3]

### 3.0 General procedure for the synthesis of HHD (2)

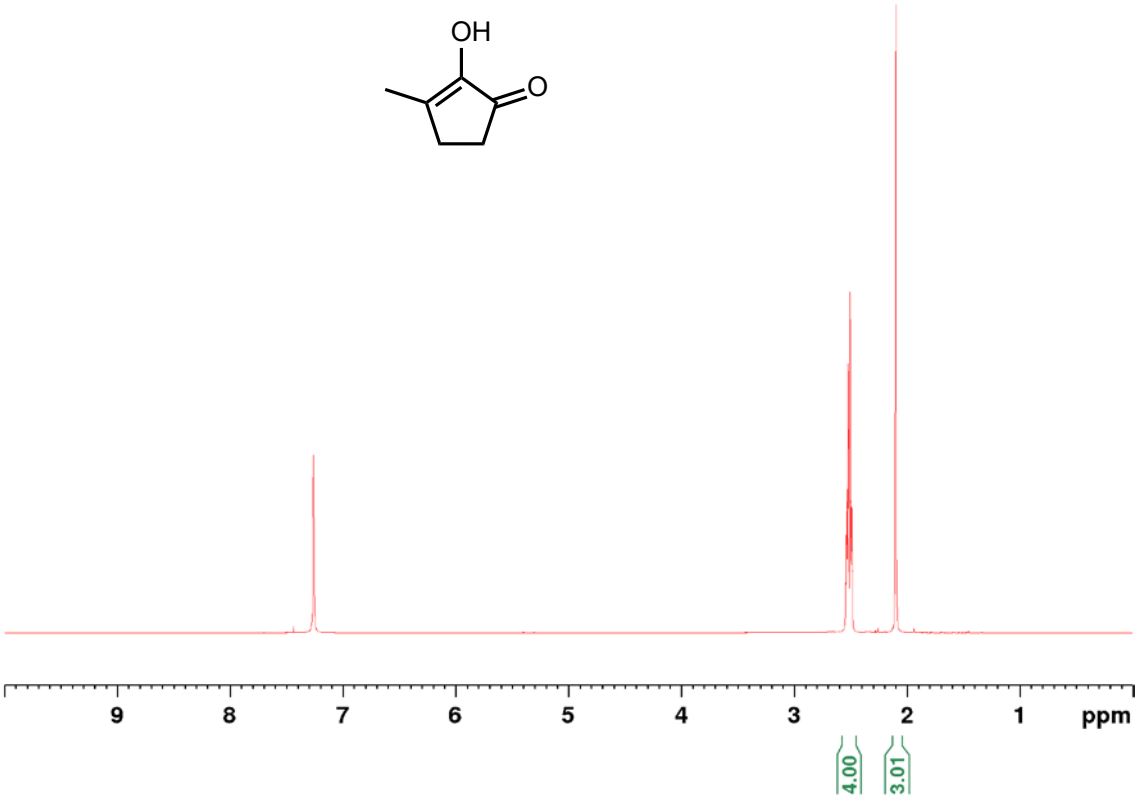
A 100 mL hastelloy autoclave vessel was charged with 5-HMF (**1**) (0.5 g, 4.0 mmol) and one of the complexes **I-VI** (0.5 mol%). The contents were dissolved in 20 mL of distilled water. The vessel was flushed three times with $N_2$ and subsequently with $H_2$. After flushing, the reactor was pressurized to with $H_2$ (10 bar) and the reaction mixture was stirred and heated to 120 $^oC$ for 2 h. After cooling to room temperature and depressurising, the yellow solution was extracted with DCM (6 x 20 mL) and the organic layer was dried over anhydrous $MgSO_4$. After filtration and evaporation to dryness, the resulting yellow oil was purified by column chromatography ($SiO_2$, ethyl acetate). Yellow precipitate of product was obtained by dissolving HHD in a minimum volume of DCM (2 mL), then pentane (10 mL) was layered on the top of the solution and left to stand at -30$^oC$ overnight. After this time, pentane was removed by decantation and resulting product dried under reduced pressure at room temperature. $^1H$ NMR (400 MHz, $CDCl_3$) δ = 4.25 (s, 2H), 3.21 (brs, 1H), 2.76 (t, *J*= 6.2 Hz, 2H), 2.56 (t, *J*=6.2 Hz, 2H), 2.12 (s, 3H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$) δ = 208.8, 206.9, 68.1, 36.8, 31.7, 29.6 ppm. HRMS-ESI (M+Na) calculated for $C_6H_{10}O_3$ 153.05222, found 153.05244, Elemental analysis (%) calculated for $C_6H_{10}O_3$: C 55.37; H 7.75; found C 55.26, H 7.56. Crystal data of HHD $C_6H_{10}O_3$, *M* = 130.14, orthorhombic, space group $Pca2_1$, *a* = 9.9247(11), *b* = 5.4114(6), *c* = 24.521(3) Å, *V* = 1316.9(3) $Å^3$, *T* = 150(2) K, *Z* = 8, 15508 reflections measured, 3169 independent reflections ($R_{int}$ = 0.0241), final *R* values ($I > 2\sigma(I)$): $R_1$ = 0.0359, $wR_2$ = 0.0958, final *R* values (all data): $R_1$ = 0.0396, $wR_2$ = 0.0994, 171 parameters.
In the solid state intermolecular O-H…O bonds are observed: O1-H…O4A: O1…O4A 2.893(3) Å, O1-H…O4A 146(4)°; O1-H…O5A: O1…O5A 2.953(3) Å, O1-H…O5A 136(4)°; O4-H…O1: O4…O1 2.899(3) Å, O4-H…O1 160(5)°; O4-H…O2: O4…O2 2.933(3) Å, O4-H…O2 129(4)°.






### 4.0 General procedure for synthesis of MCP (3)

In a Schlenk vessel under argon atmosphere, HHD **(2)** (0.25 g, 1.9 mmol) was dissolved in 5 mL of solvent and then 5 mL of aqueous solution of base (2.85 mmol) was added. The solution was stirred at 60°C and monitored by thin-layer chromatography (TLC) until complete conversion of substrate. The pH of cooled solution was adjusted to 5 using 1 M HCl, then DCM (3 x 10 mL) was used in extraction process. The organic layers were combined, dried over $MgSO_4$ and solvent evaporated under reduced pressure yielding orange solid. Crystals suitable for X-ray diffraction analysis were grown by recrystallisation of MCP in DCM/pentane mixture at -30 °C. $^1$H NMR (400 MHz, $CDCl_3$) δ = 2.54 – 2.48 (m, 4H), 2.10 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 203.6, 149.3, 145.7, 32.0, 27.1, 14.3 ppm. HRMS-ESI (M+Na) calculated for $C_6H_8O_2$ 135.04165, found 135.04175, Elemental analysis (%) calculated for $C_6H_8O_2$: C 64.27; H 7.19; found C 64.38, H 7.56. Crystal data of MCP: $C_6H_8O_2$, $M$ = 112.12, triclinic, space group $P\bar{1}$, $a$ = 6.4498(16), $b$ = 7.3336(18), $c$ = 7.3707(18) Å, $\alpha$ = 110.667(4), $\beta$ = 108.672(4), $\gamma$ = 103.791(5)°, $V$ = 283.71(12) Å$^3$, $T$ = 150(2) K, $Z$ = 2, 9173 reflections measured, 1375 independent reflections ($R_{int}$ = 0.0322), final $R$ values ($I > 2\sigma(I)$): $R_1$ = 0.0391, $wR_2$ = 0.0973, final $R$ values (all data): $R_1$ = 0.0500, $wR_2$ = 0.1046, 78 parameters.
In solid state intermolecular O-H…O hydrogen bonds are observed: O2-H…O1A: O2…O1A 2.712(2) Å, O2-H…O1A 157(2)°.
The crystal structure of MCP co-crystallized with water was determined before.[4]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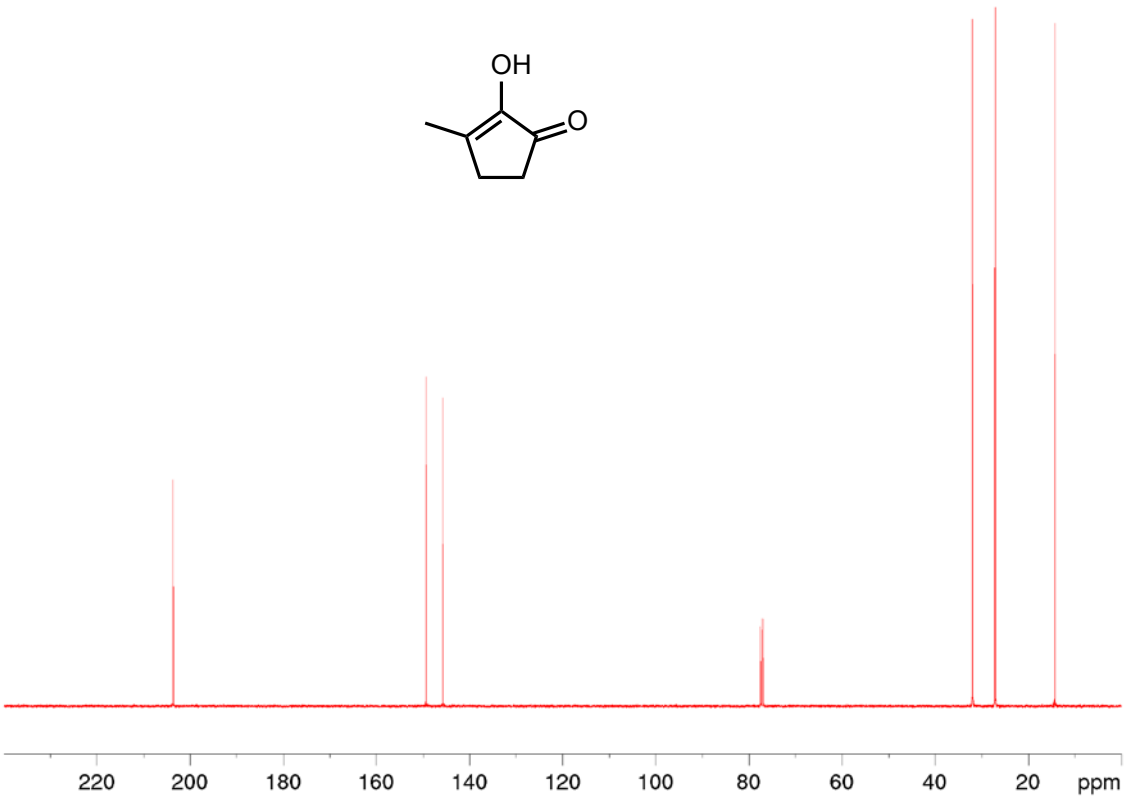
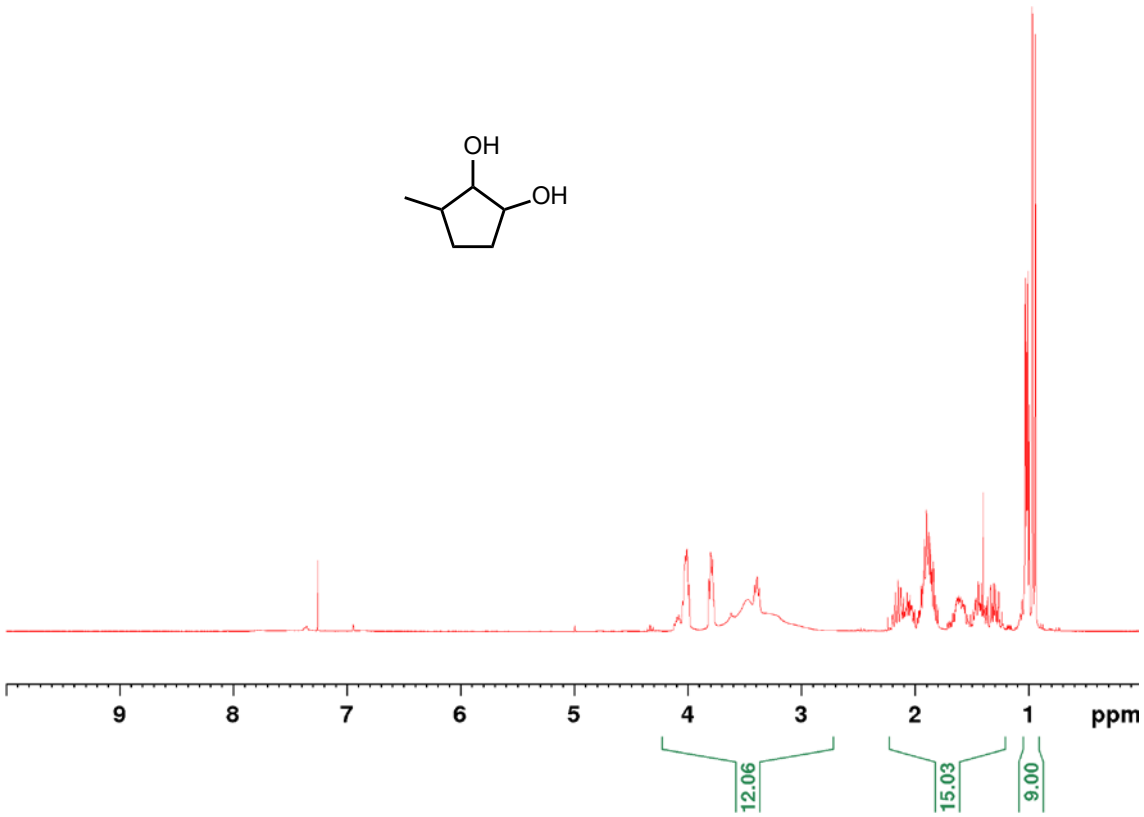

OH
O
220
200
180
160
140
120
100
80
60
40
20
ppm

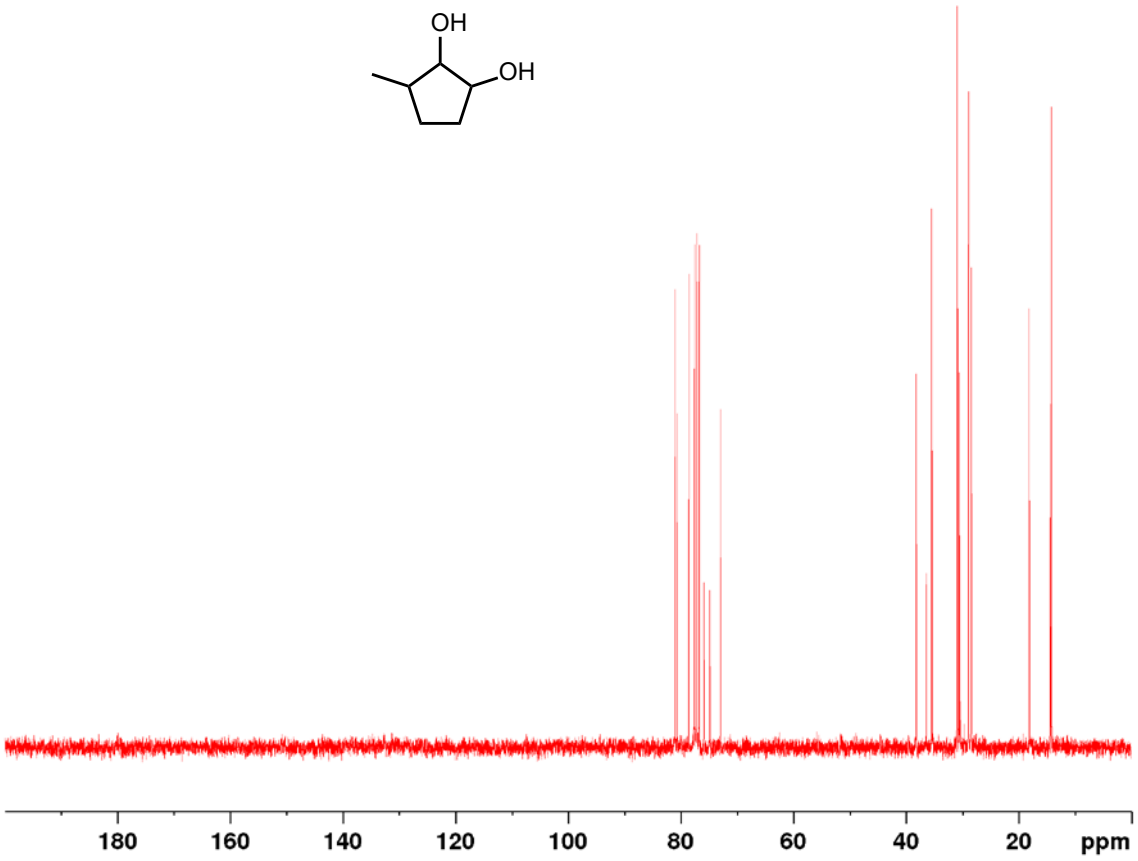
## 5.0 Synthesis of MCP (3) in a one-pot approach.

In a 100 mL hastelloy autoclave with a stirring bar, 5-HMF **(1)** (1.0 g, 7.9 mmol) and **I** (21 mg, 0.039 mmol, 0.5 mol%) were dissolved in 40 mL of distilled water. The vessel was flushed three times with $N_2$ and subsequently with $H_2$. After flushing, the reactor was pressurized to with $H_2$ (10 bar) and the reaction mixture was stirred and heated at 120 $^oC$ for 2 h. After cooling to room temperature and depressurizing, the aqueous solution of base (0.66 g, 2.85 mmol) was added and the mixture was stirred at 60 $^oC$ for another 30 minutes. The pH of the cooled solution was adjusted to 5 using 1 M HCl, then DCM (3 x 20 mL) and EtOAc (3 x 20 mL) were used in extraction process. The organic layers were combined, dried over $MgSO_4$ and solvent evaporated under reduced pressure. The resulting brown solid was purified by column chromatography ($SiO_2$; ethyl acetate:cyclohexane 3:1), yielding 0.49 g (55% yield). The $^1H$ and $^{13}C$ NMR data are identical to those reported in section 3.0.

## 6.0 Hydrogenation reaction of MCP (3)

In a 100 ml hastelloy autoclave with a stirring bar, MCP (**3)** (0.25 g, 2.2 mmol) and commercially available Ru-MACHO-BH **IV** (6.5 mg, 0.011 mmol, 0.5 mol%) were dissolved in 10 mL of dry THF. The vessel was flushed three times with $N_2$ and subsequently with $H_2$. After flushing, the reactor was pressurized to with $H_2$ (20 bar) and the reaction mixture was stirred and heated to 100 $^oC$ overnight. After cooling to room temperature and depressurizing, the yellow solution was filtered over $SiO_2$ and the solvent was removed *in vacuo* yielding 248 mg (96% yield) of yellow oil as a mixture of 3 isomers in ratio 2.3 : 1 : 3.4. $^1H$ NMR (300 MHz, $CDCl_3$, mixture of 3 isomers) δ = 4.12 – 3.37 (m, 6H), 3.74 – 2.88 (brs, 6H), 2.22 – 1.23 (m, 15H), 1.03 – 0.94 (td, 9H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 81.0, 80.7, 78.6, 75.9, 74.9, 73.0, 38.2, 36.4, 35.5, 30.9, 30.6, 30.4, 29.0, 28.9, 28.4 ppm.



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    Different Inj Volume from Sequence !     Actual Inj Volume : 0.2 µl
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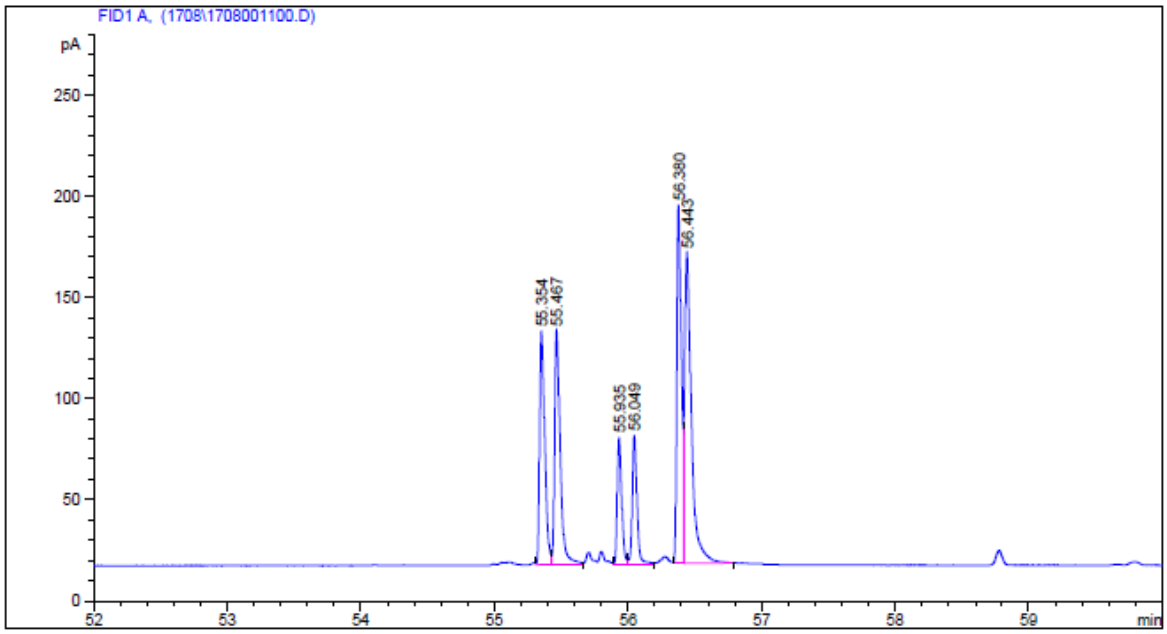


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=====================================================================
                        Area Percent Report
=====================================================================

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Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs


Signal 1: FID1 A,

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [pA*s]      [pA]        %
----|-------|----|-------|----------|----------|--------|
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   2  55.467 VV    0.0435  337.48737  116.05012 17.56588
   3  55.935 VV    0.0349  144.36667   62.61245  7.51414
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GC 9 12/4/2017 2:23:46 PM                                      Page   1 of 2

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Sample Name: BW 311

Peak RetTime Type  Width     Area      Height     Area
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   6  56.443 VB    0.0517  555.70898  153.92789 28.92409

Totals :                  1921.26675  688.65135


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                        *** End of Report ***
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### 7.0 Oxidative ring cleavage of MCP (3) to Levulinic acid (6)

In a Schlenk vessel under argon atmosphere, MCP (**3**) (0.25 g, 2.2 mmol) and sodium periodate (1.4 g, 6.5 mmol) were dissolved in 10 ml of distilled water. After stirring for 4 h at room temperature, extraction with $EtO_2$ (3 x 15 mL) and DCM (3 x 15 mL) was performed, the organic layers were combined, dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The resulting yellow oil was purified by column chromatography (silica gel, 3:1, EtOAc:Cy)). The $^{1}H$ and $^{13}C$ NMR data are identical to those reported.[5]

### 8.0 Condensation reaction of MCP (3) with diamines

In a Schlenk vessel with stirring bar and molecular sieves under an argon atmosphere, MCP (**3**) (0.25 g, 2.2 mmol) was dissolved in 5 mL of EtOH and corresponding diamine (2.4 mmol) was added. The solution was stirred at 80°C and monitored by gas chromatography (GC) until complete conversion of substrate. After cooling to room temperature, filtration over celite and evaporation to dryness, the resultant orange and brown solids were obtained with excellent yields. In case of product **8**, column chromatography was necessary to obtain a clean product.

**Table 1. Products of condensation reaction of MCP (3) with diamines**

| Entry | Substrate | Product | Time (h) | Isolated yield (%) |
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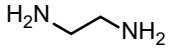
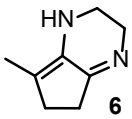
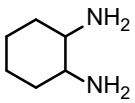
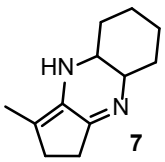
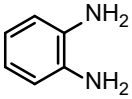
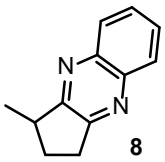
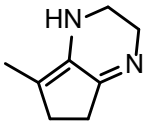
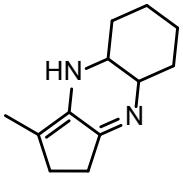
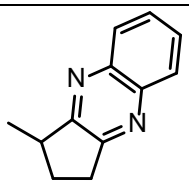
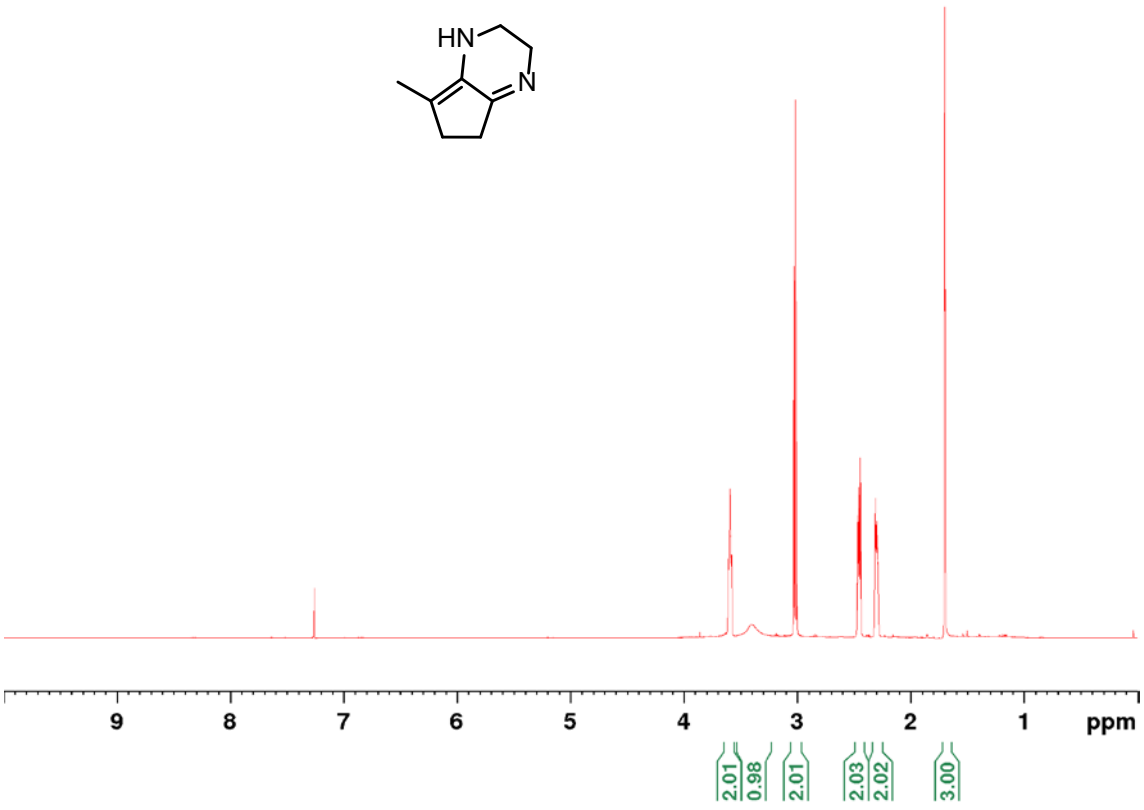
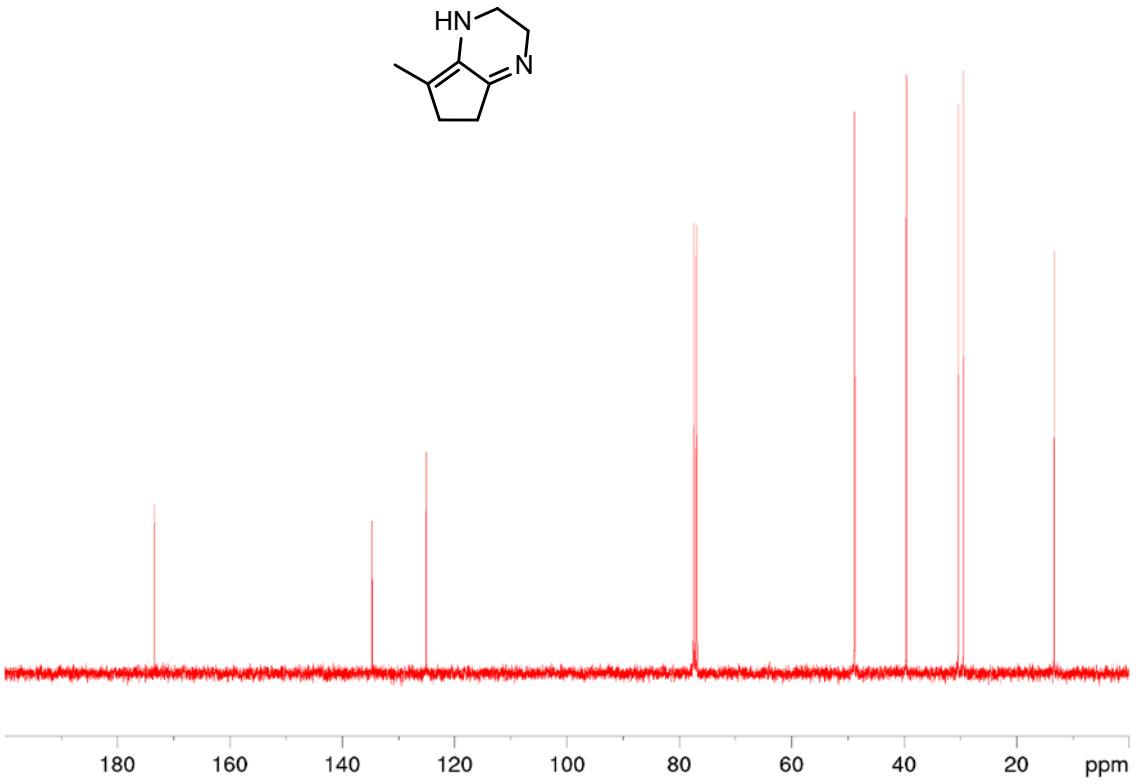
| 1 |  |  **6** | 1 | 99 |
| 2 |  |  **7** | 2 | 98 |
| 3 |  |  **8** | 72 | 96 |

**Table 2. Product data**

| | |
|---|---|
|  <br>**6** | **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 3.62 – 3.57 (m, 2H), 4.41 (brs, 1H), 3.02 (t, *J*=5.3 Hz, 2H), 2.48 – 2.43 (m, 2H), 2.32 – 2.28 (m, 2H), 1.70 (s, 3H).<br>**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ = 173.4, 134.7, 125.0, 48.8, 39.6, 30.4, 29.5, 13.3.<br>**HRMS-ESI** (M + H) calcd. for $C_8H_{12}N_2$ 137.10732, found 137.10739. |
|  <br>**7** | **$^{1}$H NMR** (400 MHz, $CDCl_3$) δ = 3.24 (brs, 1H), 2.97 – 2.88 (m, 1H), 2.55 – 2.41 (m, 3H), 2.40 – 2.26 (m, 2H), 2.24 – 2.17 (m, 1H) 1.83 – 1.72 (m, 3H), 1.72 (s, 3H), 1.44 – 1.15 (m, 4H).<br>**$^{13}$C NMR** (100 MHz, $CDCl_3$) δ = 173.1, 136.0, 125.0, 62.9, 55.2, 33.2, 32.6, 30.7, 29.3, 25.8, 24.7, 13.5.<br>**HRMS-ESI** (M + H) calcd. for $C_{12}H_{18}N_2$ 191.15428, found 191.15452. |
|  <br>**8** | **$^{1}$H NMR** (300 MHz, $CDCl_3$) δ = 8.04 – 7.95 (m, 2H), 7.65 – 7.61 (m, 2H), 3.39 – 3.28 (m, 1H), 3.20 – 3.03 (m, 2H), 2.51 (qt, *J*= 8.1 Hz, *J*= 4.4 Hz, 1H), 1.81 (dq, J=13.0 Hz, J= 8.7 Hz, 1H), 1.46 (d, 3H).<br>**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ = 163.7, 160.5, 141.8, 141.7, 129.0, 128.8, 128.8, 128.7, 38.5, 31.0, 30.8, 18.3.<br>**HRMS-ESI** (M + H) calcd. for $C_{12}H_{12}N_2$ 185.10732, found 185.10743. |

