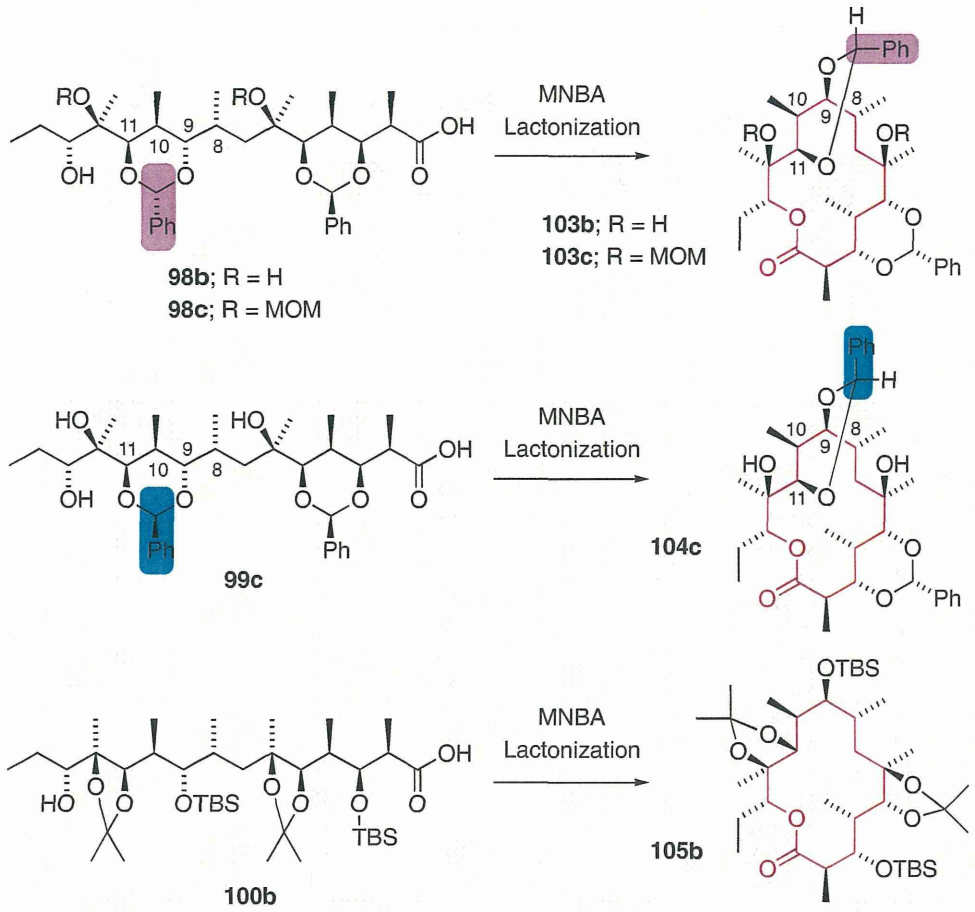
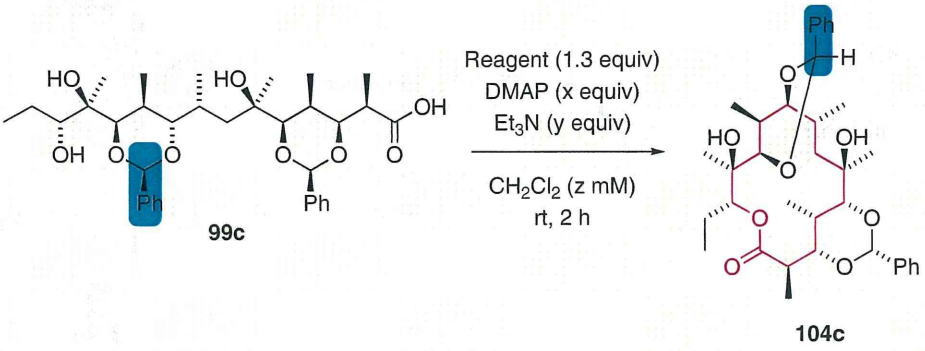


Scheme 19. The present studies for the synthesis of the erythronolide A skeleton **103b**, **103c**, **104c**, and **105b** from seco-acids **98b**, **98c**, **99c**, and **100b** using the MNBA-mediated lactonization.

due to the generation of the 1,3-diaxial repulsion between the phenyl substituent and C-8 surroundings of the aglycon (Category (i), see Figure 9 for the definition). On the other hand, the seco-acid **99c** (R^1 = Ph, R^2 = H) has a structure similar to those of **99a** and **99b** (R^1 = Mes, R^2 = H), and easy cyclization might be attained when we use **99c** as a precursor of the lactone **104c** because **99c** should have a suitable conformation to produce the desired monomeric lactone **104c** (Category (ii)). Furthermore, according to the pioneering research of Woodward, **100b** is placed in the same category as **100a** so that there would be a considerable difficulty to cyclize **100b** to form the corresponding lactone **105b** (Category (iii)). In this section, we disclose very interesting results for the lactonization of **98b**, **98c**, **99c**, and **100b** by promotion using MNBA in the presence of DMAP with or without triethylamine.

9.1 Synthesis of Macrolide 104c from Seco-acid 99c Using MNBA-Mediated Lactonization. Because it had been anticipated that the reaction of the seco-acid **99c** rapidly proceeded on the basis of other reports (vide supra), we directly added **99c** in one portion to a solution of 1.3 equivalents of MNBA, 0.2 equivalents of DMAP, and 2.6 equivalents of triethylamine in dichloromethane (5 mM) at room temperature, and fortunately, the reaction smoothly proceeded to produce the desired monomeric lactone **104c** in quite high yield (95%) as shown in Entry 1 (Table 6). Other results of the lactonization forming **104c** starting from **99c** using a symmetric anhydride as the coupling reagent are summarized in the same table. The yield increased to quantitative after a 2 h stirring of the reaction mixture using an excess amount of triethylamine (Entry 2), however, a medium yield (64%) was observed by quenching the lactonization after 10 min (Entry 3); therefore, we noticed that the catalytic use of DMAP required a sufficient time for regeneration of the promoter during the reaction process. Other coupling reagents, such as TFBA and 4-nitrobenzoic anhydride (PNBA),[62] also provided the monomeric lactone **104c** in reasonable yields, but the highest yield was expectedly attained by the MNBA-promoted reaction (Entries 4–7; cf. 2). In order to determine the necessity of requiring DMAP in this reaction, we examined the lactonization without using DMAP, and the formation of only a trace amount of **104c** was detected in this case (Entry 8). On the other hand, the use of 6.0 equivalents of DMAP afforded the desired lactone **104c** in quantitative yield after 2 h (Entry 9). Furthermore, the starting material rapidly disappeared after 10 min when using 6.0 equivalents of DMAP, and the corresponding lactone **104c** was obtained in 94% yield by this simple operation (Entry 10). It is noteworthy that the present method is applicable to a large-scale synthesis, from which the desired macrolactone **104c** was isolated in 97% yield

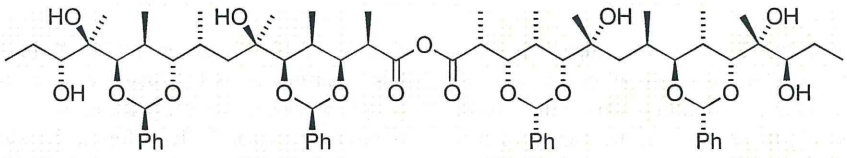
Table 6. Synthesis of Lactone **104c** from Seco-acid **99c** Using MNBA-Mediated Cyclization



