

Electronic Supplementary Information (ESI) for:

**2,2,5,5-Tetramethyltetrahydrofuran (TMTHF): A Non-Polar, Non-
Peroxide Forming Ether Replacement for Hazardous Hydrocarbon
Solvents**

Fergal Byrne,^a Bart Forier,^b Greet Bossaert,^b Charly Hoebbers,^b Thomas J. Farmer,^a James H. Clark^a
and Andrew J. Hunt*^a

- (a) Green Chemistry Centre of Excellence, Department of Chemistry, The University of York,
Heslington, York, YO10 5DD, UK.
- (b) Nitto Belgium NV, Eikelaarstraat 22, Belgium.

* E-mail: andrew.hunt@york.ac.uk | Tel: +44(0)1904324456

Table of Contents

Table of Contents.....	2
Materials and methods.....	3
Experimental procedures	4
Catalyst screening for the synthesis of 2,2,5,5-tetramethyltetrahydrofuran (TMTHF)	4
Reactive distillation process for the 1 L scale production and purification of TMTHF	6
Peroxide testing.....	6
Amidation kinetic reaction procedures	7
Esterification kinetic reaction procedures.....	8
Grignard reaction procedures.....	8
Synthesis of Poly (butyl acrylate-co-acrylic acid).....	8
PSA preparation.....	9
Kamlet-Taft solvatochromic parameters testing of MMC	9
HSPiP software predictions.....	10
ArgusLab surface mapping.....	10
Ames test for MMC.....	11
Differential scanning calorimetry (DSC) analysis of TMTHF and DTBE	12
Determination of octanol/water partition coefficient ($\text{Log } P_{(o/w)}$).....	13
LEL calculations.....	13
CHEM21 metrics calculations	14
Renewable route to TMTHF.....	17
References	17
GPC chromatograms.....	18
NMR spectra	20

Materials and methods

Materials

2,5-dimethyl-2,5-hexanediol 97%, methanesulfonic acid $\geq 99\%$, Y zeolite, KSF montmorillonite, K10 montmorillonite, Nafion SAC-13, butanoic anhydride 98%, 1-butanol 99%, 4-phenylbutanoic acid 99%, benzyl bromide 98%, benzyl chloride 99%, Magnesium chips 99.98%, 2-butanone $\geq 99\%$, anhydrous 2-methyltetrahydrofuran $\geq 99\%$, dimethyl sulfoxide 99.9%, 1,4-dioxane 99.8%, toluene 99.9%, para-cymene 99.9%, inhibitor-free anhydrous cyclopentyl methyl ether $\geq 99.9\%$, inhibitor free anhydrous tetrahydrofuran $\geq 99.9\%$, inhibitor-free anhydrous 2-methyltetrahydrofuran $\geq 99.9\%$, Nile red $\geq 99\%$, 4-nitroaniline $\geq 99\%$, and chloroform-d (CDCl_3 , 99.8% D) were purchased from Sigma-Aldrich. H-BEA Zeolites were supplied by Clariant. ZSM-5 zeolites were supplied by RS Minerals. K30 montmorillonite was supplied by Fluka. Benzylamine $\geq 98\%$, was purchased from Alfa Aesar. Chlorobenzene $\geq 99\%$ was purchased from Acros Organics. Tetrahydrofuran 99.9% was purchased from VWR. Diethyl ether 99.9%, dimethylformamide 99.9%, and sulfuric acid 95% $d=1.83$ were purchased from Fischer. QUANTOFIX[®] Peroxide 100 was purchased from Macherey-Nagel. Ames MPF 98/100 kits, 2-nitrofluorene and 4-nitroquinoline-*N*-oxide were purchased from Xenometrix. TA98 and TA100 were stored at $-70\text{ }^\circ\text{C}$. Anhydrous potassium carbonate was purchased from Fisher Scientific. *N,N*-diethyl-4-nitroaniline was purchased from VWR.

GC-MS analysis

A gas chromatograph-mass spectrometry (GC-MS) proceeded on a Perkin Elmer Clarus 500 GC along with a Clarus 560 S quadrupole mass spectrometer. The equipment was equipped with a DB5HT capillary column (30 $\text{m} \times 250\text{ }\mu\text{m} \times 0.25\text{ }\mu\text{m}$ nominal, max temperature $430\text{ }^\circ\text{C}$). The carrier gas utilised in GC-MS was helium with flow rate at 1.0 mL/min, and the split ratio used was 10:1. The injector temperature was $330\text{ }^\circ\text{C}$. During the GC-MS test, the initial temperature of the oven was at $50\text{ }^\circ\text{C}$ for 4 minutes. After that, the temperature increased with a rate of $10\text{ }^\circ\text{C}/\text{min}$ to $300\text{ }^\circ\text{C}$ and held for 10 minutes. The Clarus 500 quadrupole mass spectrum was conducted in electron ionisation (EI) mode at 70 eV with the source temperature and the quadrupole both at $300\text{ }^\circ\text{C}$. The m/z mass scan was in the range of 40 to 640 m/z . The data was collected by the PerkinElmer enhanced TurboMass (Ver. 5.4.2) chemical software. Each GC-MS sample consisted of 20-40 mg product mixture and 1.5 mL DCM or acetone as GC-MS solvent.

¹H NMR and ¹³C NMR analysis

The ¹H NMR and ¹³C NMR spectra in this work were recorded by a JEOL JNM-ECS 400 MHz spectrometer. 16 scans were utilised for ¹H NMR analysis, and 256 scans were utilised for ¹³C NMR analysis. The NMR data was processed and analysed by ACD/NMR Processor Academic Edition software (Ver. 12.01).

UV vis. Analysis

The UV vis. spectra were recorded on a JENWAY, 6705 UV/Vis. spectrophotometer in quartz cuvettes at $25\text{ }^\circ\text{C}$.

GC-FID analysis

An Agilent 6890N gas chromatograph with a flame ionisation detector (GC-FID), fitted with a ZB5HT capillary column (30 m×250 μm×0.25 μm nominal, max temperature 400 °C) was used in this work. Helium was used as the carrier gas at a flow rate of 2.0 mL/min. The split ratio was 30:1. The initial oven temperature was 40 °C which was held for 1 minute at which point it was increased at a rate of 10 °C/min to 300 °C. injection temperature was 250 °C and the detector temperature was 300 °C.

Experimental procedures

Catalyst screening for the synthesis of 2,2,5,5-tetramethyltetrahydrofuran (TMTHF)

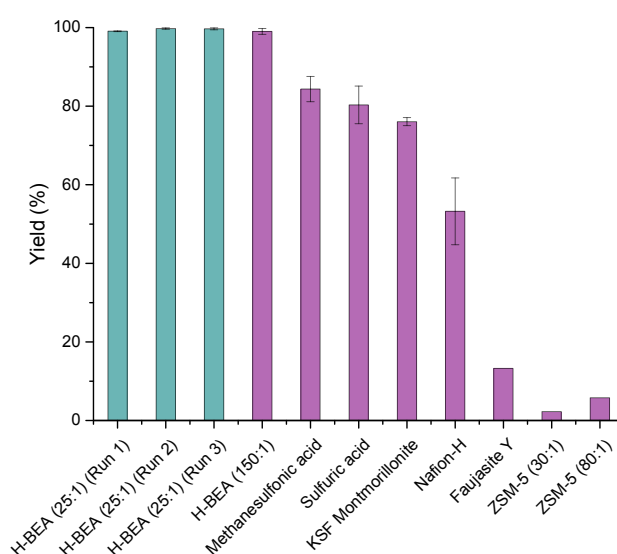


Figure S1. The catalyst screening results shown as yields calculated by ^1H NMR.

The chosen catalyst (50 mg for solid catalysts, 0.9 mmol for liquid catalysts) was added to molten 2,5-dimethylhexane-2,5-diol (5 g, 34 mmol). The reaction mixture was stirred and heated to 110 °C on a heating plate for 90min. Yields and conversions were calculated by ^1H NMR and are shown in Figure S1. The peaks and structures of TMTHF, 2,5-dimethyl-2,5-hexanediol and side products used for calculation are shown in Figure S2

[TMTHF]. ^1H NMR (400 MHz, CDCl_3): δ 1.81 (s, 4H), 1.21 (s, 12H); ^{13}C NMR (400 MHz, CDCl_3): δ 29.75, 38.75, 80.75; IR 2968, 2930, 2968, 1458, 1377, 1366, 1310, 1265, 1205, 1144, 991, 984, 885, 849, 767 cm^{-1} ; m/z (%): (ESI-MS) 128 (40) [M^+].

[**1** (2,5-Dimethyl-2,4-hexadiene)] ^1H NMR (400 MHz, CDCl_3): δ 5.94 (s, 2H); ^{13}C NMR (400 MHz, CDCl_3): δ 132.21, 121.31, 26.30, 18.05.

