HETEROCYCLES, Vol. 76, No. 2, 2008, pp. 1313 - 1328. © The Japan Institute of Heterocyclic Chemistry
Received, 5th April, 2008, Accepted, 13th May, 2008, Published online, 19th May, 2008. COM-08-S(N)96

2,6-DIMETHYL-4-NITROBENZOIC ANHYDRIDE (DMNBA): AN EFFECTIVE COUPLING REAGENT FOR THE SYNTHESIS OF CARBOXYLIC ESTERS AND LACTONES

Isamu Shiina* and Ryo Miyao

Department of Applied Chemistry, Faculty of Science, Tokyo University of Science, Kagurazaka, Shinjuku-ku, Tokyo 162-8601 Japan. E-mail: shiina@rs.kagu.tus.ac.jp

The authors dedicate this paper to Professor Ryoji Noyori on the celebration of his 70th birthday.

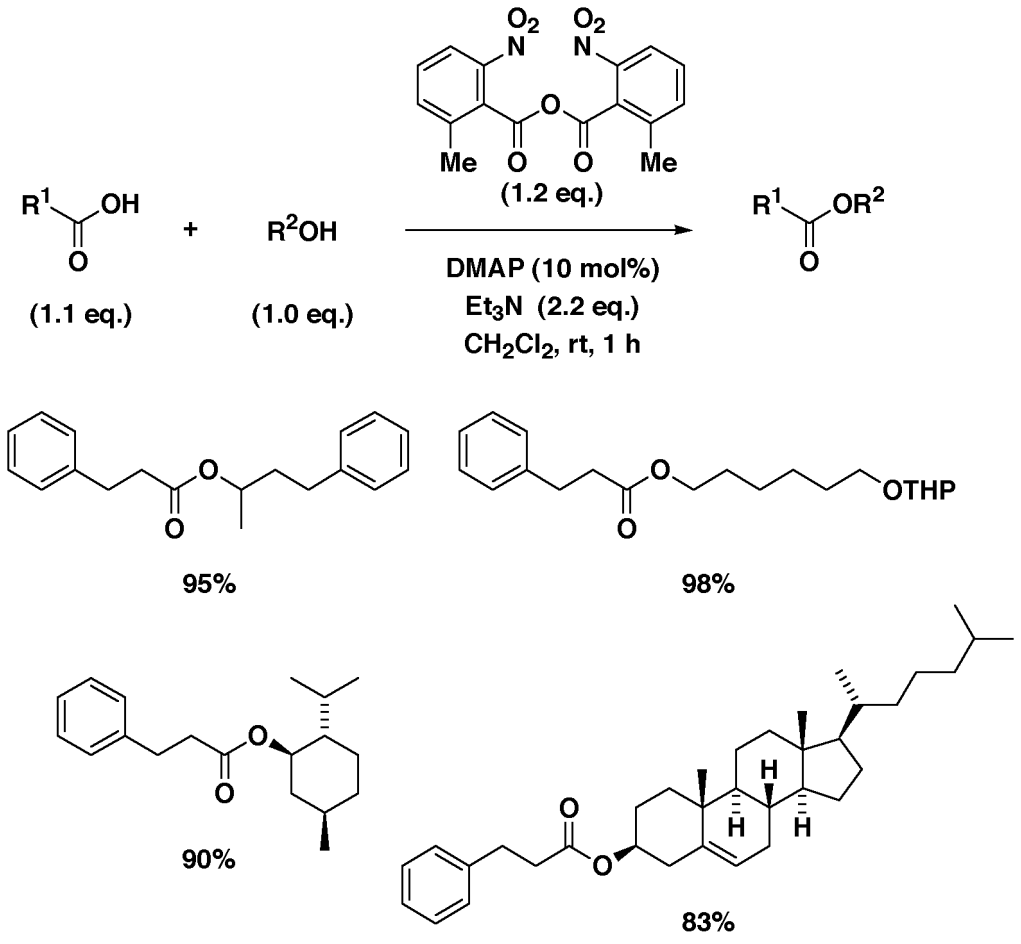
Abstract – Various carboxylic esters are obtained at room temperature in excellent yields with high chemoselectivities from nearly equimolar amounts of carboxylic acids and alcohols using 2,6-dimethyl-4-nitrobenzoic anhydride with triethylamine by the promotion of 4-(dimethylamino)pyridine. The efficiency of the esterification is compared to those of other dehydrations using substituted benzoic anhydrides as coupling reagents. This method was successfully applied to the synthesis of *threo*-aleuritic acid lactone and the desired 17-membered ring compound was prepared in high yield at room temperature from the corresponding free trihydroxycarboxylic acid using 2,6-dimethyl-4-nitrobenzoic anhydride in the presence of 4-(dimethylamino)pyridine.

INTRODUCTION

While numerous esterifications using Brϕnsted and Lewis acid catalysts have been reported, a few methods have actually been utilized for the effective preparation of carboxylic esters from equimolar amounts of carboxylic acids and alcohols under mild conditions.[1] Especially, it is 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.

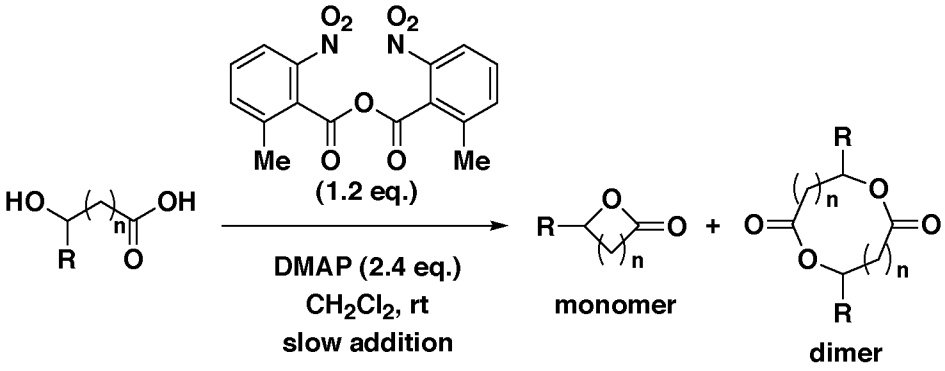
Recently, we reported several useful methods for the synthesis of carboxylic acid derivatives using substituted benzoic anhydrides under acidic or basic conditions.[2-4] For example, nearly equimolar amounts of carboxylic acids and alcohols react in the presence of 2-methyl-6-nitrobenzoic anhydride (MNBA) with nucleophilic catalysts such as 4-(dimethylamino)pyridine (DMAP) or 4-(dimethylamino)pyridine *N*-oxide (DMAPO) to produce the corresponding carboxylic esters in high yields (Scheme 1).[3] The intermediary mixed-anhydride, which functions as a reactive acylating reagent for alcohols to produce the desired carboxylic esters with high product-selectivities, was formed during the initial part of the reaction using MNBA.



