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Triflic Acid Mediated Dealkylative Lactonisation via NMR-Observable Alkyloxonium Intermediates

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Keywords: Lactones / Triflic acid / Allylmalonates / Intermediates / Kinetics

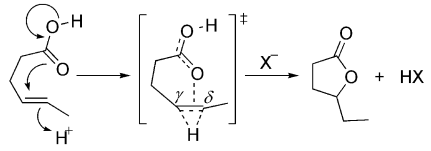
Trifluoromethanesulfonic acid (TfOH) efficiently induces the dealkylative cyclisation of pent-4-enoates to generate γ-lactones with high selectivity. For primary alkyl esters bearing an additional alkene, only monolactonisation occurs, even in the presence of excess TfOH. The kinetics of the reaction have been studied by ^{1}H NMR spectroscopy, which reveal that the TfOH acid undergoes a self-catalysed reaction with the pent-4-enoate to generate an oxonium triflate intermediate (rate ≈ $k_{obsd.}$[TfOH]^2[ester]^1), possibly via the dimer $(TfOH)_2$. The oxonium triflate intermediate then evolves to the γ-lactone according to unimolecular kinetics, liberating MeOTf in an S_Ni reaction. ^{2}H-labelling experiments with TfOD suggest that the acid protonates the carbonyl moiety of the ester, with subsequent intramolecular delivery of D^+ to the alkene. The resulting carbocation is transient, being rapidly captured intramolecularly to generate the oxonium species. Reversibility in this step mediates equilibration of diastereomeric oxonium intermediates via the carbocation.

Introduction

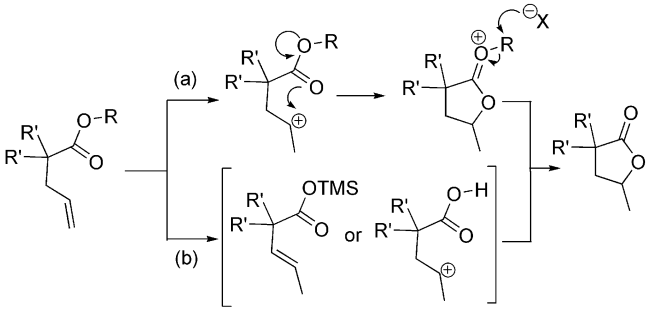
Although the reaction of olefinic acids with electrophiles (E^+ or H^+) to give cyclic γ- or δ-lactones and ketones has been known for over half a century,[1] the direct dealkylative lactonisation of pent-4-enoates by electrophilic addition to the alkene has been less well studied. This process has recently emerged as a side-reaction occurring under transition metal catalysed and Lewis acid catalysed cycloisomerisation of 1,*n*-dienes (*n* = 6, 7).[2]

The acid-catalysed lactonisation of pent-4-enoic acids is generally assumed to involve *trans* addition to the double bond in a concerted or near-concerted mechanism. Ring-closure via a transition state with a greater overlap between the 2p orbitals of the carbonyl oxygen atom and the vacant orbital of the γ-carbocation, as compared to the δ-carbocation, can then explain the selective formation of γ-lactones over δ-lactones (Scheme 1).[3]

A variety of mechanisms have been proposed for the Bronsted acid ("HX") *mediated*, albeit Lewis acid *catalysed*, dealkylative lactonisation of dialkyl allylmalonates.[4–6] All of the mechanisms invoke the formation of carbocationic species by addition of a Lewis or Bronsted acid to the alkene followed by addition of the alkyl or carbonyl oxygen atom, and then dealkylation of the resultant oxonium species [– RX, Scheme 2 (a)].[4] Prior ester cleavage and then capture of the alkene (or carbocation) by the resultant carboxylic acid (or acid derivative) has also been proposed [Scheme 2 (b)].[5] This mechanism is also proposed for the analogous reaction of olefinic nitriles.[6]



Scheme 1. Mechanism proposed for the lactonisation of olefinic acids.[3]



Scheme 2. Mechanisms proposed for the lactonisation of olefinic esters.[4,5]

trans-Addition has also been proposed for dealkylative lactonisation of olefinic esters by E^+, with formation of cyclic oxonium salts stabilised by resonance (Scheme 3). Isola-

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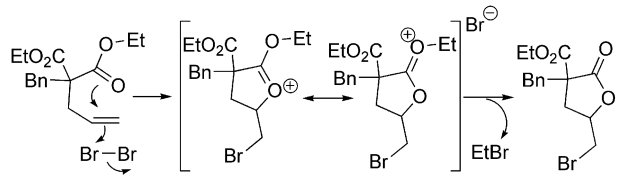
tion of alkyl bromides in the reaction of bromine with allylmalonates and inversion of configuration of the expelled alkyl group (S_N2), supported this mechanism.[7]



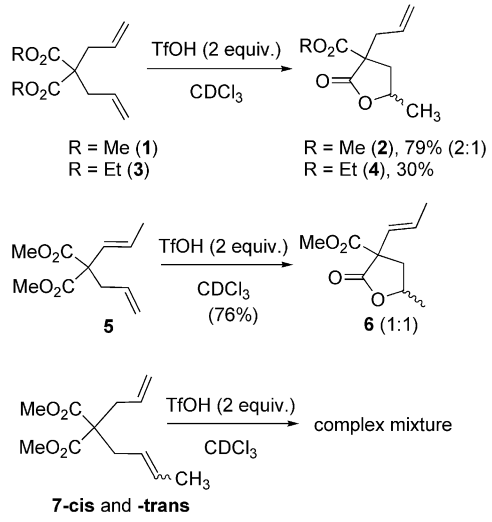
Scheme 3. Bromolactonisation of diethyl allyl(benzyl)malonate.[7]

As part of an ongoing investigation into acid-catalysed rearrangements of (alkene)alkylpalladium complexes,[8] we noted that trifluoromethanesulfonic acid ("triflic acid", TfOH) mediates dealkylative lactonisation of dialkyl diallylmalonates.[9] Herein we report a mechanistic study of the lactonisation reaction, including kinetic measurements, detection of intermediates by NMR spectroscopy, and ^{2}H-labelling experiments.

Results and Discussion

Dealkylative Lactonisation of Allylmalonates

The reaction of dimethyl diallylmalonate (**1**, Scheme 4) with TfOH gives lactone **2** as a mixture of two diastereoisomers (2:1) in good yield. Intriguingly, only monolactonisation was observed, even when 2 equiv. of the acid were used, leaving one allyl unit unreacted. A similar result was obtained with the ethyl derivative **3**, although in lower yields.[10] The reaction did not proceed with *p*TsOH·H_2O in toluene at 40 °C, or HBF_4·Et_2O in $CHCl_3$ at room temperature.

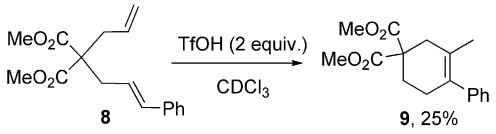


Scheme 4. Dealkylative monolactonisation of diallylmalonates.

When the 1,5-diene **5** (Scheme 4) was submitted to the reaction conditions, lactone **6** was obtained, where the cyclisation occurs only with the allyl unit in a 5-*exo* manner.

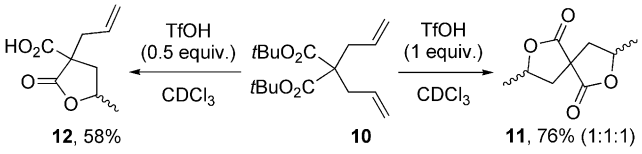
The reaction of the (allyl)(crotyl) derivatives **7-cis** and **7-trans** (Scheme 4) with TfOH gave complex mixtures containing both γ- and δ-lactones.

No lactonisation product was observed in the reaction of the phenyl-substituted derivative (**8**, Scheme 5), and only cyclohexene **9** (tentatively assigned by NMR) could be isolated in a moderate yield.



