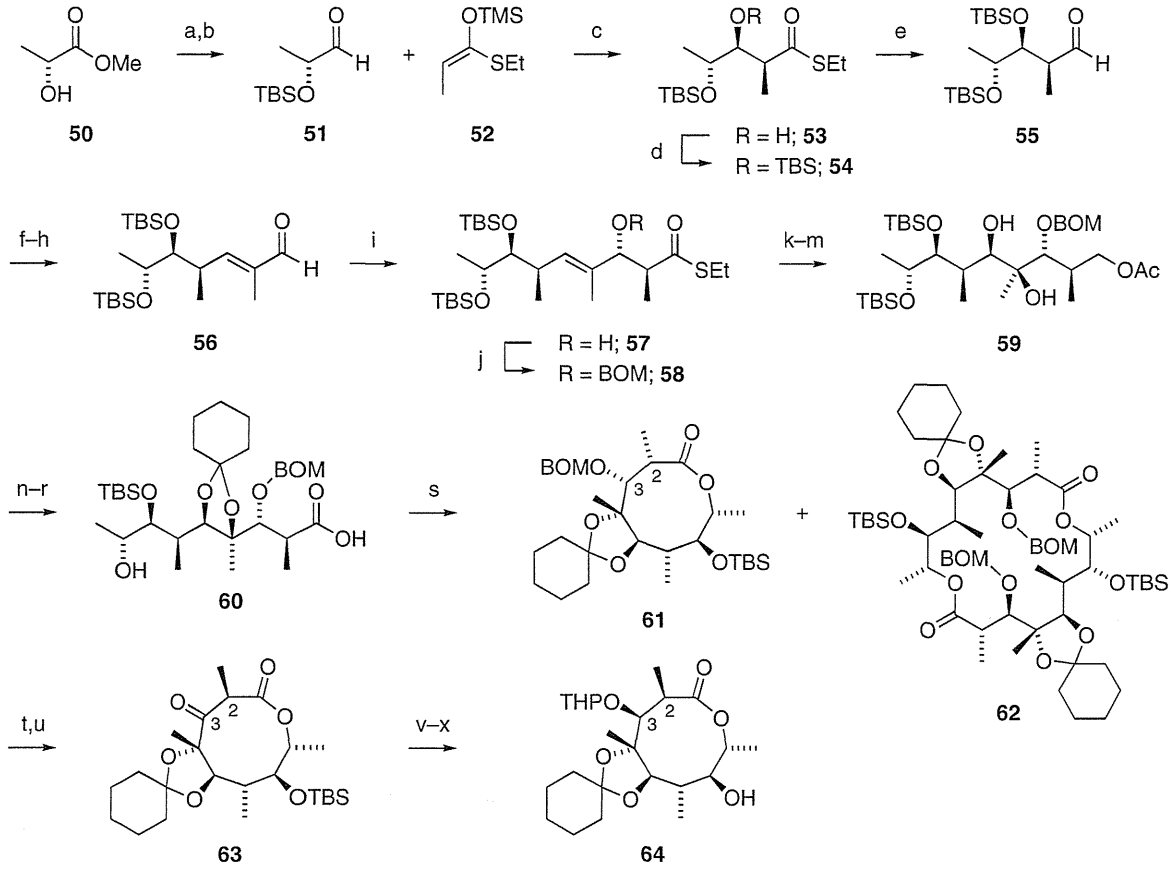
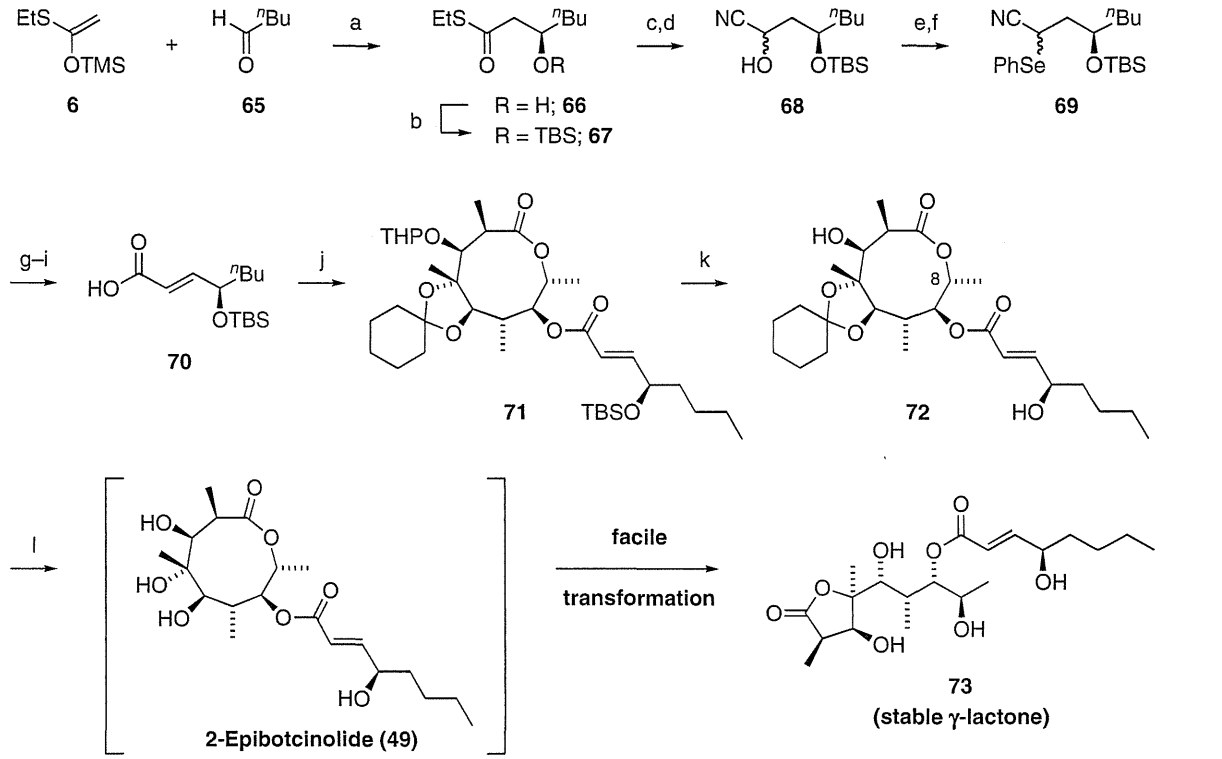


Scheme 11. Synthesis of 9-membered ring core of 2-epibotcinolide (**49**). *Reagents and conditions*: (a) TBSCl, NaH, THF, rt (82%); (b) DIBAL, CH_2Cl_2, −78 °C (92%); (c) Sn(II)-complex **A**, $^nBu_2Sn(OAc)_2$, EtCN, −78 °C (83%, single stereoisomer); (d) TBSOTf, 2,6-dimethylpyridine, CH_2Cl_2, 0 °C (95%); (e) Et_3SiH, Pd/C, acetone, 0 °C (quant.); (f) $Ph_3P{=}C(Me)CO_2Et$, toluene, 100 °C (95%); (g) L-Selectride, THF, rt (92%); (h) TPAP, NMO, MS 4 Å, CH_2Cl_2, 0 °C (97%); (i) $EtCO_2SEt$, LHMDS, THF, −78 °C, (88%, **57**/stereoisomers = 57/24/10/9); (j) BOMCl, $^iPr_2NEt$, CH_2Cl_2, 60 °C (96%); (k) Red-Al, toluene, 0 °C (quant.); (l) Ac_2O, DMAP, Py, 0 °C (quant.); (m) OsO_4, Py, rt (65%, α/β = 1/1); (n) 1-methoxycyclohexene, CSA, CH_2Cl_2, rt (97%); (o) K_2CO_3, MeOH, rt (90%); (p) TPAP, NMO, MS 4 Å, CH_2Cl_2, 0 °C; (q) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$, rt (91% in 2 steps); (r) HF·Py, THF, rt (59% based on 87% conversion); (s) MNBA, DMAP, CH_2Cl_2, rt (71% of **61** with 7% of **62**); (t) H_2, $Pd(OH)_2$, EtOH, rt (quant); (u) TPAP, NMO, MS 4 Å, CH_2Cl_2, 0 °C; then silica gel PTLC (82%); (v) $NaBH_4$, MeOH, rt (77%); (w) DHP, CSA, CH_2Cl_2, rt (86%); (x) TBAF, THF, 0 °C (98%).

