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**EXPEDITIOUS SYNTHESIS OF CARBOXYLIC ESTERS AND HIGH-YIELDING MACROLACTONES USING TRIFLUOROMETHYL-SUBSTITUTED BENZOIC ANHYDRIDES WITH 4-(DIMETHYLAMINO)PYRIDINE: AN EVALUATION OF THE REACTIVITIES OF AROMATIC ACID ANHYDRIDES AS DEHYDRATION REAGENTS COMPARED WITH 2-METHYL-6-NITROBENZOIC ANHYDRIDE**

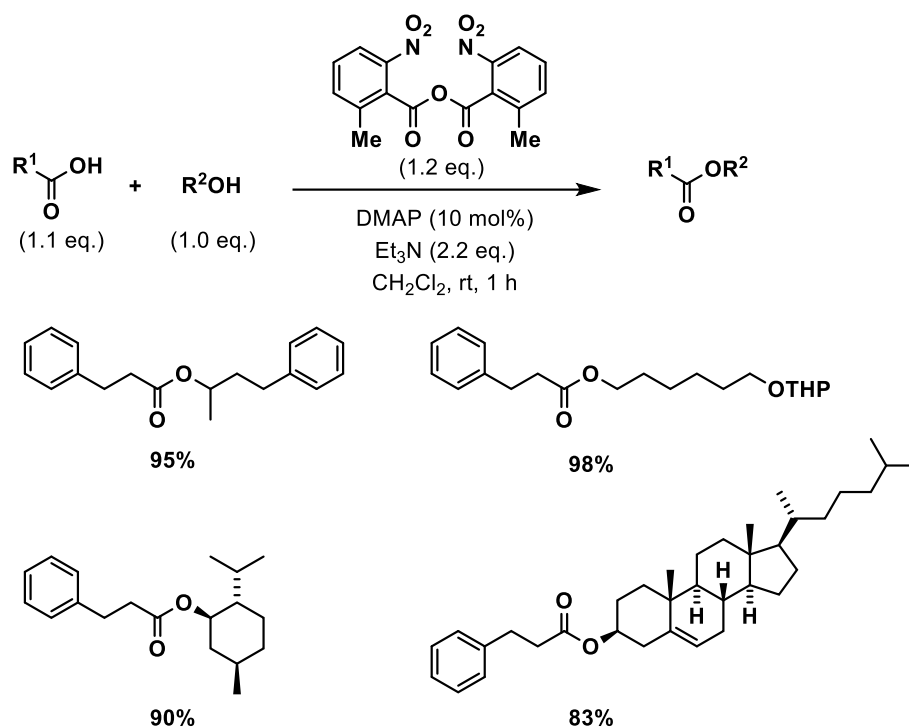
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**Abstract** – Trifluoromethyl-substituted benzoic anhydrides as structural congeners of 2-methyl-6-nitrobenzoic anhydride (MNBA) were prepared and investigated for comparative reactivity in the synthesis of carboxylic esters and macrolactones. 2-Fluoro-6-(trifluoromethyl)benzoic anhydride (FTFBA) was found to be a promising dehydrating agent in the presence of 4-(dimethylamino)pyridine (DMAP), and was successfully employed in the synthesis of *threo*-aleuritic acid lactone in good yield with high chemoselectivity.

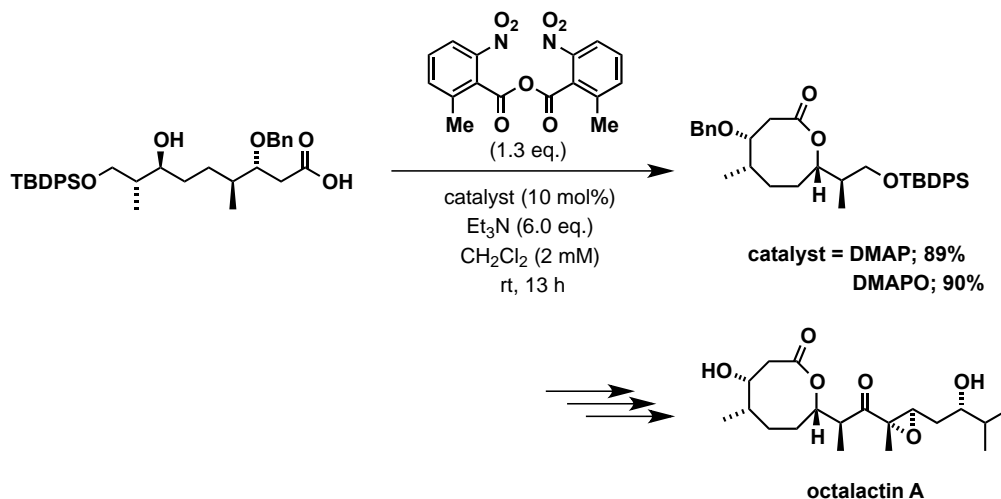
## INTRODUCTION

Synthesis of carboxylic esters and lactones is a fundamental and important process for obtaining natural products or useful artificial compounds in organic chemistry.<sup>1</sup> Coupling reactions between activated derivatives of carboxylic acids and alcohols were employed to perform high yielding esterification reactions with equimolar amounts of carboxylic acids and alcohols under mild conditions.<sup>2</sup> In 2002, we first developed a highly useful condensation reaction for the synthesis of carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols using 2-methyl-6-nitrobenzoic anhydride (MNBA) as the dehydrating reagent and by adding a catalytic amount of 4-(dimethylamino)pyridine (DMAP) or 4-(dimethylamino)pyridine *N*-oxide (DMAPO) in the presence of triethylamine (**Scheme 1**).<sup>3</sup>



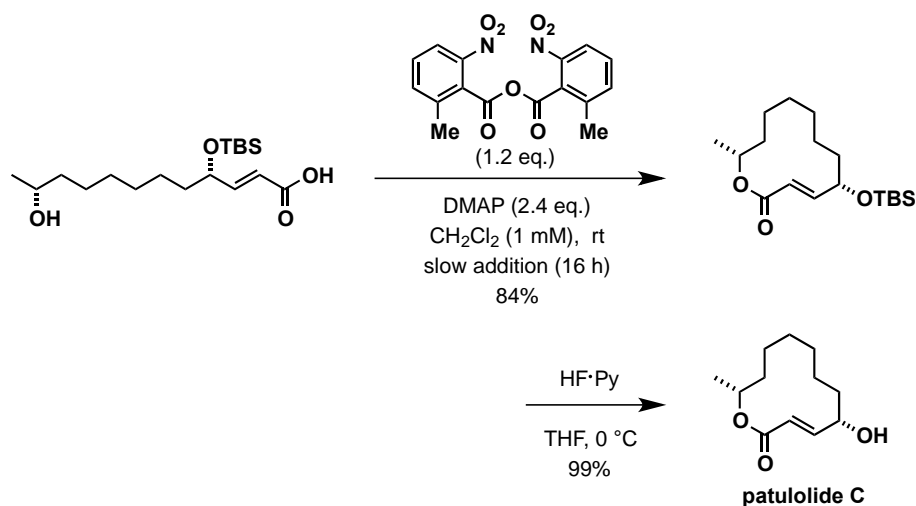
**Scheme 1.** Efficient dehydration condensation reaction using MNBA, as developed by Shiina (2002)

This highly efficient condensation reaction proceeds smoothly at room temperature; therefore, it has been adapted into a convenient and powerful method for the synthesis of a variety of macrolactones with high product selectivities *via* the mixed anhydride formation generated from the corresponding  $\omega$ -hydroxycarboxylic acids (seco acids) using MNBA with nucleophilic catalysts. A variety of lactones and related compounds were successfully prepared in high yields by this method using MNBA in the presence of DMAP or DMAPO (Scheme 2).<sup>4</sup>



**Scheme 2.** High-yielding lactonization using MNBA, as developed by Shiina (2002)

One advantage of this procedure is its simplicity; the addition of seco acids to the mixture of MNBA and promoters at a suitable temperature affords the desired macrolactones in excellent yields with high purity. After the establishment of this novel strategy, various efficient lactonizations of structurally complicated seco acids using MNBA with DMAP were reported in the total synthesis of natural products (**Scheme 3**).<sup>5</sup>