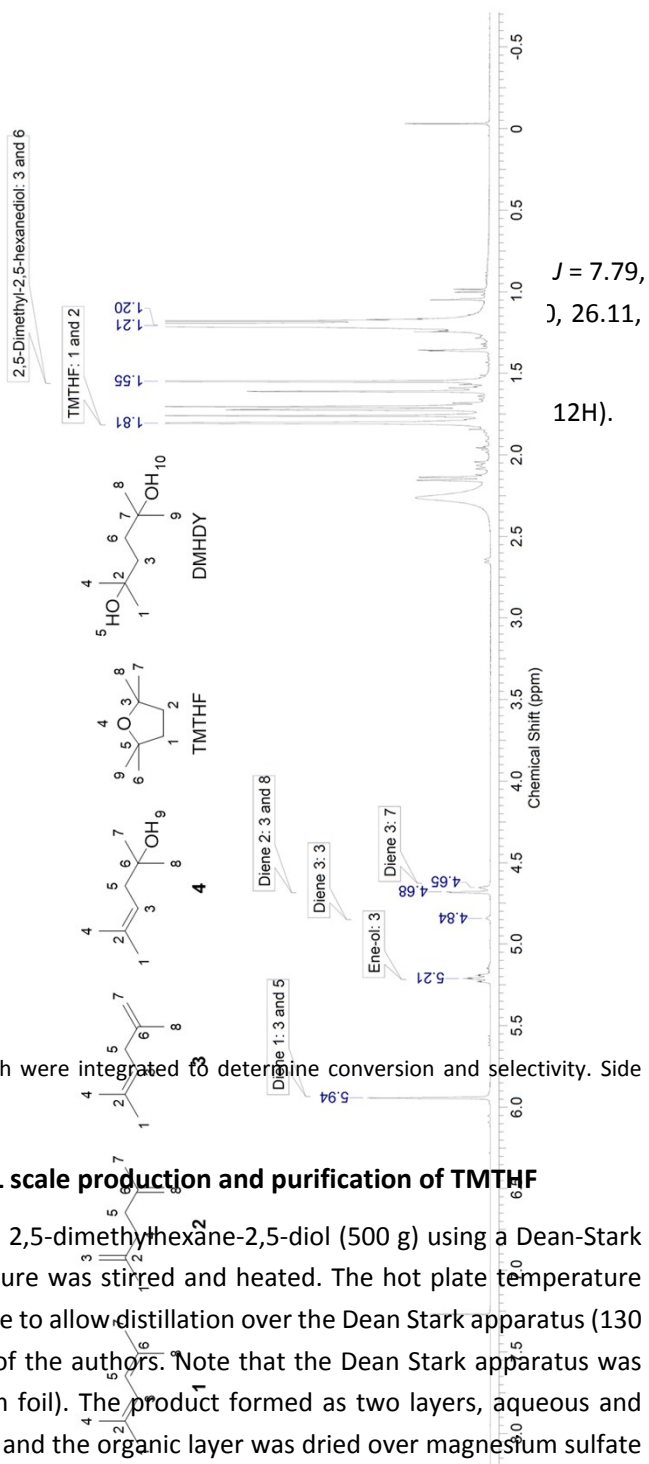
[**2** (2,5-Dimethyl-1,5-hexadiene)] ^1H NMR (400 MHz, CDCl_3): δ 4.68 (s, 4H); m/z (%): (ESI-MS) 110 (50) [M^+].

[**3** (2,5-Dimethyl-1,4-hexadiene)] ^1H NMR (400 MHz, CDCl_3): δ 4.84 (t, 1H), 4.65 (m, 2H); m/z (%):

(ESI-MS) 110 (12) [M⁺].

[4 (2,5-Dimethyl-4-hexen-2-ol)] ¹H NMR (2H), 1.75 (s, 6H), 1.64 (s, 6H); ¹³C NMR (17.95; *m/z* (%): (ESI-MS) 128 (25) [M⁺].

[DMHDY (2,5-Dimethyl-2,5-hexanediol)] :



Reactive distillation process for the 1 L scale production and purification of TMTHF

H-BEA zeolite (1 g) was added to molten 2,5-dimethylhexane-2,5-diol (500 g) using a Dean-Stark apparatus (Figure S3). The reaction mixture was stirred and heated. The hot plate temperature setting was set to a sufficient temperature to allow distillation over the Dean Stark apparatus (130 °C when using the experimental set up of the authors. Note that the Dean Stark apparatus was insulated with cotton wool in aluminium foil). The product formed as two layers, aqueous and organic. The organic layer was discarded and the aqueous layer was dried over magnesium sulfate and distilled a further two times.



Figure S3. The Dean Stark-type reactive distillation apparatus which was used to produce TMTHF on a litre scale.

Peroxide testing

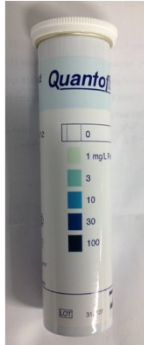
















Analysis of peroxide formation was carried out using a peroxide test strip (Macherey-Nagel, QUANTOFIXR Peroxide-100). A drop of the test solvent was placed on the test pad of the test strip and allowed to evaporate. Upon evaporation, a drop of water was added to the test pad. The concentration of peroxide present (in ppm) in the solvent was determined by comparing the colour of the test pad with the peroxide colorimetric card. No colour change indicated no peroxide present. The colour change in the test strips for each solvent at different time intervals can be seen in Table S1.

5 ml of solvent was added to a wide necked 50 ml round-bottomed flask and stirred on a stirrer hot plate. A constant flow of air was bubbled through a syringe with the tip submerged in the test solvent, connected to a compressed air tap via the neck of the flask. UV light (254 nm) was provided using a UVP 95-0007-06 Model UVGL-58 Handheld 6 Watt UV Lamp, 254/365nm Wavelength, 115V UV lamp placed above the wide neck of the flask to allow direct irradiation over a three-hour period. Control experiments were carried out by testing each solvent for peroxide formation after three hours without UV irradiation or bubbling air. Table S1 shows the peroxide formation in ppm, determined by comparing against the colorimetric card.

TMTHF was further tested under reflux and irradiated with light delivered directly to the sample by a fibre-optic cable which was passed through a septum in a three-necked round-bottomed flask.

A condenser was fitted in the middle neck while air was bubbled through a syringe via a septum in the third neck. The light source was a Xenon ILC-302UV lamp. The results of the test of TMTHF under reflux is shown and labelled as such.

Table S1. Peroxide formation shown in ppm for THF, 2-MeTHF, CPME and TMTHF.

		Solvent	T = 0 hours (ppm)		T = 3 hours (ppm)	
 <p>Scale</p>	THF	Control		10-30		10-30
		Test		10-30		>100
	2-MeTHF	Control		2		2
		Test		2		>30
	CPME	Control		1		2
		Test		1		3-10
	TMTHF	Control		0		0
		Test		0		0

Amidation kinetic reaction procedures

A solution of 0.328 g (2 mmol) of 4-phenylbutanoic acid in 4 mL of test solvent was pre-heated to 100 °C and benzylamine (0.235 g, 2.2 mmol) was added. The reaction vessel was stirred and heated to 100 °C. Conversion of benzylamine to produce *N*-Benzyl-4-phenylbutanamide was determined by taking NMR samples at various time intervals. The integrations of the benzylamine peak at 3.88 ppm and the *N*-Benzyl-4-phenylbutanamide doublet at 4.44 ppm were inputted into equation S1 to find the conversion.

[*N*-Benzyl-4-phenylbutanamide] ¹H NMR (400 MHz, CDCl₃): δ 7.34-7.12 (m, 10H), 4.45 (d, *J* = 5.5, 2H), 2.67 (t, *J* = 7.56, 2H), 2.22 (t, *J* = 7.33, 2H), 2.01 (qn, *J* = 7.4, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 172.43, 128.75, 128.51, 128.40, 127.89, 127.57, 125.98, 43.64, 35.88, 35.18, 27.11; *m/z* (ESI-MS) 253.1 (10) [M⁺].

$$C_t = \frac{[B]_0}{[A]_0} \left[\frac{I_p/H_p}{\frac{I_B}{H_B} + \frac{I_p}{H_p}} \right]$$

Equation S1.

Esterification kinetic reaction procedures

A solution of 0.967 g (5.5 mmol) of butanoic anhydride in 4 mL of test solvent was pre-heated to 100 °C and 1-butanol (0.373 g, 5 mmol) was added. The reaction vessel was stirred and heated to 50 °C. Conversion of 1-butanol to produce butyl butanoate was determined by taking NMR samples at various time intervals. The integrations of the 1-butanol triplet at 2.92 ppm and the butyl butanoate triplet at 3.34 ppm were inputted into equation S1 to find the conversion.

[Butyl butanoate] ¹H NMR (400 MHz, CDCl₃): δ 4.07 (t, *J* = 6.64, 2H), 2.28 (t, *J* = 7.33, 2H), 1.65 (m, *J* = 7.27, 4H), 1.38 (td, *J* = 7.40, 2H), 0.94 (dd, *J* = 7.21, 5.72, 6H); ¹³C NMR (400 MHz, CDCl₃): δ 173.90, 64.12, 36.30, 30.73, 19.17, 18.52, 13.73; *m/z* (%): (ESI-MS) 145.1 (8) [M+H]⁺.