99c **104c**

Entry	Reagent	*x*	*y*	*z*	Yield[a]/% **104c**	Recovery[a]/% **99c**
1	MNBA	0.2	2.6	5.0	95	0
2	MNBA	0.2	6.0	5.0	quant.	0
3[b]	MNBA	0.2	6.0	5.0	64	0
4	TFBA[d]	0.2	6.0	5.0	92	0
5	PNBA[e]	0.2	6.0	5.0	90	0
6	Bz_2O	0.2	6.0	5.0	30	21 (49)[f]
7	Piv_2O	0.2	6.0	5.0	7	32 (42)[f]
8	MNBA	0	6.0	5.0	2	49 (16)[f]
9	MNBA	6.0	0	5.0	quant.	0
10[b]	MNBA	6.0	0	5.0	94	0
11[c]	MNBA	0.2	6.0	5.0	97	0
12	MNBA	0.2	6.0	10	95	0
13	MNBA	0.2	6.0	20	91	0
14	MNBA	0.2	6.0	50	89	0
15	MNBA	0.2	6.0	100	74	0

a) Isolated yield. b) Reaction time; 10 min. c) A large amount of **99c** (2.0 g) was used as a substrate for the lactonization. d) TFBA: 4-trifluoromethylbenzoic anhydride. e) PNBA: 4-nitrobenzoic anhydride. f) Data in parentheses show yield of homogeneous anhydride of **99c**.

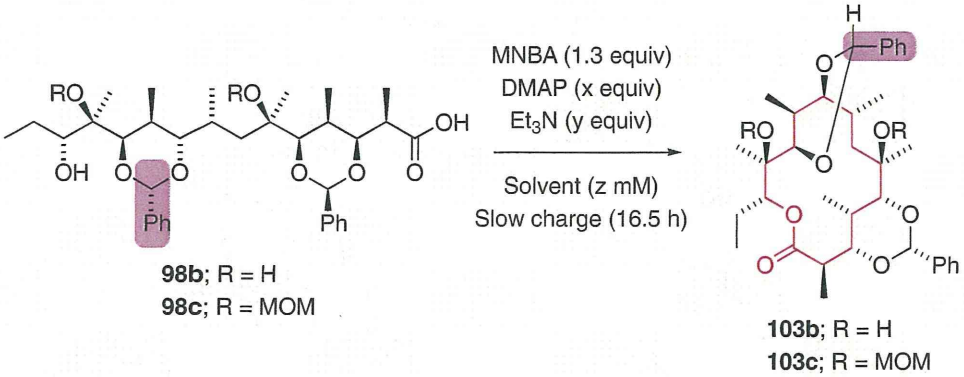


homogeneous anhydride of **99c**

starting from 2 g of the seco-acid **99c** in the presence of 1.3 equivalents of MNBA, 0.2 equivalents of DMAP, and 6.0 equivalents of triethylamine as shown in Entry 11. The yields of **104c** gradually decreased in accordance with the increasing concentrations of the reaction as shown in Entries 12–15.

9.2 Synthesis of Macrolides 103b and 103c from Seco-acids 98b and 98c Using MNBA-Mediated Lactonization. We next examined the cyclization of seco-acids **98b** and **98c**, which have unfavorable conformations for the formation of the corresponding lactone linkage. In these cases for the preparation of the corresponding lactones **103b** and **103c**, we gradually added a solution of the substrates to a mixture of the reaction promoters using a syringe pump to keep the reactants in low concentrations. However, the desired lactone **103b** was obtained in only 3% yield when the reaction was carried out at room temperature in dichloroethane as the solvent (Table 7, Entry 1). The yield of **103b** was not drastically improved by changing the reaction temperature and solvent as shown in Entry 2 because of the decomposition of **98b**, therefore, we decided to use the more stable seco-acid **98c**, in which the tertiary hydroxy groups are protected as their MOM ether forms. As shown in Entry 3, in the presence of an excess amount of DMAP (6.0 equiv) without using triethylamine, the reaction of **98c** proceeded at room temperature, but unfortunately the lactone **103c** was produced in an unsatisfactory yield (11%). Next, the reaction temperature was increased to 70, 100, and 120 °C in toluene solution, and it was found that the yields of the lactone **103c** were gradually improved to 32, 57, and 55%, respectively (Entries 4–6). The concentration of DMAP in the reaction mixture was then optimized as shown by Entries 7 and 8, and the yield of the targeted lactone **103c** finally reached an acceptable yield (62%, Entry 8). Woodward et al. reported the failure of the cyclization of the seco-acid **98a** ($R^1 = H$, $R^2 = Mes$) in Scheme 15 to produce the lactone

Table 7. Synthesis of Lactones **103b** and **103c** from Seco-acids **98b** and **98c** Using MNBA-Mediated Cyclization



98b; R = H
98c; R = MOM

103b; R = H
103c; R = MOM

Entry	*x*	*y*	*z*	Solvent	Temp./°C	Seco-acid/lactone	Yield[a]/% **103b** or **103c**
1	0.2	6.0	1.8	CH_2Cl_2	rt	**98b**/**103b**	3
2	0.2	6.0	1.8	toluene	100	**98b**/**103b**	25
3	6.0	0	1.8	CH_2Cl_2	rt	**98c**/**103c**	11
4	6.0	0	1.8	toluene	70	**98c**/**103c**	32
5	6.0	0	1.8	toluene	100	**98c**/**103c**	57
6	6.0	0	1.8	toluene	120	**98c**/**103c**	55
7	6.0	0	0.9	toluene	100	**98c**/**103c**	48
8	12.0	0	0.9	toluene	100	**98c**/**103c**	62

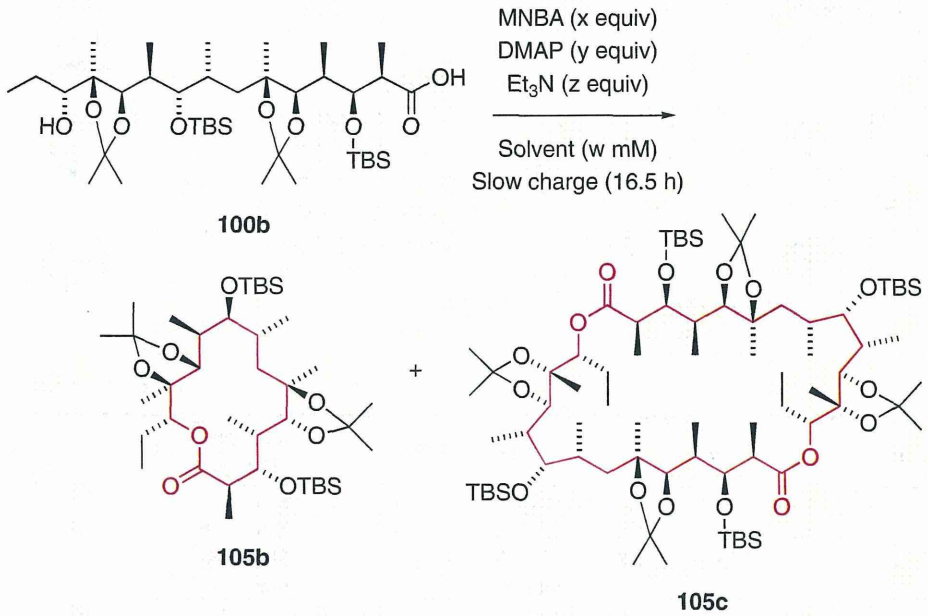
a) Isolated yield.

