Electronic Supplementary Material (ESI) for RSC Sustainability.

Supporting information

Eco-Friendly Synthesis of Cardanol-Based AB Monomer for Formaldehyde-Free Phenolic Thermosets

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1. General information

Materials: Cardanol (NX 2026) was provided by Cardolite. Sulfuric acid (H_2SO_4), phosphorous acid, phosphotungstic acid, formic acid, sodium periodate ($NaIO_4$), p-toluenesulfonic acid (APTS), t-amyl alcohol, magnesium sulfate, silica and 30%/50%-hydrogen peroxide were purchased from Sigma-Aldrich. Cyclohexane, acetonitrile (MeCN), ethanol and ethyl acetate were purchased from Analytic Lab. All these reagents were used as received.

Characterizations and measurements. All new compounds were characterized by spectroscopic data. Reactions were monitored by TLC using aluminium silica gel ($60F_{254}$). They were carried out on a plate of 0.20 mm silica gel. For revelations, UV (λ = 254 nm) light was provided (Universal UV lamp CAMAC). A phosphomolybdic acid solution or $KMnO_4$ solution was used to reveal the TLC plate if necessary. Purification by flash chromatography was performed using silica gel 60H (40-63µ).

Nuclear magnetic resonance (NMR). The NMR spectra were recorded on a Brüker DRX 300 or Brüker ALS 300 (^1H: 300 MHz, ^{13}C: 75 MHz). Chemical shifts are given with reference to residual DMSO or $CHCl_3$ central peaks: 2.50 and 7.26 ppm for proton, 39.52 and 77.16 ppm for carbon, respectively. *J* values are given in Hertz (Hz). Abbreviations are defined as follows: s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quadruplet, qt = quintet, hex = hexuplet, hept = heptuplet, m = multiplet, br = broad.

Gas chromatography (GC). The gas chromatography analyses were performed using a Shimadzu GC (GC-2025) apparatus equipped with a ZB-5-MS capillary column (30 m length, 0.25 mm i.d., 0.25 µm film thickness). The carrier gas was N_2, at a total flow of 113.2 mL/min, a column flow at 1.09 mL/min and the injection mode is split (ratio 1:100). The column temperature was initially at 100°C for 3 min, and then was gradually increased to 315°C (35°C/min) and the temperature was kept during 6 min. The injector and FID temperature were respectively set at 250°C and 315°C.

Mass spectroscopy (MS). The mass spectra were performed in positive-ion mode on a hybrid quadrupole time-of-flight mass spectrometer (MicroTOFQ-II, Bruker Daltonics, Bremen) with an Electrospray Ionization (ESI) ion source. The flow of spray gas was at 0.6 bar and the capillary voltage was 4.5 kV. The solutions were injected at 180 µL/h in a mixture of solvents (methanol/dichloromethane/water 45/40/15). The mass range of the analysis was 50-1000 m/z and the calibration was done with sodium formate.

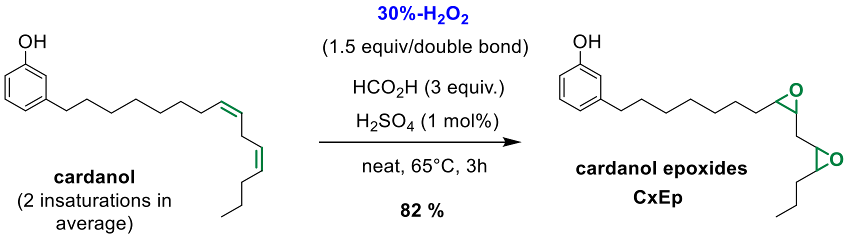
Infra-red (IR). The infra-red spectra were recorded in a SMART iTR-Nicolet iS10 spectrometer using Attenuated Total Reflectance (ATR) and the wave numbers are expressed in cm^{-1}. A first estimate of the melting point of some of our solids was performed on a Köfler bench, then it was done precisely with a BUCHI Melting point (SMPIO).

Thermogravimetric analysis (TGA). The thermogravimetric analysis (under air) of the polymers (ca. 10 mg) was carried out using a TA Instruments TGA 51 apparatus. The polymer samples were heated from room temperature to 500 °C at a heating rate of 10 °C min^{-1}.

Differential scanning calorimetry (DSC). DSC analyses, under a N_2 atmosphere, of the purified polymers (ca. 10 mg) were carried out using a TA Instruments Q100 instrument equipped with the DSC 200 F3 software. The instrument was calibrated with noble metals and checked before analysis with an indium sample (Tm = 156 °C). The heating or cooling range was from −50 °C to 150 °C at a scanning rate of 20 °C min^{-1} .

2. Procedures for the route b1 (using $NaIO_4$)

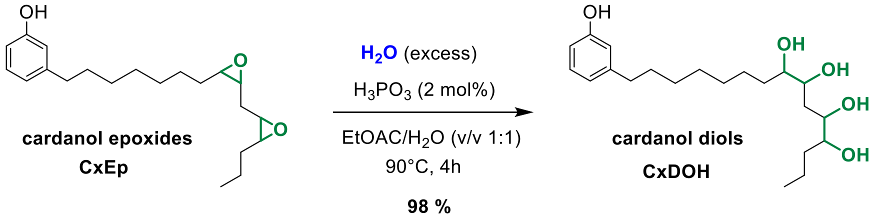
Epoxidation of cardanol to cardanol epoxides (CxEp).



Cardanol (20 g, 66.45 mmol, 1 equiv.), formic acid (9.169 g, 199.35 mmol, 3 equiv.) and H_2SO_4 (0.065 g, 0.66 mmol, 0.01 equiv.) were mixed and heated at 50°C. 30%-H_2O_2 (132.9 mmol/double bond, 1.5 equiv./double bond) was added dropwise to the mixture which was stirred at 65°C for three hours. After the completion of the reaction, there was two phases, one aqueous, one organic. The organic phase was diluted with ethyl acetate (25 mL). Water was removed by liquid/liquid extraction. The organic phase was then washed three times with water (25 mL) and dried over $MgSO_4$. After filtration, the filtrate was concentrated under vacuum.

CxEp: 18.1 g Isolated yield 82%, colorless liquid oil, ^1H NMR (300 MHz, $CDCl_3$), δ (ppm). 0.84-0.93 (m, CH_3), 0.96-1.01 (m, CH_3) 1.23–1.40 (m, CH_2), 1.41–1.63 (m, CH_2), 1.63–1.68 (m, CH_2), 1.73–1.85 (m, CH_2), 1.99-2.05 (m, CH_2-CH-EPoxy), 2.20-2.46 (m, CH_2-CH-Epoxy) 2.50-2,58 (m, CH_2), 2.78–2.85 (m, CH_2), 2.93–3.05 (m, CH-Epoxy), 3.08–3.22 (m, CH-Epoxy), 4.92–5.93 (remaining unsaturated bonds), 6.60–6.69 (m, aromatic CH), 6.69–6.73 (m, aromatic CH), 7.12 (t, *J* = 7.6, 0.8 Hz, aromatic CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm). 14.13 (CH_3), 22.54 (CH_2), 26.12-35.8 (CH_2 alkyl chain), 54.36–57.78 (CH epoxy group), 112.6 (aromatic CH), 115.41 (aromatic CH) 115–117.4 (remaining CH_2=), 120.63 (aromatic CH), 129.4 (aromatic CH), 125.8–136.5 (remaining unsaturated bonds).

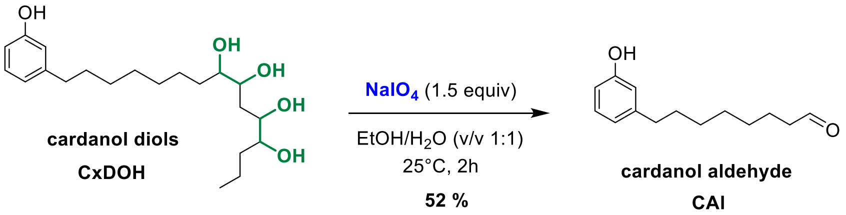
Hydrolysis of epoxidized cardanol to cardanol diols (CxDOH).



In a 100-mL round-bottom flask, **CxEp** (16.8 g, 48.55 mmol, 1 equiv.) was mixed with phosphorous acid (79.63 mg, 0.97 mmol, 0.02 equiv.), ethyl acetate (15ml) and water (15 ml) at 90°C for 4 h under mechanical stirring at reflux. Water was removed from the mixture by liquid-liquid extraction then the mixture was diluted in ethyl acetate (10 ml), washed three times with water (10 ml) and dried over $MgSO_4$. After filtration, the solvent of the organic layer was removed by vacuum.

CxDOH: 17.5 g Isolated yield 98%, colorless liquid oil, ^1H NMR (300 MHz, $CDCl_3$), δ (ppm). 0.83-0.94 (m, CH_3), 1.21–1.37 (m, CH_2), 1.37–1.50 (CH_2), 1.51–1.62 (m, CH_2), 1.63–1.69 (m, CH_2), 1.84–1.95 (m, CH_2), 1.98-2.10 (m, CH_2), 2.21-2.40 (m, CH_2), 2.48–2.56 (m, CH_2), 2.75–2.82 (m, CH_2), 3.38–3.80 (m, CH-OH), 4.05–4.26 (m, CH-OH), 4.93–5.89 (remaining unsaturated bonds), 6.62–6.67 (m, aromatic CH), 6.67–6.72 (m, aromatic CH), 7.11 (dd, J = 7.6, 0.8 Hz, aromatic CH). ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm). 14.27 (CH_3), 22.70 (CH_2), 24.98-26.1 (CH_2), 28.42-35.66 (CH_2 alkyl chain), 70-74.73 (CH-OH), 112.68 (aromatic CH), 115.48 (aromatic CH) 115–117.4 (remaining CH_2=), 120.56 (aromatic CH), 126 (remaining unsaturated bonds), 129.26 (aromatic CH).

Oxidative cleavage of cardanol diols to cardanol-aldehyde (CAl).

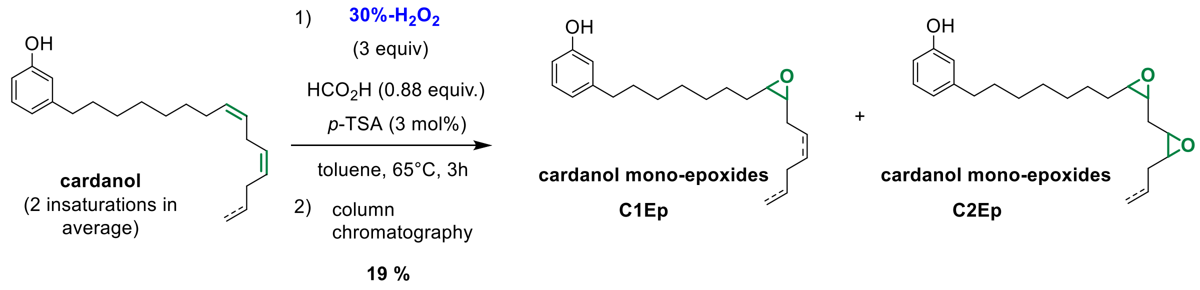


To a stirred solution of **CxDOH** (17.2 g, 43.32 mmol, 1 equiv.) in ethanol (15 mL)-H_2O (15 mL) at 25°C, $NaIO_4$ was added portion wise (13.9 g, 65 mmol 1.5 equiv.). After stirring for 2 h, the reaction mixture was filtered, the filtrate concentrated in *vacuo* and the residue extracted with ethyl acetate (25 ml), washed three times with water (25 ml). After drying with $MgSO_4$, the organic extract was concentrated, and the crude product was purified by chromatography on a silica column (cyclohexane/ethyl acetate 9:1).

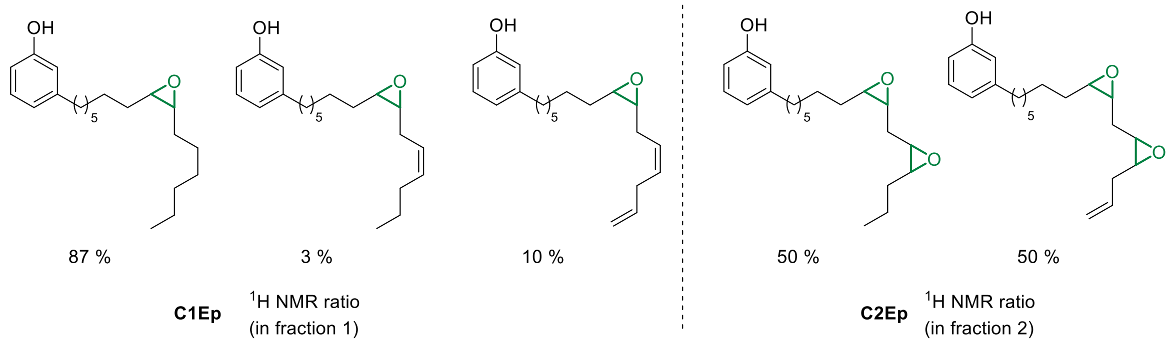
CAl: Yield before column: 95%. Isolated yield 52% 4.8 g, colorless liquid oil, ^1H NMR (300 MHz, d_6-DMSO), δ_H (ppm). 1.17–1.34 (m, 6H, 3 CH_2), 1.41–1.59 (m, 4H, 2 CH_2), 2.41 (td, J = 7.2, 1.7 Hz, 2H, CH_2-C=O), 2.47 (t, J = 7.6 Hz, 2H, CH_2-Ph), 6.44–6.66 (m, 3H, aromatic CH), 7.04 (td, J = 7.3, 1.4 Hz, 1H, aromatic CH), 9.20 (s, OH), 9.66 (s, 1H, CHO). ^{13}C NMR (75 MHz, d_6-DMSO), δ_C (ppm) 22.0 (CH_2), 28.96 (CH_2), 28.97 (CH_2), 29.1 (CH_2), 31.3 (CH_2), 35.6 ($\underline{CH_2}$-Ph), 43.4 ($\underline{CH_2}$-CHO), 113.0 (CH^{Ar}), 115.6 (CH^{Ar}), 119.4 (CH^{Ar}), 129.5 (CH^{Ar}), 144.1 (Cq), 157.7 (Cq-OH), 204.0 ($Cq_{aldehyde}$).