Grignard reaction procedures

Magnesium turnings (0.23 g, 9.7 mmol) were placed in a warmed (40 °C), argon-purged three-necked flask equipped with a magnetic stirrer, condenser and dropping funnel, along with a small number of iodine crystals (~57 mg, 0.45 mmol). 1 mL of the chosen solvent was added and the mixture was stirred and cooled to 0 °C while argon was continuously flowed via a septum. ~1 ml of a benzyl halide solution (9 mmol benzyl halide in 10 ml of the chosen solvent) was added to the reaction mixture and allowed to stir for 5 minutes, while being kept at 0 °C. The remaining benzyl halide solution was added dropwise over the course of ~30 minutes. The mixture was stirred for a further 30 minutes at which point a solution of 2-butanone (4.5 mmol 2-butanone in 10 ml of the chosen solvent) was added dropwise over the course of 30 minutes. The reaction mixture was stirred at room temperature for 2 hours at which point a sample was taken for NMR analysis to determine conversion and selectivity. The reaction mixture was then poured onto a solution of ammonium chloride (1 g) in 10 ml water. The products were extracted using diethyl ether (3 x 10 ml), dried using MgSO₄ and concentrated *in vacuo*. The Wurtz, **5**, (white powder) and Grignard, **6**, (colourless oil) products were isolated by column chromatography using 70:30 hexane/ethyl acetate.

[Grignard product] ¹H NMR (400 MHz, CDCl₃): δ 7.27 (m, 5H), 2.80-2.71 (dd, *J* = 13.28, 9.16 Hz, 2H), 1.53-1.48 (q, *J* = 7.63, 2H), 1.14 (s, 3H), 1.00-0.96 (t, *J* = 7.56, 3H); ¹³C NMR (400 MHz, CDCl₃): δ 137.69, 130.58, 128.16, 126.40, 72.71, 47.59, 34.20, 25.92, 8.33; *m/z* (%): (ESI-MS) 164.1 (2) [M⁺].

[Wurtz product] ¹H NMR (400 MHz, CDCl₃): δ 7.24 (m, 10H), 2.92 (s, 2H); ¹³C NMR (400 MHz, CDCl₃): δ 141.79, 128.45, 128.34, 125.91, 37.97; *m/z* (%): (ESI-MS) 181.7 (80) [M⁺].

Synthesis of Poly (butyl acrylate-co-acrylic acid)

In a 500 mL round-bottom three-necked flask, equipped with a condenser and an overhead stirrer, butyl acrylate (100 g) and acrylic acid (5 g) are mixed together with dibenzoylperoxide (0.382 g), and solvent (26.35 g). The mixture is then purged with nitrogen for at least 1 hour. Next, the mixture is heated to 70°C and stirred under a nitrogen atmosphere. Dropwise addition of solvent (219.54 g) takes place once an exothermic reaction can be observed. Finally, ageing of the mixture takes place at 80 °C for 4-6 hours until a conversion of at least 95 % is reached.

PSA preparation

A pressure sensitive adhesive composition is made from poly (butyl acrylate-co-acrylic acid). Poly (butyl acrylate-co-acrylic acid) (73.39 g, at a solid content of 27.25 %) is mixed with polyisocyanate (1.07 g, at a solid content of 75 %) and melamine resin (0.52 g, at a solid content of 58 %), dissolved in solvent. Subsequently, the solids content is reduced to 20 %. This composition was applied with a knife coater at a thickness about 25 μm onto a polyester film. The composition was dried to obtain a pressure sensitive adhesive sheet.

Kamlet-Taft solvatochromic parameters testing of MMC

The KT parameters were measured by dissolving *N,N*-diethyl-4-nitroaniline (NN) and 4-nitroaniline (NA) dyes in the test solvent (TS) and scanning on the UV vis. spectrophotometer to determine $\nu_{\max(\text{NA})}$ and $\nu_{\max(\text{NN})}$. π^* and β were then calculated using equation S2 and S3 respectively.

$$\text{Equation S2. } \pi^* = \frac{v_{\max}^{\text{H-bond}}(NN)[TS] - v_{\max}^{\text{H-bond}}(NN)[\text{cyclohexane}]}{v_{\max}^{\text{H-bond}}(NN)[DMSO] - v_{\max}^{\text{H-bond}}(NN)[\text{cyclohexane}]}$$

$$\text{Equation S3. } \beta = 0.74 \frac{v_{\text{Calculated}}[TS] - v_{\text{Observed}}[TS]}{v_{\text{Calculated}}[DMSO] - v_{\text{Observed}}[DMSO]}$$

The $v_{\text{Calculated}}$ represents the v_{\max} predicted by a baseline of non-hydrogen-bonding solvents. Deviations from this baseline are proportional to β . Equation S4 shows baseline used in this work to find β was that which was determined by Sherwood.^[1] R^2 is shown in Equation S5.

$$\text{Equation S4 } y = 1.0025x + 3.4426$$

$$\text{Equation S5 } R^2 = 0.9945$$

HSPiP software predictions

HSPiP (4th Edition 4.1.04) is computer modelling software which can predict the Hansen solubility parameters (HSPs) of an inputted molecule. HSPiP was employed to calculate the HSPs of TMTHF which are shown in Figure S5 in relation to other common solvents.

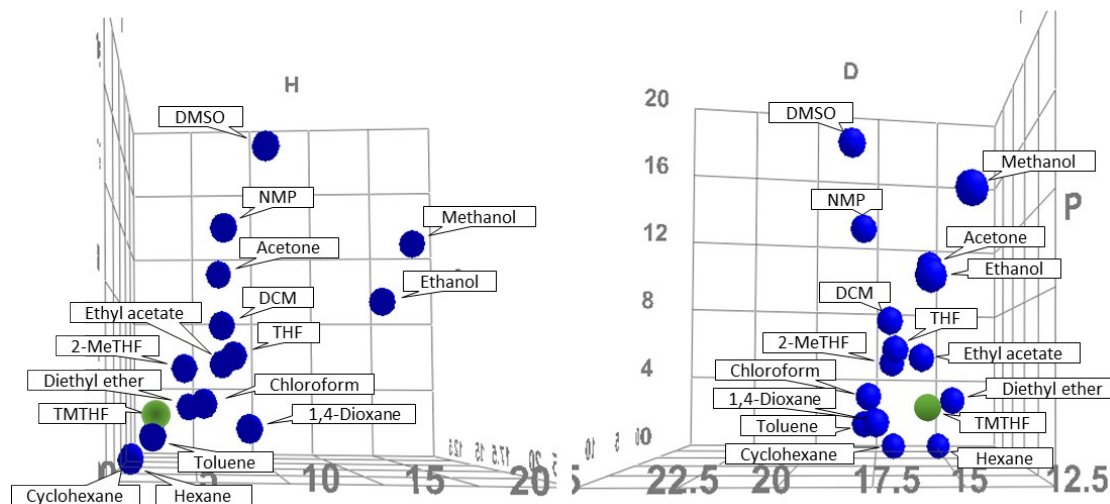


Figure S4. HSP maps showing the position of TMTHF in relation to other common solvents. TMTHF's proximity to toluene can be seen on the left while the difference between their δD can be seen on the right.

ArgusLab surface mapping

ArgusLab (obtainable at <http://www.arguslab.com/arguslab.com/ArgusLab.html>) is a free software which can be used for molecular modelling and graphics. In this work, ArgusLab was used to map the surface electrostatic potential (ESP) of a selection of molecules. The molecular geometry was optimised using the Austin Model 1 (AM1) and a restricted Hartree-Fock (RHF) calculation.

Ames test for MMC

The experiment procedure was based on manufacturer's guidelines. TA98 and TA100 were tested at 6 different concentrations (0.16 mg/mL, 0.31 mg/mL, 0.63 mg/mL, 1.25 mg/mL, 2.5 mg/mL, 5 mg/mL) of TMTFH dissolved in ethanol, as well as a positive (2 µg/mL of 2-nitrofluorene (2-NF) and 0.1 µg/mL of 4-nitroquinoline-*N*-oxide (4-NQO)) control and a negative solvent control (ethanol). The bacterial strains were allowed to grow for 90 minutes in a medium containing enough histidine to conduct about two cell divisions. After exposure, the cultures were diluted in pH indicator medium without histidine and then aliquoted into 48 wells of a 384-well plate. After 48 hours at 37 °C, a colour change from purple to yellow was observed in wells containing bacteria which underwent reversion to His⁺. The number of yellow wells were counted manually for each dose to obtain the average value. A spreadsheet which accompanies the Ames test kit generates the results and plots the graphs shown in Figure S6.

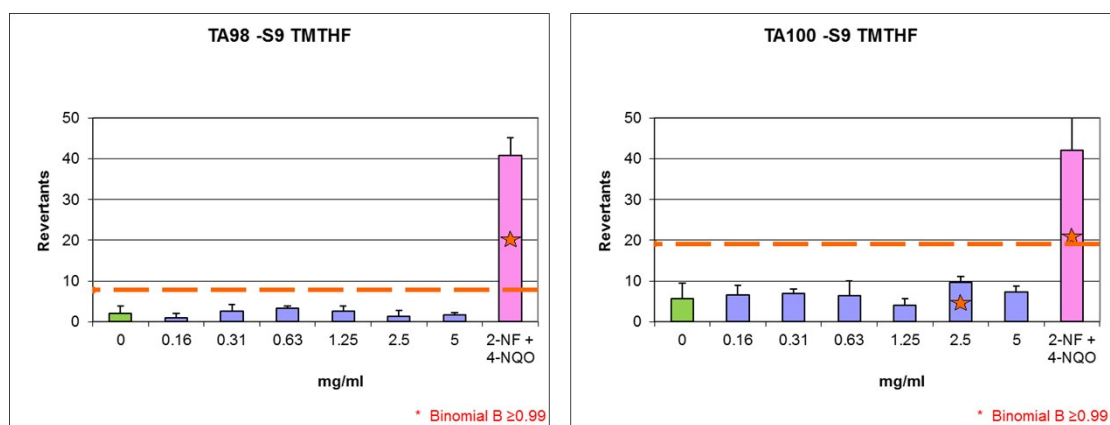


Figure S5. Ames test results at different concentrations of TMTFH in TA98 (left) and TA100 (right) bacterial strains.

