Scandium Trifluoromethanesulfonate as an Extremely Active Lewis Acid Catalyst in Acylation of Alcohols with Acid Anhydrides and Mixed Anhydrides†

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Scandium trifluoromethanesulfonate (triflate), which is commercially available, is a practical and useful Lewis acid catalyst for acylation of alcohols with acid anhydrides or the esterification of alcohols by carboxylic acids in the presence of *p*-nitrobenzoic anhydrides. The remarkably high catalytic activity of scandium triflate can be used for assisting the acylation by acid anhydrides of not only primary alcohols but also sterically-hindered secondary or tertiary alcohols. The method presented is especially effective for selective macrolactonization of *ω*-hydroxy carboxylic acids.

Introduction

The acylation of alcohols by acid anhydrides or acyl chlorides is routinely carried out in the presence of tertiary amines. 4-(Dimethylamino)pyridine (DMAP) and 4-pyrrolidinopyridine (PPY) are known to catalyze this reaction and to increase the rate of acylation by a factor of 10^4.[1] Recently, Vedejs et al. reported tributylphosphine as a similar catalyst for the acylation of alcohols.[2] Although the mechanism of tributylphosphine catalysis is not yet clear,[2,3] the remarkable catalytic activity of these basic and nucleophilic catalysts can be interpreted by assuming the formation of ion pair intermediates such as *N*-acyl-4-(dimethylamino)pyridinium carboxylates or chlorides. In addition to the above catalysts, protic or Lewis acids are also known to catalyze the acylation of alcohols with acid anhydrides. Nevertheless, there is still a great demand for acid catalysts to generate esters under mild conditions.[4−8] We theorized that there must also be *acid* catalysts with an extremely strong catalytic potential similar to that of the basic catalysts (DMAP, Bu_3P), and therefore, we have investigated the possibility of developing new classes of stable acylation catalysts that are insensitive to protic substances like alcohols and carboxylic acids. Thus, we reported in a preliminary paper that scandium triflate catalyzes the acylation of alcohols with acid anhydrides and that its catalytic activity is superior to DMAP and Bu_3P.[9] Further, *we found that this method is effective in the selective benzoylation of aliphatic alcohols in the presence of aromatic alcohols.*

Recently, Mukaiyama et al. reported a viable method for the preparation of carboxylic esters from free carboxylic acids and alcohols by combined use of *p*-(trifluoromethyl)benzoic anhydride and a catalytic amount of active titanium(IV) salt together with chlorotrimethylsilane,[10] and they applied the technique to the macrolactonization of *ω*-hydroxy carboxylic acids.[11]

Scandium triflate was found to be an extremely effective catalyst for this type of esterification. Specifically, we have carried out an esterification of aliphatic carboxylic acids by alcohols *via* mixed anhydrides by the combined use of *p*-nitrobenzoic anhydride and a catalytic amount of scandium triflate.[9] While it seemed to be difficult to synthesize aromatic carboxylic acid esters *via* mixed anhydrides in the preliminary study, *this system has been found to be useful for aromatic carboxylic acids.* Furthermore, *we were able to develop an extremely selective internal esterification of ω-hydroxy carboxylic acids to give medium and large ring lactones through the application of this procedure.* Thus, this paper reports a practical and very general approach to esters which is based on the use of a stable Lewis acid catalyst for acylation of alcohols with acid anhydrides or mixed anhydrides.[12]

Results and Discussion

Scandium Triflate-Catalyzed Acylation of Alcohols with Acid Anhydrides. We first sought various

† Dedicated to Clayton H. Heathcock on the occasion of his 60th birthday.

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(1) Reviews: (a) Cherkasova, E. M.; Bogatkov, S. V.; Golovina, Z. P. *Russ. Chem. Rev.* **1977**, *46*, 246. (b) Höfle, G.; Steglich, V.; Vorbruggen, H. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 569. (c) Scriven, E. F. V. *Chem. Soc. Rev.* **1983**, *12*, 129. Kinetics: (d) Connors, K. A.; Ebaka, C. J. *J. Pharm. Sci.* **1983**, *72*, 366. (e) Connors, K. A.; Lin, S.-F. *J. Pharm. Sci.* **1981**, *70*, 235.

(2) (a) Vedejs, E.; Diver, S. T. *J. Am. Chem. Soc.* **1993**, *115*, 3358. (b) Vedejs, E.; Bennett, N. S.; Conn, L. M.; Diver, S. T.; Gingras, M.; Lin, S.; Oliver, P. A.; Peterson, M. J. *J. Org. Chem.* **1993**, *58*, 7286.

(3) Although several attempts were made to define the structure of the phosphine-activated acylating agent by Vedejs et al., the evidence did not prove that the phosphonium carboxylate was the key intermediate.

(4) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers, Inc.: New York, 1989; p 980.

(5) Recently, $CoCl_2$-catalyzed acetylation of alcohols with acetic anhydride was reported. Iqbal, J.; Srivastava, R. R. *J. Org. Chem.* **1992**, *57*, 2001.

(6) For references on the esterification of trimethylsilyl ethers *via* acid anhydrides or mixed anhydrides using a catalytic amount of Lewis acid, see: (a) Ganem, B.; Small, V. R., Jr. *J. Org. Chem.* **1974**, *39*, 3728. (b) Mukaiyama, T.; Shiina, I.; Miyashita, M. *Chem. Lett.* **1992**, 625. (c) Mukaiyama, T.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1992**, 1747. (d) Miyashita, M.; Shiina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516.

(7) $TiCl_4 + 2AgClO_4$, $TMSO(CH_2)_nCO_2TMS$: Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1993**, 907.

(8) For references on the amidation reaction of weakly nucleophilic amines *via* mixed anhydrides using a catalytic amount of Lewis acid, see: (a) Miyashita, M.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1993**, 1053. (b) Miyashita, M.; Shina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 210. (c) Shiina, I.; Miyashita, M.; Nagai, M.; Mukaiyama, T. *Heterocycles* **1995**, 40, 141.

(9) For a preliminary communication: Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc.* **1995**, *117*, 4413, 6639 (corrections).

(10) Shiina, I.; Miyoshi, M.; Miyashita, M.; Mukaiyama, T. *Chem. Lett.* **1994**, 515.

(11) $(p\text{-}CF_3C_6H_4CO)_2O$, TMSCl, $TiCl_2(OTf)_2$: Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1994**, 677.

(12) Mukaiyama et al. very recently developed an efficient esterification between free carboxylic acids and alcohols by the combined use of octamethylcyclotetrasiloxane and a catalytic amount of titanium(IV) chloride tris(trifluoromethanesulfonate). Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1995**, 141.

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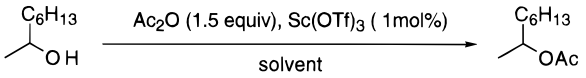
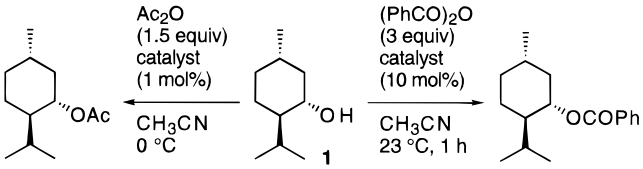
Table 1. Solvent Effect on Scandium Triflate-Catalyzed Acetylation of 2-Octanol with Acetic Anhydride



entry	solvent	condns[a] and results *T* (°C), time (h), conversn[b] (%)
1	CH_3CN	−20, 2, >95
2	CH_3NO_2	23, 0.5, >95[c]
3	toluene or CCl_4	23, 1, >95[c]
4	CH_2Cl_2 or THF	23, 2, >95[c]
5	$CHCl_3$	23, 23, 52[c]

[a] A solution of 2-octanol (0.4 M) was used. [b] The conversion was determined by ^{1}H NMR analysis of the crude product. [c] The conversion was less than 5% yield in the reaction condition of 0 °C for 2 h.

Table 2. Comparison of Catalysts in the Acylation of Menthol with Acid Anhydrides



acetylation[a] conversn[b] (%) (reaction time (min))	catalyst	benzoylation[a] conversion[b] (%)
>95 (15)	$Sc(OTf)_3$	>95
75 (55)	DMAP/Et_3N (3 equiv)	ca. 75[c]
	DMAP	23[c]
	Bu_3P	88[c]

[a] An acetonitrile solution of **1** (0.25 M) was used. [b] The conversion was determined by ^{1}H NMR analysis of the crude product. [c] See ref 2a.

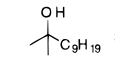
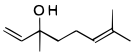
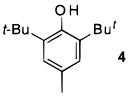
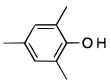
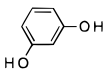
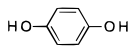
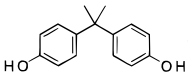
Lewis acids (1 mol %) which promote the model reaction of *sec*-phenethyl alcohol (1 equiv) with acetic anhydride (3 equiv) in dichloromethane. Among several stable metal triflates screened, we found scandium triflate to be quite effective:[13] the reaction proceeded even at 0 °C in the presence of scandium triflate, while it barely proceeded in the presence of lanthanide triflate at 0 °C. Although other Lewis acids such as $Sc(OAc)_3$, $ScCl_3 \cdot 6H_2O$, $Sc(NO_3)_3 \cdot 4H_2O$, $BF_3 \cdot Et_2O$, $SnCl_4$, and $TiCl_4$ were also screened, scandium triflate proved the most effective catalyst for the present reaction.

