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# W(OTf)<sub>6</sub> catalyzed synthesis of γ-lactones via ring contraction of macrolides or ring closing of terminal hydroxyfatty acids in ionic liquid

Zhong-Yu Xie, <sup>[a, b]</sup> Jin Deng, \* <sup>[a]</sup> and Yao Fu \* <sup>[a]</sup>

Abstract: y-Lactones are one of the important fine chemical products, which are widely used in perfumery, medicine, pesticide, dye and other fields. Herein, a new method for y-lactones preparation based on ring contraction was developed. Starting with macrolides, W(OTf)<sub>6</sub> was used to catalyze the ring-opening polymerization then depolymerization. More remarkable, the depolymerization was not a common ring-closing process, and the ring number of carbon chain was reduced one by one via rearrangement to form the most thermodynamical stable fivemembered ring compounds. A yield of 94% y-caprolactone (180 °C for 10 h) was achieved when [EMIM]OTf was chosen as the solvent, and the isolated yield was up to 85%. The interaction of various components and the reaction mechanism were studied by Fourier transform infrared (FT-IR) spectroscopy and <sup>1</sup>H Nuclear magnetic resonance (<sup>1</sup>H NMR) spectroscopy respectively. Furthermore, ylactones could be produced when the substrate was extended to the terminal hydroxyfatty acid. Unexpected, the catalyst was poisoned by 1 eq. of H<sub>2</sub>O given in the process, and thus the yield decreased greatly. In a word, the reaction is green, simple, "onepot", and high atomic utilizated (100% for macrolides and water as the only byproduct for terminal hydroxyfatty acid), which provides a promising approach to synthesise  $\gamma$ -lactones.

#### Introduction

γ-Lactones are a sort of fine chemical products with a wide range of applications. As in coconut, peach and other fruit flavour, most of them can be also extensively used in food processing, fragrance modulation of soap and cosmetics. <sup>[1]</sup> Meanwhile, they can be used as an engine fuel additives and expansion agents, also the important intermediates of pharmaceuticals, pesticides, dyes and others. <sup>[2]</sup> Furthermore, γ-lactones have totally different functions on application due to different substituents. For instance, as a sustainable platform molecule, γ-valerolactone can be used as green solvent, fuel

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additives and precursor for the polymer production; <sup>[3]</sup> and  $\gamma$ caprolactone is widely used in cream, honey aroma, vanilla beans, caramel and other fruit-flavoured compounds and tobacco flavours; similarly,  $\gamma$ -heptalactone takes parts in the preparation of flavours such as nuts, coconuts and fruits. With the continuous expansion of the applications of various  $\gamma$ lactones, it is a great desire to develop a green, simple and "one-pot" method for  $\gamma$ -lactones preparation.

As natural  $\gamma$ -lactones are rare and difficult to extract from plants and animals directly, most of them are produced through synthetic methods. Baeyer-Villiger oxidation of cyclic ketones plays an important role in the synthesis of lactones. Chrobok *et al.* described the oxidation of cyclic ketones to  $\gamma$ -lactones in 97% yield with silyl peroxides in the presence of [Hmim][Cl]:AlCl<sub>3</sub>=1:2 (AlCl<sub>3</sub>=0.67, acidic) ionic liquids. <sup>[4]</sup> Subsequently they reported that relatively high yields (89-94%) of lactones can be achieved in 1-120 min at room temperature with H<sub>2</sub>O<sub>2</sub> as the oxidant in [C<sub>4</sub>mim]Cl-GaCl<sub>3</sub>( X <sub>GaCl3</sub> = 0.75 ) Lewis acidic ionic liquid. <sup>[5]</sup> The step of Baeyer-Villiger oxidation is simple and the atomic utilization is high, however, as the starting materials, the 4-membered cyclic ketones are not stable and cheap enough to be used in large-scale industrial production of  $\gamma$ -lactones.

