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MNBA-Mediated β-Lactone Formation: Mechanistic Studies and Application for the Asymmetric Total Synthesis of Tetrahydrolipstatin

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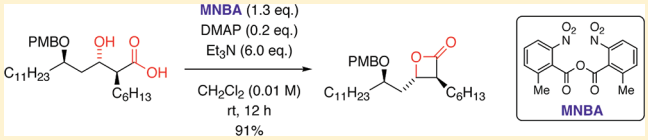
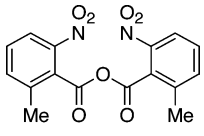
Supporting Information

ABSTRACT: Various β-lactones were prepared from β-hydroxycarboxylic acids by intramolecular dehydration condensation using MNBA, an effective coupling reagent, along with a nucleophilic catalyst. The transition state that provides the desired 4-membered ring model system is disclosed by density functional theory (DFT) calculations, and the structural features of the transition form are discussed. This method was successfully applied to the asymmetric total synthesis of tetrahydrolipstatin (THL), an antiobestic drug used in clinical treatment to inhibit the activity of pancreatic lipase.



INTRODUCTION

In 2004, we developed an effective lactonization using 2-methyl-6-nitrobenzoic anhydride (MNBA) in the presence of a nucleophilic catalyst, such as 4-(dimethylamino)pyridine (DMAP) or 4-(dimethylamino)pyridine *N*-oxide (DMAPO), under mild reaction conditions.[1] This protocol was successfully applied to the preparation of several cyclic compounds having a variety of ring sizes, such as 2-hydroxy-24-oxooctacosanolide (29-membered lactone),[2] 2-hydroxytetracosanolide (25-membered lactone),[3] (9*E*)-isoambrettolide (17-membered lactone),[4] erythronolide A (14-membered lactone),[5] 2-epibotcinolide (9-membered lactone),[6] and octalactins A and B (8-membered lactone).[7] Although these large- and medium-ring compounds could be easily synthesized from the corresponding seco-acids by MNBA lactonization as shown in the above instances,[8] there has been no report on the production of small ring compounds, such as 3- or 4-membered lactones, using MNBA.[9] Therefore, we decided to determine the efficiency of the MNBA lactonization for the preparation of 4-membered compounds (β-lactones) starting from the corresponding β-hydroxycarboxylic acids by this intramolecular dehydration coupling process.



MNBA

RESULTS AND DISCUSSION

Systematic Studies of the Generation of the 4-Membered Ring Compounds Using MNBA Lactonization. First, 3-hydroxy-5-phenylpentanoic acid (**1a**), 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 **2a** in 21% yield under the forced reaction conditions (Scheme 1).[10] On the other hand, we fortunately obtained a trisubstituted β-lactone **2b** in excellent yield when 3-hydroxy-2,2-dimethyl-5-phenylpentanoic acid (**1b**) 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 **1b** including a *gem*-dimethyl group at the α-position of the carbonyl group.[11] Next, stereoisomeric β-hydroxycarboxylic acids (**1c** and **1d**) 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 as shown in Scheme 1.[10] A significant difference between the reactivities of **1c** and **1d** was observed, and the desired diastereomers of the β-lactones (**2c** and **2d**, R^1 = Me for **2d**) were obtained from **1c** and **1d** in 13% and 69% yields, respectively. It is easily anticipated that the formation of the transition state for the unstable structure of the *cis*-2,3-disubstituted 4-membered ring in **2c** is more disfavored compared to the formation of the transition state for the more stable structure of the *trans*-2,3-disubstituted 4-membered ring in **2d**. We also discovered that the *anti*-β-hydroxycarboxylic acid **1e**, possessing a longer alkyl chain at the α-position, is more preferable for the formation of the *trans*-2,3-disubstituted β-lactone **2e**, and a higher yield was attained for the synthesis of **2e** from **1e** using the MNBA lactonization depicted in Scheme 1 (83%, $R^1 = C_6H_{13}$).[10]

Several benzylic-type β-hydroxycarboxylic acids (**1f−h**) were further prepared by the aldol reaction of benzaldehyde with suitable nucleophiles, such as acetic acid or 2-methylpropanoic acid derivatives.[10] Similar tendencies were observed during the 4-membered ring formation starting from **1f−h** with those

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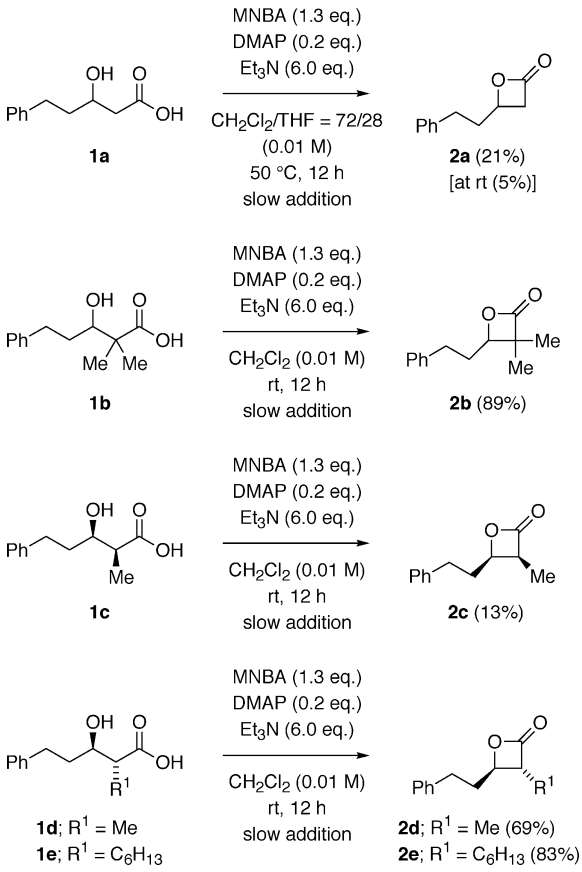
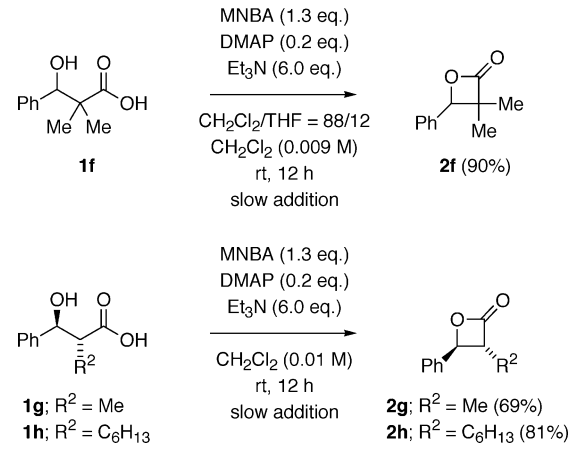
Scheme 1. MNBA Lactonization To Form a Variety of β-Lactones Derived from 3-Phenylpropanal



starting from **1a**–**e** as shown in Scheme 2 (cf. Scheme 1). For instance, the MNBA lactonization of 3-hydroxy-2,2-dimethyl-3-

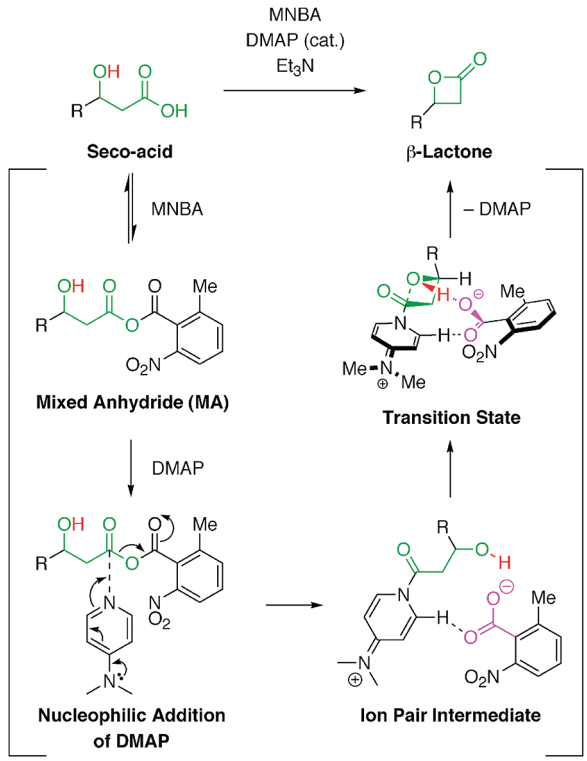
Scheme 2. MNBA Lactonization To Form a Variety of β-Lactones Derived from Benzaldehyde



phenylpropanoic acid (**1f**) smoothly proceeded to afford the trisubstituted β-lactone **2f** in excellent yield (90%). When *anti*-aldol derivatives (**1g** and **1h**) were used as seco-acids for the MNBA lactonization, it was also found that the desired *trans*-2,3-disubstituted β-lactones (**2g** and **2h**, R^2 = Me for **2g**, R^2 = C_6H_{13} for **2h**) were provided in good to high yields (69% and 81%, respectively).

Theoretical Studies of the MNBA-Mediated β-Lactone-Forming Reactions. 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.[12,13] It has already been reported that the rapid formation of the mixed anhydride (MA) from the seco-acid with MNBA is the initial step in the MNBA-mediated coupling reaction, and the successive nucleophilic addition of DMAP to MA provides the key intermediate zwitterionic species as shown in Scheme 3. Next,

Scheme 3. Reaction Pathway of the MNBA Lactonization To Form β-Lactones from 3-Hydroxycarboxylic Acids (Seco-Acids)



the intramolecular transacylation proceeds by the attack of oxygen in the activated hydroxyl group on the carbonyl carbon in the acylpyridinium part to provide the desired β-lactone in high yield.[1a] It was also disclosed by Zipse et al. that the deprotonation of the hydroxyl 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.[14]

Determination of the transition state forming the model β-lactone (**2S**) from 3-hydroxypropanoic acid (**1S**) via the zwitterionic species (**INT-S**) was carried out by using density functional theory (DFT) calculations at the B3LYP/6-31G*//B3LYP/6-31G* level.[12] We succeeded in obtaining the plausible transition structure (**TS-S**) as shown in Scheme 4, and the nature of this stationary point was verified through calculation of the vibrational frequency spectrum (ν = 221*i* cm^{-1}).[15] The distance of the forming C–O bond (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.

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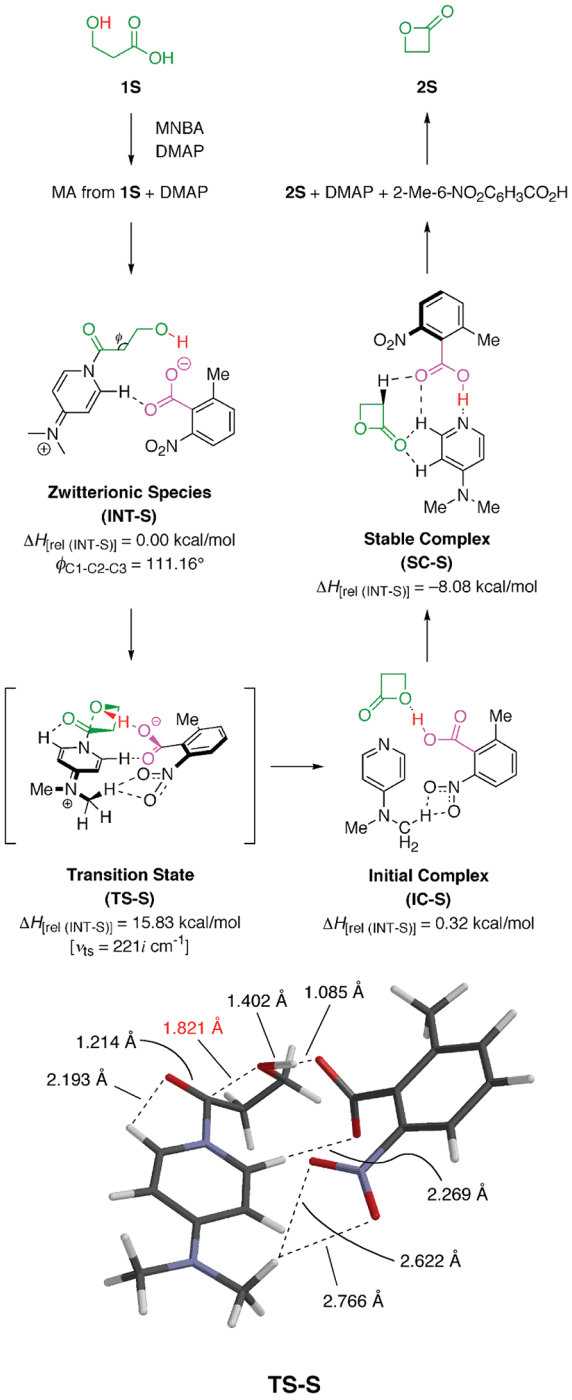
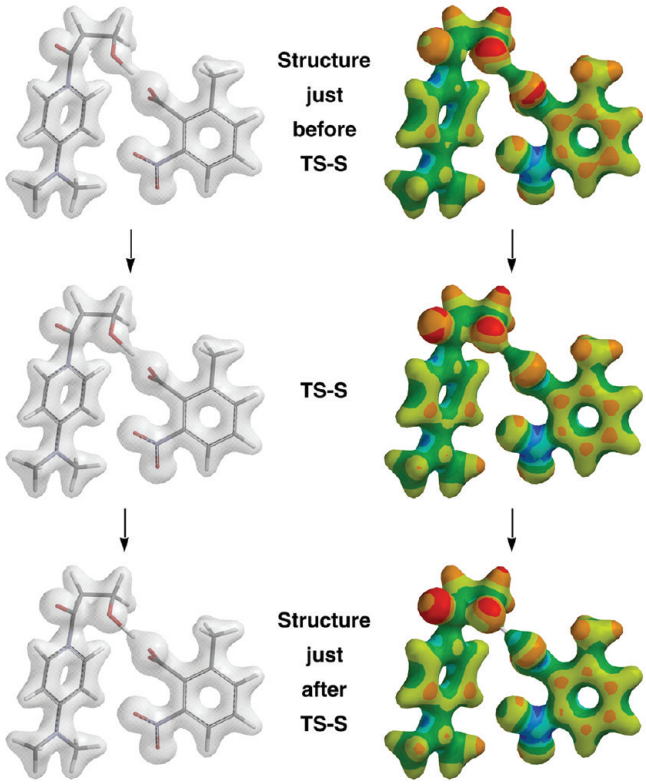
Scheme 4. Reaction Pathway and the Calculated Transition State (TS-S) To Form Propan-3-olide (2S) from 3-Hydroxypropanoic Acid (1S)



The frequency analysis of **TS-S** revealed that the nucleophilic attack of the alcohol on the carbonyl group and the deprotonation of the hydroxyl 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 (Scheme 5). 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

Scheme 5. Properties of Transition Structure (TS-S), Structure Just before TS-S, and Structure Just after TS-S:[a]



[a]Left column, bond density surface selected for limited electrons in total for showing bonding in the transition state (electron density, 0.08 electrons/au^3). Right column, electron density selected for limited electrons in total for showing atomic connectivity with local ionization potential map (electron density, 0.08 electrons/au^3).