The effect of solvents in the acetylation of 2-octanol (1 equiv) with acetic anhydride (1.5 equiv) under the influence of 1 mol % of scandium triflate is shown in Table 1. Under these conditions, the reaction proceeded faster in acetonitrile than in other organic solvents. Interestingly, the reaction was very slow in chloroform even at 23 °C.

Following this demonstration of the remarkable catalytic activity of scandium triflate, three catalysts, DMAP, Bu_3P, and $Sc(OTf)_3$, were compared for the acetylation and benzoylation of menthol (**1**) under identical conditions. The results are summarized in Table 2. It was noted that $Sc(OTf)_3$ was not deactivated by the carboxylic acid byproduct of acylation. Vedejs and Diver have reported that the DMAP/Et_3N acetylation is ca. 10-fold faster than the Bu_3P/Et_3N reaction, and the acetylations by both catalysts under amine-free conditions are somewhat slower than with Et_3N present.[2a] In view of the experimental results of Vedejs' group and our own, we might conclude that $Sc(OTf)_3$ is the most effective acylation catalyst.

To explore the generality and scope of the above scandium triflate-catalyzed acylation, the reaction was

Table 3. The $Sc(OTf)_3$-Catalyzed Acylation of Alcohols with Acid Anhydrides

entry	alcohol	$(R^1CO)_2O$[a] (equiv)	$Sc(OTf)_3$[b] (mol %)	condition[c] (°C, h)	yield[d] (%)
1	$PhCH_2CH_2CH_2OH$ **2**	Ac_2O (1.5)	0.1	rt, 1	>95
2	PhMeCHOH	Ac_2O (1.5)	0.1	rt, 1	>95
3	**1**	Ac_2O (1.5)	0.1	rt, 1	>95
4		$(EtCO)_2O$ (1.5)	1.0	0, 1	>95
5		$(t\text{-}BuCO)_2O$ (1.5)	1.0	rt, 1	>95
6		$(PhCO)_2O$ (3.0)	1.0	rt, 20	>95
7	 **3**	Ac_2O (3.0)	1.0	rt, 1	56 (39)[e]
8		Ac_2O (5.0)	1.0	0, 0.8	85 (9)[e]
9		Ac_2O (5.0)	1.0	-20, 5.5	94 (1)[e]
10[f]		Ac_2O (5.0)	[DMAP (1.0)]	rt, 5.5	< 1 (0)[e]
11		Ac_2O (5.0)	1.0	-20, 5	91 (9)[e]
12		Ac_2O[g]	0.5	-50~-43, 1	66 (5)[h]
13		Ac_2O[g]	2.0	-45, 1	76 (14)[h]
14		Ac_2O[g]	2.0	-20, 2.5	68 (8)[h]
15		Ac_2O[g]	1.0	-40, 1.3	>95 (<1)[e]
16		Ac_2O (3.0)	1.0	-20, 0.5	>95
17	 **4**	Ac_2O (1.5)	1.0	rt, 1	>95
18		$(PhCO)_2O$ (1.5)	5.0	rt, 1.3	>95
19		$(PhCO)_2O$ (1.5)	2.5	rt, 1.3	95
20		$(PhCO)_2O$ (1.5)	2.5	rt, 1	>95
21		$(PhCO)_2O$ (1.5)	2.5	rt, 0.5	92
22		$(PhCO)_2O$ (1.5)	2.5	rt, 1.2	>95

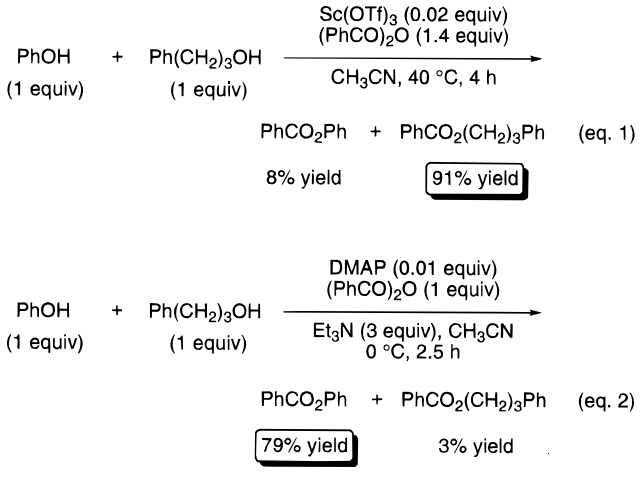
[a] Additional amount (equiv) per mol of hydroxy group. [b] Additional amount (mol %) per mol of hydroxy group. [c] An acetonitrile solution of substrate (0.25 M) was used. [d] Unless otherwise noted, isolated yield by column chromatography on silica gel was indicated. [e] Isolated yield of olefins, which are produced by the elimination of acetoxy group, was indicated in parentheses. [f] 1.0 mol % of DMAP was used in place of $Sc(OTf)_3$. [g] Acetic anhydride as a solvent was used in place of acetonitrile. [h] Chemical yield of primary acetates, which are produced by the 1,3-migration of acetoxy group, was indicated in parentheses. It was determined by ^{1}H NMR analysis of the crude product.

(13) It was previously reported that scandium triflate is a good Lewis acid catalyst for several reactions. Review: (a) Kobayashi, S. *Synlett* **1994**, 689. Meerwein−Ponndorf−Verley-type reductions: (b) Castellani, C. B.; Carugo, O.; Perotti, A.; Sacchi, D.; Invernizzi, A. G.; Vidari, G. *J. Mol. Catal.* **1993**, *85*, 65. Aldol and Michael reactions: (c) Kobayashi, S.; Hachiya, I.; Araki, M. *Synlett* **1993**, 472. Diels-Alder reaction: (d) Kobayashi, S.; Hachiya, I.; Ishitani, H. *Tetrahedron Lett.* **1993**, *34*, 3755. (e) Kobayashi, S.; Araki, M.; Hachiya, I. *J. Org. Chem.* **1994**, *59*, 3758. Allylation: (f) Hachiya, I.; Kobayashi, S. *J. Org. Chem.* **1993**, *58*, 6958. Friedel−Crafts acylation: (g) Kawada, A.; Mitamura, S.; Kobayashi, S. *Synlett* **1994**, 545. Reactions of imines: (h) Kobayashi, S.; Araki, M.; Ishitani, H.; Nagayama, S.; Hachiya, I. *Synlett* **1995**, 233.

examined with various structurally diverse alcohols and acid anhydrides. The results are summarized in Table 3. Scandium triflate is capable of acylating not only primary alcohols, but also sterically-hindered secondary or tertiary alcohols with various acid anhydrides. Surprisingly, tertiary alcohols were easily acetylated under very mild conditions. In the acetylation of 2-methyl-2-undecanol, elimination byproducts were produced together with the desired acetate (Table 3, entry 7). When the reaction was carried out in the presence of excess acetic anhydride at as low a temperature as possible (−50 to −20 °C), the relative amount of acetylation increased and the elimination products decreased (Table 3, entry 9).[14] For more acid-sensitive substrates such as allylic or benzylic tertiary alcohols, the reaction proceeded successfully using acetic anhydride as a solvent at as low a temperature as possible (−50 to −20 °C, Table 3, entries 12−15). In most cases of DMAP-catalyzed acetylation of tertiary alcohols, it is necessary to use more than 10 mol % of DMAP and an excess of amine at conditions of high concentration (Table 3, entry 9 vs entry 10).[1]

Although the acylation of menthol **1** with benzoic anhydride in the presence of 1 mol % of scandium triflate was relatively slow (Table 3, entry 6), the benzoylation of various aromatic alcohols smoothly proceeded in the presence of 2.5−5 mol % of scandium triflate at room temperature (Table 3, entries 18−22). The present reactions were very clean, and byproducts followed by Fries rearrangement of aromatic esters were not observed in a detectable amount.[29]

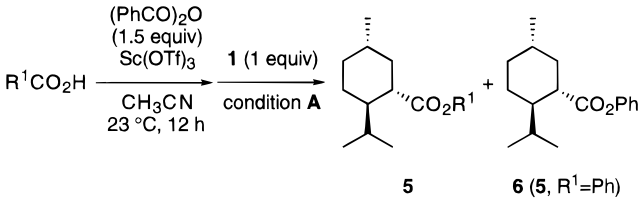
It is in general known that aromatic alcohols are predominantly acylated in the presence of aliphatic alcohols under basic or nucleophilic condition. Several useful procedures for selective acylation of aromatic alcohols have already been developed.[15] To clarify which reacts with acid anhydrides faster in the presence of scandium triflate, aromatic alcohols or aliphatic alcohols, we examined chemoselective benzoylation for a 1:1 mixture of phenol and 3-phenylpropanol (eq 1). Surprisingly, 3-phenylpropyl benzoate was obtained in 91% chemical yield and with 92% selectivity. The chemoselectivity for aliphatic alcohol which could be achieved



(14) It was ascertained by independent experiments that **3** and the corresponding acetate gradually eliminated in the presence of $Sc(OTf)_3$.

