A Rapid Esterification by Means of Mixed Anhydride and Its Application to Large-ring Lactonization[1]

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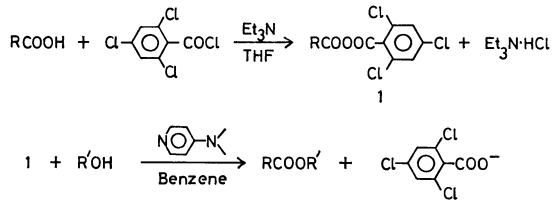
(Received September 29, 1978)

A rapid and mild esterification method using carboxylic 2,4,6-trichlorobenzoic anhydrides in the presence of 4-dimethylaminopyridine was developed. The method was also successfully applied to the synthesis of large-ring lactones, including DL-2,4,6-tridemethyl-3-deoxymethynolide.

For the preparation of large-ring lactones from the corresponding open-chain hydroxy acids, a rapid esterification reaction is necessary to overcome the unfavourable entropy factors leading to the formation of polymers. The mildness of the reaction conditions is also important if the method is to be applied to the synthesis of complex natural substances with sensitive functionalities. Most of the conventional methods have found only a limited use for this purpose. Recently, intensive studies in this field have commenced and several good lactonization methods using different types of reagents have been developed,[2] some of them having been successfully applied to the synthesis of macrolides.[3]

In the course of our studies of the synthesis of macrocyclic lactones, the remarkably high catalytic activity of 4-dimethylaminopyridine in acyl transfer reactions[4] attracted our attention, and so the esterifications with combinations of this reagent and the appropriate mixed anhydrides were examined. This paper will describe the rapid and mild esterification method using 2,4,6-trichlorobenzoic carboxylic anhydride (**1**) as the anhydride counterpart in the above combination, and its successful application to the synthesis of medium- and large-ring lactones, including DL-2,4,6-tridemethyl-3-deoxymethynolide (**8**).



Results and Discussion

Mixed Anhydrides. The esterification by means of mixed anhydride consists of two steps: the formation of the mixed anhydride, and the alcoholysis of the anhydride. Since the first step has been well-documented,[5] our effort was mainly directed toward the second step. In the choice of the acids to be examined as the components of the mixed anhydrides, the following two factors were considered: the component should be a good leaving group, and the carbonyl group of the component should be sterically hindered from the nucleophilic attack to some extent. The following acid chlorides which seemed to meet the above requirements were preliminarily examined by comparing the rate of the alcoholysis of the corresponding mixed anhydrides in the presence of 4-dimethylaminopyridine: 2,4,6-trichlorobenzoyl (**2**),[6] 2,3,6-trimethyl-4,5-dinitrobenzoyl (**3**), 2,6-dichloro-3-nitrobenzoyl (**4**),[7] 2,4,6-tribromobenzoyl (**5**),[8] 2,6-dichloro-4-nitrobenzoyl,[9] 2,6-dichlorobenzoyl,[10] 2,4,6-trichloro-3-nitrobenzoyl,[11] 2,4,6-trichloro-3,5-dinitrobenzoyl, 2,4,6-tribromo-3-nitrobenzoyl, 2,4,6-tribromo-3,5-dinitrobenzoyl, 2,6-dinitrobenzoyl,[12] 2,4,6-trimethyl-3,5-dinitrobenzoyl,[13] 2,3,6-trimethylbenzoyl,[11] 2,6-dimethoxybenzoyl,[15] and pivaloyl chloride. 2,4,6-trinitrobenzoyl[12] and 3,5-dimethyl-2,4,6-trinitrobenzoyl chloride were also examined, but these two acyl chlorides did not give well-defined mixed anhydrides with 2-methylpentanoic acid. Among the above acid chlorides, the chlorides (**2**), (**3**), (**4**), and (**5**) gave the most promising results. Figure 1 shows the relative rates of ester formation, as followed by GLPC, in the alcoholysis of the corresponding four mixed anhydrides with 2-methylpentanoic acid by 2-methyl-2-propanol at room temperature.

