Electronic Supplementary Material (ESI) for Green Chemistry.

Solvent-driven isomerization of muconates in DMSO: reaction mechanism and process sustainability

Electronic Supplementary information

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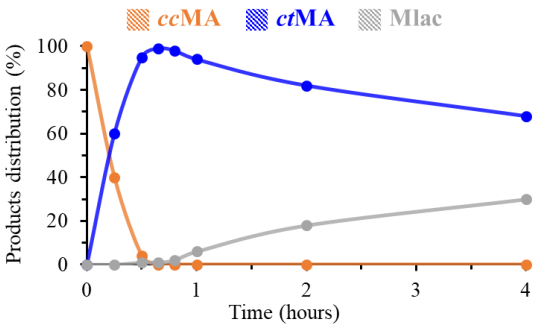

Figure S1: Time profile isomerization of 30 mM *cc*MA in 5ml water at 75 °C. The formation of *ct*MA and mono-muconolactone (Mlac) over time are plotted.

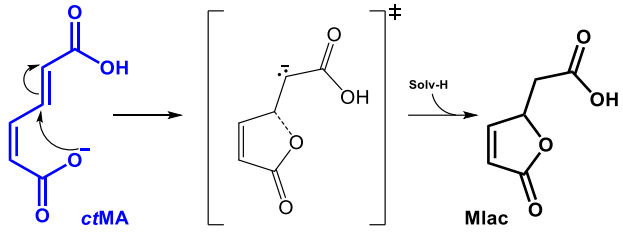

Figure S2: Reaction mechanism of the intramolecular rearrangement (lactonization) of *ct*MA into mono-muconolactone (Mlac) as described by Carraher *et al.*[1].

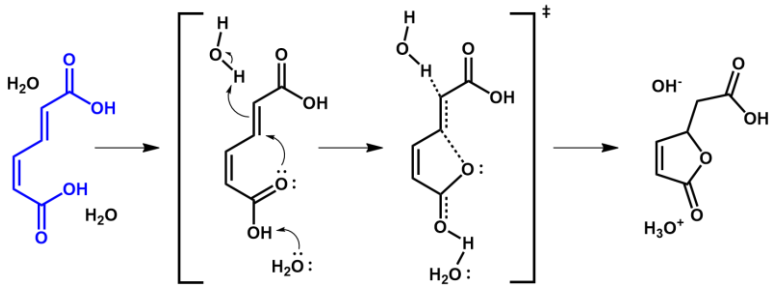

Figure S3: Proposed reaction mechanism for the water assisted intramolecular rearrangement (lactonization) of *ct*MA into mono-muconolactone (Mlac) as described by Carraher *et al.*[1]

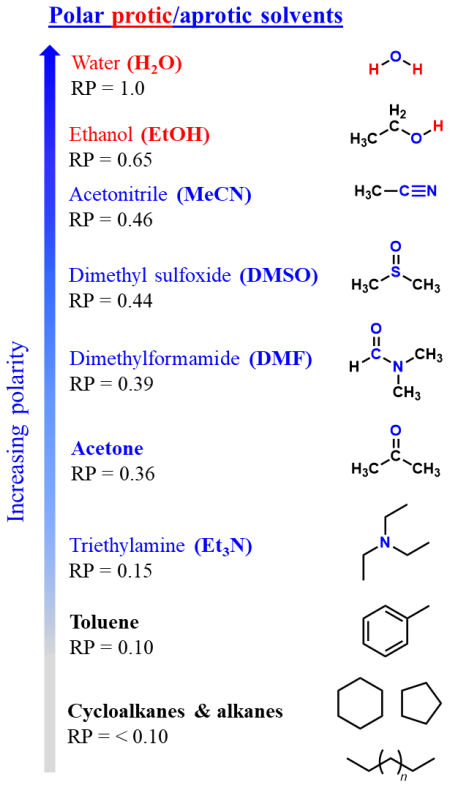

Figure S4: Comparison of the relative polarity (RP) of a selection of solvents used in this study. The solvents in red (H_2O and ethanol) are polar protic solvents, the ones in blue (MeCN, DMSO, DMF, Acetone, and Et_3N) are polar aprotic solvents, while toluene, cycloalkanes and alkanes (in black) are nonpolar solvents.

