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# An effective method for the synthesis of carboxylic esters and lactones using substituted benzoic anhydrides with Lewis acid catalysts

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**Abstract**—An efficient mixed-anhydride method for the synthesis of carboxylic esters and lactones using benzoic anhydride having electron withdrawing substituent(s) is developed by the promotion of Lewis acid catalysts. In the presence of a catalytic amount of $TiCl_2(ClO_4)_2$, various carboxylic esters are prepared in high yields through the formation of the corresponding mixed-anhydrides from 3,5-bis(trifluoromethyl)benzoic anhydride and carboxylic acids. The combined catalyst consisting of $TiCl_2(ClO_4)_2$ together with chlorotrimethylsilane functions as an effective catalyst for the synthesis of carboxylic esters from free carboxylic acids and alcohols with 4-(trifluoromethyl)benzoic anhydride. Various macrolactones are prepared from the free ω-hydroxycarboxylic acids by the combined use of 4-(trifluoromethyl)benzoic anhydride and titanium(IV) catalysts together with chlorotrimethylsilane under mild reaction conditions. The lactonization of trimethylsilyl ω-(trimethylsiloxy)carboxylates using 4-(trifluoromethyl)benzoic anhydride is also promoted at room temperature in the presence of a catalytic amount of $TiCl_2(ClO_4)_2$. An 8-membered ring lactone, a synthetic intermediate of cephalosporolide D, is successfully synthesized according to this mixed-anhydride method using 4-(trifluoromethyl)benzoic anhydride by the promotion of a catalytic amount of $Hf(OTf)_4$.


## 1. Introduction

While numerous esterifications using Brønsted and Lewis acid catalysts have been reported, a few methods have actually been utilized for the effective preparation of carboxylic esters from equimolar amounts of carboxylic acids and alcohols under mild conditions.[1] On the other hand, some acylation reactions of alkyl silyl ethers, alcohols or thiols with an excess amount of acetic or benzoic anhydrides were presented since acid anhydrides could be efficiently activated by acidic species.[2] Furthermore, it is also well known that a mixed-anhydride method using trifluoroacetic anhydride is sometimes very convenient for the generation of bulky carboxylic esters.[3]

During the course of our studies on the exploration of new catalytic synthetic reactions using Lewis acids,[4] a unique method for the preparation of carboxylic esters was developed in 1992 starting from silyl carboxylates and alkyl silyl ethers via the active intermediary mixed-anhydrides prepared in situ from silyl carboxylates with 4-(trifluoromethyl)benzoic anhydride (TFBA) using a catalytic amount of a Lewis acid such as $Sn(OTf)_2$, $TiCl_2(ClO_4)_2$, $TiCl_2(OTf)_2$, $ZrCl_2(OTf)_2$, $HfCl_2(OTf)_2$, $AlCl(OTf)_2$, $InCl(OTf)_2$, etc.[5] In 1994, we extended this method to the reaction between nearly equimolar amounts free carboxylic acids and alcohols by varying the combination of Lewis acids.[6] The corresponding carboxylic esters or lactones are obtained in high yields by treating nearly equimolar amounts of free carboxylic acids and alcohols or ω-hydroxycarboxylic acids with substituted benzoic anhydrides possessing electron withdrawing group(s) in the presence of catalytic amounts of $TiCl_2(ClO_4)_2$ or $TiCl_2(OTf)_2$ together with chlorotrimethylsilane. Yamamoto et al. also found that $Sc(OTf)_3$ or $Sc(NTf_2)_3$ is an effective Lewis acid for the promotion of this reaction in 1995 and the desired carboxylic esters including medium-sized lactones were produced in high yields.[2e–g]

In this paper, we describe in detail the results of our investigations on the effective method for the preparation of carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols using an active Lewis acid catalyst initially reported in a previous communication,[6a] and also further developments of the above reactions applied to the preparations of lactones including synthetic intermediates of natural compounds.[5c,6b,7]

*Keywords*: Carboxylic esters; Macrolactones; Medium-sized lactones; Cephalosporolide D; 4-(Trifluoromethyl)benzoic anhydride; 3,5-Bis-(trifluoromethyl)benzoic anhydride; Mixed-anhydrides; Lewis acid catalysts.
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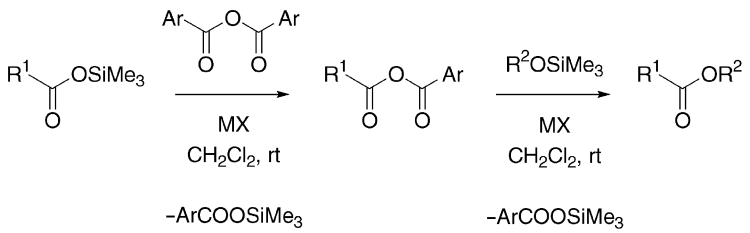



**Scheme 1.** Synthesis of carboxylic esters from silyl carboxylates with alkyl silyl ethers using benzoic anhydrides.

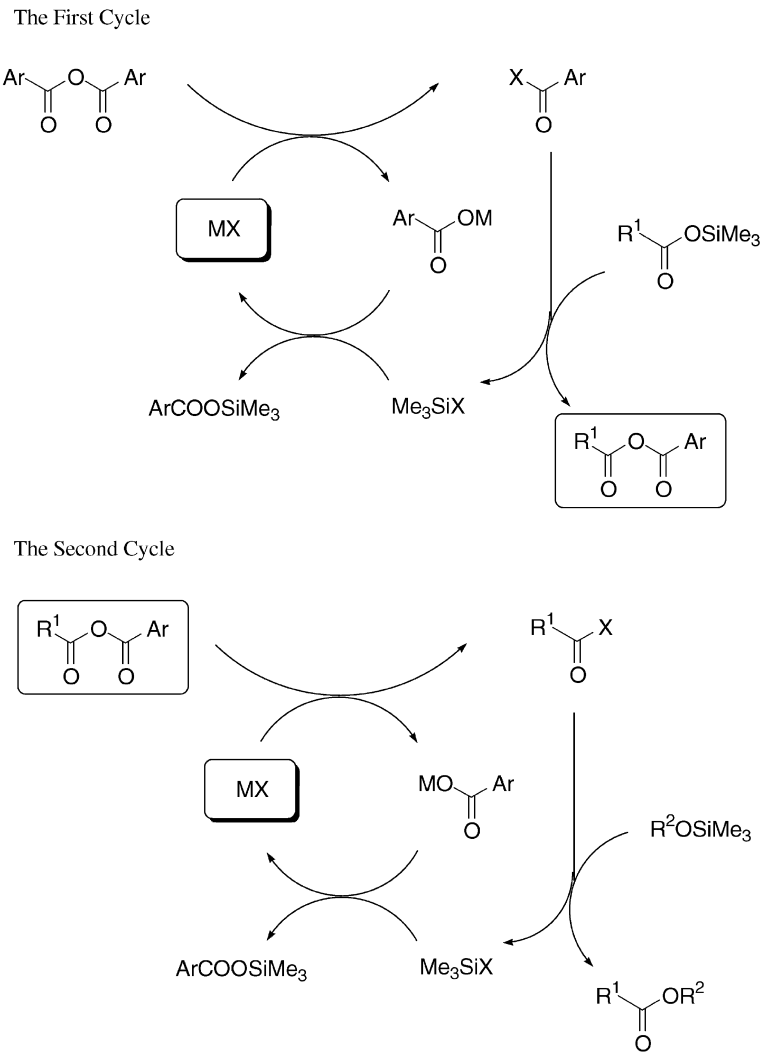
## 2. Results and discussion

### 2.1. Esterification reaction via mixed-anhydrides using benzoic anhydrides

Recently, an effective method for the synthesis of carboxylic esters from nearly equimolar amounts of silyl carboxylates and alkyl silyl ethers via mixed-anhydrides was developed by employing a substituted benzoic anhydride and a Lewis acid catalyst (Scheme 1).[5a,b] In the report, it was indicated that the following successive reactions would lead to the formation of carboxylic esters; that is, (1) the initial formation of the mixed-anhydride from benzoic anhydride and silyl carboxylates by the promotion of Lewis acid, and (2) the alcoholysis of the mixed-anhydrides by alkyl silyl ethers with the assistance of a Lewis acid.