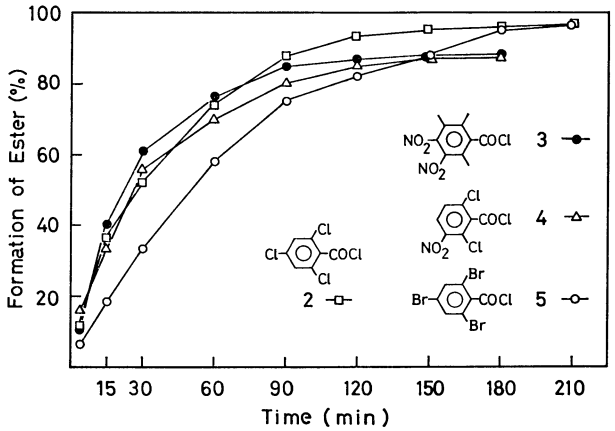


Fig. 1. Relative rates of the 2-methyl-2-propanolysis of mixed anhydrides formed from 2-methylpentanoic acid and four acid chlorides, **2**, **3**, **4**, and **5**.

2,4,6-Trichlorobenzoyl chloride (**2**) was proved to be the most satisfactory one in rate and in the yield of the alcoholysis. The reaction using the chloride (**3**) was fast but incomplete; however, it was later found that the chloride can also be used for the large-ring lactonizations.

Reaction Conditions. The following experiments were carried out by using the acid chloride (**2**) unless otherwise mentioned. Table 1 shows the relative rates of the formation of *t*-butyl 2-methylpentanoate in various solvents. Aromatic hydrocarbons, such as

benzene or toluene, were found to be the most suitable solvents for the alcoholysis step.

When the temperature of the reaction was raised, the rate of alcoholysis increased markedly without affecting the final yield; for example, *t*-butyl 2-methylpentanoate was formed almost quantitatively in 1 or 2 min in toluene at 100 °C (*cf.* entries, 1, 3, and 4 in Table 2). The amount of dimethylaminopyridine also had a significant influence on the rate of the reaction, and it was preferable to use more than one equivalent of the reagent per mole of the mixed anhydride, especially when the method was applied to large-ring lactonizations.

Table 1. Effect of solvents on the rate of ester formation[a]

Solvent	Ester formation (%)			
	4 min	15 min	30 min	60 min
Benzene	37	62	81	91
Toluene	37	59	79	95
Dioxane	20	49	71	89
Dichloromethane	10	39	59	77
Carbon tetrachloride	18	39	52	68
Pyridine	6	22	37	53
Cyclohexane	3	12	23	39
Acetonitrile	3	7	15	28

a) The formation of *t*-butyl 2-methylpentanoate was followed by GLPC.

Esterification. The results of the esterification by this method are summarized in Table 2.

As is shown in Table 2, the esters of secondary and tertiary alcohols were prepared rapidly at room temperature in good yields. In the case of primary alcohols, however, a small amount of an undesired trichlorobenzoic acid ester was formed as the by-product. The rates of the formation of benzoic acid esters were smaller than those of aliphatic acid esters. Sterically very crowded *t*-butyl pivalate could not be prepared by this method.

Lactonization. The method was then applied to

Table 2. Yields and reaction conditions of esterification using 2,4,6-trichlorobenzoyl chloride

Entry	Acid (0.3 mmol)	Alcohol[a]		Dimethyl-aminopyridine (mmol)	Time[b] (min)	Yield[c] (%)
1	2-Methyl-pentanoic acid	2-Methyl-2-propanol		0.6	90	>95
2			(2 eq.)	1.2	20	89
3			(2 eq.)	0.6	10 (80 °C)	>95
4			(2 eq.)	0.6	2 (100 °C)[d]	>95
5		2-Butanol		0.6	5	>95
6		Cyclohexanol		0.6	5	>95
7		Methanol		0.6	10	95[e]
8		Ethanol		0.6	3	95[f]
9	Cyclohexanecarboxylic acid	2-Methyl-2-propanol		0.6	20	>95
10		Cyclohexanol		0.6	20	>95
11	Benzoic acid	2-Methyl-2-propanol		0.6	270	89
12		Cyclohexanol		0.6	20	>95
13	Methyl hydrogen *meso*-2,4-dimethyl-glutarate	2-Methyl-2-propanol	(2 eq.)	0.6	60	>95[g]
14			(2 eq.)	0.6	5 (80 °C)	84[g]

a) One equivalent of alcohols to acids was used unless otherwise mentioned. b) The alcoholysis reactions were carried out at room temperature in benzene unless otherwise mentioned. c) The yields were determined by GLPC in the presence of the appropriate internal standards. d) The alcoholysis step was carried out in toluene. e) Methyl trichlorobenzoate (1.5%) was also formed. f) Ethyl trichlorobenzoate (3%) was also formed. g) No isomerization occurred at room temperature, but isomerization occurred (22%) when the reaction was carried out at 80 °C.

