

Electronic Supplementary Information

A transesterification-acetalization catalytic tandem process for the functionalization of glycerol: the pivotal role of isopropenyl acetate

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Table of contents

The acetylation of glycerol with AcOH.	S3
Figure S1.	S3
The effect of the catalyst amount.	S4
Table S1.	S4
Figure S2.	S6
The acetylation of glycerol with acetic anhydride.....	S6
Figure S3.	S7
Experiments with d ₄ -isotope labelled acetic acid	S7
Figure S4.	S8
Scheme S1.	S9
Figure S5.....	S10
Figure S6.....	S10
Figure S7.....	S11
The reaction of glycerol with Ac ₂ O and acetone	S12
Table S2.	S13
The reaction of glycerol with AcOH and acetone	S13
Table S3.	S13
Scheme S2.	S14
Scheme S3.	S14
Figure S8.....	S15
Figure S9.....	S16

The acetylation of glycerol with AcOH. A solution of glycerol (1.0 mmol) in acetic acid (10 mL; 0.1 M) was set to react in the presence of Amberlyst-15 (15.0 mg; 15 wt%, with respect to glycerol), at 30, 50, and 70 °C, respectively. The reaction mixture was analyzed by GC at intervals from 0.5 up to 24 h. The conversion of glycerol and the products distribution, both evaluated by calibration with standard solutions are shown in Figure S1.

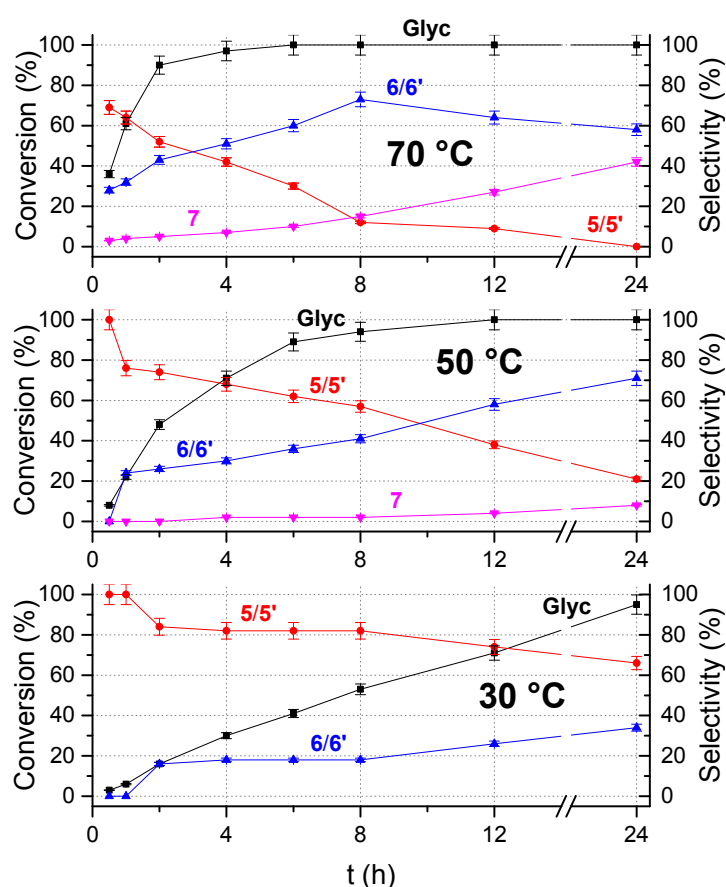
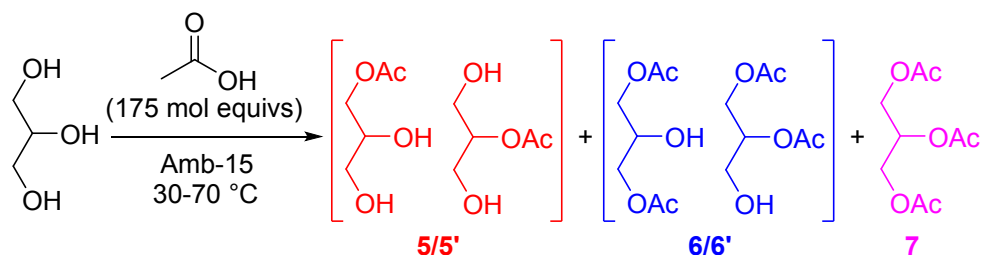


Figure S1. The reaction between glycerol and acetic acid at different temperatures of 30, 50 and 70 °C (bottom, mid, and top, respectively). Conditions: solution of glycerol (1.0 mmol) in acetic acid (10 mL, 0.1 M), Amberlyst-15 (15.0 mg; 15 wt%) as a catalyst. (-■-) Glyceral conversion; (-●-) selectivity towards monoacetin (5/5'); (-▲-) selectivity towards diacetin (6/6'); (-▼-) selectivity towards triacetin (7)

The increase of the temperature affected both the conversion and the products distribution. As T was raised from 30 to 50 and 70 °C: i) a quantitative conversion of glycerol was reached after 24, 12, and 6 h, respectively; ii) prolonged experiments proceeded with the preferential formation of products deriving from the multiple (bis and tris) acetylation of glycerol. Notably however, at comparable high conversions (ca 90%), the ratio of mono- to di-acetins (5/5':6/6') displayed by the three figures, was in a relatively narrow range from 55:40 to 65:35, thereby indicating that the relative rates of mono- and bis-acetylation of glycerol were poorly influenced by the temperature,

at least, until unconverted glycerol was present. This was manifest by comparing the selectivity towards **5/5'** and **6/6'** reached at 30, 50 and 70 °C, after 24, 8, and 2 h, respectively, and led to corroborate the observation that, regardless of the temperature, the selectivity was elusive using AcOH as an acetylating agent.

Moreover, at the highest investigated temperature (70 °C), the amount of triacetin detected after 8 h (12%) was equivalent to that (13%) achieved in half the time (4 h) in the presence of iPAC/AcOH (compare entry 3, Table 1 in the main text). This notwithstanding AcOH was in used in a very large (175) molar excess, while iPAC was equimolar with respect to glycerol. The results suggested that acetic acid was a far less active acetylating agent than iPAC.

The effect of the catalyst amount. Two experiments were carried out under the same conditions of Figure 1 (glycerol: 1.00 mmol; iPAC: 7.50 mmol; AcOH: 8.00 mmol, 0.5 mL; 30 °C), except for the glycerol:catalyst weight ratio that was changed: the amount of Amberlyst-15 was reduced to 10 and 5 wt% with respect to glycerol. Results are reported in Table S1 after 24 h. For comparison, data of Figure 1 (Amberlyst-15: 15 wt%) are also included.

Table S1. Effect of the catalyst amount on the reaction of glycerol with a mixture of iPAC/AcOH

