 

*Award Accounts*

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# An Adventurous Synthetic Journey with MNBA from Its Reaction Chemistry to the Total Synthesis of Natural Products

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After initially establishing a novel cyclization reaction of ω-hydroxycarboxylic acids (seco-acids) using 4-trifluoromethylbenzoic anhydride (TFBA) and Lewis acid catalysts to form the corresponding lactones, we discovered a more advanced method for this transformation using 2-methyl-6-nitrobenzoic anhydride (MNBA) as a coupling reagent with nucleophilic catalysts. The latter lactonization is promoted by acyl-transfer catalysts, such as 4-(dimethylamino)pyridine (DMAP), 4-pyrrolidinylpyridine (PPY), and 4-(dimethylamino)pyridine *N*-oxide (DMAPO). (+)-Ricinelaidic acid lactone ((+)-**2**) was first synthesized by the TFBA-mediated cyclization with Lewis acid catalysts, while the *threo*-aleuritic acid lactone (**20**) was alternatively synthesized by the MNBA-mediated cyclization with acyl-transfer catalysts. Using this effective lactonization technology to form the ester linkage under mild conditions, we then demonstrated the preparation of various large-, medium-, and small-sized natural and unnatural lactones including (−)-cephalosporolide D ((−)-**3**), (−)-octalactin A ((−)-**4**), (−)-octalactin B ((−)-**25**), 2-epibotcinolide (**49**), (−)- and (+)-2-hydroxytetracosanolides ((−)-**77** and (+)-**77**), (−)- and (+)-2-hydroxy-24-oxooctacosanolides ((−)-**78** and (+)-**78**), (−)-tetrahydrolipstatin ((−)-THL, (−)-**117**), and the erythromycin A skeletons **103b**, **103c**, **104c**, and **105b**. The transition structures involved in the formation of the β-lactones from the corresponding 3-hydroxycarboxylic acids were then determined using DFT calculations at the B3LYP/6-31G*//B3LYP/6-31G* level, and the reactivity of several seco-acids was successfully predicted on the basis of the calculated thermodynamic properties of the transition structures.

## 1. Introduction

The development of an effective method to provide carboxylic esters by the intermolecular dehydration condensation of carboxylic acids with an alcohol has long been a challenging topic in synthetic organic chemistry. This topic has been studied extensively; however, the application of dehydration condensation to intramolecular reactions has proven to be more difficult than expected. This is evident by the small number of efficient lactonizations that have been reported compared with the numerous new synthetic methodologies for intermolecular dehydration condensation.[1,2]

In this account, we present a method for synthesizing large-, medium-, and small-sized lactones using substituted benzoic anhydrides as useful coupling reagents. Along with a review of the development of the presented novel lactonization method over the last decade, we also describe the details of the historical background of the esterification reaction between carboxylic acids and alcohols leading to the current state described in this study.

## 2. Development of an Efficient Lactone Formation Reaction

In order to apply the fundamental intermolecular dehydration condensation (esterification) of a carboxylic acid and an alcohol to the advanced intramolecular dehydration condensation (lactonization) of ω-hydroxycarboxylic acid (seco-acid), the following three conditions must be satisfied. In other words, unless all of these conditions are satisfied, the use of the dehydration condensation method for the synthesis of lactones is impossible.

(1) The reaction must be highly efficient: The intramolecular dehydration condensation must progress between two functional groups that exist within seco-acids with a 1:1 ratio, resulting in an intrinsic demand for efficiency. In classic dehydrative esterification, thermal condensation technologies have been developed to push the acid-catalyzed equilibrium toward a suitable product through the use of a large amount of inexpensive raw material for either the carboxylic acid or alcohol. This type of approach cannot be used in an intramolecular reaction.

(2) The dehydration condensation must occur under mild conditions: In an intramolecular reaction, in addition to monomer generation, there is competition in the form of oligomeric lactone generation. Typically, when monomer lactones are the desired product, the reaction is performed under highly diluted conditions to improve the yield of this product. However, if the substrate concentration is low, there will naturally be less of an opportunity for the substrate and the activator to interact, and the reaction speed will be low. Therefore, heating under reflux in

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a toluene solution or other similarly high-temperature severe condition is required to compensate for this reduced reactivity. As a result, it is difficult to apply an ineffective intermolecular esterification, which does not proceed at low temperature, to practical lactone synthesis because the intramolecular coupling reaction must be carried out under further unfavorable conditions. Stoll et al. have already reported that it is not possible to obtain satisfactory results even if a thermal dehydration condensation method utilizing a conventional acid catalyst is applied to an intramolecular reaction.[3]

(3) The carboxy and hydroxy groups must be separately activated: Because lactonization is an intramolecular acylation of alcohol, the reaction for the carboxy group must be induced with an activator before introducing the hydroxy group. Therefore, to avoid forming by-products and promote the selective progress of targeted lactonization, it is necessary to design a reaction system in which the activator does not directly react with the hydroxy group.

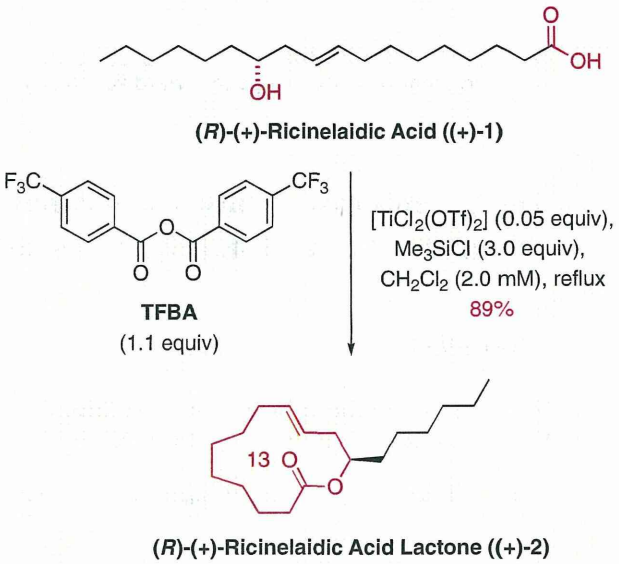
The following methods satisfy all of the above conditions and are actively utilized for the synthesis of macrolides with complex structures that include numerous functional groups: a) Corey–Nicolaou method (using *S*-pyridyl esters),[4] b) Mukaiyama method (using onium salts),[5] c) Masamune method (involving thiol ester activation),[6] d) Yamaguchi method (using 2,4,6-trichlorobenzoyl chloride and DMAP),[7] and e) Keck–Steglich method (method using DCC and DMAP·HCl).[8]

These methods have been developed by spending tremendous efforts over 30 years. Until recently, there have been no remarkable developments in regard to lactonization. Considering the above-mentioned background, we initially set forth to develop an effective esterification reaction that progresses at low temperatures. However, efficiently achieving this goal with lactonization while adequately satisfying the previously mentioned three conditions is something that has always been in our minds. Because we expected to use this method as a key step in our natural product synthesis, the development of a simple, practical, and highly reproducible method was our goal.