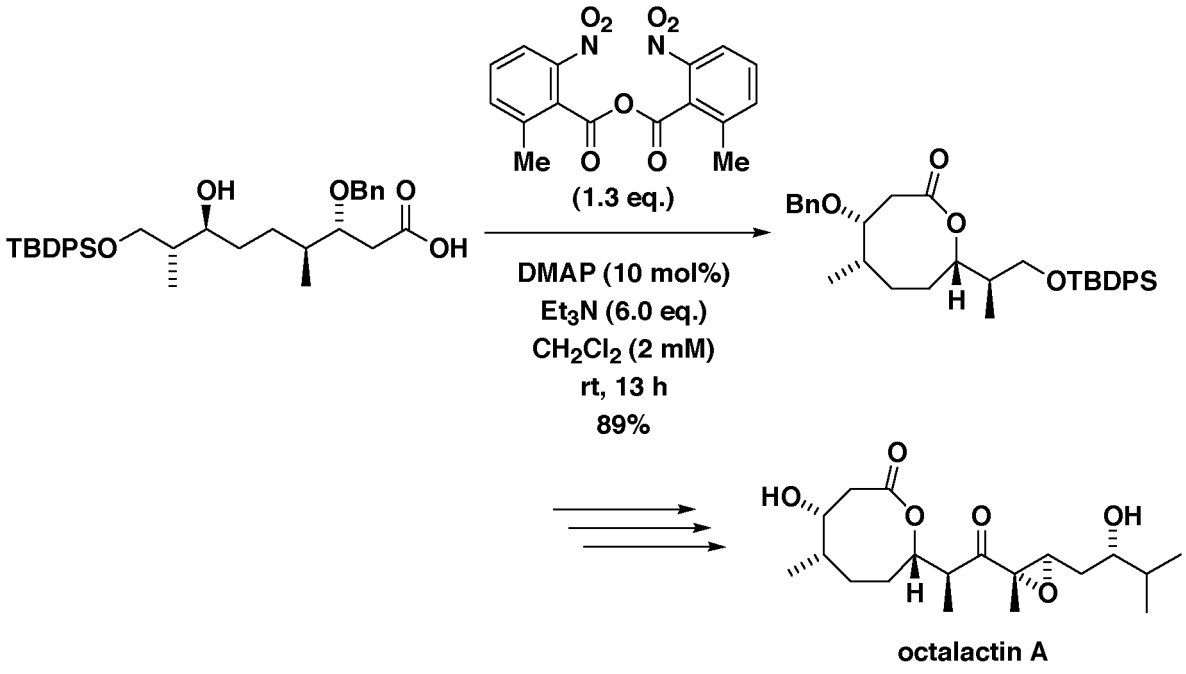
Scheme 1. Effective Synthesis of Carboxylic Esters Using MNBA

Furthermore, a convenient and powerful method for the synthesis of macrolactones with high product-selectivities *via* mixed anhydrides generated from ω-hydroxycarboxylic acids and MNBA using basic catalysts was established.[3] A variety of lactones are prepared in high yields at room temperature from the corresponding ω-hydroxycarboxylic acids with use of MNBA in the presence of DMAP (Table 1). 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.

Table 1. Effective Synthesis of Various Lactones Using MNBA



Entry	R	n	Conc. / mM	Time / h	Yield / % (Ring Number) monomer	dimer
1	H	10	1.0	15	88 (13)	5 (26)
2	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 (28)
5	H	13	1.8	15	92 (16)	1 (28)
6	H	14	1.8	15	92 (17)	<1 (34)



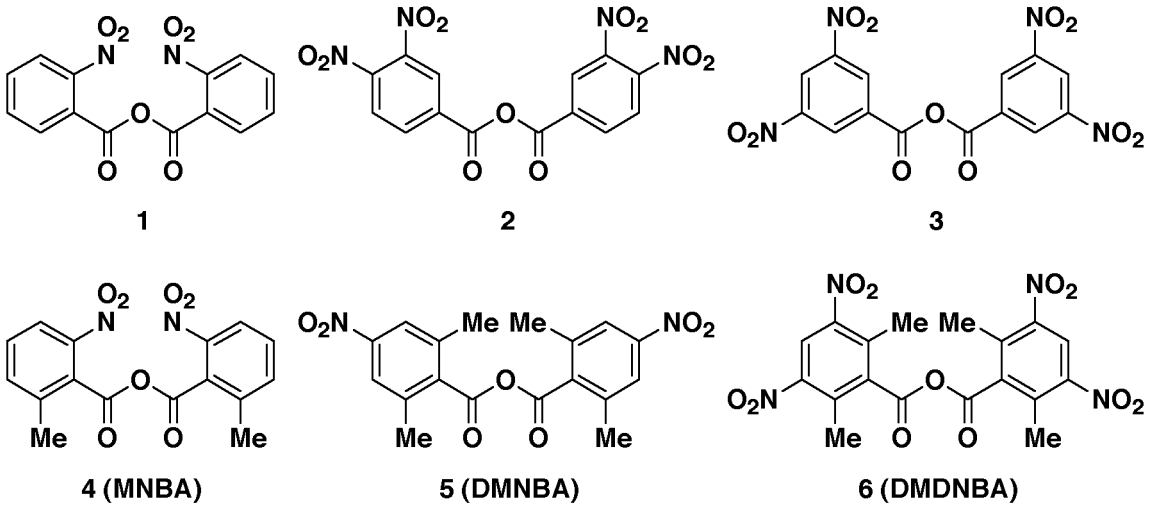
Scheme 2. Synthesis of Octalactin 8-Membered Ring Core Using MNBA

The utility of the present protocol was also demonstrated by the syntheses of the 8-membered ring moiety of octalactins A and B (Scheme 2).[3e] The cyclization reaction of the seco-acid was efficiently accelerated by MNBA with DMAP to afford the desired lactone in high yield at room temperature, and the corresponding diolide was not produced.

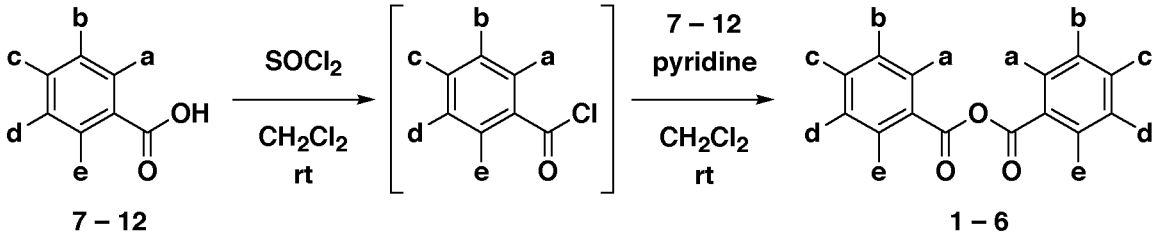
In this paper, the effect of the substituents on the aromatic ring of benzoic anhydrides in the present esterification was fully evaluated and it was found that 2,6-dimethyl-4-nitrobenzoic anhydride (DMNBA), a new coupling reagent, could be applied to the effective synthesis of carboxylic esters and lactones by the combination with DMAP.

RESULTS AND DISCUSSION

Preparation of Substituted Benzoic Anhydrides. First, synthesis of several substituted benzoic anhydrides possessing electron withdrawing groups is attempted (Scheme 3).