7.1 Synthesis of Chiral Linear Precursor and MNBA-Mediated Lactonization to Form 9-Membered Compounds. First, the preparation of the chiral linear seco-acid **60**, the precursor to the target 9-membered lactone **61**, was carried out as shown in Scheme 11. The chiral α-siloxy aldehyde **51** derived from methyl (*R*)-lactate (**50**) was treated with the KSA **52** in the presence of the chiral Sn(II)-complex **A** as a catalyst combined with $^nBu_2Sn(OAc)_2$.[14,15] The asymmetric aldol reaction smoothly proceeded, yielding only the corresponding aldol adduct **53**, which has the required stereochemistry. The secondary hydroxy group was protected as its TBS ether, and the reduction of the thioester moiety produced the aldehyde **55**.[38]

The conventional elongation of the three-carbon unit using the successive Wittig reaction, reduction with L-Selectride, and oxidation with TPAP–NMO provided the highly substituted heptenal **56**. The second aldol reaction of **56** with lithium enolate derived from *S*-ethyl propanethioate took place with moderate diastereoselectivity, and the linear 9-carbon polyoxygenated intermediate **57** was predominantly produced. When the dihydroxylation of the BOM ether **58** derived from **57** was examined using OsO_4 under several reaction conditions, all of the reactions proceeded sluggishly to afford the corresponding γ-lactones in low yields. Therefore, some of the functional groups in **58** had to be changed before the dihydroxylation of the double bond.

After the reduction of the ester function in **58** and the protection of the resulting primary hydroxy group, the product was successfully dihydroxylated to give the desired diols **59** and its diastereomer (ca. 1/1) in the presence of a stoichiometric amount of OsO_4 although the catalytic enantioselective dihydroxylation did not take place at all. The produced diol **59** was next converted to its corresponding cyclohexylidene derivative via treatment with 1-methoxycyclohexene and CSA, the subsequent hydrolysis of the acetyl group, and the final stepwise oxidation of the primary hydroxy group into the carboxylic acid part. The TBS-protecting group at C-8 was



Scheme 12. Synthesis of 9-membered ring core of 2-epibotcinolide (**49**). *Reagents and conditions*: (a) Sn(II)-complex **A**, EtCN, −78 °C (82%, 91% ee); (b) TBSOTf, 2,6-dimethylpyridine, CH_2Cl_2, 0 °C (98%); (c) Et_3SiH, Pd/C, acetone (quant.); (d) KCN, $NaHCO_3$, Et_2O/H_2O, rt; (e) MsCl, Et_3N, CH_2Cl_2, 0 °C (88% in 2 steps); (f) PhSeH, Cs_2CO_3, DMF, 0 °C (94%); (g) 30% H_2O_2, THF, 0 °C; (h) DIBAL, toluene, −78 °C (84% in 2 steps); (i) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, $^tBuOH/H_2O$, rt (97%); (j) **64**, MNBA, DMAP, Et_3N, CH_2Cl_2, rt (86%); (k) HF·Py, THF, rt (85%); (l) BBr_3, CH_2Cl_2, −45 °C (48%).

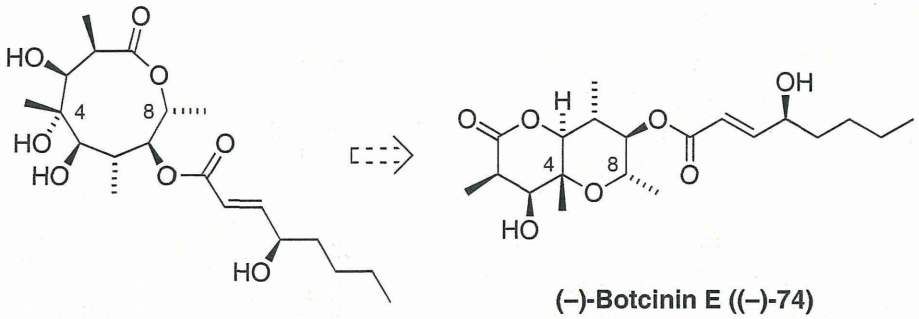
cleaved selectively, at last producing the desired seco-acid **60** needed for the formation of the 9-membered ring.

Eventually, the lactonization of the seco-acid **60** was carried out in the presence of MNBA with excess DMAP (6.0 equiv), and the desired monomeric lactone **61** was obtained in 71% yield along with the dimeric lactone **62** (7%) as shown by step (s). By contrast, a catalytic amount of DMAP was not effective for the formation of the 9-membered lactone moiety.

Before introducing the side-chain into the 9-membered lactone backbone, the stereochemistry of **61** was arranged by some transformation to the fragment coupling acceptor **64** (Scheme 11). First, the BOM group in **61** was removed by hydrogenation using $Pd(OH)_2$ under H_2 atmosphere, and the resulting β-hydroxy lactone was oxidized to (2*S*)-β-ketolactone. Epimerization at the α-position of (2*S*)-β-ketolactone took place smoothly on silica gel and the 2-epimeric (2*R*)-β-ketolactone **63** was obtained in a good yield. Stereoselective reduction from the *Re*-face of the carbonyl group at C-3 in **63** was also accomplished using $NaBH_4$ in MeOH to afford the corresponding 2-epimerized β-hydroxy lactone, which was then converted into the THP ether, and the TBS protective group was removed by TBAF to afford the key intermediate **64**.

7.2 Synthesis of Chiral Side-Chain and Completion of the Total Synthesis of 2-Epibotcinolide. The chiral side-chain **70** was next prepared as shown in Scheme 12. An asymmetric aldol reaction of KSA **6** with pentanal (**65**) was carried out in the presence of a catalytic amount of the chiral Sn(II)-complex **A**, and the aldol adduct **66** was obtained in a good yield with high enantioselectivity (91% ee).[14,15] After conversion of **66** into the corresponding TBS ether **67**, siloxy aldehyde was prepared by Fukuyama reduction.[38] The formation of cyanohydrin **68**, mesylation of the hydroxy group, and successive substitution with phenylselenol in the presence of Cs_2CO_3 afforded a mixture of the diastereomeric isomers **69**. The oxidative elimination of the phenylseleno group, followed by the reduction of the nitrile group with DIBAL and oxidation of the resulting aldehyde yielded the desired α,β-unsaturated carboxylic acid **70**.[44]

Finally, the coupling reaction between the main 9-membered ring **64** and the chiral side-chain **70** was also investigated by the MNBA esterification to form the desired skeleton containing all functionalities for producing the proposed structure of 2-epibotcinolide (**49**). The coupling product **71** was temporarily converted into the deprotected compound **72**, and the spectroscopic data on **72** were compared with those reported for the natural compounds. However, the chemical shift, especially of the methine proton (δ 4.9 ppm in CD_3OD) at C-8 of the synthetic sample **72**, was significantly different from that of the reported 2-epibotcinolide at δ 3.7 ppm in CD_3OD,[41] botcinolide at δ 3.6 ppm,[40] 4-*O*-methylbotcinolide at δ 3.6 ppm,[41] and 3-*O*-acetyl-2-epibotcinolide at δ 3.7 ppm.[41] Furthermore, the deprotection of **72** afforded the intramolecular transacylated compound **73**, which was spontaneously easily formed from the assumed 9-membered lactone **49** (Scheme 12). The struc-



Former Assumed Structure of 2-Epibotcinolide (49)

(–)-Botcinin E ((–)-74) [Revised Structure of 2-Epibotcinolide Determined by Total Synthesis]

Figure 5. Structural revision of botcinolides by Nakajima and Culter et al.,[43] and structure of (–)-botcinin E ((–)-**74**) totally synthesized by Shiina et al.[45]

ture of transacylated γ-lactone **73** was determined by comparison with the spectroscopic data on the other γ-lactones which were derived from the BOM ether **58** and its diastereomer via the dihydroxylation using OsO_4.