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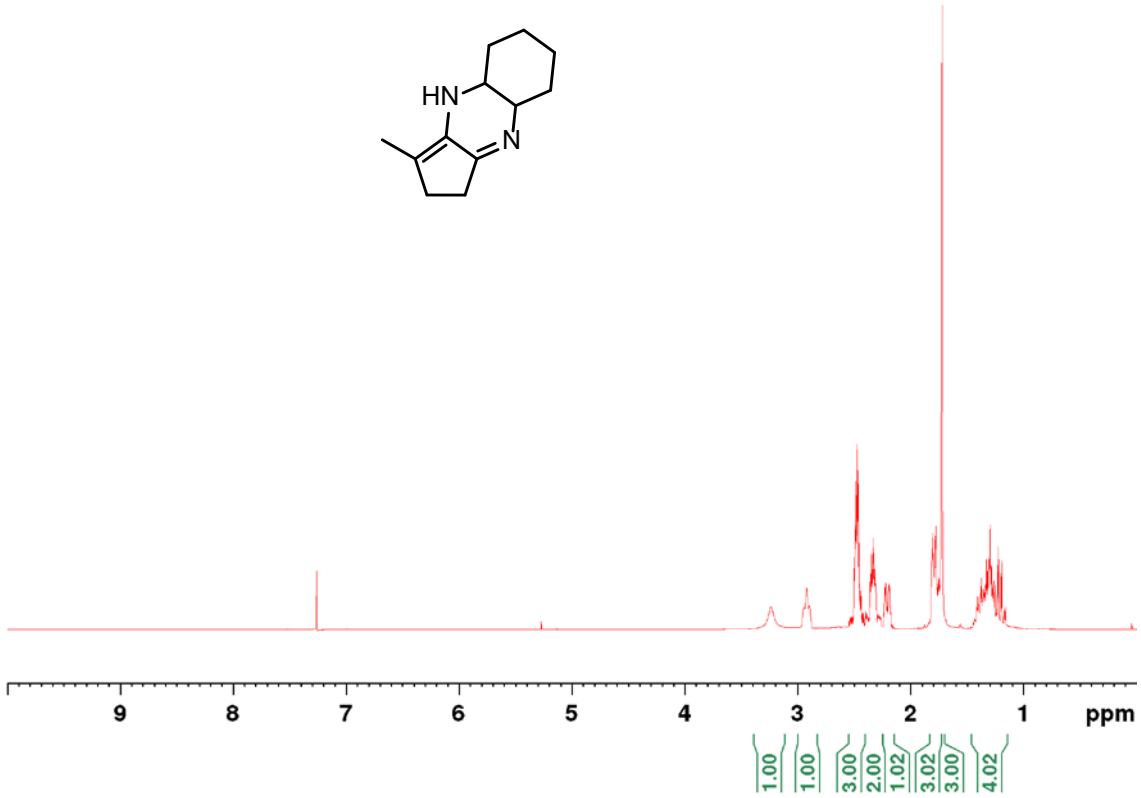
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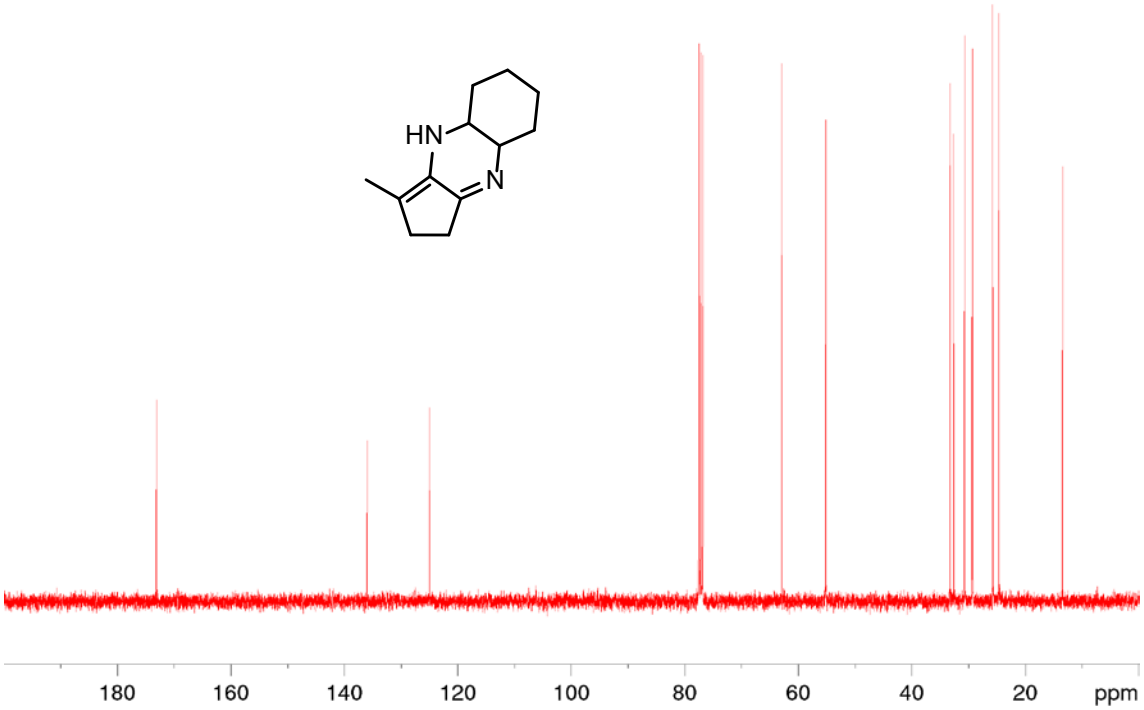
4.02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20
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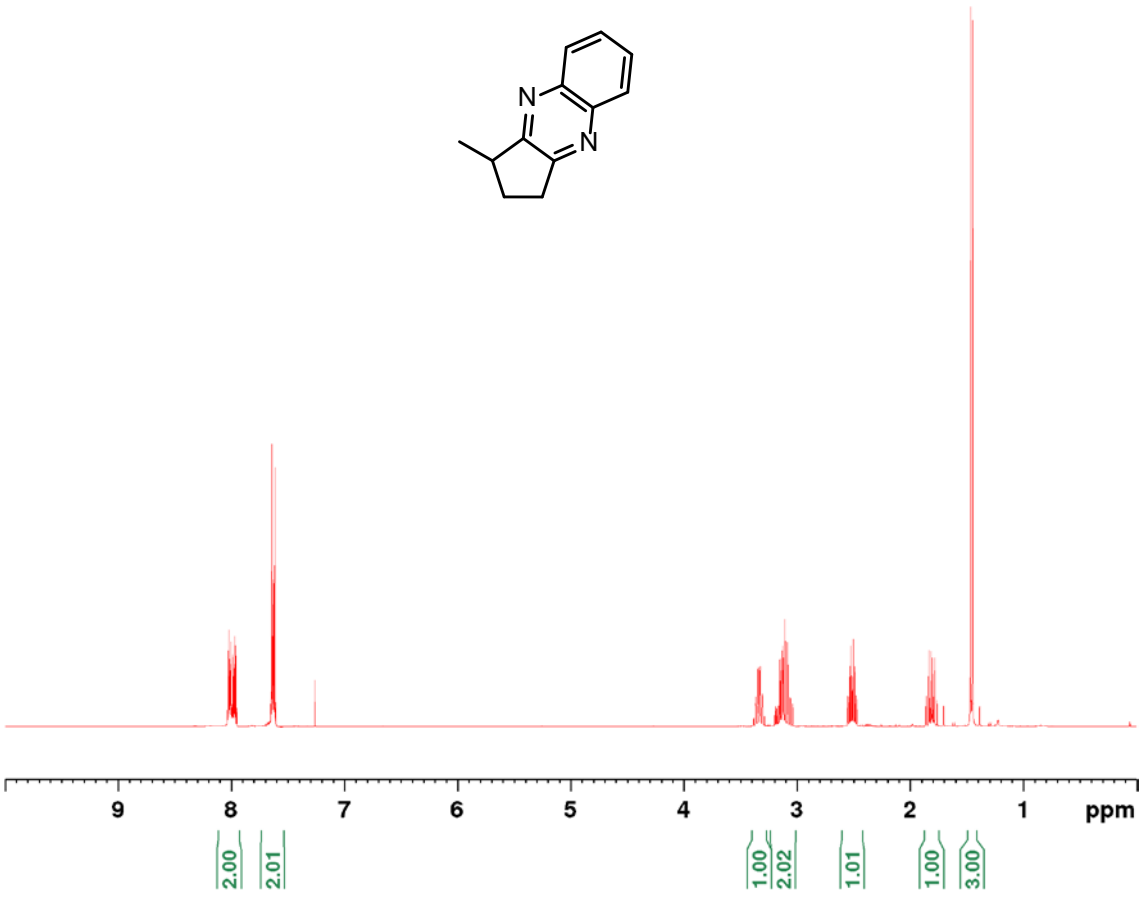
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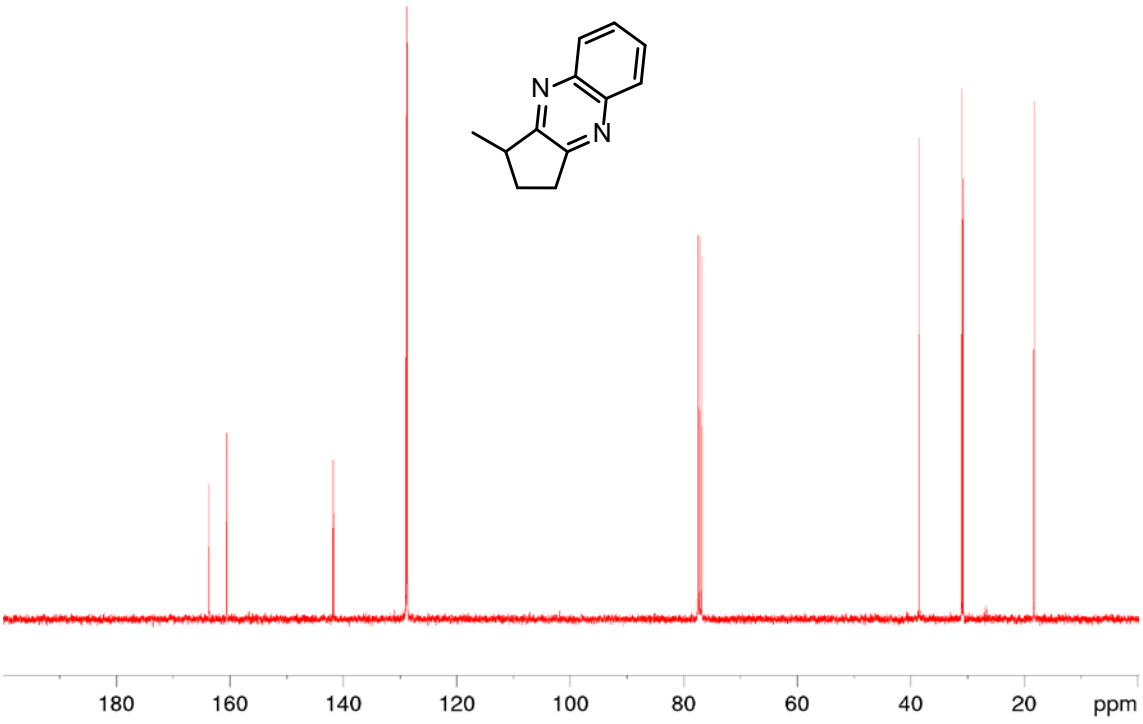
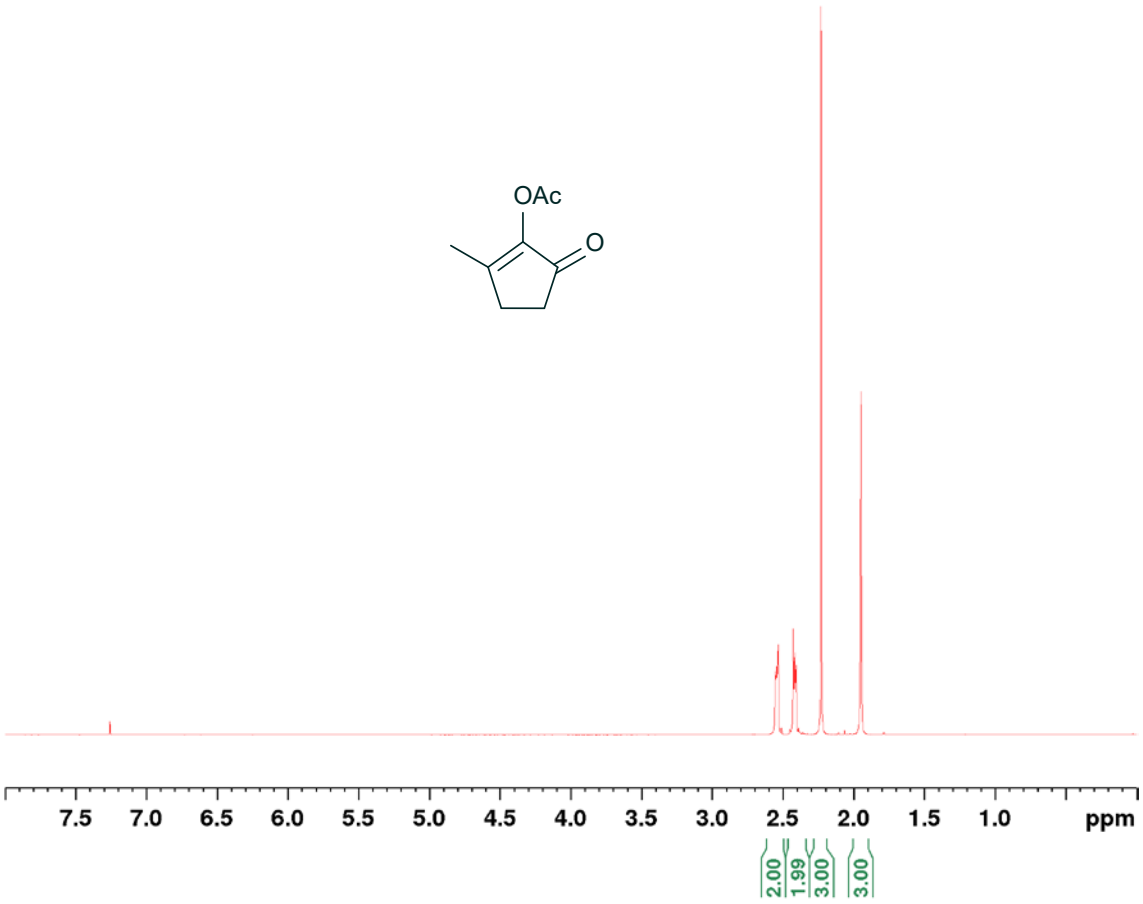



### 9.0 Acetylation of MCP (3)

In a Schlenk vessel under argon atmosphere, MCP **(3)** (0.5 g, 4.5 mmol) was dissolved in 5 mL of dry ethanol and acetic anhydride (421 µL, 4.45 mmol) and $Et_3N$ (931 µL, 6.79 mmol) were added. After stirring for 1 h at room temperature, the reaction mixture was diluted with EtOAc (5 mL) and dried under reduced pressure to afford 667 mg of pure product (97% yield). $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 2.57 – 2.52 (m, 2H), 2.45 – 2.40 (m, 2H), 2.23 (s, 3H), 1.95 (s, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 200.1, 167.6, 160.9, 146.2, 32.5, 28.0, 20.4, 15.2 ppm. HRMS-ESI (M + Na) calculated for $C_8H_{10}O_3$ 177.05222, found 177.05182.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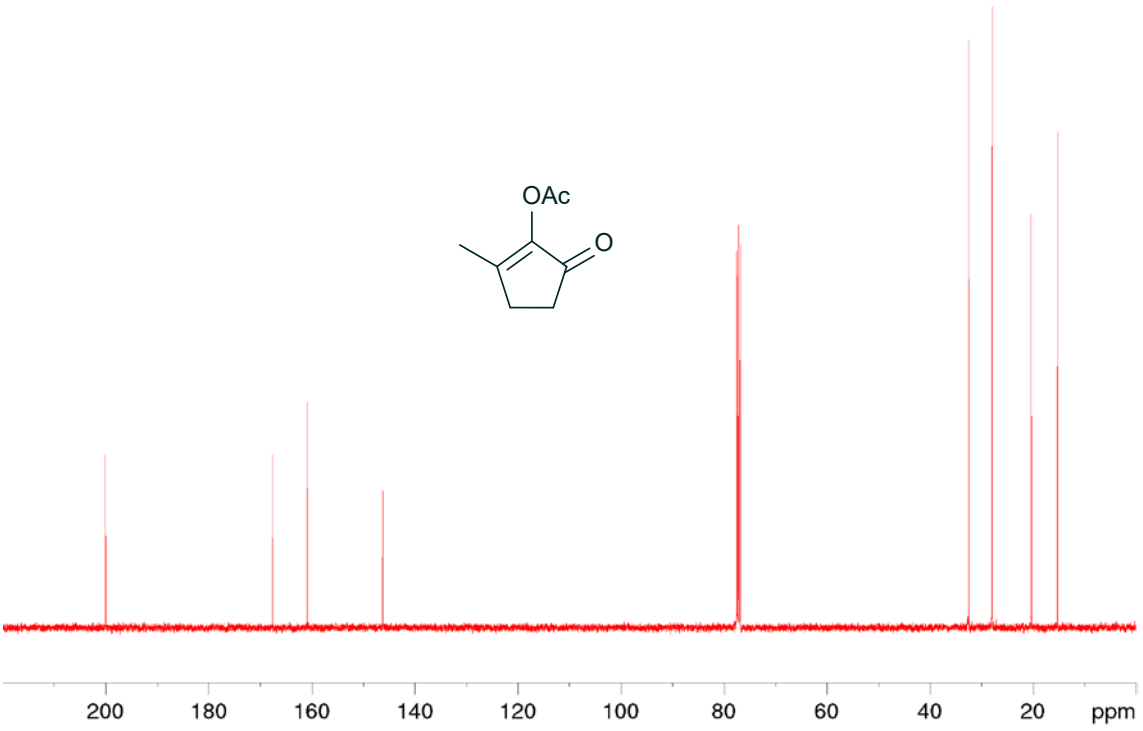
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**References**

[1] S. Wang, V. Dorcet, T. Roisnel, C. Bruneau, C. Fischmeister, *Organometallics* **2017**, 36, 708.
[2] Z. Yang, Z. Zhu, R. Luo, X. Qiu, J.-T. Liu, J.-K. Yang, W.Tang, *Green Chem*. **2017**, 19, 3296
[3] S. Ogo, N. Makihara, Y. Watanabe, *Organometallics* **1999,** *18,* 5470
[4] S.E. Fayle, J.A.Gerrard, H.E. Nursten, P.J. Steel, Acta Cryst. **1998**, 54, 404
[5] M.Maskal, E.B. Nikitin, *ChemSusChem* **2009**, 2, 423

## *9.2 Supporting Information for section 7.2*

# Electronic Supporting Information

## Efficient synthesis of biomass derived *N*-substituted 2-hydroxymethyl-5-methyl-pyrroles in two steps from 5-hydroxymethylfurfural

Bartosz Wozniak,[a] Yuehui Li,[b] Sandra Hinze,[a] Sergey Tin[a], Johannes G. de Vries*[a]

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*Johannes.devries@catalysis.de*
*[b] State Key Laboratory for Oxo Synthesis and Selective Oxidation, Suzhou Research Institute of LICP, Lanzou Institute of Chemical Physics (LICP), Chinese Academy of Sciences, Lanzhou 730000 P.R. China.*

## Contents

## 1.0 General remarks

For the hydrogenation of HMF, a 2 L hastelloy autoclave vessel with a gas uptake stirrer was used. The reaction was performed under inert conditions under an atmosphere of hydrogen gas. Paal-Knorr reactions were carried out in dried glassware with magnetic stirring under aerobic conditions. Ethanol was obtained from a solvent purification system (SPS). Commercially available chemicals were purchased from Sigma, Alfa, Strem, Abcr and TCI. 5-(Hydroxymethyl)furfural was purchased from AVA-Biochem BSL AG and used without further purification. $^{1}H$ and $^{13}C$ NMR spectra were recorded on Bruker AV 300 spectrometer. All chemical shifts are related to residual solvent peaks [$CDCl_3$: 7.26 ppm ($^{1}H$), 77.16 ppm ($^{13}C$)]. Electrospray ionization high resolution mass spectra were recorded on Agilent 6210 Time-of-Flight LC/MS (ESI). All ATR-IR data were recorded using Bruker Alpha FT-IR Spectrometer.

## 2.0 Synthesis of catalysts I

The ligand 2-(4,5-dihydro-1H-imidazol-2-yl)-4-methoxypyridine and the iridium catalyst were synthesized following a procedure described by Tang and co-workers[1]: to a mixture of $[IrCp^*Cl_2]_2$ (500 mg, 0.63 mmol) and the ligand (231 mg, 1.3 mmol) 6.0 mL of DCM was added and the solution was left to stir for 12 h at room temperature. After this time, the volume was reduced *in vacuo* and the residue was dissolved in the minimum amount of DCM, precipitated by addition of EtOAc (10 mL) and dried under reduced pressure to obtain the desired product as a yellow solid (658 mg, 89% yield). The $^{1}H$ and $^{13}C$ NMR data are identical to those reported.[1]

## 3.0 Large scale synthesis of HHD

A 2 L hastelloy autoclave vessel equipped with a gas uptake mechanical stirrer was charged with 5-HMF (**1**) (25 g, 0.2 mol) and complex **I** (80 mg, 0.075 mol%). The contents were dissolved in phosphate buffer solution (PBS, 1.0 L, pH= 2.5) and the vessel was flushed three times with $N_2$ gas and subsequently with $H_2$. After flushing, the reactor was pressurized with $H_2$ to 60 bar and the reaction mixture was stirred at 140 $^{o}$C for 1 h. After this time, the vessel was cooled to room temperature and depressurised, the yellow solution was concentrated in *vacuo* to 50 mL, the contents were extracted with DCM (6 x 40 mL), the organic layer was dried over anhydrous $MgSO_4$ and the solvent was removed under reduced pressure. The resulting yellow oil was purified by flash column chromatography ($SiO_2$, ethyl acetate) to afford the desired product as a yellow solid material (18.19 g, 71%). The $^{1}H$ and $^{13}C$ NMR data are identical to those previously reported by our group.[2]

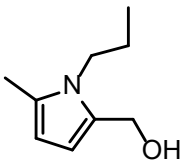
## 4.0 General procedure for Paal-Knorr synthesis

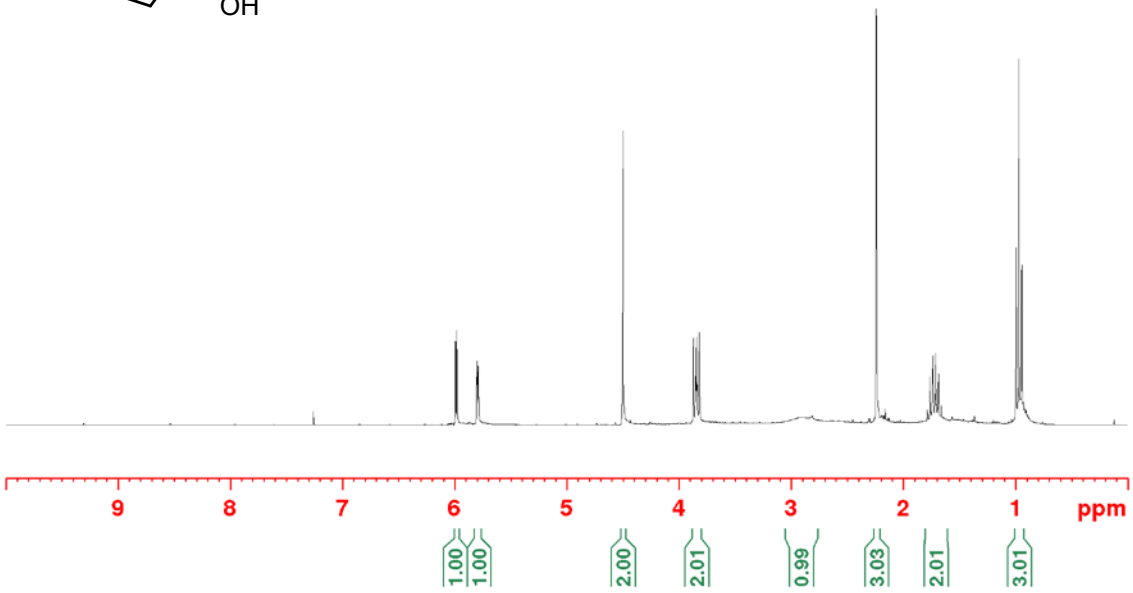
Under aerobic conditions, HHD (**2**) (130 mg, 1 mmol) was dissolved in ethanol (2.0 mL) and 1 mmol of amine was added. Reaction was stirred at room temperature and monitored by thin-layer chromatography until complete conversion of substrate was achieved. The solutions were filtered over celite and concentrated in *vacuo* yielding brown oils or solids. Unless otherwise noted, pure products were obtained and further purification methods were not required.

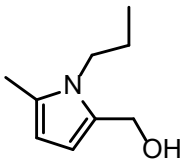
## 5.0 Analytical data of isolated products

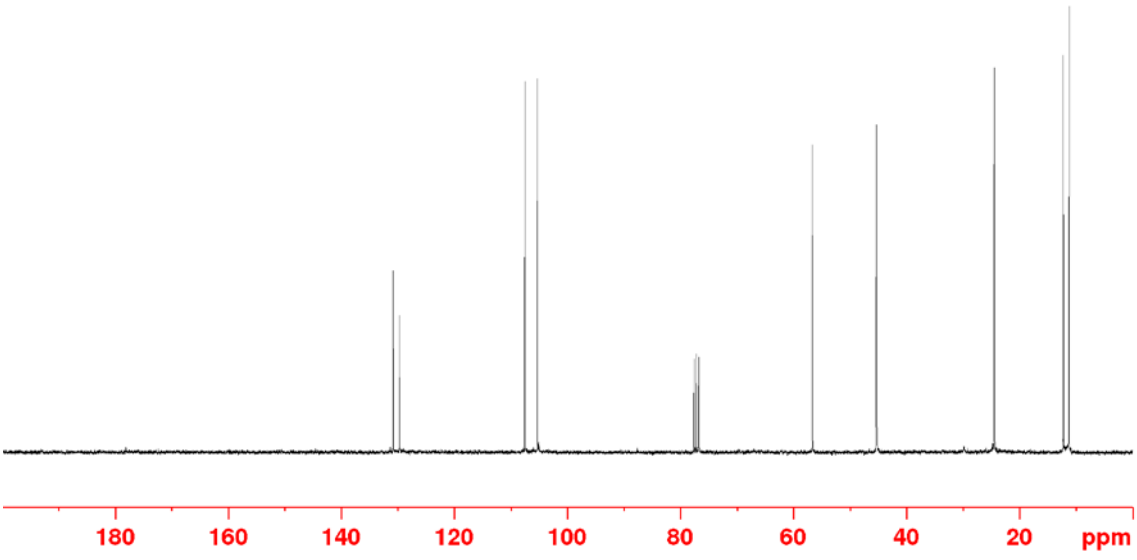
***N*-Propyl-2-hydroxymethyl-5-methylpyrrole (4a)** 82 µL (1 mmol) of propylamine was converted to 150 mg (98% yield) of *N*-Propyl-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 6.00 (d, *J*= 3.4 Hz, 1H), 5.79 (d, *J*= 3.4 Hz, 1H), 4.50 (s, 2H), 3.88-3.80 (m, 2H), 2.90 (brs, 1H), 2.24 (s, 3H), 1.80-1.63 (m, 2H), 0.97 (t, *J*= 4.4 Hz, 3H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 130.8, 129.7, 107.5, 105.3, 56.6, 45.3, 24.5, 12.2,

11.2 ppm. ATR-IR: ν(O-H) 3368; ν(C-H aromatics) 3095; ν(C-H) 2962, 2931, 2874 $cm^{-1}$. HR-MS (EI) calculated for $C_9H_{15}ON$ 153.1148, found 153.1142.

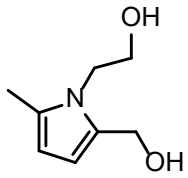


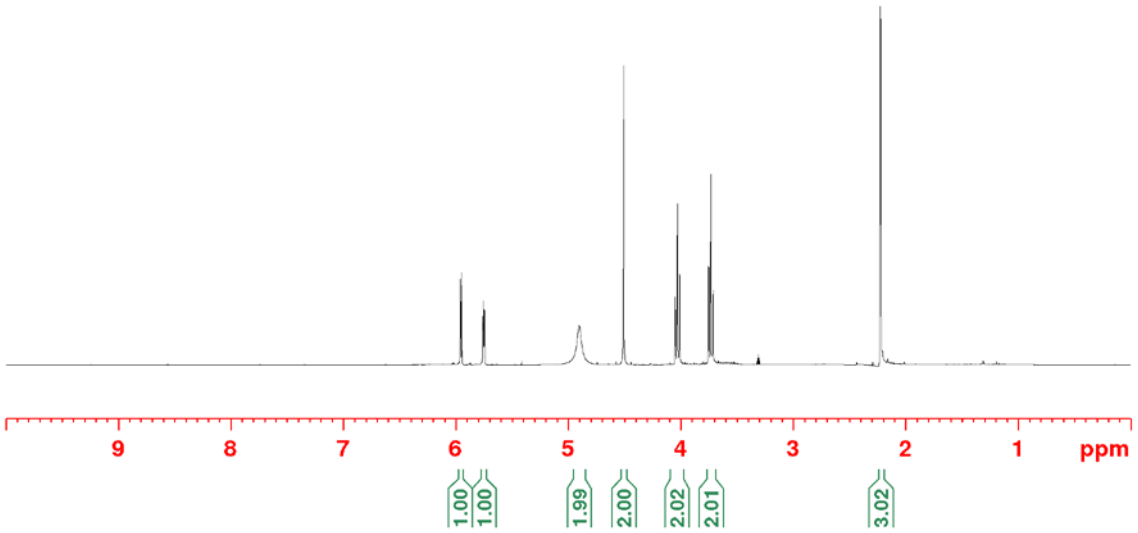



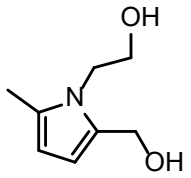



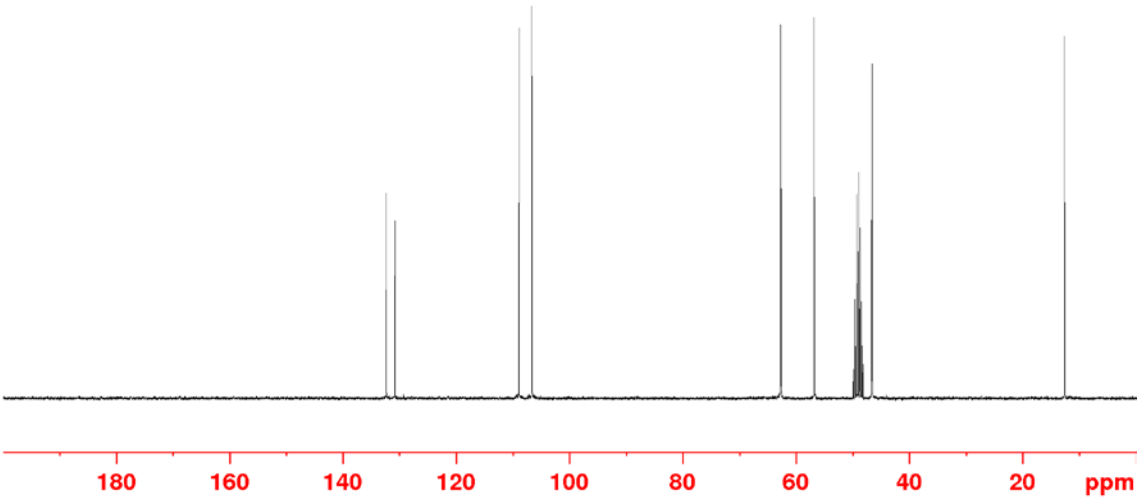



***N*-Hydroxyethyl-2-hydroxymethyl-5-methylpyrrole (4b)** 50 µL (1 mmol) of ethanolamine was converted to 153 mg (99% yield) of *N*-Hydroxyethyl-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CD_3OD$) δ = 5.95 (d, *J*= 3.4 Hz, 1H), 5.75 (d, *J*= 3.4 Hz, 1H), 4.90 (brs, 2H), 4.51 (s, 2H), 4.03 (t, J= 6 Hz, 2H), 3.73 (t, *J*= 6 Hz, 2H), 2.22 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CD_3OD$) δ = 132.3, 130.8, 108.9, 106.6, 62.7, 56.8, 46.6, 12.6 ppm. ATR-IR: ν(O-H) 3325; ν(C-H aromatics) 3098; ν(C-H) 2930, 2861 $cm^{-1}$. HR-MS (EI) calculated for $C_8H_{13}O_2N$ 155.0941, found 155.0939.

