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# Macrolactonization Reactions Driven by a Pentafluorobenzoyl Group

Guillaume Force,<sup>[a]</sup> Anna Perfetto,<sup>[b]</sup> Robert J. Mayer,<sup>[c]</sup> Ilaria Ciofini\*<sup>[b]</sup> and David Lebœuf\*<sup>[c]</sup>

[a] G. Force  
Institut de Chimie Moléculaire et des Matériaux d'Orsay (ICMMO), CNRS UMR 8182  
Université Paris-Saclay  
Bâtiment 420, 91405 Orsay, France

[b] Dr. A. Perfetto, Dr. I. Ciofini  
Chimie Paris-Tech, PSL, CNRS  
Institute of Chemistry for Health and Life Science (I-CLeHS), Theoretical Chemistry and Modelling Group (CTM)  
75005 Paris, France  
E-mail: [ilaria.ciofini@chimie-paristech.fr](mailto:ilaria.ciofini@chimie-paristech.fr)

[c] Dr. R. J. Mayer, Dr. D. Lebœuf  
Institut de Science et d'Ingénierie Supramoléculaires (ISIS), CNRS UMR 7006  
Université de Strasbourg  
8 allée Gaspard Monge, 67000 Strasbourg, France  
E-mail: [dlebœuf@unistra.fr](mailto:dlebœuf@unistra.fr)

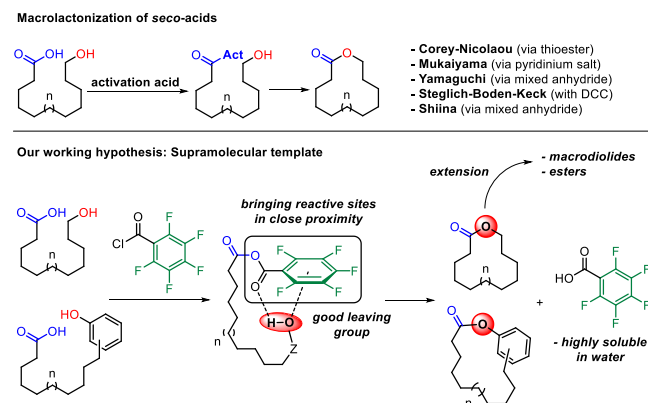
Supporting information for this article is given via a link at the end of the document.

**Abstract:** Macrolactones constitute a privileged class of natural and synthetic products with a broad range of applications in the fine chemicals and pharmaceutical industry. Despite all the progress made towards their synthesis, notably from *seco*-acids, a macrolactonization promoter system that is effective, selective, flexible, readily available, and, insofar as possible, compatible with manifold functional groups is still lacking. Herein, we describe a strategy that relies on the formation of a mixed anhydride incorporating a pentafluorophenyl group which, due to its high electronic activation enables a convenient access to macrolactones, macrodiolides and esters with a broad versatility. Kinetic studies and DFT computations were performed to rationalize the reactivity of the pentafluorophenyl group in macrolactonization reactions.

## Introduction

Macrolactones are encountered in a broad range of fine chemicals and natural products, notably marine macrolides, pharmaceuticals, cosmetics and agrochemicals.<sup>[1]</sup> They are one of the foremost pillars of the flavor and fragrance industry with compounds such as Exaltolide® (Firmenich) and Musc T® (Takasago) that are prevalent in our everyday lives.<sup>[1c]</sup> In light of their industrial relevance and the challenges associated with their synthesis, the design of efficient strategies to access macrolactones has sparked many efforts in the synthetic community and the interest in this field is not likely to wane.<sup>[2]</sup> Though the methods devised for macrolactonizations are numerous, they remain substrate-dependent and the quest for a user-friendly system applicable to a vast array of substrates is as compelling as ever. One of the most common approaches involves the macrocyclization of *seco*-acids (Scheme 1). In the seventies, a groundbreaking discovery by Yamaguchi revealed that the stoichiometric activation of the carboxylic acid via the formation of a mixed anhydride from 2,4,6-trichlorobenzoylchloride (TCBC), could be used as a driving force to promote macrocyclizations.<sup>[3]</sup> This approach was further improved by Shiina with the development of the 2-methyl-6-nitrobenzoic anhydride (MNBA) reagent and related compounds.<sup>[4]</sup> Other classic examples based on the same concept include Corey-Nicolaou,<sup>[5]</sup> Steglich-Keck-Boden<sup>[6]</sup> and Mukaiyama macrolactonizations.<sup>[7]</sup> However, most of these

methods are fraught with distinctive drawbacks that can limit their appeal. To cite but a few examples, they can require highly diluted reactions or a slow addition procedure to prevent oligomerizations. Moreover, their use is often accompanied by the formation of several side-products, which can make the purification of the targeted product cumbersome and be potentially toxic, without forgetting to mention their cost-effectiveness as they must be used in stoichiometric amounts. To answer these various challenges, synthetic chemists have mainly focused on three alternative strategies: (i) the development of catalytic systems featuring transition metals, Brønsted and Lewis acids in order to limit the formation of side products,<sup>[2i,8]</sup> (ii) the use of pre-organized substrates relying in general on non-covalent interactions to facilitate and control the macrocyclization process,<sup>[2g]</sup> and (iii) ring expansion strategies that usually do not require highly diluted reaction conditions.<sup>[2j,2m,9]</sup> However, these variants have their own limitations, such as a narrow substrate scope or the requirement for additional synthetic steps to introduce the reactive functional groups. In this context, we aimed at combining the best aspects of the various approaches to achieve a general method for macrolactonizations. Based on their respective efficacy, we reasoned that the formation of a mixed anhydride featuring pentafluorobenzoyl chloride as an activating agent might allow a convenient and optimal access to macrolactones via a supramolecular template. This type of electron-poor receptor can be suitable for numerous non-covalent