(15) (a) Orazi, O. O.; Corral, R. A.; Zinczuk, J. *Rev. Latinoamer. Quim.* **1978**, *9*, 211. (b) Illi, V. O. *Tetrahedron Lett.* **1979**, *20*, 2431. (c) Mukaiyama, T.; Pai, F.-C.; Onaka, M.; Narasaka, K. *Chem. Lett.* **1980**, 563. (d) Paradisi, M. P.; Zecchini, G. P.; Torrini, I. *Tetrahedron Lett.* **1986**, *27*, 5029.

Table 4. The $Sc(OTf)_3$-Catalyzed Acylation of Menthol with Carboxylic Acids



R^1CO_2H (equiv)	$Sc(OTf)_3$ (mol %)	condition A[a] (°C, h)	**5**[b] (% yield)	**6**[b] (% yield)
AcOH (2.0)	10	0, 1	92	0
AcOH (2.0)	5	0, 10	85	<1
AcOH (1.5)	1	23, 8	83	5
$EtCO_2H$ (2.0)	5	0, 10	77	0
$EtCO_2H$ (1.5)	1	23, 8	85	4

[a] See text. [b] Isolated yield.

with our simple procedure was quite remarkable and the inverse of that observed for DMAP-catalyzed benzoylation in the presence of triethylamine (eq 2). The change in selectivities is attributed to the difference of nucleophilicities between aromatic and aliphatic alcohols under each condition: aliphatic alcohol is more nucleophilic under acidic conditions, but on the other hand aromatic alcohol is more nucleophilic under basic conditions.

The highly catalytic system is especially attractive for large-scale synthesis (menthol (20 mmol), Ac_2O (30 mmol), CH_3CN (20 mL), $Sc(OTf)_3$ (0.002 mmol), room temperature, 1 h, 99% acetate after chromatography).

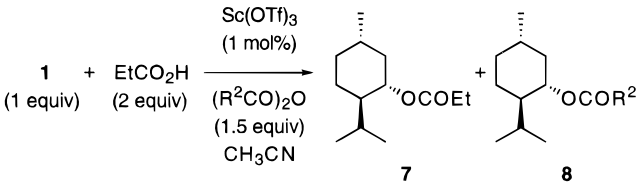
Scandium Triflate-Catalyzed Esterification between Alcohols and Carboxylic Acids in the Presence of *p*-Nitrobenzoic Anhydride. Because the acylation of menthol **1** with benzoic anhydride (Table 3, entry 6) was relatively slow in comparison with the acylation using other aliphatic carboxylic acid anhydrides (Table 3, entries 3−5), *we have developed a convenient esterification between alcohols and carboxylic acids promoted by a catalytic amount of $Sc(OTf)_3$.*

The esterification of aliphtic carboxylic acids with alcohols in the presence of an equimolar amount of benzoic anhydride would proceed smoothly if the mixed anhydride could be generated from the aliphatic carboxylic acid and benzoic anhydride in the presence of a catalytic amount of $Sc(OTf)_3$.[6−8,10,11,16] Actually, the corresponding esters were obtained in high yield with excellent chemoselectivity from menthol **1** and carboxylic acids by the following experimental procedure: after a mixture of acetic acid or propanoic acid and benzoic anhydride in acetonitrile was stirred in the presence of 1−10 mol % of $Sc(OTf)_3$ at room temperature for 12 h, menthol **1** was added to the solution precooled to 0 °C, and the mixture was stirred under conditions A (see Table 4).

The phenyl ring substituent effect of benzoic anhydride was examined to find the most suitable anhydride additive, and *p*-nitrobenzoic anhydride was found to give good reactivity and high chemoselectivity (Table 5). In the reaction using *p*-nitrobenzoic anhydride, nitromethane was more effective than acetonitrile as a solvent with respect to its solubility. *p*-(Trifluoromethyl)benzoic anhydride which was used by Mukaiyama et al. was also

(16) For a reference on DMAP-promoted esterification of alcohols with mixed anhydrides, see: Inanaga, J.; Hirata, K.; Saeki, T.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1979**, *52*, 1989.

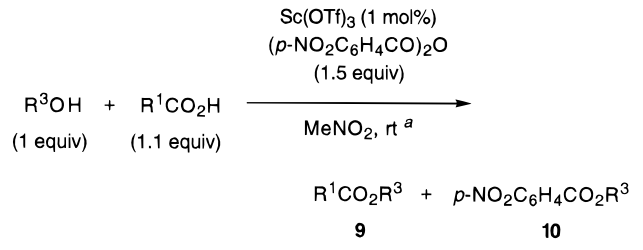
Table 5. Scandium Triflate-Catalyzed Esterification between 1 and Propanoic Acid



$(R^2CO)_2O$ R^2-	solvent	condns (°C, h)	conversn[a] (%)	ratio **7**[b]:**8**[c]
p-$NO_2C_6H_4$	$MeNO_2$	23, 2	>95	>99:<1
	MeCN	23, 3	71	>99:<1
p-$CF_3C_6H_4$		23, 2	>95	>99:<1
2,4,6-$Cl_3C_6H_2$		23, 2	<5	
Ph		23, 4	>95	88:12
t-Bu		23, 2.5	>95	85:15
Cl_3C		0, 1	>95	62:38
F_3C		0, 0.5	>95	25:75

[a] Isolated yield. [b] **7** corresponds to **5** (R^1 = Et; see Table 4). [c] **8** corresponds to **5** ($R^1 = R^2$; see Table 4).

Table 6. Scandium Triflate-Catalyzed Esterification of Alcohols with Carboxylic Acids



entry	R_3OH	R^1CO_2H	time (h)	conversn[b] (%) **9**	**10**
1	**2**	$EtCO_2H$	2	>95	0
2		*i*-$PrCO_2H$	3	>95	0
3	**1**	$EtCO_2H$	2	>95	0
4[c]		$EtCO_2H$	3	89	0
5		*i*-$PrCO_2H$	2	>95	<1
6		(*E*)-MeCH=C-$MeCO_2H$	2	>95	0
7		*t*-$BuCO_2H$	3	>95	0
8	**3**	$EtCO_2H$	2	—[d]	—[d]
9	2,6-dimethylphenol	*i*-$PrCO_2H$	3.5	>95	0
10		*t*-$BuCO_2H$	4	90	0
11[e]	**4**	$EtCO_2H$	12.5	86	2
12[f]	**2**	$PhCO_2H$	3.5	>95	2
13[f]		2,4,6-Me_3-$C_6H_2CO_2H$	0.8	>95	0
14[f]	**1**	$PhCO_2H$	16	>95	0
15[f]	PhOH	$PhCO_2H$	1	>95	0
16[f]	2,6-dimethylphenol	$PhCO_2H$	1	89	0

[a] Room temperature. [b] Isolated yield by column chromatography on silica gel. [c] 1 equiv of *p*-nitrobenzoic anhydride was used. [d] Although the esterification did proceed, the acyloxy group of the ester produced was gradually eliminated under the same conditions. [e] 10 mol % of scandium triflate and 2.0 equiv of propanoic acid were used. [f] 5 mol % of scandium triflate and 1.5 equiv of carboxylic acid were used.

very effective in this system,[6−8,10,11] but the materials from which it is made are more expensive. 2,4,6-Trichlorobenzoic anhydride which was used by Yamaguchi et al. was not effective at all.[16]

Several examples of the esterification of free alcohols with free carboxylic acids under the best conditions (additive: (*p*-$NO_2C_6H_4CO)_2O$ (1.5 equiv), solvent: $MeNO_2$) are shown in Table 6. This method gave excellent results for the reaction between various alcohols except for tertiary alcohols and carboxylic acids. *It is noteworthy that the esterification smoothly proceeded with not only aliphatic carboxylic acids but also aromatic acids such as 2,4,6-trimethylbenzoic acid.* In addition, the benzoylation of aromatic alcohols with benzoic acid, as well as the reaction of alcohols with benzoic anhydride, was much faster than that of aliphatic alcohols. The experimental procedure is extremely simple and facile: a catalytic amount of $Sc(OTf)_3$ is employed at room temperature in a mixed solution of alcohols, carboxylic acids, and *p*-nitrobenzoic anhydride to afford the desired esters in high yield, and prior preparation of mixed anhydrides is unnecessary.