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 4.[15]

Other transition states **TSs-A−D**, **TS-T**, **TS-U**, and **TS-I** that form the model *β*-lactones **2A−D**, **2T**, **2U**, and **2I** from the corresponding 3-hydroxypropanoic or 3-hydroxybutanoic acids **1A−D**, **1T**, **1U**, and **1I** were also determined at the same level (B3LYP/6-31G*//B3LYP/6-31G*) by using DFT calculations, and all of the transition states and intermediates are represented in Scheme 6.[15] The three-dimensional structures of the transition states **TSs-A−D**, **TS-T**, **TS-U**, and **TS-I** including several bond distances are figured in Scheme 7. Furthermore, the reaction coordinate profiles (MA of seco-acid → **INT** → **TS** → **IC** → **SC** → *β*-lactone) for the MNBA lactonization of the model seco-acids **1A−D**, **1T**, **1U**, and **1I** are graphically summarized in Scheme 8 with the calculated relative enthalpies ($\Delta H_{298.15}$) in Table 1. It should be noted that the structures of the model seco-acids **1A−D** correspond to those of the experimentally examined seco-acids **1a−d** in Scheme 1, and the order of the reactivities of **1a−d** (chemical yields of *β*-lactones **2a−d** at rt; 5% (**2a**), 89% (**2b**), 13% (**2c**), 69% (**2d**)) is correctly predicted by the result of the calculations as shown in Table 1 ($\Delta H_{[\text{rel (INTs)}]}$ of **TSs-A−D**; 14.14 kcal/mol (**TS-A**), 6.88 kcal/mol (**TS-B**), 12.69 kcal/mol (**TS-C**), 9.49 kcal/mol

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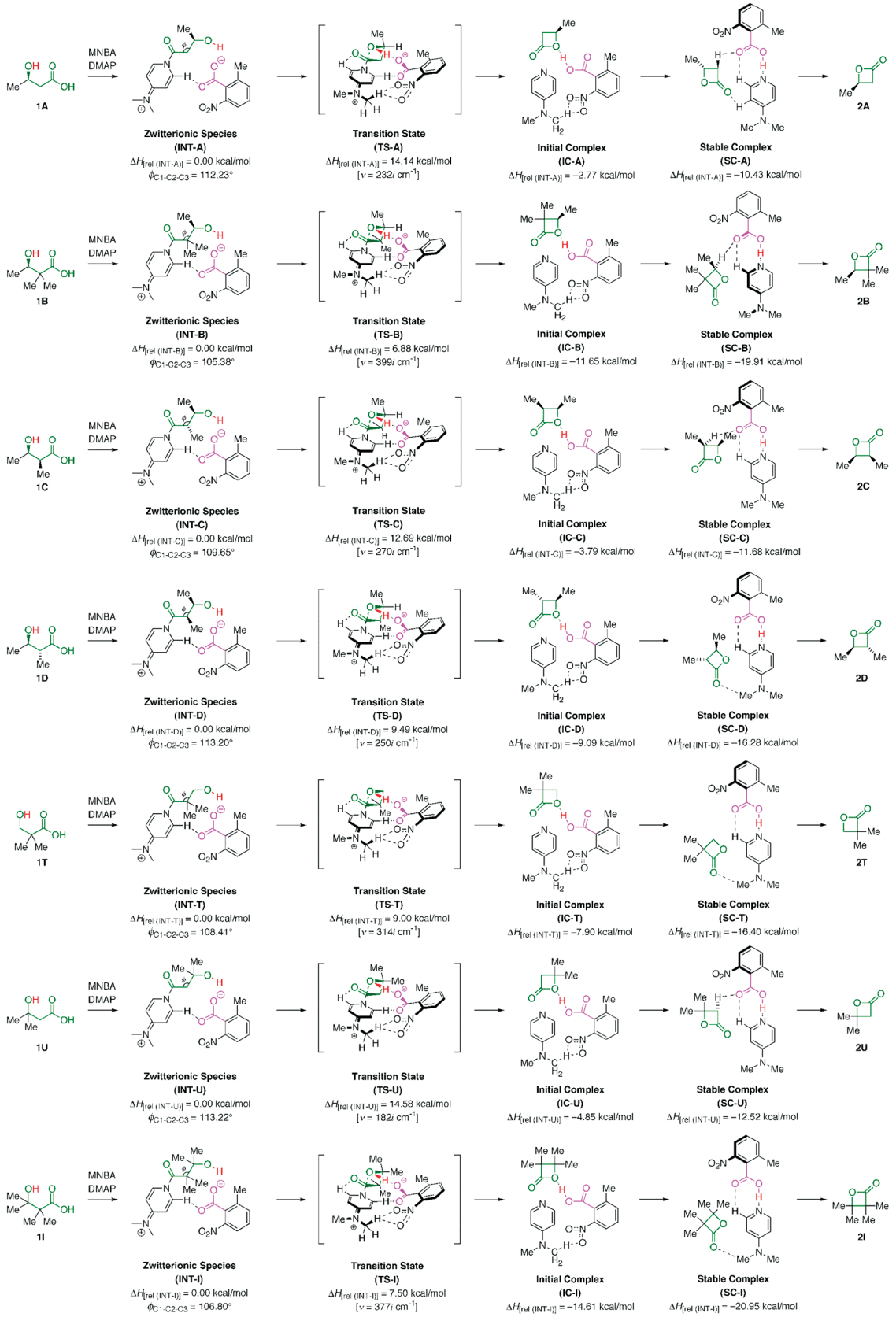
Scheme 6. Reaction Pathway and the Calculated Transition States (TSs-A–D, TS-T, TS-U, and TS-I) To Form *β*-Lactones (2A–D, 2T, 2U, and 2I) from 3-Hydroxycarboxylic Acids (1A–D, 1T, 1U, and 1I)



(**TS-D**)).[16] 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 than those in **TS-S**, **TS-A**, **TS-C**, and **TS-U** (1.821, 1.825, 1.840, and 1.857 Å,

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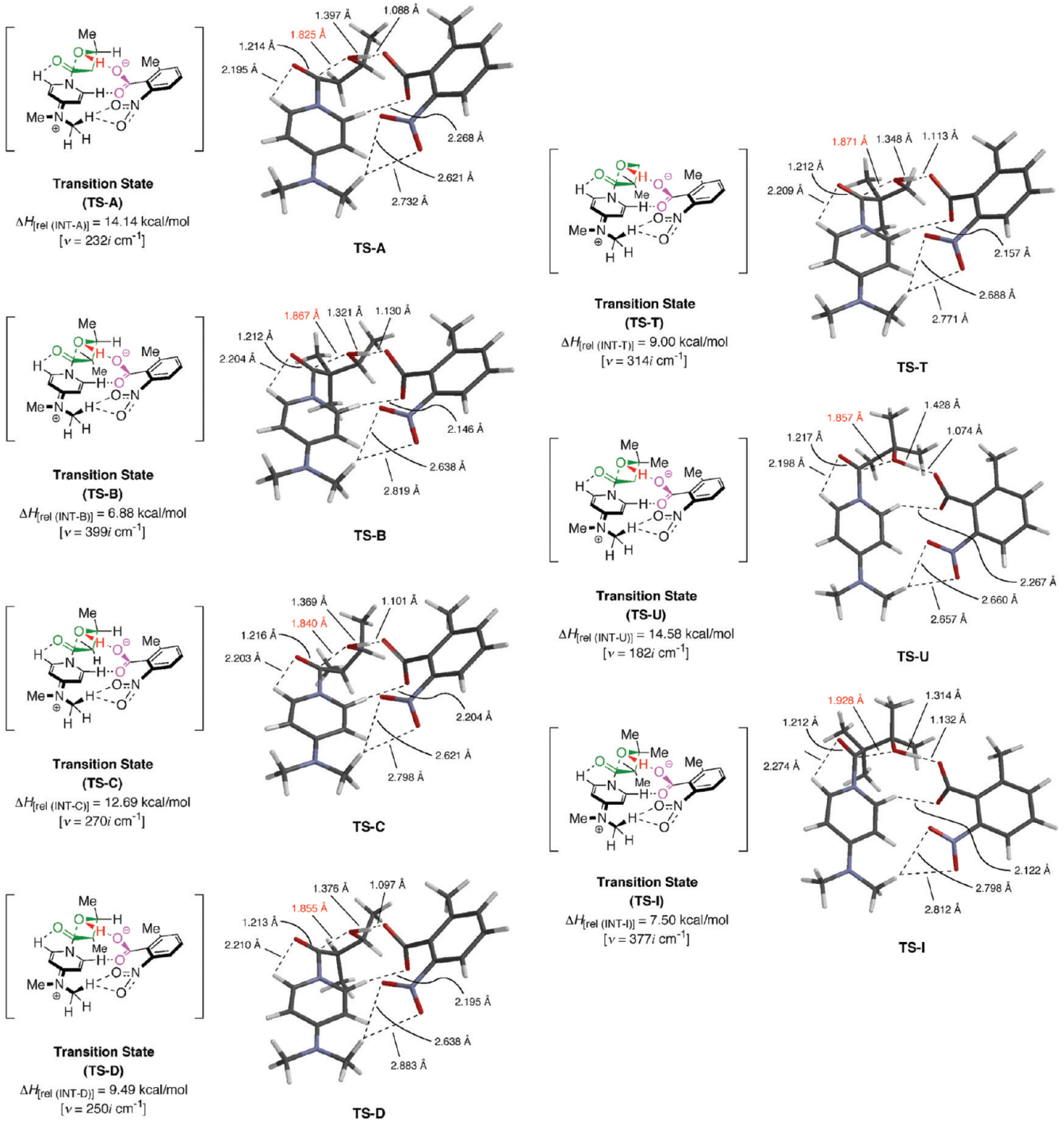
Scheme 7. Three-Dimensional Transition Structures (TSs-A–D, TS-T, TS-U, and TS-I) To Form β-Lactones (2A–D, 2T, 2U, and 2I) from 3-Hydroxycarboxylic Acids (1A–D, 1T, 1U, and 1I)



respectively); therefore, it might be anticipated that the former transition states (**TS-B**, **TS-D**, **TS-T**, and **TS-I**) have structures similar 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.[17] 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 the late stage.

This categorization finally prompted us to prepare a 2,2,3,3-tetrasubstituted seco-acid **1i** for the attempt to examine the synthetic efficiency of a highly branched β-lactone **2i** with four alkyl substituents on the 4-membered ring as shown in Scheme 9. The preferred calculated results of the model compound **1I**, a low enthalpy of the transition state **TS-I** ($\Delta H_{[\text{rel (INT-I)}]}$ = 7.50 kcal/mol) 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 **1i** should occur to form the desired β-lactone **2i** via an early

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Scheme 8. Reaction Coordinates To Form β-Lactones (2A–D, 2S–U, and 2I) from 3-Hydroxycarboxylic Acids (1A–D, 1S–U, and 1I)

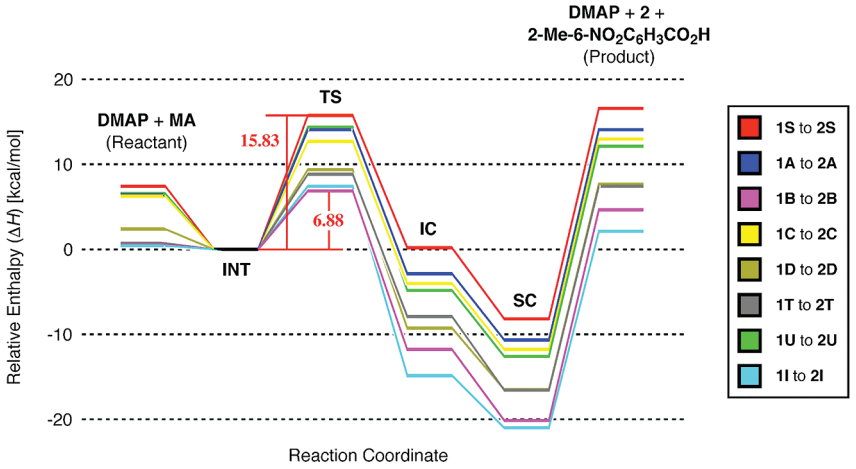

Table 1. Calculated Relative Enthalpies (Δ*H*) (in kcal mol^{-1}) of the Transition States and Intermediates for the Formation of Lactones 2A–D, 2S–U, and 2I from 3-Hydroxycarboxylic Acids (1A–D, 1S–U, and 1I) at 298.15 K at the B3LYP/6-31G*//B3LYP/6-31G* Level of Theory

	DMAP + MA from 1A-D, 1S–U, 11 (reactant)	INT-A-D INT–S-U INT-I	TS-A-D TS–S-U TS-I	IC-A-D IC–S-U IC-I	SC-A-D SC–S-U SC-I	DMAP + 2A-D, 2S–U, 21 + 2-Me-6-$NO_2C_6H_3CO_2H$ (product)
S	7.64	0.00	15.83	0.32	−8.08	16.54
A	6.73	0.00	14.14	−2.77	−10.43	14.13
B	0.73	0.00	6.88	−11.65	−19.91	4.69
C	6.47	0.00	12.69	−3.79	−11.68	13.00
D	2.42	0.00	9.49	−9.09	−16.28	7.88
T	0.90	0.00	9.00	−7.90	−16.40	7.48
U	6.80	0.00	14.58	−4.85	−12.52	12.22
I	0.56	0.00	7.50	−14.61	−20.95	2.28

Scheme 9. Synthesis of the Fully Substituted β-Lactone (2i) from 2,2,3,3-Tetrasubstituted 3-Hydroxycarboxylic Acid (1i) Using MNBA Lactonization

transition state similar to that of **TS-I**. Actually, the very effective MNBA-mediated lactonization of **1i** proceeded under the same reaction conditions, which were used in Schemes 1 and 2, and the corresponding fully substituted β-lactone **2i** was produced as expected in excellent yield (95%) according to the theoretical prediction.[18]

A *gem*-dimethyl group at the α-position of the carbonyl group produces strain which forces a decrease in the bond angle $\phi_{C1-C2-C3}$ (Thorpe–Ingold effect) as shown above (vide supra).[11] Actually, the calculated bond angles $\phi_{C1-C2-C3}$ of **INT-B** (105.38°) derived from **1B**, **INT-T** (108.41°) derived from **1T**, and **INT-I** (106.80°) derived from **1I** are much smaller than those of the intermediates **INT-S** (111.16°) derived from **1S**, **INT-A** (112.23°) derived from **1A**, and **INT-U** (113.22°) derived from **1U** as depicted in Schemes 4 and 6. These results are easily correlated with the structures of seco-acids; that is, **1B**, **1T**, and **1I** have the *gem*-dimethyl group at the α-position of the carbonyl group, although **1S**, **1A**, and **1U** have no substituent at the same position. On the other hand, the calculated bond angle $\phi_{C1-C2-C3}$ of **INT-D** derived from the *anti*-compound **1D** (113.20°) is similar to those of **INT-S** (111.16°), **INT-A** (112.23°), and **INT-U** (113.22°) as well as that of **INT-C** (109.65°) derived from *syn*-compound **1C**. Therefore, the conformational advantage of the transition state **TS-D** for cyclization might arise from not only the substituent effect of the methyl group at the C-2 position but also the