Another major source to synthesise  $\gamma$ -lactones is dicarboxylic acids, but the starting materials are limited to 1,4- or 1,5diacids. Take an example, Song *et al.* and Especel synthesized Pd/AX and Pd/TiO<sub>2</sub> successively for the hydrogenation of succinic acids to  $\gamma$ -butyrolactones. <sup>[6]</sup> Nikishin *et al.* and Li catalyzed the decarboxylation and coupling of 2,2-dimethyl-1,5pentanedioic acid with S<sub>2</sub>O<sub>8</sub><sup>2-</sup>-Ag<sup>+</sup> (or S<sub>2</sub>O<sub>8</sub><sup>2-</sup>-Ag<sup>+</sup>-Cu<sup>2+</sup>) and Ag(Phen)<sub>2</sub>OTf as catalysts respectively to obtain the corresponding  $\gamma$ -lactones in a high yield. <sup>[7]</sup>

Furthermore, in a process of tandem isomerizationlactonization, olefinic fatty acids can convert to  $\gamma$ -lactones. Angelici *et al.* confirmed that Amberlyst-15 was more suitable for the conversion of unsaturated acids into  $\gamma$ -lactones when compared to Nafion SAC-13. <sup>[8]</sup> Kanjilal *et al.* carried out the direct conversion of unsaturated fatty acids into their corresponding  $\gamma$ -lactones for the first time in the presence of a Lewis acidic ionic liquid, choline chloride  $2ZnCl_2$ . <sup>[9]</sup> Meanwhile, AgOTf was researched by Gooßen *et al.* to efficiently promote one-step isomerization- $\gamma$ -lactonization of unsaturated fatty acids. <sup>[1a]</sup> Nevertheless, the tandem reactions proceeded extremely slowly with low yields as the chain length and position of the double bond increased.

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Catalyzed by metal triflates as well, Collins *et al.* reported, efficient direct macrolactonization of seco acids can be catalyzed by Hf(OTf)<sub>4</sub> in high yield over hydrolysis even in the presence of excess water, forming a variety of macrolactones and benzolactones (55-90%), but no  $\gamma$ -lactones were produced.<sup>[1b]</sup>

Previous reports verified that metal triflates are the efficient catalysts for the ring-opening and polymerization of lactones, <sup>[10]</sup> and our earlier research involved ring-opening polymerization, ring-closing depolymerization, and ring contraction via rearrangement of lactones in the presence of W(OTf)<sub>6</sub> but without a systematic study. <sup>[11]</sup> Besides it, macrolides as the starting materials to synthesise  $\gamma$ -lactones were seldom reported excepting the work of Dumesic *et al.*, that 40% and 23% of  $\delta$ -valerolactone and  $\epsilon$ -caprolactone were reacted to form  $\gamma$ -lactones respectively over SiO<sub>2</sub>/Al<sub>2</sub>O<sub>3</sub>. <sup>[3b]</sup>

#### General work:

Baeyer-Villiger oxidation of cyclic ketones



#### Present work

Ring contraction of macrolides or ring closing of terminal hydroxyfatty acids





It is well-known that macrolides are mainly secondary metabolites of bacteria and fungi, which are abundant in nature. <sup>[12]</sup> The ring of macrolides contracted when Lewis acid metal triflates are chosen as catalysts, with further expanding the substrates to the terminal hydroxyfatty acids, thus a green, simple and high atomic utilized method to synthesise  $\gamma$ -lactones was developed when the ionic liquid [EMIM]OTf was chosen as the solvent. As an important kind of green and sustainable solvent, ionic liquids have attracted significant attention, it can

suppress the occurrence of side reactions suchlike repolymerization, and dissolve many organic or inorganic substances. <sup>[4, 13]</sup> Especially imidazolium-based ionic liquids have been extensively studied in a number of recent reports. <sup>[13]</sup> In this system, the results show that W(OTf)<sub>6</sub> is the optimum catalyst for the ring-opening polymerization of lactones then depolymerization of polyesters into monomers. The mentioned depolymerization is not a common ring closure process, the ring number of carbon chain is reduced one by one after β-H eliminated until the formation of thermodynamically stable five-membered ring compounds with the lowest systematic energy and ring tension.