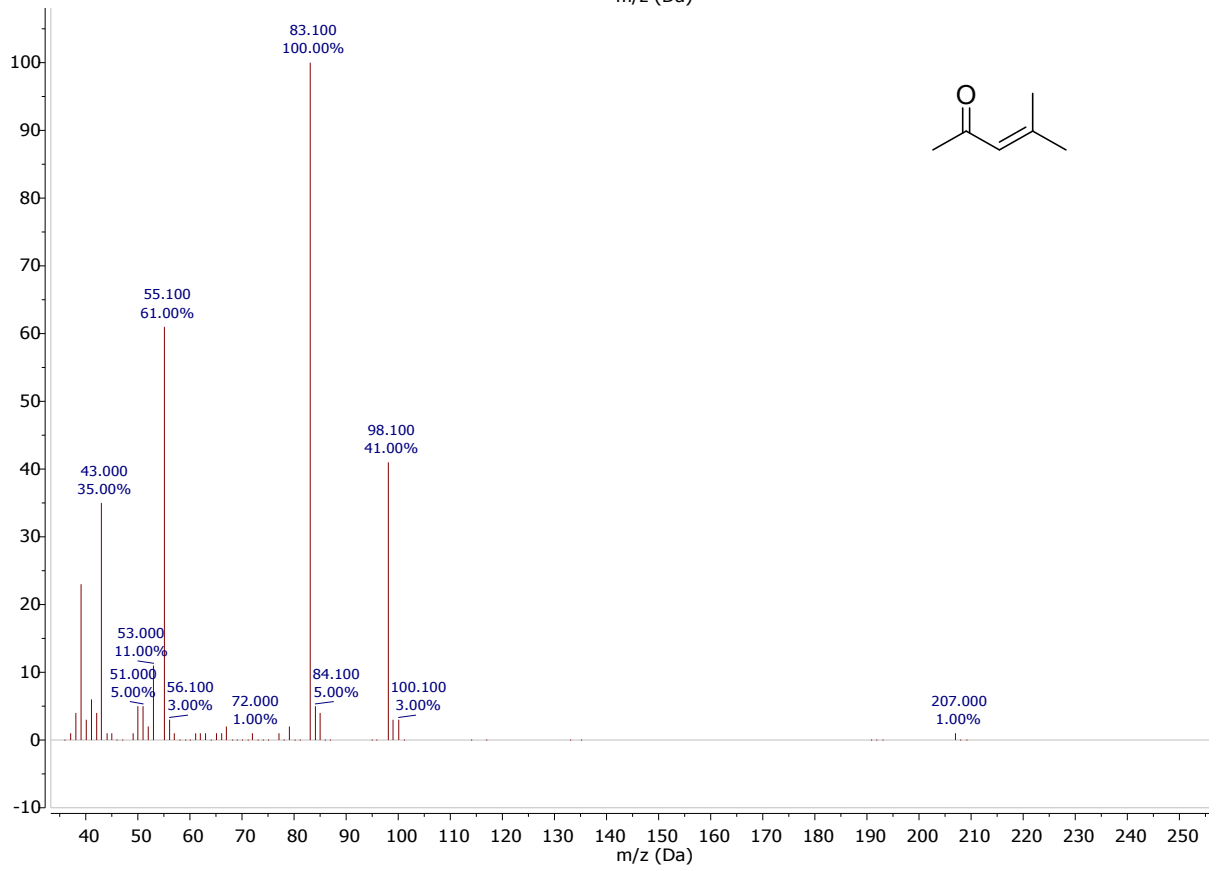
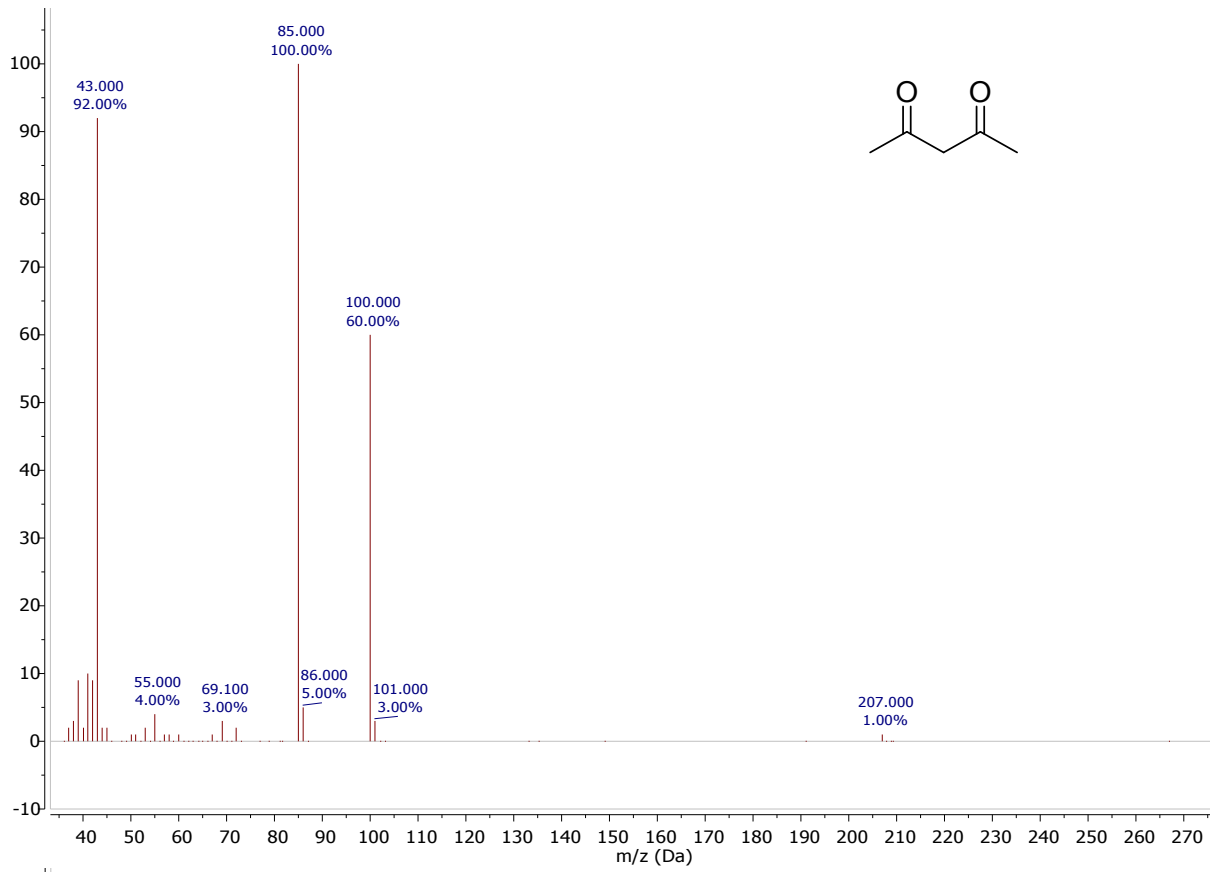
Entry	Amb-15 (wt%)	Conv. (%) ^a	Products distribution (%) ^b	
			4/4' ^c	7
1	15	≥99	50	50
2	10	≥99	61	39
3	5	≥99	67	33