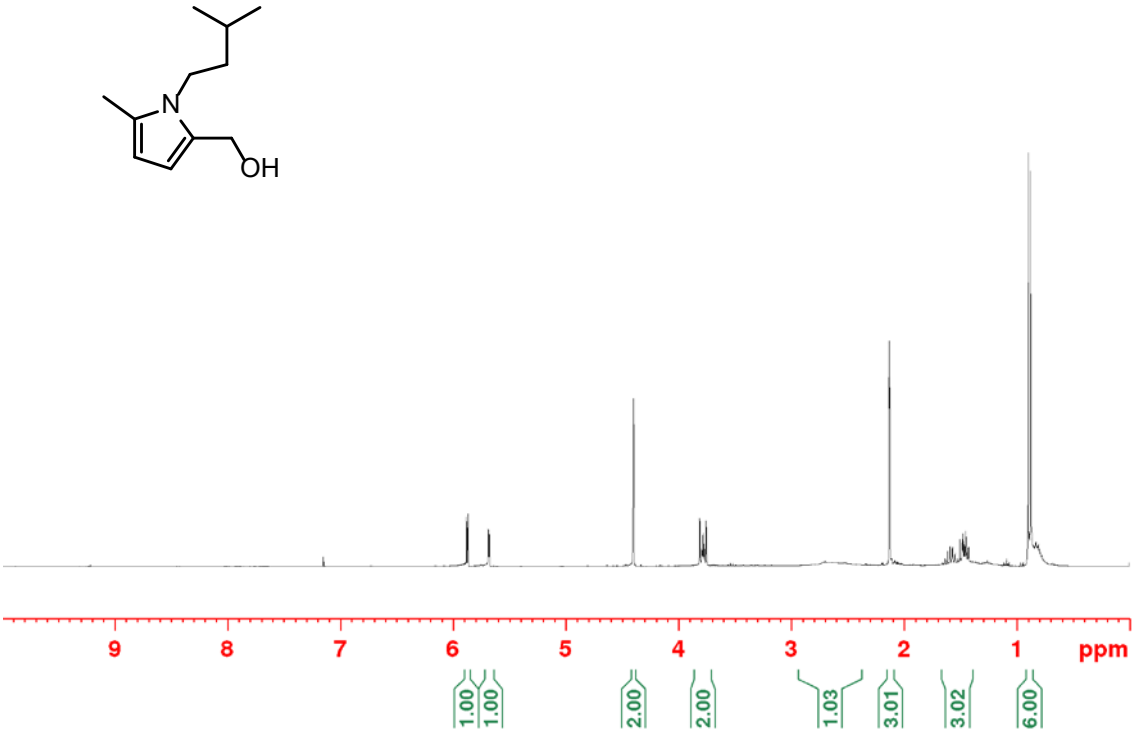


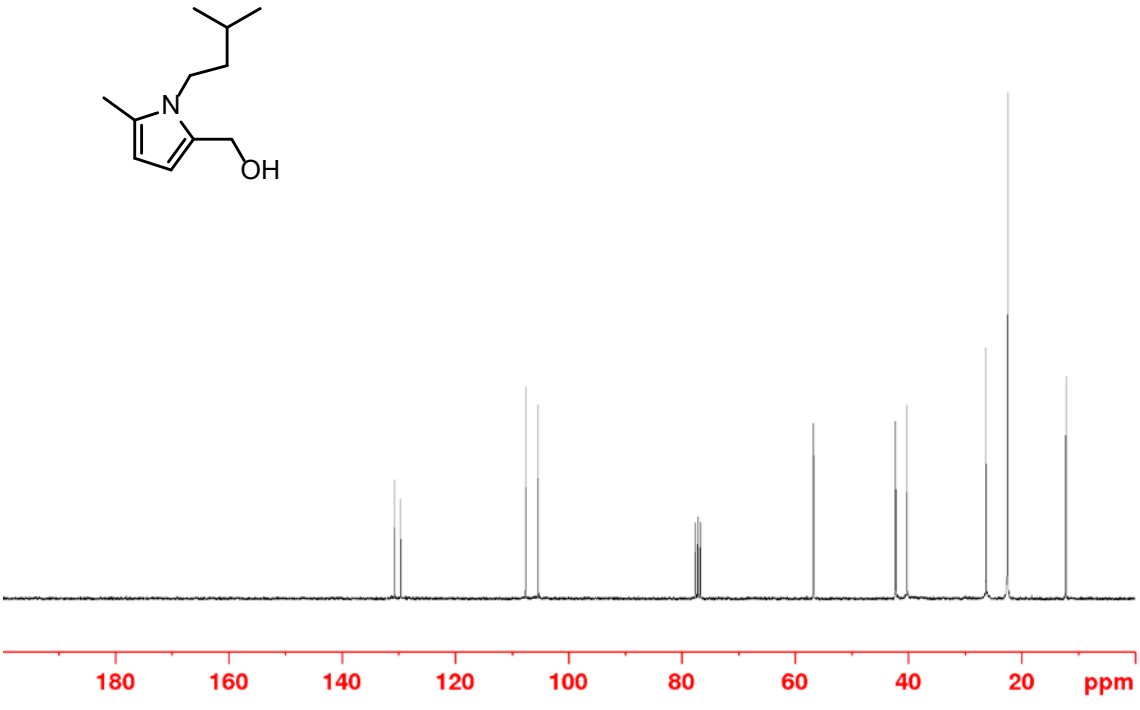



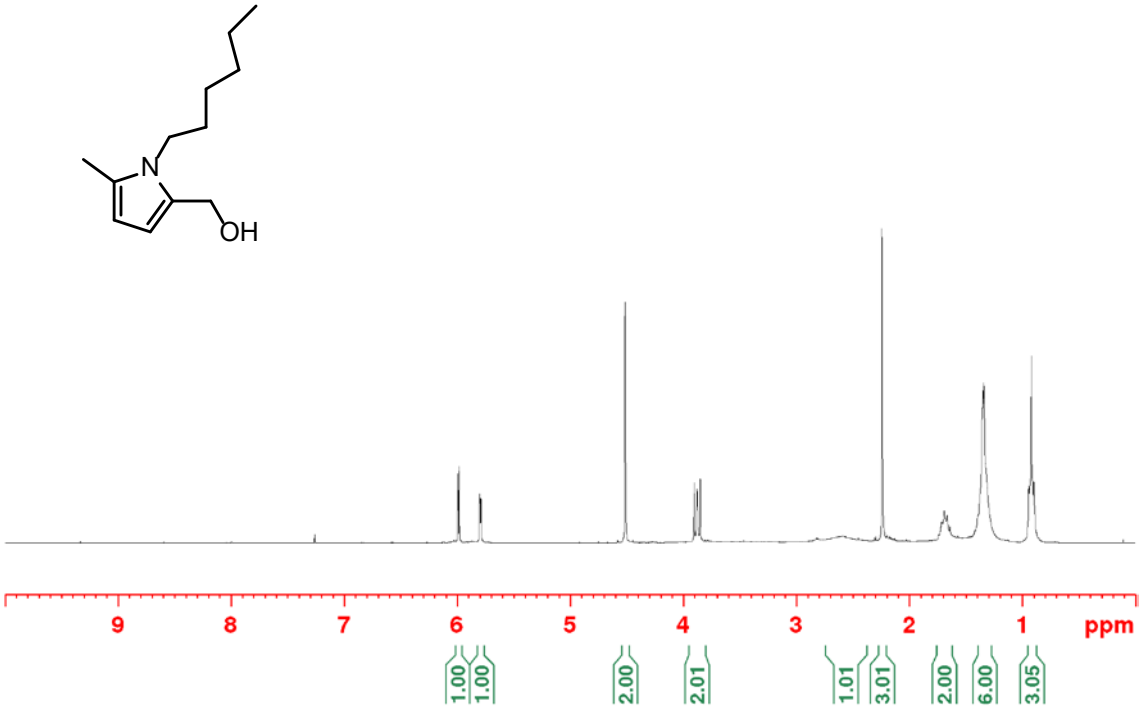



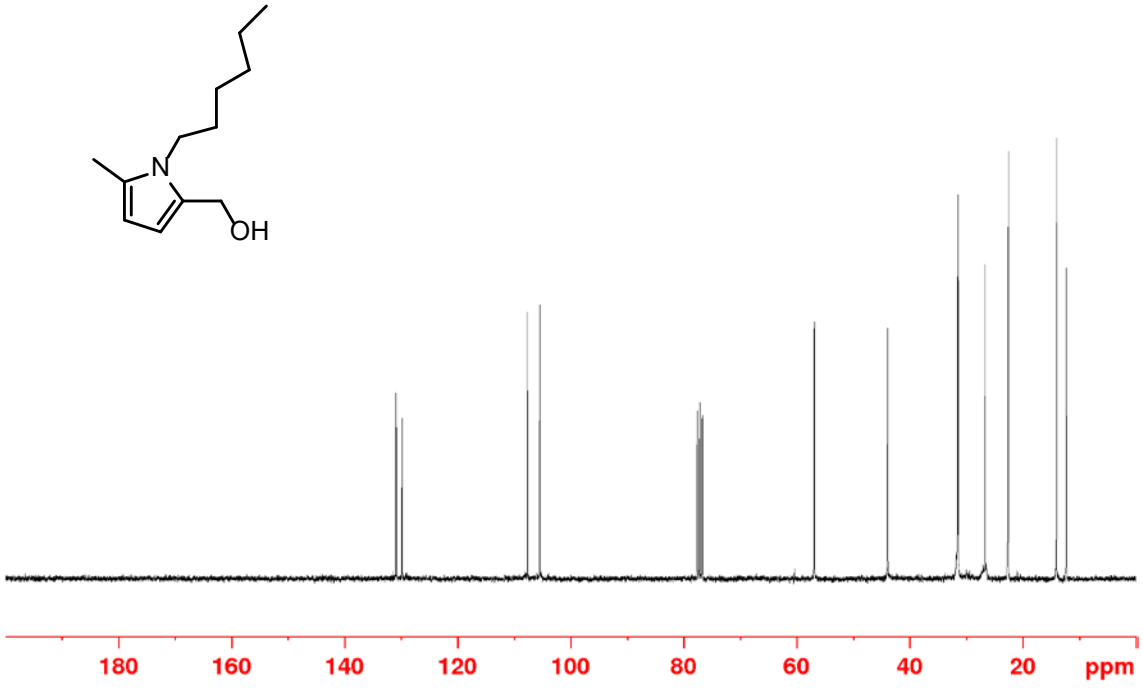
***N*-Isopentyl-2-hydroxymethyl-5-methylpyrrole** (**4c**) 50 µL (1 mmol) of isopentylamine was converted to 176 mg (97% yield) of *N*-isopentyl-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 5.98 (d, *J*= 3.4 Hz, 1H), 5.79 (d, *J*= 3.4 Hz, 1H), 4.51 (s, 2H), 3.89 (t, *J*= 8 Hz, 2H), 2.74 (brs, 1H), 2.24 (s, 3H), 1.77-1.54 (m, 3H), 1.00 (d, *J*=6.5 Hz, 6H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 130.7, 129.6, 107.6, 105.4, 56.8, 42.3, 40.2, 26.3, 22.5, 12.2 ppm. ATR-IR: ν(O-H) 3386; ν(C-H aromatics) 3098; ν(C-H) 2955, 2930, 2870 $cm^{-1}$. HR-MS (EI) calculated for $C_{11}H_{19}ON$ 181.1461, found 181.1456.



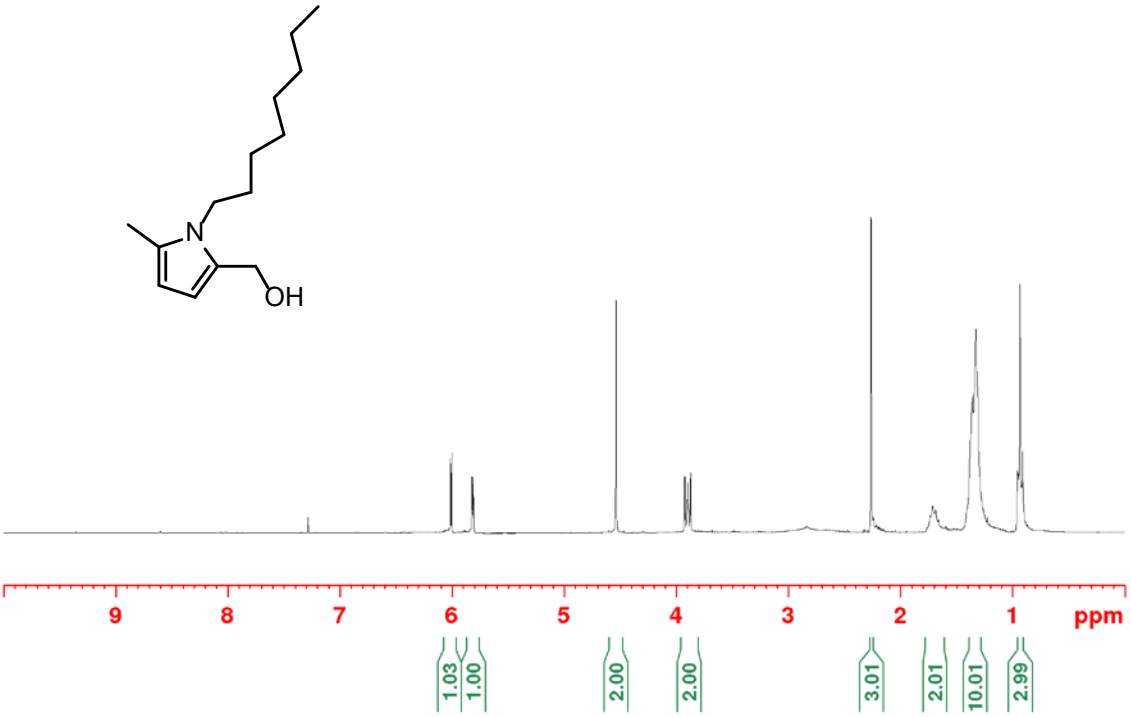



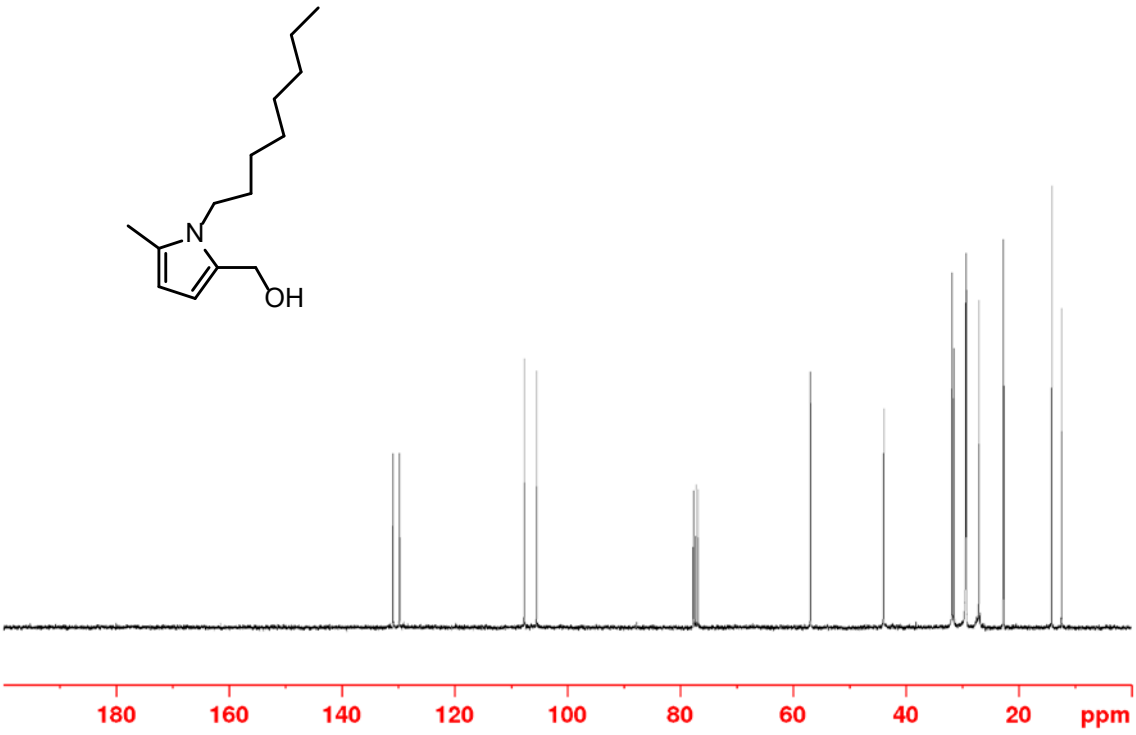
***N*-Hexyl-2-hydroxymethyl-5-methylpyrrole** (**4d**) 132 µL (1 mmol) of hexylamine was converted to 190 mg (97% yield) of *N*-Hexyl-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 5.99 (d, *J*= 3.4 Hz, 1H), 5.79 (d, *J*= 3.4, 1H), 4.51 (s, 2H), 3.92-3.82 (m, 2H), 2.60 (brs, 1H), 2.24 (s, 3H), 1.75-1.64 (m, 2H), 1.40-1.28 (m, 6H), 0.95-0.88 (m, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 130.9, 129.8, 107.6, 105.4, 56.8, 43.9, 31.5, 31.4, 26.6, 22.6, 14.0, 12.3 ppm. ATR-IR: ν(O-H) 3366; ν(C-H aromatics) 3098; ν(C-H) 2955, 2926, 2857 $cm^{-1}$. HR-MS (EI) calculated for $C_{12}H_{21}ON$ 195.1618, found 195.1617.



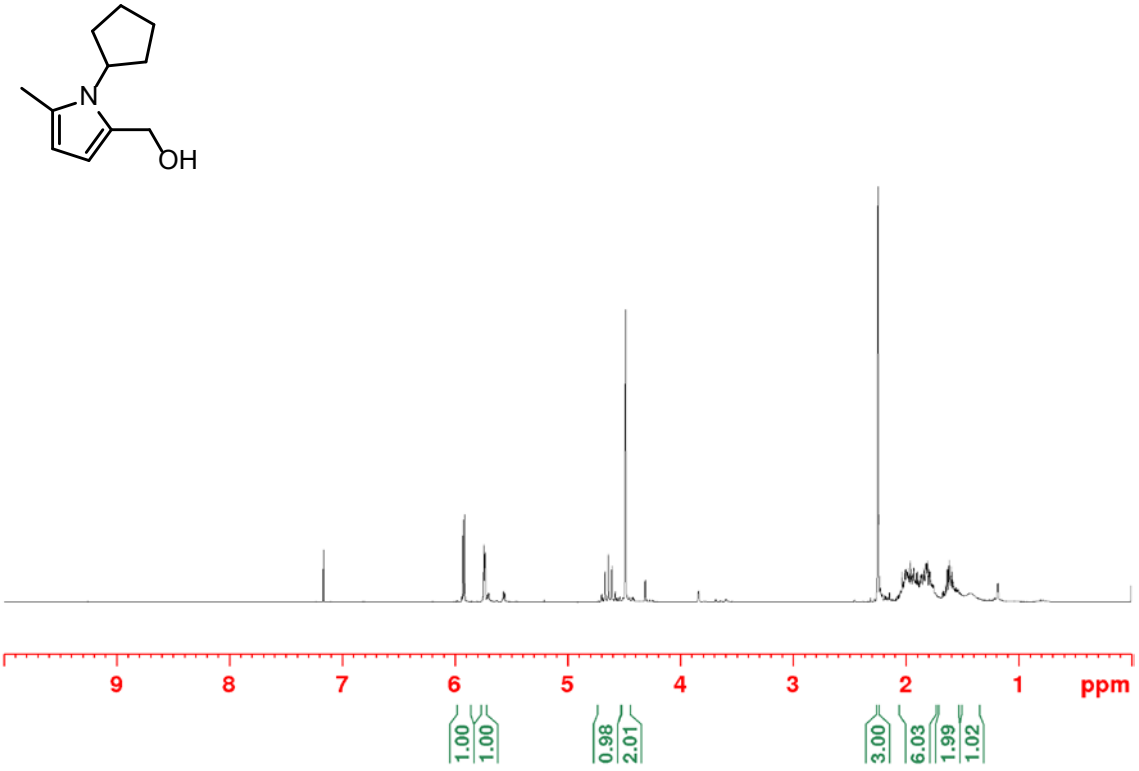



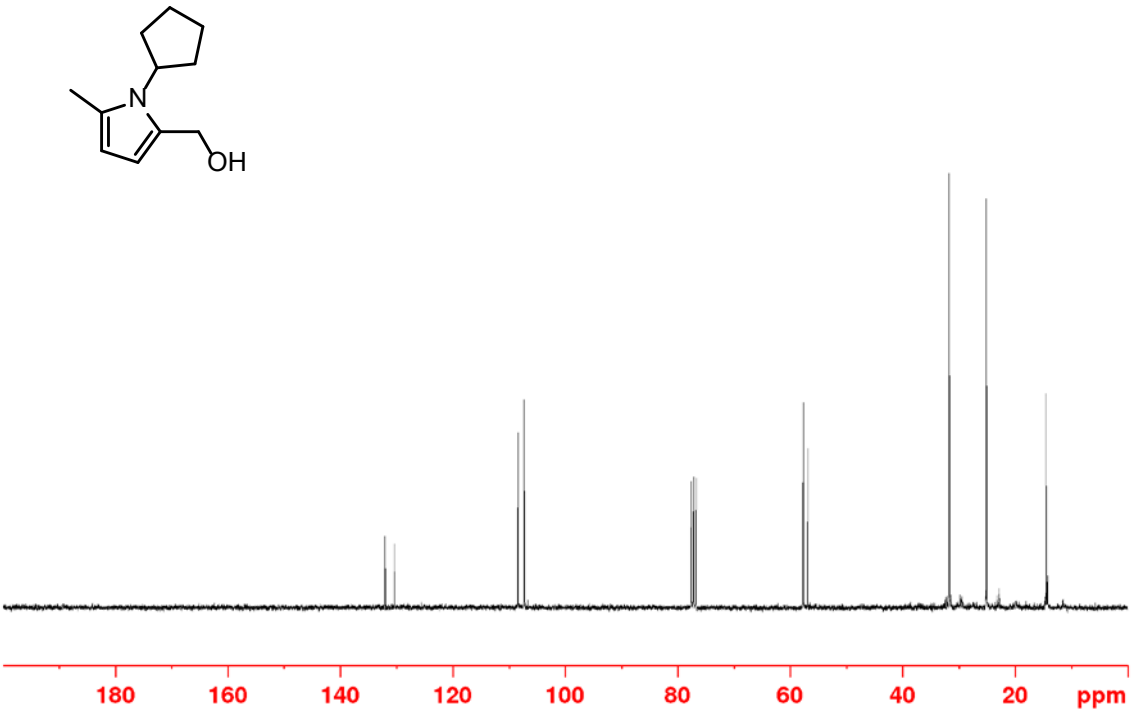
***N*-Octyl-2-hydroxymethyl-5-methylpyrrole** (**4e**) 165 µL (1 mmol) of octylamine was converted to 214 mg (96% yield) of *N*-Octyl-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 5.98 (d, *J*= 3.4 Hz, 1H), 5.79 (d, *J*= 3.4, 1H), 4.51 (s, 2H), 3.92-3.82 (m, 2H), 2.81 (brs, 1H), 2.24 (s, 3H), 1.75-1.64 (m, 2H), 1.40-1.20 (m, 10H), 0.94-0.85 (m, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 130.9, 129.8, 107.6, 105.4, 56.8, 43.9, 31.8, 31.4, 29.3, 29.2, 27.0, 22.6, 14.0, 12.3 ppm. ATR-IR: ν(O-H) 3380; ν(C-H aromatics) 3098; ν(C-H) 2954, 2923, 2854 $cm^{-1}$. HR-MS (EI) calculated for $C_{14}H_{25}ON$ 223.1931, found 233.1928.



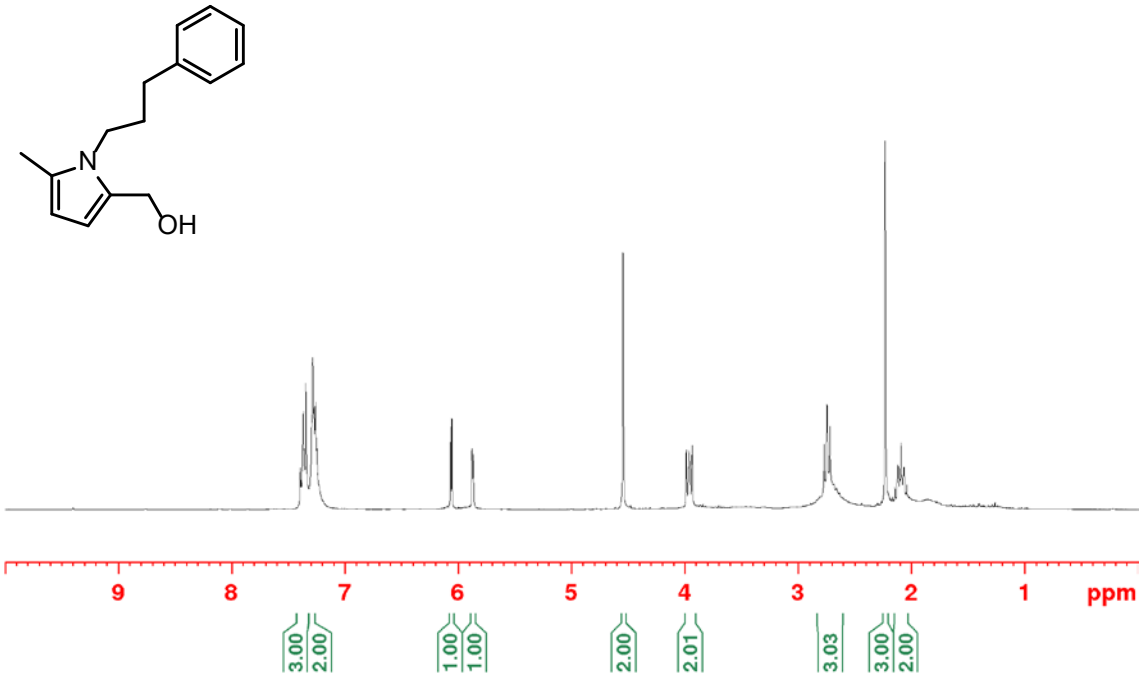



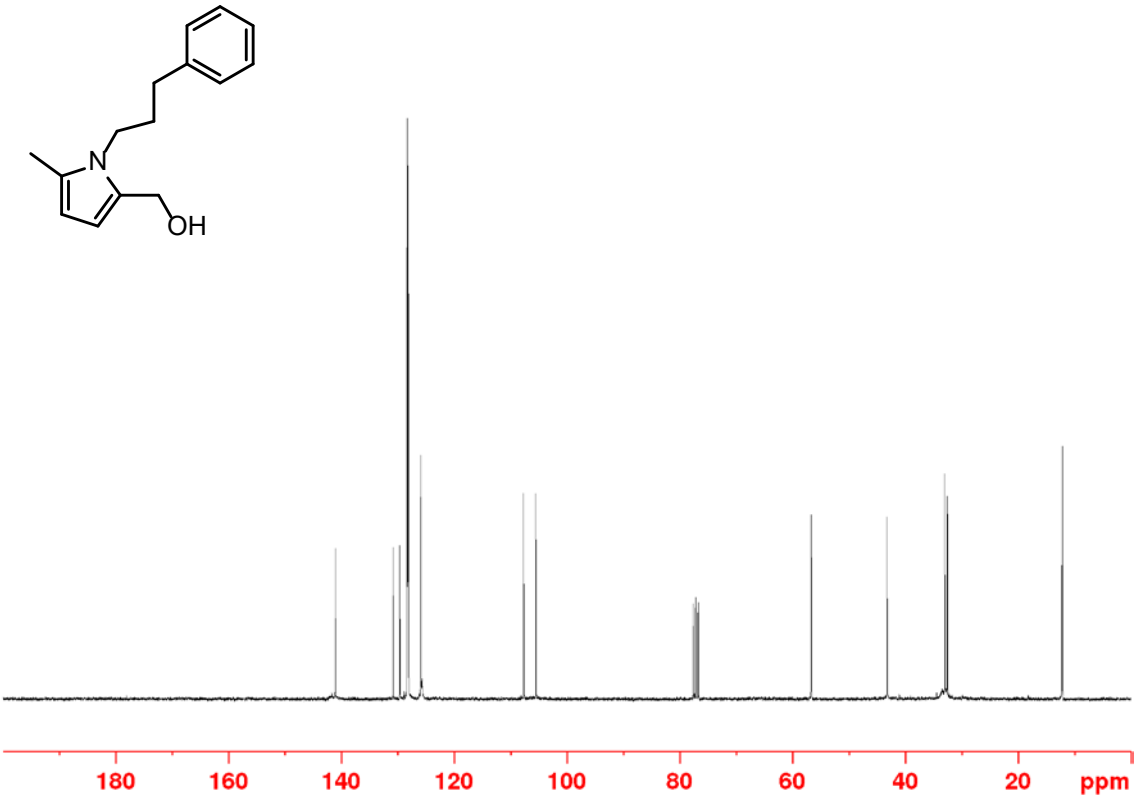
***N*-Cyclopentyl-2-hydroxymethyl-5-methylpyrrole** (**4g**) 99 µL (1 mmol) of cyclopentylamine was converted to 143 mg (80% yield) of *N*-Cyclopentyl-2-hydroxymethyl-5-methylpyrrole as a yellow solid. The product was isolated by column chromatography ($SiO_2$, cyclohexane: ethyl acetate 2:1). $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 6.01 (d, *J*= 3.4 Hz, 1H), 5.84 (d, *J*= 3.4 Hz, 1H), 4.80-4.64 (m, 1H), 4.58 (s, 2H), 2.35 (s, 3H), 2.17-1.81 (m, 6H), 1.78-1.58 (m, 2H), 1.53 (bs, 1H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 132.1, 130.4, 108.4, 107.3, 57.7, 56.9, 31.7, 25.1, 14.4 ppm. ATR-IR: ν(O-H) 3411; ν(C-H aromatics) 3095; ν(C-H) 2951, 2868 $cm^{-1}$. HR-MS (EI) calculated for $C_{11}H_{17}ON$ 179.1305, found 179.1307.



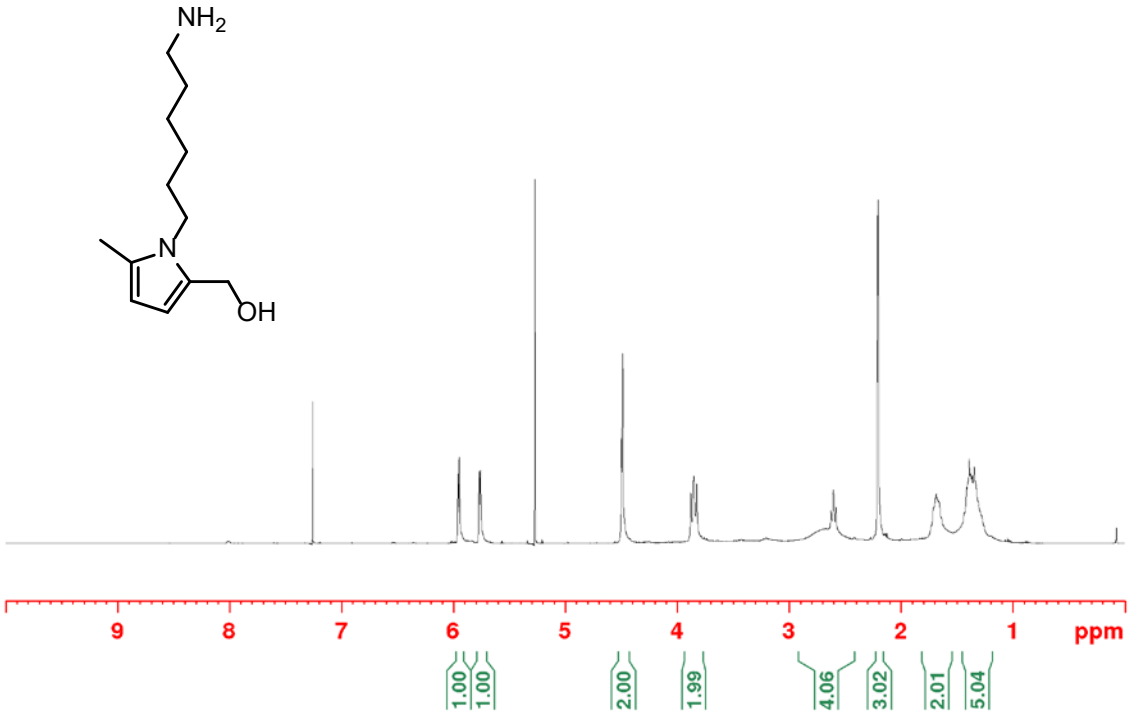



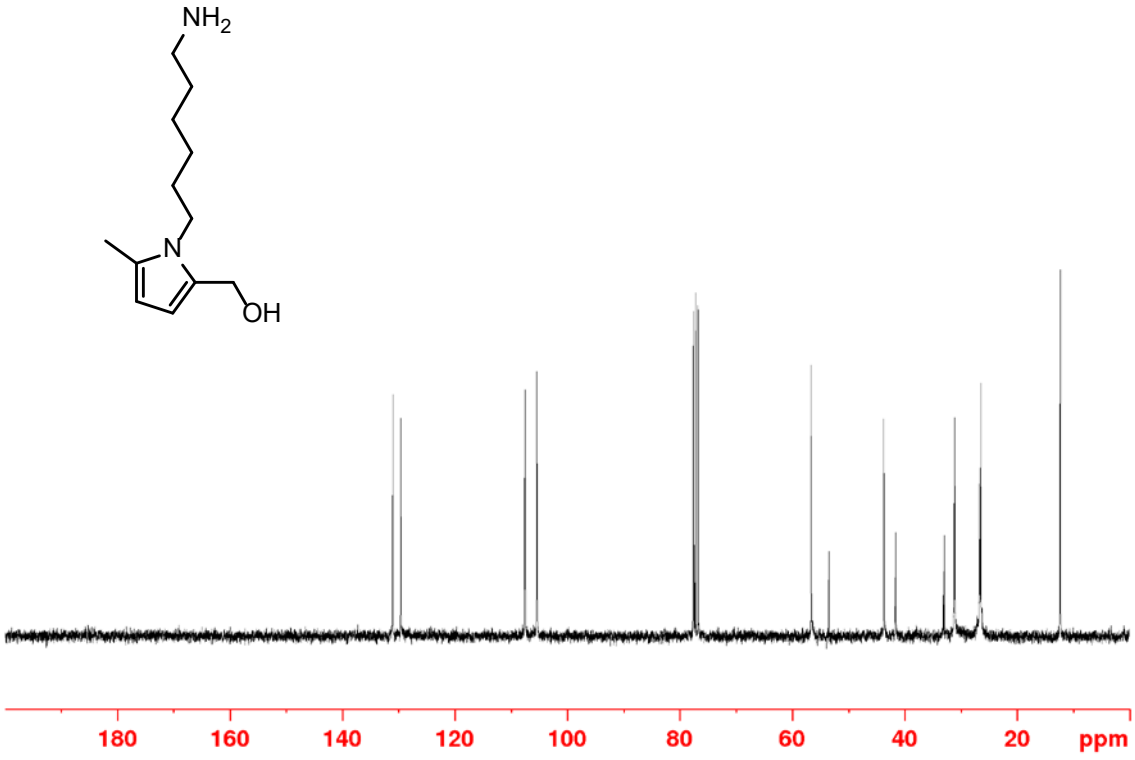
***N*-(3-Phenylpropyl)-2-hydroxymethyl-5-methylpyrrole** (**4h**) 142 µL (1 mmol) of 3-Phenyl-1-propylamine was converted to 224 mg (98% yield) of *N*-(3-Phenylpropyl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.40-7.32 (m, 3H), 7.32-7.27 (m, 2H), 6.06 (d, *J*= 3.4 Hz, 1H), 5.87 (d, *J*= 3.4 Hz, 1H), 4.55 (s, 2H), 4.00-3.90 (m, 2H), 2.83-2.61 (m, 2H), 2.72 (brs, 1H), 2.23 (s, 3H), 2.15-2.04 (m, 2H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 141.1, 130.8, 129.6, 128.3, 128.2, 128.2, 128.1, 125.9, 107.7, 105.5, 56.7, 43.2, 33.0, 32.5, 12.1 ppm. ATR-IR: ν(O-H) 3381; ν(C-H aromatics) 3085, 3062, 3026; ν(C-H) 2934, 2861 $cm^{-1}$. HR-MS (EI) calculated for $C_{15}H_{19}ON$ 229.1461, found 229.1457.



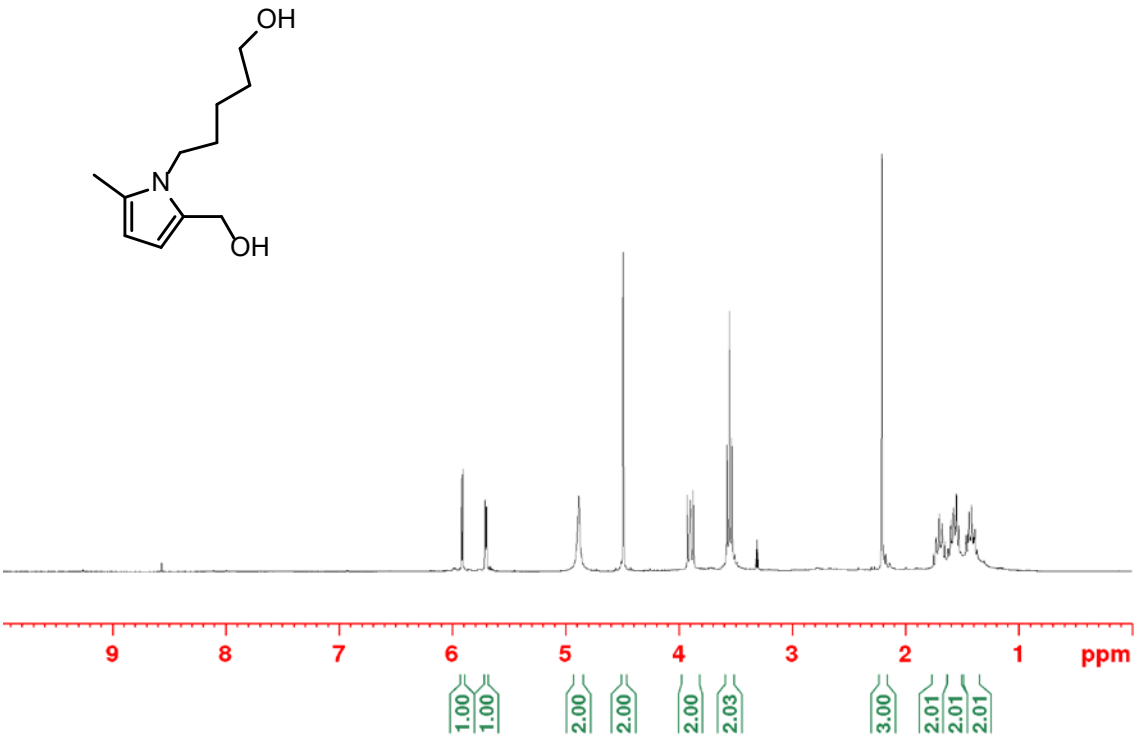



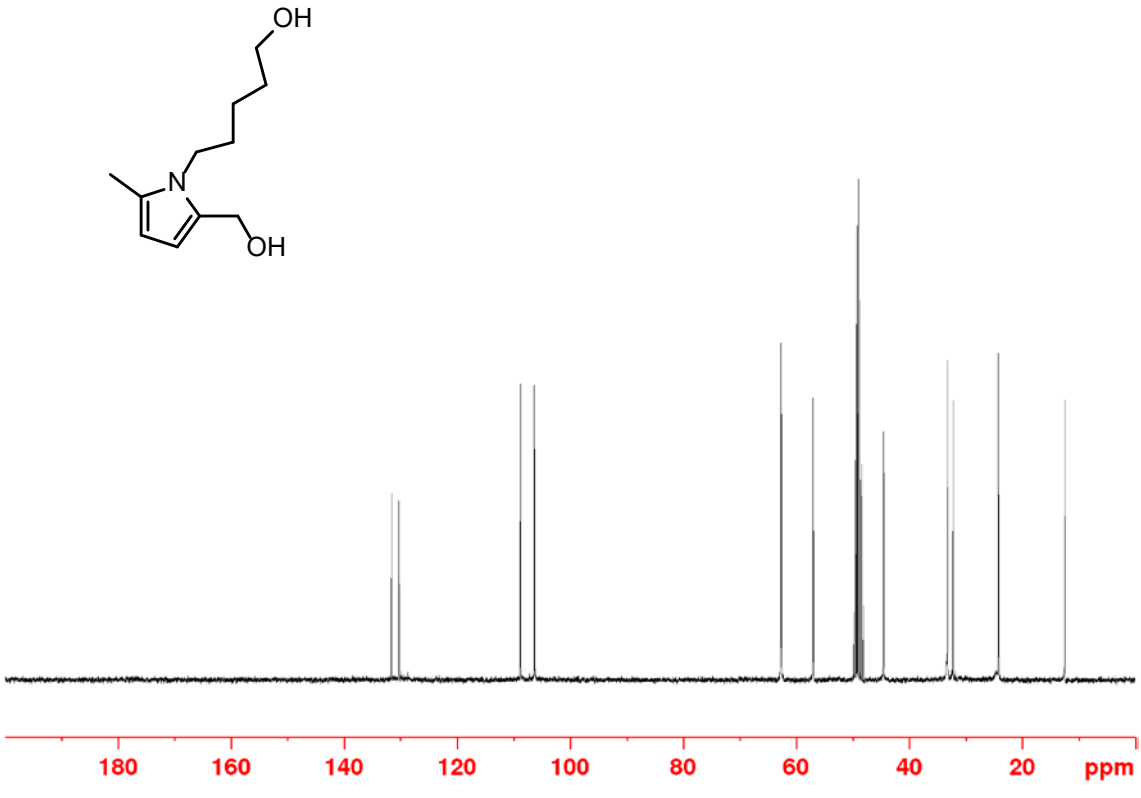
***N*-(6-Hexylamine)-2-hydroxymethyl-5-methylpyrrole** (**4i**) 130 µL (1 mmol) of 1,6-hexanediamine was converted to a 4:1 mixture of the title compound and the dimeric compound (hexane-1,6-diylbis(5-methyl-1H-pyrrole-1,2-diyl))dimethanol. The dimeric compound solidified over time and could be separated off by filtration. Thus 139 mg (66% yield) of *N*-(6-Hexylamine)-2-hydroxymethyl-5-methylpyrrole could be isolated as a brown oil. $^{1}$H NMR (300 MHz, $CD_3OD$) δ = 5.95 (d, *J*= 3.4 Hz, 1H), 5.76 (d, *J*= 3.4 Hz, 1H), 4.49 (s, 2H), 3.91-3.78 (m, 2H), 2.67 (bs, 2H), 2.60 (t, *J*= 6.7 Hz, 2H) 2.20 (s, 3H), 1.77-1.59 (m, 2H), 1.46-1.21 (m, 4H), 1.37 (bs, 1H) ppm. $^{13}$C NMR (75 MHz, $CD_3OD$) δ = 131.0, 129.7, 107.5, 105.5, 56.6, 43.8, 41.6 33.0, 31.1, 26.7, 26.5, 12.3 ppm. ATR-IR: ν(O-H) 3354; ν(N-H) 3296; ν(C-H aromatics) 3098; ν(C-H) 2929, 2857 $cm^{-1}$. HR-MS (EI) calculated for $C_{12}H_{22}ON_2$ 210.1727, found 210.1722.