103a, and Stork et al. also found that the lactonization of the seco-acid **109** (R^1 = H, R^2 = Me) in Scheme 17 did not take place at all due to the severe steric repulsion among the R^2 group and neighboring functionalities near the C-8 position. It is noteworthy that the desired lactone **103c** was produced in a relatively good yield (62%) from **98c** (R^1 = H, R^2 = Ph) using the MNBA protocol, although the structure of the present seco-acid **98c** is similar to those of **98a** and **109**.

9.3 Synthesis of Macrolide 105b and Diolide 105c from Seco-acid 100b Using MNBA-Mediated Lactonization. Our attention next focused on the lactonization of the seco-acid **100b**, which is also one of the challenging substrates, to form the corresponding lactone **105b** because Woodward reported that cyclization of **100a** (Scheme 15) did not give the desired compound. Indeed, highly dilute conditions using the slow charge method of the substrate **100b** to the reaction mixture containing 1.3 equivalents of MNBA, 0.2 equivalents of DMAP, and 6.0 equivalents of triethylamine in dichloromethane (1.8 mM) at 45 °C did not produce the monomeric lactone **105b**, but the corresponding 28-membered diolide **105c** was obtained in 18% yield along with the formation of a significant amount (43%) of a symmetric anhydride of seco-acid **100b** (Table 8, Entry 1). We used an excess amount of DMAP (6.0 equiv) instead of employing triethylamine in this reaction, and observed the formation of the monomeric lactone **105b** in 4% yield with the 30% formation of the dimer **105c** and 10% yield of the anhydride derived from **100b** (Entry 2). Further studies of the reaction in toluene solution at higher temperatures as shown in Entries 3–5 showed an improvement in the total yields of **105b** and **105c** up to 87% at 120 °C in the presence of a greater excess amount of DMAP (Entry 5). The final optimization of the concentrations of DMAP during the cyclization afforded the corresponding lactone **105b** in 16% yield with the diolide **105c** in 78% yield (Entry 8), and the total yield of the cyclized compounds reached 94%. Based on the above experimental results, it is postulated that the substrates **100a** and **100b** might possess stable linear conformations and their structures are not appropriate for forming the monomeric lactones, but suitable to produce the corresponding diolides. These tendencies of the substrates, which give dimers as the major products, depend on the nature of the seco-acid structures, and therefore, we could determine that controlling the ratio of the monomer to dimer is impossible by modification of the reaction conditions. This important but overlooked principle of the lactonization using the **100b**-type seco-acids to provide the aglycons of erythromycin A is first disclosed in this report based on the studies of the rapid ring-closure reaction using MNBA, an ultimately effective coupling reagent.

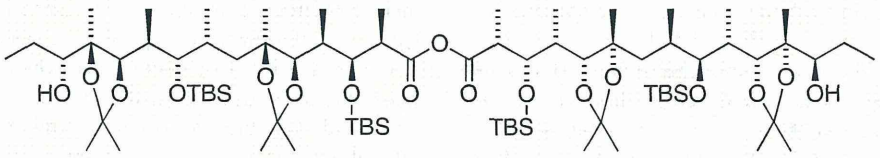
In summary, various intermediates for the synthesis of (−)-erythronolide A ((−)-**95**), an aglycon of (−)-erythromycin A ((−)-**94**), are prepared from the corresponding seco-acids using MNBA in the presence of DMAP with or without triethylamine. The efficiency of the MNBA-mediated lactonization is assessed by studying this method and comparing the results with those of the other established macrocyclization protocols. It has been finally concluded that (i) the conformationally appropriate substrate for the monomeric cyclization, such as **99c**, gave the desired lactone in excellent yield under mild reaction conditions in the presence of MNBA and DMAP, (ii) the highly-strained substrate for the cyclization, such as **98c**, also afforded the monomeric lactone in relatively good yield at 100 °C in toluene, and (iii) the seco-acid having a

Table 8. Syntheses of Lactone **105b** and Diolide **105c** from Seco-acid **100b** Using MNBA-Mediated Cyclization



Entry	*x*	*y*	*z*	*w*	Solvent	Temp./°C	Yield[a]/%		Recovery[a]/%
							105b	**105c**	**100b**
1	1.3	0.2	6.0	1.8	CH_2Cl_2	45	0	18	27 (43)[b]
2	1.3	6.0	0	1.8	CH_2Cl_2	45	4	30	26 (10)[b]
3	3.0	6.0	0	1.8	toluene	80	14	28	30 (6)[b]
4	3.0	6.0	0	1.8	toluene	120	13	69	4 (4)[b]
5	3.0	20.0	0	1.8	toluene	120	14	73	0 (4)[b]
6	3.0	20.0	0	0.9	toluene	120	16	56	0 (18)[b]
7	10.0	20.0	0	0.9	toluene	120	16	73	0
8	10.0	20.0	0	0.36	toluene	120	16	78	0

a) Isolated yield. b) Data in parentheses show yields of homogeneous anhydride of **100b**.



homogeneous amhydride of **100b**

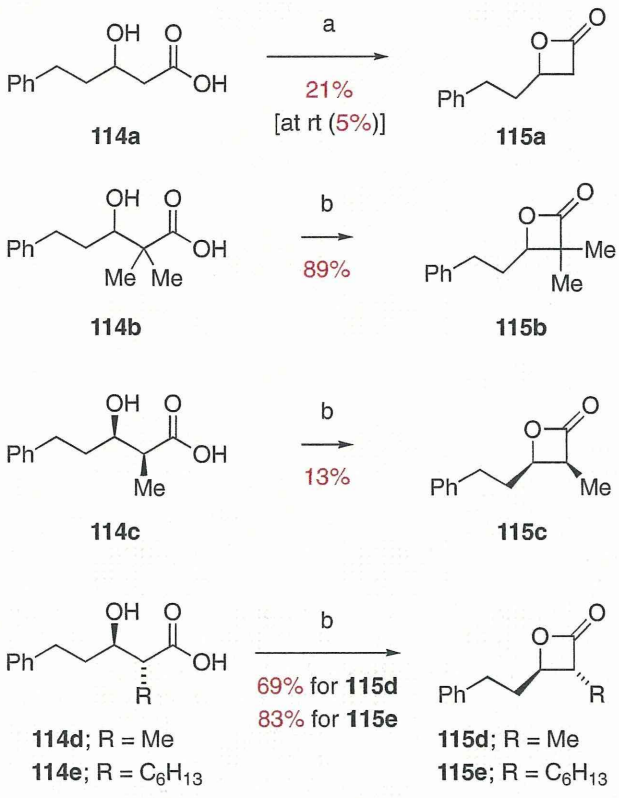
stable linear conformation, such as **100b**, which preferred dimerizing more than forming a monomeric lactone, provided the corresponding diolide in high yield with a reasonable chemoselectivity (monomer/dimer = ca. 1/5). It might absolutely depend on the reaction rates of the macrocyclization corresponding to the ring size of the 14- and 28-membered lactones.