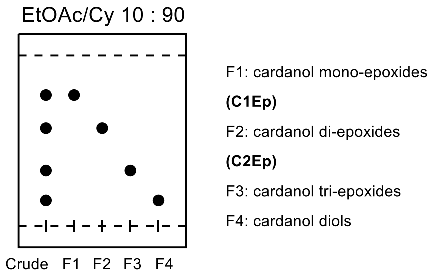
3. Procedures for the route c (thermal cleavage)

Epoxidation of cardanol to cardanol mono-epoxides (C1Ep).



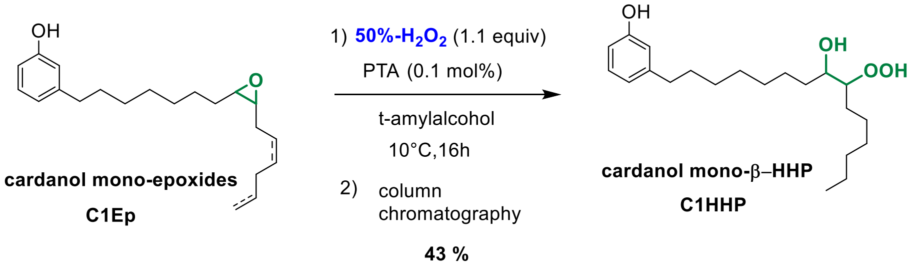
Following a modified procedure,[1] in a 250-mL flask equipped with a magnetic stirrer (800 rpm) and air condenser, cardanol (2 g, 6.8 mmol), formic acid (0.31 g, 6 mmol), *p*-toluenesulfonic acid (0.05 g, 0.232 mmol) were charged in toluene (2 mL). The mixture was slowly heated to 50 °C, and 30 wt% hydrogen peroxide (2.1 mL, 2.38 g (0.71 g of pure H_2O_2), 21 mmol) was added dropwise. The reaction was stirred at 65 °C for 3 h (the reaction was followed by TLC). The reaction mixture was quenched by a $NaHCO_3$ saturated solution (10 mL) and extracted with toluene (2*10 mL). The organic layers were combined and dried over Na_2SO_4, filtered and the filtrate was evaporated under reduced pressure to give the crude product. The residue was purified by column chromatography (cyclohexane/ethyl acetate 95:5 to 80:20). Two fractions were collected: fraction 1 with mono epoxides as major products (**C1Ep**, 400 mg, 20 % mass yield, 19 % yield based on the molar ratio of mono-epoxides (average M = 318.04 g/mol)) and fraction 2 with di-epoxides as major products (**C2Ep**, 400 mg, 20 % mass yield, 18% based on the molar ratio of di-epoxides (average M = 331.48 g/mol)).





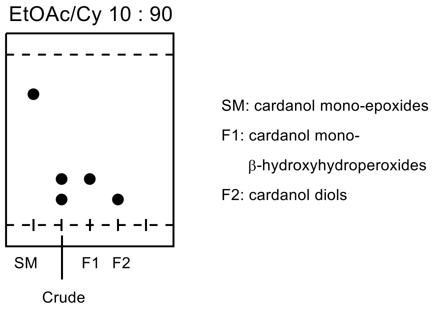
Representation of the TLC plate

Ring-opening of cardanol mono-epoxides to cardanol mono-β-hydroxy hydroperoxides (C1HHP).



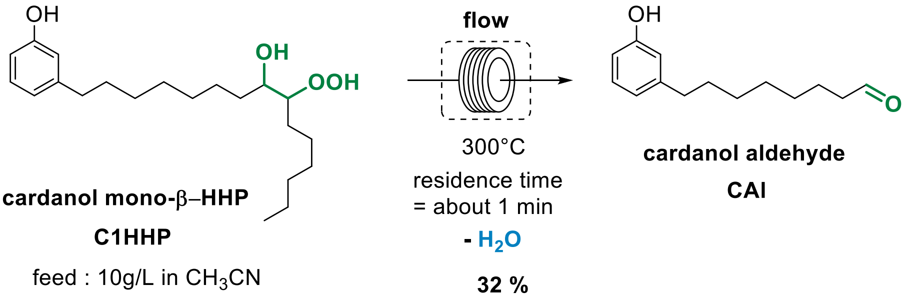
In a 100-mL double-jacketed glass reactor, a mixture of cardanol mono-epoxides **C1Ep** (400 mg, 1.2 mmol) was suspended/dissolved in t-amyl alcohol (5 mL). Phosphotungstic acid (4 mg, 0.1 mol %) was added followed by dropwise addition of H_2O_2 (50 wt% in water, 100 µL, 1.3 mmol, 1.1 equiv). The reactor was closed, purged with an argon atmosphere and stirred at 10°C for 16 hours (the reaction was monitored by GC and TLC). The reaction mixture was filtered over a celite pad and washed with ethyl acetate (10 mL). The filtrate was concentrated under reduced pressure to give the crude product. The residue was purified by column chromatography (cyclohexane/ethyl acetate 90:10 to 70:30).

C1HP (3-(8(9)-hydroperoxy-9(8)-hydroxypentadecyl)phenol): colorless liquid oil (0.175 mg, 43 % yield). ^{1}H NMR (300 MHz, *d*$_6$-DMSO) δ (ppm). δ_H (62:38 mixture of isomers) = 11.22 (s, 1H, OOH), 9.18 (s, 1H, Ar-OH), 7.03 (d, *J* = 1.4, 1H, H^{Ar}), 6.71–6.46 (m, 3H, H^{Ar}), 4.48 (d, *J* = 4.8, 1H, $OH_{\text{minor isomer}}$), 4.37 (d, *J* = 5.2, 1H, $OH_{\text{major isomer}}$), 3.90-3.55 (m, 2H, 2 CH), 2.46 (t, *J* = 7.2, 2H, CH_2), 1.69–1.12 (m, 22 H, 11 CH_2), 0.86 (t, *J* = 6.9, 3H, CH_3). ^{13}C NMR (75 MHz, *d*$_6$-DMSO) δ (ppm). δ_c = 157.21 (C^{Ar} -OH), 143.69 (C^{Ar}), 129.04 (C^{Ar}), 118.88 (C^{Ar}), 115.10 (C^{Ar}), 112.52 (C^{Ar}), 87.36 ($\underline{CH}$-OOH), 69.23 ($\underline{CH}$-OH), 35.16 (CH_2), 31.36 (CH_2), 31.22 (CH_2), 31.08 (CH_2), 30.88 (CH_2), 29.22 CH_2), 28.81 (CH_2), 28.68 (CH_2), 25.89 (CH_2), 25.75 (CH_2), 22.10 (CH_2), 22.06 (CH_2), 13.95 (CH_3). HRMS (ESI$^+$) for the major compound $[M+Na]^+$ $C_{21}H_{36}NaO_4$: requires 375.2506; found 375.2518.



Representation of the TLC plate.

Thermal cleavage of cardanol mono-β-hydroxy hydroperoxides to cardanol-aldehyde (CAl).



A solution of cardanol β-hydroxy-hydroperoxide **C1HHP** (0.150 g, 0.4 mmol) in CH_3CN (15 mL) was prepared with a concentration of 10 g/L. The solution was pumped through an oven heated at 300°C with a flow rate between 1 and 2 mL/min. Then, the solvent, heptanal and other potential volatile aldehydes were evaporated under reduced pressure to give 8-(3-hydroxyphenyl)octanal (**CAl**) (30 mg, 32 %) as a colorless oil.

4. GC chromatogram

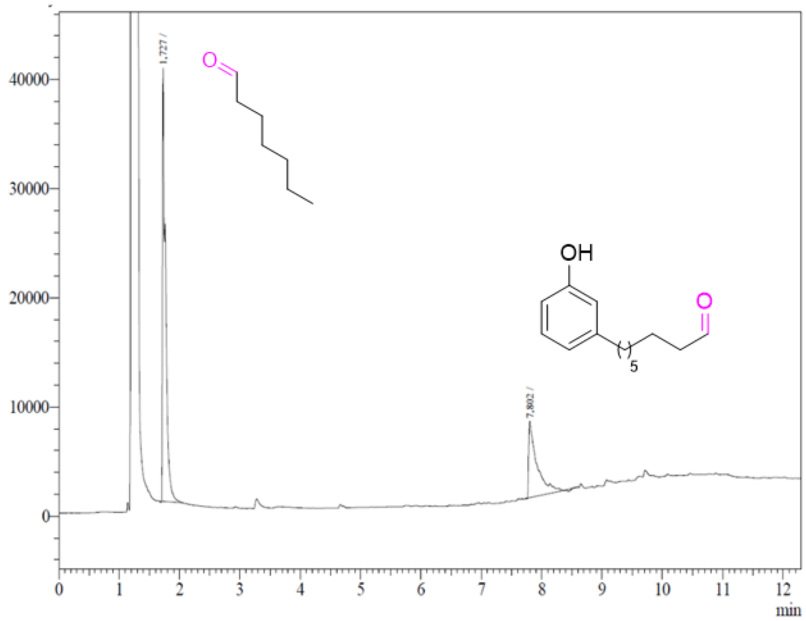


Figure S1: GC chromatogram of cardanol mono-β-hydroxy hydroperoxide (**C1HHP**), showing its degradation to heptanal and cardanol-aldehyde (**CAl**). Injector temperature = 300°C (GC method and detailed conditions are given the general information).

5. DSC of cardanol mono-β-hydroxy hydroperoxides **C1HHP**

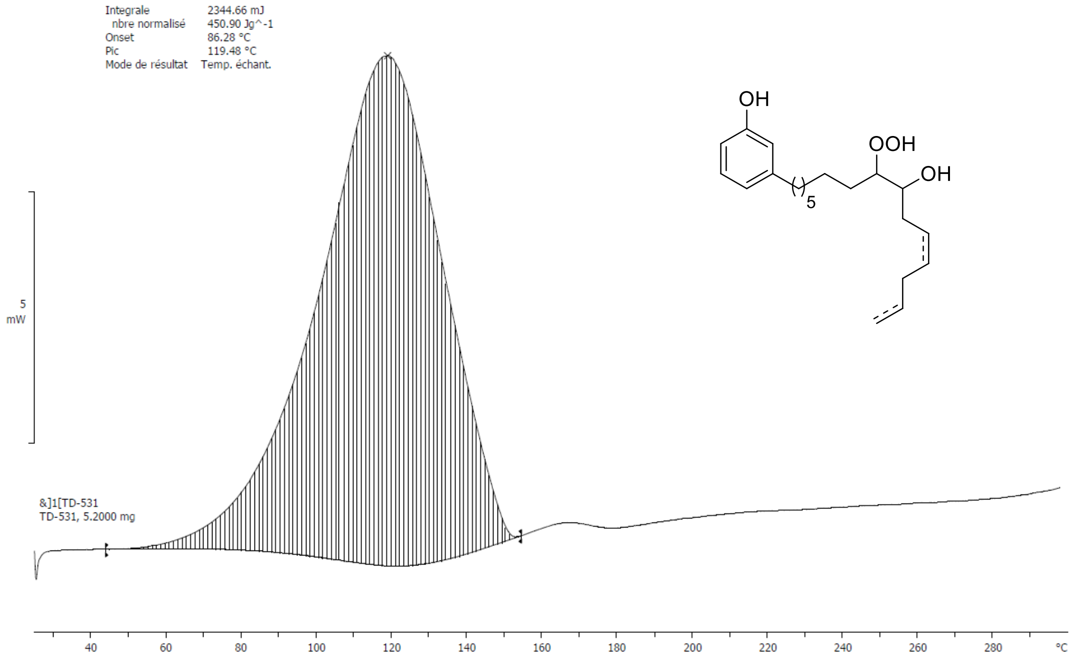
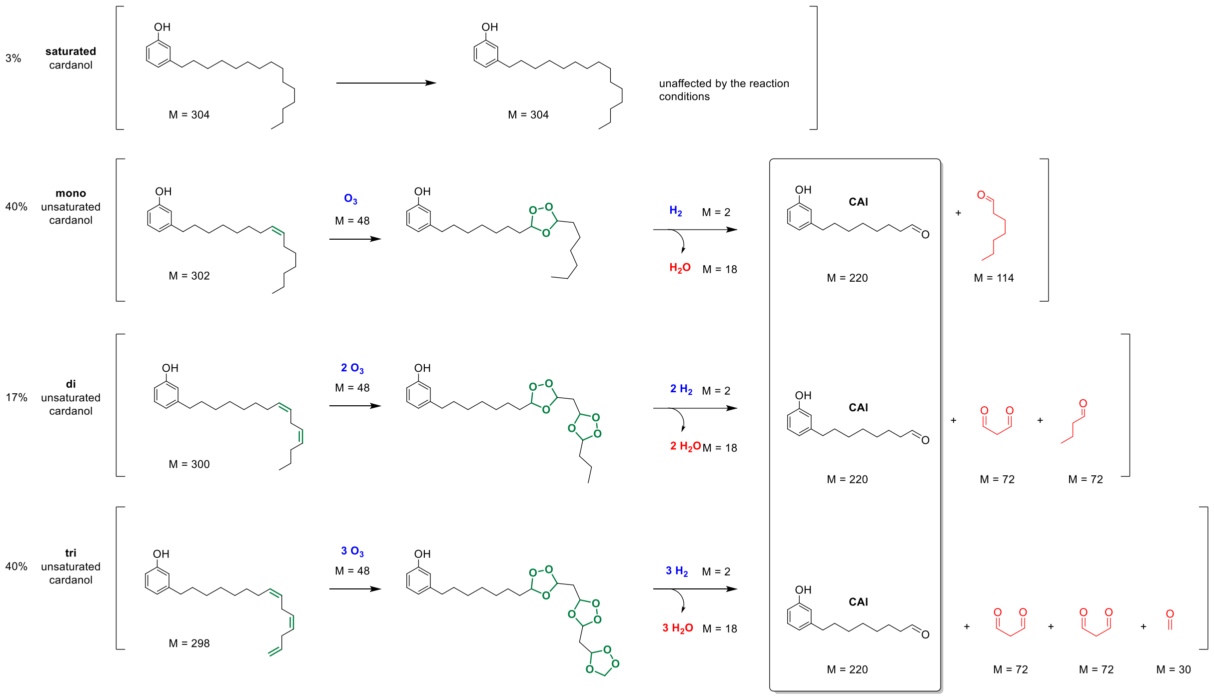


Figure S: DSC of cardanol mono-β-hydroxy hydroperoxide (**C1HHP**).

