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An Effective Use of Benzoic Anhydride and Its Derivatives for the Synthesis of Carboxylic Esters and Lactones: A Powerful and Convenient Mixed Anhydride Method Promoted by Basic Catalysts

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Various carboxylic esters are obtained at room temperature in excellent yields with high chemoselectivities from nearly equimolar amounts of carboxylic acids and alcohols using 2-methyl-6-nitrobenzoic anhydride with triethylamine by the promotion of a basic catalyst such as 4-(dimethylamino)pyridine. A variety of lactones are also prepared in high yields at room temperature from the corresponding ω-hydroxycarboxylic acids with use of 2-methyl-6-nitrobenzoic anhydride in the presence of 4-(dimethylamino)pyridine. A similar reaction occurs with triethylamine when using a catalytic amount of 4-(dimethylamino)pyridine 1-oxide as an effective promoter for the intramolecular condensation reaction. These methods are successfully applied to the synthesis of *erythro*-aleuritic acid lactone and an eight-membered-ring lactone moiety of octalactins A and B. The efficiency of the cyclizations is compared to those of other reported lactonizations.

Introduction

The synthesis of carboxylic esters is one of the most fundamental and important processes for producing natural and unnatural useful compounds in organic chemistry. To perform high-yielding esterifications with equimolar reactions of carboxylic acids and alcohols under mild conditions, the coupling reactions between activated derivatives of carboxylic acids and alcohols have been employed.[1]

Although several effective esterification reactions with acidic catalysts were recently reported,[2] it was also required to develop efficient reactions which proceed under basic conditions since acid-sensitive protective groups such as acetals or silyl ethers are sometimes needed for the total synthesis of complex molecules.

It is well-known that Mukaiyama et al. developed 1-alkyl-2-halopyridinium salts which function as useful reagents for the preparation of carboxylic esters coexisting with tertiary amines.[3] Furthermore, a convenient method for the preparation of carboxylic esters and lactones in the presence of triethylamine and 4-(dimethylamino)pyridine (DMAP) was established by Yamaguchi et al. using 2,4,6-trichlorobenzoyl chloride as a bulky acid moiety of the intermediary mixed anhydride.[4] This method was conventionally carried out by using an excess amount of bases and it requires a stepwise operation, namely, carboxylic acids are first treated with 2,4,6-trichlorobenzoyl chloride and triethylamine to generate the corresponding mixed anhydrides, then after filtration of the mixture under inert gas to remove the formed triethylammonium chloride, the filtrate containing the mixed anhydrides is next used for the acylation of alcohols with an excess amount of DMAP.

On the other hand, we reported an efficient method for the preparation of carboxylic esters from free carboxylic acids and alcohols using substituted *benzoic anhydrides* by the promotion of Lewis acids.[5] In the course of our studies utilizing benzoic anhydrides as condensation reagents,[6] it was anticipated that the following successive reactions would also lead to the formation of carboxylic esters starting from nearly equimo-

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(2) (a) Otera, J.; Dan-oh, N.; Nozaki, H. *J. Org. Chem*. **1991**, *56*, 5307−5311. (b) Izumi, J.; Shiina, I.; Mukaiyama, T. *Chem. Lett*. **1995**, 141−142. (c) Ishihara, K.; Ohara, S.; Yamamoto, H. *Science* **2000**, *290*, 1140−1142. (d) Wakasugi, K.; Misaki, T.; Yamada, K.; Tanabe, Y. *Tetrahedron Lett*. **2000**, *41*, 5249−5252. (e) Manabe, K.; Sun, X.-M.; Kobayashi, S. *J. Am. Chem. Soc*. **2001**, *123*, 10101−10102.

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(5) (a) Shiina, I.; Miyoshi, S.; Miyashita, M.; Mukaiyama, T. *Chem. Lett*. **1994**, 515−518. (b) Shiina, I.; Mukaiyama, T. *Chem. Lett*. **1994**, 677−680. (c) Shiina, I.; Fukuda, Y.; Ishii, T.; Fujisawa, H.; Mukaiyama, T. *Chem. Lett*. **1998**, 831−832. (d) Shiina, I.; Fujisawa, H.; Ishii, T.; Fukuda, Y. *Heterocycles* **2000**, *52*, 1105−1123. (e) Shiina, I. *Tetrahedron* **2004**, *60*, 1587−1599. See also: (f) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Am. Chem. Soc*. **1995**, *117*, 4413−4414, 6639 (correction). (g) Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem*. **1996**, *61*, 4560−4567. (h) Ishihara, K.; Kubota, M.; Yamamoto, H. *Synlett* **1996**, 265−266.

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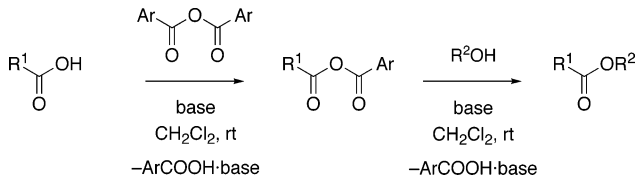


FIGURE 1. Synthesis of carboxylic esters with benzoic anhydrides.

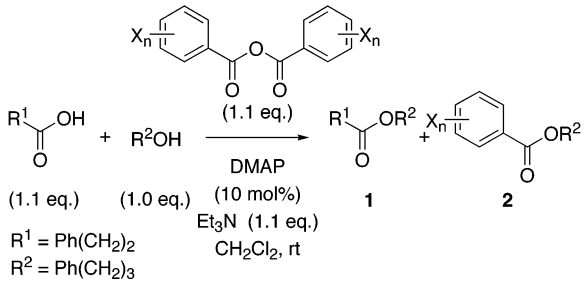
lar amounts of carboxylic acids and alcohols via the active intermediary mixed anhydrides in the presence of basic catalysts instead of acidic catalysts: that is (1) the initial formation of the mixed anhydride from the corresponding carboxylic acid with benzoic anhydride and (2) the chemoselective alcoholysis of the initially formed mixed anhydride to form the desired carboxylic ester (Figure 1). We would now like to report a new and powerful method for the synthesis of carboxylic esters and lactones using substituted benzoic anhydrides as dehydrating reagents in the presence of basic catalysts.[7]

Results and Discussion

Esterification Reaction via Mixed Anhydrides with Benzoic Anhydrides. The reaction of 1.1 M amounts of 3-phenylpropanoic acid with a 1.0 M amount of 3-phenylpropanol was initially examined in the presence of 1.1 M amounts of 3- or 4-substituted benzoic anhydride, 1.1 M amounts of triethylamine, and 10 mol % of DMAP (Table 1). When benzoic or 4-methylbenzoic anhydride was used as the dehydrating reagent, 3-phenylpropyl 3-phenylpropanoate was obtained in 69% or 82% yield along with a small amount of 3-phenylpropyl benzoate, an undesirable carboxylic ester (entry 1 or 2). Though the desired carboxylic ester was obtained with higher chemoselectivity using 4-methoxybenzoic anhydride, the reaction proceeded very slowly (entry 3). It was proven that electron-withdrawing groups increase the reactivities of the benzoic anhydrides and the desired carboxylic ester was obtained in good yields within a shorter time period; however, the chemoselectivities were rather low compared to the result with benzoic anhydride (entries 4−9 and 11).