**Scheme 1.** Approaches towards the macrolactonization of *seco*-acids

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interactions such H-bonding (with respect to the carbonyl moiety),  $\pi$ - $\pi$  interactions via a charge-transfer complex and  $\pi$ -lone pair (lp) interactions (with respect to the pentafluorophenyl moiety).<sup>[10]</sup> The latter was particularly of interest as we hypothesized that such interaction could bring both reactive sites in close proximity to favor the intramolecular macrolactonization over oligomerization processes.<sup>[11-13]</sup> Surprisingly, such interactions have hardly been used in synthesis. To the best of our knowledge, the only major application of those interactions was reported by Collins' group to aid the pre-organization in ring-closing metathesis.<sup>[14-15]</sup> In the same vein, we assumed that our approach could be applied to less reactive and underexplored phenol derivatives via  $\pi$ - $\pi$  interactions. In addition, due to the strong nucleofugality of the pentafluorobenzoate group,<sup>[16]</sup> we anticipated that, beside the possibility for supramolecular interactions, we should get a superior activation of the reacting carbonyl group for the cyclization. Lastly, pentafluorobenzoyl chloride is also inexpensive,<sup>[17]</sup> and the highly water-soluble by-product (pentafluorobenzoic acid) can be easily removed by aqueous treatment, counterbalancing the fact that a stoichiometric amount of pentafluorobenzoyl chloride had to be used. Herein, we thus describe the development of a simple and efficient protocol to access not only macrolactones but also macrodiolides and esters from aliphatic alcohols and phenols.

## Results and Discussion

**Optimization studies for the macrolactonization of seco-acids.** In our initial studies, we investigated the reactivity of **1a** to provide access to Exaltolide® (**2a**) by screening a variety of benzoyl chlorides and benzoic anhydrides in toluene (Table 1). For practical reasons, we set the reaction time at 24 h to ease the comparison between the various sources of activating agent. To test our initial assumption, we employed pentafluorobenzoyl chloride **1'a** as an activating agent and triethylamine as a base, which delivered the targeted product in 88% along with a high selectivity with respect to the macrodiolide **3a** (ratio 16:1). More importantly, NMR spectra of the crude product did not show any traces of the pentafluorobenzoic acid after an aqueous treatment with saturated sodium bicarbonate solution (see the Supporting Information for details). As anticipated, reducing the number of fluorine atoms on the benzoyl chloride reagent, which was expected to weaken the interaction between the alcohol and the arene, led to a corresponding decrease in selectivity (**1'b-1'f**). Interestingly, 3,5-bis(trifluoromethyl)benzoyl chloride **1'g** gave the same selectivity as pentafluorobenzoyl chloride **1'a** with a slightly lower yield (83%). However, the resulting benzoic acid by-product proved not to be soluble in water, which led us to discard this option. On the other hand, in the presence of electron-withdrawing groups other than fluorine, notably with Yamaguchi's reagent **1'i** and Shiina's reagent **1'm**, yields of less than 35% were observed along with decomposition of the substrate (TCBC) and formation of higher order oligomers (MNBA), emphasizing the critical role of fluorine for the reactivity. Pentafluorobenzoic anhydride **1'n** gave identical results with pentafluorobenzoyl chloride **1'a**. Reaction monitoring by <sup>1</sup>H NMR indicated that the reaction reached full conversion within 2 h. Moreover, the transformation could be achieved at room temperature (48 h), but at the expense of a lower selectivity (12:1 **2a:3a** ratio). Of note, the macrolactonization did not require the use a distilled solvent as neither the selectivity nor the yield was affected in these conditions. However, the macrolactonizations using **1'a** requires performing the reaction in diluted solution (1.5 mM in substrate) to avoid a significant decrease in yield because of the formation of oligomers. We also performed a systematic survey of bases and solvents but the initially investigated combination of triethylamine and toluene proved to be superior among those tested (see the Supporting Information for details). Predictably,

the utilization of coordinating solvents (THF and MeCN), which might compete with the alcohol for the electron-