Table 3. Isolated yield in lactonization by trichlorobenzoyl chloride method

Hydroxy acid (Ring size)	Catalyst[a] (mol. equiv.)	Time of addition (h)	Yield (%) Monomer	Dimer
$HO(CH_2)_7CO_2H$ (9)	3	8	36	23
$HO(CH_2)_{10}CO_2H$ (12)	6	5	48	20
$C_6H_{13}CH(OH)(CH_2)_{10}CO_2H$ (13)	6	1.5	67	10
$C_6H_{13}CH(OH)CH_2CH{=}CH(CH_2)_7CO_2H$ (13)	3.3	5	57	12

a) 4-Dimethylaminopyridine.

Table 4. Isolated yield in lactonization by trimethyldinitrobenzoyl chloride method

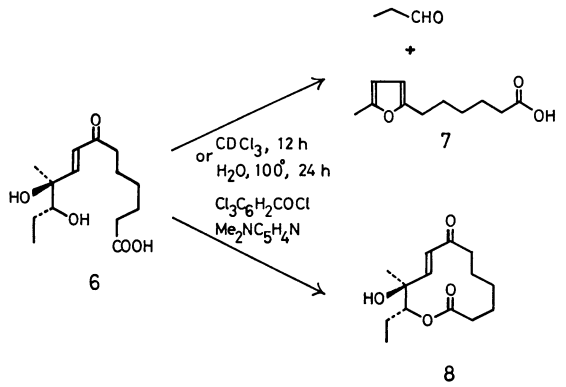
Hydroxy acid (Ring size)	Catalyst[a] (mol. equiv.)	Time of addition (h)	Yield (%) Monomer	Dimer
$HO(CH_2)_7CO_2H$ (9)	3	7	18	41
$C_6H_{13}CH(CH_2)_{10}CO_2H$ | OH (13)	6	8	58	8
$C_6H_{13}CHCH_2CH{=}CH(CH_2)_7CO_2H$ | OH (13)	3	7	58	9

a) 4-Dimethylaminopyridine.

the synthesis of macrocyclic lactones. The mixed anhydrides of the long-chain hydroxy acids could be prepared in a manner similar to that used in the above esterification. After the removal of triethylamine hydrochloride, the solution of the mixed anhydride was diluted with toluene and slowly added to a refluxing solution of dimethylaminopyridine in toluene under high-dilution conditions. In this way, nine- to thirteen-membered ring lactones were prepared. They are shown in Table 3.

The results of the experiments carried out by using 2,3,6-trimethyl-4,5-dinitrobenzoyl chloride as the condensing agent are given in Table 4. As can be seen from the table, this acid chloride is as useful as 2,4,6-trichlorobenzoyl chloride, at least for the lactonization.

Finally, the method was applied to the lactonization of the seco-acid (**6**) of DL-2,4,6-tridemethyl-3-deoxymethynolide (**8**). The seco-acid has an acid-sensitive dihydroxy enone structure, and it has been shown that the compound decomposes easily to a furan derivative (**7**) and propionaldehyde on contact with a catalytic amount of hydrochloric acid.[16] When the seco-acid was cyclized under conditions similar to those used in lactonization with 2,4,6-trichlorobenzoyl chloride, the desired DL-lactone (**8**) was isolated in 46% yield, without the formation of the furan derivative.



Experimental

All the procedures for the esterifications and the lactonizations were carried out under an atmosphere of nitrogen in order to exclude moisture. The melting points or boiling points are uncorrected. The IR spectra (Hitachi R-215) were obtained in liquid films or potassium bromide disks. The PMR spectra (Hitachi R-20B) were taken in deuteriochloroform solutions. The mass spectra (Hitachi RMU-6MG) were recorded with a direct-inlet system operating at 10—30 eV. The solvents were purified and dried by the standard methods.

Materials. 8-Hydroxyoctanoic acid was prepared by the hydrolysis of its methyl ester, which had been obtained by reducing methyl 7-chloroformylheptanoate with sodium borohydride in dioxane, and was purified by recrystallization from methanol. Mp 61 °C (lit, 58—58.5 °C).[17]

11-Hydroxyundecanoic acid was prepared by the sodium borohydride reduction of methyl 10-chloroformyldecanoate or by the diborane reduction of methyl hydrogen undecanedioate in THF at 0 °C, followed by the saponification of the resulting hydroxy ester, and was purified by sublimation. Mp 65—67 °C (lit, 65.5—66 °C).[18]

Commercial 12-hydroxyoctadecanoic acid and ricinoleic acid were purified by recrystallization and distillation, respectively.