## 3. Development of a Condensation Reaction Using Substituted Benzoic Anhydrides

We initially investigated an efficient mixed anhydride method for the synthesis of carboxylic esters and lactones using benzoic anhydrides having electron-withdrawing substituents by the promotion of Lewis acid catalysts. It was proven that the combined reagent consisting of titanium(IV) species with chlorotrimethylsilane functions as an effective catalyst for the synthesis of carboxylic esters from free carboxylic acids and alcohols with 4-trifluoromethylbenzoic anhydride (TFBA).[9] Various macrolactones including (*R*)-(+)-ricinelaidic acid lactone ((+)-**2**) are also prepared from the corresponding seco-acids by the combined use of 1.1 equivalents of TFBA and 0.05 equivalents of $[TiCl_2(OTf)_2]$ in the presence of 3.0 equivalents of chlorotrimethylsilane under mild reaction conditions (Scheme 1).[10]

For almost all of the listed carboxylic acid activation methods (a–e, vide supra for the synthesis of lactones), the activated intermediates were generated in advance before the cyclization steps. However, in our protocol, *the seco-acids are simply added to the mixture of the substituted benzoic anhydride and catalysts* to produce the desired cyclized compounds in excellent yields with high purity. In this reaction, *the substituted benzoic anhydride was used as a dehydration reagent* to temporarily generate the activated mixed anhydride species (MA) along with equilibrium processing in order to gradually form the heterogeneous MA from the homogeneous aromatic anhydride (Scheme 2).

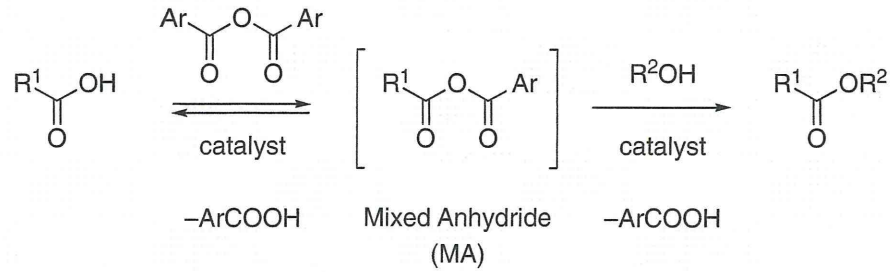



**Scheme 1.** TFBA-mediated lactonization forming (*R*)-(+)-ricinelaidic acid lactone ((+)-**2**).

The following chemoselective alcoholysis of the initially formed mixed anhydride takes place with the consumption of the mixed anhydride to produce the desired lactones in high yields. This one-pot operation procedure prevents an increase in the concentration of the activated intermediary MA, and therefore, the ratio of the monomeric lactone to that of the dimeric or oligomeric compound would be improved by easily controlling the MA concentration. This phenomenon was especially detected for the effective preparation of strained cyclic molecules involving medium-sized lactones.

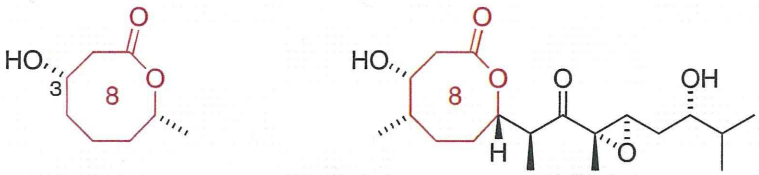
## 4. Total Synthesis of Cephalosporolide D[11]

To prove the effectiveness of lactonization using substituted benzoic anhydrides as coupling reagents, we first attempted to conduct the asymmetric total synthesis of a natural compound that has been proposed to have a medium-sized lactone structure. (−)-Cephalosporolide D ((−)-**3**), a metabolite of fungus, was isolated by Hanson et al. in 1985 from *Cephalosporium aphidicola* together with related compounds.[12] The structure containing two chiral centers and an unusual saturated 8-membered lactone was determined by MS spectra, IR absorption, $^1H$ and $^{13}C$ NMR spectral studies (Figure 1). Though the absolute stereochemistry of the hydroxy group at C-3 was suggested to be in (*S*) configuration according to Horeau's method,[12] the relative and absolute stereochemistries have not yet been determined before our total synthesis. A similar characteristic structure was also found in (−)-octalactin A ((−)-**4**), which exhibited a potent cytotoxic activity against some tumor cell lines.[13] In this section, the determination of the




Keeping low concentration of MA during the reaction by using substituted benzoic anhydride as a dehydration condensation reagent.

**Scheme 2.** Rapid formation and consumption of the mixed anhydride (MA) in the substituted benzoic anhydride method for the synthesis of carboxylic esters and lactones.




**(–)-Cephalosporolide D ((–)-3)** **(–)-Octalactin A ((–)-4)**

**Figure 1.** Structures of (–)-cephalosporolide D ((–)-**3**) and (–)-octalactin A ((–)-**4**).

stereochemistry of **3** and its asymmetric synthesis by way of TFBA-mediated lactonization are described.

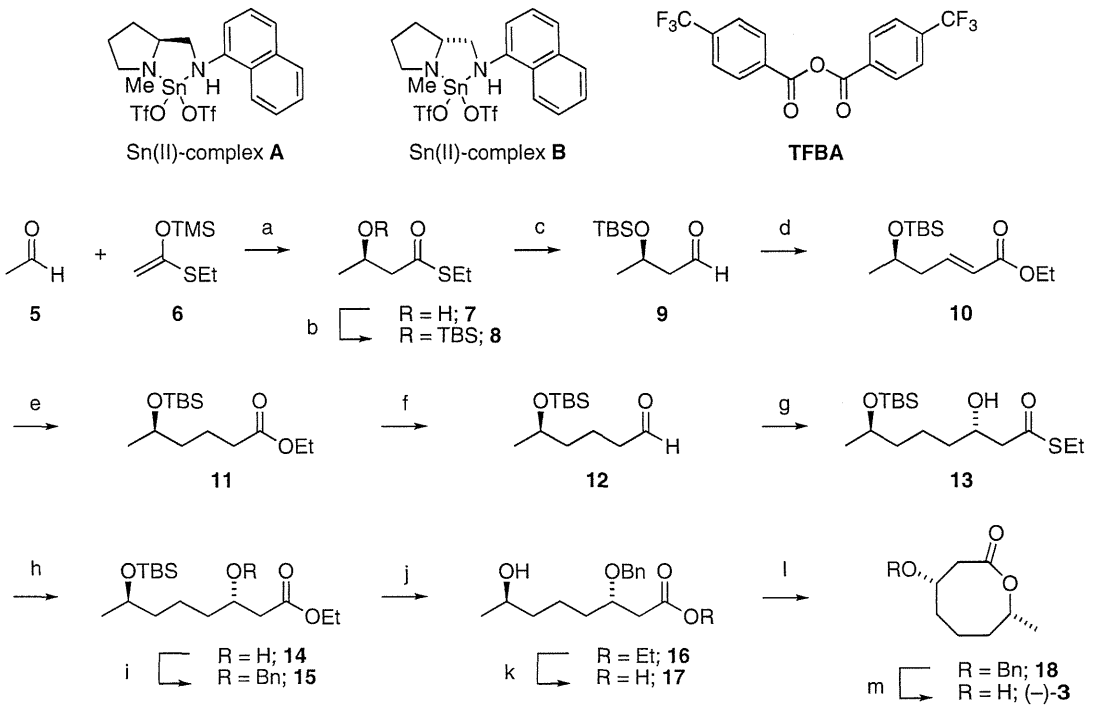
Optically active *S*-ethyl (*R*)-3-hydroxybutanethioate (**7**) was synthesized with high enantioselectivity by an asymmetric aldol reaction between acetaldehyde (**5**) and ketene silyl acetal (KSA) **6** derived from *S*-ethyl ethanethioate using chiral Sn(II)-complex **A** with $^{n}Bu_3SnF$ (Scheme 3).[14,15] Aldol **7** was converted to 3-(*tert*-butyldimethylsiloxy)butanal (**9**) in good yield after protection with a combination of TBSOTf and 2,6-dimethylpyridine and subsequent reduction with DIBAL. Horner–Wadswarth–Emmons reaction of aldehyde **9** with $(EtO)_2POCH_2COOEt$ produced *trans*-unsaturated ester **10** in high yield, and it was in turn transformed to the corresponding saturated siloxy aldehyde **12** by successive hydrogenation under hydrogen atmosphere in the presence of palladium on carbon and reduction of **11** with DIBAL.