Scheme 3. Several Substituted Benzoic Anhydrides Related to MNBA



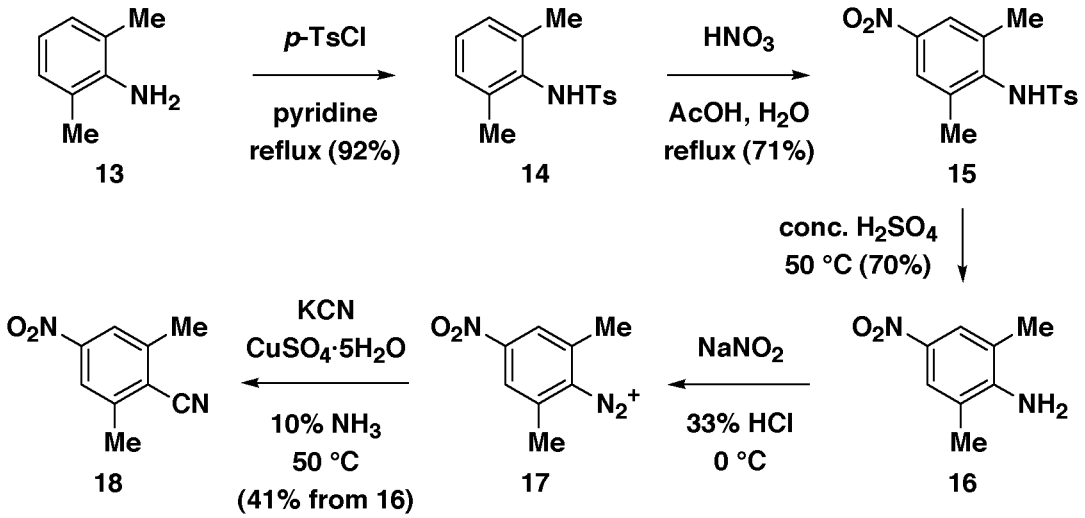
7; a=NO_2, b,c,d,e=H
8; b,c=NO_2, a,d,e=H
9; b,d=NO_2, a,c,e=H
10; a=NO_2, b,c,d=H, e=Me
11; c=NO_2, b,d=H, a,e=Me
12; b,d=NO_2, c=H, a,e=Me

1; 33%
2; 80%
3; 61%
4; 81%; (MNBA)
5; 72%; (DMNBA)
6; 34%; (DMDNBA)

Scheme 4. Synthesis of Several Substituted Benzoic Anhydrides

2-Nitrobenzoic anhydride (**1**), 3,4-dinitrobenzoic anhydride (**2**), 3,5-dinitrobenzoic anhydride (**3**) and MNBA (**4**) were simply prepared from the corresponding commercially available nitro-substituted benzoic acids **7**, **8**, **9**, and **10** according to the conventional pathway *via* formation of nitro-substituted benzoyl chloride as shown in Scheme 4.

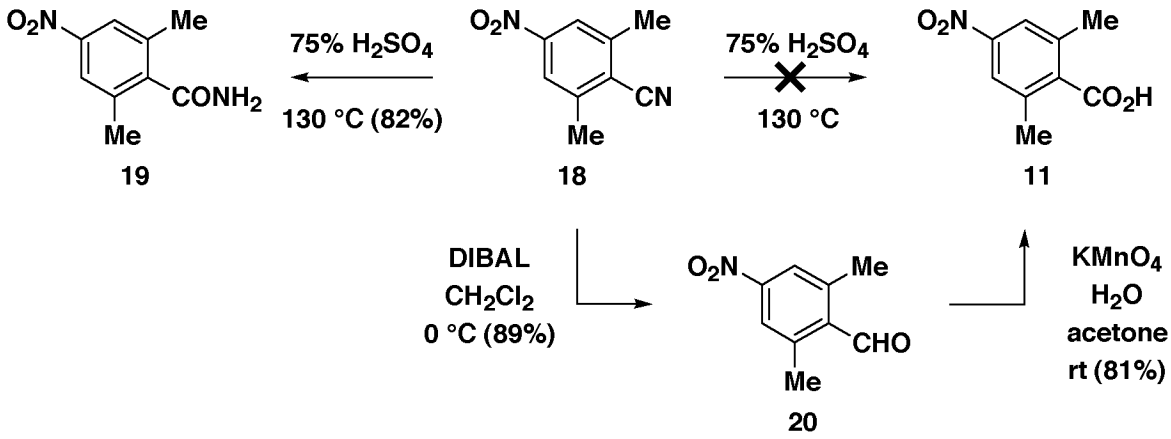
Since 2,6-dimethyl-4-nitrobenzoic acid (**11**)[5-7] could not be obtained from the commercial source, we tried to prepare **11** starting from 2,6-dimethylaniline (**13**) *via* Sandmeyer reaction as depicted in Scheme 5. Treatment of **13** with tosyl chloride in pyridine afforded sulfonamide **14** and then nitration of **14** with HNO_3/AcOH at reflux temperature produced the intermediate **15** in good yield. Deprotection of the tosyl group was performed in the presence of sulfuric acid at 50 °C to produce the desired tri-substituted aniline **16** in satisfactory yield. Sandmeyer reaction using KCN was applied to the diazonium species **17** generated from aniline **16** by the promotion of $CuSO_4 \cdot 5H_2O$ produced the tri-substituted benzonitrile **18** in 41% yield (2 steps).



Scheme 5. Synthesis of the Intermediates of DMNBA

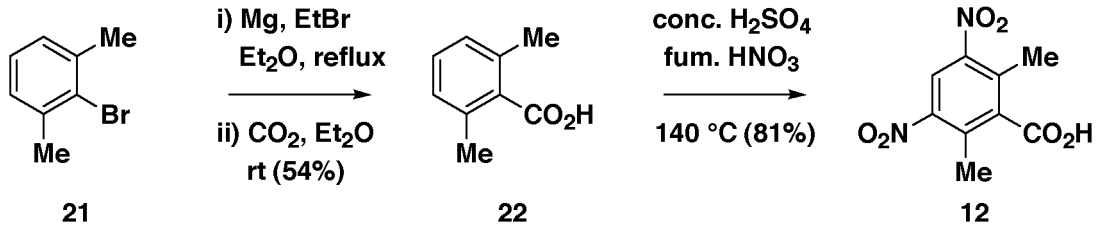
Although the attempted direct hydrolysis of nitrile **18** using sulfuric acid exclusively produced the undesired primary benzamide **19** (Scheme 6), stepwise transformation *via* reduction of **18** and oxidation of the intermediary aldehyde **20** was carried out and the target molecule **11** was obtained in nice yield. Finally, the tri-substituted benzoic acid **11** was transformed to 2,6-dimethyl-4-nitrobenzoic anhydride (DMNBA, **5**) according to Scheme 4 as described above.

Next, 2,6-dimethyl-3,5-dinitrobenzoic acid (**12**)[8] was prepared form the corresponding Grignard reagent derived from 2-bromo-1,3-dimethylbenzene (**21**) as shown in Scheme 7. Generation of the Grignard reagent from **21** and successive addition of the nucleophile to carbon dioxide smoothly proceeded to give 2,6-dimethylbenzoic acid (**22**) in 54% yield. Nitration of **22** with H_2SO_4/fuming HNO_3 at high temperature (140 °C) afforded the desired tetra-substituted benzoic acid (**12**) in good yield (81%).



Scheme 6. Synthesis of 2,6-Dimethyl-4-nitrobenzoic Acid

According to Scheme 4 as described above, 2,6-dimethyl-3,5-dinitrobenzoic anhydride (DMDNBA, **6**) was successfully obtained.