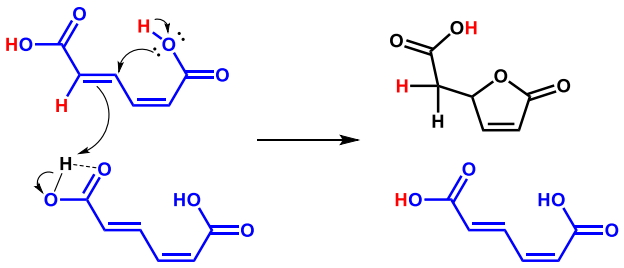

Figure S5: The reaction scheme for the autocatalyzed lactonization of *ct*MA.[1]

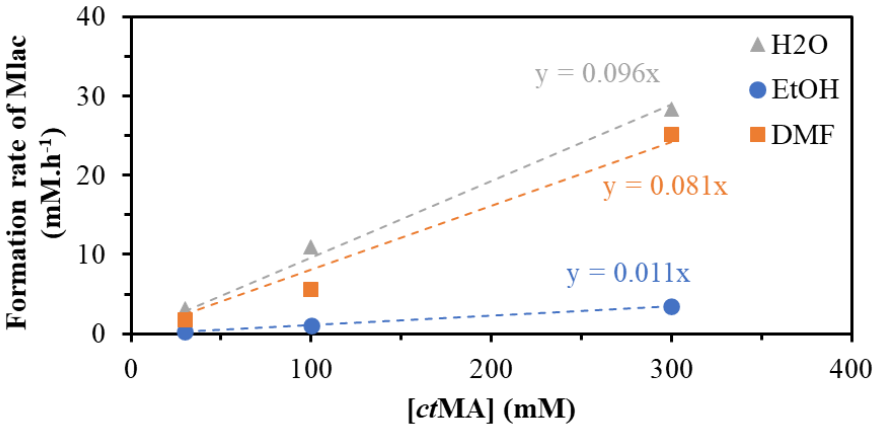

Figure S6: Estimation of the reaction order of the Mlac formation by linear plots of the Mlac formation rate versus the initial concentration of *ct*MA (30, 100, and 300 mM) in H_2O, EtOH, and DMF solvents.

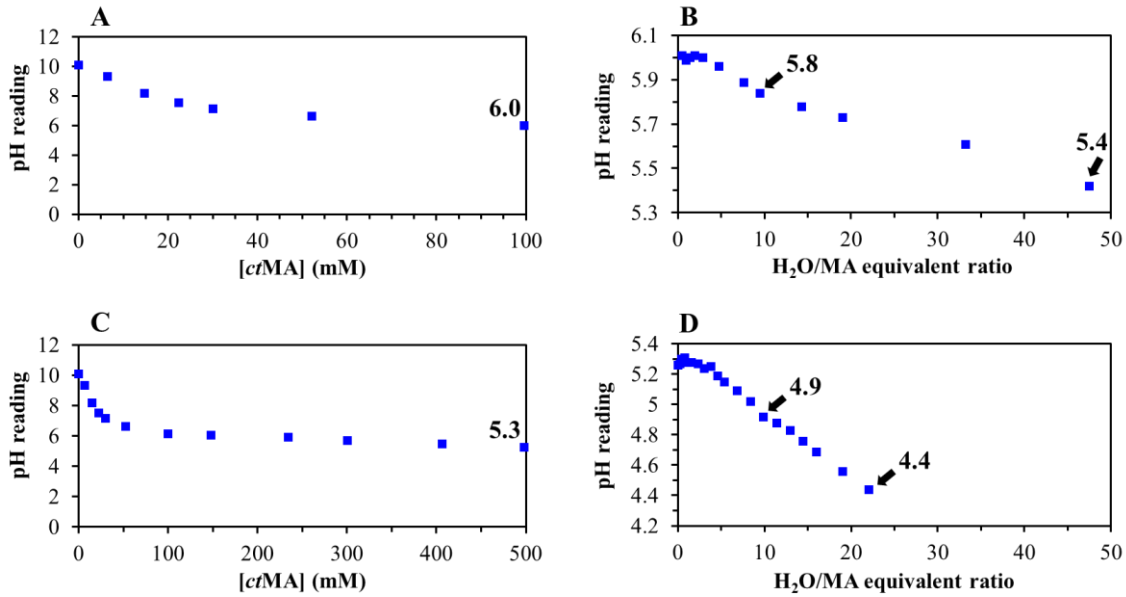

Figure S7: (**A** and **C**) The evolution in the pH reading in dry DMSO as a function of different concentrations of added *ct*MA, up to 100 mM **(A)** and up to 500 mM **(C)**. (**B** and **D**) The evolution in the pH reading as a function of the amount of added water (in molar equivalent ratio to MA. **(B)** and **(D)** are the continuation experiments after reaching 100 and 500 mM in **(A)** and **(C)**, respectively.