The reaction of the chiral aldehyde **12** with lithium enolate derived from *S*-ethyl ethanethioate gave the desired aldol **13** and its diastereomer with poor diastereoselectivity (dr = 47/53). However, the asymmetric aldol reaction between aldehyde **12** and KSA **6** in the presence of the chiral Lewis acid consisting of chiral Sn(II)-complex **B** and $^{n}Bu_3SnF$ produced the corresponding aldol **13** in good yield with high stereoselectivity (dr = 97/3). Protection of the hydroxy group in **13** using trichloromethyl benzylimidate gave the desired benzyl ether in poor yield, probably because of preferential interaction of the imidate to its thiol ester function. Therefore, thiol ester **13** was converted to the corresponding ester **14** by transesterification in the presence of $Ag(OCOCF_3)$ and $^{i}Pr_2NEt$ in EtOH. Benzylation of ester **14** using trichloromethyl benzylimidate rapidly proceeded to afford the desired alkoxy ester **15** in high yield as expected. *tert*-Butyldimethylsilyl group in **15** was removed by treatment with acetic acid and water in THF, and subsequent saponification of the resulting ester **16** with aqueous KOH afforded the desired hydroxycarboxylic acid **17** in good yield. Then, lactonization of seco-acid **17** was examined using the previously described MA method using a catalytic amount of Lewis acid and a stoichiometric amount of TFBA. Although very small amount of the desired 8-membered lactone **18** was obtained using $[TiCl_2(OTf)_2]$ as a catalyst, it was found that $Hf(OTf)_4$ effectively promoted the cyclization to afford **18** in 77% yield based on 61% conversion of the starting seco-acid **17**. This cyclization gave monomeric lactone exclusively and the corresponding diolide was not formed at all. Finally, (–)-cephalosporolide D ((–)-**3**) was prepared from lactone **18** by debenzylation. The synthetic lactone (–)-**3** was recrystallized from hexane to obtain optically and chemically pure (–)-**3** ($[\alpha]_D^{28} = -46.8$ (*c* 2.40, $CHCl_3$)). The spectroscopic properties of the synthetic crystalline sample including its optical rotation were identical to those of (–)-**3** reported by Hanson et al. ($[\alpha]_D^{20} = -46.5$ (*c* 2.23, $CHCl_3$)).[12] Furthermore, X-ray crystallography of synthetic lactone (–)-**3** showed its exact relative stereochemistry.

Thus, an efficient method for the synthesis of (–)-cephalosporolide D ((–)-**3**) was established via TFBA-mediated lactonization to construct the 8-membered lactone moiety. Absolute and relative configurations of the lactone (–)-**3** were determined by its enantioselective synthesis.

### 5. Development of MNBA and DMNBA

Since it is often necessary to handle substrates that are unstable in the presence of acids when achieving total synthesis, the development of a reaction that is catalyzed through a base as a complementary method for an acid-promoted reaction is an important milestone in synthetic organic chemistry. Although before 2001 a substituted benzoic anhydride method was developed using a Lewis acid, we expected that this reaction would be capable of being promoted even if a base was used as the




**Scheme 3.** Total synthesis of (−)-cephalosporolide D ((−)-**3**). *Reagents and conditions*: (a) Sn(II)-complex **A**, $^{n}Bu_3SnF$, $CH_2Cl_2$, −95 °C (78%, 96% ee); (b) TBSOTf, 2,6-dimethylpyridine, $CH_2Cl_2$, 0 °C (96%); (c) DIBAL, toluene, −78 °C (84%); (d) $(EtO)_2POCH_2COOEt$, NaH, THF, 0 °C (83%); (e) $H_2$, 10% Pd/C, EtOH, rt (95%); (f) DIBAL, toluene, −78 °C (90%); (g) Sn(II)-complex **B**, $^{n}Bu_3SnF$, $CH_2Cl_2$, −78 °C (89%, dr = 97/3); (h) $Ag(OCOCF_3)$, $^{i}Pr_2NEt$, EtOH, rt (93%); (i) $BnOC(CCl_3)$=NH, TfOH, $CH_2Cl_2$, rt (85% of **15**, 9% of **16**); (j) AcOH, $H_2O$, THF, rt (95%); (k) KOH, $H_2O$, MeOH, rt (67%); (l) TFBA, $Hf(OTf)_4$, MeCN, THF, reflux (1.66 mM, slow addition over a 8 h period, 77% based on 61% conversion); (m) $H_2$ (1 atm), 10% Pd/C, EtOH, rt (73% based on 90% conversion).

catalyst. Namely, in the presence of a base catalyst with high nucleophilicity such as 4-(dimethylamino)pyridine (DMAP), transacylation between an aliphatic carboxylic acid and substituted benzoic anhydrides should proceed rapidly. Additionally, the mixed anhydrides formed in situ could be activated through base catalysts, and an acyl-transfer reaction is expected to progress smoothly when another nucleophile such as an alcohol is added. If the above two-step reaction, or the generation and selective electrophilic substitution of a mixed anhydride, successively proceed in a one-pot synthesis, then it should be possible to provide the corresponding carboxylic acid derivatives in a good yield.

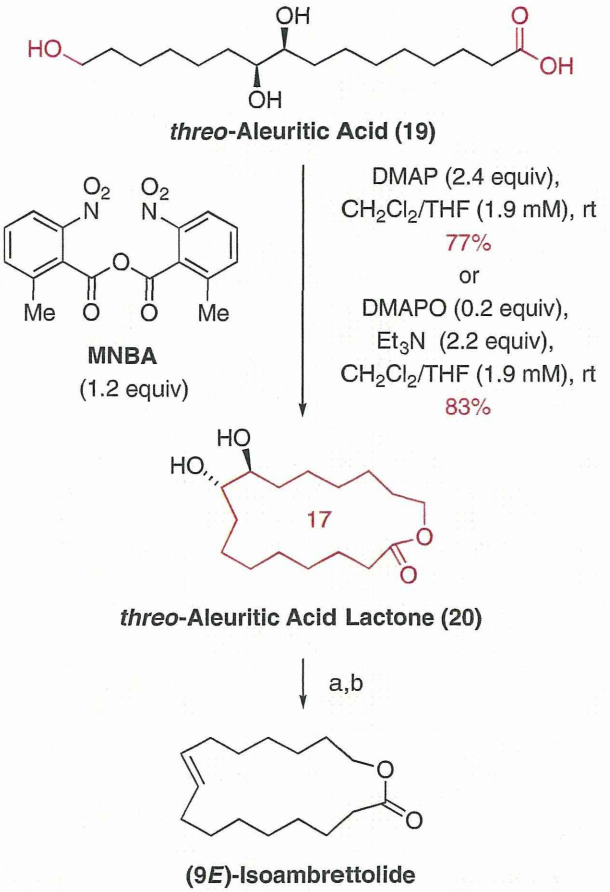
In 2002, an efficient method for the synthesis of various carboxylic esters from nearly equimolar amounts of carboxylic acids and alcohols using 2-methyl-6-nitrobenzoic anhydride (MNBA)[16] as the dehydrating reagent by the promotion of a catalytic amount of DMAP in the presence of triethylamine was successfully developed. Furthermore, a convenient method for the synthesis of a variety of macrolactones with high product selectivity via mixed anhydrides generated from seco-acids and MNBA using a nucleophilic catalyst, such as DMAP, 4-pyrrolidinylpyridine (PPY), or 4-(dimethylamino)pyridine *N*-oxide (DMAPO), was established.[17] For example, the substituted benzoic anhydride method using MNBA with DMAP was successfully applied to the formation of *threo*-aleuritic acid lactone (**20**) with oxygenated functional groups, which is a 17-membered lactone and a useful synthetic intermediate of (9*E*)-isoambrettolide.[18] The MNBA-mediated cyclization with DMAPO also produced lactone **20** directly from unprotected *threo*-aleuritic acid (**19**); therefore, it has been revealed that this pathway is extremely efficient for the preparation of the artificial perfume source (9*E*)-isoambrettolide starting from commercially available **19** via only three steps as shown in Scheme 4. The three steps detailed in Scheme 4 had yield of 83%, 91%, and 87%, respectively.