Table 2. Yields of Lactones 2a–d and 2i and Calculated Relative Gibbs Free Energies (Δ*G*) (in kcal mol^{-1}), Enthalpies (Δ*H*) (in kcal mol^{-1}), and Products of Entropies and Temperature (*T*Δ*S*) (in kcal mol^{-1}) for the Transition States TS-A–D, TS-S–U, and TS-I at 298.15 K at the B3LYP/6-31G*//B3LYP/6-31G* Level of Theory

	TS-B	TS-I	TS-T	TS-D	TS-C	TS-A	TS-U	TS-S
yield (%)	89 (**2b**)	95 (**2i**)		69 (**2d**)	13 (**2c**)	5 (**2a**)		
Δ*G*	6.56	7.16	8.84	9.32	12.66	14.04	14.50	15.80
Δ*H*	6.88	7.50	9.00	9.49	12.69	14.14	14.58	15.83
*T*Δ*S*	0.32	0.34	0.16	0.17	0.03	0.10	0.08	0.03

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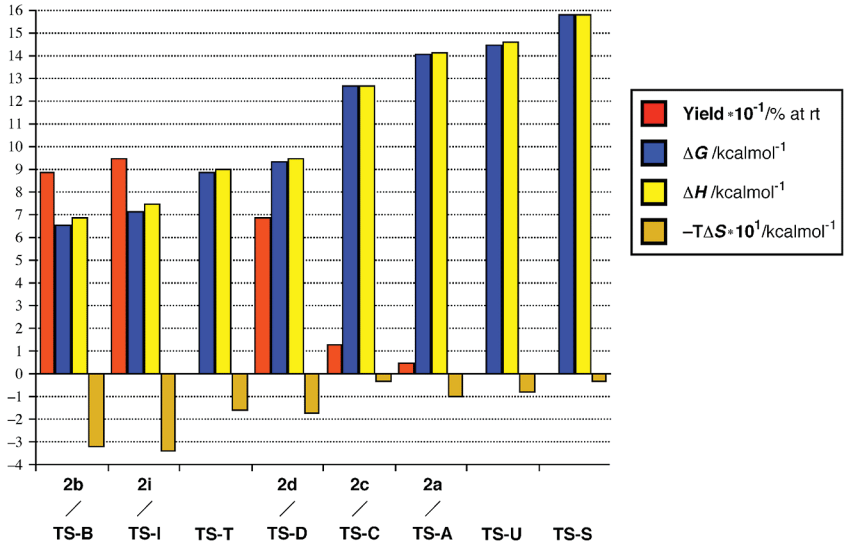
Scheme 10. Comparison of Yields of Lactones 2a–d and 2i with Thermodynamic Potentials of the Model Lactonization To Form (2A–D, 2S–U, and 2I) via the Transition States TS-A–D, TS-S–U, and TS–I

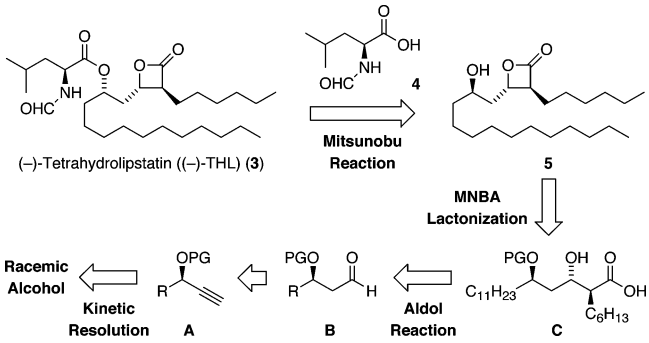


suitable direction of the additional methyl group at the C-3 position in **INT-D**. These structural restrictions in the reactants **1B**, **1D**, **1T**, and **1I** will allow the stability of the early transition states **TS-B**, **TS-D**, **TS-T**, and **TS-I** to increase. Profiles of the relative Gibbs free energies (ΔG) and enthalpies (ΔH) of transition states **TS-A–D**, **TS-S–U**, and **TS-I** are summarized in Table 2 and illustrated in Scheme 10. Apparently, these potentials for the transition states **TS-B**, **TS-D**, **TS-T**, and **TS-I** are lower (<10 kcal/mol) than those for the transition states **TS-S**, **TS-A**, **TS-C**, and **TS-U** (>12 kcal/mol). Although the participation of entropy to Gibbs free energy is not so large in every case, certainly larger products of entropies and temperature ($T\Delta S$) are observed for the transition states **TS-B**, **TS-D**, **TS-T**, and **TS-I** compared with those for the transition states **TS-S**, **TS-A**, **TS-C**, and **TS-U**. These extensive properties might be also accounted for by the easy cyclization of seco-acids **1b**, **1d**, and **1i** to afford the corresponding 2,2,3-trisubstituted β-lactone **2b**, *trans*-2,3-disubstituted β-lactone **2d**, and 2,2,3,3-tetrasubstituted β-lactone **2i** in good yields.

Asymmetric Total Synthesis of Tetrahydrolipstatin (THL). On the basis of the above systematic studies for the generation of the 4-membered ring compounds, it was determined that *trans*-2,3-disubstituted, 2,2,3-trisubstituted, or 2,2,3,3-tetrasubstituted β-lactones were easily generated from the corresponding seco-acids by the MNBA lactonization. Therefore, we further planned the total synthesis of (−)-tetrahydrolipstatin ((−)-THL) (**3**)[19,20] including the *trans*-2,3-disubstituted β-lactone part according to our continuous efforts for the synthesis of useful organic molecules. (−)-THL (**3**) has been used in 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 hydroxyl group in the serine moiety in lipase reacts with the β-lactone residue in **3** to form the corresponding ester; hence, the reaction process of the lipase-catalyzed hydrolysis of triglycerides would be prevented in the presence of **3** in vivo.[21]

Scheme 11 shows our designed asymmetric synthesis of **3** including three notable methodologies, that is, (i) the asymmetric esterification of the racemic secondary alcohol to form a chiral protected propargyl alcohol **A**,[22] (ii) the

Scheme 11. Retrosynthetic Analysis of (−)-Tetrahydrolipstatin ((−)-THL) (3)



diastereoselective Mukaiyama aldol reaction of the aldehyde **B** with ketene silyl acetal to form a seco-acid **C**,[23] and (iii) the MNBA lactonization of **C** to form a β-lactone **5**.[1] General methods for the transformation of the precursor **5** with an α-amino acid **4** into (−)-THL (**3**) have already been established by other groups;[20a] therefore, preparation of the β-lactone **5** is the crucial objective for us in these synthetic studies.

First, the racemic propargyl alcohol (±)-**6** was obtained from dodecanal with trimethylsilylacetylene according to the known conventional method via two steps including the alkynylation of dodecanal.[24] Then, the kinetic resolution of (±)-**6** using 3-phenylpropanoic acid (0.7 equiv) and pivalic anhydride (0.75 equiv) with 5 mol % of (*S*)-benzotetramisole ((*S*)-BTM)[25] was attempted (Scheme 12, eq 1)[22] to produce both the corresponding (*S*)-ester (56% ee) and the recovered alcohol (*R*)-**6** (84% ee) in good yields (58% and 39%, respectively) with moderate enantioselectivities (s = 9).[26] We have already established the remarkable asymmetric esterification using diphenylacetic acid as an acyl donor with racemic 2-hydroxy esters to afford the optically active compounds possessing excellent enantiopurities;[27] therefore, we next tried to improve the selectivity of the kinetic resolution of the racemic propargyl alcohol (±)-**6** using diphenylacetic acid as an acyl donor instead of using 3-phenylpropanoic acid (Scheme 12, eq 2). Fortunately, the selective factor drastically improved and reached a higher value (s = 34) with the enhanced

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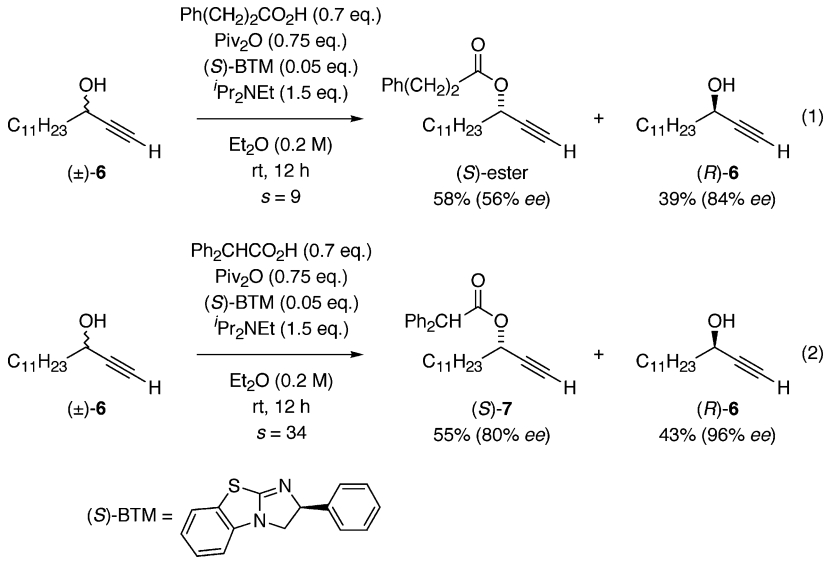
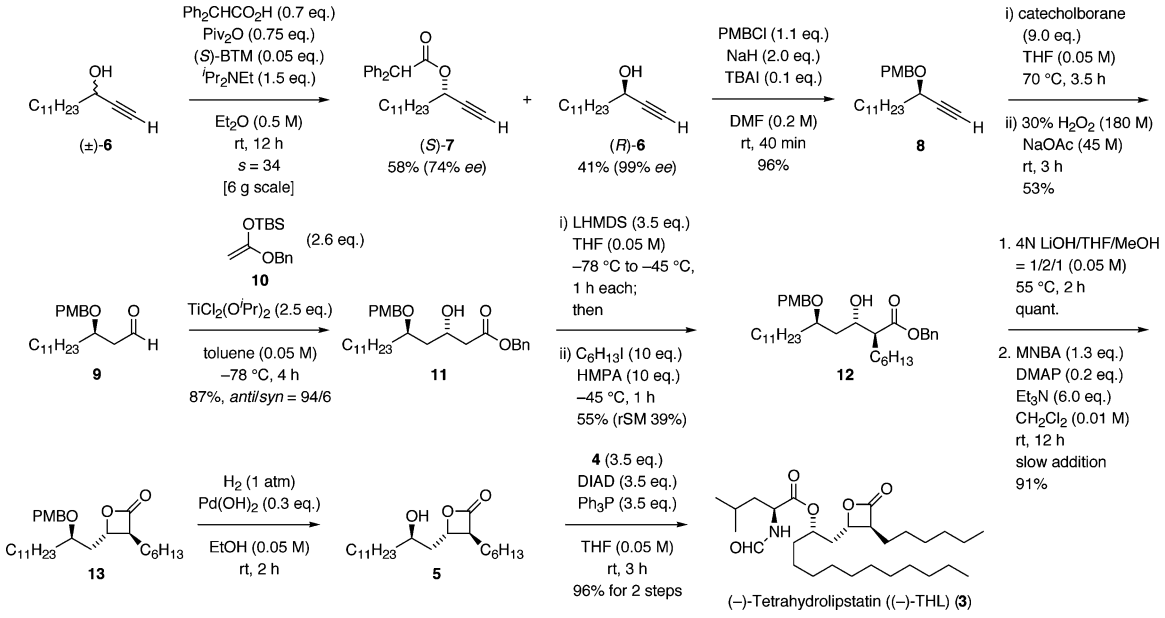
Scheme 12. Production of Chiral Alcohol (*R*)-6 by Kinetic Resolution of Racemic Alcohol (±)-6 via Asymmetric Esterification



Scheme 13. Total Synthesis of (−)-Tetrahydrolipstatin ((−)-THL) (3)



enantioselectivities of (*S*)-**7** (80% ee) and the recovered (*R*)-**6** (96% ee) in good yields (55% and 43%, respectively) when using diphenylacetic acid.

As shown in Scheme 13, the multigram scale synthesis of the optically pure (*R*)-**6** was also carried out by the kinetic resolution of a large amount of (±)-**6** (6.00 g) using diphenylacetic acid with (*S*)-BTM, and a sufficient amount (2.43 g) of the desired chiral propargyl alcohol (*R*)-**6** was obtained in good yield (41% from (±)-**6**) with a very high enantiopurity (99% ee, *s* = 34) via single operation.

Installation of the PMB protective group onto the alcohol (*R*)-**6** and the following hydroboration of the resulting alkyne **8** provided the chiral aldehyde **9** in good yield from (*R*)-**6**. The Mukaiyama aldol reaction of the β-alkoxyaldehyde **9** with ketene silyl acetal **10**, which was prepared from benzyl acetate, mediated by $TiCl_2(O^iPr)_2$ smoothly proceeded to afford the desired *anti*-1,3-diol unit **11** with a high stereoselectivity (*anti*/*syn* = 94/6).[28] The *anti*-selective alkylation at the α-position of the formed β-hydroxyester **11** was attained according to the former established method to exclusively provide the desired trisubstituted benzyl hexadecanoate **12**.[20x,z,29]

After hydrolysis of the benzyl ester **12** with lithium hydroxide, the intramolecular dehydration condensation of the resulting seco-acid was eventually examined using MNBA (1.3 equiv) combined with a catalytic amount of DMAP (0.2 equiv) and triethylamine (6.0 equiv), and the desired *trans*-2,3-disubstituted β-lactone **13** was readily produced in excellent yield (91%) by this facile procedure. On the other hand, we revealed that the MNBA lactonization using an excess amount of DMAP (6.0 equiv) in the absence of triethylamine also produced the β-lactone **13** in a similar satisfactory yield (92%).[30−33] Finally, sequential transformations of **13** by deprotection of the PMB group and the Mitsunobu reaction of the formed alcohol **5** with α-amino acid **4** furnished the targeted molecule (−)-THL (**3**) in a very high yield. All spectral data including the optical rotation of synthetic **3**

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corresponded to those of reported (−)-THL (our synthetic sample; $[\alpha]^{22}_{D}$ −32.5 (*c* 1.17, $CHCl_3$); lit.[19d] $[\alpha]^{20}_{D}$ −32.0 (*c* 1, $CHCl_3$); lit.[20i] $[\alpha]^{25}_{D}$ −33.04 (*c* 0.79, $CHCl_3$); lit.[20n] $[\alpha]^{20}_{D}$ −32.0 (*c* 0.74, $CHCl_3$); lit.[20x] $[\alpha]^{26}_{D}$ −31 (*c* 0.1, $CHCl_3$)), and all the absolute configurations of the stereogenic centers at C-2, C-3, and C-5 positions were unequivocally determined by this identification.