Acid stability tests

TMTHF (5 ml, 48.7 mmol) was added to a 25 ml round-bottomed flask and heated to the desired temperature. Acid (1 mol.%) was added and the mixture was allowed to stir for 24 hours. Degradation was measured using ^1H NMR, using either methanol- d_4 or toluene- d_8 as the solvent.

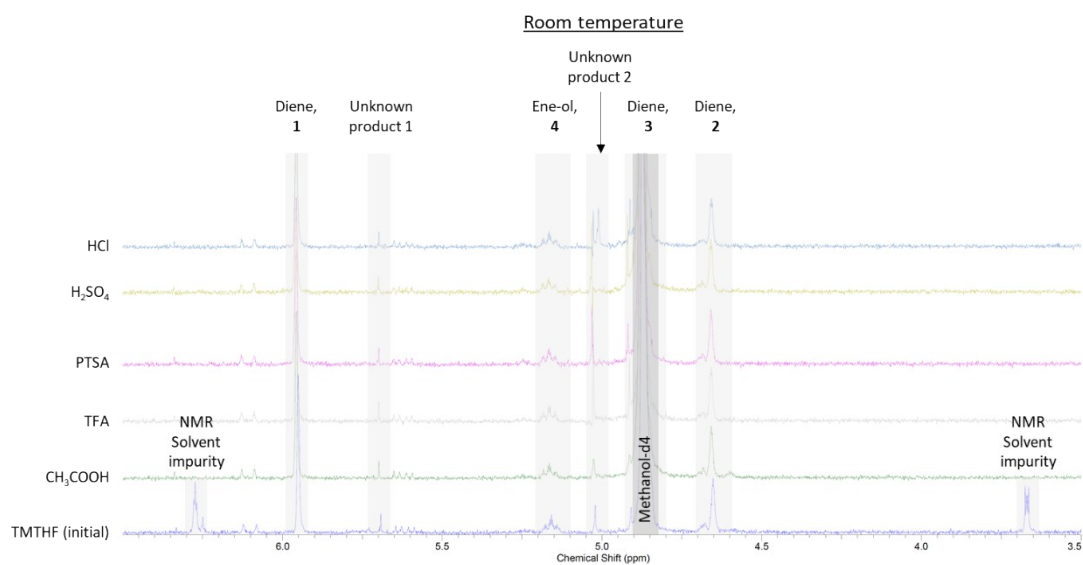


Figure S6. ^1H NMR showing degradation product peaks after TMTHF was mixed with acid and stirred at room temperature for 24 hours compared to TMTHF before testing. Small amounts of some side-products (<0.5%) were present in the fresh TMTHF before testing which can be seen in the bottom spectrum.

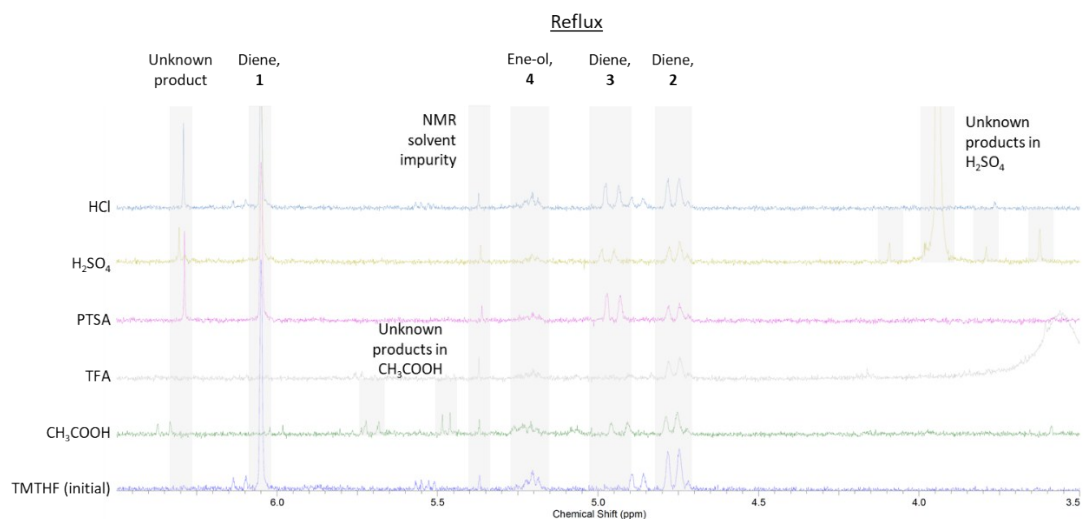


Figure S7. ^1H NMR showing degradation product peaks after TMTHF was mixed with acid and stirred under reflux for 24 hours compared to TMTHF before testing. Small amounts of some side-products (<0.5%) were present in the fresh TMTHF before testing which can be seen in the bottom spectrum.

Differential scanning calorimetry (DSC) analysis of TMTHF and DTBE

The melting point of TMTHF and DTBE were measured by DSC (TA Instruments, Q2000, V24.10) to be < -90 °C. During the testing, a small sample (~ 5 - 10 mg) was hermetically-sealed in a Tzero aluminium DSC pan. The cooling rate was 10 °C/min from 30 °C to -90 °C.

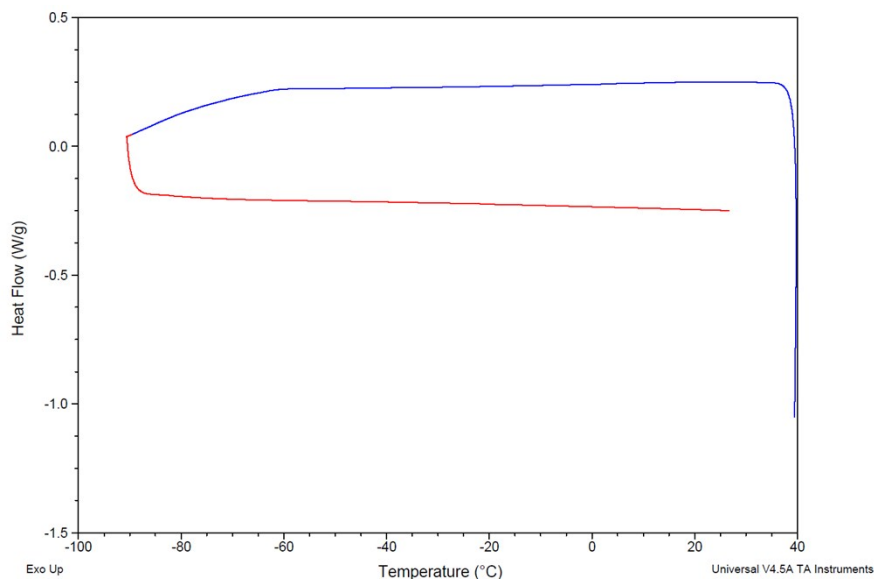


Figure S8. DSC trace of TMTHF.

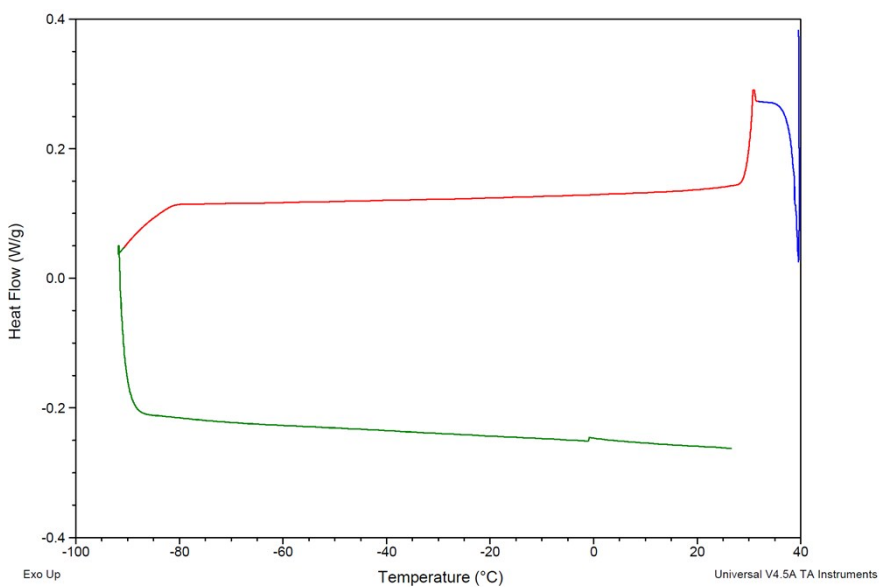


Figure S9. DSC trace of DTBE.

Determination of octanol/water partition coefficient (Log P_(o/w))

Determination of the log P_(o/w) was done by the shake flask method. 1 ml each of octanol and water were mixed in a 2.5 ml vial. 60 µL of the test sample was added and the mixed was shaken for 30 seconds and allowed to stand for at least 1 hour. Samples (50 µL) were taken from both the aqueous and organic layers and dissolved in a standard GC solution (1 ml). The standard solution was made by adding cumene (20 µL) as internal standard (IS) to methanol (20 ml). GC-FID was run according to the method described. Log P_(o/w) was obtained using Equation 1.