One of the features of the present protocol is the very simple procedure for providing the desired lactones; that is, *the addition of seco-acids to the mixture of MNBA and promoters at room temperature affords the corresponding cyclic compounds in excellent yields with high purity.* After the establishment of the novel strategy, various effective syntheses of useful molecules including natural products were reported using MNBA with DMAP or DMAPO.[19] For instance, Wu et al. developed a straightforward route to (+)-antimycin $A_{3b}$, which used MNBA lactonization in the final key step (Scheme 5).[20] Closing the dilactone ring of **21** was achieved in 62% yield from the corresponding seco-acid in the presence of ester functionality (previously 0.8%, 13.4%, or 20% yield achieved by the classical cyclization method). The overall yield (34.5%) was significantly higher than that (0.019–3.6%) of the earlier routes found by other groups.

Especially, for the preparation of the 9-membered dilactone core in (+)-antimycin $A_{3b}$ by Wu et al., the efficiency of the MNBA lactonization for the formation of the medium-sized

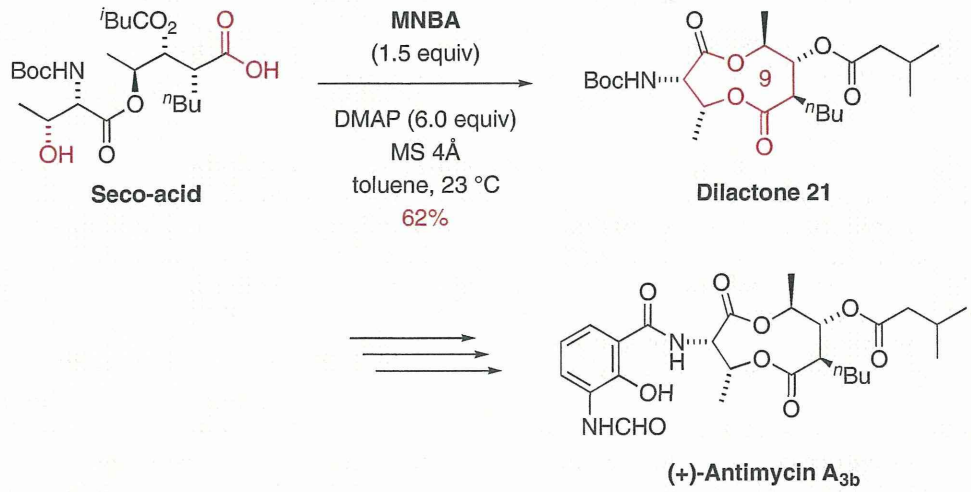
ring core was certainly evaluated by a detailed comparison with other established lactonization methods as shown in Table 1.

In 2008, we further prepared several substituted benzoic anhydrides related to MNBA (Figure 2) and the effect of the substituents on the aromatic ring of benzoic anhydrides in the present mixed anhydride method was fully evaluated.[21] The reaction of 1.1 equivalents of 3-phenylpropanoic acid with 1.0 equivalent of 3-phenylpropanol was initially examined in the presence of 1.2 equivalents of the above substituted benzoic anhydrides, 2.2 equivalents of triethylamine, and 0.1 equivalents of DMAP (Table 2). When 2-nitrobenzoic, 3,4-dinitrobenzoic, or 3,5-dinitrobenzoic anhydride (2-NBA, 3,4-DNBA, or 3,5-DNBA) was used as the dehydrating reagent, 3-phenylpropyl 3-phenylpropanoate ($R^1CO_2R^2$) was obtained in 70%, 65%, or 66% yield along with a small amount of 3-phenylpropyl benzoate derivatives ($ArCO_2R^2$), an undesirable carboxylic ester (Entry 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 carboxy group (Entries 4–6); actually, only the desired carboxylic ester was obtained with perfect chemoselectivity when using MNBA as shown in Entry 4 ($R^1CO_2R^2/ArCO_2R^2 = >500/1$). Furthermore, we found that 2,6-dimethyl-4-nitrobenzoic anhydride (DMNBA) was also a quite effective coupling reagent for providing the carboxylic ester with high chemoselectivity ($R^1CO_2R^2/ArCO_2R^2 = 210/1$) in the presence of a catalytic amount of DMAP (Entry 5). On the other hand, 2,6-dimethyl-3,5-dinitrobenzoic anhydride (DMDNBA), which possesses two electron-withdrawing groups on the 3- and 5-positions, gave somewhat lower chemical yield and chemoselectivity as shown in Entry 6 ($R^1CO_2R^2/ArCO_2R^2 = 170/1$).



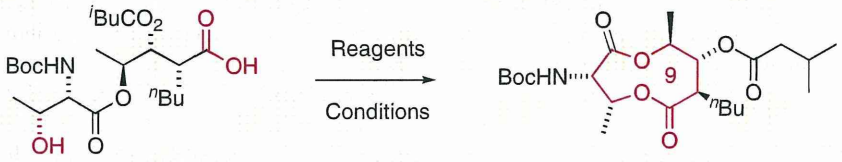

**Scheme 4.** MNBA-mediated lactonization forming *threo*-aleuritic acid lactone (**20**). *Reagents and conditions*: (a) TCDI, toluene, 130 °C (91%); (b) $P(OMe)_3$, 140 °C (87%).

Some of other applications of the MNBA- or DMNBA-mediated lactonizations for the synthesis of complex macromolecules were presented as shown below. In 2006, Doi, Takahashi, and co-workers achieved the total synthesis of the histone deacetylase (HDAC) inhibitor (−)-spiruchostatin A by the diversity-oriented synthesis to produce the library of this molecule.[22] The macrolactonization to form the 15-membered ring compound **22** (67%) was carried out at room temperature without protection of the hydroxy group in the statine unit employing the MNBA protocol combined with the use of stoichiometric amount of DMAP (Scheme 6). Yamaguchi method required 80 °C to proceed and afforded the desired lactone **22** in lower yield (40%).




**Scheme 5.** Synthesis of (+)-antimycin $A_{3b}$ intermediate **21** using MNBA-mediated cyclization of seco-acid and successive transformation of the resulting dilactone **21** into (+)-antimycin $A_{3b}$ reported by Wu et al.[20]

**Table 1.** Yields of Several Lactonization Methods for the Formation of the Synthetic Intermediate **21** of (+)-Antimycin $A_{3b}$ Reported by Wu et al.[20]




**Seco-acid** **Dilactone 21**

| Entry | Method | Reagents (equiv) | Conditions | Yield/% |
|---|---|---|---|---|
| 1 | Corey–Nicolaou | PySSPy (1.1)/$PPh_3$ (1.1)/$Cu(OTf)_2$ (1.0) | PhMe/reflux/5.5 h | 15 |
| 2 | Corey–Nicolaou | PySSPy (2.0)/$PPh_3$ (2.0)/$(CuOTf)_2$·PhH (1.1) | PhMe/reflux/2.5 h | 13 |
| 3 | Corey–Nicolaou | PySSPy (4.0)/$PPh_3$ (4.0)/$(CuOTf)_2$·PhH (1.1) | PhMe/reflux/4 h | 18 |
| 4 | Yamaguchi | TCBC (1.0)/$Et_3N$ (1.1)/DMAP (6.0) | PhMe/reflux/18 h | 0 |
| 5 | Yamaguchi | TCBC (1.6)/$Et_3N$ (2.0)/DMAP (10) | PhMe/reflux/20 h | 7 |
| 6 | Yamaguchi | TCBC (1.1)/$Et_3N$ (1.2)/DMAP (6.0) | PhMe/reflux/17 h | 10 |
| 7 | Keck–Steglich | DCC (2.0)/DMAP·HCl (2.0)/DMAP (3.0) | $CHCl_3$/reflux/21 h | 23 |
| 8 | Shiina | MNBA (1.3)/DMAP (6.0) | PhMe/20 °C/19 h | 58 |
| 9 | Shiina | MNBA (1.5)/DMAP (6.0)/MS 4 Å | PhMe/23 °C/23 h | 62 |