6. Calculations of green metrics

6.1. Atom economy

1. Atom-economy of Route a (Reductive ozonolysis)



Cardanol	$M_{\text{reactants}}$	Sum $M_{\text{reactants}}$	$M_{\text{products and waste}}$	Sum $M_{\text{products and waste}}$	Sum M(CAl)
Saturated (3%)	304	0.03 * 304 = 9.12	304	0.03 * 304 = 9.12	0
Mono-unsaturated (40%)	302 + 48 + 2 = 352	0.40 * 352 = 140.8	18 + 220 + 114 = 352	0.40 * 352 = 140.8	0.40 * 220 = 88
Di-usaturated (17%)	300 + 2 * 48 + 4 = 400	0.17 * 400 = 68	2 * 18 + 220 + 72 + 72 = 400	0.17 * 400 = 68	0.17 * 220 = 37.4
Tri-unsaturated (40%)	298 + 3 * 48 + 6 = 448	0.40 * 448 = 179.2	3 * 18 + 220 + 72 + 72 + 30 = 448	0.40 * 448 = 179.2	0.40 * 220 = 88
Total reactants		**397.12**	**Total products**	**397.12**	**0.97 * 220 = 213.4**

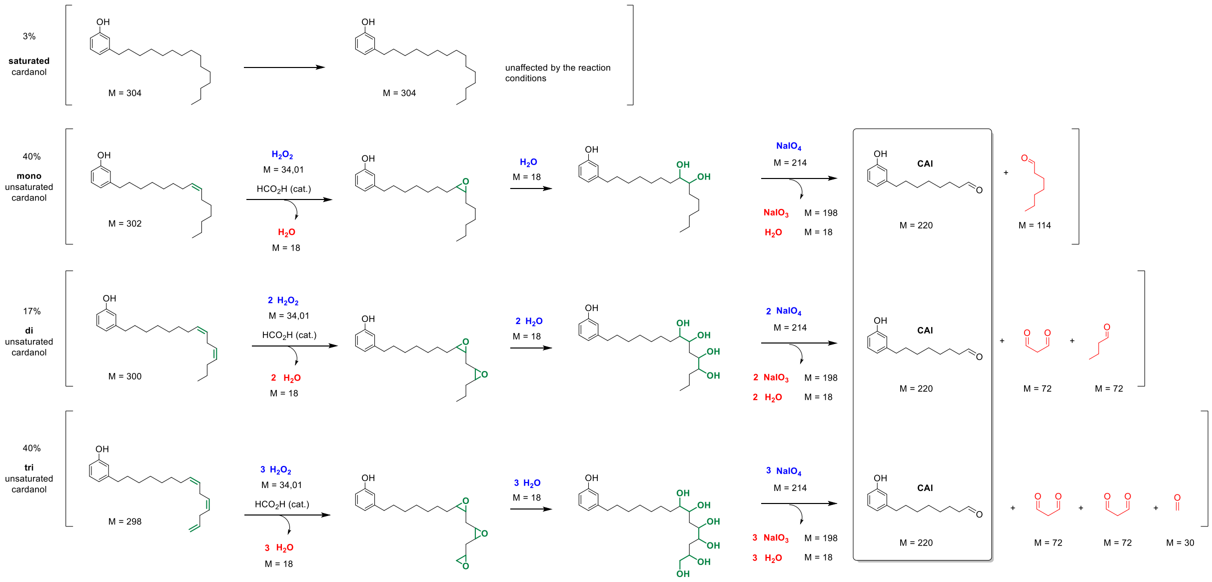
All molar masses are given in g.mol^{-1}.

Atom-economy (Route a) = M(CAl) / M(reactants) * 100 = 213.4 / 397.12 *100 = 53.7%, **~ 54%**

$M_{\text{(recovered aldehydes)}}$ = 0.40 * 114 + 0.17 * (72 + 72) + 0.40 * (72 + 72 + 30) = 139.68

Atom-economy (Route a with recovery of aldehydes) = [M(CAl) + M(aldehydes)] / M(reactants) * 100 = (213.4 + 139.68) / 397.12 *100 = 88.9%, **~ 89%**

2. Atom-economy of Route b1 (cleavage of diols with $NaIO_4$)



Cardanol	**M$_{\text{reactants}}$**	**Sum M$_{\text{reactants}}$**	**M$_{\text{products and waste}}$**	**Sum M$_{\text{products and waste}}$**	**Sum M(CAl)**
Saturated (3%)	304	0.03 * 304 = 9.12	304	0.03 * 304 = 9.12	0
Mono-unsaturated (40%)	302 + 34 + 18 + 214 = 568	0.40 * 568 = 227.2	18 + 198 + 18 + 220 + 114 = 568	0.40 * 568 = 227.2	0.40 * 220 = 88
Di-usaturated (17%)	300 + 2 * 34 + 2 * 18 + 2 * 214 = 832	0.17 * 832 = 141.44	2 * 18 + 2 * 198 + 2 * 18 + 220 + 72 + 72 = 832	0.17 * 832 = 141.44	0.17 * 220 = 37.4
Tri-unsaturated (40%)	298 + 3 * 34 + 3* 18 + 3 * 214 = 1096	0.40 * 1096 = 438.40	3 * 18 + 3 * 198 + 3 * 18 + 220 + 72 + 72 + 30 = 1096	0.40 * 1096 = 438.40	0.40 * 220 = 88
Total reactants		**816.16**	**Total products**	**816.16**	**0.97 * 220 = 213.4**

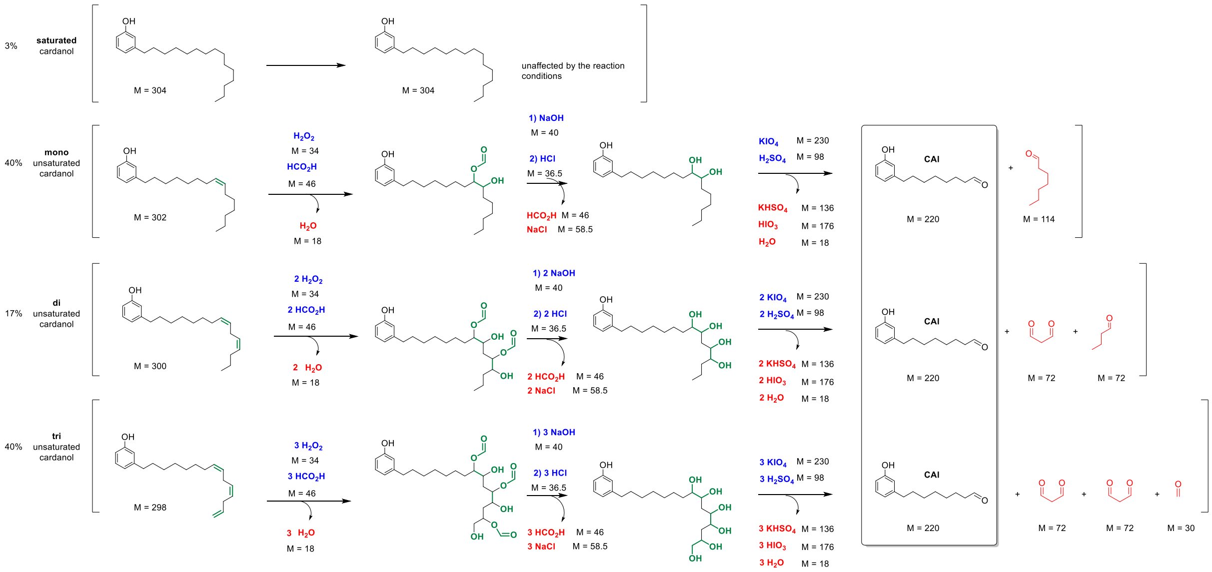
All molar masses are given in g.mol^{-1}.

<u>Atom-economy (Route b1)</u> = M(CAl) / M(reactants) * 100 = 213.4 / 816.16 *100 = 26.1%, **~ 26%**

$M_{\text{(recovered aldehydes)}}$ = 0.40 * 114 + 0.17 * (72 + 72) + 0.40 * (72 + 72 + 30) = 139.68

<u>Atom-economy (Route b1 with recovery of aldehydes)</u> = [M(CAl) + M(aldehydes)] / M(reactants) * 100 = (213.4 + 139.68) / 816.16 *100 = 43.3%, **~ 43%**

3. Atom-economy of Route b2 (cleavage of diols with KIO$_4$)



Cardanol	$M_{reactants}$	Sum $M_{reactants}$	$M_{products\ and\ waste}$	Sum $M_{products\ and\ waste}$	Sum M(CAl)
Saturated (3%)	304	0.03 * 304 = 9.12	304	0.03 * 304 = 9.12	0
Mono-unsaturated (40%)	302 + 34 + 46 + 40 + 36.5 + 230 + 98 = 786.5	0.40 * 786.5 = 314.6	18 + 46 + 58.5 + 136 + 176 + 18 + 220 + 114 = 786.5	0.40 * 786.5 = 314.6	0.40 * 220 = 88
Di-usaturated (17%)	300 + 2 * 34 + 2 * 46 + 2* 40 + 2* 36.5 + 2 * 230 + 2 * 98 = 1269	0.17 * 1269 = 215.73	2 * 18 + 2 * 46 + 2 * 58.5 + 2 * 136 + 2 * 176 + 2* 18 + 220 + 72 + 72 = 1269	0.17 * 1269 = 215.73	0.17 * 220 = 37.4
Tri-unsaturated (40%)	298 + 3 * 34 + 3 * 46 + 3 *40 + 3 * 36.5 + 3 * 230 + 3 * 98 = 1751.5	0.40 * 1751.5 = 700.6	3 * 18 + 3 * 46 + 3 * 58.5 + 3 * 136 + 3 * 176 + 3 * 18 + 220 + 72 + 72 + 30 = 1751.5	0.40 * 1751.5 = 700.6	0.40 * 220 = 88
Total reactants		**1240.05**	**Total products**	**1240.05**	**0.97 * 220 = 213.4**

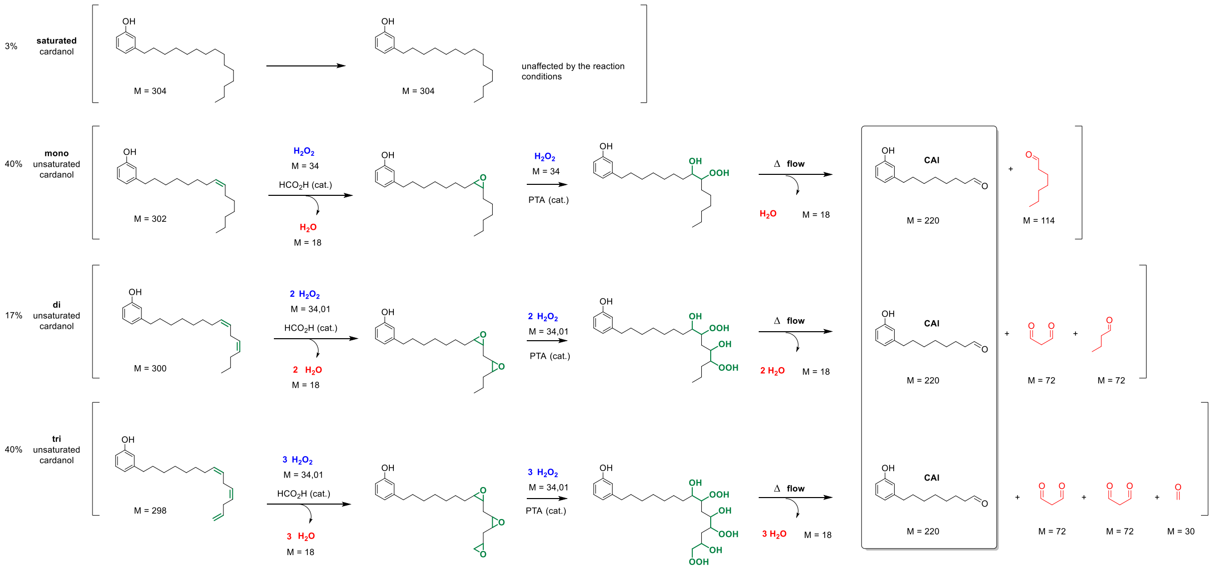
All molar masses are given in g.mol^{-1}.