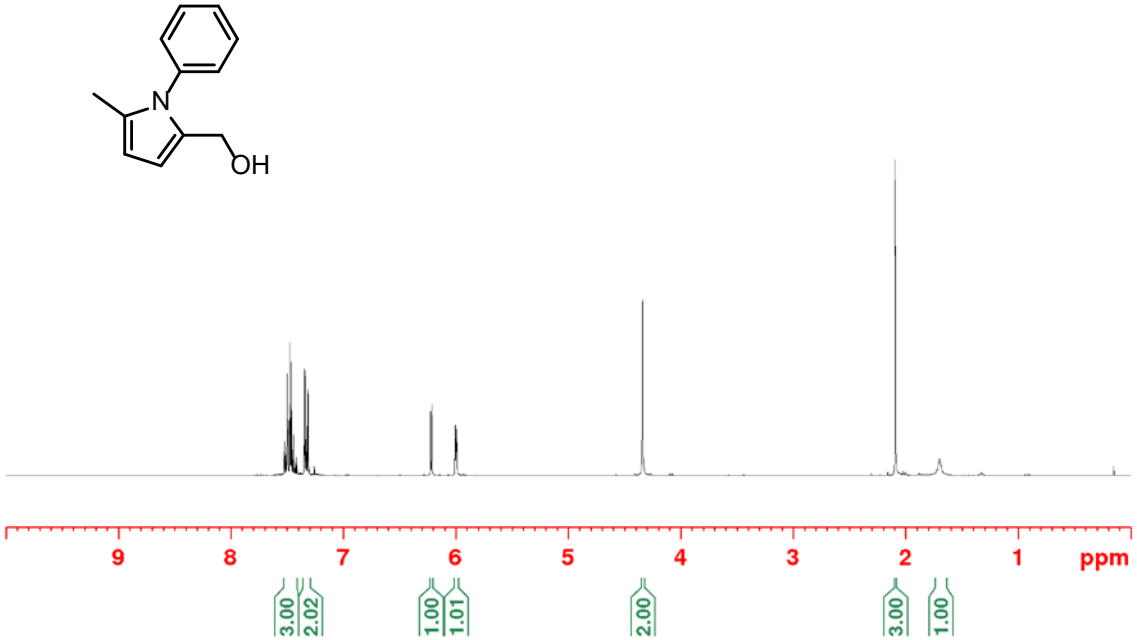



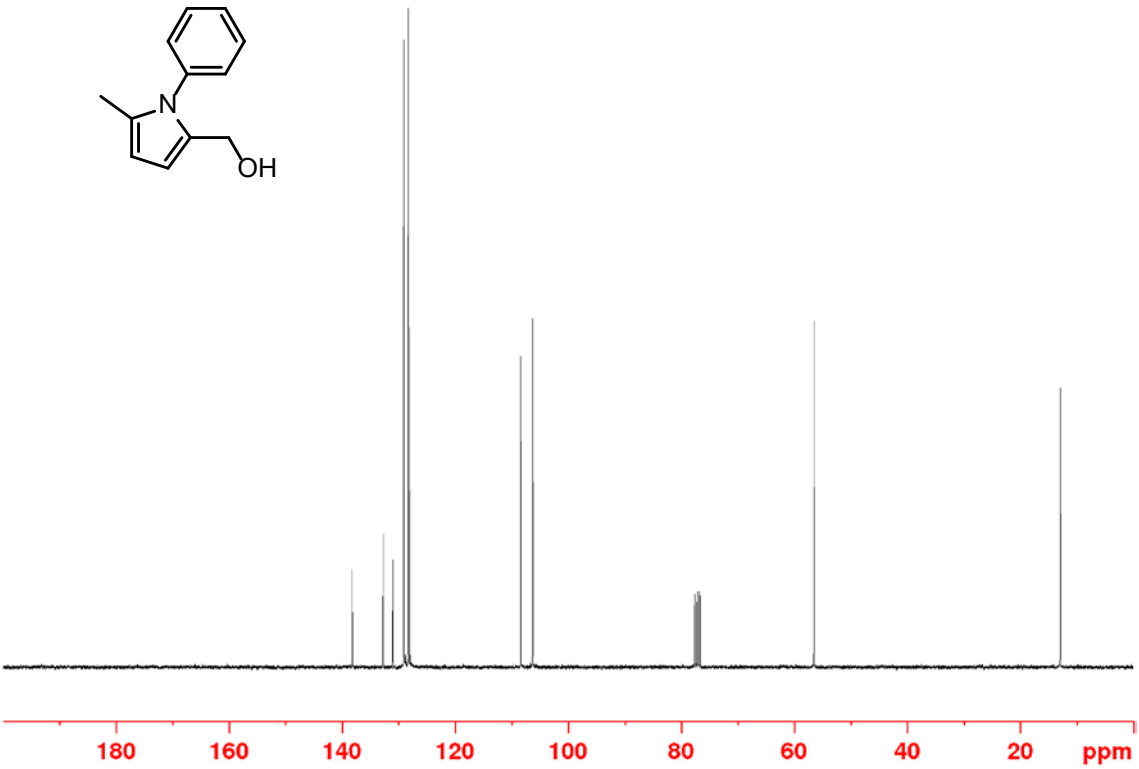
***N*-(6-Hydroxypentyl)-2-hydroxymethyl-5-methylpyrrole** (**4j**) 103 mg (1 mmol) of 5-amino-1-pentanol was converted to 196 mg (99% yield) of *N*-(6-Hydroxypentyl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CD_3OD$) δ = 5.92 (d, *J*= 3.4 Hz, 1H), 5.71 (d, *J*= 3.4 Hz, 1H), 4.90 (brs, 2H), 4.49 (s, 2H), 3.95-3.85 (m, 2H), 3.56 (t, *J*= 6.4 Hz, 2H), 2.21 (s, 3H), 1.75-1.64 (m, 2H), 1.62-1.50 (m, 2H), 1.47-1.36 (m, 2H) ppm. $^{13}$C NMR (75 MHz, $CD_3OD$) δ = 131.6, 130.3, 108.8, 106.4, 62.7, 57.0, 44.6, 33.2, 32.2, 24.2, 12.5 ppm. ATR-IR: ν(O-H) 3325; ν(C-H aromatics) 3098; ν(C-H) 2933, 2863 $cm^{-1}$. HR-MS (EI) calculated for $C_{11}H_{19}O_2N$ 197.1410, found 197.1404.



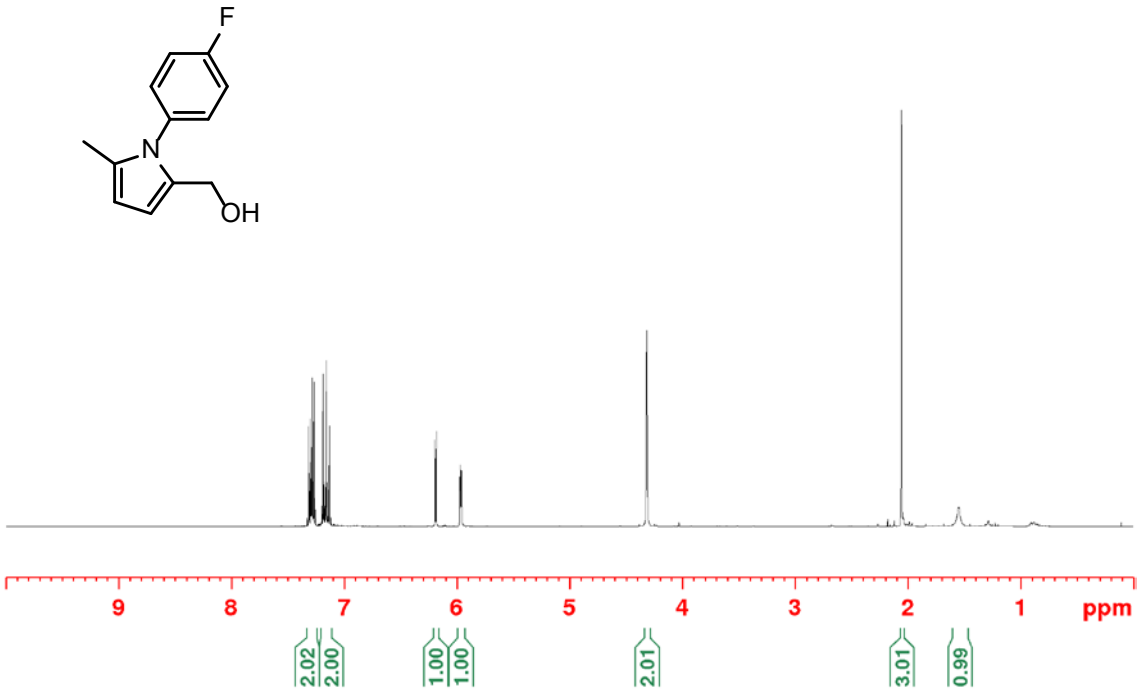



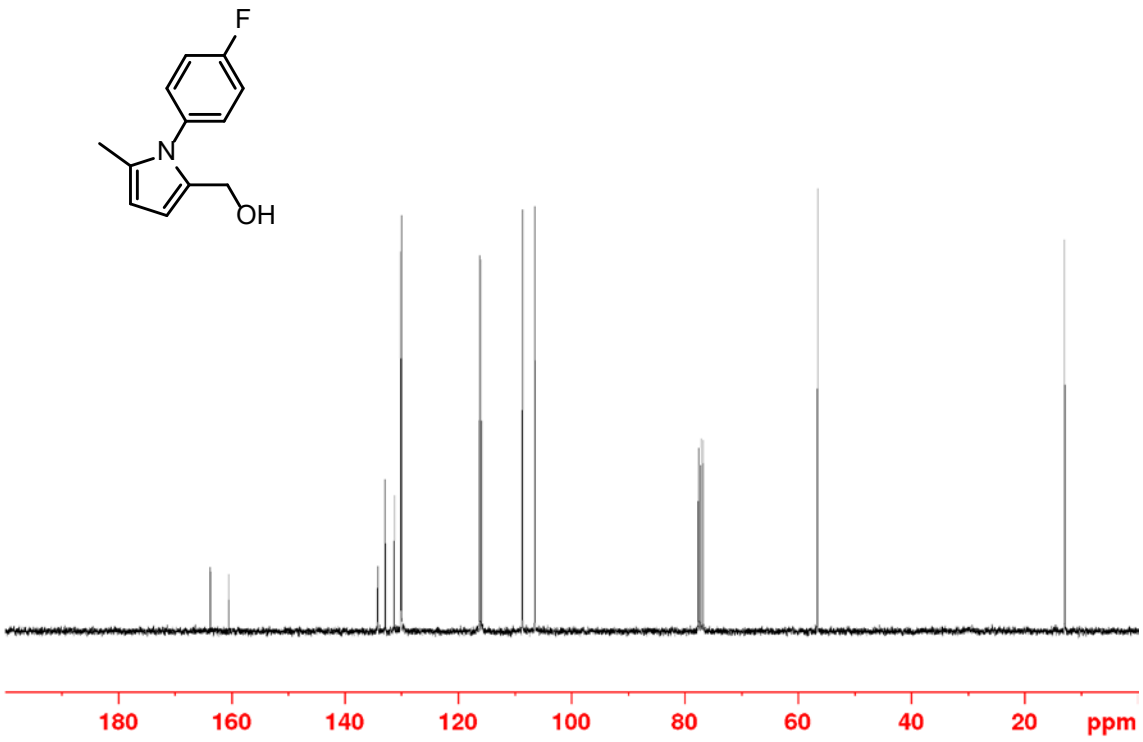
***N*-Phenyl-2-hydroxymethyl-5-methylpyrrole** (**5a**) 97 µL (1 mmol) of aniline was converted in 96% to 142 mg (76% yield) of *N*-Phenyl-2-hydroxymethyl-5-methylpyrrole as a yellow solid. The product was isolated by column chromatography ($SiO_2$, cyclohexane: ethyl acetate 2:1). $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 7.53-7.41 (m, 3H), 7.35-7.30 (m, 2H), 6.22 (d, *J*= 3.4 Hz, 1H), 6.00 (d, *J*= 3.4 Hz, 1H), 4.34 (s, 2H), 2.09 (s, 3H), 1.70 (brs, 1H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 138.2, 132.8, 131.1, 129.1, 128.3, 128.0, 108.4, 106.3, 56.5, 12.9 ppm. ATR-IR: ν(O-H) 3405; ν(C-H aromatics) 3098, 3062; ν(C-H) 2917, 2855 $cm^{-1}$ HR-MS (EI) calculated for $C_{12}H_{13}ON$ 187.0992, found 187.0989.

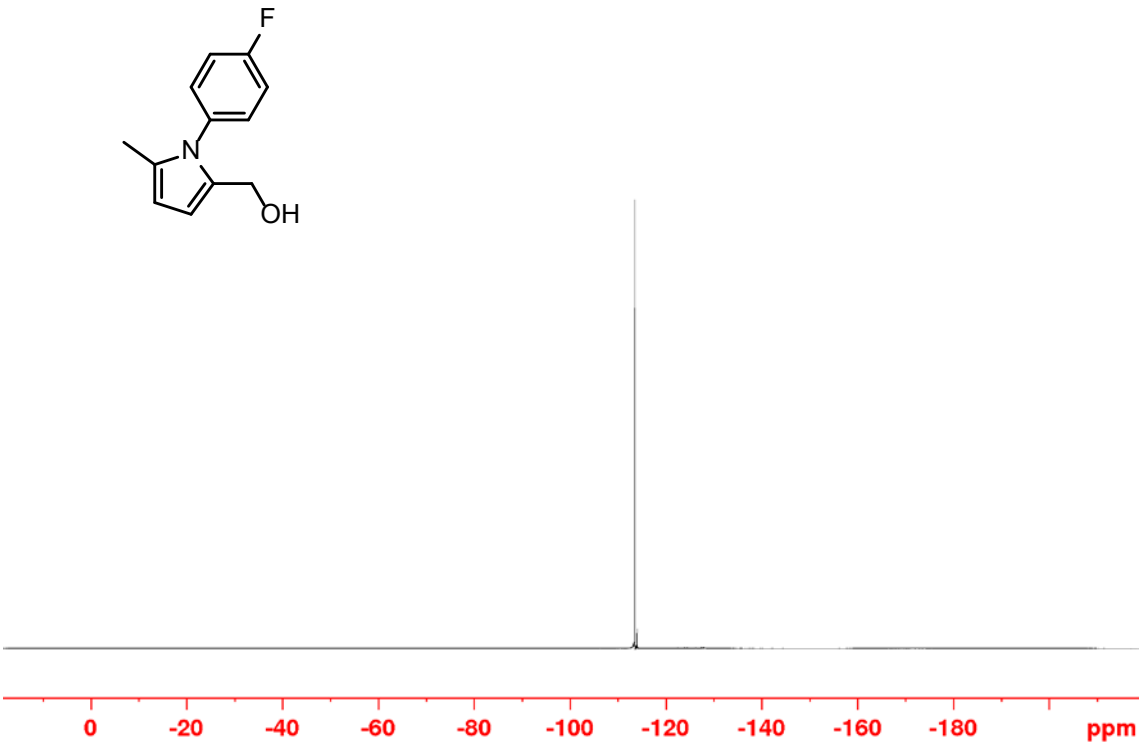


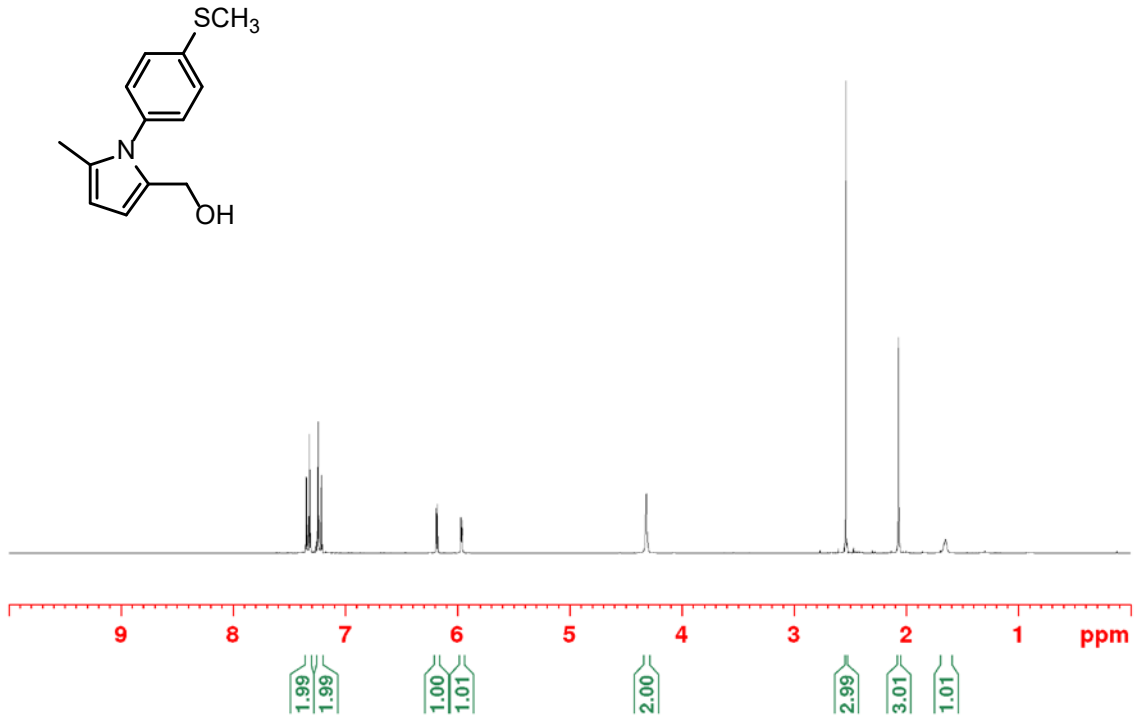
***N*-(4-Fluorophenyl)-2-hydroxymethyl-5-methylpyrrole** (**5b**) 95 µL (1 mmol) of 4-fluoroanilline was converted in 92% to 152 mg (74% yield) of *N*-(4-Fluorophenyl)-2-hydroxymethyl-5-methylpyrrole as a yellow solid. The product was isolated by column chromatography ($SiO_2$, cyclohexane: ethyl acetate 2:1). $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 7.33-7.26 (m, 2H), 7.20-7.12 (m, 2H), 6.19 (d, *J*= 3.4 Hz, 1H), 5.97 (d, *J*= 3.4 Hz, 1H), 4.32 (s, 2H), 2.06 (s, 3H), 1.55 (brs, 1H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 162.1 [d, $^{1}J$(C,F) = 248.2 Hz] , 134.2 [d, $^{2}J$(C,F) = 1.7 Hz], 132.9 , 131.3, 130.1 [d, $^{2}J$(C,F) = 4.3 Hz], 116.1 [d, $^{2}J$(C,F) = 11.2 Hz], 108.6, 106.4, 56.5, 12.9 ppm. $^{19}F$ (282 MHz, CDCl3) δ = -113.5 ppm. ATR-IR: ν(O-H) 3436; ν(C-H aromatics) 3101, 3074, 2980; ν(C-H) 2924, 2872 $cm^{-1}$. HR-MS (EI) calculated for $C_{12}H_{12}ONF$ 205.0987, found 205.0983.

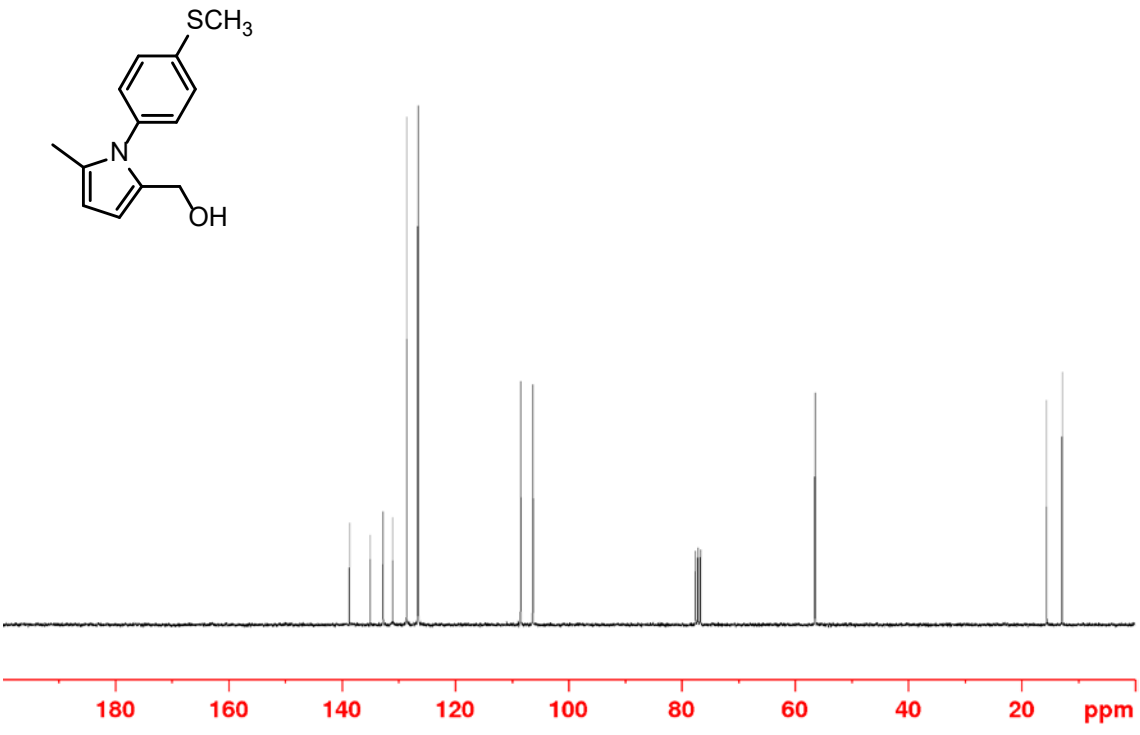


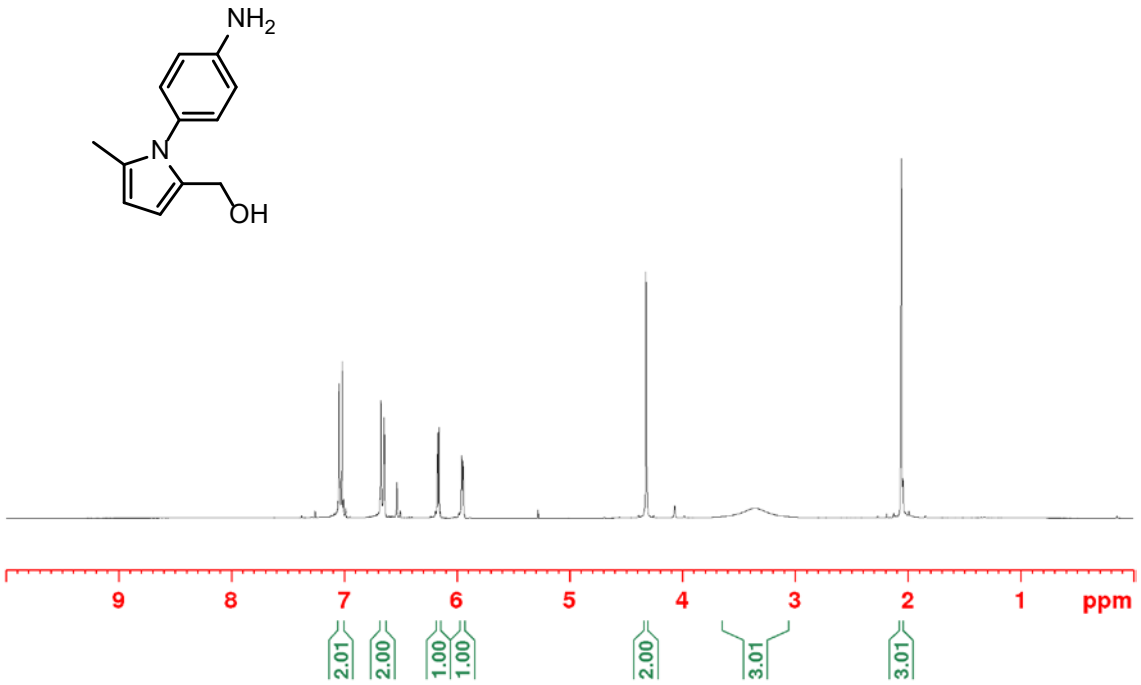

F
N
OH
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

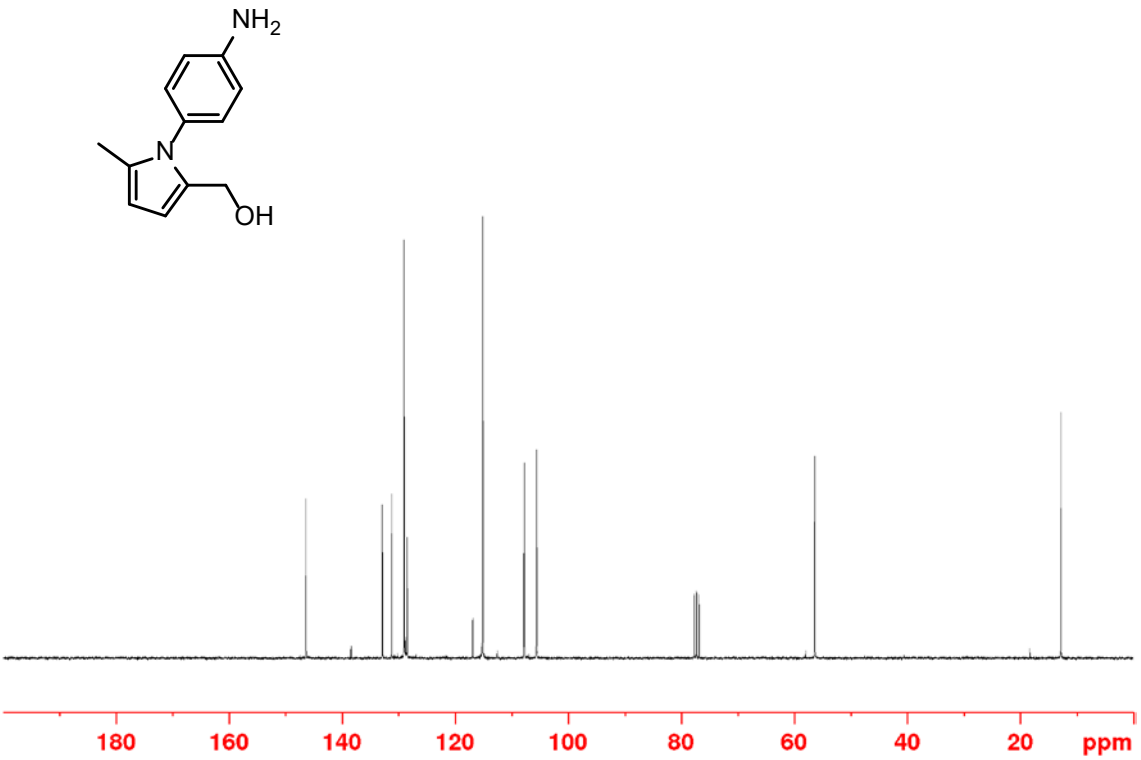
***N*-(4-Methylthiophenyl)-2-hydroxymethyl-5-methylpyrrole** (**5c**) 124 µL (1 mmol) of 4-(methylthio)aniline was converted in 97% to 182 mg (78% yield) of *N*-(4-Methylthiophenyl)-2-hydroxymethyl-5-methylpyrrole as a yellow solid. The product was isolated by column chromatography ($SiO_2$, cyclohexane: ethyl acetate 2:1). $^{1}H$ NMR (300 MHz, $CDCl_3$) δ = 7.36-7.31 (m, 2H), 7.25-7.20 (m, 2H), 6.18 (d, *J*= 3.4 Hz, 1H), 5.96 (d, *J*= 3.4 Hz, 1H), 4.32 (s, 2H), 2.54 (s, 3H), 2.07 (s, 3H), 1.65 (brs, 1H) ppm. $^{13}C$ NMR (75 MHz, $CDCl_3$) δ = 138.7, 135.0, 132.8, 131.1, 128.6, 126.6, 108.5, 106.3, 56.5, 15.6, 12.9 ppm. ATR-IR: ν(O-H) 3421; ν(C-H aromatics) 3098, 3040, 2976; ν(C-H) 2918, 2854 $cm^{-1}$. HR-MS (EI) calculated for $C_{13}H_{15}ONS$ 233.0869, found 233.0867.



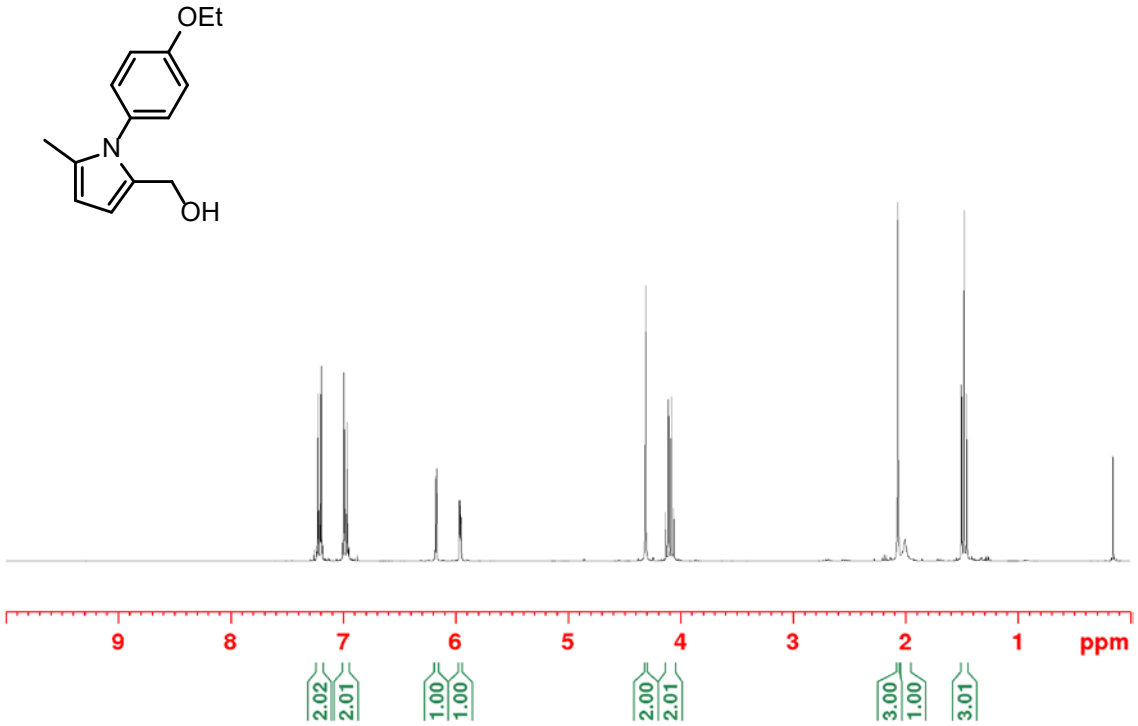



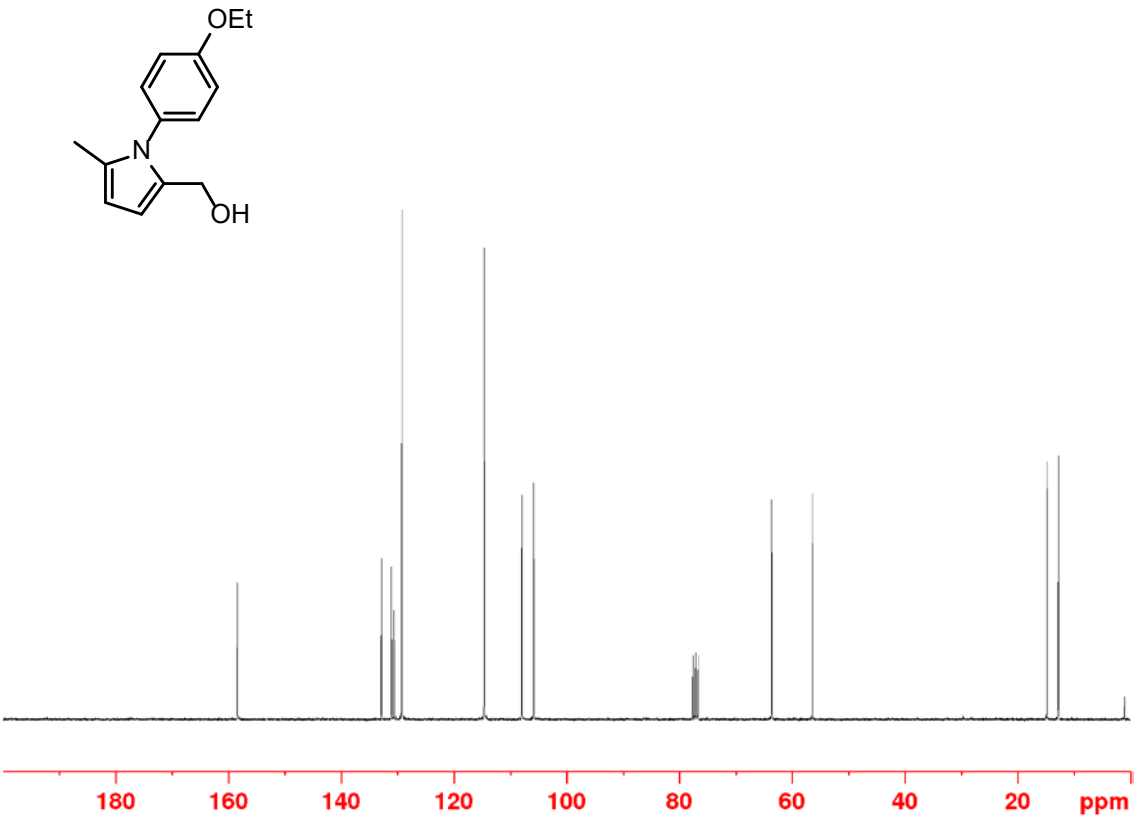
***N*-(4-Aminophenyl)-2-hydroxymethyl-5-methylpyrrole** (**5d**) 108 mg (1 mmol) of 1,4-Phenylenediamine was converted to 166 mg (82% yield) of *N*-(4-Aminophenyl)-2-hydroxymethyl-5-methylpyrrole as a brown solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.06-7.00 (m, 2H), 6.69-6.63 (m, 2H), 6.16 (d, *J*= 3.4 Hz, 1H), 5.95 (d, *J*= 3.4 Hz, 1H), 4.32 (s, 2H), 3.36 (brs, 3H), 2.06 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 146.3, 132.8, 131.2, 129.0, 128.5, 115.1, 107.7, 105.5, 56.3, 12.7 ppm. ATR-IR: ν(O-H) 3358; ν(N-H) 3218; ν(C-H aromatics) 3097, 3043, 2975; ν(C-H) 2920, 2902, 2856 cm$^{-1}$. HR-MS (EI) calculated for $C_{12}H_{14}ON_2$ 202.1101, found 202.1098.