We then tried to introduce substituents on the 2- and/or 6-position(s) of the aromatic ring of the benzoic anhydride to provide a hindrance near the carboxyl group (Table 2). A methyl or methoxy group existing on the 2- and/or 6-position(s) increases the chemoselectivity; however, the reaction sluggishly proceeded (entries 1−6). Although the reaction with benzoic anhydrides possessing electron-withdrawing groups rapidly proceeded, the chemoselectivities were not satisfactory (entries 7−9).

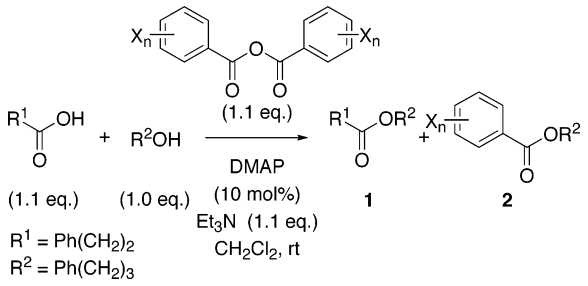
TABLE 1. Effect of 3- or 4-Substituted Benzoic Anhydrides



entry	X_n	time/h	yield[a]/%	**1**/**2**[b]
1	H	8	69	100/1
2	4-Me	1	82	38/1
3	4-MeO	20	62	170/1
4	3-Cl	1	67	32/1
5	4-Cl	1	67	36/1
6	4-NO_2	1	74	13/1
7	4-CN	1	75	17/1
8	3-CF_3	1	77	46/1
9	4-CF_3	1	70	19/1
10[c]	4-CF_3	70	36	4/1
11	3,5-$(CF_3)_2$	1	59	6/1

[a] Isolated yield of **1**. [b] Determined by ^{1}H NMR with a crude mixture. [c] The reaction was carried out in the absence of DMAP.

TABLE 2. Effect of 2- and/or 6-Substituted Benzoic Anhydrides



entry	X_n	time/h	yield[a]/%	**1**/**2**[b]
1	2-Me	24	85	100/1
2	2-MeO	24	85	>200/1
3	2,4,6-Me_3	70	56	>200/1
4	2,4-$(MeO)_2$	18	75	>200/1
5	2,6-$(MeO)_2$	18	82	>200/1
6	2-MeO-4-Cl	16	87	80/1
7	2-Cl	1	75	10/1
8	2,6-Cl_2	1	72	30/1
9	2,4,6-Cl_3	1	77	27/1
10	2-Me-6-NO_2	1	67	>200/1

[a] Isolated yield of **1**. [b] Determined by ^{1}H NMR with a crude mixture.

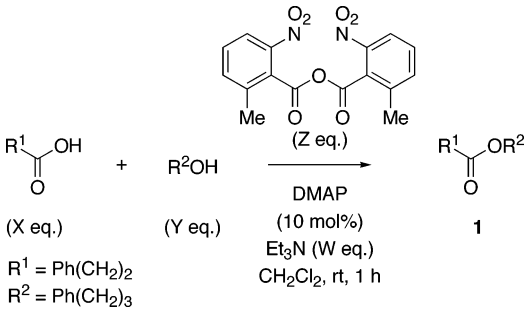
2,4,6-Trichlorobenzoic anhydride, which might afford the same mixed anhydride in the Yamaguchi protocol, gave a somewhat lower selectivity as shown in entry 9. On the other hand, we found that 2-methyl-6-nitrobenzoic anhydride (MNBA) was a quite effective dehydrating reagent for producing the carboxylic ester with high chemoselectivity in the presence of a catalytic amount of DMAP (entry 10).[7a]

The yield of the desired carboxylic ester increased to over 80% when MNBA was used as the condensation reagent with an excess amount of triethylamine, since the reaction rapidly proceeds under the influence of

(6) (a) Mukaiyama, T.; Shiina, I.; Miyashita, M. *Chem. Lett.* **1992**, 625−628. (b) Miyashita, M.; Shiina, I.; Miyoshi, S.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1516−1527. See also: (c) Mukaiyama, T.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1992**, 1747−1750. (d) Mukaiyama, T.; Izumi, J.; Miyashita, M.; Shiina, I. *Chem. Lett.* **1993**, 907−910. (e) Miyashita, M.; Shiina, I.; Mukaiyama, T. *Chem. Lett.* **1993**, 1053−1054. (f) Miyashita, M.; Shiina, I.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1994**, *67*, 210−215. (g) Shiina, I.; Miyashita, M.; Nagai, M.; Mukaiyama, T. *Heterocycles* **1995**, *40*, 141−148.

(7) Preliminary communications: (a) Shiina, I.; Ibuka, R.; Kubota, M. *Chem. Lett.* **2002**, 286−287. (b) Shiina, I.; Kubota, M.; Ibuka, R. *Tetrahedron Lett.* **2002**, *43*, 7535−7539. 2-Methyl-6-nitrobenzoic anhydride (MNBA) is commercially available from Tokyo Kasei Kogyo Co., Ltd. (TCI, M1439).

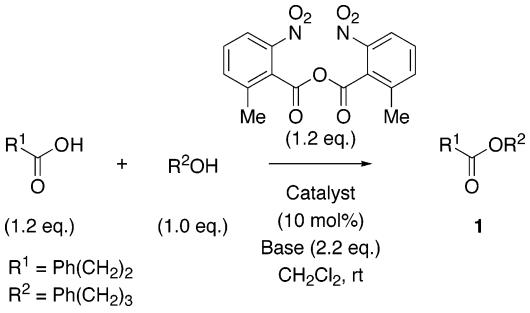
TABLE 3. Effect of Molar Ratios of Substrates and Reagents



entry	X	Y	Z	W	yield[a]/%
1	1.1	1.0	1.1	1.1	67
2	1.1	1.0	1.1	2.2	87
3	1.1	1.0	1.1	3.3	88
4	1.0	1.0	1.1	2.2	84
5	1.0	1.1	1.0	2.2	81
6	1.1	1.0	1.2	2.2	90
7	1.2	1.0	1.2	2.2	94

[a] Isolated yield.

TABLE 4. Effect of Catalysts and Bases



entry	catalyst	base	time/h	yield[a]/%
1	DMAP	$^{i}Pr_2NEt$	1	94
2	DMAP	*N*-methylpiperidine	1	87
3	DMAP	TMEDA	1	89
4	DMAP	MgO	120	91
5	DMAP	Et_3N	1	94
6	PPY	Et_3N	1	81
7	DMAPO	Et_3N	1	86
8	PPYO	Et_3N	1	82
9	pyridine	Et_3N	1	0
10	TMEDA	Et_3N	1	5
11	$^{n}Bu_3P$	Et_3N	1	9
12	CsF	Et_3N	1	24
13	none	Et_3N	1	1

[a] Isolated yield.