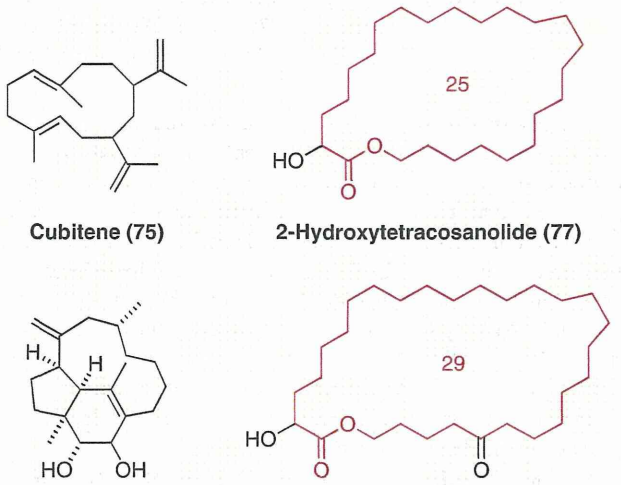
Based on the disclosed properties of **72** and **49** by our synthetic studies, the proposed 9-membered ring structures of 2-epibotcinolide (**49**) derived from nature and other related compounds are extremely doubtful and reassigned structures should be given for the exact determination of these true forms. In the accordance with our representation of these results, Nakajima's group has just shown the alternative structure (–)-**74** for 2-epibotcinolide, which has been renamed (–)-botcinin E, as depicted in Figure 5.[43] To evaluate these results, we have independently accomplished the total synthesis of (–)-botcinin E ((–)-**74**), and we finally concluded that the natural product contains a highly substituted tetrahydropyran ring connecting the C-4 and C-8 with an ether linkage.[45]

It was experimentally determined that the proposed 9-membered ring structure of 2-epibotcinolide (**49**) is very unstable and the ineluctable translactonization easily occurred to form the corresponding γ-lactone **73**, and it has been unequivocally determined that the structure of the natural product is not that of the formerly assumed lactone 2-epibotcinolide (**49**) but that of (–)-botcinin E ((–)-**74**) through our total syntheses of both compounds.[39,45]

In summary, we have accomplished the total synthesis of 2-epibotcinolide (**49**) by way of several featured synthetic approaches, that include the key cyclization using MNBA-mediated lactonization to form the 9-membered ring. Additionally, we have confirmed that there is no naturally occurring saturated 9-membered lactone through our synthetic approach to the formerly assumed structures of botcinolides. Note that the total synthesis of the complex natural molecules using the established and certain stereoselective reactions is the most reliable way to determine the definitive structure of the natural products.

8. Total Synthesis of 2-Hydroxytetracosanolide and 2-Hydroxy-24-oxooctacosanolide[46]

Termites have rigidly structured societies, consisting of a king, a queen, workers, fertile pairs, and soldiers. Termite soldiers are sterile males or sterile females, and their heads are much different in shape and size from those of the termite workers. The primary role of the soldiers is to protect their colony from intruders and predators. To do this, the soldiers of some termite species produce chemical secretions, such as terpenes, alkanes, alkenes, quinines, nitroalkenes, β-ketoaldehydes, vinyl ketones, and macrocyclic lactones.[47]

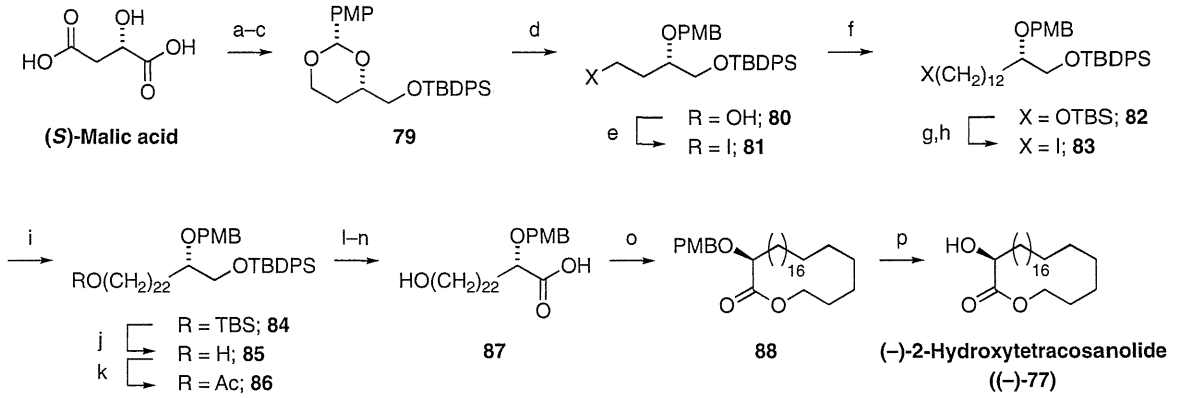


Cubitene (75) **2-Hydroxytetracosanolide (77)**

Trinervitane (76) **2-Hydroxy-24-oxooctacosanolide (78)**

Figure 6. Some defensive substances of termite soldiers.

Some diterpenes isolated from the frontal gland secretion of a termite soldier, such as cubitene (**75**) and trinervitane (**76**), are reported to be typical defensive substances that the termites use against predators (Figure 6).[48,49] Related biosynthetic and chemical synthetic studies of the cyclic terpenoids have progressed over the past several decades as reported in excellent articles.[47] On the other hand, macrocyclic molecules, such as **77** and **78**, were also extracted from the salivary defensive secretion of termites.[50,51] α-Hydroxylactone **77** was prepared from a crude mixture of the crushed heads of soldier *Armitermes neotenicus*, a species inhabiting the Republic of Guyana,[50] and α-hydroxy-24-oxolactone **78** was isolated from the salivary defensive secretion of the soldiers of African termite *Pseudacanthoterme springer*.[51]



Scheme 13. Total synthesis of (−)-2-hydroxytetracosanolide ((−)-77). *Reagents and conditions*: (a) $BH_3 \cdot SMe_2$, $B(OMe)_3$, THF, rt (97%); (b) $PMPCH(OMe)_2$, CSA, CH_2Cl_2, rt (81%); (c) TBDPSCl, imidazole, DMF, rt (83%); (d) DIBAL, CH_2Cl_2, −78 °C (92%); (e) I_2, Ph_3P, imidazole, benzene, rt (96%); (f) $TBSO(CH_2)_{10}MgBr$ (**C**), CuI, 2,2′-bipyridyl, THF, rt (90%); (g) 1 M HCl, THF, rt (96%); (h) I_2, PPh_3, imidazole, benzene, rt (92%); (i) **C**, CuI, 2,2′-bipyridyl, THF, rt (96%); (j) 1 M HCl, THF, rt (99%); (k) Ac_2O, DMAP, pyridine, rt (97%); (l) TBAF, AcOH, THF, rt (quant.); (m) TEMPO, $NaClO_2$, NaOCl, acetonitrile, rt (88%); (n) K_2CO_3, MeOH, rt (87%); (o) MNBA, DMAP, CH_2Cl_2/THF, 50 °C (87%); (p) DDQ, CH_2Cl_2/H_2O, rt (99%).