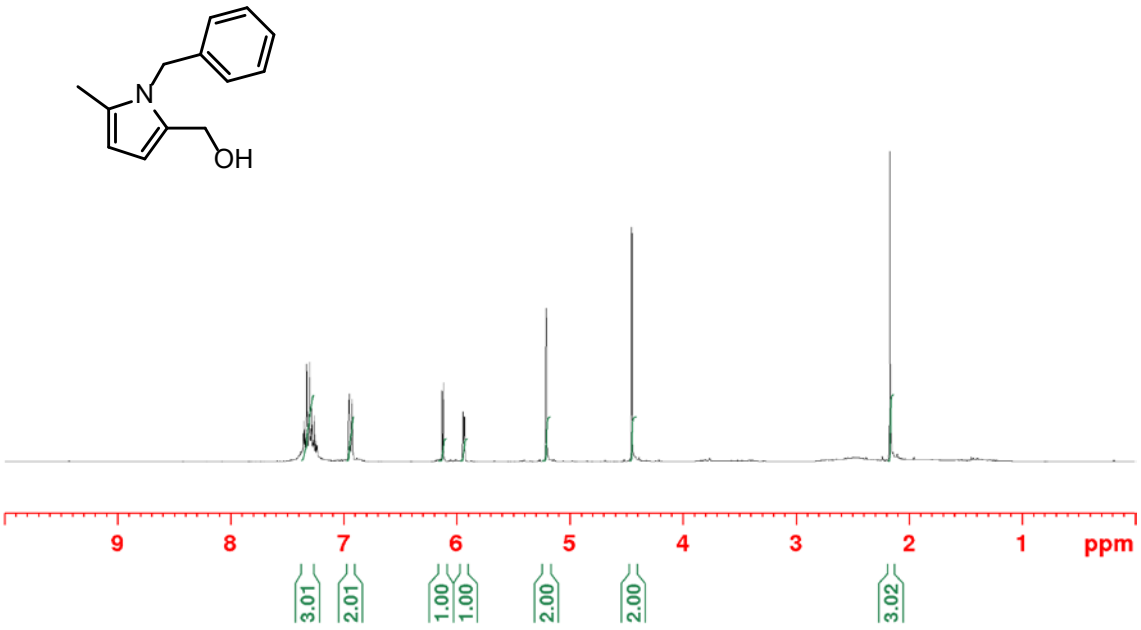



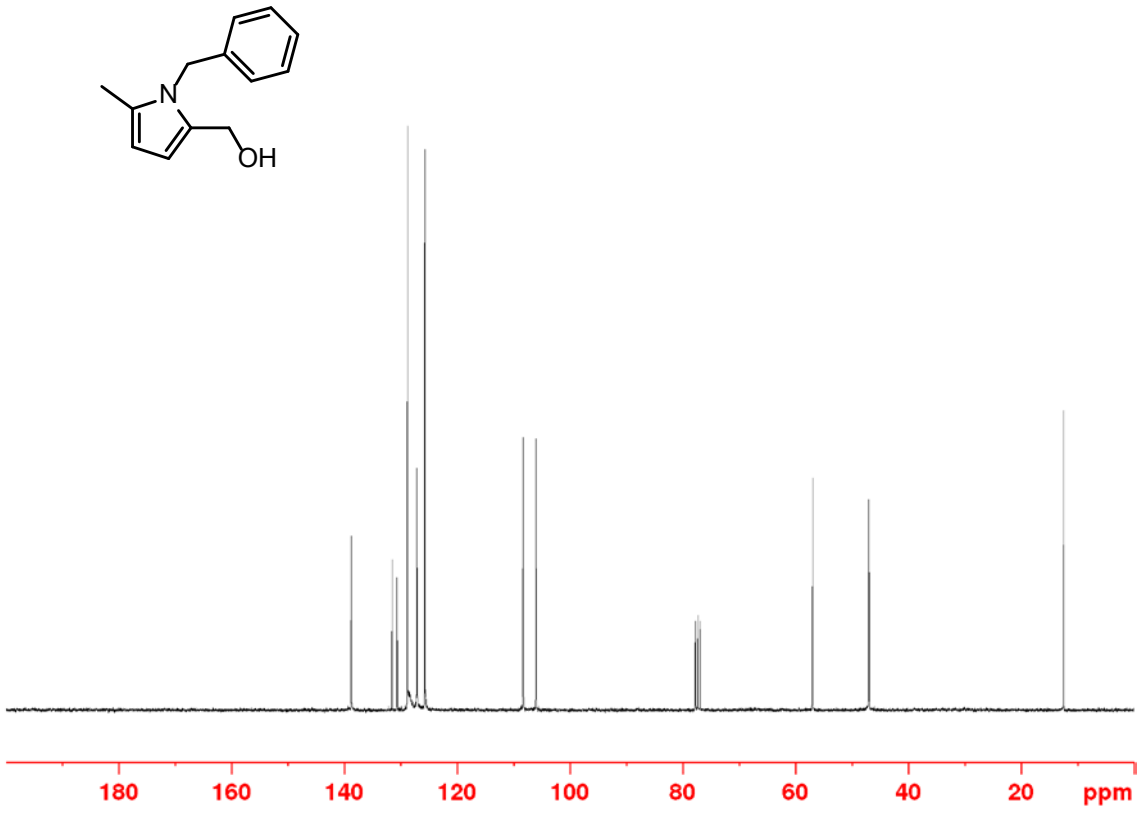
***N*-(4-Ethoxyphenyl)-2-hydroxymethyl-5-methylpyrrole** (**5e**) 129 µL (1 mmol) of p-Phenetidine was converted to 203 mg (88% yield) of *N*-(4-Ethoxyphenyl)-2-hydroxymethyl-5-methylpyrrole as a yellow oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.22-7.17 (m, 2H), 6.99-6.94 (m, 2H), 6.16 (d, *J*= 3.4 Hz, 1H), 5.96 (d, *J*= 3.4 Hz, 1H), 4.30 (s, 2H), 4.08 (q, *J*= 7.0 Hz, 2H), 2.07 (s, 3H), 1.46 (t, *J*= 7.0 Hz, 2H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 158.4, 132.8, 131.0, 129.2, 114.6, 107.9, 105.8, 63.6, 56.3, 14.7, 12.7 ppm. ATR-IR: ν(O-H) 3388; ν(C-H aromatics) 3101, 3047; 2978; ν(C-H) 2926, 2898, 2872 $cm^{-1}$. HR-MS (EI) calculated for $C_{14}H_{17}O_2N$ 231.1254, found 231.1253.



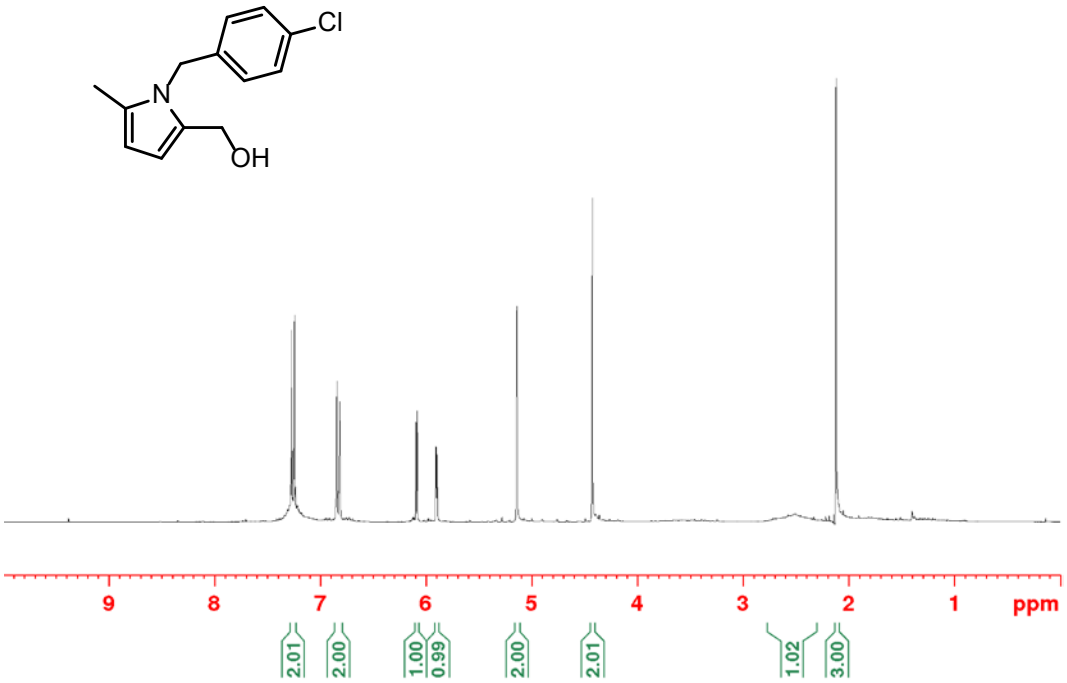



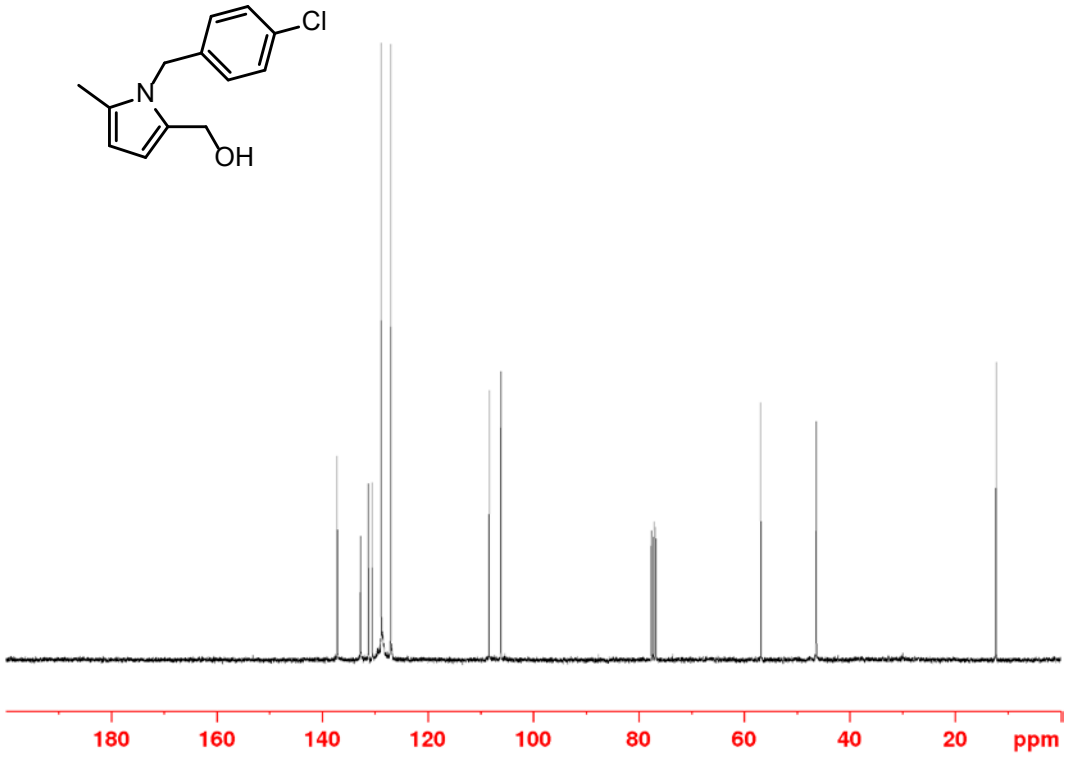
***N*-(Benzyl)-2-hydroxymethyl-5-methylpyrrole** (**6a**) 109 µL (1 mmol) benzylamine was converted to 195 mg (97% yield) of *N*-(Benzyl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.36-7.24 (m, 3H), 6.96-6.92 (m, 2H), 6.12 (d, *J*= 3.4 Hz, 1H), 5.94 (d, *J*= 3.4 Hz, 1H), 5.21 (s, 2H), 4.45 (s, 2H), 2.17 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 138.6, 131.4, 130.5, 128.6, 127.0, 125.6, 108.1, 105.9, 56.8, 46.8, 12.2 ppm. ATR-IR: ν(O-H) 3352; ν(C-H aromatics) 3087, 3062, 3029; ν(C-H) 2931, 2871 $cm^{-1}$. HR-MS (EI) calculated for $C_{13}H_{15}ON$ 201.1148, found 201.1145.



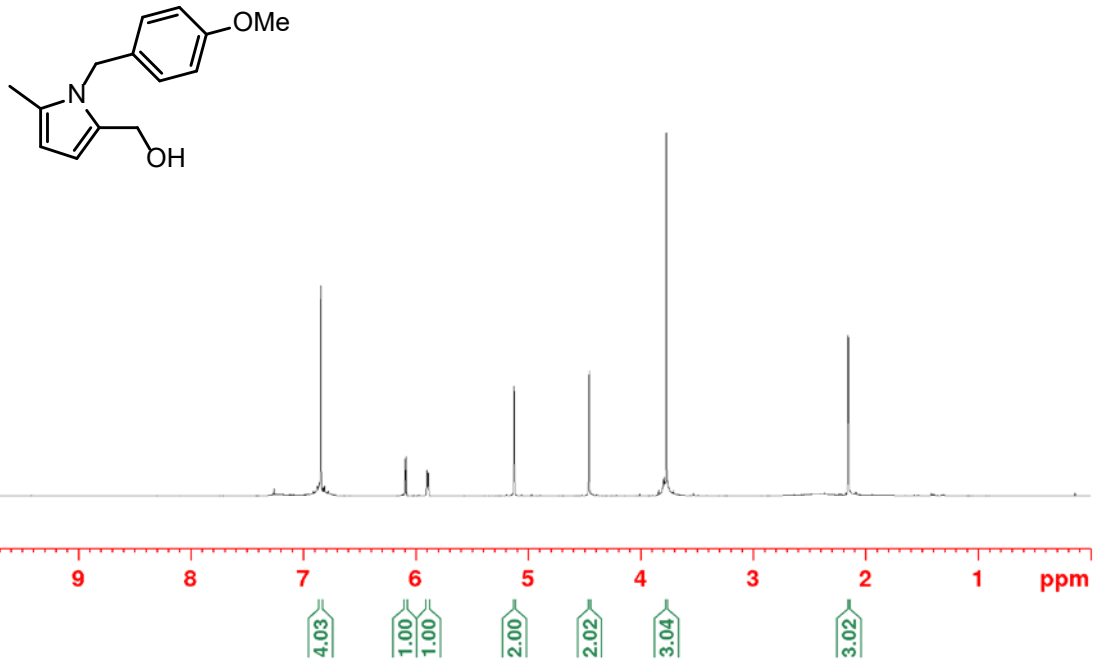



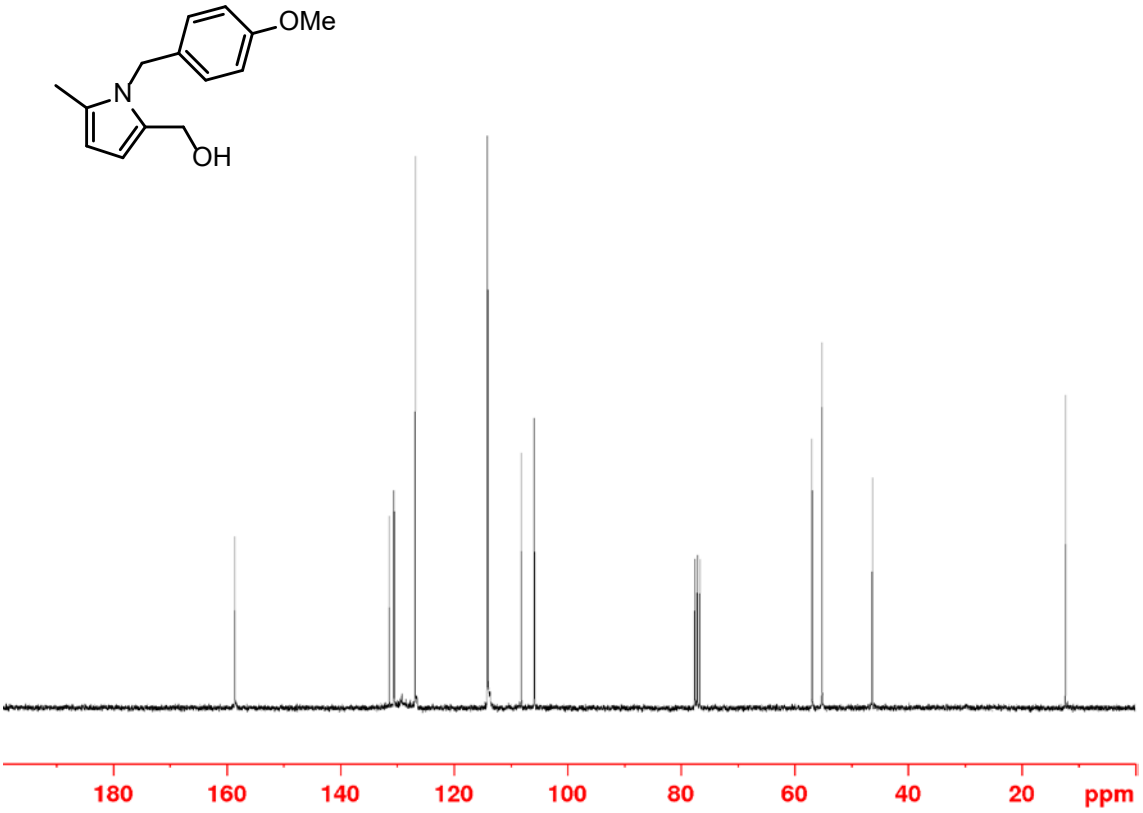
***N*-(4-Chlorobenzyl)-2-hydroxymethyl-5-methylpyrrole** (**6b**) 122 µL (1 mmol) 4-Chlorobenzylamine was converted to 233 mg (99% yield) of *N*-(4-Chlorobenzyl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.28-7.24 (m, 2H), 6.85-6.81 (m, 2H), 6.09 (d, *J*= 3.4 Hz, 1H), 5.90 (d, *J*= 3.4 Hz, 1H), 5.14 (s, 2H), 4.43 (s, 2H), 2.12 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 137.2, 132.8, 131.3, 130.5, 128.8, 127.1, 108.4, 106.2, 56.9, 46.3, 12.2 ppm. ATR-IR: ν(O-H) 3363; ν(C-H aromatics) 3099, 3047; ν(C-H) 2934, 2872 $cm^{-1}$. HR-MS (EI) calculated for $C_{13}H_{14}ONCl$ 235.0758, found 235.0758.



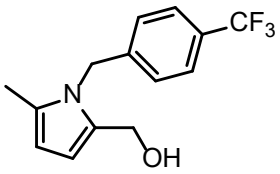



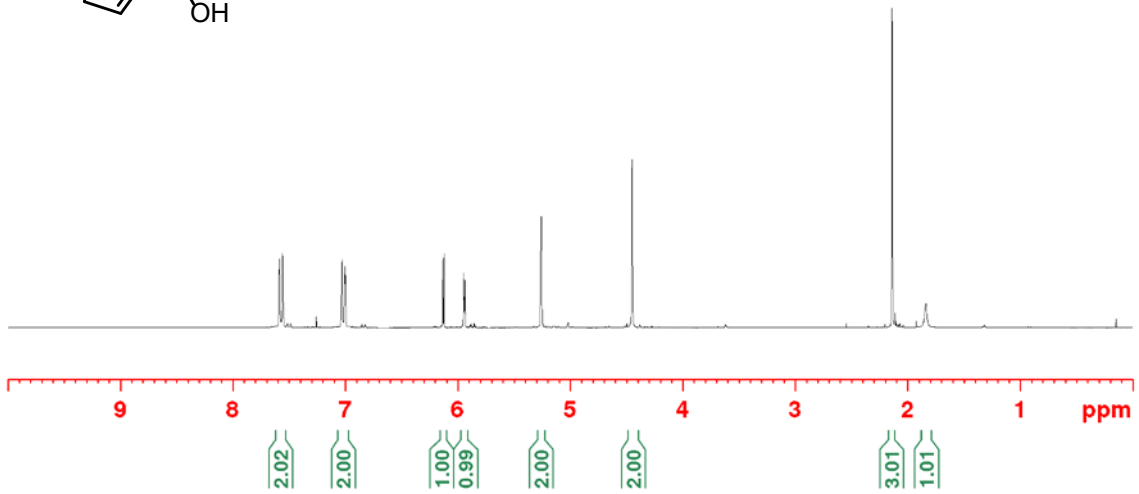
***N*-(4-Methoxybenzyl)-2-hydroxymethyl-5-methylpyrrole** (**6c**) 131 µL (1 mmol) 4-Methoxybenzylamine was converted to 229 mg (98% yield) of *N*-(4-methoxybenzyl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 6.88-6.82 (m, 4H), 6.09 (d, *J*= 3.4 Hz, 1H), 5.90 (d, *J*= 3.4 Hz, 1H), 5.13 (s, 2H), 4.46 (s, 2H), 3.77 (s, 3H), 2.15 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 158.6, 131.4, 130.6, 130.5, 126.8, 114.1, 108.1, 105.9, 56.9, 55.2, 46.3, 12.3 ppm. ATR-IR: ν(O-H) 3374; ν(C-H aromatics) 3099, 3034, 2998; ν(C-H) 2935, 2913, 2836 $cm^{-1}$. HR-MS (EI) calculated for $C_{14}H_{17}O_2N$ 231.1254, found 231.1254.

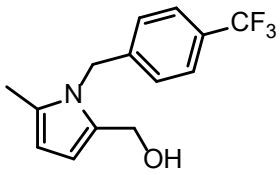


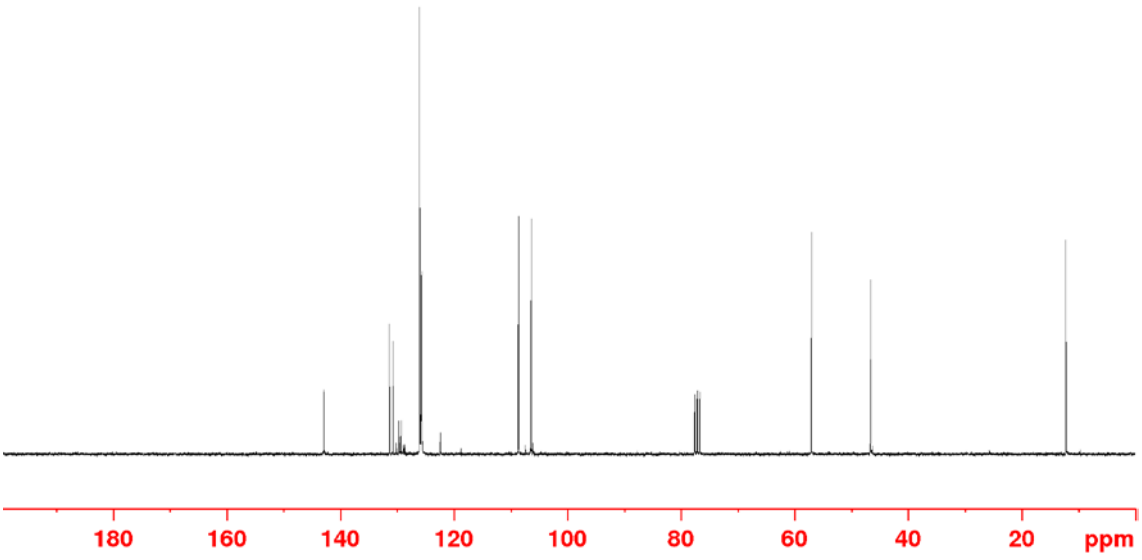



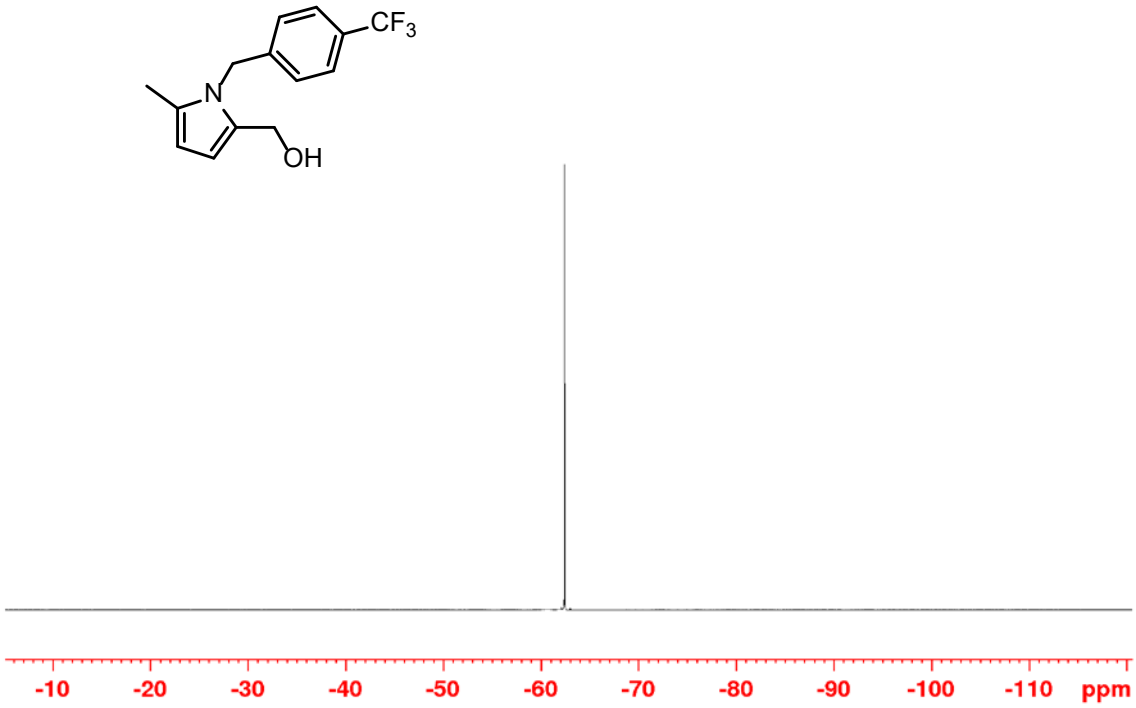
***N*-(4-Trifluoromethylbenzyl)-2-hydroxymethyl-5-methylpyrrole** (**6d**) 143 µL (1 mmol) 4-(Trifuloromethyl)benzylamine was converted to 258 mg (96% yield) of *N*-(4-trifluoromethylbenzyl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.60-7.54 (m, 2H), 7.05-6.99 (m, 2H), 6.13 (d, *J*= 3.4 Hz, 1H), 5.94 (d, *J*= 3.4 Hz, 1H), 5.26 (s, 2H), 4.45 (s, 2H), 2.14 (s, 3H), 1.84 (brs, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 142.9, 131.4, 130.7, 129.5 (q, $^{2}J$(C,F) = 32.5 Hz), 126.0, 125.8 (q, $^{2}J$(C,F) = 3.9 Hz), 124.0 (q, $^{1}J$(C,F) = 272.6 Hz), 108.6, 106.4, 57.0, 46.6, 12.2 ppm. $^{19}$F (282 MHz, CDCl3) δ = -62.4 ppm. ATR-IR: ν(O-H) 3430; ν(C-H aromatics) 3101, 3069, 3048; ν(C-H) 2934, 2913, 2861 $cm^{-1}$. HR-MS (EI) calculated for $C_{14}H_{14}ONF_3$ 269.1022, found 269.1023.