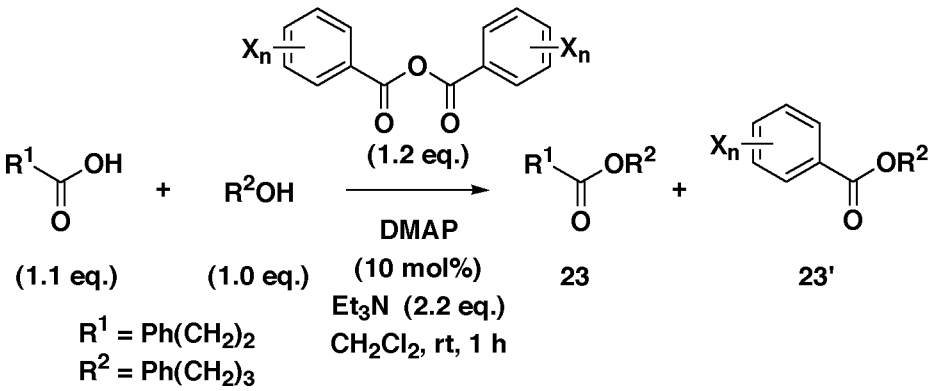


Scheme 7. Synthesis of 2,6-Dimethyl-3,5-dinitrobenzoic Acid

Esterification Reaction Using Substituted Benzoic Anhydrides. The reaction of 1.1 molar amounts of 3-phenylpropanoic acid with a 1.0 molar amount of 3-phenylpropanol was initially examined in the presence of 1.2 molar amounts of substituted benzoic anhydrides **1**-**6**, 2.2 molar amounts of triethylamine and 10 mol% of DMAP (Table 2). When 2-nitrobenzoic, 3,4-dinitrobenzoic or 3,5-dinitrobenzoic anhydride (**1**, **2**, or **3**) was used as the dehydrating reagent, 3-phenylpropyl 3-phenylpropanoate (**23**) was obtained in 70%, 65%, or 66% yield along with a small amount of 3-phenylpropyl benzoate (**23'**), an undesirable carboxylic ester (Entries 1, 2 or 3). We then tried to introduce substituents on the 2- and 6-positions of the aromatic ring of the benzoic anhydride to provide a hindrance near the carboxyl group (Entries 4-6); actually, only the desired carboxylic ester was obtained with perfect chemoselectivity when using 2-methyl-6-nitrobenzoic anhydride (MNBA, **4**) as shown in Entry 4. Furthermore, we found that 2,6-dimethyl-4-nitrobenzoic anhydride (DMNBA, **5**) was also a quite effective coupling reagent for providing the carboxylic ester with high chemoselectivity (**23**/**23'**=210/1) in the presence of a catalytic amount of DMAP (Entry 5). On the other hand, 2,6-dimethyl-3,5-dinitrobenzoic anhydride (DMDNBA, **6**), which possesses two electron withdrawing groups on the 3- and 5-positions, gave somewhat lower chemical yield and chemoselectivity as shown in Entry 6.

Several examples of carboxylic esters obtained by the present method under the optimized conditions are listed in Table 3.

Table 2. Synthesis of Carboxylic Esters Using Substituted Benzoic Anhydrides 1-6



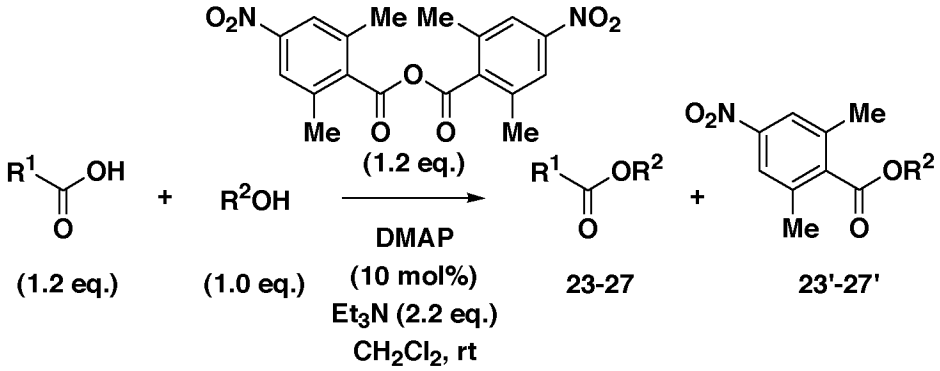
Entry	X_n	Anhydride	Yield of 23 / %	23 / 23'
1	2-NO_2	1	70	110 / 1
2	3,4-$(NO_2)_2$	2	65	100 / 1
3	3,5-$(NO_2)_2$	3	66	50 / 1
4	2-Me-6-NO_2	4 (MNBA)	83	>500 / 1
5	2,6-Me_2-4-NO_2	5 (DMNBA)	92	210 / 1
6	2,6-Me_2-3,5-$(NO_2)_2$	6 (DMDNBA)	54	170 / 1

The reaction of aliphatic alcohol gave the desired carboxylic ester in high yield with nearly perfect selectivity (Entry 1). This protocol is successfully applicable to several carboxylic acids including aromatic and α,β-unsaturated carboxylic acids, and the corresponding carboxylic esters were obtained in good to high yields under the mild reaction conditions (Entries 2 and 3). Furthermore, α,α-disubstituted and α,α,α-trisubstituted acetic acid derivatives were also employed and the corresponding carboxylic esters were obtained in excellent yields (Entries 4 and 5). Acceptable chemoselectivities were observed for all cases except for the reaction of the pivalic acid with a primary alcohol as shown in Entry 5.

Furthermore, we compared our results with those obtained according to the Yamaguchi procedure using 2,4,6-trichlorobenzoyl chloride.[9] These data are presented in the right column of Table 4 and the compared data obtained by DMNBA are shown in the left column. We observed the formation of significant amounts of the undesired alkyl 2,4,6-trichlorobenzoates (**23"-26"**) in many cases (Entries 1 (29% of **23"**), 2 (8% of **24"**), 3 (12% of **25"**), and 4 (6% of **26"**)), though our method gave almost perfect chemoselectivities. It is noted that the maximum yield of the desired ester **23** is limited to *ca.* 70% by Yamaguchi method in Entry 1 since the reaction proceeded without high chemoselectivity.

One of features of the present protocol using DMNBA is the quite simple procedure for the synthesis of a

Table 3. Synthesis of Various Carboxylic Esters Using DMNBA



Entry	R^1	R^2	Time / h	$R^1CO_2R^2$	Yield [a] / %	Ratio [b]
1	$Ph(CH_2)_2$	$Ph(CH_2)_3$	1	23	92	210 / 1
2	Ph	$Ph(CH_2)_3$	20	24	86	36 / 1
3	(*E*)-PhCH=CH	$Ph(CH_2)_3$	20	25	97	110 / 1
4	*c*-C_6H_{11}	$Ph(CH_2)_3$	20	26	98	96 / 1
5	^{t}Bu	$Ph(CH_2)_3$	20	27	92	5.5 / 1

a) Isolated yield of 23-27.
b) Ratio = The ratio of 23-27 to the corresponding benzoate 23'-27'.

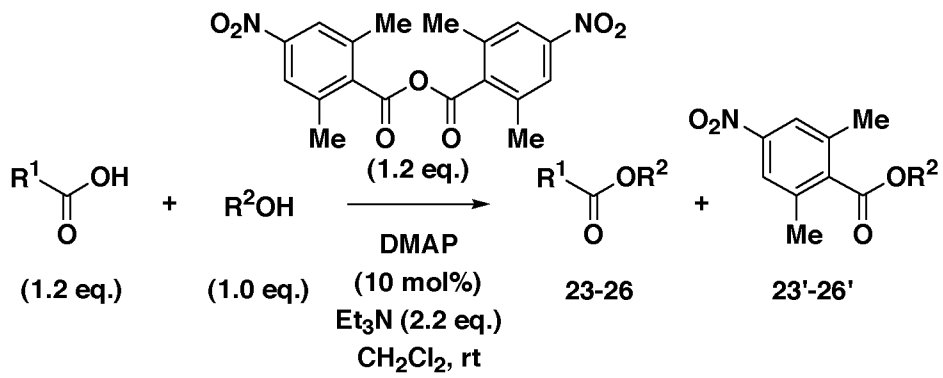
variety of carboxylic esters. The Yamaguchi method usually requires a stepwise operation, namely, carboxylic acids are treated with 2,4,6-trichlorobenzoyl chloride and triethylamine at first to generate the corresponding mixed anhydrides. After filtration of the mixture under an inert gas to remove the 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, DMNBA, triethylamine and a catalytic amount of DMAP at room temperature, the desired compounds are produced in excellent yields with high purity according to our convenient method.