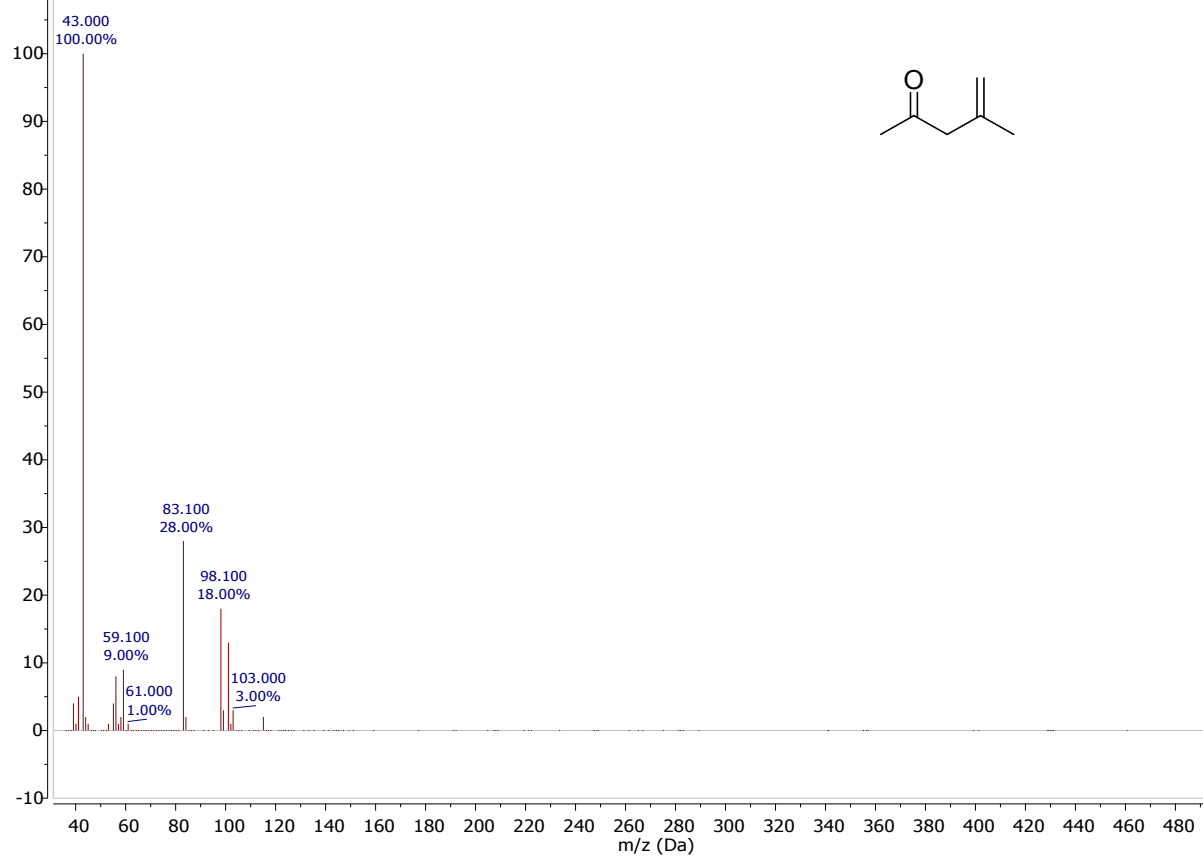
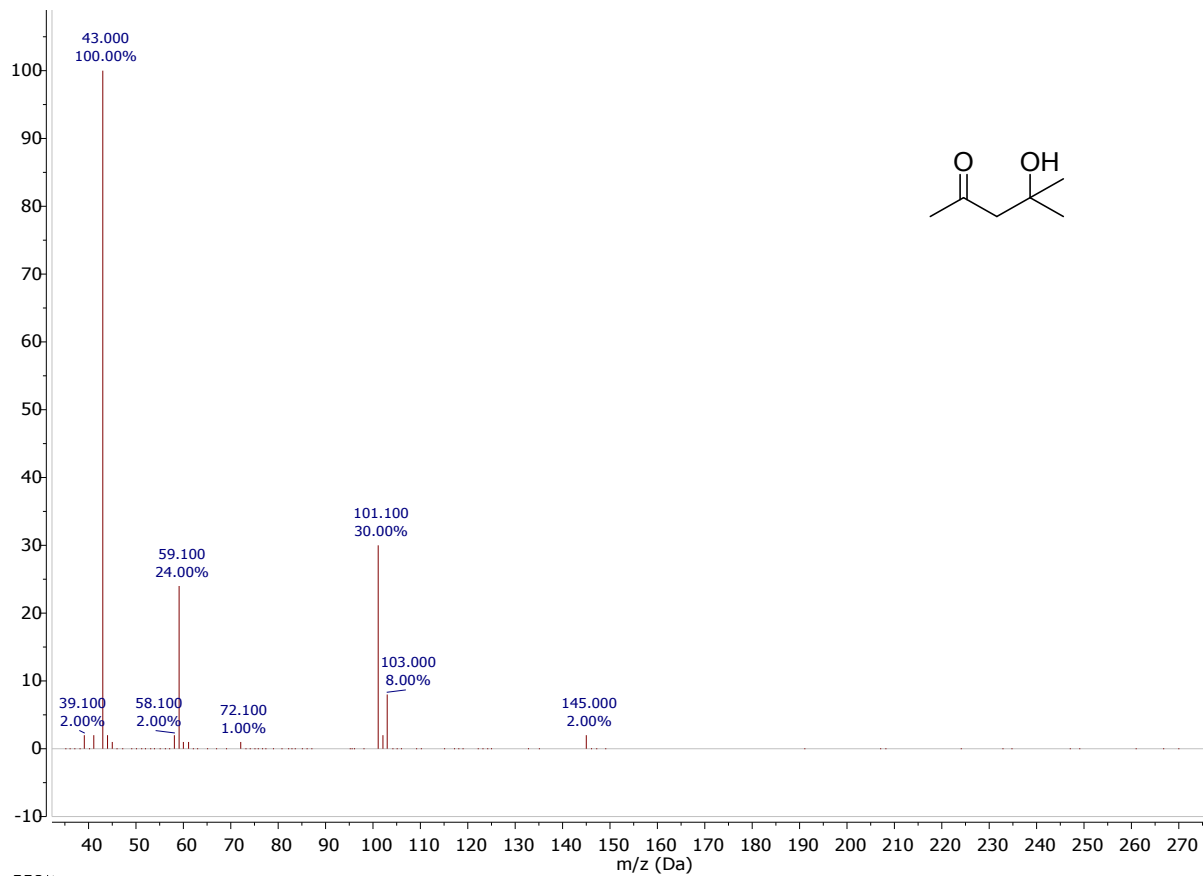
Conditions: mixture of glycerol (1.00 mmol), iPAC (7.50 mmol), and AcOH (8.00 mmol, 0.5 mL) in the presence of variable amounts of Amberlyst-15 (5.00, 10.00, and 15.00 mg; 5, 10, and 15 wt%), t = 24h. ^a Conversion of glycerol. ^b Selectivity towards compounds **4/4'** and **7** was defined as reported in the main text. ^c Total amount of isomer products

Decreasing the catalyst amount brought about a drop of the rate of all the reactions involved: after 24 h, albeit acetal acetates **4/4'** and triacetin **7** were the only observed products in all cases, the corresponding amounts increased and decreased, respectively, from 50 to 61 and 67% for **4/4'**, and from 50 to 39 and 33% for **7** (entries 1-3). Results were consistent with profiles of Figure 1 where at the highest investigated catalyst amount (15 wt%), the (**4/4'**):**7** ratio reached a maximum of ca 60:40 after 120 min, comparable to that achieved after 24 h with Amberlyst-15 at 10 wt%.

No further investigations were carried out on this aspect.

The reaction of iPAC and acetic acid. At 30 °C, after 24 h, the reaction of an equimolar mixture of isopropenyl acetate (5.0 mmol) and acetic acid in the presence of Amberlyst-15 as a catalyst (45.0 mg; 15 wt% with respect to AcOH) mainly afforded acetic anhydride (80% yield, by GC), though minor amounts by-products (≤10% with respect to Ac₂O) were detected. The mass spectra of these compounds are reported in Figure S2, and were consistent with the formation of acetylacetone, and of products of the aldol condensation of acetone, both the aldol, 4-hydroxy-4-methylpentan-2-one, and the two isomers of the α,β-unsaturated carbonyl derivative, 4-methylpent-3-en-2-one and 4-methylpent-4-en-2-one. In addition, the formation of 4-oxopentan-2-yl acetate was observed. Comparison with spectra of authentic compounds available from the NIST library of the GC/MS ChemStation afforded a match quality >60% in all cases.