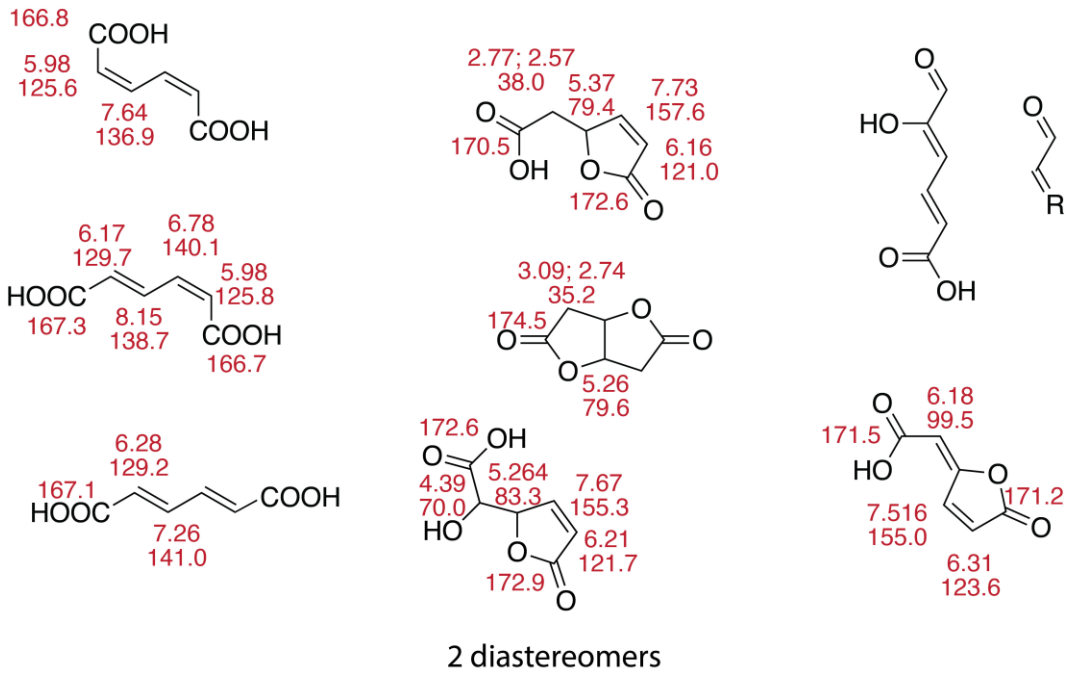

Figure S8: The identified products and side products and their respective chemical shifts observed with heteronuclear assignment spectra recorded on post-mixture. Both ^{1}H and ^{13}C chemical shifts are shown.

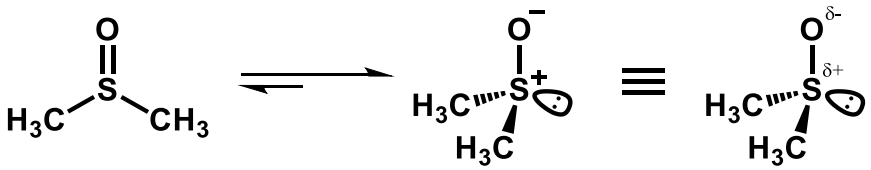

Figure S9: The molecular structure of DMSO showing it's high polarization and the partial negative charge on its oxygen atom.[2]

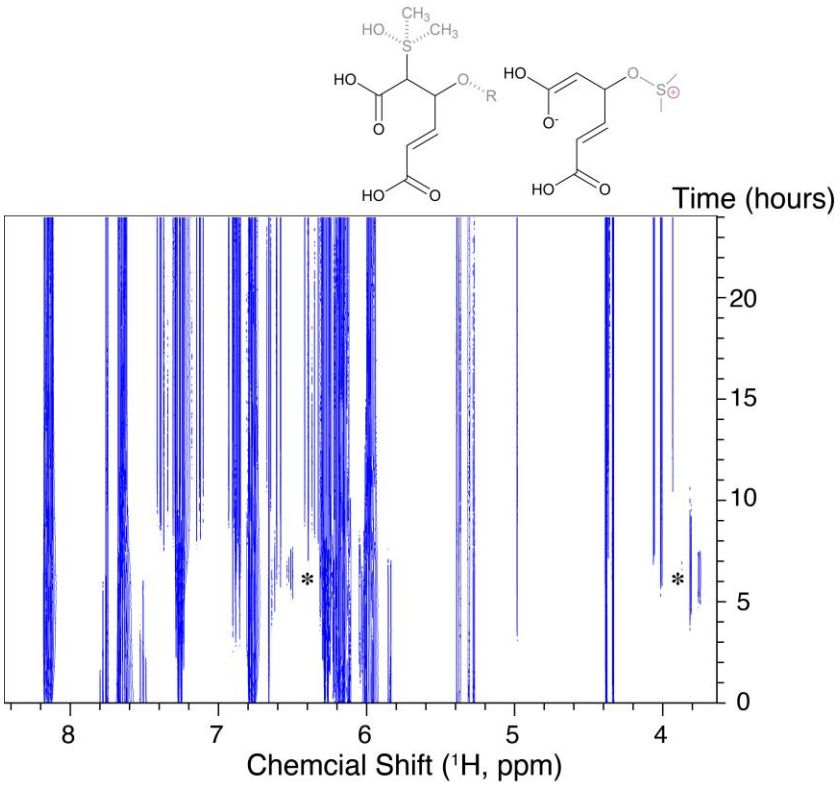

Figure S10: Real-time ^{1}H NMR reaction tracking of *ct*MA conversion, showing the formation of transient reaction intermediates marked with an asterisk. The intermediates contain sp^{3}-hybridized alcohol or ether groups (3.6-3.8 ppm), thus showing that transient addition of nucleophiles to the Michael system in *ct*MA occurs.