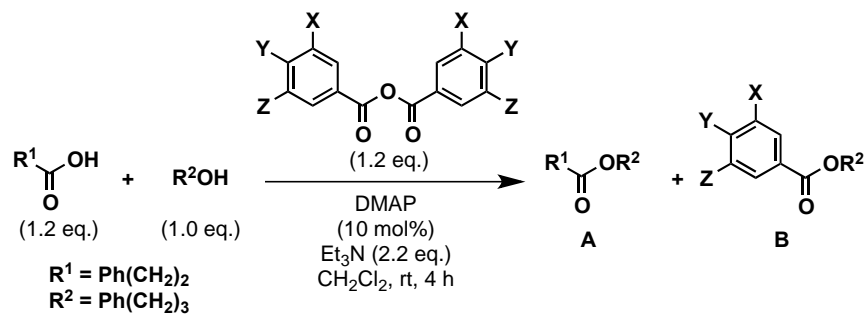


**Scheme 3.** Total synthesis of patulolide C using MNBA, as reported by Shibasaki (2003)

In this study, we report a complementary method using trifluoromethyl-substituted benzoic anhydrides for the MNBA-mediated dehydration condensation reactions in order to expand our mixed anhydride formation technology, wherein we prove that 2-fluoro-6-(trifluoromethyl)benzoic anhydride (FTFBA) accelerates reactions effectively to afford the desired esters or lactones in high yields and with high product selectivities from the corresponding carboxylic acids with alcohols or seco acids.

## RESULTS AND DISCUSSION

The esterification of 3-phenylpropanoic acid with 3-phenylpropanol was performed as a probe reaction<sup>4i</sup> for comparing the reactivity of different substitution patterns of trifluoromethyl-group-bearing benzoic anhydrides. First, the patterns of non-*ortho*-substituted (i.e., 3,4- or 3,5-disubstituted) benzoic anhydrides were examined in the presence of a catalytic amount of DMAP (10 mol%) and an excess amount of triethylamine ( $\text{Et}_3\text{N}$ ) (2.2 equiv.) as an auxiliary base in dichloromethane at room temperature, and the results are shown in **Table 1**. When a combination of the trifluoromethyl group and halogens was used as the substituent, a corresponding ester 3-phenylpropyl 3-phenylpropanoate (**A**)<sup>2b,6</sup> was obtained in good yield (entries 1–3) but with a substantially lower chemoselectivity than that obtained with MNBA (cf. entry 9). When a nitro group was used instead of the halogens, the reactions stalled at ca. 60% yield (entries 6–8). The chemoselectivities were not improved when non-*ortho*-substituted benzoic anhydrides were used.

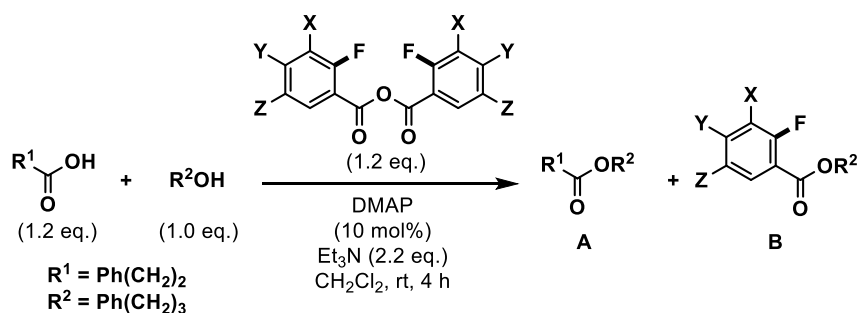
**Table 1.** Esterification using 3,4- or 3,5-disubstituted benzoic anhydrides

Entry	X,Y,Z	Yield of A / % <sup>a</sup>	A/B <sup>b</sup>
1	4-F-3-CF <sub>3</sub> ( <b>2</b> )	81	63/1
2	4-Cl-3-CF <sub>3</sub> ( <b>3</b> )	88	32/1
3	3-F-4-CF <sub>3</sub> ( <b>4</b> )	80	16/1
4	3-F-5-CF <sub>3</sub> ( <b>5</b> )	Not available <sup>c</sup>	-
5	3-Br-5-CF <sub>3</sub> ( <b>6</b> )	Not available <sup>c</sup>	-
6	4-NO <sub>2</sub> -3-CF <sub>3</sub> ( <b>7</b> )	60	67/1
7	5-NO <sub>2</sub> -3-CF <sub>3</sub> ( <b>8</b> )	61	69/1
8	3-NO <sub>2</sub> -4-CF <sub>3</sub> ( <b>9</b> )	62	37/1
9	2-Me-6-NO <sub>2</sub> (MNBA) ( <b>1</b> )	98	>500/1

<sup>a</sup> Isolated yield <sup>b</sup> Determined by <sup>1</sup>H NMR using a crude mixture.

<sup>c</sup> These benzoic anhydrides, which were not obtained in pure form, were unavailable for the reaction.

Next, disubstituted benzoic anhydrides with a fluorine atom at the *ortho*-position on each aromatic ring were investigated (**Table 2**). When a trifluoromethyl group as an additional substituent was present at the *meta*- or *para*-position on the aromatic rings, the chemoselectivities were found to be insufficient but moderate-to-good yields were obtained (entries 1–4).

**Table 2.** Esterification using *ortho*-substituted (2-F) benzoic anhydrides

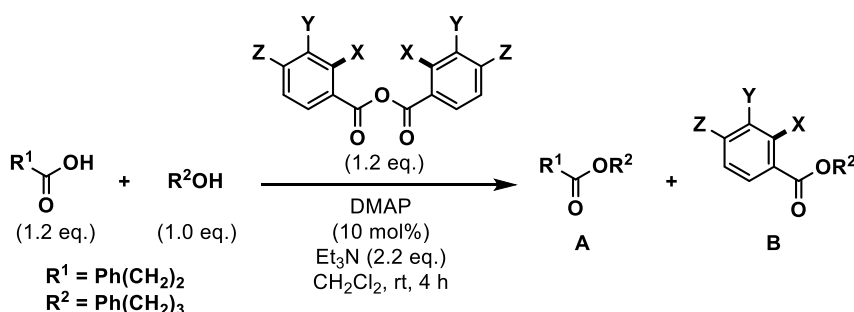
Entry	X,Y,Z	Yield of A / % <sup>a</sup>	A/B <sup>b</sup>
1	2-F-3-CF <sub>3</sub> ( <b>10</b> )	82	7.4/1
2	2-F-4-CF <sub>3</sub> ( <b>11</b> )	88	8.2/1
3	2-F-5-CF <sub>3</sub> ( <b>12</b> )	84	11/1
4	2,4,5-F <sub>3</sub> -3-CF <sub>3</sub> ( <b>13</b> )	50	1.6/1
5	2-Me-6-NO <sub>2</sub> (MNBA) ( <b>1</b> )	98	>500/1

<sup>a</sup> Isolated yield

<sup>b</sup> Determined by <sup>1</sup>H NMR using a crude mixture.

The following two structural modifications of the substituted benzoic anhydrides are assumed to have positive effects on dehydration condensation<sup>3a,c</sup>: (i) an electron-withdrawing group, such as a nitro group, on the aromatic ring increases the electrophilicity of the carboxyl group, and (ii) a bulky substituent, such as a methyl group, at the *ortho*-position on the aromatic ring providing a hindrance near the carboxyl group improves the chemoselectivity toward the desired ester. However, when a nitro or a methyl group, which is one of the components of *ortho*-substituted groups of MNBA, was introduced at the *ortho*-position instead of a fluorine atom, it was not sufficient to afford the desired ester with a high chemoselectivity equivalent to that achieved with MNBA (**Table 3**, entries 2 and 3 vs. entry 4).