■ CONCLUSION

In summary, 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 ring closures of seco-acids, 3-hydroxy-2,2-dimethyl-5-phenylpentanoic acid (**1b**) and 3-hydroxy-2,2-dimethyl-3-methyl-5-phenylpentanoic acid (**1i**), were demonstrated to afford the corresponding 2,2,3-trisubstituted *β*-lactone **2b** and 2,2,3,3-tetrasubstituted *β*-lactone **2i** in high yields (89% and 95%, respectively). These experimental results were theoretically explained by a mechanistic study by using DFT calculations for the cyclization of the model seco-acids **1B** and **1I** to form *β*-lactones **2B** and **2I** through the low energy transition states **TS-B** and **TS-I**. We also achieved the enantioselective total synthesis of (−)-tetrahydrolipstatin ((−)-THL) (**3**), an antiobestic agent used in clinical treatments, by the MNBA lactonization of the corresponding seco-acid to provide the *β*-lactone moiety of **3** 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 (±)-**6** and (ii) the diastereoselective Mukaiyama aldol reaction of the aldehyde **9** with ketene silyl acetal **10** derived from benzyl acetate, were employed for the construction of the main skeleton of **3**.

■ EXPERIMENTAL SECTION

General Information. ^1H and ^{13}C NMR spectra were recorded with chloroform (in $CDCl_3$) or dimethyl sulfoxide (in DMSO-d_6) as internal standards. In some cases, ^1H NMR assignments were supported by appropriate homonuclear correlation experiments (COSY).

All reactions were carried out under argon atmosphere in dried glassware unless otherwise noted. Dichloromethane was distilled from diphosphorus pentoxide, then calcium hydride, and dried over MS 4 Å, benzene and toluene were distilled from diphosphorus pentoxide, and dried over MS 4 Å, and THF and diethyl ether were distilled from sodium/benzophenone immediately prior to use.

Ethyl 3-Hydroxy-5-phenylpentanoate.[34] To a solution of diisopropylamine (0.650 mL, 4.62 mmol) in THF (37.3 mL) at 0 °C was added butyllithium in hexane (1.59 M, 2.60 mL, 4.13 mmol). The reaction mixture was stirred for 15 min at 0 °C, and then ethyl acetate (0.400 mL, 4.09 mmol) was added at −78 °C. After the reaction mixture had been stirred for 30 min, 3-phenylpropanal (0.490 mL, 3.73 mmol) was added at −78 °C. The reaction mixture was stirred for 2 h, and then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluant; hexane/ethyl acetate = 10/1) to afford ethyl 3-hydroxy-5-phenylpentanoate (754 mg, 91%) as a colorless oil: IR (neat) 3445, 1733 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.31−7.16 (m, 5H, Ph), 4.17 (q, *J* = 7.0 Hz, 2H, OEt), 4.02 (dddd, *J* = 3.0, 4.0, 8.5, 9.0 Hz, 1H, 3-H), 2.83 (ddd, *J* = 5.5, 9.5, 14.0 Hz, 1H, 5-H), 2.70 (ddd, *J* = 7.0, 9.5, 14.0 Hz, 1H, 5-H), 2.51 (dd, *J* = 3.0, 17.0 Hz, 1H, 2-H), 2.44 (dd, *J* = 9.0, 17.0 Hz, 1H, 2-H), 1.85 (dddd, *J* = 5.5, 8.5, 9.5, 14.0 Hz, 1H, 4-H), 1.74 (dddd, *J* = 4.0, 7.0, 9.5, 14.0 Hz, 1H, 4-H), 1.27 (t, *J* = 7.0 Hz, 3H, OEt); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 172.8, 141.7, 128.4, 128.3, 125.8, 67.1, 60.6, 41.3, 38.1, 31.7, 14.1; HRMS (ESI-TOF) calcd for $C_{13}H_{18}O_3Na$ (M + Na^+) 245.1148, found 245.1151.

3-Hydroxy-5-phenylpentanoic Acid (1a). To a solution of ethyl 3-hydroxy-5-phenylpentanoate (754 mg, 3.39 mmol) in aqueous methanol (33.9 mL with 1% water) at room temperature was added potassium carbonate (938 mg, 6.79 mmol). After the reaction mixture had been stirred for 20 h at 65 °C, it was concentrated under reduced pressure. The residue including a small amount of methanol was diluted with water, and then it was extracted with chloroform/ethanol = 7/3 and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by recrystallization from dichloromethane to afford **1a** (460 mg, 70%) as a white solid: mp 126−130 °C; IR (KBr) 3223, 1681 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.31−7.16 (m, 5H, Ph), 4.05 (dddd, *J* = 3.5, 4.0, 8.5, 8.5 Hz, 1H, 3-H), 2.82 (ddd, *J* = 5.5, 9.5, 14.5 Hz, 1H, 5-H), 2.72 (ddd, *J* = 7.0, 9.0, 14.5 Hz, 1H, 5-H), 2.59 (dd, *J* = 3.5, 17.0 Hz, 1H, 2-H), 2.52 (dd, *J* = 8.5, 17.0 Hz, 1H, 2-H), 1.88 (dddd, *J* = 5.5, 8.5, 9.0, 14.0 Hz, 1H, 4-H), 1.78 (dddd, *J* = 4.0, 7.0, 9.5, 14.0 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, DMSO-d_6) *δ* 173.2, 142.4, 128.5, 128.5, 125.8, 66.8, 42.9, 39.0, 31.5; HRMS (ESI-TOF) calcd for $C_{11}H_{14}O_3Na$ (M + Na^+) 217.0835, found 217.0840.

5-Phenylpentan-3-olide (2a).[35] To a solution of MNBA (115 mg, 0.334 mmol), DMAP (6.3 mg, 0.052 mmol), and triethylamine (0.210 mL, 1.51 mmol) in dichloromethane (12.9 mL) at 50 °C was slowly added a solution of **1a** (50.0 mg, 0.257 mmol) in THF (5.1 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at 50 °C, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 3/1) to afford **2a** (9.5 mg, 21%) as a colorless oil: IR (neat) 1824 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) *δ* 7.33−7.17 (m, 5H, Ph), 4.50 (dddd, *J* = 4.5, 5.5, 6.0, 8.0 Hz, 1H, 3-H), 3.48 (dd, *J* = 6.0, 16.0 Hz, 1H, 2-H), 3.03 (dd, *J* = 4.5, 16.0 Hz, 1H, 2-H), 2.83 (ddd, *J* = 5.5, 9.0, 14.0 Hz, 1H, 5-H), 2.72 (ddd, *J* = 7.5, 8.0, 14.0 Hz, 1H, 5-H), 2.20 (dddd, *J* = 5.5, 8.0, 8.0, 14.0 Hz, 1H, 4-H), 2.07 (dddd, *J* = 5.5, 7.5, 9.0, 14.0 Hz, 1H, 4-H); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 168.0, 140.0, 128.7, 128.4, 126.4, 70.4, 42.9, 36.4, 31.3; HRMS (ESI-TOF) calcd for $C_{11}H_{12}O_2Na$ (M + Na^+) 199.0730, found 199.0726.

Ethyl 3-Hydroxy-2,2-dimethyl-5-phenylpentanoate. To a solution of diisopropylamine (0.628 mL, 4.47 mmol) in THF (34 mL) at 0 °C was added butyllithium in hexane (1.59 M, 2.60 mL, 4.13 mmol). The reaction mixture was stirred for 15 min at 0 °C, and then ethyl 2-methylpropanoate (0.547 mL, 4.10 mmol) was added at −78 °C. After the reaction mixture had been stirred for 30 min, a solution of 3-phenylpropanal (500 mg, 3.73 mmol) in THF (3 mL) was added at −78 °C. The reaction mixture was stirred for 1.5 h, and then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluant; hexane/ethyl acetate = 10/1) to afford ethyl 3-hydroxy-2,2-dimethyl-5-phenylpentanoate (933 mg, quant) as a colorless oil: IR (neat) 3456, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) *δ* 7.33−7.15 (m, 5H, Ph), 4.14 (q, *J* = 7.2 Hz, 2H, OEt), 3.62 (ddd, *J* = 2.1, 6.9, 10.5 Hz, 1H, 3-H), 2.96 (ddd, *J* = 5.1, 9.9, 13.8 Hz, 1H, 5-H), 2.65 (ddd, *J* = 6.9, 9.6, 13.8 Hz, 1H, 5-H), 2.65 (d, *J* = 6.9 Hz, 1H, OH), 1.83−1.70 (m, 1H, 4-H), 1.69−1.54 (m, 1H, 4-H), 1.25 (t, *J* = 7.2 Hz, 3H, OEt), 1.19 (s, 3H, 2-Me), 1.16 (s, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) *δ* 177.5, 142.0, 128.3, 128.2, 125.6, 75.7, 60.4, 46.8, 33.6, 32.7, 21.8, 20.4, 13.9; HRMS (ESI-TOF) calcd for $C_{15}H_{22}O_3Na$ (M + Na^+) 273.1461, found 273.1448.

3-Hydroxy-2,2-dimethyl-5-phenylpentanoic Acid (1b). To a solution of ethyl 3-hydroxy-2,2-dimethyl-5-phenylpentanoate (933 mg, 3.73 mmol) in aqueous methanol (37.2 mL with 1% water) at room

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temperature was added potassium carbonate (1.03 g, 7.45 mmol). After the reaction mixture had been stirred for 2 h at 65 °C, it was concentrated under reduced pressure. The residue including a small amount of methanol was diluted with water, and then it was extracted with chloroform/ethanol = 7/3 and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluant; chloroform/ethanol = 15/1) to afford **1b** (662 mg, 80%) as a colorless oil: IR (neat) 3436, 1703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.18 (m, 5H, Ph), 3.66 (dd, J = 2.0, 10.5 Hz, 1H, 3-H), 2.95 (ddd, J = 5.0, 10.0, 14.0 Hz, 1H, 5-H), 2.67 (ddd, J = 7.0, 9.5, 14.0 Hz, 1H, 5-H), 1.84 (dddd, J = 2.0, 7.0, 10.0, 14.0 Hz, 1H, 4-H), 1.68 (dddd, J = 5.0, 9.5, 10.5, 14.0 Hz, 1H, 4-H), 1.24 (s, 3H, 2-Me), 1.19 (s, 3H, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.4, 141.8, 128.4, 128.4, 125.9, 76.0, 47.0, 33.3, 32.8, 22.7, 19.9; HRMS (ESI-TOF) calcd for $C_{13}H_{18}O_3Na$ ($M + Na^+$) 245.1148, found 245.1142.

2,2-Dimethyl-5-phenylpentan-3-olide (2b). To a solution of MNBA (101 mg, 0.292 mmol), DMAP (5.5 mg, 0.045 mmol), and triethylamine (0.190 mL, 1.37 mmol) in dichloromethane (13.5 mL) at room temperature was slowly added a solution of **1b** (50.6 mg, 0.228 mmol) in dichloromethane (9.0 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 3/1) to afford **2b** (41.5 mg, 89%) as a colorless oil: IR (neat) 1821 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.18 (m, 5H, Ph), 4.24 (dd, J = 4.5, 9.5 Hz, 1H, 3-H), 2.86 (ddd, J = 4.5, 9.5, 14.0 Hz, 1H, 5-H), 2.69 (ddd, J = 7.5, 9.0, 14.0 Hz, 1H, 5-H), 2.07 (dddd, J = 4.5, 9.0, 9.5, 14.0 Hz, 1H, 4-H), 1.97 (dddd, J = 4.5, 7.5, 9.5, 14.0 Hz, 1H, 4-H), 1.39 (s, 3H, 2-Me), 1.24 (s, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.3, 140.4, 128.6, 128.4, 126.3, 82.4, 53.3, 32.5, 31.7, 22.5, 16.3; HRMS (ESI-TOF) calcd for $C_{13}H_{16}O_2Na$ ($M + Na^+$) 227.1043, found 227.1034.

***S*-Ethyl (2*S*,3*R*)-3-Hydroxy-2-methyl-5-phenylpentanethioate.**[36,37] To tin(II) trifluoromethanesulfonate (592 mg, 1.42 mmol) at room temperature were added a solution of (*S*)-1-methyl-2-(1-naphthylaminomethyl)pyrrolidine (404 mg, 1.68 mmol) in dichloromethane (8.9 mL) and tributyltin fluoride (479 mg, 1.54 mmol). A solution of (*Z*)-1-ethylthio-1-(trimethylsiloxy)propene (271 mg, 1.55 mmol) in dichloromethane (2 mL) and a solution of 3-phenylpropanal (173 mg, 1.29 mmol) in dichloromethane (2 mL) were successively added at −78 °C. The reaction mixture was stirred for 13 h at −78 °C, and then saturated aqueous sodium hydrogen carbonate was added. The mixture was filtered through a short pad of Celite, and the filtrate was extracted with dichloromethane. The organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 3/1) to afford *S*-ethyl (2*S*,3*R*)-3-hydroxy-2-methyl-5-phenylpentanethioate (171 mg, 52%, 92% ee, *syn*/*anti* = 100/0) as a colorless oil: HPLC (CHIRALCEL OB-H, *i*-PrOH/hexane = 1/19, flow rate =1.0 mL/min); t_R = 9.02 min (96.0%), t_R = 17.47 min (4.0%); $[\alpha]^{22}_D$ +57.2 (*c* 0.840, $CHCl_3$); IR (neat) 3446, 1677 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.16 (m, 5H, Ph), 3.94 (dddd, J = 3.0, 3.0, 3.5, 9.5 Hz, 1H, 3-H), 2.92−2.85 (m, 2H, SEt), 2.92−2.82 (m, 1H, 5-H), 2.72−2.62 (m, 2H, 2-H, 5-H), 2.48 (br d, J = 3.0 Hz, 1H, OH), 1.82 (dddd, J = 5.5, 9.5, 10.0, 14.0 Hz, 1H, 4-H), 1.68 (dddd, J = 3.5, 6.5, 10.0, 14.0 Hz, 1H, 4-H), 1.25 (t, J = 7.5 Hz, 3H, SEt), 1.24 (t, J = 7.5 Hz, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 204.2, 141.7, 128.4, 128.4, 125.8, 71.3, 53.0, 35.8, 32.2, 23.2, 14.5, 11.5; HRMS (ESI-TOF) calcd for $C_{14}H_{20}O_2SNa$ ($M + Na^+$) 275.1076, found 275.1078.