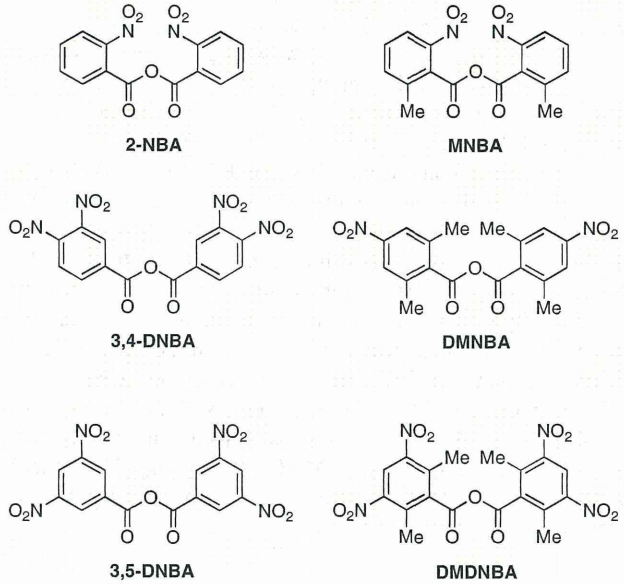
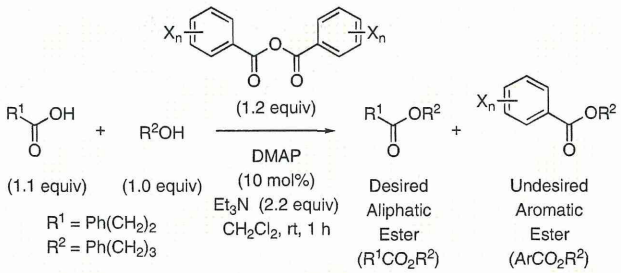



**Figure 2.** Structures of MNBA and several substituted benzoic anhydrides related to MNBA.

**Table 2.** Yields of the Desired Aliphatic Ester ($R^1CO_2R^2$) and Ratios the Desired Aliphatic Ester ($R^1CO_2R^2$) to the Undesired Aromatic Esters ($ArCO_2R^2$) in the Present Mixed Anhydride Method Using Several Substituted Benzoic Anhydrides[21]



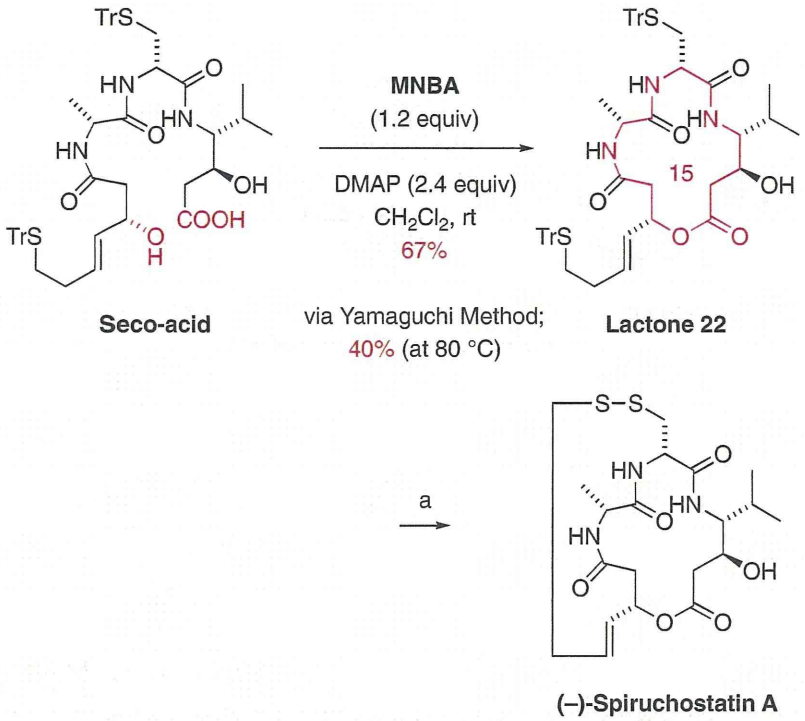

| Entry | $X_n$ | Anhydride | Yield of $R^1CO_2R^2$/% | $R^1CO_2R^2$/$ArCO_2R^2$ |
|---|---|---|---|---|
| 1 | 2-$NO_2$ | 2-NBA | 70 | 110/1 |
| 2 | 3,4-$(NO_2)_2$ | 3,4-DNBA | 65 | 100/1 |
| 3 | 3,5-$(NO_2)_2$ | 3,5-DNBA | 66 | 50/1 |
| 4 | 2-Me-6-$NO_2$ | MNBA | 83 | >500/1 |
| 5 | 2,6-$Me_2$-4-$NO_2$ | DMNBA | 92 | 210/1 |
| 6 | 2,6-$Me_2$-3,5-$(NO_2)_2$ | DMDNBA | 54 | 170/1 |

Furthermore, in the second total synthesis of (−)-spiruchostatin A reported by Katoh et al.,[23] the MNBA-mediated lactonization and other established lactonization methods were evaluated in the formation of the 15-membered lactone **23** (Table 3), and it was concluded that the present aromatic anhydride-promoted protocol is the most effective method for the preparation of the cyclic depsipeptide core structure **23** from the corresponding seco-acid bearing a silyl protective group.

Recently, Donohoe et al. accomplished asymmetric total synthesis of (−)-(*Z*)-deoxypukalide, an antipode of natural furan cembranolide (+)-(*Z*)-deoxypukalide, via the formation of the macrocycle using MNBA lactonization to afford the 14-membered ring compound **24** in 73% yield, followed by ring-closing olefin metathesis (RCM) to provide the trifused system of (−)-(*Z*)-deoxypukalide (Scheme 7).[24] They discussed the efficiency for the preparation of **24** by cyclization and revealed that MNBA-mediated lactonization gave a much higher yield than the Yamaguchi macrolactonization, which failed to give more than about 5% of the desired lactone **24**.[25]

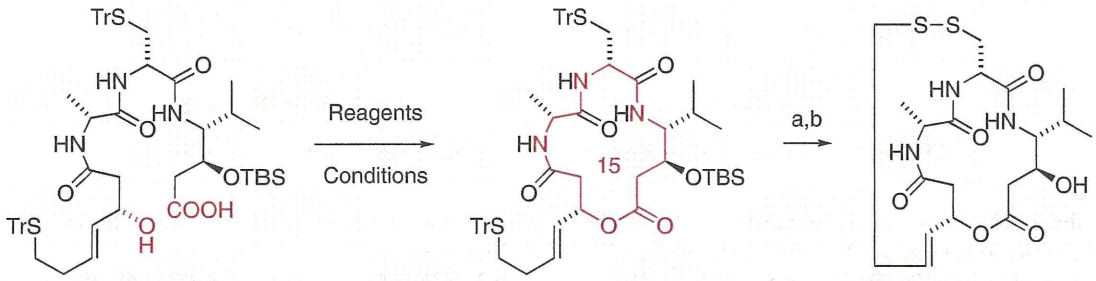
### 6. Total Synthesis of Octalactins A and B[26]

(−)-Octalactin A ((−)-**4**), a cytotoxic active compound, was isolated in 1991 from the marine bacterium *Streptomyces sp.* together with a related 8-membered lactone molecule (−)-octalactin B ((−)-**25**).[13] The octalactins consist of a highly oxidized medium-sized ring framework, and the synthesis of this peculiar complex structure has been one of the most inter-




**Scheme 6.** Synthesis of (−)-spiruchostatin A intermediate **22** using MNBA-mediated cyclization of seco-acid and successive transformation of the resulting lactone **22** into (−)-spiruchostatin A reported by Doi and Takahashi et al.[22] *Reagents and conditions*: (a) $I_2$, $MeOH/CH_2Cl_2$, rt (quant.).