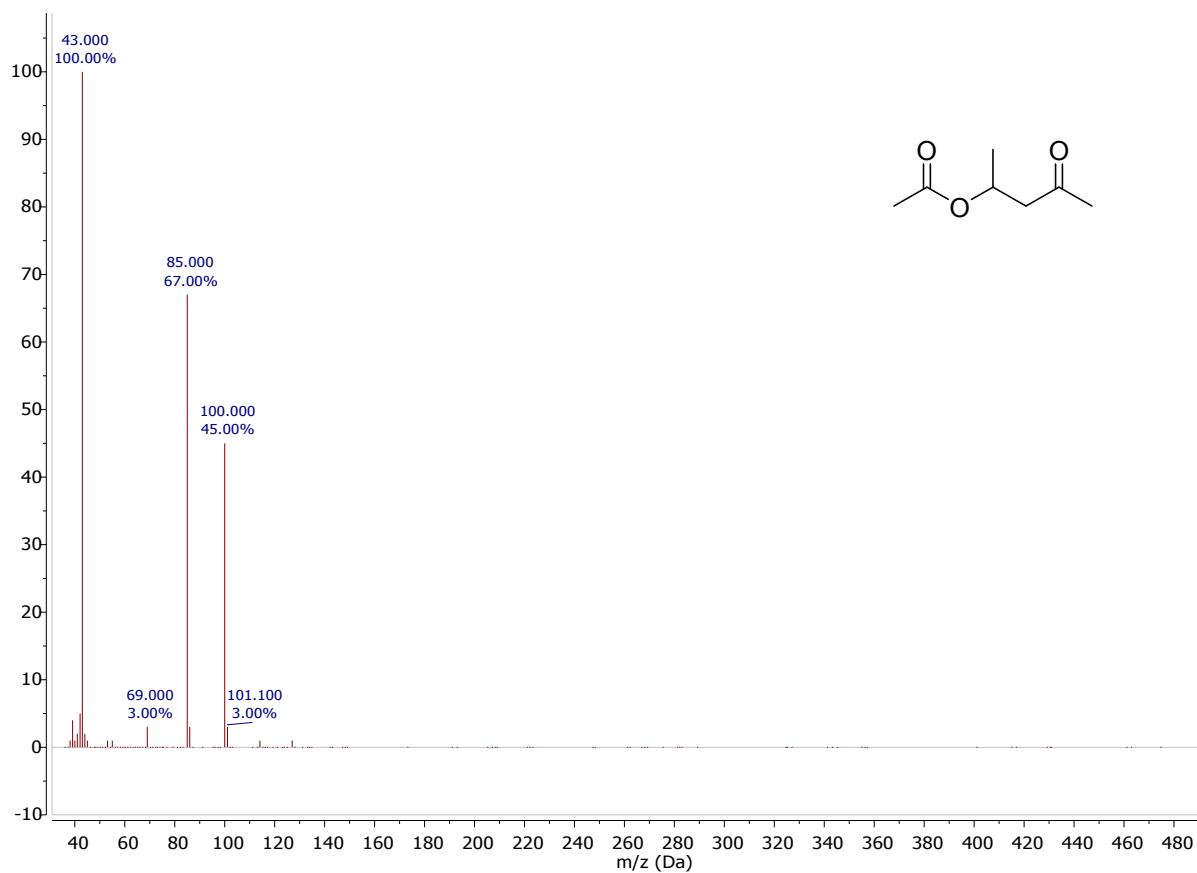


Figure S2. Mass spectra of by-products of the reaction of iPAc and acetic acid

The acetylation of glycerol with acetic anhydride. A solution of glycerol (1.00 mmol) in acetic acid (0.1 M, 10 mL) was set to react at 30 °C, in the presence of different amounts of acetic anhydride and Amberlyst-15 (15.0 mg, 15 wt% with respect to glycerol) as the catalyst. Figure S3 reports the results of four reactions in which the glycerol:Ac₂O (W) molar ratio was 5, 2, 1 and 0.2, respectively.

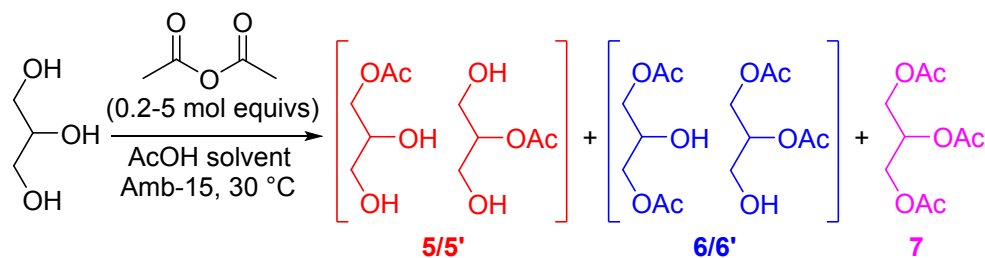
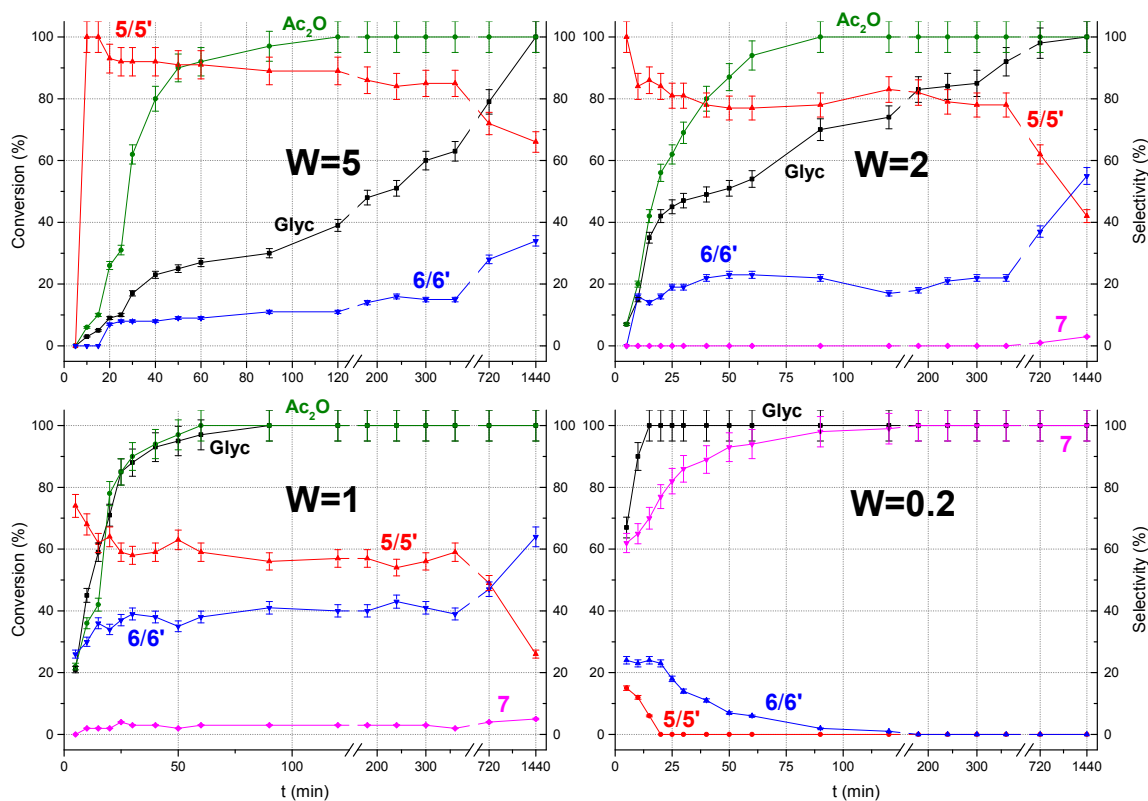


Figure S3. The reaction of a solution of glycerol (1.00 mmol) in acetic acid (10 mL; 0.1 M) carried out at 30 °C, in the presence of variable amounts of and acetic anhydride and Amberlyst-15 catalysis (15.0 mg; 15 wt%) as the catalyst. The glycerol:Ac₂O molar ratio (W) was 5, 2, 1 and 0.2: the corresponding four reaction profiles are shown in top left, top right, bottom left, and bottom right figures, respectively. (—■—) conversion of glycerol; (—●—) conversion of acetic anhydride; (—▲—) selectivity towards mono-acetins (5/5'); (—▼—) selectivity towards diacetin (6/6'); (—◆—) selectivity towards triacetin (7)

Compared to Figure S1, the acetylating capability of Ac₂O proved much better than that of AcOH. This was manifest even when sub-stoichiometric amounts of the anhydride were used: in the first 60-120 min of reaction, as long as Ac₂O was present in the reaction mixture, both the conversion of glycerol and the proportion of bis- versus mono- acetylated products [diacetins 6/6' vs mono-acetins 5/5'] were higher than that achieved with AcOH (cfr Figure S1, bottom, to Figure S2, top). No to

mention that in the same time interval, triacetin **7** was obtained as a single product when 5 molar equivs of Ac_2O were used (bottom right, Figure S2).

Notably, after the consumption of Ac_2O , all reactions slowed down significantly: the further conversion of glycerol and the formation of its multiple transesterification derivatives was ascribable to the acetylating activity of AcOH .

Experiments with d_4 -isotope labelled acetic acid. Reactions were carried out under the conditions of Figure 1 by replacing AcOH with its d_4 -isotope labelled analogue, CD_3COOD . A mixture of glycerol (1.0 mmol), iPAc (7.5 mmol), CD_3COOD (0.5 mL, 8.75 mmol), and Amberlyst-15 (15.0 mg, 15 wt%) was set to react at 30 °C, for 24 h. The GC/MS analysis of the reaction mixture proved the formation of labelled derivatives with variable D contents for each of the expected products of glycerol. Notwithstanding this complexity, at the end of the experiment (24 h), the formation of acetal acetates and triacetin was detected in analogy to what observed in Figure 1. Acetal acetates were present as two species (per each isomer), the non- and the tri-deuterated compounds, while triacetin was obtained in the form of four species, the non-, the tri-, the hexa-, and the nona-deuterated products, respectively (see Scheme 7, main text). Figure S4 reports the result by showing enlarged regions of GC/MS analyses corresponding to the two signals of solketal acetate, the most abundant 5-membered ring acetal ester (top), and the four signals of triacetin (bottom).