These compounds involve very large-sized and peculiar macrocyclic lactone moieties, however, there are only a few reports discussing the chemical production of this type of giant-sized lactone to the best of our knowledge. In addition, only a very small amount of these lactones have been isolated from the termites, therefore, absolute configurations of these lactones as well as their optical rotations have not yet been determined.

In this section, we report the effective syntheses of 2-hydroxytetracosanolide (**77**) and 2-hydroxy-24-oxooctacosanolide (**78**) using the MNBA lactonization protocol as part of our continuous efforts to apply new synthetic methodologies to produce biologically active macrolactones.

8.1 Total Synthesis of 2-Hydroxytetracosanolide. First, (*S*)-malic acid was converted into the corresponding triol by reduction with $BH_3 \cdot SMe_2$ in the presence of $B(OMe)_3$ according to the literature method (Scheme 13).[52] The triol was protected as its PMP acetal, and the resulting primary alcohol was transformed into the TBDPS ether **79**. Reductive cleavage of the PMP acetal moiety of **79** with DIBAL regioselectively produced a primary alcohol **80**, and then the hydroxy group in **80** was converted to iodine.

The coupling reaction between **81** and Grignard reagent $TBSO(CH_2)_{10}MgBr$ (**C**) was then tried in the presence of the complex consisting of CuI and 2,2′-bipyridyl, and the desired 14-carbon segment **82** was successfully obtained in high yield.[53] After cleaving the TBS group of **82**, the resulting hydroxy group was replaced with iodine. The successive cross-coupling of **83** with Grignard reagent **C** was carried out again under reaction conditions similar to those of step (f) to afford the 24-carbon segment **84**.

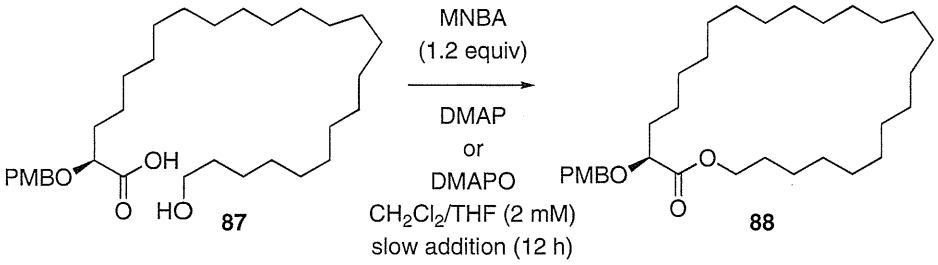
Further conversion of the linear molecule **84** into the precursor of lactone **77** was then examined. First, the TBS group was deprotected to form the corresponding alcohol **85**, and it was then acetylated to produce the intermediate **86**. After cleaving the TBDPS group using TBAF, the generated alcohol was oxidized to the corresponding carboxylic acid with 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical (TEMPO). Methanolysis of the acetyl moiety with K_2CO_3 gave the desired seco-acid **87**. Next, optimization of the reaction conditions for the lactonization of **87** was carried out as shown in Table 4.

When a solution of **87** in THF was slowly added to the reaction mixture of 1.2 equivalents of MNBA, 0.2 equivalents of DMAP, and 3.0 equivalents of triethylamine in dichloromethane over a 12 h period at 50 °C (bath temp.), the corresponding monomeric lactone **88** was obtained in 69% yield (Entry 1). Further examination using a stoichiometric amount of DMAP afforded a better yield (87%) of the desired lactone **88** (Entry 2). The catalytic use of DMAPO (0.2 equiv) with excess triethylamine (3.0 equiv) at room temperature or 50 °C also produced the cyclized product effectively, with reasonable yields of 63% and 76%, respectively (Entries 3 and 4). On the other hand, in the presence of an excess amount of DMAPO (3.0 equiv), the MNBA-mediated dehydration at 50 °C afforded the desired monomeric lactone **88** in a lower yield (53%) as shown in Entry 5. Thus, it was revealed that the use of 3.0 equivalents of DMAP or 0.2 equivalents of DMAPO with MNBA at a relatively high temperature is the most effective for the lactonization of the seco-acid **87** to provide the desired 25-membered lactone **88** (Entries 2 and 4).

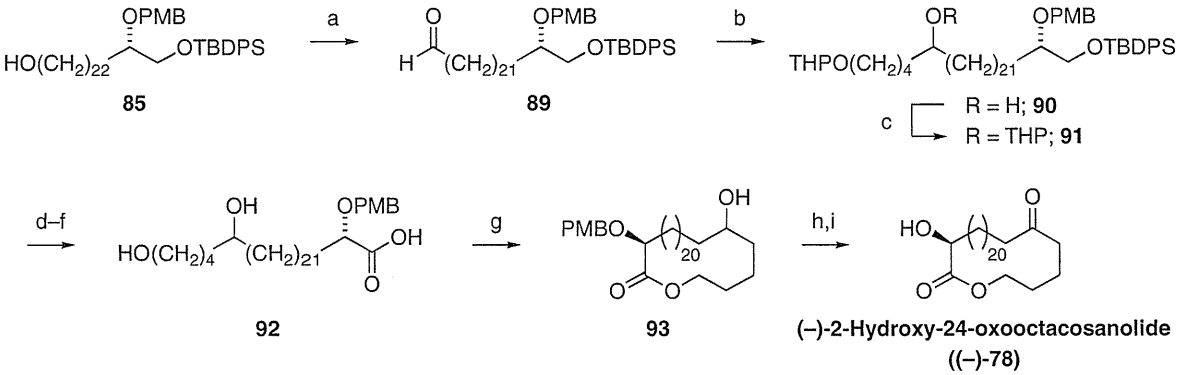
Finally, the PMB group of **88** was removed with DDQ to produce the targeted molecule, (*S*)-(−)-2-hydroxytetracosanolide ((−)-77), in high yield (Scheme 13). All spectral data including the ^1H and ^{13}C NMR chemical shifts and mass spectra of the synthetic (−)-77 corresponded to those of the natural 25-membered lactone.[50] (*R*)-(+)-2-Hydroxytetracosanolide ((+)-77) ($[\alpha]_D^{21} = +11.3$ (*c* 0.86, benzene)), an enantiomer of (−)-77 ($[\alpha]_D^{19} = -11.2$ (*c* 0.93, benzene)), was also prepared from the synthetic sample by Mitsunobu inversion with 3,5-dinitrobenzoic acid followed by debenzoylation. The enantiopurities of each compound were determined using their 3,5-dinitrobenzoate derivatives by HPLC attached to a chiral column.