*2,4,6-Trichlorobenzoyl Chloride (**2**).* According to the method in the literature, 2,4,6-trichloroaniline was converted into 2,4,6-trichlorobenzonitrile,[19] whcih was then hydrolysed to 2,4,6-trichlorobenzoic acid.[6] The acid was refluxed with thionyl chloride for 3 h. Bp 110—114 °C/9 mmHg.

*2,3,6-Trimethyl-4,5-dinitrobenzoyl Chloride (**3**).* Fuming nitric acid (4 ml) was added to a cold mixture of 2,3,6-trimethylbenzoic acid[20] (3.3 g) and concentrated sulfuric acid (12 ml), after which the mixture was kept at 40 °C for 30 min. The reaction product was then poured onto ice, and the precipitate was filtered and recrystallized from ethanol-water to give the dinitro acid (4.1 g). Mp 222 °C(dec). The acid (1.6 g) was heated with thionyl chloride (10 ml) for 12 h at 60 °C, and after the removal of thionyl chloride, the crude product was purified by sublimation. Mp 102—103 °C.

2,4,6-Trichloro-3,5-dinitrobenzoyl Chloride. 2,4,6-Trichloro-3-nitrobenzoic acid[11] (2 g) was dissolved in sulfuric acid (12 ml) heated at 85 °C, and sodium nitrate (1.7 g) was added over a period of 15 min. The mixture soon solidified. The temperature was kept at 80—90 °C for 2 h. The mixture was then worked up as usual, and the product was recrystallized from toluene. Mp 224—225 °C, 2.4 g. The dinitro acid was converted into the acid chloride by the method using phosphorus pentachloride and phosphoryl chloride and was purified by sublimation. Mp 150—152 °C.

2,4,6-Tribromo-3-nitrobenzoyl Chloride. 2,4,6-Tribromobenzoic acid[8] (3.56 g) was suspended in sulfuric acid (10 ml) and nitrated with a mixture of nitric acid (2 g) and sulfuric acid (4 g) at 0—7 °C. The mixture was kept at room temperature for 1 h, poured onto ice, filtered, and washed with dilute hydrochloric acid. Mp 186—187 °C (from toluene); 3.6 g. It was then converted into the acid chloride with phosphorus pentachloride and phosphoryl chloride. Mp 129—131 °C (from benzene-hexane).

2,4,6-Tribromo-3,5-dinitrobenzoyl Chloride. This was prepared by the method described in the case of 2,4,6-trichloro-3,5-dinitrobenzoyl chloride. 2,4,6-Tribromo-3,5-dinitroben-

Table 5. Analytical and IR data of new acids, acid chlorides, and ester

Compound (Formula)	IR (cm^{-1})	Found (Calcd) C%	H%	N%
2,3,6-Me_3-4,5-$(NO_2)_2C_6CO_2H$ ($C_{10}H_{10}N_2O_6$)	1710, 1540	47.37 (47.25	3.91 3.97	11.01 11.02)
2,3,6-Me_3-4,5-$(NO_2)_2C_6COCl$ ($C_{10}H_9ClN_2O_5$)	1795	44.09 (44.05	3.39 3.33	10.42 10.28)
2,4,6-Cl_3-3,5-$(NO_2)_2C_6CO_2H$ ($C_7HCl_3N_2O_6$)	1735, 1570, 1550	26.95 (26.65	0.34 0.32	8.26 8.88)
2,4,6-Cl_3-3,5-$(NO_2)_2C_6COCl$ ($C_7Cl_4N_2O_5$)	1840, 1775	25.18 (25.18	0.00 0	8.34 8.39)
2,4,6-Br_3-3-$(NO_2)C_6HCO_2H$ ($C_7H_2Br_3NO_4$)	1720, 1545	20.89 (20.82	0.53 0.50	3.42 3.47)
2,4,6-Br_3-3-$(NO_2)C_6HCOCl$ ($C_7HBr_3ClNO_3$)	1800, 1770	19.97 (19.91	0.21 0.24	3.25 3.32)
2,4,6-Br_3-3,5-$(NO_2)_2C_6CO_2H$ ($C_7HBr_3N_2O_6$)	1720, 1545	18.90 (18.73	0.19 0.22	6.22 6.22)
2,4,6-Br_3-3,5-$(NO_2)_2C_6COCl$ ($C_7Br_3ClN_2O_5$)	1810, 1775	18.06 (17.99	0.03 0	5.96 6.00)
3,5-Me_2-2,4,6-$(NO_2)_3C_6CO_2H$ ($C_9H_7N_3O_8\cdot H_2O$)	1690, 1545	35.65 (35.65	3.00 2.99	13.89 13.86)
3,5-Me_2-2,4,6-$(NO_2)_3C_6COCl$ ($C_9H_6ClN_3O_7$)	1760	35.49 (35.60	1.93 1.99	13.83 13.84)
s-Butyl 2-methylpentanoate[a] ($C_{10}H_{20}O_2$)	1728	69.46 (69.72	11.69 11.70)	