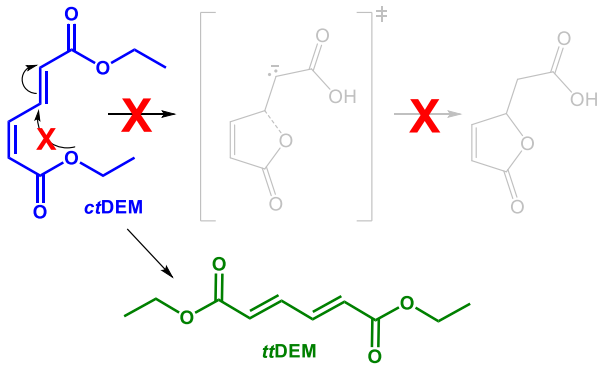

Figure S11: The role of esterification in blocking the intramolecular rearrangement (lactonization) of *ct*MA.

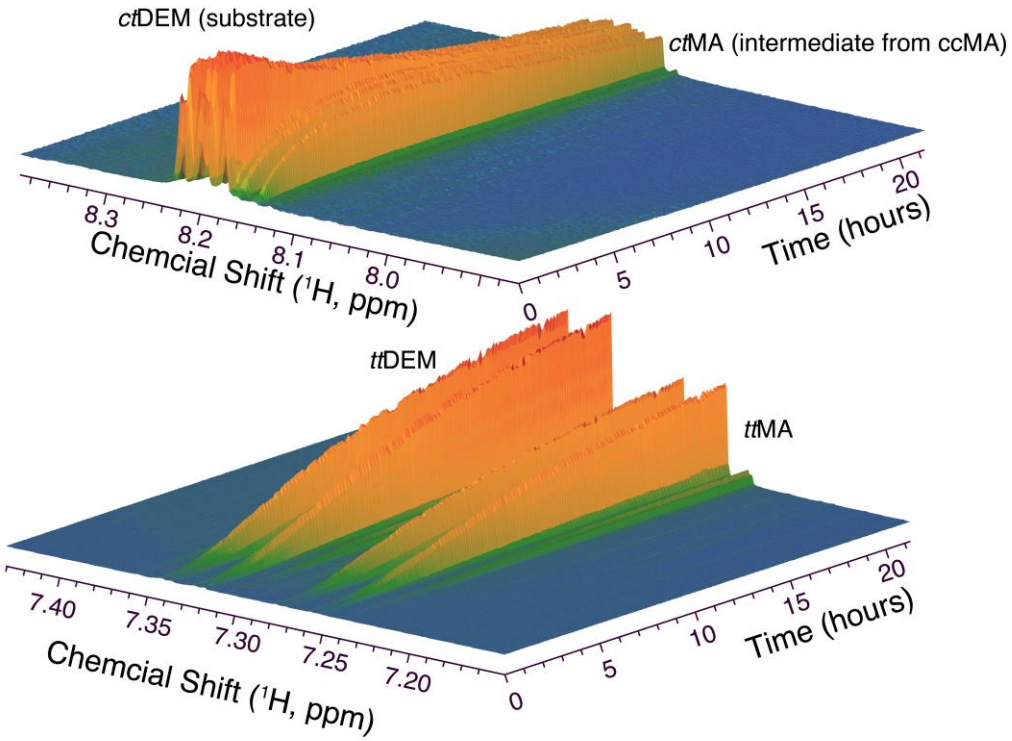

Figure S12: The *in-situ* ^{1}H-NMR spectra for the isomerization of *ct*MA and *ct*DEM into *tt*MA and *tt*DEM, respectively. The plots correspond to two separate reactions, the first for the isomerization *cc*MA to *tt*MA (*via ct*MA) and the second is the isomerization of *ct*DEM to *tt*DEM. *ct*MA is an intermediate from the first isomerization of *cc*MA to *ct*MA (*cc*MA not plotted). The reactions were performed at 100 °C in an NMR tube using 4.5 mg of each substrate and DMSO-d_6 as the solvent.