#### **Results and Discussion**

Initially, *ɛ*-caprolactone was selected as the model substrate for ring contraction to produce y-caprolactone in the presence of different metal triflates under neat conditions (solvent-free) at 150 °C (Figure 1). The results showed almost complete conversion of the feedstock and seldom six-membered  $\delta$ caprolactone existed, but the yield of ring contracting product was not very high due to the polymerization and coking. W(OTf)<sub>6</sub> showed the best catalytic effect, followed by Bi(OTf)<sub>3</sub>, then Hg(OTf)<sub>2</sub> and AgOTf. This trend is proportional to the effective charge density of the metal triflate. [14] The cation in metal triflate with higher effective charge density was very lack of charge and had stronger Lewis acidity, [15-17] that was also proved by the metal triflates we chose with the same center metal ion at different valence. The catalytic effect of Fe(OTf)<sub>3</sub> was more excellent than Fe(OTf)<sub>2</sub>, and so did Ce(OTf)<sub>4</sub> to Ce(OTf)<sub>3</sub>.



Figure 1. The screening of metal triflates in the conversion of  $\varepsilon$ caprolactone under neat conditions. Reaction conditions: 5 mM  $\varepsilon$ caprolactone, 0.5 mol% M(OTf)<sub>n</sub>, 150 °C, 10 h. Yields were determined by gas chromatography (GC) used diphenyl as internal standard.

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<b>Table 1.</b> The optimizing reaction parameters in the conversion of ε-caprolactone under neat conditions.							
Entry	W(OTf) <sub>6</sub> (mol%)	T (°C)	t (h)	C <sup>a</sup> (%) -	Y (%)		
2.10.9					γ-CL <sup>b</sup>	δ-CL °	
1	0.5	150	10	>99	70	1.8	
2	1.0	150	10	>99	77	2.8	
3	2.0	150	10	>99	77	1.8	
4	1.0	135	10	97	11	0.60	
5	1.0	180	10	>99	49	1.0	
6	1.0	150	6	>99	63	1.3	
7	1.0	150	24	>99	74	1.7	
Reactions were carried out on a scale of 5 mM. Vields were determined by							

Reactions were carried out on a scale of 5 mM. Yields were determined by GC analysis used diphenyl as internal standard. <sup>a</sup> The conversion of  $\varepsilon$ -caprolactone, <sup>b</sup> $\gamma$ -CL:  $\gamma$ -caprolactone, <sup>c</sup> $\delta$ -CL:  $\delta$ -caprolactone.

We further studied the effects of the catalyst amount (0.5 mol%, 1.0 mol%, 2.0 mol%), temperature (135 °C, 150 °C, 180 °C) and time (6 h, 10 h, 24 h) (Table 1). We found that when the amount of catalyst was increased to 1.0 mol%, the effect has been optimized, and the excessive catalyst did not play a significant role. The impact of temperature was relatively large, polymerization was still very obvious at 135 °C, but coking was serious inevitably when it rose to 180 °C. Comparatively speaking, 150 °C was a suitable temperature to avoid polymerization and reduce coking. Under the conditions, a small amount of polymers remained after 6 h, but the reaction was balanced when extended the time to 10 h, and there was no need to further prolong the reaction time. In general, the yield of y-caprolactone reached 77% (GC determined) with the catalyst amount of 1.0 mol% at 150 °C for 10 h, which was the optimal reaction conditions (Table 1, Entry 2).



Figure 2. The screening of metal triflates in the conversion of  $\epsilon$ -caprolactone in [EMIM]OTf. Reaction conditions: 1.0 mM substrate, 1.0 mol% W(OTf)\_6, 180 °C, 10 h, 1 mL pre-dried [EMIM]OTf. Yields were determined by GC analysis used diphenyl as internal standard.

 $W(OTf)_6$  as the catalyst was able to reduce the occurrence of polymerization in a large scale, but the concentration of substrate was too high under neat conditions. The presence of polymerization which cannot be avoided completely caused the increase of the viscosity of the system. As a result, mass and heat transfer were limited, which lead to the severe coking and ended up with the undesired catalytic effect. <sup>[18]</sup> Therefore, we tried to find a suitable solvent (Table 2). In comparison of

