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A Novel Method for the Preparation of Macrolides from ω-Hydroxycarboxylic Acids

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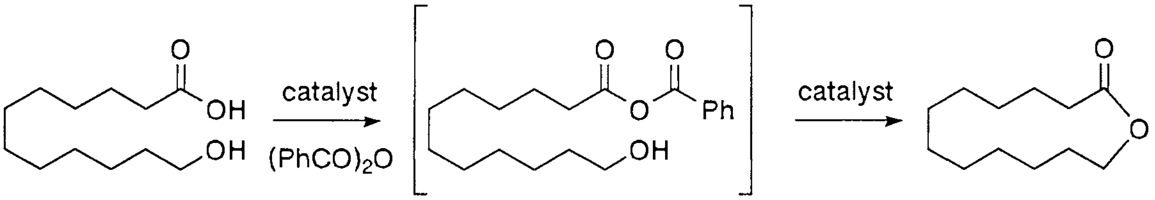
An efficient method for the synthesis of macrolides directly from ω-hydroxycarboxylic acids is established by using 4-(trifluoromethyl)benzoic anhydride and a catalytic amount of active titanium(IV) salts together with chlorotrimethylsilane under mild conditions.

Several macrolide antibiotics have become important therapeutic agents in clinical medicine. As a result, numerous derivatives of various macrolides have been synthesized and the discovery of new macrolide derivatives attracted our attention within the past decades. The chemical synthesis of macrolides made great progress owing to the development of efficient methods for the ring closure to macrolides from ω-hydroxycarboxylic acids (seco-acids) and their activated derivatives. Though a variety of methods have been reported for the synthesis of macrolides,2) there are a few reactions which proceed efficiently under acidic conditions.3) Recently, effective methods for the preparation of macrolides were reported by Inomata *et. al.* and by our group starting from silyl ω-siloxycarboxylates using various Lewis acids.4) The present communication describes a highly efficient method for the preparation of macrolides directly from ω-hydroxycarboxylic acids by combined use of 4-(trifluoromethyl)benzoic anhydride and a catalytic amount of active titanium(IV) salts together with chlorotrimethylsilane.

In the previous report, a novel condensation reaction between nearly equimolar amounts of carboxylic acids and alcohols by the combined use of 4-(trifluoromethyl)benzoic anhydride and a catalytic amount of active titanium(IV) salt together with chlorotrimethylsilane was described.5) It was anticipated then that the cyclization reaction of ω-hydroxycarboxylic acids would similarly proceed under the same reaction conditions.



When the mixture of 12-hydroxydodecanoic acid and 4-(trifluoromethyl)benzoic anhydride in dichloromethane was added over a 5 h period to the suspension of 5 mol% of titanium(IV) salt, generated in situ from 1 mol of $TiCl_4$ and 2 mol of $AgClO_4$, and 3 mol of chlorotrimethylsilane in dichloromethane at room temperature, the desired lactone was obtained in 68% yield. In order to improve the yield of the lactone, several catalysts and reaction temperature were examined, and the best result was attained when the reaction was carried out using $TiCl_2(OTf)_2$ as a catalyst in gently refluxing dichloromethane (Table 1, Entry 4).6)

Next, effect of amount of chlorotrimethylsilane and kind of the substituents in benzoic anhydrides were screened under the optimized reaction conditions. It was revealed that the existence of chlorotrimethylsilane was essential to this reaction in order to keep activity of titanium(IV) catalyst,5) and the use of 3 mol of chlorotrimethylsilane was enough to provide good result in the above reaction (See Table 2).

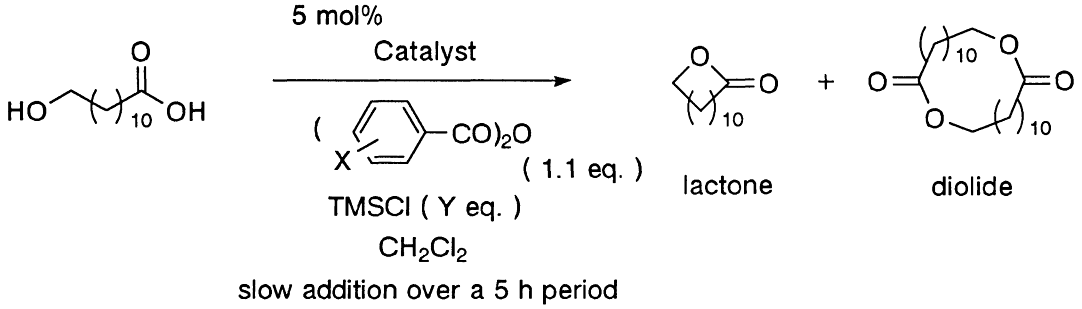


Table 1. Effect of Catalysts and Reaction Temperature

Entry	Catalyst	X	Y	Temp / °C a)	Yield / % b) lactone	 diolide
1	$TiCl_4 + 2AgClO_4$	4-CF_3	3	rt	68	3
2	$TiCl_2(OTf)_2$	4-CF_3	3	rt	29	2
3	$TiCl_2(OTf)_2$	4-CF_3	3	40	81	8
4	**$TiCl_2(OTf)_2$**	4-CF_3	3	**50**	**83**	10
5	$TiCl(OTf)_3$	4-CF_3	3	50	77	5
6	$TiCl_2(OTf)_2$	4-CF_3	3	60	55	16

a) Bath temperature.
b) Isolated yield. The reaction was carried out in 2 mM solution of CH_2Cl_2.

