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Formation of δ-Lactones with *anti*-Baeyer-Villiger Regiochemistry – Investigations into the Mechanism of the Cerium-Catalyzed Aerobic Coupling of β-Oxoesters with Enol Acetates

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Abstract: The cerium-catalyzed, aerobic coupling of β-oxoesters with enol acetates and dioxygen yields δ-lactones with a 1,4-diketone moiety. In contrast to the Baeyer-Villiger oxidation (BVO), where the higher substituted residue migrates, in this case of an oxidative C-C coupling reaction the less substituted alkyl residue undergoes a 1,2-shift. An endoperoxidic oxycarbenium ion comparable to the Criegee intermediate in the BVO is proposed as a reaction intermediate and submitted to conformational analysis by computational methods. As a result, the inverse regiochemistry is explained by a primary stereoelectronic effect. A Hammett analysis using different donor and acceptor substituted enol esters provides support for the oxycarbenium ion being the crucial intermediate in the rate determining step of the conversion. An overall mechanism is suggested with a radical chain reaction for the formation of endoperoxides from β-oxoesters, enol acetates and dioxygen with a cerium(IV) species as initiating reagent.

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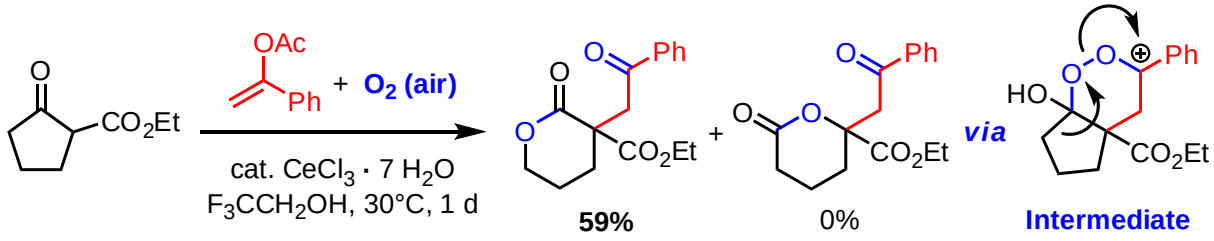
Key Topic: Reaction Mechanism

Graphical Abstract: Reaction kinetics (Hammett analysis) supported by computational methods indicate an endoperoxidic oxycarbenium ion to be the reaction intermediate for the cerium-catalyzed coupling of β-oxoesters, enol acetates and dioxygen.



Keywords: Lactones, Baeyer-Villiger oxidation, Oxidation, Peroxides, Cerium, Oxoesters, Enol esters, Hammett correlation, DFT calculations, Stereoelectronic effect

Introduction

In the year 1899 Baeyer and Villiger reported on the formation of lactones from the reaction of cyclic ketones with monopersulfuric acid.[1] Since then, this method was successfully established as an essential and extraordinary versatile method for the preparation of esters and lactones from ketones and was consequently named Baeyer-Villiger oxidation (BVO) in honor its discoverers.[2] The standard organic reagent for this reaction is nowadays *m*CPBA,[3] although several other peracids or even hydrogen peroxide or dioxygen[4] with[5] or without metal catalyst can be applied for this transformation. A particularly interesting issue is the use of monooxygenases

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in enzymatic BVO.[6] If unsymmetrically substituted ketones are submitted to the BVO, it is generally observed that the higher substituted alkyl residue or – in cases of aryl ketones – the phenyl ring is migrating. The origin of this regionselectivity was understood to be a stereoelectronic effect within the so called Criegee intermediate of the BVO (see Scheme 5 below).[7] There are however very few exceptions from this regiochemistry. One of the prominent examples for this opposite regiochemistry is the lactone formed by BVO of camphor,[8] which was already reported by Baeyer and Villiger themselves.[1]

Very recently, we have discovered a new aerobic, cerium-catalyzed coupling reaction of enol acetates and β-oxoesters leading to δ-lactones with an 1,4-dicarbonyl moiety in the side chain.[9] With this work, we would like to uncover the origin of the unusual regiochemistry of the lactone formation, which is contrary to expectations known from the BVO. This recent discovery is based on our earlier work, where we found a new route for the preparation of 1,4-diketones **5** by oxidative coupling of β-oxoesters like compound **1** with styrene.[10] Lately, we were able to improve these reactions by using enol esters **2** instead of olefins.[11] The cerium-catalyzed reaction utilizes molecular oxygen (from air) and can be regarded as an oxidative Umpolung reaction. During the course of our investigations, we had observed the formation of γ-oxo-δ-lactones **3** as byproducts. Most recently, we had optimized this transformation towards the formation of δ-lactones **3** as the main products of this cerium-catalyzed coupling of β-oxoesters **1**, enol acetates **2** and dioxygen (Scheme 1).[9] From a mechanistic point of view, we propose the initial formation of an endoperoxidic 1,2-dioxane derivative **6** by cerium-catalyzed coupling reaction of the two starting materials **1** and **2** and dioxygen. Although the exact mechanism of this radical chain reaction leading to intermediate product **6** remains unclear, we have experimental precedence for its existence. We have isolated and fully characterized several

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analogues earlier including X-ray diffraction data in some cases.[10a, 10c] Anyhow, with the assumption of intermediate product **6**, the 1,4-diketone **5** is formed by hydrolysis of the two acetal moieties of endoperoxide **6** (actually, we were able to detect hydrogen peroxide in the reaction mixture in these cases). When driving the selectivity towards lactone formation by the proper choice of reaction conditions, namely the use of CF_3CH_2OH (TFE) as the optimal solvent at 30°C, we propose the loss of an acetate ion under formation of the cationic intermediate **7**, which is facilitated by hydrogen bonding with the solvent TFE. Similar to the BVO, then heterolytic O-O bond cleavage with concerted 1,2-alkyl shift may occur. Interestingly, the primary alkyl group migrates (as depicted in structure **7**) instead of the quaternary carbon atom (structure **7'**), since compound **4** is not observed within the reaction mixture. This regiochemistry is just contrary to the one generally observed for the BVO. Therefore, we propose the term *anti*-Baeyer-Villiger (*anti*-BV) regiochemistry. In this manuscript we aim to support the mechanistic picture drawn in Scheme 1 by introduction of electron withdrawing or donating substituents at the phenyl ring in order to destabilize or stabilize a cationic oxycarbenium intermediate **7**. Furthermore, we wish to figure out whether the *anti*-BV regiochemistry is the result of an electronic or steric effect or both.

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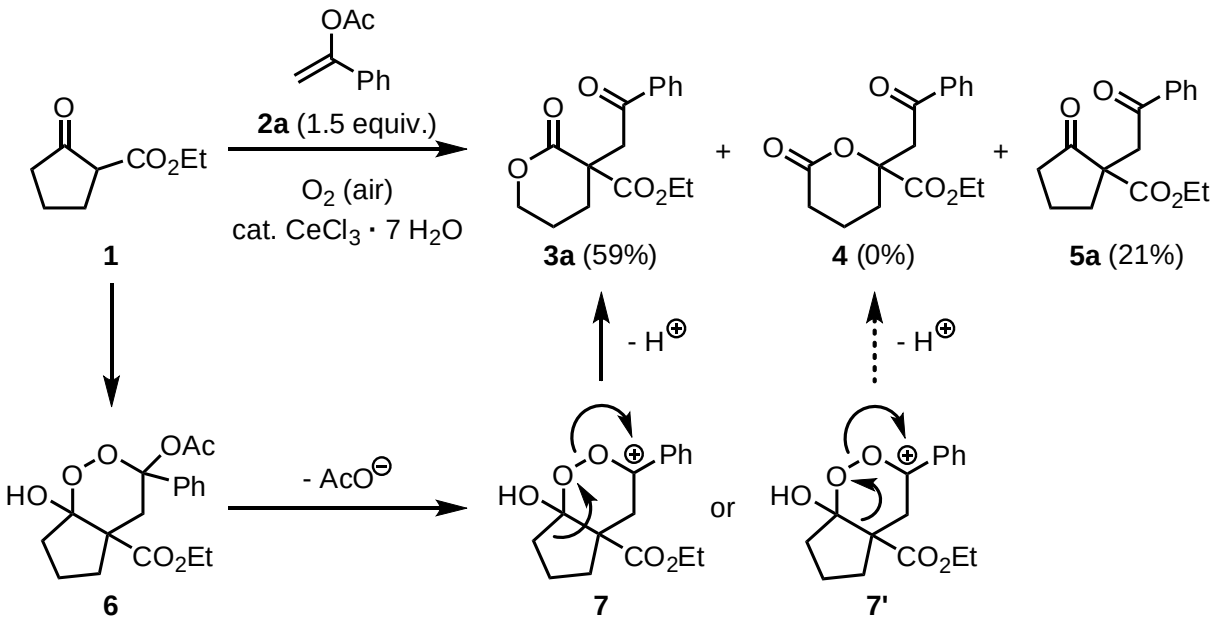

Scheme 1. Proposed mechanism for the title reaction of this investigation.

Results

BVO of model substrates. In order to find the reason for the unexpected regiochemistry of the lactone formation we have prepared some model substrates and submitted it to BVO (Scheme 2, Table 2); suitable standard conditions were first of all established for the dimethyl substituted ketone **8a**. Using an excess of *m*CPBA in the presence of $KHCO_3$ we could isolate the expected regioisomer **9a**[12] in quantitative yield (Table 1, entry 1),[13] however, the *anti*-BV regioisomer was not formed. We then adopted these conditions for the sterically more hindered benzyl-substituted ketone **8b**.[14] The expected product **9b**[15] was formed in significantly lower yield (entry 2), but importantly, an *anti*-BV product was neither isolated nor detected by GC-MS. Actually, a steric influence on the regiochemistry is not expected, since an 1,2-alkyl shift proceeds in a suprafacial manner, thus substituents R and R' should not influence the migration. Anyhow, there could be an electronic influence. Therefore, we converted the β-oxoesters **8c**[16] and **8d**,[17] but again, only

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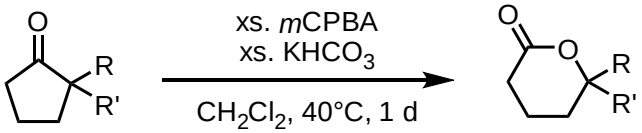
the expected regioisomers **9c** and **9d** were formed, in case of the methyl-substituted product **9c**[16b] in quantitative yield (entry 3). With more steric hindrance the yield was again lower (product **9d**, entry 4).



8a-8d **9a-9d**

Scheme 2. BVO of model substrates.