Efficient Lactonization Using DMNBA with DMAP. 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. However, macrolactonization is still the most popular method for producing cyclic compounds including carboxylic ester moieties since there are some effective methods for constructing the ester linkage.

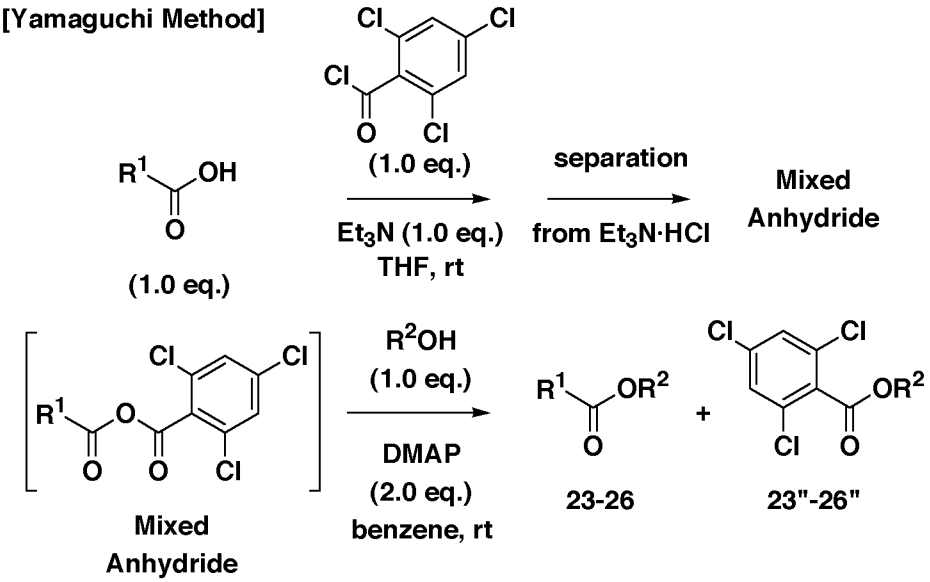
Table 5 shows the yields of the 17-membered macrolactone synthesized by the present method using MNBA[3f] or DMNBA with DMAP. All reactions were carried out at room temperature by adding a solution of trihydroxycarboxylic acid **28** to a mixture of the substituted benzoic anhydride with DMAP in dichloromethane.

Table 4. Experimental Results Comparing Two Esterification Methods

[DMNBA (Benzoic Anhydride) Method]



[Yamaguchi Method]



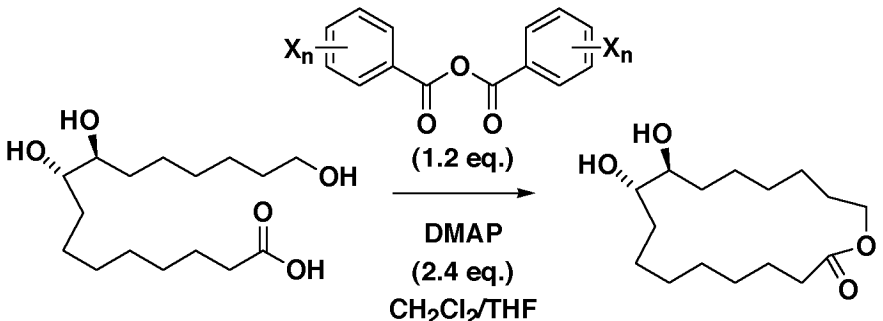
Entry	$R^1CO_2R^2$	DMNBA Method		Yamaguchi Method	
		Yield [a] / %	Ratio [b]	Yield [a] / %	Ratio [c]
1	23	92	210 / 1	58	2 / 1
2	24	86	36 / 1	85	11 / 1
3	25	97	110 / 1	82	7 / 1
4	26	98	96 / 1	89	14 / 1

a) Isolated yield of 23-26.
b) Ratio = The ratio of 23-26 to the corresponding benzoate 23'-26'.
c) Ratio = The ratio of 23-26 to the corresponding benzoate 23"-26".

The concentration in the table shows the molar amounts of seco-acid to the total volume of the solvent. Since *threo*-aleuritic acid (**28**) did not completely dissolve in the dichloromethane at room temperature,

the starting seco-acid was dissolved in THF prior to use, which was then added to the reaction mixture including MNBA or DMNBA with DMAP in dichloromethane over a 12 h period at room temperature. It is noteworthy that the best yield of **29** was attained for the macrolactonization of **28** using DMNBA with 2.4 molar amounts of DMAP (Entry 3). The difference between the yields for Entries 2 and 3 shows that DMNBA is superior to MNBA for the generation of the desired monomeric lactone **29** in this cyclization.

Table 5. Cyclization Forming 17-Membered Lactone from Free *threo*-Aleuritic Acid Using MNBA or DMNBA



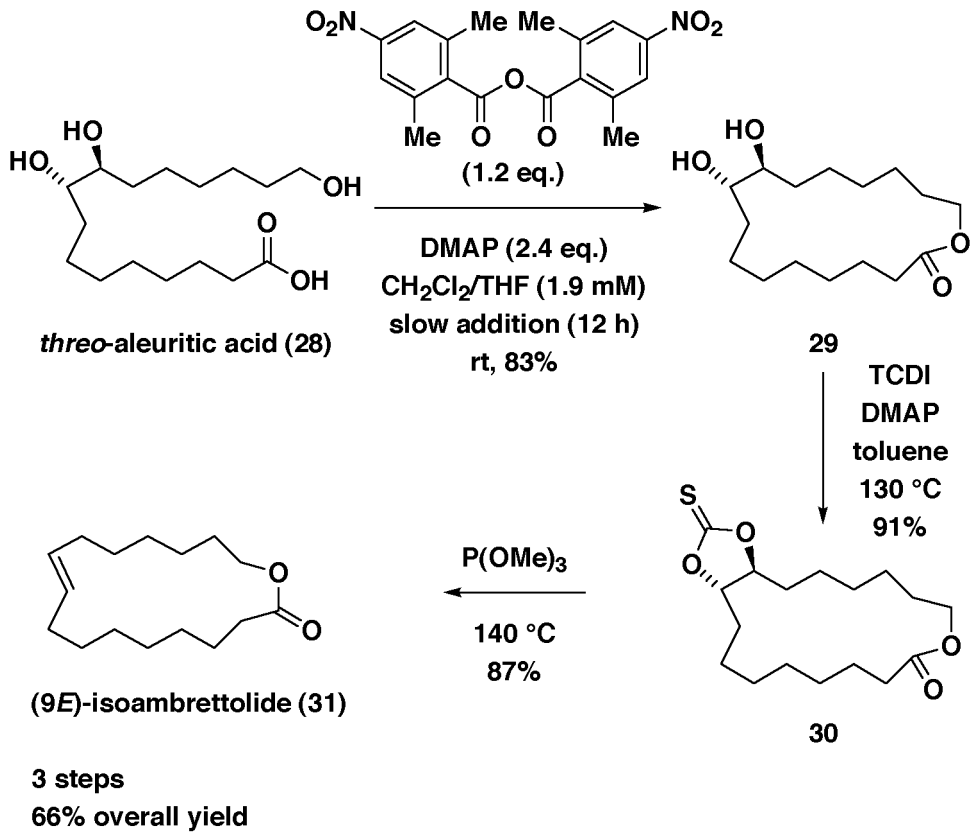
Entry	X_n	Anhydride	Yield [a] / %
1	H	$(PhCO)_2O$	69
2	2-Me-6-NO_2	4 (MNBA)	77
3	2,6-Me_2-4-NO_2	5 (DMNBA)	83

a) Isolated yield.