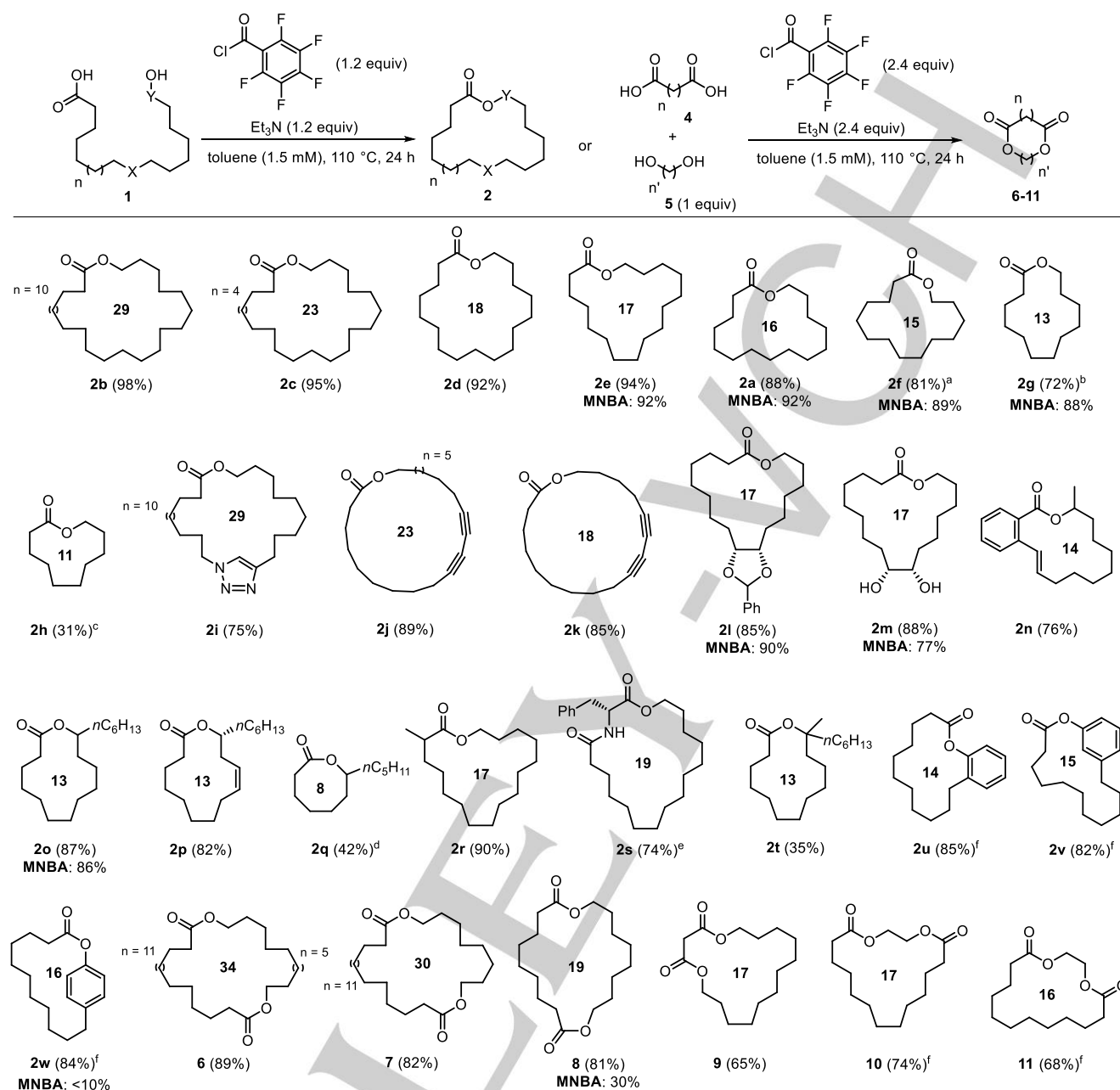
**Table 1.** Optimization of the macrolactonization of **1a**.<sup>a</sup>

<b>1a</b>	<b>2a</b> + <b>3a</b> (n = 10)
<b>1'a</b>	88% (16:1) 86% (17:1) <sup>b</sup> 83% (12:1) <sup>c</sup>
<b>1'b</b>	86% (14.5:1)
<b>1'c</b>	82% (11:1)
<b>1'd</b>	81% (9:1)
<b>1'e</b>	73% (6:1)
<b>1'f</b>	44% (4.5:1)
<b>1'g</b>	83% (16:1)
<b>1'h</b>	75% (12.5:1)
<b>1'i</b>	20% (10:1, 50% conv.)
<b>1'j</b>	- (NR)
<b>1'k</b>	- (NR)
<b>1'l</b>	32% (5:1, 100% conv.)
<b>1'm</b>	- (NR)
<b>1'n</b>	35% (4:1, 70% conv.)
<b>1'o</b>	87% (16:1)

<sup>a</sup> The yields given are the isolated yields for **2a**. The ratios were determined by <sup>1</sup>H NMR using *para*-anisaldehyde as an external standard. <sup>b</sup> Reaction conducted with toluene not distilled. <sup>c</sup> Reaction conducted at room temperature for 48 h. NR = no reaction.

poor host receptor, tends to diminish the selectivity (10:1 and 12:1, respectively).

**Scope of macrolactones and macrodiolides.** With these optimized conditions in hand, we explored the scope of the reaction using simple all-carbon linkers (**2a-2h**, Table 2). The macrolactonization was particularly effective for large ring sizes (from 17- to 29-membered rings **2b-2e**, yields up to 98%), without observing the formation of the corresponding macrodiolides. On the other hand, the proportion of macrodiolide increased with smaller ring sizes (**2f-2h**). While the yields remained high for 13- and 15-membered rings (72 and 81% yields, respectively), the ratio between macrolactone and macrodiolide attained 1:1 with 10-hydroxydecanoic acid **1h**, providing **2h** in 31% yield. Further, the reaction was compatible with various functional groups, including triazole, strained 1,3-butadiene, alkene and diol (protected or not) moieties, affording the target macrolactones in yields ranging from 65% to 89%. The method could also be applied to secondary aliphatic alcohols and carboxylic acids (**2n-2t**) and even challenging 8-membered rings such as **2q** were obtained in 42% yield.<sup>[18]</sup> In addition, the framework of resorcylic lactones (**2n**)<sup>[19]</sup> and cyclodepsipeptide **2t** were generated in 76 and 74% yields. Lastly, tertiary aliphatic alcohols were also tolerated, albeit in a lower yield (**2t**, 35%).



**Table 2.** Reaction scope for the formation of macrolactones and macrodiolides. <sup>a</sup> Ratio macrolactone/macrodilide 8:1 (separable by flash column chromatography). <sup>b</sup> Ratio macrolactone/macrodilide 8:1 (separable by flash column chromatography). <sup>c</sup> Ratio macrolactone/macrodilide 1:1 (separable by flash column chromatography). <sup>d</sup> Reaction conducted at 50 °C. <sup>e</sup> Reaction conducted at 80 °C. <sup>f</sup> Reaction conducted for 48 h.