Atom-economy (Route b2) = M(CAl) / M(reactants) * 100 = 213.4 / 1240.05 *100 = 17.2%, **~ 17%**

$M_{(recovered\ aldehydes)}$ = 0.40 * 114 + 0.17 * (72 + 72) + 0.40 * (72 + 72 + 30) = 139.68

Atom-economy (Route b2 with recovery of aldehydes) = [M(CAl) + M(aldehydes)] / M(reactants) * 100 = (213.4 + 139.68) / 1240.05 *100 = 28.5%, **~ 28%**

4. Atom-economy of Route c (thermal cleavage of β-hydroxy hydroperoxides)



Cardanol	$M_{reactants}$	Sum $M_{reactants}$	$M_{products\ and\ waste}$	Sum $M_{products\ and\ waste}$	Sum M(CAl)
Saturated (3%)	304	0.03 * 304 = 9.12	304	0.03 * 304 = 9.12	0
Mono-unsaturated (40%)	302 + 34 + 34 = 370	0.40 * 370 = 148	18 + 18 + 220 + 114 = 370	0.40 * 370 = 148	0.40 * 220 = 88
Di-usaturated (17%)	300 + 2 * 34 + 2 * 34 = 436	0.17 * 436 = 74.12	2 * 18 + 2 * 18 + 220 + 72 + 72 = 436	0.17 * 436 = 74.12	0.17 * 220 = 37.4
Tri-unsaturated (40%)	298 + 3 * 34 + 3* 34 = 502	0.40 * 502 = 200.8	3 * 18 + 3 * 18 + 220 + 72 + 72 + 30 = 502	0.40 * 502 = 200.8	0.40 * 220 = 88
Total reactants		**432.04**	**Total products**	**432.04**	**0.97 * 220 = 213.4**

All molar masses are given in g.mol^{-1}.

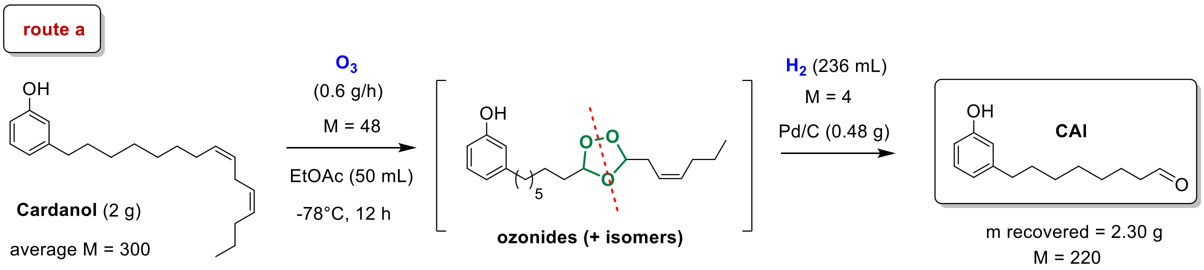
Atom-economy (Route c) = M(CAl) / M(reactants) * 100 = 213.4 / 432.04 *100 = 49.4%, **~ 49%**

$M_{(recovered\ aldehydes)}$ = 0.40 * 114 + 0.17 * (72 + 72) + 0.40 * (72 + 72 + 30) = 139.68

Atom-economy (Route c with recovery of aldehydes) = [M(CAl) + M(aldehydes)] / M(reactants) * 100 = (213.4 + 139.68) / 432.04 *100 = 81.7%, **~ 82%**

6.2. E factor

1. E factor of Route a (Reductive ozonolysis)[1]



Reactants / solvents/ catalysts	MW (g /mol)	Mass (g)	d	Volume (mL)	n (mmol)	role
Cardanol	300	2.00	-	-	6.67	Starting material
O_3	48	7.20[a]	-	-	150	oxidant
EtOAc	88	45.1	0.902	50	512.5	solvent
H_2	2	0.021[b]		236	10.54	reductant
5%-Pd / C		0.48	-	-		catalyst
Total		**54.8 g**				

The highlighted cells are the values directly taken from the reference given below. [a] The mass of ozone has been calculated with a flow of 0.6g/h for a period of 12 hours. [b] The mass of hydrogen has been calculated for a volume of 236 mL ($V_M = 22.4$ L.mol^{-1}).

The authors have recovered 2.30 g of a mixture containing unreacted cardanol (3% of the starting material) and **CAl** and other volatile aldehydes. The global yield has been calculated to 95% (see calculations of reductive ozonolysis yield).

Theoretical mass of CAl = n(cardanol) * %cleavable cardanol * M(**CAl**) = 6.67 * 0.97 * 220 = 1.42 g

Experimental mass of CAl = Theoretical mass of **CAl** * yield = 1.42 * 0.95 = **1.35 g**

E Factor (route a) = ∑[m(reactants) +m(solvents) + m(catalyst) - m(**CAl**)] / m(**CAl**) = (54.8 – 1.35) /1.35 = 39.6, ~ **40**

E Factor (route a) with 100% recovery of solvents = ∑[m(reactants) + m(catalyst) - m(**CAl**)] / m(**CAl**) = (9.7 – 1.35) / 1.35 = 6.2, ~ **6**

E Factor (route a) with 100% recovery of solvents and aldehydes as co-products = ∑[m(reactants) + m(catalyst) – (m(**CAl**) – m(other aldehydes)] / [m(**CAl**) + m(other aldehydes)] = (9.7 – 2.30) / 2.30 = 3.2, ~ **3**

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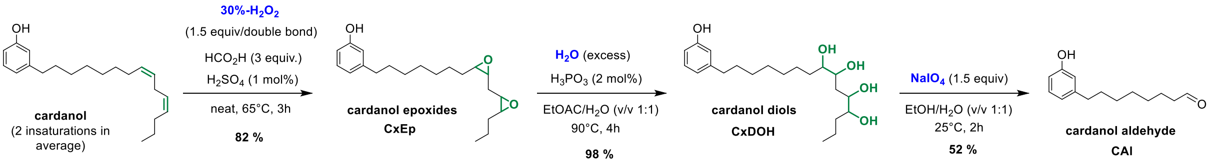
[1] M. B. Graham and H. P. Tyman, *J. Am. Oil Chem. Soc.*, 2002, **79**, 725-732.

2. E factor of Route b1 ($NaIO_4$)[2]



Reactants / solvents/ catalysts	MW (g /mol)	Mass (g)	d	Volume (mL)	n (mmol)	role
Cardanol	300[a]	20	-	-	66.45	Starting material
HCO_2H	46	9.169	1.22	7.5	199.35	Catalyst
H_2SO_4	98	0.065	1.83	0.036	0.66	Catalyst
30% H_2O_2	34	15.06	1.11	13.6	132.9	Oxidant
EtOAc	88	23	0.92	25	261.4	Solvent
H_2O	18			75		Solvent/washing
Total (step 1)		**67.29 g**[b]				
H_3PO_3	82	0.07963	1.65	-	0.97	Catalyst
EtOAc	88	13.8	0.92	15		Solvent
H_2O	18	15	1	15	833.3	Reactant
EtOAc	88	9.2	0.92	10		Solvent extraction
H_2O	18		1	30		Solvent/washing
Total (step 2) for 16.8 g of epoxides		38.08 g [b]				
Total (step 2) for 18.1 g of epoxides		**41.01 g**[d] (38.08 * 18.1/16.8)				
EtOH	46	11.84	0.789	15	257.4	Solvent
H_2O	18	15	1	15	833.3	Solvent
$NaIO_4$	214	13.9	-	-	65	Oxidant
EtOAc	88	23	0.92	25		Solvent
H_2O	18			75		Solvent/washing
Cyclohexane	84	1755	0.78	2250	20893	Solvent chromato
EtOAc	88	230	0.92	250	2614	Solvent chromato
Total (step 3) for 17.2 g of diols		2049 g [b]				
Total (step 3) for 17.5 g of diols		2085 g[b] (2049 * 17.5/17.2)				
Total (step 3) for 18.1 g of epoxides		**2246 g**[b](2085 * 18.1/16.8)				
Total (steps 1-3)		**2354 g**[b]				

The highlighted cells are the values directly taken from the reference given below. [a] *Average molecular weight of cardanol (calculated with 3% of saturated, 40% of mono-unsaturated, 17% of di-unsaturated and 40% of tri-unsaturated).* [b] *Water used for washing was not considered.*

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[2] This work

For the first step, 20 g of cardanol were used and 18.1 g of **CxEp** were recovered. For the second step, 16.8 g of **CxEp** were used and 17.5 g of **CxDOH** were recovered. For the third step, 17.2 g of **CxDOH** of were used and 4.8 g of **CAl** were recovered after column chromatography. Considering that the total amount of intermediates was not used for the each step, the quantity of **CAl** should be adjusted for the right calculations of the E factor. This would mean that 5.26 g of **CAl** would have been recovered (4.8 * (17.5/17.2) * (18.1/16.8)) in this case.

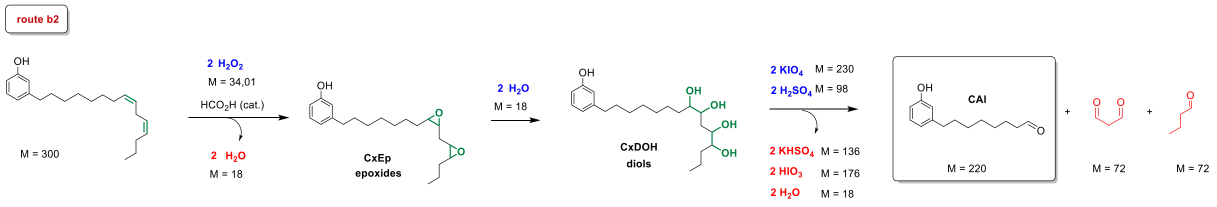
<u>E Factor (route b1)</u> = ∑[m(waste)] / m(**CAl**) = ∑[m(reactants) +m(solvents) + m(catalyst) – m(**CAl**)] / m(**CAl**) = (2354 – 5.26) / 5.26 = 446.5 ~ **447**

<u>E Factor (route b1) with 100% recovery of solvents</u> = ∑[m(reactants) + m(catalyst) – m(**CAl**)] / m(**CAl**)] = (75.76 – 5.26) / 5.26 = 13.4, ~ **13**

<u>E Factor (route b1) with 100% recovery of solvents and aldehydes as co-products</u> = ∑[m(reactants) + m(catalyst) – m(**CAl**) – m(other aldehydes)*] / [m(**CAl**) + m(other aldehydes)*] = (75.76 – 8.60) / 8.60 = 7.8, ~ **8**

* The quantity of other aldehydes was calculated as follow:
n(other aldehydes = n (**CAl**) = 5.26 / 220 = 23.9 mmol
m(other aldehydes) = n(other aldehydes) * average M(other aldehydes) = 0.0239 * 139.68 = 3.34 g

3. E factor of Route b2 (KIO_4/H_2SO_4)[3]



Reactants / solvents/ catalysts	MW (g /mol)	Mass (g)	d	Volume (mL)	n (mmol)	role
Cardanol	300[a]	2.69	-	-	8.97	Starting material
98% HCO_2H	46	21.05	1.22	17.25	457.6	Reactant/solvent/cat.
30% H_2O_2	34	1.1	1.11	50	32.4	Oxidant
H_2O				*no data*		Solvent
NaCl sat.				100		Solvent/washing
Et_2O	74	142.8	0.714	200[b]	1930	Solvent
1M NaOH	40	1.2	-	30	30	base
1M[c] HCl	36.5	1.1	-	30[c]	30	acid
Et_2O	74	142.8	0.714	200	1930	Solvent
Total (steps 1&2)		**312.74 g**[d]				
EtOH	46	47.34 (82.25)	0.789	60	1.03	Solvent
KIO_4	230	1.50 (2.61)	-	-	6.52	Oxidant precursor
1M H_2SO_4	98	7.35 (12.77)	-	75	75	Oxidant precursor
H_2O				*no data*		Solvent
Et_2O	74	71.4 (124.06)	0.714	100[e]	1930	Solvent
Total (step 3) for 0.8 g of polyols		127.59 g [d]				
Total (step 3) for 1.39 g of polyols		**221.69 g**[d]				
Total (steps 1-3)		**534.43 g**[d]				

The highlighted cells are the values directly taken from the reference given below. [a] Average molecular weight of cardanol (calculated with 3% of saturated, 40% of mono-unsaturated, 17% of di-unsaturated and 40% of tri-unsaturated). [b] No data, extrapolated from the data of the second step. [c] No data, extrapolated from the quantity of NaOH used. [d] Water, aqueous saturated NaCl solution and Na_2SO_4 were not considered. [e] No data, extrapolated from the average concentration of Et_2O used for extraction.

According to the article, the authors have recovered 1.39 g of trans-polyols from 2.69 g of cardanol. Then, they used 0.8 g of polyols to form 0.61 g of a mixture of CAl and heptanal. For the right calculations of the E factor, the quantities should be adjusted to 1.39 g of polyols, meaning that 1.06 g of a mixture of CAl and heptanal would have been recovered in that case. Therefore, the mass of polyols obtained as product after steps 1&2 and used as a starting material in step 3 could be ignored as it is a reaction intermediate.