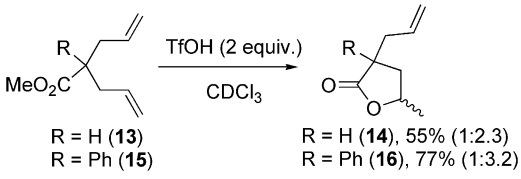
Scheme 5. Reaction of allyl(cinnamyl)malonate **8** with TfOH.

Surprisingly, the reaction of di-*tert*-butyl diallylmalonate (**10**, Scheme 6) in the presence of 1 equiv. of TfOH gave the spirolactone **11** as a 1:1:1 mixture of isomers (symmetrical-*syn*, unsymmetrical and symmetrical-*anti*).[11] This lactone has been previously reported from the reaction of olefinic nitriles with sulfuric acid,[6b] and the reaction of diallylmalonates with SbF_5.[2] The reaction of **10** with 0.5 equiv. of the acid gave the monolactonisation product **12**, in which the second allyl unit again remained unreacted, and the second *tert*-butyl ester was cleaved to the corresponding carboxylic acid.



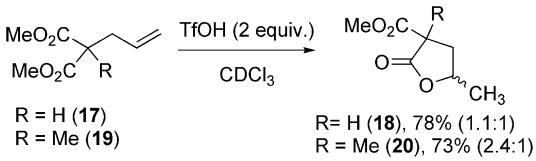
Scheme 6. Lactonisation of *tert*-butyl diallylmalonate (**10**).

The presence of a second ester is not necessary for the lactonisation to proceed, as lactones **14** and **16** were obtained in moderate to good yields from pentenoates **13** and **15** (Scheme 7).

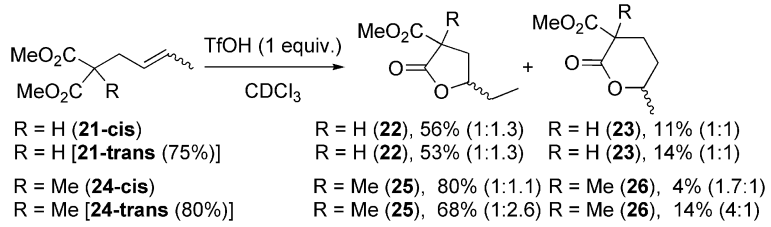


Scheme 7. Lactonisation with monoester derivatives **13** and **15**.

The monoallylmalonates **17** and **19** also gave lactones (**18** and **20**, Scheme 8) in good yields, confirming that the reaction only requires the presence of a single alkenyl unit.



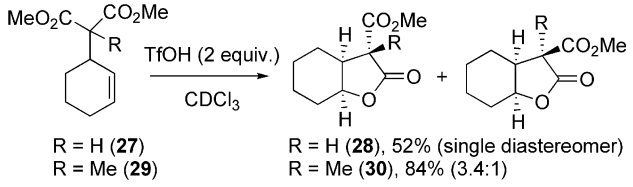
Scheme 8. Reaction of monoallylmalonates **17** and **19** with TfOH.



Scheme 9. Reaction of crotyl derivatives **21** and **24** with TfOH.

Crotyl derivatives **21** and **24** reacted with 1 equiv. of TfOH to give a mixture of the γ- (**22** and **25**) and δ-lactones (**23** and **26**, separable by column chromatography, Scheme 9), each one being a mixture of two diastereoisomers. In all the cases, isomerisation of the crotyl to the *trans* isomer was observed, and similar ratios of γ- and δ-lactones were obtained from either isomer.

Reaction of the cyclohexyl derivatives **27** and **29** with TfOH gave the bicyclic γ-lactones with moderate (**30**) to high (**28**) diastereoselectivity (Scheme 10). In these reactions small quantities of the products from the isomerisation of the double bond in the starting material were also obtained.



Scheme 10. Reaction of cyclic derivatives **27** and **29** with TfOH.

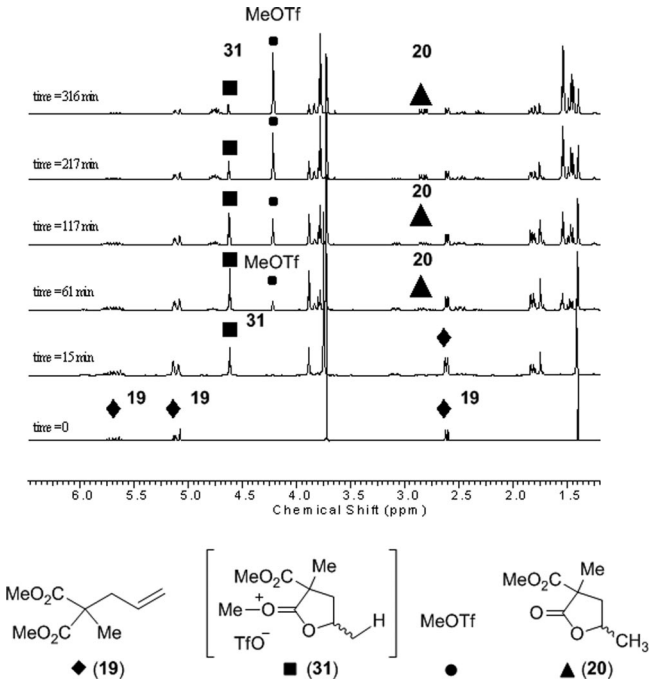


Figure 1. ^{1}H NMR spectra of the reaction of **19** with TfOH in $CDCl_3$.

Mechanistic Studies: NMR Spectroscopy, Kinetics, Simulations and ^{2}H-Labelling Experiments

Although the lactonisation reaction might be envisaged as a simple process involving olefin protonation with subsequent attack of the ester on the carbocation (see Scheme 2), the fact that only one of the two allyl units of the diallylmalonates reacts (except for **10**), even with excess of acid, suggested that the mechanism of reaction is more complex. This conclusion was supported by the study of intermediates detected by ^{1}H NMR spectroscopy and also by ^{2}H-labelling experiments.

The reactions of di- and monoallylmalonates (**1**, **17**, **19** and **29**) were monitored by ^{1}H NMR spectroscopy in $CDCl_3$, and the same behaviour was observed in all cases (see Supporting Information). As an example, Figure 1 shows the ^{1}H NMR spectra of the reaction of **19** with TfOH recorded at different times. Key results included the appearance of a singlet at δ = 4.5 ppm (■, Figure 1), that started to decay as another singlet at δ = 4.2 ppm (●, Figure 1), as well as the signals of the lactone (▲, Figure 1), started growing.

The growth and decay of the signal at $\delta \approx 4.5$ ppm was observed in all of the reactions monitored, as was the signal at δ = 4.2 ppm, which was assigned as MeOTf, a by-product of the reaction. The signal at δ = 4.5 ppm is tentatively assigned to the methyl group of an oxonium intermediate (**31**, Figure 1).[12]

Figures 2 and 3 show the reaction profiles comparing the experimentally determined temporal concentrations (in black) of the reactions of **1** and **19**, respectively, with TfOH. Both cases show the decay of the allylmalonate, the growth and decay of an intermediate and the growth of the lactone.

A good fit was obtained (grey lines, Figures 2 and 3) in all cases for a two-step mechanism, in which an oxonium intermediate is formed first and then evolves to the lactone, liberating the MeOTf (δ = 4.2 ppm) in an S_N2-type reaction.[13] However, the decay of the starting material in the first step was found to be faster than that expected for a bimolecular reaction of **1** and **19** with TfOH, and the simulation was better when 2 equiv. of TfOH were used to give a third-order rate equation for the first step of the type: rate

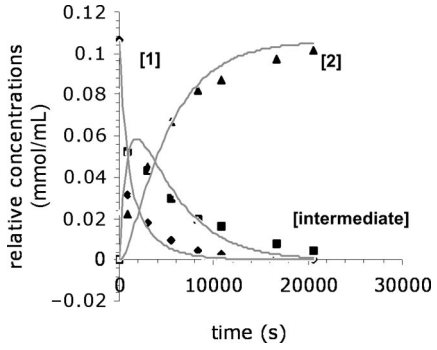


Figure 2. Graph of the reaction of **1** with TfOH. Experimental values: ♦ = diallylmalonate (**1**); ■ = intermediate; ▲ = lactone (**2**). Calculated values: grey lines, see Scheme 11 for details.