DMAP (Table 3). The use of 2.2 M amounts of triethylamine gave the similar result as that of the reaction with a 3.3 M amount of triethylamine (entries 2 and 3). The molar ratios of the carboxylic acid, alcohol, and MNBA were also examined in detail (entries 4−7), and it was revealed that **1** was obtained in nearly quantitative yield by employing slightly excessive amounts of the carboxylic acid and MNBA (entry 7).

Other tertiary amines such as *N*-ethyldiisopropylamine, *N*-methylpiperidine, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were also effective (Table 4, entries 1−3), and MgO could function as a solid base although an extension of the reaction time was required for the completion of the esterification (entry 4). An examination of the catalysts showed that not only heteroaromatic compounds such as DMAP and 4-pyrrolidinopyridine (PPY)[8] promoted the reaction but also their *N*-oxides[9] such as 4-(dimethylamino)pyridine 1-oxide (DMAPO) and 4-pyrrolidinopyridine 1-oxide (PPYO) facilitated a desirable condensation between the carboxylic acids and alcohols (entries 5−8). Pyridine, TMEDA, tributylphosphine, and CsF were ineffective for this reaction as a catalyst as shown in entries 9−12.

Several examples of carboxylic esters obtained by the present method under the optimized conditions are listed in Table 5. Including the benzyl and allyl alcohols, primary aliphatic alcohols were successfully employed and the corresponding carboxylic esters were obtained in excellent yields with complete chemoselectivities (entries 1−3). The reaction of secondary aliphatic alcohols also gave the desired carboxylic esters in high yields with perfect selectivities (entries 4−7). It is noteworthy that acid-sensitive substrates could be converted into the desired esters in high yields without forming undesirable byproducts (entries 8 and 9). This protocol is also applicable to other carboxylic acids including α,α-disubstituted, α,*β*-unsaturated, and aromatic carboxylic acids, and various aliphatic, α,*β*-unsaturated, and aromatic carboxylic esters are obtained in good to high yields under the mild reaction conditions (entries 10−22). Acceptable chemoselectivities (<1% yield of **B**) were observed for all cases except for a few combinations (entries 14−16 and 18). When using (*E*)-crotonic acid or the fumaric acid monoethyl ester for the reaction, the corresponding *β*,*γ*-unsaturated carboxylic ester or maleic acid diester was produced as a byproduct due to the base-promoted double bond migration or isomerization (entries 18 and 19, or 22).[6b,10]

Furthermore, we compared our results with those obtained according to the Yamaguchi procedure using 2,4,6-trichlorobenzoyl chloride.[4a] These data are presented in the left column of Table 6 and the compared data obtained by MNBA are shown in the right column. We observed the formation of significant amounts of the undesired alkyl 2,4,6-trichlorobenzoates (**C**) in many cases (entries 1 (6%), 2 (9%), 3 (29%), 9 (10%), 10 (6%), 12 (2%), 13 (8%), 15 (12%), and 16 (4%)), though our method gave almost perfect chemoselectivities except for entry 13 (2% yield of **B**). It is noted that the maximum yield of the desired ester **1** is limited to ca. 70% by the Yamaguchi method in entry 3 since the reaction proceeded without high chemoselectivity.

One of the features of the present protocol with MNBA is the quite simple procedure for the synthesis of a variety of carboxylic esters. The Yamaguchi method usually

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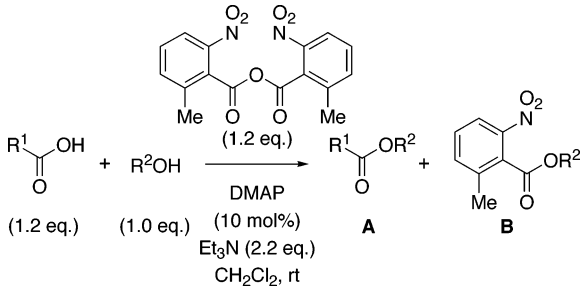
(9) (a) Ife, R. J.; Dyke, C. A.; Keeling, D. J.; Meenan, E.; Meeson, M. L.; Parsons, M. E.; Price, C. A.; Theobald, C. J.; Underwood, A. H. *J. Med. Chem.* **1989**, *32*, 1970−1977. For the modified purification see: (b) Mukaiyama, S.; Inanaga, J.; Yamaguchi, M. *Bull. Chem. Soc. Jpn.* **1981**, *54*, 2221−2222.

(10) Double bond migration: (a) Shoda, S.; Mukaiyama, T. *Chem. Lett.* **1980**, 391. (b) Shoda, S. Ph.D. Thesis, The University of Tokyo, Tokyo, Japan, 1980. *Z*−*E* isomerization: (c) Hartmann, B.; Kanazawa, A. M.; Deprés, J.-P.; Greene, A. E. *Tetrahedron Lett.* **1991**, *32*, 5077−5080. (d) Brocksom, T. J.; Coelho, F.; Deprés, J.-P.; Greene, A. E.; Freire de Lima, M. E.; Hamelin, O.; Hartmann, B.; Kanazawa, A. M.; Wang, Y. *J. Am. Chem. Soc.* **2002**, *124*, 15313−15325.

TABLE 5. Sythesis of Various Carboxylic Esters with MNBA



entry	R^1	R^2	R^1COOR^2	yield[a]/%	**A**/**B**[b]
1	$Ph(CH_2)_2$	Bn	**3**	95	>200/1
2	$Ph(CH_2)_2$	CH_2=$CHCH_2$	**4**	92	>200/1
3	$Ph(CH_2)_2$	$Ph(CH_2)_3$	**1**	94	>200/1
4	$Ph(CH_2)_2$	$Ph(CH_2)_2CHCH_3$	**5**	95	>200/1
5	$Ph(CH_2)_2$	*c*-C_6H_{11}	**6**	92	>200/1
6	$Ph(CH_2)_2$	menthyl	**7**	90	>200/1
7	$Ph(CH_2)_2$	5α-cholestan-3β-yl	**8**	83	>200/1
8	$Ph(CH_2)_2$	$C_9H_{19}C(CH_3)_2$	**9**	94[c]	>200/1
9	$Ph(CH_2)_2$	$THPO(CH_2)_6$	**10**	98	>200/1
10	$PhCH(OTBS)CH_2$	$Ph(CH_2)_3$	**11**	92	183/1
11	*c*-C_6H_{11}	$Ph(CH_2)_3$	**12**	96	143/1
12	*c*-C_6H_{11}	$Ph(CH_2)_2CHCH_3$	**13**	quant.[d]	>200/1
13	*c*-C_6H_{11}	*c*-C_6H_{11}	**14**	87	>200/1
14	^{t}Bu	$Ph(CH_2)_3$	**15**	72	7/1
15	^{t}Bu	$Ph(CH_2)_2CHCH_3$	**16**	72	73/1
16	Ph	$Ph(CH_2)_3$	**17**	92	42/1
17	Ph	$Ph(CH_2)_2CHCH_3$	**18**	88[d]	>200/1
18	(*E*)-MeCH=CH	$Ph(CH_2)_3$	**19**	78 (37/1)[e]	55/1
19	(*E*)-MeCH=CH	$Ph(CH_2)_2CHCH_3$	**20**	81 (7/1)[f]	>200/1
20	(*E*)-PhCH=CH	$Ph(CH_2)_3$	**21**	98	187/1
21	(*E*)-PhCH=CH	$Ph(CH_2)_2CHCH_3$	**22**	95	>200/1
22	(*E*)-EtO_2CCH=CH	$Ph(CH_2)_3$	**23**	90 (37/1)[g]	>200/1