Highly Selective Lactonization Catalyzed by Scandium Triflate. Since natural products of the macrolide type possess potent antibiotic, antitumoral, and other types of interesting biochemical activity, their syntheses have captured the imagination of many synthetic chemists.[17] Recent landmark achievements in the synthesis of macrolides have necessitated the development of mild and efficient methods for ring closure to macrocyclic lactones from ω-hydroxy carboxylic acids[11,18,19] or their activated derivatives.[7,16,18,20] A wide variety of methods have already been developed, and most of them are effective for preparation of 13- to 19-membered lactones.[7,11,16,19,20] However, a large quantity of diolides is usually formed in the preparation of 8- to 12-membered lactones. To our knowledge, there are no general methods for highly selective monolide synthesis; thus, considerable effort continues to be expended in search of more efficient techniques.

Scandium triflate-catalyzed acylation was found to be the method of choice for internal esterification of ω-hydroxy carboxylic acids to medium and large ring lactones. This was based on the following considerations: (1) Because lactone formation becomes relatively slow in

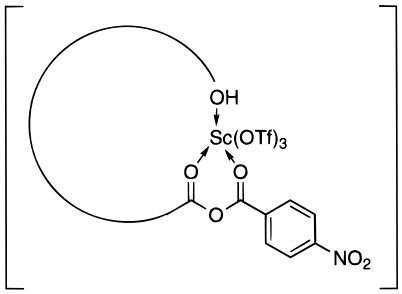
(17) *Recent Progress in the Chemical Synthesis of Antibiotics*; Lukacs, G., Ohno, M., Eds.; Springer-Verlag: Berlin, 1990.

(18) For representative reviews, see: (a) Masamune, S.; Bates, G. S.; Corcoran, J. W. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 585. (b) Nicolaou, K. C. *Tetrahedron* **1977**, *33*, 683. (c) Back, T. G. *Tetrahedron* **1977**, *33*, 3041. (d) Trost, B. M.; Fleming, I. In *Comprehensive Organic Synthesis*; Benz, G., Ed; Pergamon Press: Oxford, 1991; Vol. 6, p 323.

(19) For representative references to lactonization of ω-hydroxy carboxylic acids, see the following. 2,2′-Dipyridyl disulfide, Ph_3P: (a) Corey, E. J.; K. C. Nicolaou *J. Am. Chem. Soc.* **1974**, *96*, 5614. 2,2′-Bis(4-*tert*-butyl-*N*-alkylimidazolyl) disulfide, Ph_3P: (b) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, *28*, 3409. (c) 1-Alkyl-2-halopyridinium salts, Et_3N: (c) Mukaiyama, T.; Usui, M.; Saigo, K. *Chem. Lett.* **1976**, 49. DEAD, Ph_3P: (d) Kurihara, T.; Nakajima, Y.; Mitsunobu, O. *Tetrahedron Lett.* **1976**, *28*, 2455. $Me_2NCH(OCH_2Bu^t)_2$: (e) Vorbrüggen, H.; Krolikiewicz, K. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 876. $BF_3{\cdot}Et_2O$, polystyrene: (f) Scott, L. *Synthesis* **1976**, 738. Cyanuric chloride: (g) Venkataraman, K.; Wagle, D. R. *Tetrahedron Lett.* **1980**, *21*, 1893. Bu_2SnO: (h) Steliou, K.; Szczygielska-Nowosielska, A.; Favre, A,; Poupart, M.-A.; Hanessian, S. *J. Am. Chem. Soc.* **1980**, *102*, 7578. (i) Steliou, K.; Poupart, M.-A. *J. Am. Chem. Soc.* **1983**, *105*, 7130. *N,N,N′,N′*-Tetramethylchloroformamidinium chloride, collidine: (j) Fujisawa, T.; Mori, T.; Fukumoto, K.; Sato, T. *Chem. Lett.* **1982**, 1891. DCC, DMAP, DMAP·HCl: (k) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394. $(Bu_2ClSnOSnBu_2OH)_2$, $(Bu_2(SCN)SnOSnBu_2OH)_2$: (l) Otera, J.; Yano, T.; Himeno, Y.; Nozaki, H. *Tetrahedron Lett.* **1986**, *27*, 4501. Zeolite molecular sieves: (m) Tatsumi, T.; Sakashita, H.; Asano, K. *J. Chem. Soc., Chem. Commun.* **1993**, 1264.

(20) For representative references to lactonization of activated derivatives derived from ω-hydroxy carboxylic acids, see: 2-Pyridine thioester, $AgClO_4$ or $AgBF_4$: (a) Gerlach, H.; Thalmann, A. *Helv. Chem. Acta* **1974**, *57*, 2661. $HO(CH_2)_nCOSR$, $Hg(OCOCF_3)_2$: (b) Masamune, S.; Kamata, S.; Schilling, W. *J. Am. Chem. Soc.* **1975**, *97*, 3515. $TMSO(CH_2)_nCO_2TMS$, Pr_2BOTf: (c) Taniguchi, N.; Kinoshita, H.; Inomata, K.; Kotake, H. *Chem. Lett.* **1984**, 1347. $HO(CH_2)_nCO_2Et$, ZrO_2 (hydrous): (d) Kuno, H.; Shibagaki, M.; Takahashi, K.; Honda, I.; Matsushita, H. *Chem. Lett.* **1992**, 571. $HO(CH_2)_nCO_2CH_2CF_3$, Bu_3SnOMe: (e) White, J. D.; Green, N. J.; Fleming, F. F. *Tetrahedron Lett.* **1993**, *34*, 3515.

going from common to large ring sizes, slow addition of ω-hydroxy carboxylic acid to the medium is required for maintenance of high dilution.[20a] (2) The catalytic activity of the esterification should be high, even under high dilution. (3) The catalyst is required to activate both carboxy and hydroxy groups in an ω-hydroxy carboxylic acid and allow them to come near each other for selective internal esterification. Our acylation catalyst, scandium triflate, in Mukaiyama's esterification system is characterized by outstanding catalysis, and can coordinate with both the mixed anhydride moiety and the hydroxy group to give a possible reaction intermediate **11**. It is not yet clear whether other active intermediate species such as scandium carboxylates are produced *via* interconversion between scandium triflate and carboxylic anhydrides under the conditions.



Possible Intermediate **11**

A series of ω-hydroxy carboxylic acids, $HO(CH_2)_nCO_2H$ with $n = 5-15$, was utilized in the cyclization studies. These substrates were directly subjected to lactonization by slow addition to a mixed solution of 10−20 mol % of scandium triflate and 2 equiv of *p*-nitrobenzoic anhydride in acetonitrile at reflux. The addition was conveniently performed using a mechanically driven syringe. After completion of the reaction the monomeric lactone and the dimeric cyclic ester (diolide) were isolated. The identity of each lactone was proved by comparison with authentic sample. As indicated in Table 7, the desired lactones were obtained in good to excellent yields in all cases of $n = 5-15$. Surprisingly, few diolides or other oligomeric esters were obtained. *To the best of our knowledge, this is the most selective monomeric lactonization method available. It is particularly noteworthy that 8- to 12-membered lactones were obtained in high yields, without producing a large quantity of diolides.* The powerful efficiency of this system is demonstrated in comparison with other typical systems as shown in Table 8.

Conclusion

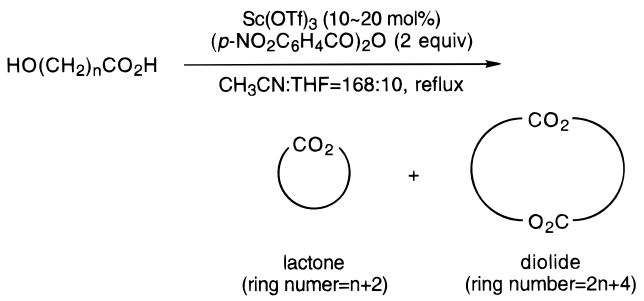
In summary, we have demonstrated that scandium triflate, which is commercially available, is a practical and useful Lewis acid catalyst for acylation of alcohols with acid anhydrides and esterification between alcohols and carboxylic acids in the presence of *p*-nitrobenzoic anhydride because of its remarkable catalytic potential and stability. The development of this method allows the preparation of lactones in excellent yield with high selectivity, regardless of ring size.

Experimental Section

General Procedures. The mass spectra were recorded with a direct-inlet system operating at 20 eV. The high-resolution mass spectra (HRMS) were conducted at Daikin Industries, Ltd., Japan. IR spectra were measured as thin films on NaCl plates unless otherwise noted. For thin layer chromatography (TLC) analysis, Merck precoated TLC plates (silica gel 60 GF^{254}, 0.25 mm) were used. The products were purified by preparative column chromatography on silica gel E. Merck 9385. Microanalyses were carried out at the School of Agriculture, Nagoya University.

Ether and tetrahydrofuran (THF) were purchased from Aldrich Chemical Co. as "anhydrous" and stored over 4A molecular sieves. Acetonitrile, nitromethane, and methylene chloride were freshly distilled from calcium hydride. Scandium trifluoromethanesulfonate purchased from Fluka was used without further purification.