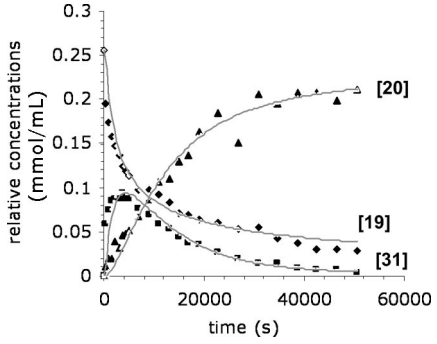


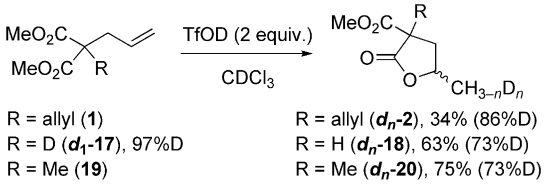
Figure 3. Graph of the reaction of **19** with TfOH. Experimental values: ♦ = diallylmalonate (**19**); ■ = intermediate (**31**); ▲ = lactone (**20**). Calculated values: grey lines, see Scheme 11 for details.

$\approx k_{obsd.}\cdot[TfOH]^2\cdot[allylmalonate]^1$ (see Scheme 11 for rate constants).

The second-order kinetic dependency on TfOH may arise from a monomer/dimer equilibrium of the triflic acid,[14] with the monomer as the prevalent species in chloroform. The dimer is then the active species in the lactonisation, with the net effect of one TfOH acting as a catalyst and the second as the reagent.[15]

The lactonisation can also be performed by using the hydrate ($TfO^-\cdot H_3O^+$), generated by stoichiometric reaction of TfOH with H_2O. However, the reaction is slower due to the low solubility of the hydrate in chloroform. Moreover, attempts to lactonise allylmalonates **1**, **17**, and **19**, by using a catalytic amount of TfOH (10 mol-%) in the presence of 1 equiv. of water or by adding the water slowly during the reaction, failed, again probably due to the low solubility of the hydrate in chloroform.

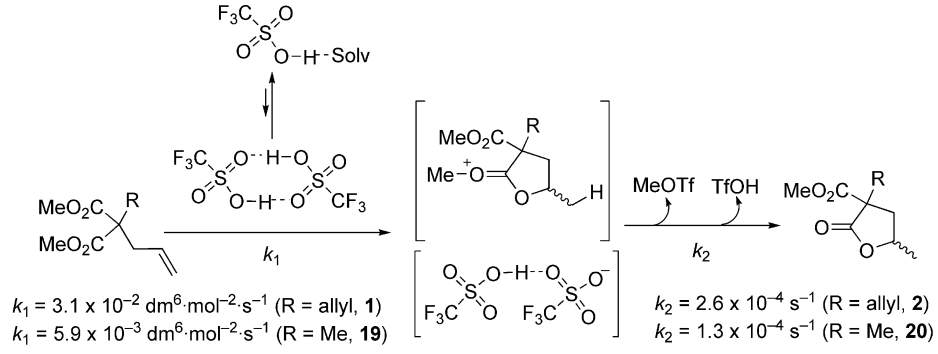
^{2}H-labelling experiments by using TfOD were carried out in order to confirm the transfer of the proton from the triflic acid. Thus, reaction of di- (**1**) and monoallylmalonates (***d*$_1$-17** and **19**) with TfOD gave the deuterated monolactones ***d*$_1$-2**, ***d*$_1$-18** and ***d*$_1$-20** (Scheme 12).[16] As expected, the deuterium atom was incorporated into the *exo*-methyl group, and whilst the isotopic purity was high, as evidenced by ^{13}C NMR and MS analysis (73–86% d_1; 1–4% d_2),[17] we did not observe deuterium in the unreacted allyl unit of ***d*$_1$-2**, ruling out the hypothesis that the reaction proceeds by initial protonation of the alkene, and suggesting an intramolecular transfer of the proton, probably from a carbonyl-protonated ester.[18,19]



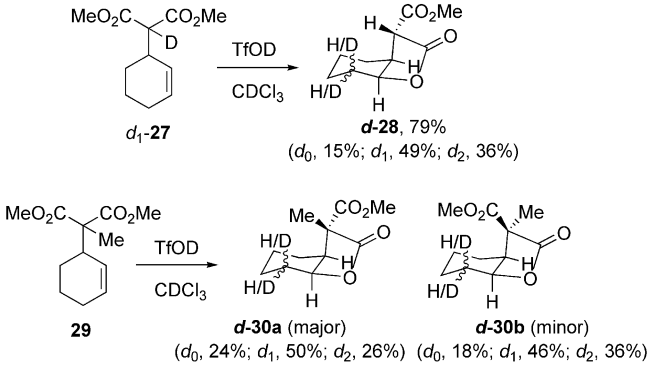
Scheme 12. Deuteration experiments with TfOD.

Reaction of the cyclohexyl derivatives (**27** and **29**, Scheme 13) with TfOD also gave the d_1-lactones (***d*$_1$-28**, ***d*$_1$-30a**, and ***d*$_1$-30b**)[20,21] with relatively high deuterium incorporation [MS analysis also revealed some d_0 and d_2 products (46–50%, d_1; 24–36%, d_2)[22] as in the case of the allyl derivatives].[17] Although analysis of lactone ***d*$_1$-28** was difficult due to overlap of the key ^{1}H NMR signals, analysis of ***d*$_1$-30** revealed partial deuteration in both positions, *cis* and *trans* to the oxygen atom in both isomers.

As lactones **30a** and **30b** did not isomerise, even in the presence of excess TfOH,[24] the generation of both dia-

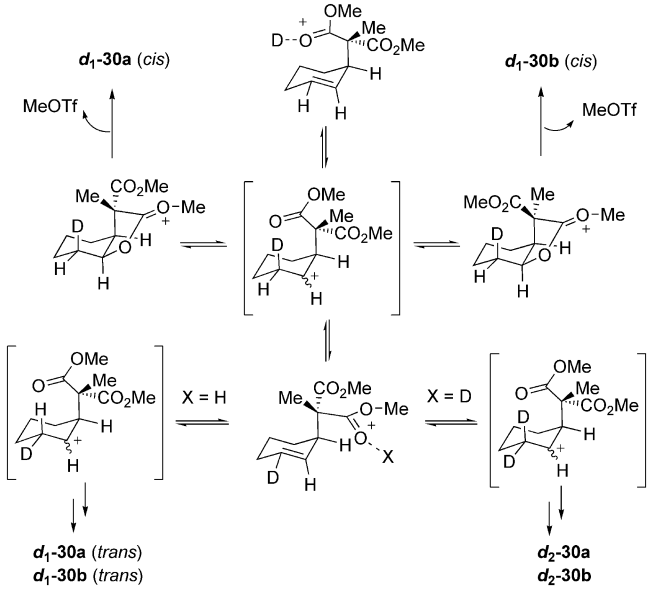


Scheme 11. Simplified two-step mechanism for the kinetics of lactonisation of di- and monoallylmalonates.