[a] Isolated yield of **A**. [b] Determined by ^{1}H NMR with a crude mixture. [c] 3.0 M amounts of carboxylic acid, 3.0 M amounts of MNBA, and 5.0 M amounts of triethylamine were used. [d] 1.3 M amounts of carboxylic acid and 1.3 M amounts of MNBA were used. [e] Ratio of **A** to 3-phenylpropyl 3-butenoate. [f] Ratio of **A** to 1-methyl-3-phenylpropyl 3-butenoate. [g] Ratio of **A** to ethyl 3-phenylpropyl maleate.

requires a stepwise operation, namely, carboxylic acids are treated with 2,4,6-trichlorobenzoyl chloride and triethylamine at first to generate the corresponding mixed anhydrides. After filtration of the mixture under an inert gas to remove the formed triethylammonium chloride, the filtrate containing mixed anhydrides is next used for the esterification of alcohols with an excess amount of DMAP. On the other hand, by only mixing carboxylic acids, alcohols, MNBA, triethylamine, and a catalytic amount of DMAP at room temperature, the desired compounds are produced in excellent yields with high purity according to our new method.

The reaction pathway was studied by ^{1}H NMR with a mixture of a carboxylic acid and MNBA under the reaction conditions (Figure 2). The formation of ca. 10 mol % of a reactive key intermediate, the pyridinium salt of methoxyacetic acid (**I**), was observed after mixing 1.2 M amounts of methoxyacetic acid, 1.2 M amounts of MNBA and a 1.0 M amount of triethylamine in the presence of 10 mol % of DMAP.[11] The addition of 3-phenylpropanol to the reaction mixture gave 3-phenylpropyl methoxyacetate in 70% yield with perfect chemoselectivity. Independently, the mixed anhydride (**II**) consisting of methoxyacetic acid and 2-methyl-6-nitrobenzoic acid was generated by the reaction of methoxyacetyl chloride with 2-methyl-6-nitrobenzoic acid in the presence of triethylamine, and it was found that there is an equilibrium among the mixed anhydride, MNBA, and methoxyacetic anhydride (ca. 4:3:3).[12] Therefore, it is postulated that the pyridinium salt (**I**) is formed by the reaction of the mixed anhydride (**II**) or homogeneous methoxyacetic anhydride with DMAP, and the successive nucleophilic addition of the alcohol to **I** gives the desired carboxylic ester in high yield. On the other hand, the activated 2-methyl-6-nitrobenzoyl pyridinium salt was not formed in the above experiment. The byproducts, the corresponding alkyl 2-methyl-6-nitrobenzoates, were therefore hardly produced in the present esterification reaction due to the stability of the 2-methyl-6-nitrobenzoate anion.

Lactonization via Mixed Anhydrides with Benzoic Anhydrides. The macrocyclic framework is one of the most basic structures for useful natural and unnatural organic molecules. Recently, several effective C−C bond-forming reactions such as transition metal-promoted coupling and olefin metathesis have been widely studied for producing cyclic compounds.[13,14] However, macrolactonization is still the most popular

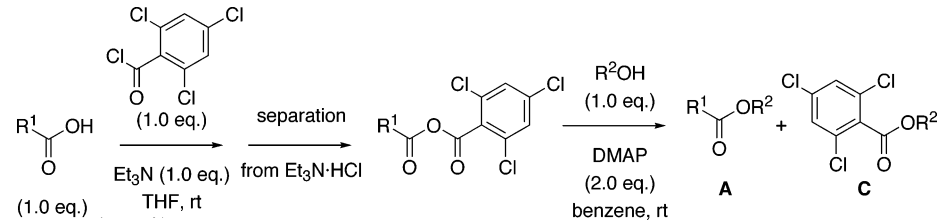
(11) The conversion yield of **I** was determined by the intensity of a ^{1}H NMR signal at 4.18 ppm (MeO in **I**).

(12) The ratio was determined by the intensity of ^{1}H NMR signals at 4.25 and 4.13 ppm (MeO in **II** and methoxyacetic anhydride).

(13) Duncton, M. A. J.; Pattenden, G. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1235−1246 and references cited therein.

(14) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388 and references cited therein.

TABLE 6. Experimental Results Compared between Two Mixed Anhydride Methods



entry	R^1	R^2	yield[a]/% [**A**/**C**][b,c]	yield[a]/% [**A**/**B**][b,d]
1	$Ph(CH_2)_2$	Bn	90 [15/1]	95 [>200/1]
2	$Ph(CH_2)_2$	$CH_2{=}CHCH_2$	85 [10/1]	92 [>200/1]
3	$Ph(CH_2)_2$	$Ph(CH_2)_3$	58 [2/1]	94 [>200/1]
4	$Ph(CH_2)_2$	$Ph(CH_2)_2CHCH_3$	92 [152/1]	95 [>200/1]
5	$Ph(CH_2)_2$	*c*-C_6H_{11}	94 [>200/1]	92 [>200/1]
6	$Ph(CH_2)_2$	menthyl	88 [>200/1]	90 [>200/1]
7	$Ph(CH_2)_2$	5α-cholestan-3β-yl	86 [70/1]	83 [>200/1]
8	$Ph(CH_2)_2$	$C_9H_{19}C(CH_3)_2$	51[e] [>200/1]	94 [>200/1]
9	$Ph(CH_2)_2$	$THPO(CH_2)_5$	62 [6/1]	98 [>200/1]
10	*c*-C_6H_{11}	$Ph(CH_2)_3$	89 [14/1]	96 [143/1]
11	*c*-C_6H_{11}	$Ph(CH_2)_2CHCH_3$	97 [187/1]	quant. [>200/1]
12	*c*-C_6H_{11}	*c*-C_6H_{11}	94 [54/1]	87 [>200/1]
13	Ph	$Ph(CH_2)_3$	85 [11/1]	92 [42/1]
14	Ph	$Ph(CH_2)_2CHCH_3$	98 [>200/1]	88 [>200/1]
15	(*E*)-PhCH=CH	$Ph(CH_2)_3$	82 [7/1]	98 [187/1]
16	(*E*)-PhCH=CH	$Ph(CH_2)_2CHCH_3$	87 [22/1]	95 [>200/1]

[a] Isolated yield of **A**. [b] Determined by ^{1}H NMR with a crude mixture. [c] The data were obtained by Yamaguchi protocol according to the procedure in ref 4a. [d] Abstracted from Table 5. [e] 38% of 2-methylundecan-2-ol was recovered.