Table 7. Selective Lactonization of ω-Hydroxy Carboxylic Acids



n	$Sc(OTf)_3$ (mol %)	slow addition[a] (h)	reaction time[b] (h)	yield[c] (%) of lactone	yield[c] (%) of diolide
5	20	15	5	>99	<1
6	20	15	5	71	<1
7	20	15	5	52	3
8	20	15	5	87	<5
9	20	15	5	77	2
10	10	15	0	78	2
11	10	6	0	91	3
12	10	15	5	94	<1
13	10	15	5	99	<1
14	10	9	0	99	<1
15	10	9	0	92	<1

[a] Slow addition of a solution of ω-hydroxy carboxylic acid in THF to a refluxing solution of $Sc(OTf)_3$ and $(p\text{-}NO_2C_6H_4CO)_2O$ in acetonitrile. [b] After addition of ω-hydroxy carboxylic acid, the reaction mixture was stirred for the hours indicated at reflux. [c] Isolated yield.

Typical Procedure for Acylation of Alcohols with Acid Anhydrides (Table 3, Entry 3)**.** To a mixture of menthol (938 mg, 6 mmol) and acetic anhydride (849 μL, 9 mmol) in acetonitrile (24 mL) was added dropwise an acetonitrile solution (60 μL, 0.006 mmol, 0.1 M) of scandium triflate at room temperature. After being stirred at room temperature for 1 h, the solution was quenched with aqueous sodium hydrogen carbonate, and the product was extracted with ether. The organic layers were dried over magnesium sulfate, filtrated, and concentrated *in vacuo* to afford the crude product. Further purification of (1*S*,3*R*,5*S*)-5-methyl-2-(1-methylethyl)-cyclohexyl acetate[23] was done by column chromatography on silica gel (1.17 g, 98% isolated yield): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (d, $J = 7.0$ Hz, 3H), 0.89 (d, $J = 7.0$ Hz, 3H), 0.90 (d, $J = 6.6$ Hz, 3H), 0.84−1.14 (m, 3H), 1.30−1.60 (m, 2H), 1.79−1.93 (m, 2H), 1.93−2.04 (m, 2H), 2.03 (s, 3H), 4.67 (dt, $J = 4.4$, 10.8 Hz, 1H).

Other esters synthesized by essentially the same procedure were the following.

3-Phenylpropyl acetate (Table 3, entry 1):[21] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90−2.01 (m, 2H), 2.05 (s, 3H), 2.69 (t, $J = 7.4$ Hz, 2H), 4.09 (t, $J = 6.5$ Hz, 2H), 7.11−7.33 (m, 5H).

1-Phenylethyl acetate (Table 3, entry 2):[22] ^{1}H NMR

(21) Alexakis, A.; Jachiet, D.; Normant, J. F. *Tetrahedron* **1986**, *42*, 5607.
(22) Mitsui, S.; Kudo, Y. *Tetrahedron* **1967**, *23*, 4271.
(23) Takahashi, K.; Shibagaki, M.; Matsushita, H. *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2353.

Table 8. Comparison of Yield (%) in the Selective Lactonization of ω-Hydroxy Carboxylic Acids Using Typical Reagents[a]

	n[b]										
reagents	5	6	7	8	9	10	11	12	13	14	15
acidic											
$Sc(OTf)_3$/$(4\text{-}NO_2C_6H_4CO)_2O$	>99 (<1)	71 (<1)	52 (3)	87 (<5)	77 (2)	78 (2)	91 (3)	94 (<1)	99 (<1)	99 (<1)	92 (<1)
$TiCl_2(OTf)_2$/TMSCl(4-$CF_3C_6H_4CO)_2O$[d]						56 (29)	83 (10)	80 (5)	89 (3)	88 (10)	88 (2)
$TiCl_4$-2$AgClO_4$/$(4\text{-}CF_3C_6H_4CO)_2O$[e,f]	70 (0)	0 (50)	0 (40)	33 (47)	70 (23)		75 (7)			89 (4)	
Pr_2BOTf[f,g]							83 (17)	89		94	85
BF_3·Et_2O/polystyrene[h]							41[c]		46[c]	77[c]	77[c]
neutral											
Bu_3SnX[i,j]					0 (82)		45 (40)	60 (22)		74 (17)	81 (14)
ZrO_2 (hydrous)[k,l]	99 (0)	49 (51)	36 (38)				8 (<1)			52 (0)	
distannoxane[m]							(82)	20	19	78	81
Bu_2SnO[n]			0 (20)			5	22			63(8)	60 (15)
$Me_2NCH(OCH_2Bu^t)_2$[o]			0 (14)								40 (17)
basic/nucleophilic											
DMAP/Et_3N/$(2,4,6\text{-}Cl_3C_6H_2CO)_2O$[p]			36 (23)			48 (20)					
DMAP/DCC/DMAP·HCl[q]							32 (32)	77 (11)		95 (trace)	96
cyanuric chloride/Et_3N[r]							70			68	85
Bu_3P/DEAD[t]	40 (53)		0 (70)				63 (32)				
1-methyl-2-chloropyridinium iodide/Et_3N[u]	89 (0)		13 (34)			61 (24)	69 (14)			84 (3)	
2,2′-(4-*t*-Bu-*N*-alkylimidazolyl) disulfide/Ph_3P[v]		0 (93)					87[c]		90[c]		83
2,2′-dipyridyl disulfide/Ph_3P[w]	71 (7)		8 (41)			47 (30)	66 (7)	68 (6)		80 (5)	85 (15)[n]

[a] Isolated yield (%) of monomeric lactones is presented. Isolated yield (%) of diolides is presented in parentheses. [b] $HO(CH_2)_nCO_2H$. [c] GLC yield (%). [d] Reference 11. [e] Reference 7. [f] ω-(Trimethylsiloxy) carboxylates were used. [g] Reference 20c. [h] Reference 19f. [i] Reference 20e. [j] 1,1,2-Trifluoroethyl esters of ω-hydroxy carboxylic acids were used. [k] Reference 20d. [l] Ethyl esters of ω-hydroxy carboxylic acids were used. [m] Reference 19l. [n] References 19h and 19i. [o] Reference 19e. [p] Reference 16. [q] Reference 19k. [r] Reference 19g. [s] Reference 19d. [t] Diethyyl azodicarboxylate (DEAD). [u] Reference 19c. [v] Reference 19b. [w] Reference 19a.

($CDCl_3$, 300 MHz) δ 1.53 (d, J = 6.6 Hz, 3H), 2.07 (s, 3H), 5.88 (q, J = 6.6 Hz, 1H), 7.26−7.41 (m, 5H).

(1*S*,3*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl propanoate (Table 3, entry 4):[24] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (d, J = 7.0 Hz, 3H), 0.81−1.10 (m, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 7.0 Hz, 3H), 1.14 (t, J = 7.6 Hz, 3H), 1.25−1.44 (m, 1H), 1.44−1.56 (m, 1H), 1.61−1.74 (m, 2H), 1.75−2.05 (m, 2H), 2.30 (q, J = 7.6 Hz, 2H), 4.68 (dt, J = 4.4, 10.8 Hz, 1H).

(1*S*,3*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl 2,2-dimethylpropanoate (Table 3, entry 5):[25] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (d, J = 7.0 Hz, 3H), 0.80−1.11 (m, 3H), 0.89 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.8 Hz, 3H), 1.19 (s, 9H), 1.30−1.44 (m, 1H), 1.44−1.56 (m, 1H), 1.62−1.72 (m, 2H), 1.82−2.00 (m, 2H), 4.62 (dt, J = 4.4, 10.8 Hz, 1H).

(1*S*,3*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl benzoate (Table 3, entry 6):[26] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.80 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.98−1.22 (m, 2H), 1.48−1.66 (m, 3H, CH), 1.68−1.80 (m, 2H), 1.90-2.18 (m, 2H), 4.94 (dt, J = 4.4, 11.0 Hz, 1H), 7.39−7.58 (m, 3H), 8.01−8.08 (m, 2H).

1,1-Dimethyldecanyl acetate (Table 3, entries 7−10): IR (film) 2928, 1857, 1736 (CO_2), 1468, 1385, 1368, 1258, 1140, 1115, 1019, 943 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.88 (t, J = 6.6 Hz, 3H), 1.19−1.40 (br, 12 H), 1.42 (s, 6H), 1.68−1.78 (m, 2H), 1.96 (s, 3H); Anal. Calcd for $C_{14}H_{28}O_2$: C, 73.63; H, 12.36. Found: C, 73.59; H, 12.39. 2-Methyl-2-undecene (byproduct): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.60 (s, 3H, C=CMeCH_3), 1.69 (d, J = 1.2 Hz, 3H, C=CCH_3Me), 5.06−5.16 (m, 1H, CH=C), other resonances could not be discerned. 2-Methyl-1-undecene (byproduct): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.71 (s, 3H, CH_3C=C), 4.62−4.70 (m, 2H, H_2C=C), other resonances could not be discerned.