**Table 3.** Esterification using mono-*ortho*-substituted (2-Cl, 2-NO<sub>2</sub>, and 2-Me) benzoic anhydrides

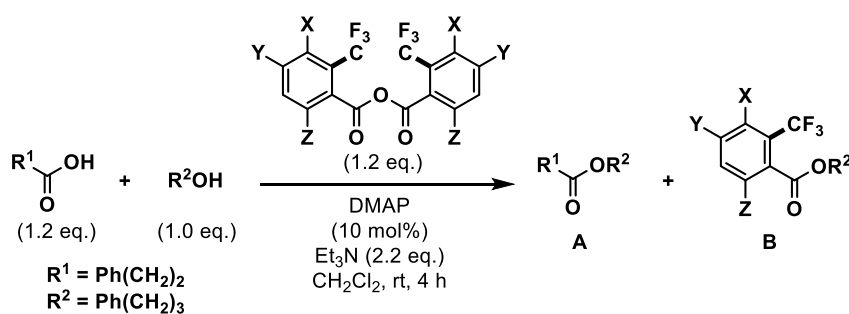


Entry	X,Y,Z	Yield of A / % <sup>a</sup>	A/B <sup>b</sup>
1	2-Cl-3-CF <sub>3</sub> ( <b>14</b> )	92	12/1
2	2-NO <sub>2</sub> -4-CF <sub>3</sub> ( <b>15</b> )	79	73/1
3	2-Me-4-CF <sub>3</sub> ( <b>16</b> )	75	109/1
4	2-Me-6-NO <sub>2</sub> (MNBA) ( <b>1</b> )	98	>500/1

<sup>a</sup> Isolated yield

<sup>b</sup> Determined by <sup>1</sup>H NMR using a crude mixture.

We further screened disubstituted benzoic anhydrides bearing a trifluoromethyl group at the *ortho*-position on each aromatic ring in order to improve both yield and chemoselectivity toward the desired ester (**Table 4**). When an additional substituent such as a fluorine or chlorine atom or a nitro group was introduced at the *meta*- or *para*-positions on the aromatic ring, a reduction in the chemoselectivities was observed (entries 2–5). We then introduced the substituents at the *ortho*-, *ortho'*-positions on the aromatic rings; it was found that the combination of a fluorine atom and a trifluoromethyl group or a methyl and trifluoromethyl group afforded the desired products in high yields with high chemoselectivities (entries 6 and 7), whereas *ortho*-disubstituted benzoic anhydrides with two trifluoromethyl groups exhibited a lower reactivity than that achieved by the above two combinations because of the overcharged steric hindrance around the carboxyl group of the aromatic acid anhydride (entry 8).

**Table 4.** Esterification using *ortho*-substituted (2-CF<sub>3</sub>) benzoic anhydrides

Entry	X,Y,Z	Yield of A / % <sup>a</sup>	A/B <sup>b</sup>
1	2-CF <sub>3</sub> ( <b>17</b> )	85	183/1
2	4-Cl-2-CF <sub>3</sub> ( <b>18</b> )	97	29/1
3	4-NO <sub>2</sub> -2-CF <sub>3</sub> ( <b>19</b> )	82	38/1
4	3-F-2-CF <sub>3</sub> ( <b>20</b> )	85	104/1
5	4-F-2-CF <sub>3</sub> ( <b>21</b> )	89	55/1
6	2-F-6-CF <sub>3</sub> ( <b>22</b> )	89	407/1
7	2-Me-6-CF <sub>3</sub> ( <b>23</b> )	95 <sup>c</sup>	171/1
8	2,6-(CF <sub>3</sub> ) <sub>2</sub> ( <b>24</b> )	82 <sup>c</sup>	>500/1

<sup>a</sup> Isolated yield <sup>b</sup> Determined by <sup>1</sup>H NMR using a crude mixture.

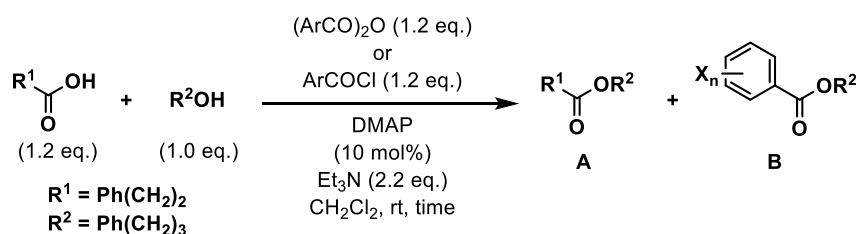
<sup>c</sup> Each reaction was performed for 24 h (entries 7 and 8), respectively.

Thus, three trifluoromethyl-substituted benzoic anhydrides, FTFBA, 2-methyl-6-(trifluoromethyl)benzoic anhydride (MTFBA), and 2,6-bis(trifluoromethyl)benzoic anhydride (2,6-BTFBA), were found to be promising dehydrating agents in the presence of DMAP.

We further examined in detail the product yields and chemoselectivities in the esterification reaction of 3-phenylpropanoic acid with 3-phenylpropanol using these three dehydrating agents for a prolonged reaction time in order to compare their reactivities with time. The results obtained are shown in **Table 5**. When FTFBA was employed with a catalytic amount of DMAP (10 mol%), the reaction proceeded rapidly for 1 h to afford the desired ester **A** in high yield (entry 1, 86%) and with high chemoselectivity (A/B = 302/1). In contrast, in the case of MTFBA and 2,6-BTFBA, the reaction proceeded sluggishly in the initial stage (for 1–4 h, entries 5–6 and 9–10) and the product yields gradually increased (for 24 h, entries 7–8 and 11–12) to the same level as that achieved with MNBA (entries 13–16) while maintaining high chemoselectivities. We then focused on the reactivity of the corresponding aromatic acid chlorides as dehydrating agents in the esterification reaction using the same method as that employed for substituted benzoic anhydrides. The reaction was performed using 2-fluoro-6-(trifluoromethyl)benzoyl chloride (FTFBC), 2-methyl-6-(trifluoromethyl)benzoyl chloride (MTFBC), and 2,6-bis(trifluoromethyl)benzoyl chloride (2,6-BTFBC) under identical conditions as those used for the reactions reported in **Table 5**; the results are shown in **Table 6**. FTFBC exhibited excellent reactivity in

the esterification to give the desired coupling product in high yields with high chemoselectivities within 1 h (entry 1), and these results were maintained for prolonged reaction times (entries 2–4). MTFBC showed the same level of reactivity and chemoselectivity as that shown by FTFBC (entries 6–8); however, a certain level of reduction in the product yield was observed as compared to that obtained using FTFBC in the initial stage of the reaction (entry 5). On employing 2,6-BTFBC, the reactivity in the initial reaction stage was observed to be significantly suppressed (entry 9, 64%), but the product yields gradually increased up to 90% (entries 10–12). In addition, 2-methyl-6-nitrobenzoyl chloride (MNBC) exhibited high reactivity in the intermolecular coupling reaction to provide the desired ester **A** with high chemoselectivity (entries 13–16).

**Table 5.** Reactivity of aromatic acid anhydrides with DMAP



Entry	(ArCO) <sub>2</sub> O	Abbreviation	time / h	Yield of A / % <sup>a</sup>	A/B <sup>b</sup>
1	(2-F-6-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub> CO) <sub>2</sub> O ( <b>22</b> )	FTFBA	1	86	302/1
2			4	89	407/1
3			12	86	406/1
4			24	89	306/1
5	(2-Me-6-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub> CO) <sub>2</sub> O ( <b>23</b> )	MTFBA	1	26	145/1
6			4	57	154/1
7			12	75	138/1
8			24	95	171/1
9	(2,6-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CO) <sub>2</sub> O ( <b>24</b> )	2,6-BTFBA	1	11	>500/1
10			4	52	>500/1
11			12	68	>500/1
12			24	82	>500/1
13	(2-Me-6-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CO) <sub>2</sub> O ( <b>1</b> )	MNBA	1	92	>500/1
14			4	98	>500/1
15			12	97	>500/1
16			24	96	>500/1

<sup>a</sup> Isolated yield <sup>b</sup> Determined by <sup>1</sup>H NMR using a crude mixture.