(2*S*,3*R*)-3-Hydroxy-2-methyl-5-phenylpentanoic Acid (1c). To a solution of *S*-ethyl (2*S*,3*R*)-3-hydroxy-2-methyl-5-phenylpentanethioate (158 mg, 0.627 mmol) in THF (11.8 mL) and water (3.9 mL) at room temperature were added lithium hydroxide (30.0 mg, 1.25 mmol) and 30% hydrogen peroxide in water (0.42 mL). After the reaction mixture had been stirred for 24 h at room temperature, 1.0 M hydrochloric acid was added at 0 °C. The acidified mixture (pH = 3) was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluant; chloroform/methanol = 30/1) to afford **1c** (109 mg, 83%) as a white solid: $[\alpha]^{22}_D$ +25.7 (*c* 0.987, $CHCl_3$); mp 77−78 °C; IR (KBr) 3381, 1705 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.20 (m, 5H, Ph), 3.99 (ddd, J = 3.5, 3.5, 9.5 Hz, 1H, 3-H), 2.89 (ddd, J = 5.5, 9.5, 14.0 Hz, 1H, 5-H), 2.71 (ddd, J = 7.0, 9.5, 14.0 Hz, 1H, 5-H), 2.65 (dq, J = 3.5, 7.5 Hz, 1H, 2-H), 1.87 (dddd, J = 5.5, 9.5, 9.5, 14.0 Hz, 1H, 4-H), 1.76 (dddd, J = 3.5, 7.0, 9.5, 14.0 Hz, 1H, 4-H), 1.25 (d, J = 7.5 Hz, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0, 141.5, 128.4, 128.4, 125.9, 71.1, 44.2, 35.3, 32.2, 10.4; HRMS (ESI-TOF) calcd for $C_{12}H_{16}O_3Na$ ($M + Na^+$) 231.0992, found 231.1001.

(2*S*,3*R*)-2-Methyl-5-phenylpentan-3-olide (2c):[38] To a solution of MNBA (104 mg, 0.301 mmol), DMAP (5.6 mg, 0.046 mmol), and triethylamine (0.193 mL, 1.39 mmol) in dichloromethane (17 mL) at room temperature was slowly added a solution of **1c** (48.2 mg, 0.231 mmol) in dichloromethane (6.2 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified twice by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 3/1 and hexane/chloroform =1/5) to afford **2c** (5.6 mg, 13%) as a colorless oil: $[\alpha]^{23}_D$ +53.0 (*c* 0.640, $CHCl_3$) [lit.[38] $[\alpha]_D$ −47.2 (*c* 2.04, $CHCl_3$) for *ent*-**2c** (>99% ee)]; IR (neat) 1820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.18 (m, 5H, Ph), 4.56 (ddd, J = 4.0, 6.5, 10.0 Hz, 1H, 3-H), 3.74 (dq, J = 6.5, 8.0 Hz, 1H, 2-H), 2.88 (ddd, J = 5.0, 8.5, 14.0 Hz, 1H, 5-H), 2.71 (ddd, J = 7.5, 9.0, 14.0 Hz, 1H, 5-H), 2.09 (dddd, J = 4.0, 8.5, 9.0, 13.5 Hz, 1H, 4-H), 1.96 (dddd, J = 5.0, 7.5, 10.0, 13.5 Hz, 1H, 4-H), 1.27 (d, J = 8.0 Hz, 3H, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.5, 140.4, 128.6, 128.5, 126.4, 74.6, 47.2, 32.0, 31.5, 8.1; HRMS (ESI-TOF) calcd for $C_{12}H_{14}O_2Na$ ($M + Na^+$) 213.0886, found 213.0878.

Ethyl (2*R,3*R**)-3-Hydroxy-2-methyl-5-phenylpentanoate.**[39] To a solution of diisopropylamine (0.12 mL, 0.854 mmol) in THF (3.8 mL) at 0 °C was added butyllithium in hexane (2.69 M, 0.310 mL, 0.834 mmol). After the reaction mixture had been stirred for 15 min at 0 °C, a solution of ethyl 3-hydroxy-5-phenylpentanoate (53.1 mg, 0.239 mmol) in THF (1 mL) was added at −78 °C. The reaction mixture was stirred for 30 min at −78 °C and for 1 h at −45 °C, and then a solution of iodomethane (0.150 mL, 2.41 mmol) in HMPA (0.420 mL, 2.41 mmol) was added at −45 °C. After the reaction mixture had been stirred for 1 h at −45 °C, saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 4/1) to afford ethyl (2*R**,3*R**)-3-hydroxy-2-methyl-5-phenylpentanoate (47.8 mg, 85%, *anti*/*syn* = 100/0) and recovered ethyl 3-hydroxy-5-phenylpentanoate (2.4 mg, 5%) as colorless oils. **Ethyl (2*R**,3*R**)-3-hydroxy-2-methyl-5-phenylpentanoate**: IR (neat) 3437, 1727 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.17 (m, 5H, Ph), 4.17 (q, J = 7.0 Hz, 2H, OEt), 3.67 (dddd, J = 3.0, 7.0, 7.0, 9.5 Hz, 1H, 3-H), 2.87 (ddd, J = 5.5, 10.0, 14.0 Hz, 1H, 5-H), 2.72 (d, J = 7.0 Hz, 1H, OH), 2.70 (ddd, J = 6.5, 9.5, 14.0 Hz, 1H, 5-H), 2.52 (dq, J = 7.0, 7.5 Hz, 1H, 2-H), 1.82 (dddd, J = 3.0, 6.5, 10.0, 13.5 Hz, 1H, 4-H), 1.74 (dddd, J = 5.5, 9.5, 9.5, 13.5 Hz, 1H, 4-H), 1.27 (t, J = 7.0 Hz, 3H, OEt), 1.21 (d, J = 7.5 Hz, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 176.0, 141.9, 128.4, 128.3, 125.8, 72.6, 60.5, 45.2, 36.6, 31.9, 14.2, 14.1; HRMS (ESI-TOF) calcd for $C_{14}H_{20}O_3Na$ ($M + Na^+$) 259.1305, found 259.1314.

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(2*R,3*R**)-3-Hydroxy-2-methyl-5-phenylpentanoic Acid (1d).** To a solution of ethyl (2*R**,3*R**)-3-hydroxy-2-methyl-5-phenylpentanoate (91.8 mg, 0.388 mmol) in methanol (0.97 mL) and THF (1.94 mL) at room temperature was added lithium hydroxide in water (4.00 M, 0.970 mL, 3.88 mmol). The reaction mixture was stirred for 30 min at room temperature and then 1.0 M hydrochloric acid was added at 0 °C. The acidified mixture (pH = 1) was extracted with diethyl ether and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; chloroform/methanol/formic acid = 900/100/3) to afford **1d** (79.1 mg, 98%) as a white solid: mp 71−72 °C; IR (KBr) 3390, 1709 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.31−7.18 (m, 5H, Ph), 3.72 (ddd, *J* = 3.0, 7.0, 9.0 Hz, 1H, 3-H), 2.87 (ddd, *J* = 5.5, 10.0, 14.0 Hz, 1H, 5-H), 2.72 (ddd, *J* = 7.0, 9.5, 14.0 Hz, 1H, 5-H), 2.59 (dq, *J* = 7.0, 7.0 Hz, 1H, 2-H), 1.88 (dddd, *J* = 3.0, 7.0, 10.0, 14.0 Hz, 1H, 4-H), 1.80 (dddd, *J* = 5.5, 9.0, 9.5, 14.0 Hz, 1H, 4-H), 1.26 (d, *J* = 7.0 Hz, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.0, 141.6, 128.4, 128.4, 125.9, 72.6, 45.3, 36.2, 31.8, 14.1; HRMS (ESI-TOF) calcd for $C_{12}H_{16}O_3Na$ (M + Na^+) 231.0992, found 231.0997.

(2*R,3*R**)-2-Methyl-5-phenylpentan-3-olide (2d).**[40] To a solution of MNBA (140 mg, 0.406 mmol), DMAP (7.6 mg, 0.062 mmol), and triethylamine (0.260 mL, 1.88 mmol) in dichloromethane (25 mL) at room temperature was slowly added a solution of **1d** (65.0 mg, 0.312 mmol) in dichloromethane (6.2 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate =3/1) to afford **2d** (40.7 mg, 69%) as a colorless oil: IR (neat) 1823 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.18 (m, 5H, Ph), 4.17 (ddd, *J* = 4.0, 5.5, 8.0 Hz, 1H, 3-H), 3.20 (dq, *J* = 4.0, 7.5 Hz, 1H, 2-H), 2.83 (ddd, *J* = 5.5, 8.5, 14.0 Hz, 1H, 5-H), 2.71 (ddd, *J* = 8.0, 8.0, 14.0 Hz, 1H, 5-H), 2.20 (dddd, *J* = 5.5, 8.0, 8.0, 14.5 Hz, 1H, 4-H), 2.09 (dddd, *J* = 5.5, 8.0, 8.5, 14.5 Hz, 1H, 4-H), 1.32 (d, *J* = 7.5 Hz, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.8, 140.0, 128.6, 128.3, 126.4, 78.6, 50.8, 35.8, 31.3, 12.4; HRMS (ESI-TOF) calcd for $C_{12}H_{14}O_2Na$ (M + Na^+) 213.0886, found 213.0876.

Ethyl (2*R,3*R**)-2-Hexyl-5-phenylpentanoate.** To a solution of diisopropylamine (0.250 mL, 1.78 mmol) in THF (6.9 mL) at 0 °C was added butyllithium in hexane (1.57 M, 1.11 mL, 1.74 mmol). The reaction mixture was stirred for 15 min at 0 °C, and then a solution of ethyl 3-hydroxy-5-phenylpentanoate (110 mg, 0.496 mmol) in THF (3 mL) was added at −78 °C. The reaction mixture was stirred for 1 h at −78 °C and for 1 h at −45 °C, and then a solution of iodohexane (0.730 mL, 4.96 mmol) in HMPA (0.860 mL, 4.94 mmol) was added. After the reaction mixture had been stirred for 2 h at −45 °C, saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 3/1) to afford ethyl (2*R**,3*R**)-2-hexyl-5-phenylpentanoate (98.2 mg, 65%, *anti*/*syn* = 100/0) and recovered ethyl 3-hydroxy-5-phenylpentanoate (28.5 mg, 26%) as colorless oils. **Ethyl (2*R**,3*R**)-2-hexyl-5-phenylpentanoate**: IR (neat) 3448, 1720 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.15 (m, 5H, Ph), 4.20 (qd, *J* = 7.2, 10.8 Hz, 1H, OEt), 4.16 (qd, *J* = 7.2, 10.8 Hz, 1H, OEt), 3.68 (dddd, *J* = 4.5, 5.1, 8.4, 8.7 Hz, 1H, 3-H), 2.86 (ddd, *J* = 6.3, 9.0, 14.1 Hz, 1H, 5-H), 2.69 (ddd, *J* = 7.5, 9.3, 14.1 Hz, 1H, 5-H), 2.65 (d, *J* = 8.4 Hz, 1H, OH), 2.43 (ddd, *J* = 5.1, 5.4, 9.0 Hz, 1H, 2-H), 1.86−1.66 (m, 3H, 4-H, 1′-H), 1.66−1.53 (m, 1H, 4-H), 1.34−1.20 (m, 8H, 2′-H, 3′-H, 4′-H, 5′-H), 1.28 (t, *J* = 7.2 Hz, 3H, OEt), 0.88 (t, *J* = 7.2 Hz, 3H, 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 141.8, 128.3, 128.3, 125.7, 71.5, 60.3, 50.9, 37.4, 32.0, 31.5, 29.5, 29.0, 27.1, 22.4, 14.2, 13.9; HRMS (ESI-TOF) calcd for $C_{19}H_{30}O_3Na$ (M + Na^+) 329.2087, found 329.2093.

(2*R,3*R**)-2-Hexyl-5-phenylpentanoic Acid (1e).** To a solution of ethyl (2*R**,3*R**)-2-hexyl-5-phenylpentanoate (98.2 mg, 0.320 mmol) in methanol (0.8 mL) and THF (1.6 mL) at room temperature was added lithium hydroxide in water (4.00 M, 0.800 mL, 3.20 mmol). The reaction mixture was stirred for 18 h at room temperature and then 1.0 M hydrochloric acid was added at 0 °C. The acidified mixture (pH = 4) was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; chloroform/methanol/formic acid = 900/100/3) to afford **1e** (78.9 mg, 88%) as a colorless oil: IR (neat) 3417, 1712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.15 (m, 5H, Ph), 3.77−3.68 (m, 1H, 3-H), 2.86 (ddd, *J* = 5.5, 9.0, 14.0 Hz, 1H, 5-H), 2.71 (ddd, *J* = 7.0, 9.5, 14.0 Hz, 1H, 5-H), 2.48 (ddd, *J* = 5.0, 5.5, 10.0 Hz, 1H, 2-H), 1.91−1.78 (m, 2H, 1′-H), 1.78−1.67 (m, 1H, 4-H), 1.67−1.56 (m, 1H, 4-H), 1.38−1.17 (m, 8H, 2′-H 3′-H, 4′-H, 5′-H), 0.87 (t, *J* = 7.0 Hz, 3H, 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 180.4, 141.6, 128.4, 128.4, 125.9, 71.6, 51.3, 37.0, 31.9, 31.5, 29.3, 29.1, 27.2, 22.5 (1′ to 5′), 14.0 (6′); HRMS (ESI-TOF) calcd for $C_{17}H_{26}O_3Na$ (M + Na^+) 301.1774, found 301.1780.

(2*R,3*R**)-2-Hexyl-5-phenylpentan-3-olide (2e).** To a solution of MNBA (56.8 mg, 0.165 mmol), DMAP (3.1 mg, 0.025 mmol), and triethylamine (0.110 mL, 0.794 mmol) in dichloromethane (10 mL) at room temperature was slowly added a solution of **1e** (35.4 mg, 0.127 mmol) in dichloromethane (2.7 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 6/1) to afford **2e** (27.6 mg, 83%) as a colorless oil: IR (neat) 1820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.34−7.17 (m, 5H, Ph), 4.22 (ddd, *J* = 4.0, 5.5, 9.0 Hz, 1H, 3-H), 3.18 (ddd, *J* = 4.0, 7.0, 8.5 Hz, 1H, 2-H), 2.82 (ddd, *J* = 5.0, 9.0, 14.0 Hz, 1H, 5-H), 2.70 (ddd, *J* = 7.5, 8.5, 14.0 Hz, 1H, 5-H), 2.18 (dddd, *J* = 5.0, 8.5, 9.0, 14.0 Hz, 1H, 4-H), 2.07 (dddd, *J* = 5.5, 7.5, 9.0, 14.0 Hz, 1H, 4-H), 1.78 (dddd, *J* = 5.5, 7.0, 10.0, 14.0 Hz, 1H, 1′-H), 1.67 (dddd, *J* = 5.0, 8.5, 9.5, 14.0 Hz, 1H, 1′-H), 1.46−1.20 (m, 8H, 2′-H 3′-H, 4′-H, 5′-H), 0.88 (t, *J* = 7.0 Hz, 3H, 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.3, 140.1, 128.6, 128.3, 126.3, 77.1, 56.2, 36.1, 31.4, 31.3, 28.8, 27.7, 26.8, 22.4, 14.0; HRMS (ESI-TOF) calcd for $C_{17}H_{24}O_2Na$ (M + Na^+) 283.1669, found 283.1678.