10. Total Synthesis of Tetrahydrolipstatin (THL) and Theoretical Studies of the MNBA-Mediated β-Lactone Forming Reactions[63]

Although large and medium ring compounds could be practically synthesized from the corresponding seco-acids by the MNBA-mediated lactonization as shown in former instances, it is pointed out that there still has been no report on the production of small ring compounds, such as 3- or 4-membered lactones, using MNBA. Therefore, we next examined to determine the efficiency of the MNBA-mediated lactonization for the preparation of 4-membered compounds (β-lactones) starting from the corresponding β-hydroxycarboxylic acids by this intramolecular dehydration coupling technology.[64]

10.1 Systematic Studies of the Generation of the 4-Membered Ring Compounds by the MNBA-Mediated Lactonization. First, 3-hydroxy-5-phenylpentanoic acid (**114a**), which was prepared from 3-phenylpropanal with ethyl acetate by the aldol reaction, was treated with MNBA and DMAP to provide the corresponding monosubstituted β-lactone **115a** in 21% yield under the forced reaction conditions (Scheme 20). On the other hand, we fortunately obtained a trisubstituted β-lactone **115b** in excellent yield when 3-hydroxy-2,2-dimethyl-5-phenylpentanoic acid (**114b**) was used as the substrate (89%). In the latter reaction, the Thorpe–Ingold effect might dramatically increase the reaction rate of the cyclization of the β-hydroxycarboxylic acid **114b** including a

gem-dimethyl group at the α-position of the carbonyl group.[65] Next, stereoisomeric β-hydroxycarboxylic acids **114c** and **114d** were synthesized from *syn*- and *anti*-aldols derived from 3-phenylpropanal with propanoic acid derivatives, and these seco-acids were subjected to the MNBA lactonization protocol. A significant difference between the reactivities of **114c** and **114d** was observed and the desired diastereomers of the β-lactones **115c** and **115d** (R = Me for **115d**) were obtained from **114c** and **114d** in 13% and 69% yields, respectively. It is easily anticipated that the formation of the transition structure for the *cis*-2,3-disubstituted 4-membered ring in **115c** is more disfavored because of steric repulsion between substituents at the C-2 and C-3 positions compared to the formation of the transition structure for the *trans*-2,3-disubstituted 4-membered ring in **115d**. We also discovered that the *anti*-β-hydroxycarboxylic acid **114e**, possessing a longer alkyl chain at the α-position, is more preferable for the formation of the *trans*-2,3-disubstituted β-lactone **115e**, and a higher yield was attained for the synthesis of **115e** from **114e** using the MNBA-mediated lactonization (83%, R = C_6H_{13}).



Scheme 20. MNBA-mediated cyclization of β-hydroxycarboxylic acids **114a–114e** to form β-lactones **115a–115e**. *Reagents and conditions*: (a) MNBA, DMAP, Et_3N, CH_2Cl_2/THF, 50 °C; (b) MNBA, DMAP, Et_3N, CH_2Cl_2, rt.

10.2 Asymmetric Total Synthesis of Tetrahydrolipstatin (THL). (−)-Tetrahydrolipstatin ((−)-THL, (−)-**117**)[66,67] (Figure 10) including the *trans*-2,3-disubstituted β-lactone part has been used in the clinical treatment as an antiobestic drug called Orlistat™ or Xenical™, which effectively functions to inhibit the activity of pancreatic lipase. It is well known that the hydroxy group in the serine moiety in lipase reacts with the β-lactone residue in (−)-**117** or its original pharmacophore (−)-lipstatin ((−)-**116**) to form the corresponding ester, hence the reaction process of the lipase-catalyzed hydrolysis of triglycerides would be prevented in the presence of (−)-**117** in vivo.[68]

Based on the systematic studies for the generation of the 4-membered ring compounds as described in Subsection **10.1**, it was determined that *trans*-2,3-disubstituted or 2,2,3-trisubstituted β-lactones were easily generated from the corresponding seco-acids by the MNBA lactonization protocol. Therefore, we further planned the total synthesis of (−)-THL ((−)-**117**) including the *trans*-2,3-disubstituted β-lactone part according to our continuous efforts for the synthesis of useful organic molecules.

First, the racemic propargyl alcohol (±)-**118** was obtained from dodecanal with trimethylsilylacetylene according to the known conventional method via two steps including the alkynylation of dodecanal.[69] Then, the kinetic resolution of (±)-**118** using 3-phenylpropanoic acid (0.7 equiv) and pivalic anhydride (0.75 equiv) with 0.05 equivalents of (*S*)-benzotetramisole ((*S*)-BTM)[70,71] was attempted (Scheme 21, eq 1) to produce both the corresponding chiral ester (*S*)-**119** (56% ee) and the recovered chiral alcohol (*R*)-**118** (84% ee) in good yields (58% and 39%, respectively) with moderate enantioselectivities ($s = 9$).[72] We have already established the remarkable asymmetric esterification using diphenylacetic acid as an acyl donor with racemic 2-hydroxyesters[73] or 2-hydroxylactones[74] to afford the optically active compounds possessing excellent enantiopurities, therefore, we next tried to improve the selectivity of the kinetic resolution of the racemic propargyl alcohol (±)-**118** using diphenylacetic acid as an acyl donor instead of using 3-phenylpropanoic acid. Fortunately, the selective factor drastically improved and reached a higher value ($s = 34$) with the enhanced enantioselectivities of (*S*)-**120** (80% ee) and the recovered (*R*)-**118** (96% ee) in good yields (55% and 43%, respectively) when using diphenylacetic acid (eq 2). The multigram-scale synthesis of the optically pure (*R*)-**118** was also carried out by the kinetic resolution of a large amount of (±)-**118** (6.00 g) using diphenylacetic acid with

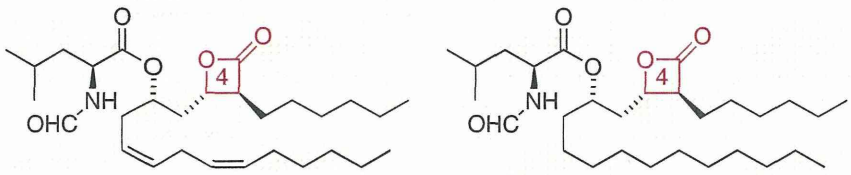
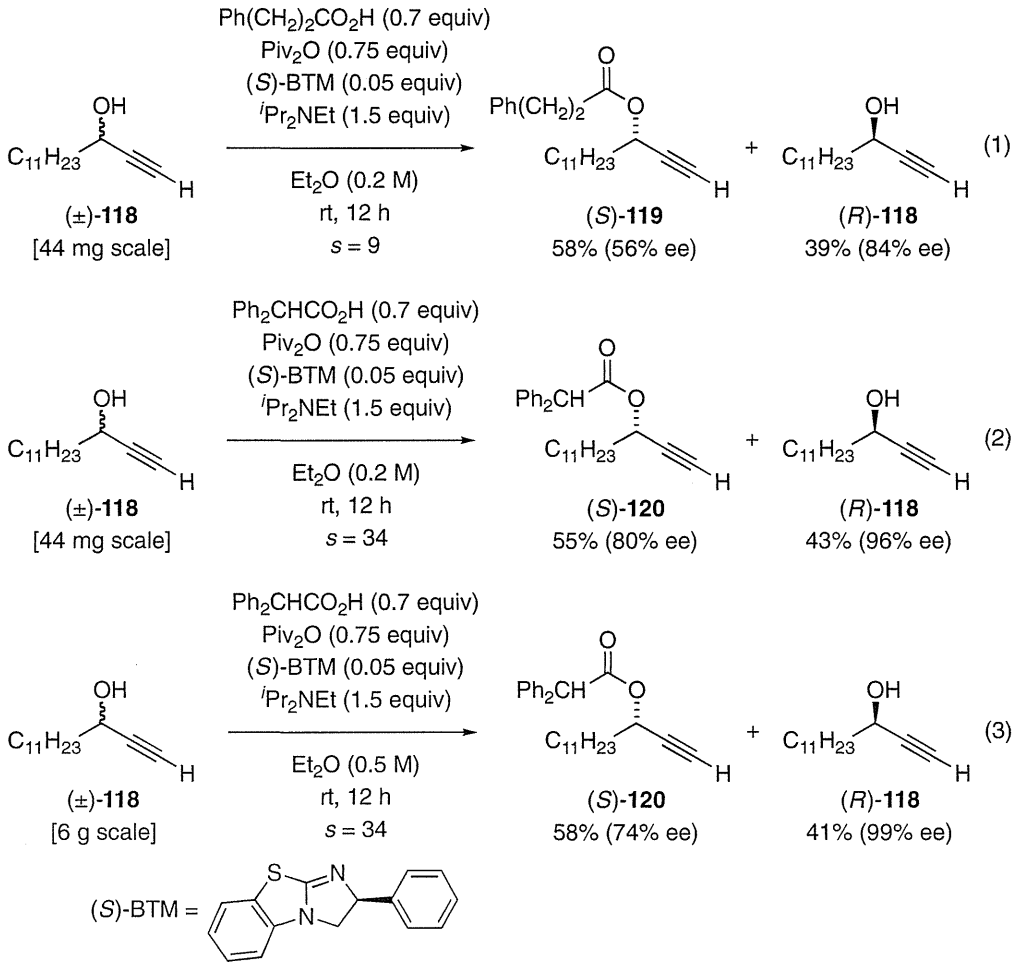