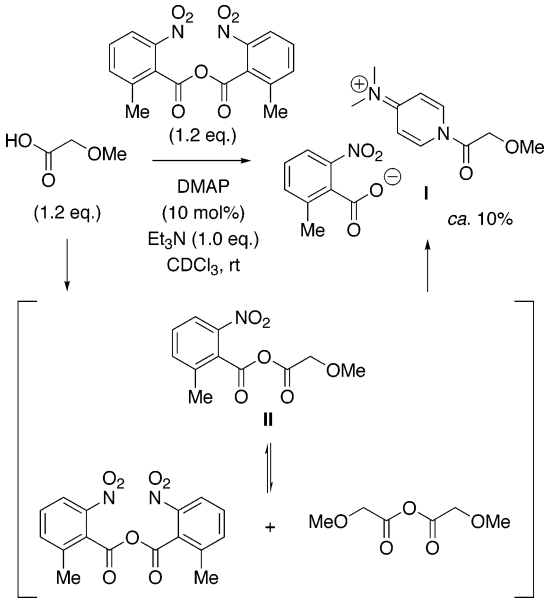
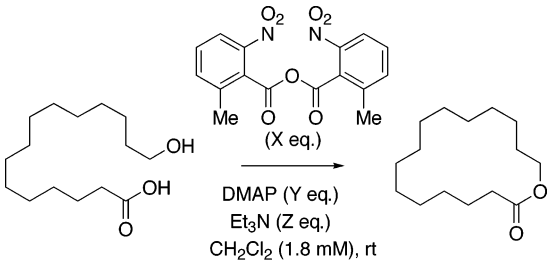


FIGURE 2. Formation of an active intermediate of the present esterification reaction.

TABLE 7. Effect of Molar Ratios of Reagents



				yield[a]/%	
entry	X	Y	Z	monomer	dimer
1	1.0	0.1	2.2	65	6
2	1.0	0.2	2.2	84	5
3	1.0	0.3	2.2	86	3
4	1.0	0.2	3.3	82	6
5	1.2	0.2	2.2	88	3
6	1.2	2.4	0	92	1

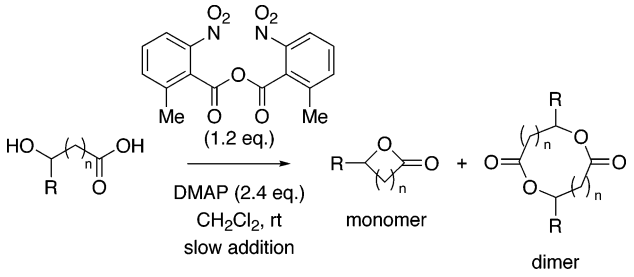
[a] Isolated yield.

method for producing cyclic compounds including carboxylic ester moieties since there are some effective methods for constructing the ester linkage.[1]

In the previous section, we developed a new condensation reaction for the synthesis of carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols using MNBA with triethylamine in the presence of DMAP. This protocol is quite effective and the desired carboxylic esters are produced in excellent yields with higher chemoselectivities compared with those obtained by the Yamaguchi esterification method. The reaction of nearly equal amounts of carboxylic acids and alcohols smoothly proceeds at room temperature, therefore, it is assumed that the MNBA method might be successfully applied to the intramolecular reaction for producing the macrocyclic compounds under mild conditions. We would now like to report a novel and efficient lactonization of ω-hydroxycarboxylic acids using MNBA, an effective condensation reagent, by the promotion of DMAP or DMAPO.[7b]

First, 15-hydroxypentadecanoic acid is employed as a model substrate for optimizing the reaction conditions (see Table 7). When a solution of 15-hydroxypentadecanoic acid in dichloromethane was slowly added to the reaction mixture of a 1.0 M amount of MNBA, 2.2 M amount of triethylamine, and 10 mol % of DMAP in

TABLE 8. Synthesis of Lactones with MNBA and DMAP



					yield[a]/% (ring size)	
entry	R	*n*	conc/mM	time/h	monomer	dimer
1	H	10	1.0	15	88 (13)	5 (26)
2[b]	C_6H_{13}	10	2.0	15	86 (13)	1 (26)
3	H	11	1.0	15	75 (14)	1 (28)
4	H	12	1.0	15	89 (15)	<1 (30)
5	H	13	1.8	15	92 (16)	1 (32)
6[c]	H	13	1.8	12	91 (16)	3 (32)
7	H	14	1.8	15	92 (17)	<1 (34)

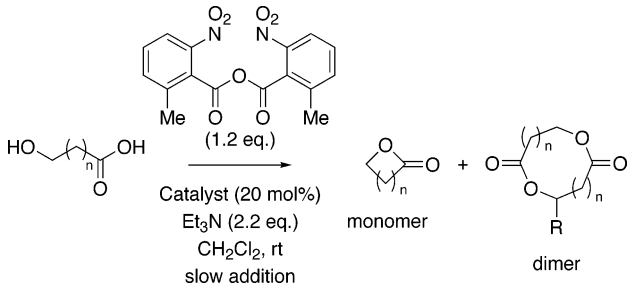
[a] Isolated yield. [b] 1.3 M amounts of MNBA and 3.5 M amounts of DMAP were used. [c] PPY was used as a base.

dichloromethane for over a 15 h period at room temperature, the corresponding monomeric lactone was obtained in 65% yield accompanied by 6% diolide and 1% triolide (entry 1). Though the yield of the desired pentadecan-15-olide increased to 84% or 86% with 20 or 30 mol % of DMAP, respectively, under the same reaction conditions, the ratio of monomer to dimer was not satisfactory as shown in entry 2 or 3. Furthermore, employing an excess amount of triethylamine decreased the ratio to some extent (entry 4). On the other hand, better product selectivity was observed when a slight excess amount of MNBA was used (entry 5). We finally used a stoichiometric amount of DMAP to MNBA in the absence of triethylamine, and the desired monomeric lactone was produced in high yield with an excellent selectivity (entry 6). In this case, DMAP works not only as an activator for the dehydration condensation but also as a base to generate the corresponding protonated pyridinium salt.

Table 8 shows the yields of the several macrolactones synthesized by the present method with MNBA and DMAP. All reactions were carried out at room temperature by adding a solution of ω-hydroxycarboxylic acids to a mixture of MNBA and DMAP in dichloromethane. Each concentration in the table shows the molar amounts of ω-hydroxycarboxylic acids to the total volume of the dichloromethane solvent. Although a small amount of diolide formed in the case of using 12-hydroxydodecanoic acid as shown in entry 1, from 14- to 17-membered-ring macrolactones were obtained in high yields and the undesired dimers were scarcely produced (entries 3−5 and 7). Since the reaction rate was not sufficiently fast when a secondary ω-hydroxycarboxylic acid was employed for the reaction, an excess amount of reagents was required to produce the excellent product selectivity (entry 2). It is also noted that this reaction could be performed by the promotion of PPY, a derivative of DMAP, as shown in entry 6.