Equation 1.

$$\text{Log } P_{(o/w)} = \frac{\text{Area}(\text{sample})_o \text{Area}(\text{IS})_w}{\text{Area}(\text{sample})_w \text{Area}(\text{IS})_o}$$

LEL calculations

Example calculation

- A container can hold 1 mole of an ideal gas and is currently full of air.
- Toluene and TMTHF are assumed to be ideal gases.

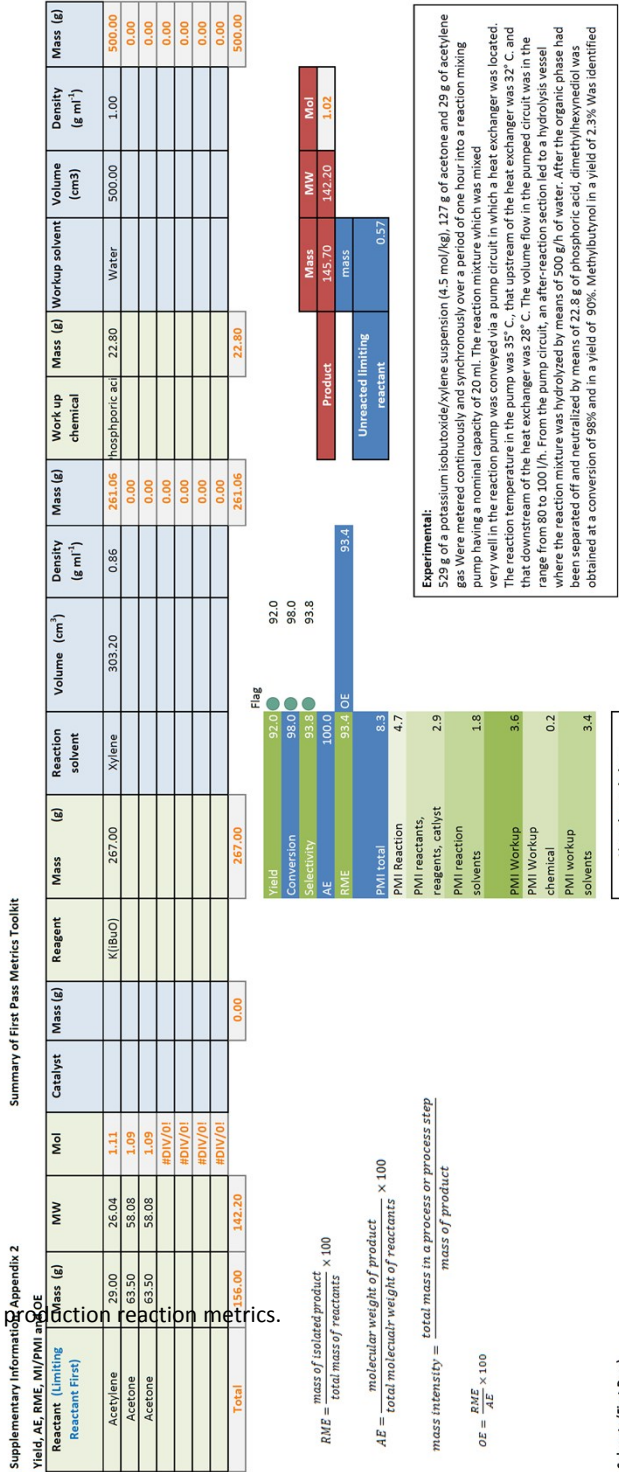
- The LEL of toluene (1.1%) allows 0.011 moles in the container before the risk of explosion.
- 0.011 moles of toluene = 1.0124 g of toluene.
- 1.0124 g of toluene = **1.1677** ml of toluene

- The LEL of TMTHF (0.9%) allows 0.009 moles in the container before a risk of explosion.
- 0.009 moles of TMTHF = 1.154 g of TMTHF
- 1.1539 g of TMTHF = **1.4388** ml of TMTHF

- **1.4388** ml TMTHF > **1.1677** ml toluene, therefore a larger volume of liquid TMTHF can evaporate into the container before a risk of explosion.

CHEM21 metrics

Figure S10. Step 1 of TMTHF production reaction metrics.



Solvents (First Pass)	Preferred solvents	Problematic solvents: (acceptable only if substitution does not offer advantages)	Hazardous solvents: These solvents have significant health and/or safety concerns.	Highly hazardous solvents: The solvents which are agreed not to be used, even in screening
	water, EtOH, nBuOH, AcOEt, AcOH, PhOMe, MeOH, tBuOH, BuOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfone	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	gluons, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	Et ₂ O, Benzene, CCl ₄ , chloroform, DCE, nitromethane, CS ₂ , HMPA
	List solvents below			
	No solvent			
	Facile recovery of catalyst/enzyme			
	catalyst/enzyme not recovered			

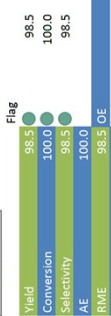
Catalyst/enzyme (First Pass)	Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	Green Flag
Use of stoichiometric quantities of reagents	Amber Flag
Use of reagents in excess	Red Flag

Figure S11. Step 2 of TMTHF Production reaction metrics.

Supplementary Information: Appendix 2 Summary of First Pass Metrics Toolkit

Yield, AE, RME, MI/PMI and OE

Reactant (Limiting Reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Work up chemical	Mass (g)	Workup solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)
Dimethylhexylenediol	110.00	142.20	0.77	Pd/Al ₂ O ₃	250.00						0.00						0.00
Hydrogen	1.55	2.02	0.77								0.00						0.00
Hydrogen	1.55	2.02	0.77								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
			#DIV/0!								0.00						0.00
Total	113.10	146.24			250.00						0.00						0.00



$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$\text{mass intensity} = \frac{\text{total mass in a process or process step}}{\text{mass of product}}$$

$$OE = \frac{RME}{AE} \times 100$$

Product	Mass	MW	Mol
Product	111.40	146.23	0.76
Unreacted limiting reactant	mass		
	0.00		

Experimental:
 The hydrogenation of crude DMHDY solution was carried out continuously over a spherical supported catalyst (diameter: 2–4 mm, 0.25% Pd on Al₂O₃) in two tube reactors connected in series. The reactors had a free reactor cross section of 656 mm², a length of 1.7 m and a fillable volume of 800 ml. The reactors were provided with external heating. The internal temperature of the reactors could be measured at the top, in the middle and in the lower part. Both reactors were charged in the middle with 250 ml of catalyst and the remaining volume was filled with inert glass spheres. After turning up the reactors, 110 g/h of feed (25.5 g/h of DMHDY) at 80 °C were metered into the first reactor. Hydrogen was likewise introduced from the top downward in a pressure-regulated manner at 30 bar. A constant offgas flow of 2 l/h was established. After leaving the reactor, part of the output was pumped back to the top of the first reactor. The amount recirculated by pumping was 50 l/h. The other part was pumped to the bottom of the second reactor where it flowed upward. Hydrogen was likewise fed in a pressure-regulated manner at 30 bar through the second reactor from the bottom upward. The offgas flow was 1 l/h. The second reactor had no liquid circulation. After leaving the second reactor, the output (116.2 g/h) was depressurized into a vessel. The yield of

Solvents (First Pass)

Preferred solvents	water, EtOH, nBuOH, AcOIPr, AcONBu, PhOMe, MeOH, tBuOH, BnOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane
Problematic solvents: (acceptable only if substitution does not offer advantages)	DMSO, cyclohexanone, DMPU, AcOH, Ac ₂ O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-TfH
Hazardous solvents: These solvents have significant health and/or safety concerns.	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane
Highly hazardous solvents: The solvents which are agreed not to be used, even in screening	Et ₂ O, Benzene, CCl ₄ , chloroform, DCE, nitromethane, CS ₂ , HMPA

Catalyst/enzyme (First Pass)	Tick
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents	Green Flag X
Use of stoichiometric quantities of reagents	Amber Flag
Use of reagents in excess	Red Flag

Facile recovery of catalyst/enzyme	Green Flag	Tick
Facile recovery of catalyst/enzyme	Green Flag X	
catalyst/enzyme not recovered	Amber Flag	

Figure S12. Step 3 of TMTHF production reaction metrics.

Renewable route to TMTHF

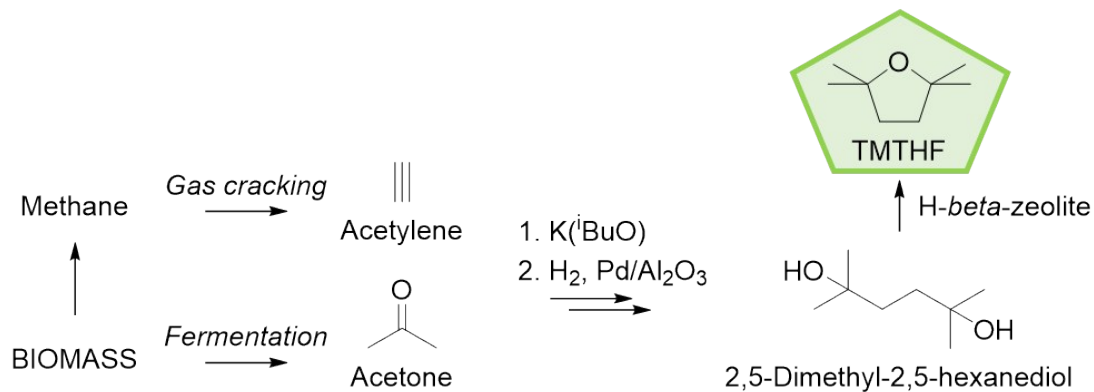


Figure S13. Potential renewable route to TMTHF using bio-based drop-in replacement molecules.