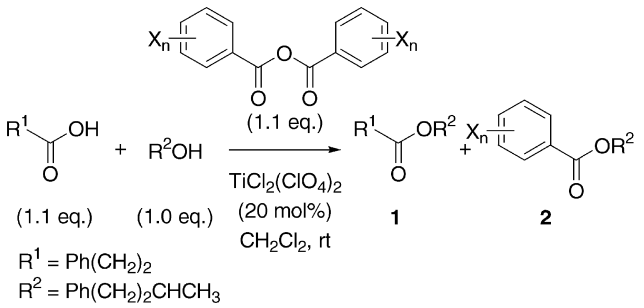
The mixed-anhydride consisting of aromatic and aliphatic acyl parts is generated in the first cycle and it will be successively consumed in the second cycle to afford the desired carboxylic ester (Scheme 2). Therefore, the mixed-anhydride formed in situ is assumed to be the most important intermediate in the catalytic process.

It was also found in previous research that the use of silyl derivatives of carboxylic acids and of alcohols was essential for the completion of the esterification reaction at room




**Scheme 2.** Catalytic cycle for the production of carboxylic esters using benzoic anhydrides as coupling reagents.

**Table 1**. Effect of substituted benzoic anhydrides




| Entry | $X_n$ | Yield[a] (%) | **1/2**[b] |
|---|---|---|---|
| 1 | H | 50 | 17/1 |
| 2 | 2-F | 82 | 70/1 |
| 3 | 3-$NO_2$ | 72 | 60/1 |
| 4 | 4-$NO_2$ | 57 | 40/1 |
| 5 | 2-$CF_3$ | 88 | 80/1 |
| 6 | 3-$CF_3$ | 87 | 180/1 |
| 7 | 4-$CF_3$ | 88 | 180/1 |
| 8 | 3,5-$(CF_3)_2$ | 89 | >200/1 |

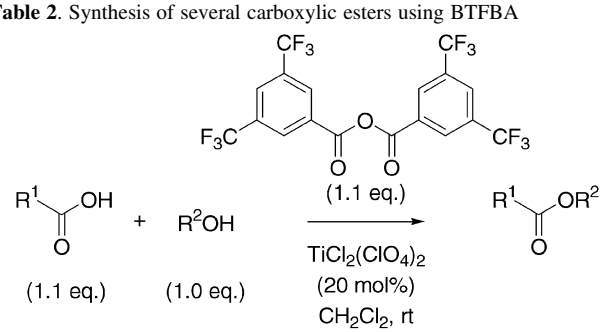
[a] Isolated yield of **1**.
[b] Determined by $^1$H NMR using a crude mixture.

temperature. Therefore, the development of further useful and convenient methods for the preparation of carboxylic esters from free carboxylic acids and alcohols was next required. However, when the condensation of 3-phenylpropanoic acid and 4-phenyl-2-butanol was carried out in the presence of TFBA and 20 mol% of $TiCl_2(ClO_4)_2$, the alcohol was not completely consumed and the desired ester was obtained in 88% yield along with a small amount of an undesirable ester, 1-methyl-3-phenylpropyl (4-trifluoromethyl)benzoate (product selectivity=180:1). Several substituted benzoic anhydrides were then examined for the reaction of free carboxylic acids and alcohols to improve the yield and chemoselectivity (Table 1). The reaction smoothly took place to afford the desired carboxylic ester in good yields using mono-substituted benzoic anhydrides having an electron withdrawing group such as fluoride, nitro and trifluoromethyl, however, the chemoselectivity was not perfect (entries 2–7). Although the formation of a small amount of 1-methyl-3-phenylpropyl (3-trifluoromethyl)-benzoate, a by-product, was observed when using (3-trifluoromethyl)benzoic anhydride as the condensation reagent, the product selectivity is nearly equal to that of the reaction using TFBA (see entries 6 and 7). It was finally determined that the desired ester was exclusively obtained when 3,5-bis(trifluoromethyl)benzoic anhydride (BTFBA) was employed as shown in entry 8.

Some examples for the synthesis of carboxylic esters from the corresponding carboxylic acids and alcohols using BTFBA and $TiCl_2(ClO_4)_2$ are shown in Table 2. In every case, the reactions smoothly proceed at room temperature in dichloromethane to give the corresponding carboxylic esters in good to high yields from nearly equimolar amounts of carboxylic acids and alcohols. It is noteworthy that pivalic acid esters, derived from a bulky carboxylic acid, were also obtained in high yields by the present reaction (entries 5 and 6).

Although the yields of the esterification using BTFBA were relatively higher compared to those obtained by TFBA, the reaction did not completely proceed under these conditions probably due to the deactivation of the catalyst. Next, several combinations of reactants were examined using the present mixed-anhydride method for the preparation of carboxylic esters in higher yields (Table 3). When trimethylsilyl 3-phenylpropanoate and 4-phenyl-2-butanol were employed in the presence of 20 mol% of $TiCl_2(ClO_4)_2$ with BTFBA, nearly the same yield of the desired ester was obtained as that for the reaction between silyl carboxylate and alkyl silyl ether (see entries 1 and 2). However, the yield slightly decreased when using 3-phenylpropanoic acid and 1-methyl-3-phenylpropyl trimethylsilyl ether as the substrates under the identical reaction conditions (entry 3). Therefore, it was assumed that the free carboxylic acid particularly deactivated the Lewis acid catalyst by ligand exchange on the catalyst. The esterification yield of the free carboxylic acid with the free alcohol was apparently lower compared to those of the other combinations (entry 4).

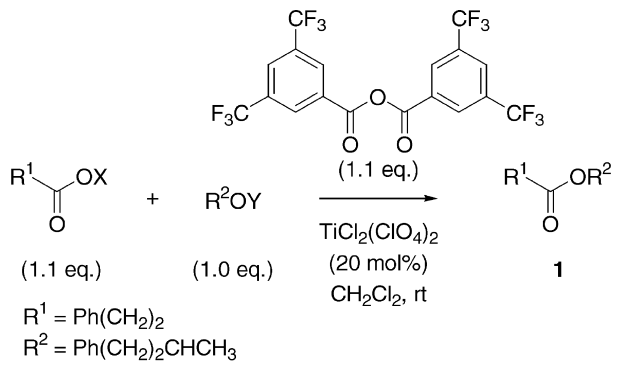
**Table 2**. Synthesis of several carboxylic esters using BTFBA




| Entry | $R^1$ | $R^2$ | $R^1COOR^2$ | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $Ph(CH_2)_2$ | $Ph(CH_2)_3$ | **3** | 91 |
| 2 | $Ph(CH_2)_2$ | $Ph(CH_2)_2CHCH_3$ | **1** | 89 |
| 3 | *c*-$C_6H_{11}$ | $Ph(CH_2)_3$ | **4** | 88 |
| 4 | *c*-$C_6H_{11}$ | $Ph(CH_2)_2CHCH_3$ | **5** | 86 |
| 5 | $^t$Bu | $Ph(CH_2)_3$ | **6** | 91 |
| 6 | $^t$Bu | $Ph(CH_2)_2CHCH_3$ | **7** | 88 |

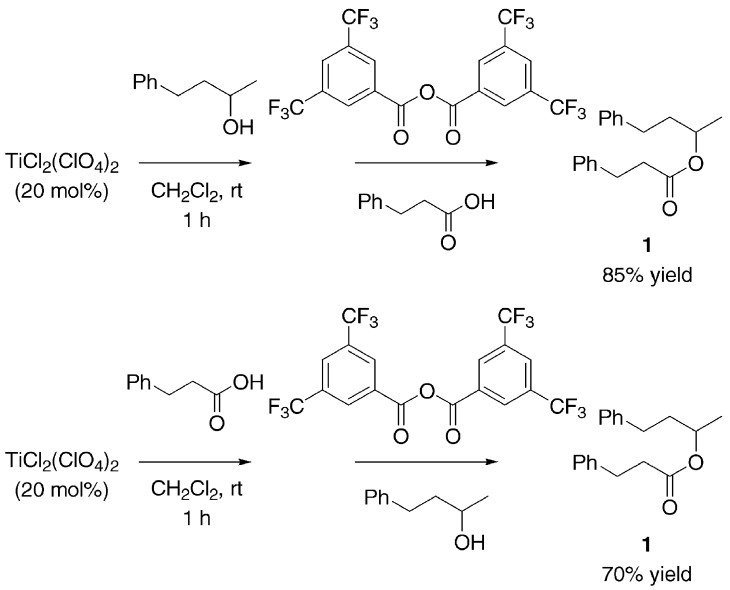
[a] Isolated yield.

**Table 3**. Synthesis of carboxylic esters using silylated or free substrates




| Entry | X | Y | Yield[a] (%) |
|---|---|---|---|
| 1 | $SiMe_3$ | $SiMe_3$ | 98 |
| 2 | $SiMe_3$ | H | 96 |
| 3 | H | $SiMe_3$ | 93 |
| 4 | H | H | 89 |

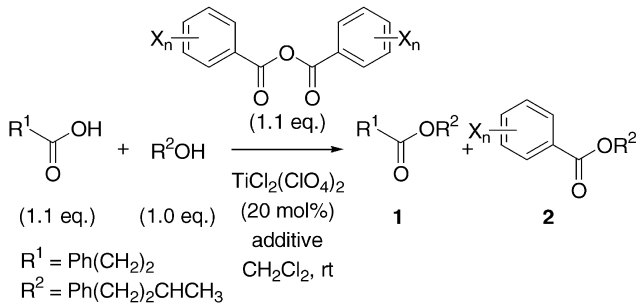
[a] Isolated yield.