Next, we tried to investigate other activators for the present reaction to improve the efficiency for producing the desired compounds with a higher ratio of monomers to dimers. After screening several basic compounds

TABLE 9. Synthesis of Lactones with MNBA with Basic Catalysts



					yield[a]/% (ring size)	
entry	catalyst	*n*	conc/mM	time/h	monomer	dimer
1	DMAP	13	1.8	15	88 (16)	3 (32)
2	DMAPO	13	1.8	14	91 (16)	<1 (32)
3	PPYO	13	1.8	13	95 (16)	<1 (32)
4	DMAPO	14	1.4	16	92 (17)	1 (34)

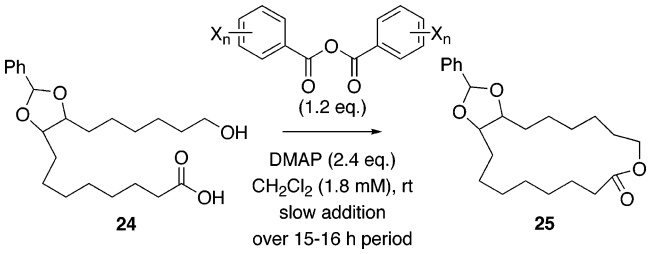
[a] Isolated yield.

including inorganic solid bases, it was proved that substituted pyridine 1-oxides are quite effective catalysts for the reaction forming large ring-size lactones with triethylamine in the presence of MNBA (Table 9). For example, the desired pentadecan-15-olide and hexadecan-16-olide were obtained in 91% and 92% yields, respectively, accompanied by only a trace and 1% of the corresponding dimers when 20 mol % of DMAPO was employed as a catalyst for the reactions with 2.2 M amounts of triethylamine at room temperature (entries 2 and 4). PPYO, a derivative of DMAPO, was also proved to be effective for the macrolactonization, and the desired pentadecan-15-olide was produced in good yield (95%) from 15-hydroxypentadecanoic acid at room temperature (entry 3). As far as we know, the present method is the first successful example utilizing pyridine 1-oxides for the effective synthesis of macrolactones.[15]

Synthesis of the Protected *erythro*-Aleuritic Acid Lactone. We further examined the effect of the substituents on the aromatic moiety of the benzoic anhydrides in our mixed anhydride method for the synthesis of a functionalized macrocyclic molecule. For this purpose, seco acid **24** was prepared from *erythro*-aleuritic acid (*erythro*-9,10,16-trihydroxyhexadecanoic acid) by treating with $PhCH(OMe)_2$ and 10-camphorsulfonic acid (CSA). In the presence of 2.4 M amounts of DMAP, the macrolactonization of **24** was then carried out with use of

(15) An effective phosphorylation was developed in 1985 using these substituted pyridine 1-oxides as promoters with condensation reagents. (a) Efimov, V. A.; Chakhmakhcheva, O. G.; Ovchinnikov, Yu. A. *Nucleic Acids Res.* **1985**, *13*, 3651−3666. (b) Efimov, V. A.; Chakhmakhcheva, O. G. *Biochimie* **1985**, *67*, 791−795. (c) Efimov, V. A.; Chakhmakhcheva, O. G. *Chem. Scr.* **1986**, *26*, 55−58. (d) Efimov, V. A.; Buryakova, A. A.; Dubey, I. Y.; Polushin, N. N.; Chakhmakhcheva, O. G.; Ovchinnikov, Yu. A. *Nucleic Acids Res.* **1986**, *14*, 6525−6540. (e) Efimov, V. A.; Buryakova, A. A.; Polushin, N. N.; Dubey, I. Y.; Chakhmakhcheva, O. G.; Ovchinnikov, Yu. A. *Nucleosides Nucleotides* **1987**, *6*, 279−282. See also, (f) Sekine, M. *J. Synth. Org. Chem. Jpn.* **1990**, *48*, 1038−1039. For the synthesis of arylsulphanilides see: (g) Savelova, V. A.; Solomoichenko, T. N.; Litvinenko, L. M. *Zh. Org. Khim.* **1972**, *8*, 1011−1018. (h) Savelova, V. A.; Belousova, I. A.; Litvinenko, L. M.; Yakovets, A. A. *Dokl. Akad. Nauk SSSR* **1984**, *274*, 1393−1398. Polymer-supported DMAPO was employed for the synthesis of phenyl benzoate from phenol with benzoyl chloride. See: (i) Zitsmanis, A.; Klyavinsh, M.; Skuyinsh, A.; Jakobsone, I. *React. Polym.* **1989**, *11*, 227−236.

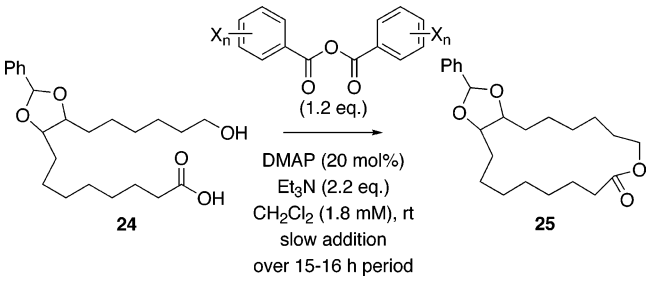
TABLE 10. Effect of Substituted Benzoic Anhydrides for the Synthesis of the Protected *erythro*-Aleuritic Acid Lactone (Stoichiometric)



		yield[a]/%	
entry	X_n	monomer	dimer
1	H	77	4
2	4-Me	71	8
3	4-MeO	29	6
4	4-Cl	83	3
5	4-NO_2	83	4
6	4-CF_3	76	3
7	2,4,6-Cl_3	79	2
8	2-Me-6-NO_2	90	2
9[b]	2-Me-6-NO_2	87	3

[a] Isolated yield. [b] PPY was used as a base.