Scheme 13. Lactonisation of cyclohexylmalonates with TfOD.[23]

stereoisotopomers suggests that the interconversion of the oxonium intermediates is relatively facile. In the case of the cyclohexyl derivative **29**, the oxonium intermediates are sterically congested due to the presence of the methyl group, and their equilibration via a carbocation, which mediates the isomerisation, would explain the moderate diastereoselectivity obtained in this reaction compared with the complete diastereoselectivity in the reaction of **27** where the substituent is H. The partial deuteration *cis* and *trans* to the oxygen atom and the d_0 and d_2 products can be explained by reversible intramolecular protonation to generate a carbocation in equilibrium with the alkene, during which H/D exchange can occur with the TfOD/TfOH (Scheme 14).



Scheme 14. Proposed isomerisation of oxonium intermediates to explain deuteration experiments. Lactone **30** is used as model.

Although intramolecular proton transfers are characterised by small effective molarities ($EM \approx 1$–10 M),[25] there are examples of efficient intramolecular proton transfer between carbon and oxygen atoms in which seven-membered cyclic transition states (including the proton) are involved, giving effective molarities up to 50 M in rigid systems.[26] Thus, the formation of the oxonium intermediates can occur by intramolecular transfer of the proton from the ester (involving a seven-membered cyclic transition state) to generate the carbocationic species, which also mediate the isomerisation of the oxonium intermediates (Scheme 14).[27] The formation of one product or the other would depend on the rate of the attack of the triflate to liberate the lactone vs. equilibration of the oxonium intermediates, these being influenced by the substituents on the alkene and the chain, and the rigidity of the system.

Conclusions

We have described the triflic acid mediated dealkylative lactonisation of mono- and diallylmalonates. A mechanistic study, including kinetics, simulations, NMR spectroscopy and ^{2}H-labelling experiments, suggests that the reaction proceeds according to a three-step mechanism, probably involving an intramolecular transfer of the proton from the protonated ester to the alkene to form, via a carbocation, an oxonium intermediate, as identified by ^{1}H NMR spectroscopy, which evolves to the final lactone by S_N2 attack of the triflate to form MeOTf as by-product.

The intramolecular addition of H^+ from the ester to the alkene[28] is supported by the monolactonisation of diallylmalonates, even with excess TfOH, and the lack of deuteration in the unreacted allyl unit. Isomerisation of the oxonium intermediates via carbocationic species, would explain the mixture of d_1 products obtained in the reaction with the cyclohexyl derivatives.

Further investigations to unambiguously assign the relative configuration of the deuterated new stereocenters of more rigid cyclohexyl derivatives, and therefore confidently distinguish *syn* or *anti* addition of the H and O atoms to the alkene are in progress. The *syn*-intramolecular addition mechanism offers the potential for an asymmetric version of this reaction by way of a chiral strong sulfonic acid.

Experimental Section

General: See Supporting Information for details of general methods and analytical techniques.

General Procedure for the Reaction of Allylmalonates with Triflic Acid: TfOH (0.15–0.40 mmol) was added to a solution of the allylmalonate (0.07–0.20 mmol) in chloroform/$CDCl_3$ (0.7–2 mL) at room temperature. The mixture was stirred for 24 h and then filtered through a pad of silica (washing with hexane/EtOAc, 10:1) to obtain the pure compounds as colourless oils. In the case of reaction with TfOD, the starting materials were pre-deuterated (MeOD, Na_{cat}, room temp., 3 h) if needed, and all the glass material washed with D_2O/dry THF/dry $CDCl_3$, and dried in the oven overnight.

Lactone 2:[29] 12 mg, 0.06 mmol, 79%. 2 isomers, 1.7:1. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.77–5.61 (m, 2×1 H, 7-H), 5.24–5.14 (m, 2×2 H, 8-H), 4.72–4.54 (m, 2×1 H, 4-H), 3.78 (s, 3 H, minor), 3.76 (s, 3 H, major), 2.84–2.56 (m, 2×2 H, 3 H + 1 H, 4-H, minor), 2.41 (d, $J_{H,H}$ = 7.3 Hz, 1 H, 4-H, major), 1.82 (dd, $J_{H,H}$ = 13.1, 10.2 Hz, 1 H, 4-H, major), 1.52 (d, $J_{H,H}$ = 10 Hz, 1 H, 4-

H minor), 1.42 (d, $J_{H,H}$ = 6.6 Hz, 3 H, 5-H, minor), 1.40 (d, $J_{H,H}$ = 6.2 Hz, 3 H, 5-H, major) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.71 (CO), 169.87 (CO), 131.91 (CH, C-7, major), 131.71 (CH, C-7, minor), 120.51 (CH_2, C-8, minor), 120.21 (CH_2, C-8, major), 75.28 (CH, C-4), 75.19 (CH, C-4), 56.17 (C-2), 55.44 (C-2), 53.21 (CH_3, ester), 53.17 (CH_3, ester), 38.96 (CH_2), 38.91 (CH_2), 38.46 (CH_2), 38.39 (CH_2), 20.78 (CH_3, C-5), 20.76 (CH_3, C-5) ppm. HMRS (CI): calcd. for $C_{10}H_{15}O_4$ [MH^+] 199.097034; found 199.096274.

Lactone *d*-2: 7 mg, 0.034 mmol, 34%. 2 isomers, 2:1. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.77–5.61 (m, 2×1 H, 7-H), 5.24–5.14 (m, 2×2 H, 8-H), 4.72–4.54 (m, 2×1 H, 4-H), 3.78 (s, 3 H, minor), 3.76 (s, 3 H, major), 2.84–2.56 (m, 2×2 H, 3 H + 1 H, 4-H, minor), 2.40 (d, $J_{H,H}$ = 7.3 Hz, 1 H, 4-H, major), 1.82 (dd, $J_{H,H}$ = 13.1, 10.2 Hz, 1 H, 4-H, major), 1.52 (d, $J_{H,H}$ = 10 Hz, 1 H, 4-H minor), 1.46–1.40 (m, 2×CH_2D) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 174.32 (CO, minor), 173.1 (CO, major), 170.38 (CO, minor), 169.88 (CO, major), 131.93 (CH, C-7, major), 131.73 (CH, C-7, minor), 120.51 (CH_2, C-8, minor), 120.20 (CH_2, C-8, major), 75.24 (CH, C-4, major), 74.60 (CH, C-4, minor), 56.18 (C-2, major), 55.45 (C-2, minor), 53.17 (CH_3, ester), 53.17 (CH_3, ester), 38.98 (CH_2), 38.47 (CH_2), 38.41 (CH_2), 37.78 (CH_2), 21.34 (s,CH_3, C-5), 20.81 (t, J_{C-D} = 19.58 Hz, CH_2D), 20.78 (s, CH_3, C-5), 20.51 (t, J_{C-D} = 19.58 Hz, CH_2D) ppm. MS (CI): *m*/*z* (%) = 199 (15) [d_0-M^+ + 1], 200 (100) [d_1-M^+ + 1], 201 (2) [d_2-M^+ + 1].

Lactone 4:[30] 6 mg, 0.025 mmol, 30%. 2 isomers.^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 5.80–5.59 (m, 2×1 H, 7-H), 5.21–5.13 (m, 2×2 H, 8-H), 4.73–4.54 (m, 2×2 H, ester), 2.80–2.53 (m, 2×2 H, 6-H), 2.40 (d, $J_{H,H}$ = 8.0 Hz, 1 H, 3-H), 1.83 (dd, $J_{H,H}$ = 13.2, 10.1 Hz, 1 H, 3-H), 1.42 (d, $J_{H,H}$ = 6.8 Hz, 3 H, 5-H), 1.40 (d, $J_{H,H}$ = 6.3 Hz, 3 H, 5-H), 1.26 (m, 2×3 H, ester) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$, 25 °C): δ = 173.71 (CO), 169.97 (CO), 132.10, 131.91, 120.51, 120.21, 75.30, 74.66, 62.37, 56.83, 55.48, 39.13, 38.48, 37.87, 31.01, 21.49, 20.91, 14.08 ppm. HMRS (CI): calcd. for $C_{11}H_{17}O_4$ [MH^+] 213.112684; found 213.111977.