**Scheme 3.** Yield of **1** using pre-treated titanium(IV) catalysts.

Furthermore, the order of addition of the free carboxylic acids and alcohols was examined to clarify the deactivation process (Scheme 3). When 4-phenyl-2-butanol was mixed with 20 mol% of $TiCl_2(ClO_4)_2$ in dichloromethane for 1 h prior to the addition of 3-phenylpropanoic acid and BTFBA, the desired ester was obtained in relatively good yield (85%). However, the titanium(IV) catalyst, which was treated with 3-phenylpropanoic acid before the esterification, gave the desired ester in 70% yield. The activity of the $TiCl_2(ClO_4)_2$ was considerably decreased in the latter case. Therefore, we next tried to employ a suitable additive which functions as a co-reagent to maintain the activity of the titanium(IV) catalyst under the influence of the free carboxylic acids.

**Table 4**. Effect of additives

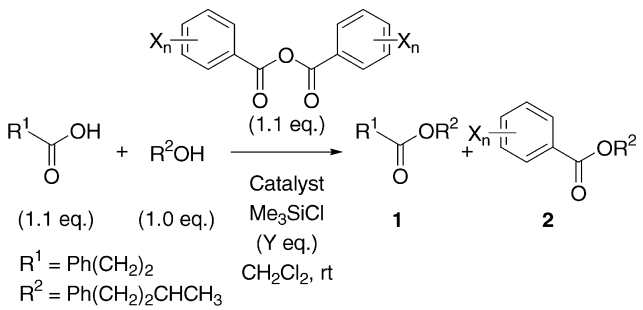



| Entry | $X_n$ | Additive | Yield[a] (%) | **1/2**[b] |
|---|---|---|---|---|
| 1 | 3-$CF_3$ | — | 87 | 180/1 |
| 2 | 3-$CF_3$ | MS 5 Å | 89 | 90/1 |
| 3 | 4-$CF_3$ | — | 88 | 180/1 |
| 4 | 4-$CF_3$ | MS 5 Å | 90 | 70/1 |
| 5 | 3,5-$(CF_3)_2$ | — | 89 | >200/1 |
| 6 | 3,5-$(CF_3)_2$ | MS 3 Å | 90 | >200/1 |
| 7 | 3,5-$(CF_3)_2$ | MS 4 Å | 78 | >200/1 |
| 8 | 3,5-$(CF_3)_2$ | MS 5 Å | 85 | 120/1 |
| 9 | 3,5-$(CF_3)_2$ | $Me_3SiCl$ (2 equiv.) | 94 | >200/1 |
| 10 | 3,5-$(CF_3)_2$ | $(Me_3Si)_2O$ (2 equiv.) | 88 | >200/1 |

[a] Isolated yield of **1**.
[b] Determined by $^1H$ NMR using a crude mixture.

First, molecular sieves (MS 5 Å) were added to the reaction mixture consisting of 3-phenylpropanoic acid and 4-phenyl-2-butanol in the presence of (3-trifluoromethyl)benzoic anhydride, TFBA or BTFBA since MS 5 Å are known to have a weak acidity. However, the reactions did not go to completion and the formation of sufficient quantities of the by-products was observed in each case (Table 4, entries 2, 4 or 8). Further screening was carried out using several ingredients such as other molecular sieves and hexamethyldisiloxane for the model reaction with BTFBA; it was found that chlorotrimethylsilane was a very effective co-reagent for keeping the activity of the titanium(IV) catalyst. In the presence of 2 mol of chlorotrimethylsilane and 1.1 mol of BTFBA, 10 mol% of $TiCl_2(ClO_4)_2$ was not deactivated during the reaction, and the desired ester was exclusively obtained in 94% yield (entry 9).

**Table 5**. Effect of catalysts and reaction conditions




| Entry | Catalyst (amount/mol%) | $X_n$ | Y | Yield[a] (%) |
|---|---|---|---|---|
| 1 | $TiCl_2(ClO_4)_2$ (10) | 3,5-$(CF_3)_2$ | 2 | 94 |
| 2 | $TiCl_2(ClO_4)_2$ (10) | 4-$CF_3$ | 2 | 95 |
| 3 | $TiCl_2(ClO_4)_2$ (10) | 4-$CF_3$ | 1 | 96 |
| 4 | $TiCl_2(ClO_4)_2$ (10) | 4-$CF_3$ | 0.5 | 97 |
| 5 | $TiCl_2(ClO_4)_2$ (10) | 4-$CF_3$ | 0.2 | 94 |
| 6 | $TiCl_2(OTf)_2$ (10) | 4-$CF_3$ | 0.2 | 78 |
| 7 | $Sn(OTf)_2$ (20) | 4-$CF_3$ | 0.2 | 78 (5)[b] |

[a] Isolated yield of **1**.
[b] Yield of 1-methyl-3-phenylpropyl 4-(trifluoromethyl)benzoate.

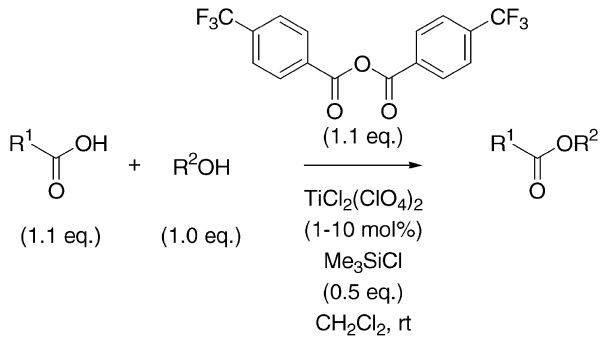
The reaction conditions were optimized using several catalysts (see Table 5). The existence of chlorotrimethylsilane was so effective that the corresponding ester was obtained in high yield without the accompanying undesired ester even though TFBA was used as the condensation reagent instead of BTFBA (entries 2–6). For example, the desired ester was exclusively produced in nearly quantitative yield when the reaction was carried out in the presence of TFBA, 10 mol% of $TiCl_2(ClO_4)_2$ and 0.5 mol of chlorotrimethylsilane (entry 4).

Various examples of the present condensation reaction are listed in Table 6. In every case, the reaction smoothly proceeded at room temperature in dichloromethane to give the corresponding esters in excellent yields from nearly equimolar amounts of free carboxylic acids and alcohols. It was also revealed that the use of 1 mol% of the catalyst was enough to produce 1-methyl-3-phenylpropyl 3-phenylpropanoate in 99% yield from the corresponding carboxylic acid and alcohol (entry 4). When using branched alcohols such as menthol and chorestanol or a hindered carboxylic acid such as pivalic acid, the corresponding carboxylic esters were also produced in high yields at room temperature (entries 6, 7, 10 or 11). The reaction of benzoic acid with primary and secondary alcohols afforded the desired alkyl benzoates with good chemoselectivities using BTFBA as the condensation reagent as shown in entries 12 and 13.

It is noted that the procedure for this synthesis is quite simple and almost pure carboxylic esters are obtained just by washing the reaction mixture with saturated aqueous $NaHCO_3$.