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[3] M. B. Graham and H. P. Tyman, *J. Am. Oil Chem. Soc.*, 2002, **79**, 725-732.

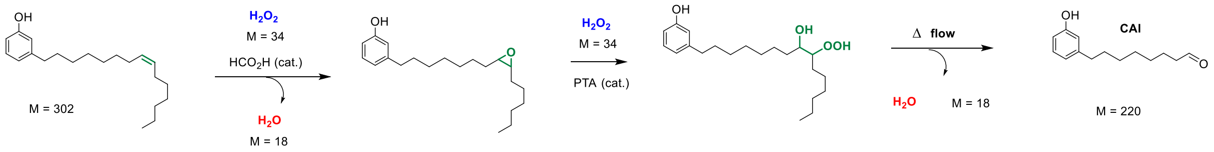
Considering that the data is given for the mixture of CAl and heptanal, the mass of CAl recovered was calculated as follow: mass mixture / [(M(CAl) / (M(CAl) + Mheptanal)] = 1.06 / (220/(220+114)) = 0.74 g of CAl would have been recovered.

E Factor (route b2) = $\sum$[m(waste)] / m(**CAl**) = $\sum$[m(reactants) +m(solvents) + m(catalyst) − m(**CAl**)] / m(**CAl**) = (534.43 – 0.74) / 0.74 = **721**

E Factor (route b2) with 100% recovery of solvents = $\sum$[m(reactants) + m(catalyst) – m(**CAl**)] / m(**CAl**)] = (21.47 – 0.74) / 0.74 = 28.0, ~ **28**

E Factor (route b2) with 100% recovery of solvents and aldehydes as co-products = $\sum$[m(reactants) + m(catalyst) – m(**CAl**) – m(other aldehydes)] / [m(**CAl**) + m(other aldehydes)] = (21.47 – 1.06) / 1.06 = 19.3, ~ **19**

4. E factor of Route c (Thermal cleavage)[4]



Reactants / solvents/ catalysts	MW (g /mol)	Mass (g)	d	Volume (mL)	n (mmol)	role
Cardanol	300^a	2	-	-	6.67	Starting material
HCO_2H	46	0.31	1.22	0.25	6.74	Catalyst
p-TSA	172	0.05	-	-	0.29	Catalyst
Toluène	92	1.74	0.87	2	18.91	Solvent
30% H_2O_2	34	2.38	1.11	2.1	21	Oxidant
$NaHCO_3$ solution	84	-	-	10	-	Solvent washing
Toluène	92	17.4	0.87	20	189.1	Solvent extraction
Cyclohexane	84	175.5	0.78	225^b	-	Solvent chromato
EtOAc	88	23	0.92	25^b	-	Solvent chromato
Total (step 1)		**222.38 g**^{c}				
PTA	2880	0.004	-	-	-	Catalyst
^{t}amylalcohol	88	4.1	0.82	5	46.6	Solvent
50% H_2O_2	34	0.11	1.11	0.1	1.62	Oxidant
EtOAc	88	9.2	0.92	10		Solvent extraction
Cyclohexane	84	31.2	0.78	40^d	-	Solvent chromato
EtOAc	88	9.2	0.92	10^d	-	Solvent chromato
Total (step 2)		**53.81 g**				
CH_3CN	41	11.85	0.79	15	289	Solvent
Total (step 3) for 150 mg of HHP		11.85 g				
Total (step 3) for 175 mg of HHP		**13.83 g** (11.85 * 175/150)				
Total (steps 1-3)		**290.02 g**^{b}				

The highlighted cells are the values directly taken from the reference given below. ^{a} *Average molecular weight of cardanol (calculated with 3% of saturated, 40% of mono-unsaturated, 17% of di-unsaturated and 40% of tri-unsaturated).* ^{b} *About 250 mL of eluent (cyclohexane/EtOAc) was used with an average proportions of 90 : 10.* ^{c} *Water used for washing was not considered.* ^{d} *About 50 mL of eluent (cyclohexane/EtOAc) was used with an average proportions of 80 : 20.*

For the first step, 2 g of cardanol were used and 400 mg of **C1Ep** were recovered. For the second step, 400 mg of **C1Ep** were used and 175 mg of **CxDOH** were recovered. For the third step, 150 mg of **CxDOH** of were used and 30 mg of **CAl** were recovered. Considering that the total amount of intermediates

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[4] This work

was not used for the each step, the quantity of **CAl** should be adjusted for the right calculations of the E factor. This would mean that 35 mg of **CAl** would have been recovered 0.03 * (175/150) in this case.

E Factor (route c) = ∑[m(waste)] / m(**CAl**) = ∑[m(reactants) +m(solvents) + m(catalyst) – m(**CAl**)] / m(**CAl**) = (290.02 – 0.035) / 0.035 = 8285 ~ **8285**

E Factor (route c) with 100% recovery of solvents = ∑[m(reactants) + m(catalyst) – m(**CAl**)] / m(**CAl**)] = (2.49 – 0.035) / 0.035 = 70.1, ~ **70**

E Factor (route c) with 100% recovery of solvents and aldehydes as co-products = ∑[m(reactants) + m(catalyst) – m(**CAl**) – m(other aldehydes)*] / [m(**CAl**) + m(other aldehydes)*] = (2.49 – 0.053) / 0.053 = 46.0, ~ **46**

6.3. Safety score (SC)

Evaluation of the safety score (SC) was established using the safety data sheets (SDS) of the products involved in the synthesis of the molecule of interest, whether reagents, catalysts or solvent, during each step: reaction, extraction, purification. A score is assigned for each category of hazard considering the number of sub-categories of this hazard. The maximum hazard category score is the category number +1. The minimum score is therefore +**1** if it is the lowest category, **0** if there is no such danger. In our view, the following hazards: corrosive, irritant and STOT, present a less significant hazard than the other hazards, their rating is therefore halved. On the contrary, because of the increased danger for humans and the process, an additional note is assigned to the following products: **+2** gas under pressure, **+3** for radioactive and/or explosive.

The SC of a product is then the sum of the notes of each category of danger present on its SDS. The SC in bold is the higher SC in the equation. The SC in blue is the SC of a solvent of the reaction. We have not considered cardanol in these equations, being the element in common of all the synthesis.

Table of Hazard class, category and SC score associated.

Hazard Class	Category	SC score
Explosives	1 to 6	3
Flammable gases	1	3
	2	2
Flammable aerosols	1	3
	2	2
Flammable liquids	1	5
	2	4
	3	3
	4	2
Flammable solids	1	1
	2	2
Gases under pressure	/	2
Oxidizing gases	1	2
Oxidizing liquids	1	4
	2	3
	3	2
Oxidizing solids	1	4
	2	3
	3	2
Acute aquatic toxicity	1	4
	2	3
	3	2
Chronic aquatic toxicity	1	5
	2	4
	3	3
	4	2

Hazard Class	Category	SC score
Acute toxicity	1	5
	2	4
	3	3
	4	2
Skin corrosion	1A	2.5
	1B	2
	1C	1.5
	2	1
Skin/Eyes irritation	1A	2.5
	1B	2
	1C	1.5
	2	1
Sensitization (skin or eye)	1A and 1B	1
Germ cell mutagenicity	1A	4
	1B	3
	2	2
Carcinogenicity	1A	4
	1B	3
	2	2
Reproductive toxicity	1A	4
	1B	3
	2	2
STOT single exposure	1	2
	2	1.5
	3	1
STOT repeated exposure	1	1.5
	2	1
Aspiration toxicity	1	3
	2	2

Ozone SC score: **21**

- Oxidizing gaz - category 1 : **+2**
- STOT single exposure - category 3 : **+1**
- Acute toxicity - category 1 : **+5**
- Skin irritation - category 2 : **+1**
- Germ cell mutagenicity - category 2 : **+2**
- STOT repeated exposure - category 2 : **+1**
- Acute aquatic toxicity - category 1 : **+4**
- Gases under pressure : **+2**
- Explosive : **+3**

Ethyle acetate SC score: **6**

- Flammable liquids - category 2 : **+4**
- Eyes irritation – category 2 : **+1**
- STOT single exposure – category 3 : **+1**

Dihydrogen SC score: **7**

- Flammable gases - category 2 : **+2**
- Gases under pressure : **+2**
- Explosive : **+3**

Hydrogen peroxide (30%) SC score : **9.5**

- Oxidizing liquids - category 1 : **+4**
- Acute toxicity - category 4 : **+2**
- Skin corrosion - category 1A : **+2.5**
- STOT single exposure – category 3 : **+1**

Sodium hydroxide SC score : **2.5**

- Skin/Eyes corrosion - category 1A : **+2.5**

Hydrochloric acid SC score: **3.5**

- Skin/Eyes corrosion - category 1A : **+2.5**
- STOT single exposure – category 3 : **+1**

Diethyl ether SC score: **8**

- Flammable liquids - category 1 : **+5**
- Acute toxicity - category 4 : **+2**
- STOT single exposure – category 3 : **+1**

Potassium periodate SC score: **8**

- Oxidizing solids - category 1 : **+4**
- Skin/Eyes corrosion - category 1C : **+1.5**
- STOT single exposure – category 3: **+1**
- STOT repeated exposure – category 1: **+1.5**

Sulfuric acid SC score: **2.5**

- Skin/Eyes corrosion - category 1A : **+2.5**

Ethanol SC score: **5**

- Flammable liquids - category 2: **+4**
- Eyes irritation – category 2 : **+1**

Formic acid SC score: 7.**5**

- Flammable liquids - category 3: **+3**
- Acute toxicity – category 4 : **+2**
- Skin corrosion – category 1A: +**2.5**

Sodium periodate SC score: **15**

- Oxidizing solids - category 1 : **+4**
- Skin/Eyes corrosion - category 1C : **+1.5**
- STOT repeated exposure – category 1: **+1.5**
- Acute aquatic toxicity - category 1: **+4**
- Chronic aquatic toxicity – category 2: **+4**

Phosphorous acid SC score: **5.5**

- STOT single exposure - category 3: **+1**
- Acute toxicity – category 4 : **+2**
- Skin corrosion – category 1A: +**2.5**

Acetonitrile SC score: **7**

- Flammable liquids - category 2: **+4**
- Acute toxicity – category 4 : **+2**
- Eye irritation – category 2: **+1**

T-amyl alcohol SC score: **8**

- Flammable liquids - category 2: **+4**
- Acute toxicity – category 4: **+2**
- Skin/Eyes corrosion – category 2: **+1**
- STOT single exposure – category 3: +**1**

Phosphotungstic acid SC score : **2**

- Skin/Eyes corrosion – category 1B: **+2**

Calculation of the safety score (SC) for the route a :

Ozone + Ethyl acetate + dihydrogen = **21** + 6 + 7 = **34**

Calculation of the safety score (SC) for the route b^1:

Formic acid + sulfuric acid + hydrogen peroxide + ethyl acetate + magnesium sulfate anhydrous + phosphorous acid + ethanol + sodium periodate = 7.5 + 2.5 + 9.5 + 6 + 0 + 5.5 + 5 + **15** = **51**

Calculation of the safety score (SC) for the route b^2:

Formic acid + hydrogen peroxide + diethyl ether + sodium chloride in water + sodium hydroxide + hydrochloric acid + ethanol + sulfuric acid + potassium periodate + sodium sulfate anhydrous = 7.5 + **9.5** + 8 + 0 + 2.5 + 3.5 + 5 + 2.5 + 8 + 0 = **46.5**

Calculation of the safety score (SC) for the route c :

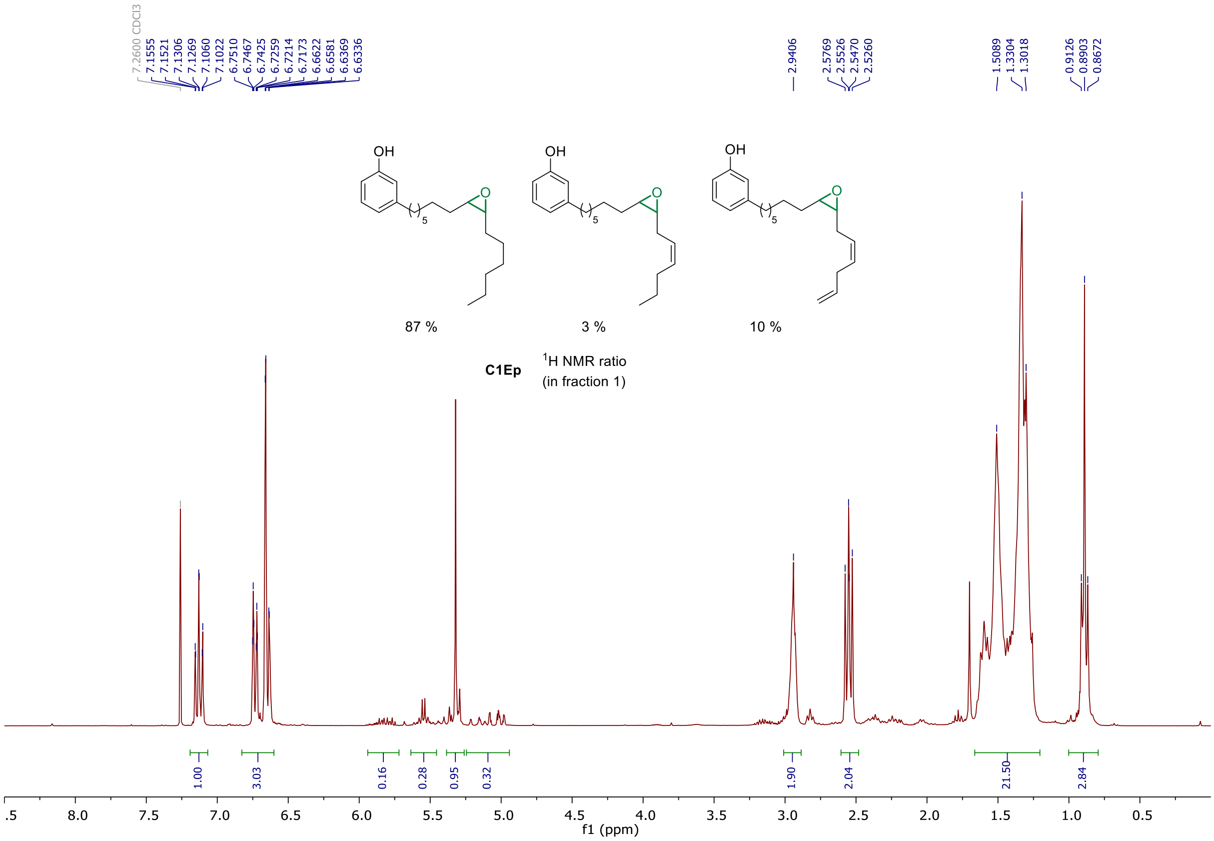
Formic acid + sulfuric acid + hydrogen peroxide + ethyl acetate + magnesium sulfate anhydrous + T-amyl alcohol + Phosphotungstic acid + Acetonitrile = 7.5 + 2.5 + **9.5** + 6 + 0 + 8 + 2 + 7 = **42.5**