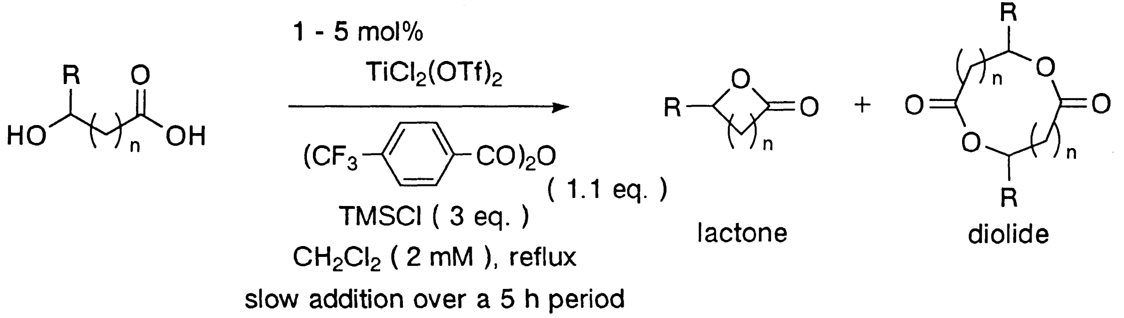
Table 2. Effect of Anhydrides and Amounts of Chlorotrimethylsilane

Entry	Catalyst	X	Y	Temp / °C a)	Yield / % b) lactone	 diolide
1	$TiCl_2(OTf)_2$	4-CF_3	0	50	31	6
2	$TiCl_2(OTf)_2$	4-CF_3	2	50	60	8
3	$TiCl_2(OTf)_2$	**4-CF_3**	**3**	50	**83**	10
4	$TiCl_2(OTf)_2$	4-CF_3	10	50	80	11
5	$TiCl_2(OTf)_2$	3,4-CF_3	3	50	51	13
6	$TiCl_2(OTf)_2$	4-F	3	50	44	14

a) Bath temperature.
b) Isolated yield. The reaction was carried out in 2 mM solution of CH_2Cl_2.

Several examples of the present cyclization reaction are demonstrated in Table 3. In entries 2-8, the corresponding lactones were obtained in higher yields compared with those of previously reported methods. In the synthesis of 12-membered ring lactone, highly diluted condition was required (Entry 1). It is noted that the 13-membered lactone derived from branched seco-acid is isolated in 91% yield as shown in Entry 3.

Table 3. Synthesis of Macrolides from ω-Hydroxycarboxylic Acids



Entry	R	n	Yield / % [a] (Ring number) lactone	diolide
1 [b]	H	9	56 (12)	29 (24)
2	H	10	83 (13)	10 (26)
3	C_6H_{13}	10	91 (13)	6 (26)
4 [c]	C_6H_{13}	10	83 (13)	16 (26)
5	H	11	80 (14)	5 (28)
6	H	12	89 (15)	3 (30)
7	H	13	88 (16)	10 (32)
8	H	14	88 (17)	2 (34)

a) Isolated yield. Each lactone was identified by GC-MS. 5 mol% of catalyst was used. The bath temperature was 50 °C. b) The reaction was carried out in 1 mM solution of CH_2Cl_2. c) One mol% of catalyst was used.

A typical experimental procedure is described for the synthesis of octadecane-12-olide: to a mixture 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 mixture of 12-hydroxyoctadecanoic acid (157.6 mg, 0.524 mmol) and 4-(trifluoromethyl)benzoic anhydride (209.5 mg, 0.578 mmol) in dichloromethane (40 ml) with a mechanically driven syringe over a 5 h period. [The hydroxy acid was dissolved in gently refluxing dichloromethane before use. Then, 4-(trifluoromethyl)benzoic anhydride was added to the solution at rt.] After addition of the solution, the reaction mixture was evaporated to 20 ml and then quenched with aq. sat. $NaHCO_3$. After usual work up, the crude product was purified by TLC on silica gel to afford lactone (135.1 mg, 0.478 mmol) and diolide (9.4 mg, 0.033 mmol) in 91% and 6% yields, respectively.

Even in the cases of labile seco-acids, the reactions proceed smoothly to afford the corresponding lactones in high yields as shown in Scheme 1. The titanium(IV) catalyst generated in situ from $TiCl_4$ and $AgClO_4$ was equally effective in this case to produce the desired lactones in high yields at room temperature. It is noteworthy to refer that (+)-(Z)-9-octadecen-12-olide and (+)-(E)-9-octadecen-12-olide are obtained in high yields without accompanying isomerization of the double bond and also the racemization.

(R) - ricinelaidic acid lactone

$[\alpha]_D^{28}$ + 41.5 ° (c 1.97, $CHCl_3$)
(ref. $[\alpha]_D$ + 41.4 ° (c 1, $CHCl_3$)) 7)

5 mol% $TiCl_2(OTf)_2$, reflux; **89% yield**
5 mol% $TiCl_4$+2$AgClO_4$, rt; **92% yield**

(R) - ricinoleic acid lactone

$[\alpha]_D^{25}$ + 31.5 ° (c 2.99, $CHCl_3$)
(ref. $[\alpha]_D$ + 32.2 ° (c 1, $CHCl_3$)) 7)

5 mol% $TiCl_2(OTf)_2$, reflux; **83% yield**
5 mol% $TiCl_4$+2$AgClO_4$, rt; **83% yield**

Scheme 1.

Thus, an efficient method for the preparation of macrolides directly from ω-hydroxycarboxylic acids was established by use of 4-(trifluoromethyl)benzoic anhydride and a catalytic amount of titanium(IV) salts together with chlorotrimethylsilane under mild conditions.

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