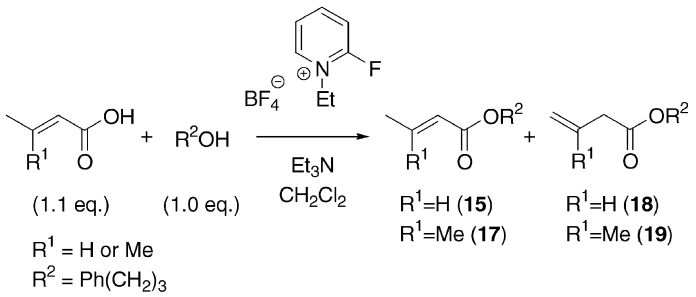
The esterification reaction of crotonic acid or 3-methyl-2-butenoic acid is a base sensitive reaction leading to the rearrangement of a double bond to form an α,β-unsaturated ester **18** or **19** even under weakly basic conditions (Scheme 4).[5b,8] For example, the esterification reaction of crotonic acid with 3-phenylpropanol using 1-ethyl-2-fluoropyridinium tetrafluoroborate and triethylamine produced a mixture of the desired ester and rearrangement product (76%, **15/18**=4:1). A similar result was also observed in the case of 3-methyl-2-butenoic acid (50%, **17/19**=1:2). Therefore, the esterification reaction between equimolar amounts of crotonic acid and alcohol has been generally carried out using DCC or thionyl chloride. It is also noted that the present method was successfully applied to the synthesis of alkyl crotonate and alkyl 3-methyl-2-butenoate from nearly equimolar amounts of carboxylic acids and alcohols under mild conditions. When 10 mol% of $TiCl_2(ClO_4)_2$ was used in the present experiment, no

**Table 6**. Synthesis of various carboxylic esters using TFBA or BTFBA



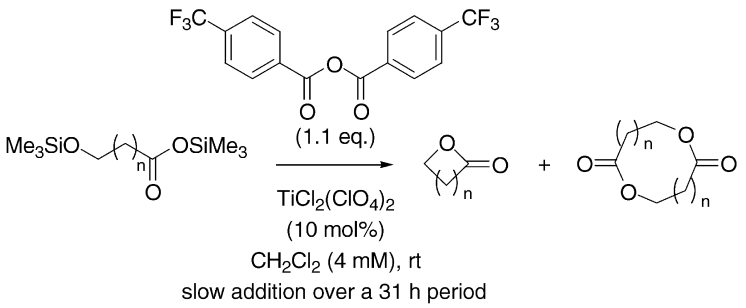

| Entry | $R^1$ | $R^2$ | $R^1COOR^2$ | Time (h) | Yield[a] (%) |
|---|---|---|---|---|---|
| 1 | $Ph(CH_2)_2$ | Bn | **8** | 12 | 93 |
| 2 | $Ph(CH_2)_2$ | $CH_2$═$CHCH_2$ | **9** | 0.5 | 92 |
| 3 | $Ph(CH_2)_2$ | $Ph(CH_2)_3$ | **3** | 0.5 | 96 |
| 4 | $Ph(CH_2)_2$ | $Ph(CH_2)_2CHCH_3$ | **1** | 13 | 97 (99)[b] |
| 5 | $Ph(CH_2)_2$ | *c*-$C_6H_{11}$ | **10** | 12 | 93 |
| 6 | $Ph(CH_2)_2$ | Menthyl | **11** | 13 | 93 |
| 7 | $Ph(CH_2)_2$ | 5α-Chorestan-3β-yl | **12** | 17 | 90 |
| 8 | *c*-$C_6H_{11}$ | $Ph(CH_2)_3$ | **4** | 0.5 | 96 |
| 9 | *c*-$C_6H_{11}$ | $Ph(CH_2)_2CHCH_3$ | **5** | 3 | 95 |
| 10 | $^t$Bu | $Ph(CH_2)_3$ | **6** | 0.5 | 95 |
| 11 | $^t$Bu | $Ph(CH_2)_2CHCH_3$ | **7** | 16 | 95 |
| 12[c] | Ph | $Ph(CH_2)_3$ | **13** | 12 | 90 (1.1)[d] |
| 13[c] | Ph | $Ph(CH_2)_2CHCH_3$ | **14** | 12 | 93 (1.5)[e] |
| 14 | (*E*)-$CH_3CH$═$CH$ | $Ph(CH_2)_3$ | **15** | 12 | 93 |
| 15 | (*E*)-$CH_3CH$═$CH$ | $Ph(CH_2)_2CHCH_3$ | **16** | 12 | 93 |
| 16 | $(CH_3)_2CH$═$CH$ | $Ph(CH_2)_3$ | **17** | 12 | 95 |

[a] Isolated yield. 10 mol% of catalyst was used.
[b] 1 mol% of catalyst was used.
[c] BTFBA was used instead of TFBA.
[d] Yield of 3-phenylpropyl 3,5-bis(trifluoromethyl)benzoate.
[e] Yield of 1-methyl-3-phenylpropyl 3,5-bis(trifluoromethyl)benzoate.




**Scheme 4.** Base-induced rearrangement in the synthesis of alkyl crotonate and 3-methyl-2-butenoate.

**Table 7**. Synthesis of lactones from silyl ω-siloxycarboxylates using TFBA




| Entry | *n* | Yield[a] (%) (ring number) | |
|---|---|---|---|
| | | Monomer | Dimer |
| 1 | 10 | 75 (13) | 4 (26) |
| 2 | 13 | 89 (16) | 2 (32) |

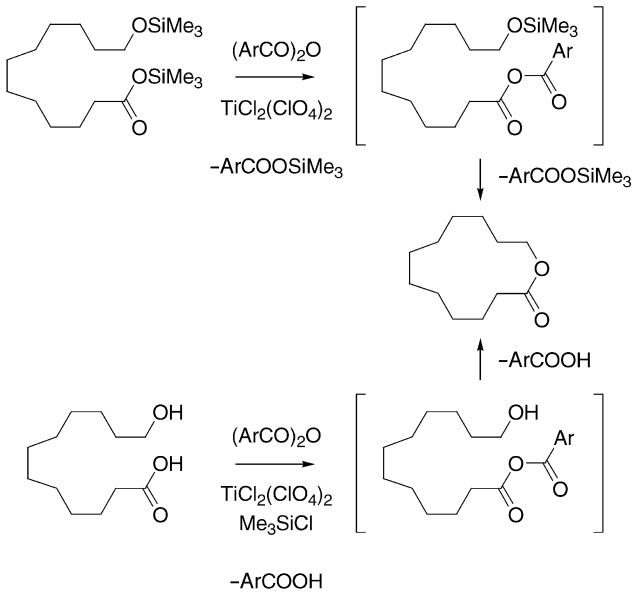
[a] Isolated yield.

rearranged product was isolated at all and the desired esters were obtained in high yields (Table 6, entries 14–16). These examples show the mildness of the conditions in the present esterification reaction.

## 2.2. Lactonization via mixed-anhydrides using benzoic anhydrides

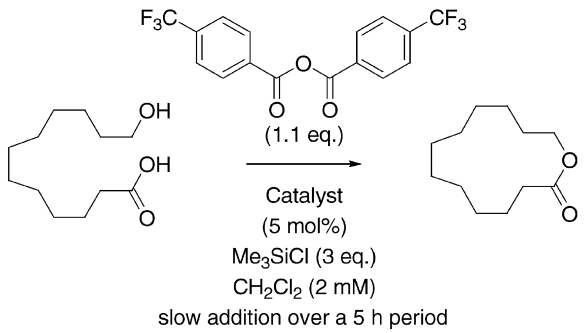
Several macrolide antibiotics have become important therapeutic agents in clinical medicine. As a result, numerous derivatives of various macrolactones have been synthesized and the discovery of new macrolide antibiotics has attracted our attention over the past two decades.[9] The chemical synthesis of macrolactones has made great progress due to the development of efficient methods for the ring closure from ω-hydroxycarboxylic acids (*seco*-acids) or their activated derivatives. Though a variety of methods have been reported for the synthesis of macrolactones,[1a] there are a few reactions which efficiently proceed under acidic conditions.[10] Recently, we developed an effective method for the preparation of macrolactones starting from the silyl derivatives of *seco*-acids via formation of the corresponding mixed-anhydrides.[5c] Namely, in the presence of TFBA and 10 mol% of $TiCl_2(ClO_4)_2$, the cyclization of trimethylsilyl ω-(trimethylsiloxy)carboxylates smoothly takes place at room temperature to afford the corresponding lactones in good to high yields as shown in Table 7.

To avoid deactivation of the titanium(IV) catalyst during the addition of the substrates to the reaction mixture, silyl derivatives of *seco*-acids were employed as precursors for the present cyclization instead of using free ω-hydroxycarboxylic acids. On the other hand, the equimolar condensation reaction between free carboxylic acids and




**Scheme 5.** Synthesis of macroactones starting from silyl ω-siloxycarboxylates or ω-hydroxycarboxylic acids using benzoic anhydrides as the condensation reagents.