Summary of the safety score and SC/number of chemicals:

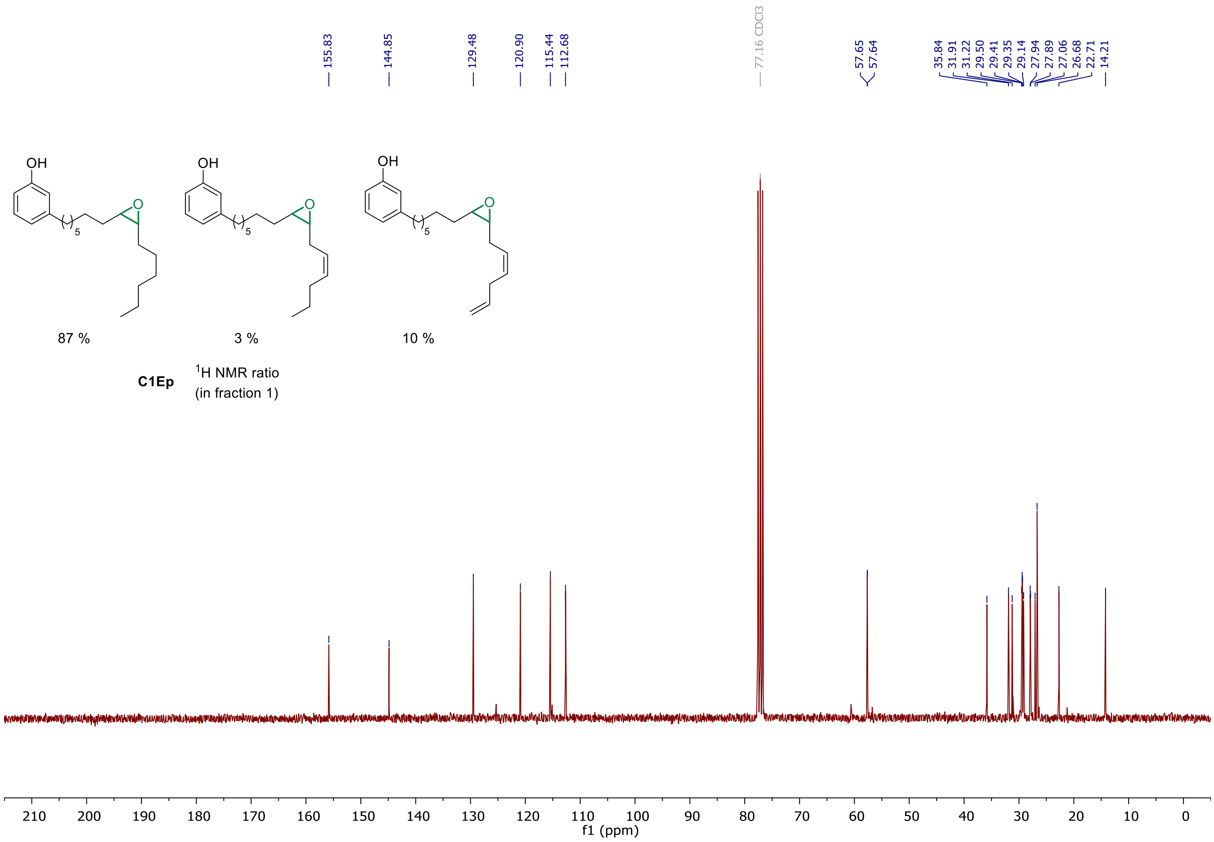
Synthesis	Steps	SC of Reactant	SC of Solvent	More hazardous molecule (pts)	Number of chemical	Total SC	Total SC/ Nbr of chemical
Route a	2	28	6	Ozone (21)	3	34	11.3
Route b^1	3	40	11	Sodium Periodate (15)	8	51	6.4
Route b^2	3	33.5	13	H_2O_2 (9.5)	10	46.5	4.3
Route c	3	21.5	21	H_2O_2 (9.5)	8	42.5	5.3

7. NMR Spectra

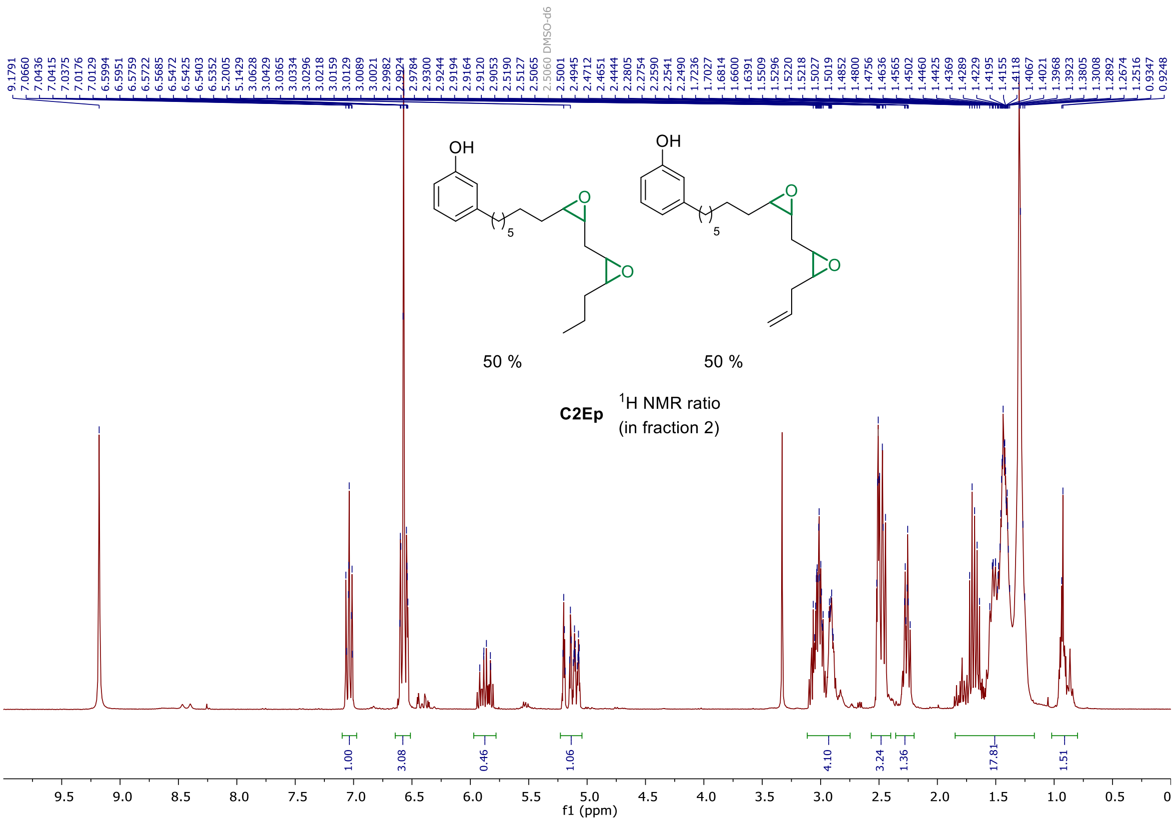
^{1}H NMR (300 MHz, *CDCl$_3$*) of cardanol mono-epoxides **C1Ep**



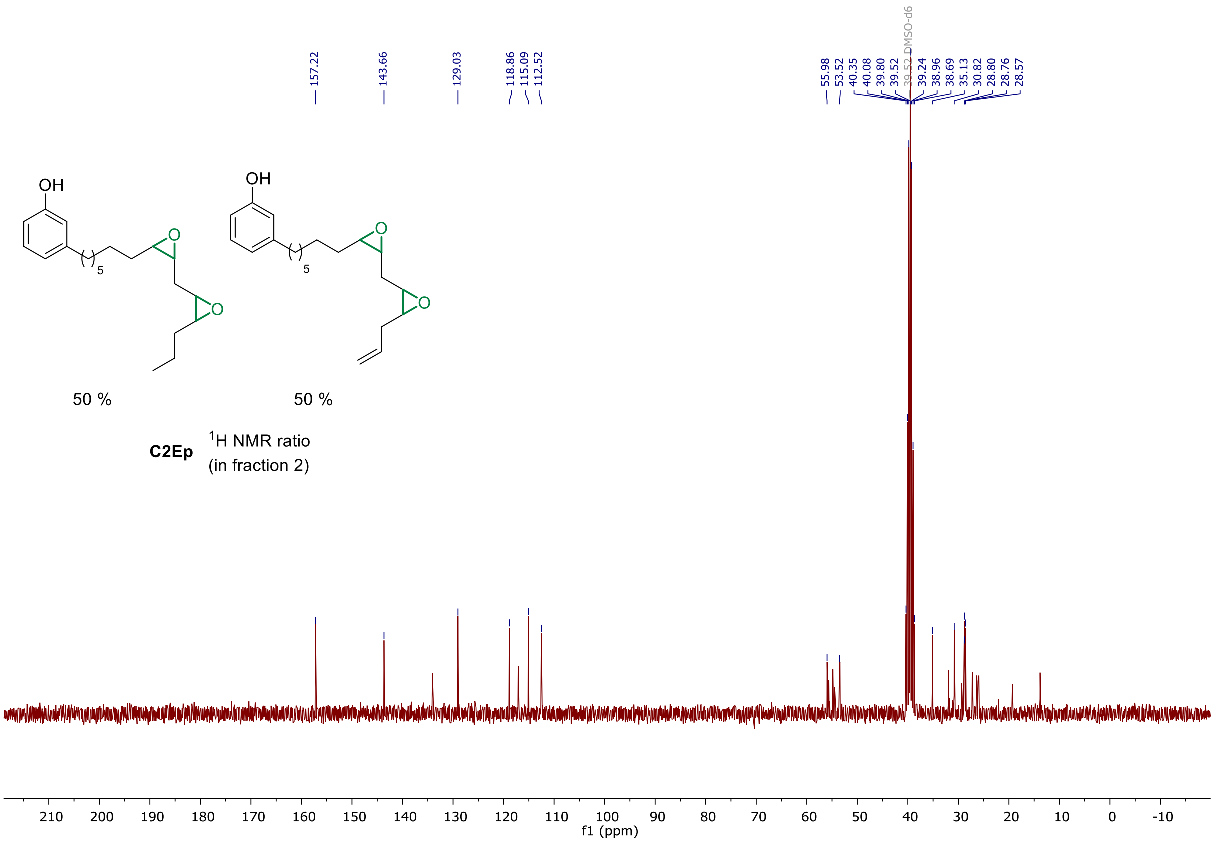
^{13}C NMR (300 MHz, *CDCl$_3$*) of cardanol mono-epoxides **C1Ep**