a) Bp 88—89 °C/38 mmHg.

zoic acid; mp 275—276 °C. The acid chloride; mp 245—246 °C.

3,5-Dimethyl-2,4,6-trinitrobenzoyl Chloride. 1,3,5-Trimethyl-2,4,6-trinitrobenzene (1 g) was boiled with concentrated nitric acid (63%, 60 ml) for 80 h. The evaporation residue of the reaction mixture was then extracted with aqueous sodium carbonate, and the extract was acidified with hydrochloric acid. The acid was recrystallized from water. Mp 224—226 °C, 0.42 g. The acid chloride (phosphorus pentachloride and phosphoryl chloride) was purified by sublimation. Mp 157—159 °C.

The IR and analytical data of the new acids and acid chlorides are summarized in Table 5.

Relative Rates of Alcoholysis of Mixed Anhydrides. The acid chloride (0.3 mmol) to be examined was added to a mixture of 2-methylpentanoic acid (37 μl, 0.3 mmol) and triethylamine (42 μl, 0.3 mmol) in THF (2 ml), after which the mixture was stirred for 20 min at room temperature. After the removal of triethylamine hydrochloride by filtration, the filtrate was evaporated under nitrogen and the residue was dissolved in dichloromethane (1 ml). To this solution we added a mixture of 2-methyl-2-propanol (56 μl, 0.6 mmol) and 4-dimethylaminopyridine (73 mg, 0.6 mmol) in dichloromethane (1 ml), and the resulting mixture was stirred at room temperature. The formation of the ester was followed by GLPC by the addition of bromobenzene (50 μl) as an internal standard. The results are partly exhibited in Fig. 1.

Comparison of Solvents. The experiments were carried out in the manner described above, except that 2,4,6-trichlorobenzoyl chloride was used as the acid chloride and that dichloromethane was replaced by the other solvents (2 ml) to be examined. The results are summarized in Table 1.

Preparation of Carboxylic Esters. Carboxylic acids (0.3 mmol) and triethylamine (0.3 mmol) reacted with trichlorobenzoyl chloride (0.3 mmol) in THF (1 ml) in the same manner as above. After the removal of triethylamine hydrochloride and the solvent,[21] the resulting anhydrides were treated with alcohols (0.3—0.6 mmol) and dimethylaminopyridine (0.6—1.2 mmol) in benzene. The yields obtained by GLPC are given in Table 2. For the isolation of the esters, the reaction mixture was diluted with ether, washed successively with 3% aqueous hydrochloric acid, water, an aqueous sodium hydrogencarbonate solution, and water, dried, and distilled. They were identified by means of the PMR and IR spectra.

Preparation of Lactones. 2,4,6-Trichlorobenzoyl (or 2,3,6-trimethyl-4,5-dinitrobenzoyl) chloride (1.0 mmol) was added to a mixture of a hydroxy acid (1.0 mmol) and triethylamine (1.1 mmol) in THF (10 ml), after which the mixture was stirred for 1—2 h (or 12 h in the case of 2,3,6-trimethyl-4,5-dinitrobenzoyl chloride) at room temperature. After removal of triethylamine hydrochloride, the filtrate was diluted with toluene (500 ml) and added under the high-dilution conditions to a refluxing solution of 4-dimethylaminopyridine (3—6 mmol) in toluene (100 ml) over a period of 1.5—8 h. The reaction mixture was worked-up in a manner similar to that used in the case of the esterification and was separated by preparative TLC (silica gel G, Merck). The crude products were purified by distillation or recrystallization (Tables 3 and 4).

8-Octanolide:[22] A colorless oil; IR 1735 cm^{-1}; PMR δ 4.28 (2H, t, J=5.2 Hz, $-CH_2O-$); MS 142 (M). The dimer:[22] Colorless needles (from petroleum ether); mp 93—93.5 °C; IR 1735 cm^{-1}; PMR δ 4.15 (4H, broad t); MS 284 (M).