Figure 10. Structures of (−)-lipstatin ((−)-**116**) and (−)-tetrahydrolipstatin ((−)-THL, (−)-**117**).



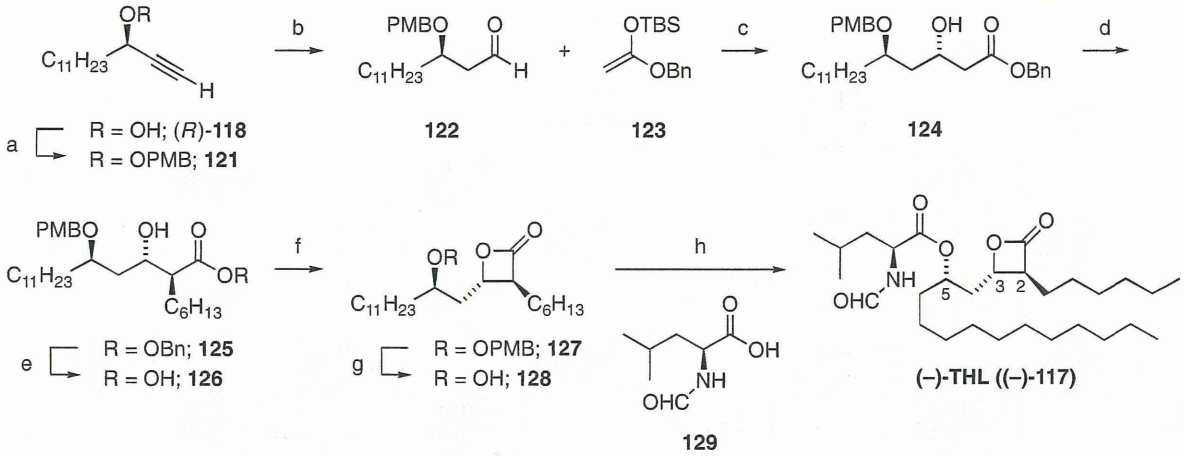
Scheme 21. Production of chiral alcohol (*R*)-**118** by the kinetic resolution of racemic alcohol (±)-**118** via asymmetric esterification.

(*S*)-BTM, and a sufficient amount (2.43 g) of the desired chiral propargyl alcohol (*R*)-**118** was obtained in good yield (41% from (±)-**118**) with a very high enantiopurity (99% ee, $s = 34$) via single operation (eq 3).

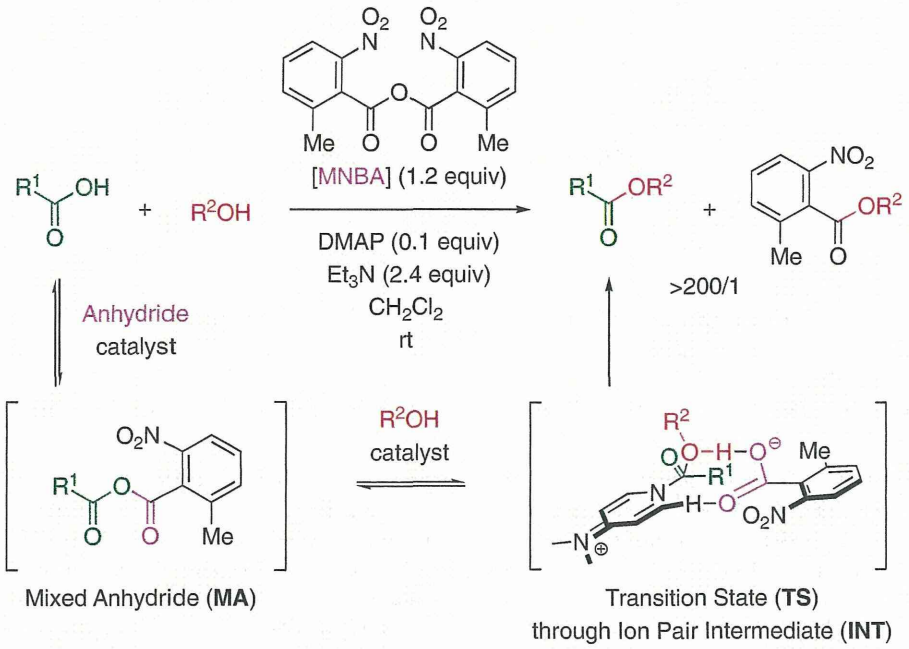
Installation of the PMB protective group onto the alcohol (*R*)-**118** and the following hydroboration of the resulting alkyne **121** provided the chiral aldehyde **122** in good yield from (*R*)-**118** (Scheme 22). The Mukaiyama aldol reaction[75] of the β-alkoxyaldehyde **122** with KSA **123**, which was prepared from benzyl acetate, mediated by $[TiCl_2(O^iPr)_2]$ smoothly proceeded to afford the desired *anti*-1,3-diol unit **124** with a high stereoselectivity (*anti*/*syn* = 94/6).[76] The *anti*-selective alkylation at the α-position of the formed β-hydroxyester **124** was attained according to the former established method to exclusively provide the desired trisubstituted benzyl hexadecanoate **125**.[67x,67z,77]

After hydrolysis of the benzyl ester **125** with lithium hydroxide, the intramolecular dehydration condensation of the resulting seco-acid **126** was eventually examined using 1.3 equivalents of MNBA combined with a catalytic amount of DMAP (0.2 equiv) and 6.0 equivalents of triethylamine, and the desired *trans*-2,3-disubstituted β-lactone **127** was readily produced in excellent yield (91%) by this facile procedure. On the other hand, we revealed that the MNBA lactonization protocol using an excess amount of DMAP (6.0 equiv) in the absence of triethylamine also produced the β-lactone **127** in a similar satisfactory yield (92%). Finally, sequential transformations of **127** by deprotection of the PMB group and the Mitsunobu reaction of the formed alcohol **128** with α-amino acid **129** furnished the targeted molecule (−)-THL ((−)-**117**) in a very high yield. All spectral data including the optical rotation of synthetic (−)-**117** corresponded to those of reported (−)-THL (our synthetic sample; $[\alpha]_D^{22} = -32.5$ (*c* 1.17, $CHCl_3$) {$[\alpha]_D^{20} = -32.0$ (*c* 1, $CHCl_3$);[66d] $[\alpha]_D^{25} = -33.04$ (*c* 0.79, $CHCl_3$);[67i] $[\alpha]_D^{20} = -32.0$ (*c* 0.74, $CHCl_3$);[67n] $[\alpha]_D^{26} = -31$ (*c* 0.1, $CHCl_3$)}),[67x] and all the absolute configurations of the stereogenic centers at the C-2, C-3, and C-5 positions were unequivocally determined by this identification.