The devised strategy is not limited to macrolactonization of aliphatic hydroxyacids, but was also extended to substrates incorporating phenols,<sup>[20]</sup> delivering the target products, notably arduous *meta*- and *para*-cyclophanes in high yields (82 to 85%), compounds that have many applications in materials science and supramolecular chemistry.<sup>[21]</sup> Nevertheless, the reaction with phenols proved to be slower as the reactions required 48 h to reach full conversion. Finally, we turned our attention to the preparation of macrodiolides (compounds **6-11**), which are widespread scaffolds in medicinal chemistry.<sup>[22]</sup> Their synthesis is known to be more challenging than the precedent case since two chemical events (esterification then macrolactonization) are involved when starting from *seco*-acids or diacids.<sup>[23]</sup> We were pleased to find that 16- to 34-membered macrodiolides could be rapidly afforded in high yields (up to 89%). Moreover, Musk T<sup>®</sup> and Zenolide<sup>®</sup> (**10** and **11**), two compounds with major industrial

applications, were generated in a single step within 48 h in 74% and 68% yields.

**Comparison with prior art.** The major strengths of our approach are (i) its compatibility with a large variety of primary, secondary, tertiary aliphatic alcohols, diols, and phenols, (ii) an inexpensive activating reagent (pentafluorobenzoyl chloride), and (iii) the easily removable side-products through a simple aqueous work-up. The key question is where our method stands compared to previous reports from the literature featuring *seco*-acids, including the methods involving the formation of a mixed anhydride (e.g., the use of MNBA) and the catalytic approaches. In the case of MNBA, we compared our data on identical substrates (see Table 1).<sup>[4c]</sup> With respect to traditional substrates, we noticed that both methods were similarly efficient. However, in the case of more challenging reactions, such as the formation of macrodiolides and macrolactones incorporating a phenol moiety, our method formed

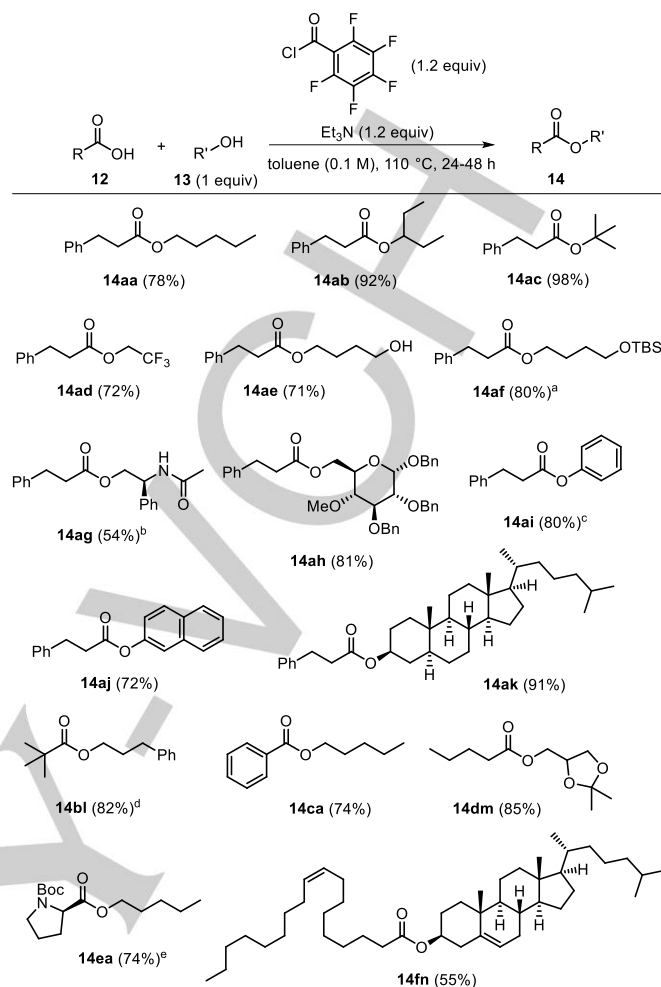
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products in significantly higher yields than the previous method, e.g., 84% vs <10% yield of **2w** and 81% vs 30% yield of **8**, respectively. Another important factor is that pentafluorobenzoyl chloride is significantly cheaper than MNBA,<sup>[17]</sup> without requiring any slow addition of the reagents during the reaction set-up. More recently, the group of Collins reported a method to access macrolactones and macrodiolides (13- to 26-membered macrolactones and macrodiolides in yields ranging from 55 to 98%) by employing  $\text{Hf}(\text{OTf})_4$  as a catalyst. However, those reactions conditions were not compatible with secondary and tertiary aliphatic alcohols and were less effective with ring sizes smaller than 13-membered rings. In turn, Zhao and co-workers depicted the use of an ynamide (*N*-ethynyl-*N*,4-dimethylbenzenesulfonamide) as a reacting agent with the carboxylic acid to deliver an enamide that undergoes a cyclization with the alcohol in the presence of *p*-toluenesulfonic acid. This strategy afforded 7- to 19-membered macrolactones in yields ranging from 52 to 96% over 2 steps. However, not only do the reaction requires the use of an expensive ynamide, but stoichiometric amounts of *N*-methyl-*N*-tosylacetamide were formed, which tends to make the purification of the products troublesome. Of note, the possibility of using substrates bearing phenols was not reported in any of those studies. Regarding the preparation of compound **10** (Musk T<sup>®</sup>), apart from industrial processes involving the thermal cleavage of oligoesters, the only macrodilactonization described led to this compound in only 20% yield *via* the use of Brønsted and Lewis acids.<sup>[24]</sup>