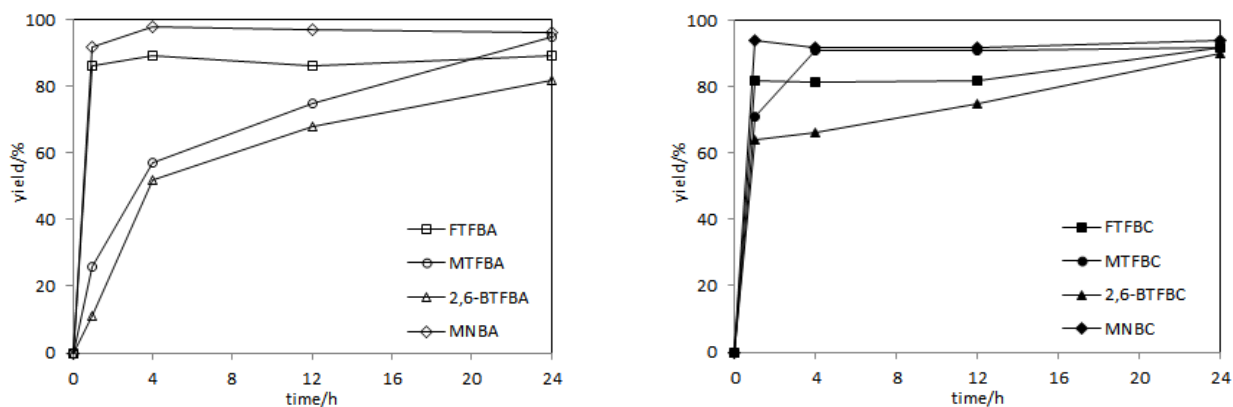
**Table 6.** Reactivity of aromatic acid chlorides with DMAP

Entry	ArCOCl	Abbreviation	time / h	Yield of A / % <sup>a</sup>	A/B <sup>b</sup>
1	2-F-6-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub> COCl ( <b>22'</b> )	FTFBC	1	82	>500/1
2			4	81	>500/1
3			12	82	>500/1
4			24	92	>500/1
5	2-Me-6-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub> COCl ( <b>23'</b> )	MTFBC	1	71	>500/1
6			4	91	>500/1
7			12	91	>500/1
8			24	92	>500/1
9 <sup>c</sup>	2,6-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COCl ( <b>24'</b> )	2,6-BTFBC	1	64	186/1
10 <sup>c</sup>			4	66	>500/1
11 <sup>c</sup>			12	75	>500/1
12 <sup>c</sup>			24	90	>500/1
13 <sup>c</sup>	2-Me-6-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COCl ( <b>1'</b> )	MNBC	1	94	>500/1
14			4	92	>500/1
15			12	92	>500/1
16			24	94	>500/1

<sup>a</sup> Isolated yield <sup>b</sup> Determined by <sup>1</sup>H NMR using a crude mixture.

<sup>c</sup> The reaction was performed using 3.0 eq. of DMAP without Et<sub>3</sub>N.

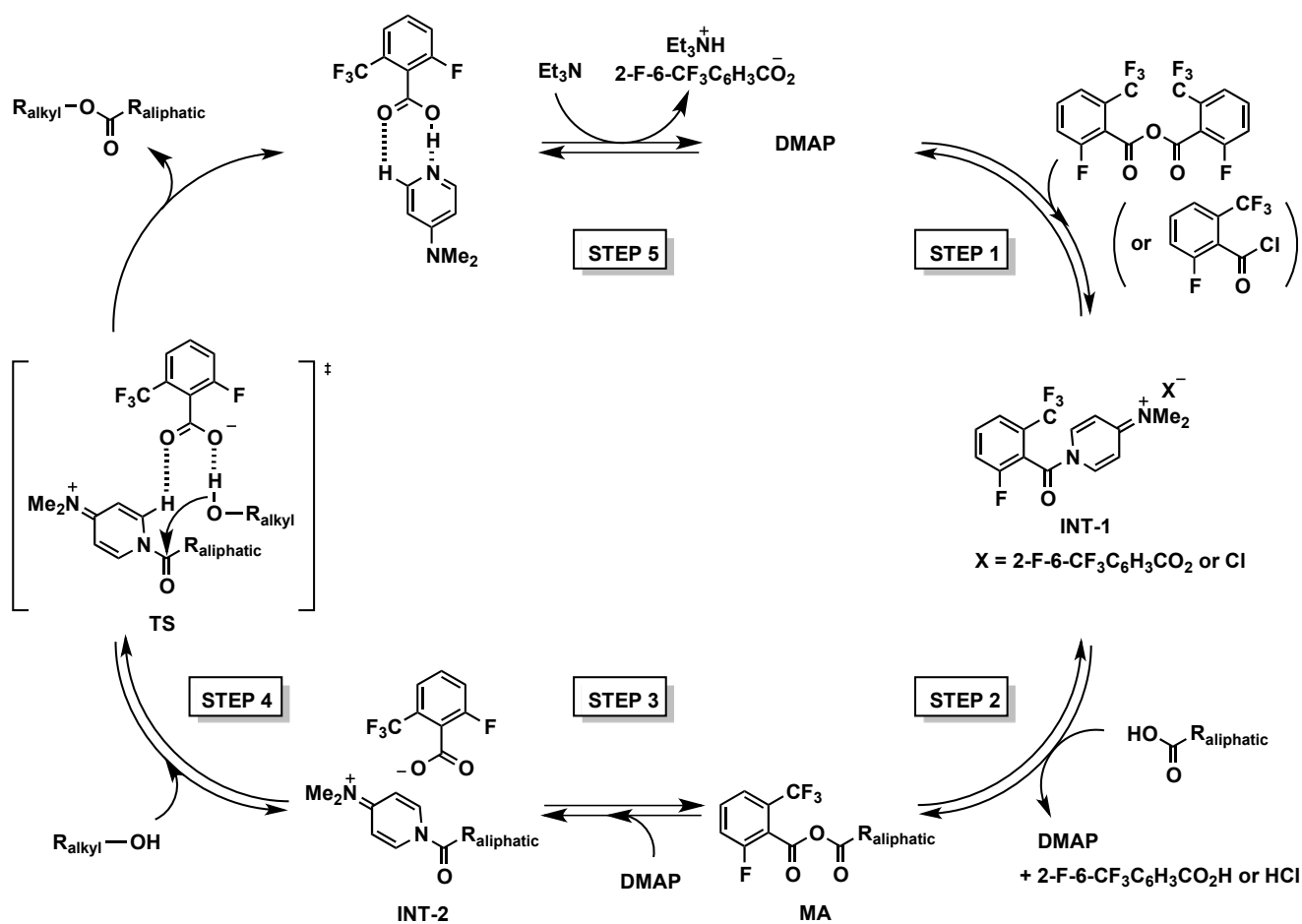
The results obtained using aromatic acid anhydrides or aromatic acid chlorides in the presence of DMAP are plotted on graphs, as shown in **Figure 1**. FTFBA is observed to have the same level of reactivity as that of MNBA, whereas MTFBA and 2,6-BTFBA exhibit lower reactivities in the initial reaction stage, probably because of the steric hindrance near the carbonyl group imparted by the additional substituent, such as a methyl or trifluoromethyl group, at the *ortho*-position on the aromatic ring of the acid anhydrides. Aromatic acid chlorides, such as MNBC, are found effective for the synthesis of carboxylic esters because of rapid formation of the reactive mixed anhydride intermediate obtained by the extraction of hydrogen chloride from acid chlorides with carboxylic acid in the presence of DMAP and Et<sub>3</sub>N.



**Figure 1.** Time courses of product yields in the esterification using substituted benzoic anhydrides (left) or substituted benzoyl chlorides (right) with DMAP.