Lactone 6: 15 mg, 0.08 mmol, 76%. 2 isomers, 1:1.1. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.84 (q, $J_{H,H}$ = 1.48 Hz, 1 H, 6-H, minor), 5.80 (q, $J_{H,H}$ = 1.96 Hz, 1 H, 6-H, major), 5.71–5.58 (m, 2×2 H, 7-H), 4.60–4.52 (m, 1 H, 4-H), 4.52–4.47 (m, 1 H, 7-H), 3.73 (s, 3 H, ester), 3.71 (s, 3 H, ester), 2.88 (dd, $J_{H,H}$ = 12.92, 5.84 Hz, 1 H, 3-H, major), 2.45 (dd, $J_{H,H}$ = 12.44, 8.8 Hz, 1 H, 3-H, minor), 2.39 (dd, $J_{H,H}$ = 13.44, 7.32 Hz, 1 H, 3-H, minor), 1.92 (dd, $J_{H,H}$ = 12.72, 9.52 Hz, 1 H, 3-H, major), 1.71–1.68 (m, 6 H, 2×8-H), 1.38 (d, $J_{H,H}$ = 6.36 Hz, 3 H, 5-H, minor), 1.36 (d, $J_{H,H}$ = 6.12 Hz, 3 H, 5-H, major) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.18 (CO), 172.89 (CO), 169.67 (CO), 169.28 (CO), 129.02 (CH, C-6), 128.88 (CH, C-6), 126.60 (CH, C-7), 125.10 (CH, C-7), 75.11 (CH, C-4), 74.57 (CH, C-4), 58.39 (C-2), 58.20 (C-2), 53.41 (CH_3, ester), 53.25 (CH_3, ester), 40.57 (CH_2, C-3), 40.34 (CH_2, C-3), 20.63 (CH_3, C-5), 20.33 (CH_3, C-5), 17.99 (2×CH_3, C-8) ppm. HMRS (CI): calcd. for $C_{10}H_{15}O_4$ [MH^+] 199.0970; found 199.0963.

Cyclic Compound 9: 5 mg, 0.017 mmol, 25%. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.29 (tt, $J_{H,H}$ = 7.1, 1.5 Hz, 2 H), 7.20 (tt, $J_{H,H}$ = 7.3, 1.5 Hz, 1 H), 7.08 (dd, $J_{H,H}$ = 8.3, 1.3 Hz, 2 H), 3.75 (s, 6 H), 2.61 (br. s, 2 H), 2.31 (m, 2 H), 2.26 (m, 2 H), 1.59 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.12, 131.27 (C), 128.43 (2×CH), 128.11 (CH), 126.40 (C), 126.36 (C), 53.76 (C), 52.73 (CH_3), 36.53 (CH_2), 29.03 (CH_2), 28.34 (CH_2), 20.55 (CH_3) ppm. HMRS (CI): calcd. for $C_{17}H_{20}O_4$ [MH^+] 288.1362; found 288.1360.

Spiro-Lactone 11:[2,6a,31] 35 mg, 0.19 mmol, 76%. 3 isomers, 1:1:1. 1st isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.02 (m, 2 H), 2.80 (ddd, $J_{H,H}$ = 12.9, 6.0, 2.6 Hz, 2 H), 1.88 (ddd, $J_{H,H}$ = 12.3, 9.6, 2.7 Hz, 2 H), 1.44 (dd, $J_{H,H}$ = 6.2, 2.6 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.55 (CO), 75.97 (CH), 54.02 (C), 40.48 (CH_2), 20.96 (CH_3) ppm. 2nd and 3rd isomers: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.97 (m, 2 H), 4.69 (m, 2 H), 2.79 (dd, $J_{H,H}$ = 12.9, 5.6 Hz, 2 H), 2.58 (dd, $J_{H,H}$ = 13.5, 8.3 Hz, 2 H), 2.31 (dd, $J_{H,H}$ = 13.2, 6.6 Hz, 2 H), 1.89 (dd, $J_{H,H}$ = 13.2, 9.9 Hz, 2 H), 1.52 (d, $J_{H,H}$ = 6.3 Hz, 6 H), 1.45 (d, $J_{H,H}$ = 6.3 Hz, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 173.82 (CO), 173.58 (CO), 76.04 (CH), 75.11 (CH), 53.99 (C), 41.71 (CH_2), 39.69 (CH_2), 21.19 (CH_3), 20.96 (CH_3) ppm. HMRS (CI): calcd. for $C_9H_{13}O_4$ [MH^+] 185.0814; found 185.0808.

Lactone 12:[32] 12 mg, 0.07 mmol, 58%. 2 isomers, 19:1. ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 9.84 (br. s, 2 H, acid), 5.79–5.61 (m, 2×1 H, 7-H), 5.25–5.13 (m, 2×2 H, 8-H), 4.79–4.67 (m, 2×1 H, 4-H), 2.85–2.57 (m, 3 H, 6-H + 1 H, 3-H), 2.47–2.42 (m, 3 H, minor), 1.88 (dd, $J_{H,H}$ = 13.5, 9.9 Hz, 1 H, 3-H), 1.45 (d, $J_{H,H}$ = 6.2 Hz, 3 H, 5-H, minor), 1.42 (d, $J_{H,H}$ = 6.3 Hz, 3 H, 5-H, major) ppm. ^{13}C NMR (67.5 MHz, $CDCl_3$, 25 °C): δ = 176.06, 174.95, 173.59, 131.65, 131.41, 120.74, 120.18, 75.63, 57.86, 56.28, 38.66, 38.35, 37.72, 20.90 ppm. HMRS (CI): calcd. for $C_9H_{12}O_4$ [MH^+] 185.081384; found 185.081275.

Lactone 14:[33] 7 mg, 0.05 mmol, 55%. 2 isomers, 1:2.3. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 5.82–5.71 (m, 2×1 H), 5.14–5.06 (m, 2×2 H), 4.64 (sext, $J_{H,H}$ = 6.4, 1.2 Hz, 1 H, minor), 4.49 (ddt, $J_{H,H}$ = 11.09, 10.4, 6.1 Hz, 1 H, major), 2.79–2.68 (m, 2×1 H), 2.66–2.52 (m, 2×1 H), 2.43 (ddd, $J_{H,H}$ = 12.6, 8.5, 5.5 Hz, 1 H, major), 2.31–2.19 (m, 2×1 H), 2.13 (dt, $J_{H,H}$ = 12.9, 7.4 Hz, 1 H, minor), 1.98 (ddd, $J_{H,H}$ = 13, 9.2, 5.5 Hz, 1 H, minor), 1.53 (dt, $J_{H,H}$ = 12.3, 10.3 Hz, 1 H, major), 1.41 (d, $J_{H,H}$ = 6.2 Hz, 3 H, major), 1.37 (d, $J_{H,H}$ = 6.5 Hz, 3 H, minor) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 178.34 (CO), 134.72 (CH, major), 134.54 (CH, minor), 117.93 (CH_2, minor), 117.60 (CH_2, major), 75.33 (CH, major), 75.17 (CH, minor), 41.15 (CH, major), 39.10 (CH, minor), 36.34 (CH_2, major), 34.82 (CH_2, minor), 34.41 (CH_2, major), 34.41 (CH_2, major), 34.30 (CH_2, minor), 21.39 (CH_3, minor), 21.06 (CH_3, major) ppm. HMRS (CI): calcd. for $C_8H_{13}O_2$ [MH^+] 141.0916; found 141.0919.