Table 1. BVO of model substrates.

Entry	Starting Material	R	R'	Product	Yield[a]
1	**8a**	Me	Me	**9a**[12]	100%
2	**8b**[14]	Me	Bn	**9b**[15]	48%
3	**8c**[16]	Me	CO_2Et	**9c**[16b]	100%
4	**8d**[17]	Bn	CO_2Et	**9d**	67%

[a] Yield of isolated product.

We then turned to the 1,4-diketone **5a** and applied the same reaction conditions as above (Scheme 3). Again, the expected BV regiochemistry dominates the product distribution (the combined yield of compounds **4** and **10** is 29%). But interestingly, the *anti*-BV product **3a** is also obtained with 13%. The low overall yield could be interpreted either in terms of steric hindrance, but also by hydrolysis of the phenyl ester moiety formed by side chain oxidation as present in compound **10**, which could have been occurred during the reaction or workup. Furthermore, we have converted oxoester **1** with *m*CPBA under the same reaction conditions. Though the starting material **1** was fully consumed after approx. 6 h, no unique reaction products were isolable after column chromatography (apart from excess of *m*CPBA and 3-$ClC_6H_4CO_2H$). The lactone expected from compound **1** by BVO was actually

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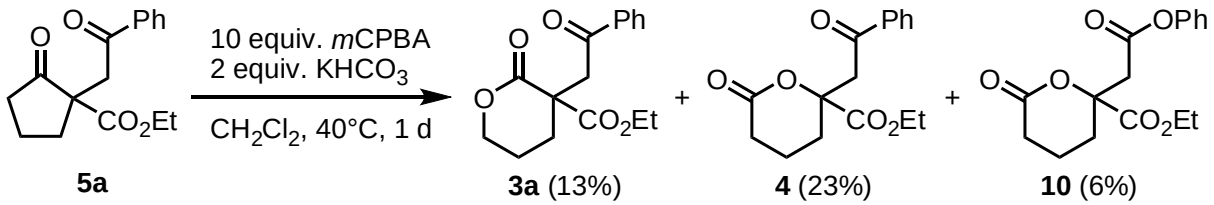
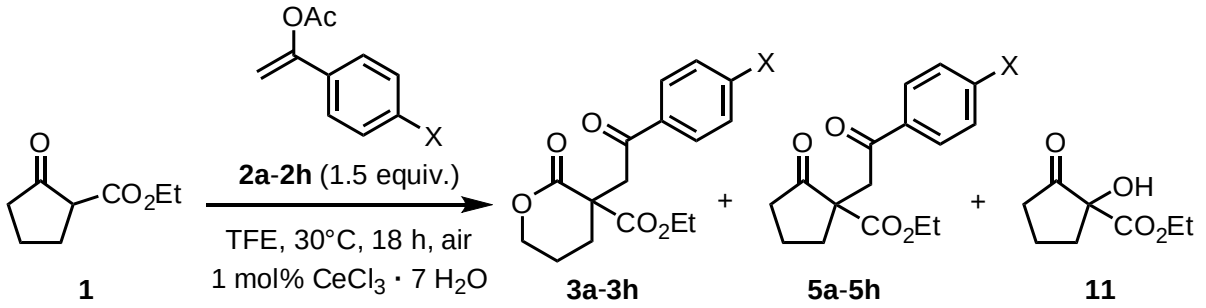
reported only once before, but accessed by a completely different route.[18]



Scheme 3. BVO of 1,4-diketone **5a**.

Conversion of substituted enol esters. In order to gain evidence for a cationic intermediate of the title reaction we investigated several enol acetates **2a**–**2h** with electron donating or accepting substituents at the *para*-position of the phenyl ring (Scheme 4). For comparison of the yields of lactones **3a**–**3h** identical reaction conditions were chosen. Apart from the main products **3a**–**3h** also the 1,4-diketones **5a**–**5h** and the α-hydroxylated compound **11**[19] were formed as byproducts, which were isolated and quantified after purification (in the case of ester **2h**, the alcohol **11** was even the main product of the conversion; Table 2, entry 8). For yields and substituents X see Table 2. Actually, the reactions of enol esters **2a**, **2b**, **2f** and **2h** were reported by us before.[9]



Scheme 4. Cerium-catalyzed aerobic conversion of oxoester **1** with several enol esters **2** under comparable conditions.

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Table 2. Results for different enol acetates **2a**–**2h**.

Entry	Enol Ester	X	Yields[a]			σ_X[b]	k_X[c]
1	**2b**	OMe	66% (**3b**)	15% (**5b**)	7% (**11**)	–0.28	0.342
2	**2c**	Me	59% (**3c**)	28% (**5c**)	2% (**11**)	–0.14	0.244
3	**2a**	H	59% (**3a**)	21% (**5a**)	0% (**11**)	0	0.276
4	**2d**	F	54% (**3d**)	19% (**5d**)	2% (**11**)	0.15	0.248
5	**2e**	Cl	47% (**3e**)	27% (**5e**)	2% (**11**)	0.24	0.212
6	**2f**	Br	44% (**3f**)	19% (**5f**)	35% (**11**)	0.26	0.213
7	**2g**	CN	35% (**3g**)	15% (**5g**)	26% (**11**)	0.70	0.148
8	**2h**	NO_2	7% (**3h**)	2% (**5h**)	36% (**11**)	0.81	0.116

[a] Yields of isolated products after chromatographic purification. [b] Hammett constant for the *para*-substituent X; values were taken from the literature.[20] [c] Rate constants (slopes in Figure 2).

The results summarized in Table 2 point out, that there is an obvious correlation of the yields of lactones **3a**–**3h** with the electron donor or acceptor properties of the *para*-substituents at the phenyl rings, which are quantified by the substituent constant σ_X. This correlation already qualitatively supports an oxycarbenium ion **7** as the intermediate of the reaction. To obtain a quantitative evidence for this correlation, the kinetics of the reaction were followed by GLC. As an essential precondition for this attempt, all compounds collected in Table 2 were available as GC-standards. The eight enol esters **2a**–**2h** were submitted to the reaction with β-oxoester **1** under the same conditions (concentrations, temperature, and stoichiometry) with mesitylene as internal integration standard. Samples were taken in defined time intervals and quenched by dilution with dichloromethane (DCM). In Figure 1, relative peak areas of lactones [**3x**] (which were obtained by division of the peak areas of product **3x** by the peak area of the internal standard mesitylene) are plotted *vs.* time. At about 12 h, the concentration of compounds **3x** reached a maximum, thereafter it decreased with a

minimal slope, probably due to decomposition reactions, e.g. ester hydrolysis or retro-Claisen reactions. Nevertheless, since this would hamper the successive analysis, only data up to 12 h were used for the numerical analysis. A precondition of the linear free energy relationship according to Hammett is first order kinetics.[20] However, data for the starting materials **1** or **2x** could not be used for this kinetic analysis for several reasons: First of all, two byproducts **5a**–**5h** and **11** are always formed with different rate constants or even different reaction order. Secondly, the integration of compound **1** was not very accurate due interconversion of the keto and enol tautomer on the GC column. Furthermore, the enol esters **2x** were used in excess. For this reason, a replacement for the concentrations of **1** or **2x** was constructed by the following term: [**3x**](12 h) - [**3x**](t), herein [**3x**](12 h) represents the "end concentration" of product **3x** at t = 12 h. The difference [**3x**](12 h) - [**3x**](t) therefore shall be equal to the portion of starting material **1,** which was converted with enol ester **2x** along the reaction pathway leading to lactone **3x**. The complementary fraction of compound **1** converted to byproducts **5x** and **11** is faded out by this operation. Consequently, the term ln{[**3x**](12 h) - [**3x**](t)} was plotted *vs.* time. In Figure 2, the graphs clearly show first order kinetics due to their linearity. Moreover, rate constants k_X can be obtained from the regression lines. These data are listed in the last column of Table 2. Finally, the Hammett correlation was established by plotting $\log(k_X/k_H)$ *vs.* the *para*-substituent constant σ_X. However, the data point for X = Me was left out, since it was not fitting at all into the linear regression line. The negative slope of this linear correlation indicates the existence of a carbenium ion in benzylic position as intermediate in the rate determining step of the lactone formation. We propose, that this species is represented by the oxycarbenium ion **7**.

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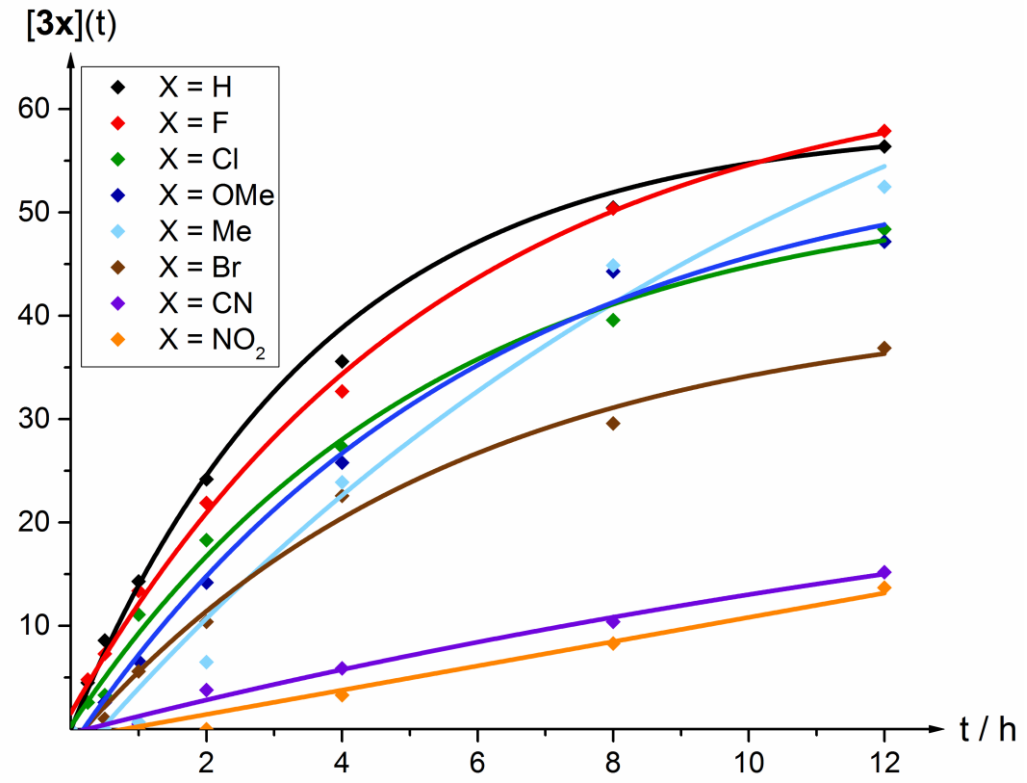

Figure 1. Emergence of products **3a–3h**; the relative peak areas [**3x**] obtained by peak areas of the lactone **3x** divided by the internal standard are plotted at the ordinate.