8.2 Total Synthesis of 2-Hydroxy-24-oxooctacosanolide. The further conversion of the 24-carbon linear segment **85** into an elongated 28-carbon seco-acid **92** was then attempted as shown in Scheme 14. The formerly prepared primary alcohol

Table 4. Evaluation of the Efficiency of the Macrolactonization Using MNBA in the Synthesis of 25-Membered Lactone **88** from Seco-acid **87**



Entry	Catalyst	Co-Base	Temp./°C	Yield/%
1	DMAP (0.2 equiv)	Et_3N (3.0 equiv)	50	69
2	DMAP (3.0 equiv)	none	50	87
3	DMAPO (0.2 equiv)	Et_3N (3.0 equiv)	rt	63
4	DMAPO (0.2 equiv)	Et_3N (3.0 equiv)	50	76
5	DMAPO (3.0 equiv)	none	50	53



Scheme 14. Total synthesis of (−)-2-hydroxy-24-oxooctacosanolide ((−)-**78**). *Reagents and conditions*: (a) PCC, CH_2Cl_2, rt (85%); (b) $THPO(CH_2)_4MgBr$ (**D**), THF, 0 °C (81%); (c) DHP, TsOH, CH_2Cl_2, rt (86%); (d) TBAF, AcOH, THF, rt (96%); (e) TEMPO, $NaClO_2$, NaOCl, MeCN, CH_2Cl_2, 35 °C; (f) 1 M HCl, THF, rt (56%, 2 steps); (g) MNBA, DMAPO, Et_3N, CH_2Cl_2/THF, 50 °C (77%); (h) TPAP, NMO, MS 4 Å, CH_2Cl_2, 0 °C (94%); (i) DDQ, H_2O, CH_2Cl_2, rt (80%).

85 was oxidized with PCC to yield an aldehyde **89**, which was then treated with Grignard reagent $THPO(CH_2)_4MgBr$ (**D**) for the elongation of the 4-carbon unit on **89** to afford **90**. The resulting secondary alcohol **90** was protected as its THP ether. Deprotection of the terminal TBDPS group of **91** by the treatment with a mixture of TBAF and acetic acid smoothly occurred to give the corresponding primary alcohol, which was directly oxidized to form a carboxylic acid. Finally, deprotection of the two THP groups of the carboxylic acid was simultaneously achieved using hydrochloric acid to afford the diol **92**, the desired seco-acid, in good yield.

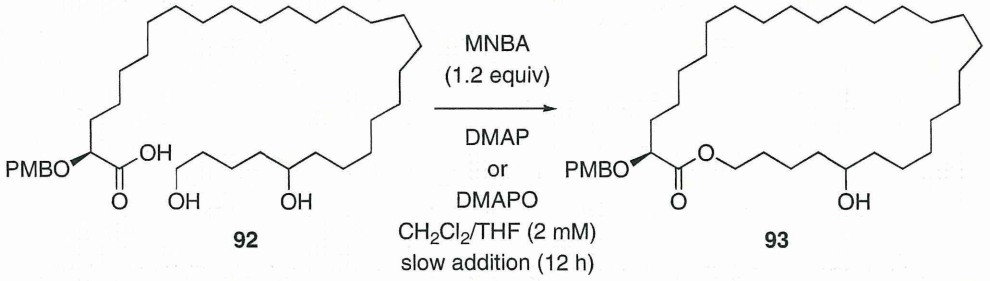
Optimization of the reaction conditions for the lactonization of **92** was eventually carried out as shown in Table 5. First, a solution of **92** in THF was slowly added to the reaction mixture containing 1.2 equivalents of MNBA and 0.2 or 3.0 equivalents of DMAP in dichloromethane over a 12 h period at 50 °C, and then the corresponding monomeric lactone **93** was obtained in a 64% or 69% yield, respectively (Entry 1 or 2).

On the other hand, when DMAPO was employed together with MNBA at room temperature, the yield of the desired monomeric lactone **93** decreased to only 29%, as shown in Entry 3. Although the stoichiometric use of DMAPO without triethylamine at 50 °C gave a significantly lower yield (38%, Entry 5), the yield of the 29-membered lactone **93** remarkably increased to 77% when the same reaction was carried out at 50 °C in the presence of a catalytic amount of DMAPO (0.2 equiv) with excess triethylamine (3.0 equiv) as described in Entry 4.

As a conclusion concerning the lactonization of **92**, it was revealed that the use of MNBA with either a stoichiometric amount of DMAP or a catalytic amount of DMAPO at 50 °C is the most effective combination for the lactonization of the seco-acid **92** to afford the desired 29-membered lactone **93** (Entries 2 and 4). These conditions, suitable for the production of the giant-size lactones **93**, are similar to those of the best reaction conditions for the synthesis of the 25-membered lactone **88** (Tables 4 and 5).

In order to compare the efficiency of this procedure for the key lactonization forming the 29-membered ring to that of the other generally effective protocols, two additional lactonizations were carried out. When the *S*-pyridyl ester method was applied to the cyclization of the seco-acid **92** using PySSPy and

Table 5. Evaluation of the Efficiency of the Macrolactonization Using MNBA in the Synthesis of 29-Membered Lactone **93** from Seco-acid **92**

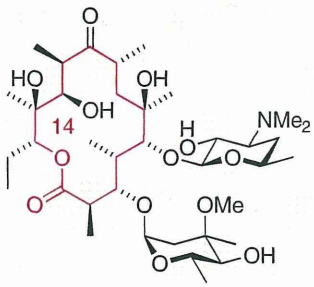


Entry	Catalyst	Co-Base	Temp./°C	Yield/%
1	DMAP (0.2 equiv)	Et_3N (3.0 equiv)	50	64
2	DMAP (3.0 equiv)	none	50	69
3	DMAPO (0.2 equiv)	Et_3N (3.0 equiv)	rt	29
4	DMAPO (0.2 equiv)	Et_3N (3.0 equiv)	50	77
5	DMAPO (3.0 equiv)	none	50	38

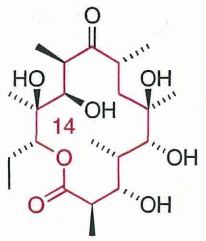
Ph_3P followed by slow addition to a gently refluxing toluene over 12 h under the standard reaction conditions (2.0 mM),[4] the desired lactone **93** was prepared in a low yield (35%). Furthermore, Yamaguchi lactonization also afforded the lactone **93** in 29% yield via the generation of the mixed-anhydride using 2,4,6-trichlorobenzoyl chloride with triethylamine although favorable conditions were employed for the ring-closing reaction of the mixed anhydride by slow addition to a solution of DMAP (3.0 equiv) in gently refluxing toluene over 12 h under highly dilute concentration (2.0 mM).[7]

The facile oxidation of **93** with TPAP/NMO was then carried out to produce a keto lactone, which was in turn converted to the final target molecule (*S*)-(−)-2-hydroxy-24-oxo-octacosanolide ((−)-**78**) by deprotection of the PMB group with DDQ/H_2O (Scheme 14). All spectral data, including the ^1H and ^{13}C NMR chemical shifts, IR absorption and mass spectra of the synthetic (−)-**78**, correspond to those of the natural 29-membered lactone.[51] The (−)-**78** ($[\alpha]_D^{21} = -9.6$ (*c* 0.96, benzene)) produced was further converted into its benzoate to determine the optical purity. Mitsunobu inversion of (−)-**78** with benzoic acid in the presence of DEAD and Ph_3P produced the corresponding antipode benzoate in good yield. HPLC analysis of the pair of enantiomers showed that these esters have very high enantiopurity (>99% ee). This result reveals that synthetic (−)-**78** and all of the other intermediates described in Scheme 14 have very high optical purities. Furthermore, (*R*)-(+)-2-hydroxy-24-oxooctacosanolide ((+)-**78**) ($[\alpha]_D^{22} = +9.54$ (*c* 0.44, benzene)), an enantiomer of (−)-**78**, was also produced by Mitsunobu inversion at the C-2 position with 3,5-dinitrobenzoic acid, followed by selective cleavage of the 3,5-dinitrobenzoate group.