Ethyl 3-Hydroxy-2,2-dimethyl-3-phenylpropanoate.[41] To a solution of diisopropylamine (0.675 mL, 4.80 mmol) in THF (37.0 mL) at 0 °C was added butyllithium in hexane (1.57 M, 2.83 mL, 4.44 mmol). The reaction mixture was stirred for 15 min at 0 °C, and then ethyl isobutyrate (0.592 mL, 4.43 mmol) was added at −78 °C. After the reaction mixture had been stirred for 30 min, benzaldehyde (0.374 mL, 3.70 mmol) was added at −78 °C. The reaction mixture was stirred for 1 h, and then saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluent; hexane/ethyl acetate = 4/1) to afford ethyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (803 mg, 98%) as a colorless oil: IR (neat) 3487, 1717 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35−7.23 (m, 5H, Ph), 4.89 (d, *J* = 4.0 Hz, 1H, 3-H), 4.19 (q, *J* = 7.2 Hz, 2H, OEt), 3.13 (d, *J* = 4.0 Hz, 1H, OH), 1.27 (t, *J* = 7.2 Hz, 3H, OEt), 1.14 (s, 3H, 2-Me), 1.12 (s, 3H, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.7, 140.0, 127.63, 127.63, 127.60, 78.6, 60.8, 47.5, 22.9, 19.0, 14.0; HRMS (ESI-TOF) calcd for $C_{13}H_{18}O_3Na$ (M + Na^+) 245.1148, found 245.1138.

3-Hydroxy-2,2-dimethyl-3-phenylpropanoic Acid (1f).[42] To a solution of ethyl 3-hydroxy-2,2-dimethyl-3-phenylpropanoate (263 mg, 1.18 mmol) in methanol (3.0 mL) and THF (6.0 mL) at 0 °C was added lithium hydroxide in water (4.00 M, 3.00 mL, 12.0 mmol). The reaction mixture was stirred for 10 h at room temperature and then 1.0 M hydrochloric acid was added at 0 °C. The acidic mixture (pH = 4)

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was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by recrystallization from dichloromethane to afford **1f** (195 mg, 85%) as a white solid: mp 134−135 °C; IR (KBr) 3383, 1697 cm^{-1}: ^1H NMR (400 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H, Ph), 4.95 (s, 1H, 3-H), 2.17 (s, 1H, OH), 1.18 (s, 3H, 2-Me), 1.18 (s, 3H, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 139.5, 128.1, 128.0, 127.7, 78.5, 47.5, 23.3, 18.7; HRMS (ESI-TOF) calcd for $C_{11}H_{14}O_3Na$ (M + Na^+) 217.0835, found 217.0833.

2,2-Dimethyl-3-phenylpropan-3-olide (2f). To a solution of MNBA (92.4 mg, 0.268 mmol), DMAP (5.0 mg, 0.041 mmol), and triethylamine (0.170 mL, 1.23 mmol) in dichloromethane (17.8 mL) at room temperature was slowly added a solution of **1f** (40.1 mg, 0.206 mmol) in THF (2.8 mL) and dichloromethane (2.8 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 9/1) to afford **2f** (32.6 mg, 90%) as a colorless oil: IR (neat) 1828 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.47−7.24 (m, 5H, Ph), 5.32 (s, 1H, 3-H), 1.58 (s, 3H, 2-Me), 0.90 (s, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.0, 135.3, 128.6, 128.4, 125.1, 82.8, 56.6, 22.4, 17.9; HRMS (ESI-TOF) calcd for $C_{11}H_{12}O_2Na$ (M + Na^+) 199.0730, found 199.0729.

Benzyl 3-Hydroxy-3-phenylpropanoate. To a solution of diisopropylamine (90.0 μL, 0.640 mmol) in THF (5.0 mL) at 0 °C was added butyllithium in hexane (1.57 M, 0.390 mL, 0.612 mmol). The reaction mixture was stirred for 15 min at 0 °C, and then benzyl acetate (83.0 μL, 0.597 mmol) was added at −78 °C. After the reaction mixture had been stirred for 30 min, benzaldehyde (50.0 μL, 0.495 mmol) was added at −78 °C. The reaction mixture was stirred for 1 h, and then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluent; hexane/ethyl acetate = 4/1) to afford benzyl 3-hydroxy-3-phenylpropanoate (130 mg, quant) as a colorless oil: IR (neat) 3451, 1734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.27 (m, 10H, Ph, Ph), 5.18 (d, J = 13.5 Hz, 1H, Bn), 5.16 (d, J = 13.5 Hz, 1H, Bn), 5.16 (ddd, J = 3.5, 3.5, 8.5 Hz, 1H, 3-H), 3.15 (d, J = 3.5 Hz, 1H, OH), 2.84 (dd, J = 8.5, 17.0 Hz, 1H, 2-H), 2.78 (dd, J = 3.5, 17.0 Hz, 1H, 2-H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 142.4, 135.5, 128.6, 128.5, 128.3, 128.2, 127.8, 125.6, 70.3, 66.6, 43.3; HRMS (ESI-TOF) calcd for $C_{16}H_{16}O_3Na$ (M + Na^+) 279.0992, found 279.0998.

Benzyl (2*R,3*S**)-3-Hydroxy-2-methyl-3-phenylpropanoate.**[43] To a solution of benzyl 3-hydroxy-3-phenylpropanoate (65.2 mg, 0.254 mmol) in THF (5.1 mL) at −78 °C was added a solution of LHMDS in THF (1.00 M, 0.890 mL, 0.890 mmol). The reaction mixture was stirred for 30 min at −78 °C and for 1 h at −45 °C, and then a solution of iodomethane (0.160 mL, 2.57 mmol) in HMPA (0.440 mL, 2.53 mmol) was added. After the reaction mixture had been stirred for 1 h at −45 °C, saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 4/1) to afford benzyl (2*R**,3*S**)-3-hydroxy-2-methyl-3-phenylpropanoate (20.8 mg, 30%, *anti*/*syn* = 100/0) and recovered benzyl 3-hydroxy-3-phenylpropanoate (36.6 mg, 56%) as colorless oils. **Benzyl (2*R**,3*S**)-3-hydroxy-2-methyl-3-phenylpropanoate:** IR (neat) 3464, 1734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.28 (m, 10H, Ph), 5.19 (d, J = 13.5 Hz, 1H, Bn), 5.16 (d, J = 13.5 Hz, 1H, Bn), 4.79 (dd, J = 5.0, 8.5 Hz, 1H, 3-H), 2.91 (d, J = 5.0 Hz, 1H, OH), 2.89 (qd, J = 7.5, 8.5 Hz, 1H, 2-H), 1.05 (d, J = 7.5 Hz, 1H, 2-Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 141.5, 135.7, 128.5, 128.4, 128.1, 128.0, 127.9, 126.6, 76.2, 66.4, 47.2, 14.4; HRMS (ESI-TOF) calcd for $C_{17}H_{18}O_3Na$ (M + Na^+) 293.1148, found 293.1148.

(2*R,3*S**)-3-Hydroxy-2-methyl-3-phenylpropanoic Acid (1g).**[44] To a solution of benzyl (2*R**,3*S**)-3-hydroxy-2-methyl-3-phenylpropanoate (65.1 mg, 0.241 mmol) in methanol (0.6 mL) and THF (1.2 mL) at 0 °C was added lithium hydroxide in water (4.00 M, 0.600 mL, 2.40 mmol). After the reaction mixture had been stirred for 3 h at room temperature, 1.0 M hydrochloric acid was added at 0 °C. The acidified mixture (pH = 4) was extracted with ethyl acetate and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 4/1) to afford **1g** (195 mg, 85%) as a white solid: mp 96−97 °C; IR (KBr) 3383, 1713 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.20 (m, 5H, Ph), 4.75−4.60 (m, 1H, 3-H), 2.85−2.70 (m, 1H, 2-H), 1.00−0.86 (m, 3H, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 182.4, 141.5, 128.4, 127.9, 127.0, 77.2, 48.1, 14.5; HRMS (ESI-TOF) calcd for $C_{10}H_{12}O_3Na$ (M + Na^+) 203.0679, found 203.0670.

(2*R,3*S**)-2-Methyl-3-phenylpropan-3-olide (2g).**[45] To a solution of MNBA (72.5 mg, 0.211 mmol), DMAP (4.0 mg, 0.032 mmol), and triethylamine (0.130 mL, 0.938 mmol) in dichloromethane (12.0 mL) at room temperature was slowly added a solution of **1g** (29.2 mg, 0.162 mmol) in dichloromethane (4.2 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluant; hexane/ethyl acetate/triethylamine = 50/10/1) to afford **2g** (18.0 mg, 69%) as a colorless oil: IR (neat) 1824 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.35 (m, 5H, Ph), 5.16 (d, J = 4.2 Hz, 1H, 3-H), 3.59 (dq, J = 4.2, 7.5 Hz, 1H, 2-H), 1.54 (d, J = 7.5 Hz, 3H, 2-Me); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 137.1, 129.1, 128.9, 125.5, 79.1, 54.6, 12.6; HRMS (ESI-TOF) calcd for $C_{10}H_{10}O_2Na$ (M + Na^+) 185.0573, found 185.0580.

Ethyl 3-Hydroxy-3-phenylpropanoate.[41,46] To a solution of diisopropylamine (0.90 mL, 6.40 mmol) in THF (24.7 mL) at 0 °C was added butyllithium in hexane (2.69 M, 2.30 mL, 6.19 mmol). The reaction mixture was stirred for 20 min at 0 °C, and then ethyl aceate (0.580 mL, 5.93 mmol) was added at −78 °C. After the reaction mixture had been stirred for 30 min, benzaldehyde (0.500 mL, 4.95 mmol) was added at −78 °C. The reaction mixture was stirred for 1 h, and then saturated aqueous ammonium chloride was added. The mixture was extracted with diethyl ether, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluent; hexane/ethyl acetate = 4/1) to afford ethyl 3-hydroxy-3-phenylpropanoate (936 mg, 97%) as a colorless oil: IR (neat) 3454, 1732 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41−7.27 (m, 5H, Ph), 5.14 (ddd, J = 3.5, 4.0, 8.5 Hz, 1H, 3-H), 4.19 (q, J = 7.5 Hz, 2H, OEt), 3.25 (d, J = 3.5 Hz, 1H, OH), 2.76 (dd, J = 8.5, 16.0 Hz, 1H, 2-H), 2.71 (dd, J = 4.0, 16.0 Hz, 1H, 2-H), 1.27 (t, J = 7.5 Hz, 3H, OEt); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.1, 142.6, 128.3, 127.6, 125.5, 70.1, 60.7, 43.3, 14.0; HRMS (ESI-TOF) calcd for $C_{11}H_{14}O_3Na$ (M + Na^+) 217.0835, found 217.0834.

Ethyl (2*R,3*S**)-2-Hexyl-3-hydroxy-3-phenylpropanoate.** To a solution of ethyl 3-hydroxy-5-phenylpropanoate (250 mg, 1.29 mmol) in THF (6.4 mL) at −78 °C was added a solution of LHMDS in THF (1.00 M, 4.50 mL, 4.50 mmol). The reaction mixture was stirred for 1 h at −78 °C and for 1 h at −45 °C, and then a solution of iodohexane (1.90 mL, 12.9 mmol) in HMPA (2.24 mL, 11.6 mmol) was added. After the reaction mixture had been stirred for 40 min at −45 °C, saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 4/1) to afford ethyl (2*R**,3*S**)-2-hexyl-3-hydroxy-3-phenylpropanoate

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(43.1 mg, 12%, *anti*/*syn* = 100/0) and recovered ethyl 3-hydroxy-5-phenylpropanoate (202 mg, 81%) as colorless oils. **Ethyl (2*R**,3*S**)-2-hexyl-3-hydroxy-3-phenylpropanoate:** IR (neat) 3464, 1734 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.18 (m, 5H, Ph), 4.71 (dd, J = 6.5, 7.5 Hz, 1H, 3-H), 4.09 (qd, J = 7.0, 12.5 Hz, 1H, OEt), 4.07 (qd, J = 7.0, 12.5 Hz, 1H, OEt), 2.83 (d, J = 6.5 Hz, 1H, OH), 2.66 (ddd, J = 4.0, 7.5, 9.5 Hz, 1H, 2-H), 1.57−1.47 (m, 1H, 1′-H), 1.28−1.20 (m, 1H, 1′-H), 1.19−1.05 (m, 11H, OEt, 2′-H, 3′-H, 4′-H, 5′-H), 0.76 (t, J = 7.5 Hz, 3H, 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 142.1, 128.4, 127.9, 126.4, 75.3, 60.5, 53.0, 31.5, 29.6, 29.0, 27.0, 22.5, 14.2, 14.0; HRMS (ESI-TOF) calcd for $C_{17}H_{26}O_3Na$ (M + Na^+) 301.1774, found 301.1762.

(2*R,3*S**)-2-Hexyl-3-hydroxy-3-phenylpropanoic Acid (1h).** To a solution of ethyl (2*R**,3*R**)-2-hexyl-3-phenylpropanoate (32.9 mg, 0.118 mmol) in methanol (0.6 mL) and THF (1.2 mL) at 0 °C was added lithium hydroxide in water (4.00 M, 0.600 mL, 2.40 mmol). After the reaction mixture had been stirred for 30 min at room temperature, 1.0 M hydrochloric acid was added at 0 °C. The acidified mixture (pH = 4) was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; chloroform/methanol = 9/1) to afford **1h** (29.0 mg, 98%) as a colorless oil: IR (neat) 3397, 1704 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30−7.10 (m, 5H, Ph), 4.74−4.53 (m, 1H, 3-H), 2.73−2.52 (m, 1H, 2-H), 1.48−1.34 (m, 1H, 1′-H), 1.27−1.13 (m, 1H, 1′-H), 1.15−0.93 (m, 11H, OEt, 2′-H, 3′-H, 4′-H, 5′-H), 0.72 (t, J = 7.5 Hz, 3H, 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 181.9, 141.9, 128.3, 127.8, 127.0, 75.9, 54.2, 31.6, 29.7, 29.2, 27.2, 22.6, 14.0; HRMS (ESI-TOF) calcd for $C_{15}H_{22}O_3Na$ (M + Na^+) 273.1461, found 273.1472.