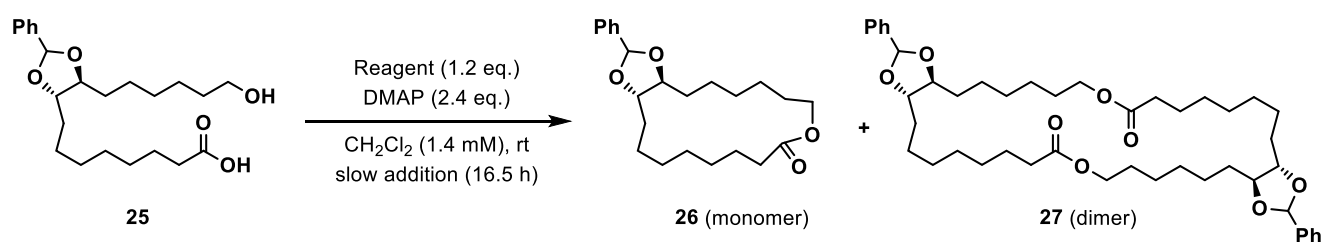
The proposed mechanism for esterification is depicted in **Figure 2**.<sup>7</sup> The formation of a pyridinium salt (INT-1) of the substituted benzoic acid with DMAP proceeds first (STEP 1), followed by the formation of mixed anhydride (MA) through the reaction of carboxylic acid with INT-1 (STEP 2). Next, the chemoselective nucleophilic substitution of DMAP with MA takes place to afford the pyridinium salt (STEP 3, INT-2), followed by the generation of the desired ester by a nucleophilic attack of the substrate alcohol with INT-2 *via* the transition state shown (STEP 4, TS). Finally, regeneration of DMAP as a free nucleophile occurs to complete its catalytic cycle (STEP 5). All the steps in this procedure are reversible except that of the ester formation via the TS. When substituted benzoyl chlorides are used instead of substituted benzoic anhydrides, the formation of INT-1 proceeds faster because of the higher electrophilicity of acid chlorides; therefore, it is postulated that product yields in the initial stage of intermolecular coupling reactions are generally higher when substituted benzoyl chlorides are used.



**Figure 2.** Proposed reaction mechanism for esterification using substituted benzoic anhydrides or substituted benzoyl chlorides.

To further compare the reactivities and chemoselectivities of the selected aromatic acid anhydrides and corresponding aromatic acid chlorides, macrolactonization of seco acid **25**<sup>4d</sup> prepared from *threo*-aleuritic acid by treatment with  $\text{PhCH}(\text{OMe})_2$  and 10-camphorsulfonic acid was performed, and the results obtained are summarized in **Table 7**. FTFBA exhibited high reactivity comparable with that of MNBA in the macrolactonization to give the desired monomeric lactone **26** in high yield with excellent chemoselectivity, accompanied with a small amount of a dimerized product **27** (entry 1 cf. entry 7). The yield and chemoselectivity of the product decreased as the size of the substituent at the *ortho*-position on each aromatic ring of the substituted benzoic anhydride became larger (entries 3 and 5 cf. entry 1).<sup>8</sup> It is experimentally determined that a combination of the substituents of FTFBA is suitable for the present lactone synthesis as well as that of the substituents of MNBA.<sup>9</sup> The yields and chemoselectivities decreased rapidly on employing corresponding substituted benzoyl chlorides (entries 2, 4, 6, and 8), whereas the use of the substituted benzoic anhydrides afforded higher yields and chemoselectivities (entries 1, 3, 5, and 7).

**Table 7.** Synthesis of the protected *threo*-aleuritic acid lactone **26**



Entry	Reagent	Abbreviation	Yield <sup>a</sup> (%)		<b>26/27</b> (mol/mol)
			<b>26</b>	<b>27</b>	
1	(2-F-6-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub> CO) <sub>2</sub> O ( <b>22</b> )	FTFBA	88	5	37/1
2	2-F-6-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub> COCl ( <b>22'</b> )	FTFBC	41	3	30/1
3	(2-Me-6-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub> CO) <sub>2</sub> O ( <b>23</b> )	MTFBA	32	20	3/1
4	2-Me-6-CF <sub>3</sub> C <sub>6</sub> H <sub>3</sub> COCl ( <b>23'</b> )	MTFBC	28	20	3/1
5	(2,6-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CO) <sub>2</sub> O ( <b>24</b> )	2,6-BTFBA	46	13	7/1
6	2,6-(CF <sub>3</sub> ) <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COCl ( <b>24'</b> )	2,6-BTFBC	10	12	2/1
7	(2-Me-6-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> CO) <sub>2</sub> O ( <b>1</b> )	MNBA	91	4	48/1
8	2-Me-6-NO <sub>2</sub> C <sub>6</sub> H <sub>3</sub> COCl ( <b>1'</b> )	MNBC	80	7	22/1
9	(2,4,6-Cl <sub>3</sub> C <sub>6</sub> H <sub>2</sub> CO) <sub>2</sub> O	TCBA	76	7	22/1
10	2,4,6-Cl <sub>3</sub> C <sub>6</sub> H <sub>2</sub> COCl	TCBC	76	13	11/1

<sup>a</sup> Isolated yield

Transformation of seco acid into a monomeric lactone requires high strain energy via the TS in an intramolecular reaction as compared to that required in facilitating an intermolecular ester formation. When 1.4 mmol of aromatic acid chloride is used as the dehydrating agent in 1 L solvent for lactone

synthesis, the concentration of the substituted benzoic acid anion ( $\text{ArCO}_2^-$ ) must be 1.4 mM; however, the concentration of  $\text{ArCO}_2^-$  must be increased to 2.8 mM when using 1.4 mmol of aromatic acid anhydride as the dehydrating agent. The lactone formation rate is proportional to the concentration of  $\text{ArCO}_2^-$ , as shown by the TS in **Figure 2**. Therefore, higher yields of the desired monomeric lactone **26** are obtained in the reactions using substituted benzoic anhydrides (entries 1, 3, 5, and 7) compared to those obtained in the reactions using substituted benzoyl chlorides (entries 2, 4, 6, and 8). Moreover, an enhancement in the rate of INT-1 production using substituted benzoyl chlorides causes an increase in the concentration of MA in the reaction system, as depicted in **Figure 2**. Thus, the chemoselectivity of the desired monomeric lactone **26** [intramolecular coupling product] over that of the undesired dimer **27** [intermolecular coupling product] ( $= \mathbf{26/27}$ ) in the reactions using substituted benzoyl chlorides as the dehydrating agents (entries 2, 4, 6, 8, and 10) decreases compared with those in the reactions using substituted benzoic anhydrides (entries 1, 3, 5, 7, and 9).

In summary, we demonstrated the utility of trifluoromethyl-substituted benzoic anhydrides that are structural congeners of MNBA, such as FTFBA, MTFBA, and 2,6-BTFBA, as promising dehydrating agents in esterification reactions. The utility of FTFBA was also exhibited by the synthesis of *threo*-aleuritic acid lactone in high yield with high product selectivity. The results suggest that this method of using trifluoromethyl-substituted benzoic anhydrides, which is complementary to MNBA-mediated dehydration condensation reaction, has enabled us to expand our mixed anhydride technology. Furthermore, MNBC is found to show fairly high reactivity among the corresponding acid chlorides in the intermolecular coupling reaction. We are now investigating other applications of these dehydrating agents for the syntheses of various natural products and valuable complex molecules in our laboratory.

## EXPERIMENTAL

### General

All reactions were performed under argon atmosphere in dried glassware unless otherwise noted. Infrared (IR) spectra were obtained using a Jasco FT/IR-4600 Fourier transform infrared spectrometer. Proton and carbon nuclear magnetic resonance ( $^1\text{H}$  and  $^{13}\text{C}$  NMR) spectra were recorded with chloroform (in  $\text{CDCl}_3$ ) on the following instruments: JEOL JNM-ECA500 ( $^1\text{H}$  at 500 MHz and  $^{13}\text{C}$  at 125 MHz). Mass spectra were determined by a Bruker Daltonics micrOTOF focus (ESI-TOF) mass spectrometer. Thin layer chromatography was performed on Wakogel B5F.