The dihydroxylactone **29** prepared by the above-mentioned method was in turn converted to the corresponding thiocarbonate **30** by treating with 1,1'-thiocarbonyldiimidazole (TCDI) and DMAP under reflux in toluene. Finally, **30** was transformed into (9*E*)-isoambrettolide (**31**) using trimethyl phosphite in 87% yield.[10] (9*E*)-Isoambrettolide is now a very attractive artificial substrate as an alternative musk resource, therefore, it has been revealed that this pathway is extremely efficient for the preparation of the artificial perfume ingredient *via* only three steps (83%, 91%, and 87% yields, respectively) starting from commercially available *threo*-aleuritic acid (**28**).

CONCLUSIONS

We have developed a new reaction that produces carboxylic esters in high yields using DMNBA and DMAP in the presence of tertiary amines. The DMNBA-promoted cyclization also provided the syn-



Scheme 8. Synthesis of the Musk Component (9*E*)-Isoambrettolide

thetic intermediary lactone of (9*E*)-isoambrettolide directly from the unprotected *threo*-aleuritic acid. It is notable that the experimental procedure is quite simple, and nearly pure carboxylic esters and lactones are obtained by only mixing DMNBA, basic promoters, and substrates. Further studies of the reaction using substituted benzoic anhydrides and other applications of the present protocol for the syntheses of useful complex molecules are now in progress.

EXPERIMENTAL

General

All reactions were carried out under argon atmosphere in dried glassware. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4A. Thin layer chromatography was performed on Wakogel B5F. All melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded with tetramethylsilane (TMS) or chloroform (in chloroform-*d*) as internal standard.

Starting materials

All reagents were purchased from Tokyo Kasei Kogyo Co., Ltd., Kanto Chemical Co., Inc., or Aldrich Chemical Co., Inc. and used without further purification unless otherwise noted. 2-Nitrobenzoic anhydride (**1**),[11] 3,4-dinitrobenzoic anhydride (**2**), 3,5-dinitrobenzoic anhydride (**3**),[11] DMNBA (**5**), and

DMDNBA (**6**) were prepared from the corresponding substituted benzoic acids (**7**-**9**, **11**, and **12**), whereas MNBA (**4**) was purchased from Tokyo Kasei Kogyo Co., Ltd. (TCI, M1439) or synthesized from 2-methyl-6-nitrobenzoic acid (**10**).[3c] 2,6-dimethyl-4-nitrobenzoic acid (**11**)[5-7] and 2,6-dimethyl-3,5-dinitrobenzoic acid (**12**)[8] were synthesized according to the literature methods.

2-Nitrobenzoic anhydride (1). Mp 131-133 °C; ^{1}H NMR ($CDCl_3$) δ 8.06 (dd, *J* = 8.2, 1.2 Hz, 2H), 7.84 (dd, *J* = 7.6, 1.5 Hz, 2H), 7.79 (ddd, *J* = 7.6, 7.3, 1.2 Hz, 2H), 7.73 (dd, *J* = 8.2, 7.3, 1.5 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 159.6, 147.2, 133.8, 132.8, 130.3, 126.1, 124.3; HR MS: calcd for $C_{14}H_8N_2O_7Na$ ($M + Na^+$) 339.0229, found 339.0402.

3,4-Dinitrobenzoic anhydride (2). Mp 161-163 °C; ^{1}H NMR (DMSO-d_6) δ 8.56 (d, *J* = 1.5 Hz, 2H), 8.41 (dd, *J* = 8.5, 1.8 Hz, 2H), 8.31 (d, *J* = 8.5 Hz, 2H); ^{13}C NMR (DMSO-d_6) δ 164.1, 144.2, 141.6, 135.9, 135.1, 126.2, 126.1.

3,5-Dinitrobenzoic anhydride (3). Mp 215-221 °C; ^{1}H NMR (DMSO-d_6) δ 9.00 (dd, *J* = 2.1, 2.1 Hz, 2H), 8.88 (d, *J* = 2.1 Hz, 4H); ^{13}C NMR (DMSO-d_6) δ 164.0, 148.4, 134.1, 128.9, 122.1.

2-Methyl-6-nitrobenzoic anhydride (4). Mp 178-180 °C; ^{1}H NMR ($CDCl_3$): δ 8.06 (d, *J* = 8.1 Hz, 2H), 7.64 (d, *J* = 7.6 Hz, 2H), 7.53 (dd, *J* = 8.1, 7.6 Hz, 2H), 2.57 (6H, s); ^{13}C NMR ($CDCl_3$) δ 160.3, 145.1, 137.9, 136.6, 130.5, 127.5, 121.7, 19.1; Anal: calcd for $C_{16}H_{12}N_2O_7$: C, 55.82; H, 3.51; N, 8.14, found: C, 55.81; H, 3.39; N, 8.07.

2,6-Dimethyl-4-nitrobenzoic anhydride (5). Mp 195-197 °C; ^{1}H NMR ($CDCl_3$) δ 7.96 (s, 4H), 2.53 (s, 12H); ^{13}C NMR ($CDCl_3$) δ 163.1, 148.6, 137.7, 136.8, 122.8, 19.9; HR MS: calcd for $C_{18}H_{16}N_2O_7Na$ ($M + Na^+$) 395.0855, found 395.0346.

2,6-Dimethyl-3,5-dinitrobenzoic anhydride (6). ^{1}H NMR ($CDCl_3$) δ 8.60 (s, 2H), 2.68 (s, 12H).

Typical Experimental Procedure for the Esterification Reaction

A typical experimental procedure is described for the reaction of 3-phenylpropanoic acid with 3-phenylpropanol (Table 3, Entry 1): To a solution of triethylamine (44.5 mg, 0.440 mmol) in CH_2Cl_2 (1.5 mL) were added DMAP (2.4 mg, 0.020 mmol), DMNBA (89.4 mg, 0.240 mmol) and 3-phenylpropanoic acid (36.0 mg, 0.240 mmol). After having been stirred for 10 min, a solution of 3-phenylpropanol (26.8 mg, 0.197 mmol) in CH_2Cl_2 (1.5 mL) was added. The reaction mixture was stirred for 1 h at rt and then saturated aqueous NH_4Cl was added at 0 °C. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford the corresponding ester **23** (48.8 mg, 92%) as a colorless oil.

3-Phenylpropyl 3-phenylpropanoate (23).[12] IR (neat) 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.31-7.13 (10H, m), 4.08 (2H, t, *J* = 6.6 Hz), 2.95 (2H, t, *J* = 7.8 Hz), 2.62 (4H, m), 1.91 (2 H, m); Found: C, 80.35; H, 7.77%. Calcd for $C_{18}H_{20}O_2$: C, 80.56: H, 7.51%.

3-Phenylpropyl benzoate (24).[12] IR (neat) 1718 cm^{-1}; ^1H NMR (CCl_4) δ 8.10-7.85 (2H, m), 7.54-7.05 (8H, m), 4.27 (2H, t, *J* = 6 Hz), 2.77 (2H, t, *J* = 8 Hz), 2.23 (2H, m); Found: C, 79.69; H, 6.97%. Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71%.