**Scope of esters.** We also investigated intermolecular esterifications (Table 3). Once more, this procedure showcased a broad functional group tolerance at a higher concentration when compared to macrolactonizations (0.1 M). The reaction proved to be compatible with primary as well as secondary and tertiary alcohols producing high yields (up to 98%). In a similar manner, primary, secondary and tertiary carboxylic acids exhibited the same efficiency. Moreover, we succeeded to accomplish the mono- acetylation of 1,4-butanediol (**14ae**) in 71% yield. Even a poorly nucleophilic alcohol, trifluoroethanol, delivered the corresponding ester **14ad** in 72% yield. Reactions of less reactive aryl alcohols such as phenol and naphthol provided the ester products in 80% and 72%, respectively, in 48 h. Of note, substrates bearing acid-sensitive functional groups (TBS, Boc and acetal) were well-tolerated. Finally, compounds of interest such as amino alcohols (**14ag**), amino acids (**14ba**), carbohydrates (**14ah**), steroids (**14ak**) and fatty acids (**14em**) underwent esterifications with yields ranging from 54% to 91%.

Having identified the pentafluorobenzoyl group as an excellent activating agent for macrolactonization processes, we next turned to study the origins of its reactivity and selectivity. In particular, we wondered whether the cyclization occurred *via* supramolecular interactions as initially hypothesized. To shed light on the mode of operation of our system, we conducted experimental studies, which were further corroborated by Density Functional Theory (DFT) computations.

**Kinetic studies.** First, we studied the kinetics of the reaction of **1a** with **1'a** in the presence of triethylamine by <sup>1</sup>H and <sup>19</sup>F NMR spectroscopy in toluene-*d*<sub>8</sub> at 23 °C (the proposed mechanism is shown in Figure 1A). From the first spectrum recorded, disappearance of the α-CH<sub>2</sub> group of **1a** was observed and a new downfield-shifted resonance appeared which we attributed to the formation of the mixed anhydride **I-1a**. While **I-1a** could not be isolated due to its slow cyclization to **2a**, evidence for its identity was found by comparison of the <sup>1</sup>H and <sup>19</sup>F NMR spectra with those of the mixed anhydride obtained by the analogous reaction of hexanoic acid with **1'a** (see the Supporting Information). Over the course of 65 h, disappearance of the <sup>1</sup>H resonance of the CH<sub>2</sub>-OH group of **I-1a** was accompanied by an increase of the signal intensity of the CH<sub>2</sub>-O-C(O) moiety of macrolactone **2a** (Figure 1B). During the first 5 h of the reaction, <sup>19</sup>F NMR shows the disappearance of the resonances of remaining **1'a** and initially the

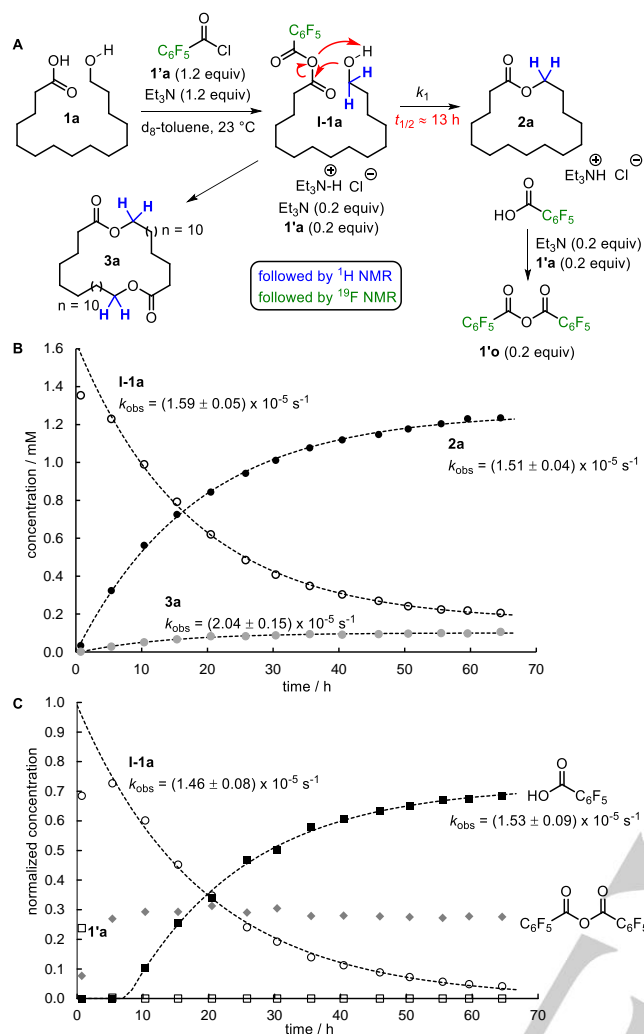


**Table 3.** Reaction scope for intermolecular esterifications. <sup>a</sup> The yield was determined by <sup>1</sup>H NMR using *para*-anisaldehyde as an external standard since the silyl group was cleaved on silica gel to give **14ae**. <sup>b</sup> Reaction conducted at 80 °C. <sup>c</sup> Phenol (2 equiv). <sup>d</sup> Alcohol **13l** (0.8 equiv). <sup>e</sup> Alcohol **13a** (1.5 equiv).

formation of pentafluorobenzoyl anhydride. Only after complete consumption of remaining **1'a**/Et<sub>3</sub>N, appearance of the <sup>19</sup>F resonances of pentafluorobenzoyl anhydride were observed (Figure 1C).