TABLE 11. Effect of Substituted Benzoic Anhydrides for the Synthesis of the Protected *erythro*-Aleuritic Acid Lactone (Catalytic)

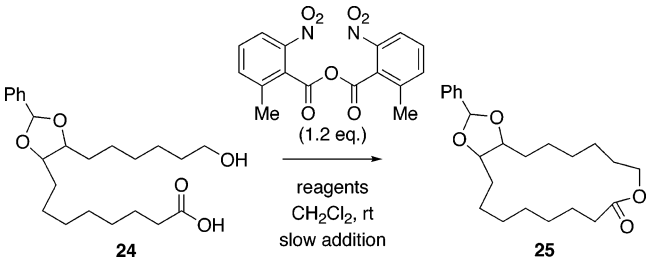


		yield[a]/%	
entry	X_n	monomer	dimer
1	H	60	8
2	4-Me	48	8
3	4-MeO	24	4
4	4-Cl	62	<1
5	4-NO_2	43	2
6	4-CF_3	53	4
7	2,4,6-Cl_3	64	6
8	2-Me-6-NO_2	69	6
9[b]	2-Me-6-NO_2	90	2

[a] Isolated yield. [b] 20 mol % of DMAPO was used as a catalyst.

several substituted benzoic anhydrides (Table 10). Although 4-methoxybenzoic anhydride afforded a poor result as shown in entry 3, other anhydrides such as benzoic or 4-methyl-, 4-chloro-, 4-nitro-, 4-trifluoromethyl-, and 2,4,6-trichlorobenzoic anhydrides gave similar yields of the desired monomer **25** (71−83%) and dimer (2−8%) (entry 1 or entries 2 and 4−7). From the point of view concerning the commercial economy, the use of cheap benzoic anhydrides is also one of the convenient ways to produce the desired compounds, for example, a simple benzoic anhydride could be utilized for the formation of **25** in relatively good yield (77%).

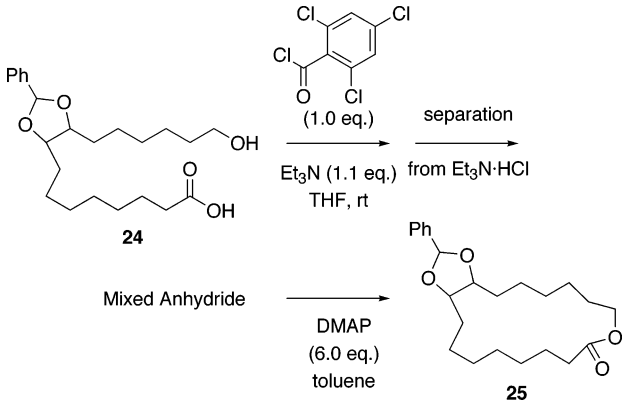
TABLE 12. Synthesis of the Protected *erythro*-Aleuritic Acid Lactone with MNBA under Several Conditions



				yield[a]/%	
entry	reagents	conc	time/h	monomer	dimer
1[b]	DMAP (2.4 eq.)	**i**	16	90	2
2[c]	DMAP (2.4 eq.)	**ii**	9	83	1
3[d]	DMAPO (20 mol %), Et_3N (2.2 eq.)	**iii**	16	90	2
4[c]	DMAPO (20 mol %), Et_3N (2.2 eq.)	**ii**	9	79	<1

[a] Isolated yield. [b] A solution of **24** (0.380 mmol) in dichloromethane (84.6 mL) was slowly added to a solution of reagents in dichloromethane (135.8 mL). [c] A solution of **24** (0.360 mmol) in dichloromethane (180.0 mL) was slowly added to a solution of reagents in dichloromethane (36.0 mL). [d] A solution of **24** (0.360 mmol) in dichloromethane (108.0 mL) was slowly added to a solution of reagents in dichloromethane (151.0 mL).

TABLE 13. Synthesis of the Protected *erythro*-Aleuritic Acid Lactone with 2,4,6-Trichlorobenzoyl Chloride under Several Conditions



				yield[a]/%	
entry	conc	temp/°C	time/h	monomer	dimer
1[b]	**i**	rt	16	33	3
2[c]	**ii**	rt	9	52	5
3[b]	**i**	120	16	43	6
4[c]	**ii**	120	9	70	9

[a] Isolated yield. [b] A solution of MA derived from **24** (0.360 mmol) in toulene (84.6 mL) was slowly added to a solution of DMAP (2.16 mmol) in toulene (135.8 mL). [c] A solution of MA derived from **24** (0.360 mmol) in toulene (36.0 mL) was slowly added to a solution of DMAP (2.16 mmol) in toulene (180.0 mL).

The best yield of **25** and product selectivity of the monomer to the dimer was attained again for the macrolactonization of **24** using MNBA with 2.4 M amounts of DMAP (entry 8). When PPY was used for the reaction under the same conditions as entry 8, **25** was also obtained in 87% yield (entry 9). Facile deprotection of **25** with acetic acid produced the *erythro*-aleuritic acid lactone in 93% yield.

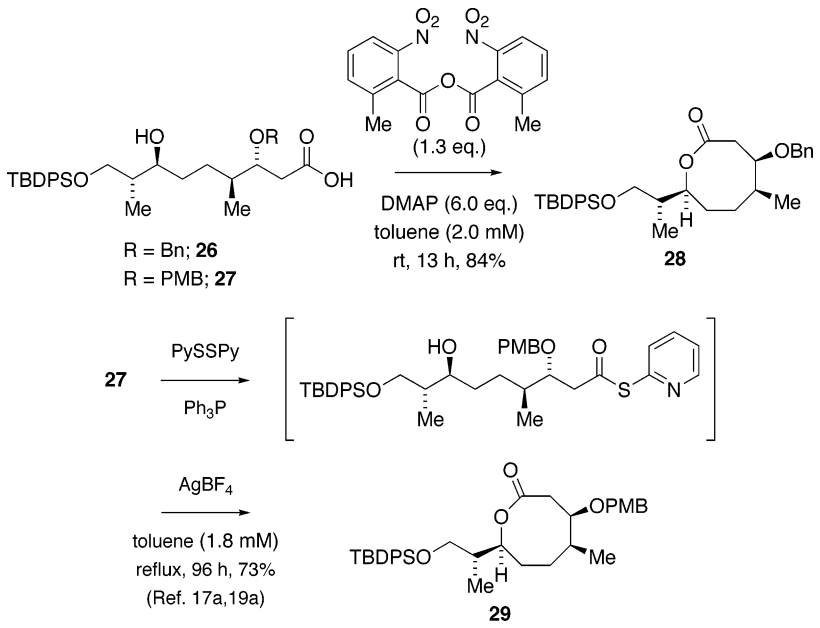


FIGURE 3. Synthesis of the eight-membered-ring lactones with MNBA or dipyridyl disulfide.

Furthermore, the catalytic reaction accelerated by 20 mol % of DMAP was carried out using several substituted benzoic anhydrides as listed in Table 11. It was found that the reaction using MNBA with triethylamine and a catalytic amount of DMAP afforded the best yield of **25** (entry 8) compared to the cases when using other benzoic anhydrides (entries 1−7). As shown in entry 9, the DMAPO-promoted cyclization cleanly took place to produce **25** in 90% yield under the influence of triethylamine.