3-Phenylpropyl (*E*)-3-phenyl-2-propenoate (25).[13] IR (neat): 1712 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.68 (1H, d, *J* = 16.0 Hz), 7.54-7.50 (2H, m), 7.43-7.35 (3H, m), 7.32-7.17 (5H, m), 6.45 (1H, d, *J* = 16.0 Hz), 4.23 (2H, t, *J* = 6.4 Hz), 2.75 (2H, dd, *J* = 7.9, 7.4 Hz), 2.04 (2H, ddt, *J* = 7.9, 7.4, 6.4 Hz); HR MS: calcd for $C_{18}H_{19}O_2$ ($M + H^+$) 267.1385, found 267.1376.

3-Phenylpropyl cyclohexanecarboxylate (26).[12] IR (neat) 1732 cm^{-1}; ^1H NMR (CCl_4) δ 7.15 (5H, s), 4.00 (2H, t, *J* = 6.0 Hz), 2.65 (2H, t, *J* = 8.0 Hz), 2.40-1.05 (13H, m); Found: C, 77.89; H, 8.90%. Calcd for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00%.

3-Phenylpropyl 2,2-dimethylpropanoate (27).[12] IR (neat) 1728 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.34-7.21 (5H, m), 4.12 (2H, t, *J* = 6.3 Hz), 2.74 (2H, t, *J* = 7.6 Hz), 2.03-1.97 (2H, m), 1.26 (9H, s); Found: C, 76.06; H, 9.21%. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15%.

Typical Experimental Procedure for the Synthesis of Lactone 29

An experimental procedure is described for the preparation of lactone **29** using DMNBA with DMAP (Table 5, Entry 3): To a solution of DMNBA (179 mg, 0.481 mmol) and DMAP (117 mg, 0.958 mmol) in CH_2Cl_2 (169 mL) at rt was slowly added a solution of *threo*-aleuritic acid (**28**) (122 mg, 0.401 mmol) in THF (40 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at rt, saturated aqueous $NaHCO_3$ was added at 0 °C. The mixture was extracted with CH_2Cl_2, and the organic layer was washed with water and brine, and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin layer chromatography to afford dihydroxylactone **29**[3f] (101 mg, 83%) as a white solid: Mp. 53.5-54.0 °C; IR (KBr): 3440, 3310, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.18-4.05 (m, 2H, 16-H), 3.50-3.41 (br m, 2H, 9-H, 10-H), 2.40 (br s, 2H, 9-OH, 10-OH), 2.31 (t, *J* = 6.8 Hz, 2H, 2-H), 1.70-1.22 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR ($CDCl_3$): δ 174.0 (1), 74.1 (9 or 10), 73.4 (10 or 9), 64.2 (16), 34.6 (2), 32.5, 31.4, 28.6, 28.2, 28.1, 27.7, 27.6, 25.4, 25.0, 23.9, 23.1 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15); Anal: calcd for $C_{16}H_{30}O_4$: C, 67.10; H, 10.56, found: C, 66.97; H, 10.54; HR MS: calcd for $C_{16}H_{31}O_4$ ($M + H^+$) 287.2222, found 287.2223.

***threo*-9,10-Thiocarbonyldioxyheptadecan-16-olide (30).**[3f]

To a solution of dihydroxylactone **29** (80.2 mg, 0.280 mmol) in toluene (14 mL) were added TCDI (499

mg, 2.80 mmol) and DMAP (3.4 mg, 0.028 mmol). After the reaction mixture had been stirred for 4 h at 130 °C, it was cooled down to rt. The mixture was concentrated by evaporation of the solvent and then the crude product was purified by thin layer chromatography to afford thiocarbonate **30** (83.8 mg, 91%) as a white solid: Mp. 73-74 °C; IR (KBr): 1720, 1280, 1180 cm^{-1}; ^1H NMR ($CDCl_3$): δ 4.55-4.43 (m, 2H, 9-H, 10-H), 4.21-4.08 (m, 2H, 16-H), 2.42-2.25 (m, 2H, 2-H), 2.10-1.21 (m, 22H, 3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15-H); ^{13}C NMR ($CDCl_3$): δ 191.4 (CS), 173.7 (1), 86.1 (9), 86.1 (10), 63.9 (16), 34.4 (2), 32.4, 32.1, 28.7, 28.3, 27.9, 27.9, 27.1, 25.6, 25.0, 23.6, 23.2 (3, 4, 5, 6, 7, 8, 11, 12, 13, 14, 15); Anal: calcd for $C_{17}H_{28}O_4S$: C, 62.16; H, 8.59, found: C, 62.05; H, 8.61; HR MS: calcd for $C_{17}H_{29}O_4S$ ($M + H^+$) 329.1786, found 329.1791.

(9*E*)-Isoambrettolide (31).[3f]

To thiocarbonate **30** (20.4 mg, 0.062 mmol) was added trimethyl phosphite (3 mL) at rt. After the reaction mixture had been stirred for 25 h at 140 °C, it was cooled down to rt. The mixture was concentrated by evaporation of the solvent and then the crude product was purified by thin layer chromatography to afford (9*E*)-isoambrettolide (**31**) (13.7 mg, 87%) as a colorless oil: IR (neat): 1730 cm^{-1}; ^1H NMR (C_6D_6): δ 5.42 (dddd, J = 15.4, 9.5, 3.5, 1.6 Hz, 1H, 9-H or 10-H), 5.32 (dddd, J = 15.4, 9.5, 3.8, 1.6 Hz, 1H, 10-H or 9-H), 4.08 (t, J = 5.4 Hz, 2H, 16-H), 2.19 (t, J = 7.0 Hz, 2H, 2-H), 2.12-1.97 (m, 4H, 8-H, 11-H), 1.62-1.50 (m, 2H, 3-H), 1.48-1.34 (m, 2H, 15-H), 1.42-1.13 (m, 14H, 4, 5, 6, 7, 12, 13, 14-H); ^{13}C NMR (C_6D_6): δ 172.9 (1), 131.4 (9 or 10), 130.8 (10 or 9), 64.0 (16), 34.9 (2), 32.2 (8 or 11), 31.8 (11 or 8), 29.2 (15), 29.9, 28.8, 28.3, 28.2, 28.1, 27.2, 27.1 (4, 5, 6, 7, 12, 13, 14), 25.3 (3); HR MS: calcd for $C_{16}H_{29}O_2$ ($M + H^+$) 253.2167, found 253.2165.

ACKNOWLEDGEMENTS

This study was partially supported by a Research Grant from Tokyo Ohka Foundation for the Promotion of Science and Technology.

REFERENCES AND NOTES

1 J. Mulzer, In *Comprehensive Organic Synthesis*; ed. by B. M. Trost and I. Fleming, Pergamon: Oxford, 1991; Vol. 6, pp. 323-380.

2 a) I. Shiina, S. Miyoshi, M. Miyashita, and T. Mukaiyama, *Chem. Lett.*, 1994, 515. b) I. Shiina and T. Mukaiyama, *Chem. Lett.*, 1994, 677. c) M. Miyashita, I. Shiina, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1994, **67**, 210. d) I. Shiina, M. Miyashita, M. Nagai, and T. Mukaiyama, *Heterocycles,* 1995, **40**, 141. e) I. Shiina, Y. Fukuda, T. Ishii, H. Fujisawa, and T. Mukaiyama, *Chem. Lett.*, 1998, 831. f) I. Shiina, H. Fujisawa, T. Ishii, and Y. Fukuda, *Heterocycles,* 2000, **52**, 1105. g) I. Shiina, *Tetrahedron,* 2004, **60**, 1587.