Summary of First Pass Metrics Toolkit

Supplementary Information: Appendix 2

Reagent (Limiting reactant First)	Mass (g)	MW	Mol	Catalyst	Mass (g)	Reagent	Mass (g)	Reaction solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)	Workup chemical	Mass (g)	Workup solvent	Volume (cm ³)	Density (g ml ⁻¹)	Mass (g)
2,5-dimethyl-2,5-hexanediol	500.00	146.23	3.42	Zeolite	1.00						0.00		0.00				0.00
Total	500.00	146.23			1.00		0.00				0.00		0.00				0.00

Flag
 99.2
 100.0
 99.2
 87.7
 99.2
 87.0 OE
 1.2
 1.2

$$RME = \frac{\text{mass of isolated product}}{\text{total mass of reactants}} \times 100$$

$$AE = \frac{\text{molecular weight of product}}{\text{total molecular weight of reactants}} \times 100$$

$$\text{mass intensity} = \frac{\text{total mass in a process or process step}}{\text{mass of product}}$$

$$OE = \frac{RME}{AE} \times 100$$

Product	Mass	MW	Mol
Product	485.00	128.21	3.39
Unreacted limiting reactant	mass		
	0.00		

Experimental:
 H-BEA zeolite (1 g) was added to molten 2,5-dimethylhexane-2,5-diol (500 g) using a Dean-Stark apparatus (Figure S3). The reaction mixture was stirred and heated. The hot plate temperature setting was set to a sufficient temperature to allow distillation over the Dean Stark apparatus (130 °C when using the experimental set up of the authors. Note that the Dean Stark apparatus was insulated with cotton wool in aluminium foil). The product formed as two layers, aqueous and organic.

Solvents (First Pass)	Preferred solvents	Problematic solvents	Hazardous solvents	Highly hazardous solvents
	water, EtOH, nBuOH, AcOEt, AcOH, PhOMe, MeOH, tBuOH, BrOH, ethylene glycol, acetone, MEK, MIBK, AcOEt, sulfolane	DMSO, cyclohexanone, DMPU, AcOH, Ac2O, Acetonitrile, AcOMe, THF, heptane, Me-cyclohexane, toluene, xylene, MTBE, cyclohexane, chlorobenzene, formic acid, pyridine, Me-THF	dioxane, pentane, TEA, diisopropyl ether, DME, DCM, DMF, DMA, NMP, methoxyethanol, hexane	Et ₂ O, Benzene, CCl ₄ , chloroform, DCE, nitromethane, CS ₂ , HMPA

Catalyst/enzyme (First Pass)	Green Flag	Amber Flag	Red Flag
Catalyst or enzyme used, or reaction takes place without any catalyst/reagents.	X		
Use of stoichiometric quantities of reagents		Amber Flag	
Use of reagents in excess			Red Flag

Green Flag	Amber Flag	Tick
Facile recovery of catalyst/enzyme		X
catalyst/enzyme not recovered	Amber Flag	

Instructions for use: Enter your data into the tables above to automatically calculate yield, AE, RME, M/PMI and OE. Use the blank boxes in the tables to enter experimental data and note the flags for each Key Parameter. **Printing tips:** This spreadsheet is designed to be printed with 'landscape', 'narrow margin' and 'fit all columns on one page' settings.

A potential renewable route to TMTHF is shown in Figure S7. Methane can be produced by anaerobic digestion or gasification^[2] of biomass. The GoBiGas project by Göteborg Energie aims to produce 30% of Göteborg's gas by 2020.^[3] Methane can be cracked in the presence of oxygen to produce acetylene as well as syngas, soot and water.^[4] The acetylene is separated and can be reacted with acetone from fermentation to produce 2,5-dimethyl-2,5-hexanediol.^[5] Cyclisation of 2,5-dimethyl-2,5-hexanediol, as reported in the main text, produces TMTHF.

References

- [1] J. Sherwood, *Bio-Based Solvents for Organic Synthesis*, phd, University of York, **2013**.
- [2] M. H. Waldner, F. Vogel, *Ind. Eng. Chem. Res.* **2005**, *44*, 4543–4551.
- [3] "GoBiGas," can be found under https://www.goteborgenergi.se/English/Projects/GoBiGas__Gothenburg_Biomass_Gasification_Project
- [4] "Further improving competitiveness - BASF Intermediates," can be found under <http://www.intermediates.basf.com/chemicals/topstory/acetylene>
- [5] "Dimethylhexanediol - CAS 110-03-2 - BASF - We create chemistry," can be found under http://www.windenergy.basf.com/group/corporate/wind-energy/en/brand/2_5_DIMETHYL_2_5_HEXANEDIOL

GPC chromatograms

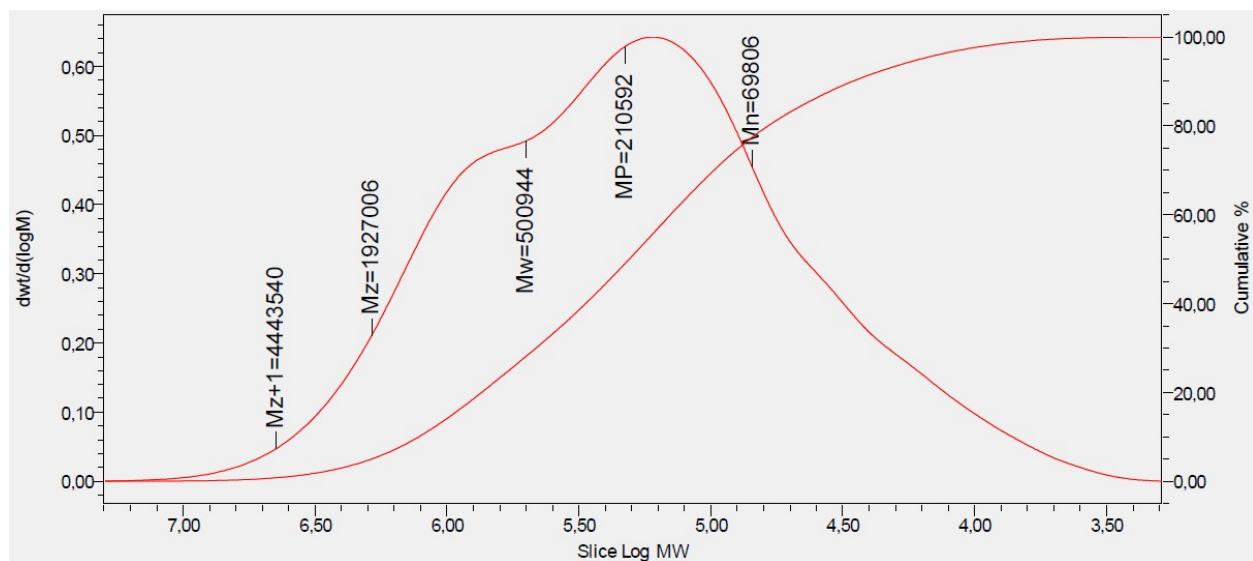


Figure S14. GPC chromatogram of Poly (butyl acrylate-co-acrylic acid) when TMTHF is used as the polymerisation solvent.

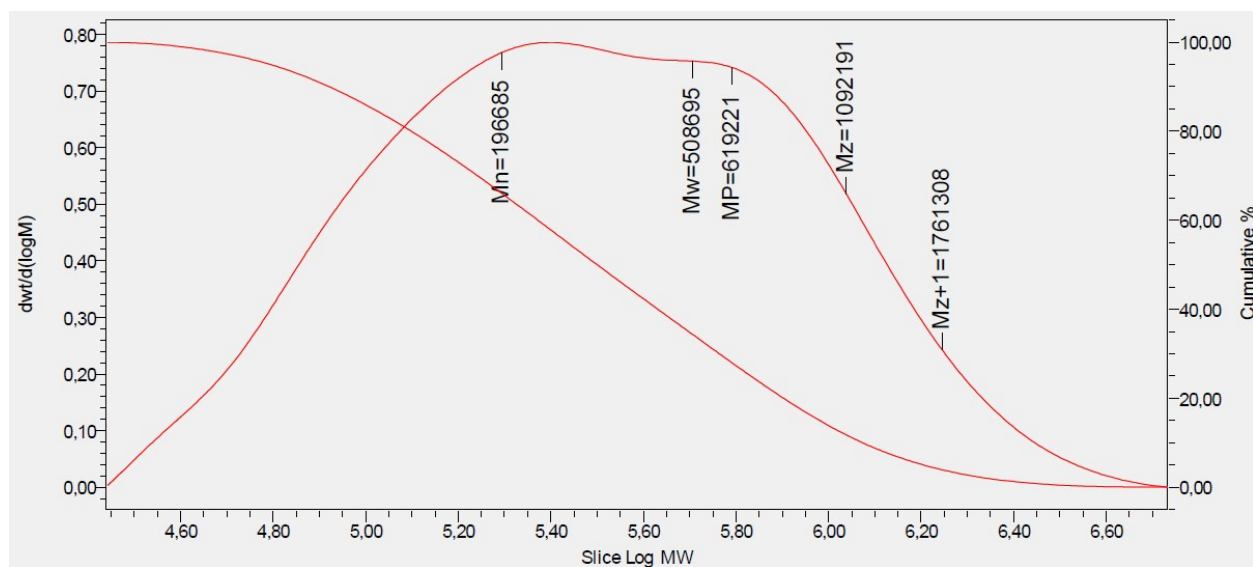


Figure S15. GPC chromatogram of Poly (butyl acrylate-co-acrylic acid) when toluene is used as the polymerisation solvent.