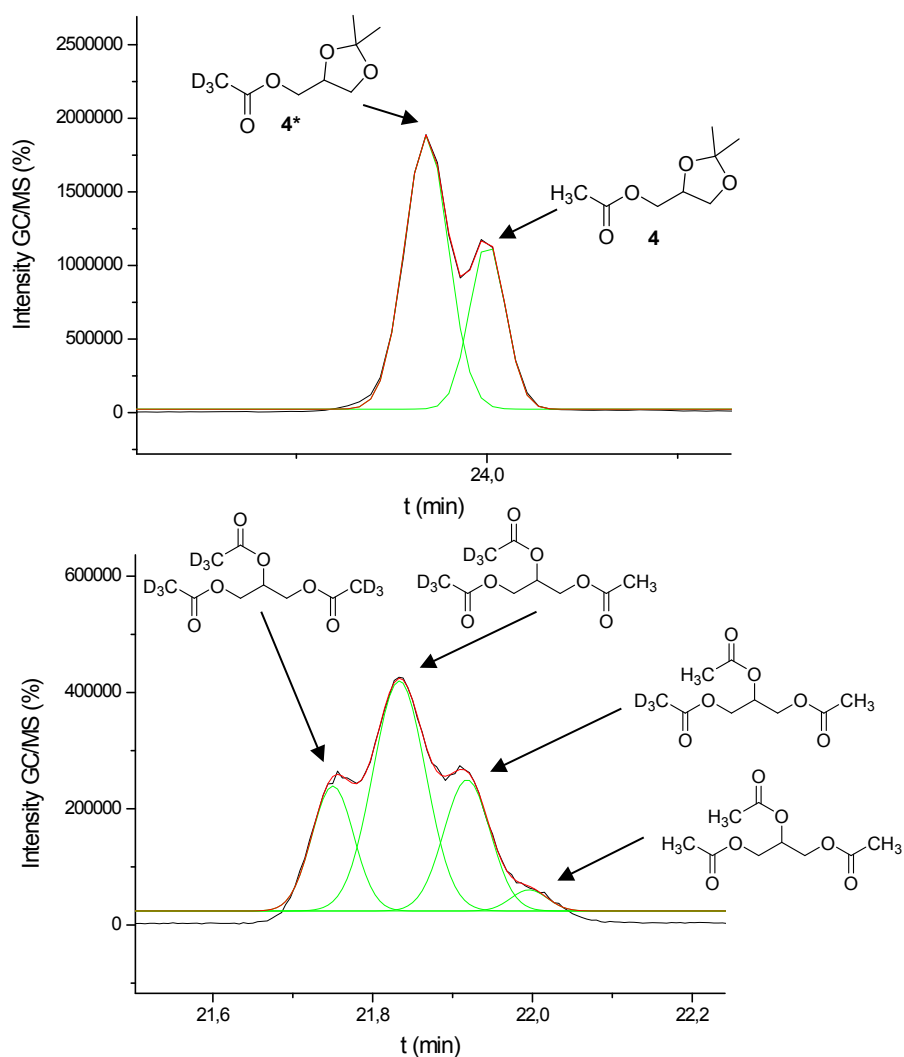
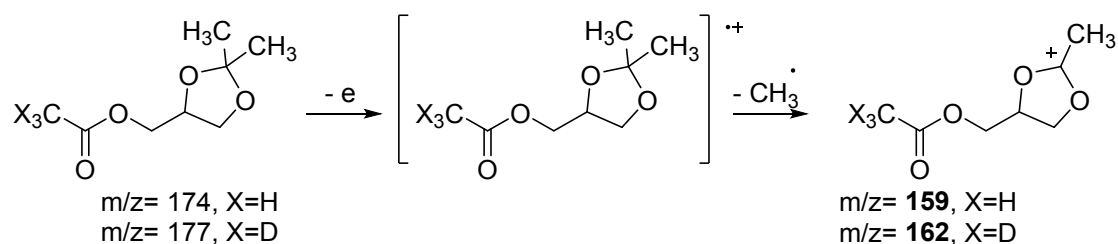


Figure S4. Top: the red profile shows the GC/MS signals for solketal acetate; the corresponding d_3 - and non-deuterated derivatives are indicated from left to right, respectively. Bottom: the red profile shows the GC/MS signals for triacetin; the corresponding d_9 -, d_6 -, d_3 - and non-deuterated derivatives are indicated from left to right, respectively. Green profiles for both top and bottom represent the deconvolution of the red profiles carried out by the “Gaussian polynomial fitting” available in the OriginPro Software (ver. 9.1)

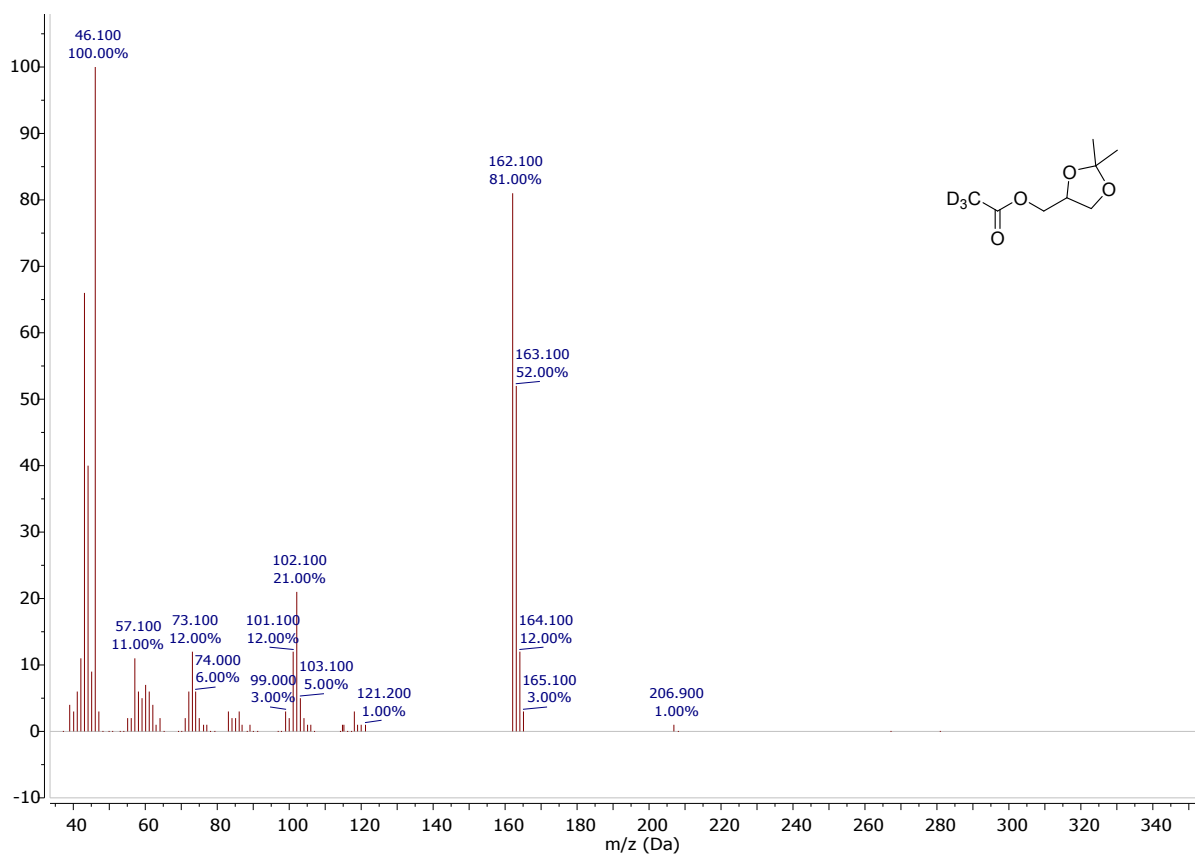
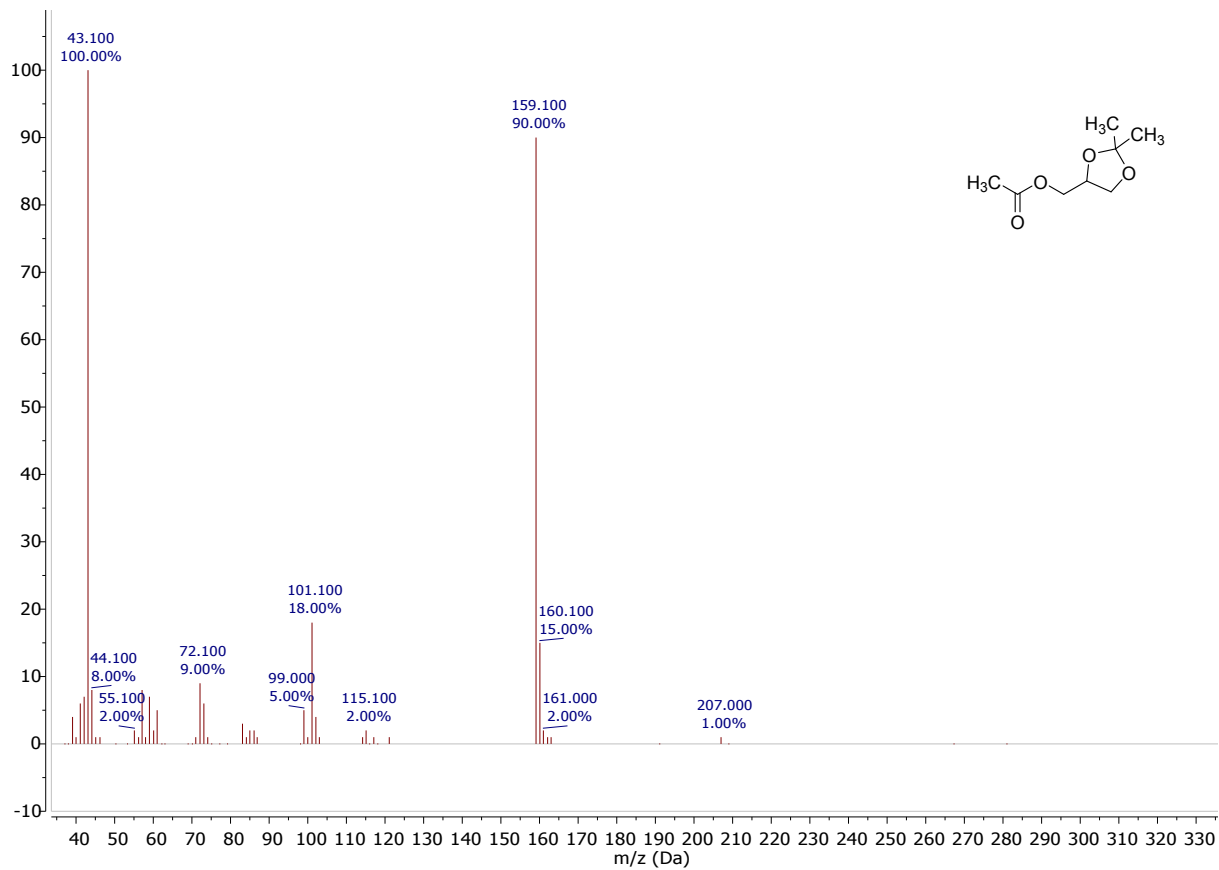
In the figure, red profiles were the authentic GC/MS analyses, while green profiles were obtained by the deconvolution of the red ones, carried out by the “Gaussian polynomial fitting” available in the OriginPro Software (ver. 9.1, Origin Lab. Corp.). Thanks to a more satisfactory resolution, signals of solketal acetate (compounds **4** and **4***, top) allowed not only a more reliable integration of the area under the corresponding peaks, but also a better reading/interpretation of GC/MS spectra, than those of different triacetins.