3 a) I. Shiina, R. Ibuka, and M. Kubota, *Chem. Lett.*, 2002, 286. b) I. Shiina, M. Kubota, and R. Ibuka, *Tetrahedron Lett.*, 2002, **43**, 7535. c) I. Shiina, M. Kubota, H. Oshiumi, and M. Hashizume, *J. Org.*

Chem., 2004, **69**, 1822. d) I. Shiina, H. Oshiumi, M. Hashizume, Y. Yamai, and R. Ibuka, *Tetrahedron Lett.*, 2004, **45**, 543. e) I. Shiina, M. Hashizume, Y. Yamai, H. Oshiumi, T. Shimazaki, Y. Takasuna, and R. Ibuka, *Chem. Eur. J.*, 2005, **11**, 6601. f) I. Shiina and M. Hashizume, *Tetrahedron,* 2006, **62**, 7934. g) I. Shiina, T. Kikuchi, and A. Sasaki, *Org. Lett.*, 2006, **8**, 4955. h) I. Shiina, Y. Takasuna, R. Suzuki, H. Oshiumi, Y. Komiyama, S. Hitomi, and H. Fukui, *Org. Lett.*, 2006, **8**, 5279. i) I. Shiina, H. Fukui, and A. Sasaki, *Nat. Protoc.*, 2007, **2**, 2312. j) I. Shiina, A. Sasaki, T. Kikuchi, and H. Fukui, *Chem. Asian J.*, 2008, **3**, 462. See also, k) I. Shiina and Y. Kawakita, *Tetrahedron*, 2004, **60**, 4729. l) I. Shiina, H. Ushiyama, Y. Yamada, Y. Kawakita, and K. Nakata, *Chem. Asian J.*, 2008, **3**, 454. m) I. Shiina and K. Nakata, *Tetrahedron Lett.*, 2007, **48**, 8314.

4 a) I. Shiina, *Chem. Rev.*, 2007, **107**, 239. Applications of the MNBA-coupling by other groups, see: b) J. Tian, N. Yamagiwa, S. Matsunaga, and M. Shibasaki, *Org. Lett.*, 2003, **5**, 3021. c) M. Inoue, T. Sasaki, S. Hatano, and M. Hirama, *Angew. Chem. Int. Ed.*, 2004, **43**, 6500. d) M. Inoue, *Bull. Chem. Soc. Jpn.*, 2006, **79**, 501. e) M. Morita, N. Mase, H. Yoda, and K. Takabe, *Tetrahedron: Asymmetry,* 2005, **16**, 3176. f) M.-T. Dinh, S. BouzBouz, J.-L. Peglion, and J. Cossy, *Synlett,* 2005, 2851. g) T. Doi, Y. Iijima, K. Shin-ya, A. Ganesan, and T. Takahashi, *Tetrahedron Lett.*, 2006, **47**, 1177. h) S. Hosokawa, M. Seki, H. Fukuda, and K. Tatsuta, *Tetrahedron Lett.*, 2006, **47**, 2439. i) K. C. Nicolaou and H. Xu, *Chem. Commun.*, 2006, 600. j) H. Tsuchikawa, N. Matsushita, N. Matsumori, M. Murata, and T. Oishi, *Tetrahedron Lett.*, 2006, **47**, 6187. k) Y. Wu and Y.-Q. Yang, *J. Org. Chem.*, 2006, **71**, 4296. l) Y. Matsuya, T. Kawaguchi, K. Ishihara. K. Ahmed, Q.-L. Zhao, T. Kondo, and H. Nemoto, *Org. Lett.*, 2006, **8**, 4609. m) K. Yamashita, S. Kobayashi, S. Tsukamoto, and M. Numazawa, *Steroids*, 2007, **72**, 50. n) T. Saito, T. Takeuchi, M. Matsuhashi, and T. Nakata, *Heterocycles*, 2007, **72**, 151. o) B. M. Trost, H. Yang, O. R. Thiel, A. J. Frontier, and C. S. Brindle, *J. Am. Chem. Soc.*, 2007, **129**, 2206. p) F. Ren, P. C. Hogan, A. J. Anderson, and A. G. Myers, *J. Am. Chem. Soc.*, 2007, **129**, 5381. q) J. R. Falck, A. He, H. Fukui, H. Tsutsui, and A. Radha, *Angew. Chem. Int. Ed.*, 2007, **46**, 4527. r) T. Ito, M. Ito, H. Arimoto, H. Takamura, and D. Uemura, *Tetrahedron Lett.*, 2007, **48**, 5465. s) J. R. Scheerer, J. F. Lawrence, G. C. Wang, and D. A. Evans, *J. Am. Chem. Soc.*, 2007, **129**, 8968. t) G. R. Pettit, T. H. Smith, S. Feng, J. C. Knight, R. Tan, R. K. Pettit, and P. A. Hinrichs, *J. Nat. Prod.*, 2007, **70**, 1073. u) D. Schweitzer, J. J. Kane, D. Strand, P. McHenry, M. Tenniswood, and P. Helquist, *Org. Lett.*, 2007, **9**, 4619. v) D. Amans, V. Bellosta, and J. Cossy, *Org. Lett.*, 2007, **9**, 4761. w) A. Honda, K. Yamashita, M. Numazawa, T. Ikegami, M. Doy, Y. Matsuzaki, and H. Miyazaki, *J. Lipid Res.*, 2007, **48**, 458. x) Y. Takada, E. Mori, M. Umehara, Y. Nakao, and J. Kimura, *Tetrahedron Lett.*, 2007, **48**, 7653. y) K. Kito, R. Ookura, S. Yoshida, M. Namikoshi, T. Ooi, and T. Kusumi, *J. Nat. Prod.*, 2007, **70**, 2022. z) J. S. Yadav, P. M. K. Reddy, M. K. Gupta, and C. J. Chary, *Synthesis*, 2007, 3639. aa) K. Yamashita, M. Takahashi, S. Tsukamoto, M. Numazawa, M. Okuyama, S. Honma, *J. Chromatogr. A*, 2007, **1173**, 120. bb) A. Yurek-George, A. R. L. Cecil, A. H. K. Mo, S. Wen, H. Rogers, F. Habens, S. Maeda, M. Yoshida, G. Packham, and A. Ganesan, *J. Med. Chem.*, 2007, **50**, 5720. cc) Y. Wu and J. Gao, *Org. Lett.*, 2008, **10**, 1533.

5 M. A. Bambenek, *Rec. Trav. Chim.*, 1963, **82**, 97.

6 O. O. Laaketehdas, BP 896 720, 1962 (*Chem. Abstr.*, 1962, **57**, 11113i).

7 P. D. Maria, A. Fontana, D. Spinelli, C. Dell'Erba, M. Novi, G. Petrillo, and F. Sancassan, *J. Chem. Soc., Perkin Trans. 2,* 1993, 649.

8 M. P. Hartshorn, J. M. Readman, W. T. Robinson, C. W. Sies, and G. J. Wright, *Aust. J. Chem.*, 1988, **41**, 373.

9 J. Inanaga, K. Hirata, H. Saeki, T. Katsuki, and M. Yamaguchi, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 1989.

10 a) E. J. Corey and R. A. E. Winter, *J. Am. Chem. Soc.*, 1963, **85**, 2677. For a review, see: b) E. Block, *Org. React.*, 1984, **30**, 457.

11 R. Adams, W. V. Wirth, and H. E. French, *J. Am. Chem. Soc.*, 1918, **40**, 424.

12 M. Miyashita, I. Shiina, S. Miyoshi, and T. Mukaiyama, *Bull. Chem. Soc. Jpn.*, 1993, **66**, 1516.

13 J. P. Parrish, E. E. Dueno, S.-I. Kim, and K. W. Jung, *Synth. Commun.*, 2000, **30**, 2687.