Lactone 16:[4d] 16 mg, 0.074 mmol, 77%. 2 isomers, 1:3.2. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 7.53–7.26 (m, 2×5 H, Ph), 5.69–5.54 (9m, 2×1 H), 5.12–5.06 (m, 2×2 H), 4.65 (sextm, $J_{H,H}$ = 6.4 Hz, 1 H, minor), 4.35 (septm, $J_{H,H}$ = 4.8 Hz, 1 H, major), 2.72–2.64 (m, 2×1 H), 2.28 (dd, $J_{H,H}$ = 13, 7.9 Hz, 1 H, minor), 2.07 (dd, $J_{H,H}$ = 12, 8 Hz, 1 H, major), 1.40 (d, $J_{H,H}$ = 8 Hz, 3 H, major), 1.34 (d, $J_{H,H}$ = 8 Hz, 3 H, minor) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.62 (CO), 138.89 (C), 133.31 (CH), 128.96 (CH, major), 128.58 (CH, minor), 127.71 (CH, major), 127.24 (CH, minor), 126.58 (CH, minor), 126.33 (CH, major), 119.37 (CH_2), 73.94 (CH, major), 73.67 (CH, minor), 53.85 (C), 44.11 (CH_2, minor), 43.79 (CH_2, minor), 41.31 (CH_2, major), 41.18 (CH_2, minor), 20.51 (CH_3) ppm. HMRS (CI): calcd. for $C_{14}H_{17}O_2$ [MH^+] 217.1229; found 217.1223.

Lactone 18:[34] 21 mg, 0.135 mmol, 78%. 2 isomers, *trans*/*cis*, 1:1.4. *trans* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.83 (sext, $J_{H,H}$ = 6.56 Hz, 1 H, 4-H), 3.81 (s, 3 H, ester), 3.64 (t, $J_{H,H}$ = 4.5 Hz, 1 H, 2-H), 2.75 (ddd, $J_{H,H}$ = 13.2, 6.84, 4.88 Hz, 1, 3-H), 2.09 (ddd, $J_{H,H}$ = 13.2, 9.52, 7.58 Hz, 1 H, 3-H), 1.43 (d, $J_{H,H}$ = 6.84 Hz, 3 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.65 (CO), 168.21 (CO), 76.61 (CH, C-4), 53.08 (CH_3, ester), 46.93 (CH, C-2), 33.54 (CH_2, C-3), 20.92 (CH_3, C-5) ppm. *cis* iso-

mer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.61 (dq, $J_{H,H}$ = 9.76, 6.36 Hz, 1 H, 4-H), 3.82 (s, 3 H, ester), 3.67 (dd, $J_{H,H}$ = 11.6, 9.28 Hz, 1 H, 2-H), 2.60 (ddd, $J_{H,H}$ = 13.2, 9.32, 6.12 Hz, 1 H, 3-H), 2.31 (ddd, $J_{H,H}$ = 13.2, 11.24, 9.28 Hz, 1 H, 3-H), 1.49 (d, $J_{H,H}$ = 6.8 Hz, 3 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.65 (CO), 168.21 (CO), 75.87 (CH, C-4), 53.00 (CH_3, ester), 47.58 (CH, C-2), 33.74 (CH_2, C-3), 20.74 (CH_3, C-5) ppm. HMRS (CI): calcd. for $C_7H_{11}O_4$ [MH^+] 159.0657; found 159.0653.

Lactone *d*-18: 44 mg, 0.28 mmol, 63%. 2 isomers, *trans*/*cis*, 1:1.4. *trans* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.83 (m, 1 H, 4-H), 3.81 (s, 3 H, ester), 3.59 (t, $J_{H,H}$ = 4.9 Hz, 1 H, 2-H), 2.71 (ddd, $J_{H,H}$ = 13.2, 6.9, 4.9 Hz, 1, 3-H), 2.05 (ddd, $J_{H,H}$ = 13.2, 9.57, 7.26 Hz, 1 H, 3-H), 1.43 (d, $J_{H,H}$ = 6.84 Hz, 3 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.66 (CO), 168.19 (CO), 75.86 (CH, C-4), 53.06 (ester, CH_3), 47.57 (CH, C-2), 33.54 (CH_2, C-3) (33.49), 20.89 (s, CH_3, C-5), 20.61 (t, $J_{C\text{-}D}$ = 19.20 Hz, CH_2D) ppm. *cis* isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.61 (m, 4-H), 3.82 (s, 3 H, ester), 3.64 (dd, $J_{H,H}$ = 11.22, 9.24 Hz, 1 H, 2-H), 2.57 (ddd, $J_{H,H}$ = 14.8, 8.91, 5.94 Hz, 1 H, 3-H), 2.32 (ddd, $J_{H,H}$ = 12.87, 11.22, 9.57 Hz, 1 H, 3-H), 1.49 (d, $J_{H,H}$ = 6.8 Hz, 3 H, 5-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.66 (CO), 168.19 (CO), 75.82 (CH, C-4), 52.97 (CH_3, ester), 46.91 (CH, C-2), 33.74 (CH_2, C-3), 33.71, 20.71 (s, CH_3, C-5), 20.45 (t, $J_{C\text{-}D}$ = 19.72 Hz, CH_2D) ppm. MS (CI): *m*/*z* (%) = 159 (31) [d_0-M^+ + 1], 160 (100) [d_1-M^+ + 1], 161 (6) [d_2-M^+ + 1].

Lactone 20:[35] 20 mg, 0.12 mmol, 73%. 2 isomers, 1:2.63. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.69 (m, 2 × 1 H, 4-H), 3.79 (s, 3 H, ester, minor), 3.77 (s, 3 H, ester, major), 2.81 (dd, $J_{H,H}$ = 13.68, 6.88 Hz, 1 H, 3-H, major), 2.47 (dd, $J_{H,H}$ = 13.2, 8.08 Hz, 1, 3-H, minor), 2.27 (dd, $J_{H,H}$ = 12.44, 6.08 Hz, 1 H, 3-H, minor), 1.76 (dd, $J_{H,H}$ = 12.96, 9.76 Hz, 1 H, 3-H, major), 1.54 (s, 3 H, 6-H, minor), 1.54 (s, 3 H, 6-H major), 1.47 (d, $J_{H,H}$ = 6.12 Hz, 3 H, 5-H, minor), 1.44 (d, $J_{H,H}$ = 6.36 Hz, 3 H, 5-H, major) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.46 (CO, minor), 175.10 (CO, major), 171.24 (CO, minor), 170.96 (CO, major), 74.76 (CH, C-4, major), 74.51 (CH, C-4, minor), 53.11 (CH_3, ester, major), 53.08 (CH_3, ester, minor), 52.10 (C-2, major), 51.55 (C-2, minor), 43.04 (CH_2, C-3, major), 41.75 (CH_2, C-3, minor), 20.99 (CH_3, C-5, minor), 20.86 (CH_3, C-6, major), 20.78 (CH_3, C-5, major), 19.95 (CH_3, C-6, minor) ppm. HMRS (CI): calcd. for $C_8H_{13}O_4$ [MH^+] 173.0814; found 173.0808.