### Starting materials

All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc., Wako Pure Chemical Industries, Ltd. or Aldrich Chemical Co., Inc. and used without further purification unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å. Triethylamine was also distilled prior to use. Meanwhile, the raw materials for the synthesis of substituted benzoic anhydrides were purchased as follows. 4-Fluoro-3-(trifluoromethyl)benzoic acid, 3-fluoro-4-(trifluoromethyl)benzoic acid, 3-fluoro-5-(trifluoromethyl)benzoic acid, 5-nitro-3-(trifluoromethyl)benzoic acid, 2-fluoro-3-(trifluoromethyl)benzoic acid, 2-fluoro-5-(trifluoromethyl)benzoic acid, 2-nitro-4-(trifluoromethyl)benzoic acid, 2-(trifluoromethyl)benzoic acid, 4-fluoro-2-(trifluoromethyl)benzoic acid, 5-fluoro-2-(trifluoromethyl)benzoic acid, and 2-fluoro-6-(trifluoromethyl)benzoic acid were purchased from Tokyo Kasei Kogyo Co., Ltd (TCI). 4-Nitro-3-(trifluoromethyl)benzoic acid, 2-fluoro-4-(trifluoromethyl)benzoic acid, 2-chloro-5-(trifluoromethyl)benzoic acid, and 4-nitro-2-(trifluoromethyl)benzoic acid were purchased from Aldrich Chemical Co., Inc. 2,4,5-Trifluoro-3-(trifluoromethyl)benzoic acid, 2-chloro-3-(trifluoromethyl)benzoic acid, 4-chloro-2-(trifluoromethyl)benzoic acid, and 2,6-bis(trifluoromethyl)benzoic acid were purchased from Wako Pure Chemical Industries, Ltd. 4-Chloro-3-tri(trifluoromethyl)benzoic acid, 3-bromo-5-(trifluoromethyl)benzoic acid, 3-nitro-4-(trifluoromethyl)benzoic acid, and 3-fluoro-2-(trifluoromethyl)benzoic acid were purchased from CombiBlocks, Inc. 2-Methyl-4-(trifluoromethyl)benzoic acid was purchased from Frontier Scientific, Inc., and 2-methyl-6-(trifluoromethyl)benzoic acid was purchased from CGeneTech, Inc. 2-Fluoro-6-(trifluoromethyl)benzoyl chloride (FTFBC) (**22'**) was purchased from Aldrich, and 2,6-bis(trifluoromethyl)benzoyl chloride (2,6-BTFBC) (**24'**) was purchased from APOLLO Scientific Ltd. All benzoic anhydrides were prepared from the corresponding substituted benzoic acids according to the reported procedure,<sup>2b</sup> whereas MNBA was purchased from TCI (M1439). TCBA<sup>3c</sup> was prepared from the corresponding substituted benzoic acid and TCBC<sup>11</sup> according to the reported procedure.<sup>2b</sup> MNBC<sup>12</sup> was purchased from TCI (M1438). *threo*-Aleuritic acid was purchased from Fluka Chemical Co., Ltd.

### Typical experimental procedure for the esterification reaction

A typical experimental procedure is described for the reaction of 3-phenylpropanoic acid with 3-phenylpropanol (**Table 4**, entry 6): To a solution of triethylamine (31  $\mu$ L, 0.22 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.9 mL) at rt were added DMAP (1.2 mg, 0.010 mmol), FTFBA (47.8 mg, 0.120 mmol) and 3-phenylpropanoic acid (18.0 mg, 0.120 mmol). After stirring for 10 min, a solution of 3-phenylpropanol (13.5 mg, 0.10 mmol) in  $\text{CH}_2\text{Cl}_2$  (0.6 mL) was added. After the reaction mixture was stirred for 4 h at rt,

saturated aqueous  $\text{NH}_4\text{Cl}$  was added at 0 °C. The mixture was extracted with  $\text{CH}_2\text{Cl}_2$ , and the organic layer was washed with water and brine, and dried over  $\text{Na}_2\text{SO}_4$ . After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (hexane/EtOAc = 2/1) to afford 3-phenylpropyl 3-phenylpropanoate (23.9 mg, 89.1%).

**4-Fluoro-3-(trifluoromethyl)benzoic anhydride (2):** Mp 89.5–91.0 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.41 (dd,  $J = 2.3, 6.5$  Hz, 2H), 8.37 (ddd,  $J = 2.3, 4.5, 9.0$  Hz, 2H), 7.41 (dd,  $J = 9.0, 9.0$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.6 (d,  $J = 267.6$  Hz), 159.8, 136.6 (d,  $J = 9.6$  Hz), 130.6 (dq,  $J = 3.8, 3.8$  Hz), 124.9 (d,  $J = 2.4$  Hz), 121.7 (q,  $J = 273.5$  Hz), 119.8 (dq,  $J = 13.2, 34.4$  Hz), 118.2 (d,  $J = 21.6$  Hz); HRMS (ESI-TOF):  $[\text{M}+\text{Na}^+]$  calcd for  $\text{C}_{16}\text{H}_6\text{F}_8\text{O}_3\text{Na}$  421.0087, found 421.0081; IR ( $\text{cm}^{-1}$ ): 1792, 1729.

**4-Chloro-3-(trifluoromethyl)benzoic anhydride (3):** Mp 127.5–129.0 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.44 (d,  $J = 2.3$  Hz, 2H), 8.23 (dd,  $J = 2.3, 8.3$  Hz, 2H), 7.73 (d,  $J = 8.3$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  159.9, 139.6, 134.4, 132.6, 129.7 (q,  $J = 32.3$  Hz), 129.6, 127.2, 122.1 (q,  $J = 273.5$  Hz); HRMS (ESI-TOF):  $[\text{M}+\text{Na}^+]$  calcd for  $\text{C}_{16}\text{H}_6\text{Cl}_2\text{F}_6\text{O}_3\text{Na}$  452.9496, found 452.9494; IR ( $\text{cm}^{-1}$ ): 1791, 1733, 1319.

**3-Fluoro-4-(trifluoromethyl)benzoic anhydride (4):** Mp 98.0–100.0 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.04 (d,  $J = 7.5$  Hz, 2H), 7.95 (d,  $J = 9.5$  Hz, 2H), 7.83 (dd,  $J = 7.5, 7.5$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  163.8 (d,  $J = 261.5$  Hz), 159.3, 133.7 (d,  $J = 7.1$  Hz), 128.2 (q,  $J = 3.5$  Hz), 126.1 (d,  $J = 4.8$  Hz), 124.2 (dq,  $J = 13.2, 32.7$  Hz), 121.8 (q,  $J = 273.4$  Hz), 118.9 (d,  $J = 22.6$  Hz); HRMS (ESI-TOF):  $[\text{M}+\text{Na}^+]$  calcd for  $\text{C}_{16}\text{H}_6\text{F}_8\text{O}_3\text{Na}$  421.0087, found 421.0086; IR ( $\text{cm}^{-1}$ ): 1793, 1733, 1422.

**4-Nitro-3-(trifluoromethyl)benzoic anhydride (7):** Mp 161.0–162.0 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.60 (d,  $J = 1.3$  Hz, 2H), 8.50 (dd,  $J = 1.3, 8.5$  Hz, 2H), 8.05 (d,  $J = 8.5$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  158.5, 151.5, 135.2, 131.7, 130.2 (q,  $J = 5.9$ ), 125.8, 124.9 (q,  $J = 23.9$ ), 121.2 (q,  $J = 274.7$  Hz); HRMS (ESI-TOF):  $[\text{M}+\text{Na}^+]$  calcd for  $\text{C}_{16}\text{H}_6\text{F}_6\text{N}_2\text{O}_7\text{Na}$  474.9977, found 474.9960; IR ( $\text{cm}^{-1}$ ): 1798, 1734, 1553.

**5-Nitro-3-(trifluoromethyl)benzoic anhydride (8):** Mp 165.0–166.0 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.14 (s, 2H), 8.85 (s, 2H), 8.72 (s, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  158.4, 148.9, 133.9 (q,  $J = 35.9$  Hz), 132.6 (q,  $J = 3.6$  Hz), 131.0, 128.3, 126.4 (q,  $J = 3.6$  Hz), 122.1 (q,  $J = 273.4$  Hz); HRMS (ESI-TOF):  $[\text{M}+\text{Na}^+]$  calcd for  $\text{C}_{16}\text{H}_6\text{F}_6\text{N}_2\text{O}_7\text{Na}$  474.9977, found 474.9994; IR ( $\text{cm}^{-1}$ ): 1795, 1736, 1545, 1329.

**3-Nitro-4-(trifluoromethyl)benzoic anhydride (9):** Mp 137.0–139.0 °C;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.58 (s, 2H), 8.48 (d,  $J = 8.0$  Hz, 2H), 8.09 (d,  $J = 8.0$  Hz, 2H);  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  158.2,

148.7, 134.0, 132.8, 129.3 (q,  $J = 6.0$  Hz), 128.9 (q,  $J = 34.7$  Hz), 126.6, 121.2 (q,  $J = 274.7$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_6N_2O_7Na$  474.9977, found 474.9962; IR ( $cm^{-1}$ ): 1802, 1740.