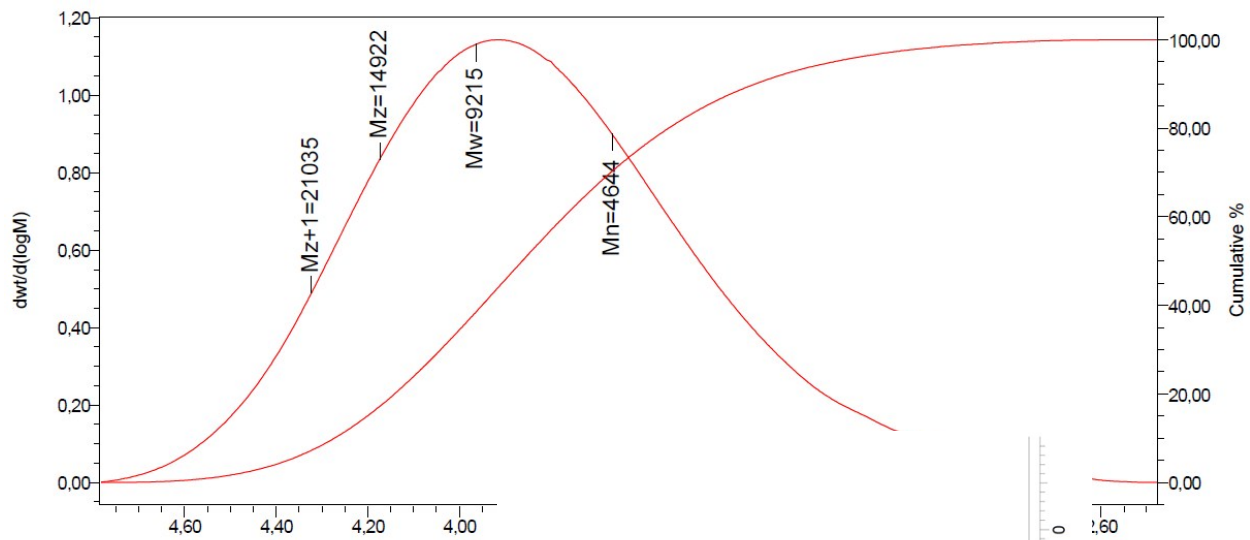
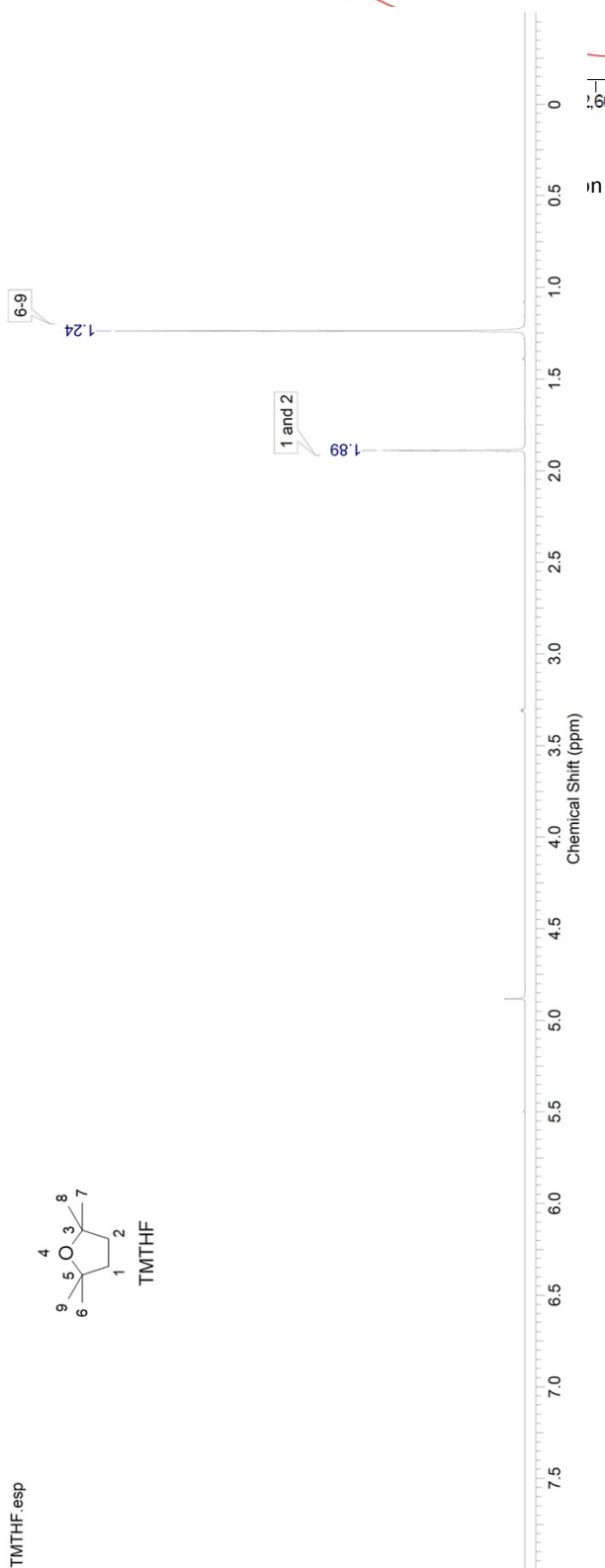


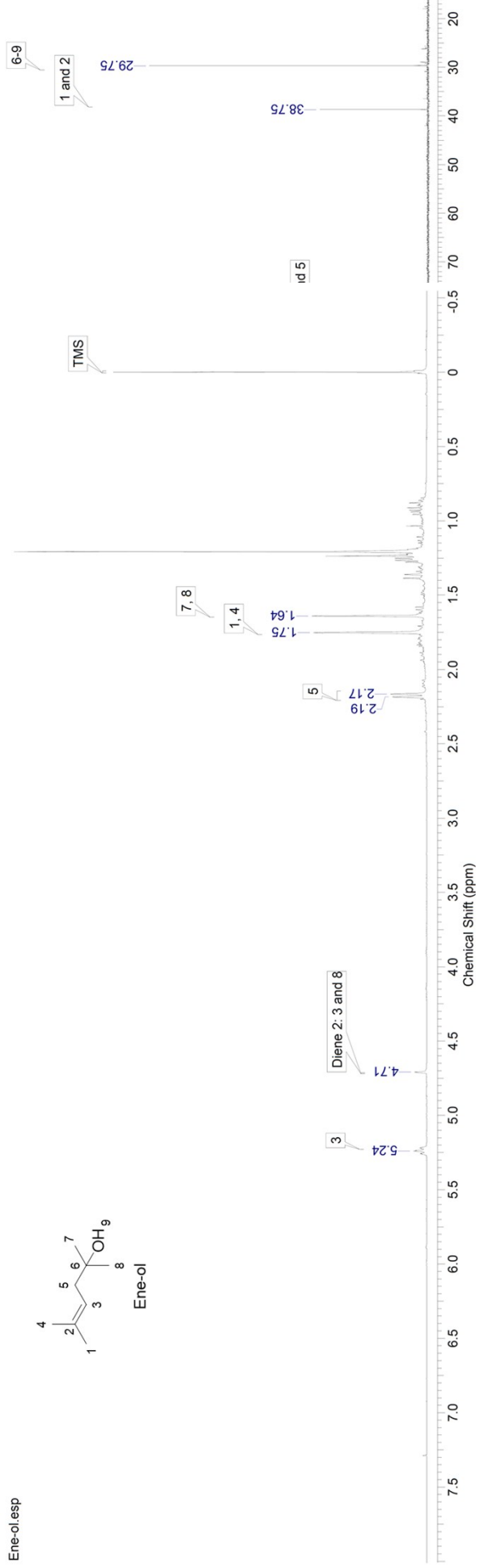
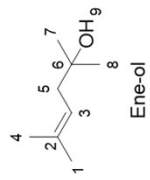
Figure S16. GPC chromatogram of Poly (butyl acryla solvent).