Entry Catalyst		Solvent	T (°C)	t (b)	C a (%)	Yield (%)	
Linuy	Odtalyst	Convent	(0)	t (II)	0 (/0)	γ-CL <sup>b</sup>	δ-CL
1	W(OTf) <sub>6</sub>	chlorobenzene	150	10	>99	17	0.50
2	W(OTf) <sub>6</sub>	m-xylene	150	10	>99	22	0.63
3	W(OTf) <sub>6</sub>	MIBK	150	10	>99	0.46	0.42
4	W(OTf) <sub>6</sub>	diglyme	150	10	>99	20	-
5	W(OTf) <sub>6</sub>	DMSO	150	10	93	2.0	2.1
6	W(OTf) <sub>6</sub>	[EMIM]OTf	150	10	97	44	4.6
7	W(OTf) <sub>6</sub>	[EMIM]OTf	150	24	>99	82	1.9
8	W(OTf)₀	[EMIM]OTf	180	10	98	94	2.0
9	-	[EMIM]OTf	180	10	<1.0%	-	-
10	W(OTf) <sub>6</sub>	[BMIM]OTf	180	10	>99	77	1.7
11	W(OTf) <sub>6</sub>	[EMIM]CI	180	10	92	-	-
12	W(OTf) <sub>6</sub>	[BMIM]CI	180	10	98	2.1	1.4
13	W(OTf) <sub>6</sub>	[EMIM]Br	180	10	99	-	11
14	W(OTf) <sub>6</sub>	[BMIM]Br	180	10	99	0.41	6.6
15	WCl <sub>6</sub>	[EMIM]OTf	180	10	>99	-	1.9
16	WCI <sub>6</sub>	[BMIM]OTf	180	10	>99	-	-
17	WCl <sub>6</sub>	[EMIM]Br	180	10	98	3.4	16
18	WCl <sub>6</sub>	[BMIM]CI	180	10	87	3.7	2.1

Reactions were carried out on a scale of 1 mM with 1 mol% catalyst in 1 mL solvent. Yields were determined by GC analysis used diphenyl as internal standard. <sup>a</sup> The conversion of  $\epsilon$ -caprolactone, <sup>b</sup> $\gamma$ -CL:  $\gamma$ -caprolactone, <sup>c</sup> $\delta$ -CL:  $\delta$ -caprolactone.

aromatic solvents previously reported (Table 2, Entry 1, 2), medium polarity solvent (Table 2, Entry 3) and high polarity solvents (Table 2, Entry 4), the ionic liquid [EMIM]OTf showed unexpected results. [1a,19] The optimal results determined by GC showed that the yield of y-caprolactone catalyzed by W(OTf)<sub>6</sub> was 94% (Table 2, Entry 8), and the isolated yield was up to 85% (Table 3, Entry 1). Fortunately, when [EMIM]OTf was used, compared with the solvent-free conditions, various metal triflates achieved good catalytic effects (Figure 2) and with less severe coking even at 180 °C. No conversion of ε-caprolactone and no products were detected during the blank experiment without metal triflate (Table 2, Entry 9) demonstrated that [EMIM]OTf had no catalytic effect on  $\epsilon$ -caprolactone. In addition, another set of experimental results showed that only when both the anion of the ionic liquid and the anion of the catalyst were OTF, it can play a good catalytic effect (Table 2, Entries 8, 10-18).

FT-IR spectroscopy was used to investigate the interactions among catalyst,  $\varepsilon$ -caprolactone and [EMIM]OTf and the results were shown in Figure 3a. Particularly, the band between 1750 cm<sup>-1</sup> to 1700 cm<sup>-1</sup> was enlarged in Figure 3b. The characteristic



**Figure 3.** FT-IR spectroscopy of  $\varepsilon$ -caprolactone (A),  $\varepsilon$ -caprolactone in [EMIM]OTf (B),  $\varepsilon$ -caprolactone catalyzed by W(OTf)<sub>6</sub> (C),  $\varepsilon$ -caprolactone catalyzed by W(OTf)<sub>6</sub> in [EMIM]OTf (D),  $\varepsilon$ -caprolactone catalyzed by WCl<sub>6</sub> (E). (a). The wavenumbers between 4000 cm<sup>-1</sup> - 400 cm<sup>-1</sup>; (b). Zoomed in the range between 1750 cm<sup>-1</sup> - 1700 cm<sup>-1</sup>.