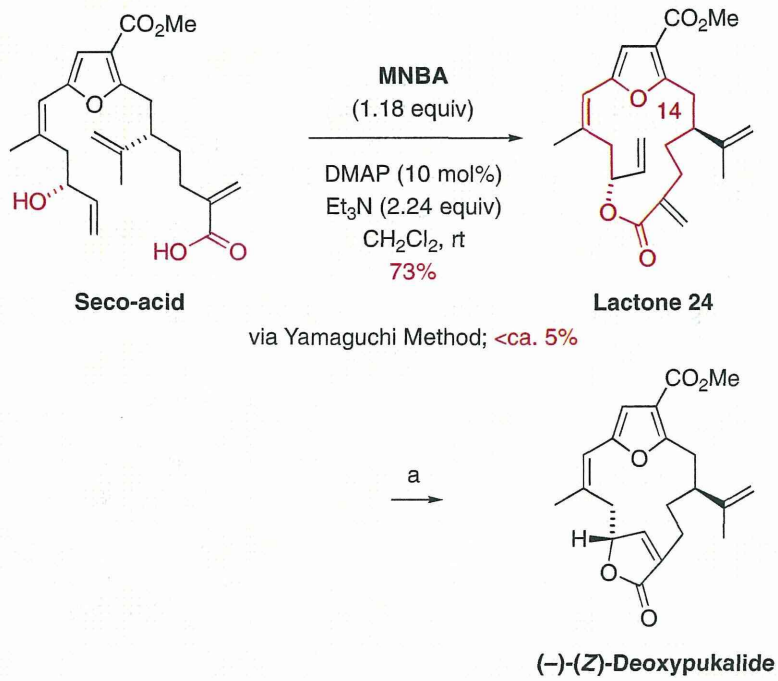
**Table 3.** Yields of Several Lactonization Methods for the Formation of the Synthetic Intermediate **23** of (−)-Spiruchostatin A Reported by Katoh et al.[23]




| Entry | Method | Reagents (equiv) | Conditions | Yield/% |
|---|---|---|---|---|
| 1 | Corey–Nicolaou | PySSPy (3.0)/$PPh_3$ (1.5) | PhMe/80 °C/10 h | 36 |
| 2 | Yamaguchi | TCBC (5.0)/$Et_3N$ (5.0)/DMAP (3.0) | PhMe/60 °C/16 h | 67 |
| 3 | Shiina | DMNBA (1.3)/DMAP (3.0) | $CH_2Cl_2$/rt/15 h | 87 |
| 4 | Shiina | MNBA (1.3)/PPY (3.0) | $CH_2Cl_2$/rt/15 h | 87 |
| 5 | Shiina | MNBA (1.3)/DMAP (3.0) | $CH_2Cl_2$/rt/15 h | 90 |

*Reagents and conditions*: (a) $I_2$, $MeOH/CH_2Cl_2$, rt (80%); (b) HF·pyridine, pyridine, rt (92%).

esting topics in organic chemistry (Figure 3).[27] The absolute configurations of (−)-**4** and (−)-**25** were independently determined in 1994 through the total synthesis of the natural octalactins starting from D- and L-3-hydroxy-2-methylpropanoic acids by Buszek et al.[28] and of the *ent*-octalactins ((+)-**4** and (+)-**25**) starting from (+)-citronellic acid by McWilliams and Clardy.[29] In 2002, Buszek et al. alternatively synthesized octalactins via the formation of the 8-membered lactone moiety using olefin metathesis.[30] Also, Holmes et al. accomplished the total synthesis of (−)-**4** and (−)-**25** in 2004 utilizing their original rearrangement reaction to form the medium-sized ring of the octalactins.[31] Some formal syntheses and related synthetic studies of octalactins have also been reported.[32] In our continuous efforts directed toward the synthesis of natural compounds having 8-membered rings, the total synthesis of (−)-**4** and (−)-**25** was planned using a similar strategy to Section **4** including the rapid lactonization using MNBA as a coupling reagent.




**Scheme 7.** Synthesis of (−)-(*Z*)-deoxypukalide intermediate **24** using MNBA-mediated cyclization of seco-acid and successive transformation of the resulting lactone **24** into (−)-(*Z*)-deoxypukalide reported by Donohoe et al.[24] *Reagents and conditions*: (a) Grubbs II, toluene, Δ (72%).

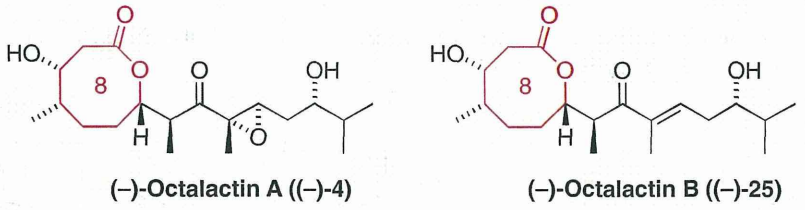


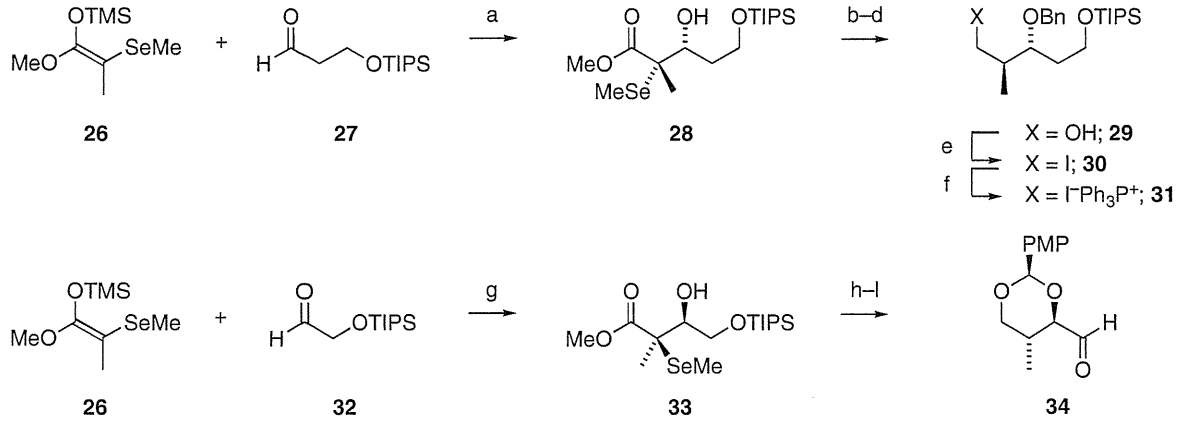

**Figure 3.** Structures of (−)-octalactin A ((−)-**4**) and (−)-octalactins B ((−)-**25**).

**6.1 Synthesis of Aldol-Type Fragments via Deselenization.** In the presence of chiral Sn(II)-complex **A** with $^{n}Bu_3SnF$, the asymmetric aldol reaction between KSA **26** derived from methyl 2-methylselenopropanoate and β-siloxyaldehyde **27** smoothly proceeded to afford *syn*-aldol **28** in good yield with high enantioselectivity (Scheme 8).[14,15] According to Guindon's diastereoselective deselenization protocol, **28** was treated with $^{n}Bu_2BOTf$ and $^{i}Pr_2NEt$, followed by $^{n}Bu_3SnH$ and $Et_3B$ to provide the corresponding *anti*-aldol unit in good yield.[33] After protection of the secondary hydroxy group by benzyl group, the ester function was reduced with $LiAlH_4$. Halogenation of the resulting primary alcohol **29** afforded iodoalkane **30**, which was further converted to the phosphonium salt **31**, a desired right-hand segment.