10.3 Determination of the Transition Structure of MNBA-Mediated Lactonization for the Formation of β-Lactones Using DFT Calculations. In order to clarify the significant difference in the reactivities among several seco-acids during the formation of the 4-membered ring systems, we have tried to disclose the reaction mechanism that produces the several multisubstituted β-lactones from the corresponding model seco-acids based on theoretical calculations.[78,79] We have already reported that the rapid formation of the mixed anhydride (MA) from the seco-acid with MNBA is the initial



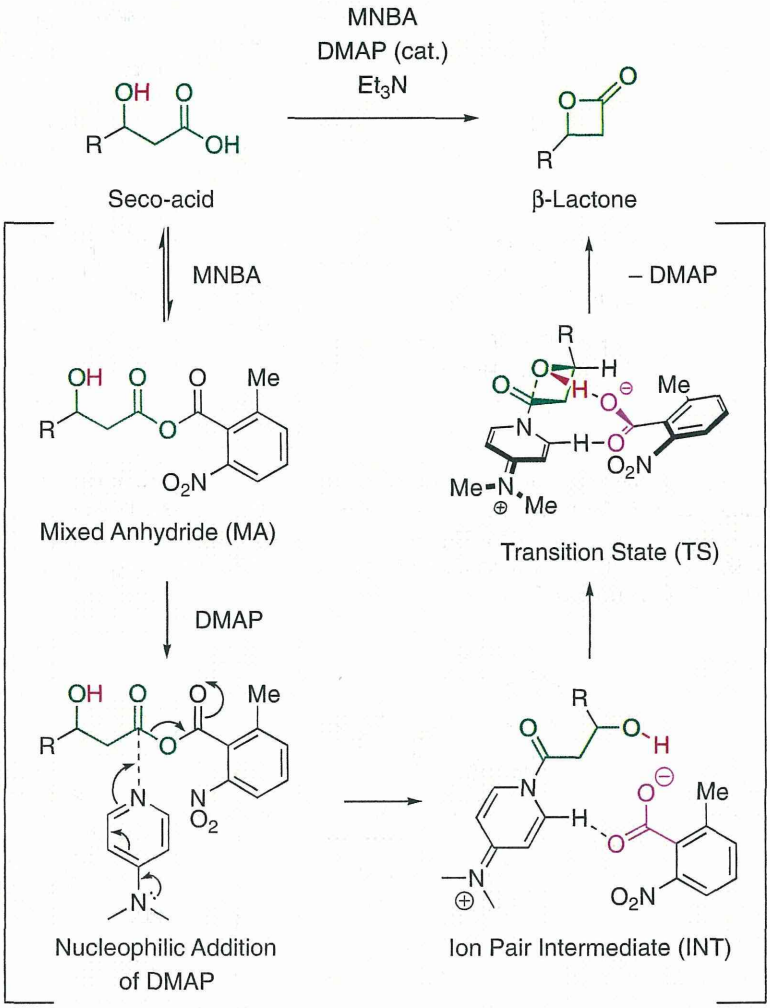
Scheme 22. Total synthesis of (−)-tetrahydrolipstatin ((−)-THL, (−)-**117**). *Reagents and conditions*: (a) PMBCl, NaH, TBAI, DMF, rt (96%); (b) (i) catecholborane, THF, 70 °C, (ii) 30% H_2O_2, NaOAc, rt (53%); (c) **123**, $[TiCl_2(O^iPr)_2]$, toluene, −78 °C (87%, *anti*/*syn* = 94/6); (d) (i) LHMDS, THF, −78 °C for 1 h, −45 °C for 1 h, then (ii) $C_6H_{13}I$, HMPA, −45 °C (90% base on 61% conversion); (e) 4 M LiOH, THF/MeOH, 55 °C (quant.); (f) MNBA, DMAP, Et_3N, CH_2Cl_2, rt (91%); (g) H_2 (1 atm), $Pd(OH)_2$, EtOH, rt; (h) **129**, DIAD, Ph_3P, THF, rt (96% for 2 steps).



Scheme 23. Proposed reaction mechanism of the MNBA-mediated dehydration condensation between carboxylic acids and alcohols to form the corresponding esters.

step in the MNBA-mediated coupling reaction as shown in Scheme 23.[17a] The successive nucleophilic addition of DMAP to MA provides the corresponding ion pair intermediate (INT) and the second nucleophilic addition of alcohol to INT proceeds to afford the desired carboxylic ester with very high chemoselectivity (>200/1) via suitable transition structure (TS). When using β-hydroxycarboxylic acid as a substrate (Scheme 24), the intramolecular transacylation takes place through TS by the attack of oxygen in the activated hydroxy group on the carbonyl carbon in the acylpyridinium part of INT to produce the desired β-lactone in high yield. It has been already disclosed by Zipse et al. that the deprotonation of the hydroxy group with the acyl anion part in the zwitterionic species to form the new oxygen–carbon bond is the rate determining step in this transacylation process.[80]