1-Methylcyclohexyl acetate (Table 3, entry 11):[5] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25−1.60 (m, 8H), 1.47 (s, 3H), 2.00 (s, 3H), 2.08−2.16 (m, 2H).

2,4,6-Trimethylphenyl benzoate (Table 3, entry 18):[27] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.15 (s, 6H), 2.30 (s, 3H), 6.92 (s, J = 2.2, 11.0 Hz, 2H), 7.66 (tt, J = 2.2, 11.0 Hz, 1H), 8.20−8.29 (m, 2H).

***o*-Phenylene dibenzoate** (Table 3, entry 19):[28,29] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.36−7.45 (m, 8H), 7.54 (tt, J = 1.4, 7.4 Hz, 2H), 8.06−8.11 (m, 4H).

***m*-Phenylene dibenzoate** (Table 3, entry 20):[29] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.14−7.22 (m, 3H), 7.45−7.57 (m, 5H), 7.65 (tt, J = 1.4, 7.4 Hz, 2H), 8.18−8.25 (m, 4H).

***p*-Phenylene dibenzoate** (Table 3, entry 21):[29] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.30 (s, 4H), 7.48−7.57 (m, 4H), 7.66 (tt, J = 1.4, 7.4 Hz, 2H), 8.18−8.25 (m, 4H).

2,2-Bis[*p*-(benzoyloxy)phenyl]propane (Table 3, entry 22):[30] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.73 (s, 6H), 7.14 (dt, J = 3.5, 13.2 Hz, 4H), 7.32 (dt, J = 3.5, 13.2 Hz, 4H), 7.44−7.58 (m, 4H), 7.64 (tt, J = 2.0, 11.0 Hz, 2H), 8.12−8.26 (m, 4H).

Phenyl benzoate (in eq 3):[31] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.11−7.24 (m, 3H), 7.32−7.49 (m, 4H), 7.57 (tt, J = 1.4, 7.4 Hz, 1H), 8.10−8.18 (m, 2H).

3-Phenylpropyl benzoate (in eq 3):[6d] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03−2.17 (m, 2H), 2.80 (t, J = 7.7 Hz, 2H), 4.34 (t, J = 6.5 Hz, 2H), 7.16−7.36 (m, 5H), 7.40−7.50 (m, 2H), 7.57 (tt, J = 1.3, 7.4 Hz, 1H), 8.0−8.08 (m, 2H).

Typical Procedure for Acetylation of Acid-Sensitive Tertiary Alcohols (Table 3, Entry 13)**.** To a solution of 3-methyl-1-dodecen-3-ol (198.4 mg, 1 mmol) in acetic anhydride (4 mL) was added dropwise a cloudy acetonitrile solution (200 μL, 0.02 mmol, 0.1 M) of scandium triflate at −45 °C. After being stirred at the same temperature for 1 h, the solution was *carefully* quenched with aqueous sodium hydrogen carbonate, and the product was extracted with ether. The organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to crude product. Purification was done by column chromatography on silica gel (eluent: hexane only−hexane/ethyl acetate, 20:1) to give the mixture of 3-acetoxy-

(24) Rupe, H. *Liebigs Ann. Chem.* **1903**, *327*, 157.
(25) Kunieda, N.; Suzuki, A.; Kinoshita, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 1143.
(26) Akiyama, F.; Tokura, N. *Bull. Chem. Soc. Jpn.* **1968**, *41*, 2690.
(27) Ray, K. B.; Weatherhead, R. H.; Pirinccioglu, N.; Williams, A. *J. Chem. Soc., Perkin Trans. 2* **1994**, 83.
(28) Döbner, O. *Liebigs Ann. Chem.* **1881**, *210*, 261.
(29) Hoefnagel, A. J.; van Bekkum, H. *Appl. Catal. A* **1993**, *97*, 87; *102*, N16 (erratum).
(30) Sasaki, A.; Kimura, Y. *Nippon Kagaku Kaishi* **1994**, *10*, 939.
(31) Kanaoka, Y.; Tanizawa, K.; Sato, E.; Yonemitsu, O. Ban, Y. *Chem. Pharm. Bull.* **1967**, *15*, 593.

3-methyl-1-dodecene and 1-acetoxy-3-methyl-2-dodecene in 90% yield with the raio of 84:16. The ratio was determined by ^{1}H NMR analysis of the crude products: IR (film) 2855, 2728, 1740, 1645, 1368, 1466, 1248, 1173, 1019, 922 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) for 3-acetoxy-3-methyl-1-dodecene δ 0.88 (t, J = 6.7 Hz, 3H), 1.26 (br, 16H), 1.52 (s, 3H), 2.01 (s, 3H), 5.10 (dd, J = 0.9, 10.9 Hz, 2H), 5.13 (dd, J = 0.9, 17.5 Hz, 1H), 5.97 (dd, J = 10.9, 17.5 Hz, 1H); ^{1}H NMR ($CDCl_3$, 300 MHz) for 1-acetoxy-3-methyl-2-dodecene δ 2.06 (s, 3H), 4.57 (t, J = 7.3 Hz, 2H), 5.33 (dt, J = 1.0, 7.3 Hz, 1H), other resonances could not be discerned for minor isomer. Anal. Calcd for $C_{15}H_{27}O_2$: C, 75.26; H, 11.37. Found: C, 75.28; H, 11.36.

Other acid-sensitive esters synthesized by essentially the same procedure were the following.

Linalyl acetate (Table 3, entry 14):[32] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.54 (s, 3H), 1.59 (s, 3H), 1.68 (s, 3H), 1.71−2.08 (m, 4H), 2.01 (s, 3H), 5.04-5.12 (m, 1H), 5.12 (dd, J = 0.9, 11.0 Hz, 1H), 5.15 (dd, J = 0.9, 17.5 Hz, 1H), 5.97 (dd, J = 11.0, 17.5 Hz, 1H).

α,α-Dimethylbenzyl acetate (Table 3, entry 15):[33] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.77 (s, 6H), 2.04 (s, 3H), 7.20−7.40 (m, 5H).

1-Ethnylcyclohexyl acetate (Table 3, entry 16):[34] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.25−1.41 (m, 1H), 1.46−1.68 (m, 5H), 1.81−1.91 (m, 2H), 2.05 (s, 3H), 2.08−2.18 (m, 2H), 2.60 (s, 1H).

2,6-Bis(1,1-dimethylethyl)-4-methylphenyl acetate (Table 3, entry 17):[35] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.34 (s, 18H), 2.32 (s, 3H), 2.35 (s, 3H), 7.12 (s, 2H).

Preparation of *p*-Nitrobenzoic Anhydride.[36] To the mixture of *p*-nitrobenzoic acid (3.34 g, 20 mmol) and *p*-nitrobenzoyl chloride (3.71 g, 20 mmol) in dichloromethane (50 mL) was added pyridine (2.02 mL, 25 mmol) dropwise at 0 °C. The reaction mixture was stirred for 15 h at room temperature and then quenched with cold water (20 mL). After usual workup, the crude product was purified by recrystallization from dichloromethane−hexane to afford *p*-nitrobenzoic anhydride (5.71 g, 90% yield).

Typical Procedure for Esterification between Alcohols and Carboxylic Acids (Table 6)**.** To a cloudy mixed solution of alcohols (1 mmol), carboxylic acids (1.1 mmol), and *p*-nitrobenzoic anhydride[31] (474 mg, 1.5 mmol) in nitromethane (4 mL) was added dropwise a cloudy solution (100 μL, 0.01 mmol, 0.1 M) of scandium triflate in acetonitrile at room temperature. After being stirred at the same temperature until alcohols were completely comsumed, the suspension was quenched with aqueous sodium hydrogen carbonate, and the product was extracted with ether. The organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to crude product. Purification was done by column chromatography on silica gel (eluent: hexane−ethyl acetate system) to give the desired ester in good yield.

The physical properties and analytical data of the esters thus obtained are listed below.

3-Phenylpropyl propanoate (Table 6, entry 1):[37] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, J = 7.5 Hz, 3H), 1.90−2.01 (m, 2H), 2.33 (q, J = 7.5 Hz, 2H), 2.69 (t, J = 7.8 Hz, 2H), 4.09 (t, J = 6.6 Hz, 2H), 7.10−7.35 (m, 5H).

3-Phenylpropyl 2-methylpropanoate (Table 6, entry 2):[6d] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (d, J = 7.0 Hz, 6H), 1.90−2.02 (m, J = 7.0 Hz, 2H), 2.55 (septet, J = 7.0 Hz, 1H), 2.69 (t, J = 7.8 Hz, 2H), 4.09 (t, J = 6.5 Hz, 2H), 7.11−7.34 (m, 5H).