As shown in Figure 1B/C, both the increase of the concentration of **2a** (Figure 1A, black points) and the disappearance of **I-1a** were found to be first-order processes which could be analyzed by least-squares fitting with the single exponential  $A[1 - \exp(-k_{\text{obs}} t)] + C$  and  $A^* \exp(-k_{\text{obs}} t) + C$ , respectively (for all individual fits, see the Supporting Information). Analogously, the relative concentrations of **I-1a** and pentafluorobenzoyl anhydride as obtained from <sup>19</sup>F NMR spectroscopy were analyzed. For all increase/decrease processes, the analogous first-order rate constant  $k_{\text{obs}} = (1.52 \pm 0.14) \times 10^{-5} \text{ s}^{-1}$  was observed, which corresponds to a half-life of  $t_{1/2} \approx 13 \text{ h}$  (Figure 1B/C). Such first-order kinetics are in line with the expected rate-determining intramolecular cyclization between the hydroxy group and the anhydride intermediate **I-1a** (Figure 1A), followed by elimination of pentafluorobenzoyl anhydride to yield **2a**.

To verify this interpretation and to exclude a bi-molecular reaction being involved in the rate-determining step, the rate constants were additionally determined at twice lower concentration of all reactants. Identical rate constants as determined for the higher-concentrated reaction were observed for the formation of **2a** and disappearance of **I-1a** with  $k_{\text{obs}} = (1.45 \pm 0.06) \times 10^{-5} \text{ s}^{-1}$  ( $k$  from <sup>1</sup>H data), thereby supporting our mechanistic interpretation. The mono-molecular nature of the rate-determining step is further



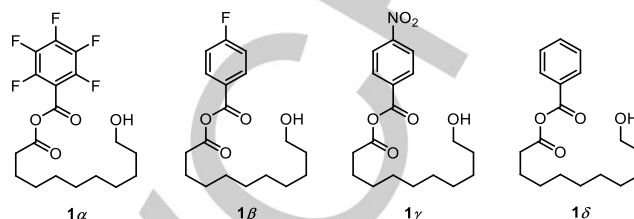
**Figure 1.** (A) Proposed reaction mechanism. (B) Kinetics followed by  $^1\text{H}$  (500 MHz) and (C)  $^{19}\text{F}$  NMR (471 MHz) NMR spectroscopy for the reaction of **1a** (1.6 mM) with **1'a** (1.8 mM) in  $d_8$ -toluene at 23 °C. The dashed line corresponds to the fitted kinetic curve used for the determination of the rate constants  $k_1$ . Note: The first data-point for **I-1a** was not included in the fitting, as the reaction does not immediately dissolve. The concentrations in (B) were determined from the integral ratios relative to tetrachloroethane used as internal standard while for (C) the normalized integral concentrations are depicted.

supported by measurement of the rate constants of the reaction (1.4 mM in **1a**) in the presence of excess Et<sub>3</sub>N (2.5 equiv) which only resulted in an insignificantly different value of  $k_{\text{obs}} = (1.62 \pm 0.06) \times 10^{-5} \text{ s}^{-1}$  ( $k$  from  $^1\text{H}$  data).

Slightly faster than intramolecular cyclization is bimolecular cyclization to dimer **3a**, which can also be described by a mono-exponential increase function. During the reaction, however, decreasing concentrations of **I-1a** disfavor the bimolecular reaction, and finally after 65 h, a ratio of **2a**:**3a** of 1:12 was observed which is in line with the observed ratio on preparative scale (Table 1). At twice lower concentration of all reactants the bimolecular reaction becomes less favored. Accordingly, a smaller rate constant for dimer-formation is observed as well as a higher selectivity for the cyclization product with **2a**:**3a** now being 22:1.

To test, if the reaction is promoted by additional hydrogen-bonding from ammonium ions (Et<sub>3</sub>NH<sup>+</sup>) formed as a by-product, the reaction was conducted in the presence of additional 0.5 equiv triethylammonium pentafluorobenzoate (Figure S7). In that case, a slightly reduced rate constant was observed compared to the standard conditions ( $k_{\text{obs}} = (1.33 \pm 0.07) \times 10^{-5} \text{ s}^{-1}$  ( $k$  from  $^1\text{H}$  data)).