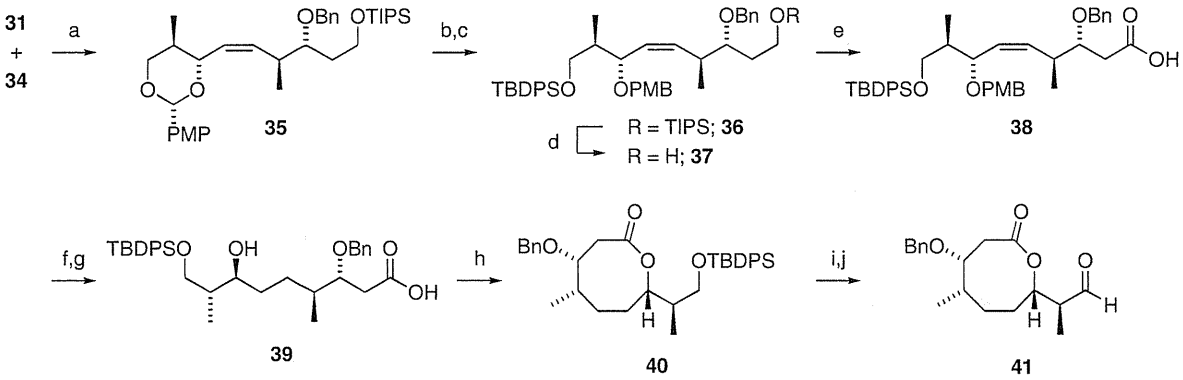
The left-hand segment **34** was prepared by the aldol reaction of KSA **26** with α-siloxyaldehyde **32** using chiral Sn(II)-complex **B** with $^{n}Bu_3SnF$ to afford *syn*-aldol **33** bearing four-carbon unit with high selectivity (Scheme 8).[14,15] The conversion of *syn*-**33** to the corresponding *anti*-aldol was also successfully carried out using the similar method for the preparation of **29**. Successive reduction of the ester group, formation of *p*-methoxybenzylidene acetal, and oxidation of the intermediary primary alcohol produced the desired chiral aldehyde **34**.[34]

**6.2 Synthesis of the Seco-acid of the 8-Membered Lactone Moiety.** Two segments **31** and **34** were coupled in the presence of NaHMDS to produce a linear polyoxy compound **35** in good yield (Scheme 9). Reductive cleavage of the acetal moiety followed by protection of the resulting primary alcohol afforded the disilyl ether **36**. Deprotection of the TIPS group and oxidation by TEMPO[35] of the primary alcohol **37** gave the corresponding carboxylic acid **38**. The desired chiral linear seco-acid **39** was then obtained by deprotection of the PMB group and hydrogenation of the double bond without removal of the benzyl group.[36]

**6.3 Formation of the 8-Membered Lactone Moiety by a Substituted Benzoic Anhydride Method.** Buszek et al. reported the successful lactonization of a similar seco-acid, which has the PMB group instead of the Bn group in **39** using the *S*-pyridyl ester method.[28,37] However, it is reported that the cyclization requires a high reaction temperature and longer reaction time (96 h); nevertheless, the reaction is accelerated by $AgBF_4$. Actually, the reaction of the *S*-pyridyl ester of **39** sluggishly proceeded even under very severe conditions (96 h




**Scheme 8.** Synthesis of fragments **31** and **34**. *Reagents and conditions*: (a) Sn(II)-complex **A**, $^n$Bu$_3$SnF, $CH_2Cl_2$, −78 °C (57%, *syn*/*anti* = 75/25, 95% ee for *syn*); (b) $^n$Bu$_2$BOTf, $^i$Pr$_2$NEt, $CH_2Cl_2$, 0 °C, then $^n$Bu$_3$SnH, Et$_3$B, −78 °C (84%, *anti*/*syn* = 90/10); (c) BnOC(CCl$_3$)=NH, TfOH, Et$_2$O, 0 °C (85%); (d) LiAlH$_4$, THF, 0 °C (98% from *anti*); (e) I$_2$, Ph$_3$P, imidazole, benzene, rt (95%); (f) Ph$_3$P, $^i$Pr$_2$NEt, CH$_3$CN, reflux (quant.); (g) Sn(II)-complex **B**, $^n$Bu$_3$SnF, $CH_2Cl_2$, −78 °C (54%, *syn*/*anti* = 79/21, 88% ee for *syn*); (h) $^n$Bu$_2$BOTf, $^i$Pr$_2$NEt, $CH_2Cl_2$, rt, then $^n$Bu$_3$SnH, Et$_3$B, −78 °C (77%, *anti*/*syn* = 94/6); (i) DIBAL, $CH_2Cl_2$, 0 °C (80%); (j) PMPCH(OMe)$_2$, CSA, $CH_2Cl_2$, rt (84% from *anti*); (k) TBAF, THF, 0 °C (95%); (l) PhSNH$^t$Bu, NCS, K$_2$CO$_3$, MS 4 Å, $CH_2Cl_2$, rt (99%).



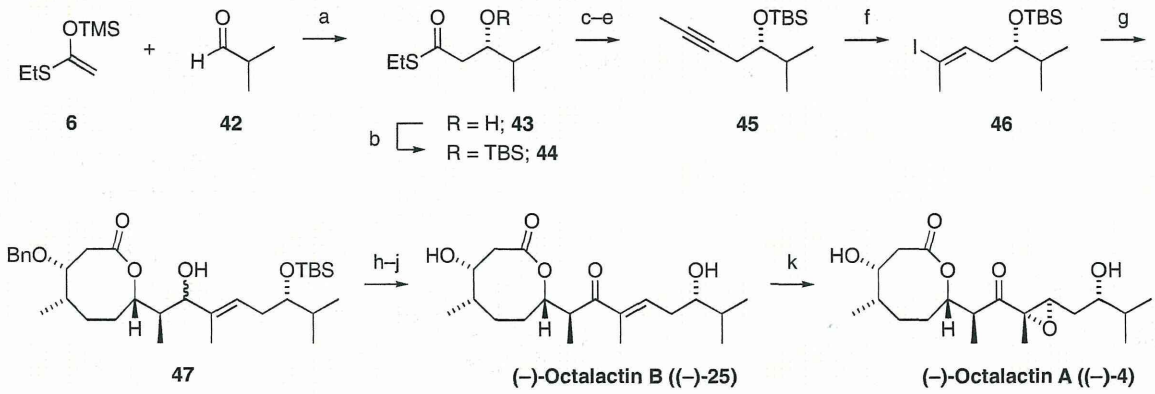

**Scheme 9.** Synthesis of lactone **41**. *Reagents and conditions*: (a) NaHMDS, toluene, −78 °C to rt (88%); (b) DIBAL, $CH_2Cl_2$, −5 or −10 °C (86%); (c) TBDPSCl, Et$_3$N, DMAP, $CH_2Cl_2$, rt (82%); (d) 1 M HCl, THF, rt (95%); (e) TEMPO, NaClO$_2$, NaClO, buffer, H$_2$O, CH$_3$CN, 35 °C (96%); (f) CAN, H$_2$O, CH$_3$CN, 0 °C (94%); (g) H$_2$, 10% Pd/C, Et$_3$N, MeOH, rt (87%); (h) MNBA, DMAP (10 mol %) or DMAPO (10 mol %), Et$_3$N, $CH_2Cl_2$, rt (89% or 90%); (i) TBAF, AcOH, THF, rt (99%); (j) TPAP, NMO, MS 4 Å, $CH_2Cl_2$, 0 °C (91%).

in refluxing toluene with $AgBF_4$) to produce our desired 8-membered lactone **40** in 63% yield. The yield of **40** decreases according to a shortened period of the reaction time; for example, only 5% of the desired lactone **40** was obtained under the intensive conditions when the reaction was quenched after 13 h. Furthermore, it was revealed that cyclization of the *S*-pyridyl ester of **39** did not take place at all at room temperature. Therefore, we decided to apply a new and rapid lactonization to produce the medium-sized lactone backbone **40** by an alternative approach as shown by step (h).