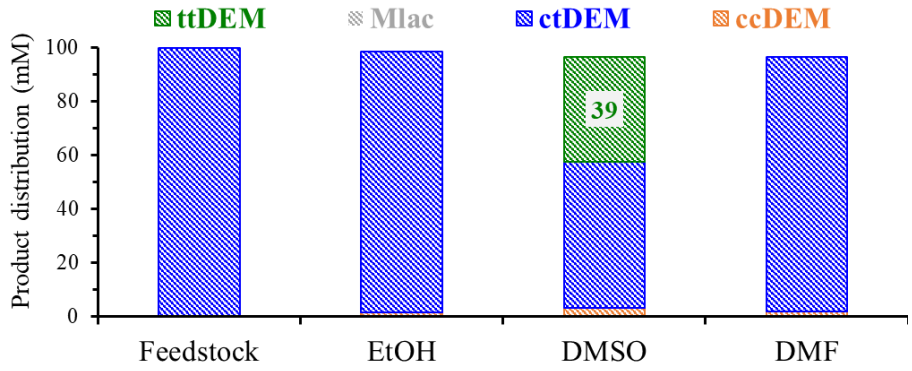

Figure S13: The product distribution (in mM) for the conversion of 100 mM *ct*DEM in EtOH, DMSO, and DMF (5 mL) at 120 °C for 4 hours. The product distribution was determined by GC analysis for the muconates (using n-heptane as external standard) and ^{1}H-NMR was used to check the possible formation of lactones.

Table S1: Evolution of the product selectivity (ttMA and Mlac) as a function of the starting pH of the reaction.

# reaction	[*ct*MA] mM / H_2O eq.	pH	*ct*MA conversion	S_{ttMA}	S_{Mlac}	*tt*MA/Mlac
1	100 / 0eq.	6.0	63.1%	19.2%	70.2%	0.27
2	100 / 2eq.	6.0	74.4%	74.7%	14.8%	5.05
3	100 / 10eq.	5.8	62.8%	67.0%	19.4%	3.45
4	100 / 47 eq.	5.4	66.1%	68.1%	20.0%	3.41
5	500 / 0eq.	5.3	48.3%	11.6%	74.9%	0.15
6	500 / 2eq.	5.3	62.8%	61.8%	26.0%	2.38
7	500 / 10eq.	4.9	49.7%	43.5%	41.4%	1.05
8	500 / 22eq.	4.4	52.4%	34.4%	52.3%	0.66

Table S2: The evolution of the productivity of the isomerization method as a function of the optimization of the reaction conditions (reaction temperature and added substrates).

Entry	[*ct*DEM] mM	Added substrates	T (°C)	Time	*tt*DEM yield (%)
1	100	2 eq. H_2O	**80 °C**	24 h	5.8
2	100	2 eq. H_2O	**100 °C**	24 h	8.1
3	100	2 eq. H_2O	**120 °C**	4 h	39.4
4	100	2 eq. H_2O	**150 °C**	1 h	76.4
5	100	**0 eq. H_2O**	150 °C	1 h	18.3
4	100	**2 eq. H_2O**	150 °C	1 h	76.4
6	100	**5 eq. H_2O**	150 °C	1 h	75.1
7	100	**10 eq. H_2O**	150 °C	1 h	77.2
8	100	**20 eq. H_2O**	150 °C	1 h	74.4
9	100	**50 eq. H_2O**	150 °C	1 h	47.1
10	100	2 eq. H_2O **2 eq. MPSO**	150 °C	1 h	72.2
11	100	2 eq. H_2O **5 eq. MPSO**	150 °C	1 h	73.7
12	100	2 eq. H_2O **20 eq. MPSO**	150 °C	1 h	68.1
13	100	2 eq. H_2O **50 eq. MPSO**	150 °C	1 h	56.4
14	100	2 eq. H_2O **1/3 vol. MPSO/DMSO**	150 °C	1 h	41.6
15	100	2 eq. H_2O **Solvent: MPSO**	150 °C	1 h	2.3
16	100	2 eq. H_2O **2 eq. sulfolane**	150 °C	1 h	75.5
17	100	2 eq. H_2O **10 eq. sulfolane**	150 °C	1 h	75.9
18	100	2 eq. H_2O **20 eq. sulfolane**	150 °C	1 h	70.1
19	100	2 eq. H_2O **50 eq. sulfolane**	150 °C	1 h	64.8
20	100	2 eq. H_2O **Solvent: sulfolane**	150 °C	1 h	1.8
21	100	2 eq. H_2O **2 eq. $DMSO_2$**	150 °C	1 h	81.2
22	100	2 eq. H_2O **10 eq. $DMSO_2$**	150 °C	1 h	82.1
23	100	2 eq. H_2O **1/3 vol. $DMSO_2$/DMSO**	150 °C	1 h	79.1

[(a)] *The productivity values are estimated using a single reaction point at the mentioned yield and reaction time, so these are not reliable rates opposed to e.g. Fig. S14.*