**2-Fluoro-3-(trifluoromethyl)benzoic anhydride (10):** Mp 87.0–89.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.29 (dd,  $J = 6.5, 7.5$  Hz, 2H), 7.94 (dd,  $J = 6.5, 7.5$  Hz, 2H), 7.45 (dd,  $J = 7.5, 7.5$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  159.8 (d,  $J = 272.4$  Hz), 157.8, 136.6, 133.3, 124.5 (d,  $J = 4.8$  Hz), 121.9 (q,  $J = 273.5$  Hz), 120.5 (dq,  $J = 13.2, 33.6$  Hz), 118.5 (d,  $J = 8.3$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_8O_3Na$  421.0087, found 421.0075; IR ( $cm^{-1}$ ): 1798, 1736.

**2-Fluoro-4-(trifluoromethyl)benzoic anhydride (11):** Mp 65.0–68.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.22 (dd,  $J = 7.3, 7.8$  Hz, 2H), 7.59 (d,  $J = 7.8$  Hz, 2H), 7.51 (d,  $J = 9.5$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  162.0 (d,  $J = 265.2$  Hz), 157.9, 137.9 (dq,  $J = 8.8, 34.0$  Hz), 133.8, 122.4 (q,  $J = 273.6$  Hz), 121.4, 120.1 (d,  $J = 9.6$  Hz), 115.0 (qd,  $J = 1.1, 57.9$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_8O_3Na$  421.0087, found 421.0081; IR ( $cm^{-1}$ ): 1798, 1729, 1429.

**2-Fluoro-5-(trifluoromethyl)benzoic anhydride (12):** Mp 97.0–98.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.38 (dd,  $J = 2.0, 6.3$  Hz, 2H), 7.94 (ddd,  $J = 2.0, 3.5, 9.0$  Hz, 2H), 7.38 (dd,  $J = 9.0, 9.0$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  164.1 (d,  $J = 268.8$  Hz), 157.7, 133.4 (q,  $J = 3.6$  Hz), 130.6 (d,  $J = 3.6$  Hz), 127.6 (q,  $J = 36.0$  Hz), 122.9 (q,  $J = 272.3$  Hz), 118.5 (d,  $J = 24.0$  Hz), 117.6 (d,  $J = 9.6$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_8O_3Na$  421.0087, found 421.0073; IR ( $cm^{-1}$ ): 1798, 1731.

**2,4,5-Trifluoro-3-(trifluoromethyl)benzoic anhydride (13):** Mp 69.0–71.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.06–8.14 (m, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  156.0, 155.9 (d,  $J = 273.5$  Hz), 152.5 (ddd,  $J = 4.7, 18.2, 275.5$  Hz), 147.1 (ddd,  $J = 3.5, 12.8, 252.9$  Hz), 123.5 (d,  $J = 20.4$  Hz), 120.5 (q,  $J = 276.0$  Hz), 114.1 (ddd,  $J = 4.8, 10.2, 12.0$  Hz), 111.0–112.0 (m); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_2F_{12}O_3Na$  492.9710, found 492.9714; IR ( $cm^{-1}$ ): 1799, 1739, 1505, 1174, 1132.

**2-Chloro-3-(trifluoromethyl)benzoic anhydride (14):** Mp 107.5–108.5 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.09 (dd,  $J = 1.5, 7.5$  Hz, 2H), 7.95 (dd,  $J = 1.5, 7.5$  Hz, 2H), 7.54 (dd,  $J = 7.5, 7.5$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  159.5, 134.8, 132.9, 131.7 (q,  $J = 5.9$  Hz), 131.1, 130.7 (q,  $J = 31.2$  Hz), 127.0, 122.3 (q,  $J = 274.7$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6Cl_2F_6O_3Na$  452.9496, found 452.9491; IR ( $cm^{-1}$ ): 1794, 1738, 1132.

**2-Nitro-4-(trifluoromethyl)benzoic anhydride (15):** Mp 120.5–121.5 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.38, 8.08 (d,  $J = 8.0$  Hz, 2H), 7.97 (d,  $J = 8.0$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  158.4, 146.8, 135.1 (q,  $J = 35.4$  Hz), 130.9, 130.9, 129.3, 122.7 (q,  $J = 274.0$  Hz), 121.9 (q,  $J = 3.6$  Hz); HRMS

(ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_6N_2O_7Na$  474.9977, found 474.9979; IR ( $cm^{-1}$ ): 1818, 1758, 1545, 1323, 1135.

**2-Methyl-4-(trifluoromethyl)benzoic anhydride (16):** Mp 93.5–94.5 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.12 (d,  $J = 8.0$  Hz, 2H), 7.59 (d,  $J = 8.0$  Hz, 4H), 2.76 (s, 6H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  161.5, 143.3, 135.0 (q,  $J = 32.4$  Hz), 131.6, 130.7, 129.0 (q,  $J = 3.7$  Hz), 123.3 (q,  $J = 273.4$  Hz), 123.0 (q,  $J = 3.7$  Hz), 21.9; HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{18}H_{12}F_6O_3Na$  413.0588, found 413.0577; IR ( $cm^{-1}$ ): 1795, 1733, 1334, 1163, 1126.

**2-(Trifluoromethyl)benzoic anhydride (17):** Mp 59.5–61.5 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.98 (d,  $J = 7.5$  Hz, 2H), 7.83 (d,  $J = 7.5$  Hz, 2H), 7.72 (dd,  $J = 7.5, 7.5$  Hz, 2H), 7.70 (dd,  $J = 7.5, 7.5$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  160.6, 132.8, 132.0, 131.2, 129.6 (q,  $J = 32.8$  Hz), 128.7, 127.2 (q,  $J = 5.2$  Hz), 123.0 (q,  $J = 273.5$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_8F_6O_3Na$  385.0275, found 385.0265; IR ( $cm^{-1}$ ): 1805, 1740, 1169, 1314.

**4-Chloro-2-(trifluoromethyl)benzoic anhydride (18):** Mp 73.0–74.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.94 (d,  $J = 8.0$  Hz, 2H), 7.82 (d,  $J = 2.0$  Hz, 2H), 7.68 (dd,  $J = 2.0, 8.0$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  159.5, 139.8, 133.0, 132.2, 131.4 (q,  $J = 33.6$  Hz), 126.7, 122.9 (q,  $J = 6.0$  Hz), 122.2 (q,  $J = 274.7$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6Cl_2F_6O_3Na$  452.9496, found 452.9510; IR ( $cm^{-1}$ ): 1791, 1729, 1302.

**4-Nitro-2-(trifluoromethyl)benzoic anhydride (19):** Mp 122.0–123.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.69 (d,  $J = 2.2$  Hz, 2H), 8.57 (dd,  $J = 2.2, 8.8$  Hz, 2H), 8.14 (d,  $J = 8.8$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  158.5, 149.8, 133.4, 132.5, 131.2 (q,  $J = 34.8$  Hz), 127.1, 124.0 (q,  $J = 273.6$  Hz), 122.8 (q,  $J = 5.0$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_6N_2O_7Na$  474.9977, found 474.9971; IR ( $cm^{-1}$ ): 1812, 1752, 1541, 1287, 1156.

**3-Fluoro-2-(trifluoromethyl)benzoic anhydride (20):** Mp 70.5–71.5 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.67 (ddd,  $J = 4.5, 7.5, 8.5$  Hz, 2H), 7.52 (d,  $J = 7.5$  Hz, 2H), 7.41 (dd,  $J = 8.5, 10.0$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  160.2 (d,  $J = 3.5$  Hz), 160.0 (d,  $J = 259.1$  Hz), 134.1 (d,  $J = 9.7$  Hz), 131.4, 124.9 (d,  $J = 3.5$  Hz), 121.9 (q,  $J = 274.7$  Hz), 120.6 (d,  $J = 21.6$  Hz), 116.3 (dq,  $J = 13.2, 33.6$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_8O_3Na$  421.0087, found 421.0102; IR ( $cm^{-1}$ ): 1809, 1749, 1297, 1135.