Figure 4. Analysis on the reaction solution at different periods by <sup>1</sup>H-NMR spectrum. Reactions conditions: 1.0 mM substrate, 1.0 mol% W(OTf)<sub>6</sub>, 180 °C, 1 mL pre-dried [EMIM]OTf. The reaction solution at different periods was characterized by <sup>1</sup>H-NMR spectroscopy after the removal of the ionic liquid. [★]: Characteristic peaks belonged to ε-caprolactone; [▼]: Characteristic peaks belonged to ε-caprolactone; [▼]: Characteristic peaks belonged to γ-caprolactone; [♦]: Characteristic peaks belonged to γ-caprolactone; (a). ε-Caprolactone as the substrate; (b). δ-Caprolactone as the substrate and reacted for 10 min.

of C=O vibration was at 1730 cm<sup>-1</sup> (Figure 3b-A). It was not moving significantly when  $\varepsilon$ -caprolactone dissolved in [EMIM]OTf (Figure 3b-B), which confirmed that [EMIM]OTf hardly interacted with the  $\varepsilon$ -caprolactone. However, with the interaction on  $\varepsilon$ -caprolactone by W(OTf)<sub>6</sub>, the C=O peak has red-shifted to 1724 cm<sup>-1</sup> (Figure 3b-C). The reason for the decrease in wavenumbers could be related to the weakening of C=O by the interaction of Lewis acidic W(OTf)<sub>6</sub> with a lone pair electrons on oxygen. <sup>[20]</sup> And when  $\varepsilon$ -caprolactone catalyzed by W(OTf)<sub>6</sub> in [EMIM]OTf, the band of C=O stretching vibration also appeared at 1724 cm<sup>-1</sup> (Figure 3b-D). For comparison, no red-shift can be seen obviously when  $\varepsilon$ -caprolactone was catalyzed by WCl<sub>6</sub>, which the C=O peak was kept still at 1730 cm<sup>-1</sup> (Figure 3b-E).

The above results suggested that only  $W(OTf)_6$  can catalyze the reaction. Moreover, the addition of [EMIM]OTf increased the yield, which was attributed to the high ionic concentration of OTf. The complexation of OTf<sup>-</sup> in the ionic liquid with the catalyst, forming triflate tungsten ionic complex such as  $[W(OTf)_7]^-$ ,  $[W_2(OTf)_{11}]^-$ , thus enhanced the Lewis acidity. <sup>[9, 21]</sup> While, in the non-OTf<sup>-</sup> ionic liquid, due to the lower concentration of OTf<sup>-</sup>, the ring contractions were prohibited (Table 2, Entries 11-14).

To further understand the reaction, mechanism studies were also carried out. The reaction solution at different periods was characterized by <sup>1</sup>H-NMR spectroscopy after the removal of the ionic liquid (Figure 4a). It was found that the peaks at ~4.45 ppm (m, 1H) corresponded to the methine hydrogen atom (CH<sub>3</sub>CH<sub>R</sub>-) of  $\gamma$ - or  $\delta$ -caprolactone. To distinguish them, the characteristic peaks at 1.38 ppm (d, J = 6.3 Hz, 3H) and 1.01 ppm (t, J = 7.4 Hz, 3H) were recognized to be the hydrogen atoms on the methyl ( $-CH_3$ ) of  $\delta$ - and  $\gamma$ -caprolactone respectively. Furthermore, the methylene hydrogen atoms of polyester adjacent to the alkyl O atom (-O-CH2-) was belonged to the multi-peaks at ~4.08 ppm (m, 2H); and those at ~2.64 ppm (m, 2H) signified the hydrogen atoms on the  $\alpha$ carbon to the carbonyl O atom ( $-CH_2CO_-$ ) of  $\varepsilon$ -caprolactone. Depending on the relative height of the characteristic peaks, we inferred the content change of each substance during the reaction. After half an hour of the initial reaction stage, large conversion of *ε*-caprolactone and obvious polymerization were observed according to <sup>1</sup>H NMR, while a slight of  $\gamma$ - and  $\delta$ caprolactone appeared. As time went on, the substrate was continuously converted, while polyester was gradually consumed. In contrary, the total amount of  $\gamma\text{-}$  and  $\delta\text{-}$ caprolactones were rising subsequently. Therefore, the substrate polymerization in the initial stage proved by electrospray ionization mass spectrometry (ESI-MS) was shown in our previous work. [11] Subsequently, the polyester was further depolymerized into the desired products. The possible depolymerization process was illustrated by the commercial poly-caprolactone with the average molecular weight up to 80,000. It was not easy to depolymerize with such

high degree of polymerization, but unexpectedly, the yield was reached up to 84% (Table 4, entry 1).