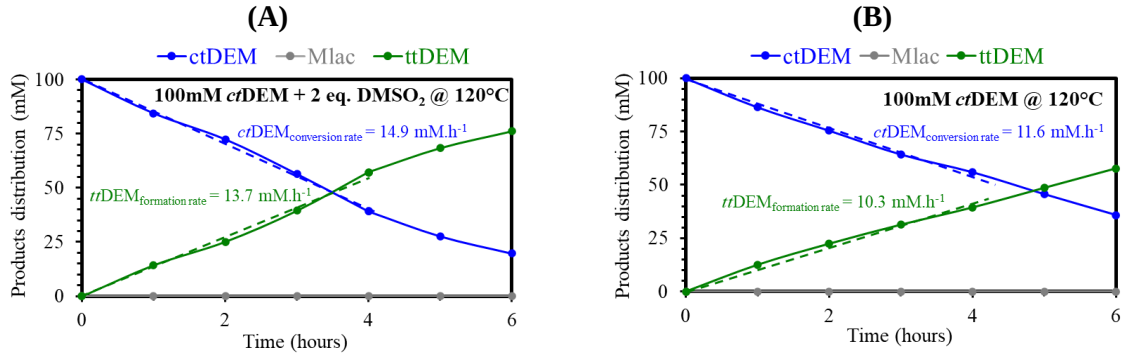

Figure S14: (A) Time profiles for the isomerization of 100 mM of *ct*DEM at 120 °C in DMSO in presence of 2 eq. H_2O and 10 eq. $DMSO_2$. The conversion rate of *ct*DEM and formation rate of *tt*DEM (slopes obtained for the points between 0 and 4 hours) are compared to the reaction in the absence of $DMSO_2$ **(B)** which corresponds to the Figure 6B in the main text. The reactions were performed in sealed glass pressure tube and the products distribution was determined by GC analysis.

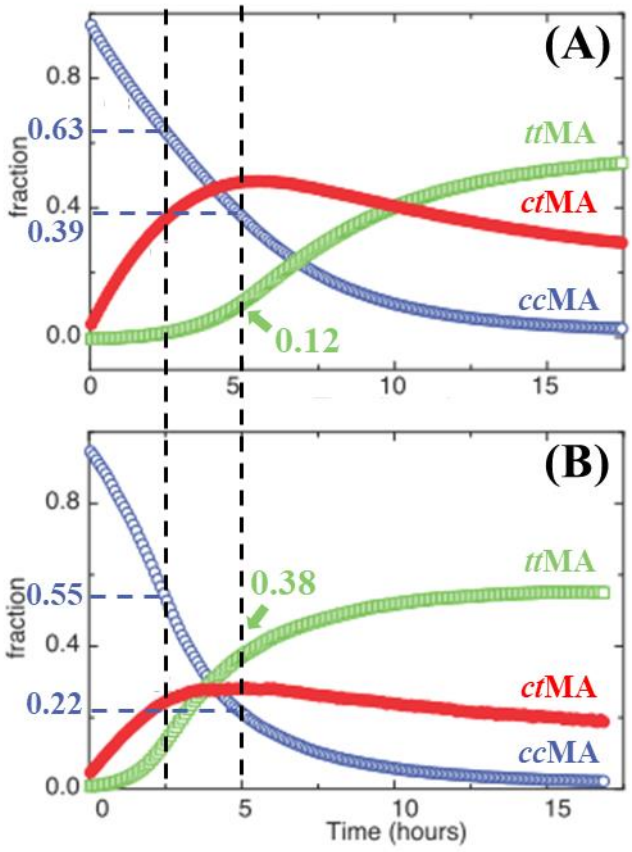

Figure S15: Time profile of the isomerization of 100 mM of *cc*MA in DMSO in the absence **(A)** and in the presence **(B)** of 10 eq. $DMSO_2$. The remaining fraction of *cc*MA after 2.5 and hours is shown in blue on the y-axis. Also, the obtained yield of *tt*MA after 5 hours is reported.

Table S3: The evolution of the productivity of the isomerization method as a function of the optimization of the reaction conditions (initial concentration of *ct*DEM).

Entry	[*ct*DEM] mM	Added substrates	T (°C)	Time	*tt*DEM yield (selectivity)	Productivity $mM.h^{-1}$
1	**30**	2 eq. H_2O	150 °C	1 h	96.0 (100%)	28.8
2	**50**	2 eq. H_2O	150 °C	1 h	81.0 (100%)	40.5
3	**100**	2 eq. H_2O	150 °C	1 h	76.4 (100%)	76.4
4	**300**	2 eq. H_2O	150 °C	1 h	66.4 (98%)	199.2
5	**500**	2 eq. H_2O	150 °C	1 h	55.9 (95%)	279.5
6	**680**	2 eq. H_2O	150 °C	1 h	48.3 (96%)	328.4
7	**1000**	2 eq. H_2O	150 °C	1 h	21.6 (98%)	216.0
				2.5 h	38.1 (97%)	152.4
				5 h	53.3 (94%)	106.6
8	**2000**	2 eq. H_2O	150 °C	1 h	7.6 (99%)	152.0
				2.5 h	14.0 (97%)	112.0
				5 h	23.7 (94%)	94.8
9	**3200**[(b)]	2 eq. H_2O	150 °C	4 h	13.5 (98%)	108.0
				20 h	40.9 (92%)	65.4

[(a)] *The productivity values are estimated using a single reaction point at the mentioned yield and reaction time, so these are not reliable rates opposed to e.g. Fig. S14.*