The investigation was then continued considering only products **4** and **4***. From deconvolution, the relative amounts of **4*** and **4** were 67% and 33%, meaning that the quantity of the tri-deuterated solketal acetate was twice as much the non-deuterated derivative. From the mass spectra recorded in the full scan (TIC, 70 eV), fragment ions at $m/z = 159$ and 162 were recognized as the most abundant and easily distinguishable ions for **4** and **4***, respectively (Figure S5).

The characteristic absence of the molecular ion peak ($M^+=174$ and 177 for **4** and **4***, respectively) was already noticed in a previous paper reported by us.¹ The fragment ions 159 and 162 were consistent with the loss of a methyl radical from the acetal ring (Scheme S1)



Scheme S1. Plausible fragmentation pathway for the formation of ions 159 and 162 from compounds **4** and **4***



re S5. Mass spectra (TIC) of product **4** (top) and **4*** (bottom)

Fig

To improve sensitivity, mass spectra were then acquired in the SIM mode on the characteristic fragment ions $m/z = 159$ and 162 (70 eV) (Figure S6).

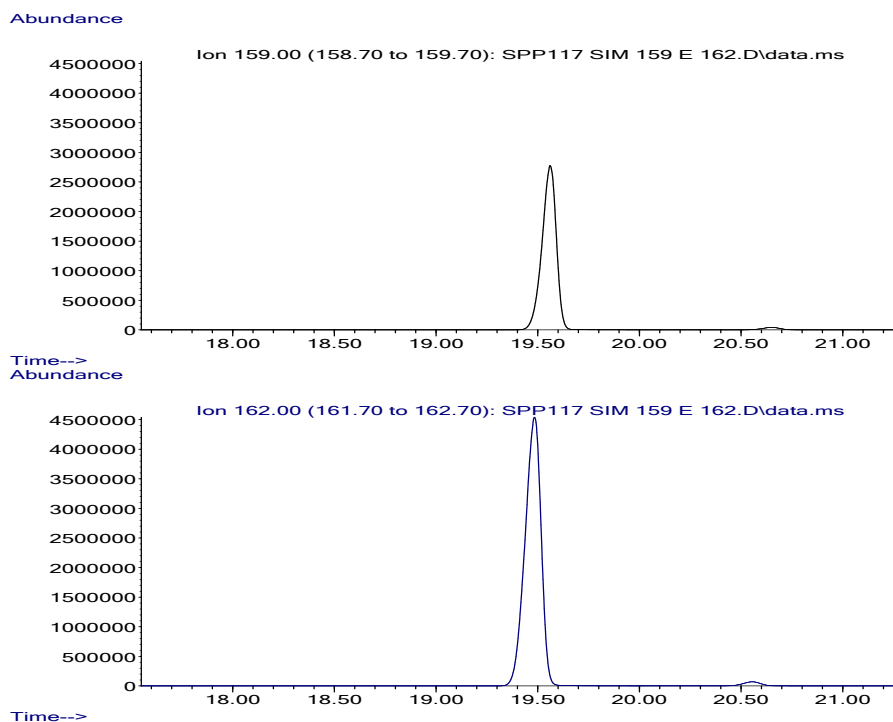


Figure S6. SIM chromatograms of selected fragment ions $m/z = 159$ and 162 for products **4** (top) and **4*** (bottom), respectively.

Integration of signals in the SIM chromatogram proved that relative areas under the peaks of target ions 159 and 162 were 65% and 35%, respectively, thereby confirming that the parent compounds **4*** and **4** were formed in a ratio of about 2:1.

The GC/MS analysis of the same reaction mixture also indicated the formation of three species of acetic anhydride, *i.e.* the non-, the tri-, and hexa-deuterated products (Figure S7).

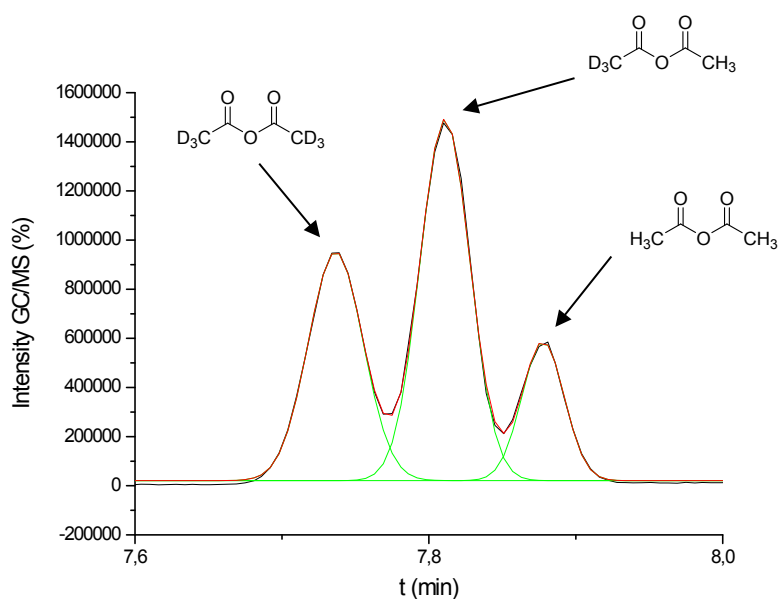


Figure S7. The red profile shows the GC/MS signals for acetic anhydride: the corresponding d_6 -, d_3 -, and non-deuterated derivatives are indicated from left to right, respectively. The green profile represents the deconvolution of the red profiles carried out by the "Gaussian polynomial fitting" available in the OriginPro Software (ver. 9.1)

From deconvolution (green profile), the integration of the area under the corresponding peaks allowed to estimate that non-deuterated, d_3 - and d_6 - species of acetic anhydride were present in a 1:3:2 ratio, respectively.