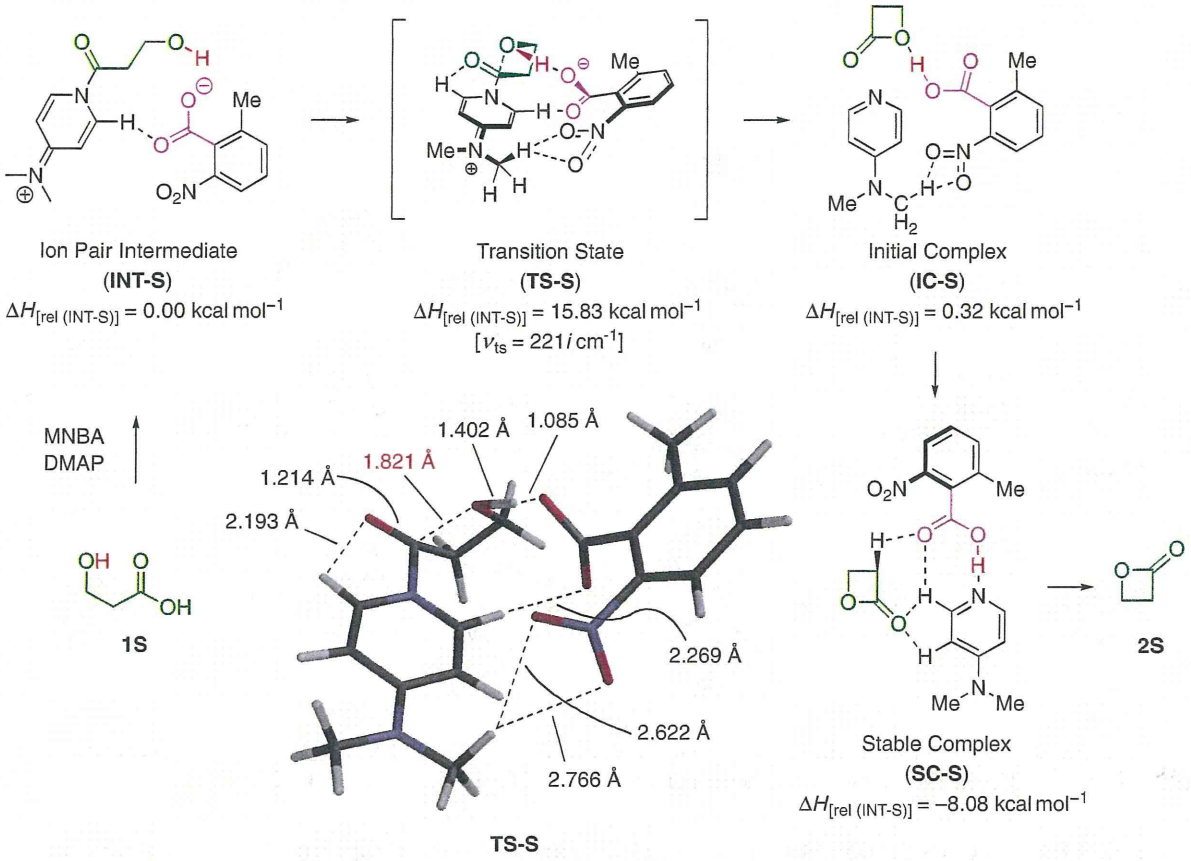
Determination of the transition state forming the model β-lactone (**2S**) from 3-hydroxypropanoic acid (**1S**) via the corresponding ion pair intermediate (**INT-S**) was carried out by using density functional theory (DFT) calculations at the B3LYP/6-31G*//B3LYP/6-31G* level.[78] We succeeded in obtaining the plausible transition structure (**TS-S**) as shown in Scheme 25, and the nature of this stationary point was verified through calculation of the vibrational frequency spectrum ($\nu = 221i\,cm^{-1}$). The distance of the forming C–O bond



Scheme 24. Reaction pathway to form β-lactones from 3-hydroxycarboxylic acids (seco-acids) using MNBA.

(between carbonyl carbon of the acid component and oxygen of hydroxy in seco-acid) is 1.821 Å, and the distance of the cleaved O–H bond (between oxygen and hydrogen in hydroxy) is 1.402 Å. The frequency analysis of **TS-S** revealed that the nucleophilic attack of the alcohol on the carbonyl group and the deprotonation of the hydroxy group with the 2-methyl-6-nitrobenzoate anion proceeded under a concerted reaction mechanism because the C–O bond-forming step and the O–H bond-cleaving process simultaneously occurred (Figure 11). The 2-methyl-6-nitrobenzoate moiety has a rigid structure in which the conformation is restricted by the attractive interaction between oxygen in the benzoate carbonyl group and hydrogen at C-2 of the pyridinium salt (2.269 Å) as well as the coordination of oxygens in the nitro group to hydrogen in one of the *N*-methyl groups in the pyridinium salt (2.622 and 2.766 Å, respectively). Furthermore, an intrinsic reaction coordinate (IRC) analysis showed that the initial complex (**IC-S**) will be first produced via the transition structure (**TS-S**), and then it transforms into the more stable complex (**SC-S**), a conformer of **IC-S**, as depicted in Scheme 25.

Other transition states **TS-A–TS-D**, **TS-T**, **TS-U**, and **TS-I** that form the model β-lactones **2A–2D**, **2T**, **2U**, and **2I** from the corresponding 3-hydroxypropanoic or 3-hydroxybutanoic acids **1A–1D**, **1T**, **1U**, and **1I** in Scheme 26 were determined at the same level (B3LYP/6-31G*//B3LYP/6-31G*) by using DFT calculations, and all the transition states are represented in Figure 12. The three-dimensional structures of the transition states **TS-A–TS-D**, **TS-T**, **TS-U**, and **TS-I** including several bond distances are also depicted in the same figure. Furthermore, the reaction coordinate profiles (MA of seco-acid → INT → TS → IC → SC → β-lactone) for the MNBA-mediated lactonization of the model seco-acids **1A–1D**, **1T**, **1U**, and **1I** are graphically summarized in Chart 1 with the calculated relative enthalpies ($\Delta H_{298.15}$) in Table 9. It should be noted that the structures of the model seco-acids **1A–1D** correspond to those of the experimentally examined seco-acids **114a–114d** in Scheme 20, and the order of the reactivities of **114a–114d** (chemical yields of β-lactones **115a–115d** at rt; 5% (**115a**), 89% (**115b**), 13% (**115c**), and 69% (**115d**)) are correctly predicted by the result of the calculations as shown in Table 9 ($\Delta H_{[\text{rel (INTs)}]}$ of **TS-A–TS-D**; 14.14 (**TS-A**), 6.88 (**TS-B**), 12.69 (**TS-C**), and 9.49 kcal mol^{-1} (**TS-D**)). The distances of the forming C–O bonds in **TS-B**, **TS-D**, **TS-T**, and **TS-I** (1.867, 1.855, 1.871, and 1.928 Å, respectively) are apparently longer



Scheme 25. Reaction pathway and the calculated transition state (**TS-S**) to form propan-3-olide (**2S**) from 3-hydroxypropanoic acid (**1S**).