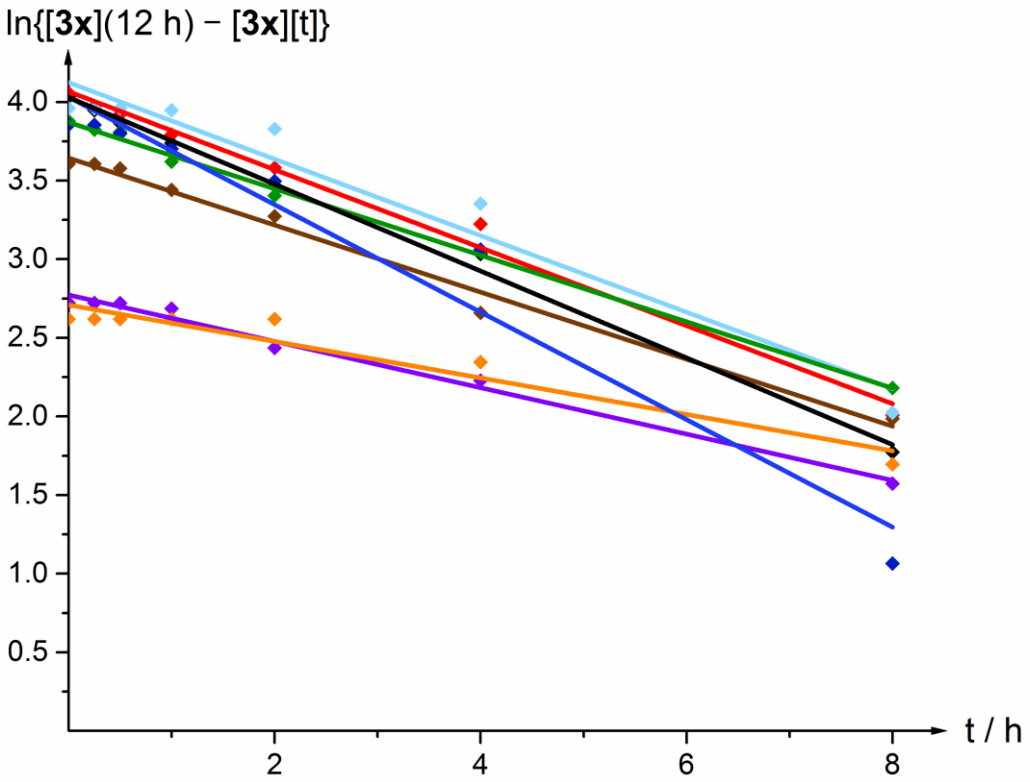

Figure 2. Plot of ln{[**3x**](12 h) – [**3x**](t)} *vs.* time; for the color code see Figure 1; the

slopes of the linear equations are the rate constants k_X.

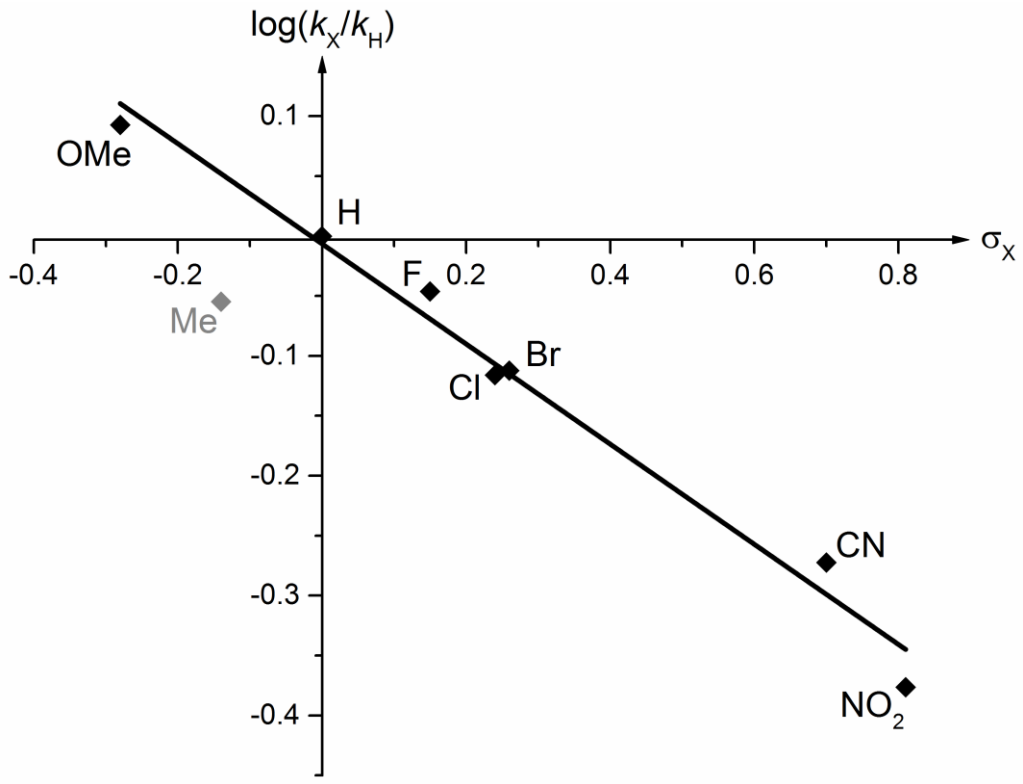

Figure 3. Hammett plot with log(k_X/k_H) *vs.* substituent (*para*) constant σ_X.

Computational Results. With two stereocenters, the reaction intermediate **7** exists as two diastereoisomers (Figure 4); they can be regarded as the *trans*- and *cis*-cyclotautomers (α- and β-anomers within the carbohydrate terminology) of a monocyclic open chain form. Whereas there has only one conformer to be considered for the *trans*-diastereoisomer **7a** (with ester E and 9-OH both axial), the *cis*-diastereoisomer could adopt two conformations **7b** (with E axial and 9-OH equatorial) and **7c** (with E equatorial and 9-OH axial). Although oxycarbenium ions **7b** and **7c** depicted in Figure 4 are enantiomeric compounds, this does not play a role for the investigation and for the following discussion, since all compounds in this study are racemates. Structure optimizations for all three isomers **7a**–**7c** were carried out using density functional theory (DFT) calculations applying the M06-2X functional and 6-311+G(d,p) basis set[21a] (all computations were done with the Gaussian09, B1

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program;[21b] see the Supporting Information for details). For these computations, *E* = CO_2Me was chosen for simplicity. A self-consistent reaction field (SCRF) calculation using the PCM model with appropriate parameter modeled the solvent TFE. This model chemistry predict compound **7c** to be the thermodynamically most stable isomer (Table 3). Both diastereoisomers **7a** (*trans*) and **7c** (*cis*) are comparable in energy (ΔE = 9 kJ mol^{-1}). The second *cis*-conformer **7b** is however ΔE = 19 kJ mol^{-1} higher than isomer **7c**, therefore, this conformation is not significantly populated at 30°C. The dihedral angles C*8*-C*9*-O*1*-O*2* (two blue bonds) and C*5*-C*9*-O*1*-O*2* (a blue and a red bond) were read out of the optimized geometries. For all three isomers, the C*5*-C*9*-O*1*-O*2* is about 60° (*syn*-gauche). The formation of a product **4** with BV constitution would require migration of the red bond C*5*-C*9* to oxygen atom O*1*, while the blue bond O*1*-O*2* is cleaved. For both more stable isomers **7a** and **7c**, the angle C*8*-C*9*-O*1*-O*2* is about 180° (antiperiplanar). Migration of the blue C*8*-C*9* bond to O*1* forms the product **3** with *anti*-BV constitution. We were able to identify the transition state for this rearrangement. The barrier is E^{rel} = 62.5 kJ mol^{-1} (G^{rel} = 54.2 kJ mol^{-1}). The energy profile and a movie visualizing the transformation are included in the supporting information.

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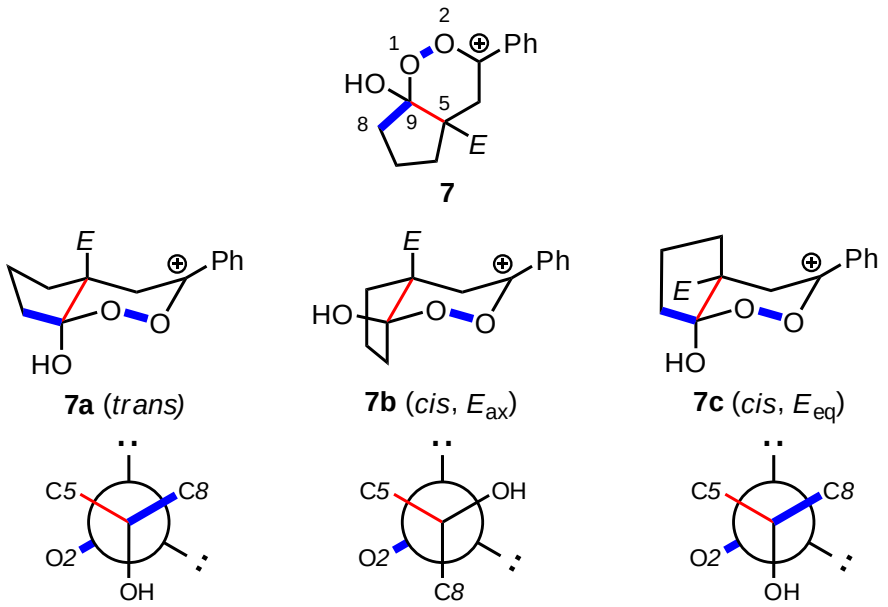

Figure 4. Oxycarbeniumion **7**, atom numbering, relative configuration of the *trans*-diastereoisomer **7a**, and the two *cis*-conformers **7b** and **7c**; Newman projections of the ecliptic conformations of the C*9*-O*1* bond show, that the blue bonds are in antiperiplanar conformation; *E* = CO_2Me.

Table 3. Calculated relative energies, E^{rel}, relative Gibbs energies at 298 K, G^{rel}, and selected structural parameters for oxycarbenium ions **7a**–**7c** [M06-2x/6-311+G(d,p)].