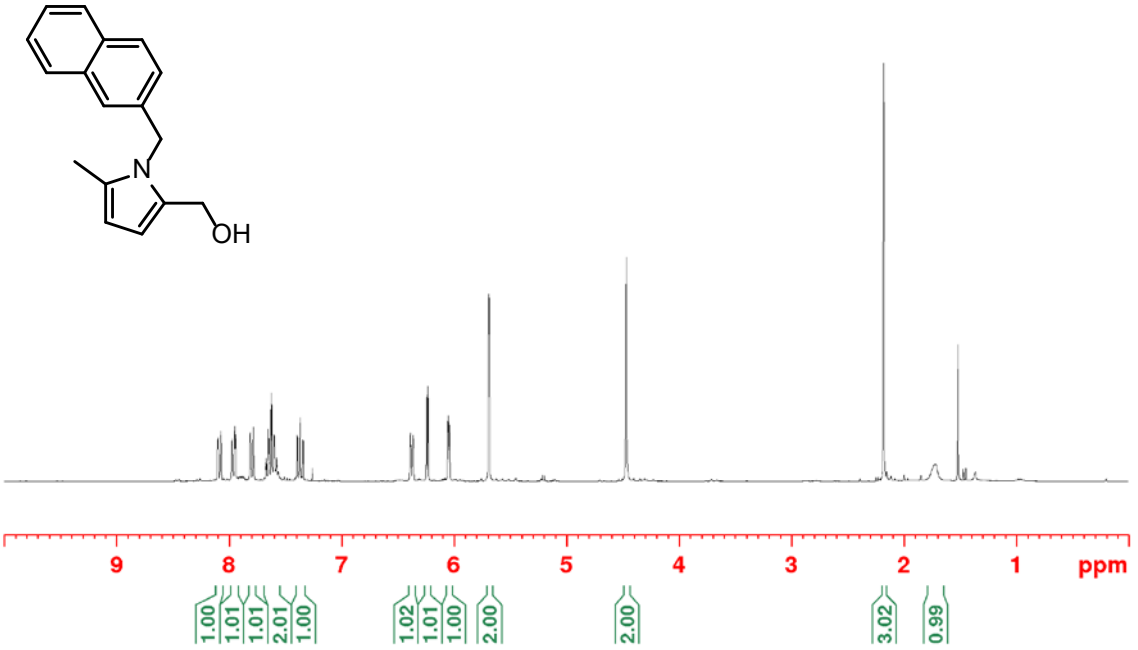



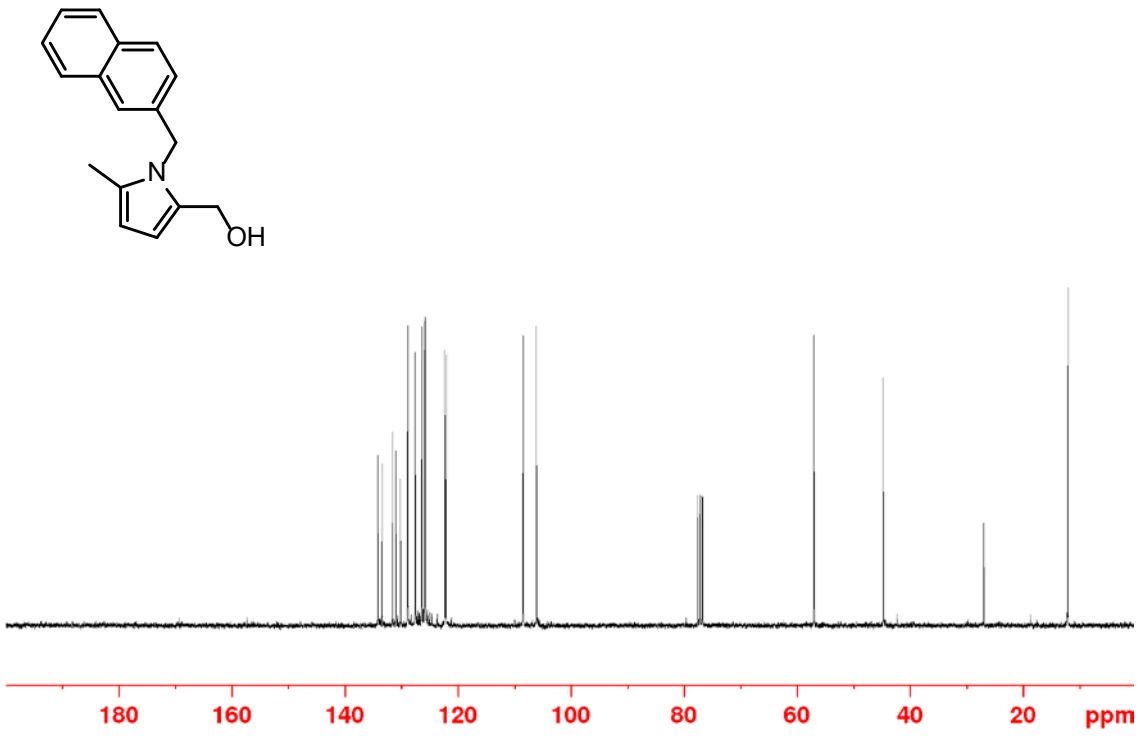



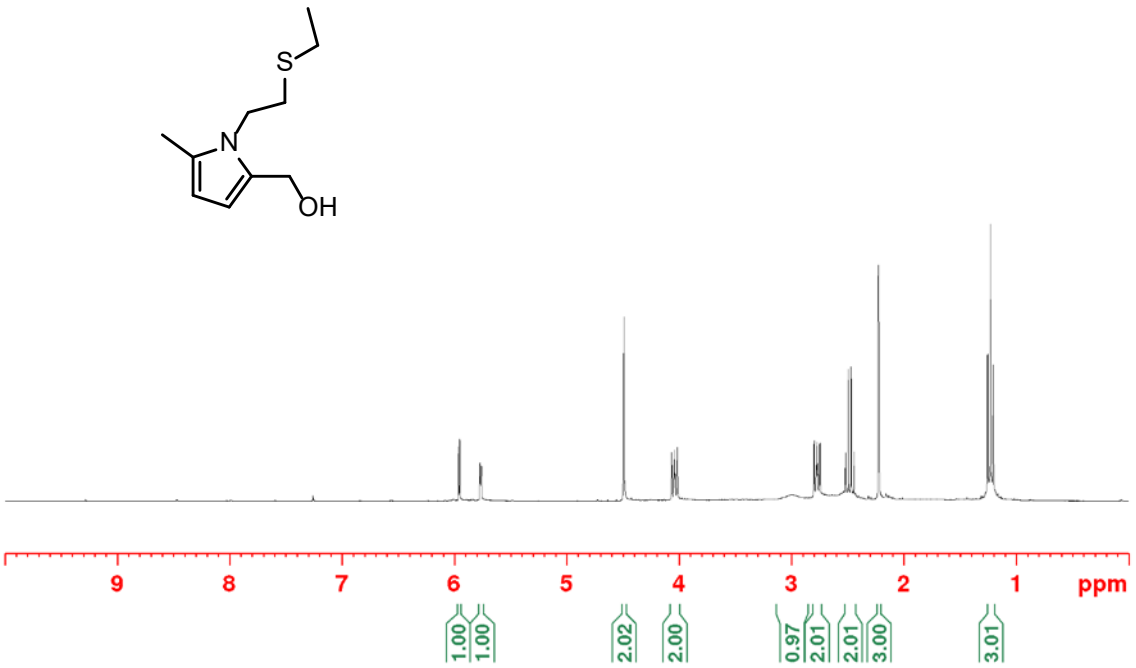

CF3
N
OH
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
ppm

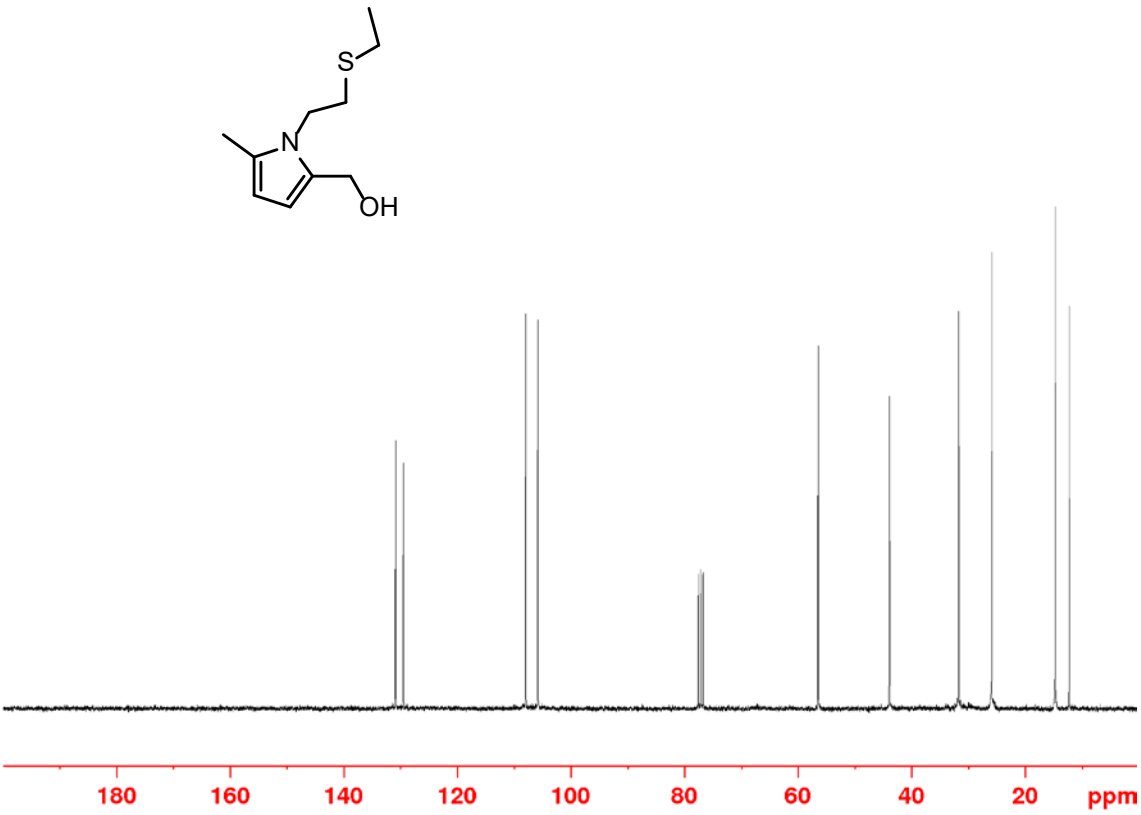
***N*-(Naphtalenemethyl)-2-hydroxymethyl-5-methylpyrrole** (**6e**) 147 µL (1 mmol) 1-Naphtalenemethylamine was converted to 221 mg (88% yield) of *N*-(Naphtalenemethyl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.11-8.06 (m, 1H), 7.98-7.93 (m, 1H), 7.80 (d, *J*= 4.1 Hz, 1H), 7.68-7.55 (m, 2H), 7.37 (t, *J*= 7.7 Hz, 1H), 6.40-6.35 (m, 1H) 6.24 (d, *J*= 3.4 Hz, 1H), 6.05 (d, *J*= 3.4 Hz, 1H), 5.69 (s, 2H), 4.47 (s, 2H), 2.18 (s, 3H) 1.72 (brs, 1H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 134.4, 133.6, 131.8, 131.0, 130.3, 129.0, 127.7, 126.5, 126.1, 126.0, 122.5, 122.3, 108.5, 106.3, 56.9, 44.9, 12.2 ppm. ATR-IR: ν(O-H) 3389; ν(C-H aromatics) 3098, 3059, 3044, 3013 ν(C-H) 2930, 2912, 2868 $cm^{-1}$. HR-MS (EI) calculated for $C_{17}H_{17}ON$ 251.1305, found 251.1305.



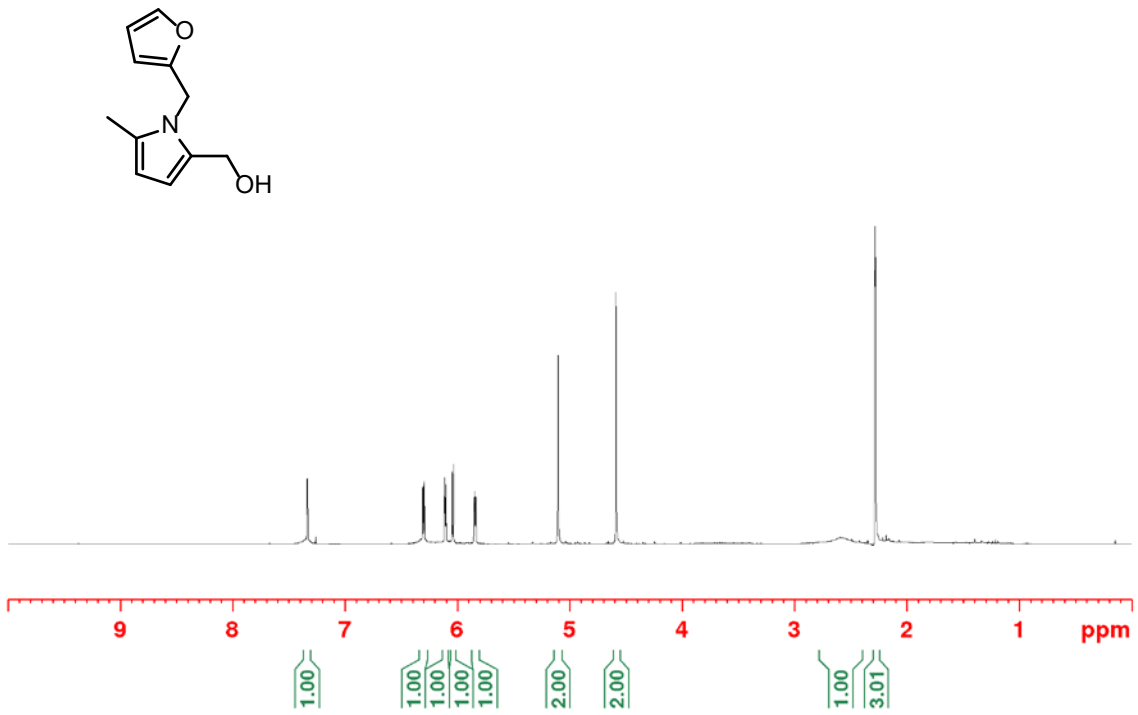



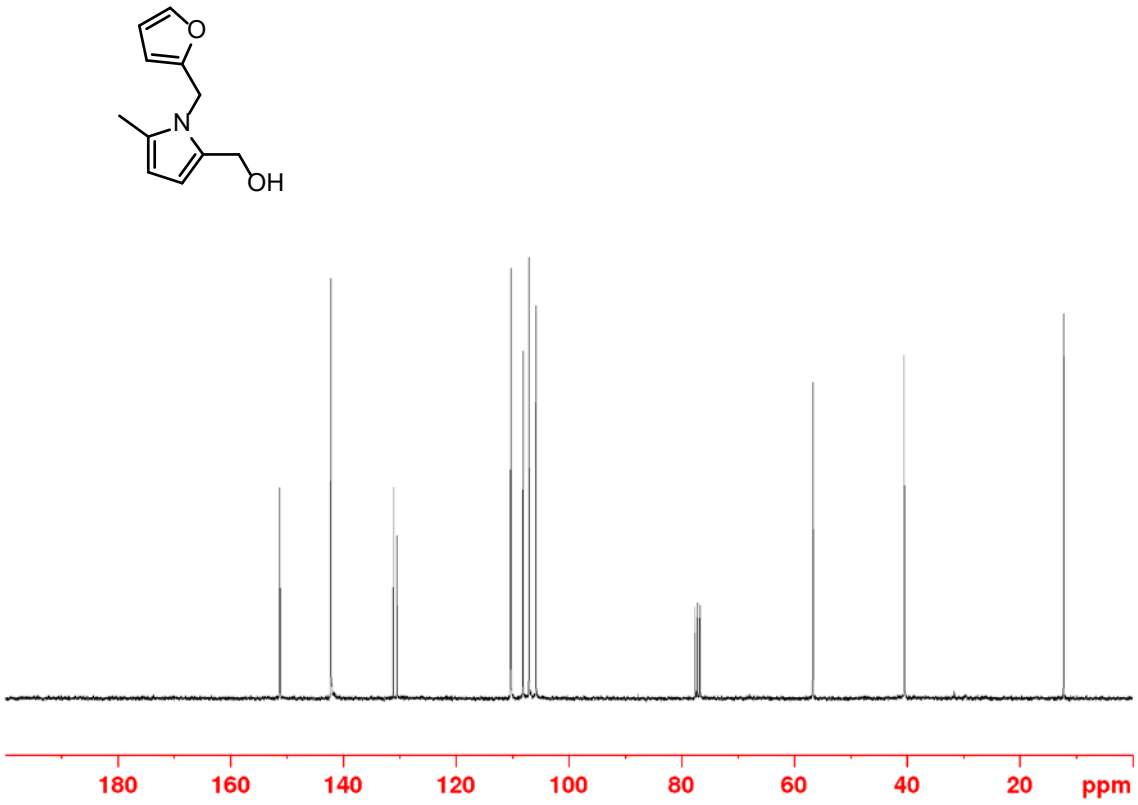
***N*-[2-Ethylthio(ethyl)]-2-hydroxymethyl-5-methylpyrrole** (**7a**) 111 µL (1 mmol) 2-(Ethylthio)ethylamine was converted to 197 mg (99% yield) of *N*-[2-Ethylthio(ethyl)]-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 5.96 (d, *J*= 3.4 Hz, 1H), 5.77 (d, *J*= 3.4 Hz, 1H), 4.49 (s, 2H), 4.08-4.00 (m, 2H), 3.00 (brs, 1H), 2.91-2.73 (m, 2H), 2.48 (q, *J*= 7.4 Hz, 2H), 2.23 (s, 3H), 1.23 (t, *J*= 7.4 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 130.9, 129.5, 108.0, 105.8, 56.5, 43.9, 31.7, 25.9, 14.7, 12.2 ppm. ATR-IR: ν(O-H) 3388; ν(C-H aromatics) 3099; ν(C-H) 2965, 2925, 2870 cm$^{-1}$. HR-MS (EI) calculated for $C_{10}H_{17}ONS$ 199.1025, found 199.1023.



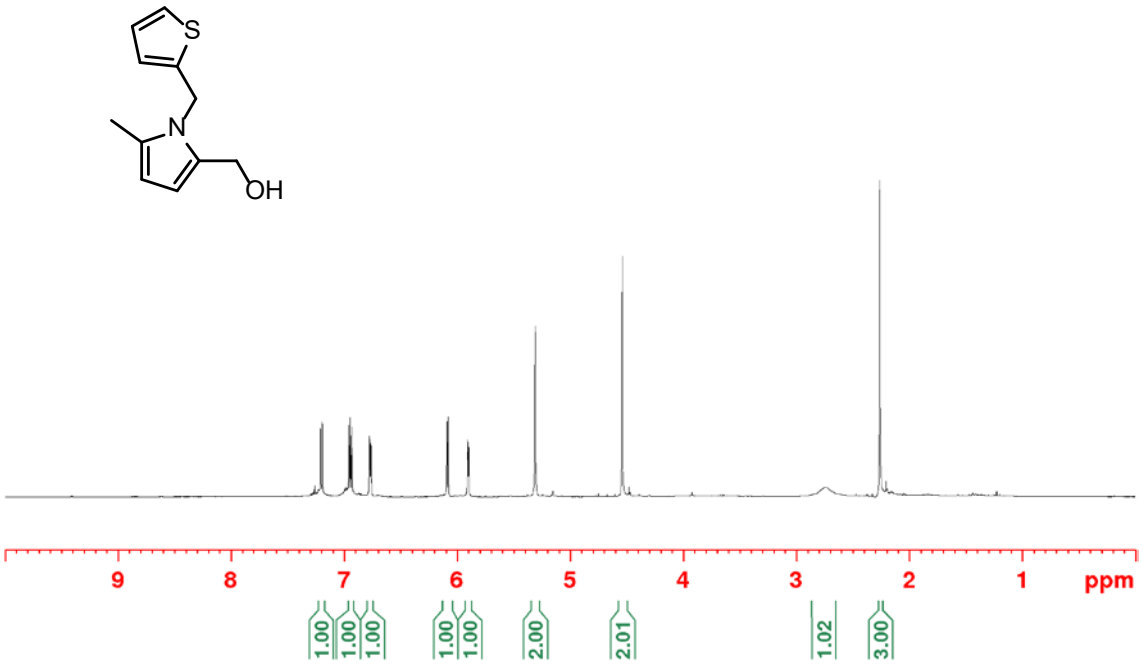



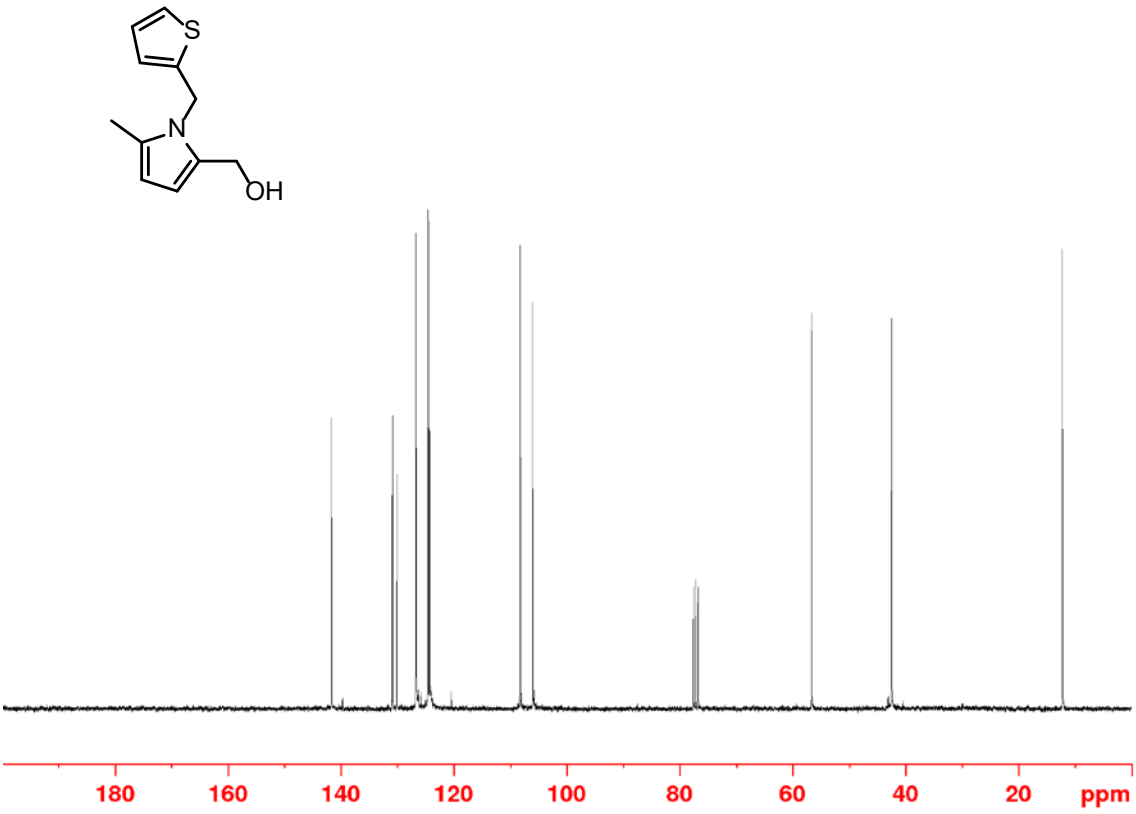
***N*-(Furfuryl)-2-hydroxymethyl-5-methylpyrrole** (**7b**) 88 µL (1 mmol) furfurylamine was converted to 183 mg (96% yield) of *N*-(Furfuryl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.34 (dd, *J*= 1.9, 0.9 Hz, 1H), 6.30 (dd, *J*= 3.3, 1.9 Hz, 1H), 6.11 (dq, *J*= 3.3, 0.8 Hz, 1H) 6.04 (d, *J*= 3.4 Hz, 1H), 5.84 (d, *J*= 3.4 Hz, 1H), 5.10 (s, 2H), 4.59 (s, 2H), 2.28 (s, 3H) ppm.$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 151.3, 142.2, 131.1, 130.5, 110.3, 108.1, 107.1, 105.8, 56.7, 40.4, 12.2 ppm. ATR-IR: ν(O-H) 3375; ν(C-H aromatics) 3115; ν(C-H) 2911 $cm^{-1}$. HR-MS (EI) calculated for $C_{11}H_{13}O_2N$ 191.0941, found 191.0939.



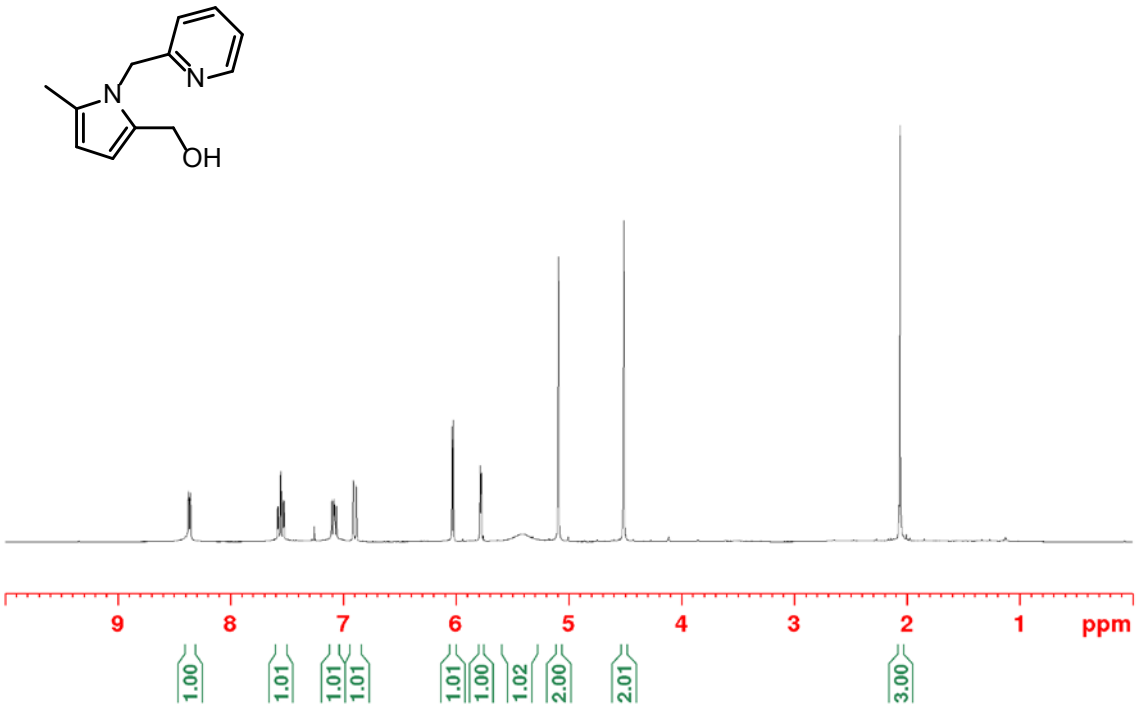



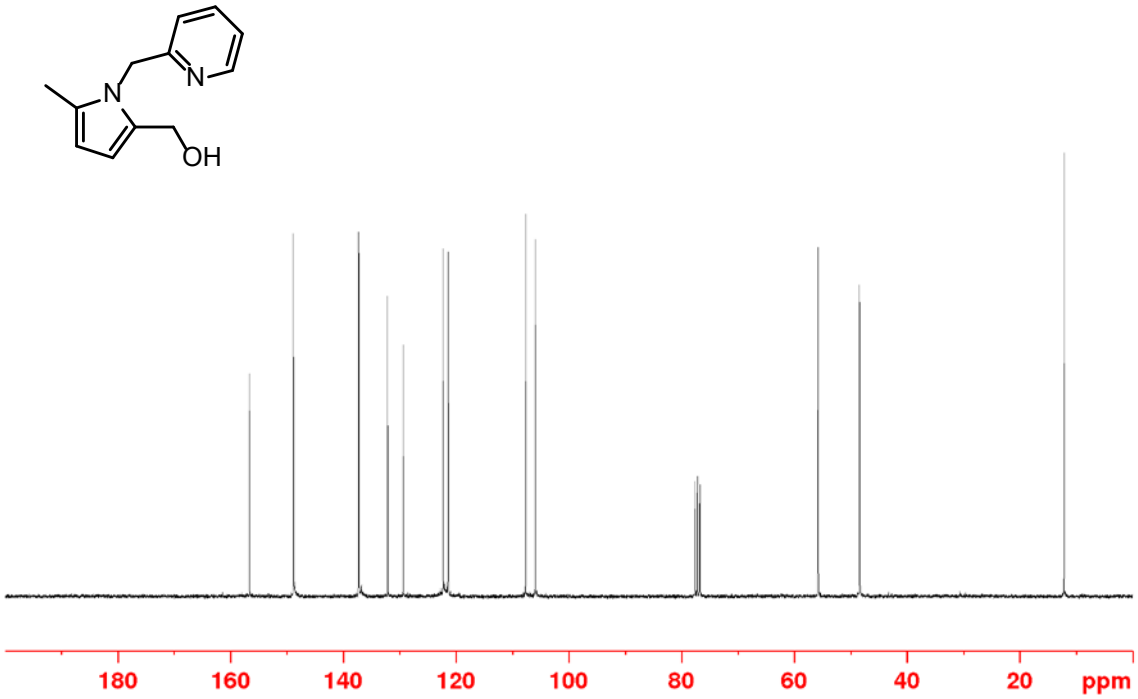
***N*-(2-Thiophenemethyl)-2-hydroxymethyl-5-methylpyrrole** (**7c**) 103 µL (1 mmol) 2-Thiophenemethylamine was converted to 205 mg (99% yield) of *N*-(2-Thiophenemethyl)-2-hydroxymethyl-5-methylpyrrole as a brown oil. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 7.20 (dd, *J*= 5.1, 1.3 Hz, 1H), 6.94 (dd, *J*= 5.4, 3.5 Hz, 1H), 6.79-6.75 (m, 1H) 6.09 (d, *J*= 3.4 Hz, 1H), 5.90 (d, *J*= 3.4 Hz, 1H), 5.31 (s, 2H), 4.54 (s, 2H), 2.26 (s, 3H) ppm.$^{13}$C NMR (75 MHz, $CDCl_3$) δ = 141.6, 130.9, 130.1, 126.7, 124.6, 124.3, 108.3, 106.0, 56.6, 42.5, 12.2 ppm. ATR-IR: ν(O-H) 3375; ν(C-H aromatics) 3101; ν(C-H) 2934, 2913, 2872 $cm^{-1}$. HR-MS (EI) calculated for $C_{11}H_{13}ONS$ 207.0712, found 207.0707.



***N*-(2-Pyridinemethyl)-2-hydroxymethyl-5-methylpyrrole** (**7d**) 130 µL (1 mmol) 2-Picolylamine was converted to 139 mg (98% yield) of *N*-(2-Pyridinemethyl)-2-hydroxymethyl-5-methylpyrrole as a brown solid. $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 8.39-8.34 (m, 1H), 7.55 (td, *J*= 7.8, 1.8 Hz, 1H), 7.12-7.04 (m, 1H), 6.90 (d, *J*= 7.8 Hz, 1H), 6.03 (d, *J*= 3.4 Hz, 1H), 5.78 (d, *J*= 3.4 Hz, 1H), 5.41 (bs, 1H), 5.09 (s, 2H), 4.51 (s, 2H), 2.06 (s, 3H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 156.7, 148.9, 137.3, 132.1, 129.4, 122.3, 121.4, 107.7, 105.9, 55.8, 48.4, 12.1 ppm. ATR-IR: ν(O-H) 3266; ν(C-H aromatics) 3100, 3052, 3014, 2969; ν(C-H) 2931, 2909, 2875 $cm^{-1}$



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[1] Z. Yang, Z. Zhu, R. Luo, X. Qiu, J.-T. Liu, J.-K. Yang, W.Tang, *Green Chem*. **2017**, 19, 3296.
[2] B. Wozniak, A. Spannenberg, Y. Li, S. Hinze, J. G. de Vries, *ChemSusChem* **2018**, *11*, 356.

## *9.3 Supporting Information for section 7.3*

# Electronic Supporting Information

## Rhenium-catalyzed deoxydehydration of renewable triols derived from sugars

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## Contents

## 1.0 General remarks

All reactions were carried out in dried glassware or hastelloy autoclave vessel with magnetic stirring under aerobic conditions or hydrogen atmosphere. Commercially available chemicals and solvents were purchased from Sigma Aldrich, ABCR and TCI as reagent grade chemicals and were used as received. Rhenium(VII) oxide was stored in the glovebox in order to avoid the formation of perrhenic acid. The deoxydehydration reactions were performed in pressure vials. The yields and conversions were calculated by NMR using dimethyl phthalate as an internal standard in $CD_3OD$. $^1H$ and $^{13}C$ NMR spectra were recorded on Bruker AV 300 or 400 NMR spectrometer. All chemicals shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. All chemical shifts are related to residual solvent peaks. All spectra were recorded at room temperature unless otherwise specified.

## 2.0 General procedures

### 2.1 Hydrogenation of HHD

A 300 mL hastelloy autoclave vessel equipped with a magnetic stirrer was charged with HHD (**2**) (1.00 g, 7.69 mmol) and Ru-MACHO-BH (cat **I**) (23 mg, 0.5 mol%). The contents were dissolved in *i*PrOH (20 mL), the vessel was flushed three times with $N_2$ and subsequently with $H_2$, the reactor was pressurized to with $H_2$ (30 bar) and the reaction mixture was stirred and heated to 100 $^oC$ for 18 h. After cooling to room temperature and depressurizing the vessel, the resulting yellow solution was filtered through silica and evaporated to dryness to afford the desired product as yellowish oil (1.01 g, 98%)

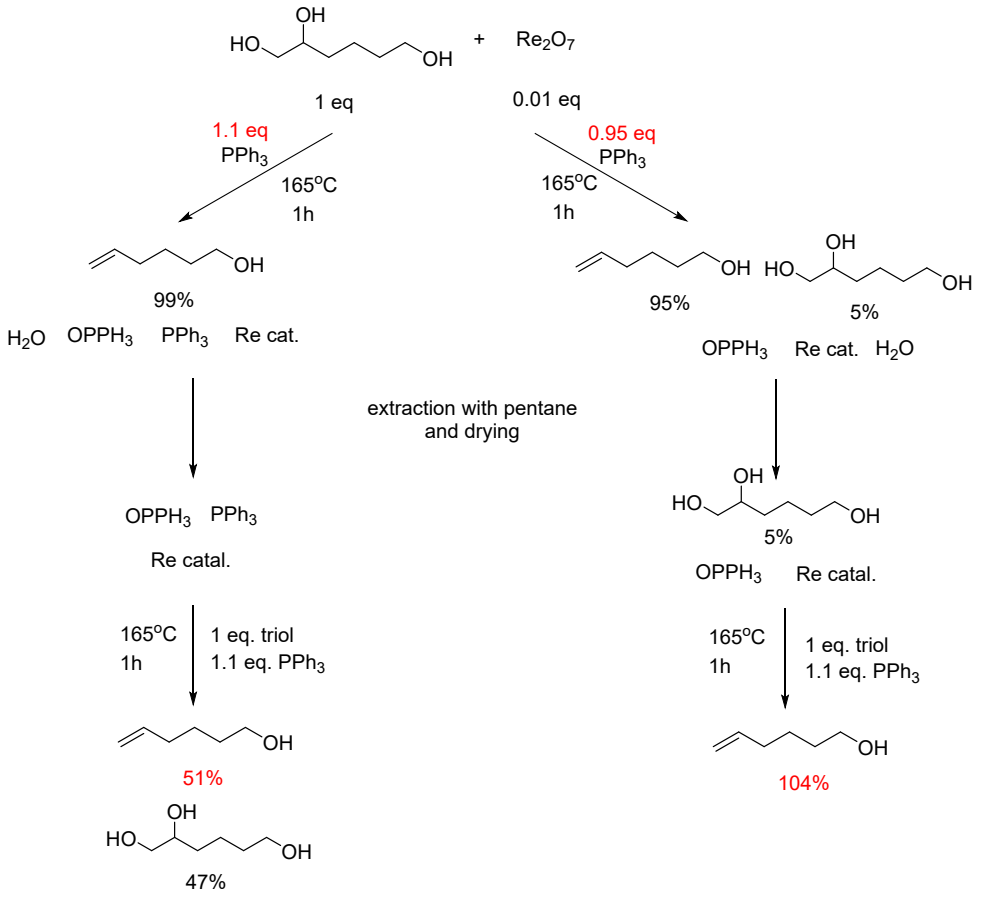
### 2.2 Screening of Re sources in DODH

Under ambient conditions 1,2,6 hexanetriol ( 134 mg, 1.00 mmol) and triphenylphosphine (288 mg, 1.10 mmol) were added to a pressure vial which was already charged with the corresponding rhenium catalyst. The reactions were stirred and heated to 165$^oC$ for one hour. After cooling to room temperature, $CD_3OD$ (0.6 mL) and dimethyl phthalate (33 μL, 0.20 mmol) were added. The content was filtered through a short plug of silica and yield was calculated by NMR.

### 2.3 Screening of reducing agents in DODH

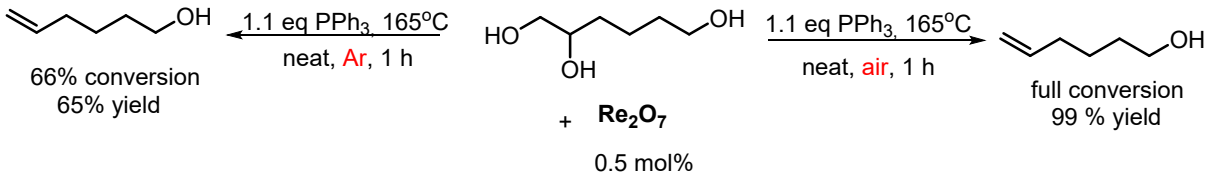
Under ambient conditions 1,2,6 hexanetriol ( 134 mg, 1.00 mmol) and corresponding reducing agent (2.00 mmol) were added to a pressure vial which was already charged with $Re_2O_7$ (2.4 mg, 0.005 mmol). The reactions were stirred and heated to 165$^oC$ for one hour. All the yields were calculated using procedure described in the section 2.2. The same reactions were performed in hastelloy autoclave when $H_2$ (7 bar) or CO (7 bar) was used as a reductant.

**2.4 Recycle experiments**




Under ambient conditions 1,2,6 hexanetriol ( 134 mg, 1.00 mmol) and triphenylphosphine (288 or 249 mg, respectively 1.10 and 0.95 mmol) (2.00 mmol) were added to a pressure vial which was already charged with $Re_2O_7$ (4.8 mg, 0.01 mmol). The reactions were stirred and heated to 165°C for one hour. After cooling to room temperature, the vial was washed 5 times with pentane (1 mL) in order to extract 5-hexen-1-ol. The remaining solid- mixture of $PPh_3O$, $PPH_3$ and catalyst ($PPh_3O$, catalyst and 5% 1,2,6-hexanetriol when 0.95 mmol of $PPH_3$ was used) was dried under vacuum and directly used in the next cycle. After addition of a new portion of 1,2,6-hexanetriol ( 134 mg, 1.00 mmol) and triphenylphosphine (288 mg, 1.10 mmol) the vial was heated again to 165°C for one hour. All the yields were calculated using procedure described in the section 2.2

**2.5 Reaction under inert conditions**




Under inert atmosphere and optimized reaction conditions: 1,2,6-hexanetriol ( 134 mg, 1.00 mmol), triphenylphosphine (288 mg, 1.10 mmol) and $Re_2O_7$ (2.4 mg, 0.005 mmol) reaction was stirred and heated to 165°C for one hour. NMR studies revealed 65% yield to the corresponding unsaturated alcohol compare to 99% when the pressure vial was charged under aerobic conditions.

**2.6 Catalytic DODH of 1,2,5-hexanetriol**

Under ambient conditions 1,2,5 hexanetriol ( 134 mg, 1.00 mmol) and triphenylphosphine (288 mg, 1.10 mmol) were added to a pressure vial charged with $Re_2O_7$. The reactions were stirred and heated to 165$^oC$ for one hour. All the yields were calculated using procedure described in the section 2.2.

**2.7 Cyclization of 1,2,5-hexanetriol**

Under ambient conditions 1,2,5 hexanetriol ( 134 mg, 1.00 mmol) was added to a pressure vial charged with catalyst (0.005 mmol) . The contents were stirred and heated to 165$^oC$ for ten minutes. All the yields were calculated using procedure described in the section 2.2.