After the depolymerization, the content of  $\gamma$ -caprolactone rose, whereas the  $\delta$ -caprolactone increased at first and then decreased. We were puzzled that the content of  $\delta$ -caprolactone was constantly low during the whole process. For this, the reaction with  $\delta$ -caprolactone as the substrate was carried out (Figure 4b). In just 10 minutes, the yield of  $\gamma$ -caprolactone was reached to 78% and almost no polymerization could be observed according to <sup>1</sup>H NMR, which was strongly proved that  $\delta$ -caprolactone was an intermediate during the formation of  $\gamma$ -caprolactone, and it was an extremely easy transformation process from  $\delta$ - to  $\gamma$ -caprolactone. That might be why only small amount of  $\delta$ -caprolactone was found in the whole process.

Based on it, we suggested the following reaction route (Scheme 2). Previous work in our group has also reported the results calculated by density functional theory (DFT) and electrospray ionization mass spectrometry (ESI-MS), demonstrating that W(OTf)<sub>6</sub> is an active catalyst for both the ring-opening polymerization of lactones and the depolymerization of polyester to monomers. [11] Metal triflate as an excellent Lewis acid, the metal center first activates the monomer upon coordination to its carbonyl oxygen to form complex 2. <sup>[10]</sup> While tungsten (VI) shows a great oxophility, which helps it to grab the oxygen easily from the Cacyl atom, thus makes the C=O bond even weaker. In ionic liquids with utter polar, charge transfer forms salt 5 consisted of a Tungsten (VI) complex coordinated by lactone (cation) and triflate (anion). At this point, C=O of another lactone approached to  $\alpha$ -C, bringing to dimerization. In this way, other lactones are all progressively transformed by iterative incorporation in sequence to form higher molar weight oligomer 7. [10a]



**Scheme 2.** Plausible mechanism of the catalytic system for ring-opening polymerization, ring-closing depolymerization, and ring contraction via rearrangement of lactones.

However, polyester depolymerization catalyzed by metal triflate is not a common ring closure process. Tungsten (VI) attacks the oxygen atom to form a coordination bond,

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thereupon  $\beta$ -H eliminates to produce the tungsten (VI) complex 8 coordinated with ester bond, which contains terminal olefin.

According to the Markovnikov rule, the electron rich oxygen atom is apt to attack the carbon atom with more substitutional groups then close the ring, so the ring number of carbon chain is reduced by one. The next stage is also ring-opening polymerization and then depolymerization along the path 1 to 9, carbon number of ring chain is reduced successively, forming the most stable thermodynamic five-membered ring 12. Generally speaking, OTf catalyzes the polymerization of lactones, and tungsten (VI) promotes the  $\beta$ -H elimination favorably at the same time. The entire reaction path is dominated by ions, while ionic liquid with the highest polar contributes to the charge separation, thus providing optimal solvent effect.

On above, such an optimal reaction system was developed that seven-membered ring lactones could be condensed to form y-lactones. And for the lactones with branches, coking became more serious as the branches lengthened, which greatly decreased the yield. (Table 3, Entries 1-7). With the further increment of the ring number, the ring tension gradually decreased while the stability of the raw material increased. Meanwhile, coking went worse along with the extension of the branch of the product, which led to a gradual decrease in yield, but when it prolonged the reaction time to 24 h, the yield increased by a certain margin (Table 3, Entries 8-10). However, the ring contraction product was not observed and the substrate did not participate in the reaction at all when 3-isochromanone was the starting materials (Table 3, Entry 11). It might be attributed to the conjugated structure of the phenyl II-bond with ester bond.

The open-chain polyesters yielded  $\gamma$ -lactones pretty easily (Table 4, Entry 1), furthermore, we extended the substrates to the open-chain terminal hydroxyl fatty acids, but the yield was significantly lower than the one of lactones unfortunately (Table

Table 4. conditions	The expanding of term s.	inal hydroxyl fatty acid	ds under optima	
Entry	Substrate	Product	Isolated yield (%)	
1	$ \left\{ \begin{array}{c} O \\ (\overline{M.W} = 80000 \end{array} \right)^{n} $	0=	84	
2	но	0=~0	57	
3	HO HO HO	0 - ()- ()-	32 (35 ª)	
4	HO HO HO	0	30 (34 ª)	
Reactions conditions: 1.0 mM substrate, 1.0 mol% W(OTf) <sub>6</sub> , 180 °C, 10 h 1 mL pre-dried [EMIM]OTf. Isolated yields were obtained by silica ge column chromatography, <sup>a</sup> Reacted for 24h.				