	Intermediate		
	7a	**7b**	**7c**
E^{rel} / kJ mol^{-1}	+9	+19	0
G^{rel} / kJ mol^{-1}	+13	+20	0
dihedral angle			
C*8*-C*9*-O*1*-O*2*	174°	69°	179°
C*5*-C*9*-O*1*-O*2*	58°	51°	66°

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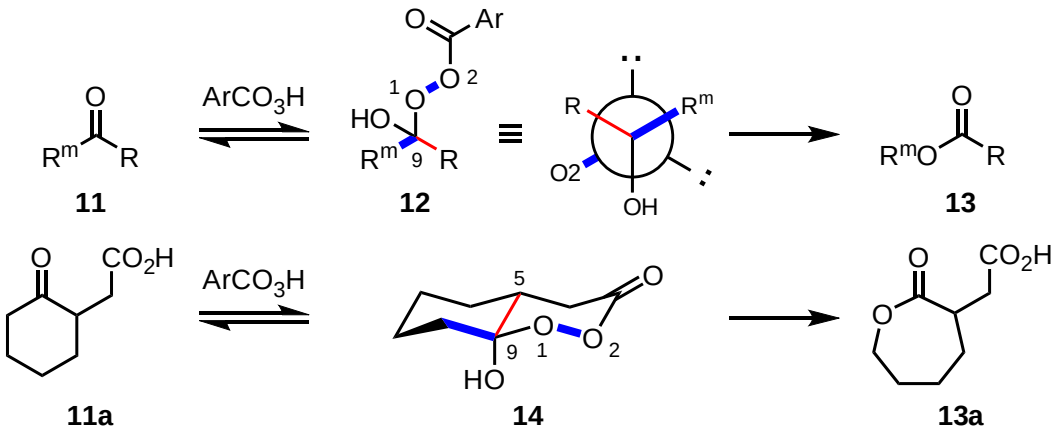
Discussion

Earlier studies on the mechanism of the BVO revealed the following picture (Scheme 5):[22] Upon a BVO of the unsymmetric ketone **11** to the ester **13**, the migrating group R^m should be positioned in antiperiplanar conformation to the O*1*-O*2* bond in the Criegee intermediate **12**. This conformation is, for example, favourable, if R^m is larger than R. This requirement is called the primary stereoelectronic effect. There is actually another, so-called secondary stereoelectronic effect, discussed in the literature, which requires the residue R^m being in antiperiplanar conformation of one of the lone pairs of the hydroxy group at C*9*. However, this secondary stereoelectronic effect does not play a role for the regioselectivity in this investigation. In order to support the primary stereoelectronic effect, Chandrasekhar and Roy[23] have performed the following experiment for an intramolecular BVO with a bicyclic Criegee intermediate **14**: The carboxylic acid side chain of ketone **11a** was transformed into the peracid which is in equilibrium with its cyclotautomer **14**. The analogy to the constitution of our proposed intermediate **7** is obvious. The two blue bonds C*8*-C*9* and O*1*-O*2* are in antiperiplanar conformation, thus, the primary carbon atom C*9* migrates rather than the tertiary C*5* leading to the product **13a** with formal *anti*-BV constitution.



Scheme 5. Conformation of the Criegee intermediate **12** of the BVO and

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Chandrasekhar's model system **11a** for the primary stereoelectronic effect; the numbers of C*9*, O*1* and O*2* and the color codes red and blue are adopted from the 1,2-dioxabicyclo[4.3.0]nonane skeleton of species **7** in Figure 4.

The question for an overall mechanistic picture is, whether an endoperoxidic 3-aryl-3-acetoxy-1,2-dioxabicyclo[4.3.0]nonane derivative **6**, an intermediate compound, which could so far neither be isolated from nor detected in the reaction mixture, exists. However, in our preceding investigations on the cerium-catalyzed, aerobic conversion of β-oxoesters or α-acetyllactones with styrene or α-methylstyrene we were able to isolate and characterize several congeners **15** of the structural type represented by proposed intermediate **6**. Five of these compounds **15a**–**15e** were even suitable for single crystal X-ray crystallography (Figure 5). One compound is monocyclic (**15c**), two are annulated (**15a** and **15b**), and two others are spirocyclic (**15d** and **15e**). The structures were already published earlier[10a, 10c] and crystal data have been deposited.[24] Structural similarities are apart from the 1,2-dioxane ring the tertiary alcohol at C*9*, the quaternary carbon center C*5* carrying an ester moiety and a phenyl substituent at C*3*. The most significant difference is of course the acetoxy group at C*3*, which is supposed to be actually the reason for the intrinsic instability of compound **6** compared to isolable compounds **15**.

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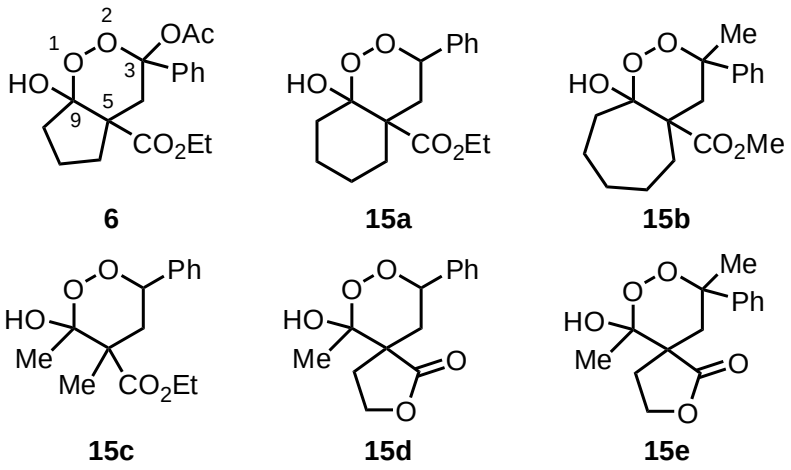

Figure 5. Comparision of postulated intermediate **6** with structurally characterized analogues **15a**–**15e**.

With the data collected above the following general view of the overall reaction mechanism can be developed; it consists of three stages:

(1) Start of the radical chain reaction (Scheme 6),

(2) propagation with coupling of enol ester **2a** and dioxygen (Scheme 7), and

(3) decomposition of the 1,2-dioxane derivative **7** (Scheme 8).

Stage (1): The radical chain reaction starts with the α-oxidation of the β-oxoester **1** by a Ce(IV) species, a process, which is actually well known for the stoichiometric oxidation of carbonyl compounds with CAN. Actually, the precatalyst in our case is a Ce(III) salt. It is proposed, that Ce(III) coordinates to the β-oxoester **1** under formation of a diketonato complex **16** (Scheme 6) in similarity of the well-known chemistry of Fe(III) and other trivalent metal ions.[25] The anionic ligand then facilitates the oxidation of Ce(III) to Ce(IV) with dioxygen and the Ce(IV)-diketonato complex **17a** is formed. Formation of a radical species **17b** with spin density at the α-position can be proposed as ligand-to-metal charge transfer within Ce(IV)-diketonato complex **17a**.[26] In the catalytic cycle, dissociation of complex **17b** liberates the ligand

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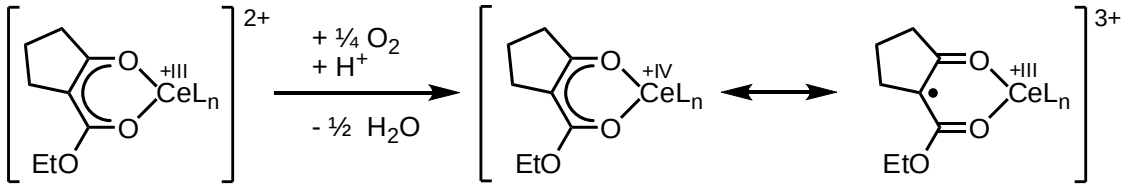
18 and Ce(III) is finally reoxidized to Ce(IV) by air (upper cycle in Scheme 7). Obviously, coordination of Ce(III) to β-oxoesters shifts the redox potential and makes this air-oxidation possible. Therefore, the β-oxoester **1** is not only the substrate of the reaction, but also plays the role of a ligand for Ce(III) centers necessary for the reoxidation their Ce(IV).



16 **17a** **17b**

Scheme 6. Start of the radical chain reaction by air-oxidation of Ce(III)-diketonato complex **16**.

The radical chain reaction of stage (2) is summarized in Scheme 7. After initial formation of the α-radical **18** by Ce(IV), addition to the enol acetale **2a** furnishes the benzyl radical **19**, which gains further stabilization by the +M-effect of the acetoxy group. Reaction of radical **19** with dioxygen leads to peroxy-species **20**, which closes the radical chain reaction by H atom abstraction from oxoester **1** with regeneration of α-radical **18** under formation of hydroperoxide **21**. The latter undergoes a cyclotautomerization to the 1,2-dioxane derivative **6**. Using the carbohydrate terminology, compound **21** defines the open-chain form, and compound **6** exists as two equilibrating α- and β-anomers (epimers at C*9*). In the case of an unspecified interruption of the radical chain mechanism, the α-radical can continuously be regenerated by Ce(IV) oxidation of the oxoester **1**. Furthermore and as pointed out above in Scheme 6, the formation of Ce(III)-diketonato complexes facilitates the reoxidation of Ce(III) complexes with dioxygen to Ce(IV) species.