First, excess DMAP (6.0 equiv) was employed as an acyl-transfer catalyst for the cyclization of **39** in the presence of 1.3 equivalents of MNBA in dichloromethane or toluene at room temperature to give the 8-membered lactone **40** in 85% or 84% yield, respectively. Next, the amount of the catalyst was gradually decreased, and it was determined that the use of 0.1 equivalents of DMAP with 6.0 equivalents of triethylamine was sufficient to produce **40** in excellent yield (89%) at room temperature. On the other hand, it has been observed that DMAPO, an oxide of DMAP, also functions as an effective acyl-transfer catalyst for our lactonization; we then examined the use of 0.1 equivalents of DMAPO combined with 6.0 equivalents of triethylamine to afford the targeted lactone in 90% yield under same conditions.

The formed **40** was then converted to the 8-membered lactone aldehyde **41** through deprotection of the TBDPS group and successive oxidation (steps (i and j)).

**6.4 Preparation of the Side Chain and Completion of the Total Synthesis.** The side chain **46** was prepared from an optically active aldol **43**, which was generated by the asymmetric aldol reaction of KSA **6** with 2-methylpropanal (**42**) as shown in Scheme 10.[14,15] The protection of **43** and the successive reduction of **44** using Et$_3$SiH with Pd/C afforded the corresponding aldehyde.[38] According to Buszek's synthesis




**Scheme 10.** Total synthesis of (−)-octalactins A ((−)-**4**) and B ((−)-**25**). *Reagents and conditions*: (a) Sn(II)-complex **A**, $^{n}Bu_3SnF$, $CH_2Cl_2$, −78 °C (65%, 94% ee); (b) TBSCl, imidazole, DMF, rt (95%); (c) $Et_3SiH$, 10% Pd/C, acetone, rt (88%); (d) $CBr_4$, $PPh_3$, $CH_2Cl_2$, −78 to 0 °C (86%); (e) $^{n}BuLi$, THF, −78 °C, then MeI, rt (91%); (f) $Cp_2ZrHCl$, benzene, sun-lamp, 35 °C, then $I_2$, 7 °C (50%); (g) $^{t}BuLi$, $Et_2O$, −78 °C, then **41** (49%, α/β = 57/43); (h) TPAP, NMO, MS 4 Å, $CH_2Cl_2$, 0 °C (75%); (i) 46% HF, $CH_3CN$, 0 °C (91%); (j) $BBr_3$, $CH_2Cl_2$, −95 to −45 °C (76%); (k) TBHP, $[VO(acac)_2]$, $CH_2Cl_2$, 5–10 °C (40% based on 70% conversion).

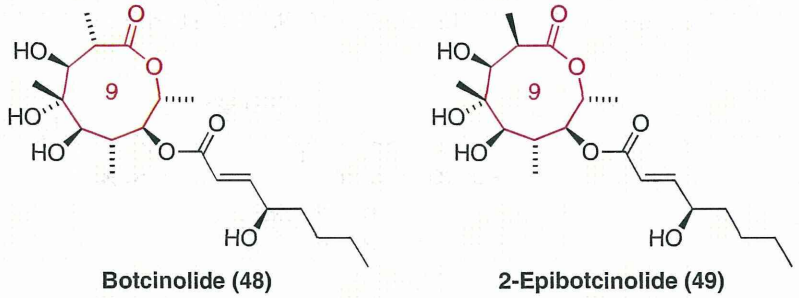



**Figure 4.** Structures of botcinolide (**48**) and 2-epibotcinolide (**49**).

of the side chain, the aldehyde was transformed into the desired vinyl iodide **46** via the siloxyalkyne **45**.[28] The side chain **46** was finally introduced to the aldehyde **41** (Scheme 9) using the method reported by McWilliams and Clardy[29] to give the multi-oxygenated 8-membered lactone **47**, a precursor of the octalactins. A mixture of diastereomers was oxidized to generate the corresponding enone, and successive deprotections of the TBS and Bn groups afforded (−)-octalactin B ((−)-**25**) (our synthetic sample; $[\alpha]_D^{23} = -124$ (*c* 0.42, $CHCl_3$) {$[\alpha]_D = -123$ (*c* 5.6, $CHCl_3$) (revised);[13,29] $[\alpha]_D = -126$;[28] $[\alpha]_D^{24} = -123$ (*c* 0.04, $CDCl_3$);[31] $[\alpha]_D = +132$ (enantiomorph)}).[29] Final conversion of (−)-octalactin B to (−)-octalactin A using TBHP was attained according to the literature method to furnish the target compound (−)-**4** (our synthetic sample; $[\alpha]_D^{23} = -148$ (*c* 0.20, $CHCl_3$) {$[\alpha]_D = -140$ (*c* 1.8, $CHCl_3$) (revised);[13,29] $[\alpha]_D = -152$;[28] $[\alpha]_D^{20} = -153$ (*c* 0.14, $CHCl_3$);[31] $[\alpha]_D = +141$ (enantiomorph)}).[29] All spectral data including optical rotations of synthetic (−)-**4** correspond to those of natural (−)-octalactin A.

Thus, a novel method for constructing the 8-membered lactone moiety of (−)-octalactins A and B is established by way of the rapid cyclization promoted by MNBA under the influence of a catalytic amount of DMAP or DMAPO. The use of catalytic amount of DMAP or DMAPO rapidly promotes formation of the medium-sized ring of the octalactins indicating the remarkable efficiency of the MNBA lactonization protocol.

## 7. Total Synthesis of Botcinolides[39]

Botcinolide was first isolated from a strain of the fungus *Botrytic cinerea* (UK185RRC) by Cutler et al. in 1993,[40] and pseudo 2-epimeric isomer, 2-epibotcinolide, was also extracted from the plant pathogen *Botrytic cinerea* (UCA992) by Collado et al. in 1996.[41] Other isomeric and homologous compounds were also prepared from a similar fungus,[42] and it was revealed that botcinolide and its relatives have a significant biological activity that inhibits the growth of several plants at low concentrations.

The structures of botcinolide (**48**) and 2-epibotcinolide (**49**) had been theorized to possess peculiar saturated 9-membered rings based on a NMR analysis including enhanced NOE techniques (Figure 4), however, the revised forms of botcinolide and 2-epibotcinolide were recently proposed on the basis of a reinvestigation of the structure by Nakajima's group.[43] Independently, we have very recently reported the method for the preparation of the target molecule **49** and questioned the structure of the proposed 2-epibotcinolide through its total synthesis.[39]

In this section, the total synthesis of the proposed structure of 2-epibotcinolide (**49**) (*pseudo*-structure of natural product) was presented using the asymmetric aldol reaction for the generation of the chiral segments to build the linear polyoxygenated synthetic intermediates followed by the rapid lactonization using MNBA to form the key 9-membered ring.