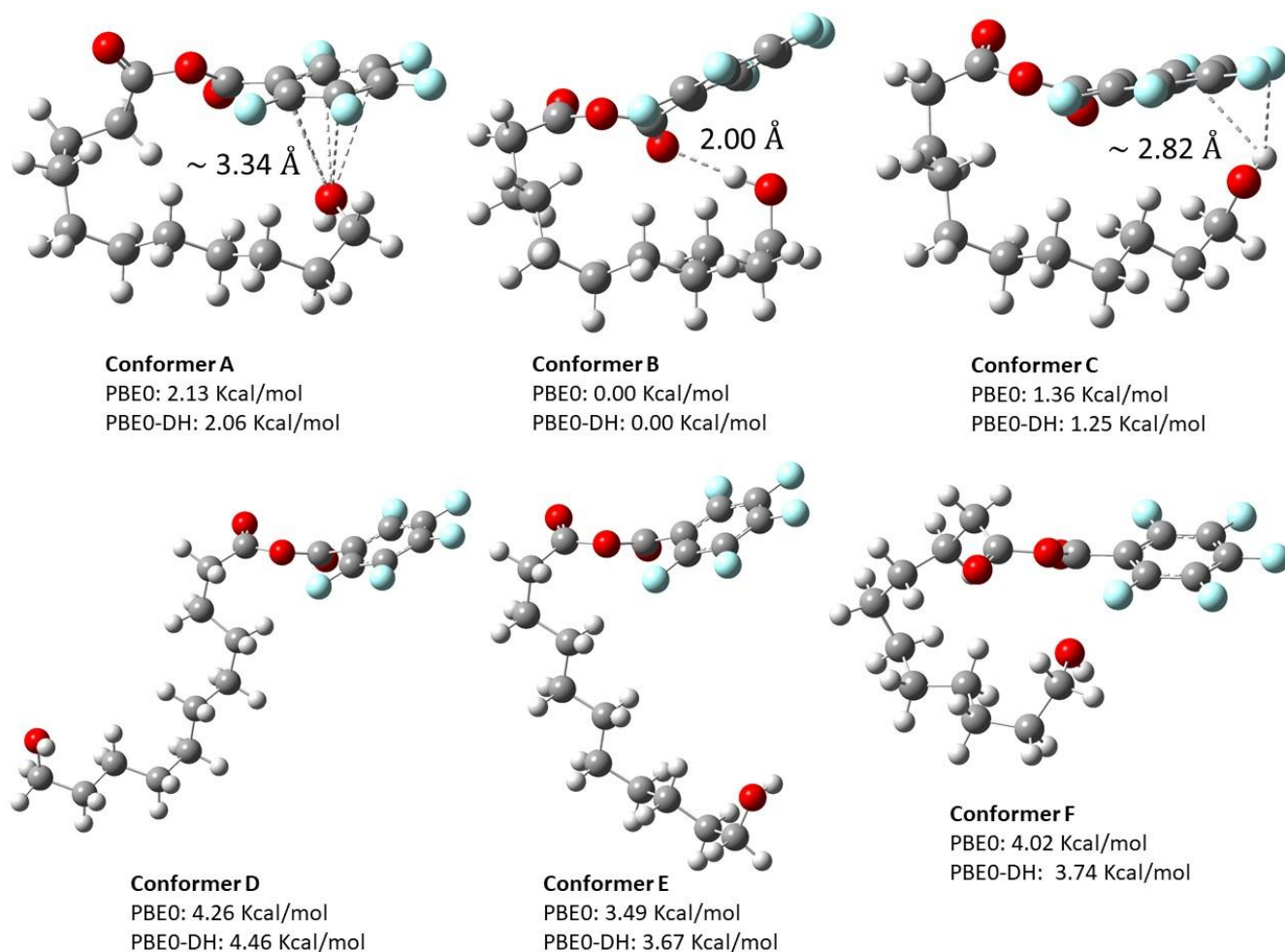
**DFT studies.** To gain further insights in the role of potential non-covalent interactions in the macrolactonization mechanism, DFT calculations (see the Supporting Information for computational details) were performed on different supramolecular template molecules (**1a-15** in Figure 2) obtained from 11-hydroxyundecanoic acid complexed with different activating agents. Namely, we considered pentafluorobenzoyl chloride (**1'a**), *p*-fluorobenzoyl chloride (**1'f**), *p*-nitrobenzoyl chloride (**1'i**) and benzoyl chloride (**1'm**) to test the effect of the presence, the nature and strength of electron-withdrawing group(s).



**Figure 2.** Structural formulae of supramolecular template molecules **1a-15**.

For each of these systems several stable conformers were obtained whose energies and 3D structures are collected in the Supporting Information. In the case of **1a** (Figure 3), the most stable conformers are the ones stabilized either by a H-bond interaction (**B** and **C**) or by a  $\pi$ -lp interaction (**A**).<sup>[11-12]</sup> Among these conformers, **A** is the conformer presenting most likely the best preorganization to access conformer **F**, which has the correct orientation to effectively react to form the final macrolactone. On the other hand, in the case of **1a**, the non-reactive conformers (**D** and **E**) are more than 3.5 kcal/mol higher in energy with respect to the most stable conformer **B**. Of note, calculations using either a global or a double hybrid functional (PBE0<sup>[25]</sup> and PBE0-DH,<sup>[26]</sup> respectively) returned the same trends, indicating that the theoretical outcomes are not an artifact of the DFT approach chosen. H bond interactions are efficient in stabilizing the conformers: The H bond interaction between the alcoholic group with the oxygen of the anhydride residue (with a distance of 2.00 Å) stabilizes the conformer **B**, while the interaction of the same alcoholic proton with the fluorine atoms of the benzoyl group stabilizes conformer **C**. This interaction is indeed weaker by 1 kcal/mol and the corresponding distance is slightly larger (in average 2.82 Å). Interestingly, in the case of the other supramolecular templates (**1β-15**), for which a decrease in reactivity and selectivity has been experimentally observed, such  $\pi$ -lp interaction could not be located. For these systems, a non-reactive conformer **A** is thermodynamically accessible presenting the reaction sites in opposite positions (Figures S8-S10). To verify the presence of non-covalent interactions involved in this reaction, we also plotted noncovalent interaction (NCI) surfaces computed for all six conformers of **1a** complex (Figure S11).<sup>[27]</sup> The NCI plots show the H-bond interactions that stabilizes the conformers **B** and **C** but, more importantly, NCI plots recovers also the  $\pi$ -lp interaction between the lone pair of the oxygen and the fluorinated ring in the case of conformers **F** and **A** that are the keys for the cyclization.