Lactone *d*-20: 22 mg, 0.13 mmol, 75%. 2 isomers, 1:2. ^{1}H NMR (270 MHz, $CDCl_3$, 25 °C): δ = 4.69 (m, 2 × 1 H, 4-H), 3.79 (s, 3 H, ester, minor), 3.77 (s, 3 H, ester, major), 2.81 (dd, $J_{H,H}$ = 13.20, 5.61 Hz, 1 H, 3-H, major), 2.47 (dd, $J_{H,H}$ = 13.2, 8.58 Hz, 1, 3-H, minor), 2.27 (dd, $J_{H,H}$ = 12.87, 6.6 Hz, 1 H, 3-H, minor), 1.76 (dd, $J_{H,H}$ = 13.20, 9.90 Hz, 1 H, 3-H, major), 1.54 (s, 3 H, 6-H, minor), 1.54 (s, 3 H, 6-H major), 1.47 (m, 2 × CH_2D) ppm. ^{13}C NMR (67.9 MHz, $CDCl_3$, 25 °C): δ = 175.47 (CO, minor), 175.10 (CO, major), 171.23 (CO, minor), 170.96 (CO, major), 74.75 (CH, C-4, major) (74.71), 74.51 (CH, C-4, minor) (74.46), 53.11 (CH_3, ester, major), 53.08 (CH_3, ester, minor), 52.10 (C-2, major), 51.55 (C-2, minor), 43.06 (CH_2, C-3, major) (43.03), 41.76 (CH_2, C-3, minor) (41.74), 21.01 (s, CH_3, C-5, minor), 20.86 (CH_3, C-6, major), 20.79 (s, CH_3, C-5, major), 20.60 (t, $J_{C\text{-}D}$ = 19.72 Hz, CH_2D), 20.52 (t, $J_{C\text{-}D}$ = 19.72 Hz, CH_2D), 19.95 (CH_3, C-6, minor) ppm. MS (CI): *m*/*z* (%) = 173 (31) [d_0-M^+ + 1], 174 (100) [d_1-M^+ + 1], 175 (6) [d_2-M^+ + 1].

Lactone 22: From **21-cis**, 26 mg, 0.15 mmol, 56%, 2 isomers, 1:1.3 (*trans*/*cis*). From **21-trans**, 24 mg, 0.14 mmol, 53%, 2 isomers, 1:1.3 (*trans*/*cis*). *trans* isomer: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 4.62 (dt, $J_{H,H}$ = 13.1, 6.9 Hz, 1 H, 4-H), 3.82 (s, 3 H, ester), 3.615 (dd, $J_{H,H}$ = 9.7, 5 Hz, 1 H, 2-H), 2.70 (ddd, $J_{H,H}$ = 13.3, 6.9, 4.9 Hz, 1 H, 3-H), 2.11 (ddd, $J_{H,H}$ = 13.1, 9.5, 7.4 Hz, 1 H, 3-H), 1.75 [m ($^3J_{H,H}$ = 7.3 Hz), 1 H, 5-H], 1.67 [m, $^3J_{H,H}$ = 5.7 Hz, 1 H, 5-H], 1.02 (t, $J_{H,H}$ = 7.4 Hz, 3 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.87, 168.25, 81.47 (CH,4), 53.10 (CH_3), 46.78 (CH, C-2), 31.47 (CH_2, C-3), 28.39 (CH_2, C-5), 9.37 (CH_3, C-6) ppm. *cis* isomer: ^{1}H NMR (600 MHz, $CDCl_3$, 25 °C): δ = 4.40 (dq, $J_{H,H}$ = 12.9, 5.9 Hz, 1 H, 4-H), 3.81 (s, 3 H, ester), 3.65 (dd, $J_{H,H}$ = 11.3, 9.3 Hz, 1 H, 2-H), 2.55 (ddd, $J_{H,H}$ = 12.9, 9.1, 5.9 Hz, 1 H, 3-H), 2.34 (ddd, $J_{H,H}$ = 12.9, 11.1, 9.5 Hz, 1 H, 3-H), 1.85 (sept, $^3J_{H,H}$ = 7.3 Hz, 1 H, 5-H), 1.74 (m, $^3J_{H,H}$ = 5.7 Hz, 1 H, 5-H),1.03 (t, $J_{H,H}$ = 7.3 Hz, 3 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.87, 168.25, 80.73 (CH,C-4), 53.02 (CH_3), 47.23 (CH, C-2), 31.67 (CH_2, C-3), 28.24 (CH_2, C-5), 9.37 (CH_3, C-6) ppm. HMRS (CI): calcd. for $C_8H_{13}O_4$ [MH^+] 173.0814; found 173.0813.

Lactone 23: From **21-cis**, 5 mg, 0.03 mmol, 11%, 2 isomers, 1:1. From **21-trans**, 6 mg, 0.04 mmol, 14%, 2 isomers, 1:1. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.51 (m, 2 × 1 H, 5-H), 3.82 (s, 3 H, ester), 3.81 (s, 3 H, ester), 3.59 (t, $J_{H,H}$ = 7.6 Hz, 1 H, 2-H), 3.52 (dd, $J_{H,H}$ = 9.3, 7.6 Hz, 1 H, 2-H), 2.33–2.09 (m, 2 × 3-H + 2 × 3-H), 2.07–1.92 (m, 2 H 4-H + 4-H), 1.75 (m, 1 H, 4-H), 1.61 (m, 1 H, 4-H), 1.42 (t, $J_{H,H}$ = 6.5 Hz, 2 × 3 H, 6-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 169.7, 169.0, 77.75 (CH), 76.95 (CH), 53.02 (CH_3, ester), 52.95 (CH_3, ester), 47.58 (CH), 45.85 (CH), 29.00 (CH_2), 27.53 (CH_2), 23.08 (CH_2), 21.79 (CH), 21.73 (CH_2), 21.43 (CH_3) ppm. HMRS (CI): calcd. for $C_8H_{13}O_4$ [MH^+] 173.0814; found 173.0817.

Lactone 25: From **24-cis**, 47 mg, 0.25 mmol, 80%, 2 isomers, 1:1.1. From **24-trans**, 48 mg, 0.25 mmol, 68%, 2 isomers, 1:2.6. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.52–4.36 (m, 2 × 1 H, 4-H), 3.77 (s, 3 H, minor), 3.76 (s, 3 H, major), 2.75 (dd, $J_{H,H}$ = 13.2, 6.0 Hz, 1 H, 3-H, major), 2.48 (dd, $J_{H,H}$ = 13.2, 8.9 Hz, 1 H, 3-H, minor), 2.20 (dd, $J_{H,H}$ = 12.9, 6.3 Hz, 1 H, 3-H, minor), 1.87–1.85 (m, 1 H, 3-H, major + 2 × 2 H, 5-H), 1.52 (s, 3 H, minor, 7-H), 1.51 (s, 3 H, major, 7-H), 1.00 (t, $J_{H,H}$ = 7.6 Hz, 3 H, 6-H, minor), 1.00 (t, $J_{H,H}$ = 7.6 Hz, 3 H, 6-H, major) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.23, 171.13, 79.70 (CH, C-4, major), 79.55 (CH, C-4, minor), 53.23 (2 × CH_3, ester), 51.81 (C-2, major), 51.34 (C-2, minor), 41.09 (CH_2, C-3, major), 39.91 (CH_2, C-3, minor), 28.48 (2 × CH_2, C-5), 21.12 (CH_3, C-7, major), 20.17 (CH_3, C-7 minor), 9.52 (2 × CH_3, C-6) ppm. HMRS (CI): calcd. for $C_9H_{15}O_4$ [MH^+] 187.0970; found 187.0965.

Lactone 26: From **24-cis**, 2 mg, 0.009 mmol, 4%, 2 isomers, 1.7:1. From **24-trans**, 9 mg, 0.04 mmol, 14%, 2 isomers, 1:4. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.57–4.49 (m, 1 H, 5-H, minor), 4.46–4.38 (m, 1 H, 5-H, major), 3.79 (s, 3 H, major), 3.78 (s, 3 H, minor), 2.50 (ddd, $J_{H,H}$ = 13.9, 8.9, 7.4 Hz, 1 H, major), 2.38–2.33 (m, 1 H, minor), 2.03–1.95 (m, 1 H, major), 1.92–1.86 (m, 1 H, minor), 1.83–1.62 (m, 2 × 2 H), 1.58 (s, 3 H, 7-H, minor), 1.57 (s, 3 H, 7-H, major), 1.43 (d, $J_{H,H}$ = 6.4 Hz, 3 H, 6-H, minor), 1.40 (d, $J_{H,H}$ = 6.3 Hz, 3 H, 6-H, major) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 78.77 (CH, C-5, minor), 75.91 (CH, C-5, minor), 53.21 (CH_3, ester, major), 53.05 (CH_3, ester, minor), 49.59 (C-2, major), 48.68 (C-2, minor), 32.45 (CH_2, minor), 29.99 (CH_2, major), 28.31 (CH_2, minor), 27.58 (CH_2, major), 23.44 (CH_3, minor), 23.21 (CH_3, major), 22.12 (CH_3, minor), 21.63 (CH_3, major) ppm. HMRS (CI): calcd. for $C_9H_{15}O_4$ [MH^+] 187.0970; found 187.0977.