**2.8 Deoxydehydration-hydrogenation reaction of 1,2,6-hexanetriol**

A 300 mL hastelloy autoclave vessel equipped with a magnetic stirrer was charged with 1,2,6-hexanetriol (134 mg, 1.00 mmol), $Re_2O_7$ (24 mg, 0.05 mmol) and a co-catalyst (if any was used). The content was dissolved in the corresponding amount of THF, the vessel was flushed three times with $N_2$ and subsequently with $H_2$. After flushing, the reactor was pressurized to with $H_2$ (30 bar) and the reaction mixture was stirred and heated to 165 $^oC$ for 5 h. After cooling to room temperature and depressurizing, the reaction mixture was filtered through short plug of silica and the volatiles were removed under reduced pressure. All the yields were calculated using procedure described in the section 2.2.

## 3.0 Isolation procedures

**3.1 $Re_2O_7$-catalyzed synthesis of unsaturated alcohols from triols**

Under ambient conditions the corresponding triol (5.00 mmol) and $PPh_3$ (1443 mg, 5.50 mmol) were added to the pre-weighted amount of $Re_2O_7$. The reactions contents were stirred and heated to 165$^oC$ until complete conversion of the substrate was achieved. After cooling to room temperature the reaction flask was directly connected to Kugelrohr and the desired unsaturated alcohol was purified by distillation. All products were obtained as colorless liquids.

### 3.2 Synthesis of 5-methyltetrahydrofurfuryl alcohol

Under ambient conditions 1,2,5 hexanetriol (134 mg, 1.00 mmol) was added to a pressure vial vial which was already charged with $Re_2O_7$ (2,4 mg, 0.005 mmol) . The reaction was stirred and heated to 165$^oC$ for ten minutes. After cooling to room temperature, the content was dissolved in EtOH (1 mL), filtrated through short plug of silica and volatiles removed under reduced pressure to afford desired product as yellow liquid (104 mg, 90%).

### 3.3 Synthesis of 1-hexanol from 1,2,6-hexanetriol

A 300 mL hastelloy autoclave vessel equipped with a magnetic stirrer was charged with 1,2,6-hexanetriol (670 mg, 5.00 mmol), $Re_2O_7$ (120 mg, 0.25 mmol) and 5% Pd/C (100 mg). The content was dissolved in THF (50 mL), the vessel was flushed three times with $N_2$ and subsequently with $H_2$, the reactor was pressurized to with $H_2$ (30 bar) and the reaction mixture was stirred and heated to 165 $^oC$ for 5 h. After cooling to room temperature and depressurizing the vessel, the reaction mixture was filtered through short plug of silica and volatiles were removed under reduced pressure. The resulting colorless oil was then purified by column chromatography ($SiO_2$; ethyl acetate:cyclohexane 1:2), yielding 1-hexanol (303 mg, 55%).

## 4.0 Analytical data of isolated products

**1,2,5-hexanetriol (3, mixture of isomers)** $^{1}$H NMR (300 MHz, MeOD) δ = 5.37-4.56 (brs, 3H), 3.78-3.69 (m, 1H), 3.62-3.54 (m, 1H), 3.51-3.40 (m, 2H), 1.69-1.53 (m, 2H), 1.53-1.31 (m, 2H), 1.18 (d, *J*= 6.3 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, MeOD) δ = 73.3, 73.1, 68.7, 68.4, 67.3, 67.2, 36.1, 36.0, 30.7, 30.6, 23.6, 23.5 ppm.

**5-hexene-1-ol (5)** $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 5.70 (ddt, $J_1$= 16.9 Hz, $J_2$= 10.3 Hz, $J_3$= 6.6 Hz, 1H), 4.94-4.81 (m, 2H), 3.76 (brs, 1H), 3.47 (t, *J*= 6.6 Hz, 2H), 2.01-1.92 (m, 2H), 1.51-1.28 (m, 4H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 138.5, 114.3, 62.0, 33.4, 31.9, 25.0 ppm.

**3-butene-1-ol (11a)** $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 5.70 (ddt, $J_1$= 17.1 Hz, $J_2$= 10.3 Hz, $J_3$= 6.9 Hz, 1H), 5.14-5.05 (m, 2H), 3.63 (q, *J*= 6.1 Hz, 2H), 2.23 (q, *J*= 6.6 Hz, 2H), 2.12 (brs, 1H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 135.0, 117.5, 61.6, 37.1 ppm.

**3-butene-2-ol (11b)** $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 5.86 (ddd, $J_1$= 16.1 Hz, $J_2$= 10.4 Hz, $J_3$= 5.7 Hz, 1H), 5.16 (dt, $J_1$= 17.3 Hz, $J_2$= 1.5 Hz, 1H), 5.01 (dt, $J_1$= 10.5 Hz, $J_2$= 1.4 Hz, 1H), 4.29-4.20 (m, 1H), 2.39 (brs, 1H) 1.22 (d, *J*= 6.5 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 142.4, 113.6, 68.9, 23.0 ppm.

**2-butene-1-ol (11c, *Z* isomer)** $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 5.60-5.51 (m, 2H), 4.15 (d, *J*= 4.3 Hz, 2H), 2.30 (brs, 1H) 1.62 (d, *J*= 4.8 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 129.4, 126.9, 58.1, 13.0 ppm.

**2-butene-1-ol (11c, *E* isomer)** $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 5.71-5.60 (m, 2H), 4.01 (d, 5.0 Hz, 2H), 2.30 (brs, 1H), 1.66 (d, *J*= 5.5 Hz, 3H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 130.3, 127.9, 63.5, 17.7 ppm.

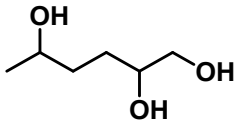
**4-pentene-1-ol (11d)** $^{1}$H NMR (400 MHz, $CDCl_3$) δ = 5.81 (ddt, $J_1$= 16.9 Hz, $J_2$= 10.2 Hz, $J_3$= 6.6 Hz, 1H), 5.03 (dq, $J_1$= 17.1 Hz, $J_2$= 1.6 Hz, 1H), 4.96 (dq, $J_1$= 10.2 Hz, $J_2$= 1.2 Hz, 1H), 3.63 (q, *J*= 6.6 Hz 2H), 2.16-2.08 (m, 2H), 1.91 (t, *J*= 5.4 Hz, 1H), 1.69-1.61 (m, 2H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$) δ = 138.4, 115.0, 62.4, 33.4, 31.8, 30.2 ppm.

**7-octene-1-ol (11e)** $^{1}$H NMR (400 MHz, MeOD) δ = 5.83 (ddt, $J_1$= 17.0 Hz, $J_2$= 10.2 Hz, $J_3$= 6.7 Hz, 1H), 5.04-4.92 (m, 2H), 4.91 (brs, 1H), 3.56 (t, *J*= 6.6 Hz 2H), 2.13-2.01 (m, 2H), 1.61-1.51 (m, 2H), 1.48-1.31 (m, 6H) ppm. $^{13}$C NMR (100 MHz, MeOD) δ = 139.9, 114.8, 62.8, 34.8, 33.5, 30.0, 30.0, 26.7 ppm.

**9-decene-1-ol (11f)** $^{1}$H NMR (400 MHz, MeOD) δ = 5.82 (ddt, $J_1$= 17.0 Hz, $J_2$= 10.3 Hz, $J_3$= 6.7 Hz, 1H), 5.04-4.91 (m, 2H), 4.91 (brs, 1H), 3.56 (t, *J*= 6.7 Hz 2H), 2.11-2.02 (m, 2H), 1.62-1.49 (m, 2H), 1.47-1.29 (m, 10H) ppm. $^{13}$C NMR (100 MHz, MeOD) δ = 139.9, 114.8, 62.9, 34.9, 33.6, 30.6, 30.6, 30.2, 30.1, 26.9 ppm.

**5-methyltetrahydrofurfuryl alcohol (9, mixture of isomers)** $^{1}$H NMR (300 MHz, MeOD) δ = 4.16-3.89 (m, 2H), 3.53-3.47 (m, 2H), 2.12-1.88 (m, 2H), 1.80-1.63 (m, 1H), 1.55-1.38 (m, 1H), 1.21 (t, *J*= 6.2 Hz, 3H) ppm. $^{13}$C NMR (75 MHz, MeOD) δ = 81.2, 80.6, 77.3, 76.6, 65.9, 65.6, 34.7, 33.8, 29.1, 28.7, 21.4, 21.2 ppm.