[(b)] *The 3200 mM concentration is an estimated concentration for a solution containing around a 1/1 volume ratio of ctDEM/DMSO (the given value is accurate within ± 10% error).*

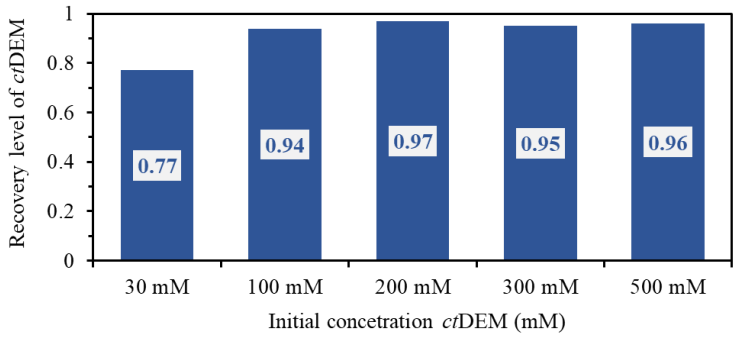

Figure S16: The recovery level of *ct*DEM from parent solutions of different concentration of *ct*DEM in DMSO. The recovery level corresponds to the isolated yield of *ct*DEM using the solvent extraction procedure.

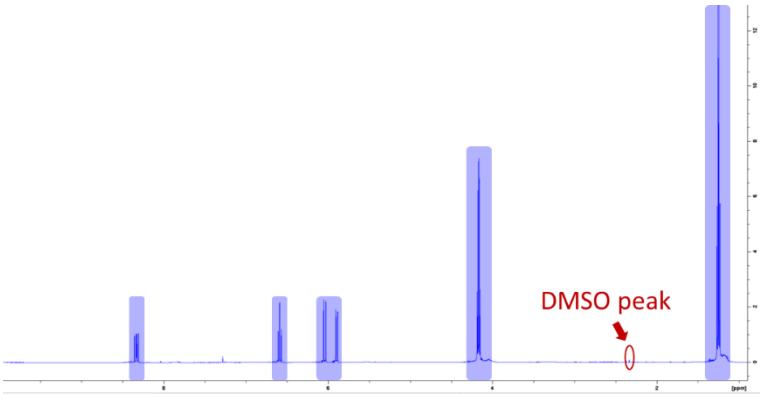

Figure S17: The ^{1}H-NMR signal (in $CDCl_3$) for *ct*DEM after extraction from DMSO solution containing an initial concentration of 500 mM. The DMSO peak is still present in the extracted *ct*DEM in a minor contribution which accounts for less than 0.5 mol.% of the amount of *ct*DEM.

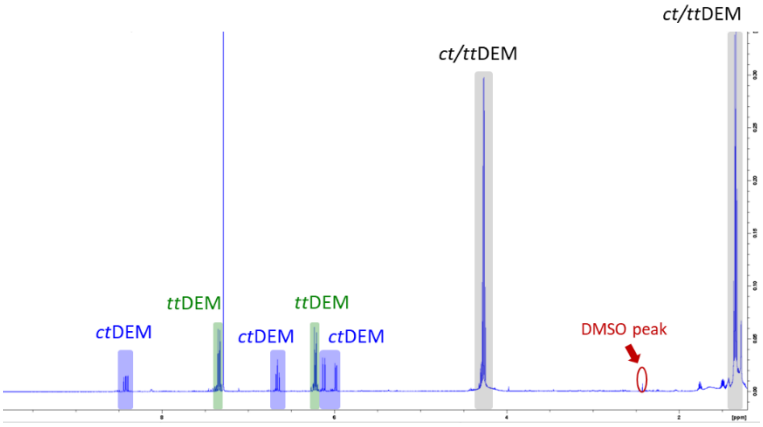

Figure S18: The ^{1}H-NMR signal (in $CDCl_3$) for a mixture of *ct*DEM and *tt*DEM after extraction from DMSO solution containing an initial concentration of 100 mM of DEMs. The DMSO peak is still present in the extracted *ct*DEM in a minor contribution which accounts for less than 1 mol.% of the amount of DEM.

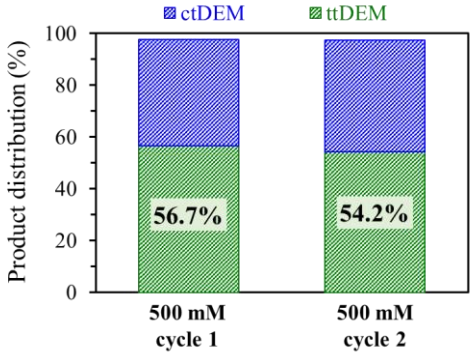

Figure S19: The isomerization results of the recovered and dried DMSO. Reaction conditions: 500 mM *ct*DEM + 2eq. H_2O in DMSO at 150°C for 1h. After the first reaction cycle, the DMSO was removed in aqueous solution (from DEMs) and further purified under reduced pressure and drying (anhydrous $MgSO_4$) and finally used in a second reaction cycle.