Lactone 28:[36] 15 mg, 0.07 mmol, 52%. 1 isomer. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.72 (dt, app. q, $J_{H,H}$ = 5.3, 5.3 Hz, 1 H), 3.78 (s, 3 H), 3.33 (d, $J_{H,H}$ = 5.3 Hz, 1 H), 2.80 (m, 1 H),

1.89–1.73 (m, 3 H), 1.59–1.49 (m, 1 H), 1.46–1.34 (m, 4 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 172.16 (CO), 167.89 (CO), 78.45 (CH), 53.28 (CH), 53.07 (CH_3), 39.13 (CH), 28.10 (CH_2), 26.31 (CH_2), 22.11 (CH_2), 20.36 (CH_2) ppm. HMRS (CI): calcd. for $C_{10}H_{15}O_4$ [MH^+] 199.0970; found 199.0969.

Lactone *d*-28: 91 mg, 0.46 mmol, 79%. 1 isomer. ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.72 (t, $J_{H,H}$ = 5.13 Hz, 1 H), 3.78 (s, 3 H), 3.33 (d, $J_{H,H}$ = 5.38 Hz, 1 H), 2.80 (m, 1 H), 1.85–1.70 (m, 2 H, 1D), 1.59–1.49 (m, 2 H), 1.48–1.35 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 171.96 (CO), (171.71), 167.69 (CO), (166.73), 78.19 (CH), 52.95 (CH_3), (52.68), 52.81 (CH), (52.22), 38.90 (CH), (38.80), 27.87 (s, CH_2), 27.51 (t, $J_{C\text{-}D}$ = 19.22 Hz, CHD), 26.05 (CH_2), (21.83), 21.79 (CH_2), (20.16), 20.07 (CH_2) ppm. MS (CI): *m*/*z* (%) = 199 (30) [d_0-M^+ + 1], 200 (100) [d_1-M^+ + 1], 201 (82) [d_2-M^+ + 1].

Lactones 30a and 30b: 20 mg, 0.93 mmol, 84%. 2 isomers, 3.4:1. **30a**, major isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.56 (dt, app. q, $J_{H,H}$ = 3.4, 3.2 Hz, 1 H, 4-H), 3.79 (s, 3 H), 2.61 (ddd, $J_{H,H}$ = 12.46, 6.11, 3.91 Hz, 1 H, 3-H), 2.25 (dm, $J_{H,H}$ = 14.66 Hz, 1 H, 5-H), 1.82–1.70 (m, 2 H, 7-H and 8-H), 1.65–1.55 (m, 2 H, 5-H and 6-H), 1.42 (s, 3 H), 1.40–1.36 (m, 1 H, 6-H), 1.28–1.21 (m, 1 H, 6-H), 1.14–1.04 (m, 1 H, 8-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.53 (CO), 171.66 (CO), 76.54 (CH), 57.85 (C), 53.06 (CH_3), 42.90 (CH), 27.34 (CH_2), 23.43 (CH_2), 23.40 (CH_2), 19.57 (CH_2), 15.15 (CH_3) ppm. **30b**, minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.63 (dt, app. q, $J_{H,H}$ = 4.4, 4.3 Hz, 1 H, 4-H), 3.79 (s, 3 H), 2.61 (ddd, $J_{H,H}$ = 10.0, 6.0, 5.6 Hz, 1 H, 3-H), 2.16 (ddd, $J_{H,H}$ = 13.9, 9.5, 5.8 Hz, 1 H, 5-H_{eq}), 1.73 (m, $J_{H,H}$ = 10, 5.4, 4.7 Hz, 1 H, 5-H_{ax}), 1.59 (s, 3 H), 1.60–1.45 (m, 6 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ = 175.53 (CO), 170.58 (CO), 75.88 (CH), 55.95 (C), 52.56 (CH_3), 45.19 (CH), 27.70 (CH_2), 23.95 (CH_2), 22.69 (CH_2), 19.96 (CH_2), 19.73 (CH_3) ppm. HMRS (CI): calcd. for $C_{11}H_{17}O_4$ [MH^+] 213.1127; found 213.1121.

Lactones *d*-30a and *d*-30b: 2 isomers, 3.4:1. **30a**, major isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.56 (t, $J_{H,H}$ = 2.93 Hz, 1 H, 4-H), 3.79 (s, 3 H), 2.61 (ddd, $J_{H,H}$ = 12.45, 6.11, 4.15 Hz, 1 H, 3-H), 2.25 [dm, 0.6 H (D), 5-H], 1.82–1.70 (m, 2 H, 7-H and 8-H), 1.60–1.55 [m, 0.5 H (D) + 1 H, 5-H and 6-H], 1.42 (s, 3 H), 1.40–1.05 (m, 3 H, 6-H, 6-H and 8-H) ppm. MS (CI): *m*/*z* (%) = 213 (48) [d_0-M^+ + 1], 214 (100) [d_1-M^+ + 1], 215 (53) [d_2-M^+ + 1]. **30b**, minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ = 4.63 (t, $J_{H,H}$ = 4.62 Hz, 1 H, 4-H), 3.78 (s, 3 H), 2.61 (m, 1 H, 3-H), 2.25 [dm, 0.6 H (D), 5-H_{eq}], 1.73 [dm, 0.5 H (D), 5-H_{ax}], 1.58 (s, 3 H), 1.55–1.00 (m, 6 H) ppm. MS (CI): *m*/*z* (%) = 213 (39) [d_0-M^+ + 1], 214 (100) [d_1-M^+ + 1], 215 (77) [d_2-M^+ + 1].

Supporting Information (see footnote on the first page of this article): Details of kinetics, simulations and NMR studies, as well as NMR spectra of the compounds.

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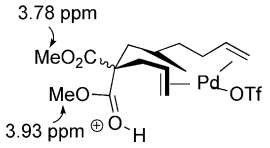
[16] The unsubstituted malonate **17** had to be pre-deuterated in the acidic position in order to achieve high incorporation of deuterium in the lactonisation, due to H/D exchange of the malonate C–H proton with the triflic acid. Lactone **d-18** was obtained with H in that position due to D/H exchange during purification by column chromatography.

[17] MS analysis also revealed some d_0 and d_2 products: Lactone **2**: d_0, 13%; d_1, 86%; d_2, 1%. Lactone **18**: d_0 23%; d_1, 73%; d_2 4%. Lactone **20**: d_0 23%; d_1, 73%; d_2 4%.

[18] This mode of addition is also in accordance with the results of the reaction of (alkene)alkylpalladium complexes with TfOH.[8]

In this case, protonation of only one of the diastereotopic esters is observed in the ^{1}H NMR spectrum (broadening of the signal at δ = 3.93 ppm), which gives the active species for the rearrangement.



[19] Protonation of the ester can also explain the easier hydrolysis of the *tert*-butyl ester to give lactone **12**.
[20] Both isomers were separable by column chromatography and were analysed independently to give similar results.
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[23] The unsubstituted malonate **27** had to be pre-deuterated in the acidic position in order to achieve high incorporation of deuterium in the lactonisation, due to H/D exchange of the malonate C–H proton with the triflic acid. Lactone ***d*-28** was obtained with H in that position due to D/H exchange during purification by column chromatography.
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