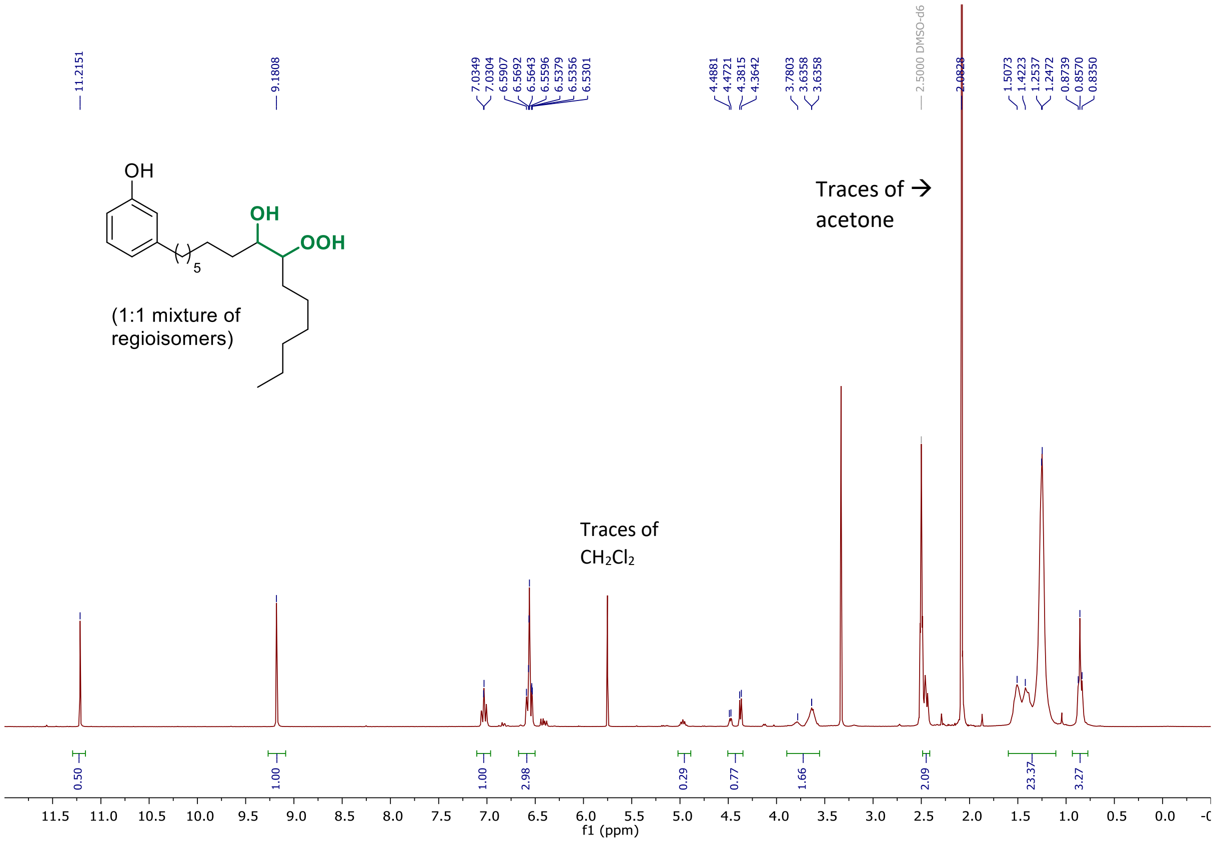
^{1}H NMR (300 MHz, *d*$_6$-DMSO) of cardanol di-epoxides **C2Ep**



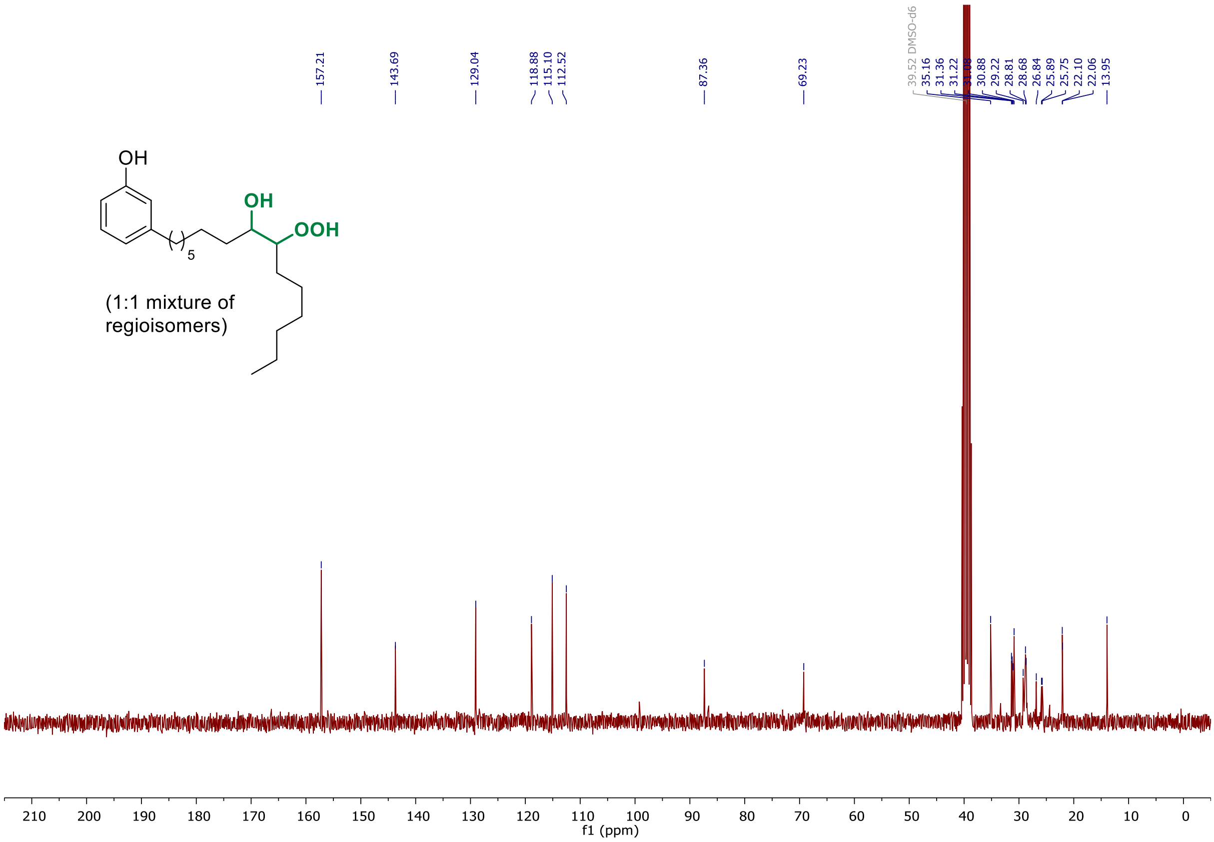
^{13}C NMR (300 MHz, *d*$_6$-DMSO) of cardanol di-epoxides **C2Ep**



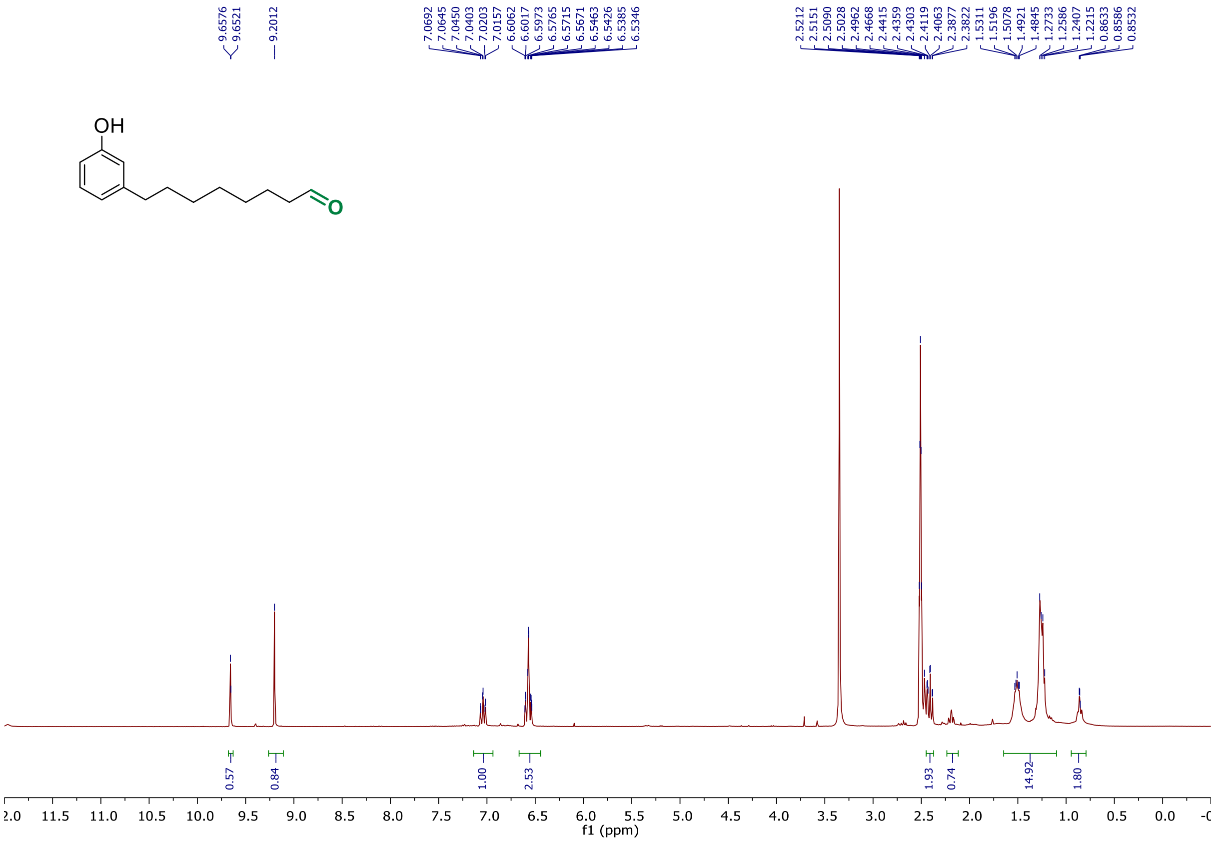
^{1}H NMR (300 MHz, d_6-DMSO) cardanol mono-β-hydroxy hydroperoxide **C1HHP**



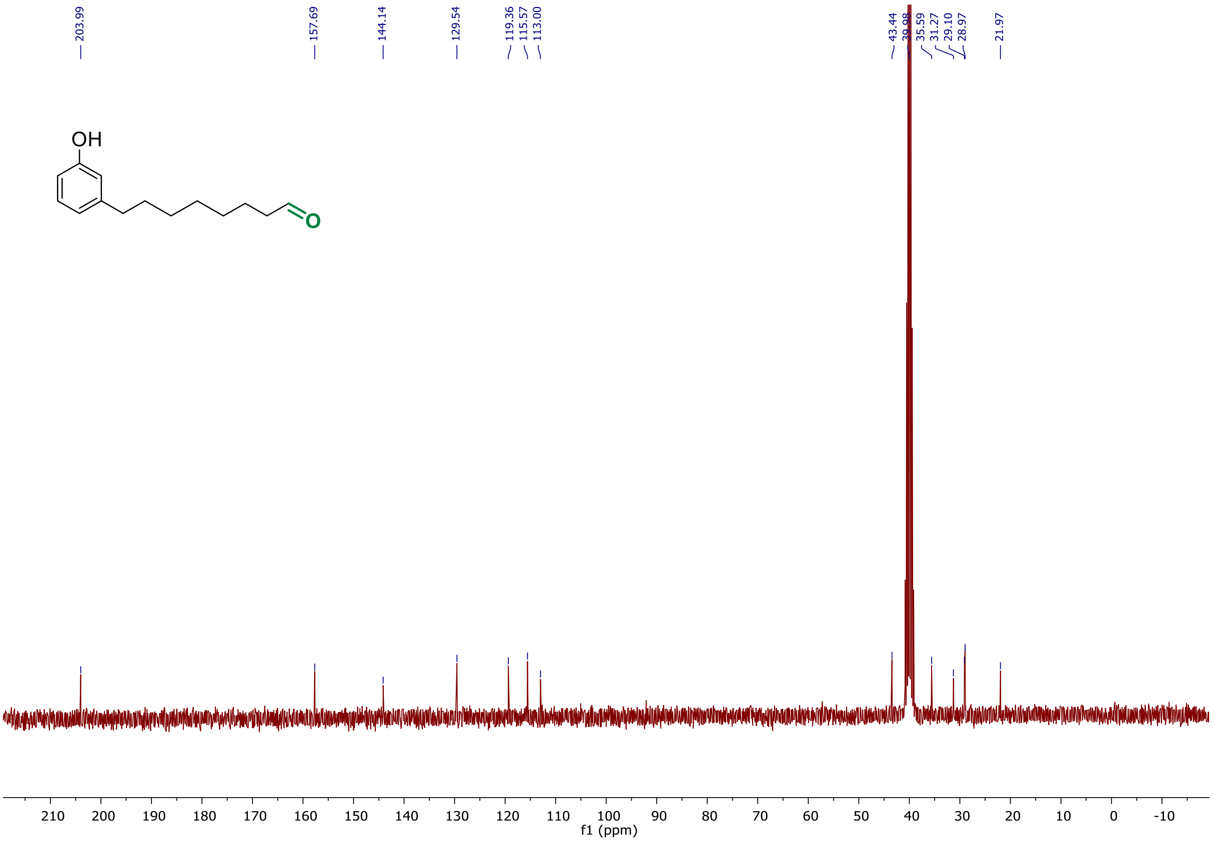
^{13}C NMR (300 MHz, d_6-DMSO) cardanol mono-β-hydroxy hydroperoxide **C1HHP**