Analysis of the green chemistry principles:

For the comparison, we selected the most common isomerization method (homogeneous iodine catalysis) that produces the *tt*-isomer base on the results showing high productivities and high concentrated systems. The reaction conditions used for the comparative study are summarized in Table S3. For a fair comparison, we selected the reaction conditions with initial concentration of 500 mM (MA or diethyl muconate DEM), or the closest possible. For example, for the iodine system, 535 mM and 118 mM conditions were selected for the isomerization of *cc*MA and *cc*DMM (dimethyl muconate), respectively.

Table S4: The evolution of the productivity of the isomerization methods as a function of the optimization of the reaction conditions (initial concentration of *ct*DEM).

Isomerization methods		$[C]_{initial}$ (mM)	*tt* yield (%)	Selectivity (%)	Solvent	Productivity (mM h^{-1})
Iodine/UV	MA[3]	535	84%	84%	THF	90
	DMM[4]	118	95%	100%	MeOH	112
Solvent driven	MA[5]	493	40%	80%	DMSO	99
Solvent driven (this work)	**DEM**	**500**	**56%**	**95%**	**DMSO**	**280**

We did not consider the first isomerization (*cc*MA to *ct*MA) in the analysis due to the ease of this step and possible occurrence during the derivatization and/or during the second isomerization step.[5–7] Also, muconic acid and muconic esters as feedstocks were treated similarly (the pre- or post-esterification step was not counted in the calculation). The acid form is the one obtained from the biotechnological production, however, muconic esters present a higher value in chemical industry for their use in polymerization and other chemical transformations.[6,8]

Table S5: Principles of green chemistry for the different isomerization methods for MA and muconates.

Principle of green chemistry	I_2 catalyzed		DMSO-driven	
	MA	DMM	MA	DEM
Waste prevention[a]	**E-factor$_1$ = 14.1** **E-factor$_2$ = 0.2** **E-factor$_3$ = 0.2**	**E-factor$_1$ = 41.8** **E-factor$_2$ = 0.1** **E-factor$_3$ = 0.1**	**E-factor$_1$ = 40.8** **E-factor$_2$ = 0.25** **E-factor$_3$ = *I***	**E-factor$_1$ = 20.6** **E-factor$_2$ = 0.8** **E-factor$_3$ = *I***
		[c]E'-factor$_1$ = 78.4		*[c]E'-factor$_1$ = 73.6*
Atom economy (AE)[b]	**AE = 100 %**	**AE = 100%**	**AE = 100%**	**AE = 100%**
		[c]AE' = 85%		*[c]AE' = 85%*
Less hazardous chemical synthesis	I_2 is a hazardous chemical	I_2 is a hazardous chemical	No hazardous reagents or catalysts are used	No hazardous reagents or catalysts are used
Safer solvents & auxiliaries	Use of hazardous solvent (THF)	Use of hazardous solvent (THF, MeOH)	Use of non-hazardous solvent (DMSO)	Use of non-hazardous solvent (DMSO)
Design for energy efficiency	1 reaction step: *room temperature*	2 steps (counting esterification): Low to moderate T°: 4 – 50 °C	1 reaction step: Moderate to high T°: 60 – 121 °C	2 steps (counting esterification): High T°: 80 – 150 °C
Use of renewable feedstock	Muconic acid is used as biobased feedstock	Muconic acid is used as biobased feedstock	Muconic acid is used as biobased feedstock	Muconic acid is used as biobased feedstock
Catalysis (vs. stoichiometric)	Homogeneous catalysis	Homogeneous catalysis	No catalysis	No catalysis
			Catalysts are preferred over stoichiometric chemistry. However, in this method no significant reduction in AE or reaction yields are observed when no catalyst is used	

[a] *E-factor$_1$ includes all waste (in weight amount), E-factor$_2$ does not take solvents into account, E-factor$_3$ assumes the catalyst can be re-used and therefore it is excluded from the total waste.*

[b] *Atom Economy (AE) based on an assumed yield of 100% without considering the loss from the esterification for DMM and DEM.*

[c] *These values are obtained when considering the esterification step in the calculation of the E-factor and AE.*

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(1) Carraher, J. M.; Pfennig, T.; Rao, R. G.; Shanks, B. H.; Tessonnier, J. P. Cis,Cis-Muconic Acid Isomerization and Catalytic Conversion to Biobased Cyclic-C6-1,4-Diacid Monomers. *Green Chem.* **2017**, *19*, 3042–3050.

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(8) Quintens, G.; Vrijsen, J.; Adriaensens, P.; Vanderzande, D.; Junkers, T. Muconic Acid Esters as Bio-Based Acrylate Mimics. *Polym. Chem.* **2019**, *40*, 5555–5563. https://doi.org/10.26434/chemrxiv.9611909.v1.