**Table 8**. Effect of catalysts and reaction temperature

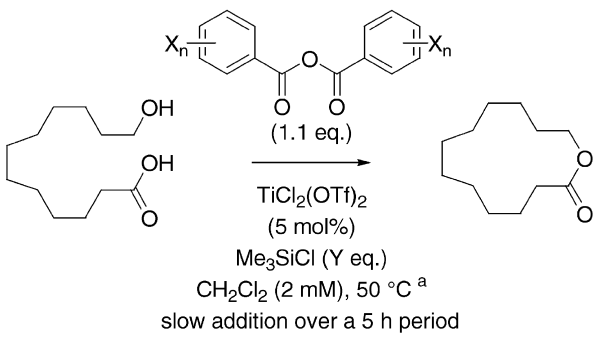



| Entry | Catalyst | Temp.[a] (°C) | Yield[b] (%) | |
|---|---|---|---|---|
| | | | Monomer | Dimer |
| 1 | $TiCl_2(ClO_4)_2$ | rt | 68 | 2 |
| 2 | $TiCl_2(OTf)_2$ | rt | 29 | 1 |
| 3 | $TiCl_2(OTf)_2$ | 40 | 81 | 4 |
| 4 | $TiCl_2(OTf)_2$ | 50 | 83 | 5 |
| 5 | $TiCl(OTf)_3$ | 50 | 77 | 3 |
| 6 | $TiCl_2(OTf)_2$ | 60 | 55 | 8 |

[a] Bath temperature.
[b] Isolated yield.

alcohols had been established in the former section by the combined use of TFBA and a catalytic amount of $TiCl_2(ClO_4)_2$ together with chlorotrimethylsilane, therefore, it was then anticipated that the direct lactonization of free ω-hydroxycarboxylic acids would function more efficiently by the promotion of Lewis acids under the influence of a co-catalyst (Scheme 5). In this section, a useful method for the preparation of macrolactones directly from ω-hydroxycarboxylic acids will be described by the combined use of TFBA and a catalytic amount of $TiCl_2(ClO_4)_2$ or $TiCl_2(OTf)_2$ together with chlorotrimethylsilane.

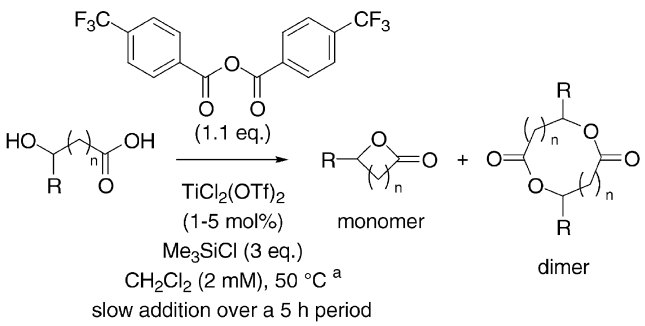
**Table 9**. Effect of benzoic anhydrides and amounts of chlorotrimethylsilane




| Entry | X | Y | Yield[b] (%) | |
|---|---|---|---|---|
| | | | Monomer | Dimer |
| 1 | 4-$CF_3$ | 0 | 31 | 3 |
| 2 | 4-$CF_3$ | 2 | 60 | 4 |
| 3 | 4-$CF_3$ | 3 | 83 | 5 |
| 4 | 4-$CF_3$ | 10 | 80 | 6 |
| 5 | 3,5-$(CF_3)_2$ | 3 | 51 | 7 |
| 6 | 4-F | 3 | 44 | 7 |

[a] Bath temperature.
[b] Isolated yield.

**Table 10**. Synthesis of lactones from ω-hydroxycarboxylic acids using TFBA




| Entry | R | *n* | Yield[b] (%) (ring number) | |
|---|---|---|---|---|
| | | | Monomer | Dimer |
| 1 | H | 10 | 83 (13) | 5 (26) |
| 2 | $C_6H_{13}$ | 10 | 91 (13) | 3 (26) |
| 3[c] | $C_6H_{13}$ | 10 | 83 (13) | 8 (26) |
| 4 | H | 11 | 80 (14) | 3 (28) |
| 5 | H | 12 | 89 (15) | 2 (30) |
| 6 | H | 13 | 88 (16) | 5 (32) |
| 7[c] | H | 13 | 63 (16) | 5 (32) |
| 8 | H | 14 | 88 (17) | 1 (34) |

[a] Bath temperature.
[b] Isolated yield. 5 mol% of catalyst was used.
[c] 1 mol% of catalyst was used.

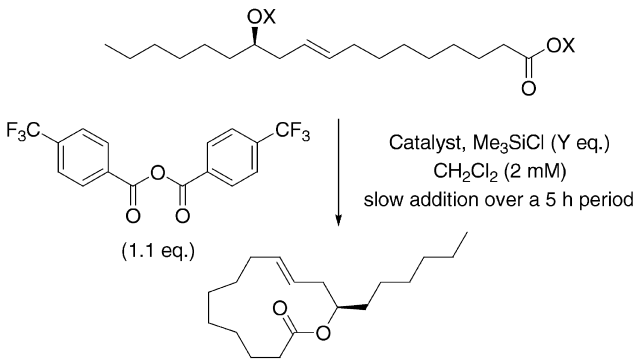
When the mixture of 12-hydroxydodecanoic acids and TFBA in dichloromethane was added over a 5 h period to the suspension of 5 mol% of $TiCl_2(ClO_4)_2$ and 3 mol of chlorotrimethylsilane in dichloromethane at room temperature, the desired macrolactone was obtained in 68% yield. In order to improve the yield of the monomeric lactone, several catalysts and reaction temperatures were examined (Table 8). As shown in entry 4, the best result was attained when using $TiCl_2(OTf)_2$ as the catalyst in gently refluxing dichloromethane.

Next, the effect of the amount of chlorotrimethylsilane and the kind of substituent(s) in benzoic anhydrides was screened under the optimized reaction conditions. It was found that the existence of chlorotrimethylsilane was essential to this reaction in order to maintain the activity of the titanium(IV) catalyst, and the use of 3 mol of chlorotrimethylsilane was enough to provide a good result for the production of the monomeric 13-membered ring lactone (see Table 9, entry 3).

Several examples of the present cyclization reaction are listed in Table 10. In entries 4–6 and 8, macrolactones including over 13-membered rings were obtained in higher yields compared with those of the previously reported methods. A 13-membered ring lactone derived from a branched *seco*-acid was also isolated in 91% yield (entry 2), and the reaction was effectively accelerated using only 1 mol% of $TiCl_2(OTf)_2$ together with chlorotrimethylsilane as shown in entry 3.

Even for the labile *seco*-acids, the reactions smoothly proceeded to afford the corresponding lactones in high yields. (+)-(*E*)-9-Octadecen-12-olide ((*R*)-ricinelaidic acid lactone)[11] and (+)-(*Z*)-9-octadecen-12-olide ((*R*)-ricinoleic

**Table 11**. Synthesis of (*R*)-ricinelaidic acid lactone using TFBA




(*R*)-ricinelaidic acid lactone

| Entry | X | Catalyst (amount/mol%) | Y | Temp.[a] (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H | $TiCl_2(OTf)$ (5) | 3 | 50 | 89 |
| 2 | H | $TiCl_2(ClO_4)_2$ (5) | 3 | rt | 92 |
| 3 | $Me_3Si$ | $TiCl_2(ClO_4)_2$ (10) | 0 | rt | 73 |

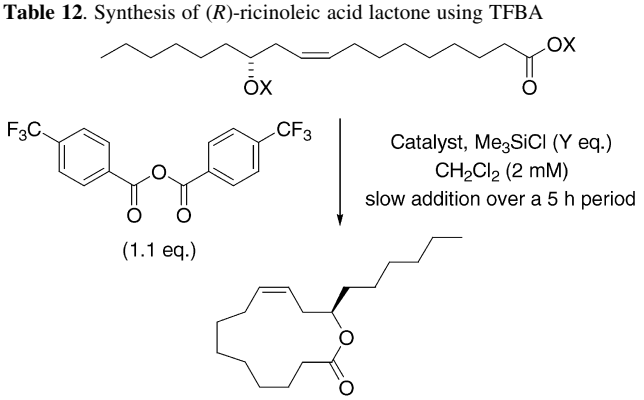
[a] Bath temperature.
[b] Isolated yield.

acid lactone)[11b,12] were respectively obtained in high yields employing 5 mol% of $TiCl_2(OTf)_2$ without any accompanying isomerization of the double bond and also racemization (Tables 11 and 12, entry 1). $TiCl_2(ClO_4)_2$ is an equally effective catalyst in these cases to produce the desired macrolactones in high yields at room temperature (entry 2). Furthermore, these unsaturated macrolides were also produced from the corresponding trimethylsilyl ω-(trimethylsiloxy)carboxylates in the presence of TFBA and a catalytic amount of $TiCl_2(ClO_4)_2$ at room temperature without using chlorotrimethylsilane as an additive (entry 3).