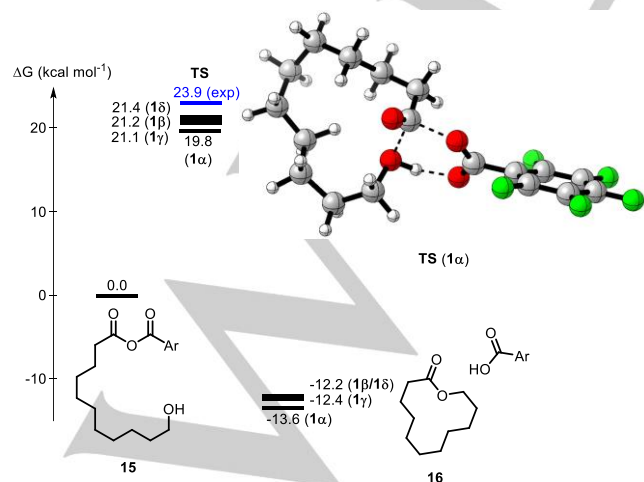
Based on the kinetic studies, we then studied the one-step reaction path leading to the final macrodiolide **16** starting from **1a-15** to validate the macrolactonization mechanism. The computed Gibbs energy diagrams for **1a-15** with respect to the most stable conformer are depicted in Figure 4. The corresponding reaction pathways computed for all templates are reported in the Supporting Information together with all corresponding optimized structures (Figures S12-S15). A simultaneously proton transfer and a cyclization leads to the formation of the final product **16**: the proton transfer takes place from the alcoholic residue towards the carboxylic oxygen, thereby leading to the ring closure with the formation of a new C–O bond. Analysis of the atomic (Mulliken) charges computed for the initial reagent (**15-1a**) reveals that the



**Figure 3.** Molecular structures of all optimized conformers of **1a** complex together with their relative energy values computed using a global hybrid (PBE0) and a double hybrid (PBE0-DH) functional.

carbonyl carbon presents a partial positive charge ( $\delta^+ = 0.32$  |e|), so that a nucleophilic attack can be envisaged from the oxygen ( $\delta^- = -0.53$  |e|). Moreover, the H-bond favors the formation of a six-membered ring structure. Thus, the corresponding transition state (**TS-1a**) lying 19.8 kcal/mol above **15-1a** clearly corresponds to a concerted ring closure and proton transfer, as indicated by the shortening of C–O (1.81 Å) bond and the simultaneous elongation of the O–H (1.02 Å) bond. The

complexes **1b-1d**, the computed activation energies are between 1.3 and 1.6 kcal/mol higher than for complex **TS-1a**, in line with the experimental observation of lower conversion for these systems (Table 1). This can be rationalized by the reacting carbonyl groups of **1b-1d** being less electrophilic as showed by the calculated partial charges on the carbon (for **1b**:  $\delta^- = -0.04$  |e|, for **1c**:  $\delta^+ = 0.19$  |e| and for **1d**:  $\delta^- = -0.04$  |e|). Consequently, the computational analysis supports our initial hypothesis that the pentafluorophenyl group is a superior promoter for macrolactonization as it increases the electrophilicity of the relevant carbonyl group and has the potential to pre-organize the substrates through  $\text{Ip}-\pi$  interactions. Those results also explain why, in the methods developed by Yamaguchi and Shiina, 4-dimethylaminopyridine (DMAP) is typically required as an acyl transfer reagent to enable the macrolactonization, which is not necessary with our method.<sup>[3,4]</sup>



**Figure 4.** Computed energy diagrams for **1a-1d**. The zero-energy value has been assigned to the reagent for each case.

## Conclusion

In summary, we have discovered an efficient and user-friendly protocol to achieve macrolactonizations, generating products that have the potential to make an impact in important applied fields such as medicinal chemistry and the fragrance industry. This transformation, which featured the formation of a mixed anhydride based on the utilization of an inexpensive activating agent (pentafluorobenzoyl chloride), displayed a remarkable efficacy to access a wide range of ring size, while overcoming most of the common limitations associated with such processes. For instance,

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this unique method could be equally applied to intramolecular macrolactonizations of *seco*-acids or to the intermolecular formation of macrodiolides from diacids and diols and even esters. Kinetic studies showed that after rapid formation of the mixed anhydride from pentafluorobenzoyl chloride (**1'a**) and the substrate, mono-molecular cyclization is the rate-determining step of the reaction. The potential formation of non-covalent interactions is underpinned by DFT computations, which indicated that, in substrates featuring the pentafluorophenyl moiety, both strong-hydrogen bonding as well as  $\pi$ -lp interactions are present. Further applications of the pentafluorophenyl moiety are presently investigated to take advantage of the unique reactivity of this structural motif.

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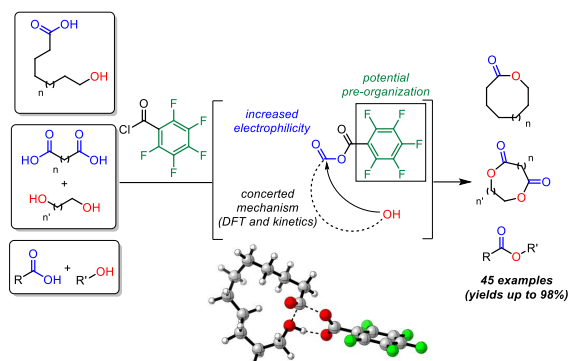
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**Keywords:** macrolactones • hydroxyacids • macrodiolides • mixed anhydride • macrocyclization

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## Entry for the Table of Contents



**Old made new again:** The onset of macrolactonizations can be initiated using the inexpensive pentafluorobenzoyl chloride as an activating agent to deliver a large variety of macrolactones, macrodiolides and esters with high efficiency through a robust protocol. Notably, this process could be easily extended to less reactive phenol derivatives.

Institute and/or researcher Twitter usernames: @djpleboeuf; @group\_ctm