(2*R,3*S**)-2-Hexyl-3-phenylpropan-3-olide (2h).** To a solution of MNBA (60.6 mg, 0.176 mmol), DMAP (3.3 mg, 0.027 mmol), and triethylamine (0.110 mL, 0.794 mmol) in dichloromethane (10.0 mL) at room temperature was slowly added a solution of **1h** (33.9 mg, 0.135 mmol) in dichloromethane (3.5 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluant; hexane/ethyl acetate/triethylamine = 50/10/1) to afford **2h** (25.4 mg, 81%) as a colorless oil: IR (neat) 1826 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.46−7.35 (m, 5H, Ph), 5.21 (d, J = 4.2 Hz, 1H, 3-H), 3.53 (ddd, J = 4.2, 6.6, 8.4 Hz, 1H, 2-H), 1.99 (dtd, J = 6.6, 9.0, 13.5 Hz, 1H, 1′-H), 1.88 (tdd, J = 6.0, 8.4, 13.5 Hz, 1H, 1′-H), 1.60−1.24 (m, 8H, 2′-H, 3′-H, 4′-H, 5′-H), 0.88 (t, J = 6.3 Hz, 3H, 6′-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3, 137.3, 129.0, 128.9, 125.5, 77.7, 59.9, 31.4, 28.9, 28.1, 26.9, 22.5, 14.0; HRMS (ESI-TOF) calcd for $C_{15}H_{20}O_2Na$ (M + Na^+) 255.1356, found 255.1345.

3-Hydroxy-2,2,3-trimethyl-5-phenylpentanoic Acid (1i). To a solution of diisopropylamine (1.30 mL, 4.25 mmol) in THF (18.5 mL) at 0 °C was added butyllithium in hexane (1.57 M, 5.66 mL, 8.89 mmol). The reaction mixture was stirred for 15 min at 0 °C, and then 2-methylpropanoic acid (0.592 mL, 4.44 mmol) was added at −45 °C. After the reaction mixture had been stirred for 2 h at 50 °C, 4-phenylbutan-2-one (0.374 mL, 3.70 mmol) was added at −45 °C. The reaction mixture was stirred for 2 h at −45 °C and for 1 h at 50 °C and then 1.0 M hydrochloric acid was added at 0 °C. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluent; chloroform/methanol = 20/1) to afford **1i** (607 mg, 70%) as a colorless oil: IR (neat) 3414, 1692 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.43−7.08 (m, 5H, Ph), 2.92−2.74 (m, 1H, 5-H), 2.74−2.55 (m, 1H, 5-H), 1.90−1.64 (m, 2H, 4-H), 1.26 (s, 3H, 3-Me), 1.22 (s, 3H, 2-Me), 1.20 (s, 3H, 2-Me); ^{13}C NMR (100 MHz, $CDCl_3$) δ 183.8, 142.5, 128.4, 128.3, 125.7, 77.2, 50.2, 38.9, 29.9, 21.5, 21.2, 21.1; HRMS (ESI-TOF) calcd for $C_{14}H_{20}O_3Na$ (M + Na^+) 259.1305, found 259.1296.

2,2,3-Trimethyl-5-phenylpentan-3-olide (2i).[9f] To a solution of MNBA (82.6 mg, 0.240 mmol), DMAP (4.5 mg, 0.037 mmol), and triethylamine (0.150 mL, 1.08 mmol) in dichloromethane (14.0 mL) at room temperature was slowly added a solution of **1i** (43.6 mg, 0.185 mmol) in dichloromethane (4.5 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 4/1) to afford **2i** (38.1 mg, 95%) as a white solid: mp 50−52 °C; IR (neat) 1805 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.33−7.18 (m, 5H, Ph), 2.74 (ddd, J = 5.0, 13.5, 13.5 Hz, 1H, 5-H), 2.68 (ddd, J = 5.0, 12.0, 13.5 Hz, 1H, 5-H), 2.17 (ddd, J = 5.0, 12.0, 14.5 Hz, 1H, 4-H), 2.06 (ddd, J = 5.0, 13.5, 14.5 Hz, 1H, 4-H), 1.59 (s, 3H, 3-Me), 1.36 (s, 6H, 2-Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.6, 141.0, 128.6, 128.1, 126.2, 85.0, 54.8, 38.7, 30.5, 20.2, 19.3, 18.4; HRMS (ESI-TOF) calcd for $C_{14}H_{18}O_2Na$ (M + Na^+) 241.1199, found 241.1192.

1-Trimethylsilyltetradec-1-yn-3-ol.[24] To a solution of trimethylsilylacetylene (9.23 g, 94.0 mmol) in THF (100 mL) at −78 °C was added butyllithium in hexane (2.69 M, 34.9 mL, 94.0 mmol). After the reaction mixture had been stirred for 1 h at −23 °C, a solution of dodecanal (15.7 g, 85.2 mmol) in THF (42 mL) was added at −78 °C. The reaction mixture was stirred for 1 h at −23 °C and then saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with water and brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluant; hexane/ethyl acetate = 40/1) to afford 1-trimethylsilyltetradec-1-yn-3-ol (21.8 g, 90%) as a colorless oil: IR (neat) 3340 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.35 (dt, J = 6.0, 6.0 Hz, 1H, 3-H), 1.73 (br d, J = 6.0, 1H, OH), 1.72−1.63 (m, 2H, 4-H), 1.49−1.37 (m, 2H, 5-H), 1.36−1.20 (m, 16H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H), 0.88 (t, J = 6.0 Hz, 3H, 14-H), 0.17 (s, 9H, TMS); ^{13}C NMR (125 MHz, $CDCl_3$) δ 107.0, 89.2, 62.9, 37.7, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.2, 25.1, 22.7, 14.1, −0.1; HRMS (ESI-TOF) calcd for $C_{17}H_{34}OSiNa$ (M + Na^+) 305.2271, found 305.2275.

Tetradec-1-yn-3-ol ((±)-6). To a solution of 1-trimethylsilyltetradec-1-yn-3-ol (533 mg, 1.90 mmol) in methanol (6.3 mL) at room temperature was added potassium carbonate (315 mg, 2.28 mmol). After the reaction mixture had been stirred for 1 h at room temperature, it was concentrated under reduced pressure. The residue was diluted with water and extracted with diethyl ether, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 8/1) to afford (±)-**6** (375 mg, 94%) as a white solid: mp 32−33 °C; IR (KBr) 3363, 3309 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 4.36 (ddd, J = 2.5, 6.0, 7.5 Hz, 1H, 3-H), 2.45 (d, J = 2.5 Hz, 1H, 1-H), 1.93 (br s, 1H, OH), 1.77−1.63 (m, 2H, 4-H), 1.51−1.40 (m, 2H, 5-H), 1.37−1.19 (m, 16H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H), 0.88 (t, J = 6.0 Hz, 3H, 14-H), ^{13}C NMR (125 MHz, $CDCl_3$) δ 85.1, 72.8, 62.3, 37.7, 31.9, 29.6, 29.6, 29.5, 29.5, 29.3, 29.2, 25.0, 22.7, 14.1; HRMS (ESI-TOF) calcd for $C_{14}H_{26}ONa$ (M + Na^+) 233.1876, found 233.1871.

(*S*)-1-Undecylprop-2-ynyl Diphenylacetate ((*S*)-7) and (*R*)-Tetradec-1-yn-3-ol ((*R*)-6). To a solution of (±)-**6** (6.00 g, 28.5 mmol) in diethyl ether (57 mL) at room temperature were successively added diphenylacetic acid (4.24 g, 20.0 mmol), diisopropylethylamine (7.45 mL, 42.8 mmol), (*S*)-BTM (360 mg, 1.43 mmol), and pivalic anhydride (4.07 mL, 21.4 mmol). After the reaction mixture had been stirred for 12 h at room temperature, saturated aqueous sodium hydrogen carbonate was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by column chromatography on silica (eluant; hexane/ethyl acetate =

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50/1) to afford the corresponding ester (*S*)-**7** (6.65 g, 58%, 74% ee) as a colorless oil and the recovered optically active alcohol (*R*)-**6** (2.43 g, 41%, 99% ee) as a white solid.

(*R*)-Tetradec-1-yn-3-ol ((*R*)-6) [99% ee]:[24] $[\alpha]^{22}_{D}$ +2.71 (*c* 1.10, $CHCl_3$). Enantiomeric excess of the optically active alcohol (*R*)-**6** was determined after converting into the corresponding ester (*R*)-**7**. HPLC (CHIRALPAK OJ-H, *i*-PrOH/hexane =1/9, flow rate = 0.5 mL/min); t_R = 22.3 min (0.47%), t_R = 26.0 min (99.53%).

(*S*)-1-Undecylprop-2-ynyl Diphenylacetate ((*S*)-7) [74% ee]. HPLC (CHIRALPAK OJ-H, *i*-PrOH/hexane = 1/9, flow rate = 0.5 mL/min); t_R = 21.8 min (86.8%), t_R = 26.7 min (13.2%); $[\alpha]^{22}_{D}$ −30.7 (*c* 1.22, $CHCl_3$); IR (neat) 3302, 1743 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.28−7.18 (m, 10H, Ph), 5.36 (ddd, *J* = 2.5, 6.0, 7.5 Hz, 1H, 3-H), 4.99 (s, 1H, 2′-H), 2.38 (d, *J* = 2.5 Hz, 1H, 1-H), 1.74−1.63 (m, 2H, 4-H), 1.30−1.10 (m, 18H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H), 0.83 (t, *J* = 7.5 Hz, 3H, 14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.4, 138.4, 138.4, 128.6, 128.6, 128.6, 128.5, 127.3, 127.2, 81.0, 73.7, 64.5, 56.9, 34.4, 31.9, 29.6, 29.6, 29.4, 29.4, 29.3, 28.9, 24.7, 22.7, 14.1; HRMS (ESI-TOF) calcd for $C_{28}H_{36}O_2Na$ ($M + Na^+$) 427.2608, found 427.2628.

(*R*)-3-(4-Methoxybenzyloxy)tetradec-1-yne (8). To a suspension of sodium hydride (55% in paraffin liquid, 41.5 mg, 0.951 mmol) in DMF (0.7 mL) at 0 °C was added a solution of (*R*)-**6** (100 mg, 0.475 mmol) in DMF (1.7 mL). After the reaction mixture had been stirred for 1 h at 0 °C, 4-methoxybenzyl chloride (0.0710 mL, 0.523 mmol) and tetrabutylammonium iodide (18.5 mg, 0.0475 mmol) were added at 0 °C. The reaction mixture was stirred for 40 min at room temperature and then saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with diethyl ether, and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; benzene/hexane = 2/1) to afford **8** (150 mg, 96%) as a colorless oil: $[\alpha]^{22}_{D}$ +88.2 (*c* 1.13, $CHCl_3$); IR (neat) 3302 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.5 Hz, 1H, PMP), 6.89 (d, *J* = 8.5 Hz, 1H, PMP), 4.74 (d, *J* = 11.0 Hz, 1H, PMB), 4.45 (d, *J* = 11.0 Hz, 1H, PMB), 4.05 (ddd, *J* = 2.5, 6.0, 7.5 Hz, 1H, 3-H), 3.81 (s, 3H, OMe), 2.46 (d, *J* = 2.5 Hz, 1H, 1-H), 1.81−1.68 (m, 2H, 4-H), 1.54−1.40 (m, 2H, 5-H), 1.39−1.18 (m, 16H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H), 0.89 (t, *J* = 6.5 Hz, 3H, 14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 130.0, 129.6, 113.8, 83.2, 73.6, 70.1, 68.1, 55.2, 35.6, 31.9, 29.6, 29.6, 29.6, 29.5, 29.3, 29.3, 25.2, 22.7, 14.1; HRMS (ESI-TOF) calcd for $C_{22}H_{34}O_2Na$ ($M + Na^+$) 353.2451, found 353.2460.

(*R*)-3-(4-Methoxybenzyloxy)tetradecanal (9). To a solution of **8** (20.5 mg, 0.0621 mmol) in THF (1.2 mL) at 0 °C was added a solution of catecholborane in THF (1.00 M, 0.560 mL, 0.560 mmol). After the reaction mixture had been stirred for 3.5 h at 70 °C, phosphate buffer (pH = 7) (2 mL) and a solution of sodium acetate (229 mg, 2.79 mmol) in water (2 mL) were added at 0 °C. The reaction mixture was stirred for 10 min at 0 °C, and then hydrogen peroxide (30% in water, 1.25 mL, 12.4 mmol) was added. After the reaction mixture had been stirred for 3 h at room temperature, the aqueous layer was saturated by the addition of potassium carbonate. The mixture was extracted with ethyl acetate, and the organic layer was dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 6/1) to afford **9** (11.5 mg, 53%) as a colorless oil: $[\alpha]^{22}_{D}$ −13.9 (*c* 1.01, $CHCl_3$); IR (neat) 1726 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.78 (dd, *J* = 2.1, 2.7 Hz, 1H, 1-H), 7.24 (d, *J* = 8.4 Hz, 2H, PMP), 6.87 (d, *J* = 8.4 Hz, 2H, PMP), 4.50 (d, *J* = 11.1 Hz, 1H, PMB), 4.44 (d, *J* = 11.1 Hz, 1H, PMB), 3.92 (dtd, *J* = 4.8, 6.0, 7.2 Hz, 1H, 3-H), 3.80 (s, 3H, OMe), 2.66 (ddd, *J* = 2.7, 7.2, 16.2 Hz, 1H, 2-H), 2.54 (ddd, *J* = 2.1, 4.8, 16.2 Hz, 1H, 2-H), 1.71−1.60 (m, 1H, 4-H), 1.60−1.48 (m, 1H, 4-H), 1.46−1.06 (m, 18H, 5-H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H), 0.88 (t, *J* = 6.6 Hz, 3H, 14-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 201.7, 159.2, 130.3, 129.3, 113.7, 73.9, 70.8, 55.1, 48.2, 34.2, 31.8, 29.6, 29.6, 29.5, 29.5, 29.5, 29.3, 25.0, 22.6, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{36}O_3Na$ ($M + Na^+$) 371.2557, found 371.2543.

Benzyl (3*S*,5*R*)-5-(4-Methoxybenzyloxy)-3-hydroxyhexadecanoate (11). To a solution of **9** (72.8 mg, 0.209 mmol) in toluene (3.5 mL) at −78 °C was added a solution of $TiCl_2$(-O*i*-Pr)$_2$ in toluene (1.00 M, 0.520 mL, 0.520 mmol). The reaction mixture was stirred for 15 min at −78 °C, and then a solution of 1-benzyloxy-1-(*t*-butyldimethylsiloxy)ethene (**10**) (144 mg, 0.543 mmol) in toluene (0.7 mL) was added. After the reaction mixture had been stirred for 4 h at −78 °C, phosphate buffer (pH = 7) was added. The mixture was extracted with dichloromethane and the organic layer was washed with saturated aqueous ammonium chloride and brine, dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product (*anti*/*syn* = 94/6, determined by ^1H NMR) was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 4/1) to afford *anti*-aldol **11** (90.2 mg, 87%) as a colorless oil: $[\alpha]^{24}_{D}$ −13.7 (*c* 0.687, $CHCl_3$); IR (neat) 3440, 1736 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H, Ph), 7.25 (d, *J* = 8.5 Hz, 2H, PMP), 6.86 (d, *J* = 8.5 Hz, 2H, PMP), 5.15 (s, 2H, Bn), 4.51 (d, *J* = 11.0 Hz, 1H, PMB), 4.43 (d, *J* = 11.0 Hz, 1H, PMB), 4.35−4.28 (m, 1H, 3-H), 3.79 (s, 3H, OMe), 3.72−3.65 (m, 1H, 5-H), 3.31 (d, *J* = 4.0 Hz, 1H, OH), 2.51 (d, *J* = 6.0 Hz, 2H, 2-H), 1.73−1.45 (m, 4H, 4-H, 6-H), 1.35−1.20 (m, 18H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H), 0.88 (t, *J* = 7.0 Hz, 3H, 16-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 159.2, 135.7, 130.5, 129.5, 128.6, 128.3, 128.2, 113.8, 76.1, 71.0, 66.4, 65.3, 55.3, 41.9, 40.0, 33.6, 31.9, 29.8, 29.7, 29.6, 29.6, 29.6, 29.3, 25.2, 22.7, 14.1; HRMS (ESI-TOF) calcd for $C_{31}H_{46}O_5Na$ ($M + Na^+$) 521.3237, found 521.3263.