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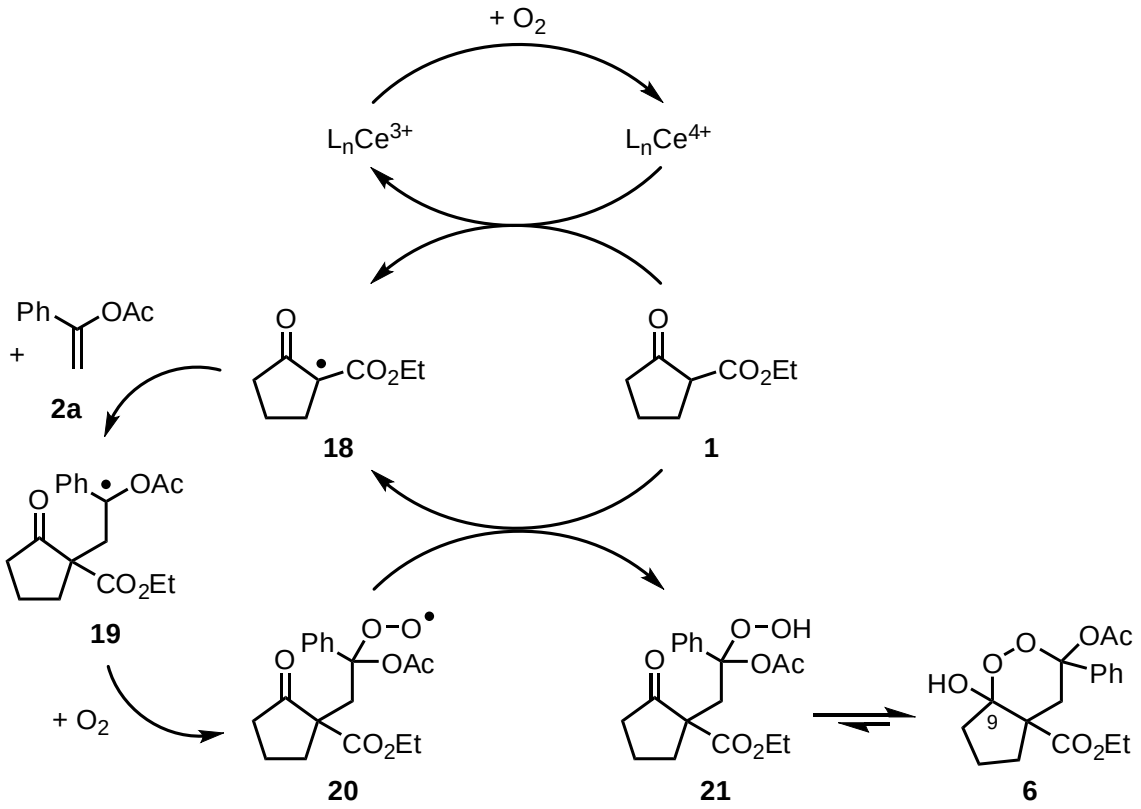

Scheme 7. Chain propagation and formation of 1,2-dioxane derivative **6**.

Finally, in stage (3), compound **6** could find two pathways for decomposition to product **3a** and byproduct **5a** (Scheme 8): First of all, acid catalyzed hydrolysis could furnish the 1,4-diketone **5a**. Byproduct of this process is hydrogen peroxide. The obviously preferred reaction pathway is, however, the loss of an acetate ion from compound **6**. We propose that this process is facilitated by H bonding of acetate to the solvent TFE. The oxycarbenium ion **7**, which could be regarded as a species analogous to the Criegee intermediate of the BVO, is particularly stabilized by conjugation with the phenyl ring as well as the oxygen atom O*2* of the dioxane moiety. Actually, the Hammett correlation depicted in Figure 3 strongly supports the formation of this intermediate cation in the rate determining step. Electron donating substituents at the *para*-position of the phenyl ring result in an acceleration of the reaction, while electron withdrawing decrease the reaction rates. Furthermore, a

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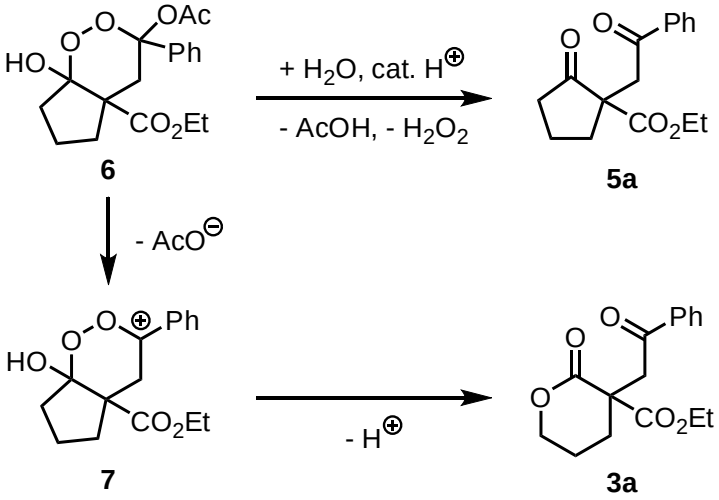
conformational analysis of the both diastereoisomers of compound **7**, namely *trans*-isomer **7a** and *cis*-isomer **7c** (Figure 4), has pointed out that only the C*8*-C*9* bond is in antiperiplanar position to the O*1*-O*2* bond. Thus, the formal *anti*-BV regiochemistry of the product is the result of the so-called primary stereoelectronic effect, which is operative in the rearrangement of the intermediate **7**. The second *cis*-conformer **7b** cannot find a pathway for decomposition to product **3a** due to the lack of appropriate antiperiplanar orientation of the migrating bonds. In addition, it is too high in energy to be significantly populated at 30°C.



Scheme 8. Decomposition of intermediate product **6** either by acid catalyzed hydrolysis under formation of 1,4-diketone **5a** or *via* oxycarbenium ion **7** with formation of lactone **3a** with *anti*-BV constitution.

Conclusion

δ-Valerolactone derivatives **3** with an 1,4-diketone moiety are formed by aerobic, cerium-catalyzed coupling of β-oxoester **1**, enol acetates **2** and dioxygen. This transformation can be regarded as an Umpolung reaction, since the normally nucleophilic α-carbon atom of the β-oxoester becomes an electrophilic radical center reacting with the electron rich olefin **2**. Furthermore, the catalyst metal cerium is non-

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toxic and environmentally benign, atmospheric oxygen is abundant and the conversion is highly atom-economic. Therefore, this reaction could be considered as a contribution to the field of sustainable chemistry. In this article, an overall mechanistic picture of the reaction was drawn consisting of three parts: (1) Initiation by a Ce(IV) species, (2) radical chain propagation and (3) decomposition of endoperoxide **6**. First of all, a radical chain reaction is started by α-oxidation of the oxoester **1** by a Ce(IV) species, which was formed by air-oxidation of Ce(III). This step is actually making the overall transformation an Umpolung. A precondition for the oxidation of Ce(III) to Ce(IV) is the coordination of the metal center to the β-oxoester **1** under formation of a diketonato-complex **16**. A respective Ce(IV)-diketonate species **17a** is then undergoing intramolecular ligand-to-metal charge transfer (complex **17b**), thus, generating a Ce(III) center and the radical species **18**. Secondly, the radical chain propagates by addition of radical **18** to the enol ester **2** before addition to dioxygen occurs. The radical chain is closed by α-hydrogen abstraction from the oxoester **1** by the peroxy radical **20** under formation of the hydroperoxide **21**, which is in equilibrium with its cyclotautomer **6**. The latter intermediate **6** could so far neither be isolated nor spectroscopically detected, although its existence is supported by structural precedence of similar endoperoxides **15**, which were formed in reactions of oxoesters with styrene or α-methyl styrene in the presence of dioxygen. The third part exhibits similarities to the BVO. Herein compound **6** eliminates an acetate ion and forms an oxycarbenium ion **7**. The existence of this ion **7** is strongly supported by the kinetics of the reaction of several donor and acceptor substituted enol acetates **2a**–**2h**. Donor substituents accelerate the reaction, whereas acceptor substituents slow it down. An analysis of the first order kinetics resulted in rate constants *k*, which were linearly correlated with the *para*-substituent constants σ in a Hammett plot. The negative slope provides

evidence for the existence of the benzyl cation **7**, which could be considered as an analog to the Criegee intermediate of the BVO. Furthermore, the relative energies and optimized conformations of three possible stereoisomers **7a**–**7c** were obtained by DFT calculations. A conformational analysis of the two relevant isomers **7a** and **7c** explains the regiochemistry of the rearrangement reaction by a primary stereoelectronic effect. In contrast to the BVO, where the higher substituted residue is migrating, the primary alkyl residue of intermediate **7** undergoes an 1,2-alkyl shift and forms the δ-valerolactone **3**.

Experimental Section

General: Preparative column chromatography was carried out using Merck SiO_2 (35–70 µm, type 60 A) with hexanes, *tert*-butyl methyl ether (MTBE), and ethyl acetate (EA) as eluents. TLC was performed on aluminum plates coated with SiO_2 F_{254}. ^{1}H-, ^{19}F- and ^{13}C-NMR spectra were recorded on a Bruker Avance DRX 500 and 300 instruments. Multiplicities of carbon signals were determined with DEPT experiments. HRMS spectra of products were obtained with a Waters Q-TOF Premier (ESI) spectrometer. IR spectra were recorded on a Bruker Tensor 27 spectrometer equipped with a "GoldenGate" diamond ATR unit. GLC analyses were performed on a Focus GC (Thermo-Fisher) on a SP-Sil 19CB capillary column (Macherey-Nagel, 30 m, 0.25 mm) with H_2 as carrier gas. The starting materials **1** and **8a** were commercially available. The following compounds were literature known and prepared according to published procedures: 2-methylcyclopentanone,[14a, 14b] **2c**,[27] **2d**,[27] **2e**,[27] **2g**,[27] **8c**,[16] and **8d**.[17] The synthesis of enol acetates **2a**, **2b**, **2f** and **2h** and their reactions of oxoester **1** yielding **3a**, **3b**, **3f**, **3h**, **5a**, **5b**, **5f**, **5h** and **11** were reported by us earlier.[9]

2-Benzyl-2-methylcyclopentanone (8b): Under exclusion of air and moisture (nitrogen atmosphere), *n*BuLi (1.2 mL of a 2.5 mol/L solution in hexane, 3.0 mmol) was added dropwise within 10 min to a solution of HMDS (0.6 mL, 3.0 mmol) in abs. hexane (1.2 mL). After heating the mixture for 1 h to reflux, abs. THF (5 mL) was added and the mixture was cooled to –78°C. A solution of 2-methylcyclopentanone (269 mg, 2.74 mmol) in abs. THF (1 mL) was added dropwise within 15 min and the mixture was stirred for further 3 h at 0°C. Benzyl bromide (515 mg, 3.01 mmol) was then added dropwise at this temperature. The resulting mixture was stirred at ambient temperature overnight, subsequently diluted with hydrochloric acid (5 mL, 1 mol/L) and extracted with Et_2O (3 x 5 mL). The combined organic layers were washed with brine (10 mL), dried ($MgSO_4$), filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography (SiO_2, hexanes/MTBE 10:1, R_f = 0.23) to yield the title compound **8b** (115 mg, 0.61 mmol, 22%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02 (s, 3H), 1.59–1.86 (m, 3H), 1.91–2.11 (m, 2H), 2.24–2.35 (m, 1H), 2.59 (d, *J* = 13.3 Hz, 1H), 2.86 (d, *J* = 13.3 Hz, 1H), 7.10–7.18 (m, 2H), 7.18–7.29 (m, 3H) ppm. The data are in accordance with literature values.[14c]

General procedure A for BVO (GPA):[13] Cyclopentanone derivative **8** (1.0 equiv.) was added to a mixture of *m*CPBA (6.0–10 equiv., 70% in H_2O) and $KHCO_3$ (2.0 equiv.) in DCM (6 L/mol). The mixture was heated to reflux for 5–24 h, subsequently cooled to ambient temperature and washed with an aqueous $NaHSO_3$ solution (10 L/mol, 10% w/w). The aqueous layer was extracted with DCM (2 x 10 L/mol). The combined organic layers were first washed with a saturated aqueous K_2CO_3 solution (10 L/mol) and then with brine (10 L/mol), dried ($MgSO_4$), filtered and the solvent was

removed *in vacuo*. The crude product was purified by column chromatography to give the lactone **9**.