^{1}H NMR (300 MHz, d_6-DMSO) 8-(3-hydroxyphenyl)octanal **CAl**

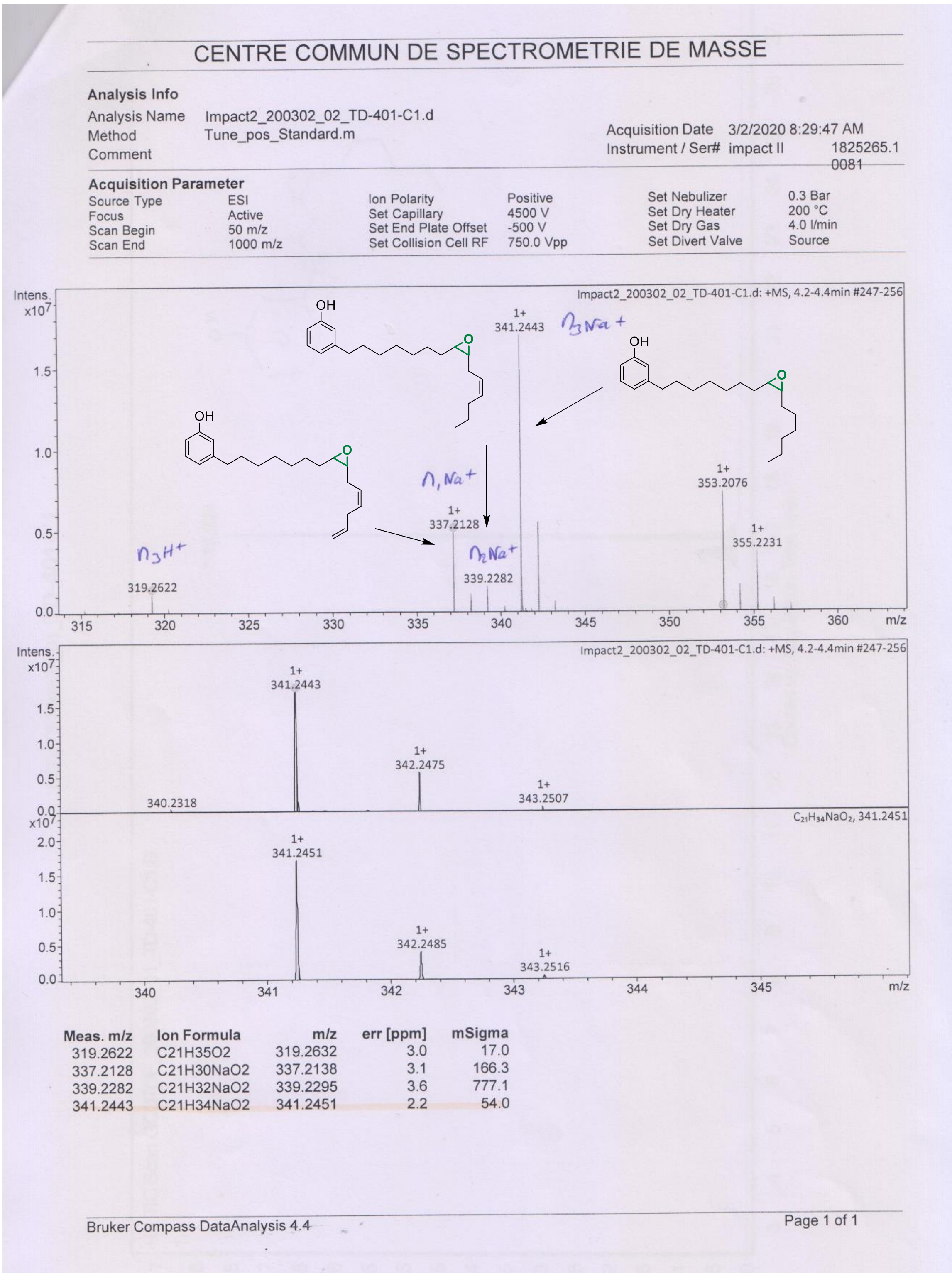


^{13}C NMR (300 MHz, d_6-DMSO) 8-(3-hydroxyphenyl)octanal **CAl**



8. HRMS

Cardanol mono-epoxides **C1Ep**.



CENTRE COMMUN DE SPECTROMETRIE DE MASSE

Analysis Info

Analysis Name Impact2_200302_02_TD-401-C1.d
Method Tune_pos_Standard.m
Comment
Acquisition Date 3/2/2020 8:29:47 AM
Instrument / Ser# impact II 1825265.10081

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	4500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	750.0 Vpp	Set Divert Valve	Source

Meas. m/z	Ion Formula	m/z	err [ppm]	mSigma
319.2622	C21H35O2	319.2632	3.0	17.0
337.2128	C21H30NaO2	337.2138	3.1	166.3
339.2282	C21H32NaO2	339.2295	3.6	777.1
341.2443	C21H34NaO2	341.2451	2.2	54.0

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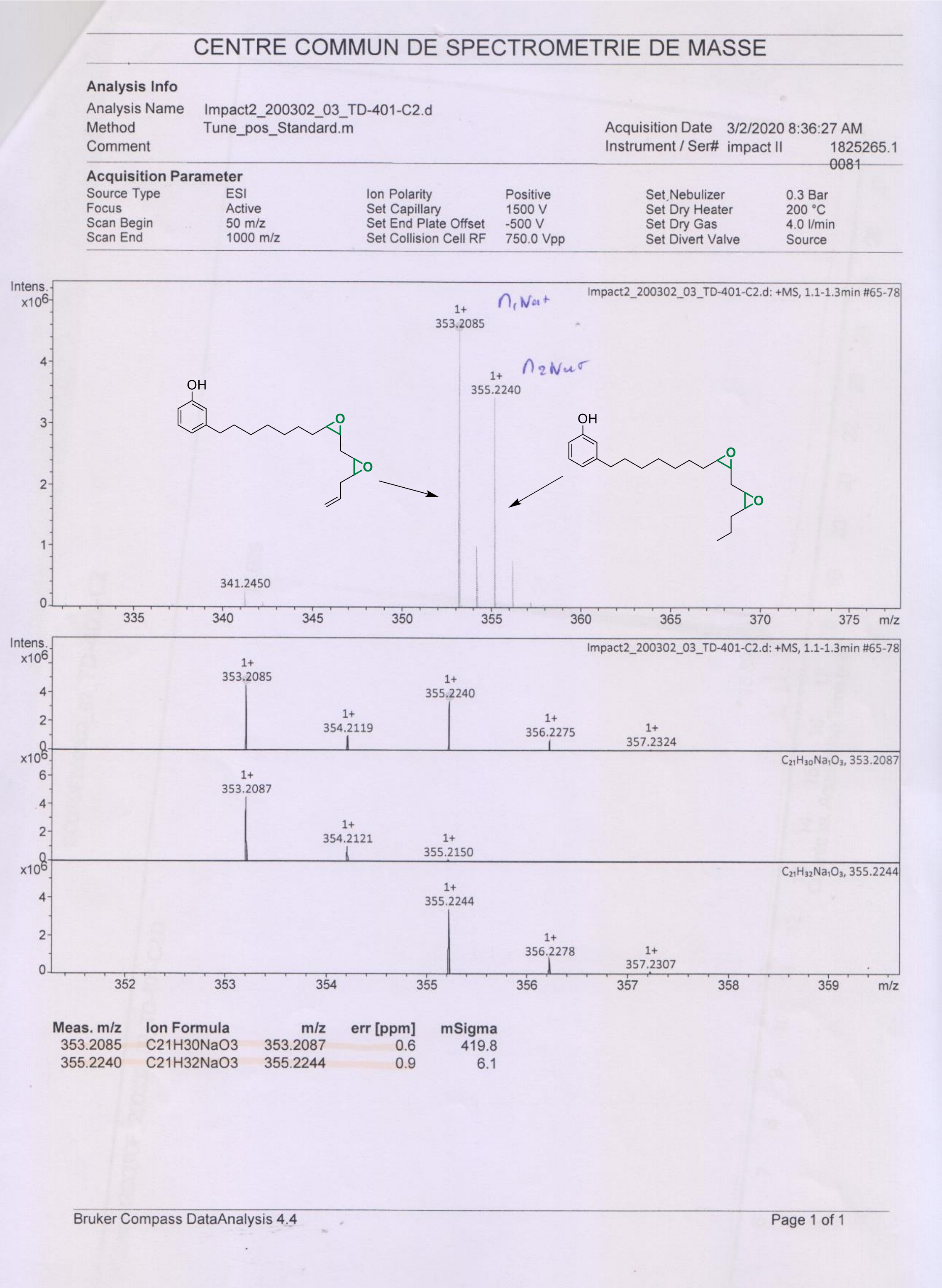
Cardanol di-epoxides **C2Ep**.



CENTRE COMMUN DE SPECTROMETRIE DE MASSE

Analysis Info

Analysis Name	Impact2_200302_03_TD-401-C2.d		
Method	Tune_pos_Standard.m	Acquisition Date	3/2/2020 8:36:27 AM
Comment		Instrument / Ser#	impact II 1825265.1 0081

Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	1500 V	Set Dry Heater	200 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	1000 m/z	Set Collision Cell RF	750.0 Vpp	Set Divert Valve	Source

n_1Na^+

n_2Na^+

Meas. m/z	Ion Formula	m/z	err [ppm]	mSigma
353.2085	C21H30NaO3	353.2087	0.6	419.8
355.2240	C21H32NaO3	355.2244	0.9	6.1

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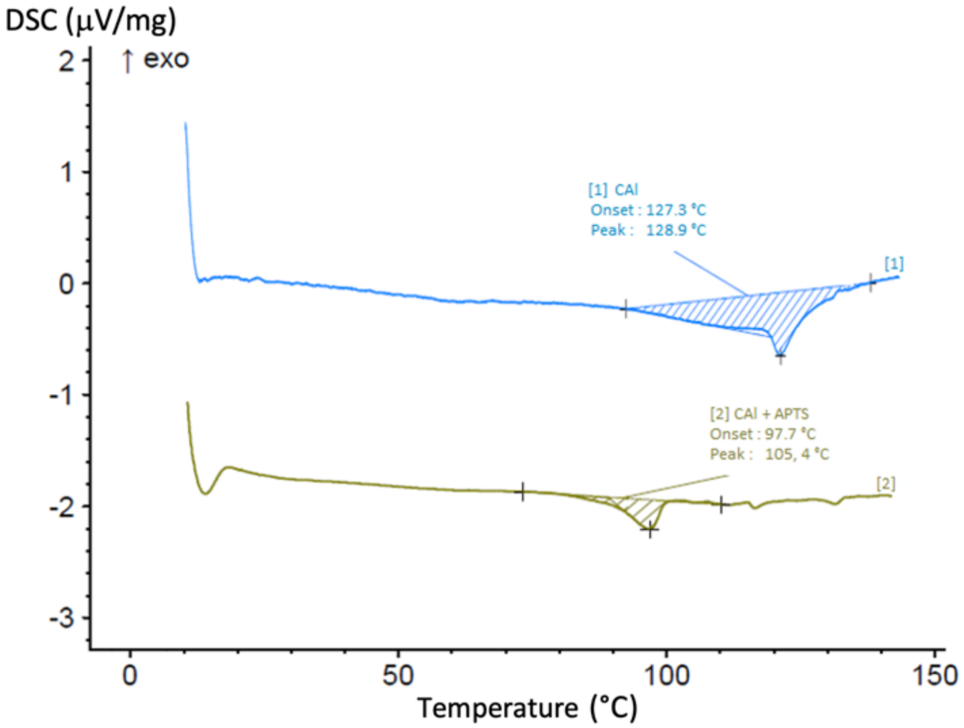
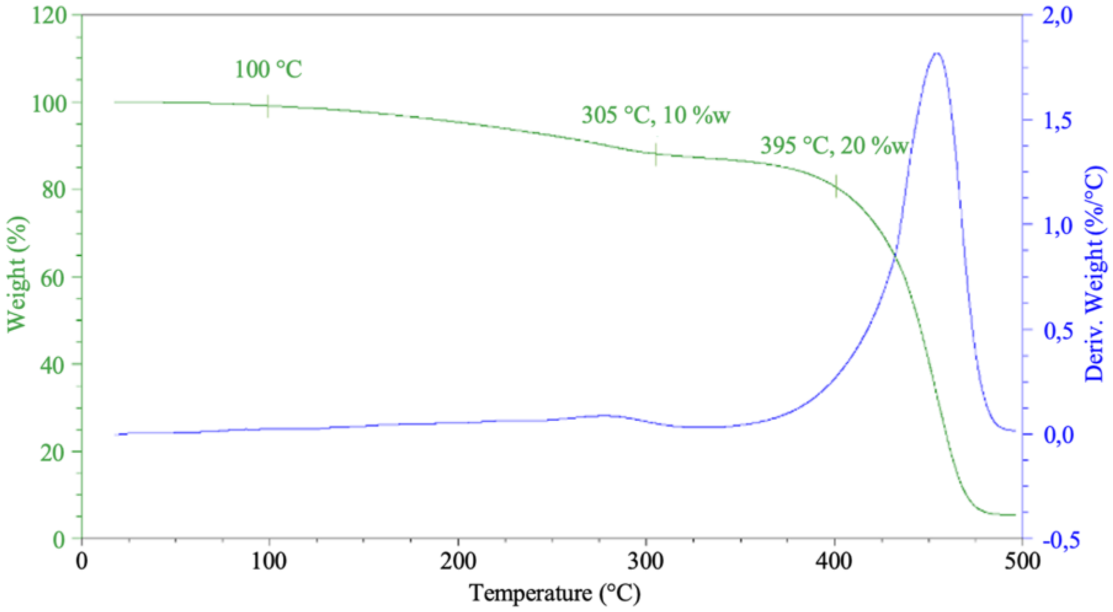
9. DSC and TGA thermograms



DSC curves from ambient temperature to 150 °C at 20 °C/min, monitoring the homopolycondensation of [1] CAl alone, [2] CAl mixed with PTSA (5 mol%).



TGA and DTG curves of **HCAlR** from room temperature to 500 °C, 10 °C/min.