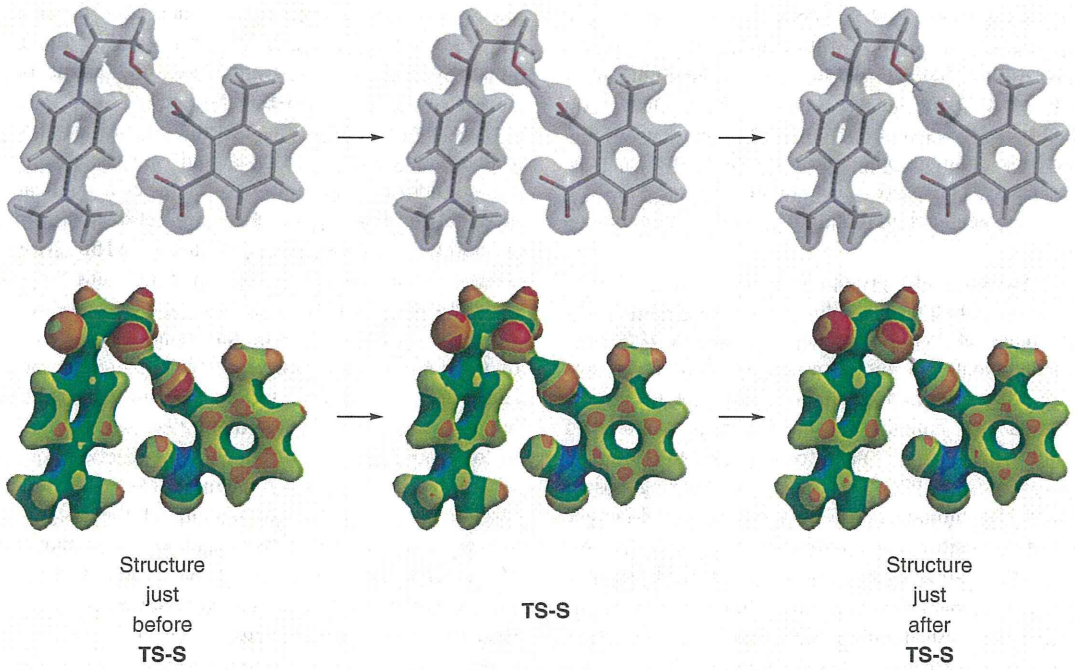
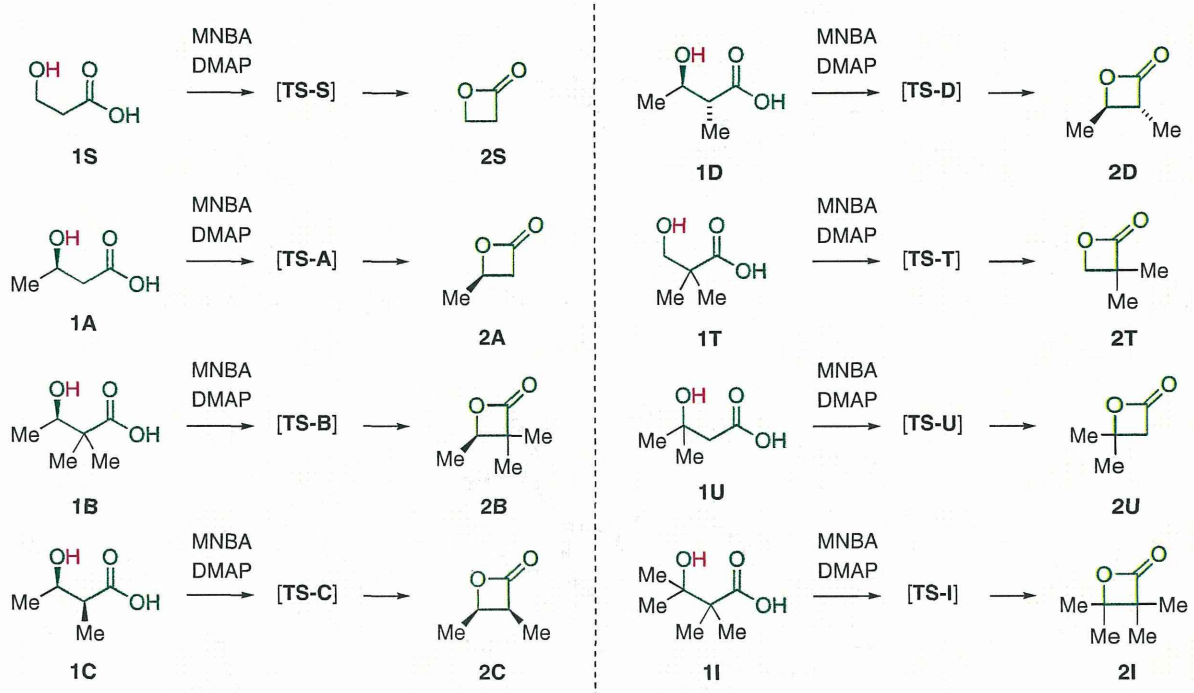


Figure 11. Properties of transition structure (**TS-S**), structure just before **TS-S**, and structure just after **TS-S**: Upper transition, bond density surface selected for limited electrons in total and demark atomic connectivity (Electron density, 0.08 electrons/au^3) for showing bonding in the transition state. Lower transition, electron density selected for limited electrons in total and demark atomic connectivity with local ionization potential map (electron density, 0.08 electrons/au^3).



Scheme 26. Model reactions for the formation of β-lactones (**2S**, **2A–2D**, **2T**, **2U**, and **2I**) starting from 3-hydroxycarboxylic acids (**1S**, **1A–1D**, **1T**, **1U**, and **1I**) via transition structures (**TS-S**, **TS-A–TS-D**, **TS-T**, **TS-U**, and **TS-I**).

than those in **TS-S**, **TS-A**, **TS-C**, and **TS-U** (1.821, 1.825, 1.840, and 1.857 Å, respectively), therefore, it might be anticipated that the former transition states (**TS-B**, **TS-D**, **TS-T**, and **TS-I**) have similar structures to those of the reactants, while the latter transition states (**TS-S**, **TS-A**, **TS-C**, and **TS-U**) resemble the products according to the Hammond postulate.[81] Our calculated results showed that the earlier transition states, such as **TS-B**, **TS-D**, **TS-T**, and **TS-I**, can release a small strain energy during the early stage in the transformation to afford the desired β-lactones, although other later transition states, such as **TS-S**, **TS-A**, **TS-C**, and **TS-U**, accumulate an excess energy until the new oxygen–carbon bond forming reaction begins in late stage.

This categorization finally prompted us to prepare a 2,2,3,3-tetrasubstituted seco-acid **114i** for the attempt to examine the synthetic efficiency of a highly branched β-lactone **115i** with four alkyl substituents on the 4-membered ring as shown in Scheme 27. The preferred calculated results of the model compound **1I**, a low enthalpy of the transition state **TS-I** ($\Delta H_{[\mathrm{rel\ (INT\text{-}I)}]} = 7.50\,\mathrm{kcal\,mol^{-1}}$) and forming a C–O bond with a long distance in **TS-I** (1.928 Å), suggest that easy ring closure of the seco-acid **114i** should occur to form the desired β-lactone **115i** via an early transition state similar to **TS-I**. Actually, the very effective MNBA-mediated lactonization of **114i** proceeded under the same reaction conditions, which were used in Scheme 20, and the corresponding fully-substituted β-lactone **115i** was produced as expected in excellent yield (95%) according to the theoretical prediction.[82] It is assumed that the conformational advantage of the transition state for cyclization of **114i** arise from not only the substituent effect of the methyl group at the C-2 position but also the suitable direction of the additional methyl group at the C-3 position in **TS-I** as depicted in Figure 12.

Profiles of the thermodynamic potentials, such as relative Gibbs free energies (ΔG) and enthalpies (ΔH), of transition states **TS-A–TS-D**, **TS-S–TS-U**, and **TS-I** are summarized in Table 10 and illustrated in Chart 2 with all β-lactone formations (Scheme 28). Apparently, thermodynamic potentials for the transition states **TS-B**, **TS-D**, **TS-T**, and **TS-I** are lower ($<10\,\mathrm{kcal\,mol^{-1}}$) than those for the transition states **TS-S**, **TS-A**, **TS-C**, and **TS-U** ($>12\,\mathrm{kcal\,mol^{-1}}$). These extensive properties might be also accounted for by the easy cyclization of seco-acids **114b**, **114d**, **114e**, **126**, and **114i** to afford the corresponding 2,2,3-trisubstituted β-lactone **115b**, *trans*-2,3-disubstituted β-lactones **115d**, **115e**, and **127**, and 2,2,3,3-tetrasubstituted β-lactone **115i** in good yields as shown in Scheme 29.

In summary, we achieved the enantioselective total synthesis of (−)-tetrahydrolipstatin ((−)-THL, (−)-**117**), an antiobestic agent used in clinical treatments, by the MNBA-mediated lactonization of the corresponding seco-acid to provide the β-lactone moiety of (−)-**117** under mild reaction conditions. Two other key steps, i.e., (i) the asymmetric esterification of diphenylacetic acid with a large amount of the racemic secondary propargyl alcohol (±)-**118**, and (ii) the diastereoselective Mukaiyama aldol reaction of the aldehyde **122** with KSA **123** derived from benzyl acetate, were employed for the construction of the main skeleton of (−)-**117**.

Additionally, we have developed a convenient method for the preparation of several β-lactones, representative of small ring compounds, having *trans*-2,3-disubstituted, 2,2,3-trisubstituted, or 2,2,3,3-tetrasubstituted patterns by using the MNBA-mediated cyclization. The effective MNBA-mediated