6,6-Dimethyltetrahydropyran-2-one (9a): According to the GPA, 2,2-dimethylcyclopentanone (**8a**, 56 mg, 0.50 mmol), *m*CPBA (744 mg, 70% in H_2O, 3.02 mmol) and $KHCO_3$ (106 mg, 1.06 mmol) in DCM (3 mL) were heated to reflux for 5 h to yield the title compound **9a** (64 mg, 0.50 mmol, 100%) after chromatography (SiO_2, hexanes/EA 1:1, R_f = 0.28) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (s, 6H), 1.72–1.74 (m, 2H), 1.85–1.90 (m, 2H), 2.46 (t, *J* = 6.9 Hz, 2H) ppm. The data were in accordance with literature values.[12]

6-Benzyl-6-methyltetrahydropyran-2-one (9b): According to the GPA, 2-benzyl-2-methylcyclopentanone (**8b**, 91 mg, 0.48 mmol), *m*CPBA (1.18 g, 70% in H_2O, 4.77 mmol) and $KHCO_3$ (95 mg, 1.00 mmol) in DCM (3 mL) were heated to reflux for 24 h to yield the title compound **9b** (48 mg, 0.23 mmol, 48%) after chromatography (SiO_2, hexanes/MTBE 1:1, R_f = 0.18) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.36 (s, 3H), 1.58–1.88 (m, 4H), 2.23–2.34 (m, 1H), 2.42–2.52 (m, 1H), 2.88 (d, *J* = 13.7 Hz, 1H), 3.00 (d, *J* = 13.7 Hz, 1H), 7.19–7.38 (m, 5H) ppm. The data were in accordance with literature values.[15]

Ethyl 2-methyl-6-oxotetrahydropyrane-2-carboxylate (9c): According to the GPA, β-oxoester **8c** (92 mg, 0.54 mmol), *m*CPBA (758 mg, 70% in H_2O, 3.07 mmol) and $KHCO_3$ (104 mg, 1.04 mmol) in DCM (3 mL) were heated to reflux for 24 h to yield the title compound **9c** (101 mg, 0.54 mmol, 100%) after chromatography (SiO_2, hexanes/MTBE 1:2, R_f = 0.23) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t,

J = 7.1 Hz, 3H), 1.58 (s, 3H), 1.63–1.88 (m, 3H), 2.17–2.21 (m, 1H), 2.36–2.62 (m, 2H), 4.15–4.26 (m, 2H) ppm. The data were in accordance with literature values.[16]

Ethyl 2-benzyl-6-oxotetrahydropyrane-2-carboxylate (9d): According to the GPA, β-oxoester **8d** (126 mg, 0.51 mmol), *m*CPBA (1.24 g, 70% in H_2O, 5.01 mmol) and $KHCO_3$ (106 mg, 1.06 mmol) in DCM (3 mL) were heated to reflux for 24 h to yield the title compound **9d** (90 mg, 0.34 mmol, 67%) after chromatography (SiO_2, hexanes/MTBE 1:1, R_f = 0.23) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.21 (t, *J* = 7.1 Hz, 3H), 1.61–1.83 (m, 3H), 2.10–2.37 (m, 2H), 2.50–2.58 (m, 1H), 3.13 (d, *J* = 14.1 Hz, 1H), 3.24 (d, *J* = 14.1 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 7.19–7.31 (m, 5H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 14.07 (CH_3), 16.99 (CH_2), 28.61 (CH_2), 29.46 (CH_2), 43.82 (CH_2), 62.17 (CH_2), 85.93 (C), 127.17 (CH), 128.21 (2 CH), 130.66 (2 CH), 134.21 (C), 169.94 (C), 171.61 (C) ppm. IR (ATR): nu(tilde) = 3031 (w), 2964 (w), 2928 (w), 1739 (vs), 1497 (w), 1455 (w), 1444 (w), 1371 (w), 1355 (w), 1329 (w), 1228 (s), 1188 (s), 1118 (m), 1083 (vs), 1052 (s), 1017 (m), 988 (w), 935 (m), 859 (w), 757 (m), 701 (s), 667 (w), 647 (w), 611 (w) cm^{-1}. HRMS (ESI): calcd. 285.1097 (for $C_{15}H_{18}NaO_4^+$); found 285.1102 [M + Na^+]. $C_{15}H_{18}O_4$ (262.31).

BVO of Ethyl 2-oxo-1-(2-oxo-2-phenylethyl)cyclopentane-1-carboxylate (5a): According to the GPA, 1,4-diketone **5a** (278 mg, 1.01 mmol), *m*CPBA (2.45 mg, 70% in H_2O, 10.0 mmol) and $KHCO_3$ (198 mg, 1.98 mmol) in DCM (6 mL) were heated to reflux for 24 h. The crude mixture was purified by column chromatography (SiO_2, hexanes/MTBE 1:1 → 1:2) to yield lactone **3a** [37 mg, 0.13 mmol, 13%, R_f = 0.28 (hexanes/MTBE 1:2)] in the first fraction as a colorless oil. Secondly, lactone **10** [17 mg, 60 µmol, 6%, R_f = 0.16 (hexanes/MTBE 1:2)] was eluted as a colorless oil. As the third fraction lactone **4** [66 mg, 0.23 mmol, 23%, R_f = 0.13 (hexanes/MTBE 1:2)]

was isolated as a colorless solid (mp. 107°C). All spectroscopic data for compound **3a** are in accordance with the literature.[9]

Ethyl 6-oxo-2-(2-oxo-2-phenylethyl)tetrahydropyran-2-carboxylate (4): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 1.76–1.93 (m, 2H), 2.02 (td, *J* = 13.6 Hz, *J* = 4.5 Hz, 1H), 2.21–2.26 (m, 1H), 2.49 (ddd, *J* = 18.5 Hz, *J* = 10.6 Hz, *J* = 8.0 Hz, 1H), 2.66–2.72 (m, 1H), 3.61 (d, *J* = 17.2 Hz, 1H), 3.67 (d, *J* = 17.2 Hz, 1H), 4.26–4.35 (m, 2H), 7.43–7.46 (m, 2H), 7.54–7.57 (m, 1H), 7.90–7.92 (m, 2H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.03 (CH_3), 16.72 (CH_2), 28.55 (CH_2), 30.26 (CH_2), 46.76 (CH_2), 62.26 (CH_2), 82.64 (C), 128.07 (2 CH), 128.60 (2 CH), 133.45 (CH), 136.38 (C), 169.39 (C), 171.36 (C), 194.14 (C) ppm. IR (ATR): nu(tilde) = 3002 (w), 2975 (w), 2923 (w), 1743 (s), 1732 (s), 1688 (s), 1596 (w), 1580 (w), 1466 (w), 1451 (w), 1440 (w), 1359 (m), 1312 (m), 1232 (m), 1196 (s), 1163 (m), 1133 (m), 1081 (s), 1054 (s), 1024 (m), 1006 (m), 978 (w), 936 (m), 859 (w), 764 (m), 747 (s), 695 (s), 687 (m), 660 (w), 623 (m) cm^{-1}. HRMS (ESI): calcd. 313.1046 (for $C_{16}H_{18}NaO_5^+$); found 313.1049 [M + Na^+]. $C_{16}H_{18}O_5$ (290.32).

Ethyl 6-oxo-2-[(phenoxycarbonyl)methyl]tetrahydropyran-2-carboxylate (10): ^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (t, *J* = 7.1 Hz, 3H), 1.74–1.83 (m, 1H), 1.89–1.95 (m, 1H), 2.04 (td, *J* = 13.7 Hz, *J* = 4.4 Hz, 1H), 2.24–2.29 (m, 1H), 2.51 (ddd, *J* = 18.5 Hz, *J* = 10.8 Hz, *J* = 7.9 Hz, 1H), 2.61–2.72 (m, 1H), 3.08 (d, *J* = 16.1 Hz, 1H), 3.37 (d, *J* = 16.1 Hz, 1H), 4.24–4.35 (m, 2H), 7.09–7.12 (m, 2H), 7.20–7.25 (m, 1H), 7.34–7.39 (m, 2H) ppm. ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$): δ = 14.11 (CH_3), 16.97 (CH_2), 28.60 (CH_2), 30.23 (CH_2), 43.26 (CH_2), 62.64 (CH_2), 82.99 (C), 121.48 (2 CH), 126.08 (CH), 129.44 (2 CH), 150.26 (C), 166.84 (C), 168.92 (C), 170.74 (C) ppm. IR (ATR): nu(tilde) = 2955 (w), 2928 (w), 2856 (w), 2364 (w), 2342 (w), 1753 (vs), 1593

(w), 1492 (w), 1459 (w), 1374 (w), 1311 (w), 1232 (m), 1196 (s), 1165 (m), 1150 (m), 1109 (w), 1085 (m), 1055 (w), 1021 (w), 938 (w), 751 (w), 691 (w) cm^{-1}. HRMS (ESI): calcd. 329.0996 (for $C_{16}H_{18}NaO_6^+$); found 329.0993 [M + Na^+]. $C_{16}H_{18}O_6$ (306.31).