**hexane-1-ol (13)** $^{1}$H NMR (300 MHz, $CDCl_3$) δ = 4.94 (brs, 1H), 3.56 (t, *J*= 6.7 Hz, 2H), 1.62-1.51 (m, 2H), 1.44-1.28 (m, 6H), 0.94 (t, *J*= 7.0 Hz, 2H) ppm. $^{13}$C NMR (75 MHz, $CDCl_3$) δ = 61.6, 32.4, 31.6, 25.4, 22.5, 13.3 ppm.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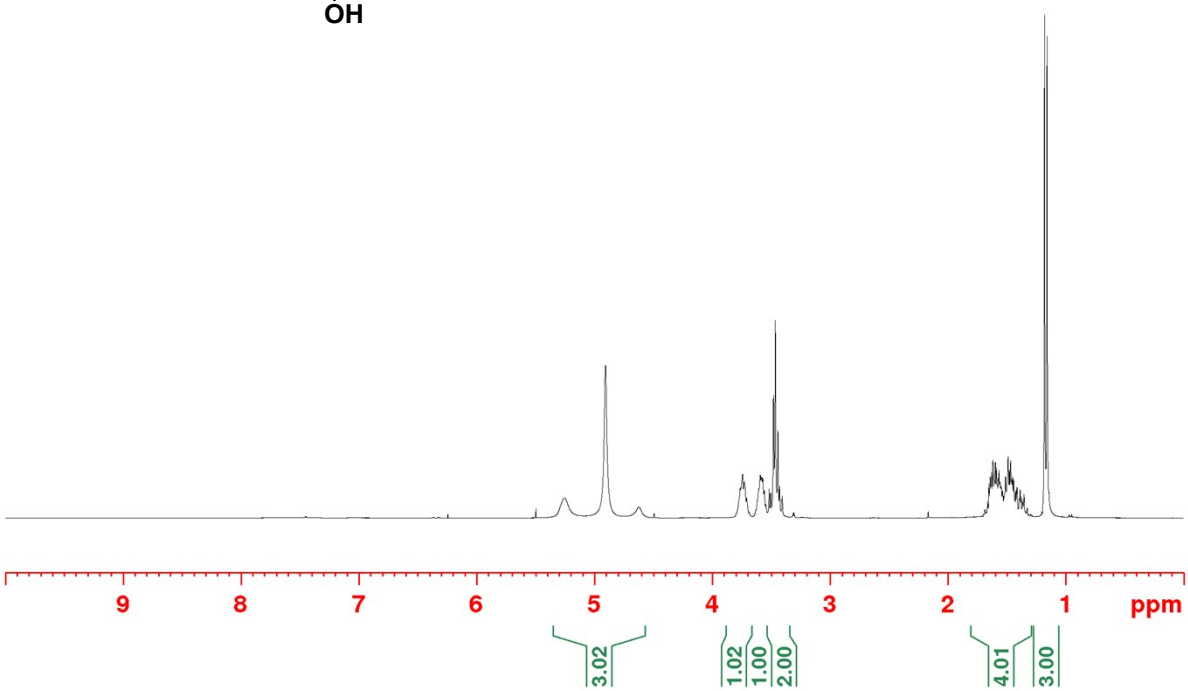
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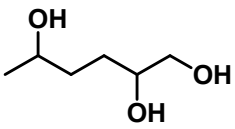
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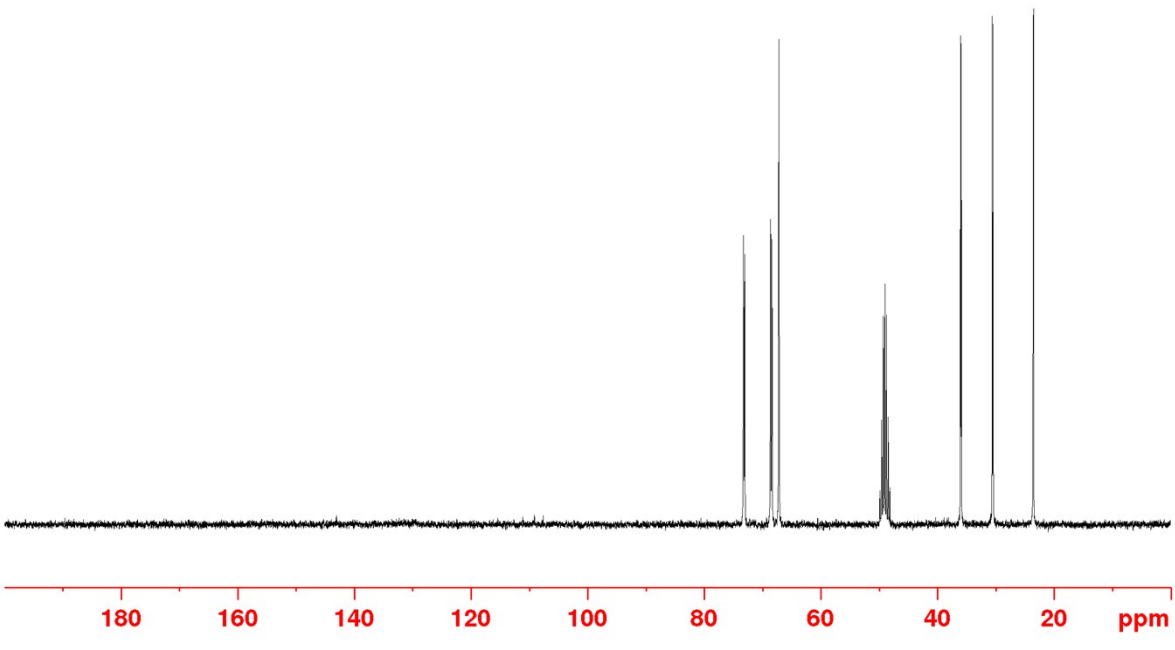
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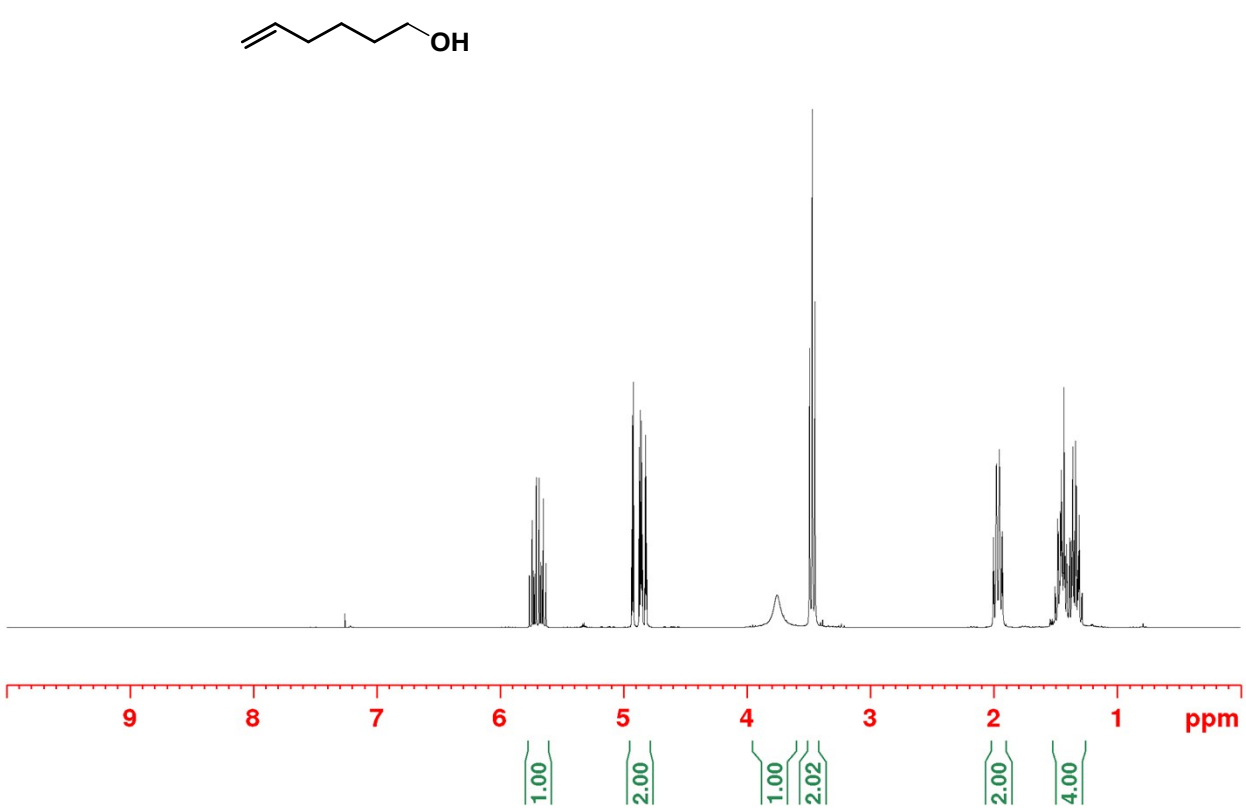
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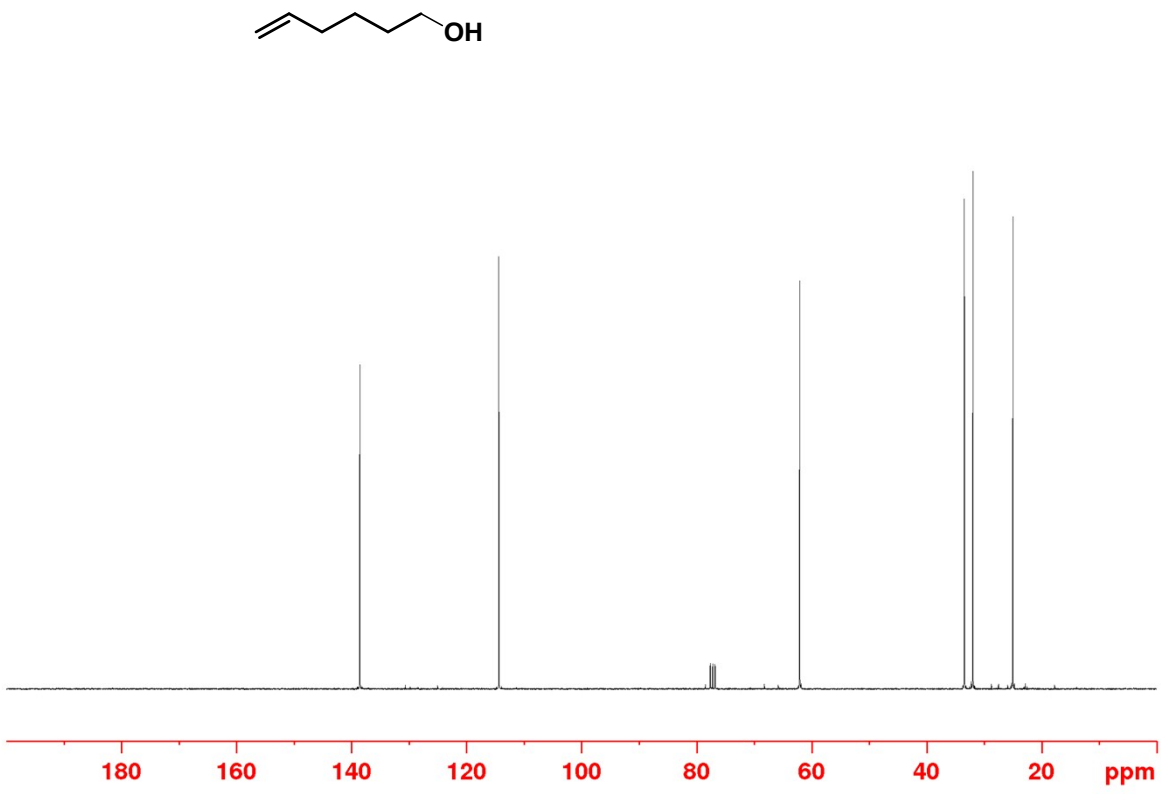
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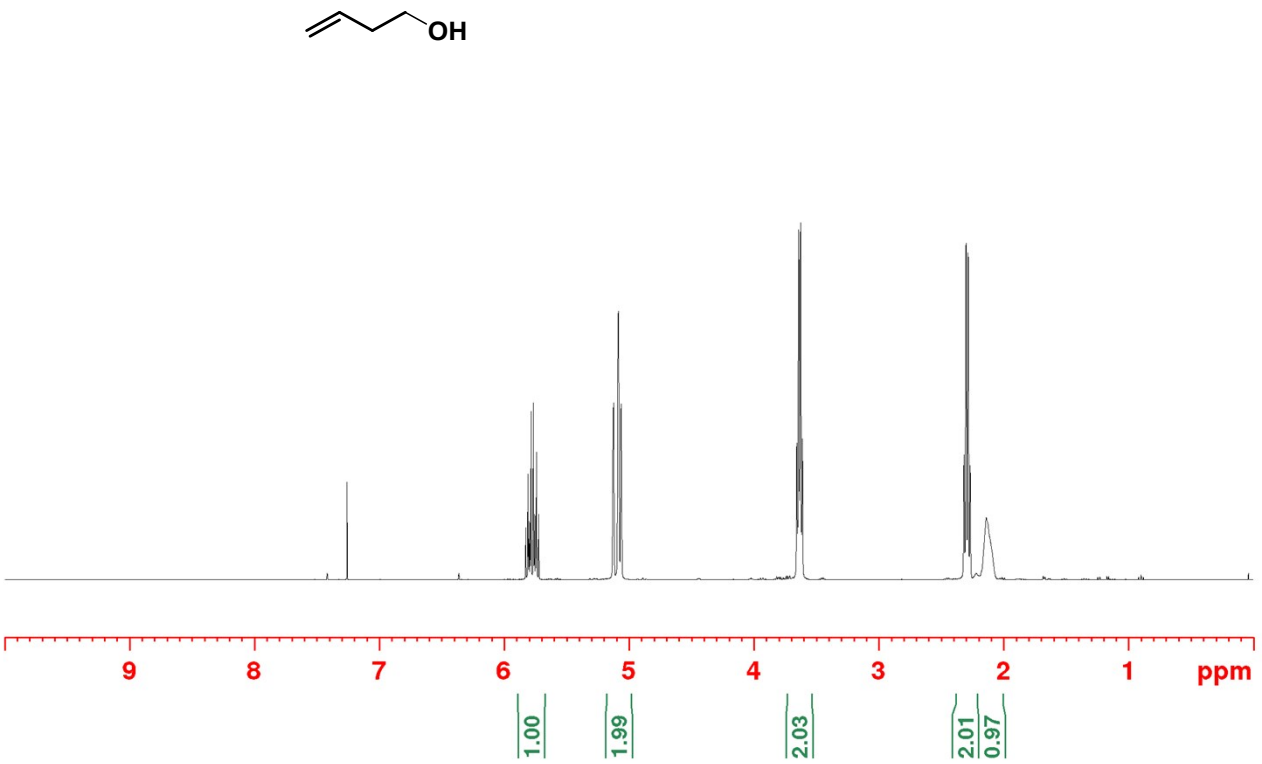
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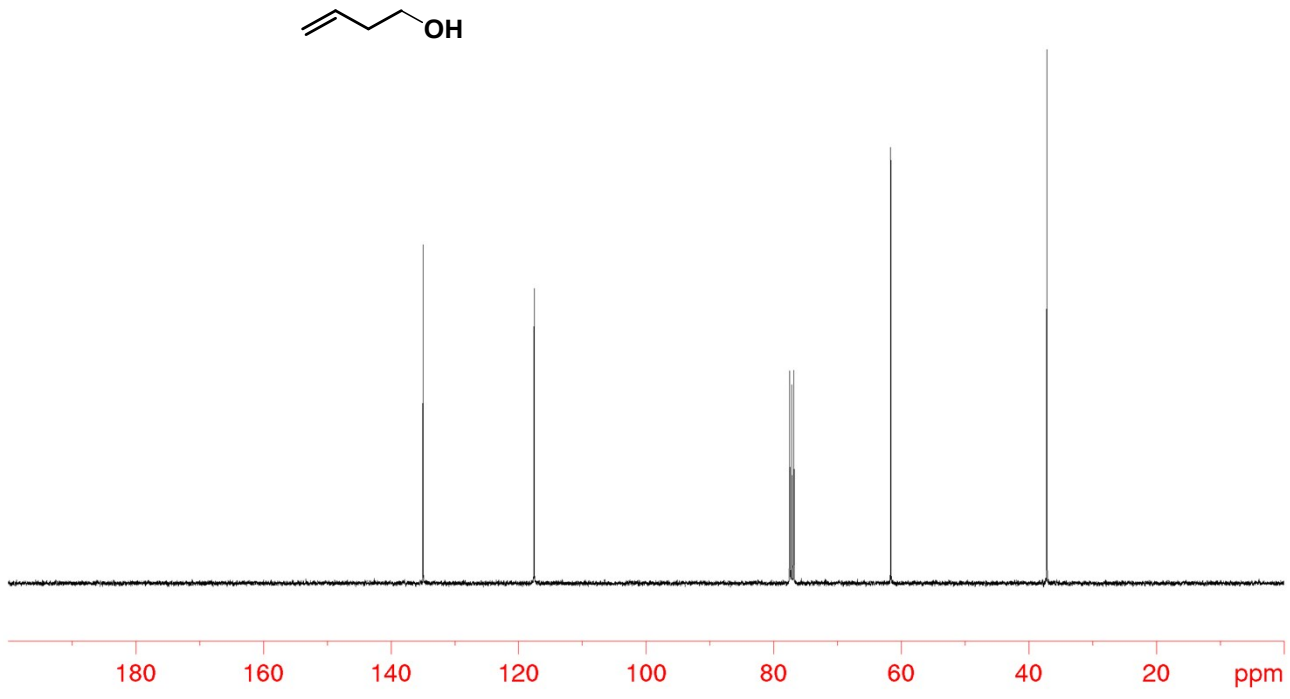
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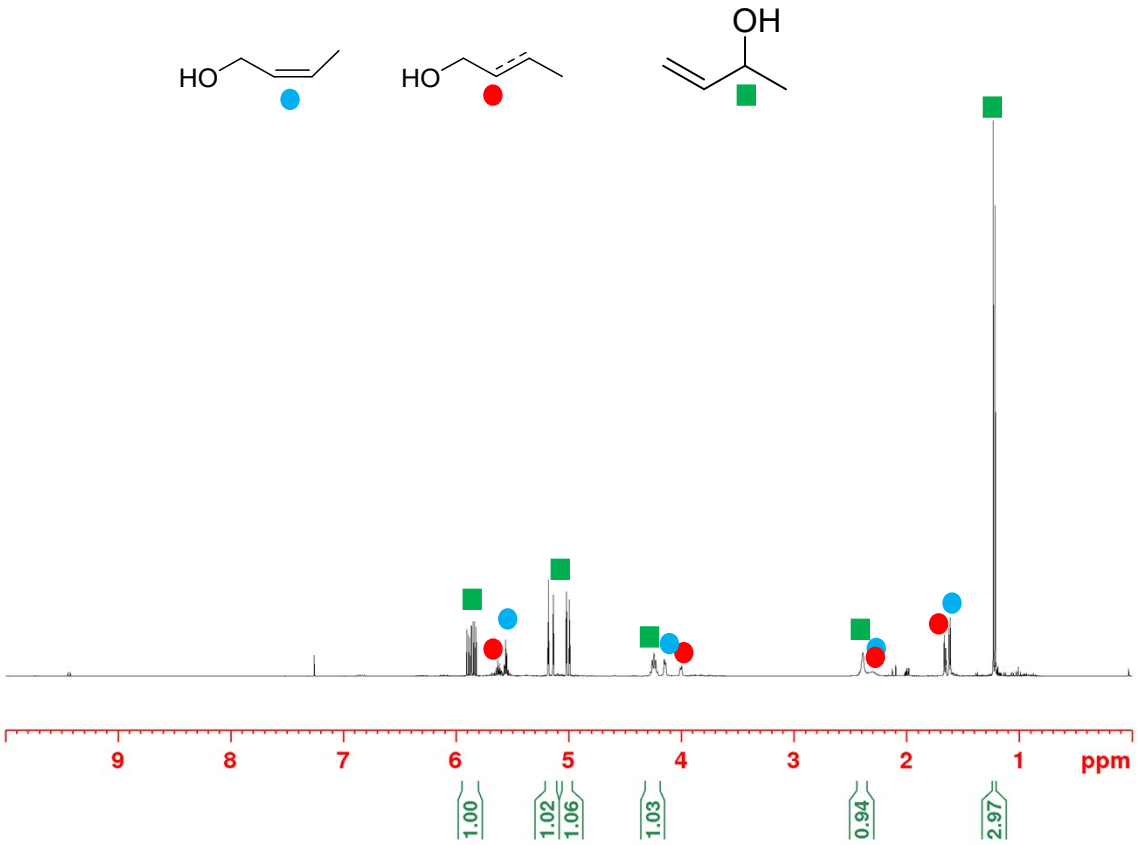
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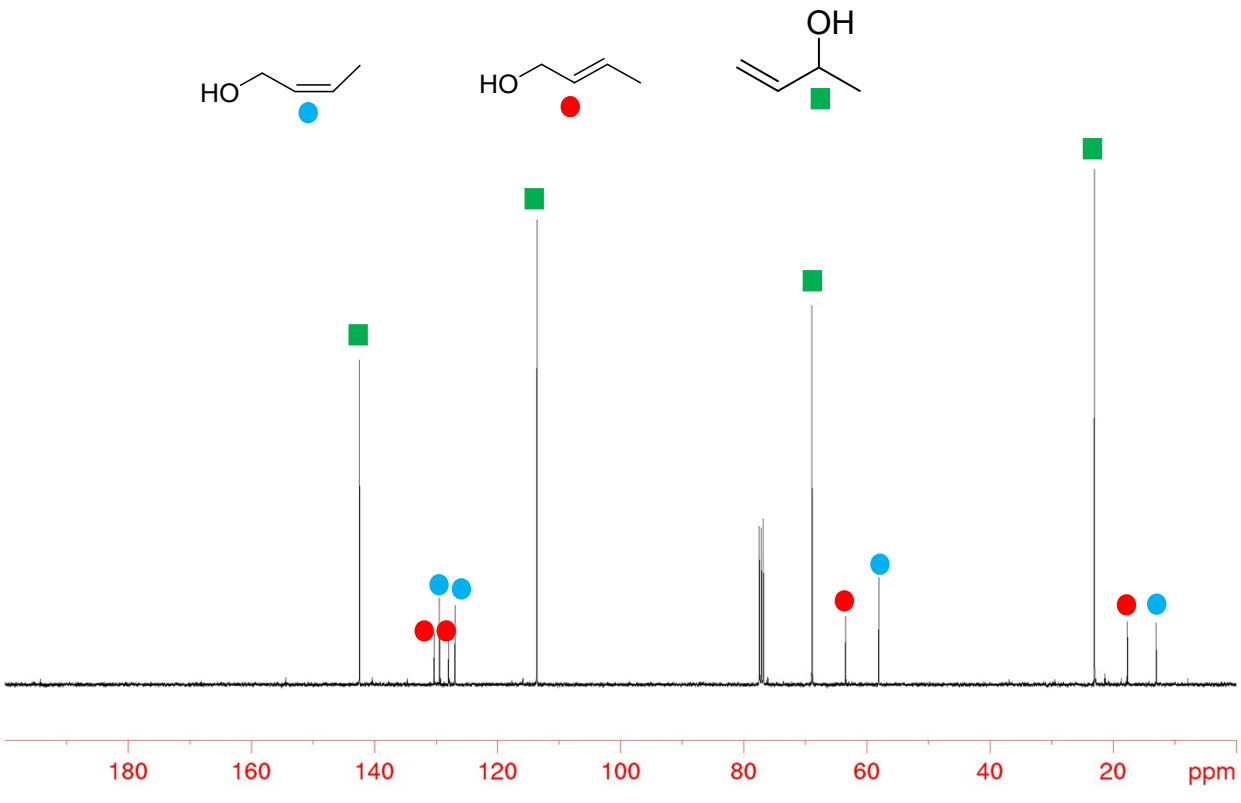
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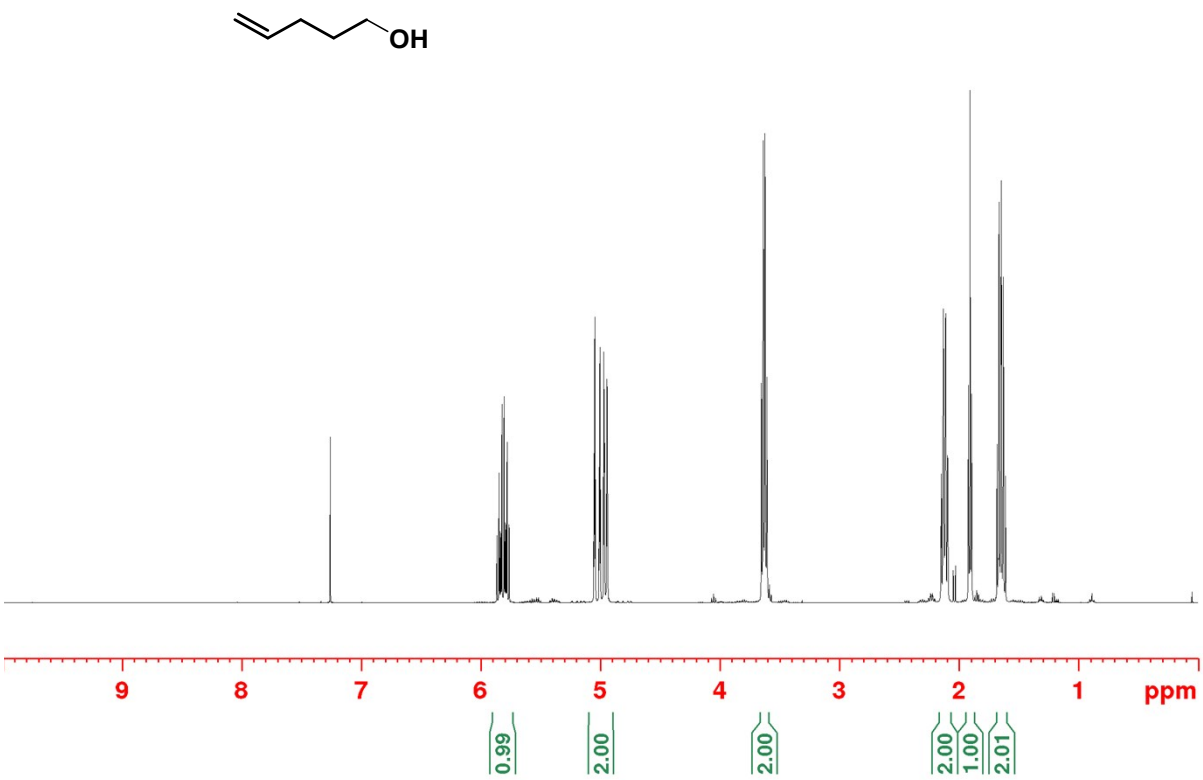
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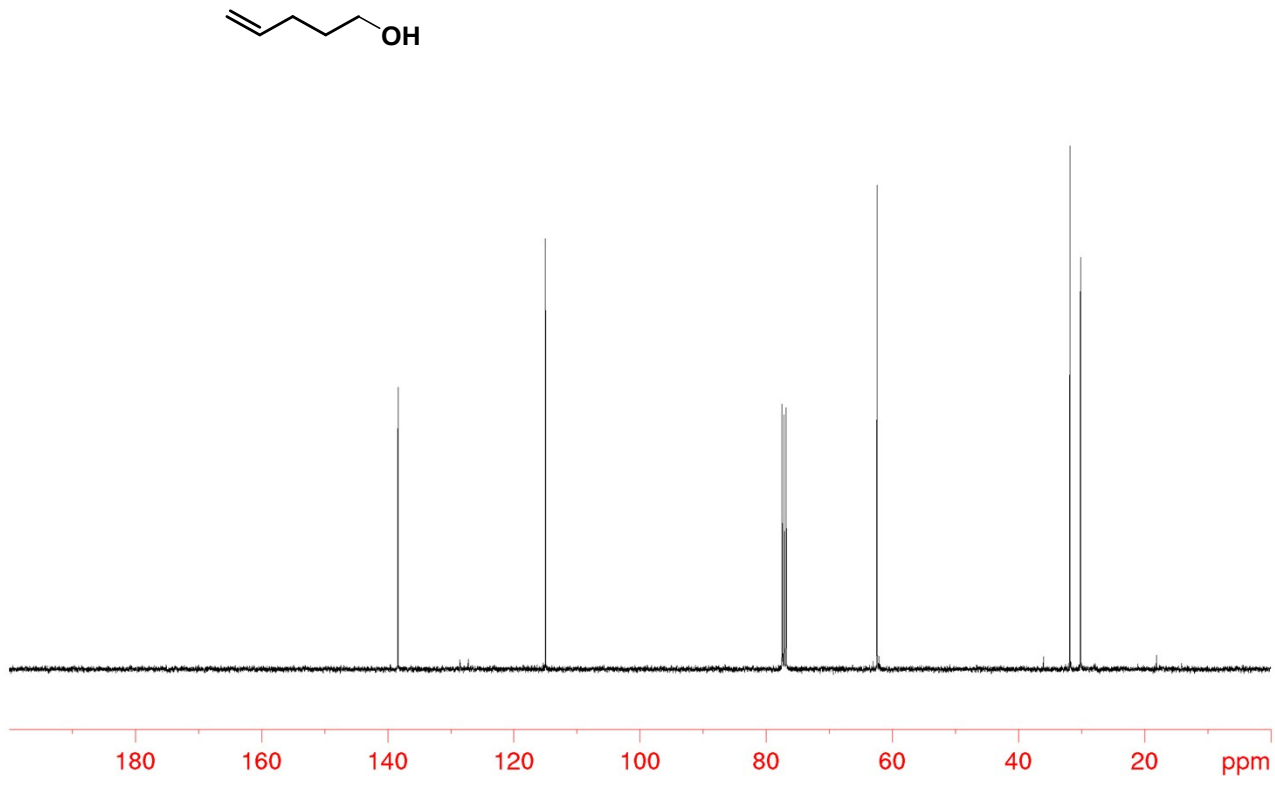
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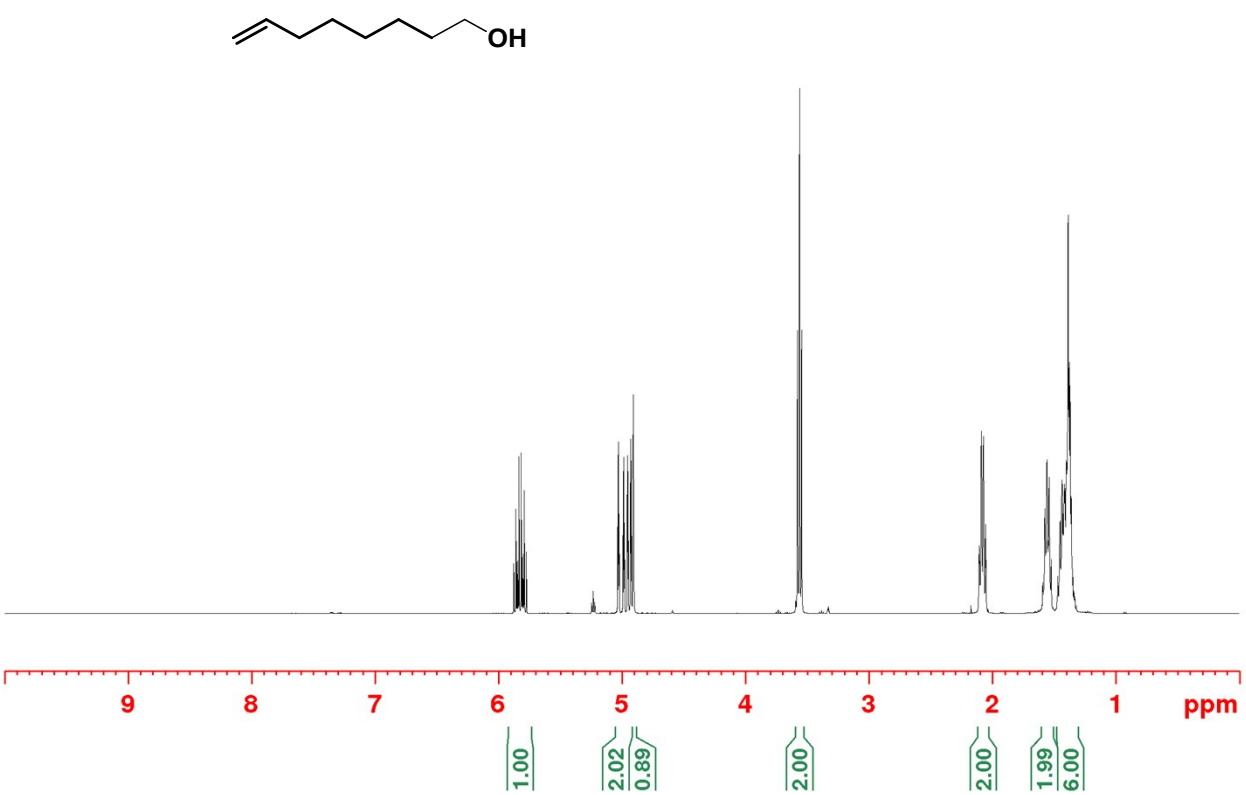
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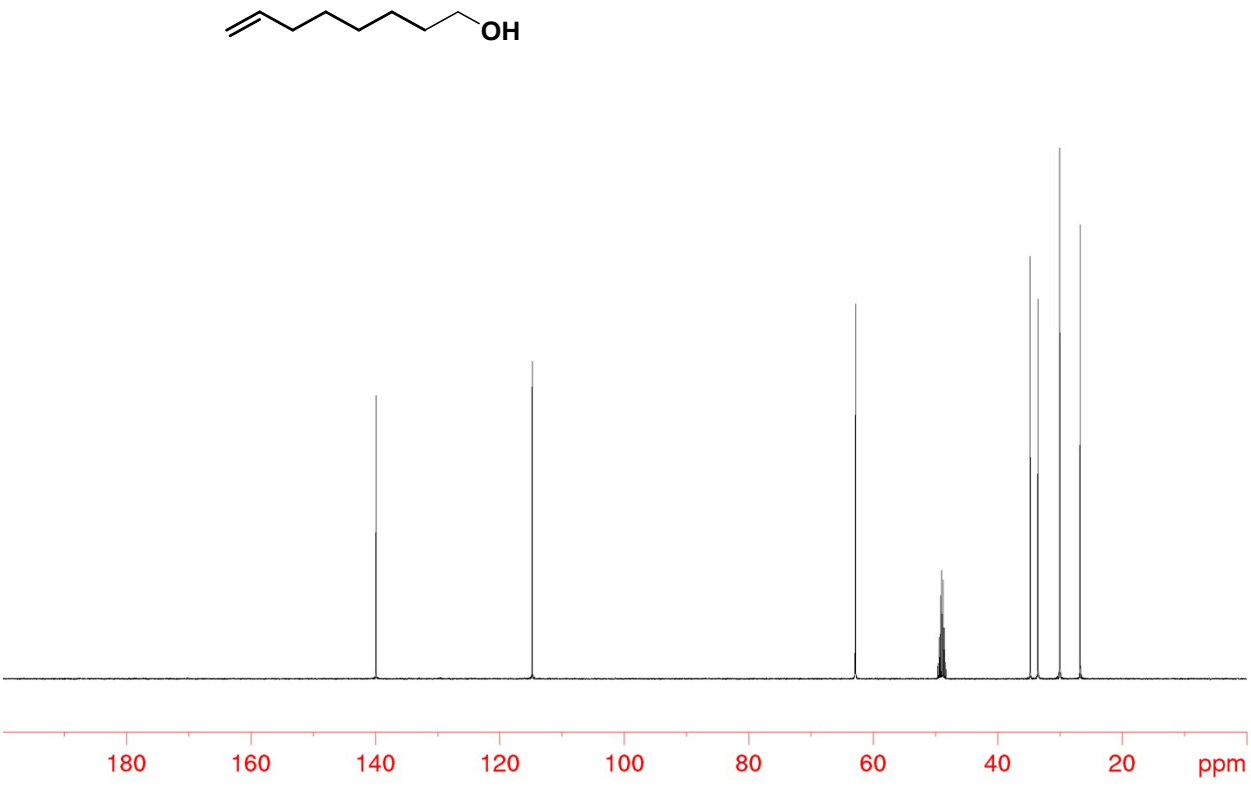
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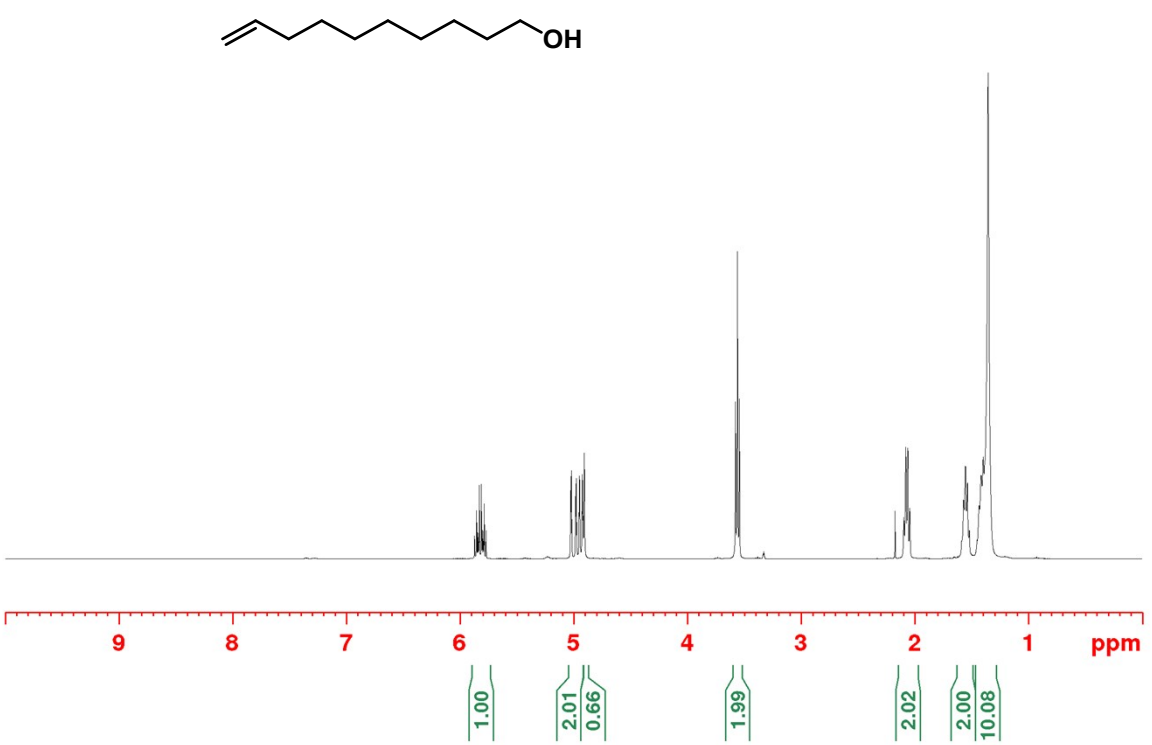
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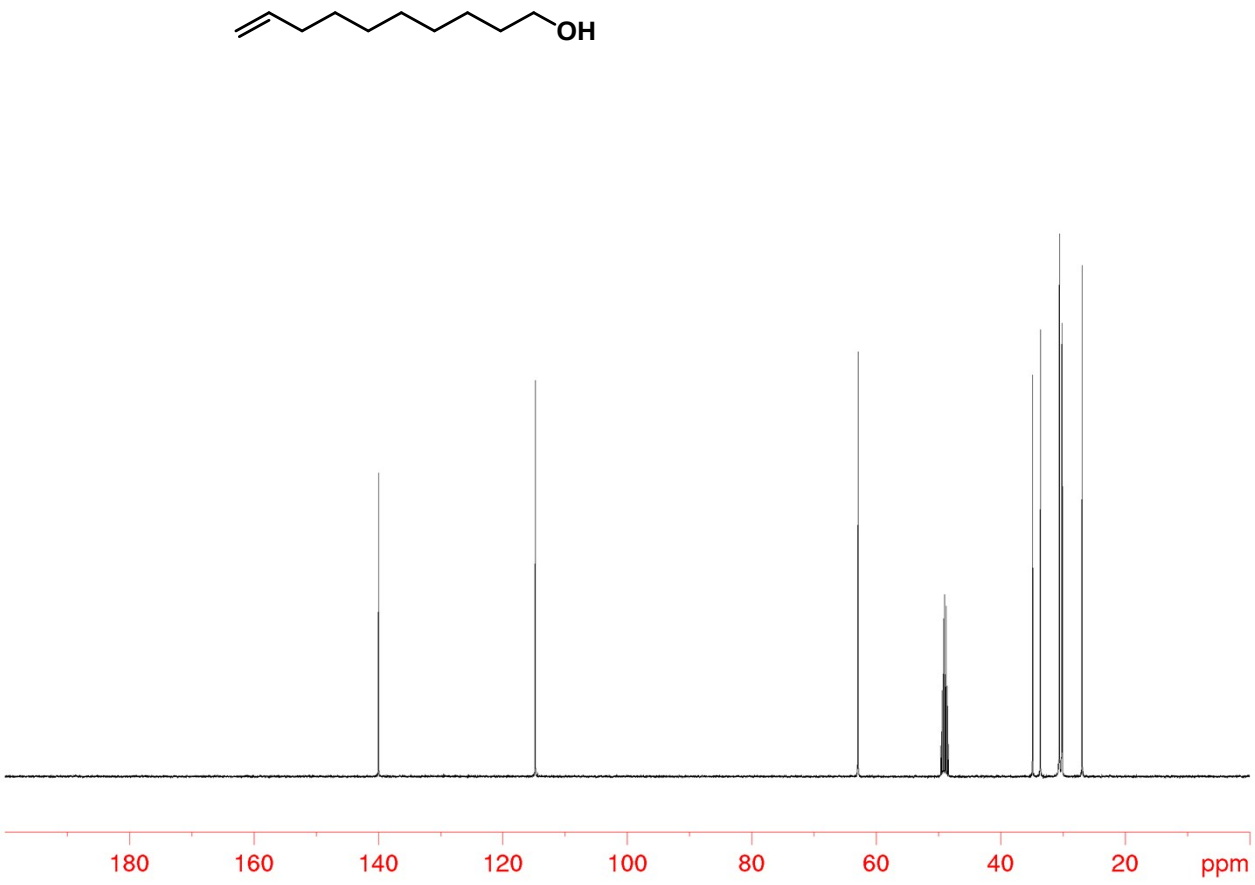
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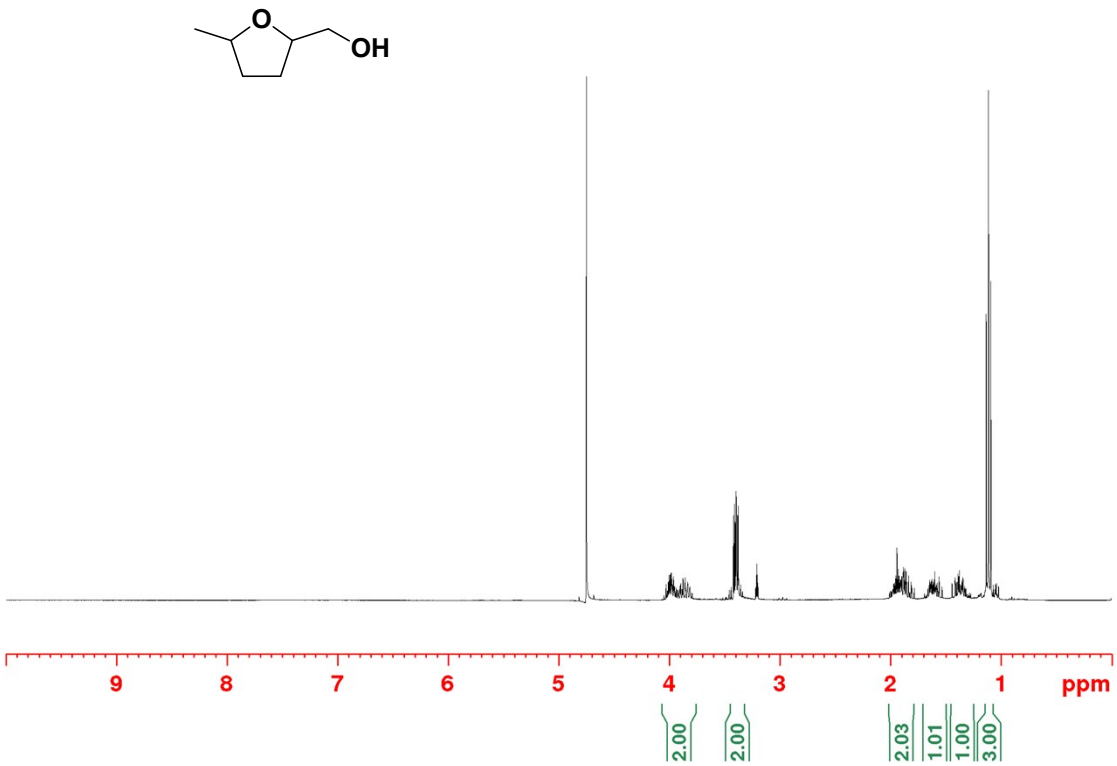
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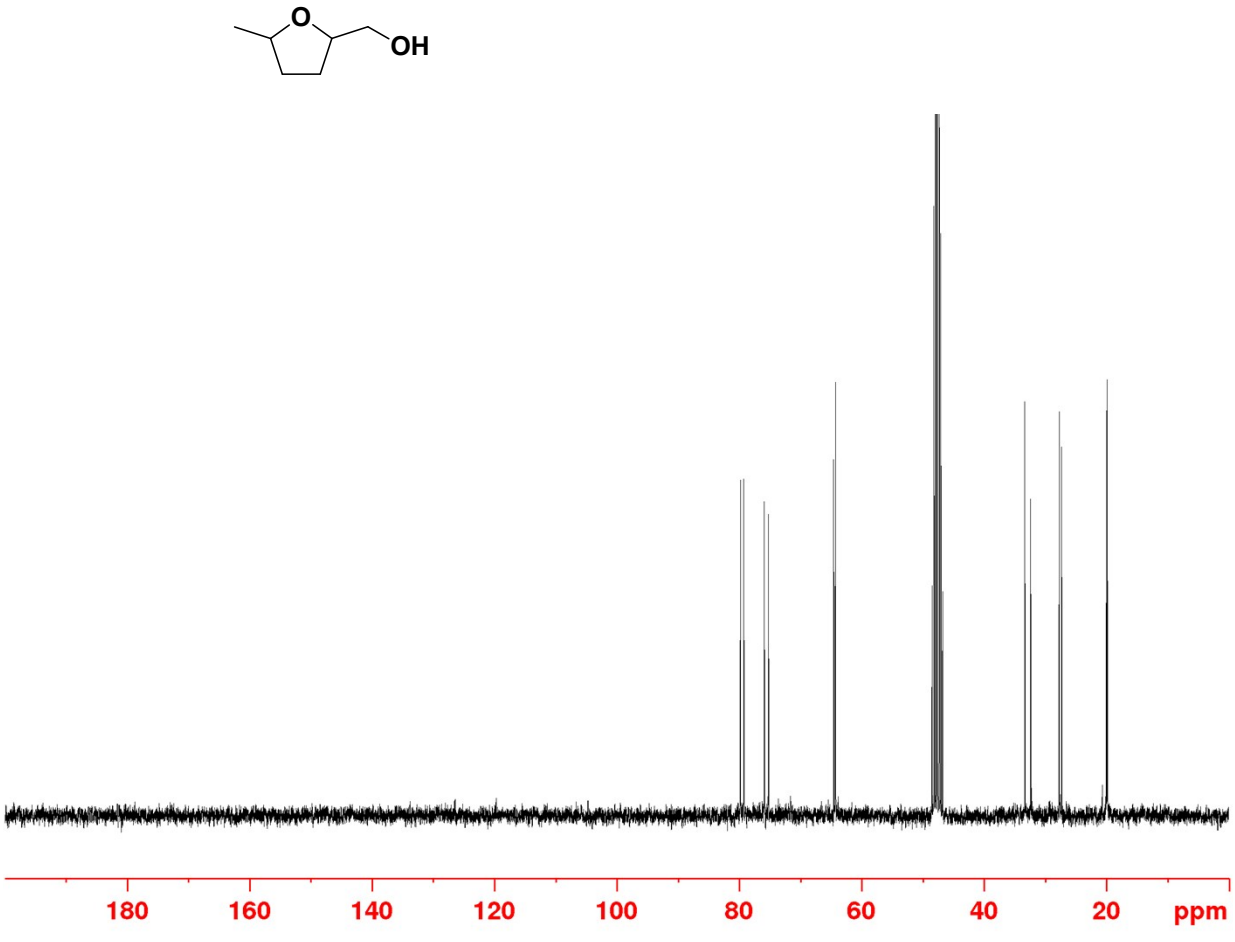
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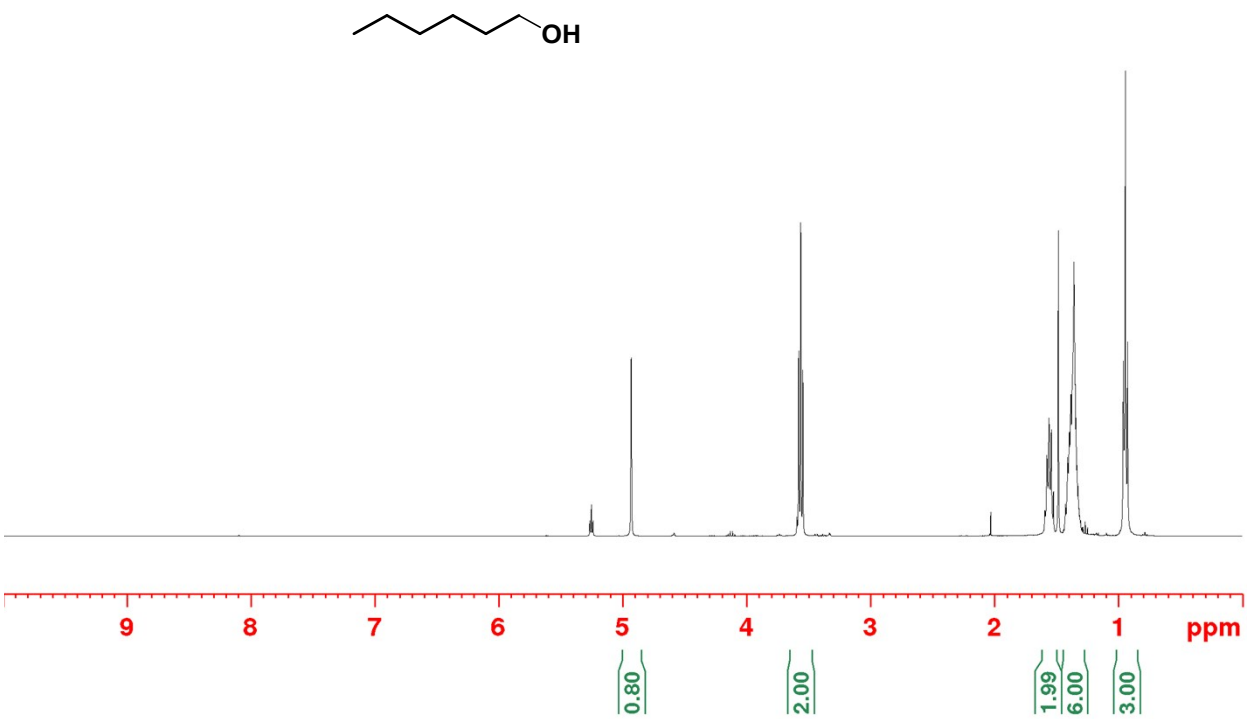
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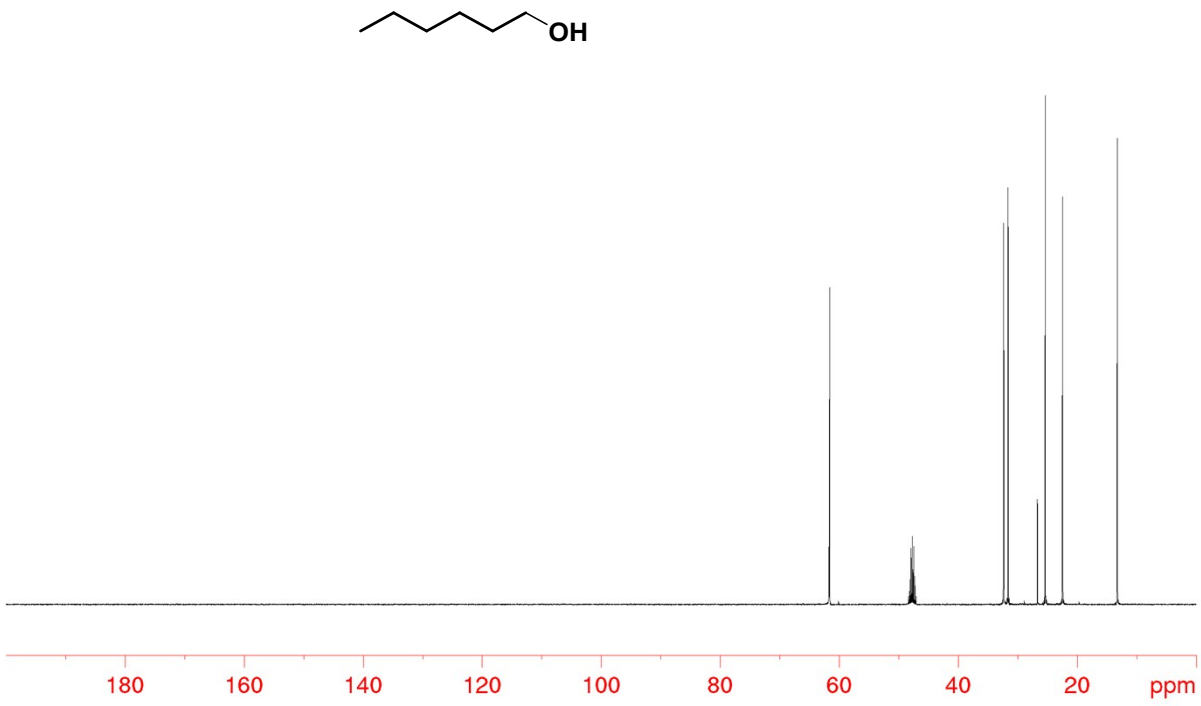
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## *9.4 Statement: Scientific Independence*

Universität Rostock
Dezernat 1
Referat 1.2

**Doktorandinnen/Doktoranden-Erklärung gemäß § 4 Absatz 1 Buchstaben g und h der Promotionsordnung der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock**

Name Bartosz Woźniak
(Name, Vorname)

Anschrift Brauergasse 3, 18055, Rostock
(Straße, PLZ, Wohnort)

Ich habe eine Dissertation zum Thema

Bio-based building blocks from 5-hydroxymethylfurfural via 1-hydroxyhexane-2,5-dione as intermediate

an der Mathematisch-Naturwissenschaftlichen Fakultät der Universität Rostock angefertigt. Dabei wurde ich von Frau/Herrn

Prof. Dr. Johannes G. de Vries

betreut.

Ich gebe folgende Erklärung ab:

1. Die Gelegenheit zum vorliegenden Promotionsvorhaben ist mir nicht kommerziell vermittelt worden. Insbesondere habe ich keine Organisation eingeschaltet, die gegen Entgelt Betreuerinnen/Betreuer für die Anfertigung von Dissertationen sucht oder die mir obliegenden Pflichten hinsichtlich der Prüfungsleistungen für mich ganz oder teilweise erledigt.

2. Ich versichere hiermit an Eides statt, dass ich die vorliegende Arbeit selbstständig angefertigt und ohne fremde Hilfe verfasst habe. Dazu habe ich keine außer den von mir angegebenen Hilfsmitteln und Quellen verwendet und die den benutzten Werken inhaltlich und wörtlich entnommenen Stellen habe ich als solche kenntlich gemacht.

## *9.5 Statement: Contributions to Published Manuscripts*

**7.1: Cyclopentanone derivatives from 5-hydroxymethylfurfural *via* 1-hydroxyhexane-2,5-dione as intermediate**

B. Wozniak, A. Spannenberg, Y. Li, S. Hinze, and J.G. de Vries, *ChemSusChem* **2018**, *11*, 356-359, DOI: 10.1002/cssc.201702100

In this work, I optimized the catalytic system for the synthesis of the title compound followed by isolation and crystallization of the product. Furthermore, I synthesized a number of follow-up products including isolation and interpretation of the analytic data. Moreover, I wrote the first version of the manuscript. My own contribution to this work is around 80%.

**7.2: Efficient synthesis of biomass-derived *N*-substituted 2-hydroxymethyl-5-methyl-pyrroles in two steps from 5-hydroxymethylfurfural**

B. Wozniak, Y. Li, S. Hinze, S. Tin, and J.G. de Vries, *Eur. J. Org. Chem.* **2018**, *11*, 2009-2012, DOI: 10.1002/ejoc.201800171

During this project, I planned the reaction design, synthesized the starting material on a large scale as well as screened primary amines for the production of pyrroles. I isolated and characterized all the compounds and wrote the first version of the manuscript. My contribution to this paper is approximately 80%.

**7.3: Rhenium-catalyzed deoxydehydration of renewable triols derived from sugars**

B. Wozniak, Y. Li, S. Tin, and J.G. de Vries, *Green Chem.* **2018**, *20*, 4433-4437, DOI: 10.1039/c8gc02387e

During the course of this project, I carried out the optimization of the reaction conditions, substrate screening and recyclability experiments. Moreover, I isolated and characterized all the products and wrote the the first version of the manuscript. My contribution to this paper is around 85%.

## *9.6 Curriculum Vitae*

**Personal details**

| | |
|---|---|
| Name: | Bartosz Woźniak |
| Born: | 30/07/1991 in Śrem, Polen |
| Address: | Brauergasse 3, 18055 Rostock, Germany |
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**Education**

| | |
|---|---|
| 03/2016 - Present | Ph.D. in Chemical Science, Leibniz Institute for Catalysis/University of Rostock, Germany |

| | |
|---|---|
| | Main topics: conversion of biomass-derived platform chemicals into valuable compounds, deoxydehydration of triols derived from sugars |
| | Advisor: Prof. Johannes G. de Vries |
| 10/2013 - 06/2015 | Master's Degree in Biological Chemistry, Adam Mickiewicz University, Posen, Polen |
| | Thesis title: "*New, catalytic method for the synthesis of alkynylsubstituted germanium compounds*" |
| | Advisor: Prof. Bogdan Marciniec |
| 10/2010 - 06/2013 | Bachelor's Degree in Biological Chemistry**,** Adam Mickiewicz University, Posen, Polen |
| | Thesis title: "*Hydrogermylation of substituted alkynes in the presence of transition metals*" |
| | Advisor: Prof. Bogdan Marciniec |
| 09/2007 - 06/2010 | Józef Wybicki Highschool**,** Śrem, Polen |
| | Major: Natural science |

**Job experience**

| | |
|---|---|
| 09/2015 - 12/2015 | Erasmus+ Trainee, University of Bergen, Norway |
| | *"Synthesis and characterization of ruthenium-based olefin metathesis catalysts"* |
| | *Advisor: Prof. Vidar R. Jensen* |
| 10/2012 - 06/2015 | Research Scientist, Adam Mickiewicz University, Wlkp |
| | Center for Advanced Technologies, Posen, Polen |
| | Contribution on European and national projects |
| | Advisors: Prof. Bogdan Marciniec, Dr. Beata Dudziec |
| | • *"Silsesquioxanes as nanofillers and modifiers of polymer composition"* |
| | • *"Inorganic catalysis – a new strategy for synthesis of organometallic reagents, polymers and nanomaterials"* |
| | • *"Synthesis of unsaturated derivatives of double-decker silsesquioxanes (DDSQ) as precursors of new organic-inorganic hybrid materials"* |

- *"Synthesis and application of new unsaturated organogermanium and organogermanesilicon compounds"*

08/2014 – 08/2014 Industrial Internship, ACRYLMED R&D, Konarzyce, Polen

Optimization and validation of processes and methods

Advisor: Joanna Adamska

**Languages**

- Polish - Native
- English - Fluent
- German - Intermediate (B2 Certificate from University of Rostock)
- Norwegian - Basic

**Publications**

- B. Wozniak, Y. Li, S. Tin, J.G. de Vries, *Green Chem.* **2018**, *20*, 4433-4437, DOI: 10.1039/c8gc02387e
- B. Wozniak, Y. Li, S. Hinze, S. Tin, J.G. de Vries, *Eur. J. Org. Chem.* **2018**, *11*, 2009-2012, DOI: 10.1002/ejoc.201800171
- B. Wozniak, A. Spannenberg, Y. Li, S. Hinze, J.G. de Vries, *ChemSusChem* **2018**, *11*, 356-359, DOI: 10.1002/cssc.201702100
- M. Rzonsowska, B. Wozniak, B. Dudziec, J. Pyziak, I. Kownacki, B. Marciniec, *Eur. J. Inorg. Chem.* **2016,** 339-346, DOI: 10.1002/ejic.201501110
- B. Dudziec, M. Rzonsowska, B. Marciniec, D. Brząkalski, B. Wozniak, *Dalton Trans.* **2014,** 43, 13201-13207, DOI: 10.1039/c4dt01950d

**Conference participation**

- 07/2018: 21st International Symposium on Homogeneous Catalysis (ISHC XXI), Amsterdam, the Netherlands. Oral presentation: "*Efficient conversion of biomass-derived 5-hydroxymethylfurfural to useful building blocks via 1-hydroxyhexane-2,5-dione as intermediate"*
- 03/2018: 51st Jahrstreffen Deutscher Katalytiker, Weimar, Germany. Poster presentation
- 03/2017: 50th Jahrstreffen Deutscher Katalytiker, Weimar, Germany. Poster presentation
- 08/2014: 57th Polish Chemical Society National Meeting, Częstochowa, Polen. Poster presentation (poster prize)

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