## 2.3. Synthesis of the 8-membered ring lactone moiety of cephalospoloride D

Cephalosporolide D (**22**), a fungus metabolite, was isolated

**Table 12**. Synthesis of (*R*)-ricinoleic acid lactone using TFBA

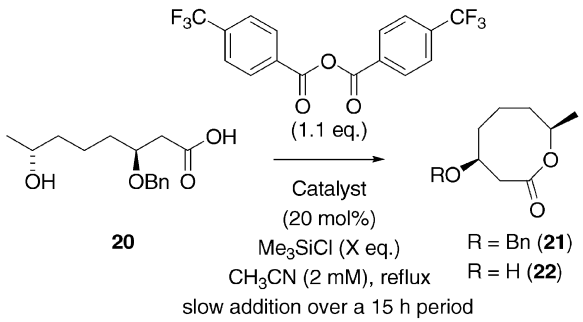



(*R*)-ricinoleic acid lactone

| Entry | X | Catalyst (amount/mol%) | Y | Temp.[a] (°C) | Yield[b] (%) |
|---|---|---|---|---|---|
| 1 | H | $TiCl_2(OTf)_2$ (5) | 3 | 50 | 83 |
| 2 | H | $TiCl_2(ClO_4)_2$ (5) | 3 | rt | 83 |
| 3 | $Me_3Si$ | $TiCl_2(ClO_4)_2$ (10) | 0 | rt | 72 |

[a] Bath temperature.
[b] Isolated yield.

**Table 13**. Synthesis of an 8-membered ring lactone using TFBA




| Entry | Catalyst | X | Yield[a] (%) | Recovery (%) |
|---|---|---|---|---|
| 1 | $TiCl_2(OTf)_2$ | 3 | 2 | 0 |
| 2 | $Sc(OTf)_3$ | 0 | 44 | 31 |
| 3 | $Zr(OTf)_4$ | 0 | 20 | 48 |
| 4 | $Hf(OTf)_4$ | 0 | 67 | 17 |

[a] Isolated yield.

in 1985 from *Cephalosporium aphidicola* together with related compounds by Hanson et al.[13] The structure contained two chiral centers and an unusual saturated 8-membered ring lactone moiety. A similar characteristic structure possessing a medium-sized lactone moiety was also found in octalactin A which exhibited a potent cytotoxic activity against some tumor cell lines.[14]

Next, lactonization of a *seco*-acid **20**, a synthetic intermediate of cephalosporolide D, was tried using the present mixed-anhydride method with a catalytic amount of a Lewis acid in the presence of TFBA.[7] First, the reaction was carried out by the promotion of a catalytic amount of $TiCl_2(OTf)_2$ together with chlorotrimethylsilane, however, several unidentifiable products were obtained and the 8-membered ring lactone **21** was obtained in only 2% yield. Since Yamamoto et al. reported that $Sc(OTf)_3$ effectively functions with this mixed-anhydride method producing medium sized lactones,[2f] we then utilized $Sc(OTf)_3$ as a catalyst combined with TFBA. The cyclization reaction of **20** was actually catalyzed to afford the desired lactone **21** in 44% yield, and 31% of **20** was recovered. To improve the yield of the desired 8-membered ring lactone, we re-investigated other Lewis acids consisting of metals in group IV as shown in Table 13. Although the reaction was not facilitated using $Zr(OTf)_4$, it was found that $Hf(OTf)_4$ is very effective for the promotion of the cyclization to produce the desired 8-membered ring lactone **21** in 67% yield.[15] Since 17% of the starting *seco*-acid **20** was recovered after the reaction, conversion yield of **21** reached 81% based on the consumed **20**. It is noted that this cyclization exclusively gave the monomeric lactone and the corresponding diolide was not formed at all.[16] Thus, an efficient method for the preparation of the synthetic precursor of cephalosporolide D was established via the effective construction of the 8-membered ring lactone moiety.

## 3. Conclusion

In summary, it is determined that the mixed-anhydride

method using a substituted benzoic anhydride provided an efficient method for the preparation of various derivatives of carboxylic acids.[17] As an example of this synthetic methodology, we demonstrated the combined use of BTFBA or TFBA and a catalytic amount of $TiCl_2(ClO_4)_2$ together with chlorotrimethylsilane for the preparation of carboxylic esters from free carboxylic acids and alcohols. An efficient and convenient method for the preparation of lactones from ω-hydroxycarboxylic acids or trimethylsilyl ω-(trimethylsiloxy)carboxylates was also established using the substituted benzoic anhydride and a catalytic amount of a Lewis acid such as $TiCl_2(ClO_4)_2$, $TiCl_2(OTf)_2$ or $Hf(OTf)_4$ under mild conditions.

## 4. Experimental

### 4.1. General methods

All melting points were measured on a Yanaco MP-S3 micro melting point apparatus. Optical rotations were recorded on a Jasco DIP-360 or a Jasco P-1020 digital polarimeter. IR spectra were recorded on a Horiba FT-300 infrared spectrometer. $^1H$ and $^{13}C$ NMR spectra were recorded on a JEOL JNM-EX270L, a JEOL JNM-AL300 or a JEOL JNM-LA500 spectrometer with tetramethylsilane (TMS), chloroform (in chloroform-*d*) or benzene (in benzene-$d_6$) as internal standard. HPLC was carried out using a Hitachi LC-Organizer, L-4000 UV Detector, L-6200 Intelligent Pump, and D-2500 Chromato-Integrator. High-resolution mass spectra were recorded on a JEOL JMS-SX102A instrument using 4-nitrobenzyl alcohol as a matrix. Column chromatography was performed on Silica gel 60 (Merck) or Wakogel B5F. Thin layer chromatography was performed on Wakogel B5F.

All reactions were carried out under argon atmosphere in dried glassware, unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å, benzene and toluene were distilled from diphosphorus pentoxide, and dried over MS 4 Å, and THF and diethyl ether were distilled from sodium/benzophenone immediately prior to use.

### 4.2. Starting materials

All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc. or Aldrich Chemical Co., Inc., and used without further purification unless otherwise noted. Titanium dichlorobis(trifluoromethanesulfonate) was prepared by the literature method.[18]

**4.2.1. 4-(Trifluoromethyl)benzoic anhydride (TFBA).** 4-(Trifluoromethyl)benzoic anhydride was purchased from Tokyo Kasei Kogyo Co., Ltd. (TCI) or synthesized from 4-(trifluoromethyl)benzoic acid and 4-(trifluoromethyl)benzoyl chloride. To a mixture of 4-(trifluoromethyl)benzoic acid (13.7 g, 72.0 mmol) and 4-(trifluoromethyl)benzoyl chloride (15.0 g, 72.0 mmol) in dichloromethane (144 mL) at 0 °C was added pyridine (6.11 mL, 75.6 mmol). The reaction mixture was stirred for 21 h at room temperature and then cold water (50 mL) was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by recrystallization from dichloromethane to afford 23.2 g (89%) of TFBA as a white solid: mp 132–133 °C; IR (KBr) 1732, 1795 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 7.79 (4H, d, $J$=8.1 Hz), 8.26 (4H, d, $J$=8.1 Hz); $^{13}C$ NMR ($CDCl_3$) $\delta$ 123.2 (q, $J$=272.2 Hz), 125.9 (q, $J$=3.9 Hz), 130.8, 131.5, 135.9 (q, $J$=33.0 Hz), 160.6.

**4.2.2. 3,5-Bis(trifluoromethyl)benzoic anhydride (BTFBA).** A mixture of 3,5-bis(trifluoromethyl)benzoic acid (5.2 g, 20 mmol) and thionyl chloride (9.5 g, 80 mmol) was stirred for 4 h at 80 °C. The solvent and thionyl chloride were distillated under reduced pressure at 50 °C and then dichloromethane (80 mL), 3,5-bis(trifluoromethyl)benzoic acid (5.2 g, 20.0 mmol) and a solution of pyridine (1.7 mL, 21 mmol) in dichloromethane (40 mL) were successively added at 0 °C. After the reaction mixture had been stirred for 21 h at room temperature, cooled water (100 mL) was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by recrystallization from dichloromethane to afford 7.0 g (70%) of BTFBA as a white solid: mp 104.5–105 °C; IR (KBr) 1712, 1805 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 8.23 (2H, s), 8.58 (4H, s); $^{13}C$ NMR ($CDCl_3$) $\delta$ 122.4 (q, $J$=272.8 Hz), 127.2 (q, $J$=3.9 Hz), 130.4 (q, $J$=4.5 Hz), 131.2, 133.1 (q, $J$=34.4 Hz), 158.2.

### 4.3. Typical experimental procedure for the synthesis of carboxylic esters using TFBA

A typical experimental procedure is described for the reaction of 3-phenylpropanoic acid with 4-phenyl-2-butanol; to a suspension of $AgClO_4$ (7.7 mg, 0.037 mmol) in dichloromethane (10.0 mL) were added a solution of $TiCl_4$ in toluene (0.50 M, 0.037 mL, 0.019 mmol) and chlorotrimethylsilane (0.118 mL, 0.930 mmol). After the reaction mixture had been stirred for 30 min, a solution of TFBA (740 mg, 2.04 mmol) and 3-phenylpropanoic acid (307 mg, 2.04 mmol) in dichloromethane (7.5 mL) and a solution of 4-phenyl-2-butanol (278 mg, 1.85 mmol) in dichloromethane (2.5 mL) were successively added. The reaction mixture was stirred for 3 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford 518 mg (99%) of 1-methyl-3-phenylpropyl 3-phenylpropanoate with an excellent chemoselectivity (>200:1).