1-(4-Methylphenyl)vinyl acetate (2c): The product was prepared by the method of Hagemeyer and Hull.[28] A mixture of 4-methylacetophenone (5.0 g, 37 mmol), isopropenyl acetate (7.5 g, 75 mmol) and four drops of conc. H_2SO_4 (ca. 80 mg) was heated to reflux for 18 h. Subsequently, the mixture was directly submitted to column chromatography (SiO_2, hexanes/MTBE 2:1, R_f = 0.47) to yield the title compound **2c** (2.65 g, 15.0 mmol, 40%) after chromatography as a light yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 2.35 (s, 3H), 4.97 (d, *J* = 1.8 Hz, 1H), 5.43 (d, *J* = 1.8 Hz, 1H), 7.13–7.19 (m, 2H), 7.34–7.39 (m, 2H) ppm. The data were in accordance with literature values.[29]

General procedure B (GPB):[27] Under exclusion of air and moisture (nitrogen atmosphere), a solution of *n*BuLi (1.05 equiv., 2.5 mol/L in hexane) was added dropwise over 10 min to a solution of HMDS (1.05 equiv.) in abs. hexane (0.5 L/mol) and the mixture was heated to reflux for 1 h. After adding abs. THF (1.5 L/mol) the solution was cooled to –78°C. At this temperature, a solution of the acetophenone derivative (1.0 equiv.) in abs. THF (1 L/mol) was added dropwise within 30 min and the mixture further stirred for 30 min. Subsequently, a solution of Ac_2O (1.05 equiv.) in abs. THF (1 L/mol) was added dropwise within 15 min and the resulting mixture was stirred for further 1.5 h at this temperature. Subsequently, the mixture was stirred overnight at ambient temperature and then was acidified with hydrochloric acid (3 L/mol, 1 mol/L) and extracted with Et_2O (3 x 1.5 L/mol). The combined organic layers

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were dried ($MgSO_4$) and the solvent was removed *in vacuo.* The residue was purified by column chromatography to yield the enolester **2**.

1-(4-Fluorophenyl)vinyl acetate (2d): According to the GPB, reaction of *n*BuLi (6.1 mL, 2.5 mol/L in hexane, 15 mmol), HMDS (3.1 mL, 15 mmol), 4-fluoroacetophenone (2.61 g, 14.5 mmol) and Ac_2O (1.55 g, 15.2 mmol) gave the title compound **2d** (2.00 g, 11.1 mmol, 77%) after chromatography (SiO_2, hexanes/MTBE 5:1, R_f = 0.32) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 5.01 (d, *J* = 2.2 Hz, 1H), 5.40 (d, *J* = 2.2 Hz, 1H), 7.01–7.07 (m, 2H), 7.42–7.47 (m, 2H) ppm. The data were in accordance with literature values.[27]

1-(4-Chlorophenyl)vinyl acetate (2e): According to the GPB, reaction of *n*BuLi (6.1 mL, 2.5 mol/L in hexane, 15 mmol), HMDS (3.1 mL, 15 mmol), 4-chloroacetophenone (2.85 g, 14.5 mmol) and Ac_2O (1.55 g, 15.2 mmol) gave the title compound **2e** (2.21 g, 11.2 mmol, 78%) after chromatography (SiO_2, hexanes/MTBE 5:1, R_f = 0.29) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.28 (s, 3H), 5.05 (d, *J* = 2.3 Hz, 1H), 5.46 (d, *J* = 2.3 Hz, 1H), 7.30–7.33 (m, 2H), 7.38–7.41 (m, 2H) ppm. The data were in accordance with literature values.[27]

1-(4-Cyanophenyl)vinyl acetate (2g): According to the GPB, reaction of *n*BuLi (7.0 mL, 2.5 mol/L in hexane, 15 mmol), HMDS (3.1 mL, 15 mmol), 4-cyanoacetophenone (2.71 g, 14.5 mmol) and Ac_2O (1.55 g, 15.2 mmol) gave the title compound **2g** (2.12 g, 11.3 mmol, 78%) after chromatography (SiO_2, hexanes/MTBE 5:1, R_f = 0.33) as a yellow liquid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.29 (s, 3H), 5.21 (d, *J* = 2.5 Hz, 1H), 5.60 (d, *J* = 2.5 Hz, 1H), 7.54–7.57 (m, 2H), 7.63–7.66 (m, 2H) ppm. The data were in accordance with literature values.[27]

Ethyl 3-[2-oxo-2-(4-methylphenyl)ethyl]tetrahydropyran-2-one-3-carboxylate (3c): $CeCl_3 \cdot 7\ H_2O$ (5 mg, 13 µmol) was added to a mixture of β-oxoester **1** (200 mg, 1.28 mmol) and enol ester **2c** (338 mg, 1.92 mmol, 1.5 equiv.) in TFE (1 mL), and the reaction mixture was stirred at 30°C for 24 h under an atmosphere of air. Subsequently, all volatile materials were removed *in vacuo* and the residue was purified by column chromatography (SiO_2, hexanes/MTBE 2:1 → 1:1) to yield 1,4-diketone **5c** [103 mg, 0.36 mmol, 28%, R_f = 0.47 (hexanes/MTBE 1:1)] in the first fraction as a colorless oil. Secondly, the α-hydroxylated compound **11** [4 mg, 20 µmol, 2%, R_f = 0.30 (hexanes/MTBE 1:1)]) was obtained as a colorless oil. As the third fraction the title compound **3c** [229 mg, 0.75 mmol, 59%, R_f = 0.13 (hexanes/MTBE 1:1)] was eluted as a colorless oil. **Lactone 3c:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.26 (t, *J* = 7.1 Hz, 3H), 1.78–1.86 (m, 1H), 2.03–2.19 (m, 3H), 2.35 (s, 3H), 3.56 (d, *J* = 18.6 Hz, 1H), 3.97 (d, *J* = 18.6 Hz, 1H), 4.12–4.29 (m, 2H), 4.47–4.55 (m, 1H), 4.60–4.71 (m, 1H), 7.17–7.23 (m, 2H), 7.78–7.85 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 13.82 (CH_3), 20.87 (CH_2), 21.46 (CH_3), 30.13 (CH_2), 45.46 (CH_2), 50.84 (C), 62.04 (CH_2), 69.83 (CH_2), 127.96 (2 CH), 129.12 (2 CH), 133.42 (C), 144.37 (C), 169.80 (C), 171.33 (C), 196.16 (C) ppm. IR (ATR): nu(tilde) = 2978 (w), 2936 (w), 1730 (s), 1718 (vs), 1659 (s), 1607 (m), 1453 (w), 1405 (m), 1351 (m), 1281 (m), 1250 (s), 1224 (s), 1197 (vs), 1180 (s), 1167 (vs), 1117 (s), 1068 (m), 1022 (m), 986 (m), 858 (w), 809 (m), 639 (m), 572 (m) cm^{-1}. HRMS (ESI): calcd. 327.1203 (for $C_{17}H_{20}NaO_5^+$); found 327.1207 [M + Na^+]. $C_{17}H_{20}O_5$ (304.34).

Ethyl 2-[2-oxo-2-(4-methylphenyl)ethyl]cyclopentanone-2-carboxylate (5c): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3H), 2.01–2.23 (m, 3H), 2.39 (s, 3H), 2.44–2.68 (m, 3H), 3.45 (d, *J* = 18.5 Hz, 1H), 3.81 (d, *J* = 18.5 Hz, 1H), 4.15 (q, *J* =

7.1 Hz, 2H), 7.21–7.26 (m, 2H), 7.80–7.85 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 13.94 (CH_3), 19.79 (CH_2), 21.60 (CH_3), 33.34 (CH_2), 37.71 (CH_2), 43.33 (CH_2), 57.40 (C), 61.56 (CH_2), 128.07 (2 CH), 129.23 (2 CH), 133.79 (C), 144.25 (C), 170.70 (C), 196.26 (C), 215.12 (C) ppm. IR (ATR): nu(tilde) = 2979 (w), 2923 (w), 1750 (s), 1721 (vs), 1679 (s), 1607 (m), 1464 (w), 1404 (m), 1352 (w), 1260 (w), 1225 (s), 1209 (m), 1181 (s), 1151 (s), 1103 (m), 1019 (w), 984 (w), 924 (w), 860 (w), 811 (m), 561 (m) cm^{-1}. HRMS (ESI): calcd. 311.1254 (for $C_{17}H_{20}NaO_4^+$); found 311.1249 [M + Na^+]. $C_{17}H_{20}O_4$ (288.34).

Ethyl 2-hydroxycyclopentanon-2-carboxylate (11): ^1H NMR (500 MHz, $CDCl_3$): δ = 1.29 (t, *J* = 7.1 Hz, 3H), 2.08–2.14 (m, 3H), 2.43–2.53 (m, 3H), 3.63 (s, 1H), 4.23–4.28 (m, 2H) ppm. The data were in accordance with literature values.[9]

Ethyl 3-[2-oxo-2-(4-fluorophenyl)ethyl]tetrahydropyran-2-one-3-carboxylate (3d): According to the procedure for **3c** given above, reaction of $CeCl_3 \cdot 7\ H_2O$ (5 mg, 13 µmol), β-oxoester **1** (202 mg, 1.28 mmol) and enol ester **2d** (347 mg, 1.92 mmol, 1.5 equiv.) in TFE (1 mL) gave a crude mixture, which was submitted to column chromatography (SiO_2, hexanes/MTBE 1:1) to yield 1,4-diketone **5d** (72 mg, 0.25 mmol, 19%, R_f = 0.43) in the first fraction as a colorless oil. Secondly, the α-hydroxylated compound **11** (5 mg, 23 µmol, 2%, R_f = 0.29) was obtained as a colorless oil. As the third fraction the title compound **3d** (212 mg, 0.69 mmol, 54%, R_f = 0.20) was eluted as a colorless solid (mp. 108°C). **Lactone 3d:** ^1H NMR (300 MHz, $CDCl_3$): δ = 1.28 (td, *J* = 7.1 Hz, *J* = 1.2 Hz, 3H), 1.78–1.91 (m, 1H), 2.05–2.25 (m, 3H), 3.55 (d, *J* = 18.5 Hz, 1H), 3.98 (d, *J* = 18.6 Hz, 1H), 4.13–4.32 (m, 2H), 4.49–4.59 (m, 1H), 4.62–4.72 (m, 1H), 7.06–7.15 (m, 2H), 7.91–8.01 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 13.91 (CH_3), 20.94 (CH_2), 30.21 (CH_2), 45.54 (CH_2),

50.96 (C), 62.25 (CH_2), 69.95 (CH_2), 115.70 (d, $^2J_{C,F}$ = 22.0 Hz, 2 CH), 130.69 (d, $^3J_{C,F}$ = 9.4 Hz, 2 CH), 132.45 (d, $^4J_{C,F}$ = 3.0 Hz, C), 165.90 (d, $^1J_{C,F}$ = 256 Hz, CF), 169.76 (C), 171.30 (C), 195.11 (C) ppm. $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$): δ = −104.18 (s, 1F) ppm. IR (ATR): nu(tilde) = 3013 (w), 2976 (w), 2939 (w), 1726 (s), 1705 (vs), 1689 (s), 1593 (s), 1508 (m), 1471 (w), 1406 (m), 1347 (m), 1297 (m), 1251 (s), 1228 (s), 1170 (vs), 1159 (vs), 1101 (s), 1024 (m), 1006 (m), 984 (m), 906 (w), 862 (s), 819 (m), 733 (w), 638 (m), 567 (s) cm^{-1}. HRMS (ESI): calcd. 331.0952 (for $C_{16}H_{17}FNaO_5^+$); found 331.0958 [M + Na^+]. $C_{16}H_{17}FO_5$ (308.31).