Benzyl (2*S*,3*S*,5*R*)-5-(4-Methoxybenzyloxy)-2-hexyl-3-hydroxyhexadecanoate (12). To a solution of **11** (32.4 mg, 0.0650 mmol) in THF (1.3 mL) at −78 °C was added a solution of LHMDS in THF (1.00 M, 0.230 mL, 0.230 mmol). The reaction mixture was stirred for 30 min at −78 °C and for 1 h at −45 °C, and then a solution of iodohexane (0.0960 mL, 0.652 mmol) in HMPA (0.113 mL, 0.649 mmol) was added. After the reaction mixture had been stirred for 3 h at −45 °C, saturated aqueous ammonium chloride was added. The mixture was extracted with ethyl acetate, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 4/1) to afford **12** (20.6 mg, 55%, *anti*/*syn* = 100/0) and recovered **11** (12.7 mg, 39%) as colorless oils. **Benzyl (2*S*,3*S*,5*R*)-5-(4-methoxybenzyloxy)-2-hexyl-3-hydroxyhexadecanoate (12):** $[\alpha]^{22}_{D}$ −17.0 (*c* 1.01, $CHCl_3$); IR (neat) 3479, 1728 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.38−7.28 (m, 5H, Ph), 7.24 (d, *J* = 8.5 Hz, 2H, PMP), 6.84 (d, *J* = 8.5 Hz, 2H, PMP), 5.18 (d, *J* = 12.0 Hz, 1H, Bn), 5.15 (d, *J* = 12.0 Hz, 1H, Bn), 4.49 (d, *J* = 11.0 Hz, 1H, PMB), 4.41 (d, *J* = 11.0 Hz, 1H, PMB), 4.00 (dddd, *J* = 2.5, 6.0, 6.5, 8.5 Hz, 1H, 3-H), 3.79 (s, 3H, OMe), 3.70−3.64 (m, 1H, 5-H), 3.06 (d, *J* = 6.0 Hz, 1H, OH), 2.45 (ddd, *J* = 4.5, 6.5, 9.5 Hz, 1H, 2-H), 1.71−1.42 (m, 6H, 4-H, 6-H, 1′-H), 1.35−1.15 (m, 26H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 2′-H, 3′-H, 4′-H, 5′-H), 0.88 (t, *J* = 7.0 Hz, 3H, 16-H), 0.86 (t, *J* = 7.0 Hz, 3H, 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 159.2, 136.0, 130.6, 129.5, 128.5, 128.3, 128.2, 113.8, 76.2, 71.0, 69.5, 66.1, 55.2, 51.8, 38.6, 33.6, 31.9, 31.6, 29.8, 29.7, 29.6, 29.6, 29.6, 29.3, 29.2, 29.1, 27.3, 25.3, 22.7, 22.5, 14.1, 14.0; HRMS (ESI-TOF) calcd for $C_{37}H_{58}O_5Na$ ($M + Na^+$) 605.4176, found 605.4164.

(2*S*,3*S*,5*R*)-5-(4-Methoxybenzyloxy)-2-hexyl-3-hydroxyhexadecanoic Acid. To a solution of **12** (19.2 mg, 0.0329 mmol) in methanol (0.18 mL) and THF (0.35 mL) at room temperature was added lithium hydroxide in water (4.00 M, 0.180 mL, 0.720 mmol). The reaction mixture was stirred for 2 h at 55 °C and then 1.0 M hydrochloric acid was added at 0 °C. The acidified mixture (pH = 4) was extracted with ethyl acetate and the organic layer was washed with brine and dried over sodium sulfate. The crude product was purified by thin-layer chromatography on silica (eluant; chloroform/methanol = 9/1) to afford (2*S*,3*S*,5*R*)-5-(4-methoxybenzyloxy)-2-hexyl-3-hydroxyhexadecanoic acid (16.2 mg, quant) as a colorless oil: $[\alpha]^{21}_{D}$ −23.0 (*c* 1.09, $CHCl_3$); IR (neat) 3430, 1710 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.0 Hz, 2H, PMP), 6.86 (d, *J* = 9.0 Hz, 2H, PMP), 4.49 (d, *J* = 11.0 Hz, 1H, PMB), 4.45 (d, *J* = 11.0 Hz, 1H,

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PMB), 4.12−3.98 (m, 1H, 3-H), 3.80−3.62 (m, 2H, 5-H), 3.78 (s, 3H, OMe) 2.42−2.26 (m, 1H, 2-H), 1.80−1.43 (m, 6H, 4-H, 6-H, 1′-H), 1.43−1.10 (m, 26H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 2′-H, 3′-H, 4′-H, 5′-H), 0.95−0.78 (m, 6H, 16-H, 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 179.4, 159.3, 130.3, 129.5, 113.8, 76.5, 71.1, 69.2, 55.2, 51.8, 38.2, 33.6, 31.9, 31.6, 29.8, 29.7, 29.6, 29.6, 29.6, 29.3, 29.3, 29.2, 27.2, 25.4, 22.7, 22.6, 14.1, 14.0; HRMS (ESI-TOF) calcd for $C_{30}H_{52}O_5Na$ (M + Na^+) 515.3707, found 515.3730.

(2*S*,3*S*,5*R*)-5-(4-Methoxybenzyloxy)-2-hexyldecan-3-olide (13). To a solution of MNBA (29.7 mg, 0.0863 mmol), DMAP (1.6 mg, 0.013 mmol), and triethylamine (0.0551 mL, 0.397 mmol) in dichloromethane (4.6 mL) at room temperature was slowly added a solution of (2*S*,3*S*,5*R*)-5-(4-methoxybenzyloxy)-2-hexyl-3-hydroxyhexadecanoic acid (32.7 mg, 0.0664 mmol) in dichloromethane (2 mL) with a mechanically driven syringe over a 12 h period. After the reaction mixture had been stirred for 1 h at room temperature, saturated aqueous sodium hydrogen carbonate was added at 0 °C. The mixture was extracted with dichloromethane, and the organic layer was washed with brine and dried over sodium sulfate. After filtration of the mixture and evaporation of the solvent, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 5/1) to afford **13** (28.7 mg, 91%) as a colorless oil: $[\alpha]^{21}_D$ −44.8 (*c* 1.00, $CHCl_3$); IR (neat) 1823 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 9.0 Hz, 2H, PMP), 6.88 (d, *J* = 9.0 Hz, 2H, PMP), 4.53 (d, *J* = 11.0 Hz, 1H, PMB), 4.43 (dt, *J* = 4.0, 6.5 Hz, 1H, 3-H), 4.37 (d, *J* = 11.0 Hz, 1H, PMB), 3.81 (s, 3H, OMe), 3.58 (tt, *J* = 5.5, 6.5 Hz, 1H, 5-H), 3.20 (dt, *J* = 4.0, 7.5 Hz, 1H, 2-H), 1.92 (dd, *J* = 5.5, 6.5 Hz, 2H, 4-H), 1.80−1.71 (m, 1H, 1′-H), 1.70−1.58 (m, 2H, 6-H, 1′-H), 1.57−1.48 (m, 1H, 6-H), 1.43−1.27 (m, 26H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 2′-H, 3′-H, 4′-H, 5′-H), 0.90−0.86 (m, 6H, 16-H, 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 159.2, 130.5, 129.3, 113.8, 75.5, 75.4, 71.2, 56.6, 55.2, 39.8, 33.9, 31.9, 31.5, 29.7, 29.6, 29.6, 29.6, 29.3, 29.3, 28.9, 27.7, 26.7, 24.7, 22.7, 22.5, 14.1, 14.0; HRMS (ESI-TOF) calcd for $C_{30}H_{50}O_4Na$ (M + Na^+) 497.3601, found 497.3598.

(2*S*,3*S*,5*R*)-5-Hydroxy-2-hexyldecan-3-olide (5).[20n] To a solution of **13** (17.3 mg, 0.0364 mmol) in ethanol (0.7 mL) at room temperature was added palladium hydroxide on carbon (1.5 mg, 0.011 mmol). The reaction mixture was stirred for 2 h at room temperature under hydrogen atmosphere. The mixture was filtered through a short pad of Celite, and the filtrate was extracted with ethyl acetate. After evaporation of the solvent, the residue was dried under reduced pressure to afford **5**. The crude product **5** was used in the following reaction without further purification. For the analysis, the crude product was purified by thin-layer chromatography on silica (eluant; hexane/ethyl acetate = 5/1) to afford pure **5** as a colorless solid: $[\alpha]^{26}_D$ −37.9 (*c* 0.678, $CHCl_3$); mp 57−58 °C; IR (KBr) 3340, 1813 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.50 (ddd, *J* = 4.0, 4.5, 8.5 Hz, 1H, 3-H), 3.90−3.77 (m, 1H, 5-H), 3.26 (ddd, *J* = 3.5, 4.0, 11.0 Hz, 1H, 2-H), 2.01−1.89 (m, 1H, 4-H), 1.89−1.70 (m, 3H, 4-H, 1′-H), 1.70−1.21 (m, 28H, 6-H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 2′-H, 3′-H, 4′-H, 5′-H), 0.88 (t, *J* = 7.5 Hz, 3H, 16-H), 0.88 (t, *J* = 7.5 Hz, 3H, 6′-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.6, 75.6, 68.5, 56.6, 41.8, 38.1, 31.9, 31.5, 29.6, 29.6, 29.5, 29.5, 29.5, 29.3, 28.9, 27.7, 26.8, 25.4, 22.7, 22.5, 14.1, 14.0; HRMS (ESI-TOF) calcd for $C_{22}H_{42}O_3Na$ (M + Na^+) 377.3026, found 377.3026.

(2*S*,3*S*,5*R*)-(−)-5-(*N*-Formyl-L-leucinyloxy)-2-hexyldecan-3-olide ((−)-THL) (3).[19,20] To a solution of crude **5** in THF (0.7 mL) at 0 °C were successively added *N*-formyl-L-leucine (**4**) (20.4 mg, 0.128 mmol), triphenylphosphine (28.7 mg, 0.109 mmol), and a solution of DIAD in toluene (1.90 M, 0.0700 mL, 0.133 mmol). The reaction mixture was stirred for 3 h at room temperature, and then it was filtered though a short pad of silica gel with ethyl acetate. After evaporation of the solvent, the crude product was purified twice by thin-layer chromatography on silica (eluant; benzene/ethyl acetate = 4/1 and hexane/diethyl ether = 1/2) to afford **3** (17.3 mg, 96% in two steps) as a colorless oil: $[\alpha]^{22}_D$ −32.5 (*c* 1.17, $CHCl_3$) [lit.[19d] $[\alpha]^{20}_D$ −32.0 (*c* 1, $CHCl_3$); lit.[20i] $[\alpha]^{25}_D$ −33.04 (*c* 0.79, $CHCl_3$); lit.[20n] $[\alpha]^{20}_D$ −32.0 (*c* 0.74, $CHCl_3$); lit.[20x] $[\alpha]^{26}_D$ −31 (*c* 0.1, $CHCl_3$)]; IR (neat) 3329, 1822, 1738, 1678 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.22 (s, 1H, CHO), 5.90 (d, *J* = 8.5 Hz, 1H, NH), 5.03 (dddd, *J* = 4.0, 5.5, 6.5, 7.0 Hz, 1H, 5-H), 4.69 (ddd, *J* = 4.0, 8.5, 13.0 Hz, 1H, 2″-H), 4.29 (ddd, *J* = 4.5, 4.5, 8.0 Hz, 1H, 3-H), 3.21 (ddd, *J* = 4.0, 4.5, 11.5 Hz, 1H, 2-H), 2.16 (dt, *J* = 7.0, 8.0, 15.0 Hz, 1H, 4-H), 2.01 (dt, *J* = 4.0, 4.5, 15.0 Hz, 1H, 4-H), 1.85−1.50 (m, 6H, 6-H, 1′-H, 3″-H), 1.50−1.15 (m, 27H, 7-H, 8-H, 9-H, 10-H, 11-H, 12-H, 13-H, 14-H, 15-H, 2′-H, 3′-H, 4′-H, 5′-H, 4″-H), 1.05−0.82 (m, 12H, 16-H, 6′-H, 5″-H, 5″-H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.9, 170.7, 160.6, 74.7, 72.7, 57.0, 49.6, 41.5, 38.7, 34.0, 31.9, 31.4, 29.6, 29.5, 29.4, 29.3, 29.3, 28.9, 27.6, 26.7, 25.1, 24.9, 22.8, 22.7, 22.5, 21.9, 21.7, 14.1, 14.0; HRMS (ESI-TOF) calcd for $C_{29}H_{53}O_5NNa$ (M + Na^+) 518.3816, found 518.3809.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR spectra on all compounds and Cartesian coordinates for all calculated intermediates and transition structures. This material is available free of charge via the Internet at http://pubs.acs.org.

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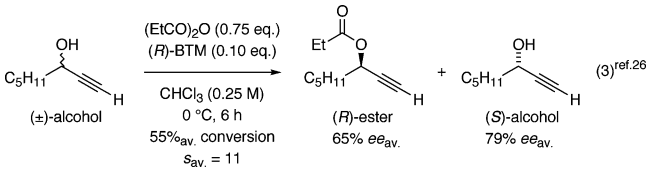

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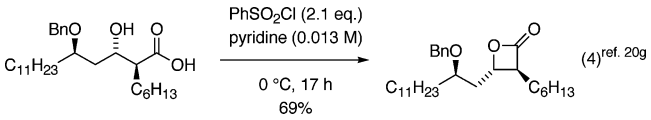

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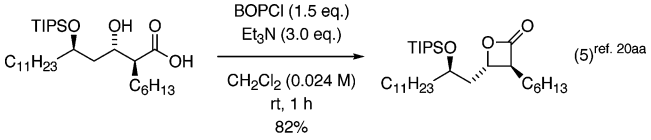

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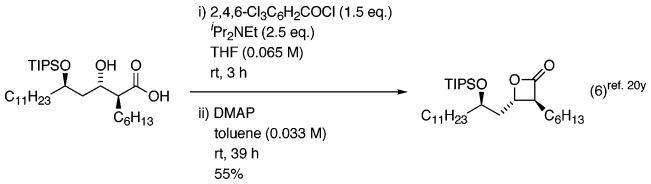

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