Thus, the substituted benzoic anhydride method was successfully applied to the formation of the 25- and 29-membered lactones **88** and **93** in good yields under mild reaction conditions. The combination of MNBA, a powerful dehydrating reagent, with DMAP or DMAPO, a novel nucleophilic catalyst, functions as a very effective promoter for the intramolecular dehydration condensation that creates the giant cyclic cores of **77** and **78**. Based on these total syntheses, the structures of the basic skeletons of **77** and **78** proposed by Prestwich et al. and Braekman et al. have been unambiguously confirmed.[50,51]



(−)-Erythromycin A ((−)-94)



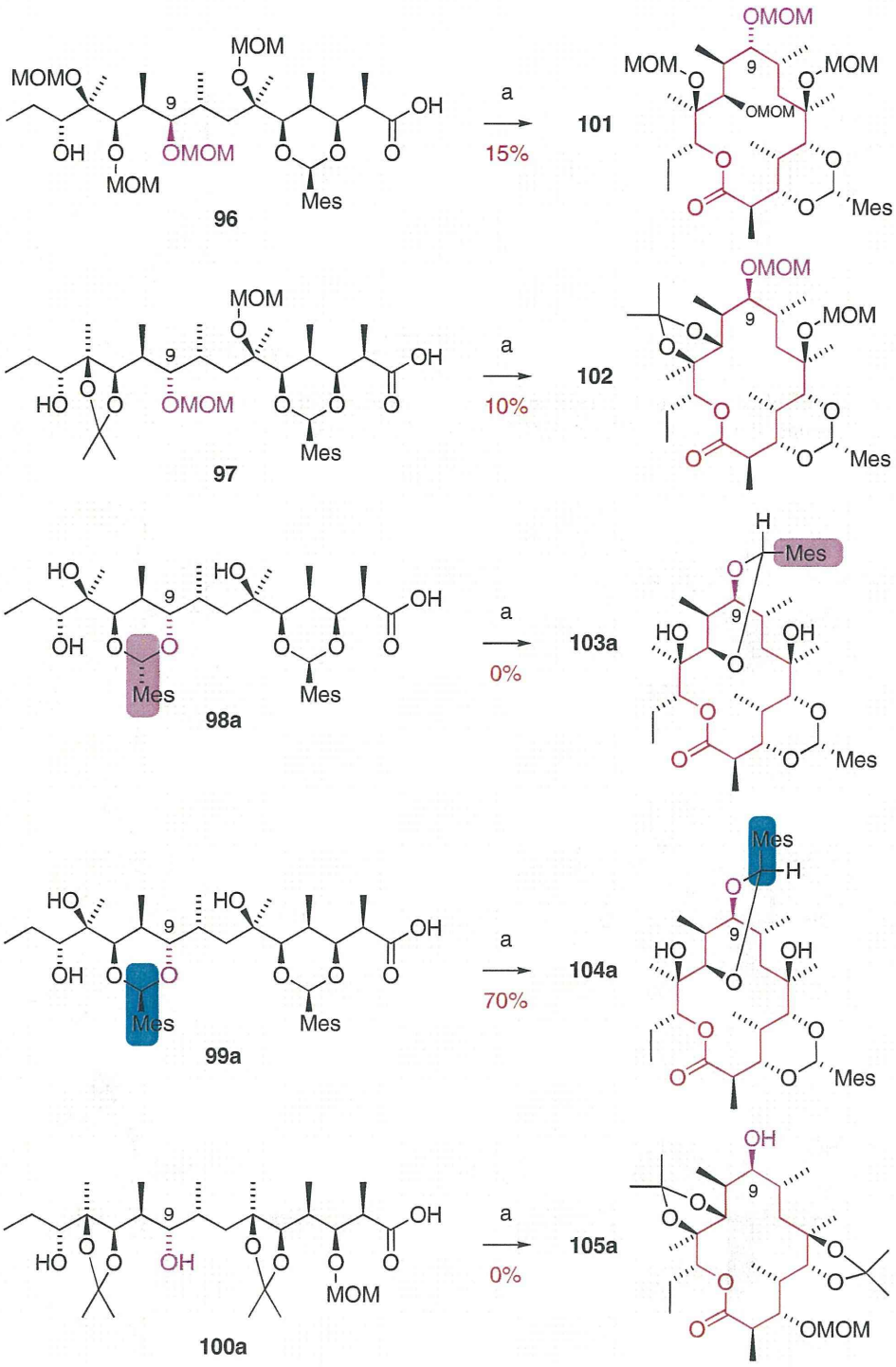
(−)-Erythronolide A ((−)-95)

Figure 7. Structures of (−)-erythrmycin A ((−)-**94**) and its aglycon, (−)-erythronolide A ((−)-**95**).

9. Evaluation of the Efficiency of the MNBA-Mediated Lactonization in the Synthesis of Erythromycin A Aglycon[54]

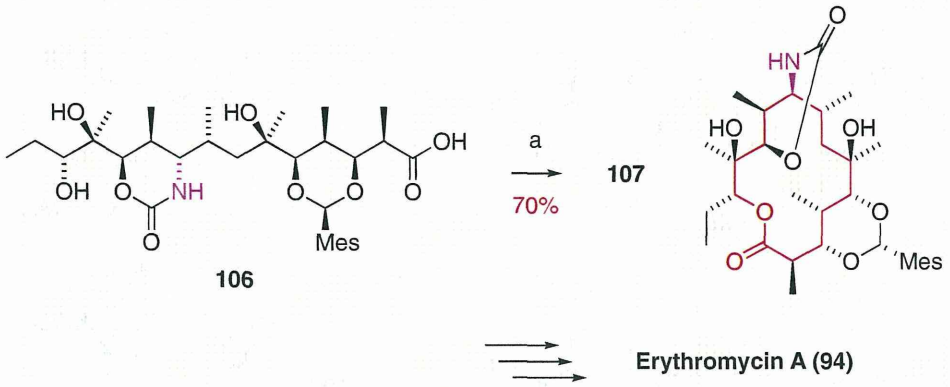
In 1981, Woodward et al. reported the total synthesis of (−)-erythromycin A ((−)-**94**, Figure 7)[55] via the effective construction of the lactone moiety using *S*-pyridyl ester method.[4] On the other hand, the total synthesis of (−)-erythronolide A ((−)-**95**) had been accomplished by Corey et al. in 1979 utilizing the double-activation method through a thiol ester intermediate.[56,57] These successful syntheses of (−)-**94** and (−)-**95** were monumental studies in the field of organic synthesis and the associated methodologies including the lactonization protocol represented significant developments in synthetic reaction technology.

In order to explore the synthetic pathway to access to (−)-erythromycin A ((−)-**94**), Woodward et al. attempted to prepare several kinds of model seco-acids by the degradation of **94** via two intermediates, (9*R*)-dihydroerythronolide A and (9*S*)-dihydroerythronolide A, and then the resulting seco-acids underwent macrocyclization using the *S*-pyridyl ester method as shown in Scheme 15. Very interesting results were