The reaction of glycerol with Ac_2O and acetone. Glycerol (1.00 mmol) was set to react with different mixtures of Ac_2O (1.00-10.00 mmol) and acetone (1.00-20.00 mmol) using Amberlyst-15 as a catalyst (15 wt%). Acetic acid (1.5 equivs. with respect to glycerol) was employed as a solvent. Experiments were carried out at 30°C, for 24 h. Results are shown in Table S2.

Table S2. The reaction of glycerol with acetone and acetic anhydride

Entry	Solvent	Glyc:Acce: Ac_2O^a (mol:mol:mol)	Conversion ^b (%)	Selectivity ^c (%)				
				3/3'	4/4'	5/5'	6/6'	7
1	AcOH (1.5 equivs.)	1:5:3	≥99		61		1	38
2		1:1:1	≥99	10	30	34	23	1
3		1:1:10	≥99		30		1	69
4		1:3:10	≥99		58		1	41
5		1:5:10	≥99		68		1	31
6		1:20:5	≥99		82			18
7		1:20:2.5	≥99	15	78		3	5

Conditions: T=30 °C, Amberlyst-15 (15 mg; 15 wt%, with respect to glycerol), t=24 h. ^a Molar ratio of the reactants. ^b Conversion of glycerol, by GC. ^c Products selectivity (by GC) calculated as described in the main text.

Under the conditions of Scheme 9 of the main text, when iPAc was replaced by Ac_2O , the selectivity towards **4/4'** did not exceed 61% (entry 1: compared to 91% achieved with iPAc). The optimization of the reactants molar ratio allowed to obtain the desired acetal acetates **4/4'** in a 82% amount only by using a significantly large excess of both acetone and acetic anhydride (20 and 5 molar equivalents, respectively), with respect to glycerol (entry 6).

The reaction of glycerol with AcOH and acetone. Glycerol (1.00 mmol) was set to react with different mixtures of AcOH (1.00-10.00 mmol) and acetone (1.00-20.00 mmol) using Amberlyst-15 as a catalyst (15 wt%). Experiments were carried out at 30°C, for 24 h. Results are shown in Table S2.

Table S3. The reaction of glycerol with acetone and acetic acid

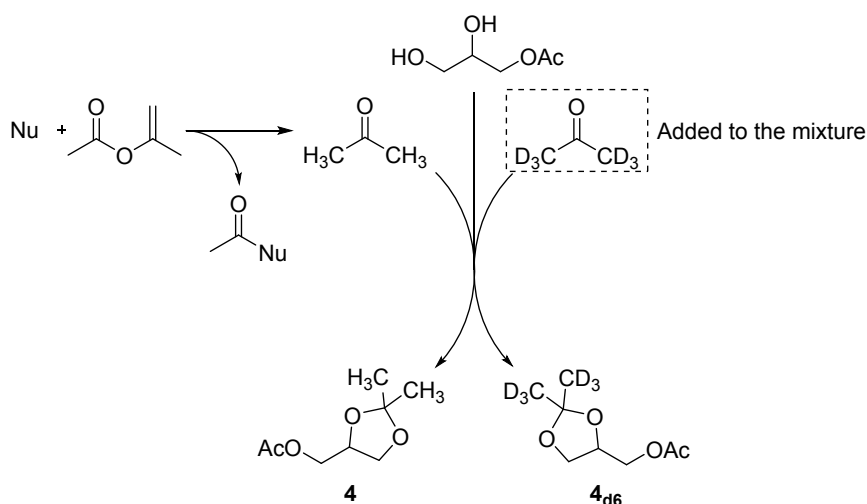
Entry	Glyc:Acce:AcOH ^a (mol:mol:mol)	Conversion ^b (%)	Selectivity ^c (%)				
			3/3'	4/4'	5/5'	6/6'	7
1	1:1:1	70	56	12	30	2	-
2	1:1:10	95	8	15	51	25	1
3	1:3:10	96	33	26	33	7	-
4	1:5:10	≥99	48	32	15	5	-
5	1:20:5	≥99	95	5	-	-	-
6	1:20:2.5	≥99	97	3	-	-	-

Conditions: T=30 °C, Amberlyst-15 (15.00 mg; 15 wt%, with respect to glycerol), t=24 h. ^a Molar ratio of the reactants. ^b Conversion of glycerol, by GC. ^c Products selectivity (by GC) calculated as described in the main text

The reaction of an equimolar mixture of glycerol, acetone and acetic acid showed that the acetalization of glycerol was favored over its acetylation: compounds **3/3'** were the most abundant products (56%; entry 1). The situation reversed using an excess AcOH (10 molar equivs) which

brought about the predominant formation of glyceryl esters as a mixture of mono- and di-acetins (**5/5'**: 51% and **6/6'**: 25%, respectively: entry 2). Thereafter, attempts to tune the products distribution by further modifying the reactants molar ratio were unsuccessful. Increasing acetone with a constant volume of AcOH allowed to increase both acetals **3/3'** and acetals esters **4/4'** up to a maximum of 48% and 32% amount, respectively (entry 4); however, further increasing the ketone and decreasing acetic acid resulted in the highly selective formation of acetals **3/3'** (95-97%, entries 5-6). Results led to conclude that the mixture of acetone and acetic acid could in no way replace the use of iPac for the selective synthesis of acetals acetates **4/4'**.

The reaction with d₆-acetone. The synthesis of acetal acetates was explored using d₆-acetone in place of acetone under the conditions of Scheme 9. A mixture of glycerol (1.00 mmol), isopropenyl acetate (4.00 mmol), d₆-acetone (5.00 mmol), acetic acid (1.50 mmol), and Amberlyst-15 (15.00 mg; 15 wt% with respect to glycerol) was set to react for 16 h at 30 °C. The experiment indicated the formation of acetal acetates in the form of two species (per each isomer), the non- and the hexa-deuterated compounds, respectively. The attention was focused on solketal acetate which was by far the most abundant isomer (97%). Scheme S2 offers a pathway for the formation of the d₆- and the non-deuterated solketal acetate.

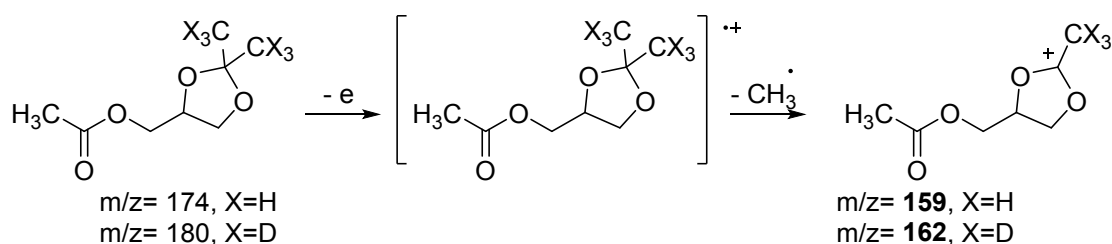


Scheme S2. Pathways for the formation the non-deuterated and the d₆- solketal acetate (**4** and **4_{d6}**, respectively)

The acetylation of any nucleophilic species available in the reaction environment (Nu: glycerol, mono- or di-acetins) by iPac, releases acetone (CH₃COCH₃) which competitively reacts with d₆-acetone (CD₃COCD₃, added to the mixture) for the acetalization of glycerol, affording the non-deuterated **4** and the d₆- solketal acetate **4_{d6}**, respectively).

GC/MS analyses recorded in the full scan (TIC, 70 eV) allowed to identify fragment ions at m/z = 159 and 162 as the most abundant and easily distinguishable ions for **4** and **4_{d6}**, respectively (Figure S5).