To compare the efficiency of our new protocols with other mixed anhydride methods, the macrolactonization of **24** was further examined. These data are summarized in Tables 12 and 13. Although the MNBA method provided excellent results at room temperature under the optimized conditions as shown in entries 1 and 3 in Table 12 (90% yield), the desired lactone **25** was obtained in moderate yield with lower product selectivity by the Yamaguchi protocol at the same temperature (Table 13, entry 2). The yield increased to 70% when the reaction was carried out at refluxing temperature in toluene according to the originally optimized procedure (Table 13, entry 4),[4a] but the product selectivity is not sufficient for producing **25** with high purity. These reactions were carried out again at room temperature under strictly identified conditions such as the concentrations (**i** and **ii**) of the substrate and reagents (compare entry 1 in Table 12 with entry 1 in Table 13; entries 2 and 4 in Table 12 with entry 2 in Table 13). In every case, the benzoic anhydride method with MNBA gave better yields in comparison with the reaction using 2,4,6-trichlorobenzoyl chloride.

Synthesis of the Eight-Membered-Ring Lactone Moiety of Octalactins A and B. Octalactins A and B were isolated from the marine bacterium *Streptomyces sp*. in 1991.[16,17] The structure of these compounds includes an unusual saturated medium-sized lactone moiety, and octalactin A exhibits a potent cytotoxic activity against some tumor cell lines.

Next, the lactonization of a seco-acid **26**, a synthetic intermediate of octalactins, was attempted by the present mixed anhydride method with use of MNBA in the presence of DMAP.[18] The cyclization reaction of **26** was efficiently accelerated by MNBA with DMAP to afford the desired lactone **28** in 84% yield at *room temperature*, and the corresponding diolide was not produced (Figure 3). Buszek et al. successfully synthesized an eight-membered-ring lactone **29** from the corresponding seco-acid **27**, which has the PMBO group instead of the BnO group at the C3 position of **26** via formation of the intermediary *S*-Py ester in refluxed toluene.[17a,19] It was reported that the cyclization of the *S*-Py ester requires a long reaction time such as 96 h even in the presence of a

(16) (a) Tapiolas, D. M.; Roman, M.; Fenical, W.; Stout, T. J.; Clardy, J. *J. Am. Chem. Soc.* **1991**, *113*, 4682−4683. (b) *Macrolide Antibiotics*, 2nd ed.; Omura, S., Ed.; Academic Press: San Diego, CA, 2002.

(17) Total syntheses: (a) Buszek, K. R.; Sato, N.; Jeong, Y. *J. Am. Chem. Soc.* **1994**, *116*, 5511−5512. (b) McWilliams, J. C.; Clardy, J. *J. Am. Chem. Soc.* **1994**, *116*, 8378−8379. (c) Buszek, K. R.; Sato, N.; Jeong, Y. *Tetrahedron Lett.* **2002**, *43*, 181−184. Formal syntheses: (d) Buszek K. R.; Jeong, Y. *Tetrahedron Lett.* **1995**, *36*, 7189−7192. (e) Kodama, M.; Matsushita, M.; Terada, Y.; Takeuchi, A.; Yoshio, S.; Fukuyama, Y. *Chem. Lett.* **1997**, 117−118. (f) Inoue, S.; Iwabuchi, Y.; Irie, H.; Hatakeyama, S. *Synlett* **1998**, 735−736. Partial syntheses: (g) Andrus, M. B.; Argade, A. B. *Tetrahedron Lett.* **1996**, *37*, 5049−5052. (h) Bach, J.; Garcia, J. *Tetrahedron Lett.* **1998**, *39*, 6761−6764. Other synthetic studies: (i) Bach, J.; Berenguer, R.; Garcia, J.; Vilarrasa, J. *Tetrahedron Lett.* **1995**, *36*, 3425−3428. (j) Hulme, A. N.; Howells, G. E. *Tetrahedron Lett.* **1997**, *38*, 8245−8248. (k) Shimoma, F.; Kusaka, H.; Wada, K.; Azami, H.; Yasunami, M.; Suzuki, T.; Hagiwara, H.; Ando, M. *J. Org. Chem.* **1998**, *63*, 920−929. (l) Harrison, J. R.; Holmes, A. B.; Collins, I. *Synlett* **1999**, 972−974. (m) Anderson, E. A.; Holmes, A. B.; Collins, I. *Tetrahedron Lett.* **2000**, *41*, 117−121. (n) Bluet, G.; Campagne, J.-M. *Synlett* **2000**, 221−222.

(18) Shiina, I.; Oshiumi, H.; Hashizume, M.; Yamai, Y.; Ibuka, R. *Tetrahedron Lett.* **2004**, *45*, 543−547.

(19) (a) Buszek, K. R.; Jeong, Y.; Sato, N.; Still, P. C.; Muino, P. L.; Ghosh, I. *Synth. Commun.* **2001**, *31*, 1781−1791. Original *S*-Py ester methods for the synthesis of macrolactones: (b) Corey, E. J.; Nicolaou, K. C. *J. Am. Chem. Soc.* **1974**, *96*, 5614−5616. (c) Gerlach, H.; Thalmann, A. *Helv. Chim. Acta* **1974**, *57*, 2661−2663. (d) Corey, E. J.; Brunelle, D. J. *Tetrahedron Lett.* **1976**, *17*, 3409−3412. See also the synthesis of unsaturated eight-membered-ring lactones: (e) Nicolaou, K. C.; McGarry, D. G.; Somers, P. K.; Kim, B. H.; Ogilvie, W. W.; Yiannikouros, G.; Prasad, C. V. C.; Veale, C. A.; Hark, R. R. *J. Am. Chem. Soc.* **1990**, *112*, 6263−6276.

silver salt as an accelerator. Therefore, we examined the *S*-Py ester method for the cyclization of **26** again under similar reaction conditions according to the reported procedure. The desired lactone **28** was also produced in satisfactory yield after 96 h; however, the macrolactonization sluggishly proceeded in refluxed toluene with the silver salt catalyst. When the reaction was carried out at room temperature, the target molecule **28** was not produced at all. On the other hand, it is noteworthy that the MNBA method gives the desired lactone in higher yield at ambient temperature within a shorter time. Thus, an efficient method for the preparation of the synthetic precursor of octalactins was established via the effective construction of the eight-membered-ring lactone moiety.[18]

Conclusion

An efficient method for the synthesis of various carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols with MNBA as the dehydrating reagent by the promotion of a catalytic amount of DMAP in the presence of triethylamine was successfully developed. Furthermore, a convenient and powerful method for the synthesis of a variety of macrolactones with high product selectivities via mixed anhydrides generated from ω-hydroxycarboxylic acids and MNBA with basic catalysts was established.[20] One of the features of the present protocol is the very simple procedure for producing the desired products, that is, the addition of ω-hydroxycarboxylic acids to the mixture of MNBA and the promoters at room temperature affords the desired macrolactones in excellent yields with high purity. The utility of the present protocol was also demonstrated by the syntheses of *erythro*-aleuritic acid lactone and the eight-membered-ring lactone moiety of octalactins A and B.

Acknowledgment. The author is grateful to Dr. Ryoutarou Ibuka for his cooperation. This study was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

Supporting Information Available: Experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

JO030367X

(20) Quite recently, the MNBA method was applied to the synthesis of patulolide C, a natural macrolactone. Tian, J.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *Org. Lett.* **2003**, *5*, 3021−3024.