Ethyl 2-[2-oxo-2-(4-fluorophenyl)ethyl]cyclopentanone-2-carboxylate (5d): ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3H), 2.00–2.24 (m, 3H), 2.45–2.69 (m, 3H), 3.42 (d, *J* = 18.5 Hz, 1H), 3.79 (d, *J* = 18.5 Hz, 1H), 4.15 (q, *J* = 7.1 Hz, 2H), 7.06–7.17 (m, 2H), 7.91–8.00 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 13.94 (CH_3), 19.78 (CH_2), 33.35 (CH_2), 37.66 (CH_2), 43.27 (CH_2), 57.41 (C), 61.65 (CH_2), 115.71 (d, $^2J_{C,F}$ = 21.9 Hz, 2 CH), 130.66 (d, $^3J_{C,F}$ = 9.4 Hz, 2 CH), 132.73 (d, $^4J_{C,F}$ = 3.0 Hz, C), 165.86 (d, $^1J_{C,F}$ = 255 Hz, CF), 170.59 (C), 195.11 (C), 214.94 (C) ppm. $^{19}F\{^1H\}$ NMR (470 MHz, $CDCl_3$): δ = −104.16 (s, 1F) ppm. IR (ATR): nu(tilde) = 2979 (w), 2923 (w), 1750 (m), 1720 (s), 1685 (s), 1506 (m), 1408 (m), 1353 (w), 1259 (w), 1221 (vs), 1156 (vs), 1101 (m), 992 (m), 835 (s), 563 (m) cm^{-1}. HRMS (ESI): calcd. 315.1003 (for $C_{16}H_{17}FNaO_4^+$); found 315.1002 [M + Na^+]. $C_{16}H_{17}FO_4$ (292.31).

Ethyl 3-[2-oxo-2-(4-chlorophenyl)ethyl]tetrahydropyran-2-one-3-carboxylate (3e): According to the procedure for **3c** given above, reaction of $CeCl_3 \cdot 7\ H_2O$ (5 mg, 13 µmol), β-oxoester **1** (201 mg, 1.28 mmol) and enol ester **2e** (380 mg, 1.92 mmol, 1.5 equiv.) in TFE (1 mL) gave a crude mixture, which was submitted to column chromatography (SiO_2, hexanes/MTBE 1:1) to yield 1,4-diketone **5e** (105 mg, 0.34

mmol, 27%, R_f = 0.47) in the first fraction as a colorless solid (mp. 97°C). Secondly, the α-hydroxylated compound **11** (5 mg, 23 µmol, 2%, R_f = 0.30) was obtained as a colorless oil. As the third fraction the title compound **3e** (195 mg, 0.60 mmol, 47%, R_f = 0.21) was eluted as a colorless solid (mp. 106°C). **Lactone 3e:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H), 1.80–1.91 (m, 1H), 2.03–2.26 (m, 3H), 3.55 (d, *J* = 18.7 Hz, 1H), 3.98 (d, *J* = 18.6 Hz, 1H), 4.13–4.32 (m, 2H), 4.49–4.59 (m, 1H), 4.61–4.75 (m, 1H), 7.35–7.47 (m, 2H), 7.81–7.95 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 13.93 (CH_3), 20.93 (CH_2), 30.20 (CH_2), 45.58 (CH_2), 50.95 (C), 62.28 (CH_2), 69.97 (CH_2), 128.89 (2 CH), 129.40 (2 CH), 134.30 (C), 140.03 (C), 169.72 (C), 171.26 (C), 195.53 (C) ppm. IR (ATR): nu(tilde) = 2981 (w), 2941 (w), 1726 (s), 1710 (vs), 1687 (s), 1586 (m), 1469 (m), 1397 (m), 1346 (m), 1282 (m), 1249 (s), 1195 (s), 1167 (vs), 1143 (m), 1088 (s), 1002 (m), 985 (m), 858 (s), 816 (s), 763 (w), 721 (m), 637 (s), 589 (m), 571 (s) cm^{-1}. HRMS (ESI): calcd. 347.0657 (for $C_{16}H_{17}ClNaO_5^+$); found 347.0662 [M + Na^+]. $C_{16}H_{17}ClO_5$ (324.76).

Ethyl 2-[2-oxo-2-(4-chlorophenyl)ethyl]cyclopentanone-2-carboxylate (5e): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, *J* = 7.1 Hz, 3H), 2.02–2.27 (m, 3H), 2.42–2.71 (m, 3H), 3.41 (d, *J* = 18.6 Hz, 1H), 3.79 (d, *J* = 18.5 Hz, 1H), 4.16 (q, *J* = 7.1 Hz, 2H), 7.35–7.49 (m, 2H), 7.80–7.93 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 13.96 (CH_3), 19.80 (CH_2), 33.36 (CH_2), 37.67 (CH_2), 43.31 (CH_2), 57.41 (C), 61.69 (CH_2), 128.93 (2 CH), 129.41 (2 CH), 134.60 (C), 139.89 (C), 170.55 (C), 195.53 (C), 214.90 (C) ppm. IR (ATR): nu(tilde) = 2987 (w), 2964 (w), 2940 (w), 1742 (vs), 1721 (vs), 1691 (vs), 1589 (m), 1469 (m), 1445 (m), 1399 (m), 1330 (w), 1260 (m), 1234 (m), 1157 (vs), 1087 (s), 994 (m), 927 (w), 848 (m), 813 (s), 733 (w), 566 (m) cm^{-1}. HRMS (ESI): calcd. 331.0708 (for $C_{16}H_{17}ClNaO_4^+$); found 331.0704 [M + Na^+]. $C_{16}H_{17}ClO_4$ (308.76).

Ethyl 3-[2-oxo-2-(4-cyanophenyl)ethyl]tetrahydropyran-2-one-3-carboxylate (3g): According to the procedure for **3c** given above, reaction of $CeCl_3 \cdot 7\ H_2O$ (6 mg, 16 µmol), β-oxoester **1** (200 mg, 1.28 mmol) and enol ester **2g** (359 mg, 1.92 mmol, 1.5 equiv.) in TFE (1 mL) gave a crude mixture, which was submitted to column chromatography (SiO_2, hexanes/MTBE 1:1) to yield the α-hydroxylated compound **11** (58 mg, 0.34 mmol, 26%, R_f = 0.28) in the first fraction as a colorless oil. Secondly, the 1,4-diketone **5g** (58 mg, 0.19 mmol, 15%, R_f = 0.23) was obtained as a colorless solid (mp. 103°C). As the third fraction the title compound **3g** (141 mg, 0.45 mmol, 35%, R_f = 0.08) was eluted as a colorless solid (mp. 131°C). **Lactone 3g:** ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, *J* = 7.1 Hz, 3H), 1.82–1.93 (m, 1H), 2.05–2.25 (m, 3H), 3.56 (d, *J* = 18.8 Hz, 1H), 3.98 (d, *J* = 18.7 Hz, 1H), 4.14–4.31 (m, 2H), 4.49–4.68 (m, 2H), 7.71–7.78 (m, 2H), 7.99–8.05 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 13.87 (CH_3), 20.82 (CH_2), 30.07 (CH_2), 45.72 (CH_2), 50.99 (C), 62.36 (CH_2), 69.99 (CH_2), 116.66 (C), 117.64 (C), 128.38 (2 CH), 132.43 (2 CH), 138.80 (C), 169.50 (C), 170.98 (C), 195.54 (C) ppm. IR (ATR): nu(tilde) = 2978 (w), 2917 (w), 2233 (w), 1721 (s), 1712 (vs), 1691 (vs), 1402 (m), 1347 (m), 1284 (m), 1249 (s), 1196 (vs), 1167 (vs), 1140 (m), 1112 (m), 1100 (m), 986 (m), 864 (m), 845 (m), 826 (s), 708 (w), 638 (m) cm^{-1}. HRMS (ESI): calcd. 338.0999 (for $C_{17}H_{17}NNaO_5^+$); found 338.1013 [M + Na^+]. $C_{17}H_{17}NO_5$ (315.33).

Ethyl 2-[2-oxo-2-(4-cyanophenyl)ethyl]cyclopentanone-2-carboxylate (5g): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.1 Hz, 3H), 2.02–2.19 (m, 3H), 2.48–2.69 (m, 3H), 3.40 (d, *J* = 18.7 Hz, 1H), 3.80 (d, *J* = 18.7 Hz, 1H), 4.14 (q, *J* = 7.1 Hz, 2H), 7.72–7.78 (m, 2H), 7.98–8.04 (m, 2H) ppm. $^{13}C\{^1H\}$ NMR (75 MHz, $CDCl_3$): δ = 13.89 (CH_3), 19.72 (CH_2), 33.27 (CH_2), 37.53 (CH_2), 43.39 (CH_2), 57.36 (C), 61.73 (CH_2),

116.56 (C), 117.72 (C), 128.37 (2 CH), 132.45 (2 CH), 139.13 (C), 170.30 (C), 195.51 (C), 214.54 (C) ppm. IR (ATR): nu(tilde) = 2985 (w), 2969 (w), 2924 (w), 2231 (m), 1741 (vs), 1717 (vs), 1690 (vs), 1604 (w), 1445 (w), 1397 (m), 1357 (w), 1257 (s), 1231 (m), 1155 (vs), 1102 (m), 996 (m), 924 (w), 839 (s), 802 (w), 576 (s) cm^{-1}. HRMS (ESI): calcd. 322.1050 (for $C_{17}H_{17}NNaO_4^+$); found 322.1057 [M + Na^+]. $C_{17}H_{17}NO_4$ (299.33).

Procedure for the reaction kinetics: $CeCl_3 \cdot 7\ H_2O$ (6 mg, 16 µmol, 1 mol%) was added to a mixture of β-oxoester **1** (250 mg, 1.60 mmol, 1.0 equiv.), mesitylene (96 mg, 0.80 mmol, 0.5 equiv., internal standard) and enol ester **2** (2.40 mmol, 1.5 equiv.) in TFE (1.5 mL). The reaction mixture was stirred at 30°C under an atmosphere of air. After 0, 0.25, 0.5, 1, 2, 4, 8, 12 and 24 h samples (ca. 20 µL) were taken under comparable conditions, diluted with DCM (0.5 mL) and analyzed by GLC.

Computational Details are given in the Supporting Information.

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