11-Undecanolide:[22] A colorless oil; IR 1730 cm^{-1}; PMR δ 4.2 (2H, broad t); MS 184 (M). The dimer:[22] Colorless needles (from hexane); mp 71—72 °C; IR 1730 cm^{-1}; PMR δ 3.9—4.4 (4H, broad t); MS 368 (M).

12-Octadecanolide: A colorless oil; bp 140 °C (bath temp) /20 mmHg; IR 1730 cm^{-1}; PMR δ 4.7—5.2 (H, m, -CHO-); MS 282 (M). Found: C, 76.40; H, 12.06%. Calcd for $C_{18}H_{34}O_2$: C, 76.54; H, 12.13%. The dimer: Colorless needles (from petroleum ether); mp 64—65 °C; IR 1730 cm^{-1}; PMR δ 4.6—5.2 (2H, m); MS 564 (M). Found: C, 76.55; H, 12.23%. Calcd for $C_{36}H_{68}O_4$: C, 76.54; H, 12.13%.

cis-9-Octadecen-12-olide: A colorless oli; bp 120 °C (bath temp)/12 mmHg; IR 1720 cm^{-1}; PMR δ 4.6—5.3 (H, m, -CHO-); 5.3—5.8 (2H, m, -CH=CH-); MS 280 (M). Found: C, 76.74; H, 11.54%. Calcd for $C_{18}H_{32}O_2$: C, 77.09; H, 11.50%. The dimer: A colorless oil; bp 160 °C (bath temp)/0.3 mmHg; IR 1720 cm^{-1}; PMR δ 4.6—5.8 (6H, m, -CHO- and -CH=CH-); MS 560 (M).

2,4,6-Tridemethyl-3-deoxymethynolide (8). A mixture of the seco-acid[16] (**6**, 272 mg, 1.0 mmol) and triethylamine (153 μl, 1.1 mmol) in THF (10 ml) was stirred for 10 min at room temperature, and then 2,4,6-trichlorobenzoyl chloride (160 μl, 1.0 mmol) was added. After stirring for 2 h at room temperature, the resulting precipitate was filtered and washed with a small amount of THF. The filtrate was diluted with benzene (500 ml) and slowly added to a refluxing solution of 4-dimethylaminopyridine (732 mg, 6 mmol) in benzene (100 ml) over a period of 40 h. The reaction mixture was washed successively with a saturated aqueous citric acid solution, water, an aqueous sodium hydrogencarbonate, and water, dried with magnesium sulfate, and evaporated. The crude product (247 mg) was separated by preparative TLC (silica gel G, Merck), with an ether-benzene mixture (2 : 1) used as the developer, to give the monomeric lactone (**8**, 116 mg, 46%), the dimer (65 mg, 26%), and the polymer (21 mg).

The Monomeric Lactone (8): Colorless needles (from dichloromethane-diisopropyl ether); mp 123 °C; IR 3520, 1725, 1680, 1620, 1225, 1150, 1085, 980 cm^{-1}; PMR δ 0.93 (3H, t, J=7.1 Hz, methyl protones of 11-ethyl), 1.2—3.0 (12H, m), 1.38 (3H, s, 10-methyl), 3.15 (H, broad s, 10-hydroxyl), 4.80 (H, dd, J=9.0 and 3.1 Hz, 11-methine), 6.29 and 6.66 (2H, q, J=16.0 Hz, 8-double bond); MS 255 (M+1), 237, 211, 196, 178, 151, 136, 135. Found: C, 65.96; H, 8.68%. Calcd for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72%. Acetate (acetic anhydride and 4-dimethylaminopyridine in dichloromethane): Colorless prisms (from dichloromethane-diisopropyl ether); mp 146—147 °C; MS 296 (M), 254, 237, 225, 211, 196, 178.

The Dimer: A colorless oil; IR 3450, 1720, 1670, 1630, 975 cm^{-1}; PMR δ 0.91 (6H, t, J=7.1 Hz), 1.36 (6H, s), 1.1—3.0 (26H, m), 4.85 (2H, dd, J=9.2 and 3.2 Hz), 6.30 and 6.84 (2H, q, J=16.0 Hz); MS 508 (M), 491, 490, 237. Diacetate: Colorless needles (from dichloromethane-diisopropyl ether); mp 182.5 °C; MS 532 (M−60), 490, 472.

This work was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education.

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