**4-Fluoro-2-(trifluoromethyl)benzoic anhydride (21):** Mp 64.0–65.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  8.06 (dd,  $J = 5.3, 9.0$  Hz, 2H), 7.55 (dd,  $J = 2.0, 8.5$  Hz, 2H), 7.39 (ddd,  $J = 2.0, 7.5, 9.0$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  164.7 (d,  $J = 258.0$  Hz), 159.4, 134.6 (d,  $J = 8.4$  Hz), 132.8 (dd,  $J = 8.4, 33.6$

Hz), 124.5, 122.1 (q,  $J = 273.5$  Hz), 119.0 (d,  $J = 21.6$  Hz), 115.7 (dq,  $J = 6.0, 25.0$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_8O_3Na$  421.0087, found 421.0065; IR ( $cm^{-1}$ ): 1801, 1735, 1304, 1145.

**2-Fluoro-6-(trifluoromethyl)benzoic anhydride (FTFBA) (22):** Mp 74.0–76.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.62–7.66 (m, 2H), 7.56 (d,  $J = 8.0$  Hz, 2H), 7.40 (dd,  $J = 4.0, 8.0$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  159.6 (d,  $J = 254.5$  Hz), 156.7, 133.0 (d,  $J = 8.4$  Hz), 129.9 (q,  $J = 33.0$  Hz), 122.3 (q,  $J = 274.7$  Hz), 122.3, 120.0 (d,  $J = 20.3$  Hz), 118.6 (d,  $J = 18.0$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{16}H_6F_8O_3Na$  421.0087, found 421.0065; IR ( $cm^{-1}$ ): 1814, 1750, 1318, 1153.

**2-Methyl-6-(trifluoromethyl)benzoic anhydride (MTFBA) (23):** Mp 105.0–106.0 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.54 (d,  $J = 7.0$  Hz, 2H), 7.45–7.50 (m, 4H), 2.50 (s, 6H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  161.6, 136.8, 134.1, 130.4, 129.6, 127.5 (q,  $J = 32.3$  Hz), 123.8 (q,  $J = 3.6$  Hz), 123.4 (q,  $J = 273.4$  Hz), 19.2; HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{18}H_{12}F_6O_3Na$  413.0588, found 413.0569; IR ( $cm^{-1}$ ): 1809, 1754.

**2-Methyl-6-(trifluoromethyl)benzoyl chloride (MTFBC) (23’):**  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.53–7.56 (m, 1H), 7.45–7.51 (m, 2H), 2.48 (s, 3H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  168.3, 135.9, 134.4, 134.1, 130.4, 125.5 (q,  $J = 33.6$  Hz), 123.9 (q,  $J = 3.6$  Hz), 123.2 (q,  $J = 273.4$  Hz), 19.1; LRMS (ESI-TOF):  $m/z$  187 ( $M^+-Cl$ ); IR ( $cm^{-1}$ ): 1797, 1324, 1177, 1138.

**2,6-Bis(trifluoromethyl)benzoic anhydride (2,6-BTFBA) (24):** Mp 163.5–164.5 °C;  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  7.96 (d,  $J = 8.0$  Hz, 4H), 7.78 (t,  $J = 8.0$  Hz, 2H);  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  157.8, 131.2, 130.1, 129.3 (q,  $J = 33.6$  Hz), 127.7, 125.5 (q,  $J = 23.3$  Hz); HRMS (ESI-TOF):  $[M+Na^+]$  calcd for  $C_{18}H_6F_{12}O_3Na$  521.0023, found 521.0006; IR ( $cm^{-1}$ ): 1828, 1767, 1343, 1299, 1137.

#### Typical experimental procedure for the synthesis of *threo*-aleuritic acid lactone 26

An experimental procedure is described for the preparation of lactone **26** using FTFBA with DMAP (Table 7, Entry 1): To a solution of FTFBA (23.9 mg, 0.060 mmol) and DMAP (14.7 mg, 0.120 mmol) in  $CH_2Cl_2$  (21.0 mL) at rt was slowly added a solution of *threo*-aleuritic acid (**25**) (19.6 mg, 0.050 mmol) in  $CH_2Cl_2$  (14.0 mL) with a mechanically driven syringe for 16.5 h. After the reaction mixture had been stirred for 1 h at rt, saturated aqueous  $NaHCO_3$  was added at 0 °C. The mixture was extracted with  $CH_2Cl_2$ , and the organic layer was washed with water and brine, and dried over  $Na_2SO_4$ . After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography (hexane/EtOAc = 3/1) to afford the desired lactone **26** (a mixture of stereoisomeric benzylidene acetals, ca. 1:1, 16.5 mg, 88.1%) as a white solid and its dimer **27** (0.9 mg, 4.8%) as a pale yellow oil.



**threo-Aleuritic acid lactone 26:** Mp 53.5–54.5 °C; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.50–7.46 (m, 2H), 7.38–7.34 (m, 3H), [5.86, 5.84] (s, 1H), 4.15 (t, *J* = 5.5 Hz, 2H), 3.84 (m, 2H), 2.40–2.30 (m, 2H), 1.91–1.29 (m, 22H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 174.0, [138.2, 138.1], 129.2, 128.3, 126.7, [102.5, 102.4], [82.1, 82.0], [80.8, 80.5], 64.2, 34.6, [32.9, 32.8], [32.1, 32.0], 28.8, 28.6, [28.5, 28.4], 28.1, 27.6, [25.7, 25.6], 25.3, 24.9, 24.7, 24.1. The values in square brackets indicate the chemical shifts of the identical carbons of two benzylidene diastereomers; HRMS (ESI-TOF): [M+H<sup>+</sup>] calcd for C<sub>23</sub>H<sub>35</sub>O<sub>4</sub> 375.2535, found 375.2526; IR (cm<sup>-1</sup>): 1732.

**threo-Aleuritic acid lactone dimer 27:** <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.50–7.45 (m, 4H), 7.39–7.34 (m, 6H), 5.86 (s, 2H), 4.08 (t, *J* = 6.5 Hz, 4H), 3.84 (m, 4H), 2.31 (t, *J* = 7.5 Hz, 4H), 1.73–1.26 (m, 44H); <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ 174.0, 138.2, 129.2, 128.3, 126.7, 102.6, [82.7, 82.6], [81.4, 81.3], 64.2, 34.4, [33.1, 33.0], [32.9, 32.8], [29.4, 29.3], [29.1, 29.0], 29.0, 28.9, 28.9, 28.5, 25.8, 25.7, 24.9; HRMS (ESI-TOF): [M+Na<sup>+</sup>] calcd for C<sub>46</sub>H<sub>68</sub>O<sub>8</sub>Na 771.4812, found 771.4827; IR (cm<sup>-1</sup>): 1733.

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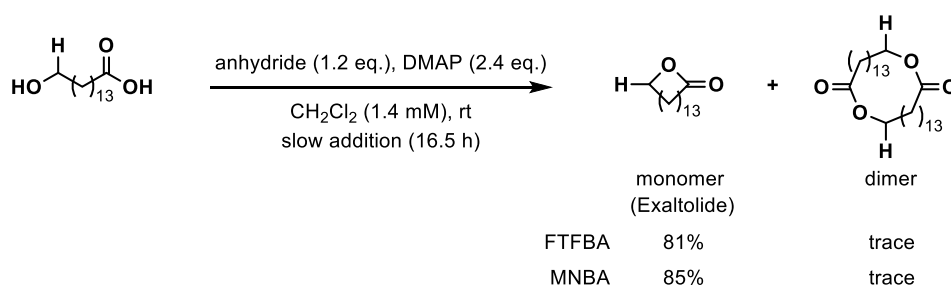
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8. In a preliminary experiment for the synthesis of the protected *threo*-aleuritic acid lactone **26** (Table 7), we investigated the reactivities of several *ortho*-substituted benzoic anhydrides, such as 2-fluorobenzoic anhydride and 2-(trifluoromethyl)benzoic anhydride, to give the desired monomeric lactone **26** in 68% and 58% yields, respectively.
9. Even when 15-hydroxypentadecanoic acid was employed, FTFBA exhibited high reactivity comparable with that of MNBA to give the desired monomeric lactone (Exaltolide, one of synthetic perfume ingredients)<sup>3b,c,10</sup> in high yield with excellent chemoselectivity as shown below.



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