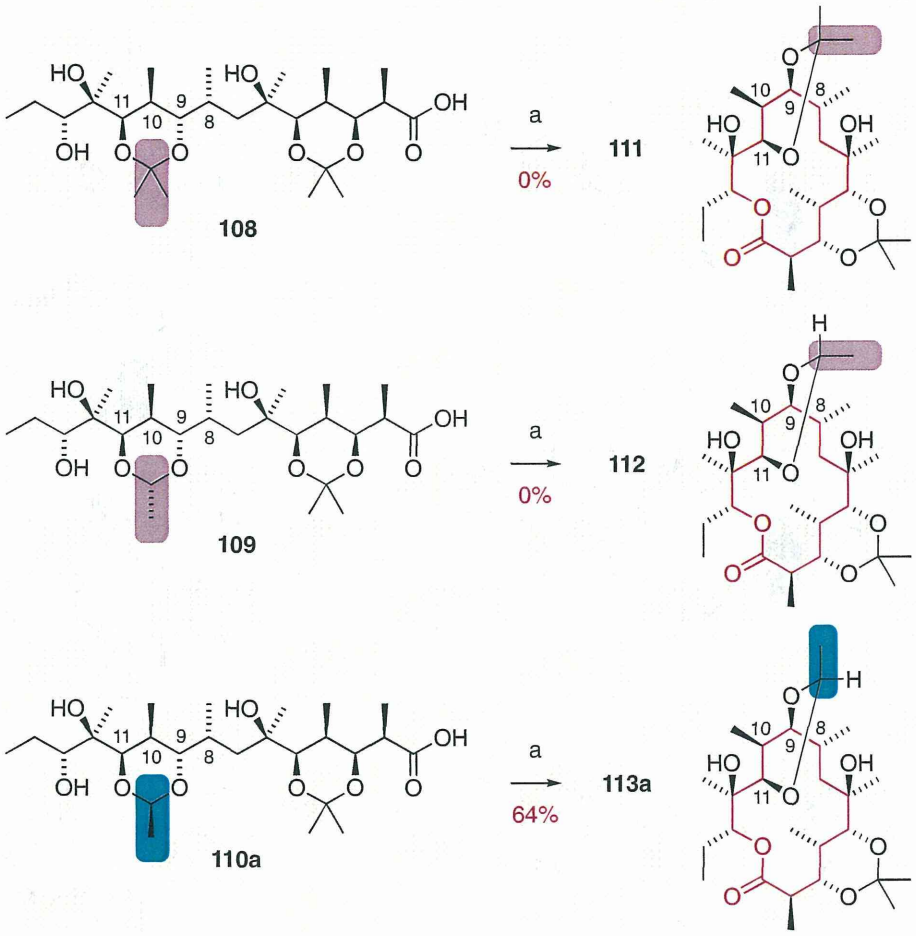


Scheme 15. Woodward's macrocyclization studies for the synthesis of polyoxy 14-membered lactones using the *S*-pyridyl ester method. *Reagents and conditions*: (a) (i) ClCOS-2-Py, Et_3N, CH_2Cl_2, 0 °C; (ii) xylene, 140 °C (Yields for the second steps were shown.).

obtained from their lactonization experiments; that is, only three compounds **96**, **97**, and **99a** afforded the desired lactones **101**, **102**, and **104a** in 15%, 10%, and 70% yields, respectively, from the corresponding *S*-pyridyl esters, although other substrates, such as **98a** and **100a**, did not produce the desired lactones **103a** and **105a** at all. They assumed that these structural requirements for the facile ring-closure of the thiol ester intermediates probably arise from the conformational properties of the substrates, which were derived from the absolute configurations at the C-9 position as well as other combinations of the protective groups masking the hydroxy groups in the seco-acids.



Scheme 16. Completion of Woodward's total synthesis of (−)-erythromycin ((−)-**94**) by the effective lactonization via **106** to form **107**. *Reagents and conditions*: (a) (i) ClCOS-2-Py, Et_3N, CH_2Cl_2, 0 °C; (ii) toluene, 110 °C (Yield for the second step was shown.).



Scheme 17. Stork's macrocyclization studies for the synthesis of (−)-erythronolide A ((−)-**95**) using Keck method. *Reagents and conditions*: (a) DCC, DMAP·TFA, $CHCl_3$/THF, reflux.

Based on the assumption from the experimental results, they newly designed a seco-acid **106**, which might have a suitable structure for the facile cyclization (Scheme 16). Actually, the lactonization of the *S*-pyridyl ester generated from **106** smoothly proceeded at 110 °C in toluene to afford the desired product **107** in 70% yield. The (9*S*)-amino analogue of erythronolide **107** was successfully transformed into the appropriate glycosyl donor for couplings with sugar segments and finally converted into the targeted molecule, (−)-erythromycin A ((−)-**94**) by Woodward et al. in 1981.[55]

In 1987, Stork and Rychnovsky revealed the origin of the efficiency for the cyclization to afford the (9*S*)-dihydroerythronolide A backbone by the conformational analysis of the precursors and products (Scheme 17).[58] Systematic studies

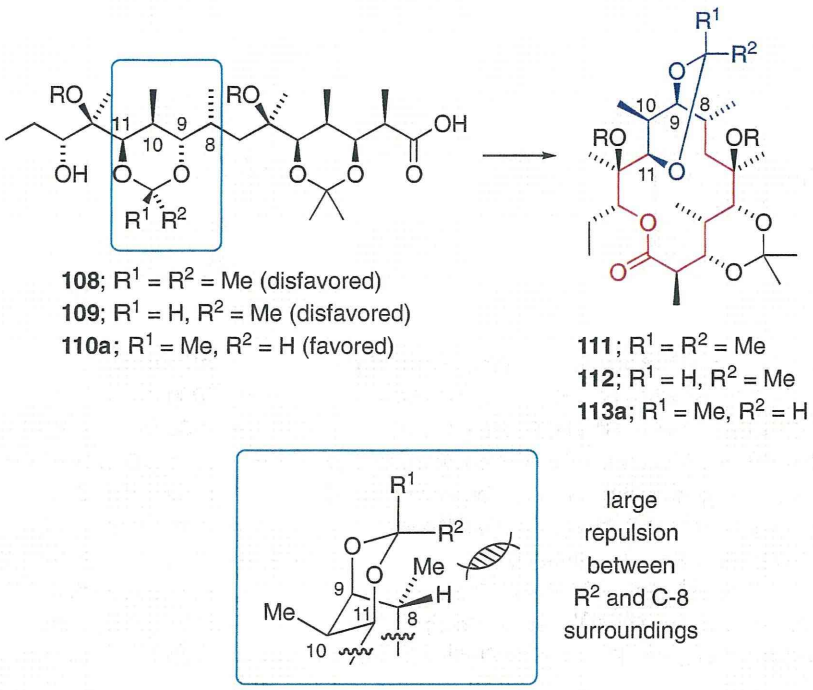
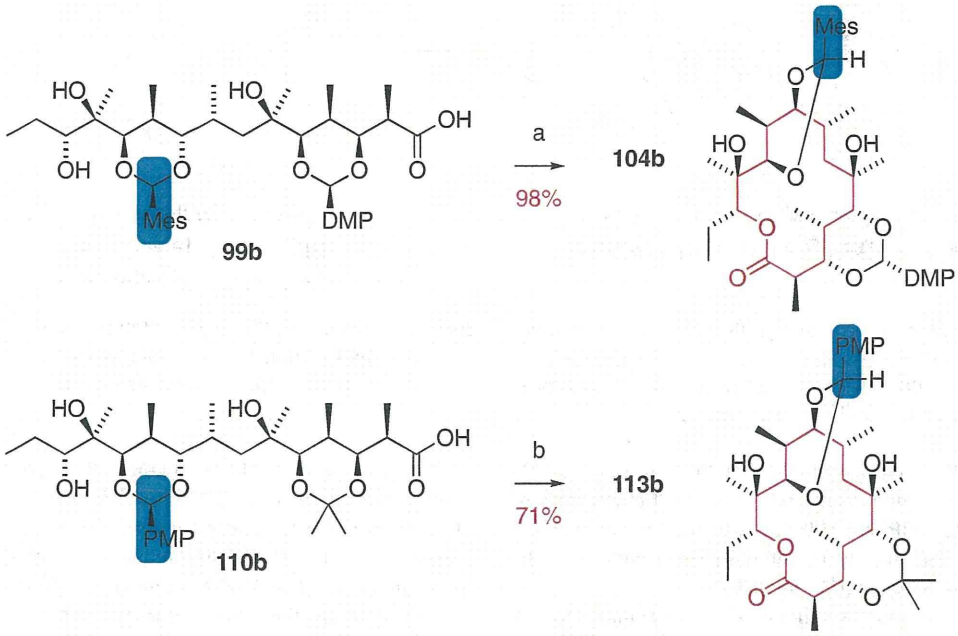


Figure 8. Stork's rationalization of the efficiency of the macrolactonization using seco-acids **108**, **109**, and **110a** to form **111**, **112**, and **113a**.