In analogy to Scheme S1, the fragment ions 159 and 162 were consistent with the loss of a methyl radical from the acetal ring (Scheme S3).



Scheme S3. Plausible fragmentation pathway for the formation of ions 159 and 162 from compounds **4** and **4_{d6}**

Although ions with $m/z = 159$ and 162 were the same selected when labelled acetic acid was used (cf. Figure S5), the analysis of mass spectra proved that compound **4*** bearing the isotopic marking on the acetyl group underwent a different fragmentation pathway with respect to compound **4_{d6}** where the marking was on the methyl group of the acetal ring. The comparison of Figure S5 and Figure S8 highlights this difference. The characteristic fragment ions for **4*** were 162 (81), 102 (21), 73 (12), 57 (11), 46 (100), 43 (66), while those for **4_{d6}** were 162 (100), 107 (30), 76 (18), 65 (12), 46 (88), 43 (86).

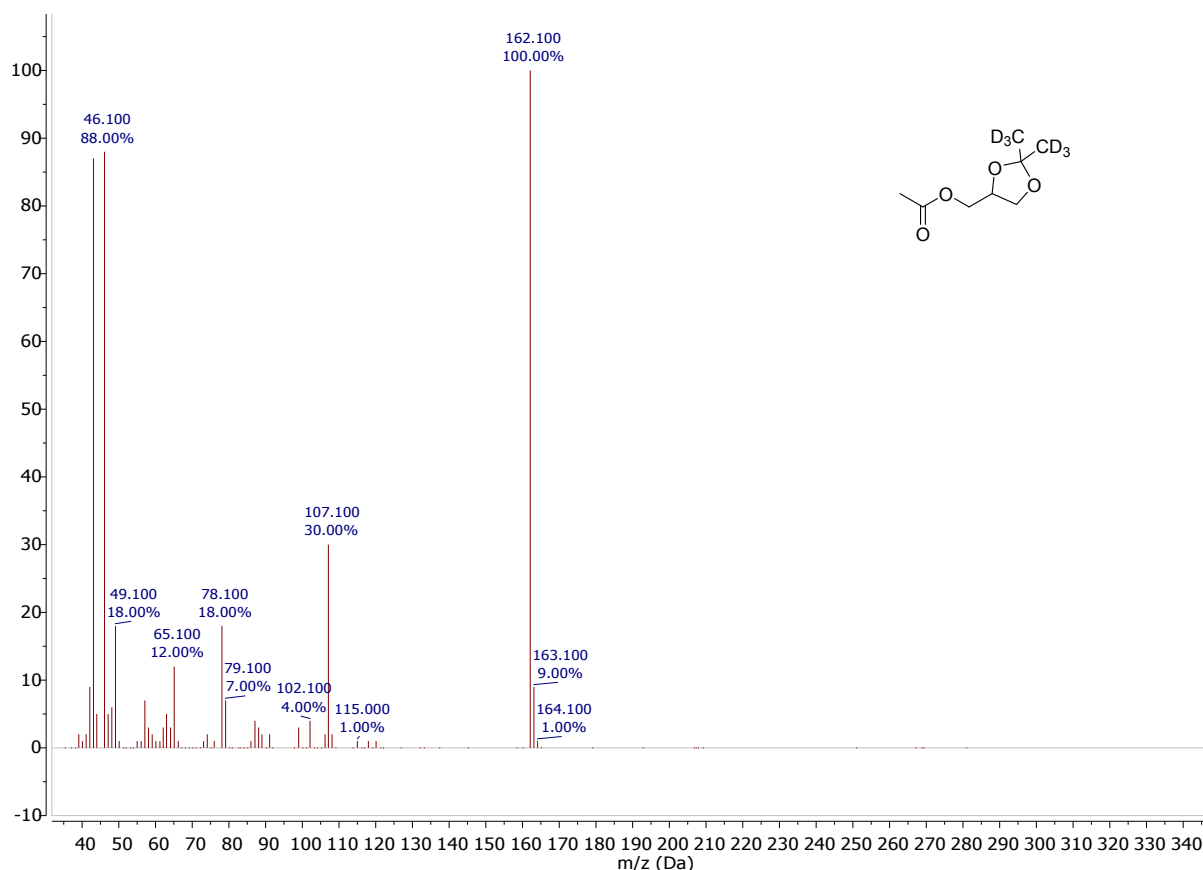
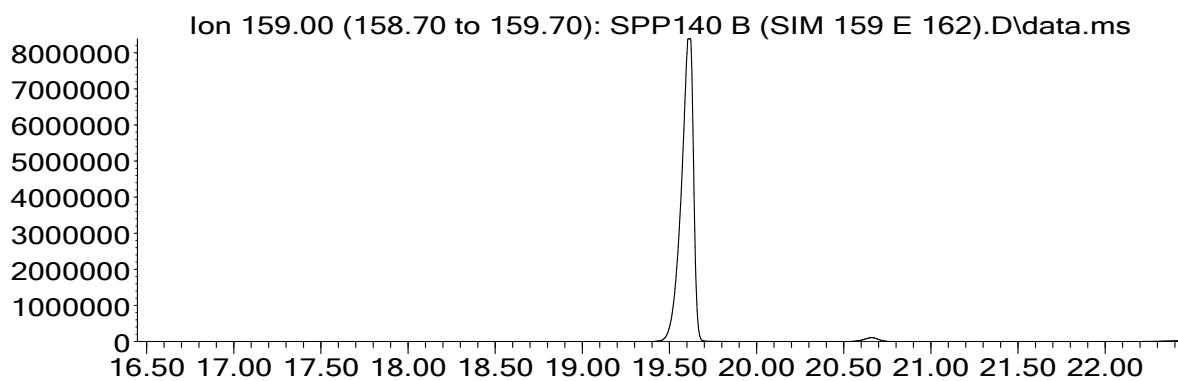


Figure S8. Mass spectra of product **4_{d6}**. For the comparison with mass spectra of product **4** see Figure S4, top

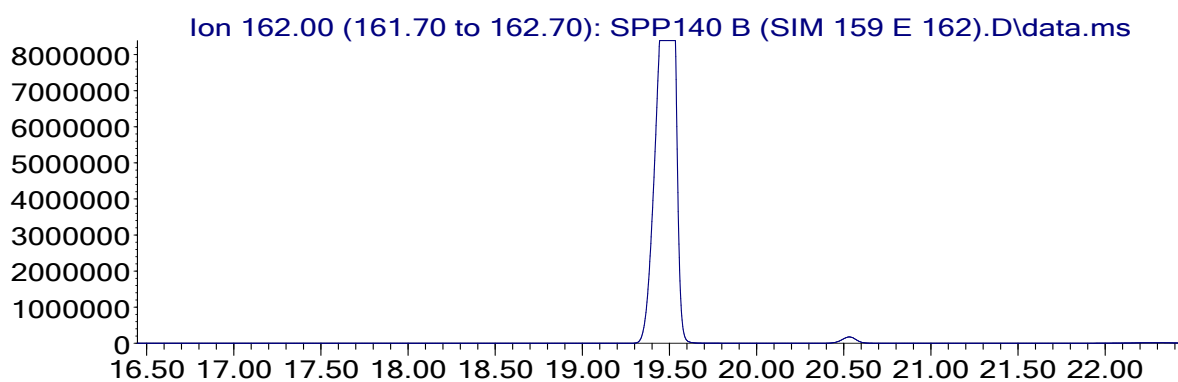
Mass spectra were then acquired in the SIM mode on the fragment ions $m/z = 159$ and 162 for compounds **4** and **4_{d6}**, respectively. (Figure S9). Integration of signals in the SIM chromatograms proved that relative areas under the peaks of target ions 159 and 162 were 65% and 35%, respectively, thereby confirming that the parent compounds **4_{d6}** and **4** were formed in a ratio of about 2:1.

Abundance



Time-->

Abundance



Time-->

Figure S9. SIM chromatograms of fragment ions $m/z = 159$ and 162 from products **4** and **4_{d6}**, respectively.

References

¹ R. Calmanti, M. Galvan, E. Amadio, A. Perosa, M. Selva, *ACS Sustainable Chem. Eng.* 2018, **6(3)**, 3964-3973, DOI: 10.1021/acssuschemeng.7b04297.