**4.3.1. 1-Methyl-3-phenylpropyl 3-phenylpropanoate[5b] (1).** IR (neat) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.21 (3H, d, $J$=6.3 Hz), 1.72–1.96 (2H, m), 2.51–2.69 (4H, m), 2.95 (2H, t, $J$=7.6 Hz), 4.94 (1H, m), 7.11–7.31 (10H, m). Found: C, 80.74; H, 7.99%. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85%.

**4.3.2. 3-Phenylpropyl 3-phenylpropanoate[19] (3).** IR (neat) 1735 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.91 (2H, m), 2.62

(4H, m), 2.95 (2H, t, $J$=7.8 Hz), 4.08 (2H, t, $J$=6.6 Hz), 7.13–7.31 (10H, m). Found: C, 80.35; H, 7.77%. Calcd for $C_{18}H_{20}O_2$: C, 80.56: H,7.51%.

**4.3.3. 3-Phenylpropyl cyclohexanecarboxylate[5b] (4).** IR (neat) 1732 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.05–2.40 (13H, m), 2.65 (2H, t, $J$=8.0 Hz), 4.00 (2H, t, $J$=6.0 Hz), 7.15 (5H, s). Found: C, 77.89; H, 8.90%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

**4.3.4. 1-Methyl-3-phenylpropyl cyclohexanecarboxylate[5b] (5).** IR (neat) 1728 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.15 (3H, d, $J$=6.0 Hz), 1.25–2.25 (13H, m), 2.25–2.80 (2H, m), 4.85 (1H, m), 7.15 (5H, s). Found: C, 78.18; H, 9.07%. Calcd for $C_{17}H_{24}O_2$: C, 78.42; H, 9.29%.

**4.3.5. 3-Phenylpropyl 2,2-dimethylpropanoate[5b] (6).** IR (neat) 1728 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.26 (9H, s), 1.97–2.03 (2H, m), 2.74 (2H, t, $J$=7.6 Hz), 4.12 (2H, t, $J$=6.3 Hz), 7.21–7.34 (5H, m). Found: C, 76.06; H, 9.21%. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%.

**4.3.6. 1-Methyl-3-phenylpropyl 2,2-dimethylpropanoate[5b] (7).** IR (neat) 1726 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22 (9H, s), 1.25 (3H, d, $J$=6.3 Hz), 1.73–2.00 (2H, m), 2.54–2.74 (2H, m), 4.91 (1H, m), 7.15–7.31 (5H, m). Found: C, 76.70; H, 9.52%. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46%.

**4.3.7. Benzyl 3-phenylpropanoate[20] (8).** IR (neat) 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.67 (2H, t, $J$=7.8 Hz), 2.96 (2H, t, $J$=7.8 Hz), 5.10 (2H, s), 7.12–7.40 (10H, m).

**4.3.8. Allyl 3-phenylpropanoate (9).** IR (neat) 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 2.66 (2H, t, $J$=7.8 Hz), 2.97 (2H, t, $J$=7.8 Hz), 4.57 (2H, td, $J$=1.3, 5.6 Hz), 5.21 (1H, tdd, $J$=1.3, 1.7, 10.6 Hz), 5.28 (1H, tdd, $J$=1.3, 1.7, 17.2 Hz), 5.89 (1H, tdd, $J$=5.6, 10.6, 17.2 Hz), 7.10–7.35 (5H, m); HR MS: calcd for $C_{12}H_{15}O_2$ ($M+H^+$) 191.1072, found 191.1073.

**4.3.9. Cyclohexyl 3-phenylpropanoate[21] (10).** IR (neat) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.10–1.19 (8H, m), 1.80 (2H, td, $J$=5.4, 9.1 Hz), 2.60 (2H, t, $J$=7.8 Hz), 2.95 (2H, t, $J$=7.8 Hz), 4.75 (1H, tt, $J$=4.4, 9.1 Hz), 7.09–7.38 (5H, m).

**4.3.10. (−)-Mentyl 3-phenylpropanoate (11).** $[\alpha]_D^{28}$=−58.0° (c 1.67, $CHCl_3$); IR (neat) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.62 (3H, d, $J$=6.9 Hz), 0.68–1.75 (14H, m), 1.78–1.93 (1H, m), 2.53 (2H, t, $J$=7.8 Hz), 2.87 (2H, t, $J$=7.8 Hz), 4.59 (1H, dt, $J$=4.6, 10.9 Hz), 7.05–7.26 (5H, m); HR MS: calcd for $C_{19}H_{29}O_2$ ($M+H^+$) 289.2167, found 289.2177.

**4.3.11. (+)-5α-Cholestan-3β-yl 3-phenylpropanoate (12).** Mp. 96–98 °C; $[\alpha]_D^{28}$=+13.2° (c 1.00, $CHCl_3$); IR (KBr) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.52–2.02 (46H, m), 2.58 (2H, t, $J$=7.8 Hz), 2.93 (2H, t, $J$=7.8 Hz), 4.69 (1H, tt, $J$=5.6, 11.2 Hz), 7.07–7.36 (5H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 12.06, 12.20, 18.65, 21.19, 22.55, 22.81, 23.83, 24.19, 27.44, 28.00, 28.23, 28.59, 31.05, 31.97, 33.98, 35.44, 35.78, 36.16, 36.26, 36.73, 39.50, 39.97, 42.57, 44.62, 54.20, 56.25, 56.39, 73.77, 126.15, 128.30, 128.41, 140.61, 172.42; HR MS: calcd for $C_{36}H_{57}O_2$ ($M+H^+$) 521.4358, found 521.4360.

**4.3.12. 3-Phenylpropyl benzoate[5b] (13).** IR (neat) 1718 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 2.23 (2H, m), 2.77 (2H, t, $J$=8 Hz), 4.27 (2H, t, $J$=6 Hz), 7.05–7.54 (8H, m), 7.85–8.10 (2H, m). Found: C, 79.69; H, 6.97%. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

**4.3.13. 1-Methyl-3-phenylpropyl benzoate[5b] (14).** IR (neat) 1716 $cm^{-1}$; $^1H$ NMR ($CCl_4$) $\delta$ 1.44 (3H, d, $J$=6 Hz), 1.74–2.23 (2H, m), 2.55–2.90 (2H, m), 5.15 (1H, m), 7.05–7.54 (8H, m), 7.98 (2H, dd, $J$=8, 2 Hz). Found: C, 80.47; H, 7.22%. Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13%.

### 4.4. Typical experimental procedure for the synthesis of α,β-unsaturated esters

The same procedure as typical experimental procedure for the catalytic esterification reaction except for using phosphate buffer (pH=7) as a reagent for quenching.

**4.4.1. 3-Phenylpropyl (*E*)-crotonate[5b] (15).** IR (neat) 1722 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.87 (3H, dd, $J$=6.9, 1.7 Hz), 1.99 (2H, tt, $J$=7.6, 6.6 Hz), 2.70 (2H, t, $J$=7.6 Hz), 4.14 (2H, t, $J$=6.6 Hz), 5.85 (1H, dq, $J$=15.0, 1.7 Hz), 6.96 (1H, dq, $J$=15.0, 6.9 Hz), 7.15–7.31 (5H, m). Found: C, 76.21; H, 8.00%. Calcd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.90%.

**4.4.2. 1-Methyl-3-phenylpropyl (*E*)-crotonate (16).** IR (neat) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.27 (3H, d, $J$=6.3 Hz), 1.70–2.06 (2H, m), 1.87 (3H, dd, $J$=1.8, 6.9 Hz), 2.50–2.76 (2H, m), 4.99 (1H, tq, $J$=6.3, 6.3 Hz), 5.84 (1H, qd, $J$=1.8, 15.4 Hz), 6.96 (1H, qd, $J$=6.9, 15.4 Hz), 7.10–7.34 (5H, m); HR MS: calcd for $C_{14}H_{19}O_2$ ($M+H^+$) 219.1385, found 219.1387.

**4.4.3. 3-Phenylpropyl 3-methyl-2-butenoate[5b] (17).** IR (neat) 1716 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.88 (3H, d, $J$=1.0 Hz), 1.95 (2H, tt, $J$=7.9, 6.6 Hz), 2.17 (3H, d, $J$=1.0 Hz), 2.69 (2H, t, $J$=7.9 Hz), 4.10 (2H, t, $J$=6.6 Hz), 5.69 (1H, q, $J$=1.3 Hz), 7.14–7.30 (5H, m). Found: C, 76.86; H, 8.37%. Calcd for $C_{14}H_{18}O_2$: C, 77.03; H, 8.31%.