4, Entries 2-4). We speculated that W(OTf)<sub>6</sub> as the catalyst was poisoned by 1 eq. of H<sub>2</sub>O which was generated during esterification, thus reducing the reactivity. To verify this speculation, 1 eq. of H<sub>2</sub>O was added into the reaction with  $\varepsilon$ -caprolactone as the substrate, while the almost equal yield as 6-hydroxycaproic acid was achieved (Scheme 3). It strongly suggested that water severely lowered the catalytic activity during esterification of terminal hydroxyl fatty acid and thus decreased the yield, and it did not help even under the extending time.



Considering that [EMIM]OTf is relatively expensive, we attempted to recycle the neat ionic liquid. As shown in Supporting Information section-VII, after 5 consecutive runs, almost no conversion loss of  $\epsilon$ -caprolactone was observed. Nevertheless, coking got more serious with the increase of cycles, thus the yield decreased slightly. 83% yield of  $\gamma$ -caprolactone was declined to at the fifth run. Unfortunately, we can hardly recycle W(OTf)<sub>6</sub> due to its homogeneity and watersensitivity, which limited the reusability of the catalyst.

#### Conclusions

We have developed a new method for the synthesis of ylactones by ring contraction. Macrolides, abundant in nature, are chosen as the reactants. The one-step conversion to  $\gamma$ lactones is green, simple, "one-pot", and high atomic utilized (100% for macrolides and water as the only byproduct for terminal hydroxyfatty acid). W(OTf)6 stood out from a series of metal triflates we screened, showing excellent catalytic activity. The next, we optimized the reaction conditions, yield of 77% ycaprolactone (150 °C for 10 h) was achieved on a scale of 1 mM by ring contraction. But when [EMIM]OTf was chosen as the solvent, the carbonation was not serious even when the temperature rose to 180 °C, and the yield of y-caprolactone increased to 94% (isolated yield is 85%). Research showed that, W(OTf)<sub>6</sub> but not [EMIM]OTf can catalyze the reaction, and the addition of the latter increased the yield. During the reaction, macrolides took part in ring-opening polymerization and then in depolymerization into monomers. More remarkable, the depolymerization is not a common ring closure process, and the ring number of carbon chain is reduced one by one after β-H elimination to form the most thermodynamical stable fivemembered ring compounds with the lowest ring strain. The application of this catalytic system is effective for the transformation of lactones with larger ring number or branches as well, but for open-chain terminal hydroxyl fatty acid, catalyst was poisoned by 1 eq. of H<sub>2</sub>O given in the ring-closing process and the yield decreased greatly. But it was optimistically that [EMIM]OTf could be efficiently recycled several times.

#### **Experimental Section**

**Materials.** All commercially available chemicals were purchased from Alfa Aesar, Adamas-beta, Energy Chemical, TCI and Aladdin.  $Zr(OTf)_4$  and  $W(OTf)_6$  were synthesized according to the literatures. <sup>[11, 15]</sup> The preparation methods of part of substrates and the NMR spectrum data were listed in **Supporting Information**. All glasswares were oven dried prior to use and all solvents were previously dried with 4Å molecular sieves. All air-and moisture-sensitive manipulations were carried out in the standard vacuum line, Schleck or glove box filled with nitrogen.

**Analytical methods.** GC analysis was acquired on a Shimadzu GC-2010 Plus GC System with a flame-ionization detector equipped with a FFAP capillary column (30 m × 0.32 mm × 0.25 µm, Agilent J&W GC Columns, NO. 1233232). Injection and detection temperatures were set both at 250 °C, initial temperature of the oven was 100 °C and then raised to 200 °C for 3 minutes at a rate of 10 °C/min. The contents of  $\gamma$ -,  $\delta$ - and  $\epsilon$ -caprolactone were determined by internal standard method. Under the above condition, the retention time of  $\gamma$ -,  $\delta$ - and  $\epsilon$ -caprolactone were 4.066 min, 4.837 min and 5.625 min respectively; while the retention time of biphenyl as internal standard was 6.502 min. The conversion of the  $\epsilon$ -caprolactone was calculated according to the following formula 1, and the yield of the products were calculated according to the formula 2 and 3:

formula 1:	C <sub><math>\epsilon</math>-caprolactone</sub> /% = 100% - $\frac{n}{n} \frac{\epsilon}{\text{substrate}} \times 100\%$
formula 2:	C $_{\delta\text{-caprolactone}}$ /% = $\frac{n_{\delta\text{-caprolactone}}}{n_{substrate}} \times 100\%$
formula 3:	C $_{\gamma\text{-caprolactone}}$ /% = $\frac{n_{\gamma\text{-caprolactone}}}{n_{substrate}} \times 100\%$

FT-IR spectroscopy were tested on a Thermo Scientific Instrument Co. U.S.A Nicolet 8700 and the scan range of wavenumbers was between  $4000 \text{ cm}^{-1} - 400 \text{ cm}^{-1}$ .

<sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were tested on a Bruker Avance 400 spectrometer and analysed with MestReNova software. Multiplicities are described using the following abbreviations: chemical shift (ppm, scale), multiplicity (s = singlet, d = doublet, t= triplet, q = quartet, m = multiplet and/or multiplet resonances, br = broad), coupling constant (Hz), and integration.

#### General procedures of optimizing reaction parameters.

 $\epsilon\text{-}Caprolactone$  and catalyst were added in a 10 mL Schleck tube equipped with a magnetic stirrer at 500 rpm. The reaction mixture was proceeded in neat conditions or 1 mL pre-dried solvent under Ar atmosphere. After the reaction, the reaction mixture was transferred out with CH\_2Cl\_2 and biphenyl was added as an internal standard. The contents of  $\gamma$ -,  $\delta\text{-}$  and  $\epsilon\text{-}$  caprolactone were determined by internal standard method using a gas chromatograph. The GC analysis and formulas were described as before.

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# General procedures of expanding the substrates and the data of NMR.

The substrate (1 mmol) and 1.0 mol% W(OTf)<sub>6</sub> were added in a 10 mL Schleck tube equipped with a magnetic stirrer at 500 rpm. The reaction mixture was stirred for 10 h (or 24 h) at 180 °C in 1 mL pre-dried [EMIM]OTf under Ar atmosphere. After the reaction, the reaction mixture was diluted with ethyl acetate then washed with saturated NaCl solution more than 10 times until the aqueous phase was clear. The organic parts were combined, dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, filtered and concentrated to obtain the target compound. Then the crude compound was purified by a short silica column with gradient elution (ethyl acetate : petroleum ether = 1:5 - 1:50). The solvent was evaporated and the desired product was obtained. All the products were characterized with NMR and the spectrum data were listed in **Supporting Information**.

#### General procedures of recycle of [EMIM]OTf.

 $\epsilon$ -Caprolactone (1 mmol) and 1.0 mol% W(OTf)\_6 were added in a 10 mL Schleck tube equipped with a magnetic stirrer at 500 rpm. The reaction mixture was stirred for 10 h at 180 °C in 1 mL pre-dried [EMIM]OTf under Ar atmosphere. The contents of  $\gamma$ -,  $\delta$ - and  $\epsilon$ -caprolactone were determined by GC analysis with biphenyl as the internal standard. After that, the solution was diluted with ethyl acetate and extracted with pure water until the aqueous phase was clear. Combined the aqueous layer then vacuum evaporated. Finally, the residue ([EMIM]OTf) was dried through oil pump to remove the trace water and for the next use.

#### **Conflicts of interest**

There are no conflicts to declare.

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Keywords:  $\gamma$ -lactones • metal triflates • ionic liquid • ring contraction • rearrangement

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Layout 2:

# **FULL PAPER**



Zhong-Yu Xie, Jin Deng, \* Yao Fu \*

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W(OTf)<sub>6</sub> catalyzed synthesis of ylactones via ring contraction of macrolides or ring closing of terminal hydroxyfatty acids in ionic liquid

Slim them: Catalyzed by W(OTf)<sub>6</sub>, macrolides contracted the ring via rearrangement to produce the stable fivemembered y-lactones in [EMIM]OTf.

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