Scheme 18. Yonemitsu's and Kochetkov's macrocyclization studies for the synthesis of (−)-erythronolide A ((−)-**95**) using the Yamaguchi and Corey methods. *Reagents and conditions*: (a) (i) 2,4,6-trichlorobenzoyl chloride, Et_3N, xylene, rt; (ii) DMAP, xylene, rt (98%); (b) (i) di(4-^{t}Bu-1-^{i}Pr-imidazol-2-yl) disulfide, Ph_3P, toluene, rt; (ii) toluene, reflux (71%).

on the structure of the cyclic compounds suggested that the close proximity of R^2 to the C-8 surroundings produced a very large 1,3-diaxial repulsion and severe presentation of the ring-forming reaction as depicted in Figure 8.

According to this structural analysis, the difficulty of the cyclization using seco-acids **108** ($R^1 = R^2 = Me$) and **109** ($R^1 = H$, $R^2 = Me$) to form the corresponding lactones **111** and **112**, respectively, was logically induced. Actually, only the cyclization of **110a** ($R^1 = Me$, $R^2 = H$) under Keck's conditions[8] using *N*,*N*′-dicyclohexylcarbodiimide (DCC) and DMAP·trifluoroacetic acid (TFA) could take place to produce the corresponding 14-membered lactone **113a** in good yield

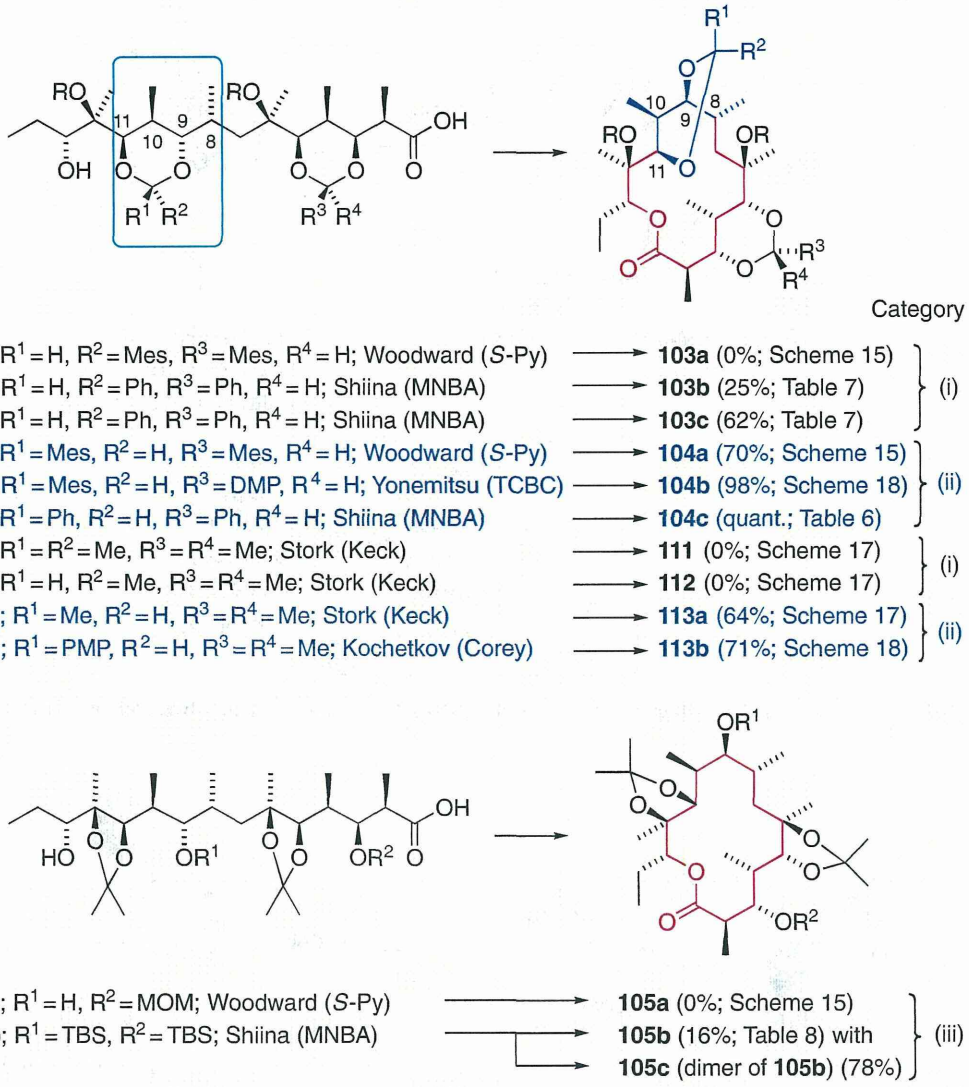


Figure 9. Systematical analysis of the macrocyclization to produce the protected (9*S*)-dihydroerythronolide A. Category (i); conformationally unfavorable substrates for cyclization, Category (ii); conformationally favorable substrates for cyclization, Category (iii); conformationally unfavorable substrates for monomeric cyclization (In the reactions using *S*-pyridyl ester method, yields for the cyclization steps were shown.).

(64%) because **110a** had a suitable structure around the C9–C11 portion for the ring-closure, whereas macrocyclization of the other substrates **108** and **109** failed to produce the desired lactones **111** and **112** due to the unfavorable structures of the C9–C11 acetal moieties in **108** and **109**.

Furthermore, the total syntheses of (−)-erythronolide A ((−)-**95**) were accomplished by Yonemitsu et al.[7c,7d,59] and Kochetkov et al.[60] as shown in Scheme 18 via the effective formation of the 14-membered lactones **104b** and **113b** starting from seco-acids **99b** (R^1 = Mes, R^2 = H; corresponding to substituents in Figures 8 and 9) and **110b** (R^1 = PMP, R^2 = H), which have similar structures to those of **99a** (R^1 = Mes, R^2 = H) and **110a** (R^1 = Me, R^2 = H). In the former cyclization, the desired lactone **104b** was easily obtained in 98% yield from the seco-acid **99b** by the modified Yamaguchi lactonization,[7] and the later ring-closure reaction was also successfully carried out using Corey's improved double-activation method[56,57] through a thiol ester intermediate generated from **110b** to provide the corresponding lactone **113b** in 71% yield. Advanced theoretical studies of the conformations of seco-acids for the facile lactonization based on the molecular mechanics calculation were also carried out by Yonemitsu and Ōsawa.[61]

Founded on the above history and background of the developments for the lactonization during the synthesis of the aglycons of (−)-erythromycin A ((−)-**94**), we selected four typical seco-acids **98b**, **98c**, **99c**, and **100b** as precursors of lactones **103b**, **103c**, **104c**, and **105b** for the evaluation of the efficiency of our lactonization protocol (Scheme 19).

The reaction facilities using these compounds for the cyclization are categorized as shown in Figure 9. The seco-acids **98b** and **98c** (R^1 = H, R^2 = Ph) have unfavorable structures for the cyclization as well as **98a** (R^1 = H, R^2 = Mes) and therefore the lactonization of **98b** and **98c** might be prevented by the conformational disadvantage to produce **103b** and **103c**