### 4.5. Typical experimental procedure for the synthesis of lactones from trimethylsilyl ω-(trimethylsiloxy)-carboxylates

A typical experimental procedure is described for the synthesis of pentadecan-15-olide; to a suspension of $AgClO_4$ (16.6 mg, 0.080 mmol) in dichloromethane (90 mL) was added a solution of $TiCl_4$ in toluene (0.5 M, 0.080 mL, 0.040 mmol). After the reaction mixture had been stired for 30 min, a solution of trimethylsilyl 15-(trimethylsiloxy)pentadecanoate (161 mg, 0.400 mmol) and TFBA (145 mg, 0.400 mmol) in dichloromethane (10 mL) was slowly added to the suspension including $TiCl_2(ClO_4)_2$ with a mechanically driven syringe over a 31 h period at room temperature. The reaction mixture was additionally stirred for 3 h at room temperature and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture

was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford 85.6 mg (89%) of pentadecan-15-olide and 3.8 mg (2%) of diolide.

### 4.6. Typical experimental procedure for the synthesis of lactones from ω-hydroxycarboxylic acids

A typical experimental procedure is described for the synthesis of octadecan-12-olide; to a suspension of $TiCl_2(OTf)_2$ (10.8 mg, 0.026 mmol) and chlorotrimethylsilane (0.2 mL, 1.57 mmol) in gently refluxing dichloromethane (220 mL) was added a solution of 12-hydroxyoctadecanoic acid (157.6 mg, 0.524 mmol) and TFBA (209.5 mg, 0.578 mmol) in dichloromethane (40 mL) with a mechanically driven syringe over a 5 h period. After addition of the solution, the reaction mixture was concentrated to ca. 20 mL by evaporation of the solvent under reduced pressure and then saturated aqueous sodium hydrogencarbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford 135.1 mg (91%) of octadecan-12-olide and 9.4 mg (3%) of diolide.

**4.6.1. Dodecan-12-olide[2f] (13-membered ring lactone).** IR (neat) 1734 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.23–1.48 (14H, m), 1.60–1.73 (4H, m), 2.33–2.38 (2H, m), 4.15 (2H, dd, $J$=4.0, 5.1 Hz); EI MS: calcd for $C_{12}H_{22}O_2$ ($M^+$) 198, found 198.

**4.6.2. Octadecan-12-olide[12c] (12-hydroxystearic acid lactone).** IR (neat) 1730 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.87 (3H, t, $J$=6.7 Hz), 1.17–1.80 (28H, m), 2.24 (1H, ddd, $J$=3.9, 9.0, 12.3 Hz), 2.43 (1H, ddd, $J$=3.6, 8.1, 12.3 Hz), 4.92 (1H, dddd, $J$=2.2, 4.3, 6.5, 8.9 Hz); EI MS: calcd for $C_{18}H_{34}O_2$ ($M^+$) 282, found 282.

**4.6.3. Tridecan-13-olide[2f] (14-membered ring lactone).** IR (neat) 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.19–1.50 (16H, m), 1.58–1.72 (4H, m), 2.35–2.39 (2H, m), 4.14 (2H, dd, $J$=4.5, 5.3 Hz); EI MS: calcd for $C_{13}H_{24}O_2$ ($M^+$) 212, found 212.

**4.6.4. Tetradecan-14-olide[2f] (15-membered ring lactone).** IR (neat) 1728 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.19–1.48 (18H, m), 1.56–1.73 (4H, m), 2.32–2.37 (2H, m), 4.13 (2H, t, $J$=4.1, 5.3 Hz); EI MS: calcd for $C_{14}H_{26}O_2$ ($M^+$) 226, found 226.

**4.6.5. Pentadecan-15-olide[2f] (16-membered ring lactone).** IR (neat) 1740 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.24–1.49 (20H, m), 1.56–1.72 (4H, m), 2.33 (2H, dd, $J$=6.6, 7.1 Hz), 4.13 (2H, dd, $J$=5.4, 5.6 Hz); EI MS: calcd for $C_{15}H_{28}O_2$ ($M^+$) 240, found 240.

**4.6.6. Hexadecan-16-olide[2f] (17-membered ring lactone).** IR (neat) 1736 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 1.22–1.45 (22H, m), 1.55–1.71 (4H, m), 2.32 (2H, dd, $J$=6.6, 6.9 Hz), 4.12 (2H, t, $J$=5.6 Hz); EI MS: calcd for $C_{16}H_{30}O_2$ ($M^+$) 254, found 254.

**4.6.7. (+)-(*E*)-9-Octadecen-12-olide[11] ((*R*)-ricinelaidic acid lactone).** $[\alpha]_D^{26}$=+41.3° (c 1.85, $CHCl_3$); IR (neat) 1732 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.88 (3H, t, $J$=6.6 Hz), 1.19–1.71 (20H, m), 2.06–2.55 (6H, m), 4.92–5.00 (1H, m), 5.33–5.53 (2H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.0, 22.5, 23.4, 24.5, 25.6, 25.7, 26.1, 27.3, 29.1, 29.5, 31.7, 31.8, 33.8, 35.2, 73.8, 124.8, 132.4, 174.4; EI MS: calcd for $C_{18}H_{32}O_2$ ($M^+$) 280, found 280.

**4.6.8. (+)-(*Z*)-9-Octadecen-12-olide[11b,12] ((*R*)-ricinoleic acid lactone).** $[\alpha]_D^{28}$=+32.0° (c 1.77, $CHCl_3$); IR (neat) 1732 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$ 0.80 (3H, t, $J$=7.0 Hz), 1.10–1.70 (20H, m), 2.06–2.55 (6H, m), 4.92–5.00 (1H, m), 5.13–5.33 (2H, m); $^{13}C$ NMR ($CDCl_3$) $\delta$ 14.0, 22.5, 23.7, 25.3, 26.9, 27.1, 27.5, 29.1, 29.7, 31.7, 32.2, 34.1, 35.0, 37.7, 73.0, 126.3, 134.2, 173.7; EI MS: calcd for $C_{18}H_{32}O_2$ ($M^+$) 280, found 280.

### 4.7. Experimental procedure for the synthesis of an 8-membered ring lactone moiety of cephalosporolide D

To a solution of $Hf(OTf)_4$ (28.6 mg, 0.037 mmol) and TFBA (133.8 mg, 0.369 mmol) in acetonitrile (78 mL) at reflux temperature was added a solution of 3-benzyloxy-7-hydroxyoctanoic acid (**20**) (49.2 mg, 0.184 mmol) in THF (4.6 mL) with a mechanically driven syringe over a 15 h period. After the reaction mixture had been stirred for 5 h at reflux temperature, saturated aqueous sodium hydrogencarbonate (1.9 mL) was added at room temperature. The mixture was concentrated by evaporation of the solvent and then it was extracted with diethyl ether, and the organic layer was washed with brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by preparative thin layer chromatography to afford 30.5 mg (67%) of 3-benzyloxyoctan-7-olide (**21**) and 8.4 mg (17%) of recovered **20** as colorless oils.

**4.7.1. 3-Benzyloxyoctan-7-olide (21).** IR (neat): 1720 $cm^{-1}$; $^1H$ NMR ($CDCl_3$): $\delta$ 1.26 (3H, d, $J$=6.3 Hz, 8-H), 1.02–1.33 (1H, m, 5-H), 1.46–1.96 (5H, m, 4-H, 5-H, 6-H), 2.67 (1H, dd, $J$=6.6, 11.9 Hz, 2-H), 2.71 (1H, dd, $J$=4.3, 11.9 Hz, 2-H), 3.62–3.77 (1H, m, 3-H), 4.44 (1H, d, $J$=11.9 Hz, Bn-H), 4.61 (1H, d, $J$=11.9 Hz, Bn-H), 4.69 (1H, dqd, $J$=5.3, 6.3, 10.5 Hz, 7-H), 7.14–7.39 (5H, m, Ph); $^{13}C$ NMR($CDCl_3$): $\delta$ 18.9 (5), 21.3 (8), 32.9 (4), 37.7 (2), 38.3 (6), 70.1 (Bn), 75.3 (7), 77.3 (3), 127.5 (Ph), 127.6 (Ph), 128.3 (Ph), 138.1 (Ph), 172.3 (1). Anal. calcd for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.15; H, 8.03; HR MS: calcd for $C_{15}H_{21}O_3Na$ ($M+Na^+$) 249.1491, found 249.1539.

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