NMR spectra

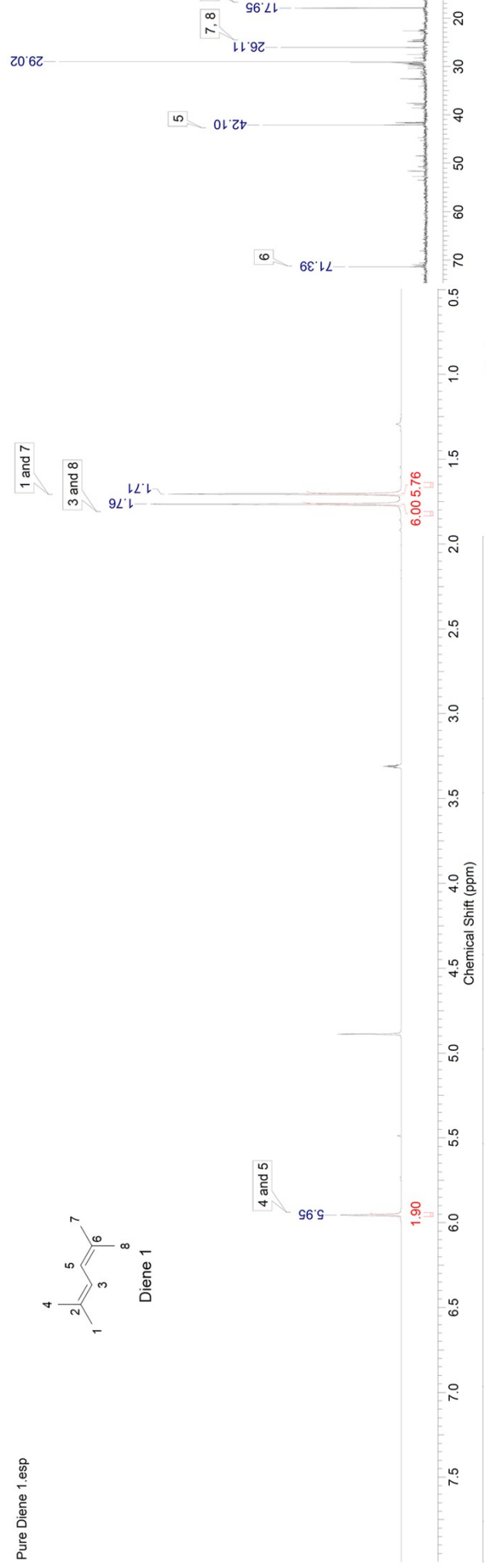
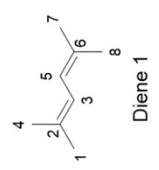


TMTHF.esp

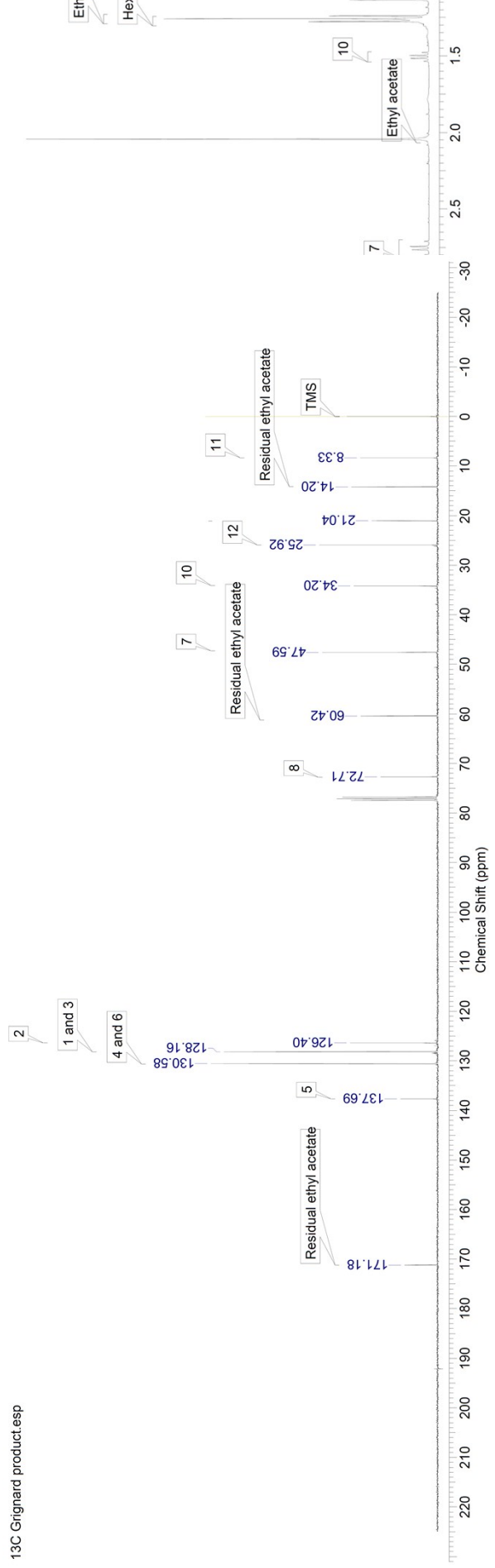
Ene-ol esp

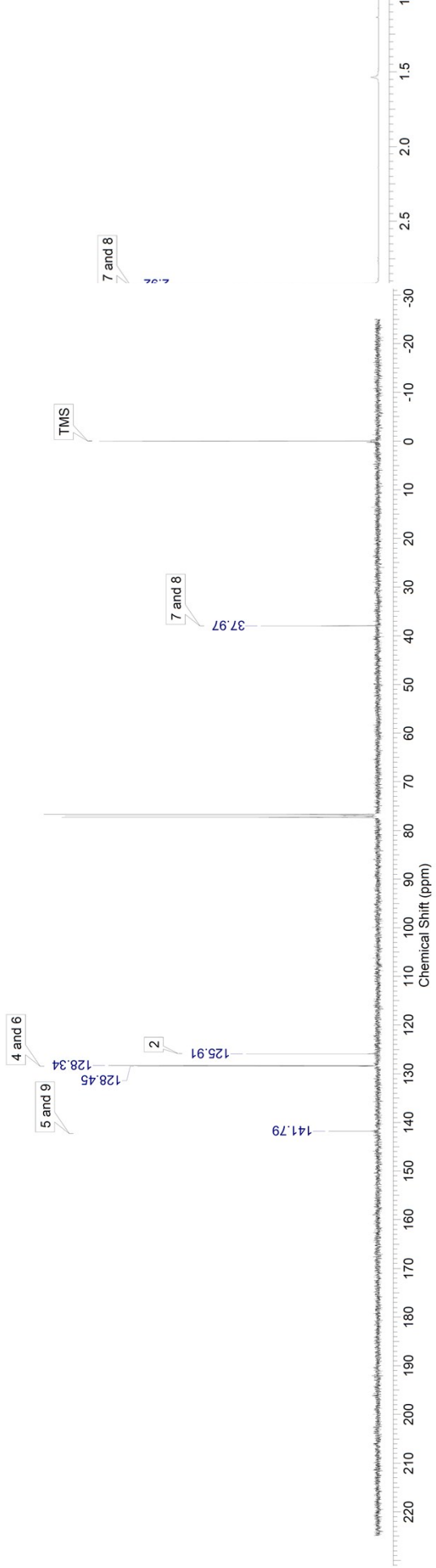


Pure Diene 1.esp

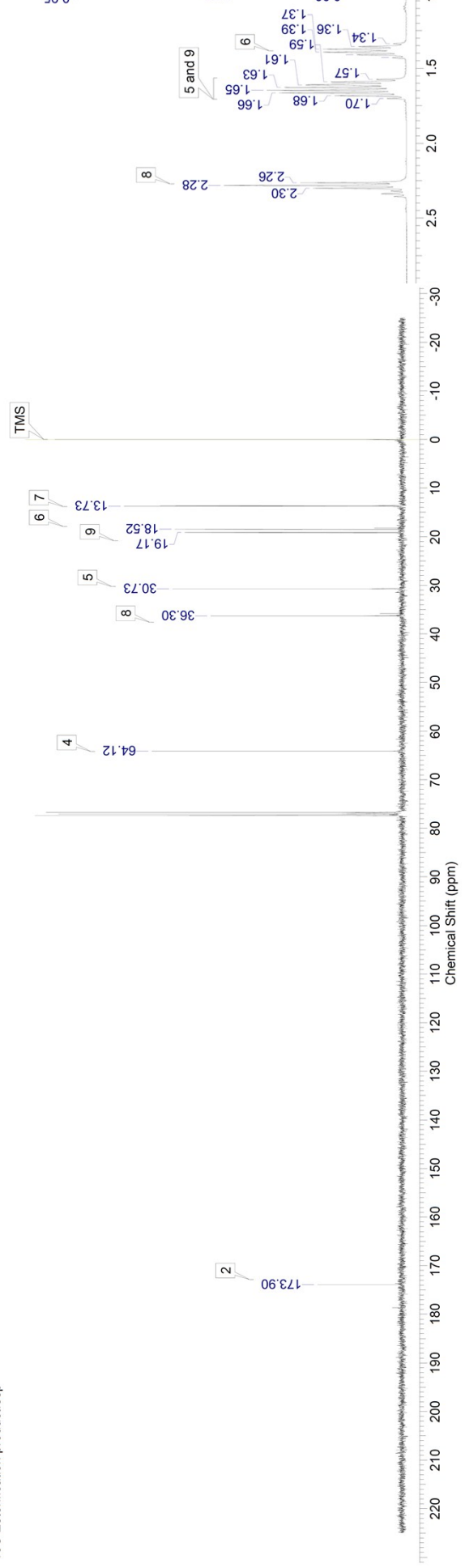


13C Grignard product.esp





13C Esterification product esp



13C Amidation product. esp