(1*S*,3*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl 2-methylpropanoate (Table 6, entry 5):[38] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.75 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.1 Hz, 3H), 0.90 (d, J = 6.4 Hz, 3H), 0.81−1.10 (m, 3H), 1.15 (d, J = 6.9 Hz, 3H), 1.16 (d, J = 6.9 Hz, 3H), 1.32−1.59 (m, 2H), 1.62−1.74 (m, 2H), 1.82−2.02 (m, 2H), 2.51 (septet, J = 6.9 Hz, 1H), 4.65 (dt, J = 4.4, 10.9 Hz, 1H).

(1*S*,3*R*,5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl (*E*)-2-methyl-2-butenoate (Table 6, entry 6):[6d] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.76 (d, J = 6.9 Hz, 3H), 0.89 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 6.5 Hz, 3H), 0.84−1.16 (m, 3H), 1.38−1.58 (m, 2H), 1.63−1.74 (m, 2H), 1.78 (dd, J = 1.0, 7.1 Hz, 3H), 1.83 (t, J = 1.2 Hz, 3H), 1.85−1.94 (m, 1H), 1.98−2.08 (m, 1H), 4.73 (dt, J = 4.2, 10.8 Hz, 1H), 6.83 (qq, J = 1.2, 7.1 Hz, 1H).

2,6-Dimethyphenyl 2-methylpropanoate (Table 6, entry 9)**:** IR (film) 2977, 1755, 1530, 1470, 1169, 1134, 1095, 1046, 770 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.36 (d, J = 7.0 Hz, 6H), 2.14 (s, 6H), 2.87 (septet, J = 7.0 Hz, 1H), 7.04 (s, 3H). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.95; H, 8.40.

2,6-Dimethylphenyl 2,2-dimethylpropanoate (Table 6, entry 10):[39] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41(s, 9H), 2.13 (s, 6H), 7.04 (s, 3H).

2,6-Bis(1,1-dimethylethyl)-4-methylphenyl propanoate (Table 4, entry 11):[40] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, J = 7.6 Hz, 3H), 1.32 (s, 18H), 2.31 (s, 3H), 2.64 (q, J = 7.6 Hz, 2H), 7.11 (s, 2H).

3-Phenylpropyl 2,4,6-trimethylbenzoate (Table 6, entry 13): IR (film) 2955, 1725 (CO_2), 1613, 1455, 1266, 1169, 1082, 853, 747 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.01−2.13 (m, 2H), 2.29 (s, 3H), 2.31 (s, 6H), 2.71−2.79 (m, 2H), 4.33 (t, J = 6.6 Hz, 2H), 6.87 (s, 2H), 7.16−7.34 (m, 5H). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.79; H, 7.82.

2,6-Dimethylphenyl benzoate (Table 6, entry 16):[27] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.20 (s, 6H), 7.08−7.13 (m, 3H), 7.53 (tt, J = 1.3, 7.5 Hz, 2H), 8.2−8.3 (m, 2H).

Preparation of ω-Hydroxy Carboxylic Acids. The hydroxycarboxylic acids, $HO(CH_2)_nCO_2H$ with n = 9, 11, 14, and 15, are commercially available. The hydroxycarboxylic acids, $HO(CH_2)_nCO_2H$ with n = 5−8, 10, and 12, were obtained by saponification of the corresponding lactones which in turn were prepared by Baeyer−Villiger oxidation of commercially available cycloalkanones. Purified samples of the intermediate lactones also served as reference materials for comparison with the products of hydroxy acid cyclization. 14-Hydroxytetradecanoic acid (n = 13) was prepared by selective hydrolysis of diethyl tetradecanedioate to monocarboxylic acid, subsequent reduction to the primary alcohol, and hydrolysis of the remaining ester unit.[41]

Typical Procedure for Baeyer−Villiger Oxidation of Cycloalkanones. A mixture of cycloalkanone (5 mmol), 3-chloroperoxybenzoic acid (7.5 mmol), 2,6-di-*tert*-butyl-4-methylphenol (200 mg), and 1,2-dichloroethane (15 mL) was refluxed for 12−24 h in the dark. After being cooled to room temperature, the mixture was treated with aqueous sodium hydrogen sulfite and aqueous sodium hydrogen carbonate. The organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification was done by column chromatography on silica gel (eluent: hexane−ethyl acetate system) to give the desired lactone in good yield (50−90%).

Typical Procedure for Saponification of Lactones. A mixture of the corresponding lactone (4 mmol), potassium hydroxide (16 mmol), water (1 mL), and methanol (10 mL) was stirred for 2−5 h and rotary evaporated to near dryness. Then 4 N HCl (30 mL) was added, and the mixture was extracted with ethyl acetate twice, dried over Na_2SO_4, and concentrated *in vacuo*. The crude products were separated by column chromatography on silica gel eluting with hexane/ethyl acetate 2:1, ethyl acetate only, and then ethyl acetate/methanol/acetic acid 125:25:1 to obtain ω-hydroxy carboxylic acid included silica gel. Finally, the pure ω-hydroxy carboxylic acid was

(32) Höfle, G.; Steglich, W. *Synthesis* **1972**, 619.
(33) Burghardt, A.; Kulicki, Z.; Stec, Z.; Zawadiak, J. *Pol. J. Appl. Chem.* **1993**, *37*, 243.
(34) Brittelli, D. R.; Boswell, G. A., Jr. *J. Org. Chem.* **1981**, *46*, 312.
(35) Volod'kin, A.; Rasuleva, D.; Ershov, V. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1972**, 178.
(36) Carpenter, F. H. *J. Am. Chem. Soc.* **1948**, *70*, 2964.
(37) Yamaguchi, M.; Tsukamoto, Y.; Minami, T. *Chem. Lett.* **1990**, 1223.
(38) Ralitsch, M.; Ciccio, J.; Calzada, J. *Rev. Latinoam. Quim.* **1982**, *13*, 16.
(39) Takimoto, S.; Inanaga, J.; Katsuki, T.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2335.
(40) Heathcock, C. H.; Young, S. D.; Hagen, J. P.; Pirrung, M. C.; White, C. T.; VanDerveer, D. *J. Org. Chem.* **1980**, *45*, 3846.
(41) Ogawa, T.; Fang, C.-L.; Suemune, H.; Sakai, K. *J. Chem. Soc., Chem. Commun.* **1991**, 1438.

obtained by filtration of silica gel after extraction into THF (80 − >95% yield).

Typical Procedure for Selective Lactonization of ω-Hydroxy Carboxylic Acids (Table 7). *p*-Nitrobenzoic anhydride (253 mg, 0.8 mmol) was dissolved in dry acetonitrile (169 mL), and a cloudy solution of scandium triflate (0.8 mL, 0.08 mmol, 0.1 M) in acetonitrile was added to the solution at room temperature under argon. A solution of ω-hydroxy carboxylic acid (10 mL, 0.4 mmol, 0.04 M) in THF was added slowly from a mechanically driven syringe over 15 h to the mixed solution at reflux under argon, and the reaction mixture was further stirred for 5 h at reflux. After being cooled to room temperature, the solution was quenched with aqueous saturated sodium hydrogen carbonate (4 mL). The resulting mixture was concentrated under reduced pressure and extracted with ether twice. The organic layers were dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification was done by column chromatography on silica gel (eluent: hexane−ethyl acetate system) to give the desired lactone in good yield. In some cases, diolide was afforded as minor product.

The physical properties and analytical data of the lactones thus are listed below.

6-Hexanolide ($n = 5$):[42,43] IR (film) 2936, 2865, 1732 (CO_2), 1476, 1439, 1393, 1348, 1327, 1293, 1169 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.60−1.94 (m, 6H), 2.60−2.65 (m, 2H), 4.23 (t, $J = 4.4$ Hz, 2H).

7-Heptanolide ($n = 6$):[42] IR (film) 2932, 2863, 1731 (CO_2), 1453, 1354, 1298, 1235, 1130, 1096, 1076 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.51−1.70 (m, 4H), 1.73−1.94 (m, 4H), 2.55 (t, $J = 6.4$ Hz, 2H), 4.35 (t, $J = 5.6$ Hz, 2H).

1,9-Dioxacyclohexadecane-2,10-dione ($n = 6$):[42] IR ($CHCl_3$) 3021, 2940, 2863, 1725 (CO_2), 1458, 1389, 1266, 1192, 1157, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25−1.50 (m, 8H), 1.60−1.77 (m, 8H), 2.32−2.39 (m, 4H), 4.10 (t, $J = 5.3$, 4H); MS (EI, 20 eV) m/z (rel intensity) 256 (6, M^+), 238 (77, $M^+ - 18[H_2O]$), 142 (47), 129 (100), 127 (49), 126 (34), 124 (19).

8-Octanolide ($n = 7$):[16,42] IR (film) 2934, 2867, 1736 (CO_2), 1460, 1375, 1356, 1331, 1271, 1238, 1144 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.35−1.55 (m, 4H), 1.56−1.87 (m, 6H), 2.29 (t, $J = 6.7$ Hz, 2H), 4.29 (t, $J = 5.8$ Hz, 2H).

1,10-Dioxacycloocatadecane-2,11-dione ($n = 7$):[16,42] IR ($CDCl_3$) 2936, 2860, 1721 (CO_2), 1460, 1387, 1275, 1237, 1156, 1103, 1063 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.45 (m, 12H), 1.52−1.74 (m, 8H), 2.32 (t, $J = 6.9$ Hz, 4H), 4.13 (t, $J = 5.7$ Hz, 4H); MS (CI) m/z 285 (MH^+).

9-Nonanolide ($n = 8$):[42] IR (film) 2957, 2870, 1732 (CO_2), 1468, 1294, 1273, 1252, 1238, 1167, 1152, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.35 (m, 2H), 1.41−1.60 (m, 6H), 1.71−1.85 (m, 4H), 2.31−2.37 (m, 2H), 4.28 (t, $J = 5.3$ Hz, 2H).

1,11-Dioxacycloicosane-2,12-dione ($n = 8$):[42] IR ($CHCl_3$) 2934, 2859, 1725 (CO_2) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.45 (m, 16H), 1.50−1.75 (m, 8H), 2.33 (t, $J = 6.7$ Hz, 4H), 4.07−4.12 (m, 4H); MS (EI, 20 eV) m/z (rel intensity) 312 (20, M^+), 294 (82, $M^+ - 18$ [H_2O]), 138 (100).

10-Decanolide ($n = 9$):[42] IR (film) 1947, 1867, 1732 (CO_2), 1466, 1449, 1381, 1354, 1248, 1183, 1157 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.60 (m, 10H), 1.68−1.81 (m, 4H), 2.10−2.18 (m, 2H), 4.18 (t, $J = 4.8$ Hz, 2H); MS (EI, 20 eV) m/z (rel intensity) 170 (42, M^+), 152 (66, $M^+ - 18$ [H_2O]), 127 (100), 113 (84), 110 (72, $M^+ - 60$[AcOH]).

1,12-Dioxacyclododocosane-2,13-dione ($n = 9$):[42] IR ($CHCl_3$) 3021, 2932, 2857, 1721 (CO_2), 1466, 1387, 1339, 1264, 1235, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.45 (m, 20H), 1.55−1.70 (m, 8H), 2.31 (t, $J = 6.9$ Hz, 4H), 4.11 (t, $J = 5.8$ Hz, 4H); MS (EI, 20 eV): m/z (rel intensity) 340 (40, M^+), 322 (100, $M^+ - 18$ [H_2O]), 281 (32), 257 (35), 213 (37), 171 (55), 152 (82), 110 (44).

11-Undecanolide ($n = 10$):[16,42] IR (film) 2932, 2865, 1736 (CO_2), 1466, 1447, 1244, 1221, 1175, 1142, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.47 (m, 10H), 1.48−1.60 (m, 2H), 1.60−1.80 (m, 4H), 2.33−2.41 (m, 2H), 4.20 (t, $J = 5.1$ Hz, 2H).

1,13-Dioxacyclotetradocosane-2,14-dione ($n = 10$):[16,42] IR ($CHCl_3$) 2930, 2857, 1723 (CO_2), 1387, 1262, 1235, 1184, 1157, 1105, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13−1.44 (m, 24H), 1.55−1.71 (m, 8H), 2.31 (t, $J = 7.0$ Hz, 4H), 4.11 (t, $J = 6.0$ Hz, 4H); HRMS (FAB) for $C_{22}H_{41}O_4$ $[MH]^+$, calcd 369.3005, found 369.2987.

12-Dodecanolide ($n = 11$):[42] IR (film) 2932, 2863, 1734 (CO_2), 1339, 1252, 1142, 1096, 1051 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.25−1.49 (m, 14H), 1.61−1.73 (m, 4H), 2.32−2.40 (m, 2H), 4.16 (t, $J = 5.3$ Hz, 2H); MS (EI, 20 eV) m/z (rel intensity) 198 (100, M^+), 180 (83, M^+-18[H_2O]), 162 (81), 138 (98, $M^+ - 60$ [CH_3CO_2H]), 136 (79), 110 (60).

1,14-Dioxacyclohexacosane-2,15-dione ($n = 11$):[42] IR ($CHCl_3$) 2930, 2857, 1723 (CO_2), 1466, 1387, 1182, 1107 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.22−1.43 (m, 28H), 1.55−1.69 (m, 8H), 2.31 (t, $J = 7.1$ Hz, 4H), 4.10 (t, $J = 6.0$ Hz, 4H); MS (FD) m/z 397 (MH^+).

13-Tridecanolide ($n = 12$):[42] IR (film) 2930, 2861, 1736 (CO_2), 1460, 1385, 1347, 1242, 1208, 1169, 1105 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15−1.50 (m, 16H), 1.59−1.72 (m, 4H), 2.34−2.41 (m, 2H), 4.15 (t, $J = 5.2$ Hz, 2H).

1,15-Dioxacyclooctacosane-2,16-dione ($n = 12$):[42] IR ($CHCl_3$) 2930, 2857, 1725 (CO_2), 1466, 1266, 1238, 1179, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.10−1.45 (m, 32H), 1.55−1.71 (m, 8H), 2.32 (t, $J = 7.0$ Hz, 4H), 4.10 (t, $J = 6.0$ Hz, 4H); HRMS (FAB) for $C_{26}H_{49}O_4$ $[MH]^+$, calcd 425.3631, found 425.3613.

14-Tetradecanolide ($n = 13$):[42] IR (film) 2928, 2859, 1732 (CO_2), 1458, 1348, 1142, 1109, 965 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.50 (m, 18H), 1.51−1.78 (m, 4H), 2.31−2.40 (m, 2H), 4.14 (t, $J = 5.2$ Hz, 2H); HRMS (CI) for $C_{14}H_{27}O_2$ $[MH]^+$, calcd 227.2011, found 227.1992.

1,16-Dioxacyclotriacontane-2,17-dione ($n = 13$):[42] IR ($CHCl_3$) 2930, 2857, 1721 (CO_2), 1466, 1179, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.15−1.43 (br, 36H), 1.44−1.70 (m, 8H), 2.31 (t, $J = 7.1$ Hz, 4H), 4.09 (t, $J = 5.9$ Hz, 4H); HRMS (CI) for $C_{28}H_{53}O_4$ $[MH]^+$, calcd 453.3944, found 453.3971.

15-Pentadecanolide ($n = 14$):[42] IR (film) 2930, 2859, 1736 (CO_2), 1460, 1350, 1167, 1109, 1013, 758 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.49 (m, 20H), 1.58−1.71 (m, 4H), 2.33 (t, $J = 6.6$ Hz, 2H), 4.14 (t, $J = 5.3$ Hz, 2H); MS (EI, 20 eV) m/z (rel intensity) 240 (83, M^+), 222 (100, $M^+ - 18[H_2O]$), 180 (79, $M^+ - 60$ [CH_3CO_2H]), 152 (37), 138 (49), 124 (54), 110 (70).

1,17-Dioxacyclodotriacontane-2,18-dione ($n = 14$):[42,44] IR ($CHCl_3$) 2930, 2857, 1721 (CO_2), 1466, 1277, 1237, 1179, 1111, 1075 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18−1.41 (m, 40H), 1.56−1.70 (m, 8H), 2.31 (t, $J = 7.0$ Hz, 4H), 4.09 (t, $J = 6.1$ Hz, 4H); MS (EI, 20 eV) m/z (rel intensity) 481 (72, M^+), 463 (82, $M^+ - 18$ [H_2O]), 283 (52), 241 (100), 220 (65).

16-Hexadecanolide ($n = 15$):[42] IR (film) 2928, 2857, 1736 (CO_2), 1460, 1387, 1350, 1242, 1167, 1109, 1069 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.45 (m, 22H), 1.57−1.72 (m, 4H), 2.32 (t, $J = 6.6$ Hz, 2H), 4.13 (t, $J = 5.6$ Hz, 2H); MS (EI, 20 eV): m/z (rel intensity) 254 (100, M^+), 236 (92, $M^+ - 18$ [H_2O]), 208 (15), 194 (51, $M^+ - 60$ [AcOH]), 192 (28), 166 (19), 152 (31), 138 (31), 124 (29), 110 (43).

1,18-Dioxacyclotetracontane-2,19-dione ($n = 15$):[42] IR ($CHCl_3$) 2928, 2857, 1717 (CO_2), 1179, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.20−1.42 (m, 44H), 1.57−1.70 (m, 8H), 2.30 (t, $J = 7.2$ Hz, 4H), 4.09 (t, $J = 6.1$ Hz, 4H); MS (FD) m/z 509 (MH^+).

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(42) Stoll, M.; Rouvé, A. *Helv. Chim. Acta* **1935**, *18*, 1087.

(43) Van Natta, F. J.; Hill, J. W.; Carothers, W. H. *J. Am. Chem. Soc.* **1934**, *56*, 455.

(44) Jaeger, D. A.; Ippoliti, J. T. *J. Org. Chem.* **1981**, *46*, 1964.